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Studies on the synthesis of the pyrido-azepine Stemona alkaloids

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Studies on the Synthesis of the Pyrido-Azepine *Stemona* Alkaloids

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"This thesis is presented as part of the requirements for the award of the Degree of Doctor of Philosophy of the University of Wollongong"

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CERTIFICATION

I, DAU XUAN DUC, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Chemistry, Faculty of Science, Medicine and Health, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

DAU XUAN DUC
August 2015

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ABSTRACT

The main aim of this project was to develop a new synthetic methodology towards the total synthesis of the pentacyclic *Stemona* alkaloid stemocurtisine by first preparation of a tricyclic A-B-C ring precursor and then its tetracyclic ether derivative by an oxidative photolysis reaction.

In Chapter 2, we report our efforts to construct the A-ring of stemocurtisine using three different synthetic strategies. Synthetic strategy 1 failed due to unexpected ring opening of the hemiaminal product formed from the reactions between alkynyl Grignard reagents and a glutarimide derivative. Synthetic strategy 2 was not efficient due to the unsucessful conversion of a terminal alkynyltrimethylsilane to its corresponding propiolate methyl ester following the method of Kondo. Using synthetic strategy 3 we obtained the racemic desired ene-yne lactam A-ring derivative in 11 synthetic steps and in 12.1% overall yield from 4-pentyne-1-ol. In Chapter 3, we describe our successful method to construct the bicyclic A-B ring system of stemocurtisine following Mori's ene-yne ring-closing metathesis procedure. The successful synthesis of the tricyclic A-B-C ring system of stemocurtisine is also discussed in this chapter. The synthesis of this tricyclic compound was achieved via a bromolactonization process using NBS/PhSeSePh followed by a base-catalysed elimination of the resulting bromolactone. Our attempts to reduce the resulting α,β-unsaturated lactone to its saturated derivative were not initially successful using the standard reducing reagents $NaBH_4/NiCl_2$ or $NaBH_4$/CuCl. However, reduction of this α,β-unsaturated lactone using Mg/MeOH provided the saturated lactone derivative as a single diastereomer having the desired relative configuration at C-1, C-3a, C-11, C-11a and C-11b as stemocurtisine. Making the ether bridge of stemocurtisine was examined on two different substrates, a tricyclic hydroxyl piperidinone and a tricyclic hydroxy piperidine. Treatment of the piperidinone substrate under oxidative photochemical conditions gave an unexpected aldehyde byproduct having an *O*-acetyl hemiaminal structure. Detailed NMR analysis of this compound indicated that the piperidinone had undergone oxidative cleavage to give a bicyclic compound. The structure of this compound is only

tenuous since the NMR spectroscopic and the MS spectromertic data were not consistent.

Chapter 4 reports on an alternative pathway to construct the A-B ring system and our attempts to make the A-B-C ring system of stemocurtisine. The key step of this approach involves the use of the borono-Mannich reaction to prepare a piperidine-diene. A RCM reaction of this compound led to the corresponding pyrrido[1,2-*a*]azepine. Esterification of the hydroxyl group followed by epoxidation of this bicyclic compound resulted in the corresponding epoxide. Base-catalysed cylization was then attempted to convert this epoxide ester to a tricyclic compound. Under several reaction conditions this attempted cyclization was not successful and only the unreacted starting material was recovered.

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List of Abbreviation

9-BBN	9-Borabicyclo[3,3,1]nonane
Ac	Acetyl
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
Ar	Aromatic
BAIB	Bis-acetoxy iodobenzene
Bn	Benzyl
Boc	*tert*-Butyloxylcarbonyl
b	broad
Bu	Butyl
Bz	Benzoyl
CAN	Ceric(IV) ammonium nitrate
Cbz	Benzyloxylcarbonyl
COSY	Correlation spectroscopy
Cy	Cyclohexyl
d	doublet
dd	doublet of doublet
δ	chemical shift
DBU	1,8 Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless Enhanced Proton spin Transfer
DIAD	Diisopropylazadicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIEA	Diiisopropylethylamine
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	*N*,*N*- Dimethylformamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
Et_3N	Triethylamine

EtOAc	Ethyl acetate
equiv	equivalent
Fmoc	Florenylmethyloxycarbonyl
h	hour
HMDS	Hexamethyldisilylamine
HMBC	Heteronuclear Multiple-Bond Correlation
HMPA	Hexamethylphosphoramide
HSQC	Heteronuclear Single-Quantum Correlation
Hz	Hertz
i	*iso*
IC_{50}	The concentration of a drug that is required for 50% inhibition
ID_{50}	The effective dose for 50% inhibition
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithiumdiisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LiOTf	Lithium trifluromethanesulfonate
m	multiplet
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
M	Molar
Me	Methyl
M.p	Melting point
Ms	Mesyl, Methanesulfonyl
MS	Mass spectrometry
MW	Microwave
M.S.	Molecular sieves
NBS	*N*-Bromo succinimide
*N*MO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
o	*ortho*

p	*para*
PCC	Pyridine chlorochromate
Pg	Protecting Group
Ph	Phenyl
Ph_3P	triphenylphosphine
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	Piridinium 4-toluenesulfonate
Pr	Propyl
p-Ts	tosyl, *para*-toluenesulfonyl
pyr	Pyridine
q	quartet
RCM	Ring closing metathesis
R_f	Relative mobility
rt	room temperature
s	singlet
t	triplet
t	*tert*
TBAF	*tetra*-*n*-butylammonium fluoride
TBAI	*tetra*-*n*-butylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxyl
Tf	Triflyl, Trifluromethanesulfonyl
TFA	Trifluroacetic acid
TFE	Trifluroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammoniumperruthenate
Ts	Tosylate

CHAPTER 1: INTRODUCTION

1.1 Stemona Alkaloids

1.1.1 Introduction to the *Stemona* alkaloids

The *Stemona* alkaloids represent a unique class of natural products exclusively isolated from the monocotyledonous family *Stemonaceae*, mainly distributed in South East Asia.[1] Structurally the alkaloids are characterised by the presence of either a pyrrolo[1,2-*a*]azepine (**Figure 1.1**, n = 1), the most common type, or a pyrido[1,2-*a*]azepine core structure (**Figure 1.1**, n = 2**).**[2]

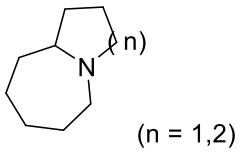


Figure 1.1: Core structure of the *Stemona* alkaloids

The *Stemonaceae* family consists of three genera, *Stemona*, *Croomia*, and *Stichoneuron*, comprising about 30 species. These plants are found in South East Asia, Northern Australia, China, Japan, and Northern America. *Stemona* is the largest genus with about 25 species mainly occurring as twinning herbs with perennial tuberous roots. Many species prefer a seasonal climate and occur in rather dry areas.[2]

Figure 1.2: Photograph of *Stemona japonica* [3]

Herbal extracts made from plants belonging to the *Stemonaceae* family have been used in folk medicine in East Asia for thousands of years, with three species of the *Stemona* genus (*S. tuberosa*, *S. japonica* and *S. sessilifolia*) being listed in the 2000 edition of the Chinese Pharmacopoedia as antitussive medicinal herbs.[4] In fact, the dried roots from these species, known as '*Bai Bu*' in Chinese traditional medicine, '*Bach Bo*' in Vietnam and '*Non Tai Yak*' or '*Pong Mot Ngam*' in Thailand, are used to suppress coughing, and are claimed to have antituberculosis, antibacterial, antifungal and antihelmintic properties.[5]

1.1.2 Structural classification

Based on biosynthetic considerations Greger[1] classified the *Stemona* alkaloids into three skeletal types: (I) stichoneurine-type (tuberostemonine-type); (II) protostemonine-type; and (III) croomine-type alkaloids. These three types differ by the carbon chains attached to C-9 of the pyrrolo[1,2-*a*]azepine nucleus (**Figure 1.3**).

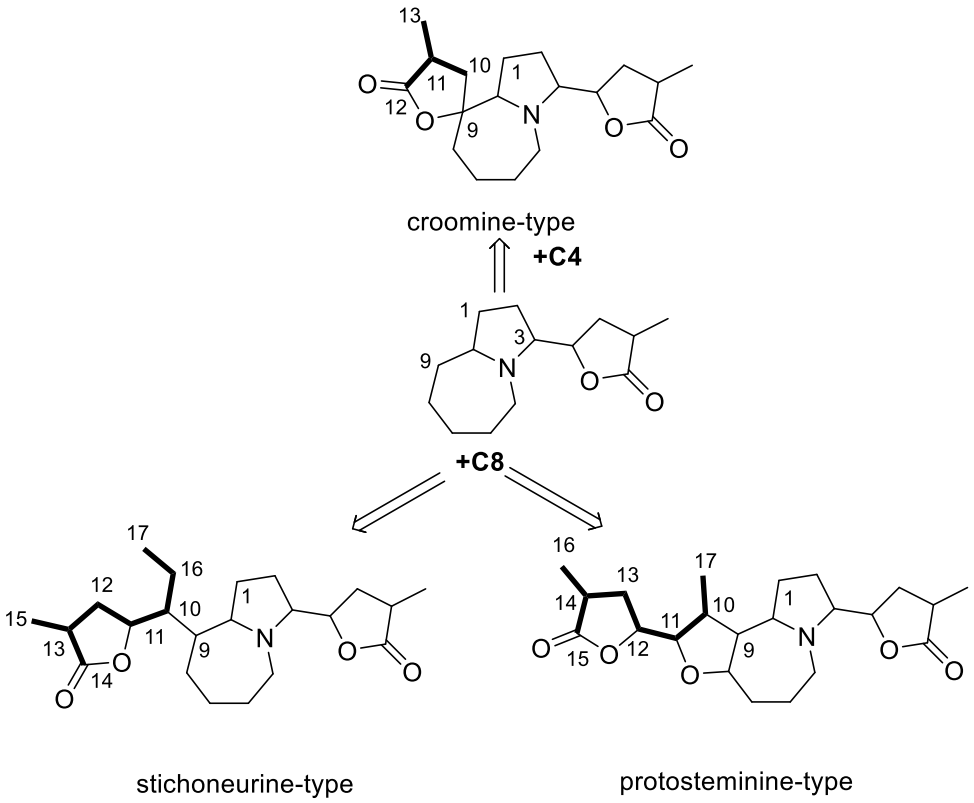


Figure 1.3: Greger's classification of the *Stemona* alkaloids[1]

In 2010 Pilli organized the *Stemona* alkaloids into eight different structural groups (**Figure 1.4**): stenine (**I**); stemoamide (**II**); tuberostemospironine (**III**); stemoamine (**IV**); parvistemoline (**V**); stemofoline (**VI**); stemocurtisine (**VII**); and a miscellaneous group (**VIII**), formed from those alkaloids which do not display the structural motifs mentioned above, or are the sole representative of a new group.[2] Groups **I**-**VII** are shown in **Figure 1.4**. Representative examples of the eight groups are shown in **Figure 1.5**.

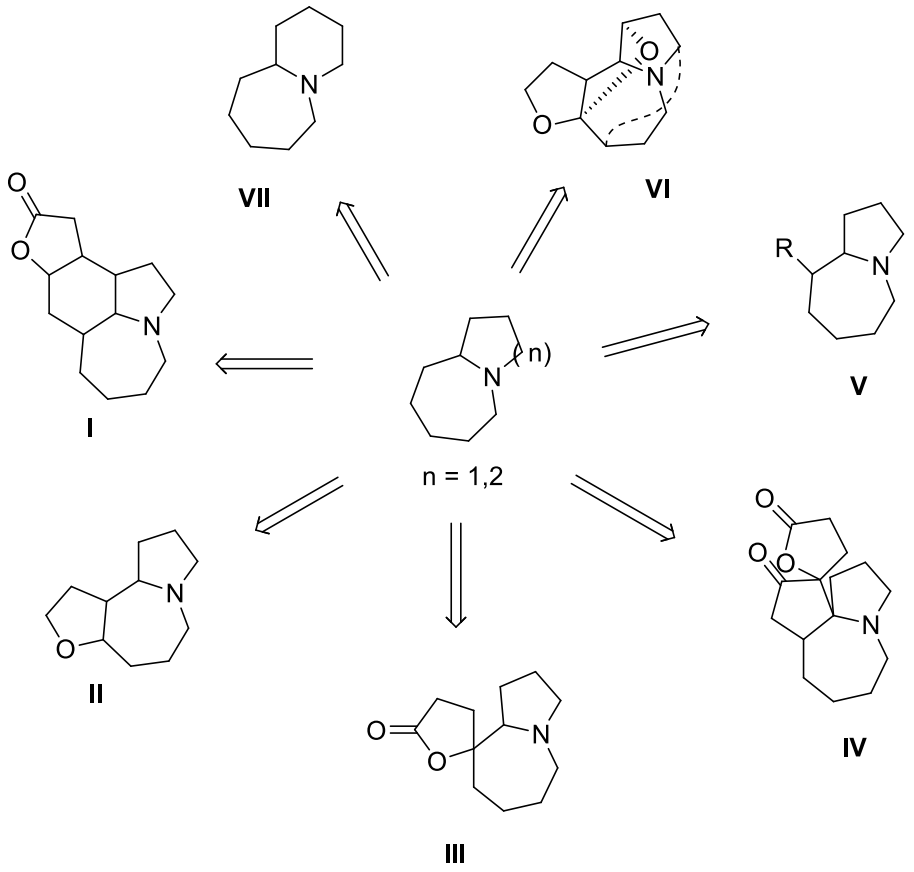


Figure 1.4: Pilli's classification of the *Stemona* alkaloids[2]

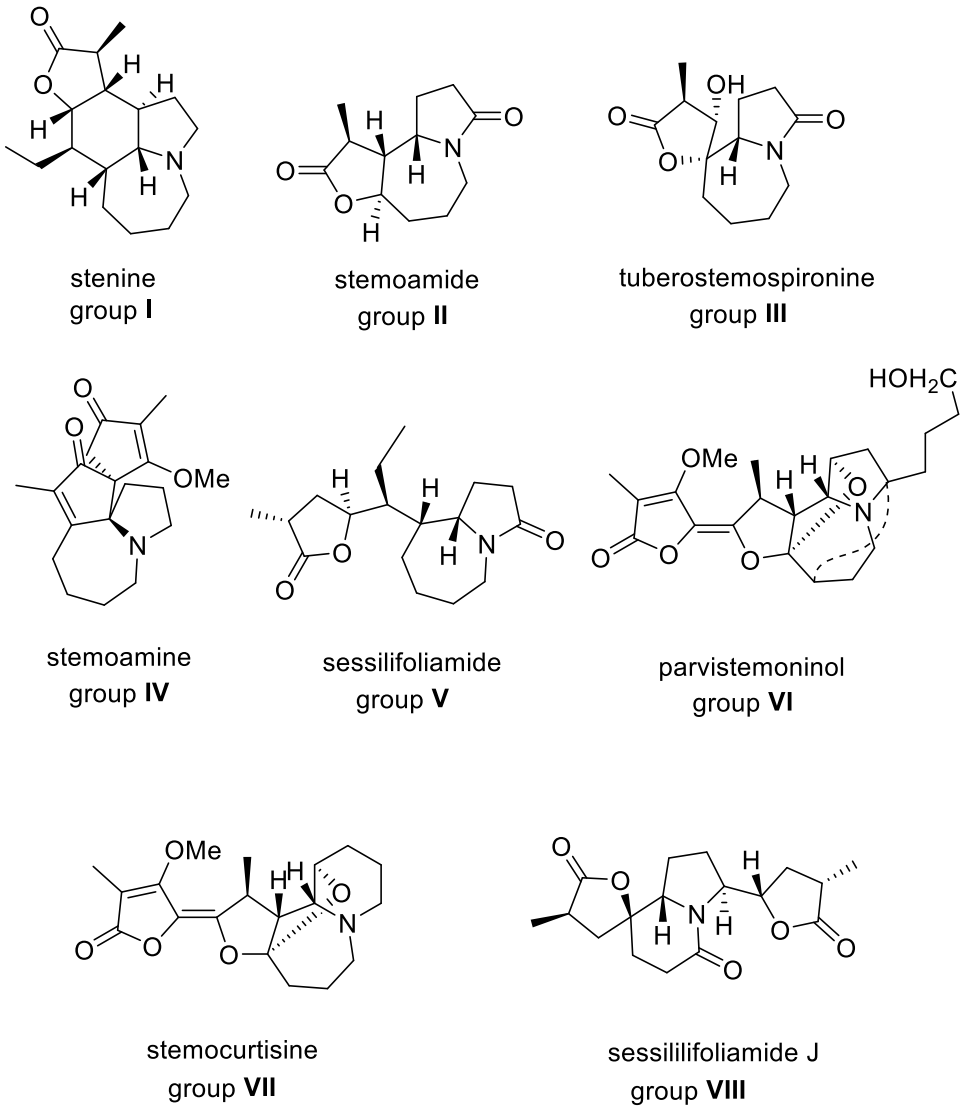
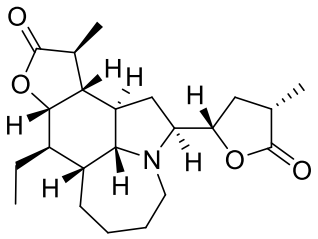


