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Synthesis of novel compounds based on reticuline scaffold for new drugs discovery

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Synthesis of Novel Compounds Based on the Reticuline Scaffold for New Drugs Discovery.

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

Doctor of Philosophy

From

University of Wollongong



Tam-Dan (Uta) Batenburg-Nguyen

B. Adv. Med Chem (Hons)

Department of Chemistry

University of Wollongong

Wollongong, Australia

December, 2005

Declaration

I, Tam-Dan (Uta) Batenburg-Nguyen hereby declare that all materials presented in this thesis, submitted in the fulfillment of the requirements for the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, are exclusively of my own work. These materials have not been submitted for qualifications at any other academic institution, unless otherwise referenced or acknowledged.

Tam-Dan (Uta) Batenburg-Nguyen

December, 2005

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List of Abbreviations.

α_1, α_2 receptor	Alpha adrenoceptors
A ₁ , A _{2A} , A ₃	Adenosine receptors
Ag ₂ CO ₃	Silver carbonate
AgOAc	Silver acetate
AgOCOCF ₃	Silver trifluoroacetate
Ag ₃ PO ₄	Silver phosphate
APV	Amprenavir
ATPase	Adenosine 5'-Triphosphatase
AT ₁ receptor	Angiotensin receptor
AZT	Azidothymidine
β_1 receptor	Beta adrenoceptor
B ₂ receptor	Bradykinin receptor
BBi	Bisbenzylisoquinoline
Boc	<i>tert</i> -Butoxycarbonyl group
<i>n</i> -BuLi	<i>n</i> -Butyl lithium
BZD receptor	Benzodiazepine receptor
CS	(<i>S</i>)-Canadine synthase
CC ₅₀	Cytotoxic concentration (the concentration that was required to reduce cell growth by 50 %)
CCK receptor	Cholecystokinin receptor
CDCl ₃	Deuteriochloroform
CH ₃ CN	Acetonitrile
CH ₃ OH	Methanol

CI ⁺	Chemical Ionisation
CM	Cross metathesis
CNS	Central Nervous System
CXCR2, CCR1	Chemokine receptors
COR	Condeinone reductase
CNMT	(<i>S</i>)-Coclaurine- <i>N</i> -methyltransferase
gCOSY	Correlated Spectroscopy
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
CuI	Copper Iodide
CYP80P	Cytochrome P ₄₅₀ -dependent hydroxylase
d	Days
D1, D2S receptors	Dopamine receptors
DA transporter	Dopamine transporter
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDC	2,3'- Dideoxycytidine
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMG	<i>N,N</i> -Dimethylglycine
DOP receptor	Delta opiate receptor
DPPP	1,3-Bis(diphenylphosphino)propane
<i>E. coli</i>	<i>Escherichia coli</i>
EC ₅₀	Effective concentration (the concentration of an agonist that produces 50 % of the maximum possible response for that agonist)

EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
<i>E. faecalis</i>	<i>Enterococcus faecalis</i>
EFV	Efavirenz
EI ⁺	Electron impact
ESMS	Electrospray mass spectrometry
ES ⁺	Electrospray (positive ion mode)
ET _A receptor	Endothelin receptor
Et ₃ N	Triethylamine
EtOAc	Ethyl acetate
GFP	Green fluorescent protein
GABA receptor	Gamma-amino butyric acid receptor
GAL ₂ receptor	Galanin receptor
h	Hour
H1, H2 receptors	Histamine receptors
HBr	Hydrogen bromide
HCl	Hydrochloric acid
HIV	Human Immunodeficiency Virus
HOAc	Acetic acid
HOBt	1-Hydroxy-1H-benzotriazole
HRMS	High resolution mass spectrometry
gHMBC	Heteronuclear Multiple Quantum Correlation
gHSQC	Heteronuclear Single Quantum Correlation
5HT receptors	5-Hydroxytryptamine, serotonin receptors
HIV-tat	Human Immunodeficiency Virus-transactivator

IC ₅₀	Inhibitory concentration (the concentration required to inhibit cell growth by 50 %)
K ₂ CO ₃	Potassium carbonate
KF	Potassium fluoride
K ₂ OsO ₄ ·2H ₂ O	Potassium osmate-dihydrate
KOP receptor	Kappa opiate receptor
LiAlH ₄	Lithium aluminium hydride
μM	Micromolar
M ₂ , M ₃ receptors	Muscarinic receptors
MDR	Multiple-Drug Resistance
min	Minutes
ML ₁ receptor	Melatonin receptor
MOP receptor	Mu opiate receptor
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NADPH	Nicotinamide adenine dinucleotide phosphate
NaHCO ₃	Sodium bicarbonate
NaBH ₄	Sodium borohydride
NaCNBH ₃	Sodium cyanoborohydride
Na ₂ EDTA	Disodium ethylenediaminetetraacetic acid
NaIO ₄	Sodium metaperiodate
nM	Nanomolar
NaOH	Sodium hydroxide
NaOAc	Sodium acetate
NE receptor	Norepinephrine receptor
NH ₃	Ammonia

NIS	<i>N</i> -Iodosuccinimide
NK ₃ receptor	Neurokinin receptor
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
NT1 receptor	Neurotensin receptor
NVP	Nevirapine
6OMT	(<i>S</i>)-Norcoclaurine-6- <i>O</i> -methyltransferase
4'OMT	4'- <i>O</i> -Methyltransferase
ORL1 receptor	Opiate receptor-like receptor
<i>P.aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
Pet. Spirit	Petroleum Spirit
Pd(OAc) ₂	Palladium acetate
Pd/C	Palladium on activated carbon
PdCl ₂	Palladium chloride
PGP	P-Glycoprotein
PPh ₃	Triphenylphosphine
PRD	Pharmaceutical Research and Developement
PTLC	Preparative thin layer chromatography
RCM	Ring closing metathesis
R _f	Retention factor
RISC	RNA-induced silencing complex
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interference
hpRNAs	Hair-pin ribonucleic acid

siRNAs	Small interfering ribonucleic acid
$\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$	Ruthenium trichloride trihydrate
ROM	Ring opening metathesis
RT	Room temperature
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
SI	Selective Index ($\text{CC}_{50}/\text{EC}_{50}$)
SMT	(<i>S</i>)-Scoulerine-9- <i>O</i> -methyltransferase
SOCl_2	Thionyl chloride
SST receptor	Somatostatin receptor
STOX	Tetrahydroberberine oxidase
<i>N</i> -TFA	<i>N</i> -trifluoroacetyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl or tetramethylsilane (NMR)
Ts	<i>p</i> -Toluenesulfonyl
TsOH	<i>p</i> -Toluenesulfonic acid
V1a receptor	Vasopressin receptor
VIP1 receptor	Human vasoactive intestinal peptide receptor
Y1, Y2 receptors	Hypothalamic neuropeptide receptors

Abstract.

This thesis examines the synthesis of a library of benzyl- and bisbenzylisoquinolines (BBI) derivatives based on the reticuline motif. These compounds were assessed for their; i) cytotoxicity on 3 cancer cell lines, ii) activity on HIV-infected cells, iii) antibacterial activity, and iv) CNS receptor binding affinities.

Chapter 2 describes the employment of palladium-catalysed Stille, Heck and Sonogashira coupling reactions to synthesise a library of BBI derivatives. 2'-Vinyl- (**67**), 2'-allyl- (**68**) and 2'-iodo (**58**) derivatives of racemic, *N*-TFA protected, norlaudanosine were used as the key building blocks in this investigation. The key 2'-vinyl- and 2'-allyl-norlaudanosine derivatives **67** and **68**, respectively were readily prepared from palladium-catalysed Stille coupling reactions of the 2'-iodonorlaudanosine derivative **58** and vinyl- or allyl-tributylstannane. The Heck coupling reactions between the 2'-vinyl-norlaudanosine derivative **67** and the 2'-iodonorlaudanosine derivative **58** gave not only the desired stilbene BBI derivative **65** but also the unexpected 1,1-disubstituted regioisomer **69**. This unexpected regioisomer was a result of the electron rich nature of both starting materials that favoured a cationic palladium intermediate. The best Heck coupling reaction conditions involved the use of Pd(OAc)₂, DMG, NaOAc and NMP at 130 °C. These conditions gave the highest yield and the best regioisomer selectively in favour of the BBI derivative **65**. Fortunately these regioisomers were readily separated by triturating the product mixture with methanol. The Heck coupling reaction between the 2'-allylnorlaudanosine derivative **68** and the aryl iodide **58** successfully afforded the three carbon tethered BBI derivative **66** in moderate yield.

It was found, however, that these Heck coupling reaction conditions were only efficient with aryl iodide precursors. This was evident from the attempted

intramolecular Heck coupling reactions on the aryl bromide precursor **89**, to give the macrocyclic BBI derivative **88**. The optimised Heck coupling reaction conditions failed to produce the desired product, while more traditional Heck coupling conditions gave the required product in poor yield (15 %).

The unsaturated BBI derivative **65** and its regioisomer **69** were subjected to hydrogenation conditions over Pd/C under a hydrogen atmosphere. However, the regioisomer **69** was found to be too sterically hindered and did not undergo the hydrogenation reaction, while derivative **65** encountered solubility problems and only *rac*-**65** underwent the hydrogenation reaction to give *rac*-**80**, leaving the less soluble *meso*-**65** intact. The compounds *rac*-**80** and *meso*-**65** were readily separated by column chromatography.

Chapter 2 also described the successful synthesis of the targeted acetylinic BBI derivative **63** *via* coupling of the 2'-ethynylbenzylisoquinoline derivative **84** with the aryl iodide **58**, using a Pd/Cu catalysed Sonogashira coupling reaction, followed by *N*-TFA deprotection of the *N*-TFA 2'-ethynylbenzylisoquinoline derivative **83**.

The synthesis of a library of 2'-arylvinyl- and 2'-arylallyl-benzylisoquinolines derivatives using the optimised Heck coupling reaction conditions developed in Chapter 2 is described in Chapter 3. This set of compounds included benzylisoquinolines having either an exocyclic *N,N*-dimethylamino (**92-103**) or *N*-acetamido (**104-107**) substituent. A third group of compounds (**108-111**) in this set had the exocyclic amino or amido group completely excluded. It was found that the Heck coupling reaction of the 2'-vinyllaudanosine derivative **67** and the aryl iodides **118**, **119**, **131** and **135** afforded only one regioisomer, unlike the Heck coupling between **67** and **58** in Chapter 2, which gave the two regioisomers **65** and **69**. The Heck coupling reactions between the 2'-allyllaudanosine derivative **68** and the aryl iodides **118**, **119**, **131** and **135** gave two

regioisomers **115a,b**; **116a,b**; **129a,b** and **137a,b**, respectively, due to two possible sites of palladium hydride elimination.

In Chapter 4, the use of the ruthenium-catalysed CM and RCM reactions toward the successful synthesis of the four carbon tethered BBI derivatives, **138-142**, in both unsaturated and saturated forms (*via* hydrogenation reactions) was described. The synthesis of the analogous two and three carbon tethered BBI derivatives *via* this method proved less efficient.

Chapter 5 reported the synthesis of a library of aminoalkyl benzyloquinoline derivatives, incorporating both cyclic and acyclic amines (**155-162**). These analogues were obtained by a simple reductive amination methodology involving the reaction of commercially available amines with the aldehydes **186** and **187**, which were generated from the 2'-vinyl- and 2'-allyllaudanosine derivatives **67** and **68**, respectively. The initially planned pathway to one of these aldehydes involved the rearrangement of the epoxide **188**, however this epoxide was too unstable under the reaction conditions and readily underwent ring opening with *m*-chlorobenzoic acid. An alternative pathway using oxidative cleavage of the diols **190** and **191**, which were generated from dihydroxylation of the 2'-vinyl- and 2'-allyllaudanosine derivatives, **67** and **68**, respectively, was found to be more successful for the synthesis of these aldehydes.

Chapter 5 also described the synthesis of an additional class of aminoalkyl benzyloquinoline derivatives, **163** and **164**, containing a β -amino alcohol moiety. Retro-synthetic analysis showed two possible synthetic pathways which were either *via* the ring opening of the cyclic sulfates **195** and **196** or *via* the nucleophilic displacement of the tosylates **197** and **198** with an amine nucleophile. The latter pathway proved more successful and afforded the β -amino alcohol derivatives **163** and **164**, however, the yields of these reactions should be optimised in future studies.

The synthesis of the benzyloisoquinoline derivatives containing a nine- and ten-membered heterocyclic ring, **165-167**, was also described in Chapter 5. The synthesis of these analogues was initially attempted *via* the intramolecular reductive amination reaction between an aldehyde moiety at the C2' position of **219** and its free isoquinoline amino group. However, the synthesis of the aldehyde moiety *via* the hydrolysis of its protected diacetal form was very difficult; therefore an alternative synthesis was developed. This method involved an intramolecular nucleophilic displacement of the chloride of the α -chloroacetamides **214** and **215** by the free isoquinoline amino moiety. This method successfully afforded the nine- and ten-membered ring benzyloisoquinoline derivatives **165** and **167** in moderate yields (42-57 %). Lithium aluminium hydride reduction of **165** gave the corresponding cyclic diamino derivative **166** in high yield.

Some of the benzyl- and bis-benzyloisoquinoline derivatives reported in Chapters 2-5 were sent for biological testing for their cytotoxicity on 3 cancer cell lines, activity on HIV-infected cells, their antibacterial activity and CNS receptor binding affinities. The BBI derivatives showed higher activity on cancer cell lines than the corresponding benzyloisoquinoline derivatives. Various BBI and benzyloisoquinoline derivatives have showed promising CNS-receptor binding affinities, especially for 5HT receptors and more prominently on the 5-HT_{1B}, 5-HT_{2A} and 5-HT₇ receptors. At this stage, a clear structure-activity trend could not be discerned and the mode of action of these analogues was not clear. Further results on the awaiting analogues may help to develop pharmacophore models for CNS active compounds in the future, and eventually, allow the design and development of more selective and potent ligands.

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“ The difficult situations give us an unparalleled chance to growth. You don’t need to seek them out; they will find you. Rise up to meet them.”- Stephanie Dowrick.

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“ Listen to the teachings of your hearts. At the end of each day, find something to be thankful for. Give thanks. Sleep in peace.”- Stephanie Dowrick.

I would like to dedicate this thesis to my family, Mum and Unity. Thank you for your supports and encouragement over the past years. Thank you Mum, for those beautiful home cooked meals, and those nagging times of telling me to eat when I was too busy writing up. Thank you Mum for just being there. Thanks to Unity for just being a cool sister.

It's easy to be pleasant and gracious when things go our ways. The challenging of maturity is to be pleasant and gracious when things do not go our way.”- Stephanie Dowrick.

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Chapter 1 Introduction



The **top1** mutant of the opium poppy (*Papaver somniferum*) generates commercially useful drug precursors instead of full-fledged morphine. The seed capsule of a natural morphine-producing poppy (left) oozes sap that's whiter than the latex of the morphine-free poppy mutant (right).

<http://opioids.com/opium/poppy-engineering.html>

1.1. History of Natural Products.

For thousands of years, plants have been used for their medicinal properties to treat diseases and to promote health and well-being.¹ Records from as early as 3000 B.C in China, traced to the Emperor Shennung, described 365 medicinal plants used for such purposes.² In India, traditional medicine was documented in the Ayurveda in around 900 BC.³ Knowledge of medicinal plants crossed to the Mediterranean countries through trade and immigration, where Egyptians had recorded medicinal plants in the Ebers papyrus around 1550 BC.^{4,5} In ancient Greece, Hippocrates had characterised more than 200 medicinal plants in the period of 460 B.C,⁶ while in Arabia, 1400 medicinal preparations were recognised from medicinal plants in the period of 1100 A.D.^{7,8} In Europe after the 10th century, herbal medicines became very popular.⁹ The development of drugs based on natural products also has a long history. In 1991, almost half of the best selling drugs were natural products, or derivatives of natural products.^{10,11} In 1996, the US market for natural supplements was worth over \$14 billion in sales.^{10,12} Much effort has been directed into investigating and isolating the active constituents of these plants which are generally secondary plant metabolites.¹³

1.2. Primary *Versus* Secondary Plant Metabolites.

All plant species synthesise essential compounds called primary metabolites. Examples include lipids, carbohydrates, proteins and chlorophyll¹⁴ all of which are important for plant growth and survival.^{15,16} However, plants also do produce secondary metabolites that are specific to certain cell types. Common secondary metabolites include alkaloids, terpenoids and phenolics (flavonols, flavones, tannins, lignin and coumarins).^{14,17} Initially, secondary metabolites were considered to be waste products or otherwise functionless molecules.¹⁸ However, toward the end of the 19th century, Stahl

et al. had advocated that plants use them as a chemical defence against natural predators such as herbivores, harmful organisms, viruses and other plants.¹⁹ This chemical defence hypothesis was ignored for 60-70 years until Fraenkel reopened the debate in 1959.²⁰ It is now widely accepted that secondary metabolites are essential for the fitness and survival of plants.²¹ They also serve other functions such as signalling compounds, which include the attraction of pollinating or seeding animals by colour (e.g. betalains, anthocyanins, and carotenoids), fragrances (terpenes) or sweet substances (sugars).²² Among the more than 50,000 secondary metabolites that are known today, over 12,000 are alkaloids.²³

1.3. What is an Alkaloid?

The term “alkaloid” was first proposed by the pharmacist W. Meissner in 1891, meaning “alkaline-like”.²⁴ Alkaloids have been classified as basic compounds derived from amino acids containing one or more heterocyclic nitrogen atoms. Often they have complex molecular structures and manifest significant biological activities.²³ They are isolated predominantly, but not exclusively, from plants. They are also found in animals (e.g. shellfish) and fungi.^{21,23} Among the 12,000 known alkaloids, it is estimated that they are present in only 10-15 % of all vascular plants.²³ They are rarely found in cryptogamic (seedless plants), gymnosperms (e.g. pines) or monocotyledons (e.g. sugar cane), yet occur abundantly in dicotyledons. Many well-characterised alkaloids have been isolated from the roots, seeds, leaves or bark of some 40 different plants families.²³

1.4. Types of Alkaloids and Their Applications.

Alkaloids are diverse in their chemical composition, and can be classified according to their biogenetic origin. The large majority of alkaloids have been derived

either directly or indirectly from amino acids, such as tyrosine, arginine, lysine, histidine, ornithine, tryptamine and tryptophan.¹⁸

A classic example is *d*-tubocurarine **1** (Figure 1.1) which is extracted from the leaves of *Chondrodendron tomentosum*. It is an alkaloid derived from the amino acid tyrosine.¹⁰ It is the active component of the arrow poison used by South American Indians,²⁵ and acts by binding to the motor neuron end-plate receptors and thus denying access to the neurotransmitter acetylcholine, resulting in muscle paralysis.²⁶

Various species of *Ephedra* have a long history of use in herbal medicine as decongestants for asthma, bronchitis, and other respiratory ailments. The active principle is a phenylalanine-derived alkaloid called ephedrine **2** (Figure 1.1). Ephedrine **2** enhances the release of norepinephrine from sympathetic neurons and stimulates *alpha* and *beta*-receptors. It relaxes bronchial smooth muscle and therefore is used as a decongestant and for temporary relief of shortness of breath caused by asthma.²⁷

Cocaine **3** (Figure 1.1), extracted from the coca plant, is an example of a tropane-type alkaloid which is derived from the amino acid ornithine. It is a potent stimulant that has a long history of use and abuse in both Western and non-Western countries.^{28,29} Cocaine continues to be the most frequently mentioned illicit substance reported to the Drug Abuse Warning Network (DAWN) by hospital emergency departments in the U.S.A.³⁰ Cocaine **3** blocks the neuronal reuptake of the excitatory neurotransmitters dopamine and norepinephrine.³¹ When consumed, physical effects of cocaine include constricted blood vessels, dilated pupils, and increased body temperature, heart rate, and blood pressure.³²

Reserpine **4** (Figure 1.1) is an indole alkaloid derived from tryptophan. It was extracted from the root of *Rauwolfia serpentina* plants found extensively in Africa. As a

traditional herbal medicine in ancient India, the roots of *R. serpentina* were brewed as a tea and used to treat hypertension, insanity, snakebite, and cholera.³³

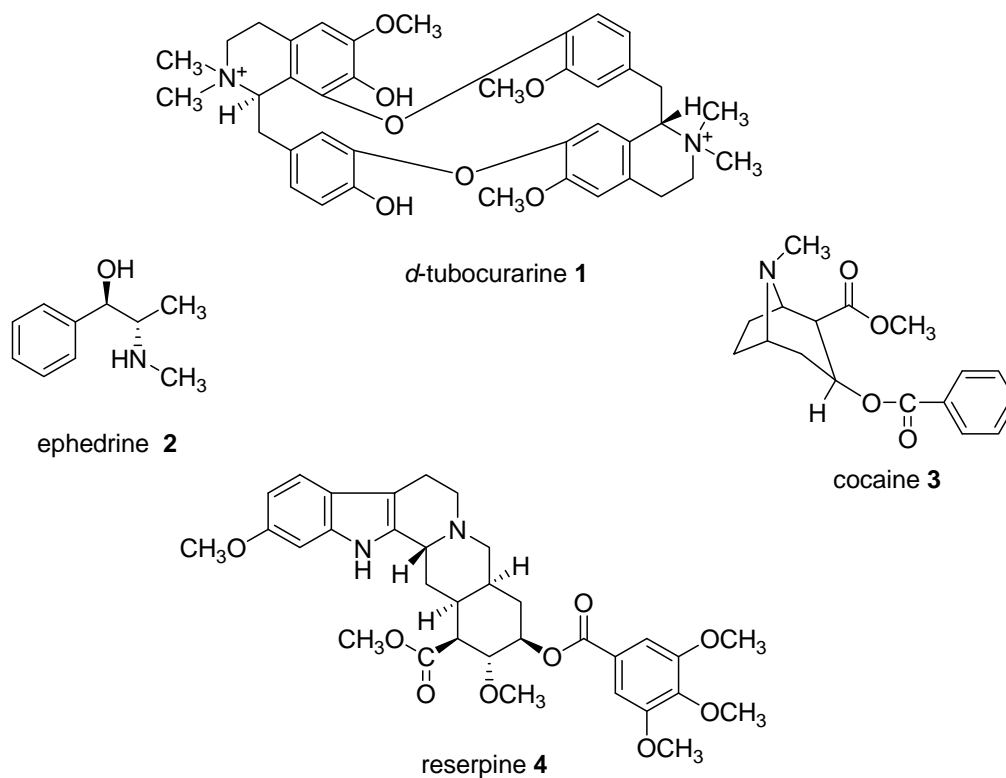


Figure 1.1 The structures of amino acid-derived alkaloids: *d*-tubocurarine **1**, tyrosine-derived; ephedrine **2**, phenylalanine-derived; cocaine **3**, ornithine derived and reserpine **4**, tryptophane-derived.

The purine-based alkaloid caffeine **5** occurs naturally in coffee beans, tea leaves, guarana, cocoa pods, and kola nuts. Today it is the most widely used stimulant in the world and is an ingredient in a wide variety of food and beverages.³⁴ Caffeine antagonizes presynaptic adenosine receptors, facilitating catecholamine release. It also acts as a vasodilator in the CNS, reducing blood pressure and headache symptoms.³⁴

Aconitine **6** is a diterpene alkaloid found in species of *Aconitum*. Before and during the Middle Ages, aconitine was used as a poison for spears, darts and arrows during hunting. It interferes with the transmission of the nerve impulses to the muscle leading to immediate paralysis.^{35,36}

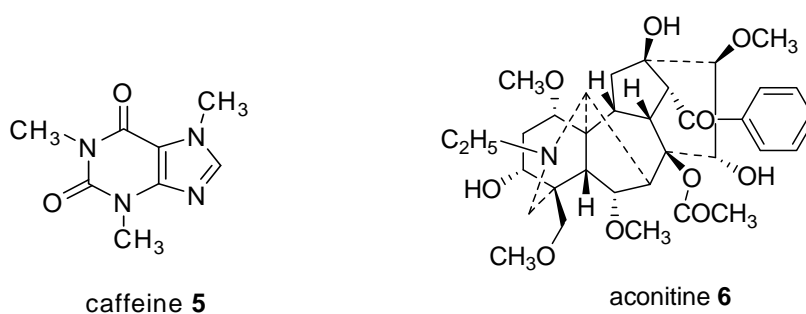
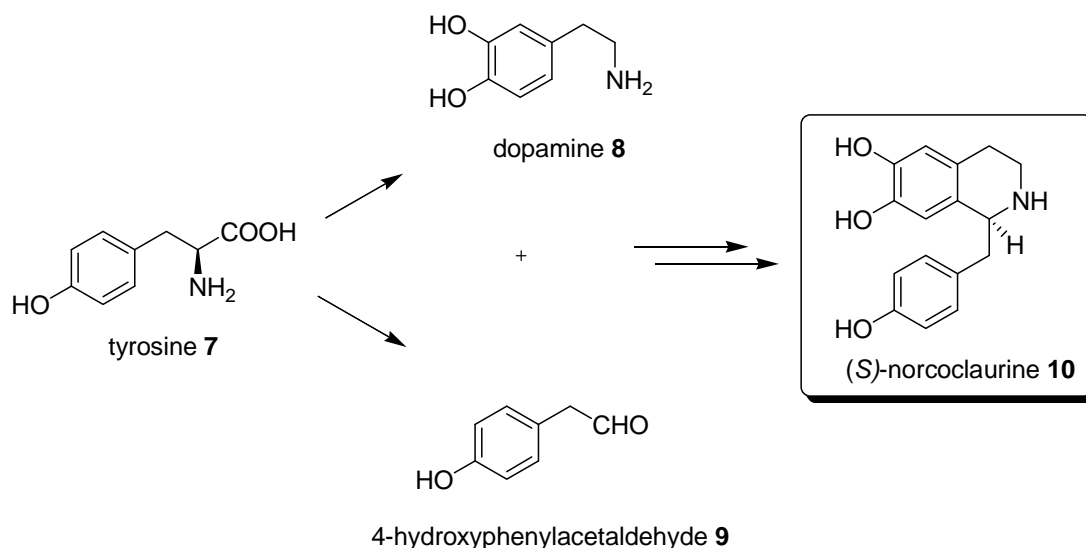


Figure 1.2 The structures of purine-based and diterpene-derived alkaloids.

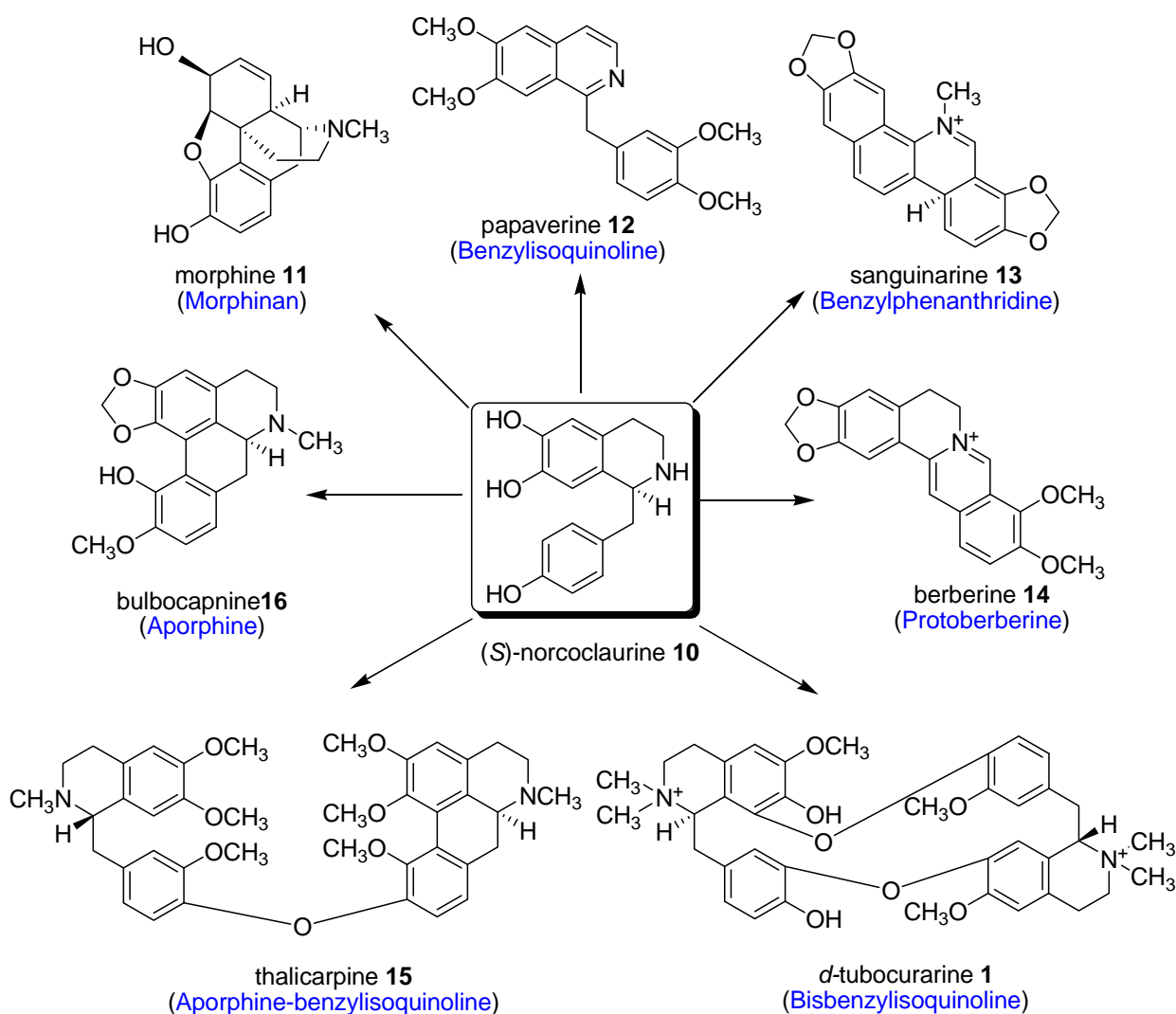
1.5. Benzyloquinoline Alkaloids.

Since the discovery and characterisation of alkaloids in opium poppy, *Papaver Somniferum*, in the early 1800s, a large number of benzyloquinoline alkaloids have been isolated. These alkaloids are formed from two molecules of tyrosine **7**, which have been converted to dopamine **8** and 4-hydroxyphenylacetaldehyde **9** via a series of *ortho*-hydroxylation, deamination, and decarboxylation reactions.²⁶ An enzymatically catalysed condensation of these two molecules yields (*S*)-norcoclaurine **10**, which is the central precursor of all benzyloquinolines and related alkaloids (Scheme 1.1).



Scheme 1.1 The condensation of dopamine **8** and 4-hydroxyphenylacetaldehyde **9** to give (*S*)-norcoclaurine **10**.

Over 2,500 benzyloquinolines and related alkaloids are known to be derived from precursor **10**. Notable examples include: a) the morphinan alkaloid, morphine **11**;³⁷ b) the vasodilator benzyloquinoline alkaloid, papaverine **12**;³⁸ c) the antimicrobial benzylophenanthridine alkaloid, sanguinarine **13**;³⁹ d) the antimicrobial protoberberine alkaloid, berberine **14**;⁴⁰ e) the muscle relaxant bisbenzyloquinoline alkaloid, *d*-tubocurarine **1**;⁴¹ g) the cytotoxic aporphine-benzyloquinoline alkaloid, thalicarpine **15**;⁴² and f) the dopamine antagonist aporphine alkaloid, bulbocapnine **16**⁴³ (Scheme 1.2).

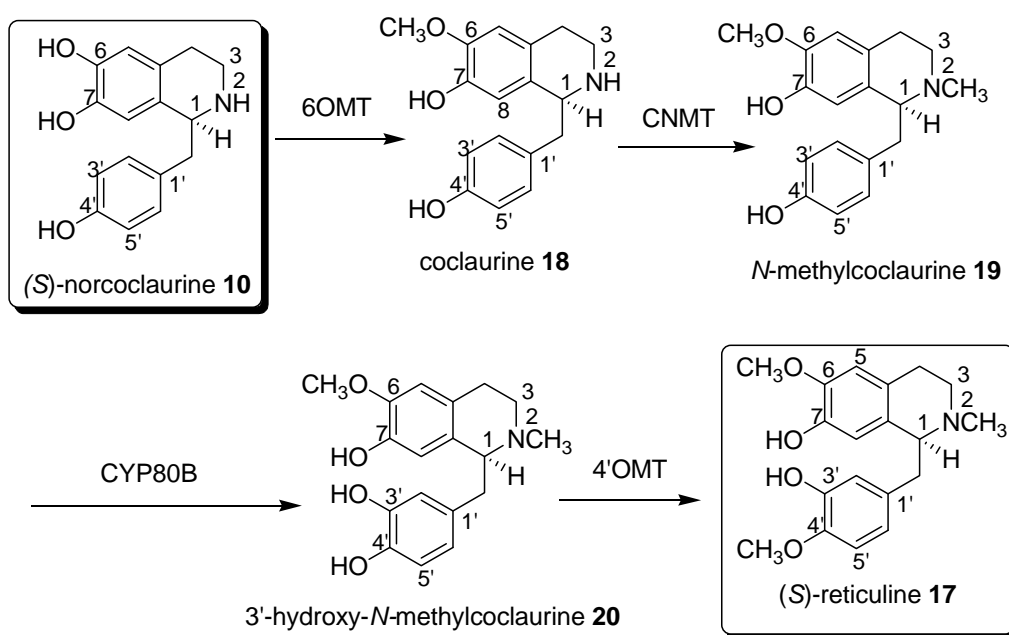


Scheme 1.2 The various groups of benzyloquinoline and related alkaloids derived from (*S*)-norcoclaurine **10**.

In the biosynthesis of most of these alkaloids, (*S*)-norcoclaurine **10** is converted into the key branch point intermediate, (*S*)-reticuline **17**.

1.6. (*S*)-Reticuline.

(*S*)-Reticuline **17**, a benzyloisoquinoline alkaloid first isolated from *Annona reticulata*,⁴⁴ was shown to be one of the principal alkaloids in opium.⁴⁵ It functions as a dopamine blocking agent⁴⁶ in the CNS and also stimulates hair growth.⁴⁷



Scheme 1.3 The formation of (*S*)-reticuline **17** from (*S*)-norcoclaurine **10**.

(*S*)-Reticuline **17** is biosynthesised from **10** *via* a series of hydroxylation and methylation reactions as shown in Scheme 1.3. (*S*)-norcoclaurine **10** is converted to coclaurine **18** by (*S*)-norcoclaurine-6-*O*-methyltransferase (6OMT). Methylation of **18** is catalysed by (*S*)-coclaurine-*N*-methyltransferase (CNMT) to give *N*-methylcoclaurine **19**. Hydroxylation of the 3' position of **19** is catalysed by a cytochrome P₄₅₀-dependent hydroxylase (CYP80B), and finally 4'-*O*-methyltransferase (4'OMT) methylates the 4'-hydroxyl group of **20** to give (*S*)-reticuline **17**.^{48,49}

Elucidation of the biosynthetic pathway of the opium poppy alkaloids, several bisbenzylisoquinoline, benzylisoquinoline and related alkaloids revealed (*S*)-reticuline **17** as a common precursor. Sections 1.8-1.11 will discuss the biosynthesis of several alkaloids classes derived from (*S*)-reticuline **17**.

1.7. The Opium Poppy.



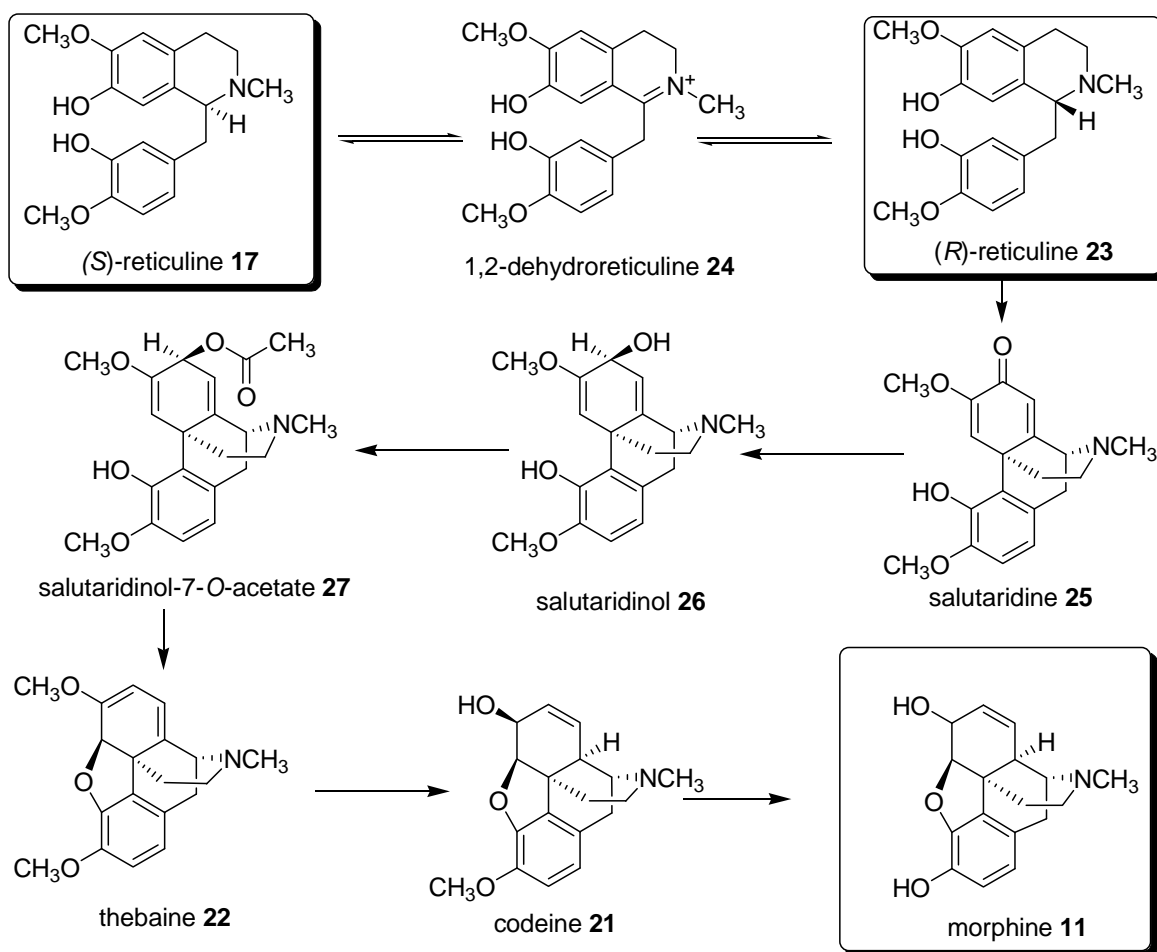
Figure 1.3 Opium poppy's flower and seed capsule.⁵⁰

The opium poppy, *Papaver somniferum*, is one of the oldest cultivated medicinal plants in history. The oldest evidence for its usage comes from the period 3000-2500 BC.⁵¹ It produces more than 80 different benzylisoquinoline and related alkaloids.⁵² The alkaloids morphine **11** and codeine **21**, two of the most important analgesics in use today, accumulate in the latex of the poppy (Figure 1.3). The latex is collected by lancing the unripe seed capsule of the poppy. It is dried and extracted with solvent to primarily afford morphine **11** (12 % of the dried latex) with lesser amounts of codeine **21** and thebaine **22**.⁴⁸ Other important alkaloids from this plant include the vasodilator, papaverine **12** and the anti-microbial sanguinarine **13**.⁵³ In 1965, Hanssen *et al.* demonstrated that opium contains 60 % (*S*)-reticuline **17** and 40 % (*R*)-reticuline **23**.⁴⁵ (*S*)-Reticuline **17** is the key branch point intermediate, where subsequent stereo- and

regio-specific oxidation leads to structurally diverse members such as, the morphinan alkaloid **11**, the benzophenanthridine alkaloid **13** and the protoberberine alkaloid **14**.⁵⁴

1.8. Biosynthesis of Morphinan Alkaloids.

Hanssen *et al.* established that only (*R*)-reticuline **23** had the correct configuration to serve as the direct precursor of the morphinan-type alkaloids.^{55,56}

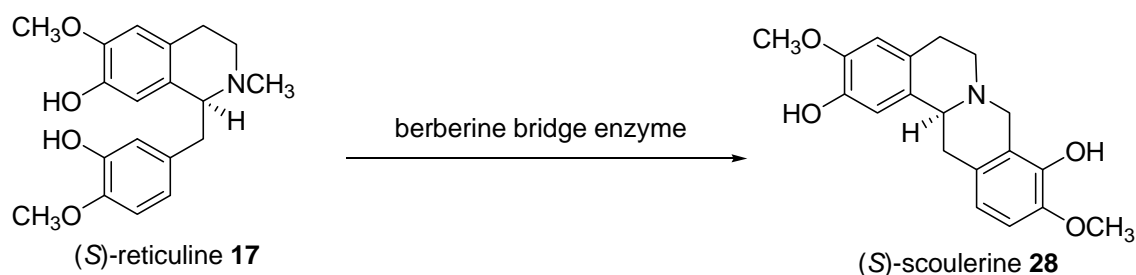


Scheme 1.4 Biosynthesis of morphine **11**.

Therefore, as shown in Scheme 1.4, (*S*)-reticuline **17** was converted to its enantiomer **23** *via* the intermediate formation of 1,2-dehydroreticuline **24**, enabling the formation of the morphinan alkaloids to possess the (*R*)-configuration at the benzylic position. The next step involved an oxidative cyclisation of **23** catalysed by a cytochrome P₄₅₀-dependent enzyme found in the young poppy capsule to form

salutaridine **25**. The conversion of salutaridine **25** to salutarinol **26** was catalysed by NADPH-7-oxidoreductase. Monoacetylation of **26** affords salutaridinol-7-*O*-acetate **27**, which undergoes spontaneous ring closure at pH 8-9 to produce the oxide bridge between C4 and C5, giving thebaine **22**. A series of regio-selective, enzymatically catalysed demethylation and *O*-methylation reactions lead to the formation of codeine **21** and eventually morphine **11**.⁵⁷

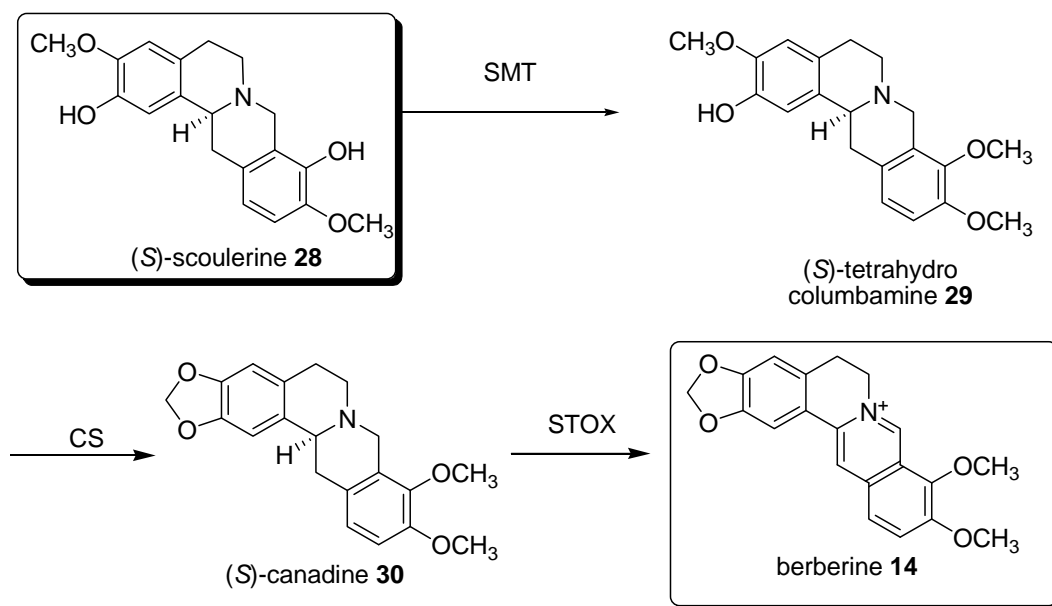
1.9. Biosynthesis of Protoberberine and Benzophenanthridine Alkaloids.



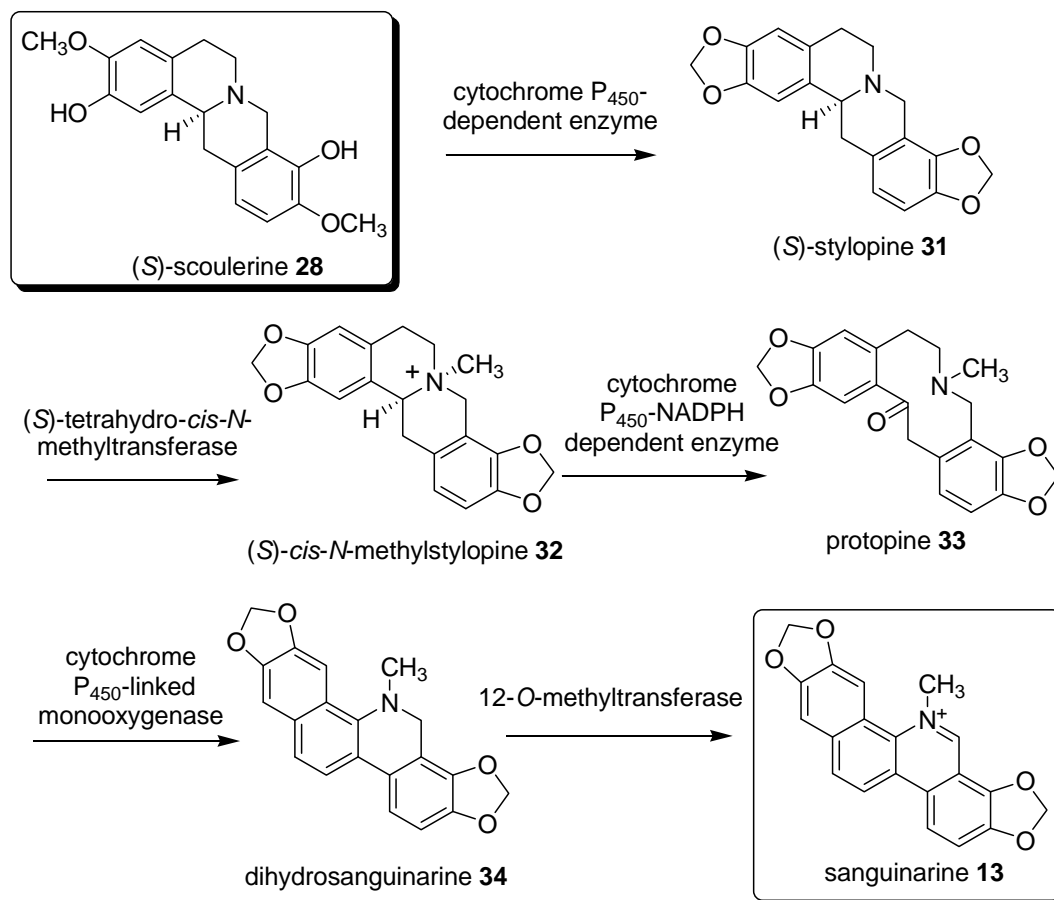
Scheme 1.5 The first committed step in the production of berberine **14** and sanguinarine **13**.

The alkaloids berberine **14** and sanguinarine **13** are also derived from (S)-reticuline **17**. The first committed step in the production of protoberberine and benzophenanthridine type alkaloids involves the conversion of **17** to (S)-scoulerine **28** by the berberine bridge enzyme (Scheme 1.5).

From this point, the enzyme (S)-scoulerine-9-*O*-methyltransferase (SMT) catalyses the conversion of **28** to give (S)-tetrahydrocolumbamine **29** (Scheme 1.6). The enzyme (S)-canadine synthase (CS) catalyses the formation of the methylenedioxy-bridge to give (S)-canadine **30**. (S)-Canadine **30** can act as a substrate for the enzyme tetrahydroberberine oxidase (STOX) and is converted to berberine **14**.⁴⁹



Scheme 1.6 Biosynthesis of the protoberberine alkaloid, berberine **14**.



Scheme 1.7 Biosynthesis of the benzophenanthridine alkaloid, sanguinarine **13**.

Alternatively, as outlined in Scheme 1.7, a cytochrome P₄₅₀-dependent enzyme converts **28** to (*S*)-stylopine **31** by the introduction of a methylenedioxy bridge, followed by *N*-methylation catalysed by (*S*)-tetrahydro-*cis*-*N*-methyltransferase to give (*S*)-*cis*-*N*-methylstylopine **32**. Oxidation at C14 is catalysed by a cytochrome P₄₅₀-NDAPH-dependent enzyme to give the ten-membered ring compound protopine **33**. Hydroxylation and *O*-methylation of **33** and dihydrosanguinarine **34**, using cytochrome P₄₅₀-monooxygenase and 12-*O*-methyltransferase, ultimately gives sanguinarine **13**.⁵⁸

1.10. Bisbenzylisoquinoline Alkaloids.

Since the discovery of *d*-tubocurarine **1**, the active constituent of the arrow poison used by South American Indians, more interests have been directed toward the discovery of additional bisbenzylisoquinoline (BBI) alkaloids due to their diverse structures and varied pharmacological effects.⁵⁹

BBI alkaloids are derived from two benzylisoquinoline units, linked by either an ether linkage,⁵⁹ a methyleneoxy bridge⁶⁰ or a direct carbon carbon bond.^{61,62} The variety of structural patterns in the BBI alkaloids are due to differences in: a) the presence or absence of aromatic oxygen substituents, e.g. OCH₃ or OH; b) the number of ether or carbon-carbon linkages; c) the nature of the ether linkage, e.g. *via* a diphenyl ether or a benzylphenyl ether; and d) the position of the ether or carbon linkage.⁶³ Based on these differences, BBI alkaloids can be classified into different groups which will be discussed accordingly.

Diphenyl linked BBI alkaloids were recently isolated and are characterised by a single tail to tail diphenyl linkage between the benzyl moieties, with either no linkage or up to two diphenyl ether linkages in the top portion of the molecule. To date, only 7 BBI alkaloids having a single diphenyl linkage have been isolated, all possessing the (*R,R*)-configuration.⁶³ Two examples of this type of alkaloid are pisopowine **35**, having

both its nitrogens and all oxygens methylated, and pisopowamine **36**, having one secondary amino group and two hydroxyl groups (Figure 1.4).⁶⁴ Examples of the BBI alkaloids possessing a tail to tail diphenyl linkage and either one or two diphenyl ether head to head linkages between the isoquinoline groups are cordobine **37**, (+)-tiliarine **38** (an *in vitro* inhibitor of human melanoma cells) and cordobimine **39** (a Ca^{2+} channel blocker).^{61,65} The latter alkaloid was isolated with singular chirality at C1, due to formation of an imine in one of the isoquinoline rings (Figure 1.4).

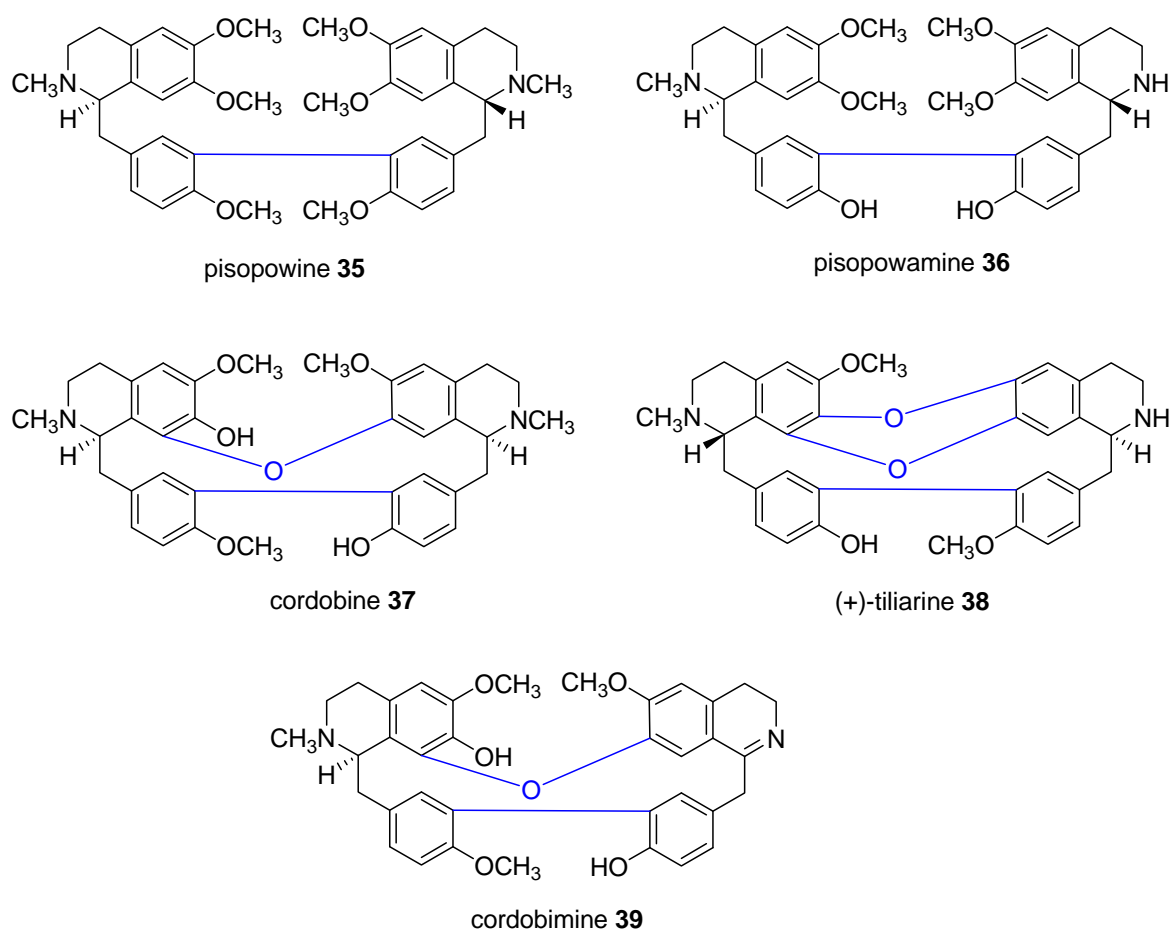


Figure 1.4 BBI alkaloids containing a single diphenyl linkage with either no linkage or up to two diphenyl ether linkages in the top portion of the molecule.

The BBI alkaloids possessing one to three diphenyl ether linkages are probably one of the most abundant alkaloids isolated to date. Such alkaloids are identified as

having one, two or three diphenyl ether linkages, originating from different ring positions.⁶³ The vasodilator, dauricine **40**,⁶⁶ and the platelet aggregator, fanchinoline **41**,⁶⁷ are examples of alkaloids having one and two diphenyl ether linkage(s), respectively, connected in a head to head and tail to tail manner (Figure 1.5). However, neferine **42** (exhibiting cytotoxicity on multidrug resistant cancer cell lines), and curine **43** (a vasodilator) are linked in a head to tail fashion.^{68,69} The antimalarial compound 2-*N*-methylteboline **44** is an example of a BBI alkaloid with a three diphenyl ether linkages. Most of the alkaloids in this group are di-*N*-methylated, but a limited number of these alkaloids have a secondary isoquinoline amino group or an imine moiety.

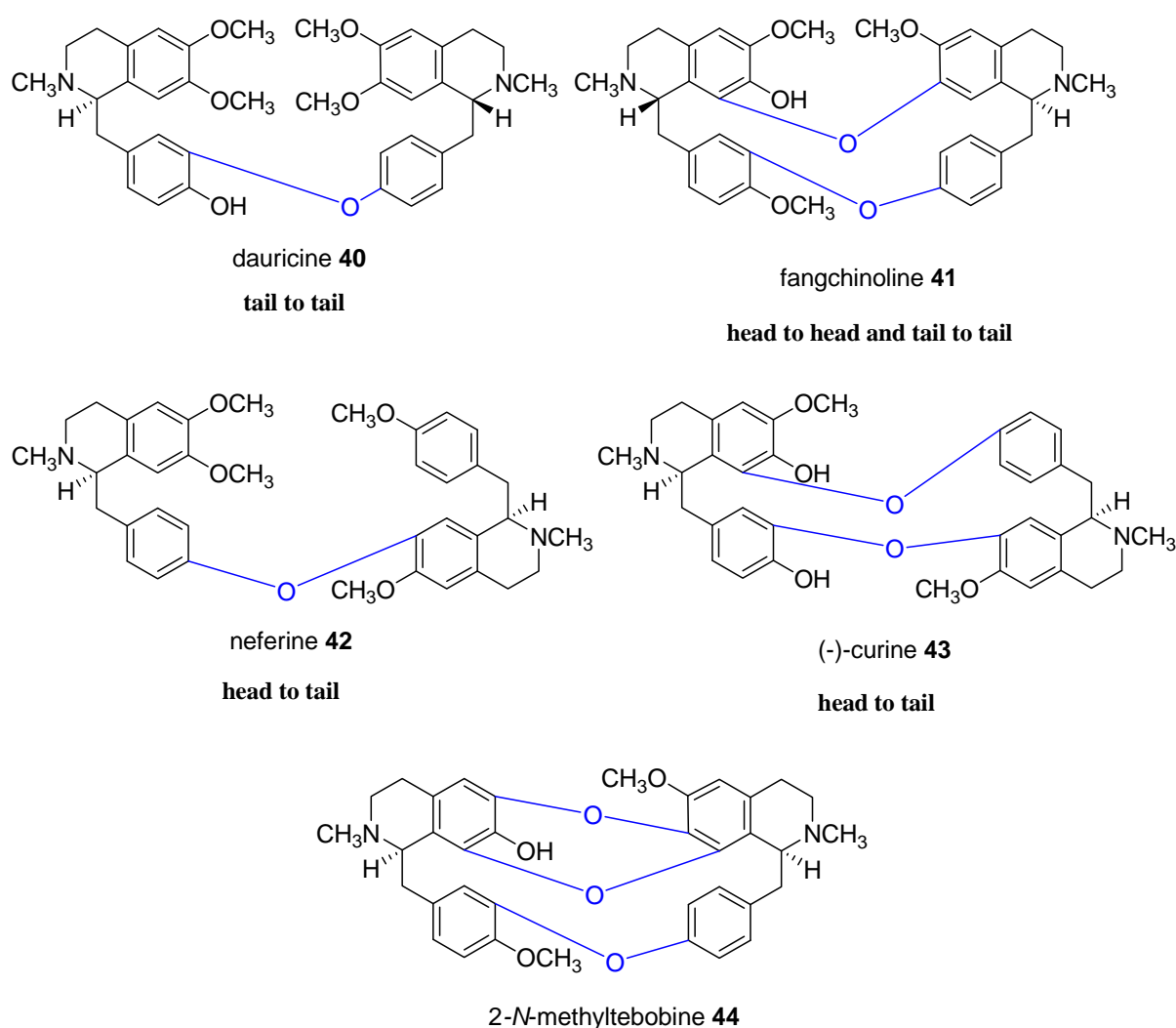


Figure 1.5 The BBI alkaloids containing one or up to three diphenyl ether linkages.

The BBI alkaloids characterised by a head to tail methyleneoxy linkage, plus one or two diphenyl ether linkages, comprise of a very small group of alkaloids (Figure 1.6). Most of the tri-ether linked alkaloids have the (*R,R*)-configuration exemplified by the antiparasmodial agent insularine **45**.⁷⁰ The remaining alkaloids can vary in configuration, having either (*R,S*)-, or (*R,R*)-configuration as well as having only one stereogenic centre due to the formation of an imine in one of the isoquinoline rings, eg. the neuromuscular blocking agent warifteine **46**.^{60,71}

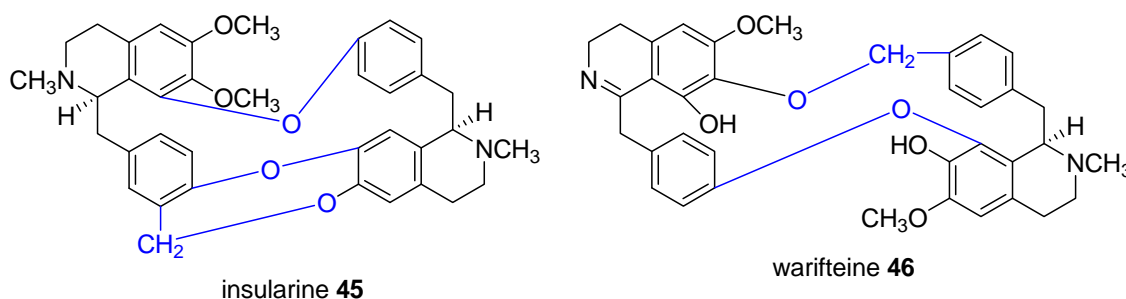


Figure 1.6 Examples of BBI alkaloids containing a methyleneoxy linkage and one or two diphenyl ether linkages.

1.11. Aporphine-Benzylisoquinoline Alkaloids.

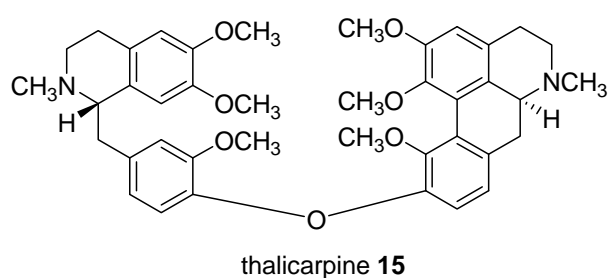
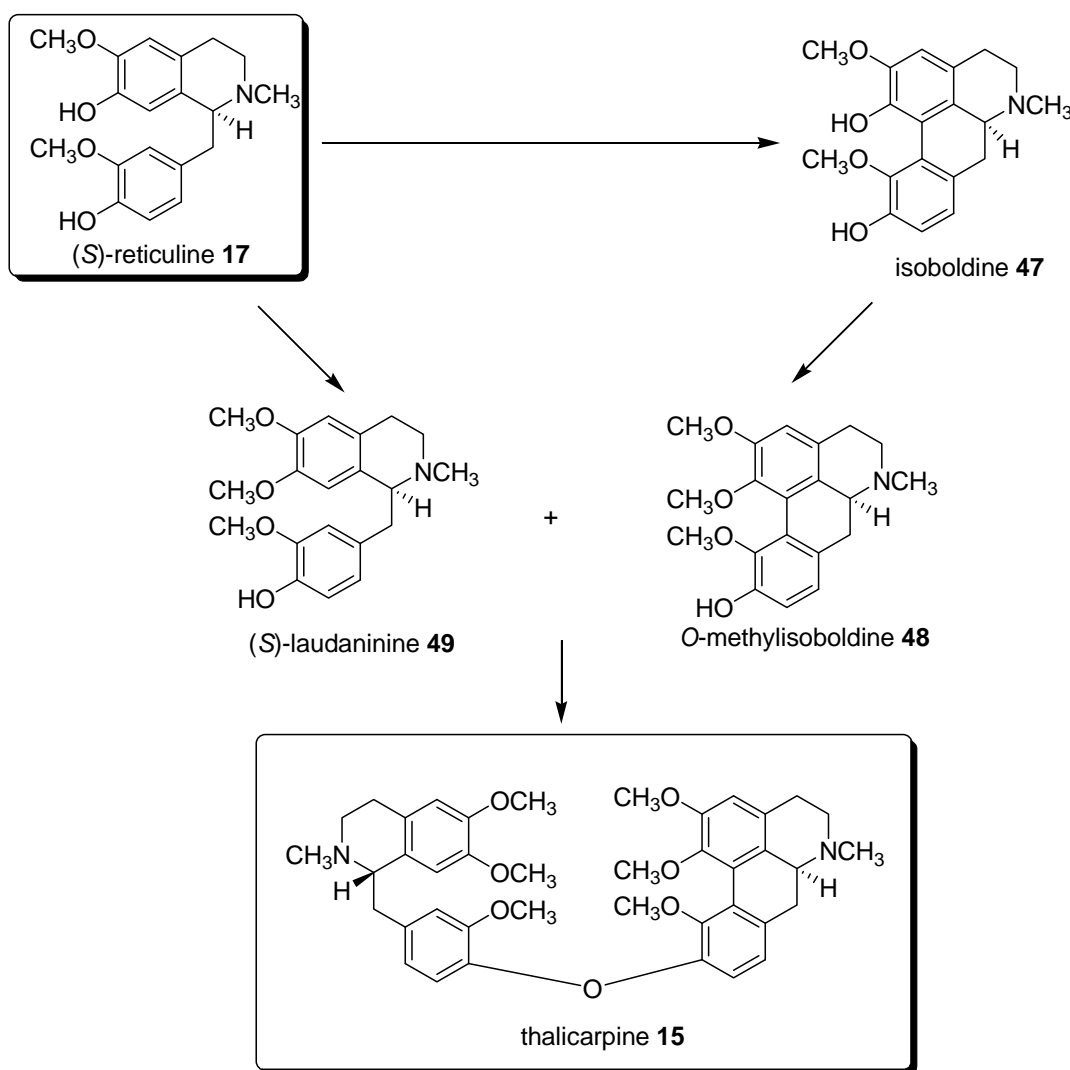


Figure 1.7 Structure of thalicarpine **15** and the plant *Thalictrum Dasycarpum*.⁷²

Thalicarpine **15** was first isolated by Kupchan *et al.* and is an example of the aporphine-benzylisoquinoline alkaloids.^{73,74} It has been isolated from several species of the genus *Thalictrum* including *T. dasycarpum*, *T. minus* and the genus *Hernandia*.

Within this species of plant, reticuline was also detected.⁷⁴ A detailed study by Sidjimov *et al.* in 1982 revealed that (*S*)-reticuline **17** was a precursor of both the benzyloisoquinoline and aporphine moieties.^{75,76} The aporphine moiety in the plant is formed by the intramolecular oxidative coupling of reticuline. The most likely biosynthetic pathway of thalicarpine starts with the *o*, *p*-oxidative cyclisation of **17** to the aporphine, (*S*)-isoboldine **47**, which is methylated to give the *O*-methylisoboldine **48**. (*S*)-Reticuline is converted to (*S*)-laudanine **49** which undergoes intermolecular oxidative coupling with **48** to give thalicarpine **15** (Scheme 1.8).^{71,75}



Scheme 1.8 The biosynthetic pathway of thalicarpine **15**.

1.12. Benzyl-, Bisbenzyl- and Aporphine-Benzylisoquinoline Alkaloids- Role as Anticancer Agents.

Cancer is a generic term that refers to the uncontrolled multiplication and spread of abnormal body cells.⁷⁷ Cancer cells are distinguished from normal cells by the uncontrolled proliferation, dedifferentiation and loss of function.⁷⁸ The ability of these abnormal cells (i.e. tumour cells) to invade the surrounding tissues resulting in metastasis that can eventually lead to mortality.⁷⁹ Cancer is one of the major causes of death worldwide; it varies in phenotypes and aggressiveness and therefore in responsiveness to therapeutic drugs. Compounds obtained from plant sources have a long history of use in the treatment of cancer.⁸⁰ Examples include vinblastine and vincristine, commonly used in the treatment of chronic lymphocytic leukemia and Hodgkin's disease.⁸¹ However, resistance to these drugs has occurred highlighting the need for new anticancer agents.⁸²

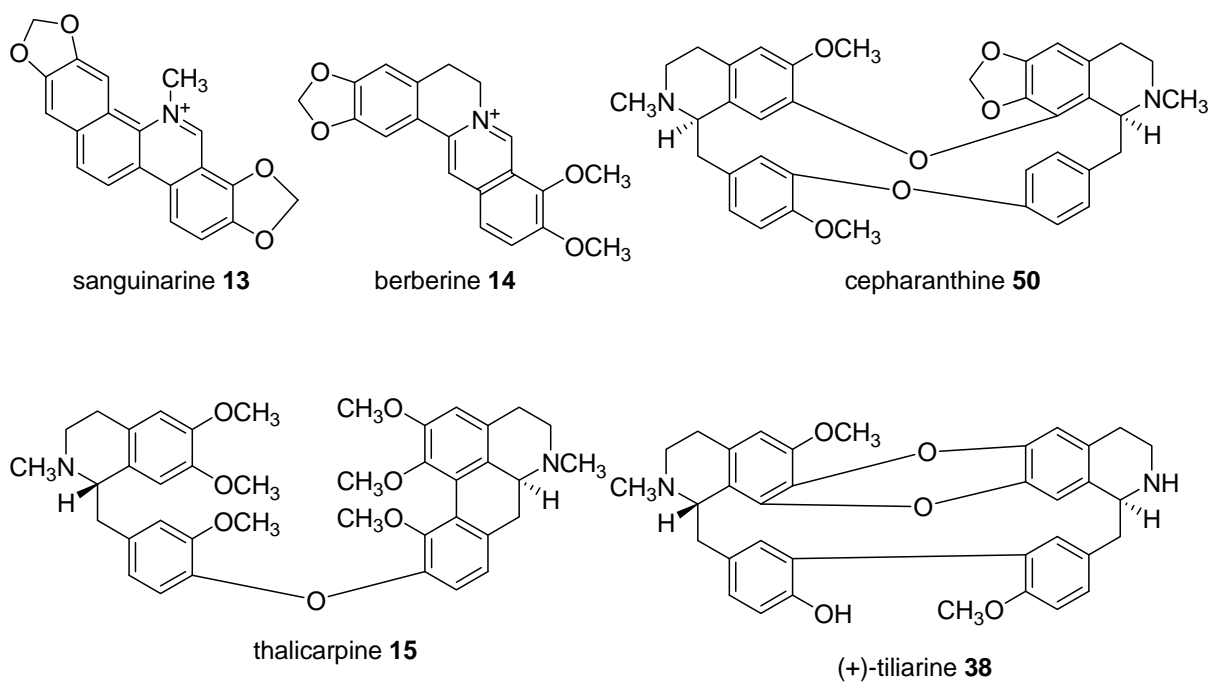


Figure 1.8 Structures of benzyl-, bisbenzyl- and aporphine-benzylisoquinoline alkaloids with anticancer activities.

Sanguinarine **13** and berberine **14** (Figure 1.8) act on cells by binding to microtubules, inhibiting enzymes including Na^+ , K^+ -ATPase, uncoupling oxidative phosphorylation and by intercalation with GC rich regions of DNA. Berberine **14** has been reported to reduce the *in vivo* growth of brain tumour cells and teratocarcinoma cells.^{81,83}

Cepharanthine **50**, a BBI alkaloid, extracted from the root of *Stephania cephrantha hayata*, was shown to inhibit tumour growth when compared to that of the untreated control.⁸¹ Thalicarpine **15** is a potent antileukemic agent and also effective against sarcoma cells. Clinical trials with thalicarpine revealed good tolerability with a lack of nephrotoxicity and hepatotoxicity.⁸³ (S)-Tiliarine **38** behaves as a selective *in vitro* inhibitor of human melanoma cell growth (Figure 1.8).⁶¹

1.13. Bisbenzylisoquinoline Alkaloids – Role as Antimalarial Agents.

Malaria is still the world's most prevalent disease responsible for the deaths of 2-3 million people annually, of which at least 1 million are children.⁸⁴ Today, it is estimated that nearly half of the world's population is at risk of malarial infection, and the disease is more common among the developing countries in Africa, East Asia, China and India.^{85,86} There are four known species of human malarial parasite of worldwide significant, causing symptoms of different severity and duration.⁸⁷ *Plasmodium falciparum* species cause the most severe infections and are the focus of majority of antimalarial research worldwide.⁸⁸ The first antimalarial drug was quinine, followed soon after by chloroquine.⁸⁹ Unfortunately, after early success, the malarial parasite *P. falciparum* became resistant to chloroquine.^{90,91} Active compound alternatives to chloroquine such as artemisinin, a plant-based antimalarial drug isolated from *Artemisia annua*, are being developed to combat this disease.^{89,92}

Several BBI alkaloids possess high antimalarial activities (Figure 1.9). (+)-2-*N*-Methyltelobine **44** was found to inhibit the growth of cultured chloroquine-resistant and sensitive strains of *P. falciparum*.⁹² Another BBI alkaloid, dehatrine **51**, isolated from the wood of *Beilschiedia madang* exhibited inhibitory activity comparable to quinine against the proliferation of the malarial pathogen *P. falciparum*.^{92,93} Costaricine **52**, isolated from the bark of *Nectandta salicifolia*, was shown to have antiplasmodial activity *in vitro* against a chloroquine-sensitive and chloroquine-resistance strain of *P. falciparum*.⁴²

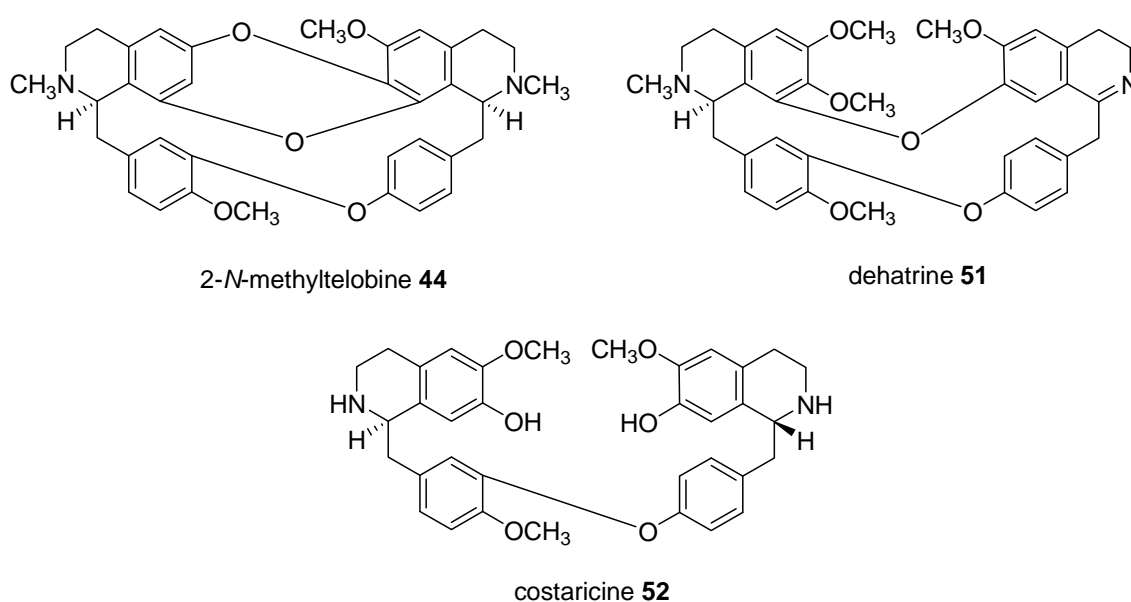
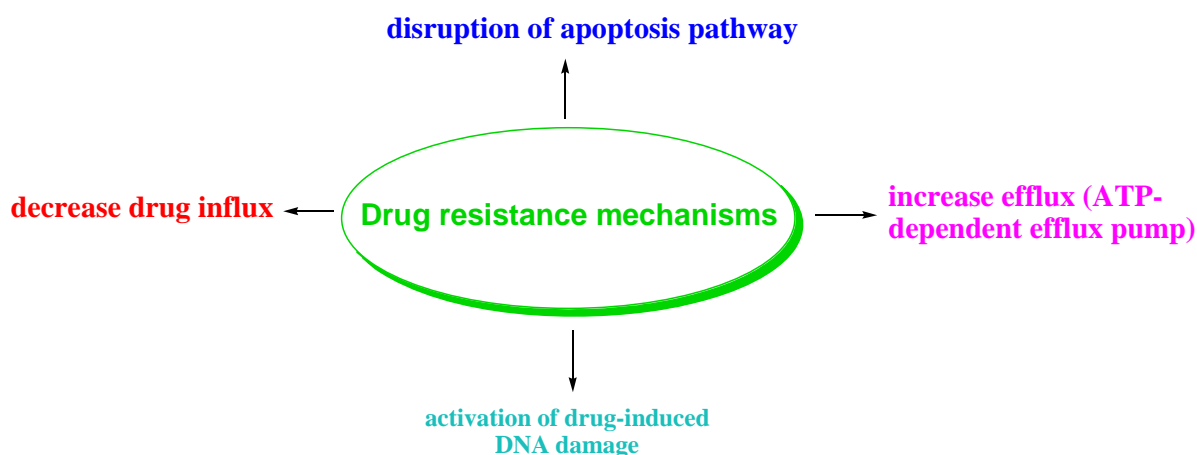


Figure 1.9 Structures of bisbenzylisoquinoline alkaloids exhibiting antimalarial activities.

1.14. Benzyl-, Bisbenzyl- and Aporphine-Benzylisoquinoline Alkaloids - Role in combating Multidrug Resistance.

Multidrug resistance (MDR) has become a significant problem in pharmaceutical development. The number of diseases that have experienced various levels of drug resistance is steadily increasing, and this includes cancer, malaria, HIV/AIDS, tuberculosis as well as most bacterial infections.¹⁰



Scheme 1.9 Cellular factors that cause drug resistance.

There are several cellular factors that cause cells to become resistant to therapeutic drugs (Scheme 1.9). One mechanism is for the cell to increase the activity of efflux pumps such as the ATP-dependent transporter P-glycoprotein (PGP). These transporters increase drug efflux and thus lowering the intracellular drug concentration. Examples of anticancer drugs affected by this mechanism include the vinca alkaloids, vinblastine and vincristine.⁹⁴

Resistance is also mediated by reduced drug uptake, which arises from having the water soluble drug adhere to a transporter protein rather than entering the cells, thus decreasing the intracellular drug concentration. A cancer drug that is affected by this mechanism is cisplatin.⁹⁵

Multidrug resistance (MDR) can also result from the activation of co-ordinately regulated detoxifying systems, such as DNA repair and activation of cytochrome P₄₅₀, an enzyme involved in drug metabolism and detoxification.⁹⁶

Finally, resistance can result from defective apoptotic pathways. During chemotherapy, cells might acquire changes such as alteration of ceramide levels, or activation of check points in the cell cycle, preventing initiation of apoptosis.⁹⁷

The BBI alkaloid tetradrine **53** (Figure 1.10), isolated from the root of *Stephania tetrandra* has been found to possess significant antineoplastic activity, especially against MDR cancer cells.⁷⁷ Another BBI alkaloid, dauricine **40**, was also found to enhance the cytotoxicity of MDR-related drugs *via* modulation of PGP.³⁷

An aporphine alkaloid, roemerine **54** (Figure 1.10), isolated from the leaves of *Annona senegalensis* was found to enhance the cytotoxicity response mediated by vinblastine in cancer cells.³⁷ The known anticancer active compounds cepharanthine **50** and thalicarpine **15** (Figure 1.10) can also enhance cytotoxicity in multidrug resistance cancer cell lines.⁸¹ Compound **15** was shown to fully reverse 490-fold resistance to adriamycin in a MDR human breast cancer cell line overexpressing PGP.⁹⁸

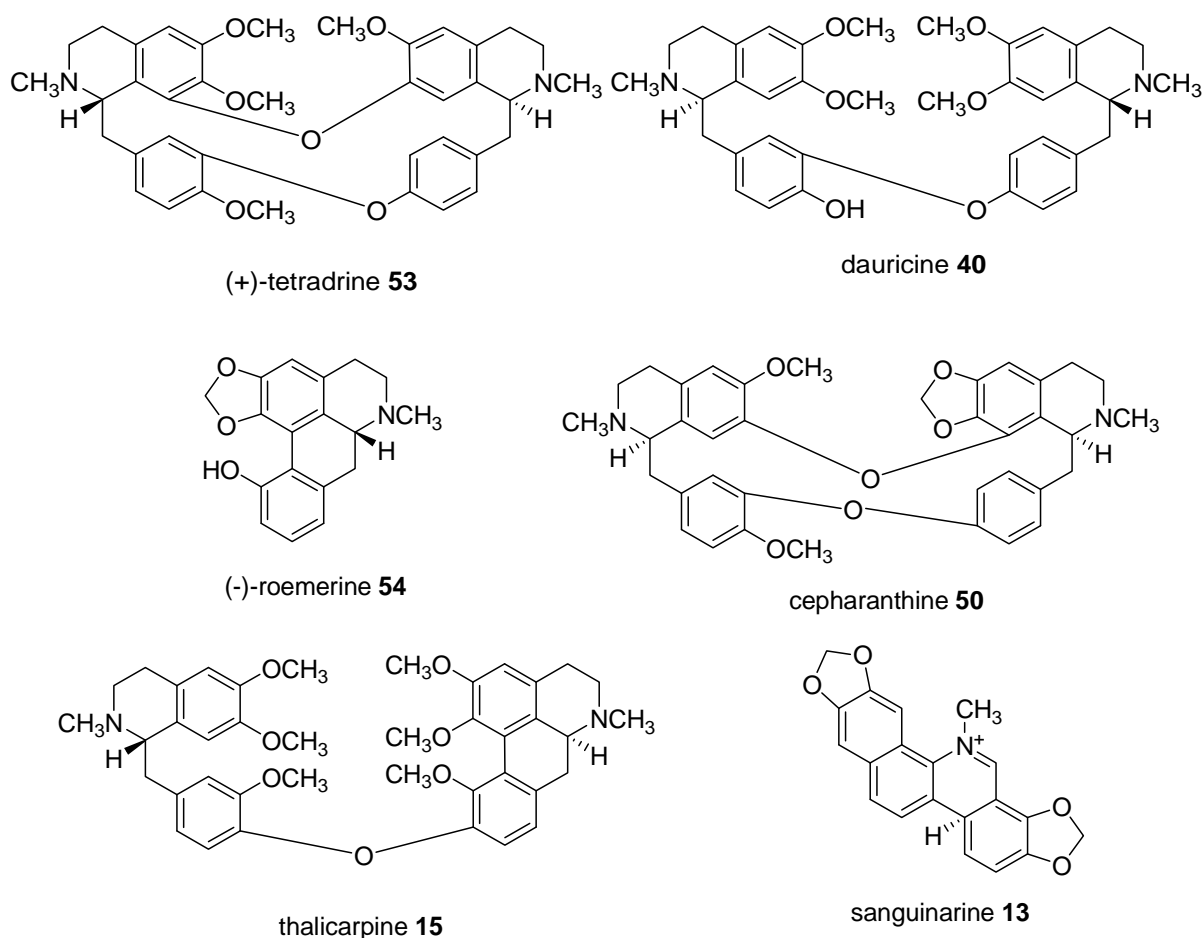


Figure 1.10 Structures of benzyl-, bisbenzyl-, and aporphines-benzylisoquinoline alkaloids that enhance the cytotoxicity of other drugs in MDR cancer cell lines.

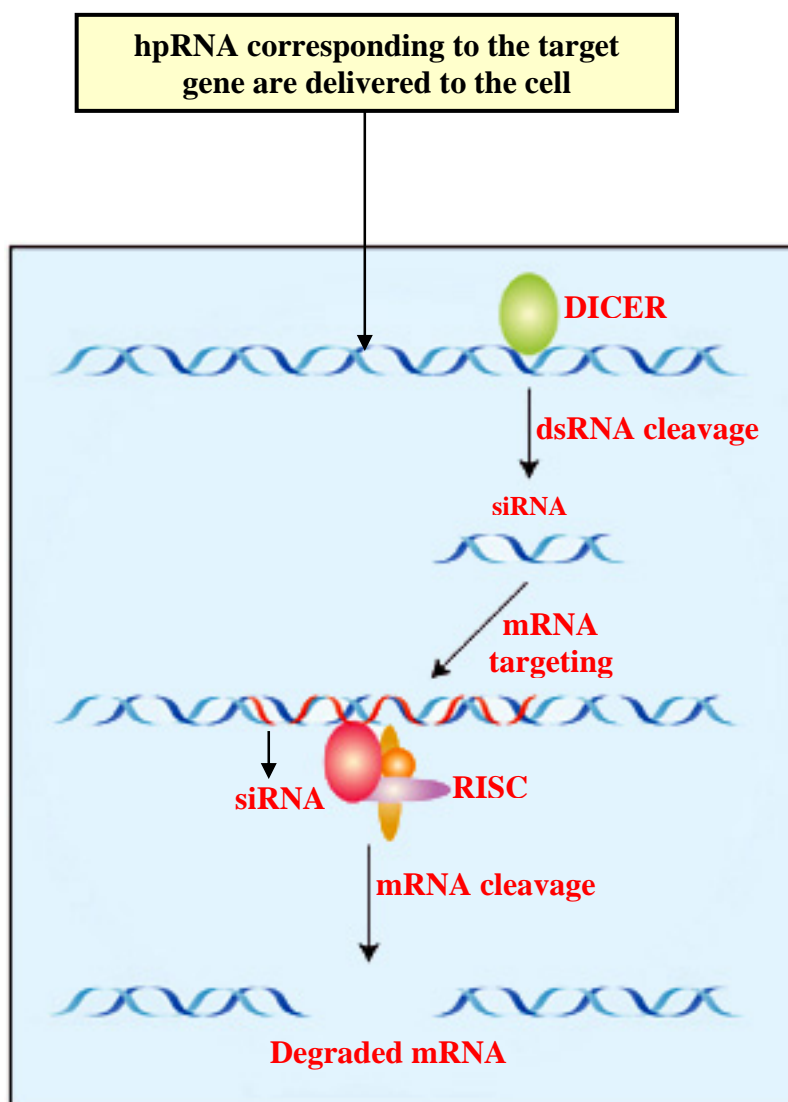
Recently, sanguinarine **13** (Figure 1.10) was also found to reverse MDR by behaving as a selective cell-active inhibitor of mitogen-activated protein kinase phosphatase-1, a phosphatase that is overexpressed in many human tumours and can protect cells from apoptosis caused by DNA-damaging agents.⁹⁹

1.15. Metabolic Engineering of the Opium Poppy.

The plant *Papaver somniferum* is an important source of medicinal opiates such as morphine, codeine, and related alkaloids, including papaverine and sanguinarine.⁶³ In Australia, commercial poppy growing is limited to a small area of about 20000 ha in the island state of Tasmania, which currently produces about 40 % of the world's legal traded opiates.¹⁰⁰ The alkaloid content in harvested poppy straw in Tasmania ranges from 1.5 % to 2.7 % on a dry weight basis. Higher content in the poppy crop would enhance the financial return to the growers and make the industry more competitive.¹⁰⁰ Plant metabolic engineering has been proposed as a means for increasing the level of valuable products or removing undesired metabolites.⁴⁸

Allen *et al.*⁵⁷ in Australia and Page *et al.*⁴⁸ in Canada have used RNA interference (RNAi) to silence all members of the multigene codeinone reductase (COR), an enzyme that catalyses the reduction of codeinone to codeine. RNAi involves the stable transformation of plants with an inverted repeat construct that express hair-pin RNA (hpRNAs) corresponding to the target gene. These hpRNAs, which form double-stranded RNA *in vivo*, trigger a silencing response that results in the generation of small interfering RNA (siRNAs). This directly causes degradation of both the hpRNA transcript and the target mRNA (Scheme 1.10).^{48,57,101} These methods reduced the COR enzyme activity and the level of morphine was substantially lowered. However the level of (*S*)-reticuline, seven steps upstream in the morphine pathway, was observed to be increased.⁵⁷ This research opened up the possibility of forcing an accumulation of a

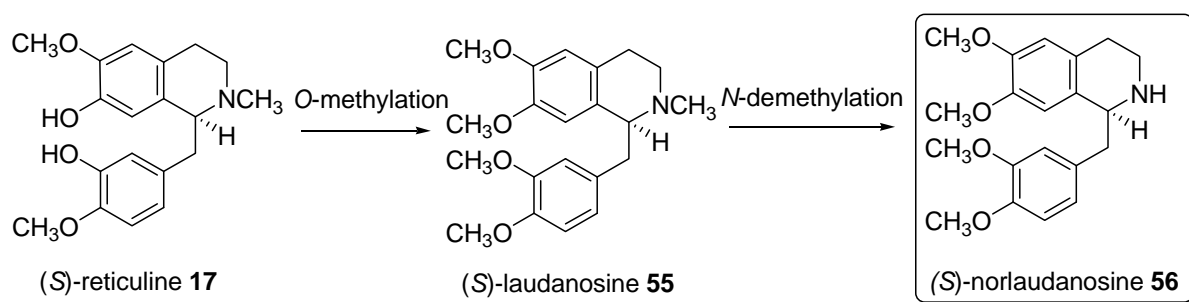
large amount of (*S*)-reticuline in opium poppy, providing a source of this molecule for the synthesis of new bioactive compounds potentially having novel pharmaceutical activities.



Scheme 1.10 The mechanism of RNA interference (RNAi).^{102,103} hpRNA corresponding to the target gene are delivered to the cell. This dsRNA is cleaved into small fragments of small interfering RNA (siRNAs) by an enzyme called DICER. The siRNAs incorporate into an RNA-induced silencing complex (RISC). The siRNAs-RISC complex binds to the complimentary part of the messenger RNA (mRNA), resulting in the degradation of mRNA and the loss of protein formation.

1.16. Project Aims.

Despite numerous benzyl- and bisbenzylisoquinoline alkaloids being identified and isolated from plants, there are limited effective anticancer and antimalarial agents among these. With a possible supply of (*S*)-reticuline from metabolically engineered opium poppy from Tasmanian Alkaloids, we planned to prepare a library of novel benzyl- and bisbenzylisoquinoline derivatives using (*S*)-reticuline **17** or its derivatives (*S*)-laudanosine **55** or (*S*)-norlaudanosine **56** as the starting point (Scheme 1.11). These compounds were anticipated to have potent cytotoxic activities and have multidrug resistance reversal activity by inhibiting the activity of P-glycoprotein.



Scheme 1.11 Conversion of (*S*)-reticuline **17** to (*S*)-norlaudanosine **56**.

However, since the availability of **17** was limited, our initial study focused on the use of racemic norlaudanosine **57** as the starting material which can be readily synthesised using literature procedures (Chapter 2).

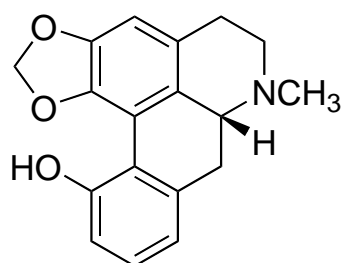
Among the BBI alkaloids tested for biological activities, many of these carry either an ether linkage, or di or tri-ether linkage. There are only a handful of BBI alkaloids that possess a direct carbon-carbon linkage (Section 1.8). Furthermore, none of the BBI alkaloids isolated have more than one direct C-C linkage. It is notable that most linkages occur through one or more oxygen atoms on either the head or tail moieties; however, none have a tether across two isoquinoline nitrogens.

Therefore, the general aims of this project were to synthesise the 6 different types of novel benzyloisoquinoline derivatives **A-E** (Scheme 1.12), starting from *N*-trifluoroacetyl-iodolaudanosine **58**, and then screening these for their biological activities at CNS receptors, their cytotoxicities on cancer cell lines, their activities on HIV infected cells and their anti-infective and anti-fungi activities.

Specifically, we planned to prepare:

1. The bisbenzyloisoquinolines derivatives tethered by either a single all carbon tether (group **A**) or by two all carbon tethers (group **B**) (Scheme 1.12). In group **A**, the number of carbons in the tether of the BBI derivatives would range from two to four and this tether can be either saturated (alkane) or unsaturated (alkene or alkyne). The BBI derivatives **B** would have a four carbon tether between the two isoquinoline nitrogens and the second unsaturated tether across the two C2' positions.
2. Group **C** benzyloisoquinolines having a tether at the C2' position of the benzyl group to a substituted aromatic ring (Scheme 1.12). The aromatic ring could either have an amino group tethered by one or two carbons, or have no nitrogen present. The effect of alkylating the isoquinoline nitrogen of this group of compounds would also be investigated.
3. Group **D** benzyloisoquinolines having the C2' position of the benzyl moiety tethered to different types of cyclic or acyclic amines. An additional hydroxy group introduced in the *beta* position of the amine in the case of group **E** will also be examined.
4. The novel Group **F** derivatives that would have a medium sized heterocyclic ring structure.

Results and Discussions - Chapter 2-6.



(-)-roemerine

The leaves of plant species *Annona senegalensis* from which the aporphine alkaloid roemerine (enhanced cytotoxicity in MDR cancer cell lines) was isolated.

Chapter 2 Synthesis of Bisbenzylisoquinolines

Derivatives *via* Palladium-Mediated Cross

Coupling Reactions.

2.1. Introduction.

This chapter focuses on the synthesis of the BBI derivatives **59-63** (Figure 2.1) having a two or three carbon tether between the two benzylisoquinoline moieties in a tail to tail fashion. The BBI derivatives **59** and **60** were prepared *via* palladium-catalysed Heck coupling reactions, while the BBI derivative **63** was prepared *via* a Sonogashira coupling reaction. The dihydro BBI analogues **61** and **62**, of **59** and **60**, were prepared by hydrogenation of **59** and **60**, respectively. The synthesis of the macrocyclic bis-tether BBI **64** was attempted *via* an intramolecular Heck coupling reaction.

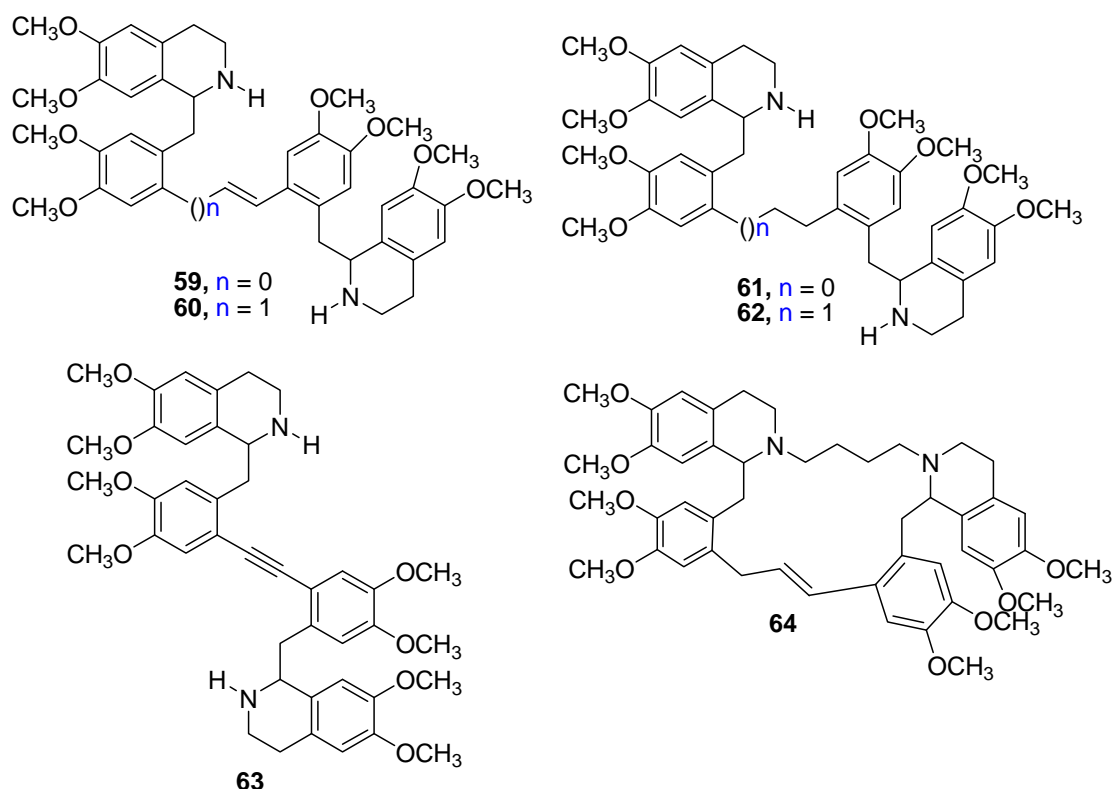
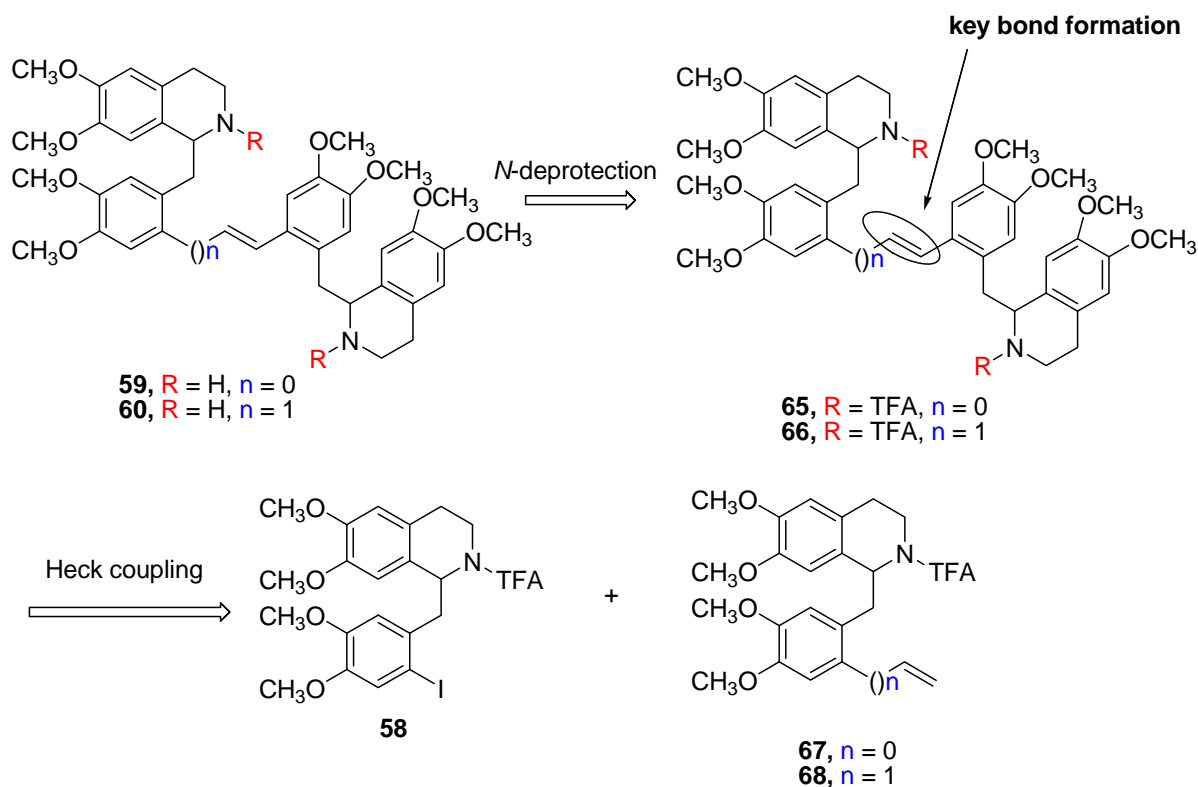


Figure 2.1 The targeted mono-tethered and bis-tethered BBI derivatives.

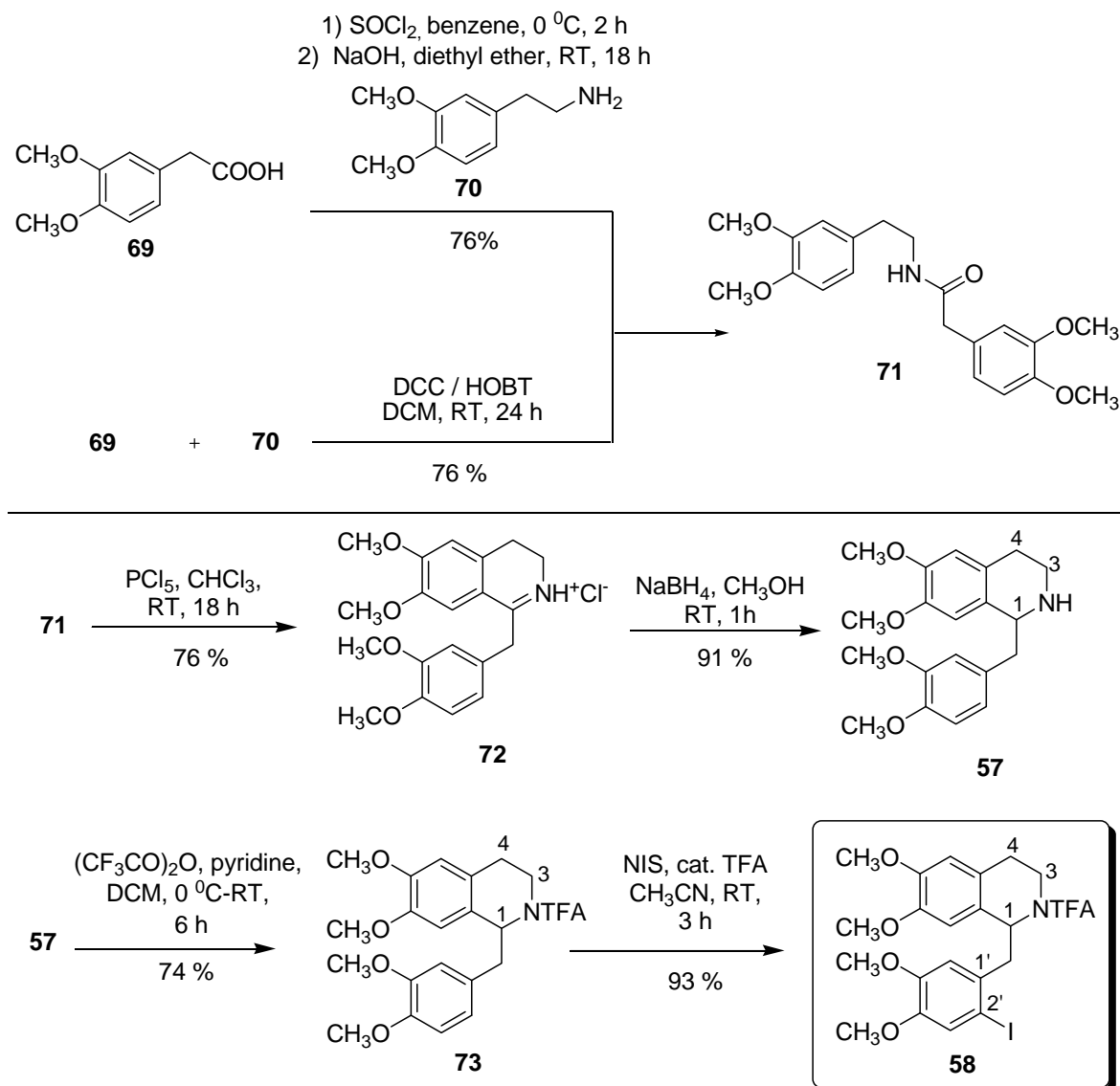
2.2. Synthetic approach to tethered BBI derivatives *via* the Heck coupling reaction.



Scheme 2.1 Retrosynthesis of the mono-tethered derivatives **59** and **60**.

The targeted BBI derivative **59** and **60** can, in principle, be obtained by *N*-trifluoroacetyl (*N*-TFA) cleavage of the intermediate *N*-protected BBI derivatives **65** and **66**, respectively. The formation of the tether in these intermediates, using a palladium-catalysed Heck coupling reaction, was the key step towards the synthesis of these targets. In order to carry out the Heck coupling reactions, the preparation of the coupling partners, the 2'-iodinated norlaudanosine derivative **58** and the olefins **67** and **68** was required.

2.3. Synthesis of the 2'-iodonorlaudanosine derivative **58**.



Scheme 2.2 The overall synthesis of the aryl iodide **58**.

The overall synthesis of the *N*-TFA protected 2'-iodonorlaudanosine **58** started with the amide coupling reaction of commercially available 3,4-dimethoxyphenyl acetic acid **69** with 2-(3,4-dimethoxyphenyl)ethylamine **70** to give the corresponding amide **71** in good yields (76 %). This was carried out following two different methods (Scheme 2.2). The initial approach involved the conversion of the acid **69** into the acid chloride using thionyl chloride and its subsequent reactions with the phenylethylamine **70** in the

presence of base (NaOH) to give the known amide **71** in high yield (88 %).¹⁰⁴ The structure of the amide **71** was confirmed by a characteristic amide proton resonance at δ 5.66 (t, 1H, J 5.3 Hz, NH) in the ¹H NMR spectrum. While the above approach afforded the amide in good yield, the intermediate acid chloride presented handling and storage problems because of its reactive nature. Therefore, as an alternative approach, the amide coupling reagents dicyclohexylcarbodiimide (DCC) and 1-hydroxy-1H-benzotriazole (HOBt) were used to facilitate the formation of the amide **71** in good yield (73 %).¹⁰⁵ The melting point obtained for the amide **71** (104-106 °C) was lower than that reported in the literature (118-120 °C).¹⁰⁶ Bischler-Napieralski cyclisation¹⁰⁷ of the amide **71** gave compound **72** as an iminium hydrochloride salt in 76 % yield. This salt was highly hygroscopic and had a melting point of 120-124 °C which was lower than that reported in the literature (~180 °C).¹⁰⁸ Reduction of **72** with NaBH₄ gave racemic norlaudanosine **57** in 91 % yield.¹⁰⁹ The melting point obtained for **57** (204-206 °C) was slightly lower than that reported in the literature (217-219 °C).^{106,109}

Since the objective of the project was to synthesise various benzyl- and bisbenzyl-isoquinoline derivatives, the choice of *N*-protection for the isoquinoline nitrogen was critical because the free amino group could interfere with the organometallic catalysts, such as palladium or ruthenium, by metal coordination. Generally, there are several groups used for *N*-protection, most commonly is the acid labile *tert*-butoxycarbonyl group (Boc).¹¹⁰ However, this protecting group was thought to be unsuitable for the intended chemistry as many synthetic reactions require high temperatures, which could possibly result in the cleavage of this protecting group. The trifluoroacetyl group is less commonly used in the protection of a free amino group,¹¹¹ however it was chosen for its more thermally stable nature and its ease of deprotection at RT under basic conditions using for example, potassium carbonate (K₂CO₃) or

ammonia (NH₃). Treatment of **57** with trifluoroacetic anhydride and pyridine afforded the *N*-protected compound **73** as a yellow solid in 74 % yield. A single crystal of **73** was prepared and the structure of **73** was confirmed by X-ray crystallography (Figure 2.2), however the melting point obtained for **73** (116-120 °C) was much lower compared to the literature value (136-137 °C).¹¹²

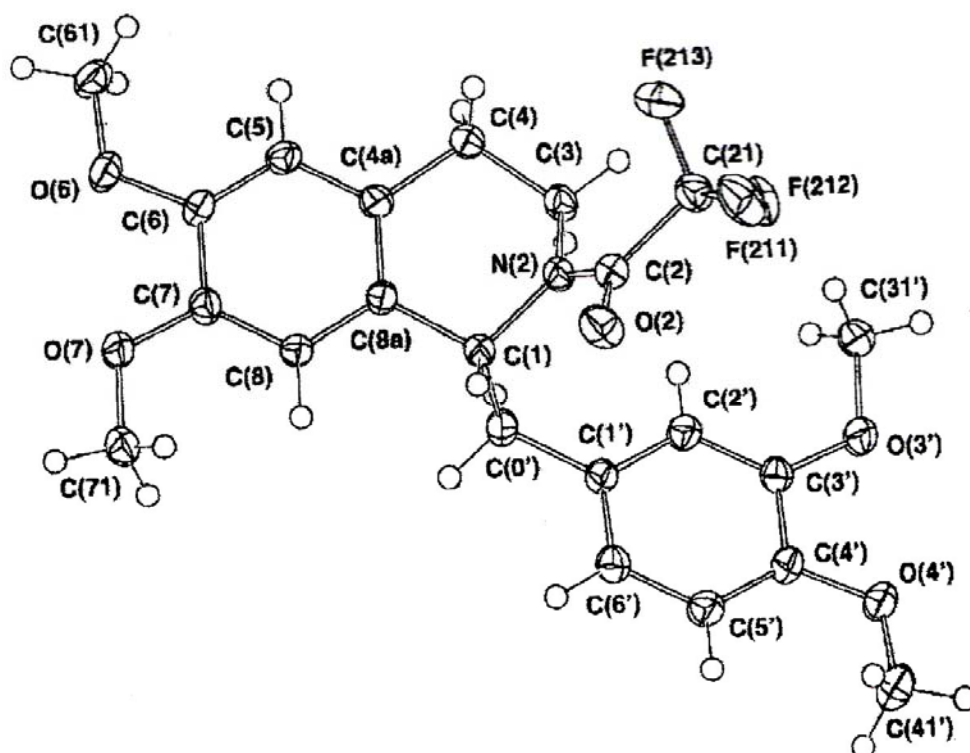
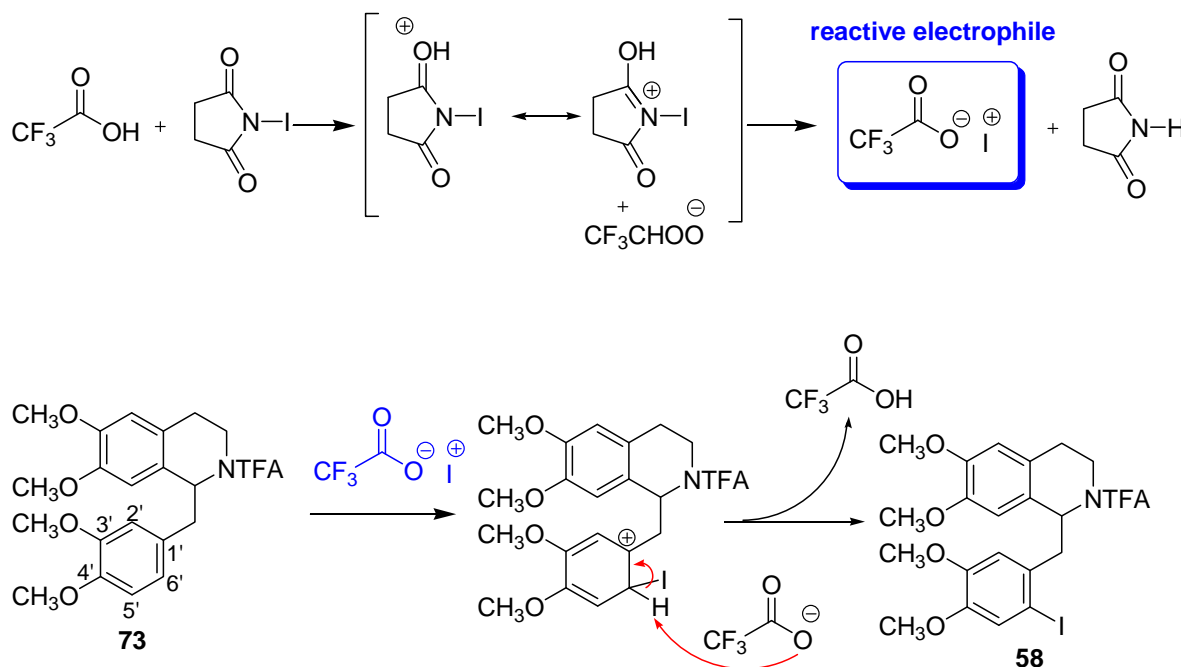


Figure 2.2 The single crystal X-ray structure of **73**. Note: The X-ray crystallographic numbering is different from the systematic numbering.

The successful transformation of the free amine **57** to the corresponding amide **73** was also evident from ¹H NMR analysis by the appearance of the more deshielded H1 proton signal at δ 5.54 (dd, 1H, *J* 6.9, 6.0 Hz, H1) compared to that of the free amine **57** at δ 4.09 (dd, 1H, *J* 8.6, 4.4 Hz, H1). The presence of the trifluoroacetyl group was observed in the ¹³C NMR spectrum of **73** with resonances at δ 152.9 (q, *J* 35.3 Hz, COCF₃) and 114.9 (q, *J* 226.2 Hz, COCF₃).

The derivative **58** containing the essential iodo group at the C2' position was obtained by treating **73** with a combination of *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoroacetic acid (TFA) (Scheme 2.2). This reagent combination had been found to be an excellent system for the regioselective iodination of activated aromatic compounds.¹¹³ The resulting electrophilic species in these iodination reactions is iodine trifluoroacetate ($\text{CF}_3\text{CO}_2\text{I}$). Iodination of **73** is expected to occur at the C6' position of **73** for steric (the isoquinoline aromatic ring is more hindered) and electronic reasons (*para* to the C3' and *ortho* to the C1' alkyl substituent) as shown in Scheme 2.3. The iodination of **73** proceeded in high yield (93 %) and afforded the desired derivative **58** of which the structure was confirmed by the appearance of 4 aromatic singlet resonances in the ^1H NMR spectrum. The low and high resolution MS was consistent with the molecular formula of **58**.



Scheme 2.3 The proposed mechanism of iodination using NIS/TFA.

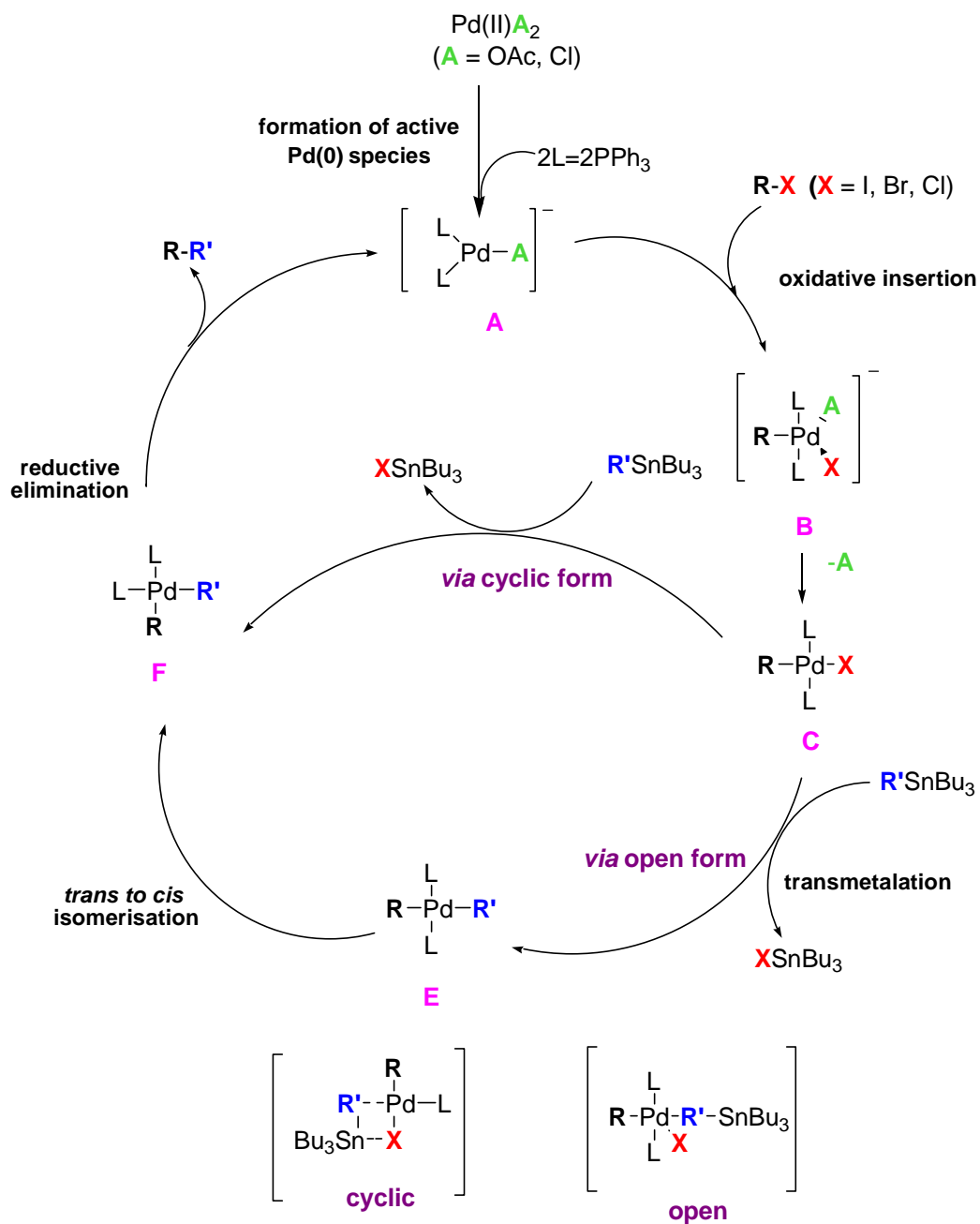
2.4. Synthesis of olefins 67 and 68 via Stille coupling reactions.

2.4.1. Background on Stille coupling reactions.

Stille cross-coupling reactions refer to the palladium-catalysed couplings of organostannane compounds with aryl halides or triflates.^{114,115} The first examples of Stille couplings were disclosed during the period 1976-1977 by the research groups of Eaborn and Kosugi.^{116,117} In 1978, Stille and co-workers carried out extensive synthetic and mechanistic work on this type of reaction, making it a powerful and the most widely used method for carbon-carbon bond formation.¹¹⁸ This was mainly due to the advantages of the trialkylorganostannane species over more reactive organometallic species (e.g. Grignard reagents) in being more readily available and tolerant of many functional groups.¹¹⁹

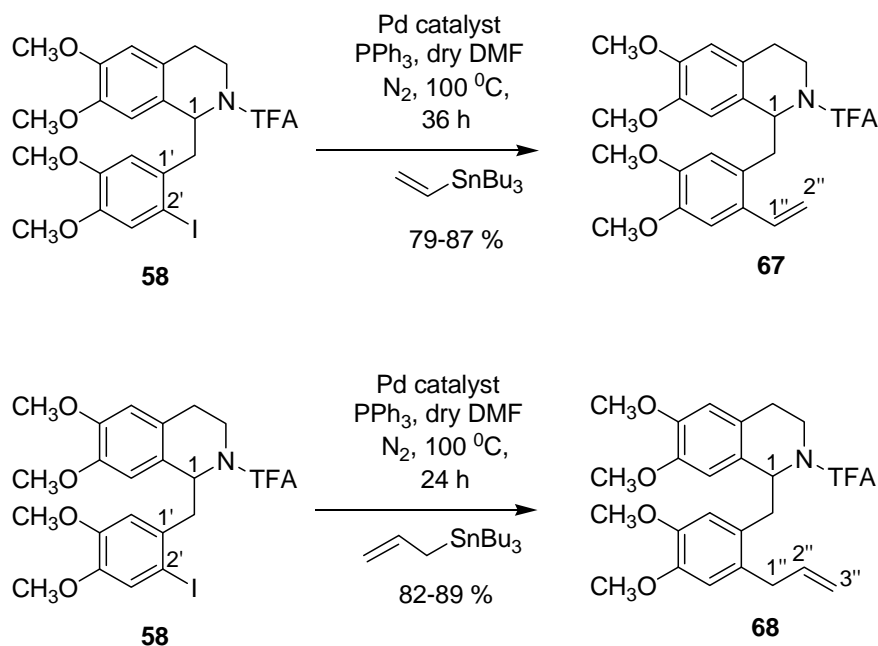
The Stille coupling cycle consists of four main steps: oxidative insertion, transmetalation, *trans-cis* isomerisation and reductive elimination (Scheme 2.4). Initially, the active palladium species was proposed to be the neutral Pd(0) species resulting from the reduction of palladium(II) salts e.g. Pd(OAc)₂ or PdCl₂ in the presence of ligands such as triphenylphosphine.¹²⁰ However, after a detailed mechanistic study of the Stille coupling reactions by Espinet and co-workers, the active Pd(0) species were instead found to be the anionic complexes [Pd(OAc)L₂]⁻ or [PdClL₂]⁻, the former being the result of the slow intramolecular reduction of [Pd(OAc)₂(PPh₃)₂].¹²¹ The reactive anionic Pd(0) species enters the catalytic cycle and undergoes oxidative addition with RX to give the *trans* [RPdXL₂] complex **C** possibly *via* the five-coordinate complex **B**. Complex **C** subsequently undergoes a transmetalation step where the organostannane exchanges with the halide. This process can occur *via* the open form intermediate to generate the *trans* complex **E**, which can isomerise rapidly to the *cis* complex **F**. Alternatively, it was found that the halide in compound **C** can exchange with the R'

group on the organostannane *via* a cyclic intermediate to give the *cis* complex **F** directly. In the last step of the catalytic cycle, the coupled product is eliminated *via* reductive elimination, releasing the Pd(0) to re-enter the catalytic cycle.



Scheme 2.4 The mechanism of the Stille coupling reaction.

2.4.2. Application of Stille couplings in the synthesis of **67** and **68**.



Scheme 2.5 The Stille coupling of derivative **58** to give the vinyl and allyl derivatives **67** and **68**, respectively.

Table 2.1 Summary of the Stille coupling reactions of **58**.

Entry	Palladium catalyst	Organostannane	Time of reaction (h)	Product	Yield (%)
1	PdCl_2	$\text{CH}_2=\text{CH-Sn(Bu)}_3$	36	67	79
2	Pd(OAc)_2	$\text{CH}_2=\text{CH-Sn(Bu)}_3$	36	67	87
3	PdCl_2	$\text{CH}_2=\text{CH-CH}_2\text{-Sn(Bu)}_3$	24	68	82
4	Pd(OAc)_2	$\text{CH}_2=\text{CH-CH}_2\text{-Sn(Bu)}_3$	24	68	89

The allylation and vinylation reactions of the aryl iodide **58** with tributylvinylstannane and allyltributylstannane were carried out using a literature procedure for other aryl iodides.¹²² These reactions gave the olefins **67** and **68**, respectively. The effect of varying the nature of the palladium catalysts on these reactions was examined, using either PdCl_2 or Pd(OAc)_2 and the outcomes are recorded

in Table 2.1. The yields obtained from the corresponding olefins were high for both cases using Pd(OAc)₂ or PdCl₂ (79 % to 89 % yield). It was found that Pd(OAc)₂ gave slightly higher yields compared to PdCl₂ for reactions involving either tributylvinylstannane or allyltributylstannane. The reactions of **58** with allyltributylstannane took 24 h at 110 °C while the reaction of **58** with tributylvinylstannane required 36 h at the same temperature.

The high reaction yields were due to the successful and efficient removal of the stannane by-products. The stannane by-products are hazardous and proved difficult to remove from the reaction mixture using column chromatography. However, as the stannane impurities were found to be insoluble in acetonitrile, they were successfully removed by dissolving the crude reaction mixture in acetonitrile and washing the solution with either hexane or petroleum spirits. Purification of the stannane-free crude reaction mixtures by column chromatography routinely provided pure samples of **67** and **68** in high yields.

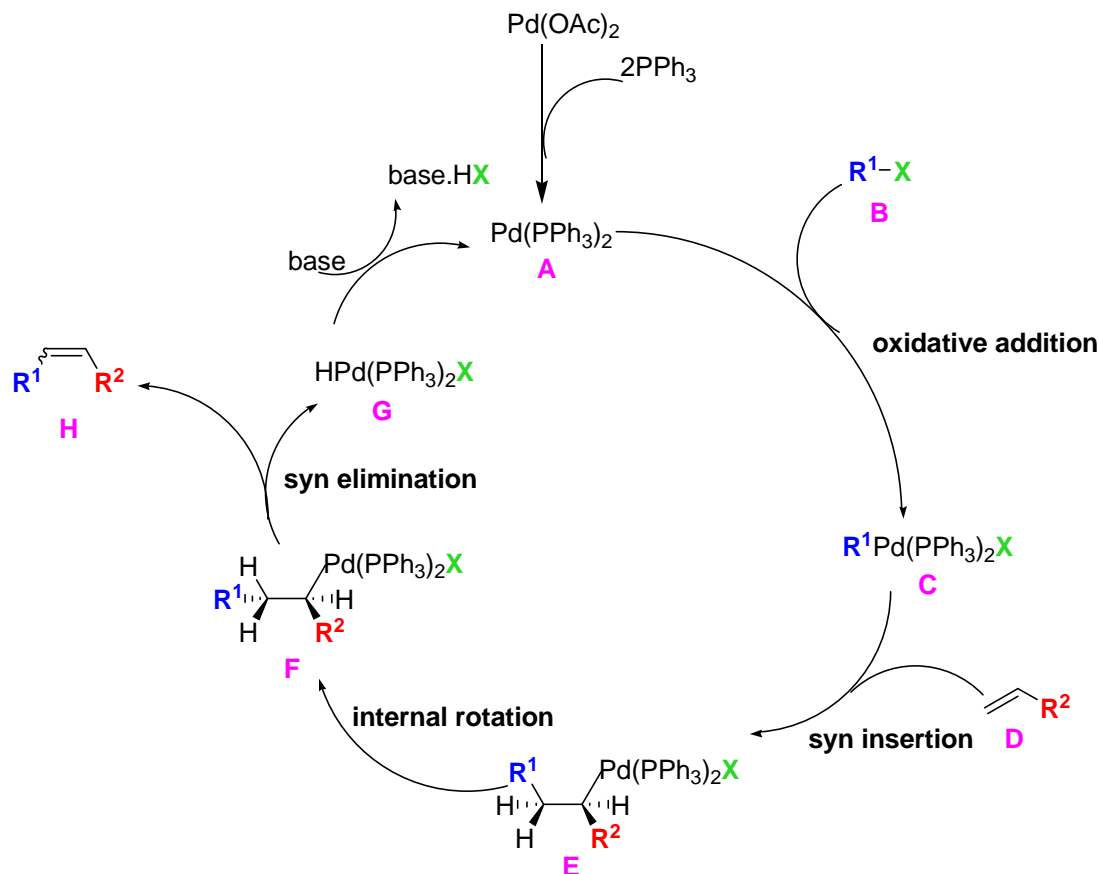
The structures of compounds **67** and **68** were confirmed by single crystal X-ray structural analysis (Figure 2.3). The structure of **67** was also confirmed by ¹H NMR analysis which showed the characteristic vinyl proton resonances at δ 6.81 (dd, 1H, *J* 17.0, 11.0 Hz, H1''), 5.46 (d, *J* 17.0 Hz, 1H, H2''(*E*)) and 5.13 (d, 1H, *J* 11.0 Hz, H2''(*Z*)). The allylic olefinic proton signals in derivative **68** appeared in the ¹H NMR spectrum at δ 5.82 (m, 1H, H2''), 5.02 (dd, 1H, *J* 10.2, 0.9 Hz, H3''(*Z*)) and 4.94 (dd, 1H, *J* 17.2, 0.9 Hz, H3''(*E*)). Low and high resolution MS analysis were consistent with the molecular formula of **67** and **68**.

