Studies towards the total synthesis of polyhydroxylated pyrrolidine alkaloids isolated from the Japanese Paper Mulberry Broussonetia Kazinoki (Moraceae)

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Studies towards the Total Synthesis of Polyhydroxylated Pyrrolidine Alkaloids isolated from the Japanese Paper Mulberry Broussonetia kazinoki (Moraceae)

Employing the Petasis borono-Mannich Reaction in the Synthesis of Cyclic Phytosphingosine Derivatives

A thesis submitted in fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

- PhD -

from the
University of Wollongong

by
Marc Etienne Bouillon
Dipl.-Chem.

Faculty of Science
2012
Declaration

I hereby declare that the present thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy in the Faculty of Science, University of Wollongong, is wholly my own work unless due reference is provided. This document has not been submitted for qualifications at any other academic institution.

Marc Etienne Bouillon

Wollongong, 09/01/2013
For My Parents
“If you start something, you finish it.
You don’t stop until you get it right.
And if you don’t get it right, you start over again,
And you keep on going as long as have to.
That’s the way it is. That’s what you do.”

PETER JACKSON – The Lovely Bones

“The courage to start something needs to be matched with the discipline to finish it.”

SCOTT H. YOUNG
Abstract

Polyhydroxylated alkaloids, also known as iminosugars and azasugars, are natural products that structurally resemble sugar molecules but contain a cyclic-bound basic nitrogen atom in lieu of the ring oxygen. Certain iminosugars have attracted increasing attention as potential antiviral, anticancer and antidiabetic agents due to their inhibitory activity against several glycosidases, enzymes that hydrolyse the terminal glycosidic bond of various polysaccharides. The broussonetines are a subgroup within the class of iminosugars that is characterised by a polyhydroxylated pyrrolidine moiety and a thirteen carbon side chain attached at the pseudo-anomeric position. As such, they can be regarded as derivatives of the also naturally occurring small iminosugars DMDP and D-AB1. Furthermore, their structure and proposed biosynthetic pathway also relates them to another group of natural products, namely the sphingoid bases ("sphingosines") and their cyclic derivatives including 2,6-disubstituted 3-piperidinol alkaloids like cassine and carnavaline. The broussonetine family consists of more than 30 members which have been isolated since 1995 from the bark extracts of the Japanese Paper Mulberry, *Broussonetia kazinoki* (Moraceae) by G. KUSANO et al. Glycosidase inhibitory activity assays demonstrated that almost all broussonetines are exceptional inhibitors of \( \beta \)-glycosidases with IC\(50\) values in the nanomolar range. Broussonetines C and E in particular display excellent \( \beta \)-galactosidase inhibitory activity with IC\(50\) values of \( 3.6 \times 10^{-8} \) and \( 2.0 \times 10^{-9} \) mol/L, respectively.

Retrosynthetically, the broussonetines were divided into two fragments, the pyrrolidine moiety and a side chain building block, which were planned to be coupled via a Wittig reaction in the case of broussonetine C and a Grignard reaction in the case of broussonetine E. As a key step for the assembly of the pyrrolidine moiety, the substrate controlled diastereoselective Petasis reaction of 3,5-di-O-benzyl-L-xylofuranose, readily available in three simple steps from L-xylose, was to be employed. A subsequent stereospecific S\(\_8\)2/5-\(exo\)-tet-cyclisation followed by O-benzyl protection and an oxidative double cleavage would ultimately provide the desired pyrrolidine carbaldehyde as building block. Via a small modification of the synthesis route this approach would also be used to synthesise DMDP. However, due to the relative expensive cost of L-xylose compared to its cheap natural enantiomer, D-xylose was eventually used in the synthesis providing the unnatural enantiomers of the natural products.
Nevertheless, these enantiomers are gaining increasing interest due to the discovery that, in many cases, they are by far more potent and specific glycosidase inhibitors than their natural counterparts.

L-DMDP was synthesised in four steps from the known compound 3,5-di-O-benzyl-D-xylofuranose. The Petasis reaction of this xylose derivative provided stereoselectively the desired anti-1,2-amino alcohol 7/6 in excellent d.e. (> 99%). This amino alcohol was then cyclised in a stereospecific S\textsubscript{N}2/5-exo-tet-cyclisation via the regioselective O-mesylation at C-2 to give pyrrolidine 7/12. Ozonolysis of the styryl double bond in 7/12 and the hydrogenolysis of the remaining benzyl protecting groups concluded the synthesis. Serendipitously, the ozonolysis of 7/12 also provided the C-5 decarbinolated pyrrolidine 7/24 which after hydrogenolysis afforded the known iminosugar L-AB1.

The synthesis of pyrrolidine carbaldehyde 8/2, on the other hand, proved to be unexpectedly complicated. Several attempts to obtain the aldehyde via the oxidative double bond cleavage of the fully benzyl-protected pyrrolidine 8/1 were unsuccessful due to the low stability of the target compound and the formation of various by-products. After a number of failed attempts, the synthesis of 8/2 eventually succeeded via a detour from the pyrrolidine diol 7/23. The primary hydroxy group of 7/23 was trityl protected followed by the C-4 O-benzylation of 8/54. The consequent trityl ether cleavage afforded the pyrrolidine alcohol 8/9 which was subsequently oxidised via a Swern oxidation to the required aldehyde building block.

The pyrrolidine carbaldehyde was then successfully coupled with two simplified side chain fragments via a Wittig reaction and Grignard reaction, respectively, affording the two model compounds (−)-10'-deoxobroussonetine C and E after hydrogenolysis. An attempt to invert the configuration of the secondary (6\text{R})-alcohol 9/12, obtained from the Grignard coupling reaction, to the desired (6\text{S})-epimer resulted in ring-expansion of the pyrrolidine ring ultimately affording the novel polyhydroxylated piperidine, (−)-(6\text{S})-(12'-hydroxydodecyl)moranoline, after hydrogenolysis.

The synthesis of (−)-broussonetine C, however, remained unsuccessful due to unforeseen problems during the final step, the hydrogenolysis of the benzyl protecting groups in the (−)-broussonetine C precursor 10/20. The chosen reaction conditions resulted in a cyclisation-reduction sequence of the side chain terminus providing the novel tetrahydrofuran derivative 10/23, designated as (−)-broussonetine C2.
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<td>ac</td>
<td>acetonide</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobis(isobutynitrile)</td>
</tr>
<tr>
<td>All</td>
<td>allyl</td>
</tr>
<tr>
<td>APG</td>
<td>Angiosperm Phylogeney Group</td>
</tr>
<tr>
<td>APT</td>
<td>Attached Proton Test</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>1 atmosphere = $10^5$ Pa</td>
</tr>
<tr>
<td>ATR</td>
<td>Attenuated Total Reflectance</td>
</tr>
<tr>
<td>ax</td>
<td>axial</td>
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<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
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<td>BHT</td>
<td>2,6-di-tert-butyl-para-cresol (butylated hydroxytoluene)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
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<td>tert-butyloxycarbonyl</td>
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<td>BORSM</td>
<td>based on recovered starting material</td>
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<td>CAM</td>
<td>ceric ammonium molybdate</td>
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<td>ceric ammonium nitrate / cerium(IV) ammonium nitrate</td>
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<td>cat.</td>
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<td>Cbz</td>
<td>benzoylcarbonyl</td>
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<td>CDI</td>
<td>carbonyl diimidazole (1,1-carbonyl-bis-1H-imidazole)</td>
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<td>Chx</td>
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<tr>
<td>COD</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>conc.</td>
<td>concentrated</td>
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<td>correlation spectroscopy</td>
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<td>CSA</td>
<td>camphor-10-sulfonic acid</td>
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<tr>
<td>DAM</td>
<td>di-para-anisylmethyl = bis(4-methoxyphenyl)methyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
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<td>DCM</td>
<td>dichloromethane</td>
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<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
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<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>DE</td>
<td>diethyl ether</td>
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<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
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<td>DET</td>
<td>diethyl tartrate</td>
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<td>DFT</td>
<td>density functional theory</td>
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<td>DHP</td>
<td>3,4-dihydro-2H-pyran</td>
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<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
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<td>DIPEA</td>
<td>diisopropylethylamine</td>
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<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
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<td>DMA</td>
<td>N,N-dimethylacetamide</td>
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<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
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<td>DMDP</td>
<td>2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine</td>
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<td>DME</td>
<td>1,2-dimethoxyethane</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>DMPU</td>
<td>N,N'-dimethylpropylene urea</td>
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<td>DMS</td>
<td>dimethylsulfide</td>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
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<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>EA</td>
<td>ethyl acetate</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<td>exc.</td>
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<tr>
<td>Fm</td>
<td>formyl</td>
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<tr>
<td>Fmoc</td>
<td>9-fluorenlymethoxycarbonyl</td>
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<tr>
<td>Glc</td>
<td>glucopyranosyl</td>
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<tr>
<td>Hex</td>
<td>hexyl</td>
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<tr>
<td>HFIP</td>
<td>1,1,1,3,3,3-hexafluoro-iso-propanol</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
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<tr>
<td>HSQC</td>
<td>Heteronuclear Single Quantum Correlation</td>
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<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>IBX</td>
<td>o-iodoxybenzoic acid</td>
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<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>inhibitor concentration at 50% inhibition of enzyme</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>IXC</td>
<td>ion-exchange chromatography</td>
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<tr>
<td>K&lt;sub&gt;i&lt;/sub&gt;</td>
<td>inhibition constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature</td>
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<td>MCR</td>
<td>multicomponent reaction</td>
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<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimal Inhibitory Concentration</td>
</tr>
<tr>
<td>2-MOP</td>
<td>2-methoxypropene</td>
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<tr>
<td>m.p.</td>
<td>melting point</td>
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<tr>
<td>Ms</td>
<td>mesyl, methanesulfonyl</td>
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List of Abbreviations

**Abbreviation** | **Description**
--- | ---
MS | Mass Spectrometry
MS 4Å | Molecular Sieves 4Å
MTPA | $\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenylacetyl
n/a | not assessed
NCS | $N$-chlorosuccinimide
NMM | $N$-methylmorpholine
NMO | $N$-methylmorpholine-$N$-oxide
NMR | Nuclear Magnetic Resonance
NOE | Nuclear Overhauser Effect
o/n | overnight
PBM | Petasis borono-Mannich
PCC | pyridinium chlorochromate
PDA | Photodiode Array Detector
Pd/C | palladium on charcoal
PDC | pyridinium dichromate
PE | Petrol ether
PG | Protecting Group
Ph | phenyl
PMB | $para$-methoxybenzyl
ppm | parts per million
PPTS | pyridinium $para$-toluenesulfonate
Pr | propyl
psi | pounds per square inch
PTSA | $para$-toluenesulfonic acid
py | pyridine
PyBOP | benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
quant. | quantitative
RCM | Ring-closing metathesis
REDAL | Sodium $bis$(2-methoxyethoxy)aluminium hydride
$R_f$ | ratio of fronts
rt | room temperature
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>sat.</td>
<td>saturated</td>
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<tr>
<td>SPT</td>
<td>serine palmitoyltransferase</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>TBAT</td>
<td>tetrabutylammonium difluorotriphenylsilicate</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butylidimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
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<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethylpiperidine-(N)-oxid</td>
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<tr>
<td>TES</td>
<td>triethylsilyl</td>
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<tr>
<td>TMEDA</td>
<td>(N,N,N',N)-tetramethylethylenediamine</td>
</tr>
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<td>TMS</td>
<td>tetramethylsilane</td>
</tr>
<tr>
<td>Tf</td>
<td>triflyl, trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-trifluoroethanol</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran-2-yl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>tol</td>
<td>tolyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>TPS</td>
<td>triphenylsilyl</td>
</tr>
<tr>
<td>Tr</td>
<td>trityl, triphenylmethyl</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl, para-toluenesulfonyl</td>
</tr>
<tr>
<td>URL</td>
<td>Uniform Resource Locator</td>
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List of Abbreviations
This thesis describes the syntheses of unnatural iminosugar derivatives employing the Petasis borono-Mannich reaction as a key step. Target molecules were the C2-symmetric polyhydroxylated pyrrolidine 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) as well as its two C-5 homologues, the broussonetines C and E (broussonetine C being the 1’-deoxyanalogue of E).

Chapter 1 gives a detailed review over the still expanding class of polyhydroxylated alkaloids including their distribution in nature, structural diversity and biological activities including their glycosidase inhibition. On the basis of selected examples their therapeutic applications for the treatment diabetes type II as well as their potential as therapeutic agents against AIDS and cancer is also described.

Chapter 2 introduces the broussonetines as a subgroup of polyhydroxylated pyrrolidine alkaloids, summarises their glycosidase inhibitory activities and explains their proposed biosynthetic pathway which eventually relates them to another family of natural products, the sphingoid bases (“sphingosines”) and their cyclic derivatives. A review about these compounds including their natural sources and biological activities is given.

Chapter 3 describes all to date published syntheses of broussonetine congeners from the first synthesis of broussonetine C by YODA et al. in 1999 to the most recent of broussonetine F by CHIDA and co-workers in 2011. A comparative summary at the end of the chapter is also given.

Chapter 4 gives a review over the syntheses of polyhydroxylated alkaloids performed in the PYNE group to this date.

Chapter 5 provides a minireview about the Petasis borono-Mannich reaction and its application in the synthesis of natural products and therapeutic agents.

Chapter 6 outlines the project aims of this thesis and the synthetic strategy towards the target molecules broussonetines C and E as well as their smaller congener DMDP inspired by the work of DONDONI and co-workers as well as IKOTA et al.

Chapter 7 illustrates the successful syntheses of L-DMDP and L-AB1 from D-xylose employing the Petasis reaction of 3,5-di-O-benzyl-D-xylofuranose with benzylamine and (E)-styrylboronic acid as a key step.
Preface

Chapter 8 exemplifies the synthesis of the pyrrolidine carbaldehyde 8/2 as the required building block for the broussonetine syntheses with a focus on the difficulties encountered during the oxidative cleavage of the styryl double bond of compound 8/1.

Chapter 9 describes the syntheses of (–)-10'-deoxobroussonetines C and E as model studies with the purpose of testing the coupling reactions of the pyrrolidine carbaldehyde building block with a simple side chain fragment via Wittig and Grignard reactions, respectively.

Chapter 10 reports the unfortunately unsuccessful attempt to synthesise (–)-broussonetine C as well as the structure elucidation of the instead obtained novel polyhydroxylated pyrrolidine base, consequently designated as (–)-broussonetine C2.

Chapter 11 provides an outlook towards future work arisen from this thesis. Improvements to the introduced syntheses and alternative synthesis schemes are presented.

Appendix 1, originally conceived as a introductory chapter about alkaloids, was about to be omitted from the final version of the thesis due to structural reasons. However, since quite a lot time and effort was invested in the composition of this chapter, it was decided to add it as an annex. Thus, Appendix 1 presents a general summary about alkaloids, describes a classification system of this vast group of natural products with well-known examples for each class, shows their therapeutic applications as well as their abuse as recreational drugs by means of prominent examples.

Appendix 2 depicts the full $^1$H and $^{13}$C NMR spectra of selected intermediates as well as all final products that have been synthesised in the course of this project. The IR spectra of all novel polyhydroxylated pyrrolidine and piperidine alkaloids are also shown.
Chapter 1. Polyhydroxylated Alkaloids

1.1 Introduction

Polyhydroxylated alkaloids, also known as sugar-shaped alkaloids, iminosugars, or azasugars are compounds mimicking the structures of monosaccharides. These sugar mimics, in which the ring oxygen has been replaced by nitrogen, are regarded by some as one of the most interesting discoveries in the field of natural products in recent years and are of special synthetic interest for our research group. Due to their structural resemblance to carbohydrates these alkaloids bind specifically to the active sites of various glycosidases, i.e. sugar processing enzymes, by mimicking the positive charge of the glycosyl cation intermediate in the enzyme-catalysed glycoside hydrolysis. Glycosidases are involved in a wide range of important biological processes, such as intestinal digestion, posttranslational processing of glycoproteins and the lysosomal catabolism of glycoconjugates.\textsuperscript{[1]} Certain iminosugars have incited increasing interest as potential antiviral, anticancer and antidiabetic agents as well as agrochemicals since most of these effects have been proven to result from the direct or indirect inhibition of glycosidases.\textsuperscript{[2]} The recognition that these alkalioidal sugar mimics might have enormous therapeutic potential for many diseases including the two deadliest known to mankind, i.e. cancer and AIDS, has led to increasing interest and demand for them.\textsuperscript{[3−13]} In this chapter the distribution and structural diversity of naturally occurring iminosugars along with their biological activity and therapeutic application will be reviewed; furthermore, the prospects of iminosugars and their derivatives as new therapeutic agents will be described.

1.2 The Distribution and Structural Diversity of Polyhydroxylated Alkaloids

Naturally occurring iminosugars were originally categorised into five structural classes: polyhydroxylated piperidines, pyrrolidines, pyrrolizidines (two fused pyrrolidine rings with nitrogen at the bridgehead), indolizidines (a pyrrolidine ring adjacent to a piperidine ring with nitrogen at the bridgehead) and nortropanes. However, with the isolation and characterisation of novel polyhydroxylated alkaloids which feature an unsaturated pyrroline ring, one might now consider these iminosugars as a sixth discrete class.
1.2.1 Polyhydroxylated Piperidine Alkaloids – Iminopyranoses

Aminosugars such as D-glucosamine (2-amino-2-deoxy-D-glucopyranose, 1/1), D-mannosamine (2-amino-2-deoxy-D-mannopyranose, 1/2) and D-galactosamine (2-amino-2-deoxy-D-galactopyranose, 1/3), in which the hydroxyl group at C-2 of the monosaccharide is replaced by an amino group (Figure 1.1), are widespread in nature. In particular, the N-acetyl derivatives of 2-aminosugars are ubiquitous constituents of glycoproteins.\[^4\]

By contrast, the corresponding C-5 amino-substituted analogues of monosaccharides are considerably rarer. Only three naturally occurring examples are known, these being the glucose, mannose and galactose derivatives (Figure 1.2) which have been isolated from strains of the *Streptomyces* bacteria. As with sugar aldoses, these C-5 substituted aminosugars exist primarily as cyclical structures to form compounds (with both α- and β- anomers) that are analogous to the respective pyranoses but in which the ring oxygen of the monosaccharide is replaced by a nitrogen atom. Hence, they were given the term iminosugar.\[^4\]

The first natural occurring iminosugar to be discovered was C-5 substituted aminoglucose (5-amino-5-deoxy-D-glucopyranose, 1/4) in 1966 by INOYE *et al.*\[^14\] “Glucosimine”, as it might have simply been called, was originally described as an antibiotic from *Streptomyces roseochromogenes* R-468 but, following structural characterisation, it was given the trivial name nojirimycin after its isolation from *Streptomyces nojiriensis* SF-426.\[^15\] As well as having

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**Figure 1.1.** Common 2-amino-2-deoxy-pyranoses.

**Figure 1.2.** Naturally occurring 5-amino-5-deoxy-pyranoses.
Chapter 1. Polyhydroxylated Alkaloids

antimicrobial activity, nojirimycin (1/4) was found to be a potent inhibitor of both α- and β-glucosidases,[17] which was not very surprising given its structural mimicry of glucose. As a matter of fact, it was the potent inhibition of glycosidases by culture broths of further *Streptomyces* sp. (Figure 1.3) that led to the isolation of the two other iminosugars in the following time: the α-mannosidase inhibitor 5-amino-5-deoxy-D-mannopyranose, known as mannojirimycin or nojirimycin B (1/5), from *Streptomyces lavandulae* SF-425[18] and the β-galactosidase inhibitor 5-amino-5-deoxy-D-galactopyranose, known as galactonojirimycin or galactostatin (1/6), from *Streptomyces lydicus* PA-5726[19–21].

Soon after the discovery of naturally occurring iminosugars in microorganisms, researchers also began to isolate polyhydroxylated piperidine alkaloids from plants. The first to be obtained was fagomine (1/7) from the seeds of the common buckwheat *Fagopyrum esculentum* (Polygonaceae, Figure 1.4) in 1974 by SAKAMURA et al.[22] followed by moranoline (1,5-dIDEOXY-1,5-imino-D-glucitol, 1/8) in 1976 from the roots of a Mulberry species (Moraceae, Figure 1.5) by YAGI and co-workers[23].

![Fagomine](image1.png)

![Moranoline](image2.png)

Figure 1.3. [16] Slide culture of a *Streptomyces* sp. grown on tap water agar. Branching filaments, abundant aerial mycelia and long chains of small spores are visible, all of which are characteristic of *Streptomyces* spp.

Figure 1.4. [24] Seeds and wither flowers of *Fagopyrum esculentum* (Polygonaceae), also known as the common buckwheat. Despite the common name and the grain-like use of the crop, buckwheat is not a cereal or grass. It is called a pseudocereal to emphasise that it is not related to wheat.[24]

Figure 1.5. [25] Fruits and leaves of the Black Mulberry, *Morus nigra* (Moraceae). The imino-pyranose moranoline, originally isolated from the roots of a not otherwise specified *Morus* species, was later also obtained from the leaves of *M. nigra* by EVANS et al.[26] in 1985 and the leaves of *M. bombycis* by ASANO et al.[27] in 1994.
YAGI et al. noticed that moranoline was identical to the iminosugar nojirimycin except that it lacked the anomeric hydroxyl group at C-1. In fact, this 1-deoxy derivative (1-deoxynojirimycin, 1/8) had already been synthesised in 1967 by PAULSEN and co-workers from L-sorbofuranose as well as INOUYE et al. in 1968 via the reduction of nojirimycin with NaBH₄ or catalytic hydrogenation over PtO₂. Later it was later also found as a natural product to be produced by *Streptomyces lavandulae* and bacteria of several *Bacillus* species. As a consequence, by the time when its C-2 epimer 1/9 was discovered in the seeds of the legume *Lonchocarpus sericeus* by FELLOWS and co-workers, the name 1-deoxynojirimycin had already taken such precedence that 2-epi-DNJ was named accordingly as 1-deoxymannojirimycin (DMJ, 1/9) reflecting the D-mannose configuration of the hydroxy groups. DMJ has since been isolated from many disparate species including both tropical and temperate plants from quite unrelated families such as Leguminosae, Euphorbiaceae, Asparagaceae, Campanulaceae, and Commelinaceae and is therefore regarded to be a fairly widespread plant metabolite. In addition, DMJ has been reported as bacterial product from *Streptomyces lavandulae* GC-148 and *S. subrutilus* ATCC 27467 (Streptomycetaceae) by EZURE et al. as well as HUTCHINSON and co-workers.

The first *N*-alkylated iminosugar, *N*-methyl-DNJ (1/14), was isolated by ASANO et al. in 1994 from the roots of the White Mulberry, *Morus alba* (Moraceae) together with various glycosides of DNJ such as 4-DO-glucosyl-DNJ (1/179) and 6-DO-galactosyl-DNJ (1/180). The *N*-methylated homologue of DMJ (1/15) was also discovered by ASANO and co-workers, this time in 2001 in the bark of *Angylocalyx pynaertii*, a legume growing in tropical Africa (Figure 1.7). *N*-Methyl-DMJ was accompanied by DMJ, its 6-DO-α-L-rhamnopyranoside (1/183) and the DNJ diastereoisomers 1-deoxyaltronojirimycin (1/11) and 1-deoxygulonojirimycin (1/12, Figure 1.8). DMJ was later also found in the pod extracts...
of the same plant along with 1,2-dideoxynojirimycin (fagomine, 1/7), 1,6-dideoxynojirimycin (1/20) and 1,3,4-trideoxynojirimycin (1/21) by ASANO et al. in 2002 (Figure 1.10).[^36]

![Figure 1.8](image1.png)

**Figure 1.8.** 1-Deoxynojirimycin (moranoline) and its naturally occurring diastereoisomers and homologues.

The 1,2-dideoxyhomologue of DNJ (1/7), originally isolated in 1974 from the seeds of the common buckwheat *Fagopyrum esculentum* (Polygonaceae) and named fagomine (see above),[^22] was later also discovered in various other plant sources such as the seeds of the Moreton Bay Chestnut, *Castanospermum australe* (Leguminosae)[^47], and the roots of the White Mulberry, *Morus alba* (Moraceae), in the latter case accompanied by its C-3 epimer 1/17.[^45] Fagomine also occurs as its 4-O-β-D-glucopyranoside (1/185) in the seeds of the African legume *Xanthocercis zambesiaca* (Figure 1.9).[^48] A further investigation of the leaves and roots of the same plant by ASANO and co-workers in 1997 led to the anew isolation of fagomine, this time together with its two diastereomers, 3-epi-fagomine.

![Figure 1.9](image2.png)

**Figure 1.9.** Leaves and flowers of the African legume *Xanthocercis zambesiaca* (Leguminosae) also known as Nyala tree.
Chapter 1. Polyhydroxylated Alkaloids

(1/17) and 3,4-di-epi-fagomine (1/18) (Figure 1.10), as well as 3-O-β-D-glucopyranosylfagomine (1/184) and the already known 4-O-β-D-glucopyranoside (Figure 1.78). From the roots of the Chinese Wolfberry, Lycium chinense (Solanaceae), known as “Ti-koppi” in Chinese traditional medicine, fagomine and its 6-deoxyderivative (1/19) have been isolated along with numerous polyhydroxylated nortropane alkaloids (see Section 1.2.6). The α-1-C-hydroxymethylated homologue of fagomine (1/23) was found as constituent in the Thai crude drug “Non Tai Yak” which consists of Stemona tuberosa (Stemonaceae) roots.

In 2005 ASANO and co-workers investigated the constituents of the Thai medicinal plant “Thopthaep”, Connarbus ferrugineus (Combretaceae), which is used traditionally as an ointment to treat scabies, and as an oral drug to treat stomach ache and constipation. Among the polyhydroxylated alkaloids they isolated were the previously unknown DNJ diastereomer 1-deoxyallonojirimycin (DAJ, 1/13) (Figure 1.9) as well as novel 1,4-dideoxyderivatives of nojirimycin: 1,4-dideoxymannojirimycin (1/24), 1,4-dideoxyaltronojirimycin (1/25), 1,4-dideoxyallonojirimycin (1/26) (Figure 1.10).

Figure 1.10. Dideoxyderivatives of nojirimycin including fagomine and its naturally occurring derivatives.
Chapter 1. Polyhydroxylated Alkaloids

glycosides of DMJ, the 2-O-α-D-galactopyranoside (1/178) and the 3-O-β-D-glucopyranoside (1/186) (Figure 1.78), together with DMJ and DNJ.\[51\]

Polyhydroxylated piperidine-2-carboxylic acids (polyhydroxypipelicolic acids) are also known. The first examples, 2S-carboxy-4R,5S-dihydroxypiperidine (1/27) and 2S-carboxy-4S,5S-dihydroxypiperidine (1/28), were isolated by MARLIER et al. in 1976 from the leaves of the Poison vine, Derris elliptica (Leguminosae).\[53\] A further trihydroxylated piperolic acid was discovered by MANNING and co-workers in the seeds of the legume Baphia racemosa (Fabaceae) in 1984.\[54\] 2S-carboxy-3R,4R,5S-trihydroxypiperidine or (2S,3R,4R,5S)-3,4,5-trihydroxypipericolic acid (1/29), respectively, which became also known under the acronym BR1, is a mimic of glucuronic acid and was found to be a specific inhibitor of human liver β-D-glucuronidase and α-L-iduronidase by WINCHESTER et al. in the same year.\[55\]

![Figure 1.11](image)

**Figure 1.11.** Baphia racemosa (Fabaceae). The name Baphia is derived from the Greek word “βάφω” which means “dye”, referring to the red dye made from the heartwood of the tropical African species, and racemosa relates to the racemose flower arrangement.

![Figure 1.12](image)

**Figure 1.12.** Naturally occurring polyhydroxylated piperidine-2-carboxylic acids (polyhydroxypipelicolic acids).

Higher substituted homologues of nojirimycin in which the hydroxy group on the anomeric carbon is replaced by a hydroxymethyl group also occur naturally. α-Homonojirimycin (α-HNJ, 1/30) was isolated from the neotropical liana Omphalea diandra (Euphorbiaceae) (Figure 1.13) in 1988 by KITE et al. as a first example.\[56\] This C-1 hydroxymethyl-substituted NJ derivative was later also detected in adults, pupae, and eggs of the neotropical moth Urania fulgens (Uraniidae) whose larvae feed on O. diandra.\[57\] In 1997, ASANO and co-workers found that the aqueous ethanol extract of Aglaonema treubii (Araceae), a very common indoor foliage plant and native to the tropical rainforests of South-East Asia, potently inhibits α-glucosidase. The investigation of the constituents of this extract yielded
five novel hydroxymethylated NJ derivatives additionally to α-HNJ: β-homonojirimycin (β-HNJ, 1/34), α-homomannojirimycin (α-HMJ, 1/31), β-homomannojirimycin (β-HMJ, 1/35), α-homoallonojirimycin (α-HAJ, 1/32), and β-homoaltronojirimycin (β-HALJ, 1/36) (Figure 1.14).[58] The structure of α-HAJ was originally reported to be α-homogulonojirimycin (α-HGJ, 1/33) (= α-3,4-di-epi-homonojirimycin), but later revised by MARTIN et al. to be α-4-epi-homonojirimycin (= α-homoallonojirimycin, 1/32) on the basis of NMR analyses and synthetic studies.[59]
Further polyhydroxylated piperidine alkaloids with a hydrophobic alkyl substituent at the pseudo-anomeric position have been reported in 2000 by ASANO and co-workers. The α-HNJ homologues adenophorine (1/37), 1-deoxyadenophorine (1/38) and 5-deoxyadenophorine (1/39) (Figure 1.15) along with the two glycosides 1-O-β-D-glucopyranosyl-adenophorine (1/188) (Figure 1.80) and 1-O-β-D-glucopyranosyl-5-deoxyadenophorine (not shown) as well as α-1-C-ethylfagomine (1/22) and β-1-C-butyl-1-deoxygalactonojirimycin (1/44) were isolated from the mercantile Chinese crude drug “Sha-sheng” which consists of the roots of Adenophora spp. (Campanulaceae). A further investigation of the Adenophora triphylla var. japonica root extracts ten years later by KATO and co-workers resulted in the additional isolation of β-1-C-butenyl-1-deoxygalactonojirimycin (1/45) and 2,3-dideoxy-β-1-C-ethyl-1-deoxygalactonojirimycin (1/46) (Figure 1.18).

In 2002, ASANO and co-workers examined the extract constituents of the bulbs of the Siberian Squill, Scilla sibirica (Asparagaceae, Figure 1.17) after the GC-MS analysis of this extract had pointed to the existence of many different polyhydroxylated alkaloids. Among the numerous discovered iminosugars were also seven iminopyranoses including one glycoside. Besides the already known polyhydroxy-piperidines DNJ, DMJ and DALJ, two new iminopyranoses could be isolated and characterised as the 7-deoxyhomologues of α-HNJ and α-HMJ, consequently named α-7-deoxyhomonojirimycin (α-7-deoxy-HNJ, 1/41) and α-7-deoxyhomomannojirimycin (α-7-deoxy-HMJ, 1/42) (Figure 1.18). Furthermore, β-1-L-homofuconojirimycin (β-HFJ, 1/40), which had also been found a year before in the bark of the legume Angylocalyx pynaertii (Leguminosae), could be identified. The β-1-C-ethyl-derivative of DMJ (1/43) was discovered five years later by KATO et al. as one of the alkaloidal polyhydroxy-
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constituents of an extract obtained from the bulbs of *Scilla socialis* (Asparagaceae, Figure 1.62). Interestingly, a number of the above introduced iminopyranoses, such as $\beta$-HNJ, $\alpha$-HMJ, $\beta$-HMJ and $\beta$-HFJ, had been chemically synthesised prior to their discovery as natural products in search for novel therapeutic glycosidase inhibitors.$^{[63-66]}$

![Structural formulas of iminopyranoses](image)

**Figure 1.18.** Further 1-C-alkylated iminopyranoses.

The isolation and characterisation of three novel and unique 1-C-alkylated piperidine iminosugars, the batzellasides A, B and C (Figure 1.20), was reported in 2005 by CREWS *et al.*$^{[68]}$ As unusual as their structure also is their natural source. Whereas all to date known naturally occurring iminosugars were either isolated from plant or microbial sources, the batzellasides originate from a sponge of the *Batzella* genus (Demoacidonidae, Figure 1.19), collected off the west coast of Madagascar in 2000. They represent the first and only example of polyhydroxylated alkaloids being isolated from a marine animal organism. Then again, sponges are known to be hosts for various microbial life forms. Having that in mind and considering that several iminopyranoses have been isolated from bacterial sources, the batzellasides could also be produced by an undetected microbe living in the sponge.

![Image of Batzella genus sponge](image)

**Figure 1.19.$^{[67]}$** A sponge of the *Batzella* genus (Demoacidonidae), first example of an marine animal organism as source of polyhydroxylated alkaloids.
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Figure 1.20. General structure of the batzellasides.

The batzellasides can be considered as derivatives of 3,4-di-epi-fagomine (1/18) with a long alkyl side chain attached at the pseudoanomeric position of the piperidine ring. The initially unspecified absolute configuration of the C-2’ stereocentre was only recently determined through the separate total synthesis of both epimers of batzellaside B by YODA et al.[69] These three new piperidine alkaloids show antibacterial potency against Staphylococcus epidermidis with MIC values in the micromolar range, however, tests towards glycosidase inhibitory activity have not been published to date. Like the structurally related brossosartines (see Chapter 2, Figure 2.3), the batzellasides are also considered to be cyclic derivatives of sphingosine (2/29) or phytoshingosine (2/32), respectively, which relates them to a broad range of further natural products isolated from various sources including marine sponges like the penaresidin and jaspine alkaloids (see Chapter 2, Sections 2.6.2 and 2.6.3).

1.2.2 Polyhydroxylated Pyrrolidine Alkaloids – Iminofuranoses

The first naturally occurring iminofuranose to be discovered was the polyhydroxylated pyrrolidine DMDP (2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine, 1/51) which was isolated from the leaves of the legume Derris elliptica (Figure 1.21) by WELTER and co-workers in 1976.[71] Although its simple NMR spectra with three peaks in $^{13}$C NMR and four spin systems in $^1$H NMR suggested a simple symmetrical structure, initially considered meso-structures were ruled out after the discovery that the compound is optically active. The absolute configuration of DMDP was eventually determined by demonstrating that it had an identical optical rotation to $2R,5R$-dihydroxymethyl-3$R,4R$-dihydroxypyrrolidine obtained via enantiospecific synthesis by FLEET et al.[72] DMDP was first described as a mimic of β-D-fructofuranose (1/50),
although it has been demonstrated to be a good glucosidase inhibitor. The analogy of DMDP with β-D-fructofuranose (more correctly 2-deoxy-β-D-fructofuranose) has been cited frequently in the literature,[3-9] but given the relationship of α-homonojirimycin (1/30) as the homologue of nojirimycin (α-D-glucosimine, 1/4), DMDP might also be considered as the homologue of α-D-arabinosimine (1/53) (Figure 1.22).

The isolation of DMDP has been reported from many disparate species of plants and microorganisms since,[5, 6, 8] and often it co-occurs with DMJ, suggesting a common biosynthetic precursor for both compounds. In contrast, of the nine other possible DMDP diastereoisomers, only two have been found to also occur naturally (Figure 1.25). The C-3 epimer 2,5-dideoxy-2,5-imino-D-altritol (DALDP or DIA, 1/55) has been discovered only very recently in the root extracts of Adenophora triphylla var. japonica (Campanulaceae, Figure 1.16) in 2010 by KATO and co-workers.[74] Five years earlier ASANO et al.[51] had isolated 2,3-di-epi-DMDP, better known as 2,5-dideoxy-2,5-imino-D-glucitol (DGDP or DIDG, 1/54), from the methanolic extracts of three Thai medical plants: the roots of Stemona tuberosa (Stemonaceae, Figure 1.23), the wood of Albizia myriophylla (Leguminosae, Figure 1.81) and the leaves and twigs of Connarus ferrugineus (Combretaceae).
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On the other hand, the 6-deoxy derivative of DMDP (1,2,5-trideoxy-2,5-imino-D-mannitol, 1/57), has already been known since 1993. Having been isolated from the seeds of *Angylocalyx pynaertii* (Leguminosae, Figure 1.24) by MOLYNEUX and co-workers, this iminofuranose has shown weak β-mannosidase inhibitory activity.\(^{[76]}\) A further examination of the bark of *A. pynaertii* additionally yielded the 6-deoxy-DMDP dia-stereoisomers 1,2,5-trideoxy-2,5-imino-L-glucitol (1/58), 1,2,5-trideoxy-2,5-imino-D-altritol (1/59), and 1,2,5-trideoxy-2,5-imino-D-fucitol (1/60), all of which proved to be more or less effective α-L-fucosidase inhibitors (Figure 1.25).\(^{[35]}\)

![Figure 1.24](image)

*Angylocalyx* sp. (Leguminosae), growing in the Korup National Park, Cameroon. The bark of *A. pynaertii* is the original source of 6-deoxy-DMDP and its diastereoisomers 1/58, 1/59, and 1/60.

![Figure 1.25](image)

DMDP, its N-methyl homologue and stereoisomers DIA and DIDG as well as 6-deoxyimino furanoses.
The 1-deoxy derivative of D-arabinosimine, 1,4-dideoxy-1,4-imino-D-arabinitol (1/61), has been isolated in 1985, almost simultaneously, from both, the fruits of the legume Angylocalyx boutiqueanus (Leguminosae) by NASH et al.\cite{79} and the fronds of the fern Arachniodes standishii (Polypodiaceae, Figure 1.26) by HATANAKA and co-workers\cite{80}. The correct absolute configuration of this compound was subsequently determined by WILLIAMS et al.\cite{81}, and it has since been known under the acronym D-AB1 (Figure 1.28). D-AB1 was subsequently found in diverse range of plant species, occasionally accompanied by its 2-\(O\)- and 5-\(O\)-\(\beta\)-D-glucosides\cite{27, 36, 45} as well as its \(N\)-methyl and \(N\)-hydroxyethyl derivatives (1/65, 1/66).\cite{35, 36} Two diastereoisomers of D-AB1, 1-deoxy-D-ribosimine and 1-deoxy-D-xylosimine, also occur naturally (Figure 1.28). 1,4-Dideoxy-1,4-imino-D-ribitol (D-RB1, 1/62) has been isolated from the White Mulberry, Morus alba (Moraceae), in 1994\cite{45} and 1,4-dideoxy-1,4-imino-D-xylitol (1/63) from Angylocalyx pynaertii in 2001\cite{35}, both by ASANO and co-workers.

![Figure 1.26.](image1.png) The upside-down fern, Arachniodes standishii (Polypodiaceae), one of the natural sources of D-AB1.

![Figure 1.27.](image2.png) Leaves of the Chinese Mulberry, Morus bombycis (Moraceae), source of DNJ, \(N\)-methyl-DNJ, fagomine, nortropanoline, and D-AB1 and as well as DNJ and D-AB1 glucosides.

![Figure 1.28.](image3.png) 1-Deoxyiminofuranoses.
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The seeds of the Moreton Bay Chestnut a.k.a. Blackbean (Castanospermum australe), a legume native to Australia (Figure 1.42), are a rich source of various mono- and bicyclic iminosugars including 2-hydroxymethyl-3-hydroxypyrrolidine (2-deoxy-D-AB1, 1/68), which was discovered by WILLIAMS et al.[82] in 1985 and became known by the code CYB-3. Its N-hydroxyethyl derivative (1/67) was isolated six years later from the same source by MOLYNEUX and co-workers[83] together with several known polyhydroxylated pyrrolizidine and indolizidine alkaloids (e.g. australine and castanospermine, see Figures 1.44 and 1.55) and is regarded as a putative biosynthetic precursor for these compounds.

The improvement and progress in isolation methods and techniques of natural products in the past 15 years was accompanied by the discovery of numerous 1-C-alkylated analogues of D-AB1 and DMDP. In 1997, the first natural occurring DMDP homologue, 2,5-di-deoxy-2,5-D-glycero-D-manno-heptitol (homoDMDP, 1/69) was found in the leaves of the common bluebell, Hyacinthoides non-scripta (Asparagaceae, Figure 1.29) by NASH and co-workers.[86] Two years later, homo-DMDP, which can be regarded as a ring-contracted form of α-HNJ (1/30), was also discovered in the immature fruits and stalks of H. non-scripta by ASANO et al. accompanied by its 7-O-apiside (1/192) and 7-O-β-D-xylopyranoside (1/191).[87] Further DMDP homologues were discovered in a related Asparagaceae species: 2,5,6-Trideoxy-2,5-imino-D-manno-heptitol (6-deoxy-homo-DMDP, 1/70) and 2,5,6-trideoxy-2,5-imino-D-gulo-heptitol (1/71) were found in the bulb extract of the Common Hyacinth, Hyacinthus orientalis (Figure 1.30), along with the already described iminopyranoses DNJ, DMJ, α-HNJ, β-HNJ, α-HMJ, and β-HMJ.[38] Compound 1/70 was found to be a potent inhibitor of rice α-glucosidase and rat intestinal maltase, while 1/71 was observed to be a good inhibitor of α-L-fucosidase.[38] In a further exploration for glycosidase inhibitors in the Asparagaceae plant family ASANO et al.[88] also isolated two novel D-AB1
derivatives from the bulbs of the Peruvian lily, *Scilla peruviana* (Figure 1.31), bearing a 2-hydroxypropyl and a 1,2-dihydroxypropyl side arm at the pseudoanomeric C-1 position, respectively. However, α-1-C-(2-hydroxypropyl)-D-AB1 (1/75) and α-1-C-(1,2-dihydroxypropyl)-D-AB1 (1/76) have shown to be only moderate α- and β-glycosidase inhibitors.\[88]\n
Polyhydroxylated pyrrolidine alkaloids with longer alkyl substituents than homoDMDP are also known. Between 1997 and 2003 KUSANO and co-workers\[90]\ reported the isolation and characterisation of a large variety of D-AB1 and DIL derivatives with diverse C\(_{13}\) side chains at the pseudoanomeric C-1 position from the branches of the Japanese Paper Mulberry, *Broussonetia kazinoki* (Moraceae), consequently designated as broussonetines (see Chapter 2, Figure 2.3).\[91]\ Two further compounds of similar structure were later found in quite unrelated species: α-1-C-(1,5,7,12,13-pentahydroxytridecyl)-D-AB1 (1/79) was isolated by ASANO and co-workers\[88]\ in 2004 from the bulb extract of *Scilla peruviana* (Asparagaceae) whereas α-1-C-(1",2",11"-trihydroxyundec-4"-enyl)-DIL-2-O-α-D-glucoside (1/77) was found by KATO et al.\[92]\ in the hot water extract of *Adenophora triphylla* var. *japonica* (Campanulaceae) roots six years later. The same plant is also the source of another DMDP homologue with a shorter side chain; 6-C-butyl-DMDP (1/74) was first reported by ASANO and co-workers in 2000 and showed inhibitory activity toward almond β-glucosidase with an IC\(_{50}\) in the micromolar range (Figure 1.32).\[41]\ Interestingly, 6-C-butyl-DMDP and the iminopyranose β-1-C-butyl-1-deoxygalactonojirimycin (1/44, see Section 1.2.1, Figure 1.18), also found in *Adenophora* spp., possess the same carbon backbone. Hence, both alkaloids could be biosynthesised by the five- or six-membered ring closure of a common precursor.

\[89\] The Portuguese Squill, *Scilla peruviana* (Asparagaceae), also known as Cuban lily and Caribbean Jewel, is a evergreen perennial, native to Portugal and Spain.

Figure 1.31. The Portuguese Squill, *Scilla peruviana* (Asparagaceae), also known as Cuban lily and Caribbean Jewel, is a evergreen perennial, native to Portugal and Spain.

Figure 1.32. 1-C-alkylated polyhydroxylated pyrrolidine alkaloids.
An unusual group of polyhydroxy-pyrrolidines, in which an aryl moiety was found to be directly attached to the C-2 position of the pyrrolidine ring, was isolated from the Asian bellflower, *Codonopsis clematidea* (Campanulaceae, Figure 1.33), a herb used in folk medicine to improve hepatic function. Members of this group include *codonopsine* (1/80), *codonopsinine* (1/81) and *codonopsinol* (1/82) which were found to exhibit antibiotic and hypotensive activity without affecting the central nervous system. Codonopsine and codonopsinine were discovered by Russian researchers in 1969, who later on made incorrect stereostructural
assignments based on $^1$H NMR coupling constants. The correct stereochemistry of codonopsinine was established by KIBAYASHI et al. in 1986.\[^{[94]}\]

Furthermore, two structural related alkaloids were reported by KUSANO et al.\[^{[91, 96]}\] in 2001. Radicamines A (1/83) and B (1/84) were isolated from the plant Lobelia chinensis (Campanulaceae, Figure 1.35), a herb prescribed in traditional Chinese folk medicine as a diuretic, a haemostat, and a carcinostatic agent for stomach cancer. The radicamines were subsequently found to exhibit $\alpha$-glucosidase inhibitory activity. The structures and relative stereochemistry of both compounds were determined on the basis of extensive NMR studies, the absolute configurations, however, were wrongly assigned by comparing the specific rotations with that of natural codonopsinine (1/81) and its antipode. The total syntheses of the proposed structures and comparison of the optical rotations of the synthetic and the natural products eventually led to the revision of the absolute stereochemistry.
1.2.3 Polyhydroxylated Pyrroline Alkaloids

The alkaloid nectrisine (3,4-dihydroxy-5-hydroxymethyl-1-pyrroline, 1/85) was long time considered to be a unique member of the class of iminosugars. Until the isolation of broussonetines U (1/86) and U1 (1/87) in 2001, it was the only polyhydroxylated alkaloid that consisted of an unsaturated pyrroline ring as imino moiety. Nectrisine, a.k.a. FR-900483, was isolated as a new type of immunomodulator from the culture broth of the fungus Nectria lucida F-4490 (Ascomycetes) in 1988 by SHIBATA et al. [97]. This alkaloid was found to induce the expression of Ia antigen and to restore the immune response depressed by immunosuppressive factors of tumours. It also possesses potent $\alpha$-glucosidase- and $\alpha$-mannosidase inhibitory activities. [98] Nectrisine has also been reported to have antiviral activity. It has been shown to inhibit the Friend leukaemia retrovirus in vivo in mice and also potentiates the activity of the HIV drug AZT. [99]

![Figure 1.37. Polyhydroxylated pyrroline alkaloids.](image)

The only two other known polyhydroxylated pyrroline alkaloids to date are the broussonetines U (1/86) and U1 (1/87), members of the broussonetine alkaloids family. They were isolated in 2001 from branches of the Japanese Paper Mulberry, Broussonetia kazinoki (Moraceae, Figure 1.38), by KUSANO et al. [90a,b] and can be considered as derivatives of ent-nectrisine with a C$_{13}$ side chain at C-5. It is noteworthy that, in contrast to nectrisine and other pyrrolidine iminosugars, these two compounds are assumed to possess an all-($S$)-configuration of the ring stereocentres rather than the usual all-($R$) due to comparisons of the optical rotations with other broussonetines.

![Figure 1.38. The Japanese Paper Mulberry, Broussonetia kazinoki (Moraceae).](image)
1.2.4 Polyhydroxylated Indolizidine Alkaloids

There are three groups of bicyclic polyhydroxylated heterocycles, one with two five-membered rings (pyrrolizidine) and two with one five- and one six-membered ring (indolizidines and nortropanes) fused together. These bicyclic alkaloids have a less obvious structural relationship to monosaccharides but in each case the configuration of the hydroxyl substituents on the ring can be compared to those of sugars (Figure 1.41).

![Figure 1.39. General core structure of the indolizidine alkaloids.](image)

The first discovered bicyclic iminosugar was the trihydroxylated indolizidine alkaloid swainsonine (1/92), isolated from the legume *Swainsona canescens* (Fabaceae, Figure 1.40).\[103\] Shortly afterwards, seeds from a further Australian legume, *Castanospermum australe*, were found to contain another polyhydroxylated indolizidine, accordingly designated as castanospermine (1/88).\[104\] This indolizidine may be regarded as a bicyclic derivative of DNJ with an ethylene bridge between the hydroxymethyl group and the ring nitrogen (Figure 1.41).

![Figure 1.40. *Swainsona canescens* (Fabaceae), also known as Poison pea in Australia and Locoweed in North America. Consumption of *S. canescens* by livestock causes the disorder "pea struck" also known as "locoism".](image)

Two epimeric forms of castanospermine, the 6-epimer 1/94 and the 6,7-diepimer 1/95, co-occur with castanospermine in *C. australe*, together with the 7-deoxyderivative 1/96 of
Chapter 1. Polyhydroxylated Alkaloids

6-epi-castanospermine.[106, 107] 6-epi-Castanospermine (1/94) possesses the D-manno configuration in the piperidine ring but does not inhibit lysosomal (acidic) α-mannosidase, yet, it is a good inhibitor of the cytosolic (neutral) α-mannosidase.[108] 7-Deoxy-6-epi-castanospermine (1/96) and 6,7-di-epi-castanospermine (1/95), on the other hand, were found to be only weak inhibitors of fungal amylglucosidase. Furthermore, two deoxyderivatives of swainsonine, lentiginosine (1/90) and its epimer 2-epi-lentiginosine (1/91), have been isolated from the leaves of the freckled milkvetch, Astragalus lentiginosus (Fabaceae, Figure 1.93), a relative of Swainsona canescens.[109]

The latest addition to the polyhydroxylated indolizidines is the iminosugar steviamine (1/93) which was isolated in 2010 from leaf material of Stevia rebaudiana (Asteraceae, Figure 1.43) and leaves and bulbs of Veltheimia capensis (Asparagaceae) by NASH et al.[111] The structure of steviamine differs from the other polyhydroxylated indolizidines in an additional methyl group at C-5 and an additional hydroxymethyl group at C-3. Steviamine is a very specific inhibitor of α-N-acetylgalactosaminidase, an enzyme that is rarely assayed but has important functions in the body.[112]
1.2.5 Polyhydroxylated Pyrrolizidine Alkaloids

Polyhydroxylated pyrrolizidine alkaloids with a carbon branch at C-1 have been known since the 1930s when first members of this group were isolated from *Senecio* species (Asteraceae). These compounds are common constituents of a large number of plants, among them are medicinal herbs such as butterbur (*Petasites hybridus*, Asteraceae), coltsfoot (*Tussilago farfara*, Asteraceae) (Figure 1.45), and comfrey (*Symphytum officinale*, Boraginaceae). Many of these alkaloids act as a constitutive plant defence mechanism, and depending on the structure and substitution pattern of the pyrrolizidine ring system, several derivatives display hepatotoxic and carcinogenic properties. The toxicity is particularly high for those derivatives, which contain at least one ester moiety, usually at the C-1 hydroxymethyl group, and a double bond between C-1 and C-2. Prominent examples of pyrrolizidines with toxic properties are supinidine (1/109), heliotridine (1/110), retronecine (1/111), and their corresponding esters. The carcinogenic properties arise from hepatic metabolism of pyrrolizidines such as retronecine (1/111) to pyrrole derivatives which are strong alkylating agents and induce DNA cross-linking. On the other hand, pyrrolizidine alkaloids without the 1,2-double bond like platynecine (1/99), hastanecine (1/97), rosmarinecine (1/103) and isoretronecanol (not shown) do not display these toxicities.[114]

Platynecine (1/99), originally found in *Senecio platyphyllos* (Asteraceae) in 1935 by Orekhov et al. as one of the first necine bases,[116] is the pyrrolizidine moiety of several macrolactone alkaloids including platyphylline and neoplatyphilline. Its C-2 hydroxy homologue rosmarinecine (1/103) has been isolated from various plants in the *Senecio* genus (Asteraceae) including *S. hadiensis* (Figure 1.46) and *S. rosmarinifolius*. The rosmarinecine diastereomer croalbinecine (1/104) was isolated together with its macrocyclic diester derivative croalbidine (1/113) from the herbaceous plant *Crotalaria albida*. 
Figure 1.47. General structure of the necine bases. R = H or OH. All members of this group have the hydroxymethyl substituent at C-1 in common.

Figure 1.48. Examples of C-1 substituted pyrrolizidine alkaloids ("necine bases").

Figure 1.49. Examples of macrocyclic diesters incorporating a necine base.
(Fabaceae) in 1973 by SAWHNEY et al.\textsuperscript{[118]} Eight years later in 1981, the angelic acid ester of croalbinecine was found in the flowering plant Heliotropium ovalifolium (Boraginaceae) by MOHANRAJ et al. and consequently named heliofoline (1/108) after its natural source.\textsuperscript{[119]} The 1,2-unsaturated necine base crotaucine (1/112) was found conjugated to a variety of pyrrolizidine alkaloids in plants of the Crotalaria genus. Upon the re-examination of leaves and twigs gathered from C. agatiflora (Fabaceae) grown in Australia (Figure 1.50), six new alkaloids were isolated, all containing crotanecine as the necine base moiety. Retronecine (1/111), heliotridine (1/110) and supinidine (1/109) were detected in the seeds of Crotalaria spectabilis (Fabaceae).\textsuperscript{[120]} Hastanecine was discovered in 1945 along with its macrocyclic diester derivative hastacine as constituents of the aerial parts of Cacalia hastata (Asteraceae) by MENSHIKOV and co-workers.\textsuperscript{[121]} Seven years later MENSHIKOV et al. also found two further pyrrolizidine alkaloids in Tournefortia sibirica (Boraginaceae) extracts.\textsuperscript{[122]} These alkaloids were designated as turneforcine and turnefordicine (1/98) due to the misspelling of the generic name of the source plant in the original publication as “Turneforcia”, an error that was later transferred to the Chemical Abstracts database. Macronecine (1/102) and its C-1 angelic ester derivative macrophylline were isolated from extracts of Senecio macrophyllus (Asteraceae) by DANILLOVA et al.\textsuperscript{[123]} in 1955. The 7α-epimer of 1/102 and its corresponding C-1 angelic ester derivative were found more than 23 years later in 1978 by YAMADA et al.\textsuperscript{[124]} in extracts of the giant butterbur, Petasites japonicus (Asteraceae), and were accordingly named petasinine and petasinecine (1/101) after their natural source.

To the best of our knowledge the necine bases have not been assayed towards potential glycosidase inhibitory activity. However, in 2006 GOTI and co-workers reported the synthesis of the two unnatural rosmarinecine and crotanecine analogues 1/116 and 1/117 (Figure 1.51) which were tested for their inhibitory activities towards several commercially available glycosidase enzymes. Interestingly, whereas (6R)-hydroxy-7α-epi-rosmarinecine (1/116) showed no significant inhibition of the tested glycosidases, apart from a weak inhibition of α-mannosidase from jack beans, 7α-epi-crotanecine (1/117) was found to be a potent and selective inhibitor of α-mannosidases from jack beans and almonds with IC\textsubscript{50} values in the micromolar range.\textsuperscript{[125]}
Polyhydroxylated pyrrolizidines with a hydroxy-methyl substituent at the C-3 position on the other hand gained attention in medicinal chemistry because of their potential antiviral properties (Figure 1.54). The first two polyhydroxylated pyrrolizidines to be discovered, australine (1/120) and alexine (1/118) (Figure 1.55), were isolated at about the same time from *Castanospermum australe* (Figure 1.53) and *Alexa leiopetala*[^126] (Leguminosae), a member of a closely related genus. Australine can be regarded as a derivative of 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, 1.51) with an ethylene bridge between the hydroxymethyl group and the ring nitrogen. However, whereas DMDP is a potent inhibitor of mammalian digestive β-glucosidase and β-galactosidase with IC\(_{50}\) values in the micromolar range, australine does not inhibit these glycosidases, but is instead a good inhibitor of amyloglucosidase (IC\(_{50}\) = 5.8 µM).

Co-occurring with australine in *C. australe* are its C-1 and C-3 epimers, 1/212 and 1/122.[^128,^129] The C-7 epimer 1/125, however, originally identified as a natural product from *C. australe*, was in fact incorrectly described in the original paper as identification was based on a comparison with erroneous NMR data published for australine. Therefore, 7-epi-australine can no longer be regarded as a natural product. Reinvestigation of the natural occurrence of 7-epi-australine in *C. australe* led to the isolation of two new australine epimers, 2,3-di-epi-australine (1/123) and 2,3,7-tri-epi-australine (1/124) (Figure 1.55) as well as the 2-O-β-D-glucopyranoside of 1-epi-australine (1/196, Figure 1.87).[^130]
Since australine and alexine are epimeric to one another at the bridgehead position, it has been assumed to be likely that a similar series of alexine epimers might also exist along with alexine in *Alexa* species. However, it was only very recently in 2010, that NASH *et al.* reported the isolation and characterisation of 1-epi-alexine from the stems and leaves of *C. australale*, the only detected naturally occurring epimer of alexine to date.\[^{[131]}\]

The isolation of a pyrrolizidine-3-carboxylic acid from the leaves of *Alexa grandiflora* was reported by DE S. PEREIRA *et al.* in 1991.\[^{[132]}\] This compound, designated as 7α-epi-alexaflorine (1/126) (perhaps better named australiflorine), is the first example of a naturally occurring α-amino acid with a pyrrolizidine core. The absolute and relative configurations of 1/126 could be established by single crystal X-ray crystallographic analysis. When assayed regarding its glycosidase inhibitory activity, 7α-epi-alexaflorine was found to be a much weaker inhibitor against a wide range of enzymes than many other polyhydroxylated pyrrolizidines with IC\(_{50}\) values only in the millimolar range.\[^{[132]}\]
The first pentahydroxylated pyrrolizidine was isolated by NASH and co-workers from the bark of the evergreen tree *Casuarina equisetifolia* (Casuarinaceae, Figure 1.56) in 1994.\(^{[135]}\) Accordingly named casuarine (1/127), it was also found two years later together with its 6-O-α-D-glucopyranoside (1/197) in the leaf extracts of *Eugenia jambolana* (Myrtaceae), which is a well-known tree in India for the therapeutic value of its seeds, leaves, and fruits against diabetes and bacterial infections.\(^{[136]}\) Glycosidase inhibition studies performed by FLEET *et al.* identified casuarine as a very specific inhibitor of α-glucosidases from various sources including yeast, rice and *Bacillus* bacteria.\(^{[137]}\) In 2000, casuarine was again detected, this time together with its C-6 epimer 1/129 in the leaves of the related species *Eugenia uniflora* (Myrtaceae, Figure 1.57) by ARISAWA *et al.*\(^{[138]}\) However, due to incorrect structure elucidation these two compounds were originally described as indolizidine alkaloids named uniflorine A and B. The unambiguous synthesis of the proposed structure for uniflorine A and extensive NMR comparison studies in our group on the natural product with the NMR data reported for casuarine led to the conclusion that uniflorine B in fact is casuarine and uniflorine A its C-6 epimer (Figure 1.58). This hypothesis was finally confirmed by the enantioselective synthesis of 6-epi-casuarine in our group. The only other naturally occurring epimer of casuarine is its C-3 epimer 1/128 that was isolated by FLEET *et al.* from the shrub *Myrtus communis* (Myrtaceae) in 2006.\(^{[137]}\)
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Until the isolation of casuarine, polyhydroxylated pyrrolizidines with a hydroxymethyl substituent at C-3 have been believed to be of very restricted natural occurrence. The alexines and australines have only been found in two small genera of the Leguminosae (Castanospermum and Alexa). However, this estimation drastically changed, when a large number of novel pyrrolizidine alkaloids were isolated from members of the entirely unrelated Asparagaceae plant family. The hyacinthacines, designated after the today obsolete name Hyacinthaceae for the Scilloideae subfamily within the Asparagaceae, are divided into three groups regarding the number of hydroxy groups at the B-ring: The A series carries none, the B series one and the C series two additional hydroxy groups. The first hyacinthacines to be reported were B1 (1/137) and B2 (1/138) from the immature fruits and stalks of the English Bluebell, Hyacinthoides non-scripta, and hyacinthacine C1 (Figure 1.64) from the bulbs of the Spanish Bluebell, Scilla campanulata (Figure 1.60), by ASANO and co-workers in 1999. Shortly after, the same research group isolated four further hyacinthacines, A1 (1/130), A2 (1/131), A3 (1/132) and B3 (1/139), together with the already known hyacinthacine C1 from the bulbs of the closely related Grape Hyacinth, Muscari armeniacum (Figure 1.59).

During their investigations into the biologically active constituents of extracts obtained from the branches of the Japanese Paper Mulberry, Broussonetia kazinoki (Moraceae), KUSANO et al. isolated a new pyrrolizidine alkaloid which exhibits inhibitory activities against several β-glycosidases in the micro- to nanomolar range. It was designated as broussonetine N (1/153) and represents the first pyrrolizidine found in the Moraceae plant family (Figure 1.61).

* Recent work on the phylogeny of plant families by the Angiosperm Phylogeny Group (APG) has led to some significant revisions of family boundaries, with a number of genera being moved from one family to another, and some families being assimilated within other families. Thus, according to the amended APG III system of 2009 the formerly discrete Hyacinthaceae family, which includes the genera Scilla, Hyacinthus and Muscari, is now part of the Asparagaceae as a new subfamily under the revised name “Scilloideae”.

[Figure 1.59. Muscari armeniacum (Asparagaceae), generally known as Grape Hyacinth, is an herbaceous plant of the Scilloideae subfamily. The bulb of M. armeniacum is the source of numerous polyhydroxylated alkaloids including hyacinthacines A1, A2, A3, B3 and C1.]

[Figure 1.60. The Spanish bluebell Scilla campanulata syn. Scilla hispanica syn. Hyacinthoides hispanica (Asparagaceae).]
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Figure 1.61. The hyacinthacines.
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![Images of chemical structures]

**α-5-C-(3-Hydroxybutyl)-hyacinthacine A2 (1/152)**

**Broussonetine N (α-5-C-(1,10-Dihydroxy-6-oxodecyl)hyacinthacine A2) (1/153)**

**Figure 1.61 cont’d. The hyacinthacines.**

Broussonetine N can be regarded as derivative of hyacinthacine A2 with a C₁₀ side chain at the C-5 position.

One of the best established approaches to find novel natural products in plants is to examine close taxonomic relatives. With this premise in mind, ASANO and co-workers continued to investigate the constituents of further species in the *Scilla* genus. This approach was facilitated by the fact that many species of the *Muscari* and *Scilla* genera are commercially available garden plants, hence, plant material was easy to obtain in large quantities. Their investigations eventually resulted in the discovery of 17 novel polyhydroxypyrrolizidines from the bulbs of the Siberian Squill, *Scilla sibirica*[^39] (Figure 1.17) (hyacinthacines A4 (1/133), A5 (1/134), A6 (1/135), A7 (1/136), B3 (1/139), B4 (1/140), B5 (1/141), B6 (1/142)) and the Silver Squill, *Scilla socialis*[^62] (Figure 1.62) (hyacinthacines B7 (1/143), C2 (1/144), C3 (1/145), C4 (1/146), C5 (1/147) and C-5 hydroxybutyl-substituted A2 (1/152)), as well as C-5 hydroxy-alkylated derivatives of 7-**epi**-australine (1/148) and hyacinthacine A1 (1/149, 1/150 and 1/151) from the bulbs of the Portuguese Squill, *Scilla peruviana*[^88] (Figure 1.31). In total, 24 new polyhydroxylated pyrrolizidine alkaloids were discovered between 1999 and 2007 along with known and novel iminofuranoses and iminopyranoses (see Sections 1.2.1 and 1.2.2).

It should be noted that all proposed structures of the hyacinthacines as shown in Figure 1.61 were determined by ASANO and co-workers on the basis of 2D NMR experiments (*H-H-COSY, HMQC, HMBC*), NOE correlations and interpretation of the **J_3_1H** coupling patterns and constants, but not single-crystal X-ray analysis. As a consequence, three of the purported structures were recently confirmed to be wrong by total synthesis (highlighted in red in...
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Figure 1.61). The spectroscopic data sets of synthetic hyacinthacine C3 (1/145), synthesised by YODA et al. in 2009[144], synthetic hyacinthacine B7 (1/143), synthesised in 2010 by Christopher AU in our research group[145] (see Chapter 4, Section 4.2.6) and synthetic hyacinthacine C5 (1/147), synthesised by YU and co-workers in 2011[146], did not match the reported sets of the natural products, evidently proving that the assigned structures for these three alkaloids are incorrect. Verified by total synthesis, however, are to date the structures of hyacinthacines A1, A2, A3, A6, A7, B1, B2, B3, and C2.

How challenging it can be to determine the correct structure of a compound just on the basis of NMR data can be seen by the example of hyacinthacines C1 and C4. ASANO and co-workers assigned both alkaloids with the same structure as shown in Figure 1.63 although their $^1$H and $^{13}$C NMR data as well as their optical rotation clearly indicate that both compounds are not identical.

A comparison of the NOE interactions shows that both compounds share the same NOE correlations with the exception of an additional NOE between H-1 and H-7a for hyacinthacine C4 (highlighted in red in Figure 1.63). The lack of this NOE link in hyacinthacine C1 led to the proposal that C1 might in fact be 1-epi-hyacinthacine C4 (Figure 1.64). Nevertheless, a confirmation of this hypothesis by total synthesis has to be done yet.

Figure 1.63. NOE interactions detected for hyacinthacines C1 and C4.

Figure 1.64. Proposed structure of hyacinthacine C1 as 1-epi-hyacinthacine C4.
1.2.6 Polyhydroxylated Nortropane Alkaloids

Tropane alkaloids are a well-established group of natural products with valuable pharmacological properties which have been frequently and comprehensively reviewed.[147, 148, 149] Scopolamine and related tropane alkaloids (see Appendix 1, Figure A1.3) occur mainly in the Solanaceae plant family and bear a methyl substituent on the nitrogen atom. In contrast, nortropane alkaloids (i.e. those lacking the N-methyl group) have been rarely isolated, although they occur occasionally as minor constituents in plants containing tropane alkaloids.

In the late 1980s a French research group, interested in the identification of metabolites produced by plant roots that might act as nutritional mediators of specific plant-bacterium relationships, discovered the first nortropane-type polyhydroxylated alkaloids as constituents of the roots and root exudates of the hedge bindweed, *Calystegia sepium* (Convolvulaceae), a twining vine common in temperate zones of the world.[151] Designated after their natural source as calystegines, they represent a unique subgroup of the tropane alkaloids. The nomenclature used for the calystegines is derived from their chromatographic behaviour during the original isolation from *C. sepium*. The tri- and tetrahydroxy calystegines were initially separated as two spots, A and B, after paper electrophoresis, and each of these was then resolved into their isomeric components by liquid chromatography to give calystegines A₁, A₂, A₃, A₄, B₁ and B₂. Of these, only the structures of calystegines A₃ (1/156), B₁ (1/161) and B₂ (1/162) have been elucidated.[152]

![Figure 1.65](image) The Hedge Bindweed, *Calystegia sepium* (Convolvulaceae), also known as Larger Bindweed, Rutland Beauty, Bugle Vine, and Heavenly Trumpets.

![Figure 1.66](image) General structure of the 1-hydroxynortropane alkaloids (calystegines).

Their late discovery, almost 160 years after that of the first tropane alkaloid atropine (see Appendix 1, Figure A1.3) in 1833, is due to at least two reasons. In contrast to the classical tropane alkaloids (i) the calystegines occur in very low concentrations and (ii) they cannot
be isolated by the classical procedures used for the usually lipophilic traditional alkaloids (e.g. extraction of the free bases by means of lipophilic organic solvents) due to their highly polar properties. Thus, they have been overlooked for such a long time.

The calystegines detected in this first study have also been found in another convolvulaceous species, the Field Bindweed, *Convolvulus arvensis*, a common trailing and twinning herb of the temperate zones, as well as in the notorious solanaceous perennial herb *Atropa belladonna*, (deadly nightshade a.k.a. poison black cherry), native to European deciduous woods. To date, the structures of in total 15 calystegines have been elucidated including five trihydroxynortropanes (A3, A5 – A8), six tetrahydroxy congeners (B1 – B6), and two pentahydroxy derivatives (C1, C2). With the exception of A3 (1/156), B1 (1/161), B2 (1/162) (*Calystegia sepium*, Figure 1.65) and C1 (1/167) (*Morus alba*, Moraceae), they have been discovered in solanaceous species: A5 (1/157) and B3 (1/163) in *Physalis alkekengi*[^154] (Figure 1.67), A6 (1/158) and A8 (1/160) in *Hyoscyamus niger*[^6, 155] (Figure 1.72), A7 (1/159) and B5 (1/165) in *Lycium chinense*[^50] (Figure 1.71), B4 (1/164) and B6 (1/166) in *Scopolia japonica*[^16, 156] (Figure 1.70). Besides free calystegines, several glycosides have been isolated and characterised, e.g. the 3-O-β-D-glucopyranoside of B1 (1/194) from *Nicandra physalodes*[^157] (Figure 1.83) as well as the 4-O-α-D-galactopyranoside of B2 (1/195) from *Morus alba* (fruits)[^158], *Atropa belladonna* (Figure 1.68) and *Solanum tuberosum*[^159] (Figure 1.69), respectively (see Section 1.2.7, Figure 1.84).

[^154]: Physalis alkekengi (Solanaceae) a.k.a. Bladder cherry, Chinese lantern, Japanese lantern, or Winter cherry. Easily identifiable by the large, bright orange to red papery covering over its fruit, which resemble Chinese lanterns. It is native from southern Europe east across southern Asia to Japan.

[^155]: Hyoscyamus niger

[^156]: Scopolia japonica

[^157]: Nicandra physalodes

[^158]: Morus alba

[^159]: Solanum tuberosum
A survey on the occurrence of polyhydroxylated nortropane alkaloids in plants of the Solanaceae and Convolvulaceae revealed that the calystegines are widely distributed in these families. The presence of calystegines in the Solanaceae is documented for 12 genera, *Atropa*, *Brunfelsia*, *Datura*[^163^], *Duboisia*[^164^], *Hyoscyamus*, *Lycium*, *Mandragora*, *Nicandra*, *Physalis*, *Scopolia*, *Solanum*[^165^], and *Withania*[^166^]. The calystegines appear to be further widely distributed in the Convolvulaceae family. EICH and co-workers[^167^] reported their occurrence in 30 species belonging to 15 genera of the Convolvulaceae by GC-MS analysis.

Calystegines have originally been differentiated from other tropane alkaloids by the lack of the N-methyl group and the presence of a hydroxy group at the bicyclic ring bridgehead. However, more recently, it was discovered that the Chinese Wolfberry, *Lycium chinense* (Solanaceae, Figure 1.71), also produces N-methylated calystegines B2 (1/170) and C1 (1/171), which are the first tropane-type alkaloids of the calystegine family.[^50^] Like the hydroxy group on the anomeric carbon of nojirimycin (1/4), the bridgehead hydroxy group of the calystegines derives from the cyclisation of a tautomeric form which for the calystegines is an appropriately hydroxylated 4-amino-cycloheptanone. The corresponding alcohol of the monocyclic tautomer of calystegine A5, 1-amino-2,3,5-trihydroxycycloheptane (1/154), has been isolated from the Bladder Cherry, *Physalis alkekengi* (Solanaceae), and is assumed to be a precursor or degradative product.[^3^]

![Scheme 1.1. The proposed biosynthetic or degradative pathway of calystegine A5.[^3^]](image-url)
An exceptional position is taken by calystegine N$_1$ (1/169), a nortropane in which the bridgehead hydroxy group is replaced by an amino group thus forming an amino analogue of calystegine B$_2$ (1/162). This compound has been discovered as a constituent of *Hyoscyamus niger* (Solanaceae) in 1996 (Figure 1.72). However, there are doubts if it is really a natural product. It may be just an artefact formed from calystegine B$_2$ during the isolation procedure using aqueous ammonia solution. In any case, calystegine N$_1$ is not very stable; it has been converted in part to calystegine B$_2$ even on storage at 4 °C.\cite{155}

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**Figure 1.72.** *Hyoscyamus niger,* also known as Stinking Nightshade or Black Henbane, is a plant of the family Solanaceae that originated in Eurasia, though it is now globally distributed.

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Trihydroxy-substituted calystegines are summarised in the A series, tetrahydroxy-substituted in the B series and pentahydroxy-substituted in the C series. Calystegine B$_2$ is also known under the name nortropanoline.
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Since their discovery in the late 1980s the calystegines remained the only group of polyhydroxylated nortropanes for more than a decade. This changed with the isolation and characterisation of novel ψ-nortropine derivatives by KUSANO et al., reported in 2002.[171] Their investigation of the constituents of the ripened fruits of the White Mulberry, *Morus alba* (Moraceae, Figure 1.74), afforded five new polyhydroxylated nortropane alkaloids 1/173 – 1/177 along with 3β-nortropanol (ψ-nortropine, 1/172) (Figure 1.76) and six new ω-amino acids, the morusimic acids A – F (2/80 – 2/85, Chapter 2, Figure 2.31). These unusual nortropanes all have a hydroxy group at C-3 in common but lack the bridgehead hydroxy group at C-1 wherefore they can be considered as 1-deoxy derivatives of the calystegines (Figure 1.75). An α-glucosidase inhibition assay performed by KUSANO and co-workers identified the 3β-nortropanols 1/175, 1/176 and 1/177 as weak inhibitors with IC₅₀ values comparable to fagomine (1/7) whereas compounds 1/172, 1/173 and 1/174 showed no inhibition towards the tested enzyme.[171]

![Figure 1.75. General Structure of the 3β-hydroxynortropane (ψ-nortropine) alkaloids.](image)

![Figure 1.76. 3β-Nortropanol and its derivatives, isolated from the ripened fruits of *Morus alba* (Moraceae).](image)
1.2.7 Glycosides

To date glycosides are known for five of the six iminosugar classes, the exception being the pyrrolines, but by far the most numerous are glycosides of the piperidines. There was a relatively early report about the isolation of the 4-O-β-D-glucoside of fagomine (1/185) from the African legume *Xanthocercis zambesiaca* (Leguminosae) by FLEET *et al.* in 1985 (Figure 1.77). However, other glycosides remained elusive until known iminosugar-producing plants were re-examined using improved isolation techniques.

![Figure 1.77](image-url) The African legume *Xanthocercis zambesiaca* (Leguminosae) growing in Botswana, commonly known as Nyala tree.

![Figure 1.78](image-url) Selected examples of glycopyranosyliminopyranoses.

**Figure 1.78.** Selected examples of glycopyranosyliminopyranoses.
In 1988, α-homonojirimycin (\(1/30\)) was isolated from the leaves of the Jamaican navel spurge, *Omphalea diandra* (Euphorbiaceae, Figure 1.13) as the first naturally occurring 1-C-alkylated DNJ derivative (see Section 1.2.1, Figure 1.14).\(^{[56]}\) Interestingly, prior to the isolation of α-HNJ, its 7-O-β-D-glucopyranoside (\(1/187\)) had been designed as a potential drug for the treatment of diabetes mellitus by RHINEHART et al. in 1987 and became known under the code name MDL 25637 (Figure 1.80).\(^{[174]}\) Ten years later, it was eventually found as a natural product from whole plants of *Aglaonema treubii* (Araceae, Figure 1.79) by ASANO et al.\(^{[58]}\) and has since been isolated from many diverse plant sources such as the bulbs of the common garden hyacinth, *Hyacinthus orientalis* (Asparagaceae, Figure 1.30), and the aerial parts of the Asiatic dayflower, *Commelina communis* (Commelinaeae). The 1-deoxyderivative of MDL 25637, 1-O-β-D-glucopyranosyl-adenophorine (\(1/188\), Figure 1.80), also occurs naturally as constituent of the Chinese crude drug “Sha-sheng” which consists of *Adenophora* radix (Campanulaceae).

The Thai traditional crude drug “Cha em thai”, obtained from the pantropical tree *Albizia myriophylla* (Leguminosae, Figure 1.81), is used as remedy for cough and sore throats and as a substitute for liquorice owing its sweet taste. Besides several triterpene saponins the wood of this plant was found to have high contents of DMJ and DMDP including several of their glucopyranoside derivatives. The ion-exchange
resin chromatography of the aqueous MeOH extract led to the isolation of DMJ (1/9), DMDP (1/51) and DIDG (1/54) as well as 2-O-β-D-glucopyranosyl-DMJ (1/181), 4-O-β-D-glucopyranosyl-DMJ (1/182), and 3-O-β-D-glucopyranosyl-DMDP (1/189). The isolation of 1/189 from this plant is the first report of a glycoside of DMDP.\[51\]

![Chemical structures](image1)

Various glycosides of polyhydroxylated nortropane alkaloids have also been discovered and characterised such as the 3-O-β-D-glucopyranoside of calystegine B1 (1/194), isolated from the fruits of *Nicandra physalodes* (Solanaceae, Figure 1.83) by NASH and co-workers\[157\] in 1996, as well as the 4-O-α-D-galactopyranoside of calystegine B2 (1/195), isolated from the fruits of *Morus alba* (Moraceae) in 2001 by ASANO et al.\[158\], respectively (Figure 1.84). It should be noted that 3-O-β-D-glucopyranosylcalystegine B1 potently inhibits rice α-glucosidase, a remarkable finding since its aglycon calystegine B1 is not an inhibitor of α-glucosidase but a potent inhibitor of β-glucosidases.\[177\]
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3-\(\beta\)-d-glucopyranosylcalystegine B1

4-\(\alpha\)-d-galactopyranosylcalystegine B2

Figure 1.84. Representative examples of calystegine glycosides.

To date the natural occurrence of only two polyhydroxypyrrolizidine glycosides and one polyhydroxyindolizidine glycoside has been reported. The 2-\(\beta\)-d-glucopyranoside of 1-\(\alpha\)-australine (1/196) and 8-\(\beta\)-d-glucopyranoside of castanospermine (1/198) were isolated in 2003 by ASANO et al. from the seeds of the Moreton Bay chestnut, Castanospermum australe (Leguminosae, Figure 1.85), accompanied by various other polyhydroxylated piperidines, pyrrolizidines and indolizidines.\[130\] Glycosidase inhibitory activity assays by ASANO and co-workers proved 2-\(\beta\)-glucopyranosyl-1-\(\alpha\)-australine (1/196) to be an excellent \(\alpha\)-glucosidase inhibitor with IC\(_{50}\) values in the low micromolar range. 8-\(\beta\)-glucopyranosylcastanospermine (1/198) had not been assayed.

The 6-\(\alpha\)-d-glucopyranoside of casuarine (1/197) had already been obtained in 1996 by WORMALD et al. together with its aglycon casuarine from the bark of the horsetail she-oak, Casuarina equisetifolia (Casuarinaceae), and the leaves of the Jambolan plum, Eugenia jambolana (Myrtaceae, Figure 1.86).\[136\] The most noteworthy biological activity of 6-\(\alpha\)-d-glucopyranosylcasuarine is its potent inhibition of porcine kidney trehalase. All powerful trehalase inhibitors reported to date are pseudodisaccharides, such as MDL 25637 (7-\(\beta\)-d-glucopyranosyl-\(\alpha\)-homonojirimycin (1/187)), 6-\(\alpha\)-d-glucopyranosylcasuarine (1/197), salbostatin (1/209) trehazolin (1/210), and validoxylamine A (the aglycon
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of validamycin (1/216)), with \( K_i \) values in the nanomolar range. The extremely high affinity of these pseudodisaccharide inhibitors to trehalase derives from the synergistic interactions of the alkaloid subunit with the subsite for catalysis and the sugar (or cyclitol) unit with the subsite for recognition on the active centre of the enzyme.\(^{[180]}\) Trehalose is a blood sugar in insects and a major storage sugar in fungi and yeast. Trehalase inhibitors are therefore expected to have potential as insecticides and fungicides.

![Figure 1.87](image)

**Figure 1.87.** Naturally occurring glycosides of polyhydroxylated pyrrolizidine and indolizidine alkaloids.

### 1.2.8 Miscellaneous

#### 1.2.8.1 Bulgecinine

\((-\)-Bulgecinine (1/199) is the amino acid constituent of the naturally occurring bulgecin glycopeptides. The bulgecins A (1/201), B (1/202) and C (1/203) are potent \( \beta \)-lactam synergists isolated from the culture broth of the *Pseudomonas* species *P. acidophila* and *P. mesoacidophila* in 1985 by SHINAGAWA *et al.*\(^{[181, 182]}\) \[(Figure 1.88).\] Although devoid of antibacterial activity themselves the bulgecins induce characteristic morphological changes called bulge formation in the cell wall of Gram-negative bacteria in association with \( \beta \)-lactam antibiotics such as sulfazecin and isosulfazecin, which are also produced by *P. acidophila* and *P. mesoacidophila*, respectively. As a result of bulge formation, the activity of these antibiotics is effectively enhanced, and the bacteria are killed at lower \( \beta \)-lactam concentrations.\(^{[183]}\) The structure of
(-)-bulgecinine has been determined unequivocally by spectroscopic and crystallographic studies to be (2S,4S,5R)-4-hydroxy-5-hydroxymethylproline (1/199).

Glycosidase inhibitory studies of bulgecinine have not reported to date, however, in 2010 FLEET et al. compared the glycosidase and glycogen phosphorylase inhibition profiles of DMDP with the synthetic derivative 3-hydroxybulgecinine (1/200) and found that this compound shows weak inhibition of some α-glucosidases and glycogen phosphorylase but no inhibition of any other enzyme. The introduction of a carboxyl group to DMDP (giving 3-hydroxybulgecinine) reduced the potency of the parent iminosugar significantly to the millimolar IC$_{50}$ range.

Figure 1.88. The bulgecins.

1.2.8.2 Gualamycin

In the group of polyhydroxylated pyrrolidines the microbial secondary metabolite gualamycin (1/204) is an exotic and unique congener concerning its complex structure. Gualamycin was isolated by a Japanese research group in 1995 from the culture broth of *Streptomyces* sp. NK11687 and was shown to exhibit acaricidal activity (i.e. possessing a lethal effect on mites). It can be regarded as a DMDP derivative with a highly functionalised extended side chain at the pseudomeric position, yet, glycosidase-inhibitory activity tests with this compound have not been described to date.
1.2.8.3 Kifunensine

Kifunensine, a.k.a. FR 900494 (1/205), was isolated in 1987 from the actinomycete strain Kitasatospora kifunense 9482 by I MANAKA and co-workers.\cite{188} It can be regarded as a cyclic oxamide derivative of 1-amino-1-deoxymannojirimycin. Its unique structure and absolute configuration was determined two years later by HASHIMOTO et al. on the basis of chemical derivatisation, various NMR experiments and X-ray crystallographic analysis.\cite{189, 190} Kifunensine proved to be an effective Jack bean α-mannosidase I inhibitor but does not show any activity against plant α-mannosidase II.\cite{191} Furthermore, it possesses a promising immunomodulatory activity as well as inhibitory activity against the processing of viral influenza glucoproteins in kidney cells.

1.2.8.4 Mannostatin A

In 1989 AOYAGI and co-workers reported the isolation of an unusual pentasubstituted cyclopentane from the culture filtrate of the soil microorganism Streptoverticillium verticillus var. quintum ME3-AG3. This compound proved to be a strong inhibitor of rat epididymal α-mannosidase and was consequently named mannostatin A (1/206) due to its potent inhibitory effect.\cite{192} A corresponding sulfoxide of mannostatin A was also isolated and designated as mannostatin B. The structure and relative stereochemistry of 1/206 were first deduced by NMR and mass spectrometry, the absolute stereochemistry was later confirmed by X-ray diffraction.\cite{193} Although its structure with an exocyclic amino group does not qualify mannostatin A as an iminosugar per se, it blocked Golgi processing mannosidase II more effectively when compared to swainsonine (1/92) with an IC$_{50}$ of 10–15 nM. Furthermore, mannostatin A competitively inhibited jack bean, mung bean, and rat liver lysosomal α-mannosidases with IC$_{50}$ values of 70, 450, and 160 nM, respectively.\cite{194} This potent activity is intriguing since mannostatin A bears little resemblance either to D-mannose or to a manno-pyranosyl cation, the purported intermediate in polysaccharide hydrolysis.\cite{195} It is even more fascinating to note that the enantiomer of 1/206, which more closely resembles the...
putative transition state structure for manno pyranoside hydrolysis, does not exhibit any mannosidase inhibitory activity at all.\textsuperscript{[196,197]}

1.2.8.5 Pochonicine

A unique polyhydroxylated pyrrolizidine alkaloid designated as pochonicine (1/207) was isolated from a solid fermentation culture of the fungal strain \textit{Pochonia suchlasporia} var. \textit{suchlasporia} TAMA 87 in 2009 by Nitoda and co-workers.\textsuperscript{[198]} Its relative structure was determined via NMR and MS techniques to be the 7-hydroxyhyacinthacine B\textit{i} derivative (or its enantiomer) shown above in which the hydroxymethyl functionality at C-3 has been replaced by an acetamidomethyl group. Pochonicine exhibits potent inhibition against $\beta$-$N$-acetylglucosaminidases (GlcNAcases) of various organisms including insects, fungi, mammals, and a plant (Jack bean) but no inhibition against $\alpha$- and $\beta$-glucosidases. The GlcNAcase inhibitory activity of pochonicine is comparable to that of nagstatin (1/223), a further strong GlcNAcase inhibitor of natural origin (see Section 1.5.3, Figure 1.98). To date, the distribution of polyhydroxylated pyrrolizidine alkaloids including the australines and hyacinthacines has been restricted to plants; pochonicine therefore represents the first example of such a compound from a fungal source.\textsuperscript{[198]}

1.2.8.6 Siastatin B

Sialidases (neuraminidases, $N$-acytelyneuraminate glycohydrolases) are enzymes that cleave $N$-acyetyl-neuraminic acid from the non-reducing ends of glycoconjugates and thereby mediate a variety of biological functions such as immune response, oncogenesis, metastasis of tumours, sperm penetration and viral infection. Siastatin B (1/208) is a broad spectrum sialidase inhibitor, isolated from a culture filtrate of the microorganism \textit{Streptomyces verticillus} var. \textit{quintum} MB695-A4 and characterised as an unusual $6$-acetamido-$3$-piperidinecarboxylate by Umekawa and co-workers in 1974.\textsuperscript{[199]} The charge distribution in the siastatin B zwitterion resembles that in the $N$-acytelyneuraminate oxocarbenium ion, the putative intermediate in the enzyme-catalysed reaction (Figure 1.89). This may account for its effectiveness in binding sialidases.\textsuperscript{[200]}
1.2.8.7 Salbostatin

Salbostatin (1/209) is a basic, non-reducing pseudodisaccharide which consists of the unsaturated amino-cyclitol valienamine (1/218) linked to 2-amino-1,5-anhydro-2-deoxyglucitol. It was isolated in 1994 from the fermentation culture of *Streptomyces albus* ATCC 21838 (Figure 1.90) by VÉRTESY et al.\(^{[202]}\). Despite having a similar chemical structure as acarviosine (1/213) and other pseudodisaccharides, salbostatin does not inhibit the enzymes saccharase and maltase from porcine small intestine, and only weakly inhibits murine liver aldose reductase. Salbostatin also shows no antibiotic activity, however, it does effectively inhibit porcine kidney trehalase with a \(K_i\) of \(1.8 \times 10^{-7}\) M.\(^{[202]}\)
1.2.8.8 Trehazolin

The pseudodisaccharide trehazolin (1/210) was isolated from the culture broth of the bacteria *Micromonospora* strain SANK 62390 in 1991 by ANDO *et al.*\(^{[203]}\). It was found to be a strong and specific inhibitor of trehalase, the enzyme that specifically hydrolyses \(\alpha,\alpha\)-trehalose to two glucose units. As such, trehazolin has a potential application as insecticide since trehalose is the principal blood sugar found in insects and is used to support various energy-requiring functions.

The structure of trehazolin was deduced from degradation experiments as well as \(^1\)H NMR studies and was eventually confirmed via total synthesis by SHIOZAKI and co-workers\(^{[204]}\) in 1994 who also established its absolute configuration. Trehazolin consists of an \(\alpha\)-D-glucopyranose moiety that is bonded via a cyclic isourea group to the unique aminocyclopentitol trehazolamine (1/212) (Figure 1.91). Synthetic 5-epi-trehazolin, previously proposed as the structure of trehalostatin, which had been isolated as a purported trehalase inhibitor from the culture broth of *Amycolatopsis trehalostatica*, has been shown not to possess any observable inhibitory activity against trehalase. This result indicated that the initial structure assigned for trehalostatin is incorrect, and that its structure is identical with that of trehazolin.\(^{[205]}\)

Trehalamine (1/211), the aglycon of trehazolin (Figure 1.91), also occurs naturally. It was found in the culture broths of two trehazolin producing strains, *Micromonospora* sp. SANK 62390 and *Amycolatopsis* sp. SANK 60791.\(^{[206]}\) However, trehalamine and trehazolamine were found to be only poor inhibitors of trehalase with IC\(_{50}\) values in the low millimolar range. On the other hand, they inhibited more potently rat intestinal sucrase (IC\(_{50}\) = \(6.8 \times 10^{-5}\) M for 1/211) and sweet almond \(\beta\)-glucosidase (IC\(_{50}\) = \(5.6 \times 10^{-6}\) M for 1/212) than trehazolin.

![Figure 1.91. Trehalamine and its hydrolysis derivative trehazolamine.](image-url)
1.3 Polyhydroxylated Alkaloids as Glycosidase Inhibitors

Most of the polyhydroxylated alkaloids listed above have been studied in detail towards their glycosidase inhibitory activity. Glycosidases (sometimes also called glycoside hydrolases) are enzymes that catalyse the hydrolysis of the glycosidic bonds in complex carbohydrates and glycoconjugates. They are found in essentially all domains of life and are vital for the existence and survival of all living organisms due to the broad diversity of functions in which they are involved. For example, digestive glycosidases break down large polysaccharides such as starch to release monomeric sugar molecules which can then be taken up and be used as energy source by the organism. In cell lysosomes\(^1\) glycosidases degrade waste glycoconjugates. A wide range of glycosidases can be found intracellularly in the endoplasmic reticulum\(^{II}\) and the Golgi apparatus\(^{III}\) where they are involved in the biosynthesis and processing of the oligosaccharide moieties of glycoproteins. These oligosaccharide chains are responsible for the correct functioning of the proteins by stabilising them and ensuring that they have the correct conformation\(^8\).

There are two fundamental mechanisms of enzymatic glycoside hydrolysis\(^{207}\) differentiated by the stereochemical outcome of the catalysed reaction; the glycosidic bond can be cleaved either with inversion or retention of the anomeric configuration. Thus, the corresponding enzyme is referred to as an inverting or retaining glycosidase, respectively. Abbreviated mechanisms of glycosidic bond cleavage for these two classes of enzyme are shown below in Scheme 1.2, the example shown being that of a $\beta$-glucosidase. The active site of each enzyme class is shown simplified as two key carboxylic residues. Other residues which are also involved in binding and complexing of the substrates have been omitted from the scheme for clarity, and because they vary with each enzyme.

Inverting glycosidases work via a one-step mechanism through the direct cleavage of the glycosidic bond by water, with one carboxylic acid acting as a proton donor to facilitate the aglycon departure, while the other serves as a proton acceptor to deprotonate the water as it attacks. In this case the two carboxylic acids must be sufficiently separated to allow the substrate and a water molecule to be placed between them.
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Scheme 1.2. Mechanisms of inverting (top) and retaining (bottom) glycosidases, illustrated with a β-glucosidase.

Retaining glycosidases operate via a two-step mechanism in which each step is resulting in inversion, leading to a net retention of stereochemistry. In the first step one of the carboxylic acids acts as a proton donor, protonating the leaving group oxygen, while the other carboxylate acts as a nucleophile, attacking at the sugar anomeric centre and forming a covalent glycosyl enzyme intermediate. In the second step the now deprotonated carboxylate residue acts as a base and assists a nucleophilic attack of a water molecule at the anomeric centre to displace the sugar of the enzyme. This mechanism requires the two carboxylic acid residues to be much closer together, since the nucleophile attacks directly onto the sugar.

Polyhydroxylated alkaloids can be extremely potent and specific inhibitors of glycosidases by mimicking the pyranosyl or furanosyl moiety of their natural substrates. When a polyhydroxylated alkaloid binds to the active site of a glycosidase, it has been suggested that protonation of the compounds nitrogen leads to the formation of an ion pair between the inhibitor (i.e. the iminosugar) and a carboxylate anion in the active site of the enzyme (Figure 1.92).
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Figure 1.92. Comparison of DNJ and DMDP with the carboxonium ion transition state of enzymatic glycoside hydrolysis.

The protonated inhibitor closely resembles the carboxonium ion transition state for the hydrolysis of the neutral substrate and therefore the enzyme has a high affinity for the molecule. Nevertheless, the strength of the binding and hence the effectiveness of the inhibition depends to a large degree on the pK$_a$ of the inhibitor and the pH optimum of the enzyme. Moreover, there are also individual differences in the inhibition of enzymes of the same type within the same cell. For example, there are multiple forms of $\alpha$-mannosidases in human liver cells which are structurally, functionally and genetically quite distinct.$^{208}$ They also have different cellular locations. The lysosomal $\alpha$-mannosidase, which degrades glycoconjugates, has an acidic pH optimum (around 4.0) whereas the cytosolic$^{[IV]}$ $\alpha$-mannosidase functions best at near neutral pH (6.5). There are also two forms of $\alpha$-mannosidase in the Golgi apparatus ($\alpha$-mannosidase I and II, respectively) which are involved in glycoprotein processing, as is another $\alpha$-mannosidase which is associated with the endoplasmic reticulum. The lysosomal, Golgi II and neutral cytosolic $\alpha$-mannosidases are all inhibited by polyhydroxylated alkaloids with the same substituents and chirality as mannofuranose (e.g. swainsonine, 1/92) whereas Golgi $\alpha$-mannosidase I is inhibited by mannopyranose analogues such as DMJ (1/9).$^{209}$

1.4 Mammalian Toxicity of Polyhydroxylated Alkaloids

It is not surprising that compounds that so efficiently affect the carbohydrate metabolism of animal organisms like polyhydroxylated alkaloids have also been reported to exhibit toxic effects and are known to cause some severe livestock poisoning. In fact, it was the toxicity to livestock of the legumes Swainsona canescens and Castanospermum australe that first led to the isolation of the alkaloids swainsonine (1/92) and castanospermine (1/88).
Livestock in Australia eating *Swainsona* species suffered from a neurophysiological disorder called “pea struck” which is due to decreased α-mannosidase activity resulting in accumulation of mannose-rich oligosaccharides in the cell lysosomes. This results in neuronal vacuolation, axonal dystrophy, loss of cellular function and ultimately death.\[212\] Cattle suffering from the syndrome “locoism” in the Western parts of the United States was also found to be due to feeding on swainsonine-containing locoweeds (*Astragalus* and *Oxytropis* species).\[213, 214\] Furthermore, poisoning of animals in China by *Oxytropis ochrocephala* (Figure 1.94) and *O. kansuensis* has also been shown to be due to the presence of swainsonine (1/92). Although the concentration of swainsonine in all plants found to be responsible for livestock poisonings is very low, swainsonine can accumulate within tissues of the body as it is able to permeate cell membranes freely due to its hydro- and lipophilic properties. However, once inside the lysosomes it becomes protonated due to the low pH and therefore slowly concentrates within the cell.\[215\] For that reason, poisoning by swainsonine generally takes several weeks of ingestion before it becomes apparent. Symptoms of swainsonine poisoning in livestock on ingestion of plants containing this compound include depression, tremors, nervousness, emaciation, gastrointestinal malfunction and reproductive abnormalities such as abortion and birth defects. However, if affected animals are denied access to plants containing swainsonine early enough, lysosomal function will return to normal as the alkaloid is excreted from the body via the urine.\[216\]

The seeds of the Moreton Bay Chestnut, *Castanospermum australe*, contain the potent α- and β-glucosidase inhibitor castanospermine (1/88) at a concentration of approximately 0.3% of the dry weight of the seed.\[104\] Pigs, cattle and horses have been reported to be poisoned when they fed on the seeds. The main symptom is gastroenteritis due to the inhibition of intestinal digestive disaccharidases like sucrase, maltase and trehalase. Other symptoms include myocardial degeneration and nephrosis.\[217\] The poisoning can be so
severe that animals die.\textsuperscript{[218]} Moreover, castanospermine inhibits the activity of lysosomal $\alpha$-glucosidase which leads to the accumulation of glycogen within the lysosomes.\textsuperscript{[219]} This mimics the situation of the genetically-determined lysosomal storage disorder “glycogenosis type II”, a.k.a. Pompe’s disease, which is caused by a deficiency of lysosomal $\alpha$-glucosidase.\textsuperscript{[220]}

1.5 Therapeutic Potential of Polyhydroxylated Alkaloids

Although there are more than 200 polyhydroxylated alkaloids known today, only very few of them are commercially available or easily obtainable in larger amounts from their natural sources. Those of which are (principally DNJ, DMJ, castanospermine and swainsonine) have been studied in depth for their therapeutic and biochemical applications. Therefore, most of the following consideration about the therapeutic applications of iminosugars is based on this limited number of compounds simply because these are the only ones that are readily available. Nevertheless, it should also be noted that the doses required for beneficial effects in a disease treatment are generally below those causing the toxicities described in Section 1.4.

1.5.1 Antidiabetic agents

Due to their glycosidases inhibitory activity these enzymes became the first therapeutic targets for iminosugars. A large number of naturally occurring polyhydroxylated alkaloids are potent inhibitors of various $\alpha$-glucose-based disaccharidases that are involved in mammalian digestion such as sucrase, maltase, isomaltase, lactase, trehalase, \textit{etc.} These enzymes are expressed at the surface of the brush border epithelial cells in the small intestine. In the late 1970s it was realised that inhibitors of these enzymes could be used therapeutically in the oral treatment of the non-insulin-dependent diabetes mellitus (NIDDM) also known as type 2 diabetes.

DNJ (1/8) was among the first iminosugars tested as potential antidiabetic agent, however, it was found that the \textit{in vivo} activity of DNJ against intestinal glucosidases was significantly lower than that seen in \textit{in vitro} experiments. This circumstance launched a synthetic program to find DNJ derivatives with enhanced activity. The $N$-alkyl derivatives were found to be to most effective which led to the development of $N$-hydroxyethyl-DNJ also known as miglitol.
By inhibiting the breakdown of complex carbohydrates in the gut, miglitol reduces glucose uptake and so reduces the postprandial rise in blood glucose which is characteristic of diabetes. Miglitol became approved as drug for use in type 2 diabetes treatment in December 1996 and is sold on the market under trade names GLYSET® in the USA and DIASTABOL® in the EU. However, miglitol also leads to considerable gastrointestinal discomfort due to undigested polysaccharides and is substantially absorbed from the gut into the bloodstream where it causes further side effects.

Since the late 1960s the researchers of BAYER had searched for inhibitors of intestinal sucrase for the treatment of diabetes and eventually isolated the pseudotetrasaccharide acarbose from the fermentation broth of the *Actinoplanes* strain SE 50. After intensive clinical trials acarbose became approved as drug for the oral type 2 diabetes treatment and was introduced on the German market in 1990 under the trade name GLUCOBAY®. It has since been successfully marketed in Europe and the United States where it is known under the brand name PRECOSE®. The structure of acarbose comprises the aminosugar acarviosine and one maltose unit and has similar action like miglitol but is not appreciably absorbed into the bloodstream. It is also a useful tool for the diagnosis of the lysosomal storage disorder, Pompe’s disease.

Figure 1.95. Miglitol and acarbose, two approved drugs for the treatment of non-insulin-dependent (type 2) diabetes mellitus.
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The glycosidase inhibitory activity of acarbose arises from the allylic imino linkage of its acarviosine moiety. A similar structural element is also found in the antibiotic validamycin A (1/216) which was isolated from the culture broth of the bacteria *Streptomyces hygroscopicus* var. *limoneus*. From the same source were later also the carboglucosylamines validamine (1/217), valienamine (1/218) and valiolamine (1/219) obtained (Figure 1.96). Of these three compounds valiolamine proved to be the most potent glycosidase inhibitor; it inhibits pig intestinal maltase and sucrase with IC$_{50}$ values in the micro- and nanomolar range, respectively. HORII and co-workers set out to enhance its $\alpha$-glucosidase inhibitory activity and synthesised numerous $N$-substituted valiolamine derivatives. The very simple derivative voglibose (1/220) was obtained by reductive amination of valiolamine with dihydroxyacetone (Figure 1.96). Its IC$_{50}$ values towards maltase and sucrase are in the low nanomolar range (15 nM and 4.6 nM), respectively. Today, voglibose is also an approved drug for the treatment of type 2 diabetes and traded under the names BASEN® (TAKEDA Pharmaceutical Co.) in Japan and VOGLIB® (Mascot Health Series) in India.

![Figure 1.96](image)

**Figure 1.96.** Carboglucosylamines, isolated from the culture broth of *Streptomyces hygroscopicus* var. *limoneus*, and the synthetic derivative voglibose, a further approved drug for the treatment of type 2 diabetes.
The polyhydroxylated pyrrolidine 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1, 1/61) is the latest drug candidate for type 2 diabetes treatment and currently in the clinical test phase. D-AB1 decreases glucagon-induced as well as spontaneous hyperglycaemia by inhibition of hepatic glycogen phosphorylase.\cite{12}

Castanospermine (1/88), which can be considered as a bicyclic derivative of DNJ, was also considered as a potential type 2 diabetes drug. However, due to its toxicity, this compound is now regarded to be unsuitable for therapeutic use. Attempts to synthesise better tolerated derivatives of castanospermine were unsuccessful.\cite{228}

### 1.5.2 Antiviral agents

Another therapeutic application of polyhydroxylated alkaloids is as antiviral agents. \(\alpha\)-Glucosidase inhibitors, such as castanospermine and DNJ, have been demonstrated to decrease the infectivity of the human immunodeficiency virus (HIV) \textit{in vitro} at concentrations which are not cytotoxic to lymphocytes. In contrast, \(\alpha\)-mannosidase inhibitors like swainsonine and DMJ have no effect on HIV.\cite{229−231} Castanospermine and DNJ also reduce the infectivity of further retroviruses including the feline equivalent of HIV\cite{232} and the human cytomegalovirus (CMV), an opportunistic pathogen co-occurring with AIDS.\cite{233}

HIV primarily infects cells of the immune system. Crucial for the infection is the interaction between the CD4 receptor, a membrane glycoprotein found on the surface of T-lymphocytes and other cells of the immune system, and the viral envelope glycoproteins gp120 and gp41. In the presence of castanospermine and DNJ the glycosylation sequence of these viral glycoproteins is changed. Although this does not prevent the formation of viral particles, they no longer have the ability to interact correctly with the CD4 receptor. Hence, they are no longer infectious.\cite{231, 234}

In 1988 FLEET and co-workers conducted trials to determine the necessary structural features in polyhydroxylated alkaloids to exhibit antiviral activity.\cite{230, 235} It was revealed that \(N\)-alkyl substituted DNJ derivatives were more potent \textit{in vivo} than the natural product. In particular, \(N\)-butyl-DNJ (1/221, Figure 1.97) had enhanced anti-HIV activity, possibly because the aliphatic chain increased uptake into the cells. This compound was chosen as a therapeutic candidate and was evaluated in phase II clinical trials. However, oral administration in combination with dideoxynucleoside derivatives that target the viral reverse transcriptase
activity such as AZT caused diarrhoea, abdominal pain and weight loss in human trial participants.\textsuperscript{[236]} In view of these side effects chemical modifications of NB-DNJ were undertaken to eliminate the gastrointestinal toxicity. This resulted in the development of GLYCOVIR\textsuperscript{®} (1/222), the tetrabutyrylated ester of NB-DNJ (Figure 1.97).\textsuperscript{[237]} GLYCOVIR\textsuperscript{®} is a prodrug which is metabolised in the gastrointestinal mucous membranes after its absorption from the intestines to release the active agent NB-DNJ into the plasma and by this way effectively avoiding diarrhoea.\textsuperscript{[237]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure197.png}
\caption{The antiviral agents \textit{N}-butyl-DNJ and GLYCOVIR\textsuperscript{®}.}
\end{figure}

\subsection{1.5.3 Anticancer agents}

Although a number of polyhydroxylated alkaloids have been reported to show anticancer activity, most of the research has been focused on the indolizidine alkaloid swainsonine (1/92) as a drug candidate for the management of human malignancies. Swainsonine inhibits the growth of tumour cells and prevents their spreading from the primary tumour to secondary sites (a process known as metastasis). This antimetastatic effect has been attributed to its direct stimulatory effect on the immune system.\textsuperscript{[8]} Swainsonine activates the augmentation of natural antitumour defences such as natural killer cells (peripheral blood lymphocytes), T-lymphocytes and macrophages.\textsuperscript{[238, 239]} It also increases the susceptibility of cancer cells to natural killer cells and lymphokine-activated killer cell\textsuperscript{[IV]} cytotoxicity. Direct antitumour activity has also been reported upon the observation that human tumour cells revert to normal when treated with swainsonine. The results form the tissue culture and animal studies were so encouraging that the efficacy of swainsonine was examined in phase I clinical trials in patients with either leukaemia or breast, colon, lung, pancreatic, or head and neck cancers. The patient with head and neck cancer had over 50\% tumour remission, and two others showed symptomatic improvement. However, the test patients also developed liver
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cell damage from the treatment and suffered from pulmonary oedema.\textsuperscript{[240]} Other adverse effects included fatigue, anorexia, abdominal pain and neurological symptoms.\textsuperscript{[241]} In 1993, DENNIS and co-workers synthesised derivatives of swainsonine with lipophilic groups attached to either the C-2 or C-8 position. The 2-carboxyloxy ester analogues were found to be relatively poor $\alpha$-mannosidase inhibitors \textit{in vitro} but to have comparable activities to swainsonine \textit{in vivo}. This led to the assumption that these compounds act as prodrugs which are hydrolysed by intracellular esterases to release swainsonine only once they are inside tumour or lymphoid cells. As such they are expected to have improved pharmacological properties and reduced side effects.\textsuperscript{[242]}

Glycoside hydrolases other than processing glycosidases have also been considered as potential targets for anticancer therapy. $\beta$-$N$-acetylglucosaminidases have been investigated due to their altered expression in a range of human cancer cell types. These enzymes release $N$-acetyl-$D$-glucosamine from glycoproteins, and a number of inhibitors have been isolated from natural sources. These include nagstatin (1\textsuperscript{223}) which was isolated in 1992 from the fermentation broth of the strain \textit{Streptomyces amakusaensis} MG846-ff3 by AOYAGI and co-workers.\textsuperscript{[243]} Nagstatin can be considered as a nitrogenous $N$-acetyl-$D$-glucosamine analogue fused with an imidazole ring.\textsuperscript{[244]} It is a strong inhibitor of bovine kidney $\beta$-$N$-acetylglucosaminidase with an IC\textsubscript{50} in the nanomolar range (4 nM). Further synthetic inhibitors of these enzymes comprise 2-acetamido-1,5-imino-1,2,5-trideoxy-$D$-glucitol\textsuperscript{[245]} (1\textsuperscript{224}) and the 6-acetamido derivative of castanospermine\textsuperscript{[246]} (1\textsuperscript{225}) (Figure 1.98).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure198.png}
\caption{Naturally occurring (top) and synthetic (bottom) $\beta$-$N$-acetylglucosaminidase inhibitors.}
\end{figure}
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The compounds pyrostatin A and B, isolated from *Streptomyces sp. SA-3501* by AOYAGI and co-workers in 1995 have been reported to be strong β-N-acetylglucosaminidase inhibitors with inhibition constants in the micromolar range. However, a recent comparison of the NMR spectral data of the pyrostatins has led to their structural revision; it was shown that the pyrostatins A and B are identical to 5-hydroxectoine (1/228) and ectoine (1/229), respectively (Figure 1.99). The ectoines are known as compatible solutes which serve as protective substances by acting as osmolytes and thus help microorganisms survive extreme osmotic stress. The ectoines are found in high concentrations in halophilic bacteria and confer resistance towards salt and temperature stress. Enzymatic experiments performed by APPEL and LENTZEN demonstrated that neither ectoine nor 5-hydroxyectoine exhibit an inhibitory effect on β-N-acetylglucosaminidase. The previously reported inhibition by pyrostatins A and B may therefore be due to the contamination of the compound preparations with a strong β-N-acetylglucosaminidase inhibitor that possesses an inhibition constant in the nanomolar range.

![Figure 1.99. Originally proposed (left) and revised structures (right) of pyrostatins A and B.](image)

Forodesine (also known as Immucillin H, 1/230) is an orally-available transition-state analogue inhibitor of purine nucleoside phosphorylase (PNP), a purine salvage pathway enzyme that is essential for the proliferation of T-cells and B-cells. Typically, T- and B-cells are an essential part of the body’s immune system, but when they multiply uncontrollably, they can cause various forms of cancer. Inhibiting PNP produces selective suppression of T- and B-cells by inducing apoptosis in both types of cells. Forodesine is currently under investigation for the treatment of relapsed B-cell chronic lymphocytic leukaemia (B-CLL) in phase II clinical trials.
1.6 Glossary

[I] Lysosomes are spherical shaped organelles that contain enzymes that break up waste materials and cellular debris. They are found in animal cells, while in yeast and plants the same roles are performed by lytic vacuoles. Lysosomes digest excess or worn-out organelles, food particles, and engulfed viruses or bacteria. Lysosomes fuse with vacuoles and dispense their enzymes into the vacuoles, digesting their contents. The name lysosome derives from the Greek words lysis, which means to separate; and soma, which means body. They are frequently nicknamed "suicide-bags" or "suicide-sacs" by cell biologists due to their role in autolysis.[252]

[II] The endoplasmic reticulum (ER) is an eukaryotic cell organelle that forms an interconnected network of tubules, vesicles, and cisternae within cells. Rough endoplasmic reticulums synthesise proteins, while smooth endoplasmic reticulums synthesise lipids and steroids, metabolise carbohydrates and steroids, and regulate calcium concentration, drug detoxification, and attachment of receptors on cell membrane proteins.[253]

[III] The Golgi apparatus is an organelle found in most eukaryotic cells. The primary function of the Golgi apparatus is to process and package macromolecules, such as proteins and lipids, after their synthesis and before they make their way to their destination; it is particularly important in the processing of proteins for secretion.[254]

[IV] The cytosol or intracellular fluid is the liquid found inside cells. In eukaryotes this liquid is separated by cell membranes from the contents of the organelles suspended in the cytosol, such as the mitochondrial matrix inside the mitochondrion. The cytosol is a complex mixture of substances dissolved in water. Although water forms the large majority of the cytosol, its structure and properties within cells is not well understood. Although once thought to be a simple solution of molecules, multiple levels of organisation exist in the cytosol. These include concentration gradients of small molecules such as calcium, large complexes of enzymes and protein complexes. The entire contents of a eukaryotic cell within cell membrane, minus the contents of the cell nucleus, are referred to as the cytoplasm.[255]
A lymphokine-activated killer cell (also known as a LAK cell) is a white blood cell that has been stimulated to kill tumour cells. If lymphocytes are cultured in the presence of Interleukin 2, it results in the development of effector cells which are cytotoxic to tumour cells.