Figure 1.5: Representative alkaloids of the eight groups of *Stemona* alkaloids

1.1.3 Isolation and bioactivities

The first *Stemona* alkaloid isolated was tuberostemonine **1**, from *S. tuberosa* by Suzuki[6] in 1934, but only until 1967 was its structure fully elucidated.[7] It was also the first *Stemona* alkaloid to be tested for its biological activity. The althelminthic activity of this alkaloid was determined against *Angiostrongylus cantonensis, Dipylidium canium,* and *Fasciola hepatica*. This alkaloid affected the mobility of these helminthic worms.[8] Tuberostemonine was identified as the bioactive principle responsible for the insectidal activity of *S. tuberosa* against the larvea of *Spodoptera*

littoralis, with activity levels comparable to those of the commercial insecticide azadirachtin.[9]

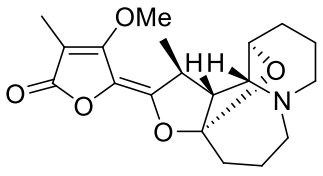


tuberostemonine **1**

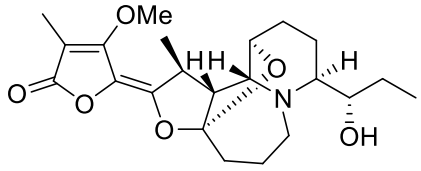
Figure 1.6: Tuberostemonine, the first isolated *Stemona* alkaloid

More than 190 *Stemona* alkaloids have now been isolated and structurally elucidated, some of them have significant bioactivities.[1,2a] In this section, we discuss some recent publications concerned with both the isolation and biological activities of the *Stemona* alkaloids.

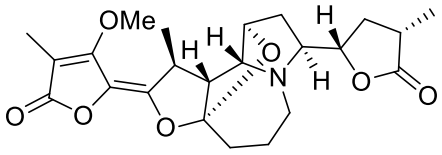
The Pyne group and collaborators in Thailand isolated two new *Stemona* alkaloids, stemocurtisine **2**[10] and stemocurtisinol **3**,[11] which possessed a new pyrido[1,2-*a*]azepine skeleton, along with oxyprotosteminine **4** (**Figure 1.7**) from the roots of *S. curtisii* in 2003-2004. These compounds were shown to exhibit good larvicidal activity on malarial carrying mosquito larvae. The isolated alkaloids were significantly more active than the crude extract. Among them, oxyprotostemonine **4** was the most potent (**Table 1.1**).



stemocurtisine **2**



stemocurtisinol **3**



oxyprotostemonine **4**

Figure 1.7: *Stemona* alkaloids isolated by the Pyne group[10,11]

Treatment	LC_{50} (ppm)
Ethanol crude extract	81
Stemocurtisine **2**	18
Stemocurtisinol **3**	39
Oxyprotostemonine **4**	4

Table 1.1: Larvicidal activity of *S. curtisii* extract and compounds **2-4** on mosquito larvae [11]

The Greger group isolated eight new *Stemona* alkaloids, stemokerrin **5**, methoxystemokerrin-*N*-oxide **6**, oxystemokerrin **7**, oxystemokerrin-*N*-oxide **8**, pyridostemin **9** (stemocurtisine **2**), dehydroprotostemonine **10**, oxyprotostemonine **4** and stemocochinine **11** (**Figure 1.7**) from four *Stemona* species together with four known compounds stemofoline **12**, 2'-hydroxystemofoline **13**, protostemonine **14**, and parvistemonine **15**. Alkaloids **5**-**9** all had the pyrido[1,2-*a*]azepine core structure. Pyridostemine **9** was the same as stemocurtisine **2**. These alkaloids were tested for toxicity and growth inhibition against neonate larvae of *Spodostera littoralis* in comparison with the most active derivative 1',2'-didehydrostemofoline. Among these alkaloids, stemofoline **12** was the most toxic, followed by oxystemokerrin **7** (IC_{50} values of 2.0 and 5.9 ppm, respectively).[12]

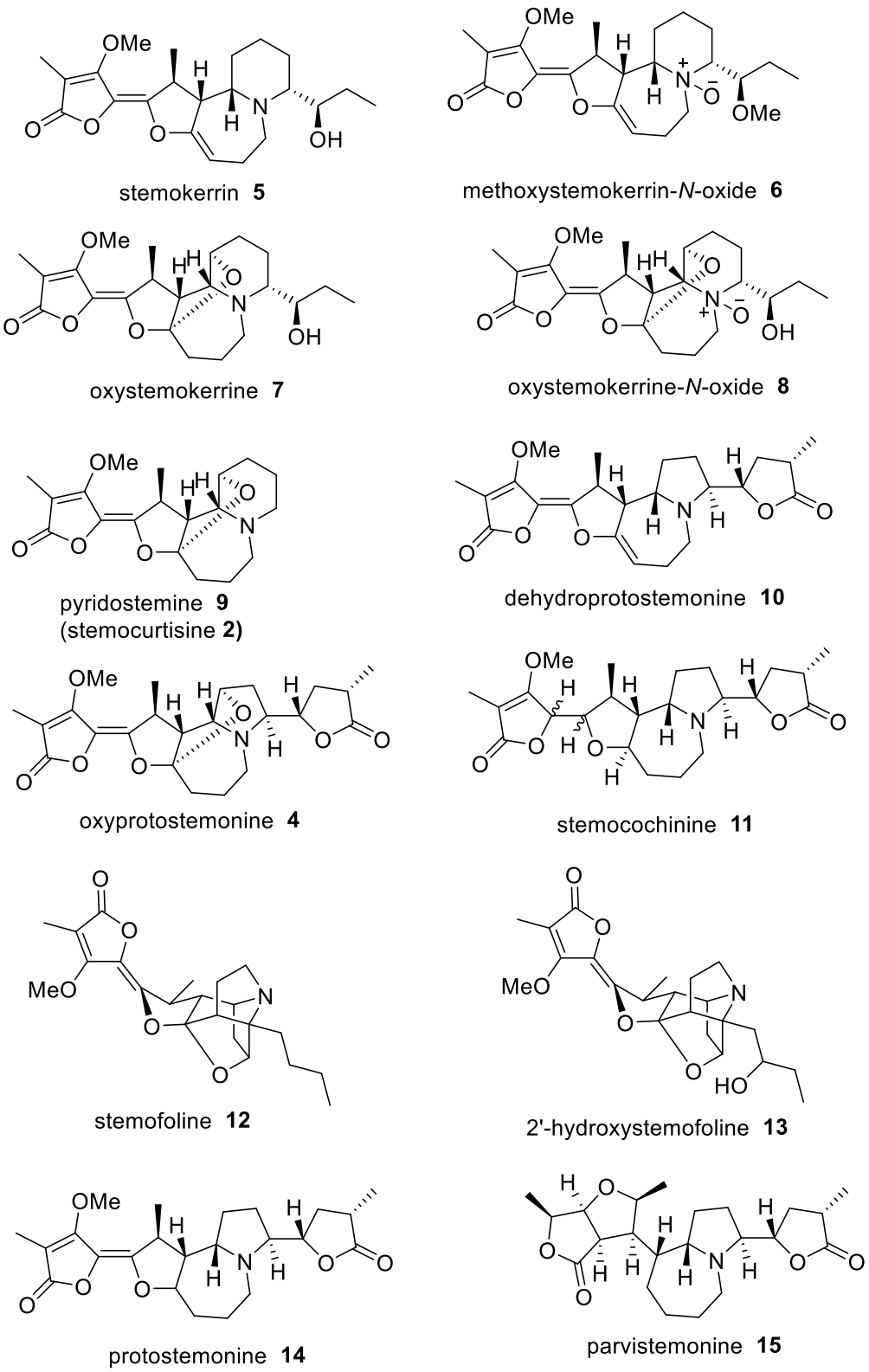


Figure 1.8: *Stemona* alkaloids isolated by the Greger group[12]

In 2007, Yang and collaborators isolated five new *Stemona* alkaloids; 6β-hydroxystemofoline **16**, 16-hydroxystemofoline **17**, neostemofoline **18**, protostemodiol **19** and 13-demethoxy(11*S**,12*R**)-dihydroprotostemonine **20** (**Figure 1.9**). These alkaloids, together with stemofoline **12** were tested *in vitro* on neurons isolated from the pest insect *Heliothis virescens*. All of them were active. Compounds **16**-**18** and stemofoline **12** acted as agonists, whereas **19** and **20** were antagonists at the insect nicotinic acetylcholine receptors (nAChRs). The authors indicated that the significant insectidal activities of the stemofolines may be related to the defence system of the *Stemona* plants.[13]

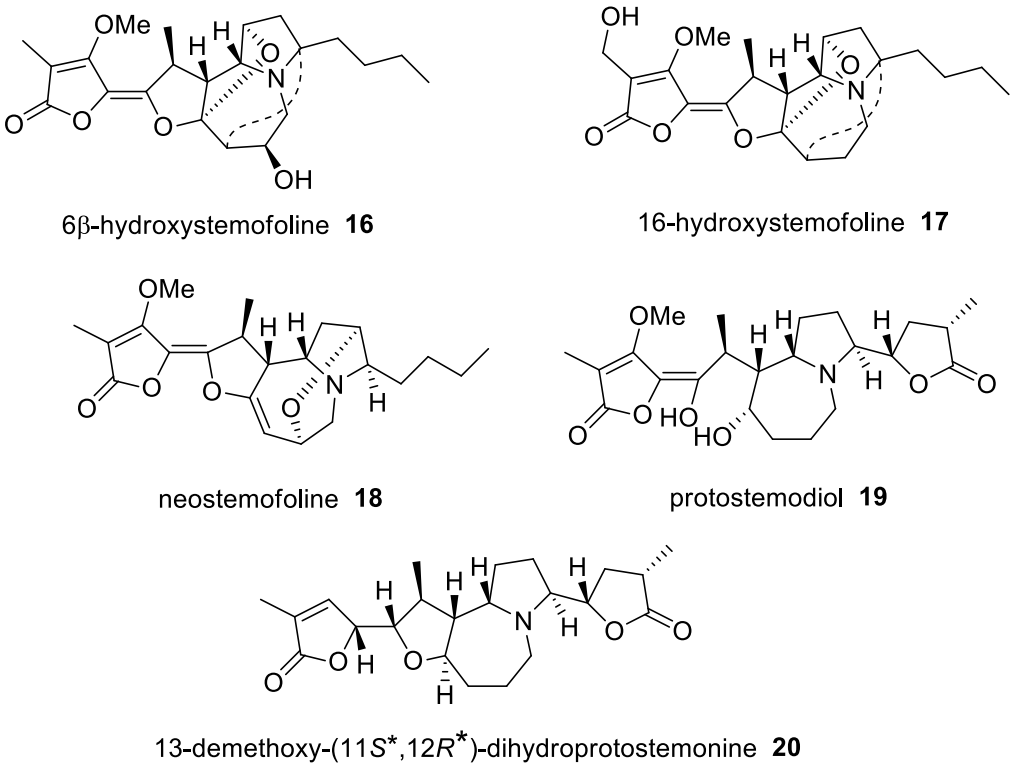
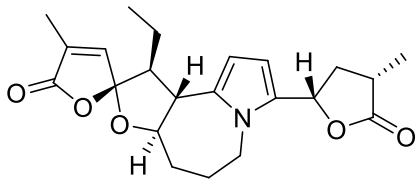


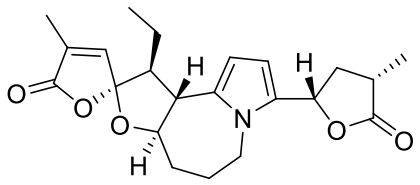
Figure 1.9: Five new *Stemona* alkaloids from the leaves of *S. japonica*[13]

In 2005, the Lin group isolated and structurally elucidated five new *Stemona* alkaloids, bisdehydrostemoninine **21**, isobisdehydrostemoninine **22**, bisdehydroneostemonine **23**, and bisdehidrostemoninine A **24** and B **25** from the roots of *S. japonica* (**Figure 1.10)**.[14] Compound **21** displayed significant antitussive activity in the citric acid-induced guinea pig cough model (ID_{50} = 188 ± 13 μM). Later the same group isolated seven new *Stemona* alkaloids, tuberocrooline **26**, 10-

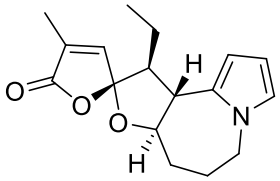
hydroxycroomine **27** (R = OH), dehydrocroomine **28**, tuberostemoline **29**, tridehydrotuberosteminine **30**, 9α-bisdehydrotuberostemonine **31** and 9α-bisdehydrotuberostemonine A **32 (Figure 1.11**) from the leaves of same species. Two of these alkaloids, compounds **26** and **27** (R = OH), along with croomine **27** (R = H) and tuberospironine (two of ten known *Stemona* alkaloids isolated at the same time) were tested for antitussive activity employing the same method. Croomine **27** (R = H) was the most active compound showing a dose-dependent inhibition of coughing with an ID_{50} value of 0.18 mmol/kg.[15] This group also successfully isolated five new alkaloids from the roots of *S. tuberosa*. These were, stemoenonine **33**, 9a-*O*-methylstemoenonine **34**, oxystemoenonine **35**, 1,9a-*seco*-stemoenonine **36** and oxystemonine **37** (**Figure 1.12**) along with a known compound stemoninoamide **38**. Alkaloids **33**, **34**, **38** and stemoninine **39** were screened for their antitussive activities. Compounds **38** and **39** exhibited strong antitussive activity after oral and intraperitoneal administrations (ID_{50} = 0.33 and 0.26 mmol/kg, respectively).[16]



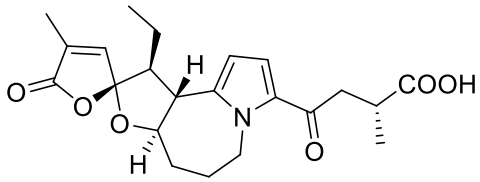
bisdehydrostemoninine **21**



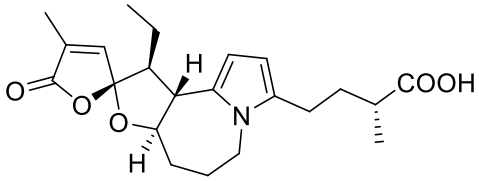
isobisdehydrostemoninie **22**



bisdehydroneostemoninine **23**



bisdehydrostemonines A **24**



bisdehdrostemoninines B **25**

Figure 1.10: Alkaloids isolated by the Lin group from the roots of *S. japonica*[14]