2.5. Synthesis of the BBI derivative 65 via a palladium-catalysed Heck coupling reaction.

2.5.1. Background on Heck coupling reactions.

The Heck coupling reaction is defined as a coupling reaction between an olefin and an organic halide catalysed by a palladium catalyst.¹²³ This reaction was discovered by Richard F. Heck in the late 1960s.¹²³ Since then, Heck coupling reactions have become one of the most versatile methods for carbon-carbon bond formation with applications to the synthesis of bioactive compounds, natural products and high performance materials.^{124,125} Traditionally, the reaction is generally carried out by combining the organic halide (aryl, vinyl or benzyl), a slight excess of the olefin, a slight excess of a base and a sub-stoichiometric amount of a palladium complex and triarylphosphine. The homogenous solution is commonly either heated in a round bottom flask under a nitrogen atmosphere or heated in a sealed tube.¹²⁶ While some Heck coupling reactions have been reported to proceed with 2.5-5 mol % of palladium catalyst, catalysts loadings of 10-20 mol % equivalent are often necessary to ensure a smooth conversion to the desired product.¹²⁷ Palladium is often used in conjunction with triphenylphosphine in 1 : 2 ratio,¹²⁷ resulting in the *in situ* generation of the coordinatively unsaturated 14-electron Pd(0) species, Pd(PPh₃)₂ which is assumed to be an active complex in the catalytic cycle.¹²⁸ A simplified mechanism of the Heck coupling reaction is outlined in Scheme 2.6.¹²⁹ (see Scheme 2.8 for a more detailed reaction mechanism). The Heck coupling starts with the reduction of a palladium(II) species (e.g. Pd(OAc)₂) to palladium(0) (e.g. Pd(PPh₃)₂). This reactive species enters the catalytic cycle to undergo oxidative addition with the aryl halide (R¹-X), generating an aryl palladium(II) complex **C**. The next stage involves the *syn* insertion of complex **C** with the alkene **D** to give complex **E**. Internal rotation of complex **E** occurs to allow *syn*

elimination of a palladium hydride species **G**, and affords the coupled product **H**. The palladium hydride species **G** reacts with the base to regenerate $\text{Pd}(\text{PPh}_3)_2$.

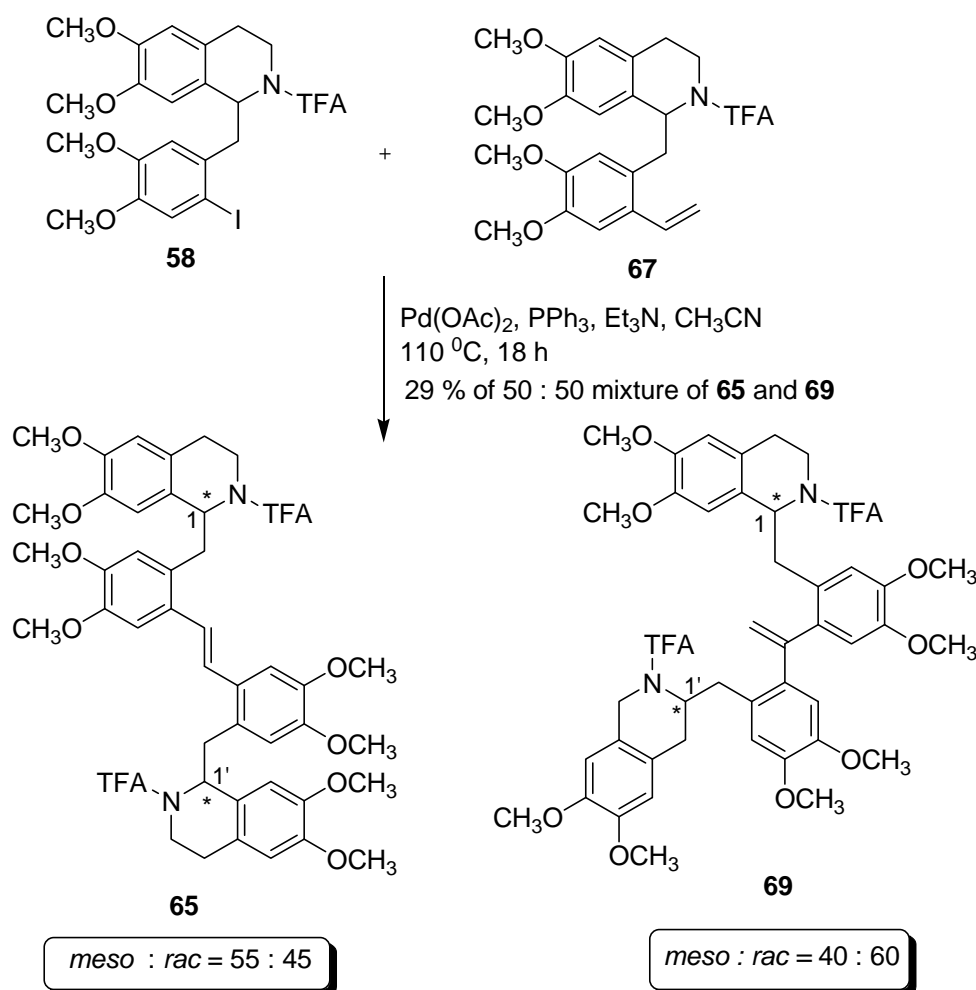


Scheme 2.6 The catalytic cycle of the palladium mediated Heck coupling reaction.

2.5.2. Application of the Heck coupling reaction to the synthesis of **65**.

The racemic compounds **58** and **67** were initially subjected to the traditional Heck coupling reaction conditions using $\text{Pd}(\text{OAc})_2$ and triphenylphosphine (1 : 2) with CH_3CN as the solvent and triethylamine as the base at 100°C for 18 h. Stilbene **65** was obtained, along with the unexpected regioisomer **69**, in a 50 : 50 mixture in 29 % yield. These compounds co-eluted on silica gel and could not be separated by column chromatography. However, the separation of these regioisomers was possible based on their different solubility properties. Compound **65** was found to be insoluble in

methanol, however the regioisomer **69** was found to have a high solubility in this solvent, therefore separation of **65** and **69** was facilitated by adding methanol to the mixture. Compound **65** was filtered off as a white solid, leaving the regioisomer **69** in the methanol solution which was further purified by column chromatography to afford **69** as a yellow oil.



Scheme 2.7 The Heck coupling reactions between **58** and **67** using traditional Heck coupling reaction conditions.

The stilbene **65** was obtained as a 55 : 45 mixture of diastereomers (*meso* (*R,S*) and racemic (*R,R* and *S,S*) forms) from ^1H NMR analysis. The 1,2-disubstitution pattern of the olefin group of **65** was evident by the characteristic olefinic proton signal at δ 7.58 (s, 2H, $\text{CH}=\text{CH}$) for *meso*-**65** and at δ 7.56 (s, 2H, $\text{CH}=\text{CH}$) for *rac*-**65**. It was not

possible to determine from ^1H NMR analysis whether the (*E*)- or (*Z*)-alkene was obtained due to the symmetrical nature of compound **65**. However, based on previous reports on Heck coupling reactions,¹³⁰ olefinic products have been obtained as either 100 % the (*E*)-isomer or predominantly the (*E*)-isomer, therefore **65** was most likely to be the (*E*)-isomer.

To assist in the assignment of the meso and racemate forms of **65**, (*S,S*)-**65** and (*S,S*)-**69** were prepared from (*S*)-norlaudanosiene **56** which was kindly provided by Dr A. Ung (Department of Chemistry, UOW). The ^1H NMR spectrum of (*S,S*)-**65** allowed a clear identification of the major diastereomer as the meso and the minor diastereomer as the racemate (Figure 2.4). Although this reaction was only done on a small scale, sufficient amounts of (*S,S*)-**65** and (*S,S*)-**69** were obtained for ^1H NMR analysis (Figure 2.4). A small amount of the pure meso isomer could also be isolated by trituration of a mixture of *rac*-**65** and *meso*-**65** with a small amount of DCM. *Meso*-**65** was found to have a slightly higher solubility than *rac*-**65**. Thus, instant removal of the DCM layer at this stage allowed the isolation of relatively pure *meso*-**65** for ^1H NMR analysis (Figure 2.4).

The ^1H NMR spectrum of (*S,S*)-**65** (Figure 2.4, middle spectrum) clearly showed five singlet (2 H each) resonances corresponding to the two sets of four different aromatic protons and the two olefinic protons. On the other hand, the ^1H NMR spectrum of *meso*-**65** (Figure 2.4, bottom spectrum) showed overlapping signals for the olefinic and the H3' and H3'' aromatic protons. The H1/H1' proton signals of *meso*-**65** appeared more deshielded at δ 5.47 (dd, 2H, *J* 9.5, 5.4 Hz, H1, H1') compared to those of (*S,S*)-**65** at δ 5.43 (dd, 2H, *J* 10.5, 3.3 Hz, H1, H1').

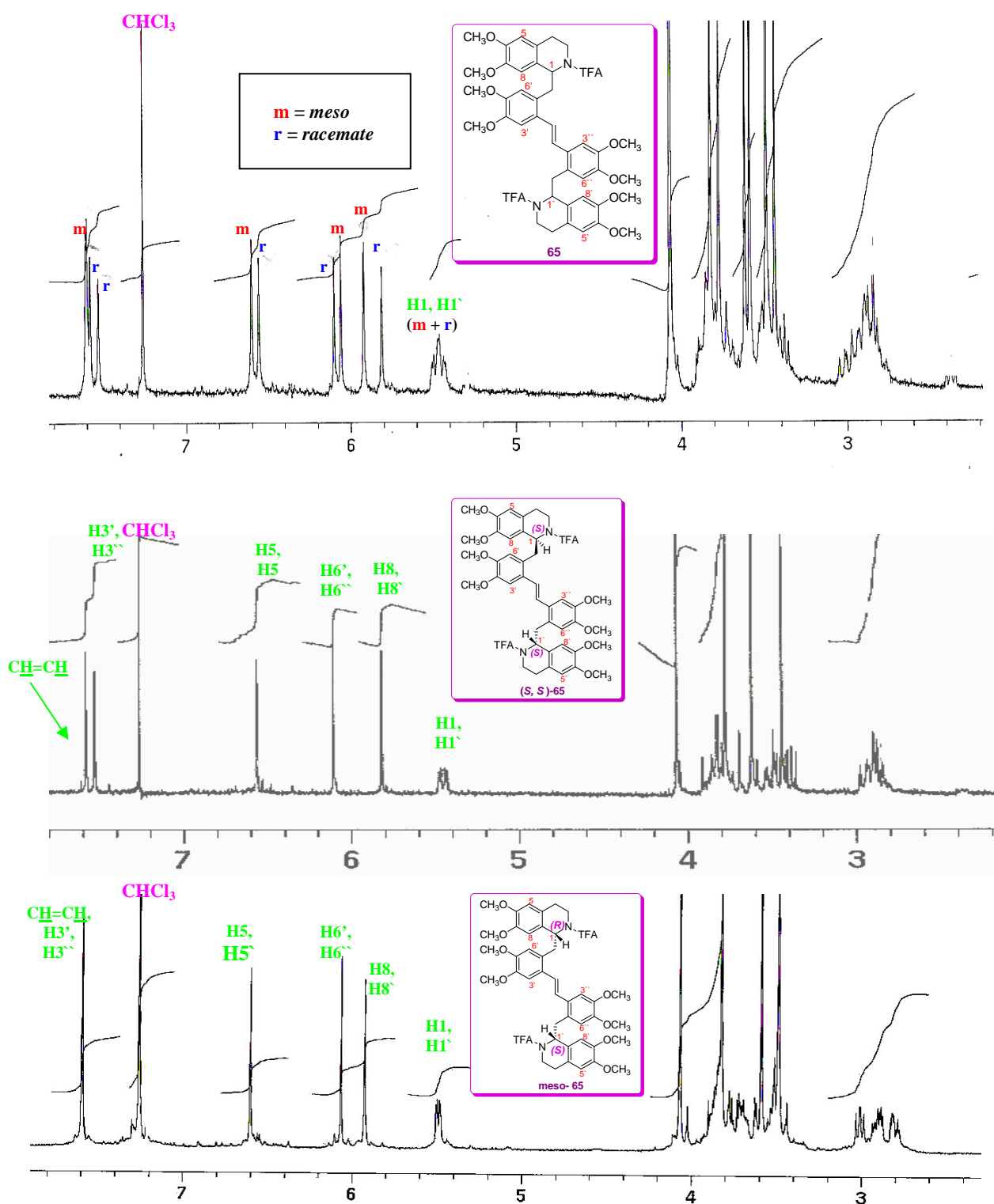


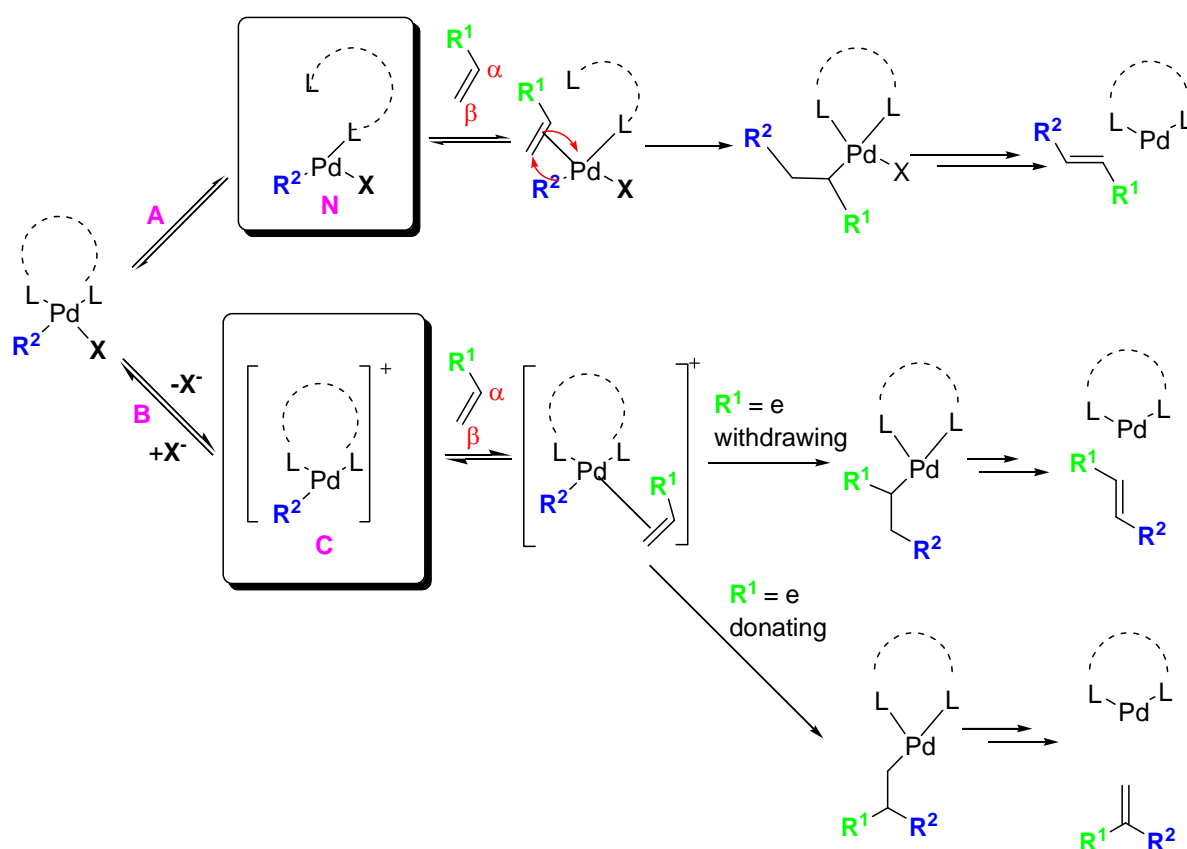
Figure 2.4 The ^1H NMR spectra (300 MHz, CDCl_3) of the mixture of *meso*-**65** and *rac*-**65** (top), (*S,S*)-**65** (middle) and *meso*-**65** (bottom).

The unexpected 1,1-disubstituted regioisomer **69** was obtained as a 60 : 40 mixture of *rac*-**69** and *meso*-**69**. Compound **69** was readily identified from its counterpart **65** by ^1H NMR spectroscopy by the presence of the two proton olefinic singlet resonances at δ 4.95 (s, 2H, $\text{C}=\text{CH}_2$) for the major and at δ 4.78 (s, 2H, $\text{C}=\text{CH}_2$) for the minor diastereomeric isomer. The assignment of *rac*-**69** and *meso*-**69** was also possible by comparison of their ^1H NMR spectra with that of the (*S,S*)-**69**. Since the synthesis of (*S,S*)-**65** and (*S,S*)-**69** was only done on a small scale, (*S,S*)-**69** was not obtained in pure form; however, the olefinic signal of (*S,S*)-**69** was clearly observed at δ 4.95 (s, 2H, $\text{C}=\text{CH}_2$), indicating that the major diastereomer of **69** was certainly *rac*-**69** and therefore the minor diastereomer was *meso*-**69**.

The formation of the two regioisomeric products, **65** and **69**, could be explained in light of the mechanistic studies by Cabri *et al.*¹²⁹ and Deeth *et al.*¹³¹ Their studies outlined two possible insertion pathways that can determine the regioselectivity of the Heck reaction (Scheme 2.8).

These pathways are distinguished by whether the ligand or the halide dissociates from the palladium to provide a vacant site for the incoming alkene. If a phosphine ligand detaches and the halide is retained, the active species immediately prior to the insertion step is the neutral complex $[\text{R}^2\text{PdXL}]$ **N**. However, if the halide is removed, the active species is the cationic complex $[\text{R}^2\text{PdRL}_2]^+$ **C**. The regioselectivity was reported to depend on both the reaction conditions (neutral **A** *versus* cationic **B** pathway) and the alkene substituents. Under neutral conditions, the aryl group R^2 attacks the less substituted β -carbon of the monosubstituted alkene, suggesting that the process is controlled by steric factors. Under “cationic” conditions, the site of attack varies with the electronic nature of the alkene substituents. Electron donating substituents can activate the α carbon to be attacked by $[\text{R}^2\text{PdL}_2]^+$, thus favour the 1,1-

substitution product, while electron withdrawing substituents deactivate the α carbon and activate the β carbon, leading to the 1,2-substitution product.¹³¹

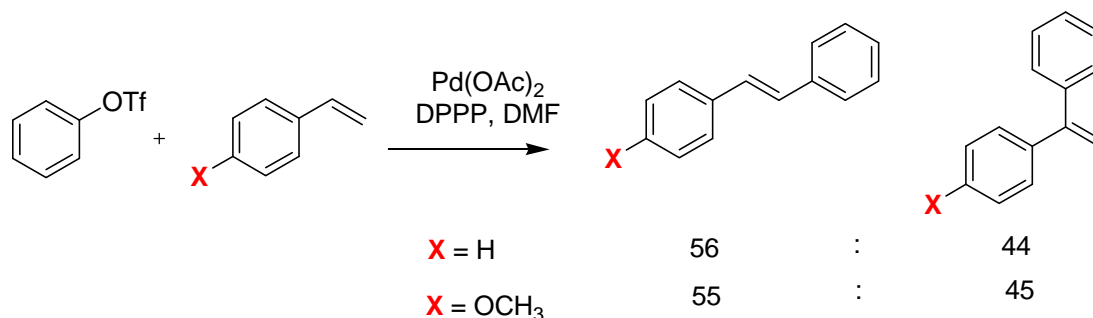


Scheme 2.8 The proposed mechanism of two possible insertion pathways. Pathway **A**: *via* dissociation of the neutral ligand. Pathway **B**: *via* dissociation of an anionic ligand.

In general, bidentate phosphine ligands and/or the triflate counterion ($\text{X} = \text{OTf}$, a poor coordinating ion) usually favour “cationic” intermediates while monodentate phosphine and coordinating ions (e.g. halide) usually favour neutral intermediates.¹²⁹

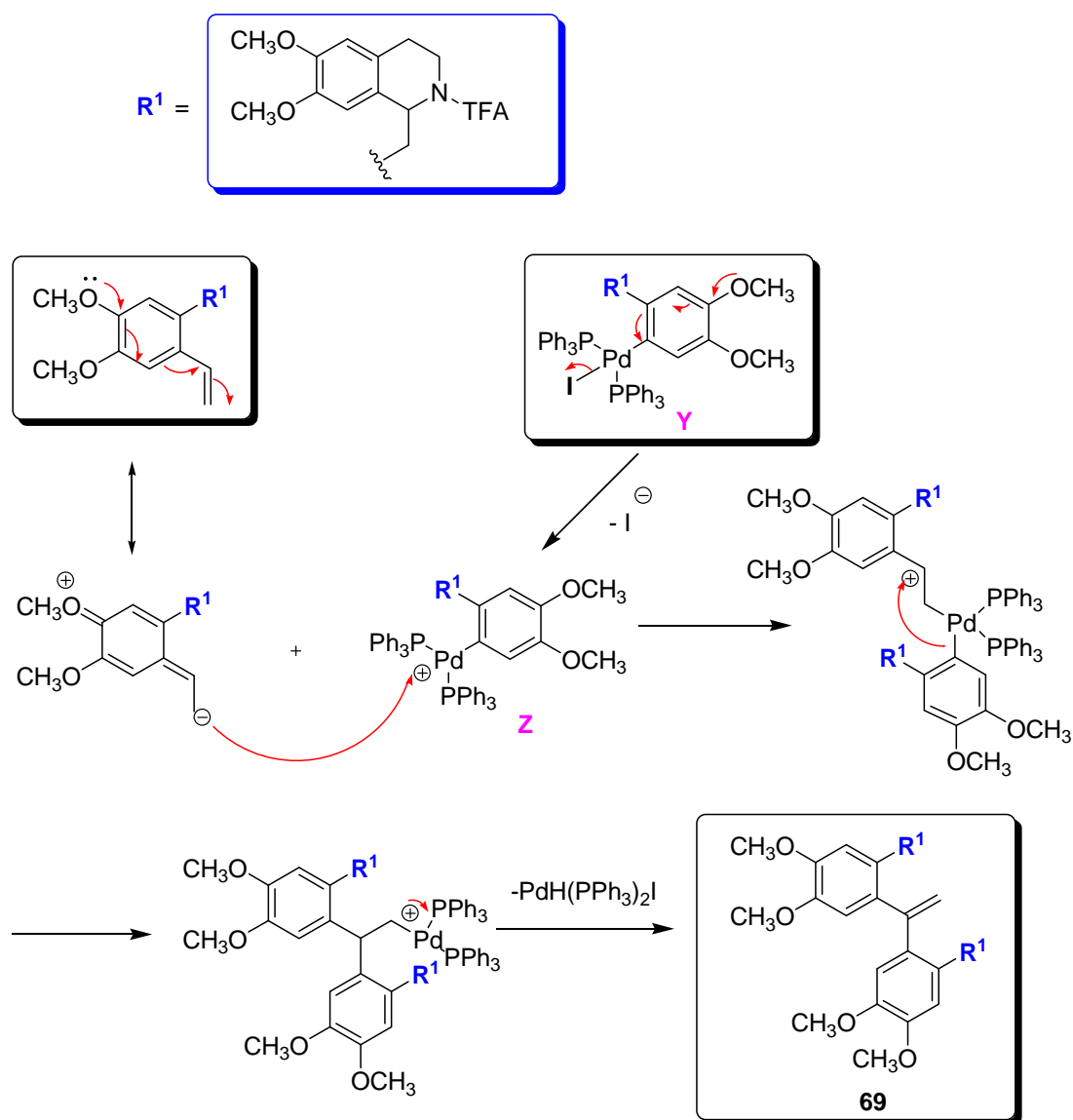
Under the original Heck coupling reaction conditions ($\text{Pd}(\text{OAc})_2$, Et_3N , 2 h, 100 $^\circ\text{C}$), the palladium catalysed reactions of iodobenzene and styrene gives exclusively (*E*)-stilbene (**74**) in 75 % isolated yield (Scheme 2.9).¹³²

Under similar conditions, Norrby¹³⁴ found insignificant differences in regioselectivity between styrene and *p*-methoxystyrene, both substrates gave significant amounts (44-45 %) of the α -substituted styrene product (Scheme 2.11).



Scheme 2.11 Heck coupling using the bidentate ligand DPPP.¹³⁴

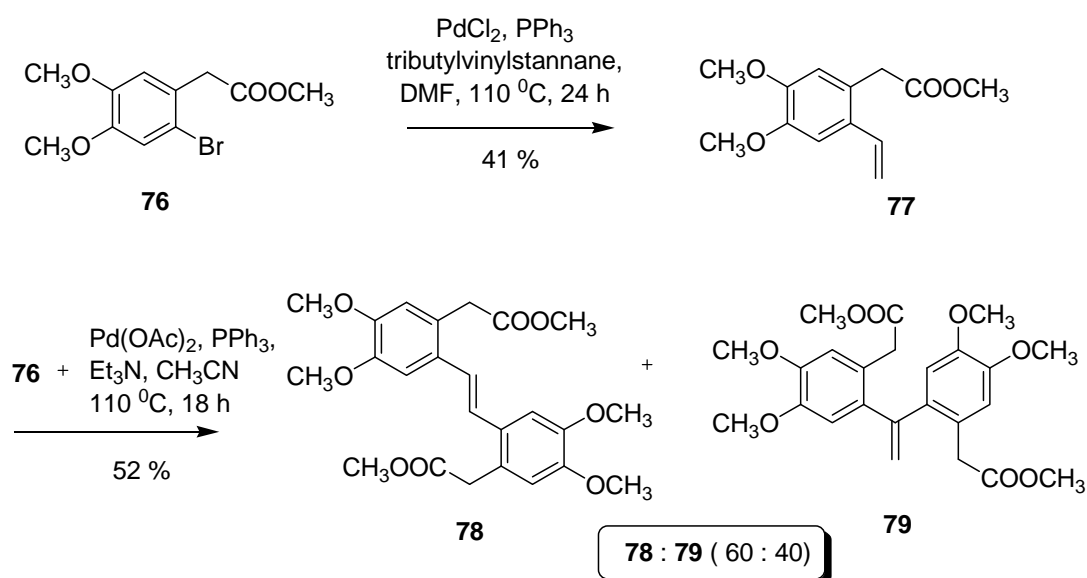
According to the reported mechanism in Scheme 2.8, the formation of regioisomer **69**, as a 50 : 50 mixture with **65**, resulted from a Heck coupling reaction occurring *via* pathway **B**. It appears that electronic factors favour the formation of the 1,1-disubstituted alkene product **69** in our study because the β -styrene carbon is electron rich due to the two methoxy substituents on the aromatic ring. The resulting polarisation of the styrene double bond would favour attack of the palladium complex at the β position, leading to the 1,1-disubstituted product **69** (Scheme 2.12). Furthermore, the two methoxy substituents on the aryl iodide ring might assist in the loss of the iodide from its corresponding arylpalladium(II) iodide intermediate **Y** giving the cationic arylpalladium(II) intermediate **Z**, which would be expected to favour the formation of **69**.



Scheme 2.12 A proposed mechanism for the formation of regioisomer **69**.

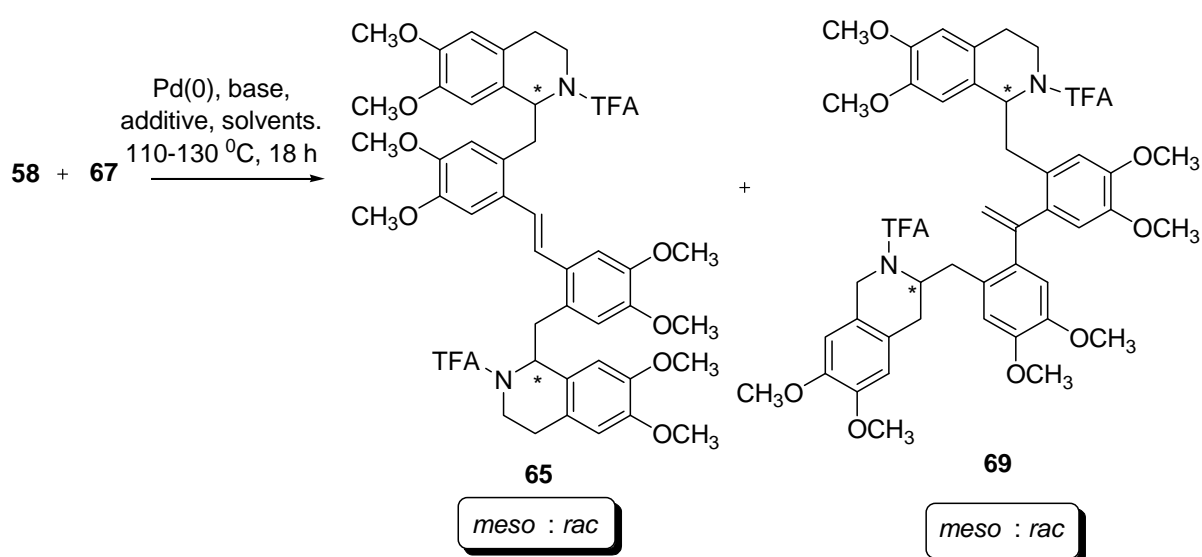
In order to further support the proposed mechanism outlined in Scheme 2.12, the electron rich alkene **77** was subjected to the same Heck coupling reaction conditions with the aryl bromide **76** (Scheme 2.13). Under these conditions, the stilbene **78** was obtained along with its regioisomer **79** in a ratio of 60 : 40. These results were consistent with the results obtained from the Heck coupling reactions between the vinylaudanosine derivative **67** and the iodolaudanosine derivative **58**. The products **78** and **79** were identified from each other by the different positions of the olefinic

resonances at δ 7.11 (s, 2H, $\text{CH}=\text{CH}$) for **78** and at δ 5.40 (s, 2H, $\text{C}=\text{CH}_2$) for **79**. The formation of **79** was consistent with our proposed hypothesis that a cationic arylpalladium(II) species was involved when dealing with electron rich aryl halides and alkenes.



Scheme 2.13 Heck coupling reaction of methoxylated styrene **77** and bromo derivative **76**.

2.5.3. Heck coupling reactions-optimization of yields and a study of regioselectivity.



Scheme 2.14 The general Heck coupling reaction.

Table 2.2 The outcomes of the Heck coupling reactions between compound **58** and **67** at 130 °C for 18 h.Note. * These reactions were heated at 110 °C.

Entry	58 (mol. equiv.)	67 (mol. equiv.)	Catalyst (10 mol. % equiv.)	Additive (s) (2 mol. equiv.)	Base (2 mol. equiv.)	Solvent	65 : 69 ratio	Yield (%) (65 + 69)	D.r. of 65 <i>(meso : rac)</i>	D.r. of 69 <i>(rac : meso)</i>
1*	1	1.2	Pd(OAc) ₂	PPh ₃	Et ₃ N	CH ₃ CN	50 : 50	29	55 : 45	60 : 40
2*	1	1.2	PdCl ₂	PPh ₃	Et ₃ N	CH ₃ CN	n/a	0	n/a	n/a
3*	1	1.2	PdCl ₂	PPh ₃ + AgOAc	Et ₃ N	CH ₃ CN	n/a	0	n/a	n/a
4	1	1	Pd(OAc) ₂	DMG	NaOAc	NMP	80 : 20	65	55 : 45	60 : 40
5	1	1	Pd(OAc) ₂	PPh ₃	NaOAc	NMP	60 : 40	50	55 : 45	60 : 40
6	1	1	Pd(OAc) ₂	none	NaOAc	NMP	40 : 60	54	45 : 55	60 : 40
7	1	1	Pd(OAc) ₂	PPh ₃	AgOAc	NMP	100 : 0	9	70 : 30	n/a
8	1	1	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	NMP	100 : 0	9	30 : 70	n/a
9	1	1	Pd(OAc) ₂	DMG	Ag ₂ CO ₃	NMP	50 : 50	9	55 : 45	55 : 45
10	1	1	Pd(OAc) ₂	DMG	NaOAc + Ag ₃ PO ₄	NMP	90 : 10	24	55 : 45	60 : 40

To investigate the factors which control the regioselectivity between compound **65** and its regioisomer **69**, a series of Heck coupling reactions using different palladium catalysts and additives were carried out. These conditions were also anticipated to improve the yields obtained for the products **65** and **69**. All reactions were performed in a sealed tube at 110-130 °C for 18 h. The outcomes of the Heck reactions of **58** and **67** are summarised in Table 2.2.

The reactions described in entries 1 and 2 employed the traditional Heck coupling conditions using Pd(OAc)₂ and PdCl₂, respectively as the catalysts. The outcome in entry 1 has been discussed in section 2.5.2, where a 50 : 50 ratio of **65** and **69** was obtained in low yield (29 %). Changing the catalyst from Pd(OAc)₂ to PdCl₂ (entry 2) appeared to render the reaction inactive as no product was obtained. The starting materials had decomposed under the high reaction temperature. Addition of AgOAc under the same reaction conditions as entry 2 was anticipated to assist in the generation of the electrophilic cationic complex in order to favour the formation of the 1,1-disubstituted regioisomeric product **69**. However, in this case, no product was isolated, only some starting material and decomposed material were obtained (entry 3).

At this stage, more modern Heck coupling reaction conditions were employed. Entries 4-6 use *N*-methylpyrrolidinone (NMP) as the solvent and NaOAc as the base, with variations in the types of additives.¹³⁵ Many researchers have used *N,N*-dimethylglycine (DMG) as an alternative additive to triphenylphosphine due to its relatively low cost and ease of product purification.¹³⁶ The role of DMG in these reactions has not been ascertained. The use of NMP and Pd(OAc)₂ and DMG as the additive (entry 4), resulted in a significantly higher yield (65 %) of a mixture of the regioisomers **65** and **69** with a much enhanced regioselectivity of 80 : 20 in favour of **65**. The regioselectivity (60 : 40) and yield (50 %) were both lower when DMG was

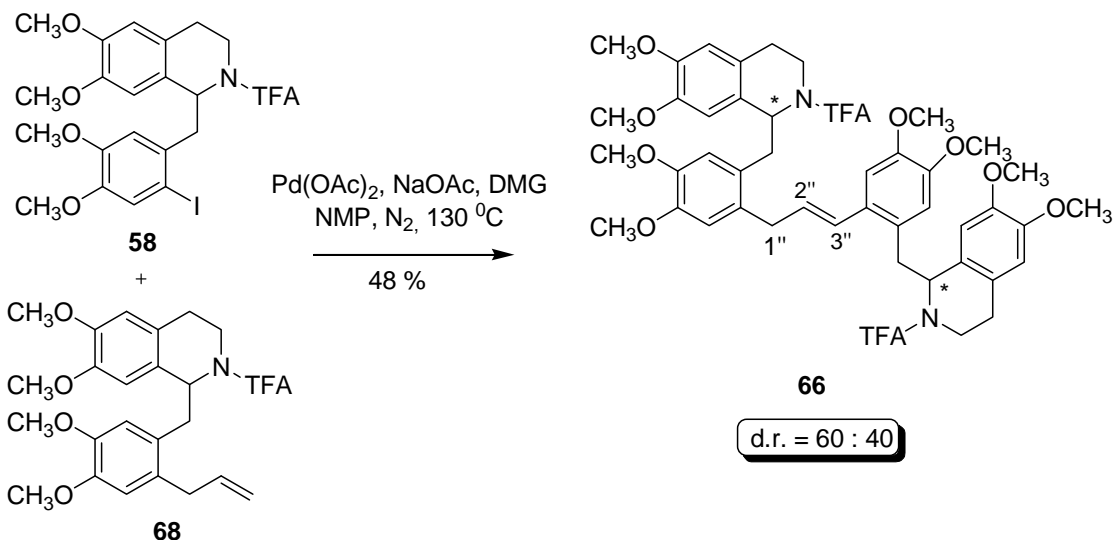
replaced by PPh_3 (Table 2, entry 5). When the additives DMG or PPh_3 were omitted (entry 6), the yield of **65** and **69** remained moderate (54 %), however the major regioisomer was the 1,1-disubstituted derivative **69** (**65** : **69** = 40 : 60).

Entries 7 and 8 examined the replacement of the NaOAc with an alternative base, silver acetate (AgOAc) and silver carbonate (Ag_2CO_3). Many publications have indicated the use of silver salts as a halogen abstracting agent, creating cationic palladium complex intermediates,^{137,138} forcing the *syn* insertion step of the Heck catalytic cycle to proceed according to pathway **B** in Scheme 2.7. With this mechanism operating on our electron rich alkene system, an increase in regioselectivity in favour of the 1,1-disubstituted alkene product **69** was anticipated. The results obtained interestingly deviated from our assumption and only product **65** was obtained in very low yield (9 %). Entry 9 examined a similar reaction condition to entry 8, except that PPh_3 was replaced by DMG. In this case, only a 9 % yield of a mixture of **65** and **69** was obtained. Therefore it was observed that the use of AgCO_3 or AgOAc was not desirable for these substrates.

The last entry in Table 2.1 (entry 10) examined the results of having two different bases in the reaction. It was observed that the use of NaOAc gave the highest product yields, hence a mixture of NaOAc and silver phosphate (Ag_3PO_4) were used with the hope of increasing the product yield and regioselectivity. Under these conditions, a better regioselectivity was observed (**65** : **69** = 90 : 10) however the yield was reduced to 24 %. The regioselectivity however was not expected for the addition of silver salts.

In summary, it can be concluded that employment of $\text{Pd}(\text{OAc})_2$ as the catalyst, DMG as the additive, NaOAc as the base and NMP as the solvent at 130 °C would be the best conditions for subsequent Heck coupling reactions.

2.6. Synthesis of the non-symmetrical bisbenzylisoquinoline **66** via the Heck coupling reaction.



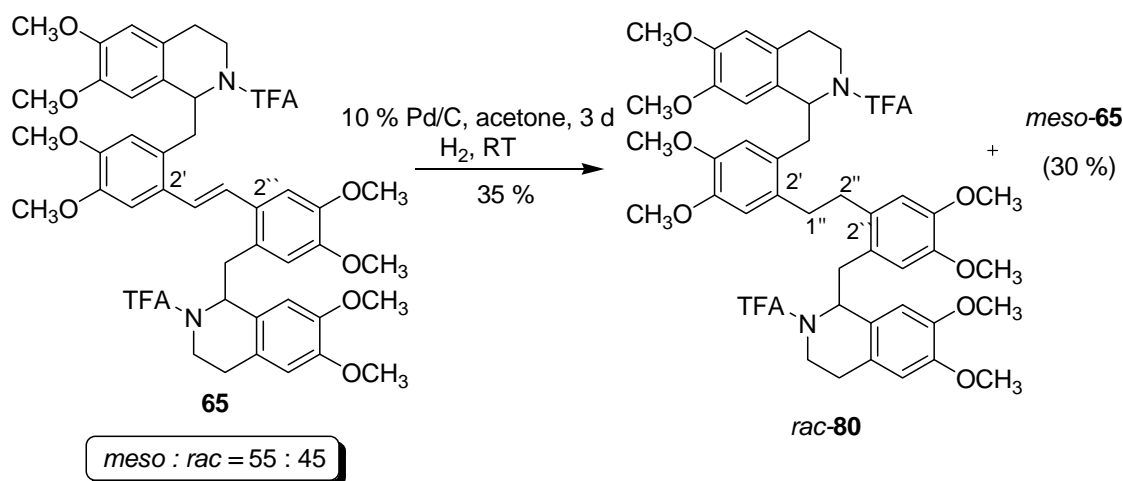
Scheme 2.15 Synthesis of the non-symmetrical three carbon tethered BBI derivative **66**.

The optimised Heck coupling reaction conditions were employed using the racemic iodide **58** and the racemic 2'-allyllaundanosine derivative **68** to afford the three carbon tethered BBI derivative **66** in moderate yield (48 %). In this case only the regioisomer **66** was formed. A 60 : 40 mixture of diastereomers was produced due to the presence of the two stereogenic centres in the product **66**. This unequal mixture suggested that *meso*-**66** and *rac*-**66** either formed or decomposed at different rates. The relative low yield for the reaction and the absence of both starting materials suggested that selective decomposition of one diastereomer of the product had occurred. In the ^1H NMR spectrum of **66**, eight pairs of aromatic singlet signals were observed which corresponded to the eight different aromatic protons present in the two diastereomers of **66**. These eight pairs of signals resulted from the loss of symmetry introduced by the non-symmetrical three carbon tether. The distinctive olefinic signals were observed at δ 6.42 (d, 1H, J 14.1 Hz, $\text{H}_{3''}$) and 5.95 (m, 1H, $\text{H}_{2''}$) for both isomers of **66** in the ^1H

NMR spectrum indicating that only (*E*)-**66** had formed. The corresponding olefinic carbon signals were also observed in the ^{13}C NMR spectrum at δ 129.5 (CH-3'') and 127.5 (CH-2'') and δ 129.7 (CH-3'') and 127.6 (CH-2'') for the major and minor diastereomers of **66**, respectively.

2.7. Synthesis of saturated tethered bisbenzylisoquinoline derivatives *via* hydrogenation.

2.7.1. Synthesis of the saturated tethered BBI derivative **80**.



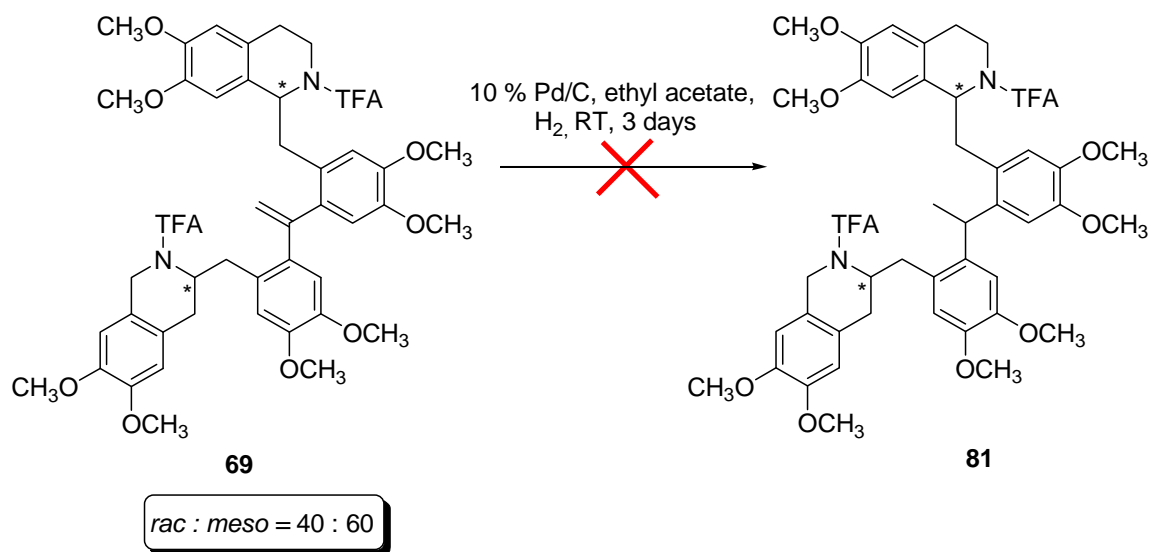
Scheme 2.16 Hydrogenation of the double bond of **65**.

The BBI derivative **80** containing a saturated ethylene tether across the C2' positions was also desirable and was obtained from the corresponding alkene **65** by hydrogenation over 10 % Pd/C under a hydrogen atmosphere (1 atm). These hydrogenation reactions are commonly performed in methanol or ethyl acetate. However, as discussed previously in Section 2.5.2, the alkene **65** had poor solubility in these solvents but was soluble in DCM. However, hydrogenation reactions in DCM have been found in our laboratory to be unsuccessful, therefore its use as the solvent was avoided. Other solvents were tested including CH₃CN and DMF, however none of these were found to dissolve compound **65**. However, compound **65** was found to be

partially soluble in acetone, therefore the hydrogenation reaction was performed in a large volume of acetone which was stirred continuously for 3 d under a hydrogen atmosphere. From ^1H NMR analysis, only *rac*-**65** underwent hydrogenation to afford to the corresponding product *rac*-**80** while *meso*-**65** remained unreacted. This outcome indicated that *meso*-**65** had a lower solubility in acetone than *rac*-**65** and therefore did not undergo hydrogenation. *Meso*-**65** and *rac*-**80** were separated by adding methanol to the mixture and filtering off the solid *meso*-**65** which was recovered in 30 % yield. The product, *rac*-**80**, was obtained by removal of the methanol in a yield of 35 %. The structure of *rac*-**80** was confirmed by the disappearance of the alkene protons signals at δ 7.58 (s, 2H, $\text{CH}=\text{CH}$) in the ^1H NMR spectrum and the appearance of the newly formed CH_2 proton signals at δ 2.82 (s, 4H, H1'' , H2''). The structure of *rac*-**80** was further confirmed by ^{13}C NMR and MS analysis.

2.7.2. Attempted synthesis of saturated BBI derivative **81**.

The regioisomer **69** was also subjected to catalytic hydrogenation, and ethyl acetate was used as the solvent. However, while alkene **69** was soluble in the reaction solution, it was completely unreactive and no product was obtained after 3 d and only starting material was recovered. Molecular modeling of *meso*-**69** and *rac*-**69** (structure not shown) (Spartan Pro, AM1 force field) showed that both sides of the olefin group were highly hindered by the benzyloquinoline substituents, thus preventing compound **69** from approaching close to the hydrogen-bound palladium surface in order to undergo hydrogenation. While this hydrogenation may have been successful at higher pressures of hydrogen, this was not attempted.



Scheme 2.17 The attempted hydrogenation of **69**.

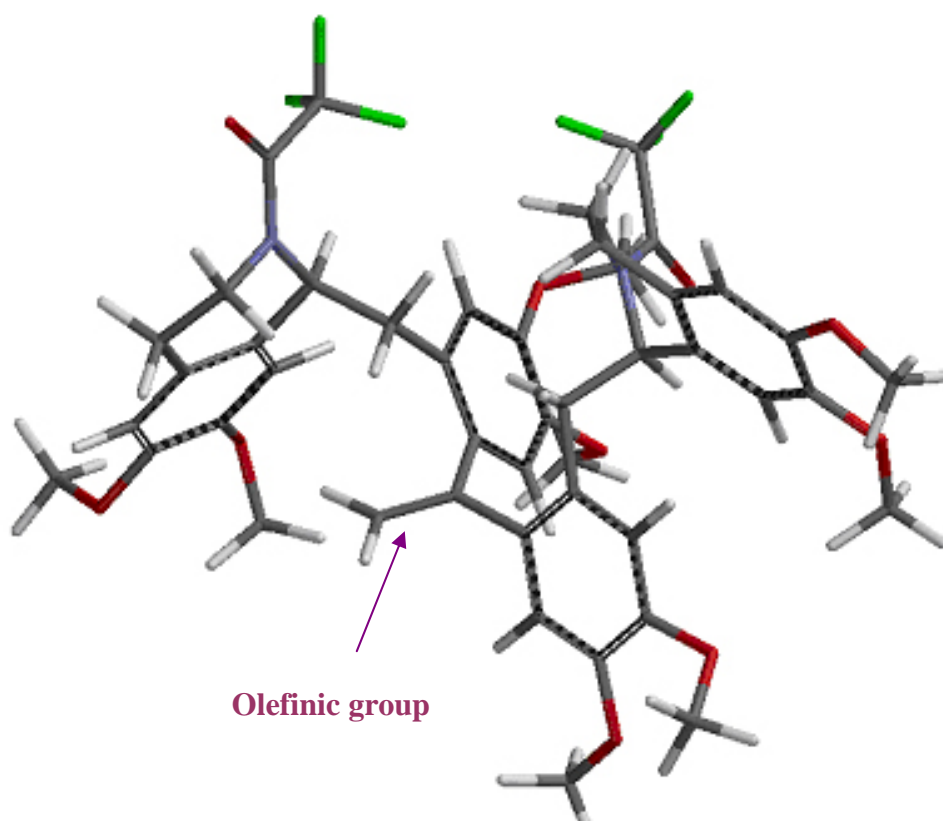
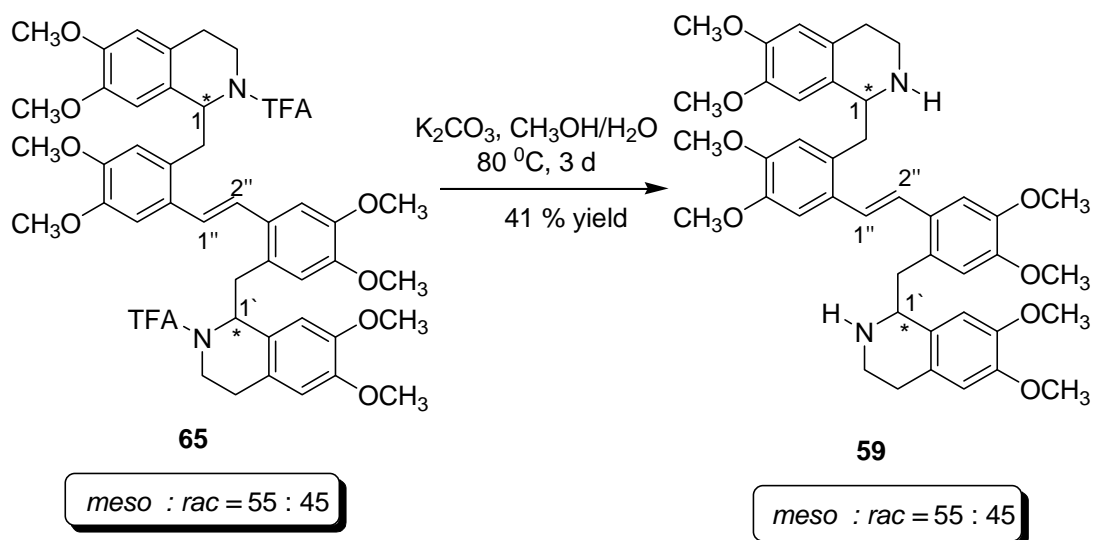


Figure 2.5 3D representations of *meso*-**69** (Spartan Pro, AM1) showing the sterically hindered environment of the olefinic group.

2.8. N-TFA deprotections.

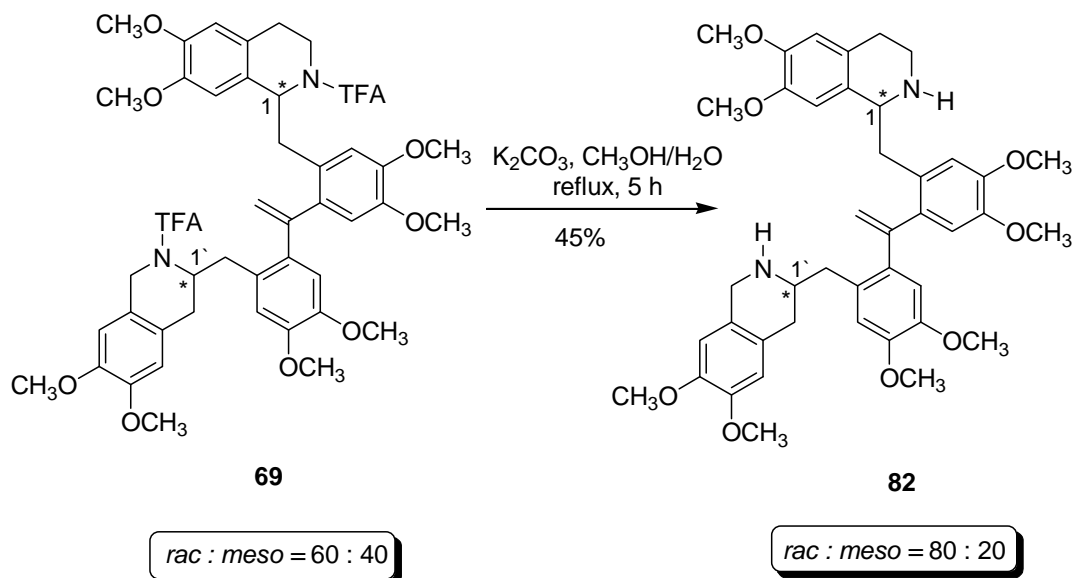
2.8.1. N-TFA deprotection of **65**.



Scheme 2.18 N-TFA deprotection of derivative **65**.

Base (K_2CO_3)-catalysed deprotection of the N-TFA group of **65** (d.r. = 55 : 45) at RT in CH_3OH was not possible because of poor solubility problems, therefore the reaction mixture was heated at $80\text{ }^\circ\text{C}$ in a large volume of solvent to enable complete solubility of the substrate. The reaction was complete in 3 d and afforded the desired product **59** (d.r. = 55 : 45) in 41 % yield. The structure of **59** was confirmed by the loss of the resonances for H1/H1' protons at δ 5.47 (dd, 2H, J 9.5, 5.4 Hz, H1, H1') for *meso*-**65** and at δ 5.45 (dd, 2H, J 10.2, 3.3 Hz, H1, H1') for *rac*-**65** form. The signals for the newly formed H1/H1' protons of **59** were observed at δ 4.17 (dd, 2H, J 9.0, 4.5 Hz, H1, H1') for *meso*-**59** and at δ 4.14 (dd, 2H, J 11.1, 3.9 Hz, H1, H1') for *rac*-**59**. This characteristic upfield shift for the H1 signal was due to the loss of the electron withdrawing amide functionality. The olefinic signals of **59** were observed in the 1H NMR spectrum at δ 7.07 (s, 2H, $\underline{CH=CH}$) for *meso*-**59** and at δ 7.16 (s, 2H, $\underline{CH=CH}$) for *rac*-**59**.

2.8.2. *N*-TFA deprotection of **69**.



Scheme 2.19 *N*-deprotection of derivative **69**.

The regioisomer **69** was subjected to the same basic hydrolysis reaction conditions as applied to compound **65**, however the reaction was complete as indicated from TLC analysis in 5 h and afforded the corresponding product **82** in 45 % yield. However, the ratio of the diastereomers had changed from 60 : 40 in **69** to 80 : 20 in **82**. This change in diastereomeric ratio could be a result of the more selective decomposition of one diastereomer of **82** under the reaction conditions or preferential or partial hydrolysis of one diastereomer of **69**. However, partial hydrolysis products of **69** were not detected by TLC and/or isolated by column chromatography.

While still uncertain about the stereochemical identities of these diastereomers, it is assumed the major diastereomer was *rac*-**82** due to the fact that it was the major diastereomer in the starting material **69**, however, because of the low yield of **82**, we can not be certain. The two diastereomers of **82** were separated by PTLC and their ^1H NMR spectra are shown in Figure 2.6. The complete *N*-TFA cleavage of **69** was evident from the presence of the characteristic, relatively more shielded H1/H1' proton signals

at δ 4.10 (dd, 2H, J 10.2, 4.5 Hz, H1, H1') for the major diastereomer and at δ 4.06 (dd, 2H, J 8.4, 6.6 Hz, H1, H1') for the minor diastereomer.

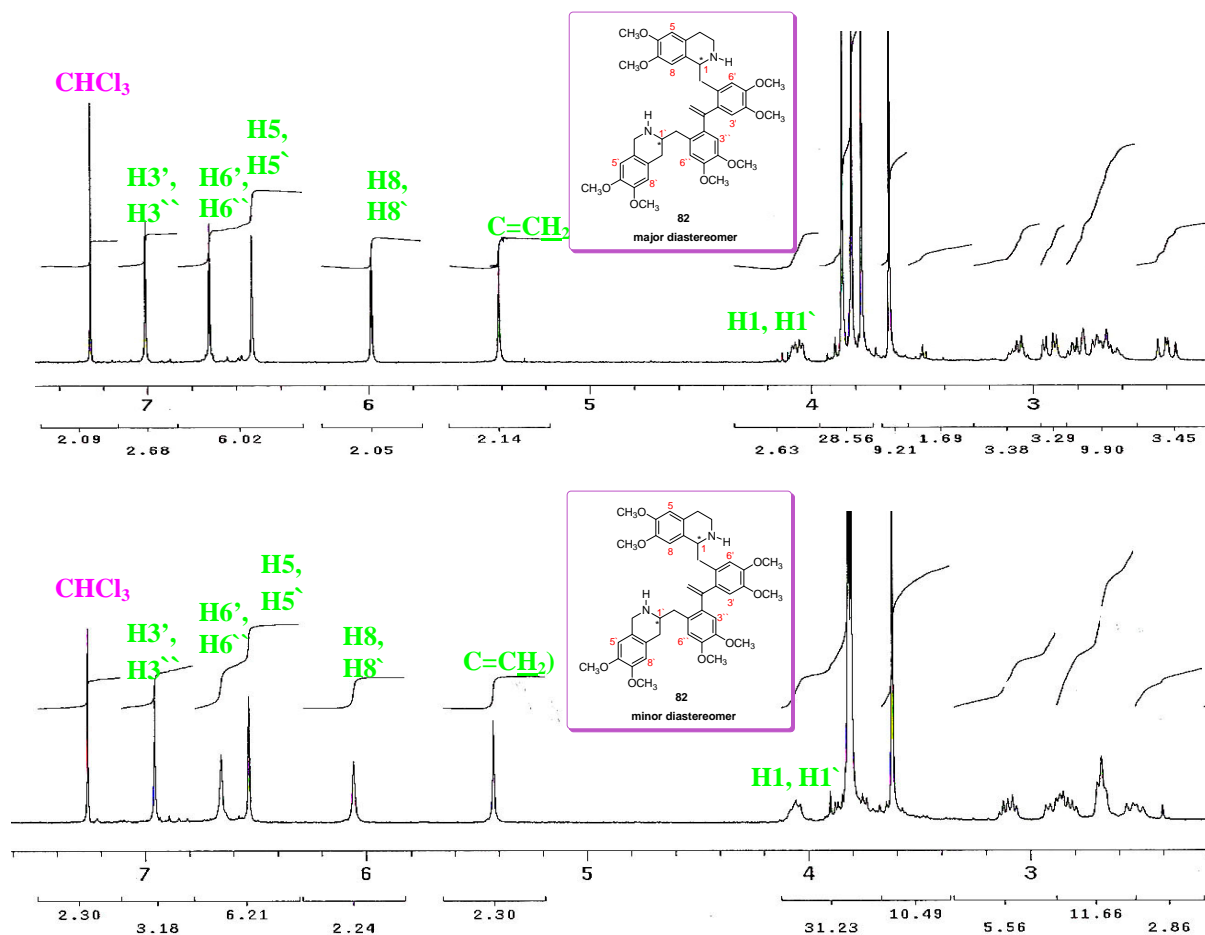
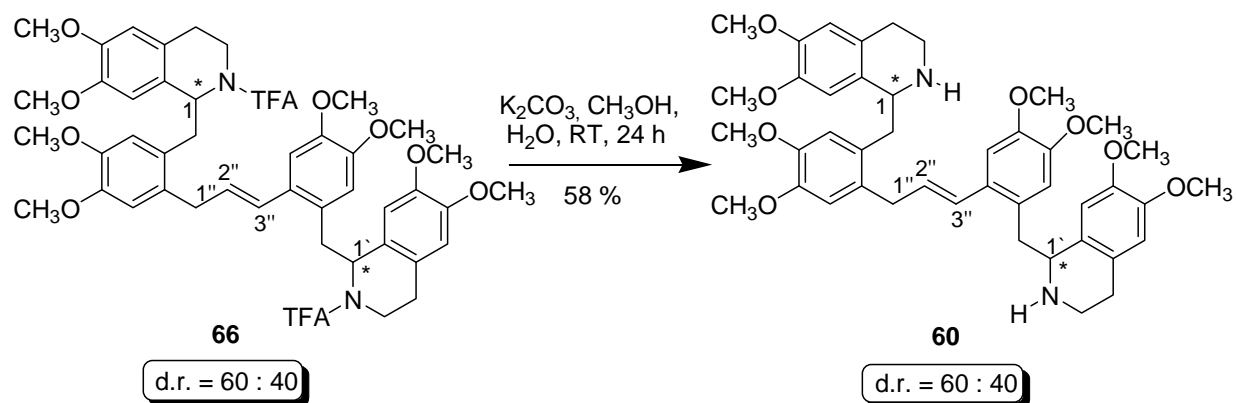


Figure 2.6 ¹H NMR spectra (300 MHz, CDCl₃) of the major (top) and the minor (bottom) diastereomer of derivative **82**.

2.8.3. *N*-TFA deprotection of **66**.

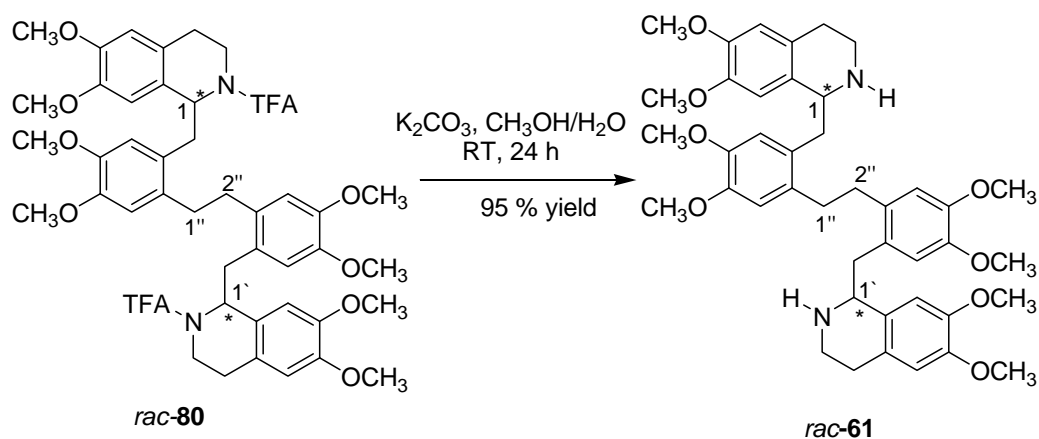
N-TFA deprotection of **66** (d.r. = 60 : 40) was achieved using the same deprotection conditions described previously, however the reaction was maintained at RT for 24 h and afforded the desired product **60** in a moderate yield (58 %) (Scheme 2.20).



Scheme 2.20 *N*-deprotection of derivative **66**.

Two diastereomers of **60** were observed in a ratio of 60 : 40. The success of the *N*-TFA deprotection was confirmed from ^1H NMR analysis that showed pairs of relatively more shielded H1/H1' proton resonances for **60** at δ 4.11 (dd, 1H, J 8.4, 5.4 Hz, H1') and 4.03 (m, 1H, H1) for the major diastereomer and at δ 4.14 (m, 1H, H1') and 4.05 (m, 1H, H1) for the minor diastereomer as a result of the loss of the amide functionality. ESMS analysis of **60** also confirmed its molecular structure.

2.8.4. *N*-TFA deprotection of *rac*-**80**.



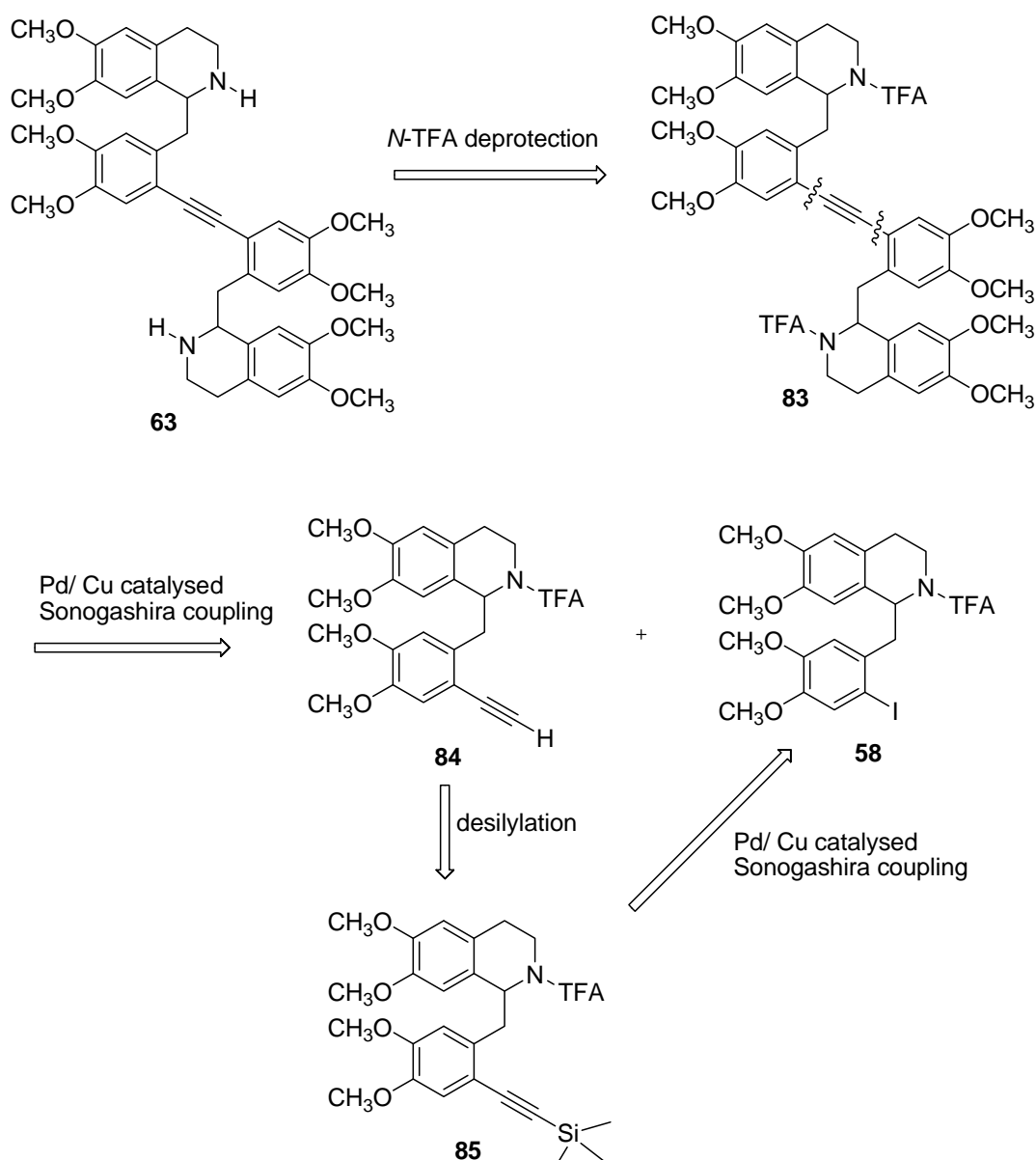
Scheme 2.21 *N*-deprotection of *rac*-**80**.

As mentioned previously in Section 2.8.1, only *rac*-**80** was obtained from the hydrogenation reaction of **65**, therefore only *rac*-**80** was subjected to the *N*-TFA deprotection reaction at RT for 24 h to afford the corresponding amine, *rac*-**61** in 95 %

yield. The formation of *rac*-**61** was evident by the loss of the H1/H1' proton signal at δ 5.40 (dd, 1H, J 8.4, 5.1 Hz, H1, H1') in *rac*-**80** which was replaced with a more shielded H1/H1' signal at δ 4.05 (dd, 1H, J 9.3, 5.1 Hz, H1, H1') in *rac*-**61** due to the loss of the amide functionality.

2.9. Synthesis of an Acetylenic Tethered Bis-benzylisoquinoline *via* the Sonogashira coupling reaction.

2.9.1. Retrosynthesis of the targeted acetylenic BBI derivative **63**.

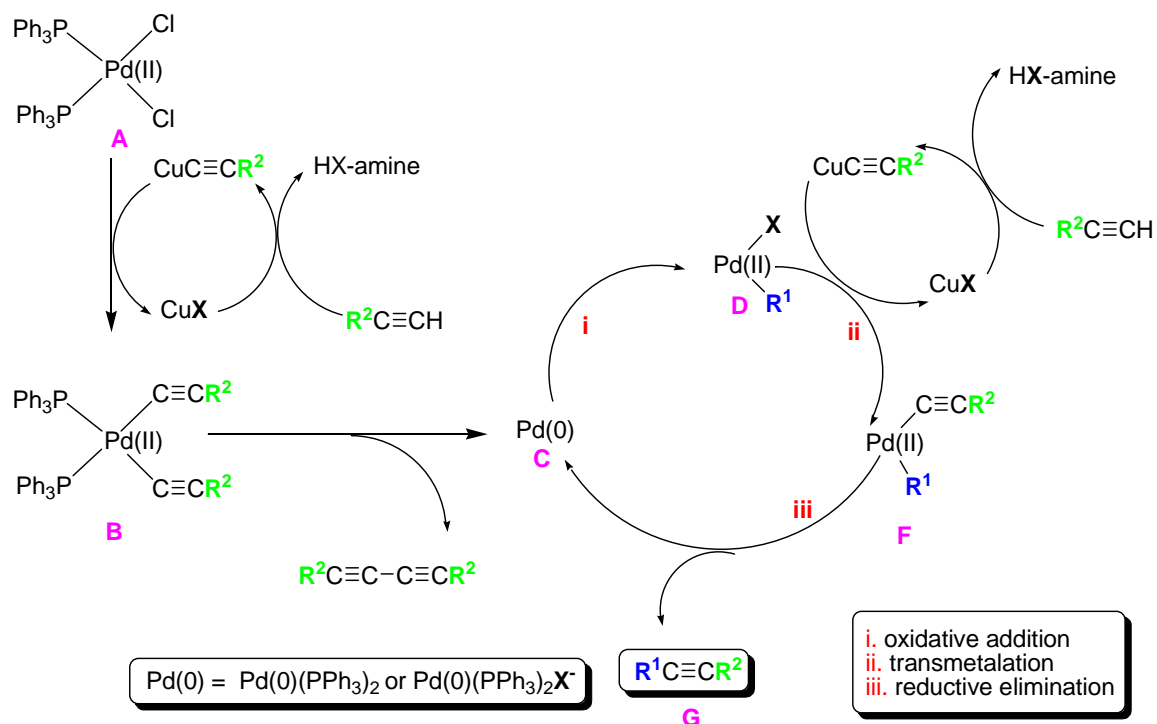


Scheme 2.22 A retrosynthesis of acetylenic BBI derivative **63**.

Our retrosynthesis of the acetylenic BBI derivative **63** is outlined in Scheme 2.22. The targeted BBI derivative **63** can be obtained by *N*-TFA cleavage of the key BBI derivative **83**. Alkyne **83** can be derived using a Sonogashira coupling reaction between the acetylinic laudanosine derivative **84** and the 2'-iodonorlaudanosine derivative **58**. The terminal acetylene **84** could be obtained from desilylation of the intermediate **85**, which could be synthesised by a Sonogashira cross-coupling reaction between the 2'-iodonorlaudanosine **58** and trimethylsilylacetylene using standard Sonogashira coupling reaction conditions.¹³⁹

2.9.2. Background on the Sonogashira coupling reactions.

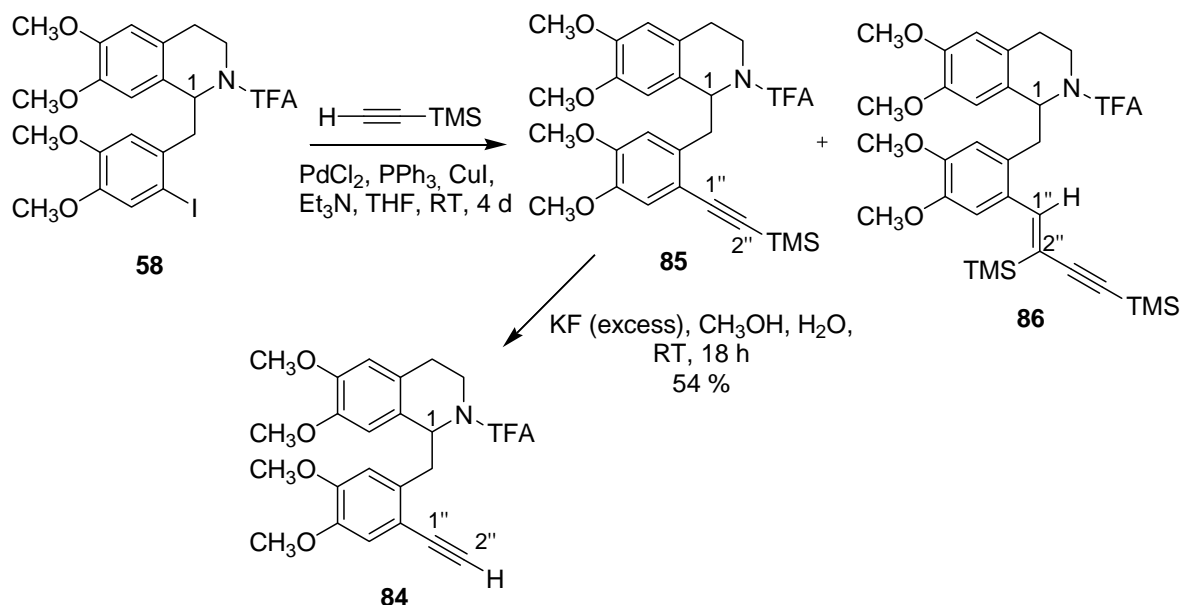
Palladium catalyst is not only useful in the Stille and Heck coupling reactions but it is widely used in other types of carbon-carbon bond forming reactions such as the Sonogashira cross coupling reaction.¹⁴⁰ The Sonogashira reaction is the term used for the Pd/Cu-catalysed cross-coupling reaction of terminal acetylenes with an aryl halide.¹⁴⁰ The Pd-catalysed cross-coupling reaction between terminal acetylenes and aryl halides was initially reported in 1975 as an extension of the Heck coupling reaction. Through systematic studies on transition metal acetylene chemistry, Cu was employed as a co-catalyst. Eventhough there are studies reporting some Cu-free Sonogashira coupling reactions,¹⁴¹ the application of Pd-Cu-catalysed cross-coupling of aryl halides with terminal acetylene is widely employed.¹⁴⁰ The reactions are run under mild conditions, with 3-5 mol. % of palladium and 3-10 mol. % of CuI generally required.¹⁴⁰ The Pd/Cu-catalysed cross-coupling of an aryl halide and terminal acetylenes occurs in a similar catalytic fashion to the Stille and Heck coupling reactions, and the proposed mechanism is outlined in Scheme 2.23.¹⁴⁰



Scheme 2.23 The overall mechanism of Pd/Cu catalysed Sonogashira coupling reaction.

The initial step, in common with the Stille and Heck coupling reactions, involves the generation of catalytically active Pd(0) species **C**. In many cases, Pd(OAc)₂ or PdCl₂ and two molar equivalents of a phosphine, and a terminal alkyne are used to generate *in situ* the catalytic complex **C**. The Cu mediates the exchange of the terminal alkyne with either the OAc[−] or the Cl[−] from **A** and generates the Pd-acetylide complex **B**, which undergoes reductive elimination to give the acetylene dimer and the active Pd(0) species **C**. The active species undergoes oxidative insertion with the aryl halide (R¹-X) in a similar fashion to the Heck cycle to give the Pd(II) intermediate **D**. Complex **D** undergoes transmetalation with the Cu-acetylide to give the alkynyl-Pd(II) complex **F**. Upon reductive elimination, the desired coupled product **G** is obtained with regeneration of the active Pd(0) species **C** to repeat the catalytic cycle.

2.9.3. Synthesis of acetylenic BBI derivatives **84** and **85**.



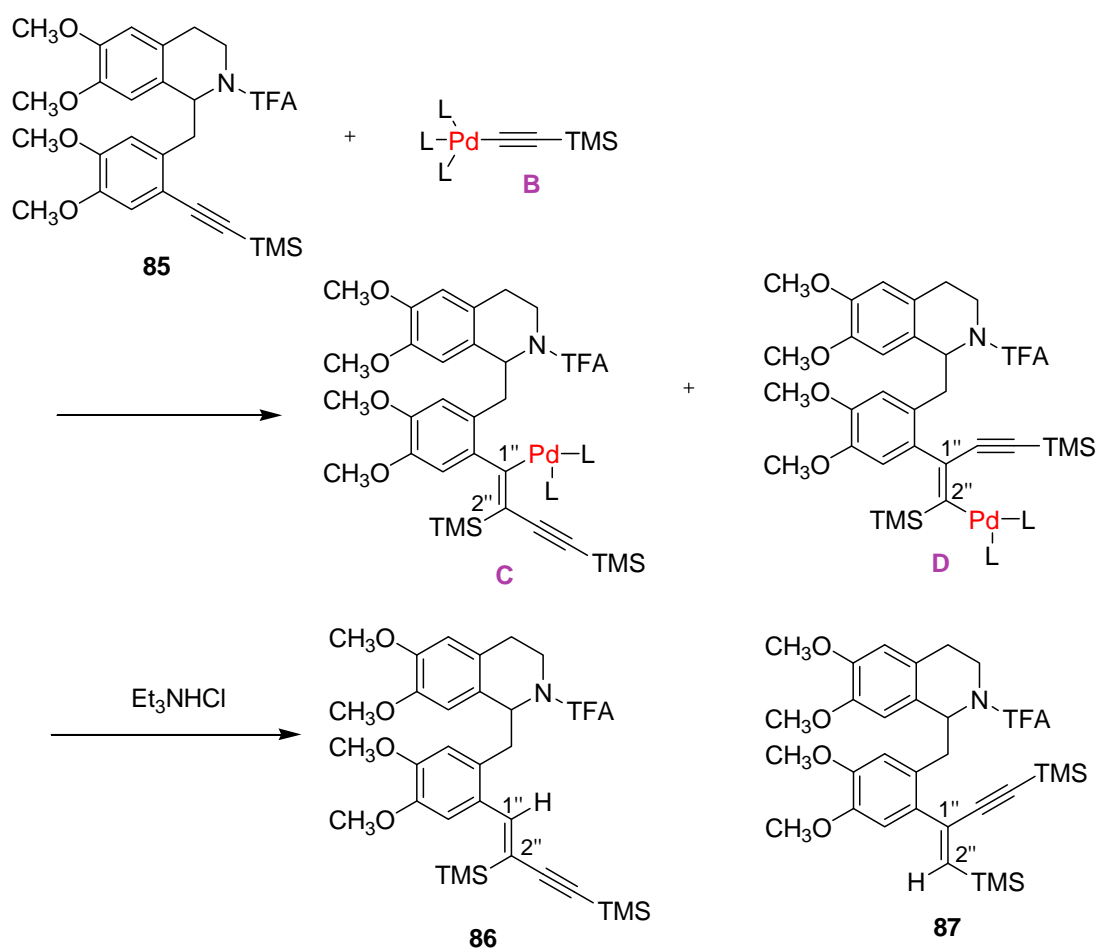
Mol. equiv. of TMS-acetylene	Yield of 85 (%)	Yield of 86 (%)
1.5	92	0
3	45	52

Scheme 2.24 Generation of the acetylenic laudanosine derivatives **84** and **85**.

The aryl iodide **58** was treated with TMS-acetylene (1.5 mol. equiv.), $\text{Pd}(\text{OAc})_2$, PPh_3 , CuI and triethylamine with stirring at RT for 4 d to afford **85** as a brown solid in an excellent yield of 92 % after purification (Scheme 2.24). The structure of **85** was confirmed by the appearance of the TMS signals at δ 0.16 (s, 9H, $\text{Si}(\text{CH}_3)_3$) in the ^1H NMR spectrum and the trimethylsilylethynyl signals at δ 103.7 ($\text{ArC}\equiv\text{CSi}(\text{CH}_3)_3$), 95.9 ($\text{C}\text{Si}(\text{CH}_3)_3$) and 0.1 ($\text{Si}(\text{CH}_3)_3$) in the ^{13}C NMR spectrum.

According to the mechanism outlined in Scheme 2.23, an excess amount of TMS-acetylene was needed to generate the active $\text{Pd}(0)(\text{PPh}_3)_2$ species. However, when 3 mol. equiv. of TMS-acetylene was added, double addition of TMS-acetylene was observed to give the ene-yne **86** as the major product over the desired compound **85** (Scheme 2.24). Compounds **85** and **86** were readily separated by column

chromatography. The structure of the unexpected compound **86** was confirmed by ^1H NMR spectral analysis, with the appearance of two signals at δ 0.16 (s, 9H, $\text{Si}(\text{CH}_3)_3$) and 0.13 (s, 9H, $\text{Si}(\text{CH}_3)_3$), corresponding to the two sets of trimethylsilyl groups, and a singlet at δ 8.15 (s, 1H, H1'') corresponding to the newly formed olefinic proton. An ion at m/z 634 corresponding to the MH^+ ion of **86** was also observed by ESMS, which further confirmed the structure of **86**. A possible mechanism for the formation of **86** is shown in Scheme 2.25.



Scheme 2.25 A possible mechanism for the formation of Sonogashira by-product **86** or **87**.

The formation of **86** can be rationalised as arising from the palladium mediated addition of $\text{TMSC}\equiv\text{CH}$ across the alkyne group of **85** (Scheme 2.25). Under this

mechanism, the regioisomeric side products **86** and/or **87** can be formed. Similar side products to **86** and **87** have been observed previously in related Sonogashira reactions.¹⁴² However, in our reaction, only one side product was obtained and it was likely to be compound **86** based on the preferential addition of the acetylide to the less sterically hindered carbon (C2'') of the acetylinic group of **85**. In addition, previous studies^{143,144} suggested that the methine proton at the C1'' position of **86** would be highly deshielded compared to the methine proton at C2'' position of **87** (Figure 2.7). Therefore compound **86** was the more likely side product obtained in this reaction because of the highly deshielded alkene methine signal at δ 8.15 (s, 1H, H1'') in the ¹H NMR spectrum.

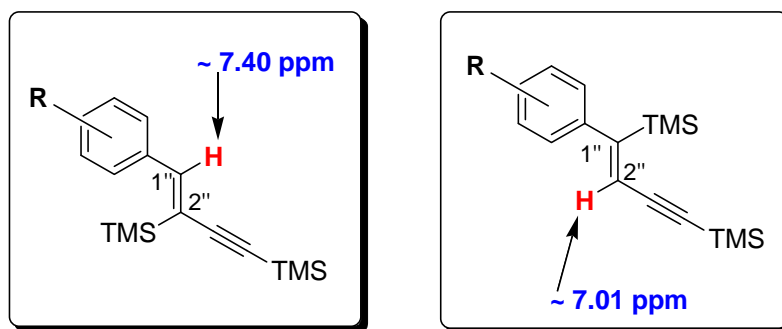


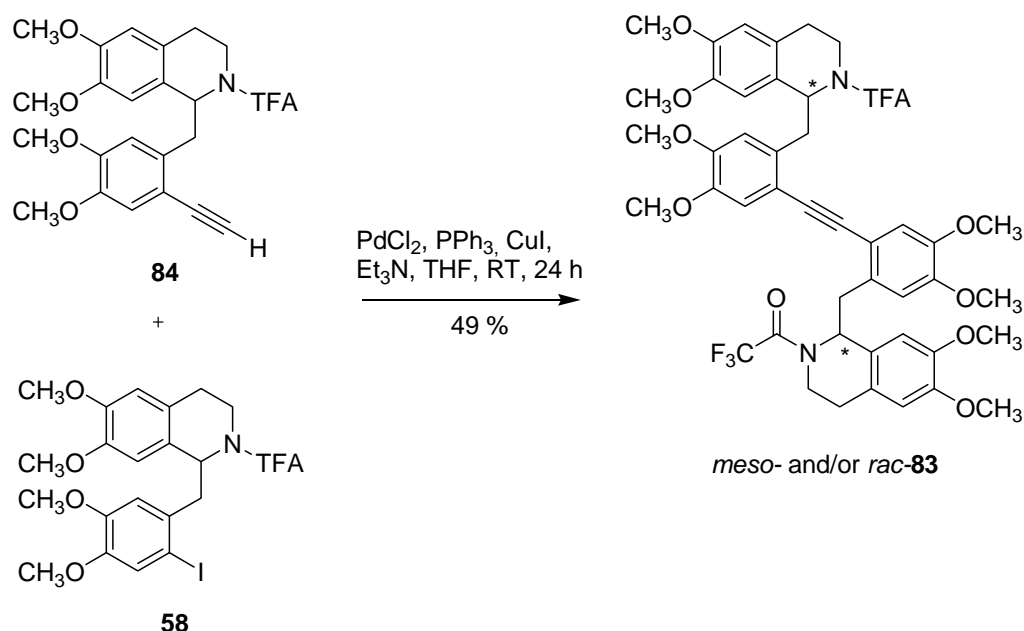
Figure 2.7 The ¹H NMR (CDCl₃) showing the chemical shifts of the benzylic CH (position a) (left)¹⁴³ and the CH at position b (right)¹⁴⁴ of similar compounds in the literature.

Desilylation of **85** with KF and CH₃OH/H₂O gave the corresponding primary alkyne **84** as a brown oil in 54 % (Scheme 2.24). The low yield was a result of the additional cleavage of the *N*-TFA protected group of **84** under the basic reaction conditions which was evident from the presence of a much more polar spot indicated by TLC analysis. The structure of compound **84** was confirmed by the appearance of the terminal alkyne proton signals as a singlet at δ 3.16 (s, 1H, ArC≡CH) in the ¹H NMR

spectrum. The low and high resolution mass spectra were consistent with the molecular formula of compound **84**.

2.9.4. Synthesis of acetylenic BBI derivative **83**.

Sonogashira coupling between the newly formed acetylene **84** with the aryl iodide **58** successfully afforded the acetylinic bisbenzylisoquinoline **83** as a white solid in 49 % yield. The reaction in this case only required a 24 h period for complete consumption of the starting materials and occurred much more rapidly than the previous Sonogashira coupling reaction (Scheme 2.26).



Scheme 2.26 Sonogashira coupling reaction between acetylene **84** and iodolaudnosine **58**.

Compound **83** has two stereogenic centres and was therefore expected to be a mixture of *meso*-**83** and *rac*-**83**. However, the ¹H NMR analysis showed essentially one isomer with four singlet signals appearing in the aromatic region rather than the expected eight singlet signals. This result was different to that observed with the previously synthesised BBI derivatives. This apparent stereoselectivity could be a result of preferential formation of either the *meso* or the racemic product. The heat of

formations of (*S,S*)-**83** and *meso*-**83** calculated from Spartan Pro (AM1) (Figure 2.8) indicated the *rac*-**83** had a more negative heat of formation and therefore would be most likely the product under thermodynamically and perhaps kinetically (as in this case) controlled conditions. Alternatively, because of the rigid nature of the acetylinic tether in compound **83**, the two stereogenic centres may be too remote to interact and thus the two diastereomers have the same ¹H NMR and ¹³C NMR spectra. The latter scenario was considered to be the more likely reason.

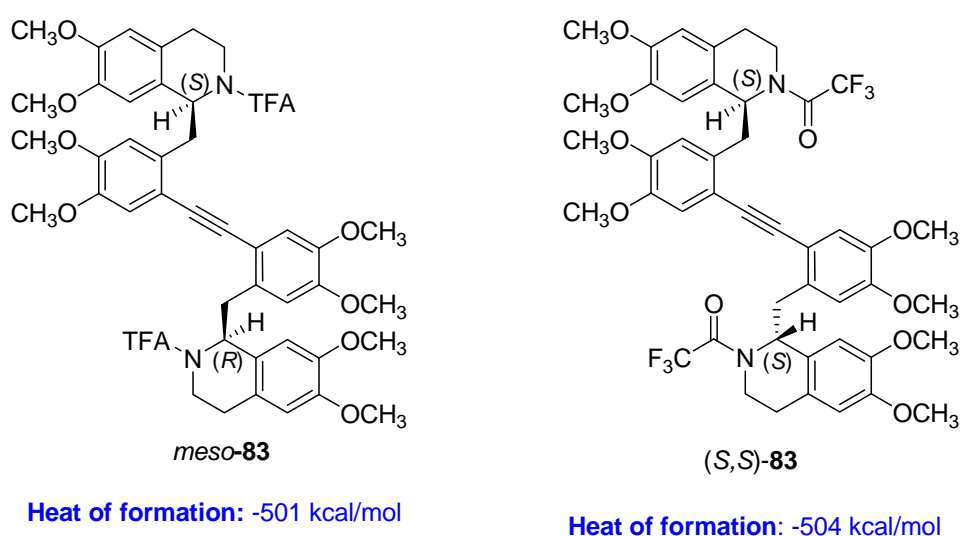
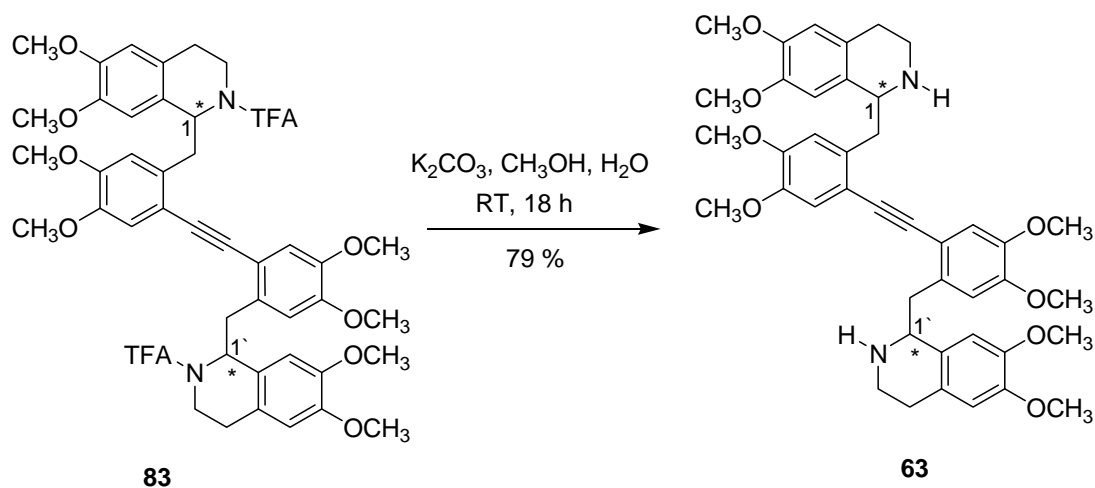


Figure 2.8 Heats of formation of *meso*-**83** and (*S,S*)-**83** calculated using Spartan Pro (AM1).

2.9.5. *N*-TFA deprotection of **83**.



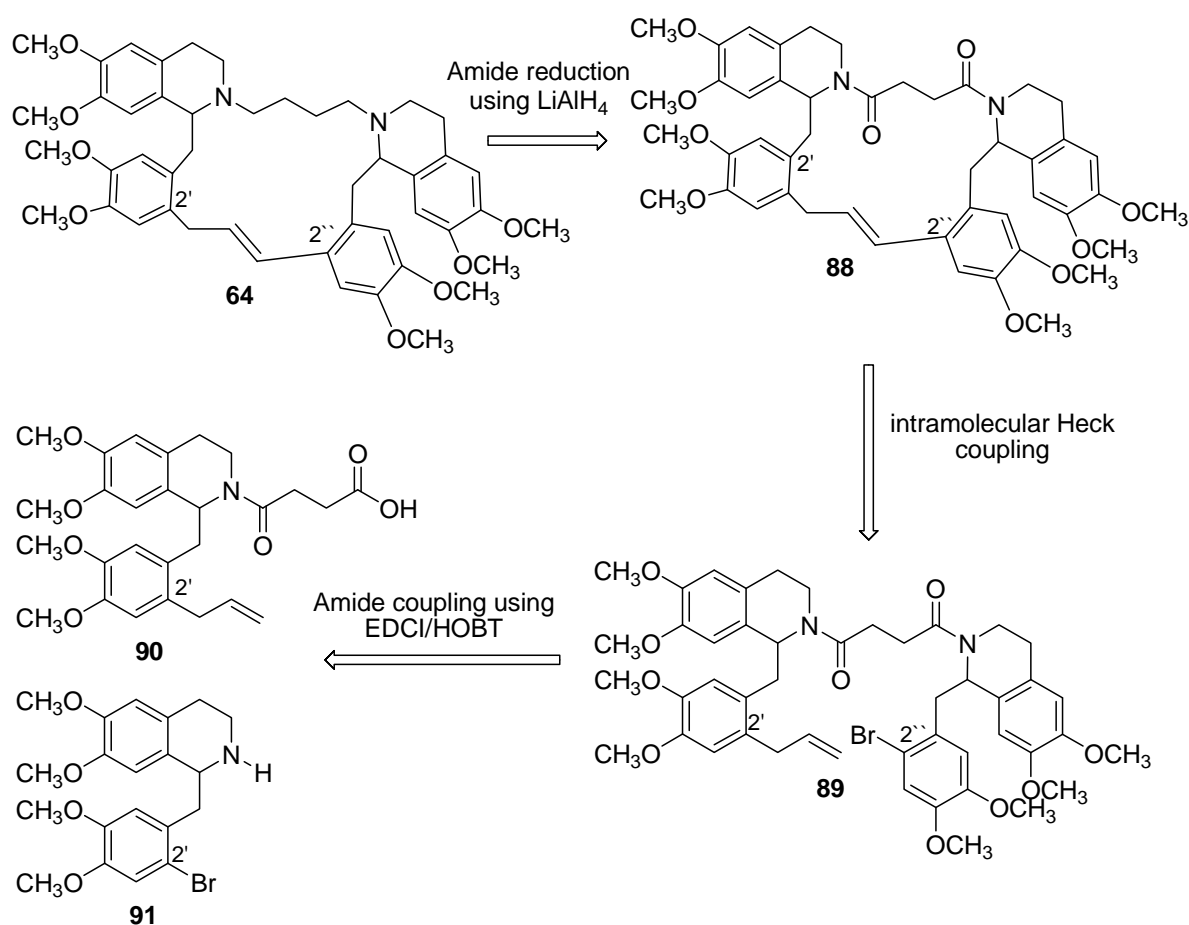
Scheme 2.27 *N*-deprotection of derivative **83**.

Compound **83** was subjected to *N*-TFA cleavage at RT and the product **63** was obtained as an apparent single diastereomer in 79 % yield. The ^1H NMR spectrum of **63** displayed four aromatic proton signals and more shielded H1/H1' proton signals at δ 4.73 (t, 2H, *J* 7.5 Hz, H1, H1') thus confirming the structure of **63**. Compound **63** was further confirmed by low and high MS analysis.

When the above reaction was heated at reflux, only decomposition material was obtained and no product or starting material was isolated. It was concluded that these *N*-TFA cleavage reactions should only be heated when solubility of the substrate was a problem, in order to minimise decomposition reactions.

2.10. Intramolecular Heck coupling reactions.

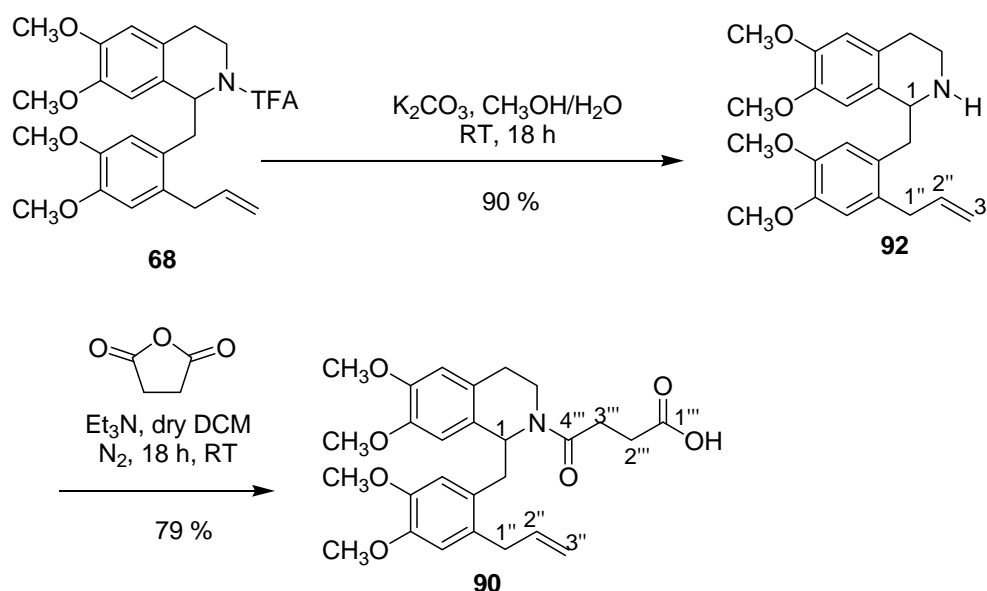
2.10.1. Retrosynthesis of the Bis-tethered BBI derivative 64.



Scheme 2.28 The retrosynthesis of bis-tethered BBI derivative **64**.

The bis-tethered BBI derivative **64** can in principle be obtained *via* the carbonyl reduction of the amide **88** using LiAlH_4 as the reducing agent. The four carbon tether across the isoquinoline nitrogens of the macrocyclic amide **88** can be formed by an amide coupling reaction between the carboxylic acid **90** and the amine **91**. A subsequent Heck coupling reaction of **89** would form the three carbon tether across the C2' positions of the benzyl groups.

2.10.2. Synthesis of the carboxylic acid **90**.



Scheme 2.29 The synthesis of the acid **90**.

The racemic amino precursor **92** was obtained in 90 % yield by a simple base-catalysed *N*-TFA deprotection of **68**. The free amine **92** was clearly observed by TLC analysis with the relative decrease in R_f value resulting from the polar nature of the free amino group. ^1H NMR analysis of **92** showed a signal at δ 4.17 (dd, 1H, J 8.7, 5.7 Hz, H1) which corresponded to the relatively more shielded H1 proton resulting from cleavage of the *N*-TFA group. The olefinic group of **92** was observed by the signals at δ 5.91 (m, 1H, H2''), 5.06 (dd, 1H, J 9.6, 1.8 Hz, H3''(Z)) and 5.01 (dd, 1H, J 17.1, 1.8

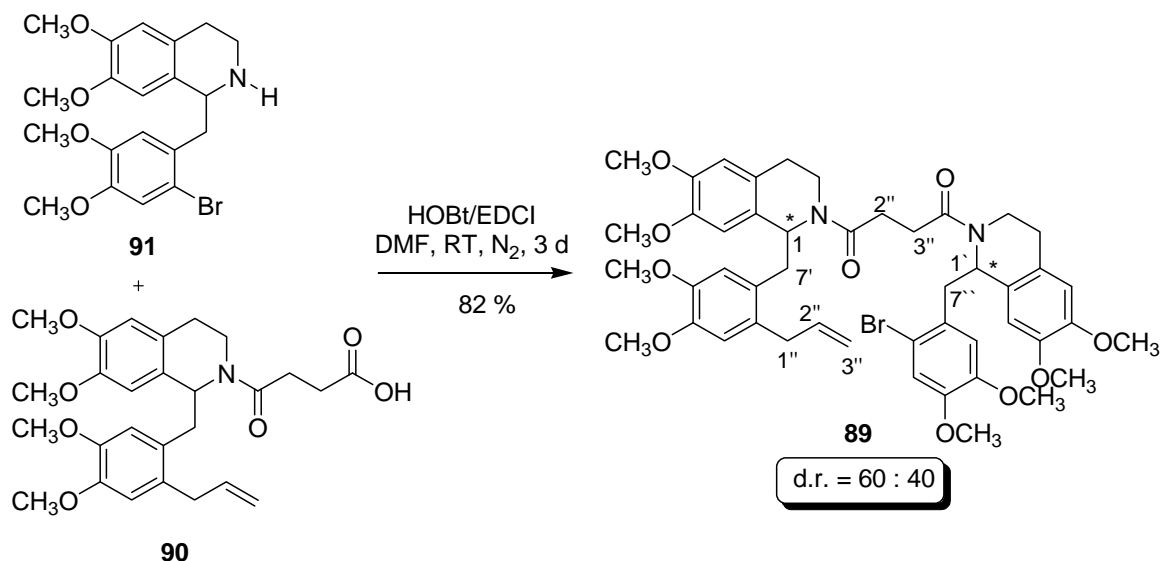
Hz, H3''(*E*)). The high resolution mass spectrum also corresponded to the molecular formula of **92**.

The carboxylic acid **90** was successfully synthesised from succinic anhydride *via* nucleophilic ring opening with amine **92**.¹⁴⁵ The introduction of the carboxylic moiety at the isoquinoline nitrogen of **90** resulted in the appearance of a major and a minor amide rotamer in a ratio of 70 : 30.

The new H1 proton signal of **90** was observed in the ¹H NMR spectrum at δ 5.51 (dd, 1H, *J* 9.0, 4.8 Hz, H1) for both the major and the minor rotamers. The olefinic group of **90** was observed in the ¹H NMR spectrum by the resonances at δ 5.76 (m, 1H, H2''), 4.95 (dd, 1H, *J* 10.2, 1.8 Hz, H3''(*Z*)) and 5.01 (dd, 1H, *J* 17.1, 1.8 Hz, H3''(*E*)) for the major amide rotamer and at δ 5.94 (m, 1H, H2''), 5.11 (dd, 1H, *J* 10.2, 1.8 Hz, H3''(*Z*)) and 5.00 (dd, 1H, *J* 15.0, 1.8 Hz, H3''(*E*)) for the minor amide rotamer. The 4-oxobutanoic moiety of **90** was confirmed by the appearance of the methylene signals at δ 2.75 (m, 4H, H3''', H2''') for the major rotamer and at δ 1.87 (m, 4H, H2''', H3''') for the minor rotamer. The ¹³C NMR spectrum of **90** showed two new carbonyl resonances at δ 175.5 and 169.8 for the major rotamer.

2.10.3. Construction of the Carbon Tether between the Isoquinoline Nitrogens via EDCI/HOBT Coupling.

To construct the four carbon tether between the isoquinoline nitrogens, the racemic carboxylic acid **90** was coupled with the racemic amine **91**, which was kindly provided by Dr Alison Ung (Department of Chemistry, UOW), using EDCI/HOBT to successfully afford the BBI derivative **89** in high yield (82 %). The reaction occurred slowly over 3 d, possibly due to the sterically hindered nature of the secondary amine component **91**. The formation of the tethered product **89** was readily observed by the appearance of a less polar spot during TLC analysis.



Scheme 2.30 Synthesis of the derivative **89** *via* amide coupling.

The ¹H NMR analysis of **89** was complicated by the presence of rotamers and racemic diastereomers. In the ¹H NMR spectrum, signals for the two sets of methylene protons across the tether were identified at δ 2.64 (m, 4H, H2''', H3''') for the major diastereomer and at δ 2.28 (m, 4H, H2''', H3''') for the minor diastereomer. There were also two sets of H1 and H1' proton signals observed at δ 5.47 (dd, 1H, *J* 9.0, 4.8, H1') and 5.18 (dd, 1H, *J* 9.0, 4.8, H1) for the major diastereomer and at δ 5.42 (dd, 1H, *J* 9.0, 4.2, H1') and 5.13 (dd, 1H, *J* 9.0, 4.2, H1) for the minor diastereomer, consistent with the two different isoquinoline moieties of racemic **89**.

2.10.4. Formation of the Carbon-Carbon Tether Across C2' Position via Intramolecular Heck Coupling.

The BBI **89** was subjected to the intramolecular Heck coupling reaction using the previously optimised Heck coupling reaction conditions using Pd(OAc)₂, DMG, NaOAc and NMP. However, under these conditions, none of the desired product **88** was observed as indicated from TLC and ¹H NMR analysis, and only the precursor **89** was recovered. This result indicated that the developed Heck coupling reaction conditions

which normally verified the presence of a diastereomeric mixture. Since the yield was low, it is suggested that one diastereomer had preferentially undergone the Heck coupling reaction. However, the remaining unreacted diastereomer might have been lost during the purification process or might have decomposed during the reaction. Due to the limited quantity of compound **88** (12 mg), it was not subjected to further carbonyl reduction with LiAlH₄.

In conclusion, five of the initially six targeted BBI derivatives and the additional analogues *meso*-**82** and *rac*-**82**, were successfully prepared for biological testing. The results of these tests are discussed in Chapter 6.

Chapter 3 Synthesis of 2'-Arylvinyl and 2'-Arylallyl Benzyloquinoline Derivatives.

3.1. Introduction

This chapter discusses the application of the optimised Heck coupling reactions conditions described in Chapter 2 for the synthesis of the 2'-arylvinyl- and 2'-arylallyl-benzyloquinolines derivatives **92-97** having an exocyclic *N,N*-dimethylamino group. The saturated derivatives **98-103** were readily prepared by hydrogenation of **92-97**, respectively.

These benzyloquinoline derivatives (Figure 3.1) were designed to mimic some of the structural features of the BBI derivatives described in Chapter 2 by having two amino moieties, however with significantly reduced molecular weight in favour of Lipinski's rules for good pharmaceutical drug-like properties.^{146,147}

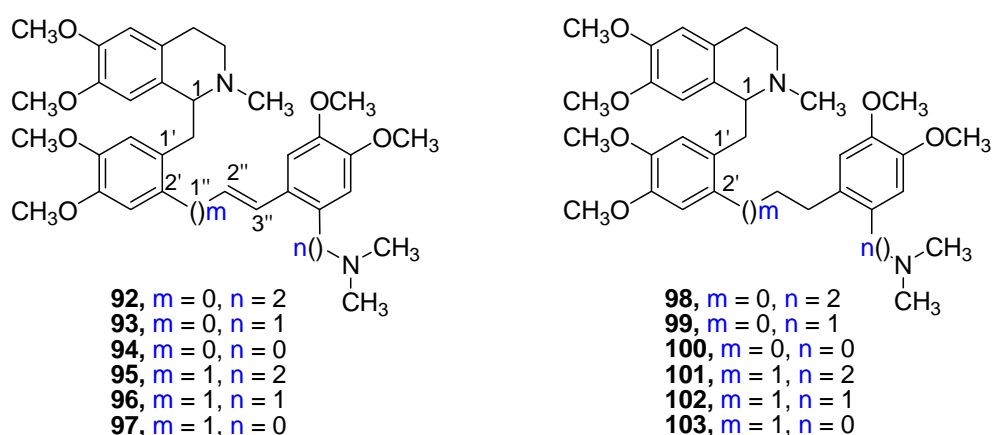


Figure 3.1 The targeted benzyloquinoline derivatives having an exocyclic *N,N*-dimethylamino group.

The second group of the targeted benzyloquinoline derivatives (Figure 3.2) had the *N,N*-dimethylamino moiety replaced with a *N*-acetamido group in order to examine the effect on biological activity of retaining an amino group with diminished ability to protonate at physiological pH. The exocyclic amino substituents of the

benzylisoquinoline derivatives in Figure 3.1 were excluded entirely from the compounds in the third targeted group, **108-111**, and the effect of this change on the biological activity of these compounds would be investigated.

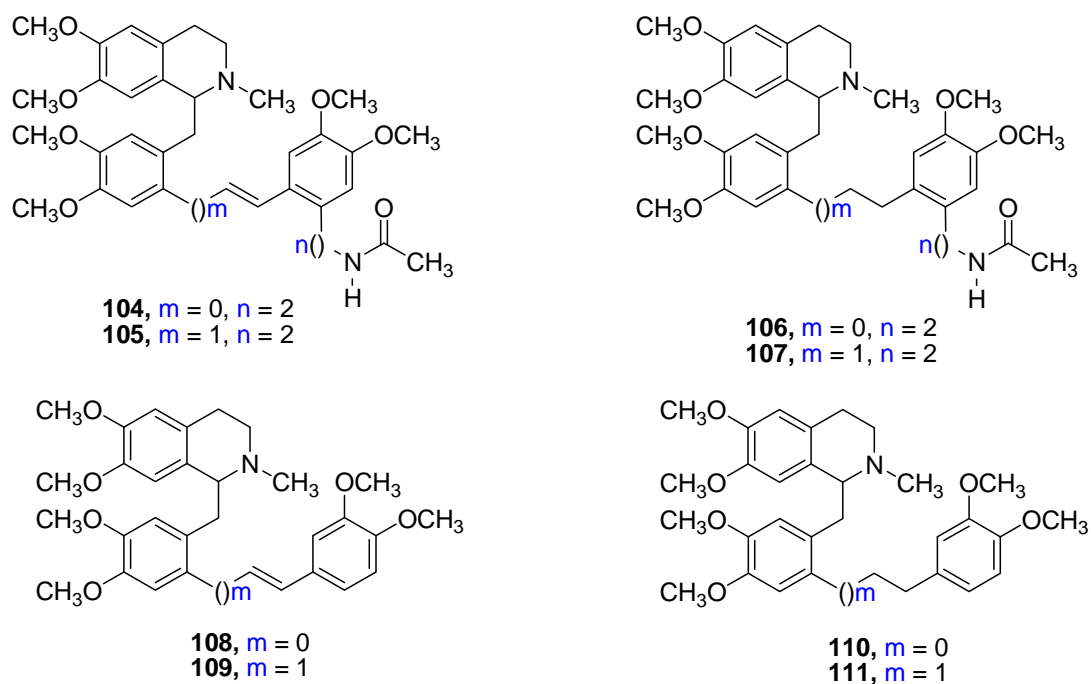
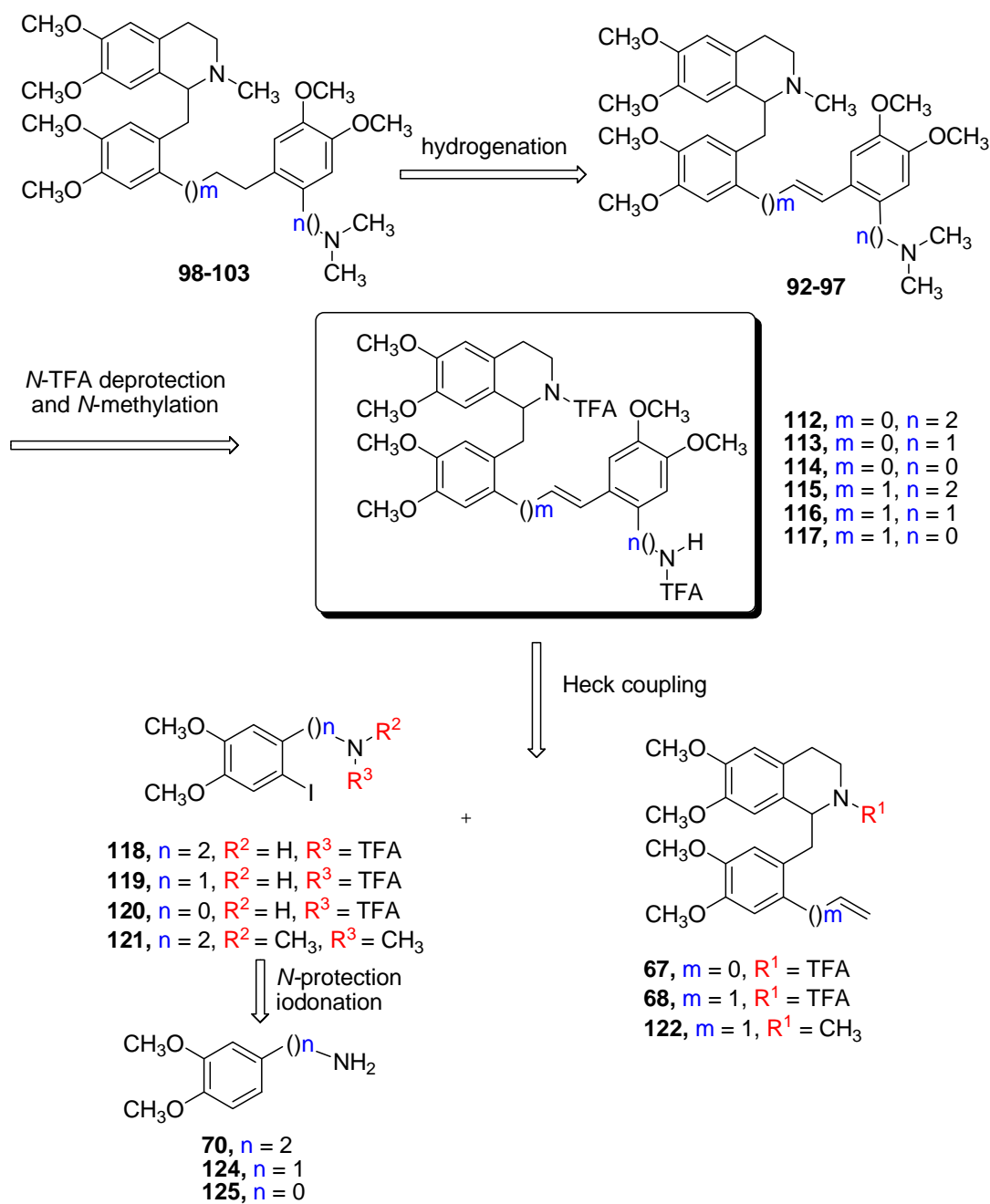


Figure 3.2 The targeted benzylisoquinoline derivatives having *N*-acetyl moieties (top) and having the exocyclic amino moieties removed (bottom).

3.2. Synthesis of exocyclic *N,N*-dimethylamino benzylisoquinoline derivatives.

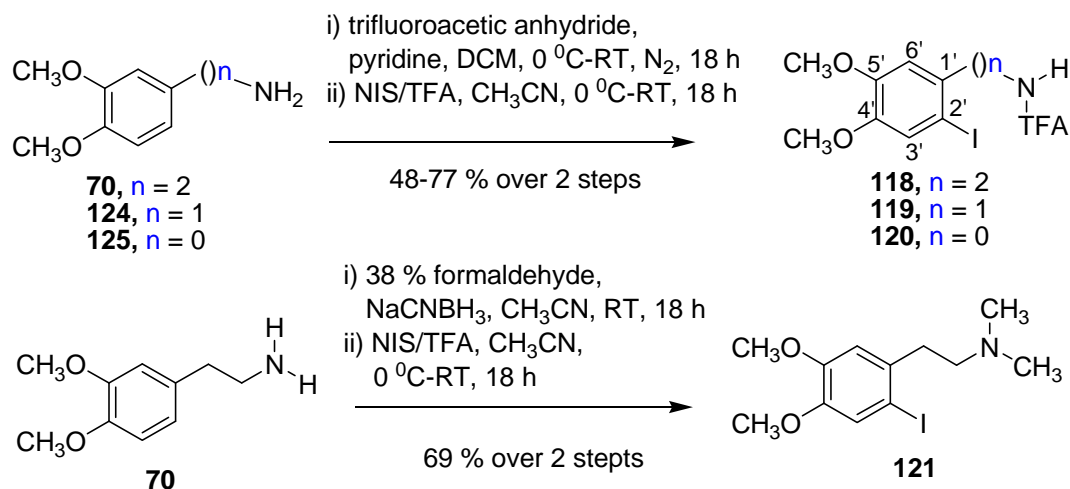
The key step in the generation of the targeted benzylisoquinoline derivatives **92-97** was the formation of the carbon-carbon double bond. This key bond forming step was achieved utilising the optimised Heck coupling reaction conditions developed in Chapter 2, using $\text{Pd}(\text{OAc})_2$ as a catalyst, DMG as the additive, and NaOAc as the base in a sealed tube with heating at 130°C . This reaction allowed the coupling of the *N*-TFA laudanosine precursors **67** and **68** with the *N*-TFA protected aryl iodides **118-120** (Scheme 3.1). These aryl iodides were synthesised from the commercially available amines **70**, **124** and **125**. A Heck coupling reaction between the *N*-methylated

precursors **122** and **121** was also examined as an alternative, more direct, synthesis of the targeted derivative **95**.



Scheme 3.1 The retrosynthesis of the exocyclic *N,N*-dimethylamino benzyloisoquinoline derivatives.

3.1.1. Preparation of *N*-protected aryl iodides.



Scheme 3.2 Synthesis of *N*-TFA protected aryl iodides **118-120** and the *N,N*-dimethyl aryl iodide **121**.

The *N*-TFA protected aryl iodides **118-120** were synthesised according to the procedures developed in Chapter 2. The success of the *N*-trifluoroacetylation of **70**, **124** and **125** was indicated by the formation of a new compound with a significant increase in *R_f* value indicated by TLC analysis. The crude reaction mixtures from these reactions were then subjected to electrophilic iodination with NIS/TFA. The desired aryl iodides **118-120** were obtained in 48-77 % overall yields after purification by column chromatography.

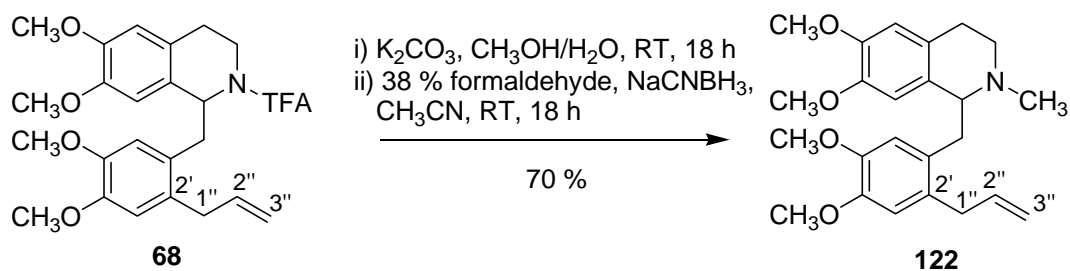
The phenylethylamine derivative **118** was obtained as a yellow solid in 77 % yield over the 2 steps. ¹H NMR analysis of **118** confirmed the presence of the iodo substituent by the appearance of the two aromatic singlet signals at δ 7.17 (s, 1H, H3') and 6.65 (s, 1H, H6'). The amide functionality was confirmed by the broad singlet resonance at δ 6.62 (bs, 1H, NH), corresponding to the amide proton. In the ¹³C NMR spectrum, the *N*-TFA group was identified by signals at δ 155.4 (q, *J* 36.9 Hz, COCF₃) and 113.9 (q, *J* 285.4 Hz, COCF₃).

The benzylamine derivative **119** was obtained in a slightly lower yield over the two steps (48 %). ^1H NMR analysis of this compound **119** showed the expected aromatic and amide proton signals at δ 7.16 (s, 1H, H3') and 6.83 (bs, 2H, H6' and NH), respectively. The benzylic proton resonances in **119** were found at δ 4.45 (d, 2H, J 6.0 Hz, H1).

The aniline derivative **120** was obtained in 58 % overall yield. Two aromatic proton signals at δ 7.79 (s, 1H, H3') and 7.17 (s, 1H, H6') and the amide proton signal at δ 8.11 (bs, 1H, NHCOCF_3) in the ^1H NMR spectrum confirmed the structure of **120**.

In order to examine the Heck coupling reactions on a *N,N*-dimethylated system, the *N,N*-dimethylphenylethylamine **121** was synthesised by reductive methylation of 2-(3,4-dimethoxyphenyl)ethylamine **70** with 38 % formaldehyde and NaCNBH_3 , followed by iodination with NIS/TFA. Normally, only a catalytic amount of TFA was needed to generate the active iodination species ($\text{CF}_3\text{COO}_2\text{I}$), however, in the case of the *N,N*-dimethylated derivative of **121** (structure not shown), protonation of the amino group occurred, thus the catalytic amount of TFA that was required to generate the electrophilic iodine species (Scheme 2.3, Chapter 2) was not available. For this reason, more than a stoichiometric amount of TFA (1.2 mol. equiv.) was used to afford **121** as a yellow oil in 69 % yield over the 2 steps. ^1H NMR analysis of **121** showed a signal for the *N,N*-dimethylamino group at δ 2.26 (s, 6H, $\text{N}(\text{CH}_3)_2$), and two aromatic proton signals at δ 7.12 (s, 1H, H3') and 6.68 (s, 1H, H6'), confirming the correct structure of **121**.

3.1.2. Preparation of 2'-allyllaudanosine 122.

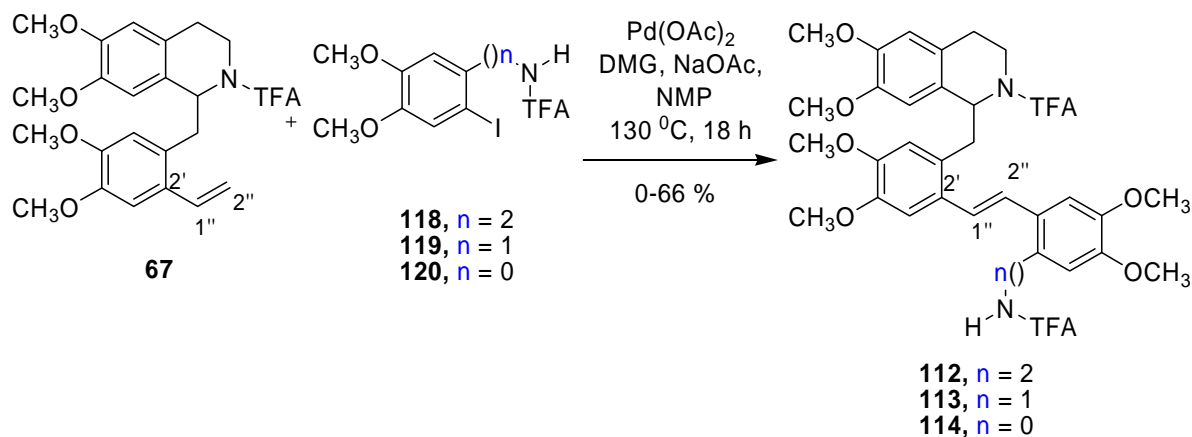


Scheme 3.3 Synthesis of the 2'-allyllaudanosine derivative **122**.

The 2'-allyllaudanosine derivative **122** was also prepared as a substrate for the subsequent Heck coupling reactions by the initial deprotection of the *N*-TFA group of **68** using K_2CO_3 in a mixture of $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ at RT to give the free amine. The free amine was subjected, without purification, to reductive *N*-methylation conditions using 38 % formaldehyde and NaCNBH_3 to give 2'-allyllaudanosine **122** in 70 % yield over the 2 steps. The structure of **122** was confirmed by ^1H NMR analysis which showed a newly formed singlet resonance at δ 2.52 (s, 3H, NCH_3) corresponding to the *N*-methyl protons.

3.1.3. Synthesis of the benzyloquinoline derivatives 112-117 via Heck coupling reactions.

3.1.3.1. Synthesis of 112-114.



Scheme 3.4 The general procedure for the Heck coupling reaction of **67** with aryl iodides **118-120**.

Table 3.1 A summary of Heck coupling reactions of **67** with aryl iodides **118-120**.

Entry	Coupling partners		Product	Yield (%)	(<i>E</i>) : (<i>Z</i>) ratio
1	67	118	112	66	100 : 0
2	67	119	113	38	100 : 0
3	67	120	114	none	n/a

The results of the cross coupling reactions between the styrene **67** and the aryl iodides **118-120** using the optimised Heck coupling conditions (Scheme 3.4) are summarised in Table 3.1

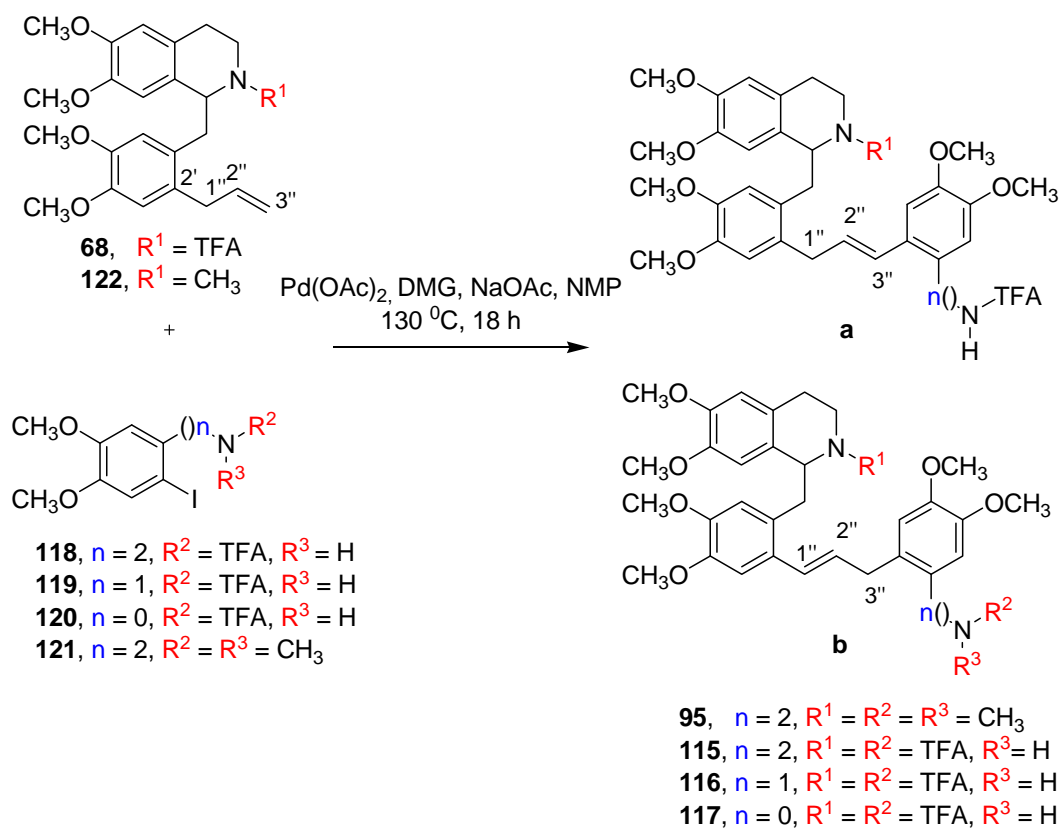
In entry 1, the Heck coupling reaction between the *N*-TFA protected vinyl norlaudanosine **67** and the iodo-phenylethylamine derivative **118** afforded the corresponding stilbene **112** in 66 % yield. ¹H NMR analysis of **112** showed the exclusive formation of the (*E*)-isomer with two characteristic doublet signals at δ 7.33 (d, 1H, *J* 15.9 Hz, H2'') and 7.15 (d, 1H, *J* 15.9 Hz, H1'') for the two different alkene protons. The structure of (*E*)-isomer was confirmed by the presence of only six aromatic proton signals in the ¹H NMR spectrum, with a small amount of an amide rotamer also present (*ca.* 5 %).