1.7 References

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[25] URL: http://static.zoonar.de/img/www_repository3/58/d7/68/10_1d2f28da90903b71834e7f10365a93ad.jpg (Morus nigra) [16/08/2012]


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[60] URL: http://pharm1.pharmazie.uni-greifswald.de/systematik/7_bilder/yamasaki/yamas004.jpg (*Adenophora triphylla* var. *japonica*) [16/08/2012]


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[70] URL: [http://tribes.tribenetwork.com/yourdailyflower/photos/35e84c27-e971-4fd7-8587-fa5913116fa8](http://tribes.tribenetwork.com/yourdailyflower/photos/35e84c27-e971-4fd7-8587-fa5913116fa8) (*Derris elliptica*) [16/08/2012]


[75] URL: [http://eol.org/pages/28298/overview](http://eol.org/pages/28298/overview) (*Angylocalyx oligophyllus*) [16/08/2012]


[77] URL: [http://mygarden.uperho.com/ferns0304.htm](http://mygarden.uperho.com/ferns0304.htm) (*Arachniodes standishii*) [16/08/2012]

[78] URL: [http://aoki2.si.gunma-u.ac.jp/BotanicalGarden/HTMLs/kuwa.html](http://aoki2.si.gunma-u.ac.jp/BotanicalGarden/HTMLs/kuwa.html) (*Morus bombycis*) [16/08/2012]


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[89] URL: [http://www.callalilyshop.pacificcallas.com/caribbeanjewel.htm](http://www.callalilyshop.pacificcallas.com/caribbeanjewel.htm) (Scilla peruviana) [16/08/2012]

(g) M. Shibano, D. Tsukamoto, R. Fujimoto, Y. Masui, H. Sugimoto, G. Kusano,
Chapter 1. Polyhydroxylated Alkaloids


[100] URL: [http://www.pfaf.org/user/Plant.aspx?LatinName=Broussonetia+kazinoki](http://www.pfaf.org/user/Plant.aspx?LatinName=Broussonetia+kazinoki) (*Broussonetia kazinoki*) [16/08/2012]


Chapter 1. Polyhydroxylated Alkaloids


[110] URL: http://www.rain-tree.com/Plant-Images/stevia-pic.htm (Stevia rebaudiana) [16/08/2012]


[115] URL: http://botany.cz/cs/senecio-hadiensis/ (Senecio hadiensis) [16/08/2012]


[117] URL: http://www.zimbabweflora.co.zw/speciesdata/images/16/164090-3.jpg (Crotalaria agatiflora) [16/08/2012]


Chapter 1. Polyhydroxylated Alkaloids


[127] URL: [http://www.pfaf.org/user/Plant.aspx?LatinName=Castanospermum+australe](http://www.pfaf.org/user/Plant.aspx?LatinName=Castanospermum+australe) (*Castanospermum australe* flowers) [16/08/2012]


Chapter 1. Polyhydroxylated Alkaloids


[141] URL: [http://www.flickr.com/photos/49123099@N08/4497961768/](http://www.flickr.com/photos/49123099@N08/4497961768/) (*Scilla campanulata*) [16/08/2012]


Chapter 1. Polyhydroxylated Alkaloids

[153] URL: http://de.wikipedia.org/wiki/Lampionblume (Physalis alkekengi) [16/08/2012]


[168] URL: http://en.wikipedia.org/wiki/Wolfberry (Lycium chinense) [16/08/2012]

[169] URL: http://www.awl.ch/heilpflanzen/hyoscyamus_niger/index.htm (Hyoscyamus niger) [16/08/2012]
Chapter 1. Polyhydroxylated Alkaloids

[170] URL: http://de.wikipedia.org/wiki/Weiße_Maulbeere (Morus alba) [16/08/2012]


[172] URL: http://www.africaimagelibrary.com/media/875ce752-1afe-11e0-ad5b-914d76721a06-nyala-tree-xanthocercis-zambesiaca-tuli-block-botswana (Xanthocercis zambesiaca) [16/08/2012]


[178] URL: http://www.nurgapuuool.ee/pic/foorum/austrtaim07/castanospermum_australe.JPG (Castanospermum australe seedpods) [16/08/2012]

[179] URL: http://www.flickriver.com/photos/dinesh_valke/2175528970/ (Eugenia jambolana) [16/08/2012]


Chapter 1. Polyhydroxylated Alkaloids


[201] URL: [http://lv-microbcollect.lviv.ua/strain_card.htm?id=8](http://lv-microbcollect.lviv.ua/strain_card.htm?id=8) (*Streptomyces albus*).

[16/08/2012]


[211] URL: http://www.nwipb.cas.cn/kxcb/kpwz/201009/t20100927_2975088.html (Oxytropis ochrocephala) [16/08/2012]


Chapter 1. Polyhydroxylated Alkaloids


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Chapter 1. Polyhydroxylated Alkaloids
Chapter 2. The Broussonetines and the Sphingosines

2.1 The Broussonetines

An exceptional subgroup in the still expanding class of iminosugars is characterised by a polyhydroxylated pyrrolidine moiety and a thirteen carbon side chain attached at C-5. First members of this alkaloid family were isolated by KUSANO et al. in 1995 from the hot water extracts of the bark of the Japanese Paper Mulberry, *Broussonetia kazinoki* (Moraceae) (Japanese name “himekouzo”), a deciduous tree distributed throughout South-east China, Korea, Taiwan, and Japan (Figures 2.1 and 2.2). Its cortex is a raw material for the handmade Japanese paper known as “washi”, and its branches, leaves, and fruits have been used as a diuretic, a tonic, and a suppressant of oedema in Chinese folk medicine.

To date, KUSANO and co-workers have reported the isolation and structure determination of 32 congeners of this unique alkaloid family, consequently named “Broussonetines” after their natural source.[2, 3]

The isolated compounds have demonstrated glycosidase inhibitory activity which is hardly surprising given their structural resemblance to the known iminosugars D-AB1 and DMDP. Like these two alkaloids most of the broussonetines have the (2R,3R,4R,5R)-configuration around the periphery of the pyrrolidine ring, although a small subset of seven compounds (broussonetinines A and B as well as broussonetines A, B, Q, V and X) have the (3S)-configuration as it is found in the unnatural pyrrolidine 1,4-dideoxy-1,4-imino-D-lyxitol (DIL). Additionally, three of the broussonetines possess a deviant imino moiety. These are broussonetine N with a pyrrolizidine nucleus and broussonetines U and U1 with an unsaturated pyrroline ring (Figure 2.3).

---

* The plant was given the systematic name *Broussonetia kazinoki* in honour of the French biologist Pierre Marie Auguste BROUSSONET (1761-1807), appointed professor of botany at Montpellier. The epithet kazinoki refers to a place in Japan.
Chapter 2. The Broussonetines and the Sphingosines

Figure 2.4. Classification of the broussonetines into three groups.

The pyrrolizidine broussonetine N is also included in this division since it can be interpreted as D-AB1 derivative in which part of the side chain is fused onto the nitrogen atom forming the bicyclic pyrrolizidine structure.

2.2 Glycosidase Inhibitory Activity

KUSANO and co-workers assayed the glycosidase inhibitory activities of broussonetines A – Q against \( \alpha \)-glucosidase (from yeast), \( \beta \)-glucosidase (from sweet almond), \( \beta \)-galactosidase (from bovine liver), \( \alpha \)-mannosidase (from jack beans), and \( \beta \)-mannosidase (from snail) and compared the inhibitory activities to those of the well-known iminosugars 1-deoxynojirimycin (DNJ, \( \text{1/8} \)), 1-deoxymannojirimycin (DMJ, \( \text{1/9} \)), 1-deoxygalactonojirimycin (DGAJ, \( \text{1/10} \)) and 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, \( \text{1/51} \)).[3] The results are shown in Table 2.1.

Two key findings should be noted. Firstly, almost all tested broussonetines are excellent inhibitors of \( \beta \)-glycosidases. Secondly, most broussonetines are at least as potent or in some cases by a factor of 100 more powerful inhibitors (e.g. broussonetines E and G) than the well-examined inhibitors DNJ, DMJ, DGAJ and DMDP. Keeping these results in mind plus considering that for a good inhibitor to become a potential drug, it has to satisfy a number of conditions such as stability in the stomach and membrane permeability, which often requires the presence of lipophilic moieties, the broussonetines are now regarded as a potential new generation of carbohydrate-controlled therapeutic agents against many diseases including type 2 diabetes, cancer and viral infections such as HIV.[3]
Figure 2.3. The broussonetines.
Chapter 2. The Broussonetines and the Sphingosines

Table 2.1. Concentration of inhibitor required to produce 50% inhibition of enzyme act (IC$_{50}$) (KUSANO et al. 2002).[3]

<table>
<thead>
<tr>
<th>Broussonetine</th>
<th>α-Glucosidase (Yeast)</th>
<th>β-Glucosidase (Sweet Almond)</th>
<th>β-Galactosidase (Bovine Liver)</th>
<th>α-Mannosidase (Jack Beans)</th>
<th>β-Mannosidase (Snail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>NI</td>
<td>NI</td>
<td>1.6 × 10$^{-7}$</td>
<td>3.0 × 10$^{-7}$</td>
<td>NI</td>
</tr>
<tr>
<td>A’</td>
<td>NI</td>
<td>NI</td>
<td>1.0 × 10$^{-7}$</td>
<td>2.9 × 10$^{-7}$</td>
<td>NI</td>
</tr>
<tr>
<td>B</td>
<td>NI</td>
<td>NI</td>
<td>3.6 × 10$^{-8}$</td>
<td>NI</td>
<td>1.0 × 10$^{-7}$</td>
</tr>
<tr>
<td>B’</td>
<td>NI</td>
<td>NI</td>
<td>2.9 × 10$^{-8}$</td>
<td>NI</td>
<td>1.0 × 10$^{-7}$</td>
</tr>
<tr>
<td>C</td>
<td>NI</td>
<td>NI</td>
<td>3.6 × 10$^{-8}$</td>
<td>NI</td>
<td>3.2 × 10$^{-7}$</td>
</tr>
<tr>
<td>D</td>
<td>NI</td>
<td>2.9 × 10$^{-8}$</td>
<td>3.2 × 10$^{-9}$</td>
<td>NI</td>
<td>3.2 × 10$^{-7}$</td>
</tr>
<tr>
<td>E</td>
<td>3.3 × 10$^{-6}$</td>
<td>5.5 × 10$^{-6}$</td>
<td>2.0 × 10$^{-9}$</td>
<td>NI</td>
<td>2.3 × 10$^{-8}$</td>
</tr>
<tr>
<td>F</td>
<td>1.5 × 10$^{-6}$</td>
<td>1.0 × 10$^{-8}$</td>
<td>4.1 × 10$^{-9}$</td>
<td>NI</td>
<td>2.8 × 10$^{-8}$</td>
</tr>
<tr>
<td>G</td>
<td>NI</td>
<td>2.4 × 10$^{-9}$</td>
<td>2.0 × 10$^{-9}$</td>
<td>NI</td>
<td>7.6 × 10$^{-7}$</td>
</tr>
<tr>
<td>H</td>
<td>NI</td>
<td>3.6 × 10$^{-8}$</td>
<td>3.2 × 10$^{-9}$</td>
<td>NI</td>
<td>3.2 × 10$^{-7}$</td>
</tr>
<tr>
<td>J</td>
<td>NI</td>
<td>NI</td>
<td>2.9 × 10$^{-7}$</td>
<td>NI</td>
<td>3.0 × 10$^{-7}$</td>
</tr>
<tr>
<td>K</td>
<td>2.6 × 10$^{-8}$</td>
<td>5.0 × 10$^{-9}$</td>
<td>5.0 × 10$^{-9}$</td>
<td>NI</td>
<td>2.0 × 10$^{-7}$</td>
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<tr>
<td>L</td>
<td>1.7 × 10$^{-8}$</td>
<td>4.0 × 10$^{-9}$</td>
<td>8.1 × 10$^{-6}$</td>
<td>NI</td>
<td>2.0 × 10$^{-7}$</td>
</tr>
<tr>
<td>M</td>
<td>NI</td>
<td>NI</td>
<td>5.8 × 10$^{-7}$</td>
<td>2.9 × 10$^{-7}$</td>
<td>3.3 × 10$^{-7}$</td>
</tr>
<tr>
<td>N</td>
<td>1.4 × 10$^{-9}$</td>
<td>1.7 × 10$^{-7}$</td>
<td>8.2 × 10$^{-6}$</td>
<td>NI</td>
<td>8.2 × 10$^{-6}$</td>
</tr>
<tr>
<td>O</td>
<td>2.4 × 10$^{-9}$</td>
<td>2.0 × 10$^{-7}$</td>
<td>6.0 × 10$^{-7}$</td>
<td>NI</td>
<td>7.6 × 10$^{-6}$</td>
</tr>
<tr>
<td>Q</td>
<td>1.4 × 10$^{-9}$</td>
<td>6.0 × 10$^{-7}$</td>
<td>2.0 × 10$^{-7}$</td>
<td>NI</td>
<td>2.0 × 10$^{-5}$</td>
</tr>
<tr>
<td>DMDP</td>
<td>3.3 × 10$^{-6}$</td>
<td>9.0 × 10$^{-6}$</td>
<td>2.2 × 10$^{-6}$</td>
<td>9.0 × 10$^{-6}$</td>
<td>NI</td>
</tr>
<tr>
<td>DNJ</td>
<td>9.3 × 10$^{-7}$</td>
<td>5.8 × 10$^{-7}$</td>
<td>1.2 × 10$^{-6}$</td>
<td>9.0 × 10$^{-6}$</td>
<td>NI</td>
</tr>
<tr>
<td>DMJ</td>
<td>1.4 × 10$^{-9}$</td>
<td>9.4 × 10$^{-7}$</td>
<td>8.1 × 10$^{-7}$</td>
<td>NI</td>
<td>8.1 × 10$^{-7}$</td>
</tr>
<tr>
<td>DGJ</td>
<td>1.3 × 10$^{-7}$</td>
<td>1.3 × 10$^{-7}$</td>
<td>1.3 × 10$^{-7}$</td>
<td>1.3 × 10$^{-7}$</td>
<td>NI</td>
</tr>
</tbody>
</table>

A’ = Broussonetinine A ; B’ = Broussonetinine B ; NI = no inhibition ; IC$_{50}$ values in mol/L

2.3 The Biosynthesis of the Broussonetines

All broussonetines comprise a basic C$_{18}$ skeleton. To elucidate the biosynthetic route of these alkaloids KUSANO et al.[5] grew specimen of the source plant (B. kazinoki) on an aseptic medium while feeding them with $^1$C-1-D-glucose and analysed the now $^1$C-enriched isolated alkaloids. The $^1$C NMR spectra of the examined broussonetines C, E and J2 showed the presence of nine enhanced signals (C-1, C-4, C-6, C-8, C-10, C-12, C-14, C-16 and C-18). This observed pattern indicated that the C$_{18}$ skeleton of the broussonetines is formed similar to the sphingosine (2/29) and phytosphingosine (2/32) biosynthesis via the enzymatic condensation of D-serine with a coenzyme A activated palmitoyl rest. The palmitoyl rest is beforehand assembled through the acetate-malonate pathway. After coupling of both building blocks and some further transformations the intramolecular ring-closure occurs via a N-π-cyclisation to form the pyrrolidine ring (Scheme 2.1).[3, 5]
Scheme 2.1. Proposed biosynthetic pathway of the broussonetines.\textsuperscript{[3, 5]}

- \( ^{13} \text{C} \), P = phosphate rest

Broussonetines U and U1, possessing an \textit{all-\textit{S}}-configured pyrroline ring, are assumed to be formed by the condensation of \textit{L}-serine instead of \textit{D}-serine with palmitoyl-CoA.
2.4 The Sphingoid Bases (“Sphingosines”) and Related Amino Alcohols

KUSANO’s findings relate the broussonetines to a vast number of other natural products with a similar origin: the sphingoid bases (“sphingosines”) and sphingoid base-like compounds including their cyclic derivatives.

This class of amino alcohols is now known to encompass hundreds of compounds which vary in chain length, number, position, and stereochemistry of double bonds, hydroxyl groups, and other functionalities. Some have especially intriguing features, such as the tail-to-tail combination of two sphingoid bases in the α,ω-sphingoids produced by sponges. Most of these compounds participate in cell structure and regulation, and some (such as the fumonisins) disrupt normal sphingolipid metabolism and cause plant and animal disease. Many of the naturally occurring and synthetic sphingoid bases are cytotoxic against cancer cells and pathogenic microorganisms or have other potentially useful bioactivities; hence, they offer promise as pharmaceutical leads.[6]

Sphingosine (2/29) itself is a C18 amino alcohol with an unsaturated hydrocarbon chain, that forms a primary part of the sphingolipids,[7] a class of cell membrane lipids that include the ceramides, a family of lipid molecules. Ceramides, such as glucosylceramide (2/31), are composed of sphingosine and a fatty acid (Figure 2.5) and are found in high concentrations within cell membranes. They are one of the component lipids that make up sphingomyelin (2/30), one of the major lipids in the lipid bilayer. Sphingolipids play important roles in signal transmission, cell recognition, differentiation, proliferation, and apoptosis of cells (a form of programmed cell death).[8] They were discovered in brain extracts by J.L.W. THUDICHUM[9] in 1884 and were named after the mythological creature Sphinx because of their enigmatic nature.[10]

![Figure 2.5. Structures of sphingosine and the sphingolipids sphingomyelin and glucosylceramide.](image-url)
Chapter 2. The Broussonetines and the Sphingosines

2.5 The Structural Diversity of the Sphingoid Bases

The first product of the *de novo* sphingoid base biosynthesis, 3-ketosphinganine (2/34), is often not detected in organisms and tissues, because under most circumstances it is rapidly reduced to sphinganine (2/33).\[11\] Sphinganine (dihydrosphingosine) is an early intermediate in the *de novo* biosynthesis of sphingosine (2/29) and one of the major sphingoid bases found in many organisms.\[6\] Phytosphingosine (4-hydroxysphinganine) (2/32) is another sphingoid base, most abundant in keratinocyte\[1\] and characteristic of epidermal ceramide (Figure 2.6).\[8\]

![Phytosphingosine (4-Hydroxysphinganine) 2/32 Sphinganine (Dihydrosphingosine) 2/33](image)

![3-Ketosphinganine 2/34 (4E,14Z)-Sphingadiene 2/35](image)

![6-Hydroxysphingosine 2/36 5-Hydroxy-3E-sphingosine 2/37](image)

**Figure 2.6.** Sphingoid bases found in mammalian tissues.

Variation in the number and position of double bonds and hydroxy groups of the sphingosines leads to a great diversity within this group of compounds. For example, plasma, brain, and human aorta contain a (4E,14Z)-sphingadiene (2/35)\[12, 13\], and 6-hydroxysphingosine (2/36) is present in skin sphingolipids\[14, 15\]. An unusual sphingosine with the double bond between C-3 and C-4, 5-hydroxy-3E-sphingosine (2/37), has been found in acid-hydrolysed brain extracts\[16\] (Figure 2.6).

Fungi, plants, insects, and aquatic organisms extend the structural and compositional variation of natural sphingoid bases even further, as illustrated in Figure 2.8. Structural variations include the length of the carbon backbone and the number, location and configuration of the double bonds. Insects have primarily C\(_{14}\) and C\(_{16}\) sphingoid bases\[17, 18\] such as the
conjugated diene 2/38 found in *Drosophila* species\(^{[20]}\). Phytosphingosine-type compounds with double bonds such as 2/39 and 2/41 are common backbones found in plants.\(^{[21]}\) Sphingoid bases with three double bonds, such as in triene 2/40, are found in the spermatozoa of the Northern Pacific starfish, *Asterias amurensis* (Figure 2.7)\(^{[22]}\), and the branched version, triene 2/42, has been identified in squid nerve sphingomyelin\(^{[23]}\).

![Figure 2.7](image-url). *Asterias amurensis* (Asteriidae), commonly called the Northern Pacific Seastar.

![Figure 2.8](image-url). Sphingoid bases found in various organisms other than mammals.

![Figure 2.9](image-url). *Aplidium* sp., commonly known as sea pork, is marine tunicate that is living in a colonial form: each small orange spot is a single individual.

Sponges and tunicates are another source of sphingoid bases with interesting features such as aplidiasphingosine (2/44), a sphingosine derivative with a terpenoid alkyl chain. This compound was isolated from a marine tunicate *Aplidium* species (Figure 2.9) by RINEHART and CARTER in 1977 and has been noted to exhibit antimicrobial and antitumoral activity.\(^{[25]}\)
Chapter 2. The Broussonetines and the Sphingosines

In the early 1990s the calicogorgins (represented by calicogorgin A (2/45)), a unique group of 3-keto-sphinganine derivatives with a furan moiety incorporated into the carbon backbone, were isolated from the sea whip (gorgonian) *Calicogorgia granulosa* (Plexauridae) by OUCHI et al. (Figure 2.10). These compounds act as potent repellents with lethal activities against the marine gastropod mollusk *Drupella fragum* (Muricidae), a sea snail feeding on the gorgonian.\[27\]

Several species of fungi produce sphingosine-like compounds that mimic metabolites of the sphingolipid metabolism and disrupt early steps in the sphingosine and ceramide biosynthesis by inhibiting the enzyme serine palmitoyltransferase (SPT). One of the most effective SPT inhibitors is the serine derivative ISP-1, also known as myriocin (2/46), named autonomously after its two natural sources, the fungi *Myriococum albomyces*\[29\] and *Isaria sinclairii*\[30\] (Clavicipitaceae, Figure 2.11). ISP-1/myriocin has been studied most extensively not only because of its high potency as SPT inhibitor with an IC\textsubscript{50} in the nano-molar range but also because it exhibits potent immunosuppressive activity (although SPT inhibition is not obligatory for immunosuppression).\[31\] It has been found that ISP-1/myriocin interferes with the production of cytotoxic ceramides in response to a wide variety of
Chapter 2. The Broussonetines and the Sphingosines

stresses\(^{[32]}\), suppresses virus infectivity\(^{[33, 34]}\) alters brain amines\(^{[35]}\) and suppresses atherosclerotic lesions\(^{[36–38]}\).

In the course of the search for a less toxic form of ISP-1/myriocin as immunosuppressive agent \(2/46\) was used as a template and resulted in the development of the drug FTY720 \((2/47)\) also referred to as fingolimod (see Chapter 5, Section 5.4).\(^{[39]}\) Elimination of side chain functionalities and removal of chiral centres was part of the simplification process. Today, fingolimod (trade name GILENYA\textsuperscript{®}, NOVARTIS\(^{[40]}\)) is an immunomodulating drug, approved for the treatment of multiple sclerosis.

Fungi are also the source of diverse sphingosine-like compounds that inhibit ceramide synthases, the enzymes that are responsible for the acylation of sphingoid bases.\(^{[42, 43]}\) The first to be identified were the fumonisins (represented by fumonisin B\(1\) \((2/48)\)), which are mycotoxins produced by the fungus \textit{Fusarium verticilloides} also known as \textit{Fusarium moniliforme}.\(^{[44]}\) This fungus commonly infests maize (Figure 2.12) and causes diseases of plants\(^{[45]}\) and animals (including humans)\(^{[46, 47]}\) that consume the fungal metabolites as food contaminants\(^{[48]}\). It is not surprising that the fumonisins have a wide range of pathologic effects since inhibition of ceramide synthase causes not only the depletion of ceramides and other complex sphingolipids but also the build-up of highly bioactive compounds including sphinganine, sphinganine 1-phosphate, \textit{N}-acetylsphingamide and other related sphingoid bases.\(^{[46, 47]}\)

**Figure 2.12.**\(^{[41]}\) Maize cob infested by the corn mold \textit{Fusarium verticilloides} syn. \textit{F. moniliforme}.
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In addition to the relatively complex fumonisins, plants and marine organism produce a wide variety of simpler 1-deoxysphingosines, even a species that is identical to sphinganine (2/33) but lacking the C-1 hydroxy group. This compound, spisulosine (2/49), has been isolated from the Atlantic surf clam, *Spisula polynyma* (Mactridae, Figure 2.13). It is also referred to as ES-285 as an investigational marine anticancer drug since it inhibits the proliferation of numerous cancer cell lines.\[51, 52\]

Other spisulosine-related compounds include the polyunsaturated obscuraminols (represented by obscuraminol A (2/50)) and the crucigasterins (represented by crucigasterin 277 (2/51)). The obscuraminols were isolated by SALVÀ *et al.*\[54\] in 2001 from a chloroform extract of the ascidian *Pseudodistoma obscurum* (Figure 2.14) which displayed cytotoxicity against human lung and colon carcinoma tumour cell lines. However, the isolated compounds were only mildly cytotoxic.\[54\] The crucigasterins, isolated from the related Mediterranean sponge *Pseudodistoma crucigaster* by RINEHART *et al.*\[55\] are similar to the obscuraminols but possess the opposite (2R,3S)- rather than (2S,3R)-configuration. The crucigasterins show antimicrobial activity against *Bacillus spp.* and are cytotoxic against mouse lymphocytic leukaemia cells.\[55\]
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There are also 1-deoxysphingosines with five- and six-membered rings as part of the side chain. Representatives for these compounds are amaminols A (2/52) and B (2/53) which were isolated in 1999 from an unidentified tunicate of the Polyclinidae family by FUSETANI et al.[56] These compounds might be formed via cyclisation of a polyene such as obscuraminol A (2/50) or crucigasterin 277 (2/51). Both amaminols are cytotoxic against murine leukaemia cells.[56]

Furthermore, there is a series of compounds that resemble two-headed sphingosines i.e. two sphingoid bases connected tail to tail. Oceanin (2/54), the C-3 aglycon of oceanapiside isolated from the sponge *Oceanapia phillipensis* (Phloeodictyidae),[57, 58] represents such an \( \alpha,\omega \)-sphingosine-like compound with sphinganine on one end and 3-\textit{epi}-spisulosine at the other end. It has been proposed that the purpose of two-headed sphingoid bases is to allow these compounds simultaneous interaction with two binding sites on the same target or perhaps concomitant binding with more than one target for a more efficient biological response.[59]
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2.6 Cyclic Derivatives of the Sphingosines – Diversity and Occurrence

A general structural modification of the sphingosines concerns their cyclisation into various types of conformationally constrained derivatives. This results in the formation of three- to six-membered rings with an usually endo-cyclic bound nitrogen atom. In rare cases, however, an exo-cyclic amino group is also found. As an example, Figure 2.15 shows some possible modes of cyclisation of the basic phytosphingosine backbone that lead to a variety of known natural products including the already discussed broussonetines.

\[ \text{Pyrrolidine containing skeleton} \quad \text{“Broussonetines”} \]
\[ \text{Piperidine containing skeleton} \quad \text{“Batzellasides”} \]
\[ \text{Tetrahydrofuran containing skeleton} \quad \text{“Jaspines”} \]
\[ \text{Azetidine containing skeleton} \quad \text{“Penaresidines”} \]

Figure 2.15. Modes of cyclisation of the general phytosphingosine backbone.

2.6.1 Three-membered Cyclic Derivatives

\[ \text{3-Keto-sphinganine backbone} \quad \text{Azirine containing skeleton} \]

Scheme 2.2. Origin of the azirine core structure.
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The simplest aza-heterocycle is the aziridine (azacyclopene) ring found in 4E-(R)-dysidazirine (2/55) and (S)-antazirine (2/56), which were isolated from the marine sponge Dysidea fragilis (Dysideidae, Figure 2.16) in 1988 by Ireland et al.\(^{61}\) and 1995 by Faulkner and co-workers\(^{62}\), respectively. These two compounds do not formally qualify as sphingoid bases since they are not amino alcohols. However, it is easy to envision how the aziridine ring might be formed via a 2-amino-3-keto intermediate (Scheme 2.2) similar to that formed in the sphingosine and broussonetine biosynthesis (Scheme 2.1).

\[
\begin{align*}
\text{4E-(R)-dysidazirine (2/55)} & \quad \text{(S)-antazirine (2/56)} \\
\end{align*}
\]

2.6.2 Four-membered Cyclic Derivatives

A small group of natural phytosphingosine-derived alkaloids possessing a four-membered azetidine ring have also been reported (Figure 2.18).

\[
\begin{align*}
\text{Phytosphingosine backbone} & \quad \rightarrow & \quad \text{Azetidine containing skeleton} \\
\end{align*}
\]

Scheme 2.3. Origin of the azetidine core structure.

In 1991, the penaresidins A (2/57) and B (2/58) were isolated from a Penares sponge by Kobayashi \textit{et al.} found in the waters of Okinawa.\(^{64}\) Their absolute configurations were established via \(^1\)H NMR studies on their N-acetyl O-MTPA ester derivatives and eventually confirmed by total synthesis of penaresidin B (2/57) and its stereoisomers by the same research group.\(^{65}\) Three years later, Crews \textit{et al.}
reported the isolation of another azetidine alkaloid from the related Indo-Pacific sponge *Penares sollasi* (Anconinidae, Figure 2.17). Designated as penazetidin A (2/59), it was found to exhibit potent protein kinase C inhibitory activity.\cite{66} The absolute configuration of the azetidine ring, confirmed by synthesis\cite{67}, is identical to that in the penaresidins while the stereochemistry of the side chain has not been elucidated so far. All *Penares* alkaloids show cytotoxicity against a variety of cell types including lung and colon cancer cell lines as well as antibacterial activity against Gram-positive bacteria.\cite{68}

![Penaresidin A (2/57)](image1.png) ![Penaresidin B (2/58)](image2.png) ![Penazetidin A (2/59)](image3.png)

**Figure 2.18.** The *Penares* alkaloids.

### 2.6.3 Five-membered Cyclic Derivatives

The five–membered cyclic phytosphingosine-analogues can be divided into two groups: The tetrahydrofuran derivatives with an *exo*-cyclic amino group and the pyrrolidine derivatives with *endo*-cyclic imino functionality (Scheme 2.4). This group also comprises the broussonetines with its 32 congeners (Figure 2.3).

![Scheme 2.4](image4.png)

**Scheme 2.4.** Origin of the pyrrolidine and tetrahydrofuran core structures.
In 2002, Higa et al.\textsuperscript{[70]} isolated an anhydrophytosphingosine from the marine sponge \textit{Pachastrissa pathologica} (Figure 2.19) and named it after its natural source pachastrissamine. One year later, Debitus et al.\textsuperscript{[71]} reported the isolation of two related natural products from the marine sponge \textit{Jaspis serpentina} (Figure 2.20). Designated as jaspine A (2/61) and B (2/60), jaspine B was found to be identical to pachastrissamine. Jaspine A was identified to be an oxazolidine derivative of 2/60.

Pachastrissamine was found to be a highly cytotoxic compound, especially when compared to the parent phytosphingosine, pointing to the tetrahydrofuran fragment to be the potentially relevant pharmacophore. As Génisson et al. reported jaspine B is able to trigger apoptosis in melanoma cells, likely through an increase of the intracellular ceramide levels resulting from the inhibition of sphingomyelin synthase.\textsuperscript{[73]}

Pramanicin (2/62) is an interesting sphingoid base-like pyrrolidin-2-one alkaloid isolated from the fungal fermentation culture of a \textit{Stagonospora} species by Schwartz et al. in 1994.\textsuperscript{[74]} Similar to the broussonetines, pramanicin is composed of a polar polyhydroxylated pyrrolidine head with a long nonpolar carbon side chain. However, in contrast to the broussonetines, the side chain of pramanicin is connected at C-3 of the pyrrolidinone moiety. Pramanicin was found to have antimicrobial activity and induces apoptosis in Jurkat leukaemia cells.\textsuperscript{[75]}
2.6.4 Six-membered Cyclic Derivatives

Cyclisation on the C-6 position of sphingoid bases (Scheme 2.5) is found in a large number of 2,6-disubstituted piperidine-3-ol alkaloids mainly isolated from various vegetal sources such as *Prosopis* and *Cassia* species. Together with their 1-deoxyanalogues these piperidine alkaloids form the largest group of cyclic sphingosine derivatives.

The folkloric medicinal use of the genus *Prosopis* prompted its investigation for biologically active compounds and resulted in the isolation of several new bioactive alkaloids of the 2,6-disubstituted 3-piperidinol type. In 1966 Khuong-Huu and co-workers reported the isolation of the first two piperidine-3-ol alkaloids from the legume *Prosopis africana* (Fabaceae, Figure 2.21) subsequently named prosopine (2/63) and prosopinine (2/64). In the following years the same authors isolated six further alkaloids from the roots of the same plant and termed them as prosopinine (2/65), prosophylline (2/66), isoprosopine A (2/67) and B (2/68), prosafrine (2/69) and prosafrinine (2/70) (Figure 2.22).
Prosopine, prosopinine and to a lesser extent the other Prosopis alkaloids display local anesthetic properties\textsuperscript{[80]}, as well as weak antibiotic activities\textsuperscript{[8]} and have been found to act on the central nervous system.\textsuperscript{[81]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{3-Piperidinol-Alkaloids.png}
\caption{3-Piperidinol alkaloids isolated from Prosopis africana.}
\end{figure}

The presence of 2,6-disubstituted 3-piperidinol in the leaf extracts of another Prosopis species, Prosopis juliflora, (Fabaceae, Figure 2.23) was first reported by AHMAD and co-workers in 1978.\textsuperscript{[83]} The isolated new alkaloids were named accordingly after their natural source juliflorine (\textit{2/72}), julifloricine (not shown) and julifloridine (\textit{2/71}), however, only the structure of julifloridine could be elucidated through spectroscopic data.\textsuperscript{[84]} One year later HESSE \textit{et al.} reported the structural elucidation of juliprosopine, an alkaloid also isolated from the leaves of \textit{P. juliflora}.\textsuperscript{[85]} On comparison of the published data of juliflorine with that of juliprosopine it was found that these compounds were identical (Figure 2.24).
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Spicigerine \((2/73)\), originally isolated from the leaves of *Prosopis spicigera* (Fabaceae) in 1974 by JEWERS and co-workers,\(^{[87]}\) was the first \(\omega\)-amino acid with a piperidine-3-ol moiety to be discovered. In 2005 it was also detected in the ethanolic extracts of the related legume *Prosopis cineraria* (Fabaceae, Figure 2.25) and found an unusual technological application: In their search for green alternatives to toxic chemicals SHARMA et al.\(^{[88]}\) tested spicigerine containing *P. cineraria* extracts for their effectiveness to combat corrosion of mild steel and showed that spicigerine provided good protection.

A wide variety of diastereomers, regioisomers and chain length variants of prosafrine \((2/69)\) and prosafrinine \((2/70)\) have been found in several *Cassia* and *Senna* species (Figure 2.29). Cassine \((2/74)\) was the first to be discovered in 1963 by R.J. HIGHET.\(^{[90]}\) It was isolated from the leaves and branches of *Cassia excelsia* (Fabaceae) and later found in many related species of the Fabaceae family such as *Prosopis ruscifolia* and *Senna racemosa*.\(^{[91]}\) Antimicrobial screening of cassine revealed its inhibitory activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans* in micromolar concentrations. In 1966 LYTHGOE and VERNENGO isolated cassine again this time together with its C-11’ hydroxy analogue \(2/75\) from the leaves of *Cassia carnavaal* (Figure 2.26) consequently named carnavaline after its natural source.\(^{[92]}\)
Ten years later WELTER et al. isolated the alkaloids spectaline (2/76) and spectalinine (2/77) for the first time from the leaves and seeds of Cassia spectabilis (Fabaceae, Figure 2.27) accompanied by cassine (2/74) and carnavaline (2/75) as well as their C-6 epimers, iso-6-cassine and iso-6-carnavaline (not shown). Spectaline and spectalinine showed moderate cytotoxicity in the Vero monkey and Chinese hamster ovary cell cytotoxicity assays. Additional investigation of the alkaloidal constituents of the flowers and green fruits of C. spectabilis by BOLZANI et al. in 2004 yielded three further piperidine alkaloids: 7-hydroxy-spectaline (2/78), 3-O-acetyl-spectaline and iso-6-spectaline (not shown).

In 1995 KINGSTON and co-workers discovered three new piperidine alkaloids, leptophyllin A (2/79), 3-O-acetyl-leptophyllin A and leptophyllin B (not shown) via the bioassay-guided fractionation of the leaf extract of Cassia leptophylla (Fabaceae, Figure 2.28). Other constituents of C. leptophylla included the four already known piperidine-3-ols spectaline (2/76), spectalinine (2/77), carnavaline (2/75) and iso-6-carnavaline. 2/75, 2/77, 2/76 and its 3-O-acetyl derivative showed DNA-damaging properties in biological activity tests using a mutant yeast assay.
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The roots of the White Mulberry, *Morus alba* (Moraceae) have been known for a long time as a source for various polyhydroxylated pyrrolidine and piperidine alkaloids such as D-RB1 (1/62), moranoline (1/8), and fagomine (1/7). In the course of their studies on the biologically active constituents of Moraceae species, KUSANO *et al.*[98] also examined the components of the white ripened fruits of *M. alba* grown in Turkey (Figure 2.30). Their investigations afforded six new nortropane alkaloids (see Chapter 1, Figure 1.74) along with six new ω-amino acids designated as morusimic acids A – F (2/80 – 2/85, Figure 2.31). The morusimic acids C – F also feature the 2,6-disubstituted piperidine-3-ol moiety, characteristic for the related *Cassia* and *Prosopis* alkaloids, which classifies them as cyclic sphingosine analogues. In fact, morusimic acid E (2/84) possesses the same stereochemical configuration at C-2 and C-3 as it is found in natural sphingosine (2/29). The structures of morusimic acids A (2/80) and B (2/81) (B being the aglycon of A), however, differ in the ring size and the position of the hydroxy group. It is assumed that the pyrrolidine ring originates from ring contraction of the piperidine-3-ol moiety followed by a rearrangement with the hydroxy group being shifted to the C-2 side arm[100].

Figure 2.29 cont’d. Piperidine-3-ol alkaloids isolated from *Cassia* and *Senna* species.

![Figure 2.29](image)

![Figure 2.30](image)

Figure 2.30. Ripened fruits of the White Mulberry, *Morus alba* (Moraceae).

Figure 2.31. The morusimic acids A – F.
KUSANO and co-workers also tested the morusimic acids for α-glucosidase inhibition but none of them showed inhibitory activity. Then again, this result was not very surprising since these compounds lack the required polyhydroxylated ring structure present in iminosugars like the broussonetines (Figure 2.3) and the moranolines (see Chapter 1, Figure 1.8).[98]

2,6-Disubstituted piperidine-3-ol alkaloids with polyenic side chains are also known (Figure 2.33). The first two discovered were cryptophorine (2/86) and cryptophorinine (2/87), isolated from the leaves of the Madagascan buckthorn Bathiorhamnus cryptophorus (Rhamnaceae) in 1974 by BRUNETON and CAVÉ.[101] Ten years later micropine (2/88) was detected as the major alkaloidal component in the ethanolic leaf extract of Microcos philippinensis (Tiliaceae).[102] This extract showed antimicrobial activity against several pathogenic bacteria strains including Staphylococcus aureus (“golden staph”), Streptococcus pyogenes and Pseudomonas aeruginosa.

The traditional use of essences from the related shrub Microcos paniculata (Tiliaceae, Figure 2.32) in the control of head lice prompted a study on their insecticidal activity. Both the dichloromethane and methanol extracts of M. paniculata stem bark showed toxic and growth-inhibitory effects on the second instar larvae of the mosquito Aedes aegyptii. This led to the isolation of microconine (2/89) in 1998 by KUMAR and co-workers as the biologically active ingredient.[104]
Structurally related are the corydendramines A (2/90) and B (2/91) which were isolated in 2000 from the marine hydroid Corydendrium parasiticum (Clavidae) by Lindquist et al.\cite{105} These compounds were found to act as feeding deterrents from potential hydroid predators.

Diamine analogues of the piperidin-3-ol alkaloids have been isolated from the sponges Pseudodistoma kanoko and Pseudodistoma megalarva (Pseudodistomidae, Figure 2.34). Members of this alkaloid family, accordingly designated as pseudodistomins A – F (2/92 – 2/97), vary in the stereochemical configuration of the piperidine moiety, the length of the side chain as well as the number and position of the double bonds (Figure 2.35). Some have been found to be cytotoxic against murine lymphoma cells, which makes them interesting antitumor candidates, however, others were found to cause DNA damage in cell culture.\cite{107–109}

![Figure 2.34](image)

The sponge Pseudodistoma megalarva (Pseudodistomidae).

![Figure 2.35](image)

The pseudodistomins.

2.6.5 Bicyclic Derivatives

In addition to the monocyclic piperidine derivatives there are also bicyclic sphingoid base analogues known with quinolizidine and decahydroquinoline moieties. The bicyclic structures hereby originate from the fusion of the piperidine ring with parts of the side chain either
directly to the nitrogen atom forming the quinolizidine system of pictamine and the clave-
pictines (Figure 2.37), or the α-position next to the N-atom affording the decahydroquinoline skeleton of the lepadins (Figures 2.39 and 2.41).

Independent investigations of the constituents of the marine tunicate *Clavelina picta* (Figure 2.36) by FAULKNER et al. as well as CARDELLINA and co-workers in 1991 yielded the quinolizidine alkaloids pictamine (2/98) and its side chain homologues clavepictine A (2/99) and B (2/100) as first members of this group (Figure 2.37). Clavepictines A and B have been found to inhibit growth of murine leukaemia and human solid tumour cell lines at concentrations less than 9 µg/mL and effectively kill each cell line at less than 25 µg/mL.[111, 112]

The lepadins are further examples of bicyclic sphingoid base-like compounds. This alkaloid family comprises eight members all of which possess a cis-decahydroquinoline (cis-1-azadecaline) core structure. First congeners of this family, the lepadins A – C (Figure 2.39), were isolated from the predatory flatworm *Prostheceraeus villatus* and its tunicate prey *Clavelina lepadiformis* (Figure 2.38) by STEFFAN[114] in 1991 as well as ANDERSEN and co-workers[115] in 1995. Lepadins A (2/101) and B (2/102)
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exhibit significant \textit{in vitro} cytotoxicity against human cancer cell lines whereas lepadin C (2/103) was inactive.

![Figure 2.39. cis-Decahydroquinoline alkaloids isolated from \textit{Clavelina lepadiformis}.](image)

In 2002, WRIGHT \textit{et al.}\textsuperscript{[116]} reported the discovery and characterisation of three further \textit{cis}-decahydroquinoline alkaloids from a tunicate species, belonging to the genus \textit{Didemnum}, that were structurally related to the lepadins found in \textit{C. lepadiformis} and therefore named lepadins D – F (2/104 – 2/106). Biological activity assays performed by the same research group showed that all compounds exhibit antiplasmodial and antitypanosomal properties with lepadins E (2/105) and F (2/106) being the most potent.\textsuperscript{[116]}

Examinations of the Great Barrier Reef ascidian \textit{Aplidium tabascum} by CARROLL \textit{et al.} in 2002 resulted in the isolation of two new \textit{cis}-decahydroquinoline alkaloids, the lepadins G (2/107) and H (2/108), together with the already known lepadin F. Lepadins E – G differ from the earlier discovered lepadins A – D in that they all incorporate a fully saturated 5'-hydroxyoctyl side chain attached at C-5, an unsaturated C\textsubscript{8} ester moiety attached to C-3, and display opposite stereochemistry at C-3 and C-5. Lepadins G and H are epimers at C-2 (Figure 2.41).\textsuperscript{[118]}
Figure 2.41. cis-Decahydroquinoline alkaloids isolated from Didemnum sp. and Aplidium tabascum.
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2.7 Summary

The broussonetines are novel pyrroline and pyrrolidine alkaloids isolated from the Japanese Paper Mulberry, *Broussonetia kazinoki*. Their polyhydroxylated head moiety classifies them as derivatives of the known iminosugars DIL, D-AB1, DMDP, and as such, they exhibit remarkable \( \beta \)-glycosidase inhibitory activity. Furthermore, their principal C\(_{18}\) skeleton composed of a polar head and a nonpolar lipophilic tail biosynthetically also relates them to the sphingoid bases and their cyclic derivatives such as the jaspines, penaresidins, and the 2,6-disubstituted 3-piperidinol alkaloids isolated from various *Cassia* and *Prosopis* species as well as the morusimic acids. Together with the batzellasides, the broussonetines form the intersection between the polyhydroxylated alkaloids and the cyclic sphingosine derivatives (Figure 2.42).

![Figure 2.42. The broussonetines as intersection of cyclic sphingoid base-like and polyhydroxylated alkaloids.](image-url)
Keratinocytes are the predominant cell type in the epidermis, the outermost layer of the human skin, constituting 95% of the cells found there. The primary function of keratinocytes is the formation of a barrier against environmental damage such as pathogens (bacteria, fungi, parasites, viruses), heat, UV radiation and water loss. A number of structural proteins (filaggrin, keratin), enzymes (proteases), lipids and antimicrobial peptides (defensins) contribute to maintain the important barrier function of the skin. Once pathogens start to invade the upper layers of the epidermis, keratinocytes can react with the production of proinflammatory mediators and in particular chemokines which attract leukocytes to the site of pathogen invasion. Keratinisation is part of the physical barrier formation cornification, in which the keratinocytes produce more and more keratin and eventually undergo programmed cell death. The fully cornified keratinocytes that form the outermost layer are constantly shed off and replaced by new cells. The average renewal/turnover time for the epidermis is 21 days.\textsuperscript{[119]}
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2.9 References


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[89] URL: [http://farm1.static.flickr.com/174/392134006_3b8e328409.jpg](http://farm1.static.flickr.com/174/392134006_3b8e328409.jpg) ([Cassia carnava](http://farm1.static.flickr.com/174/392134006_3b8e328409.jpg)l) [17/08/2012]


[93] URL: [http://www.sunshine-seeds.de/thumbs/senna_spectabilis.jpg](http://www.sunshine-seeds.de/thumbs/senna_spectabilis.jpg) ([Cassia spectabilis](http://www.sunshine-seeds.de/thumbs/senna_spectabilis.jpg)) [17/08/2012]


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[113] URL: http://www.habitas.org.uk/marinelife/tunicata/clalep.jpg (*Clavelina lepadiformis*) [17/08/2012]


Chapter 3. Syntheses of the Broussonetines

3.1 Introduction

Although the first publications about the isolation and structure elucidation of the broussonetines by KUSANO et al. date back to 1997,\(^1\) synthetic activity in the field of these alkaloids has been very scarce until recently. Indeed, until 2009 only three total syntheses for broussonetines C and G had been published. The first total synthesis of a member of the broussonetine family in enantiopure form was carried out in 1999 by YODA and co-workers, who prepared broussonetine C from D-tartaric acid as the chiral starting material.\(^2\) Four years later, a second total synthesis of broussonetine C was reported by PERLMUTTER et al., once again with a member of the chiral pool, D-arabinose, as the starting material.\(^3\) In the same year, the third and for a long time last total synthesis has been reported by TROST and co-workers, who synthesised broussonetine G by means of a palladium-based asymmetric catalytic procedure.\(^4\) Then, after a six years hiatus, CARDA et al. published their convergent syntheses of broussonetines C, D, M, O, and P in 2009 based on the cross-metathesis reaction of various side chain fragments with a common pyrrolidine building block derived from the amino acid D-serine.\(^5, 6\) At about the same time Indian PhD student K.A. DURUGKAR investigated the convergent syntheses of broussonetines C and G in a similar approach also by means of a olefin metathesis cross-coupling of side chain olefins with two different pyrrolidine building blocks derived from L-sorbose.\(^7\) Finally, in 2011, CHIDA et al. reported the first total synthesis of broussonetine F starting from diethyl L-tartrate and employing an orthoamide Overman rearrangement as a cornerstone in their synthesis.\(^8\) In addition, BRIMBLE and co-workers, being interested in the stereoselective synthesis of spiroketal compounds, reported a synthesis for the side chain fragment of broussonetine H in 2003.\(^9\) These syntheses will be reviewed in the following sections.

3.2 The First Total Synthesis of Broussonetine C by YODA et al.

The first total synthesis of broussonetine C was reported by the Japanese research group of Hidemi YODA in 1999 as part of their program to synthesise various polyhydroxylated alkaloids employing the C2-symmetric imide 3/1 as key intermediate (Figure 3.1).\(^2, 10–12\)
Figure 3.1. YODA’s C₂-symmetric imide 3/1 as key intermediate in the syntheses of various polyhydroxylated alkaloids.

Thus, TIPS-protected imide 3/1, obtained in two steps from D-tartaric acid, was treated with 10-undecenylmagnesium bromide at ambient temperature as the side chain introducing step to give a tertiary γ-hydroxylactam intermediate, which subsequently underwent BF₃-etherate-promoted reductive deoxygenation with triethylsilane, leading to the trans-substituted lactam 3/3 in 96% de. After oxidative cleavage of the terminal double bond in 3/3 the resulting aldehyde 3/4 was coupled with benzyloxypropylmagnesium bromide to give the secondary alcohol 3/5 which was consequently oxidised to the ketone 3/6 with pyridinium chlorochromate. This was followed by a series of transprotection reactions which finally led to the N-Boc-bis-O-benzyl-protected lactam 3/8. Vinylimagnesium bromide addition to 3/8 and subsequent reduction of the intermediate labile tertiary α-hydroxy-pyrrolidine with NaBH₄ in the presence of CeCl₃ provided the ring-opened product 3/9 as a single diastereomer with the desired (S)-configuration at the newly formed stereocentre. Mesylation of the secondary hydroxy group followed by a SN₂-cyclisation reaction gave the tetrasubstituted pyrrolidine 3/10 with the requisite all-trans-configuration. The double bond in 3/10 was transformed via the three-step sequence (1) dihydroxylation, (2) oxidative cleavage, and (3) reduction into the primary alcohol 3/11. Finally, a two-step deprotection procedure completed the total synthesis giving broussonetine C in 9.2% yield over 22 steps from D-tartaric acid (Scheme 3.1).[2]
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Scheme 3.1. First total synthesis of broussonetine C by YODA et al. (1999).

Reagents and conditions: (a) PMBNH₂, xylene, reflux; (b) TIPSCI, imidazole, DMF, 43% over 2 steps; (c) undec-10-enylmagnesium bromide, THF, rt; (d) Et₃SiH, BF₃·Et₂O, DCM, -78 °C to -50 °C, 96% de, 83% over 2 steps; (e) OsO₄, NMO, acetone-H₂O (1 : 1), 99%; (f) NaIO₄, Et₂O-H₂O (1 : 1); (g) benzylloxypropylmagnesium bromide, THF, 0 °C, 85% over 2 steps; (h) PCC, DCM, MS 4Å, 90%; (i) TBAF, THF, 92%, (j) BnBr, Ag₂O, EtOAc, 100%; (k) CAN, MeCN, 70%; (l) Et(OH)$_2$, cat. PTSA, benzene, reflux, 96%; (m) Boc$_2$O, Et$_3$N, DMAP, DCM, 100%; (n) vinylmagnesium bromide, THF, -78 °C; (o) NaBH₄-CeCl₃, MeOH, -45 °C, 78% over 2 steps; (p) MsCl, Et$_3$N, DCM; (q) t-BuOK, THF, 92% over 2 steps; (r) OsO₄, NMO, acetone-H₂O (1 : 1), 100%; (s) NaIO₄, Et₂O-H₂O (1 : 1); (t) NaBH₄, MeOH, 92% over 2 steps; (u) Pd black, 4.4% HCOOH-MeOH; (v) conc. HCl, EtOAc, 83% over 2 steps; 9.2% yield over 22 steps from d-tartaric acid, 21.3% yield over 20 steps from C₂-symmetric imide 3/1.
3.3 The Second Total Synthesis of Broussonetine C by Perlmutter et al.

In 2003, Patrick Perlmutter and Filisaty Vounatsos from Monash University reported a second total synthesis for broussonetine C, this time D-arabinose served as the chiral pool starting material. Comparable to Yoda’s approach this linear synthesis also employed 10-undecenylmagnesium bromide as the side chain introducing reagent. As the Grignard coupling partner previously reported 2,3-di-O-benzyl-5-O-(tert-butyldimethylsilyl)-D-arabinose \((3/13)\) was chosen. The latter was prepared in six steps from the commercially available sugar in 49% overall yield.\(^{[13, 3]}\) Addition of 10-undecenylmagnesium bromide to \(3/13\) provided the alcohol \(3/14\) with less than 5% of its chromatographically separable diastereoisomer. Trans-protection of the terminal TBS ether into the corresponding benzylidene acetal gave compound \(3/15\) with the hydroxy group at C-5 being the only one left unprotected. Introduction of nitrogen at this position was effected via mesyl-activation of the hydroxy group and subsequent treatment of the mesylate with NaN\(_3\) under inversion of the stereochemistry at C-5 providing the azide \(3/16\) as a single isomer. This was followed by a regioselective Lewis-acid promoted ring-opening reaction of the benzylidene acetal to afford the tris-O-benzyl-protected tetraol \(3/17\). To obtain the requisite \(\text{all-}(R)\)-stereochemistry in the pyrrolidine ring later on, the configuration of the stereocentre at C-2 in \(3/18\) had to be inverted which was achieved employing Mitsunobu conditions. The subsequent Staudinger reduction of the azide moiety under neutral conditions gave the free amine which was Boc-protected providing carbamate \(3/19\) as the pivotal cyclisation precursor. As in Yoda’s synthesis an intramolecular S\(_N\)2-cyclisation reaction with concomitant inversion at C-2 was achieved by treatment of the mesyl-activated alcohol with potassium tert-butoxide to give the pyrrolidine \(3/19\) in which all the stereocentres had the required \((R)\)-configuration of the natural product. In the final steps of the synthesis the terminal double bond was dihydroxylated followed by the oxidative cleavage of the diol to yield the aldehyde \(3/20\). This aldehyde was then treated with benzoyloxypropylmagnesium bromide and the resulting mixture of diastereomeric alcohols was oxidised to the corresponding ketone \(3/21\) using Dess-Martin periodinane. Completion of the synthesis was achieved by hydrogenolysis of the benzyl ethers over palladium on carbon under an atmosphere of hydrogen, followed by acidic hydrolysis of the Boc protecting group to give broussonetine C in 1.7% yield over 24 steps from D-arabinose (Scheme 3.2).\(^{[3]}\)
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Scheme 3.2. Second total synthesis of broussonetine C by PERLMUTTER et al. (2003).

Reagents and conditions: (a) EtSH, conc. HCl, 80%; (b) 2,2-dimethoxypropane, cat. PPTS, acetone, 81%; (c) NaH, BnBr, TBAI, THF, 100%; (d) TFA-THF-H₂O (1 : 2 : 1), 88%; (e) TBSCl, imidazole, DMF, rt, 87%; (f) HgO, HgCl₂, acetone-H₂O (10 : 1), 60 °C; (g) undecenylmagnesium bromide, THF, rt, 80% over 2 steps; (h) HCl (2 M in MeOH), 0 °C, 86%; (i) benzaldehyde dimethyl acetal, cat. PTSA, DCM, -20 °C to rt, 70%; (j) MsCl, Et₃N, DCM, 0 °C to rt; (k) NaN₃, DMF, 60 °C, 80% over 2 steps; (l) AlCl₃, BH₃·NMe₃, THF, 0 °C to rt, 89%; (m) DEAD, Ph₃P, p-nitrobenzoic acid, THF, rt, 88%; (n) Ph₂P, THF-H₂O (10 : 1), 60 °C, 85%; (o) NaOH, MeOH, rt, 76%; (p) Boc₂O, Et₃N, THF, 0 °C to rt, 80%; (q) MsCl, Et₃N, DCM, 0 °C to rt; (r) t-BuOK, THF, 0 °C to rt, 93% over 2 steps; (s) K₂OsO₄·2 H₂O, NMO, acetone-H₂O (1 : 1), rt; (t) NaIO₄, Et₂O-H₂O (1 : 1), rt, 88% over 2 steps; (u) benzoxypropylmagnesium bromide, THF, 0 °C to rt, 70%; (v) Dess-Martin periodiniane, DCM, 0 °C to rt, 90%; (w) Pd/C, 5% AcOH in MeOH, H₂, rt, 70%; (x) TFA, DCM, 0 °C, 60%; 1.7% yield over 24 steps from D-arabinose.
3.4 Enantioselective Total Synthesis of Broussonetine G by TROST et al.

TROST’s synthesis of broussonetine G in 2003 was the first convergent non-linear synthetic approach for a broussonetine congener. It also stands out as the only non-chiral pool broussonetine synthesis to date in which most stereocentres were established via asymmetric transition metal-catalysed reactions. Key step of TROST’s synthesis was the palladium-catalysed asymmetric allylic alkylation reaction (Pd AAA) of racemic butadiene monoxide with two different nitrogen nucleophiles (Scheme 3.3). This Pd-catalysed reaction works as a dynamic kinetic asymmetric transformation (DYKAT) in which deracemisation of the starting material is achieved to result in an enantiomerically enriched product. DYKAT reactions differ from traditional kinetic asymmetric reactions in that both enantiomers of the racemic starting material are converted into a single chiral product, hence allowing potential yields of 100% of a particular enantiomer as opposed to only 50% for a traditional kinetic resolution process.[14]

\[ \text{Scheme 3.3. Construction of the pyrroline precursor via two DYKAT reactions.} \]

The synthesis of broussonetine G began with the assembly of the side chain fragment via the addition of 1-pentyne to δ-valerolactone, followed by protection of the primary alcohol as a trityl ether to give the alkynone 3/22. Reduction of 3/22 by applying Noyori’s enantioselective transfer hydrogenation protocol yielded the secondary propargyl alcohol 3/23 in 96% ee. After performing the alkyne zipper reaction (KH, 1,3-diaminopropane) on 3/23 and protection of the secondary alcohol as a THP ether the now terminal alkyne 3/24 was alkylated with ethyleneoxide providing the desired homopropargyl alcohol. After acid-catalysed global deprotection, the resulting triol 3/25 underwent the requisite regioselective palladium-catalysed spiroketalisation reaction affording the desired 5,6-spiroketal 3/26 with excellent diastereoselectivity (d.r. 97 : 3). The high stereoselectivity of this cyclisation was attributed to the anomeric effect. Consequent substitution of the primary hydroxy group in 3/26 with bromine concluded the synthesis of the side chain building block (Scheme 3.4).[4]
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Scheme 3.4. Synthesis of the spiroketal side chain fragment for broussonetine G.

Reagents and conditions: (a) n-BuLi, 1-pentyne, THF, -78 °C to rt, 94%; (b) TrCl, Et₃N, DMAP, DMF, rt, 77%; (c) (R,R)-3/28 (3 mol%), t-PrOH, rt, 91%, 96% ee; (d) KH (10 equiv), 1,3-diaminopropane, THF, 79%; (e) DHP, PPTS, DCM, rt, 76%; (f) n-BuLi, AlMe₃, BF₃·OEt₂, Et₂O, -78 °C, then ethylene oxide, -78 °C to rt, 76%; (g) 1% HCl in MeOH, 95%; (h) [PdCl₂(PhCN)₂] (2 mol%), MeCN-THF (3 : 2), 85%, d.r. 97 : 3; (i) PPh₃Br₂, imidazole, THF, 91%; 21.4% over 9 steps from δ-valerolactone.

The synthesis of the pyrroline building block began with the palladium-catalysed asymmetric addition of phthalimide to butadiene monoxide (2-vinyloxirane, 3/29) (DYKAT reaction I) providing the imido alcohol 3/30 in a highly regio- and enantioselective fashion (98% ee). After cleavage of the imide the liberated 1,2-amino alcohol was protected as a cyclic carbamate with triphosgene to give the vinyloxazolidinone 3/31. This compound served as the substrate for the second Pd AAA (DYKAT reaction II) which furnished the desired diene 3/32 with excellent diastereoselectivity (d.r. 93 : 7). Protection of the homoallylic alcohol in 3/32 as a benzyl ether, followed by a ring-closing metathesis reaction with Grubbs' second-generation catalyst provided the 2,5-dihydropyrrole 3/33 which after saponification of the oxazolidinone moiety and protection of the resulting amine as a Cbz-carbamate gave the primary alcohol 3/34. Subsequent oxidation of the alcohol with Dess-Martin periodinane delivered the aldehyde 3/35 which was the originally aspired coupling partner with the side chain fragment 3/27 (Scheme 3.5).[4]
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Scheme 3.5. Synthesis of the pyrroline aldehyde 3/35 as the originally considered building block (TROST et al. 2003).

Reagents and conditions: (a) phthalimide, [(C$_3$H$_5$)PdCl]$_2$ (0.4 mol%), (R,R)-3/36 (1.2 mol%), Na$_2$CO$_3$, DCM, rt, 94%, 98% ee; (b) ethylenediamine, EtOH, reflux, 84%; (c) triphosgene, NaHCO$_3$, toluene-H$_2$O, 0 ºC, 85%; (d) butadiene monoxide, [Pd$_2$(dba)$_3$] · CHCl$_3$ (0.25 mol%), (R,R)-3/36 (0.75 mol%), DBU (1 mol%), DCM, rt, 91%, d.r. 93 : 7; (e) NaH, BnBr, TBAI, THF, rt, 84%; (f) Grubbs’ 2nd generation catalyst (1.2 mol%), DCM, reflux, 87%; (g) NaOH, EtOH-H$_2$O (3 : 1), reflux; (h) CbzCl, NaHCO$_3$, Na$_2$CO$_3$, H$_2$O, 0 ºC to rt, 99% over 2 steps; (i) Dess-Martin periodinane, DCM, 0 ºC, 95%.

However, several attempts of TROST et al. to couple the side chain building block 3/27 under various conditions with this aldehyde always resulted in very poor yields and a disappointing 1 : 1 diastereomeric ratio of alcohols. The failure of the coupling reaction therefore led to an alternate strategy (Scheme 3.6).

TEMPO-catalysed oxidation of the alcohol 3/34 led to a carboxylic acid which was converted into the Weinreb amide 3/37. The subsequent coupling of this amide with the Grignard reagent derived from the bromide 3/27 led to a ketone which was diastereoselectively reduced with DIBAl-H to give a 4.3 : 1 diastereomeric mixture of alcohols, the major diastereomer bearing the desired (R)-configuration for the natural product (established by $^1$H NMR analysis of the (R)- and (S)-O-methylmandelates of 3/38). Epoxidation of the dihydropyrrole 3/38 led to a mixture of epoxides, both of which gave the same triol 3/39 as a single diastereomer upon hydrolysis with aqueous TFA. Removal of all protecting groups by palladium-catalysed hydrogenolysis concluded the synthesis of broussonetine G over a total of 24 steps in 0.95% overall yield from commercially available starting materials with the longest linear sequence being 15 steps.$^{[4]}$
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Scheme 3.6. Conclusion of the synthesis of broussonetine G by Trost et al. (2003).

Reagents and conditions: (a) TEMPO, NaOCl, NaHCO$_3$, KBr, acetone-H$_2$O, 0°C, 89%; (b) HNMe(OMe) · HCl, PyBOP, i-Pr$_2$NEt, DCM, 81%; (c) 1. 3/27 (1.2 equiv), Mg, THF, reflux to rt, 2. 3/37, rt, 65%; (d) DIBAL-H, Et$_2$O, 0°C, 76%, d.r. 81 : 19; (e) 1,1,1-trifluoroacetone, oxone, Na$_2$CO$_3$, MeCN-H$_2$O, 0°C, 68%; (f) TFA, THF-H$_2$O, 65°C, 73%; (g) Pd/C, MeOH, HCl, H$_2$ (1 atm), rt, 95%, 5.6% yield over 15 steps from butadiene monoxide.

3.5 Convergent, Stereoselective Syntheses of Broussonetines C, D, M, O and P by CARDA et al.

CARDA et al. were the first to synthesise several broussonetines from a common pyrrolidine building block via cross-metathesis reactions with different side chain fragments. As chiral starting material for their pyrrolidine core structure CARDA and co-workers used Garner’s (R)-aldehyde (3/41) which in turn was synthesised in four steps from the amino acid D-serine according to an improved, high-yielding route by Taylor et al.$^{[15]}$ Garner’s (R)-aldehyde (3/41) was then transformed into the known Weinreb amide 3/43 in four further steps including an (E)-selective Wittig reaction followed by an asymmetric dihydroxylation using Sharpless’ AD-mix-β to introduce the two secondary alcohol groups of the forthcoming pyrrolidine ring.$^{[16]}$ A Grignard reaction of the Weinreb amide 3/43 with 3-butenylmagnesium bromide afforded a ketone, which was then stereoselectively reduced with L-selectride to give the secondary alcohol 3/44. Mesylation of 3/44 followed by acid treatment of the intermediate mesylate provided the pyrrolidine 3/45 in a one-pot reaction which encompassed three transformations: successive cleavage of the Boc and acetonide protecting groups.
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followed by intramolecular nucleophilic ring-closure with inversion of the stereochemistry to form the pyrrolidine moiety of the natural products. In the final step the pyrrolidine 3/45 was converted into the less polar oxazolidinone 3/46 with carbodiimazole to give the imminent coupling partner in the subsequent cross-metathesis reactions (Scheme 3.7).\[5]\n
![Diagram of the pyrrolidine building block 3/46 synthesis](image)

**Scheme 3.7.** Synthesis of the pyrrolidine building block 3/46 (CARDA et al. 2009).

Reagents and conditions: (a) Boc₂O, aq. NaOH, dioxane, 0 °C to rt; (b) HNMe(OMe) · HCl, EDCI, NMM, DCM, -15 °C; (c) 2,2-DMOP, acetone, BF₃ · OEt₂, rt, 88% over 3 steps; (d) LiAlH₄, THF, 0 °C, 100%; (e) Ph₃P=CHCO₂Et, THF, reflux, 90%; (f) AD-mix-β, CH₃SO₂NH₂, t-BuOH/H₂O, 0 °C, 93%; (g) Ag₂O, BnBr, Et₂O, rt, 89%; (h) HNMe(OMe) · HCl, t-PrMgCl, THF, -20 °C to -10 °C, 96%; (i) 3-butenylMgBr, THF, 0 °C, 97%; (j) L-selectride, -78 °C, 85%, d.r. > 95 : 5; (k) MsCl, Et₃N, DCM, 0 °C; (l) TFA, DCM, 0 °C, 73% over 2 steps; (m) CDI, DMAP, toluene, reflux, 94%; 35.6% yield over 13 steps from D-serine.

The side chain fragments for broussonetines C, D, O and P were prepared via standard methods as shown in Schemes 3.8 and 3.9. Thus, Weinreb amides 3/47 and 3/50, prepared from γ-butyrolactone and δ-valerolactone, respectively, were first O-silylated and then allowed to react with alkenyllithium reagents, obtained in turn via halogen-lithium exchange of the corresponding bromides. This gave the ketones 3/49 (R = TPS, fragment for broussonetines C and O), 3/53 (R = TBPDS, fragment for broussonetine D) and 3/54 (R = TPS, fragment for broussonetine P) as appropriate coupling partners with the pyrrolidine moiety 3/46 in the following cross-metathesis reactions.\[5, 6\]
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Reagents and conditions: (a) Me₂AlCl, HNMe(OMe) · HCl, DCM, 0 °C to rt; (b) TPSCI, imidazole, DMF, rt, 90% over 2 steps; (c) t-BuLi, 7-bromo-heptene, THF, -78 °C to rt, 80%; 72% over 3 steps from γ-butyrolactone.


Reagents and conditions: (a) AlMe₃, HNMe(OMe) · HCl, DCM, 0 °C to rt, 91.5%; (b) TBDPSCI, imidazole, DMF, rt, 85%; (c) TPSCI, imidazole, DMF, rt, 90%; (d) t-BuLi, 6-bromo-hexene, THF, -78 °C to rt, 80%; 62.2 % over 3 steps from δ-valerolactone for R = TBDPS, 65.9% for R = TPS.


Reagents and conditions: (a) NaH, TBSCl, THF, 45%; (b) (COCl)₂, DMSO, Et₃N, DCM, -78 °C to rt; (c) allylMgBr, (+)-DIP-Cl, Et₂O, -78 °C, 92% ee, 76% over 2 steps; (d) 9-BBN, THF, 0 °C to rt, then MeOH, 6 M NaOH, 30% H₂O₂, 0 °C to 50 °C, 85%; (e) NaH, BnBr, TBAI, 0 °C to reflux, 84%; (f) TBAF, THF, rt, 85%; (g) Dess-Martin periodinane, DCM, rt; (h) Ph₃PMeBr, n-BuLi, THF, rt to -78 °C to rt, 65% over 2 steps; 13.5% yield over 8 steps from 1,7-heptanediol.
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As for the side chain fragment of broussonetine M, applying Brown’s asymmetric allylation procedure to the aldehyde $3/55$ furnished the homoallyl alcohol $3/56$ in $92\%$ ee. Hydroboration-oxidation of the terminal olefinic bond, benzylation of the two hydroxy groups and desilylation provided the primary alcohol $3/57$, which was subsequently oxidised with Dess-Martin periodinane to the aldehyde $3/58$. Wittig olefination of the latter finally afforded the terminal alkene $3/59$ (Scheme 3.10).\(^5\)

Cross-metathesis reactions of the pyrrolidine building block $3/46$ with the relevant side chain fragment in the presence of Grubbs’ second generation catalyst under microwave irradiation afforded the respective coupling products in acceptable yields ($60\%$ - $62\%$) and $4 : 1$ $\left(E\right)\left/Z\right.$-selectivity together with the homodimers of the initial olefins (not shown in Scheme 3.11).

Scheme 3.11. Final steps in the syntheses of broussonetines C, D and M by CARDA et al. (2009).

Reagents and conditions: (a) 10 mol% Grubbs’ 2nd generation catalyst, DCM, MW irradiation, 100 ºC, 60% for C and D, 62% for M, $\left(\left(E\right) : \left(Z\right) = 4 : 1\right.$; (b) NaOH, EtOH, reflux; (c) 10 mol% Pd/C, H$_2$, 6 M HCl, MeOH, rt, 66% over 2 steps for C, 68% for D, 70% for M.
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Without separating the olefinic \((E)/(Z)\)-isomers, the precursors for broussonetines C, D and M were directly subjected to alkaline hydrolytic conditions, which caused cleavage of both the oxazolidinone ring and silyl groups, followed by catalytic hydrogenation/hydrogenolysis in acidic medium. This affected simultaneous saturation of the olefinic double bond and cleavage of the benzyl groups to yield the respective broussonetines (Scheme 3.11).\cite{5,6}

As for the preparation of broussonetines O and P, the isolation of the pure \((E)\)-olefins was necessary. This required lengthy and repeated chromatographic separation of the \((E)/(Z)\)-mixtures after cleavage of the cyclic carbamate and silyl groups with ethanolic NaOH to obtain reasonably pure \((E)\)-isomers. Finally, cleavage of the two benzyl ethers in the latter compounds was achieved through their treatment with BCl\(_3\) at low temperature affording broussonetines O and P in 12.2\%\(^a\) and 14.0\%\(^c\) yield over 12 steps from Garner’s \((R)\)-aldehyde, respectively (Scheme 3.12).\cite{6}

\begin{align*}
\text{Broussonetine O} \\
\text{Broussonetine P}
\end{align*}

\textbf{Scheme 3.12.} Final steps in the syntheses of broussonetines O and P by CARDA et al. (2009).
Reagents and conditions: (a) 10 mol\% Grubbs’ 2\textsuperscript{nd} generation catalyst, DCM, MW irradiation, 100 °C, 60\%, \((E) : (Z) = 4 : 1\); (b) NaOH, EtOH, reflux, 72\% (c) chromatographic isomer separation\(^a\), then BCl\(_3\), DCM -78 °C, 70\% for O, 80\% for P.

\footnote{CARDA et al. did not give a yield for their separation efforts, they only mentioned that they obtained a fraction that was reasonably pure for further reactions. The real overall yield for broussonetines O and P is therefore considerably lower than the calculated overall yield that results just from the chemical transformations.}
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3.6 Second Total Synthesis of Broussonetine G and Attempted Synthesis of Broussonetine C by DURUGKAR

In 2010, excerpts of the PhD thesis of Kulbhushan A. DURUGKAR‡ from the National Chemical Laboratory in Pune, India were published online describing his total synthesis of broussonetine G as well as his affords to obtain broussonetine C via a cross-metathesis approach similar to the work of CARDA et al. As a starting point for his syntheses DURUGKAR used the pyrrolidine alkaloid DMDP and converted it into the diverse pyrrolidine building blocks 3/67, 3/79 and 3/82 (Schemes 3.13, 3.17 and 3.18). The DMDP, however, was not isolated from natural sources but synthesised employing the protocol of HITZ and CARD, one of the first reported syntheses of DMDP.[17] Therefore, DURUGKAR’s synthetic approach can essentially be divided into four stages: 1. Synthesis of DMDP from L-sorbose; 2. Conversion of DMDP into the fully protected pyrrolidine olefins 3/67, 3/79 and 3/82; 3. Synthesis of the respective side chain olefins 3/74 and 3/78; and 4. Coupling of the two olefinic building blocks via a cross-metathesis reaction.[7]

According to the protocol of HITZ and CARD, L-sorbose was first converted into the tosylate 3/60 in two low-yielding steps. After acetylation of the two remaining hydroxyl groups the tosyl group was substituted with the azide group under inversion of the stereochemistry at C-5 giving compound 3/61 in 56% yield over two steps. Saponification of the acetate moieties under basic conditions followed by the hydrolysis of the acetonide with acidic ion-exchange resin afforded 5-azido-5-deoxy-D-fructose (3/62) as a crystalline solid. Catalytic hydrogenation of this azide under elevated pressure eventually gave DMDP (1/51) as a single diastereomer in nearly quantitative yield.[7]

The obtained DMDP was then converted in five further steps to the N-Cbz-protected pyrrolidine carbalddehyde 3/65 which was reacted with 3-butenylmagnesium bromide to give a diastereomeric mixture of alcohols 3/66 in an unrevealed ratio. Treatment of 3/66 with NaH finally afforded the oxazolidinone 3/67 as the aspired pyrrolidine building block for the cross-metathesis coupling reaction (Scheme 3.13).[7]

‡ To this date, DURUGKAR’s work has not been published in a peer-reviewed journal.
As for the spiroketal side chain fragment of broussonetine G, commercially available, inexpensive D-mannitol served as starting material which was converted into acetonide-protected (R)-glyceraldehyde (3/68) in two steps via standard procedures. Extension of this aldehyde by an ethylene group to its homologue 3/69 was achieved in three steps including a HWE olefination and DIBAL-H reduction. The two-step Horner-Wittig reaction of aldehyde 3/69 with diphenyl(tetrahydro-2-furanyl)phosphine oxide then afforded the enol ether 3/71 which upon acetonide cleavage with camphorsulfonic acid cyclised in situ to the spiroketal alcohol 3/72. Alcohol 3/72 was eventually subjected to a Swern oxidation followed by a
Wittig olefination to give the desired spiroketal olefin \(3/74\) in 24% yield over 10 steps from D-mannitol (Scheme 3.14).

**Scheme 3.14.** Synthesis of the spiroketal side chain fragment of broussonetine G (DURUGKAR 2010).

Reagents and conditions: (a) 2,2-dimethoxypropane, PTSA, DMSO, rt, 16 h, 64%; (b) NaIO\(_4\)/SiO\(_2\), DCM, rt, 30 min, 93%; (c) Ph\(_3\)PCHCO\(_2\)Et, DCM, rt, 3 h, 91%; (d) Pd/C, H\(_2\) (1 atm), EtOAc, rt, 2 h, 95%; (e) DIBAL-H, DCM, –78 °C, 1 h, 74%; (f) diphenyl(tetrahydro-2-furanyl)phosphine oxide, LDA, –78 °C, 30 min; (g) KO\(_2\)Bu, THF, 0 °C to rt, 1 h; (h) CSA, THF, 0 °C to rt, 24 h, 76% over 3 steps; (i) (COCl)\(_2\), DMSO, Et\(_3\)N, –78 °C, 1 h; (j) methyltriphenylphosphonium bromide, \(\nu\)-BuLi, THF, 0 °C, 1 h, 84% over 2 steps; 24.3% over 10 steps from D-mannitol.

**Scheme 3.15.** Final steps in the synthesis of broussonetine G by DURUGKAR (2010).

Reagents and conditions: (a) spiroketal olefin \(3/74\), 20 mol% Grubbs’ 1st generation catalyst, DCM, rt, 48 h, 51%, \((E): (Z)\)-ratio not given; (b) Pd(OH)\(_2\)/C, H\(_2\) (40 psi), rt, 6 h; (c) NaOH, EtOH/H\(_2\)O, 80 °C, 12 h, 45% over 2 steps; 0.22% yield over 17 steps from \(\nu\)-sorbose, 0.05% over a total of 27 steps.
To conclude the synthesis of broussonetine G both building blocks were coupled via a cross-metathesis reaction giving the desired olefin 3/75 as a mixture of \((E)/(Z)\)-isomers in an unrevealed ratio along with the respective homodimers. Hydrogenation of the double bond with concomitant cleavage of the \(O\)-benzyl protecting groups followed by the saponification of the oxazolidinone moiety finally provided broussonetine G in 0.2% yield over 17 steps from L-sorbose (Scheme 3.15).[7]

DURUGKAR also attempted to synthesise broussonetine C in a similar fashion. At first the keto side chain fragment was synthesised in three steps starting from 9-decen-1-ol. Oxidation with IBX afforded the aldehyde 3/76 which was reacted with benzyloxypropylmagnesium bromide to give the secondary alcohol 3/77. The IBX oxidation of 3/77 then provided the requisite 10-keto olefin 3/78 as building block in 58% yield (Scheme 3.16).[7]

\[ \text{9-Decene-1-ol} \xrightarrow{\text{a}} \text{3/76} \xrightarrow{\text{b}} \text{3/77} \xrightarrow{\text{c}} \text{3/78} \]

**Scheme 3.16.** Synthesis of the keto side chain fragment of broussonetine C (DURUGKAR 2010).
Reagents and conditions: (a) IBX, DMSO, 0 °C, 1 h, 91%; (b) benzyloxypropylmagnesium bromide, THF, 0 °C to rt, 2 h, 82%; (c) IBX, DMSO, 0 °C, 1 h 78%; 58.2% over 3 steps.

Since broussonetine C lacks the hydroxy group at C-1’ of the side chain DURUGKAR had to synthesise a different, simpler pyrrolidine building block. Therefore, aldehyde 3/65 was directly transformed into olefin 3/79 via a Wittig reaction with methyltriphenylphosphonium bromide. Cross-coupling of this pyrrolidine building block 3/79 with the keto side chain fragment 3/78 employing Grubbs’ 2\(^{\text{nd}}\) generation catalyst then afforded the desired olefin 3/80 in 31% yield as an \((E)/(Z)\)-mixture in an undisclosed ratio (Scheme 3.17).[7]

\[ \text{3/65} \xrightarrow{\text{a}} \text{3/79} \xrightarrow{\text{b}} \text{3/80} \]

**Scheme 3.17.** DURUGKAR’s first attempt to finalise broussonetine C.
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Scheme 3.17 cont’d. DURUGKAR’s first attempt to finalise broussonetine C.

Reagents and conditions: (a) methyltriphenylphosphonium bromide, NaNH₂, THF, rt, 8 h, 85%; (b) keto olefin 3/78, 10 mol% Grubbs’ 2nd generation catalyst, DCM, rt, 24 h, 31%, (E) : (Z)-ratio not given; (c) various hydrogenation conditions, no product isolated.

However, all attempts to obtain pure broussonetine C after the hydrogenation of the double and simultaneous O-benzyl cleavage under various conditions were unsuccessful due to the formation of numerous unidentified by-products.

Therefore, in a second effort to obtain broussonetine C, DURUGKAR decided to change the protecting group of the imino moiety. Applying the Boc instead of the Cbz group would allow a more controlled two-step deprotection sequence similar to the final steps of the earlier reported syntheses of broussonetine C (see Schemes 3.1 and 3.2).[7]

Scheme 3.18. DURUGKAR’s second attempt to finalise broussonetine C.

Reagents and conditions: (a) Boc₂O, Et₃N, DCM, 0 °C to rt, 16 h, 83%; (b) cat. TEMPO, trichloroisocyanuric acid DCM 0 °C to rt, 20 min, 89%; (c) methyltriphenylphosphonium bromide, NaNH₂, THF, rt, 8 h, 87%; (d) keto olefin 3/78, 10 mol% Grubbs’ 2nd generation catalyst, DCM, rt, 24 h, 28%, (E) : (Z)-ratio not given; (e) TFA, MeOH, rt, 2 h; (f) Pd/C, H₂ (1 atm), conc. HCl, MeOH, rt, 16 h, no product isolated.
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For this reason tris-benzylated DMDP 3/64 was Boc-protected under standard conditions and then converted into the requisite pyrrolidine building block 3/82 in two further steps. Cross-coupling under the same conditions as described for the Cbz-analogue provided the olefin 3/83 in 28% yield again as (E)/(Z)-mixture in an unrevealed ratio. However, the deprotection of compound 3/83 proved again to be futile. Hydrogenation either first or after cleavage of the Boc group gave in both cases an inseparable mixture of products with broussonetine C being only a minor by-product (Scheme 3.18).[7] This unexpected and surprising outcome stands in contrast to the previously reported syntheses by YODA, CARDA, and PERLMUTTER et al., in which the deprotection steps under similar conditions were successful and pure broussonetine C was obtained.[2, 3, 5, 6]

3.7 The First Total Synthesis of Broussonetine F by CHIDA et al.

The to this date most recent total synthesis of a broussonetine congener was reported in 2011 by the Japanese research group of Noritaka CHIDA.[8] CHIDA’s group has been exploring new strategies to obtain biologically active natural products by using sigmatropic rearrangements of allylic diols with complete chirality transfer. The employed allylic diols were derived from naturally occurring chiral polyols such as carbohydrates and tartaric acid. With this concept CHIDA et al. had been able to developed new enantioselective total syntheses for biologically active complex molecules such as the natural products (−)-kainic acid[18] (3/84) and (−)-agelastatin A[19] (3/85) as well as the synthetic antiinfluenza agent A-315675[20] (3/86, Figure 3.2).

![Figure 3.2. Former synthetic targets of the CHIDA group that have been synthesised via sigmatropic rearrangements of allylic diols.](image)

To study the feasibility of an orthoamide Overman rearrangement based strategy in total synthesis CHIDA and co-workers chose this time broussonetine F as the synthetic target.
Furthermore, considering a universal and flexible route towards the broussonetine family with its variety of side chains, they envisioned a late-state coupling between a common pyrrolidine unit and a variable side chain fragment via a Suzuki-Miyaura coupling reaction. This strategy would then allow the synthesis of various members of the broussonetine family in the future.

CHIDA’s convergent synthesis of broussonetine F is outlined in Scheme 3.19. It began with the selective formation of the cyclic orthoamide 3/90 from the allylic 1,2-diol 3/89, which was prepared from diethyl L-tartrate in eight synthetic steps including a (Z)-selective Horner-Wadsworth-Emmons olefination to install the double bond in the intermediate ester 3/88. With diol 3/89 in hand, an extensive survey had to be done to determine the right reaction conditions to efficiently transform 3/89 into the orthoamide 3/90 while simultaneously suppressing the bisimidation of the diol as a side reaction. Eventually it was found that the addition of a catalytic amount of DBU (0.1 equiv) to a solution of 3/89 and trichloroacetonitrile (1.3 equiv) in DCM at 0 °C resulted in the selective formation of the cyclic orthoamide 3/90, along with just a trace amount of the bisimide.\[8\]

To find the optimal conditions for the subsequent orthoamide Overman rearrangement proved to be equally demanding. Since prolonged reaction times caused severe decomposition of the starting material CHIDA et al. screened various additives in the reaction to improve the yield of the allylic amide 3/91. In the end the best result was achieved by the addition of a catalytic amount (5 mol%) of 2,6-di-tert-butylhydroxytoluene (BHT) to the reaction mixture. This reduced the rate of decomposition to give the amide 3/91 in 56% yield together with 27% of the recovered starting material 3/90. The reaction proceeded thereby under complete chirality transfer with 3/91 isolated as a single diastereomer.\[8\]

CHIDA and co-workers then proceeded with the construction of the polyhydroxylated pyrrolidine unit. This afforded the installation of the three secondary hydroxy groups at C-3, C-4 and C-1’ prior to the cyclisation. After protection of the allylic alcohol in 3/91 as a MOM ether, stereoselective dihydroxylation of the double bond was accomplished under Sharpless’ asymmetric conditions giving the diol 3/92 in 61% isolated yield after recrystallisation of the initially obtained 3 : 1 diastereomeric mixture. Benzyl protection of the two newly formed hydroxy groups and oxidative PMB deprotection with DDQ then allowed the stereoselective introduction of the C-1’ alcohol functionality via a chelation-controlled Hosomi-Sakurai allylation reaction. At first, Swern oxidation of the primary alcohol 3/93

Reagents and conditions: (a) 2,2-dimethoxypropane, cat. PTSA, MS 4A, CHCl₃, reflux, 94%; (b) LiAlH₄, Et₂O, reflux, 78%; (c) PMBCl, NaH, DMF/THF (1 : 1), 0 °C to rt, 72%; (d) (COCl)₂, DMSO, Et₃N, DCM –78 °C to rt; (e) (PhO)₂P(O)CH₂CO₂Et, NaH, THF, –78 °C, 84% over 2 steps, E : Z = 1 : 7; (f) DIBAl-H, PhMe, –78 °C, 62% of Z-allylic alcohol, 21% of E-allylic alcohol; (g) BnBr, NaH, DMF, 0 °C to rt, 94%; (h) 80% AcOH, 35 °C, 88%; (i) CCl₃CN (1.3 equiv), DCM, 0 °C, then DBU (0.1 equiv), 86%; (j) BHT (5 mol%), t-BuPh, 180 °C, sealed tube, 56%; (k) MOMCl, DIPEA, NaI, DCE, 40 °C, 91%; (l) AD-mix-β, CH₃SO,NH₂, tBuOH/H₂O (1 : 1), 0 °C, 100%, d.r. = 3 : 1, then recrystallisation, 61% single diastereoisomer; (m) BnBr, NaH, TBAI, DMF, 0 °C, 92%, (n) DDQ, DCM/H₂O (4 : 1), rt, 90%; (o) (COCl)₂, DMSO, Et₃N, DCM, –78 °C to rt; (p) allytrimethylsilane, MgBr₂ · Et₂O, DCM, 82% over 2 steps; (q) BnBr, NaH, TBAI, DMF, 0 °C to rt, 77%; (r) conc. HCl, MeOH, rt, 97%; (s) MsCl, Et₃N, DCM, 0 °C, 79%; (t) 4 M NaOH, EtOH, 80 °C, 81%; (u) CbzCl, 0.5 M NaOH/EtOAc (1 : 1), 0 °C to rt, 95%; 1.9% over 21 steps from diethyl L-tartrate.
provided the requisite aldehyde, which was immediately treated with allyltrimethylsilane and MgBr₂ · Et₂O to afford the secondary alcohol 3/94 as single diastereomer. This secondary alcohol was then protected as a benzyl ether, followed by the three-step exchange of the MOM group with the mesyl group. Hydrolysis of the trichloroacetyl group in 3/95 with aqueous NaOH in refluxing ethanol resulted in concomitant cyclisation to form the pyrrolidine core which was subsequently converted into its benzyl carbamate derivative 3/96 (Scheme 3.19).[8]

To complete the total synthesis of broussonetine F, the remaining task was the coupling of the pyrrolidine building block with the side chain fragment (Scheme 3.21). This was achieved by a palladium-catalysed Suzuki-Miyaura coupling reaction of the borane intermediate 3/101 with the vinyl iodide 3/100 in the presence of triphenylarsane and caesium carbonate to furnish the alkene 3/102 in 73% yield. Vinyl iodide 3/100, in turn, had been synthesised beforehand in four steps from δ-valerolactone in 20% overall yield (Scheme 3.20).[8]

Scheme 3.20. Synthesis of the side chain fragment for broussonetine F (CHIDA et al. 2011).
Reagents and conditions: (a) 4-but-1-enylmagnesiumbromide, CeCl₃, THF, −78 °C; (b) Ac₂O, pyridine, rt, 53% over 2 steps; (c) O₃, DCM, −78 °C, then PPh₃, rt, 93%; (d) CrCl₂, CHI₃, THF, rt, E : Z = 4.8 : 1, then HPLC, 8% Z-vinyllic iodide, 41% E-vinyllic iodide; 20.2% over 4 steps from δ-valerolactone.

In the final two steps simultaneous removal of all benzyl groups, the Cbz group and the double bond was realised under acidic hydrogenolytic conditions over Perlman’s catalyst. The methanolysis of the remaining acetate group in 3/103 finally concluded the total synthesis of broussonetine F over 25 steps in 1.3% overall yield from diethyl L-tartrate.[8]
3.8 Synthesis of the Spiroketal Side Chain Fragment of Broussonetine H by BRIMBLE et al.

At about the same time TROST et al. published their synthesis of broussonetine G, Margaret BRIMBLE and co-workers from the University of Auckland, New Zealand, reported a synthesis for the spiroketal fragment of broussonetine H.\(^9\) Since BRIMBLE’s research at this time mainly focused on the stereoselective synthesis of spiroketal compounds rather than polyhydroxylated alkaloids their publication only describes the synthesis of the terminal functionalised side chain fragment. However, they envisioned to couple this fragment with a fully protected pyrrolidine aldehyde building block in a Grignard reaction similar to the original idea of TROST et al.\(^4\) (Scheme 3.22).
Chapter 3. Syntheses of the Broussonetines


BRIMBLE’s synthesis of the side chain fragment of broussonetine H is shown in Scheme 3.23. Starting from L-glutamic acid, diazotisation of the latter afforded an intermediate γ-lactone carboxylic acid which was reduced to the triol 3/104 with lithiumaluminium hydride. This triol was then converted in five further steps into the terminal O-TBDPS-protected epoxide 3/107 which was subsequently alkylated with lithium trimethylsilylacetylide under Yamaguchi conditions to give the secondary alcohol 3/108. The trimethylsilyl group was then removed, and the secondary hydroxy group protected as its benzyl ether to afford the alkyne 3/109. The acetylide anion derived from compound 3/109 was reacted with δ-valerolactone to afford a mixture of the keto-alcohol 3/110 and its hemiacetal 3/111. This mixture was treated with hydrogen in the presence of palladium on charcoal to simultaneously hydrogenate the triple bond and effect cleavage of the benzyl ether to give compound 3/112. However, to the surprise of BRIMBLE et al., compound 3/112 had spontaneously assembled into spiroketal 3/113 under the applied reaction conditions. An anticipated second acid-catalysed step for this transformation was therefore not required. In the final steps the TBDPS protecting group of 3/113 was cleaved with TBAF and the liberated primary alcohol 3/114 was converted via its mesylate into the aspired spiroketal bromide 3/115.\[9\]

A major drawback of BRIMBLE’s approach was the loss of stereochemical integrity during the first steps of the synthesis. The Mosher ester derivative of the primary alcohol 3/114 was prepared and $^{19}$F NMR analysis established that the enantiomeric excess was only 70%. Consequent comparison of $[\alpha]_D$ values for compounds 3/105 and 3/107 with those previously reported in the literature revealed great differences suggesting that considerable racemisation had taken place during the conversion of L-glutamic acid to acetonide 3/105. BRIMBLE and co-workers concluded that epimerisation at C-2 had occurred during the formation of
acetonide 3/105 from triol 3/104 as proposed by SUGAI et al.[21] in a preceding paper. In a refined synthesis this intermediate should therefore be avoided.[9]


Reagents and conditions: (a) NaNO₂, HCl, H₂O, 0 °C, 54%; (b) LiAlH₄, THF, reflux, 47%; (c) PTSA, acetone, rt, 85%; (d) TBDPSCI, imidazole, DCM, rt, 87%; (e) PPTS, MeOH, rt, 72%; (f) TsCl, Et₃N, DMAP, DCM, rt, 95%; (g) NaH, 18-crown-6, THF, rt, 86%; (h) HC≡CSiMe₃, n-BuLi, BF₃·OEt₂, THF, -78 °C, 92%; (i) NaOMe, MeOH, rt, 94%; (j) NaH, BnBr, TBAI, DMF, rt, 88%; (k) n-BuLi, BF₃·OEt₂, THF, -78 °C, then δ-valerolactone, 86%; (l) Pd/C, H₂, EtOAc, rt, 86%; (m) TBAF, THF, rt, 96%; (n) MsCl, DMAP, pyridine, rt, 78%; LiBr, acetone, reflux, 85%; 4.0% yield over 15 steps from L-glutamic acid.
### Table 3.1. The broussonetine syntheses in comparison.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pyrrolidine alkaloid</th>
<th>Starting materials</th>
<th>Number of steps</th>
<th>Overall yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yoda et al.</strong>&lt;sup&gt;2&lt;/sup&gt; (1999)</td>
<td>Broussonetine C</td>
<td>D-tartaric acid</td>
<td>22 in total</td>
<td>9.2% from D-tartaric acid</td>
</tr>
<tr>
<td><strong>Peltomäki et al.</strong>&lt;sup&gt;3&lt;/sup&gt; (2003)</td>
<td>Broussonetine C</td>
<td>D-arabinose</td>
<td>24 in total</td>
<td>1.7% from D-arabinose</td>
</tr>
<tr>
<td><strong>Trost et al.</strong>&lt;sup&gt;4&lt;/sup&gt; (2003)</td>
<td>Broussonetine G</td>
<td>butadiene monoxide&lt;br&gt;(2-vinyloloxirane),&lt;br&gt;δ-valerolactone</td>
<td>10 (pyrrolidine building block)&lt;br&gt;9 (side chain fragment)&lt;br&gt;24 in total</td>
<td>5.6% from butadiene monoxide over 15 steps&lt;br&gt;4.0% from δ-valerolactone over 14 steps&lt;br&gt;0.95% in total over 24 steps</td>
</tr>
<tr>
<td><strong>Carda et al.</strong>&lt;sup&gt;5, 6&lt;/sup&gt; (2009)</td>
<td>Broussonetine C</td>
<td>γ-butyrolactone</td>
<td>3 (side chain fragment)&lt;br&gt;19 in total</td>
<td>14.1% from D-serine over 16 steps&lt;br&gt;10.2% in total over 19 steps</td>
</tr>
<tr>
<td></td>
<td>Broussonetine D</td>
<td>δ-valerolactone</td>
<td>3 (side chain fragment)&lt;br&gt;19 in total</td>
<td>14.5% from D-serine over 16 steps&lt;br&gt;9.0% in total over 19 steps</td>
</tr>
<tr>
<td></td>
<td>Broussonetine M</td>
<td>d-serine&lt;br&gt;1,7-heptanediol</td>
<td>13 (pyrrolidine building block)&lt;br&gt;24 in total</td>
<td>15.4% from D-serine over 16 steps&lt;br&gt;5.9% from 1,7-heptanediol over 11 steps&lt;br&gt;2.1% in total over 24 steps</td>
</tr>
<tr>
<td></td>
<td>Broussonetine O</td>
<td>γ-butyrolactone</td>
<td>3 (side chain fragment)&lt;br&gt;19 in total</td>
<td>10.8%&lt;sup&gt;a&lt;/sup&gt; from D-serine over 16 steps&lt;br&gt;7.8%&lt;sup&gt;a&lt;/sup&gt; in total over 19 steps</td>
</tr>
<tr>
<td></td>
<td>Broussonetine P</td>
<td>δ-valerolactone</td>
<td>3 (side chain fragment)&lt;br&gt;19 in total</td>
<td>12.3%&lt;sup&gt;a&lt;/sup&gt; from D-serine over 16 steps&lt;br&gt;8.1%&lt;sup&gt;a&lt;/sup&gt; in total over 19 steps</td>
</tr>
<tr>
<td><strong>Durugkar</strong>&lt;sup&gt;7&lt;/sup&gt; (2010)</td>
<td>Broussonetine G</td>
<td>L-sorbose,&lt;br&gt;D-mannitol</td>
<td>14 (pyrrolidine building block)&lt;br&gt;10 (side chain fragment)&lt;br&gt;27 in total</td>
<td>0.22% from L-sorbose over 17 steps&lt;br&gt;5.6% from D-mannitol over 13 steps&lt;br&gt;0.05% in total over 27 steps</td>
</tr>
<tr>
<td><strong>Chida et al.</strong>&lt;sup&gt;8&lt;/sup&gt; (2011)</td>
<td>Broussonetine F</td>
<td>diethyl L-tartrate,&lt;br&gt;δ-valerolactone</td>
<td>21 (pyrrolidine building block)&lt;br&gt;4 (side chain fragment)&lt;br&gt;29 in total</td>
<td>1.3% from diethyl L-tartrate over 25 steps&lt;br&gt;13.7% from δ-valerolactone over 8 steps&lt;br&gt;0.26% in total over 29 steps</td>
</tr>
</tbody>
</table>

<sup>a</sup> see footnote of Scheme 3.12.
3.9 References


Chapter 3. Syntheses of the Broussonetines


Chapter 4. Syntheses of Polyhydroxylated Alkaloids

4.1 Introduction

The synthesis of various biological active natural products with an anti-configured α-amino-hydroxy structural element presents a main research focus of our research group. Of particular interest for us hereby is the development of new, efficient and flexible synthetic routes that lead to polyhydroxylated pyrrolidine, pyrrolizidine, indolizidine, and nortropane alkaloids which incorporate this structural feature. Representative examples of these alkaloids that have already been successfully synthesised in our group are shown in Figure 4.1.

\[ \text{Australine} \quad 1/120 \]
\[ 1,7\text{-Di-}epi\text{-australine} \quad 4/1 \]
\[ \text{Swainsonine} \quad 1/92 \]

\[ \text{3-epi-Australine} \quad 1/122 \]
\[ 7\text{-epi-Australine} \quad 1/125 \]

\[ \text{Calystegine B4} \quad 1/164 \]

\[ \text{Casuarine (Uniflorine B)} \quad 1/127 \]
\[ \text{Hyacinthacine B3} \quad 1/139 \]
\[ \text{Castanospermine} \quad 1/88 \]

\[ \text{Uniflorine A} \quad 1/129 \]
\[ \text{purported Hyacinthacine B7} \quad 1/143 \]
\[ \text{putative Uniflorine A} \quad 4/2 \]

**Figure 4.1.** Former synthetic targets of the PYNE group incorporating a 1,2-anti-amino-hydroxyl structural element (highlighted in red).
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

The two synthetic methods that have been employed to prepare these chiral 1,2-anti-amino alcohols are shown in Scheme 4.1. These include the aminolysis of chiral vinyl epoxides and the Petasis borono-Mannich reaction of chiral α-hydroxy aldehydes.\[^4\]

1. **Aminolysis of vinyl epoxides**

\[
\begin{align*}
\text{R}^1\text{O} & \quad \text{R}^2\text{NH}_2 \\
\text{R}^1\text{OH} & \quad \text{NH} \quad \text{R}^2
\end{align*}
\]

2. **Petasis borono-Mannich Reaction of α-hydroxy aldehydes**

\[
\begin{align*}
\text{R}^1\text{OH} & \quad \text{R}^2\text{NH}_2 \\
\text{R}^1\text{OH} & \quad \text{NH} \quad \text{R}^2
\end{align*}
\]

Scheme 4.1. Methods of preparing chiral 1,2-anti-amino alcohols employed in the PyNE group.\[^4\]

### 4.2 Synthesis of Polyhydroxylated Alkaloids via the Aminolysis of Chiral Vinyl Epoxides

At the beginning of this research project in 2001, the requisite 1,2-anti-amino alcohols were prepared from the aminolysis of chiral vinyl epoxides. These vinyl epoxides are accessible via a six-step synthesis starting from commercial available ω-hydroxy alkynes as shown in Scheme 4.2. The respective alcohols were first protected as PMB ethers 4/3 followed by homologation of the terminal alkyne with formaldehyde. Reduction of the newly formed propargylic alcohols 4/4 with REDAL then afforded the (E)-allylic alcohols 4/5 which were asymmetrically epoxidised employing Sharpless’ protocol. The resulting epoxy alcohols 4/6 were subsequently converted to the chiral vinyl epoxides 4/8 via Swern oxidation followed by Wittig olefination. The obtained vinyl epoxides were then used in the following for the synthesis of the alkaloids (−)-swainsonine (1/92) and the two unnatural australine epimers (+)-1,7-di-epi-australine (4/1) and (−)-7-epi-australine (1/125) by former PhD students Karl Lindsay and Minyan Tang.\[^5\, ^6\]

Scheme 4.2. Synthesis of the chiral vinyl epoxides as precursors for the aminolysis reaction.\[^5\, ^6\]
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

Scheme 4.2 cont’d. Synthesis of the chiral vinyl epoxides as precursors for the aminolysis reaction.\cite{5,6}
Reagents and conditions: (a) NaH, PMBBr, THF, rt, 22 h, 92% (n = 1), 97% (n = 2); (b) n-BuLi, (CH$_2$O)$_n$, THF, 0 °C to rt, 20 h, 79% (n = 1), 82% (n = 2); (c) REDAL, THF, rt, 4 h, 89% (n = 1), 93% (n = 2); (d) (−)-DET or (−)-DIPT, Ti(i-PrO)$_4$, t-BuOOH, MS 4Å, DCM, −40 °C to −20 °C, o/n, 43 – 86% (n = 1, 2); (e) (COCl)$_2$, DMSO, TEA, DCM, −60 °C to −50 °C, 30 min; (f) CH$_3$PPh$_3$Br, KHMDS, THF, 0 °C, 2 h, 77% (n = 1), 81% (n = 2) over 2 steps.

The syntheses of swainsonine and the epimeric australines are outlined in Schemes 4.3, 4.4 and 4.5. Starting from commercially available 3-butyn-1-ol and 4-pentyn-1-ol, respectively, the desired chiral vinyl epoxides were synthesised in six consecutive steps according to Scheme 4.2. Aminolysis of these epoxides with either allylamine (in the case of the swainsonine synthesis) or (S)-1-(benzyloxy)but-3-en-2-amine (4/9) (in the case of the australines syntheses) gave the key intermediates, 1,2-anti-amino alcohols 4/10 and 4/20, in a total of seven synthetic steps from the commercially available starting materials in 31% and 34% overall yield, respectively.\cite{5,6}

4.2.1 Minyan TANG’s Synthesis of (+)-1,7-Di-epi-australine

The 1,2-amino alcohol 4/10 was subsequently converted to (+)-1,7-epi-australine in eleven further steps including a ring-closing metathesis to install the pyrrolidine ring, a syn-dihydroxylation reaction to introduce the 1,2-diol functionality, and an intramolecular N-alkylation under Mitsunobu conditions to complete the pyrrolizidine bicyclus (Scheme 4.3). The obtained synthetic product had spectroscopic data identical to that earlier described in the literature for this compound, and its specific optical rotation also closely matched that previously reported.\cite{5,7}

Scheme 4.3. M. TANG’s synthesis of (+)-1,7-di-epi-australine (2003).\cite{5,7}
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

Scheme 4.3 cont’d. M. TANG’s synthesis of (+)-1,7-di-epi-australine (2003).[5, 7]
Reagents and conditions: (a) LiOTf, MeCN, 120 ºC, sealed tube, 72 h, 98%; (b) triphosgene, Et,N, DCM, rt, 2 h, 79%; (c) Grubbs’ 1st generation catalyst, DCM, reflux, 44 h, 73%; (d) K₂OsO₄ · 2 H₂O, NMO, acetone, H₂O, rt, 24 h, 82%; (e) Ac₂O, pyridine, rt, 24 h, 76%; (f) DDQ, DCM, H₂O, rt, 2 h, 88%; (g) NaOH, EtOH, 70 ºC, sealed tube; (h) DIAD, PPh₃, pyridine, 0 ºC, 2.5 h; (i) Ac₂O, pyridine, rt, 24 h, 20% over 3 steps; (j) PdCl₂, H₂, MeOH, rt, 1.5 h; (k) Ac₂O, pyridine, rt, 24 h, 84% over 2 steps; (l) NaOMe, MeOH, rt, 15 h, 92%; 4.8% yield over 12 steps from vinyl epoxide 4/8a.

4.2.2 Minyan TANG’s Synthesis of (~)-7-epi-Australine

The synthesis of (~)-7-epi-australine required the inversion of the stereochemistry at C-7 in the pyrrolo[1,2-c]oxazol-3-one 4/15. This was achieved in a regioselective manner via ring-opening of its cyclic sulfate derivative 4/16 with caesium benzoate, the regioselectivity being controlled by the benzyloxymethyl group at C-5 (Scheme 4.4).

Scheme 4.4. M. TANG’s synthesis of 7-epi-australine (2004).[5, 7]
Scheme 4.4 cont’d. M. TANG’s synthesis of 7-epi-australine (2004).[5, 7]

Reagents and conditions: (a) 1. SOCl₂, Et₃N, DCM, 0 °C, 30 min; 2. RuCl₃·3 H₂O, NaIO₄, CCl₄/MeCN/H₂O (2 : 2 : 3), rt, 2 h, 80%; (b) 1. PhCOOH, Cs₂CO₃, DMF, 40 °C, 23 h; 2. conc. H₂SO₄, THF, H₂O, rt, 18 h, 56%; (c) DDQ, DCM, H₂O, rt, 2 h, 75%; (d) NaOH, EtOH, 70 °C, 19 h, 61%; (e) DIAD, PPh₃, THF, 0 °C, 3 h; (f) Ac₂O, pyridine, rt, 21 h, 22% over 3 steps; (g) PdCl₂, H₂, MeOH, rt, 1 h; (h) Ac₂O, pyridine, rt, 15 h, 94%; (i) K₂CO₃, MeOH, rt, 24 h, 97%; 1.9% yield over 13 steps from vinyl epoxide 4/8a.

(−)-7-epi-Australine was finally obtained in a total yield of 1.9% over 13 steps from the vinyl epoxide 4/8a. Spectroscopic data as well as the specific optical rotation of the synthesised compound were nearly identical to that reported in the literature.[5, 7]

4.2.3 Karl LINDSAY’s Synthesis of (−)-Swainsonine

As in TANG’s syntheses of the australine epimers the intermediate pyrrolo[1,2-c]oxazol-3-one 4/21 was prepared from the respective vinyl epoxide 4/8b which in turn was synthesised in six steps from 4-pentyn-1-ol according to Scheme 4.2. Aminolysis of 4/8b with allylamine in the presence of lithium triflate under microwave heating at 110 °C gave the requisite amino alcohol 4/20 in 88% yield. This amino alcohol was then transformed to (−)-swainsonine in ten further steps that involved a ring-closing metathesis to establish the pyrrolidine ring, a syn-selective dihydroxylation reaction to introduce the vicinal diol functionality, and a 6-exo-tet cyclisation under Appel conditions to complete the bicyclic indolizidine nucleus. Removal of all protecting groups in the final two steps delivered (−)-swainsonine after purification by basic ion-exchange chromatography in 18.4% overall yield from vinyl epoxide 4/8b. This synthetic compound had identical spectroscopic data to an authentic sample of the natural product.[6, 8]
The intermediate oxazolidinones in these syntheses proved to be of special preparative value. Besides being an exceptionable stable protecting group for the vicinal 1,2-aminohydroxy functionality that allowed to easily perform ring-closing metathesis reactions to give the pyrrolo[1,2-c]oxazol-3-one ring system, the bicyclic structure was also found to function as a stereodirecting group in the syn-DH reaction. This high level of diastereoselectivity can be explained to be based on a stereoelectronic effect as an examination of the HOMO about the alkene moiety of the pyrrolo[1,2-c]oxazol-3-one bicyclic ring system shows (Figure 4.2). \[^9\]
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

The non-bonding orbital bearing the electron pair on the N-atom overlaps more effectively with the π-system of the alkene moiety on the concave α-face of the molecule making this face more prone to dihydroxylation. The β-benzylloxymethyl substituent at C-5 in TANG’s australine syntheses also contributes partially to the diastereofacial selectivity, since the DH reaction of LINDSAY’s similar system, which lacks this C-5 substituent, was less diastereoselective. This stereodirecting effect of the pyrrolo[1,2-c]oxazol-3-one bicyclic ring system on the DH reaction was later further utilised in the syntheses of several other polyhydroxylated alkaloids in our research group.

4.3 Synthesis of Polyhydroxylated Alkaloids via the Petasis borono-Mannich Reaction of Chiral α-Hydroxy Aldehydes

Although the aminolysis of vinyl epoxides strategy has successfully been proven to be a reliable and flexible concept for the synthesis of several alkaloids, its major disadvantage is the necessity of seven synthetic steps from ω-hydroxy alkynes to obtain the requisite 1,2-anti-amino alcohols. Therefore, the investigation of shorter alternative methods for the synthesis of these compounds became prime directive in our group.

In 1998, N. PETASIS and co-workers reported a novel one-pot, three-component method to synthesise 1,2-anti-amino alcohols via a modified Mannich reaction of aryl or vinyl boronic acids with primary or secondary amines and chiral α-hydroxaldehydes. To test the feasibility of this method for alkaloid synthesis, uniflorine A was chosen as the synthetic target. The proposed structure of uniflorine A (4/2) was deduced from NMR analysis to be similar to that of castanospermine (1/88), except for the stereochemistry at C-1 and the extra hydroxy group at C-2 (see Figure 4.1).
4.3.1 Andrew DAVIS’ Synthesis of Putative Uniflorine A

Retrosynthetic analysis suggested that the target compound 4/2 could be acquired from the precursor 4/25 using a ring-closing metathesis and a $N$-alkylative 6-\textit{exo}-tet cyclisation reaction to prepare the 5- and 6-membered rings of 4/2, respectively. The 1,2-\textit{anti}-amino alcohol 4/25 was expected to be readily obtained from the Petasis borono-Mannich reaction of L-xylose with allylamine and (\textit{E})-styrylboronic acid, followed by chemo- and regioselective $N$- and $O$-protection reactions.$^{[4, 11, 12]}$

![Scheme 4.6. Retrosynthetic analysis of putative uniflorine A.$^{[4, 11, 12]}$](image)

As it happened, the requisite Petasis reaction gave the desired amino tetraol 4/25 in 73% as a single diastereomer after purification by ion-exchange chromatography (Scheme 4.8). The stereochemical outcome of this reaction can be rationalised by the minimisation of the 1,3-allylic strain in the reactive conformation of the intermediate iminium boronate 4/26 as shown in Scheme 4.7.