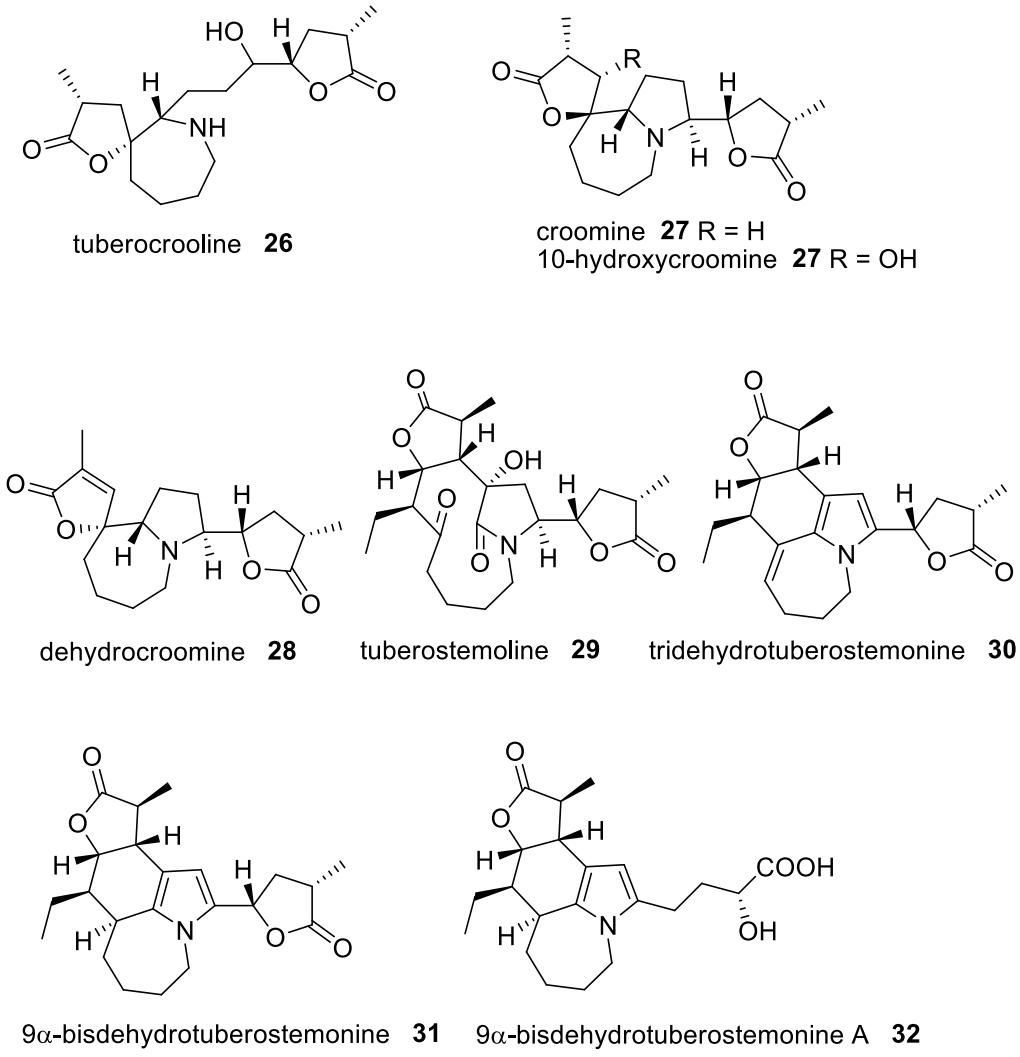


Figure 1.11: *Stemona* alkaloids from the leaves of *S. japonica*[15]

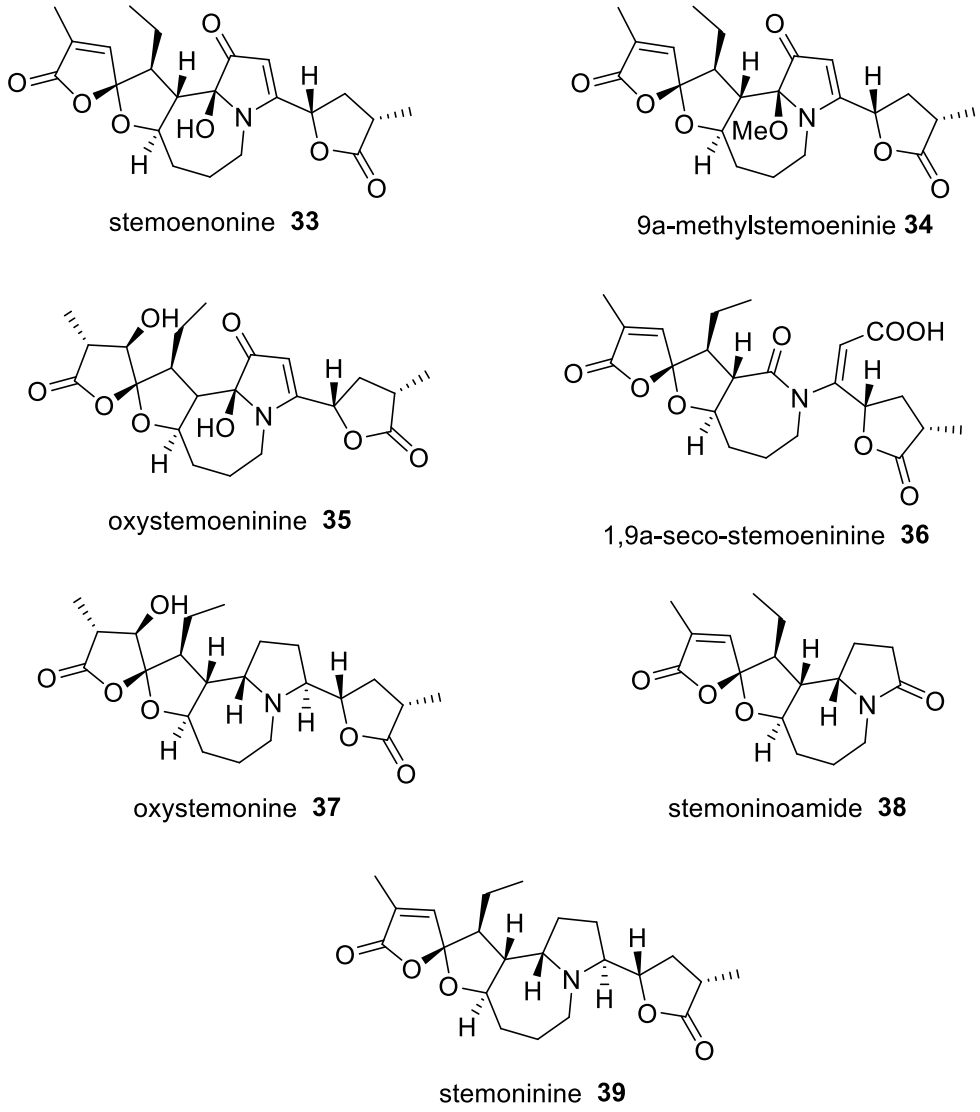
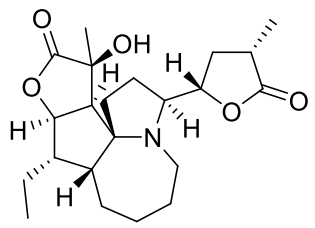
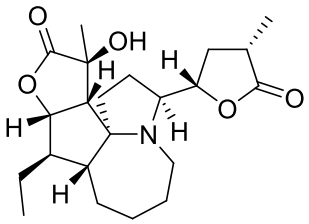


Figure 1.12: Alkaloids isolated by the Lin group from the roots of *S. tuberosa*[16]

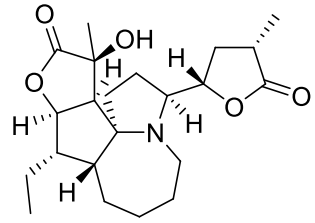
Another important bioactivity of the *Stemona* alkaloids is their acetylcholinesterase (AChE) inhibitory properties. Four new alkaloids, sessilistemonamine A-C **40-42** and dihydrostemoninine **43** (**Figure 1.13**) were isolated from the roots of *S. sessilifolia* and tested for this property by Wang and collaborators.[17] Compounds **40** and **41** were moderately active (IC_{50} values of 68.8±9.5 and 17.1±2.5 μM, respectively) but much less than huperzine A (IC_{50} = 0.021±0.016 μM), which was used as the positive control.



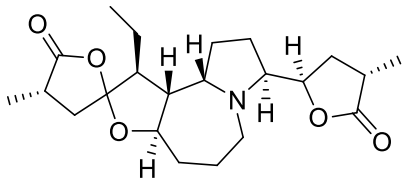
sessilistemonamine A **40**



sessilistemonamine B **41**



sessilistemonamine C **42**



dihydrostemoninie **43**

Figure 1.13: Four new *Stemona* alkaloids isolated by the Wang group[17]

In 2013, the Pyne group isolated three new *Stemona* alkaloids: stichoneurine C **44**, stichoneurien D **45** and stichoneurine E **46** from *Stichoneuron halabalensis* along with known compounds (+)-α-tocopherol **47** and (*R*)-(+)-goniothalamin **48 (Figure 1.14)**, and four known *Stemona* alkaloids, bisdehydoxystemoninine A **24**, stemoninine **39**, sessilistemonamine C **42** and sessilistemonamine A **40**. Except for compounds **44** and **45**, they were tested as inhibitors of electric eel and human AChE. Compounds **24**, **39** and **48** showed significant inhibitory activity against human AChE (IC_{50} values of 5.52±0.13; 3.74±0.09; and 7.24±0.52 μM, respectively) but were less active than galantamine (IC_{50} = 0.54±1.25 μM), the positive control.[18] Later, the same group obtained two more new *Stemona* alkaloids, javastemonine A **49** and javastemonine B **50**, together with known alkaloids 13-demethoxy-(11*S**,12*R**)-dihydroprotostemonine **20**, stemocochinine **11** and isoprotostemonine **51** (**Figure 1.15**) from *S. javanica*. All compounds except for **44** were tested for antiplasmodial and hAChE inhibitory activities and their cytotoxicities. Compounds **20** and **51** demonstrated moderate *in vitro* antiplasmodial activity against two *P. falciparum* strains (IC_{50} values of 17.7±3.7 and 16.0±4.2 μg/mL, respectively). However none of these compounds showed mammalian cell line cytotoxicities against KB or Vero cells or AChE inhibitory activity.[19]

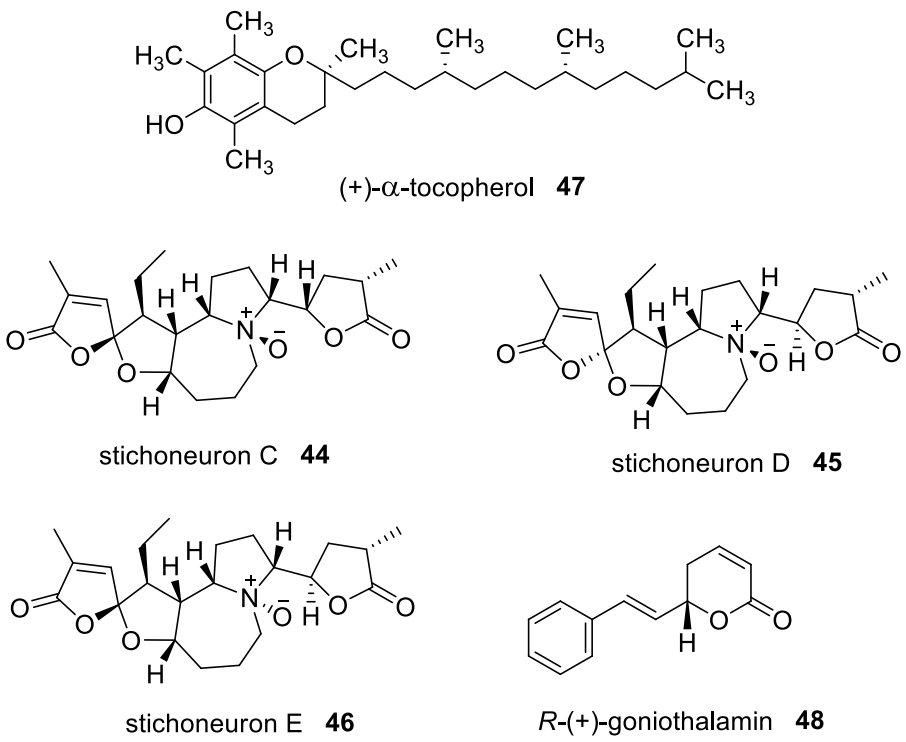


Figure 1.14: *Stemona* alkaloids and known compounds from *S. halabalensis*[18]

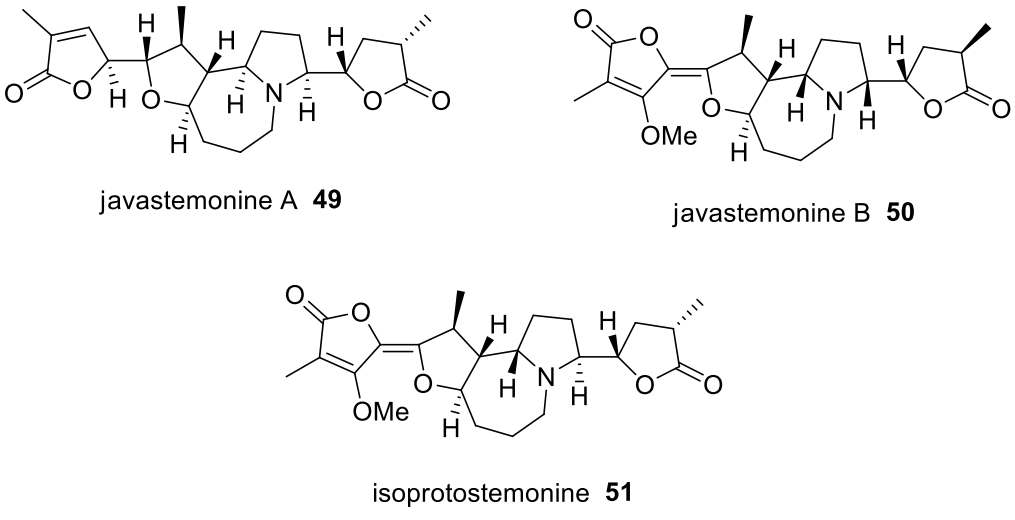


Figure 1.15: *Stemona* alkaloids from *S. javanica*[19]

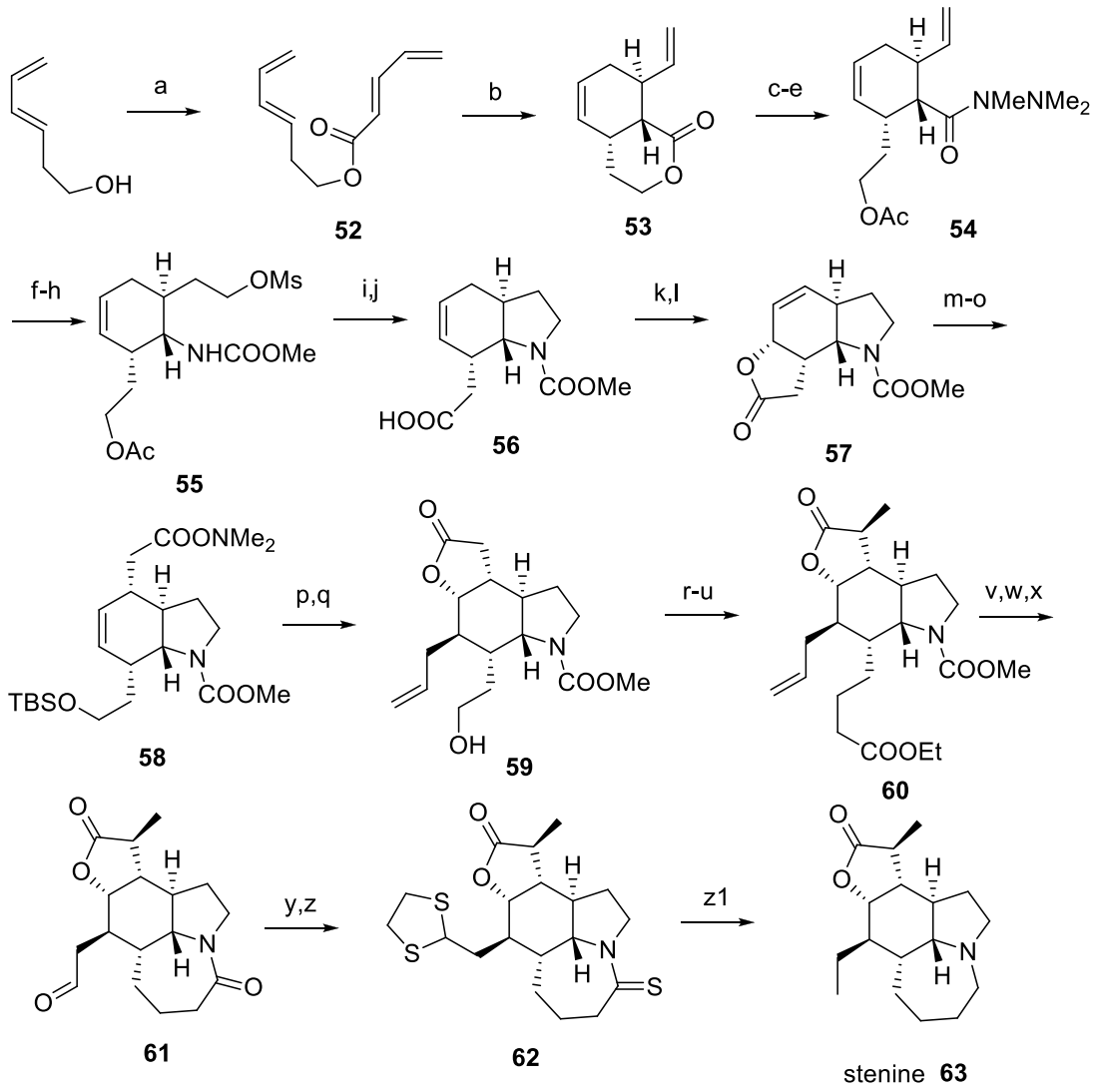
1.1.4 Synthesis of the *Stemona* alkaloids.