The Heck coupling reaction of **67** with the *N*-TFA benzylamine derivative **119** (Table 3.1, entry 2) gave only (*E*)-**113**. This was confirmed by the presence of the alkene signals at δ 7.51 (d, 1H, *J* 16.2 Hz, H2'') and 7.02 (d, 1H, *J* 16.2 Hz, H1'') and six aromatic proton signals in the ¹H NMR spectrum. A small amount of an amide rotamer was also observed (*ca.* 5 %). The yield of **113** obtained in this case was 38 %.

When the *N*-TFA protected aniline **120** was used as the coupling partner with **67** (Table 3.1, entry 3), none of the corresponding product **114** was obtained. Only small

amounts of the starting materials were recovered due to decomposition of these compounds or of the product.

3.1.3.2. Synthesis of 95 and 115-117.



Scheme 3.5 The general procedure for the Heck coupling reactions of **68** and **122** with aryl iodides **118-121**.

Table 3.2 A summary of Heck coupling reactions of **122** and **68** with the aryl iodides **118-121**.

Entry	Coupling partners		Products	Yield (%)	Ratio of regioisomers (a : b)
1	122	121	95a, 95 b	6	70 : 30
2	68	118	115a, 115b	66	60 : 40
3	68	119	116a, 116b	39	60 : 40
4	68	120	117	none	n/a

The results of the cross-coupling reactions between the 2'-allyllaunosine derivatives **122** and **68** with aryl iodides **118-121** using the optimised Heck coupling reaction conditions (Scheme 3.5) are summarised in Table 3.2. Entry 1 of Table 3.2 shows the Heck coupling reaction of the coupling partners **121** and **122**, having both the isoquinoline and the aromatic unit *N*-methylated. In entries 2-4, however, the *N*-TFA protecting groups were employed in both coupling partners.

In entry 1 (Table 3.2), the Heck coupling reaction between *N*-methylated allyl launosine **122** and the *N,N*-dimethylated amine **121** afforded the corresponding product **95**, however in low yield (6 %). The low yield could be due to the lone electron pairs on the nitrogen of the precursors which could co-ordinate to the palladium, reducing its catalytic function. Furthermore, being very polar in nature, the product **95** was very difficult to purify by column chromatography, thus reducing the yield. A 70 : 30 ratio of the two (*E*)-isomers (**95a** and **95b**) were observed in the ¹H NMR spectrum with the major isomer **95a** showing olefinic resonances at δ 6.33 (d, 1H, *J* 16.0 Hz, H3'') and 5.93 (dt, 1H, *J* 16.0, 6.0 Hz, H2''), confirming its (*E*)-geometry. The minor isomer **95b** had the olefinic signals at δ 6.27 (d, 1H, *J* 15.5 Hz, H1'') and 5.99 (dt, 1H, *J* 15.5, 6.5 Hz, H2''). These regioisomers could not be separated and NOESY experiments were performed on the mixture of the two (*E*)-isomer of **95** (Figure 3.3). The major (*E*)-isomer of **95** (**95a**) showed a NOESY cross peak between δ 6.33 (d, 1H, *J* 16.0 Hz, H3'') and δ 2.64 (dd, 1H, 12.0, 6.0 Hz, H7'''), while the minor (*E*)-isomer of **95** (**95b**) showed a NOESY cross peak between δ 6.27 (d, 1H, *J* 15.5 Hz, H1'') and δ 3.45 (dd, 1H, *J* 9.0, 4.5 Hz, H1).

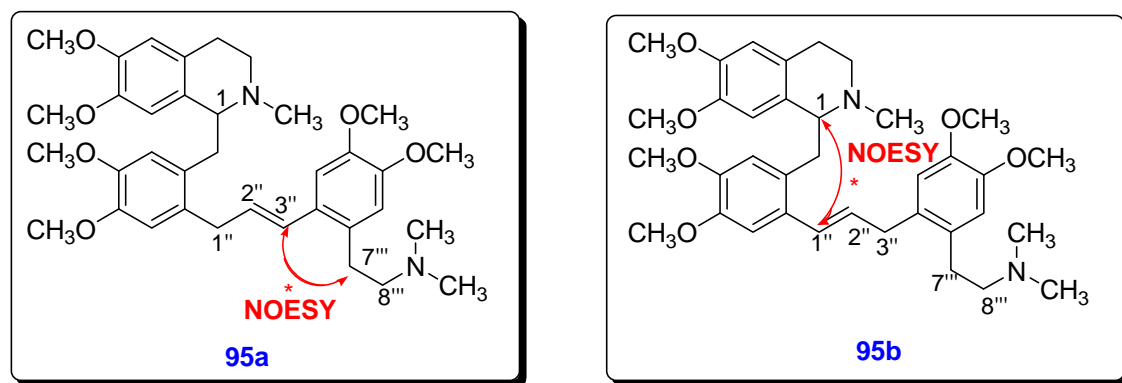
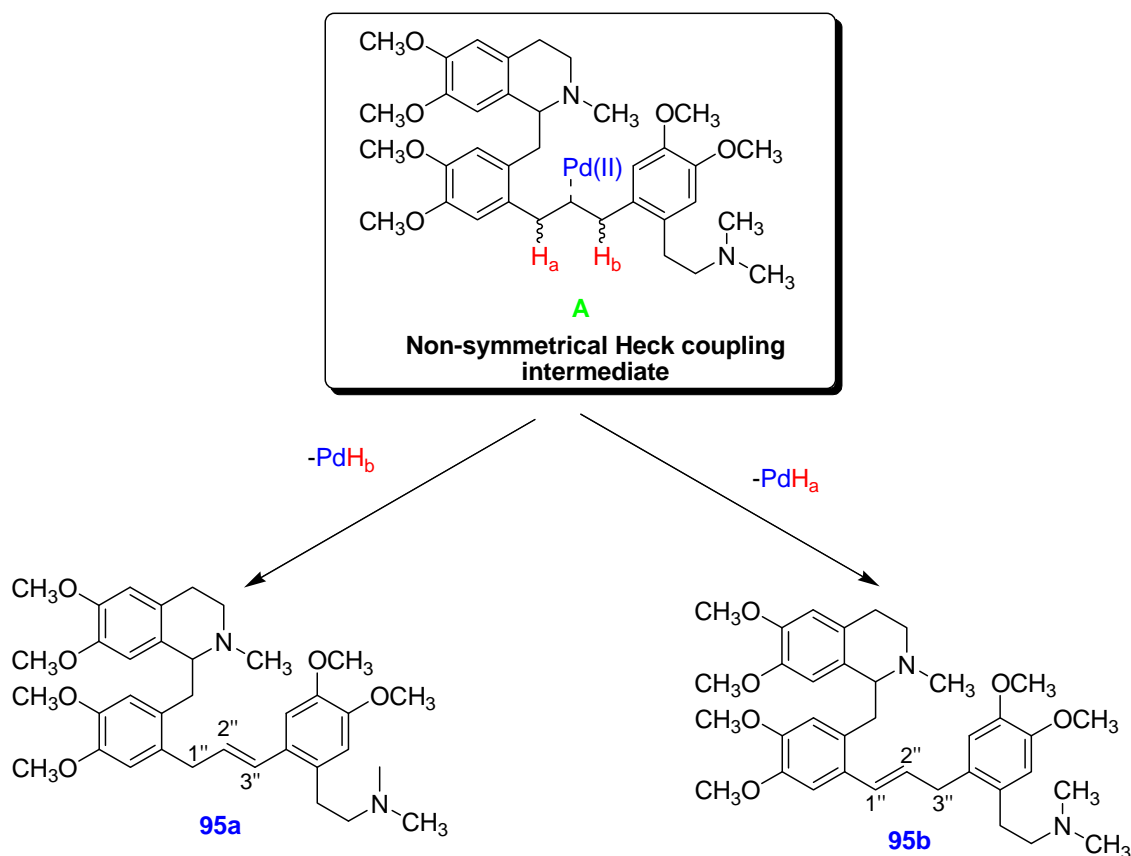


Figure 3.3 The identification of the major regioisomer **95a** and the minor regioisomer **95b** by NOESY experiments.



Scheme 3.6 The proposed mechanism for the formation of the two (*E*)-isomers **95a** and **95b** (palladium ligands not shown).

The formation of the two (*E*)-alkene isomers **95a** and **95b**, can be explained *via* the proposed palladium(II) intermediate **A** shown in Scheme 3.6. In the catalytic cycle, the last step involves the elimination of a palladium hydride species to form the double

bond of the alkene product. In this case, the palladium intermediate **A** is flanked by two similar pairs of methylene protons and palladium hydride can therefore be eliminated from either the phenyl side to give the (*E*)-isomer **95a** or from the laudanosine side to give the (*E*)-isomer **95b**. The factors that favour the choice of elimination remains unclear at this stage, but clearly the elimination is favoured towards the less hindered aryl substituent.

The outcomes of the Heck couplings reactions of the *N*-TFA protected 2'-allyllaundanosine derivative **68** with the aryl iodides **118-120** (Entries 2-4, Table 3.2) were consistent with the results observed previously in Table 3.1. The Heck coupling reactions of **68** with iodides **118** and **119** in entries 2 and 3 afforded the corresponding products **115** in higher yield (66 %) and **116** in lower yield (39 %), respectively. However none of the corresponding Heck product was obtained from the *N*-TFA protected aniline derivative **120** (entry 4).

The ¹H NMR spectrum of product **115** showed the formation of two (*E*)-isomers (**115a** and **115b**) in a 60 : 40 ratio and a small amount of an amide rotamer (*ca.* 5 %). These isomers could not be separated by TLC. The ¹H NMR spectrum of **115** showed olefinic signals for the major isomer **115a** at δ 6.49 (d, 1H, *J* 15.6 Hz, H3'') and 6.00 (dt, 1H, *J* 15.6, 6.9 Hz, H2''), confirming its (*E*)-geometry. The minor (*E*)-alkene product **115b** had olefinic signals at δ 6.72 (d, 1H, *J* 15.6 Hz, H1'') and 5.97 (dt, 1H, *J* 15.6, 6.9 Hz, H2'').

The ¹H NMR spectrum of **116** also showed signals for the two (*E*)-products **116a** at δ 6.49 (d, 1H, *J* 15.9 Hz, H3'') and 6.12 (dt, 1H, *J* 15.9, 6.3 Hz, H2'') and **116b** at δ 6.67 (dt, 1H, *J* 16.5, 6.3 Hz, H2'') and δ 6.59 (d, 1H, *J* 16.5 Hz, H1'') in a ratio of 60 : 40. The olefinic chemical shifts for **116a** and **116b** were consistent with those of

115a and **115b**, respectively, with the minor regioisomer having olefinic resonances further downfield compared to those of the major isomer.

From the Heck coupling studies in Table 3.1 and 3.2, it can be observed that the Heck coupling reactions proceed best when both coupling partners were protected with the *N*-TFA rather than the *N*-methyl group. It was also observed that the closer the amino substituents were to the aromatic unit in the aryl iodide component, the lower the yield of the Heck coupling product.

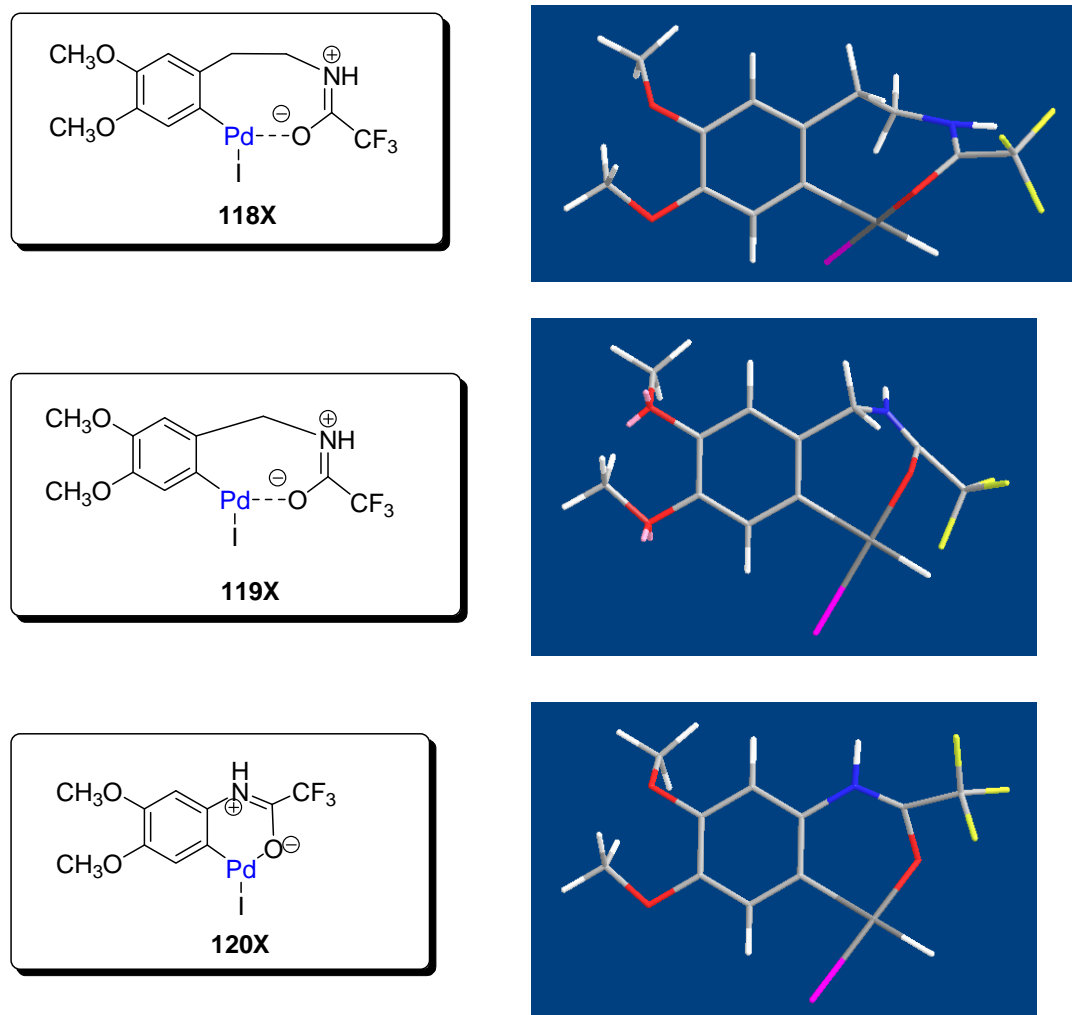
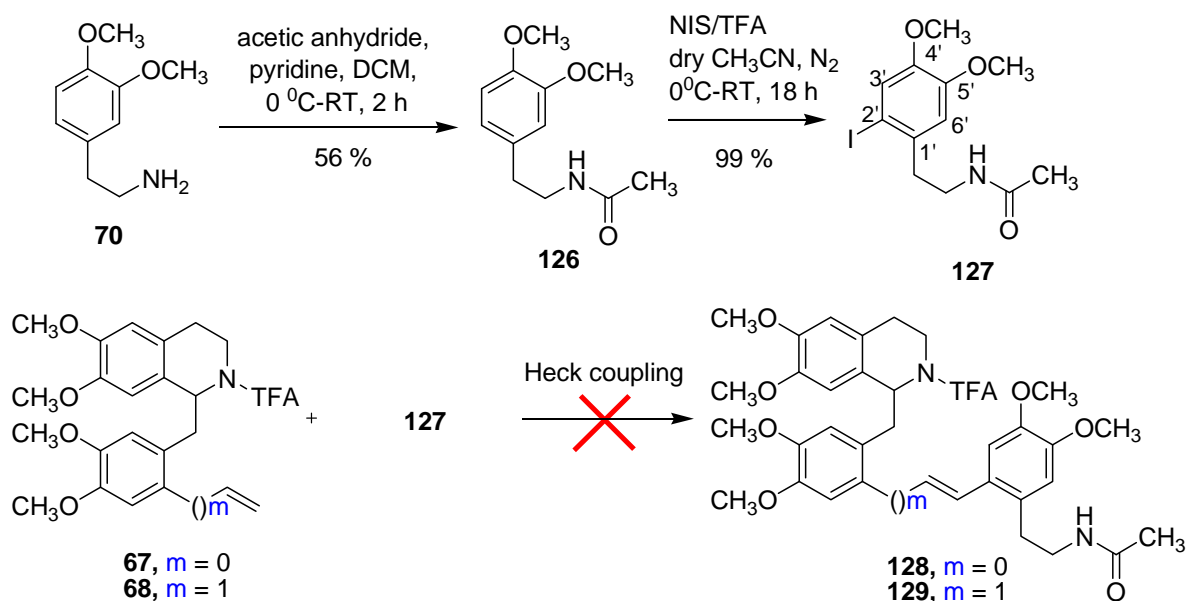


Figure 3.4 Proposed chelated intermediates in Chem 3D representations of **118X** (top), **119X** (middle) and **120X** (bottom), (fourth ligand on Pd not identified).

The effect of shortening the side chain in **118-120** in lowering the yields of the Heck coupling reactions with **67** and **68** can be explained by the formation of the chelated intermediates **118X-120X** (Figure 3.4). Such chelated intermediates would be more favoured in the case of **120X** (6-membered chelated ring) and less favoured in the case of **118X** (8-membered chelated ring) and **119X** (7-membered chelated ring). The formation of the more stable chelated ring **120X** may explain why the Heck coupling reactions of **67** and **68** with **120** gave none of the desired product. Conversely, the higher instability of **118X** compared to **119X** could explain the higher yields from the Heck coupling reactions of **118** over **119** with **67** and **68**.

3.2. Synthesis of *N*-Acetyl benzylisoquinoline derivatives.

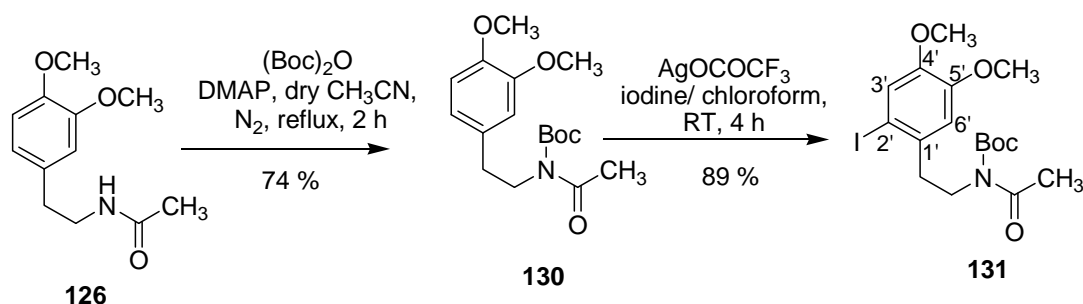


Scheme 3.7 The initial synthetic strategy for **128** and **129**.

With the aim of preparing the *N*-acetamido analogues **128** and **129**, the aryl iodide **127** was prepared (Scheme 3.7). The initial synthetic scheme was similar to that of Scheme 3.1 and 3.2, where the aryl iodide **127** was synthesised from the phenylethylamine derivative **123** by the initial *N*-acetylation with acetic anhydride to give **126**, followed by iodination (Scheme 3.7).

The structure of the amide **126** was confirmed by the presence of an amide proton signal at δ 5.58 (bs, 1H, NH) and the methyl proton signal at δ 1.95 (s, 3H, COCH₃) in the ¹H NMR spectrum. The structure of the iodinated product **127** was confirmed by ¹H NMR analysis by the presence of the two aromatic signals at δ 7.16 (s, 1H, H3') and 6.70 (s, 1H, H6').

Surprisingly, the Heck coupling reactions between **127** and **67** or **68** gave none of the desired products **128** or **129**, respectively, with only a small amount of **67** and **68** being recovered. It was suggested that the *N*-acetyl group, unlike the corresponding *N*-TFA group, might not be sufficiently deactivating and may allow the formation of a more stable chelated Pd-intermediate (Figure 3.4), thus preventing the reaction to proceed. Therefore the doubly *N*-protection form of **127** (**131**) was prepared with both a *N*-acetyl and a *N*-Boc protecting group.



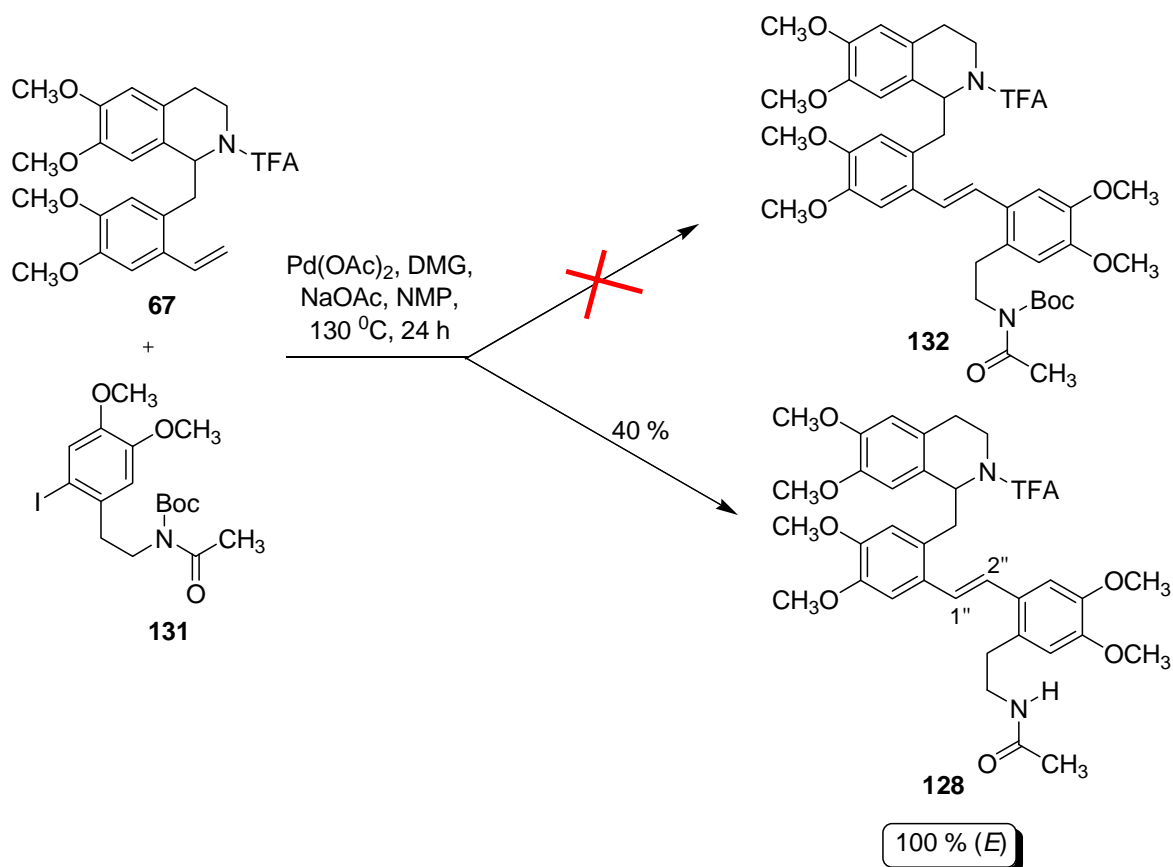
Scheme 3.8 Synthesis of the *N*-Boc, *N*-acetyl aryl iodide **131**.

The *N*-Boc protection of **126** was achieved using di-(*tert*-butylcarbamate) and DMAP with heating at reflux in CH₃CN for 2 h. This afforded the corresponding *N*-acetyl, *N*-Boc derivative **130** in 74 % yield. The successful *N*-protection with both the acetyl and the Boc groups in **130** was confirmed by the acetyl signal at δ 2.41 (s, 3H, COCH₃) and the *tert*-butyl signal at δ 1.44 (s, 9H, OC(CH₃)₃) in the ¹H NMR spectrum. Two carbonyl signals were also observed in the ¹³C NMR spectrum of **131** at δ 172.9 (C=OCH₃) and 153.1 (C=OO(CH₃)₃) corresponding to the acetyl groups and Boc groups,

respectively. The ^{13}C NMR signals at δ 28.0 ($\text{C}(\underline{\text{CH}}_3)_3$) and 27.0 ($\text{CO}\underline{\text{CH}}_3$) also confirmed the presence of the Boc and the acetyl groups.

The next step in Scheme 3.8 involved the iodination of **130** to give the corresponding aryl iodide **131**. An alternative iodination method to the normally used NIS/TFA system was considered because of the acid labile nature of the *N*-Boc group. Therefore, silver trifluoroacetate and iodine in chloroform solution was employed, which afforded the corresponding aryl iodide **131** in high yield (89 %). The successful iodination of **130** was confirmed by the replacement of three aromatic doublet signals (with *ortho* and *meta* couplings) with two aromatic singlet signals at δ 7.16 (s, 1H, H3') and 6.67 (s, 1H, H6') in the ^1H NMR spectrum, which corresponded to the aromatic structure of compound **131**. The acetyl and Boc group signals were retained at δ 2.45 (s, 3H, $\text{CO}\underline{\text{CH}}_3$) and 1.41 (s, 9H, $\text{OC}(\underline{\text{CH}}_3)_3$). A new quaternary carbon signal was observed at δ 88.2 in the ^{13}C NMR spectrum of **131** corresponding to the aromatic C2' position that was now substituted by an iodo group. MS analysis also confirmed the structure of **131**.

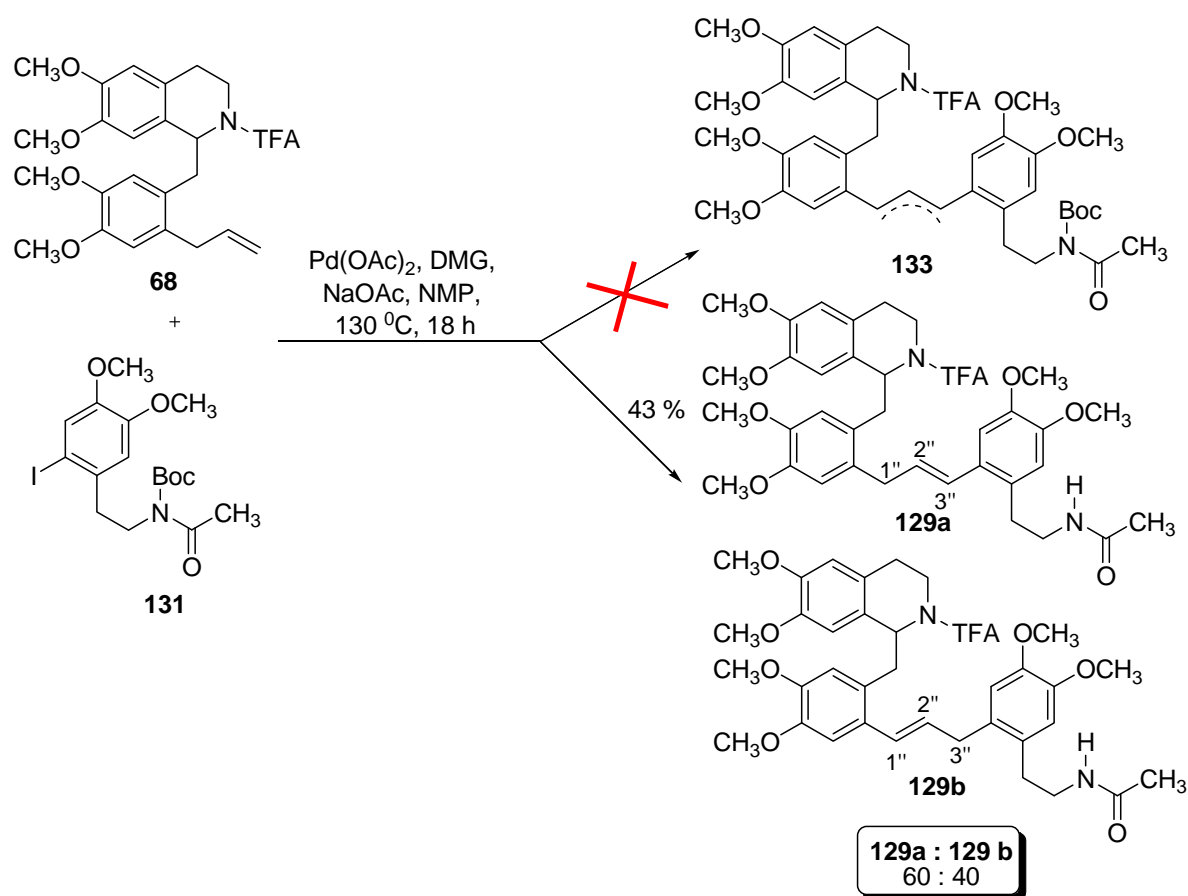
The Heck coupling reaction between the 2'-vinyllaudanosine derivative **67** and the *N*-acetyl, *N*-Boc derivative **131** did not give the corresponding product **132**, however the *N*-Boc deprotected derivative **128** was obtained in 40 % due to cleavage of the *N*-Boc group under the relatively harsh thermal conditions (Scheme 3.9). The relative moderate yield suggested that *N*-Boc deprotection was occurring after the Heck coupling reaction.



Scheme 3.9 Heck coupling reaction between **67** and aryl iodides **131**.

Compound **128** was isolated as a yellow oil and its (*E*)-stereochemistry was evident by the alkene signals in the ^1H NMR spectrum at δ 7.47 (d, 1H, J 16.2 Hz, H2'') and 7.27 (d, 1H, J 16.2 Hz, H1''). The presence of the *N*-acetyl group and the loss of the *N*-Boc group was also confirmed by the amide proton signal at δ 5.67 (bs, 1H, NH) and the methyl signal at δ 1.88 (s, 3H, COCH_3).

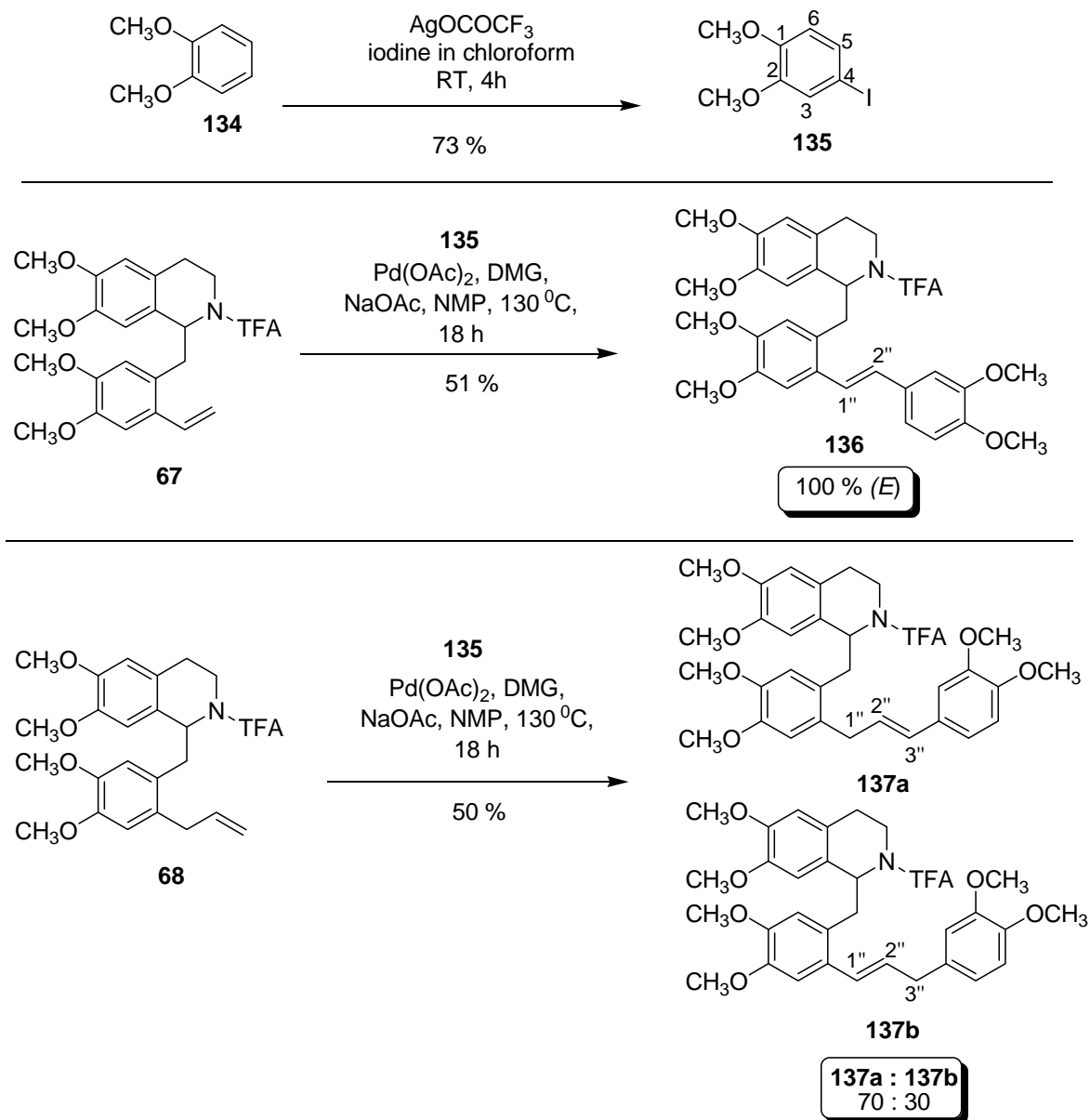
The Heck coupling reaction between the 2'-allyllauidanosine derivative **68** and the *N*-acetyl, *N*-Boc derivative **131** also did not give the corresponding product **133**, however a mixture of the *N*-Boc deprotected derivatives **129a** and **129b** was obtained in 43 % yield. (Scheme 3.10).



Scheme 3.10 The Heck coupling between **68** and **131**.

Compound **129** was isolated as a yellow oil and was a mixture of two (*E*)-isomers in a ratio of 60 : 40 as evident by the presence of the alkene proton signals for **129a** at δ 6.54 (d, 1H, J 16.5 Hz, H3'') and 6.04 (dt, 1H, J 16.5, 6.0 Hz, H2'') and for **129b** at δ 6.67 (d, 1H, J 16.5 Hz, H1'') and 6.04 (dt, 1H, J 16.5, 6.0 Hz, H2''). The relative olefinic chemical shifts of **129a** and **129b** were consistent with those of **116a,b** and **115a,b**, respectively. The amide proton signal at δ 6.18 (bs 1H, NH) and the acetyl proton signal at δ 1.94 (s, 3H, COCH_3) were also observed which confirmed the presence of the *N*-acetyl group.

3.3. Synthesis of veratrole linked benzyloquinoline derivatives.



Scheme 3.11 The overall synthesis of veratrole linked benzyloquinoline derivatives **136** and **137**.

Heck coupling reactions were also carried out on compounds **67** and **68** with 4-iodoveratrole **135** to obtain the corresponding products **136** and **137** having the exocyclic amino moiety excluded entirely.

Prior to the Heck coupling reaction, iodination of commercially available 1,2-dimethoxybenzene (veratrole) **134** was performed using silver trifluoroacetate and iodine in chloroform. After stirring for 4 h, the corresponding iodinated compound **135**¹⁴⁸ was obtained in 73 % yield. The successful iodination was confirmed by the presence of three aromatic proton signals in the ¹H NMR spectrum at δ 7.20 (dd, 1H, *J* 8.4, 2.1 Hz, H5), 7.08 (d, 1H, *J* 2.1 Hz, H3) and 6.58 (d, 1H, *J* 8.4 Hz, H6), indicating the loss of compound symmetry caused by the attachment of the iodo substituent. A new quaternary carbon signal at δ 82.8 in the ¹³C NMR spectrum, corresponding to the iodine substituted carbon, was also observed.

Iodide **135** was subjected to the Heck coupling reaction conditions with both **67** and **68** to give the corresponding benzyloquinoline-veratrole adducts **136** and **137** (mixture of **137a** and **137b**) in yields of 51 % and 50 %, respectively.

The ¹H NMR spectrum of compound **136** displayed (*E*)-alkene proton signals at δ 7.47 (d, 1H, *J* 15.9 Hz, H2'') and 6.84 (d, 1H, *J* 15.9 Hz, H1''). Only one (*E*)-isomer was obtained, and a small amount of an amide rotamer was also detected (*ca.* 5 %). The structure of compound **136** was also confirmed by high resolution MS analysis.

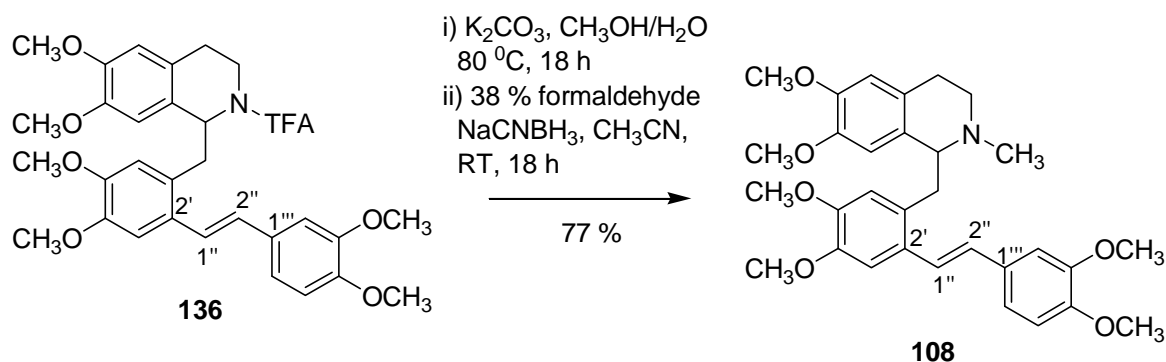
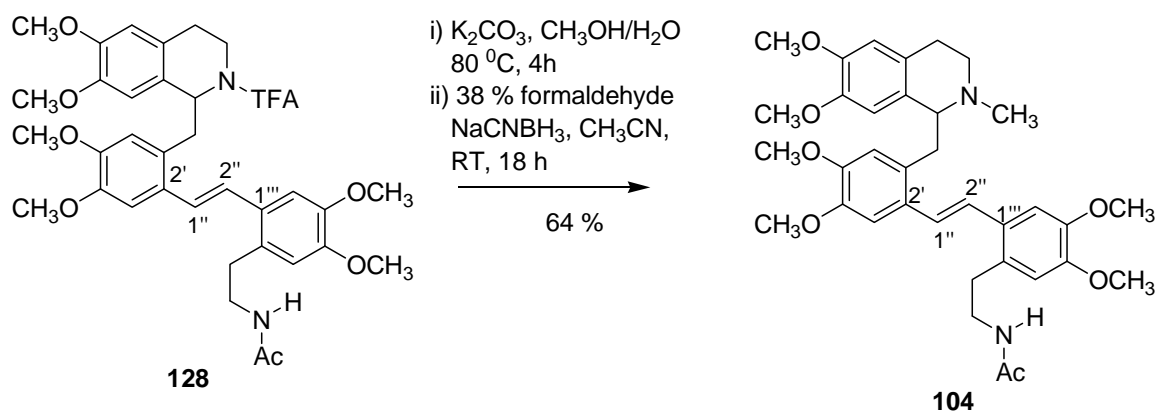
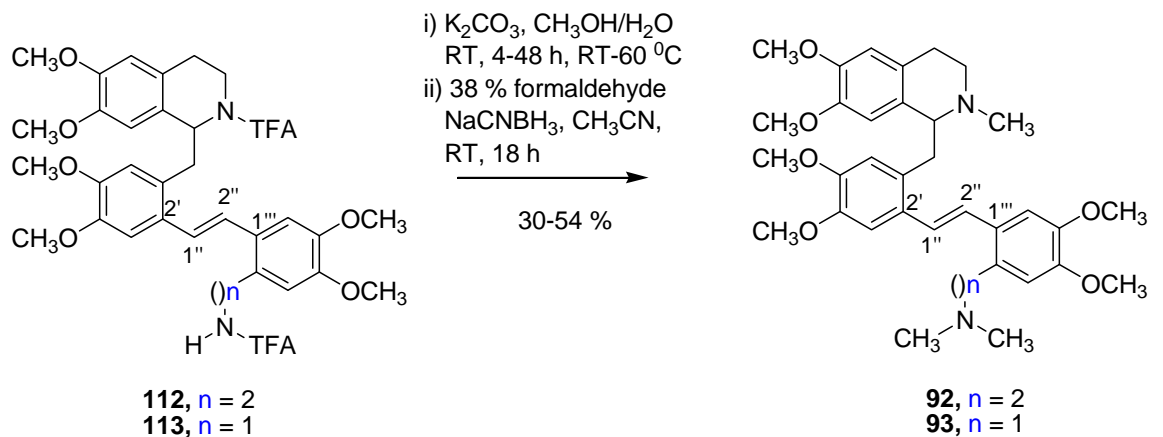
¹H NMR analysis of the two (*E*)-regioisomers of **137** showed a 70 : 30 mixture of **137a** and **137b** with the olefinic proton signals of **137a** observed at δ 6.21 (d, 1H, *J* 15.6 Hz, H3''), 6.09 (m, 1H, H2'') and those of **137b** at δ 6.53 (d, 1H, *J* 15.6 Hz, H1'') and 6.09 (m, 1H, H2''). Their relative chemical shifts were consistent with their proposed structures. The enhanced amount of **137a** over **137b** was consistent with the larger differences in steric size between the relatively small veratrole ring and the larger benzyloquinoline ring.

3.4. *N*-TFA deprotections and reductive *N*-methylations.

The Heck coupling products were *N*-TFA deprotected and then reductively *N*-methylated to afford the targeted benzyloquinoline derivatives as outlined in Schemes 3.12 and 3.13. The *N*-TFA deprotections were carried out using K₂CO₃ in aqueous methanol. The temperatures and the times of these deprotections varied according to the solubility of the starting materials in aqueous methanol. The subsequent reductive *N*-methylation reactions were all maintained at RT for 18 h. The results of these reactions are summarised in Tables 3.3 and 3.4.

The stilbene derivatives (Table 3.3) were generally less soluble in methanol than their propenyl analogues (Table 3.4), therefore slightly higher reaction temperatures were generally needed to successfully cleave the *N*-TFA group of the stilbene compounds. The progress of the *N*-TFA deprotection reactions were monitored by TLC and their completions were indicated by a sharp decrease in the R_f values of their products, due to an increase in polarity, due to their free amino group. The deprotected products were unstable and therefore they were subjected to reductive *N*-methylation without purification to minimise their decomposition.

3.4.1. *N*-TFA deprotection and reductive *N*-methylation of 2'-arylvinyl benzyloquinoline derivatives.



Scheme 3.12 The *N*-TFA deprotection and *N*-methylation of the *N*-TFA stilbene derivatives.

Table 3.3 Summary of the *N*-TFA deprotection and reductive *N*-methylation reactions to obtain the targeted benzyloquinoline derivatives **92**, **93**, **104** and **108**.

Entry	Precursor	<i>N</i> -TFA deprotection temp.	<i>N</i> -TFA deprotection time (h)	<i>N</i> - methylation time (h)	Product	Overall yield (%)	Isomer ratios (<i>E</i>) : (<i>Z</i>)
1	112	RT	48	18	92	30	30 : 70
2	112	60 °C	15	18	92	54	100 : 0
3	113	60 °C	18	18	93	33	40 : 60
4	128	80 °C	4	18	104	64	70 : 30
5	136	80 °C	18	18	108	77	80 : 20

When the *N*-TFA deprotection of **112** was performed at RT (entry 1, Table 3.2), a 48 h period was needed to complete the reaction. However, the prolonged deprotection time was undesirable due to the instability of the product leading to its decomposition and the low yield (30 %) of the corresponding derivative **92**. Surprisingly under these conditions, **92** was obtained as a 30 : 70 mixture of (*E*) and (*Z*) isomers. This was evident by the alkene signals observed in the ¹H NMR spectrum at δ 6.61 (d, 1H, *J* 12.0 Hz, H2'') and 6.41 (d, 1H, *J* 12.0, H1'') for the major (*Z*)-isomer, and at δ 6.97 (d, 1H, *J* 15.9 Hz, H2'') and 6.87 (d, 1H, *J* 15.9 Hz, H1'') for the minor (*E*)-isomer. However, when the *N*-TFA cleavage was carried out at the higher temperature of 60 °C, only (*E*)-**92** was obtained in 54 % yield. It was proposed that the higher reaction temperature may have encouraged the isomerisation of (*Z*)-**92** to the more stable (*E*)-**92**.

These results suggest that the free di-amine of **112** had isomerised to its (*Z*)-isomer during the *N*-deprotection reaction. This might be explained by a favourable intramolecular H-bonding between the amino moieties in the (*Z*)-isomer (Figure 3.5).

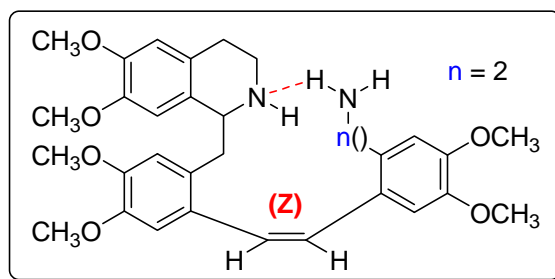


Figure 3.5 The proposed H-bonded intermediate for the favourable formation of (*Z*)-**92** in the *N*-deprotection of (*E*)-**112**.

A similar isomerisation was observed in the product **93** (entry 3), where it was initially obtained as 100 % of the (*Z*)-isomer even though its precursor was 100 % (*E*)-**113**. The (*Z*)-geometry of **93** was evident by the alkene signals at δ 6.71 (d, 1H, *J* 12.0 Hz, H2'') and 6.38 (d, 1H, *J* 12.0 Hz, H1''). However, after a solution of (*Z*)-**93** was allowed to stand for a day in sunlight, a 40 : 60 mixture of (*E*)-**93** and (*Z*)-**93** was obtained, with the signals for (*E*)-**93** alkene appearing at δ 7.22 (d, 1H, *J* 15.3 Hz, H2'') and 6.87 (d, 1H, *J* 15.3 Hz, H1''). It was expected that more of the more stable (*E*)-isomer would be formed if the sample was allowed to stand in daylight for a longer period of time.

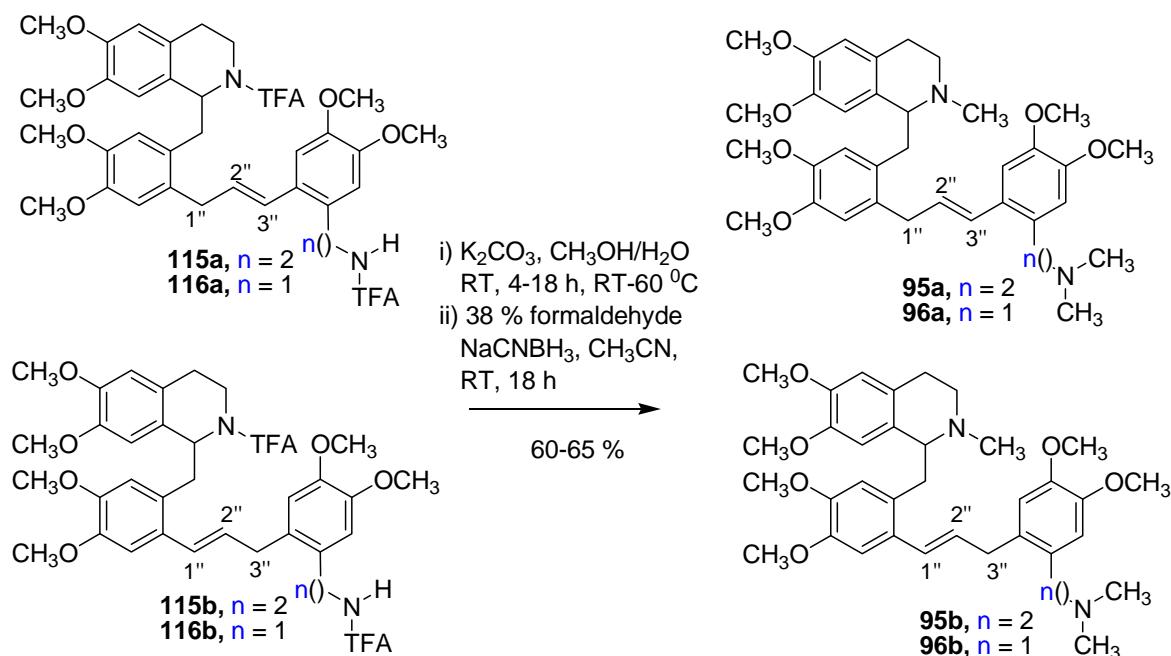
¹H NMR analysis of compound **104** also showed a mixture of (*E*)- and (*Z*)-isomers in ratio of 70 : 30, with the alkene signals of the major (*E*)-**104** observed at δ 7.00 (d, 1H, *J* 15.9 Hz, H2'') and 6.78 (d, 1H, *J* 15.9 Hz, H1'') and the minor (*Z*)-**104** at δ 6.53 (d, 1H, *J* 12.0 Hz, H2'') and 6.28 (d, 1H, *J* 12.0 Hz, H1'').

Compound **108** was also isolated as an 80 : 20 mixture of (*E*)- and (*Z*)-isomers from ¹H NMR analysis showing the olefinic resonances of (*E*)-**108** at δ 6.92 (d, 1H, *J*

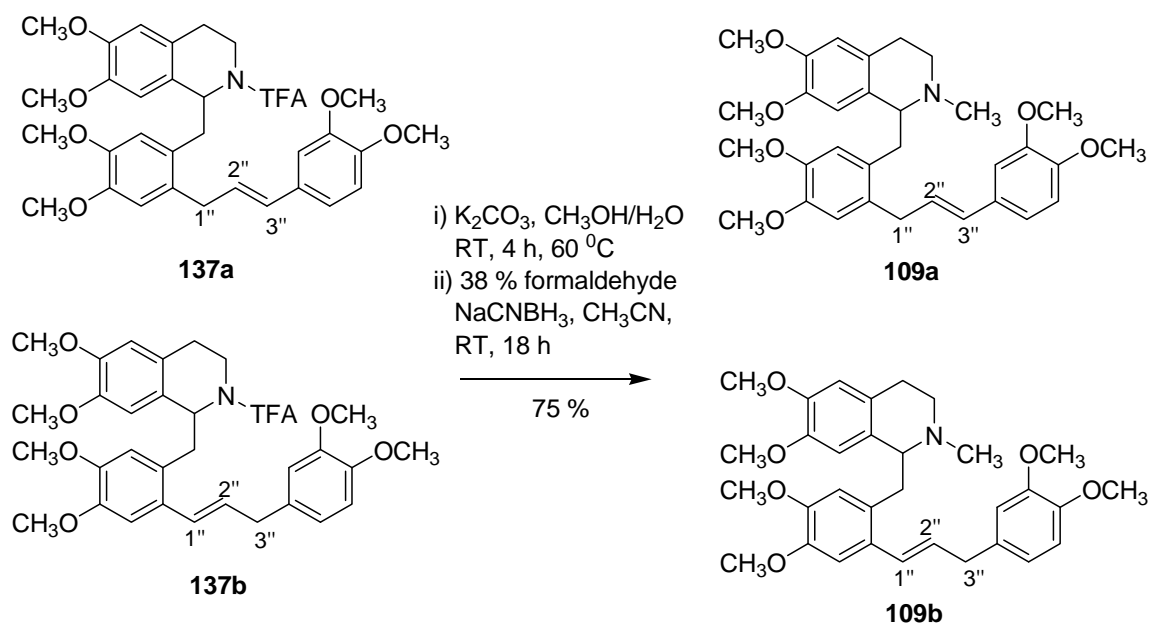
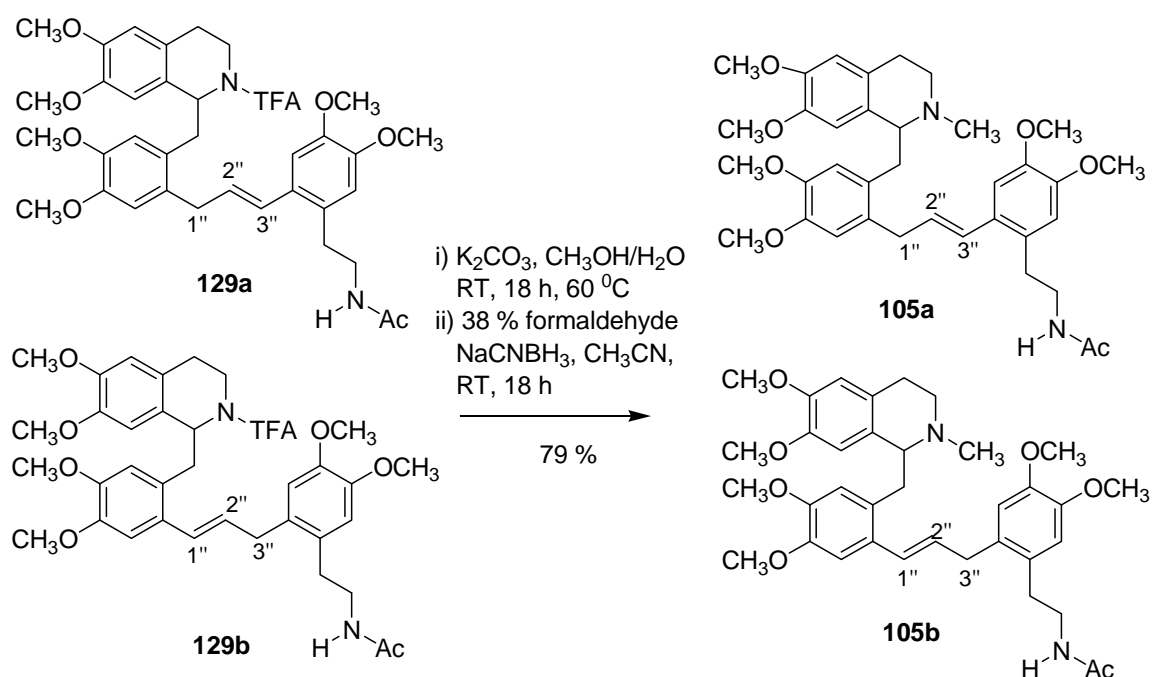
15.9 Hz, H2'') and 6.66 (d, 1H, *J* 15.9 Hz, H1'') and the minor (*Z*)-**108** olefinic signals at δ 6.43 (d, 1H, *J* 11.1 Hz, H2'') and 6.20 (d, 1H, *J* 11.1 Hz, H1'').

It was observed that during the formation of the stilbenes **92**, **93**, **104** and **108** summarised in Table 3.2, that (*E*) to (*Z*) isomerisation had occurred during the hydrolysis of the *N*-TFA precursors **112**, **113**, **128** and **136** since these precursors all consistently had the (*E*)-geometry, however the corresponding products **92**, **93**, **104** and **108** were all obtained as mixtures of (*E*)- and (*Z*)-isomers. The isolation of **108** as a mixture of (*E*)- and (*Z*)-isomers, however, did not support the H-bonded intermediate shown in Figure 3.5 as the only reason for (*E*) to (*Z*) isomerisation, which was most likely initiated by light and heat.

3.4.2. *N*-TFA deprotection and reductive *N*-methylation of 2'arylallyl benzyloquinoline derivatives.



Scheme 3.13 The *N*-TFA deprotection and reductive *N*-methylation of the *N*-TFA benzyloquinoline derivative **115** and **116**.



Scheme 3.14 The *N*-TFA deprotection and reductive *N*-methylation of the *N*-TFA benzylisoquinoline derivatives **129** and **137**.

Table 3.4 Summary of the *N*-TFA deprotection and reductive *N*-methylation to obtain the targeted benzyloquinoline derivatives **95**, **96**, **105** and **109**.

Entry	Pre-cursor	<i>N</i> -TFA deprotection temp.	<i>N</i> -TFA deprotection time (h)	<i>N</i> -methylation time (h)	Product	Yield (%)	Ratio of regioisomer a: b
1	115	RT	18	18	95	65	60 : 40
2	116	60 °C	4	18	96	60	60 : 40
3	129	60 °C	18	18	105	79	70 : 30
4	137	60 °C	4	18	109	75	70 : 30

Using a similar sequence of reactions, the *N*-TFA protected compounds **115**, **116**, **129** and **131** were converted to their fully *N*-methylated derivatives **95**, **96**, **105** and **109**, respectively. The results of these reactions are summarised in Table 3.4. In general, the yields of these products were higher than those in Table 3.3.

Among the allyl derivatives in Table 3.4, two (*E*)-isomers were consistently observed. In compound **95**, two pairs of olefinic signals were observed in a ratio of 60 : 40 with the major (*E*)-isomer (**95a**) signals being detected in the ¹H NMR spectrum at δ 6.33 (d, 1H, *J* 16.0 Hz, H3'') and 5.93 (dt, 1H, *J* 16.0, 6.5 Hz, H2'') and the minor (*E*)-isomer (**95b**) at δ 6.27 (d, 1H, *J* 16.0 Hz, H3'') and 5.99 (dt, 1H, *J* 16.0, 6.5 Hz, H2''). In compounds **96**, **105** and **109**, two pairs of (*E*)-isomers in ratio of 60 : 40 for **96** and 70 : 30 for **105** and **109** were observed from ¹H NMR analysis. All compounds had an (*E*)-alkene coupling constant of 15-16 Hz. Unlike their *N*-TFA precursors, the major *N*-methylated derivatives had olefinic chemical shifts for H3'' slightly downfield than H3'' in the minor isomers.

The characteristic isoquinoline *N*-methyl signals of these derivatives were observed between δ 2.5-2.6 (s, 3H) in the ¹H NMR spectra of the *N*-methylated compounds. These observations were also confirmed by the presence of *N*-methyl

signals between δ 42-46 in the ^{13}C NMR spectra. The benzyloquinoline derivatives **95** and **96** showed the characteristic *N,N*-dimethylamino signals in the ^1H NMR spectra between δ 2.2-2.3 (s, 6H). In all cases, the H1 protons signals observed in the ^1H NMR spectra at around δ 5.5 (1H) in the *N*-TFA precursors, had shifted upfield to δ 3.5-3.7 (1H) after base hydrolysis and reductive *N*-methylation. In some cases, the detection of the H1 proton was problematic due to signal overlapping with the methoxy group resonances, however, the detection of the H1 proton was possible in these cases using gCOSY and gHSQC experiments.

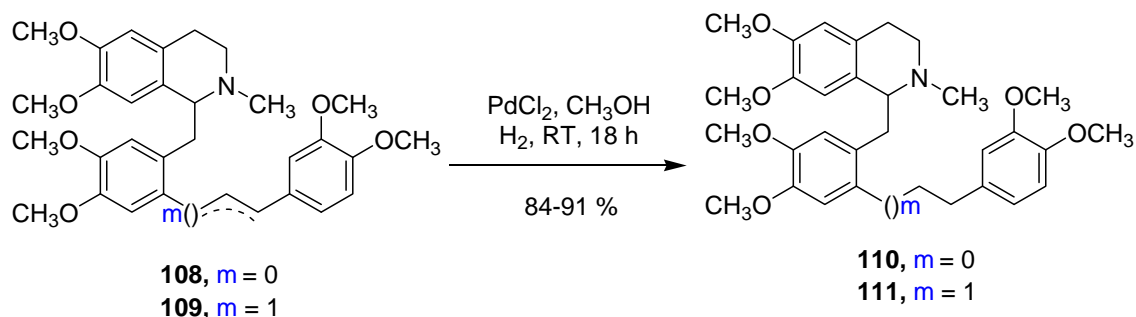
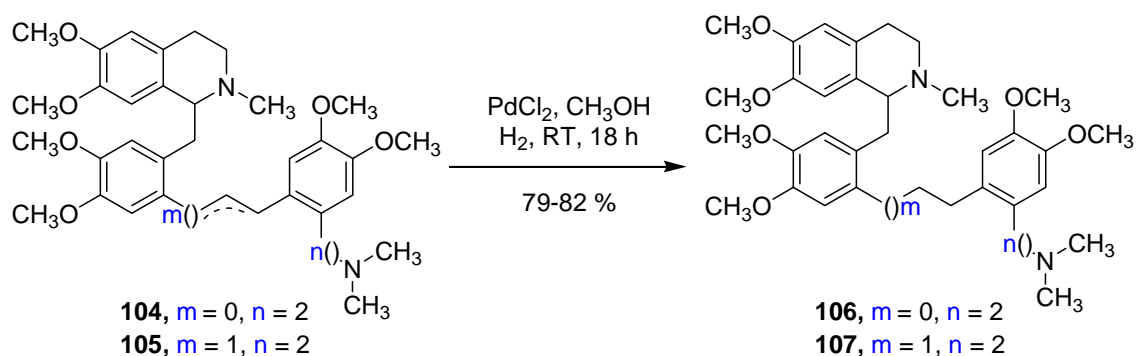
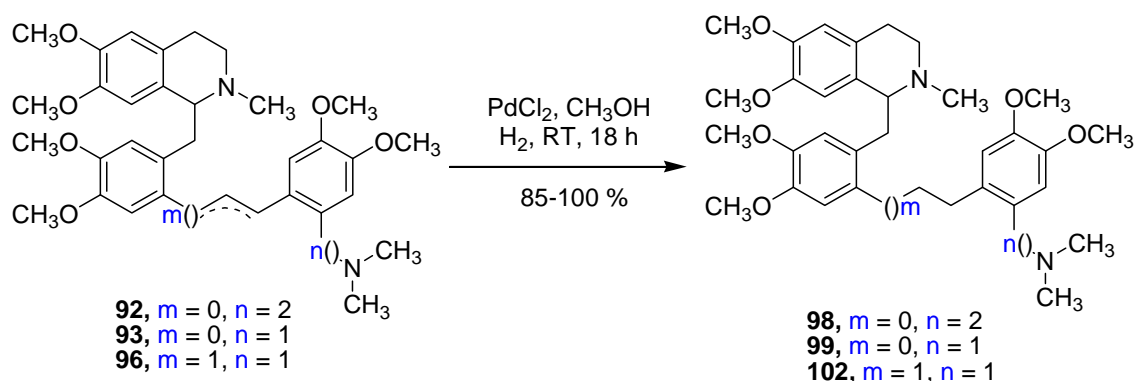
Overall, the eight novel benzyloquinoline derivatives shown in Schemes 3.12-3.14 were successfully synthesised.

3.5. Hydrogenation reactions.

Hydrogenation of the alkene moiety in compounds **92**, **93**, **96**, **104**, **105**, **108** and **109** over PdCl_2 under a hydrogen atmosphere (1 atm) successfully gave the corresponding alkane products in high yields (Scheme 3.15 and Table 3.5).

Table 3.5 Summary of hydrogenation results.

Entry	Precursors	m	n	Products	Yield (%)
1	92	0	2	98	85
2	93	0	1	99	88
3	104	0	2	106	79
4	108	0	n/a	110	91
5	96	1	1	102	100
6	105	1	2	107	82
7	109	1	n/a	111	84



Scheme 3.15 Hydrogenation of unsaturated derivatives.

In the 2'-arylvinyll series, the olefinic signals between δ 5.8-7.2 were replaced by the newly formed multiplet signals between δ 2.3-2.8 for the corresponding ethylene (CH_2CH_2) protons in the products. In the 2'-aryllallyl series, the three newly formed triplet signals between δ 1.5-2.5 in the ^1H NMR spectra corresponded to the newly formed propylene ($\text{CH}_2\text{CH}_2\text{CH}_2$) signals in the products. The ^{13}C NMR spectra of the reduced products showed the replacement of the olefinic CH signals at δ 110-120 with

the newly formed CH₂ signals in the δ 33-35 region. Overall, seven saturated derivatives were successfully synthesised from their unsaturated precursors. These derivatives as well as the eight unsaturated *N*-methylated derivatives described in this Chapter contributed to our library of novel benzyloquinoline derivatives.

Chapter 4 Synthesis of Bisbenzylisoquinolines

Derivatives *via* Ruthenium Mediated Olefin Metathesis.

4.1. Introduction.

In this Chapter, the ruthenium mediated cross metathesis (CM) reaction will be examined as a method to synthesise the novel mono-tethered BBI derivatives **138** and **139** and their dihydro analogues **140** and **141**, as well as the previously prepared BBI derivatives **59** and **60**. The synthesis of the conformationally restricted bis-tethered BBI **142** *via* a ruthenium catalysed ring closing metathesis (RCM) reaction will also be discussed accordingly.

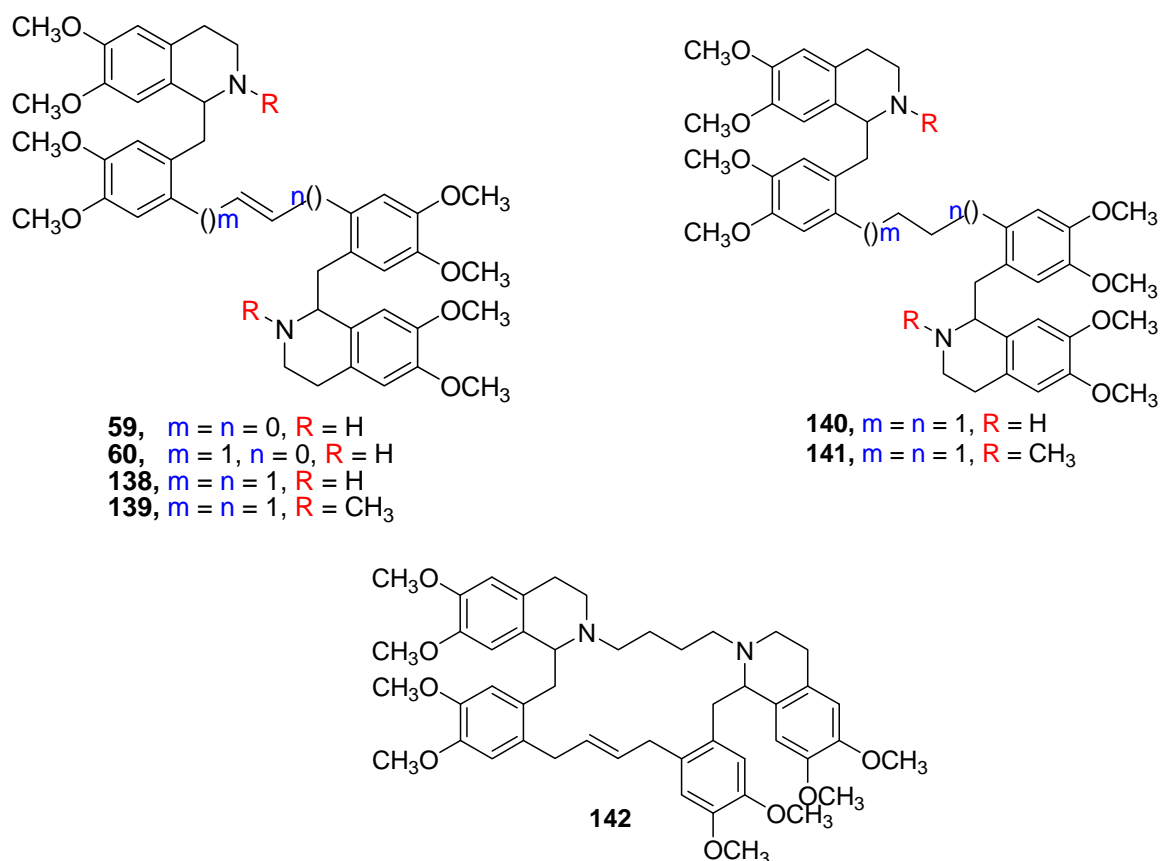


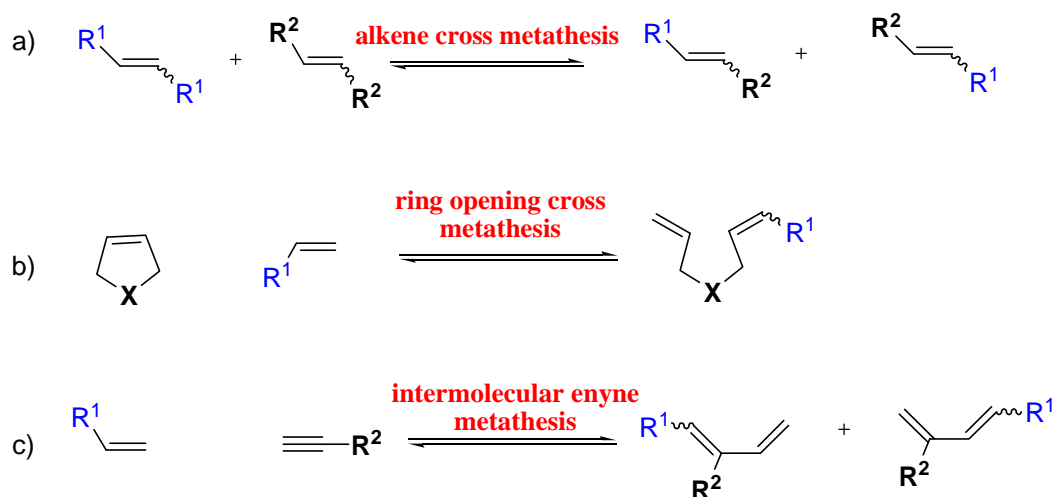
Figure 4.1 The generic structures of the targeted mono- and bis-tethered BBI derivatives.

4.2. Olefin cross metathesis.

4.2.1. Background on cross metathesis reactions.

Olefin CM reactions are convenient synthetic methods to prepare functionalised and higher olefins from simple olefin precursors.¹⁴⁹ CM is formally described as the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by a metal-carbene complex.¹⁵⁰

CM has found numerous applications as a carbon-carbon bond forming tool.¹⁵¹ The process of CM is catalytic, using typically 1-5 mol % of catalyst, and can provide high yields of olefinic products under mild conditions in a relatively short reaction time.¹⁵² The CM reaction can tolerate a wide range of functional groups and gaseous ethylene is usually the only by-product, which is an important consideration in industrial applications.¹⁵³



Scheme 4.1 The variations of intermolecular cross metathesis.^{154,155}

There are three main variations of intermolecular CM which are shown in Scheme 4.1: a) alkene cross metathesis, b) ring opening cross metathesis and c) intermolecular enyne metathesis.¹⁵⁴ Of these three types, the alkene CM reaction is of particular interest in terms of the aims of this project.

The alkene CM reaction remains an under-utilised area of olefin metathesis, compared to the well known ring-opening metathesis (ROM) and ring closing metathesis (RCM). This has been the prominent result of factors such as the lack of a strong enthalpic driving force in the case of ring-strain release in ROM, or the entropic advantages of intramolecular reactions in RCM reactions.¹⁵⁶ Therefore, the type of catalyst used is of great importance. Widely used olefin metathesis catalysts are Grubbs' first and second generation ruthenium catalysts, **143** and **144**, respectively, and the Schrock molybdenum catalyst **145**. Their structures are shown in Figure 4.2.

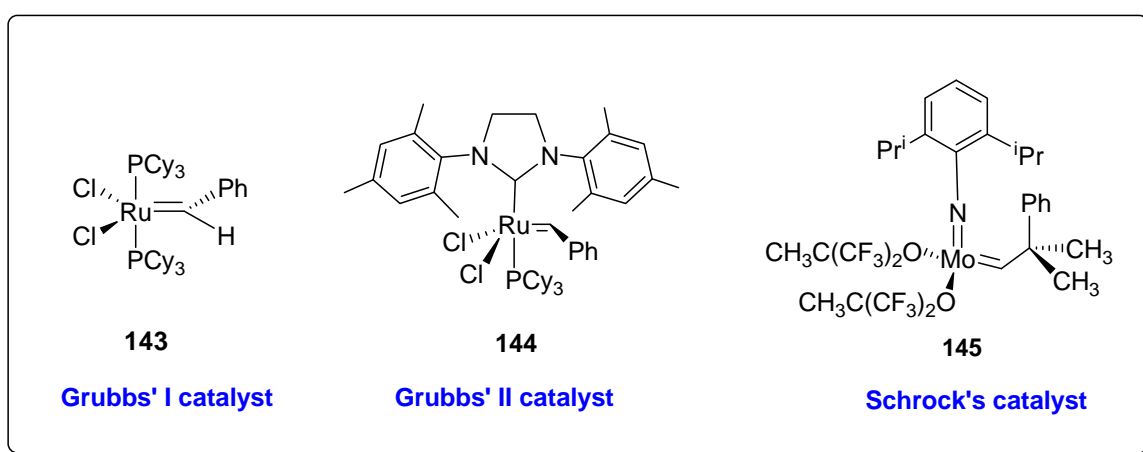
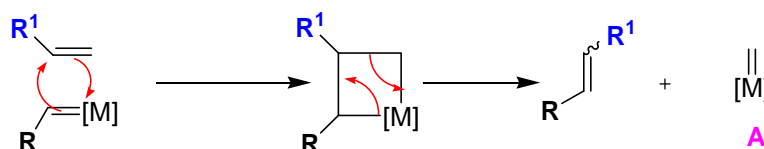


Figure 4.2 The structures of the commonly used olefin metathesis catalysts.

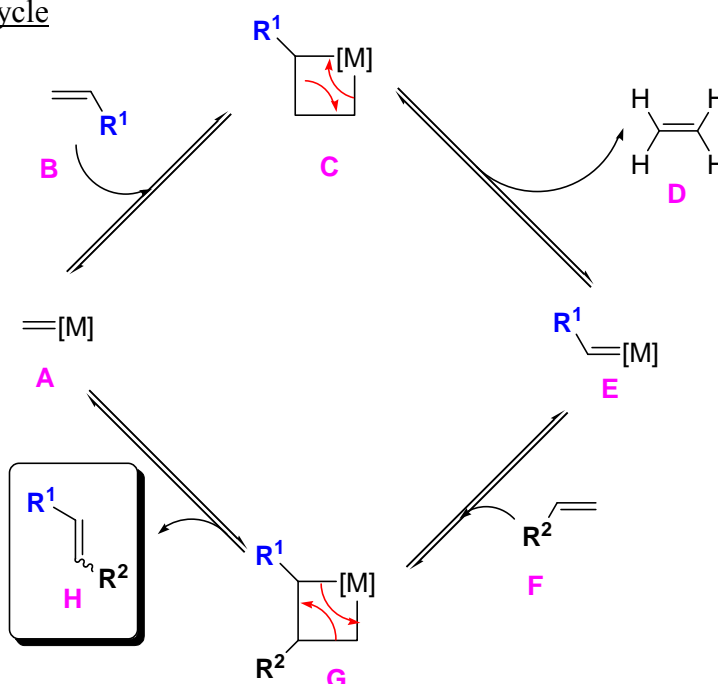
Grubbs' ruthenium carbene catalysts, **143** and **144**, are now preferred over the Schrock catalyst **145** for several reasons. Firstly the molybdenum complex **145** has poor functional group tolerance. Secondly, it is air, moisture and impurities sensitive and finally it is thermally unstable and quite costly.¹⁵⁶ The ruthenium catalysts however, have greater functional group tolerance and can be handled under nitrogen.¹⁵⁷ Their catalytic activities are not significantly reduced when exposed to air or moisture, unlike their molybdenum based counterparts, which require vacuum line and dry box conditions.^{157,158}

The mechanism of the CM reaction involves the initial formation of a metallacyclobutane, which collapses to give the transition metal carbene **A**. This species enters the catalytic cycle, and reacts with olefin **B** in a [2+2]-cycloaddition to give the metallacyclobutane **C**. This species subsequently collapses to release ethene **D** and affords a new metal carbene **E**. This metal carbene undergoes another [2+2]-cycloaddition reaction with the olefin **F**, following the collapse of the metallacyclobutane **G** to give the CM product **H** and the regenerated transition metal carbene **A** for another catalytic cycle.¹⁵⁴

Initiation



Catalytic cycle



Scheme 4.2 The catalytic cycle of the olefin cross metathesis.¹⁵⁴

In most CM reactions, major concerns encountered are the efficiency and selectivity of the cross coupling products. Many increasingly active catalysts have been

developed to achieve high yields of the cross coupled products with minimal amount of competing homocoupled (self-metathesis) products. However, the ability to accurately predict the selectivity of CM reactions remains a relevant issue for the practical application of CM.

4.2.2. *Studies towards the selectivity of cross metathesis.*

In a recent investigation by Grubbs and coworkers,¹⁴⁹ four distinct types of olefins were categorised to allow one to predict both selective and non-selective CM reactions (Figure 4.3).

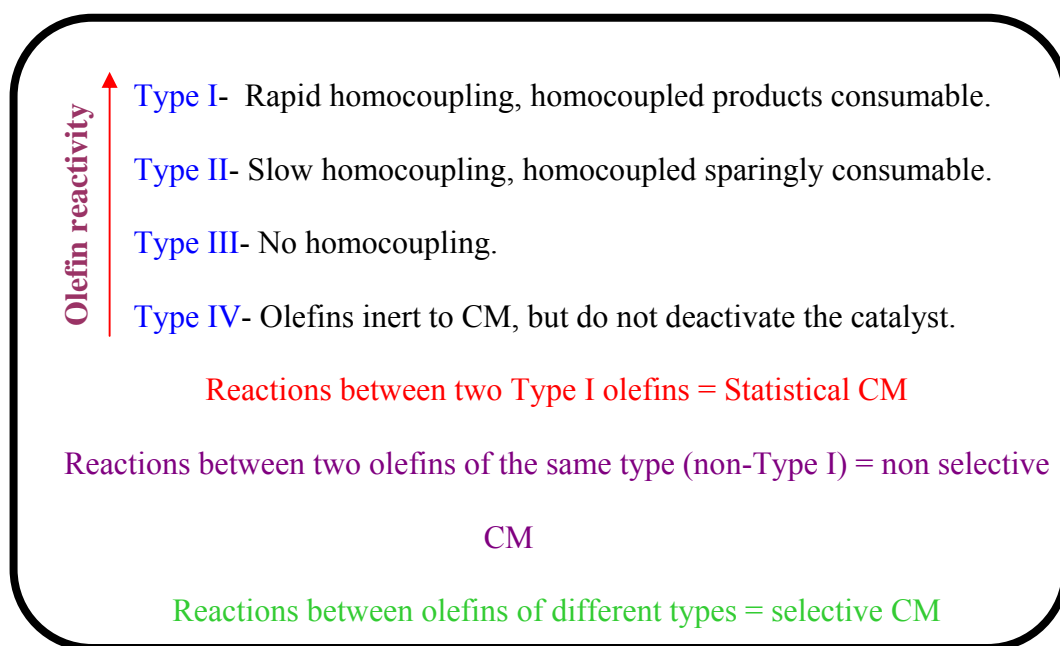
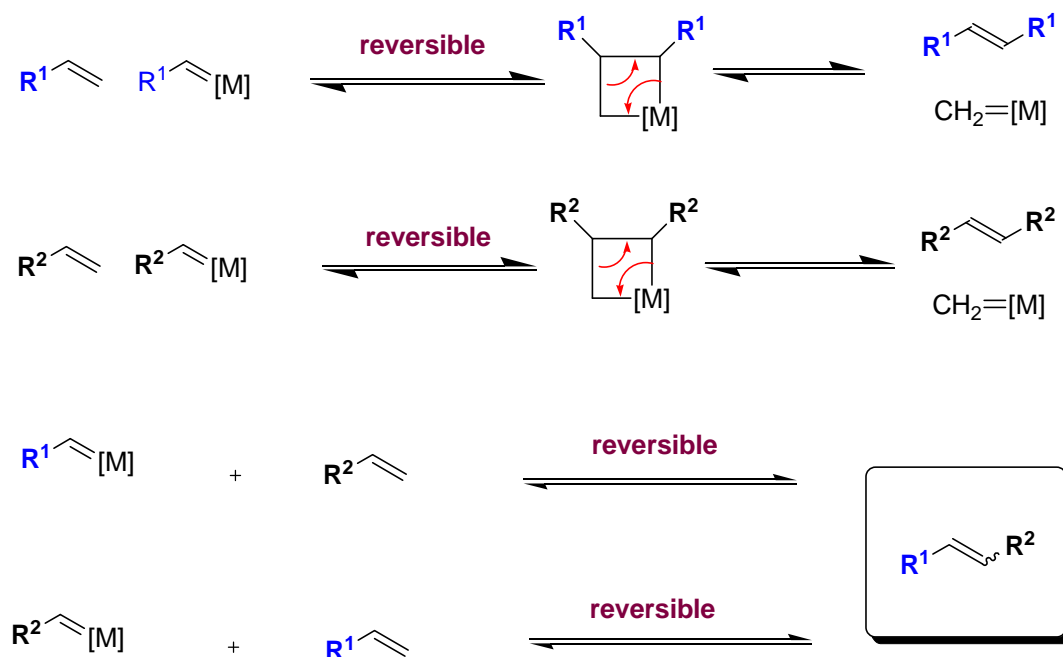


Figure 4.3 Olefin categorisation and rules for selectivity.

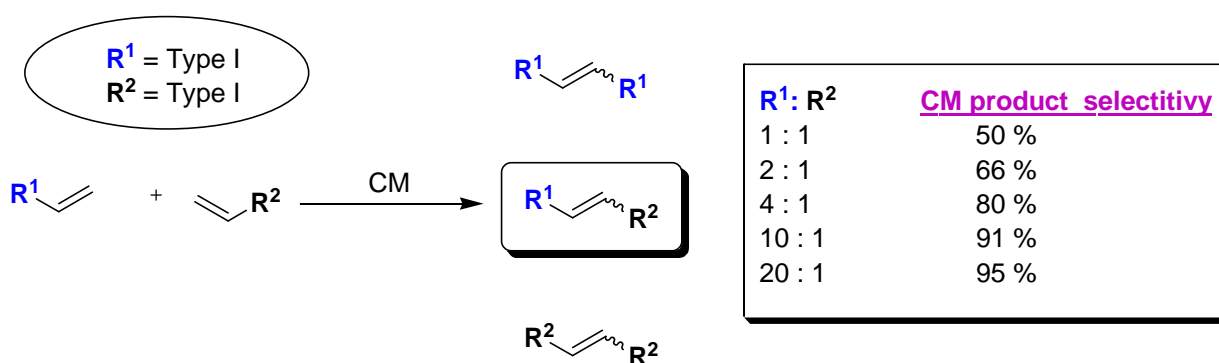
4.2.2.1. Statistical cross metathesis of two Type I Olefins.

When two Type I olefins are used in CM reactions, the rates of homocoupling reactions are similar and the activities of the resulting homocoupled product towards a secondary metathesis reactions are high. Secondary metathesis is the subsequent reaction of a homocoupled olefin with the propagating catalyst to reversibly regenerate

the starting olefin (Scheme 4.3). Therefore the desired cross coupled products will be equilibrated with the various homodimers through secondary metathesis resulting in a statistical mixture of olefinic products. For these reactions, 10 mol. equiv. of one CM partner is normally required to provide >90 % of the desired CM products (Scheme 4.4).



Scheme 4.3 CM products obtained through secondary metathesis.

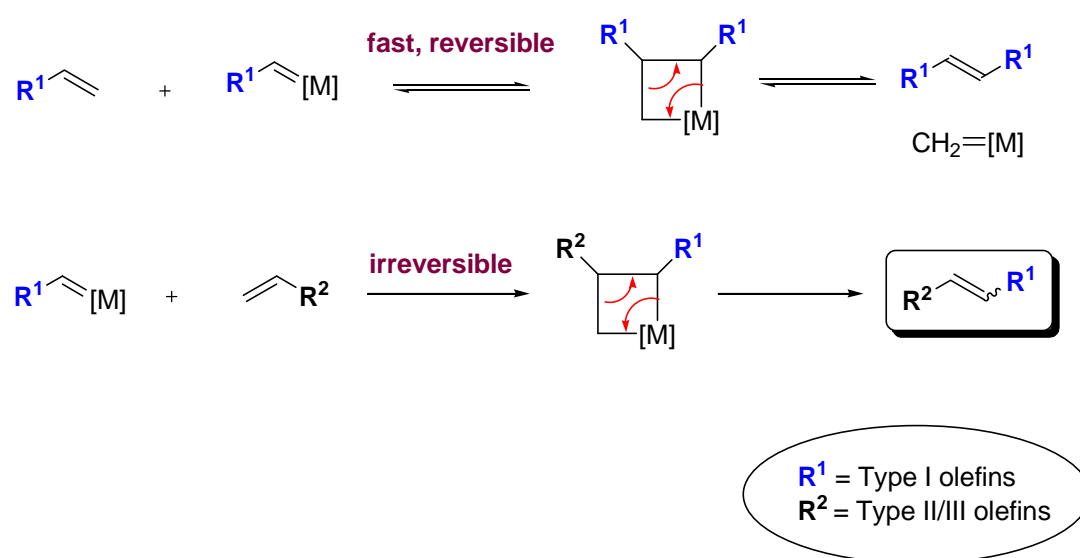


Scheme 4.4 Statistical distribution of CM products.

4.2.2.2. Selective cross metathesis among two different types of olefins.

To avoid the formation of the statistical product mixtures mentioned above, selective CM reactions can be designed using olefins from two different types, whose homocoupling rates are significantly different from the rate of CM product formation (Scheme 4.5).

In these reactions, typical Type I homocoupled product ($R^1CH=CHR^1$) readily undergoes secondary metathesis with Type II/III olefins ($CH_2=CHR^2$) to give the desired cross-coupled product. However, due to the slow homocoupling rate of Type II/III olefins and the inability of the desired cross coupled product to undergo secondary metathesis, good yields of the desired CM product are obtained.



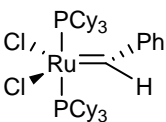
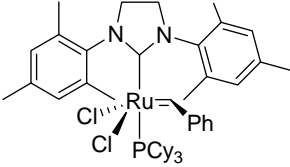
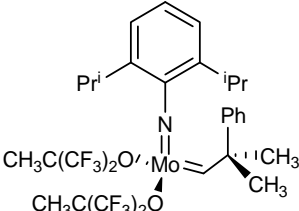
Scheme 4.5 Selective Cross metathesis of Type I with Type II/III olefins.

4.2.3. Categories of olefins.

Examples of olefins of different types are categorised in Table 4.1, with sterically unhindered, electron-rich olefins categorised as Type I and increasingly hindered and electron deficient olefins falling into Type II through to Type IV. While simple modification of the steric or electronic properties of an olefin is sufficient to

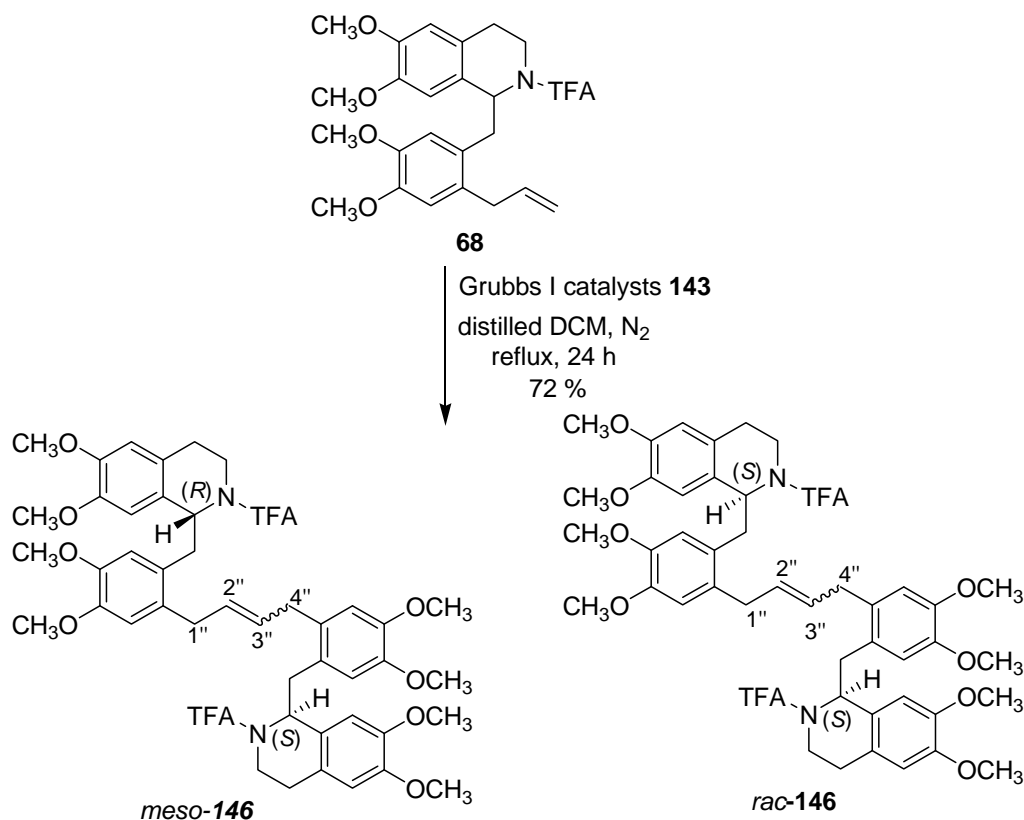
change its reactivity leading to a selective CM reactions, CM selectivity can also be achieved by using a more sensitive catalyst.

Table 4.1 Olefin categories for selective CM.

Olefin type	 143	 144	 145
Type I	Terminal alkenes; allyl silane; 1 ⁰ allyl alcohols, ethers or esters; allyl halides	Terminal olefins; 1 ⁰ allylic alcohols or esters; styrene (no large ortho units); allyl sulfides; protected allyl amines	Terminal olefins; allyl silanes
Type II	Styrene; 2 ⁰ allylic alcohol; vinyl dioxane; vinyl boronates	Styrene (large ortho units); acrylamines; acrolein; vinyl ketones; 2 ⁰ allylic alcohol	Styrene; allyl stannanes
Type III	Vinyl siloxane	1,1-Disubstituted olefins; non-bulky trisubstituted olefins; 3 ⁰ allylic alcohol (protected)	3 ⁰ Allyl amines; acrylonitrile
Type IV	1,1-Disubstituted olefins; 3 ⁰ allylic amines (protected)	Vinyl nitro olefins; trisubstituted allyl alcohol (protected)	1,1-Disubstituted olefins

For example, styrene is strictly a Type II olefin under Grubbs' I catalyst, however it is categorised as a Type I olefin when the more sensitive Grubbs' II catalyst is employed. These olefinic properties as well as the use of Grubbs' catalyst will be examined as a tool towards the synthesis of the target benzyl- and bisbenzylisoquinoline derivatives.

4.3. Formation of the four carbon-tethered BBI derivative **146** via cross metathesis reactions.



Scheme 4.6 Cross metathesis reaction of the 2'-allyllaunosine derivative **68** (Type I olefin). Note- only the (*S,S*) enantiomer shown for *rac-146*.

Utilising the ability of Type I olefin to homocouple rapidly, the racemic 2'-allyllaunosine derivative **68** (an example of Type I terminal alkene) was treated with 10 mol. % of the Grubbs' I catalyst **143** and the reaction was heated at reflux in freshly distilled DCM for 24 h under a nitrogen atmosphere. The homocoupled product **146** was readily obtained in 72 % yield after purification. Cho and co-workers have demonstrated the effective removal of the ruthenium by-products by treatment of the crude product with activated carbon, followed by column chromatography on silica gel.¹⁵⁹ However, removal of the ruthenium by-products in this manner was not necessary due to the higher polarity of the CM product **146** compared to the much less polar ruthenium by-products, allowing them to be separated effectively.

The ^1H NMR spectrum of **146** showed a broad overlapping signal for the olefinic and H1 and H1' protons at *ca.* δ 5.4. Because of the symmetry of this compound, the olefinic protons are equivalent, therefore it was not possible to measure the coupling constant or determine the (*E*)- or (*Z*)-olefin geometry of **146** (Figure 4.4).

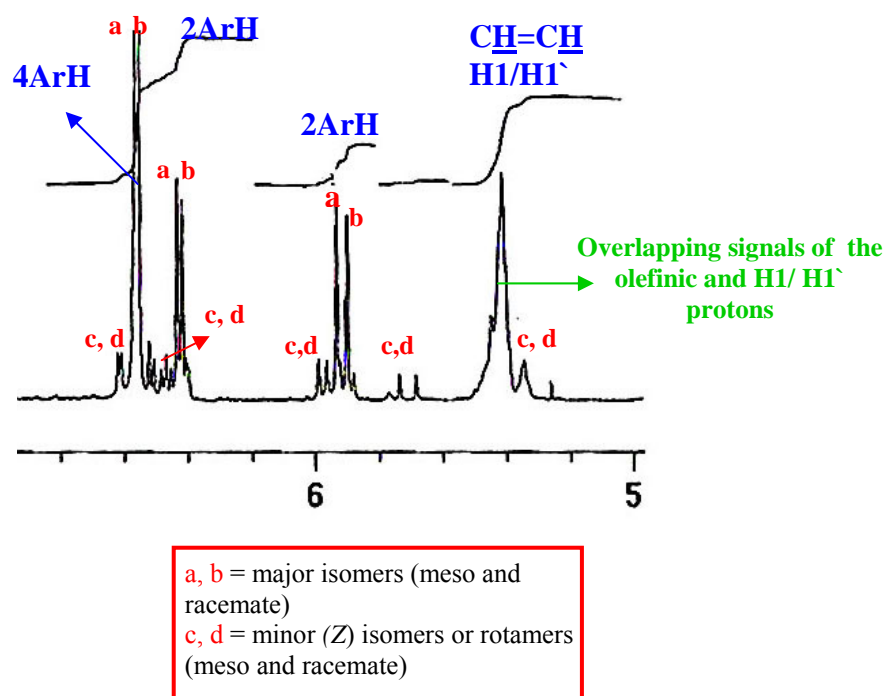
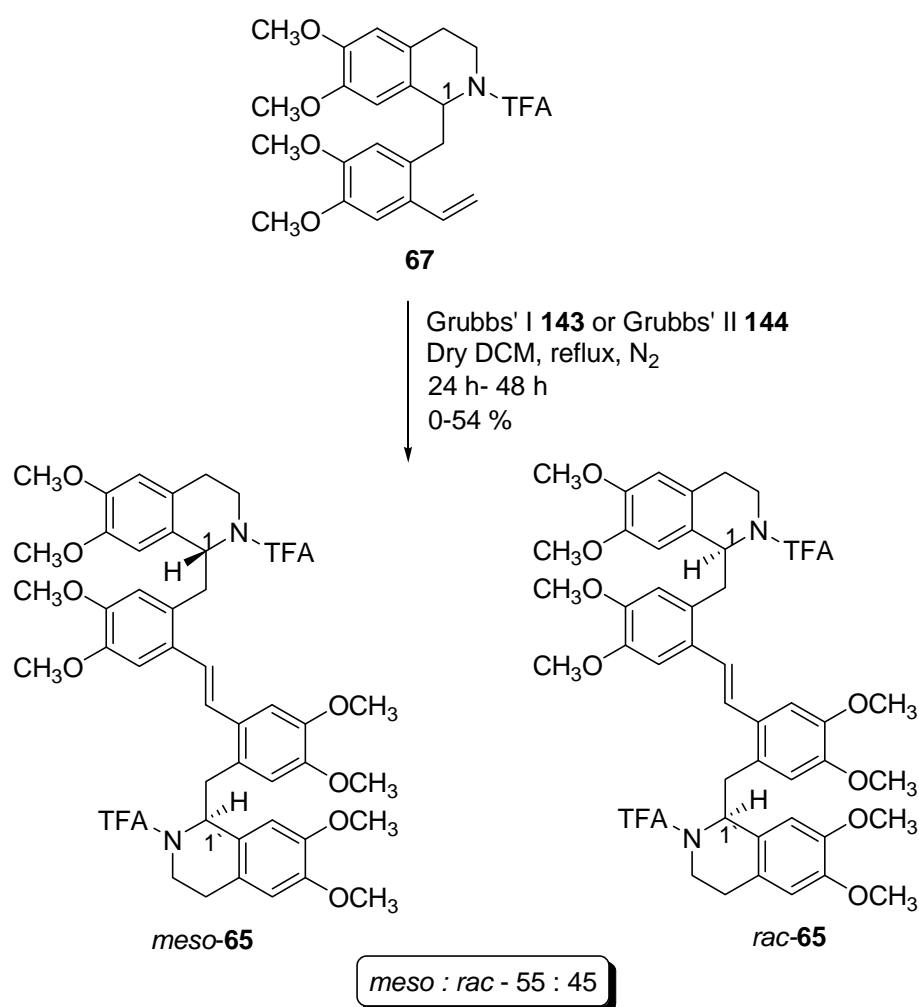


Figure 4.4 ^1H NMR spectrum (300 MHz, CDCl_3) of the aromatic region of **146** showing pairs of aromatic signals.

^1H NMR analysis showed signals for two major isomers in a ratio of 55 : 45, which were assumed to be the meso and the racemic forms of **146**. These were indicated by the doubling up of the major aromatic proton signals **a** and **b**, in the ^1H NMR spectrum. Based on the previous studies on the CM reactions of Type I olefins,¹⁶⁰ the (*E*)-olefin geometry was expected for these major isomers. A pair of minor signals (**c** and **d**) were also observed in the ^1H NMR spectrum of **146** representing either amide rotamers or a different alkene geometry (*Z*) to that of the major products. These signals comprised *ca.* 20 % of the product mixture. Further experiments were consistent with the minor isomer being (*Z*)-**146** (Section 4.7.1).

4.4. Formation of the two carbon-tethered BBI derivative **65** via cross metathesis.

The 2'-vinyllaudanosine derivative **67** was subjected to the same CM conditions as in Scheme 4.6 using 10 mol. % of Grubbs' I catalyst **143** over a period of 24-72 h. Under these conditions, no homocoupled product **65** was observed. The result obtained was not surprising since the styrene **67** is hindered due to the closeness of the *ortho* isoquinoline moiety, which would be classified as a Type II olefin, resulting in a slow homocoupling reaction rate with catalyst **143**.



Scheme 4.7 Cross metathesis of the 2'-vinyllaudanosine derivative **67**. Note- only (*S,S*)-**65** was shown for *rac*-**65**.

Table 4.2 Summary of ruthenium mediated CM reactions of styrene **67**.

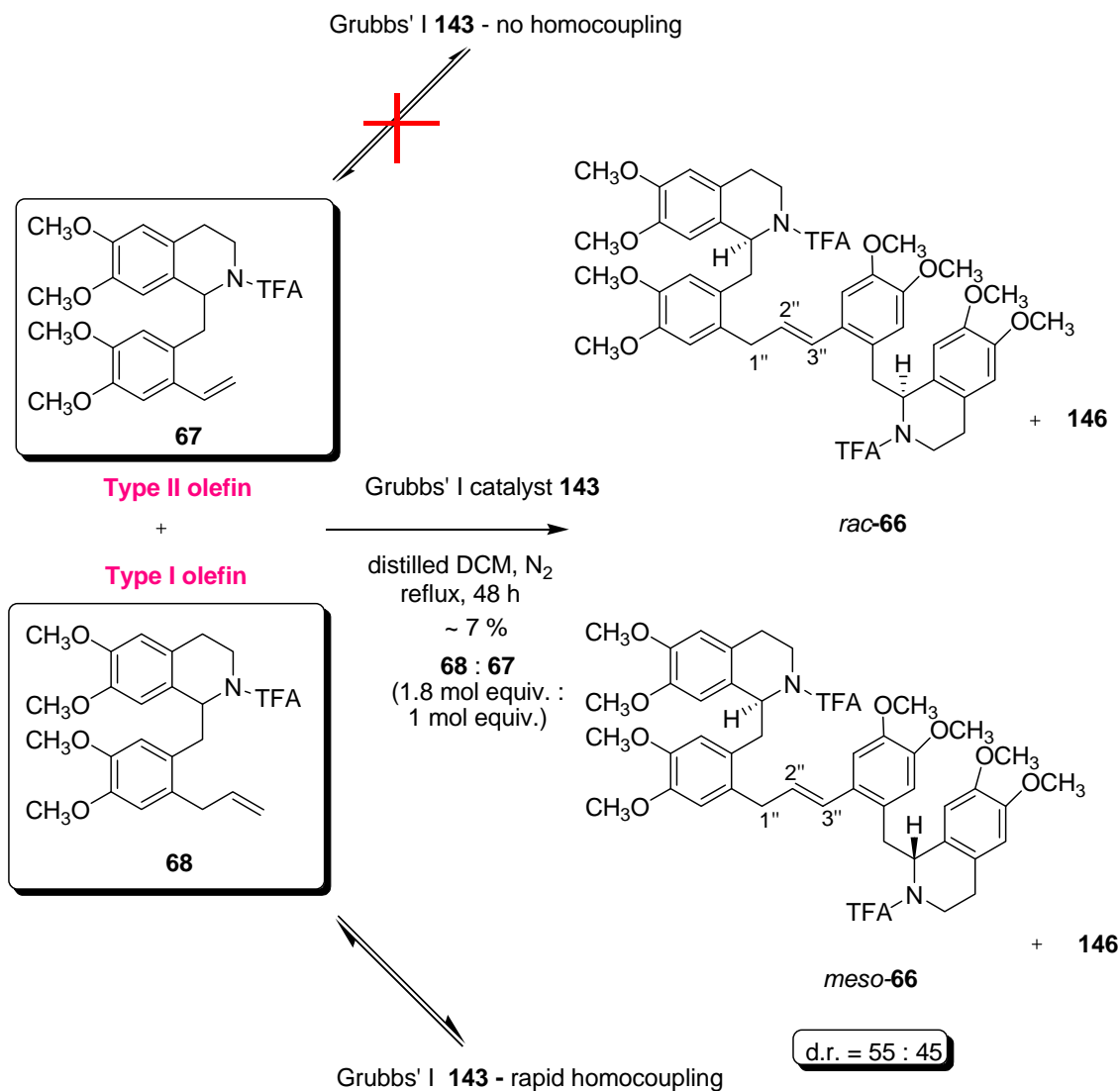
Catalyst	Time of reaction (h)	Product	Yield (%)	Diastereomer ratio	Rotamer ratio
Grubbs' I (143)	24	65	0	n/a	n/a
Grubbs' I (143)	72	65	0	n/a	n/a
Grubbs' II (144)	48	65	54	55 : 45	95 : 5

Table 4.1 indicated that Grubbs' II catalyst **144** would increase the reactivity of a non-bulky styrene to a level of a Type I olefin, however, a very bulky styrene would still react as a Type II olefin. At this stage, the question arose as to whether the more active Grubbs' II catalyst **144** would sufficiently increase the reactivity of the styrene **67** to the level of a Type I olefin and allow for its rapid homocoupling reaction. In the event, a solution of the styrene **67** and Grubbs' II catalyst **144** (10 mol. %) was heated at reflux for 48 h and the homocoupled product **65** was obtained in 54 % yield. The starting styrene **67** was also recovered in 17 % yield. The reaction yield might have been improved if a longer reaction time was permitted or if fresh catalyst was added after 48 h, however, these variations were not examined.

Compound **65** was identical spectroscopically to that obtained in Chapter 2 with the ratio of the meso and racemic forms being 55 : 45. The geometry of the double bond in **65** was anticipated to be 100 % (*E*) although this could not be readily determined by NMR due to the symmetry of **65**. Chang and co-worker have reported 100 % (*E*)-stilbenes being obtained from CM reactions of different styrene systems which supported our proposed (*E*)-olefin geometry for **65**.¹⁶¹ It is also noted that employment of the CM reaction to generate the stilbene **65** had an advantage over the previously employed Heck coupling reactions described in Chapter 2 as it afforded the desired product **65** as the sole regioisomer.

4.5. Cross metathesis between a Type I and a Type II olefin.

4.5.1. Formation of the three carbon-tethered BBI derivative **66** via cross metathesis.



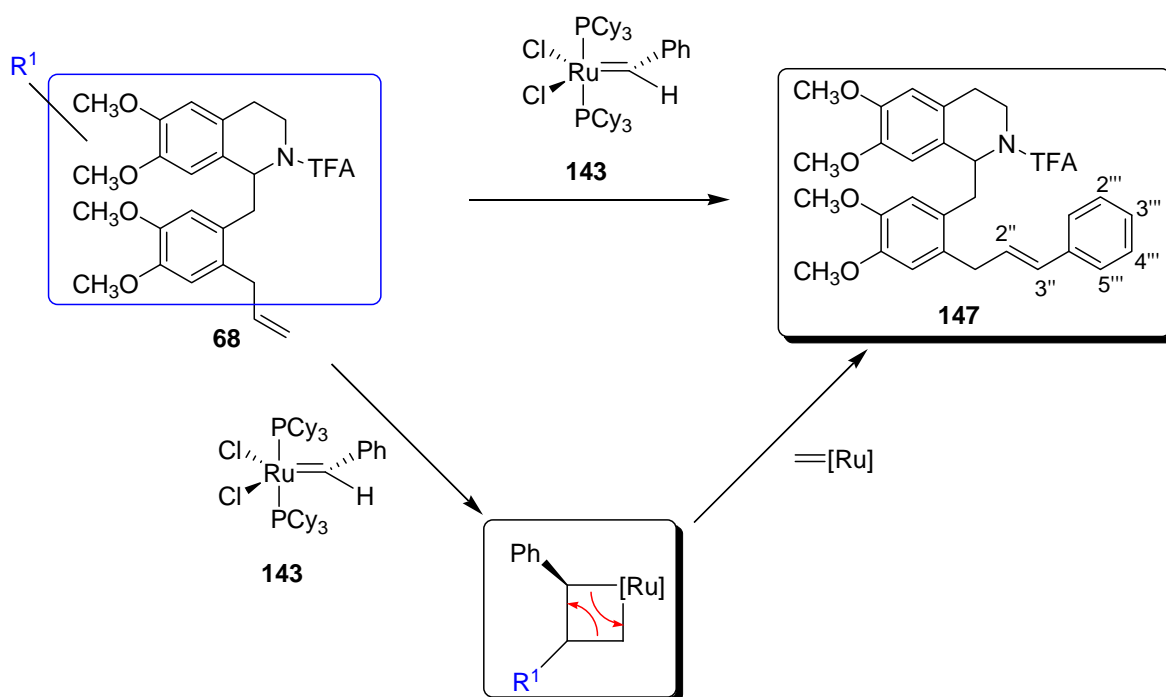
Scheme 4.8 CM between Type I olefin **68** and Type II olefin **67**. Note- only (*S,S*)-**66** was shown for *rac*-**66**.

In Sections 4.3 and 4.4, the homocoupling properties of the 2'-allyllaudanosine derivative **68** (Type I olefin) and the 2'-vinyllaudanosine derivative **67** (Type II olefin) were investigated. In this section, the cross metathesis reaction between the Type I olefin **68** (1.8 mol. equiv.) and Type II olefin **67** (1 mol. equiv.) was carried out in DCM solution at reflux temperature. The less reactive Grubbs' I catalyst **143** was chosen for

this study since it was shown above that the Grubbs' II catalyst **144** increased the reactivity of the styrene **67** to the Type I level and this may result in a non-selective CM reaction.

After a 24 h period, TLC analysis indicated the formation of a small amount of a more polar compound consistent with the previously synthesised derivative **66** (Chapter 2) along with significant amounts of unreacted **67** and **68**. The reaction mixture was heated at reflux for an additional 24 h, however, the TLC analysis was similar to the TLC analysis obtained after 24 h, therefore, it was considered that the catalyst might have become inactive. The addition of a fresh batch of catalyst would be expected to improve this yield in the future.

The crude reaction mixture was purified by column chromatography to recover approximately 50 % of a mixture of the starting materials **67** and **68**. A more polar fraction was obtained in approximately 15 % yield. However, ^1H NMR analysis of this fraction indicated the presence of the desired CM product **66** (prepared by Heck coupling reaction in Chapter 2) and the homocoupled product **146** in a 1 : 1 ratio.

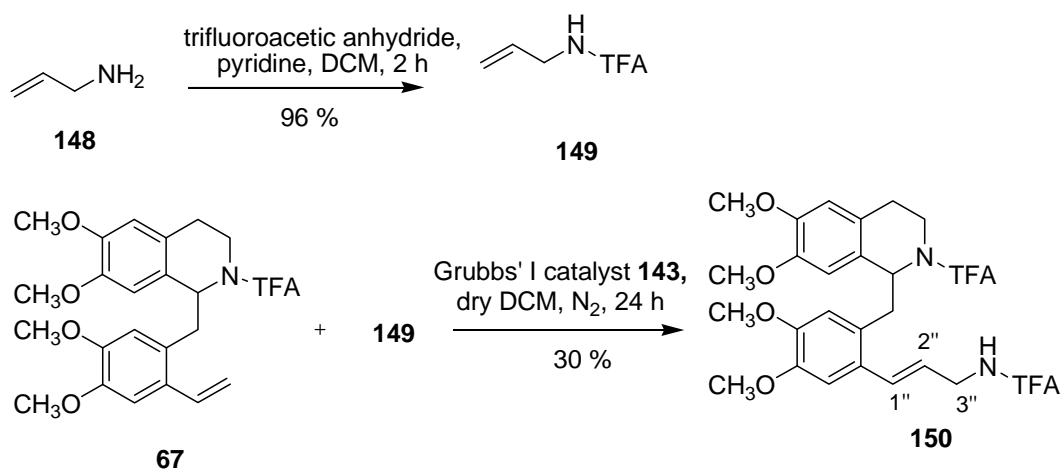


Scheme 4.9 The proposed mechanism for the formation of the byproduct **147**.

In some cases, the by-product **147**, arising from the CM reaction of **68** and Grubbs' catalyst **143**, was also observed (Scheme 4.9), which was evident from ^1H NMR analysis by the alkene signals at δ 6.27 (d, 1H, J 16.0 Hz, H3'') and 6.17 (dt, 1H, J 16.0, 6.0 Hz, H2''). The aromatic signals in the styrene portion of **147** were observed at δ 7.27 (m, 2H, H1''', H5'''), 7.25 (m, 2H, H2''', H4''') and 7.20 (m, 1H, H3''').

To investigate if steric factors were responsible for the low conversion rate in the formation of **66**, the CM reaction of **67** with a less hindered alkene **149** was investigated. This study would also provide an interesting product for future biological testing.

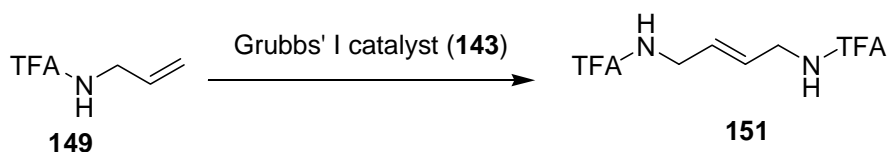
4.5.2. Formation of the substituted styrene derivative **150** via cross metathesis.



Scheme 4.10 The CM reaction between Type II olefin **67** and Type I olefin **149**.

Allylamine **148** was treated with trifluoroacetic anhydride to give a 96 % yield of the *N*-TFA protected amine **149** without the need for further purification. The amine **149** was subjected to the CM reaction using Grubbs' I catalyst **143** and the 2'-vinyl-6,6'-dimethoxy-2,2'-biphenyl derivative **67**. This reaction gave the corresponding CM product **150** in 30 % yield along with the recovered styrene **67** in 54 % yield. The reaction was

repeated for an additional 48 h, however, no significant change was observed in conversion to the product **150**, rather there was more decomposition material obtained. ^1H NMR analysis of **150** showed the expected (*E*)-alkene signals at δ 6.76 (d, 1H, *J* 15.5 Hz, H1'') and 5.98 (dt, 1H, *J* 15.5, 5.5 Hz, H2''). The amide proton signal was also observed at δ 7.62 (bs, 1H, NH) confirming the structure of **150**. MS analysis of **150** also confirmed its molecular formula.



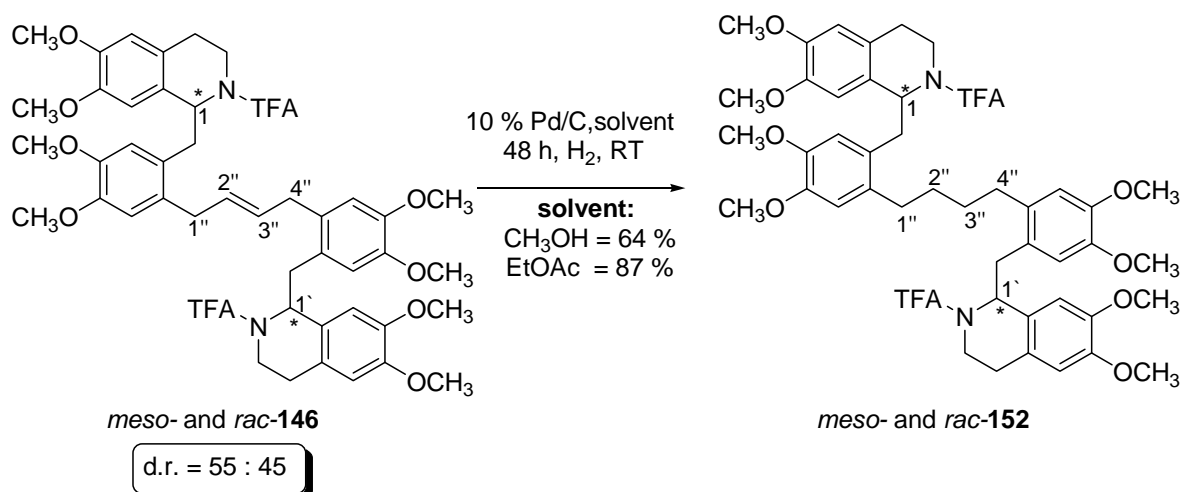
Scheme 4.11 CM of allylamine **149**.

In one of the minor column chromatography fractions, traces of the starting material **149** and the homocoupled product **151** were observed. The small amount of **151** was evident from ^1H NMR analysis with the multiplet signal at δ 5.43 (2H) corresponding to the alkene protons.

From the above results, it was evident that poor yields arose from the CM reaction of **67** with both hindered (**68**) and unhindered (**149**) allyl systems. As part of our future work, perhaps CM reactions of these systems could be examined using the more active Grubbs' II catalyst (**144**).

4.6. Synthesis of the saturated tethered bis-benzylisoquinoline derivative **152**.

The synthesis of the unsaturated BBI derivative **152** was carried out using the same hydrogenation procedure as described previously for the BBI derivative **66** in Chapter 2 using palladium on activated carbon. In this case methanol and ethyl acetate were chosen as solvents for the hydrogenation reactions.



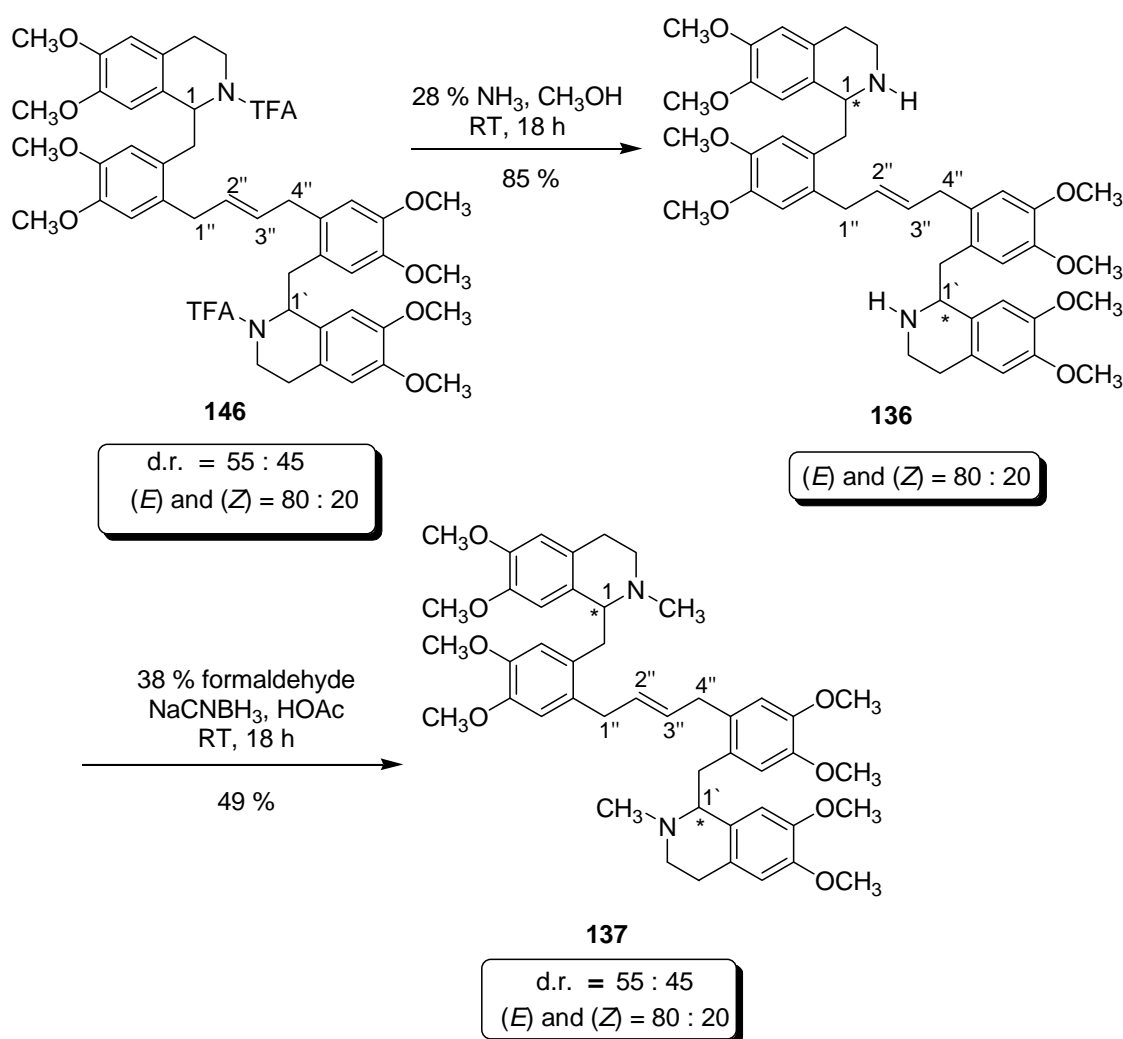
Scheme 4.12 Hydrogenation of derivative **146**.

In both cases, the hydrogenated product **152** was obtained in moderate to high yield and had a slightly higher R_f value than **146** from TLC analysis. Using methanol as the solvent proved to be problematic during the work up procedure because some palladium residues were difficult to remove upon initial filtration of the reaction mixture, therefore further filtration was required thus lowering the yield of **152** to 64 %. Alternatively, the less polar solvent ethyl acetate afforded the desired product **152** in a higher purity and in a yield of 87 %.

The ^1H NMR spectrum of **152** showed only four aromatic proton signals. This suggested that due to the more flexible and extended nature of the saturated tether, the ^1H NMR analysis was not able to distinguish between the meso and the racemate forms of **152**. A minor amide rotamer was also detected (*ca.* 5 %). Evidence for the successful hydrogenation of the double bond of **146** was the replacement of the olefinic signal at δ 5.43 (m, 2H, $\text{CH}=\text{CH}$) in **146** with the multiplet signals at δ 2.40 (m, 4H) and 1.49 (m, 4H) in **150** representing the newly formed methylenes of the butyl tether. HRMS analysis of **150** indicated the expected molecular formula.

4.7. *N*-Trifluoroacetyl deprotection and reductive *N*-methylation.

4.7.1. *N*-TFA deprotection and reductive *N*-methylation of BBI derivative **146**.



Scheme 4.13 *N*-TFA deprotection and reductive *N*-methylation of **146**.

N-TFA deprotection of **146** was carried out using 28 % NH₃ in methanol at RT and afforded the corresponding amine **136** in good yield (85 %). ¹H NMR analysis of **136** showed an 80 : 20 mixture of two isomers. Since the *N*-TFA groups had been removed, these isomers could not be rotamers. We concluded that **136** was an 80 : 20

mixture of (*E*)- and (*Z*)-isomers and that when the *N*-TFA group was removed, the meso and racemate forms have identical NMR spectra.

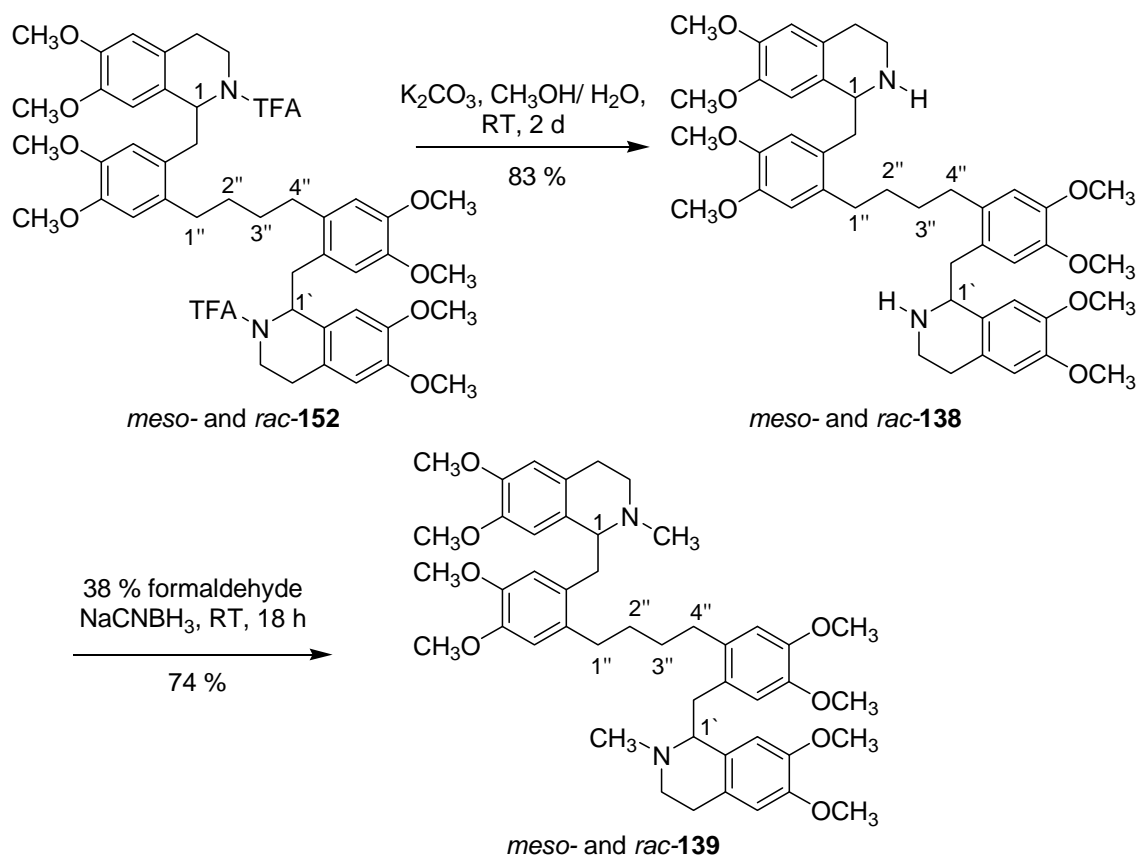
¹H NMR analysis of **136** showed the characteristic H1 and H1' proton signals at δ 4.06 (dd, 2H, *J* 9.0, 4.8 Hz, H1, H1'). The olefinic proton signals of **136** which were obscured by the H1 and H1' proton signals in compound **146**, were now clearly visible at δ 5.44 (bs, 2H, CH=CH) for the major (*E*)-isomer and δ 5.61 (bs, 2H, CH=CH) for the minor (*Z*)-isomer. MS analysis of **136** also confirmed its structure.

The amine **136** was subjected to reductive *N*-methylation to give the corresponding *N*-methylated compound **137** in moderate yield. The *N*-methylated products **137** however clearly showed the meso and racemic forms of (*E*)-**137** in a 55 : 45 ratio by ¹H NMR analysis. The characteristic *N*-methyl signals of **137** were observed in the ¹H NMR spectrum at δ 2.51 (s, 6H, 2 x NCH₃) for the meso and the racemic forms. ¹H NMR analysis also showed 20 % of a minor pair of isomers that were thought to be the meso and racemate forms of (*Z*)-**137**.

4.7.2. N-TFA deprotection and reductive N-methylation of the BBI derivative 152.

The *N*-TFA deprotection of **152** was carried out using K₂CO₃ in aqueous methanol over 2 d at RT to afford **138** in good yield of 83 %. Perhaps raising the reaction temperature to a 60 °C might have shortened the reaction time. As observed in the starting material **152**, the meso and racemic forms of **138** could not be distinguished with only four aromatic singlet resonances were observed in the ¹H NMR spectrum. The structure of the amine **138** was confirmed by the characteristic signals for the H1 and H1' protons at δ 4.10 (dd, 2H, *J* 4.4, 2.4 Hz, H1, H1'). The deprotected product **138** was subsequently *N*-methylated to afford the corresponding product **139** in 74 % yield. Similar to **138**, the meso and racemate forms of **139** could not be distinguished in the ¹H

NRM spectrum. The characteristic *N*-methyl signals of **139** were observed at δ 2.54 (s, 6H, 2 x NCH₃) in the ¹H NMR spectrum.



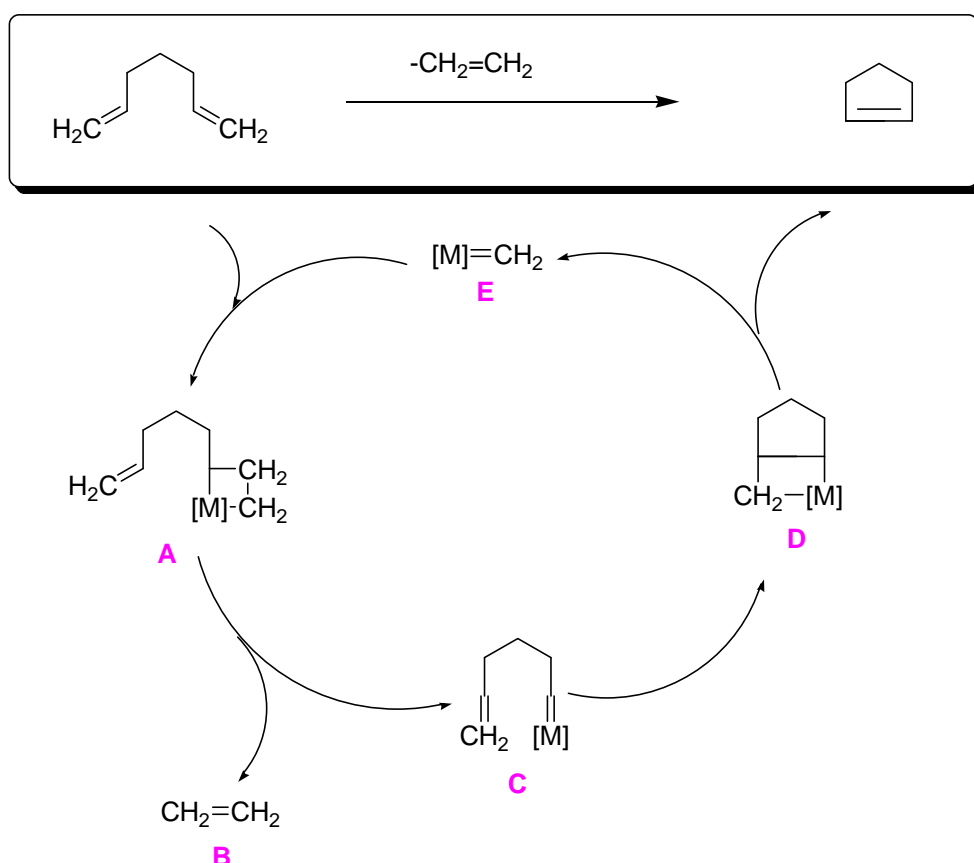
Scheme 4.14 *N*-TFA deprotection and reductive *N*-methylation of **152**.