![Scheme 4.7. Proposed mechanism of the Petasis borono-Mannich reaction.$^{[4, 12]}$](image)

The amino tetraol 4/25 was then converted to 4/2 in eight further synthetic steps in an overall yield of 7% from commercially available L-xylose. The structure of 4/2 was later unequivocally confirmed by a single-crystal X-ray study of its pentaacetate derivative. However, the $^1$H and $^{13}$C NMR data for the synthetic product did not match with those reported for uniflorine A, neither did the hydrochloride salt of 4/2. It was therefore concluded that the originally proposed structure for uniflorine A was incorrect.$^{[4, 11, 12]}$
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\[ \text{L-Xylose} \quad \text{Allylamine} \quad (E)-\text{Styrylboronic acid} \]

\[ \begin{array}{c}
\text{L-Xylose} \\
\text{Allylamine} \\
(E)-\text{Styrylboronic acid}
\end{array} \]

\[ 4/25 \]

\[ \begin{array}{c}
b, c, d \\
e, f \\
g
\end{array} \]

\[ 4/27 \]

\[ 4/28 \]

\[ \begin{array}{c}
h \\
i
\end{array} \]

\[ 4/29 \]

\[ 4/30 \]

\[ 4/2 \]

**Scheme 4.8.** A. DAVIS’ synthesis of putative (-)-uniflorine A (2004).\[^{11, 12}\]

Regents and conditions: (a) EtOH, rt, 16 h, IXC, 73%; (b) Boc\(_2\)O, Et\(_3\)N, MeCN/DMF, 0 °C, 4 h, then rt, 14 h, 51%; (c) TrCl, pyridine, rt, 18 h, 68%; (d) Grubbs’ 1st generation catalyst, DCM, reflux, 18 h, 86%; (e) K\(_2\)OsO\(_4\)· 2 H\(_2\)O, NMO, acetone, H\(_2\)O, rt, 30 h, 88%, >99% de; (f) NaH, BnBr, TBAI, THF, 50 °C, 3 d, 76%; (g) TFA, anisole, DCM, 0 °C, 2 h, 37% (4/29) and 54% (4/30); (h) PPh\(_3\), CBr\(_4\), Et\(_3\)N, DCM, 0 °C, 2 h, 54%; (i) PdCl\(_2\), H\(_2\) (1 atm), MeOH, rt, 2 h, IXC, then recrystallisation, 63%; 6.8% over 9 steps from L-xylose.

### 4.3.2 Theeraphan MACHAN’s Synthesis of (+)-Castanospermine

The efficiency of the Petasis approach to indolizidine alkaloids was then once again proven with the synthesis of (+)-castanospermine (1/88) by Theeraphan MACHAN, a visiting scientist from Thailand, in 2003.\[^{13}\] His synthesis is outlined in Scheme 4.9. Employing the same amino tetraol 4/25 as starting point for this synthesis, the main difference to the original synthesis of putative uniflorine A lay in the installation of the hydroxyl group at C-1.

Amino tetraol 4/25 was converted into its oxazolidin-2-one derivative upon treatment with triphosgene under basic conditions. Based on the results of previous syntheses of polyhydroxylated alkaloids in our group, it was expected that the \textit{syn}-dihydroxylation of the double bond would selectively furnish the corresponding diol with the requisite stereochemistry for the synthesis of the target alkaloid and opposite to the observed selectivity in DAVIS’ synthesis. As it turned out, osmium(VIII)-catalysed \textit{syn}-dihydroxylation furnished...
the desired diol 4/32 in 60% isolated yield after separation of its minor diastereomer by column chromatography. The diol 4/32 was then converted via the cyclic sulfate 4/33 and its regioselective reductive ring-opening with sodium borohydride in dimethylacetamide into the required alcohol 4/34. The following 6-exo-tet cyclisation after base catalysed hydrolysis of the oxazolidinone moiety proved to be surprisingly complicated. Attempts to cyclise the aminotriol 4/35 under Appel conditions were unsuccessful, however, applying Mitsunobu conditions produced the desired indolizidine in a low yield of 25% though due to the formation of unexpected isomeric by-products (not shown in Scheme 4.9). After removal of the remaining benzyl protecting groups using PdCl₂/H₂, (+)-castanospermine was obtained in 0.76% overall yield from L-xylose. Spectroscopic data of this synthetic compound matched very closely to that reported in the literature.[13]


Reagents and conditions: (a) allylamine, (E)-styrylboronic acid, EtOH, rt, 16 h, ion-exchange chromatography, 73%; (b) triphosgene, Et₃N, THF, rt, 10 h, 53%; (c) TrCl, pyridine, rt, 20 h, 87%; (d) NaH, BnBr, TBAI, THF, 50 ºC, 4 d, 56%; (e) Grubbs’ 2nd generation catalyst, DCM, reflux, 48 h, 88%; (f) K₂OsO₄ · 2 H₂O, NMO, acetone/H₂O, rt, 48 h, d.r. = 83 : 17, 84% combined yield, 60% isolated yield; (g) 1. SOCl₂, Et₃N, DCM; 2. RuCl₃, NaIO₄, 64%; (h) NaBH₄, DMA, rt, 6 h; 2. conc. H₂SO₄, H₂O, THF, rt, 20 h, 63%; (i) NaOH, H₂O, MeOH, microwave, 110 ºC, 2 h, 80%; (j) DIAD, Ph₃P, THF, 0 – 5 ºC, 48 h, 25%; (k) PdCl₂, H₂, MeOH, rt, 1 h, ion-exchange chromatography, 95%; 0.76% yield over 11 steps from l-xylose.
4.3.3 Thunwadee RITTHIWIGROM’s Syntheses of Uniflorine A, Casuarine and 3-epi-Australine

Since the discovery that the originally proposed structure of uniflorine A was wrong, efforts were undertaken in our group to determine the correct structure of this alkaloid.\cite{14} By altering DAVIS’ original synthesis, former PhD student Thunwadee RITTHIWIGROM finally succeeded in 2008 in proving that uniflorine A actually is the C-6 epimer of the known pyrrolizidine alkaloid casuarine.\cite{15} In the process, this modification then gave rise not only to the accurate structure of uniflorine A but also other polyhydroxylated pyrrolizidine alkaloids, including casuarine and 3-epi-australine, from a common precursor (4/36).\cite{16,17}

As in DAVIS’ approach, RITTHIWIGROM’s synthesis started with the Petasis reaction of L-xylose with allylamine and (E)-styrylboronic acid to give the by then well known amino-tetraol 4/25 which was subsequently converted into the 2,5-dihydropyrrole 4/36 in three further steps (Scheme 4.10).\cite{16,17}

![Scheme 4.10. Synthesis of the common precursor 4/36 for uniflorine A, casuarine and 3-epi-australine.\cite{16,17}](image-url)

Reagents and conditions: (a) allylamine, (E)-styrylboronic acid, EtOH, rt, 16 h, ion-exchange chromatography, 91%; (b) Boc₂O, Et₃N, MeOH, rt, 3 d, 75%; (c) 2,2-DMOP, PPTS, acetone, rt, 20 h, 55%; (d) Grubbs’ 1st generation catalyst, DCM, reflux, 18 h, 94%; 35.3% yield over 4 steps from L-xylose.
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The versatility of this intermediate as precursor for the syntheses of several pyrrolizidine alkaloids, including casuarine and 3-epi-australine, was then demonstrated in the following by simple modifications of the synthetic route. These syntheses are outlined in the following schemes.

Scheme 4.11. T. RITTHIWIGROM’s synthesis of (−)-uniflorine A (6-epi-casuarine) (2010).[16, 17]

Reagents and conditions: (a) K₂OsO₄ · 2 H₂O, NMO, acetone, H₂O, rt, 24 h, 68%; (b) NaH, BnBr, TBAI, THF, rt, 1 d, 86%; (c) HCl, MeOH, rt, 24 h, 76%; (d) TBSCl, imidazole, DMAP, DCM, rt, 2 d, 85%; (e) DIAD, Ph₃P, Et₃NHCl, pyridine, rt, 3 d, 76%; (f) HCl, MeOH, rt, 5 h, 66%; (g) PdCl₂, H₂ (1 atm), MeOH, rt, ion-exchange chromatography, 74%; 4.9% over 11 steps from L-xylose.

At first, the 2,5-dihydropyrrole 4/36 was transformed to 6-epi-casuarine in seven further steps and 4.9% overall yield from L-xylose (Scheme 4.11). The NMR spectral data sets and specific rotations of the synthetic and the natural product were essentially identical unequivocal proving that uniflorine A is in fact 6-epi-casuarine. The 2,5-dihydropyrrole building block 4/36 was then employed as a starting point for the syntheses of (+)-casuarine (Scheme 4.12), 3-epi-australine (Scheme 4.13) and australine (not shown).[16, 17]

The synthesis of (+)-casuarine from 4/36 required a modified strategy to that for (−)-uniflorine A to achieve the inverted stereochemistry at C-6. To reach this goal the synthesis plan involved the regioselective ring-opening of epoxide 4/43 with an oxygen nucleophile. Thus, when 4/43 was treated under the conditions reported by SARACOGLU et al.[18] using NaHSO₄ as both the acid catalyst and the nucleophilic species in refluxing DCM, followed by the addition of water to hydrolyse the intermediate sulfate, the desired diol 4/44 was obtained as a 92 : 8 diastereomeric mixture in 51% yield. Hydrogenolysis of the remaining benzyl protecting groups over PdCl₂/H₂ gave (+)-casuarine in total of 13 synthetic steps and 6.2%
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

overall yield from L-xylose. Its diastereomeric purity was 95 : 5 according to $^1$H NMR spectroscopic analysis.\cite{16, 17}

\begin{align*}
\text{4/36} & \quad \rightarrow \quad \text{4/37} \\
\text{4/38} & \quad \rightarrow \quad \text{4/39} \\
\text{4/40} & \quad \rightarrow \quad \text{4/41} \\
\text{4/42} & \quad \rightarrow \quad \text{4/43} \\
\text{4/44} & \quad \rightarrow \quad \text{(+)-Casuarine}
\end{align*}

Scheme 4.12. T. RITTHIWIGROM’s synthesis of (+)-casuarine (2010).\cite{16, 17}

Reagents and conditions: (a) NaH, BnBr, TBAI, THF, rt, 18 h, 92%; (b) HCl, MeOH, rt, 30 h, 76%; (c) TBSCl, imidazole, DMAP, THF, rt, 1 d, 81%; (d) FmocCl, THF, sat. Na$_2$CO$_3$, 0 °C, 3 h, 94%; (e) CF$_3$COCH$_3$, oxone, NaHCO$_3$, MeCN/H$_2$O, 0 °C, 2 h, 81%; (f) MsCl, Et$_3$N, DCM, 0 °C, 3 h, 94%; (g) piperidine, MeCN, rt, 15 h, 96%; (h) NaHSO$_4$, DCM, reflux, 2 d, then H$_2$O, rt, 1 h, d.r. = 92 : 8, 51%; (i) PdCl$_2$, H$_2$ (1 atm), MeOH, rt, 1.5 h, ion-exchange chromatography, d.r. = 95 : 5, 93%; 6.2% yield over 13 steps from L-xylose.

The synthesis of naturally occurring (−)-3-epi-australine from the epoxide 4/45 required an inversion of configuration of the free secondary hydroxyl group. This was achieved by applying Mitsunobu’s protocol with para-nitrobenzoic acid. Basic hydrolysis of the inverted para-nitrobenzoate resulted in simultaneous N-Fmoc cleavage affording the amino alcohol 4/46 which was subjected to a N-alkylative S$_2$N$_2$/exo-tet cyclisation under Mitsunobu conditions to give the desired pyrrolizidine 4/47. Reductive ring-opening of the epoxide with LiAlH$_4$ at rt gave pyrrolizidine 4/48 in 41% isolated yield together with its separable C-6 regioisomer (not shown). In the final steps of the synthesis, the configuration at C-7 in 4/48 was inverted by a second Mitsunobu inversion to give alcohol 4/49. This compound underwent hydrogenolysis under acidic conditions with PdCl$_2$/H$_2$ to deliver diastereomERICALLY pure 3-epi-australine after ion-exchange chromatography in a total of 16 synthetic steps and 1.8% overall yield from L-xylose.\cite{16, 17}
4.3.4 Morwenna Baird’s Synthesis of Calystegine B4

With the synthesis of calystegine B4 the hitherto successful synthetic concept for pyrrolizidine and indolizidine alkaloids with the Petasis reaction as key step was now extended to nortropane alkaloids. Morwenna Baird’s synthesis of calystegine B4 is outlined in Scheme 4.14. To obtain the right stereochemical configuration of the hydroxyl and amino groups in the final product, D-lyxose was chosen as starting material this time. The Petasis reaction of this commercially available pentose with benzylamine and (E)-styrylboronic acid gave the aminotetraol 4/50 as a single diastereomer in 82% yield. The Petasis product was transformed in the following to calystegine B4 in eight additional steps as shown in Scheme 4.14.\(^{19}\)
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

Scheme 4.14 cont’d. M. BAIRD’s synthesis of calystegine B4 (2010).\(^{[19]}\)

Reagents and conditions: (a) EtOH, rt, 3 d, 82%; (b) Boc\(_2\)O, Et\(_3\)N, MeOH, rt, 3 d, 89%; (c) TrCl, pyridine, rt, 1 d, 81%; (d) BnBr, Ag\(_2\)O, TBAI, rt, 16 h, 87%; (e) PTSA, CHCl\(_3\), MeOH, rt, 16 h, 85%; (f) Dess-Martin periodinane, DCM, rt, 1.5 h for 4/52 from 4/51; 0.5 h, 79% for 4/56 from 4/54; 0.5 h, 80% for 4/57 from 4/55; (g) vinylMgBr, THF, 0 °C to rt, 3 h, 29% over 2 steps for 4/53, 23% over 2 steps for 4/54; (h) Grubbs’ 2\(^{nd}\) generation catalyst, DCM, microwave, 90 °C, 1.5 h, 77% for 4/55 from 4/53; 2 h, 57% for 4/57 from 4/56; (i) 1. Pd(OH)\(_2\)/C, H\(_2\) (1 atm), THF/H\(_2\)O, rt, 4.5 h; 2. PdCl\(_2\), H\(_2\) (1 atm), THF/H\(_2\)O, rt, 4 h; 3. PdCl\(_2\), H\(_2\) (1 atm), MeOH, rt, 1.5 h, then basic ion-exchange chromatography, 51%; 6.3% over 10 steps from D-lyxose.

It is worth mentioning that the intermediate diastereomeric dienes 4/53 and 4/54 showed different reaction rates in their ring-closing metathesis reactions. The RCM reaction of 4/53 using Grubbs 2\(^{nd}\) generation catalyst under microwave heating at 90 °C for 90 min gave the desired cycloheptenol 4/55 in 77% yield. The RCM reaction of the diastereomer 4/54 under the same conditions, however, was by far slower and gave the epimeric cycloheptene (not shown) in only 37% yield, even though three times the amount of Grubbs’ catalyst compared to 4/53 was used. It was speculated that the difference in the RCM reaction rates for 4/53 and 4/54 was due to the varying coordination behaviour of the secondary hydroxyl group to the ruthenium centre in the intermediates A and B (see Figure 4.3). In intermediate B such coordination would make it energetically more difficult for the ruthenium carbene double
bond to be parallel to the styrene double bond as required for the RCM process resulting in a much reduced reaction rate. This difference in the RCM reaction rates eventually led to the alternate synthetic route for alcohol 4/54 via the styryl enone 4/56 to the cycloheptenone 4/57.[19]

Figure 4.3. The difference in the RCM reaction rates of the epimeric dienes 4/53 and 4/54.[19]

With the evolution of the Petasis approach to a potent and flexible method for the synthesis of a variety of polyhydroxylated alkaloids by now, its application as a general synthetic method was still problematic since enantiomerically pure α-hydroxyaldehydes other than carbohydrates were not generally available. Nevertheless, a more recent paper by EVANS et al. showed that these valuable substrates could be prepared in situ via the Sharpless asymmetric dihydroxylation (SAD) reaction of vinyl sulfones.[20] This new method allowed a much more rapid access to these valuable building blocks. More specifically, the derived anti-1,2-amino alcohol diene products, obtained by their Petasis reaction with allylic amines, are useful precursors for alkaloid synthesis as former PhD student Christopher AU demonstrated by a short, formal synthesis of (−)-swainsonine.

4.3.5 Christopher AU’s Formal Synthesis of (−)-Swainsonine

The necessary (E)-vinyl sulfones can easily be prepared from their corresponding terminal alkenes either via cross metathesis with phenyl vinyl sulfone or by iodosulfonation followed by elimination of HI. Treatment of the TBDPS-protected vinyl sulfone 4/59 with AD-mix-β
followed by the Petasis reaction of the crude oxidation product with allylamine and (E)-styrylboronic acid gave the desired anti-1,2-amino alcohol diene $4/61$ in an overall yield of 38% in 93% enantiomeric excess. Although the overall yield of $4/61$ can only be considered as moderate, the significant brevity of this approach (three consecutive steps) compares more than favourably with the at the beginning of this chapter presented aminolysis of vinyl epoxides with allylic amines, which required seven synthetic steps from commercially available starting materials. The moderate yield most likely reflects the instability of the intermediate $\alpha$-hydroxy aldehyde $4/60$.\[21, 22\]

The anti-1,2-amino alcohol $4/61$ was then converted in four steps to the literature known indolizidine $4/65$ as shown in Scheme 4.15 including the ring-closing metathesis of $4/64$, employing Ti(OiPr)$_4$ as complexing agent for the basic amino group. This literature known compound ($4/65$) has previously been used by the BLECHERT group for the synthesis of $(-)$-swainsonine in 2002.\[23\] AU then went on and extended this synthetic strategy to the synthesis of the pyrrolizidine alkaloids hyacinthacine B3 and B7.

Scheme 4.15. C. AU’s formal synthesis of $(-)$-swainsonine (2006).\[21, 22\]

Reagents and conditions: (a) Sharpless asymmetric dihydroxylation with AD-mix-$\beta$; (b) allylamine, (E)-styrylboronic acid, DCM, rt, 40 h, 38%, 93% ee; (c) TBOSOTf, 2,6-lutidine, DCM, 0 °C, 2.5 h, 70%; (d) KOH, MeOH, reflux, 7 h, 60%; (e) Ph$_3$P, CBr$_4$, Et$_3$N, DCM, 0 °C, 2 h, 71%; (f) Ti(OiPr)$_4$, Grubbs’ 2nd generation catalyst, DCM, reflux, 2.5 h, 80%.
4.3.6 Christopher Au’s Syntheses of Hyacinthacine B3 and Purported Hyacinthacine B7

The synthesis of hyacinthacine B3 and hyacinthacine B7 started with commercially available (S)- and (R)-4-penten-2-ol, respectively. These two separate syntheses are summarised in Scheme 4.16.

**Scheme 4.16.** C. Au’s syntheses of hyacinthacine B3 and purported hyacinthacine B7 (2010).[24]

Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, rt, 18 h, a: 90%, b: 86%; (b) phenyl vinyl sulfone, Grubbs’ 2nd generation catalyst, DCM, microwave, 90 ºC, 1 h, a: 68%, b: 71%; (c) DHQD-IND-OsO₄, CH₂SO₂NH₂, t-BuOH/H₂O, rt, 24 h; (d) DCM, rt, 2 d, a: 53%, b: 40% over 2 steps; (e) triphosgene, Et₃N, DCM, rt, 16 h, a: 81%, b: 54%; (f) Grubbs’ 2nd generation catalyst, DCM, microwave, 90 ºC, 1 h, a: 76%, b: 87%; (g) K₂OsO₄·2 H₂O, NMO, acetone/H₂O, rt, 18 h, a: 88%, b: 89%; (h) NaH, BnBr, TBAI, THF, rt, 18 h, a: 100%, b: 94%; (i) DDQ, DCM/H₂O, rt, 4 h, a: 89%, b: 92%; (j) NaOH, EtOH, microwave, 110 ºC, 1 h, a: 84%, b: 91%; (k) MsCl, Et₃N, DCM, 0 ºC, 1.5 h, a: 63%, b: 51%; (l) PdCl₂, H₂ (1 atm), MeOH, 8 h, then basic ion-exchange chromatography, a: 68%, b: 84%; 5.6% over 12 steps for hyacinthacine B3 from (S)-4-Penten-2-ol, 3.4% for purported hyacinthacine B7 from (R)-4-Penten-2-ol, respectively.
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For the synthesis of hyacinthacine B3 (1/139), (S)-penten-2-ol was at first transformed to the pyrrolo[1,2-c]oxazol-3-one 4/69a in six steps including the asymmetric dihydroxylation of vinyl sulfone 4/66a and the consequent Petasis reaction of the resulting intermediate α-hydroxy aldehyde 4/67a as key steps. As in the previous work of our group, the bicyclic oxazolidinone 4/69a proved once more to be a stereodirecting protecting group for the upcoming syn-dihydroxylation of its double bond. In the event, the Os(VIII)-catalysed syn-DH of 4/69a provided the desired diol 4/70a as single diastereoisomer. This diol was consequently converted to hyacinthacine B3 in five further steps. The spectroscopic data of the synthetic compound matched very closely to that reported for the natural product, hence proving its originally assigned structure to be correct.\textsuperscript{[22, 24]}

The proposed structure of hyacinthacine B7 (1/143) was prepared in an analogous fashion starting from (R)-4-penten-2-ol. The yields and diastereoselectivities were essentially the same except for the conversion of vinyl sulfone 4/66b into the amino alcohol 4/68b. After the Petasis reaction the overall yield of 4/68b from 4/66b was only 40% since a significant amount of the other diastereoisomer of 4/68b (20%) had also been formed. It was suspected that this diastereomer arises in the conversion of 4/66b into the α-hydroxy aldehyde 4/67b due to a mismatched situation between the chiral reagent and the chiral substrate.\textsuperscript{[22, 24]}

However more importantly, the NMR spectroscopic data of the synthetic final product did not match with that reported for hyacinthacine B7. NOESY NMR analysis confirmed the relative configuration of the synthetic compound to be identical with that assigned for the natural product. It was therefore concluded that the proposed structure of hyacinthacine B7 is incorrect,\textsuperscript{[22, 24]} and work is now continuing in our group to ascertain the correct structure.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4_4.png}
\caption{Proposed correct structure of hyacinthacine B7 (= 5-epi-hyacinthacine B5).}
\end{figure}
Chapter 4. Syntheses of Polyhydroxylated Alkaloids

4.4 Summary

The synthesis of polyhydroxylated alkaloids incorporating an \textit{anti}-configured \(\alpha\)-amino-hydroxy structural element represents a main research focus of our research group. In the early stages of this research project, it has been demonstrated that the sequential application of the aminolysis reaction of chiral vinyl epoxides paired with a ring-closing metathesis is a successful strategy for the synthesis of various polyhydroxylated pyrrolizidine and indolizidine alkaloids including swainsonine and australine epimers. With the employment of the Petasis borono-Mannich reaction, the requisite intermediate chiral \textit{anti}-1,2-amino alcohols were considerably easier accessible, and in combination with the tandem RCM/syn-DH reaction, it allowed a more rapid access to several representatives of the polyhydroxylated alkaloid family. Furthermore, it has been shown that the intermediate pyrrolo-[1,2-\(c\)]oxazol-3-ones are valuable substrates for diastereoselective manipulations due to their bicyclic nature. With the developed synthesis methodology, it was possible to confirm or refute the structures of several polyhydroxylated alkaloids as seen in the examples of the hyacinthacines B3 and B7. Furthermore, the new methodology allowed the revision of the originally wrongly assigned pyrrolizidine uniflorine A and elucidate its correct structure via total synthesis.

4.5 References

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Chapter 4. Syntheses of Polyhydroxylated Alkaloids
Chapter 5. The Petasis borono-Mannich Reaction

5.1 Introduction

Multicomponent reactions (MCRs) are transformations whereby more than two reactants combine in a sequential manner to give highly selective products that retain the majority of the atoms of the starting materials. These reactions have become an important tool in the discovery of new drug leads due to the possibility to create large libraries of compounds by the simple modification of a substituent which leads to a diverse set of new molecules. Such a reaction is the Petasis borono-Mannich reaction.[1, 2]

In 1993, Nicos A. PETASIS and his co-worker Irini AKRITOPOULOU reported a novel, efficient three-component synthesis of allylic amines based on a modified Mannich reaction where vinylboronic acids served as the nucleophilic component. PETASIS himself called this new reaction the Boronic Acid Mannich (BAM) reaction but in the following years it became known as the Petasis borono-Mannich (PBM) or simply the Petasis reaction. PETASIS’ initial studies involved reactions of vinylboronic acids with the condensation products of a secondary amine and paraformaldehyde (Scheme 5.1). Under these conditions, the amine 5/1 is converted to the aminomethanol derivative 5/3 which reacts with the vinylboronic acid 5/4 to give the allylamine product 5/5 with complete retention of the geometry of the double bond. The reaction is conveniently carried out by heating a mixture of paraformaldehyde (5/2) and the secondary amine 5/1 at 90 °C in toluene or dioxane for ten minutes. This is followed by the addition of the vinylboronic acid 5/4 to this mixture and stirring either at 25 °C for several hours or at 90 °C for 30 minutes. The work-up procedure includes a simple acid-base extraction to remove any unreacted vinylboronic acid affording the allylic amine usually in a high yield.[3]

Most likely, the reaction proceeds via the attack of the aminomethanol intermediate 5/3 on the electrophilic boron leading to an “ate”-complex. Subsequent vinyl transfer provides the allylic amine 5/5 with boronic acid as side product (Scheme 5.2).[1]
Chapter 5. The Petasis borono-Mannich Reaction

Scheme 5.2. Proposed mechanism for the Petasis reaction of formaldehyde with secondary amines and vinylboronic acids.[1]

As a proof of principle PETASIS et al. employed their method for the one-step synthesis of naftifine (5/6). This tertiary allylamine is a potent antifungal agent applied in the treatment of opportunistic fungal infections, particularly with AIDS, cancer and other immunocompromised conditions. The reaction of paraformaldehyde with $N$-methyl-$N$-1-naphthylmethylamine in 1,4-dioxane at 90 °C gave the requisite aminomethanol intermediate which was treated with $(E)$-styrylboronic acid at 90 °C for 30 min to afford naftifine in 82% after aqueous work-up (Scheme 5.3).[3]

Following their seminal work with paraformaldehyde PETASIS went on and explored the use of various other carbonyl compounds as components in the borono-Mannich reaction. In 1997, PETASIS and Ilia ZAVIALOV showed that $\alpha$-keto acids such as glyoxylic acid also undergo the transformation to afford $\alpha$-amino acids (Scheme 5.4).[4] Some examples are shown in Table 5.1.
Table 5.1. Examples of α-amino acids synthesised via the PBM reaction of α-keto acids with primary or secondary amines and substituted vinylboronic acids.4

<table>
<thead>
<tr>
<th>α-Keto acid</th>
<th>Amine</th>
<th>Boronic acid</th>
<th>α-Amino acid / Yield</th>
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<td><img src="image-2.png" alt="Image" /></td>
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<td><img src="image-14.png" alt="Image" /></td>
<td><img src="image-15.png" alt="Image" /></td>
<td><img src="image-16.png" alt="Image" /> / 76%</td>
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</tbody>
</table>

In 2001, PETASIS and Sougato BORAL expanded the borono-Mannich reaction further to the use of salicylaldehydes as carbonyl component demonstrating that these aromatic aldehydes also react with amines and boronic acids providing the corresponding aminomethylphenol derivatives in a single step (Scheme 5.5). However, it should be noted that in this case secondary amines were found to be the better substrates giving higher yields than primary ones (Table 5.2).5

Scheme 5.5. The Petasis reaction of salicylaldehydes with primary or secondary amines and aryl- or vinylboronic acids giving aminomethylphenol derivatives.
Table 5.2. Examples of aminomethylphenol derivatives synthesised via the PBM reaction of salicylaldehydes with primary or secondary amines and aryl- or vinylboronic acids.\textsuperscript{9}

<table>
<thead>
<tr>
<th>Salicylaldehyde</th>
<th>Amine</th>
<th>Boronic acid</th>
<th>Aminomethylphenol / Yield</th>
</tr>
</thead>
</table>
| \[
\begin{array}{c}
\text{OH} \\
\text{H} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{N} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{B} \\
\text{OH}
\end{array}
\] | \[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph}
\end{array}
\]
| 81% |
| \[
\begin{array}{c}
\text{OH} \\
\text{H} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{N} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{B} \\
\text{OH}
\end{array}
\] | \[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph}
\end{array}
\]
| 70% |
| \[
\begin{array}{c}
\text{OH} \\
\text{H} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{Boc} \\
\text{N} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{OH} \\
\text{B} \\
\text{OH}
\end{array}
\] | \[
\begin{array}{c}
\text{OMe} \\
\text{N} \\
\text{Ph}
\end{array}
\]
| 63% |
| \[
\begin{array}{c}
\text{OH} \\
\text{H} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{B} \\
\text{OH}
\end{array}
\] | \[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Ph}
\end{array}
\]
| 32% |

When enantiopure $\alpha$-hydroxy aldehydes are employed as the carbonyl component in the PBM reaction, $\textit{anti}$-configured $\beta$-amino alcohols are obtained with a $\textit{de}$ greater than 99\% (Scheme 5.6).\textsuperscript{6–8}

\[
\text{R}^1\text{C}(\text{OH})\text{H} + \text{R}^2\text{N}^\text{R}^3 + \text{HOBR}^4 \rightarrow \text{R}^1\text{H} + \text{R}^2\text{N}^\text{R}^3\text{N}^\text{R}^4
\]

$\alpha$-hydroxy aldehyde  $1^\text{st}$ or $2^\text{nd}$ amine  aryl- or vinylboronic acid  $\textit{anti}$-$\beta$-amino alcohol

\textbf{Scheme 5.6.} The PBM reaction of $\alpha$-hydroxy aldehydes with primary or secondary amines and aryl- or vinylboronic acids affording stereoselectively $\textit{anti}$-$\beta$-amino alcohol.
Chapter 5. The Petasis borono-Mannich Reaction

At present this is the most commonly applied version of the Petasis reaction which has been used in recent years for the syntheses of various therapeutic drugs and natural products, particularly in our research group for the syntheses of several polyhydroxylated alkaloids as presented in Chapter 4. Table 5.3 shows a number of examples of PBM reactions with various \( \alpha \)-hydroxy aldehydes.

Table 5.3. Examples of \( \beta \)-amino alcohols synthesised via the PBM reaction of \( \alpha \)-hydroxy aldehydes with primary or secondary amines and substituted aryl- or vinylboronic acids.\(^6\text{-}\text{8}\)

<table>
<thead>
<tr>
<th>( \alpha )-Hydroxy aldehyde</th>
<th>Amine</th>
<th>Boronic acid</th>
<th>( \beta )-Amino alcohol / Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{HOCH(OH)} )</td>
<td>( \text{H}_3\text{C}\text{NH} )</td>
<td>( \text{HOBOC} )</td>
<td>( \text{HOCH(OH)} \text{O} \text{N} \text{Me} \text{Ph} ) 87%</td>
</tr>
<tr>
<td>( \text{HOCH(OH)} )</td>
<td>( \text{Ph} \text{NH}_2 )</td>
<td>( \text{HOBOC} )</td>
<td>( \text{HOCH(OH)} \text{O} \text{NPh} ) 86%</td>
</tr>
<tr>
<td>( \text{HOCH(OH)} )</td>
<td>( \text{Ph} \text{NHMe} \text{Ph} )</td>
<td>( \text{HOBOC} )</td>
<td>( \text{HOCH(OH)} \text{O} \text{NPh} \text{OMe} ) 63%</td>
</tr>
<tr>
<td>( \text{HOCH(OH)} )</td>
<td>( \text{Ph} \text{OCH(OH)} \text{H} \text{N} \text{H2N} \text{Ph} )</td>
<td>( \text{HOBOC} )</td>
<td>( \text{HOCH(OH)} \text{O} \text{NPh} \text{p-MeOPh} ) 30%</td>
</tr>
<tr>
<td>( \text{HOCH(OH)} )</td>
<td>( \text{Ph} \text{OCH(OH)} \text{H} \text{N} \text{H2N} \text{Ph} )</td>
<td>( \text{HOBOC} )</td>
<td>( \text{HOCH(OH)} \text{O} \text{NPh} \text{OMe} ) 90%</td>
</tr>
<tr>
<td>( \text{HOCH(OH)} )</td>
<td>( \text{Ph} \text{OCH(OH)} \text{H} \text{N} \text{H2N} \text{Ph} )</td>
<td>( \text{HOBOC} )</td>
<td>( \text{HOCH(OH)} \text{O} \text{NPh} \text{OMe} ) 75%</td>
</tr>
</tbody>
</table>
5.2 Mechanistic Considerations

Soon after the pioneering work of PETASIS and his co-workers on the borono-Mannich reaction, the first mechanism were proposed. Two different mechanistic pathways were suggested by PETASIS, HANSEN and RAULT. PETASIS et al. assumed that the reaction proceeds via the initial reaction between the amine and the aldehyde to give an iminium-ion intermediate which is co-ordinated by the boronic acid to form a boronate-complex as depicted in Path A of Scheme 5.7.\(^5\) The subsequent intramolecular group transfer from the boron centre to the iminium carbon then leads to the carbon-carbon bond formation. HANSEN and RAULT, on the other hand, proposed that the reaction starts with the formation of the boronate-complex from the \(\alpha\)-hydroxy aldehyde, and the generation of the iminium ion is the second step as shown in Path B of Scheme 5.7.\(^9, 10\) Recent DFT calculations performed by TAO and LI, however, were supportive for only one of the two proposed pathways, indicating that the one previously described by PETASIS et al. (Path A) is the most favourable.\(^11\)

\[\text{Scheme 5.7. Proposed mechanisms for the PBM reaction of } \alpha\text{-hydroxy aldehydes.}^{[2, 11]}\]

As PETASIS and ZAVIALOV demonstrated in their pioneering work the PBM reaction of \(\alpha\)-hydroxy aldehydes is highly stereoselective. The exclusive formation of the diastereomeric \textit{anti}-\(\beta\)-amino alcohols is observed starting from racemic \(\alpha\)-hydroxy aldehydes, while a single enantiomer is obtained when enantiomerically pure starting materials were employed. From
our research group it was suggested that in the case of vinylboronic acids, the diastereoselectivity arises from that reactive conformation of the intermediate ate-complex, in which the 1,3-allylic strain is reduced to a minimum (Scheme 5.8).\[12\]

Scheme 5.8. Proposed origin of the diastereoselectivity in the Petasis reaction through minimisation of the 1,3-allylic strain.\[12\]

From these simple beginnings the Petasis reaction evolved into an important and diverse tool in organic chemistry that is used nowadays frequently in the development of new drugs and the synthesis of natural products. Some selected examples are given in the following.

5.3 Synthesis of (+)- and (−)-Cytoxazone by SUGIYAMA et al.

(−)-Cytoxazone (5/9a) is a novel cytokine modulator produced by a Streptomyces species.\[13, 14\] A short total synthesis of this natural product was accomplished by SUGIYAMA and co-workers over five steps employing the PBM reaction as key step. The 3-amino-1,2-propanediol 5/7 was assembled by the Petasis reaction of DL-glyceraldehyde with (R)-1-(1-naphthyl)ethylamine and para-methoxyphenylboronic acid to provide 5/7 as a 1 : 1 mixture of diastereoisomers. These diastereoisomers could be separated by column chromatography at a later stage in the synthesis as their oxazolidinone derivatives 5/8a and 5/8b and were consequently transformed into (−)- and (+)-cytoxazone, respectively (Scheme 5.9).\[15\]
Chapter 5. The Petasis borono-Mannich Reaction

\[ \text{DL-glyceraldehyde} + (R)-1-(1-naphthyl)ethylamine + p\text{-methoxyphenylboronic acid} \rightarrow \]

\[ \text{5/7} \rightarrow \text{5/8a} \rightarrow \text{5/8b} \rightarrow \text{5/9a} \rightarrow \text{5/9b} \]

**Scheme 5.9.** Short synthesis of both enantiomers of cytoxazone by **SUGIYAMA et al.** (2004).[^1]

Reagents and conditions: (a) DL-glyceraldehyde, (R)-1-(1-naphthyl)ethylamine, p-methoxyphenylboronic acid, EtOH, reflux, 3 d, 50 \%; (b) TBSCI, Et$_3$N, DMAP, DCM, rt, 30 h; (c) CDI, DCM, rt, 4 d; (d) 6 M aq. HCl, 23 h, rt, separation of diastereoisomers by column chromatography on SiO$_2$, 29\% 5/8a and 16\% 5/8b over three steps; (e) MsOH, anisole, MeNO$_2$, 50 °C, 6 h, 90\% (−)-5/9a, 86\% (+)-5/9b; 13\% over 5 steps for (−)-cytoxazone, 7\% for (+)-cytoxazone, respectively.

### 5.4 Synthesis of the Immunosuppressive Agent FTY720 (Fingolimod) by **ISHII et al.**

One of the most studied sphingoid base-like compounds is the immunosuppressive agent FTY720 (2/47), also referred to as fingolimod, which was developed in the search for a less toxic form of the serine palmitoyltransferase inhibitor ISP-1/myriocin (2/46, see Chapter 2, Section 2.5).[^2] FTY720 does not inhibit this enzyme but is phosphorylated in the cell by sphingosine kinase to FTY720-P which acts as a desensitiser for the sphingosine 1-phosphate receptor resulting in immunosuppression. Although its mechanism of action is not fully
understood, FTY720 appears to reduce the number of circulating T-lymphocytes by inhibiting lymphocyte egress from peripheral lymph nodes. Because of this effect, FTY720 efficiently prevents transplant rejection and is currently evaluated in human clinical trials for safety and tolerability in renal transplantation. Furthermore, it has shown promising results in phase II trials for multiple sclerosis treatment.\cite{16–18}

Due to its potent therapeutic activity and simple structure, ISHII and co-workers set out to develop a short and convenient synthesis for FTY720 employing the Petasis reaction as the key step. The required vinylboronic acid for the PBM reaction is not commercially available but was synthesised in three steps from 4-octylbenzaldehyde via a Corey-Fuchs alkyne synthesis followed by the hydroboration-hydrolysis of the intermediate alkyne 5/11 to yield the desired \((E)-2-(4\text{-octylphenyl})\text{vinyl-boronic acid (5/12).}\) The Petasis reaction of \(5/12\) with dihydroxyacetone and benzylamine then provided the aminodiol 5/13 which upon hydrogenation afforded FTY720 in 27.6\% yield over a total of five steps (Scheme 5.10).\cite{19}

Scheme 5.10. Concise synthesis of the immunosuppressive agent FTY720 by ISHII et al. (2005).\cite{19}

Reagents and conditions: (a) PPh\(_3\), CBr\(_4\), CH\(_2\)Cl\(_2\), 0 °C, 1 h, 83%; (b) \(n\)-BuLi, THF, –78 °C, 1 h, then rt, 2 h, 84%; (c) catecholborane (1 M in THF), 80 °C, 4 h; (d) EtOH, rt, 36 h, 44\% over 2 steps; (e) Pd/C, H\(_2\) (1 atm), 10\% aq. HCl, EtOH, 90%; 27.6\% over 5 steps from 4-octylbenzaldehyde.
5.5 Synthesis of rac-Clopidogrel by KALINSKI et al.

Clopidogrel is an oral, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. It is marketed by BRISTOL-MYERS SQUIBB and SANOFI-AVENTIS under the trade name PLAVIX® and was the world’s second-highest-selling pharmaceutical in 2005.\(^{[20]}\) In 2008, KALINSKI and co-workers studied the use of several multicomponent reactions as a method for the preparation of clopidogrel in its racemic form and showed that this drug can be synthesised efficiently via a two-step synthesis with a Petasis reaction as the key step. Despite the better yields achieved through the synthesis via an Ugi threecomponent reaction, the PBM reaction of glyoxylic acid with 4,5,6,7-tetrahydrothieno[3,2-c]pyridine and 2-chlorophenylboronic acid allowed the preparation of the clopidogrel precursor \(5/14\) in 49\% yield. Subsequent acidic esterification afforded the desired product \(5/15\) in 44\% overall yield (Scheme 5.11).\(^{[21]}\)

\[ \text{2-Chlorophenylboronic acid} + \text{Glyoxylic acid} + \text{4,5,6,7-Tetrahydrothieno[3,2-c]pyridine} \rightarrow \]

| Reagents and conditions: (a) DMF, rt, 7 d, 49\%; (b) conc. H\(_2\)SO\(_4\), MeOH, reflux, 3 d, 90\%; 44\% over 2 steps from glyoxylic acid. |

![Scheme 5.11. Synthesis of (±)-clopidogrel by KALINSKI et al.(2008).](image)

5.6 Synthesis of Sialic Acids and Novel Analogues by WONG et al.

Sialic acids are a family of monosaccharides of which more than 50 natural derivatives have been identified. The best-known members of this family are \(N\)-acetylneuraminic acid and its 5-glycolylamido derivative Neu5Gc. Sialic acids are recognised to be involved in various biological processes such as cell–cell recognition, blood coagulation and fertilisation, but also in the pathogenesis of various inflammatory diseases, cancer metastasis and virus infections.\(^{[22]}\)
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As a result, increasing attention has been paid recently to the utilisation of sialic acids and their analogues as probes or inhibitors in biological and medicinal research. Some sialic acid analogues have even achieved commercial success such as RELENZA® and TAMIFLU® for the treatment of influenza.\textsuperscript{[23, 24]} However, a challenge still remaining in this area is the development of new concise and efficient, yet stereochemically flexible, synthetic methods for these compounds.

In 2006 WONG and co-workers set out to develop such a new synthetic route. Their synthesis of D-\textit{N}-glycolylneuraminic acid (5/20) as a representative example is shown in Scheme 5.12.\textsuperscript{[25]}

\textbf{Scheme 5.12.} Synthesis of D-\textit{N}-glycolylneuraminic acid by WONG et al. (2006).\textsuperscript{[25]}

Reagents and conditions: (a) EtOH/H\textsubscript{2}O (4 : 1), 50 °C, 3 d; (b) TFA, 50 °C; (c) \textit{N}-2-acetoxyacetylsuccinimide, 50\% over 3 steps; (d) 1,4-dioxane, 30 °C, 80\%; (e) 0.05 M NaOMe in MeOH, then H\textsubscript{2}O, 55\%; 22\% over 5 steps from D-arabinose.

WONG et al. achieved their goal by employing inexpensive D-arabinose as starting material in a Petasis reaction with di-\textit{para}-anisylmethylamine and dibutylvinylboronate. The dibutylvinylbononic acid ester was chosen as boronic component since the free acid is an unstable compound that decomposes rapidly at room temperature. An interesting aspect of this PBM
reaction is the necessity of water as a co-solvent, the slightly higher reaction temperature (50 °C rather than rt) and the increased reaction time (72 instead of 24 hours) for a successful outcome. This indicates that the boronic ester is hydrolysed in situ to the acid prior to its reaction with the intermediate iminium ion.\[25\]

Rather than isolating the highly polar Petasis product 5/16 WONG et al. went on to transform this amine in a one-pot process by two further reactions into the less polar amide 5/17. This amide was then converted into the target compound D-N-glycolylneuraminic acid (5/20) via a [2+3]-cycloaddition of amide 5/17 with the N-tert-butyl nitrone 5/18 followed by the base-catalysed \(\beta\)-elimination and ester hydrolysis of 5/19.\[25\]

To prove the flexibility of their synthesis route WONG et al. then continued to synthesise several unnatural sialic acid derivatives by employing different carbohydrates as starting materials in their developed one-pot Petasis coupling approach. In this way, the unnatural enantiomer of N-acetylneuraminic acid (5/24) as well as the truncated and elongated sialic acid derivatives 5/22 and 5/26 were obtained (Scheme 5.13).\[25\] It is worth mentioning that WONG’s Petasis approach, unlike other published sialic acid syntheses, did not require any protecting group manipulations and therefore gave rapid access to the desired compounds.

Scheme 5.13. Synthesis of truncated and elongated sialic acid derivatives by WONG et al. (2006).\[25\]
5.7 Synthesis of Iminosugars via a Petasis-type Aminocyclisation by WONG et al.

After the successful preparation of sialic acids WONG et al. went on to study the use of the Petasis reaction in the synthesis of iminosugars. They envisioned a concise synthesis of polyhydroxylated pyrrolidine and piperidine alkaloids via a Petasis-type aminocyclisation reaction of *in situ* generated di- and trihydroxydialdehydes. As a representative example WONG and co-workers intended the synthesis of (+)-DMDP (1/51) starting from commercially available 3,4-*O*-isopropylidene-D-mannitol. Initially, they planned to generate the requisite 2,3-dihydroxysuccinaldehyde (5/28) from this partly protected D-mannitol derivative and react it *in situ* in a Petasis reaction with ammonia and (E)-styrylboronic acid to afford the bis-styryl pyrrolidine 5/29 in a one-pot sequence. Ozonolysis of 5/29 followed by reduction with NaBH₄ would finally give the aspired natural iminosugar (+)-DMDP in two steps (Scheme 5.14).[26]

![Chemical structures](image)

**Scheme 5.14.** Synthesis plan for (+)-DMDP via a Petasis-type aminocyclisation by WONG et al. (2009).[26] (a) oxidative diol cleavage; (b) acid-catalysed acetonide cleavage; (c) Petasis reaction with NH₃ and (E)-styrylboronic acid; (d) ozonolysis then NaBH₄ reduction.

To avoid the use of toxic Pb-containing reagents, WONG et al. employed PhI(OAc)₂ as agent for the oxidative diol cleavage in the starting material to afford the intermediate dialdehyde 5/27. Further addition of 0.1 M H₂SO₄ to the reaction mixture removed the acetonide protecting group to generate the required 2,3-dihydroxysuccinaldehyde (5/28) as immediate precursor in the Petasis reaction. To their surprise the Petasis aminocyclisation of 5/28 with concentrated ammonia and (E)-styrylboronic acid did not produce the anticipated *all-trans-(2R,3R,4R,5R)-diastereomer* of the *bis*-vinylated pyrrolidine 5/29 but its C₂-symmetric (2S,3R,4R,5S)-diastereomer 5/30 instead (Scheme 5.15).[26]
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Scheme 5.15. Concise synthesis of (2S,3R,4R,5S)-DMDP via a Petasis-type aminocyclisation by WONG et al. (2009).[26]
Reagents and conditions: (a) 1. PhI(OAc)$_2$, MeOH/DCM (2 : 1), rt, 5 h; 2. 0.1 M H$_2$SO$_4$, rt, o/n, then AcOH; 3. conc. aq. NH$_3$, (E)-styrylboronic acid, MeOH, rt, 3 d, 70% over 3 steps; (b) 1. HClO$_4$ in MeOH, 2. O$_3$, MeOH, $-78$ °C, 3. NaBH$_4$, $-78$ °C to rt, o/n, 85%; 59.5% over 2 steps from 3,4-O-isopropylidene-ß-mannitol.

To rationalise this observation WONG and co-workers suggested that the reaction proceeds via two cyclic iminium ions 5/32 and 5/34 as shown in Scheme 5.16. Initially the dialdehyde 5/28 reacts with ammonia to form a first pyrrolidinium ion (5/32). Coordination of the styrylboronic acid then promotes cis-addition of the vinyl group to the C-terminus of the iminium double bond (5/33). This step produces a new pyrrolidinium ion (5/34) that undergoes a second cis-vinylation (5/35) finally affording the pyrrolidine 5/30. This mechanism explains why the cis- and not the trans-product is obtained in the condensation.[26]
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With pyrrolidine 5/30 in hand WONG et al. then focused on the ozonolysis of the styryl double bonds to obtain the DMDP stereoisomer 5/31. However, under standard ozonolysis-reduction conditions only mixtures of unidentified products were obtained. It was hypothesised that the free imino group may interfere in the reaction. To overcome this problem, WONG and co-workers decided to protonate the imino group and in this way protect it from possible oxidation. After testing a number of acids they found that by adding HClO₄ to the MeOH solution of 5/30, the ozonolysis occurred smoothly yielding the desired tetrahydroxylated pyrrolidine 5/31 in 85% after reduction with NaBH₄.[26]

By employing the above synthesis route WONG and co-workers were also able to prepare further five- and six-membered iminosugars (Table 5.4).

Table 5.4. Iminosugars synthesised by WONG et al. via their two-step Petasis aminocyclisation-ozonolysis protocol.[26]

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product of aminocyclisation</th>
<th>Product of ozonolysis</th>
<th>Overall yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-O-isopropylidene-d-mannitol</td>
<td><img src="image" alt="Structure" /></td>
<td>2,5-Dideoxy-2,5-imino-L-iditol (5/31)</td>
<td>85%</td>
</tr>
<tr>
<td>3,4-O-isopropylidene-L-mannitol</td>
<td><img src="image" alt="Structure" /></td>
<td>2,5-Dideoxy-2,5-imino-D-iditol (5/42)</td>
<td>85%</td>
</tr>
<tr>
<td>(3R,4S)-tetrahydro-2,5-dimethoxy-3,4-furandiol</td>
<td><img src="image" alt="Structure" /></td>
<td>2,5-Dideoxy-2,5-imino-D-galactitol (5/43)</td>
<td>75%</td>
</tr>
<tr>
<td>1,2-O-Isopropylidene α-D-glucofuranose</td>
<td><img src="image" alt="Structure" /></td>
<td>β-Homoidonojirimycin</td>
<td>5/44 80%</td>
</tr>
</tbody>
</table>
Table 5.4 cont'd. Iminosugars synthesised by WONG et al. via their two-step Petasis aminocyclisation-ozonolysis protocol.\[26\]

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product of aminocyclisation</th>
<th>Product of ozonolysis</th>
<th>Overall yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-(O)-Isopropylidene-(\alpha)-D-allofuranose</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
<td>55.25%</td>
</tr>
<tr>
<td>2,3-(O)-isopropylidene-(\alpha),(\beta)-D-mannofuranose</td>
<td><img src="image3" alt="Structure" /></td>
<td><img src="image4" alt="Structure" /></td>
<td>45.0%</td>
</tr>
<tr>
<td>1,2-(O)-Isopropylidene-(\alpha)-D-galactofuranose</td>
<td><img src="image5" alt="Structure" /></td>
<td><img src="image6" alt="Structure" /></td>
<td>44.0%</td>
</tr>
</tbody>
</table>

The starting materials for these syntheses were 1,2- or 2,3-\(O\)-isopropylidene-protected \(D\)-glucose, \(D\)-mannose, \(D\)-galactose, and \(D\)-allose, which were either commercially available or readily synthesised by known procedures. The same one-pot reaction sequence of \(\text{PhI(OAc)}_2\) oxidation, \(\text{H}_2\text{SO}_4\) hydrolysis, and Petasis aminocyclisation provided the \(\text{bis-vinylated intermediums}\ 5/36 - 5/41\), which were ozonolysed to the not naturally occurring iminosugars \(5/42 - 5/46\) including the already discussed iminopyranose \(\alpha\)-homogulonojirimycin (1/33) (see Chapter 1, Figure 1.14) with overall yields between 40 to 60%.\[26\]

### 5.8 Synthesis of \((\pm)\)-6-Deoxycastanospermine by BATEY et al.

R.A. BATEY and co-workers developed a modification of the PBM reaction that occurs via \(N\)-acyliminium ions derived from \(N\)-protected-2,3-dihydroxypyrrolidine derivatives.\[27\] The formation of the \(N\)-acyliminium ion was achieved by treating \(N\)-Cbz-2,3-dihydroxypyrrolidine
5/52 with BF$_3$-etherate at low temperature. Subsequent vinyl transfer from an alkenylboronic ester provided the cis-2,3-disubstituted pyrrolidines in good to excellent yields and diastereoselectivity. This method was then utilised by BATEY *et al.* in the total synthesis of racemic 6-deoxycastanospermine (5/58) (Scheme 5.17).[28]

Scheme 5.17. Synthesis of (±)-6-deoxycastanospermine by BATEY *et al.* (2000).[28]  
Reagents and conditions: (a) Ac$_2$O, Et$_3$N, DMAP, DCM, 0 °C to rt, 86%; (b) 1. Chx$_2$BH, THF, 0 °C to rt, 2. Me$_3$NO (2 equiv), 3. ethylene glycol, PhMe, reflux, 64%; (c) NaOH, Na$_2$S$_2$O$_8$, AgNO$_3$, H$_2$O, 60%; (d) CbzCl, DIPEA, PhH, reflux to rt, 67%; (e) OsO$_4$, Me$_3$NO, acetone/H$_2$O (10 : 1), rt, α/β, 63%; (f) alkenylboronate 5/48, BF$_3$ · Et$_2$O, DCM, −78 °C to rt, 99%, d.r. > 98 : 2; (g) OsO$_4$, NMO, acetone, H$_2$O, 82% (d.r. = 77 : 23); (h) TBSCl, 2,6-lutidine, DCM, 0 °C, 70% 5/55, 23% 5/56; (i) NaOMe, MeOH, rt, 88%; (j) TPAP, NMO, MS 4 Å, DCM, rt, 83%; (k) Pd/C, H$_2$, MeOH, rt; (l) TFA, H$_2$O, rt, then ion-exchange chromatography, 77% over 2 steps; 8.0% yield over 10 steps from pyrrolidine, 4.4% yield over a total of 12 steps.
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The requisite N-Cbz-2,3-dihydroxypyrrolidine 5/52 and boronic ester 5/48 were synthesised according to literature-known procedures. The Petasis coupling of both compounds under the modified conditions then gave the desired cis-2,3-disubstituted pyrrolidine 5/53 in an excellent yield (99%) and diastereoselectivity (d.r. > 98 : 2). This intermediate was then converted into the target compound 5/58 in six further steps comprising a cis-dihydroxylation of the double bond to introduce the hydroxy groups at C-7 and C-8 and a ring-closing reductive amination to complete the bicyclic indolizidine structure finally affording (±)-6-deoxycastanospermine after global O-TBS deprotection in 4.4% yield over a total twelve steps.\[28\]

5.9 Conclusion

The Petasis borono-Mannich reaction has proven to be a very versatile tool in organic synthesis, allowing a multitude of different compounds to be obtained including therapeutic drugs and natural products. Regarding the reactivity of the components used in this reaction, some conclusions can easily be drawn. The use of secondary amines is preferable over primary ones, since the latter usually give poorer yields due to the lower reactivity of their iminium ions formed with the carbonyl component. Nevertheless, when bulky primary amines are employed in the reaction, yields can be achieved that equal the ones when secondary amines are used. Concerning the boronic component, vinylboronic acids are the most reactive in the Petasis reaction usually affording the desired products in good to excellent yields. However, these are not the only boronic compounds to be used in this reaction. Allyl- and arylboronic acids, heterocyclic derivatives, such as thienyl and pyridyl boronic acids, as well as boronic acid esters and potassium trifluoroborates can also be applied as the boron component. With regards of the aldehyde component, the three most applied in order of their reactivity are glycolaldehyde derivatives (α-hydroxy aldehydes), glyoxylic acid and salicylaldehyde.^[1, 2^]

Furthermore, in this chapter it has been shown by means of selected examples how this reaction has been successfully employed as the key step in the syntheses of various medicinal drugs and natural products including the in the previous chapter presented syntheses of polyhydroxylated alkaloids performed in our research groups.
Chapter 5. The Petasis borono-Mannich Reaction

5.10 References


Chapter 5. The Petasis borono-Mannich Reaction


Chapter 6. Background and Synthetic Strategy

6.1 Project Aims

When this project commenced in 2007, there were only three syntheses reported in the literature for two of the 32 existing broussonetines. As derivatives of the polyhydroxylated pyrrolidine alkaloids D-AB1 (1/61) and DMDP (1/51) the broussonetines represented new and challenging synthesis targets for our research group. The aims of this project therefore became to expand the in Chapter 4 introduced Petasis approach to the synthesis of DMDP and members of the broussonetine alkaloid family and to develop a

- **convenient.**
  - easy to accomplish
  - easy to scale-up

- **convergent.**
  - as many different broussonetines from one common precursor as possible

- **and concise**
  - as few steps as possible

synthesis for these diverse alkaloids and their smaller relative DMDP. In particular, the broussonetines C (2/6) and E (2/9) with their identical pyrrolidine moiety and similar side chains were chosen as principal targets.

6.2 Retrosynthesis

The retrosynthetic analysis for the broussonetines C and E is outlined in Scheme 6.1. Considering a convergent and universal route towards the broussonetine family with its diversity of side chains, it was decided to realise a late-stage coupling reaction between a common pyrrolidine building block 6/1 and the side chain fragment 6/2 by either a Wittig reaction consequently affording D-AB1 derivatives like broussonetine C, or a Grignard reaction furnishing the hydroxy group at C-1' and subsequently leading to DMDP derivatives like broussonetine E.

Pyrrolidine 6/3 would be constructed by the N-alkylative S$_{2}$2/5-*exo*-tet cyclisation of the open chain precursor 6/4. This precursor, in turn, could be synthesised from the partly
benzyl-protected L-xylose derivative 6/5 via its Petasis reaction with benzylamine and (E)-styrylboronic acid.

Indeed, N/O-benzyl protected polyhydroxylated pyrrolidine carbaldehydes like 6/1 are known compounds that have been utilised as intermediate building blocks in Wittig and Grignard reactions for the syntheses of more complex iminosugars in the past.\textsuperscript{[1-3]} Two of these syntheses by DONDONI and co-workers as well as IKOTA et al. are presented in the following sections.

6.3 Synthesis of (+)-DMDP and Imino-C-disaccharides by DONDONI et al.

The Wittig olefination strategy to complete the C\textsubscript{18} broussonetine skeleton via the coupling reaction of a pyrrolidine building block with a side chain synthon was adopted from the syntheses of imino-C-disaccharides by DONDONI and co-workers. In their seminal work published in 2002, DONDONI et al. developed a short synthesis for (+)-DMDP and the
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Pyrrolidine carbaldehyde 6/1 starting from previously known tris-O-benzylated L-xylofuranose (Scheme 6.2) and showed that the intermediate aldehyde 6/1 can be used as a building block in Wittig reactions to form various imino-C-disaccharides.\[4\]

\[ \text{HO}_2\text{C} \]
\[
\begin{align*}
\text{HO} & \quad \text{3 steps} \\
\text{HO} & \quad \text{a} \\
\text{HO} & \quad \text{b} \\
\text{HO} & \quad \text{c} \\
\text{HO} & \quad \text{d} \\
\text{HO} & \quad \text{e} \\
\text{HO} & \quad \text{f} \\
\text{HO} & \quad \text{g} \\
\text{HO} & \quad \text{(+)-DMDP}
\end{align*}
\]

Scheme 6.2. Synthesis of (+)-DMDP and the pyrrolidine carbaldehyde 6/1 by DONDONI et al. (2002).\[4\]

Reagents and conditions: (a) BnNHOH, 110 °C, 30 min, 82%; (b) n-BuLi, 2-bromothiazole, Et₂O, −70 °C, 6 h, 55%; (c) Cu(OAc)₂·H₂O, Zn dust, AcOH, H₂O, 70 °C, 45 min, 95%; (d) Tf₂O, pyridine, 40 °C, 30 min, 71%; (e) 1. TiOMe, MeCN, rt, 30 min; 2. NaBH₄, MeOH, 0 °C to rt; 3. AgNO₃, MeCN/H₂O (10 : 1), 10 min, 85%, 90% purity; (f) NaBH₄, MeOH, 0 °C to rt, 15 min, 72% over 2 steps; (g) 20% Pd(OH)₂/C, H₂ (1 atm), AcOH, rt, 12 h, then ion-exchange chromatography on Dowex 1X8 (100–200 mesh), 78%; 17.1% over 7 steps from 2,3,5-tri-O-benzyl-L-xylofuranose.

In the first step 2,3,5-tri-O-benzyl-L-xylofuranose (6/6) was heated with N-benzylhydroxylamine under solvent-free conditions at 110 °C to afford the hydroxylamine 6/7 in 82% yield. Compound 6/7, being in equilibrium with its open chain nitrone form 6/8, was then treated with in situ generated 2-lithiothiazole to give the anti-adduct 6/9 and its syn-isomer (not shown) in a 4 : 1 ratio and 72% combined yield. These adducts were separated by column chromatography, and the major anti-diastereomer was reduced in the following step to the amino alcohol 6/10 using Zn-Cu couple. Treatment of 6/10 with triflic anhydride in pyridine
initiated the \(N\)-alkylative \(S\_2/5\)-exo-tet cyclisation via displacement of the intermediate C-2 triflate ester with inversion of the stereochemistry to afford the 2-thiazolyl pyrrolidine 6/11. In the final steps, the thiazole ring of 6/11 was hydrolytically cleaved to the pyrrolidine carbaldehyde 6/1 which was subsequently reduced to the primary alcohol 6/12. The hydrogenolysis of 6/12 over Pearlman’s catalyst eventually afforded (+)-DMDP in 17.1% overall yield over seven steps from 2,3,5-tri-O-benzyl-L-xylofuranose.\[^{[4]}\]

A key step in this synthesis was the hydrolytic ring scission of the 2-substituted thiazole 6/11 to release the aldehyde 6/1. This conversion involved a sequence of three simple transformations: 1. the \(N\)-methylation of the thiazole ring to the \(N\)-methylthiazolium salt 6/13; 2. the exhaustive reduction of 6/13 to the thiazolidine 6/14; and 3. the heavy metal ion-mediated hydrolysis of 6/14 to the aldehyde 6/1 (Scheme 6.3).\[^{[5]}\]

![Scheme 6.3. Mechanism for the aldehyde release from 2-substituted thiazoles.](image)

The \(N\)-alkylation of 6/11 to the \(N\)-methylthiazolium salt 6/13 was needed to activate the quite inert thiazole ring towards its cleavage to the aldehyde 6/1. Methyl triflate hereby proved to be the reagent of choice since the also tested methyl iodide was less effective. This activation was followed by the complete reduction of 6/13 with \(\text{NaBH}_4\) to the intermediate thiazolidine 6/14 which is subsequently degraded to the desired aldehyde 6/1 via its treatment
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with heavy metal salts such as HgCl₂, CuCl₂ or AgNO₃ in a MeCN/H₂O mixture whereat AgNO₃ was found to be the most efficient.⁴,⁵

Although the pyrrolidine carbaldehyde 6/1 could not be purified by column chromatography due to extensive decomposition during the process, it turned out to be stable enough to be used as building block in the syntheses of two novel imino-C-disaccharides. Thus, the Wittig reaction of the aldehyde 6/1 with a slight excess (1.2 equiv) of the ylide generated in situ from the D-galactopyranosyl phosphonium iodide 6/15 with n-butyllithium at −30 ºC gave the desired olefin 6/16 as mixture of (E)- and (Z)-isomers in a 1 : 1 ratio (Scheme 6.4).⁴

Scheme 6.4. Syntheses of imino-C-disaccharides via Wittig reaction of the pyrrolidine carbaldehyde 6/1 with the sugar-derived phosphonium iodides 6/15 and 6/18 (DONDONI et al. 2002).⁴

Reagents and conditions: (a) n-BuLi (1.6 M in hexane), HMPA, MS 4Å, THF, −30 ºC, 2 h, 46%, E : Z = 1 : 1 for 6/16; −50 ºC, 2 h, 54%, Z : E ≥ 99 : 1 for 6/19; (b) TsNHNH₂, 1 M aq. NaOAc, DME, 85 ºC, 5 h; (c) 1. 20% Pd(OH)₂/C, H₂ (7 bar), 4 h, 2. Amberlite IR-120 (H⁺), 3. gel permeation column chromatography on Sephadex LH-20 (10 : 1 MeOH-H₂O), 61% 6/17, 45% 6/20 over 2 steps; 6/5% 6/17 and 5.6% 6/20 over 8 steps from 2,3,5-tri-O-benzyl-L-xylofuranose, respectively.
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The Wittig coupling of aldehyde 6/1 with the ylide derived from D-ribofuranosyl phosphonium iodide 6/18 at \(-50^\circ C\), on the other hand, provided the respective olefin 6/19 mainly as its (Z)-isomer contaminated with only a trace amount of the (E)-form. Then again, the stereochemical outcome of the Wittig reaction was not of great importance since the double bond was determined to be reduced in the following step anyway.

The reduction of the double bond was carried out by \textit{in situ} generated diimide from \textit{para}-toluenesulfonhydrazide giving the respective alkanes in 77% and 60% yield. This step, although unnecessary on first sight, was done to examine the stereochemistry of the sugar moiety after the Wittig reaction. NMR analysis of the alkanes confirmed the \(\alpha\)-D-galactopyranose configuration in 6/16 whereas the stereochemistry of the sugar-moiety in 6/19 proved to have been inverted from the D-ribo- to that of L-lyxofuranose in the course of the Wittig coupling. It has been suggested that this epimerisation takes places through an open-chain intermediate arising from the cleavage of the O–C-4 bond.

In the final steps, the intermediate alkanes and were \(N/O\)-debenzylated via catalytic hydrogenation over Pearlman’s catalyst followed by acetal cleavage with acidic Amberlite IR 120 ion-exchange resin. Purification by gel permeation chromatography on Sephadex LH-20 finally afforded the desired imino-C-disaccharides 6/17 and 6/20 in 6.5% and 5.6% yield over eight steps from 2,3,5-tri-O-benzyl-L-xylofuranose, respectively (Scheme 6.4).\[^4\]

6.4 Synthesis of D-AB1, (−)-1-\textit{epi}−Swainsonine and (+)-1,8-Di-\textit{epi}−swainsonine by IKOTA and HANAKI

The concept to couple the pyrrolidine building block 6/1 with the side chain fragment 6/2 via a Grignard reaction and generate the requisite C-1’ hydroxy group of broussonetine E in the process was inspired by the syntheses of D-AB1 as well as the two unnatural swainsonine epimers 6/32 and 6/33 by IKOTA and HANAKI. These syntheses, published in 1987, are shown in Schemes 6.5 and 6.6.\[^6, 7\]

Commercially available (S)-pyroglutamic acid served as chiral starting material which was converted in the first two steps to the MOM-protected alcohol 6/21. MOM-ether 6/21 was further transformed into the unsaturated lactam 6/22 via \(N\)-benzylation followed by a previously reported selenenylation-deselenenylation procedure. \textit{syn}-Dihydroxylation of 6/22 with catalytic OsO\(_4\) and in the presence of NMO in aqueous acetone gave the diol 6/23 as a
single diastereomer. After its bis-\(O\)-benzylation under standard conditions, the resulting \(cis\)-dibenzylether 6/24 was epimerised at the 3-position to its \(trans\)-diastereomer 6/25 with NaOMe in a mixture of MeOH-THF at room temperature. Reduction of the lactam carbonyl group with BH\(_3\)/Me\(_2\)S-complex followed by the cleavage of the MOM-ether furnished the pyrrolidine alcohol 6/26. Debenzylation of 6/26 with 10\% palladium on charcoal under an atmosphere of hydrogen in the presence of hydrochloric acid finally afforded D-AB1 in its hydrochloride form (1/61a) in 7.4\% overall yield over ten steps from \((S)\)-pyroglutamic acid.\[6\]

Scheme 6.5. Synthesis of D-AB1 by IKOTA and HANAKI (1987).\[6\]

Reagents and conditions: (a) 1. SOCl\(_2\), MeOH; 2. NaBH\(_4\), EtOH, 89\%; (b) MOMCl, \(N,N\)-diethylaniline, 73\%; (c) BnBr, NaH, DMF/THF, 83\%; (d) 1. LDA, PhSeBr, THF, \(-78\ ^\circ C\); 2. 30\% H\(_2\)O\(_2\), EtOAc, 64\%; (e) cat. OsO\(_4\), NMO, acetone/H\(_2\)O, 65\%; (f) BnBr, NaH, DMF/THF, 85\%; (g) NaOMe, MeOH/THF, rt, 65\%; (h) BH\(_3\)·Me\(_2\)S, THF, reflux; (i) aq. HCl, MeOH, 70 \(^\circ C\), 78\% over 2 steps; (j) 10\% Pd/C, H\(_2\), HCl, EtOH, 77\%; 7.4\% over 10 steps from \((S)\)-pyroglutamic acid.

On the other hand, Swern oxidation of the alcohol 6/26 gave the pyrrolidine carbaldehyde 6/27 which was further used as building block for the synthesis of the two swainsonine epimers 6/32 and 6/33. In the event, IKOTA and HANAKI discovered that the stereochemical outcome of the coupling reaction of 6/27 with organometallic reagents can be controlled by the type of reagent employed. When aldehyde 6/27 was treated with allylmagnesium chloride in THF at \(-78\ ^\circ C\) the allylic alcohols 6/28 and 6/29 were obtained in 81\% combined yield in a 1.6 : 1 ratio in favour for the \((R)\)-alcohol 6/28. Reaction of aldehyde 6/27 with lithium
diallylcuprate in ether at $-78^\circ$C, however, afforded the allylic alcohols 6/28 and 6/29 in 68% yield in a 1 : 2.2 ratio in favour for the (S)-alcohol 6/29 this time. Obviously, the reaction of 6/27 with a Grignard reagent or a Normant cuprate showed opposite diastereoselectivity. The two allylic alcohols were consequently converted in four further steps to the swainsonine epimers 6/32 and 6/33. After $O$-benzylation of the secondary hydroxy group in 6/28, the terminal double bond was converted into the primary alcohol 6/30 via hydroboration-oxidation. Mesylation of 6/30 followed by catalytic hydrogenolysis of all benzyl groups finally furnished (−)-1-epi-swainsonine (6/32) after purification by ion-exchange chromatography in 1.9% yield over 15 steps from (S)-pyroglutamic acid. By a parallel series of reactions, 6/29 was transformed to (+)-1,8-di-epi-swainsonine (6/33) in the same overall yield of 1.9%.\[7\]

**Scheme 6.6.** Synthesis of (−)-1-epi-swainsonine and (+)-1,8-di-epi-swainsonine by Ikota and Hanaki (1987).\[7\]

Reagents and conditions: (a) (COCl)$_2$, DMSO, Et$_3$N, DCM, $-78^\circ$C; (b) allylmagnesium chloride, THF, $-78^\circ$C, 50% (6/28), 31% (6/29) over 2 steps; (c) lithium diallylcuprate, Et$_2$O, $-78^\circ$C, 21% (6/28), 47% (6/29) over 2 steps; (d) BnBr, NaH, DMF/THF; (e) 1. BH$_3$, THF; 2. 30% H$_2$O$_2$, 12% aq. NaOH, 63% (6/30), 66% (6/31) over 2 steps; (f) MsCl, Et$_3$N, DCM; (g) 10% Pd/C, H$_2$, HCl, EtOH, then ion-exchange chromatography on Dowex 50W-X8, 62% (6/32), 65% (6/33) over 2 steps; 1.9% over 15 steps from (S)-pyroglutamic acid for 1-epi-swainsonine and 1,8-di-epi-swainsonine, respectively.
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6.5 3,5-Di-O-benzyl-L-xylofuranose as the Petasis Precursor

A negative aspect of the Petasis approach towards polyhydroxylated alkaloids is the high polarity of the Petasis product when pure, unmodified carbohydrates are used as starting materials. This makes an efficient purification of the obtained aminopolyols hard and tedious. Furthermore, the necessity to do quite a lot protecting group manipulations to get to the desired final product dreadfully lengthens the synthesis and demands a carefully considered orthogonal protecting group strategy as seen in the syntheses of uniflorine A, casuarine and 3-epi-australine by T. RITTHIWIGROM (see Chapter 4, Section 4.2.3).[8, 9] It became therefore one of the aims of this PhD project to modify the Petasis approach in a way that would minimise these protecting group manipulations. This was to be achieved by employing an already partly protected sugar derivative as carbonyl component in the Petasis reaction. Retrosynthetic analysis led to 3,5-di-O-benzyl-L-xylofuranose (6/5) as the appropriate starting material bearing the essential free OH-group in the α-position to the carbonyl functionality as the coordination site for the boronic acid (Figure 6.1). Furthermore, the second free OH-group at C-4 would allow the subsequent regioselective 5-exo-tet cyclisation once the open chain precursor 6/4 is assembled.

![Figure 6.1. 3,5-Di-O-benzyl-L-xylofuranose as the Petasis precursor.](image)

6.6 Synthesis Plan towards DMDP and the Broussonetines C and E

With the results of our retrosynthetic analysis for the broussonetine alkaloids in mind and the premise to develop a short and simple synthesis, a concise four-step route was conceived for DMDP and the pyrrolidine carbaldehyde 6/1 as synthon for the broussonetines C and E
(Scheme 6.7). 3,5-Di-O-benzyl-L-xylofuranose (6/5), although not commercially available but easily obtainable in three steps from L-xylose by known procedures,[10, 11] would be employed in a Petasis reaction with benzyl amine and (E)-styrylboronic acid to give the amino diol 6/4 in one step. This compound would then directly be subjected to an \( N \)-alkylative 5-exo-tet cyclisation with concomitant inversion of the configuration at C-2 furnishing the styryl pyrrolidine 6/3 with the desired all-trans stereochemistry. From this key intermediate the synthesis could either be directed towards DMDP via the conversion of the styryl double bond into a hydroxy group followed by a concluding hydrogenolysis of the benzyl protecting groups. Alternatively, benzylation of the remaining free OH-group at C-4 followed by the oxidative cleavage of the styryl double bond into a carbonyl functionality would give rise of the pyrrolidine carbaldehyde building block 6/1.

Scheme 6.7. Synthesis plan for (+)-DMDP and the pyrrolidine carbaldehyde building block 6/1.

(a) Petasis reaction with benzylamine and (E)-styrylboronic acid; (b) \( N \)-alkylative S\(_2\)2/5-exo-tet cyclisation; (c) ozonolysis; (d) hydrogenolysis (N/O-debenzylation); (e) \( O \)-benzylation; (f) oxidative cleavage of the double bond.

According to the procedure of DONDONI et al.\(^{[4]}\) (Scheme 6.4) pyrrolidine carbaldehyde 6/1 would be coupled in a Wittig reaction with the side chain building block, phosphonium iodide 6/36, furnishing the olefin 6/37 most likely in its (Z)-configuration. Global deprotection
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with concomitant reduction of the double under acidic hydrogenolytic conditions would then yield our second synthesis target, (+)-broussonetine C (Scheme 6.8).

Scheme 6.8. Synthetic plan towards (+)-broussonetine C. 
(a) Wittig reaction of pyrrolidine carbaldehyde 6/1 with phosphonium iodide 6/36; (b) global deprotection under acidic hydrogenolytic conditions.

Coupling of the pyrrolidine carbaldehyde 6/1 with the side chain fragment in form of a Grignard reagent, on the other hand, would lead to the broussonetine E precursor 6/39. The stereochemical outcome of this reaction has to be investigated, however, as IKOTA and HANAKI have shown,\(^7\) the preference for one or the other epimer can be directed by the type of the organometallic reagent employed in the coupling reaction (see Scheme 6.6). The concluding cleavage of all protecting groups would then provide our desired third synthetic target, (+)-broussonetine E (Scheme 6.9).

Scheme 6.9. Synthetic plan towards (+)-broussonetine E. 
(a) Grignard reaction of pyrrolidine carbaldehyde 6/1 with alkylmagnesium bromide 6/39, then chromatographic separation of the epimeric alcohols, if necessary; (b) global deprotection under acidic hydrogenolytic conditions.
6.7 Synthesis of (−)-Codonopsinine by ISHIBASHI et al.

Interestingly, 3,5-di-O-benzyl-L-xylofuranose had already been employed as starting material in a previous synthesis of an iminosugar. In 2003, ISHIBASHI and co-workers reported the preparation of the polyhydroxylated alkaloid (−)-codonopsinine (1/81) in 13 steps from this L-xylose derivative.[12] Their synthetic route is depicted in Scheme 6.10.

Scheme 6.10. Synthesis of (−)-codonopsinine by ISHIBASHI et al. (2003).[12]

Reagents and conditions: (a) 2,2,2-Trichloroethanol, cat. PTSA, DCM, 39 °C, 72%; (b) NaH, MOMCl, THF/DMF, −20 °C; (c) Zn dust, NaOAc, HOAc, 80% over 2 steps; (d) NH₂OTBDPS, cat. PPTS, MgSO₄, benzene, reflux; (e) MsCl, Et₃N, toluene, 0 °C, 98% over 2 steps; (f) TBAT (1.05 equiv.), MS 4Å, THF, reflux, 15 min, 72%; (g) 4-methoxyphenylmagnesium bromide, THF, −45 °C, 5 min, 95%; (h) Zn dust, aq. NH₄Cl, EtOH, reflux; (i) methyl chloroformate, aq. NaHCO₃, DCM, 99% over 2 steps; (j) 10% Pd/C, H₂, MeOH; (k) TsCl, pyridine/DCM, 86% over 2 steps; (l) LiAlH₄, THF, reflux, 92%; (m) 3 N HCl, MeOH, 50 °C, 97%; 29.3% over 13 steps from 3,5-di-O-benzyl-L-xylofuranose.

The introduction of nitrogen to the carbohydrate skeleton was effected via the treatment of the lactol 6/41, prepared beforehand in three steps from 6/5, with tert-butyldiphenylsilyl oxyamine. The subsequent mesylation of the intermediate imino alcohol yielded the mesylate.
which upon desilylation with TBAT cyclised to the five-membered nitrone \( 6/43 \). Key step of the synthesis was the following stereoselective Grignard addition of 4-methoxyphenylmagnesium bromide to this cyclic nitrone to introduce the pseudoanomeric aryl-substituent of the target compound eventually affording the hydroxylamine \( 6/44 \) as a single diastereomer in 95\% yield. This hydroxylamine was then converted to \((-\)-codonopsinine in six further steps in an excellent overall yield of 29.3\% from 3,5-di-\( O\)-benzyl-L-xylofuranose.\[12\]

### 6.8 3,5-Di-\( O\)-benzyl-D-xylofuranose as Starting Material in the Synthesis of Natural Products as well as Unnatural Analogues

In addition to the codonopsinine synthesis 3,5-di-\( O\)-benzyl-D-xylofuranose has been a popular starting point in the past for a diverse range of other natural products and unnatural analogues comprising the already in Chapter 2 introduced amino alcohol sphingosine\[13\] (\( 2/29 \)) and its cyclic derivatives jaspine B\[14\] (\( 2/60 \)) and the penaresidins\[15\] (\( 2/57, 2/58 \)). Other natural products that have been synthesised by incorporating this carbohydrate derivative as starting material or synthon include:

- **Sesbanimide A**

\[
\begin{align*}
&\text{H}_2\text{C} & &\text{O} & &\text{H} & &\text{B} & &\text{O} \\
&\text{H}_2\text{C} & &\text{OH} & &\text{HO} & &\text{C} & &\text{NH}
\end{align*}
\]

\((+-\)-Sesbanimide A

Sesbanimide A and its C-11 epimer sesbanimide B are two potent antitumor alkaloids that have been isolated from the seeds of the poison bean *Sesbania drummondii* (Figure 6.2) by POWELL *et al.* in 1983.\[17\] A number of leguminous plants belonging to the *Sesbania* genus are notorious for the toxicity of their seeds to livestock and fowl. POWELL *et al.* reported that alcoholic extracts of *Sesbania* seeds are markedly cytotoxic against KB cells *in vitro* and showed significant inhibitory activity against P388 murine leukaemia *in vivo*. Further investigations resulted in the isolation and structure elucidation of sesbanimides A and B as the antileukaemic principles with A being the major and most active component. The sesbanimides have unique tricyclic structures in which the glutarimide A-ring, 1,3-dioxane B-ring, and tetrahydrofuran C-ring are linked by the two single bonds. The first total synthesis was accomplished by TERASHIMA *et al.* in 1988 incorporating 3,5-di-\( O\)-benzyl-D-xylofuranose to construct parts of the AB-ring system.\[10\]
Trilobatin B is a novel lignan, isolated from the trilobate liverwort *Bazzania trilobata* (Figure 6.3) by Becker *et al.*[19] in 1997. The lignans are a group of polyphenolic secondary metabolites with antioxidant activity. They belong to the phyto-estrogens, i.e., compounds found in plants that act as estrogen-mimics. Lignans are capable of binding to estrogen receptors and interfering with the cancer-promoting effects of estrogen on breast tissue. In 2004, Yoda *et al.* reported the asymmetric synthesis of the tetrahydrofuran segment of Trilobatin B by employing 3,5-di-\text{O}-benzyl-D-xylofuranose as starting material.[20]

Kotalanol

Hot water infusions prepared from the roots and stems of *Salacia reticulata* (Celastraceae) (Figure 6.4) have been extensively used as a specific remedy for diabetes in traditional Ayurvedic medicine. In 1998, Yoshihara *et al.*[22] examined the physiologically active components of *S. reticulata* stems and roots and isolated a new potent \(\alpha\)-glucosidase inhibitor which they named kotalanol derived from the Singhinalase name of *S. reticulata*, *Kotala himbutu*. The structure of kotalanol was elucidated to be an intramolecular salt comprised of a 1-deoxy-4-thio-D-arabinofuranosyl sulfonium cation and an S-bound 1-deoxyheptosyl-3-sulfate side chain. Kotalanol was found to be a very potent competitive inhibitor of rat intestine \(\alpha\)-glucosidases with IC\(_{50}\) values in the low micromolar range. Since kotalanol resembles the structure of iminosugars in which the ring-nitrogen has been replaced with a positively charged sulfur atom, its glucosidase inhibitory activity is not very surprising. In 2011, Murakawa and co-workers synthesised diastereomers of kotalanol in order to investigate the role of the side chain stereochemistry for the \(\alpha\)-glucosidase inhibitory activity.[23] 3,5-Di-\text{O}-benzyl-D-xylofuranose was used as synthon for the construction of the side chain. The SAR studies eventually showed that the stereoinversion at C-3’ and C-4’ of kotalanol significantly decreased the inhibitory activities against maltase and sucrase, whereas the inhibitory activity against isomaltase sustained.[23]

Further compounds incorporating 3,5-di-\text{O}-benzyl-D-xylofuranose as a synthon are summarised in Figure 6.5 with the original carbohydrate skeleton highlighted in red in each depicted structure.[24–29]
Figure 6.5. Natural products and analogues as well as artificial amino acids and nucleosides that have been synthesised starting from 3,5-di-O-benzyl-D-xylofuranose. [10, 13–15, 20, 23–29]
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6.9 L-Xylose versus D-Xylose

One might consider it ironic that in order to obtain the natural enantiomers of DMDP and the broussonetines according to the synthesis plan presented in Scheme 6.7, the unnatural enantiomer of xylose has to be employed as starting material (Figure 6.6). As a chemical not being derived from natural sources (−)-L-xylose is unsurprisingly by far more expensive than its natural counterpart, (+)-D-xylose. At the time of the beginning of this PhD project the chemical supplier SIGMA-ALDRICH offered 25 g of L-xylose for 299.88 AUD which equals 1.80 AUD per mmol whereas 500 g of D-xylose was sold for only 151.98 AUD which corresponds closely to 0.05 AUD per mmol. In other terms, L-xylose was 36 times more expensive than its natural D-analogue.

With these economic considerations in mind, it was decided to start a first approach of the synthesis with the inexpensive D-xylose to establish the synthetic route and optimise reaction conditions and yields where needed. If successful, the synthesis was supposed to be repeated with L-xylose at a later stage of the project to obtain the natural enantiomers. Then again, synthesising the unnatural enantiomers of our target molecules was not considered to be futile; these compounds are gaining more and more attention in recent years when first reports demonstrated that some synthetic unnatural iminosugars are in fact more potent and specific glycosidase inhibitors than their natural counterparts.30–33

![Figure 6.6. L-xylose versus D-xylose.](image-url)
6.10 Synthesis of L-DMDP by Fleet et al.

In 2004, Fleet and co-workers reported the second total synthesis of L-DMDP starting from D-gulonolactone. The introduction of nitrogen to the carbohydrate scaffold was effected via the displacement of the intermediate C-2 triflate ester with azide. Key step of this synthesis was the following epimerisation of the trans-2-azido-lactone 6/50 to the thermodynamically more stable cis-2-azido-lactone 6/51. Reduction of 6/51 with lithium borohydride in THF then afforded the triol 6/52 with the carbohydrate now at the correct oxidation level to form the desired final product. This was achieved via the conversion of the triol 6/52 into the 5-mesylate 6/54 in four further steps which upon hydrogenation in the presence of palladium on carbon cyclised to the fully O-TBS protected iminosugar 6/55. The cleavage of all protecting groups with methanolic hydrogen chloride then concluded the synthesis of (–)-L-DMDP in an overall yield of 16.7% over eleven steps (Scheme 6.11).

Scheme 6.11. Synthesis of L-DMDP by Fleet et al. (2004).[^34]

Reagents and conditions: (a) 2-MOP, PTSA, DMF, 0 °C, 2 h, 95%; (b) Tf₂O, pyridine, MeCN, N₂, –30 °C, 3 h; (c) NaN₃, DMF, rt, 26 h, 74% over 2 steps; (d) PPTS, DMF, N₂, rt, 7 d, 68%; (e) LiBH₄, THF, N₂, –30 °C, 3 h, 87%; (f) TBSOTf, pyridine, DCM, N₂, rt, 14 h, 88%; (g) AcOH/H₂O (4 : 1), 70 – 74 °C, 1 h, 82%; (h) TBSCl, pyridine, N₂, rt, 18 h, 90%; (i) MsCl, pyridine, DMAP, DCM, N₂, rt, 1 h, 81%; (j) Pd/C, H₂, NaOAc, EtOAc, rt, 18 h, 85%; (k) HCl/MeOH, rt, 17 h, 90%; 16.7% over 11 steps from D-gulonolactone.

[^34]: The first total synthesis of L-DMDP was reported in 1998 by Colobert et al. starting from (–)-dimethyl 2,3-O-isopropylidene-L-tartrate with an overall yield of 8.2% over 11 steps.[^35]
FLEET et al. then investigated the potential of L-DMDP as glycosidase inhibitor and compared it to its natural enantiomer DMDP. Their results are summarised in Table 6.1.

Table 6.1. Comparison of the inhibitory effect of (+)-DMDP and (–)-L-DMDP on various glycosidases (FLEET et al. 2004).

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>IC₅₀ (µM) (+)-DMDP</th>
<th>IC₅₀ (µM) (–)-L-DMDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-glucosidase (rice)</td>
<td>370</td>
<td>1.5</td>
</tr>
<tr>
<td>α-sucrase (rat intestine)</td>
<td>81</td>
<td>0.1</td>
</tr>
<tr>
<td>α-sucrase (porcine)</td>
<td>55</td>
<td>1.5</td>
</tr>
<tr>
<td>α-maltase (rat intestine)</td>
<td>NI</td>
<td>1.4</td>
</tr>
<tr>
<td>α-isomalzate (rat intestine)</td>
<td>75</td>
<td>0.05</td>
</tr>
<tr>
<td>β-glucosidase (almond)</td>
<td>17</td>
<td>NI</td>
</tr>
<tr>
<td>β-galactosidase (bovine liver)</td>
<td>4.6</td>
<td>NI</td>
</tr>
</tbody>
</table>

NI = No inhibition (less than 50% inhibition at 1000 µM)

Two main conclusions can be drawn. Firstly, synthetic (–)-L-DMDP is a highly specific inhibitor of a number of plant and mammalian α-glucosidases being between 2 and 4 orders of magnitude more potent than the enantiomeric natural product (+)-DMDP. Secondly, whereas (+)-DMDP exhibits a relatively broad profile of various α- and β-glycosidases with moderate to good inhibitory activity, (–)-L-DMDP shows no inhibition at all against the tested β-glycosidases in FLEET’s assays. This differential inhibition of glycosidases therefore implies considerable subtlety in the recognition of these pyrrolidine inhibitors by the enzymes.\[30, 34\]

6.11 Synthesis of 1-C-Alkyl-L-arabinoiminofuranoses by TAKAHATA et al.

As an extension to FLEET’s work on L-DMDP, TAKAHATA and co-workers synthesised L-AB1 derivatives with simple linear alkyl substituents of varying length (C₂ – C₁₁) attached at the pseudoanomeric position.\[36\] The asymmetric synthesis of these 1-C-alkyl-L-arabinoiminofuranoses (6/63) was achieved in similar fashion to TROST’s broussonetine G synthesis using an asymmetric allylic alkylation (AAA) and a ring-closing metathesis (RCM) as key reactions.\[37\] However, in contrast to TROST’s approach, TAKAHATA et al. employed a Negishi cross-coupling reaction to combine their pyrroline building block 6/60 with the side chain synthons (Scheme 6.12). Since the Negishi coupling permits the introduction of a multitude of substituents, this synthetic approach could also be used to synthesise several broussonetine congeners.
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Scheme 6.12. Synthesis of 1-C-alkyl-L-arabinoiminofuranoses by Takahata et al. (2011).[^36]

Reagents and conditions: (a) [Pd₂(dba)₃] · CHCl₃, (S,S)-6/64, DBU, DCM, rt, 91%; (b) Grubbs’ II catalyst, DCM, reflux, 71%; (c) I₂, imidazole, PPh₃, DCM, 88%; (d) CH₃(CH₂)ₙZnX (n = 0 – 9, X = Br, I), Ni(COD)₂, (R,R)-iPr-Pybox, DMA, rt; (e) 1,1,1-trifluoroacetone, oxone, NaHCO₃, MeCN/H₂O, EDTA, 0 °C; (f) CF₃COOH, THF/H₂O (3 : 2), 80 °C; (g) NaOH, EtOH/H₂O, 100 °C; the yields are summarised in Table 6.2.

Table 6.2. Summary of the isolated yields obtained in the synthesis of iminosugars 6/63a – 6/63j.[^36]

<table>
<thead>
<tr>
<th>n</th>
<th>Alkyl substituent</th>
<th>Product</th>
<th>Yield of the Negishi cross coupling</th>
<th>Combined yield of steps e – g</th>
<th>Overall yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CH₂CH₃</td>
<td>6/63a</td>
<td>69%</td>
<td>51%</td>
<td>20.0%</td>
</tr>
<tr>
<td>2</td>
<td>-(CH₂)₂CH₃</td>
<td>6/63b</td>
<td>63%</td>
<td>58%</td>
<td>20.7%</td>
</tr>
<tr>
<td>3</td>
<td>-(CH₂)₃CH₃</td>
<td>6/63c</td>
<td>78%</td>
<td>43%</td>
<td>19.0%</td>
</tr>
<tr>
<td>4</td>
<td>-(CH₂)₄CH₃</td>
<td>6/63d</td>
<td>63%</td>
<td>52%</td>
<td>18.6%</td>
</tr>
<tr>
<td>5</td>
<td>-(CH₂)₅CH₃</td>
<td>6/63e</td>
<td>69%</td>
<td>55%</td>
<td>21.6%</td>
</tr>
<tr>
<td>6</td>
<td>-(CH₂)₆CH₃</td>
<td>6/63f</td>
<td>69%</td>
<td>59%</td>
<td>23.1%</td>
</tr>
<tr>
<td>7</td>
<td>-(CH₂)₇CH₃</td>
<td>6/63g</td>
<td>68%</td>
<td>35%</td>
<td>13.5%</td>
</tr>
<tr>
<td>8</td>
<td>-(CH₂)₈CH₃</td>
<td>6/63h</td>
<td>72%</td>
<td>49%</td>
<td>20.0%</td>
</tr>
<tr>
<td>9</td>
<td>-(CH₂)₉CH₃</td>
<td>6/63i</td>
<td>66%</td>
<td>30%</td>
<td>11.2%</td>
</tr>
<tr>
<td>10</td>
<td>-(CH₂)₁₀CH₃</td>
<td>6/63j</td>
<td>71%</td>
<td>45%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>
In accordance with the synthesis shown in Scheme 6.12, ten homologues of 6-deoxy-L-DMDP (n = 0) were obtained and tested for inhibitory activity against various rat intestinal α-glucosidases. The test results are summarised in Table 6.3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Maltase IC_{50} [µM]</th>
<th>Isomaltase IC_{50} [µM]</th>
<th>Sucrase IC_{50} [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/63a</td>
<td>2.6</td>
<td>11</td>
<td>0.68</td>
</tr>
<tr>
<td>2</td>
<td>6/63b</td>
<td>1.7</td>
<td>47</td>
<td>0.26</td>
</tr>
<tr>
<td>3</td>
<td>6/63c</td>
<td>0.2</td>
<td>4.7</td>
<td>0.032</td>
</tr>
<tr>
<td>4</td>
<td>6/63d</td>
<td>0.71</td>
<td>18</td>
<td>0.19</td>
</tr>
<tr>
<td>5</td>
<td>6/63e</td>
<td>0.51</td>
<td>11</td>
<td>0.11</td>
</tr>
<tr>
<td>6</td>
<td>6/63f</td>
<td>0.38</td>
<td>16</td>
<td>0.24</td>
</tr>
<tr>
<td>7</td>
<td>6/63g</td>
<td>0.32</td>
<td>75</td>
<td>0.45</td>
</tr>
<tr>
<td>8</td>
<td>6/63h</td>
<td>0.84</td>
<td>171</td>
<td>1.4</td>
</tr>
<tr>
<td>9</td>
<td>6/63i</td>
<td>1.2</td>
<td>606</td>
<td>1.7</td>
</tr>
<tr>
<td>10</td>
<td>6/63j</td>
<td>3.9</td>
<td>NI</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>Acarbose</td>
<td>0.16</td>
<td>NI</td>
<td>2.9</td>
</tr>
<tr>
<td>12</td>
<td>Voglibose</td>
<td>0.18</td>
<td>5.2</td>
<td>0.37</td>
</tr>
<tr>
<td>13</td>
<td>Miglitol</td>
<td>0.59</td>
<td>39</td>
<td>1.0</td>
</tr>
</tbody>
</table>

NI: less than 50% inhibition at 1000 µM.

Some of the prepared compounds showed potent inhibitory activities against rat intestinal maltase with IC_{50} values comparable to those of commercial drugs used in the treatment of type 2 diabetes such as acarbose (1/215), voglibose (1/220), and miglitol (1/214). Among the compounds tested, the inhibitory activity against rat intestinal sucrase of 6/63c (IC_{50} = 0.032 µM) was especially strong when compared to the above listed commercial drugs.

6.12 Summary

The syntheses of the iminofuranoses DMDP and its two pseudoanomerically alkyl-substituted derivatives, the broussonetines C and E, were designated as the aims of this PhD project. A synthesis scheme was conceived that would allow the convergent assembly of the broussonetine congeners through the combination of the pyrrolidine carbaldehyde building block 6/1 with the respective side chain synthons via either a Wittig or Grignard reaction. The pyrrolidine building block as well as DMDP, in turn, would be constructed employing the Petasis
borono-Mannich reaction as the key step to stereoselectively assemble the requisite amino diol intermediate 6/4. The usage of pyrrolidine carbaldehyde 6/1 as building block in Wittig coupling reactions had previously been reported by DONDONI et al.\cite{4} for the preparation of imino-C-disaccharides. A key step in DONDONI’s synthesis was the hydrolytic ring scission of the 2-substituted thiazole 6/11 to release the requisite pyrrolidine carbaldehyde building block 6/1. The strategy to couple the pyrrolidine building block with the side chain fragment 6/2 via a Grignard reaction and generate the requisite C-1’ hydroxy group of broussonetine E in the process was inspired by the syntheses of the two unnatural swainsonine epimers 6/32 and 6/33 by IKOTA and HANAKI.\cite{7}

The retrosynthetic analysis identified 3,5-di-\(\text{O-}\)benzyl-L-xylofuranose as the appropriate starting material to establish the required all-(R)-configuration of the pyrrolidine ring of our target compounds. This xylose derivative and its enantiomer, 3,5-di-\(\text{O-}\)benzyl-D-xylo-furanose, have been used in the past as starting materials and synthons of a diverse range of compounds including artificial amino acids and nucleosides as well as natural products and analogues such as the alkaloid (+)-sesbanimide A\cite{10} (6/47), the lignan (−)-trilobatin B\cite{20} (6/48) and the glycosidase inhibitor (+)-kotalanol\cite{21} (6/49). Furthermore, ISHIBASHI and co-workers\cite{12} described the preparation of the polyhydroxylated pyrrolidine alkaloid (−)-codonopsinine (1/81) in 13 steps from this L-xylose derivative in 2003. 3,5-Di-\(\text{O-}\)benzyl-L-xylofuranose (6/5) is not commercially available but can easily be prepared in three steps from L-xylose. However, due to the relative high cost of L-xylose compared to its natural D-enantiomer, it was decided to use the inexpensive D-xylose in a first approach ultimately yielding the unnatural enantiomers of the respective polyhydroxyalkaloids. Although unnatural, these iminosugars are gaining increasing attention in recent years when first reports revealed that some of these compounds are in fact more potent and specific glycosidase inhibitors than their natural counterparts. As FLEET and co-workers\cite{34} could demonstrate L-DMDP, prepared in 11 steps from D-gulonolactone, is a highly specific inhibitor of a number of plant and mammalian α-glucosidases being between 2 and 4 orders of magnitude more potent than the enantiomeric natural product DMDP. In addition to FLEET’s work, TAKAHATA et al.\cite{36} could show that some synthetic pseudoanomeric alkylated L-AB1 derivatives (1-C-alkyl-L-arabinonoiminofuranoses) are equally strong as or even better α-glucosidase inhibitors than the commercial drugs acarbose (1/215), voglibose (1/220), and miglitol (1/214) which are currently used in the treatment of type 2 diabetes.
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6.13 References


Chapter 7. Synthesis of L-DMDP

To date, the majority of the synthetic approaches to DMDP and its stereoisomers use carbohydrates or carbohydrate derivatives as starting materials for the straightforward installation of the four neighbouring stereocentres.\[^{[1–37]}\] Introduction of the amino function in the carbohydrate scaffold is then accomplished by reductive amination or by nucleophilic substitution of one hydroxyl group with a nitrogen nucleophile like azide or benzylamine. These syntheses often involve prolonged protection-deprotection steps resulting in low overall yields. In contrast, the distinct advantage of our synthesis plan with the Petasis reaction as key step (Scheme 6.7) is its brevity; only four transformations are necessary to convert 3,5-di-\(O\)-benzyl-D-xylofuranose into the first synthesis target, L-DMDP. 3,5-Di-\(O\)-benzyl-D-xylofuranose, though not commercially available, is a known compound that can easily be synthesised on a large scale in three steps from D-xylose.\[^{[38–42]}\]

### 7.1 Synthesis of 3,5-Di-\(O\)-benzyl-D-xylofuranose

Adopting the synthesis of TERASHIMA et al.\[^{[38]}\], D-xylose was treated with acetone in the presence of anhydrous copper(II) sulphate and a catalytic amount of sulfuric acid followed by subsequent hydrolysis of the initially formed bis-acetonide with 0.2% aqueous hydrochloric acid to give the mono-acetonide 7/1 in quantitative yield.\[^{[43]}\] Benzylation of 7/1 under standard conditions (NaH, BnBr, TBAI) provided the bis-benzyether 7/2 in 85% yield. Alternatively, the acetonide was also benzylated with BnCl and KOH in refluxing 1,4-dioxane as reported by YANG et al.\[^{[44]}\] giving compound 7/2 in a slightly lower yield of 82% (Scheme 7.1). Nevertheless, this method is especially attractive for large scale conversions since benzylchloride is approximately ten times cheaper per gram than benzylbromide.

![Scheme 7.1. Synthesis of 3,5-di-\(O\)-benzyl-1,2-\(O\)-isopropylidene-\(\alpha\)-D-xylofuranose (7/2).](image)

Reagents and conditions: (a) 1. acetone, cat. H\(_2\)SO\(_4\), anhydrous CuSO\(_4\), 25 °C, 28 h, then conc. NH\(_3\), 2. 0.2% HCl, 25 °C, 3.5 h, then NaHCO\(_3\), quant.; (b) NaH, BnBr, TBAI, THF, 0 °C to reflux, 85%; (c) KOH, BnCl, 1,4-dioxane, reflux, 4 h, 82%.
In contrast to the first two steps which gave good yields of the respective xylose derivatives, the third step, the cleavage of the isopropylidene acetal with conc. HCl in glacial AcOH as described by TERASHIMA et al.\cite{38}, led to the formation of the 2-acetate by-product 7/4, not mentioned in the original paper which consequently diminished the yield of the desired compound 7/3 (Scheme 7/2). It was suspected that ester 7/4 arose via the acid-catalysed formation of the 1-acetate derivative of 7/3 followed by acetyl migration to the C-2 OH-group.

![Scheme 7.2. Acetonide cleavage under the conditions described by TERASHIMA et al. (1985/1988).](image)

Reagents and conditions: (a) conc. HCl, AcOH, rt, 5 min, 74% 7/3, 9% 7/4.

Figure 7.1 shows the significant region of the \(^1\)H NMR spectrum of the 2-\(O\)-acetylated by-product 7/4. The position of the acetate group at C-2 was confirmed by an HMBC correlation between H-2 and the acetate’s carbonyl functionality.

![Figure 7.1. \(^1\)H NMR spectrum (500 MHz, CDCl\(_3\)) of the C-2 \(O\)-acetylated by-product 7/4.](image)

2-\(O\)-acetyl-3,5-di-\(O\)-benzyl-\(\alpha\),\(\beta\)-D-xylofuranose; \(^3\)J\(\alpha\)-\(H_2\) \(\approx\) 4 Hz; \(^3\)J\(\beta\)-\(H_2\) = 0 Hz.

To prohibit the formation of this by-product and consequently improve the yield of the desired compound 7/3, a method to hydrolyse the isopropylidene acetal had to be applied that would not involve any acetate sources. Acetic acid as a solvent and ethyl acetate for the work-up process were therefore omitted. YONEMITSU and co-workers reported the use of
4 N HCl in refluxing THF for the cleavage of the isopropylidene acetal in 7/2 during their synthesis of the polyketide antibiotic salinomycin.\cite{45} However, when YONEMITSU’s conditions were employed in the hydrolysis a new by-product was obtained. Acid-catalysed ring-opening of the solvent THF led to the formation of 1,4-butanediol which reacted with 3,5-di-O-benzyl-D-xylofuranose to give the mixed acetal 7/5 in 16% yield (Scheme 7.3).

Scheme 7.3. Acetonide cleavage under the conditions reported by YONEMITSU et al. (1989).
Reagents and conditions: (a) 4 N HCl, THF, reflux, 3 h, 69% 7/3, 16% 7/5.

Figure 7.2 displays the significant section of the $^1$H NMR spectrum of the 1-O-(4’-hydroxybutyl) acetal by-product 7/5. The C-1 substituent was determined to have the β-configuration due to the H-1,H-2-coupling constant of 0 Hz indicating a dihedral angle close to 90°. In case of the substituent being in the α-configuration a larger $J$ value for the H-1,H-2-coupling around 3.7 Hz would have been expected as observed in the α-acetonides 7/1 and 7/2 as well as the α-anomer of acetate 7/4.

![Figure 7.2. $^1$H NMR spectrum (500 MHz, CDCl₃) of the 1-O-(4’-hydroxybutyl) acetal by-product 7/5, 3,5-di-O-benzyl-1-O-(4’-hydroxybutyl)-β-D-xylofuranose.](image)

Ultimately, we applied the conditions described by LAFAONT et al.\cite{46} for the hydrolysis of 7/2 and used 1 N aqueous $H_2SO_4$ in refluxing 1,4-dioxane to cleave the acetonide leading to an improved yield of 85% for 7/3 without the formation of any by-product. The significant
region of the $^1$H NMR spectrum of recrystallised 7/3 is shown in Figure 7.3. The ratio of the $\alpha$- and $\beta$-anomer was determined to be approximately 3 : 1 via the integration of the signals of the anomeric protons (H-1$\alpha$ and H-1$\beta$).

Figure 7.3. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the Petasis precursor 7/3, 3,5-di-O-benzyl-$\alpha,\beta$-D-xylofuranose.

7.2 Petasis reaction

With sufficient amounts of 3,5-di-O-benzyl-$\alpha,\beta$-D-xylofuranose in hand, it was time to test this sugar derivative in the key step of the synthetic route, its Petasis reaction with benzylamine and (E)-styrylboronic acid to establish the key intermediate, amino alcohol 7/6 (Scheme 7.4).

Initially, the conditions originally proposed by Petasis et al.\textsuperscript{[47]} for the synthesis of $\beta$-amino alcohols were applied (EtOH, 25 ºC, 24 h), furnishing compound 7/6 only in a moderate yield of 53%. Furthermore, $^1$H NMR analysis of the obtained product revealed that it was contaminated with residual boronic acid and other unidentified polar by-products that could not be separated by column chromatography. Although most published examples
of Petasis reactions mention no aqueous work-up claiming that the crude product is pure enough for further transformations or that chromatography methods provide pure Petasis products, it was found that an aqueous work-up was inevitable to obtain pure amino alcohol 7/6. Best results to eliminate these polar impurities were achieved by washing the ethereal solution of the crude amino alcohol 7/6 twice with aqueous 1 M NaOH before submitting the concentrated syrupy residue to column chromatography. This treatment finally provided pure 7/6 (Figure 7.4) in an improved yield of 65%.

Having successfully solved the purification problem, the next step was to find the right reaction conditions with the goal to improve the yield of the key step. The focus hereby was on the effect of different solvents and solvent mixtures on the above Petasis reaction. The results are shown in Table 7.1.

The initial experiments employed common solvents like dichloromethane, methanol, ethanol, and ethanol-water mixtures (Table 7.1, entries 1 to 7). These modifications, however, did not result in any significant improvement of the yields. As a matter of fact, the yields changed for the worse, only the use of anhydrous MeOH under dry conditions resulted in a slightly increased yield from 66% to 73%. However, following a recent development in borono-Mannich chemistry to apply fluorinated alcohols like 1,1,1,3,3,3-hexafluoro-iso-propanol (HFIP) and 2,2,2-trifluoroethanol (TFE) as solvent or co-solvent, it was found that TFE as solvent in the Petasis reaction worked with remarkable success. The yield of 7/6
could be improved from 73% (entry 7) up to 93% (entry 9). Moreover, the purity of the crude product was considerably better than the purity of products obtained when MeOH or EtOH were used as solvents. Although TFE is a much more expensive solvent than MeOH or EtOH the excellent yield of 93% justified the use of this less common solvent. The exact reason why these fluorinated alcohols in some cases have such an outstanding effect on the yield and/or the rate of Petasis reactions is yet unknown. It is generally assumed that the effect originates in their enhanced ability to stabilise polarised or ionic intermediates and transition states. The increased acidity of these solvents may also play a role in the efficiency of the process possibly due to a catalytic effect on the formation of the intermediate iminium ion.[48]

Table 7.1. Solvent effect on the yield of amino alcohol 7/6 in the Petasis reaction.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 7/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH, 25 °C, 24 h, no aqueous work-up</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>EtOH, 25 °C, 24 h, then Et\textsubscript{2}O, 2 × 1 M NaOH</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>EtOH/H\textsubscript{2}O (4 : 1), 25 °C, 24 h, then Et\textsubscript{2}O, 2 × 1 M NaOH</td>
<td>26% \textsuperscript{b}</td>
</tr>
<tr>
<td>4</td>
<td>EtOH/H\textsubscript{2}O (4 : 1), 50 °C, 24 h, no aqueous work-up</td>
<td>34%</td>
</tr>
<tr>
<td>5</td>
<td>DCM, 25 °C, 24 h, then 1 × 2 M NaOH</td>
<td>25%</td>
</tr>
<tr>
<td>6</td>
<td>MeOH, 25 °C, 24 h, then DCM, 2 × 1 M NaOH</td>
<td>66%</td>
</tr>
<tr>
<td>7</td>
<td>Dry MeOH, 25 °C, 24 h, then Et\textsubscript{2}O, 2 × 1 M NaOH</td>
<td>73%</td>
</tr>
<tr>
<td>8</td>
<td>Dry MeOH/HFIP (9 : 1), 25 °C, 24 h, then Et\textsubscript{2}O, 2 × 1 M NaOH</td>
<td>70%</td>
</tr>
<tr>
<td>9</td>
<td>TFE, 25 °C, 24 h, then Et\textsubscript{2}O, 2 × 1 M NaOH</td>
<td>93%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions were carried out on a 1 mmol scale with the indicated work-up procedure. The yields refer to the amount of product obtained after column chromatography.

\textsuperscript{b}Based on recovered (E)-styrylboronic acid.

7.3 \textit{N}-alkylative 5-\textit{exo}-tet cyclisation

The Petasis reaction was followed by the \textit{N}-alkylative 5-\textit{exo}-tet cyclisation of the amino alcohol 7/6 to form the requisite pyrrolidine 7/12. This step required the initial regioselective activation of the hydroxy group at C-2 followed by the nucleophilic attack of the benzylamino nitrogen resulting in ring-closure. Concomitant inversion of the configuration at C-2 would ultimately afford the pyrrolidine ring with the desired \textit{all-trans} stereochemistry.

Similar S\textsubscript{N}2-cyclisation reactions have been applied in natural product synthesis in the past to complete the bicyclic nuclei various of polyhydroxylated pyrrolizidine and indolizidine alkaloids.
In the final steps of their australine synthesis in 2007, TROST and co-workers regioselectively activated the primary hydroxy group of the pyrrolidine 7/7 for cyclisation via its conversion into a mesylate leaving group at low temperature (−30 °C). Warming the reaction mixture to 0 °C triggered the 5-exo-tet ring-closure affording the bis-benzylated australine precursor 7/8 in 74% yield (Scheme 7.5).[54]

One year later, DONOHOE et al. efficiently used the same method in their syntheses of the epimeric hyacinthacines A6 and A7. In a one-pot reaction pyrrolidine alcohols 7/9 were mesylated and in situ cyclised to afford the epimeric pyrrolizidines 7/10 in 75% and 83% yield, respectively. Nevertheless, in this case regioselectivity was of no concern since all except one hydroxy groups were masked with protecting groups (Scheme 7.6).[55]

The mesylation-cyclisation protocol was later also successfully adopted in our research group by Chris AU in his syntheses of hyacinthacine B3 and the purported structure of hyacinthacine B7 (see Chapter 4, Scheme 4.16).[56, 57] Encouraged by these positive examples, a solution of amino alcohol 7/6 in DCM was treated with 1.075 equivalents of MsCl in the presence of an excess amount of Et₃N (3.5 equivalents) at −10 °C followed by gradually
warming of the reaction mixture to reflux temperature. As in TROST’s synthesis, the secondary OH-group at C-2 was regioselectively mesylated furnishing the desired pyrrolidinol 7/12 after a S±2/5-exo-tet cyclisation in 66% yield (Scheme 7.7).