The interesting biological activities and synthetically challenging polycyclic structures of the *Stemona* alkaloids have prompted numerous synthetic studies and the total synthesis of many *Stemona* alkaloids have been reported.[2a,b,c] Herein, we review the total syntheses of selected *Stemona* alkaloids, one from each of the structural groups defined by Pilli.[2]

1.1.4.1 The total synthesis of Stenine 63

Stenine, a representative group **I** *Stemona* alkaloid, was first synthesized by Hart *et al*. in 1993.[20] The synthesis started from (*E*)-3,5-hexendienol, which was treated sequentially with *n*-BuLi and (*E*)-2,4-pentadienoyl chloride to give the ester **52** quantitatively (**Scheme 1.1**). Heating a solution of **52** in toluene at reflux temperature in the presence of the Lewis acid Et_2AlCl gave the bicyclic lactone **53** via an "*endo*"-type transition state. Treatment of this lactone with hydrazine provided an acyl hydrazine, which was exhaustively *N*-methylated (K_2CO_3, MeI) and then acetylation of the resulting primary alcohol provided the acetate **54**. Thermolysis of **54** by heating at reflux in mesitylene followed by addition of methanol to the intermediate isocyanate gave a methyl carbamate. Hydroboration of the terminal alkene of this carbamate using 9-BBN followed by oxidation with $NaBO_3.4H_2O$ gave the primary alcohol, which was then converted to the primary mesylate **55**. Cyclization of this compound to an indoline was achieved by treatment with MeLi, which acted as a base to deprotonate the carbamate NH and generated the nucleophilic *N*-lithiated species. Under these conditions, the acetyl group was also cleaved. Jones' oxidation of the resulting alcohol provided the acid **56**, which was transformed into the lactone **57** by iodo-lactonization followed by dehydrohalogenation using DBU. Before treatment with *N*,*N*-dimethylacetamide dimethyl acetal giving **58**, *via* a Claisen rearrangement reaction, the lactone was reduced with $NaBH_4$, followed by protection of the resulting primary alcohol as a TBS ether. Treatment of **58** with I_2 gave the corresponding *trans*-iodo-lactone with loss of the TBS group, which was converted to **59** by a free radical Keck allylation reaction with allyltributyl stannane/AIBN. α-Methylation of the lactone (LDA, MeI) of **59**, followed by Swern oxidation of the

primary alcohol afforded the corresponding aldehyde, which was transformed to **60** by Wittig olefination ($Ph_3P=CHCO_2Et$) and 1,4-reduction (Red-Al, CuBr) of the double bond.



Reaction conditions: (a) BuLi, Et_2O, then $CH_2CHCHCHCOCl$, -78 °C to rt, (100%); (b) Et_2AlCl, toluene, (49%); (c) NH_2NH_2, MeOH, reflux, (87%); (d) K_2CO_3, MeI, reflux, (100%); (e) CH_3COCl, 0 °C to rt, (100%), (f) mesitylene, reflux, then MeOH, reflux, (94%), (g) 9-BBN, THF, 0 °C to rt, (95%); (h) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, (100%), (i) MeLi , THF, -78 °C to rt, (94%); (j) Jones' reagent, acetone, 0 °C, (83%); (k) I_2, THF-H_2O- aq. $NaHCO_3$, 0 °C to rt, (95%); (l) DBU, toluene, reflux, (98%); (m) $NaBH_4$, 2-methyl-2-propanol, MeOH, 50 °C then rt, (100%); (n) TBSCl, DMAP, Et_3N, CH_2Cl_2, (97%); (o) *N, N*-dimethylacetamide dimethyl acetal, reflux, (93%); (p) I_2, THF-H_2O, (75%); (q) , allyltributyltin, AIBN, benzene, reflux, (83%), (r) LDA, THF, MeI, HMPA, -78 °C, (87%); (s) ClCOCOCl, DMSO, CH_2Cl_2, -78 °C, (99%); (t) $Ph_3P=CHCOOEt$, $CHCl_3$, reflux, (91%); (u) Red-Al, CuBr, THF-*t* BuOH, -78 °C, (85%); (v) Me_3SiI, $CHCl_3$, rt, (94%); (w) mesitylene, reflux, (91%); (x) OsO_4, $NaIO_4$, THF-H_2O, (84%); (y) $HSCH_2CH_2SH$, SiO_2-$SOCl_2$, CH_2Cl_2, rt, (100%); (z) Lawesson's reagent, CH_2Cl_2, rt, (100%), (z1) W-2 Raney nickel, C_2H_5OH, reflux, (80%)

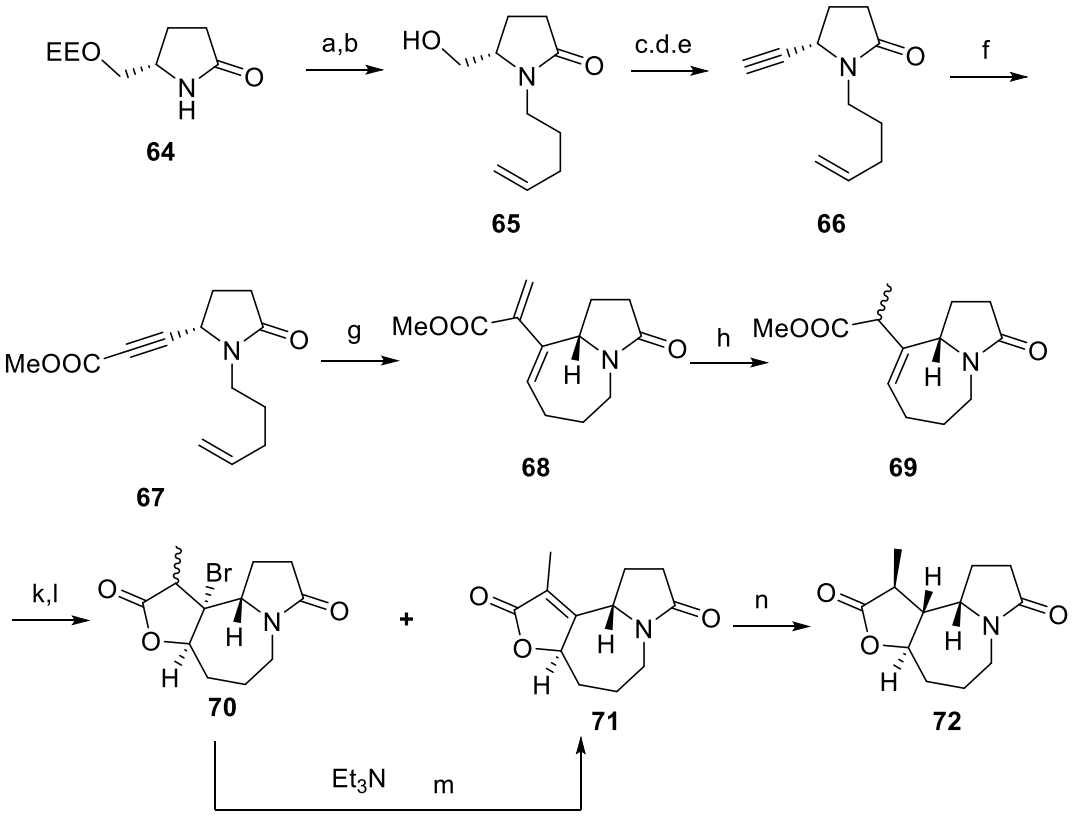
Scheme 1.1: Hart's synthesis of stenine **63**[20]

The carbamate group of **60** was removed by treatment with TMSI in $CHCl_3$ and then cyclization of the resulting amino-ester to the lactam was achieved by heating at reflux temperature in mesitylene. Dihydroxylation of the terminal alkene of the resulting tetracyclic product, followed by oxidation by $NaIO_4$ provided aldehyde **61**. This was converted to a thioketal before treatment with Lawesson's reagent providing thiolactam **62**. The synthesis was completed by the reduction of the thioketal and thiolactam over Raney Ni affording stenine **63**, in 27 synthetic steps from (*E*)-3,5-hexendienol (**Scheme 1.1)**.[20] Stenine has also been synthesized by Wifp,[21] Aubé,[22] Padwa,[23] Morimoto,[24] Zhang,[25] and Fujioka.[26]

1.1.4.2 The total synthesis of stemoamide 72

Stemoamide **72**, the simplest group **II** *Stemona* alkaloid, has attracted considerable synthetic attention. Mori and Kinoshita[27] completed the total synthesis of this alkaloid in 14 steps with 9% overall yield from (-)-pyroglutamic acid (**Scheme 1.2**). Their synthesis started from compound **64**, which was prepared from pyroglutamic acid as described in the literature.[28] *N*-alkylation of the sodium salt of **64** with 5-bromo-1-pentene proceeded smoothly in DMF and was followed by hydrolysis of the ethoxy ethyl (EE) group with TsOH in MeOH to afford alcohol **65**. Swern oxidation of **65** was followed by treatment with CBr_4 and PPh_3 to provide the corresponding 1,1-dibromoalkene, which was treated with *n*-BuLi at -98 ºC to produce the ene-yne **66**. The terminal alkyne of **66** was deprotonated by LDA and reacted with methyl chloroformate (ClCOOMe) to furnish the methyl ester **67**. Treatment of this ene-yne with Grubbs' 1st generation ruthenium catalyst led to the bicyclic compound **68** via an ene-yne ring-closing metathesis (RCM) reaction. The structures of Grubbs' 1st and 2nd generation ruthenium catalysts are shown in **Figure 1.16**. 1,4-Hydride reduction of the enoate group of **68** with $NaBH_4$ in MeOH gave **69** as an inseparable mixture of diastereoisomers. These esters were converted to their corresponding acids, which underwent bromo-lactonization by treatment with $CuBr_2$ on alumina to form a mixture of lactones **70** and **71**. Bromide **70** underwent hydrogenbromide elimination to form **71** by treatment with Et_3N. Stereoselective 1,4-reduction of **71** by $NaBH_4$ in MeOH in the presence of $NiCl_2.7H_2O$ then furnished stemoamide **72** (**Scheme 1.2**). The mechanism of this reduction reactions is discussed in more detail in Chapter **4** of

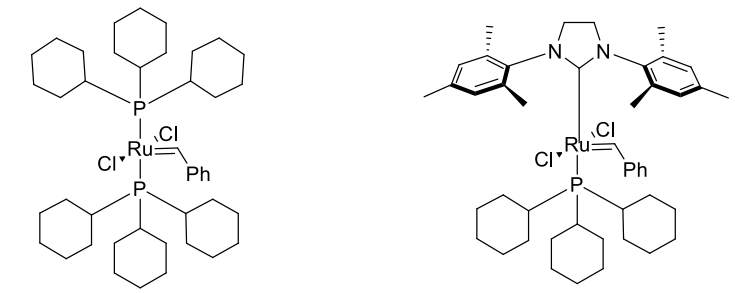
this thesis. This alkaloid was also synthesized by Jacobi,[29,30] Gurjar,[31] Olivo,[32] Somfai,[33] Cossy,[34] Bates,[35] Honda,[36] and Sibi.[37] Stemonine, another group **II** *Stemona* alkaloid, was successfully synthesized by Williams.[38]



Reaction conditions: (a) 5-bromo-pent-1-ene, DMF, NaH, (89%); (b) TsOH, MeOH, (91%); (c) $(COCl)_2$, DMSO, Et_3N; (d) CBr_4, PPh_3, (87%, 2 steps); (e) BuLi, THF, -98 °C, (72%); (f) LDA, HMPA, ClCOOMe, THF, (68%); (g) Grubbs' 1st generation Ru catalyst, CH_2Cl_2, (87%); (h) $NaBH_4$, MeOH, (85%); (k) NaOH, MeOH-H_2O; (l) $CuBr_2$ on alumina, (31%, 2 steps); (m) Et_3N, EtOAc; (n) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, (76%)

.