4.8. Synthesis of the bis-tethered BBI derivative **142**.

This section will discuss the synthesis of the conformationally restricted BBI derivative **142** having a four carbon tether between the two isoquinoline amino groups and the C2' position of both benzyl moieties. The retrosynthesis of the macrocyclic BBI derivative **142** (Scheme 4.15) is similar to that described in Chapter 2. However, in this case, the tether between the C2' position of the benzyl groups would be formed by a ruthenium catalysed ring closing metathesis (RCM) reaction from the diene precursor **154**. The four carbon tether between the nitrogens can be formed by an amide coupling reaction between the previously synthesised carboxylic acid **90** and the free amine **92**.

The four carbon tether between the isoquinoline nitrogens was formed by an amide coupling reaction between **90** and **92** using EDCI/ HOBt to afford the less polar tethered amide **154** in 62 % yield (Scheme 4.16). The reaction occurred slowly over 3 d, possibly due to the sterically hindered nature of the secondary amine component **92**. ^1H NMR analysis of **154** showed the presence of the meso and racemic forms of **154** in a ratio (not necessarily respectively) of 55 : 45. In addition, two amide rotamer forms of these isomers were also detected and accounted for 30 % of the mixture. The structure of compound **154** was confirmed by ESMS analysis.

4.8.2. Ring closing metathesis (RCM) of diene **154**.

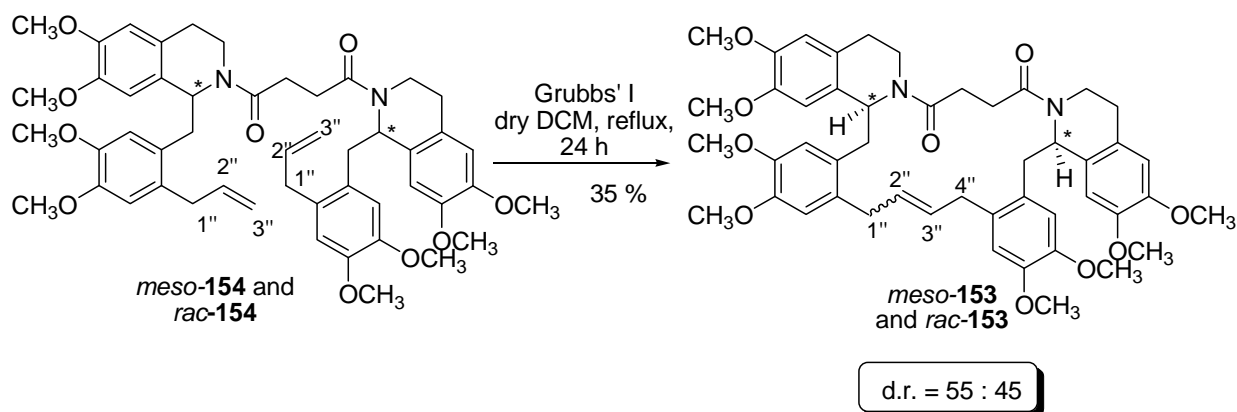


Scheme 4.17 The general mechanism of ring closing metathesis (RCM).

RCM is widely used in the synthesis of many novel and highly functionalised cyclic derivatives. The importance of Grubbs' catalyst in this type of olefin metathesis

has been discussed briefly in Section 2.4.1.¹⁵² RCM, similar to CM discussed previously, involves the formation of metallacyclobutane **A** in a [2+2]-cycloaddition, a key intermediate which collapses to give the transition metal carbene **C**, with the generation of ethylene as the by-product. This complex reacts intramolecularly with the neighbouring olefin in another [2+2]-cycloaddition to give another metallacyclobutane **D** which subsequently collapses to release the RCM product and regenerates the transition metal carbene **E** to repeat the cycle (Scheme 4.17).

RCM of **154** was used to construct the tether between the C2' positions of the benzyl groups by subjecting a solution of **154** to Grubbs' I catalyst in dry DCM at reflux for 24 h which afforded the ring closed derivative **153** in 35 % yield (Scheme 4.18).



Scheme 4.18 The RCM of the diene **153**.

¹H NMR analysis of **153** showed a mixture of diastereomers in a 55 : 45 ratio. The major and minor diastereomers of **153** were extremely difficult to completely separate by PTLC. The major diastereomer **153-d1** could be obtained in *ca.* 95 % purity by PTLC while **153-d2** was more difficult to purify. The ¹H NMR spectra of these isomers are shown in Figure 4.5.

The major diastereomer **153-d1** appeared as one isomer in the ¹H NMR spectrum and showed only four aromatic singlet resonances. Interestingly, the minor

diastereomer **153-d2** showed ^1H NMR resonances for two isomers in a 55 : 45 ratio. These two isomers could arise from either amide rotamers, or from (*E*)- and (*Z*)-isomers. Further experiments indicated that these two isomers were rotamers (Section 4.5.4, Figure 4.8).

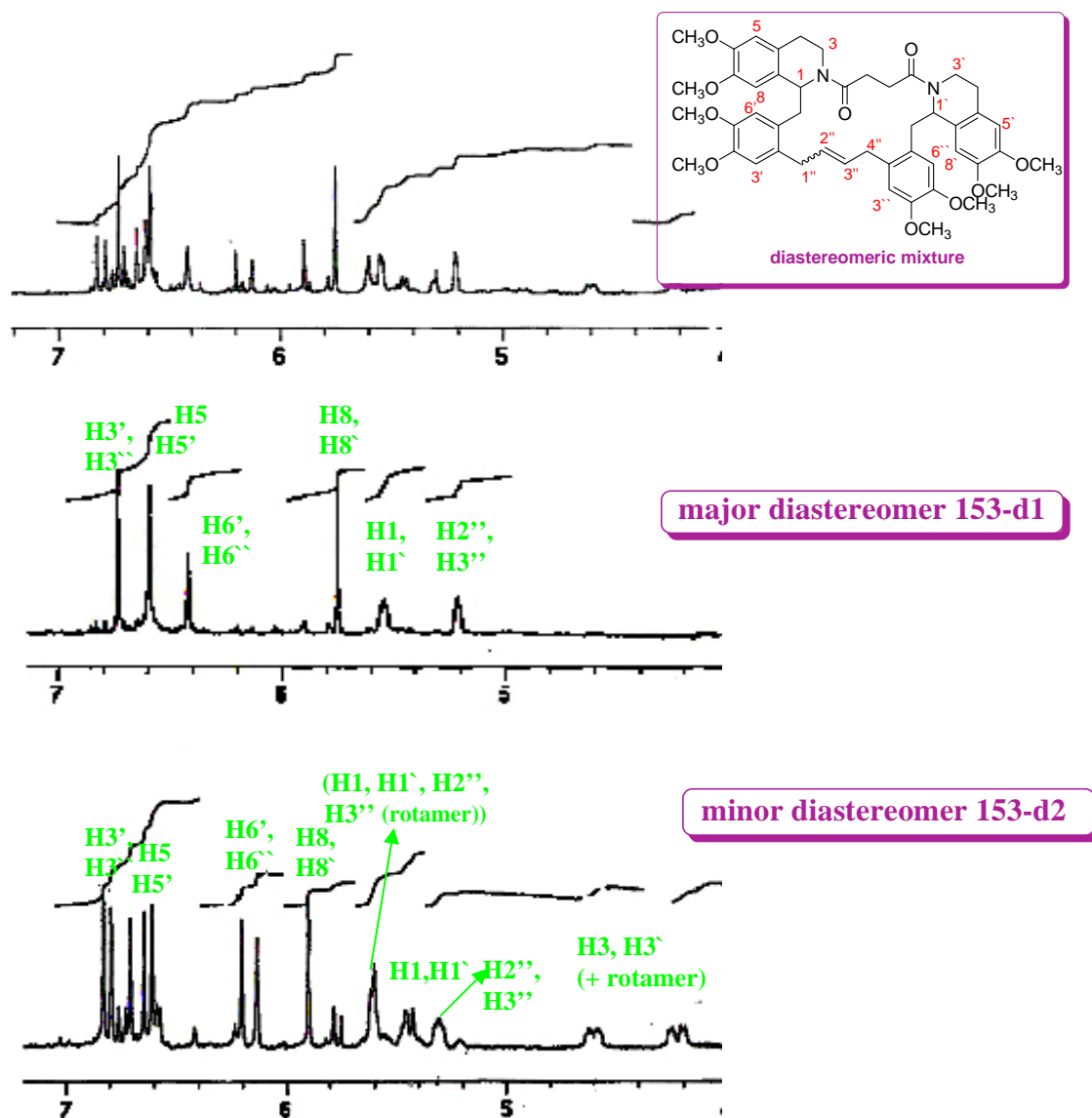


Figure 4.5 The ^1H NMR spectra (300 MHz, CDCl_3) of the aromatic region of the diastereomeric mixture of **153** (top), the major diastereomer **153-d1** (middle) and minor diastereomer **153-d2** (traces of the **153-d1**) (bottom).

The heats of formations of the (*E*)-isomer and (*Z*)-isomer of *meso*-**153** and *rac*-**153** were calculated using Spartan Pro and the AM1 forcefield (Figure 4.6).

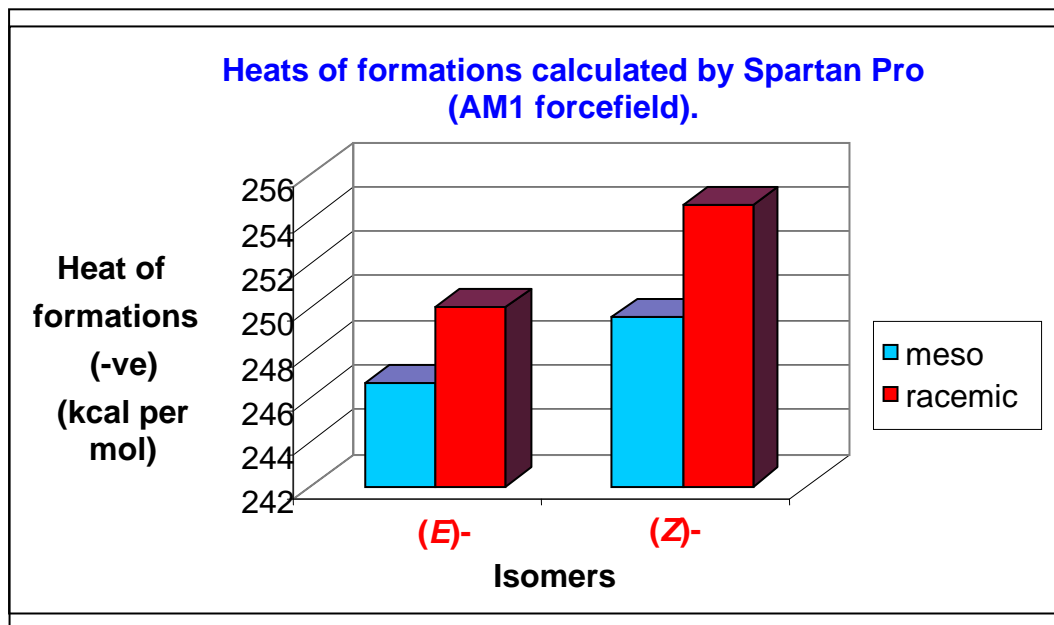


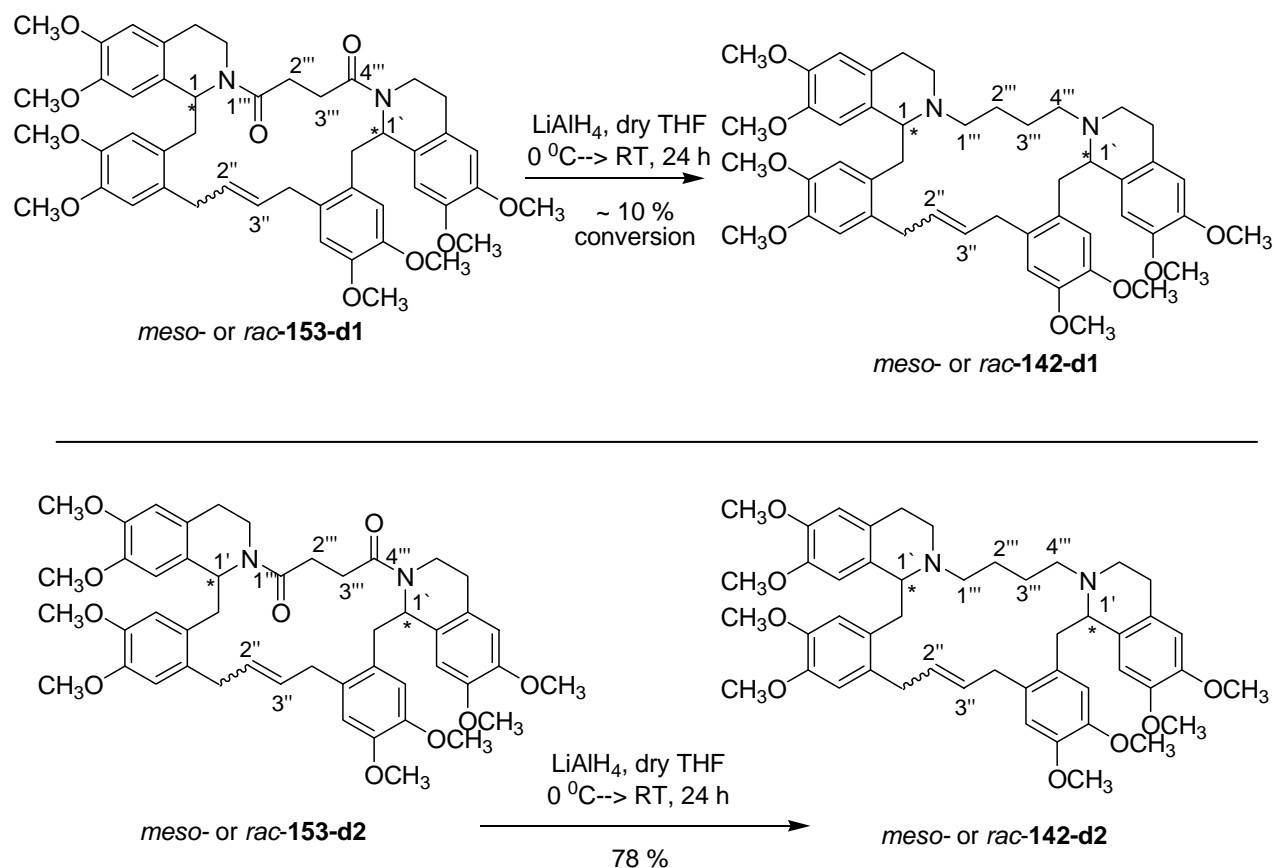
Figure 4.6 Heat of formation calculations for the ring closed derivative **153** (Spartan Pro, AM1 forcefield).

Based on these calculations, it was predicted that the (*Z*)-isomer of *rac*-**153** and *meso*-**153** had the larger (more negative) heat of formation and therefore was expected to be thermodynamically more stable than the corresponding (*E*)-isomer. Therefore it was speculated that **153-d1** was (*Z*)-*rac*-**153** and **153-d2** was (*Z*)-*meso*-**153**. However, due to the symmetry of **153**, it was not possible to exactly identify the (*Z*)- or (*E*)-geometry of these isomers based on ¹H NMR analysis.

4.8.3. Synthesis of Compound **142**-Reduction of the carbonyl by LiAlH₄.

The major and minor diastereomers **153-d1** and **153-d2**, respectively, were individually subjected to carbonyl reduction reaction using LiAlH₄.^{162,163} After 24 h, only the minor diastereomer **153-d2** had undergone carbonyl reduction and gave the corresponding bisamine **142-d2** in 78 % yield. The successful formation of compound **142-d2** was evident from the replacement of the eight aromatic proton signals of **153-d2**

with four newly formed aromatic proton signals of **142-d2** in the ^1H NMR spectrum (Figure 4.7), due to the lack of amide rotamers resulting from the reduction of the carbonyl groups in **153-d2**.



Scheme 4.19 Carbonyl reduction of the major diastereomer **153-d1** and the minor diastereomer **153-d2** by LiAlH_4 .

The ^1H NMR spectrum of **142-d2** showed a relatively more shielded H1/H1' proton signal at δ 3.67 (m, 2H, H1, H1') compared with that in **153-d2**. The successful carbonyl reduction of **153-d2** was evident by the newly formed methylene signals of the tether between the isoquinoline nitrogens in the ^1H NMR spectrum at δ 2.58 (m, 4H) and 1.56 (m, 4H).

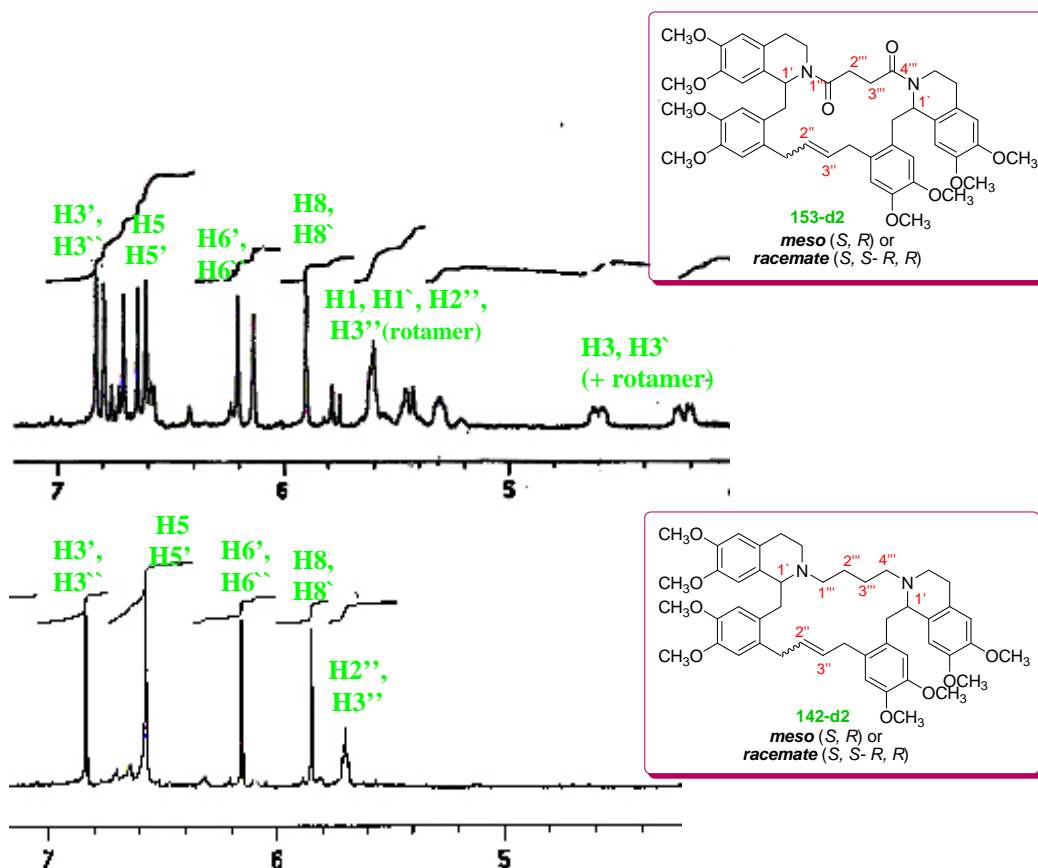


Figure 4.7 ¹H NMR spectrum (300 Hz, CDCl₃) of the aromatic regions of the minor diastereomer **153-d2** (top) and its reduced form **142-d2** (bottom).

The major diastereomer **153-d1**, however, showed only *ca.* 10 % conversion to its bisamine after 24 h with the aromatic signals of **153-d1** still clearly visible in the ¹H NMR spectrum of the crude reaction mixture. Due to limited time and material, the LiAlH₄ reduction of this crude mixture was not repeated.

The different rate of carbonyl reduction between the major diastereomer **153-d1** and the minor diastereomer **153-d2** could be explained using molecular models generated by Spartan Pro. The (*Z*)-*rac*-**153** shown in Figure 4.10 has a more open conformation than (*Z*)-*meso*-**153** which is more folded. Therefore carbonyl reduction could occur more rapidly in the case of (*Z*)-*rac*-**153** compared to (*Z*)-*meso*-**153**.

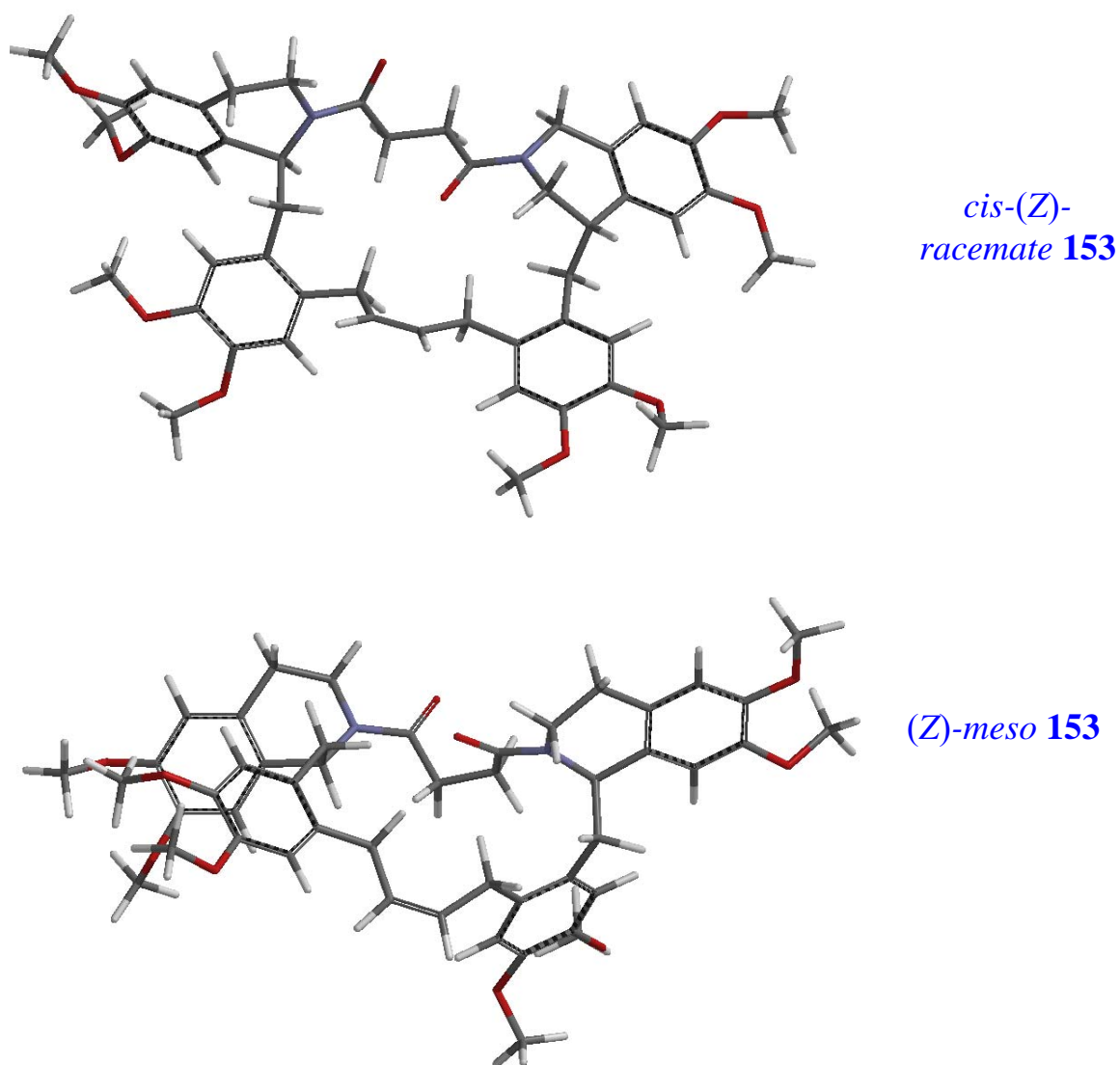


Figure 4.8 Spartan generated (AM1 forcefield) structures of *(Z)-rac-153* (top) and *(Z)-meso-153* (bottom) showing the more open conformation of *(Z)-rac-153* compared to the more folded one for *(Z)-meso-153*.

Overall, five of the initially targeted compounds (**138**, **139**, **140-142**) were successfully synthesised using CM and RCM reactions. However, attempted synthesis of the BBI derivatives **65** and **66** using CM reactions proved less efficient than the Heck coupling methodology described in Chapter 2.

Chapter 5 Synthesis of 2'-Aminoalkyl Benzyloquinoline derivatives and medium sized ring analogues.

5.1. Introduction.

There is an emerging class of CNS active compounds that contain an amino group appended to a heterocyclic base structure, for example the high affinity 5HT_{1A} receptor agonist **repinotan**¹⁶⁴ and the 5HT₇ active molecule **SB-691673**.¹⁶⁵ Medium sized ring CNS active compounds are known, including the D1-antagonist **LE 300**¹⁶⁶ and the partial D1/D5 agonist **SCH 39166**.¹⁶⁷⁻¹⁶⁹

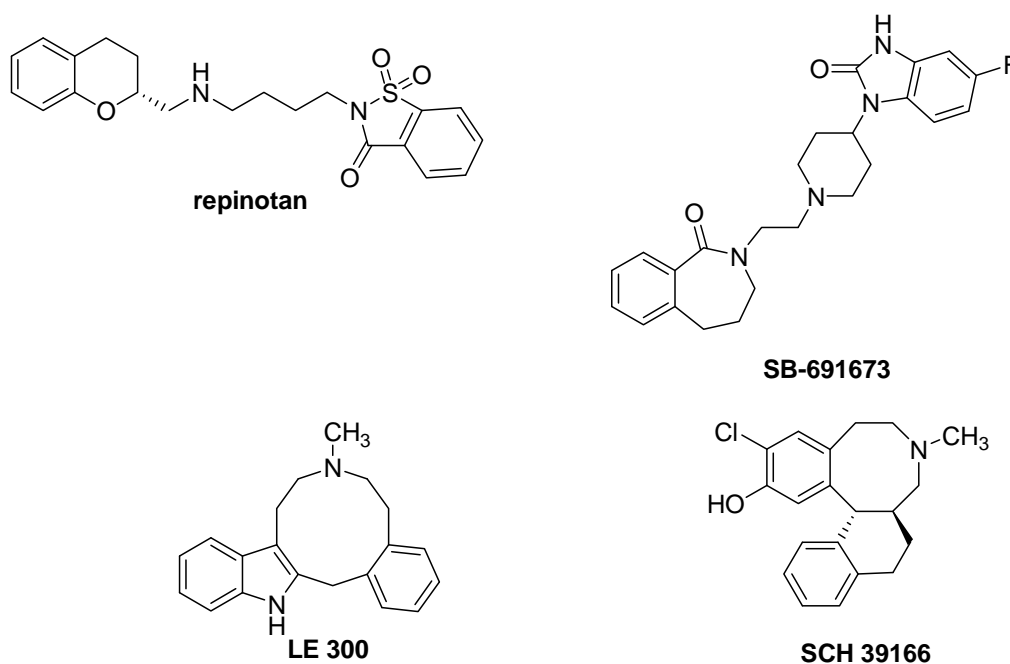


Figure 5.1 The structures of known CNS active compounds.

Many CNS active molecules also contain a β -amino alcohol moiety and examples of these are the patented β_3 -adrenergic receptor agonists of the general structure formula¹⁷⁰ shown in Figure 5.2.

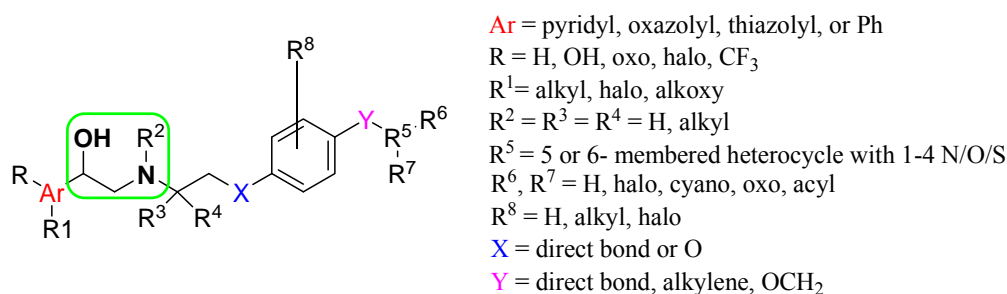


Figure 5.2 The structural formula of β_3 -adrenergic receptor agonists.¹⁷⁰

Therefore, in this project, a new class of target molecules **155-162** were proposed having the benzyloquinoline linked directly to an aminoalkyl moiety at the C2' position. Different types of amines would be attached including cyclic and acyclic amines. Benzyloquinoline derivatives **163** and **164**, with a β -amino alcohol moiety at the C2' position, were also proposed for synthesis and bioassay at CNS receptors. The nine and ten membered ring benzyloquinoline derivatives **165-168** were also targeted (Figure 5.3).

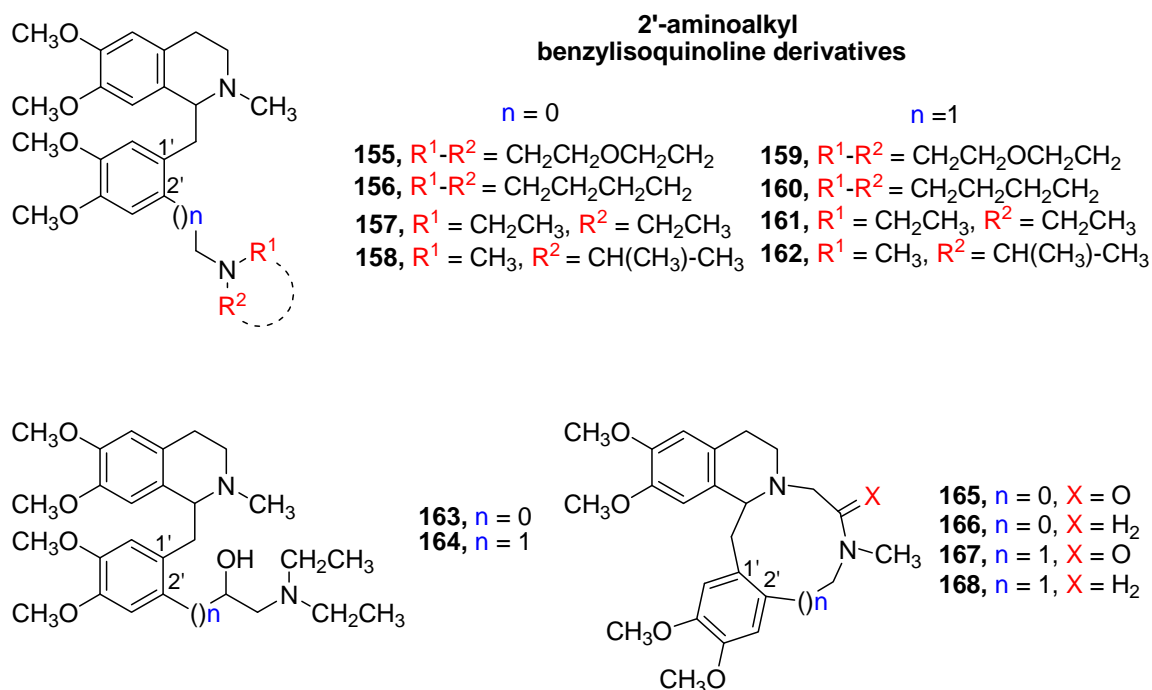
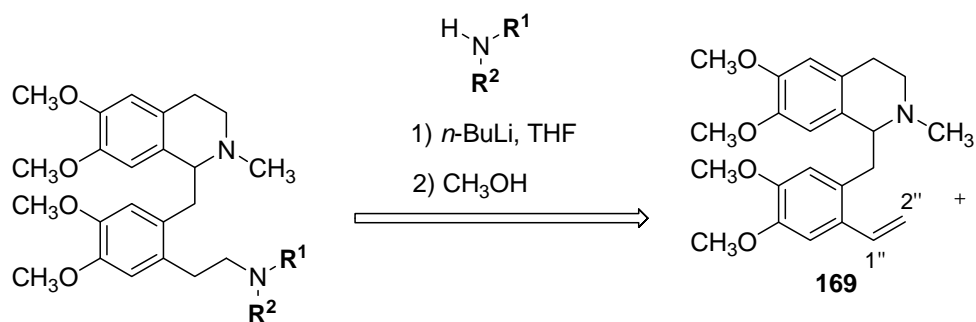


Figure 5.3 The targeted benzyloquinoline derivatives containing 2'-aminoalkyl substituents (**155-162**), a 2'- β -amino alcohol substituent (**163-164**) and the medium sized ring targets (**165-168**).

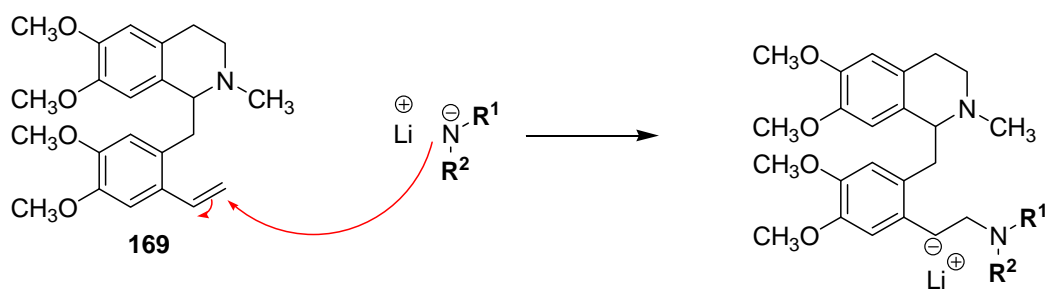
5.2. Synthesis of 2'-aminoalkylbenzylisoquinoline derivatives.

5.2.1. Synthetic approach of 155-162 via the addition of lithium amide to the 2'-vinylaudanosine derivative 169.



Scheme 5.1 Retrosynthesis of 2'-aminoalkyl benzylisoquinoline derivatives *via* lithium amide addition to **169**.

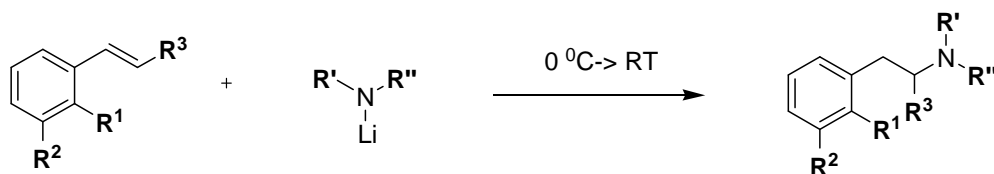
Initially, the formation of 2'-aminoalkylbenzylisoquinoline derivatives was approached by addition of lithium amides to the styrene derivative **169** (Scheme 5.1). The mechanism behind the synthesis involved the reaction of the amine with *n*-butyl lithium to generate the corresponding lithium amide. This reactive nucleophile was anticipated to attack the double bond of **169** to generate the corresponding 2'-aminoalkyl derivatives (Scheme 5.2).



Scheme 5.2 The mechanism of the proposed synthesis of 2'-aminoalkyl derivatives *via* lithium amide addition.

The addition of lithium amides to styrene has been investigated by Seijas towards the preparation of β -phenylethylamines derivatives.¹⁷¹ This work demonstrated

the successful addition of the lithium salts of primary and secondary amines to several styrene derivatives in moderate to high yields (Scheme 5.3 and Table 5.1).



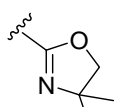
Scheme 5.3 Reactions of styrene derivatives with lithium amides.¹⁷¹

Table 5.1 Summary of reactions of styrene derivatives with lithium amides.¹⁷¹

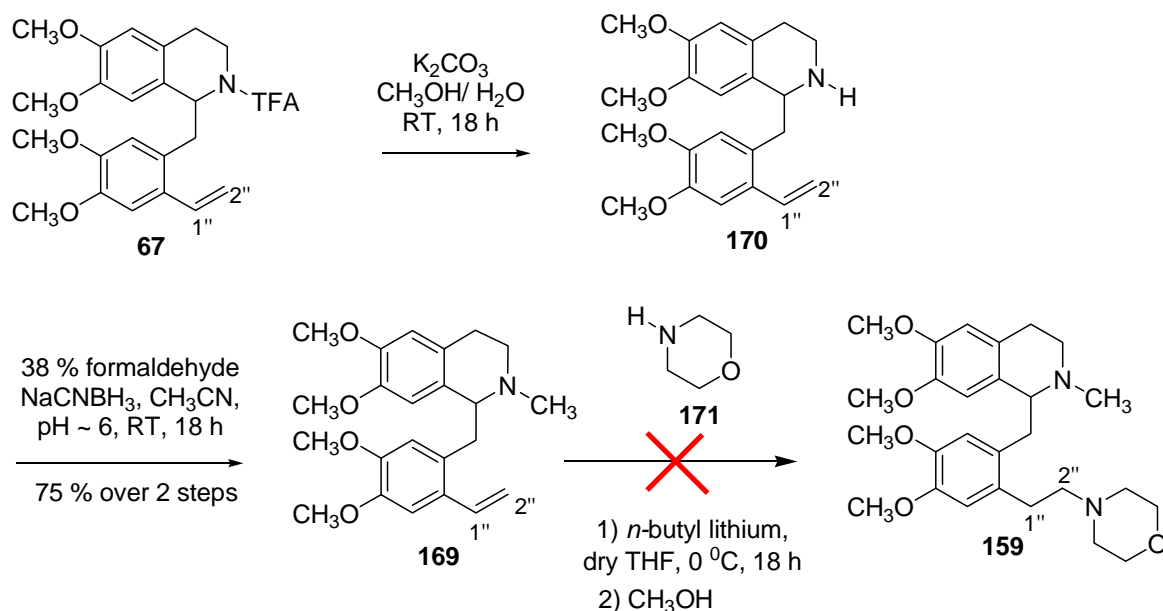
Entry	R ¹	R ²	R ³	R'	R''	Temp.	Product yield (%)
1	COOH	H	H	CH ₂ CH ₃	CH ₂ CH ₃	0 °C	61
2	COOH	H	H	CH ₂ CH ₂ -O-CH ₂ CH ₂		0 °C	85
3	H	H	H	CH ₂ CH ₃	CH ₂ CH ₃	0 °C	69
4	H	H	H	CH ₂ CH ₂ -O-CH ₂ CH ₂		0 °C	73
5	H	H	CH ₃	CH ₂ CH ₂ CH ₂ CH ₂		RT	58
6	H	H	CH ₃	CH ₂ CH ₂ -O-CH ₂ CH ₂		RT	52
7		OCH ₃	H	CH ₂ CH ₃	CH ₂ CH ₃	0 °C	94
8		OCH ₃	H	CH ₂ CH ₂ -O-CH ₂ CH ₂		0 °C	98

Primary lithium amides generally afforded poorer yields than secondary amides.

When the olefinic group of the styrene was substituted (R³ = CH₃) (entries 5-6 and Table 5.1), the reaction yields were lower. In entries 7-8 (Table 5.1), the attachment of an *ortho*-oxazoline and a *meta*-methoxy moiety to the styrene ring resulted in increased yields, presumably due to the stabilisation of the intermediate benzylic anion by *ortho*-chelation. Therefore, these results prompted us to try this method with the styrene derivative **169**.



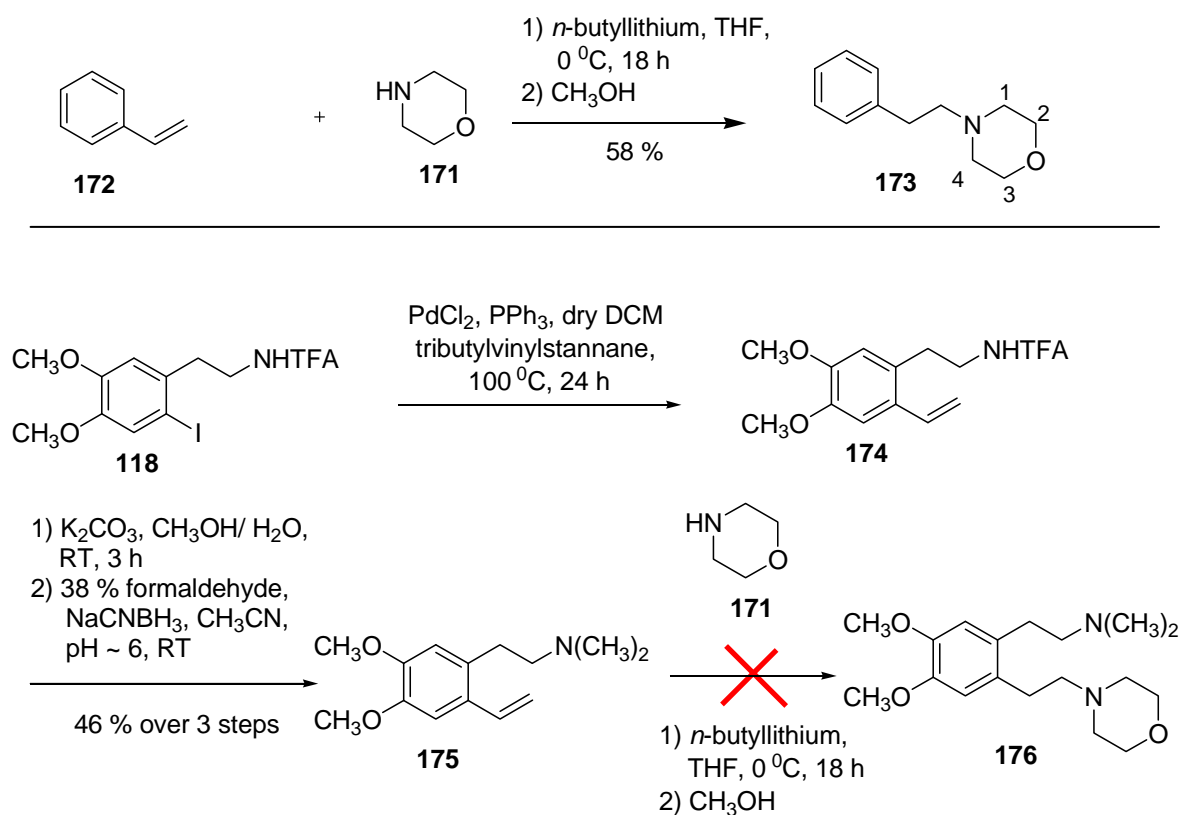
5.2.2. Attempted Synthesis of 159 via the addition of lithium morpholinamide to the 2'-vinyllaudanosine derivative 169.



Scheme 5.4 Attempted synthesis of **159** using lithium morpholinamide and the 2'-vinyllaudanosine derivative **169**.

The 2'-vinyllaudanosine derivative **169** was prepared from the *N*-TFA derivative **67** in 75 % overall yield (Scheme 5.4). Morpholine **171** was treated with *n*-butyl lithium and then a solution of **169** in THF was added at 0 °C. The solution was stirred at 0 °C for 18 h. ¹H NMR analysis of the crude reaction mixture showed only unreacted **169** and no morpholine ethylene signals for the expected product were observed. It was suggested that the vinyl group of **169** was too electron rich to react with the lithium morpholinamide nucleophile. To verify this suggestion, two models studies were conducted on the addition of lithium morpholinamide to styrene itself (**172**) and the electron rich styrene derivative **175** (Scheme 5.5).

5.2.3. Model study of lithium morpholinamide addition to substituted and unsubstituted styrene.

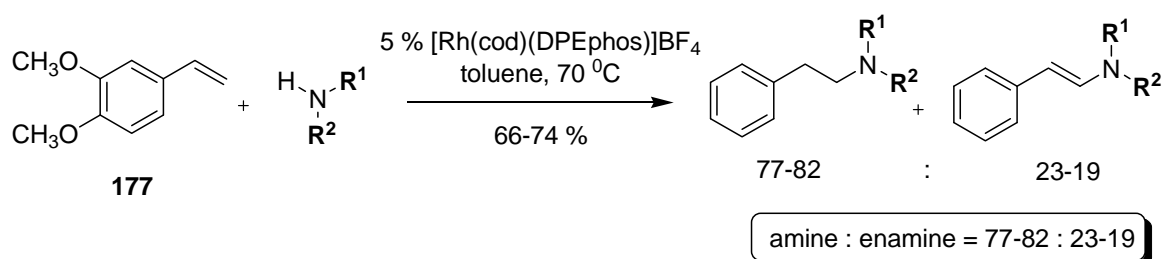


Scheme 5.5 Model study of lithium morpholinamide with styrene **172** (top) and the electron rich styrene **175** (bottom).

When lithium morpholinamide was treated with styrene (**172**) at 0 °C for 18 h, the corresponding product **173** was obtained in 58 % yield, which was lower than the literature yield of 73 %.¹⁷¹ The desired product **173** was confirmed by the appearance of the morpholine signals at δ 3.70 (t, 4H, J 4.5 Hz, H2, H3) and 2.47 (t, 4H, J 4.5 Hz, H1, H4), and the disappearance of the olefinic signals associated with **172**. However, under the same conditions, the more electron rich styrene **175** did not give the corresponding product **176** and only the starting material **175** was recovered. At this stage, efforts were re-directed to alternative approaches such as the rhodium-catalysed hydroamination (Scheme 5.6) or a reductive amination method (Scheme 5.7).

5.2.4. Rhodium-catalysed hydroaminations.

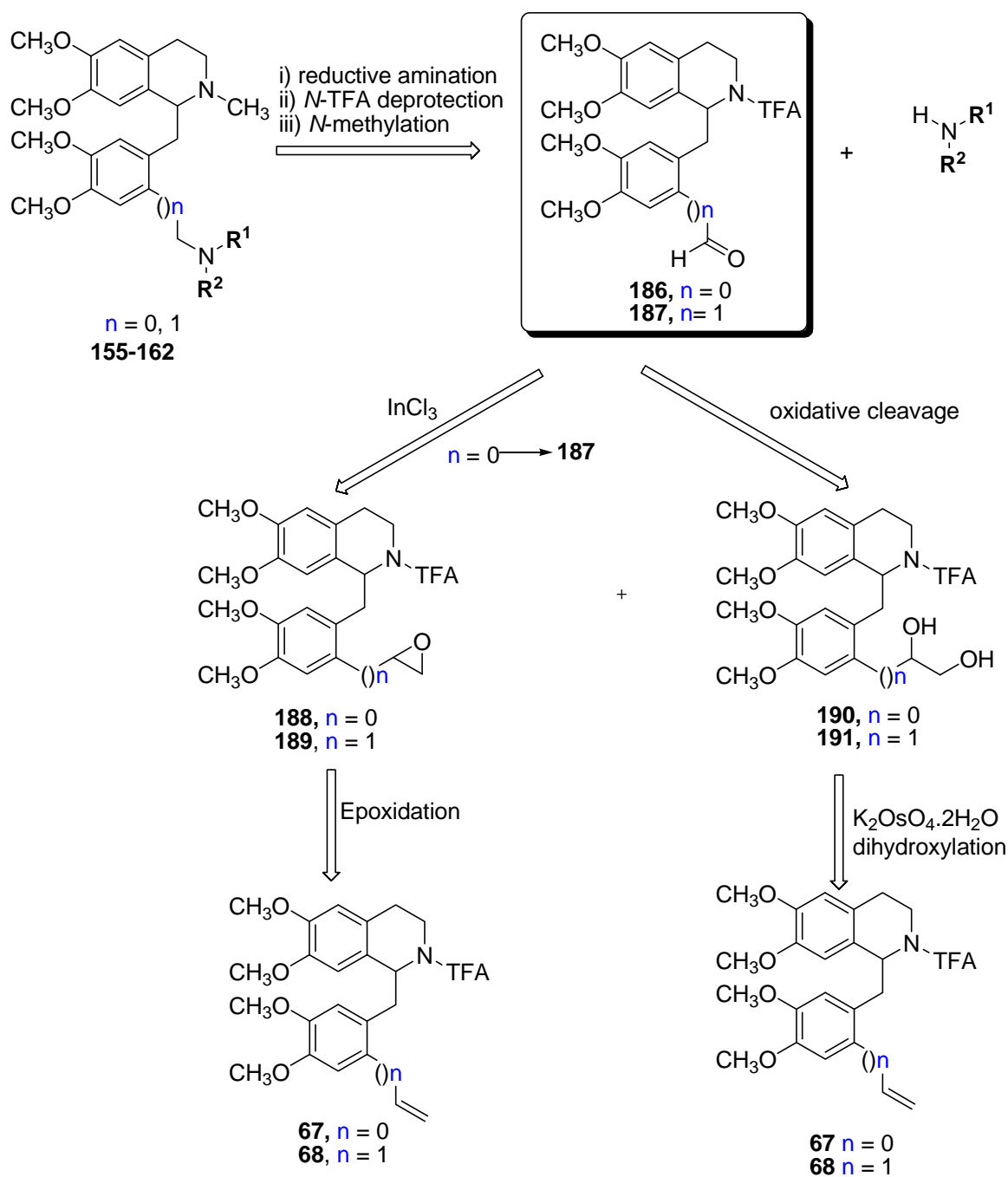
Hartwig and co-workers¹⁷² have examined the rhodium-catalysed hydroamination of styrenes to generate the corresponding β -phenylethylamines (Scheme 5.6). This method provided an alternative approach to the hydroamination of styrene **169** since it was reported to work on both electron-rich and neutral styrenes, however, enamines were also obtained as side products. Additionally, the rhodium catalyst required handling under dry box conditions, and therefore an alternative synthetic method was sought toward our targeted compounds.



Scheme 5.6 Hydroamination of styrene catalysed by rhodium.¹⁷²

5.2.5. Synthetic approach to 155-162 via reductive amination methodology.

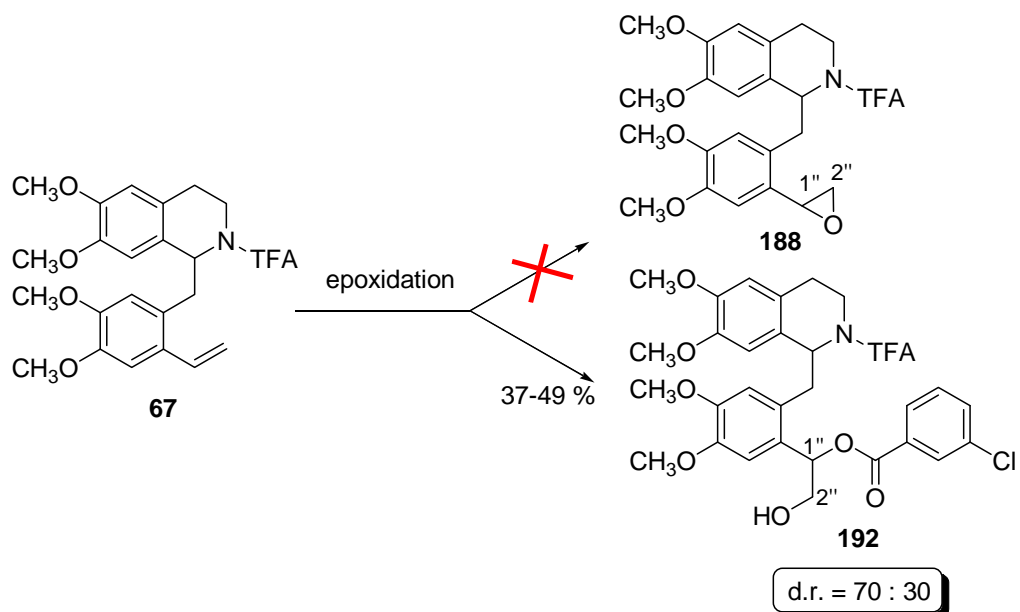
An alternative method to prepare our targeted compounds, the reductive amination of the aldehydes **186** and **187** with amines was examined. Aldehyde **187** could in principle be synthesised by Lewis acid catalysed rearrangement of the epoxide **188**, while the epoxide **189** would give the homologue of aldehyde **187**. Alternatively, the aldehydes **186** and **187** could be prepared *via* oxidative cleavage of the diols **190** and **191**, respectively (Scheme 5.7).



Scheme 5.7 Two synthetic approaches to the aldehydes **186** and **187**.

5.2.6. Attempted synthesis of the epoxide **188** and the synthesis of epoxide **189**.

When the 2'-vinyllaudanosine derivative **67** was subjected to standard epoxidation conditions¹⁷³ using *m*CPBA in DCM at RT for 2 h (Table 5.2, entry 1), the expected product **188** was not obtained. Instead the reaction afforded the product **192**, formed from ring opening of the epoxide **188** with *m*-chlorobenzoic acid, in 37 % yield.

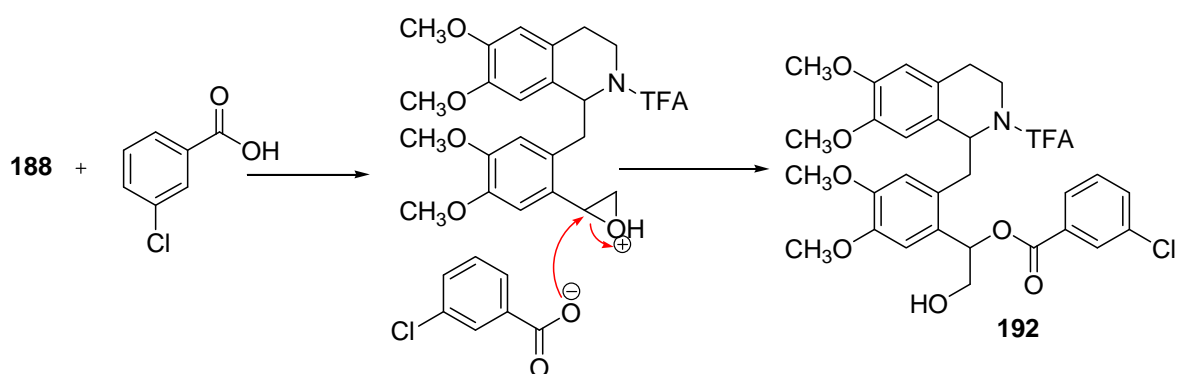


Scheme 5.8 The attempted synthesis of the epoxide **188**.

Table 5.2 Epoxidation reactions of **67**.

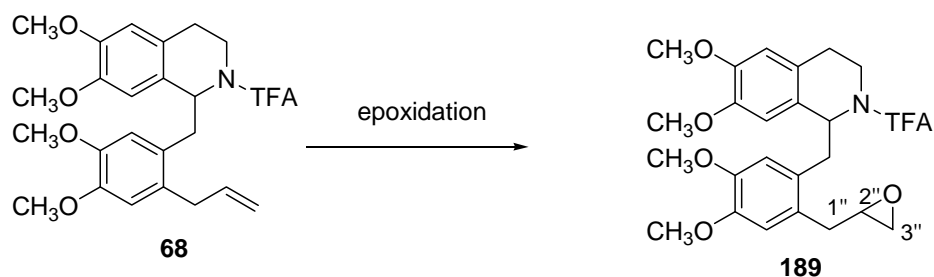
Entry	Reagents and conditions of epoxidation	Products	Yield (%)
1	<i>m</i> CPBA, DCM, RT, 2 h	188	none
		192	37
2	<i>m</i> CPBA + NaHCO ₃ , DCM, RT, 2 h	192	49

¹H NMR analysis of **192** showed a 70 : 30 mixture of diastereomeric products. The structure of compound **192** was evident from the extra aromatic signals between δ 7.3-7.9 that integrated for 4 protons in the ¹H NMR spectrum. ESMS analysis showed a signal at *m/z* 660 that corresponded to the molecular weight plus sodium (M+Na⁺) of **192**. The proposed mechanism for the formation of **192** is outlined in Scheme 5.9.



Scheme 5.9 The proposed mechanism for the formation of the ring-opened product **192**.

Because the epoxide **188** has a 2'-phenyl substituent, that is highly electron rich and can readily stabilise an incipient benzylic carbonium ion, it is very prone to ring opening, especially under acid catalysed conditions. Therefore, epoxide **188** was formed but readily underwent ring opening with the generated *m*-chlorobenzoic acid to give the ester **192**. It was anticipated that the epoxide ring opening problem could be overcome by the addition of base such as solid Na_2CO_3 to the *m*CPBA solution. However, this additive ran the risk of cleavage of the *N*-TFA group of **188**. A milder base, NaHCO_3 , was therefore used in 2 mol. equiv.; however, the ring opened product **192** was still obtained in 49 % yield (Table 5.2, entry 2).



Scheme 5.10 Synthesis of the epoxide **189**.

Table 5.3 Epoxidation reactions of **68**.

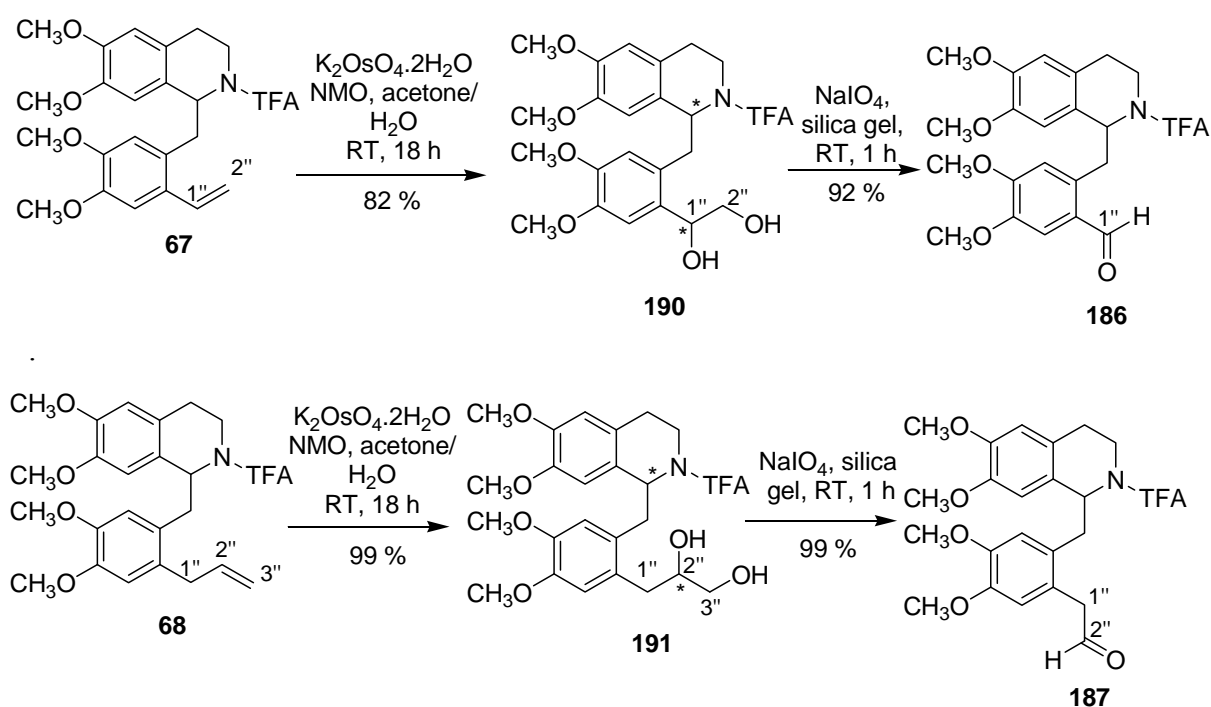
Entry	Reagents and conditions of epoxidation	Products	Yield (%)
1	<i>m</i> CPBA, DCM, RT, 2 h	189	28
2	trifluoroacetone, oxone, Na ₂ EDTA CH ₃ CN, NaHCO ₃ , 0 °C, 24 h	189	none
3	1) K ₂ OsO ₄ ·2H ₂ O, NMO, acetone, water, RT, 18 h. 2) HBr/HOAc, 40 °C, 18 h 3) K ₂ CO ₃	decomposition	

When the 2'-allyllaunosine derivative **68** was treated with *m*CPBA (Table 5.3, entry 1), many products were evident from TLC analysis. One of these products, with a lower *R_f* than **68**, corresponded to the epoxide **189** which was isolated in 28 % yield. Some starting material was also recovered in this case, and other fractions isolated appeared to be decomposition products. The structure of the desired epoxide **189** was confirmed by EIMS analysis which showed an ion at *m/z* 495 for the molecular ion (*M*⁺). ¹H NMR analysis of **189** showed a 55 : 45 mixture of diastereomers which was evident by the doubling up of aromatic proton signals. ¹H NMR analysis of **189** showed the proton resonances for the epoxide side chain at δ 3.60 (m, 1H, H2''), 2.78 (m, 1H, H1''), 2.57 (t, 1H, *J* 4.7 Hz, H1''), 2.72 (m, 1H, H3'') and 2.47 (dd, 1H, *J* 4.8, 2.1 Hz, H3'') for the major diastereomer.

Since the yield of the epoxide **189** was low, other alternative epoxidation methods were examined. In entry 2 (Table 5.3), epoxidation was carried out using trifluoroacetone and oxone in acetonitrile at 0 °C.¹⁷⁴ No corresponding product was obtained in this case and only unreacted starting material was recovered. The last

method, involved firstly an osmium-catalysed dihydroxylation reaction, followed by treatment of the corresponding diol with HBr/acetic acid and subsequent addition of base to generate the corresponding epoxide product.¹⁷⁵ However, under these conditions, no epoxide product was obtained, and the starting material had decomposed to give a black coloured mixture. Therefore generation of aldehydes *via* rearrangement of the epoxides **188** and **189** was not further pursued due to the difficulty encountered in the epoxidation of **67** and **68**. It was anticipated that a procedure involving oxidative cleavage of the diols **190** and **191** might be more productive.

5.2.7. Synthesis of the aldehydes **186** and **187** *via* oxidative cleavage of diols.



Scheme 5.11 The synthesis of the aldehyde **186** and **187** *via* oxidative cleavage of the diols **190** and **191**.

The formation of the diols **190** and **191** from **67** and **68**, respectively was successful using a catalytic amount of potassium osmate-dihydrate ($K_2OsO_4 \cdot 2H_2O$) and a slightly more than a stoichiometric amount of *N*-methylmorpholine *N*-oxide (NMO) as

a co-oxidant.¹⁷⁶ The corresponding diols **190** and **191** were obtained in 82 % and 99 % yield, respectively.

The successful dihydroxylation reaction of **190** was confirmed by TLC analysis with a decrease in the R_f value of the product compared to that of the starting material. The diol **190** was an 80 : 20 mixture of the two racemic diastereomers due to the two stereogenic centres in the product. The olefinic ^1H NMR signals in the precursor **67** were replaced by the benzylic CH proton signal of compound **190** at δ 5.08 (dd, 1H, J 8.1, 4.2 Hz, H1'') for the major and at δ 4.94 (dd, 1H, J 8.4, 4.2 Hz, H1'') for the minor diastereomer. The expected methylene signals CH_2OH of **190** overlapped with the methoxy signals and therefore these signals were only detected by the assistance of gCOSY and gHSQC experiments. These appeared as multiplets at δ 3.62 for the major and at δ 3.73 for the minor diastereomer. The resonances for CH-1'' and CH_2 -2'' of **190** were observed at δ 70.7 and 67.3, respectively in the ^{13}C NMR spectrum for the major diastereomer of **190**. EIMS analysis of **190** showed a M^+ signal at m/z 499 which confirmed the structure of **190**.

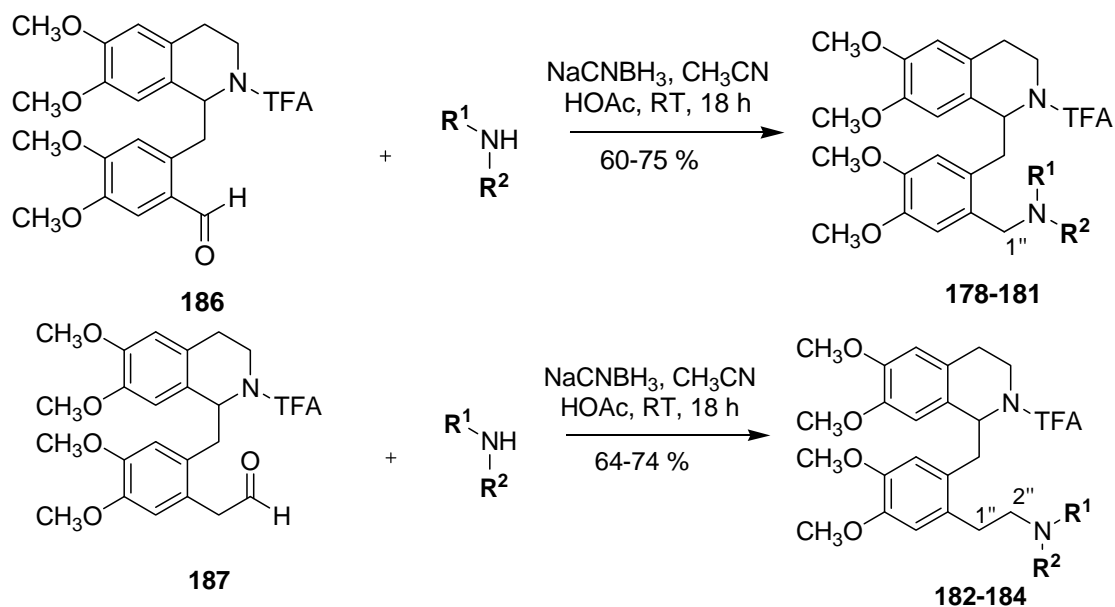
The diol **191** was obtained as a 60 : 40 mixture of racemic diastereomers from ^1H NMR analysis. The structure of the diol **191** was confirmed by ^1H NMR analysis from the presence of signals for the methine proton at δ 3.94 (m, 1H, H2'') and the diastereotopic methylene protons at δ 3.79 (m, 1H, H3'') and 3.58 (m, 1H, H3'') for the major isomer. The characteristic methine signals for the minor isomer were observed at δ 3.86 (m, 1H, H2''). The methylene signals for H3'' in the minor isomer were difficult to observe directly since they were overlapped with the methoxy signals. Their presence was confirmed by 2D NMR analysis.

The diols **190** and **191** were subjected to the oxidative cleavage conditions using sodium metaperiodate.¹⁷⁷ A study by Zhong *et al.* reported an improved silica gel-supported metaperiodate reagent in powdered form for the efficient and facile preparation of aldehydes from vicinal diols. This oxidative cleavage powder can be conveniently prepared by adding silica gel to an aqueous solution of sodium metaperiodate. This powder can be stored in a bottle for a month with negligible loss of activity.¹⁷⁷

Oxidative cleavage of the diols **190** and **191** were easily carried out by stirring a suspension of the vicinal diols and the powdered supported metaperiodate reagent in DCM at RT. Due to the unstable nature of the aldehydes **186** and **187**, extreme care was taken to monitor the progress of these reactions by TLC. Solutions of these aldehydes were immediately filtered upon completion of the reaction to minimise decomposition, affording the aldehydes **186** and **187** in yields of 92 % and 99 %, respectively.

The expected aldehyde CH signal for **186** was observed by ¹H NMR analysis at δ 9.90 (s, 1H, CHO) and the presence of the carbonyl signal was also detected at δ 190.8 in the ¹³C NMR spectrum. Similarly, the expected aldehyde signal of **187** was observed at δ 9.61 (t, 1H, *J* 2.1 Hz, CHO) in the ¹H NMR spectrum. The benzylic CH₂ signals of **187** were obscured by the methoxy signals and were therefore only partially observed as a multiplet at δ 3.54 (2H). In the ¹³C NMR spectrum, a newly formed carbonyl signal was observed at δ 199.6, which confirmed the presence of the aldehyde. The structures of **186** and **187** were confirmed by MS analysis. These aldehydes were subjected to the following reductive amination process immediately after their ¹H and ¹³C NMR spectra were obtained.

5.2.8. Synthesis of the 2'-aminoalkylbenzylisoquinoline derivatives via reductive amination.



Scheme 5.12 The reductive amination of aldehydes **186** and **187** with amines.

Table 5.4 Synthesis of amino benzylisoquinoline analogues by reductive amination.

Entry	R ¹	R ²	Product #	Yield (%)
1	CH ₂ CH ₂ -O-CH ₂ CH ₂		178	60
2	CH ₂ CH ₂ CH ₂ CH ₂		179	74
3	CH ₂ CH ₃	CH ₂ CH ₃	180	75
4	H	CH(CH ₃) ₂	181	64
5	CH ₂ CH ₂ -O-CH ₂ CH ₂		182	64
6	CH ₂ CH ₂ CH ₂ CH ₂		183	74
7	CH ₂ CH ₃	CH ₂ CH ₃	184	68

Scheme 5.12 and Table 5.4 summarises the reductive amination results between the aldehydes **186** and **187** and four different amines. These reactions were performed using an excess amount of the amine and 1.3 mol. equiv. of NaCNBH₃ in CH₃CN

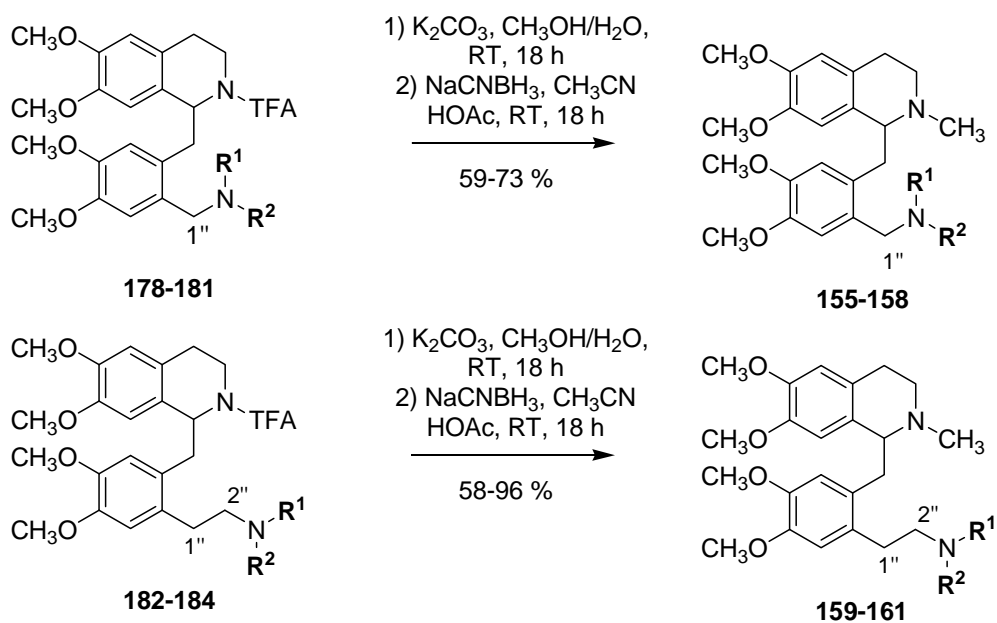
solution that was adjusted to pH 6 using glacial acetic acid. The reaction was stirred at RT for 18 h and the products were purified by column chromatography. The 2'-aminoalkylbenzylisoquinoline derivatives **178-184** were successfully obtained in yields of 60-75 %.

The benzylic protons at the C1'' position of **178-181** were diastereotopic due to the stereogenic centre at the C1 position and appeared as two mutually coupled doublet signals in the δ 3.20- 3.45 region of their ^1H NMR spectra. The products **178-181** were fully characterised by spectroscopic methods (see Experimental section). The structures of the products **182-184** were confirmed by ^1H NMR spectroscopy by the multiplet signals between δ 2.25-2.65 which corresponded to the ethylene proton signals at the C1'' and C2'' positions. These compounds were also fully characterised by spectroscopic methods (see experimental section).

Overall, the above reductive amination procedure was an effective method to synthesise a small library of seven 2'-aminoalkylbenzylisoquinoline derivatives which represent a new class of benzylisoquinolines.

5.2.9. *N*-TFA deprotection and *N*-methylation of 178-184.

The final 2'-aminoalkylbenzylisoquinoline derivatives required for biological testing were obtained by base-catalysed cleavage of the TFA group of **178-184**, followed by reductive *N*-methylation using the procedures previously described in Chapter 3. The final products **155-161** were obtained in moderate to high yields (Scheme 5.13). In these cases, the cleavage of the *N*-TFA protecting group was carried out at RT over 18 h without experiencing the solubility problems observed for the compounds in Chapters 2 and 3. The results of these base-catalysed *N*-TFA deprotection and *N*-methylation reactions are summarised in Table 5.5.



Scheme 5.13 *N*-TFA deprotection and *N*-methylation of **178-184**.

Table 5.5 Summary of the *N*-TFA cleavage and *N*-methylation reactions.

Entries	R ¹	R ²	N-TFA cleavage and N-methylation	
			Product #	Overall yield (%)
1	CH ₂ CH ₂ -O-CH ₂ CH ₂		155	73
2	CH ₂ CH ₂ CH ₂ CH ₂		156	71
3	CH ₂ CH ₃	CH ₂ CH ₃	157	58
4	H	CH(CH ₃) ₂	158 (R ¹ =CH ₃)	59
5	CH ₂ CH ₂ -O-CH ₂ CH ₂		159	85
6	CH ₂ CH ₂ CH ₂ CH ₂		160	69
7	CH ₂ CH ₃	CH ₂ CH ₃	161	69

The lower overall yields entries 3 and 4 of Table 5.5 were a result of the polar nature of the bis-amine products. It was thought that significant quantities of these

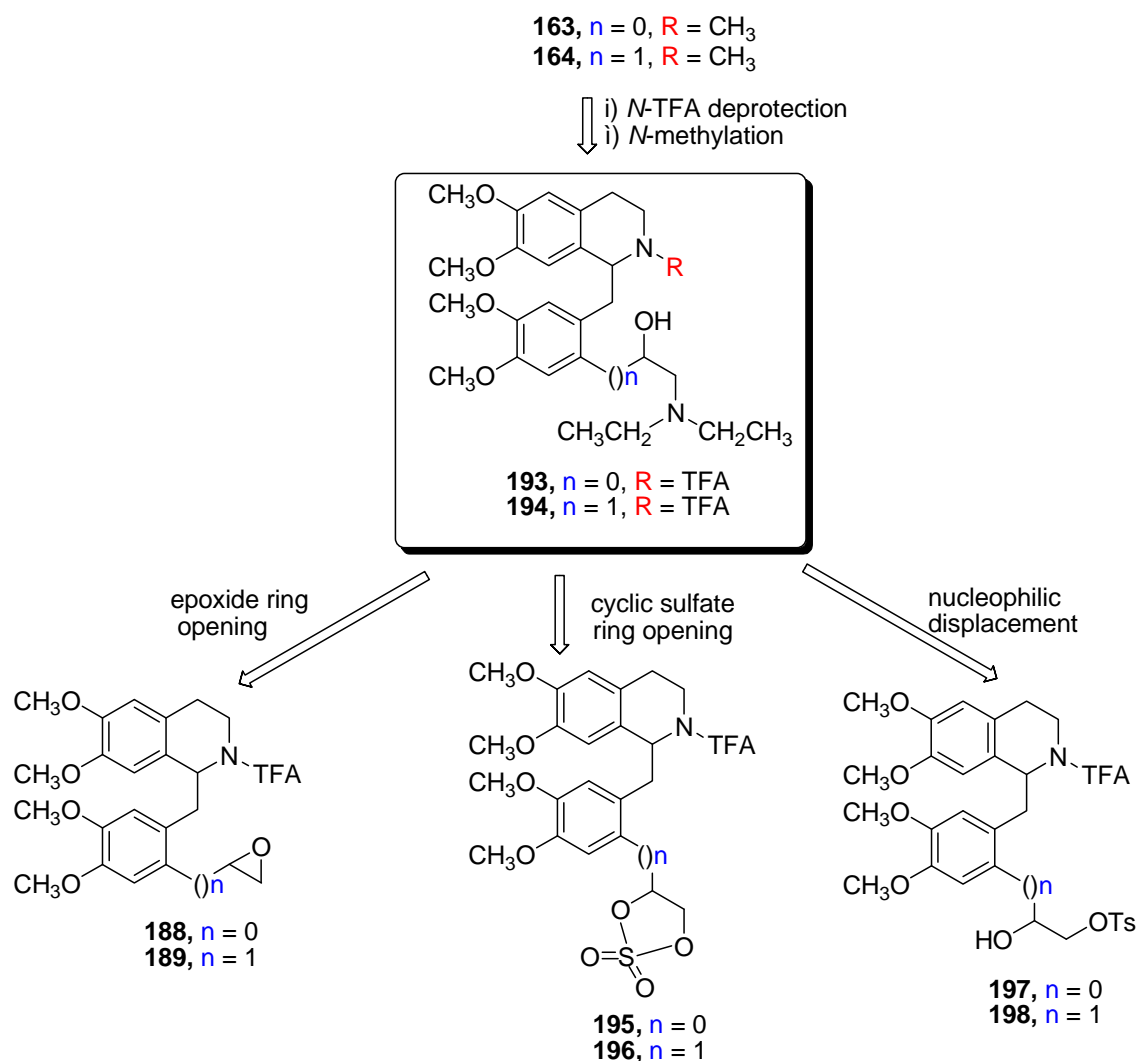
compounds were retained on the silica gel during column chromatography even though ammonia was employed as a co-eluent.

In the ^1H NMR spectra of the final products **155-161**, in addition to the characteristic signals of the each amine, the expected isoquinoline *N*-methyl signals in the range of δ 2.52-2.55 (s, 3H) were also observed and confirmed the structure of the methylated products. The structures of the products **155-161** were also confirmed by MS analysis.

5.3. Synthesis of benzyloisoquinoline derivatives containing a β -amino alcohol moieties.

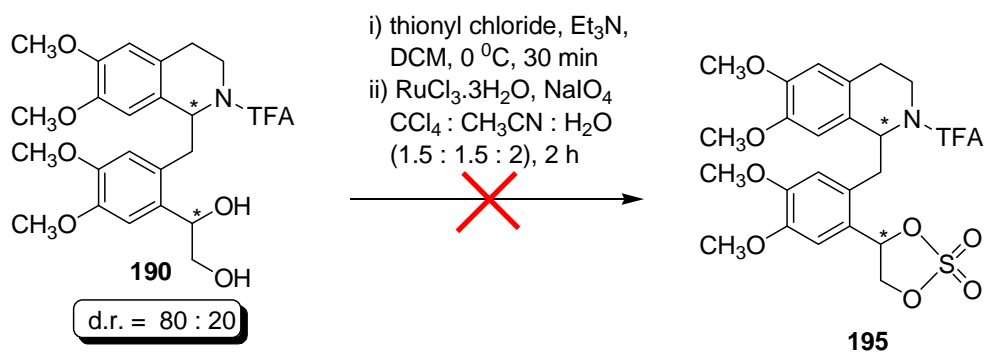
5.3.1. Strategy toward the synthesis of benzyloisoquinolines containing a β -amino alcohol moiety.

The synthesis of the targeted β -amino alcohol derivatives **163** and **164** can, in principal, can be approached by three different routes (Scheme 5.14). The shortest route would be *via* ring opening of the epoxides **188** and **189**, however as discussed in section 5.2.6, formation of these epoxides had proven problematic, and furthermore ring opening of epoxide **188** would be expected to give the regiosisomer of **193**. Therefore a synthetic approach *via* the ring opening of the cyclic sulfates **195** and **196** was proposed. Ring opening of **195**, however would most likely give the regioisomer of **193**. Alternatively, the nucleophilic displacement of a good leaving group such as the primary tosylate groups in **197** and **198** by an amine nucleophile was proposed to generate the corresponding β -amino alcohol derivatives **193** and **194**. The required cyclic sulfates **195** and **196** or the tosylate derivatives **197** and **198** can in principle be synthesised from the corresponding diols **190** and **191**.



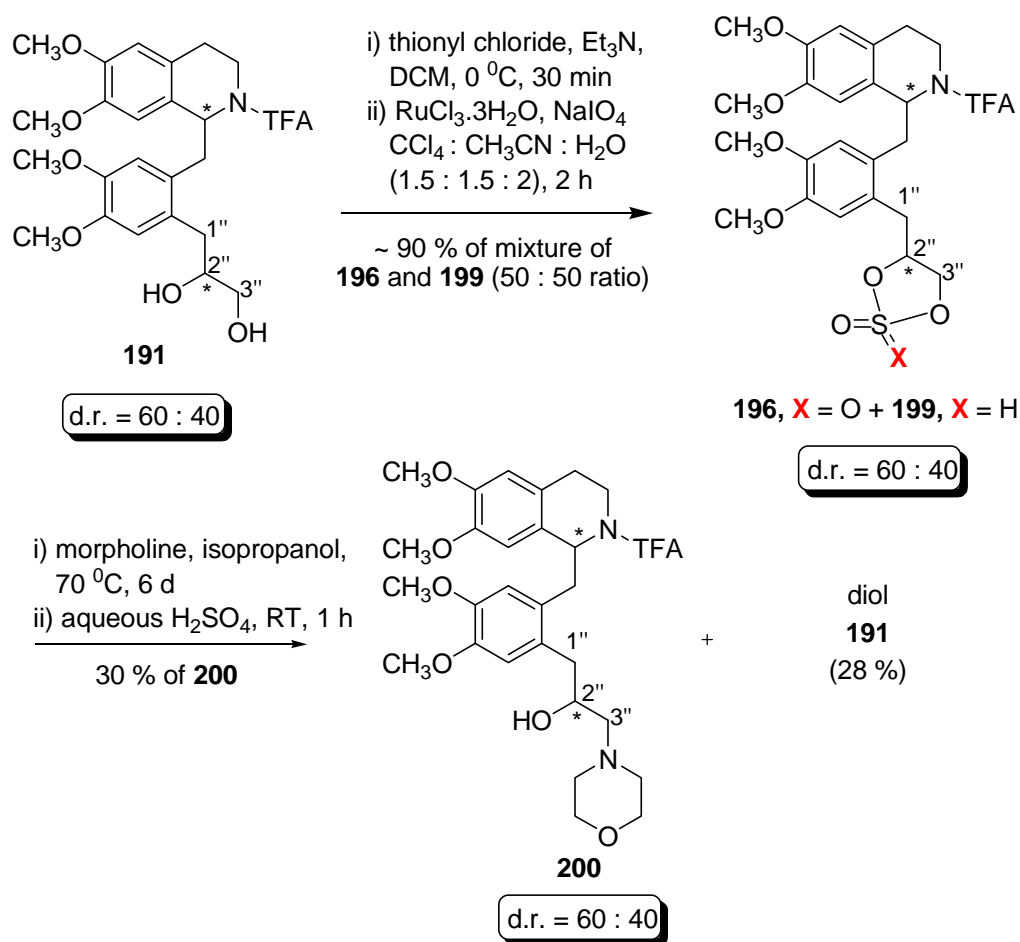
Scheme 5.14 The retrosynthetic strategy for the benzylisoquinoline derivatives containing the β -amino alcohol.

5.3.2. Synthesis of β -amino alcohols via ring opening of cyclic sulfates.



Scheme 5.15 Attempted synthesis of the cyclic sulfate **195**.

The cyclic sulfate **195** was anticipated to be obtained from the corresponding diol **190** *via* two synthetic steps using thionyl chloride to generate the cyclic sulfite, followed by oxidation with $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4 to give the corresponding cyclic sulfate **195**.¹⁷⁸ The diol **190**, however, gave none of the desired cyclic sulfate **195**, but many unidentifiable products. It was suspected that this cyclic sulfate was unstable due to the electron rich benzyl substituent, in a similar fashion to the styrene epoxide **188**.



Scheme 5.16 Synthesis of the cyclic sulfate **196** and the β -amino alcohol **200**.

The reaction of the diol **191** with thionyl chloride, followed by oxidation by $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4 after 2 h gave a mixture of the desired cyclic sulfate **196** and unoxidised cyclic sulfite **199** as a 50 : 50 mixture. The cyclic sulfate **196** and cyclic sulfite **199** had the same R_f value by TLC analysis and therefore could not be separated.

Molecular ion signals for both **196** and **199** in the mixture were detected at m/z 576.8 and m/z 559.9, respectively, from ESMS analysis.

Analysis of this mixture showed resonances of the methine protons of **196** in the ^1H NMR spectrum at δ 5.07 (t, 1H, J 6.5 Hz, H2'') and 4.92 (t, 1H, J 6.5 Hz, H2'') for the major and minor diastereomers, respectively in a ratio of 60 : 40. The diastereotopic ethylene signals at the C3'' position of the cyclic sulfate **196** were observed at δ 4.65 (dd, 1H, J 9.0, 6.5 Hz, H3'') and 4.58 (dd, 1H, J 9.0, 6.5 Hz, H3'') for the major diastereomer, and at δ 4.80 (dd, 1H, J 9.0, 6.5 Hz, H3'') and 4.30 (dd, 1H, J 9.0, 6.5 Hz, H3'') for the minor isomer.

The methine protons of the cyclic sulfite **199** were also observed in a ratio of 60 : 40 at δ 4.53 (m, 1H, H2'') for major and at δ 4.41 (m, 1H, H2'') for the minor diastereomer. The diastereotopic methylene signals at C3'' position of the cyclic sulfite **199** was observed at δ 4.04 (dd, 1H, J 8.0, 6.5 Hz, H3'') and 3.99 (dd, 1H, J 8.0, 6.5 Hz, H3'') for the major diastereomer. The H3'' protons of the minor diastereomer of **199** were obscured by the methoxy signals.

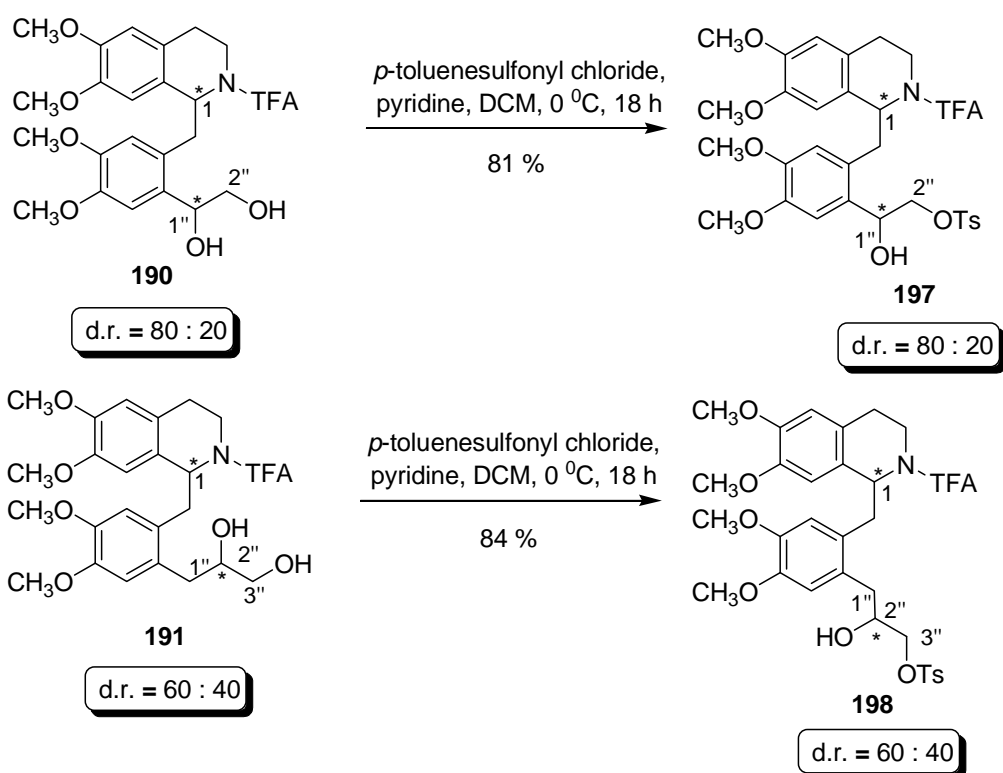
The mixture of **196** and **199** was not reoxidised at this stage but was heated at 70 $^\circ\text{C}$ with morpholine in isopropanol for 6 d, followed by acid-catalysed hydrolysis of the intermediate β -amino sulfate to give many fractions by TLC analysis. Purification of the reaction mixture by column chromatography gave the diol **191** (28 % yield) and a more polar fraction that corresponded to the morpholino alcohol product **200** in 30 % yield relative to the quantity of the cyclic sulfate **196** in the mixture of **196** and **199** (Scheme 5.16).

The desired product **200** was a 60 : 40 mixture of diastereomers by ^1H NMR analysis. The morpholine signals of **200** were observed in the ^1H NMR spectrum at δ 3.68 (m, 4H) and 2.38 (m, 4H) which overlapped for the major and the minor

diastereomers. The recovery of the diol **191** (28 %) indicated hydrolysis of the unreacted cyclic sulfite **199** and perhaps some unreacted cyclic sulfate **196**.

Since the ring opening of the cyclic sulfate **196** afforded the corresponding product **200** in only low yield (30 %) and the reaction was time consuming (70 °C for 6 d), attention was directed toward the methodology utilising the nucleophilic displacement of the tosylate **198**. Additionally, the unavailability of the cyclic sulfate **195** demonstrated the need for the alternative synthetic strategy involving nucleophilic displacement of the *O*-tosylate **197**.

5.3.3. Synthesis of the *O*-tosylate benzyloquinoline derivatives **197** and **198**.



Scheme 5.17 Synthesis of the *O*-tosylate benzyloquinoline derivatives **197** and **198**.

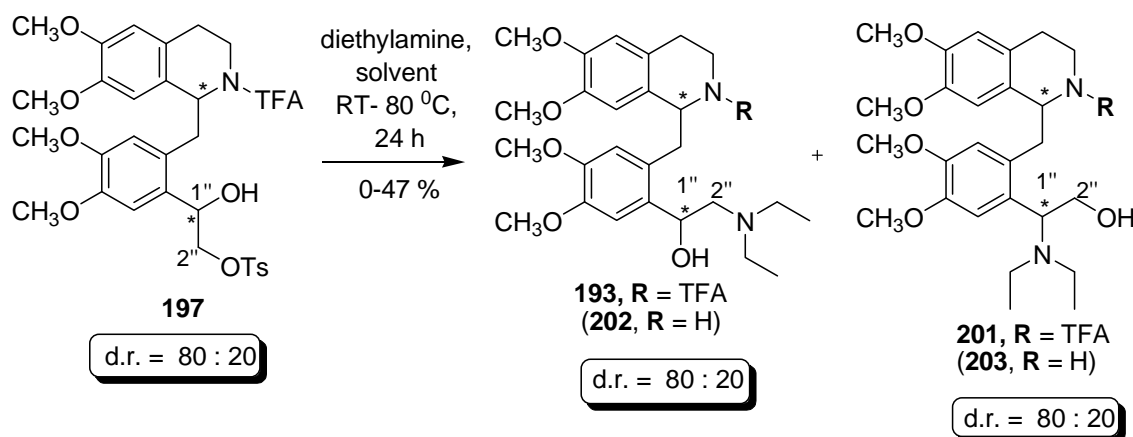
The synthesis of the primary tosylate derivatives **197** and **198** was easily achieved in good yield by reacting the diols **190** and **191**, respectively with *p*-toluenesulfonyl chloride in pyridine at 0 °C (Scheme 5.17).

The desired tosylate **197** was obtained as a 80 : 20 mixture of racemic diastereomers based on ^1H NMR analysis. The characteristic signals of the tosylate group of **197** were observed in the ^1H NMR spectrum at δ 7.73 (d, 2H, J 8.8 Hz) and 7.27 (d, 2H, J 8.8 Hz) for the major diastereomer and at δ 7.71 (d, 2H, J 8.8 Hz) and 7.28 (d, 2H, J 8.8 Hz) for the minor diastereomer. The CH_3 signals of the tosylate group was observed at δ 2.39 (s, 3H, ArCH_3) for the major and at δ 2.03 (s, 3H, ArCH_3) for the minor diastereomer. The diastereotopic methylene proton signals at the C2'' position had shifted downfield to δ 4.21 (dd, 1H, J 11.0, 2.5 Hz, H2'') and 4.02 (dd, 1H, J 11.0, 9.0 Hz, H2'') compared to the precursor **190** at δ 3.62 (m, 2H, H2''), confirming the attachment of the tosylate group at the C2'' position. The structure of **197** was confirmed by MS analysis.

The tosylate **198** was obtained as a 60 : 40 mixture of racemic diastereomers by ^1H NMR analysis. The tosylate group of **198** was observed by the aromatic signals in the ^1H NMR spectrum at δ 7.75 (d, 2H, J 8.0 Hz) and 7.31 (d, 2H, J 8.5 Hz) for the both the major and minor diastereomers. The methyl signals of the tosylate group were also observed in the ^1H NMR spectrum at δ 2.02 (s, 3H, ArCH_3) for the major and at δ 2.41 (s, ArCH_3) for the minor diastereomer. The H3'' methylene proton signals of the major isomer of **198** appeared more deshielded at δ 4.02 (dd, 1H, J 10.5, 4.0 Hz, H3'') and 3.97 (dd, 1H, J 10.5, 6.0 Hz, H3'') compared to that of precursor **191** at δ 3.79 (m, 1H, H3'') and 3.58 (m, 1H, H3''). The low and high resolution MS analysis of **198** also indicated the desired molecular formula.

5.3.4. Synthesis of β -amino alcohols 193, 201, 163 and 204.

Displacement of the *O*-tosylate group of compound **197** with diethylamine was carried out using different solvents and reaction temperatures and the results are summarised in Scheme 5.18 and Table 5.6.



Scheme 5.18 The displacement of the *O*-tosylate group of **197** giving two regioisomers.

Table 5.6 Examination of solvent and temperature variations on the displacement of the tosylate group of **197**.

Entry	Solvent	Temperature	Time (h)	Yield (%)	Regioisomer (193 : 201)
1	none	50 °C	24	0	n/a
2	none	65 °C	24	0	n/a
3	none	80 °C	48	0	n/a
4	CH ₃ CN	RT	24	0	n/a
5	CH ₃ CN	80 °C	24	47	10 : 90
6	CH ₃ OH	80 °C	24	21	60 : 40
7	CH ₃ OH*	65 °C	24	n/o	n/o

Note- * The yield of entry 7 was not obtained (n/o). Due to the presence of NH compounds **202** and **203**, the mixture was taken through to the *N*-TFA deprotection and *N*-methylation reactions (Scheme 5.21).

The tosylate **197** was treated initially with an excess amount of diethylamine in a sealed tube without the use of another solvent. However it was observed that at various reaction temperatures ranging from RT to 80 °C over a course of 24 to 48 h, no desired products were obtained and an increase in temperature in this case only resulted in decomposition products.

When CH₃CN was used as the reaction solvent at RT, none of the desired products was obtained and only starting tosylate **197** was recovered (entry 4, Table 5.6). However, when the acetonitrile solution was heated to 80 °C for 24 h (entry 5, Table 5.6), a 10 : 90 mixture of the regioisomers **193** and **201** was obtained, respectively in a higher yield (47 %). Surprisingly, this reaction was almost entirely selective for the regioisomer **201**. In this case the detrifluoroacetylated products **202** and **203** were not observed.

The two regioisomers **193** and **201**, although visible as two fractions of close proximity by TLC analysis, were not separated at this stage, however ¹H NMR analysis of the mixture of **193** and **201** shows the characteristic benzylic CH signals at the C1'' position which distinctively identified the two regioisomers **193** and **201** (Figure 5.4).

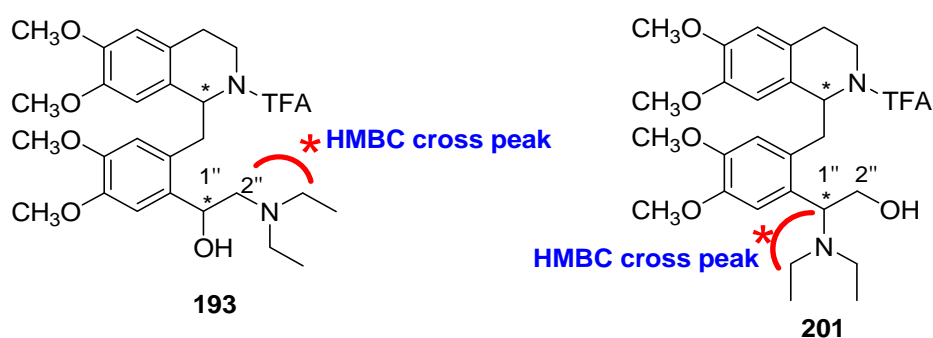
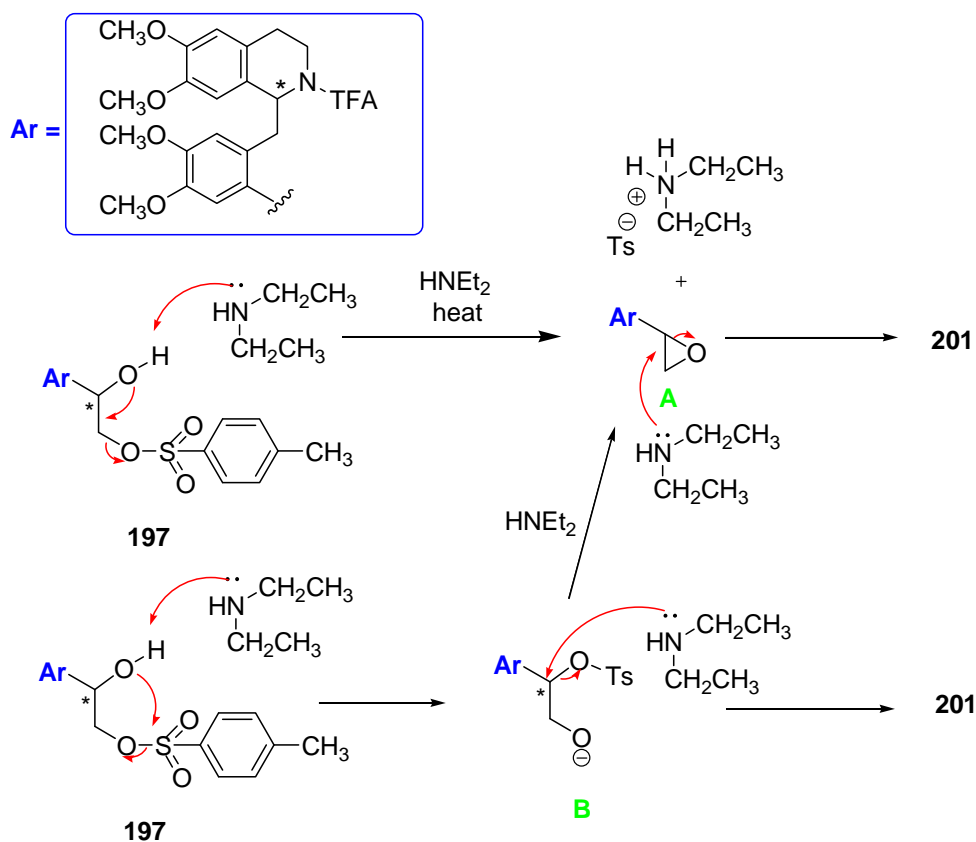


Figure 5.4 HMBC analysis of the two regioisomers **193** and **201**.

In the desired product **193**, the CH-1'' signal was more deshielded due to the benzylic hydroxyl group and appeared at δ 4.93 (dd, 1H, *J* 7.5, 5.0 Hz, H1'') for the major and at δ 4.54 (d, 1H, *J* 12.5 Hz, H1'') for the minor diastereomer in the ¹H NMR

spectrum. The structure of compound **193** was confirmed by the cross peak between the methylene protons at δ 2.52 (m, 1H, H2'') and 2.32 (t, 1H, J 4.5 Hz, H2'') in the ^1H NMR spectrum and the NCH_2 carbon at δ 46.9 in the ^{13}C NMR spectrum in gHMBC experiments (Figure 5.4).

The benzylic CH signal of the regioisomer **201** in comparison, was more shielded due to the direct attachment to the nitrogen and appeared at δ 4.11 (t, 1H, J 5.5 Hz, H1'') for the major and at δ 4.02 (t, 1H, J 6.0 Hz, H1'') for the minor diastereomer. gHMBC experiments also indicated a cross peak between H1'' in the ^1H NMR spectrum and the NCH_2 peak in the ^{13}C NMR spectrum (Figure 5.4), confirming the structure of the regioisomer **201**. The proposed mechanism of the formation of **201** is outlined in Scheme 5.19.



Scheme 5.19 The proposed mechanism for the formation of the regioisomer **201**.

The formation of **201** suggested that diethylamine had acted as a base to assist in the formation of either the epoxide intermediate **A** (**188**), and/or the secondary tosylate **B**. The latter would also produce the epoxide **A** (Scheme 5.19). The benzylic position of the epoxide would be more reactive due to the electron rich aromatic ring that can strongly stabilise the incipient carbonium ion that forms upon epoxide ring opening.

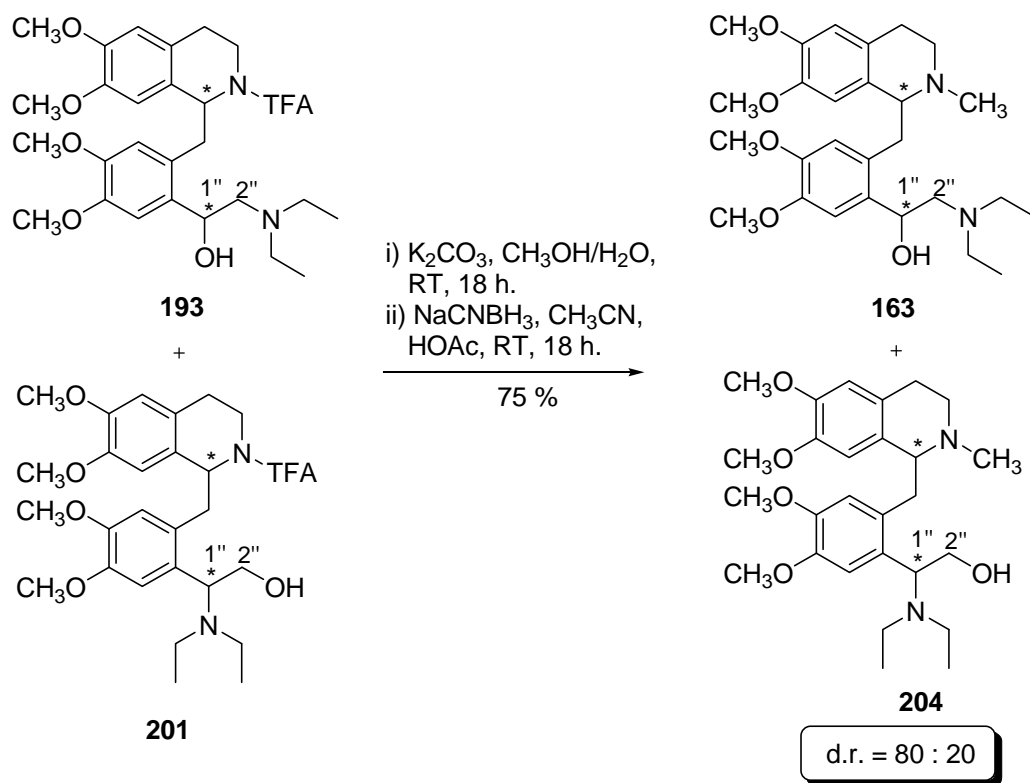
When methanol was used as the solvent at 80 °C (entry 6), a 60 : 40 mixture of the regioisomers **193** and **201**, respectively was obtained in low yield (21 %). It was suggested that the high temperature resulted in decomposition of the tosylate starting material or the product, or the detrifluoroacetylation of these compounds. Therefore, the temperature of the reaction mixture was lowered to 65 °C (entry 7). Under this condition, numerous products were also observed from TLC analysis. The crude reaction mixture was analysed by ESMS and a prominent ion peak was observed at m/z 555.1 which corresponded to the MH^+ signal of the desired β -amino alcohol product **193** and/or its regioisomer **201**. There was also an ion at m/z 459.2 that corresponded to MH^+ of the *N*-deprotected products **202** or **203**. The presence of the amines **202** and **203** was also suggested from the polar fractions observed by TLC analysis.

5.3.5. *N*-TFA deprotection and reductive *N*-methylation of **193** and **201**.

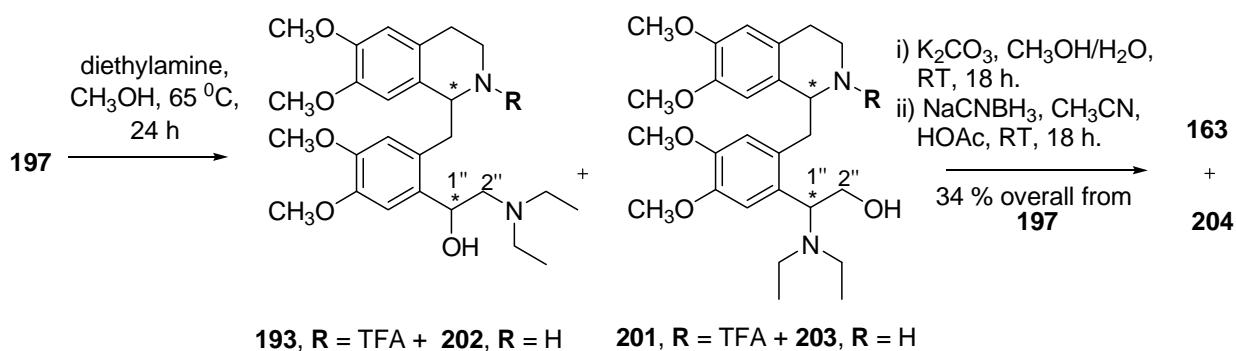
A mixture of the β -amino alcohol products **193** and **201** was subjected to *N*-TFA deprotection and reductive *N*-methylation reaction conditions (Scheme 5.20), affording the *N*-methylated products **163** and **204** (ratio = 60 : 40, respectively) in 75 % yield.

Alternatively, the crude product mixture of **193**, **201**, **202** and **203** was taken directly to the *N*-TFA deprotection and reductive *N*-methylation reactions to give the *N*-methylated products **163** and **204** (ratio = 60 : 40, respectively) in 34 % overall yield from **197** (Scheme 5.21). The extreme polar nature of these products might have

contributed to these low overall yields and some material may have remained on the silica gel during the purification process, even though ammonia was added to the eluting solvent. The mixture of **163** and **204** was successfully separated by PTLC. The structures of **163** and **204** were confirmed by NMR and MS studies.



Scheme 5.20 *N*-TFA deprotection and reductive *N*-methylation of a mixture of **193**, **201**.



Scheme 5.21 *N*-TFA deprotection and reductive *N*-methylation of a mixture of **193**, **202**, **201** and **203**.

¹H NMR spectrum of compound **163** showed a 80 : 20 mixture of diastereomers which were separated by PTLC. The major diastereomer of **163** displayed the characteristic methine proton signal at δ 4.76 (dd, 1H, J 9.5, 2.5 Hz, H1'') in the ¹H NMR spectrum and at δ 65.5 in the ¹³C NMR spectrum. The H1'' proton signal of the minor diastereomer **163** was observed at δ 4.57 (dd, 1H, J 10.0, 3.0 Hz, H1''). The diethylamino signals in the ¹H NMR spectrum of both diastereomers of **163** were observed at a similar chemical shift to those in compound **193**.

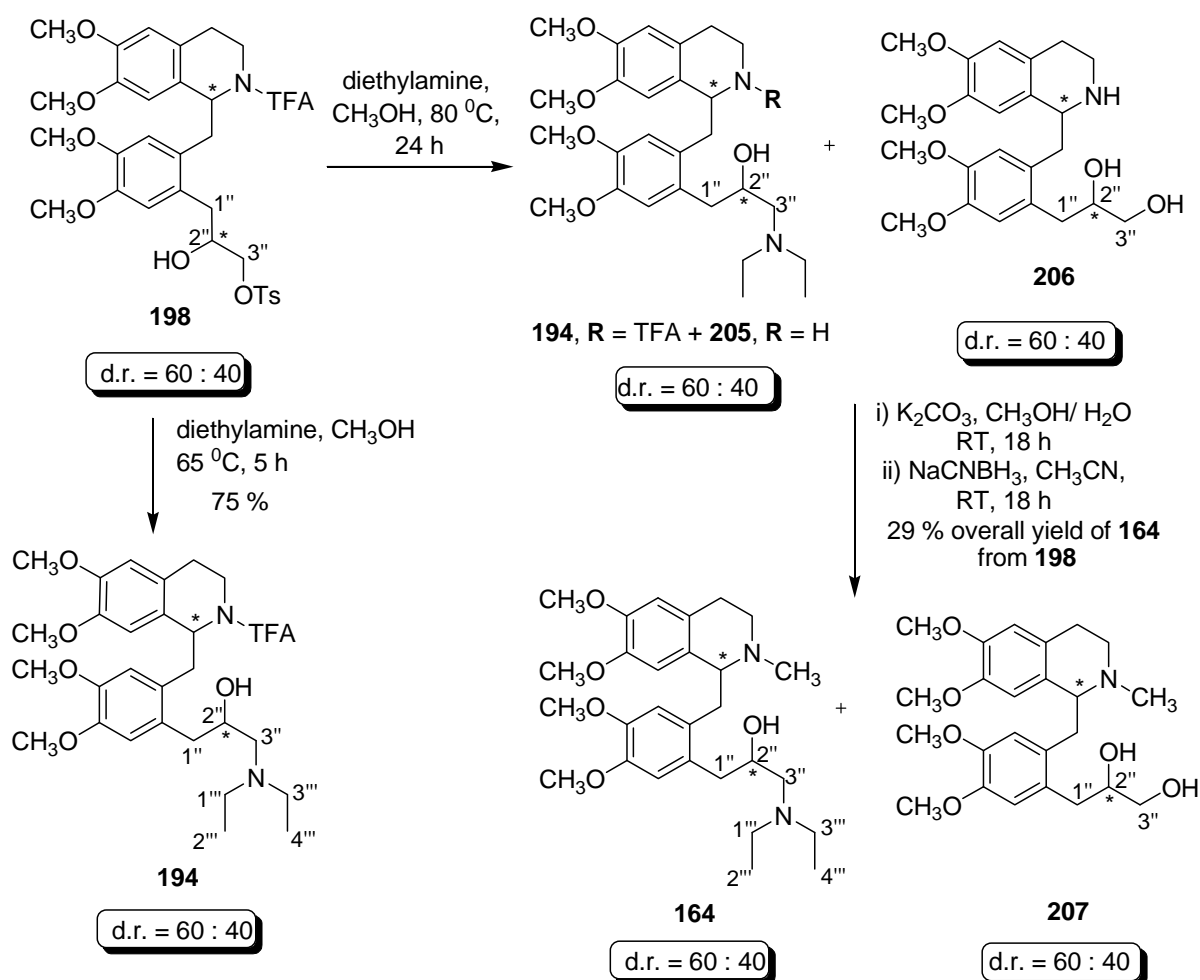
The *N*-methylated β -amino alcohol derivative **204** was also obtained as a 80 : 20 mixture of diastereomers prior to purification by PTLC. However, after separation by PTLC, only the major diastereomer was obtained as evident from the four aromatic proton singlet resonances in the ¹H NMR spectrum, therefore it appeared that the minor diastereomer of **204** was lost during PTLC purification.

The methine signal of the major diastereomer of **204** was detected at δ 3.70 (t, 1H, J 6.0 Hz, H1'') in the ¹H NMR spectrum which was consistent with its proposed structure. In the ¹³C NMR spectrum, the CH-1'' signal was observed at δ 66.0. The more deshielded, hydroxy substituted, methylene protons at C2'' position were observed at δ 4.07 (dd, 1H, J 10.0, 6.0 Hz, H2'') and 4.01 (t, 1H, J 10.0, 6.0 Hz, H2''). The diethylamino signals of **204** were observed at δ 2.63 (m, 2H, NCH₂), 2.54 (m, 2H, NCH₂), and 0.94 (t, 6H, J 7.0 Hz, 2 x NCH₂CH₃).

5.3.6. *Synthesis of β -amino alcohols 194, 164 and diol 207.*

Treatment of the tosylate **198** with an excess amount of diethylamine in methanol at 65 °C for 5 h afforded the corresponding β -amino alcohol **194** in 75 % yield (Scheme 5.22). As expected, the product **194** was significantly more polar than the tosylate precursor **198** by TLC analysis. The ¹H NMR spectrum of **194** showed signals

for two diastereomers (ratio = 60 : 40) as evident from the doubling up in characteristic resonances. The structure of **194** was confirmed by the characteristic proton signals of the diethylamine moiety at δ 2.47 (m, 4H, NCH_2) for the major and at δ 2.60 (m, 4H, NCH_2) for the minor diastereomer. The methyl proton signals of the diethylamino group of **194** were overlapped at δ 0.99 (t, 6H, J 7.0 Hz, NCH_2CH_3) for both the major and minor components. The presence of the hydroxy group was confirmed by the adjacent CH signal in the ^1H NMR spectrum at δ 3.60 (m, 1H, $\text{H}_{2''}$) for both the diastereomers and the corresponding CH signal at δ 68.1 ($\text{CH}_{-2''}$) in the ^{13}C NMR and DEPT spectrum of **194**. The structure of **194** was further confirmed by ESMS analysis.



Scheme 5.22 The displacement of the *O*-tosylate group of **198** by diethylamine.

When the temperature of the above reaction was raised to 80 °C, numerous baseline fractions were observed from TLC analysis, which suggested that the *N*-TFA group may have cleaved to give the corresponding amine **205** or other unidentified products. ESMS analysis of the mixture also showed the presence of the diol **206** with an ion at m/z 417.8 (MH^+). This reaction mixture was not separated and it was taken through to the next set of steps of *N*-TFA deprotection and reductive *N*-methylation, giving the *N*-methylated β -amino alcohol **164** in 29 % overall yield for the three steps from the tosylate **198**. The extreme polar nature of the product **164** might have contributed to the low overall yield.

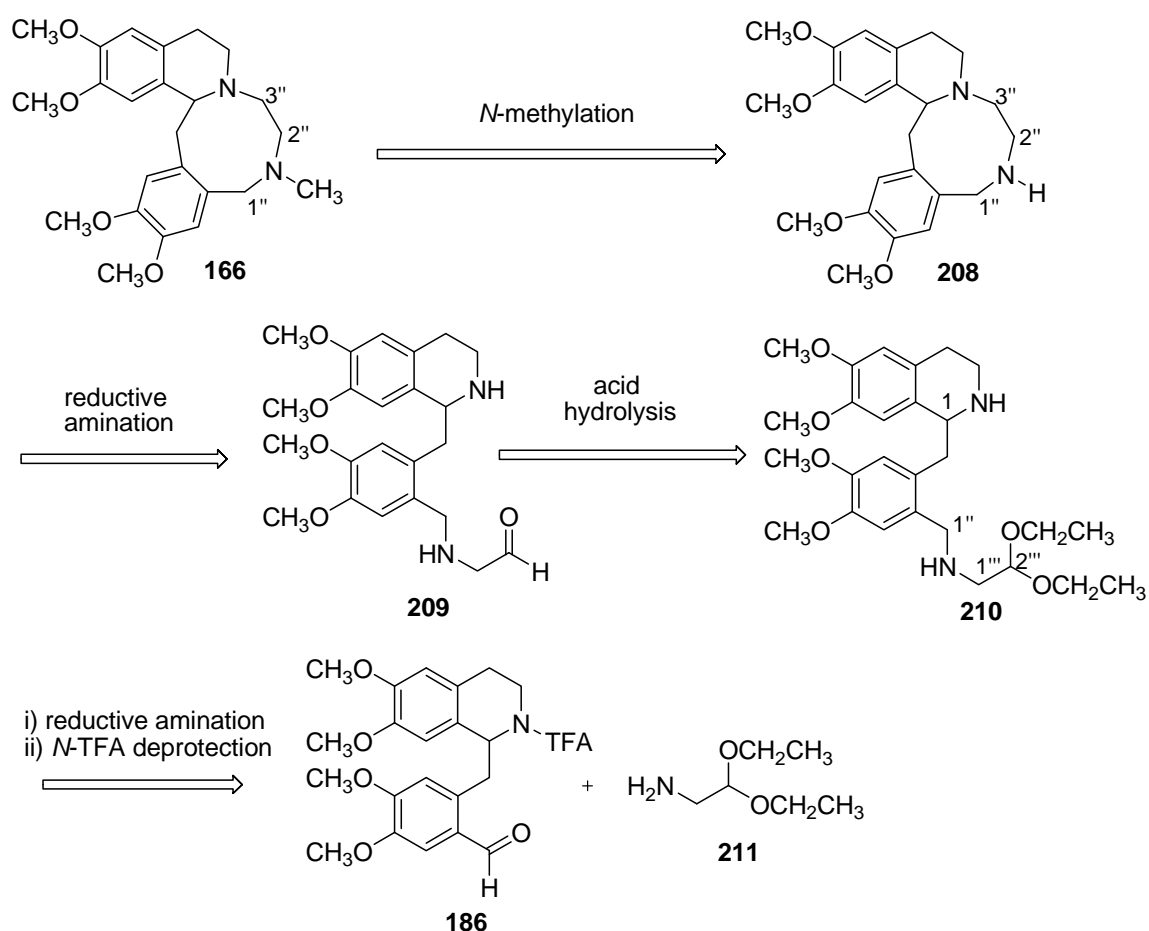
The characteristic *N*-methyl signal of **164** was observed in the 1H NMR spectrum at δ 2.51 (s, 3H, NCH_3) for the major and at δ 2.53 (s, 3H, NCH_3) for the minor diastereomer which were in a ratio of 60 : 40, respectively. Two diethylamino signals were observed in 1H NMR spectrum at δ 2.59 (m, 2H, NCH_2CH_3), 2.49 (m, 2H, NCH_2CH_3) for the major and at δ 2.56 (m, 2H, NCH_2CH_3), 2.45 (m, 2H, NCH_2CH_3) for the minor diastereomer. The methyl signals of the diethylamino moiety were found to be overlapped at δ 0.99 (t, 6H, J 7.5 Hz, 2 x NCH_2CH_3) in the 1H NMR spectrum for both diastereomers. The structure of **164** was confirmed by ESMS analysis.

The *N*-methylated diol **207** was also isolated in 11 % overall yield from **198** and its *N*-methyl peaks were observed in 1H NMR spectrum at δ 2.28 (s, 3H, NCH_3) and δ 2.48 (s, 3H, NCH_3) for the major and minor diastereomers (60 : 40 ratio), respectively. The structure of **207** was also confirmed by ESMS analysis.

5.4. Synthesis of benzyloquinoline derivatives containing a nine- and ten-membered ring.

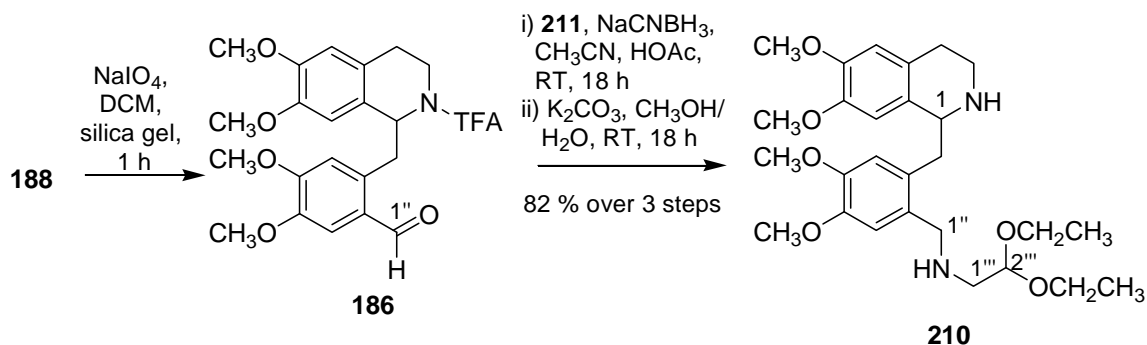
5.4.1. Synthetic strategy toward the synthesis of a nine-membered ring benzyloquinoline derivative.

The synthesis of the nine membered ring benzyloquinoline derivative **166** was proposed utilising the newly developed reductive amination method in Section 5.2.8 to facilitate the intramolecular coupling between the aldehyde and the amine group of **209** to provide the medium ring compound **208** (Scheme 5.23).



Scheme 5.23 Retrosynthesis of the nine-membered ring benzyloquinoline derivative **166**.

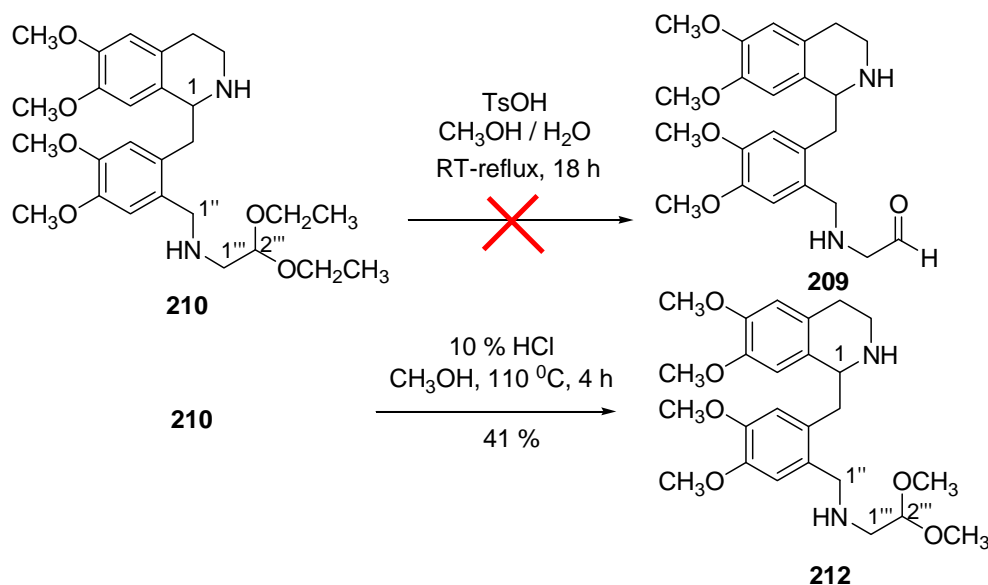
5.4.2. Synthesis of the free diamino compound **210**.



Scheme 5.24 The synthesis of the diamino compound **210**.

The synthesis started with the reductive amination reaction between the aldehyde **186** and commercially available aminoacetaldehyde diethylacetal **211**. Base-catalysed *N*-TFA deprotection then afforded the desired product **210** in 82 % overall yield from **188**. The structure of the amine **210** was confirmed by the presence of the ethoxy signals at δ 3.65 (dq, 2H, J 14.5, 6.5 Hz, OCHHCH_3), 3.50 (dq, 2H, J 14.5, 6.5 Hz, OCHHCH_3) and 1.14 (t, 6H, J 6.5 Hz, 2 x OCH_2CH_3) in the ^1H NMR spectrum. The structure of amine **210** was also confirmed by ESMS analysis with a MH^+ signal at m/z 488.6.

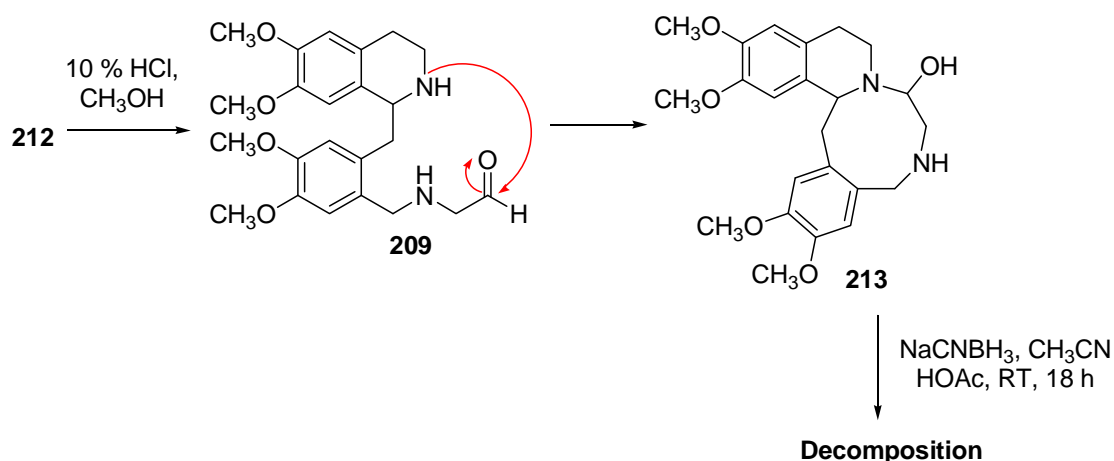
5.4.3. Synthesis of the aldehyde **209** by acid hydrolysis .



Scheme 5.25 The attempted hydrolysis of the diethylacetal group in **210**.

The next step in the proposed scheme involved the conversion of the acetal group of amine **210** into the corresponding aldehyde **209** by acid hydrolysis. However, the acid hydrolysis step highlighted in Scheme 5.25 proved extremely difficult.

When TsOH/CH₃OH/H₂O was used in the hydrolysis reaction at RT to reflux temperature, no product was obtained, and only that of the starting material **210** was recovered. A stronger hydrolysis condition using 10 % HCl with heating at 110 °C was employed, however, the desired aldehyde **209** was not obtained. Instead, the diethyl acetal groups had undergone exchange with the solvent methanol as evident by the loss of the diethyl acetal signals and the appearance of a newly formed methoxy signal at δ 3.37 (s, 6H, CH(OCH₃)₂) due to the formation of dimethoxy acetal **212**. This compound was isolated in 47 % yield and its structure was further confirmed by MS analysis with a MH⁺ ion at m/z 461.1.