![Scheme 7.7. N-alkylative S±2/5-exo-tet cyclisation of amino diol 7/6 via regioselective C-2 O-mesylation.](image)

Reagents and conditions: (a) MsCl, Et3N, DCM, –10 °C to max. 20 °C; (b) 20 °C to 40 °C (gentle reflux), 3 h, 66% 7/12, 6% 7/13.

It is noteworthy that in the present case the intermediate C-2 mesylate was stable enough to be isolated and characterised when the reaction and purification process were performed at a temperature of 20 °C or below. Figure 7.5 shows the significant region of the 1H NMR spectrum of the 2-mesylated Petasis product 7/11. Characteristic is the downfield shift of the H-2 signal geminal to the mesyl group when compared to its unmesylated amino diol precursor 7/6 (Figure 7.4).

![Figure 7.5. 1H NMR spectrum (300 MHz, CDCl3) of the 2-mesylated Petasis product 7/11.](image)

(2R,3R,4S,5S,6E)-5-benzylamino-1,3-bis(benzyloxy)-4-hydroxy-7-phenylhept-6-en-2-yl methanesulfonate.
Furthermore, a small amount of a mesylated by-product was also formed. Due to the fact that this compound had a nearly identical $R_f$ value to that of pyrrolidinol 7/12, it was impossible to separate both compounds by column or preparative thin layer chromatography. It was assumed that this by-product most likely might be the C-4 mesylate 7/13 (Figure 7.6). To verify this assumption a small amount of pyrrolidinol 7/12 was mesylated under standard conditions eventually confirming the by-product to be indeed the C-4 mesylate of 7/12 (Figure 7.7).

Figure 7.6. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the cyclised Petasis product 7/12 contaminated with a small amount of its C-4 mesylate. Signals of the mesylate by-product are annotated in red.

Figure 7.7. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the C-4 mesylated pyrrolidine 7/13. 
(2S,3S,4S,5S)- $N$-benzyl-3-benzyloxy-2-benzyloxymethyl-5-strylypyrrolidin-4-yl methanesulfonate.
To avoid the formation of this mesylate by-product an alternative cyclisation method was also explored. In 1992 MULZER and co-workers showed in the final steps of their (–)-castanospermine synthesis that a S\(_{N}\)\(_{2}\)-cyclisation also can be initiated employing Appel conditions (PPh\(_3\)/CBr\(_4\)/Et\(_3\)N). Under these conditions the OH-group gets activated as triphenylphosphonium ether prior to the ring-closure leaving triphenylphosphane oxide as by-product. In MULZER’s approach pyrrolidinol 7/14 was treated with PPh\(_3\) and CBr\(_4\) in the presence of Et\(_3\)N at 0 °C finally affording the desired indolizidine 7/15 in 78% yield (Scheme 7.8).

```
\[
\begin{align*}
\text{OH} & \quad \text{BnO} & \quad \text{H} & \quad \text{OBn} \quad \text{a} \quad \text{BnO} & \quad \text{N} & \quad \text{OBn} & \quad \text{b} \quad \text{OH} & \quad \text{BnO} & \quad \text{H} & \quad \text{OBn} \\
7/14 & \quad \rightarrow & \quad 7/15 & \quad \rightarrow & \quad \text{(-)-Castanospermine}
\end{align*}
\]
```

Scheme 7.8. Final steps in the synthesis of (–)-castanospermine by MULZER et al. (1992).

Reagents and conditions: (a) PPh\(_3\), CBr\(_4\), Et\(_3\)N, MeCN, 0 °C to rt, 35 h, 78%; (b) 10% Pd/C, H\(_2\) (3 bar), HCl, MeOH, rt, 2 d, 90%.

This method was later also used in our research group by Andrew DAVIS as part of his synthesis of the originally proposed structure of uniflorine A (see Chapter 4, Scheme 4.8). More recently in 2008 SOMFAI et al. also used Appel conditions to complete the pyrrolizidine skeleton of (+)-alexine. Treatment of pyrrolidinol 7/16 with in situ generated Appel salt in the presence of Et\(_3\)N at room temperature prompted cyclisation furnishing pyrrolizidine 7/17 in 64% yield (Scheme 7.9).

```
\[
\begin{align*}
\text{OH} & \quad \text{SiMe}_2\text{Ph} & \quad \text{BnO} & \quad \text{H} & \quad \text{OBn} & \quad \text{SiMe}_2\text{Ph} \quad \text{a} \quad \text{SiMe}_2\text{Ph} & \quad \text{BnO} & \quad \text{H} & \quad \text{OBn} & \quad \text{SiMe}_2\text{Ph} & \quad \text{OH} & \quad \text{OH} \\
7/16 & \quad \rightarrow & \quad 3 \text{ steps} & \quad \rightarrow & \quad 7/17 & \quad \rightarrow & \quad (+)-Alexine
\end{align*}
\]
```

Scheme 7.9. N-alkylative S\(_{N}\)2/5-exo-tet cyclisation in the synthesis of (+)-alexine by SOMFAI et al. (2008).

Reagents and conditions: (a) PPh\(_3\), CBr\(_4\), Et\(_3\)N, rt, 1 h, 64%.

Thus, when Appel conditions were applied to amino diol 7/6 the S\(_{N}\)2/5-exo-tet cyclisation proceeded smoothly with inversion of the configuration at C-2 affording pyrrolidinol 7/12 as the single product this time in 65% yield after column chromatography (Scheme 7.10). Figure 7.8 shows the significant region of the \(^1\)H NMR spectrum of pure pyrrolidinol 7/12.
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Scheme 7.10. N-alkylative S_{2}/2-exo-tet cyclisation of amino diol 7/6 under Appel conditions.

Reagents and conditions: (a) PPh_{3}, CBr_{4}, Et_{3}N, DCM, –5 °C to 40 °C, 4 h, 65%.

Figure 7.8. ¹H NMR spectrum (500 MHz, CDCl_{3}) of the pure cyclised Petasis product 7/12.
(2S,3S,4S,5S)-N-benzyl-3-benzyloxy-2-benzyloxymethyl-5-styrylpyrrolidin-4-ol.

7.4 Ozonolysis

With pyrrolidinol 7/12 in hand, the first synthesis target, L-DMDP, was only two steps away. The remaining tasks were the oxidative cleavage of the styryl double bond followed by the hydrogenolysis of the benzyl protecting groups.

Transformation of the double bond into a primary hydroxy group could be achieved via two ways. A longer three-step procedure would consist of the syn-dihydroxylation of 7/12 with OsO_{4} followed by the oxidative cleavage of the vicinal diol with either NaIO_{4} or Pb(OAc)_{4} and a concluding reduction of the intermediate aldehyde with NaBH_{4}. A faster and more convenient way would involve the ozonolysis of the double bond and reduction of the in situ generated ozonide affording the desired pyrrolidine diol 7/23 in one step. Indeed, GÉNISSON and co-workers had performed such ozone-mediated double bond cleavages on
similar compounds in 2006. To prevent possible \(N\)-oxidation during the reaction, GÉNISSON et al. converted the basic pyrrolidines into their pyrrolidinium chloride salts (7/20a – c) prior to their treatment with ozone in a methanolic solution at low temperature. Reduction of the intermediary ozonides with NaBH\(_4\) then provided the respective pyrrolidine diols 7/21a – c in moderate to good yields (Scheme 7.11).\(^{[62]}\)

\[
\begin{align*}
\text{Scheme 7.11. Ozonolyses of 2-vinyl pyrrolidin-3-ols by GÉNISSON et al. (2006).}^{[62]} \\
\text{Reagents and conditions: (i) HCl, MeOH, 0 °C; (ii) O}_{3}, \text{MeOH, –78 °C; (iii) NaBH}_{4}, \text{MeOH, –78 °C to –10 °C, 68% (7/21a), 70% (7/21b), 52% (7/21c).}
\end{align*}
\]

Following GÉNISSON’s protocol a solution of the 5-styryl pyrrolidinol 7/12 in Et\(_2\)O was initially treated with a 2 M ethereal solution of HCl at 0 °C giving the insoluble pyrrolidinium chloride salt 7/22 as a grey foamy solid after evaporation of all volatiles in high vacuum. This salt was then dissolved in a mixture of DCM and MeOH and subjected to ozonolysis at –78 °C. Reduction of the intermediate ozonide with excess NaBH\(_4\) yielded the desired pyrrolidine diol 7/23 in 56% after column chromatography.

\[
\text{Figure 7.9. } ^1H \text{ NMR spectrum (500 MHz, CDCl}_3\text{) of the L-DMDP precursor 7/23, } (2S,3S,4S,5S)-N\text{-benzyl-3-benzyloxy-2-benzyloxymethyl-5-hydroxymethylpyrrolidin-4-ol.}
\]

220
Figure 7.9 shows the significant region of the $^1$H NMR spectrum of 7/23. Interestingly, all proton signals around the periphery of the pyrrolidine ring (H-2 – H-5) appear as singlets indicating that the dihedral angle between these protons must be close to 90°.

Surprisingly, a second less polar product was also obtained in 28% yield. This compound could be identified as the pyrrolidinol 7/24 in which the original C-5 styryl substituent had been completely cleaved off (Scheme 7.12). The fully assigned central region of its $^1$H NMR spectrum is shown in Figure 7.10.

![Scheme 7.12. Ozonolysis-reduction of the 5-styrylpyrrolidinium chloride 7/22.](image)

Reagents and conditions: (a) O$_3$ (~33% in O$_2$), DCM/MeOH (1:1), –78 °C, then NaBH$_4$, –78 °C to rt, 56% 7/23, 28% 7/24.

The two diastereotopic protons at C-5 were assigned to the α- and β-configuration via their coupling constants with the neighbouring proton at C-4. Similar to compound 7/5 the dihedral angle between H-4 and the proton in the β-configuration at C-5 of pyrrolidinol 7/24 is also almost 90° resulting in a coupling constant of 0 Hz for H-4/H$_β$-5.

![Figure 7.10. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the L-AB1 precursor 7/24.](image)

(2S,3S,4S)-N-benzyl-3-benzyloxy-2-benzyloxymethylpyrrolidin-4-ol; $^3$J$_{H_4,H_{\alpha}-5}$ = 3.3 Hz, $^3$J$_{H_4,H_{\beta}-5}$ = 0 Hz.
A plausible mechanism for the loss of this substituent is depicted in Scheme 7.13. It involves fragmentation of the intermediary secondary ozonide $7/25$ leading to the formation of the pyrrolinium ion $7/26$ that is subsequently reduced by $\text{NaBH}_4$ to the observed pyrrolidine derivative $7/24$.

Dr. Ben Greatrex from the University of New England in Armidale, New South Wales offered another possible mechanism for the loss of the C-5 substituent at an one-day organic chemistry symposium 2009 in Sydney, after a presentation was given about this work. He suggested that the fragmentation of the ozonide $7/27$ occurs via a two-step mechanism involving the initial formation of the bicyclic oxazetidine derivative $7/28$. This oxazetidine then undergoes cycloreversion liberating the pyrrolinium ion $7/26$ which is then reduced to the observed pyrrolidinol $7/24$ (Scheme 7.14).

Both mechanism feature the initial deprotonation of the pyrrolidinium nitrogen which eventually triggers the fragmentation of the secondary ozonide. This spawned the idea to
facilitate the process by adding a base like Et$_3$N to the reaction mixture with the goal to increase the yield of pyrrolidinol 7/24 (Scheme 7.15). If successful then this small modification in the work-up procedure of the ozonolysis reaction could be used to divert the synthesis route to also prepare the known iminosugar L-AB1$^{[63-67]}$ (7/32).  

Scheme 7.15. Facilitation of the secondary ozonide fragmentation through the addition of Et$_3$N.

As it turned out treatment of the secondary ozonide 7/25 with Et$_3$N at –78 °C prior to the reduction with NaBH$_4$ indeed promoted the formation of pyrrolidinol 7/24. The yield of this L-AB1 precursor could be increased from 28% to nearly 50% whereas the yield of pyrrolidine diol 7/23 dropped down from 56% to less than half (25%).

When the ozonolysis reaction was performed on the 5-styrylpyrrolidinol 7/12 that was obtained via the mesylate-promoted 5-exo-tet cyclisation, two further minor by-products could be isolated. Unsurprisingly, these compounds turned out to be the pyrrolidinyl methanesulfonates 7/30 and 7/31 originating from the C-4 mesylate contamination of 7/12.

Figure 7.11. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the 5-hydroxymethylpyrrolidinyl mesylate 7/30, (2S,3R,4S,5S)-N-benzyl-3-benzyloxy-2-benzyloxymethyl-5-hydroxymethylpyrrolidin-4-yl methanesulfonate.
To confirm the structures of these two compounds, pure C-4 mesylate 7/13 was also subjected to ozonolysis in a separate experiment affording the 5-hydroxymethylpyrrolidinyl methanesulfonate 7/30 (Figure 7.11) and its decarbinolated C-5 derivative 7/31 (Figure 7.12) in 50% and 34% yield, respectively (Scheme 7.16).

Scheme 7.16. Ozonolysis-reduction of the 4-O-mesylpyrrolidinium chloride 7/29.
Reagents and conditions: (a) O\textsubscript{3} (~33% in O\textsubscript{2}), DCM/MeOH (1 : 1), –78 °C, then NaBH\textsubscript{4}, –78 °C to rt, 50% 7/30, 34% 7/31.

7.5 Hydrogenolysis

In the final step, the remaining benzyl protecting groups of 7/23 were cleaved by hydrogenolysis at atmospheric pressure over Pd-enriched Pearlman’s catalyst\cite{68} in acetic acid. Purification of the crude product by ion exchange chromatography on basic Dowex 1X8 (100-200 mesh) resin gave pure L-DMDP (6/56) in 97% yield. Figures 7.13 and 7.14 show the \textsuperscript{1}H NMR spectra of 6/56 measured in CD\textsubscript{3}OD and D\textsubscript{2}O, respectively. The presence of only four signals indicated C2-symmetry of the molecule with four sets of two magnetically equivalent protons.
By applying the same conditions to pyrrolidinol 7/24 the known iminosugar L-AB1 (7/32) was obtained in 100% yield. The $^1$H NMR spectra of 7/32 recorded in CD$_3$OD and D$_2$O, respectively, are depicted in Figures 7.15 and 7.16. Since L-AB1 does not exhibit C2-symmetry like its 5-alkylated homologue L-DMDP, all seven CH-protons possess distinct signals in the spectra.

Spectroscopic data for both synthesised compounds were in agreement with the published data of the natural products$^{69, 70}$ except the specific optical rotations which were of opposite sign to those of the naturally occurring enantiomers (Table 7.4).

Figure 7.13. $^1$H NMR spectrum (300 MHz) of L-DMDP, (2S,3S,4S,5S)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol (6/56) in CD$_3$OD.

Figure 7.14. $^1$H NMR spectrum (500 MHz) of L-DMDP, (2S,3S,4S,5S)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol (6/56) in D$_2$O.
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Figure 7.15. $^1$H NMR spectrum (500 MHz) of L-AB1, (2S,3S,4S)-2-hydroxymethylpyrrolidine-3,4-diol in CD$_3$OD.

Figure 7.16. $^1$H NMR spectrum (500 MHz) of L-AB1, (2S,3S,4S)-2-hydroxymethylpyrrolidine-3,4-diol in D$_2$O.

Figure 7.17. Facsimile of the originally published $^1$H NMR spectrum (300 MHz, D$_2$O) of naturally occurring D-AB1, isolated from *Angylocalyx boutiqueanus* (Leguminosae) by Nash et al. (1985).[^70]
Chapter 7. Synthesis of L-DMDP

Table 7.2. $^1$H- and $^{13}$C NMR spectral data for L-DMDP.

<table>
<thead>
<tr>
<th></th>
<th>$^1$H NMR (D$_2$O)</th>
<th>$^{13}$C NMR (D$_2$O)</th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.64 (dd, J = 6.3, 11.6 Hz, H$_A$-1, H$_A$-6)</td>
<td>64.93 (2 × CH$_2$, C-1, C-6)</td>
<td>3.58 (dd, J = 6.2, 11.1 Hz, H$_A$-1, H$_A$-6)</td>
<td>64.57 (2 × CH$_2$, C-1, C-6)</td>
</tr>
<tr>
<td>2</td>
<td>64.93 (2 × CH$_2$, C-1, C-6)</td>
<td>3.58 (dd, J = 6.2, 11.1 Hz, H$_A$-1, H$_A$-6)</td>
<td>64.57 (2 × CH$_2$, C-1, C-6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.73 (dd, J = 4.3, 11.6 Hz, H$_B$-1, H$_B$-6)</td>
<td>64.93 (2 × CH$_2$, C-1, C-6)</td>
<td>3.58 (dd, J = 6.2, 11.1 Hz, H$_A$-1, H$_A$-6)</td>
<td>64.57 (2 × CH$_2$, C-1, C-6)</td>
</tr>
<tr>
<td>4</td>
<td>3.73 (dd, J = 4.3, 11.6 Hz, H$_B$-1, H$_B$-6)</td>
<td>64.93 (2 × CH$_2$, C-1, C-6)</td>
<td>3.58 (dd, J = 6.2, 11.1 Hz, H$_A$-1, H$_A$-6)</td>
<td>64.57 (2 × CH$_2$, C-1, C-6)</td>
</tr>
<tr>
<td>5</td>
<td>3.04 (m, 2H, H-2, H-5)</td>
<td>2.99 (m, 2H, H-2, H-5)</td>
<td>63.60 (2 × CH$_2$, C-2, C-5)</td>
<td>63.60 (2 × CH, C-2, C-5)</td>
</tr>
<tr>
<td>6</td>
<td>3.04 (m, 2H, H-2, H-5)</td>
<td>2.99 (m, 2H, H-2, H-5)</td>
<td>63.60 (2 × CH$_2$, C-2, C-5)</td>
<td>63.60 (2 × CH, C-2, C-5)</td>
</tr>
</tbody>
</table>

$^\delta$ ppm. $^1$H NMR measured at 500 MHz; $^{13}$C NMR measured at 125 MHz, respectively.

Table 7.3. $^1$H- and $^{13}$C NMR spectral data for L-AB1.

<table>
<thead>
<tr>
<th></th>
<th>$^1$H NMR (D$_2$O)</th>
<th>$^{13}$C NMR (D$_2$O)</th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.66 (dd, J = 6.4, 11.6 Hz, H$_A$-1)</td>
<td>64.89 (CH$_2$, C-1)</td>
<td>3.64 (dd, J = 5.6, 11.1 Hz, H$_A$-1)</td>
<td>63.17 (CH$_2$, C-1)</td>
</tr>
<tr>
<td>2</td>
<td>64.89 (CH$_2$, C-1)</td>
<td>3.64 (dd, J = 5.6, 11.1 Hz, H$_A$-1)</td>
<td>63.17 (CH$_2$, C-1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.98 (q, J = 5.6, H-2)</td>
<td>67.98 (CH, C-2)</td>
<td>2.84 (dd, J = 3.8, 5.5 Hz, H-3)</td>
<td>80.65 (CH, C-3)</td>
</tr>
<tr>
<td>4</td>
<td>2.98 (q, J = 5.6, H-2)</td>
<td>67.98 (CH, C-2)</td>
<td>2.84 (dd, J = 3.8, 5.5 Hz, H-3)</td>
<td>80.65 (CH, C-3)</td>
</tr>
<tr>
<td>5</td>
<td>53.36 (CH$_2$, C-5)</td>
<td>53.18 (CH$_2$, C-5)</td>
<td>53.36 (CH$_2$, C-5)</td>
<td>53.18 (CH$_2$, C-5)</td>
</tr>
<tr>
<td>6</td>
<td>53.36 (CH$_2$, C-5)</td>
<td>53.18 (CH$_2$, C-5)</td>
<td>53.36 (CH$_2$, C-5)</td>
<td>53.18 (CH$_2$, C-5)</td>
</tr>
</tbody>
</table>

$^\delta$ ppm. $^1$H NMR measured at 500 MHz; $^{13}$C NMR measured at 125 MHz, respectively.

Table 7.4. Comparison of the specific optical rotations obtained for L-DMDP and L-AB1 with those reported in the literature including their natural enantiomers.

<table>
<thead>
<tr>
<th></th>
<th>L-DMDP</th>
<th>L-AB1</th>
<th>D-AB1</th>
<th>L-AB1</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[^\alpha]_D^{20}$</td>
<td>$+56.4^{(69)}$</td>
<td>$+53.4^c$</td>
<td>$+7.8^{(64)}$</td>
<td>$-8.3^c$</td>
</tr>
<tr>
<td>$[^\alpha]_D^{25}$</td>
<td>$+53.8^{(31)}$</td>
<td>$+53.4^c$</td>
<td>$+4.4^{(71)}$</td>
<td>$-4.4^c$</td>
</tr>
<tr>
<td>$[^\alpha]_D^{20}$</td>
<td>$+55.8^{(44)}$</td>
<td>$+55.6^c$</td>
<td>$+37.9^{(64)}$ (HCl salt, $[^\alpha]_D^{25}$</td>
<td>$-32.1^c$ (HCl salt, $[^\alpha]_D^{25}$</td>
</tr>
<tr>
<td>$[^\alpha]_D^{20}$</td>
<td>$+55.8^{(44)}$</td>
<td>$+55.6^c$</td>
<td>$+37.9^{(64)}$ (HCl salt, $[^\alpha]_D^{25}$</td>
<td>$-32.1^c$ (HCl salt, $[^\alpha]_D^{25}$</td>
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<tr>
<td>$[^\alpha]_D^{20}$</td>
<td>$+55.8^{(44)}$</td>
<td>$+55.6^c$</td>
<td>$+37.9^{(64)}$ (HCl salt, $[^\alpha]_D^{25}$</td>
<td>$-32.1^c$ (HCl salt, $[^\alpha]_D^{25}$</td>
</tr>
<tr>
<td>$[^\alpha]_D^{20}$</td>
<td>$+55.8^{(44)}$</td>
<td>$+55.6^c$</td>
<td>$+37.9^{(64)}$ (HCl salt, $[^\alpha]_D^{25}$</td>
<td>$-32.1^c$ (HCl salt, $[^\alpha]_D^{25}$</td>
</tr>
</tbody>
</table>

$^a$ optical rotation measured using the JASCO DIP-370 polarimeter;
$^b$ optical rotation measured using the JASCO P-2000 polarimeter;
$^c$ optical rotation reported in the stated literature reference.
7.6 Summary

The synthesis of (–)-L-DMDP (6/56), the enantiomer of the naturally occurring iminosugar (+)-DMDP (1/51), has been accomplished in seven consecutive steps from the inexpensive commercially available carbohydrate D-xylose. First steps were the transformation of D-xylose into its known derivative 3,5-di-O-benzyl-D-xylofuranose in 72% overall yield. The key step of the synthesis was the following one-pot three-component Petasis borono-Mannich reaction of this D-xylose derivative with benzylamine and (E)-styrylboronic acid which provided the amino diol 7/6 as a single diastereomer in an excellent yield of 93%. The subsequent N-alkylative SN2/5-exo-tet cyclisation with inversion of the configuration at C-2 furnished the desired pyrrolidine ring with the required all-trans stereochemistry in 65% yield. The pyrrolidinol 7/12 was then subjected to an ozonolysis reaction of the styryl double bond which provided the pyrrolidine diol 7/23 in 56% yield.

Scheme 7.17. Synthesis of L-DMDP.

Reagents and conditions: (a) 1. acetone, cat. H2SO4, anhydrous CuSO4, 25 ºC, 28 h, then conc. NH4OH, 2. 0.2% HCl, 25 ºC, 3.5 h, then NaHCO3, quant.; (b) NaH, BnBr, TBAI, THF, 0 ºC to reflux, 85%; (c) 1 N H2SO4, 1,4-dioxane, reflux, 3.5–4 h, 85%; (d) benzyamine, (E)-styrylboronic acid, TFE, 25 ºC, 24 h, 93%; (e) PPh3, CBr4, Et3N, DCM, –5 ºC to 40 ºC, 4 h, 65%; (f) 1. HCl (2 M in Et2O), Et2O, 0 ºC, 2. O3 (~33% in O2), DCM/MeOH (1 : 1), –78 ºC, then NaBH4, –78 ºC to rt, 56%; (g) Pd-enriched Pearlman’s catalyst, H2 (1 atm), AcOH, rt, 18 h, 97%; 23.8% over 7 steps from D-xylose, 32.9% over 4 steps from 3,5-di-O-benzyl-D-xylofuranose, respectively.
The concluding hydrogenolytic cleavage of the benzyl protecting groups over Pd-enriched Pearlman’s catalyst finally afforded L-DMDP in an overall yield of 23.8% from D-xylose or in 32.9% yield over four steps from the known compound 3,5-di-O-benzyl-D-xylofuranose, respectively (Scheme 7.17).

Serendipitously, a small modification of the synthesis also gave access to the known iminosugar L-AB1 (7/32). Treatment of the intermediate secondary ozonide with Et₃N during the ozonolysis work-up of 7/12 promoted a fragmentation process which provided the L-AB1 precursor 7/24 in 50% yield. The following final hydrogenolysis of the remaining benzyl groups then afforded L-AB1 in 21.9% yield over 7 steps from D-xylose or 30.3% over 4 steps from 3,5-di-O-benzyl-D-xylofuranose, respectively (Scheme 7.18).


Reagents and conditions: (a) 3 steps, 72%, see Scheme 7.17; (b) 2 steps, 61%, see Scheme 7.17, (c) 1. HCl (2 M in Et₂O), Et₂O, 0 °C, 2. O₃ (~33% in O₂), DCM/MeOH (1:1), –78 °C, 3. Et₃N, –78 °C to –5 °C, 2 h, then NaBH₄, –5 °C to rt, 2 h, 50%; (d) Pd-enriched Pearlman’s catalyst, H₂ (1 atm), AcOH, rt, 18 h, 100%; 21.9% over 7 steps from D-xylose, 30.3% over 4 steps from 3,5-di-O-benzyl-D-xylofuranose, respectively.
7.7 References


Chapter 7. Synthesis of L-DMDP


Chapter 7. Synthesis of L-DMDP


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Chapter 7. Synthesis of L-DMDP


Chapter 8. Synthesis of Pyrrolidine Carbaldehyde 8/2

After the successful synthesis of L-DMDP we focused on our next synthetic target, the pyrrolidine carbaldehyde 8/2 as building block for our broussonetine syntheses. In theory, only two more steps had to be done to obtain this aldehyde from pyrrolidinol 7/12: the free hydroxy group at C-4 had to be benzyl-protected followed by the oxidative cleavage of the styryl double bond to form the carbonyl functionality in 8/2 (Scheme 8.1). However, this turned out to be much more challenging than expected.

Scheme 8.1. Final steps in the synthesis of the pyrrolidine carbaldehyde 8/2.

(a) C-4 O-benzylation; (b) oxidative double bond cleavage.

8.1 O-Benzylaion

The procedure for the C-4 O-benzylation of 7/12 was based on two literature references: CHE’s synthesis of the pyrrolizidine alkaloid platynecine (1/99) from 2004[1] (Scheme 8.2) and DHAVALE’s synthesis of the indolizidine alkaloid 1,2-di-epi-lentiginosine (8/7) from 2006[2] (Scheme 8.3). Both syntheses feature starting materials that contain N-benzylated pyrrolidine moieties similar to our styryl pyrrolidinol 7/12.

Scheme 8.2. The O-benzylation step in CHE’s synthesis of *rac*-platynecine (2004).[1]

Reagents and conditions: (a) NaH, BnBr, THF, 0 °C, 1 h, then rt, 12 h; (b) 9-BBN, THF, reflux, 5 h, then EtOH, 3 M NaOH, 30% aq. H₂O₂, 0 °C, then rt, 3 h, 86% over 2 steps.
Scheme 8.3. The O-benzylation step in DHAVALE’s synthesis of 1,2-di-epi-lentiginosine (2006).[2]
Reagents and conditions: (a) NaH, BnBr, cat. TBAI, 0 °C to 25 °C, 5 h, 82%.

According to CHE’s and DHAVALE’s protocols, styryl pyrrolidinol 7/12 was treated with a slight excess of NaH at 0 °C followed by the addition of a near-stoichiometric amount of benzyl bromide and a catalytic amount of TBAI at 25 °C. The conversion proceeded slowly, and the reaction control via TLC as well as ESI-MS after overnight stirring at 25 °C still indicated the presence of starting material in the reaction mixture. Therefore, additional small amounts of all three reagents were added. Warming of the mixture or even refluxing to accelerate the reaction was not considered since it was expected that such a treatment would promote per-benzylation of the basic nitrogen affording a polar, potentially water-soluble dibenzyl pyrrolidinium salt (8/8). After further 24 hours stirring at 25 °C ESI-MS control finally showed full conversion of the starting material. The C-4 benzyl ether 8/1 was eventually obtained in an excellent yield of 94% after purification by column chromatography (Scheme 8.4).

Scheme 8.4. C-4 O-benzylation of styryl pyrrolidinol 7/12.
Reagents and conditions: (a) NaH, BnBr, cat. TBAI, 0 °C to 25 °C, 48 h, 94%.

Figure 8.1 shows the significant region of the 1H NMR spectrum of compound 8/1 featuring a third set of benzylic proton signals between 4.4 and 4.6 ppm for the newly introduced benzyl group.
Chapter 8. Synthesis of Pyrrolidine Carbaldehyde 8.2

8.2 Oxidative Cleavage of the Double Bond

With ample amounts of the fully benzyl-protected pyrrolidine 8/1 in hand, we now focused on the oxidative cleavage of the styryl double bond. This, on paper, simple appearing reaction however turned out to be more sophisticated than expected.

8.2.1 Attempted Ozonolysis to the Aldehyde

In a first approach it was attempted to obtain the carbaldehyde 8/2 directly via the ozonolysis of styryl pyrrolidine 8/1 and treatment of the intermediate secondary ozonide with Me₂S (Scheme 8.5).

![Scheme 8.5. Attempted synthesis of pyrrolidine carbaldehyde 8/2 via ozonolysis of styryl pyrrolidine 8/1. Reagents and conditions: (a) 1. HCl (2 M in Et₂O), Et₂O, 0 °C, 2. O₃ (~33% in O₂), DCM, −78 °C, then N₂, Me₂S, −78 °C to rt, column chromatography.]
However, efforts to purify the crude pyrrolidine carbaldehyde by a short column chromatography over silica gel led to extensive decomposition. Indeed, the only compound that was retrieved and identified from the column was benzaldehyde. Then again, this outcome was not unexpected and confirmed DONDONI’s observation about the moderate stability of this compound. Nevertheless, the purity of the pyrrolidine carbaldehyde was an absolute imperative for the success of the following Wittig and Grignard coupling reactions since the benzaldehyde by-product would undoubtedly have interfered in these reactions. It was therefore decided to do a short detour and convert the styryl pyrrolidine 7/12 first into the alcohol 8/9 which would then be oxidised to pyrrolidine carbaldehyde 8/2 in a second step after purification and separation form the benzylalcohol by-product (Scheme 8.6).

\[ \begin{array}{c}
\text{8/1} \\
\text{8/9} \\
\text{8/2}
\end{array} \]

Scheme 8.6. Two-step detour to the pyrrolidine carbaldehyde building block 8/2 via alcohol 8/9. (a) Ozonolysis-reduction; (b) Swern oxidation.

8.2.2 Ozonolysis of the Pyrrolidinium Chloride

In order to obtain the pyrrolidine alcohol 8/9 via the ozonolysis of the styryl double bond, the beforehand successfully employed protocol of GÉNISSON et al. was now applied to the pyrrolidine 8/1. As in the case of pyrrolidinol 7/12, the styryl pyrrolidine 8/1 was initially converted into its pyrrolidinium chloride salt to protect the basic nitrogen from oxidation. This salt was then dissolved in a mixture of DCM and MeOH and subjected to ozonolysis at \(-78^\circ\text{C}\) followed by reduction of the intermediate secondary ozonide with NaBH₄. Surprisingly though, instead of isolating pure pyrrolidine alcohol 8/9 after column chromatography, a complex mixture of multiple inseparable compounds was obtained. ESI-MS analysis of the product mixture indicated the presence of the desired alcohol but also various other compounds with smaller and higher molecular weights. Since this outcome of the reaction was not observed from the ozonolysis of styryl pyrrolidinol 7/12 which bears a free hydroxy group at C-4 neighbouring the reaction centre, it was assumed that this OH-group might have a stabilising effect that was lost with its benzylation.
Two repetitions of the experiment in pure MeOH and pure DCM as solvents were subsequently performed but both gave similar results. In the latter case, however, it was possible to isolate and purify one of the many products in about 9% yield after three-time repeated column chromatography and eventually identify it as the N-debenzylated lactam 8/10 (Figure 8.2).

After these startling results, an in-depth literature search was done to find alternative procedures for the ozonolysis reaction. This search yielded three further references with successful ozonolytic double bond cleavages similar to our case and the example of GÉNISSON et al.\[4\]. The major difference in each case was the acid employed to prevent N-oxidation.

### 8.2.3 Ozonolysis of the Pyrrolidinium Trifluoroacetate

In their synthesis of tricyclic thrombin\(^*\) inhibitors DIEDERICH et al. used trifluoroacetic acid to protect the basic nitrogen in 8/11 from oxidation and converted the vinylic double bond directly to the aldehyde 8/13 via ozonolysis (Scheme 8.7).\[5\]

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\(^*\) Thrombin is a serine protease protein that plays an important role during the blood coagulation cascade of mammals, the process which ultimately results in the stemming of blood loss.

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[Figure 8.2. \(^1\)H NMR spectrum (500 MHz, CDCl\(_3\)) of the N-debenzylated lactam 8/10, (2S,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-oxopyrrolidine.]

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Scheme 8.7. Ozonolysis step in the synthesis of tricyclic thrombin inhibitors by DIEDERICH et al. (2006).\[5\]
Reagents and conditions: (i) O$_3$, TFA, DCM, –78 ºC, 20 min; (ii) Me$_2$S, DCM, –78 ºC to 25 ºC, 16 h, 84%.

According to DIEDERICH’s procedure, the styryl pyrrolidine 8/1 was treated with trifluoroacetic acid to generate its TFA salt 8/14. In contrast to the pyrrolidinium chloride the trifluoroacetate formed not a foamy solid during the drying process in high vacuum but remained a dark purple viscous liquid. This liquid was then dissolved in DCM and submitted to ozonolysis at –78 ºC. Deviant to DIEDERICH et al.\[5\] the intermediate ozonide was not treated with Me$_2$S but reduced with NaBH$_4$/EtOH to directly attain the wanted alcohol 8/9. However, unexpectedly, four products were obtained in low yields after work-up and column chromatography. The main products turned out to be an inseparable mixture of the desired alcohol 8/9 and its C-5 epimer 8/15 in a 1 : 1 ratio and in about 20% combined yield (Scheme 8.8).

Reagents and conditions: (i) TFA (1 M in DCM), DCM, 0 ºC; (ii) O$_3$, DCM, –78 ºC; (iii) NaBH$_4$, EtOH, 0 ºC to rt.

Further isolated products were the pyrrolidine 8/16 (Figure 8.3) in which the C-5 substituent had been cleaved off and its 5-oxo derivative, the lactam 8/17 (Figure 8.4). The loss of the C-5 substituent as side reaction had already been observed during the ozonolysis of 7/12 in the synthesis of L-DMDP (see Chapter 7, Scheme 7.12) and was therefore not that surprising.
New, however, was the formation of the lactam 8/17 as by-product. This lactam may result from the oxidation of the intermediate pyrrolinium ion 8/18 by ozone as illustrated in Scheme 8.9.

Scheme 8.9. Proposed mechanism for the oxidation of pyrrolinium ion 8/18 by ozone.

Figure 8.4. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the lactam 8/17.

$(2S,3S,4R)$-$N$-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-oxopyrrolidine.
Alternatively, a mechanism is thinkable in which the initial primary ozonide 8/20 rearranges and subsequently fragmentises via the oxazetine 8/21 to the pyrrolinium cation 8/18 and the peroxide anion 8/22. This peroxide fragment could then react with 8/18 as the oxidising agent affording the observed lactam 8/17 and 2-hydroxy-2-phenylacetaldehyde (8/24) as by-product (Scheme 8.10).

Scheme 8.10. Alternative mechanism for the formation of the pyrrolidine lactam 8/17.

### 8.2.4 Ozonolysis of the Pyrrolidinium Bisulfate

Due to the poor result of DIEDERICH’s method we tried next a procedure introduced by BEHR and co-workers. In 2005 BEHR et al.\textsuperscript{[6]} reported the syntheses and evaluation on chitin synthase activity of the DMDP stereoisomers 2,5-dideoxy-2,5-imino-D-glucitol (DGDP, 1/54) and 2,5-dideoxy-2,5-imino-L-iditol (L-DIDP, 5/31). Prior to the final N/O-debenzylation step BEHR and co-workers installed the hydroxymethyl substituent at C-5 via the ozonolysis of the vinylic double bond of 8/25 and 8/28. To avoid oxidation of the free amine BEHR et al. performed the ozonolysis on the bisulfate salts 8/26 and 8/29 providing the desired alcohols in 56% and 91% yield, respectively (Scheme 8.11).\textsuperscript{[6]}
Scheme 8.11. Ozonolyses of N-benzylated 5-vinylpyrrolidines by BEHR et al. (2005).\[^6\]

Reagents and conditions: (i) conc. H\(_2\)SO\(_4\), Et\(_2\)O, 0 °C; (ii) O\(_3\), DCM, −50 °C, then Me\(_2\)S; (iii) NaBH\(_4\), EtOH, 0 °C to rt, 56% 8/27, 91% 8/30.

Following BEHR’s procedure a solution of styryl pyrrolidine 8/1 in Et\(_2\)O was treated drop-wise with concentrated sulfuric acid at 0 °C to form the insoluble bisulfate salt as a thick off-white cream. After decanting the supernatant the precipitate was dried in high vacuum affording the pyrrolidinium bisulfate 8/31 as a slightly pink foamy solid. This solid was then dissolved in DCM and submitted to ozonolysis at −50 °C. After full consumption of the starting material the reaction mixture was treated with Me\(_2\)S at −50 °C followed by NaBH\(_4\)/EtOH at 0 °C. However, after aqueous work-up and separation by column chromatography five products were obtained similar to the ozonolysis of the trifluoroacetate 8/14 (Scheme 8.12).


Reagents and conditions: (i) conc. H\(_2\)SO\(_4\), Et\(_2\)O, 0 °C; (ii) O\(_3\), DCM, −50 °C, then Me\(_2\)S, N\(_2\), −50 °C to 0 °C; (iii) NaBH\(_4\), EtOH, 0 °C to rt.

23% isolated yield

15% isolated yield
3% isolated yield
6.5% isolated yield
trace

44% combined yield
Chapter 8. Synthesis of Pyrrolidine Carbaldehyde 8.2

Main products were the wanted pyrrolidine alcohol 8/9 and its C-5 epimer 8/15 in 44% combined yield and a ratio of 6 : 1 in favour of the desired diastereomer. Via a second chromatography it was possible for the first time to separate small amounts of the pure epimeric alcohols from this mixture in 15% and 3% yield, respectively. Unsurprisingly, the pyrrolidine 8/16 and the lactam 8/17 were also obtained as by-products. In addition to these already known compounds, a trace amount of the C-3 benzoyl ester 8/32 (Figure 8.5) was isolated as a new by-product as well.

Figure 8.5. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the C-3 benzoyl ester 8/32. (2S,3S,4S,5S)-N-benzyl-3-(benzoyloxy)-4-(benzyloxy)-2-(benzyloxymethyl)-5-(hydroxymethyl)pyrrolidine.

The oxidation of benzyl ethers to benzoyl esters by ozone is a known transformation which has been introduced by Defaye et al. in 1985 as a mild oxidative O-debenzylation method. Normally, however, this oxidation only occurs at temperatures close to 0 °C. Reaction products are benzoic esters which are usually saponified with sodium methoxide in methanol yielding the respective deprotected alcohols in good to excellent yields.\[7\]

8.2.5 Ozonolysis of the Pyrrolidinium Perchlorate

In 2009, at about the time we experimented on the oxidative double bond cleavage with ozone, Wong et al.\[8\] published a short communication about the syntheses of unnatural iminofuranoses and -pyranoses via a Petasis-type aminocyclisation which also included an ozonolysis step of styryl double bonds similar to our case (see Chapter 5, Section 5.7). To overcome problems with the decomposition of the basic starting materials during the
Chapter 8. Synthesis of Pyrrolidine Carbaldehyde 8.2

Ozonolysis reaction WONG and co-workers converted the respective piperidine and pyrrolidine dienes into the corresponding perchlorates and achieved high yields of the desired iminosugars. Scheme 8.13 shows the exemplary final ozonolysis-reduction step of WONG’s DIDP synthesis.[8]

\[
\]
Reagents and conditions: (i) HClO\textsubscript{4} in MeOH; (ii) O\textsubscript{3}, MeOH, −78 °C; (iii) NaBH\textsubscript{4}, −78 °C to rt, o/n, 85%.

Without high hopes after the upsetting previous results it was decided to give WONG’s method a chance as one final try. Accordingly to WONG’s procedure the styryl pyrrolidine \[8/1\] was converted into its pyrrolidinium perchlorate salt \[8/34\] and treated with ozone in a methanolic solution at −78 °C (Scheme 8.14). However, as in the case of the ozonolysis of the pyrrolidinium chloride, multiple products were obtained from this experiment. ESI-MS analysis of the crude product mixture showed the potential presence of the desired alcohol along with several other compounds with higher and lower molecular weights. Attempts to isolate the wanted alcohol \[8/9\] from the crude product mixture failed.

\[
\text{Scheme 8.14. Formation and ozonolysis of the pyrrolidinium perchlorate 8/34.}\[10.5ex]
\text{Reagents and conditions: (i) HClO}_4 \text{ in MeOH, 0 °C; (ii) O}_3, \text{MeOH, −78 °C; (iii) NaBH}_4, −78 °C to rt, 3 h.}\ [10.5ex]
\]

Nevertheless, we succeeded to identify and characterise one of the many products; \[N\text{-}(\text{methoxy}(\text{phenyl})\text{methyl})\text{lactam} 8/35\] was isolated after two-time column chromatography in 13% yield as a single diastereomer. This compound most likely originated from the reaction of a reactive intermediate with the solvent methanol. Figure 8.6 shows the significant region of its \(^1\text{H}\) NMR spectrum with the characteristic OMe singlet at 3.49 ppm.
8.3 The Diol Detour

After the failed attempts to efficiently cleave the styryl double bond in one step with ozone, it was decided to give an alternative, more elaborate three-step method a try. This involved the initial syn-dihydroxylation of the double bond followed by the oxidative cleavage of the intermediate diol and finally the reduction of the in situ generated aldehyde. As for the ozonolysis there was also precedence in the literature for this method.

As part of their (+)-alexine synthesis in 2008, SOMFAI and co-workers employed a Lemieux-Johnson oxidation to convert the terminal olefin 8/36 into the aldehyde 8/37. This aldehyde was not isolated but reduced with NaBH₄ in situ to the primary alcohol 8/38 in 72% overall yield (Scheme 8.15).[9]

Scheme 8.15. Lemieux-Johnson oxidation/reduction sequence in the synthesis of (+)-alexine by SOMFAI et al. (2008).[9]
Reagents and conditions: (i) OsO₄, NaIO₄, pyridine, MeCN/H₂O (1 : 1), rt, 3 h; (ii) NaBH₄, MeOH, 0 °C, 20 min, 72%.
In the final synthesis steps of the not naturally occurring fucosidase inhibitor 1,2,5-trideoxy-2,5-imino-D-allitol (8/44), PALMER and JÄGER dihydroxylated the double bond of the vinyl pyrrolidine 8/39 with OsO$_4$/NMO yielding the diol 8/40 in 83%. This diol was oxidatively cleaved with Pb(OAc)$_4$ after exchanging the N-benzyl protecting group with the more electron-poor benzyloxycarbonyl group. The transprotection was necessary to attain the more stable intermediate aldehyde 8/42. This aldehyde was then reduced with NaBH$_4$ to afford the alcohol 8/43 which was finally stripped from its remaining protecting groups to provide the desired iminosugar in 46% from olefin 8/39 (Scheme 8.16).[10]

As an alternative to the ozonolysis step in their DGDP synthesis from 2005 (Scheme 8.11), BEHR and co-workers also investigated the three step sequence syn-dihydroxylation, oxidative glycol cleavage and reduction to convert the vinyl double bond of 8/25 into the hydroxymethyl substituent. Although this procedure was more time consuming, a better yield (83%) of the DGDP precursor 8/27 could be obtained (Scheme 8.17).[6]
8.3.1 syn-Dihydroxylation

With these encouraging examples in mind we submitted our styryl pyrrolidine 8/1 to syn-dihydroxylation conditions as described by PALMER and JÄGER\[10\] as well as BEHR and co-workers\[6\]. Apprehensions that the phenyl substituent of the styryl double bond could slow down or even inhibit the reaction were unfounded; as in the example of BEHR et al. the reaction was finished after 24 hours providing the diastereomeric diols 8/46 \((d.r.~ 60 : 40)\) in 74\% combined yield. The repetition of the reaction with the solid potassium osmate salt instead of the volatile osmium(VIII) oxide as dihydroxylation agent gave the two syn-diols in the same diastereomeric ratio and a slightly better yield of 78\% (Scheme 8.18).

Scheme 8.18, syn-Dihydroxylation of the styryl pyrrolidine 8/1.
Reagents and conditions: (a) cat. OsO₄ (0.01\% solution in t-BuOH), NMO, acetone/H₂O (7 : 1), rt, 24 h, 74\% combined yield of 8/46a and 8/46b; (b) cat. K₂OsO₄ · 2 H₂O, NMO, acetone/H₂O (9 : 1), rt, 32 h, 78\% combined yield of 8/46a and 8/46b.

Although the separation of the two diastereomers was not necessary for the further course of the synthesis, small amounts of both diols were isolated by column chromatography to obtain pure analytical samples. Nevertheless, the absolute configurations of the respective
phenethyl side chains were not ascertained. Figures 8.7 and 8.8 shows the $^1$H NMR spectra of the two diastereomeric syn-diols.

**Figure 8.7.** $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the less polar diol 8/46.

(2S,3S,4S,5S)-$N$-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(1',2'-dihydroxyphenethyl)pyrrolidine.

**Figure 8.8.** $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the more polar diol 8/46.

(2S,3S,4S,5S)-$N$-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(1',2'-dihydroxyphenethyl)pyrrolidine.

Furthermore, the two regioisomeric $\alpha$-hydroxy ketones 8/47 and 8/48 were obtained as minor by-products from the reaction, each in about 5% yield. While ketone 8/47 proved to be a stable and storable compound, its regioisomer 8/48 exhibited the same unstable character as the aimed for pyrrolidine carbaldehyde 8/2. Indeed, the sample of this compound entirely decomposed during the overnight measurement of the $^{13}$C NMR spectrum so that only a $^1$H NMR spectrum could be obtained.
8.3.2 Attempted Oxidative Diol Cleavage with NaIO₄

In 1997 ZHONG and SHING introduced an improved facile glycol cleavage oxidation using silica gel-supported sodium metaperiodate as reagent.⁹¹ Advantages of this method are the typically short reaction times and the simple work-up procedure by filtering off the silica-bond reagent usually providing the respective aldehydes in excellent purity and yields. Applying SHING’s protocol to our diastereomeric diol mixture, 8/46 was dissolved in DCM and treated with freshly prepared silica gel-supported NaIO₄ at 0 ºC. The reaction, however, took longer than expected; full conversion was only reached after four hours and two further additions of extra periodate reagent. After filtration the crude product mixture was diluted with EtOH and reduced with NaBH₄. To our surprise we did not obtain the expected pyrrolidine alcohol 8/9; instead, the separation of the complex product mixture by column chromatography yielded the already known lactam 8/17 (Figure 8.4) in 11% yield followed by a mixture of the epimeric piperidinols 8/49 and 8/50 in 14% combined yield. A second chromatography of this mixture eventually provided pure samples of the two piperidinols in 4% and 3% yield, respectively (Scheme 8.19). Further products could not be isolated and identified.

![Scheme 8.19](image)

Scheme 8.19. Attempted oxidative diol cleavage with NaIO₄ and reduction with NaBH₄.
Reagents and conditions: (a) NaIO₄ on SiO₂, DCM, 0 ºC, 4 h; (b) NaBH₄, EtOH, 0 ºC, 90 min.

We suspect that the rather long reaction time caused the decomposition of the fragile intermediate carbaldehyde 8/2 prior to the treatment of the reaction mixture with NaBH₄. The obtained piperidinol epimers 8/49 and 8/50 are probably the result of a side reaction in
which the periodate group acted as a leaving group. Nucleophilic attack of the basic pyrrolidine nitrogen on the neighbouring as periodate ester activated OH-group in 8/51 led to the formation of the aziridinium ion intermediate 8/52 which after rearrangement afforded the ring-enlarged piperidine carbenium ion 8/53. This carbenium ion was then attacked by water from both faces resulting in the observed epimeric piperidine alcohols (Scheme 8.20).

Scheme 8.20. Proposed mechanism for the ring-expansion with NaIO₄.

The absolute configurations of the respective new stereocentre at C-5 for both obtained piperidines were determined via comparison of the coupling constants of the pseudoanomeric protons at C-6 for each epimer. For the L-DNJ derivative with an equatorial hydroxy group at C-5 (8/49) a Hₐₓ⁻5/Hₐₓ⁻6 coupling with a coupling constant at about 8 Hz according to the Karplus equation would be expected. For the L-DMJ derivative, on the other hand, with an axial hydroxy group at C-5 (8/50) a small coupling constant in the range of 0 – 2 Hz for the Hₐₓ⁻5/Hₐₓ⁻6 coupling would be characteristic.

The ¹H NMR spectrum of compound 8/49 (Figure 8.9) shows a doublet of doublets at 2.16 ppm for one of the pseudoanomeric protons at C-6 with the two coupling constants of 11.5 Hz (geminal coupling of Hₐₓ⁻6 with Hₐₓ⁻6) and 8.3 Hz, respectively. This compares well with the expected value of 8 Hz for the axial-axial coupling. This coupling constant also matched one of the four J values obtained for the dddd-signal of H-5 at 3.66 ppm (J₁ = 3.8 Hz → Hₐₓ⁻5/Hₐₓ⁻6 coupling, J₂ = 4.5 Hz → H-5/OH-5 coupling, J₃ = 7.4 Hz → Hₐₓ⁻4/Hₐₓ⁻5 coupling, J₄ = 8.2 Hz → Hₐₓ⁻5/Hₐₓ⁻6 coupling). This confirmed compound 8/49 to be the tetrabenzylated L-DNJ derivative.
The $^1$H NMR spectrum of compound 8/50 (Figure 8.10) on the other hand contains a doublet of doublets at 2.17 ppm with the two coupling constants of 12.4 Hz (geminal coupling of $H_{ax}$-6 with $H_{eq}$-6) and 1.1 Hz, respectively. This also corresponds well with the expected value for an equatorial-equatorial coupling according to the Karplus equation. Thus, compound 8/50 was confirmed to be the tetrabenzylated L-DMJ derivative.
8.3.3 Criegee Oxidation and Reduction

In a second effort to obtain pyrrolidine alcohol 8/9 via the oxidative scission and reduction of the diastereomeric syn-diols 8/46 the method of CRIEGEE\textsuperscript{[12]} was applied. Treatment of 8/46 with Pb(OAc)\(_4\) in DCM at 0 °C indeed afforded the desired alcohol 8/9, unfortunately again contaminated with its C-5 epimer 8/15 and the lactam 8/17 in the in Scheme 8.21 stated ratio. Attempts to separate the mixture by column chromatography were inefficient and aborted after the second unsuccessful run.

\[
\begin{align*}
\text{Scheme 8.21. Criegee oxidation/reduction sequence of the syn-diols 8/46.} \\
\text{Reagents and conditions: (i) Pb(OAc)\(_4\), K\(_2\)CO\(_3\), DCM, 0 °C, 1 h; (ii) NaBH}_4, \text{EtOH, 0 °C to rt, 1 h, 51% combined yield.}
\end{align*}
\]

8.4 The Trityl Detour

Since all attempts to obtain alcohol 8/9 from the styryl pyrrolidine 8/1 or its dihydroxy derivative 8/46 were either inefficient or failed entirely, the decision was made to abandon this synthesis route. A lot of time and material was lost during the fruitless search for an effective way to convert the styryl double bond of 8/1 into the desired hydroxymethyl substituent. However, given that the ozonolysis-reduction step of styryl pyrrolidin-4-ol 7/12 to the diol 7/23 proved to be reliable conversion with reproducible results we decided to give a detour via this diol a chance. This detour involved the temporary protection of the primary hydroxy group as a trityl ether (Scheme 8.22). Other bulky OH-protecting groups like TBS and TBDPS were initially also considered but dismissed due to the relative high costs of the respective silyl chlorides compared to the low price of trityl chloride. Furthermore, silyl protecting groups are prone to migrate to neighbouring hydroxy groups under basic conditions, a side reaction that is not known for the trityl group.
According to the new synthesis plan, the pyrrolidine diol 7/23 was monotritylated under standard conditions (TrCl, Et₃N, DMAP) at the primary OH group providing the trityl pyrrolidinol 8/54 (Figure 8.11) in 87% yield.

The trityl pyrrolidinol 8/54 was then O-benzylated again under standard conditions at the remaining free hydroxy group at C-4 to give the fully protected pyrrolidine 8/55 in 88% yield. In the final step the trityl group of this polyether pyrrolidine was cleaved off again using TFA finally providing the so long desired for pyrrolidine alcohol 8/9 (Figure 8.12) in 86% yield.
Figure 8.12. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the pyrrolidine alcohol 8/9, (2S,3S,4S,5S)-N-benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-(hydroxymethyl)pyrrolidine.

The obtained spectroscopic data for 8/9 were in good agreement with the data reported by DONDONI et al.$^3$ except the specific optical rotation which differed by almost 10º from our designated value ($\lbrack \alpha \rbrack _{D}^{20} = +28.5^\circ$; $\lbrack \alpha \rbrack _{D}^{20} = -19.3^\circ$ for ent-8/9 by DONDONI et al.). This difference can partly be explained by the differing temperatures during the two measurements.

8.5 Swern Oxidation

With pure alcohol 8/9 finally in hand, the desired carbaldehyde 8/2 was only one step away; alcohol 8/9 just needed to be oxidised to its aldehyde congener. As for the method to be applied for this conversion, we adopted the protocol of IKOTA and HANAKI who had reported oxidations of similar substrates as part of their synthesis of the indolizidine alkaloid (−)-swainsonine and its unnatural C-8 epimer.$^{[13]}$ Thus, the Swern oxidation of the pyrrolidine alcohol 8/9 ultimately provided the so hard and long worked for aldehyde 8/2 (Figure 8.13) in quantitative yield without notable epimerisation or decomposition during the process. As for 8/9 the obtained NMR spectroscopic data obtained for the aldehyde 8/2 compared well with the data reported for ent-8/2 by DONDONI and co-workers.$^3$ A specific optical rotation was not assessed due to the low stability of the compound in solution at room temperature.
Figure 8.13. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the crude pyrrolidine carbaldehyde 8/2. $(25,35,45,55$)-N-benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-formylypyrrolidine.

Aldehyde 8/2 had already proven to be a fragile and unstable compound which rapidly epimerises and decomposes when kept longer than 30 minutes at room temperature. Storage in a freezer at $-20 \, ^\circ\text{C}$ just decelerated the process but did not prevent or stop it. Indeed, during the attempt to obtain a $^{13}$C NMR spectrum of a concentrated sample of this compound within one hour at $25 \, ^\circ\text{C}$, heavy epimerisation and decomposition occurred. The measurement of an acceptable $^{13}$C NMR spectrum only succeeded at a measuring temperature of $-25 \, ^\circ\text{C}$ with just minor decomposition taking place. Therefore, for the further synthesis of the broussonetines, the aldehyde 8/2 was only prepared immediately before the next step and was directly employed in the following coupling reaction.

8.6 Summary

The synthesis of the pyrrolidine carbaldehyde 8/2 proved to be more demanding than initially expected. First attempts to obtain the desired aldehyde building block or its alcohol congener 8/9 from the direct precursor 8/1 via the oxidative double bond cleavage by ozone either completely failed or yielded unsatisfactory results. Only the ozonolysis-reduction of the pyrrolidinium bisulfate 8/31 afforded a small amount of pure pyrrolidine alcohol 8/9, unfortunately in no more than 15% yield. All other assessed literature-based methods either gave complex product mixtures or provided the alcohol 8/9 in an inseparable mixture with its C-5 epimer.
Attempts to attain the carbaldehyde 8/2 via the oxidative cleavage of the syn-diols 8/46 were also futile. Although the dihydroxylation of the styryl pyrrolidine 8/1 provided the diastereomeric syn-diols 8/46 in good yield, the following oxidative diol cleavage/reduction sequence failed due to the epimerisation and decomposition of the intermediate aldehyde under the applied reaction conditions and the occurrence of side reactions including the ring-expansion of the pyrrolidine moiety to piperidine alcohols.

The synthesis of the pyrrolidine carbaldehyde 8/2 eventually succeeded via a little detour from the pyrrolidine diol 7/23 (Scheme 8.23) which, in turn, was obtained in six steps from D-xylose as described in Chapter 7. Tritylation of the primary hydroxy group of 7/23 followed by 4-O-benzylation under standard conditions and detritylation provided the pyrrolidine alcohol 8/9 in 66% yield over three steps. This alcohol was finally oxidised by the method of SWERN\(^{[14]}\) without notable epimerisation and decomposition to afford the required carbaldehyde in 16.3% over ten steps from D-xylose.

![Scheme 8.23. Synthesis of pyrrolidine carbaldehyde 8/2.](image)

Reagents and conditions: (a) see Scheme 7.17, 24.5% over 6 steps; (b) TrCl, Et\(_3\)N, cat. DMAP, DCM, 25 °C, 20 h, 87%; (c) NaH, BnBr, TBAI, THF, 0 °C to 25 °C, 48 h, 88%; (d) TFA, DCM/MeOH (1:1), 0 °C to 25 °C, 3 h, 86%; (e) (COCl)\(_2\), DMSO, Et\(_3\)N, –78 °C to 0 °C, quant.; 16.3% over 10 steps from D-xylose.
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8.7 References


Chapter 9. (–)-10'-Deoxobroussonetines C and E – Two Model Studies

The purpose of these model studies was to synthesise simplified versions of the broussonetines C and E with the emphasis to test several key reactions as well as work-up and purification procedures that would be utilised later in the synthesis of the natural products. In particular, the Wittig and Grignard coupling reactions of the labile pyrrolidine carbaldehyde 8/2 with the respective side chain fragments were of interest.

In our first model study we planned to test the reaction conditions for the Wittig reaction of 8/2 as reported by DONDONI et al.\cite{1} and to determine the outcome of the reaction regarding its yield and (E)/(Z)-selectivity. Furthermore, it had to be clarified if the aldehyde 8/2 would be stable enough under the reaction conditions or if it would epimerise as observed in the ozonolysis resections of 8/1.

The main purpose of our second model study was to test the Grignard coupling reaction of aldehyde 8/2 with a simple and quickly obtainable side chain building block and to determine the stereochemical outcome of the reaction. It was planned to repeat the coupling reaction with various organometallic reagents and observe if the type of metalorganic compound employed would have an effect on the (R)/(S)-selectivity as reported by IKOTA et al.\cite{2}

Furthermore, the hydrogenolysis conditions for the removal of the benzyl protecting groups in the final step as well as work-up and various purification methods of the crude iminosugars had to be examined.

As model compounds the 10'-deoxoderivatives 9/1 and 9/2 of broussonetines C and E were chosen comprising the same C_{18} skeleton of the natural products but lacking the carbonyl functionality at C-10'. Without this carbonyl group the requisite side chain building blocks for both compounds were rapidly obtainable via three simple steps from commercially available starting materials granting fast access to the desired target compounds.

Model compound I: (–)-10'-Deoxobroussonetine C (9/1)
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Model compound II : (–)-10'-Deoxobroussonetine E (9/2)

9.1 Synthesis of (–)-10'-Deoxobroussonetine C as Model Compound I

9.1.1 3 × S₉₂ – Synthesis of the Model Side Chain

The required phosphonium iodide 9/5 as side chain building block for model compound I was synthesised in three simple steps from commercially available 12-bromo-1-dodecanol. Firstly, its hydroxy group was protected as a benzyl ether under standard conditions to give alkyl bromide 9/3. The reaction proceeded slowly but with quantitative yield after 2 days stirring at 50 °C. TBAI was omitted from the reaction so as to not promote a possible self-coupling of the starting material. The following Finkelstein reaction with NaI in acetone then provided the more reactive iodide 9/4 which was subsequently heated at reflux with PPh₃ in toluene for 20 hours to afford the desired Wittig salt, phosphonium iodide 9/5 in 96% yield over three steps (Scheme 9.1).

Scheme 9.1. Synthesis of the side chain for model compound I.
Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to 50 °C, 48 h, 100%; (b) NaI, acetone, 25 °C, 16 h, 100%; (c) PPh₃, toluene, reflux, 20 h, 96%, 95.7% over 3 steps.

9.1.2 Wittig Reaction

With both building blocks now in hand the time had come to test the next crucial step of the synthesis, the coupling of both components via a Wittig olefination reaction. Successful Wittig reactions of pyrrolidine carbaldehyde 8/2 had been described before by DONDONI et al.[1] (see Chapter 6, Scheme 6.4) wherefore their conditions were now chosen to perform
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the reaction. Thus, a solution of phosphonium iodide 9/5 in THF with HMPA as cation solvating co-solvent was cooled to −50 °C and then treated with a commercial 1.6 M n-BuLi solution. In the process it was discovered that at temperatures below −50 °C the reaction mixture became too viscous to be magnetically stirred; a precise temperature control was therefore essential. Upon adding the first drops of n-BuLi the mixture immediately turned intensively orange indicating the formation of the required ylide. After completed n-BuLi addition a solution of freshly prepared pyrrolidine carbaldehyde 8/2 was added dropwise to the ylide solution. The reaction was quenched with pH 7 phosphate buffer after 2 hours further stirring at −50 °C. The desired olefin was finally obtained after the usual aqueous work-up and column chromatography in 85% yield (Scheme 9.2).

Scheme 9.2. Wittig coupling of the pyrrolidine carbaldehyde 8/2 with the phosphonium iodide 9/5.
Reagents and conditions: (a) n-BuLi, THF, HMPA, −50 °C, then pyrrolidine carbaldehyde 8/2, 2 h, 85%.

Analysis by 1H and 13C NMR spectroscopy revealed the product to be predominantly the (Z)-configured olefin 9/6 containing only about 2% of the (E)-isomer (Figure 9.1). The (Z)-configuration of the double bond was confirmed by the coupling constant of the olefinic protons (1JH-6/H-7 = 10.7 Hz) and the chemical shift of the allylic CH2-group (C-8) in the 13C NMR spectrum (27.7 ppm calculated, 27.6 ppm observed versus 33.7 ppm calculated, 32.4 ppm observed for the (E)-isomer). The coupling constant for the olefinic protons of minor (E)-isomer could not be assessed due to signal overlapping.

Interestingly, a small amount of an unexpected by-product was also isolated which resulted from the dimerisation-like reaction of excess phosphonium iodide 9/5 with its ylide form. Olefin 9/7 was obtained in 19% yield based on the amount of phosphonium iodide 9/5 employed in the reaction. Its (Z)-configuration was deduced from the 13C NMR chemical shift of the allylic CH2-groups but not undoubtedly proven.
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9.1.3 Hydrogenolysis

The final step at the end of a natural product synthesis can often also be one of the most challenging. Although the execution of the reaction itself might be a simple task, in most of the cases, however, a nonpolar starting material is transformed into a polar, often exceedingly functionalised product for which a purification via column chromatography with the usual organic solvent mixtures does not apply. This is especially true in the case of polyhydroxylated alkaloid synthesis where the final step often involves the deprotection of the amino and hydroxy groups leading to a highly polar, typically water-soluble substance. To find an effective purification method which separates the product from the often also water-soluble impurities like inorganic salts hereby poses the biggest challenge. In the case of the broussonetines the constitution of these compounds with their hydrophilic head moiety and their lipophilic tail make matters even worse which is reflected in the already published syntheses of broussonetine congeners. The purification procedure hereby usually involves multiple techniques like column chromatography\textsuperscript{[3, 4]}, ion-exchange chromatography\textsuperscript{[3, 4]}, reverse-phase chromatography\textsuperscript{[5]} and/or recrystallisation\textsuperscript{[6]}. Therefore, in order to develop an efficient procedure for the isolation and purification of these iminosugars with their hydrophobic substituents, it was decided to first practise with a compound that was easier available in larger amounts than model compound I. (5S)-Phenethyl-L-AB1 (9/8) was the substance of choice, readily obtainable via the hydrogenation of the ozonolysis precursor 8/1.
Hence, styryl pyrrolidine 8/1 was hydrogenated under same conditions as described for L-DMDP and L-AB1 (see Chapter 7, Section 7.5). However, due to the low solubility of the starting material in acetic acid a mixture of ethyl acetate and methanol was used as solvent system. Concentrated hydrochloric acid was added to facilitate the benzyl cleavage (Scheme 9.3). In fact, when the acid was omitted in a first hydrogenation trial only benzyl cleavage at the primary hydroxy group at C-1 was observed after overnight stirring.

\[
\text{Scheme 9.3. Hydrogenolytic debenzylation of styryl pyrrolidine 8/1 with concomitant reduction of the double bond.}
\]

Reagents and conditions: (a) Pd-enriched Pearlman's catalyst, H\(_2\) (1 atm), 10 M HCl, EtOAc/MeOH (1 : 1), rt, 18 h, 81%.

On the other hand, the addition of the hydrochloric acid later also complicated the purification of the deprotected product. Due to neutralisation of the acid with concentrated ammonia solution the crude product became contaminated with ammonium chloride which had nearly identical solubility properties like the obtained iminosugar. A column chromatography over basified silica gel did not entirely remedy the problem since the parts of the NH\(_4\)Cl moved together with the pyrrolidine through the column bed. Although not visible in the recorded \(^1\)H NMR spectra (Figures 9.2 – 9.4), gravimetric analysis of the obtained white powder confirmed that the product still contained inorganic salts since the calculated yield was greater than 100%. Thus, to free the phenethyl pyrrolidine 9/8 from the NH\(_4\)Cl contamination the mixture was subjected to an ion-exchange chromatography on basic Dowex 1X8 100-200 exchange resin affording compound 9/8 as a brittle pale yellow solid. Separated from the NH\(_4\)Cl \(^1\)H NMR analysis of the obtained solid now showed a new organic impurity that probably originated from the Dowex resin. Nevertheless, the complete purification was finally achieved upon the discovery that the acetate salt of the pyrrolidine 9/8 had only low solubility in chloroform-methanol mixtures. Thus, recrystallisation of 9/8 as its acetate salt from MeOH/CHCl\(_3\) (15 : 85) ultimately afforded pure (5S)-phenethyl-L-AB1 acetate as a white amorphous powder in 81% yield.
NMR measurements of iminosugars are highly pH-dependable due to presence of the basic nitrogen of the amino group. Figures 9.2 and 9.3 show both the $^1$H NMR spectra of (5S)-phenethyl-1-AB1 (9/8) measured in deuterated methanol yet at different protonation states of the amino group. The signals of protons situated in proximity to the amino group of 9/8 in its acetate salt form are all downfield shifted (Figure 9.3) compared to the free base form of 9/8 (Figure 9.2). This downfield shift is a result of the decreased shielding due to the protonation of the amino group. The closer the proximity of the H-atom to the protonated amino group the stronger is the downfield shift of its $^1$H NMR signal.
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Figure 9.4. $^1$H NMR spectrum (500 MHz) of (–)-(5S)-phenethyl-L-AB1, (–)-(2S,3S,4S,5S)-2-hydroxymethyl-5-phenethylpyrrolidine-3,4-diol (9/8) in C$_5$D$_5$N.

The same conditions applied for the hydrogenolysis of compound 9/8 were subsequently also employed for the debenzylolation/double bond reduction of the Wittig product 9/6. The purification procedure, however, was slightly altered to circumvent the problems encountered with the separation of the ammonium chloride. After filtration of the hydrogenation catalyst all volatiles were evaporated including excess hydrochloric acid. The residual crude pyrrolidium chloride was then neutralised by ion-exchange chromatography on basic Dowex 1X8 100-200 ion-exchange resin, eluted first with H$_2$O/MeOH (1 : 1) and then pure MeOH. Further purification was achieved by repeated column chromatography (two runs) over basic silica gel. A concluding recrystallisation from MeOH/CHCl$_3$ (1 : 1) afforded (–)-10'-deoxobroussonetine C (9/1) as an off-white amorphous powder in 64% yield. The lower yield compared to (5S)-phenethyl-L-AB1 can be explained with the low solubility of 9/1 in methanol which caused some loss of material during the chromatographic purification processes.

Ironically, in order to obtain acceptable NMR spectra of 9/1, the compound had to be protonated again to improve the solubility in the used deuterated solvents. Figures 9.5 and 9.6 show the significant regions of the $^1$H NMR spectra of (–)-10'-deoxobroussonetine C (9/1) as its pyrrolidium chloride in pyridine-d$_5$ and its trifluoroacetate in methanol-d$_4$. We found that pyridine-d$_5$ was the solvent of choice since it provided a better resolved spectrum with fewer signals overlapping. It should be noted that the deuterated pyridine was not strong enough to deprotonate compound 9/1 again, the pyrrolidine remained protonated in the
solution. A full $^1$H NMR spectrum of model compound I in its deprotonated free base form in C$_5$D$_5$N is shown in the spectra annexe (Figure A2.52).

Figure 9.5. $^1$H NMR spectrum (500 MHz) of (–)-10'-deoxobroussonetine C hydrochloride, (–)-(2S,3S,4S,5S)-3,4-dihydroxy-2-hydroxymethyl-5-(13'-hydroxytridecyl)pyrrolidinium chloride in C$_5$D$_5$N.

Figure 9.6. $^1$H NMR spectrum (500 MHz) of (–)-10'-deoxobroussonetine C trifluoroacetate, (–)-(2S,3S,4S,5S)-3,4-dihydroxy-2-hydroxymethyl-5-(13'-hydroxytridecyl)pyrrolidinium trifluoroacetate in CD$_3$OD.

9.1.4 Summary

(–)-10'-Deoxobroussonetine C was synthesised as model study in 8.5% yield over a total of 15 steps from D-xylose and 12-bromo-1-dodecanol. A key step of the synthesis was the coupling of the two building blocks, the pyrrolidine carbaldehyde 8/2 and the phosphonium iodide 9/5, via Wittig olefination which provided the (Z)-configured olefin 9/6 in a good yield of 85%.
A concluding hydrogenolytic debenzylation with concomitant reduction of the double bond over Pd-enriched Pearlman’s catalyst\(^7\) in acidic medium afforded the desired pyrrolidine derivative in 64% yield (Scheme 9.4).

\[
\begin{align*}
\text{12-Bromo-1-dodecanol} & \quad \text{a, b, c} & \quad \text{BnO} \quad \text{OBn} \\
\text{9/5} & \quad \text{BnO} \quad \text{OBn} & \quad \text{Bn} \\
\text{d} & \quad \text{BnO} & \quad \text{Bn} \\
\text{9/6} & \quad \text{HO} \quad \text{OH} & \quad \text{HO} \quad \text{OH} \\
\end{align*}
\]

\text{(-)-10’-Deoxobroussonetine C}

Scheme 9.4. Synthesis of (-)-10’-deoxobroussonetine C.

Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to 50 °C, 48 h; (b) NaI, acetone, 25 °C, 16 h; (c) PPh\(_3\), toluene, reflux, 20 h, 96% over 3 steps; (d) \(n\)-BuLi, THF, HMPA, -50 °C, pyrrolidine carbaldehyde 8/2, 2 h, 85%; (e) Pd-enriched Pearlman’s catalyst, \(H_2\) (1 atm), 2 M HCl in MeOH/EtOAc (1 : 1), 25 °C, 18 h, 64%; 52.2% over 5 steps from 12-bromo-1-dodecanol, 8.9% over 12 steps from D-xylose, 8.5% over a total of 15 steps.

9.2 Syntheses of (-)-10’-Deoxobroussonetine E

9.2.1 Synthesis of the Side Chain Fragment for Model Compound II

Although the synthesis of the model side chain as described in Scheme 9.1 proved to be an reliable and high yielding way to obtain this building block in a short amount of time, the synthetic route had to be changed for model compound II due to delivery problems of 12-bromo-1-dodecanol by the supplier. Hence, inexpensive 1,12-dodecandiol was employed as starting material this time. In the first step the diol was monobenzylated with benzyl bromide over freshly precipitated silver(I) oxide according to a procedure by BOUZIDE and SAUVÉ.\(^8\)

The yield was only moderate (69% borsm) but an appropriately sized approach provided enough material to carry on with the synthesis. Exchange of the unprotected hydroxy group with bromide under Appel conditions (PPh\(_3\)/CBr\(_4\)) provided the required alkyl bromide 9/3 in 90.5% yield.
Treatment of this bromide with acid-washed magnesium turnings in dry THF at 50 °C afforded the requisite Grignard reagent \( \text{9/10} \) as building block for model compound II. Unfortunately, the selected reaction conditions also promoted a Wurtz-type coupling of unreacted alkyl bromide \( \text{9/3} \) with parts of the already formed organometallic reagent giving the dimer \( \text{9/11} \) in an unknown amount (Scheme 9.5). This compound was later separated from the crude Grignard products (see next paragraph) in 20% yield based on the amount of benzyl 12-bromododecanyl ether \( \text{9/3} \) employed in the reaction.

**Scheme 9.5.** Synthesis of the side chain for model compound II.

Reagents and conditions: (a) \( \text{Ag}_2\text{O}, \text{BnBr, EtOAc, rt, 24 h, 69% borsm; (b) PPh}_3, \text{CBr}_4, \text{THF/McCN, 0 °C to 25 °C, 18 h, 90.5%; (c) Mg, THF, rt to 50 °C, 3 h.} \)

**9.2.2 Grignard Reaction**

Inspired by the work of Ikota and Hanaki\(^2\) (see Chapter 6, Section 6.4) freshly prepared pyrrolidine carbaldehyde \( \text{8/2} \) was treated with the above prepared Grignard reagent \( \text{9/10} \) at low temperature (–78 °C). It was imagined that the basic nitrogen of the pyrrolidine ring in the \( \alpha \)-position to the carbonyl group would have a chelating effect that would preferentially afford only one of the two possible secondary alcohols. Regrettably, this selectivity was not observed. The ratio of the two secondary alcohols, determined by \( ^1\text{H NMR} \) spectroscopy, was just 3 : 2 in favour of the more polar epimer (Scheme 9.6). Then again, this outcome matched the result observed by Ikota and Hanaki\(^2\) in their Grignard reaction (see Chapter 6, Scheme 6.6).

The separation of both epimeric alcohols was difficult but succeeded via repeated column chromatography. After six runs both epimers were obtained in pure form in 39% and 26% yield, respectively, with the more polar epimer being the major product. \( ^1\text{H NMR} \) spectra of both alcohols are shown in Figures 9.7 and 9.8.
Scheme 9.6. Grignard coupling of pyrrolidine carbaldehyde 8/2 with 12-(benzyloxy)dodecylmagnesium bromide. Reagents and conditions: (a) THF, $-78 \, ^\circ\text{C}$ to rt, 18 h, d.r. 3 : 2, 66% combined yield, 39% 9/12, 26% 9/13 after 6 column chromatographic runs.

Figure 9.7. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the more polar Grignard product, the (6R)-alcohol 9/12.

Figure 9.8. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the less polar Grignard product, the (6S)-alcohol 9/13.
To determine the absolute configuration of the new stereocentre at C-6 for both epimers, small samples of both alcohols were converted into the respective (R)- and (S)-MTPA esters. The analysis according to a modified protocol of the Mosher method by KAKISAWA et al.\cite{9} is summarised in Figure 9.9. It identified the more polar major product as the (6R)-alcohol and the less polar minor product as the (6S)-epimer.

Figure 9.9. Summary of the ∆δ-values according to the Mosher protocol. The obtained data for the MTPA esters confirm the (6R)-configuration of the more polar epimer (top) and the (6S)-configuration of the less polar epimer (bottom). Protons annotated in red lay behind, protons annotated in blue lay in front of the MTPA plain. Annotations in black possess no analytic value.

### 9.2.3 Attempted Mitsunobu Inversion

Initially, it was planned to repeat the coupling reaction with various other organometallic side chain reagents like lithium organyls and lithium dialkylcuprates and compare the results of the reaction regarding the stereochemical outcome and yields. Nevertheless, due to time constraints towards the end of this project this plan was dismissed. Instead, we tried the improve the yield of the (6S)-alcohol 9/13 by converting the unwanted (6R)-alcohol 9/12 into its desired epimer via a Mitsunobu inversion. Adopting the conditions of PAHL and
MEYER,\cite{10} a solution of (6R)-alcohol 9/12 in its pyrrolidinium formate form was first treated with freshly prepared PPh$_3$-DEAD betaine-adduct followed by anhydrous formic acid in dry THF. However, the obtained product after work-up and repeated column chromatography (four runs) did not turn out to be the expected (6S)-formate 9/16; instead it could be identified as the piperidin-5-yl formate ester 9/17. According to the mechanism proposed in Scheme 9.10, it was assumed that the ring-enlargement reaction would have afforded the (5R)-configured piperidine as shown in Scheme 9.7, nevertheless, the absolute configuration of 9/17 was not confirmed until NOE experiments were performed on the fully deprotected final product 9/30 (see Section 9.2.4, Figure 9.17).

Furthermore, a small amount of the (6R)-formate ester 9/18 was also obtained which upon saponification with aqueous NaOH in EtOH/1,4-dioxane (1:1) could be reduced back to the (6R)-alcohol 9/12 again. The wanted (6S)-formate 9/16 was not observed.

![Scheme 9.7. Attempted Mitsunobu inversion of the (6R)-alcohol 9/12.](image)

Reagents and conditions: (a) 1. 1 M HCOOH in THF, rt, 2. PPh$_3$, DIAD, HCOOH, THF, 0 °C to 25 °C, 18 h, 73% 9/17, 22% 9/18; (b) NaOH, EtOH/1,4-dioxane/H$_2$O (1:1:1), 90 °C, 2.5 h, 94%.

The ring-enlargement of polyhydroxylated pyrrolidines to piperidines under Mitsunobu conditions is a known phenomenon that has already been reported by DONDONI et al. in 2004.\cite{11} The treatment of 2-thiazolyl pyrrolidine 9/19 with DIAD in the presence of PPh$_3$ and various oxygen nucleophiles always resulted in ring-expansion in moderate to good yields depending on the nucleophile employed (Scheme 9.8).
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Scheme 9.8. Ring-expansion of 2-thiazolyl pyrrolidine 9/19 under Mitsunobu conditions by DONDONI et al. (2004).[11]
Reagents and conditions: (a) PPh$_3$, R-OH, DIAD, THF, 80 °C, 2 h.

DONDONI and co-workers then made use of this transformation in a short synthesis of the not naturally occurring iminosugar 1-deoxy-L-allonojirimycin (9/23) (Scheme 9.9). After the ring-expansion of the 2-thiazolyl pyrrolidine 9/19 to the corresponding piperidine 9/21c using diphenylacetic acid as the oxygen nucleophile, the thiazole moiety was hydrolysed to the alcohol 9/22 as described in Chapter 6, Section 6.3. The subsequent saponification of the ester moiety and hydrogenolysis of the benzyl protecting groups provided the desired artificial iminosugar in 37% yield over 5 steps.[11]

Reagents and conditions: (a) PPh$_3$, Ph$_2$CHCOOH, DIAD, THF, 80 °C, 2 h, 74%; (b) 1. TfOMe, MeCN, MS 4Å, rt, 15 min; 2. NaBH$_4$, MeOH, 0 °C to rt, 10 min; 3. AgNO$_3$, MeCN/H$_2$O (10 : 1), 5 min, 82%, 95% purity; (c) NaBH$_4$, Et$_2$O/MeOH (5 : 2), 0 °C to rt, 5 min, 90%; (d) 0.1 M NaOMe in MeOH, rt, 2 h; (e) Pd(OH)$_2$/C, H$_2$ (1 atm), AcOH, rt, 5 h, 72% over 2 steps, 37.3% over 5 steps from 2-thiazolyl pyrrolidine 9/19.

Regarding the mechanism, DONDONI and co-workers suggested that the reaction proceeds via a condensed aziridinium ion intermediate 9/25 which undergoes nucleophilic attack by the oxygen nucleophile (in our case the formate anion) at the tertiary carbon atom C-5 to
give stereospecifically the ring-enlarged piperidine system (red arrows in Scheme 9.10). Nucleophilic attack of the formate anion at the tertiary carbon atom C-6, on the other hand, explains the formation of the as by-product obtained pyrrolidine (6R)-formate ester 9/18 with retention of the absolute configuration at C-6 (green arrows in Scheme 9.10).[11]

Scheme 9.10. Mechanism of the ring-expansion under Mitsunobu conditions with two S$_2$N$_2$-inversions affording stereospecifically the piperidin-5-yl formate 9/17.

The outcome of the reaction was surprising since it was expected that the protonation of the pyrrolidine nitrogen would have drastically reduced its nucleophilicity. As a consequence, the intramolecular nucleophilic attack on the activated hydroxy group at C-6 should have been inhibited. However, the protonation was apparently reversible with a sufficient amount of basic pyrrolidine present (probably in an equilibrium with its protonated form) to react as intramolecular nucleophile.

A plausible alternative mechanism for the ring-expansion is shown in Scheme 9.11. It suggests that the aziridinium ion 9/25 at first expands to the piperidine carbenium ion 9/26 which is subsequently attacked by the formate anion. In this case, however, the nucleophile could have approached the piperidine ring from either of the two ring faces which would consequently have produced the two epimeric piperidin-5-yl formate esters 9/17 and 9/27. Still, the (5S)-formate ester 9/27 was not observed wherefore this mechanism is most likely incorrect.
The piperidin-5-yl formate ester 9/17 was subsequently saponified under basic aqueous conditions to give piperidin-5-ol 9/28 in 92% yield (Scheme 9.13). It was intended to confirm the proposed relative and absolute configuration of the piperidine moiety via NOE experiments, however, due to the overlapping of many key signals in the $^1$H NMR spectrum (Figure 9.10) no definitive conclusion could be drawn. The configuration of the piperidine ring was eventually confirmed via NOE measurements on the fully deprotected compound 9/30 (see Section 9.2.4, Figure 9.17).
9.2.4 Hydrogenolysis

By using the optimised hydrogenolysis conditions, the (6S)-alcohol 9/13 was debenzylated to give crude (–)-10'-deoxobroussonetine E (9/2) as its hydrochloride salt. The purification procedure, however, was once again slightly altered to test the protocol reported by CARDA and co-workers[^3, 4] in their broussonetine syntheses. After filtration of the hydrogenation catalyst and evaporation of all volatiles, the residue was dissolved in a small amount of MeOH and treated dropwise with a 7 M methanolic NH₃ solution until basic pH was reached. The obtained deprotonated compound was then chromatographed over basic silica gel followed by an ion-exchange chromatography, this time on Dowex 50WX4-200 resin. The adsorbed material was eluted with 1 M aqueous NH₃ solution until complete recovery of the product. A concluding recrystallisation from MeOH/2 N HCl in Et₂O (1 : 1) afforded pure (–)-10'-deoxobroussonetine E (9/2) as its hydrochloride salt. This purification procedure proved to be the most effective not only regarding the achieved purity of the final product but also the accomplished excellent yield of 92%. Figures 9.11 – 9.13 show the ¹H NMR spectra of (–)-10'-deoxobroussonetine E hydrochloride recorded in methanol-d₄ and pyridine-d₅ as well as its free base form measured in methanol-d₄.

**Figure 9.11.** ¹H NMR spectrum (500 MHz) of (–)-10'-deoxobroussonetine E hydrochloride, (–)-(2S,3S,4S,5S)-5-((1'S)-1',13'-dihydroxytridecyl)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidinium chloride in C₅D₅N.

Signals of protons in the pyrrolidine moiety of the hydrochloride salt are downfield shifted when compared to the free base form due to the deshielding effect of the protonated amino group.

[^3]: CARDA et al., 2010
[^4]: CARDA et al., 2011
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Figure 9.12. $^1$H NMR spectrum (500 MHz) of (–)-10'-deoxobroussonetine E hydrochloride, (–)-(2S,3S,4S,5S)-5-((1'S)-1',13'-dihydroxytridecyl)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidinium chloride in CD$_3$OD.

Figure 9.13. $^1$H NMR spectrum (500 MHz) of (–)-10'-deoxobroussonetine E, (–)-(2S,3S,4S,5S)-5-((1'S)-1',13'-dihydroxytridecyl)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine (9/2) in CD$_3$OD.

The recovered (6R)-alcohol 9/12 from the failed Mitsunobu inversion was also submitted to a hydrogenolysis reaction affording a small amount of (–)-1'-epi-10'-deoxobroussonetine E (9/29) in 67% yield. The significant regions of the $^1$H NMR spectrum of 9/29 in methanol-d$_4$ are depicted in Figure 9.14. Intriguingly, the spectrum shows distinct differences to the one of its epimer 9/2 (Figure 9.13) although only one stereocentre is inverted.
Lastly, 5-hydroxy piperidine 9/28 was also debenzylated and purified employing the by now established reaction conditions and optimised purification protocol to afford (–)-(6S)-(12’-hydroxydodecyl)moranoline (9/30) in 87% yield. As in the case of (–)-10’-deoxobroussonetine C (9/1) the solubility of the moranoline derivative in methanol-d4 and pyridine-d5 was very low. In order to attain acceptable NMR spectra (Figures 9.15 and 9.16) samples of the compound had be converted to its trifluoroacetate salt to be sufficiently soluble in the employed deuterated solvents.

![Figure 9.14](image)

**Figure 9.14.** $^1$H NMR spectrum (500 MHz) of (–)-1’-epi-10’-deoxobroussonetine E, (–)-(2S,3S,4S,5S)-5-((1’R)-1’,13’-dihydroxytridecyl)-2-(hydroxymethyl)pyrrolidine-3,4-diol (9/29) in CD$_3$OD.

![Figure 9.15](image)

**Figure 9.15.** $^1$H NMR spectrum (500 MHz) of (–)-(6S)-(12’-hydroxydodecyl)moranoline trifluoroacetate, (–)-(2S,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(12’-hydroxydodecyl)-2-(hydroxymethyl)piperidinium trifluoroacetate in C$_5$D$_5$N.
To confirm the relative and consequently the absolute configuration of the piperidine moiety of the C-6 alkylated ent-moranoline derivative 9/30, 1D NOE measurements were performed on its trifluoroacetate salt in methanol-d4. The sample was especially useful due to its excellent resolution with (almost) every proton of the piperidine ring owing a distinct signal in the $^1$H NMR spectrum (Figure 9.16). These measurements are summarised in Figure 9.17 and confirm the proposed (2$\text{S}$,3$\text{S}$,4$\text{S}$,5$\text{R}$,6$\text{S}$)-configuration of the piperidine ring with the two hydroxy groups at C-4 and C-5 being anti to each other and the side chain substituent at C-6 and the OH-group at C-5 standing syn.

**Figure 9.16.** $^1$H NMR spectrum (500 MHz) of (–)-(6$\text{S}$)-(12$'$-hydroxydodecyl)moranoline trifluoroacetate, (–)-(2$\text{S}$,3$\text{S}$,4$\text{S}$,5$\text{R}$,6$\text{S}$)-3,4,5-trihydroxy-6-(12$'$-hydroxydodecyl)-2-(hydroxymethyl)piperidinium trifluoroacetate in CD$_3$OD.

**Figure 9.17.** Detected NOE’s on the C-6 alkylated ent-moranoline derivative 9/30. NOE’s highlighted with red arrows are of significant analytical value and confirm the (2$\text{S}$,3$\text{S}$,4$\text{S}$,5$\text{R}$,6$\text{S}$)-configuration of the piperidine ring. NOE’s depicted with dashed arrows were only weak.
9.2.5 Summary

(−)-10'-Deoxobroussonetine E was synthesised as model study in 2.4% yield over a total of 15 steps from D-xylose and 1,12-dodecanediol. A key step of the synthesis was the coupling of the two building blocks, the pyrrolidine carbaldehyde 8/2 and benzylxoydodecylmagnesium bromide (9/10), via a Grignard reaction which provided the two epimeric alcohols 9/12 and 9/13 in 39% and 26% yield, respectively. The absolute configuration of both alcohols was assigned by applying Mosher’s protocol to samples of the respective (R)- and (S)-MTPA ester derivatives of 9/14 and 9/15. The desired (6S)-alcohol 9/13 was eventually debenzylated under hydrogenolytic conditions over Pd-enriched Pearlman’s catalyst\textsuperscript{[7]} in acidic medium affording the wanted L-DMDP derivative 9/2 in 92% yield (Scheme 9.12).

\[ \text{Scheme 9.12. Synthesis of (–)-10'-deoxobroussonetine E.} \]

Reagents and conditions: (a) Ag$_2$O, BnBr, EtOAc, rt, 24 h, 69 % borsm; (b) PPh$_3$, CBr$_4$, THF/MeCN, 0 °C to 25 °C, 18 h, 90.5%; (c) Mg, THF, rt to 50 °C, 3 h; (d) pyrrolidine carbaldehyde 8/2, THF, −78 °C to rt, 18 h, d.r. 3 : 2, 66% combined yield, 39% 9/12, 26% 9/13; (e) Pd-enriched Pearlman’s catalyst, H$_2$ (1 atm), 10 M HCl, MeOH/EtOAc (1 : 1), 25 °C, 18 h, 92%; 14.9% over 5 steps from 1,12-dodecanediol, 3.9% over 12 steps from D-xylose, 2.4% over a total of 15 steps.

The attempt to invert the configuration at C-6 of alcohol 9/12 to attain more of the desired (6S)-epimer 9/13 under Mitsunobu conditions resulted unexpectedly in ring-expansion of the pyrrolidine moiety. Saponification of the intermediate formate ester 9/17 afforded the 5-hydroxy piperidine 9/28 in 67.5% yield over two steps. The hydrogenolysis of the benzyl protecting groups over Pd-enriched Pearlman’s catalyst\textsuperscript{[7]} in acidic medium subsequently
provided the (6S)-alkylated Moranoline derivative 9/30 in 2.4% yield over a total of 17 steps from D-xylose and 1,2-dodecanediol (Scheme 9.13). The relative and the absolute configuration of the piperidine moiety were eventually confirmed by NOE measurements performed on a sample of the piperidinium trifluoroacetate salt in methanol-d4.

Reagents and conditions: (a) 1. 1 M HCOOH in THF, rt, 2. PPh3, DIAD, HCOOH, THF, 0 °C to 25 °C, 18 h, 73%; (b) NaOH, EtOH/1,4-dioxane/H2O (1 : 1 : 1), 90 °C, 2.5 h, 92%; (c) Pd-enriched Pearlman’s catalyst, H2 (1 atm), 10 M HCl, MeOH/EtOAc (1 : 1) 25 °C, 18 h, 89%; 14.5% over 7 steps from 1,12-dodecanediol, 3.8% over 14 steps from D-xylose, 2.4% over a total of 17 steps.
9.3 References


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Chapter 10. Attempted Synthesis of (−)-Broussonetine C

The successful synthesis of (−)-10'-deoxobroussonetine C (9/1) had demonstrated that the DONDONI approach with the Wittig reaction as key coupling step is an efficient way for the convergent synthesis of 1'-deoxybroussonetines like broussonetine C. The aldehyde 8/2 proved to be sufficiently stable to be combined with the side chain phosphonium iodide 9/5 under the applied conditions to complete the C_{18} skeleton of the target molecule without notable epimerisation or decomposition. The consequent next step in this project would therefore have been to replicate the synthesis with L-xylose to obtain the natural enantiomer of DMDP as well as the pyrrolidine carbaldehyde 6.1 with the accurate absolute configuration as synthon for (+)-broussonetines C and combine it with a side chain fragment bearing the requisite carbonyl group at C-10' in a masked form (see Chapter 6, Section 6.6).

However, due to time constraints at the end of this project it was not possible to repeat the synthesis with L-xylose as planned. Instead, it was decided to prepare the unnatural enantiomer of broussonetine C since we still had ample amounts of the pyrrolidine carbaldehyde 8/2 in form of its alcohol precursor 8/9 at hand. Yet, this was not considered to be a drawback in light of the fact that these unnatural iminosugar enantiomers and derivatives often possess more potent and specific glycosidase inhibitory activity than their natural counterparts (see Chapter 6, Sections 6.10 and 6.11).[1−5]

10.1 Synthesis of the Side Chain Fragment

10.1.1 Choosing a Synthesis from Several Options

In contrast to the synthesis of the pyrrolidine building block 8/2 for which we had a specific concept in mind with the Petasis reaction as key step, we had no presettings or limitations for the assembly of the side chain synthon except the availability of the starting materials. Principally, the C_{12} carbon skeleton of 10/7 with its carbonyl group at C-4 could be constructed via three different ways:

- combination of a C_{10} with a C_{2} segment,
- combination of a C_{9} with a C_{3} segment, or
- combination of a C_{8} with a C_{4} segment.
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With these basic concepts in mind a thorough search for commercially available starting materials was conducted. The results of this search are listed below.*

- **C$_{10}$ + C$_2$**
  - 1,2-Epoxy-9-decene
    - $1.18$ per mmol
  - Benzyl 2-bromoethylether
    - $7.61$ per mmol

- **C$_9$ + C$_3$**
  - 1,9-Nonanediol
    - $0.49$ per mmol
  - 3-Benzyloxy-1-propanol
    - $2.19$ per mmol
  - 9-Decen-1-ol
    - $1.46$ per mmol
  - Benzyl 3-bromopropylether
    - $6.87$ per mmol
  - 9-Decenoic acid
    - $1.56$ per mmol
  - 8-Nonen-1-ol
    - $2.28$ per mmol
  - 8-Nonenoic acid
    - $28.28$ per mmol

- **C$_8$ + C$_4$**
  - 1,8-Octanediol
    - $0.27$ per mmol
  - γ-Butyrolactone
    - $0.10$ per mmol
  - 8-Bromo-1-octene
    - $10.44$ per mmol
  - 4-Benzylxy-1-butanol
    - $2.14$ per mmol
  - 8-Bromo-1-octanol
    - $12.46$ per mmol
  - 4-Benzylxybutyric acid
    - $3.00$ per mmol

* The quoted prices refer to the School of Chemistry’s preferred chemicals supplier, SIGMA-ADHRICH Australia, as listed online on 01/06/2012. The list price in AUD per gram for each compound was translated to its value in AUD per mmol for comparison reasons.
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Scheme 10.1. Pathways to the phosphonium iodide 10/7 as side chain building block for broussonetine C.

(a) aminolysis; (b) O-benzylolation; (c) Weinreb amidation; (d) magnesium insertion; (e) Grignard addition; (f) Dess-Martin or TPAP oxidation; (g) ketal formation; (h) hydroboration-oxidation; (i) Garegg reaction; (j) Wittig salt formation; (k) ketal formation with concomitant O-TBS cleavage; (l) ozonolysis; (m) O-TBS protection; (n) Swern oxidation.
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Based on the available compounds a number of possible synthesis paths leading to the phosphonium iodide 10/7 were developed and summarised in Scheme 10.1. The selection criteria in favour of one synthesis route beside the price of the starting material included the number of steps, the ability to scale-up, the complexity of the reactions and the expected overall yield.

After careful consideration of all factors, the synthesis starting from cheap 9-decen-1-ol was chosen as depicted in Scheme 10.2. Although this path was not the shortest of all presented in Scheme 10.1, the easy execution with anticipated high yields for every transformation as well as the ability to scale-up were pivotal for our decision.

As shown in Scheme 10.2, 9-decen-1-ol would be O-TBS protected in the first step followed by the oxidative cleavage of the double bond to afford the aldehyde 10/2. This aldehyde would then be treated with freshly prepared benzyloxypropylmagnesium bromide to install the terminal C₃ unit of the side chain. Oxidation of the secondary alcohol 10/3 would subsequently yield the requisite carbonyl group at C-4. Protection of this ketone as 1,3-dioxolane ketal under acidic conditions would expectantly occur with concomitant cleavage of the TBS protecting group and provide the hydroxy ketal 10/5 in one step. Substitution of the hydroxy group with iodine under Garegg conditions was intended to give iodide 10/6 which...
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upon treatment with triphenylphosphane would eventually provide the desired phosphonium iodide 10/7 as side chain building block of broussonetine C in seven steps.

10.1.2 Preparation of 1-Benzylloxy-12-(tert-butyldimethylsilyloxy)dodecan-4-ol (10/3)

The synthesis of the side chain synthon commenced with the O-TBS protection of 9-decen-1-ol. This was achieved by treating a solution of the alcohol in DCM with TBS chloride in the presence of triethylamine and a catalytic amount of DMAP. After three hours the TBS ether was obtained in an excellent yield of 97%. For the following oxidative double bond cleavage of olefin 10/1 to attain the aldehyde 10/2 two methods were explored. In a first attempt the olefin 10/1 was dihydroxylated with a catalytic amount of osmium tetroxide in the presence of stoichiometric NMO to afford the diol 10/8 in near quantitative yield. The crude diol was then treated with sodium periodate in a heterogenic water/ether mixture to yield the desired aldehyde 10/2 in 89.5% over two steps. In a second approach the olefin 10/1 was submitted to an ozonolysis reaction which upon work-up with PPh₃ provided aldehyde 10/2 in a better yield of 96% in one step. The C₁₂ skeleton of 10/7 was eventually completed by treating the aldehyde 10/2 with benzyloxypropylmagnesium bromide which, in turn, was freshly prepared from commercially available 1-benzyloxy-3-bromopropane prior to the reaction. Thus, the secondary alcohol 10/3 was obtained in 83% yield (Scheme 10.3).

Scheme 10.3. Preparation of 1-benzyloxy-12-(tert-butyldimethylsilyloxy)dodecan-4-ol (10/3).

Reagents and conditions: (a) TBSCI, Et₃N, DMAP, DCM, 0 °C to 25 °C, 3 h, 97%; (b) OsO₄, NMO, acetone/H₂O (1 : 1), 25 °C, 5 h; (c) NaIO₄, Et₃O/H₂O (1 : 1), 25 °C, 5 h, 89.5% over 2 steps; (d) 1. O₃, DCM, –78 °C, 2. N₂, PPh₃, –78 °C to 0 °C, 3 h, 96%; (e) benzyloxypropylmagnesium bromide, THF, 0 °C to rt, 2 h, 83%.
10.1.3 Oxidation of Alcohol 10/3 to Ketone 10/4

According to our synthesis scheme, it was planned to oxidise the secondary alcohol 10/3 to the ketone 10/4 employing Dess-Martin periodinane\textsuperscript{[7]}. Thus, a first small-scale test approach (1 mmol) was performed which afforded the desired ketone in an excellent yield of 94%. Nevertheless, since commercial Dess-Martin periodinane is a rather expensive reagent (at that time supplier SIGMA-ALDRICH offered 25 g D.-M.-P. for $528.00), it was decided to explore cheaper alternative oxidation methods that would provide the ketone in an equally high yield. The reaction conditions and results of these experiments are summarised in Scheme 10.4 and Table 10.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dess-Martin oxidation</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>Corey-Kim oxidation</td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td>PCC oxidation</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td>PDC oxidation</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>TPAP oxidation</td>
<td>86%</td>
</tr>
<tr>
<td>6</td>
<td>Swern oxidation</td>
<td>85%</td>
</tr>
<tr>
<td>7</td>
<td>Mukaiyama oxidation</td>
<td>96%</td>
</tr>
</tbody>
</table>

All experiments were performed on a 1 mmol scale.

Two key findings should be noted. Firstly, all tested oxidation methods afforded the ketone 10/4 in good to excellent yields. Secondly, the oxidation under Mukaiyama conditions\textsuperscript{[13]} with N-chlorosuccinimide and a catalytic amount of N-\textit{tert}-butylbenzenesulfonylamide yielded the
best result with 96%, topping even the yield of the Dess-Martin oxidation. However, since
the preparation of the commercially not available N-tert-butylbenzenesulfenamide was
considered to be a comparably harder and more time-consuming process than the synthesis
of Dess-Martin reagent, we decided to stick to the original synthesis plan and prepared the
required amount of periodinane from cheap ortho-iodobenzoic acid by ourselves. Hence, the
second scaled-up Dess-Martin oxidation (33.3 mmol) of alcohol 10/3 with self-made periodinane
afforded the ketone 10/4 in the same high yield of 94%.

10.1.4 Conversion of Ketone 10/4 to Ketal 10/5

The next step in our synthesis scheme was the protection of the carbonyl group in 10/4 as a
1,3-dioxolane ketal. It was anticipated that under the usually employed acidic reaction
conditions, the TBS protecting group would simultaneously be cleaved off so that we would
obtain the primary alcohol 10/5 in one step. Thus, following the classic procedure by
STERZYCKI[14], a mixture of ketone 10/4, ethylene glycol and a catalytic amount of PPTS in
benzene was heated at reflux with water separation by a Dean-Stark trap for 18 hours. To our
surprise we obtained two products that were readily separable by column chromatography.
The more polar one was the desired hydroxy ketal 10/5, the second less polar one could be
identified as the silyloxy ketal 10/9. Assuming that the applied acid was not strong enough
to entirely cleave the TBS ether, the experiment was repeated, this time with PTSA as
catalyst. However, the outcome of the reaction was virtually identical; the TBS ether ketal
10/9 and the hydroxy ketal 10/5 were again obtained in an almost 1 : 2 ratio. Hence, in a
third and final effort, the conversion was performed with an excess amount of PTSA and a
prolonged reaction time, only to yield nearly the same result again (Scheme 10.5).

Scheme 10.5, Conversion of ketone 10/4 to ketal 10/5 - path A.
Reagents and conditions: (a) HO(CH₂)₂OH, cat. PPTS, benzene, reflux, 18 h, 36% 10/9, 62% 10/5; (b) HO(CH₂)₂OH,
cat. PTSA, benzene, reflux, 18 h, 30% 10/9, 60% 10/5; (c) HO(CH₂)₂OH, exc. PTSA, benzene, reflux, 36 h, 29%
10/9, 58% 10/5; (d) TBAF, THF, 25 °C, 2.5 h, 94%.
Chapter 10. Attempted Synthesis of (−)-Broussonetine C

Although it was possible to finalise the TBS cleavage with TBAF in a second step, we decided to change the synthesis route and prepare alcohol 10/5 via a two-step procedure. In a first step the TBS protecting group was cleaved off with TBAF providing the hydroxy ketone 10/10 in 95% yield. In the second step the carbonyl group of 10/10 was converted into the ketal 10/5 as above described with ethylene glycol and PPTS under water separation affording the 1,3-dioxolane in 96% yield (Scheme 10.6).

Scheme 10.6. Conversion of ketone 10/4 to ketal 10/5 - path B.
Reagents and conditions: (a) TBAF, THF, 25 ºC, 2.5 h, 95%; (b) HO(CH₂)₂OH, PPTS, benzene, reflux, 18 h, 96%.

In a curiosity driven side experiment it was tested if the ketone 10/4 could also be transformed into the dibenzylketal 10/11 via its conversion with benzylalcohol. Although there was no precedent in the literature for such a reaction, a solution of ketone 10/4 in benzene was heated at reflux with an excess amount of benzylalcohol and PTSA under water separation for 18 hours. The result of this experiment is shown in Scheme 10.7.

Scheme 10.7. O-TBS to O-Bn transprotection under acidic conditions.
Reagents and conditions: (a) BnOH, PTSA, benzene, reflux, 18 h, 64.5% 10/12, 21% 10/10.

Instead of obtaining the wanted dibenzylketal 10/11, two other products were isolated from the reaction mixture; the more polar minor product was the TBS deprotected alcohol 10/10. The second less polar major product could be identified as the bisbenzylated ketone 10/12. Although numerous procedures for the benzyl protection of hydroxy groups have been described in the literature, the PTSA-catalysed benzylation with benzylalcohol has not been reported to date. We assume that the benzyl ether 10/12 results from the reaction of
10/10 with a benzyl cation formed in situ via the protonation and following water loss of the benzylalcohol as shown in Scheme 10.8.

![Scheme 10.8. Mechanism of the acid-catalysed benzyl protection of hydroxy ketone 10/10 with benzylalcohol.](image)

10.1.5 Conversion of Alcohol 10/5 to Phosphonium Iodide 10/7

To conclude the synthesis of phosphonium iodide 10/7 as side chain building block, the alcohol 10/5 had first to be converted into the alkyl iodide 10/6. Thus, in a first test approach 10/5 was treated with iodine in the presence of triphenylphosphane and imidazole (Garegg conditions\(^6\)) to prepare the iodide 10/6 in one step. However, to our surprise we did not only obtain the desired ketal iodide 10/6 but also its ketone analogue 10/13 in an inseparable 2 : 1 mixture. Perplexed by this result, we started a second attempt this time trying to convert the alcohol 10/5 into the alkyl bromide 10/14 under Appel conditions\(^{15}\). The outcome, however, was almost the same; the ketal bromide 10/14 was obtained together with its ketone analogue 10/15 again in an inseparable mixture in this case in an almost 1 : 1 ratio (Scheme 10.9).

![Scheme 10.9. Attempted hydroxy-halogen substitution under Garegg and Appel conditions.](image)

Reagents and conditions: (a) PPh\(_3\), I\(_2\), imidazole, DCM, 0 °C to 25 °C, o/n, 93% combined yield;
(b) PPh\(_3\), CBr\(_4\), THF/MeCN (3 : 1), 0 °C to 25 °C, o/n, 68% combined yield.
Slowly but surely the uneasy feeling increased that the PPh$_3$ reagent might be involved in the experienced ketal cleavage. A literature search was performed to investigate if the observed ketal deprotection under Appel conditions$^{[15]}$ had been reported before. And indeed, in 1996 KERR and co-workers described the cleavage of ketals and acetals under neutral, anhydrous conditions using triphenylphosphane and carbon tetrabromide.$^{[16]}$ The proposed mechanism for the deprotection reaction involves the coordination of the electrophilic phosphonium adduct of CBr$_4$ and PPh$_3$ to one oxygen of the dioxolane group. Subsequent successive displacement by two equivalents of bromide ion liberates the respective carbonyl compound in addition to the observed by-products, triphenylphosphane oxide and 1,2-di-bromoethane. The ketal cleavage under Garegg conditions$^{[6]}$ had no literature precedent, nevertheless, the transformation should proceed similar to the mechanism depicted in Scheme 10.10.

To circumvent the encountered problems we decided to convert the alcohol 10/5 into iodide 10/6 via its mesylate derivative 10/16 in two steps. The substitution of the mesylate with iodide under Finkelstein conditions$^{[17]}$ eventually provided the desired alkyl iodide 10/6 in 97% yield over two steps. To finally obtain phosphonium iodide 10/7 a solution of alkyl iodide 10/6 in toluene was heated at reflux with a slight excess of PPh$_3$ for 42 hours. As in the above described cases ketal cleavage also occurred under these conditions, gratifyingly however only as a minor side reaction providing the two Wittig salts 10/7 and 10/17 as an inseparable mixture in 99% combined yield (Scheme 10.11). This mixture was used in the following Wittig reaction.
Chapter 10. Attempted Synthesis of (−)-Broussonetine C

Scheme 10.11. Conversion of alcohol 10/5 to phosphonium iodide 10/7.

Reagents and conditions: (a) MsCl, Et$_3$N, DCM, 0 °C to 25 °C, 18 h, 100%; (b) NaI, MeCN, 50 °C, 2 h, 97%; (c) PPh$_3$, toluene, reflux, 42 h, 92% 10/7.

Figure 10.1 shows the significant excerpts of the $^1$H NMR spectrum of 10/7. Interestingly, although the 1,3-dioxolane moiety at C-4 is unsymmetrically substituted, its CH$_2$-groups form a sharp singlet at 3.9 ppm rather than the expected multiplet signals for each proton.

Figure 10.1. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the Wittig salt 10/7,
(1-benzyloxy-4-(1',2'-ethanediyo)dodecan-12-yl)triphenylphosphonium iodide.

10.2 Wittig Reaction and Ketal Hydrolysis

With phosphonium iodide 10/7 finally in hand the time had come to combine both building blocks and complete the C$_{18}$ core structure of our target compound. For the Wittig coupling the same conditions were chosen that were successfully employed in the synthesis of model compound I. Thus, a solution of the side chain phosphonium iodide in THF with HMPA as co-solvent was cooled to −50 °C and then treated with a commercial 1.6 M $n$-BuLi solution to
form the intensive orange ylide intermediate. Upon completed \( n \)-BuLi addition a solution of freshly prepared pyrrolidine carbaldehyde 8/2 was added dropwise. After 2 hours further stirring at \(-50^\circ C\) the reaction was quenched with pH 7 phosphate buffer. Purification of the crude product by column chromatography yielded the desired olefin in 85% (Scheme 10.12). As in the case of model compound I a small quantity of the dimerised phosphonium salt was obtained as by-product of the Wittig reaction. Olefin 10/19 was obtained in 18% yield based on the amount of phosphonium iodide 10/7 employed in the reaction. Its (\(Z\))-configuration was deduced from the \(^{13}\)C NMR chemical shift of the allylic CH\(_2\)-group (27.2 ppm observed in contrast to 33.7 ppm calculated for the (\(E\))-configured olefin) but not undoubtedly proven.

Scheme 10.12. Wittig coupling of pyrrolidine carbaldehyde 8/2 with phosphonium iodide 10/7.
Reagents and conditions: (a) \( n \)-BuLi, THF, HMPA, \(-50^\circ C\), then pyrrolidine carbaldehyde 8/2, 2 h, 85%.