Scheme 1.2: Synthesis of stemoamide **72**[28]

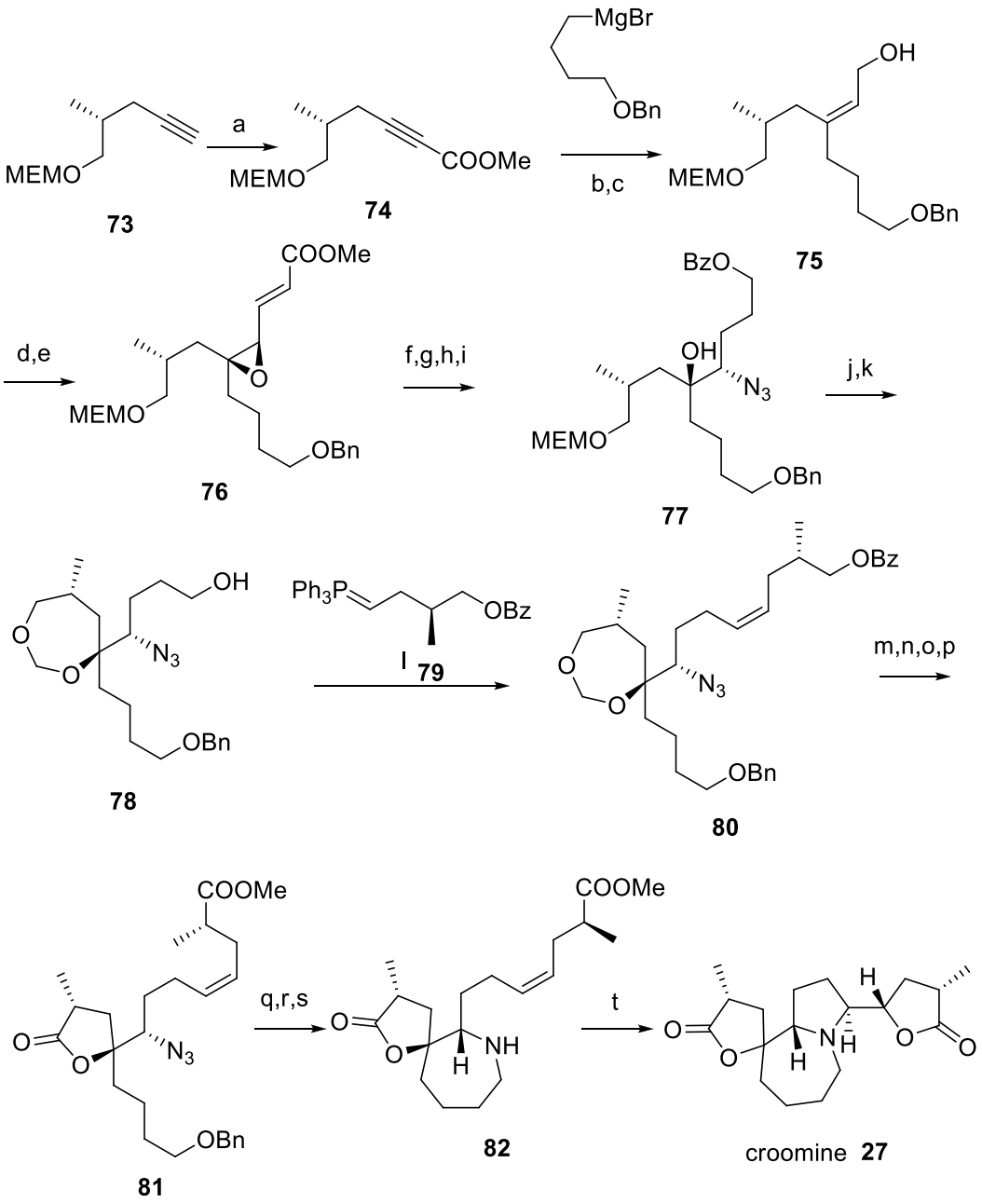


Grubbs' 1st generation Ru catalyst Grubbs' 2nd generation Ru catalyst

Figure 1.16: The structures of Grubbs' ruthenium catalysts

1.1.4.3 The total synthesis of croomine 27 (R = H)

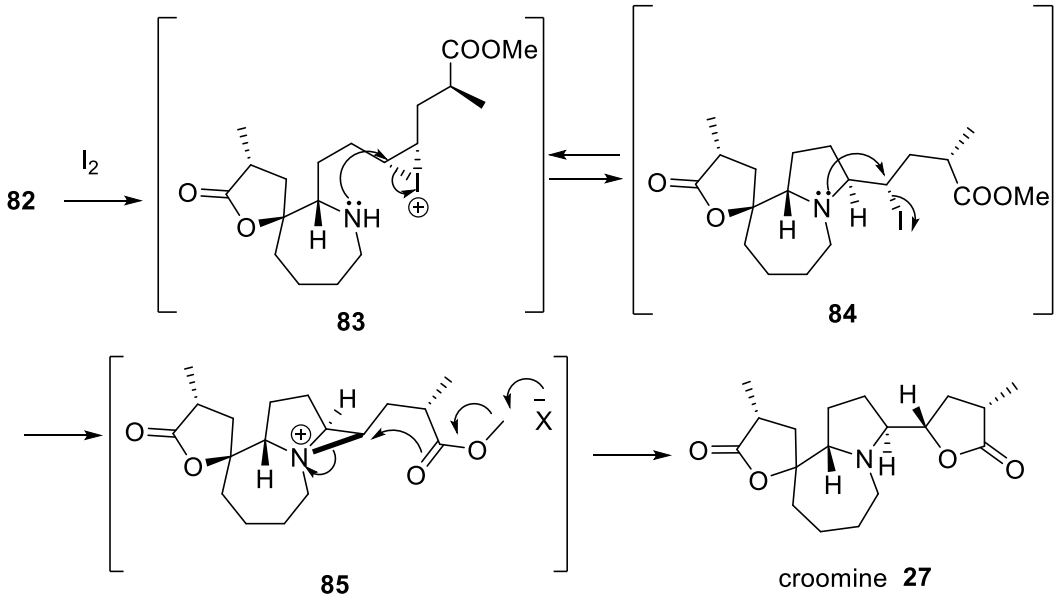
The first total synthesis of a *Stemona* alkaloid was reported by Williams *et al.*[39] in 1989, and was concerned with the preparation of (+) croomine **27** (R = H) (group **III**). Methyl (*S*)-2-methyl-3-hydroxypropionate was converted to the alkyne **73** in four steps using standard methods (**Scheme 1.3**). Homologation of **73** (*n*-BuLi, ClCOOMe) gave the ester **74**, which underwent a copper-catalysed conjugate addition reaction by the Grignard reagent $BnO(CH_2)_4MgBr$, followed by reduction of the ester group with DIBAL-H to the desired *Z*-allylic alcohol **75**. Sharpless asymmetric epoxidation of **75** gave an epoxy alcohol (dr = 13:1), which upon Swern oxidation afforded the corresponding aldehyde, which was converted to the epoxy ester **76** (*E*:*Z* ratio of 6:1) by Wittig olefination with $Ph_3P{=}CHCO_2Et$. Reduction of the ester group of **76** with $LiBH_4$, followed by hydrogenation of the double bond, provided the saturated alcohol. This alcohol then was protected as a benzoate ester. Regioselective epoxide ring opening with lithium azide in DMPU at 110 ºC gave the azide **77**. Treatment of **77** with $BF_3.Et_2O$ yielded the saturated dioxepine, then saponification of the benzoate group afforded the corresponding alcohol **78**. Swern oxidation of this alcohol, followed by Wittig olefination with ylide **79** afforded (*Z*)-**80**. Acid hydrolysis of the acetal of **80**, followed by saponification of the benzoate group provided a triol, which was oxidized by Jones' reagent to form an acid-γ-lactone, giving **81** after treatment of the acid with diazomethane. Removal of the benzyl ether with BCl_3 and subsequent Swern oxidation provided the azido aldehyde which underwent an intramolecular Staudinger/aza-Wittig reaction followed by reduction with $NaBH_4$ to form **82**. The mechanisms of the Staudinger and aza-Wittig reactions are discussed in more detail in Chapter 2 of this thesis. Croomine **27** was then achieved in a single step by treating **82** with I_2 (**Scheme 1.3**). The yield of this final step was only 25% with 50-60% of the starting material reisolated. In this synthesis, croomine was obtained in 24 synthetic steps.



Reaction conditions : (a) BuLi, THF, -78 °C then ClCOOMe, (63%); (b) $BnO(CH_2)_4MgBr$, $Me_2S.CuBr$, TMEDA, Et_2O, -78 °C, (95%); (c) DIBAL, CH_2Cl_2, -78 °C, (98%); (d) $Ti(O\text{-}i\text{-}Pr)_4$ (10% mol), D-DIPT, *t*- BuOOH, MS 4 Å, CH_2Cl_2, -50 °C, (83%); (e) ClCOCOCl (1.2 eq), DMSO (2.4 eq), CH_2Cl_2, Et_3N (2.5 eq), -78 °C to 0 °C then $Ph_3P{=}CHCOOCH_3$ (1.2 eq), 0 °C to rt, (89%); (f) $LiBH_4$ (1.2 eq), Et_2O, MeOH (2 eq), 0 °C, (81%); (g) 5% Rh/Al_2O_3, H_2 (1 atm), THF, (62%); (h) BzCl (1.1 eq), Et_3N, CH_2Cl_2, 0 °C to rt, (97%); (i) LiN_3 (10 eq), DMPU, 110 °C, (94%); (j) $BF_3.Et_2O$ (1.2 eq), CH_2Cl_2, 0 °C, (81%); (k) LiOH, THF, aq MeOH, (97%); (l) ClCOCOCl 1.2 eq), DMSO (2.4 eq), CH_2Cl_2 (2.5 eq), -78 °C to 0 °C, (91%), then ylide **75**, THF, -10 °C, (70-81%); (m) aq. HBF_4, MeOH, (72%); (n) LiOH, THF, MeOH, H_20, 22 °C, (86%), (o) Jones' reagent, THF, 0 °C; (p) CH_2N_2, Et_2O (78% 2 steps); (q) BCl_3, CH_2Cl_2, -78 °C to 0 °C, then MeOH, -78 °C, (77%); (r) ClCOCOCl (1.2 eq), DMSO (2.4 eq), CH_2Cl_2, Et_3N (2.5 eq), -78 °C to 0 °C, (92%), (s) Ph_3P (4.6 eq), THF, 22 °C, then $NaBH_4$ (1.5 eq), MeOH, (90%); (t) I_2 (1.5 eq); CH_2Cl_2, Et_2O, 22 °C, (25%).

Scheme 1.3: Synthesis of croomine **27** (R = H)[39]

The proposed mechanism of this double cyclization step is shown in **Scheme 1.4**. Iodine attacked the alkene group of **82** to form the iodonium ion intermediate **83**. This first step is thought to be reversible and can give two interconverting diasteromeric iodonium ion intermediates (only one is shown in **Scheme 1.4**). The intermediate **83** cycles faster than its diasteromer giving **84** as the kinetically favoured product. This undergoes nucleophilic addition by the vicinal tertiary amine to form the salt **85**. Intramolecular cyclization of this aziridinium salt by participation of the nearby ester group results in croomine **27**. In 2001, this group reported the total synthesis of stemospironine,[40] another group **III** *Stemona* alkaloid. Later, in 2012, this alkaloid was synthesized along with some of its epimers by Figueredo *et al.*[41]



Scheme 1.4: Proposed mechanism of the iodine-mediated cyclization of **82**[39]

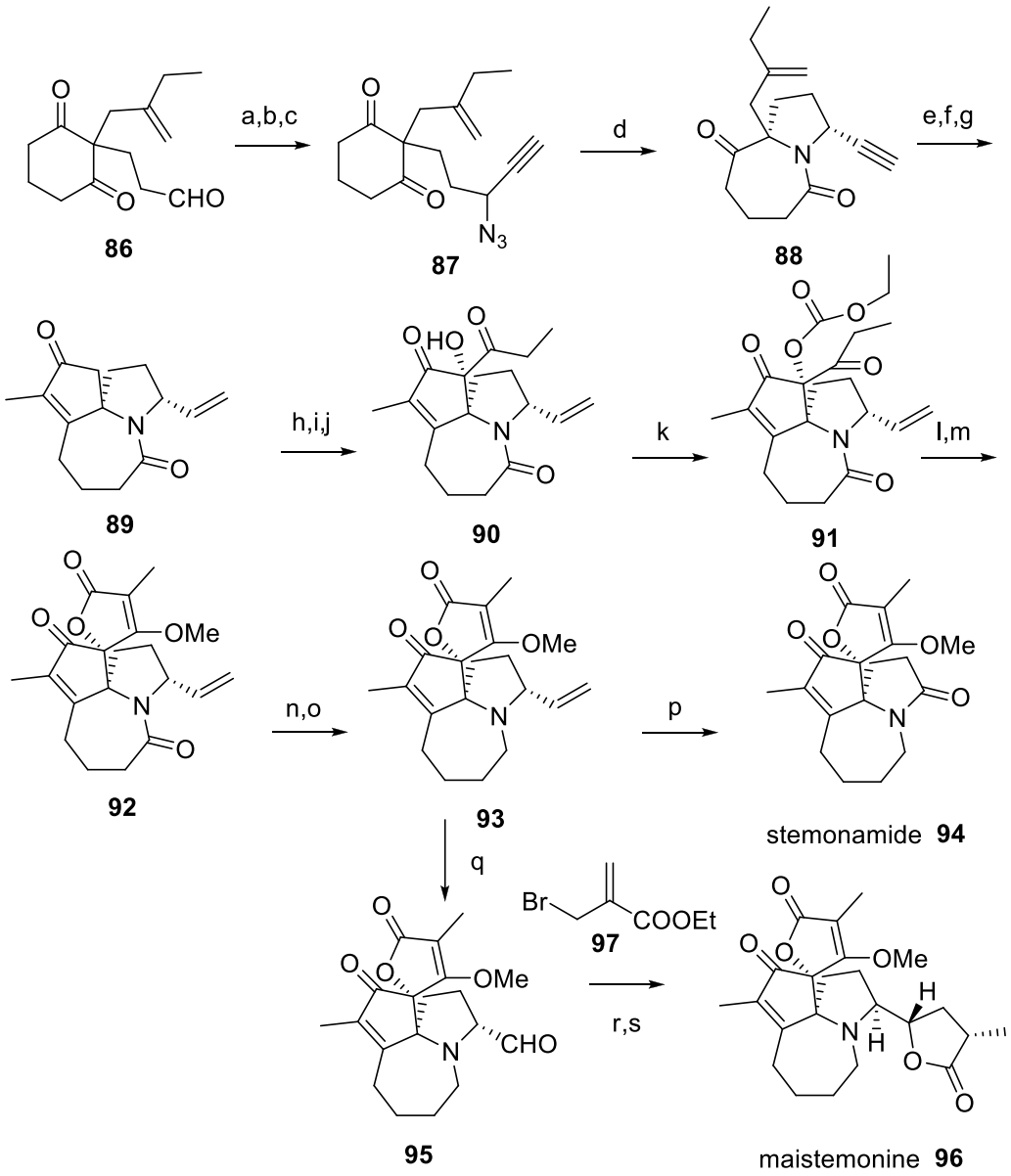
1.1.4.4 The total synthesis of (±) stemonamide 94 and (±) maistemonine 96

The total synthesis of (±) stemonamide **94**, a group **IV** *Stemona* alkaloid, was completed by Tu *et al.*[42] along with that of (±) maistemomine. Their synthesis started with the tricarbonyl compound **86** (**Scheme 1.5**). Selective addition of ethynylmagnesium chloride to the aldehyde of **86**, followed by mesylation of the resulting alcohol gave the mesylate intermediate, which was converted to **87** by azide

substitution. The intramolecular Schmidt reaction[43] proceeded by treatment of **87** with $TiCl_4$ in CH_2Cl_2 to furnish **88** as a single isomer. The proposed mechanism of the intramolecular Schmidt reaction, which explains the exclusive formation of **88**, is illustrated in **Scheme 1.6**. There are two possible outcomes for the addition of the azide group to the two carbonyl groups of **87**, these are intermediates **98** and **99**. Compare to the intermediate **98**, intermediate **99** is much less stable due to the unfavourable steric interactions between the alkene and the alkyne groups as shown in **Scheme 1.6**, thus only intermediate **98** is formed at this stage. In the next stage, the product is formed by Cl_3Ti-O assisted migration of the C-C bond to a C-N bond as shown in **Scheme 1.6**. Ozonolysis of **88** to an ethyl ketone, followed by Lindlar reduction[44] of the alkyne group produced the corresponding terminal olefin, which was transformed to the tricyclic ketone **89** by a base catalysed (K_2CO_3/MeOH) aldol condensation process. Deprotonation of **89** with LiHMDS followed by treatment with propanal afforded the corresponding β-hydroxy ketone, which was oxidized by Dess-Martin periodinane to a β-dicarbonyl compound. This was converted to the tertiary alcohol **90** as the major product in 74% yield by treatment with $CeCl_3.7H_2O$ in *i*-PrOH under an oxygen atmosphere. Reaction with ethyl chloroformate gave the carbonate **91**, which was converted to **92** via an intramolecular ketone enolate-ester condensation (Claisen-type condensation) reaction by treatment with KHMDS followed by *O*-methylation with diazomethane. *O*-methylation of the lactam by MeOTf followed by a chemoselective reductive removal the lactam carbonyl with $NaCNBH_3$ furnished the tertiary amine **93**. (±) Stemonamide **94** was achieved from **93** by a Johnson-Lemieux oxidation at elevated temperature (40 ºC), prolonged reaction time (10 h) and with an excess of $NaIO_4$ (1.5 equiv).