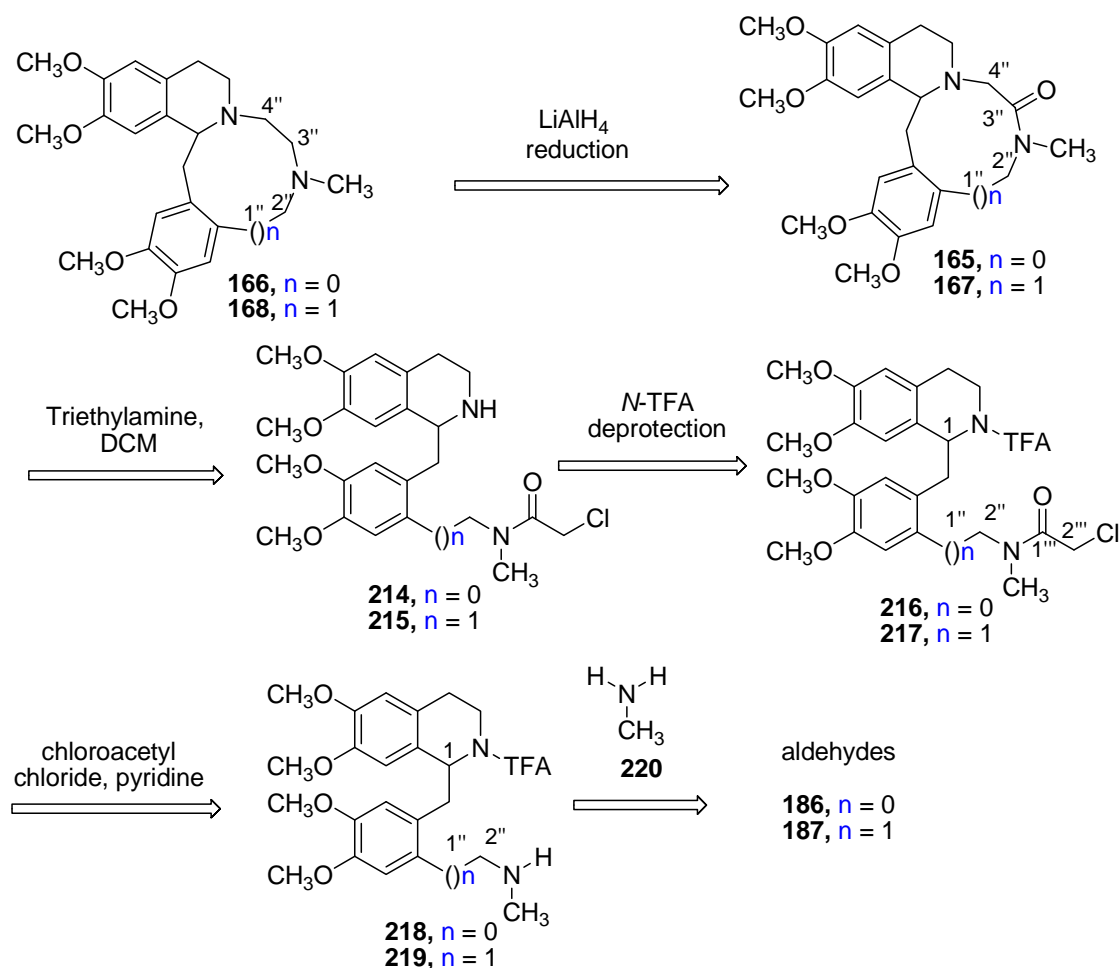


Scheme 5.26 The formation of the cyclised compound **213**.

Compound **212** was resubjected to the acidic hydrolysis conditions using 10 % aqueous HCl with heating at reflux for 23 h. ¹H NMR analysis of the newly formed product indicated that the dimethoxy signal at δ 3.36 (s, 6H, CH(OCH₃)₂) had disappeared, however, the expected aldehyde signal in the δ 9-10 region was not observed. The ESMS analysis showed a MH⁺ signal at m/z 415.0 which would be

expected for the desired aldehyde **209** or the hemiaminal **213** shown in Scheme 5.26. The latter compound **213** would be more consistent with the ^1H NMR analysis, Although its structure was not certain, compound **213** was subjected to the reductive amination conditions with NaCNBH_3 , however no identifiable products were obtained. Since the above synthesis proved problematic, an alternative approach using an intramolecular *N*-alkylation reaction was examined (Scheme 5.27).

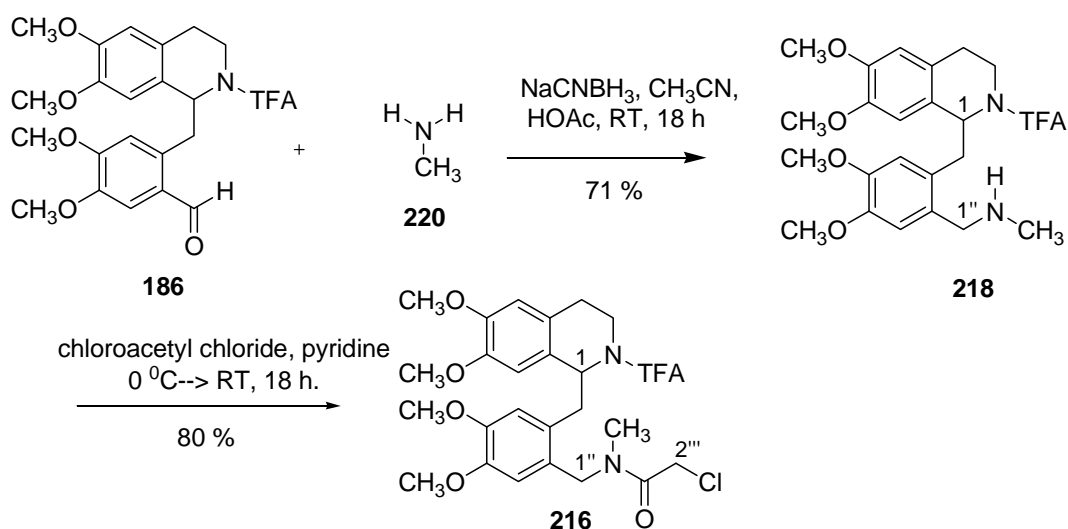
5.4.4. Retrosynthesis of the nine and ten membered ring benzyl-isoquinolines.



Scheme 5.27 The alternative retrosynthetic pathway toward the nine and ten membered ring benzylisoquinoline derivatives.

An alternative pathway outlined in Scheme 5.27 involved more synthetic steps than the previously proposed scheme (Scheme 5.23). The initial step utilised the reductive amination methodology to couple aldehydes **186** and **187** with methylamine **220**, followed by *N*-acylation with chloroacetyl chloride to give the α -chloroacetamides **216** and **217**, respectively. Hydrolysis of the *N*-TFA group of **216** and **217** would expose the free amino groups for an intramolecular S_N2 displacement of the chloride to provide the desired medium ring compounds **165** and **167**, which can undergo carbonyl reduction to give the targeted analogues **166** and **168**, respectively.

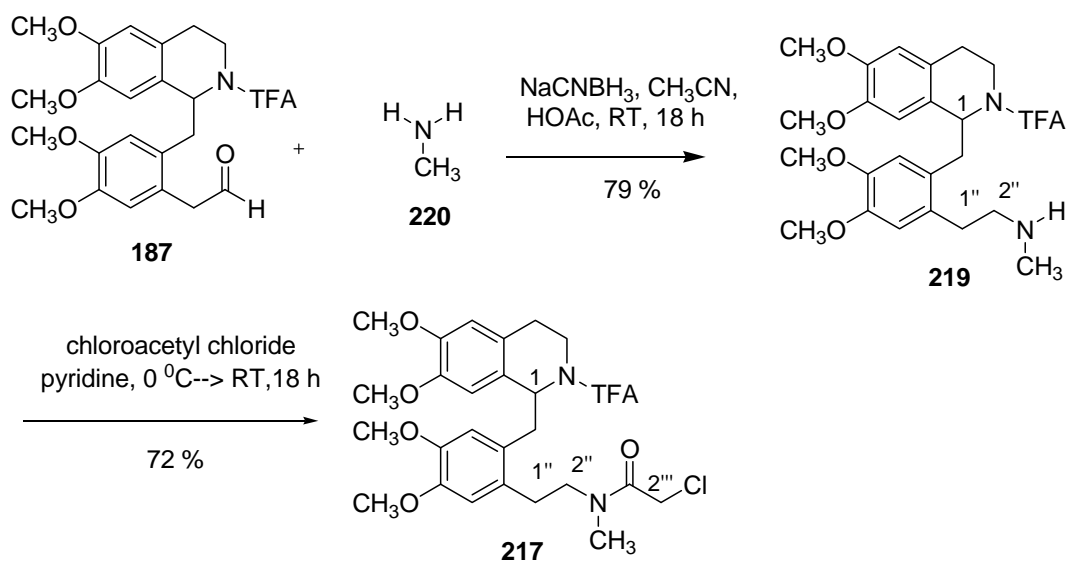
5.4.5. Synthesis of the benzyloquinolines **216** and **217** containing an α -chloroacetamido moiety.



Scheme 5.28 Synthesis of α -chloroacetamido derivative **216**.

The aldehyde **186** was subjected to a reductive amination reaction with methylamine and afforded the corresponding benzyloquinoline **218** in 71 % yield. The structure of **218** was confirmed by the characteristic *N*-methyl proton signal in the ^1H NMR spectrum at δ 2.37 (s, 3H, NCH_3). HRMS analysis of **218** showed the correct molecular formula. The amine **218** subsequently underwent *N*-acylation with chloroacetyl chloride to give the corresponding α -chloroacetamide **216** in 80 % yield.

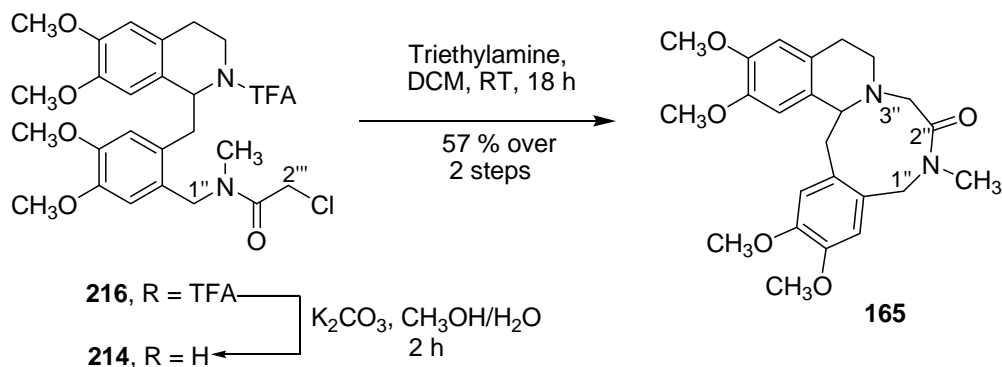
The methylene protons at the C2''' position of **216** appeared as an AB quartet at δ 4.01 (ABq, 2H, J 6.6 Hz) in the ^1H NMR spectrum. The methylene protons at the C1'' position of **216** were also diastereotopic and appeared as doublets at δ 4.48 (d, 1H, J 14.7 Hz) and 4.26 (d, 1H, J 14.7 Hz). Compound **216** was also confirmed by MS analysis.



Scheme 5.29 Synthesis of the α -chloroacetamido derivative **217**.

The aldehyde **187** was subjected to a similar reductive amination reaction with methylamine (Scheme 5.29) and afforded the corresponding *N*-methylated product **219** in 79 % yield which had the characteristic *N*-methyl proton signals in the ^1H NMR spectrum at δ 2.37 (s, 3H, NCH_3). The amine **219** underwent *N*-acylation with chloroacetyl chloride to give the corresponding α -chloroacetamide **217** in 72 % yield. In contrast to **216**, the α -chloroacetamino methylene protons of compound **217** at the C2''' position were observed as a singlet at δ 4.01 (s, 2H) in the ^1H NMR spectrum. The methylene protons at the C1'' and C2'' positions of **217** appeared at δ 2.57 (m, 2H, H1'') and at δ 3.45 (dt, 1H, J 9.6, 3.6 Hz, H2'') and 3.25 (m, 1H, H2''), respectively in the ^1H NMR spectrum. ESMS analysis of **217** also confirmed its structure.

5.4.6. Synthesis of benzyisoquinolines **165** and **167** via displacement of the chloride.

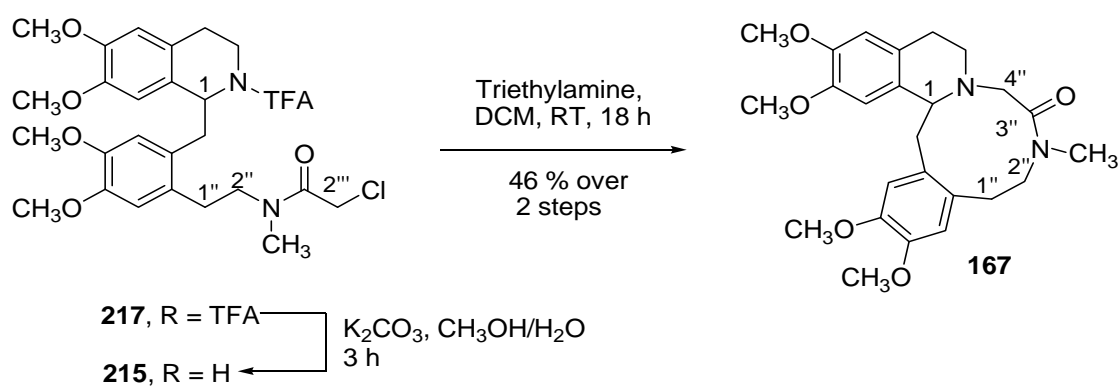


Scheme 5.30 Intramolecular *N*-alkylation of α -chloroacetamide **216** to give **165**.

The α -chloroacetamino group in **216** and **217** was relatively stable with no decomposition being observed on storage at RT. However, the chloride being a relatively sensitive leaving group, could pose a problem when being subjected to the basic *N*-TFA cleavage conditions. Under these conditions, the solvent methanol could easily replace the chloride by an $\text{S}_{\text{N}}2$ substitution reaction, therefore the *N*-TFA deprotection reaction was maintained firmly at RT and was monitored carefully by TLC analysis to minimise these possible side reactions.

The *N*-TFA deprotection reaction of compound **216** was complete after 2 h and afforded the corresponding amine **214** (Scheme 5.30) as evident from a significant decrease in its R_{f} value due to the polar nature of the free amine. The reaction mixture was gently evaporated under reduced pressure to remove methanol, with the water bath maintained at RT to minimise the possibility of exchange between the chloro group and methanol. After the removal of the methanol, DCM was added to the crude mixture, followed by addition of triethylamine as a base to facilitate the intramolecular *N*-alkylation between the isoquinoline amino group and the α -chloroacetyl moiety. The *N*-alkylation reaction of **214** was complete after 18 h at RT as indicated by a new

compound of higher R_f from TLC analysis. Purification by column chromatography afforded the desired product **165** in 57 % yield over the two steps. The ^1H NMR spectrum of **165** showed the methylene protons adjacent to the carbonyl group (C3'' position) as a broad singlet at δ 3.52 (bs, 2H, H3''). The benzylic methylene protons at the C1'' position of compound **165** were observed in the ^1H NMR spectrum as broad singlets at δ 4.22 (bs, 1H) and 3.52 (bs, 1H). The structure of **165** was further confirmed by ESMS analysis.



Scheme 5.31 Intramolecular *N*-alkylation of α -chloroacetamide **217** to give **167**.

The base-catalysed hydrolysis of the *N*-TFA group of compound **217** was complete after 3 h. This was evident from the formation of a new compound of a lower R_f seen by TLC analysis that corresponded to the free amine **215**. After removal of methanol, the crude product was subjected to the *N*-alkylation conditions (Scheme 5.31) to give the corresponding cyclised product **167** in 46 % overall yield. The methylene protons of compound **167** at C1'' and C2'' were observed as multiplets in the ^1H NMR spectrum at δ 2.77 (m, 1H, H1'') and 2.22 (m, 1H, H1'') and at δ 2.87 (m, 1H, H2'') and 2.77 (m, 1H, H2''), respectively. The methylene protons which are adjacent to the carbonyl group (C4'' position) of **167** were observed as a broad singlet at δ 3.47 (bs, 2H) in the ^1H NMR spectrum.

The relatively moderate yields of the products **165** and **167** were accounted for by a few factors. Firstly, the risk of the chloro group being exchanged with the solvent, thus preventing the intramolecular cyclisation from proceeding. This factor was observed more prominently in compound **217** since the time required for *N*-TFA cleavage (3 h) was slightly longer than that of compound **216** (2 h). The yields for the corresponding products **167** were lowered (46 %) due to the formation of methanolysis products **221** and **222** which were evident from the emergence of baseline TLC fractions which gave signals m/z 569.2 and 473.1, respectively, in their mass spectra (Figure 5.5). These side products were not obtained in pure form and therefore a full NMR study was not conducted. The formation of the methanolysis by-products similar to **221** and **222** in the intramolecular *N*-alkylation of **216** was also suggested by TLC analysis, however, a similar MS analysis was not conducted in this case.

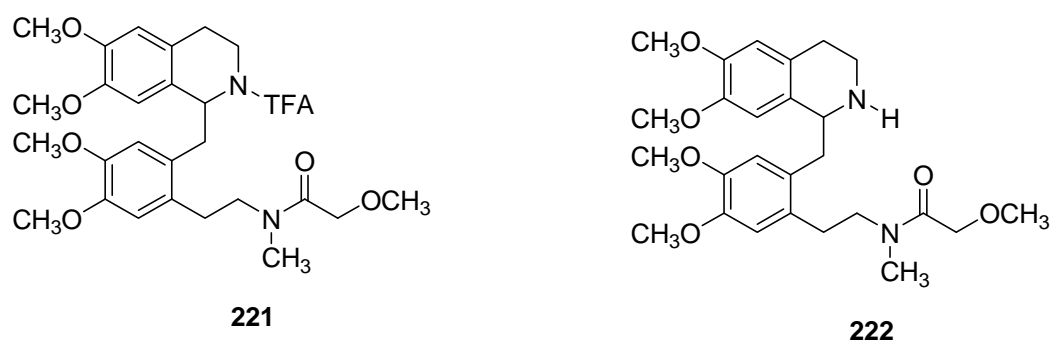


Figure 5.5 The methanolysis by-products from the *N*-acylation reaction of **217**.

Another factor which contributed to the low yields of the products **165** and **167** was the formation of the macrocyclic compounds **223** and **224**, respectively as shown in Figure 5.6. Their presence was confirmed by ESMS analysis. The MH^+ signals at m/z 853.1 and 881.0 for **223** and **224**, respectively, were observed in this case. These compounds also remained near the TLC silica plate baseline under the solvent system (50 % ethyl acetate and petroleum spirit).

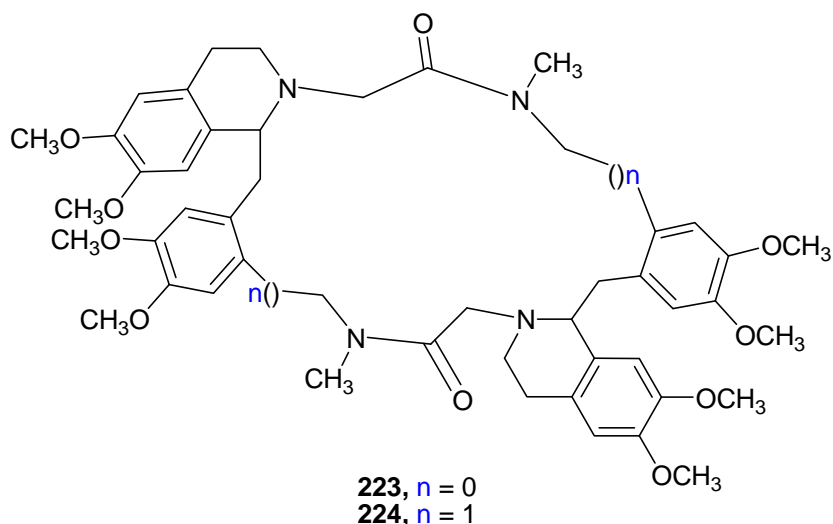
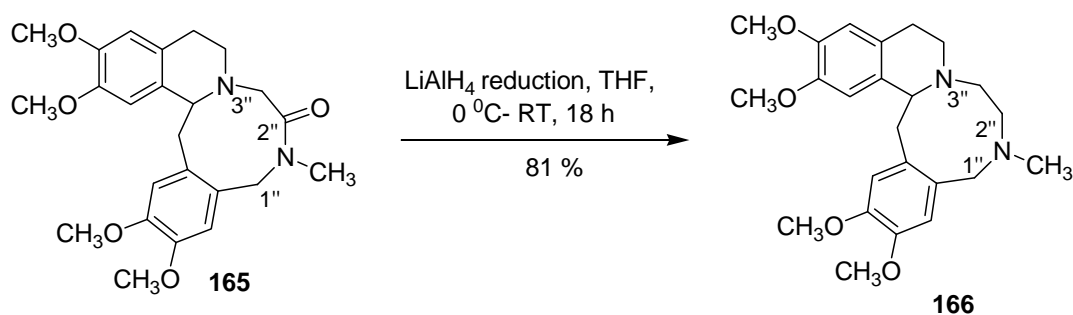


Figure 5.6 The proposed macrocyclic products **223** and **224** formed from intermolecular cyclisation.

NMR studies of these compounds were not conclusive. The NMR spectra were very complex possibly due to amide rotamers and the meso and racemate forms. The formation of these macrocyclic compounds could be overcome by further increasing the dilution factor to favour the intramolecular cyclisation.

5.4.7. Reduction of the carbonyl of **165** to give the corresponding amino compound **166**.



Scheme 5.32 Reduction of the carbonyl group of **165**.

Compound **165** was subjected to amide reduction reactions using LiAlH₄ and the corresponding product **166** was obtained in 81 % yield. The successful carbonyl reduction was confirmed by the significant increase in polarity observed from TLC

analysis due to loss of the amide functionality and the formation of the more polar tertiary amine.

Analysis of the ^1H NMR spectrum of **166** revealed the newly formed methylene proton resonances for H2'' at δ 2.79 (m, 1H), 2.57 (m, 1H) and for H3'' at δ 3.10 (m, 1H), 2.79 (m, 1H). These newly observed methylene proton signals confirmed the successful reduction of the amide carbonyl group of **165** to the corresponding amine **166**. The benzylic protons of **166** were observed more prominently at δ 4.49 (d, 1H, J 12.5 Hz, H1'') and 3.42 (d, 1H, J 12.5 Hz, H1''). The structure of compound **166** was also confirmed by ^{13}C NMR and MS analysis.

Due to time constraints and the limited amount of starting material, the carbonyl reduction of **167** was deferred for future work.

Chapter 6 Biological Testing.

6.1. Introduction.

The *N*-TFA deprotected and *N*-methylated benzyl- and bisbenzylisoquinoline derivatives described in Chapters 2-5 were submitted for cytotoxicity studies on 3 cancer cell lines, for anti-HIV and antibacterial bioassays and for receptor binding studies. Although over 45 compounds were sent for biological testing, only the results for a limited number of compounds have been received at this stage and these results are discussed accordingly.

6.2. Cytotoxicity on Cancer Cell Lines.

6.2.1. Testing procedures.

The cytotoxicity studies were conducted at the Peter MacCallum Cancer Institute in Melbourne, Australia. The cytotoxicity of these compounds was initially conducted using a pre-screen assay against human cancer cell lines including the lung cancer cells **H460**, human breast carcinoma **MCF-7** and CNS cell line **SF-268**. The results for each test are reported as a percentage of cell growth when compared to the control cells. For any of these cell lines, compounds which reduced the cell growth by more than 95 % at 20 μ M concentration in prescreen assays, were then evaluated for their IC₅₀ (the concentration required to inhibit cell growth by 50 %). The IC₅₀ values are reported in micromolar (μ M) concentrations.

6.2.2. Cytotoxic Pre-screen assay.

The results of the pre-screen assay on the three cell lines are summarised in Table 6.1. These compounds are arranged in a decreasing order of cytotoxicity for **H460** (lung), **MCF-7** (breast) and **SF-268** (CNS) cell lines.

The compounds **136** (**UB007**), **138** (**UB009**) and **139** (**UB010**) inhibited cell growth by 99.7-79 % across the three cell lines at 20 μ M concentration. These compounds showed higher cytotoxicity values (up to 10 fold) compared to that of thalicarpine **15**, a known alkaloid with anticancer activities (reviewed in Chapter 1). Therefore, these three compounds were chosen for IC₅₀ determination. Interestingly, thalicarpine **15** showed similar cytotoxicity to **137** (**UB008**), however compound **15** was tested at 25 μ M concentration.

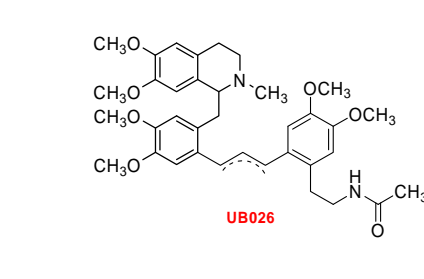
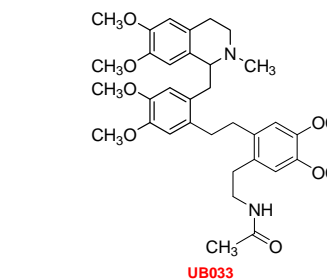
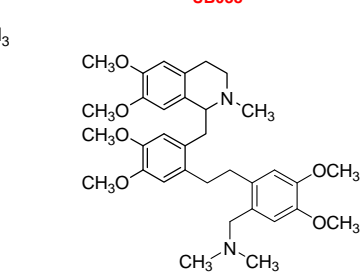
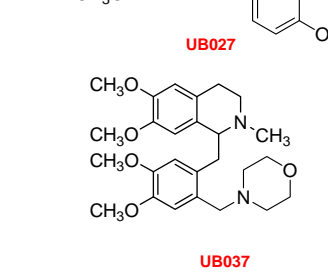
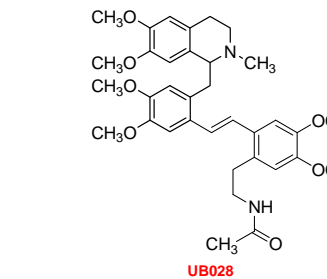
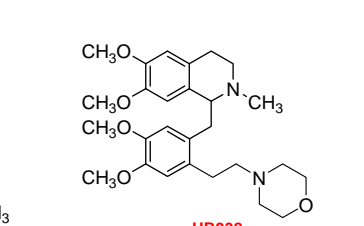
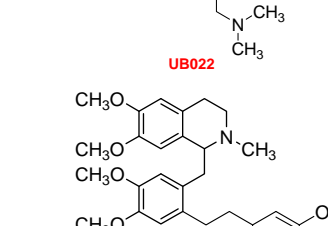
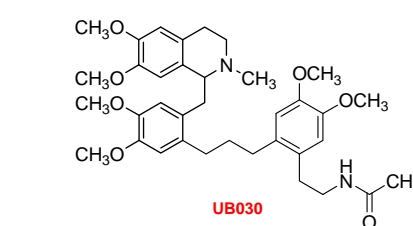
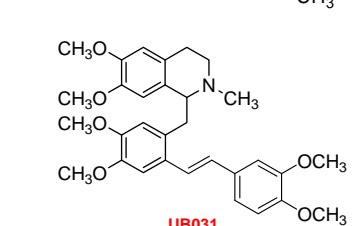
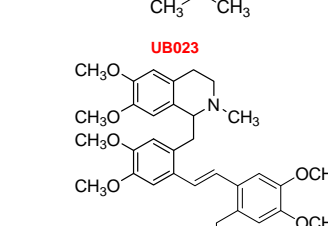
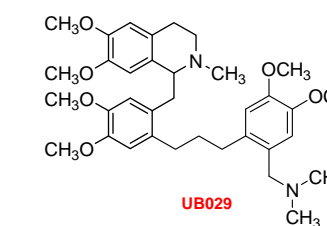
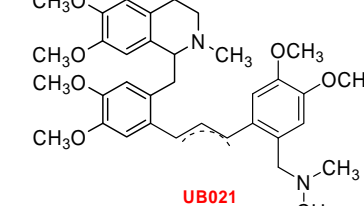
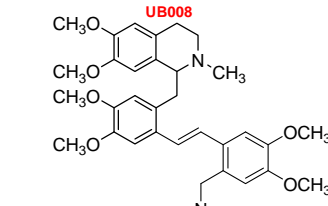
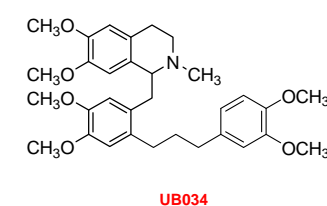
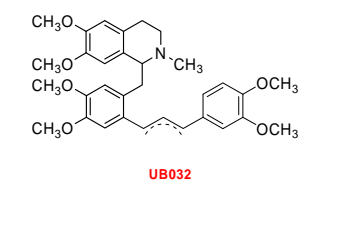
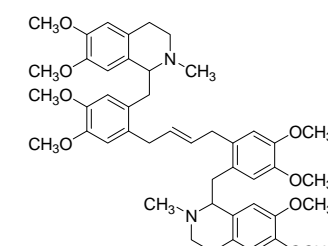
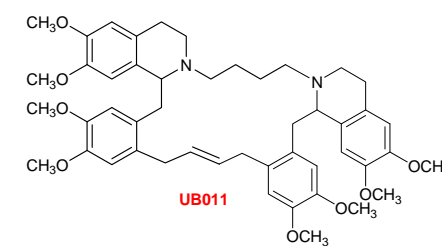
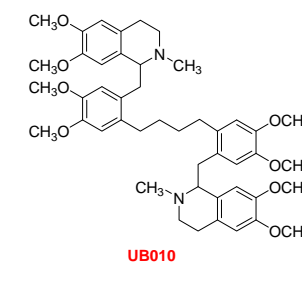
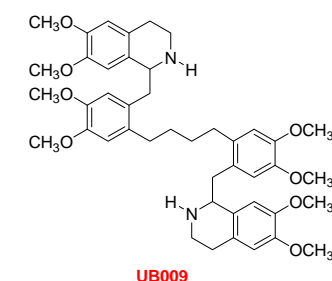
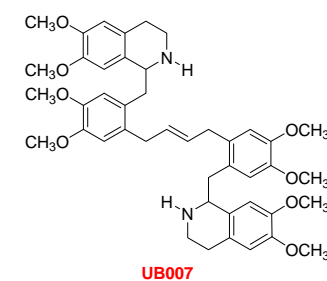
Table 6.2 IC₅₀ (μ M) values of the three most active analogues determined from the initial pre-screen assay. (note-ND-not determined).

Compound number	Testing code	IC ₅₀ (μ M)		
		H460 (lung)	MCF-7 (breast)	SF-268 (CNS)
136	UB007	6.0, 6.7	ND	ND
138	UB009	8.5, 9.9	7.9, 12	26, 23
139	UB010	11, 9.6	20, 12	27, 24

IC₅₀ values were obtained for the three most active analogues **UB007**, **UB009** and **UB010** and these are listed in Table 6.2. **UB007** was the most cytotoxic analogue, and is a bisbenzylisoquinoline tethered by an unsaturated four carbon tether. When reduction of the double bond of **UB007** to give **UB009** occurred, the IC₅₀ value was slightly reduced. This might suggest that the more rigid alkene tether holds the two isoquinolines in a more favourable orientation for binding to the target site. When the two nitrogens of **UB007** were *N*-methylated (**UB010**) or linked by a four carbon tether (**UB011**), the cytotoxicity decreased slightly (Table 6.2).

Table 6.1 Cytotoxic pre-screen assay of the benzyl- and bisbenzylisoquinoline derivatives at 20 μ M. *-Thalicarpine was tested at 25 μ M.

Compound number	Testing code	Percentage cell growth (%) at 20 μ M		
		H460 (lung)	MCF-7 (breast)	SF-268 (CNS)
136	UB007	0.3	1.7	0.7
138	UB009	1	3	1
139	UB010	3	21	5
142-d2	UB011	3	25	57
137	UB008	15	66	34
109a,b	UB032	31	54	86
111	UB034	49	62	92
93	UB023	50	45	80
96a,b	UB021	57	70	83
102	UB029	62	82	89
92	UB022	67	68	78
108	UB031	79	89	98
107	UB030	79	91	94
110	UB027	85	85	94
159	UB038	89	94	95
104	Ub028	93	92	97
155	UB037	93	106	104
99	UB025	94	80	95
106	UB033	94	97	103
105a,b	UB026	95	87	98
* Thalicarpine 15		15	63	54



Interestingly, the analogues carrying the NH group in the case of **UB007** and **UB009** were significantly more cytotoxic than the *N*-methylated analogues such as **UB008** and **UB010**. However, the compounds mentioned above had insufficient cytotoxicity to be a drug lead for a new anticancer drug.

The results obtained in Table 6.1 indicated that the bisbenzylisoquinolines (BBI) derivatives (**UB007-011**) were more active on human cancer cell lines than the corresponding mono-benzylisoquinoline derivatives. Therefore it can be observed that the bisbenzylisoquinoline motif has an important effect on the cytotoxic activity including those with two NH groups. Surprisingly, the monoamino benzylisoquinoline **UB032** and **UB034** were more active than the corresponding bis-amino compound **UB029** while their *N*-acetamido analogues **UB026** and **UB028** were less active.

These results provided some insight into the structure requirement for cytotoxicity, with the bisbenzylisoquinoline skeleton showing the highest cytotoxicity.

6.3. Anti-HIV Testing.

The anti-HIV testing was carried out at TIBOTEC, Belgium. The analogues were tested in an anti-viral replication assay and cytotoxicity assay. The anti-viral assay directly measured the ongoing replication of the virus in MT4 cells *via* the specific interaction of HIV-tat (a protein that helps to produce new HIV RNA genomes) with long terminal repeats (LTR) sequences coupled to green fluorescent protein (GFP). In the toxicity assay, a reduced expression of the GFP reporter protein serves as a marker for the cellular toxicity of a compound. These compounds were tested in an anti-viral assay on two different HIV strains: 1) **SM026** and **SM052**- These strains contained different point mutations that cause resistance against *reverse transcriptase* inhibitors; 2) **T13275** and **T13299**- These strains contained mutations that cause resistance against *reverse transcriptase* inhibitors and *protease* inhibitors; and 3) **IIIB**- Wild type.

To be identified as active and selective for HIV strains, a compound should show a SI (selective index) value of at least a 4-fold difference between the CC₅₀ (the cytotoxic concentration that was required to reduce cell growth by 50 %) and EC₅₀ (the effective concentration of an agonist that produces 50 % of the maximum possible response for that agonist). The results summaries in Table 6.3 are arranged in decreasing order of selectivity.

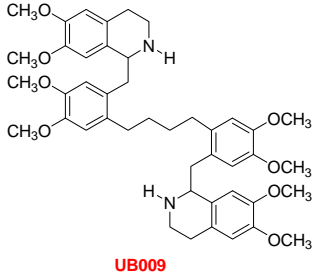
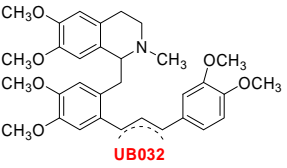
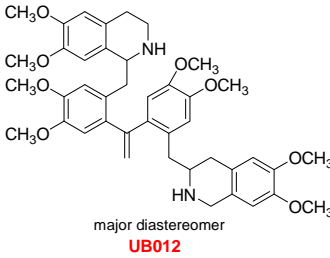
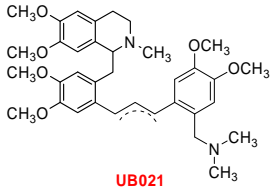
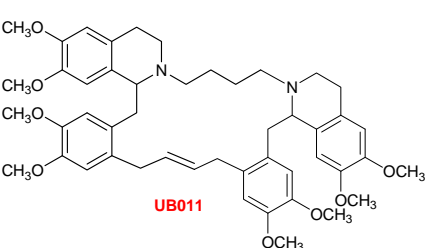
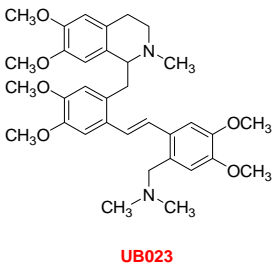
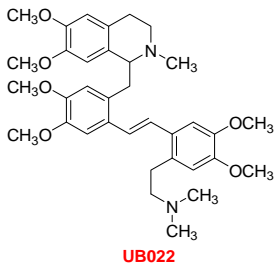
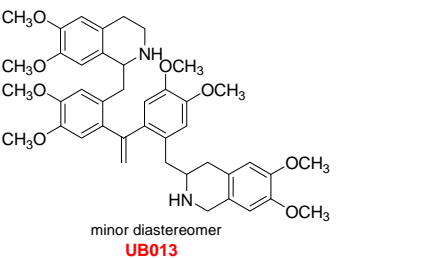
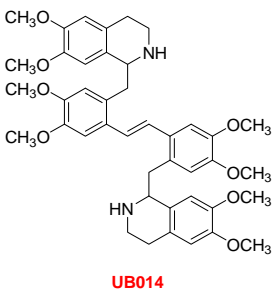
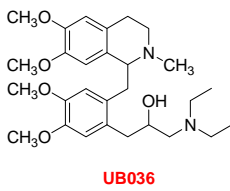
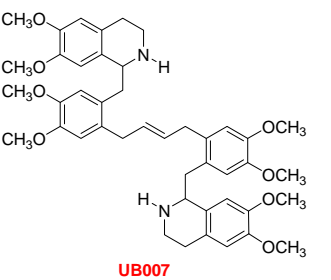
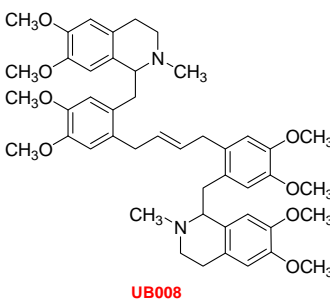
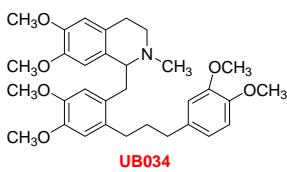
The results in Table 6.3 indicate that out of the 13 compounds tested, only analogue **UB034** exhibited more than a 4-fold difference between its toxicity (CC₅₀) and its antiviral activity measurement (EC₅₀). Although **UB034** is selective on HIV infected cells, its EC₅₀ was too high compared to that of known drugs such as AZT, 3TC etc. (Table 6.4) to be considered as a candidate for drug development. Analogue **UB007** had the lowest EC₅₀ in all assays as well as the lowest CC₅₀ indicating that the high activity in the HIV infected strains was due to its cytotoxicity rather than its selectivity on HIV infected cells.

Table 6.4 Antiviral activity on the reference compounds on HIV infected cells.

Compound	IIB	SM026	SM052	T13275
	EC ₅₀ (μM)	EC ₅₀ (μM)	EC ₅₀ (μM)	EC ₅₀ (μM)
AZT	0.12	0.14	0.16	0.05
DDC	1.63	1.70	1.74	0.23
NVP	0.05	1.25	1.25	1.25
EFV	0.003	0.08	0.08	0.08
APV	0.07	0.19	0.20	1.25

Table 6.3 Summary of Anti-HIV testing. (Note- ND- not determined, d.- diastereomer).

Compound number	Testing code	SI value (CC ₅₀ / EC ₅₀ -IIB)	CMV-Tox	IIB	SMO26	SM052	T13275	T13299
			CC ₅₀ (μM)	EC ₅₀ (μM)	EC ₅₀ (μM)	EC ₅₀ (μM)	EC ₅₀ (μM)	EC ₅₀ (μM)
111	UB034	4.3	>32.0	7.4	14.0	----	3.54	----
137	UB008	2.6	20.6	7.9	15.4	13.6	18.9	15.7
136	UB007	2.4	6.4	2.7	3.3	3.0	3.5	3.7
164	UB036	2.3	>32.0	13.8	>32.0	ND	12.1	ND
59	UB014	2.1	>32.0	15.1	9.4	15.9	24.1	16.3
82-minor d.	UB013	1.8	27.0	14.7	11.7	16.9	>32	16.2
92-	UB022	1.8	32.0	17.9	12.4	---	8.59	----
93	UB023	1.7	15.4	9.3	8.2	---	6.53	----
142-d2	UB011	1.7	25.0	15.1	20.6	29.4	22.6	24.9
96a,b	UB021	1.5	20.3	13.9	14.0	---	16.72	---
82-major d.	UB012	1.0	>32.0	>32.0	14.8	>32.0	>32.0	>32.0
109a, b	UB032	1.0	>32.0	>32.0	>32.0	----	12.4	----
138	UB009	0.9	12.8	14.0	13.7	13.5	14.8	14.3

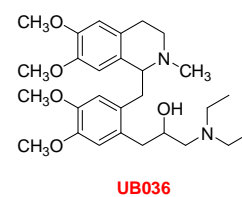
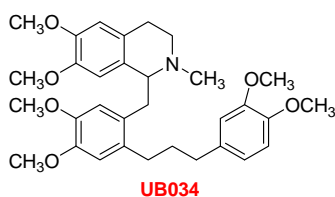
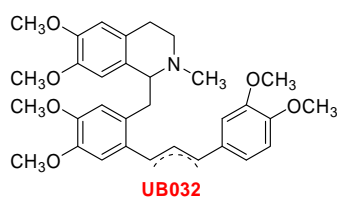


6.4. Anti-Bacterial Testing.

The anti-bacterial testing was conducted at PRD Raritan, USA. The anti-bacterial assays were carried out across a variety of bacterial strains and the results of four benzyloisoquinoline derivatives were obtained and summarised in Table 6.5. These analogues were found to be inactive (MIC > 128 µg/mL) against any of the bacterial strains tested.

Table 6.5 Summary of anti-bacterial testing.

Comp-pound #	Code	MIC (µg/mL)			
		<i>S. aureus</i> ATCC29213	MRSA OC3726	MRSA OC2878	<i>S. aureus</i> OC4172
109a,b	UB032	>128	>128	>128	>128
111	UB034	>128	>128	>128	>128
164	UB036	>128	>128	>128	>128
		OC4172 + serum	<i>E. faecalis</i> ATCC29212	<i>E. faecium</i> OC3312	<i>E. coli</i> OC2530
109a,b	UB032	>128	>128	>128	>128
111	UB034	>128	>128	>128	>128
164	UB036	>128	>128	>128	>128
		<i>E. coli</i> OC2605	<i>E. coli</i> OC40	<i>E. coli</i> ATCC2592 2	<i>P.aeruginosa</i> ATCC27853
109a,b	UB032	>128	>128	>128	>128
111	UB034	>128	>128	>128	>128
164	UB036	>128	>128	>128	>128



6.5. *In vitro* CNS Receptor Binding Studies.

6.5.1. *Testing procedure.*

The *in vitro* testing was conducted at Cerep Corporation in France. The prepared benzyl- and bis-benzylisoquinoline analogues were tested for biological activities on 50 different CNS receptors.

The activities in Table 6.6 were expressed as % control specific binding, which is a measure of the specific binding exerted by the controlled ligand in the presence of the tested drug. Therefore the drug is considered **active** when measurement of the % control specific binding is **low**, indicating the ineffective binding of the control ligand in the presence of the drug.

The activities were also expressed as % inhibition of control specific binding (Table 6.7), which is the measure of the direct inhibition activity of the tested drug exerted on the controlled ligand. Therefore the drug is considered **active** when the % inhibition of control specific binding is **high**.

The testing concentration was initially conducted at 10 μM , however the cut off was later set at 1 μM concentration.

Table 6.6 Receptor binding activity studies. Measurement of % Control Specific Binding. (Note- d.- diastereomer).

[illegible]

Note: Due to this extensive raw data, the % specific control measurement is colour coded as follow:

	control specific binding = <5 %
	control specific binding = 5 → 15 %
	control specific binding = > 15 %

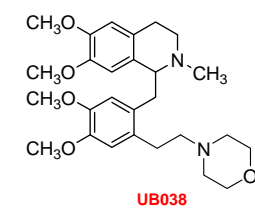
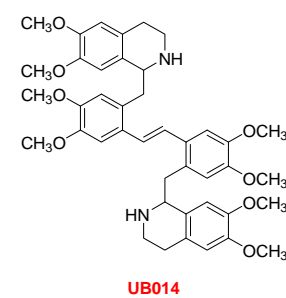
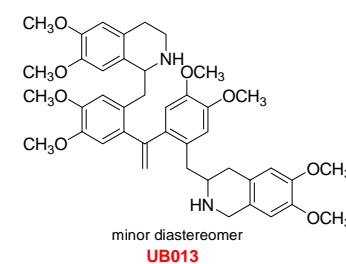
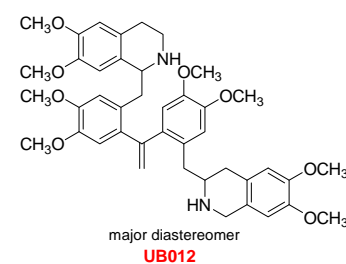
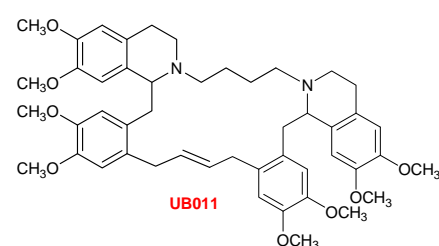
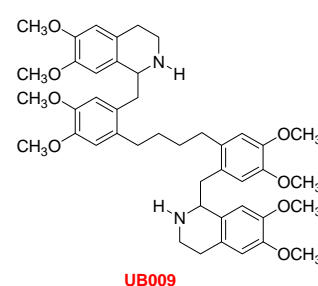
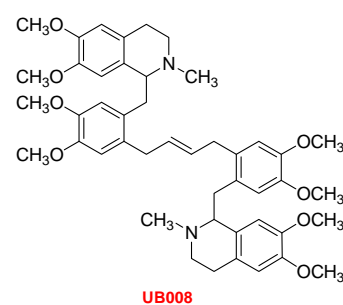
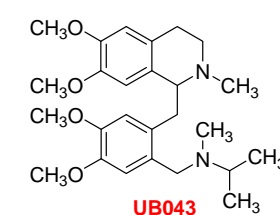
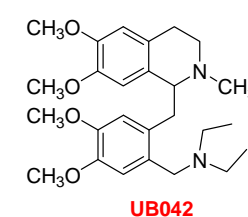
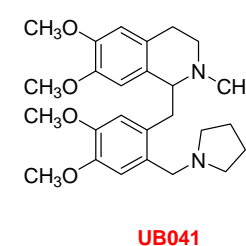
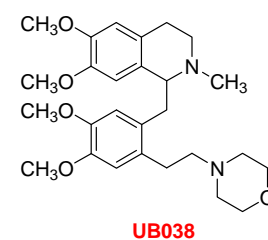
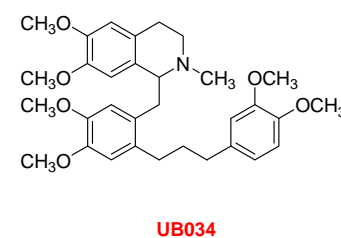
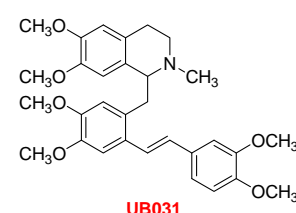
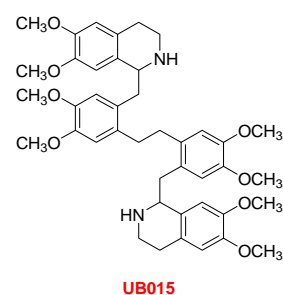
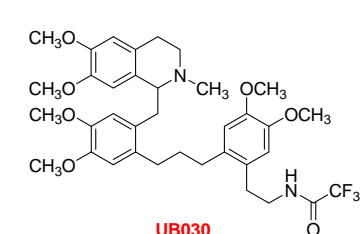
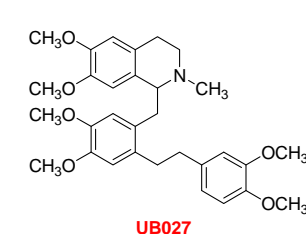
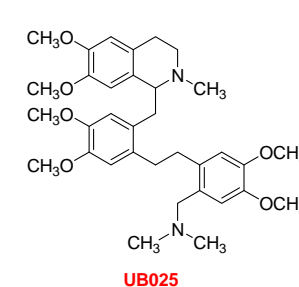
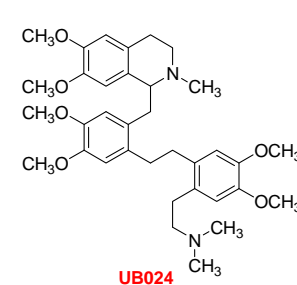
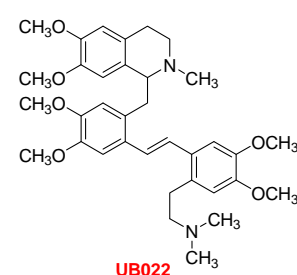
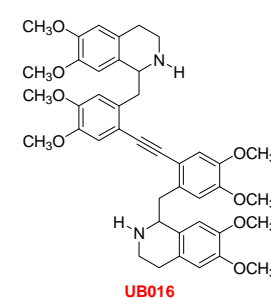


Table 6.7 Receptor binding activity studies. Measurement of % inhibition of control specific binding.

[illegible]

	Inhibition of Control Specific Binding <50 %
	Inhibition of Control Specific Binding 50→ 90 %
	Inhibition of Control Specific Binding 90-95 %
*	These analogues were tested at concentration of 1μM.



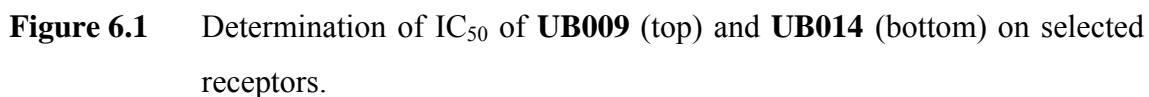
6.5.2. *Results of receptor binding assays.*

The activities shown in Table 6.6 are expressed as % of control specific binding, therefore only compounds displaying a 15 % or less of control specific binding of the ligand was considered to have activity. The results are colour coded with the analogues having activities as yellow or purple. The light blue colour indicates the inactive compounds. Out of the seven tested analogues in Table 6.6, only analogues **UB009** and **UB014** exhibited interesting activities at the α_2 and 5-HT_{1B} and 5-HT_{2A} receptors.

Table 6.7 summaries the % inhibition of control specific binding of the prepared benzyl- and bisbenzylisoquinoline analogues. The first 6 analogues in Table 6.7 were tested at 10 μ M concentration and they all inhibit more than 50 % of control specific binding at selected receptors. Therefore, the IC₅₀ of these analogues are predicted to be less than 10 μ M. The two analogues in Table 6.7 that exhibit interesting receptor binding activities were **UB016** and **UB022**. **UB016** had 50-90 % inhibition at A3, α_1 , D1, ML, M1-M3 receptors, 5-HT_{1A}, 1B, 2A, 6 receptors and the Na⁺ and Ca²⁺ channels. This analogue had particularly high activity on α_2 receptors and 5-HT₇ receptors which inhibited from 90 to 95 % of control specific binding at 10 μ M concentration. **UB022** also showed 50-90 % inhibition at the similar receptors as **UB016**, and was especially active on the M₁ receptor with over 90 % inhibition of control specific receptor binding.

The last seven compounds in Table 6.7 were tested at a 1 μ M concentration, where the concentration cut off was increased to detect only the most active compounds. Therefore at this dilute concentration, none of the last seven analogues listed in Table 6.7 exhibit any significant activity.

Analogues **UB009** and **UB014** were subjected to further assay at the receptors of interest in order to determine their IC₅₀ values. These analogues were tested at three different concentrations of 1 µM, 100 nM and 10 nM. The concentration at 50 % inhibition of control specific binding will determine the IC₅₀. The results are summarised in Figure 6.1.

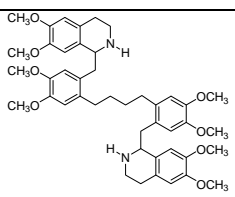
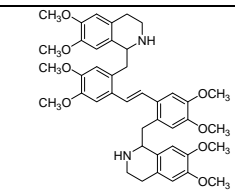
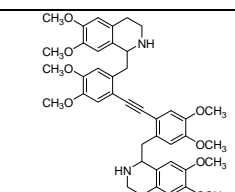
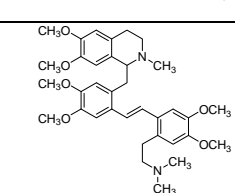


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HT_{1B} and 5-HT₇. Similarly, **UB014** is active at the serotonin receptor 5-HT_{1B} with an IC₅₀ value of approximately 500 nM.

The IC₅₀ results of **UB022** and **UB016** are yet to be determined. However, **UB016** had reasonably high activity on α_2 and 5-HT₇ receptors and inhibited 90 to 95 % of control specific binding at 10 μ M concentration. Therefore, it is estimated that the **UB016** is selective at α_2 and 5-HT₇ receptors with IC₅₀ values in the 10-100 nM range. **UB022** is selectively active at the M₁ receptor with over 90 % inhibition of control specific receptor binding, therefore the IC₅₀ would be anticipated to be approximately in 10-100 nM activity range.

Table 6.8 Summary of active analogues particularly at 5HT receptors subtypes.

Active analogues	Structure	Receptors selectivity	Approximate IC ₅₀ measurements (nM)
UB009		5-HT _{2A} , 5-HT ₇ and 5-HT _{1B}	5-HT _{2A} (550) 5-HT ₇ (900) 5-HT _{1B} (1000)
UB014		5-HT _{1B}	500
UB016		α_2 and 5-HT ₇	ND
UB022		M ₁	ND

6.5.4. Potential pharmaceutical applications of UB009, UB014, UB016 and UB022.

UB009, UB014, UB016 are active on several 5-HT receptors, especially of subtypes 5-HT_{1B}, 5-HT_{2A} and 5-HT₇. They are structurally different to the already known 5-HT_{1B} (e.g. **225**),^{179,180} 5-HT_{2A} (e.g. **226**)¹⁸¹ and 5-HT₇ active analogues (e.g. **227**¹⁸² and **228**¹⁶⁵) (Figure 6.2) and their modes of action are yet to be determined.

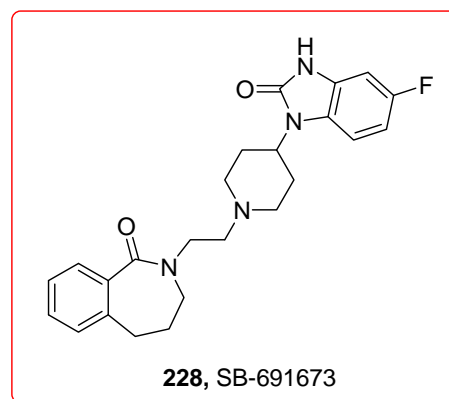
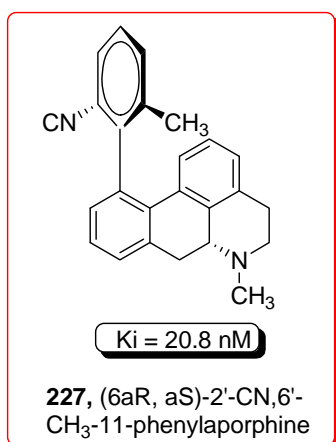
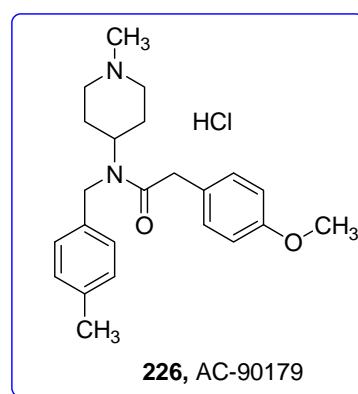
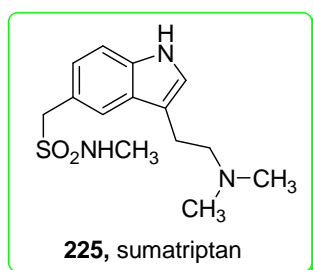


Figure 6.2 Structures of known 5-HT_{1B} (green), 5-HT_{2A} (blue) and 5-HT₇ (red) active ligands.

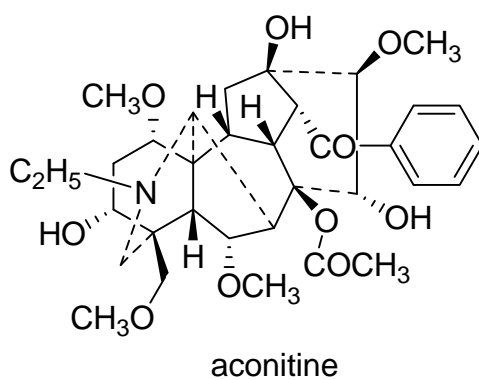
Research has implicated the importance of active analogues at 5-HT_{1B}, 5-HT_{2A} and 5-HT₇ receptors in the treatment of CNS disorders such as migraine and Schizophrenia. For example, the 5-HT_{1B} receptor has been implicated in the acute attack of migraine¹⁸³ and the 5-HT_{1B} agonist sumatriptan **225** has been marketed as an

antimigraine agent.¹⁸⁰ The 5-HT₇ receptor has also been reported to play an excitatory role in the neurosystem and that it may be involved in hyperalgesic pain and neurogenic inflammation which is normally observed in migraine patients.¹⁸⁴ Clinical neuropharmacology studies also indicated that the 5-HT_{2A} receptor is closely linked with migraine¹⁸⁵ and Schizophrenia.¹⁸⁶ Antipsychotic drugs having high affinity at 5-HT_{2A} receptor were reported to improve certain aspects of cognitive function in Schizophrenia patients.¹⁸¹ Therefore **UB009**, **UB014** and **UB016** being active and selective on 5-HT_{1B}, 5-HT_{2A} and 5-HT₇, would have possible applications as pharmaceutical drugs in the treatment of CNS disorders such as migraine and Schizophrenia. **UB022** showed activity at the M1 receptor which also has possible applications toward the treatment of CNS disorders, as studies have indicated that successful therapy of Alzheimer's disease could be based on activation of the M1 receptor.¹⁸⁷

Chapter 7 Conclusion And Future Directions.



http://www.toyen.uio.no/botanisk/nbf/plantefoto/aconitum_septentrionale_Norman_Hagen01.jpg.



Aconitum species containing the alkaloid aconitine, which was used as poisons for weapons during the Middle Ages.

7.1. Conclusion.

7.1.1. *Synthetic methodology.*

The synthesis of eleven bisbenzylisoquinoline derivatives having a single tether (group **A**) or two tethers (group **B**) were successfully achieved (Chapter 2 and 4). Within the group **A** targeted analogues, the mono-tethered BBI derivative **59** was successfully synthesised *via* **65** using phosphine-free, Heck coupling reactions. The best Heck coupling reaction condition found involved the use of Pd(OAc)₂, DMG, NaOAc and NMP at 130 °C. However, it was found that due to the electron rich nature of the dimethoxy aryl groups in **67**, the 1,1-disubstituted regioisomer **69** was also obtained. This product also provided the interesting analogue **82** for biological testing (Chapter 2).

The synthesis of the stilbene **65** was attempted *via* the cross metathesis reaction using both Grubbs' I and II catalysts (Chapter 4). The CM reaction of **67** did not occur when Grubbs' I catalyst was used, however, the employment of Grubbs' II catalyst afforded the desired BBI **65** in a moderate yield, in similar yield to that obtained using the Heck coupling reaction in Chapter 2. The CM reaction, however, had the advantage of affording compound **65** as the sole regioisomer.

The optimised Heck coupling reaction conditions developed in Chapter 2 were employed in the synthesis of the three carbon tethered BBI derivative **66** in moderate yields (Chapter 2). The attempted synthesis of **66** using the CM reaction (Chapter 4) between the 2'-vinyllaudanosine derivative **67** (Type II olefin) and the 2'-allyllaundanosine derivative **68** (Type I olefin) using Grubbs' I catalyst, proved ineffective as only ~ 7 % of **66** was obtained. Furthermore, the homocoupled product of **68** (**146**) was also obtained in this reaction and could not be separated from **66**. It was concluded that the synthesis of **66** was most effective using the Heck coupling reaction.

The intramolecular Heck coupling reaction of the aryl bromide **89** using the optimised Heck coupling reaction conditions did not afford the corresponding double tethered BBI derivative **88** (Group **B** analogue). This compound was obtained in low yield, however using the more traditional Heck coupling reaction conditions (Chapter 2). Replacement of the bromide in **89** with the iodide might have enhanced the reactivity and yield of this reaction.

The acetylenic tethered BBI **83**, and ultimately **63**, was successfully synthesised by a Pd/Cu catalysed Sonogashira coupling reaction between the aryl iodide **58** and acetylenic derivative **84** (Chapter 2). The synthesis of the precursor of **84** (**85**) was successfully obtained by a Sonogashira coupling reaction between aryl iodide **58** and TMS-acetylene. Interestingly, the use of a relatively large excess of TMS-acetylene to the aryl iodide **58** resulted in further addition of TMS-acetylene across the acetylenic group of **85**, to give the ene-yne **86**.

The CM reaction proved effective in the synthesis of the four carbon tethered BBI derivative **146** using Grubbs' I catalyst. *N*-TFA deprotection of **146** gave the targeted BBI derivative **136**, while *N*-methylation of this compound afforded the targeted BBI derivative **137**, in moderate to high yields, respectively (Chapter 4). The RCM reaction of diene **154** resulted in a low yield of the RCM product **153** (Group **B** analogue), due to difficulty in its purification.

Group **C** benzyloquinolines with a tether at the C2' position of the benzyl group to a substituted aromatic ring were successfully synthesised in moderate to high yields (33-79 %) using the optimised Heck coupling reaction conditions (Chapter 3). 1,1-Disubstituted products were not obtained as observed in the case of the synthesis of the BBI derivative **65**. The three carbon tethered benzyloquinoline derivatives **115**,

116, **129** and **137** were all obtained as a mixture of (*E*)-isomers, resulting from the two possible paths of palladium hydride elimination.

Several saturated BBI derivatives (Chapter 2 and 4) and benzyloisoquinoline derivative (Chapter 3) were effectively synthesised using two hydrogenation methods employing either Pd/C in EtOAc or CH₃OH, or PdCl₂ in CH₃OH. The latter catalyst was more effective for *N*-methylated unsaturated benzyloisoquinoline analogues (Chapter 3).

The synthesis of 2'-aminoalkylbenzyloisoquinoline derivatives **155-162** was attempted *via* several pathways. One attempted pathway included the addition of lithium amide to the olefinic group of the 2'-vinylaudanosine derivative **67**, which was found ineffective due to electron rich nature of the vinyl group because of the aryl methoxy substituents in **67**. Reductive amination of aldehydes **186** and **187** with several amines proved more effective (Chapter 5).

The targeted β -amino alcohol derivatives **163** and **164** *via* **193** and **194** were approached by two main routes. The initially planned route involved the ring opening of the cyclic sulfates **195** and **196** with amines, however, the cyclic sulfate **196** was not obtained in pure form, and the synthesis of cyclic sulfate **195** was not possible due to its instability. The latter, more successful route, involved the nucleophilic displacement of the primary tosylates **197** and **198** by an amine nucleophile to generate the corresponding β -amino alcohol derivatives **193** and **194**, respectively. The overall yields of the target analogues **163** and **164** from the tosylates **197** and **198**, should be optimised in future studies (Chapter 5).

The synthesis of novel Group **F** derivatives (compound **165**, **166**, **167** and **168**) having a medium sized heterocyclic ring structure were attempted by the intramolecular reductive amination method between the isoquinoline amino group and the aldehyde moiety at the C2' position of compound **209**. However, generation of the aldehyde

moiety of **209** by acid hydrolysis of the acetal protection group in **210** proved difficult using either the weaker acid, TsOH or the stronger acid, 10 % aqueous HCl. An alternative, more successful methodology involved the intramolecular nucleophilic displacement of the chloro group in **217** and **218**, which afforded the corresponding medium sized ring derivative **165** and **167** in moderate yields (42-57 %). Lithium aluminium reduction of **165** gave the medium sized heterocyclic compound **166** in good yield (81 %).

7.1.2. Biological activity.

The targeted benzyl- and bisbenzylisoquinoline derivatives were assessed for their i) cytotoxicity on 3 cancer cell lines; ii) activity on infected anti-HIV cells; iii) antibacterial activity and iv) CNS receptor binding affinities (Chapter 6).

The bisbenzylisoquinolines (BBI) derivatives **136**, **138**, **139**, **142-d2** (**UB007**, **UB009**, **UB010**, **UB011**) were more active on cancer cell lines than the corresponding mono-benzylisoquinoline derivatives. These results provided some insight into the structure requirement for cytotoxicity, with the bisbenzylisoquinoline skeleton showing the highest cytotoxicity. BBI derivatives **136** and **138** having a secondary isoquinoline amino group (**UB007** and **UB009**) exhibited higher cytotoxicity than the corresponding tertiary amino *N*-methylated analogues **137** and **139** (**UB008** and **UB010**).

None of the BBI and benzylisoquinoline derivatives tested against HIV-infected cells showed any significant activity or selectivity for HIV infected cells.

Compounds **138**, **59** and **63** (**UB009**, **UB014** and **UB016**) were found to be active and selective on 5-HT_{1B}, 5-HT_{2A} and 5-HT₇ receptors. These compounds may be developed further in the future with possible applications as pharmaceutical drugs for the treatment of CNS disorders, such as migraine and schizophrenia. Compound **92**

(UB022) showed activity at the M1 receptor suggesting potential molecules for the treatment of CNS disorders such as Alzheimer's disease.

7.2. Future directions.

7.2.1. Synthetic methodology.

A library of benzyl- and bisbenzylisoquinoline derivatives was successfully synthesised *via* the various synthetic methodologies described above, however, none of these compounds were enantiomerically pure because the starting precursor, norlaudanosine **58** was racemic. The racemic nature of **58** affected the diastereomeric outcomes of the synthesised bisbenzylisoquinolines and therefore, their characterisations were made more complicated. Furthermore, the testing of racemic compounds may have had significant affects on the biological results. Therefore, future work should focus on the synthesis of enantiomerically pure norlaudanosine **57**, *via* asymmetric reduction or hydrogenation of the prochiral iminium salt **72** (Scheme 2.2).^{188,189,190}

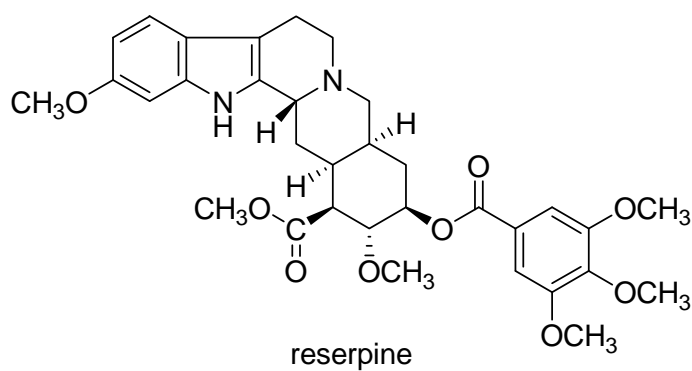
7.2.2. Biological SAR studies.

While a number of benzyl- and bisbenzylisoquinoline derivatives were tested for biological activities, a substantial amount of other benzyl- and bisbenzylisoquinoline derivatives are still waiting to be tested. At the present time, there are some compounds that are cytotoxic on cell lines and have good affinity for CNS receptors, yet, their modes of actions are unknown. Biological results on outstanding compounds may allow for the future development of pharmacophore models for CNS active compounds and the design and development of more selective and potent ligands.

Chapter 8 Experimental



<http://natural1.it/photo/rauwolfia-serpentina.jpg>



The plant species *Rauwolfia serpentina*. *R. serpentina*'s root was brewed as tea to treat hypertension, insanity and snake bites. Its root extracts contain the indole alkaloid reserpine.

8.1. General

8.1.1. Solvents and Reagents.

Reagents and anhydrous solvents were purchased from Sigma-Aldrich Pty Ltd, Lancaster or Merck with the exception of anhydrous DCM and THF. Anhydrous DCM was distilled from calcium hydride and stored over molecular sieves. Anhydrous THF was distilled from sodium in the presence of benzophenone. All other solvents were used as supplied.

8.1.2. Nuclear Magnetic Resonance Spectroscopy.

¹H NMR spectra

Unless stated otherwise, ¹H NMR spectra were acquired on a Varian Unity 300 NMR spectrometer, running at 299.5 MHz at 298 K. Chemical shift are quoted in δ values in ppm and are referenced relative to the chemical shift of CDCl₃ (7.24 ppm) unless otherwise noted. Some spectra were acquired on a Varian Innova (500.6 MHz) NMR spectrometer. Coupling constant (*J*) values are reported in Hz, with signal multiplicities designated as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), quartet (q), doublet of triplet (dt), triplet of doublet (td), multiplet (m), broad singlet (bs), quintet (quin), doublet of quartet (dq), AB quartet (ABq). Uncertainties: Chemical shift (± 0.01 ppm), coupling constants (± 0.1 Hz). The order in which the signal was described in the text is multiplicity, number of protons (integration), coupling constant (*J*), and assignment. All coupling constant (*J*) values of minor isomers are given whenever possible. ¹H NMR assignments were based on analysis of gCOSY, gNOESY, gHSQC and gHMBC experiments.

^{13}C NMR spectra.

Unless stated otherwise, ^{13}C NMR spectra were acquired on a Varian Unity 300 NMR spectrometer, running at 74.99 MHz at 298 K. Some spectra were acquired on a Varian Innova (125.1 MHz) NMR spectrometer. Chemical shifts are quoted in δ values in ppm and are referenced relative to the chemical shift of CDCl_3 (77.0 ppm) unless otherwise noted. Resonances were assigned as followed: Chemical shift (assignment). ^{13}C NMR assignments were based DEPT, gHSQC and gHMBC experiments.

8.1.3. Mass spectrometry.

The low-resolution chemical ionization (isobutene, CI^+) mass spectra were obtained on a QP-5000 mass spectrometer equipped with a CI-50 chemical ionization controller. The direct probe insertion method was used to acquire data. The electrospray (ES^+) mass spectra were obtained using a VG Quattro spectrometer.

High resolution mass spectra (HRMS) (both CI^+ and EI^+) were determined on a VG Autospec spectrometer using PFK (perfluorokerosene) as the reference. HRMS (ES^+) was obtained using a Micromass Q-ToF-2TM spectrometer.

The principal ion peaks (m/z values) are stated with their intensity given as a percentage of the base peak ion.

8.1.4. Melting points.

The melting points were recorded on a Gallenham MF-370 capillary tube, melting point apparatus and are uncorrected. The values are expressed in degrees Celsius ($^{\circ}\text{C}$). Uncertainties in the quoted values are $\pm 2^{\circ}\text{C}$.

8.1.5. Polarimetry.

Specific rotations are measured using a 10 mm or a 50 mm cell, and a Jasco DIP-370 digital polarimeter. They are reported by the following convention: specific rotation [10^{-1} . deg. cm³ g⁻¹] (concentration, solvent). Uncertainties in the quoted values are ± 5 %.

8.1.6. Chromatography.

Column chromatography.

Column chromatography was performed using Merck GF 254 flash silica gel (40-63 μ m) packed by the slurry method. Small scale separations (< 2.0 g) were performed using either a 10 mm or a 20 mm diameter column. Large scale separations (> 2.0 g) were performed using a 50 mm diameter column, each with the stated solvent system.

Thin layer chromatography (TLC) and Preparative thin layer chromatography (PTLC).

TLC was performed using aluminium-backed Merck sorbent silica gel. Compounds were detected under a 254 nm ultraviolet lamp if applicable, or by staining with acidified, aqueous solutions of ammonium molybdate and cerium(IV) sulfate, followed by development with a 1400 W heat gun.

Visualisation of the separated bands in PTLC was done using a 254 nm ultraviolet lamp.

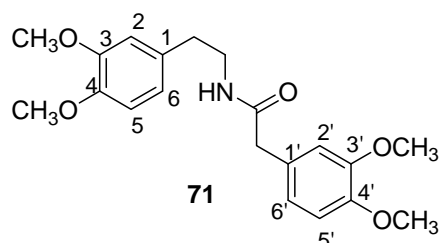
8.1.7. Outline of the experimental section.

The experimental section is divided into four parts. Each part outlines the experimental procedures and spectroscopic data for the individual Chapters (2-5). Each part has been further divided into subsections where applicable, based on reaction types.

8.2. Experimental for Chapter 2.

8.2.1. Synthesis of 2'-Iodolaudanosine (58).

N-[2-(3, 4-Dimethoxyphenyl)ethyl]-2-(3', 4'-dimethoxyphenyl)acetamide (**71**).



To a suspension of 3,4-dimethoxyphenylacetic acid **69** (10.2 g, 52.0 mmol) in dry benzene (30 mL) was added excess thionyl chloride (9.87 g, 83.0 mmol, 7.2 mL). Stirring at RT was continued until the acid

dissolved (approximately 2 h). Excess thionyl chloride was evaporated and the residue was dissolved in diethyl ether (40 mL). The solution was added to a stirred mixture of 2-(3,4-dimethoxyphenyl)ethylamine **70** (10.1 g, 55.7 mmol, 9.4 mL), diethyl ether (50 mL) and 10 M NaOH (3.2 mL) and the resulting mixture was stirred for 18 h. The precipitate formed was filtered, washed with water before drying to give **71** (14.2 g, 76 %) as a white solid.¹⁰⁶

Alternative method:

To a mixture of 3,4-dimethoxyphenylacetic acid **69** (10.0 g, 51.0 mmol), 2-(3,4-dimethoxyphenyl)ethylamine **70** (11.5 g, 63.5 mmol, 10.7 mL), HOBT (7.90 g, 58.5 mmol) and DCC (12.10 g, 58.6 mmol) was added dry DCM (130 mL) under a N₂ atmosphere and the mixture was stirred for 24 h at RT. The urea byproduct was filtered under vacuum and washed with DCM. The DCM solution was washed with H₂O (3 x), dried (MgSO₄) and evaporated to give a solid. The solid was recrystallised from CH₃OH and diethyl ether (1 : 1) to give **71** (13.9 g, 76 %) as white needles.¹⁰⁶ The spectra data of **71** were identical to that reported in the literature.

R_f 0.33 (CH₃OH : EtOAc (1 : 4)).

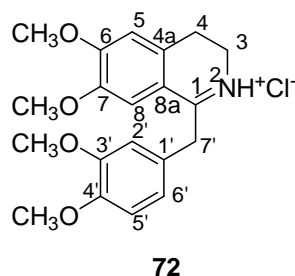
m.p. 104-106 °C, **lit.**¹⁰⁶ **m.p.** 118-120 °C.

¹H NMR: δ 6.71 (d, 1H, *J* 8.4 Hz, H5), 6.63 (dd, 1H, *J* 8.4, 2.4 Hz, H6), 6.63 (d, 1H, *J* 8.1 Hz, H5'), 6.62 (d, 1H, *J* 2.4 Hz, H2), 6.55 (d, 1H, *J* 1.8 Hz, H2'), 6.45 (dd, 1H, *J* 8.1, 1.8 Hz, H6'), 5.66 (t, 1H, *J* 5.3 Hz, NH), 3.97 (s, 3H, OCH₃-4'), 3.77 (s, 3H, OCH₃-3'), 3.74 (s, 6H, 2 x OCH₃), 3.39 (s, 2H, ArCH₂CO), 3.36 (dd, 2H, *J* 6.9, 5.3 Hz, NHCH₂CH₂Ar), 2.61 (t, 2H, *J* 6.9 Hz, NHCH₂CH₂Ar).

¹³C NMR: δ 171.6 (CO), 149.3 (C3'), 149.1 (C3), 148.4 (C4'), 148.8 (C4), 131.2 (C1), 127.4 (C1'), 121.7 (CH-6), 120.8 (CH-6'), 112.5 (CH-5'), 111.9 (CH-2), 111.6 (CH-2'), 111.3 (CH-5), 56.1 (OCH₃), 56.0 (3 x OCH₃), 43.5 (ArCH₂CO, NHCH₂CH₂Ar), 35.1 (NHCH₂CH₂Ar).

MS (CI⁺): *m/z* 360.1 (MH⁺, 60 %), 382.1 (M+Na⁺, 100 %). **HRMS (EI⁺):** calcd for C₂₀H₂₅NO₅, 359.1733 (M⁺). Found 359.1720.

3,4-Dihydro-6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)methylisoquinoline hydrochloride (72).¹⁰⁸



The amide **71** (8.66 g, 24.1 mmol) was dissolved in chloroform (50 mL). Phosphorus pentachloride (12.9 g, 61.9 mmol) was added slowly and the reaction was stirred for 18 h.¹⁹¹ The solvent was evaporated to give a yellow solid. CH₃OH (5 mL) was added slowly, followed by the addition diethyl ether (200 mL) and stirring was continued for several min. The ether was removed using a pipette and the yellow solid was dried under vacuum to give the iminium salt **72** (6.97 g, 76 %).¹⁹¹ The spectral data for **72** were not reported in the literature.

m.p. 120-124 °C, **lit.**¹⁰⁸ **m.p.** 180 °C.

R_f 0.57 (CH₃OH : EtOAc (5 : 95)).

¹H NMR: δ 7.33 (s, 1H, H5), 7.16 (d, 1H, *J* 1.8 Hz, H2'), 6.88 (dd, 1H, *J* 8.5, 1.8 Hz, H6'), 6.75 (s, 1H, H8), 6.73 (d, 1H, *J* 8.5 Hz, H5'), 4.56 (s, 2H, H7'), 3.94 (s, 3H,

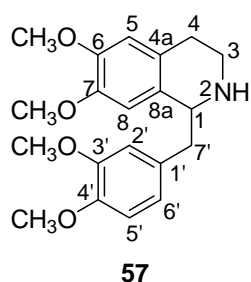
OCH₃-3'), 3.91 (t, 2H, *J* 8.0 Hz, H3), 3.84 (s, 3H, OCH₃-4'), 3.78 (s, 3H, OCH₃-6), 3.44 (s, 3H, OCH₃-7), 2.97 (t, 2H, *J* 8.0 Hz, H4).

¹³C NMR: δ 174.5 (C=N), 156.0 (C3'), 149.3 (C6), 148.4 (C4'), 148.3 (C7), 134.0 (C4a), 125.7 (C8a), 121.1 (CH-6'), 117.0 (C1'), 112.3 (CH-5), 112.3 (CH-2'), 111.4 (CH-5'), 110.8 (CH-8), 56.4 (OCH₃-4'), 56.3 (OCH₃-3'), 55.1 (OCH₃-6), 55.7 (OCH₃-7), 40.8 (CH₂-3), 38.0 (CH₂-7'), 25.1 (CH₂-4).

MS (ES⁺): *m/z* 342.1 (MH⁺, 100 %).

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)

methylisoquinoline (57).¹⁰⁶



To a solution of the iminium salt **72** (6.97 g, 18.4 mmol) in methanol (75 mL) was added sodium borohydride (1.00 g, 26.3 mmol). The mixture was stirred for 1 h at RT. After removal of the solvent, the residue was diluted with sat. Na₂CO₃ solution and extracted with EtOAc. The combined EtOAc extracts were dried

(MgSO₄) and the solvent was removed to give pure amine **57** (5.79 g, 91 %) as a yellow solid. The spectral data for **57** were identical to that reported in the literature.

R_f 0.36 (CH₃OH : EtOAc (5 : 95)).

m.p. 204-206 °C, **lit.**¹⁰⁶ **m.p.** 217-219 °C.

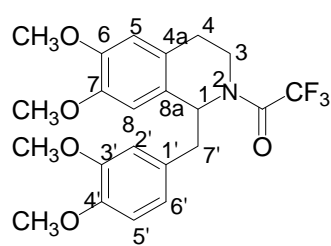
¹H NMR: δ 6.80 (d, 1H, *J* 7.4 Hz, H5'), 6.77 (d, 1H, *J* 1.5 Hz, H2'), 6.74 (dd, 1H, *J* 7.4, 1.5 Hz, H6'), 6.63 (s, 1H, H5), 6.56 (s, 1H, H8), 4.09 (dd, 1H, *J* 9.3, 4.3 Hz, H1), 3.83 (s, 3H, OCH₃-4'), 3.82 (s, 3H, OCH₃-3'), 3.80 (s, 3H, OCH₃-6), 3.74 (s, 3H, OCH₃-7), 3.18 (dd, 1H, *J* 11.1, 5.7 Hz, H3), 3.14 (dd, 1H, *J* 13.5, 4.3 Hz, H7'), 2.88 (m, 1H, H3), 2.84 (dd, 1H, *J* 13.5, 9.3 Hz, H7'), 2.67 (m, 2H, H4).

¹³C NMR: δ 149.1 (C3'), 147.8 (C6), 148.6 (C4'), 148.8 (C7), 131.7 (C1'), 130.7 (C4a), 127.7 (C8a), 121.6 (CH-6'), 112.6 (CH-5'), 112.0 (CH-8), 111.5 (CH-2'), 109.5

(CH-5), 57.1 (CH-1), 56.2 (OCH₃-4'), 56.1 (OCH₃-3'), 56.1 (OCH₃-6), 56.0 (OCH₃-7), 42.5 (CH₂-3), 41.2 (CH₂-7'), 29.8 (CH-4).

MS (ES⁺): *m/z* 344.1 (MH⁺, 50 %), 356.0 (M+Na⁺, 40 %). **HRMS (ES⁺):** calcd for C₂₀H₂₆NO₄, 344.1862 (MH⁺). Found 344.1848.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3',4'-dimethoxyphenyl)methylisoquinoline (73).¹¹²



73

To a solution of the amine **57** (2.94 g, 8.59 mmol) in dry DCM (30 mL) at 0 °C was added dry pyridine (3.12 g, 39.4 mmol, 3.2 mL) under N₂, followed by the addition of trifluoroacetic anhydride (3.6 g, 17.1 mmol, 2.4 mL). The mixture was brought to RT and stirred for 6 h. The reaction mixture was diluted with DCM and washed with H₂O. The DCM solution was dried (MgSO₄) and evaporated to give a brown solid which was purified by column chromatography (EtOAc : Pet. spirit (4 : 6)) to afford **73** (2.71 g, 74 %) as a yellow solid that had spectral data identical to that reported in the literature.¹¹² The structure of **73** was also confirmed by X-ray structural analysis. Compound **73** was a 95 : 5 mixture of rotamers.

(*S*)-**73** (1.27 g, 67 %) was obtained by the same method as above using (*S*)-**57** (1.49 g, 4.31 mmol), dry DCM (30 mL), dry pyridine (681 mg, 0.62 mL) and trifluoroacetic anhydride (1.17 g, 5.61 mmol).

R_f 0.43 (EtOAc : Pet. spirit (4 : 6)).

(*S*)-**73**: [α]_D²⁵ + 58 (1.5, CHCl₃).

m.p. (*rac*-**73**) 116-120 °C, **lit.**¹¹² **m.p.** (*rac*-**73**) 136-137 °C.

¹H NMR of the major rotamer: δ 6.72 (d, 1H, *J* 8.2 Hz, H5'), 6.57 (dd, 1H, *J* 8.2, 2.1 Hz, H6'), 6.76 (s, 1H, H5), 6.55 (d, 1H, *J* 2.1 Hz, H2'), 6.29 (s, 1H, H8), 5.54 (dd, 1H, *J*

6.9, 6.0 Hz, H1), 3.86 (dt, 1H, J 12.3, 4.2 Hz, H3), 3.83 (s, 3H, OCH₃-4'), 3.82 (s, 3H, OCH₃-6), 3.76 (s, 3H, OCH₃-3'), 3.67 (s, 3H, OCH₃-7), 3.42 (m, 1H, H3), 3.09 (d, 1H, J 6.0 Hz, H7'), 3.06 (d, 1H, J 6.9 Hz, H7'), 2.85 (m, 1H, H4), 2.62 (m, 1H, H4).

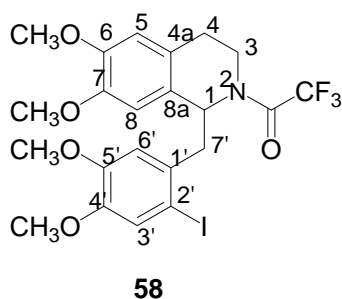
¹H NMR of the minor rotamer (in part): δ 6.77 (d, 1H, J 8.1 Hz, H5'), 6.51 (d, 1H, J 1.8 Hz, H2'), 5.93 (s, 1H, H8), 4.98 (dd, 1H, J 7.8, 4.8 Hz, H1), 4.54 (m, 1H, H3), 3.54 (s, 3H, OCH₃-7), 3.14 (m, 1H, H4), 2.98 (m, 1H, H4).

¹³C NMR of the major rotamer: δ 152.9 (q, J 35.2 Hz, COCF₃), 146.0 (C3'), 145.4 (C4'), 145.3 (C7), 144.7 (C6), 126.6 (C1'), 123.8 (C4a), 122.3 (C8a), 119.1 (CH-6'), 114.9 (q, J 226.2 Hz, COCF₃), 110.0 (CH-5), 108.3 (CH-5', CH-2'), 107.6 (CH-8), 53.1 (4 x OCH₃), 52.7 (CH-1), 38.6 (CH₂-7'), 37.8 (CH₂-3), 25.8 (CH₂-4).

¹³C NMR of the minor rotamer (in part): δ 126.5 (C1'), 119.3 (CH-6'), 110.2 (CH-5), 108.6 (CH-5', CH-2'), 107.7 (CH-8), 107.7 (CH-8), 40.6 (CH₂-7'), 35.1 (CH₂-3), 24.4 (CH₂-4).

MS (ES⁺): m/z 440.1 (MH⁺, 50 %). **HRMS (EI⁺):** calcd for C₂₂H₂₄NO₅F₃, 439.1607 (M⁺). Found 439.1587.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-(2'-iodo-4',5'-dimethoxyphenyl)methyl-6,7-dimethoxyisoquinoline (58).



The trifluoroacetamide **73** (5.09 g, 11.6 mmol) and *N*-iodo succinimide (3.31 g, 14.7 mmol) were dissolved in dry CH₃CN (60 mL). The mixture was cooled to 0 °C and trifluoroacetic acid (430 mg, 3.77 mmol, 0.28 mL) was added dropwise. The mixture was brought to RT and stirred

for 3 h. The solvent was evaporated and the residue was redissolved in EtOAc. The solution was washed with H₂O (3 x), brine, saturated Na₂S₂O₃, H₂O and saturated NaHCO₃. The EtOAc solution was dried (MgSO₄) and evaporated to give a solid that

was recrystallised from EtOAc to give **58** (6.12 g, 93 %) as a yellow solid. Compound **58** was a 95 : 5 mixture of rotamers.

(*S*)-**58** (1.08 g, 72 %) was also obtained by the same method as above using (*S*)-**73** (1.17 g, 2.66 mmol), *N*-iodo succinimide (710 mg, 3.19 mmol) and trifluoroacetic acid (91 mg, 0.789 mmol, 0.06 mL).

R_f 0.47 (EtOAc : Pet. spirit (1 : 4)).

(*S*)-**58**: $[\alpha]_{\text{D}}^{25} + 54$ (0.93, CHCl₃).

m.p. (*rac*-**58**) 148-150 °C.

¹H NMR of the major rotamer: δ 7.20 (s, 1H, H6'), 6.76 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.52 (s, 1H, H8), 5.71 (dd, 1H, *J* 8.1, 6.3 Hz, H1), 4.03 (dt, 1H, *J* 13.2, 3.3 Hz, H3), 3.86 (s, 3H, OCH₃-4'), 3.84 (s, 3H, OCH₃-6), 3.79 (s, 3H, OCH₃-5'), 3.74 (s, 3H, OCH₃-7), 3.71 (m, 1H, H3), 3.29 (dd, 1H, *J* 14.1, 6.3 Hz, H7'), 3.17 (dd, 1H, *J* 14.1, 8.1 Hz, H7'), 2.97 (m, 1H, H4), 2.78 (m, 1H, H4).

¹H NMR of the minor rotamer (in part): δ 6.71 (s, 1H, H3'), 6.63 (s, 1H, H5), 6.40 (s, 1H, H8), 5.07 (t, 1H, *J* 7.2 Hz, H1), 3.85 (s, 3H, OCH₃-6), 3.78 (s, 3H, OCH₃-5'), 3.71 (s, 3H, OCH₃-7).

¹³C NMR of the major rotamer: δ 156.1 (q, *J* 35.0 Hz, COCF₃), 149.4 (C5'), 148.7 (C4'), 148.6 (C7), 148.0 (C6), 132.3 (C1'), 126.7 (C4a), 125.2 (C8a), 121.7 (CH-6'), 114.0 (q, *J* 241.2 Hz, COCF₃), 113.2 (CH-3'), 111.3 (CH-5), 110.4 (CH-8), 89.9 (C2'), 56.3 (OCH₃-4'), 56.2 (OCH₃-5', OCH₃-6), 56.2 (OCH₃-7), 54.5 (CH-1), 46.6 (CH₂-7'), 40.4 (CH₂-3), 29.0 (CH₂-4).

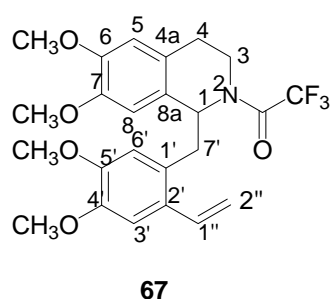
¹³C NMR of the minor rotamer (in part): δ 118.5 (CH-6), 114.5 (CH-3'), 111.6 (CH-5), 110.0 (CH-8), 45.7 (CH₂-7'), 38.0 (CH₂-3), 27.7 (CH₂-4).

MS (ES⁺): *m/z* 565.9 (MH⁺, 25 %). **HRMS (EI⁺):** calcd for C₂₂H₂₃NO₅F₃I, 565.0573 (M⁺). Found 565.0578.

8.2.2. General method for Stille coupling reactions.

To a thick walled tube (sealed tube) containing a solution of the 2'-iodolaudanosine **58**, PdCl₂ and PPh₃ in dry DMF under N₂ was added allyltributylstannane or tributylvinylstannane. The tube was sealed under a N₂ atmosphere and the mixture was stirred and heated at 110 °C for 36 h. The solution was cooled, diluted with DCM and washed with H₂O (4 x) and then brine. The DCM layer was evaporated and the residue was redissolved in CH₃CN and extracted with hexane. The CH₃CN layer was evaporated and the residue was purified by column chromatography (EtOAc: Pet. spirit (1 : 1)) (unless indicated otherwise) to afford the pure products.

(*RS*) 1-(2'-Ethenyl-4',5'-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**67**).



The 2'-iodolaudanosine derivative **58** (492 mg, 0.870 mmol), Pd(OAc)₂ (16 mg, 0.071 mmol), PPh₃ (43 mg, 0.174 mmol) and tributylvinylstannane (333 mg, 1.04 mmol, 0.29 mL) in dry DMF (10 mL) under N₂ was treated as described above using the general Stille coupling reaction conditions to afford a residue which was purified by column chromatography to afford **67** (352 mg, 87 %) as a yellow solid. The yellow solid was recrystallised from EtOAc : Pet. spirit (1 : 1) and its structure was confirmed by X-ray structural analysis. Compound **67** was a 95 : 5 mixture of rotamers.

R_f. 0.48 (EtOAc: Pet. spirit (1 : 1)).

m.p. 132-134 °C.

¹H NMR of the major rotamer (500 MHz): δ 6.97 (s, 1H, H3'), 6.81 (dd, 1H, *J* 17.0, 11.0 Hz, H1''), 6.56 (s, 1H, H8), 6.39 (s, 1H, H5), 6.08 (s, 1H, H6'), 5.50 (t, 1H, *J* 7.0

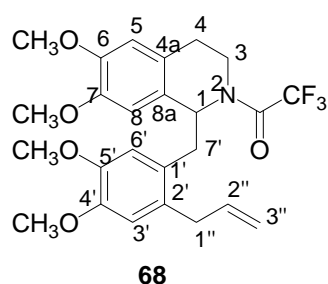
Hz, H1), 5.46 (d, 1H, *J* 17.0 Hz, H2''(*E*)), 5.13 (d, 1H, *J* 11.0 Hz, H2''(*Z*)), 3.87 (dt, 1H, *J* 9.0, 4.0 Hz, H3), 3.87 (s, 3H, OCH₃-4'), 3.82 (s, 3H, OCH₃-6), 3.70 (s, 3H, OCH₃-7), 3.63 (m, 1H, H3), 3.57 (s, 3H, OCH₃-5'), 3.16 (d, 2H, *J* 7.0 Hz, H7'), 2.89 (m, 1H, H4), 2.71 (m, 1H, H4).

¹H NMR of the minor rotamer (in part): δ 6.57 (s, 1H, H8), 6.41 (s, 1H, H5), 5.84 (s, 1H, H6'), 3.84 (s, 3H, OCH₃-4'), 3.84 (s, 3H, OCH₃-6), 3.78 (s, 3H, OCH₃-7), 3.51 (s, 3H, OCH₃-5').

¹³C NMR of the major rotamer (125 MHz): (signals for COCF₃ and COCF₃ were not observed), δ 148.8 (C4'), 148.5 (C6), 148.3 (C7), 147.6 (C5'), 133.9 (CH-1''), 130.4 (C2'), 127.3 (C4a), 126.4 (C8a), 125.4 (C1'), 114.5 (CH₂-2''), 114.1 (CH-3'), 111.2 (CH-5), 111.0 (CH-8), 108.5 (CH-6'), 56.2 (OCH₃-4'), 56.2 (OCH₃-6), 56.1 (OCH₃-7), 56.0 (OCH₃-5'), 55.6 (CH-1), 41.0 (CH₂-3), 38.2 (CH₂-7'), 28.7 (CH₂-4).

MS (ES⁺): *m/z* 466.1 (MH⁺, 50 %). **HRMS (EI⁺):** calcd for C₂₄H₂₆NO₅F₃, 465.1763 (M⁺). Found 465.1762.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-(4',5'-dimethoxy-2'-(2''-propenyl)-phenyl)methyl-6,7-dimethoxyisoquinoline (68).



The 2'-iodolaudanidine derivative **58** (711 mg, 1.26 mmol), Pd(OAc)₂ (23 mg, 0.102 mmol), PPh₃ (61 mg, 0.232 mmol), allyltributylstannane (499 mg, 1.51 mmol, 0.46 mL) and dry DMF (5 mL) under N₂ was treated as described above using the general Stille coupling reaction conditions to afford an oil which was purified by column chromatography to give **68** (536 mg, 89 %) as a white solid. Compound **68** was recrystallised from diethyl ether and its structure was confirmed by X-ray structural analysis. Compound **68** was a 95 : 5 mixture of rotamers.

R_f 0.63 (EtOAc : Pet. spirit (1 : 1)).

m.p. 140-144 °C.

¹H NMR of the major rotamer: δ 6.62 (s, 1H, H3'), 6.58 (s, 1H, H5), 6.53 (s, 1H, H6'), 6.00 (s, 1H, H8), 5.82 (m, 1H, H2''), 5.49 (dd, *J* 8.1, 6.0 Hz, 1H, H1), 5.02 (dd, 1H, *J* 10.2, 0.9 Hz, H3''(Z)), 4.94 (dd, 1H, *J* 17.2, 0.9 Hz, H3''(E)), 3.85 (s, 3H, OCH₃-4'), 3.84 (s, 3H, OCH₃-6), 3.96 (m, 1H, H3), 3.76 (s, 3H, OCH₃-7), 3.69 (m, 1H, H3), 3.56 (s, 3H, OCH₃-5'), 3.12 (dd, 2H, *J* 4.8, 1.5 Hz, H1''), 3.04 (d, 1H, *J* 6.0 Hz, H7'), 3.03 (d, 1H, *J* 8.1 Hz, H7'), 2.90 (m, 1H, H4), 2.77 (m, 1H, H4).

¹H NMR of the minor rotamer (in part): δ 6.55 (s, 1H, H8), 3.80 (s, 3H, OCH₃-6), 3.49 (s, 3H, OCH₃-5')

¹³C NMR of the major rotamer: (signals for COCF₃ and COCF₃ were not observed), δ 148.4 (C4'), 148.1 (C6), 147.4 (C7), 147.4 (C5'), 137.5 (CH-2''), 131.2 (C2'), 127.4 (C4a), 126.6 (C8a), 125.1 (C1'), 115.9 (CH₂-3''), 114.2 (CH-3'), 113.1 (CH-5), 111.2 (CH-8), 110.9 (CH-6'), 56.2 (OCH₃-4'), 56.1 (OCH₃-6), 55.8 (OCH₃-7, OCH₃-5'), 55.6 (CH-1), 40.8 (CH₂-3), 39.1 (CH₂-1''), 36.7 (CH₂-7'), 28.7 (CH₂-4).

¹³C NMR of the minor rotamer (in part): δ 114.9 (CH-3'), 113.8 (CH-5), 111.5 (CH-8), 111.4 (CH-6'), 27.4 (CH₂-4).

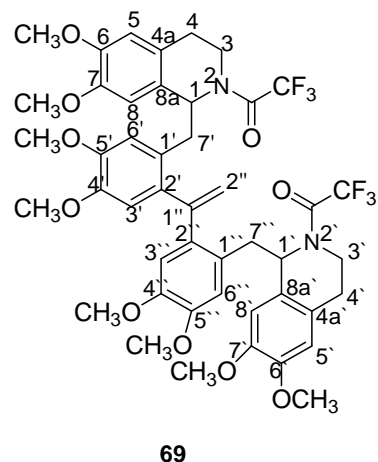
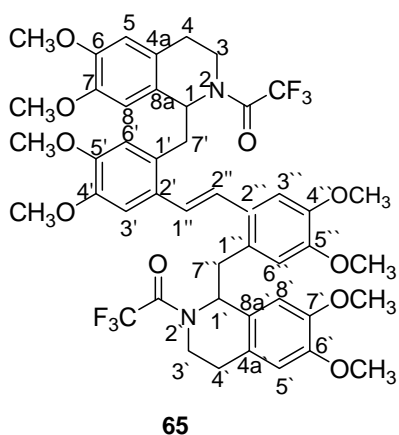
MS (CI⁺): *m/z* 480 (MH⁺, 100 %). **HRMS (CI⁺):** calcd for C₂₅H₂₉NO₅F₃, 480.1998 (MH⁺). Found 480.2000.

8.2.3. General method for Heck coupling reactions.

A mixture of palladium acetate, *N,N*-dimethylglycine (DMG), sodium acetate and both coupling partners were placed in a thick walled tube (sealed tube) under N₂. Dry *N*-methylpyrrolidinone (NMP) was added and the reaction mixture was bubbled with argon prior to sealing the tube. The reaction mixture was heated at 130 °C for 18 h. The reaction mixture was cooled and then diluted with DCM and the solution was

washed with H₂O (3 x), brine and dried (MgSO₄). The solution was evaporated to give a dark oil that was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) (unless otherwise stated) to give the desired product.

(1*RS*, 1'*RS*) and (*R*, *S*) (*E*) 2',2''-(1'',2''-Ethenediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (65) and **(1*RS*, 1'*RS*) and (*R*, *S*) (*E*) 2',2''-(1'',1''-Ethenediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (69).**



The 2'-iodolaudanidine derivative **58** (203 mg, 0.354 mmol), the 2'-vinyllaudanidine derivative **67** (166 mg, 0.354 mmol), Pd(OAc)₂ (8 mg, 0.035 mmol), DMG (73 mg, 0.708 mmol), NaOAc (56 mg, 0.708 mmol) and dry NMP (5 mL) under N₂ were treated as described above in the general Heck coupling reaction procedure to give a crude mixture. To the mixture was added methanol (5 mL) and the desired product **65** which precipitated out as a white solid (164 mg, 54 %). The regioisomer **69** remained in the solution and was purified by column chromatography (DCM : EtOAc : Pet. spirit (3 : 2 : 3)) to give **69** (36 mg, 12 %) as a yellow oil. Compound **65** was a 55 : 45 mixture of diastereomers. Compound **69** was a 60 : 40 mixture of diastereomers. A minor rotamer (~ 5 %) was also observed in the ¹H NMR spectra of both **65** and **69**.

Compounds **65** and **69** were also prepared according to the conditions outlined in Table 2.2 under, essentially, the same conditions using the quantities of catalyst, base and additives shown in the Table.

A small amount of (*S,S*)-**65** (13 mg, 15 %) was obtained under the same Heck coupling reaction conditions using a mixture of (*S*)-**67** (60 mg, 0.105 mmol) and (*S*)-**58** (80 mg, 0.171 mmol), Pd(OAc)₂ (3 mg, 0.013 mmol), DMG (27 mg, 0.258 mmol), NaOAc (21 mg, 0.258 mmol) and NMP (2 mL). A mixture of (*S*)-**67** and (*S*)-**58** (67 mg) was also recovered. (*S,S*)-**69** was also observed in the reaction, however, not in significant quantity or purity.

Stilbene **65**.

R_f. 0.31 (DCM : EtOAc : Pet. spirit (3 : 2 : 3)).

(*S,S*)-**65**: $[\alpha]_{\text{D}}^{25} + 29$ (0.84, CHCl₃).

m.p. (*meso*-**65** and *rac*-**65**) 226-228 °C.

¹H NMR of the major diastereomer, *meso*-65: δ 7.58 (s, 4H, CH=CH, H3', H3''), 6.58 (s, 2H, H5, H5''), 6.05 (s, 2H, H6', H6''), 5.91 (s, 2H, H8, H8''), 5.47 (dd, 2H, *J* 9.5, 5.4 Hz, H1, H1''), 4.05 (s, 6H, OCH₃-5', OCH₃-5''), 3.85 (dd, 2H, *J* 8.1, 3.9 Hz, H3, H3'), 3.81 (s, 6H, OCH₃-4', OCH₃-4''), 3.69 (m, 2H, H3, H3'), 3.57 (s, 6H, OCH₃-6, OCH₃-6'), 3.53 (t, 2H, *J* 13.2, 5.4 Hz, H7', H7''), 3.47 (s, 6H, OCH₃-7, OCH₃-7'), 2.99 (dd, 2H, *J* 13.2, 9.5 Hz, H7', H7''), 2.87 (m, 2H, H4, H4'), 2.78 (m, 2H, H4, H4').

¹H NMR of the minor rotamer of *meso*-65 (in part): δ 7.45 (s, 2H, H3', H3''), 7.53 (s, 2H, CH=CH), 5.79 (s, 2H, H8, H8''), 6.48 (s, 2H, H5, H5'). 3.76 (s, 6H, OCH₃-5', OCH₃-5''), 3.71 (s, 6H, OCH₃-4', OCH₃-4''), 3.60 (s, 6H, OCH₃-6, OCH₃-6'), 3.42 (s, 6H, OCH₃-7, OCH₃-7').

¹³C NMR of the major diastereomer, *meso*-65: δ 156.1 (q, *J* 35.5 Hz, COCF₃), 148.9 (C5', C5''), 148.3 (C4', C4''), 148.2 (C6, C6'), 147.1 (C7, C7'), 130.0 (C1', C1''),

127.1 (C2', C2''), 126.1 (C4a, C4a'), 125.5 (C8a, C8a'), 125.0 ($\underline{\text{CH}}=\underline{\text{CH}}$), 115.2 (CH-6', CH-6''), 113.5 (q, J 270.1 Hz, $\text{CO}\underline{\text{C}}\text{F}_3$), 111.9 (CH-8, CH-8'), 111.1 (CH-5, CH-5'), 108.5 (CH-3', CH-3''), 56.1 ($\text{O}\underline{\text{CH}}_3\text{-4'}$, $\text{O}\underline{\text{CH}}_3\text{-4''}$, $\text{O}\underline{\text{CH}}_3\text{-6}$, $\text{O}\underline{\text{CH}}_3\text{-6'}$, $\text{O}\underline{\text{CH}}_3\text{-7}$, $\text{O}\underline{\text{CH}}_3\text{-7'}$), 55.8 ($\text{O}\underline{\text{CH}}_3\text{-5'}$, $\text{O}\underline{\text{CH}}_3\text{-5''}$), 55.5 (CH-1, CH-1'), 41.4 (CH₂-3, CH-3'), 38.9 (CH₂-7', CH₂-7''), 28.6 (CH₂-4, CH₂-4').

¹H NMR of the minor diastereomer, *rac*-65: δ 7.56 (s, 2H, $\underline{\text{CH}}=\underline{\text{CH}}$), 7.51 (s, 2H, H3', H3''), 6.54 (s, 2H, H5, H5'), 6.09 (s, 2H, H6', H6''), 5.80 (s, 2H, H8, H8'), 5.43 (dd, 2H, J 10.5, 3.3 Hz, H1, H1'), 3.99 (s, 6H, $\text{OCH}_3\text{-5'}$, $\text{OCH}_3\text{-5''}$), 3.80 (m, 2H, H3, H3'), 3.76 (s, 6H, $\text{OCH}_3\text{-4'}$, $\text{OCH}_3\text{-4''}$), 3.60 (s, $\text{OCH}_3\text{-6}$, $\text{OCH}_3\text{-6'}$), 3.49 (m, 2H, H3', H3''), 3.42 (s, $\text{OCH}_3\text{-7}$, $\text{OCH}_3\text{-7'}$), 3.38 (m, 2H, H7', H7''), 2.93 (dd, 2H, J 13.2, 10.5 Hz, H7', H7''), 2.91 (m, 2H, H4, H4'), 2.86 (m, 2H, H4, H4').

¹³C NMR of the minor diastereomer, *rac*-65: δ 156.1 (q, J 35.5 Hz, $\underline{\text{CO}}\text{CF}_3$), 148.9 (C5', C5''), 148.3 (C4', C4''), 148.2 (C6, C6'), 147.1 (C7, C7'), 130.0 (C1', C1''), 127.1 (C2', C2''), 126.1 (C4a, C4a'), 125.5 (C8a, C8a'), 125.0 ($\underline{\text{CH}}=\underline{\text{CH}}$), 115.2 (CH-6', CH-6''), 113.5 (q, J 270.1 Hz, $\text{CO}\underline{\text{C}}\text{F}_3$), 111.9 (CH-8, CH-8'), 111.1 (CH-5, CH-5'), 108.5 (CH-3', CH-3''), 56.1 ($\text{O}\underline{\text{CH}}_3\text{-4'}$, $\text{O}\underline{\text{CH}}_3\text{-4''}$, $\text{O}\underline{\text{CH}}_3\text{-6}$, $\text{O}\underline{\text{CH}}_3\text{-6'}$, $\text{O}\underline{\text{CH}}_3\text{-7}$, $\text{O}\underline{\text{CH}}_3\text{-7'}$), 55.8 ($\text{O}\underline{\text{CH}}_3\text{-5'}$, $\text{O}\underline{\text{CH}}_3\text{-5''}$), 55.5 (CH-1, CH-1'), 41.4 (CH₂-3, CH-3'), 38.9 (CH₂-7', CH₂-7''), 28.6 (CH₂-4, CH₂-4').

MS (ES⁺): m/z 925.1 (M+Na⁺, 100 %). **HRMS (ES⁺):** calculated for C₄₆H₄₉N₂O₁₀F₆, 903.3291 (MH⁺). Found 903.3251.

Regioisomer 69.

R_f 0.25 (DCM : EtOAc : Pet. spirit (3 : 2 : 3)).

¹H NMR of the major diastereomer, *rac*-69: δ 6.61 (s, 2H, H3', H3''), 6.52 (s, 4H, H5, H5', H6', H6''), 5.94 (s, 2H, H8, H8'), 5.39 (t, 2H, J 7.5 Hz, H1, H1'), 4.95 (s, 2H, C= $\underline{\text{CH}}_2$), 3.84 (s, 6H, $\text{OCH}_3\text{-5'}$, $\text{OCH}_3\text{-5''}$), 3.82 (s, 6H, $\text{OCH}_3\text{-4'}$, $\text{OCH}_3\text{-4''}$), 3.74 (s,

6H, OCH₃-6, OCH₃-6'), 3.73 (m, 2H, H3, H3'), 3.56 (s, 6H, OCH₃-7, OCH₃-7'), 3.22 (m 2H, H3, H3'), 2.82 (m, 4H, H7', H7'', H4, H4'), 2.65 (m, 4H, H7', H7'', H4, H4').

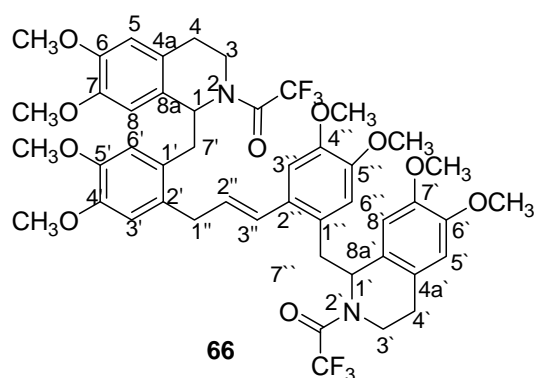
¹H NMR of the minor diastereomer, *meso*-69 (in part): δ 6.65 (s, 2H, H3', H3''), 6.56 (s, 2H, H5, H5'), 5.92 (s, 2H, H8, H8'), 5.49 (s, 2H, H1, H1'), 4.78 (s, 2H, C=CH₂), 3.79 (s, 6H, OCH₃-5', OCH₃-5''), 3.78 (s, 6H, OCH₃-4', OCH₃-4''), 3.76 (s, 6H, OCH₃-6, OCH₃-6'), 3.51 (s, 6H, OCH₃-7, OCH₃-7').

¹³C NMR of the major diastereomer, *rac*-69: δ 155.9 (q, *J* 35.0 Hz, COCF₃), 148.6 (C4', C4''), 148.5 (C6, C6'), 147.9 (C5', C5''), 147.8 (C7, C7'), 135.7 (C=CH₂), 127.4 (C1', C1'', C2', C2''), 126.9 (C4a, C4a'), 125.0 (C8a, C8a'), 120.8 (C=CH₂), 114.1 (CH-3', CH-3''), 113.8 (CH-5, CH-5'), 112.5 (q, *J* 224.8 Hz, COCF₃), 111.2 (CH-6, CH-6'), 110.4 (CH-8, CH-8'), 56.2 (OCH₃-4', OCH₃-4''), 56.2 (OCH₃-6, OCH₃-6'), 56.1 (OCH₃-5', OCH₃-5''), 55.7 (OCH₃-7, OCH₃-7'), 55.4 (CH-1, CH-1'), 41.4 (CH₂-3, CH₂-3'), 38.1 (CH₂-7', CH₂-7''), 28.8 (CH₂-4, CH₂-4').

¹³C NMR of the minor diastereomer, *meso*-69 (in part): δ 135.8 (C=CH₂), 127.3 (C1', C1'', C2', C2''), 124.8 (C8a, C8a'), 120.5 (C=CH₂), 38.0 (CH₂-7', CH₂-7'').

MS (ES⁺): *m/z* 925.0 (M+Na⁺, 20 %). **HRMS (ES⁺):** calculated for C₄₆H₄₉N₂O₁₀F₆, 903.3291 (MH⁺). Found 903.3315.

(1*RS*, 1'*RS*) and (*R*, *S*) (*E*) 2',2''-(1'',3''-Prop-2''-enediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (66).



The 2'-iodolaudanosiine derivative **58** (255 mg, 0.462 mmol), the 2'-allyllaudanosiine derivative **68** (232 mg, 0.462 mmol), Pd(OAc)₂ (12 mg, 0.046 mmol), DMG (95

mg, 0.927 mmol), NaOAc (73 mg, 0.927 mmol) and dry NMP (5 mL) were treated as described above using the general Heck coupling reaction procedure to give a dark oil. The oil was purified by column chromatography to give the desired product **66** (199 mg, 48 %) as a yellow solid. Product **66** was a 60 : 40 mixture of diastereomers and a minor rotamer (~ 5 %) was also observed in the ^1H NMR spectrum.

R_f. 0.19 (EtOAc : Pet. spirit. (1 : 1)).

m.p. 102-104 $^{\circ}\text{C}$

^1H NMR of the major diastereomer: δ 6.86 (s, 1H, H3''), 6.68 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.53 (s, 1H, H5'), 6.48 (s, 1H, H6'), 6.42 (d, 1H, J 14.1 Hz, H3''), 6.37 (s, 1H, H6''), 5.97 (s, 2H, H8, H8'), 5.95 (m, 1H, H2''), 5.47 (dd, 2H, J 8.7, 5.7 Hz, H1, H1'), 3.88 (m, 2H, H3, H3'), 3.79 (s, 12H, OCH₃-6, OCH₃-6', OCH₃-4', OCH₃-4''), 3.53 (m, 2H, H3, H3'), 3.70 (s, 6H, OCH₃-7, OCH₃-7'), 3.48 (s, 6H, OCH₃-5', OCH₃-5''), 3.20 (m, 2H, H1''), 3.05 (m, 4H, H7', H7''), 2.80 (m, 2H, H4, H4'), 2.68 (m, 2H, H4, H4').

^1H NMR of the minor diastereomer (in part): δ 6.85 (s, 1H, H3''), 6.67 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.53 (s, 1H, H5'), 6.47 (s, 1H, H6'), 6.42 (d, 1H, J 14.1 Hz, H3''), 6.36 (s, 1H, H6''), 6.00 (s, 1H, H8), 5.92 (s, 1H, H8'), 5.43 (dd, 2H, J 8.7, 5.7 Hz, H1, H1'), 3.74 (s, 12H, OCH₃-6, OCH₃-6', OCH₃-4', OCH₃-4''), 3.66 (s, 6H, OCH₃-7, OCH₃-7'), 3.46 (s, 6H, OCH₃-5', OCH₃-5'').

^{13}C NMR of the major diastereomer: δ 155.9 (q, J 36.1 Hz, COCF₃), 148.2 (C6, C6'), 148.1 (C4', C4''), 147.3 (C5', C5''), 147.1 (C7, C7'), 131.5 (C1''), 129.8 (C1'), 129.5 (CH-3''), 127.5 (CH-2''), 127.1 (C2''), 126.5 (C2'), 126.2 (C4a'), 126.0 (C4a), 125.1 (C8a'), 125.0 (C8a), 114.1 (q, J 286.5 Hz, COCF₃), 114.0 (CH-6'), 133.8 (CH-6''), 113.0 (CH-3'), 110.9 (CH-5, CH-5'), 110.6 (CH-8, CH-8'), 108.5 (CH-3''), 55.8 (8 x

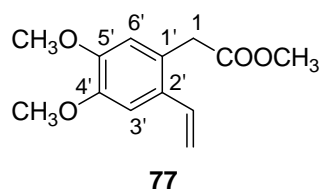
OCH₃), 55.3 (CH-1, CH-1'), 40.6 (CH₂-3, CH₂-3'), 38.0 (CH₂-7', CH₂-7''), 36.0 (CH₂-1''), 28.4 (CH₂-4, CH₂-4').

¹³C NMR of the minor diastereomer (in part): δ 148.1 (C6, C6'), 147.9 (C4', C4''), 147.1 (C5', C5''), 147.0 (C7, C7'), 131.5 (C1''), 129.8 (C1'), 129.7 (CH-3''), 127.6 (CH-2''), 127.2 (C2''), 126.5 (C2'), 126.3 (C4a'), 126.0 (C4a), 125.1 (C8a'), 125.0 (C8a), 114.0 (CH-6'), 133.7 (CH-6''), 113.1 (CH-3'), 110.8 (CH-5, CH-5'), 110.7 (CH-8, CH-8'), 108.4 (CH-3''), 40.6 (CH₂-3, CH₂-3'), 37.9 (CH₂-7', CH₂-7''), 36.1 (CH₂-1''), 28.5 (CH₂-4, CH₂-4').

MS (ES⁺) *m/z* 916.72 (MH⁺, 10 %), *m/z* 954.74 (M+K⁺, 100 %). **HRMS (ES⁺)** calcd for C₄₇H₅₁N₂O₁₀F₆, 917.3448 (MH⁺). Found 917.3451.

8.2.4. Trial Heck coupling reaction with a less hindered alkene.

Methyl 2'-ethenyl-3',4'-dimethoxyphenylacetate (**77**).



To sealed tube containing a mixture of methyl 2-bromo-3,4-dimethoxyphenylacetate **76** (754 mg, 2.59 mmol), PdCl₂ (39 mg, 0.259 mmol) and PPh₃ (123 mg, 0.518 mmol) in dry DMF (6 mL) was added tributylvinylstannane (980 mg, 3.11 mmol, 0.9 mL) under a N₂ atmosphere. The reaction mixture was stirred and heated at 110 °C for 24 h. The reaction was worked up using a similar method to that described for the synthesis of **67** to give an oil. The oil was purified by column chromatography (EtOAc : Pet spirit (1 : 1)) to give **77** (251 mg, 41 %) as a yellow oil.

R_f. 0.71 (EtOAc : Pet.spirit (1 : 1)).

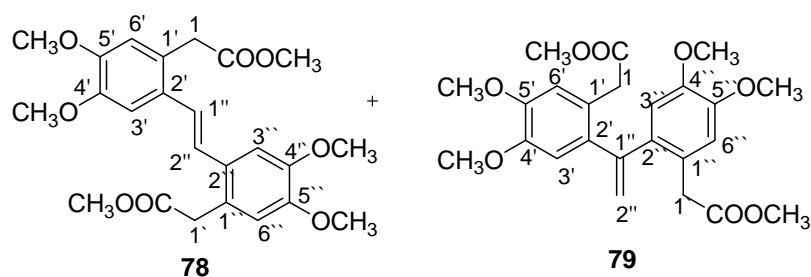
¹H NMR: δ 7.00 (s, 1H, H3'), 6.83 (dd, 1H, *J* 17.4, 10.8 Hz, CH=CH₂), 6.78 (s, 1H, H6'), 5.54 (dd, 1H, *J* 17.4, 1.2 Hz, CH=CH₂(*E*)), 5.22 (dd, 1H, *J* 10.8, 1.2 Hz, CH=CH₂(*Z*)), 3.87 (s, 3H, OCH₃-4'), 3.85(s, 3H, OCH₃-5'), 3.65 (s, 3H, COOCH₃), 3.62 (s, 2H, H1).

^{13}C NMR: δ 171.9 (COOCH_3), 148.7 ($\text{C4}'$), 148.3 ($\text{C5}'$), 133.7 (CH=CH_2), 129.7 ($\text{C2}'$), 124.1 ($\text{C1}'$), 114.4 (CH=CH_2), 113.4 ($\text{CH-6}'$), 108.6 ($\text{CH-3}'$), 55.9 (2 x OCH_3), 51.9 (COOCH_3), 38.2 ($\text{CH}_2\text{-1}$).

MS (ES^+): m/z 237 (MH^+ , 100 %). **HR (EI^+):** calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$, 236.1049 (M^+).

Found 236.1045.

Dimethyl 2',2'-(1'',2''-eth-(*E*)-enediyl)-bis-[4',5'-dimethoxyphenyl]acetate (78**)**
and **dimethyl 2',2'-(1'',1''-eth-(*E*)-enediyl)-bis-[4',5'-dimethoxyphenyl]acetate (**79**).**



To a sealed tube containing a mixture of methyl 2-bromo-3,4-dimethoxyphenylacetate **76** (223 mg, 0.66 mmol), methyl 2-ethenyl-3,4-dimethoxyphenylacetate **77** (235 mg, 0.990 mmol), $\text{Pd}(\text{OAc})_2$ (23 mg, 0.099 mmol) and PPh_3 (47 mg, 0.199 mmol) in dry CH_3CN (4 mL) was added triethylamine (301 mg, 2.97 mmol) under a N_2 atmosphere. The mixture was bubbled with argon prior to sealing the tube. The reaction mixture was stirred and heated at 110°C for 24 h. The mixture was diluted with DCM, washed with H_2O (3 x), and then brine and the DCM layer was dried (MgSO_4) and evaporated to give a dark oil. The oil was purified by column chromatography (EtOAc : Pet. Spirit (1 : 1)) to give **78** (92 mg, 31 %) and **79** (61 mg, 21 %) as yellow oils. A mixture of **76** and **77** (225 mg) was also recovered and they could not be separated.

Stilbene 78.

R_f 0.45 (EtOAc : Pet. spirit (1 : 1)).

¹H NMR: δ 7.11 (s, 2H, CH=CH), 7.07 (s, 2H, H3', H3''), 6.75 (s, 2H, H6', H6''), 3.94 (s, 6H, OCH₃-4', OCH₃-4''), 3.89 (s, 6H, OCH₃-5', OCH₃-5''), 3.71 (s, 4H, H1, H1'), 3.70 (s, 6H, 2 x COOCH₃).

¹³C NMR: δ 172.3 (COOCH₃), 148.9 (C4', C4''), 148.6 (C5', C5''), 129.9 (C2', C2''), 126.8 (CH=CH), 124.7 (C1', C1''), 113.8 (CH-6', CH-6''), 109.1 (CH-3', CH-3''), 56.2 (4 x OCH₃), 52.4 (2 x COOCH₃), 39.0 (CH₂-1, CH₂-1').

Regioisomer 79.

R_f 0.34 (EtOAc: Pet. Spirit (1 : 1)).

¹H NMR: δ 6.72 (s, 2H, H3', H3''), 6.70 (s, 2H, H6', H6''), 5.40 (s, 2H, C=CH₂), 3.85 (s, 6H, OCH₃-4', OCH₃-4''), 3.80 (s, 6H, OCH₃-5', OCH₃-5''), 3.58 (s, 4H, H1, H1'), 3.52 (s, 6H, 2 x COOCH₃).

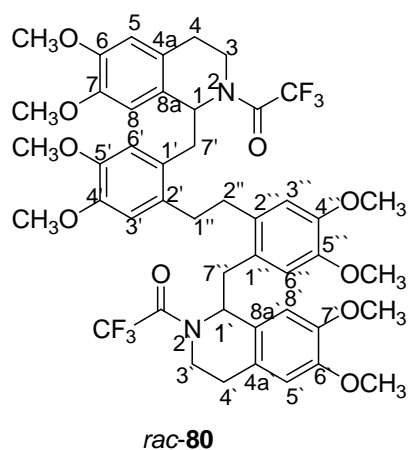
¹³C NMR: δ 172.3 (COOCH₃), 148.5 (OCH₃-4', OCH₃-4''), 148.0 (OCH₃-5', OCH₃-5''), 135.0 (C1', C1'', C=CH₂), 124.2 (C2', C2''), 120.0 (C=CH₂), 114.0 (CH-6', CH-6''), 113.8 (CH-3', CH-3''), 56.1 (4 x OCH₃), 52.0 (2 x COOCH₃), 38.4 (CH₂-1, CH₂-1').

MS (CI⁺): *m/z* 445 (MH⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₄H₂₉O₈, 445.1862 (MH⁺).

Found 445.1887.

8.2.5. Hydrogenation reactions.

(1*RS*, 1'*RS*) and (R,S) 2',2''-(1'',2''-Ethanediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (80).



To a solution of alkene **65** (73 mg, 0.083 mmol) in acetone (80 mL) was added 10 % Pd/C (10 mg) in a round bottom flask sealed with a suba seal. The flask was purged with nitrogen and then a hydrogen filled

balloon was secured on top of the flask, allowing the hydrogen to circulate inside the flask. The reaction mixture was stirred at RT for 3 d under a H₂ atmosphere. Nitrogen was then bubbled into the solution for 2 min before then Pd/C was filtered. The filtrate was evaporated to give a mixture of *rac*-**80** and *meso*-**65**. Purification by column chromatography (DCM : EtOAc : Pet. spirit (3 : 2 : 3)) gave pure *rac*-**80** (26 mg, 35 %) a yellow oil and pure *meso*-**65** (22 mg, 30 %).

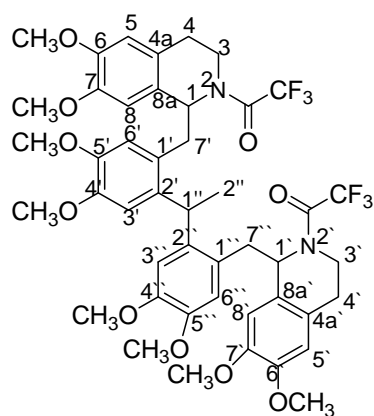
R_f. 0.39 (DCM : EtOAc : Pet. spirit (3 : 2 : 3)).

¹H NMR: δ 6.62 (s, 2H, H3', H3''), 6.57 (s, 2H, H5, H5''), 6.30 (s, 2H, H6', H6''), 5.90 (s, 2H, H8, H8''), 5.40 (dd, 2H, *J* 8.4, 5.1 Hz, H1, H1''), 3.98 (m, 2H, H3, H3'), 3.82 (s, 6H, OCH₃-4', OCH₃-4''), 3.79 (s, 2H, OCH₃-5', OCH₃-5''), 3.66 (s, 2H, OCH₃-6, OCH₃-6'), 3.59 (m, 2H, H3, H3'), 3.48 (s, 6H, OCH₃-7, OCH₃-7'), 2.94 (dd, 2H, *J* 13.5, 5.1 Hz, H7', H7''), 2.82 (s, 4H, H1'', H2''), 2.81 (dd, 2H, *J* 13.5, 8.4 Hz, H7', H7''), 2.72 (m, 4H, H4, H4').

¹³C NMR: (signals for COCF₃ and COCF₃ were not observed), δ 148.1 (C4', C4''), 147.8 (C6, C6'), 147.0 (C5', C5''), 146.8 (C7, C7'), 132.7 (C2', C2''), 126.8 (C1', C1''), 126.1 (C4a, C4a'), 124.9 (C8a, C8a'), 114.2 (CH-6', CH-6''), 112.9 (CH-3', CH-3''), 110.9 (CH-5, CH-5'), 110.8 (CH-8, CH-8'), 55.8 (8 x OCH₃), 55.5 (C1, C1'), 40.7 (CH₂-3, CH₂-3'), 38.0 (CH₂-7', CH₂-7''), 33.5 (CH₂-1'', CH₂-2''), 29.0 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 905.1 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₄₆H₅₁N₂O₁₀F₆, 905.3448 (MH⁺). Found 905.3411.