Figure 10.2. \(^{1}\)H NMR spectrum (500 MHz, CDCl\(_3\)) of the Wittig product 10/18, (+)-(2\(^S\),3\(^S\),4\(^S\),5\(^S\))-\(N\)-benzyl-3,4-bis(benzyloxy)-5-\((1^{1}Z\)-13\(^{1}\)-benzyloxy-10\(^{1}\)-1\(^2\)-ethanediroy)-tridec-1\(^1\)-enyl)-2-(benzyloxymethyl)pyrrolidine.
The $^1$H and $^{13}$C NMR spectroscopic analyses disclosed the product to be the predominantly (Z)-configurated olefin containing about 2% of the (E)-isomer. The significant regions of its $^1$H NMR spectrum are shown in Figure 10.2.

With the C$_{18}$ skeleton of broussonetine C now complete, we started the deprotection of the functional groups. In a first step the 1,3-dioxolane was hydrolysed back to its ketone predecessor (Scheme 10.13). Treatment of Wittig product 10/18 with 1 M H$_2$SO$_4$ in 1,4-dioxane at 50 °C for 24 hours afforded the broussonetine C precursor 10/20 in 96% yield.

![Scheme 10.13. Ketal hydrolysis of the Wittig product 10/20.](image)

Reagents and conditions: (a) 1 M H$_2$SO$_4$, 1,4-dioxane, 50 °C, 24 h, 96%.

Since the starting material and the product displayed the same $R_f$ value in the TLC analysis, the progress of the reaction was monitored by $^1$H NMR spectroscopy via the disappearance of the ketal singlet at 3.9 ppm (Figure 10.2) and the simultaneous appearance of the two characteristic triplets at 2.35 and 2.49 ppm representing the CH$_2$-groups next to the liberated carbonyl group (Figure 10.3).

![Figure 10.3. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the (–)-broussonetine C precursor 10/20.](image)

(–)-(2S,3S,4S,5S)-N-benzyl-3,4-bis(benzyloxy)-5-((1'Z)-13'-benzyloxy-10'-oxotridec-1'-enyl)-2-(benzyloxymethyl)pyrrolidine.
10.3 Hydrogenolysis

In the final step all benzyl protecting groups had to be cleaved off with concomitant saturation of the double bond. This was deemed to be an easy task especially after the process optimisation achieved with the synthesis of the model compounds I and II. Thus, the (–)-broussonetine C precursor 10/20 was dissolved in a MeOH/EtOAc/conc. HCl mixture and submitted to the hydrogenolysis reaction employing the usual Pd black/Pd(OH)$_2$/C mixture as hydrogenation catalyst. However, to our surprise the reaction control via ESI-MS after overnight stirring under an atmosphere of H$_2$ did not only show the expected M+H$^+$-peak of the wanted product (346 Da) but also multiple other signals in the range between 300 and 400 Da with a signal at 330 Da presenting the base peak. Puzzled by this result, the reaction mixture was filtered from the Pd-catalyst and concentrated _in vacuo_. The subsequent $^1$H NMR spectroscopic analysis of the obtained crude material revealed it to be a mixture of at least four compounds: one major product and smaller amounts of other substances with the desired (–)-broussonetine C (identified by the signals of the CH$_2$-groups flanking the side chain carbonyl group) being only a minor component. A first separation from less polar impurities was achieved by column chromatography over basic silica gel (elution with a CHCl$_3$/MeOH/NH$_3$ (7 N in MeOH) gradient) providing the polar components including the main product as a pale yellow foamy solid. An attempt to further purify the major product by recrystallisation from MeOH/CHCl$_3$ mixtures failed. It was therefore decided to separate all compounds by preparative high performance liquid chromatography. Although this proved to be a hard and tedious process, we succeeded in the end to isolate the main product as a white amorphous powder in 41.5% yield. Nevertheless, we did not manage to get hold of the target product, (–)-broussonetine C (10/21). The NMR data of all other isolated compounds and compound mixtures did not match the set reported for the natural product.

In the aftermath we focused on elucidating the structure of the obtained main product. Judging from the obtained $^1$H and $^{13}$C NMR spectra of the compound recorded in different solvents and at two different pH values (Figures 10.4 – 10.6) the pyrrolidine moiety appeared to be intact and unaltered, the side chain terminus, however, seemed to have been transformed into a new substructure. The absence of the two distinctive triplets at 2.44 and 2.71 ppm for the CH$_2$-groups flanking the carbonyl function in the $^1$H NMR spectrum, the lack of the typical downfield carbonyl signal at 210.8 ppm in the $^{13}$C NMR spectrum as well as
the non-existence of the characteristic C=O band in the IR spectrum all confirmed the loss of the carbonyl group at C-15. Furthermore, the splitting pattern of the terminal CH$_2$-group as two distinct quartets, one for each proton at 3.67 and 3.84 ppm (Figure 10.4), indicated the formation of a new stereocentre close to the original side chain end.

![Figure 10.4](image.png)

**Figure 10.4.** $^1$H NMR spectrum (500 MHz) of (–)-broussonetine C$_2$, (–)-(25,35,45,55)-2-(hydroxymethyl)-5-(9’-(tetrahydrofuran-2’-yl)nonyl)pyrrolidine-3,4-diol (10/23) in C$_5$D$_5$N.

Taking all these findings into account we concluded that the terminal γ-hydroxy ketone moiety of the side chain must have cyclised in a first step to the hemiacetal 10/22 which was subsequently reduced to the tetrahydrofuran derivative 10/23 under the applied conditions.

![Scheme 10.14](image.png)

**Scheme 10.14.** Hydrogenolysis of the pentabenzyalted pyrrolidine 10/20.

Reagents and conditions: (a) Pd-enriched Pearlman’s catalyst, H$_2$ (1 atm), 10 M HCl, MeOH/EtOAc (1 : 1), 25 ºC, 18 h, 41.5%;
Chapter 10. Attempted Synthesis of (–)-Broussonetine C

The intermediate hemiacetal form (10/22) and the finally obtained novel tetrahydrofuranyl derivative (10/23) were given the names broussonetine C1 and broussonetine C2, respectively. The digits hereby indicate the number of further transformations that occurred to the mother compound broussonetine C (10/21).

The proposed structure for (–)-broussonetine C2 was eventually confirmed by 2D NMR experiments and the comparison of published $^{13}$C NMR data of 2-substituted THF derivatives with our own recorded data for 10/23 (Table 10.2).$^{[18,19]}$

Table 10.2. $^{13}$C NMR data of (–)-broussonetine C2 and published 2-substituted THF derivatives.$^{[18,19]}

<table>
<thead>
<tr>
<th>Carbon</th>
<th>$\delta$ [ppm] (125 MHz, C$_5$D$_5$N)</th>
<th>$\delta$ [ppm] (125 MHz, CD$_3$OD)</th>
<th>$\delta$ [ppm] (50 MHz, CDCl$_3$)</th>
<th>$\delta$ [ppm] (75 MHz, CDCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>67.53</td>
<td>68.56</td>
<td>67.47</td>
<td>67.61</td>
</tr>
<tr>
<td>C-2</td>
<td>26.02</td>
<td>26.63</td>
<td>26.56</td>
<td>26.48</td>
</tr>
<tr>
<td>C-3</td>
<td>31.71</td>
<td>32.36</td>
<td>31.75</td>
<td>31.99</td>
</tr>
<tr>
<td>C-4</td>
<td>79.39</td>
<td>80.96</td>
<td>79.63</td>
<td>79.56</td>
</tr>
<tr>
<td>C-5</td>
<td>36.15</td>
<td>36.75</td>
<td>35.96</td>
<td>35.82</td>
</tr>
</tbody>
</table>

Figure 10.5. $^1$H NMR spectrum (500 MHz) of (–)-broussonetine C2, (–)-(2S,3S,4S,5S)-2-(hydroxymethyl)-5-(9'-{(tetrahydrofuran-2'-yl)nonyl})pyrrolidine-3,4-diol (10/23) in CD$_3$OD.
Chapter 10. Attempted Synthesis of (–)-Broussonetine C

Figure 10.6. $^1$H NMR spectrum (500 MHz) of (–)-broussonetine C trifluoroacetate, (–)-(2S,3S,4S,5S)-3,4-dihydroxy-2-(hydroxymethyl)-5-(9'-tetrahydrofuran-2'-yl)nonyl)pyrrolidinium trifluoroacetate in CD$_3$OD.

The outcome of our hydrogenolysis reaction was unexpected and surprising. Tetrahydrofuran formation under acidic hydrogenolytic conditions had not been reported in any of the published broussonetine C syntheses before. Then again, DURUGKAR$^{[20]}$ stated having troubles in his final deprotection steps, however without giving details regarding the products he obtained. One can only speculate that he might have encountered similar problems. On first sight it seems reasonable to assume that the acidic conditions of the hydrogenation would facilitate the formation the hemiacetal 10/22 followed by its reduction to the finally obtained tetrahydrofuran derivative 10/23 (Scheme 10.14). Nevertheless, neither PERLMUTTER$^{[22]}$ nor CARDA et al.$^{[23]}$ mentioned this reaction in their broussonetine C syntheses although they applied similar acidic hydrogenation conditions. On the other hand, YODA et al.$^{[21]}$ stated that they cleaved the benzyl ethers prior to hydrolysing the 1,3-dioxolane to avoid acetal formation. This might be a hint that YODA and co-workers experienced this problem before or at least expected it. A comparison of the hydrogenolysis conditions employed in the three published broussonetine C syntheses shows that PERLMUTTER and CARDA et al. used palladium on charcoal as catalyst whereas YODA and co-workers employed palladium black (Scheme 10.15). Indeed, NISHIMURA and co-workers reported in 1985 that platinum and palladium blacks obtained from vapourised metals have been found to efficiently catalyse acetal formation in the hydrogenation of 4-methylcyclohexanone in ethanol,$^{[24]}$ however without proposing a plausible mechanism for this conversion. Furthermore, hydrogenations with Pearlman’s catalyst have been used in the past to reduce hemiacetals like 10/22 to tetrahydrofuran
Thus, the extraordinary outcome of our hydrogenolysis might simply be explained by the usage of the wrong catalyst in the reaction. 

Scheme 10.15. Comparison of the final deprotection steps in the reported syntheses of (+)-broussonetine C.

Reagents and conditions:
- **YODA et al.** (1999): (a) Pd black, 4.4% HCOOH in MeOH; (b) conc. HCl, EtOAc, 83% over 2 steps.
- **PERLMUTTER et al.** (2003): (c) Pd/C, 5% AcOH in MeOH, H₂ (1 atm), rt, 18 h, 70%; (d) TFA, DCM, 0 °C, 2 h, 60%.
- **CARDA et al.** (2009): (e) NaOH, EtOH, reflux, 8 h, 72%; (f) 10% Pd/C, H₂ (1 atm), MeOH, 6 M HCl, rt, 16 h, 92%.
Chapter 10. Attempted Synthesis of (−)-Broussonetine C

Scheme 10.16 shows a plausible mechanism for the tetrahydrofuran formation under the applied acidic hydrogenolysis conditions. In a first step the terminal γ-hydroxy ketone moiety cyclised to its hemiacetal form 10/22 (broussonetine C1). This could either have occurred via the classic acid-catalysed pathway as shown or via the undefined Pd black-catalysed mechanism as reported by NISHIMURA et al.\[24\] In the subsequent second step the hemiacetal was reduced to the tetrahydrofuran end product 10/23 (−)-broussonetine C2) via the Pd(OH)\(_2\)/C-catalysed hydrogenation of the intermediate furanium ion 10/31.\[25, 26\]

**Scheme 10.16. Proposed mechanism for the tetrahydrofuran formation under acidic hydrogenolytic reaction conditions.**

### 10.4 Summary

After the successful syntheses of the pyrrolidine carbaldehyde 8/2 and model compound I, the synthesis of (−)-broussonetine C continued with the preparation of the side chain fragment starting from commercially available 9-decen-1-ol. O-TBS protection of the hydroxy group and ozonolysis of the double bond yielded the aldehyde 10/2 which was treated with freshly prepared benzzyloxypropylmagnesium bromide to afford the secondary alcohol 10/3.
Chapter 10. Attempted Synthesis of (–)-Broussonetine C

Scheme 10.17. Attempted synthesis of (–)-broussonetine C.

Reagents and conditions: (a) TBSCI, Et3N, DMAP, DCM, 0 °C to 25 °C, 3 h, 97%; (b) 1. O3, DCM, –78 °C, 2. N2, PPh3, –78 °C to 0 °C, 3 h, 96%; (c) benzzyloxypropylmagnesium bromide, THF, 0 °C to rt, 2 h, 83%; (d) Dess-Martin periodinane, DCM, 0 °C to 25 °C, 2 h, 94%; (e) TBADF, THF, 25 °C, 2.5 h, 95%; (f) HO(CH2)2OH, PPTS, benzene, reflux, 18 h, 96%; (g) MsCl, Et3N, DCM, 0 °C to 25 °C, 18 h, 100%; (h) NaI, MeCN, 50 °C, 2 h, 97%; (i) PPh3, toluene, reflux, 42 h, 92%; (j) n-BuLi, THF, HMPA, –50 °C, pyrrolidine carbaldehyde 8/2, 2 h, 85%; (k) 1 M H2SO4, 1,4-dioxane, 50 °C, 24 h, 96%; (l) Pd-enriched Pearlman’s catalyst, H2 (1 atm), 10 M HCl, MeOH/EtOAc (1 : 1), 25 °C, 18 h, 41.5%; 20.1% over 12 steps from 9-decen-1-ol, 5.5% over 13 steps from D-xylose, respectively, 3.3% over a total of 22 steps.
Chapter 10. Attempted Synthesis of (−)-Broussonetine C

The consequent oxidation of 10/3 with Dess-Martin periodinane followed by the \(O\)-TBS deprotection with TBAF provided the hydroxy ketone 10/10 which was subsequently protected as 1,3-dioxolane ketal with ethylene glycol. The attempted substitution of the hydroxy group with iodine under Garegg conditions in one step, however, did not succeed due to the parallel occurring ketal cleavage. The alcohol 10/5 was therefore first converted into the mesylate derivative 10/16 followed by its substitution with iodide. The final treatment of alkyl iodide 10/6 with \(\text{PPh}_3\) in refluxing toluene provided phosphonium iodide 10/7 as side chain synthon in an excellent yield of 59.4% over nine steps.

The coupling of the side chain building block with pyrrolidine carbaldehyde 8/2 was achieved as in the synthesis of model compound I before via Wittig olefination which provided the predominantly (\(Z\))-configured olefin 10/18 in a good yield of 85%. Hydrolysis of the 1,3-dioxolane ketal then yielded the ketone 10/20 as direct precursor of (−)-broussonetine C. The concluding hydrogenolysis, however, did not afford the desired final product presumably due to the use of the wrong catalyst system. Instead, a novel polyhydroxylated pyrrolidine base was obtained in which the terminal \(\gamma\)-hydroxy ketone moiety had cyclised to the intermediate hemiacetal 10/22 which was subsequently reduced to the tetrahydrofuran derivative 10/23 under the applied reaction conditions. This compound, consequently named (−)-broussonetine C2 to reflect its origin from 10/21, was obtained in 3.3% yield over a total of 22 steps starting from \(\text{D-xylose}\) and \(9\)-decen-1-ol (Scheme 10.17).
10.5 References


   


   

   


Chapter 10. Attempted Synthesis of (–)-Broussonetine C


Chapter 11. Future Work

11.1 Synthesis of Broussonetine C – Revision of the Final Deprotection Steps

As explicated at the end of Chapter 10, the most likely reason for the tetrahydrofuran formation at the side chain terminus of (–)-broussonetine C was the use of palladium black in combination with Pearlman’s catalyst under acidic conditions in the final hydrogenolysis step. To overcome this encountered problem in a future approach, the application of one of the four following procedures is proposed:

11.1.1 Applying CARDA’s Deprotection Protocol

CARDA and co-workers\(^1\) demonstrated in the final steps of their broussonetine C synthesis that the cleavage of the benzyl protecting groups under acidic hydrogenolytic conditions is possible if palladium on carbon is chosen as catalyst (see Chapter 3, Section 3.5). The occurrence of side reactions was not reported. By adopting their procedure it should therefore be possible to debenzylate the (–)-broussonetine C precursor 10/20 over Pd/C under aqueous acidic conditions at atmospheric H\(_2\) pressure, or under neutral conditions at elevated H\(_2\) pressure without THF formation (Scheme 11.1).

![Scheme 11.1. Synthesis of (–)-broussonetine C via cleavage of the benzyl groups under hydrogenolytic reaction conditions with Pd/C.](image)

(a) hydrolysis of the ketal; (b) hydrogenolysis over Pd/C under aqueous acidic conditions at atmospheric H\(_2\) pressure, or under neutral conditions at elevated H\(_2\) pressure.
11.1.2 Applying YODA’s Deprotection Protocol

In the final steps of their broussonetine C synthesis YODA and co-workers\(^2\) deprotected their broussonetine C precursor by first cleaving all benzyl ethers followed by the concomitant acidic hydrolysis of the ketal and the N-Boc group (see Chapter 3, Section 3.2). Transferring this protocol to our synthesis, the broussonetine C precursor 10/18 should first be debenzylated under neutral hydrogenolytic conditions (if necessary at elevated H\(_2\) pressure) or mild acidic conditions that would not harm the ketal. In a second step the 1,3-dixolane in 11/1 would then be hydrolysed to give broussonetine C (Scheme 11.2).

Scheme 11.2. Synthesis of (–)-broussonetine C by applying YODA’s two-step deprotection protocol.
(a) hydrogenolysis over Pd-catalyst under mild acidic conditions at atmospheric H\(_2\)-pressure, or under neutral conditions at elevated H\(_2\)-pressure; (b) hydrolysis of the ketal.

11.1.3 Cleavage of the Benzyl Groups under Non-hydrogenolytic Conditions

As an alternative to the hydrogenolytic methods employing Pd-catalysts, there are also miscellaneous other procedures reported in the literature to remove benzyl protecting groups. Boron halides like BCl\(_3\) and BBr\(_3\) effectively cleave benzyl amines and ethers liberating the respective amino and hydroxy groups in moderate to good yields.\(^3\) Indeed, CARDA et al.\(^1\) used BCl\(_3\) to remove the benzyl groups in the final step of the syntheses of broussonetines P and O in order to retain the double bonds present in the side chain of these two molecules. This afforded the two natural products in 70% and 80% yield, respectively (see Chapter 3, Scheme 3.12). Nevertheless, a negative aspect of this method remains of course the high toxicity of these reagents.
Chapter 11. Future Work

Scheme 11.3. Synthesis of (−)-broussonetine C via cleavage of the benzyl groups under non-hydrogenolytic reaction conditions.
(a) reduction of the double bond under non-hydrogenolytic conditions (e.g. TsNHNH$_2$, aq. NaOAc, DME, elevated temperature); (b) hydrolysis of the ketal; (c) cleavage of the benzyl groups under non-hydrogenolytic conditions (e.g. BCl$_3$, DCM, low temperature).

11.1.4 Linear Synthesis with an Orthogonal Protecting Group Strategy

In the unlikely case that all above proposed methods to suppress tetrahydrofuran formation should fail, an alternative synthesis plan was developed with an orthogonal protecting group strategy for the terminal hydroxy group. This plan is shown in Scheme 11.4.

The Wittig reaction of pyrrolidine carbaldehyde 8/2 with the simplified phosphonium iodide 11/3 would install the middle section of the side chain. Reduction of the double bond in the Wittig product 11/4 under non-hydrogenolytic conditions$^4$ followed by removal of the TBS protecting group would give the primary alcohol 11/6. The Swern oxidation of this alcohol would afford the aldehyde 11/7 which upon treatment with commercially available allylmagnesium bromide would yield the allylalcohol 11/8. The Dess-Martin oxidation of 11/8 and ketalisation of the resulting ketone 11/9 would provide the allylic 1,3-dioxolane 11/10 which would be converted to the terminal alcohol 11/11 via Brown’s hydroboration-oxidation method$^{5, 6}$. Masking of this alcohol as acetate ester 11/12 would allow the hydrolysis of the ketal and the cleavage of all benzyl groups without this group interfering. The final saponification of the acetate ester 11/13 would eventually provide (−)-broussonetine C in 11 steps from pyrrolidine carbaldehyde 8/2. Hemiacetal or even THF formation under the basic hydrolysis conditions is most unlikely. Nevertheless, due to its extended number of steps this synthesis plan would only be realised as a last resort if everything else fails.
Scheme 11.4. Alternative synthesis plan for (–)-broussonetine C with an orthogonal protecting group strategy.
(a) Wittig reaction of pyrrolidine carbaldehyde 8/2 with phosphonium iodide 11/3; (b) reduction of the double bond; (c) O-TBS deprotection; (d) Swern oxidation; (e) Grignard reaction of aldehyde 11/4 with allylmagnesium bromide; (f) Dess-Martin oxidation; (g) ketal formation; (h) hydroboration-oxidation of the terminal double bond; (i) O-acetylation; (j) N/O-debenzylation under acid hydrogenolytic conditions with concomitant ketal cleavage; (k) saponification of the acetate ester; 11 steps from pyrrolidine carbaldehyde 8/2.
Chapter 11. Future Work

11.2 Synthesis of Broussonetine E – Revision of the Coupling Reaction

The synthesis of (–)-10'-deoxobroussonetine E has shown that the pyrrolidine carbaldehyde 8/2 effectively undergoes Grignard reactions affording the diastereomeric secondary alcohols 9/12 and 9/13 in an overall moderate but acceptable yield of 66% (see Chapter 9, Scheme 9.6). Nevertheless, the diastereoselectivity of the reaction with its 3 : 2 ratio in favour of the undesired 1'-hydroxy epimer is inefficient and requires improvement. As IKOTA and HANAKI[7] have demonstrated with their syntheses of unnatural swainsonine epimers (Chapter 6, Scheme 6.6), the stereoselectivity of the coupling reaction can be controlled by the type of organometallic reagent added to the aldehyde (Scheme 11.5).

Due to time restrictions at the end of this project it was not possible to test different organometallics for their behaviour regarding the stereoselectivity and yield of the reaction. To render the search for the optimal organometallic reagent less time consuming, the coupling reactions should first be performed with a simpler, commercially available side chain building block such as butyl lithium or butylmagnesium bromide. Further organometallic reagents could easily be obtained via transmetallation reactions from these compounds or via halogen-metal exchange reactions from 1-bromobutane. These optimisation efforts could eventually be used for the total synthesis of the naturally occurring iminosugar 6-C-butyl-DMDP[8] (Scheme 11.6).

Scheme 11.5. Diastereoselectivity of the addition of different organometallic reagents to aldehyde 6/27 (IKOTA and HANAKI, 1987).[7]

Scheme 11.6. Proposed synthesis of 6-C-butyl-DMDP (1/73).
Chapter 11. Future Work

Scheme 11.6 cont'd. Proposed synthesis of 6-\text{-}C\text{-}butyl\text{-}DMDP (1/73).

(a) coupling of pyrrolidine carbaldehyde 6/1 with different organometallics \([M = \text{Li, Mg, Cu}^+, \text{Zn, Sn, In, etc.}]\); 
(b) hydrogenolysis of the benzyl groups.

Scheme 11.7. Revised synthesis of broussonetine E.

(a) coupling of pyrrolidine carbaldehyde 6/1 with the appropriate organometallic reagent 11/15 \([M = \text{Li, Mg, Cu}^+, \text{Zn, Sn, In, etc.}]\); (b) \(O\)-benzylation; (c) \(O\)-TBS deprotection with TBAF; (d) Swern oxidation; (e) Grignard reaction with benzyloxypropylmagnesium bromide; (f) Dess-Martin oxidation; (g) hydrogenolysis of the benzyl groups; 7 steps from pyrrolidine carbaldehyde 6/1.
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The optimised reaction conditions would then be used in the following for the synthesis of broussonetine E. Coupling of the carbaldehyde 6/1 with the terminal \( O \)-TBS protected organometallic reagent 11/15 under the optimised reaction conditions would afford the preferentially \( (R) \)-configurated secondary alcohol 11/16. Benzyl protection of this alcohol would be followed by the cleavage of the terminal TBS ether to yield the alcohol 11/18. This alcohol would subsequently be oxidised to the aldehyde 11/19 and then be treated with benzylxypropylmagnesium bromide to complete the carbon skeleton of the target molecule. Oxidation of the secondary alcohol 11/20 to the ketone 11/21 would be followed by \( N/O \)-debenzylation, as well under optimised conditions to prevent tetrahydrofuran formation of the side chain terminus, to give broussonetine E in seven steps from pyrrolidine aldehyde 6/1 (Scheme 11.7). Compared with the original proposed synthesis plan, this route would overall be two steps shorter since the protection/deprotection steps of the carbonyl functionality would be omitted.

11.3 Alternative Synthesis of Broussonetine E via Sakurai Allylation

Parallel to their allylation experiments with different allylorganometallic reagents, IKOTA and HANAKI also investigated to addition of allyltrimethylsilane to carbaldehyde 6/27 under Sakurai conditions. They achieved a very high Felkin-Anh diastereoselectivity with allyl-alcohol 6/28 being isolated as the only diastereoisomer (Scheme 11.8), unfortunately in only a moderate yield of 48\% though. IKOTA and HANAKI explained this effect by cyclic chelate formation between TiCl\(_4\) and the \( \alpha \)-aminocarbonyl group of 6/27 in which the nucleophile approaches from the less hindered side to yield 6/28 exclusively.\(^9\)

![Scheme 11.8. Sakurai allylation of aldehyde 6/27 (IKOTA and HANAKI, 1990).\(^9\)](image)
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Based on IKOTA's and HANAKI's finding an alternative synthesis of broussonetine E is suggested in the following with the Sakurai allylation of pyrrolidine carbaldehyde 6/1 as key step to diastereoselectively introduce the hydroxy group at C-1'. Benzyl protection of the newly formed OH-group in 11/22 followed by ozonolysis of the terminal double bond in 11/23 would afford aldehyde 11/24 as novel building block for broussonetine E and further C-1' hydroxylated broussonetine congeners. The Wittig reaction of 11/24 with the phosphonium iodide 11/25 would yield the olefin 11/26 which upon hydrolysis of the ketal would give ketone 11/27 as direct precursor for the natural product. The concluding hydrogenolysis of the benzyl protecting groups with simultaneous reduction of the double bond under optimised conditions would finally provide broussonetine E in six steps from the pyrrolidine carbaldehyde 6/1. (Scheme 11.9).

(a) Sakurai reaction of pyrrolidine aldehyde 6/1 with allyltrimethylsilane; (b) O-benzylation; (c) ozonolysis; (d) Wittig reaction; (e) ketal hydrolysis; (f) hydrogenolysis of the benzyl ethers; 6 steps from pyrrolidine carbaldehyde 6/1.
11.4 Alternative Synthesis of Broussonetine E via Vinylation of $N$-Tritylpyrrolidine Carbaldehyde 11.31

In 2003 CHEMLA and co-workers\textsuperscript{[10]} reported that $N$-tritylprolinal shows an exceptional high Felkin-Anh diastereoselectivity in its reaction with various organometallic nucleophiles, leading to the straightforward highly stereoselective access to syn-proline-derived amino alcohols. Selected examples of their results are shown in Table 11.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organometallic reagent</th>
<th>Solvent</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-BuLi</td>
<td>Et(_2)O</td>
<td>65\textsuperscript{a}</td>
<td>93 : 7</td>
</tr>
<tr>
<td>2</td>
<td>$n$-BuMgBr</td>
<td>Et(_2)O</td>
<td>78\textsuperscript{a}</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>3</td>
<td>MeMgCl</td>
<td>Et(_2)O</td>
<td>90\textsuperscript{a}</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>4</td>
<td>$i$-PrMgBr</td>
<td>Et(_2)O</td>
<td>76\textsuperscript{a}</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>5</td>
<td>VinylMgCl</td>
<td>Et(_2)O</td>
<td>94\textsuperscript{a}</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>6</td>
<td>TMS–C≡C–Li</td>
<td>Et(_2)O</td>
<td>88\textsuperscript{a}</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>7</td>
<td>PhMgBr</td>
<td>Et(_2)O</td>
<td>90\textsuperscript{a}</td>
<td>&gt;98 : 2</td>
</tr>
<tr>
<td>8</td>
<td>AllylMgBr</td>
<td>Et(_2)O</td>
<td>85\textsuperscript{b}</td>
<td>63 : 37</td>
</tr>
</tbody>
</table>

\textsuperscript{a} isolated yield of the major diastereomer after column chromatography. 
\textsuperscript{b} isolated yield of the diastereomeric mixture.

CHEMLA’s findings initiated the idea to replace the $N$-benzyl with the trityl group and to synthesise the $N$-tritylated derivative 11/31 of pyrrolidine carbaldehyde 6/1 as modified building block for the broussonetine E synthesis. The Petasis reaction of 3,5-di-$O$-benzyl-L-xylofuranose with commercially available tritylamine and (E)-styryl boronic acid would afford the $N$-trityl amino diol 11/28 which could be converted in four further steps to the $N$-trityl pyrrolidine carbaldehyde 11/31 (Scheme 11.10). The effect of the $O$-benzyl substituents on the diastereoselectivity in the following addition of vinylmagnesium chloride to 11/31 is yet unknown and would have to be investigated, but it is expected to be of similar proportion as reported by CHEMLA et al.\textsuperscript{[10]} for the $N$-tritylprolinal example (Table 11.1, Entry 5). Subsequent cleavage of the $N$-trityl group and treatment of the resulting $\alpha$-hydroxy pyrrolidine with triphosgene under basic conditions would provide the vinyl oxazolidinone 11/33 which
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could be coupled in a cross-metathesis reaction with 4-keto-11-dodecenyl acetate to give the olefin 11/34 as direct precursor for broussonetine E. Hydrogenolysis of the benzyl ethers with concomitant reduction of the double bond followed by simultaneous oxazolidinone and acetate saponification would finally yield broussonetine E in 11 steps from 3,5-di-O-benzyl-L-xylofuranose. Vinyl oxazolidinone 11/33 could also be used as novel building block for the synthesis of further C-1' hydroxy broussonetines similar to the works of DURUGKAR\cite{11} and CARDA \textit{et al.}\cite{11, 12} (see Chapter 3, Sections 3.5 and 3.6).

![Scheme 11.10](image)

\textbf{Scheme 11.10.} Alternative synthesis plan for broussonetine E inspired by CHEMLA \textit{et al.}

(a) Petasis reaction of 3,5-di-O-benzyl-L-xylofuranose with tritylamine and (E)-styrylboronic acid; (b) \textit{N}-alkylative \textit{5-exo-tet} cyclisation; (c) \textit{O}-benzylolation; (d) ozonolysis; (e) Swern oxidation; (f) Grignard reaction with vinylmagnesium bromide; (g) \textit{N}-deitylation; (h) oxazolidinone formation with triphosgene; (i) cross-metathesis with 4-keto-11-dodecenyl acetate (j) hydrogenolysis of the benzyl ethers with concomitant reduction of the double bond; (k) oxazolidinone and acetate saponification; 11 steps from 3,5-di-O-benzyl-L-xylofuranose.
11.5 Alternative Synthesis Plan for Broussonetine C and E inspired by Professor H.H. MEYER

In order to overcome the encountered difficulties with the oxidative cleavage of the styryl double bond of pyrrolidine 8/1 and the problems caused by the instability of the pyrrolidine carbaldehyde 8/2 Professor Hartmut MEYER from the Leibniz University of Hannover in Germany proposed the following alterations to the synthesis route after a presentation was given about this work. Rather than employing benzylamine in the Petasis reaction, Prof. MEYER suggested to use an amine whose aryl rest could be exchanged with a carbamate protecting group for the nitrogen in course of the synthesis. For example, the PMB group, introduced via the Petasis reaction with para-methoxybenzylamine, could be cleaved off under oxidative conditions with DDQ or CAN at the stage of pyrrolidine 11/36 and be replaced with the Cbz protecting group.\[13, 14\] This exchange would afford a more stable pyrrolidine carbaldehyde 11/38 that should be less likely to decompose as reported by PALMER and JÄGER\[15\] in their synthesis of 1,2,5-trideoxy-2,5-imino-D-allitol (see Chapter 8, Scheme 8.16). Secondly, instead of styrylboronic acid Prof. MEYER recommended to apply iso-butenylboronic acid\[16\] in the Petasis reaction. As a result the olefin 11/37 would liberate only volatile acetone as by-product in its oxidative cleavage with ozone. A chromatographic purification of the crude aldehyde 11/38 as in the case of benzaldehyde as by-product would not be necessary anymore, and the olefin could directly be converted to the desired building block without going a detour via the pyrrolidine alcohol derivative (see Chapter 8, Section 8.3). The Wittig coupling of 11/38 with the phosphonium iodide 10/7 followed by the hydrolysis of the ketal and the hydrogenolysis of the benzyl groups with concomitant reduction of the double would ultimately provide broussonetine C in eight steps from 3,5-di-O-benzyl-L-xylofuranose (Scheme 11.11).

Scheme 11.11. Alternative synthesis plan for broussonetines C and E (inspired Prof. H.H. MEYER).
(a) Petasis reaction of 3,5-bis-O-benzyl-L-xylofuranose with para-methoxybenzylamine and iso-butenylboronic acid.
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Scheme 11.11 cont’d. Alternative synthesis plan for broussonetines C and E (inspired Prof. H.H. Meyer).

(b) N-alkylative 5-exo-tet cyclisation; (c) O-benzylation; (d) N-PMB cleavage with CAN or DDQ; (e) N-Cbz protection; (f) ozonolysis; (g) Wittig reaction; (h) ketal hydrolysis (i) hydrogenolysis; (j) stereoselective epoxidation; (k) regioselective epoxide ring-opening; 8 steps from 3,5-bis-O-benzyl-L-xylofuranose for broussonetine C, 10 steps for broussonetine E, respectively.
Furthermore, the double bond of the Wittig product 11/39 could also be used for the synthesis of broussonetine E. The stereoselective epoxidation of olefin 11/39 followed by the regioselective epoxide ring-opening would provide the secondary alcohol 11/41 as direct precursor of the natural product. The concluding removal of all protecting groups under optimised conditions would finally yield broussonetine E in ten steps from 3,5-di-\(O\)-benzyl-1-xylofuranose.

### 11.6 Employing DMDP as Starting Material for the Synthesis of Broussonetines C and E

As an alternative to MEYER’s proposal and extension to DURUGKAR’s\(^{11}\) broussonetine G synthesis (see Chapter 3, Section 3.6) DMDP itself could be used as starting material for the synthesis of the broussonetine alkaloids. Our scaleable synthesis of DMDP would allow the preparation of a sufficient amount of the \(C_2\)-symmetric iminosugar which could then be converted in five easy steps into the \(N\)-Cbz protected pyrrolidine carbaldehyde 3/65 as shown in Scheme 11.12. This aldehyde would then be employed in the synthesis of broussonetines C and E as described in the previous section via its Wittig reaction with phosphonium iodide 10/7. The special charm of this synthesis scheme would be to use a simple natural product for the preparation of the more complex broussonetines.

**Scheme 11.12.** Alternative synthesis plan for broussonetines C and E from DMDP.
Scheme 11.12 cont’d. Alternative synthesis plan for broussonetines C and E from DMDP.

(a) oxazolidinone formation with triphosgene; (b) tris-O-benzylolation; (c) oxazolidinone saponification; (d) N-Cbz protection; (e) Swern oxidation; (f) Wittig reaction; (g) ketal hydrolysis; (h) hydrogenolysis; (i) stereoselective epoxidation; (j) regioselective epoxide ring-opening; 8 steps from DMDP for broussonetine C, 10 steps for broussonetine E, respectively.

11.7 Ozone-free Alternative Synthesis Plans

As explicated in detail in Chapter 8 the synthesis of pyrrolidine carbaldehyde 8/2 via the oxidative cleavage of the styryl double of pyrrolidine 8/1 proved to be a tedious task which, in the end, was only achieved by diverting the original synthetic route and adding three more steps to the synthesis (tritylation, detritylation, Swern oxidation, see Scheme 8.22). In the process of solving this problem alternative synthesis plans were developed that do not contain the malicious oxidative cleavage step simply by substituting the styryl boronic acid in the Petasis reaction at the beginning of the synthesis. These alternative synthesis plans are briefly introduced in the following.

11.7.1 Alternative Synthesis Plan for Broussonetine C inspired by DONDONI et al.

DONDONI and co-workers demonstrated in 2002 that the pyrrolidine carbaldehyde 6/1 can efficiently be synthesised via the hydrolytic ring scission of a 2-substitusted thiazole precursor (see Chapter 6, Section 6.3).[41] Based on their findings a synthesis for carbaldehyde 6/1 and further for broussonetine C was envisioned that would incorporate DONDONI’s aldehyde release from 2-substituted thiazoles as a key step. This synthesis is outlined in Scheme 11.13.
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The Petasis reaction of 3,5-di-O-benzyl-L-xylofuranose with benzylamine and commercially available 2-thiazolylboronic acid would afford the amino diol 11/43 with the requisite thiazole substituent installed at C-5. The 5-exo-tet cyclisation of 11/43 followed by C-4 O-benzylation would give rapid access to the required pyrrolidine carbaldehyde precursor 6/11 which upon hydrolytic degradation under the conditions described by Dondoni et al. would eventually provide the desired carbaldehyde building block 6/1 in just four steps from 3,5-di-O-benzyl-L-xylofuranose.

Scheme 11.13. Alternative synthesis plan for broussonetine C inspired by Dondoni et al.
(a) Petasis reaction of 3,5-di-O-benzyl-L-xylofuranose with benzylamine and 2-thiazolylboronic acid; (b) N-alkylative 5-exo-tet cyclisation; (c) O-benzylation; (d) aldehyde release from the 2-thiazole moiety; (e) Wittig reaction with phosphonium iodide 11/3; (f) reduction of the double bond; (g) O-TBS deprotection with TBAF; (h) Swern oxidation; (i) Grignard reaction with benzylxypropylmagnesium bromide; (j) Dess-Martin or TPAP oxidation; (k) hydrogenolysis; 11 steps from 3,5-bis-O-benzyl-L-xylofuranose for broussonetine C.

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Coupling of this aldehyde with the Wittig salt \(11/3\) and subsequent saturation of the double bond would give the pyrrolidine \(11/45\). Cleavage of the terminal TBS ether followed by Swern oxidation of the liberated hydroxy group would afford the aldehyde \(11/46\) which would be treated with benzyloxypropylmagnesium bromide to complete the broussonetine carbon skeleton. Oxidation of the secondary alcohol would provide the ketone \(11/47\) as direct precursor of the desired natural product. The concluding debenzylation under optimised conditions would finally afford broussonetine C in eleven steps from 3,5-di-O-benzyl-L-xylofuranose (Scheme 11.13).

11.7.2 Alternative Synthesis Plan for Broussonetine C via Petasis Reaction with Allylboronic Acid

A key problem of the developed broussonetine synthesis is the only moderate stability of pyrrolidine carbaldehyde \(8/2\) characterised by its tendency to epimerise and eventually decompose shortly after its formation. One reason for these properties is possibly the close proximity of the aldehyde carbonyl functionality to the basic \(N\)-benzyl amino group of the pyrrolidine ring. Moving the aldehyde further down the side chain and away from the pyrrolidine moiety could therefore help to gain a more stable pyrrolidine aldehyde building block. This could be achieved by employing allylboronic acid instead of a vinylboronic acid in the Petasis reaction with 3,5-di-O-benzyl-L-xylofuranose and benzylamine affording the amino diol \(11/48\) with a terminal double bond. The usual 5-\textit{exo}-tet cyclisation of \(11/48\) followed by its C-4 \(O\)-benzylation would provide the allylic pyrrolidine \(11/49\) which could be converted into aldehyde \(11/51\) in two further steps via a sequential hydroboration-oxidation reaction followed by a Swern oxidation. This aldehyde would contain a ethyl spacer between the pyrrolidine ring and its carbonyl group and would therefore be less prone to decompose. Epimerisation at C-5 would be eliminated. A Wittig reaction, now with the shorter side chain fragment \(11/25\), and subsequent cleavage of all protecting groups under optimised conditions would conclude the broussonetine C synthesis (Scheme 11.14).
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(a) allylmagnesium bromide addition to trimethylborate (b) Petasis reaction with 3,5-di-O-benzyl-L-xylofuranose and benzylamine; (c) \(N\)-alkylative 5-\textit{exo}-tet cyclisation; (d) \(O\)-benzylation; (e) hydroboration-oxidation; (f) Swern oxidation; (g) Wittig reaction; (h) ketal hydrolysis; (i) hydrogenolysis; 9 steps from allylmagnesium bromide.

Unfortunately, allylboronic acid is not commercially available but could easily be synthesised by treating allylmagnesium bromide with trimethylborate followed by the hydrolysis of the intermediate allylborate.\[^{17}\] Nevertheless, Petasis reactions with allylboronic acid have not been reported to date, and its reactivity regarding borono-Mannich chemistry would have to be investigated.
11.7.3 Alternative Synthesis Plan for Broussonetine C via Petasis Reaction with \((E)-3-(\text{tert-Butyldimethylsilyloxy})\text{prop-1-enylboronic Acid}

As an alternative to the above suggested allylboronic acid, a terminal \(O\)-protected 3-hydroxy-1-propenylboronic acid could also be used to install the aldehyde functionality further down the side chain later in the synthesis. For example, employing \((E)-3-(\text{tert-butyldimethylsilyloxy})\text{prop-1-enylboronic acid (11/54)}\) in the Petasis reaction with 3,5-di-\(O\)-benzyl-L-xylofuranose and benzyl-amine would afford the amino diol 11/55 with a terminal TBS-protected hydroxy group. The usual \(S_n2/5\)-exo-tet cyclisation of 11/55 followed by its C-4 \(O\)-benzylation would provide the vinyl pyrrolidine 11/57 which upon reduction of the double under non-hydrolytic conditions and removal of the TBS protecting group would provide the primary alcohol 11/50. The Swern oxidation of 11/50 and subsequent Wittig reaction of the intermediate aldehyde 11/51 with the shorter phosphonium iodide 11/25 would yield the olefin 11/52 as direct precursor for broussonetine C. The concluding cleavage of all protecting groups under optimised conditions would eventually provide broussonetine C in nine steps from 3,5-bis-\(O\)-benzyl-L-xylofuranose.

Like allylboronic acid, 3-hydroxy-1-propenylboronic acid is not commercially available. The \(O\)-TBS protected derivative 11/54, however, is an already known compound that could be synthesised in two steps from propargylalcohol following published procedures as shown in Scheme 11.15.[18]

Scheme 11.15. Proposed synthesis of broussonetine C via Petasis reaction with \((E)-3-(\text{tert-butyldimethylsilyloxy})\text{prop-1-enylboronic acid.}
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Scheme 11.15 cont’d. Proposed synthesis of broussonetine C via Petasis reaction with
(E)-3-(tert-butyldimethylsilyloxy)prop-1-enylboronic acid.
(a) O-TBS protection of propargylalcohol; (b) hydroboration-hydrolysis with catecholborane or dichloroborane-dioxane complex; (c) Petasis reaction with 3,5-di-O-benzyl-L-xylofuranose and benzylamine; (d) N-alkylative 5-exo-tet cyclisation; (e) O-benzylation; (f) reduction of the double bond; (g) O-TBS deprotection with TBAF; (h) Swern oxidation; (i) Wittig reaction; (j) ketal hydrolysis; (k) OBn hydrogenolysis and saturation of the double bond; 9 steps for broussonetine C from 3,5-di-O-benzyl-L-xylofuranose.

11.7.4 Alternative Synthesis Plan for Broussonetine C starting from 9-Decyne-1-ol

A further ozone-free synthesis plan for broussonetine C involves the idea to introduce the side chain middle section already in the first step via the Petasis reaction of 3,5-di-O-benzyl-L-xylofuranose with terminal O-protected (E)-10-hydroxydec-1-enylboronic acid. The requisite 1-decenyl boronic, in turn, could be obtained in two or three steps from commercially 9-decyne-1-ol following published procedures [19]. The 5-exo-tet cyclisation of the Petasis product, amino diol 11/60, and its subsequent C-4 O-benzylation would afford pyrrolidine 11/61 which could be converted into broussonetine C in four further steps (Scheme 11.16). This elegant synthesis would provide rapid access to broussonetine C and further C-1'-deoxybroussonetines. Nevertheless, a negative aspect of this synthesis plan are the relative high costs of the starting materials, 9-decyne-1-ol and catecholborane, for the synthesis of the required boronic acid.
(a) O-protection (PG = PMB, Tr, TBS, TDS, TPS, TIPS or TBDPS); (b) hydroboration-hydrolysis with catecholborane or dichloroborane-dioxane complex; (c) Petasis reaction with 3,5-di-O-benzyl-L-xylofuranose and benzylamine; (d) N-alkylative 5-exo-tet cyclisation; (e) O-benzylation; (f) terminal O-deprotection; (g) Swern oxidation; (h) Grignard reaction with benzyloxypropylmagnesium bromide; (i) Dess-Martin or TPAP oxidation; (j) hydrogenolysis; 10 steps from 9-decyne-1-ol.

11.8 Alternative Synthesis Plan for Broussonetine E and homoDMDP starting from D-Glyceraldehyde

So far, all above introduced substitute synthesis schemes for broussonetine E feature 3,5-di-O-benzyl-L-xylofuranose as carbonyl component in the Petasis reaction. A further alternative approach leading to broussonetine E and its smaller congener homoDMDP was inspired by the work of TROST et al.\(^{20}\) and employs commercially available D-glyceraldehyde as starting material. Its Petasis reaction with TROST’s (S)-1-(benzyloxy)-3-buten-2-amine and (E)-styrylboronic acid would initially afford the amino diol 11/64. N-Cbz protection under Schotten-Baumann conditions followed by the ring-closing metathesis of the diene system with Grubbs’ second generation catalyst would afford the pyrroline 11/66. As TROST and co-workers have demonstrated, the epoxidation of such pyrrolines followed by the acidic hydrolysis of the
intermediate epoxides exclusively yields trans-configurated dihydroxy pyrrolidines like 11/67. The concomitant cleavage of the Cbz and benzyl groups under hydrogenolytic conditions would eventually provide homoDMDP in six steps from D-glyceraldehyde.

On the other hand, tetraol 11/67 could be converted in four steps into the aldehyde 11/70 according to Scheme 11.17 which upon coupling with phosphonium iodide 11/71 in a Wittig reaction would afford the olefin 11/72. Hydrolysis of the ketal followed by the cleavage of the Cbz and benzyl groups with simultaneous saturation of the double bond would provide broussonetine E in twelve steps from D-glyceraldehyde. The special appeal of this synthesis route is the already present hydroxy group at C-1' in the right absolute configuration derived from the chiral starting material. Therefore, it does not have to be diastereoselectively installed in the course of the synthesis.

Scheme 11.17. Alternative synthesis plan for homoDMDP and broussonetine E starting from D-glyceraldehyde.
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Scheme 11.17 cont’d. Alternative synthesis plan for homoDMDP and broussonetine E starting from D-glyceraldehyde.

(a) Petasis reaction of D-glyceraldehyde with (S)-1-(benzyloxy)-3-buten-2-amine and (E)-styrylboronic acid, (b) N-Cbz protection; (c) ring-closing metathesis with Grubbs’ 2nd generation catalyst; (d) epoxidation; (e) acidic epoxide hydrolysis; (f) hydrogenolysis; (g) O-SiR$_3$ protection; (h) tris-O-benzylation; (i) O-SiR$_3$ deprotection; (j) Swern oxidation; (k) Wittig reaction; (l) ketal cleavage; (m) hydrogenolysis; 6 steps for homoDMDP from D-glyceraldehyde, 12 steps for broussonetine E, respectively.
11.9 References


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Conclusions

In the course of this PhD project a convergent and flexible synthesis for polyhydroxylated pyrrolidine alkaloids has been developed. This synthesis is a further development and refinement of the Petasis reaction approach towards polyhydroxylated pyrrolizidine and indolizidine alkaloids which has been developed in the PYNE group and has been employed to prepare several members of these alkaloid groups in the decade (see Chapter 4).

The polyhydroxylated pyrrolidine alkaloid DMDP as well as its C-5 alkyl-substituted derivatives, the broussonetines C and E, were chosen as target compounds for this PhD project. A synthesis scheme was conceived that would allow the convergent assembly of the broussonetine congeners through the combination of a pyrrolidine carbaldehyde building block with the respective side chain synthons via either a Wittig or a Grignard reaction. The pyrrolidine building block as well as DMDP, in turn, would be constructed employing the Petasis borono-Mannich reaction as key step to stereoselectively assemble the requisite amino diol intermediate. The retrosynthetic analysis identified L-xylose as the appropriate starting material to establish the required all-(R)-configuration of the pyrrolidine ring of our target compounds. However, due to the relative high cost of L-xylose compared to its natural D-enantiomer on the one hand, and time constraints at the end of this project on the other hand, only syntheses starting from D-xylose were realised which, in the end, yielded only iminosugars with the unnatural all-(S)-configuration around the pyrrolidine periphery.

The synthesis of (–)-L-DMDP, the enantiomer of the naturally occurring iminosugar (+)-DMDP, has been accomplished in seven consecutive steps from the inexpensive commercially available carbohydrate D-xylose. First steps were the transformation of D-xylose into its known derivative 3,5-di-O-benzyl-D-xylofuranose in 72.2% overall yield. The key step of the synthesis was the following one-pot three-component Petasis borono-Mannich reaction of this D-xylose derivative with benzylamine and (E)-styrylboronic acid which provided the amino diol 7/6 as a single diastereomer in an excellent yield of 93%. The subsequent N-alkylative S_N2/exo-tet cyclisation with inversion of the configuration at C-2 furnished the desired pyrrolidine ring with the required all-(S)-stereochemistry in 65% yield. The pyrrolidinol 7/12 was then subjected to an ozonolysis reaction of the styrly double bond which provided the pyrrolidine diol 7/23 in 56% yield. The concluding hydrogenolytic cleavage of
the benzyl protecting groups over Pd-enriched Pearlman’s catalyst finally afforded L-DMDFP in an overall yield of 23.8% from D-xylose or in 32.9% yield over four steps from the known compound 3,5-di-O-benzyl-D-xylofuranose, respectively (Scheme 7.17).

Serendipitously, a small modification of the synthesis also gave access to the known iminosugar L-AB1. Treatment of the intermediate secondary ozonide with Et₃N during the ozonolysis work-up of 7/12 promoted a fragmentation process which provided the L-AB1 precursor 7/24 in almost 50% yield. The following final hydrogenolysis of the remaining benzyl groups then afforded L-AB1 in 21.9% yield over seven steps from D-xylose or 30.3% over four steps from 3,5-di-O-benzyl-D-xylofuranose, respectively (Scheme 7.18).

The synthesis of the (5S)-phenethyl derivative of L-AB1 (9/8) was used as model study to test the reaction and work-up conditions as well as to examine different purification methods that would later be employed in the final hydrogenation step of the broussonetine syntheses. As such (–)-(5S)-phenethyl-L-AB1 was obtained in seven steps from D-xylose in 33.6% overall yield.

The synthesis of the pyrrolidine carbaldehyde 8/2 as building block for the broussonetines C and E proved to be much more demanding than initially expected. First attempts to obtain the desired synthon from the direct precursor 8/1 via the oxidative double bond cleavage by ozone either completely failed or yielded unsatisfactory results. Efforts to attain the carbaldehyde via the oxidative cleavage of the diol 8/46 were also futile. Although the dihydroxylation of the styryl pyrrolidine 8/1 provided the respective diastereomeric syn-diols in good yield, the following oxidative diol cleavage/reduction sequence failed due to the epimerisation and decomposition of the intermediate aldehyde under the applied reaction conditions and the occurrence of side reactions including the ring-expansion of the pyrrolidine moiety to piperidine alcohols.

The synthesis of the required aldehyde building block 8/2 eventually succeeded via a little detour from the pyrrolidine diol 7/23 (Scheme 8.23) which, in turn, was obtained in six steps from D-xylose as described in Chapter 7. Tritylation of the primary hydroxy group of 7/23 followed by C-4 O-benzyla and detritylation under standard conditions provided the pyrrolidine alcohol 8/9 in 66.4% yield over three steps. This alcohol was finally oxidised by the method of Swern without notable epimerisation and decomposition to afford the desired aldehyde in 16.3% over ten steps from D-xylose.
Conclusions

Prior to the synthesis of the actual target compounds, two model studies were conducted to examine the feasibility of our synthesis scheme regarding the coupling reactions of the two building blocks via Wittig olefination and Grignard addition, respectively.

(−)-10'-Deoxobroussonetine C was synthesised as a first model study for the synthesis of 1'-deoxybroussonetine congeners from D-xylose and 12-bromo-1-dodecanol in 8.5% yield over a total of 15 steps. The key step of the synthesis was the coupling of the two building blocks, the pyrrolidine carbaldehyde 8/2 and the phosphonium iodide 9/5, via a Wittig olefination which provided the predominantly (Z)-configured olefin 9/6 in a good yield of 85%. A concluding hydrogenolytic debenzylation with concomitant reduction of the double bond over Pd-enriched Pearlman’s catalyst in acidic medium afforded the desired pyrrolidine derivative in 64% yield (Scheme 9.4).

(−)-10'-Deoxobroussonetine E was prepared in 2.4% yield over a total of 15 steps from D-xylose and 1,12-dodecanediol as a second model study for the synthesis of 1'-hydroxybroussonetine congeners. The key step of this synthesis was the coupling of the pyrrolidine carbaldehyde 8/2 and benzyloxydodecylmagnesium bromide 9/10 via a Grignard reaction which provided the two epimeric alcohols 9/12 and 9/13 in 39% and 26% yield, respectively. The absolute configuration of both alcohols were assigned by employing Mosher’s protocol to samples of the respective (R)- and (S)-MTPA ester derivatives of 9/12 and 9/13. The required (6S)-alcohol 9/13 was eventually debenzylated under hydrogenolytic conditions over Pd-enriched Pearlman’s catalyst in acidic medium affording the desired L-DMDP derivative 9/2 in almost 92% yield (Scheme 9.12). The debenzylation of an analytical sample of the (6R)-alcohol 9/12 under the same condition provided (−)-1’-epi-10’-deoxobroussonetine E in 2.7% yield over a total of 15 steps from the same starting materials.

The attempt to invert the configuration at C-6 of alcohol 9/12 under Mitsunobu conditions to attain more of the desired (6S)-epimer resulted unexpectedly in ring-expansion of the pyrrolidine moiety. Saponification of the intermediate formate ester 9/17 afforded the 5-hydroxy piperidine 9/28 in 67.5% yield over two steps. The hydrogenolysis of the benzyl protecting groups over Pd-enriched Pearlman’s catalyst in acidic medium subsequently provided the (6S)-alkylated ent-moranoline derivative 9/30 in 2.4% yield over a total of 17 steps from D-xylose and 1,2-dodecanediol (Scheme 9.13). The relative and absolute configuration of the piperidine moiety were eventually confirmed by NOE measurements performed on a sample of the piperidinium trifluoroacetate salt in methanol-d4.
Conclusions

After the successful synthesis of model compound I an attempt was undertaken to synthesise (−)-broussonetine C. The requisite phosphonium iodide 10/7 as side chain synthon was synthesised in 59.4% yield over nine steps from commercially available 9-decen-1-ol. The coupling of this side chain building block with the pyrrolidine carbaldehyde 8/2 was achieved as in the synthesis of model compound I before via Wittig olefination which provided the predominantly (Z)-configurated olefin 10/18 in a good yield of 85%. Hydrolysis of the 1,3-dioxolane ketal then yielded the ketone 10/20 as direct precursor of (−)-broussonetine C. The concluding hydrogenolysis, however, did not afford the desired final product, presumably due to the usage of the wrong catalyst system. Instead, a novel polyhydroxylated pyrrolidine base was obtained in which the terminal γ-hydroxy ketone moiety had cyclised to the intermediate hemiacetal 10/22 which was subsequently reduced to the tetrahydrofuran derivative 10/23 under the applied reaction conditions. This compound, consequently named (−)-broussonetine C2 to reflect its origin from 10/21, was obtained in 3.3% yield over a total of 22 steps starting from D-xylose and 9-decen-1-ol (Scheme 10.17).

![Image of chemical structures](image-url)

**Figure 12.1.** Summary of the iminosugars that have been synthesised in the course of this PhD project.
Table 12.1. $^1$H- and $^{13}$C NMR Spectral Data for (−)-(S5)-Phenethyl-1-AB1 (9/8).

<table>
<thead>
<tr>
<th></th>
<th>$^1$H NMR (C$_6$D$_5$N) (free base)</th>
<th>$^{13}$C NMR (C$_6$D$_5$N) (free base)</th>
<th>$^1$H NMR (CD$_3$OD) (free base)</th>
<th>$^{13}$C NMR (CD$_3$OD) (free base)</th>
<th>$^1$H NMR (CD$_3$OD) (pyrrolidinium acetate)</th>
<th>$^{13}$C NMR (CD$_3$OD) (pyrrolidinium acetate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.21 (dd, 1H, $J$ = 5.8, 11.1 Hz, $H_{\text{A-1}}$)</td>
<td>62.88 (CH$_2$, C-1)</td>
<td>3.59 (dd, 1H, $J$ = 6.0, 11.4 Hz, $H_{\text{A-1}}$)</td>
<td>63.32 (CH$_2$, C-1)</td>
<td>3.78 (dd, 1H, $J$ = 6.4, 11.9 Hz, $H_{\text{A-1}}$)</td>
<td>63.61 (CH$_2$, C-1)</td>
</tr>
<tr>
<td></td>
<td>4.27 (dd, 1H, $J$ = 3.9, 11.1 Hz, $H_{\text{B-1}}$)</td>
<td></td>
<td>3.67 (dd, 1H, $J$ = 4.0, 11.4 Hz, $H_{\text{B-1}}$)</td>
<td>3.84 (dd, 1H, $J$ = 3.9, 11.9 Hz, $H_{\text{B-1}}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.86 (br dt, 1H, $J$ = 4.1, 6.1 Hz, H-2)</td>
<td>65.06 (CH, C-2)</td>
<td>2.99 (&quot;dd&quot;*, 1H, $J$ = 6.2, 10.6 Hz, H-2)</td>
<td>64.49 (CH, C-2)</td>
<td>3.42 (td, 1H, $J$ = 4.1, 6.3 Hz, H-2)</td>
<td>65.61 (CH, C-2)</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4.69 (t, 1H, $J$ = 6.5 Hz, H-3)</td>
<td>79.71 (CH, C-3)</td>
<td>3.77 (t, 1H, $J$ = 6.6 Hz, H-3)</td>
<td>79.70 (CH, C-3)</td>
<td>3.95 (t, 1H, $J$ = 6.0 Hz, H-3)</td>
<td>77.36 (CH, C-3)</td>
</tr>
<tr>
<td>4</td>
<td>4.46 (t, 1H, $J$ = 6.7 Hz, H-4)</td>
<td>83.67 (CH, C-4)</td>
<td>3.65 (t, 1H, $J$ = 6.8 Hz, H-4)</td>
<td>83.74 (CH, C-4)</td>
<td>3.88 (t, 1H, $J$ = 6.2 Hz, H-4)</td>
<td>81.08 (CH, C-4)</td>
</tr>
<tr>
<td>5</td>
<td>3.61 (dt, 1H, $J$ = 4.9, 7.9 Hz, H-5)</td>
<td>62.31 (CH, C-5)</td>
<td>2.90 (cd, 1H, $J$ = 5.3, 7.8 Hz, H-5)</td>
<td>62.22 (CH, C-5)</td>
<td>3.31 (m, 1H, H-5)</td>
<td>60.29 (CH, C-5)</td>
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<td>6</td>
<td>2.15 (m, 1H, H$_{\text{A-6}}$)</td>
<td>37.02 (CH$_2$, C-6)</td>
<td>1.73 (m, 1H, H$_{\text{A-6}}$)</td>
<td>37.54 (CH$_2$, C-6)</td>
<td>2.01 (m, 1H, H$_{\text{A-6}}$)</td>
<td>34.75 (CH$_2$, C-6)</td>
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<td></td>
<td>2.36 (m, 1H, H$_{\text{B-6}}$)</td>
<td></td>
<td>1.97 (m, 1H, H$_{\text{B-6}}$)</td>
<td></td>
<td>2.15 (ddd, $J$ = 6.3, 10.3, 12.7 Hz, H$_{\text{B-6}}$)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.89 (ddd, 1H, $J$ = 6.2, 10.4, 13.7 Hz, H$_{\text{A-7}}$)</td>
<td>33.44 (CH$_3$, C-7)</td>
<td>2.66 (ddd, 1H, $J$ = 6.2, 10.3, 13.7 Hz, H$_{\text{A-7}}$)</td>
<td>34.02 (CH$_3$, C-7)</td>
<td>2.78 (m, 2H, H$_{\text{B-7}}$)</td>
<td>33.37 (CH$_3$, C-7)</td>
</tr>
<tr>
<td></td>
<td>3.04 (ddd, 1H, $J$ = 5.3, 10.7, 13.7 Hz, H$_{\text{B-7}}$)</td>
<td></td>
<td>2.77 (ddd, 1H, $J$ = 5.5, 10.6, 13.8 Hz, H$_{\text{B-7}}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>7.19 (m, 1H, ortho-Ph-H)</td>
<td>126.03 (para-Ph-CH)</td>
<td>7.14 (&quot;t&quot;, 1H, $J$ = 6.9 Hz, para-Ph-H)</td>
<td>126.83 (para-Ph-CH)</td>
<td>7.18 (m, 1H, ortho-Ph-H)</td>
<td>127.28 (para-Ph-CH)</td>
</tr>
<tr>
<td></td>
<td>7.26 – 7.31 (m, 4H, ortho-Ph-H)</td>
<td>128.72 (2 × ortho-Ph-CH)</td>
<td>7.23 – 7.31 (m, 4H, ortho-Ph-H)</td>
<td>129.47 (2 × ortho-Ph-CH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&amp; meta-Ph-H</td>
<td>128.92 (2 × meta-Ph-CH)</td>
<td></td>
<td>129.60 (2 × meta-Ph-CH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>143.04 (ipso-Ph-C$_6$)</td>
<td></td>
<td></td>
<td>143.43 (ipso-Ph-C$_6$)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*overlapped signals; δ [ppm]; $^1$H NMR measured at 500 MHz; $^{13}$C NMR measured at 125 MHz, respectively.
Table 12.2. $^1$H- and $^{13}$C NMR Spectral Data for (-)-10'-Deoxobroussonetone C (9/1).

<table>
<thead>
<tr>
<th></th>
<th>$^1$H NMR (C$_2$D$_2$N) (free base)</th>
<th>$^{13}$C NMR (C$_2$D$_2$N) (free base)</th>
<th>$^1$H NMR (C$_2$D$_2$N) (pyrrolidinum chloride)</th>
<th>$^{13}$C NMR (C$_2$D$_2$N) (pyrrolidinum chloride)</th>
<th>$^1$H NMR (CD$_2$OD) (pyrrolidinum trifluoroacetate)</th>
<th>$^{13}$C NMR (CD$_2$OD) (pyrrolidinum trifluoroacetate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.17\textsuperscript{a} (dd, 1H, $J$ = 6.0, 10.3 Hz, H$_8$-1)\textsuperscript{b} 4.22\textsuperscript{a} (dd, 1H, $J$ = 3.8, 10.5 Hz, H$_9$-1)</td>
<td>65.24 (CH, C-2)  4.32 (m, 1H, H-2)</td>
<td>65.26 (CH, C-2)  3.46 (dt, 1H, $J$ = 3.9, 6.2 Hz, H-2)</td>
<td>65.72 (CH, C-2)  3.34 (m, 1H, H-4)</td>
<td>64.51 (CH, C-5)  3.32 (q, 1H, $J$ = 7.1 Hz, H-5)</td>
<td>64.52 (CH, C-5)  3.28 (m, 1H, H-6)</td>
</tr>
<tr>
<td>2</td>
<td>3.77 ($^d$, 1H, $J$ = 4.3 Hz, H-2)</td>
<td>80.55 (CH, C-3)  4.95 (t, 1H, $J$ = 6.7 Hz, H-3)</td>
<td>76.70 (CH, C-3)  3.97 (t, 1H, $J$ = 5.9 Hz, H-3)</td>
<td>76.70 (CH, C-3)  3.97 (t, 1H, $J$ = 5.9 Hz, H-3)</td>
<td>76.70 (CH, C-3)  3.97 (t, 1H, $J$ = 5.9 Hz, H-3)</td>
<td>76.70 (CH, C-3)  3.97 (t, 1H, $J$ = 5.9 Hz, H-3)</td>
</tr>
<tr>
<td>3</td>
<td>4.38 (t, 1H, $J$ = 6.2 Hz, H-4)</td>
<td>84.57 (CH, C-4)  4.70 (t, 1H, $J$ = 7.1 Hz, H-4)</td>
<td>80.57 (CH, C-4)  3.34 (m, 1H, H-4)</td>
<td>80.57 (CH, C-4)  3.34 (m, 1H, H-4)</td>
<td>80.57 (CH, C-4)  3.34 (m, 1H, H-4)</td>
<td>80.57 (CH, C-4)  3.34 (m, 1H, H-4)</td>
</tr>
<tr>
<td>4</td>
<td>3.49 ($^d$, 1H, $J$ = 4.4 Hz, H-5)</td>
<td>62.98 (CH, C-5)  4.11 (q, 1H, $J$ = 7.4 Hz, H-5)</td>
<td>64.52 (CH, C-5)  3.28 (q, 1H, $J$ = 7.1 Hz, H-5)</td>
<td>64.52 (CH, C-5)  3.28 (q, 1H, $J$ = 7.1 Hz, H-5)</td>
<td>64.52 (CH, C-5)  3.28 (q, 1H, $J$ = 7.1 Hz, H-5)</td>
<td>64.52 (CH, C-5)  3.28 (q, 1H, $J$ = 7.1 Hz, H-5)</td>
</tr>
<tr>
<td>5</td>
<td>1.50 – 1.80 (m, 2H, H$_8$-6, H$_9$-7)</td>
<td>35.88 (CH$_2$, C-6)  2.35 (m, 2H, H$_8$-6)</td>
<td>31.83 (CH$_2$, C-6)  1.74 (m, 1H, H$_8$-6)</td>
<td>32.06 (CH$_2$, C-6)  1.68 (m, 1H, H$_9$-6)</td>
<td>32.06 (CH$_2$, C-6)  1.68 (m, 1H, H$_9$-6)</td>
<td>32.06 (CH$_2$, C-6)  1.68 (m, 1H, H$_9$-6)</td>
</tr>
<tr>
<td>6</td>
<td>1.47 – 1.59 (m, 3H, H$_8$-7, H$_9$-16)</td>
<td>27.35 (CH$_2$, C-7)  1.75 (m, 1H, H$_8$-7)</td>
<td>26.91 (CH$_2$, C-7)  1.42 – 1.57 (m, 4H, H$_7$-7, H$_8$-17)</td>
<td>27.20 (CH$_2$, C-7)  1.42 – 1.57 (m, 4H, H$_7$-7, H$_8$-17)</td>
<td>27.20 (CH$_2$, C-7)  1.42 – 1.57 (m, 4H, H$_7$-7, H$_8$-17)</td>
<td>27.20 (CH$_2$, C-7)  1.42 – 1.57 (m, 4H, H$_7$-7, H$_8$-17)</td>
</tr>
<tr>
<td>7</td>
<td>1.19 – 1.44 (m, 1H, H$_8$-8 – H$_9$-15)</td>
<td>29.94, 30.02, 30.03, 30.29 (8 × CH$_2$, C-8 – C-15)</td>
<td>29.63, 29.68, 29.80, 29.87, 29.90, 30.01 (8 × CH$_2$, C-8 – C-15)</td>
<td>30.04, 30.46, 30.61, 30.65, 30.73, 30.75, 30.76 (8 × CH$_2$, C-8 – C-15)</td>
<td>30.04, 30.46, 30.61, 30.65, 30.73, 30.75, 30.76 (8 × CH$_2$, C-8 – C-15)</td>
<td>30.04, 30.46, 30.61, 30.65, 30.73, 30.75, 30.76 (8 × CH$_2$, C-8 – C-15)</td>
</tr>
<tr>
<td>8</td>
<td>1.47 – 1.59 (m, 3H, H$_8$-16, H$_9$-7)</td>
<td>26.56 (CH$_2$, C-16)</td>
<td>26.54 (CH$_2$, C-16)</td>
<td>26.96 (CH$_2$, C-16)</td>
<td>26.96 (CH$_2$, C-16)</td>
<td>26.96 (CH$_2$, C-16)</td>
</tr>
<tr>
<td>9</td>
<td>1.76 (m, 2H, H$_8$-17)</td>
<td>33.83 (CH$_2$, C-17)</td>
<td>33.81 (CH$_2$, C-17)</td>
<td>33.87 (CH$_2$, C-17)</td>
<td>33.87 (CH$_2$, C-17)</td>
<td>33.87 (CH$_2$, C-17)</td>
</tr>
<tr>
<td>10</td>
<td>3.59 (t, 2H, $J$ = 6.4 Hz, H$_7$-18)</td>
<td>62.16 (CH$_2$, C-18)</td>
<td>62.15 (CH$_2$, C-18)</td>
<td>63.02 (CH$_2$, C-18)</td>
<td>63.02 (CH$_2$, C-18)</td>
<td>63.02 (CH$_2$, C-18)</td>
</tr>
</tbody>
</table>

\( ^a \) overlapped signals; \( \delta \) [ppm]; \( ^1\)H NMR measured at 500 MHz; \( ^{13}\)C NMR measured at 125 MHz, respectively.
Table 12.3. $^1$H- and $^{13}$C NMR Spectral Data for (−)-$^{10}$-Deoxobroussonetine E (9/2).

<table>
<thead>
<tr>
<th>$^1$H NMR (C$_2$D$_2$N)</th>
<th>$^{13}$C NMR (C$_2$D$_2$N)</th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(pyrrolidinium chloride) (pyrrolidinium chloride) (pyrrolidinium chloride) (pyrrolidinium chloride) (free base) (free base)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 4.49 (m, 2H, H$_2$-1)</td>
<td>58.68 (CH$_2$, C-1)</td>
<td>3.79 (dd, 1H, J = 5.3, 12.1 Hz, H$_5$-1)</td>
<td>58.60 (CH$_2$, C-1)</td>
<td>3.55 – 3.63* (m, 2H, H$_5$-1, H-6)</td>
<td>63.44 (CH$_2$, C-1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.84* (dd, 1H, J = 3.6, 12.1 Hz, H$_6$-1)</td>
<td></td>
<td>3.67 (dd, 1H, J = 4.1, 11.1 Hz, H-1)</td>
<td></td>
</tr>
<tr>
<td>2 4.24 (ddd, 1H, J = 3.5, 4.5, 8.0 Hz, H-2)</td>
<td>64.63 (CH, C-2)</td>
<td>3.37 – 3.42 (m, 2H, H-2, H-5)</td>
<td>64.84 (CH, C-2)</td>
<td>3.01 (<em>dd</em>, 1H, J = 6.0, 10.6 Hz, H-2)</td>
<td>65.02 (CH, C-2)</td>
</tr>
<tr>
<td>3 5.07 (t, 1H, J = 8.0 Hz, H-3)</td>
<td>76.39 (CH, C-3)</td>
<td>3.97 (dd, 1H, J = 6.8, 8.4 Hz, H-3)</td>
<td>76.68 (CH, C-3)</td>
<td>3.78 (t, 1H, J = 6.3 Hz, H-3)</td>
<td>80.18 (CH, C-3)</td>
</tr>
<tr>
<td>4 5.28 (t, 1H, J = 7.5 Hz, H-4)</td>
<td>75.12 (CH, C-4)</td>
<td>4.23 (t, 1H, J = 7.0 Hz, H-4)</td>
<td>75.09 (CH, C-4)</td>
<td>4.00 (t, 1H, J = 6.3 Hz, H-4)</td>
<td>79.40 (CH, C-4)</td>
</tr>
<tr>
<td>5 4.29 (dd, 1H, J = 2.1, 7.8 Hz, H-5)</td>
<td>65.72 (CH, C-5)</td>
<td>3.37 – 3.42 (m, 2H, H-5, H-2)</td>
<td>66.03 (CH, C-5)</td>
<td>2.89 ('t', 1H, J = 5.5 Hz, H-5)</td>
<td>67.01 (CH, C-5)</td>
</tr>
<tr>
<td>6 4.71 (m, 1H, H-6)</td>
<td>69.67 (CH, C-6)</td>
<td>3.88* (td, 1H, J = 3.2, 6.9 Hz, H-6)</td>
<td>70.04 (CH, C-6)</td>
<td>3.55 – 3.63* (m, 2H, H-6, H$_5$-1)</td>
<td>73.87 (CH, C-6)</td>
</tr>
<tr>
<td>7 2.01 (m, 1H, H$_5$-7)</td>
<td>34.17 (CH$_2$, C-7)</td>
<td>1.62 (q, 2H, J = 7.2 Hz, H$_2$-7)</td>
<td>34.62 (CH$_2$, C-7)</td>
<td>1.44 – 1.64 (m, 5H, H$_7$-7, H$_9$-8, H$_7$-17)</td>
<td>35.11 (CH$_2$, C-7)</td>
</tr>
<tr>
<td>2.15 (m, 1H, H$_9$-7)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 1.12 – 1.36 (m, 14H, H$_3$-9 – H$_3$-15)</td>
<td>26.61 (CH$_2$, C-8)</td>
<td>1.27 – 1.42 (m, 18H, H$_1$-8 – H$_2$-16)</td>
<td>26.83 (CH$_2$, C-8)</td>
<td>1.27 – 1.41 (m, 17H, H$_5$-8, H$_2$-9 – H$_2$-16)</td>
<td>27.13 (CH$_2$, C-8)</td>
</tr>
<tr>
<td>16 1.45 – 1.55 (m, 3H, J = 7.4 Hz, H$_1$-8, H$_2$-16)</td>
<td>29.83, 29.88, 29.91, 29.99 (7 × CH$_3$, C-9 – C-15)</td>
<td>30.62, 30.66, 30.71, 30.73, 30.76 (7 × CH$_3$, C-9 – C-15)</td>
<td>30.80 (7 × CH$_3$, C-9 – C-15)</td>
<td>26.95 (CH$_3$, C-16)</td>
<td></td>
</tr>
<tr>
<td>1.71* (m, 1H, H$_8$-8)</td>
<td>26.52 (CH$_2$, C-16)</td>
<td></td>
<td>26.97 (CH$_2$, C-16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 1.76* (quin, 2H, J = 7.1 Hz, H$_2$-17)</td>
<td>33.78 (CH$_2$, C-17)</td>
<td>1.52 (quin, 2H, J = 6.8 Hz, H$_2$-17)</td>
<td>33.68 (CH$_2$, C-17)</td>
<td>1.44 – 1.64 (m, 5H, H$_7$-17, H$_7$-7, H$_9$-8)</td>
<td>33.67 (CH$_2$, C-17)</td>
</tr>
<tr>
<td>18 3.89 (t, 2H, J = 6.6 Hz, H$_7$-18)</td>
<td>62.14 (CH$_2$, C-18)</td>
<td>3.53 (t, 2H, J = 6.7 Hz, H$_2$-18)</td>
<td>63.04 (CH$_2$, C-18)</td>
<td>3.54* (t, 2H, J = 6.7 Hz, H$_1$-18)</td>
<td>63.02 (CH$_2$, C-18)</td>
</tr>
</tbody>
</table>

* overlapped signals; δ [ppm]; $^1$H NMR measured at 500 MHz, $^{13}$C NMR measured at 125 MHz, respectively.
### Table 12.4. $^1$H- and $^{13}$C NMR Spectral Data for (-)-(65)-(12'-Hydroxydodecyl)moranoline (9/30).

<table>
<thead>
<tr>
<th></th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
<th>$^1$H NMR (CD$_3$OD)</th>
<th>$^{13}$C NMR (CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.64–4.72 (m, 2H, H$_{a-1}$, H-5)</td>
<td>58.93 (CH$_3$, C-1)</td>
<td>3.83 (dd, 1H, J = 3.6, 11.9 Hz, H$_{a-1}$)</td>
<td>58.51 (CH$_3$, C-1)</td>
<td>3.51 (m, 1H, H$_{a-1}$)</td>
<td>63.49 (br, CH$_3$, C-1)</td>
</tr>
<tr>
<td></td>
<td>4.75 (dd, 1H, J = 5.7, 11.9 Hz, H$_{a-1}$)</td>
<td>4.00 (dd, 1H, J = 7.2, 11.9 Hz, H$_{a-1}$)</td>
<td>3.87 (dd, 1H, J = 3.1, 10.8 Hz, H$_{a-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.06 (br, 1H, H-2)</td>
<td>58.49 (br, CH, C-2)</td>
<td>3.33 (m, 1H, H-2)</td>
<td>59.58 (br, CH, C-2)</td>
<td>2.76 (m, 1H, H-2)</td>
<td>57.34 (br)</td>
</tr>
<tr>
<td>3</td>
<td>4.53 (t, 1H, J = 7.5 Hz, H-3)</td>
<td>70.08 (CH, C-3)</td>
<td>3.63 (t, 1H, J = 6.4 Hz, H-3)</td>
<td>69.43 (CH, C-3)</td>
<td>3.13 (t, 1H, J = 8.8 Hz, H-3)</td>
<td>73.95 (br)</td>
</tr>
<tr>
<td>4</td>
<td>4.62 (t, 1H, J = 8.1 Hz, H-4)</td>
<td>74.37 (CH, C-4)</td>
<td>3.72 (t, 1H, J = 6.4 Hz, H-4)</td>
<td>72.61 (br, CH, C-4)</td>
<td>3.45 (t, 1H, J = 8.8 Hz, H-4)</td>
<td>75.84 (br)</td>
</tr>
<tr>
<td>5</td>
<td>4.64–4.72 (m, 2H, H-5, H$_{a-1}$)</td>
<td>70.98 (CH, C-5)</td>
<td>3.78 (dd, 1H, J = 3.5, 6.4 Hz, H-5)</td>
<td>70.29 (CH, C-5)</td>
<td>3.59 (dd, 1H, J = 5.3, 9.1 Hz, H-5)</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>4.31 (dd, 1H, J = 6.3, 10.8 Hz, H-6)</td>
<td>56.05 (br, CH, C-6)</td>
<td>3.46 (td, 1H, J = 3.5, 6.9 Hz, H-6)</td>
<td>54.90 (br, CH, C-6)</td>
<td>3.04 (m, 1H, H-6)</td>
<td>56.48 (br)</td>
</tr>
<tr>
<td>7</td>
<td>2.17 (m, 1H, H$_{a-1}$)</td>
<td>26.89 (br, CH$_3$, C-7)</td>
<td>1.63 (m, 1H, H$_{a-1}$)</td>
<td>27.62 (br, CH$_3$, C-7)</td>
<td>1.42–1.56 (m, 3H, H$<em>{a-1}$, H$</em>{a-1}$)</td>
<td>25.94 (br)</td>
</tr>
<tr>
<td></td>
<td>2.46 (m, 1H, H$_{a-1}$)</td>
<td>1.93 (m, 1H, H$_{a-1}$)</td>
<td></td>
<td>1.66 (m, 1H, H$_{a-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.70–1.80 (m, 4H, H$_2$-8, H$_2$-17)</td>
<td>27.24 (CH$_3$, C-8)</td>
<td>1.45 (m, 2H, H$_2$-8)</td>
<td>27.05 (CH$_3$, C-8)</td>
<td>1.22–1.42 (m, 18H, H$_2$-8–H$_2$-16)</td>
<td>27.39 (CH$_3$, C-8)</td>
</tr>
<tr>
<td>16</td>
<td>1.29–1.37 (m, 4H, H$_2$-9, H$_2$-15)</td>
<td>26.79, 29.80, 29.87</td>
<td>1.26–1.41 (m, 16H, H$_2$-9–H$_2$-16)</td>
<td>30.50, 30.55, 30.64,</td>
<td>30.65, 30.74, 30.76,</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1.13–1.29 (m, 10H, H$_2$-10–H$_2$-14)</td>
<td>29.89, 30.00 (7 × CH$_3$, C-9–C-15)</td>
<td>30.67, 30.73, 30.75,</td>
<td>30.78 (7 × CH$_3$, C-9–C-15)</td>
<td>30.78, 30.80, 30.82</td>
<td></td>
</tr>
<tr>
<td>15 (quin, 2H, J = 7.5 Hz, H$_2$-16)</td>
<td>26.54 (CH$_3$, C-16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.99 (CH$_3$, C-16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1.70–1.80 (m, 4H, H$_2$-17, H$_2$-8)</td>
<td>33.80 (CH$_3$, C-17)</td>
<td>1.52 (quin, 2H, J = 6.8 Hz, H$_2$-17)</td>
<td>33.70 (CH$_3$, C-17)</td>
<td>1.42–1.56 (m, 3H, H$_2$-17, H$_2$-7)</td>
<td>33.72 (CH$_3$, C-17)</td>
</tr>
<tr>
<td>18</td>
<td>3.89 (t, 2H, J = 6.6 Hz, H$_2$-18)</td>
<td>62.16 (CH$_3$, C-18)</td>
<td>3.54 (t, 2H, J = 6.7 Hz, H$_2$-18)</td>
<td>63.07 (CH$_3$, C-18)</td>
<td>3.53 (t, 2H, J = 6.7 Hz, H$_2$-18)</td>
<td>63.06 (CH$_3$, C-18)</td>
</tr>
</tbody>
</table>

*a overlapped signals; δ [ppm]; $^1$H NMR measured at 500 MHz; $^{13}$C NMR measured at 125 MHz, respectively.*
Table 12.5. \(^1\)H- and \(^13\)C NMR Spectral Data for (−)-Broussonetine C\(_2\) (10/23).

<table>
<thead>
<tr>
<th></th>
<th>(^1)H NMR (C(_6)D(_5)) (free base)</th>
<th>(^13)C NMR (C(_6)D(_5)) (free base)</th>
<th>(^1)H NMR (CD(_3)OD) (free base)</th>
<th>(^13)C NMR (CD(_3)OD) (pyrrolidinium trifluoroacetate)</th>
<th>(^1)H NMR (CD(_3)OD) (pyrrolidinium trifluoroacetate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.16(^a) (dd, 1H, (J = 5.9, 10.6) Hz, H(_\alpha)-1)</td>
<td>6.39 (CH(_2), C-1)</td>
<td>3.55 – 3.60 (m, 2H, H(_\alpha)-1, H-4)</td>
<td>63.46 (CH(_3), C-1)</td>
<td>3.76 – 3.88 (m, 5H, H(<em>2)-1, H-4, H-15, H(</em>\alpha)-18)</td>
</tr>
<tr>
<td></td>
<td>4.22(^a) (dd, 1H, (J = 3.8, 10.6) Hz, H(_\beta)-1)</td>
<td>3.65 (dd, 1H, (J = 4.2, 11.2) Hz, H(_\beta)-1)</td>
<td></td>
<td></td>
<td>59.60 (CH(_3), C-1)</td>
</tr>
<tr>
<td>2</td>
<td>3.72 – 3.82(^a) (m, 2H, H-2, H-15)</td>
<td>65.20 (CH, C-2)</td>
<td>2.95 (dt, 1H, (J = 4.3, 6.3) Hz, H-2)</td>
<td>64.48 (CH, C-2)</td>
<td>3.45 (dt, 1H, (J = 4.0, 6.2) Hz, H-2)</td>
</tr>
<tr>
<td>3</td>
<td>4.65 (t, 1H, (J = 6.4) Hz, H-3)</td>
<td>80.52 (CH, C-3)</td>
<td>3.74(^a) (t, 1H, (J = 6.5) Hz, H-3)</td>
<td>79.80 (CH, C-3)</td>
<td>3.96 (t, 1H, (J = 5.8) Hz, H-3)</td>
</tr>
<tr>
<td>4</td>
<td>4.37 (t, 1H, (J = 6.4) Hz, H-4)</td>
<td>84.52 (CH, C-4)</td>
<td>3.55 – 3.60 (m, 2H, H-4, H(_\alpha)-1)</td>
<td>83.81 (CH, C-4)</td>
<td>3.76 – 3.88 (m, 5H, H-4, H(<em>2)-1, H-15, H(</em>\alpha)-18)</td>
</tr>
<tr>
<td>5</td>
<td>3.48 (br, 1H, H-5)</td>
<td>62.96 (CH, C-5)</td>
<td>2.83 (dt, 1H, (J = 5.1, 7.5) Hz, H-5)</td>
<td>62.71 (CH, C-5)</td>
<td>3.32(^a) (q, 1H, (J = 6.9) Hz, H-5)</td>
</tr>
<tr>
<td>6</td>
<td>1.65 – 1.80(^a) (m, 3H, H(_\alpha)-6, H(<em>2)-17, H(</em>\alpha)-9)</td>
<td>35.82 (CH(_2), C-6)</td>
<td>1.66 (m, 1H, H(_\alpha)-6)</td>
<td>35.45 (CH(_2), C-6)</td>
<td>1.72 (m, 1H, H(_\alpha)-6)</td>
</tr>
<tr>
<td></td>
<td>2.01 (m, 1H, H(_\alpha)-6)</td>
<td></td>
<td></td>
<td></td>
<td>1.82 – 1.96 (m, 3H, H(_\alpha)-6, H(_2)-17)</td>
</tr>
<tr>
<td>7</td>
<td>1.52(^a) (m, 1H, H(_\alpha)-7)</td>
<td>27.32 (CH(_2), C-7)</td>
<td>1.36 – 1.49(^a) (m, 7H, H(<em>2)-7, H(</em>\alpha)-6, H(<em>\alpha)-13, H(</em>\alpha)-14, H(_\alpha)-16)</td>
<td>27.79 (CH(_2), C-7)</td>
<td>1.35 – 1.52(^a) (m, 5H, H(<em>2)-7, H(</em>\alpha)-13, H(<em>\alpha)-14, H(</em>\alpha)-16)</td>
</tr>
<tr>
<td></td>
<td>1.57 – 1.67(^a) (m, 2H, H(<em>\alpha)-7, H(</em>\alpha)-14)</td>
<td></td>
<td></td>
<td></td>
<td>27.18 (CH(_2), C-7)</td>
</tr>
<tr>
<td>8</td>
<td>1.22(^a) (br s, 8H, H(_2)-8 – H(_2)-11)</td>
<td>29.87, 29.94, 29.98, 30.03, 30.26(^a)</td>
<td>1.32(^a) (s, 10H, H(<em>2)-8 – H(<em>2)-12, H(</em>\alpha)-13, H(</em>\alpha)-16)</td>
<td>30.68, 30.70, 30.74, 30.85, 30.91(^a)</td>
<td>1.33(^a) (s, 11H, H(_2)-8 – H(<em>2)-12, H(</em>\alpha)-13)</td>
</tr>
<tr>
<td>15</td>
<td>1.24 – 1.40(^a) (m, 4H, H(<em>2)-12, H(</em>\alpha)-13, H(_\alpha)-16)</td>
<td>1.36 – 1.49(^a) (m, 7H, H(<em>2)-13, H(</em>\alpha)-6, H(<em>\alpha)-7, H(</em>\alpha)-14, H(_\alpha)-16)</td>
<td></td>
<td></td>
<td>1.33(^a) (s, 11H, H(_2)-8 – H(<em>2)-12, H(</em>\alpha)-13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.76 (CH(_2), C-13)</td>
<td></td>
<td></td>
<td>30.38, 30.43, 30.56, 30.68, 30.82(^a)</td>
</tr>
<tr>
<td>14</td>
<td>1.40 – 1.50(^a) (m, 2H, H(<em>\alpha)-14, H(</em>\alpha)-16)</td>
<td>36.15 (CH(_2), C-14)</td>
<td>1.54 (m, 1H, H(_\alpha)-14)</td>
<td>36.75 (CH(_2), C-14)</td>
<td>1.54(^a) (m, 1H, H(_\alpha)-14)</td>
</tr>
<tr>
<td></td>
<td>1.57 – 1.67(^a) (m, 2H, H(<em>\alpha)-14, H(</em>\alpha)-17)</td>
<td></td>
<td></td>
<td></td>
<td>36.74 (CH(_2), C-14)</td>
</tr>
<tr>
<td>16</td>
<td>1.85 (m, 1H, H(_\alpha)-16)</td>
<td>31.71 (CH(_2), C-16)</td>
<td>2.00 (m, 1H, H(_\alpha)-16)</td>
<td>32.36 (CH(_2), C-16)</td>
<td>2.00 (m, 1H, H(_\alpha)-16)</td>
</tr>
<tr>
<td>17</td>
<td>1.65 – 1.80(^a) (m, 3H, H(<em>2)-17, H(</em>\alpha)-6)</td>
<td>26.02 (CH(_2), C-17)</td>
<td>1.89 (m, 2H, H(_\alpha)-17)</td>
<td>26.63 (CH(_2), C-17)</td>
<td>1.82 – 1.96 (m, 3H, H(<em>2)-17, H(</em>\alpha)-6)</td>
</tr>
<tr>
<td>18</td>
<td>3.67 (q, 1H, (J = 7.5) Hz, H(_\alpha)-18)</td>
<td>67.53 (CH(_2), C-18)</td>
<td>3.70(^a) (dt, 1H, (J = 6.3, 7.9) Hz, H(_\alpha)-18)</td>
<td>68.56 (CH(_2), C-18)</td>
<td>3.70 (dd, 1H, (J = 7.8, 14.3) Hz, H(_\alpha)-18)</td>
</tr>
<tr>
<td></td>
<td>3.84(^a) (q, 1H, (J = 7.5) Hz, H(_\alpha)-18)</td>
<td></td>
<td>3.76 – 3.86 (m, 2H, H(_\alpha)-18, H-15)</td>
<td></td>
<td>3.76 – 3.88 (m, 5H, H(_\alpha)-18, H(_2)-1, H-4, H-15)</td>
</tr>
</tbody>
</table>

\(^a\) overlapped signals; \(\delta\) [ppm]: \(^1\)H NMR measured at 500 MHz; \(^13\)C NMR measured at 125 MHz, respectively.
Conclusions
Experimental Section

E.1 Methods and Materials

E.1.1 Solvents and Chemicals

Commercially available starting materials, reagents and solvents were purchased from SIGMA-ALDRICH, FLUKA, MERCK or AJAX FINECHEM, and were used without further purification unless stated otherwise.

Tetrahydrofuran (THF) was predried over molecular sieves 4A and distilled from sodium wire/benzophenone under an atmosphere of nitrogen.

Dichloromethane (DCM) was dried over activated, neutral Brockmann type I alumina under a positive pressure of nitrogen and was stored over activated molecular sieves 4A.

Dry acetonitrile (MeCN), ethyl ether (Et$_2$O), ethanol (EtOH), methanol (MeOH), benzyl alcohol (BnOH), benzene (PhH) and toluene (PhMe) were purchased from SIGMA-ALDRICH as anhydrous solvents in sure-sealed™ 1 L glass bottles.

Dry acetone (Me$_2$CO) was obtained by distillation from boric anhydride (B$_2$O$_3$) under an atmosphere of nitrogen.

Water (H$_2$O) was purified and deionised on a MILLIPORE RiOs™ 5 Century water purification system.

Triethylamine (Et$_3$N) and pyridine (C$_5$H$_5$N) were distilled from and stored over KOH pellets.

E.1.2 General Reaction Conditions

Air- and/or moisture sensitive reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. For this purpose every utilised glass apparatus was heated under high vacuum with a heat gun and flushed with nitrogen after cooling to room temperature prior to usage.

The progress of reactions was monitored by thin-layer chromatography and/or low resolution mass spectrometry.

All prepared compounds were dried thoroughly under high vacuum. All quoted reaction yields were obtained only after this drying process.
E.1.3 Nuclear Magnetic Resonance Spectroscopy

$^1$H and $^{13}$C NMR spectra were recorded on VARIAN Premium Shielded 500, Unity INOVA 500 and Mercury 300 spectrometers with tetramethylsilane (CDCl$_3$, CD$_3$OD, C$_6$D$_5$N) or 2,2,3,3-tetradeutero-3-(trimethylsilyl)propionic acid sodium salt (D$_2$O) as internal standard, respectively. NMR signal assignments are based on $H,H$-COSY, APT, HSQC and HMBC experiments. $^1$H NMR signal multiplicities are reported by the following convention:

- $s$ = singlet,
- $d$ = doublet,
- $t$ = triplet,
- $q$ = quartet,
- $quin$ = quintet,
- $m$ = multiplet,
- $dd$ = doublet of doublets,
- $ddd$ = doublet of doublet of doublets,
- $dt$ = doublet of triplets,
- $dq$ = doublet of quartets,
- $br$ = broad.

Overlapping signals are marked with the ordinal indicator (º). Benzylic signals are indicated with an asterisk (*). Apparent $^1$H NMR signal multiplicities are set in quotation marks ("_").

E.1.4 Infrared Spectroscopy

IR spectra were recorded with a NICOLET AVATAR 360 and a SHIMADZU MIRacle 10 FT-IR spectrometer by the single reflection ATR method. Characteristic absorption bands are stated in wave numbers [cm$^{-1}$] using the following abbreviations to specify their intensity and shape:

- $vs$ = very strong
- $s$ = strong
- $m$ = medium
- $w$ = weak
- $br$ = broad

E.1.5 Mass Spectrometry

Electron impact mass spectra (EI) were obtained with a SHIMADZU GCMS-QP5050 gas chromatograph mass spectrometer (low resolution) and a FISONS INSTRUMENTS VG Autospec (high resolution). Electrospray ionisation mass spectrometry (ESI) was performed with a WATERS MICROMASS Platform LCZ (low resolution) and a MICROMASS Q-TOF Ultima API spectrometer (high resolution).

High resolution mass spectroscopy was employed in lieu of elemental analysis, $^1$H and $^{13}$C NMR spectroscopy were used to determine the purity of synthesised compounds.

E.1.6 Melting Points

Melting points were obtained using a GALLENKAMP MF-370 capillary melting point apparatus and are uncorrected.
E.1.7 Polarimetry

Optical rotations were determined at a wavelength of 589.3 nm (sodium D line) using a 1 mL quartz cell either with the JASCO DIP-370 digital polarimeter at room temperature (years one and two) or the JASCO P-2000 digital polarimeter equipped with the Peltier thermostatted cell holder PCT-203 enabling measurements at a constant temperature of 25 °C (years three to five). The solvent used and the concentration of each sample are stated for every compound. Ten measurements were usually taken and the average was used to calculate the specific rotation.

E.1.8 Chromatography

Column chromatography was carried out on silica gel 60 from MERCK (40–63 µm) using either mixtures of petrol ether (PE, boiling range 40–60 °C) and ethyl acetate (EA) or chloroform and methanol. Unless stated otherwise crude products were absorbed on silica gel prior to their loading on the column bed.

Analytical thin-layer chromatography was performed on MERCK aluminium TLC plates precoated with silica gel 60 F254 (0.25 mm thickness) using cerium sulfate/ammonium molybdate, basic potassium permanganate, anisaldehyde, vanillin or ninhydrin solutions as staining agents.

E.1.9 High Performance Liquid Chromatography

Analytical HPLC was performed on a WATERS HPLC system consisting of a 717plus Autosampler, 600 Controller unit, In-line Degasser AF, and 2996 Photodiode Array Detector using a PHENOMENEX GEMINI C18 reversed phase LC column 100 × 2 mm (length × internal diameter), 5 µm (particle size), 110 Å (pore size).

Separation and purification of compounds by preparative HPLC was achieved employing a Waters PrepLC 150 mL System equipped with a 2489 UV/vis Detector using a PHENOMENEX GEMINI C18 reversed phase LC column AXIA packed, 150 × 21.2 mm (length × internal diameter), 5 µm (particle size), 110 Å (pore size). Solvents were filtered through WHATMAN 0.45 µm nylon membranes and purged 30 minutes with helium prior to usage.
E.2 Nomenclature

In general, new substances were named according to the IUPAC nomenclature rules. However, these rules were not strictly applied to every compound to circumvent confusions that would have arisen from changing numeration within one synthesis line. Instead, the following convention has been used for naming and numbering of new substances, in particular of all pyrrolidine derivatives:

1. In continuance of the numbering introduced with the Petasis product, i.e.

\[(2R,3R,4S,5S,6E)-5\text{-benzylamino}-1,3\text{-bis(benzyloxy)}-7\text{-phenyl-6-heptene-2,4-diol}\]

![Diagram of compound 1]

the hydroxymethyl substituent at the 2-position of every pyrrolidine derivative was assigned as carbon 1 (C-1) and the pseudoanomeric position of the pyrrolidine ring as carbon 5 (C-5), e.g.

\[(2S,3S,4S)-N\text{-benzyl-3-benzyloxy-2-benzyloxymethylpyrrolidine-4-ol}\]

![Diagram of compound 2]

2. This numbering pattern is continued for substituents attached at the pseudoanomeric position, e.g.

\[(2S,3S,4S,5S)-N\text{-benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-hydroxymethylpyrrolidine}\]

![Diagram of compound 3]
3. Long alkyl substituents at the pseudoanomeric position are numbered accordingly. However, in the name of these compounds, the side chains are annotated with the prime symbol ('). Thus, C-6 is equivalent with C-1', C-7 with C-2', etc., e.g.

\[
(2S,3S,4S,5S)\text{-N-}\text{benzyl-3,4-bis(benzyloxy)-5-((1'Z)-13'-benzyloxy-10'-oxotridec-1'eny}-\text{l)-2-(benzyloxymethyl)pyrrolidine}
\]
E.3  Synthesis of L-DMDP and L-AB1

(-)-1,2-O-Isopropylidene-α-D-xylofuranose (7/1)

To dry acetone (300 mL) were added in order, concentrated H$_2$SO$_4$ (1.5 mL), anhydrous CuSO$_4$ (30.0 g) and D-xylose (15.1 g, 100 mmol). The mixture was vigorously stirred under an atmosphere of N$_2$ for 28 h at 20 ºC by which time the CuSO$_4$ was removed by filtration through a pad of celite. The filter cake was washed thoroughly with additional acetone, and the combined filtrate and washings were basified by rapid addition of concentrated NH$_3$ solution (4.8 mL) resulting in a change of colour from intensive yellow to pale yellow. Precipitated (NH$_4$)$_2$SO$_4$ was filtered off, and the solvent was evaporated under reduced pressure to afford a yellow syrupy residue. This residue was then treated with 0.2% HCl solution (165 mL, 0.24 M) and stirred for 3.5 h at 20 ºC followed by neutralisation with solid NaHCO$_3$ (3.36 g) to pH 7-8. The neutralised solution was subsequently concentrated in vacuo, and the residual slurry was one time co-evaporated with a mixture of toluene (50 mL) and EtOH (60 mL). The residue was then dissolved in chloroform (100 mL), dried over excess MgSO$_4$, filtered from inorganic salts and evaporated to dryness to give acetonide 7/1 (19.0 g, 100 mmol) in quantitative yield as a yellow viscous oil which was used in the next step without further purification.

Yield : 100%

Chemical formula : C$_8$H$_{14}$O$_5$

Molecular weight : 190.19

Appearance : Yellow viscous oil

TLC : $R_f = 0.42$ (100% EtOAc), CAM, Vanillin

Opt. rotation : $[\alpha]_{D}^{25} = -19.1^\circ$ (c = 2.0 g/100 mL H$_2$O)

Literature ref. : $[\alpha]_{D}^{25} = -19.2^\circ$ (c = 1.0 g/100 mL H$_2$O)$^{[1]}$

$^1$H NMR (500 MHz, CDCl$_3$) δ [ppm] : 1.33 (s, 3H, ac-CH$_3$), 1.49 (s, 3H, ac-CH$_3$), 2.84 (dd, 1H, $J_1 = 5.0$ Hz, $J_2 = 7.7$ Hz, OH-5), 4.05 (ddd, 2H, $J_1 = 2.8$ Hz, $J_2 = 7.9$ Hz, $J_3 = 12.5$ Hz, H$_A$-5, OH-3), 4.13 (dt, 1H, $J_1 = 4.4$ Hz, $J_2 = 12.5$ Hz, H$_B$-5), 4.18 (q, 1H, $J = 3.1$ Hz, H-4), 4.33 (t, 1H, $J = 3.1$ Hz, H-3), 4.53 (d, 1H, $J = 3.7$ Hz, H-2), 5.99 (d, 1H, $J = 3.7$ Hz, H-1).

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$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 26.18 (CH$_3$, ac), 26.78 (CH$_3$, ac), 61.23 (CH$_2$, C-5), 77.04 (CH, C-3), 78.62 (CH, C-4), 85.67 (CH, C-2), 104.88 (CH, C-1), 111.83 (C$_{aq}$, ac).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3561 (w), 3340 (w), 3270 (w), 2982 (w), 2968 (w), 2926 (w), 2914 (w), 2886 (w), 1451 (w), 1386 (w), 1374 (m), 1322 (w), 1291 (w), 1257 (w), 1222 (m), 1208 (m), 1164 (m), 1109 (m), 1064 (vs), 1005 (vs), 908 (w), 892 (m), 881 (m), 861 (m), 830 (m), 794 (m).

HRMS (EI) calculated for C$_8$H$_{15}$O$_5$ [M + H$^+$] : 191.0919, found 191.0911.

(–)-3,5-Di-O-benzyl-1,2-O-isopropylidene-$\alpha$-D-xylofuranose (7/2)

Procedure A : To the suspension of sodium hydride (60% dispersion in mineral oil, 14.4 g, 360 mmol, 3.6 equiv) in anhydrous THF (300 mL) was slowly added a solution of acetonide 7/1 (19.0 g, 100 mmol, 1.0 equiv) in anhydrous THF (100 mL) at 0 °C under an atmosphere of nitrogen. The mixture was then heated at reflux for 5 min. After recooling to rt, benzyl bromide (28.5 mL, 41.05 g, 240 mmol, 2.4 equiv) and TBAI (5.54 g, 15 mmol, 0.15 equiv) were added, and the mixture was heated at reflux for further 15 min after which time TLC analysis confirmed full consumption of the starting material. The reaction mixture was then quenched by the addition of water (200 mL) under cooling in an ice bath and subsequently extracted with Et$_2$O (3 × 200 mL). The combined ethereal extracts were dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography to give the bis-benzylated acetonide 7/2 (31.45 g, 84.9 mmol) as a pale yellow viscous oil.

CC : 8.0 cm × 16 cm, $V_{Fr} = 250$ mL, eluent PE/EA 100 : 0 → 80 : 20

Yield : 85%

Procedure B : To the solution of 1,2-O-isopropylidene-$\alpha$-D-xylofuranose (19.0 g, 100 mmol, 1.0 equiv) in anhydrous 1,4-dioxane (200 mL) was added benzyl chloride (63.3 g, 500 mmol, 5 equiv) followed by powdered KOH (56.1 g, 1000 mmol, 10 equiv). The mixture was heated at reflux without stirring under an atmosphere of N$_2$. After 4 h TLC analysis showed complete conversion of the starting material. The supernatant was then decanted and the solid residue
dissolved in H₂O. After extraction of the aqueous phase with Et₂O (4 × 200 mL) the ethereal phases were combined with the supernatant of the reaction mixture, dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by column chromatography afforded the desired bis-benzylated acetonide 7/2 (30.5 g, 82.3 mmol) as a pale yellow viscous oil.

CC : ∅ 8.0 cm × 16 cm, V₉ = 250 mL, eluent PE/EA 100 : 0 → 80 : 20

Yield : 82%

Chemical formula : C₂₂H₂₆O₅

Molecular weight : 370.44

Appearance : Pale yellow viscous oil

TLC : Rf = 0.39 (DE/PE = 1 : 2), CAM

Opt. rotation : [α]D²⁵ = −52.9º (c = 10 g/100 mL CHCl₃)

Literature ref. : [α]D²⁰ = −48.4º (c = 1.0 g/100 mL CHCl₃)²

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 1.31 (s, 3H, ac-CH₃), 1.48 (s, 3H, ac-CH₃), 3.74 (dd, 1H, J₁ = 6.2 Hz, J₂ = 9.8 Hz, Hₐ-5), 3.78 (dd, 1H, J₁ = 6.2 Hz, J₂ = 9.8 Hz, Hₐ-5), 3.97 (d, 1H, J = 12.0 Hz, Hₐ-3*), 4.52 (d, 1H, J = 12.0 Hz, Hₐ-5*), 4.59 (d, 1H, J = 3.6 Hz, H-2), 4.60 (d, 1H, J = 12.0 Hz, Hₐ-5*), 4.65 (d, 1H, J = 12.1 Hz, Hₐ-3*), 5.93 (d, 1H, J = 3.7 Hz, H-1), 7.24 – 7.34 (m, 10H, 10 × Ph-H).

¹³C NMR (125 MHz, CDCl₃) δ [ppm] : 26.30 (CH₃, ac), 26.79 (CH₃, ac), 67.56 (CH₂, C-5), 72.00 (CH₂, C-3*), 73.53 (CH₂, C-5*), 79.23 (CH, C-4), 81.73 (CH, C-3), 82.37 (CH, C-2), 105.05 (CH, C-1), 111.66 (C₆H₅, ac), 127.57, 127.64, 127.78, 128.57, 128.35, 128.43 (10 × Ph-CH), 137.53, 138.03 (2 × Ph-C₆H₅).

IR (neat) ν [cm⁻¹] : 2987 (w) [C–H], 2932 (w) [C–H], 2864 (w) [C–H], 1497 (w), 1455 (w), 1373 (m), 1253 (w), 1214 (m), 1165 (m), 1075 (vs) [C–O], 1018 (s), 889 (w), 860 (w), 735 (m).

HRMS (EI) calculated for C₂₂H₂₆O₅ [M⁺] : 370.1780, found 370.1785.
Experimental Section

(+)-3,5-Di-\textit{O}-benzyl-\textit{\alpha},\textit{\beta}-\textit{D}-xylofuranose (7/3)

\begin{center}
\begin{tikzpicture}
\node (alpha) at (0,0) {\includegraphics[width=0.2\textwidth]{alpha.png}};
\node (beta) at (2,0) {\includegraphics[width=0.2\textwidth]{beta.png}};
\end{tikzpicture}
\end{center}

\textbf{Procedure A} : To a solution of bis-benzylated acetonide 7/2 (3.0 g, 8.1 mmol) in AcOH (30 mL) was added 10 M HCl (60 mL) at rt. After stirring for 5 min a solution of NaOH (24.0 g, 600 mmol) in water (60 mL) was added dropwise under cooling in an ice bath followed by extraction with ethyl acetate (3 × 100 mL). The combined organic extracts were washed successively with saturated NaHCO\textsubscript{3} solution and brine, dried over MgSO\textsubscript{4}, filtered and concentrated \textit{in vacuo}. Purification of the crude residue by column chromatography yielded pure bis-benzylated \textit{D}-xylofuranose 7/3 (1.98 g, 5.99 mmol) as a pale yellow syrup that solidified at rt overnight to an off-white wax-like solid.

\textbf{CC} : \varnothing 3.3 cm × 11 cm, \textit{V}_{\text{Fr}} = 45 mL, eluent EA/PE 50 : 50 → 100 : 0

\textbf{Yield} : 74%

\textbf{Procedure B} : To a solution of the bis-benzylated acetonide 7/2 (30.562 g, 82.5 mmol) in THF (300 mL) was added 4 M HCl (75 mL) at rt. The mixture was heated at reflux for 3 h by which time TLC analysis revealed full conversion of the starting material. After cooling to rt the mixture was neutralised by the addition of NaHCO\textsubscript{3} (22.8 g) in small portions. The organic solvent was subsequently evaporated under reduced pressure, and the remaining aqueous residue was concentrated to approx. 50 mL. This aqueous residue was then extracted thoroughly with DCM (5 ×100 mL), and the organic phases were dried over MgSO\textsubscript{4}, filtered from inorganic salts and concentrated \textit{in vacuo}. The crude product was purified by column chromatography to afford the desired bis-benzylated \textit{D}-xylofuranose 7/3 (18.85 g, 57 mmol) as a bright yellow wax-like solid.

\textbf{CC} : \varnothing 8.0 cm × 16.5 cm, \textit{V}_{\text{Fr}} = 250 mL, eluent EA/PE 40 : 60 → 90 : 10

\textbf{Yield} : 69%

\textbf{Procedure C} : To a solution of the bis-benzylated acetonide 7/2 (31.5 g, 85.0 mmol) in 1,4-dioxane (300 mL) was added 1 N H\textsubscript{2}SO\textsubscript{4} (50 mL) at rt. The stirred mixture was heated at
reflux until TLC analysis indicated the complete conversion of the starting material (3.5 – 4 h). After cooling to rt the mixture was neutralised by the addition of 1 M NaHCO₃ solution (55 mL). The organic solvent was evaporated under reduced pressure and the volume of the aqueous remainder reduced to approx. 50 mL. This aqueous residue was then extracted thoroughly with DCM (5 × 100 mL). The organic phases were subsequently dried over MgSO₄, filtered and concentrated in vacuo. Purification of the dark yellow crude product by column chromatography gave the bis-benzylated D-xylofuranose 7/3 (23.9 g, 72.3 mmol) as a mixture of anomers (~ 3 : 1) as a pale yellow wax-like solid.

CC : ∅ 8 cm × 16 cm, VFr = 200 mL, eluent EA/PE 50 : 50 → 90 : 10

Yield : 85% 85.1%

Chemical formula : C₁₉H₂₂O₅

Molecular weight : 330.37

TLC : Rf = 0.38 (EA/PE = 2 : 1), CAM

Melting point : ϑm = 66 – 68 °C (recryst. from toluene/n-hexane), lit.[³] mp : ϑm = 70 – 71 °C

Optical rotation : [α]D₂⁰⁺ = +14.7º (c = 1.15 g/100 mL CHCl₃) after 24 h equilibration at rt.