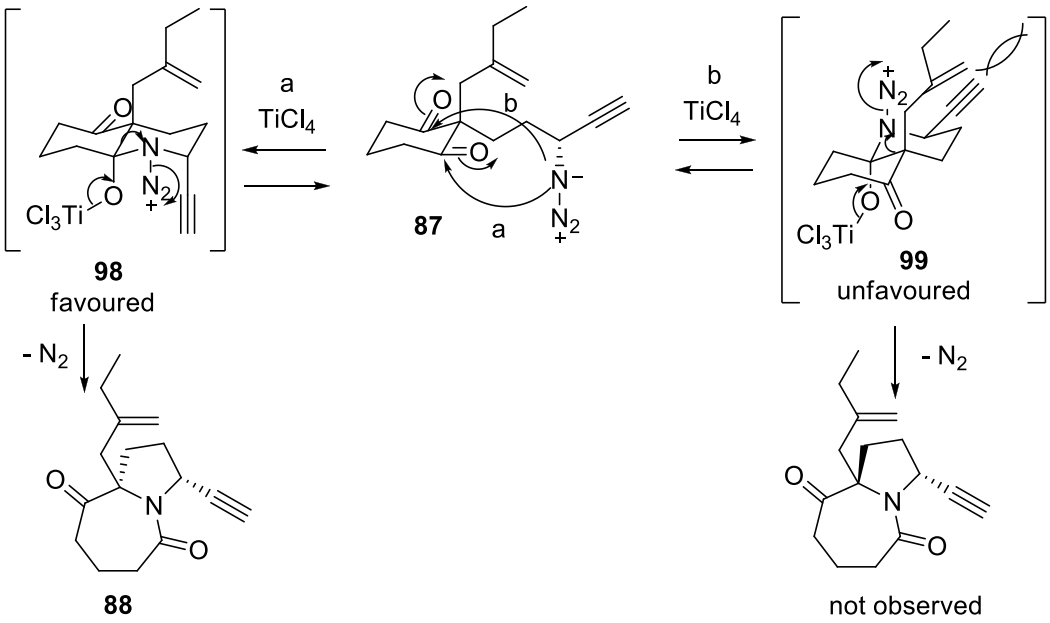
A further three more steps were performed to obtain maistemonine. Johnson-Lemieux oxidation of **93** under milder conditions (rt, 3.5 h) afforded the aldehyde **95**, which was transformed to the unstable α-methylene-γ-lactone by reaction of the aldehyde with the organozinc reagent prepared *in situ* from ethyl bromomethylacrylate **97** and zinc in THF. Reduction of the *exo*-cyclic methylene group of the resulting γ-lactone product by H_2 over Pd/C catalyst provided (±) maistemonine **96** (**Scheme 1.5**). In a separate study this group also completed the

total synthesis of stemonamine.[45] Other total syntheses of group **IV** *Stemona* alkaloids were performed by Kende,[46] and Ishibashi.[47,48]



Reaction conditions: (a) HCCMgCl, THF; (b) MsCl, DMAP, pyridine, CH_2Cl_2, (50%, 2 steps); (c) NaN_3, (84%); (d) $TiCl_4$, CH_2Cl_2, (72%); (e) O_3, (82%); (f) H_2, Lindlar Pd, MeOH; (g) K_2CO_3, MeOH, (93%, 2 steps); (h) CH_3CH_2CHO, LHMDS, THF, (98%); (i) DMP, CH_2Cl_2; (j) $CeCl_3.7H_2O$, O_2, *i*-PrOH, (74%, 2 steps); (k) ClCOOEt, Et_3N, DMAP, CH_2Cl_2, (99%); (l) KHMDS, THF; (m) CH_2N_2, CH_2Cl_2, (76%, 2 steps); (n) MeOTf, CH_2Cl_2; (o) $NaBH_3CN$, (95%, 2 steps); (p) K_2OsO_4, NMO, acetone-H_2O, then excess of $NaIO_4$, (83%); (q) K_2OsO_4, NMO, acetone-H_2O, then $NaIO_4$, (64%); (r) **97**, Zn, THF; (s) H_2, Pd/C, EtOH, (66%, 2 steps).

Scheme 1.5: Synthesis of stemonamide **94** and maistemonine **96**[42]

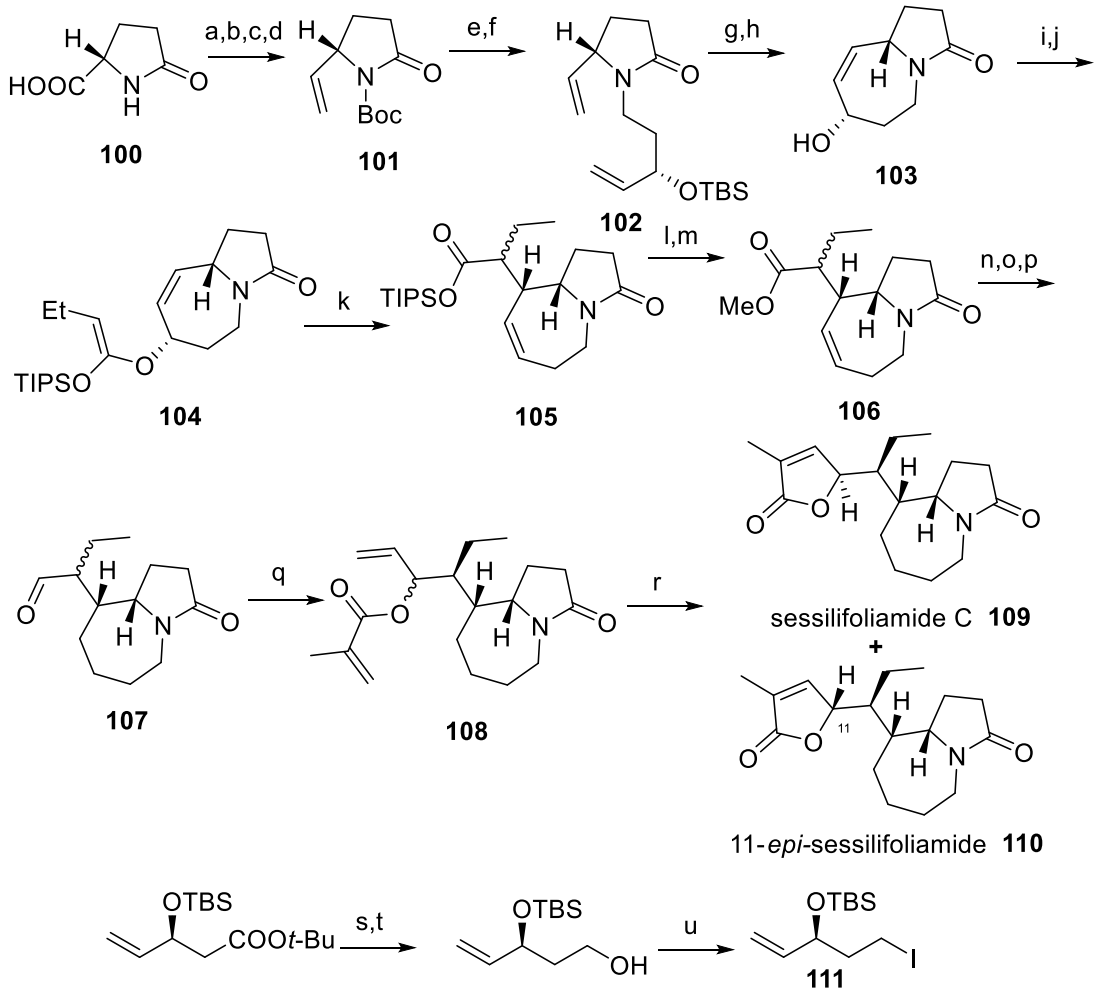


Scheme 1.6: Proposed mechanism for the intramolecular Schmidt reaction[43]

1.1.4.5 The total synthesis of sessilifoliamide C 109

In 2011, Wifp[49] reported the total synthesis of sessilifoliamide C **109**, a group **V** *Stemona* alkaloid, from (*S*)-pyroglutamic acid **100** (**Scheme 1.7**). The acid group of **100** was converted to its ethyl thioester before protecting the pyrrolidinone nitrogen by the Boc group. Fukuyama reduction (Pd/C, Et_3SiH) of the resulting *N*-Boc thioester gave an aldehyde, which was transformed to the alkene **101** by the Wittig olefination process. Removal of the Boc of group of **101** with TFA followed by *N*-alkylation using iodide **111** under basic conditions (NaOH, H_2O) furnished **102**. This compound was converted to the bicycle **103** by ring-closing metathesis using Grubbs' 2nd generation ruthenium catalyst followed by acid promoted (*p*-TsOH, MeOH) cleavage of the TBS group. Acylation of **103** with butyric acid and EDC.HCl afforded the corresponding ester, which upon enolisation by LiHMDS followed by trapping with TIPSCl resulted in the (*Z*)-silyl ketene acetal **104**. Heating this intermediate at reflux in degassed xylene resulted in an Ireland-Claisen rearrangement furnishing **105**, which was simply converted to the methyl ester **106** (dr = 6:1) by removal of the TBS group followed by methylation of the corresponding acid with $TMSCHN_2$. This compound was hydrogenated and then the ester group was reduced with $LiBH_4$ to the corresponding alcohol before Swern oxidation to give aldehyde **107**, from which the desired isomer was isolated by

column chromatography. This adduct was exposed to vinylmagnesium bromide followed by treatment with methacryloyl chloride providing a mixture of diasteromeric acrylates **108** (dr = 2:1). Ring-closing metathesis of this mixture led to a separable mixture of sessilifoliamide C **109** and its epimer at C_{11} (84% yield total) **110**, from which 3 mg of pure **109** was isolated for structural elucidation (**Scheme 1.7**). Two other group **V** *Stemona* alkaloids were synthesized by Lindsley in 2013, stemaphylline and stemaphylline-*N*-oxide.[50]

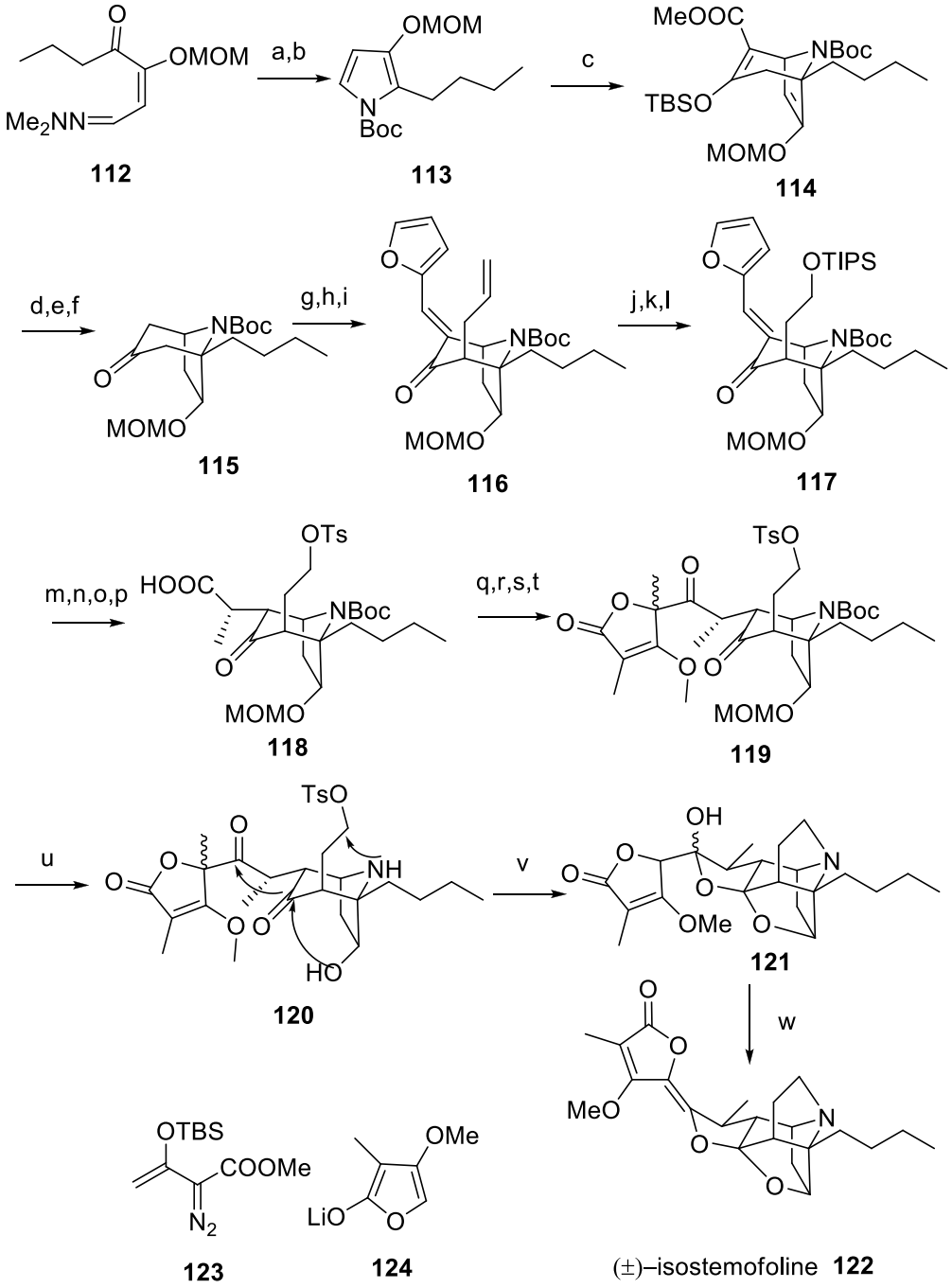


Reaction conditions : (a) DCC, EtSH, DMAP, CH_2Cl_2- DMF, (71%); (b) Boc_2O, DMAP, CH_3CN, (83%); (c) Pd/C, EtSiH, acetone; (d) $MePPh_3Br$, *t*-BuOK, THF, (96%); (e) TFA, CH_2Cl_2, (95%); (f) **111**, Bu_4NHSO_4, NaOH, H_2O, toluene, rt, (75%); (g) Grubbs' 2nd generation Ru catalyst, CH_2Cl_2,(91%); (h) *p*-TsOH, MeOH, (90%); (i) *n*- C_3H_7COOH, EDC.HCl, DMAP, CH_2Cl_2, (92%); (j) LiHMDS, TIPSCl, THF-HMPA, -78 °C; (k) xylene, degassed, 140 °C, 3h; (l) TBAF, THF; (m) $TMSCHN_2$ (21% for 4 steps, dr = 6:1); (n) Pd/C, H_2, MeOH, (99%); (o) $LiBH_4$, THF, (58-71%); (p) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, (89%); (q) $CH_2CHMgBr$, THF, -78 °C to rt, then methacryloyl chloride, (59%,dr = 2:1); (r) Grubbs' 2nd generation Ru catalyst, CH_2Cl_2 (84% yield for **109** and **110**), (s) DIBAL-H, toluene, -78 °C; (t) $NaBH_4$, MeOH, (87%); (u) I_2, PPh_3, imidazole, CH_3CN-THF, (95%).