Attempted synthesis of (1*RS*, 1'*RS*) and (*R,S*) 2',2''-(1'',1''-Ethanediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (81).



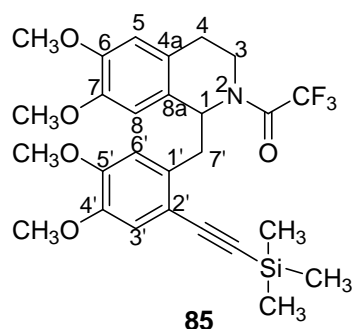
81

To a solution of alkene **69** (64 mg, 0.073 mmol) in ethyl acetate (2 mL) was added 10 % Pd/C (10 mg) in a round bottom flask sealed with a suba seal. The flask was purged with nitrogen and then a hydrogen filled balloon was secured on top of the flask, allowing the hydrogen to circulate inside the flask. The reaction mixture was stirred at RT for 3 d under a H₂ atmosphere. Nitrogen

was then bubbled into the solution for 2 min before then Pd/C was filtered. The filtrate was evaporated to give a yellow oil. TLC and NMR analysis of the yellow oil indicated only unreacted starting material (**69**).

8.2.6. Sonagashira coupling Reactions.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(trimethylsilylethynyl)phenyl)methylisoquinoline (85).



85

Compound **58** (300 mg, 0.530 mmol), PdCl₂ (5 mg, 0.027 mmol), PPh₃ (14 mg, 0.053 mmol) and CuI (10 mg, 0.053 mmol) were added to a dry flask under a N₂ atmosphere. Dry THF (45 mL) was added followed by the addition of Et₃N (80 mg, 0.795 mmol, 0.11 mL). The solution was

stirred for 5 min before TMS-acetylene (78 mg, 0.795 mmol, 0.11 mL) was added. The reaction was stirred at RT for 4 d. The solvent was evaporated and the crude mixture was purified by column chromatography (DCM : EtOAc : Pet. spirit (3 : 1 : 3)) to give **85** (266 mg, 92 %) as a brown solid. Compound **85** was a 95 : 5 mixture of rotamers.

R_f 0.77 (DCM : EtOAc : Pet. spirit (3 : 1: 3)).

m.p. 114-118 °C.

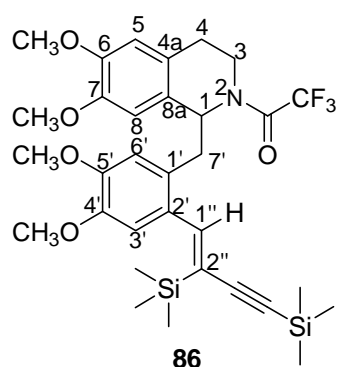
¹H NMR of the major rotamer: δ 6.85 (s, 1H, H3'), 6.65 (s, 1H, H6'), 6.56 (s, 1H, H5), 6.33 (s, 1H, H8), 5.66 (t, 1H, *J* 7.2, 6.9 Hz, H1), 3.93 (dt, 1H, *J* 12.0, 4.5 Hz, H3), 3.82 (s, 6H, OCH₃-4' and OCH₃-5'), 3.78 (s, 3H, OCH₃-6), 3.69 (s, 3H, OCH₃-7), 3.63 (dt, 1H, *J* 11.7, 4.5 Hz, H3), 3.42 (dd, 1H, *J* 13.5, 6.9 Hz, H7'), 3.13 (dd, 1H, *J* 13.5, 7.2 Hz, H7'), 2.90 (m, 1H, H4), 2.70 (m, 1H, H4), 0.16 (s, 9H, Si(CH₃)₃).

¹³C NMR of the major rotamer: δ 155.4 (q, *J* 34.3 Hz, C=O), 149.4 (C4'), 148.3 (C5'), 147.6 (C6), 147.5 (C7), 132.5 (C2'), 126.8 (C1'), 124.9 (C4a), 115.7 (C8a), 114.6 (CH-3'), 114.5 (q, *J* 204.9 Hz, C=O), 112.3 (CH-6'), 111.1 (CH-5), 110.4 (CH-8), 103.7 (ArC≡CSi(CH₃)₃), 95.9 (CSi(CH₃)₃), 56.0 (OCH₃-4'), 55.9 (OCH₃-5', OCH₃-6 and OCH₃-7), 54.7 (CH-1), 40.3 (CH₂-3), 39.5 (CH₂-7'), 28.7 (CH₂-4), 0.1 (Si(CH₃)₃).

¹³C NMR of the minor rotamer (in part): δ 40.7 (CH₂-3), 37.9 (CH₂-7'), 27.3 (CH₂-4).

MS (CI⁺): *m/z* 536 (MH⁺, 10 %). **HRMS (EI⁺):** calcd for C₂₇H₃₂NO₅F₃Si, 535.2002 (M⁺). Found 535.1984.

(*R,S*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2''-trimethylsilyl-2''-(trimethylsilylethynyl)ethenyl)phenyl)methylisoquinoline (86).



Compound **58** (300 mg, 0.530 mmol), PdCl₂ (4.5 mg, 0.027 mmol), PPh₃ (13.6 mg, 0.053 mmol) and CuI (10 mg, 0.053 mmol) were added to a dry flask under a N₂ atmosphere. Dry THF (45 mL) was added to the mixture followed by the addition of Et₃N (161 mg, 1.59 mmol, 0.11 mL). The solution was stirred for 5 min before TMS-acetylene (158

mg, 1.59 mmol, 0.22 mL) was added. The reaction was stirred at RT for 4 d. The

solvent was evaporated and the crude mixture was purified by column chromatography (DCM : EtOAc : Pet. spirit (3 : 1 : 3)) to give a mixture of **86** (175 mg, 52 %) as a brown oil, and **85** (130 mg, 45 %) as a brown solid.

86.

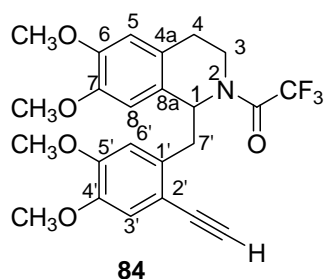
R_f 0.74 (DCM : EtOAc : Pet. spirit (3 : 1: 1)).

¹H NMR: δ 8.15 (s, 1H, H1''), 6.66 (s, 1H, H3'), 6.56 (s, 2H, H6', H5), 5.97 (s, 1H, H8), 5.45 (dd, 1H, *J* 8.4, 5.4 Hz, H1), 3.83 (s, 3H, OCH₃-4'), 3.82 (m, 1H, H3), 3.80 (s, 3H, OCH₃-5'), 3.80 (s, 3H, OCH₃-6), 3.61 (m, 1H, H3), 3.52 (s, 3H, OCH₃-7), 3.18 (dd, 1H, *J* 13.5, 8.4 Hz, H7'), 3.12 (dd, 1H, *J* 13.5, 5.4 Hz, H7'), 2.90 (m, 1H, H4), 2.74 (m, 1H, H4), 0.16 (s, 9H, Si(CH₃)₃), 0.13 (s, 9H, Si(CH₃)₃).

¹³C NMR: (signals for C=O and C≡C were not observed), δ 149.1 (C4'), 148.5 (C5', C6), 147.5 (C7), 141.3 (CH-1''), 129.9 (C2'), 128.7 (C1'), 126.1 (C4a), 125.1 (C8a), 123.2 (C2''), 113.6 (CH-3'), 111.4 (CH-6'), 111.1 (CH-5, CH-8), 110.7 (C≡CSi(CH₃)₃), 106.4 (C≡CSi(CH₃)₃), 56.0 (4 x OCH₃, CH-1), 41.1 (CH₂-3), 37.9 (CH₂-7'), 28.6 (CH₂-4), 0.35 (Si(CH₃)₃), 0.10 (Si(CH₃)₃).

MS (ES⁺): *m/z* 634 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₄H₂₄NO₅F₃, 634.2653 (MH⁺). Found 634.2610.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-ethynylphenyl)methylisoquinoline (**84**).



A mixture of **85** (130 mg, 0.240 mmol) in CH₃OH (2 mL) and H₂O (0.5 mL) was added KF (150 mg, 2.59 mmol). The suspension was stirred at RT for 18 h. The solvent was evaporated and the residue was redissolved in EtOAc. The

reaction mixture was washed with 0.1 M HCl then brine and dried (MgSO₄). The solvent was evaporated to give an oil which was purified by column chromatography

(DCM : EtOAc : Pet. spirit (3 :1: 4)) to give **84** (60 mg, 54 % yield) as a brown oil.

Compound **84** was a 95 : 5 mixture of rotamers.

R_f. 0.38 (DCM : EtOAc : Pet. spirit (3 : 1 : 4)).

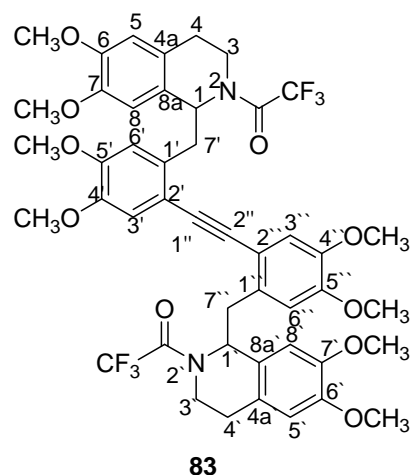
¹H NMR of the major rotamer: δ 6.95 (s, 1H, H3'), 6.59 (s, 1H, H6'), 6.56 (s, 1H, H5), 6.55 (s, 1H, H8), 5.76 (dd, *J* 7.8, 5.7 Hz, H1), 3.98 (dd, 1H, *J* 13.5, 4.8 Hz, H3), 3.86 (s, 6H, OCH₃-4' and OCH₃-5'), 3.75 (s, 6H, OCH₃-6 and OCH₃-7), 3.62 (m, 1H, H3), 3.47 (dd, 1H, *J* 13.8, 5.7, H7'), 3.17 (dd, 1H, *J* 13.8, 7.8 Hz, H7'), 3.16 (s, 1H, ArC≡CH), 2.91 (m, 1H, H4), 2.69 (m, 1H, H4).

¹H NMR of the minor rotamer (in part): δ 6.97 (s, 1H, H3'), 6.61 (s, 1H, H6'), 6.43 (s, 1H, H5), 6.36 (s, 1H, H8).

¹³C NMR of the major rotamer: δ 155.8 (q, *J* 34.3 Hz, COCF₃), 149.7 (C4'), 148.4 (C5'), 147.9 (C6), 147.8 (C7), 133.2 (C2'), 127.1 (C1'), 125.3 (C4a), 115.0 (CH-3'), 114.5 (C8a), 114.0 (q, *J* 225.1 Hz, COCF₃), 112.7 (CH-6'), 111.2 (CH-5), 110.4 (CH-8), 82.6 (ArC≡CH), 79.6 (ArC≡CH), 56.1 (3 x OCH₃), 56.0 (OCH₃-7), 54.8 (CH-1), 40.4 (CH₂-3), 39.8 (CH₂-7'), 28.9 (CH₂-4).

MS (CI⁺): *m/z* 464.1 (MH⁺, 100 %). **HRMS (EI⁺):** calcd for C₂₄H₂₄NO₅F₃, 463.1607 (M⁺). Found 463.1606.

(1*RS*, 1'*RS*) and (R,*S*) 2',2''-(1'',2''-Ethynediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (83).



To a mixture of 2'-iodolaudanidine **58** (144 mg, 0.255 mmol), **84** (118 mg, 0.255 mmol), PdCl₂ (2 mg, 0.0127 mmol), PPh₃ (7 mg, 0.026 mmol) and CuI (5 mg, 0.026 mmol) under a N₂ atmosphere was added distilled THF (10 mL). Et₃N (39 mg, 0.383 mmol,

0.051 mL) was subsequently added and the mixture was stirred at RT for 24 h. The solvent was evaporated and the residue was purified by column chromatography (DCM : CH₃OH : Pet. spirit (3 : 1 : 4)) to give **83** (113 mg, 49 %) as a white solid. Compound **83** was a 95 : 5 mixture of rotamers.

Rf. 0.26 (DCM : CH₃OH : Pet. spirit (3 : 1: 4)).

m.p. 168-172 °C.

¹H NMR of the major rotamer: δ 7.17 (s, 2H, H3', H3''), 6.63 (s, 2H, H6', H6''), 6.58 (s, 2H, H5, H5''), 6.51 (s, 2H, H8, H8''), 5.69 (dd, 2H, *J* 8.0, 6.0 Hz, H1, H1''), 4.02 (bd, 2H, *J* 13.5 Hz, H3, H3'), 3.84 (s, 6H, OCH₃-4', OCH₃-4''), 3.82 (s, 2H, OCH₃-5', OCH₃-5''), 3.76 (s, 2H, OCH₃-6, OCH₃-6'), 3.73 (s, 6H, OCH₃-7, OCH₃-7'), 3.68 (m, 2H, H3, H3'), 3.26 (dd, 2H, *J* 14.1, 6.0 Hz, H7', H7''), 3.13 (dd, 2H, *J* 14.1, 8.0 Hz, H7', H7''), 2.94 (m, 2H, H4, H4'), δ 2.78 (m, 2H, H4, H4').

¹H NMR of the minor rotamer (in part): δ 6.66 (s, 2H, H6', H6''), 6.59 (s, 2H, H5, H5''), 6.50 (s, 2H, H8, H8''), 5.05 (s, 2H, H1, H1').

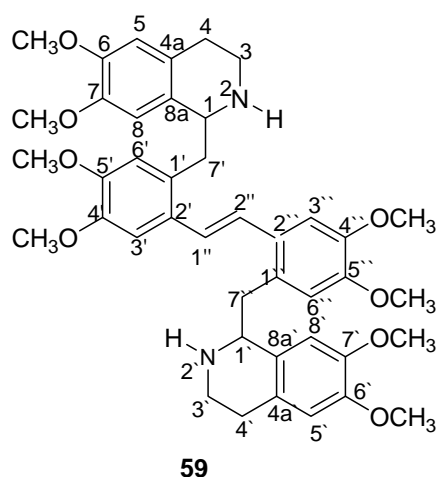
¹³C NMR of the major rotamer: δ 155.5 (q, *J* 38.4 Hz, COCF₃), 150.3 (C4', C4''), 148.5 (C5', C5''), 148.1 (C6, C6'), 147.9 (C7, C7'), 134.5 (C2', C2''), 127.1 (C1', C1''), 125.2 (C4a, C4a'), 118.6 (q, *J* 254.2 Hz, COCF₃), 115.0 (CH-3', CH-3''), 114.1 (C8a, C8a'), 112.6 (CH-6', CH-6''), 111.3 (CH-5, CH-5'), 110.2 (CH-8, CH-8'), 81.1 (ArC≡CAr), 56.2 (OCH₃-4', OCH₃-4''), 56.1 (OCH₃-6, OCH₃-6'), 55.0 (CH-1, CH-1'), 40.2 (CH₂-3, CH₂-3'), 40.1 (CH₂-7', CH₂-7''), 29.0 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 901.3 (MH⁺, 50 %). **HRMS (ES⁺):** calcd for C₄₆H₄₇N₂O₁₀F₆, 901.3135 (MH⁺). Found 901.3066.

8.2.7. General method for *N*-TFA deprotection.

To a solution of the *N*-TFA protected amine in a mixture of CH₃OH and H₂O was added solid K₂CO₃. The reaction mixture was stirred at RT for 18 h. The CH₃OH was evaporated and the residue was dissolved in EtOAc. The solution was washed with H₂O (3 x) and then brine and evaporated to give a yellow oil. The oil was purified by column chromatography (CH₃OH : EtOAc: NH₃ (4 : 6 : 0.1)) (unless stated otherwise) to give the free amine.

(1*RS* and 1'*RS*) and (*R,S*) 2',2''-(1'',2''-Eth-(*E*)-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (59).



The *N*-TFA protected stilbene **65** (108 mg, 0.123 mmol), CH₃OH (5 mL), H₂O (0.6 mL) and K₂CO₃ (89 mg, 0.641 mmol) were treated as described above using the general *N*-TFA deprotection reaction procedure except that the mixture was heated at 80 °C for 3 d to give a yellow oil. The oil was purified by column chromatography to give **59**

(36 mg, 41 %) as a yellow oil. The product **59** was a 55 : 45 mixture of *meso*-**59** and *rac*-**59**.

R_f. 0.07 (CH₃OH : EtOAc (4 : 6)).

¹H NMR of *meso*-59: δ 7.07 (s, 2H, CH=CH), 6.72 (s, 2H, H3', H3''), 6.64 (s, 2H, H6', H6''), 6.57 (s, 2H, H5, H5''), 6.55 (s, 2H, H8, H8''), 4.17 (dd, 2H, *J* 9.0, 4.5 Hz, H1, H1'), 3.87 (s, 6H, OCH₃-4', OCH₃-4''), 3.84 (s, 6H, OCH₃-5', OCH₃-5''), 3.83 (s, 6H, OCH₃-6, OCH₃-6''), 3.71 (s, 6H, OCH₃-7, OCH₃-7''), 3.31 (dd, 2H, *J* 13.8, 4.5 Hz, H7', H7''), 3.20 (dt, 2H, *J* 12.0, 4.6 Hz, H3, H3''), 2.98 (dd, 2H, *J* 13.8, 9.0 Hz, H7', H7''), 2.89 (dt, 2H, *J* 12.0, 5.4 Hz, H3, H3''), 2.72 (t, 4H, *J* 5.4 Hz, H4, H4').

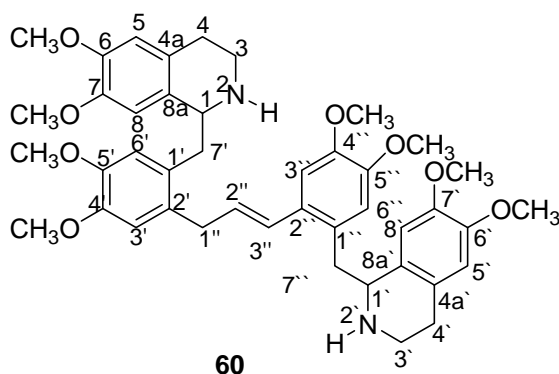
¹H NMR of *rac*-59 (in part): δ 7.16 (s, 2H, $\underline{\text{CH}}=\underline{\text{CH}}$), 6.74 (s, 2H, H3', H3''), 6.71 (s, 2H, H6', H6''), 6.59 (s, 2H, H5, H5'), 6.57 (s, 2H, H8, H8'), 4.14 (dd, 2H, J 11.1, 3.9 Hz, H1, H1'), 3.90 (s, 6H, OCH_3 -4', OCH_3 -4''), 3.86 (s, 6H, OCH_3 -5', OCH_3 -5''), 3.71 (s, 6H, OCH_3 -6, OCH_3 -6'), 3.50 (s, 6H, OCH_3 -7, OCH_3 -7').

¹³C NMR of *meso*-59: δ 148.9 (C5', C5''), 148.3 (C4', C4''), 147.8 (C6, C6'), 147.2 (C7, C7'), 130.7 (C1', C1''), 130.1 (C2', C2''), 130.0 (C4a, C4a'), 127.6 (C8a, C8a'), 126.8 ($\underline{\text{CH}}=\underline{\text{CH}}$), 113.9 (CH-6', CH-6''), 112.1 (CH-3', CH-3''), 110.0 (CH-5, CH-5'), 109.4 (CH-8, CH-8'), 57.0 (CH-1, CH-1'), 56.3 (OCH_3 -5', OCH_3 -5''), 56.2 (OCH_3 -4', OCH_3 -4''), OCH_3 -6, OCH_3 -6'), 56.1 (OCH_3 -7, OCH_3 -7'), 40.9 (CH₂-3, CH₂-3'), 40.1 (CH₂-7', CH₂-7''), 29.8 (CH₂-4, CH₂-4').

¹³C NMR of *rac*-59 (in part): δ 148.3 (C4', C4''), 147.4 (C7, C7'), 130.8 (C1', C1''), 130.3 (C2', C2''), 129.2 (C4a, C4a'), 128.3 ($\underline{\text{CH}}=\underline{\text{CH}}$), 113.5 (CH-6', CH-6''), 109.9 (CH-5, CH-5'), 56.6 (CH-1, CH-1'), 55.9 (OCH_3 -7, OCH_3 -7'), 41.1 (CH₂-3, OCH_3 -3'), 40.0 (CH₂-7', CH₂-7''), 28.6 (CH₂-4, CH₂-4').

MS (ES⁺): m/z 710.92 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₄₂H₅₁N₂O₈, 711.3645 (MH⁺). Found 711.3662.

(1*RS*, 1'*RS*) and (1*RS*, 1'*SR*) 2',2''-(1'',3''-Prop-2(*E*)-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (60).



Compound **66** (152 mg, 0.170 mmol), CH₃OH (8 mL), H₂O (2 mL) and K₂CO₃ (118 mg, 0.850 mmol) was treated as described above using the general *N*-TFA deprotection procedure to give an oil. The oil was purified by column

chromatography to give **60** (72 mg, 58 %) as a yellow oil. Product **60** was a 60 : 40 mixture of diastereomers.

R_f 0.1 (CH₃OH : EtOAc : NH₃ (1 : 4 : 0.1)).

¹H NMR of the major diastereomer: δ 6.96 (s, 1H, H3''), 6.73 (s, 2H, H3', H5''), 6.64 (d, 1H, *J* 15.0 Hz, H3''), 6.63 (s, 1H, H5'), 6.58 (s, 2H, H6', H6''), 6.49 (s, 1H, H8'), 6.48 (s, 1H, H8), 6.10 (m, 1H, H2''), 4.11 (dd, 1H, *J* 8.4, 5.4 Hz, H1'), 4.03 (m, 1H, H1), 3.82 (s, 24H, 8 x OCH₃), 3.51 (d, 2H, *J* 6.3 Hz, H1''), 3.17 (dd, 2H, *J* 13.2, 5.4 Hz, H7', H7''), 3.12 (dd, 2H, *J* 12.0, 6.9 Hz, H3, H3'), 2.87 (dd, 2H, *J* 13.2, 8.4 Hz, H7', H7''), 2.81 (dd, 2H, *J* 12.0, 5.1 Hz, H3, H3'), 2.70 (m, 4H, H4, H4').

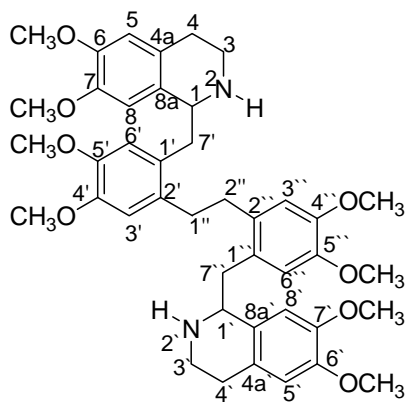
¹H NMR of the minor diastereomer (in part): δ 6.72 (s, 2H, H3', H5''), 6.62 (s, 1H, H5'), 6.53 (s, 2H, H6', H6''), 6.46 (s, 1H, H8'), 6.42 (s, 1H, H8), 6.07 (m, 1H, H2''), 4.14 (m, 1H, H1'), 4.05 (m, 1H, H1), 3.70 (s, 24H, 8 x OCH₃).

¹³C NMR of the major diastereomer: δ 148.3 (C6, C6'), 148.0 (C4', C4''), 147.8 (C5', C5''), 147.1 (C7, C7'), 131.1 (C1'), 131.0 (C1''), 129.8 (CH-3''), 129.5 (C2', C2''), 128.9 (C4a, C4a'), 128.3 (C8a, C8a'), 127.5 (CH-2''), 114.0 (CH-3'), 113.5 (CH-3''), 112.1 (CH-6', CH-6'', CH-5, CH-5'), 109.8 (CH-8), 109.3 (CH-8'), 56.2 (8 x OCH₃, CH-1), 41.2 (CH₂-3, CH₂-3'), 39.4 (CH₂-7', CH₂-7''), 36.6 (CH₂-1''), 29.6 (CH₂-4, CH₂-4').

¹³C NMR of the minor diastereomer (in part): δ 131.0 (C1''), 129.7 (CH-3''), 129.5 (C2', C2''), 128.5 (C8a, C8a'), 127.4 (CH-2''), 113.9 (CH-3'), 36.7 (CH₂-1''), 29.7 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 724.88 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₄₃H₅₃N₂O₈, 725.3802 (MH⁺). Found 725.3783.

(1*RS*, 1'*RS*) and (*R,S*) 2',2''-(1'',2''-Ethanediy)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (**61**).



rac-**61**

Compound *rac*-**80** (4 mg, 0.003 mmol), CH₃OH (1 mL), H₂O (0.5 mL) and K₂CO₃ (12 mg, 0.085 mmol) was treated as described above using the general *N*-TFA deprotection reaction procedure to afford *rac*-**61** (3 mg, 95 % yield) as a yellow oil without the need for further purification.

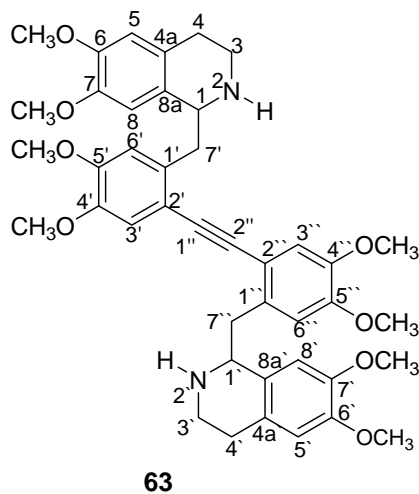
R_f. 0.14 (DCM : EOAc : CH₃OH : NH₃ (10 : 5 : 1 : 0.1)).

¹H NMR: δ 6.67 (s, 2H, H3', H3''), 6.57 (s, 2H, H5, H5'), 6.55 (s, 2H, H6', H6''), 6.43 (s, 2H, H8, H8'), 4.05 (dd, 2H, *J* 9.3, 5.1 Hz, H1, H1'), 3.82 (s, 6H, OCH₃-4', OCH₃-4''), 3.80 (s, 6H, OCH₃-5', OCH₃-5''), 3.75 (s, 6H, OCH₃-6, OCH₃-6'), 3.67 (s, 6H, OCH₃-7, OCH₃-7'), 3.14 (dd, 2H, *J* 12.3, 6.3 Hz, H3, H3'), 3.06 (dd, 2H, *J* 13.8, 5.1 Hz, H7', H7''), 2.84 (dd, 2H, *J* 12.3, 6.6 Hz, H3, H3'), 2.82 (s, 4H, H1'', H2''), 2.75 (dd, 2H, *J* 13.8, 9.3 Hz, H7', H7''), 2.66 (m, 4H, H4, H4').

¹³C NMR: δ 147.5 (C5', C5''), 147.4 (C4', C4''), 147.2 (C6, C6'), 146.8 (C7, C7'), 132.5 (C1', C1''), 132.0 (C2', C2''), 131.9 (C4a, C4a'), 127.0 (C8a, C8a'), 113.4 (CH-6', CH-6''), 112.9 (CH-3', CH-3''), 111.7 (CH-5, CH-5'), 109.6 (CH-8, CH-8'), 56.4 (CH-1, CH-1'), 55.8 (8 x OCH₃), 40.7 (CH₂-3, CH₂-3'), 38.9 (CH₂-7', CH₂-7''), 34.1 (CH₂-1'', CH₂-2''), 29.3 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 713.3 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₄₂H₅₃N₂O₈, 713.3802 (MH⁺). Found 713.3781.

(1*RS*, 1'*RS*) and (R,S) 2',2''-(1'',2''-Ethynediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (63).



Compound **83** (56 mg, 0.062 mmol), CH₃OH (20 mL), H₂O (2 mL) and K₂CO₃ (44 mg, 0.311 mmol) were treated as described above using the general *N*-TFA deprotection reaction procedure to afford an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (1 : 5)) to give **63** (34 mg, 79 % yield) as a brown solid.

R_f. 0.06 (EtOAc).

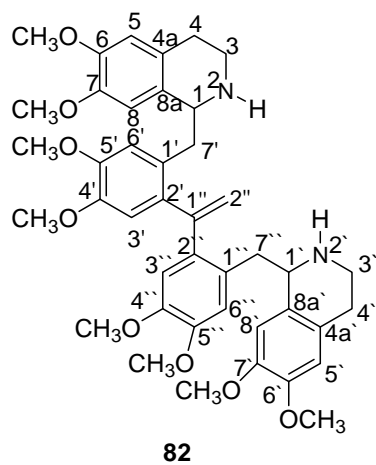
m.p. 208-210 °C.

¹H NMR: δ 7.20 (s, 2H, H3', H3''), 7.00 (s, 2H, H6', H6''), 6.59 (s, 2H, H5, H5'), 6.35 (s, 2H, H8, H8'), 4.73 (t, 2H, *J* 7.5 Hz, H1, H1'), 3.84 (s, 6H, OCH₃-4', OCH₃-4''), 3.82 (s, 6H, OCH₃-5', OCH₃-5''), 3.81 (s, 6H, OCH₃-6, OCH₃-6'), 3.65 (s, 6H, OCH₃-7, OCH₃-7'), 3.51 (td, 2H, *J* 12.0, 4.5 Hz, H3, H3'), 3.36 (d, 4H, *J* 7.5 Hz, H7', H7''), 3.25 (m, 2H, H4, H4'), 3.13 (td, 2H, *J* 12.0, 4.5 Hz, H3, H3'), 2.94 (m, 2H, H4, H4').

¹³C NMR: δ 149.9 (C4', C4''), 149.5 (C5', C5''), 149.3 (C6, C6'), 148.0 (C7, C7'), 131.1 (C2', C2''), 124.9 (C1', C1'', C4a, C4a'), 124.3 (C8a, C8a'), 122.0 (CH-3', CH-3''), 115.0 (CH-6', CH-6''), 110.9 (CH-5, CH-5'), 110.2 (CH-8, CH-8'), 89.9 (ArC≡CAr), 57.2 (OCH₃-4', OCH₃-4'', OCH₃-5', OCH₃-5''), 56.5 (OCH₃-6, OCH₃-6', OCH₃-7, OCH₃-7'), 55.3 (CH-1, CH-1'), 45.7 (CH₂-3, CH₂-3'), 40.2 (CH₂-7', CH₂-7''), 26.3 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 709.1 (MH⁺, 5 %). **HRMS (ES⁺):** calcd for C₄₂H₄₉N₂O₈, 709.3489 (MH⁺). Found 709.3474.

(1*RS*, 1'*RS*) and (*R,S*) 2',2''-(1,1-Ethenediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (**82**).



Compound **69** (38 mg, 0.044 mmol), CH₃OH (3 mL), H₂O (0.6 mL) and K₂CO₃ (30 mg, 0.218 mmol) were treated as described above using the general *N*-TFA deprotection reaction procedure except that the reaction mixture was heated at 80 °C for 5 h to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (4 : 6)) to give **82** (14 mg, 45 %) as a yellow oil.

The product **82** was obtained as a diastereomeric mixture which was separated by PTLC (DCM : EtOAc : CH₃OH : NH₃ (10 : 5 : 1: 0.1)) into the major diastereomer (11 mg) and minor diastereomer (3 mg).

R_f. (major diastereomer): 0.30 (DCM : EtOAc : CH₃OH : NH₃ (10 : 5 : 1: 0.1)).

R_f. (minor diastereomer): 0.24 (DCM : EtOAc : CH₃OH : NH₃ (10 : 5 : 1: 0.1)).

¹H NMR of the major diastereomer: δ 7.01 (s, 2H, H3', H3''), 6.72 (s, 2H, H6', H6''), 6.53 (s, 2H, H5, H5'), 5.99 (s, 2H, H8, H8'), 4.10 (dd, 2H, *J* 10.2, 4.5 Hz, H1, H1'), 3.86 (s, 6H, OCH₃-4', OCH₃-4''), 3.82 (s, 6H, OCH₃-5', OCH₃-5''), 3.77 (s, 6H, OCH₃-6, OCH₃-6'), 3.65 (s, 6H, OCH₃-7, OCH₃-7'), 3.06 (dt, 2H, *J* 11.8, 5.1 Hz, H3, H3'), 2.92 (m, 2H, *J* 13.8, 4.5 Hz, H7' _ H7''), 2.80 (ddd, 2H, *J* 11.8, 6.6, 4.8 Hz, H3, H3'), 2.67 (m, 4H, H4, H4'), 2.40 (dd, 2H, *J* 13.8, 10.2 Hz, H7' _ H7'').

¹H NMR of the minor diastereomer: δ 6.96 (s, 2H, H3', H3''), 6.66 (s, 2H, H6', H6''), 6.53 (s, 2H, H5, H5'), 6.06 (s, 2H, H8, H8'), 4.06 (dd, 2H, *J* 8.4, 6.6 Hz, H1, H1'), 3.80 (s, 18H, OCH₃-4', OCH₃-4'_, OCH₃-5', OCH₃-5'_, OCH₃-6, OCH₃-6'), 3.62 (s, 6H, OCH₃-7, OCH₃-7'), 3.10 (dt, 2H, *J* 12.0, 5.7 Hz, H3, H3'), 2.90 (dd, 2H, *J* 13.8,

6.0 Hz, H7', H7''), 2.84 (dd, 2H, *J* 11.7, 5.4 Hz, H3, H3'), 2.68 (t, 4H, *J* 5.7 Hz, H4, H4'), 2.53 (dd, 2H, *J* 13.8, 8.4 Hz, H7', H7'').

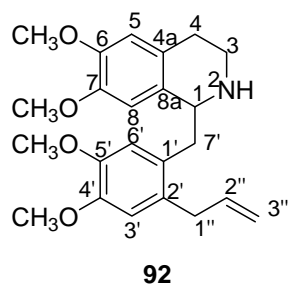
¹³C NMR of the major diastereomer: δ 150.9 (C4', C4''), 148.5 (C5', C5''), 147.5 (C6, C6'), 147.2 (C7, C7'), 133.6 (C2', C2'' and C=CH₂), 130.8 (C1', C1''), 129.2 (C4a, C4a'), 129.2 (C8a, C8a'), 120.2 (ArC=CH₂), 115.2 (CH-3', CH-3''), 114.6 (CH-6', CH-6''), 111.9 (CH-5, CH-5'), 108.7 (CH-8, CH-8'), 56.2 (OCH₃-4', OCH₃-4''), 56.0 (OCH₃-5', OCH₃-5'', OCH₃-6, OCH₃-6'), 55.6 (OCH₃-7, OCH₃-7'), 54.9 (CH-1, CH-1'), 41.4 (CH₂-3, CH-3'), 40.4 (CH₂-7', CH₂-7''), 29.7 (CH₂-4, CH₂-4').

¹³C NMR of the minor diastereomer: δ 150.7 (C4', C4''), 148.6 (C5', C5''), 147.6 (C6, C6'), 147.0 (C7, C7'), 134.6 (C2', C2'' and C=CH₂), 131.0 (C1', C1''), 129.4 (C4a, C4a'), 127.1 (C8a, C8a'), 119.9 (C=CH₂), 114.7 (CH-3', CH-3''), 114.3 (CH-6', CH-6''), 112.0 (CH-5, CH-5'), 109.7 (CH-8, CH-8'), 56.2 (OCH₃-4', OCH₃-4'', OCH₃-5' OCH₃-5''), 56.0 (OCH₃-6, OCH₃-6'), 55.9 (OCH₃-7, OCH₃-7'), 55.4 (CH-1, CH-1'), 41.0 (CH₂-3, CH-3'), 40.5 (CH₂-7', CH₂-7''), 29.6 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 711.2 (MH⁺, 100 %), 733.2 (M+Na⁺, 80 %). **HRMS (ES⁺):** calcd for C₄₂H₅₁N₂O₈, 711.3645 (MH⁺). Found 711.3660.

8.2.8. Intramolecular Heck coupling reactions.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2''-propenyl)-phenyl)methylisoquinoline (92).



N-TFA protected amine **68** (70 mg, 0.146 mmol), K₂CO₃ (100 mg, 0.730 mmol), CH₃OH (7 mL) and H₂O (1 mL) were treated as described above using the general *N*-TFA deprotection procedure to give a yellow oil. The oil was purified by column

chromatography (CH₃OH : EtOAc (1 : 5)) to afford the amine **92** (50 mg, 90 %) as a yellow oil.

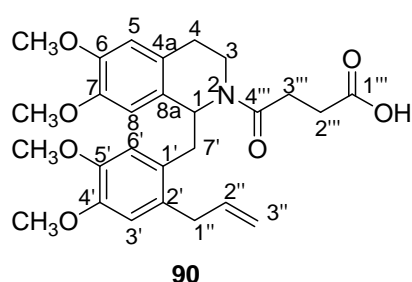
R_f 0.21 (CH₃OH : EtOAc (1 : 5)).

¹H NMR: δ 6.73 (s, 2H, H3'), 6.71 (s, 1H, H6'), 6.58 (s, 1H, H5), 6.44 (s, 1H, H8), 5.91 (m, 1H, H2''), 5.06 (dd, 1H, *J* 9.6, 1.8 Hz, H3''(*Z*)), 5.01 (dd, 1H, *J* 17.1, 1.8 Hz, H3''(*E*)), 4.17 (dd, 1H, *J* 8.7, 5.7 Hz, H1), 3.85 (s, 6H, OCH₃-4', OCH₃-5'), 3.82 (s, 3H, OCH₃-6), 3.73 (s, 3H, OCH₃-7), 3.32 (d, 2H, *J* 6.0 Hz, H1''), 3.27 (dd, 1H, *J* 12.0, 6.3 Hz, H3), 3.22 (dd, 1H, *J* 13.8, 5.7 Hz, H7'), 2.97 (dd, 1H, *J* 12.0, 5.7 Hz, H3), 2.89 (dd, 1H, *J* 13.8, 8.7 Hz, H7'), 2.73 (m, 2H, H4).

¹³C NMR: δ 147.9 (C4', C5'), 147.5 (C6), 147.2 (C7), 137.6 (CH-2''), 130.8 (C2'), 129.9 (C1'), 129.0 (C4a), 127.0 (C8a), 115.9 (CH₂-3''), 114.0 (CH-3'), 113.4 (CH-6'), 112.0 (CH-5), 109.8 (CH-8), 56.4 (OCH₃-4'), 56.3 (OCH₃-5'), 56.2 (OCH₃-6), 56.1 (OCH₃-7, CH-1), 40.8 (CH₂-1''), 38.2 (CH₂-7'), 37.0 (CH₂-3), 29.2 (CH₂-4).

MS (CI⁺): *m/z* 384 (MH⁺, 60 %). **HRMS (CI⁺):** calcd for C₂₃H₃₀NO₄, 384.2175 (MH⁺). Found 384.2178.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1(4',5'-dimethoxy-2'-(2''-propenyl)-phenyl)methylisoquinoline 2-(4-oxo)butanoic acid (90).



To a solution of the amine **92** (332 mg, 0.867 mmol) in dry DCM (8 mL) was added triethylamine (0.14 mL), followed by succinic anhydride (174 mg, 1.73 mmol) under a N₂ atmosphere. The reaction mixture was stirred at RT for 18 h. The organic layer was evaporated and the residue was redissolved in EtOAc. The solution was washed with 1M KHSO₄ (2 x), then brine. The solution was dried (MgSO₄) and evaporated and the crude mixture was purified by column chromatography (CH₃OH : EtOAc (1 : 5)) to give **90** (334 mg, 79 %) as a white solid. The product **90** was a 70 : 30 mixture of rotamers by ¹H NMR analysis.

R_f 0.71 (CH₃OH : EtOAc (1 : 5)).

m.p. 138-140 °C.

¹H NMR of the major rotamer: δ 6.63 (s, 1H, H5), 6.59 (s, 1H, H3'), 6.56 (s, 1H, H6'), 5.93 (s, 1H, H8), 5.76 (m, 1H, H2''), 5.51 (dd, 1H, *J* 9.0, 5.1 Hz, H1), 4.95 (dd, 2H, *J* 10.2, 1.8 Hz, H3''(Z)), 5.01 (dd, 1H, *J* 17.1, 1.8 Hz, H3''(E)), 3.85 (s, 3H, OCH₃-5'), 3.83 (s, 3H, OCH₃-6), 3.75 (s, 3H, OCH₃-7), 3.68 (m, 2H, H3), 3.50 (s, 3H, OCH₃-4'), 3.11 (dd, 1H, *J* 12.5, 5.1 Hz, H4), 3.02 (dd, 1H, *J* 13.5, 5.1 Hz, H7'), 3.00 (d, 2H, *J* 6.3 Hz, H1''), 2.89 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.82 (dd, 1H, *J* 12.5, 6.3 Hz, H4), 2.75 (m, 4H, H2''', H3''').

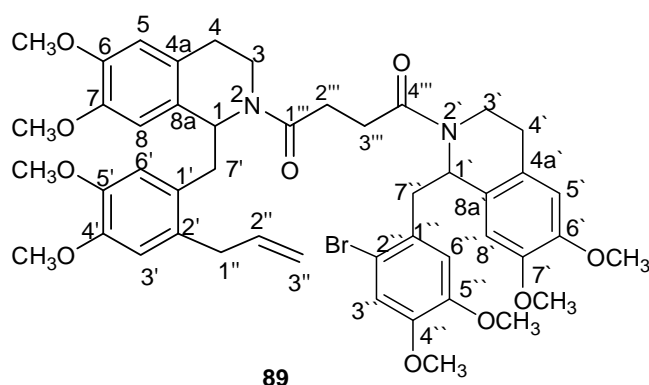
¹H NMR of the minor rotamer (in part): δ 6.69 (s, 1H, H3'), 6.63 (s, 1H, H6'), 6.49 (s, 1H, H5), 6.44 (s, 1H, H8), 5.94 (m, 1H, H2''), 5.11 (d, 1H, *J* 10.2, 1.8 Hz, H3''(Z)), 5.00 (d, 1H, *J* 15.0, 1.8 Hz, H3''(E)), 4.85 (m, 1H, H1), 4.73 (ddd, 1H, *J* 8.4, 5.7, 2.4 Hz, H3), 3.87 (s, 3H, OCH₃-5'), 3.81 (s, 3H, OCH₃-7), 3.79 (s, 3H, OCH₃-4'), 3.32 (d, 2H, *J* 6.3 Hz, H1''), 3.21 (m, 1H, H4), 3.10 (m, 1H, H7'), 2.90 (m, 1H, H4), 2.86 (m, 1H, H7'), 1.87 (m, 4H, H2''', H3''').

¹³C NMR of the major rotamer: δ 175.5 (COOH), 169.8 (NCO), 146.9 (C5'), 146.5 (C4'), 146.1 (C6), 145.9 (C7), 136.4 (CH-2''), 130.0 (C1'), 127.2 (C2'), 126.7 (C4a), 124.6 (C8a), 114.4 (CH₂-3''), 113.1 (CH-6'), 111.6 (CH-3'), 110.1 (CH-5), 109.8 (CH-8), 54.9 (OCH₃-4', OCH₃-5'), 54.9 (OCH₃-6), 54.6 (OCH₃-7), 53.0 (CH-1), 40.5 (CH₂-3), 37.0 (CH₂-7'), 35.3 (CH₂-1'', CH₂-4), 27.7 (CH₂-2'''), 27.2 (CH₂-3''').

¹³C NMR of the minor rotamer (in part): δ 175.3 (COOH), 170.2 (NCO), 147.3 (C5'), 147.2 (C3'), 146.6 (C6), 146.4 (C7), 136.1 (CH-2''), 129.3 (C1'), 126.8 (C2'), 126.4 (C4a), 125.5 (C8a), 115.0 (CH₂-3''), 113.0 (CH-6'), 112.3 (CH-3'), 110.5 (CH-5), 108.9 (CH-8), 56.7 (CH-1), 37.8 (CH₂-7'), 36.0 (CH₂-1''), 35.0 (CH₂-3), 26.9 (CH₂-2'''), 26.2 (CH₂-3''').

MS (ES⁺): m/z 484 (MH⁺, 70 %). **HRMS (ES⁺):** calcd for C₂₇H₃₄NO₇, 484.2335 (MH⁺). Found 484.2329.

(1*RS*, 1'*RS*) and (*R,S*) 2'- (2''-Propenyl)-2''-bromo-2,2'-(1''',4'''-dioxo-1''',4'''-butanediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl] isoquinoline (89).



89

To a suspension of the amine **92** (148 mg, 0.349 mmol), the acid **90** (142 mg, 0.290 mmol), HOBT (44 mg, 0.319 mmol) and EDCI (61 mg, 0.319 mmol) was added dry DMF (6 mL) under a N₂

atmosphere. The reaction was stirred at RT for 3 d. The crude mixture was diluted with DCM and washed with H₂O (4 x) and then brine. The DCM was evaporated to give an oil which was purified by column chromatography (CH₃OH : EtOAc (1 : 5)) to give **89** (212 mg, 82 %) as a yellow solid. The product **89** was obtained as a 60 : 40 mixture of diastereomers which were each a 70 : 30 mixture of rotamers.

R_f 0.74 (CH₃OH : EtOAc (1 : 5)).

m.p. 145-148 °C.

¹H NMR of the major diastereomer: δ 6.96 (s, 1H, H3''), 6.57 (s, 5H, H3', H5, H5', H6', H8'), 6.34 (s, 1H, H6''), 5.89 (s, 1H, H8), 5.69 (m, 1H, H2''), 5.47 (dd, 1H, *J* 9.0, 4.8 Hz, H1'), 5.18 (dd, 1H, *J* 9.0, 4.8 Hz, H1), 4.91 (m, 2H, H3''), 3.84 (s, 18H, 6 x OCH₃), 3.80 (m, 4H, H3, H3'), 3.72 (s, 6H, OCH₃-4', OCH₃-4''), 3.23 (m, 1H, H4'), 3.05 (m, 1H, H4), 3.01 (m, 2H, H1''), 2.79 (m, 4H, H7', H7''), 2.64 (m, 6H, H4', H4, H2''', H3''').

¹H NMR of the minor diastereomer (in part): δ 7.03 (s, 1H, H3''), 6.59 (s, 5H, H3', H5, H5', H6', H8'), 6.20 (s, 1H, H6''), 5.84 (s, 1H, H8), 5.62 (m, 1H, H2''), 5.42 (dd, 1H, J 9.9, 4.2 Hz, H1'), 5.13 (dd, 1H, J 9.9, 4.2 Hz, H1), 5.04 (m, 2H, H3''), 2.28 (m, 4H, H2''', H3''').

¹H NMR of the minor rotamer of both diastereomers (in part), (note-* represents the rotamer of the minor diastereomer): δ 7.02 (s, 1H, H3''), 6.95 (s, 1H, H3''*), 6.54 (s, 5H, H3', H5, H5', H6', H8'), 6.52 (s, 5H, H3', H5, H5', H6', H8'*), 5.88 (s, 1H, H8), 5.86 (s, 1H, H8*), 4.72 (m, 2H, H3, H3'), 2.56 (m, 2H, H3'''), 2.30 (m, 2H, H2''').

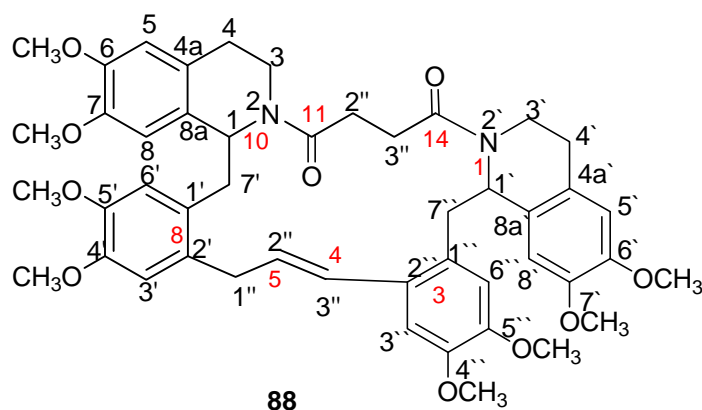
¹³C NMR of the major diastereomer: δ 171.1 (2 x NCO), 148.3 (C5', C5'', C4', C4''), 148.1 (C6, C6'), 147.5 (C7, C7'), 137.7 (CH-2''), 132.3 (C1', C1''), 132.2 (C2', C2''), 128.8 (C4a, C4a'), 128.6 (C8a, C8a'), 115.7 (CH-6', CH6''), 115.3 (CH₂-3''), 111.6 (CH-3', CH-3''), 111.1 (CH-5, CH-5'), 110.8 (CH-8, CH-8'), 56.1 (8 x OCH₃), 53.5 (CH-1, CH-1''), 42.6 (CH₂-3'), 41.0 (CH₂-7''), 38.4 (CH₂-3), 36.6 (CH₂-7'), 36.0 (CH₂-1''), 29.1 (CH₂-3''', CH₂-2'''), 28.7 (CH₂-4'), 28.1 (CH₂-4).

¹³C NMR of the minor diastereomer (in part): δ 131.2 (C1', C1''), 129.8 (C2', C2''), 128.3 (C4a, C4a'), 126.8 (C8a, C8a'), 111.3 (CH-3', CH-3''), 111.0 (CH-5, CH5'), 110.3 (CH-8, CH8'), 35.7 (CH₂-1'').

MS (ES⁺): m/z 886.79 (MH⁺, 10 %). **HRMS (ES⁺):** calcd for C₄₇H₅₆N₂O₁₀Br, 887.3118 (MH⁺). Found 887.3137.

(1*RS*, 1'*RS*) and (*R,S*) (*E*) 1,10-(1,2)-Di-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolina)-3,8-(1,2)-di-(3,4-dimethoxy)benzenacyclo-(11,14-dioxo)-propadeca-4-phenone (88**).**

Note: The red colours represent the systematic numbering of the macrocyclic system.



To a mixture of **89** (71 mg, 0.080 mmol), Pd(OAc)₂ (2 mg, 0.008 mmol) and PPh₃ (4 mg, 0.016 mmol) in a thick walled tube was added dry CH₃CN (2 mL) under a N₂ atmosphere.

Triethylamine (25 mg, 0.240 mmol, 0.04 mL) was added and the reaction was bubbled with argon for 5 min prior to sealing the tube. The solution mixture was stirred and heated at 110 °C for 24 h. The solution was diluted with DCM, washed with H₂O, and then brine. The DCM layer was evaporated to give an oil which was purified by column chromatography (CH₃OH : EtOAc (1 : 9)) to give **88** (12 mg, 15 %) as a yellow oil.

R_f: 0.61 (CH₃OH : EtOAc (1 : 9)).

¹H NMR: δ 6.93 (d, 1H, *J* 15.3 Hz, H3''), 6.86 (s, 1H, H5'), 6.81 (s, 1H, H5), 6.64 (s, 1H, H3''), 6.59 (s, 1H, H3'), 6.49 (s, 1H, H6''), 6.02 (s, 1H, H6'), 5.92 (m, 1H, H2''), 5.90 (s, 1H, H8'), 5.88 (s, 1H, H8), 5.66 (dd, 1H, *J* 9.0, 3.0 Hz, H1'), 5.55 (dd, 1H, *J* 9.0, 3.0 Hz, H1), 4.40 (dd, 1H, *J* 13.5, 9.6 Hz, H3'), 3.91 (m, 1H, H3), 3.88 (s, 3H, OCH₃-5''), 3.85 (s, 6H, OCH₃-5', OCH₃-7), 3.83 (s, 3H, OCH₃-7'), 3.73 (s, 3H, OCH₃-6), 3.57 (s, 3H, OCH₃-6'), 3.49 (s, 6H, OCH₃-4', OCH₃-4''), 3.67 (m, 1H, H3), 3.43 (m, 1H, H3'), 3.40 (m, 2H, H3'''), 3.34 (d, 2H, *J* 7.5 Hz, H1''), 3.20 (m, 2H, H7'', H7'), 3.04 (dd, 1H, *J* 13.2, 3.0 Hz, H7'), 2.99 (d, 1H, *J* 13.2, 9.0 Hz, H7'), 2.70 (m, 2H, H4, H4'), 2.40 (m, 1H, H2'''), 2.24 (m, 1H, H2''').

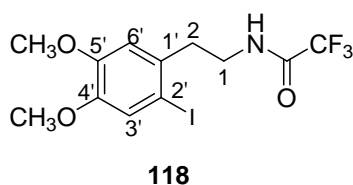
^{13}C NMR: δ 172.1 ($\underline{\text{CO}}$), 171.2 ($\underline{\text{CO}}$), 147.9 ($\text{C6}'$), 147.7 (C6), 147.5 ($\text{C4}'$, $\text{C4}''$), 147.3 ($\text{C5}''$), 147.0 ($\text{C5}'$), 146.6 ($\text{C7}'$), 146.2 (C7), 132.1 ($\text{CH-3}''$), 132.4 ($\text{C1}''$), 130.1 ($\text{C1}'$), 129.1 ($\text{C2}''$), 128.8 ($\text{C2}'$), 128.7 ($\text{CH-2}''$), 128.1 ($\text{C4a}''$), 126.0 (C4a), 126.5 (C8a , $\text{C8a}''$), 115.7 ($\text{CH-6}''$), 113.7 ($\text{CH-6}'$), 113.1 ($\text{CH-3}''$), 111.9 ($\text{CH-3}'$), 111.1 ($\text{CH-5}''$), 110.9 (CH-5), 110.8 ($\text{CH-8}''$), 109.5 (CH-8), 51.7 (8 x OCH_3), 54.8 ($\text{CH-1}''$), 54.3 (CH-1), 41.7 ($\text{CH}_2\text{-3}''$), 41.1 ($\text{CH}_2\text{-3}$), 40.2 ($\text{CH}_2\text{-7}''$), 39.0 ($\text{CH}_2\text{-7}'$), 36.6 ($\text{CH}_2\text{-1}''$), 29.7 ($\text{CH}_2\text{-3}'''$), 28.6 ($\text{CH}_2\text{-2}'''$), 28.3 ($\text{CH}_2\text{-4}'$), 28.0 ($\text{CH}_2\text{-4}$).

MS (ES^+): m/z 807.09 (MH^+ , 5 %), m/z 844.86 ($\text{M}+\text{K}^+$, 20 %). **HRMS (ES^+):** calcd for $\text{C}_{47}\text{H}_{55}\text{N}_2\text{O}_{10}$, 807.3857 (MH^+). Found 807.3842.

8.3. Experimental for Chapter 3.

8.3.1. Synthesis of precursors 118, 119, 120, 126, 127, 130, 131 and 135.

N-[2-(2'-Iodo-4',5'-dimethoxyphenyl)ethyl]trifluoroacetamide (118).



To a solution of 2-(3',4'-dimethoxyphenyl)ethylamine **123** (1.00 g, 5.50 mmol) in dry DCM (25 mL) at 0 $^{\circ}\text{C}$ was added dry pyridine (87 mg, 6.05 mmol, 0.87 mL) under a N_2 atmosphere. Trifluoroacetic anhydride (1.50 g, 7.15 mmol, 2.2 mL) was subsequently added dropwise and the mixture was stirred at RT for 2 h. The reaction mixture was diluted with DCM, washed with H_2O , dried (MgSO_4) and then evaporated to give a yellow solid (1.63 g). The solid (1.63 g) and NIS (1.58 g, 7.06 mmol) were dissolved in dry CH_3CN (40 mL) and the mixture was cooled to 0 $^{\circ}\text{C}$ and then trifluoroacetic acid (190 mg, 1.70 mmol, 0.116 mL) was added dropwise. The solution was brought to RT and stirred for 18 h. The mixture was evaporated *in vacuo*, and the residue was redissolved in EtOAc. The solution was washed with H_2O , brine, sat. $\text{Na}_2\text{S}_2\text{O}_3$, and sat. NaHCO_3 . The solution was dried (MgSO_4), filtered and then evaporated to give a

yellow solid. The solid was purified by column chromatography (EtOAc : hexane (3 : 7)) to afford **118** (1.48 g, 77 % over 2 steps) as a yellow solid.

R_f. 0.62 (EtOAc : Pet. spirit (1 : 1)).

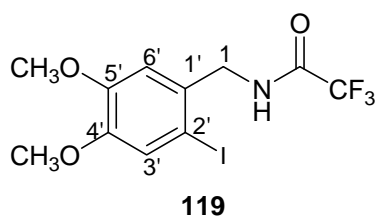
m.p. 118-120 °C.

¹H NMR: δ 7.17 (s, 1H, H3'), 6.65 (s, 1H, H6'), 6.62 (bs, 1H, NH), 3.80 (s, 3H, OCH₃-4'), 3.78 (s, 3H, OCH₃-5'), 3.61 (q, 2H, *J* 6.9 Hz, H1), 2.92 (t, 2H, *J* 6.9 Hz, H2).

¹³C NMR: δ 155.4 (q, *J* 36.9 Hz, C=O), 149.6 (C4'), 148.6 (C5'), 132.8 (C1'), 121.9 (CH-6'), 113.9 (q, *J* 285.4 Hz, C=O), 112.6 (CH-3'), 88.0 (C2'), 56.3 (OCH₃-4'), 56.0 (OCH₃-5'), 39.5 (CH₂-1), 39.0 (CH₂-2).

MS (EI⁺): *m/z* 403.1 (M⁺, 20 %). **HRMS (ES⁺):** calcd for C₁₂H₁₃NO₃F₃I, 402.9892 (M⁺). Found 402.9890.

***N*-(2'-Iodo-4',5'-dimethoxyphenyl)methyltrifluoroacetamide (119).**



The title compound was prepared using the same procedure as described above for the synthesis of **118** using initially 3,4-dimethoxybenzylamine **124** (1.00 g, 5.98 mmol), DCM (25 mL), pyridine (94 mg, 11.96

mmol, 0.94 mL) and trifluoroacetic anhydride (1.64 g, 7.78 mmol, 2.4 mL) and then NIS (1.29 g, 5.70 mmol), CH₃CN (20 mL) and trifluoroacetic acid (158 mg, 1.33 mmol, 0.096 mL). The crude mixture was recrystallised from EtOAc to give the desired product **119** (1.10 g, 48 % over 2 steps) as a yellow solid. Compound **119** was a 95 : 5 mixture of rotamers.

R_f. 0.76 (EtOAc : Pet. spirit (5 : 3)).

m.p. 132-134 °C.

¹H NMR of the major rotamer: δ 7.16 (s, 1H, H3'), 6.83 (bs, 2H, H6' and NH), 4.45 (d, 2H, *J* 6.0 Hz, H1), 3.80 (s, 3H, OCH₃-4'), 3.79 (s, 3H, OCH₃-5').

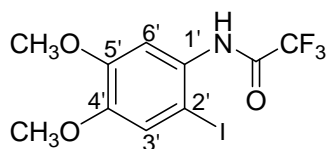
¹H NMR of the minor rotamer (in part): δ 4.39 (d, 2H, J 6.0 Hz, H1).

¹³C NMR of the major rotamer: δ 157.4 (q, J 35.1 Hz, COCF_3), 149.7 (C4'), 149.6 (C5'), 130.9 (C1'), 121.8 (CH-3'), 115.9 (q, J 286.4, COCF_3), 113.3 (CH-6'), 87.4 (C2'), 56.3 (OCH_3 -4'), 56.1 (OCH_3 -5'), 48.3 (CH₂-1).

¹³C NMR of the minor rotamer (in part): δ 120.6 (CH-3'), 111.5 (CH-6').

MS (ES⁺): m/z 427.71 (M+K⁺, 20 %). **HRMS (ES⁺):** calcd for C₁₁H₁₁NO₃F₃NaI, 411.9633 (MH⁺). Found 411.9644.

***N*-(2'-Iodo-4',5'-dimethoxyphenyl)trifluoroacetamide (120).**



120

The title compound was prepared using the same procedure as described above for the synthesis of **118** using initially 3,4-dimethoxyaniline **124** (1.00 g, 6.53 mmol), DCM (25 mL), pyridine (1.03 g, 13.06 mmol, 1.03 mL) and trifluoroacetic anhydride (1.79 g, 8.52 mmol, 1.2 mL) and then NIS (1.37 g, 6.33 mmol), CH₃CN (20 mL) and trifluoroacetic acid (189 mg, 1.59 mmol, 0.12 mL). The crude mixture was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) to give the desired product **120** (1.43 g, 58 % over 2 steps) as a white solid.

R_f. 0.43 (EtOAc : Pet. spirit (1 : 1)).

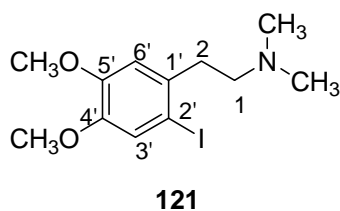
m.p. 124-126 °C.

¹H NMR: δ 8.11 (bs, 1H, NHCOCF_3), 7.79 (s, 1H, H3'), 7.17 (s, 1H, H6'), 3.87 (s, 3H, OCH_3 -4'), 3.85 (s, 3H, OCH_3 -5').

¹³C NMR: (signals for COCF_3 and COCF_3 were not observed), δ 148.9 (C4'), 148.0 (C5'), 129.6 (C1'), 120.6 (CH-3'), 106.1 (CH-6'), 78.2 (C2'), 56.5 (OCH_3 -4'), 56.4 (OCH_3 -5').

MS (ES⁺): m/z 375 (M⁺, 40 %). **HRMS (ES⁺):** calcd for C₁₀H₉NO₃F₃I, 374.9579 (M⁺). Found 374.9595.

***N,N*-Dimethyl-[2-(2'-Iodo-4',5'-dimethoxyphenyl)ethyl]amine (**121**).**



To a solution of the amine **70** (1.00 g, 5.50 mmol, 0.92 mL) in CH₃CN (30 mL) was added 38 % formaldehyde (24 mL), followed by NaCNBH₃ (893 mg, 14.35 mmol). The reaction mixture was stirred for 20 min before the pH was adjusted to ~ 6 by the addition of glacial acetic acid. The reaction mixture was stirred at RT for 18 h. The CH₃CN was evaporated and the residue taken up in DCM. The DCM solution was washed with 1M NaOH, water, brine and dried (K₂CO₃) to give an oil. This oil was placed under high vacuum for 10 min. To the crude oil was added dropwise trifluoroacetic acid (10 mL) at 0 °C, followed by NIS (1.79 g, 7.96 mmol) in small portions at a time and the solution was stirred for 2 h at 0 °C. The mixture was brought to RT and stirred for another 1h. The mixture was cooled to 0 °C and poured onto ice and water. The solution was basified with 10 % NaOH to bring the pH to approximately 9. The basic aqueous layer was extracted with chloroform, washed with H₂O, brine and dried (K₂CO₃) to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc : NH₃ (1 : 9 : 0.1)) to afford **121** (1.23 g, 69 % over 2 steps) as a yellow oil.

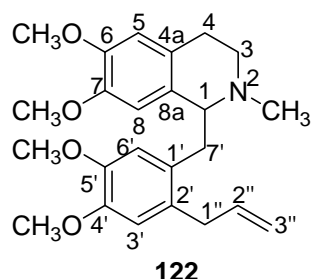
R_f. 0.53 (CH₃OH : EtOAc : NH₃ (1 : 9 : 0.1)).

¹H NMR: δ 7.12 (s, 1H, H3'), 6.68 (s, 1H, H6'), 3.77 (s, 3H, OCH₃-4'), 3.75 (s, 3H, OCH₃-5'), 2.76 (t, 2H, *J* 8.4 Hz, H1), 2.40 (t, 2H, *J* 8.4 Hz, H2), 2.26 (s, 6H, N(CH₃)₂).

¹³C NMR: δ 149.5 (C4'), 149.1 (C5'), 135.4 (C1'), 121.7 (CH-3'), 112.5 (CH-6'), 88.2 (C2'), 60.1 (CH₂-1), 56.3 (OCH₃-4'), 56.1 (OCH₃-5'), 45.5 (N(CH₃)₂), 38.7 (CH₂-2).

MS (ES⁺): *m/z* 336 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₁₂H₁₉O₂NI, 336.0461 (MH⁺). Found 336.0454.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2-propenyl)-phenyl)methyl-2-methylisoquinoline (122).



To a solution of **68** (438 mg, 0.91 mmol) in a mixture of CH₃OH (30 mL) and H₂O (2 mL) was added K₂CO₃ (632 mg, 4.57 mmol). The reaction mixture was stirred at 40 °C for 2 h. The methanol was evaporated and the residue was redissolved in CH₃CN (6 mL). The solution was treated with 38 % formaldehyde (7 mL), followed by the addition of NaCNBH₃ (144 mg, 2.26 mmol). The reaction mixture was stirred at RT for 20 min before the pH was adjusted to ~ 6 using acetic acid. The reaction was stirred at RT for 18 h. The solvent was evaporated and the residue redissolved in DCM. The DCM layer was washed with 1M NaOH, H₂O and brine. The DCM layer was dried (K₂CO₃) and evaporated to afford an oil which was purified by column chromatography (CH₃OH : EtOAc : NH₃ (25 : 75 : 1)) to give **122** (254 mg, 70 % over 2 steps) as a yellow oil.

R_f. 0.25 (CH₃OH : EtOAc (1 : 1)).

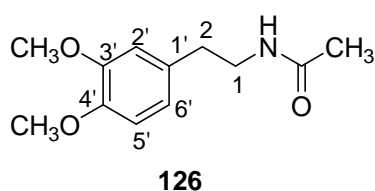
¹H NMR: δ 6.58 (s, 1H, H3'), 6.53 (s, 1H, H5), 6.52 (s, 1H, H6'), 5.78 (m, 1H, H2''), 5.68 (s, 1H, H8), 4.97 (dd, 1H, *J* 9.9, 1.8 Hz, H13''(Z)), 4.87 (dd, 1H, *J* 15.0, 1.5 Hz, H3''(E)), 3.79 (s, 6H, OCH₃-4', OCH₃-6), 3.74 (s, 3H, OCH₃-7), 3.62 (dd, 1H, *J* 9.3, 4.8 Hz, H1), 3.39 (s, 3H, OCH₃-5'), 3.27 (m, 1H, H3), 3.05 (dd, 1H, *J* 13.5, 4.8 Hz, H7'), 2.96 (d, 2H, *J* 6.0 Hz, H1''), 2.88 (m, 1H, H3), 2.74 (m, 1H, H4), 2.73 (dd, 1H, *J* 13.5, 9.3 Hz, H7'), 2.57 (m, 1H, H4), 2.52 (s, 3H, NCH₃).

¹³C NMR: δ 147.5 (C4', C6), 146.2 (C7), 146.1 (C5'), 137.6 (CH-2''), 131.1 (C2'), 130.0 (C4a), 128.7 (C8a), 125.7 (C1'), 115.7 (CH₂-3''), 114.4 (CH-3'), 112.9 (CH-5), 111.5 (CH-8), 111.4 (CH-6'), 64.3 (CH-1), 56.1 (OCH₃-4', OCH₃-6), 56.0 (OCH₃-7),

55.5 (OCH₃-5'), 46.3 (CH₂-3), 42.6 (NCH₃), 37.1 (CH₂-1'), 36.8 (CH₂-7'), 25.3 (CH₂-4).

MS (CI⁺): *m/z* 398 (MH⁺, 30 %). **HRMS (ES⁺):** calcd for C₂₄H₃₂O₄N, 397.2253 (MH⁺). Found 397.2242.

***N*-[2-(3',4'-Dimethoxyphenyl)ethyl]acetamide (**126**).¹⁹²**



To a solution of 2-(3,4-dimethoxyphenyl)ethylamine **70** (1.00 g, 5.50 mmol) in dry DCM (25 mL) was added dry pyridine (860 mg, 10.9 mmol, 0.88 mL) at 0 °C under

N₂. Acetic anhydride (730 mg, 7.15 mmol, 0.67 mL) was subsequently added and the mixture was stirred for 2 h at RT. DCM (30 mL) was then added and the solution was washed with H₂O. The solution was dried (MgSO₄) and then evaporated to give a solid which was purified by column chromatography (EtOAc : Pet. spirit (6 : 4)) to afford **126** (640 mg, 56 %) as a white solid which had spectral data identical to that reported in the literature.¹⁹²

R_f. 0.27 (EtOAc : Pet. spirit (6 : 4)).

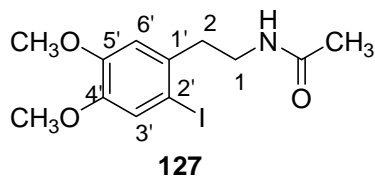
m.p. 86-89 °C. **lit.**¹⁹² **m.p.** 95-98 °C.

¹H NMR: δ 6.82 (d, 1H, *J* 8.4 Hz, H5'), 6.73 (dd, 1H, *J* 8.4, 1.8 Hz, H6'), 6.72 (d, 1H, *J* 1.8 Hz, H2'), 5.58 (bs, 1H, NH), 3.88 (s, 3H, OCH₃-4'), 3.87 (s, 3H, OCH₃-3'), 3.50 (dd, 2H, *J* 12.9, 7.0 Hz, H2), 2.77 (t, 2H, *J* 7.0 Hz, H1), 1.95 (s, 3H, COCH₃).

¹³C NMR: δ 170.0 (COCH₃), 149.0 (C4'), 147.7 (C3'), 131.3 (C1'), 120.6 (CH-2'), 111.9 (CH-6'), 111.3 (CH-5'), 55.9 (OCH₃-4'), 55.8 (OCH₃-5'), 40.7 (CH₂-1), 35.1 (CH₂-2), 23.2 (COCH₃).

MS (ES⁺): *m/z* 224 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₁₂H₁₈NO₃, 224.1287 (MH⁺). Found 224.1281.

***N*-[2-(2'-Iodo-4',5'-dimethoxyphenyl)ethyl]acetamide (**127**).**



To a solution of **126** (400 mg, 1.79 mmol) and NIS (521 mg, 2.32 mmol) in dry CH₃CN (10 mL) was added TFA (64 mg, 0.557 mmol, 0.039 mL) at 0 °C under N₂. The

solution was brought to RT and stirred for 18 h. The mixture was evaporated, and the residue was redissolved in EtOAc. The solution was washed with H₂O, brine, sat. Na₂S₂O₃, and sat. NaHCO₃. The solution was dried (MgSO₄), filtered and then evaporated to give a yellow solid. The solid was purified by column chromatography (EtOAc : hexane (3 : 7)) to afford **127** (617 mg, 99 %) as white solid.

R_f. 0.11 (EtOAc : Pet. spirit (5 : 3)).

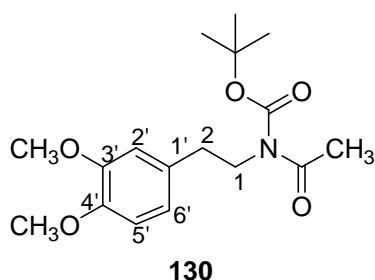
m.p. 86-88 °C.

¹H NMR: δ 7.16 (s, 1H, H_{3'}), 6.70 (s, 1H, H_{6'}), 5.74 (bs, 1H, NH), 3.80 (s, 6H, 2 x OCH₃), 3.42 (q, 2H, *J* 4.2 Hz, H₁), 2.84 (t, 2H, *J* 4.2 Hz, H₂), 1.93 (s, 3H, COCH₃).

¹³C NMR: δ 170.3 (C=OCH₃), 149.4 (C_{4'}), 148.2 (C_{5'}), 133.9 (C_{1'}), 121.6 (CH-3'), 112.6 (CH-6'), 88.0 (C_{2'}), 55.1 (OCH₃-4'), 55.9 (OCH₃-5'), 39.8 (CH₂-1), 39.6 (CH₂-2), 29.5 (COCH₃).

MS (ES⁺): *m/z* 350 (MH⁺, 45 %). **HRMS (ES⁺):** calcd for C₁₂H₁₇NO₃I, 350.0253 (MH⁺). Found 350.0240.

***N*-[2-(3',4'-Dimethoxyphenyl)ethyl]-*N*-(1,1-dimethylethyloxycarbonyl)acetamide (**130**).**



A solution of amide **126** (640 mg, 2.87 mmol), di-(*tert*-butylcarbamate) (750 mg, 3.44 mmol) and DMAP (35 mg, 0.287 mmol) in dry CH₃CN (20 mL) was heated at reflux under a N₂ atmosphere for 2 h. The reaction was

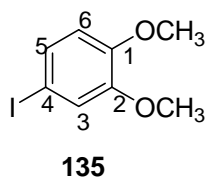
m.p. 74-80 °C.

¹H NMR: δ 7.16 (s, 1H, H3'), 6.67 (s, 1H, H6'), 3.85 (t, 1H, *J* 7.2 Hz, H1), 3.80 (s, 3H, OCH₃-4'), 3.79 (s, 3H, OCH₃-5'), 2.87 (t, 1H, *J* 7.2 Hz, H2), 2.45 (s, 3H, COCH₃), 1.41 (s, 9H, OC(CH₃)₃).

¹³C NMR: δ 173.3 (C=OCH₃), 153.2 (C=OOC(CH₃)₃), 149.5 (C4'), 148.3 (C5'), 134.6 (C1'), 121.6 (CH-3'), 121.8 (CH-6'), 88.2 (C2'), 83.1 (C(CH₃)₃), 56.3 (OCH₃-4'), 56.0 (OCH₃-5'), 44.5 (CH₂-1), 39.1 (CH₂-2), 28.1 (C(CH₃)₃), 27.2 (COCH₃).

MS (ES⁺): *m/z* 450 (MH⁺, 10 %), 472 (M+Na⁺, 100 %). **HRMS (ES⁺):** calcd for C₁₇H₂₅NO₅I, 450.0778 (MH⁺). Found 450.0772.

4-Iodo-1,2-dimethoxybenzene (**135**).¹⁴⁸



To a stirred suspension of 1,2-dimethoxybenzene **134** (600 mg, 4.34 mmol, 0.39 ml) and silver trifluoroacetate (1.06 g, 4.78 mmol) was added dropwise a solution of iodine (1.32 g, 5.21 mmol) in chloroform (20 mL). The mixture was left to stir at RT for 4 h. The

mixture was worked up in a similar manner to that described above in the synthesis of **131** to give a yellow oil which was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) to give the desired product **135** (840 mg, 73 %) as a yellow oil.

R_f 0.84 (EtOAc : Pet. spirit (1 : 1)).

¹H NMR: δ 7.20 (dd, 1H, *J* 8.4, 2.1 Hz, H5), 7.08 (d, 1H, *J* 2.1 Hz, H3), 6.58 (d, 1H, *J* 8.4 Hz, H6), 3.82 (s, 3H, OCH₃-1), 3.81 (s, 3H, OCH₃-2).

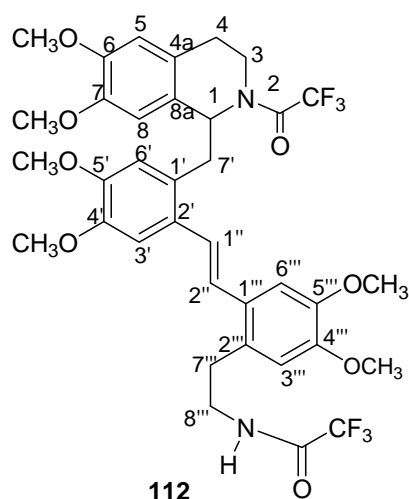
¹³C NMR: δ 149.8 (C2), 149.2 (C1), 121.8 (CH-5), 120.3 (CH-3), 113.2 (CH-6), 82.8 (C4), 56.1 (OCH₃-2), 56.0 (OCH₃-1).

MS (ES⁺): *m/z* 265.1 (MH⁺, 30 %).

8.3.2. General method for Heck coupling reactions.

A mixture of palladium acetate, *N,N*-dimethyl glycine (DMG), sodium acetate and both coupling partners were placed in a thick walled tube under N₂. Dry *N*-methyl pyrrolidinone (NMP) was added and the reaction mixture was bubbled with argon prior to sealing the tube. The reaction mixture was heated at 130 °C for 18 h. The mixture was cooled and then diluted with DCM and the solution was washed with H₂O (4 x), brine and dried (MgSO₄). The solution was evaporated to give a dark oil that was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) to give the desired product.

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2'''-(trifluoroacetylaminoethyl))phenyl-ethenyl]phenylmethyloquinoline (112).



The 2'-vinylaudanosine derivative **67** (265 mg, 0.56 mmol), aryl iodide **118** (157 mg, 0.56 mmol), Pd(OAc)₂ (12.6 mg, 0.056 mmol), DMG (116 mg, 1.12 mmol), NaOAc (88 mg, 1.12 mmol) and NMP (5 mL) were treated as described above in the general Heck coupling reaction procedure to give a dark oil that was purified by column chromatography to afford **112** (273 mg, 66 %) as a white solid. Compound **112**

was a 95 : 5 mixture of rotamers.

R_f. 0.33 (EtOAc : Pet. spirit (1 : 1)).

m.p. 184-186 °C.

¹H NMR of the major rotamer: δ 7.37 (s, 1H, H_{3'}), 7.33 (d, 1H, *J* 15.9 Hz, H_{2''}), 7.27 (s, 1H, H_{6'''}), 7.15 (d, 1H, *J* 15.9 Hz, H_{1''}), 6.74 (t, 1H, *J* 4.8 Hz, NH), 6.60 (s,

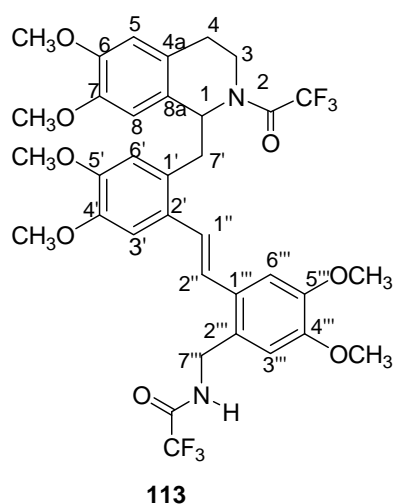
1H, H3'''), 6.55 (s, 1H, H5), 6.25 (s, 1H, H6'), 5.83 (s, 1H, H8), 5.42 (dd, 1H, *J* 9.9, 4.5 Hz, H1), 4.01 (s, 3H, OCH₃-4'''), 3.97 (s, 3H, OCH₃-5'), 3.86 (s, 3H, OCH₃-5'''), 3.80 (m, 1H, H3, H8'''), 3.74 (s, 3H, OCH₃-4'), 3.66 (s, 3H, OCH₃-7), 3.50 (m, 2H, H3, H8'''), 3.42 (s, 3H, OCH₃-6), 3.38 (dd, 1H, *J* 13.2, 4.5 Hz, H7'), 2.99 (m, 2H, H7'''), 2.93 (dd, 1H, *J* 13.2, 9.9 Hz, H7'), 2.86 (m, 2H, H4).

¹H NMR of the minor rotamer (in part): δ 5.24 (dd, 1H, *J* 9.6, 1.5 Hz, H1).

¹³C NMR of the major rotamer: δ 157.6 (q, *J* 34.3 Hz, COCF₃), 148.8 (C4'''), 148.6 (C5'), 148.5 (C5'''), 148.3 (C4'), 148.2 (C7), 147.0 (C6), 129.9 (C2'''), 129.2 (C1'), 128.0 (C1'''), 127.3 (C2'), 125.9 (C4a), 125.4 (CH-2''), 125.3 (C8a), 125.2 (CH-1''), 115.9 (q, *J* 286.1 Hz, COCF₃), 114.9 (CH-6'), 114.8 (CH-3'''), 111.4 (CH-8), 110.9 (CH-5), 108.8 (CH-3'), 108.3 (CH-6'''), 56.3 (OCH₃-4'''), 56.0 (CH-1), 55.9 (OCH₃-5', OCH₃-5''', OCH₃-4'), 55.6 (OCH₃-7, OCH₃-6), 41.5 (CH₂-3), 41.3 (CH₂-8'''), 38.9 (CH₂-7'), 32.2 (CH₂-7'''), 28.5 (CH₂-4).

MS (ES⁺): *m/z* 741.1 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₆H₃₉N₂O₈F₆, 741.2611 (MH⁺). Found 741.2637.

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2''')-(trifluoroacetylaminomethyl))phenyl-ethenyl]phenylmethylisoquinoline (113).



The 2'-vinylisoquinoline derivative **67** (255 mg, 0.55 mmol), aryl iodide **119** (214 mg, 0.55 mmol), Pd(OAc)₂ (14 mg, 0.055 mmol), DMG (85 mg, 1.10 mmol), NaOAc (113 mg, 1.10 mmol) and NMP (5 mL) were treated as described above in the general Heck coupling reaction procedure to give a dark oil which

was purified by column chromatography to afford **113** (157 mg, 38 %) as a white solid. 2'-Vinylaudanosine **67** (48 mg, 19 %) and deiido-**119** (27 mg, 19 %) were also isolated. Compound **113** was a 95 : 5 mixture of rotamers.

R_f. 0.33 (EtOAc : Pet. spirit (1 : 1)).

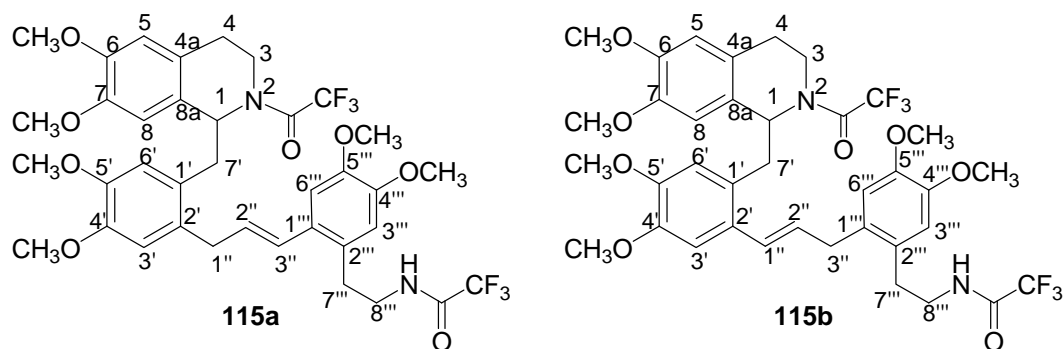
m.p. 116-118 °C.

¹H NMR of the major rotamer: δ 7.54 (s, 1H, H3'), 7.51 (d, 1H, *J* 16.2 Hz, H2''), 7.21 (s, 1H, H6'''), 7.02 (d, 1H, *J* 16.2 Hz, H1''), 6.75 (s, 1H, H3'''), 6.63 (t, 1H, *J* 5.8 Hz, NH), 6.55 (s, 1H, H5), 6.12 (s, 1H, H6'), 5.77 (s, 1H, H8), 5.38 (dd, 1H, *J* 9.9, 3.8 Hz, H1), 4.74 (dd, 1H, *J* 14.5, 5.8 Hz, H7'''), 4.57 (dd, 1H, *J* 14.5, 4.5 Hz, H7''), 4.06 (s, 3H, OCH₃-4'''), 3.97 (s, 3H, OCH₃-5'), 3.88 (s, 3H, OCH₃-5'''), 3.79 (m, 1H, H3), 3.74 (s, 3H, OCH₃-4'), 3.70 (m, 1H, H3), 3.61 (s, 3H, OCH₃-7), 3.46 (dd, 1H, *J* 12.9, 3.8 Hz, H7'), 3.41 (s, 3H, OCH₃-6), 2.90 (dd, 1H, *J* 12.9, 9.9 Hz, H7'), 2.86 (m, 2H, H4).

¹³C NMR of the major rotamer: (signals for COCF₃ and COCF₃ were not observed), δ 149.6 (C4'''), 148.6 (C5'), 148.4 (C5'''), 148.3 (C4'), 148.1 (C7), 146.9 (C6), 129.6 (C2'''), 129.2 (C1'), 127.1 (C1'''), 125.6 (C2', C4a), 125.2 (C8a, CH-2''), 123.8 (CH-1''), 114.9 (CH-6'), 113.2 (CH-3'''), 111.3 (CH-8), 110.7 (CH-5), 108.6 (CH-3'), 107.8 (CH-6'''), 56.2 (OCH₃-4'''), 56.1 (OCH₃-5'), 56.0 (OCH₃-5'''), 55.9 (OCH₃-4'), 55.8 (OCH₃-7, CH-1), 55.8 (OCH₃-6), 41.9 (CH₂-7'''), 41.3 (CH₂-3), 38.8 (CH₂-7'), 28.3 (CH₂-4).

MS (ES⁺): *m/z* 727 (MH⁺, 10 %), 749.2 (M+Na⁺, 20 %). **HRMS (ES⁺):** calcd for C₃₅H₃₇N₂O₈F₆, 727.2454 (MH⁺). Found 727.2420.

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4'''',5''''-dimethoxy-2''''-(trifluoroacetylaminoethyl))phenyl-2''-propenyl]phenylmethyloquinoline (**115a**) and (*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4'''',5''''-dimethoxy-2''''-(trifluoroacetylaminoethyl))phenyl-1''-propenyl]phenylmethyloquinoline (**115b**).



The 2'-allyllaundanosine derivative **68** (173 mg, 0.360 mmol) and aryl iodide **118** (152 mg, 0.54 mmol), Pd(OAc)₂ (10 mg, 0.054 mmol), DMG (75 mg, 0.72 mmol), NaOAc (59 mg, 0.72 mmol) and NMP (5 mL) were treated as described above in the Heck coupling reaction procedure to give a dark oil which was purified by column chromatography to afford **115** (180 mg, 66 %) as a clear oil. The product was isolated as a 60 : 40 mixture of (*E*)-**115a** and (*E*)-**115b**. Compounds **115a** and **115b** were a 95 : 5 mixture of rotamers.

R_f. 0.62 (EtOAc : Pet. spirit (1 : 1)).

¹H NMR of (*E*)-115a: δ 7.31 (s, 1H, NH), 6.90 (s, 1H, H6'''), 6.67 (s, 1H, H3'''), 6.59 (s, 1H, H6'), 6.57 (s, 1H, H5), 6.49 (d, 1H, *J* 15.6 Hz, H3''), 6.40 (s, 1H, H3'), 6.00 (dt, 1H, *J* 15.6, 6.9 Hz, H2''), 6.00 (s, 1H, H8), 5.47 (t, 1H, *J* 6.7 Hz, H1), 3.86 (m, 1H, H3), 3.81 (s, 12H, OCH₃-3''', OCH₃-4''', OCH₃-5' and OCH₃-7), 3.73 (m, 1H, H3), 3.66 (s, 3H, OCH₃-4'), 3.50 (m, 1H, H1''), 3.49 (s, 3H, OCH₃-6), 3.41 (q, 2H, *J* 8.4, H8'''), 3.28 (dd, 1H, *J* 10.2, 6.9 Hz, H1'), 3.10 (d, 2H, *J* 6.7 Hz, H7'), 2.91 (dt, 1H, *J* 10.2, 5.4, H4), 2.81 (t, 2H, *J* 8.4 Hz, H7'''), 2.74 (m, 1H, H4).

¹H NMR of (*E*)-115b (in part): δ 7.53 (bs, 1H, NH), 6.92 (s, 1H, H6'''), 6.73 (s, 1H, H3'''), 6.72 (d, 1H, *J* 15.6 Hz, H1''), 6.73 (s, 1H, H6'), 6.22 (s, 1H, H3'), 5.97 (dt, 1H, *J* 15.6, 5.1 Hz, H2''), 5.88 (s, 1H, H8), 5.44 (t, 1H, *J* 4.5 Hz, H1), 3.62 (s, 3H, OCH₃-4'), 3.54 (m, 2H, H3''), 3.43 (s, 3H, OCH₃-6), 2.94 (m, 1H, H4), 2.66 (m, 1H, H4).

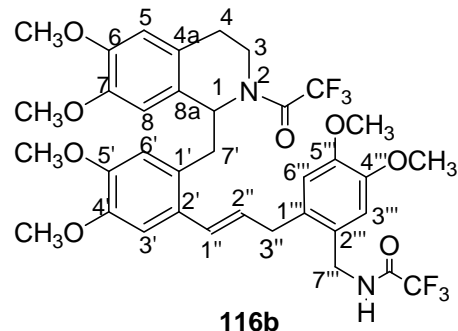
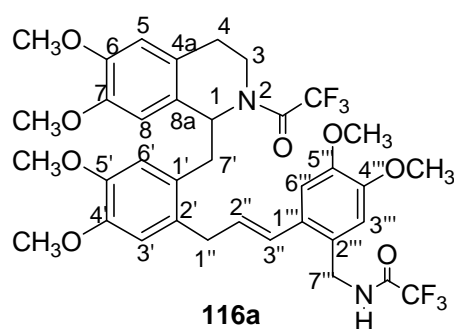
¹H NMR of the minor rotamer for both (*E*)-isomers (in part): (note- * - represents the isomer **115b**). δ 6.84 (s, 1H, H6'''), 6.79 (s, 1H, H6'''), 5.85 (s, 1H, H8), 5.68 (s, 1H, H8*), 2.99 (d, 2H, *J* 9.3 Hz, H7').

¹³C NMR of (*E*)-115a: (signals for COCF₃ and COCF₃ were not observed), δ 148.8 (C4'''), 148.3 (C7, C5''', C5'), 147.5 (C4'), 147.3 (C6), 131.4 (C1'), 130.5 (C1'''), 129.2 (CH-2''), 128.6 (C2'), 127.6 (C2'''), 127.4 (CH-3''), 126.2 (C4a), 125.5 (C8a), 114.5 (CH-6'''), 112.9 (CH-3'), 111.2 (CH-3'''), 111.1 (CH-8), 110.9 (CH-5), 108.4 (CH-6'), 56.1 (6 x OCH₃), 56.1 (CH-1), 41.1 (CH₂-8'''), 41.0 (CH₂-3), 37.9 (CH₂-7'), 36.7 (CH₂-1''), 32.3 (CH₂-7'''), 28.6 (CH₂-4).

¹³C NMR of (*E*)-115b (in part): δ 147.9 (C4'), 147.2 (C6), 129.5 (CH-2''), 128.5 (C2'), 128.0 (CH-1''), 126.5 (CH-6'''), 126.0 (C4a), 114.7 (CH₆''), 113.5 (CH-3'''), 111.1 (CH-3'), 108.9 (CH-6'), 55.8 (CH-1), 41.2 (CH₂-8'''), 40.8 (CH₂-3), 39.0 (CH₂-7'), 37.0 (CH₂-3''), 32.2 (CH₂-7''').

MS (ES⁺): *m/z* 755.0 (MH⁺, 10 %). A good quality HR could not be obtained.

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4'''',5''''-dimethoxy-2''''-(trifluoroacetylaminomethyl))phenyl-2''-propenyl]phenylmethyloquinoline (**116a**) and (*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4'''',5''''-dimethoxy-2''''-(trifluoroacetylaminomethyl))phenyl-1''-propenyl]phenylmethyloquinoline (**116b**).



The 2'-allyllaundanosine derivative **68** (250 mg, 0.54 mmol), aryl iodide **119** (109 mg, 0.54 mmol), Pd(OAc)₂ (13 mg, 0.054 mmol), DMG (83 mg, 1.07 mmol), NaOAc (111 mg, 1.07 mmol), NMP (5 mL) were treated as above in the general Heck coupling reaction procedure to give a dark oil which was purified by column chromatography to give **116** (157 mg, 39 % yield) as a yellow oil. The product was isolated as a 60 : 40 mixture of (*E*)-**116a** and (*E*)-**116b**. Compounds **116a** and **116b** were a 95 : 5 mixture of rotamers.

R_f 0.34 (EtOAc : Pet. spirit (1 : 1)).

¹H NMR of (*E*)-116a: δ 7.01 (bs, 1H, NH), 6.92 (s, 1H, H6'''), 6.79 (s, 1H, H3'''), 6.69 (s, 1H, H6'), 6.58 (s, 1H, H5), 6.49 (d, 1H, *J* 15.9 Hz, H3''), 6.38 (s, 1H, H3'), 6.12 (dt, 1H, *J* 15.9, 6.3 Hz, H2''), 6.02 (s, 1H, H8), 5.48 (t, 1H, *J* 6.9 Hz, H1), 4.46 (dd, 1H, *J* 14.5, 5.0 Hz, H7'''), 4.38 (dd, 1H, *J* 14.5, 5.0 Hz, H7'''), 3.92 (m, 1H, H3), 3.83 (s, 12H, OCH₃-3''', OCH₃-4''', OCH₃-5', OCH₃-7), 3.70 (m, 1H, H3), 3.68 (s, 3H, OCH₃-4'), 3.54 (s, 3H, OCH₃-6), 3.52 (m, 1H, H1''), 3.36 (m, 1H, H1''), 3.10 (dd, 2H, *J* 10.0, 7.0 Hz, H7'), 2.93 (m, 1H, H4), 2.79 (m, 1H, H4).

¹H NMR of (*E*)-116b (in part): δ 7.31 (bs, 1H, NH), 6.94 (s, 1H, H6'''), 6.83 (s, 1H, H3'''), 6.75 (s, 1H, H6'), 6.67 (dt, 1H, *J* 16.5, 6.3 Hz, H2''), 6.59 (d, 1H, *J* 16.5 Hz, H1''), 6.57 (s, 1H, H5), 6.12 (s, 1H, H3'), 5.79 (s, 1H, H8), 5.27 (dd, 1H, *J* 10.0, 4.5 Hz, H1), 4.56 (dd, 1H, *J* 14.5, 5.0 Hz, H7'''), 4.48 (dd, 1H, *J* 14.5, 5.0 Hz, H7''), 3.80 (s, 12H, OCH₃-3''', OCH₃-4''', OCH₃-5', OCH₃-7), 3.62 (s, 3H, OCH₃-4'), 3.44 (s, 3H, OCH₃-6), 3.46 (m, 1H, H3''), 3.36 (m, 1H, H3'), 3.17 (m, 2H, H7').

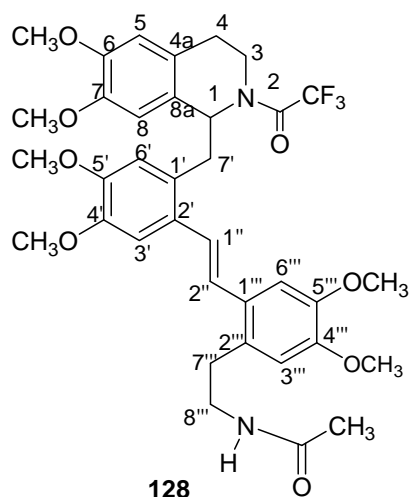
¹H NMR of the minor rotamers (in part): (note-* indicates the rotamer of isomer **116b**). δ 6.94 (s, 1H, H6'''), 6.92 (s, 1H, H6''''*), 6.81 (s, 1H, H3'), 6.31 (s, 1H, H6'), 6.29 (s, 1H, H6'*), 5.99 (s, 1H, H8), 5.91 (s, 1H, H8*).

¹³C NMR of (*E*)-116a: (signals for COCF₃ and COCF₃ were not observed), δ 149.1 (C4'''), 148.5 (C5'''), 148.3 (C5'), 148.1 (C7), 147.3 (C4'), 147.2 (C6), 130.8 (C2'), 130.6 (CH-2''), 129.2 (CH-3''), 129.1 (C2'''), 127.3 (C1'), 126.9 (C1'''), 126.1 (C8a), 125.1 (C4a), 114.4 (CH-3'), 113.3 (CH-6'), 113.2 (CH-3'''), 111.0 (CH-8, CH-5), 108.9 (CH-6'''), 55.8 (6 x OCH₃), 55.5 (CH-1), 41.4 (CH₂-7'''), 40.7 (CH₂-3), 38.0 (CH₂-7'), 36.2 (CH₂-1''), 29.4 (CH₂-4).

¹³C NMR of (*E*)-116b (in part): δ 148.8 (C4'''), 148.3 (C5'''), 148.2 (C5'), 148.0 (C7), 147.5 (C4'), 146.9 (C6), 130.7 (CH-2'', C2'''), 129.1 (CH-1''), 129.0 (C2'), 127.5 (C1'), 126.4 (C1'''), 125.8 (C8a), 125.4 (C4a), 114.6 (CH-3'), 113.6 (CH-6'), 113.0 (CH-3'''), 110.8 (CH-8, CH-5), 108.2 (CH-6'''), 55.2 (CH-1), 41.5 (CH₂-7'''), 38.6 (CH₂-3), 28.4 (CH₂-4).

MS (ES⁺): *m/z* 741.2 (MH⁺, 10 %), 758.2 (M+Na⁺, 20 %). **HRMS (ES⁺):** calcd for C₃₆H₃₉N₂O₈F₆, 741.2611 (MH⁺). Found 741.2592.

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4'''',5''''-dimethoxy-2''')-(acetylaminoethyl))phenyl-ethenyl]phenylmethyloquinoline (**128**).



The 2'-vinylaudanosine derivative **67** (223 mg, 0.48 mmol), aryl iodide **131** (216 mg, 0.48 mmol), Pd(OAc)₂ (12 mg, 0.048 mmol), DMG (74 mg, 0.96 mmol), NaOAc (99 mg, 0.96 mmol) and NMP (5 mL) were treated as described above in the general Heck coupling reaction procedure to give a dark oil that was purified by column chromatography (EtOAc) to afford **128** (130 mg, 40 % yield) as a yellow oil. Compound **128** was a 95 : 5 mixture of rotamers.

R_f 0.52 (EtOAc).

¹H NMR of the major rotamer: δ 7.49 (s, 1H, H3'''), 7.47 (d, 1H, *J* 16.2 Hz, H2''), 7.36 (s, 1H, H6'''), 7.27 (d, 1H, *J* 16.2 Hz, H1''), 6.66 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.19 (s, 1H, H6'), 5.87 (s, 1H, H8), 5.67 (bs, 1H, NH), 5.48 (dd, 1H, *J* 9.6, 3.9 Hz, H1), 4.06 (s, 3H, OCH₃-4'''), 4.03 (s, 3H, OCH₃-5'), 3.89 (s, 3H, OCH₃-5'''), 3.82 (m, 1H, H3), 3.80 (s, 3H, OCH₃-4'), 3.71 (m, 1H, H3), 3.65 (s, 3H, OCH₃-7), 3.46 (s, 3H, OCH₃-6), 3.45 (m, 2H, H8'''), 3.42 (m, 1H, H7'), 3.00 (m, 1H, H7'), 2.98 (m, 2H, H7'''), 2.84 (m, 2H, H4), 1.88 (s, 3H, COCH₃).

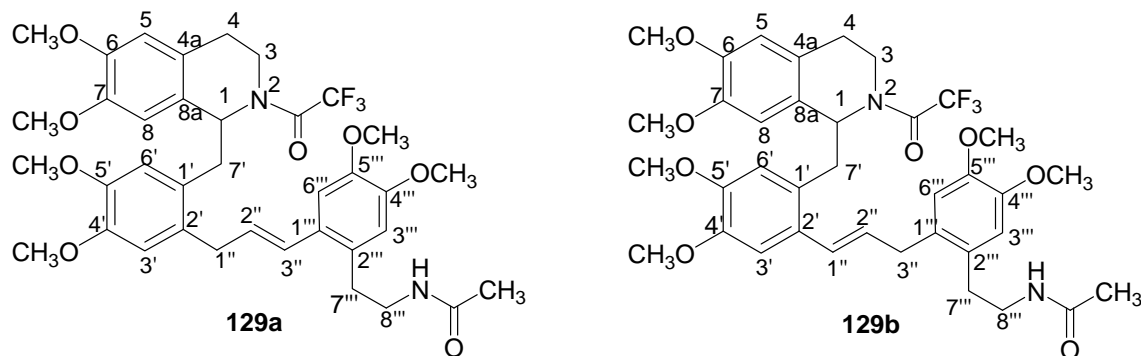
¹H NMR of the minor rotamer (in part): δ 6.85 (d, 1H, *J* 15.0 Hz, H2''), 6.70 (d, 1H, *J* 15.0 Hz, H1'').

¹³C NMR of the major rotamer: δ 170.4 (C=OCH₃), 156.6 (q, *J* 37.5 Hz, C=OCF₃), 148.9 (C4'''), 148.7 (C5'), 148.4 (C5''', C4'), 148.3 (C7), 147.1 (C6), 130.1 (C1''', C2'''), 129.5 (C1'), 129.2 (C2'), 126.0 (C4a), 125.9 (CH-2''), 125.3 (CH-1''), 124.8

(C8a), 115.8 (q, J 276.6 Hz, COCF₃), 114.9 (CH-6'''), 113.0 (CH-3'''), 111.5 (CH-8), 111.0 (CH-5), 108.7 (CH-3'), 108.5 (CH-6'), 56.5 (OCH₃-4'''), 56.4 (CH-1), 56.1 (OCH₃-5', OCH₃-5'''), 56.0 (OCH₃-4'), 56.0 (OCH₃-7), 55.7 (OCH₃-6), 41.4 (CH₂-8'''), 40.9 (CH₂-3), 38.9 (CH₂-7'''), 32.7 (CH₂-7'), 28.6 (CH₂-4), 23.4 (COCH₃).

MS (ES⁺): m/z 687.1 (MH⁺, 10 %). **HRMS (ES⁺):** calcd for C₃₆H₄₂N₂O₈F₃, 687.2893 (MH⁺). Found 687.2897.

(RS) (E) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2''')-(acetylaminoethyl))phenyl-2''-propenyl]phenylmethyloisoquinoline (129a) and **(RS) (E) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2''')-(acetylaminoethyl))phenyl-1''-propenyl]phenylmethyloisoquinoline (129b)**.



The 2'-allyllaundanosine derivative **68** (211 mg, 0.44 mmol), aryl iodide **131** (199 mg, 0.440 mmol), Pd(OAc)₂ (11 mg, 0.044 mmol), DMG (69 mg, 0.880 mmol), NaOAc (91 mg, 0.880 mmol) and NMP (5 mL) were treated as described above in the general Heck coupling reaction procedure to give an oil. The oil was purified by column chromatography (EtOAc) to give **129** (130 mg, 43 %) as a yellow oil. The product was obtained as a 60 : 40 mixture of (*E*)-**129a** and (*E*)-**129b**. Compound **129a** and **129b** were a 95 : 5 mixture of rotamers.

R_f 0.52 (100 % EtOAc).

¹H NMR of (*E*)-129a: δ 6.92 (s, 1H, H6'''), 6.71 (s, 1H, H3'''), 6.64 (s, 1H, H6'), 6.60 (s, 1H, H5), 6.54 (d, 1H, J 16.5 Hz, H3''), 6.45 (s, 1H, H3'), 6.18 (bs 1H, NH), 6.04 (dt,

1H, *J* 16.5, 6.0 Hz, H2''), 6.04 (s, 1H, H8), 5.54 (t, 1H, *J* 6.6 Hz, H1), 3.92 (m, 1H, H3), 3.73 (m, 1H, H3), 3.86 (s, 12H, OCH₃-5''', OCH₃-4''', OCH₃-4' and OCH₃-6), 3.71 (s, 3H, OCH₃-5'), 3.62 (m, 1H, H8'''), 3.53 (s, 3H, OCH₃-7), 3.50 (m, 1H, H8'''), 3.36 (d, 2H, *J* 6.0 Hz, H1''), 3.15 (m, 2H, H7''), 2.85 (m, 4H, H7''', H4), 1.94 (s, 3H, COCH₃).

¹H NMR of (*E*)-129b (in part): δ 6.94 (s, 1H, H6'''), 6.73 (s, 1H, H3'''), 6.67 (s, 1H, *J* 16.0 Hz, H1''), 6.29 (s, 1H, H6'), 6.04 (dt, 1H, *J* 16.5, 6.0 Hz, H2''), 5.95 (s, 1H, H8), 5.43 (m, 1H, H1), 3.67 (s, 3H, OCH₃-5'), 3.50 (s, 3H, OCH₃-7), 3.48 (m, 2H, H3''), 1.91 (s, 3H, COCH₃).

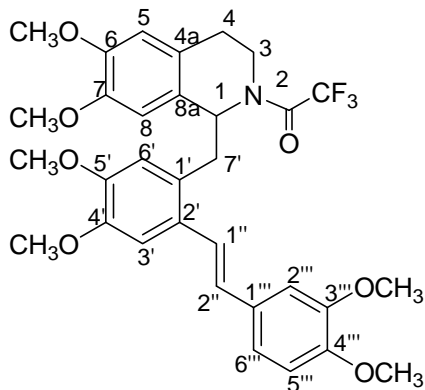
¹H NMR of the minor rotamers of both isomers (in part). (note-* indicates the rotamer of **129b**): δ 6.83 (s, 1H, H3'''), 6.81 (s, 1H, H3'''), 5.81 (s, 1H, H8), 5.78 (s, 1H, H8).

¹³C NMR of (*E*)-129a: (signals for C=O and COCF₃ were not observed), δ 170.4 (C=OCH₃), 148.7 (C4'''), 148.5 (C5'''), 148.2 (C5'), 147.8 (C7), 147.5 (C4'), 147.4 (C6), 131.5 (C2'), 130.5 (CH-2''), 129.1 (C2'''), 128.8 (CH-3''), 128.2 (C1'), 127.5 (C1'''), 126.4 (C8a), 125.3 (C4a), 114.6 (CH-3'), 113.1 (CH-6'), 111.2 (CH-3''', CH-8), 111.0 (CH-5), 109.0 (CH-6'''), 56.0 (6 x OCH₃), 55.7 (CH-1), 41.0 (CH₂-8'''), 40.8 (CH₂-3), 38.1 (CH₂-7'), 36.5 (CH₂-1''), 33.0 (CH₂-7'''), 28.7 (CH₂-4), 23.4 (COCH₃).

¹³C NMR of (*E*)-219b (in part): δ 171.5 (C=OCH₃), 148.3 (C4'''), 148.0 (C5'''), 147.7 (C7), 130.1 (C2'), 129.8 (CH-2''), 129.5 (C2'''), 128.7 (CH-1''), 126.5 (C1'''), 126.3 (C8a), 125.2 (C4a), 113.5 (CH-3'), 113.3 (CH-6'), 112.1 (CH-3'''), 111.6 (CH-8), 108.7 (CH-6'''), 55.4 (CH-1), 40.8 (CH₂-3), 38.7 (CH₂-7'), 36.8 (CH₂-3''), 32.6 (CH₂-7'''), 29.9 (CH₂-4), 23.3 (COCH₃).

MS (ES⁺): *m/z* 701.1 (MH⁺, 70 %). **HRMS (ES⁺):** calcd for C₃₇H₄₄N₂O₈F₃, 701.3050 (MH⁺). Found 701.3077.

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(3''',4'''-dimethoxyphenyl)ethenyl)]phenylmethyloquinoline (136).



136

The 2'-vinyl laudanosine derivative **136** (350 mg, 0.75 mmol), aryl iodide **135** (210 mg, 0.790 mmol), Pd(OAc)₂ (19 mg, 0.085 mmol), DMG (116 mg, 1.50 mmol), NaOAc (155 mg, 1.50 mmol) and NMP (6 mL) were treated as described above in the general Heck coupling reaction procedure to give a brown oil.

This was purified by column chromatography to afford **136** (231 mg, 51 %) as a white solid.

R_f 0.39 (EtOAc : Pet. spirit (1 : 1)).

m.p. 194-196 °C.

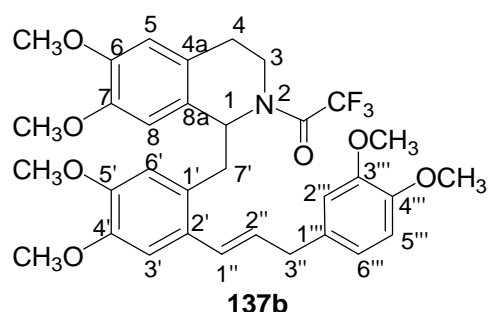
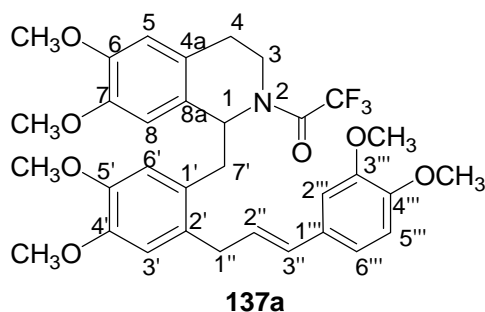
¹H NMR: δ 7.47 (d, 1H, *J* 15.9 Hz, H2''), 7.44 (d, 1H, *J* 1.2 Hz, H2'''), 7.17 (s, 1H, H3'), 6.97 (dd, 1H, *J* 8.4, 1.2 Hz, H6'''), 6.84 (d, 1H, *J* 15.9 Hz, H1''), 6.83 (d, 1H, *J* 8.4 Hz, H5'''), 6.50 (s, 1H, H5), 6.21 (s, 1H, H6'), 5.87 (s, 1H, H8), 5.49 (dd, 1H, *J* 9.9, 4.2 Hz, H1), 4.04 (s, 3H, OCH₃-3'''), 3.94 (s, 3H, OCH₃-4'''), 3.91 (s, 3H, OCH₃-4'), 3.81 (m, 2H, H3), 3.79 (s, 3H, OCH₃-6), 3.66 (s, 3H, OCH₃-5'), 3.48 (dd, 1H, *J* 13.2, 4.2 Hz, H7'), 3.46 (s, 3H, OCH₃-7), 2.96 (dd, 1H, *J* 13.2, 9.9 Hz, H7'), 2.86 (m, 2H, H4).

¹³C NMR: δ 156.3 (q, *J* 35.8 Hz, COCF₃), 149.7 (C3'''), 149.1 (C4'''), 148.5 (C4'), 148.4 (C6), 147.3 (C5'), 147.1 (C7), 131.0 (C1'), 130.1 (C1'''), 129.1 (CH-2''), 127.4 (C2'), 126.1 (C4a), 125.5 (C8a), 123.3 (CH-1''), 120.8 (CH-6'''), 115.2 (CH-6'), 114.1 (q, *J* 286.3 Hz, COCF₃), 111.6 (CH-3'), 111.1 (CH-2'''), 111.0 (CH-5), 108.4 (CH-8), 108.1 (CH-5'''), 55.3 (OCH₃-3'''), 56.2 (OCH₃-4'''), 56.1 (OCH₃-4'), 56.1 (OCH₃-6),

56.0 (OCH₃-5'), 55.4 (CH-1), 55.8 (OCH₃-7), 41.4 (CH₂-3), 38.9 (CH₂-7'), 28.6 (CH₂-4).

MS (ES⁺): *m/z* 602.1 (MH⁺, 60 %). **HRMS (ES⁺):** calcd for C₃₂H₃₅NO₇F₃, 602.2366 (MH⁺). Found 602.2332.

(RS) (E) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(3''',4'''-dimethoxyphenyl)-2''-propenyl)]phenylmethyloquinoline (137a) and **(RS) (E) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(3''',4'''-dimethoxyphenyl)-1''-propenyl)]phenylmethyloquinoline (137b)**.



The 2'-allyllaudoquinoline derivative **68** (147 mg, 0.31 mmol), aryl iodide **137** (81 mg, 0.31 mmol), Pd(OAc)₂ (8 mg, 0.031 mmol), DMG (48 mg, 0.61 mmol), NaOAc (64 mg, 0.61 mmol) and NMP (3 mL) were treated as described above in the general Heck coupling reaction procedure to give an oil which was purified by column chromatography to afford **137** (108 mg, 50 %) as a yellow oil. This product was isolated as a 70 : 30 mixture of (*E*)-**137a** and (*E*)-**137b**.

R_f 0.71 (EtOAc : Pet. spirit (1 : 1)).

¹H NMR of (*E*)-137a: δ 6.83 (d, 1H, *J* 6.0 Hz, H5'''), 6.80 (dd, 1H, *J* 6.0, 3.0 Hz, H6'''), 6.77 (s, 1H, H3'), 6.74 (d, 1H, *J* 3.0 Hz, H2'''), 6.68 (s, 1H, H5), 6.57 (s, 1H, H6'), 6.21 (d, 1H, *J* 15.6 Hz, H3''), 6.09 (m, 1H, H2''), 6.04 (s, 1H, H8), 5.53 (t, 1H, *J* 6.6 Hz, H1), 3.91 (dt, 1H, *J* 12.0, 4.2 Hz, H3), 3.63 (dt, 1H, *J* 12.0, 4.2 Hz, H3), 3.83 (s, 12H, OCH₃-3''', OCH₃-4''', OCH₃-4', OCH₃-6), 3.76 (s, 3H, OCH₃-5'), 3.54 (s, 3H,

OCH₃-7), 3.41 (m, 1H, H1''), 3.29 (m, 1H, H1''), 3.09 (m, 2H, H7'), 2.80 (m, 1H, H4), 2.70 (m, 1H, H4).

¹H NMR of (E)-137b (in part): δ 6.91 (s, 1H, H3'), 6.85 (s, 1H, H5), 6.40 (s, 1H, H6'), 6.02 (s, 1H, H8), 6.53 (d, 1H, *J* 15.6 Hz, H1''), 6.09 (m, 1H, H2''), 3.70 (s, 3H, OCH₃-5'), 3.50 (s, 3H, OCH₃-7), 3.36 (d, 2H, *J* 6.6 Hz, H3''), 3.20 (m, 1H, H7'), 3.01 (m, 1H, H7'), 2.85 (m, 2H, H4).

¹³C NMR of (E)-137a: (signals for COCF₃ and COCF₃ were not observed), δ 149.1 (C3'''), 148.6 (C4'''), 148.3 (C4'), 148.2 (C6), 147.4 (C5'), 147.3 (C7), 131.3 (C1'), 130.5 (C1'''), 130.1 (CH-2''), 127.8 (C2'), 127.3 (CH-3''), 126.5 (C4a), 125.0 (C8a), 119.1 (CH-6'''), 114.2 (CH-6'), 113.2 (CH-3'), 112.2 (CH-2'''), 111.1 (CH-5), 111.0 (CH-8), 108.7 (CH-5'''), 56.1-55.7 (6 x OCH₃), 55.4 (CH-1), 40.7 (CH₂-3), 39.3 (CH₂-1''), 38.1 (CH₂-7'), 29.6 (CH₂-4).

¹³C NMR of (E)-137b (in part): δ 148.0 (C6), 147.3 (C7), 130.6 (C1'''), 130.0 (CH-2''), 127.5 (CH-1''), 126.7 (C2'), 126.3 (C4a), 125.2 (C8a), 120.6 (CH-6'''), 114.2 (CH-6'), 111.4 (CH-5), 110.8 (CH-8), 38.2 (CH₂-7'), 35.9 (CH₂-3'').

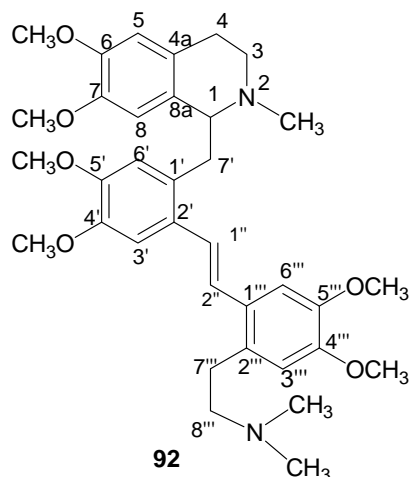
MS (EI⁺): *m/z* 615 (M⁺, 10 %). **HRMS (EI⁺):** calcd for C₃₃H₃₆NO₇F₃, 615.2443 (M⁺). Found 615.2444.

8.3.3. General method for N-TFA deprotection and reductive N-methylation.

To a solution of the N-TFA protected amine in a mixture of CH₃OH and H₂O was added K₂CO₃. The resulting solution was stirred at 60 °C for 18 h. CH₃OH was then evaporated and the residue was dissolved in CH₃CN and 38 % formaldehyde was added, followed by NaCNBH₃. Acetic acid was added after 20 min of stirring to adjust the pH to 6-7. The reaction mixture was then left to stir at RT for 18 h. The CH₃CN was evaporated and the residue was redissolved in DCM. The DCM layer was washed with

1M NaOH, dried (MgSO₄) and evaporated to give a crude mixture which was purified by column chromatography to afford the *N*-methylated product.

(*RS*) (*E* and *Z*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2'''-(dimethylaminoethyl))phenyl-ethenyl]phenylmethyl-2-methylisoquinoline (92**).**



The *N*-protected amine **112** (263 mg, 0.34 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation procedure using initially K₂CO₃ (257 mg, 1.72 mmol), CH₃OH (70 mL) and H₂O (2 mL) and then 38 % formaldehyde (12 mL), CH₃CN (15 mL) and NaCNBH₃ (83 mg, 1.34 mmol) to give an oil. The oil was purified by

column chromatography (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)) to afford the *N*-methylated analogues (*E*)-**92** (109.2 mg, 54 % over 2 steps) as a white solid.

(Note: When the hydrolysis was carried out at 60 °C, the product **92** was obtained as 100 % the (*E*)-isomer, however when the hydrolysis was done at RT, the product **92** was obtained as a 70 : 30 mixture of (*Z*)- and (*E*)-isomers in 30 % yield).

R_f. 0.12 (EtOAc : CH₃OH (1 : 1)).

m.p. 158-160 °C.

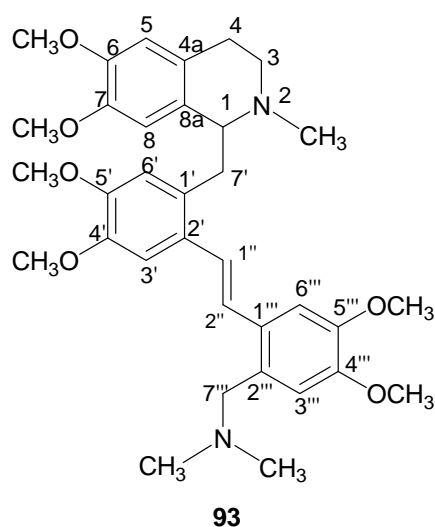
¹H NMR of (*E*)-92: δ 7.04 (s, 1H, H3'), 6.97 (d, 1H, *J* 15.9 Hz, H2''), 6.91 (s, 1H, H6'''), 6.87 (d, 1H, *J* 15.9 Hz, H1''), 6.65 (s, 1H, H3'''), 6.48 (s, 1H, H5), 6.44 (s, 1H, H6'), 5.74 (s, 1H, H8), 3.88 (s, 3H, OCH₃-4'''), 3.86 (s, 3H, OCH₃-5'), 3.85 (s, 3H, OCH₃-5'''), 3.74 (s, 3H, OCH₃-4'), 3.71 (s, 3H, OCH₃-7), 3.68 (dd, 1H, *J* 9.3, 4.3 Hz, H1), 3.27 (dd, 1H, *J* 13.2, 4.3 Hz, H7'), 3.22 (dd, 1H, *J* 5.6, 2.9 Hz, H3), 3.04 (s, 3H, OCH₃-6), 2.84 (m, 2H, H7'''), 2.83 (dd, 1H, *J* 13.2, 9.3 Hz, H7'), 2.77 (m, 2H, H3, H4), 2.59 (m, 1H, H4), 2.54 (s, 3H, NCH₃), 2.46 (m, 2H, H8'''), 2.28 (s, 6H, N(CH₃)₂).

¹³C NMR of (E)-92: δ 148.7 (C5'''), 148.4 (C4'''), 147.8 (C4'), 147.7 (C5'), 147.5 (C6), 146.1 (C7), 130.7 (C1'''), 130.3 (C2'), 129.9 (C1'), 128.7 (C2''' and C4a), 126.0 (CH-2''), 130.3 (C8a), 125.5 (CH-1''), 114.5 (CH-6'), 113.0 (CH-3'''), 111.5 (CH-8), 111.26 (CH-5), 108.5 (CH-6'''), 108.6 (CH-3'), 64.3 (CH-1), 61.3 (CH₂-8'''), 56.0 (OCH₃-5', OCH₃-7, OCH₃-5''' and OCH₃-4'''), 55.8 (OCH₃-4'), 55.4 (OCH₃-6), 46.5 (CH₂-3), 45.5 (N(CH₃)₂), 42.8 (NCH₃), 37.9 (CH₂-7'), 31.6 (CH₂-7'''), 25.6 (CH₂-4).

¹H NMR of (Z)-92: δ 7.66 (s, 1H, H3'), 6.61 (d, 1H, *J* 12.0 Hz, H2''), 6.59 (s, 1H, H6'', H3'''), 6.54 (s, 1H, H5), 6.53 (s, 1H, H6'), 6.41 (d, 1H, *J* 12.0 Hz, H1''), 5.97 (s, 1H, H8), 3.82 (s, 6H, OCH₃-4''', OCH₃-5'), 3.80 (m, 1H, H1), 3.73 (s, 3H, OCH₃-5'''), 3.51 (s, 3H, OCH₃-4'), 3.48 (s, 3H, OCH₃-7), 3.45 (s, 3H, OCH₃-6), 3.23 (m, 1H, H3), 3.15 (dd, 1H, *J* 13.5, 5.1 Hz, H7'), 2.87 (m, 1H, H3), 2.79 (m, 4H, H4, H7', H7'', H7'''), 2.58 (m, 1H, H7'''), 2.51 (s, 3H, NCH₃), 2.45 (m, 2H, H8'''), 2.29 (s, 6H, N(CH₃)₂).

MS (ES⁺): *m/z* 593.3 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₅H₄₉N₂O₆, 593.3591 (MH⁺). Found 593.3572.

(RS) (E and Z) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2'''-(dimethylaminomethyl))phenyl-ethenyl]phenylmethyl-2-methylisoquinoline (93).



The *N*-protected amine **113** (54 mg, 0.074 mmol) were treated as described above in the general *N*-TFA deprotection and *N*-methylation procedure using initially K₂CO₃ (51 mg, 0.37 mmol), CH₃OH (25 mL) and H₂O (2 mL) and then 38 % formaldehyde (10 mL), CH₃CN (10 mL) and NaCNBH₃ (18 mg, 0.29 mmol) to give an oil. The oil was purified by column chromatography (EtOAc

: CH₃OH : NH₃ (5 : 5 : 0.1)) to afford **93** (14 mg, 33 % over 2 steps) as a yellow oil.

Note: Initially the product **93** was obtained as 100 % the (Z) isomer, however after approximately 1 week, **93** was a 40 : 60 mixture of (E)- and (Z)-isomers, respectively.

R_f. 0.19 (EtOAc : CH₃OH (1 : 1)).

¹H NMR of (Z)-93: δ 6.85 (s, 1H, H3'), 6.71 (d, 1H, *J* 12.0 Hz, H2''), 6.60 (s, 1H, H6'''), 6.58 (s, 1H, H3'''), 6.53 (s, 1H, H5), 5.52 (s, 1H, H6'), 6.38 (d, 1H, *J* 12.0 Hz, H1''), 5.97 (s, 1H, H8), 3.91 (dd, 1H, *J* 4.8, 3.3 Hz, H1), 3.85 (s, 3H, OCH₃-4'''), 3.84 (s, 3H, OCH₃-5'), 3.83 (s, 3H, OCH₃-5'''), 3.75 (s, 3H, OCH₃-4'), 3.52 (s, 3H, OCH₃-7), 3.47 (m, 1H, H1), 3.46 (s, 3H, OCH₃-6), 3.35 (d, 2H, *J* 2.1 Hz, H7'''), 3.25 (m, 1H, H3), 3.14 (dd, 1H, *J* 12.6, 4.8 Hz, H7'), 2.92 (m, 1H, H3), 2.86 (dd, 1H, *J* 12.6, 3.9 Hz, H7'), 2.79 (m, 1H, H4), 2.62 (m, 1H, H4), 2.53 (s, 3H, NCH₃), 2.04 (s, 6H, N(CH₃)₂).

¹H NMR of (E)-93 (in part): δ 7.22 (d, 1H, *J* 15.3 Hz, H2''), 7.11 (s, 1H, H3'), 6.98 (s, 1H, H6'''), 6.87 (d, 1H, *J* 15.3 Hz, H1''), 6.85 (s, 1H, H3'''), 6.60 (s, 1H, H5), 6.51 (s, 1H, H6'), 5.76 (s, 1H, H8), 3.93 (s, 3H, OCH₃-4'''), 3.91 (s, 3H, OCH₃-5'), 3.90 (s, 3H, OCH₃-5'''), 3.78 (s, 3H, OCH₃-4'), 3.75 (s, 3H, OCH₃-7), 3.78 (m, 1H, H1), 3.52 (s, 3H, OCH₃-6), 3.35 (m, 1H, H3), 3.28 (m, 3H, H7''', H7'), 2.85 (m, 4H, H7', H3, H4), 2.54 (s, 3H, NCH₃), 2.26 (s, 6H, N(CH₃)₂).

¹³C NMR of (Z)-93: δ 148.4 (C5'''), 148.2 (C4'''), 147.8 (C4'), 147.6 (C5'), 147.0 (C6), 146.4 (C7), 130.8 (C1'''), 129.5 (C2'), 129.3 (CH-2''), 128.3 (C1'), 127.9 (C2''', C4a), 126.0 (CH-1''), 125.7 (C8a), 114.0 (CH-6'), 112.9 (CH-3'''), 112.7 (CH-8), 111.5 (CH-5), 111.5 (CH-6'''), 108.8 (CH-3'), 64.2 (CH-1), 61.32 (CH₂-7'''), 56.0 (OCH₃-5', OCH₃-7, OCH₃-5''', OCH₃-4'''), 55.8 (OCH₃-4'), 55.6 (OCH₃-6), 46.4 (CH₂-3), 45.6 (N(CH₃)₂), 42.7 (NCH₃), 38.2 (CH₂-7'), 25.2 (CH₂-4).

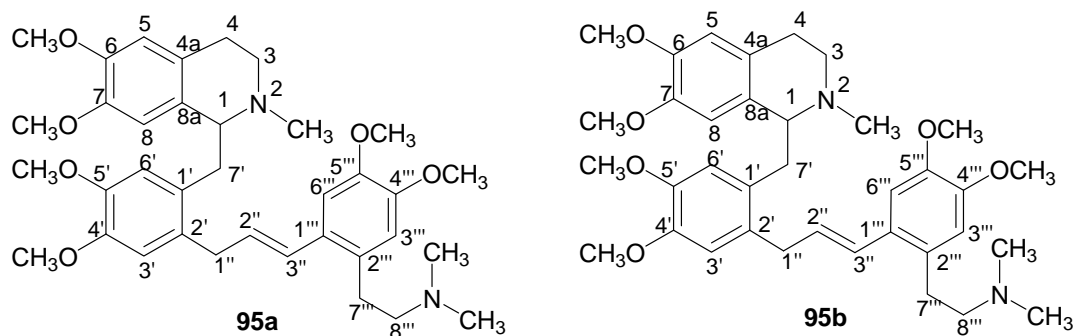
¹³C NMR of (E)-93 (in part): δ 148.3 (C5'''), 147.5 (C5'), 130.3 (C1'''), 129.7 (C2'), 128.7 (C1'), 126.3 (CH-2''), 126.0 (CH-1''), 125.6 (C8a), 114.6 (CH-6'), 113.6 (CH-

3'''), 112.8 (CH-8), 111.7 (CH-5), 111.3 (CH-6'''), 108.4 (CH-3'), 64.4 (CH-1), 61.7 (CH₂-7'''), 38.0 (CH₂-7'), 25.6 (CH₂-4), 42.8 (NCH₃).