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 2.45 (br s, 1H, OH-2β), 2.94 (d, 1H, J = 5.9 Hz, OH-2α), 3.67 (m, 2H, H₂-5α), 3.73 (dd, 1H, J₁ = 5.0 Hz, J₂ = 10.0 Hz, H₅α), 3.77 (dd, 1H, J₁ = 5.0 Hz, J₂ = 10.0 Hz, H₅β), 3.94 (d, 1H, J = 11.5 Hz, OH-1β), 3.98 (dd, 1H, J₁ = 2.9 Hz, J₂ = 5.0 Hz, H-3α), 4.00 (dd, 1H, J₁ = 2.7 Hz, J₂ = 5.1 Hz, H-3β), 4.17 (br, 1H, H-2α), 4.23 (d, 1H, J = 3.8 Hz, OH-1α), 4.25 (br, 1H, H-2β), 4.42 (q, 1H, J = 5.1 Hz, H-4β), 4.47 (dd, 1H, J₁ = 5.0 Hz, J₂ = 11.2 Hz, H-4α), 4.49 (d, 1H, J = 11.8 Hz, H₅-5α), 4.50 (d, 1H, J = 12.0 Hz, H₅-5β), 4.57 (d, 1H, J = 12.1 Hz, H₅-5α), 4.60 (d, 1H, J = 11.8 Hz, H₅-5β), 4.55 (d, 1H, J = 12.3 Hz, H₅-3β), 4.65 (d, 1H, J = 11.7 Hz, H₅-3β), 4.66 (d, 1H, J = 12.0 Hz, H₅-3α), 5.10 (d, 1H, J = 11.0 Hz, H-1β), 5.47 (d, J = 3.7 Hz, 1H, H-1α), 7.24 – 7.34 (m, 20H, 20 × Ph-H, α & β).

¹³C NMR (125 MHz, CDCl₃) δ [ppm] : 68.96 (CH₂, C-5β), 69.06 (CH₂, C-5α), 71.87 (CH₂, C-3'α), 72.66 (CH₂, C-3'β), 73.48 (CH₂, C-5'α), 73.62 (CH₂, C-5'β), 75.48 (CH, C-2α), 77.37 (CH, C-4α), 79.12 (CH, C-2β), 79.88 (CH, C-4β), 82.81 (CH, C-3β), 83.52 (CH, C-3α), 96.02 (CH, C-1α), 103.38 (CH, C-1β), 127.53, 127.70, 127.73, 127.74, 127.82, 127.88, 127.89, 128.02, 128.35, 128.38, 128.43, 128.52 (20 × Ph-CH, α & β), 137.31, 137.57 (2 × ipso-Ph-Cq, OBn, β), 137.81 (2 × ipso-Ph-Cq, OBn, α).
Experimental Section

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 3340 (m) [O–H], 3032 (vw), 2919 (vw), 1497 (w), 1454 (m), 1407 (w), 1370 (w), 1327 (w), 1166 (m), 1097 (vs) [C–O], 1044 (vs), 1027 (s), 974 (s), 908 (m), 886 (m), 836 (w), 799 (m), 735 (vs).

HRMS (ESI) calculated for C$_{19}$H$_{22}$O$_{5}$Na [M + Na$^+$]: 353.1365, found 353.1376.

2-O-Acetyl-3,5-di-O-benzyl-$\alpha$,$\beta$-D-xylofuranose (7/4)

Acetate 7/4 was obtained as a minor by-product from the hydrolysis of bis-benzylated acetonide 7/2 with concentrated HCl in AcOH according to procedure A after separation by column chromatography as a colourless oil (282 mg, 0.76 mmol).

Yield: 9%

Chemical formula: C$_{21}$H$_{24}$O$_{6}$

Molecular weight: 372.41

Appearance: colourless oil

TLC: $R_f$ = 0.66 (EA/PE = 75 : 25), CAM

Opt. rotation [$\alpha$]$^D_25$ : n/a due to the product’s composition as mixture of anomers

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 2.07 (s, 3H, OAc-CH$_3$, $\beta$), 2.10 (s, 3H, OAc-CH$_3$, $\alpha$), 3.19 (d, 1H, $J = 7.2$ Hz, OH-1$\alpha$), 3.66$''$ (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 10.2$ Hz, H$_A$-5$\alpha$), 3.71$'$ (dd, 1H, $J_1 = 4.8$ Hz, $J_2 = 10.1$ Hz, H$_B$-5$\alpha$), 3.74$''$ (dd, 1H, $J_1 = 5.3$ Hz, $J_2 = 9.9$ Hz, H$_A$-5$\beta$), 3.76$'$ (d, 1H, $J = 11.6$ Hz, OH-1$\beta$), 3.78$'$ (dd, 1H, $J_1 = 5.6$ Hz, $J_2 = 9.9$ Hz, H$_B$-5$\beta$), 4.05 (d, 1H, $J = 4.1$ Hz, H-3$\beta$), 4.19 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 5.3$ Hz, H-3$\alpha$), 4.35 (q, 1H, $J = 5.3$ Hz, H-4$\beta$), 4.44 (q, 1H, $J = 5.5$ Hz, H-4$\alpha$), 4.52$'$ (d, 1H, $J = 12.3$ Hz, H$_A$-3$\beta$), 4.54$'$ (d, 1H, $J = 11.9$ Hz, H$_A$-5$\beta$), 4.55$'$ (d, 1H, $J = 12.3$ Hz, H$_A$-5$\alpha$), 4.57$'$ (d, 1H, $J = 11.9$ Hz, H$_A$-3$\alpha$), 4.58$'$ (d, 1H, $J = 12.1$ Hz, H$_B$-5$\alpha$), 4.61$'$ (d, 1H, $J = 11.8$ Hz, H$_B$-5$\beta$), 4.67 (d, 1H, $J = 12.1$ Hz, H$_B$-3$\alpha$), 4.75 (d, 1H, $J = 11.7$ Hz, H$_B$-3$\beta$), 5.08 (t, 1H, $J = 3.8$ Hz, H-2$\alpha$), 5.17 (s, 1H, H-2$\beta$), 5.20 (d, $J = 11.4$ Hz, 1H, H-1$\beta$), 5.63 (dd, 1H, $J_1 = 4.3$ Hz, $J_2 = 6.9$ Hz, H-1$\alpha$), 7.24 – 7.35 (m, 2 × 10H, 20 × Ph-H, $\alpha$ & $\beta$).
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\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta \) [ppm] : 20.77 (CH\(_3\), OAc, \(\alpha\)), 20.84 (CH\(_3\), OAc, \(\beta\)), 68.53 (CH\(_2\), C-5\(\beta\)), 68.56 (CH\(_2\), C-5\(\alpha\)), 72.29 (CH\(_2\), C-2\(\beta\)), 72.61 (CH\(_2\), C-2\(\alpha\)), 73.51 (CH\(_2\), C-3\(\beta\)), 73.66 (CH\(_2\), C-3\(\alpha\)), 73.69 (CH\(_2\), C-5\(\beta\)), 77.00 (CH, C-4\(\alpha\)), 78.08 (CH, C-2\(\alpha\)), 79.63 (CH, C-2\(\beta\)), 80.11 (CH, C-3\(\beta\)), 80.46 (2 \times CH, C-4\(\beta\), C-3\(\alpha\)), 95.21 (CH, C-1\(\alpha\)), 101.10 (CH, C-1\(\beta\)), 127.79, 127.84, 127.96, 128.17, 128.42, 128.55 (10 \times Ph-CH, \(\beta\)), 127.61, 127.66, 127.73, 127.87, 128.34 (10 \times Ph-CH, \(\alpha\)), 136.90, 137.67 (2 \times C\(_q\), OBn, \(\beta\)), 137.52, 138.05 (2 \times C\(_q\), OBn, \(\alpha\)), 169.81 (CO, OAc, \(\alpha\)), 169.88 (CO, OAc, \(\alpha\)).

IR (neat) \(\tilde{\nu} \) [cm\(^{-1}\)] : 3440 (br) [O–H], 2922 (w) [C–H], 1741 (s) [C=O], 1497 (w), 1454 (m), 1372 (w), 1357 (vs), 1047 (vs) [C–O], 911 (w), 738 (vs).

HRMS (EI) calculated for C\(_{21}\)H\(_{24}\)O\(_6\) [M\(^+\)] : 372.1573, found 372.1539.

HRMS (ESI) calculated for C\(_{21}\)H\(_{24}\)O\(_6\)Na [M + Na\(^+\)] : 395.1471, found 395.1498.

(–)-3,5-Di-O-benzyl-1-O-(4'-hydroxybutyl)-\(\beta\)-D-xylofuranose (7/5)

\[\text{\(\tilde{\nu} \) [cm\(^{-1}\)] : 3440 (br) [O–H], 2922 (w) [C–H], 1741 (s) [C=O], 1497 (w), 1454 (m), 1372 (w), 1357 (vs), 1047 (vs) [C–O], 911 (w), 738 (vs).} \]

\(\text{HRMS (EI) calculated for C}\(_{21}\)H\(_{24}\)O\(_6\) [M\(^+\)] : 372.1573, found 372.1539.} \]

\(\text{HRMS (ESI) calculated for C}\(_{21}\)H\(_{24}\)O\(_6\)Na [M + Na\(^+\)] : 395.1471, found 395.1498.} \]

\(\text{4’-Hydroxybutyl acetal 7/5 was obtained as a minor by-product from the hydrolysis of} \)

\(\text{the bis-benzylated acetonide 7/2 with 4 M HCl in refluxing THF according to procedure B} \)

\(\text{after separation by column chromatography as a yellow oil (282 mg, 0.76 mmol).} \)

\(\text{Yield : 16\%} \)

\(\text{Chemical formula : C}_{23}\text{H}_{30}\text{O}_{6} \)

\(\text{Molecular weight : 402.48} \)

\(\text{Appearance : Yellow oil} \)

\(\text{TLC :} \) \(Rf = 0.64 \) (EA/PE = 2 : 1), CAM

\(\text{Optical rotation :} \) \(\left[\alpha\right]_D^{25} = -44.9^\circ\) (\(c = 2.04 \text{ g/100 mL CHCl}_3\))

\(\text{H NMR (500 MHz, CDCl}_3) \) \(\delta \) [ppm] : 1.68 (m, 2H, H\(_2\)-2'), 1.80 (m, 2H, H\(_2\)-3'), 2.30 (br, 1H, OH-2'), 3.43 (dt, 1H, \(J_1 = 6.0 \text{ Hz, } J_2 = 9.6 \text{ Hz, H}_A-1'\)), 3.50 (t, 2H, \(J = 6.6 \text{ Hz, H}_2-4'\)), 3.67 (dd, 1H, \(J_1 = 7.3 \text{ Hz, } J_2 = 10.4 \text{ Hz, H}_A-5\)), 3.75 (m, 2H, H\(_2\)-H\(_2\)-1', H\(_2\)-H\(_2\)-5), 3.94 (dd, 1H, \(J_1 = 3.0 \text{ Hz, } J_2 = 6.0 \text{ Hz, H}\)-3), 4.20 (s, 1H, H\(_2\)-H-2'), 4.46 (ddd, \(J_1 = 4.9 \text{ Hz, } J_2 = 6.6 \text{ Hz, } J_3 = 8.9 \text{ Hz, H}-4), 4.51 (d, 1H, J=} \)

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12.0 Hz, H\textsubscript{A}-3*), 4.54\textsuperscript{a}(d, 1H, J = 12.0 Hz, H\textsubscript{A}-5*), 4.58\textsuperscript{a}(d, 1H, J = 12.0 Hz, H\textsubscript{B}-5*), 4.61\textsuperscript{a}(d, 1H, J = 11.8 Hz, H\textsubscript{B}-3*), 4.87 (d, 1H, J = 1.5 Hz, H-1), 7.24 – 7.35 (m, 10H, 10 × Ph-H).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) [ppm]: 26.91 (CH\textsubscript{2}, C-2'), 29.46 (CH\textsubscript{2}, C-3'), 44.90 (CH\textsubscript{2}, C-4'), 67.24 (CH\textsubscript{2}, C-1'), 69.85 (CH\textsubscript{2}, C-5), 72.20 (CH\textsubscript{2}, C-3*), 73.42 (CH\textsubscript{2}, C-5*), 79.43 (CH, C-2), 79.90 (CH, C-4), 83.51 (CH, C-3), 108.12 (CH, C-1), 127.54, 127.58, 127.73, 127.78, 128.33, 128.38 (10 × Ph-CH), 137.88, 138.20 (2 × Ph-Cq).

IR (neat) \(\tilde{\nu}\) [cm\textsuperscript{-1}]: 3410 (br) [O–H], 3031 (w), 2920 (w) [C–H], 2870 (w) [C–H], 1497 (w), 1454 (m), 1344 (w), 1257 (w), 1208 (w), 1092 (vs) [C–O], 1054 (vs) [C–O], 1028 (s), 910 (w), 843 (w), 814 (w), 736 (vs).

HRMS (ESI) calculated for C\textsubscript{23}H\textsubscript{34}NO\textsubscript{4} [M + NH\textsubscript{4}\textsuperscript{+}]: 420.2386, found 420.2397.

\((+)-(2R,3R,4S,5S,6E)-5\text{-Benzylamino-1,3-bis(benzyloxy)-7-phenyl-6-heptene-2,4-diol (7/6)}\)

\[ \text{To a suspension of 3,5-di-O-benzyl-D-xylofuranose (3304 mg, 10.0 mmol, 1.0 equiv) in TFE (50 mL) was added benzylamine (1072 mg, 10 mmol, 1 equiv) at rt. After 5 min stirring the mixture became a clear solution whereupon (E)-styrylboronic acid (1480 mg, 10 mmol, 1 equiv) was added. This mixture was stirred at 25 ºC for 24 h under an atmosphere of N}_2.\text{ After cautious evaporation of the solvent the amber viscous residue was dissolved in Et}_2O (100 mL) and washed with 1 M NaOH solution (2 × 50 mL). Without further treatment the organic phase was carefully concentrated to dryness, and the residue was purified by column chromatography affording amino diol 7/6 (4886 mg, 9.33 mmol) as a bright amber caramel.}\]

CC : \(\varnothing\) 4.6 cm × 7 cm, \(V_{fr} = 65\) mL, eluent EA/PE 30 : 70 → 100 : 0

Yield : 93%

Chemical formula : C\textsubscript{34}H\textsubscript{37}NO\textsubscript{4}

Molecular weight : 523.68

Appearance : Bright amber caramel
Experimental Section

TLC : \( R_f \) variable due to polarity of compound

Optical rotation : \([\alpha]_D^{25} = +51.3^\circ\) (c = 1.53 g/100 mL CHCl₃)

\([\alpha]_D^{25} = +51.5^\circ\) (c = 3.01 g/100 mL CHCl₃)

\( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) [ppm] : 2.81 (br, 1H, NH), 3.37 (dd, 1H, \( J_1 = 5.9 \) Hz, \( J_2 = 8.7 \) Hz, H-5), 3.60 (m, 3H, H\( \alpha \)-5\(*\), H-2), 3.76 (t, 1H, \( J_1 = 3.9 \) Hz, H-3), 3.83 (d, 1H, \( J_1 = 13.0 \) Hz, H\( \beta \)-5\(*\)), 3.88 (t, 1H, \( J_1 = 5.1 \) Hz, H-4), 4.05 (td, 1H, \( J_1 = 3.6 \) Hz, \( J_2 = 5.6 \) Hz, H-2), 4.46 (d, 1H, \( J_1 = 11.8 \) Hz, H\( \alpha \)-1\(*\)), 4.50 (d, 1H, \( J_1 = 11.8 \) Hz, H\( \beta \)-1\(*\)), 4.56 (d, 1H, \( J_1 = 11.2 \) Hz, H\( \alpha \)-3\(*\)), 4.63 (d, 1H, \( J_1 = 11.2 \) Hz, H\( \beta \)-3\(*\)), 6.09 (dd, 1H, \( J_1 = 8.8 \) Hz, \( J_2 = 15.9 \) Hz, H-6), 6.48 (d, 1H, \( J_1 = 15.9 \) Hz, H-7), 7.18 – 7.38 (m, 20H, 20 \( \times \) Ph-H).

\( ^13C \) NMR (125 MHz, CDCl₃) \( \delta \) [ppm] : 50.73 (CH\( _2 \), C-5\(*\)), 62.81 (CH, C-5), 70.36 (CH, C-2), 71.15 (CH\( _2 \), C-1), 72.88 (CH, C-4), 73.32 (CH\( _2 \), C-1\(*\)), 74.21 (CH\( _2 \), C-3\(*\)), 79.52 (CH, C-3), 126.48, 127.06, 127.68, 127.71, 127.80, 127.83, 128.08, 128.38, 128.40, 128.42, 128.44, 128.57 (20 \( \times \) Ph-CH), 128.22 (CH, C-6), 133.56 (CH, C-7), 136.56 (Styryl-C\( _q \)), 137.92 (C\( _q \), OBn), 138.02 (C\( _q \), OBn), 139.67 (C\( _q \), NBn).

IR (neat) \( \tilde{\nu} \) [cm\(^{-1}\)] : 3029 (w), 2864 (w), 1495 (w), 1453 (w), 1363 (w), 1208 (s) [C=O], 1028 (m), 971 (m), 910 (w), 847 (w), 813 (w), 738 (s), 699 (vs).

HRMS (ESI) calculated for C\(_{34}\)H\(_{38}\)NO\(_4\) [M + H\(^+\)] : 524.2801, found 524.2792.

\(+\)-(2\( \delta \),3\( \delta \),4\( \delta \),5\( \delta \))-N-Benzyl-3-benzyloxy-2-benzylloxymethyl-5-styrylpyrrolidin-4-ol (7/12)

\( (+) \)-(2\( \delta \),3\( \delta \),4\( \delta \),5\( \delta \))-N-Benzyl-3-benzyloxy-2-benzylloxymethyl-5-styrylpyrrolidin-4-ol (7/12)

Procedure A (regioselective C-2 O-mesylation and 5-exo-tet cyclisation) : To the solution of amino diol 7/6 (2959 mg, 5.65 mmol, 1.0 equiv) in dry DCM (56 mL) was added Et\( _3 \)N (2001 mg, 2.76 mL, 19.8 mmol, 3.5 equiv) at 0 °C under an atmosphere of N\(_2\). The mixture was then cooled to -10 °C followed by the dropwise addition of a MsCl solution (696 g, 6.1 mmol, 1.075 equiv) in dry DCM (12 mL) via a dropping funnel. After complete addition the reaction mixture was gradually warmed to 40 °C over 3 h and stirred for further 30 min under gentle
reflux. By this time ESI-MS indicated full conversion of the starting material. The solution was subsequently concentrated under reduced pressure, and the pulpy amber residue was directly purified by column chromatography without further work-up to afford 2044 mg of a pale yellow syrup. NMR spectroscopic analysis of the product revealed it to be a mixture of the desired pyrrolidinol 7/12 and its 4-mesylate ester derivative 7/13 in a ratio of 92 : 8. Further attempts to separate both compounds by column and preparative thin layer chromatography were futile due to their nearly identical $R_f$-values.

$\text{CC} : \varnothing 3.3 \text{ cm} \times 11 \text{ cm}, V_{Fr} = 25 \rightarrow 45 \text{ mL}, \text{eluent EA/PE} 15 : 85 \rightarrow 25 : 75$

$\text{Yield} : 66\% \text{ pyrrolidin-4-ol} 7/12 / 6\% \text{ pyrrolidine 4-mesylate} 7/13$

$\text{Optical rotation} : [\alpha]_{D}^{25} = +24.0^\circ (c = 2.15 \text{ g}/100 \text{ mL CHCl}_3)$ (92 : 8 - mixture of OH : OMs)

**Procedure B** (5-exo-tet cyclisation under Appel conditions) : To the solution of amino diol 7/6 (524 mg, 1.0 mmol, 1.0 equiv) in dry DCM (10 mL) was added a solution of PPh$_3$ (288.5 mg, 1.1 mmol, 1.1 equiv) in dry DCM (3 mL) at 0°C under an atmosphere of N$_2$. The mixture was cooled to –5°C and slowly treated (15 min) with a solution of CBr$_4$ (365 mg, 1.1 mmol, 1.1 equiv) in dry DCM (3 mL). After completion of addition the mixture was stirred at 0°C for one further hour. Then a solution of Et$_3$N (354 mg, 4.0 mmol, 4.0 equiv) in dry DCM (4 mL) was added dropwise (10 min) while allowing the reaction mixture slowly to warm to rt. The mixture was then stirred at rt for an additional hour and finally at 40°C under gentle reflux for 30 min. All volatiles were subsequently evaporated in vacuo, and the brown pulpy residue was absorbed on SiO$_2$. Purification by column chromatography afforded pure pyrrolidinol 7/12 (331 mg, 0.65 mmol) as an amber orange syrup.

$\text{CC} : \varnothing 1.7 \text{ cm} \times 10 \text{ cm}, V_{Fr} = 23 \text{ mL}, \text{eluent EA/PE} 15 : 85 \rightarrow 20 : 80$

$\text{Yield} : 65\%$

**Chemical formula** : C$_{34}$H$_{35}$NO$_3$

**Molecular weight** : 505.66

**Appearance** : Amber orange syrup

**TLC** : $R_f = 0.41$ (DE/PE = 50 : 50), CAM

**Optical rotation** : $[\alpha]_{D}^{25} = +21.9^\circ (c = 3.0 \text{ g}/100 \text{ mL CHCl}_3)$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 3.24 ("d", 1H, $J = 2.1$ Hz, H-2), 3.50 (m, 3H, H$_2$-1, OH-4), 3.69 (d, 1H, $J = 9.7$ Hz, H-5), 3.79 (d, 1H, $J = 14.3$ Hz, H$_A$-5*), 3.85 (d, 1H, $J = 14.3$ Hz, H$_B$-5*), 4.00" (s, 1H, H-3), 4.03" (d, 1H, $J = 10.5$ Hz, H-4), 4.50" (d, 1H, $J = 12.0$ Hz, H$_A$-1*), 4.53" (d, 1H,
Experimental Section

\( J = 11.8 \text{ Hz, } H_{A-1}^1 \), 4.54\(^{\text{d}}\)(d, 1H, \( J = 11.7 \text{ Hz, } H_{A-3} \)), 4.65 (d, \( J = 11.7 \text{ Hz, } 1H, H_{A-3} \)), 6.34 (d, 1H, \( J = 15.9 \text{ Hz, } H-7 \)), 6.47 (dd, 1H, \( J_1 = 9.7 \text{ Hz, } J_2 = 15.9 \text{ Hz, } H-6 \)), 7.18 – 7.38 (m, 20H, 20 \( \times \) Ph-H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) [ppm] : 52.02 (CH\(_2\), C-5\(^*\)), 67.11 (CH, C-2), 69.43 (CH\(_2\), C-1), 71.55 (CH\(_2\), C-3\(^*\)), 72.74 (CH, C-5), 73.59 (CH\(_2\), C-1\(^*\)), 78.08 (CH, C-4), 87.92 (CH, C-3), 126.40, 126.68, 127.39, 127.62, 127.70, 127.79, 127.86, 128.15, 128.20, 128.38, 128.47, 128.50 (20 \( \times \) Ph-CH), 128.24 (CH, C-6), 133.32 (CH, C-7), 136.95 (Styryl-C\(_q\)), 137.67 (C\(_q\), OBn), 138.18 (C\(_q\), OBn), 139.88 (C\(_q\), NBn).

IR (neat) \( \tilde{\nu} \) [cm\(^{-1}\)] : 3029 (w), 2865 (w), 1495 (m), 1453 (m), 1363 (m), 1243 (w), 1209 (w), 1092 (s), 1075 (s), 1028 (m), 970 (m), 910 (w), 805 (w), 740 (vs).

HRMS (ESI) calculated for C\(_{34}\)H\(_{36}\)NO\(_3\) [M + H\(^+\)] : 506.2695, found 506.2706.

(\(+\)-(2\(R\),3\(R\),4\(S\),5\(S\),6\(E\))-5-Benzylamino-1,3-bis(benzyloxy)-4-hydroxy-7-phenylhept-6-en-2-yl methanesulfonate (7/11)

The intermediate C-2 mesylate 7/11 from the S\(_\text{N}2\)-exo-tet cyclisation of the amino diol 7/6 with MsCl can be obtained when the temperature during the reaction and purification is kept below 20 °C. According to procedure A the solution of amino diol 7/6 (1047 mg, 2.0 mmol, 1.0 equiv) in dry DCM (10 mL) was treated with a near-stoichiometric amount of MsCl (240.5 mg, 2.1 mmol, 1.05 equiv) in the presence of excess Et\(_3\)N (810 mg, 8.0 mmol, 4.0 equiv) at 0 °C. Evaporation of all volatiles after 2 h and purification of the residue by column chromatography at 18 °C gave mesylate 7/11 (812 mg, 1.35 mmol) as a yellow oil.

CC : \( \emptyset \) 2.0 cm \( \times \) 11 cm, \( V_{Fr} = 25 \) mL, eluent EA/PE 25 : 75 \( \rightarrow \) 30 : 70

Yield : 67.5%

Chemical formula : C\(_{35}\)H\(_{39}\)NO\(_6\)S

Molecular weight : 601.75

Appearance : Yellow oil
Experimental Section

TLC : $R_f = 0.27$ (DE/PE = 1 : 1), CAM

Opt. rotation $[\alpha]^25_D = +20.3^\circ$ ($c = 4.32$ g/100 mL CHCl$_3$)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ [ppm] : 2.22 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 7.0$ Hz, H-4), 2.73 (dd, 1H, $J_1 = 3.0$ Hz, $J_2 = 8.9$ Hz, H-5), 3.03 (s, 3H, OMs-CH$_3$), 3.33 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 7.0$ Hz, H-3), 3.58 (dd, 1H, $J_1 = 3.1$, $J_2 = 11.0$ Hz, H$_A$-1), 3.67 (d, 1H, $J = 13.8$ Hz, H$_B$-5*), 3.85 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 11.0$ Hz, H$_B$-1), 4.05 (d, 1H, $J = 13.8$ Hz, H$_B$-5*), 4.45$^a$ (d, 1H, $J = 11.7$ Hz, H$_A$-1*), 4.50$^a$ (d, 1H, $J = 12.1$ Hz, H$_A$-3*), 4.52$^a$ (d, 1H, $J = 11.6$ Hz, H$_B$-1*), 4.75 (d, 1H, $J = 12.0$ Hz, H$_B$-3*), 5.10 (dt, 1H, $J_1 = 3.2$ Hz, $J_2 = 8.1$ Hz, H-2), 6.17 (dd, 1H, $J_1 = 8.9$ Hz, $J_2 = 15.7$ Hz, H-6), 6.69 (d, 1H, $J = 15.7$ Hz, H-7), 7.36 – 7.24 (m, 20H, 20 × Ph-H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ [ppm] : 38.87 (CH$_3$, OMs), 44.69 (CH, C-5), 45.14 (CH, C-4), 55.66 (CH$_2$, C-5*), 69.60 (CH$_3$, C-1), 72.24 (CH$_2$, C-3*), 73.26 (CH$_2$, C-1*), 77.97 (CH, C-3), 82.09 (CH, C-2), 123.41 (CH, C-6), 126.28, 126.90, 127.85, 127.90, 127.94, 127.99, 128.20, 128.33, 128.44, 128.48, 128.66 (20 × Ph-CH), 135.63 (CH, C-7), 136.43 (Styryl-C$_q$), 137.25 (C$_q$, OBn), 137.53 (C$_q$, OBn), 139.50 (C$_q$, NBn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3063 (w) 3028 (w), 2936 (w), 2863 (w), 1701 (w), 1639 (w), 1601 (w), 1582 (w), 1497 (w), 1454 (m), 1358 (s), 1204 (w), 1173 (vs), 1103 (s), 1076 (m), 1045 (m), 1026 (m), 968 (m), 918 (s), 802 (m), 745 (vs).

HRMS (ESI) calculated for C$_{35}$H$_{40}$NO$_6$S [M + H$^+$] : 602.2576, found 602.2570.

(+)-(2S,3S,4S,5S)-N-Benzyl-3-benzyloxy-2-benzyloxymethyl-5-styrylpyrrolidin-3-yl methanesulfonate (7/13)

To the mixture of pyrrolidinol 7/12 (506 mg, 1.0 mmol, 1.0 equiv) and Et$_3$N (304 mg, 3.0 mmol, 3.0 equiv) in dry DCM (5 mL) was added a solution of MsCl (138 mg, 1.2 mmol, 1.2 equiv) in dry DCM (1 mL) at 0 ºC under an atmosphere of N$_2$. The mixture was stirred at 0 ºC for 30 min and was then allowed to warm to rt over 30 min. After further stirring at 25 ºC
for 30 min ESI-MS control showed full conversion of the starting material. All volatiles were subsequently evaporated under reduced pressure and the residue directly purified by column chromatography to afford the mesylate 7/13 (543 mg, 0.93 mmol) as a reddish brown syrup.

CC : ∅ 1.7 cm × 10 cm, V<sub>Fr</sub> = 20 mL, eluent EA/PE 15 : 85 → 25 : 75

Yield : 93%

Chemical formula : C<sub>35</sub>H<sub>37</sub>NO<sub>5</sub>S

Molecular weight : 583.74

Appearance : Reddish brown syrup

TLC : R<sub>f</sub> = 0.41 (DE/PE = 1 : 1), CAM

Opt. rotation [α]<sup>25</sup> = +26.2º (c = 3.7 g/100 mL CHCl<sub>3</sub>)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ [ppm] : 2.87 (s, 3H, OMs-CH<sub>3</sub>), 3.29 (ddd, 1H, J<sub>1</sub> = 3.3 Hz, J<sub>2</sub> = 3.7 Hz, J<sub>3</sub> = 5.3 Hz, H-2), 3.47 (dd, 1H, J<sub>1</sub> = 3.8 Hz, J<sub>2</sub> = 9.9 Hz, H<sub>A</sub>-1), 3.56 (dd, 1H, J<sub>1</sub> = 5.5 Hz, J<sub>2</sub> = 9.9 Hz, H<sub>B</sub>-1), 3.67 (d, 1H, J = 14.3 Hz, H<sub>A</sub>-5*), 3.87 (dd, 1H, J<sub>1</sub> = 4.1 Hz, J<sub>2</sub> = 9.6 Hz, H-5), 3.97 (d, 1H, J = 14.3 Hz, H<sub>B</sub>-5*), 4.23 (t, 1H, J = 3.0 Hz, H-3), 4.47<sup>ü</sup> (d, 1H, J = 12.2 Hz, H<sub>A</sub>-1*), 4.50<sup>ü</sup> (d, 1H, J = 12.1 Hz, H<sub>B</sub>-1*), 4.60 (d, 1H, J = 11.8 Hz, H<sub>A</sub>-3*), 4.65 (d, 1H, J = 11.8 Hz, H<sub>B</sub>-3*), 4.95 (dd, 1H, J<sub>1</sub> = 3.1 Hz, J<sub>2</sub> = 3.8 Hz, H-4), 6.23 (dd, 1H, J<sub>1</sub> = 9.6 Hz, J<sub>2</sub> = 15.8 Hz, H-6), 6.47 (d, 1H, J = 15.8 Hz, H-7), 7.18 – 7.38 (m, 20H, 20 × Ph-H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ [ppm] : 38.73 (CH<sub>3</sub>, OMs), 51.42 (CH<sub>2</sub>, C-5*), 64.80 (CH, C-2), 68.89 (CH, C-5), 69.49 (CH<sub>2</sub>, C-1), 71.91 (CH<sub>2</sub>, C-3*), 73.35 (CH<sub>2</sub>, C-1*), 84.70 (CH, C-3), 87.50 (CH, C-4), 126.42 (CH, C-6), 126.57, 126.82, 127.70, 127.76, 127.80, 127.96, 128.11, 128.24, 128.39, 128.59 (20 × Ph-CH), 135.48 (CH, C-7), 136.25 (Styryl-C<sub>q</sub>), 137.69 (C<sub>q</sub>, OBn), 138.05 (C<sub>q</sub>, OBn), 139.03 (C<sub>q</sub>, NBn).

IR (neat) ν [cm<sup>-1</sup>] : 3028 (w), 2862 (w), 1495 (w), 1453 (m), 1360 (s), 1256 (w), 1175 (vs), 1095 (s), 1077 (s), 1028 (m), 954 (vs), 841 (s), 743 (vs).

HRMS (ESI) calculated for C<sub>35</sub>H<sub>36</sub>NO<sub>5</sub>S [M + H<sup>+</sup>] : 584.2471, found 584.2478.
Experimental Section

(+)-(2S,3S,4S,5S)-N-Benzyl-3-benzyloxy-2-benzyloxymethyl-5-hydroxymethyl-pyrrolidin-4-ol (7/23)

Step 1 (Preparation of the pyrrolidinium chloride 7/22): To the solution of styrylpyrrolidinol 7/12 (1012 mg, 2.0 mmol, 1.0 equiv) in Et₂O (6 mL) was added dropwise a 2 M solution of HCl in Et₂O (1.1 mL) at 0 °C to form the insoluble hydrochloride salt. The supernatant was then carefully decanted and the residual precipitate dried in high vacuum affording the pyrrolidinium chloride 7/22 as a grey foamy solid.

Step 2 (Ozonolysis): The pyrrolidinium chloride 7/22 was dissolved in a 1:1 mixture of dry DCM and MeOH (40 mL) and subjected to ozonolysis (~33% O₃ in O₂) at -78 °C. A change of colour from yellow to grey and finally greyish blue (O₃ in solution) could be observed during the course of the reaction. Excess O₃ was then displaced by flushing the mixture with N₂ for 5 min whereupon the blue colour disappeared. The mixture was subsequently treated with an excess amount of NaBH₄ (454 mg, 12.0 mmol, 6.0 equiv) at -78 °C and left vigorously stirring under a gentle stream of N₂ while slowly warming to rt (~3 h). After 1 h additional stirring at rt a 1 M solution of NH₄Cl (20 mL) was added to decompose surplus NaBH₄ whereupon a strong evolution of H₂ began. When the H₂ evolution finally had ceased, a 1 M solution of NaHCO₃ (20 mL) was added to basify the mixture. After subsequent extraction with DCM (4 × 40 mL) the organic phases were dried over MgSO₄, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography to afford the pyrrolidine diol 7/23 (483 mg, 1.11 mmol) as a yellow syrup.

CC: ∅ 2.0 cm × 10 cm, VFr = 25 mL, eluent: EA/PE 25:75 → 75:25

Yield: 56%

Chemical formula: C₂₇H₃₁NO₄

Molecular weight: 433.55

Appearance: Yellow syrup

TLC: Rf = 0.19 (DE/PE = 3:1), CAM

Optical rotation: [α]D²⁵ = +22.8° (c = 3.7 g/100 mL CHCl₃)
**Experimental Section**

**1H NMR (500 MHz, CDCl₃) δ [ppm] :**

- 3.03 (br, 1H, OH-6), 3.11 (s, 1H, H-5), 3.30 (s, 1H, H-2), 3.34 (dd, 1H, J₁ = 1.7 Hz, J₂ = 10.1 Hz, Hₐ-1), 3.66” (dd, 1H, J₁ = 1.5 Hz, J₂ = 11.5 Hz, Hₐ-6), 3.67” (dd, 1H, J₁ = 3.1 Hz, J₂ = 10.0 Hz, Hᵦ-1), 3.73 (dd, 1H, J₁ = 3.4 Hz, J₂ = 11.5 Hz, Hᵦ-6), 3.77 (d, 1H, J = 14.3 Hz, Hₐ-5*), 3.84 (s, 1H, H-3), 3.88 (d, 1H, J = 11.6 Hz, OH-4), 3.91 (d, 1H, J = 14.3 Hz, Hᵦ-5*), 4.18 (d, 1H, J = 9.8 Hz, H-4), 4.49” (d, 1H, J = 11.6 Hz, Hₐ-1*), 4.49” (d, 1H, J = 11.8 Hz, Hᵦ-1*), 4.54 (d, J = 11.6 Hz, 1H, Hᵦ-1*), 4.64 (d, J = 11.7 Hz, 1H, Hᵦ-3*), 7.19 – 7.40 (m, 15H, 15 × Ph-H).

**13C NMR (125 MHz, CDCl₃) δ [ppm] :**

- 51.06 (CH₂, C-5*), 60.60 (CH₂, C-6), 65.54 (CH, C-2), 68.95 (CH₂, C-1), 71.25 (CH₂, C-3*), 72.34 (CH, C-5), 73.84 (CH₂, C-1*), 77.59 (CH, C-4), 87.63 (CH, C-3), 126.96, 127.78, 127.79, 127.94, 128.22, 128.29, 128.41, 128.45, 128.66 (15 × Ph-CH), 136.86 (Cₜ, OBn), 137.56 (Cₜ, OBn), 139.13 (Cₜ, NBn).

**IR (neat) ~ [cm⁻¹] :**

- 3400 (br) [O−H], 3030 (w), 2867 (w), 1495 (w), 1453 (m), 1363 (w), 1207 (w), 1090 (vs) [C−O], 1072 (vs) [C−O], 1028 (s), 910 (w), 821 (w), 737 (vs).

**HRMS (ESI) calculated for C₂₇H₃₂NO₄ [M + H⁺] :**

434.2331, found 434.2329.

(+)-(3S,4S,5S)-N-Benzyl-3-benzyloxy-2-benzyloxymethylpyrrolidin-4-ol (7/24)

Pyrrolidinol 7/24 was obtained as a major by-product from the ozonolysis of styrylpyrrolidinol 7/12 after separation by column chromatography as a colourless oil (225 mg, 0.56 mmol) in 28% yield. Via a slight modification of the work-up procedure 7/24 could be obtained as the main product of the above reaction.

The pyrrolidinium chloride 7/22 (650 mg, 1.2 mmol) was dissolved in a 1 : 1 mixture of dry DCM and MeOH (24 mL) and treated with ozone (~ 33% O₃ in O₂) at –78 °C until a pale blue colour in the mixture remained. After being flushed with N₂ to displace excess O₃, the reaction mixture was quenched with Et₃N (1.2 mL) and left under a blanket of N₂ with vigorous stirring while slowly warming to –5 °C (~ 2 h). The mixture was then treated with an excess amount of NaBH₄ (272 mg, 7.2 mmol) at –5 to 0 °C and additionally stirred for 2 h
Experimental Section

at rt after which time 1 M NH₄Cl solution (12 mL) was added to decompose surplus NaBH₄ followed by 1 M NaHCO₃ solution after the H₂ evolution had ceased. The mixture was subsequently extracted with DCM (3 × 36 mL), and the organic phases were dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by column chromatography afforded the title compound, pyrrolidinol 7/24, as a pale yellow oil in 50% yield (240 mg, 0.6 mmol). Pyrrolidine diol 7/23 was also obtained as a by-product in 25% yield (129 mg, 0.3 mmol).

CC : ∅ 1.7 cm × 10 cm, Vfr = 22 – 23 mL, eluent : EA/PE 25 : 75 → 75 : 25
Yield : 50%

Chemical formula : C₂₆H₃₀NO₃
Molecular weight : 403.51

Appearance : Colourless to pale yellow oil

TLC : Rf = 0.33 (DE/PE = 3 : 1), CAM

Optical rotation : [α]D²⁵ = +4.3º (c = 1.525 g/100 mL CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 2.67 (dd, 1H, J₁ = 3.5 Hz, J₂ = 9.9 Hz, Hα-5), 2.82 (dd, 1H, J₁ = 2.9 Hz, J₂ = 5.4 Hz, H-2), 2.93 (d, 1H, J = 10.0 Hz, Hβ-5), 3.42 (dd, 1H, J₁ = 3.5 Hz, J₂ = 9.8 Hz, Hα-1), 3.51 (dd, 1H, J₁ = 3.1 Hz, J₂ = 9.7 Hz, Hβ-1), 3.57 (d, 1H, J = 13.3 Hz, Hα-5*), 3.85 (s, 1H, H-3), 3.98 (d, 1H, J = 13.3 Hz, Hβ-5*), 4.02 (d, 1H, J = 3.1 Hz, H-4), 4.50º (d, 1H, J = 11.9 Hz, Hα-1*), 4.52º (d, 1H, J = 12.0 Hz, Hβ-3*), 4.54º (d, 1H, J = 12.0 Hz, Hβ-1*), 4.59 (d, 1H, J = 11.9 Hz, Hβ-3*), 7.21 – 7.35 (m, 15H, 15 × Ph-H).

¹³C NMR (125 MHz, CDCl₃) δ [ppm] : 58.47 (CH₂, C-5*), 59.77 (CH₂, C-5), 69.37 (CH, C-2), 70.12 (CH, C-1), 71.39 (CH₂, C-3*), 73.24 (CH, C-4, 73.53 (CH₂, C-1*), 87.68 (CH, C-3), 126.98, 127.61, 127.65, 127.66, 127.73, 128.23, 128.39, 128.44, 128.67 (15 × Ph-CH), 137.81 (Cq, OBN), 138.14 (Cq, OBN), 139.12 (Cq, NBN).

IR (neat) ν [cm⁻¹] : 3400 (br) [O–H], 3030 (w), 2916 (w), 2862 (w), 1496 (m), 1454 (m), 1364 (m), 1209 (m), 1093 (vs), 1028 (s), 986 (m), 911 (m), 838 (m), 737 (vs).

HRMS (ESI) calculated for C₂₆H₃₀NO₃ [M + H⁺] : 404.2226, found 404.2224.
Experimental Section

(+)-(2S,3S,4S,5S)-N-Benzyl-3-benzyl oxy-2-benzoxymethyl-2-hydroxymethyl-pyrrolidin-4-yl methanesulfonate (7/30)

Pyrrolidinyl methansulfonate 7/30 was obtained from the ozonolysis reaction of the styryl-pyrrolidinyl methansulfonate 7/29 (584 mg, 1.0 mmol) after purification by column chromatography as a pale yellow oil (257 mg, 0.503 mmol) following the procedure described for the ozonolysis of styryl pyrrolidine 7/12.

Yield: 50%

Chemical formula: C_{28}H_{33}NO_{6}S

Molecular weight: 511.63

Appearance: Pale yellow oil

TLC: \( R_f = 0.36 \) (DE/PE = 3 : 1), CAM

Optical rotation: \( [\alpha]_{D}^{25} = +26.0^\circ \) (\( c \) = 5.21 g/100 mL CHCl\textsubscript{3})

\(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) [ppm]: 2.49 (br, 1H, OH-6), 2.89 (s, 3H, OMs-CH\textsubscript{3}), 3.33 (dd, 1H, \( J_1 = 3.6 \) Hz, \( J_2 = 6.0 \) Hz, H-5), 3.39 (m, 1H, H-2), 3.50 (dd, 1H, \( J_1 = 4.2 \) Hz, \( J_2 = 10.1 \) Hz, H-3*), 3.53 (dd, 1H, \( J_1 = 6.3 \) Hz, \( J_2 = 9.9 \) Hz, H-1*), 3.75 (m, 2H, H-2*), 3.81 (d, 1H, \( J = 14.3 \) Hz, H\textsubscript{A}-1*), 3.95 (d, 1H, \( J = 14.3 \) Hz, H\textsubscript{B}-1*), 4.18 (t, 1H, \( J = 2.2 \) Hz, H-3*), 4.44 (d, 1H, \( J = 11.9 \) Hz, H\textsubscript{A}-5*), 4.48 (d, 1H, \( J = 12.1 \) Hz, H\textsubscript{B}-5*), 4.58 (s, 2H, H\textsubscript{2}-3*), 5.10 (dd, 1H, \( J_1 = 2.4 \) Hz, \( J_2 = 3.6 \) Hz, H-4), 7.21 - 7.36 (m, 15H, 15 × Ph-H).

\(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) [ppm]: 38.14 (CH\textsubscript{3}, OMs), 50.91 (CH\textsubscript{2}, C-5*), 58.75 (CH\textsubscript{2}, C-6), 64.90 (CH, C-2), 67.15 (CH, C-5), 68.33 (CH\textsubscript{2}, C-1), 71.77 (CH\textsubscript{2}, C-3*), 73.37 (CH\textsubscript{2}, C-1*), 83.75 (CH, C-3), 85.29 (CH, C-4), 127.17, 127.75, 127.89, 127.94, 128.05, 128.42, 128.46, 128.53 (15 × Ph-CH), 137.32, 137.89 (2 × Ph-C\textsubscript{q}, OBN), 138.55 (Ph-C\textsubscript{q}, NBn).

IR (neat) \( \bar{\nu} \) [cm\textsuperscript{-1}]: 3400 (br) [O–H], 3029 (w), 2925 (w), 2861 (w), 1495 (w), 1454 (m), 1358 (s), 1207 (w), 1175 (vs), 1096 (s), 1073 (s), 1028 (m), 956 (s), 851 (m), 739 (vs) 720 (w), 702 (s).

HRMS (ESI) calculated for C\textsubscript{28}H\textsubscript{34}NO\textsubscript{6}S [M + H\textsuperscript{+}]: 512.2107, found 512.2116.
Experimental Section

(+)-(3S,4S,5S)-N-Benzyl-3-benzylxy-2-benzyloxymethylpyrrolidin-4-yl methanesulfonate (7/31)

Pyrrolidinyl methansulfonate 7/31 was obtained as a major by-product from the ozonolysis reaction of the styrylpyrrolidinyl methansulfonate 7/29 after separation by column chromatography as a yellow syrup (164 mg, 0.34 mmol).

Yield : 34%

Chemical formula : C_{27}H_{31}NO_{5}S

Molecular weight : 481.60

Appearance : Yellow syrup

TLC : R_{f} = 0.52 (DE/PE = 3 : 1), CAM

Optical rotation : [\alpha]_{D}^{23} = +21.5^{\circ} (c = 3.57 g/100 mL CHCl_{3})

{^1}H NMR (500 MHz, CDCl_{3}) \delta [ppm] : 2.75 (dd, 1H, J_{1} = 5.0 Hz, J_{2} = 11.7 Hz, H_{\alpha}-5), 2.83^\circ(q, 1H, J = 5.1 Hz, H-2), 2.86^\circ(s, 3H, OMs-\text{CH}_{3}), 3.11 (d, 1H, J = 11.6 Hz, H_{\beta}-5), 3.46 (d, 1H, J = 13.4 Hz, H_{\alpha}-5^\ast), 3.56 (m, 2H, H_{2}-1), 4.07^\circ(d, 1H, J = 4.6 Hz, H-3), 4.10^\circ(d, 1H, J = 13.4 Hz, H_{\beta}-5^\ast), 4.51 (s, 2H, H_{2}-1^\ast), 4.57 (d, 1H, J = 11.9 Hz, H_{\alpha}-3^\ast), 4.66 (d, 1H, J = 11.7 Hz, H_{\beta}-3^\ast), 5.01 (d, 1H, J = 5.0 Hz, H-4), 7.26 – 7.34 (m, 15H, 15 \times Ph-H).

{^{13}}C NMR (125 MHz, CDCl_{3}) \delta [ppm] : 38.63 (CH_{3}, OMs), 57.30 (CH_{2}, -C-5), 58.31 (CH_{2}, -C-5^\ast), 68.50 (CH, C-2), 70.05 (CH_{2}, -C-1), 71.86 (CH_{2}, -C-3^\ast), 73.32 (CH_{2}, -C-1^\ast), 82.26 (CH, C-4), 85.12 (CH, C-3), 127.21, 127.64, 127.73, 127.86, 127.96, 128.32, 128.38, 128.41, 128.87 (15 \times Ph-CH), 137.53, 137.88 (2 \times Ph-C_{o}), OBn), 138.12 (C_{p}, NBn).

IR (neat) \bar{\nu} [cm^{-1}] : 3029 (w), 2863 (w), 1495 (w), 1454 (m), 1362 (m), 1268(w), 1207 (w), 1175 (vs), 1096 (s), 1083 (s), 1028 (m), 956 (s), 851 (m), 737 (vs) 720 (w).

HRMS (ESI) calculated for C_{27}H_{32}NO_{5}S [M + H^+] : 482.2001, found 482.2009.
Experimental Section

(–)-(2S,3S,4S,5S)-2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine (6/56)

(–)-2,5-Dideoxy-2,5-imino-L-mannitol, L-DMDP

To a suspension of Pd-enriched Pearlman’s catalyst (35 mg Pd black + 46 mg Pd(OH)$_2$/C) in AcOH (2 mL) was added a solution of pyrrolidine diol 7/23 (420 mg, 0.97 mmol) in AcOH (3 mL) at rt. The reaction flask was evacuated under gentle vacuum and flushed three times with H$_2$ and then left with vigorous stirring under an atmosphere of H$_2$ at 25 ºC overnight (18 h) by which time ESI-MS indicated full conversion of the starting material. The catalyst was subsequently removed by filtration through a pad of celite and rinsed thoroughly with AcOH. The combined filtrate and washings were then evaporated to dryness affording crude L-DMDP as a dark orange syrup. Purification of the crude material by aqueous ion-exchange chromatography on basic DOWEX 1X8 (100-200 mesh) resin provided pure L-DMDP (153 mg, 0.94 mmol) as a colourless oil that solidified overnight to white, hygroscopic, needle-shaped crystals.

IXC : $\varnothing$ 2.0 cm × 10 cm, $V_F$ = 21 – 22 mL, resin : DOWEX 1X8 (OH$^-$), eluent : water

Yield : 97%

Chemical formula : C$_6$H$_{13}$NO$_4$

Molecular weight : 163.17

Appearance : White, hygroscopic, needle-shaped crystals

Opt. rotation :

$[\alpha]_D^{25}$ = –53.4º ($c$ = 3.2 g/100 mL H$_2$O),

$[\alpha]_D^{25}$ = –53.1º ($c$ = 2.01 g/100 mL H$_2$O),

$[\alpha]_D^{25}$ = –55.6º ($c$ = 2.01 g/100 mL MeOH);

lit. for (–)-DMDP : $[\alpha]_D^{25}$ = –54.3º ($c$ = 0.3 g/100 mL H$_2$O);[4]

$[\alpha]_D^{25}$ = –52.7º ($c$ = 0.28 g/100 mL H$_2$O);[5]

lit. for (+)-DMDP : $[\alpha]_D^{20}$ = +56.4º ($c$ = 7.0 g/100 mL H$_2$O);[6]

$[\alpha]_D^{20}$ = +53.8º ($c$ = 0.32 g/100 mL H$_2$O);[7]

$[\alpha]_D^{25}$ = +55.8º ($c$ = 1.0 g/100 mL H$_2$O);[8]
Experimental Section

$^1$H NMR (500 MHz, D$_2$O) δ [ppm] : 3.04 (m, 2H, H-2, H-5), 3.64 (dd, 2H, $J_1$ = 6.3 Hz, $J_2$ = 11.6 Hz, H$_A$-1, H$_A$-6), 3.73 (dd, 2H, $J_1$ = 4.3 Hz, $J_2$ = 11.6 Hz, H$_B$-1, H$_B$-6), 3.85 (ddd, 2H, $J_1$ = 4.6 Hz, $J_2$ = 6.9 Hz, $J_3$ = 8.6 Hz, H-3, H-4).

$^{13}$C NMR (125 MHz, D$_2$O) δ [ppm] : 64.41 (2 × CH, C-2, C-5), 64.93 (2 × CH$_2$, C-1, C-6), 80.74 (2 × CH, C-3, C-4).

$^1$H NMR (500 MHz, CD$_3$OD) δ [ppm] : 2.99 (m, 2H, H-2, H-5), 3.58 (dd, 2H, $J_1$ = 6.2 Hz, $J_2$ = 11.1 Hz, H$_A$-1, H$_A$-6), 3.68 (dd, 2H, $J_1$ = 4.1 Hz, $J_2$ = 11.1 Hz, H$_B$-1, H$_B$-6), 3.77 (ddd, 2H, $J_1$ = 4.1, $J_2$ = 6.2 Hz, $J_3$ = 7.7 Hz, H-3, H-4).

$^{13}$C NMR (125 MHz, CD$_3$OD) δ [ppm] : 63.60 (2 × CH, C-2, C-5), 64.57 (2 × CH$_2$, C-1, C-6), 79.79 (2 × CH, C-3, C-4).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3380 (br), 3259 (m), 2917 (w), 2857 (w), 1466 (w), 1446 (w), 1403 (m), 1379 (w), 1355 (w), 1341 (w), 1252 (w), 1211 (w), 1181 (w), 1150 (vs), 1120 (m), 1102 (w), 1058 (vs), 1051 (vs), 1019 (vs), 974 (s), 920 (w), 820 (s), 762 (w), 752 (m), 737 (m), 727 (w), 710 (w), 684 (m).

HRMS (ESI) calculated for C$_6$H$_{14}$NO$_4$ [M + H$^+$] : 164.0923, found 164.0930.

(-)-(2S,3S,4S)-2-Hydroxymethylpyrrolidine-3,4-diol (7/32)

1,4-Dideoxy-1,4-imino-L-arabinitol, L-AB1

To the suspension of Pd-enriched Pearlman’s catalyst (35 mg Pd black + 46 mg Pd(OH)$_2$/C) in AcOH (2 mL) was added a solution of pyrrolidinol 7/24 (404 mg, 1 mmol) in AcOH (3 mL) at rt. The reaction flask was evacuated under gentle vacuum and backfilled three times with H$_2$ and then left with vigorous stirring under an atmosphere of H$_2$ at 25 ºC overnight (18 h) by which time ESI-MS indicated full conversion of the starting material. The catalyst was subsequently removed by filtration through a pad of celite and rinsed thoroughly with AcOH. The combined filtrate and washings were then evaporated to dryness affording crude L-AB1 as a dark orange syrup. Purification of the crude material by aqueous ion-exchange chromatography on basic DOWEX 1X8 (100-200 mesh) resin provided pure L-AB1 (133 mg, 1 mmol) as a colourless gum.
Experimental Section

IXC : $\varnothing$ 2.0 cm × 5 cm, $V_{Fr} = 12 – 13$ mL, resin : DOWEX 1X8 (OH$^-$), eluent : water

Yield : 100%

Chemical formula : C$_5$H$_{11}$NO$_3$

Molecular weight : 133.15

Appearance : Colourless gum

TLC : $R_f$ = n/a due to the high polarity of the compound

Opt. rotation :

$[\alpha]_D^{25} = -8.3^\circ$ (c = 6.15 g/100 mL H$_2$O),

$[\alpha]_D^{25} = -4.4^\circ$ (c = 6.3 g/100 mL MeOH),

$[\alpha]_D^{25} = -32.1^\circ$ (HCl salt, c = 5.28 g/100 mL H$_2$O);

lit. for L-AB1:

$[\alpha]_D^{25} = -34.6^\circ$ (HCl salt, c = 0.37 g/100 mL H$_2$O),\textsuperscript{[9]}

$[\alpha]_D^{25} = -32.9^\circ$ (HCl salt, c = 0.32 g/100 mL H$_2$O),\textsuperscript{[10]}

$[\alpha]_D^{20} = -11.9^\circ$ (c = 0.044 g/100 mL MeOH);\textsuperscript{[11]}

$[\alpha]_D^{20} = -12.0^\circ$ (c = 0.21 g/100 mL MeOH),\textsuperscript{[12]}

lit. for D-AB1:

$[\alpha]_D^{20} = +4.4^\circ$ (c = 0.09 g/100 mL H$_2$O),\textsuperscript{[13]}

$[\alpha]_D^{25} = +7.8^\circ$ (c = 0.46 g/100 mL H$_2$O),\textsuperscript{[9]}

$[\alpha]_D^{25} = +37.9^\circ$ (HCl salt, c = 0.53 g/100 mL H$_2$O).\textsuperscript{[9]}

$^1$H NMR (500 MHz, D$_2$O) $\delta$ [ppm] : 2.84 (dd, 1H, $J_1 = 4.0$ Hz, $J_2 = 12.2$ Hz, H$_A$-5), 2.98 (q, 1H, $J = 5.6$ Hz, H-2), 3.12 (dd, 1H, $J_1 = 5.8$ Hz, $J_2 = 12.2$ Hz, H$_B$-5), 3.66 (dd, 1H, $J_1 = 6.4$ Hz, $J_2 = 11.6$ Hz, H$_A$-1), 3.73 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 11.6$ Hz, H$_B$-1), 3.84 (dd, 1H, $J_1 = 3.8$ Hz, $J_2 = 5.5$ Hz, H-3), 4.15 (dt, 1H, $J_1 = 3.9$ Hz, $J_2 = 5.8$ Hz, H-4).

$^{13}$C NMR (125 MHz, D$_2$O) $\delta$ [ppm] : 53.36 (CH$_2$, C-5), 64.89 (CH$_2$, C-1), 67.98 (CH, C-2), 80.30 (CH, C-4), 81.88 (CH, C-3).

$^1$H NMR (500 MHz, CD$_3$OD) $\delta$ [ppm] : 2.84 (dd, 1H, $J_1 = 2.9$ Hz, $J_2 = 11.9$ Hz, H$_A$-5), 2.93 (q, 1H, $J = 4.9$ Hz, H-2), 3.06 (dd, 1H, $J_1 = 5.2$ Hz, $J_2 = 11.9$ Hz, H$_B$-5), 3.64 (dd, 1H, $J_1 = 5.6$ Hz, $J_2 = 11.1$ Hz, H$_A$-1), 3.69 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 11.1$ Hz, H$_B$-1), 3.80 (*t*, 1H, $J = 3.7$ Hz, H-3), 4.00 (m, 1H, H-4).

$^{13}$C NMR (125 MHz, CD$_3$OD) $\delta$ [ppm] : 53.18 (CH$_2$, C-5), 63.17 (CH$_2$, C-1), 68.27 (CH, C-2), 79.25 (CH, C-4), 80.65 (CH, C-3).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3286 (br) [N–H/O–H], 2929 (m) [C–H], 1665 (w), 1420 (m), 1333 (m), 1108 (m), 1052 (vs) [C–O], 1014 (s), 849 (s), 839 (s), 747 (s), 725 (s), 712 (s).

HRMS (ESI) calculated for C$_5$H$_{11}$NO$_3$ [M + H$^+$] : 134.0817, found 134.0823.
E.4 Synthesis of Pyrrolidine Carbaldehyde 8/2

(+)-(25,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-styrylpyrrolidine (8/1)

To the suspension of NaH (60% dispersion in mineral oil, 360 mg, 9.0 mmol, 1.5 equiv) in anhydrous n-hexane (9 mL) was added dropwise a solution of pyrrolidinol 7/12 (3034 mg, 6.0 mmol, 1 equiv) in anhydrous THF (40 mL) under an atmosphere of N₂ at 0 °C. This mixture was stirred for 25 min while warming to rt. A solution of BnBr (1180 mg, 6.9 mmol, 1.15 equiv) in dry THF (7 mL) followed by a catalytic amount of TBAI (0.9 mmol, 0.15 equiv) were then added at rt whereupon the mixture was left stirring at 25 °C under a blanket of N₂. ESI-MS analysis after 24 h indicated still the presence of unconverted starting material in the reaction mixture wherefore additional NaH (240 mg, 6.0 mmol, 1.0 equiv), BnBr (205 mg, 1.2 mmol, 0.2 equiv) and TBAI (222 mg, 0.6 mmol, 0.1 equiv) were added. After further stirring for 24 h the mixture was cooled to 0 °C, diluted with Et₂O (50 mL) and quenched with H₂O (50 mL). After extraction of the aqueous phase with Et₂O (4 × 50 mL) the organic phases were dried over MgSO₄, filtered and concentrated in vacuo to give an orange, syrupy residue. Purification of the residue by column chromatography afforded the title compound as a yellow syrup that darkened and solidified upon storage at 4 °C. Recrystallisation of this solid from MeOH gave fully benzylated pyrrolidine 8/1 (3375 mg, 5.66 mmol) as an off-white, wax-like solid.

CC : ∅ 3.5 cm x 10 cm, V_Fr = 45 mL, eluent EA/PE 0 : 100 → 10 : 90
Yield : 94%

Chemical formula : C₄₁H₄₁NO₃
Molecular weight : 595.79
Appearance : Off-white, wax-like solid
TLC : R_f = 0.46 (DE/PE = 1 : 4), CAM
Melting point : θ_m = 68–69 °C (recryst. from MeOH)
Optical rotation : [α]_D^20 = +24.4° (c = 4.8 g/100 mL CHCl₃)
[α]_D^25 = +22.9° (c = 5.3 g/100 mL CHCl₃)
1H NMR (500 MHz, CDCl3) δ [ppm] : 3.31 (m, 1H, H-2), 3.54 (dd, 1H, J1 = 4.3 Hz, J2 = 9.6 Hz, Hα-1), 3.58 (dd, 1H, J1 = 6.0 Hz, J2 = 9.6 Hz, Hβ-1), 3.66 (d, 1H, J = 14.4 Hz, Hα-5*), 3.75 (dd, 1H, J1 = 4.6 Hz, J2 = 9.3 Hz, H-5), 3.94 (dd, 1H, J1 = 3.2 Hz, J2 = 4.3 Hz, H-4), 3.97 (d, 1H, J = 14.5 Hz, Hβ-5*), 4.07 (t, 1H, J = 3.0 Hz, H-3), 4.46 (d, 1H, J = 12.2 Hz, Hα-1*), 4.49 (d, 1H, J = 12.1 Hz, Hβ-1*), 4.50 (d, 1H, J = 12.0 Hz, Hα-3*), 4.51 (d, 1H, J = 12.0 Hz, Hα-4*), 4.55 (d, 1H, J = 12.0 Hz, Hβ-3*), 4.58 (d, 1H, J = 12.0 Hz, Hβ-4*), 6.25 (dd, 1H, J1 = 9.3 Hz, J2 = 15.9 Hz, H-6), 6.45 (d, 1H, J = 15.8 Hz, H-7), 7.18 – 7.35 (m, 25H × Ph-H).

13C NMR (125 MHz, CDCl3) δ [ppm] : 51.44 (CH2, C-5*), 64.11 (CH, C-2), 69.33 (CH, C-5), 69.33 (CH2, C-1), 71.95 (CH2, C-3*), 71.81 (CH2, C-4*), 73.24 (CH2, C-1*), 85.87 (CH, C-3), 88.17 (CH, C-4), 126.40, 126.53, 127.48, 127.51, 127.52, 127.66, 127.75, 127.83, 128.10, 128.20, 128.27, 128.28, 128.30, 128.50 (25 × Ph-CH), 129.92 (CH, C-6), 133.52 (CH, C-7), 136.89 (Styryl-Cq), 138.28, 138.31, 138.37 (3 × Ph-Cq, OBn), 139.70 (Ph-Cq, NBn).

IR (neat) ν [cm⁻¹] : 3062 (w), 3034 (w), 2905 (w), 2852 (w), 1495 (w), 1454 (w), 1363 (w), 1281 (w), 1212 (w), 1181 (w), 1126 (w), 1112 (w), 1089 (m), 1077 (s), 1023 (w), 1005 (w), 979 (w), 969 (w), 953 (w), 916 (w), 860 (w), 821 (w), 751 (vs), 735 (m), 698 (vs), 677 (w).

HRMS (ESI) calculated for C41H42NO3 [M + H⁺] : 596.3165, found 596.3154.

(+)-(2S,3S,4R)-3,4-bis(benzyloxy)-2-benzyloxyethyl-5-oxopyrrolidine (8/10)

Lactam 8/10 (45 mg, 0.11 mmol) was the only product to be isolated and identified from the ozonolysis-reduction reaction of the pyrrolidinium chloride of styryl pyrrolidine 8/1 (759 mg, 1.2 mmol) according to the procedure of GÉNISSON et al.[14] after separation and three-time purification by column chromatography.

CC : ∅ 1.7 cm × 10 cm, VFr = 22 mL, eluent EA/PE 7.5 : 92.5 → 75 : 25

Yield : 9%

Chemical formula : C26H27NO4

Molecular weight : 417.50
**Appearance** : Pale yellow oil

**TLC** : $R_f = 0.13$ (DE/PE = 2 : 1), CAM

**Optical rotation** : $[\alpha]_{D}^{25} = +2.6^\circ$ ($c = 1.0$ g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 3.31 (t, 1H, $J = 8.9$ Hz, H$_{\alpha}$-1), 3.60 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 9.5$ Hz, H$_{\beta}$-1), 3.66 (ddd, 1H, $J_1 = 3.6$ Hz, $J_2 = 5.9$ Hz, $J_3 = 8.9$ Hz, H-2), 3.88 (t, 1H, $J = 6.0$ Hz, H-3), 4.22 (d, 1H, $J = 6.3$ Hz, H-4), 4.46 (d, 1H, $J = 12.4$ Hz, H$_{\alpha}$-1*), 4.48 (d, 1H, $J = 12.4$ Hz, H$_{\beta}$-1*), 4.49 (d, 1H, $J = 11.8$ Hz, H$_{\alpha}$-3*), 4.60 (d, 1H, $J = 11.7$ Hz, H$_{\beta}$-3*), 4.79 (d, 1H, $J = 11.6$ Hz, H$_{\alpha}$-4*), 5.10 (d, 1H, $J = 11.6$ Hz, H$_{\beta}$-4*), 5.98 (s, 1H, NH), 7.20 – 7.42 (m, 15H, 15 × Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 55.98 (CH, C-2), 71.47 (CH$_2$, C-1), 72.27 (CH$_2$, C-3*), 72.59 (CH$_2$, C-4*), 73.47 (CH$_2$, C-1*), 80.63 (CH, C-4), 81.09 (CH, C-3), 127.79, 127.85, 127.92, 127.97, 127.99, 128.34, 128.43, 128.46, 128.54 (15 × Ph-CH), 137.37, 137.38, 137.53 (3 × Ph-C$_q$), 172.72 (CO, C-5).

**IR (neat)** $\tilde{\nu}$ [cm$^{-1}$] : 3410 (br) [N–H], 3223 (w), 3031 (w), 2866 (w), 1714 (m) [C=O], 1453 (m), 1358 (w), 1106 (s) [C–O], 1027 (m), 690 (vs).

**HRMS (ESI)** calculated for C$_{26}$H$_{38}$NO$_4$ [M + H$^+$] : 418.2018, found 418.2027.

(+)-(2$S$3$S$,4$S$)-$N$-Benzy1-3,4-bis(benzyloxy)-2-benzzyloxyethylpyrrolidine (8/16)

Pyrrolidine 8/16 (133 mg, 0.27 mmol) was obtained as a major by-product from the ozonolysis-reduction reaction of the pyrrolidinium bisulfate 8/31 (833 mg, 1.2 mmol) after separation by column chromatography according to the procedure of BEHR et al.$^{[15]}$

**CC** : ∅ 1.7 cm × 10 cm, $V_{Fr} = 15 – 16$ mL, eluent EA/PE 10 : 90 → 15 : 85

**Yield** : 22.5%

**Chemical formula** : C$_{33}$H$_{35}$NO$_3$

**Molecular weight** : 493.64

**Appearance** : Pale yellow oil
Experimental Section

TLC : $R_f = 0.42$ (DE/PE = 1 : 2), CAM

Optical rotation : $[\alpha]_D^{25} = +38.4^\circ$ ($c = 5.07$ g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 2.56 (dd, 1H, $J_1 = 5.1$ Hz, $J_2 = 10.6$ Hz, H$_{\alpha-5}$), 2.87 (q, 1H, $J = 5.3$ Hz, H-2), 3.04 (d, 1H, $J = 10.7$ Hz, H$_{\beta-5}$), 3.49 (d, 1H, $J = 13.3$ Hz, H$_A^{-5*}$), 3.60 (d, 2H, $J = 5.6$ Hz, H$_2$-1), 3.91 (m, 2H, H-3, H-4), 4.13 (d, 2H, $J = 13.5$ Hz, H$_B^{-5*}$), 4.38 (d, 1H, $J = 12.2$ Hz, H$_A^{-4*}$), 4.45 (d, 1H, $J = 12.4$ Hz, H$_B^{-4*}$), 4.51 (2s, 4H, H$_2$-1*, H$_2$-3*), 7.21 – 7.35 (m, 20H, 20 × Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 56.97 (CH$_2$, C-5), 59.11 (CH$_2$, C-5*), 68.45 (CH, C-2), 70.87 (CH$_2$, C-4*), 71.31 (CH$_2$, C-1), 71.39 (CH$_2$, C-3*), 73.20 (CH$_2$, C-1*), 81.57 (CH, C-4), 85.89 (CH, C-3), 126.87, 127.47, 127.55, 127.56, 127.66, 127.74, 127.75, 128.15, 128.30, 128.94 (20 × Ph-CH), 138.22, 138.42 (3 × Ph-C$_q$, OBn), 138.82 (Ph-C$_q$, Nbn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3029 (w), 2865 (w), 1495 (w), 1454 (m), 1366 (w), 1269 (w), 1206 (w), 1096 (vs) [C−O], 1028 (m), 909 (w), 845 (w), 735 (vs).

HRMS (ESI) calculated for C$_{33}$H$_{36}$NO$_3$ [M + H$^+$] : 494.2695, found 494.2687.

$^{(+)-(2S,3S,4S,5R)-N-Benzyl-3,4-bis(benzyloxy)-2-benzylxymethyl-5-hydroxymethyl-pyrrolidine (8/15)}$

Pyrrolidine alcohol 8/15 (20 mg, 0.04 mmol) was obtained as a minor by-product from the ozonolysis-reduction reaction of the pyrrolidinium bisulfate 8/31 (833 mg, 1.2 mmol) according to the procedure of BEHR et al.$^{[15]}$ after separation by column chromatography.

CC : $\emptyset$ 1.7 cm × 11 cm, $V_{Fr} = 15 – 16$ mL, eluent EA/PE 10 : 90 → 30 : 70

Yield : 3%

Chemical formula : C$_{34}$H$_{37}$NO$_4$

Molecular weight : 523.66

Appearance : Yellow oil

TLC : $R_f = 0.25$ (DE/PE = 1 : 1), CAM
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Optical rotation : $\left[\alpha\right]_D^{25} = +21.8^\circ$ (c = 1.0 g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 3.04 ("d", 1H, $J = 4.0$ Hz, H-2), 3.15 (s, 1H, H-5), 3.31 (dd, 1H, $J_1 = 3.1$ Hz, $J_2 = 9.7$ Hz, H$_A$-1), 3.41 (m, 2H, H$_B$-1, H$_A$-6), 3.58 (m, 1H, H$_B$-6), 3.82 (d, 1H, $J = 14.0$ Hz, H$_A$-5*), 3.86 (d, 1H, $J = 14.0$ Hz, H$_B$-5*), 4.05 (m, 1H, H-4), 4.16 (t, 1H, $J = 5.0$ Hz, H-3), 4.37 (d, 1H, $J = 12.4$ Hz, H$_A$-1*), 4.40 (d, 1H, $J = 12.5$ Hz, H$_B$-1*), 4.48, 4.53 (2d, 2H, $J_1 = 11.8$ Hz, $J_2 = 11.3$ Hz, H$_A$-3*, H$_A$-4*), 4.55, 4.64 (2d, 2H, $J_1 = 11.0$ Hz, $J_2 = 11.7$ Hz, H$_B$-3*, H$_B$-4*), 7.22 – 7.35 (m, 20H, 20 $\times$ Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 58.82 (CH$_2$, C-5*), 60.33 (CH$_2$, C-6), 64.48 (CH, C-5), 66.68 (CH, C-2), 69.88 (CH$_2$, C-1), 72.18*, 72.25* (2 $\times$ CH$_2$, C-3*, C-4*), 73.11 (CH$_2$, C-1*), 82.29 (CH, C-3), 83.51 (CH, C-4), 127.23, 127.56, 127.60, 127.69, 127.77, 127.80, 127.81, 128.32, 128.34, 128.46, 128.97 (20 $\times$ Ph-CH), 137.87, 138.21, 138.44 (3 $\times$ Ph-C$_q$, OBn), 139.12 (Ph-C$_q$, Nb).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3480 (br) [O$-$H], 3029 (w), 2866 (w), 1496 (w), 1454 (m), 1365 (w), 1205 (w), 1095 (vs), 1072 (vs), 1028 (m), 908 (w), 819 (w), 736 (vs).

HRMS (ESI) calculated for C$_{34}$H$_{38}$NO$_5$ [M + H$^+$] : 524.2801, found 524.2813.

(+)-(2S,3S,4R)-N-methoxy(phenyl)methyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-oxo-pyrrolidine (8/35)

$N$-(methoxy(phenyl)methyl)lactam 8/35 (82 mg, 0.15 mmol) was the only product to be isolated and identified from the ozonolysis-reduction reaction of the pyrrolidinium perchlorate 8/34 (834 mg, 1.2 mmol) after separation and two-time purification by column chromatography according to the procedure of WONG et al.$^{[16]}$

CC : $\varnothing$ 1.7 cm $\times$ 10 cm, $V_{Fr} = 24$ mL, eluent EA/PE 7.5 : 92.5 $\rightarrow$ 25 : 75

Yield : 13%

Chemical formula : C$_{34}$H$_{33}$NO$_5$

Molecular weight : 537.65
Appearance : Yellow syrup

TLC : $R_f = 0.30$ (DE/PE = 1 : 1), CAM

Optical rotation : $[\alpha]_{D}^{25} = +8.0^\circ$ ($c = 1.7$ g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 3.27 (dt, 1H, $J_1 = 3.5$ Hz, $J_2 = 6.7$ Hz, H-2), 3.49 (s, 3H, OCH$_3$), 3.54 (dd, 1H, $J_1 = 6.4$ Hz, $J_2 = 9.7$ Hz, H$_{A-1}$), 3.58 (dd, 1H, $J_1 = 3.1$ Hz, $J_2 = 9.7$ Hz, H$_{B-1}$), 4.19 (d, 1H, $J = 4.0$ Hz, H-4), 4.22 (t, 1H, $J = 3.8$ Hz, H-3), 4.39 (2d, 2H, $J_1 = 12.0$ Hz, $J_2 = 11.6$ Hz, H$_A-1^*$, H$_B-1^*$), 4.45 (2d, 2H, $J_1 = 11.8$ Hz, $J_2 = 11.6$ Hz, H$_A-3^*$, H$_B-3^*$), 4.82 (d, 1H, $J = 11.8$ Hz, H$_A-4^*$), 5.04 (d, 1H, $J = 11.8$ Hz, H$_B-4^*$), 6.38 (s, 1H, H-5*), 7.12 – 7.16, 7.21 – 7.41 (2m, 20H, 20 $\times$ Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 56.34 (OCH$_3$), 58.69 (CH, C-2), 68.26 (CH$_2$, C-1), 71.71 (CH$_3$, C-3*), 72.46 (CH$_2$, C-4*), 72.99 (CH$_2$, C-1*), 78.00 (CH, C-3), 81.24 (CH, C-4), 82.77 (CH, C-5*), 126.14, 127.48, 127.57, 127.78, 127.83, 127.87, 128.19, 128.25, 128.31, 128.33, 128.42, 128.51 (20 $\times$ Ph-CH), 136.38 (Ph-C$_q$, NBn), 137.51, 137.58, 137.94 (3 $\times$ Ph-C$_q$, OBN), 173.22 (CO, C-5).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3031 (w), 2865 (w), 1705 (m) [C=O], 1496 (w), 1454 (m), 1416 (w), 1358 (w), 1275 (w), 1213 (w), 1174 (w), 1096 (s), 1074 (s), 1028 (m), 909 (m), 824 (w), 733 (vs).

HRMS (ESI) calculated for C$_{34}$H$_{35}$NO$_5$Na [M + Na$^+$] : 560.2413, found 560.2426.

(+)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-(1’,2’-dihydroxyphenyl)pyrrolidine (8/46)

Procedure A : To the mixture of styryl pyrrolidine 8/1 (596 mg, 1.0 mmol, 1.0 equiv) and NMO (141 mg, 1.2 mmol, 1.2 equiv) in acetone/water (1 : 1, 10 mL) was added a solution of OsO$_4$ in $t$-BuOH (0.5 mL, 10 mg/1 mL, 0.05 equiv). The reaction mixture was stirred for 8 h at rt and then treated with a further portion of NMO (141 mg, 1.2 mmol, 1.2 equiv) and OsO$_4$ solution (0.5 mL, 0.05 equiv). After a total reaction time of 24 h solid Na$_2$SO$_3$ (500 mg) and
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silica gel (1 g) were added and the heterogeneous mixture was concentrated in vacuo. Purification by column chromatography yielded the brown, syrupy diol 8/46 (467 mg, 0.74 mmol) as mixture of diastereomers (d.r. = 60 : 40).

CC : ∅ 1.7 cm × 10 cm, VFr = 15–16 mL, eluent EA/PE 10 : 90 → 40 : 60
Yield : 74%

Procedure B : To the solution of styryl pyrrolidine 8/1 (596 mg, 1.0 mmol, 1.0 equiv) in acetone/water (9 : 1, 10 mL) was added NMO (246 mg, 2.1 mmol, 2.1 equiv) in one portion followed by solid K₂OsO₄·2 H₂O (18.4 mg, 0.05 mmol, 0.05 equiv). The reaction mixture was stirred at rt for 32 h by which time TLC analysis showed full conversion of the starting material. The mixture was then concentrated in vacuo without further treatment to give a black, oily residue. Purification by column chromatography afforded the diastereomeric diols 8/46a and 8/46b (d.r. = 60 : 40) as a brown syrup.

CC : ∅ 1.7 cm × 10 cm, VFr = 15–16 mL, eluent EA/PE 10 : 90 → 30 : 70
Yield : 78%

Chemical formula : C₄₁H₄₃NO₅

Molecular weight : 629.78

Appearance : Brown syrup

TLC : Rf = 0.48 (DE/PE = 2 : 1), CAM (less polar, minor diastereoisomer)
Rf = 0.38 (DE/PE = 2 : 1), CAM (more polar, major diastereoisomer)

Optical rotation : [α]D²⁵ = +13.4° (c = 1.1 g/100 mL CHCl₃) (less polar, minor diastereoisomer)
[α]D²⁵ = +45.0° (c = 2.7 g/100 mL CHCl₃) (more polar, major diastereoisomer)

¹H NMR (500 MHz, CDCl₃) δ [ppm] (less polar, minor diastereoisomer) : 3.28 (dd, 1H, J₁ = 2.6 Hz, J₂ = 5.1 Hz, H-5), 3.55 (m, 1H, H-2), 3.62 (dd, 1H, J₁ = 7.0 Hz, J₂ = 9.6 Hz, Hₐ-1), 3.70 (dd, 1H, J₁ = 5.7 Hz, J₂ = 9.7 Hz, Hₐ-1), 3.74 (t, 1H, J = 4.7 Hz, H-6), 3.99" (d, 1H, J = 13.8 Hz, Hₐ-5"), 4.00" (s, 1H, H-4), 4.04 (d, 1H, J = 13.7 Hz, Hₐ-5"), 4.11 ("d", 1H, J = 1.7 Hz, H-3), 4.29" (d, 1H, J = 11.8 Hz, Hₐ-4"), 4.32" (d, 1H, J = 11.9 Hz, Hₐ-4"), 4.42 (s, 2H, Hₐ-1"), 4.49 (d, 1H, J = 12.0 Hz, Hₐ-3"), 4.54 (d, 1H, J = 12.0 Hz, Hₐ-3"), 4.64 (d, 1H, J = 4.0 Hz, H-7), 7.15 – 7.40 (m, 25H, 25 × Ph-H).

¹³C NMR (125 MHz, CDCl₃) δ [ppm] (less polar, minor diastereoisomer) : 53.27 (CH₂, C-5"), 64.48 (CH, C-2), 67.11 (CH₂C-1), 68.32 (CH, C-5), 71.19 (CH₂, C-4"), 71.69 (CH₂, C-3"), 73.12 (CH₂, C-1"), 73.79 (CH, C-7), 74.81 (CH, C-6), 84.47 (CH, C-3), 86.41 (CH, C-4), 126.59, 127.18,
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127.52, 127.56, 127.58, 127.61, 127.83, 127.91, 128.32, 128.39, 128.45, 128.46, 128.56 (25 × Ph–CH), 137.66, 137.79, 138.06 (3 × Ph–Cq, OBN), 138.95 (Ph–Cq, NBn), 141.15 (PhEt–Cq).

\(^1^H\) NMR (500 MHz, CDCl\(_3\)) δ [ppm] (more polar, major diastereoisomer) : 2.96 (s, 1H, H-5), 3.45 (m, 2H, H-2, H-1), 3.61 ("d", 1H, J = 4.9 Hz, H-5*), 3.78" (d, 1H, J = 14.2 Hz, H-1*), 3.81" (d, 1H, J = 7.8 Hz, H-6), 4.06 (s, 1H, H-3), 4.30" (s, 1H, H-4), 4.33" (d, 1H, J = 12.1 Hz, H-5*), 4.43" (d, 1H, J = 11.9 Hz, H-1*), 4.49" (d, 1H, J = 11.9 Hz, H-3*), 4.56" (d, 1H, J = 12.0 Hz, H-3*), 4.57" (d, 1H, J = 7.6 Hz, H-7), 7.13 – 7.43 (m, 25H, 25 × Ph–H).

\(^1^C\) NMR (125 MHz, CDCl\(_3\)) δ [ppm] (more polar, major diastereoisomer) : 51.20 (CH\(_2\), C-5*), 3.36 (CH, C-2), 66.74 (CH\(_2\)-C-1), 68.82 (CH, C-5), 71.07 (CH\(_2\), C-3*), 71.68 (CH, C-3), 73.03 (CH, C-6), 73.17 (CH\(_2\), C-1*), 75.18 (CH, C-7), 81.64 (CH, C-3), 83.55 (CH, C-4), 127.05, 127.32, 127.43, 127.51, 127.84, 127.92, 127.97, 128.08, 128.25, 128.42, 128.47 (25 × Ph–CH), 137.66, 137.68, 138.12 (3 × Ph–Cq, OBN), 138.70 (Ph–Cq, NBn), 140.23 (PhEt–Cq).

IR (neat) \(\tilde{\nu} \ [cm^{-1}] \) : 3455 (br) [O–H], 3030 (w), 2866 (w), 1495 (w), 1454 (m), 1366 (w), 1205 (m), 1090 (vs), 1028 (s), 910 (w), 840 (w), 737 (vs).

HRMS (ESI) calculated for C\(_{41}\)H\(_{44}\)NO\(_5\) [M + H\(^+\)] : 630.3219, found 630.3208.

Oxidative diol cleavage and reduction

To the vigorously stirred solution of the diastereomeric diols 8/46 (567 mg, 0.9 mmol, 1.0 equiv) in DCM (10 mL) was added silica gel-supported NaIO\(_4\) reagent (1.2 mmol NaIO\(_4\)/1 g SiO\(_2\), 2.7 g, 3.24 mmol, 3.6 equiv) at 0 °C. After 4 h stirring at 0 °C the mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with DCM (3 × 5 mL) to give a clear, dark orange solution. This solution was diluted with EtOH (10 mL) and treated with NaBH\(_4\) (137 mg, 3.6 mmol, 4 equiv) at 0 °C. The reaction was quenched after 90 min by the addition on 1 M NH\(_4\)Cl solution (10 mL) followed by 1 M NaHCO\(_3\) solution (10 mL). After extraction of the aqueous phase with DCM (3 × 40 mL) the organic phases

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were dried over MgSO₄, filtered and concentrated \emph{in vacuo}. Column chromatography of the residue afforded three products in low yields (besides the obvious BnOH), however, none of them was the desired pyrrolidine alcohol 8/9.

CC : \( \varnothing \ 1.7 \text{ cm} \times 11 \text{ cm} \), \( V_\text{Fr} = 15–16 \ \text{ mL} \), eluent \( \text{EA/PE} \ 10 : 90 \rightarrow 30 : 70 \)

The three obtained products could be identified as the following compounds:

\((-)-(2S,3S,4R)-N\text{-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-oxopyrrolidine (8/17)}\)

\[\text{Isolated yield : 11\% (52 mg)}\]
\[\text{Chemical formula : C}_{33}\text{H}_{33}\text{NO}_{4}\]
\[\text{Molecular weight : 507.62}\]
\[\text{Appearance : Yellow oil}\]
\[\text{TLC : } R_f = 0.40 (\text{DE/PE} = 1 : 1), \text{ CAM}\]
\[\text{Optical rotation : } [\alpha]_D^{25} = -4.1^\circ (c = 2.77 \text{ g/100 mL CHCl}_3)\]

\(\text{H NMR (500 MHz, CDCl}_3) \delta [\text{ppm}] : 3.41^\circ (\text{dd, 1H, } J_1 = 4.2 \text{ Hz, } J_2 = 9.7 \text{ Hz, } H_A-1), 3.43^\circ (\text{m, 1H, H-2}), 3.51 (\text{dd, 1H, } J_1 = 3.0 \text{ Hz, } J_2 = 9.7 \text{ Hz, } H_B-1), 4.02 (\text{d, 1H, } J = 15.2 \text{ Hz, } H_A-5^*), 4.07 (\text{t, 1H, } J = 5.2 \text{ Hz, H-3}), 4.24 (\text{d, 1H, } J = 5.4 \text{ Hz, H-4}), 4.33 (\text{d, 1H, } J = 11.9 \text{ Hz, H_A-1*}), 4.38 (\text{d, 1H, } J = 11.9 \text{ Hz, H_B-1*}), 4.45 (\text{d, 1H, } J = 11.6 \text{ Hz, H_A-3*}), 4.57 (\text{d, 1H, } J = 11.6 \text{ Hz, H_B-3*}), 4.84 (\text{d, 1H, } J = 11.6 \text{ Hz, H_A-4*}), 4.99 (\text{d, 1H, } J = 15.0 \text{ Hz, H_B-5*}), 5.14 (\text{d, 1H, } J = 11.6 \text{ Hz, H_B-4*}), 7.13 – 7.43 (\text{m, 20H, 20 × Ph-H}).\]

\(\text{C NMR (125 MHz, CDCl}_3) \delta [\text{ppm}] : 44.21 (\text{CH}_2, \text{C-5*}), 55.42 (\text{CH, C-2}), 67.26 (\text{CH}_2, \text{C-1}), 72.13 (\text{CH}_2, \text{C-3*}), 72.41 (\text{CH}_2, \text{C-4*}), 73.15 (\text{CH}_2, \text{C-1*}), 78.74 (\text{CH, C-3}), 80.95 (\text{CH, C-4}), 127.45, 127.85, 127.89, 127.91, 127.98, 128.31, 128.38, 128.41, 128.43, 128.58 (20 × \text{Ph-CH}), 136.19 (\text{Ph-C}_q, \text{NBn}), 137.47, 137.51, 137.75 (3 × \text{Ph-C}_q, \text{OBn}), 171.36 (\text{CO, C-5}).\]

\(\text{IR (neat) } \tilde{\nu} [\text{cm}^{-1}] : 3031 (\text{w}), 2902 (\text{w}), 2868 (\text{w}), 1699 (\text{m, [C=O]}), 1451 (\text{m}), 1247 (\text{w}), 1106 (\text{s}).\)

\(\text{HRMS (ESI) calculated for C}_{33}\text{H}_{34}\text{NO}_4 [M + H^+] : 508.2488, \text{ found 508.2484.}\)
(2S,3S,4S,5R)-N-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidin-5-ol (8/49)

Isolated yield: 4% (19 mg)

Chemical formula: C_{34}H_{37}NO_4

Molecular weight: 523.66

Appearance: Yellow oil

TLC: \( R_f = 0.28 \) (DE/PE = 1:1), CAM

Optical rotation: \( [\alpha]_{D}^{25} = \pm 0.0^\circ \) (c = 1.03 g/100 mL CHCl_3)

\(^1\)H NMR (500 MHz, CDCl_3) \( \delta \) [ppm]: 2.16 (dd, 1H, \( ^2J = 11.5 \text{ Hz}, ^3J_{aa} = 8.3 \text{ Hz}, H_{ax}-6) \), 2.48 (d, 1H, \( J = 4.3 \text{ Hz}, \text{OH-5) } \), 2.68 (dt, 1H, \( J_1 = 3.3 \text{ Hz, } J_2 = 6.9 \text{ Hz, H-2) } \), 2.98 (dd, 1H, \( ^2J = 11.6 \text{ Hz, } J_1 = 4.0 \text{ Hz, H}_{eq}-6) \), 3.41 (t, 1H, \( J = 7.4 \text{ Hz, H-4) } \), 3.51 (d, 1H, \( J = 13.4 \text{ Hz, H}_{A}-2^*), 3.66^a (dddd, 1H, \( J_1 = 3.8 \text{ Hz, } J_2 = 4.5 \text{ Hz, } J_3 = 7.4 \text{ Hz, } J_4 = 8.2 \text{ Hz, H-5) } \), 3.71^a (t, 1H, \( J = 7.4 \text{ Hz, H-3) } \), 3.79^a (dd, 1H, \( J_1 = 3.4 \text{ Hz, } J_2 = 10.5 \text{ Hz, H}_{A}-1) \), 3.82^a (dd, 1H, \( J_1 = 3.7 \text{ Hz, } J_2 = 10.5 \text{ Hz, H}_{B}-1) \), 3.99 (d, 1H, \( J = 13.4 \text{ Hz, H}_{B}-2^*), 4.47 (s, 2H, H_{2-1^*}), 4.53 (d, 1H, \( J = 11.3 \text{ Hz, H}_{A}-3^*), 4.65 (d, 1H, \( J = 11.7 \text{ Hz, H}_{A}-4^*), 4.75 (d, 1H, \( J = 11.1 \text{ Hz, H}_{B}-3^*), 4.81 (d, 1H, \( J = 11.7 \text{ Hz, H}_{B}-4^*), 7.20 - 7.36 (m, 20H, 20 \times \text{Ph-H) } \).

\(^{13}\)C NMR (125 MHz, CDCl_3) \( \delta \) [ppm]: 53.94 (CH_2, C-6), 57.34 (CH_2, C-2^*), 63.51 (CH, C-2), 65.58 (CH_2, C-1), 69.04 (CH, C-5), 73.28 (CH_2, C-1^*), 73.98 (CH_2, C-3^*), 74.12 (CH_2, C-4^*), 77.89 (CH, C-3), 84.57 (CH, C-4), 126.99, 127.64, 127.66, 127.71, 127.76, 127.78, 127.96, 128.22, 128.38, 128.41, 128.54, 129.00 (20 \times \text{Ph-CH) }, 138.04, 138.21, 138.56 (3 \times \text{Ph-C_9, OBn) }, 138.62 (\text{Ph-C_9, NBN) } \).

IR (neat) \( \tilde{\nu} \) [cm\(^{-1}\)]: n/a

HRMS (ESI) calculated for C_{34}H_{38}NO_4 \([M + H^+]\): 524.2801, found 524.2819.
(+)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)piperidin-5-ol (8/50)

Isolated yield: 3% (15 mg)

Chemical formula: C_{34}H_{37}NO_{4}

Molecular weight: 523.66

Appearance: Yellow oil

TLC: $R_f = 0.16$ (DE/PE = 1 : 1), CAM

Optical rotation: $[\alpha]_D^{25} = +24.9^\circ$ ($c = 0.745$ g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]:
- 2.17 (dd, 1H, $^2J = 12.3$ Hz, $^3J_{ax} = 1.1$ Hz, H$_{ax}$-6),
- 2.18 (br, 1H, OH-5),
- 2.48 (dt, 1H, $J = 2.9$ Hz, $J = 8.2$ Hz, H-2),
- 2.90 (dd, 1H, $^2J = 12.4$ Hz, $^3J_{ax} = 4.7$ Hz, H$_{eq}$-6),
- 3.39 (d, 1H, $J = 13.4$ Hz, H$_{A}$-2$^*$),
- 3.46 (dd, 1H, $J = 3.1$ Hz, $J = 8.4$ Hz, H-4),
- 3.78 (dd, 1H, $J = 12.4$ Hz, $^3J_{ax} = 4.7$ Hz, H$_{eq}$-6),
- 3.81 (dd, 1H, $J = 2.7$ Hz, $J = 10.4$ Hz, H$_B$-1$^*$),
- 3.89 (t, 1H, $J = 8.5$ Hz, H-3),
- 3.91 (m, 1H, H-5),
- 4.15 (d, 1H, $J = 13.5$ Hz, H$_B$-2$^*$),
- 4.44 (s, 2H, H$_2$-1$^*$),
- 4.52 (d, 1H, $J = 11.1$ Hz, H$_A$-3$^*$),
- 4.63 (d, 1H, $J = 11.9$ Hz, H$_A$-4$^*$),
- 4.69 (d, 1H, $J = 11.8$ Hz, H$_B$-4$^*$),
- 4.89 (d, 1H, $J = 11.0$ Hz, H$_B$-3$^*$),
- 7.21 – 7.36 (m, 20H, 20 $\times$ Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm]:
- 54.22 (CH$_3$, C-6),
- 56.97 (CH$_2$, C-2$^*$),
- 64.65 (CH, C-2),
- 65.08 (CH, C-5),
- 66.96 (CH$_2$, C-1),
- 71.46 (CH$_2$, C-4$^*$),
- 73.13 (CH$_3$, C-1$^*$),
- 74.92 (CH$_2$, C-3$^*$),
- 75.79 (CH, C-3),
- 83.29 (CH, C-4),
- 127.07, 127.60, 127.66, 127.71, 127.84, 127.86, 127.99, 128.33,
- 128.36, 128.41, 128.99 (20 $\times$ Ph-CH),
- 138.10, 138.19, 138.55 (3 $\times$ Ph-C$_q$, OBN),
- 138.58 (Ph-C$_q$, NBn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: n/a

HRMS (ESI) calculated for C$_{34}$H$_{38}$NO$_4$ [M + H$^+$]: 524.2801, found 524.2806.
Experimental Section

(+)-(2S,3S,4S,5S)-N-Benzyl-3-benzylxoy-2-benzyloxymethyl-5-trityloxymethylpyrrolidin-4-ol (8/54)

To the mixture of pyrrolidine diol 7/23 (434 mg, 1.0 mmol, 1.0 equiv) and Et₃N (202 mg, 279 µL, 2.0 mmol, 2.0 equiv) in anhydrous DCM (5 mL) were added trityl chloride (350 mg, 1.25 mmol, 1.25 equiv) and DMAP (12.2 mg, 0.1 mmol, 0.1 equiv) at rt. The mixture was stirred under an atmosphere of N₂ at 25 °C for 20 h by which time TLC analysis indicated complete conversion of the starting material. The mixture was subsequently concentrated in vacuo, and the pulpy orange residue was directly purified by column chromatography without further treatment to afford the desired pyrrolidinol trityl ether 8/54 (590 mg, 0.87 mmol) as a yellow caramel.

CC: Ø 1.7 cm x 10 cm, Vf = 12 – 13 mL, eluent EA/PE 0 : 100 → 40 : 60
Yield: 87%

Chemical formula: C₄₆H₄₅NO₄

Molecular weight: 675.85

Appearance: Yellow caramel

TLC: Rf = 0.29 (DE/PE = 2 : 3), CAM

Optical rotation: [α]D²⁵ = +5.0° (c = 5.13 g/100 mL CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ [ppm]: 3.10 ("d", 1H, J = 2.1 Hz, H-2), 3.23 (m, 1H, H-6), 3.28 (m, 1H, H-5), 3.34 (m, 2H, H₃-1, H₃-6), 3.47 (dd, 1H, J₁ = 3.0 Hz, J₂ = 10.0 Hz, H₅-1), 3.68 (d, 1H, J = 14.3 Hz, H₅-5*), 3.82 (d, 1H, J = 14.3 Hz, H₅-5*), 3.86 (s, 1H, H-3), 4.20 (s, 1H, H-4), 4.43" (d, 1H, J = 12.0 Hz, H₃-3*), 4.45" (s, 2H, H₂-1*), 4.55 (d, 1H, J = 12.1 Hz, H₈-3*), 7.14 – 7.40 (m, 30H, 30 × Ph-H).

¹³C NMR (125 MHz, CDCl₃) δ [ppm]: 51.71 (CH₂, C-5*), 62.65 (CH₂, C-6), 65.92 (CH, C-2), 69.10" (CH, C-5), 69.16" (CH₂, C-1), 71.37 (CH₂, C-3*), 73.49 (CH₂, C-1*), 76.82 (CH, C-4), 86.80 (C₉, C-6*), 87.94 (CH, C-3), 126.62, 126.83, 127.41, 127.52, 127.70, 127.87, 127.99, 128.14, 128.28, 128.47, 128.67 (30 × Ph-CH), 137.55, 138.29 (2 × Ph-C₉, OBn), 139.67 (Ph-C₉, NBn), 144.06 (3 × Ph-C₉, OTr).
IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 3440 (br) [O–H], 3028 (w), 2866 (w), 1493 (m), 1449 (m), 1364 (w), 1211 (w), 1155 (w), 1073 (vs) [C–O], 1028 (s), 1002 (m), 900 (w), 845 (w), 744 (vs).

HRMS (ESI) calculated for C$_{46}$H$_{46}$O$_4$ [M + H$^+$]: 676.3427, found 676.3431.

(±)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-2-benzylxymethyl-5-trityloxymethyl-pyrrolidine (8/55)

To the suspension of NaH (60% dispersion in mineral oil, 180 mg, 4.5 mmol, 1.5 equiv) in anhydrous n-hexane (5 mL) was added dropwise a solution of pyrrolidinol 8/54 (2028 mg, 3.0 mmol, 1.0 equiv) in anhydrous THF (15 mL) at 0 ºC. This mixture was stirred for 30 min under an atmosphere of N$_2$ while warming to rt. A solution of BnBr (590 mg, 3.45 mmol, 1.15 equiv) in anhydrous THF (5 mL) followed by a catalytic amount of TBAI (0.45 mmol, 0.15 equiv) were then added at rt whereupon the mixture was left stirring at 25 ºC under a blanket of N$_2$. ESI-MS analysis after 24 h indicated still the presence of unconverted starting material in the reaction mixture wherefore additional NaH (120 mg, 3.0 mmol, 1.0 equiv), BnBr (103 mg, 0.6 mmol, 0.2 equiv) and TBAI (111 mg, 0.3 mmol, 0.1 equiv) were added. After further stirring for 24 h the reaction mixture was cooled to 0 ºC, quenched with H$_2$O (20 mL) and diluted with Et$_2$O (40 mL). After extraction of the aqueous phase with Et$_2$O (3 × 30 mL) the organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo. Purification of the residue by column chromatography provided the title compound (2027 mg, 2.65 mmol) as a yellow foamy caramel.

CC : $\varnothing$ 3.0 cm × 11.5 cm, $V_{Fr}$ = 45 mL, eluent EA/PE 0 : 100 → 10 : 90
Yield : 88%
Chemical formula : C$_{53}$H$_{51}$NO$_4$
Molecular weight : 765.98
Appearance : Yellow foamy sticky caramel
TLC : $R_f$ = 0.41 (DE/PE = 1 : 3), CAM
Optical rotation: \([\alpha]_D^{25} = +17.2^\circ\) (\(c = 5.1\) g/100 mL CHCl₃)

\(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) [ppm]: 3.25\(^\circ\) (m, 2H, H₂-6), 3.31\(^\circ\) (m, 2H, H₂-2, H₂-5), 3.57\(^\circ\) (d, 2H, \(J = 5.5\) Hz, H₁-1), 3.58\(^\circ\) (d, 1H, \(J = 14.1\) Hz, H₆-5\(^*\)), 3.97 (t, 1H, \(J = 3.0\) Hz, H-3), 4.02 (d, 1H, \(J = 14.5\) Hz, H₆-5\(^*\)), 4.06 (t, 1H, \(J = 2.8\) Hz, H-3), 4.43 (s, 2H, H₂-1\(^*\)), 4.45 – 4.51 (m, 4H, H₂-3\(^*\), H₂-4\(^*\)), 7.15 – 7.40 (m, 35H, 35 × Ph-H).

\(^1^3\)C NMR (125 MHz, CDCl₃) \(\delta\) [ppm]: 51.50 (CH₂, C-5\(^*\)), 62.15 (CH₂, C-6), 64.93\(^\circ\), 65.00\(^\circ\) (2 × CH, C-2, C-5), 69.73 (CH₂, C-1), 71.36\(^\circ\), 71.42\(^\circ\) (2 × CH₂, C-3\(^*\), C-4\(^*\)), 73.12 (CH₂, C-1\(^*\)), 85.46 (CH, C-3), 85.69 (CH, C-4), 86.83 (C₆H₅, C-6\(^*\)), 126.48, 126.82, 127.38, 127.42, 127.59, 127.64, 127.69, 127.71, 128.06, 128.13, 128.22, 128.25, 128.74 (35 × Ph-CH), 138.35 (Ph-C₆H₅, OBn), 138.47 (Ph-C₆H₅, OBn), 138.51 (Ph-C₆H₅, OBn), 139.64 (Ph-C₆H₅, NBn), 144.0 (3 × Ph-C₆H₅, OTr).

IR (neat) \(\tilde{\nu}\) [cm\(^{-1}\)]: 3085 (w), 3061 (w), 3029 (w), 2858 (w), 1494 (m), 1450 (m), 1365 (w), 1316 (w), 1207 (w), 1154 (w), 1092 (vs), 1073 (vs), 1028 (m), 1002 (m), 901 (w), 740 (vs).

HRMS (ESI) calculated for C\(_{53}\)H\(_{52}\)NO\(_4\) [M + H\(^+\)]: 766.3896, found 766.3901.

(+)-(2\(^S\),3\(^S\),4\(^S\),5\(^S\))-N-Benzyl-3,4-bis(benzyloxy)-2-benzoxymethyl-5-hydroxymethyl-pyrrolidine (8/9)

To the solution of pyrrolidinyl trityl ether 8/55 (919.2 mg, 1.2 mmol) in DCM (2.4 mL) and MeOH (2.4 mL) was added TFA (2.4 mL) at 0 °C. The mixture was then stirred at 25 °C for 2 h by which time ESI-MS analysis revealed complete conversion of the starting material. The mixture was subsequently neutralised by the addition of 1 M K\(_2\)CO₃ solution (24 mL) and further diluted with DCM (20 mL). After extraction of the aqueous phase with DCM (3 × 20 mL) the organic phases were dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by column chromatography provided pyrrolidine alcohol 8/9 (542 mg, 1.04 mmol) as a pale yellow syrup.

CC: \(\varnothing\) 1.7 cm × 11 cm, \(V_{Fr} = 15 – 16\) mL, eluent EA/PE 0 : 100 → 10 : 90

Yield: 86%
Chemical formula : C_{34}H_{37}NO_{4}
Molecular weight : 523.66
Appearance : Pale yellow syrup
TLC : \( R_f = 0.21 \) (DE/PE = 2 : 3), CAM
Optical rotation : \( [\alpha]_D^{28} = +28.5^\circ \) (c = 2.4 g/100 mL CHCl_3)

\(^1\)H NMR (500 MHz, CDCl_3) \( \delta \) [ppm] : 2.75 (br, 1H, OH-6), 3.18 (s, 1H, H-5), 3.44 (dd, 1H, \( J_1 = 5.5 \) Hz, \( J_2 = 5.8 \) Hz, H-2), 3.54 (dd, 1H, \( J_1 = 7.5 \) Hz, \( J_2 = 9.3 \) Hz, H_A-1), 3.60 (m, 1H, H_A-6), 3.61 (dd, 1H, \( J_1 = 4.2 \) Hz, \( J_2 = 9.4 \) Hz, H_B-1), 3.72 (dd, 1H, \( J_1 = 3.2 \) Hz, \( J_2 = 11.5 \) Hz, H_B-6), 3.82 (d, 1H, \( J = 14.2 \) Hz, H_A-5*), 3.90 (d, 1H, \( J = 14.2 \) Hz, H_B-5*), 4.03 (s, 1H, H-3), 4.07 (d, 1H, \( J = 3.4 \) Hz, H-4), 4.42 (d, 1H, \( J = 12.1 \) Hz, H_A-1*), 4.46 (d, 1H, \( J = 12.0 \) Hz, H_B-1*), 4.47 (2d, 2H, \( J = 12.1 \) Hz, \( J_2 = 11.8 \) Hz, H_A-3*, H_A-4*), 4.51 (m, 1H, H_A-6), 4.53 (2d, 2H, \( J = 11.6 \) Hz, \( J_2 = 11.9 \) Hz, H_B-3*, H_B-4*), 7.21 – 7.35 (m, 20H, 20 \times \) Ph-H).

\(^{13}\)C NMR (125 MHz, CDCl_3) \( \delta \) [ppm] : 51.08 (CH_2, C-5*), 59.93 (CH_2,C-6), 64.54 (CH, C-2), 67.72 (CH, C-5), 68.03 (CH_2, C-1), 71.18 (CH_2, C-3*), 71.76 (CH_2, C-4*), 73.23 (CH_2, C-1*), 83.53 (CH, C-3), 85.80 (CH, C-4), 126.96, 127.56, 127.59, 127.63, 127.67, 127.86, 128.01, 128.32, 128.37, 128.39, 128.41 (20 \times \) Ph-CH), 137.93, 138.12, 138.18 (3 \times \) Ph-C_q, OBn), 139.08 (Ph-C_q, NBn).

IR (neat) \( \tilde{\nu} \) [cm\(^{-1}\)] : 3480 (br) [O–H], 3029 (w), 2866 (w), 1496 (w), 1454 (m), 1365 (w), 1205 (w), 1095 (vs), 1072 (vs), 1028 (m), 908 (w), 819 (w), 736 (vs).

HRMS (ESI) calculated for C_{34}H_{38}NO_{4} [M + H\(^+\)] : 524.2801, found 524.2803.

\((2S,3S,4S,5R)-N\text{-}\text{Benzyl}-3,4\text{-bis(benzyloxy)}-2\text{-(benzyloxymethyl)pyrrolidine-5-carbaldehyde (8/2)}\)

To a solution of oxalyl chloride (305 mg, 2.4 mmol, 1.2 equiv) in dry DCM (10 mL) was carefully added anhydrous DMSO (375 mg, 4.8 mmol, 2.4 equiv) in such a way that the temperature of the mixture did not exceed –65 °C. After recooling to –78 °C the solution of pyrrolidine alcohol 8/9 (1048 mg, 2.0 mmol, 1.0 equiv) in dry DCM (8 mL) was added drop-
Experimental Section

wise yet again keeping the temperature of the mixture below –60 ºC during the addition. The reaction mixture was stirred for further 20 min at –78 ºC, then dry Et₃N (1012 mg, 1.4 mL, 10.0 mmol, 5.0 equiv) was added below –60 ºC. After completed addition the reaction mixture was stirred for another 10 min at –78 ºC and then allowed to slowly warm to 0 ºC (~2.5 h). After additional stirring for 30 min at 0 ºC the reaction mixture was quenched with water (10 mL) and diluted with Et₂O (20 mL). The organic layer was then washed successively with saturated aqueous NaHCO₃ solution (1 × 10 mL) followed by half-saturated aqueous NaCl solution (1 × 10 mL) and was finally dried over MgSO₄. Filtration and evaporation of all volatiles under reduced pressure afforded the crude pyrrolidine carbaldehyde 8/2 (1042 mg, 2.0 mmol) in quantitative yield as an amber orange syrup which was directly used in the next step without further purification. Pyrrolidine carbaldehyde 8/2 is an unstable compound that rapidly epimerises and eventually decomposes when kept too long at rt. Storage at –20 ºC decelerates the process but does not prevent or stop it. The aldehyde should therefore only be prepared immediately before the following coupling reaction.

Yield : quantitative

Chemical formula : C₃₄H₃₅NO₄

Molecular weight : 521.66

Appearance : Amber orange syrup

TLC : Rf n/a due to instability of compound

Optical rotation : [α]D²⁵ n/a due to instability of compound

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 3.52 (m, 1H, H-2), 3.57 (m, 2H, H₂-1), 3.63 (t, 1H, J = 3.8 Hz, H-5), 3.90 (d, 1H, J = 13.9 Hz, H₅-5*), 4.04 (dd, 1H, J = 2.9 Hz, J = 4.2 Hz, H-3), 4.04 (d, 1H, J = 13.8 Hz, H₅-5*), 4.10 (t, 1H, J = 2.3 Hz, H-4), 4.42 (d, 1H, J = 11.9 Hz, H₅-1*), 4.44 (d, 1H, J = 12.1 Hz, H₅-1*), 4.47 (d, 1H, J = 12.3 Hz, H₅-1*), 4.49 (d, 1H, J = 12.1 Hz, H₅-1*), 4.51 (d, 1H, J = 12.1 Hz, H₅-1*), 4.52 (d, 1H, J = 11.8 Hz, H₅-1*), 7.20 – 7.35 (m, 20H, 20 × Ph-H), 9.49 (d, 1H, J = 3.7 Hz, H-6).

¹³C NMR (125 MHz, CDCl₃, –25 ºC) δ [ppm] : 52.78 (CH₂, C-5*), 65.06, (CH, C-2), 68.51, (CH₂, C-1), 71.41 (CH₂, C-3/4*), 71.56 (CH₂, C-4/3*), 73.16 (CH₂, C-1*), 74.94, (CH, C-5), 83.65, (CH, C-3), 84.93, (CH, C-4), 127.30, 127.62, 127.64, 127.73, 127.81, 128.33, 128.37, 128.39, 128.51 (20 × Ph-CH), 137.25, 137.62, 137.89, 138.28 (4 × ipso-Ph-C₆), 203.45 (CH, C-6).

IR (neat) ν [cm⁻¹] : n/a due to instability of compound

E.5 Synthesis of (−)-10’-Deoxobroussonetine C and (−)-(5S)-Phenethyl-1-AB1

12-Benzyloxdodecan-1-ol (9/9)

To a stirred solution of 1,12-dodecanediol (25.0 g, 123.6 mmol, 1.0 equiv) in EtOAc (600 mL) was added benzyl bromide (24.5 g, 17 mL, 143.1 mmol, 1.16 equiv) and freshly prepared Ag$_2$O (43.0 g, 185.6 mmol, 1.5 equiv). This heterogeneous mixture was vigorously stirred overnight (22.5 h) at rt under an atmosphere of N$_2$. Subsequent filtration through a pad of Celite and evaporation of all volatiles gave a mixture of mono- and bis-benzylated products as well as unreacted starting material. Separation by column chromatography afforded the mono-benzylated alcohol 9/9 (13.0 g, 44.45 mmol) as a colourless liquid as well as the recovered diol (12.0 g, 59.3 mmol) as a white solid.

**CC:** ∅ 8.0 cm × 16 cm, $V_{Fr} = 200$ mL, eluent EA/PE 5 : 95 → 100 : 0

**Yield:** 36%; 69% borsm

**Chemical formula:** C$_{19}$H$_{32}$O$_2$

**Molecular weight:** 292.46

**Appearance:** Colourless liquid

**TLC:** $R_f = 0.34$ (DE/PE = 50 : 50), CAM

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 1.22 – 1.38 (m, 16H, H$_2$-3 – H$_2$-10), 1.55$v$ (’quin”, 2H, $J = 7.1$ Hz, H$_2$-2), 1.61$v$ (’quin”, 2H, $J = 7.0$ Hz, H$_2$-11), 3.46 (t, 2H, $J = 6.7$ Hz, H$_2$-12), 3.62 (t, 2H, $J = 6.6$ Hz, H$_2$-1), 4.50 (s, 2H, H$_2$-12*), 7.27 (m, 1H, para-Ph-H), 7.34 (”d”, 4H, $J = 4.4$ Hz, 2 × ortho-Ph-H, 2 × meta-Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm]: 25.74 (CH$_2$, C-3), 26.19 (CH$_2$, C-10), 29.42, 29.48, 29.56, 29.57, 29.58, 29.59 (6 × CH$_2$, C-4 – C-9), 29.77 (CH$_2$, C-11), 32.81 (CH$_2$, C-2), 63.08 (CH$_2$, C-1), 70.54 (CH$_2$, C-12), 72.85 (CH$_2$, C-12*), 127.45 (para-Ph-CH, OBn), 127.62 (2 × ortho-Ph-CH, OBn), 128.33 (2 × meta-Ph-CH, OBn), 138.70 (ipso-Ph-C$_q$, OBn).