Scheme 1.7: Synthesis of sessilifoliamide C **109** and 11-*epi*-sessilifoliamide **110**[49]

1.1.4.6 The total synthesis of (±)-isostemofoline 122

The first total synthesis of (±)-isostemofoline **122**, having a complex caged structure (a group **VI** *Stemona* alkaloid), was reported by Kende and co-workers (**Scheme 1.8**).[51] The synthesis started with the hydrazone **112**, which was prepared from 1,2-hexanediol in three synthetic steps (48% yield). This underwent reductive cyclization with sodium persulfate to afford the pyrrole **113**, after *N*-protection by the Boc group. A [4+3]-cycloaddition of **113** and diazoester **123** promoted by rhodium octanoate dimer gave the bicyclic compound **114**, which underwent an enol silane deprotection (TBAF), an *exo*-specific hydrogenation (Pd/C, H_2) and a nucleophilic decarboxylation (DMSO, H_2O, 150 ºC) reaction sequence to produce the bicyclic ketone **115**. Aldol condensation of **115** with furfuraldehyde (NaOH/MeOH) furnished the enone **116**, after allylation promoted by LiHMDS. Johnson-Lemieux oxidation of the alkene group followed by reduction of the corresponding aldehyde provided the desired primary alcohol, which was protected as the TIPS ether **117**. Conjugated addition of MeLi to **117**, followed by a series of functional group interconversions including oxidative cleavage of the furan with oxone, resulted in the acid **118**. Treatment of this product with *i*-BuOCOCl, followed by reduction of the resulting mixed anhydride with $NaBH_4$/MeOH provided the corresponding primary alcohol, which was oxidised to the corresponding aldehyde by using the Dess-Martin periodinane reagent. Addition of the lithiated anion **124** to this aldehyde, followed by Dess-Martin oxidation furnished **119** (dr = 2:1). Treatment **119** with TFA gave the intermediate **120**, which underwent a triple cyclization by adjustment to pH = 10 to furnish **121**. This cyclization process included two intramolecular ketal forming reactions and an intramolecular *N*-alkylated reaction. In the final step, dehydration of **121** by Tf_2O afforded (±)-isostemofoline **122**, however in only 12% yield (**Scheme 1.8**). The synthesis of **122** was completed in 27 steps and less than 0.1% overall yield from 1,2-hexanediol. The total synthesis of two other group **VI** *Stemona* alkaloids, (±)-16,17-didehydro-16(*E*)-stemofoline and (±)-16,17-didehydro-4(*E*),16(*E*)-stemofoline was completed by Overman.[52] Recently, Huang reported the total synthesis of (+)-methoxystemofoline and (+)-isomethoxystemofoline.[53]

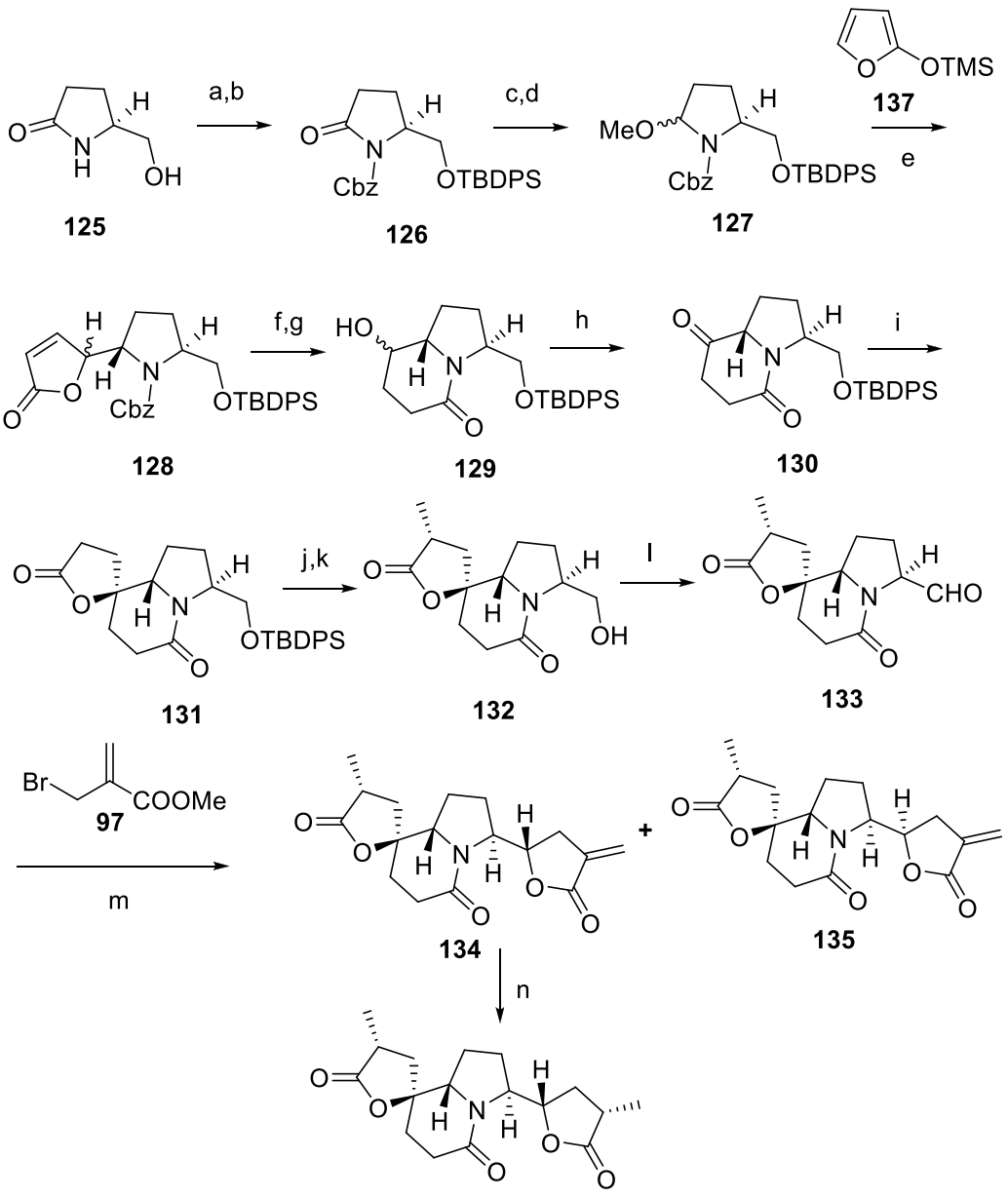


Reaction conditions: (a) $Na_2S_2O_4$, EtOH, H_2O, 90 °C, (35%); (b) Boc_2O, DMAP, CH_3CN, (72%); (c) **123,** rhodium octanoate dimer, pentane, reflux, (90%); (d) TBAF, THF, (65%); (e) H_2, Pd/C, MeOH, (90%); (f) H_2O, DMSO, 150 °C, (90%); (g) furfuraldehyde, NaOH, MeOH, H_2O, (90%); (h) LiHMDS, DMPU, THF, 0 °C, then allyl iodide, rt, (90%); (i) toluene, reflux, (86%); (j) K_2OsO_4, $NaIO_4$, Et_2O, H_2O, rt; (k) $Zn(BH_4)_2$, THF, -10 °C, (52%, 2 steps); (l) TIPSCl, imidazole, DMF, (93%); (m) MeLi, DMPU, Et_2O, -40 °C, (85%); (n) TBAF, THF, (90%); (o) TsCl, pyridine, $CHCl_3$, (90%); (p) O_3, CH_2Cl_2, Me_2S, (65%); (q) BuOCOCl, *N*-methylmorpholine, THF, 0 °C; (r) $NaBH_4$, MeOH; (s) DMP, CH_2Cl_2, (30%, 3 steps); (t) **124**, THF, -78 °C, (56%, dr =2:1); (u) DMP, CH_2Cl_2, (61%); (v) TFA, sat. aq. $NaHCO_3$, (63%); (w) Tf_2O, CH_2Cl_2 (12%)

Scheme 1.8: Synthesis of (±)-isostemofoline **122**[51]

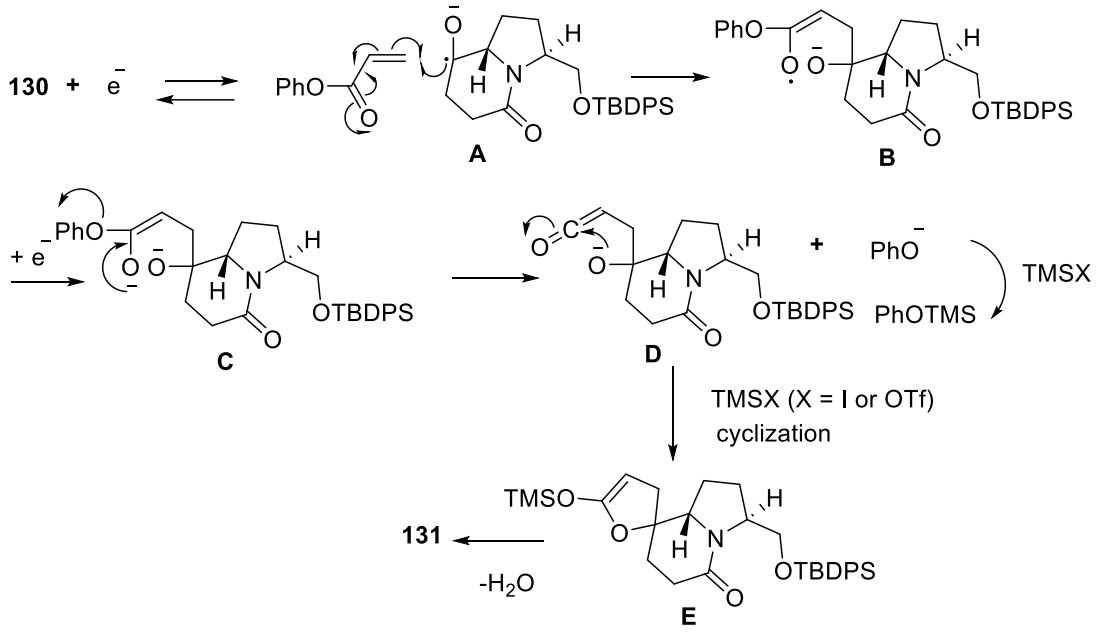
1.4.1.7 The total synthesis of sessilifoliamide J 136

The total synthesis of sessilifoliamide J **136**, a group **VIII** *Stemona* alkaloid, was achieved by Huang and coworkers in 2012.[54]Their synthesis started from commercially available (*S*)-pyroglutaminol **125** (**Scheme 1.9**). *N*-Cbz protection, followed by *O*-TBDPS protection gave **126**. Partial reduction of the lactam carbonyl of **126** with DIBAL-H afforded a mixture of hemiaminals, which was transformed to the mixture of hemiaminal ethers **127** by treatment with CSA in methanol. A vinylogous Mannich reaction[55] between **127** and the furan **137** proceeded under $BF_3.Et_2O$ catalyst to afford the lactone **128** as a mixture of diastereomers (dr = 85:15). Reductive removal of the Cbz group and hydrogenation of the alkene group, followed by exposure of the resulting amine to NaOMe/MeOH provided the indolizidinone **129**. Oxidation of this mixture gave the ketone **130**, which was subjected Corey lactonization[56] by treatment with phenyl acetate, Zn-Hg, TMSOTf, LiI, and SmI_2 in THF to form **131** as a diastereomeric mixture (dr > 20:1). The proposed mechanism for the Corey lactonization is shown in **Scheme 1.10**. The reaction of **130** was initiated by the addition of an electron generated from SmI_2/Zn-Hg to **130** to form the ketyl radical **A**. Michael addition of the radical **A** to phenyl acrylate formed the radical anion **B**. This anion accepted one electron (from SmI_2/Zn-Hg) to generate the dianion **C**. Elimination of PhO^- from **C** resulted in the ketene **D**. Cyclization of the ketene **D** was promoted by TMSOTf to form the tricyclic intermediate **E**. Hydrolysis of **E** (during the work-up process) yielded the tricycle **131**. The desired isomer **131** was separated as the major compound by column chromatography (**Scheme 1.9**). Methylation of **131** initiated by deprotonation by LiHMDS produced almost exclusively **132**, after removing the TBDPS group by treatment with TBAF. Swern oxidation of **132** led to the aldehyde **133**, which was treated with the organozinc reagent prepared *in situ* from **97** and Zn at reflux temperature to provide a chromatographically separable mixture of diastereomers **134** and **135** (dr = 41:59) in excellent yield. Hydrogenation of the desired diastereomer **134** furnished sessilifoliamide J **136**. This total synthesis proceeded in 6.7% overall yield through 14 steps from **124** (**Scheme 1.9**).



Reaction conditions: (a) TBDPSCl, imidazole, DMF; (b) $NaN(TMS)_2$, CbzCl, THF, -78 °C 1 h then rt 3 h; (c) DIBAL-H, THF, -45 °C; (d) CSA, MeOH, 0 °C, (92%, 2 steps); (e) **137**, $BF_3.Et_2O$, CH_2Cl_2, -78 °C, (97%); (f) 10% Pd/C, H_2, MeOH, EtOH, rt; (g) MeOH, NaOMe, 0 °C, (95%, 2 steps); (h) TPAP, NMO, CH_2Cl_2, 4Å MS, 0 °C to rt; (i) 10% SmI_2, Zn-Hg, TMSOTf, phenyl acrylate, LiI, THF, (61%, 2 steps, dr = 2:1); (j) LiHMDS, THF, MeI, -78 °C, (72%); (k) Py.HF, THF, rt, (85%); $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, (m) **97**, Zn, THF, reflux, (90%, 2 steps, dr = 49:51)); (n) 10% Pd/C, H_2, EtOH, (99%);

Scheme 1.9: Synthesis of sessilifoliamide J **136**[54]



Scheme 1.10: Proposed mechanism for the Corey lactonization reaction[56]

1.2 Proposed synthetic approach

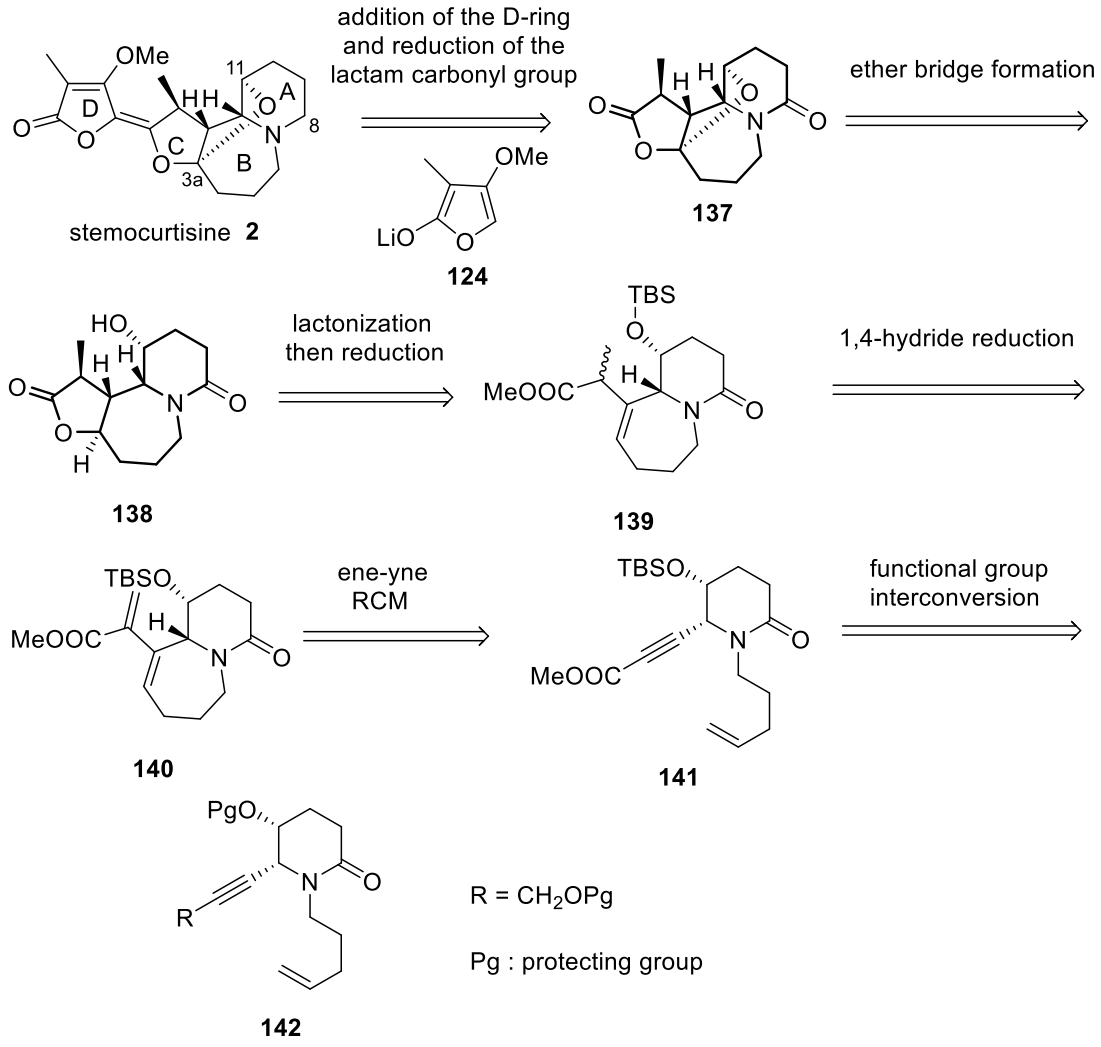
1.2.1 Aims of this project

Although the total syntheses of many pyrrolo[1,2-*a*]azepine *Stemona* alkaloids have been reported, none of them involves the synthesis of a member of the stemocurtisine group (group **VII**), which possesses the pyrido[1,2-*a*]azepine core structure. The aim of this project was to investigate the total synthesis of stemocurtisine **2** based on the retrosynthesic analysis shown in **Scheme 1.11**. The major challenges in this synthesis are: (1) Controlling the relative stereochemistry of the five stereogenic centres in **2**; (2) The formation of the ether bridge between C-1 and C-9 of **2**; and (3) Obtaining the (*Z*) geometry of the alkene moiety between the C and D rings.