MS (ES⁺): *m/z* 577 (MH⁺, 20%). **HRMS (ES⁺):** calcd for C₃₄H₄₅O₆N₂, 577.3278 (MH⁺).

Found 577.3299.

(*RS*) (*E*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(dimethylaminoethyl))phenyl-2''-propenyl]phenylmethyl-2-methylisoquinoline (95a) and (*RS*) (*E*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(dimethylaminoethyl))phenyl-1''-propenyl]phenylmethyl-2-methylisoquinoline (95b).



The *N*-protected amine **115** (134 mg, 0.180 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation procedure using initially K₂CO₃ (100 mg, 0.725 mmol), CH₃OH (20 mL) and H₂O (2 mL), and then 38 % formaldehyde (10 mL), CH₃CN (15 mL) and NaCNBH₃ (50 mg, 0.76 mmol) to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (3 : 7: 0.1)) to give **95** (72 mg, 67 % over 2 steps) as a white oil. The product was obtained as a 60 : 40 mixture of **95a** and **95b**, respectively.

Alternatively, a mixture of **95a** and **95b** was obtained directly using the general Heck coupling reaction procedure starting with the *N*-methylated precursor **122** (254 mg, 0.64 mmol), **121** (142 mg, 0.42 mmol), Pd(OAc)₂ (9 mg, 0.042 mmol), DMG (84 mg, 0.84 mmol), NaOAc (66 mg, 0.84 mmol) and NMP (5 mL). Under these conditions, a 70: 30 mixture of (*E*)-**95a** and (*E*)-**95b** was obtained (14 mg, 6 % yield).

R_f 0.13 (EtOAc : CH₃OH (1 : 1))

¹H NMR of (E)-95a (500 MHz): δ 6.84 (s, 1H, H6'''), 6.62 (s, 1H, H3'), 6.56 (s, 1H, H3'''), 6.54 (s, 1H, H5), 6.50 (s, 1H, H6'), 6.33 (d, 1H, *J* 16.0 Hz, H3''), 5.72 (s, 1H, H8), 5.93 (dt, 1H, *J* 16.0, 6.0 Hz, H2''), 3.75 (s, 3H, OCH₃-4'), 3.74 (s, 3H, OCH₃-4'''), 3.73 (s, 6H, OCH₃-5''', OCH₃-7), 3.70 (s, 3H, OCH₃-5'), 3.65 (dd, 1H, *J* 9.0, 5.0, H1), 3.38 (m, 1H, H1''), 3.36 (s, 3H, OCH₃-6), 3.19 (ddd, 1H, *J* 12.5, 9.5, 5.0 Hz, H3), 3.12 (m, 1H, H1'), 3.07 (dd, 1H, *J* 13.5, 5.0 Hz, H7'), 2.84 (m, 1H, H4), 2.76 (dd, 1H, *J* 13.5, 9.0 Hz, H7''), 2.72 (m, 1H, H3), 2.64 (dd, 1H, *J* 12.0, 6.0 Hz, H7'''), 2.53 (m, 1H, H4), 2.48 (s, 3H, NCH₃), 2.42 (m, 1H, H8'''), 2.32 (m, 1H, H8''), 2.20 (m, 1H, H7'''), 2.18 (s, 6H, N(CH₃)₂).

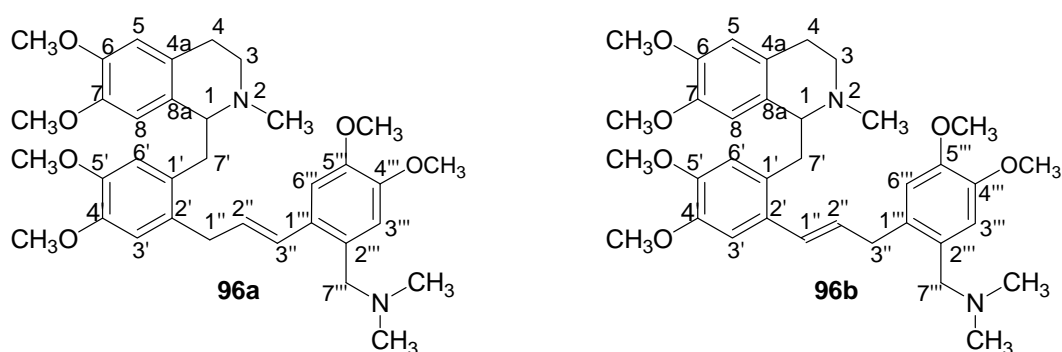
¹H NMR of (E)-95b (in part): δ 6.86 (s, 1H, H3'''), 6.64 (s, 1H, H3'), 6.62 (s, 1H, H6'''), 6.47 (s, 1H, H5), 6.28 (s, 1H, H6'), 6.27 (d, 1H, *J* 15.5 Hz, H1''), 5.61 (s, 1H, H8), 5.99 (dt, 1H, *J* 15.5, 6.5 Hz, H2''), 3.45 (dd, 1H, *J* 9.0, 4.5 Hz, H1), 3.78 (s, 3H, OCH₃-4'), 3.77 (s, 3H, OCH₃-5'), 3.36 (s, 3H, OCH₃-6), 2.38 (s, 3H, NCH₃), 2.23 (s, 6H, N(CH₃)₂).

¹³C NMR of (E)-95 (125 MHz): δ 148.3 (C5'''), 147.4 (C7, C4'', C5', C4'), 146.0 (C6), 131.1 (C1'), 129.8 (C1'''), 129.5 (C2'), 129.1 (CH-2''), 128.4 (C2''', C4a), 127.4 (CH-3''), 125.5 (C8a), 114.2 (CH-6), 113.0 (CH-3'), 112.8 (CH-3'''), 111.5 (CH-8), 111.3 (CH-5), 108.7 (CH-6'''), 64.1 (CH-1), 60.6 (CH₂-8'''), 55.71 (OCH₃-5', OCH₃-4''', OCH₃-5''', OCH₃-7, OCH₃-4'), 55.6 (OCH₃-6), 46.0 (CH₂-3), 44.9 (N(CH₃)₂), 42.2 (NCH₃), 36.9 (CH₂-7'), 35.7 (CH₂-1''), 30.8 (CH₂-7'''), 24.8 (CH₂-4).

¹³C NMR of (E)-95 (in part): δ 147.87 (C4'''), 147.16 (C4'), 145.9 (C6), 130.1 (C1'''), 129.9 (C2'), 129.4 (CH-2''), 128.0 (CH-1''), 125.4 (C8a), 114.5 (CH-6), 113.7 (CH-5'''), 113.0 (CH-3'), 108.8 (CH-6'''), 63.5 (CH-1), 60.9 (CH₂-8'''), 45.9 (CH₂-3), 45.0 (N(CH₃)₂), 42.1 (NCH₃), 37.1 (CH₂-7'), 35.8 (CH₂-3''), 30.7 (CH₂-7'''), 24.9 (CH₂-4).

MS (ES⁺): m/z 605 (MH⁺, 70 %). **HRMS (ES⁺):** calcd for C₃₆H₄₉N₂O₆, 605.3591 (MH⁺). Found 605.3583.

(RS) (E) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(dimethylaminomethyl))phenyl-2''-propenyl]phenylmethyl-2-methylisoquinoline (96a) and **(RS) (E) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(dimethylaminomethyl))phenyl-1''-propenyl]phenylmethyl-2-methylisoquinoline (96b)**.



The *N*-protected amine **116** (57 mg, 0.077 mmol) was treated using the general *N*-TFA deprotection and reductive *N*-methylation procedure using initially K₂CO₃ (53 mg, 0.380 mmol), CH₃OH (10 mL) and H₂O (2 mL) and then 38 % formaldehyde (10 mL), CH₃CN (10 mL) and NaCNBH₃ (19 mg, 0.300 mmol) to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)) to afford **96** (27 mg, 60 % over 2 steps) as a yellow oil. The product was obtained as a 60 : 40 mixture of (*E*)-**96a** and (*E*)-**96b**.

R_f. 0.37 (CH₃OH : EtOAc : NH₃ (3 : 2 : 0.1)).

¹H NMR of (*E*)-96a: δ 6.89 (s, 1H, H6'''), 6.67 (s, 1H, H3'), 6.59 (s, 1H, H3'''), 6.58 (d, 1H, *J* 15.6 Hz, H3''), 6.56 (s, 1H, H5), 6.36 (s, 1H, H6'), 5.96 (dt, 1H, *J* 15.6, 4.8 Hz, H2''), 5.79 (s, 1H, H8), 3.84 (s, 3H, OCH₃-5'), 3.83 (s, 3H, OCH₃-4'''), 3.81 (s, 3H, OCH₃-5'''), 3.77 (s, 6H, OCH₃-7), 3.67 (m, 1H, H1), 3.43 (s, 3H, OCH₃-4') 3.41 (m, 2H, H7'''), 3.28 (s, 3H, OCH₃-6), 3.22 (m, 1H, H3), 3.14 (d, 2H, *J* 4.8 Hz, H1''),

3.09 (m, 1H, H7'), 2.86 (m, 1H, H3), 2.80 (m, 1H, H7'), 2.77 (m, 1H, H4), 2.60 (m, 1H, H4), 2.55 (NCH₃), 2.15 (N(CH₃)₂).

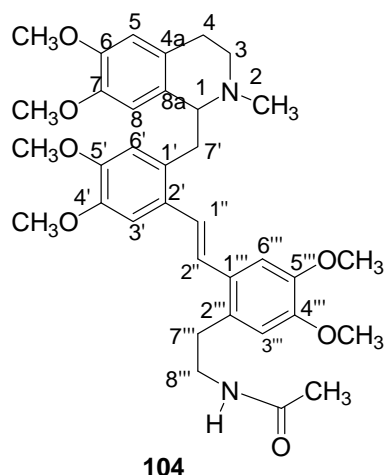
¹H NMR of (E)-96b (in part): δ 6.84 (s, 1H, H6'''), 6.73 (s, 1H, H3'), 6.65 (s, 1H, H3'''), 6.54 (s, 1H, H5), 6.38 (d, 1H, *J* 15.6 Hz, H1''), 6.33 (s, 1H, H6'), 6.04 (dt, 1H, *J* 15.6, 4.8 Hz, H2''), 5.67 (s, 1H, H8), 3.86 (s, 3H, OCH₃-5'''), 3.85 (s, 3H, OCH₃-4'''), 3.80 (s, 3H, OCH₃-5'), 3.70 (s, 3H, OCH₃-7), 3.61 (m, 1H, H1), 3.51 (d, 2H, *J* 4.8 Hz, H3''), 3.37 (s, 3H, OCH₃-4'), 3.32 (s, 3H, OCH₃-6), 2.38 (s, 3H, NCH₃), 2.20 (s, 6H, N(CH₃)₂).

¹³C NMR of (E)-96a: δ 148.3 (C5'''), 148.1 (C7), 147.8 (C4'''), 147.6 (C5'), 147.4 (C4'), 146.2 (C6), 131.6 (C1'), 130.2 (C1'''), 129.7 (CH-2''), 128.5 (CH-3''), 129.1 (C2'), 128.6 (C8a, C4a), 128.1 (C2'''), 114.5 (CH-6'), 113.5 (CH-3'), 113.2 (CH-3'''), 111.6 (CH-8), 111.5 (CH-5), 108.7 (CH-6'''), 64.6 (CH-1), 61.3 (CH₂-7'''), 56.2 (4 x OCH₃), 56.0 (OCH₃-4'), 55.6 (OCH₃-6), 46.5 (CH₂-3), 45.6 (N(CH₃)₂), 42.8 (NCH₃), 37.4 (CH₂-7'), 36.3 (CH₂-1''), 25.4 (CH₂-4).

¹³C NMR of (E)-96b (in part): δ 148.2 (C5'''), 146.2 (C6), 131.3 (C1'), 129.9 (C1'''), 129.8 (CH-2''), 128.4 (CH-1''), 128.9 (C2'), 128.1 (C2'''), 125.9 (C4a), 114.7 (CH-6), 113.7 (CH-3'''), 113.3 (CH-3'), 111.7 (CH-8), 111.5 (CH-5), 109.1 (CH-6'''), 64.0 (CH-1), 61.4 (CH₂-7'''), 46.5 (CH₂-3), 45.7 (N(CH₃)₂), 42.7 (NCH₃), 37.7 (CH₂-7'), 36.1 (CH₂-3''), 25.6 (CH₂-4).

MS (ES⁺): *m/z* 591.3 (MH⁺, 50 %). **HRMS (ES⁺):** calcd for C₃₅H₄₇N₂O₆, 591.3434 (MH⁺). Found 591.3423.

(*RS*) (*E* and *Z*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2'''-(acetaminoethyl))phenyl-ethenyl]phenylmethyl-2-methylisoquinoline (**104**).



The *N*-protected amine **128** (79 mg, 0.12 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation using initially K_2CO_3 (82 mg, 0.59 mmol), CH_3OH (20 mL) and H_2O (2 mL), except that the mixture was heated at 80 °C for 4 h and then 38 % formaldehyde (5 mL), CH_3CN (5 mL) and $NaCNBH_3$ (10 mg, 0.153 mmol) to give an oil.

The oil was purified by column chromatography ($EtOAc: CH_3OH: NH_3$ (5 : 5 : 0.1)) to afford **104** (76 mg, 64 % over 2 steps) as a white oil. The product **104** was obtained as a 70: 30 mixture of the (*E*) and (*Z*)-isomer, respectively.

R_f. 0.13 ($EtOAc: CH_3OH$ (5 : 5)).

¹H NMR of (*E*)-104: δ 7.16 (s, 1H, H3'), 7.00 (d, 1H, *J* 15.9 Hz, H2''), 6.91 (s, 1H, H6'''), 6.78 (d, 1H, *J* 15.9 Hz, H1''), 6.62 (s, 1H, H3'''), 6.48 (s, 2H, H5, H6'), 5.83 (t, 1H, *J* 6.6 Hz, NH), 5.69 (s, 1H, H8), 3.95 (s, 3H, OCH_3 -4'''), 3.89 (s, 3H, OCH_3 -5'), 3.85 (s, 3H, OCH_3 -5'''), 3.80 (m, 1H, H1), 3.79 (s, 3H, OCH_3 -4'), 3.69 (s, 3H, OCH_3 -7), 3.39 (OCH_3 -6), 3.44 (m, 1H, H7'), 3.39 (m, 2H, H3), 3.32 (m, 1H, H8'''), 2.88 (m, 1H, H8'''), 2.84 (m, 2H, H7''', H4), 2.79 (m, 2H, H7', H7'''), 2.71 (m, 1H, H4), 2.59 (s, 3H, NCH_3), 1.82 (s, 3H, $COCH_3$).

¹H NMR of (*Z*)-104 (in part): δ 7.24 (s, 1H, H3'), 6.64 (s, 1H, H6'''), 6.57 (s, 1H, H5), 6.53 (d, 1H, *J* 12.0 Hz, H2''), 6.49 (s, 1H, H6'), 6.28 (d, 1H, *J* 12.0 Hz, H1''), 6.04 (bs, 1H, NH), 5.81 (s, 1H, H8), 3.83 (s, 3H, OCH_3 -4'''), 3.84 (s, 3H, OCH_3 -5'''), 3.73 (s,

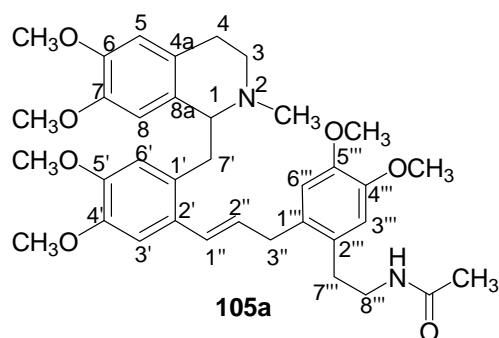
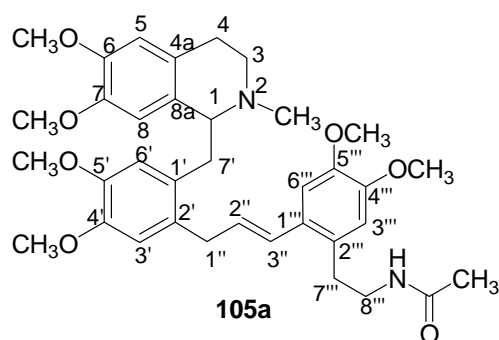
3H, OCH₃-7), 3.46 (s, 3H, OCH₃-4'), 3.44 (s, 3H, OCH₃-6), 2.52 (s, 3H, NCH₃), 1.84 (s, 3H, COCH₃).

¹³C NMR of (E)-104: δ 170.4 (C=OCH₃), 148.8 (C5'''), 148.6 (C4'''), 148.2 (C4'), 147.9 (C6, C5'), 146.3 (C7), 129.9 (C1''', C2'), 129.6 (C1', C2'''), 129.3 (C4a, C8a), 125.9 (CH-2''), 125.5 (CH-1''), 114.5 (CH-6'), 113.1 (CH-3'), 111.6 (CH-8), 111.3 (CH-5), 108.8 (CH-3''', CH-6'''), 64.5 (CH-1), 56.5 (6 x OCH₃), 46.0 (CH₂-8'''), 45.2 (NCH₃), 41.0 (CH₂-3), 38.0 (CH₂-7'), 32.0 (CH₂-7'''), 29.8 (CH₂-4), 24.5 (COCH₃).

¹³C NMR of (Z)-104 (in part): δ 148.3 (C5''', C4'''), 148.0 (C4'), 147.8 (C6), 147.2 (C5'), 147.4 (C7), 129.8 (C2', C1'''), 129.3 (C1', C2'''), 128.6 (C4a, C8a), 128.0 (CH-2''), 127.7 (CH-1''), 112.6 (CH-3'), 112.7 (CH-5), 112.3 (CH-6'), 111.5 (CH-8), 64.2 (CH-1), 42.1 (NCH₃), 40.5 (CH₂-3), 38.1 (CH₂-7'), 32.9 (CH₂-7'''), 31.1 (CH₂-4), 23.4 (COCH₃).

MS (ES⁺): *m/z* 605 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₅H₄₅N₂O₇, 605.3227 (MH⁺). Found 605.3245.

(RS) (E) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(acetylaminoethyl))phenyl-2''-propenyl]phenylmethyl-2-methylisoquinoline (105a) and (RS) (E) 1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(acetylaminoethyl))phenyl-1''-propenyl]phenylmethyl-2-methylisoquinoline (105b).



The *N*-protected amine **129** (84 mg, 0.120 mmol) was treated as described above in the general *N*-TFA deprotection and *N*-methylation procedure using initially K₂CO₃ (86

mg, 0.62 mmol), CH₃OH (5 mL) and H₂O (2 mL) and then 38 % formaldehyde (5 mL), CH₃CN (5 mL) and NaCNBH₃ (11 mg, 0.16 mmol) to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)) to afford **105** (61 mg, 79 % over 2 steps) as a white oil. The product was obtained as a 70 : 30 mixture of (*E*)-**105a** and (*E*)-**105b**, respectively.

R_f. 0.27 (EtOAc : CH₃OH (1 : 1)).

¹H NMR of (*E*)-105a: δ 6.86 (s, 1H, H6'''), 6.67 (s, 1H, H3'), 6.64 (s, 1H, H3'''), 6.61 (s, 1H, H5), 6.59 (s, 1H, H6'), 6.41 (d, 1H, *J* 15.6 Hz, H3''), 6.12 (t, 1H, *J* 6.3, NH), 5.91 (dt, 1H, *J* 15.6, 6.3 Hz, H2''), 5.66 (s, 1H, H8), 3.80 (s, 12H, OCH₃-5''', OCH₃-4''', OCH₃-5', OCH₃-7), 3.80 (m, 1H, H1), 3.69 (s, 3H, OCH₃-4'), 3.36 (s, 3H, OCH₃-6), 3.40 (d, 2H, *J* 6.3 Hz, H1''), 3.39 (m, 1H, H7'), 3.25 (m, 1H, H8'''), 3.15 (m, 3H, H3, H7'), 2.94 (m, 1H, H8'''), 2.70 (m, 4H, H7'', H4), 2.56 (s, 3H, NCH₃), 1.89 (s, 3H, COCH₃).

¹NMR of (*E*)-105b (in part): δ 6.87 (s, 1H, H6'''), 6.68 (s, 1H, H3'''), 6.55 (s, 1H, H5), 6.52 (s, 1H, H6'), 6.30 (d, 1H, *J* 15.6 Hz, H1''), 6.33 (s, 1H, H3'), 5.97 (dd, 1H, *J* 15.6, 6.0 Hz, H2''), 5.61 (s, 1H, H8), 3.71 (s, 3H, OCH₃-4'), 3.59 (m, 1H, H1), 3.42 (s, 3H, OCH₃-6), 2.46 (s, 3H, NCH₃), 1.91 (s, 3H, COCH₃).

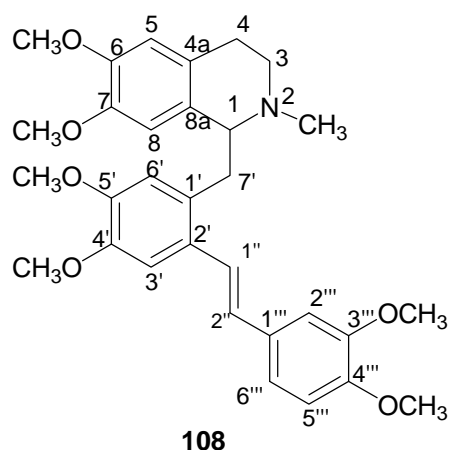
¹³C NMR of (*E*)-105a: δ 170.2 (C=OCH₃), 148.5 (C5'''), 148.1 (C7), 147.7 (C4'''), 147.5 (C5', C4'), 145.9 (C6), 131.5 (C1', C1'''), 129.9 (C2', C2'''), 129.2 (CH-2''), 128.6 (C4a), 128.2 (CH-3''), 125.6 (C8a), 114.4 (CH-6'), 113.1 (CH-3'), 112.7 (CH-5), 111.6 (CH-8), 111.3 (CH-3'''), 109.1 (CH-6'''), 64.5 (CH-1), 56.1 (4 x OCH₃), 55.9 (OCH₃-4'), 55.3 (OCH₃-6), 46.3 (CH₂-8'''), 42.6 (NCH₃), 42.5 (CH₂-1''), 36.9 (CH₂-3), 36.1 (CH₂-7'), 32.9 (CH₂-7'''), 25.3 (CH₂-4), 23.3 (COCH₃).

¹³C NMR of (*E*)-105b (in part): δ 148.8 (C5'''), 147.6 (C4'''), 147.5 (C4'), 147.4 (C5'), 148.0 (C6), 130.5 (C1', C1'''), 129.9 (C2', C2'''), 129.6 (CH-2''), 129.2 (C2',

C2'''), 128.8 (C4a), 128.1 (CH-1'') 125.4 (C8a), 114.5 (CH-6'), 113.5 (CH-3'), 112.9 (CH-5), 111.4 (CH-8), 108.9 (CH-6'''), 63.8 (CH-1), 55.8 (OCH₃-4'), 55.3 (OCH₃-6), 46.1 (CH₂-8'''), 42.4 (NCH₃), 40.7 (CH₂-3''), 37.3 (CH₂-3), 36.3 (CH₂-7'), 32.4 (CH₂-7''').

MS (ES⁺): *m/z* 619 (MH⁺, 10 %). **HRMS (ES⁺):** calcd for C₃₆H₄₇N₂O₇, 619.3383 (MH⁺). Found 619.3351.

(RS) (E and Z) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''- (3''',4'''-dimethoxyphenyl)ethenyl]phenylmethyl-2-methylisoquinoline (108).



The *N*-protected amine **136** (56 mg, 0.093 mmol) was treated as described above in the general *N*-TFA deprotection and reduction *N*-methylation procedure using initially K₂CO₃ (65 mg, 0.460 mmol), CH₃OH (20 mL) and H₂O (2 mL) and then 38 % formaldehyde (5 mL), CH₃CN (5 mL) and NaCNBH₃ (8 mg, 0.12 mmol) to give an oil. The

oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)) to give the methylated analogue **108** (37 mg, 77 % over 2 steps) as a white oil. The product **108** was obtained as a 80 : 20 mixture of (*E*)- and (*Z*)-isomers, respectively.

R_f 0.47 (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)).

¹H NMR of (*E*)-108: δ 7.05 (s, 1H, H3'), 6.96 (dd, 1H, *J* 6.9, 2.1 Hz H6'''), 6.92 (d, 1H, *J* 15.9 Hz, H2''), 6.83 (d, 1H, *J* 9.0 Hz, H5'''), 6.69 (d, 1H, *J* 3.3 Hz, H2'''), 6.66 (d, 1H, *J* 15.9 Hz, H1''), 6.50 (s, 1H, H5), 6.49 (s, 1H, H6'), 5.67 (s, 1H, H8), 3.93 (s, 3H, OCH₃-3'''), 3.92 (s, 3H, OCH₃-4'''), 3.89 (s, 3H, OCH₃-5'), 3.79 (m, 1H, H1), 3.78 (s, 3H, OCH₃-7), 3.72 (s, 3H, OCH₃-4'), 3.41 (s, 3H, OCH₃-6), 3.40 (m, 2H, H3, H7'),

2.95 (m, 1H, H4), 2.86 (m, 2H, H3, H7'), 2.68 (dd, 1H, *J* 13.8, 4.2 Hz, H4), 2.62 (s, 3H, NCH₃), 2.16 (s, 3H, COCH₃).

¹H NMR of (*Z*)-**108** (in part): δ 6.64 (s, 1H, H5), 6.57 (s, 1H, H6'), 6.43 (d, 1H, *J* 11.1 Hz, H2''), 6.20 (d, 1H, *J* 11.1 Hz, H1''), 5.96 (s, 1H, H8), 2.17 (s, 3H, COCH₃).

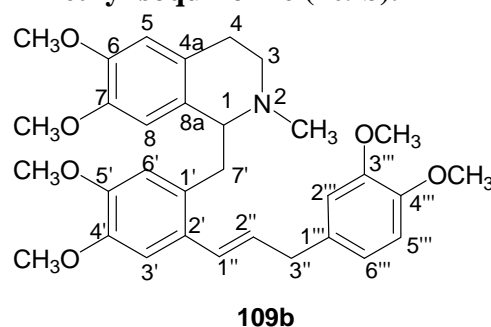
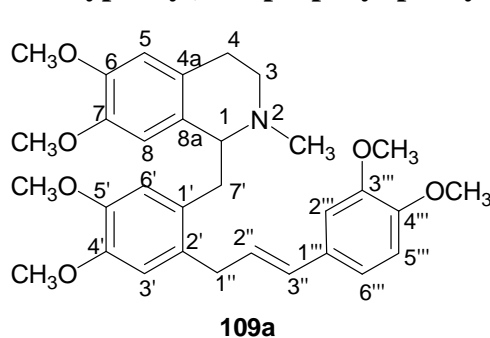
¹³C NMR of (*E*)-**108**: δ 149.1 (C3'''), 148.7 (C4'''), 148.3 (C4'), 147.7 (C6), 147.4 (C5'), 146.1 (C7), 131.0 (C1'), 130.1 (C1'''), 129.7 (C2'), 127.9 (C4a), 127.9 (CH-2''), 125.5 (C8a), 124.3 (CH-1''), 119.4 (CH-6'''), 114.4 (CH-2'''), 111.6 (CH-8), 111.3 (CH-6', CH-5), 108.8 (CH-5'''), 108.4 (CH-3'), 64.2 (CH-1), 55.9 (4 x OCH₃), 55.7 (OCH₃-4'), 55.3 (OCH₃-6), 46.3 (CH₂-3), 42.6 (NCH₃), 37.8 (CH₂-7'), 25.4 (CH₂-4).

¹³C NMR of (*Z*)-**108** (in part): δ 147.4 (C6), 147.2 (C5'), 146.4 (C7), 130.5 (C1'), 129.9 (C1'''), 129.8 (C2'), 129.2 (C4a), 127.6 (CH-2''), 126.0 (C8a), 122.2 (CH-1''), 114.1 (CH-5), 112.7 (CH-2'''), 112.3 (CH-6'''), 111.3 (CH-8), 111.2 (CH-6'), 110.7 (CH-5'''), 63.8 (CH-1), 55.6 (OCH₃-4'), 55.5 (OCH₃-6), 46.3 (CH₂-3), 42.5 (NCH₃), 38.2 (CH₂-7'), 25.1 (CH₂-4).

MS (EI⁺): *m/z* 519.29 (M⁺, 5 %). HRMS (ES⁺): calcd for C₃₁H₃₈NO₆, 520.2699 (MH⁺).

Found 520.2675.

(*RS*) (*E*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(3''',4'''-dimethoxyphenyl)-2''-propenyl)]phenylmethyl-2-methylisoquinoline (**109a**) and (*RS*) (*E*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(3''',4'''-dimethoxyphenyl)-1''-propenyl)]phenylmethyl-2-methylisoquinoline (**109b**).



The *N*-protected amine **137** (100 mg, 0.16 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation procedure using initially K₂CO₃ (99 mg, 0.71 mmol), CH₃OH (5 mL) and H₂O (2 mL) and then 38 % formaldehyde (6 mL), CH₃CN (6 mL) and NaCNBH₃ (12 mg, 0.18 mmol) to give an oil. This was purified by column chromatography (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)) to give the methylated analogue **109** (66 mg, 75 % over 2 steps) as a white oil. The product **109** was obtained as a 70 : 30 mixture of (*E*)-**109a** and (*E*)-**109b**, respectively.

R_f: 0.80 (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)).

¹H NMR of (*E*)-109a: δ 6.82 (s, 1H, H3'), 6.79 (d, 1H, *J* 1.8 Hz, H2''), 6.72 (dd, *J* 5.4, 1.8 Hz, H6''), 6.64 (s, 1H, H5), 6.60 (s, 1H, H6'), 6.54 (d, 1H, *J* 5.4 Hz, H5''), 6.16 (d, 1H, *J* 15.6 Hz, H3''), 6.04 (dt, 1H, *J* 15.6, 6.3 Hz, H2''), 5.73 (s, 1H, H8), 3.84 (s, 3H, OCH₃-3''), 3.83 (s, 3H, OCH₃-4''), 3.81 (s, 3H, OCH₃-5'), 3.78 (s, 3H, OCH₃-7), 3.73 (m, 1H, H1), 3.71 (s, 3H, OCH₃-4'), 3.41 (s, 3H, OCH₃-6), 3.39 (m, 1H, H1''), 3.09 (d, 1H, *J* 6.3 Hz, H1'), 3.25 (m, 1H, H3), 3.22 (m, 1H, H7'), 2.93 (m, 1H, H3), 2.80 (m, 1H, H7'), 2.68 (m, 1H, H4), 2.61 (dt, 1H, *J* 13.8, 4.2 Hz, H4), 2.55 (s, 3H, NCH₃).

¹H NMR of (*E*)-109b (in part): δ 6.91 (s, 1H, H3'), 6.76 (s, 1H, H5), 6.38 (s, 1H, H6'), 6.38 (d, 1H, *J* 15.6 Hz, H1''), 5.99 (dt, 1H, *J* 15.6, 6.0 Hz, H2''), 5.67 (s, 1H, H8), 3.40 (s, 3H, OCH₃-6), 2.51 (NCH₃).

¹³C NMR of (*E*)-109a: δ 149.2 (C3''), 148.6 (C4''), 149.2 (C4'), 147.8 (C6), 147.7 (C5'), 146.3 (C7), 131.5 (C1'), 130.8 (C1''), 130.5 (CH-2''), 129.6 (C2'), 129.3 (C4a), 127.5 (CH-3''), 125.4 (C8a), 119.2 (CH-2''), 113.2 (CH-5), 111.5 (CH-8), 111.5 (CH-5''), 111.3 (CH-6''), 108.8 (CH-3', CH-6'), 64.4 (CH-1), 56.2 (5 x OCH₃), 55.6 (OCH₃-6), 46.1 (CH₂-3), 42.4 (NCH₃), 39.4 (CH₂-1'), 37.2 (CH₂-7'), 36.0 (CH₂-4).

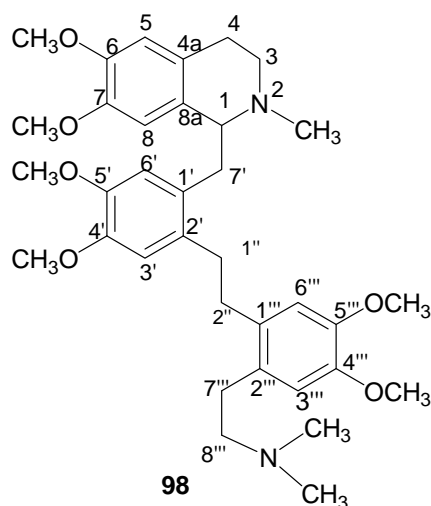
^{13}C NMR of (*E*)-109b (in part): δ 147.8 (C4'), 147.7 (C6), 147.5 (C5'), 146.3 (C7), 133.8 (C1'), 133.0 (C1'''), 129.9 (CH-2''), 129.8 (C2'), 125.7 (C4a), 128.4 (CH-1''), 125.7 (C8a), 120.8 (CH-2'''), 112.3 (CH-5), 117.8 (CH-5'''), 111.4 (CH-6'''), 109.0 (CH-3'), 64.0 (CH-1), 37.8 (CH₂-3').

MS (ES^+): m/z 534.4 (MH^+ , 100 %). **HRMS (ES^+):** calcd for $\text{C}_{32}\text{H}_{40}\text{NO}_6$, 534.2865 (MH^+). Found 534.2865.

8.3.4. General method for Hydrogenation reactions.

To a solution of the starting alkene in CH_3OH was added PdCl_2 . The solution was bubbled with argon. A hydrogen filled balloon was secured on top of the flask and the reaction mixture was left to stir for 24 h at RT. The solution was bubbled with argon to displace any remaining hydrogen before the palladium was filtered. The CH_3OH was evaporated and the residue was redissolved in dichloromethane and washed with 1M NaOH. The DCM layer was evaporated to give the pure product without the need for further purification.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5''')-dimethoxy-2''')-(dimethylaminoethyl))phenyl-ethyl]phenylmethyl-2-methylisoquinoline (98).



The alkene **92** (30 mg, 0.051 mmol) was treated as described above in the general hydrogenation reaction procedure using PdCl_2 (14 mg, 0.079 mmol) and CH_3OH (12 mL) to give **98** (26 mg, 85 %) as a yellow oil.

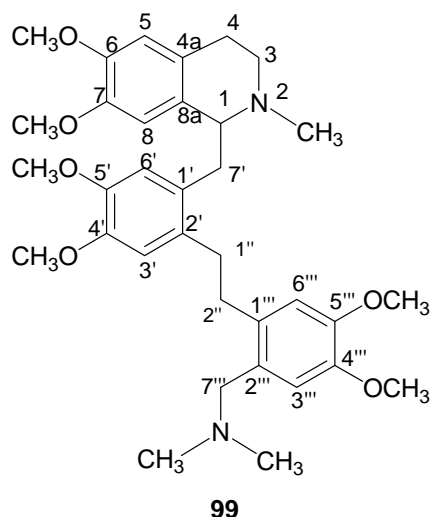
R_f 0.29 (CH₃OH: EtOAc : NH₃ (5 : 5 : 0.1)).

¹H NMR: δ 6.61 (s, 1H, H3'), 6.53 (s, 1H, H6'''), 6.52 (s, 1H, H3'''), 6.48 (s, 1H, H5), 6.44 (s, 1H, H6'), 5.72 (s, 1H, H8), 3.82 (s, 3H, OCH₃-5'''), 3.79 (s, 3H, OCH₃-4'), 3.75 (s, 3H, OCH₃-4'''), 3.74 (s, 3H, OCH₃-5'), 3.73 (s, 3H, OCH₃-6), 3.61 (dd, 1H, *J* 9.3, 4.4 Hz, H1), 3.40 (s, 3H, OCH₃-7), 3.18 (m, 1H, H3), 3.00 (dd, 1H, *J* 13.2, 4.4 Hz, H7'), 3.00 (m, 1H, H3), 2.68 (dd, 1H, 13.2, 9.3 H7'), 2.76 (m, 2H, H7'''), 2.55 (m, 6H, H4, H1'' and H2''), 2.52 (s, 3H, NCH₃), 2.35 (dd, 2H, *J* 9.8, 6.8 Hz, H8'''), 2.40 (s, 6H, N(CH₃)₂).

¹³C NMR: δ 147.6 (C5'''), 147.4 (C4''' and C4'), 147.3 (C5'), 147.3 (C6), 146.2 (C7), 133.0 (C1'''), 131.8 (C2'), 130.3 (C1'), 129.9 (C2'''), 129.0 (C4a), 128.8 (C8a), 114.3 (CH-6'), 113.1 (CH-3'''), 113.0 (CH-8), 113.0 (CH-5), 111.6 (CH-6'''), 111.5 (CH-3'), 64.7 (CH-1), 61.6 (CH₂-8'''), 56.2 (OCH₃-4', OCH₃-7, OCH₃-3''', OCH₃-4'''), 56.0 (OCH₃-6), 55.6 (OCH₃-5'), 46.6 (CH₂-3), 45.6 (N(CH₃)₂), 42.9 (NCH₃), 37.1 (CH₂-7'), 34.4 (CH₂-2''), 34.1 (CH₂-1''), 31.0 (CH₂-7'''), 25.6 (CH₂-4).

MS (ES⁺): *m/z* 593.3 (MH⁺, 95 %). **HRMS (ES⁺):** calcd for C₃₅H₄₉N₂O₆, 593.3591 (MH⁺). Found 593.3572.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2'''-(dimethylaminomethyl))phenyl-ethyl]phenylmethyl-2-methylisoquinoline (99).



The alkene **93** (21 mg, 0.036 mmol) was treated as above in the general hydrogenation reaction procedure using PdCl₂ (10 mg, 0.056 mmol) and CH₃OH (6 mL) to give **99** (18 mg, 88 %) as a yellow oil.

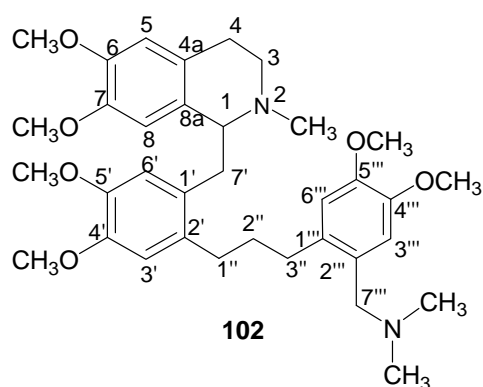
R_f 0.43 (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)).

¹H NMR: δ 6.77 (s, 2H, H6'''), 6.54 (s, 1H, H3'), 6.52 (s, 2H, H3''' and H5), 6.49 (s, 1H, H6'), 5.75 (s, 1H, H8), 3.83 (s, 3H, OCH₃-5'''), 3.79 (s, 3H, OCH₃-4'''), 3.78 (s, 3H, OCH₃-5'), 3.77 (s, 3H, OCH₃-7), 3.76 (s, 3H, OCH₃-4'), 3.63 (dd, 1H, *J* 8.7, 4.8 Hz, H1), 3.47 (m, 1H, H3), 3.41 (s, 3H, OCH₃-6), 3.23 (dd, 1H, *J* 13.5, 4.8 Hz, H7'), 3.19 (dd, 1H, *J* 8.1, 5.4 Hz, H3), 3.16 (s, 2H, H7'''), 3.05 (dd, 1H, *J* 13.5, 8.7 Hz, H7'), 2.56 (m, 6H, H4, H1'' and H2''), 2.53 (s, 3H, NCH₃), 2.15 (N(CH₃)₂).

¹³C NMR: δ 148.0 (C5'''), 147.6 (C7), 147.4 (C4'''), 147.1 (C5'), 147.1 (C4'), 146.2 (C6), 133.1 (C1', C1''', C2'), 129.4 (C8a), 128.4 (C2'''), 125.3 (C4a), 114.1 (CH-6'), 113.5 (CH-3'''), 112.9 (CH-3'), 112.8 (CH-8), 111.4 (CH-5), 111.3 (CH-6'''), 64.6 (CH-1), 61.0 (CH₂-7'''), 56.1 (OCH₃-5', OCH₃-7, OCH₃-5''', OCH₃-4'''), 55.9 (OCH₃-4'), 55.5 (OCH₃-6), 46.3 (CH₂-3), 45.3 (N(CH₃)₂), 42.5 (NCH₃), 37.1 (CH₂-7'), 34.3 (CH₂-2''), 33.9 (CH₂-1''), 29.9 (CH₂-4).

MS (ES⁺): *m/z* 579.56 (MH⁺, 5 %). A good HRMS could not be obtained.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2''''-(dimethylaminomethyl))phenyl-propyl]phenylmethyl-2-methylisoquinoline (102).



The alkene **96** (20 mg, 0.034 mmol) was treated as described above in the general hydrogenation reaction procedure using PdCl₂ (9 mg, 0.051 mmol) and CH₃OH (3 mL) to give **102** (21 mg, 100 %) as a yellow oil.

R_f 0.31 (CH₃OH : EtOAc : NH₃ (6 : 4 : 0.1)).

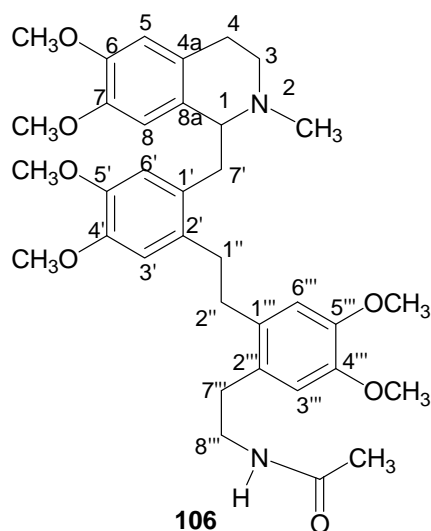
¹H NMR: δ 6.81 (s, 1H, H6'''), 6.60 (s, 1H, H3'), 6.58 (s, 1H, H3'''), 6.54 (s, 1H, H5), 6.52 (s, 1H, H6'), 5.68 (s, 1H, H8), 3.84 (s, 3H, OCH₃-5'''), 3.82 (s, 3H, OCH₃-4'''),

3.80 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-7), 3.60 (m, 1H, H1), 3.40 (s, 3H, OCH₃-4'), 3.22 (s, 3H, OCH₃-6), 3.12 (m, 1H, H3), 3.05 (dd, 1H, *J* 13.3, 4.1 Hz, H7'), 2.86 (m, 1H, H3), 2.67 (dd, 1H, *J* 13.3, 9.3 Hz, H7'), 2.57 (m, 4H, H1'', H4), 2.51 (s, 3H, NCH₃), 2.26 (t, 2H, *J* 6.9 Hz, H3''), 2.15 (N(CH₃)₂), 1.71 (m, 2H, H2'').

¹³C NMR: δ 147.8 (C5'''), 147.5 (C7), 147.4 (C4'''), 147.0 (C5', C4'), 146.0 (C6), 133.8 (C1'), 133.5 (C1'''), 129.5 (C2'), 128.8 (C8a), 128.7 (C2'''), 125.7 (C4a), 114.3 (CH-6'), 113.4 (CH-3'''), 112.6 (CH-3', CH-8), 111.4 (CH-5), 111.3 (CH-6'''), 64.5 (CH-1), 61.07 (CH₂-7'''), 56.1 (4 x OCH₃), 55.9 (OCH₃-4'), 55.4 (OCH₃-6), 46.3 (CH₂-3), 45.6 (N(CH₃)₂), 42.6 (NCH₃), 37.0 (CH₂-7'), 33.2 (CH₂-1''), 32.2 (CH₂-3''), 29.8 (CH₂-2''), 25.3 (CH₂-4).

MS (ES⁺): *m/z* 593.0 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₃₅H₄₉N₂O₆, 593.3591 (MH⁺). Found 593.3606.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(4''',5'''-dimethoxy-2'''-(acetylaminoethyl))phenyl-ethyl]phenylmethyl-2-methylisoquinoline (106).



The alkene **93** (25 mg, 0.049 mmol) was treated as described above in the general hydrogenation reaction procedure using PdCl₂ (16 mg, 0.090 mmol) and CH₃OH (30 mL) to give **106** (21 mg, 72 %) as a yellow oil.

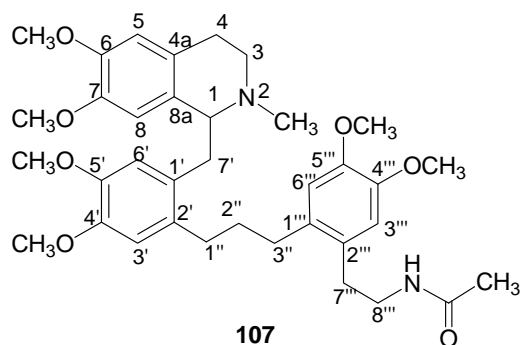
R_f 0.50 (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)).

¹H NMR: δ 6.62 (s, 1H, H6'''), 6.57 (s, 1H, H3'''), 6.54 (s, 1H, H3'), 6.49 (s, 1H, H5), 6.46 (s, 1H, H6'), 6.21 (bs, 1H, NH), 5.62 (s, 1H, H8), 3.81 (s, 6H, OCH₃-5''', OCH₃-5'), 3.79 (s, 6H, OCH₃-4''', OCH₃-4'), 3.76 (s, 3H, OCH₃-6), 3.64 (m, 1H, H1), 3.37 (s, 3H, OCH₃-7), 3.30 (m, 2H, H8'''), 3.15 (m, 2H, H3, H7'), 2.92 (m, 1H, H4), 2.84 (m, 1H, H3), 2.55 (m, 6H, H7', H4, H7''', H2''), 2.56 (s, 3H, NCH₃), 2.47 (m, 2H, H1''), 1.94 (s, 3H, COCH₃).

¹³C NMR: δ 170.3 (COCH₃), 147.9 (C5''', C4'''), 147.5 (C4', C6), 147.3 (C5', C7), 132.9 (C1', C1'''), 131.9 (C2', C2'''), 128.9 (C4a, C8a), 114.4 (CH-5), 113.1 (CH-6'), 112.9 (CH-3'''), 112.9 (CH-6'''), 111.6 (CH-8), 111.4 (CH-3'), 64.8 (CH-1), 56.2 (4 x OCH₃), 56.1 (OCH₃-4'), 55.4 (OCH₃-6), 46.2 (CH₂-8'''), 42.2 (NCH₃), 40.9 (CH₂-3, CH₂-7'), 37.6 (CH₂-7'''), 34.5 (CH₂-2''), 34.2 (CH₂-1''), 33.2 (CH₂-4), 23.4 (COCH₃).

MS (ES⁺): m/z 607.4 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₅H₄₇N₂O₇, 607.3383 (MH⁺). Found 607.3386.

(RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(4''',5'''-dimethoxy-2'''-(dimethylaminoethyl))phenyl-propyl]phenylmethyl-2-methylisoquinoline (107).



The alkene **105** (29 mg, 0.047 mmol) was treated as described above in the general hydrogenation reaction procedure using PdCl₂ (18 mg, 0.10 mmol) and CH₃OH (5 mL) to give **107** (24 mg, 82 % yield) as a yellow oil.

R_f 0.57 (CH₃OH : EtOAc : NH₃ (6 : 4 : 0.1)).

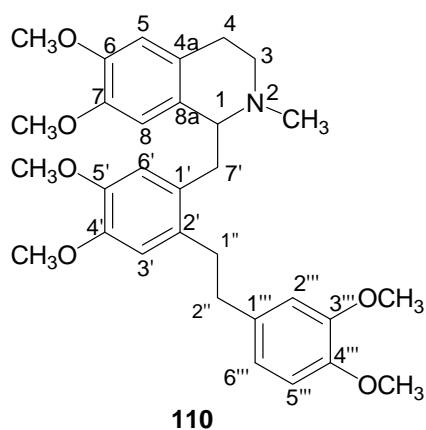
¹H NMR: δ 6.64 (s, 1H, H6'''), 6.62 (s, 1H, H3'''), 6.59 (s, 1H, H3'), 6.54 (s, 1H, H5), 6.49 (s, 1H, H6'), 5.64 (s, 1H, H8), 3.82 (s, 3H, OCH₃-5'''), 3.81 (s, 3H, OCH₃-4'''),

3.79 (s, 6H, OCH₃-4', OCH₃-6), 3.74 (s, 3H, OCH₃-5'), 3.64 (m, 1H, H1), 3.38 (s, 3H, OCH₃-7), 3.33 (m, 2H, H8'''), 3.18 (m, 2H, H3, H7'), 2.92 (dd, 1H, *J* 9.9, 5.7 Hz, H4), 2.85 (m, 1H, H3), 2.66 (m, 3H, H7', H7'''), 2.57 (m, 1H, H4), 2.55 (s, 3H, NCH₃), 2.50 (t, 2H, *J* 7.6 Hz, H1''), 2.30 (t, 2H, *J* 7.6 Hz, H3''), 1.93 (s, 3H, COCH₃), 1.68 (quin, 2H, *J* 7.6 Hz, H2'').

¹³C NMR: δ 170.4 (COCH₃), 147.1 (C5''', C4'''), 147.3 (C4', C6), 147.0 (C5', C7), 133.9 (C1', C1'''), 132.6 (C2', C2'''), 129.0 (C4a, C8a), 114.7 (CH-5), 113.0 (CH-6'), 112.9 (CH-3'''), 112.7 (CH-6''), 111.7 (CH-8), 111.3 (CH-3'), 64.8 (CH-1), 56.1 (4 x OCH₃), 56.0 (OCH₃-4'), 55.5 (OCH₃-6), 40.9 (CH₂-3, CH₂-8'''), 32.6 (NCH₃, CH₂-7'), 32.3 (CH₂-4, CH₂-7'''), 33.1 (CH₂-1'', CH₂-3''), 29.8 (CH₂-2''), 23.5 (COCH₃).

MS (ES⁺): *m/z* 621.4 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₆H₄₉N₂O₇, 621.3540 (MH⁺). Found 621.3555.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(3''',4'''-dimethoxy phenyl)ethyl]phenylmethyl-2-methylisoquinoline (110).



The alkene **108** (18 mg, 0.035 mmol) was treated as described above in the general hydrogenation reaction procedure using PdCl₂ (10 mg, 0.056 mmol) and CH₃OH (20 mL) to give **110** (17 mg, 91 % yield) as a light purple oil.

R_f 0.36 (CH₃OH : EtOAc : NH₃ (6 : 4 : 0.1)).

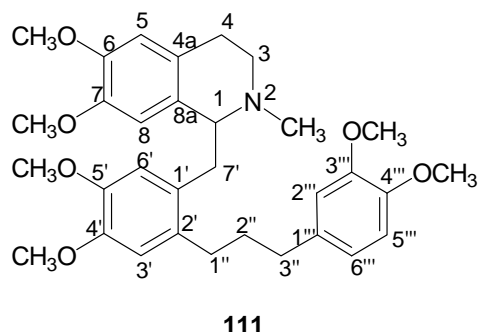
¹H NMR: δ 6.73 (d, 1H, *J* 8.1 Hz, H5'''), 6.59 (dd, 1H, *J* 8.1, 1.8 Hz, H6'''), 6.56 (d, 1H, *J* 1.8 Hz, H2'''), 6.54 (s, 3H, H3', H5, H6'), 5.72(s, 1H, H8), 3.82 (s, 6H, OCH₃-3''', OCH₃-4'''), 3.80 (s, 3H, OCH₃-4'), 3.78 (s, 3H, OCH₃-6), 3.76 (s, 3H, OCH₃-5'),

3.64 (dd, 1H, J 9.3, 4.2 Hz, H1), 3.40 (s, 3H, OCH₃-7), 3.25 (m, 1H, H3), 3.08 (dd, 1H, J 13.2, 4.2, H7'), 2.95 (m, 1H, H4), 2.80 (m, 1H, H3), 2.69 (dd, 1H, J 13.2, 9.3 Hz, H7'), 2.60 (m, 3H, H4, H2''), 2.55 (bs, 5H, NCH₃, H1'').

¹³C NMR: δ 148.9 (C5'''), 147.8 (C4'''), 147.5 (C4', C6), 147.2 (C5'), 146.3 (C7), 134.7 (C1'), 133.1 (C1'''), 129.4 (C2'), 128.1 (C4a), 125.3 (C8a), 120.5 (CH-6'''), 114.4 (CH-5), 112.88 (CH-3'), 112.11 (CH-2'''), 111.60 (CH-8), 111.45 (CH-6'), 111.41 (CH-5'''), 64.65 (CH-1), 56.1 (5 x OCH₃), 55.6 (OCH₃-6), 46.3 (CH₂-3), 42.5 (NCH₃), 37.2 (CH₂-2''), 37.19 (CH₂-1''), 34.56 (CH₂-7'), 25.13 (CH₂-4).

MS (ES⁺): m/z 522 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₁H₄₀NO₆, 522.2856 (MH⁺). Found 522.2850.

(RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-(3''',4''')-dimethoxyphenyl)propyl]phenylmethyl-2-methylisoquinoline (111).



The alkene **109** (54 mg, 0.12 mmol) was treated as described above in the general hydrogenation reaction procedure using PdCl₂ (46 mg, 0.26 mmol) and CH₃OH (5 mL) to give **111** (50 mg, 84 %) as a yellow oil.

R_f 0.39 (CH₃OH : EtOAc : NH₃ (6 : 4 : 0.1)).

¹H NMR: δ 6.76 (d, 1H, J 7.5 Hz, H5'''), 6.65 (dd, 1H, J 8.1, 0.6 Hz, H6'''), 6.64 (d, 1H, J 0.6 Hz, H2'''), 6.59 (s, 1H, H3'), 6.53 (s, 1H, H5), 6.51 (s, 1H, H6'), 5.68 (s, 1H, H8), 3.84 (s, 6H, OCH₃-5''', OCH₃-4'''), 3.81 (s, 3H, OCH₃-4'), 3.80 (s, 3H, OCH₃-6), 3.75 (s, 3H, OCH₃-5'), 3.59 (dd, 1H, J 9.3, 4.5 Hz, H1), 3.40 (s, 3H, OCH₃-7), 3.11 (m, 1H, H3), 3.04 (dd, 1H, J 13.5, 4.5, H7'), 2.85 (m, 1H, H4), 2.77 (m, 1H, H3), 2.67 (dd, 1H, J 13.5, 9.4 Hz, H7'), 2.52 (t, 1H, J 8.4 Hz, H4), 2.49 (bs, 5H, NCH₃, H1''), 2.24 (t, 2H, J 7.2 Hz, H3''), 1.73 (m, 2H, H2'').

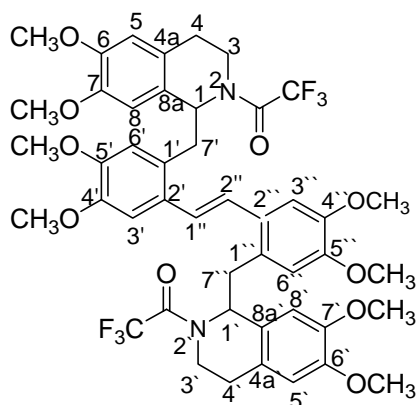
¹³C NMR: δ 148.9 (C5'''), 147.4 (C4'''), 147.3 (C4'), 147.2 (C6), 146.9 (C5'), 146.0 (C7), 134.9 (C1'), 133.7 (C1'''), 129.5 (C2'), 128.8 (C4a), 125.7 (C8a), 120.3 (CH-6'''), 114.2 (CH-5), 112.5 (CH-3'), 111.9 (CH-2'''), 111.4 (CH-8), 111.3 (CH-6', CH-5'''), 64.5 (CH-1), 56.1 (4 x OCH₃), 55.9 (OCH₃-4'), 55.4 (OCH₃-6), 46.4 (CH₂-3), 42.6 (NCH₃), 37.0 (CH₂-7'), 35.6 (CH₂-1''), 33.0 (CH₂-3''), 31.9 (CH₂-2''), 25.3 (CH₂-4).

MS (CI⁺): *m/z* 536 (MH⁺, 40 %). **HRMS (ES⁺):** calcd for C₃₂H₄₆NO₆, 536.3012 (MH⁺). Found 536.3019.

8.4. Experimental for Chapter 4.

8.4.1. Cross metathesis reactions.

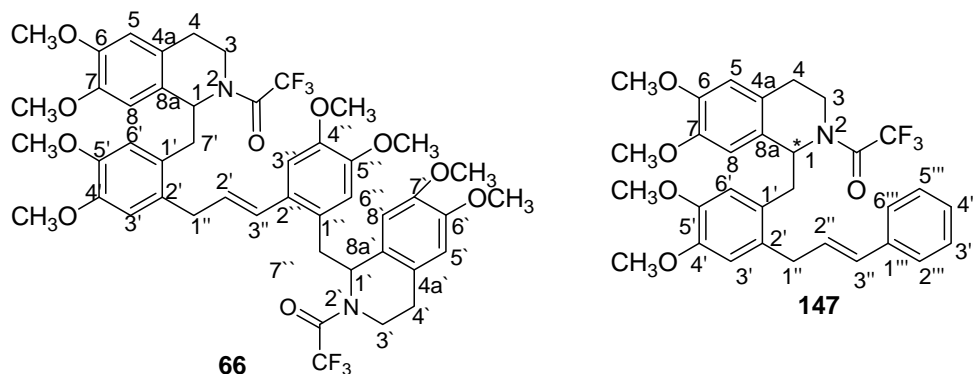
(1*RS*, 1'*RS*) and (*R*, *S*) (*E*) 2',2''-(1'',2''-Ethenediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (**65**).



65

A mixture of the 2'-vinyllaudanosine derivative **67** (113 mg, 0.243 mmol) and Grubbs' II catalyst **144** (31 mg, 0.036 mmol) was dissolved in dry DCM (2 mL) under a N₂ atmosphere and the solution was heated at reflux for 48 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) to afford pure **65** (55 mg, 54 %). Compound **65** was isolated as a 55 : 45 mixture of *meso*-**65** and *rac*-**65**. The starting material **67** (19 mg, 17 %) was also recovered. The spectral data of **65** obtained from this reaction were identical to that obtained from the Heck coupling reactions in Chapter 2.

(1*RS*, 1'*RS*) and (1*RS*, 1'*SR*) (*E*) 2',2''-(1'',3''-Prop-2''-enediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (**66**) and (*RS*) (*E*) 1-(2'-Cinnamyl-4',5'-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**147**).



To a mixture of the 2'-vinylaudanosine derivative **67** (63 mg, 0.134 mmol), the 2'-allyllyaudanosine derivative **68** (114 mg, 0.244 mmol) and Grubbs' I catalyst **143** (11 mg, 0.013 mmol) was added dry DCM (2 mL) under a N₂ atmosphere and the solution was heated at reflux for 48 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) to give a mixture (18 mg) of the desired product **66** and the homocoupled product **146** which has the same R_f and could not be separated. The starting materials **67** (16 mg 26 %) and **68** (26 mg, 27 %) were also recovered. Compound **147** (8 mg) was also isolated as a 95 : 5 mixture of rotamers.

147.

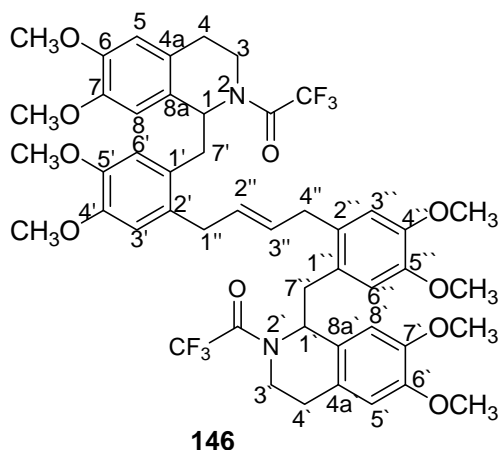
R_f. 0.69 (Pet. spirit : DCM : EtOAc (10 : 5 : 5))

¹H NMR of the major rotamer (500 MHz): δ 7.27 (m, 2H, H_{2'''}, H_{6'''}), 7.25 (m, 2H, H_{3'''}, H_{5'''}) and 7.20 (m, 1H, H_{4'''}), 6.67 (s, 1H, H_{3'}), 6.57 (s, 1H, H₅), 6.55 (s, 1H, H_{6'}), 6.27 (d, 1H, *J* 16.0 Hz, H_{3''}), 6.17 (dt, 1H, *J* 16.0, 6.0 Hz, H_{2''}), 6.02 (s, 1H, H₈), 5.51 (dd, 1H, *J* 7.5, 6.5 Hz, H₁), 3.92 (m, 1H, H₃), 3.82 (s, 6H, OCH₃-4', OCH₃-

6), 3.76 (s, 3H, OCH₃-5'), 3.68 (m, 1H, H3), 3.52 (s, 3H, OCH₃-7), 3.28 (dd, 2H, *J* 12.0, 6.0 Hz, H1''), 3.08 (m, 2H, H7'), 2.91 (m, 1H, H4), 2.76 (m, 1H, H4).

¹H NMR of the minor rotamer (in part): δ 5.81 (s, 1H, H8), 3.84 (s, 6H, OCH₃-4', OCH₃-6), 3.74 (s, 3H, OCH₃-5'), 3.54 (s, 3H, OCH₃-7).

(1*RS*, 1'*RS*) and (*R*, *S*) (*E* and *Z*) 2',2''-(1'',4''-But-2''-enediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (146**).**



A mixture of the 2'-allyllaudanosine derivative **68** (400 mg, 0.854 mmol) and Grubbs I catalyst **143** (70 mg, 0.085 mmol) was dissolved in dry DCM (2 mL) under a N₂ atmosphere and the solution was heated at reflux for 24 h. The solvent was evaporated and the crude product was purified by column chromatography

(EtOAc : Pet. spirit (1 : 1)) to afford pure **146** (284 mg, 72 %) as a mixture of (*E*)- and (*Z*)-isomers (80 : 20) in both meso and racemate forms (55 : 45).

R_f 0.19 (EtOAc : Pet. spirit (1 : 1)).

¹H NMR of the major (*E*)-diastereomer: δ 6.58 (s, 4H, H3', H3'', H5, H5'), 6.46 (s, 2H, H8, H8'), 5.95 (s, 2H, H6', H6''), 5.43 (m, 4H, H1, H1' and CH=CH), 3.87 (dt, 2H, *J* 9.0, 3.6 Hz, H3, H3'), 3.83 (s, 6H, OCH₃-4', OCH₃-4''), 3.78 (s, 6H, OCH₃-6, OCH₃-6'), 3.71 (s, 6H, OCH₃-7, OCH₃-7'), 3.54 (m, 2H, H3, H3'), 3.49 (s, 6H, OCH₃-5', OCH₃-5''), 3.08 (m, 4H, H1'', H4''), 2.99 (m, 4H, H7', H7''), 2.89 (m, 2H, H4, H4'), 2.76 (m, 2H, H4, H4').

¹H NMR of the minor (*E*)-diastereomer (in part): 6.44 (s, 4H, H8, H8'), 5.93 (s, 4H, H6', H6''), 3.47 (s, 6H, OCH₃-5', OCH₃-5'').

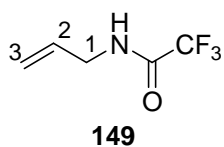
¹H NMR of the major (Z)-isomer (in part): δ 6.01 (s, 4H, H8, H8'), 5.98 (s, 4H, H6', H6''), 3.73 (s, 6H, OCH₃-7, OCH₃-7''), 3.44 (s, 6H, OCH₃-5', OCH₃-5'').

¹³C NMR of the major (E)-diastereomer: δ 156.0 (q, *J* 35.6 Hz, COCF₃), 148.4 (C4', C4''), 147.4 (C6, C6''), 146.2 (C7, C7''), 142.2 (C5', C5''), 131.8 (C2', C2''), 130.4 (CH=CH), 127.3 (C4a, C4a'), 126.5 (C8a, C8a'), 125.1 (C1', C1''), 116.8 (q, *J* 286.3 Hz, COCF₃), 114.3 (CH-6', CH-6''), 113.1 (CH-8, CH-8'), 111.1 (CH-3', CH-3''), 111.9 (CH-5, CH-5''), 56.1 (6 x OCH₃), 55.8 (OCH₃-5', OCH₃-5''), 55.5 (CH-1, CH-1'), 40.8 (CH₂-1'', CH₂-4''), 38.2 (CH₂-7', CH₂-7''), 35.5 (CH₂-3, CH₂-3'), 28.7 (CH₂-4, CH₂-4').

¹³C NMR of the minor (E)-diastereomer (in part): δ 27.4 (CH₂-4, CH₂-4').

MS (ES⁺): *m/z* 931 (MH⁺, 10 %), 953.2 (M+Na⁺, 15 %). **HRMS (ES⁺):** calcd for C₄₈H₅₃N₂O₁₀F₆, 931.3604 (MH⁺). Found 931.3592.

***N*-Allyl-trifluoroacetamide (**149**).**¹⁹³

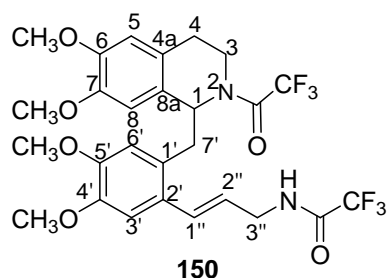


To a solution of allylamine **148** (76 mg, 1.33 mmol, 0.1 mL) in dry DCM (2 mL) at 0 °C under a N₂ atmosphere was added pyridine (0.21 mL, 2.66 mmol), and then trifluoroacetic anhydride (2.06 g, 1.60 mmol, 0.64 mL). The reaction mixture was brought to RT and left to stir for 2 h. The crude mixture was diluted with DCM, washed with citric acid, H₂O (2 x) and brine. The solution was dried (MgSO₄) and evaporated to give **149** (195 mg, 96 %) as a yellow oil which was pure by ¹H NMR analysis and did not require further purification. The spectroscopic data of **149** corresponded to that reported in the literature.¹⁹³

¹H NMR: δ 7.30 (bs, 1H, NH), 5.84 (m, 1H, H2), 5.24 (d, 1H, *J* 17.5 Hz, H3(*E*)), 5.21 (d, 1H, *J* 10.5 Hz, H3(*Z*)), 5.96 (t, 2H, *J* 6.0 Hz, H1).

¹³C NMR: δ 157.6 (q, *J* 38.1 Hz, COCF₃), 131.9 (CH-2), 118.2 (CH₂-3), 117.2 (q, *J* 285.5 Hz, COCF₃), 42.4 (CH₂-1).

(*RS*) (*E*) 2-Trifluoroacetyl-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(3''-trifluoroacetyl-1''-propenyl)phenyl]methyloquinoline (150**).**



To a mixture of the 2'-vinylaudanosine derivative **67** (88 mg, 0.189 mmol), *N*-TFA allylamine **149** (40 mg, 0.261 mmol) and Grubbs' I catalyst **143** (15 mg, 0.019 mmol) was added dry DCM (2 mL) under a N₂

atmosphere and the solution was heated at reflux for 48 h. The solvent was evaporated and the crude product was purified by column chromatography (EtOAc : Pet. spirit (1 : 1)) to give the desired product **150** (34 mg, 30 %) as a yellow oil. The starting material **67** (48 mg, 54 %) was also recovered.

R_f. 0.38 (EtOAc : Pet. spirit (1 : 1)).

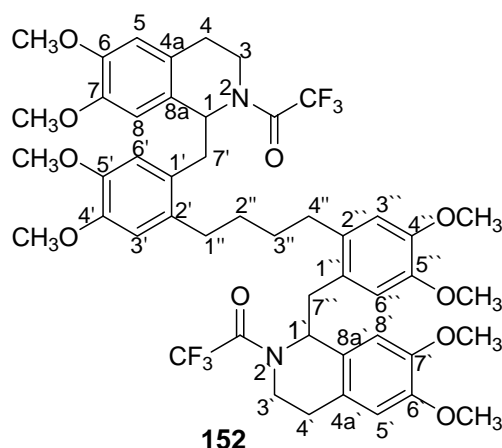
¹H NMR: δ 7.62 (bs, 1H, NH), 6.94 (s, 1H, H3'), 6.76 (d, 1H, *J* 15.5 Hz, H1''), 6.60 (s, 1H, H5), 6.26 (s, 1H, H6'), 5.98 (dt, 1H, *J* 15.5, 5.5 Hz, H2''), 5.69 (s, 1H, H8), 5.35 (dd, 1H, *J* 10.0, 3.5 Hz, H1), 4.19 (dt, 1H, *J* 15.5, 5.5 Hz, H3''), 4.09 (dt, 1H, *J* 15.5, 5.5 Hz, H3''), 3.93 (m 1H, H3), 3.87 (s, 3H, OCH₃-5'), 3.82 (s, 3H, OCH₃-7), 3.70 (m, 1H, H3), 3.66 (s, 3H, OCH₃-4'), 3.44 (s, 3H, OCH₃-6), 3.23 (dd, 1H, *J* 13.0, 3.5 Hz, H7'), 2.93 (m, 1H, H4), 2.91 (dd, 1H, *J* 13.0, 10.0 Hz, H7'), 2.78 (m, 1H, H4).

¹³C NMR: δ 157.4 (q, *J* 36.6 Hz, C=O(CF₃)), 156.1 (q, *J* 36.7 Hz, C=O(CF₃)), 148.4 (C4', C5'), 148.2 (C7), 146.9 (C6), 129.6 (CH-1''), 128.7 (C1'), 127.0 (C2'), 125.9 (C4a), 124.5 (C8a), 123.9 (CH-2''), 118.3 (q, *J* 286.1 Hz, C=O(CF₃)), 116.5 (q, *J* 286.0 Hz, C=O(CF₃)), 114.8 (CH-6'), 111.3 (CH-8), 111.0 (CH-5), 109.1 (CH-3'), 56.0 (OCH₃-5', OCH₃-7), 55.9 (OCH₃-4'), 55.5 (OCH₃-6), 55.3 (CH-1), 41.3 (CH₂-3''), 40.9 (CH-3), 39.6 (CH₂-7'), 28.4 (CH₂-4).

MS (EI⁺): *m/z* 590 (M⁺, 30 %). **HRMS (ES⁺):** calcd for C₂₇H₂₉ N₂O₆F₆, 591.1930 (MH⁺). Found 591.1959.

8.4.2. Hydrogenation reactions.

(1*RS*, 1'*RS*) and (*R*, *S*) 2',2''-(1'',4''-Butanediyl)-bis-[2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (**152**).



To a solution of the alkene **146** (284 mg, 0.308 mmol) in EtOAc (5 mL) was added 10 % Pd/C (21 mg) in a round bottom flask sealed with a suba seal. The flask was purged with nitrogen and then a hydrogen filled balloon was secured on top of the flask, allowing the hydrogen to circulate inside the flask. The reaction mixture

was stirred at RT for 48 h under a H₂ atmosphere. Nitrogen was then bubbled into the solution for 2 min before the Pd/C was filtered. The filtrate was evaporated to give pure **152** (248 mg, 87 %) as a yellow oil.

R_f. 0.85 (EtOAc: Pet. spirit (1 : 1)).

¹H NMR: δ 6.62 (s, 2H, H3', H3''), 6.58 (s, 2H, H5, H5'), 6.45 (s, 2H, H8, H8'), 6.00 (s, 2H, H6', H6''), 5.45 (dd, 2H, *J* 8.1, 5.7 Hz, H1, H1'), 3.89 (dt, 2H, *J* 12.0, 5.0 Hz, H3, H3'), 3.83 (s, 12H, OCH₃-4', OCH₃-4'', OCH₃-7, OCH₃-7'), 3.68 (s, 6H, OCH₃-6, OCH₃-6'), 3.63 (m, 2H, H3, H3'), 3.50 (s, 6H, OCH₃-5', OCH₃-5''), 3.05 (m, 2H, H4', H4''), 2.93 (m, 4H, H7', H7''), 2.76 (m, 2H, H4, H4'), 2.40 (m, 4H, H1'', H4''), 1.49 (m, 4H, H2'', H3'').

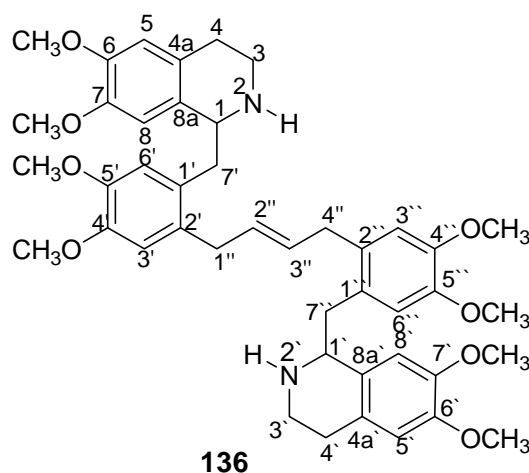
¹³C NMR: δ 155.1 (q, *J* 35.5 Hz, C=O(CF₃)), 148.4 (C4', C4''), 148.0 (C6, C6'), 147.3 (C7, C7'), 147.0 (C5', C5''), 134.0 (C2', C2''), 126.8 (C4a, C4a'), 126.5 (C8a, C8a'), 125.2 (C1', C1''), 114.3 (CH-6', CH-6''), 113.8 (q, *J* 286.9 Hz, C=O(CF₃)), 112.6 (CH-8, CH-8'), 111.1 (CH-3', CH-3''), 111.0 (CH-5, CH-5'), 56.1 (OCH₃-4', OCH₃-4''), 56.0 (OCH₃-7, OCH₃-7'), 55.8 (OCH₃-5', OCH₃-5''), 55.6 (CH-1,

CH-1'), 40.8 (CH₂-3, CH₂-3'), 32.2 (CH₂-7', CH₂-7''), 38.2 (CH₂-4, CH₂-4'), 31.7 (CH₂-1'', CH₂-4''), 28.7 (CH₂-2'', CH₂-3'').

MS (ES⁺): *m/z* 933.3 (MH⁺, 70 %). **HRMS (ES⁺):** calcd for C₄₈H₅₅N₂O₁₀F₆, 933.3761 (MH⁺). Found 933.3800.

8.4.3. *N*-TFA deprotection.

(1*RS*, 1'*RS*) and (*R*, *S*) (*E* and *Z*) 2',2''-(1'',4''-But-2''-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (**136**).



To a solution of the *N*-TFA protected amine **146** (243 mg, 0.262 mmol) in CH₃OH (2 mL) was added dropwise 28 % aqueous NH₃ (2 mL). The reaction mixture was stirred at RT for 18 h. The solvent was evaporated and the residue was purified by column chromatography (CH₃OH : EtOAc (1 : 4)) to

give **136** (189 mg, 85 % yield) as a yellow solid. Compound **136** was obtained as a 80 : 20 mixture of (*E*) and (*Z*) isomers, respectively.

R_f. 1.3 (EtOAc).

m.p. 158-160 °C.

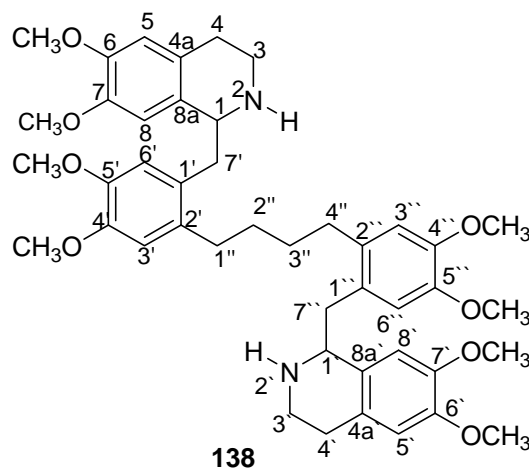
¹H NMR of (*E*)-136: δ 6.68 (s, 2H, H3', H3''), 6.65 (s, 2H, H5, H5'), 6.57 (s, 2H, H8, H8'), 6.46 (s, 2H, H6', H6''), 5.44 (bs, 2H, CH=CH), 4.06 (bs, 2H, *J* 9.0, 4.8 Hz, H1, H1'), 3.84 (s, 6H, OCH₃-4', OCH₃-4''), 3.81 (s, 6H, OCH₃-6, OCH₃-6'), 3.79 (s, 6H, OCH₃-7, OCH₃-7'), 3.71 (s, 6H, OCH₃-5', OCH₃-5''), 3.31 (d, 4H, *J* 3.3 Hz, H1'', H4''), 3.19 (m, 2H, H3, H3'), 3.15 (dd, 2H, *J* 12.9, 6.0 Hz, H7', H7''), 2.85 (m, 4H, H7', H7'', H3, H3'), 2.72 (dt, 4H, *J* 9.2, 6.2 Hz, H4, H4').

¹H NMR of (Z)-136 (in part): δ 6.71 (s, 2H, H3', H3''), 6.64 (s, 2H, H5, H5'), 6.47 (s, 2H, H6', H6''), 5.61 (bs, 2H, CH=CH), 4.15 (m, 1H, H1).

¹³C NMR of (E)-136: δ 147.7 (C4', C4'', C6, C6'), 146.7 (C7, C7'), 147.1 (C5', C5''), 131.4 (C2', C2''), 130.7 (C4a, C4a'), 130.1 (CH=CH), 129.3 (C8a, C8a'), 127.6 (C1', C1''), 114.0 (CH-6', CH-6''), 113.4 (CH-8, CH-8'), 112.1 (CH-3', CH-3''), 101.8 (CH-5, CH-5'), 56.6 (CH-1, CH-1'), 56.2 (OCH₃-4', OCH₃-4''), 56.1 (OCH₃-6, OCH₃-6', OCH₃-7, OCH₃-7'), 56.2 (OCH₃-5', OCH₃-5''), 41.0 (CH₂-3, CH₂-3'), 39.5 (CH₂-7', CH₂-7''), 35.8 (CH₂-1'', CH₂-4''), 29.7 (CH₂-4, CH₂-4')

MS (ES⁺): m/z 739 (MH⁺, 10 %). **HRMS (ES⁺):** calcd for C₄₄H₅₅N₂O₈, 739.3958 (MH⁺). Found 739.3950.

(1RS, 1'RS) and (R, S) 2',2''-(1'',4''-Butyldiyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (138).



To a solution of the *N*-TFA protected amine **152** (247 mg, 0.267 mmol) in a mixture of CH₃OH (20 mL) and H₂O (2 mL) was added K₂CO₃ (184 mg, 1.34 mmol). The resulting solution was stirred at RT for 2 d. The CH₃OH was evaporated and the residue was dissolved in EtOAc. The solution was

washed with H₂O (3 x), brine and then dried (MgSO₄). The EtOAc was evaporated and the residue was purified by column chromatography (CH₃OH: EtOAc : NH₃ (1 : 5 : 0.1)) to afford the amine **138** (164 mg, 83 %) as yellow solid.

R_f 0.09 (CH₃OH: EtOAc : NH₃ (1 : 5 : 0.1)).

m.p. 130-134 °C.

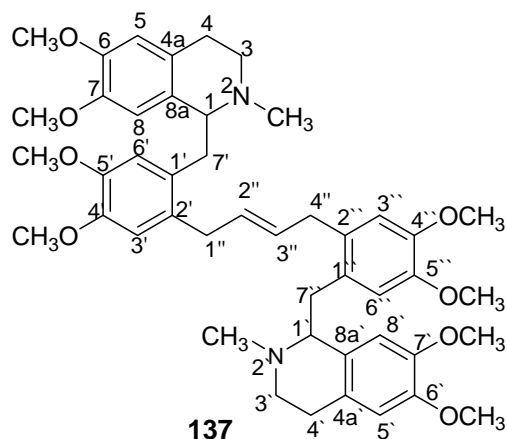
¹H NMR: δ 6.64 (s, 4H, H3', H3'', H6', H6''), 6.56 (s, 2H, H5, H5'), 6.46 (s, 2H, H8, H8'), 4.10 (dd, 2H, J 4.4, 2.4 Hz, H1, H1'), 3.82 (s, 12 H, OCH₃-4', OCH₃-4'', OCH₃-5', OCH₃-5''), 3.78 (s, 6H, OCH₃-6, OCH₃-6'), 3.70 (s, 6H, OCH₃-7, OCH₃-7'), 3.15 (m, 4H, H3, H3' and H7', H7''), 2.83 (m, 4H, H3, H3' and H7', H7''), 2.70 (m, 4H, H4, H4'), 2.58 (m, 4H, H1'', H4''), 2.32 (bs, 2H, 2 x NH), 1.60 (m, 4H, H2'', H3'').

¹³C NMR: δ 147.8 (C4', C4''), 147.7 (C5', C5''), 147.2 (C6, C6'), 147.1 (C7, C7'), 133.7 (C2', C2''), 133.7 (C1', C1''), 128.7 (C4a, C4a'), 127.4 (C8a, C8a'), 114.0 (CH-3', CH-3''), 112.9 (CH-6', CH-6''), 112.0 (CH-5, CH-5'), 110.0 (CH-8, CH-8'), 56.7 (CH-1, CH-1'), 56.2 (OCH₃-4', OCH₃-4'', OCH₃-5', OCH₃-5''), 56.1 (OCH₃-6, OCH₃-6', OCH₃-7, OCH₃-7'), 40.9 (CH₂-3, CH₂-3'), 39.2 (CH₂-7', CH₂-7''), 32.8 (CH₂-4, CH₂-4'), 32.0 (CH₂-1'', CH₂-4''), 29.9 (CH₂-2'', CH₂-3'').

MS (ES⁺): m/z 741.5 (MH⁺, 30 %). **HRMS (ES⁺):** calcd for C₄₄H₅₇N₂O₈, 741.4150 (MH⁺). Found 741.4121.

8.4.4. *N*-Methylation.

(1*RS*, 1'*RS*) and (*R*, *S*) (*E* and *Z*) 2',2''-(1'',4''-But-2''-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl-2-methyl]isoquinoline (137).



To a solution of the amine **136** (37 mg, 0.501 mmol) in CH₃CN (1 mL) was added 38 % formaldehyde (2 mL). NaCNBH₃ (18 mg, 0.260 mmol) was subsequently added and the reaction mixture was stirred at RT for 20 min. The pH was then adjusted to 6-7 using glacial acetic acid and the reaction mixture was stirred

at RT for 18 h. The solvent was evaporated and the residue was dissolved in EtOAc.

The solution was washed with sat. K_2CO_3 (2 x) then dried ($MgSO_4$) and evaporated to give an oil which was purified by column chromatography (DCM : EtOAc : CH_3OH : NH_3 (10 : 5 : 1 : 0.1)) to afford **137** (19 mg, 49 % yield) as a yellow oil. Compound **137** was a 80 : 20 mixture of (*E*)- and (*Z*)- isomers, respectively for both *meso*-**137** and *rac*-**137** (d.r. = 55 : 45).

R_f 0.39 (DCM : EtOAc : CH_3OH : NH_3 (10 : 5 : 1 : 0.1)).

¹H NMR of (*E*)-137, major diastereomer: δ 6.54 (s, 2H, H3', H3''), 6.53 (s, 2H, H5, H5'), 6.50 (s, 2H, H8, H8'), 5.68 (s, 2H, H6', H6''), 5.71 (bs, 2H, $\underline{CH=CH}$), 3.80 (s, 6H, $\underline{OCH_3-4'}$, $\underline{OCH_3-4''}$), 3.76 (s, 6H, $\underline{OCH_3-6}$, $\underline{OCH_3-6'}$), 3.74 (s, 6H, $\underline{OCH_3-7}$, $\underline{OCH_3-7'}$), 3.62 (dd, 2H, *J* 8.4, 4.2 Hz, H1, H1'), 3.39 (s, 6H, $\underline{OCH_3-5'}$, $\underline{OCH_3-5''}$), 3.19 (m, 2H, H3, H3'), 3.07 (dd, 2H, *J* 13.5, 4.2 Hz, H7', H7''), 2.91 (t, 4H, *J* 4.5 Hz, H1'', H4''), 2.87 (dd, 2H, *J* 13.5, 8.4 Hz, H7', H7''), 2.81 (m, 4H, H3, H3', H4, H4'), 2.58 (m, 2H, H4, H4'), 2.51 (s, 6H, 2x $\underline{NCH_3}$).

¹H NMR of (*E*)-137, minor diastereomer (in part): δ 6.49 (s, 2H, H8, H8'), 5.67 (s, 2H, H6', H6''), 3.41 (s, 6H, $\underline{OCH_3-5'}$, $\underline{OCH_3-5''}$).

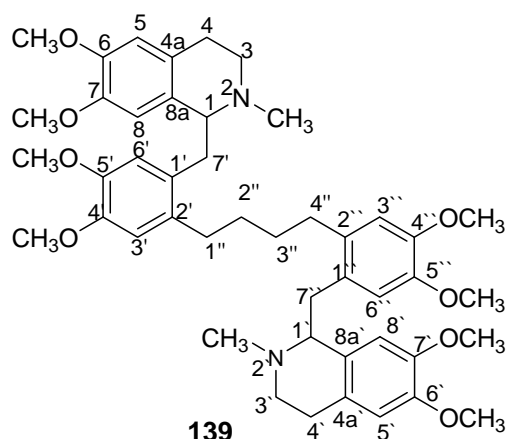
¹H NMR of (*Z*)-137 (in part): δ 6.57 (s, 2H, H3', H3''), 6.56 (s, 2H, H5, H5'), 5.71 (s, 2H, H6', H6'').

¹³C NMR of (*E*)-137, major diastereomer: δ 148.5 (C4', C4''), 148.0 (C6, C6'), 147.5 (C7, C7'), 146.7 (C5', C5''), 132.0 (C2', C2''), 130.3 ($\underline{CH=CH}$), 130.1 (C4a, C4a'), 128.5 (C8a, C8a'), 125.9 (C1', C1''), 114.6 (CH-6', CH-6''), 113.1 (CH-8, CH-8'), 111.5 (CH-3', CH-3''), 111.4 (CH-5, CH-5'), 64.5 (CH-1, CH-1'), 56.3 ($\underline{OCH_3-4'}$, $\underline{OCH_3-4''}$), 56.2 ($\underline{OCH_3-6}$, $\underline{OCH_3-6'}$), 56.1 ($\underline{OCH_3-7}$, $\underline{OCH_3-7'}$), 55.6 ($\underline{OCH_3-5'}$, $\underline{OCH_3-5''}$), 45.1 (CH₂-3, CH₂-3'), 41.0 (2 x $\underline{NCH_3}$), 37.2 (CH₂-7', CH₂-7''), 35.6 (CH₂-1'', CH₂-4''), 23.4 (CH₂-4, CH₂-4'),

¹³C NMR of (*E*)-137, minor diastereomer (in part): δ 64.7 (CH-1, CH-1'), 40.7 (2 x NCH₃), 35.6 (CH₂-1'', CH₂-4''), 22.9 (CH₂-4, CH₂-4').

MS (ES⁺): m/z 767.5 (MH⁺, 10 %). **HRMS (ES⁺):** calcd for C₄₆H₅₉N₂O₈, 767.4271 (MH⁺). Found 767.4234.

(1*RS*, 1'*RS*) and (*R*, *S*) 2',2''-(1'',4''-Butyldiyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl-2-methyl]isoquinoline (139).



The amine **138** (73 mg, 0.099 mmol) was treated as described above in the synthesis of **137** using CH₃CN (2 mL), 38 % formaldehyde (4 mL) and NaCNBH₃ (36 mg, 0.514 mmol) to give an oil which was purified by column chromatography (DCM : EtOAc : CH₃OH :

NH₃ (10: 5 : 1: 0.1)) to give **139** (56 mg, 74 %) as a yellow oil.

R_f 0.37 (DCM : EtOAc : CH₃OH : NH₃ (10: 5 : 1: 0.1)).

¹H NMR: δ 6.58 (s, 2H, H3', H3''), 6.55 (s, 2H, H5, H5'), 6.52 (s, 2H, H8, H8'), 5.74 (s, 2H, H6, H6'), 3.82 (s, 6H, OCH₃-4', OCH₃-4''), 3.81 (s, 6H, OCH₃-6, OCH₃-6'), 3.76 (s, 6H, OCH₃-7, OCH₃-7'), 3.66 (dd, 2H, *J* 9.3, 4.5 Hz, H1, H1'), 3.43 (s, 6H, OCH₃-5', OCH₃-5''), 3.23 (ddd, 2H, *J* 13.2, 8.1, 3.6 Hz, H3, H3'), 3.10 (dd, 2H, *J* 13.5, 4.5 Hz, H7', H7''), 2.90 (m, 2H, H3, H3'), 2.73 (m, 2H, H4, H4'), 2.72 (dd, 2H, *J* 13.5, 9.3 Hz, H7', H7''), 2.60 (m, 2H, H4, H4'), 2.54 (s, 6H, 2 x NCH₃), 2.42 (m, 4H, H1'', H4''), 2.11 (m, 4H, H2'', H3'').

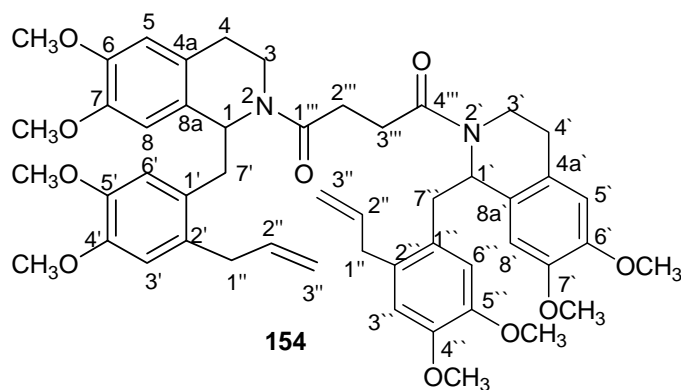
¹³C NMR: δ 147.9 (C4', C4''), 147.6 (C6, C6'), 147.0 (C7, C7'), 146.4 (C5', C5''), 133.9 (C2', C2''), 128.7 (C4a, C4a'), 127.5 (C8a, C8a'), 124.9 (C1', C1''), 114.4 (CH-3', CH-3''), 112.8 (CH-5, CH-5'), 111.6 (CH-8, CH-8'), 111.4 (CH-6', CH-6''), 64.6 (CH-1, CH-1'), 56.2 (OCH₃-4', OCH₃-4'' and OCH₃-6, OCH₃-6'), 56.0 (OCH₃-7,

OCH₃-7'), 55.6 (OCH₃-5', OCH₃-5''), 31.6 (CH₂-1'', CH₂-4''), 24.7 (CH₂-2'', CH₂-3'').

MS (ES⁺): *m/z* 769.4 (MH⁺, 30 %). **HRMS (ES⁺):** calcd for C₄₆H₆₁N₂O₈, 769.4428 (MH⁺). Found 769.4396.

8.4.5. Ring closing metathesis reactions.

(1*RS*, 1'*RS*) and (R, S) 2,2'-(1''',4'''-Dioxo-1''',4'''-butanediyl)-2',2''-(1'',4''-prop-2-enediyl)-bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxyphenyl)methyl]isoquinoline (154).



To a mixture of the acid **90** (64 mg, 0.131 mmol), amine **92** (50 mg, 0.131 mmol), HOBT (20 mg, 0.144 mmol) and EDCI (25 mg, 0.131 mmol) was added dry DMF (3 mL) under a N₂

atmosphere. The mixture was stirred at RT for 3 d. EtOAc was added and the solution was washed with H₂O (3 x) then dried (MgSO₄) and evaporated to give a solid which was purified by column chromatography (CH₃OH : EtOAc (1 : 5)) to give **154** (69 mg, 62 %) as a white solid. Compound **154** was a 55 : 45 mixture of diastereomers. A minor rotamer of **154** (30 %) was also observed.

R_f 0.88 (CH₃OH : EtOAc (1 : 5)).

m.p. 142-144 °C.

¹H NMR of the major diastereomer: δ 6.56 (s, 6H, H3', H3'', H5, H5', H6', H6''), 5.89 (s, 2H, H8, H8'), 5.74 (m, 2H, 2 x H2''), 5.50 (dd, 2H, *J* 8.7, 4.2 Hz, H1, H1'), 4.93 (m, 4H, 2 x H3''), 3.81 (s, 6H, OCH₃-5', OCH₃-5''), 3.79 (s, 6H, OCH₃-7, OCH₃-7'), 3.81 (m, 2H, H3, H3'), 3.72 (s, 6H, OCH₃-6, OCH₃-6'), 3.60 (m, 2H, H3, H3'),

3.46 (s, 6H, OCH₃-4', OCH₃-4''), 3.00 (d, 4H, *J* 5.7 Hz, 2 x H1''), 2.98 (m, 2H, H7', H7''), 2.86 (m, 2H, H7', H7''), 2.81 (m, 4H, H4, H4'), 2.77 (bs, 4H, H2''', H3''').

¹H NMR of the minor diastereomer (in part): δ 6.59 (s, 2H, H3', H3''), 6.57 (s, 2H, H5, H5''), 6.53 (s, 2H, H6', H6''), 5.88 (s, 2H, H8, H8''), 5.82 (m, 2H, 2 x H2''). 5.48 (dd, 2H, *J* 8.7, 4.2 Hz, H1, H1'), 4.99 (m, 4H, H3, H3'), 3.71 (s, 6H, OCH₃-7, OCH₃-7'), 3.45 (s, 6H, OCH₃-6, OCH₃-6'), 3.46 (s, 6H, OCH₃-4', OCH₃-4''), 3.08 (m, 2H, H7', H7''), 3.02 (d, 4H, *J* 5.7 Hz, 2 x H1'').

¹H NMR minor rotamer of both diastereomers (in part): note:-*- indicates the minor diastereomer. δ 6.64 (s, 2H, H3', H3''), 6.50 (s, 2H, H5, H5''), 6.47 (s, 2H, H5*, H5'*), 6.36 (s, 2H, H6', H6''), 6.34 (s, 2H, H6'* , H6''*), 5.93 (s, 2H, H8, H8''), 5.84 (s, 2H, H8*, H8'*), 5.40 (dd, 2H, *J* 9.9, 5.1 Hz, H1, H1'), 5.39 (dd, 2H, *J* 9.9, 5.1 Hz, H1*, H1'*), 4.70 (m, 2H, 2 x H3''), 4.57 (m, 2H, 2 x H3''*)

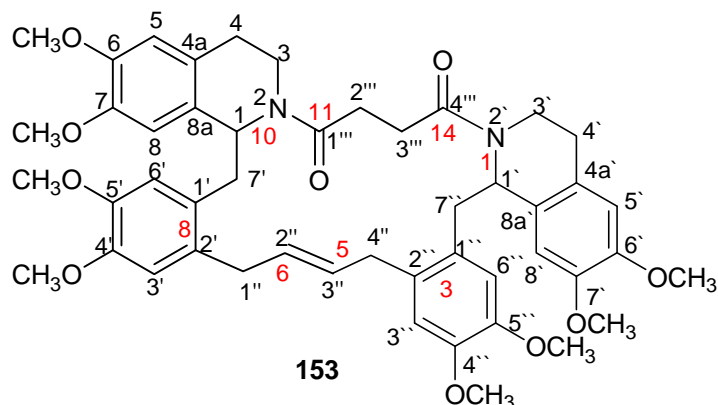
¹³C NMR of the major diastereomer: δ 171.1 (C=O), 148.0 (C5', C5''), 147.7 (C7, C7', C6, C6''), 147.3 (C4', C4''), 137.2 (2 x CH-2''), 131.2 (C8a, C8a''), 128.7 (C4a, C4a''), 128.4 (C1', C1''), 126.1 (C2', C2''), 115.7 (2 x CH₂-3''), 114.0 (CH-3', CH-3''), 112.5 (CH-6', CH-6''), 111.0 (CH-8, CH-8''), 110.8 (CH-5, CH-5''), 55.8 (8 x OCH₃), 54.5 (CH-1, CH-1'), 41.1 (CH₂-3, CH₂-3'), 38.1 (CH₂-7', CH₂-7''), 36.3 (2 x CH₂-1''), 28.9 (CH₂-4, CH₂-4'), 28.4 (CH₂-2''', CH₂-3''').

¹³C NMR of the minor diastereomer (in part): δ 171.1 (C=O), 148.3 (C5', C5''), 147.7 (C7, C7', C6, C6''), 146.7 (C4', C4''), 137.1 (2 x CH-2''), 132.0 (C8a, C8a''), 115.3 (2 x CH₂-3''), 57.2 (CH-1, CH-1'), 41.1 (CH₂-3, CH₂-3'), 38.7 (CH₂-7', CH₂-7''), 36.9 (2 x CH₂-1''), 29.0 (CH₂-4, CH₂-4'), 27.9 (CH₂-2''', CH₂-3''').

MS (ES⁺): *m/z* 849.5 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₅₀H₆₁N₂O₁₀, 849.4326 (MH⁺). Found 849.4376.

(1*RS*, 1'*RS*) and (*R*, *S*) 1,10-(1,2)-Di-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolina)-3,8-(1,2)-di-(3,4-dimethoxy)benzenacyclo-(11,14-dioxo)-tetradeca-5-phene (153).

Note: The red colours represent the systematic numbering of the macrocyclic system



A solution of **154** (44 mg, 0.056 mmol) and Grubbs' I catalyst **143** (5mg, 0.006 mmol) in dry DCM (25 mL) was heated at reflux for 24 h under a N₂ atmosphere. The solvent was evaporated and

the crude oil was purified by column chromatography (CH₃OH : EtOAc (2 : 8)) to give **153** (16 mg, 35 %) as a clear oil. Compound **153** was a 55 : 45 mixture of diastereomers which were separated by PTLC.

153-d1.

R_f 0.69 (CH₃OH : EtOAc (2 : 8)).

¹H NMR: δ 6.71 (s, 2H, H3', H3''), 6.57 (s, 2H, H5, H5'), 6.40 (s, 2H, H6', H6''), 5.73 (s, 2H, H8, H8'), 5.53 (dd, 2H, *J* 6.0, 2.4 Hz, H1, H1'), 5.19 (t, 2H, *J* 4.8 Hz, H2'', H3''), 3.84 (s, 12H, OCH₃-5', OCH₃-5'', OCH₃-7, OCH₃-7'), 3.81 (m, 2H, H3, H3'), 3.73 (s, 6H, OCH₃-6, OCH₃-6'), 3.60 (m, 4H, H1'', H4''), 3.49 (dd, 2H, *J* 12.6, 5.4 Hz, H3, H3'), 3.37 (s, 6H, OCH₃-4', OCH₃-4''), 3.35 (m, 2H, H2''', H3'''), 3.30 (dd, 2H, *J* 13.3, 6.0 Hz, H7', H7''), 2.99 (dd, 2H, *J* 13.3, 2.4 Hz, H7', H7''), 2.62 (m, 2H, H4, H4'), 2.33 (m, 2H, H4, H4'), 2.18 (dt, 2H, *J* 14.1, 4.8 Hz, H2''', H3''').

¹³C NMR: δ 171.5 (C=O), 147.8 (C5', C5''), 147.4 (C7, C7'), 147.3 (C6, C6'), 145.9 (C4', C4''), 133.3 (C8a, C8a'), 129.4 (CH-2'', CH-3''), 128.3 (C4a, C4a'), 127.6 (C1', C1''), 127.3 (C2', C2''), 114.4 (CH-8, CH-8'), 112.9 (CH-3', CH-3''), 111.3 (CH-6',

CH-6''), 110.8 (CH-5, CH5'), 56.0 (OCH₃-5', OCH₃-5'', OCH₃-7, OCH₃-7'), 55.8 (OCH₃-6, OCH₃-6'), 55.3 (OCH₃-4', OCH₃-4''), 55.0 (CH-1, CH-1'), 41.7 (CH₂-3, CH₂-3'), 37.9 (CH₂-7', CH₂-7''), 31.5 (CH₂-1'', CH₂-4''), 28.3 (CH₂-2''', CH₂-3'''), 28.1 (CH₂-4, CH₂-4').

153-d2.

R_f : 0.66 (CH₃OH : EtOAc (2 : 8)).

¹H NMR of the major rotamer: δ 6.81 (s, 2H, H3', H3''), 6.69 (s, 2H, H5, H5'), 6.59 (s, 2H, H6', H6''), 5.88 (s, 2H, H8, H8'), 5.43 (dd, 2H, *J* 9.0, 3.6 Hz, H1, H1'), 5.29 (t, 2H, *J* 8.4 Hz, H2'', H3''), 4.20 (m, 2H, H3, H3'), 3.85 (s, 6H, OCH₃-5', OCH₃-5''), 3.83 (s, 6H, OCH₃-7, OCH₃-7'), 3.60 (s, 6H, OCH₃-6, OCH₃-6'), 3.59 (s, 6H, OCH₃-4', OCH₃-4''), 3.78 (m, 2H, H3, H3'), 3.55 (m, 2H, H1'', H4''), 3.08 (m, 2H, H1'', H4''), 2.90 (m, 4H, H7', H7''), 2.70 (m, 2H, H4, H4'), 2.49 (m, 2H, H4, H4'), 2.31 (m, 4H, H2''', H3''').

¹H NMR of the minor rotamer (in part): δ 6.77 (s, 2H, H3', H3''), 6.63 (s, 2H, H5, H5'), 6.18 (s, 2H, H6', H6''), 6.11 (s, 2H, H8, H8'), 5.58 (m, 4H, H1, H1', H2'', H3''), 4.58 (m, 2H, H3, H3'), 4.20 (m, 2H, H3, H3'), 3.90 (s, 6H, OCH₃-5', OCH₃-5''), 3.87 (s, 6H, OCH₃-7, OCH₃-7'), 3.78 (s, 6H, OCH₃-6, OCH₃-6'), 3.48 (s, 6H, OCH₃-4', OCH₃-4), 2.77 (m, 4H, H7', H7''), 2.64 (m, 2H, H4, H4'), 2.39 (m, 2H, H4, H4').

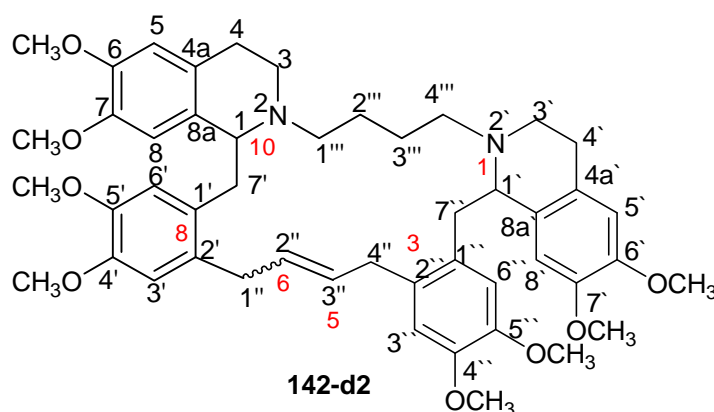
¹³C NMR of the major rotamer: δ 171.7 (C=O), 148.5 (C5', C5''), 146.8 (C7, C7'), 147.0 (C6, C6'), 147.8 (C4', C4''), 132.2 (C8a, C8a'), 128.6 (CH-2'', CH-3''), 128.3 (C4a, C4a'), 128.1 (C1', C1''), 128.0 (C2', C2''), 115.5 (CH-8, CH-8'), 112.2 (CH-3', CH-3''), 110.6 (CH-6', CH-6''), 110.0 (CH-5, CH5'), 56.0 (OCH₃-5', OCH₃-5'', OCH₃-7, OCH₃-7'), 55.8 (OCH₃-6, OCH₃-6'), 55.3 (OCH₃-4', OCH₃-4''), 54.8 (CH-1, CH-1'), 41.5 (CH₂-3, CH₂-3'), 39.7 (CH₂-7', CH₂-7''), 31.8 (CH₂-1'', CH₂-4''), 29.8 (CH₂-2''', CH₂-3'''), 27.0 (CH₂-4, CH₂-4').

^{13}C NMR of the minor rotamer (in part): δ 132.4 (C8a, C8a'), 128.7 (CH-2'', CH-3''), 128.2 (C4a, C4a'), 111.8 (CH-3', CH-3''), 36.1 (CH₂-3, CH₂-3'), 35.0 (CH₂-7', CH₂-7''), 26.2 (CH₂-4, CH₂-4').

MS (ES⁺): m/z 821.5 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₄₆H₅₇N₂O₁₀, 821.4013 (MH⁺). Found 821.4033.

**(1*RS*, 1'*RS*) and (*R*, *S*) (*Z*) or (*E*) 1,10-(1,2)-Di-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolina)-3,8-(1,2)-di-(3,4-dimethoxy)benzenacyclotetradeca-5-
phene (**142-d2**).**

Note: The red colours represent the systematic numbering of the macrocyclic system



To a slurry of LiAlH₄ (13 mg, 0.348 mmol) in THF (1 mL) at 0 °C under a N₂ atmosphere was added a solution of the amide **153-d2** (24 mg, 0.029 mmol) in dry THF (1 mL).

The resulting mixture was brought to RT and was stirred for 24 h. The solution was treated subsequently with H₂O (0.14 mL), 1M NaOH (0.14 mL) and H₂O (0.46 mL). The mixture was left to stir for 1 h. The solids were filtered and washed with EtOAc. The solution was dried (MgSO₄) and then evaporated to give **142-d2** (18 mg, 78 %) as a white oil.

R_f. 0.06 (CH₃OH : EtOAc (2 : 8)).

^1H NMR: δ 6.82 (s, 2H, H3', H3''), 6.56 (s, 2H, H5, H5'), 6.13 (s, 2H, H6', H6''), 5.83 (s, 2H, H8, H8'), 5.68 (t, 2H, J 4.2 Hz, H2'', H3''), 3.85 (s, 6H, OCH₃-5', OCH₃-5''), 3.82 (s, 6H, OCH₃-7, OCH₃-7'), 3.60 (s, 6H, OCH₃-6, OCH₃-6'), 3.67 (m, 6H, H1'', H4'' and H1', H1'), 3.51 (s, 6H, OCH₃-4', OCH₃-4''), 3.26 (m, 4H, H3, H3', H7', H7''),

2.84 (dd, 2H, *J* 10.8, 4.2 Hz, H3, H3'), 2.75 (dd, 2H, *J* 13.2, 9.0 Hz, H7', H7''), 2.58 (m, 4H, H1''', H4'''), 2.42 (m, 4H, H4, H4'), 1.56 (m, 4H, H2''', H3''').

¹³C NMR: δ 147.5 (C5', C5''), 147.3 (C7, C7'), 146.3 (C6, C6'), 145.2 (C4', C4''), 131.4 (C1', C1''), 130.1 (C2', C2'', CH-2'', CH-3''), 129.0 (C4a, C4a'), 126.1 (C8a, C8a'), 115.46 (CH-6', CH-6''), 112.5 (CH-3', CH-3''), 112.0 (CH-8, CH-8'), 111.4 (CH-5, CH-5'), 62.1 (CH-1, CH-1'), 56.1 (OCH₃-5', OCH₃-5''), 55.8 (OCH₃-7, OCH₃-7', OCH₃-6, OCH₃-6'), 55.5 (OCH₃-4', OCH₃-4''), 52.7 (CH₂-1''', CH₂-4'''), 43.1 (CH₂-3, CH₂-3'), 40.8 (CH₂-7', CH₂-7''), 30.6 (CH₂-1'', CH₂-4''), 25.4 (CH₂-2''', CH₂-3'''), 23.7 (CH₂-4, CH₂-4').

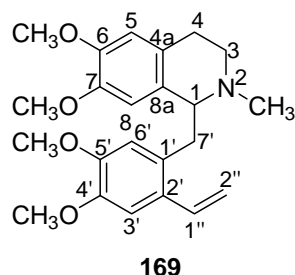
MS (ES⁺): *m/z* 793.5 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₄₈H₆₁N₂O₈, 793.4428 (MH⁺). Found 793.4393.

8.5. Experimental for Chapter 5.

8.5.1. Synthesis of 2'-aminoalkylbenzylisoquinoline derivatives.

Synthesis of 169, 173, 175, 189 and 192.

(*RS*) 1-(2'-Ethenyl-4',5'-dimethoxyphenyl)methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (169).



To a solution of the 2'-vinylaudanosine derivative **67** (227 mg, 0.487 mmol) in a mixture of CH₃OH (20 mL) and H₂O (3 mL) at RT was added K₂CO₃ (339 mg, 2.436 mmol). The reaction mixture was stirred for 18 h at RT. The CH₃OH was

evaporated and the residue was dissolved in CH₃CN (10 mL). 38 % Formaldehyde (8 mL) was added to the solution, followed by NaCNBH₃ (41 mg, 0.633 mmol). The reaction was stirred for 20 min at RT and the pH was adjusted to ~6 using glacial acetic acid. The reaction mixture was stirred for 18 h at RT. The solvent was evaporated and

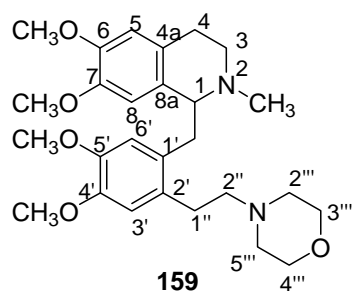
the residue was dissolved in DCM and washed with 1M aqueous NaOH, H₂O (2 x) and dried (K₂CO₃) to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc : NH₃ (3 : 7 : 0.1)) to give **169** (140 mg, 75 % overall) as a yellow oil.

R_f. 0.25 (CH₃OH : EtOAc (1 : 1)).

¹H NMR: δ 6.97 (s, 1H, H3'), 6.73 (dd, 1H, *J* 17.4, 10.8 Hz, H1''), 6.54 (s, 1H, H5), 6.39 (s, 1H, H6'), 5.72 (s, 1H, H8), 5.45 (dd, 1H, *J* 17.4, 1.2 Hz, H2''(*E*)), 5.11 (dd, 1H, *J* 10.8, 1.2 Hz, H2''(*Z*)), 3.86 (s, 3H, OCH₃-4'), 3.80 (s, 3H, OCH₃-6), 3.72 (s, 3H, OCH₃-7), 3.64 (m, 1H, H1), 3.56 (m, 1H, H3), 3.43 (s, 3H, OCH₃-5'), 3.27 (m, 1H, H3), 3.24 (dd, 1H, *J* 13.5, 4.8 Hz, H7'), 2.84 (m, 1H, H4), 2.76 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.61 (m, 1H, H4), 2.54 (s, 3H, NCH₃).

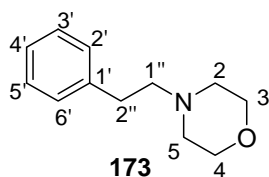
MS (ES⁺): *m/z* 384 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₂₃H₃₀NO₄, 384.2175 (MH⁺). Found 384.2180.

Attempted synthesis of (*RS*) 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4',5'-dimethoxy-2'-(2''-morpholinoethyl)phenyl)methyl-2-methylisoquinoline (159**).**



To a solution of **169** (139.5 mg, 0.364 mmol) in dry THF (4 mL) was added a solution of lithium morpholinamide, prepared by the addition of *n*BuLi to a solution of morpholine (79.3 mg, 0.91 mmol, 0.1 mL) in dry THF (1 mL) at 0 °C. The reaction mixture was kept at 0 °C for 18 h. The reaction mixture as quenched with CH₃OH and the solvent was evaporated. The residue was purified to retrieve only a quantitative amount of starting material **169** which was confirmed by TLC and ¹H NMR analysis.

***N*-(2''-Phenylethyl)morpholine (**173**).^{171,172}**



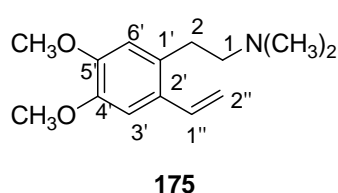
To a solution of styrene (52 mg, 0.50 mmol, 0.06 mL) in dry THF (4 mL) was added a solution of lithium morpholinamide, prepared by the addition of *n*BuLi to a solution of morpholine (218 mg, 2.50 mmol, 0.21 mL) in dry THF (1 mL) at 0 °C. The reaction mixture was kept at 0 °C for 18 h. The reaction mixture was quenched with CH₃OH and the solvent was evaporated. The reaction mixture was purified by column chromatograph (EtOAc : Pet. spirit (2 : 8)) to afford **173** (54 mg, 57 %) as an orange oil. The spectral data of **173** were identical to that reported in the literature.^{171,172}

R_f 0.46 (EtOAc : Pet. spirit (2 : 8)).

¹H NMR: δ 7.23 (m, 2H, H_{2'}, H_{6'}), 7.17 (m, 3H, H_{3'}, H_{4'}, H_{5'}), 3.70 (t, 4H, *J* 4.5 Hz, H₃, H₄), 2.81 (t, 4H, *J* 4.6 Hz, H_{1''}), 2.77 (t, 4H, *J* 4.6 Hz, H_{2''}), 2.47 (t, 4H, *J* 4.5 Hz, H₂, H₅).

¹³C NMR: δ 128.5 (CH-2', CH-6'), 128.2 (CH-3', CH-5'), 125.8 (CH-4'), 66.8 (CH₂-3, CH₂-4), 60.6 (CH₂-1''), 53.5 (CH₂-2, CH₂-5), 46.3 (CH₂-2'').

***N,N*-Dimethyl 2-(2'-ethenyl-4',5'-dimethoxyphenyl)ethylamine (**175**).**



To a solution of amine **118** (500 mg, 1.29 mmol), PdCl₂ (22.9 mg, 0.129 mmol), PPh₃ (67 mg, 0.258 mmol) in dry DMF (5 mL) was added tributylvinylstannane (492 mg, 1.55 mmol, 0.45 mL) under N₂. The reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was added DCM, washed with H₂O (4 x) and the solvent was dried (MgSO₄) and evaporated to give a crude oil. CH₃CN was added and the solution was washed with hexane to remove the stannane impurities. The CH₃CN was evaporated and the residue was dissolved in a mixture CH₃OH (5 mL) and H₂O (1 mL). Solid K₂CO₃ (547 mg, 3.93 mmol) was added and the reaction mixture was stirred for 3 h. The

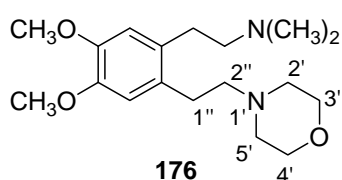
CH₃OH was evaporated and the residue was dissolved in CH₃CN (20 mL). 38 % Formaldehyde (15 mL) was added to the solution, followed by NaCNBH₃ (133 mg, 2.03 mmol). The reaction mixture was stirred for 20 min at RT before the pH was adjusted to ~ 6 using glacial acetic acid. The reaction mixture was then stirred at RT for 18 h. The CH₃CN was evaporated and the residue was dissolved in DCM, washed with 1M aqueous NaOH, H₂O (3 x) and brine. The DCM layer was dried (K₂CO₃) and evaporated to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc : NH₃ (1 : 9 : 0.1)) to afford **175** (138 mg, 46 % overall from **118**) as a yellow oil.

R_f. 0.50 (CH₃OH : EtOAc : NH₃ (1 : 4 : 0.1)).

¹H NMR: δ 6.98 (s, 1H, H3'), 6.88 (dd, 1H, *J* 17.1, 10.8 Hz, H1''), 6.62 (s, 1H, H6'), 5.52 (dd, 1H, *J* 17.1, 1.2, H2''(*E*)), 5.18 (dd, 1H, *J* 10.8, 1.2 Hz, H2''(*Z*)), 3.84 (s, 3H, OCH₃-4'), 3.80 (s, 3H, OCH₃-5'), 3.48 (t, 2H, *J* 6.6 Hz, H1), 2.86 (t, 2H, *J* 6.6 Hz, H2), 2.27 (s, 6H, NCH₃).

¹³C NMR: δ 148.7 (C4'), 147.4 (C5'), 133.7 (CH-1''), 130.2 (C2'), 128.5 (C1'), 133.4 (CH₂-2''), 112.7 (CH-3'), 108.3 (CH-6'), 60.9 (CH₂-1), 55.8 (OCH₃-4'), 45.2 (OCH₃-5'), 31.2 (CH₂-2).

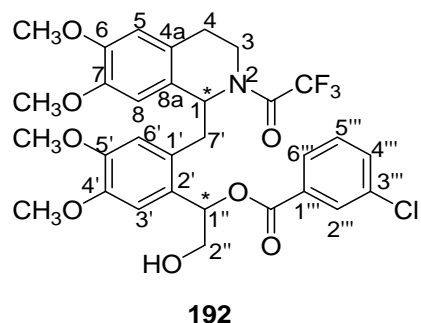
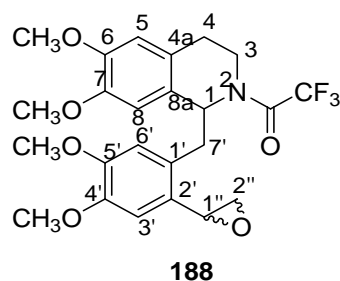
Attempted synthesis of *N,N*-Dimethyl 2'-(2''-morpholinoethyl)-2-(4',5'-dimethoxy phenyl)ethylamine (176).



To a solution of **175** (123 mg, 0.523 mmol) in dry THF (5 mL) was added a solution of lithium morpholinamide, prepared by the addition of *n*BuLi to a solution of morpholine (168 mg, 2.62 mmol, 0.24 mL) in dry THF (1 mL) at 0 °C. The reaction mixture was kept at 0 °C for 18 h. The reaction mixture was quenched with CH₃OH and

the solvent was evaporated. The residue was purified to retrieve only a quantitative amount of starting material **175** which was confirmed by TLC and ^1H NMR analysis.

Attempted synthesis of (1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1[4',5'-dimethoxy-2'-(oxiran-1''-yl)phenyl]methylisoquinoline (188**) and synthesis of (1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 1-[2'-(1''-(3'''-Chlorophenylcarbonyloxy)-2''-hydroxyethyl)-4',5'-dimethoxyphenyl]methyl-2-trifluoroethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**192**).**



To a solution of the 2'-vinyllaudanosine derivative **67** (283 mg, 0.608 mmol) in dry DCM (10 mL) at 0°C was added a solution of *m*CPBA (371 mg, 1.83 mmol) in dry DCM (10 mL). The reaction was brought to RT and stirred for 2 h. The reaction mixture was washed with saturated NaHCO_3 , H_2O (3 x) and brine. The solution mixture was dried (MgSO_4) and evaporated to give an oil which was purified (EtOAc : Pet. spirit (6 : 4)) to give not the desired epoxide **188** but the ring opened product **192** (143 mg, 48 %) as a green solid. Product **192** was a 70 : 30 mixture of diastereomers.

192.

R_f 0.26 (EtOAc : Pet. spirit (4 : 6)).

m.p. 78-80 $^\circ\text{C}$.

^1H NMR of the major diastereomer: δ 7.79 (d, 1H, J 2.1 Hz, H2'''), 7.89 (dd, 1H, J 7.8, 1.2 Hz, H6'''), 7.51 (dd, 1H, J 7.8, 2.1 Hz, H4'''), 7.34 (t, 1H, J 7.8 Hz, H5'''), 6.93 (s, 1H, H3'), 6.60 (s, 1H, H5), 6.48 (s, 1H, H8), 6.38 (s, 1H, H6'), 6.46 (t, 1H, J

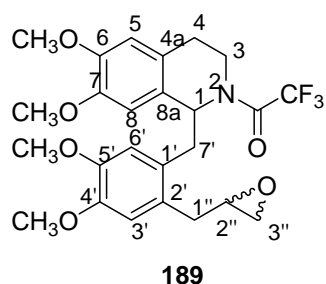
6.3 Hz, H1''), 5.80 (dd, 1H, *J* 7.2, 6.9 Hz, H1), 4.03 (dd, 1H, *J* 10.2, 6.3 Hz, H2''), 3.93 (dd, 1H, *J* 12.0, 5.7 Hz, H3), 3.82 (s, 6H, OCH₃-7, OCH₃-5'), 3.88 (m, 1H, H2''), 3.78 (m, 1H, H3), 3.73 (s, 3H, OCH₃-4'), 3.66 (s, 3H, OCH₃-6), 3.38 (dd, 1H, *J* 14.0, 6.9 Hz, H7'), 3.03 (dd, 1H, *J* 14.0, 7.2 Hz, H7'), 2.98 (m, 1H, H4), 2.88 (m, 1H, H4).

¹H NMR of the minor diastereomer (in part): δ 6.95 (s, 1H, H3'), 6.34 (s, 1H, H8), 6.46 (dd, 1H, *J* 7.5, 4.5 Hz, H1''), 5.95 (s, 1H, H6'), 5.42 (dd, 1H, *J* 9.3, 3.6 Hz, H1), 3.86 (s, 3H, OCH₃-7), 3.78 (s, 3H, OCH₃-5'), 3.68 (s, 3H, OCH₃-4'), 3.50 (s, 3H, OCH₃-6), 3.49 (m, 1H, H7'), 3.10 (m, 1H, H7').

¹³C NMR of the major diastereomer: δ 165.1 (ArCOOCH), 156.5 (q, *J* 37.5 Hz, COCF₃), 149.1 (C4'), 148.8 (C5'), 148.5 (C7), 147.8 (C6), 134.8 (C1'''), 133.4 (CH-4'''), 132.0 (C3'''), 130.0 (CH-2'''), 129.9 (CH-5'''), 128.6 (C1'), 128.5 (C2'), 128.0 (CH-6'''), 126.7 (C4a), 124.8 (C8a), 115.2 (q, *J* 279 Hz, COCF₃), 114.1 (CH-6'), 111.1 (CH-5), 111.0 (CH-8), 109.9 (CH-3'), 74.2 (CH-1'), 65.6 (CH₂-2''), 56.3 (OCH₃-6), 56.2 (OCH₃-4'), 56.1 (OCH₃-5', OCH₃-7), 55.8 (CH-1), 40.8 (CH₂-3), 39.6 (CH₂-7'), 28.9 (CH₂-4).

MS (ES⁺): *m/z* 660 (M+Na⁺, 50 %). **HRMS (ES⁺)** calcd for C₃₁H₃₁NO₈F₃NaCl, 660.1588 (M+Na⁺). Found 660.1620.

(1*RS*, 2'')*RS*) and (1*RS*, 2'')*SR*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1[4',5'-dimethoxy-2'-(oxiran-2''-yl-methyl)phenyl]methylisoquinoline (189).



To a solution of the 2'-allyllaundanosine derivative **68** (112 mg, 0.213 mmol) in dry DCM (3 mL) at 0 °C was added a solution of *m*CPBA (87 mg, 0.426 mmol) in dry DCM (3 mL). The reaction was brought to RT and stirred for 18 h.

The reaction mixture was washed subsequently with sat. NaHCO₃, H₂O, brine and dried (MgSO₄) and evaporated to give an oil. The oil was purified (EtOAc : Pet. spirit (6 : 4))

to give the epoxide **189** (30 mg, 28 %) as a yellow oil. The derivative **68** (33 mg, 29 %) was also recovered. Epoxide **189** was obtained as a 55 : 45 mixture of diastereomers.

R_f 0.33 (EtOAc : Pet. spirit (6 : 4)).

¹H NMR of the major diastereomer: δ 6.72 (s, 1H, H3'), 6.58 (s, 1H, H5), 6.51 (s, 1H, H6'), 6.01 (s, 1H, H8), 5.45 (t, 1H, *J* 7.5 Hz, H1), 3.91 (dt, 1H, *J* 13.5, 4.8 Hz, H3), 3.83 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.71 (s, 3H, OCH₃-4'), 3.70 (m, 1H, H3), 3.60 (m, 1H, H2''), 3.52 (s, 3H, OCH₃-6), 2.99 (m, 2H, H7'), 2.89 (m, 1H, H4), 2.82 (m, 1H, H4), 2.78 (m, 1H, H1''), 2.72 (m, 1H, H3''), 2.57 (t, 1H, *J* 4.7 Hz, H1''), 2.47 (dd, 1H, *J* 4.7, 2.1 Hz, H3'').

¹H NMR of the minor diastereomer (in part): δ 6.48 (s, 1H, H6'), 5.97 (s, 1H, H8), 3.72 (s, 3H, OCH₃-4'), 3.53 (s, 3H, OCH₃-6), 3.10 (m, 2H, H7'), 2.61 (m, 1H, H1''), 2.42 (dd, 1H, *J* 4.8, 2.1 Hz, H3'').

¹³C NMR of the major diastereomer: (signals for COCF_3 and COCF_3 were not observed), δ 148.2 (C5', C7), 148.0 (C4'), 147.9 (C6'), 128.7 (C1'), 127.6 (C2'), 125.2 (C4a), 124.9 (C8a), 114.1 (CH-6'), 113.2 (CH-3'), 110.9 (CH-5, CH-8), 55.8 (4 x OCH₃, CH-1), 52.3 (CH-2''), 46.6 (CH₂-3''), 40.7 (CH₂-3), 38.1 (CH₂-7'), 34.4 (CH₂-1''), 28.4 (CH₂-4).

¹³C NMR of the minor diastereomer (in part): δ 128.5 (C1'), 125.2 (C4a), 124.9 (C8a), 114.1 (CH-6'), 112.9 (CH-3'), 110.8 (CH-5, CH-8), 46.8 (CH₂-3''), 34.6 (CH₂-1'').

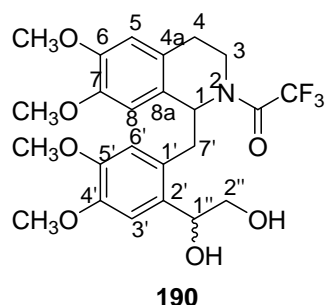
MS (EI⁺): *m/z* 495 (M⁺, 20 %). **HRMS (ES⁺):** calcd for C₂₅H₂₇NO₅F₃, 478.1841 (M-H₂O⁺). Found 478.1845.

General method for dihydroxylation.