**IR (neat) $\tilde{\nu}$ [cm$^{-1}$]:** 3400 (br) [O–H], 2926 (s) [C–H], 2853 (s) [C–H], 1496 (w), 1455 (m), 1362 (w), 1205 (w), 1101 (s), 1075 (s), 1055 (m), 1028 (m), 907 (w), 843 (w), 835 (w), 818 (w), 735 (vs), 697 (vs), 681 (m).

**HRMS (EI) calculated for C$_{19}$H$_{32}$O$_2$ [M$^+$]:** 292.2402, found 292.2402.
12-Benzyl-1-bromododecane (9/3)

**Method A** (from 12-benzylbenzododecan-1-ol via Appel reaction): To the mixture of 12-benzylbenzododecan-1-ol (13.0 g, 44.45 mmol, 1.0 equiv) and PPh₃ (17.5 g 66.7 mmol, 1.5 equiv) in dry THF (225 mL) was added dropwise a solution of CBr₄ (22.1 g 66.7 mmol, 1.5 equiv) in dry MeCN (75 mL) at 0 °C. After overnight stirring (18 h) at 25 °C all volatiles were evaporated under reduced pressure to give a pulpy residue. Purification by column chromatography afforded the dodecanyl bromide 9/3 (14.3 g, 40.2 mmol) as a colourless liquid.

**Yield**: 90.5%

**Method B** (from 12-bromododecan-1-ol via Williamson ether synthesis): To the suspension of NaH (60 % dispersion in mineral oil, 226.4 mg, 5.66 mmol, 1.5 equiv) in anhydrous n-hexane (6 mL) and anhydrous THF (6 mL) was added a solution of 12-bromo-1-dodecanol (1000 mg, 3.77 mmol, 1.0 equiv) and benzyl bromide (968 mg, 5.66 mmol, 1.5 equiv) in dry THF (12 mL) at 0 °C under an atmosphere of N₂. The mixture was stirred for 30 min while warming to rt and then for further 24 h at 50 °C. TLC analysis after this period of time indicated incomplete conversion of the starting material. Therefore, additional NaH (151 mg, 3.77 mmol, 1 equiv) and benzyl bromide (323 mg, 1.89 mmol, 0.5 equiv, diluted with 6 mL dry THF) were added, and the mixture was stirred for further 24 h at 50 °C. The mixture was then quenched with ice water (20 mL) and diluted with Et₂O (40 mL). After extraction of the aqueous phase with Et₂O (3 × 30 mL), the organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. Column chromatography afforded the benzyl ether 9/3 (1340 mg, 3.77 mmol) as a clear, colourless liquid.

**Yield**: 100%

**Chemical formula**: C₁₉H₃₁BrO

**Molecular weight**: 355.35

**Appearance**: colourless liquid

**TLC**: $R_f = 0.28$ (100% PE), CAM

$R_f = 0.54$ (DE/PE = 5 : 95), CAM
Experimental Section

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 1.27 (br s, 12H, H$_2$-4 – H$_2$-9), 1.35 (br quin, 2H, J = 7.2 Hz, H$_2$-10), 1.42 (br quin, 2H, J = 7.2 Hz, H$_2$-3), 1.61 ("quin", 2H, J = 7.1 Hz, H$_2$-11), 1.85 ("quin", 2H, J = 7.2 Hz, H$_2$-2), 3.40 (t, 2H, J = 6.9 Hz, H$_2$-1), 3.46 (t, 2H, J = 6.6 Hz, H$_2$-12), 4.50 (s, 2H, H$_2$-12*), 7.27 (m, 1H, para-Ph-H), 7.34 ("d", 4H, J = 4.4 Hz, 2 $\times$ ortho-Ph-H, 2 $\times$ meta-Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 26.19 (CH$_2$, C-10), 28.18 (CH$_2$, C-3), 28.76 (CH$_2$, C-4), 29.42, 29.48, 29.51, 29.54, 29.56 (5 $\times$ CH$_2$, C-5 – C-9), 29.78 (CH$_2$, C-11), 32.85 (CH$_2$, C-2), 34.05 (CH$_2$, C-1), 70.53 (CH$_2$, C-12), 72.85 (CH$_2$, C-12*), 127.44 (para-Ph-CH, OBn), 127.60 (2 $\times$ ortho-Ph-CH, OBn), 128.32 (2 $\times$ meta-Ph-CH, OBn), 138.72 (ipso-Ph-C$_q$, OBn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 2925 (s) [C–H], 2853 (s) [C–H], 1496 (w), 1454 (w), 1361 (w), 1252 (w), 1204 (w), 1101 (vs) [C–O], 1028 (m), 905 (w), 818 (w), 733 (vs).

HRMS (EI) calculated for C$_{19}$H$_{31}$IO$_7$Br [M$^+$] : 354.1558, found 354.1568.

HRMS (EI) calculated for C$_{19}$H$_{31}$O$_8$Br [M$^+$] : 356.1538, found 356.1542.

12-Benzylloxy-1-iodododecane (9/4)

To the solution of 12-benzyloxy-1-bromododecane (1333 mg, 3.75 mmol, 1.0 equiv) in dry acetone (8 mL) was added a solution of NaI (1687 mg, 11.25 mmol, 3.0 equiv) in dry acetone (8 mL) at rt. The mixture was stirred at 25 °C overnight (16 h). Precipitated NaBr was then filtered off, and the filtrate was concentrated in vacuo. The pulpy yellow residue was purified without further treatment via a short-bed column chromatography to afford the required dodecyl iodide 9/4 (1506 mg, 3.74 mmol) as a clear, colourless liquid.

CC : ∅ 3.0 cm $\times$ 7 cm, $V_{Fr}$ = 25 mL, eluent EA/PE 0 : 100 $\rightarrow$ 2 : 98

Yield : 100%

Chemical formula : C$_{19}$H$_{31}$IO

Molecular weight : 402.36

Appearance : clear, colourless liquid

TLC : $R_f$ = 0.49 (DE/PE = 5 : 95), CAM
**Experimental Section**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 1.27 (s, 12H, H$_2$-4 – H$_2$-9), 1.36 (br m, 4H, H$_2$-3, H$_2$-10), 1.61 ("quin", 2H, $J = 7.0$ Hz, H$_2$-11), 1.81 (quin, 2H, $J = 7.2$ Hz, H$_2$-2), 3.18 (t, 2H, $J = 7.1$ Hz, H$_2$-1), 3.46 (t, 2H, $J = 6.6$ Hz, H$_2$-12), 4.50 (s, 2H, H$_2$-12*), 7.27 (m, 1H, para-Ph-H), 7.34 ("d", 4H, $J = 4.4$ Hz, 2 × ortho-Ph-H, 2 × meta-Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm]: 7.32 (CH$_2$, C-1), 26.19 (CH$_2$, C-10), 28.54, 29.40, 29.47, 29.51, 29.53, 29.56 (6 × CH$_2$, C-4 – C-9), 29.77 (CH$_2$, C-11), 30.50 (CH$_2$, C-3), 33.57 (CH$_2$, C-2), 70.52 (CH$_2$, C-12), 72.85 (CH$_2$, C-12*), 127.44 (para-Ph-CH, OBn), 127.59 (2 × ortho-Ph-CH, OBn), 128.32 (2 × meta-Ph-CH, OBn), 138.72 (ipso-Ph-C$_q$, OBn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 2924 (vs) [C$-$H], 2852 (s) [C$-$H], 1496 (w), 1454 (m), 1362 (w), 1204 (w), 1177 (w), 1101 (vs) [C$-$O], 1028 (m), 908 (w), 734 (vs).

HRMS (EI) calculated for C$_{19}$H$_{31}$IO [M$^+$]: 402.1420, found 402.1441.

**(12-Benzxyloxydodecyl)triphenylphosphonium iodide (9/5)**

\[
\begin{align*}
\text{Ph} & \quad \text{P}^+ \quad \text{I}^- \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{Ph}
\end{align*}
\]

The mixture of 12-benzyloxy-1-iodododecane (1506 mg, 3.74 mmol, 1.0 equiv) and PPh$_3$ (1082 mg, 4.125 mmol, 1.1 equiv) in dry toluene (15 mL) was heated at reflux for 20 h. After this period of time the toluene was evaporated in vacuo, and the residue was purified via a short-bed column chromatography to provide the desired phosphonium iodide 9/5 (2384 mg, 3.59 mmol) as a pale yellow caramel.

CC: $\varnothing$ 3.0 cm × 6 cm, $V_{fr} = 25$ mL, eluent DCM/MeOH 0 : 100 → 90 : 10

Yield: 96%

Chemical formula: C$_{37}$H$_{46}$IOP

Molecular weight: 664.64

Appearance: Pale yellow caramel

TLC: $R_f = 0.62$ (DCM/MeOH = 90 : 10), CAM

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 1.16 – 1.29 (m, 12H, H$_2$-4 – H$_2$-9), 1.33 (m, 2H, H$_2$-10), 1.59 ("quin", 2H, $J = 7.1$ Hz, H$_2$-11), 1.63 (m, 4H, H$_2$-2, H$_2$-3), 3.46 (t, 2H, $J = 6.6$ Hz, H$_2$-12), 3.61 (m, 2H, H$_2$-1), 4.49 (s, 2H, H$_2$-12*), 7.27 (m, 1H, para-Ph-H, OBn), 7.33 ("d", 4H, $J = 4.3$ Hz,
Experimental Section

2 × ortho-Ph-H, 2 × meta-Ph-H, OBn), 7.72 (m, 6H, 6 × ortho-Ph-H, PPh₃), 7.81 (m, 9H, 6 × meta-Ph-H, 3 × para-Ph-H, PPh₃).

$^{13}$C NMR (125 MHz, CDCl₃) δ [ppm] : 22.59 (d, $J_{CP} = 4.4$ Hz, CH₂, C-3), 23.16 (d, $J_{CP} = 50.0$ Hz, CH₂, C-1), 26.16 (s, CH₂, C-10), 29.16, 29.44, 29.46, 29.47, 29.51 (m, 6 × CH₂, C-4 – C-9), 29.75 (s, CH₂, C-11), 30.46 (d, $J_{CP} = 15.4$ Hz, CH₂, C-2), 70.53 (s, CH₂, C-12), 72.82 (s, CH₂, C-12*), 118.11 (d, $J = 85.8$ Hz, 3 × ipso-Ph-C̈, PPh₃), 127.42 (s, para-Ph-CH, OBn), 127.58 (s, 2 × ortho-Ph-CH, OBn), 128.30 (s, 2 × meta-Ph-CH, OBn), 130.59 (d, $J_{CP} = 12.6$ Hz, 6 × ortho-Ph-CH, PPh₃), 133.66 (d, $J_{CP} = 10.0$ Hz, 6 × meta-Ph-CH, PPh₃), 135.16 (d, $J_{CP} = 3.0$ Hz, 3 × para-Ph-CH, PPh₃), 138.71 (s, ipso-Ph-C̈, OBn).

IR (neat) $\tilde{\nu}$ [cm⁻¹] : 2925 (m) [C–H], 2853 (m) [C–H], 1587 (w), 1484 (w), 1454 (w), 1437 (s), 1363 (w), 1315 (w), 1190 (w), 1161 (w), 1112 (vs), 1028 (w), 996 (m), 835 (w), 788 (vs), 723 (vs).

HRMS (ESI) calculated for C₃₇H₄₆OP [M⁺] : 537.3286, found 537.3295.

(+)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-5-((1'Z)-13'-benzyloxytridec-1'-enyl)-2-(benzoxymethyl)pyrrolidine (9/6)

![Chemical Structure](image_url)  

The solution of phosphonium iodide 9/5 (831 mg, 1.25 mmol, 1.25 equiv) in a mixture of dry THF (4 mL) and dry HMPA (2 mL) was cooled to −50 °C under an atmosphere of N₂. To this solution was added $n$-BuLi (1.6 M solution in hexane, 0.8 mL, 1.25 mmol, 1.25 equiv) followed by a solution of the pyrrolidine carbaldehyde 8/2 (522 mg, 1 mmol, 1 equiv) in dry THF (2 mL). The reaction mixture was stirred for 2 h at −50 °C, then quenched with 1 M phosphate buffer (10 mL, pH 7) and finally extracted with Et₂O (3 × 10 mL). The combined organic phases were subsequently dried over MgSO₄, filtered and concentrated in vacuo.

Purification of the residue by column chromatography provided the desired pyrrolidine olefin 9/6 (665 mg, 0.85 mmol) (E : Z ratio = 2 : 98) as a pale yellow oil.

CC : Ø 2.0 cm × 10 cm, $V_{fr} = 21 – 22$ mL, eluent EA/PE 1 : 99 → 10 : 90
**Experimental Section**

**Yield**: 85%

**Chemical formula**: C_{53}H_{65}NO_{4}

**Molecular weight**: 780.09

**Appearance**: Pale yellow oil

**TLC**: \( R_f = 0.35 \) (DE/PE = 1 : 4), CAM

**Optical rotation**: \( [\alpha]_D^{25} = +36.8^\circ \) \( (c = 5.02 \text{ g/100 mL CHCl}_3) \)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) [ppm]: 1.16 – 1.31\(^\circ\) (m, 14H, H\(_2\)-9 – H\(_2\)-15), 1.35\(^\circ\) (m, 2H, H\(_2\)-16), 1.61 (quin, 2H, \( J = 7.1 \text{ Hz} \), H\(_2\)-17), 1.91 (m, 2H, H\(_2\)-8), 3.23 (m, 1H, H-2), 3.45 (t, 2H, \( J = 6.7 \text{ Hz} \), H\(_2\)-18), 3.53\(^\circ\) (dd, 1H, \( J_1 = 4.2 \text{ Hz}, J_2 = 9.6 \text{ Hz} \), H\(_A\)-1), 3.57\(^\circ\) (dd, 1H, \( J_1 = 5.9 \text{ Hz}, J_2 = 9.5 \text{ Hz} \), H\(_B\)-1), 3.59\(^\circ\) (dd, 1H, \( J_1 = 4.6 \text{ Hz}, H-4 \)), 3.93 (d, 1H, \( J = 14.4 \text{ Hz} \), H\(_A\)-5\(^*\)), 3.98 (dd, 1H, \( J_1 = 3.3 \text{ Hz}, J_2 = 4.6 \text{ Hz} \), H-5), 4.03 (t, 1H, \( J = 3.1 \text{ Hz} \), H-3), 4.44 (d, 1H, \( J = 12.0 \text{ Hz} \), H\(_A\)-1\(^*\)), 4.44 – 4.53\(^\circ\) (m, 4H, H\(_B\)-1\(^*\), H\(_2\)-3\(^*\), H\(_A\)-4\(^*\)), 4.49\(^\circ\) (s, 2H, H\(_2\)-18\(^*\)), 4.57 (d, 1H, \( J = 12.0 \text{ Hz} \), H\(_B\)-4\(^*\)), 5.45 (t, 1H, \( J = 10.5 \text{ Hz} \), H-6), 5.60 (dt, 1H, \( J_1 = 7.3 \text{ Hz}, J_2 = 10.9 \text{ Hz} \), H-7), 7.15 – 7.35 (m, 25H, 25 \times \text{ Ph-H}).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) [ppm]: 26.21 (CH\(_2\), C-16), 27.55 (CH\(_2\), C-8), 29.61 (CH\(_2\), C-17), 29.37, 29.50, 29.53, 29.61, 29.70, 29.78 (6 \times \text{ CH}_2, C-9 – C-15), 51.01 (CH\(_2\), C-5\(^*\)), 62.71 (CH, C-5), 63.82 (CH, C-2), 69.50 (CH\(_2\), C-1), 70.52 (CH\(_2\), C-18), 71.50 (CH\(_2\), C-3\(^*\)), 71.69 (CH\(_2\), C-4\(^*\)), 72.84 (CH\(_2\), C-18\(^*\)), 73.20 (CH\(_2\), C-1\(^*\)), 86.03 (CH, C-3), 88.69 (CH, C-4), 126.44, 127.43, 127.45, 127.58, 127.62, 127.81, 128.06, 128.12, 128.24, 128.25, 128.31 (25 \times \text{ Ph-CH}), 129.05 (CH, C-6), 134.43 (CH, C-7), 138.41, 138.47, 138.54, 138.73 (4 \times \text{ ipso-Ph-C}_q, \text{ OBn}), 139.97 (\text{ ipso-Ph-C}_q, \text{ NBn}).

**IR** (neat) \( \bar{\nu} \) [cm\(^{-1}\)]: 3063 (w), 3029 (w), 2924 (m) [C–H], 2852 (m) [C–H], 1495 (w), 1454 (m), 1362 (w), 1308 (w), 1206 (w), 1099 (vs) [C–O], 1075 (s), 1028 (m), 907 (w), 846 (w), 819 (w), 734 (vs).

**HRMS (ESI)** calculated for C\(_{53}\)H\(_{65}\)NO\(_4\) [M + H\(^+\)]: 780.4992, found 780.4998.
(12Z)-1,24-Bis(benzyloxy)tetracos-12-ene (9/7)

Olefin 9/7 was obtained as a minor by-product from the above Wittig reaction as a pale yellow oil (66 mg, 0.12 mmol) in 19% yield (based on the amount of phosphonium iodide 9/5 employed in the reaction).

Yield : 19%

Chemical formula : C_{38}H_{60}O_{2}

Molecular weight : 548.88

Appearance : Pale yellow oil

TLC : \( R_f = 0.63 \) (DE/PE = 1 : 4), CAM

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta [\text{ppm}] \) : 1.26\(^e\) (s, 24H, H\(_2\)-4 – H\(_2\)-9, H\(_2\)-16 – H\(_2\)-21), 1.33\(^e\) (m, 8H, H\(_2\)-3, H\(_2\)-10, H\(_2\)-15, H\(_2\)-22), 1.61 ("quin", 4H, \( J = 7.2 \text{ Hz} \), H\(_2\)-2, H\(_2\)-23), 2.01 ("q", 4H, \( J = 6.3 \text{ Hz} \), H\(_2\)-11, H\(_2\)-14), 3.46 (t, 4H, \( J = 6.6 \text{ Hz} \), H\(_2\)-1, H\(_2\)-24), 4.51 (s, 4H, H\(_2\)-1*, H\(_2\)-24*), 5.35 (m, 2H, H-12, H-13), 7.27 (m, 2H, 2 × \text{para-Ph-H} \), 7.33 ("d", 8H, \( J = 4.3 \text{ Hz} \), 4 × \text{ortho-Ph-H} \), 4 × \text{meta-Ph-H} \).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta [\text{ppm}] \) : 26.21 (2 × CH\(_2\), C-3, C-22), 27.22 (2 × CH\(_2\), C-11, C-14), 29.33, 29.51, 29.57, 29.62, 29.64 (14 × CH\(_2\), C-4 – C-10, C-15 – C-21), 29.79 (2 × CH\(_2\), C-2, C-23), 70.53 (2 × CH\(_2\), C-1, C-24), 72.85 (2 × CH\(_2\), C-1*, C-24*), 127.43 (2 × \text{para-Ph-CH} \), 127.59 (4 × \text{ortho-Ph-CH} \), 128.32 (4 × \text{meta-Ph-CH} \), 129.89 (2 × CH, C-12, C-13), 138.73 (2 × \text{ipso-Ph-C} \).

IR (neat) \( \tilde{\nu} [\text{cm}^{-1}] \) : 2917 (vs), 2848 (vs), 1467 (m), 1455 (w), 1364 (w), 1118 (vs), 1093 (m), 1028 (w), 757 (m), 736 (vs), 721 (m), 702 (s).

HRMS (EI) calculated for C\(_{38}\)H\(_{60}\)O\(_2\) [M\(^+\)] : 548.4593, found 548.4594.
Experimental Section

\((-\left(2S,3S,4S,5S\right)\text{-2-Hydroxymethyl-5-(13'-hydroxytridecyl)pyrrolidine-3,4-diol (9/1)}}

\((-\text{-10'-Deoxobroussonetine C}}

\[
\begin{align*}
\text{To the suspension of Pd-enriched Pearlman's catalyst (53 mg Pd black + 70 mg Pd(OH)\text{\textsubscript{2}}/C) in 2 M methanolic HCl (2.5 mL) was added a solution of pentabenzylated pyrrolidine 9/6 (390 mg, 0.5 mmol) in EtOAc (2.5 mL). The reaction flask was evacuated under gentle vacuum and flushed three times with H}_2\text{ and then left overnight (18 h) under an atmosphere of H}_2\text{ with vigorous stirring at 25 }\degree\text{C by which time reaction control via ESI-MS indicated full conversion of the starting material. The catalyst was subsequently removed by filtration through a pad of Celite and rinsed thoroughly with MeOH. Removal of all volatiles under reduced pressure gave the crude debenzylated product which was chromatographed on basic DOWEX 1X8 100-200 ion-exchange resin (Ø 2.0 cm \times 5 cm). Elution was carried out first with H}_2\text{O/MeOH (1 : 1) and then pure MeOH until complete recovery of the product. Further purification of the obtained material was achieved by repeated column chromatography (2 runs) over basic silica gel. A concluding recrystallisation from MeOH/CHCl\text{\textsubscript{3}} (1 : 1) afforded the pure l-AB1 derivative 9/1 (106 mg, 0.32 mmol) as an off-white amorphous powder.}
\end{align*}
\]

\[\text{1}\text{st CC : }Ø 1.6 \text{ cm } \times 5 \text{ cm, } V_{F_r} = 7 \text{ mL,}
\]
\[\text{elution with CHCl\textsubscript{3}/MeOH/NH}_3\text{ (7 N in MeOH) 98 : 0 : 2 \to 60 : 38 : 2}
\]
\[\text{2}\text{nd CC : }Ø 1.7 \text{ cm } \times 2.5 \text{ cm, } V_{F_r} = 10 \text{ mL,}
\]
\[\text{elution with CHCl\textsubscript{3}/MeOH/NH}_3\text{ (7 N in MeOH) 95 : 3 : 2 \to 60 : 38 : 2}
\]

Yield : 64%  

Chemical formula : C\textsubscript{18}H\textsubscript{37}NO\textsubscript{4}  

Molecular weight : 331.49  

Appearance : Off-white amorphous powder  

Melting point : \(\theta_m = 131 \degree\text{C (recryst. from MeOH/CHCl\textsubscript{3})}}

Optical rotation : \([\alpha]_{D}^{25} = -25.3^\circ (c = 1.59 \text{ g/100 mL MeOH})

^{1}\text{H NMR (500 MHz, CD}_3\text{OD) }\delta \text{ [ppm] (pyrrolidinium trifluoroacetate) : 1.27 - 1.42 (m, 18H, H\textsubscript{2}-8 - H\textsubscript{2}-16), 1.42 - 1.57 (m, 4H, H\textsubscript{2}-7, H\textsubscript{2}-17), 1.74 (m, 1H, H\textsubscript{A}-6), 1.88 (m, 1H, H\textsubscript{B}-6), 3.32"
Experimental Section

("q", 1H, J = 7.1 Hz, H-5), 3.46 (dt, 1H, J1 = 3.9 Hz, J2 = 6.2 Hz, H-2), 3.53 (t, 2H, J = 6.6 Hz, H-18), 3.80 (dd, 1H, J1 = 6.6 Hz, J2 = 12.0 Hz, H-A-1), 3.84 (m, 1H, H-4), 3.86 (dd, 1H, J1 = 4.2 Hz, J2 = 12.1 Hz, H-B-1), 3.97 (t, 1H, J = 5.9 Hz, H-3).

13C NMR (125 MHz, CD3OD) δ [ppm] (pyrrolidinium trifluoroacetate) : 26.96 (CH2, C-16), 27.20 (CH2, C-7), 30.40, 30.46, 30.61, 30.73, 30.75, 30.76 (8 × CH2, C-8 – C-15), 32.06 (CH2, C-6), 33.67 (CH2, C-17), 59.55 (CH2, C-1), 63.02 (CH2, C-18), 64.51 (CH, C-5), 65.72 (CH, C-2), 76.70 (CH, C-3), 80.40 (CH, C-4).

1H NMR (500 MHz, C5D5N) δ [ppm] (free base) : 1.19 – 1.44 (m, 16H, H2-8 – H2-15), 1.47 – 1.59 (m, 3H, H-A-7, H2-16), 1.60 – 1.80 (m, 2H, H-A-6, H-B-7), 1.76 (m, 2H, H2-17), 2.03 (m, 1H, H-B-6), 3.49 ("d", 1H, J = 4.4 Hz, H-5), 3.77 ("d", 1H, J = 4.3 Hz, H-2), 3.89 (t, 2H, J = 6.4 Hz, H-18), 4.17 (dd, 1H, J1 = 6.0 Hz, J2 = 10.3 Hz, H-A-1), 4.22 (dd, 1H, J1 = 3.8 Hz, J2 = 10.5 Hz, H-B-1), 4.38 (t, 1H, J = 6.2 Hz, H-4), 4.66 (t, 1H, J = 6.1 Hz, H-3).

13C NMR (125 MHz, C5D5N) δ [ppm] (free base) : 26.56 (CH2, C-16), 27.35 (CH2, C-7), 29.94, 30.02, 30.03, 30.29 (8 × CH2, C-8 – C-15), 33.83 (CH2, C-17), 35.88 (CH2, C-6), 62.16 (CH2, C-18), 62.98 (CH, C-5), 63.95 (CH2, C-1), 65.24 (CH, C-2), 80.55 (CH, C-3), 84.57 (CH, C-4).

1H NMR (500 MHz, C5D5N) δ [ppm] (pyrrolidinium chloride) : 1.12 – 1.42 (m, 16H, H2-8 – H2-15), 1.51 (quin, 2H, J = 7.5 Hz, H2-16), 1.75 (m, 1H, H-A-7), 1.77 (m, 2H, H2-17), 1.85 (m, 1H, H-B-7), 2.35 (m, 2H, H2-6), 3.89 (t, 2H, J = 6.55 Hz, H2-18), 4.11 (q, 1H, J = 7.4 Hz, H-5), 4.32 (m, 1H, H-2), 4.49 (m, 2H, H2-1), 4.70 (t, 1H, J = 7.1 Hz, H-4), 4.95 (t, 1H, J = 6.7 Hz, H-3).

13C NMR (125 MHz, C5D5N) δ [ppm] (pyrrolidinium chloride) : 26.54 (CH2, C-16), 26.91 (CH2, C-7), 29.63, 29.68, 29.80, 29.87, 29.90, 30.01 (8 × CH2, C-8 – C-15), 31.83 (CH2, C-6), 33.81 (CH2, C-17), 59.45 (CH2, C-1), 62.15 (CH2, C-18), 62.94 (CH, C-5), 65.26 (CH, C-2), 76.48 (CH, C-3), 80.57 (CH, C-4).

IR (neat) ν [cm−1] : 3294(br) [N–H/O–H], 3107(br) [N–H/O–H], 2916 (vs) [C–H], 2849 (vs) [C–H], 1475 (m), 1464 (m), 1439 (w), 1414 (w), 1398 (w), 1360 (w), 1337 (w), 1260 (w), 1227 (w), 1215 (w), 1182 (w), 1154 (m), 1123 (m), 1057 (vs) [C–O], 1049 (vs) [C–O], 1036 (s), 1016 (m), 1001 (m), 988 (s), 972 (m), 932 (w), 904 (w), 854 (w), 827 (w), 797 (w), 777 (w), 756 (w), 729 (m), 719 (m).

HRMS (ESI) calculated for C18H38NO4 [M + H+] : 332.2801, found 332.2810.
Experimental Section

(--)-(2S,3S,4S,5S)-2-Hydroxymethyl-5-phenethylpyrrolidine-3,4-diol (9/8)

(--)-(5S)-Phenethyl-L-AB1

To the suspension of Pd-enriched Pearlman’s catalyst (140 mg Pd(OH)$_2$/C + 106 mg Pd black) in a mixture of 10 M HCl (3.3 mL) and MeOH (15 mL) was added a solution of the styrylpyrrolidine 8/1 (1787 mg, 3.0 mmol) in EtOAc (15 mL). The reaction vessel was evacuated under gentle vacuum and flushed three times with H$_2$ and then left with vigorous stirring overnight (18 h) under an atmosphere of H$_2$ at 25 °C after which time reaction control via ESI-MS indicated full conversion of the starting material. The catalyst was subsequently re-moved by filtration through a pad of Celite and rinsed thoroughly with MeOH. The combined filtrate and washing were then basified with a 7 M methanolic NH$_3$ solution (5 mL). NH$_4$Cl precipitated in the course of the process. An attempt to filter the NH$_4$Cl off was unsuccessful. Evaporation to dryness under reduced pressure gave a sticky, slightly yellow mixture of NH$_4$Cl and the debenzylated product. This mixture was then elutriated with 2 M methanolic NH$_3$ solution (3 mL) and absorbed on SiO$_2$ (3 g). Column chromatography over basified SiO$_2$ afforded (5S)-phenethyl-L-AB1 as an off-white solid that still contained NH$_4$Cl according to gravimetric analysis (yield greater than 100%). Further purification was achieved by ion-exchange chromatography on basic DOWEX 1X8 100-200 ion-exchange resin (Ø 2.0 cm × 10 cm, eluted first with H$_2$O/MeOH (1 : 1) and then pure MeOH) followed by recrystallisation of 9/8 as its acetate salt from MeOH/CHCl$_3$ (15 : 85) to yield pure (5S)-phenethyl-L-AB1 acetate (721 mg, 2.42 mmol) as a white solid.

CC : Ø 3 cm × 6 cm, $V_{Fr} = 50$ mL, eluent CHCl$_3$/MeOH/NH$_3$ (7 N in MeOH) 95 : 3 : 2 → 80 : 18 : 2

Yield : 81%

Chemical formula : C$_{13}$H$_{19}$NO$_3$ (free base), C$_{15}$H$_{23}$NO$_5$ (pyrrolidinium acetate)

Molecular weight : 237.29 (free base), 297.35 (pyrrolidinium acetate)

Appearance : White solid

TLC : $R_f = 0.43$ (CHCl$_3$/MeOH = 75 : 25 on basified TLC plates), CAM, ninhydrin

Opt. rotation : \[ \alpha \]$_D^{25} = -45.3^\circ$ (c = 2.35g/100 mL MeOH) (free base)

\[ \alpha \]$_D^{25} = -31.2^\circ$ (c = 1.12 g/100 mL MeOH) (pyrrolidinium acetate)

Melting point : $\theta_{m} = 122-123$ °C (acetate salt, recryst. from CHCl$_3$/MeOH 15 : 85)
**Experimental Section**

$^{1}H$ NMR (500 MHz, $CD_{3}$N) $\delta$ [ppm] (free base) : 2.15 (m, 1H, H$_{A}$-6), 2.36 (m, 1H, H$_{B}$-6), 2.89 (ddd, 1H, $J_{1}$ = 6.2 Hz, $J_{2}$ = 10.4, $J_{3}$ = 13.7 Hz, H$_{A}$-7), 3.04 (ddd, 1H, $J_{1}$ = 5.3 Hz, $J_{2}$ = 10.7 Hz, $J_{3}$ = 13.7 Hz, H$_{B}$-7), 3.61 (dt, 1H, $J_{1}$ = 4.9 Hz, $J_{2}$ = 7.9 Hz, H-5), 3.86 (br dt, 1H, $J_{1}$ = 4.1 Hz, $J_{2}$ = 6.1 Hz, H-2), 4.21 (dd, 1H, $J_{1}$ = 5.8 Hz, $J_{2}$ = 11.1 Hz, H$_{A}$-1), 4.27 (dd, 1H, $J_{1}$ = 3.9 Hz, $J_{2}$ = 11.1 Hz, H$_{B}$-1), 4.46 (t, 1H, $J$ = 6.7 Hz, H-4), 4.69 (t, 1H, $J$ = 6.5 Hz, H-3), 7.19 (m, 1H, para-Ph-H), 7.26 – 7.31 (m, 4H, ortho- & meta-Ph-H).

$^{13}$C NMR (125 MHz, $CD_{3}$N) $\delta$ [ppm] (free base) : 33.44 (CH$_{2}$, C-7), 37.02 (CH$_{2}$, C-6), 62.31 (CH, C-5), 62.88 (CH$_{2}$, C-1), 65.06 (CH, C-2), 79.71 (CH, C-3), 83.67 (CH, C-4), 126.03 (para-Ph-CH), 128.72 (2 × ortho-Ph-CH), 128.92 (2 × meta-Ph-CH), 143.04 (ipso-Ph-C$_{q}$).

$^{1}H$ NMR (500 MHz, CD$_{3}$OD) $\delta$ [ppm] (free base) : 1.73 (m, 1H, H$_{A}$-6), 1.97 (m, 1H, H$_{B}$-6), 2.66 (ddd, 1H, $J_{1}$ = 6.2 Hz, $J_{2}$ = 10.3 Hz, $J_{3}$ = 13.7 Hz, H$_{A}$-7), 2.77 (ddd, 1H, $J_{1}$ = 5.5 Hz, $J_{2}$ = 10.6 Hz, $J_{3}$ = 13.8 Hz, H$_{B}$-7), 2.90 (td, 1H, $J_{1}$ = 5.3 Hz, $J_{2}$ = 7.8 Hz, H-5), 2.99 (dd, 1H, $J_{1}$ = 6.2 Hz, $J_{2}$ = 10.6 Hz, H-2), 3.59 (dd, 1H, $J_{1}$ = 6.0 Hz, $J_{2}$ = 11.4 Hz, H$_{A}$-1), 3.65 (t, 1H, $J$ = 6.8 Hz, H-4), 3.67 (dd, 1H, $J_{1}$ = 4.0 Hz, $J_{2}$ = 11.4 Hz, H$_{B}$-1), 3.77 (t, 1H, $J$ = 6.6 Hz, H-3), 7.14 (t, 1H, $J$ = 6.9 Hz, para-Ph-H), 7.17 – 7.29 (m, 4H, ortho- & meta-Ph-H).

$^{13}$C NMR (125 MHz, CD$_{3}$OD) $\delta$ [ppm] (free base) : 34.02 (CH$_{2}$, C-7), 37.54 (CH$_{2}$, C-6), 62.22 (CH, C-5), 63.32 (CH$_{2}$, C-1), 64.49 (CH, C-2), 79.70 (CH, C-3), 83.74 (CH, C-4), 126.83 (para-Ph-CH), 129.37 (2 × ortho-Ph-CH), 129.41 (2 × meta-Ph-CH), 143.43 (ipso-Ph-C$_{q}$).

$^{1}H$ NMR (500 MHz, CD$_{3}$OD) $\delta$ [ppm] (pyrrolidinium acetate) : 1.91 (s, 3H, OAc-CH$_{3}$), 2.01 (m, 1H, H$_{A}$-6), 2.15 (ddt, 1H, $J_{1}$ = 6.3 Hz, $J_{2}$ = 10.3 Hz, $J_{3}$ = 12.7 Hz, H$_{B}$-6), 2.78 (m, 2H, H$_{2}$-7), 3.31 (m, 1H, H-5), 3.42 (td, 1H, $J_{1}$ = 4.1 Hz, $J_{2}$ = 6.3 Hz, H-2), 3.78 (dd, 1H, $J_{1}$ = 6.4 Hz, $J_{2}$ = 11.9 Hz, H$_{A}$-1), 3.84 (dd, 1H, $J_{1}$ = 3.9 Hz, $J_{2}$ = 11.9 Hz, H$_{B}$-1), 3.88 (t, 1H, $J$ = 6.2 Hz, H-4), 3.95 (t, 1H, $J$ = 6.0 Hz, H-3), 7.18 (m, 1H, para-Ph-H), 7.23 – 7.31 (m, 4H, ortho- & meta-Ph-H).

$^{13}$C NMR (125 MHz, CD$_{3}$OD) $\delta$ [ppm] (pyrrolidinium acetate) : 23.61 (br, CH$_{3}$, OAc), 33.37 (CH$_{2}$, C-7), 34.75 (CH$_{2}$, C-6), 60.29 (CH, C-5), 63.61 (CH$_{2}$, C-1), 65.61 (CH, C-2), 77.36 (CH, C-3), 81.08 (CH, C-4), 127.28 (para-Ph-CH), 129.47 (2 × ortho-Ph-CH), 129.60 (2 × meta-Ph-CH), 142.15 (ipso-Ph-C$_{q}$), 179.46 (br, CO, OAc).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] (acetate salt) : 3480(w), 3306(m), 3223(m), 3001(m), 2982(m), 2951(m), 2932(m), 2860(w), 2804(w), 2669(w), 2578(w), 2432(m), 2301(w), 2025(w), 1977(w), 1649(m), 1601(w), 1539(vs), 1493(m), 1479(m), 1452(s), 1410(vs), 1368(m), 1352(s), 1337(s), 1315(m), 1263(m), 1209(w), 1167(m), 1138(s), 1117(m), 1109(m), 1088(s), 1072(m), 1045(s), 1022(vs), 1003(m), 932(m), 918(m), 856(w), 754(vs), 700(vs).

HRMS (ESI) calculated for C$_{13}$H$_{20}$NO$_{3}$ [M + H$^+$] : 238.1443, found 238.1440.
E.6 Synthesis of (−)-10′-Deoxobroussonetine E
and (−)-(6S)-(12′-Hydroxydodecyl)moranoline

(+)-(2S,3S,4S,5R)-N-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-[(1′R)-13′-benzyloxy-1′-hydroxytridecyl]pyrrolidine (9/12) and

(+)-(2S,3S,4S,5R)-N-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-[(1′S)-13′-benzyloxy-1′-hydroxytridecyl]pyrrolidine (9/13)

\[
\begin{align*}
\text{Step 1 (Preparation of benzyloxydodecylmagnesium bromide):} & \quad \text{To acid washed magnesium turnings (583 mg, 24 mmol, 2.0 equiv) covered with a layer of dry THF (8 mL) was added a} \\
& \quad \text{solution of 1-benzyloxy-12-bromododecane (4264 mg, 12 mmol, 1.0 equiv) in one portion.} \\
& \quad \text{The mixture was vigorously stirred under an atmosphere of N}_2 \text{ first at rt for 30 min then at} \\
& \quad 50 \degree \text{C for 3 h during which time the magnesium slowly dissolved to form a pale greenish} \\
& \quad \text{grey solution of the desired Grignard reagent. After 3 h the solution was decanted from} \\
& \quad \text{residual magnesium and directly used in the following Grignard reaction.} \\
\text{Step 2 (Grignard addition):} & \quad \text{To the solution of crude pyrrolidine carbaldehyde 8/2 (3130 mg,} \\
& \quad 6.0 \text{ mmol, 1.0 equiv) in anhydrous THF (18 mL) was slowly added a solution of freshly} \\
& \quad \text{prepared benzyloxydodecylmagnesium bromide (estimated concentration 0.4 M – 0.5 M in} \\
& \quad \text{THF, 24 mL, 1.6 – 2.0 equiv) at −78 \degree \text{C under an atmosphere of N}_2.} \text{ \text{The mixture was stirred} \\
& \quad \text{overnight (16 h) while slowly warming to rt and was then quenched with 1 M NH}_4\text{Cl} \\
& \quad \text{solution (30 mL) followed by its dilution with Et}_2\text{O (60 mL). This heterogeneous mixture was} \\
& \quad \text{subsequently washed with 1 M NaHCO}_3 \text{ solution (30 mL) whereupon copious precipitation} \\
& \quad \text{of Mg(OH)}_2/\text{MgCO}_3 \text{ occurred. The organic phase was separated, dried over MgSO}_3 \text{ and} \\
& \quad \text{concentrated } \text{in vacuo. Purification by column chromatography afforded a 3 : 2 mixture of the} \\
& \quad \text{epimeric pyrrolidine alcohols 9/12 and 9/13 in favour of the (R)-epimer 9/12 in 66% combined} \\
& \quad \text{yield. Separation of both epimers was achieved via repeated column chromatography (6 runs) giving the more polar} \\
& \quad (R)-alcohol 9/12 (1882 mg, 2.34 mmol) as a yellow and the less polar} \\
& \quad (S)-alcohol 9/13 (1245 mg, 1.56 mmol) as an orange oil.}
\end{align*}
\]
Experimental Section

1st CC : \( \phi 6 \text{ cm} \times 12.5 \text{ cm} \), \( V_{Fr} = 200 \text{ mL} \), eluent EA/PE 0 : 100 \( \rightarrow \) 25 : 75

Combined yield : 66%

Chemical formula : \( \text{C}_{53}\text{H}_{67}\text{NO}_{5} \)

Molecular weight : 798.10

IR (neat) \( \tilde{\nu} \) [cm\(^{-1}\)] : 2926 (m), 2853 (m), 1495 (w), 1454 (m), 1363 (w), 1306 (w), 1206 (w), 1096 (s), 1075 (s), 1028 (m), 909 (w), 840 (w), 818 (w), 735 (s), 697 (vs).

More polar \((6R)\)-alcohol \((9/12)\)

Isolated yield : 39% (after 6 chromatographic separations)

Appearance : yellow oil

TLC : \( R_f = 0.35 \) (DE/PE = 40 : 60), CAM

Optical rotation : \( [\alpha]^{25}_D = +5.3^\circ \) (\( c = 4.23 \text{ g}/100 \text{ mL} \ \text{CHCl}_3 \))

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) [ppm] : 1.18 – 1.31" (m, 14H, H\(_2\)-9 – H\(_2\)-15), 1.34" (m, 3H, H\(_A\)-7, H\(_2\)-16), 1.48 (m, 3H, H\(_B\)-7, H\(_2\)-8), 1.60 (quin, 2H, \( J = 7.1 \text{ Hz} \), H\(_2\)-17), 3.09 (dd, 1H, \( J_1 = 3.4 \text{ Hz} \), \( J_2 = 5.1 \text{ Hz} \), H\(_5\)), 3.27 (br, 1H, OH-6), 3.45 (m, 3H, \( J = 6.7 \text{ Hz} \), H-2, H\(_2\)-18), 3.59" (m, 1H, H\(_6\)), 3.61" (dd, 1H, \( J_1 = 6.6 \text{ Hz} \), \( J_2 = 9.8 \text{ Hz} \), H\(_{A}\)-1), 3.68 (dd, 1H, \( J_1 = 5.4 \text{ Hz} \), \( J_2 = 9.8 \text{ Hz} \), H\(_{B}\)-1), 3.89" (m, 1H, H-4), 3.90" (m, 1H, \( J = 13.6 \text{ Hz} \), H\(_{A}\)-5\(^*\)), 3.97 (d, 1H, \( J = 14.0 \text{ Hz} \), H\(_A\)-5\(^*\)), 4.12 (dd, 1H, \( J_1 = 2.0 \text{ Hz} \), \( J_2 = 3.5 \text{ Hz} \), H-3), 4.42 (s, 2H, H\(_2\)-1\(^*\)), 4.47 (s, 2H, H\(_2\)-4\(^*\)), 4.48" (d, 1H, \( J = 12.0 \text{ Hz} \), H\(_A\)-3\(^*\)), 4.49" (s, 2H, H\(_2\)-18\(^*\)), 4.52" (d, 1H, \( J = 12.0 \text{ Hz} \), H\(_B\)-3\(^*\)), 7.20 – 7.36 (m, 25H, 25 \times \text{Ph-H}.

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) [ppm] : 26.19 (CH\(_3\), C-16), 26.48 (CH\(_2\), C-8), 29.49, 29.60, 29.63, 29.70 (7 \times \text{CH}_2, C-9 – C-15), 29.77 (CH\(_3\), C-17), 34.58 (CH\(_2\), C-7), 53.22 (CH\(_2\), C-5\(^*\)), 64.08 (CH, C-2), 67.33 (CH\(_3\), C-1), 70.52 (CH\(_2\), C-18), 70.85 (CH, C-5), 71.94 (CH, C-6), 71.46 (CH\(_2\), C-4\(^*\)), 71.57 (CH\(_2\), C-3\(^*\)), 72.82 (CH\(_2\), C-18\(^*\)), 73.10 (CH\(_2\), C-1\(^*\)), 84.54 (CH, C-3), 86.92 (CH, C-4), 126.89, 127.41, 127.55, 127.58, 127.59, 127.64, 127.72, 127.78, 128.19, 128.30, 128.35, 128.38, 128.40 (25 \times \text{Ph-CH}), 137.97, 138.07, 138.11, 138.72 (4 \times ipso-Ph-C\(_q\), OBn), 139.37 (ipso-Ph-C\(_q\), NBn).

HRMS (ESI) calculated for \( \text{C}_{53}\text{H}_{68}\text{NO}_{5} \) [M + H\(^+\) ] : 798.5097, found 798.5102.
Experimental Section

Less polar (6S)-alcohol (9/13)

\[
\begin{align*}
&\text{Isolated yield:} \quad 26\% \quad \text{(after 6 chromatographic separations)} \\
&\text{Appearance:} \quad \text{orange oil} \\
&\text{TLC:} \quad R_f = 0.45 \quad \text{(DE/PE 40 : 60), CAM} \\
&\text{Optical rotation:} \quad [\alpha]_{D}^{25} = +25.1^\circ \quad (c = 5.41 \text{ g/100 mL CHCl}_3)
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 1.25$^\text{a}$ (s, 14H, H$_2$-9 – H$_2$-15), 1.32 – 1.42$^\text{a}$ (m, 4H, H$_A$-7, H$_A$-8, H$_A$-16), 1.42 – 1.52$^\text{a}$ (m, 2H, H$_B$-7, H$_B$-8), 1.61 (‘quin’, 2H, $J = 7.0$ Hz, H$_2$-17), 3.02 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 3.2$ Hz, H-5), 3.24 (s, 1H, OH-6), 3.46 (m, 3H, $J = 6.7$ Hz, H-2, H-18), 3.52 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 3.5$ Hz, H-4), 4.36 (d, 1H, $J = 11.6$ Hz, H$_A$-1*), 4.38 (d, 1H, $J = 12.1$ Hz, H$_A$-4*), 4.41 (d, 1H, $J = 12.1$ Hz, H$_B$-4*), 4.42 (d, 1H, $J = 11.7$ Hz, H$_B$-1*), 4.45 (d, 1H, $J = 12.2$ Hz, H$_A$-3*), 4.49 (s, 2H, H$_2$-18*), 4.50 (d, 1H, $J = 12.2$ Hz, H$_B$-3*), 7.18 – 7.36 (m, 25H, 25 $\times$ Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm]: 26.20 (CH$_2$, C-16), 26.29 (CH$_2$, C-8), 29.50, 29.61, 29.63, 29.66, 29.78, 29.82 (8 $\times$ CH$_2$, C-9 – C-15, C-17), 33.47 (CH$_2$, C-7), 50.87 (CH$_2$, C-5*), 63.10 (CH, C-2), 66.38 (CH$_2$, C-1), 67.69 (CH, C-6), 70.53 (CH$_2$, C-18), 70.74 (CH$_2$, C-3*), 71.44 (CH$_2$, C-4*), 71.93 (CH, C-5), 72.83 (CH$_2$, C-18*), 73.17 (CH$_2$, C-1*), 81.88 (CH, C-3), 83.35 (CH, C-4), 126.97, 127.42, 127.47, 127.48, 127.59, 127.69, 128.13, 128.27, 128.31, 128.33, 128.40 (25 $\times$ Ph-CH), 137.98, 138.07, 138.22, 138.73 (4 $\times$ ipso-Ph-C$_q$, OBn), 138.81 (ipso-Ph-C$_q$, OBn).

HRMS (ESI) calculated for C$_{53}$H$_{68}$NO$_5$ [M + H$^+$]: 798.5097, found 798.5092.
Experimental Section

1,24-Bis(benzyloxy)tetracosane (9/11)

Bisbenzyl ether 9/11 (674 mg, 1.22 mmol) was obtained as by-product from the above Grignard reaction as a white solid in 20% yield (based on the amount of benzyl 12-bromododecanyl ether (9/3) employed in the reaction). 9/11 is the result of a Wurtz-type coupling reaction of benzyloxydodecylmagnesium bromide (9/10) with 1-benzyloxy-12-bromododecane (9/3) during the preparation of the Grignard reagent.

Yield : 20%

Chemical formula : C_{38}H_{62}O_{2}

Molecular weight : 550.90

Appearance : white solid

TLC : \( R_f = 0.26 \) (DE/PE = 5 : 95), CAM

Melting point : \( \vartheta_m = 64 – 67 \, ^\circ\text{C} \)

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) [ppm] : 1.25 (s, 36H, H\(_2\)-4 – H\(_2\)-21), 1.34 (m, 4H, H\(_2\)-3, H\(_2\)-22), 1.61 ("quin", 4H, \( J = 7.0 \) Hz, H\(_2\)-2, H\(_2\)-23), 3.46 (t, 4H, \( J = 6.6 \) Hz, H\(_2\)-1, H\(_2\)-24), 4.50 (s, 4H, H\(_2\)-1*, H\(_2\)-24*), 7.27 (m, 2H, 2 \( \times \) para-Ph-H), 7.33 ("d", 8H, \( J = 4.3 \) Hz, 4 \( \times \) ortho-Ph-H, 4 \( \times \) meta-Ph-H).

\( ^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)) \( \delta \) [ppm] : 26.21 (2 \( \times \) CH\(_2\), C-3, C-22), 29.50, 29.62, 29.63, 29.68, 29.70, 29.72, 29.79 (20 \( \times \) CH\(_2\), C-2, C-4 – C-21, C-23), 70.54 (2 \( \times \) CH\(_2\), C-1, C-24), 72.85 (2 \( \times \) CH\(_2\), C-1*, C-24*), 127.44 (2 \( \times \) para-Ph-CH), 127.60 (2 \( \times \) ortho-Ph-CH), 128.32 (2 \( \times \) meta-Ph-CH), 138.74 (2 \( \times \) ipso-Ph-C\(_q\)).

IR (neat) \( \tilde{\nu} \) [cm\(^{-1}\)] : 2919 (vs), 2845 (vs), 2796 (w), 1497 (w), 1471 (m), 1454 (w), 1365 (w), 1208 (w), 1123 (m), 1108 (s), 1074 (w), 1028 (w), 1013 (w), 976 (w), 906 (w), 736 (s), 720 (m), 696 (s).

HRMS (EI) calculated for C\(_{38}\)H\(_{62}\)O\(_2\) [M\(^+\)] : 550.4750, found 550.4749.
General procedure for the esterification of secondary alcohols with Mosher’s MTPA-chlorides

The solution of the respective secondary alcohol (0.1 – 0.15 mmol, 1.0 equiv) and a catalytic amount of DMAP (0.1 – 0.3 equiv) in anhydrous DCM (2 mL) is treated consecutively with dry Et$_3$N (5.0 – 10.0 equiv) and the respective MTPA-Cl (3.0 equiv) at 0 °C under an atmosphere of N$_2$. After stirring at 25 °C overnight (16 h) the mixture is diluted with 1 M phosphate buffer (pH 7) solution. Extraction of the aqueous phase with DCM (3 × 4 mL) is followed by drying of the organic phases over MgSO$_4$ and concentration in vacuo. Purification of the crude residue by column chromatography affords the respective MTPA-ester.

$$(+)-(2S,3S,4S,5S)-N$-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-((1'R)-13'-benzylxyo-1-((2'R)-3',3',3'-trifluoro-2'-methoxy-2'-phenylpropanoyloxy)tridecyl)pyrrolidine (9/14a)$$

**CC :** $\varnothing$ 1.5 cm × 10 cm, $V_{fr} = 6 – 7$ mL, eluent EA/PE 5 : 95 → 12.5 : 87.5

**Yield :** 95%

**Chemical formula :** C$_{63}$H$_{74}$F$_3$NO$_7$

**Molecular weight :** 1014.26

**Appearance :** Pale brown oil

**TLC :** $R_f = 0.43$ (DE/PE = 25 : 75), CAM

**Optical rotation :** $[\alpha]_D^{25} = +53.6^\circ$ (c = 6.6 g/100 mL CHCl$_3$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 0.93 (br, 1H, H$_{A-8}$), 1.03 – 1.33" (m, 15H, H$_{B-9}$ – H$_{2-15}$), 1.36" (m, 2H, H$_2$-16), 1.48 (dddd, 1H, $J_1 = 3.4$ Hz, $J_2 = 7.1$ Hz, $J_3 = 10.5$ Hz, $J_4 = 19.1$ Hz, H$_{A-7}$), 1.62 ("quin", 2H, $J = 7.0$ Hz, H$_2$-17), 1.92 ("quin", 1H, $J = 7.2$ Hz, H$_{B-7}$), 3.37 (t, 1H, $J = 3.7$ Hz, H-5), 3.46" (t, 2H, $J = 6.7$ Hz, H$_2$-18), 3.47" (s, 3H, MTPA-OCH$_3$), 3.50" (dd, 1H, $J_1 = 4.5$ Hz, $J_2 = 8.3$ Hz, H-2), 3.55 (t, 1H, $J = 8.6$ Hz, H$_{A-1}$), 3.68 (dd, 1H, $J_1 = 4.3$ Hz, $J_2 = 8.9$ Hz, H$_{B-1}$), 3.94" (d, 1H, $J = 14.6$ Hz, H$_{A-5}$), 3.98" (d, 1H, $J = 14.6$ Hz, H$_{B-5}$), 4.05 (m, 2H, H-3, H-4), 4.36 (d, 1H, $J = 11.4$ Hz, H$_{A-4}$), 4.39" (s, 2H, H$_{2-1}$), 4.41" (d, 1H, $J = 11.5$ Hz, H$_{B-4}$), 4.43"
Experimental Section

(d, 1H, \(J = 12.1 \text{ Hz, } H_\alpha-3^*\)), 4.50 (s, 2H, \(H_2-18^*\)), 4.51 (d, 1H, \(J = 12.0 \text{ Hz, } H_\beta-3^*\)), 5.22 (m, 1H, HC-6), 7.14 – 7.34 (m, 28H, 28 \times \text{Ph-H}), 7.53 (d, 2H, \(J = 7.8 \text{ Hz, } 2 \times \text{ortho-Ph-H, MTPA}\)).

\(^{13}\text{C NMR (125 MHz, CDCl}_3\text{) }\delta \text{ [ppm]}: 26.01 (\text{CH}_2, C-8), 26.22 (\text{CH}_2, C-16), 28.73 (\text{CH}_2, C-7), 29.26, 29.39, 29.50, 29.52, 29.61, 29.63 (7 \times \text{CH}_2, C-9 – C-15), 29.79 (\text{CH}_2, C-17), 52.16 (\text{CH}_2, C-5^*), 55.50 (\text{OCH}_3, \text{MTPA}), 63.71 (\text{CH}, C-2), 66.76 (\text{CH}_2, C-1), 70.04 (\text{CH}, C-5), 70.53 (\text{CH}_2, C-18), 70.91 (\text{CH}_2, C-3^*), 71.39 (\text{CH}_2, C-4^*), 72.84 (\text{CH}_2, C-18^*), 73.22 (\text{CH}_2, C-1^*), 76.38 (\text{CH}, C-6), 82.92 (\text{CH}, C-3), 84.37 (\text{CH}, C-4), 84.56 (q, \(J_{CF} = 27.4 \text{ Hz, } C_q, \text{MTPA}\)), 123.46 (q, \(J_{CF} = 288.6 \text{ Hz, CF}_3, \text{MTPA}\)), 126.86, 127.31, 127.43, 127.45, 127.47, 127.49, 127.59, 127.60, 128.07, 128.20, 128.23, 128.27, 128.28, 128.31, 129.35 (30 \times \text{Ph-CH}), 132.55 (\text{Ph-C}_q, \text{MTPA}), 137.99, 138.19, 138.32, 138.72 (4 \times \text{Ph-C}_q, \text{OBn}), 139.39 (\text{Ph-C}_q, \text{NBn}), 166.55 (\text{CO, MTPA}).

IR (neat) \(\tilde{\nu} \text{ [cm}^{-1}]\): 3421 (w), 3278 (w), 3211 (w), 2927 (m), 2854 (m), 1743 (m), 1699 (m), 1496 (w), 1466 (m), 1454 (m), 1405 (m), 1360 (w), 1269 (m), 1239 (s), 1190 (m), 1169 (m), 1140 (m), 1074 (s), 1046 (s), 1014 (s), 975 (m), 909 (w), 833 (w), 783 (w), 737 (vs), 720 (m), 697 (vs), 679 (w).

HRMS (ESI) calculated for \(\text{C}_{63}\text{H}_{75}\text{F}_3\text{NO}_7\) [\(M + H^+\)] : 1014.5496, found 1014.5529.

\((+)-(2S,3S,4S,5S)-N-\text{Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-}((1'R)-13'-\text{benzyloxy-1-}((2'S)-3',3',3''-\text{trifluoro-2''-methoxy-2''-phenylpropanoyloxy)tridecyl)}\text{pyrrolidine (9/14b)}

\begin{align*}
\text{CC} : \emptyset 1.5 \text{ cm} \times 10 \text{ cm}, V_{Fr} = 6 – 7 \text{ mL, eluent EA/PE 5 : 95 \rightarrow 12.5 : 87.5} \\
\text{Yield} : 88\% \\
\text{Appearance} : \text{Colourless oil} \\
\text{Chemical formula} : \text{C}_{65}\text{H}_{72}\text{F}_3\text{NO}_7 \\
\text{Molecular weight} : 1014.26 \\
\text{TLC} : R_f = 0.44 (\text{DE/PE = 25 : 75}), \text{CAM}
\end{align*}
Optical rotation: $\left[\alpha\right]_{D}^{25} = +21.0^\circ$ (c = 6.6 g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 1.09 (br, 1H, H$_A$-8), 1.12 – 1.32 (m, 15H, H$_B$-8, H$_2$-9 – H$_2$-15), 1.36 (m, 2H, H$_2$-16), 1.56 (m, 1H, H$_A$-7), 1.61 ("quin", 2H, $J = 7.1$ Hz, H$_2$-17), 1.98 (m, 1H, H$_B$-7), 3.29 (t, 1H, $J = 3.4$ Hz, H-5), 3.45 (s, 3H, MTPA-OCH$_3$), 3.46 (t, 2H, $J = 6.7$ Hz, H$_2$-18), 3.49 (m, 1H, H-2), 3.51 (t, 1H, $J = 8.2$ Hz, H$_A$-1), 3.66 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 8.0$ Hz, H$_B$-1), 3.95 (s, 2H, H$_2$-4*), 3.99 (s, 2H, H-3, H-4), 4.22 (s, 2H, H$_2$-18*), 5.19 (m, 1H, H-6), 7.10 – 7.35 (m, 28H, 28 $\times$ Ph-H), 7.48 (d, 2H, $J = 7.6$ Hz, 2 $\times$ ortho-Ph-H, MTPA).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm]: 26.22 (CH$_2$, C-16), 26.35 (CH$_2$, C-8), 29.00 (CH$_2$, C-7), 29.36, 29.45, 29.51, 29.55, 29.62, 29.63 (7 $\times$ CH$_2$, C-9 – C-15), 29.79 (CH$_2$, C-17), 52.23 (CH$_2$, C-5*), 55.39 (OCH$_3$, MTPA), 63.85 (CH, C-2), 67.02 (CH$_2$, C-1), 69.82 (CH, C-5), 70.53 (CH$_2$, C-18), 70.90 (CH$_2$, C-3*), 71.16 (CH$_2$, C-4*), 72.84 (CH$_2$, C-18*), 73.17 (CH$_2$, C-1*), 76.76 (CH, C-6), 83.30 (CH, C-3), 84.12 (CH, C-4), 84.70 (q, $J_{CF} = 27.5$ Hz, C$_q$, MTPA), 123.34 (q, $J_{CF} = 288.5$ Hz, CF$_3$, MTPA), 126.84, 127.38, 127.46, 127.55, 127.58, 127.59, 128.09, 128.13, 128.25, 128.30, 128.31, 129.41 (30 $\times$ Ph-CH), 132.28 (Ph-C$_q$, MTPA), 138.14, 138.22, 138.36, 138.73 (4 $\times$ Ph-C$_q$, OBn), 139.45 (Ph-C$_q$, NBn), 166.48 (CO, MTPA).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 2926 (m), 2854 (m), 1743 (m), 1701 (w), 1496 (w), 1454 (m), 1405 (w), 1363 (w), 1256 (m), 1240 (m), 1188 (m), 1169 (m), 1104 (s), 1046 (m), 1027 (m), 1015 (m), 993 (m), 976 (m), 910 (w), 843 (w), 832 (w), 815 (w), 783 (w), 735 (vs), 697 (vs), 681 (m).

HRMS (ESI) calculated for C$_{63}$H$_{75}$F$_3$NO$_7$ [M + H$^+$]: 1014.5496, found 1014.5538.

(+-)(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-((1'S)-13'-benzyloxy-1-((2'R)-3',3''-trifluoro-2''-methoxy-2''-phenylpropanoyloxy)tridecyl)pyrrolidine (9/15a)

CC: $\emptyset$ 1.5 cm × 10 cm, $V_{Fr}$ = 6 – 7 mL, eluent EA/PE 5 : 95 $\rightarrow$ 12.5 : 87.5
Experimental Section

Yield : 89%

Appearance : Pale yellow oil

Chemical formula : $C_{63}H_{74}F_3NO_7$

Molecular weight : 1014.26

TLC : $R_f = 0.41$ (DE/PE = 25 : 75), CAM

Optical rotation : $[\alpha]^D_{D} = +21.8^\circ$ (c = 4.53 g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 1.10 – 1.32 (m, 16H, H$_2$-8 – H$_2$-15), 1.66 (m, 2H, H$_2$-7), 3.14 (br, 1H, H-2), 3.18 (d, 1H, J = 14.2 Hz, H$_A$-5*), 3.21 (d, 1H, J = 6.3 Hz, H-5), 3.40 (d, 2H, J = 5.2 Hz, H$_2$-1), 3.46 (t, 2H, J = 6.7 Hz, H$_2$-18), 3.50 (s, 3H, MTPA-OC$_3$H$_7$), 3.93 (m, 2H, J = 14.2 Hz, H-4, H$_B$-5*), 4.02 (t, 1H, J = 2.4 Hz, H-3), 4.34 (d, 1H, J = 11.9 Hz, H$_A$-3*), 4.38 (s, 2H, H$_2$-1*), 4.42 (d, 1H, J = 12.0 Hz, H$_B$-3*), 4.45 (d, 1H, J = 11.9 Hz, H$_A$-4*), 4.50 (s, 2H, H$_2$-18*), 4.53 (d, 1H, J = 11.8 Hz, H$_B$-4*), 5.40 ("dd", 1H, $J_1$ = 5.0 Hz, $J_2$ = 7.3 Hz, H-6), 7.12 – 7.36 (m, 28H, 28 × Ph-H), 7.58 (d, 2H, J = 7.4 Hz, 2 × ortho-Ph-H, MTPA).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 26.01 (CH$_2$, C-8), 26.22 (CH$_2$, C-16), 29.28, 29.46, 29.52, 29.62, 29.63 (8 × CH$_2$, C-7, C-9 – C-15), 29.79 (CH$_2$, C-17), 50.98 (CH$_2$, C-5*), 55.7 (OCH$_3$, MTPA), 62.30 (CH, C-2), 66.81 (CH$_2$, C-1), 68.61 (CH, C-5), 70.54 (CH$_2$, C-18), 71.12 (CH$_2$, C-3*), 71.35 (CH$_2$, C-4*), 72.85 (CH$_2$, C-18*), 73.18 (CH$_2$, C-1*), 76.10 (CH, C-6), 84.24 (CH, C-3), 84.49 (CH, C-4), 84.58 (q, $\delta_C = 27.2$ Hz, C$_q$, MTPA), 123.43 (q, $\delta_C = 288.4$ Hz, CF$_3$, MTPA), 126.65, 127.44, 127.52, 127.61, 127.65, 127.71, 127.78, 128.01, 128.03, 128.21, 128.24, 128.29, 127.32, 129.34 (30 × Ph-CH), 132.23 (Ph-C$_q$, MTPA), 138.00, 138.18, 138.37, (3 × Ph-C$_q$, OBn), 138.72 (2 × Ph-C$_q$, OBn at C-18 & NBn), 166.24 (CO, MTPA).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 2927 (m) [C–H], 2854 (m) [C–H], 1744 (m) [C=O], 1558 (w), 1541 (w), 1522 (w), 1507 (w), 1497 (w), 1472 (w), 1455 (m), 1362 (w), 1255 (w), 1169 (m), 1102 (s), 1027 (m), 994 (w), 735 (s), 697 (vs), 678 (m).

HRMS (ESI) calculated for $C_{63}H_{72}F_3NO_7$ [M + H$^+$] : 1014.5496, found 1014.5563.
Experimental Section

(+)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-2-benzyloxymethyl-5-((1'S)-13'-benzyloxy-1-((2'S)-3",3",3"-trifluoro-2"-methoxy-2"-phenylpropanoyloxy)tridecyl)pyrrolidine (9/15b)

Yield : 87%
Appearance : Pale yellow oil
Chemical formula : C₆₃H₇₄F₃NO₇
Molecular weight : 1014.26
TLC : Rf = 0.42 (DE/PE = 25 : 75), CAM
Optical rotation : \[\alpha\]D²⁵ = +5.6º (c = 6.6 g/100 mL CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 1.08 – 1.32 (m, 16H, H₂-8 – H₂-15), 1.36 (m, 2H, H₂-16), 1.62 (m, 4H, H₂-7, H₂-17), 3.25 (m, 2H, H-2, H-5), 3.44 (d, 1H, J = 13.6 Hz, Hₐ-5*), 3.46 (t, 2H, J = 6.6 Hz, H₂-18), 3.53 (d, 2H, J = 5.2 Hz, H₂-1), 3.59 (s, 3H, MTPA-OCH₃), 4.03 (s, 1H, H-3), 4.15 (dd, 1H, J₁ = 1.8 Hz, J₂ = 6.3 Hz, H-4), 4.23 (d, 1H, J = 13.7 Hz, Hₐ-5*), 4.34 (d, 1H, J = 12.1, Hₐ-3*), 4.42 (s, 2H, H₂-1*), 4.43 (d, 1H, J = 11.5 Hz, Hₐ-4*), 4.46 (d, 1H, J = 12.0 Hz, H₂-3*), 4.47 (d, 1H, J = 11.6 Hz, H₂-18*), 5.54 (dd, 1H, J₁ = 4.0 Hz, J₂ = 8.5 Hz, H-6), 7.10 – 7.35 (m, 28H, 28 × Ph-H), 7.72 (d, 2H, J = 7.8 Hz, 2 × ortho-Ph-H, MTPA).

¹³C NMR (125 MHz, CDCl₃) δ [ppm] : 25.78 (CH₃, C-8), 26.21 (CH₃, C-16), 29.26, 29.40, 29.51, 29.61 (7 × CH₂, C-9 – C-15), 29.79 (CH₃, C-2), 30.79 (CH₂, C-7), 51.27 (CH₂, C-5*), 55.91 (OCH₃, MTPA), 62.52 (CH, C-2), 66.94 (CH₂, C-1), 69.87 (CH, C-5), 70.53 (CH₂, C-18), 71.17 (CH₂, C-3*), 71.47 (CH₂, C-4*), 72.84 (CH₂, C-18*), 73.21 (CH₂, C-1*), 73.99 (CH, C-6), 84.30 (CH, C-3), 84.65 (q, JCF = 27.4 Hz, C₉, MTPA), 84.83 (CH, C-4), 123.57 (q, JCF = 289.0 Hz, CF₃, MTPA), 126.69, 127.43, 127.52, 127.60, 127.71, 127.92, 127.94, 128.11, 128.14, 128.23, 128.28, 128.31, 129.29 (30 × Ph-CH), 132.52 (Ph-C₉, MTPA), 138.00, 138.18, 138.21, 138.39 (4 × Ph-C₉, OBn), 138.72 (Ph-C₉, NBn), 166.28 (CO, MTPA).
Experimental Section

IR (neat) \( \tilde{\nu} [\text{cm}^{-1}] : 2927 (\text{m}) [\text{C–H}], 2854 (\text{m}) [\text{C–H}], 1744 (\text{m}) [\text{C=O}], 1631 (\text{w}), 1605 (\text{m}), 1585 (\text{s}), 1574 (\text{m}), 1545 (\text{m}), 1497 (\text{w}), 1484 (\text{w}), 1466 (\text{w}), 1454 (\text{m}), 1390 (\text{s}), 1365 (\text{m}), 1252 (\text{s}), 1213 (\text{s}), 1163 (\text{s}), 1119 (\text{s}), 1029 (\text{s}), 994 (\text{w}), 960 (\text{w}), 925 (\text{w}), 899 (\text{w}), 890 (\text{m}), 874 (\text{w}), 862 (\text{m}), 856 (\text{m}), 844 (\text{w}), 837 (\text{w}), 811 (\text{s}), 793 (\text{w}), 746 (\text{s}), 697 (\text{vs}), 689 (\text{s}), 683 (\text{m}), 679 (\text{m}).

HRMS (ESI) calculated for C_{63}H_{75}F_{3}NO_{7} [M + H^+] : 1014.5496, found 1014.5532.

\((-\text{)(2S,3S,4S,5S)}\)-5-(1'\text{S})-1',13'-dihydroxytridecyl)-5-(hydroxymethyl)pyrrolidine-3,4-diol

\((-\text{)}\)-10'-Deoxobroussonetine E (9/2)

\[
\text{\includegraphics[width=0.5\textwidth]{molecule.png}}
\]

The pentabenzylated pyrrolidine 9/13 (1378 mg, 1.73 mmol) was dissolved in EtOAc (9 mL) and added to the suspension of Pd-enriched Pearlman’s catalyst (81 mg Pd(OH)_2/C + 61 mg Pd black) in a mixture of 10 M HCl (2 mL) and MeOH (9 mL) at rt. The mixture was vigorously stirred at 25 °C under an atmosphere of H_2 overnight (18 h) after which time ESI-MS indicated full conversion of the starting material. The catalyst was subsequently removed by filtration through a pad of Celite and rinsed thoroughly with MeOH. All volatiles were evaporated in vacuo to give a residue which was dissolved in MeOH (8.5 mL) and treated dropwise with a 7 M methanolic NH_3 solution until basic pH. Evaporation to dryness under reduced pressure gave the crude debenzylated product which was chromatographed over basic silica gel (Ø 2.0 cm x 5 cm, V_{el} = 15 mL, elution with CHCl_3/MeOH/NH_3 (7 N in MeOH) 95 : 3 : 2 \rightarrow 70 : 28 : 2). The obtained material was further purified by ion-exchange chromatography on DOWEX 50WX4-200 resin (Ø 2.0 cm x 8.5 cm, acidified with 1 M HCl). After rinsing the column with distilled water (75 mL = 5 x column bed volume) the adsorbed material was eluted with 1 M aqueous NH_3 solution until complete elution of the product. A concluding recrystallisation from MeOH/2 N HCl in Et_2O (1 : 1) afforded the pure L-DMDP derivative 9/2 (609 mg, 1.58 mmol) as its hydrochloride salt.

Yield : 92%
Chemical formula: C_{18}H_{37}NO_{5} (free pyrrolidine base); C_{18}H_{38}ClNO_{5} (pyrrolidinium chloride)

Molecular weight: 347.49 (free pyrrolidine base); 383.95 (pyrrolidinium chloride)

Appearance: White Powder

Melting point: ϑ_m = 132–133 °C (pyrrolidinium chloride, recryst. from MeOH)

Optical rotation: [α]_{D}^{25} = –23.5° (free base, c = 1.0 g/100 mL MeOH)
[α]_{D}^{25} = –13.8° (HCl salt, c = 1.0 g/100 mL MeOH)

1H NMR (500 MHz, CD_{3}OD) δ [ppm] (pyrrolidinium chloride): 1.27 – 1.42 (m, 18H, H_2-8 – H_2-16), 1.52 (quin, 2H, J = 6.8 Hz, H_2-17), 1.62 (q, 2H, J = 7.2 Hz, H_2-7), 3.37 – 3.42 (m, 2H, H-2, H-5), 3.53 (t, 2H, J = 6.7 Hz, H_2-18), 3.79 (dd, 1H, J_1 = 5.3 Hz, J_2 = 12.1 Hz, H_A-1), 3.84 (ddd, 1H, J_1 = 3.6 Hz, J_2 = 12.1 Hz, H_B-1), 3.88 (td, 1H, J_1 = 3.2 Hz, J_2 = 6.9 Hz, H-6), 3.97 (dd, 1H, J_1 = 6.8 Hz, J_2 = 8.4 Hz, H-3), 4.23 (t, 1H, J = 7.0 Hz, H-4).

13C NMR (125 MHz, CD_{3}OD) δ [ppm] (pyrrolidinium chloride): 26.83 (CH_2, C-8), 26.97 (CH_2, C-16), 30.62, 30.66, 30.71, 30.73, 30.76 (7 × CH_2, C-9 – C-15), 33.68 (CH_2, C-17), 34.62 (CH_2, C-7), 58.60 (CH_2, C-1), 63.04 (CH_2, C-18), 64.84 (CH, C-2), 66.03 (CH, C-5), 70.04 (CH, C-6), 75.09 (CH, C-4), 76.68 (CH, C-3).

1H NMR (500 MHz, CD_{3}OD) δ [ppm] (free base): 1.27 – 1.41 (m, 17H, H_A-8, H_2-9 – H_2-16), 1.44 – 1.64 (m, 5H, H_2-7, H_B-8, H_2-17), 2.89 (t", 1H, J = 5.5 Hz, H-5), 3.01 ("dd", 1H, J_1 = 6.0 Hz, J_2 = 10.6 Hz, H-2), 3.54 (t, 2H, J = 6.7 Hz, H_2-18), 3.55 – 3.63 (m, 2H, H_A-1, H-6), 3.67 (dd, 1H, J_1 = 4.1 Hz, J_2 = 11.1 Hz, H_B-1), 3.78 (t, 1H, J = 6.3 Hz, H-3), 4.00 (t, 1H, J = 6.3 Hz, H-4).

13C NMR (125 MHz, CD_{3}OD) δ [ppm] (free base): 26.83 (CH_2, C-8), 27.13 (CH_2, C-16), 30.62, 30.71, 30.75, 30.80 (7 × CH_2, C-9 – C-15), 33.67 (CH_2, C-17), 35.11 (CH_2, C-7), 63.02 (CH_2, C-18), 63.44 (CH_2, C-1), 65.02 (CH, C-2), 67.01 (CH, C-5), 73.87 (CH, C-6), 79.40 (CH, C-4), 80.18 (CH, C-3).

1H NMR (500 MHz, C_{5}D_{5}N) δ [ppm] (pyrrolidinium chloride): 1.12 – 1.36 (m, 14H, H_2-9 – H_2-15), 1.45 – 1.55 (m, 3H, J = 7.4 Hz, H_A-8, H_2-16), 1.71 (m, 1H, H_B-8), 1.76 (quin, 2H, J = 7.1 Hz, H_2-17), 2.01 (m, 1H, H_A-7), 2.15 (m, 1H, H_B-7), 3.89 (t, 2H, J = 6.6 Hz, H_2-18), 4.24 (ddd, 1H, J_1 = 3.5 Hz, J_2 = 4.5 Hz, J_3 = 8.0 Hz, H-2), 4.29 (dd, 1H, J_1 = 2.1 Hz, J_2 = 7.8 Hz, H-5), 4.49 (m, 2H, H_2-1), 4.71 (m, 1H, H-6), 5.07 (t, 1H, J = 8.0 Hz, H-3), 5.28 (t, 1H, J = 7.5 Hz, H-4).

13C NMR (125 MHz, C_{5}D_{5}N) δ [ppm] (pyrrolidinium chloride): 26.52 (CH_2, C-16), 26.61 (CH_2, C-8), 29.83, 29.88, 29.91, 29.99 (7 × CH_2, C-9 – C-15), 33.78 (CH_2, C-17), 34.17 (CH_2,
C-7), 58.68 (CH₂, C-1), 62.14 (CH₂, C-18), 64.63 (CH, C-2), 65.72 (CH, C-5), 69.67 (CH, C-6), 75.12 (CH, C-4), 76.39 (CH, C-3).

IR (neat) \(\tilde{\nu} [\text{cm}^{-1}]\): 3368(s) [N–H/O–H], 3256(m) [N–H/O–H], 3211(m) [N–H/O–H], 3013(m), 2957(m), 2914(vs) [C–H], 2849(vs) [C–H], 2162(w), 1977(w), 1580(w), 1476(m), 1460(m), 1416(m), 1358(m), 1317(m), 1256(w), 1215(m), 1186(m), 1144(m), 1119(s), 1099(m), 1076(vs) [C–O], 1049(m), 1020(m), 989(s), 970(m), 946(m), 939(m), 912(w), 881(m), 854(w), 839(w), 731(m), 718(m).

HRMS (ESI) calculated for C₁₈H₃₈NO₅ [M + H⁺] : 348.2750, found 348.2747.

(--)-(2S,3S,4S,5S)-5-((1'R)-1',13'-Dihydroxytridecyl)-2-(hydroxymethyl)pyrrolidine-3,4-diol, (--)-1'-'epi'-10'-Deoxybroussonetine E (9/29)

The pentabenzylated pyrrolidine 9/12 (120 mg, 0.15 mmol) was dissolved in EtOAc (1.5 mL) and added to the suspension of Pd-enriched Pearlman’s catalyst (21 mg Pd(OH)₂/C + 16 mg Pd black) in a mixture of 10 M HCl (165 \(\mu\)L) and MeOH (1.5 mL) at rt. The mixture was vigorously stirred at 25 °C under an atmosphere of H₂ overnight (18 h) after which time ESI-MS indicated full conversion of the starting material. The catalyst was subsequently removed by filtration through a pad of Celite and rinsed thoroughly with MeOH. The filtrate was subsequently neutralised by the addition of 7 M methanolic NH₃ solution and then evaporated in vacuo to give a white solid mixture of NH₄Cl and the debenzylated product. The crude residue was elutriated with 2 M methanolic NH₃ solution (1 mL) and adsorbed on SiO₂.

Purification by column chromatography over basic silica gel afforded (--)-1'-'epi'-10'-Deoxybroussonetine E (9/29) (35 mg, 0.1 mmol) as an off-white amorphous solid.

CC : \(\odot\) 1.7 cm \(\times\) 5 cm, \(V_f\) = 12–13 mL, elution with CHCl₃/MeOH/NH₃ (7 N in MeOH) 95 : 3 : 2 \(\rightarrow\) 80 : 18 : 2

Yield : 67%

Chemical formula : C₁₈H₃₇NO₅

Molecular weight : 347.49
Experimental Section

**Appearance**: Off-white amorphous solid

**Melting point**: n/a due to the lack of sufficient material

**Optical rotation**: $[\alpha]_D^{25} = -5.1^\circ$ (free pyrrolidine base, $c = 1.0 \text{ g/100 mL MeOH}$)

1H NMR (500 MHz, CD$_3$OD) $\delta$ [ppm]: 1.26 – 1.46 (m, 15H, H$^-8$, H$_2^-9$ – H$_2^-15$), 1.53$^\circ$ (m, 3H, H$_8^-8$, H$_2^-17$), 1.61$^\circ$ (m, 2H, H$_2^-7$), 3.28 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 7.6$ Hz, H-5), 3.42 (m, 1H, H-2), 3.54 (t, 2H, $J = 6.7$ Hz, H$_2^-18$), 3.87 (m, 3H, H$_2^-1$, H-6), 4.03 (m, 2H, H-3, H-4).

13C NMR (125 MHz, CD$_3$OD) $\delta$ [ppm]: 26.50 (CH$_2$, C-8), 26.93 (CH$_2$, C-16), 30.51, 30.57, 30.64, 30.68, 30.71 (7 × CH$_2$, C-9 – C-15), 33.64 (CH$_2$, C-17), 35.40 (CH$_2$, C-7), 59.01 (CH$_2$, C-1), 63.01 (CH$_2$, C-18), 64.95 (CH, C-2), 67.69 (CH, C-5), 69.00 (CH$_2$, C-6), 76.10 (CH, C-3), 77.29 (CH, C-4).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 3367(s) [N–H/O–H], 3255(m) [N–H/O–H], 3242(m) [N–H/O–H], 3012(m), 2956(m), 2915(vs) [C–H], 2848(vs) [C–H], 2768 (w), 1579(w), 1475(m), 1460(m), 1415(m), 1357(m), 1337(m), 1317(m), 1266(w), 1215(m), 1186(m), 1143(m), 1118(s), 1100(m), 1077(vs) [C–O], 1050(m), 1021(m), 990(s), 971(m), 946(m), 940(m), 912(w), 882(m), 732(m), 718(m).

HRMS (ESI) calculated for C$_{18}$H$_{38}$NO$_5$ [M + H$^+$]: 348.2750, found 348.2737.

(--),(2$S$,3$S$,4$R$,5$R$,6$S$)-N-Benzyl-3,4-bis(benzyloxy)-6-(12'-benzyloxydodecyl)-2-(benzyloxy-methyl)piperidin-5-yl formate (9/17)

![Chemical Structure](image_url)

**Step 1** (Preparation of the pyrrolidinium formate): To the solution of (R)-alcohol 9/12 (1596 mg, 2.0 mmol, 1.0 equiv) in THF (10 mL) was added dropwise a 1 M solution of formic acid in THF (2.1 mL) to form the pyrrolidinium formate. All volatiles were then evaporated under reduced pressure to give the formate salt as an orange viscous syrup.

**Step 2** (Mitsunobu reaction): To a solution of PPh$_3$ (1050 mg, 4 mmol, 2 equiv) in anhydrous THF (5 mL) was added dropwise a solution of DIAD (809 mg, 4 mmol, 2 equiv) in anhydrous
Experimental Section

THF (5 mL) at 0 °C under an atmosphere of N₂. The precipitation of the white PPh₃-DIAD betaine-adduct could be observed during the addition. After 30 min additional stirring at 0 °C a mixture of the pyrrolidinium formate and formic acid (166 mg, 3.6 mmol, 1.8 equiv) in dry THF (5 mL) were added dropwise at 0 °C. After complete addition the reaction mixture was stirred for further 10 min at 0 °C and then overnight (18 h) at 25 °C by which time the mixture had become homogenous again. All volatiles were evaporated in vacuo to give a dark yellow syrupy residue which was divided between saturated NaHCO₃ solution (6 mL) and DCM (12 mL). The organic phase was subsequently washed with further bicarbonate solution (6 mL) followed by the extraction of the combined aqueous phases with DCM (2 × 12 mL). The organic phases were dried over MgSO₄, filtered and concentrated in vacuo.

Purification of the crude material was achieved by repeated column chromatography (4 runs) to afford the piperidine formate ester 9/17 (1208 mg, 1.46 mmol) as a yellow syrup.

1st CC: ∅ 2.5 cm × 10 cm, Vf = 26–27 mL, eluent EA/PE 2.5 : 97.5 → 15 : 85
2nd CC: ∅ 2.5 cm × 15 cm, Vf = 30 mL, eluent EA/PE 2.5 : 97.5 → 12.5 : 87.5
3rd CC: ∅ 2.0 cm × 16 cm, Vf = 26–27 mL, eluent EA/PE 2.5 : 97.5 → 10 : 90
4th CC: ∅ 1.5 cm × 14 cm, Vf = 12–13 mL, eluent EA/PE 2.5 : 97.5 → 10 : 90

Yield: 73%

Chemical formula: C₅₄H₆₇NO₆
Molecular weight: 826.11

Appearance: Yellow syrup

TLC: Rf = 0.38 (DE/PE = 25 : 75), CAM

Optical rotation: [α]D²⁵ = −19.2° (c = 7.49 g/100 mL CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ [ppm]: 1.06 (br, 2H, H₂-8), 1.12 – 1.32″(m, 14H, H₂-9 – H₂-15), 1.36″ (m, 3H, H-7, H₂-16), 1.54″ (m, 1H, H-10-7), 1.61″ ("quin", 2H, J = 7.0 Hz, H₂-17), 2.95 (quin, 1H, J = 4.8 Hz, H-6), 3.11 (ddd, 1H, J₁ = 2.2 Hz, J₂ = 3.5 Hz, J₃ = 6.3 Hz, H-2), 3.46 (t, 2H, J = 6.7 Hz, H₂-18), 3.73 (dd, 1H, J₁ = 2.2 Hz, J₂ = 10.2 Hz, H₆-1), 3.86 (m, 4H, H₁-1, H-3, H-4, H₆-2*), 4.21 (d, 1H, J = 14.3 Hz, H₆-2*), 4.34 (d, 1H, J = 11.9 Hz, H₁-1*), 4.39 (d, 1H, J = 11.9 Hz, H₆-1*), 4.49 (s, 2H, H₂-18*), 4.62 (d, 1H, J = 10.8 Hz, H₁-3*), 4.71 (d, 1H, J = 11.1 Hz, H₆-4*), 4.80″ (d, 1H, J = 11.0 Hz, H₂-4*), 4.82″(d, 1H, J = 10.4 Hz, H₁-3*), 5.28 (dd, 1H, J₁ = 5.5 Hz, J₂ = 8.4 Hz, H-5), 7.18 – 7.38 (m, 25H, 25 × Ph-H), 7.99 (s, 1H, OFm-H).

¹³C NMR (125 MHz, CDCl₃) δ [ppm]: 25.12 (CH₂, C-7), 26.21 (CH₂, C-16), 26.56 (CH₂, C-8), 29.45, 29.49, 29.57, 29.59, 29.61, 29.63, (7 × CH₂, C-9 – C-15), 29.78 (CH₂, C-17), 52.87 (CH₂,
Experimental Section

C-2*, 56.61 (CH, C-6), 68.84 (CH₂, C-1), 70.53 (CH₂, C-18), 72.32 (CH, C-3), 72.84 (CH₂, C-18*), 72.94 (CH₂, C-1*), 74.88 (CH₂, C-3*), 75.18 (CH₂, C-4*), 78.11 (CH, C-3), 78.94 (CH₂, C-1*, C-18), 79.28 (CH, C-5), 79.48 (CH₂, C-18*), 79.58 (CH₂, C-1*), 79.88 (CH₂, C-3*), 82.07 (CH, C-4), 126.70, 127.42, 127.49, 127.51, 127.59, 127.64, 127.73, 127.82, 128.02, 128.29, 128.31, 128.38, 128.41, 128.54 (25 × Ph-CH), 138.05, 138.40, 138.48, 138.72 (4 × ipso-Ph-C, OBn), 140.65 (ipso-Ph-C, NBn), 160.45 (CO, OFm).

IR (neat)  ᵉ [cm⁻¹] : 3063 (w), 3031 (w), 2925 (m), 2853 (m), 1727 (m) [C=O], 1496 (w), 1454 (m), 1362 (w), 1172 (s), 1100 (s), 1074 (s), 1028 (m), 907 (w), 840 (w), 820 (w), 800 (w), 779 (w), 748 (s), 734 (vs), 697 (vs), 679 (m).

HRMS (ESI) calculated for C₅₄H₆₇NO₆ [M + H⁺] : 826.5047, found 826.5042.

(+-)(2S,3S,4S,5S)-N-benzyl-3,4-bis(benzyloxy)-2-((1'R)-13'-benzyloxy-1'-(formyloxy)-tridecyl)-5-(benzyloxymethyl)pyrrolidine (9/18)

The pyrrolidine (R)-formate ester 9/18 was obtained as a minor by-product from the Mitsunobu reaction of the (R)-alcohol 9/12 with formic acid after separation by column chromatography as described above as an orange syrup (357 mg, 0.43 mmol).

Yield : 22%

Chemical formula : C₅₄H₆₇NO₆

Molecular weight : 826.11

Appearance : Orange syrup

TLC : Rf = 0.31 (DE/PE = 25 : 75), CAM

Optical rotation : [α]D²⁵ = +23.7° (c = 2.85 g/100 mL CHCl₃)

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 1.05 (br, 1H, H₆-8), 1.12 – 1.32 (m, 15H, H₈-8, H₂-9 – H₂-15), 1.35 (m, 2H, H₂-16), 1.49 (dddd, 1H, J₁ = 4.4 Hz, J₂ = 5.7 Hz, J₃ = 10.1 Hz, J₄ = 19.6 Hz, H₆-7), 1.61 ("quin", 2H, J = 7.0 Hz, H₂-17), 1.83 (m, 1H, H₈-7), 3.27 (t, 1H, J = 4.2 Hz, H-5), 3.46 (t, 2H, J = 6.6 Hz, H₂-18), 3.50 (m, 2H, H₃-1, H-2), 3.64 (dd, 1H, J₁ = 4.1 Hz, J₂ = 8.7 Hz,
Experimental Section

H$_{19}$(C-1), 3.92 (s, 2H, H$_2$-5*), 3.99 (d, 1H, $J = 3.5$ Hz, H-4), 4.02 (s, 1H, H-3), 4.36 (d, 1H, $J = 11.9$ Hz, H$_A$-1*), 4.40 (d, 1H, $J = 11.9$ Hz, H$_B$-1*), 4.44 (s, 2H, H$_2$-4*), 4.45 (d, 1H, $J = 12.1$ Hz, H$_A$-3*), 4.49 (s, 2H, H$_2$-18*), 4.53 (d, 1H, $J = 12.1$ Hz, H$_B$-3*), 5.09 (m, 1H, H-6), 7.18 – 7.36 (m, 25H, 25 × Ph-H), 8.01 (s, 1H, OFm-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 25.97 (CH$_2$, C-8), 26.21 (CH$_2$, C-16), 29.07 (CH$_2$, C-7), 29.40, 29.48, 29.49, 29.56, 29.61 (7 × CH$_2$, C-9 – C-15), 29.78 (CH$_2$, C-17), 52.41 (CH$_2$, C-5*), 63.80 (CH, C-2), 66.88 (CH$_2$, C-1), 69.43 (CH, C-5), 70.53 (CH$_2$, C-18), 71.03 (CH$_2$, C-3*), 71.44 (CH$_2$, C-4*), 72.83 (CH$_2$, C-18*), 73.15 (CH$_2$, C-1*), 74.12 (CH, C-6), 83.74 (CH, C-3), 84.77 (CH, C-4), 126.81, 127.42, 127.47, 127.49, 127.53, 127.58, 127.62, 127.65, 128.04, 128.26, 128.28, 128.29, 128.31 (25 × Ph-CH), 138.16, 138.22, 138.40, 138.73 (4 × ipso-Ph-C$_{ip}$, OBn), 139.48 (ipso-Ph-C$_{ip}$, NBn), 160.87 (CO, OFm).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3031 (w), 2926 (m), 2854 (m), 1736 (m) [C=O], 1496 (w), 1454 (m), 1366 (m), 1240 (s), 1099 (s), 1075 (s), 1028 (m), 955 (m), 908 (w), 845 (w), 816 (w), 735 (vs), 697 (vs), 681 (w).

HRMS (ESI) calculated for C$_{54}$H$_{68}$NO$_6$ [M + H$^+$] : 826.5047, found 826.5041.

(−)-(2$^S$,3$^S$,4$^S$,5$^R$,6$^S$)-N-Benzyl-3,4-bis(benzyloxy)-6-(12′-benzyloxydodecyl)-2-(benzyloxy-methyl)piperidin-5-ol (9/28)

The solution of piperidine formate ester 9/17 (1157 mg, 1.4 mmol, 1.0 equiv) in a mixture of EtOH (7 mL), 1,4-dioxane (7 mL) and H$_2$O (7 mL) was treated with NaOH (560 mg, 14.0 mmol, 10.0 equiv) followed by heating of the mixture to 90 °C for 2.5 h. The alkaline solution was then neutralised with aqueous 1 N H$_2$SO$_4$ (7 mL) at rt, and the organic solvents were evaporated in vacuo. The aqueous residue was subsequently extracted with Et$_2$O (3 × 15 mL) followed by drying (MgSO$_4$), filtering and concentrating of the ethereal extracts under
reduced pressure. Column chromatography of the residue afforded the desired piperidine alcohol 9/28 (1032 mg, 1.3 mmol) as a colourless oil.

CC: 0.16 cm × 10 cm, V_{fr} = 12 – 13 mL, eluent EA/PE 7.5 → 15 : 85

Yield: 92%

Appearance: Colourless oil

Chemical formula: C_{53}H_{67}NO_{5}

Molecular weight: 798.10

TLC: R_f = 0.49 (DE/PE = 40 : 60), CAM

Optical rotation: [α]_{D}^{25} = −6.1º (c = 2.68 g/100 mL CHCl₃)

^1H NMR (500 MHz, CDCl₃) δ [ppm]:
1.13 – 1.33 (m, 16H, H₂-8 – H₂-15), 1.35 (m, 2H, H₂-16), 1.53 (m, 2H, H₂-7), 1.61 ("quin", 2H, J = 7.0 Hz, H₂-17), 2.67 (br s, 1H, OH-5), 2.94 (m, 1H, H-6), 3.18 ("q", 1H, J = 5.3 Hz, H-2), 3.46 (t, 2H, J = 6.7 Hz, H₂-18), 3.72 (t, 2H, J = 6.3 Hz, H-4), 3.78 (m, 3H, H₃-1, H-3, H-5), 3.85 (dd, 1H, J₁ = 5.3 Hz, J₂ = 9.8 Hz, H₃-1), 3.92 (d, 1H, J = 14.2 Hz, H₃-2*), 4.02 (d, 1H, J = 14.2 Hz, H₃-2*), 4.36 (s, 2H, H₂-1*), 4.50 (s, 2H, H₂-18*), 4.53 (d, 1H, J = 11.3Hz, H₅-3*), 4.60 (dd, 1H, J = 11.4 Hz, H₃-3*), 4.63 (d, 1H, J = 11.6 Hz, H₅-4*), 4.77 (d, 1H, J = 11.6 Hz, H₅-4*), 7.16 – 7.36 (m, 25H, 25 × Ph-H).

^13C NMR (125 MHz, CDCl₃) δ [ppm]:
26.21 (CH₂, C-16), 26.65 (br, CH₂, C-7), 26.99 (CH₃, C-8), 29.51, 29.62, 29.63, 29.65, 29.79, 29.84 (8 × CH₂, C-9 – C-15, C-17), 52.84 (CH₂, C-2*), 56.76 (br, CH, C-6), 57.23 (CH, C-2), 67.86 (CH₃, C-1), 69.80 (CH, C-5), 70.55 (CH₂, C-18), 72.84 (CH₂, C-18*), 72.97 (CH₂, C-1*), 73.13 (br, CH₂, C-3*), 73.79 (br, CH₂, C-4*), 76.90 (br, CH, C-3), 81.42 (br, CH, C-4), 126.56, 127.43, 127.46, 127.53, 127.55, 127.60, 127.62, 127.70, 127.72, 128.04, 128.28, 128.32, 128.35, 128.39, 128.49 (25 × Ph-CH), 138.23, 138.31, 138.51, 138.74 (4 × ipso-Ph-C₉, OBn), 141.27 (Ph-ipso-C₉, NBn).

IR (neat) ν [cm⁻¹]: 3028 (w), 2924 (m), 2855 (m), 1497 (w), 1454 (m), 1396 (w), 1362 (m), 1315 (w), 1250 (w), 1207 (w), 1096 (s), 1076 (s), 1026 (m), 988 (w), 961 (w), 941 (w), 907 (w), 826 (w), 733 (vs).

HRMS (ESI) calculated for C_{53}H_{68}NO₅ [M + H⁺]: 798.5097, found 798.5111.
Experimental Section

\((\text{--})-(2\text{S,3S,4S,5R,6S})-6-(12'\text{-Hydroxydodecyl})-2-(\text{hydroxymethyl})\text{piperidine-3,4,5-triol,} \)

\((\text{--})-(6\text{S})-(12'\text{-hydroxydodecyl})\text{moranoline (9/30)} \)

To the suspension of Pd-enriched Pearlman’s catalyst (70 mg \(\text{Pd(OH)}_2/C + 35 \text{ mg Pd black}\)) in a mixture of 10 M HCl (770 \(\mu\)l) and MeOH (3.5 mL) was added a solution of pentabenzylated piperidine 9/28 (553 mg, 0.7 mmol) in EtOAc (3.5 mL). The reaction vessel was evacuated and flushed three times with \(\text{H}_2\) and then left overnight (18 h) under an atmosphere of \(\text{H}_2\) with vigorous stirring at 25 \(^\circ\)C after which time ESI-MS indicated full conversion of the starting material. The catalyst was subsequently removed by filtration through a pad of Celite and rinsed thoroughly with MeOH. Removal of all volatiles under reduced pressure gave a residue which was dissolved in MeOH (3.5 mL) and treated dropwise with a 7 M methanolic \(\text{NH}_3\) solution until basic pH. Evaporation to dryness under reduced pressure gave the crude debenzylated product which was chromatographed over basic silica gel (\(\Phi\) 1.6 cm \(\times\) 5 cm, \(V_F = 10 \text{ mL, elution with CHCl}_3/\text{MeOH}/\text{NH}_3\) (7 N in MeOH) 95 : 3 : 2 \(\rightarrow\) 70 : 28 : 2). Further purification of the obtained material was achieved by ion-exchange chromatography on DOWEX 50WX4-200 resin (\(\Phi\) 2.0 cm \(\times\) 5 cm, acidified with 1 M HCl). After rinsing the column with distilled water (75 mL = 5 \(\times\) column bed volume) the adsorbed material was eluted with 1 M aqueous \(\text{NH}_3\) solution until complete elution of the product. A concluding recrystallisation from MeOH afforded the pure L-DNJ derivative 9/30 (211 mg, 0.61 mmol) as a white powder.

**Yield:** 87%

**Appearance:** White Powder

**Chemical formula:** \(\text{C}_{18}\text{H}_{37}\text{NO}_5\)

**Molecular weight:** 347.49

**Melting point:** \(\vartheta_m = 135–136 \, ^\circ\)C (recryst. from MeOH)

**Optical rotation:** \([\alpha]_{D}^{25} = -14.1 ^\circ\) (piperidinium trifluoroacetate, \(c = 1.0 \text{ g/100 mL MeOH}\))

\(^1\text{H NMR (500 MHz, CD}_3\text{OD) } \delta \text{ ppm (free base):} 1.22 – 1.42 \text{ (m, 18H, H}_2\text{-8 – H}_2\text{-16), 1.42 – 1.56 \text{ (m, 3H, H}_A\text{-7, H}_2\text{-17), 1.66 \text{ (m, 1H, H}_B\text{-7), 2.76 \text{ (m, 1H, H-2), 3.04 \text{ (m, 1H, H-6), 3.13 (t,} \)
Experimental Section

1H, J = 8.8 Hz, H-3), 3.45 (t, 1H, J = 8.8 Hz, H-4), 3.51 (m, 1H, H-1), 3.53 (t, 2H, J = 6.7 Hz, H-18), 3.59 (dd, 1H, J1 = 5.3 Hz, J2 = 9.1 Hz, H-5), 3.87 (dd, 1H, J1 = 3.1 Hz, J2 = 10.8 Hz, H-1).

\[\text{\(^{1}H\ NMR\ (500 MHz, CD}_{3}\text{OD}\ \delta\ [ppm]\) (piperidinium trifluoroacetate): 1.26 – 1.41 (m, 16H, H-9 – H-16), 1.52 (m, 2H, H-8), 1.52 (quin, 2H, J = 6.8 Hz, H-17), 1.63 (m, 1H, H-7), 1.93 (m, 1H, H-7), 3.34 (m, 1H, H-2), 3.46 (td, 1H, J1 = 3.5 Hz, J2 = 6.9 Hz, H-6), 3.54 (t, 2H, J = 6.7 Hz, H-18), 3.63 (t, 1H, J = 6.4 Hz, H-3), 3.72 (dd, 1H, J1 = 3.5 Hz, J2 = 6.4 Hz, H-5), 3.83 (dd, 1H, J1 = 3.9 Hz, J2 = 11.9 Hz, H-1), 4.00 (dd, 1H, J1 = 7.2 Hz, J2 = 11.9 Hz, H-1).

\[\text{\(^{13}C\ NMR\ (125 MHz, CD}_{3}\text{OD}\ \delta\ [ppm]\) (free base): 25.94 (br), 26.99 (CH2, C-16), 27.39, 30.65, 30.74, 30.76, 30.80, 30.82, 33.72 (CH2, C-17), 56.48 (br), 57.34 (br), 63.06 (CH2, C-18), 63.49 (br, CH2, C-1), 71.16 (ex br), 73.95 (br), 75.84 (br).

\[\text{\(^{13}C\ NMR\ (125 MHz, CD}_{3}\text{OD}\ \delta\ [ppm]\) (piperidinium trifluoroacetate): 26.99 (CH2, C-16), 27.05 (CH2, C-8), 27.62 (br, CH2, C-7), 30.50, 30.55, 30.64, 30.67, 30.73, 30.75, 30.78 (CH2, C-9 – C-15), 33.70 (CH2, C-17), 54.90 (br, CH, C-6), 58.51 (CH2, C-1), 59.58 (br, CH, C-2), 63.07 (CH2, C-18), 69.43 (CH, C-3), 70.29 (CH, C-5), 72.61 (br, CH, C-4).

\[\text{\(^{1}H\ NMR\ (500 MHz, C}_{5}\text{D}_{5}\text{N}\ \delta\ [ppm]\) (piperidinium trifluoroacetate): 1.13 – 1.29 (m, 10H, H-10 – H-14), 1.29 – 1.37 (m, 4H, H-9, H-15), 1.50 (quin, 2H, J = 7.5 Hz, H-16), 1.70 – 1.80 (m, 4H, H-8, H-17), 2.17 (m, 1H, H-7), 2.46 (m, 1H, H-7), 3.89 (t, 2H, J = 6.6 Hz, H-18), 4.06 (br, 1H, H-2), 4.31 ("dd", 1H, J1 = 6.3 Hz, J2 = 10.8 Hz, H-6), 4.53 (t, 1H, J = 7.5 Hz, H-3), 4.62 (t, 1H, J = 8.1 Hz, H-4), 4.64 – 4.72 (m, 2H, H-1, H-5), 4.75 (dd, 1H, J1 = 5.7 Hz, J2 = 11.9 Hz, H-1).

\[\text{\(^{13}C\ NMR\ (125 MHz, C}_{5}\text{D}_{5}\text{N}\ \delta\ [ppm]\) (piperidinium trifluoroacetate): 26.54 (CH2, C-16), 26.89 (br, CH2, C-7), 27.24 (CH2, C-8), 29.67, 29.80, 29.87, 29.89, 30.00 (CH2, C-9 – C-15), 33.80 (CH2, C-17), 56.05 (br, CH, C-6), 58.49 (br, CH, C-2), 58.93 (CH2, C-1), 62.16 (CH2, C-18), 70.08 (CH, C-3), 70.98 (CH, C-5), 74.37 (CH, C-4).

\[\text{IR (neat) } \tilde{\nu} \ [cm^{-1}]: 3501 (w), 3284 (m) [N–H/O–H], 3256 (s) [N–H/O–H], 2914 (vs) [C–H], 2849 (s) [C–H], 2160 (w), 1979 (w), 1468 (s), 1418 (w), 1361 (m), 1308 (w), 1265 (w), 1215 (w), 1157 (w), 1117 (m), 1096 (vs) [C–O], 1055 (s) [C–O], 1026 (vs) [C–O], 999 (s), 976 (s), 951 (m), 889 (m), 872 (m), 847 (m), 814 (m), 754 (m), 718 (s).

\[\text{HRMS (ESI) calculated for C}_{18}\text{H}_{38}\text{NO}_{5} [M + H^{+}] : 348.2750, found 348.2750.\]
E.7  Synthesis of (–)-Broussonetine C2

1-tert-Butyldimethylsilyloxydec-9-ene (10/1)

To the mixture of 9-decen-1-ol (10.0 g, 64.0 mmol, 1.0 equiv), DMAP (586 mg, 4.8 mmol, 0.75 equiv) and Et₃N (9.8 g, 13.5 mL, 96.8 mmol, 1.51 equiv) in anhydrous DCM (200 mL) was added dropwise a solution of TBSCl (13.3 g, 88 mmol, 1.375 equiv) in anhydrous DCM (88 mL) at 0 °C under an atmosphere of N₂. After overnight stirring (24 h) at 25 °C the mixture was concentrated under reduced pressure, and the pulpy orange residue was divided between H₂O (65 mL) and Et₂O (65 mL). The organic phase was once washed with H₂O (65 mL) followed by extraction of the combined aqueous phases with Et₂O (3 × 130 mL). The ethereal phases were then dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by column chromatography afforded the TBS ether 10/1 (16.76 g, 62.0 mmol) as a colourless liquid.

CC : ∅ 8.0 cm × 24 cm, V_fr = 250 mL, eluent EA/PE 0 → 2.5 → 97.5

Yield : 97%

Appearance : Colourless liquid

Chemical formula : C₁₆H₃₄O₅Si

Molecular weight : 270.53

TLC : Rf = 0.37 (100% PE), CAM

¹H NMR (500 MHz, CDCl₃) δ [ppm] : 0.05 (s, 6H, 2 × CH₃, OTBS), 0.89 (s, 9H, 3 × tert-Bu-CH₃, OTBS), 1.29s (s, 8H, H₂-3 – H₂-6), 1.37s (br quin, 2H, J = 6.7 Hz, H₂-7), 1.50 (br quin, 2H, J = 6.8 Hz, H₂-2), 2.04 (q, 2H, J = 7.0 Hz, H₂-8), 3.59 (t, 2H, J = 6.6 Hz, H₂-1), 4.93 (dd, 1H, J₁ = 1.1 Hz, J₂ = 10.2 Hz, H₆-10), 4.99 (dd, 1H, J₁ = 1.5 Hz, J₂ = 17.1 Hz, H₆-10), 5.81 (ddt, J₁ = 6.7 Hz, J₂ = 10.2 Hz, J₃ = 16.9 Hz, H-9).

¹³C NMR (125 MHz, CDCl₃) δ [ppm] : −5.24 (2 × CH₃, OTBS), 18.39 (tert-Bu-C₄, OTBS), 25.79 (CH₂, C-3), 26.00 (3 × tert-Bu-CH₃, OTBS), 28.93 (CH₂, C-7), 29.09, 29.39, 29.48 (3 × CH₂, C-4 – C-6), 32.89 (CH₂, C-2), 33.82 (CH₂, C-8), 63.33 (CH₂, C-1), 114.10 (CH₂, C-10), 139.23 (CH, C-9).
Experimental Section

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 2928 (m) [C−H], 2856 (m) [C−H], 1472 (w), 1464 (w), 1255 (m), 1100 (s) [C−O], 1006 (w), 992 (w), 938 (w), 909 (m), 835 (vs), 812 (m), 774 (vs), 745 (m), 725 (w), 708 (w).

HRMS (EI) calculated for C$_{16}$H$_{33}$OSi [M$^+$−H]: 269.2301, found 269.2296.

9-((tert-Butyldimethylsilyloxy)nonanal (10/2)

![Chemical Structure](image)

**Method A - Step 1 (Dihydroxylation)**: To the solution of 1-((tert-butyldimethylsilyloxy)dec-9-ene (541 mg, 2.0 mmol, 1.0 equiv) in a 1 : 1 acetone/water mixture (10 mL) was added a catalytic amount of OsO$_4$ (28 mg, 0.11 mmol, 0.055 equiv) followed by NMO (312 mg, 2.66 mmol, 1.33 equiv) at rt. The dark brown mixture was stirred at 25 °C for 5 h after which time TLC analysis indicated complete conversion of the starting material. Aqueous 1 M Na$_2$SO$_3$ solution (10 mL) was then added, and the mixture was stirred for another hour at rt. The aqueous mixture was subsequently extracted with EtOAc (4 × 20 mL), followed by drying (MgSO$_4$), filtering and concentrating *in vacuo* of the organic phases to give the crude diol 10/8 as a dark brown oil.

**Method A - Step 2 (Oxidative diol cleavage)**: A solution of NaIO$_4$ (1284 mg, 6.0 mmol, 3.0 equiv) in H$_2$O (6 mL) was added in one portion to the solution of the crude diol 10/8 in Et$_2$O (6 mL). This heterogeneous mixture was vigorously stirred at rt for 5 h after which time TLC analysis showed full conversion of the starting material. The mixture was then diluted with H$_2$O (12 mL) and extracted with EtOAc (3 × 12 mL). The organic phases were subsequently dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification of the crude product was achieved via a short-bed column chromatography to afford the requisite aldehyde 10/2 (488 mg, 1.79 mmol) as a colourless liquid.

**CC**: $\varnothing$ 2.0 cm × 5 cm, $V_{Fr} = 25$ mL, eluent EA/PE 0 : 100 → 3 : 97

**Yield**: 89.5% over 2 steps

**Method B (Ozonolysis)**: Ozone (~33% in O$_2$) was bubbled through the solution of 1-((tert-butyldimethylsilyloxy)dec-9-ene (271 mg, 1.0 mmol, 1.0 equiv) in dry DCM (10 mL) at −78 °C until a light blue colour persisted. After flushing the solution with N$_2$ for 3 min to displace
excess O₃, a solution of PPh₃ (393 mg, 1.5 mmol, 1.5 equiv) in DCM (1 mL) was added in one portion. The resulting mixture was then slowly warmed to 0 °C (~3 h) and subsequently concentrated in vacuo to give a white, pulpy residue. Purification by column chromatography afforded the desired aldehyde 10/2 (263 mg, 0.964 mmol) as a colourless liquid.

**Yield**: 96%

**Chemical formula**: C₁₅H₃₂O₂Si

**Molecular weight**: 272.50

**Appearance**: Colourless liquid

**TLC**: R_f = 0.25 (DE/PE = 5 : 95), CAM

**¹H NMR** (500 MHz, CDCl₃) δ [ppm]: 0.05 (s, 6H, 2 × CH₃, OTBS), 0.89 (s, 9H, 3 × tert-Bu-CH₃, OTBS), 1.31 (br s, 8H, H₂-4 – H₂-7), 1.50 (br quin, 2H, J = 6.7 Hz, H₂-8), 1.63 (m, 2H, H₂-3), 2.42 (dt, 2H, J₁ = 1.8 Hz, J₂ = 7.4 Hz, H₂-2), 3.59 (t, 2H, J = 6.6 Hz, H₂-9), 9.76 (t, 1H, J = 1.7 Hz, H-1).

**¹³C NMR** (125 MHz, CDCl₃) δ [ppm]: -5.25 (2 × CH₃, OTBS), 18.38 (tert-Bu-C₉, OTBS), 22.08 (CH₂, C-3), 25.74 (CH₂, C-7), 26.00 (3 × tert-Bu-CH₃, OTBS), 29.12, 29.21, 29.34 (3 × CH₂, C-4, C-5, C-6), 32.83 (CH₂, C-8), 43.91 (CH₂, C-2), 63.25 (CH₂, C-9), 202.86 (CHO, C-1).

**IR** (neat) ν [cm⁻¹]: 2929 (m) [C−H], 2857 (m) [C−H], 1728 (m) [C=O], 1463 (w), 1389 (w), 1360 (w), 1255 (m), 1097 (s) [C−O], 1006 (w), 938 (w), 835 (vs), 775 (vs), 729 (w), 713 (w).

**HRMS** (EI) calculated for C₁₅H₃₁O₂Si [M⁺ − H]: 271.2093, found 271.2098.

**10-(tert-Butyldimethylsilyloxy)decane-1,2-diol (10/8)**

![diagram](attachment:diagram.png)

The intermediate diol 10/8 of the above two-step oxidative double bond cleavage (method A) was used in the next step without purification, however, a small amount (approx. 35 mg) of the crude product was purified by column chromatography to obtain an analytical sample.

**Yield**: 96%

**Chemical formula**: C₁₆H₃₆O₃Si
Experimental Section

Molecular weight : 304.54

Appearance : Pale brown oil

TLC : R_f = 0.27 (DE/PE = 3 : 1), CAM

1H NMR (500 MHz, CDCl_3) δ [ppm] : 0.05 (s, 6H, 2 × CH_3), 0.89 (s, 9H, 3 × tert-Bu-CH_3), 1.30 (br s, 10H, H_2-3 – H_2-7), 1.43 (m, 2H, H_2-8), 1.50 (br quin, 2H, J = 6.7 Hz, H_2-2), 2.40 (br, 2H, OH-9, OH-10), 3.43 (dd, 1H, J_1 = 7.6 Hz, J_2 = 11.0 Hz, H_A-10), 3.59 (t, 2H, J = 6.7 Hz, H_2-1-2), 3.64 (dd, 1H, J_1 = 2.8 Hz, J_2 = 11.1 Hz, H_10), 3.70 (m, 1H, H-9).

13C NMR (125 MHz, CDCl_3) δ [ppm] : –5.24 (2 × CH_3), 18.39 (tert-Bu-Cq, OTBS), 25.54 (CH_2, C-7), 25.78 (CH_2, C-3), 26.00 (3 × tert-Bu-CH_3, OTBS), 29.37, 29.52, 29.60 (3 × CH_2, C-4 – C-6), 32.86 (CH_2, C-2), 33.18 (CH_2, C-8), 63.32 (CH_2, C-1), 66.82 (CH_2, C-10), 72.34 (CH, C-9).

IR (neat) ν [cm⁻¹] : 3379 (br) [O–H], 2929 (m) [C–H], 2856 (m) [C–H], 1463 (w), 1388 (w), 1361 (w), 1255 (m), 1098 (s) [C–O], 1006 (w), 939 (vs), 835 (vs), 812 (m), 774 (s), 726 (w), 708 (w).

HRMS (EI) calculated for C_{16}H_{37}O_3Si [M + H⁺] : 305.2512, found 305.2507.

1-Benzylxoy-12-(tert-butyldimethylsilyloxy)dodecan-4-ol (10/3)

Step 1 (Preparation of benzyloxypropylmagnesium bromide) : To dry, acid-washed magnesium turnings (292 mg, 12.0 mmol) was added a solution of 1,2-dibromoethane (11 µL) in anhydrous THF (5 mL). This mixture was heated at reflux for 10 min under an atmosphere of N_2. Then the first half (2.5 mL) of a 1-benzyloxy-3-bromopropane solution (2291 mg, 10.0 mmol) in anhydrous THF (5 mL) was added dropwise under carefully heating until the start of the magnesium insertion occurred (the solution turned slightly turbid and refluxed without external heating). The remainder of the 1-benzyloxy-3-bromopropane solution was then slowly added to the mixture in a way that the exothermic reaction gently sustained the reflux of the solvent. When the exothermic reaction finally had seized, the mixture was heated at reflux for an additional hour and was then allowed to cool to rt to give 10 mL of an estimated 1 M benzyloxypropylmagnesium bromide solution.
Step 2 (Grignard addition): To the solution of 9-(tert-butyldimethylsilyloxy)nonanal (545 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added dropwise the freshly prepared 1 M benzylxoypropylmagnesium bromide solution (4 mL, 4 mmol, 2 equiv) at 0 °C. After 2 h stirring at rt additional Grignard solution (2 mL) was added. After one further hour stirring at rt the mixture was quenched with aqueous 1 M NH₄Cl solution (6 mL) and H₂O (4 mL) under cooling in an ice bath. The mixture was subsequently extracted with Et₂O (4 × 10 mL), and the organic phases were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography afforded the secondary alcohol 10/3 (704 mg, 1.67 mmol) as a colourless liquid.

**CC:** ∅ 2.0 cm × 10 cm, Vᵣᵢₐₜ = 25 mL, eluent EA/PE 5 : 95 → 20 : 80

**Yield:** 83%

**Chemical formula:** C₂₅H₄₆O₃Si

**Molecular weight:** 422.72

**Appearance:** Colourless liquid

**TLC:** Rᵢ = 0.25 (DE/PE = 1 : 2), CAM

**¹H NMR (500 MHz, CDCl₃) δ [ppm]:** 0.05 (s, 6H, 2 × CH₃, OTBS), 0.89 (s, 9H, 3 × tert-Bu-CH₃, OTBS), 1.29 (s, 8H, H₂-7 – H₂-10), 1.37 – 1.54 (m, 7H, H₃-3, H₂-5, H₂-6, H₂-11), 1.59 – 1.69 (m, 1H, H₃-3), 1.73 (m, 2H, H₂-2), 2.22 (br, 1H, OH), 3.51 (t, 2H, f = 6.0 Hz, H₂-1), 3.59 (t, 3H, f = 6.6 Hz, H-4, H₂-12), 4.52 (s, 2H, H₂-1*), 7.25 – 7.38 (m, 5H, 5 × Ph-H).

**¹³C NMR (125 MHz, CDCl₃) δ [ppm]:** −5.24 (2 × CH₃, OTBS), 18.39 (tert-Bu-C₆, OTBS), 25.75, 25.80 (2 × CH₂, C-6, C-10), 26.00 (3 × tert-Bu-CH₃, OTBS), 26.22 (CH₂, C-2), 29.40, 29.61, 29.77 (3 × CH₂, C-7, C-8, C-9), 32.88 (CH₂, C-11), 34.70 (CH₂, C-3), 37.52 (CH₂, C-5), 63.33 (CH₂, C-12), 70.57 (CH₂, C-1), 71.62 (CH, C-4), 73.03 (CH₂, C-1*), 127.62 (para-Ph-CH), 127.70 (2 × ortho-Ph-CH), 128.40 (2 × meta-Ph-CH), 138.21 (ipso-Ph-C₆).

**IR (neat) ν [cm⁻¹]:** 3400 (br) [O−H], 2929 (m) [C−H], 2855 (m) [C−H], 1462 (w), 1454 (w), 1387 (w), 1361 (w), 1254 (m), 1205 (w), 1098 (vs) [C−O], 1006 (m), 938 (w), 835 (vs), 814 (vs), 775 (s), 733 (m).

**HRMS (EI) calculated for C₂₅H₄₆O₃Si [M⁺]:** 422.3216, found 422.3206.
1-Benzylxoy-12-(tert-butyldimethylsilyloxy)dodecan-4-one (10/4)

Method A (PCC oxidation): To the solution of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv) in dry DCM (5 mL) were added PCC (323 mg, 1.5 mmol, 1.5 equiv) and activated MS 4Å powder (323 mg) at rt. The dark brown heterogeneous mixture was vigorously stirred for 2.5 h at 25 °C after which time additional PCC (323 mg, 1.5 mmol, 1.5 equiv) and molecular sieves (323 mg) were added to complete the reaction. After 5 h stirring TLC analysis revealed full conversion of the starting material. The mixture was filtered through a pad of Celite, and the filter cake was washed thoroughly with DCM. Filtrate and washings were concentrated under reduced pressure to give a dark brown residue. Purification of the crude product by column chromatography afforded the desired ketone 10/4 (373 mg 0.886 mmol) as a colourless liquid in 89% yield.

Method B (Dess-Martin oxidation): To the suspension of Dess-Martin periodinane (849 mg, 2.0 mmol, 2.0 equiv) in dry DCM (2 mL) was added dropwise a solution of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv) in dry DCM (6 mL) at 0 °C under an atmosphere of N₂. After 2 h stirring at 25 °C TLC analysis showed full conversion of the starting material. The mixture was subsequently treated with Na₂S₂O₅ · 5 H₂O (2482 mg, 10.0 mmol) dissolved in saturated NaHCO₃ solution (10 mL) and then vigorously stirred for further 10 min. After extraction of the aqueous phase with DCM (3 × 10 mL) the combined organic phases were dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by column chromatography provided the required ketone 10/4 (396 mg 0.941 mmol) as a colourless liquid in 94% yield.

Method C (Corey-Kim oxidation): To the stirred solution of NCS (200 mg, 1.5 mmol, 1.5 equiv) in anhydrous toluene (6 mL) was added DMS (150 µl, 125 mg, 2.0 mmol, 2.0 equiv) at 0 °C under an atmosphere of N₂. After cooling the mixture to –25 °C a solution of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv) in anhydrous toluene (1 mL) was added dropwise. The mixture was stirred at –25 °C for further 2 h and then treated dropwise with Et₃N (210 µl, 152 mg, 1.5 mmol, 1.5 equiv). After additional 5 min stirring the mixture was diluted with Et₂O (20 mL) and then consecutively washed with half-saturated NaCl solution (1 × 10 mL).
and saturated NaHCO₃ solution (1 × 10 mL). The organic phase was subsequently dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by column chromatography afforded the desired ketone 10/4 (346 mg 0.822 mmol) as a colourless liquid in 82% yield.

**Method D** (TPAP oxidation): To the vigorously stirred mixture of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv), NMO (176 mg, 1.5 mmol, 1.5 equiv) and activated MS 4Å powder (500 mg) in anhydrous DCM/MeCN (9 : 1, 5 mL) was added TPAP (17.6 mg, 0.05 mmol, 0.05 equiv) in one portion at 0 ºC under an atmosphere of N₂. The mixture was then stirred at 25 ºC for 30 min after which time TLC analysis indicated complete conversion of the starting material. All volatiles were subsequently evaporated under reduced pressure, and the black pulpy residue was loaded on a short silica gel column (2 × 4 cm). Elution with petrol ether/EtOAc (1 : 1) followed by concentration in vacuo gave the crude ketone as a pale yellow fluid. Further purification was achieved by column chromatography to afford the title compound (363 mg, 0.863 mmol) as a colourless liquid in 86% yield.

**Method E** (PDC oxidation): To the vigorously stirred suspension of activated MS 4Å powder (500 mg) in dry DCM (2 mL) were added in order a solution of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv) in dry DCM (3 mL) and PDC (564 mg, 1.5 mmol, 1.5 equiv) followed by glacial AcOH (100 µL) at rt. After 90 min stirring at 25 ºC TLC analysis revealed full conversion of the starting material. The solvent was subsequently evaporated under reduced pressure and the pulpy, dark brown residue purified by chromatography to afford the required ketone 10/4 (377 mg, 0.896 mmol) in 90% yield.

**Method F** (Swern oxidation): To the stirred solution of oxalyl chloride (152.4 mg, 1.2 mmol, 1.2 equiv) in anhydrous DCM (4 mL) was added DMSO (187.5 mg, 2.4 mmol, 2.4 equiv) at –78 ºC under an atmosphere of N₂. After 5 min the solution of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv) in anhydrous DCM (4 mL) was added dropwise to the mixture keeping the temperature below –60 ºC. After further 15 min stirring at –78 ºC the mixture was treated slowly with dry Et₃N (697 µL, 506 mg, 5.0 mmol, 5.0 equiv) yet again maintaining the temperature below –60 ºC. After additional 10 min at –78 ºC the mixture was allowed to slowly warm to 0 ºC (~2 h) and then stirred at this temperature for further 30 min before being quenched with H₂O (8 mL). The mixture was subsequently extracted with DCM (3 × 8 mL), and the
combined organic phases were consecutively washed with 2 N HCl (16 mL), then 0.5 N HCl (16 mL) to remove residual Et$_3$N and finally saturated NaHCO$_3$ solution. Drying over MgSO$_4$ and filtering was followed by concentration in vacuo to give the crude ketone as pale yellow fluid. Purification of the crude product by column chromatography provided the desired ketone 10/4 (358 mg 0.851 mmol) as a colourless liquid in 85% yield.

**Method G** (Mukaiyama oxidation) : To the stirred mixture of K$_2$CO$_3$ (1382 mg, 10.0 mmol, 10.0 equiv), activated MS 4Å powder (1000 mg) and NCS (145 mg, 1.1 mmol, 1.1 equiv) in anhydrous DCM (4 mL) were added a solution of alcohol 10/3 (423 mg, 1.0 mmol, 1.0 equiv) in dry DCM (3 mL) followed by the solution of N-tert-butylbenzenesulphonamide (9 mg, 50.0 µmol) in dry DCM (3 mL) at 0 ºC under an atmosphere of N$_2$. After stirring at 0 ºC for 1 h TLC analysis indicated complete conversion of the starting material. The mixture was consequently filtered through a pad of Celite followed by the addition of a 10% Na$_2$CO$_3$ solution (10 mL) to the filtrate. The mixture was then extracted with DCM (3 × 10 mL), and the combined organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo.

The crude product was purified by column chromatography to afford the desired ketone 10/4 (404 mg, 0.96 mmol) as a colourless liquid in 96% yield.

**CC** : Ø 1.7 cm × 10 cm, V$_{Fr}$ = 22 mL, eluent EA/PE 2.5 : 97.5 → 7.5 : 92.5

**Yield** : Method A – PCC oxidation : 89%
Method B – Dess-Martin oxidation : 94%
Method C – Corey-Kim oxidation : 82%
Method D – TPAP oxidation : 86%
Method E – PDC oxidation : 90%
Method F – Swern oxidation : 85%
Method G – Mukaiyama oxidation : 96%

**Chemical formula** : C$_{25}$H$_{44}$O$_3$Si

**Molecular weight** : 420.70

**Appearance** : Colourless liquid

**TLC** : $R_f = 0.38$ (DE/PE = 20 : 80), CAM

$^1$H NMR (500 MHz, CDCl$_3$) δ [ppm] : 0.04 (s, 6H, 2 × CH$_3$, OTBS), 0.89 (s, 9H, 3 × tert-Bu-CH$_3$, OTBS), 1.28 (s, 8H, H$_2$-7 – H$_2$-10), 1.50" (br quin, 2H, $J = 7.1$ Hz, H$_2$-11), 1.54" (br quin, 2H, $J = 6.6$ Hz, H$_2$-6), 1.88 (quin, 2H, $J = 6.6$ Hz, H$_2$-2), 2.38 (t, 2H, $J = 7.5$ Hz, H$_2$-5), 2.51 (t, 2H,
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$J = 7.2 \text{ Hz, } H_2-3)$, 3.47 (t, 2H, $J = 6.1 \text{ Hz, } H_2-1$), 3.59 (t, 2H, $J = 6.6 \text{ Hz, } H_2-12$), 4.48 (s, 2H, $H_2-1^*$), 7.25 – 7.37 (m, 5H, 5 $\times$ Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : –5.25 (2 $\times$ CH$_3$, OTBS), 18.38 (tert-Bu-C$_q$, OTBS), 23.85, 23.89 (2 $\times$ CH$_2$, C-2, C-6), 25.76 (CH$_2$, C-10), 25.99 (3 $\times$ tert-Bu-CH$_3$, OTBS), 29.21, 29.26, 29.40 (3 $\times$ CH$_2$, C-7, C-8, C-9), 32.85 (CH$_2$, C-11), 39.29 (CH$_2$, C-3), 42.92 (CH$_2$, C-5), 63.29 (CH$_2$, C-12), 69.38 (CH$_2$, C-1), 72.85 (CH$_3$, C-1*), 127.56 (para-Ph-CH), 127.63 (2 $\times$ ortho-Ph-CH), 128.36 (2 $\times$ meta-Ph-CH), 138.43 (ipso-Ph-C$_q$), 211.00 (CO, C-4).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 2928 (m) [C−H], 2856 (m) [C−H], 1715 (m) [C=O], 1463 (m), 1455 (w), 1410 (w), 1361 (w), 1255 (m), 1205 (w), 1097 (vs) [C−O], 1028 (w), 1006 (w), 939 (w), 835 (vs), 775 (vs), 736 (m).

HRMS (EI) calculated for C$_{25}$H$_{44}$O$_3$Si [M$^+$] : 420.3060, found 420.3051.

1-Benzylxy-12-hydroxydodecan-4-one (10/10)

To the solution of TBS ether 10/4 (421 mg, 1.0 mmol, 1.0 equiv) in THF (5 mL) was added a solution of TBAF trihydrate (473 mg, 1.5 mmol, 1.0 equiv) in THF (1.5 mL) at rt. The mixture turned immediately pale yellow. After 2.5 h stirring at 25 °C TLC analysis indicated full conversion of the starting material. The mixture was then diluted with Et$_2$O (6 mL) and poured into H$_2$O (6 mL). After extraction of the aqueous phase with Et$_2$O (3 $\times$ 12 mL) all ethereal phases were dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford the alcohol 10/10 (290 mg, 0.946 mmol) as a colourless liquid.

CC : $\varnothing$ 1.7 cm $\times$ 10 cm, $V_{Fr} = 22$ mL, eluent EA/PE 25 : 75 $\rightarrow$ 33 : 67

Yield : 95%

Chemical formula : C$_{19}$H$_{30}$O$_3$

Molecular weight : 306.44

Appearance : Colourless liquid

TLC : $R_f = 0.27$ (DE/PE = 75 : 25), CAM

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$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 1.30 (m, 8H, H$_2$-7 – H$_2$-10), 1.54 (quin, 4H, $J = 7.1$ Hz, H$_2$-6, H$_2$-11), 1.88 (quin, 2H, $J = 6.7$ Hz, H$_2$-2), 2.38 (t, 2H, $J = 7.5$ Hz, H$_2$-5), 2.51 (t, 2H, $J = 7.2$ Hz, H$_2$-3), 3.47 (t, 2H, $J = 6.4$ Hz, H$_2$-1), 3.61 (t, 2H, $J = 6.6$ Hz, H$_2$-12), 4.47 (s, 2H, H$_2$-1*), 7.25 – 7.36 (m, 5H, 5 $\times$ Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 23.79 (CH$_2$, C-6), 23.88 (CH$_2$, C-2), 25.65 (CH$_2$, C-10), 29.13, 29.19, 29.33 (3 $\times$ CH$_2$, C-7, C-8, C-9), 32.74 (CH$_2$, C-11), 39.32 (CH$_2$, C-3), 42.88 (CH$_2$, C-5), 63.00 (CH$_2$, C-12), 69.38 (CH$_2$, C-1), 72.86 (CH$_2$, C-1*), 127.57 (para-Ph-CH), 127.64 (2 $\times$ ortho-Ph-CH), 128.37 (2 $\times$ meta-Ph-CH), 138.41 (ipso-Ph-C$_q$), 211.05 (CO, C-4).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3400 (br) [O$^-$H], 2929 (s) [C$-$H], 2856 (m) [C$-$H], 1710 (s), 1496 (w), 1454 (m), 1411 (w), 1363 (m), 1313 (w), 1206 (w), 1098 (vs) [C$-$O], 1076 (vs), 1028 (s), 950 (w), 912 (w), 833 (w), 738 (vs).

HRMS (EI) calculated for C$_{19}$H$_{30}$O$_3$ [M$^+$] : 306.2195, found 306.2187.

1-Benzyloxy-12-hydroxydodecane 4-(1',2'-ethanediyl)ketal (10/5)

Method A (from hydroxyketone 10/10) : To the solution of 1-benzyloxy-12-hydroxydodecan-4-one (421 mg, 1.0 mmol, 1.0 equiv) in dry benzene (5 mL) were added 1,2-ethanediol (1 mL) and PPTS (377 mg, 1.5 mmol, 1.5 equiv). The mixture was heated at reflux with water separation via a Dean-Stark trap overnight (18 h) after which time the solvent was evaporated under reduced pressure. The residue was dissolved in Et$_2$O (40 mL) and washed with saturated NaHCO$_3$ solution (1 $\times$ 10 mL). The ethereal phase was subsequently dried over MgSO$_4$, filtered and concentrated in vacuo. Purification of the residue by column chromatography provided the desired ketal 10/5 (336 mg, 0.959 mmol) as a pale yellow liquid.

CC : $\emptyset$ 1.7 cm $\times$ 10 cm, $V_{Fr}$ = 16 – 17 mL, eluent EA/PE 25 : 75 $\rightarrow$ 50 : 50
Yield : 96%

Method B (from silyloxyketone 10/4) : In accordance with method A, 1-benzyloxy-12-(tert-butyldimethylsilyloxy)dodecan-4-one (421 mg, 1.0 mmol) was converted to the hydroxyketal
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10/5 with concomitant cleavage of the TBS protecting group. Ketal 10/5 (218 mg, 0.622 mmol) was obtained in 62% yield after column chromatography as pale yellow liquid.

CC : ∅ 1.7 cm × 10 cm, V_Fr. = 16 – 17 mL, eluent EA/PE 5 : 95 → 50 : 50
Yield : 62%
Chemical formula : C_{21}H_{34}O_4
Molecular weight : 350.49
Appearance : Pale yellow liquid
TLC : R_F = 0.23 (DE/PE = 2 : 1), CAM

^1^-H NMR (500 MHz, CDCl_3) δ [ppm] : 1.24 – 1.39 (m, 10H, H_2-6 – H_2-10), 1.47 (br, 1H, OH), 1.54^a (quin, 2H, J = 7.0 Hz, H_2-11), 1.59^o (m, 2H, H_2-5), 1.68 (m, 4H, H_2-2, H_2-3), 3.47 (m, 2H, H_2-1), 3.62 (t, 2H, J = 6.6 Hz, H_2-12), 3.92 (s, 4H, H_2-1', H_2-2'), 4.50 (s, 2H, H_2-1*), 7.27 (m, 1H, para-Ph-H, OBn), 7.33 (^d*, 4H, J = 4.6 Hz, 2 × ortho-Ph-H, 2 × meta-Ph-H, OBn).

^13^-C NMR (125 MHz, CDCl_3) δ [ppm] : 23.79 (CH_2, C-6), 24.21 (CH_2, C-2), 25.71 (CH_2, C-10), 29.32, 29.52, 29.81 (3 × CH_2, C-7, C-8, C-9), 32.76 (CH_2, C-11), 33.59 (CH_2, C-3), 37.25 (CH_2, C-5), 62.97 (CH_2, C-12), 64.92 (2 × CH_2, C-1', C-2'), 70.46 (CH_2, C-1), 72.77 (CH_2, C-1*), 111.66 (CO_2, C-4), 127.47 (para-Ph-CH, OBn), 127.59 (2 × ortho-Ph-CH, OBn), 128.32 (2 × meta-Ph-CH, OBn), 138.61 (ipso-Ph-C=O, OBn).

IR (neat) ν [cm⁻¹] : 3420 (br), 2928 (m), 2854 (m), 1496 (w), 1455 (w), 1361 (w), 1313 (w), 1206 (w), 1074 (vs) [C–O], 1029 (s), 949 (m), 839 (w), 806 (w), 795 (w), 780 (w), 737 (s), 711 (w), 698 (s), 679 (m).

HRMS (ESI) calculated for C_{21}H_{34}O_4Li [M + Li⁺] : 357.2617, found 357.2604.

1-Benzyloxy-12-(tert-butyldimethylsilyloxy)dodecane 4-(1',2'-ethanediyl)ketal (10/9)

Siloyloxyketal 10/9 was obtained as a major by-product from the ketalisation reaction of 1-benzyloxy-12-(tert-butyldimethylsilyloxy)dodecan-4-one (10/4) with 1,2-ethanediol and PPTS (method B) after separation by column chromatography as a colourless liquid (166 mg, 0.357 mmol).
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CC: ∅ 1.7 cm × 10 cm, Vfr = 16–17 mL, eluent EA/PE 5 : 95 → 50 : 50

Yield: 36%

Chemical formula: C_{27}H_{48}O_{4}Si

Molecular weight: 464.75

Appearance: Colourless liquid

TLC: Rf = 0.23 (DE/PE = 2 : 1), CAM

¹H NMR (500 MHz, CDCl₃) δ [ppm]: 0.04 (s, 6H, 2 × CH₃, OTBS), 0.89 (s, 9H, tBu, OTBS), 1.28 (s, 8H, H₂-7 – H₂-10), 1.34 (m, 2H, H₂-6), 1.50 (br quin, 2H, J = 6.7 Hz, H₂-11), 1.59 (m, 2H, H₂-5), 1.68 (m, 4H, H₂-2, H₂-3), 2.15 (m, 2H, H₂-1), 3.59 (t, 2H, J = 6.6 Hz, H₂-12), 3.92 (s, 4H, H₂-1', H₂-2'), 4.50 (s, 2H, H₂-1'), 7.27 (m, 1H, para-Ph-H, OBn), 7.33 (d, 4H, J = 4.6 Hz, 2 × ortho-Ph-H, 2 × meta-Ph-H, OBn).

¹³C NMR (125 MHz, CDCl₃) δ [ppm]: -5.24 (2 × CH₃, OTBS), 18.39 (C₉, OTBS), 23.85 (CH₂, C-6), 24.22 (CH₂, C-2), 25.80 (CH₂, C-10), 26.00 (3 × CH₃, tBu-OTBS), 29.39, 29.60, 29.89 (3 × CH₂, C-7, C-8, C-9), 32.88 (CH₂, C-11), 33.61 (CH₂, C-3), 37.30 (CH₂, C-5), 63.32 (CH₂, C-12), 64.94 (2 × CH₂, C-1', C-2'), 70.47 (CH₂, C-1), 72.78 (CH₂, C-1'), 111.68 (CO₂, C-4), 127.46 (para-Ph-CH, OBn), 127.59 (2 × ortho-Ph-CH, OBn), 128.33 (2 × meta-Ph-CH, OBn), 138.64 (ipso-Ph-C₉, OBn).

IR (neat) ν [cm⁻¹]: 2929 (m) [C−H], 2855 (m) [C−H], 1471 (w), 1361 (w), 1307 (w), 1254 (m), 1207 (w), 1098 (vs) [C−O], 1006 (w), 947 (m), 835 (vs), 814 (m), 775 (s), 734 (m), 698 (m), 687 (w), 677 (w).

HRMS (ESI) calculated for C_{27}H_{49}O_{4}Si [M + H⁺]: 465.3400, found 465.3378.

HRMS (ESI) calculated for C_{27}H_{48}O_{4}SiLi [M + Li⁺]: 471.3482, found 471.3466.

1,12-Bis(benzyloxy)dodecan-4-one (10/12)

Bis(benzyloxy)ketone 10/12 was obtained as the main product from a failed attempt to synthesise 9,9,12-tris(benzyloxy)dodecan-1-ol. In accordance to method A the mixture of 1-benzyloxy-12-((tert-butyldimethylsilyloxy)dodecan-4-one (421 mg, 1.0 mmol, 1.0 equiv), benzyl alcohol (1 mL) and PTSA (190 mg, 1.0 mmol, 1.0 equiv) in dry benzene (5 mL) was
heated at reflux with water separation by a Dean-Stark trap. Purification of the residue after aqueous work-up afforded the bis(benzyloxy)ketone 10/12 (256 mg, 0.645 mmol) as a white solid in 64.5% yield. 1-benzyloxy-12-hydroxydodecan-4-one (10/10) (64 mg, 0.21 mmol) was obtained as a minor by-product from the reaction as a yellow liquid in 21% yield.

\[ \text{CC} : \emptyset 1.7 \text{ cm} \times 10 \text{ cm}, V_{fr} = 16-17 \text{ mL}, \text{ eluent EA/PE } 5 : 95 \rightarrow 50 : 50 \]

\[ \text{Yield : 64.5\%} \]

\[ \text{Chemical formula : C}_{26}H_{36}O_3 \]

\[ \text{Molecular weight : 396.56} \]

\[ \text{Appearance : White solid} \]

\[ \text{TLC} : R_f = 0.38 \text{ (DE/PE = 1 : 2), CAM} \]

\[ \text{Melting point} : \vartheta_m = 38-39 \degree \text{C} \]

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \delta [\text{ppm}] : 1.27^a (m, 6H, H$_2$-7 – H$_2$-9), 1.34^a (br quin, 2H, J = 6.9 Hz, H$_2$-10), 1.54^a (quin, 2H, J = 7.3 Hz, H$_2$-6), 1.60^a (quin, 2H, J = 6.9 Hz, H$_2$-11), 1.88 (quin, 2H, J = 6.8 Hz, H$_2$-2), 2.37 (t, 2H, J = 7.5 Hz, H$_2$-5), 2.50 (t, 2H, J = 7.2 Hz, H$_2$-3), 3.45^a (t, 2H, J = 6.7 Hz, H$_2$-12), 3.47^a (t, 2H, J = 6.2 Hz, H$_2$-1), 4.47^a (s, 2H, H$_2$-1*), 4.49^a (s, 2H, H$_2$-12*), 7.24 – 7.36 (m, 10H, 10 × Ph-H).} \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3 \delta [\text{ppm}] : 23.81 (CH$_2$, C-6), 23.88 (CH$_2$, C-2), 26.13 (CH$_2$, C-10), 29.16, 29.27, 29.33 (3 × CH$_2$, C-7, C-8, C-9), 29.73 (CH$_2$, C-11), 39.28 (CH$_2$, C-3), 42.87 (CH$_2$, C-5), 69.37 (CH$_2$, C-1), 70.45 (CH$_2$, C-12), 72.83 (2 × CH$_2$, C-1*, C-12*), 127.43, 127.54 (2 × para-Ph-CH, OBN), 127.59, 127.60 (4 × ortho-CH, OBN), 128.31, 128.34 (4 × meta-CH, OBN), 138.42, 138.69 (2 × ipso-C$_q$, OBN), 210.93 (CO, C-4).} \]

\[ \text{IR (neat) } \tilde{\nu} [\text{cm}^{-1}] : 2931 (m), 2854 (m), 2799 (w), 1714 (s) [C=O], 1498 (w), 1481 (w), 1458 (m), 1419 (w), 1368 (s), 1354 (w), 1311 (w), 1288 (w), 1259 (w), 1124 (vs), 1104 (vs), 1077 (s), 1024 (m), 982 (w), 970 (w), 742 (vs), 728 (s).} \]

\[ \text{HRMS (ESI) calculated for C}_{26}H_{36}O_3Li [M + Li^+] : 403.2824, found 403.2809.} \]
Experimental Section

1-Benzylxy-12-(methanesulfonyloxy)dodecane 4-(1',2'-ethanediyl)ketal (10/16)

To the mixture of hydroxyketal 10/5 (7711 mg, 22.0 mmol, 1.0 equiv) and Et$_3$N (5566 mg, 55.0 mmol, 2.5 equiv) in dry DCM (55 mL) was slowly added a solution of MsCl (2772 mg, 24.2 mmol, 1.1 equiv) in dry DCM (55 mL) at 0 °C under an atmosphere of N$_2$. The mixture is stirred at 25 °C for 2 h after which time additional MsCl was added (504 mg, 4.4 mmol, 0.2 equiv) to complete to conversion. After overnight stirring (18 h) the mixture was diluted with Et$_2$O (550 mL) and washed with water (110 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated in vacuo. Purification of the residue by column chromatography afforded the desired mesylate ketal 10/16 (9411 mg, 21.96 mmol) as a colourless liquid.

CC : Ø 1.7 cm × 10 cm, V$_{Fr}$ = 22 – 23 mL, eluent EA/PE 25 : 75 → 40 : 60

Yield : 100% 99.8%

Chemical formula : C$_{22}$H$_{36}$O$_6$S

Molecular weight : 428.58

Appearance : Colourless liquid

TLC : R$_f$ = 0.35 (DE/PE = 3 : 1), CAM

$^1$H NMR (500 MHz, CDCl$_3$) δ [ppm] : 1.23 – 1.43 (m, 10H, H$_2$-6 – H$_2$-10), 1.59 (m, 2H, H$_2$-5), 1.68° (m, 4H, H$_2$-2, H$_2$-3), 1.74° (quin, 2H, J = 7.1 Hz, H$_2$-11), 2.99 (s, 3H, OMs-CH$_3$), 3.47 (m, 2H, H$_2$-1), 3.92 (s, 4H, H$_2$-1', H$_2$-2'), 4.21 (t, 2H, J = 6.6 Hz, H$_2$-12), 4.50 (s, 2H, H$_2$-1°), 7.27 (m, 1H, para-Ph-H, OBn), 7.33 (°d°, 4H, J = 4.6 Hz, 2 × ortho-Ph-H, 2 × meta-Ph-H, OBn).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ [ppm] : 23.75 (CH$_2$, C-6), 24.23 (CH$_2$, C-2), 25.40 (CH$_2$, C-10), 28.93, 29.10, 29.35, 29.74 (4 × CH$_2$, C-7, C-8, C-9, C-11), 33.62 (CH$_2$, C-3), 37.23 (CH$_2$, C-5), 37.36 (CH$_3$, OMs), 64.94 (2 × CH$_2$, C-1', C-2'), 70.15 (CH$_2$, C-12), 70.46 (CH$_2$, C-1), 72.78 (CH$_2$, C-1°), 111.62 (CO$_2$, C-4), 127.47 (para-Ph-CH, OBn), 127.58 (2 × ortho-Ph-CH, OBn), 128.33 (2 × meta-Ph-CH, OBn), 138.63 (ipso-Ph-C$_0$, OBn).

IR (neat) V [cm$^{-1}$] : 2938 (m), 2858 (w), 1455 (w), 1355 (s), 1207 (w), 1174 (vs), 1076 (s), 972 (s), 948 (vs), 827 (m), 739 (m), 716 (m).

HRMS (ESI) calculated for C$_{22}$H$_{36}$O$_6$S [M + H$^+$] : 429.2311, found 429.2326.
Experimental Section

1-Benzzyloxy-12-iodododecane 4-(1',2'-ethanediyl)ketal (10/6)

To the solution of mesylate 10/16 (6429 mg, 1.0 mmol, 1.0 equiv) in dry MeCN (75 mL) was added NaI (11.25 g, 75.0 mmol, 5.0 equiv) in one portion at rt resulting in an instant colour change to yellow. The mixture was then vigorously stirred at 50 °C under an atmosphere of N2. White, pulpy NaOMs precipitated from the solution during the course of the reaction. After 2 h TLC analysis showed full conversion of the starting material. The thick, mushy mixture was then divided between Et2O (375 mL) and H2O (75 mL) and washed with half-saturated NaCl solution (75 mL). Extraction of the combined aqueous phases with Et2O (3 x 150 mL) was followed by drying of the ethereal phases over MgSO4, filtering and concentrating in vacuo. Purification of the yellow residue by column chromatography provided the desired iodoketal 10/6 (6724 mg, 14.6 mmol) as a pale yellow liquid. This compound was found not to be very stable especially when exposed to daylight. It should therefore be used in the next step as soon as possible.

CC : ∅ 4.5 cm x 11 cm, VFr = 100 mL, eluent EA/PE 2.5 : 97.5 → 10 : 90
Yield : 97%
Chemical formula : C21H33IO3
Molecular weight : 460.39
Appearance : Pale yellow liquid
TLC : RF = 0.35 (DE/PE = 1 : 3), CAM

1H NMR (500 MHz, CDCl3) δ [ppm] : 1.29" (s, 6H, H2-7 – H2-9), 1.37" (m, 4H, H2-6, H2-10), 1.60 (m, 2H, H2-5), 1.68 (m, 4H, H2-2, H2-3), 1.81 (dt, 2H, J1 = 7.1 Hz, J2 = 14.5 Hz, H2-11), 3.18 (t, 2H, J = 7.0 Hz, H2-12), 3.48 (m, 2H, H2-1), 3.92 (s, 4H, H2-1', H2-2'), 4.50 (s, 2H, H2-1*), 7.27 (m, 1H, para-Ph-H, OBn), 7.33 ("d", 4H, J = 4.3 Hz, 2 x ortho-Ph-H, 2 x meta-Ph-H, OBn).

13C NMR (125 MHz, CDCl3) δ [ppm] : 7.26 (CH2, C-12), 23.76 (CH2, C-6), 24.22 (CH2, C-2), 28.44 (CH2, C-9), 29.34 (CH2, C-8), 29.77 (CH2, C-7), 30.47 (CH2, C-10), 33.52 (CH3, C-11), 33.60 (CH2, C-3), 37.24 (CH2, C-5), 64.93 (2 x CH2, C-1', C-2'), 70.45 (CH2, C-1), 72.77 (CH2, C-1*), 111.63 (CO2, C-4), 127.46 (Ph-para-CH, OBn), 127.57 (2 x Ph-ortho-CH, OBn), 128.32 (2 x Ph-meta-CH, OBn), 138.63 (Ph-ipso-Cq, OBn).
Experimental Section

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 2927 (m), 2854 (m), 1454 (m), 1360 (w), 1312 (w), 1205 (m), 1163 (m), 1099 (vs), 1075 (vs), 1028 (m), 947 (m), 837 (w), 740 (s), 734 (s).

HRMS (ESI) calculated for C$_{21}$H$_{33}$IO$_3$Li [M + Li$^+$]: 467.1635, found 467.1642.

(1-Benzzyloxy-4-(1',2'-ethanedioxy)dodecan-12-yl)triphenylphosphonium iodide (10/7)

![Chemical Structure](image)

To the solution of iodoketal 10/6 (6722 mg, 14.6 mmol, 1.0 equiv) was added PPh$_3$ (4406 mg, 16.8 mmol, 1.15 equiv) in one portion at rt. The mixture was heated at reflux with exclusion of light for 18 h after which time reaction control by NMR and TLC both confirmed incomplete conversion of the starting material. Therefore, additional PPh$_3$ (1149 mg, 4.4 mmol, 0.3 equiv) was added, and the mixture was refluxed for further 24 h. The solvent was then evaporated under reduced pressure and the residue purified by via a short-bed column chromatography to afford the required phosphonium iodide ketal 10/7 (13.46 mmol) as an inseparable mixture (10412 mg, ratio 93 : 7) with its ketone derivative 10/17 (1 mmol).

CC: $\varnothing$ 4.5 cm $\times$ 7 cm, $V_F$ = 100 mL, eluent DCM/MeOH 100 : 0 $\rightarrow$ 90 : 10

Yield: 92% (Ketal); 7% (Ketone)

Chemical formula: C$_{39}$H$_{48}$IO$_3$P

Molecular weight: 722.67

Appearance: Pale yellow caramel

TLC: $R_f$ = 0.06 (100% DCM), CAM

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] (ketal only): 1.18 – 1.33 (br m, 8H, H$_2$-6 – H$_2$-9), 1.55 (m, 2H, H$_2$-5), 1.63$^a$ (m, 4H, H$_2$-10, H$_2$-11), 1.66$^a$ (m, 4H, H$_2$-2, H$_2$-3), 3.47 (t, 2H, $J = 5.5$ Hz, H$_2$-1), 3.70 (m, 2H, H$_2$-12), 3.91 (s, 4H, H$_2$-1', H$_2$-2'), 4.49 (s, 2H, H$_2$-1$'$), 7.26 (m, 1H, para-Ph-H, OBn), 7.33 ("d", 4H, $J = 4.4$ Hz, 2 $\times$ ortho-Ph-H, 2 $\times$ meta-Ph-H, OBn), 7.71 ("td", 6H, $J_1 = 3.4$ Hz, $J_2 = 7.7$ Hz, 6 $\times$ ortho-Ph-H, PPh$_3$), 7.77 – 7.87 (m, 9H, 6 $\times$ meta-Ph-H, 3 $\times$ para-Ph-H, PPh$_3$).
Experimental Section

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] (ketal only): 22.57 (d, $J_{CP} = 4.5$ Hz, CH$_2$, C-11), 23.15 (d, $J_{CP} = 50.0$ Hz, CH$_2$, C-12), 23.69 (s, CH$_2$, C-6), 24.20 (s, CH$_2$, C-2), 29.04, 29.09, 29.71 (3s, 3 $\times$ CH$_2$, C-7, C-8, C-9), 30.41 (d, $J_{CP} = 15.5$ Hz, CH$_2$, C-10), 33.60 (s, CH$_2$, C-3), 37.18 (s, CH$_2$, C-5), 64.92 (s, 2 $\times$ CH$_2$, C-1', C-2'), 70.47 (s, CH$_2$, C-1), 72.75 (s, CH$_2$, C-1*), 111.55 (s, CO$_2$, C-4), 118.09 (d, $J = 86.0$ Hz, 3 $\times$ ipso-Ph-CH$_q$, PPh$_3$), 127.44 (s, para-Ph-CH, OBn), 127.57 (s, 2 $\times$ ortho-Ph-CH, OBn), 128.31 (s, 2 $\times$ meta-Ph-CH, OBn), 130.60 (d, $J_{CP} = 12.5$ Hz, 6 $\times$ ortho-Ph-CH, PPh$_3$), 133.65 (d, $J_{CP} = 10.0$ Hz, 6 $\times$ meta-Ph-CH, PPh$_3$), 135.17 (d, $J_{CP} = 2.7$ Hz, 3 $\times$ para-Ph-CH, PPh$_3$), 138.63 (s, ipso-Ph-C$_q$, OBn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 2929 (m), 2855 (m), 1587 (w), 1484 (w), 1454 (w), 1437 (s), 1361 (w), 1316 (w), 1204 (w), 1160 (w), 1112 (vs), 1073 (s), 1028 (m), 996 (m), 949 (m), 795 (w), 776 (w), 743 (vs), 723 (vs), 691 (vs).

HRMS (ESI) calculated for C$_{39}$H$_{48}$O$_3$P [M$^+$]: 595.3341, found 595.3370.

(+)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-5-[1'(Z)-13'-benzyloxy-10'-1",2"-ethanedioxy-tridec-1'-enyl]-2-(benzyloxymethyl)pyrrolidine (10/18)

The solution of phosphonium iodide 10/7 (4336 mg, 6.0 mmol, 1.2 equiv) in a mixture of dry THF (22 mL) and dry HMPA (11 mL) was cooled to –50 ºC under an atmosphere of N$_2$. To this solution was added $n$-BuLi (1.6 M solution in hexane, 3.7 mL, 6.0 mmol, 2.0 equiv) followed by a solution of the pyrrolidine carbaldehyde 8.2 (2608 mg, 5.0 mmol, 1.0 equiv) in dry THF (10 mL). The reaction mixture was stirred for 2 h at –50 ºC, then quenched with 1 M phosphate buffer (100 mL, pH 7) and finally extracted with Et$_2$O (3 $\times$ 100 mL). The organic phase was subsequently dried over MgSO$_4$, filtered and concentrated in vacuo. Purification of the yellow, syrupy residue by column chromatography provided the predominantly (Z)-configured pyrrolidine olefin 10/18 (3555 mg, 4.24 mmol) as a pale yellow oil ($E : Z$ ratio $= 2 : 98$).

CC: ⌀ 3.5 cm $\times$ 18 cm, $V_{Fr} = 65$ mL, eluent EA/PE 10 : 90 $\rightarrow$ 20 : 80
Experimental Section

Yield: 85%

Chemical formula: C_{55}H_{67}NO_{6}

Molecular weight: 838.12

Appearance: Pale yellow oil

TLC: $R_f = 0.35$ (DE/PE = 2:3), CAM

Optical rotation: $[\alpha]^2_{D} = +38.1^\circ$ ($c = 4.85$ g/100 mL CHCl$_3$)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm]: 1.15 – 1.29 (m, 8H, H$_2$-9 – H$_2$-12), 1.33 (br m, 2H, H$_2$-13), 1.58 (m, 2H, H$_2$-14), 1.66 – 1.71 (m, 4H, H$_2$-16, H$_2$-17), 1.90 (m, 2H, H$_2$-8), 3.23 (m, 1H, H-2), 3.47 (m, 2H, H$_2$-18), 3.53 (dd, 1H, $J_1 = 4.2$ Hz, $J_2 = 9.7$ Hz, H$_A$-1), 3.57 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 9.5$ Hz, H$_A$-1), 3.59 (d, 1H, $J = 14.4$ Hz, H$_A$-5*), 3.81 (dd, 1H, $J_1 = 3.3$ Hz, $J_2 = 4.5$ Hz, H-4), 3.90 (br m, 2H, H$_2$-13), 3.98 (d, 1H, $J = 14.5$ Hz, H$_A$-5*), 3.99 (s, 4H, H$_2$-1", H$_2$-2"), 3.99 (d, 1H, $J = 10.5$ Hz, H-6), 5.19 (dt, 1H, $J_1 = 3.1$ Hz, $J_2 = 10.8$ Hz, H-7), 5.15 – 5.35 (m, 25H, 25 × Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm]: 23.85 (CH$_2$, C-13), 24.22 (CH$_2$, C-17), 27.54 (CH$_2$, C-8), 29.32, 29.51, 29.69, 29.90 (4 × CH$_2$, C-9 – C-12), 33.62 (CH$_2$, C-16), 37.31 (CH$_2$, C-14), 51.02 (CH$_2$, C-5*), 62.70 (CH, C-5), 63.85 (CH, C-2), 64.92 (2 × CH$_2$, C-1", C-2"), 69.51 (CH$_2$, C-1), 70.46 (CH$_2$, C-18), 71.49 (CH$_2$, C-3*), 71.68 (CH$_2$, C-4*), 72.76 (CH$_2$, C-18*), 73.20 (CH$_2$, C-1*), 86.03 (CH, C-3), 88.68 (CH, C-4), 111.63 (CO$_2$, C-15), 126.44, 127.44, 127.56, 127.58, 127.60, 127.80, 128.05, 128.13, 128.24, 128.25, 128.31 (25 × Ph-CH), 129.05 (CH, C-6), 134.37 (CH, C-7), 138.40, 138.46, 138.52, 138.63 (4 × Ph-C$_q$, OBn), 139.96 (Ph-C$_q$, NBn).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$]: 3028 (m), 2928 (m), 2855 (m), 1454 (m), 1362 (m), 1315 (w), 1246 (w), 1207 (m), 1096 (s), 1076 (s), 1026 (m), 949 (m), 907 (w), 833 (w), 737 (vs).

HRMS (ESI) calculated for C$_{55}$H$_{68}$NO$_6$ [M + H$^+$]: 838.5047, found 838.5058.
Experimental Section

(12Z)-1,24-Bis(benzyloxy)-4,21-bis(ethane-1,2-dioxy)tetracos-12-ene (10/19)

Olefin 10/19 was obtained as a minor by-product from the above Wittig reaction as a yellow oil (366 mg, 0.55 mmol) in 18% yield (based on the amount of phosphonium iodide 10/7 applied in the reaction).

Yield : 18%

Chemical formula : C_{42}H_{64}O_{6}

Molecular weight : 664.95

Appearance : Yellow oil

TLC : $R_f = 0.24$ (DE/PE = 1 : 4), CAM

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ [ppm] : 1.24 – 1.38 (m, 20H, H$_2$-6 – H$_2$-10, H$_2$-15 – H$_2$-19), 1.60 (m, 4H, H$_2$-5, H$_2$-20), 1.68 (m, 8H, H$_2$-2, H$_2$-3, H$_2$-22, H$_2$-23), 2.00 (m, 4H, H$_2$-11, H$_2$-14), 3.47 (m, 4H, H$_2$-1, H$_2$-24), 3.92 (s, 8H, H$_2$-4', H$_2$-4", H$_2$-21', H$_2$-21"), 4.50 (s, 4H, H$_2$-1*, H$_2$-24*), 5.34 (m, 2H, H-12, H-13), 7.27 (m, 2H, 2 × para-Ph-H), 7.33 ("d", $J = 4.4$ Hz, 8H, 4 × ortho-Ph-H, 4 × meta-Ph-H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ [ppm] : 23.85 (2 × CH$_2$, C-6, C-19), 24.22 (2 × CH$_2$, C-2, C-23), 27.22 (2 × CH$_2$, C-11, C-14), 29.26, 29.53, 29.77, 29.91 (8 × CH$_2$, C-7 – C-10, C-15 – C-18), 33.61 (2 × CH$_2$, C-3, C-22), 37.30 (2 × CH$_2$, C-5, C-20), 64.93 (4 × CH$_2$, C-4', C-4", C-21', C-21"), 70.48 (2 × CH$_2$, C-1, C-24), 72.77 (2 × CH$_2$, C-1*, C-24*), 111.67 (2 × CO$_2$, C-4, C-21), 127.45 (2 × para-Ph-CH), 127.58 (2 × ortho-Ph-CH), 128.32 (2 × meta-Ph-CH), 129.86 (2 × CH, C-12, C-13), 138.66 (2 × ipso-Ph-C$_6$).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 2924 (s) [C–H], 2855 (s) [C–H], 1454 (m), 1404 (w), 1362 (m), 1312 (w), 1273 (w), 1207 (m), 1100 (vs) [C–O], 1075 (vs) [C–O], 1030 (m), 949 (m), 907 (w), 883 (w), 849 (w), 826 (w), 737 (vs).

HRMS (EI) calculated for C$_{38}$H$_{60}$O$_2$ [M$^+$] : 664.4703, found 664.4704.
Experimental Section

(+)-(2S,3S,4S,5S)-N-Benzyl-3,4-bis(benzyloxy)-5-((1'Z)-13'-benzoxy-10'-oxotridec-1'-enyl)-2-(benzyloxymethyl)pyrrolidine (10/20)

The mixture of pyrrolidine ketal 10/18 (2935 mg, 3.5 mmol, 1.0 equiv) and aqueous 1 M H_2SO_4 (3.5 mL) in 1,4-dioxane (14 mL) was stirred at 50 °C for 24 h. A change of colour from colourless to red could be observed during the course of the reaction. After cooling to rt the mixture was neutralised with 2 M NaOH (3.5 mL) and further basified by the addition of saturated NaHCO_3 solution (3.5 mL). Extraction with excess DCM was followed by drying of the combined organic phases over MgSO_4/K_2CO_3 (1 : 1), filtration and concentration in vacuo. The orange residue was purified by column chromatography to afford the desired pyrrolidine ketone 10/20 (2674 mg, 3.37 mmol) as a pale yellow oil.

Chemical formula : C_{53}H_{63}NO_5

Molecular weight : 794.07

Appearance : Pale yellow oil

TLC : R_f = 0.38 (DE/PE = 2 : 3), CAM

Optical rotation : [α]_D^25 = +40.6° (c = 2.78 g/100 mL CHCl_3)

H NMR (500 MHz, CDCl_3) δ [ppm] : 1.20 s (6H, H_2-10 – H_2-12), 1.24 m (2H, H_2-9), 1.51 s (br quin, 2H, J = 6.9 Hz, H_2-13), 1.84 – 1.95 (m, 4H, H_2-8, H_2-17), 2.35 (t, 2H, J = 7.5 Hz, H_2-14), 2.49 (t, 2H, J = 7.2 Hz, H_2-16), 3.23 (m, 1H, H-2), 3.47 (t, 2H, J = 6.1 Hz, H_2-18), 3.53 dd (1H, J_1 = 4.1 Hz, J_2 = 9.7 Hz, H_A-1), 3.57 dd (1H, J_1 = 5.9 Hz, J_2 = 9.5 Hz, H_B-1), 3.59 d (1H, J = 14.4 Hz, H_A-5*), 3.81 (dd, 1H, J_1 = 3.3 Hz, J_2 = 4.5 Hz, H-4), 3.93 (d, 1H, J = 14.4 Hz, H_B-5*), 3.98 (dd, 1H, J_1 = 4.8 Hz, J_2 = 10.0 Hz, H-5), 4.03 (t, 1H, J = 3.1 Hz, H-3), 4.43 – 4.48 m (2H, H_2-1*, H_2-3*, H_A-4*), 4.47 s (2H, H_2-18*), 4.56 (d, 1H, J = 12.0 Hz, H_B-4*), 5.45 (t, 1H, J = 10.5 Hz, H-6), 5.59 (dt, 1H, J_1 = 7.3 Hz, J_2 = 11.0 Hz, H-7), 7.15 – 7.35 (m, 25H, 25 × Ph-CH).
Experimental Section

$^{13}$C NMR (125 MHz, CDCl$_3$) δ [ppm] : 23.82 (CH$_3$, C-13), 23.89 (CH$_3$, C-17), 27.51 (CH$_2$, C-8), 29.17, 29.19, 29.29 (3 × CH$_2$, C-10 – C-12), 29.63 (CH$_3$, C-9), 39.28 (CH$_2$, C-16), 42.88 (CH$_2$, C-14), 51.02 (CH$_2$, C-5*), 62.72 (CH, C-5), 63.86 (CH, C-2), 69.38 (CH$_2$, C-18), 69.51 (CH$_2$, C-1), 71.50 (CH$_2$, C-3*), 71.69 (CH$_2$, C-4*), 72.84 (CH$_2$, C-18*), 86.03 (CH, C-3), 88.72 (CH, C-4), 126.45, 127.44, 127.45, 127.56, 127.58, 127.59, 127.61, 127.80, 128.06, 128.13, 128.24, 128.35 (25 × Ph-CH), 129.14 (CH, C-6), 134.30 (CH, C-7), 138.41, 138.43, 138.46, 138.55 (4 × Ph-ipo$	ext{so}$-C$_q$, OBn), 139.97 (Ph-ipo$	ext{so}$-C$_q$, NBn), 210.86 (CO, C-15).

IR (neat) $\tilde{\nu}$ [cm$^{-1}$] : 3063 (w), 3028 (w), 3005 (w), 2928 (m) [C−H], 2855 (m) [C−H], 1713 (m) [C=O], 1493 (w), 1454 (m), 1408 (w), 1362 (m), 1308 (w), 1250 (w), 1207 (w), 1096 (s) [C−O], 1026 (m), 1003 (w), 988 (w), 957 (w), 907 (w), 841 (w), 737 (vs).

HRMS (ESI) calculated for C$_{53}$H$_{64}$NO$_5$ [M + H$^+$] : 794.4784, found 794.4798.

$^{(-)}$(2S,3S,4S,5S)-2-(Hydroxymethyl)-5-[9'-tetrahydrofuran-2'-yl)nonyl]pyrrolidine-3,4-diol; $^{(-)}$Broussonetine C2 (10/23)

The pentabenzylated pyrrolidine 10/20 (2382 mg, 3.0 mmol) was dissolved in EtOAc (15 mL) and added to the suspension of Pd-enriched Pearlman’s catalyst (140 mg Pd(OH)$_2$/C + 106 mg Pd black) in a mixture of 10 M HCl (3.3 mL) and MeOH (15 mL) at rt. The mixture was vigorously stirred at 25 °C under an atmosphere of H$_2$ overnight (18 h) after which time the catalyst was removed by filtration through a pad of Celite and rinsed thoroughly with MeOH. All volatiles were then evaporated in vacuo to give an orange semi-solid residue. This residue was subsequently dissolved in MeOH (15 mL) and treated dropwise with a 7 M methanolic NH$_3$ solution until basic pH affording a yellow semi-solid after evaporation to dryness. TLC, ESI-MS and NMR of this material revealed it to be a complex mixture of products with the above tetrahydrofuranyl pyrrolidine derivative 10/23 being the main component. A first separation was achieved by column chromatography over basic silica gel ($\Theta$ 3.0 cm × 6 cm, $V_F$ = 26 mL, elution with CHCl$_3$/MeOH/NH$_3$ (7 N in MeOH) 95 : 3 : 2 → 80 : 18 : 2) providing 588 mg of the main product as a pale yellow foamy solid. The obtained
Experimental Section

Material was further purified by preparative high performance liquid chromatography (2 runs @ 5–6 injections*). The fractions containing the main product were first concentrated under reduced pressure and subsequently lyophilised affording the pure title compound (410 mg, 1.24 mmol) as a white powder.

**HPLC**: Column: PHENOMENEX GEMINI C18 reversed phase LC column AXIA packed, 150 × 21.2 mm (length × internal diameter), 5 µm (particle size), 110 Å (pore size)

*1st run*: Injection volume (6 × 1 mL containing approx. 100 mg substance each time)
- Solvent: MeCN/H₂O (33 : 67), adjusted to pH 12 with ammonia solution
- Flow rate: 24 mL/min
- Column temperature: ambient
- Detection wavelength of PDA: 215 nm
- Retention time of combined fractions: 1 – 11 min

*2nd run*: Injection volume (5 × 1 mL containing approx. 100 mg substance each time)
- Solvent: MeCN/H₂O (22 : 78), adjusted to pH 12 with ammonia solution
- Flow rate: 24 mL/min
- Column temperature: ambient
- Detection wavelength of PDA: 210 nm
- Retention time of combined fractions: 48 – 62 min

**Yield**: 41.5%

**Chemical formula**: C₁₈H₃₅NO₄

**Molecular weight**: 329.47

**Appearance**: White powder

**Melting point**: ϑₘ = 108–109 ºC (free pyrrolidine base)

**Optical rotation**: [α]₂⁵D = −34.6° (c = 1.0 g/100 mL MeOH)

**1H NMR (500 MHz, C₅D₅N) δ [ppm]** (free base): 1.22° (br s, 8H, H₂-8 – H₂-11), 1.24 – 1.40° (m, 4H, H₂-12, H₆-13, H₆-16), 1.40 – 1.50° (m, 2H, H₈-13, H₆-14), 1.53° (m, 1H, H₆-7), 1.57 – 1.67° (m, 2H, H₆-7, H₆-14), 1.65 – 1.80° (m, 3H, H₆-6, H₂-17), 1.85 (m, 1H, H₆-16), 2.01 (m, 1H, H₆-6), 3.49 (br dd, 1H, J₁ = 4.2 Hz, J₂ ≈ 7.2 Hz, H-5), 3.67 (q, 1H, J = 7.5 Hz, H₆-18), 3.72 – 3.82° (m, 2H, H-2, H-15), 3.84° (q, 1H, J = 7.5 Hz, H₆-18), 4.16° (dd, 1H, J₁ = 5.9 Hz, J₂ =

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* In order to achieve an optimal resolution under the applied conditions, it was found not to exceed a loading mass of 100 mg per injection.
Experimental Section

10.6 Hz, H₆₋₁), 4.22" (dd, 1H, J₁ = 3.8 Hz, J₂ = 10.6 Hz, H₆₋₁), 4.37 (t, 1H, J = 6.4 Hz, H₋₄), 4.65 (t, 1H, J = 6.4 Hz, H₋₃).

¹³C NMR (125 MHz, C₅D₅N) δ [ppm] (free base) : 26.02 (CH₂, C-17), 26.76 (CH₂, C-13), 27.32 (CH₂, C-7), 29.87, 29.94, 29.98, 30.03 (4 × CH₂, C-8 – C-11), 30.26 (CH₂, C-12), 31.71 (CH₂, C-16), 35.82 (CH₂, C-6), 36.15 (CH₂, C-14), 62.96 (CH, C-5), 63.92 (CH₂, C-1), 65.20 (CH, C-2), 67.53 (CH₃, C-18), 79.39 (CH, C-15), 80.52 (CH, C-3), 84.52 (CH, C-4).

¹H NMR (500 MHz, CD₃OD) δ [ppm] (free base) : 1.32 (s, 10H, H₂₋₈ – H₂₋₁₂), 1.36 – 1.49 (m, 7H, H₋₇, H₋₁₃, H₋₁₄, H₋₁₆), 1.54 (m, 1H, H₋₁₄), 1.66 (m, 1H, H₋₆), 1.82 – 1.96 (m, 2H, H₋₁₇), 2.00 (m, 1H, H₋₁₆), 2.83 (dt, 1H J₁ = 5.1 Hz, J₂ = 7.5 Hz, H₋₂), 2.95 (dt, 1H J₁ = 4.3 Hz, J₂ = 6.3 Hz, H₋₂), 3.55 – 3.60 (m, 2H, H₋₁, H₋₄), 3.65 – 3.70 (dd, 1H, J₁ = 4.2 Hz, J₂ = 11.2 Hz, H₋₁ ), 3.70 (dt, 1H, J₁ = 6.3 Hz, J₂ = 7.9 Hz, H₋₁₈), 3.74 (t, 1H, J = 6.5 Hz, H₋₃), 3.76 – 3.86 (m, 2H, H₋₁₅, H₋₁₈).

¹³C NMR (125 MHz, CD₃OD) δ [ppm] (free base) : 26.63 (CH₂, C-17), 27.39 (CH₂, C-13), 27.79 (CH₂, C-7), 30.68, 30.70, 30.74, 30.85, 30.91 (5 × CH₂, C-8 – C-12), 32.36 (CH₂, C-16), 35.45 (CH₂, C-6), 36.75 (CH₂, C-14), 62.71 (CH, C-5), 63.46 (CH₂, C-1), 64.46 (CH, C-2), 68.56 (CH₂, C-18), 79.80 (CH, C-3), 80.96 (CH, C-15), 83.81 (CH, C-4).

¹H NMR (500 MHz, CD₃OD) δ [ppm] (pyrrolidinium trifluoroacetate) : 1.33 (s, 11H, H₂₋₈ – H₂₋₁₂, H₋₁₃), 1.35 – 1.52 (m, 5H, H₋₇, H₋₁₃, H₋₁₄, H₋₁₆), 1.54 (m, 1H, H₋₁₄), 1.72 (m, 1H, H₋₆), 1.82 – 1.96 (m, 3H, H₋₁₆–H₋₁₇), 2.00 (m, 1H, H₋₁₆), 3.32 (q, 1H, J = 6.9 Hz, H₋₅), 3.45 (dt, 1H J₁ = 4.0 Hz, J₂ = 6.2 Hz, H₋₂), 3.70 (dd, 1H, J₁ = 7.8 Hz, J₂ = 14.3 Hz, H₋₁₈), 3.76 – 3.88 (m, 5H, H₋₁₅, H₋₁₆, H₋₁₈), 3.96 (t, 1H, J = 5.8 Hz, H₋₃).

¹³C NMR (125 MHz, CD₃OD) δ [ppm] (pyrrolidinium trifluoroacetate) : 26.63 (CH₂, C-17), 27.18 (CH₂, C-7), 27.39 (CH₂, C-13), 30.38, 30.43, 30.56, 30.68, 30.82 (5 × CH₂, C-8 – C-12), 32.09 (CH₂, C-6), 32.37 (CH₂, C-16), 36.74 (CH₂, C-14), 59.60 (CH₂, C-1), 64.61 (CH, C-5), 65.81 (CH, C-2), 68.59 (CH₂, C-18), 76.81 (CH, C-3), 80.47 (CH, C-4), 80.97 (CH, C-15).

IR (neat) ν [cm⁻¹] : 3379(br) [N–H/O–H], 3175(br) [N–H/O–H], 2922(s) [C–H], 2851(s) [C–H], 2507(br), 2160(br), 1979(w), 1483(w), 1466(m), 1437(w), 1393(m), 1383(m), 1358(w), 1337(w), 1325(w), 1250(w), 1219(w), 1179(w), 1151(m), 1121(s), 1057(vs) [C–O], 1032(s) [C–O], 989(s), 934(m), 922(m), 905(m), 824(m), 791(m), 768(m), 721(m).

E.8 References


Appendix 1. Alkaloids

Alkaloids are a group of natural products which contain one or more, mostly heterocyclic bound, basic nitrogen atom(s) and often exhibit a distinctive pharmacological effect. For that reason they are used as medications, as recreational drugs, or in entheogenic rituals. Examples are the local anaesthetic and stimulant cocaine, the stimulants caffeine and nicotine, the analgesic morphine, and the antiarrhythmic agent quinidine (Figure A1.1).

Although alkaloids act on a diversity of metabolic systems in humans and animals, they almost uniformly invoke a bitter taste. Beside hydrogen, carbon and nitrogen, molecules of alkaloids often also contain oxygen and rarely sulfur, chlorine, bromine or phosphorus.[1]

The term “alkaloid” was introduced in 1819 by the German pharmacist Carl Friedrich Wilhelm MEISSNER, and is deduced from the Latin word “alkali” (which, in turn, comes from the Arabic “al qualia” meaning “plant ashes”) and the Greek suffix “είδος” (“type”, “similarity”) or “ειδω” (“to appear”).[2] Essentially, it describes a plant-derived substance with an alkali-like character. However, the term only became widely recognised after the publication of a detailed review article about alkaloids by O. JACOBSEN in Albert LADENBURG’s Handwörterbuch der Chemie in 1882.[3a]

There is no unique naming method for alkaloids.[3b] Many individual names are formed by adding the suffix “-ine” to the scientific name of the species the alkaloid had initially been isolated from. For example, atropine was first isolated from deadly nightshade, Atropa belladonna (Figure A1.4), strychnine was obtained from the seeds of deciduous tree Strychnos nux-vomica (Figures A1.14 and A1.15).* If several alkaloids are extracted from one source, then their names often contain the suffixes “-idine”, “-anine”, “-aline”, “-inine”, etc.

* The suffix ‘ine’ is a Greek feminine patronymic suffix and means ‘daughter of’; hence, for example, ‘atropine’ means ‘daughter of Atropa (belladonna)’.
Appendix 1. Alkaloids

The boundaries between alkaloids and other nitrogen-containing natural compounds are not clear-cut. In view of the fact that pure amino acids, peptides, nucleic acids, and synthetic organic nitrogen bases such as aniline are not counted among the alkaloids, Manfred Hesse gave the following general definition: “Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character.” Nevertheless, even in the literature, the distinction of alkaloids from other N-containing natural products is often not definite. For example, some pyrrolidine- and piperidine-alkaloids isolated from the White Mulberry tree (Morus alba) bearing a C12 side chain with terminal carboxyl group are also referred to as ω-amino acids.

![Morusimic acid B](image)

Morusimic acid B - Pyrrolidine alkaloid or ω-amino acid?

Alkaloids are produced as secondary metabolites by a large variety of living organisms, including bacteria, fungi, and animals, predominantly however by higher plants – about 10 – 25% of those contain alkaloids. Some of the especially alkaloid-rich higher plant families include the buttercup or crowfoot plants (Ranunculaceae), poppy plants (Papaveraceae) (Figure A1.2) and the nightshade plants (Solanaceae). On the other hand, coniferous woods and lower plants (ferns, mosses, algae) are in general alkaloid-free. The alkaloid content in plants is usually within a few percent and is inhomogeneous over the plant tissues.

Depending on the type of plant, the maximum concentration can be found either in the leaves, fruits, seeds, roots or bark. In many cases, it is not unusual to find a whole family of structural related alkaloids in a plant rather than just one single compound. Typically, members of an alkaloid family differ in their stereochemical composition and/or their positioning and variation of substituents (for an example from the tropane alkaloid family see Figure A1.3). Furthermore, different parts of the same plant may contain different alkaloids.
Appendix 1. Alkaloids

![Chemical structures of (+)-Atropine, (--)-Hyoscyamine, and (--) Scopolamine](image)

**Figure A1.3.** Alkaloids found in certain plants of the Solanaceae family including henbane (*Hyoscyamus niger*) and deadly nightshade (*Atropa belladonna*) (Figure A1.4). Scopolamine is the C-6-C-7-epoxide of hyoscyamine, hyoscyamine, in turn, is the levorotary isomer to atropine.\[9, 10\]

All three compounds exhibit muscarinic antagonist effects, i.e. act as competitive antagonist at muscarinic acetylcholine receptors and block the neurotransmitter acetylcholine in the central and the peripheral nervous system. As such, they are used as anticholinergic, antimuscarinic drugs in medicine to treat gastrointestinal disorders and Parkinson’s decease amongst others.\[3c, 3d, 11−14\]

**Figure A1.4.** *Atropa belladonna*, commonly known as Devil’s Berries, Death Cherries or Deadly Nightshade, is a perennial herbaceous plant in the Solanaceae family, native to Europe, North Africa, and Western Asia. The genus term “atropa” is derived from the name of the Greek goddess Atropos. In the Greek mythology, Atropos was one of the three goddesses of fate and destiny who would determine the course of a man’s life with Atropos being the one who would eventually end it by cutting their thread of life with her “abhorred shears”. The epithet “belladonna” is derived from Italian and means “beautiful lady”. Drops prepared from the belladonna plant were used to dilate women’s pupils, an effect considered attractive.\[16\]

All parts of the plant are extremely toxic and contain various tropane alkaloids including atropine,\[7\] hyoscyamine and scopolamine. The symptoms of belladonna poisoning include sensitivity to light, blurred vision, tachycardia (accelerated heart rate), loss of balance, slurred speech, confusion, hallucinations, delirium, and convulsions. The berries usually pose the greatest danger because they resemble blueberries and have a somewhat sweet taste. The consumption of two to five berries by children and ten to twenty berries by adults are reported to be lethal.\[16\]

Beside plants, alkaloids are also found in several types of bacteria and fungi. Examples are the antibacterial (+)-preussin which has been isolated from the fermentation broth of the mould fungus *Aspergillus ochraceus*\[17, 18\] and the structurally more complex alkaloid (–)-quinocarcin, a secondary metabolite produced by the bacteria *Streptomyces melanovinaceus*, showing notable antitumor activity.\[19\] Further examples from higher fungi include (+)-muscarine and muscimol. Muscarine is found in certain mushrooms, particularly in *Inocybe* and *Clitocybe* species, such as the deadly ivory funnel *C. dealbata*. The isoxazole alkaloid muscimol (a.k.a. agarin and pantherine) is the major psychoactive agent present in many mushrooms of the *Amanita* genus.
Appendix 1. Alkaloids

Muscarine was first isolated from the fungus *Amanita muscaria* in 1869 and was long thought to be the active hallucinogenic agent. The levels of muscarine in *A. muscaria*, however, are minute when compared with other poisonous fungi such as the deadly ivory funnel (*Clitocybe dealbata*) and therefore are too insignificant to play a role in the symptoms of poisoning. The pharmacologically more relevant compound and principal psychoactive alkaloid from this mushroom is muscimol, also known as agarin and pantherine. Muscimol is a potent GABA<sub>A</sub> agonist, activating the receptor for the brain’s major inhibitory neurotransmitter, γ-aminobutyric acid (GABA) and, as such, is a powerful neurotoxin.

Since many alkaloids are neurotoxins or exhibit a neurological effect, alkaloids of animal origin are comparatively seldom. Examples include the neurotoxic steroidal alkaloid samandarine from the skin glands of the fire salamander (*Salamandra salamandra*) (Figure A1.6) and the potent neurotoxin tetrodotoxin which has been isolated from various marine animals such as the blue-ringed octopus (*Hapalochlaena lunulata*) (Figure A1.7) and members the pufferfish family (Tetraodontidae).

Samandarine is the main steroidal alkaloid of the skin glands of the fire salamander (*Salamandra salamandra*). It is extremely toxic, causing strong muscle convulsions (muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body) and high blood pressure combined with hyperventilation (“overbreathing”) in vertebrates.
Appendix 1. Alkaloids

Tetrodotoxin

Tetrodotoxin (also known as "tetradox") is a potent neurotoxin with no known antidote. It blocks action potentials in nerves by binding to the voltage-gated, fast sodium channels in nerve cell membranes, essentially preventing any affected nerve cells from firing by blocking the channels used in the process. Its name derives from Tetrodontiformes, the name of the order that includes the pufferfish, porcupinefish, ocean sunfish and triggerfish, several species of which carry the toxin. Although tetrodotoxin was discovered in these fish and found in several other animals (e.g. blue-ringed octopus), it is actually produced by certain symbiotic bacteria, such as *Pseudoalteromonas tetraodonis*, that reside within these animals.\[3h, 28, 29\]

The relevance of alkaloids for the living organism that is producing them, however, is often not clearly evident. Initially, it was assumed that alkaloids are the final products of nitrogen metabolism in plants, and urea in mammals. Later it was shown, though, that almost all alkaloid-producing plants can also be grown alkaloid-free and this hypothesis was refuted. Most of the known functions of alkaloids are related to protection. For example, the aporphine alkaloid liriodenine produced by the tulip tree (Figure A1.8) protects it from parasitic mushrooms.\[3i\] In addition, the presence of alkaloids in a plant prevents it from being eaten by insects and chordate animals. Eventually, alkaloids are also known to regulate plant growth.
A1.2 Classification

The total number of alkaloids so far isolated from (or detected in) plant and animal organisms, fungi, and bacteria is enormous. According to rough estimates, taking all naturally occurring structural types into account, more than 10,000 different alkaloids exist. To cope with so many compounds, it is necessary to implement some sort of classification. This is, however, difficult since there is probably no other class of natural products that is characterised by such a great structural diversity. In comparison, steroids, flavonoids, and saccharides are confined to only a few basic skeleton types. Historically, first classification methods combined alkaloids by the common natural source like a certain type of plant. This classification was justified by the lack of knowledge about the structure of alkaloids and is now considered out-dated. More modern classifications are based on structural relationship (e.g. quinoline-, indole-, piperidine-, pyrrolidine-, pyridine-alkaloids, etc.) or biogenetic precursors (e.g. ornithine, lysine, tyrosine, tryptophan, etc.). Nevertheless, these classification systems still require compromises in borderline cases; for example, the alkaloid nicotine contains a pyridine fragment from nicotinamide and a pyrrolidine part from ornithine and therefore can be assigned to both classes.

Nowadays, alkaloids are generally divided into five major classes according to the position of the $N$-atom in the main structural element:

1. Heterocyclic alkaloids (“true alkaloids”);
2. Protoalkaloids;
3. Polyamine alkaloids;
4. Peptide alkaloids;
5. Terpene and steroid alkaloids.

**Class 1** – Heterocyclic alkaloids, also known as “true alkaloids” contain nitrogen in a heterocycle and normally originate from amino acids. These class comprises the majority of the known alkaloids today. As an exception of the rule, this class also includes purine alkaloids even though they are not derived from amino acids. Some examples are shown on the following pages.
Appendix 1. Alkaloids

(+)-Hygrine

Hygrine is a simple pyrrolidine alkaloid found mainly in coca leaves. It was first isolated in 1889 accompanying cocaine.\(^{[3i, 34]}\)

(+)-Coniine

Coniine is a poisonous alkaloid found in poison hemlock and the yellow pitcher plant, and contributes to hemlock's fetid smell. It is a neurotoxin which disrupts the peripheral nervous system with death caused by respiratory paralysis.\(^{[3j, 35]}\)

(-)-Ecgone

Ecgone is a tropane alkaloid found naturally in coca leaves together with the structural related cocaine. Unlike cocaine, ecgonine has no psychoactive effect and is therefore not addictive.\(^{[36]}\)

(-)-Retronecanol

Retronecanol, isolated from \textit{Crotalaria} \textit{sp.} (Leguminosae), commonly known as rattlepods, is a deoxyderivative of the necine alkaloid family. All necine alkaloids contain a 1-hydroxymethyl group in the pyrrolizidine ring system and comprise the majority of the pyrrolizidine alkaloids.\(^{[3l, 37]}\)

(+)-Tashiromine

Tashiromine is a naturally occurring indolizidine alkaloid, isolated from an Asian deciduous shrub \textit{Maackia tashiroi}.\(^{[38-40]}\)

(-)-Lupinine

Lupinine is a bitter tasting, simple quinolizidine alkaloid present in various \textit{Lupinus} spp. of Leguminosae plants. Lupinine in combination with other alkaloids causes lupin poisoning which affects people that eat incorrectly prepared lupin beans.\(^{[3m, 41]}\)

Figure A1.9. Structures of some simple mono- and bicyclic alkaloids.

- Xanthine alkaloids

Caffeine

Pure caffeine is a bitter, white crystalline substance with psychoactive stimulant properties. It was isolated from coffee in 1821 by French chemists CAVENTOU and PELLETIER who named it after the French word for coffee (café), “cafeine”, which became the English word “caffeine”. Caffeine is found in varying quantities in the beans, leaves, and fruit of several plants, where it acts as a natural pesticide that paralyses and kills certain insects feeding on them. It is most commonly consumed by humans in infusions extracted from coffee berries, which contain the coffee seed, or “bean”, are produced by several species of the small evergreen bush of the genus \textit{Coffee}. The two most commonly grown are the highly regarded \textit{Coffee arabica}, and the ‘robusta’ form of the hardier \textit{Coffee canephora}.\(^{[42]}\)
Appendix 1. Alkaloids

from the bean of the coffee plant (Figure A1.10) and the leaves of the tea bush, as well as from various foods and drinks containing products derived from the kola nut (Figure A1.11). In humans, caffeine acts as a central nervous system (CNS) stimulant, temporarily warding off drowsiness and restoring alertness. Caffeine is the world’s most widely consumed legal psychoactive substance. Furthermore, caffeine has diuretic properties when administered in sufficient doses. Regular users, however, develop a strong tolerance to this effect. Caffeine is metabolised in the liver into three metabolic dimethylxanthines, each of which has its own effects on the body: paraxanthine (84%), theobromine (12%), and theophylline (4%).[3n, 43, 44]

Figure A1.11. Kola nuts, the seeds of *Cola nitida* and *Cola acuminata* (Malvaceae), trees native to the tropical rainforests of Africa.

Paraxanthine is not produced by plants and is only observed in nature as a metabolite of caffeine in animals. It has the effect of increasing lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma.[3n, 43, 46]

Theobromine is the primary alkaloid found in cocoa and chocolate. the amount of theobromine in cocoa powder can vary from 2% to at least 10% usually having higher concentrations in “dark” than “milk” chocolate. Theobromine dilates blood vessels and increases urine volume.[3n, 43, 47]

Theophylline is naturally found in tea leaves and cocoa beans, although only in trace amounts significantly less than therapeutic doses. It relaxes smooth muscles of the bronchi, and is used to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels attained from caffeine metabolism.[3n, 43, 48]

Figure A1.12. Structures of the most familiar xanthine alkaloids.

• Ergoline alkaloids

The structural skeleton of ergoline is contained in a diverse range of alkaloids. Ergoline alkaloids were first isolated from ergot, a fungus that infects grain and causes the disease ergotism which is distinguished by convulsive and gangrenous symptoms. Furthermore, ergoline alkaloids are found in the seeds of members of the Convolvulaceae plant family including the Mexican species *Rivea corymbosa*, the Hawaiian baby woodrose (*Argyreia nervosa*) as well as the morning glory species *Ipomoea violacea* and *I. tricolor*. The principal alkaloids in these seeds are ergine and its optical isomer isoergine, with several other lysergic acid derivatives present in lesser amounts.

Natural and synthetic ergoline derivatives are used clinically for the purpose of vasoconstriction and in the treatment of migraines and Parkinson’s disease. Perhaps the most famous ergoline derivative is the psychedelic drug LSD.[3n, 49–52]
Appendix 1. Alkaloids

Figure A1.13. Ergot kernels (sclerota) on rye spikes. Ergot or ergot fungi refers to a group of fungi of the Claviceps genus. The most prominent member of this group is *Claviceps purpurea* (Clavicipitaceae). This fungus grows on rye and related plants and produces alkaloids that can cause “ergotism” in humans and other mammals who consume grains contaminated with its fruiting structure. The ergot sclerotium contains high concentrations (up to 2% of dry mass) of the alkaloid ergotamine, and other alkaloids of the ergoline group that are biosynthesised by the fungus. Medicinal usage of ergot fungus began in the 16th century to induce childbirth, hence its German name “Mutterkorn”.\(^{[56]}\)

![Ergotamine](image)

Ergotamine is an ergopeptine and part of the ergoline alkaloid family. It is the principal alkaloid produced by the ergot fungus, *Claviceps purpurea*, and related fungi in the Clavicipitaceae family. Ergotamine is used medicinally for treatment of acute migraine attacks (sometimes in combination with caffeine). The antimigraine effect is due to constriction of the intracranial extracerebral blood vessels. Ergotamine was first isolated from the ergot fungus by Arthur STOLL at SANDOZ laboratories in 1918 and marketed as Gynergen in 1921 to prevent post-partum haemorrhage (bleeding after childbirth). It is also a precursor for psychoactive drug LSD.\(^{[3q, 49−51, 53−55]}\)

Figure A1.14. *Ipomoea violacea* is a perennial species of the morning glory genus, that occurs throughout the tropics, growing in coastal regions. It is commonly called Beach Moonflower or Sea Moonflower as the flowers open at night. The seeds of *I. violacea* contain various ergoline alkaloids, the most dominant being ergine and ergometrine. The alkaloids are produced not by the plant itself, but by fungi associated with it, and are transmitted to the plant via its seeds.

![Ipomoea violacea](image)

Ergine, also known as D-lysergic acid amide (LSA) or D-lysergamide, and ergometrine (ergonovine), are two of the principle alkaloids that occur in some fungi of the Claviceps genus and members of the Convolvulaceae plant family including *Rivea corymbosa*, *Argyreia nervosa* (Hawaiian baby woodrose) *Ipomoea tricolor*, and *I. violacea*. Furthermore, ergine has also been found in high concentrations of 20 µg/g dry weight in the grass *Stipa robusta* (sleepygrass) infected with an *Acremonium* endophytic fungus together with other ergot alkaloids. Ergine is a precursor for the synthetic hallucinogenic drug LSD, however, its own psychedelic activity is not very distinctive, especially when compared to LSD. Ergometrine has found a medical use in obstetrics to facilitate delivery of the placenta and to prevent bleeding after childbirth by causing smooth muscle tissue in the blood vessel walls to narrow, thereby reducing blood flow.\(^{[3q, 50, 51, 53−57, 58]}\)
Appendix 1. Alkaloids

- Strychnine and Brucine

Strychnos nux-vomica (Loganiaceae) is a deciduous tree native to India and Southeast Asia. It is a major source of the highly poisonous alkaloids strychnine and brucine, derived from the seeds inside the tree’s round, green to orange fruit. The seeds contain approximately 1.5% strychnine.

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\begin{align*}
\text{Figure A1.15.} & \quad \text{[64]} \\
\text{Strychnos nux-vomica (Loganiaceae) is a deciduous tree native to India and Southeast Asia. It is a major source of the highly poisonous alkaloids strychnine and brucine, derived from the seeds inside the tree’s round, green to orange fruit. The seeds contain approximately 1.5% strychnine.} & \quad \text{[65]}
\end{align*}
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\[
\begin{align*}
\text{Figure A1.16.} & \quad \text{[65]} \\
\text{Dried Strychnos nux-vomica seeds.} & \quad \text{[60, 61, 62]}
\end{align*}
\]

\[
\begin{align*}
\text{Figure A1.16.} & \quad \text{[65]} \\
\text{Dried Strychnos nux-vomica seeds.} & \quad \text{[60, 61, 62]}
\end{align*}
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\begin{align*}
\text{Figure A1.15.} & \quad \text{[64]} \\
\text{Strychnos nux-vomica (Loganiaceae) is a deciduous tree native to India and Southeast Asia. It is a major source of the highly poisonous alkaloids strychnine and brucine, derived from the seeds inside the tree’s round, green to orange fruit. The seeds contain approximately 1.5% strychnine.} & \quad \text{[65]}
\end{align*}
\]

\[
\begin{align*}
\text{Figure A1.16.} & \quad \text{[65]} \\
\text{Dried Strychnos nux-vomica seeds.} & \quad \text{[60, 61, 62]}
\end{align*}
\]

Strychnine is a very toxic, colourless crystalline alkaloid used as a pesticide, particularly for killing small vertebrates such as birds and rodents. Strychnine causes muscular convulsions and eventually death through asphyxia or sheer exhaustion. Although it is best known as a poison, small doses of strychnine were once used in medications as a stimulant, as a laxative, and as a treatment for other stomach ailments. The most common source are the seeds of the tree Strychnos nux-vomica. Strychnine is one of the most bitter substances known. Its taste is detectable in concentrations as low as 1 ppm.\[^{[3r, 60–62]}\]

\[
\begin{align*}
\text{Figure A1.15.} & \quad \text{[64]} \\
\text{Strychnos nux-vomica (Loganiaceae) is a deciduous tree native to India and Southeast Asia. It is a major source of the highly poisonous alkaloids strychnine and brucine, derived from the seeds inside the tree’s round, green to orange fruit. The seeds contain approximately 1.5% strychnine.} & \quad \text{[65]}
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\[
\begin{align*}
\text{Figure A1.16.} & \quad \text{[65]} \\
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\begin{align*}
\text{Figure A1.15.} & \quad \text{[64]} \\
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\[
\begin{align*}
\text{Figure A1.16.} & \quad \text{[65]} \\
\text{Dried Strychnos nux-vomica seeds.} & \quad \text{[60, 61, 63]}
\end{align*}
\]

The alkaloid brucine is isostructural to strychnine with methoxy groups at the aromatic ring. Despite the structural relationship to strychnine, it is slightly less poisonous as it only causes paralysis of the peripheral motor nerves. For medicinal purposes, brucine is primarily used in the regulation of high blood pressure and other comparatively benign cardiac ailments.\[^{[3s, 60, 61, 63]}\]

\[
\begin{align*}
\text{Figure A1.15.} & \quad \text{[64]} \\
\text{Strychnos nux-vomica (Loganiaceae) is a deciduous tree native to India and Southeast Asia. It is a major source of the highly poisonous alkaloids strychnine and brucine, derived from the seeds inside the tree’s round, green to orange fruit. The seeds contain approximately 1.5% strychnine.} & \quad \text{[65]}
\end{align*}
\]

\[
\begin{align*}
\text{Figure A1.16.} & \quad \text{[65]} \\
\text{Dried Strychnos nux-vomica seeds.} & \quad \text{[60, 61, 63]}
\end{align*}
\]

Class 2 – Alkaloids with N-atoms in an exocyclic position including aliphatic amines. These alkaloids are also called “protoalkaloids” and originate from amino acids as well. Prominent examples are the β-phenylethylamine derivatives ephedrine and mescaline as well as fungal alkaloid muscarine.
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- **Mescaline**

Mescaline is a naturally occurring psychedelic phenethylamine alkaloid, used mainly as an entheogen. It occurs naturally in the peyote cactus (*Lophophora williamsii*), the San Pedro cactus (*Echinopsis pachanoi*) and the Peruvian Torch cactus (*Echinopsis peruviana*), as well as in a number of other members of the Cactaceae plant family. Dried peyote has been used for over 3000 years by Native Americans in Mexico religious ceremonies. Novelist Aldous HUXLEY described his experience with mescaline in *The Doors of Perception*; Hunter S. THOMPSON recounted his use of mescaline in *Fear and Loathing in Las Vegas*.66

![Mescaline](image)

**Figure A1.17**. Peyote, (*Lophophora williamsii*), is a small, spineless cactus. It is native to southwestern Texas and through Mexico and contains a large spectrum of phenethylamine alkaloids of which the principal one is mescaline. The mescaline content of *L. williamsii* is about 0.4% fresh (undried) and 3-6% dried.

- **Ephedrine and Pseudoephedrine**

Ephedrine is an alkaloid derived from various plants in the genus *Ephedra* (family *Ephedraceae*). It is a sympathomimetic amine commonly used as a stimulant, appetite suppressant, concentration aid, decongestant, and to treat hypotension associated with anaesthesia. In traditional Chinese medicines, the herb má huáng (*Ephedra sinica*) contains ephedrine and pseudoephedrine as its principal active constituents.3, 68, 69

The salts pseudoephedrine hydrochloride and pseudoephedrine sulfate are found in many over-the-counter preparations either as a single ingredient as a nasal/sinus decongestant and stimulant, or, more commonly, in combination with nonsteroidal antiinflammatory drugs (e.g., aspirin, ibuprofen, paracetamol, etc.). Pseudoephedrine is a diastereomer of ephedrine and is readily reduced into methamphetamine or oxidised into methcathinone.70

![Ephedra](image)

**Figure A1.18**. *Ephedra sinica* (Ephedraceae). *Ephedra* is a genus of gymnosperm shrubs, the only genus in the family *Ephedraceae*. Plants of the *Ephedra* genus, including *E. sinica* and others, have traditionally been used by indigenous people for a variety of medicinal purposes, including treatment of asthma, hay fever, and the common cold.
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**Class 3** – Polyamine alkaloids are derivatives of the polyamines putrescine, spermidine and spermine.[72] Some examples are shown in Figure A1.19 below.

![Polyamine Alkaloids](image)

**Figure A1.19.** The polyamines putrescine, spermidine and spermine as well as some examples of polyamine alkaloids.

**Class 4** – Peptide alkaloids are cyclic peptides containing a basic nitrogen atom in a side chain. These alkaloids are further distinguished by the number of atoms forming the peptide ring.[3x] Examples are shown in Figure A1.20.

![Peptide Alkaloids](image)

**Figure A1.20.** Examples of peptide alkaloids.
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Class 5 – Terpene and steroid alkaloids are alkaloid-like compounds which do not originate from amino acids. Examples are the diterpene-alkaloid delphinine and steroidal alkaloid batrachotoxin.

Delphinine is a toxic alkaloid found in plants from the Delphinium family. It is acting as an allosteric modulator of voltage gated sodium channel and producing hypotension (low blood pressure), bradycardia (‘heart slowness’) and cardiac arrhythmia. These effects make it highly poisonous, but in very small doses, it has some uses in herbal medicine.[81–84]

Figure A1.21. \([85]\) Delphinium elatum-hybrids. Delphinium is a genus of about 300 species of perennial flowering plants in the buttercup family Ranunculaceae. The common name is larkspur; Other names are lark’s heel, lark’s claw and knight’s spur. The scientific name comes from the Latin word for dolphin, alluding to the shape of the opening flower. All parts of the plant contain the alkaloid delphinine and are very poisonous, causing vomiting when eaten, and death in larger amounts. In small amounts, extracts of the plant have been used in herbal medicine. Larkspur, especially tall larkspur, is a significant cause of cattle poisoning on rangelands in the western United States. Death is through cardiotoxic and neuromuscular blocking effects, and can occur within a few hours of ingestion.

Figure A1.22. \([89]\) Phyllobates terribilis (Dendrobatidae), the Golden Poison Frog or the Golden Dart Frog, endemic to the Pacific coast of Colombia. The golden poison frog is not venomous, but poisonous; venomous animals use their toxins to kill their prey. Like most poison dart frogs, \(P. \text{terribilis}\) uses poison only as a self-defence mechanism and not for killing prey. The most venomous animal is the box jellyfish, which is only slightly less toxic than \(P. \text{terribilis}\).\([90]\)

Batrachotoxin is an extremely potent cardiotoxic and neurotoxic steroidal alkaloid found in certain species of the frog family Dendrobatidae, especially \(Dendrobates\) and \(Phyllobates\), furthermore in melyrid beetles, and birds (\(Pitohui\), \(Ifrita kowaldi\), \(Colluricincla megarrhyncha\)). The name comes from the Greek words 'batrachos' meaning frog, and 'toxine' meaning poison. The Golden Poison Frog's skin is drenched in this alkaloid poison which prevents nerves from transmitting impulses, leaving the muscles in an inactive state of contraction. However, the frog does not produce batrachotoxin itself. It is believed that the frog gets the poison from eating beetles or other insects in their native habitat.\([39, 86–88]\)
Appendix 1. Alkaloids

A1.3 Medicinal Applications

The use of alkaloid-containing plant parts in traditional folk medicine has a long history, and thus, when the first alkaloids were synthesised in the 19th century, they immediately found application in clinical practice. Many alkaloids are still used in medicine, usually in form of their salts, including the following:

- **Reserpine**

  ![Reserpine](image)

  The indole alkaloid reserpine possesses antipsychotic and antihypertensive efficacy and is used for the control of high blood pressure and for the relief of psychotic symptoms. Furthermore, it is also used to treat symptoms of dyskinesia in patients suffering from Huntington’s disease. The antihypertensive actions of reserpine result from its ability to deplete catecholamines and other monoamine neurotransmitters from the peripheral sympathetic nerve endings. These substances are usually involved in controlling heart rate, force of cardiac contraction and peripheral resistance. Reserpine was first isolated in 1952 from the dried root of *Rauwolfia serpentina* (Indian snakeroot), and had been used for centuries in India for the treatment of insanity and as a tranquilliser. In the management of hypertension, however, it is rarely used nowadays due to its numerous interactions and side effects.\[^{3z, 91, 92}\]

- **Squalamine**

  ![Squalamine](image)

  The steroidal alkaloid squalamine, which was originally isolated from stomach tissues of the dogfish shark *Squalus acanthias*, is used in medicine as an effective broadspectrum antibiotic. Furthermore, it has been found recently that it possesses a powerful antiangiogenesis effect, meaning it inhibits the growth of blood vessels. Because of this function, squalamine lactate is in the process of being tested as a treatment of fibrodysplasia ossificans progressiva, a rare disease where connective tissue will ossify when damaged.\[^{94, 95, 96}\]
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- **Tubocurarine**

  ![Tubocurarine structure]
  
  Tubocurarine (also known as D-tubocurare) is a mono-quaternary alkaloid obtained from the bark of the South American plant *Chondrodendron tomentosum*. It is used as a neuromuscular-blocking drug or skeletal muscle relaxant, administered adjunctively in anaesthesia to provide skeletal muscle relaxation during surgery or mechanical ventilation. The word curare comes from the South American Indian name for the arrow poison "ourare". Tubocurarine is so called because the plant samples containing the curare were stored and shipped to Europe in tubes.\[^{[98-100]}\]

- **Vincamine**

  ![Vincamine structure]
  
  Vincamine is a peripheral vasodilator that increases blood flow to the brain. It is an indole alkaloid found in the leaves of *Vinca minor*, comprising about 25-65% of the indole alkaloids found in *Vinca minor* by weight. Vincamine is often used as a nootropic agent (memory enhancer or cognitive enhancer) to combat the effects of ageing.\[^{[102-104]}\]

- **Ajmaline**

  ![Ajmaline structure]
  
  Ajmaline is a class la cardiac antiarrhythmic agent. Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmia). The compound was first isolated in 1931 from the roots of *Rauwolfia serpentina* and was named after Hakim Ajmal KHAN, one of the most illustrious practitioners of Unani medicine in South Asia.\[^{[106-108]}\]
Appendix 1. Alkaloids

- **Codeine**

  ![Codeine](image)

  Codeine or 3-methylmorphine is an opiate used for its analgesic (pain relief, from Greek *an-* = "without" and *algos* = "pain"), antitussive (cough suppressant), and antidiarrheal (relief for diarrhoea) properties. The name codeine is derived from the Greek word *kodeia* for "poppy head". Codeine is considered a prodrug, since it is metabolised *in vivo* to the primary active compounds morphine and codeine-6-glucuronide.\[^{[3ee, 110, 111]}\]

- **Emetine**

  ![Emetine](image)

  Emetine is used as both an antiprotozoal drug and a powerful emetic (hence the name). It is the principal alkaloid isolated from the ipecac root (*Psychotria ipecacuanha*), a species of flowering plant in Rubiaceae family, native to Brazil. Early use of emetine was in the form of oral administration of the ipecac root extract ("syrup of ipecac") to induce vomiting. Although it is a potent antiprotozoal, the drug also can interfere with muscle contractions, leading to cardiac failure in some cases.\[^{[3ff, 113-116]}\]\[^{[113, 114, 115, 116]}\]

- **Galanthamine**

  ![Galanthamine](image)

  Galanthamine is used for the treatment of mild to moderate Alzheimer's disease and various other memory impairments like vascular dementia. Galanthamine is a competitive and reversible cholinesterase inhibitor. It reduces the action of AChE and therefore tends to increase the concentration...
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of the neurotransmitter acetylcholine in the brain. It is hypothesised that this action might relieve some of the symptoms of Alzheimer’s. Natural source of Galanthamine are the bulbs and flowers of *Galanthus caucasicus* (Caucasian snowdrop), *Galanthus nivalis* (common snowdrop) (Amaryllidaceae) and related genera.[118]

- **Physostigmine**

![(-)-Physostigmine (Eserine)](image)

Physostigmine is a parasympathomimetic agent, specifically, a reversible cholinesterase inhibitor alkaloid, originally isolated from the Calabar bean (*Physostigma venenosum*). It is also known as eserine, derived the West African name for the Calabar bean “éséré”. Physostigmine is used to treat myasthenia gravis (an autoimmune neuromuscular disease leading to fluctuating muscle weakness), glaucoma, Alzheimer’s disease and delayed gastric emptying. It has been shown to improve the short term memory.[120–122]

- **Quinine**

![(-)-Quinine](image)

Quinine occurs naturally in the bark of the cinchona tree, and possesses antipyretic (fever-reducing), antimalarial, analgesic (painkilling), antiinflammatory properties. It is a stereoisomer of quinidine which, unlike quinine, is an antiarrhythmic. Quinine was the first effective treatment for malaria caused by *Plasmodium falciparum*, and remained the antimalarial drug of choice until the 1940s, when other more effective drugs replaced it. Nevertheless, quinine is still used to treat the disease in certain critical situations, i.e., as in impoverished regions.[124–129]

Many synthetic and semisynthetic drugs are structural modifications of alkaloids, which were designed to enhance or change the primary effect of the alkaloid and reduce unwanted side effects. For example, naloxone, an opioid receptor antagonist, is a derivative of thebaine[130] which is a constituent of opium. Hydrocodone is another semi-synthetic opioid derived from either of two naturally occurring opiates: codeine and thebaine. It is used to treat moderate to severe pain and as an antitussive to treat cough.
Appendix 1. Alkaloids

Prior to the development of relatively low-toxic synthetic pesticides, some alkaloids, such as the salts of nicotine and anabasine, were used as insecticides in agriculture. However, their use was limited due to their toxicity to humans.\(^\text{[133]}\)

Nicotine is named after the tobacco plant \textit{Nicotiana tabacum}, which in turn is named after Jean NICOT DE VILLEMAIN, French ambassador in Portugal, who sent plant and seeds from Brazil to Paris in 1560 and promoted their medicinal use. It functions as an antiherbivore chemical with particular specificity to insects; therefore nicotine was widely used as an insecticide in the past. In low concentrations (an average cigarette yields about 1 mg of absorbed nicotine), the substance acts as a stimulant in mammals and is the main factor responsible for the dependence-forming properties of tobacco smoking.\(^\text{[3kk, 134, 135]}\)\(^\text{[136,137, 138, 139]}\)

Anabasine is a pyridine alkaloid found in the tobacco tree \textit{Nicotiana glauca}, a close relative of the common tobacco plant \textit{Nicotiana tabacum}. Anabasine is a nicotinic acetylcholine receptor agonist. In high doses, it produces a depolarising block of nerve transmission, which can cause symptoms similar to those of nicotine poisoning and, ultimately, death by cardiac arrest.\(^\text{[3l, 136–139]}\)

In modern society preparations of plant extracts containing alkaloids and later pure alkaloids have a long history of abuse as psychoactive drugs. Cocaine and cathinone are stimulants of the central nervous system (CNS).\(^\text{[141]}\) Morphine and codeine are strong narcotic pain killers.\(^\text{[142]}\) Mescaline and many of the indole alkaloids such as psilocybine, dimethyltryptamine and ibogaine have hallucinogenic effects.
Psilocybine (O-phosphoryl-4-hydroxy-\(N,N\)-dimethyltryptamine) is the prodrug for the classical hallucinogen psilocine (4-hydroxy-\(N,N\)-dimethyltryptamine), the active metabolite of psilocybine, which responsible for the psychoactive effects of the drug. Psilocybine is rapidly dephosphorylated in the body to psilocine which then acts as a partial agonist to several receptors involved with the neurotransmission of serotonin.\[^{[139, 143, 144]}\]

Psilocybe \(\text{zapotecorum}\) (Strophariaceae), the “magic mushroom”, source of the alkaloid psilocybine. \textit{Psilocybe} is a genus of small mushrooms growing worldwide. This genus is best known for its species with psychedelic or hallucinogenic properties, widely known as "magic mushrooms", though the majority of species does not contain hallucinogenic compounds. Psilocybine-containing mushrooms are used both recreationally and traditionally, for spiritual purposes as entheogens.

### A1.4 Alkaloids as Precursors of Psychoactive Drugs

Some alkaloids are also used as starting materials for semisynthetic psychoactive drugs. For example, ephedrine and pseudoephedrine which do not possess strong psychoactive effects themselves, are precursors to generate the stimulants methcathinone and methamphetamine. Further examples include the bis-acetylated derivative of the analgesic morphine known as the infamous heroin, and the diethylamide of lysergic acid which, in turn, is a derivative of the ergot alkaloid ergine.

- **Methamphetamine**

  Colloquially known as "meth" or "crystal meth", methamphetamine (desoxyephedrine) is a psycho-stimulant of the phenethylamine and amphetamine class of drugs. It increases alertness, concentration, energy, and in high doses, can induce euphoria, enhance self-esteem, and increase libido. Methamphetamine has high potential for abuse and addiction by activating the psychological reward system via triggering a cascading release of dopamine and norepinephrine in the brain. Methamphetamine is illicitly synthesised and then sold in a crystalline form resembling small shards of odourless, bitter-tasting crystals; leading to the colloquial nickname "crystal meth". Then again, methamphetamine has certain medical uses such as treatment of morbid obesity, narcolepsy and ADHD.\[^{[146]}\]
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- **Methcathinone**

Methcathinone is a psychoactive stimulant, sometimes used as a recreational drug and considered addictive. It is a potent CNS stimulant and dopamine re-uptake inhibitor. Chronic high dosage use may result in acute mental confusion ranging from mild paranoia to psychosis. Methcathinone is most commonly made by the oxidation of ephedrine or pseudoephedrine with potassium permanganate as the oxidant.[147]

- **Heroin**

Heroin (diacetylmorphine), also known as diamorphine or morphine diacetate, is an opioid analgesic synthesised via the bis-acetylation of morphine with acetic anhydride. When used in medicine it is typically applied as an analgesic to treat severe pain. However, as with other opioids, diacetylmorphine is also severely abused as a recreational drug. Frequent and regular administration is associated with tolerance and physical dependence, which finally develops into acute addiction. Ironically, the development of heroin originates in the prevention of morphine addiction. From 1898 through to 1910, the German drug company Bayer marketed diacetylmorphine as an over the counter drug under the trademark name Heroin. The name was derived from the Greek word “Heros” because of its perceived “heroic” effects upon a user. It was chiefly developed as a non-addictive morphine substitute and cough suppressant since morphine, applied as cough medicine at the time, was persistently abused as a recreational drug. However, contrary to Bayer’s advertising as “non-addictive”, it was discovered that heroin rapidly metabolises into morphine in the brain. As such, heroin is essentially a quicker acting form of morphine, and it soon had one of the highest rates of dependence amongst its users. Today, diacetylmorphine is prescribed under the name “Diamorphine” as a strong analgesic in a few countries including the United Kingdom. Its use includes the treatment for acute pain, such as in severe physical trauma, myocardial infarction, post-surgical pain, and chronic pain, including end-stage cancer and other terminal illnesses. In other countries the use of heroin is forbidden by law, and it is more common to use morphine or other strong opioids in these situations.[14n, 148]

- **Lysergic acid diethylamide (LSD)**

Lysergic acid diethylamide, also known as lysergide and colloquially as “acid”, is a semisynthetic psychedelic drug of the ergoline alkaloid family, well known for its psychological effects which can include altered thinking processes, closed and open eye visuals, an altered sense of time and synaesthesia. It is used mainly as an entheogen, recreational drug, and as an agent in psychedelic therapy. LSD is non-addictive, not known to cause brain damage, and has extremely low toxicity relative to dose, although in rare cases adverse psychiatric reactions such as anxiety or delusions are possible. The commonly used acronym “LSD” comes from its early code name LSD-25, which is an abbreviation for the German “Lysergsäurediethylamid” followed by a sequential number. LSD is an ergoline
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derivative. It is commonly synthesised by reacting diethylamine with an activated form of lysergic acid. Lysergic acid, in turn, is made by alkaline hydrolysis of lysergamides like ergotamine, a substance derived from the ergot fungus, or from ergine (lysergic acid amide, LSA), a compound that is found in morning glory (Ipomoea tricolor) and Hawaiian baby woodrose (Argyreia nervosa) seeds. LSD was first synthesised in 1938 by Swiss chemist Albert Hofmann at the Sandoz Laboratories in Basel, Switzerland as part of a research program searching for medically useful ergot alkaloid derivatives. LSD’s psychedelic properties were discovered 5 years later when Hofmann himself accidentally ingested an unknown quantity of the chemical.[3q, 149]

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[3] M. Hesse, Alkaloids – Nature’s Curse of Blessing?, Verlag Helvetica Chimica Acta Zürich – Wiley-VCH 2002, (a) pp. 1–3; (b) p. 5; (c) pp. 5, 33, 303, 305, 310, 315, 316, 351, 352, 354; (d) pp. 33, 35, 303, 352, 354, 365; (e) pp. 76, 81, 82, 309, 329, 330; (f) pp. 329, 330; (g) p. 165 (Note 31); (h) p. 396; (i) pp. 43, 44, 284; (j) pp. 13, 258; (k) pp. 8, 31, 118–125, 153, 172, 185, 203–205, 301, 310, 315, 316, 326, 327, 329; (l) p. 63; (m) pp. 65, 66; (n) pp. 73, 111 (Note 83), 305, 316, 367–373, 378; (o) p. 73; (p) pp. 73, 111 (Note 83), 309, 378, 379; (q) pp. 12, 15, 29, 84, 107 (Note 27), 239, 308, 330–337; (r) pp. 7, 19, 21, 198, 230, 231, 315, 317, 319–321; (s) pp. 315, 319; (t) pp. 76, 258; (u) p. 61; (v) pp. 285, 286; (w) pp. 82, 83; (x) p. 84; (y) pp. 295 – 297; (z) pp. 26, 27, 107 (Note 23), 308; (aa) p. 297; (bb) pp. 101, 113 (Note 110), 308; (cc) pp. 22, 107 (Note 16), 192, 194, 224, 234 (Note 32), 309; (dd) pp. 23, 24, 107 (Note 19), 303; (ee) pp. 97–99, 109 (Note 61), 202, 273, 275, 276, 301, 305, 315; (ff) pp. 41, 109 (Note 47), 246, 253, 254, 316, 318; (gg) p. 53; (hh) pp. 28, 258, 309; (ii) pp. 3, 57, 110 (Note 68), 246, 253, 255, 309, 317, 318, 366, 367; (jj) pp. 198, 202 (Note 37), 269, 270, 273–276, 279, 281, 301, 302, 315; (kk) pp. 32, 33, 108 (Note 34), 124, 125, 200, 292, 316, 351, 364, 365; (ll) pp. 32, 33, 292; (mm) pp. 15, 16; (nn) pp. 198, 199, 347, 349.
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[15] URL: http://www.giftinfo.uni-mainz.de/gift_de/pflanzen/Tollkirsche.html [22/08/2012]


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[34] URL: http://en.wikipedia.org/wiki/Hygrine [22/08/2012]


(b) N.J. Leonard, Senecio Alkaloids, The Alkaloids: Chemistry and Physiology 1965, 6, 35–121.


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[56] URL: http://de.wikipedia.org/wiki/Mutterkorn [14/08/2012]
[57] URL: http://de.wikipedia.org/wiki/Ergin [09/01/2013]
[58] URL: http://de.wikipedia.org/wiki/Ergometrin [09/01/2013]
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[70] URL: http://de.wikipedia.org/wiki/Pseudoephedrin [22/08/2012]


[73] URL: http://de.wikipedia.org/wiki/Putrescin [22/08/2012]


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[97] URL: http://2.bp.blogspot.com/_L2iPRVDhLQY/SEHz-efZ3mI/AAAAAAAAJZ8/Or-L2EGBvQ0/s400/Chondrodendron+tomentosum++Curare.jpg [22/08/2012]


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[142] URL: http://de.wikipedia.org/wiki/Morphin [22/08/2012]
[146] URL: http://de.wikipedia.org/wiki/Methamphetamin [22/08/2012]
[147] URL: http://de.wikipedia.org/wiki/Methcathinon [22/08/2012]
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Figure A2.4. $^{13}$C NMR spectrum (125 MHz, CDCl$_3$) of 
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(−)-(2S,3S,4S,5S)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol.

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(−)-(2S,3S,4S,5S)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol.
Appendix 2. Selected IR and NMR Spectra

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$(-)$-(2S,3S,4S,5S)-2,5-bis(hydroxymethyl)pyrrolidine-3,4-diol.

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(–)-(2S,3S,4S)-2-hydroxymethylpyrrolidine-3,4-diol.
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(→)(2S,3S,4S)-2-hydroxymethylpyrrolidine-3,4-diol.
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Figure A2.42. $^{13}$C NMR spectrum (125 MHz, CD$_3$OD) of $(-)-(5S)$-phenethyl-L-AB1 (9/8), $(-)-(2S,3S,4S,5S)$-2-hydroxymethyl-5-phenethylpyrrolidine-3,4-diol.
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Figure A2.49. $^{13}$C NMR spectrum (125 MHz, CD$_3$OD) of (–)-10'-deoxobroussonetine C trifluoroacetate, (–)-(2S,3S,4S,5S)-3,4-dihydroxy-2-(hydroxymethyl)-5-(13'-hydroxytridecyl)pyrrolidinium trifluoroacetate.
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(−)-(2S,3S,4S,5S)-2-hydroxymethyl-5-(13'-hydroxytridecyl)pyrrolidine-3,4-diol.

Figure A2.53. $^{13}$C NMR spectrum (125 MHz, C$_5$D$_5$N) of (−)-10'-deoxobroussonetine C (9/1).

(−)-(2S,3S,4S,5S)-2-hydroxymethyl-5-(13'-hydroxytridecyl)pyrrolidine-3,4-diol.
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with (top) and without (bottom) wave number annotations.
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**Figure A2.63.** $^{13}$C NMR spectrum (125 MHz, CD$_3$OD) of (–)-1’-epi-10’-deoxobroussonetine E (9/29),
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(–)-(2S,3S,4S,5S)-2-(hydroxymethyl)-5-(9′-(tetrahydrofuran-2′-yl)nonyl)pyrrolidine-3,4-diol.

Figure A2.67. $^{13}$C NMR spectrum (125 MHz, CD$_3$OD) of (–)-broussonetine C2 (10/23).

(–)-(2S,3S,4S,5S)-2-(hydroxymethyl)-5-(9′-(tetrahydrofuran-2′-yl)nonyl)pyrrolidine-3,4-diol.
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