To a solution of the olefin in acetone was added potassium osmate dihydrate (K₂Os₄.2H₂O), followed by *N*-methylmorpholine *N*-oxide (NMO). H₂O was

subsequently added and the mixture was stirred at RT for 18 h. Sodium sulfite (NaSO_3) was added and stirred for 30 min before the acetone was evaporated. H_2O was added and the mixture was extracted with DCM. The combined DCM extracts were washed with brine, dried (MgSO_4), and evaporated to give an oil. The oil was purified by column chromatography (EtOAc) to afford the desired product.

(1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2'-(1'',2''-dihydroxyethyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (190).



A solution of the olefin **67** (135 mg, 0.290 mmol) in acetone (3 mL) was treated as described above in the general dihydroxylation reaction procedure using $\text{K}_2\text{Os}_4 \cdot 2\text{H}_2\text{O}$ (6 mg, 0.015 mmol), NMO (72 mg, 0.609 mmol) and H_2O (1 mL). Purification by column chromatography gave the diol

190 (119 mg, 82 %) as light yellow oil. The diol **190** was obtained as a 80 : 20 mixture of diastereomers.

R_f 0.39 (EtOAc).

¹H NMR of the major diastereomer: δ 6.99 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.31 (s, 1H, H6'), 6.08 (s, 1H, H8), 5.48 (dd, 1H, J 8.2, 5.8 Hz, H1), 5.08 (dd, 1H, J 8.1, 4.2 Hz, H1''), 3.94 (dt, 1H, J 13.5, 3.6 Hz, H3), 3.85 (s, 3H, OCH_3 -7), 3.84 (s, 3H, OCH_3 -5'), 3.78 (dt, 1H, J 12.6, 4.8 Hz, H3), 3.69 (s, 3H, OCH_3 -4'), 3.62 (m, 2H, H2''), 3.57 (s, 3H, OCH_3 -6), 3.17 (dd, 1H, J 13.5, 5.8 Hz, H7'), 3.03 (dd, 1H, J 13.5, 8.2 Hz, H7'), 2.95 (m, 1H, H4), 2.80 (m, 1H, H4).

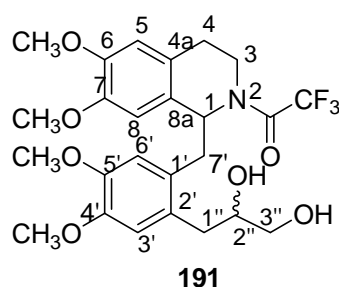
¹H NMR of the minor diastereomer (in part): δ 6.95 (s, 1H, H3'), 6.49 (s, 1H, H5), 6.23 (s, 1H, H6'), 5.59 (t, 1H, J 7.5 Hz, H1), 4.94 (dd, 1H, J 8.1, 4.2 Hz, H1''), 3.77 (s, 3H, OCH_3 -7), 3.73 (m, 2H, H2''), 3.68 (s, 3H, OCH_3 -4'), 3.26 (m, 1H, H7').

¹³C NMR of the major diastereomer: δ 156.3 (q, J 36.1 Hz, COCF_3), 148.1 (C5', C7), 147.6 (C4'), 147.0 (C6), 131.8 (C1'), 126.2 (C2'), 125.9 (C4a), 124.6 (C8a), 118.2 (q, J 285.1, COCF_3), 114.2 (CH-6'), 111.4 (CH-8), 110.8 (CH-5), 109.6 (CH-3'), 70.7 (CH-1''), 67.3 (CH₂-2''), 55.7 (4 x OCH₃), 55.5 (CH-1), 40.6 (CH₂-3), 38.0 (CH₂-7'), 28.2 (CH₂-4).

¹³C NMR of the minor diastereomer (in part): δ 132.1 (C1'), 126.1 (C2'), 124.4 (C8a), 114.4 (CH-6'), 110.2 (CH-5'), 109.5 (CH-3'), 67.5 (CH₂-2''), 28.3 (CH₂-4).

MS (EI⁺): m/z 499 (M⁺, 20 %). **HRMS (ES⁺):** calcd for C₂₄H₂₈NO₇F₃Na, 522.1716 (M+Na⁺). Found 522.1724.

(1*RS*, 2''*RS*) and (1*S*, 2''*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2'-(2'',3'''-dihydroxypropyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (191).



A solution of the olefin **68** (120 mg, 0.255 mmol) in acetone (7 mL) was treated as described above in the general dihydroxylation reaction procedure using K₂Os₄.2H₂O (6 mg, 0.015 mmol), followed by NMO (63 mg, 0.537 mmol) and H₂O (1 mL) except the reaction mixture stirred for 5 h at RT. The crude oil was purified by column chromatography (EtOAc) to give the diol **191** (130 mg, 99 %) as clear oil. The diol **191** was obtained as a 60 : 40 mixture of diastereomers. **R_f** 0.38 (EtOAc).

¹H NMR of the major diastereomer: δ 6.71 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.39 (s, 1H, H6'), 6.27 (s, 1H, H8), 5.47 (dd, 1H, J 5.4, 3.3 Hz, H1), 4.02 (dt, 1H, J 8.1, 3.0 Hz, H3), 3.94 (m, 1H, H2''), 3.84 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.79 (m, 1H, H3''), 3.72 (m, 1H, H3), 13.69 (s, 3H, OCH₃-4'), 3.58 (m, 1H, H3''), 3.52 (s, 3H, OCH₃-6), 3.13 (dd, 1H, J 8.1, 3.3 Hz, H7'), 3.02 (dd, 1H, J 8.1, 5.4 Hz, H7'), 2.92 (m, 1H, H1''), 2.87 (m, 1H, H4), 2.87 (m, 1H, H4), 2.73 (m, 1H, H1'').

¹H NMR of the minor diastereomer (in part): δ 6.70 (s, 1H, H3'), 6.44 (s, 1H, H6'), 6.01 (s, 1H, H8), 5.59 (dd, 1H, *J* 5.4, 3.3 Hz, H1), 3.86 (m, 1H, H2''), 3.74 (s, 3H, OCH₃-4'), 3.66 (s, 3H, OCH₃-6), 3.15 (dd, 1H, *J* 8.1, 3.3 Hz, H7'), 3.03 (dd, 1H, *J* 8.1, 5.4 Hz, H7'), 2.95 (m, 1H, H1''), 2.73 (m, 1H, H1'').

¹³C NMR of the major diastereomer: (signals for COCF_3 and COCF_3 were not observed), δ 148.3 (C7), 148.2 (C5'), 147.5 (C6), 147.3 (C4'), 129.3 (C1'), 127.7 (C2'), 126.2 (C4a), 124.6 (C8a), 114.5 (CH-6'), 113.3 (CH-3'), 111.0 (CH-8, CH-5), 73.1 (CH-2''), 66.2 (CH₂-3''), 55.0 (4 x OCH₃), 55.7 (CH-1), 40.8 (CH₂-3), 38.6 (CH₂-7'), 35.7 (CH₂-1''), 28.5 (CH₂-4).

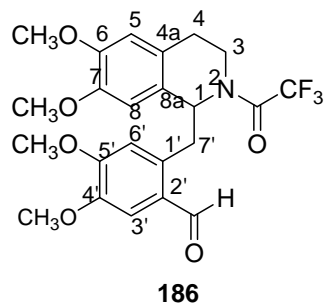
¹³C NMR of the minor diastereomer (in part): δ 148.3 (C7), 147.3 (C6), 148.0 (C5'), 147.1 (C4'), 129.0 (C1'), 127.9 (C2'), 126.6 (C4a), 124.8 (C8a), 114.0 (CH-6'), 113.1 (CH-3'), 110.9 (CH-5), 110.4 (CH-8), 72.9 (CH-2''), 66.0 (CH₂-3''), 55.6 (CH-1), 40.4 (CH₂-3), 38.5 (CH₂-7'), 36.0 (CH₂-1''), 28.6 (CH₂-4).

MS (EI⁺): *m/z* 513 (M⁺, 20 %). **HRMS (ES⁺):** calcd for C₂₅H₃₁NO₇F₃, 514.2053 (MH⁺). Found 514.2064.

General method for oxidative cleavage of diols.

To a warm solution of NaIO₄ in H₂O was added silica gel with vigorous stirring. The powder was cooled and a solution of the diol in DCM was added. The mixture was stirred vigorously for 1 h at RT. The DCM layer was collected by pipetting and the silica was washed several times with DCM. The combined DCM washings were evaporated to give pure aldehydes without the need for further purification.

(*RS*) 1-(2'-Formyl-4',5'-dimethoxyphenyl)methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (186).



Silica gel coated with NaIO₄ was prepared as above using NaIO₄ (827 mg, 3.89 mmol), H₂O (2 mL) and silica gel (1.7 g). To this powder was added a solution of the vicinal diol **190** (167 mg, 0.335 mmol) in DCM (3 mL) which was treated as described above in the general oxidative cleavage reaction procedure to afford the pure aldehyde **186** (144 mg, 92 %) as a white solid.

R_f. 0.80 (EtOAc).

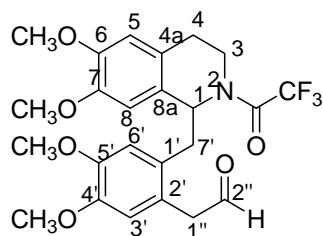
m.p. 154-158 °C.

¹H NMR: δ 9.90 (bs, 1H, CHO), 7.28 (s, 1H, H3'), 6.74 (s, 1H, H5), 6.59 (s, 2H, H6', H8), 5.64 (dd, 1H, *J* 8.7, 5.7 Hz, H1), 3.92 (s, 3H, OCH₃-7), 3.88 (s, 3H, OCH₃-5'), 3.84 (s, 3H, OCH₃-4'), 3.79 (s, 3H, OCH₃-6), 3.68 (m, 3H, H3, H7'), 3.15 (dd, 1H, *J* 13.5, 8.1 Hz, H7'), 2.91 (m, 1H, H4), 2.73 (m, 1H, H4).

¹³C NMR: (signals for COCF₃ and COCF₃ were not observed), δ 190.8 (CHO), 153.0 (C4'), 148.3 (C6), 148.0 (C5'), 147.8 (C7), 134.1 (C2'), 127.6 (C4a), 126.5 (C1'), 124.7 (C8a), 114.6 (CH-6'), 113.9 (CH-3'), 110.9 (CH-8), 110.3 (CH-5), 56.0 (OCH₃-7, OCH₃-5'), 55.9 (OCH₃-4', OCH₃-6), 55.1 (CH-1), 40.3 (CH₂-3), 37.7 (CH₂-7'), 28.6 (CH₂-4).

MS (EI⁺): *m/z* 467 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₃H₂₅NO₆F₃, 468.1634 (MH⁺). Found 468.1642.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-oxoethyl)phenyl]methylisoquinoline (187).



187

Silica gel coated with NaIO₄ was prepared as above using NaIO₄ (676 mg, 3.18 mmol), H₂O (2 mL) and silica gel (1.7 g). To this solution was added a solution of diol **191** (134 mg, 0.265 mmol) in DCM (3 ml) which was reacted as described above in the general oxidative cleavage reaction procedure to give the pure aldehyde **187** (127 mg, 99 %) as a clear oil. Compound **187** was a 95 : 5 mixture of rotamers.

R_f 0.88 (EtOAc).

¹H NMR of the major rotamer: δ 9.61 (t, 1H, *J* 2.1 Hz, CHO), 6.60 (s, 2H, H3', H5), 6.50 (s, 1H, H6'), 6.02 (s, 1H, H8), 5.33 (dd, 1H, *J* 8.7, 5.4 Hz, H1), 3.90 (dt, 1H, *J* 12.6, 4.5 Hz, H3), 3.86 (s, 6H, OCH₃-7, OCH₃-5'), 3.74 (s, 3H, OCH₃-4'), 3.67 (dd, 1H, *J* 8.4, 3.6 Hz, H3), 3.55 (s, 3H, OCH₃-6), 3.54 (m, 2H, H1''), 3.07 (dd, 1H, *J* 13.5, 5.4 Hz, H7'), 2.91 (dd, 1H, *J* 13.5, 8.9 Hz, H7'), 2.87 (m, 1H, H4), 2.81 (m, 1H, H4).

¹H NMR of the minor rotamer (in part): δ 9.43 (bs, CHO), 5.87 (s, 1H, H8).

¹³C NMR of the major rotamer: δ 199.6 (CHO), 156.1 (q, *J* 35.8 Hz, COCF₃), 148.3 (C4'), 148.2 (C6), 148.2 (C5'), 147.2 (C7), 128.4 (C2'), 125.9 (C4a), 124.9 (C1'), 123.4 (C8a), 116.5 (q, *J* 286.4 Hz, COCF₃), 114.5 (CH-6'), 113.9 (CH-3'), 110.9 (CH-8), 110.8 (CH-5), 56.0 (OCH₃-7), 55.9 (OCH₃-5', OCH₃-4'), 55.7 (OCH₃-6), 55.6 (CH-1), 47.8 (CH₂-1''), 40.8 (CH₂-3), 38.5 (CH₂-7'), 28.6 (CH₂-4).

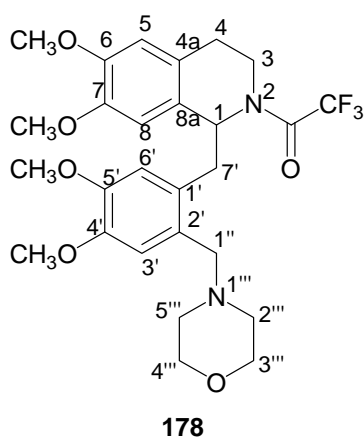
¹³C NMR of the minor rotamer (in part): δ 199.0 (CHO), 40.9 (CH₂-3), 55.4 (CH-1), 47.9 (CH₂-1'').

MS (EI⁺): *m/z* 481 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₄H₂₇NO₆F₃, 482.1790 (MH⁺). Found 482.1812.

General method of reductive amination.

To a solution of the aldehyde and the amine in CH₃CN was added NaCNBH₃. The reaction was stirred at RT for 20 min before glacial acetic acid was added to adjust the pH to ~ 6. The resulting solution was stirred for 18 h at RT. The CH₃CN was evaporated and the residue was dissolved in DCM. The solution was washed subsequently with H₂O (3 x), sat. Na₂CO₃, brine and dried (MgSO₄) to give an oil. The oil was purified by column chromatography to afford the pure product.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-Dimethoxy-2'-(morpholino)methylphenyl]methylisoquinoline (178).



A mixture of the aldehyde **186** (58 mg, 0.125 mmol), morpholine (0.10 mL), CH₃CN (15 mL) and NaCNBH₃ (10 mg, 0.162 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (EtOAc) to afford **178** (40 mg, 60 %) as a clear oil. Compound **178** was a 95 : 5 mixture of

rotamers.

R_f 0.38 (EtOAc).

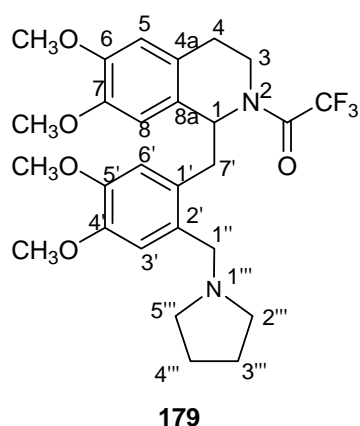
¹H NMR of the major rotamer: δ 6.73 (s, 1H, H3'), 6.59 (s, 1H, H5), 6.47 (s, 1H, H6'), 6.24 (s, 1H, H8), 5.78 (t, 1H, *J* 7.2 Hz, H1), 4.00 (m, 1H, H3), 3.83 (s, 6H, OCH₃-7, OCH₃-5'), 3.75 (dt, 1H, *J* 7.8, 6.7 Hz, H3), 3.74 (s, 3H, OCH₃-4'), 3.65 (t, 4H, *J* 4.8 Hz, H3''', H4'''), 3.61 (s, 3H, OCH₃-6), 3.41 (d, 1H, *J* 12.9 Hz, H1''), 3.22 (dd, 1H, *J* 13.5, 7.2 Hz, H7'), 3.19 (d, 1H, *J* 12.9 Hz, H1''), 3.08 (dd, 1H, *J* 13.5, 7.2 Hz, H7'), 2.87 (m, 1H, H4), 2.77 (m, 1H, H4), 2.41 (m, 4H, H2''', H5''').

¹H NMR of the minor rotamer (in part): δ 6.71 (s, 1H, H3'), 6.50 (s, 1H, H6'), 5.96 (s, 1H, H8).

¹³C NMR of the major rotamer: (signals for COCF_3 and COCF_3 were not observed), δ 148.2 (C4'), 147.9 (C6), 147.4 (C5', C7), 128.9 (C2'), 128.7 (C8a), 127.2 (C1'), 124.8 (C4a), 114.2 (CH-3'), 114.1 (CH-6'), 111.0 (CH-5), 110.4 (CH-8), 67.0 (CH₂-3''', CH₂-4'''), 61.4 (CH₂-2''', CH₂-5'''), 55.9 (OCH₃-7, OCH₃-5'), 55.8 (OCH₃-4'), 55.7 (OCH₃-6), 55.0 (CH-1), 53.7 (CH₂-1''), 40.1 (CH₂-3), 37.9 (CH₂-7'), 28.7 (CH₂-4).

MS (EI⁺): *m/z* 538 (M⁺, 30 %). **HRMS (ES⁺):** calcd for C₂₇H₃₄N₂O₆F₃, 539.2369 (MH⁺). Found 539.2363.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(pyrrolidinyl)methylphenyl]methylisoquinoline (179).



A mixture of the aldehyde **186** (91 mg, 0.194 mmol), *N*-pyrrolidine (0.10 mL), CH₃CN (3 mL) and NaCNBH₃ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (4 : 6)) to afford **179** (77 mg, 74 %) as a

light yellow oil. Compound **179** was a 95 : 5 mixture of rotamers.

R_f 0.20 (CH₃OH : EtOAc (4 : 6)).

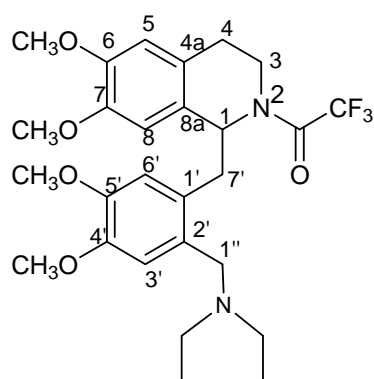
¹H NMR of the major rotamer: δ 6.97 (s, 1H, H3'), 6.59 (s, 1H, H5), 6.34 (s, 1H, H6'), 6.04 (s, 1H, H8), 5.44 (dd, 1H, *J* 8.1, 6.1 Hz, H1), 3.93 (m, 1H, H3), 3.87 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.80 (m, 1H, H3), 3.69 (s, 3H, OCH₃-4'), 3.56 (s, 3H, OCH₃-6), 3.42 (d, 1H, *J* 6.6 Hz, H1''), 3.38 (d, 1H, *J* 6.6 Hz, H1''), 3.16 (dd, 1H, 13.5, *J* 6.1 Hz, H7'), 3.08 (dd, 1H, *J* 13.5, 8.1 Hz, H7'), 2.90 (m, 1H, H4), 2.79 (m, 5H, H4, H2''', H5'''), 1.88 (m, 4H, H3''', H4''').

¹H NMR minor rotamer (in part): δ 6.79 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.44 (s, 1H, H6'), 6.04 (s, 1H, H8).

¹³C NMR of the major rotamer: (signals for COCF_3 and COCF_3 were not observed), δ 148.3 (C4', C6), 148.1 (C5'), 147.2 (C7), 128.3 (C2'), 126.9 (C1'), 126.2 (C4a), 125.1 (C8a), 114.4 (CH-6'), 113.5 (CH-3'), 111.0 (CH-5), 110.7 (CH-8), 56.5 (CH₂-1''), 56.2 (OCH₃-7), 56.0 (OCH₃-5'), 55.8 (OCH₃-4', OCH₃-6), 55.7 (CH-1), 53.6 (CH₂-2'''), 40.8 (CH₂-3), 38.4 (CH₂-7'), 28.5 (CH₂-4), 23.3 (CH₂-3''', CH₂-4''').

MS (EI⁺): *m/z* 522 (M⁺, 20 %). **HRMS (ES⁺):** calcd for C₂₇H₃₄N₂O₅F₃, 523.2420 (MH⁺). Found 523.2435.

(*R,S*) 1-[2'-(Diethylamino)methyl-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-dihydro-6,7-dimethoxyisoquinoline (180).



180

A mixture of aldehyde **186** (112 mg, 0.239 mmol), diethylamine (0.2 mL), CH₃CN (3 mL) and NaCNBH₃ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (4 : 6)) to afford **180** (83 mg, 75 %) as a light yellow oil. Compound **180** was

a 95 : 5 mixture of rotamers.

R_f 0.33 (CH₃OH : EtOAc (4 : 6)).

¹H NMR of the major rotamer: δ 6.85 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.56 (s, 1H, H6'), 6.12 (s, 1H, H8), 5.55 (t, 1H, *J* 7.8, 6.0 Hz, H1), 3.92 (dt, 1H, *J* 7.8, 3.3 Hz, H3), 3.82 (s, 6H, OCH₃-7, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.69 (m, 1H, H3), 3.57 (s, 3H, OCH₃-6), 3.32 (dd, 1H, *J* 13.5, 7.8 Hz, H7'), 3.28 (d, 1H, *J* 13.5 Hz, H1''), 3.16 (d, 1H,

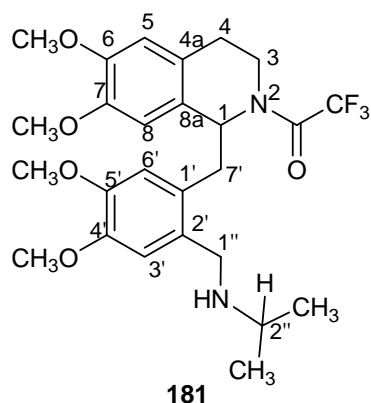
J 13.5 Hz, H1''), 3.04 (dd, 1H, J 13.5, 6.0 Hz, H7'), 2.92 (m, 1H, H4), 2.73 (m, 1H, H4), 2.43 (q, 4H, J 6.9 Hz, 2 x NCH₂CH₃), 0.93 (t, 6H, J 6.9 Hz, 2 x NCH₂CH₃).

¹H NMR of the minor rotamer (in part): δ 6.79 (s, 1H, H3'), 5.85 (s, 1H, H8), 3.79 (s, 6H, OCH₃-7, OCH₃-5'), 3.48 (s, 3H, OCH₃-6).

¹³C NMR of the major rotamer: (signals for C=O and C=O were not observed), δ 148.4 (C4'), 147.7 (C6), 147.7 (C5'), 147.5 (C7), 128.5 (C2', C8a), 127.2 (C1'), 125.0 (C4a), 114.0 (CH-3'), 113.6 (CH-6'), 111.2 (CH-5), 110.7 (CH-8), 55.2 (OCH₃-7), 56.1 (OCH₃-5'), 55.1 (OCH₃-4'), 55.9 (OCH₃-6), 55.7 (CH-1), 55.5 (CH₂-1''), 46.5 (2 x NCH₂CH₃), 40.6 (CH₂-3), 37.7 (CH₂-7'), 28.8 (CH₂-4), 11.5 (2 x NCH₂CH₃).

MS (EI⁺): m/z 524 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₇H₃₅N₂O₅F₃, 525.2576 (MH⁺). Found 525.2563.

(*R,S*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(isopropylamino)methylphenyl]methylisoquinoline (181).



A mixture of aldehyde **186** (112 mg, 0.239 mmol), isopropylamine (0.2 mL), CH₃CN (3 mL) and NaCNBH₃ (16 mg, 0.252 mmol) was reacted as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (4 : 6)) to afford **181**

(67 mg, 64 %) as a light yellow oil. Compound **181** was a 95 : 5 mixture of rotamers.

R_f 0.17 (CH₃OH : EtOAc (4 : 6)).

¹H NMR of the major rotamer: δ 6.80 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.54 (s, 1H, H6'), 6.12 (s, 1H, H8), 5.58 (t, 1H, J 8.1, 6.6 Hz, H1), 3.93 (m, 1H, H3), 3.83 (s, 3H, OCH₃-7), 3.81 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.67 (m, 1H, H3), 3.56 (s, 3H, OCH₃-6), 3.48 (d, 1H, J 12.6 Hz, H1''), 3.43 (d, 1H, J 12.6 Hz, H1''), 3.20 (dd, 1H, J

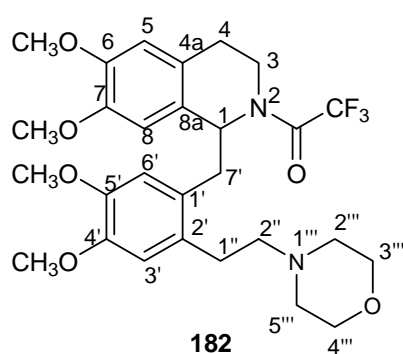
13.8, 8.1 Hz, H7'), 3.05 (dd, 1H, *J* 13.8, 6.6 Hz, H7'), 2.91 (m, 1H, H4), 2.80 (hept, 1H, *J* 2.4 Hz, H2''), 2.91 (dt, 1H, *J* 12.6, 6.0 Hz, H4), 1.04 (d, 3H, *J* 2.4 Hz, CH(CH₃)CH₃), 1.02 (d, 3H, *J* 2.4 Hz, CH(CH₃)CH₃).

¹H NMR of the minor rotamer (in part): δ 6.76 (s, 1H, H3'), 5.92 (s, 1H, H8), 3.77 (s, 3H, OCH₃-5'), 3.49 (s, 3H, OCH₃-6).

¹³C NMR of the major rotamer: (signals for C=O and C=O were not observed), δ 148.4 (C4'), 148.0 (C6), 147.9 (C5'), 147.5 (C7), 131.9 (C2'), 127.9 (C8a), 126.9 (C1'), 125.1 (C4a), 114.1 (CH-3'), 113.1 (CH-6'), 111.2 (CH-5), 110.7 (CH-8), 56.0 (OCH₃-7), 56.1 (OCH₃-5'), 55.1 (OCH₃-4'), 55.9 (OCH₃-6), 55.8 (CH-1), 49.3 (CH₂-1''), 49.2 (CH-2''), 40.7 (CH₂-3), 38.0 (CH₂-7'), 28.8 (CH₂-4), 23.1 (CH(CH₃)CH₃), 22.1 (CH(CH₃)CH₃).

MS (EI⁺): *m/z* 510 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₆H₃₄N₂O₅F₃, 511.2421 (MH⁺). Found 511.2395.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(morpholino)ethyl)phenyl]methylisoquinoline (182).



A mixture of aldehyde **187** (80 mg, 0.166 mmol), morpholine (0.1 mL), CH₃CN (6 mL), NaCNBH₃ (16 mg, 0.252 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (4 : 6)) to afford **182** (59 mg, 64 %) as a clear oil.

Compound **182** was a 95 : 5 mixture of rotamers.

R_f 0.25 (CH₃OH : EtOAc (4 : 6)).

¹H NMR of the major rotamer: δ 6.66 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.52 (s, 1H, H6'), 6.01 (s, 1H, H8), 5.48 (t, 1H, *J* 6.9 Hz, H1), 3.92 (dt, 1H, *J* 13.5, 5.1 Hz, H3), 3.81

(s, 6H, OCH₃-7, OCH₃-5'), 3.72 (s, 3H, OCH₃-4'), 3.67 (t, 4H, *J* 4.7 Hz, H3''', H4'''), 3.65 (m, 1H, H3), 3.53 (s, 3H, OCH₃-6), 3.05 (d, 2H, *J* 6.9 Hz, H7'), 2.90 (m, 1H, H4), 2.74 (m, 1H, H4), 2.60 (m, 1H, H2''), 2.49 (m, 1H, H2''), 2.40 (t, 4H, *J* 4.7 Hz, H2''', H5'''), 2.38 (m, 1H, H1''), 2.29 (m, 1H, H1'').

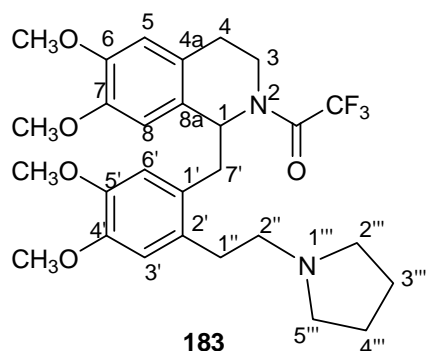
¹H NMR of the minor rotamer (in part): δ 6.64 (s, 1H, H3'), 6.56 (s, 1H, H5), 5.75 (s, 1H, H8), 3.81 (s, 6H, OCH₃-7, OCH₃-5'), 3.77 (s, 3H, OCH₃-4'), 3.45 (s, 3H, OCH₃-6).

¹³C NMR of the major rotamer: δ 156.1 (q, *J* 35.3 Hz, COCF₃), 148.5 (C4'), 148.1 (C6), 147.5 (C5'), 147.4 (C7), 131.5 (C1'), 127.2 (C2'), 126.6 (C4a), 125.2 (C8a), 116.7 (q, *J* 286.5 Hz, COCF₃), 114.2 (CH-6'), 113.1 (CH-3'), 111.2 (CH-5), 110.9 (CH-8), 67.2 (CH₂-3''', CH₂-4'''), 60.5 (CH₂-2''), 55.8 (4 x OCH₃), 55.7 (CH-1), 53.9 (CH₂-2''', CH₂-5'''), 40.9 (CH₂-3), 38.2 (CH₂-7'), 29.7 (CH₂-1''), 28.7 (CH₂-4).

¹³C NMR of the minor rotamer (in part): δ 147.9 (C5'), 147.1 (C7), 131.8 (C1'), 127.0 (C2'), 126.0 (C4a), 111.2 (CH-5), 110.4 (CH-8), 65.9 (CH₂-3''', CH₂-4'''), 60.1 (CH₂-2''), 53.8 (CH₂-2''', CH₂-5'''), 40.9 (CH₂-3), 39.2 (CH₂-7'), 31.8 (CH₂-1''), 27.4 (CH₂-4).

MS (ES⁺): *m/z* 552.81 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₈H₃₆N₂O₆F₃, 553.2525 (MH⁺). Found 553.2486.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-[4',5'-Dimethoxy-2'-(2''-(*N*-pyrrolidinyl)ethyl)phenyl]methyloisoquinoline (183).



A mixture of aldehyde **187** (71 mg, 0.149 mmol), pyrrolidine (0.2 mL), CH₃CN (3 mL) and NaCNBH₃ (12 mg, 0.194 mmol) was treated as described above in the general reductive amination reaction procedure to give an oil. The oil was purified by

column chromatography (CH₃OH : EtOAc (4 : 6)) to afford **183** (61 mg, 74 %) as a light yellow oil. Compound **183** was a 95 : 5 mixture of rotamers.

R_f 0.20 (CH₃OH : EtOAc (4 : 6)).

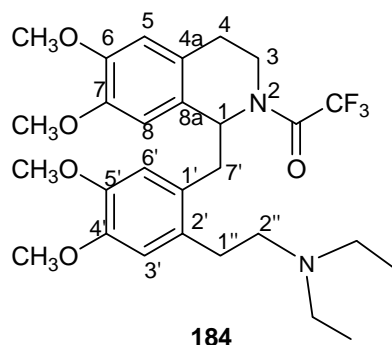
¹H NMR of the major rotamer: δ 6.64 (s, 1H, H3'), 6.60 (s, 1H, H5), 6.56 (s, 1H, H6'), 6.02 (s, 1H, H8), 5.50 (dd, 1H, *J* 8.4, 5.7 Hz, H1), 3.93 (dt, 1H, *J* 13.8, 5.4 Hz, H3), 3.89 (s, 6H, OCH₃-7, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.67 (m, 1H, H3), 3.53 (s, 3H, OCH₃-6), 3.05 (dd, 1H, *J* 13.5, 8.4 Hz, H7'), 3.02 (dd, 1H, *J* 13.5, 5.7 Hz, H7''), 2.91 (m, 1H, H4), 2.74 (m, 1H, H4), 2.50 (m, 4H, H2''', H5'''), 2.52 (m, 2H, H1''), 2.35 (m, 2H, H2''), 1.76 (m, 4H, H3''', H4''').

¹H NMR of the minor rotamer (in part): 6.61 (s, 1H, H3'), 5.75 (s, 1H, H8), 3.39 (s, 3H, OCH₃-6).

¹³C NMR of the major rotamer: (signals for C=O and C=O were not observed), δ 148.2 (C4'), 148.8 (C6), 147.2 (C5', C7), 131.44 (C2'), 127.0 (C4a), 126.3 (C1'), 124.8 (C8a), 113.6 (CH-5), 111.7 (CH-3'), 110.9 (CH-6'), 110.4 (CH-8), 57.7 (CH₂-2''), 55.9 (OCH₃-7, OCH₃-5'), 55.6 (OCH₃-4', OCH₃-6, CH-1), 54.0 (CH₂-2''', CH₂-5'''), 40.5 (CH₂-3), 37.8 (CH₂-7'), 31.9 (CH₂-1''), 28.5 (CH₂-4), 23.4 (CH₂-3''', CH₂-4''').

MS (EI⁺): *m/z* 536 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₈H₃₆N₂O₅F₃, 537.2576 (MH⁺). Found 537.2581.

(*RS*) 1-[2'-(2''-(Diethylamino)ethyl)-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (184**).**



A mixture of aldehyde **187** (132 mg, 0.274 mmol), diethylamine (0.2 mL), CH₃CN (3 mL) and NaCNBH₃ (22 mg, 0.356 mmol) was treated as described above in the general reductive amination reaction procedure to

give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (4 : 6)) to afford **184** (100 mg, 68 %) as a light yellow oil. Compound **184** was a 95 : 5 mixture of rotamers.

R_f. 0.21 (CH₃OH : EtOAc (4 : 6)).

¹H NMR of the major rotamer: δ 6.63 (s, 1H, H3'), 6.57 (s, 2H, H5, H6'), 6.03 (s, 1H, H8), 5.49 (dd, 1H, *J* 8.4, 6.0 Hz, H1), 3.93 (dt, 1H, *J* 13.5, 5.7 Hz, H3), 3.82 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-4'), 3.67 (m, 1H, H3), 3.54 (s, 3H, OCH₃-6), 3.10 (dd, 1H, *J* 13.5, 8.4 Hz, H7'), 3.03 (dd, 1H, *J* 13.5, 6.0 Hz, H7'), 2.89 (m, 1H, H4), 2.75 (m, 1H, H4), 2.55 (q, 4H, *J* 6.9 Hz, 2 x NCH₂CH₃), 2.50 (m, 4H, H1'', H2''), 1.01 (t, 6H, *J* 6.9 Hz, 2 x NCH₂CH₃).

¹H NMR of the minor rotamer (in part): δ 6.60 (s, 1H, H3'), 3.52 (s, 3H, OCH₃-6).

¹³C NMR of the major rotamer: δ 155.6 (q, *J* 36.2 Hz, COCF₃), 148.2 (C4'), 147.89 (C6), 147.2 (C5', C7), 131.5 (C2'), 127.0 (C4a), 126.3 (C1'), 124.9 (C8a), 116.0 (q, *J* 286.3 Hz, COCF₃), 113.8 (CH-5), 112.8 (CH-3'), 110.9 (CH-6'), 110.5 (CH-8), 55.9 (OCH₃-7, OCH₃-5', CH-1), 54.6 (OCH₃-4', OCH₃-6), 54.2 (CH₂-2''), 46.6 (2 x NCH₂CH₃), 40.7 (CH₂-3), 38.0 (CH₂-7'), 29.6 (CH₂-1''), 28.5 (CH₂-4), 11.5 (2 x NCH₂CH₃).

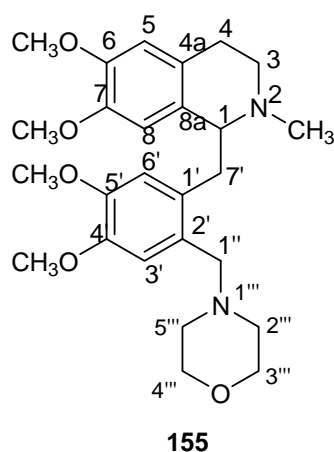
MS (EI⁺): *m/z* 538 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₈H₃₈N₂O₅F₃, 539.2733 (MH⁺). Found 539.2734.

General method for *N*-Trifluoroacetyl deprotection and reductive *N*-Methylation of 178-184.

The *N*-TFA protected amine was dissolved in a mixture of CH₃OH and H₂O. To this was added K₂CO₃ and the resulting solution was stirred at RT for 18 h. CH₃OH was removed and the residue was dissolved in CH₃CN. 38 % Formaldehyde was added followed by NaCNBH₃. Glacial acetic acid was added after 20 min of stirring to

adjusted the pH to ~ 6 . The reaction mixture was stirred at RT for 18 h. CH_3CN was evaporated and the residue was redissolved in DCM. The DCM layer was washed with sat. K_2CO_3 and dried (MgSO_4). Evaporation of the DCM extracts gave the crude product which was purified by column chromatography to afford the pure *N*-methylated analogues.

(*RS*) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(morpholino)methyl phenyl]methyl-2-methylisoquinoline (155).



The *N*-TFA protected amine **178** (40 mg, 0.074 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K_2CO_3 (50 mg, 0.370 mmol), CH_3OH (5 mL) and H_2O (1 mL), except it was stirred at 80°C for 3 h, then using 38 % formaldehyde (3mL), CH_3CN (3 mL) and NaCNBH_3 (6 mg, 0.096 mmol) to give an oil. The

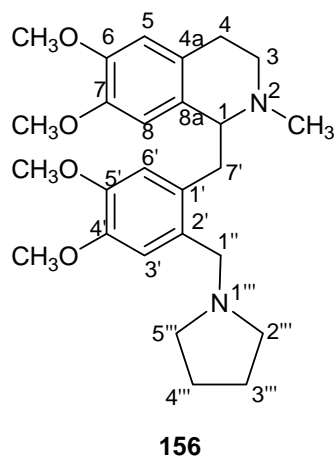
oil was purified by column chromatography ($\text{CH}_3\text{OH} : \text{EtOAc} : \text{NH}_3$ (6 : 4 : 0.1)) to afford **155** (25 mg, 73 %) as a clear oil.

R_f. 0.34 ($\text{CH}_3\text{OH} : \text{EtOAc} : \text{NH}_3$ (6 : 4 : 0.1)).

^1H NMR: δ 6.80 (s, 1H, H3'), 6.58 (s, 1H, H5), 5.41 (s, 1H, H6'), 5.71 (s, 1H, H8), 3.85 (s, 3H, OCH_3 -7), 3.84 (s, 3H, OCH_3 -5'), 3.81 (dd, 1H, J 9.0, 5.2 Hz, H1), 3.76 (s, 3H, OCH_3 -4'), 3.66 (t, 4H, J 2.7 Hz, H3''', H4'''), 3.44 (s, 3H, OCH_3 -6), 3.28 (m, 1H, H3), 3.19 (d, 1H, J 12.9 Hz, H1''), 3.17 (dd, 1H, J 13.5, 5.2 Hz, H7'), 2.96 (dd, 1H, J 13.4, 9.0 Hz, H7'), 3.07 (d, 1H, J 12.9 Hz, H1''), 2.85 (m, 1H, H4), 2.81 (dt, 1H, J 9.3, 3.0 Hz, H3), 2.63 (dd, 1H, J 5.7, 3.0 Hz, H4), 2.56 (s, 3H, NCH_3), 2.36 (t, 4H, J 2.7 Hz, H2''', H5''').

MS (ES⁺): m/z 457.1 (MH⁺, 40 %). **HRMS (ES⁺):** calcd for C₂₇H₃₉N₂O₅, 471.2859 (MH⁺). Found 471.2865.

(RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy 1-[4',5'-dimethoxy-2'-(pyrrolidinyl)methylphenyl]methyl-2-methylisoquinoline (156).



The *N*-TFA protected amine **179** (79 mg, 0.148 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reactions procedure by initially using K₂CO₃ (101 mg, 0.740 mmol), CH₃OH (5 mL) and H₂O (1 mL) and then 38 % formaldehyde (3mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (6 : 4 : 0.1)) to afford **156** (48 mg, 71 % yield) as a light yellow oil.

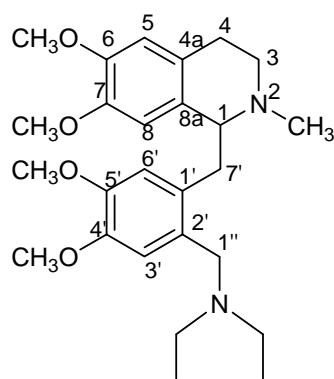
R_f 0.34 (EtOAc : CH₃OH : NH₃ (6 : 4 : 0.1)).

¹H NMR: δ 6.91(s, 1H, H3'), 6.55 (s, 1H, H5), 5.44 (s, 1H, H6'), 5.76 (s, 1H, H8), 3.82 (s, 3H, OCH₃-7), 3.84 (s, 3H, OCH₃-5'), 3.84 (m, 1H, H1), 3.80 (s, 3H, OCH₃-6), 3.49 (d, 1H, *J* 12.9 Hz, H1''), 3.42 (s, 3H, OCH₃-4'), 3.29 (d, 1H, *J* 12.9 Hz, H1''), 3.22 (m, 1H, H3), 3.20 (dd, 1H, *J* 13.2, 4.8 Hz, H7'), 2.89 (m, 1H, H3), 2.84 (m, 1H, *J* 13.2, 5.4 Hz, H7'), 2.78 (m, 1H, H4), 2.58 (m, 1H, H4), 2.52 (s, 3H, NCH₃), 2.41 (bs, 4H, H2'''), 1.70 (bs, 4H, H3''', H4''').

¹³C NMR: δ 147.5 (C4', C6), 147.2 (C5'), 147.2 (C7), 130.8 (C2', C4a), 129.4 (C1'), 125.9 (C8a), 114.9 (CH-5), 113.4 (CH-3'), 111.8 (CH-6'), 111.5 (CH-8), 64.1 (CH-1), 57.8 (CH₂-1''), 56.3 (OCH₃-7), 56.1 (OCH₃-5', OCH₃-4'), 55.5 (OCH₃-6), 54.3 (CH₂-2''', CH₂-5'''), 46.3 (CH₂-3), 42.7 (NCH₃), 37.1 (CH₂-7'), 25.1 (CH₂-4), 23.8 (CH₂-3''', CH₂-4''').

MS (ES⁺): m/z 441.1 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₆H₃₆N₂O₄, 441.2753 (MH⁺). Found 441.2777.

(*RS*) 1-[2'-(Diethylamino)methyl-4',5'-dimethoxyphenyl]methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (157).



157

The *N*-TFA protected amine **180** (75 mg, 0.161 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (109 mg, 0.810 mmol), CH₃OH (2 mL) and H₂O (1 mL), except it was stirred for 4 h, then using 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil

was purified by column chromatography (CH₃OH : EtOAc : NH₃ (6 : 4 : 0.1)) to afford **157** (41 mg, 58 %) as a light yellow oil.

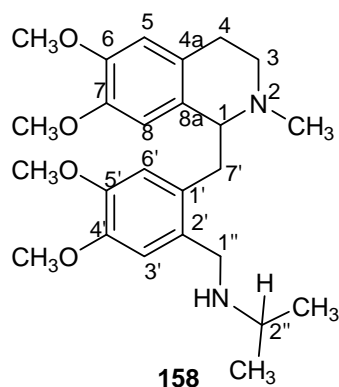
R_f 0.32 (CH₃OH : EtOAc : NH₃ (6 : 4 : 0.1)).

¹H NMR: δ 6.88 (s, 1H, H3'), 6.54 (s, 1H, H5), 5.51 (s, 1H, H6'), 5.69 (s, 1H, H8), 3.83 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.74 (s, 3H, OCH₃-6), 3.70 (dd, 1H, *J* 9.0, 4.8, H1), 3.40 (s, 3H, OCH₃-4'), 3.26 (m, 1H, H3), 3.18 (d, 1H, *J* 13.5 Hz, H1''), 3.08 (dd, 2H, *J* 13.5, 4.8 Hz, H7'), 2.98 (d, 1H, *J* 13.5 Hz, H1''), 2.89 (dd, 1H, *J* 9.6, 3.0 Hz, H3), 2.84 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.77 (m, 1H, H4), 2.60 (m, 1H, H4), 2.54 (s, 3H, NCH₃), 2.40 (m, 4H, 2 x NCH₂CH₃), 0.90 (t, 6H, *J* 6.9 Hz, 2 x NCH₂CH₃).

¹³C NMR: δ 147.3 (C4'), 147.2 (C6), 146.9 (C5'), 145.9 (C7), 131.1 (C2'), 130.7 (C4a), 128.9 (C1'), 125.6 (C8a), 114.8 (CH-5), 113.1 (CH-3'), 111.3 (CH-6'), 111.2 (CH-8), 64.1 (CH-1), 56.0 (CH₂-1'), 55.9 (OCH₃-7), 55.8 (OCH₃-5'), 55.3 (OCH₃-4'), 55.0 (OCH₃-6), 46.6 (2 x NCH₂CH₃), 46.0 (CH₂-3), 42.5 (NCH₃), 36.5 (CH₂-7'), 25.1 (CH₂-4), 11.6 (2 x NCH₂CH₃).

MS (ES⁺): m/z 443.2 (MH⁺, 100 %). **HRMS (ES⁺)** calcd for C₂₆H₃₉N₂O₄, 443.2910 (MH⁺). Found 443.2928.

(RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(isopropylamino)methyl)phenyl]methyl-2-methylisoquinoline (158).



The *N*-TFA protected amine **181** (60 mg, 0.136 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (91 mg, 0.680 mmol), CH₃OH (3 mL) and H₂O (1 mL), except it was stirred for 4 h, then using 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)) to afford **158** (36 mg, 59 %) as a light yellow oil

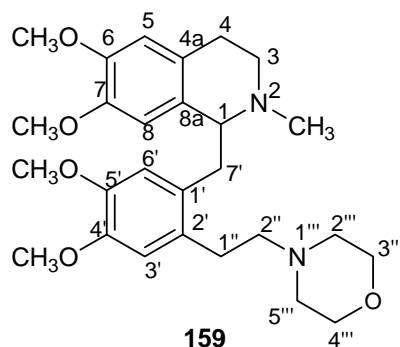
R_f 0.34 (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)).

¹H NMR: δ 6.82 (s, 1H, H_{3'}), 6.54 (s, 1H, H₅), 5.52 (s, 1H, H_{6'}), 5.67 (s, 1H, H₈), 3.82 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-6), 3.72 (m, 1H, H₁), 3.39 (s, 3H, OCH₃-4'), 3.27 (m, 1H, H₃), 3.12 (d, 1H, *J* 12.9 Hz, H_{1''}), 3.08 (dd, 1H, *J* 13.5, 4.8 Hz, H_{7'}), 2.95 (d, 1H, *J* 12.9 Hz, H_{1''}), 2.90 (m, 5H, H₄, H_{7'}, H₃, H_{2''}), 2.57 (m, 1H, H₄), 2.54 (s, 3H, NCH₃), 0.94 (t, 6H, *J* 2.1 Hz, CH(CH₃)CH₃).

¹³C NMR: δ 147.6 (C_{4'}), 147.5 (C₆), 147.2 (C_{5'}), 146.0 (C₇), 130.5 (C_{2'}, C_{4a}), 128.0 (C_{1'}), 125.1 (C_{8a}), 114.3 (CH-5), 113.4 (CH-3'), 111.3 (CH-6'), 111.1 (CH-8), 64.2 (CH-1), 56.1 (OCH₃-7), 55.9 (OCH₃-5'), 55.8 (OCH₃-4'), 55.3 (OCH₃-6), 54.4 (CH₂-1''), 53.2 (CH-2''), 45.9 (CH₂-3), 36.7 (CH₂-7'), 35.8 (NCH₃), 24.9 (CH₂-4), 17.7 (CH(CH₃)CH₃), 17.2 (CH(CH₃)CH₃).

MS (ES⁺): m/z 443.1 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₆H₃₉N₂O₄, 443.2910 (MH⁺). Found 443.2910.

(RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(morpholino)ethyl)phenyl]methyl-2-methylisoquinoline (159).



The *N*-TFA protected amine **182** (50 mg, 0.092 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (91 mg, 0.68 mmol), CH₃OH (3 mL) and H₂O (1 mL), then 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (10 mg, 0.164 mmol) to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)) to afford **159** (37 mg, 85 %) as a light yellow oil.

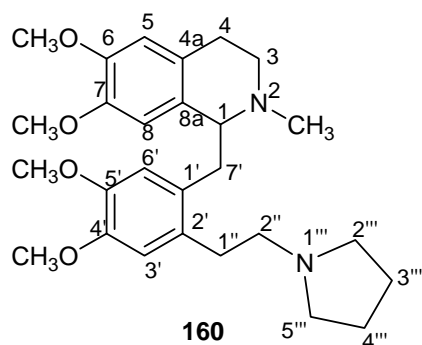
R_f 0.30 (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)).

¹H NMR: δ 6.61 (s, 1H, H3'), 6.55 (s, 1H, H5), 6.53 (s, 1H, H6'), 5.68 (s, 1H, H8), 3.80 (s, 3H, OCH₃-7), 3.78 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-4'), 3.67 (t, 4H, *J* 4.5 Hz, H2''', H5'''), 3.63 (m, 1H, H1), 3.38 (s, 3H, OCH₃-6), 3.25 (m, 1H, H3), 3.15 (dd, 1H, *J* 13.2, 4.2 Hz, H7'), 2.91 (m, 1H, H4), 2.83 (m, 1H, H3), 2.74 (dd, 1H, *J* 13.2, 9.6 Hz, H7'), 2.60 (m, 1H, H4), 2.53 (s, 3H, NCH₃), 2.38 (t, 4H, *J* 5.1 Hz, H3''', H4'''), 2.34 (m, 2H, H2''), 2.20 (m, 2H, H1'').

¹³C NMR: δ 147.4 (C4'), 147.3 (C6), 147.1 (C5'), 146.0 (C7), 131.0 (C2'), 129.4 (C4a), 128.1 (C1'), 125.2 (C8a), 114.0 (CH-5), 112.8 (CH-3'), 111.2 (CH-6', CH-8), 66.8 (CH₂-3''', CH₂-4'''), 64.3 (CH-1), 59.9 (CH₂-2''), 55.9 (OCH₃-7), 55.9 (OCH₃-5'), 55.7 (OCH₃-4'), 55.3 (OCH₃-6), 53.5 (CH₂-2''', CH₂-5'''), 45.9 (CH₂-3), 42.2 (NCH₃), 37.1 (CH₂-7'), 29.5 (CH₂-1''), 24.7 (CH₂-4).

MS (ES⁺): m/z 471.1 (MH⁺, 40 %). **HRMS (ES⁺):** calcd for C₂₇H₃₉N₂O₅, 471.2859 (MH⁺). Found 471.2865.

(RS) 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[4',5'-dimethoxy-2'-(2''-(pyrrolidino)ethyl) phenyl]methyl-2-methylisoquinoline (160).



The *N*-TFA protected amine **183** (38 mg, 0.076 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by using initially K₂CO₃ (52 mg, 0.381 mmol), CH₃OH (5 mL) and H₂O (1 mL), then 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (10 mg, 0.164 mmol) to give an oil. The oil purified by column chromatography (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)) to afford **160** (25 mg, 69 %) as a light yellow oil.

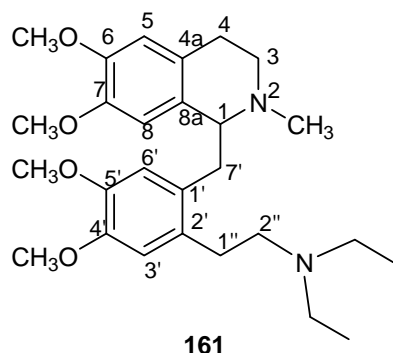
R_f 0.30 (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)).

¹H NMR: δ 6.63 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.54 (s, 1H, H6'), 5.74 (s, 1H, H8), 3.81 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.66 (dd, 1H, *J* 9.0, 4.5 Hz, H1), 3.42 (s, 3H, OCH₃-6), 3.24 (m, 1H, H3), 3.09 (dd, 1H, *J* 13.5, 4.5 Hz, H7'), 2.90 (m, 1H, H4), 2.81 (m, 1H, H3), 2.78 (dd, 1H, *J* 13.5, 9.0 Hz, H7'), 2.61 (m, 1H, H4), 2.54 (s, 3H, NCH₃), 2.36 (m, 4H, H1'', H2''), 2.46 (t, 4H, *J* 3.9 Hz, H2''', H5'''), 1.75 (t, 4H, *J* 3.9 Hz, H3''', H4''').

¹³C NMR: δ 149.4 (C4'), 148.9 (C6), 148.4 (C5'), 147.0 (C7), 128.4 (C2'), 126.3 (C4a), 121.5 (C1'), 120.2 (C8a), 115.0 (CH-5), 113.0 (CH-3'), 111.7 (CH-6'), 111.5 (CH-8), 65.2 (CH₂-2''), 56.4 (OCH₃-7, OCH₃-5'), 56.2 (OCH₃-4'), 55.6 (OCH₃-6), 53.3 (CH₂-1), 47.1 (CH₂-2''', CH₂-5'''), 45.3 (CH₂-3), 44.3 (NCH₃), 40.0 (CH₂-7'), 37.8 (CH₂-1''), 27.4 (CH₂-4), 21.4 (CH₂-3''', CH₂-4''').

MS (ES⁺): m/z 454.92 (MH⁺, 20 %). **HRMS (ES⁺):** calcd for C₂₇H₃₉N₂O₄, 455.2910 (MH⁺). Found 455.2907.

(RS) 1-[2'-(2''-(Diethylamino)ethyl)-4',5'-dimethoxyphenyl]methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (161).



The *N*-TFA protected amine **184** (80 mg, 0.149 mmol) was treated as described above in the general *N*-TFA deprotection and reductive *N*-methylation reaction procedure by initially using K₂CO₃ (100 mg, 0.735 mmol), CH₃OH (5 mL) and H₂O (1 mL), then 38 % formaldehyde (3 mL), CH₃CN (3 mL) and NaCNBH₃ (20 mg, 0.328 mmol) to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)) to afford **161** (65 mg, 69 %) as a light yellow oil.

R_f 0.31 (EtOAc : CH₃OH : NH₃ (4 : 6 : 0.1)).

¹H NMR: δ 6.61 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.54 (s, 1H, H6'), 5.71 (s, 1H, H8), 3.81 (s, 3H, OCH₃-7), 3.79 (s, 3H, OCH₃-5'), 3.76 (s, 3H, OCH₃-4'), 3.66 (dd, 1H, *J* 9.0, 4.2 Hz, H1), 3.40 (s, 3H, OCH₃-6), 3.23 (m, 1H, H3), 3.09 (dd, 1H, *J* 13.0, 4.2 Hz, H7'), 2.89 (m, 1H, H4), 2.83 (m, 1H, H3), 2.78 (dd, 1H, *J* 13.0, 9.0 Hz, H7'), 2.59 (m, 1H, H4), 2.55 (s, 3H, NCH₃), 2.52 (q, 4H, *J* 4.2 Hz, 2 x NCH₂CH₃), 2.50 (m, 2H, H2''), 2.35 (dt, 2H, *J* 12.3, 4.1 Hz, H1''), 1.00 (t, 6H, *J* 4.2 Hz, 2 x NCH₂CH₃).

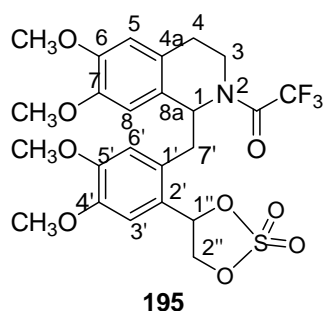
¹³C NMR: δ 148.2 (C4', C6), 148.0 (C5'), 146.5 (C7), 129.0 (C2', C4a), 125.9 (C1'), 124.8 (C8a), 114.0 (CH-5), 112.7 (CH-3'), 111.2 (CH-6'), 111.0 (CH-8), 64.5 (CH-1), 56.0 (OCH₃-7, OCH₃-5'), 55.7 (OCH₃-4', OCH₃-6), 55.2 (CH₂-2''), 45.9 (2 x NCH₂CH₃), 45.3 (CH₂-3), 41.2 (NCH₃), 36.8 (CH₂-7'), 27.3 (CH₂-1''), 23.4 (CH₂-4), 8.8 (2 x NCH₂CH₃).

MS (ES⁺): m/z 456.94 (MH⁺, 30 %). **HRMS (ES⁺):** calcd for C₂₇H₄₁N₂O₄, 457.3066 (MH⁺). Found 457.3060.

8.5.2. Synthesis of β -hydroxy alcohol derivatives.

Attempted synthesis of the cyclic sulfates **195** and the synthesis of **196**.

(1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 2-Trifluoroacetyl-3,4-dihydro-1-[2'-(1'',2''-dihydroxyethyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline 1'',2''-cyclic sulfate (195**).**



To a solution of diol **190** (63 mg, 0.127 mmol) in dry DCM (2 mL) was added triethylamine (30 mg, 0.292 mmol, 0.042 mL), followed by thionyl chloride (19 mg, 0.159 mmol, 0.011 mL) at 0 °C and the reaction mixture was stirred for 30 min. H₂O (15 mL) was added and the product was extracted with DCM. The DCM layer was washed with H₂O (3 x), brine and dried (MgSO₄). The solvent was evaporated to give a brown oil. The oil was dissolved in a mixture of CCl₄ : CH₃CN : H₂O (1.5 : 1.5 : 2) (5 mL) and RuCl₃.H₂O (2 mg, 0.007 mmol) was added, followed by NaIO₄ (54 mg, 0.254 mmol). The reaction mixture was stirred at RT for 2.5 h. Diethyl ether (2 mL) was added and the organic phase was washed with H₂O (3 x), sat. NaHCO₃, brine and dried (MgSO₄). The solvent was evaporated to give a yellow oil, however, ¹H NMR analysis of the crude mixture showed none of the desired product **195** and only that of the decomposition materials.

Hz, H2''), 4.65 (dd, 1H, *J* 9.0, 6.5 Hz, H3''), 4.58 (dd, 1H, *J* 9.0, 6.5 Hz, H3''), 3.91 (dt, 1H, *J* 8.5, 6.0 Hz, H3), 3.83 (s, 6H, OCH₃-7, OCH₃-5'), 3.72 (m, 1H, H3), 3.71 (s, 6H, OCH₃-4', OCH₃-6), 3.15 (dd, 1H, *J* 13.6, 8.0 Hz, H7'), 3.01 (dd, 1H, *J* 13.5, 5.5 Hz, H7'), 2.93 (m, 3H, H1'', H4), 2.81(m, 1H, H4).

¹H NMR of the minor diastereomer (in part): δ 6.66 (s, 1H, H3'), 6.62 (s, 1H, H5), 6.46 (s, 1H, H6'), 5.90 (s, 1H, H8), 5.40 (dd, 1H, *J* 8.0, 5.5 Hz, H1), 4.92 (t, 1H, *J* 6.5 Hz, H2''), 4.80 (dd, 1H, *J* 9.0, 6.5 Hz, H3''), 4.30 (dd, 1H, *J* 9.0, 6.5 Hz, H3''), 3.72 (s, 6H, OCH₃-4', OCH₃-6).

MS (ES⁺): *m/z* 576.8 (MH⁺, 20 %).

199.

R_f 0.79 (EtOAc).

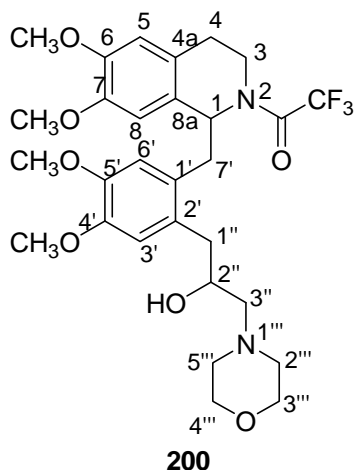
¹H NMR (in part): δ 6.66 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.47 (s, 1H, H6'), 6.02 (s, 1H, H8), 5.37 (dd, 1H, *J* 7.5, 2.5 Hz, H1), 4.53 (m, 1H, H2''), 4.04 (dd, 1H, *J* 8.0, 6.5 Hz, H3''), 3.99 (dd, 1H, *J* 8.0, 6.5 Hz, H3''), 3.90 (m, 2H, H3), 3.83 (s, 6H, OCH₃-7, OCH₃-5'), 3.55 (s, 3H, OCH₃-4'), 3.50 (s, 3H, OCH₃-6).

¹H NMR minor diastereomer (in part): δ 6.68 (s, 1H, H3'), 6.60 (s, 1H, H5), 6.48 (s, 1H, H6'), 6.01(s, 1H, H8), 5.34 (dd, 1H, *J* 7.5, 2.5 Hz, H1), 4.41 (m, 1H, H2''), 3.83 (s, 6H, OCH₃-4', OCH₃-6), 3.56 (s, 3H, OCH₃-4'), 3.52 (s, 3H, OCH₃-6).

MS (ES⁺): *m/z* 559.9 (MH⁺, 100 %).

Synthesis of morpholino alcohol product 200.

(1*RS*, 2''*RS*) (1*RS*, 2''*SR*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[2'-(2''-hydroxy-3''-morpholinopropyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (200).



To the solution mixture of **196** and **199** (131 mg, 0.228 mmol) in isopropanol (5 mL) was added morpholine (0.1 mL). The reaction was heated at 70 °C for 6 d. To the reaction mixture was added aqueous H₂SO₄ (5 mL) and the reaction mixture was stirred at RT for 1 h. The isopropanol was evaporated and the residue was dissolved in DCM. The DCM layer was washed with sat. NaHCO₃

(2 x), H₂O and brine and then dry (MgSO₄). The DCM extracts were evaporated to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc (7 : 1)) to give **200** (21 mg, ~ 30 % relative to **196**) as a yellow oil. Compound **200** was a 60 : 40 mixture of diastereomers. The diol **191** (33 mg, 28 %) was also isolated.

R_f 0.21 (CH₃OH : EtOAc (7 : 1)).

¹H NMR of the major diastereomer: δ 6.74 (s, 1H, H₅), 6.59 (s, 1H, H_{3'}), 6.55 (s, 1H, H_{6'}), 6.02 (s, 1H, H₈), 5.49 (dd, 1H, *J* 7.8, 5.7 Hz, H₁), 3.95 (dt, 1H, *J* 13.5, 4.5 Hz, H₃), 3.84 (s, 6H, OCH₃-7, OCH₃-5'), 3.73 (s, 3H, OCH₃-4'), 3.72 (s, 3H, OCH₃-6), 3.70 (m, 1H, H_{2''}), 3.68 (m, 4H, H_{3'''}, H_{4'''}), 3.60 (m, 1H, H₃), 3.17 (dd, 1H, *J* 12.9, 5.7 Hz, H_{7'}), 3.09 (dd, 1H, *J* 12.9, 7.8 Hz, H_{7'}), 2.93 (m, 1H, H₄), 2.80 (m, H₄), 2.60 (m, 2H, H_{1''}), 2.54 (m, 1H, H_{3''}), 2.47 (m, 1H, H_{3''}), 2.38 (m, 4H, H_{2'''}, H_{5'''}).

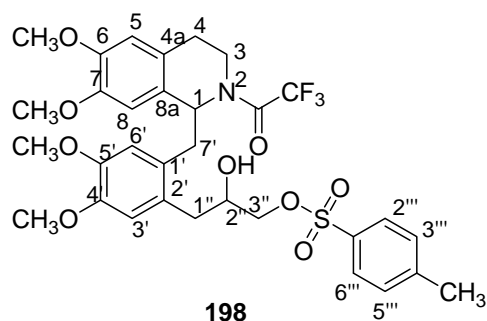
¹H NMR of the minor diastereomer (in part): δ 6.74 (s, 1H, H₅), 6.59 (s, 1H, H_{3'}), 6.50 (s, 1H, H_{6'}), 6.09 (s, 1H, H₈), 5.55 (t, 1H, *J* 6.9 Hz, H₁), 3.58 (OCH₃-4'), 3.51 (s, 3H, OCH₃-6).

H6'), 6.08 (s, 1H, H8), 5.64 (t, 1H, *J* 8.0 Hz, H1), 5.21 (t, 1H, *J* 5.0 Hz, H1''), 3.86 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.55 (s, 3H, OCH₃-6), 2.03 (s, 3H, ArCH₃).

¹³C NMR of the major diastereomer: (signals for $\underline{\text{C}}\text{OCF}_3$ and $\text{CO}\underline{\text{C}}\text{F}_3$ were not observed), δ 148.4 (C4'), 148.3 (C7), 147.5 (C5'), 144.9 (C6), 132.8 (C4'''), 129.8 (CH-2''', CH-6'''), 129.5 ($\underline{\text{C}}\text{SO}_3$), 127.9 (CH-3''', CH-5'''), 127.8 (C2'), 126.7 (C4a), 126.4 (C1'), 124.6 (C8a), 113.9 (CH-6'), 111.0 (CH-5), 110.7 (CH-8), 109.5 (CH-3'), 73.8 (CH₂-2''), 68.6 (CH-1''), 55.9 (OCH₃-7), 55.8 (OCH₃-5'), 55.8 (OCH₃-4'), 55.7 (OCH₃-6), 55.2 (CH-1), 40.4 (CH₂-3), 38.1 (CH₂-7'), 28.4 (CH₂-4), 21.5 (CCH₃).

MS (ES⁺): *m/z* 675.9 (M+Na⁺, 10 %). **HRMS (ES⁺):** calcd for C₃₁H₃₄NO₉F₃NaS, 676.1804 (MH⁺). Found 676.1823.

(1*RS*, 2''*RS*) (1*RS*, 2''*SR*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1-[2'-(2''-hydroxy-3''-(4-methylphenylsulfonyloxy)propyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxyisoquinoline (198).



Tosylation of the hydroxyl group of **191** was carried out as described above in the synthesis of **197** using a mixture of the diol **191** (139 mg, 0.279 mmol) and tosylchloride (80 mg, 0.418 mmol) in dry DCM (2 mL) to give a solid. The

solid was purified by column chromatography (EtOAc) to give **198** (195 mg, 84 %) as a white solid. Compound **198** was a 60 : 40 mixture of diastereomers.

R_f 0.75 (EtOAc).

m.p. 62-66 °C.

¹H NMR of the major diastereomer: δ 7.75 (d, 2H, *J* 8.0, H2''', H6'''), 7.31 (d, 2H, *J* 8.5 Hz, H3''', H5'''), 6.65 (s, 1H, H5), 6.63 (s, 1H, H3'), 6.45 (s, 1H, H6'), 5.97 (s, 1H, H8), 5.41 (dd, 1H, *J* 8.5, 5.5 Hz, H1), 4.02 (dd, 1H, *J* 10.5, 4.0 Hz, H3''), 3.97 (dd, 1H,

J 10.5, 6.0 Hz, H3''), 3.91 (m, 1H, H2''), 3.83 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.75 (m, 2H, H3), 3.71 (s, 3H, OCH₃-4'), 3.51 (s, 3H, OCH₃-6), 3.04 (m, 2H, H7'), 2.94 (m, 1H, H4), 2.84 (m, 1H, H1''), 2.66 (m, 1H, H1''), 2.55 (m, 1H, H4), 2.02 (s, 3H, ArCH₃).

¹H NMR of the minor diastereomer (in part): δ 6.62 (s, 1H, H3'), 6.51 (s, 1H, H6'), 6.10 (s, 1H, H8), 5.74 (t, 1H, J 7.0 Hz, H1), 3.75 (s, 3H, OCH₃-4'), 3.59 (s, 3H, OCH₃-6), 2.41 (s, 3H, ArCH₃).

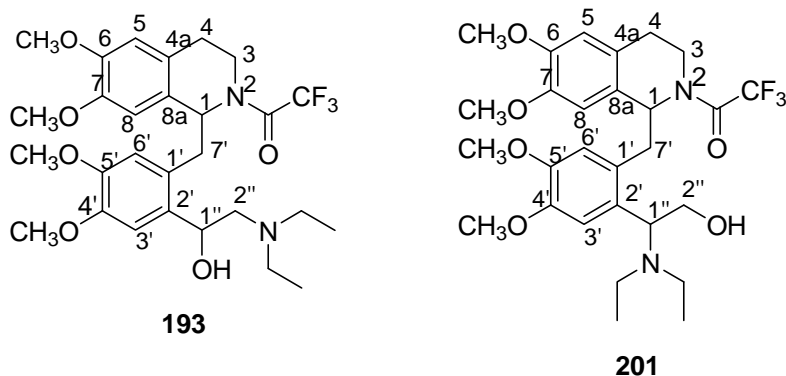
¹³C NMR of the major diastereomer: δ 156.2 (q, J 36.8, COCF₃), 148.5 (C7), 148.2 (C4'), 147.7 (C5'), 144.9 (C6), 145.3 (CSO₃), 132.9 (C4''), 130.1 (CH-3'', CH-5''), 128.7 (C1'), 128.1 (CH-2'', CH-6'', C4a), 126.3 (C2'), 125.2 (C8a), 116.7 (q, J 287.5 Hz, COCF₃), 114.5 (CH-6'), 113.6 (CH-5), 111.3 (CH-3'), 110.6 (CH-8), 73.3 (CH₂-3''), 70.6 (CH-2''), 56.2 (OCH₃-7), 55.1 (OCH₃-5'), 56.0 (OCH₃-4'), 55.9 (OCH₃-6), 55.8 (CH-1), 41.1 (CH₂-3), 38.6 (CH₂-7'), 35.6 (CH₂-4), 28.6 (CH₂-1''), 21.8 (CCH₃).

¹³C NMR of the minor diastereomer (in part): δ 148.5 (C7), 148.3 (C4'), 147.8 (C5'), 147.6 (C6), 147.4 (CSO₃), 132.8 (C4''), 130.2 (CH-3'', CH-5''), 128.5 (C1'), 128.1 (CH-2'', CH-6'', C4a), 126.5 (C2'), 125.0 (C8a), 114.2 (CH-6'), 113.4 (CH-5), 111.1 (CH-3'), 110.7 (CH-8), 72.9 (CH₂-3''), 70.6 (CH-2''), 40.8 (CH₂-3), 38.4 (CH₂-7'), 36.0 (CH₂-4), 28.7 (CH₂-1''), 21.8 (CCH₃).

MS (ES⁺): m/z 705.72 (M+K⁺, 100 %). **HRMS (ES⁺):** calcd for C₃₂H₃₇NO₉F₃S, 668.2141 (MH⁺). Found 668.2142.

Synthesis of 193, 194 and 201.

(1*RS*, 1''*RS*) (*R,S*) 1[2'-(2''-Diethylamino-1''-hydroxyethyl)-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**193**) and (1*RS*, 1''*RS*) 1[2'-(1''-Diethylamino-2''-hydroxyethyl)-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**201**).



To a mixture of **197** (86 mg, 0.132 mmol) and diethylamine (0.3 mL) was added CH₃CN (3 mL) and the solution mixture was heated at 80 °C for 24 h. The solvent was evaporated and the crude mixture was purified by column chromatography (EtOAc followed by CH₃OH: EtOAc (1 : 4)) to give a mixture of **193** and **201** (10 : 90) (34 mg, 47 %) as white solid. Starting material **197** (19 mg, 22 %) was also retrieved. Product **193** and **201** were a 80 : 20 mixture of diastereomers. Compound **193** and **201** were not separated at this stage.

193.

R_f. 0.70 (CH₃OH : EtOAc (1 : 4)).

¹H NMR of the major diastereomer (500 MHz): δ 7.08 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.39 (s, 1H, H6'), 6.27 (s, 1H, H8), 5.53 (t, 1H, *J* 6.0 Hz, H1), 4.93 (dd, 1H, *J* 7.5, 5.0 Hz, H1''), 3.95 (dt, 1H, *J* 13.5, 5.0 Hz, H3), 3.88 (s, 3H, OCH₃-7), 3.87 (s, 3H, OCH₃-5'), 3.66 (s, 3H, OCH₃-4'), 3.72 (m, 1H, H3), 3.53 (s, 3H, OCH₃-6), 3.23 (m, 1H, H7'), 3.01 (m, 1H, H7'), 2.95 (m, 1H, H4), 2.81 (m, 1H, H4), 2.68 (m, 2H, NCH₂CH₃), 2.53

(m, 2H, NCH₂CH₃), 2.52 (m, 1H, H2''), 2.32 (t, 1H, *J* 4.5 Hz, H2''), 1.03 (t, 3H, *J* 7.0 Hz, NCH₂CH₃), 0.96 (t, 3H, *J* 7.5 Hz, NCH₂CH₃).

¹H NMR of the minor diastereomer (in part): δ 7.06 (s, 1H, H3'), 6.52 (s, 3H, H5), 6.42 (s, 3H, H6'), 6.26 (s, 3H, H8), 4.54 (d, 1H, *J* 12.5 Hz, H8').

¹³C NMR of the major diastereomer: (signals for COCF₃ and COCF₃ were not observed), δ 148.6 (C7), 148.2 (C5'), 147.6 (C4'), 147.5 (C6), 134.1 (C1'), 126.5 (C4a, C2'), 125.1 (C8a), 114.2 (CH-6'), 110.6 (CH-8), 109.6 (CH-3', CH-5'), 65.5 (CH-1''), 60.8 (CH₂-2''), 55.9 (OCH₃-7), 55.8 (OCH₃-5'), 55.8 (OCH₃-4'), 55.7 (OCH₃-6), 55.8 (CH-1), 46.9 (NCH₂CH₃), 40.9 (CH₂-3), 38.2 (CH₂-7'), 28.7 (CH₂-4), 12.0 (NCH₂CH₃).

¹³C NMR of the minor diastereomer (in part): δ 133.8 (C1'), 113.8 (CH-6'), 109.3 (CH-3'), 66.3 (CH-8'), 47.2 (NCH₂CH₃).

201.

R_f 0.41 (CH₃OH: EtOAc (1 : 4)).

¹H NMR of the major diastereomer (500 MHz): δ 7.02 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.32 (s, 1H, H6'), 6.04 (s, 1H, H8), 5.48 (dd, 1H, *J* 8.5, 6.0 Hz, H1), 4.11 (t, 1H, *J* 5.5 Hz, H1''), 3.95 (dt, 1H, *J* 13.5, 5.0 Hz, H3), 3.90 (m, 1H, H2''), 3.86 (s, 3H, OCH₃-7), 3.84 (s, 3H, OCH₃-5'), 3.73 (s, 3H, OCH₃-4'), 3.72 (m, 1H, H3), 3.71 (m, 1H, H2''), 3.56 (s, 3H, OCH₃-6), 3.26 (dd, 1H, *J* 13.5, 6.0 Hz, H7'), 3.08 (dd, 1H, *J* 13.5, 8.5 Hz, H7'), 2.95 (m, 1H, H4), 2.81 (m, 1H, H4), 2.66 (m, 2H, NCH₂CH₃), 2.52 (m, 2H, NCH₂CH₃), 1.03 (t, 3H, *J* 7.5 Hz, NCH₂CH₃), 0.96 (t, 3H, *J* 7.5 Hz, NCH₂CH₃).

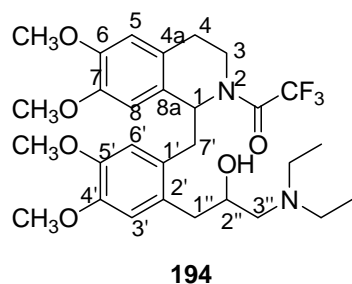
¹H NMR of the minor diastereomers (in part): δ 6.95 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.27 (s, 1H, H6'), 6.03 (s, 1H, H8), 5.60 (t, 1H, *J* 6.0 Hz, H1), 4.02 (t, 1H, *J* 6.0 Hz, H1''), 3.83 (s, 3H, OCH₃-5'), 3.66 (s, 3H, OCH₃-4'), 3.53 (s, 3H, OCH₃-6).

¹³C NMR of the major diastereomer: (signals for COCF₃ and COCF₃ were not observed) δ 148.6 (C7), 148.2 (C5'), 147.6 (C4'), 147.5 (C6), 132.1 (C1'), 128.2 (C2'),

126.5 (C4a), 125.1 (C8a), 114.7 (CH-6'), 111.5 (CH-3'), 111.3 (CH-5, CH-8), 64.5 (CH₂-2''), 61.6 (CH-1''), 56.2 (OCH₃-7), 56.1 (OCH₃-5'), 56.1 (OCH₃-4'), 55.9 (OCH₃-6), 55.6 (CH-1), 42.9 (2 x NCH₂CH₃), 40.9 (CH₂-3), 38.8 (CH₂-7'), 28.7 (CH₂-4), 12.0 (2 x NCH₂CH₃).

MS (ES⁺): *m/z* 555.1 (MH⁺, 50 %). **HRMS (ES⁺):** calcd for C₂₈H₃₈N₂O₆F₃, 555.2682 (MH⁺). Found 555.2668.

(1*RS*, 2''*RS*) (1*RS*, 2''*SR*) 1[2'-(2''-Diethylamino-1''-hydroxypropyl)-4',5'-dimethoxyphenyl]methyl-2-trifluoroacetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (194**).**



Aminolysis of **198** was performed as described above for the synthesis of **193**, using a mixture of **198** (51 mg, 0.076 mmol) and diethylamine (0.4 mL) in CH₃OH (2 mL) except that the mixture was heated at 65 °C for 5 h. The

solvent was evaporated and the crude mixture was purified by column chromatography (EtOAc followed by CH₃OH: EtOAc : NH₃ (4 : 6 : 0.1)) to give **194** as a white solid (33 mg, 75 %). Compound **194** was a 60 : 40 mixture of diastereomers.

R_f 0.26 (CH₃OH: EtOAc : NH₃ (4 : 6 : 0.1)).

m.p. 95-100 °C.

¹H NMR of the major diastereomer (500 MHz): δ 6.76 (s, 1H, H5), 6.59 (s, 1H, H3'), 6.54 (s, 1H, H6'), 6.05 (s, 1H, H8), 5.55 (dd, 1H, *J* 8.5, 5.5 Hz, H1), 3.74 (dt, 1H, *J* 8.5, 5.5 Hz, H3), 3.85 (s, 3H, OCH₃-7), 3.84 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-4'), 3.60 (m, 1H, H2''), 3.67 (m, 1H, H3), 3.53 (s, 3H, OCH₃-6), 3.17 (dd, 1H, *J* 13.5, 5.5 Hz, H7'), 3.10 (dd, 1H, *J* 13.5, 8.5 Hz, H7''), 2.82 (m, 1H, H4), 2.76 (m, 1H, H4), 2.55 (dd, 1H, *J* 13.5, 6.5 Hz, H1''), 2.47 (m, 5H, 2 x NCH₂CH₃, H1''), 2.41 (dt, 1H, *J* 9.0, 3.5 Hz, H3''), 2.30 (dt, 1H, *J* 9.0, 2.0 Hz, H3''), 0.99 (t, 6H, *J* 7.0 Hz, NCH₂CH₃).

¹H NMR of the minor diastereomer (in part): δ 6.77 (s, 1H, H5), 6.49 (s, 1H, H6'), 6.10 (s, 1H, H8), 5.51 (dd, 1H, *J* 8.5, 6.0 Hz, H1), 3.95 (dt, 1H, *J* 8.5, 4.5 Hz, H3), 3.73 (OCH₃-4'), 3.63 (m, 1H, H3), 3.59 (s, 3H, OCH₃-6), 3.10 (m, 2H, H7'), 2.95 (m, 1H, H4), 2.92 (m, 1H, H4), 2.60 (m, 4H, NCH₂CH₃).

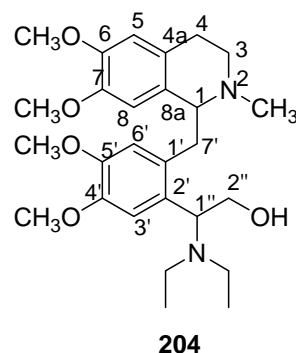
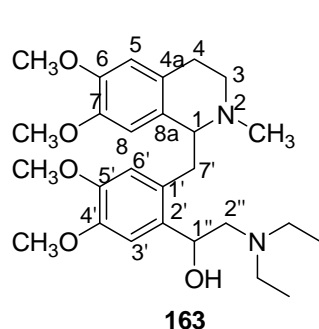
¹³C NMR of the major diastereomer: (signals for C=O and C=O were not observed), δ 148.4 (C7), 148.0 (C5'), 147.5 (C4'), 147.4 (C6) 130.2 (C2'), 127.9 (C1'), 126.6 (C4a), 125.0 (C8a), 114.5 (CH-6'), 113.5 (CH-5), 111.1 (CH-3', CH-8), 68.1 (CH-2''), 59.6 (CH₂-3''), 56.1 (OCH₃-7, OCH₃-5'), 56.0 (OCH₃-4'), 55.9 (OCH₃-6), 55.6 (CH-1), 47.3 (NCH₂CH₃), 40.9 (CH₂-3), 37.5 (CH₂-7'), 37.6 (CH₂-1''), 28.8 (CH₂-4), 12.0 (NCH₂CH₃).

¹³C NMR of the minor diastereomer (in part): δ 148.3 (C7), 148.0 (C5'), 147.3 (C6), 130.6 (C2'), 127.7 (C1'), 125.1 (C8a), 114.2 (CH-6'), 111.0 (CH-3', CH-8), 113.8 (CH-5), 68.4 (CH-2''), 59.4 (CH₂-3''), 55.7 (CH-1), 47.4 (NCH₂CH₃), 37.5 (CH₂-1'').

MS (EI⁺): *m/z* 568 (M⁺, 10 %). **HRMS (ES⁺):** calcd for C₂₉H₄₀N₂O₆F₃, 569.2838 (MH⁺). Found 569.2802.

N-TFA deprotection and reductive N-Methylation of 193, 194 and 201.

(1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 1[2'-(2''-Diethylamino-1''-hydroxyethyl)-4',5'-dimethoxyphenyl]methyl- 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (163) and (1*RS*, 1''*RS*) and (1*RS*, 1''*SR*) 1[2'-(1''-Diethylamino-2''-hydroxyethyl)-4',5'-dimethoxyphenyl]methyl- 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (204).



To a mixture of the regoisomer **193** and **201** (27 mg, 0.048 mmol) in CH₃OH (2 mL) and H₂O (1 mL) was added K₂CO₃ (33 mg, 0.240 mmol) and the reaction mixture was stirred at RT for 2 h. The solvent was removed and the residue was dissolved in CH₃CN (2 mL). 38 % formaldehyde (2 mL) and NaCNBH₃ (4 mg, 0.063 mmol) were subsequently added and the mixture was stirred for 20 min at RT before the pH was adjusted to ~6 using glacial acetic acid. The resulting solution was stirred at RT for 18 h. The solvent was evaporated and the residue was dissolved in DCM. The solution was washed with sat. Na₂CO₃ and H₂O (2 x), dried (K₂CO₃) to give a crude mixture which was purified by column chromatography (CH₃OH : EtOAc : NH₃ (5: 5 : 0.1)) to give a mixture of regoisomers **163** and **204** (17 mg, 75 %). Purification of the mixture by PTLC (CH₃OH : EtOAc : NH₃ (5: 5 : 0.1)) gave the pure samples of regoisomer **163** (11 mg, 46 %) and **204** (7 mg, 29 % yield).

Alternatively, a mixture of **193** and **201** and their *N*-TFA cleaved products **202**, **203** were subjected to the same condition as described above to give a mixture of regoisomer **163** and **204** (60 : 40) (32 mg, 0.063 mmol) in 34 % overall yield from **197** (128 mg, 0.196 mmol).

163 (major diastereomer).

R_f 0.53 (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)).

¹H NMR of the major diastereomer (500 MHz): δ 7.02 (s, 1H, H3'), 6.54 (s, 1H, H5), 6.45 (s, 1H, H6'), 5.88 (s, 1H, H8), 4.76 (dd, 1H, *J* 9.5, 2.5 Hz, H1''), 3.87 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.74 (s, 3H, OCH₃-4'), 3.72 (s, 1H, *J* 7.5, 5.0 Hz, H1), 3.47 (s, 3H, OCH₃-6), 3.18 (m, 1H, H3), 3.13 (dd, 1H, *J* 14.0, 5.0 Hz, H7'), 2.85 (m, 1H, H3), 2.77 (m, 2H, H7', H4), 2.61 (m, 2H, NCH₂CH₃), 2.51 (dd, 3H, NCH₂CH₃, H4), 2.48 (s, 3H, NCH₃), 2.31 (dd, 1H, *J* 13.0, 2.5 Hz, H2''), 2.30 (t, 1H, *J* 13.0, 10.0 Hz, H2''), 1.01 (t, 6H, *J* 7.0 Hz, 2 x NCH₂CH₃).

¹³C NMR of the major diastereomer (125 MHz): δ 147.7 (C7, C5'), 147.6 (C4'), 146.4 (C6), 133.4 (C2'), 129.0 (C1'), 128.5 (C4a), 125.7 (C8a), 114.1 (CH-6'), 111.6 (CH-5), 111.2 (CH-3'), 109.2 (CH-8), 65.5 (CH-1''), 64.4 (CH-1), 56.9 (CH₂-2''), 55.9 (OCH₃-7, OCH₃-5'), 55.6 (OCH₃-4'), 55.5 (OCH₃-6), 47.0 (NCH₂CH₃), 46.4 (CH₂-3), 42.6 (NCH₃), 37.4 (CH₂-7'), 25.1 (CH₂-4), 11.6 (NCH₂CH₃).

163 (minor diastereomer).

R_f 0.60 (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1))

¹H NMR of the minor diastereomer (500 MHz): δ 7.00 (s, 1H, H3'), 6.52 (s, 1H, H5), 6.40 (s, 1H, H6'), 6.08 (s, 1H, H8), 4.57 (dd, 1H, *J* 10.0, 3.0 Hz, H1''), 3.90 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.69 (s, 4H, OCH₃-4'), 3.67 (m, 1H, H1), 3.60 (s, 3H, OCH₃-6), 3.15 (m, 1H, H3), 3.13 (m, 1H, H7'), 2.89 (m, 1H, H3), 2.70 (m, 2H, H7', H4), 2.60 (m, 4H, 2 x NCH₂CH₃), 2.57 (m, 2H, H4), 2.52 (s, 3H, NCH₃), 2.43 (m, 2H, H2''), 1.06 (t, 6H, *J* 7.0 Hz, 2 x NCH₂CH₃).

204.

R_f 0.62 (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)).

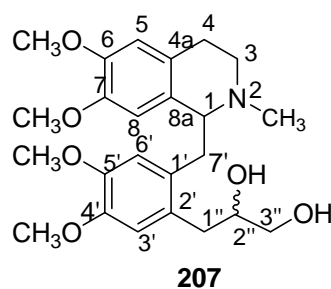
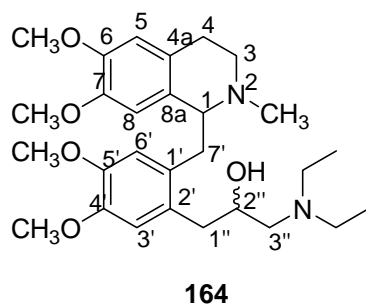
¹H NMR: (500 MHz) δ 7.10 (s, 1H, H3'), 6.60 (s, 1H, H5), 6.58 (s, 1H, H6'), 6.41 (s, 1H, H8), 4.07 (dd, 1H, *J* 10.0, 6.0 Hz, H2''), 4.01 (dd, 1H, *J* 10.0, 6.0 Hz, H2''), 3.87 (s, 3H, OCH₃-7), 3.85 (s, 3H, OCH₃-5'), 3.83 (s, 3H, OCH₃-4'), 3.77 (s, 3H, OCH₃-6), 3.70 (t, 1H, *J* 6.0 Hz, H1''), 3.64 (m, 1H, H1), 3.31 (m, 1H, H3), 3.22 (dd, 1H, *J* 14.0, 9.0 Hz, H7'), 2.94 (m, 1H, H4), 2.87 (m, 1H, H3), 2.70 (dd, 1H, *J* 14.0, 3.5 Hz, H7'), 2.63 (m, 2H, NCH₂CH₃), 2.54 (m, 2H, NCH₂CH₃), 2.51 (m, 1H, H4), 2.31 (s, 3H, NCH₃), 0.94 (t, 6H, *J* 7.0 Hz, 2 x NCH₂CH₃).

¹³C NMR (125 MHz): δ 148.4 (C5'), 148.2 (C7), 148.1 (C4'), 147.6 (C6), 131.6 (C2'), 128.4 (C1'), 128.3 (C4a), 125.7 (C8a), 113.5 (CH-6'), 111.7 (CH-5), 111.6 (CH-3'), 110.0 (CH-8), 66.0 (CH-1''), 64.6 (CH-1), 62.7 (CH₂-2''), 56.3 (OCH₃-7, OCH₃-5'),

56.2 ($\text{OCH}_3\text{-4'}$), 56.1 ($\text{OCH}_3\text{-6}$), 45.0 (NCH_2CH_3), 43.1 ($\text{CH}_2\text{-3}$), 41.9 (NCH_3), 39.6 ($\text{CH}_2\text{-7'}$), 22.8 ($\text{CH}_2\text{-4}$), 11.1 (NCH_2CH_3).

MS (ES^+): m/z 473.2 (MH^+ , 5 %). **HRMS** (ES^+): calcd for $\text{C}_{27}\text{H}_{41}\text{N}_2\text{O}_5$, 473.3015 (MH^+). Found 473.3009.

(1*RS*, 2''*RS*) (1*RS*, 2''*SR*) 1[2'-(3''-Diethylamino-2''-hydroxypropyl)-4',5'-dimethoxyphenyl]methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (164) and (1*RS*, 2''*RS*) (1*RS*, 2''*SR*) 1,2,3,4-tetrahydro-1-[2'-(2'',3''-dihydroxypropyl)-4',5'-dimethoxyphenyl]methyl-6,7-dimethoxy-2-methylisoquinoline (207).



To a solution **198** (98 mg, 0.147 mmol) in CH_3OH (3 mL) was added diethylamine (2 mL). The solution was heated at 80°C for 24 h to give a crude mixture of **194** and *N*-TFA cleaved products **205** and **206**. An extra portion of CH_3OH (2 mL) and H_2O (1 mL) was added, followed by the addition of K_2CO_3 (50 mg, 0.360 mmol). The reaction mixture was stirred for 2 h at RT. The solvent was removed and the residue was dissolved in CH_3CN (2 mL). To this solution was added 38 % formaldehyde (2 mL), followed by NaCNBH_3 (12 mg, 0.187 mmol). The mixture was stirred for 20 min at RT before the pH was adjusted to ~ 6 using glacial acetic acid. The resulting solution was stirred at RT for 18 h. The solvent was evaporated, washed with sat. Na_2CO_3 and H_2O (x 2) and dried (K_2CO_3) to give a crude mixture which was purified by column chromatography ($\text{CH}_3\text{OH} : \text{EtOAc} : \text{NH}_3$ (5 : 5 : 0.1)) to give **164** (21 mg, 29 % overall from **198**) as a yellow oil. Product **164** was obtained as a 60 : 40

mixture of diastereomers. The diol **207** (7 mg, 11 % overall from **198**) was also obtained as a yellow solid and as a 60 : 40 mixture of diastereomers.

164.

R_f. 0.06 (CH₃OH : EtOAc).

¹H NMR of the major diastereomer (500 MHz): δ 6.77 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.55 (s, 1H, H6'), 5.88 (s, 1H, H8), 3.85 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.75 (s, 3H, OCH₃-4'), 3.70 (dd, 1H, *J* 10.0, 4.0 Hz, H2''), 3.67 (dd, 1H, *J* 8.0, 3.0 Hz, H1), 3.50 (s, 3H, OCH₃-6), 3.26 (m, 1H, H3), 3.15 (m, 1H, H7'), 3.90 (m, 1H, H4), 3.82 (m, 1H, H7'), 3.29 (m, 1H, H3), 2.62 (dt, 1H, *J* 12.0, 4.5 Hz, H4), 2.59 (m, 2H, NCH₂CH₃), 2.51 (s, 3H, NCH₃), 2.49 (m, 2H, NCH₂CH₃), 2.37 (m, 2H, H3''), 2.35 (dd, 1H, *J* 13.0, 4.0 Hz, H1''), 2.27 (dd, 1H, *J* 12.5, 10.0, Hz, H1''), 0.99 (t, 6H, *J* 7.5 Hz, 2 x NCH₂CH₃).

¹H NMR of the minor diastereomer (in part): δ 6.75 (s, 1H, H3'), 6.56 (s, 1H, H5), 6.49 (s, 1H H6'), 5.92 (s, 1H, H8), 3.85 (s, 3H, OCH₃-7), 3.73 (s, 3H, OCH₃-4'), 3.52 (s, 3H, OCH₃-6), 3.18 (s, 1H, H3), 3.12 (m, 1H, H7'), 2.56 (m, 2H, NCH₂CH₃), 2.53 (s, 3H, NCH₃), 2.45 (m, 2H, NCH₂CH₃).

¹³C NMR of the major diastereomer (125 MHz): δ 147.6 (C7), 147.5 (C5'), 147.3 (C4'), 146.4 (C6), 130.4 (C4a), 130.3 (C1'), 130.1 (C2'), 125.8 (C8a), 114.9 (CH-6'), 113.3 (CH-5), 111.6 (CH-3'), 111.6 (CH-8), 68.3 (CH-2''), 64.7 (CH-1), 59.7 (CH₂-3''), 56.2 (OCH₃-7), 56.2 (OCH₃-5'), 56.1 (OCH₃-4'), 56.0 (OCH₃-6), 55.7 (CH-1), 47.4 (NCH₂CH₃), 46.5 (NCH₃), 37.9 (CH₂-7'), 37.7 (CH₂-1''), 25.4 (CH₂-4), 12.2 (NCH₂CH₃).

¹³C NMR of the minor diastereomer (in part): δ 147.3 (C5'), 147.2 (C4'), 146.4 (C6), 128.9 (C2'), 126.1 (C8a), 113.6 (CH-5), 111.4 (CH-8), 68.5 (CH-2''), 64.6 (CH-1), 59.6

(CH₂-3''), 55.69 (CH-1), 46.8 (NCH₃), 37.8 (CH₂-7'), 37.7 (CH₂-1''), 25.2 (CH₂-4), 12.2 (NCH₂CH₃).

MS (ES⁺): *m/z* 486.7 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₈H₄₃N₂O₅, 487.3172 (MH⁺). Found 487.3195.

207.

R_f. 0.03 (CH₃OH : EtOAc).

m.p. 138-141 °C.

¹H NMR of the major diastereomer (500 MHz): δ 6.72 (s, 1H, H3'), 6.69 (s, 1H, H5), 6.59 (s, 1H, H6'), 6.43 (s, 1H, H8), 3.90 (m, 1H, H2''), 3.86 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.82 (s, 3H, OCH₃-4'), 3.79 (s, 3H, OCH₃-6), 3.70 (m, 1H, H1), 3.66 (dd, 1H, *J* 11.5, 3.5 Hz, H3''), 3.50 (dd, 1H, *J* 11.5, 6.5 Hz, H3''), 3.21 (m, 1H, H3), 3.13 (dd, 1H, *J* 14.0, 6.0 Hz, H7'), 2.85 (m, 1H, H3), 2.77 (m, 1H, H4), 2.72 (dd, 1H, *J* 14.0, 8.5 Hz, H7'), 2.65 (m, 2H, H1''), 2.58 (m, 1H, H4), 2.28 (s, 3H, NCH₃).

¹H NMR of the minor diastereomer (in part): δ 6.65 (s, 1H, H3'), 6.53 (s, 1H, H5), 6.36 (s, 1H, H6'), 6.13 (s, 1H, H8), 3.86 (s, 3H, OCH₃-7, OCH₃-5'), 3.73 (s, 3H, OCH₃-4'), 3.66 (m, 1H, H1), 3.52 (m, 1H, H2''), 3.54 (s, 3H, OCH₃-6), 3.00 (dd, 1H, *J* 14.0, 4.5 Hz, H7'), 2.85 (m, 1H, H3), 2.72 (dd, 1H, *J* 14.0, 8.5 Hz, H7'), 2.87 (m, 1H, H3), 2.70 (m, 1H, H4), 2.48 (s, 3H, NCH₃), 2.36 (m, 1H, H4).

¹³C NMR of the major diastereomer (125 MHz): δ 148.0 (C7), 147.7 (C5'), 147.3 (C6), 146.9 (C4'), 130.9 (C1'), 129.9 (C2'), 129.7 (C4a), 126.2 (C8a), 113.8 (CH-6', CH-3'), 111.5 (CH-8, CH-5), 73.2 (CH-2''), 68.0 (CH₂-3''), 66.1 (CH-1), 56.0 (4 x OCH₃), 46.6 (CH₂-3), 42.6 (CH₂-7'), 40.0 (CH₂-1''), 36.1 (CH₂-4).

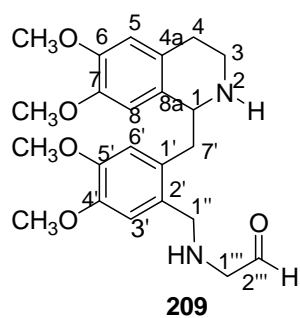
¹³C NMR of the minor diastereomer (125 MHz): δ 148.1 (C7), 147.8 (C5'), 147.6 (C6, C4'), 130.9 (C1'), 129.9 (C2'), 129.7 (C4a), 126.2 (C8a), 113.9 (CH-6'), 112.9

¹H NMR: (500 MHz) δ 6.84 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.60 (s, 1H, H6'), 6.54 (s, 1H, H8), 4.61 (t, 1H, J 5.0 Hz, H2'''), 4.19 (dd, 1H, J 8.0, 4.5 Hz, H1), 3.83 (s, 3H, OCH₃-7), 3.81 (s, 3H, OCH₃-5'), 3.80 (m, 2H, H3), 3.78 (s, 3H, OCH₃-4'), 3.75 (s, 3H, OCH₃-6), 3.65 (dq, 2H, J 14.5, 6.5, OCHHCH₃), 3.50 (dq, 2H, J 14.5, 6.5, OCHHCH₃), 3.22 (dd, 1H, J 13.5, 4.5 Hz, H7'), 3.07 (dd, 1H, J 12.5, 6.5 Hz, H1''), 2.86 (m, 2H, H7', H1''), 2.76 (d, 2H, J 5.0 Hz, H1'''), 2.76 (m, 2H, H4), 1.14 (t, 6H, J 6.5 Hz, 2 x OCH₂CH₃).

¹³C NMR: δ 147.7 (C4'), 147.3 (C6), 147.1 (C5'), 146.9 (C7), 130.1 (C2'), 129.5 (C8a), 129.1 (C1'), 127.1 (C4a), 113.1 (CH-5), 112.8 (CH-3'), 111.4 (CH-6'), 109.3 (CH-8), 101.6 (CH-2'''), 62.1 (2 x OCH₂CH₃), 55.8 (CH-1), 55.9 (OCH₃-7), 55.6 (OCH₃-5', OCH₃-4'), 55.5 (OCH₃-6), 51.4 (CH₂-1'''), 50.7 (CH₂-3), 40.4 (CH₂-1''), 38.6 (CH₂-7'), 28.8 (CH₂-4), 15.0 (2 x OCH₂CH₃).

MS (ES⁺): m/z 488.6 (MH⁺, 100 %).

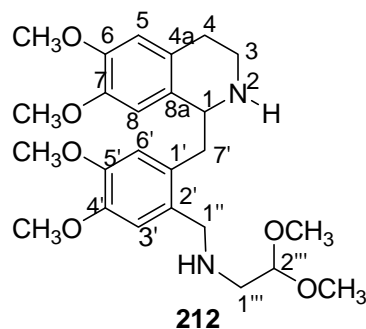
Attempted synthesis of (*RS*) 1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(2-oxoethylamino)methylphenyl]methyl-6,7-dimethoxyisoquinoline (209**).**



To a solution of **210** (71.3 mg, 0.146 mmol) in a mixture of CH₃OH (2 mL) and H₂O (1 mL) was added TsOH (75.3 mg, 0.438 mmol) to bring the pH to ~ 3. The reaction mixture was stirred at RT for 18 h. ESMS indicated only the unreacted **210**.

The reaction was heated at 80 °C for 18 h, however only the precursor **210** was recovered and none of the desired aldehyde **209** was obtained.

(*RS*) 1,2,3,4-Tetrahydro-1[4',5'-dimethoxy-2'-(2,2-dimethoxyethylamino)methyl phenyl]methyl-6,7-dimethoxyisoquinoline (212**).**



To a solution of the amine **210** (116 mg, 0.225 mmol) in CH₃OH (3 mL) was added 10 % aqueous HCl (1 mL).

The mixture was heated at reflux for 4 h. The solution was basified with K₂CO₃ (excess) to about pH ~6. The CH₃OH was evaporated and the residue was dissolved in

DCM. The solution was washed with H₂O (3 x), brine and dried (K₂CO₃) to give **212** (37 mg, 41 %) as a yellow oil.

R_f 0.1 (CH₃OH : EtOAc and NH₃ (5 : 5 : 0.1)).

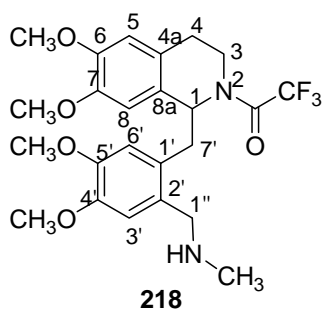
¹H NMR: δ 6.86 (s, 1H, H3'), 6.75 (s, 1H, H5), 6.65 (s, 1H, H6'), 6.60 (s, 1H, H8), 4.51 (t, 1H, *J* 5.3 Hz, H2'''), 4.26 (dd, 1H, *J* 8.7, 3.9 Hz, H1), 3.86 (s, 3H, OCH₃-7), 3.83 (s, 3H, OCH₃-5'), 3.81 (s, 3H, OCH₃-4'), 3.80 (m, 2H, H3), 3.79 (s, 3H, OCH₃-6), 3.37 (s, 6H, 2 x OCH₃), 3.27 (m, 1H, H7'), 3.11 (dd, 1H, *J* 12.6, 4.2 Hz, H1''), 2.91 (m, 2H, H7', H1''), 2.80 (dd, 2H, *J* 5.3, 2.1 Hz, H1'''), 2.68 (m, 2H, H4).

¹³C NMR: δ 148.4 (C4'), 148.3 (C6), 147.9 (C5'), 147.7 (C7), 133.4 (C2'), 129.4 (C8a), 128.6 (C1'), 127.6 (C4a), 114.7 (CH-5), 113.6 (CH-3'), 111.9 (CH-6'), 109.8 (CH-8), 103.8 (CH-2'''), 56.2 (OCH₃-7, OCH₃-5'), 56.1 (OCH₃-4', OCH₃-6), 54.6 (CH-8), 54.5 (2x OCH₃), 51.3 (CH₂-1'''), 53.9 (CH₂-3), 40.9 (CH₂-1''), 39.1 (CH₂-7'), 29.0 (CH₂-4).

MS (ES⁺): *m/z* 461.1 (MH⁺, 50 %).

Synthesis of amines 218 and 219.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(methylamino)methylphenyl]methyl-6,7-dimethoxyisoquinoline (218).



To a solution of the aldehyde **186** (136 mg, 0.290 mmol) and 33 % aqueous methylamine (0.05 mL) in CH₃CN (3 mL) was added NaCNBH₃ (24 mg, 0.377 mmol). The reaction was stirred at RT for 20 min before the pH was adjusted to ~ 6 using glacial acetic acid. The resulting solution was stirred for 18 h at RT. The CH₃CN was evaporated and the residue was dissolved in DCM. The solution was washed with H₂O (3 x), sat. Na₂CO₃, brine and dried (MgSO₄) to give an oil. The oil was purified by column chromatography (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)) to afford **218** as a clear oil (100 mg, 71 %). Compound **218** was a 95 : 5 mixture of rotamers.

R_f 0.35 (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)).

¹H NMR of the major rotamer (500 MHz): δ 6.83 (s, 1H, H3'), 6.57 (s, 1H, H5), 6.48 (s, 1H, H6'), 6.08 (s, 1H, H8), 5.53 (t, 1H, *J* 7.0 Hz, H1), 3.89 (dt, 1H, *J* 13.5, 4.5 Hz, H3), 3.82 (s, 3H, OCH₃-7), 3.80 (s, 3H, OCH₃-5'), 3.72 (s, 3H, OCH₃-4'), 3.69 (dt, 1H, *J* 13.5, 3.5 Hz, H3), 3.54 (s, 3H, OCH₃-6), 3.50 (bs, 2H, H1''), 3.11 (d, 2H, *J* 7.0 Hz, H7'), 2.89 (m, 1H, H4), 2.76 (m, 1H, H4), 2.37 (s, 3H, NCH₃).

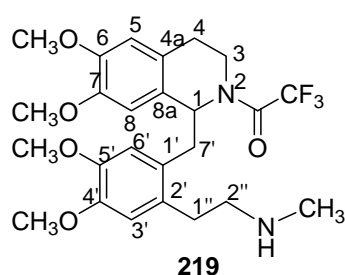
¹H NMR of the minor rotamer (in part): δ 6.77 (s, 1H, H3'), 6.53 (s, 1H, H5), 6.52 (s, 1H, H6'), 5.95 (s, 1H, H8), 5.09 (t, 1H, *J* 6.0 Hz, H1), 4.56 (dd, 1H, *J* 6.5 Hz, H3), 3.75 (s, 3H, OCH₃-5').

¹³C NMR of the major rotamer: δ 156.0 (q, *J* 36.5 Hz, C=O), 148.1 (C4'), 147.7 (C6), 147.7 (C5'), 147.2 (C7), 130.4 (C2'), 127.7 (C8a), 126.5 (C1'), 124.8 (C4a), 116.4 (q, *J* 287.5 Hz, C=O), 114.0 (CH-5), 112.7 (CH-3'), 110.9 (CH-6'), 110.6 (CH-

8), 58.9 (OCH₃-7), 55.8 (OCH₃-5'), 55.8 (OCH₃-4'), 55.6 (CH-1), 55.5 (OCH₃-6), 52.8 (CH₂-1''), 40.6 (CH₂-3), 37.8 (CH₂-7'), 36.0 (NCH₃), 28.4 (CH₂-4).

MS (ES⁺): *m/z* 483 (MH⁺, 30 %). **HRMS (ES⁺):** calcd for C₂₄H₃₀N₂O₅F₃, 483.2107 (MH⁺). Found 483.2135.

(RS) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(methylamino)ethyl phenyl]methyl-6,7-dimethoxyisoquinoline (219).



A mixture of aldehyde **187** (131 mg, 0.272 mmol) and 33 % aqueous methylamine (0.05 mL) in CH₃CN (3 mL) was added NaCNBH₃ (22 mg, 0.354 mmol). The mixture was treated as described above for the synthesis of **218** to give an oil. The oil was purified by column chromatography (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)) to afford **219** as a yellow oil (82 mg, 62 % yield). Compound **219** was a 95 : 5 mixture of rotamers.

R_f 0.25 (EtOAc : CH₃OH : NH₃ (5 : 5 : 0.1)).

¹H NMR of the major rotamer: δ 6.65 (s, 1H, H3'), 6.58 (s, 1H, H5), 6.53 (s, 1H, H6'), 5.98 (s, 1H, H8), 5.48 (t, 1H, *J* 6.0 Hz, H1), 3.93 (dt, 1H, *J* 13.5, 5.0 Hz, H3), 3.82 (s, 6H, OCH₃-7, OCH₃-5'), 3.73 (s, 3H, OCH₃-4'), 3.69 (td, 1H, *J* 12.5, 3.0 Hz, H3), 3.52 (s, 3H, OCH₃-6), 3.08 (d, 2H, *J* 6.0 Hz, H7'), 2.92 (m, 1H, H4), 2.78 (m, 1H, H4), 2.64 (t, 2H, *J* 6.5 Hz, H2''), 2.60 (m, 1H, H1''), 2.55 (dd, 1H, *J* 13.5, 6.5 Hz, H1''), 2.37 (s, 3H, NCH₃).

¹H NMR of the minor rotamer (in part): δ 6.62 (s, 1H, H3'), 3.78 (s, 3H, OCH₃-4'), 3.45 (s, 3H, OCH₃-6).

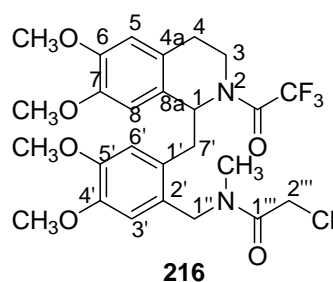
¹³C NMR of the major rotamer: δ 156.0 (q, *J* 36.9 Hz, COCF₃), 148.5 (C4'), 147.2 (C6), 147.5 (C5'), 147.4 (C7), 131.2 (C2'), 127.5 (C4a), 126.0 (C1'), 125.1 (C8a), 114.3 (CH-5), 116.9 (q, *J* 287.5 Hz, COCF₃), 112.9 (CH-3'), 111.2 (CH-6'), 110.9 (CH-

8), 56.2 (OCH₃-7), 55.6.1 (OCH₃-5'), 56.1 (OCH₃-4'), 55.9 (CH-1), 55.8 (OCH₃-6), 53.1 (CH₂-2''), 40.9 (CH₂-3), 38.2 (CH₂-7'), 36.3 (NCH₃), 32.4 (CH₂-1''), 28.7 (CH₂-4).

MS (ES⁺): *m/z* 497.1 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₅H₃₂N₂O₅F₃, 497.2263 (MH⁺). Found 497.2237.

Synthesis of chloro-*N*-methylacetamides 216 and 217.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(2-chloromethylcarbonyl)-*N*-methyl-aminomethyl]phenyl]methyl-6,7-dimethoxyisoquinoline (216).



To a solution of **218** (99 mg, 0.206 mmol) in dry DCM (5 mL) was added triethylamine (42 mg, 0.412 mmol, 0.06 mL) at 0 °C followed by chloroacetyl chloride (30 mg, 0.268 mmol, 0.02 mL). The reaction was brought to RT and stirred for 18 h. The DCM layer was diluted and extracted with 10 % aqueous NaOH, washed with H₂O (2 x) and brine. The DCM layer was dried (K₂CO₃) and evaporated to give an oil. The oil was purified by column chromatography (EtOAc) to give **216** (92 mg, 80 % yield) as a clear oil. Compound **216** was a 95 : 5 mixture of rotamers.

R_f. 0.67 (EtOAc).

¹H NMR of the major rotamer: δ 6.63 (s, 2H, H3', H6'), 6.58 (s, 1H, H5), 6.25 (s, 1H, H8), 5.45 (t, *J* 7.3 Hz, H1), 4.48 (d, 1H, *J* 14.7 Hz, H1''), 4.26 (d, 1H, *J* 14.7 Hz, H1'''), 4.01 (ABq, 2H, 6.6 Hz, H2'''), 3.66 (dd, 1H, *J* 4.5, 1.8 Hz, H3), 3.81 (s, 6H, OCH₃-7, OCH₃-5'), 3.79 (s, 3H, OCH₃-4'), 3.58 (m, 1H, H3), 3.62 (s, 3H, OCH₃-6), 3.18 (dd, 1H, *J* 13.5, 8.1 Hz, H7'), 2.95 (dd, 1H, *J* 13.5, 6.9 Hz, H7''), 2.85 (m, 2H, H4), 2.83 (s, 3H, NCH₃).

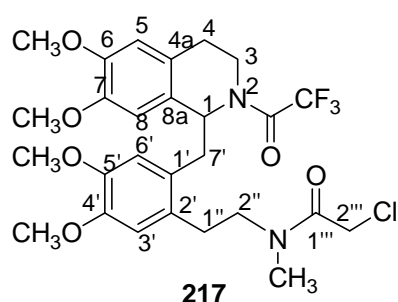
¹H NMR of the minor rotamer (in part): δ 6.50 (s, 1H, H5), 6.20 (s, 1H, H8).

^{13}C NMR of the major rotamer: (signals for COCF_3 and COCF_3 was not observed), δ 166.5 (COCH_2Cl), 148.7 ($\text{C4}'$), 147.4 (C7), 148.1 ($\text{C5}'$), 147.5 (C6), 128.8 ($\text{C2}'$), 127.4 ($\text{C1}'$), 126.5 (C4a), 125.1 (C8a), 114.4 ($\text{CH-3}'$), 113.4 ($\text{CH-6}'$), 111.1 (CH-5), 110.9 (CH-8), 56.3 ($\text{OCH}_3\text{-7}$), 56.1 ($\text{OCH}_3\text{-5}'$, $\text{OCH}_3\text{-4}'$), 56.0 ($\text{OCH}_3\text{-6}$), 55.4 (CH-1), 48.3 ($\text{CH}_2\text{-1}''$), 41.9 ($\text{CH}_2\text{-2}'''$), 40.8 ($\text{CH}_2\text{-3}$), 37.7 ($\text{CH}_2\text{-7}'$), 34.6 (NCH_3), 28.8 ($\text{CH}_2\text{-4}$),

^{13}C NMR of the minor rotamer (in part): δ 114.9 (CH-3), 113.6 ($\text{CH-6}'$), 111.3 (CH-5), 50.6 ($\text{CH}_2\text{-1}''$), 42.7 ($\text{CH}_2\text{-2}'''$), 41.1 ($\text{CH}_2\text{-3}$), 38.0 ($\text{CH}_2\text{-7}'$), 28.5 ($\text{CH}_2\text{-4}$).

MS (ES^+): m/z 581.0 ($\text{M}+\text{Na}^+$, 10 %). **HRMS (ES^+):** calcd for $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_6\text{F}_3\text{ClNa}$, 581.1642 ($\text{M}+\text{Na}^+$). Found 581.1641.

(*RS*) 2-Trifluoroacetyl-1,2,3,4-tetrahydro-1[4',5'-dimethoxy-2'-(*N*-(2-chloromethyl carbonyl)-*N*-ethyl-aminomethyl)phenyl]methyl-6,7-dimethoxyisoquinoline (217**).**



To a solution of **219** (73 mg, 0.152 mmol) in dry DCM (5 mL) was added triethylamine (31 mg, 0.304 mmol, 0.041 mL) at 0 °C, followed by chloroacetyl chloride (22 mg, 0.198 mmol, 0.013 mL). The reaction mixture was brought to RT and stirred for 18 h. The mixture

was worked up as described above in the synthesis of **216** to give an oil. The oil was purified by column chromatography (EtOAc) to give **217** (63 mg, 72 %) as a clear oil. Compound **217** was a 95 : 5 mixture of rotamers.

R_f 0.60 (EtOAc).

^1H NMR of the major rotamer: δ 6.61 (s, 1H, $\text{H3}'$), 6.58 (s, 1H, $\text{H6}'$), 6.55 (s, 1H, H5), 6.13 (s, 1H, H8), 5.46 (dd, 1H, J 8.4, 6.3 Hz, H1), 4.01 (s, 2H, $\text{H2}'''$), 3.90 (dt, 1H, J 5.4, 2.1 Hz, H3), 3.81 (s, 6H, $\text{OCH}_3\text{-7}$, $\text{OCH}_3\text{-5}'$), 3.79 (m, 1H, H3), 3.75 (s, 3H, $\text{OCH}_3\text{-4}'$), 3.57 (s, 3H, $\text{OCH}_3\text{-6}$), 3.45 (dt, 1H, J 9.6, 3.6 Hz, $\text{H2}''$), 3.25 (m, 2H, $\text{H2}''$, $\text{H7}'$), 3.18 (m, 1H, $\text{H7}'$), 2.97 (s, 3H, NCH_3), 2.82 (m, 2H, H4), 2.57 (m, 2H, $\text{H1}''$).

¹H NMR of the minor rotamer (in part): δ 6.59 (s, 1H, H3'), 6.40 (s, 1H, H5), 5.90 (s, 1H, H8), 5.36 (dd, 1H, J 9.3, 4.8 Hz, H1), 3.67 (s, 6H, OCH₃-7, OCH₃-5'), 3.63 (s, 3H, OCH₃-4'), 3.50 (s, 3H, OCH₃-6).

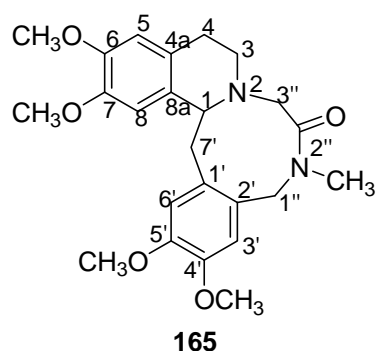
¹³C NMR of the major rotamer: (signals for $\underline{\text{COCF}}_3$ and $\text{CO}\underline{\text{CF}}_3$ were not observed), δ 116.1 ($\underline{\text{COCH}}_2\text{Cl}$), 148.1 (C4'), 147.9 (C7), 147.4 (C5'), 147.1 (C6), 129.8 (C2'), 127.6 (C1'), 126.3 (C4a), 124.8 (C8a), 114.0 (CH-3'), 112.8 (CH-6), 110.8 (CH-5), 110.6 (CH-8), 56.9 (OCH₃-7), 56.8 (OCH₃-5'), 55.8 (OCH₃-4'), 55.7 (OCH₃-6), 55.6 (CH-1), 50.4 (CH₂-2''), 41.3 (CH₂-2'), 40.5 (CH₂-3), 37.8 (CH₂-7'), 36.3 (NCH₃), 29.7 (CH₂-1'), 28.4 (CH₂-4).

¹³C NMR of the minor rotamer (in part): δ 129.2 (C2'), 127.2 (C1'), 125.1 (C8a), 114.4 (CH-3), 112.6 (CH-6'), 110.9 (CH-5).

MS (ES⁺): m/z 573.0 (MH⁺, 100 %), 575 (M+2H⁺, 40 %). **HRMS (ES⁺):** calcd for C₂₇H₃₃N₂O₆F₃Cl, 573.1979 (MH⁺). Found 573.1985.

Synthesis of nine and ten membered ring compounds 165-167.

(RS) 3-(1,2)-Benzena-5-(1,2)-isoquinolinacyclo-1-aza-7-oxo-heptaphane (165).



To a solution of **216** (92 mg, 0.165 mmol) in CH₃OH (4 mL) and H₂O (1 mL) was added K₂CO₃ (112 mg, 0.825 mmol), and the mixture was stirred at RT for 3 h. The CH₃OH was gently removed under pressure (without warming the water bath) to give an aqueous residue. To the mixture was added DCM (10 mL), followed by the addition of triethylamine (0.3 mL). The reaction was stirred for 18 h at RT. The DCM layer was washed with H₂O (3 x), brine and then dried (K₂CO₃). The solvent was

removed to give an oil which was purified by column chromatography (EtOAc) to give **165** (41 mg, 57 % yield) as a yellow oil.

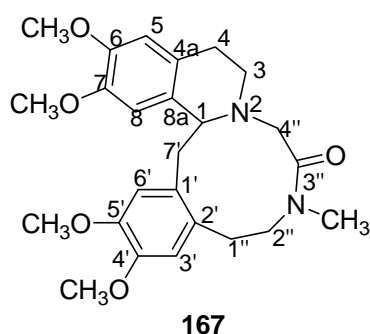
R_f 0.35 (EtOAc).

¹H NMR δ 6.69 (s, 1H, H3'), 6.61 (s, 1H, H5), 6.41 (s, 1H, H6'), 5.96 (s, 1H, H8), 4.22 (bs, 1H, H1''), 3.99 (t, 1H, *J* 7.0 Hz, H1), 3.88 (s, 3H, OCH₃-7), 3.82 (s, 3H, OCH₃-5'), 3.79 (s, 3H, OCH₃-4'), 3.52 (s, 3H, OCH₃-6), 3.52 (bs, 6H, OCH₃-6, H3'', H1''), 3.34 (m, 1H, H7'), 3.09 (s, 3H, NCH₃), 2.86 (dt, 1H, *J* 10.5, 3.6 Hz, H3), 2.77 (dd, 1H, *J* 14.0, 3.0 Hz, H7'), 2.56 (ddd, 1H, *J* 14.0, 10.5, 2.5 Hz, H3), 2.27 (bs, 2H, H4).

¹³C NMR δ 172.1 (C=O), 147.6 (C4'), 147.5 (C7), 147.4 (C5', C6), 130.0 (C2'), 129.8 (C1'), 129.2 (C4a), 129.0 (C8a), 115.0 (CH-8), 112.0 (CH-5), 111.0 (CH-6'), 110.4 (CH-3'), 64.0 (CH-1), 62.1 (CH₂-3''), 56.6 (OCH₃-7), 56.1 (OCH₃-5', OCH₃-4'), 55.8 (OCH₃-6), 54.5 (CH₂-1''), 49.7 (CH₂-3), 40.7 (CH₂-7'), 36.2 (NCH₃), 30.0 (CH₂-4).

MS (ES⁺): *m/z* 427.1 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₄H₃₁N₂O₅, 427.2233 (MH⁺). Found 427.2227.

(*RS*) 4-(1,2)-Benzena-6-(1,2)-isoquinolinacyclo-1-aza-8-oxo-octaphane (167).



The synthesis of the title compound **167** was carried out using the conditions described above for the synthesis of **165** starting with **217** (63 mg, 0.108 mmol), CH₃OH (3 mL), H₂O (1 mL) and K₂CO₃ (112 mg, 0.825 mmol).

This was followed by intramolecular cyclisation using DCM (10 mL) and triethylamine (0.3 mL) to give an oil which was purified by column chromatography (EtOAc) to give **167** (31 mg, 46 % yield) as a yellow oil.

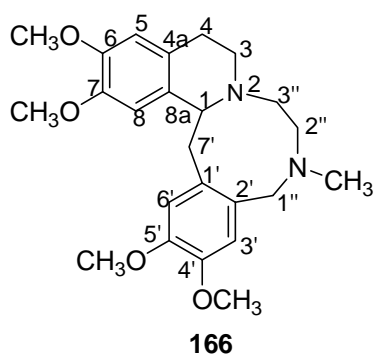
R_f 0.48 (EtOAc).

¹H NMR: δ 6.71 (s, 1H, H3'), 6.60 (s, 1H, H6'), 6.53 (s, 1H, H5), 6.36 (s, 1H, H8), 4.10 (m, 1H, H3), 4.01 (m, 1H, H3), 3.90 (s, 3H, OCH₃-7), 3.86 (s, 3H, OCH₃-5'), 3.85 (s, 3H, OCH₃-4'), 3.83 (m, 1H, H1), 3.70 (s, 3H, OCH₃-6), 3.47 (bs, 2H, H4''), 3.33 (m, 2H, H7'), 3.16 (m, 1H, H4), 3.05 (m, 1H, H4), 3.04 (s, 3H, NCH₃), 2.87 (m, 1H, H2''), 2.77 (m, 2H, H2'', H1''), 2.22 (m, 1H, H1'').

¹³C NMR: δ 171.4 (C=O), 148.5 (C4'), 147.9 (C7), 147.5 (C5'), 147.1 (C6), 131.7 (C2'), 131.6 (C1'), 128.6 (C4a), 127.9 (C8a), 114.7 (CH-8), 113.4 (CH-6'), 111.4 (CH-5), 110.6 (CH-3'), 65.1 (CH-1), 60.8 (CH₂-4''), 56.4 (OCH₃-7), 56.3 (OCH₃-5'), 56.2 (OCH₃-4'), 56.1 (OCH₃-6), 53.0 (CH₂-2''), 52.7 (CH₂-3, CH₂-7'), 35.3 (NCH₃), 33.8 (CH₂-1'', CH₂-4).

MS (ES⁺): m/z 441.1 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₅H₃₃N₂O₅, 441.2389 (MH⁺). Found 441.2380.

(RS)-3-(1,2)-Benzena-5-(1,2)-isoquinolinacyclo-1-aza-heptaphane (166).



To a slurry of LiAlH₄ (38 mg, 1.02 mmol) in dry THF (1 mL) was added a solution of the amide **165** (21 mg, 0.048 mmol) in dry THF (1 mL) under a N₂ atmosphere at 0 °C. The resulting mixture was brought to RT and stirred for 18 h. H₂O (0.2 mL), 1M aqueous NaOH (0.2 mL), H₂O (0.5 mL) were added subsequently and the

reaction was stirred for 1 h. The solid was filtered and washed with EtOAc. The solution was dried (K₂CO₃) and evaporated to give **166** (16 mg, 81 %) as a clear oil without the need for further purification.

R_f 0.15 (CH₃OH : EtOAc : NH₃ (5 : 5 : 0.1)).

¹H NMR δ 6.83 (s, 1H, H3'), 6.64 (s, 1H, H6'), 6.58 (s, 2H, H5, H8), 4.49 (d, 1H, *J* 13.0 Hz, H1''), 4.22 (bs, 1H, H1), 3.90 (s, 3H, OCH₃-7), 3.86 (OCH₃-5'), 3.85 (OCH₃-4'), 3.83 (OCH₃-6), 3.42 (d, 1H, *J* 13.0 Hz, H1''), 3.40 (m, 1H, H7'), 3.10 (m, 2H, H3, H3''), 2.79 (m, 3H, H3, H3'', H2''), 2.68 (dd, 1H, *J* 13.5, 1.5 Hz, H7'), 2.57 (m, 3H, H2'', H4), 2.52 (s, 3H, NCH₃).

¹³C NMR δ 147.6 (C4'), 147.4 (C7), 147.3 (C5'), 147.1 (C6), 134.0 (C2'), 132.2 (C1'), 131.5 (C4a), 127.5 (C8a), 114.4 (CH-3'), 113.8 (CH-6), 111.2 (CH-5), 110.7 (CH-8), 61.5 (CH-1), 58.1 (CH₂-1''), 56.2 (OCH₃-7), 56.0 (OCH₃-5'), 56.0 (OCH₃-4'), 55.8 (OCH₃-6), 52.0 (CH₂-2''), 51.9 (CH₂-3), 48.0 (CH₂-7'), 42.6 (NCH₃), 29.7 (CH₂-3''), 27.1 (CH₂-4).

MS (ES⁺): *m/z* 413.2 (MH⁺, 100 %). **HRMS (ES⁺):** calcd for C₂₄H₃₃N₂O₄, 413.2440 (MH⁺). Found 413.2406.

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