1.2.2 Retrosynthetic analysis of stemocurtisine

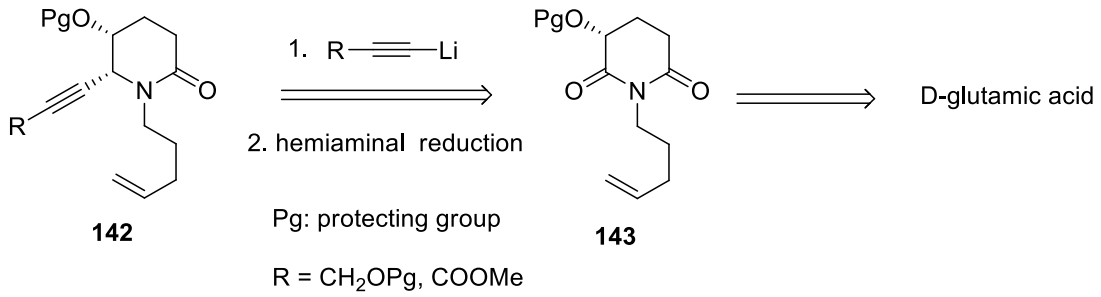
Our restrosynthetic analysis indicated that stemocurtisine **2** could be prepared in principle from the tetracyclic compound **137** following the method described by

Olivo using the lithiated anion **124** to introduce the D-ring[57] then reduction of the lactam carbonyl group. This compound could be obtained from the tricyclic compound **138** by a photochemical oxidative cyclization process promoted by I_2 in the presence of $PhI(OAc)_2$ (BAIB).[58] Tricycle **138** could be obtained from **139** by a lactonization then a reduction reaction sequence according to the procedures of Mori (compare with **Scheme 1.2**).[27] This material can be achieved from **140** by a 1,4-hydride reduction of the enoate moiety.[27] The bicycle **140** could be obtained from **141** via an ene-yne ring-closing metathesis reaction by analogy to the work of Mori (**Scheme 1.2)**. The piperidinone **141** could be synthesized from the lactam **142** via functional group interconversions. The lactam **142** could be in principle synthesized via three different synthetic pathways (synthetic strategies 1-3).



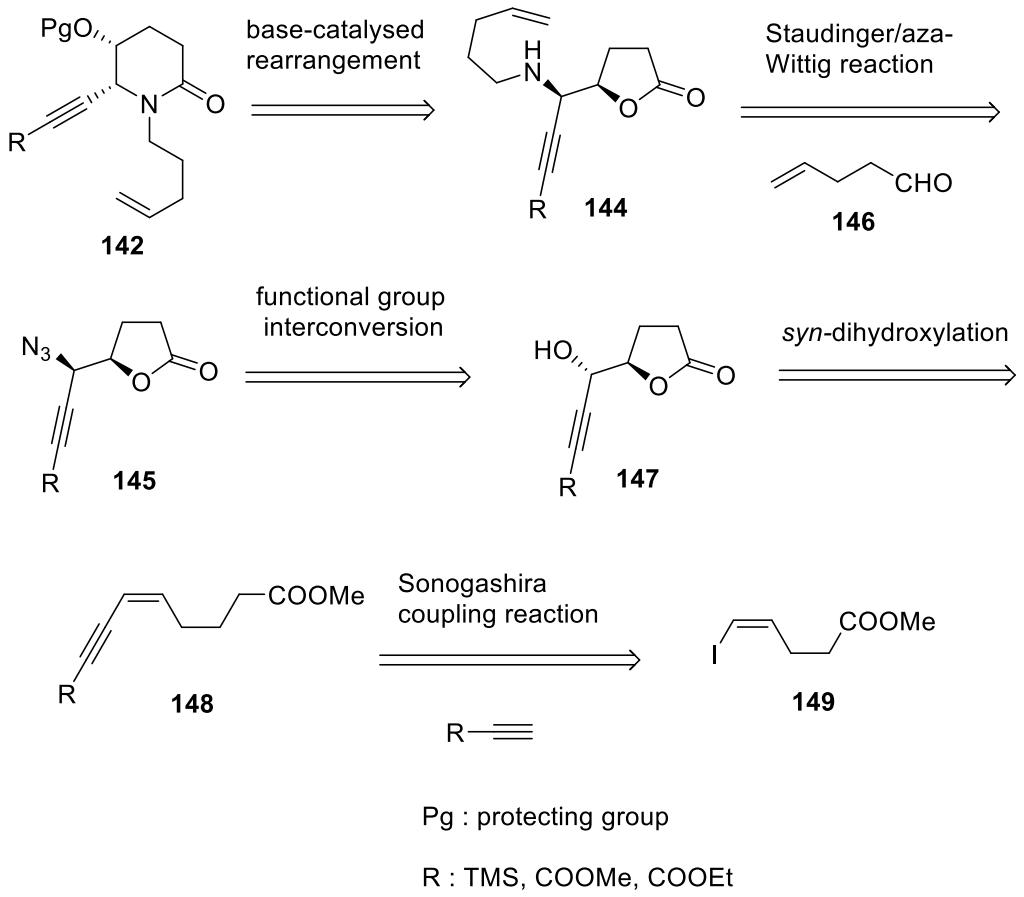
Scheme 1.11: Retrosynthetic analysis of stemocurtisine **2**

Following the retrosynthesis shown in **Scheme 1.12** (synthetic strategy 1), compound **142** could be obtained from the imide **143** via nucleophilic addition of the corresponding lithiated terminal alkyne followed by stereoselective reduction of the resulting hemiaminal product. Imide **143** could be prepared from D-glutamic acid following Ruan's procedure.[59]



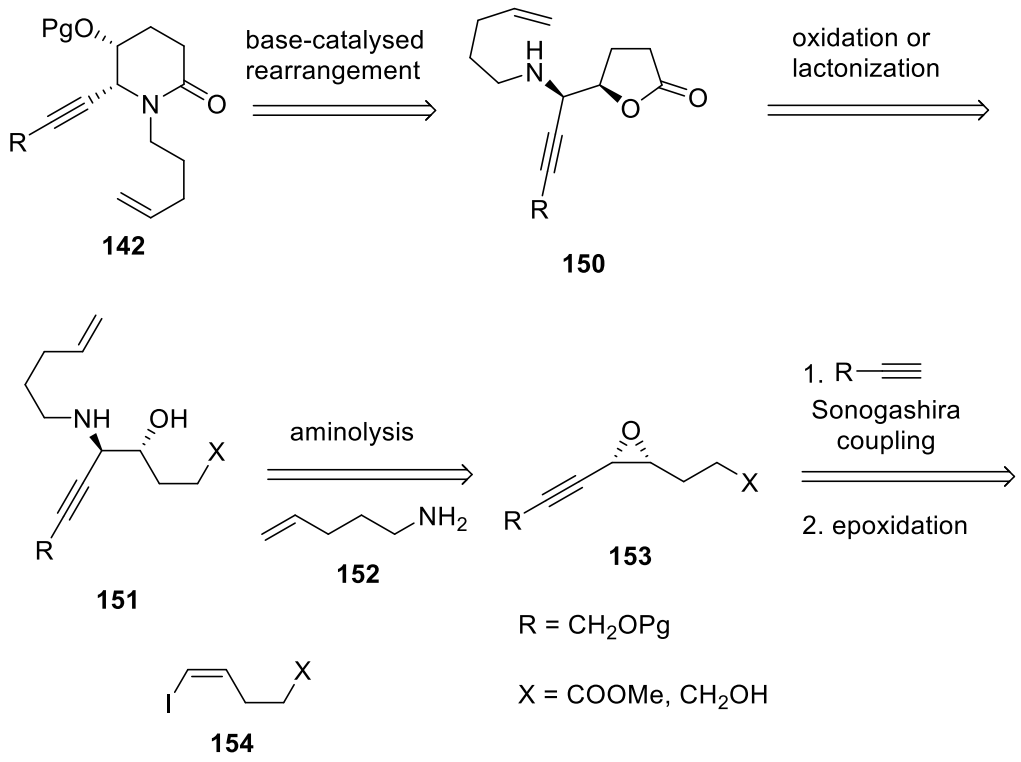
Scheme 1.12: Restrosynthetic analysis of **142** (synthetic strategy 1)

Following synthetic strategy 2 shown in **Scheme 1.13**, compound **142** could be obtained from the lactone **144** via a base-catalysed amino-lactone to hydroxy-lactam rearrangement. Compound **144** could be prepared from the azide **145** via a Staudinger/aza-Wittig reaction with aldehyde **146**. Azide **145** could be prepared from alcohol **147** via a functional group interconversion. Compound **147** could be obtained from the ene-yne **148** via a *syn*-dihydroxylation process. The ene-yne **148** could be synthesized from the iodide **149** via a Sonogashira coupling reaction with an appropriate terminal alkyne.



Scheme 1.13: Restrosynthetic analysis of **142** (synthetic strategy 2)

Following synthetic strategy 3 shown in **Scheme 1.14**, compound **142** could be synthesized from the lactone **150** (R = CH_2OPg) via a base-catalysed rearrangement. Lactone **150** could be obtained from compound **151** via an oxidation reaction (X = CH_2OH) or lactonization process (X = COOMe). Amino alcohol **151** could be prepared from the epoxide **153** via an aminolysis reaction with amine **152**. Epoxide **153** could be obtained from the iodide **154** via a Sonogashira coupling reaction followed by an epoxidation process.

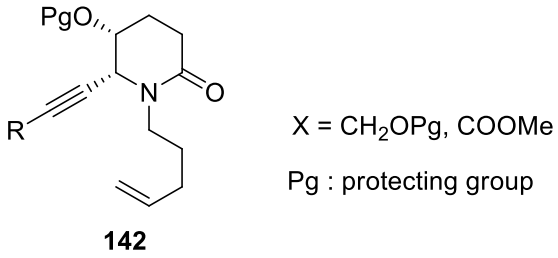


Scheme 1.14: Restrosynthetic analysis of **142** (synthetic strategy 3)

Our overall synthetic plan towards the synthesis of stemocurtisine was to consecutively construct the A, A-B, and A-B-C ring systems of this alkaloid, respectively and then the ether-bridge to produce **137**. In Chapter 2 we report on several different approaches (using synthetic strategies 1-3) to make the A- ring. Construction of the A-B, and A-B-C ring systems and attempts to make the ether linkage are discussed in Chapter 3. Chapter 4 reports on an alternative synthetic strategy to prepare the A-B-C ring system from L-glutamic acid using a ring-closing reaction of an enolate anion onto an epoxide.

CHAPTER 2: SYNTHESIS OF THE RING A OF STEMOCURTISINE

This chapter reports on our successful and unsuccessful attempts to prepare a highly functionalised A-ring precursor, of the general structure **142**, of stemocurtisine **2** using the synthetic strategies 1-3 described in **Schemes 1.12**, **1.13** and **1.14** of Chapter 1.

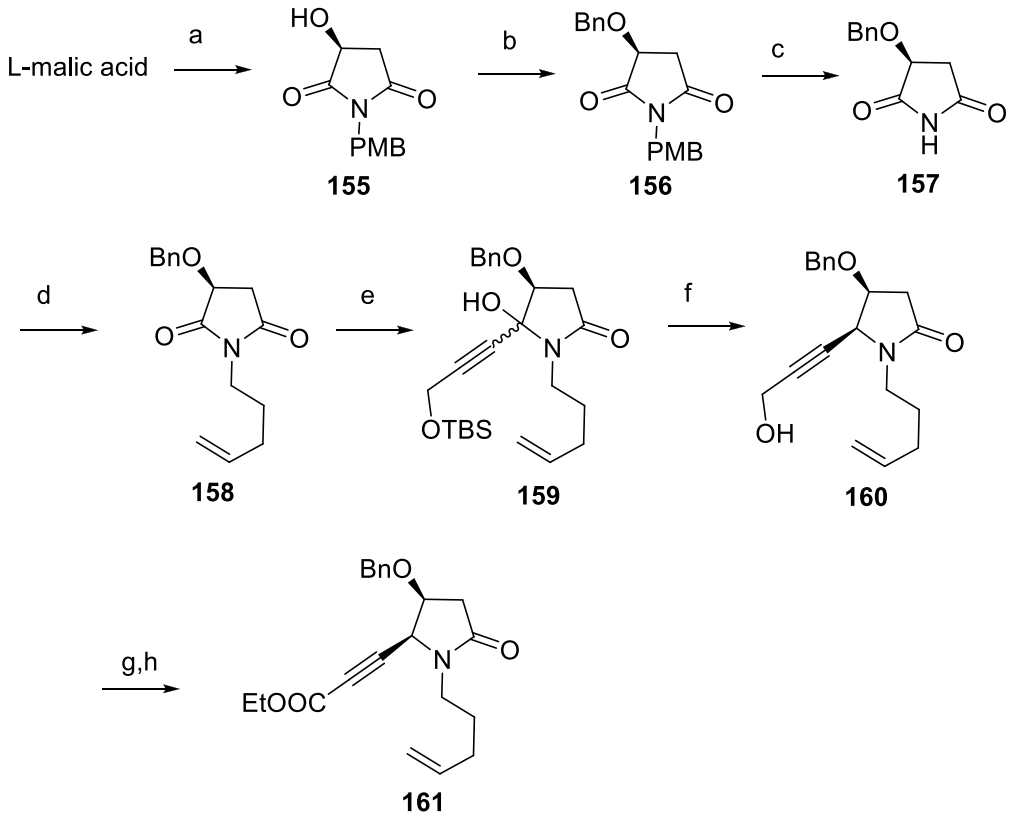


142

Figure 2.1: General structure of the A-ring target lactam **142**

2.1 First attempts from L-glutamic acid (synthetic strategy 1)

Earlier a PhD student (Swamy) working in our laboratory reported the synthesis of the 5-membered ring ene-yne lactam analogue **161** to our target compound **142** (R = COOMe) (**Scheme 2.1**).[60] The synthesis started from L-malic acid and resulted in the synthesis of **161** in seven synthetic steps. Heating a solution of L-malic acid and $PMBNH_2$ in xylene at reflux temperature gave the imide **155**, which was protected as the benzyl ether **156** by *O*-benzylation under basic conditions. Oxidative removal of the PMB group of **156** by CAN, followed by *N*-alkylation of the resulting imide afforded **158**. Nucleophilic addition of the lithium acetylide $TBSOCH_2CCLi$, prepared *in situ* from the corresponding terminal alkyne and *n*-BuLi, to the more electrophilic carbonyl group of **158** provided a diasteromeric mixture of the hemiaminals **159** (dr = 2:1). This mixture underwent reduction and TBS deprotection by $NaCNBH_3$/HOAc to provide the *cis*-isomer **160** in 58% yield. The primary alcohol **160** was then oxidized with Jones' reagent followed by esterification to provide the ester **161**.



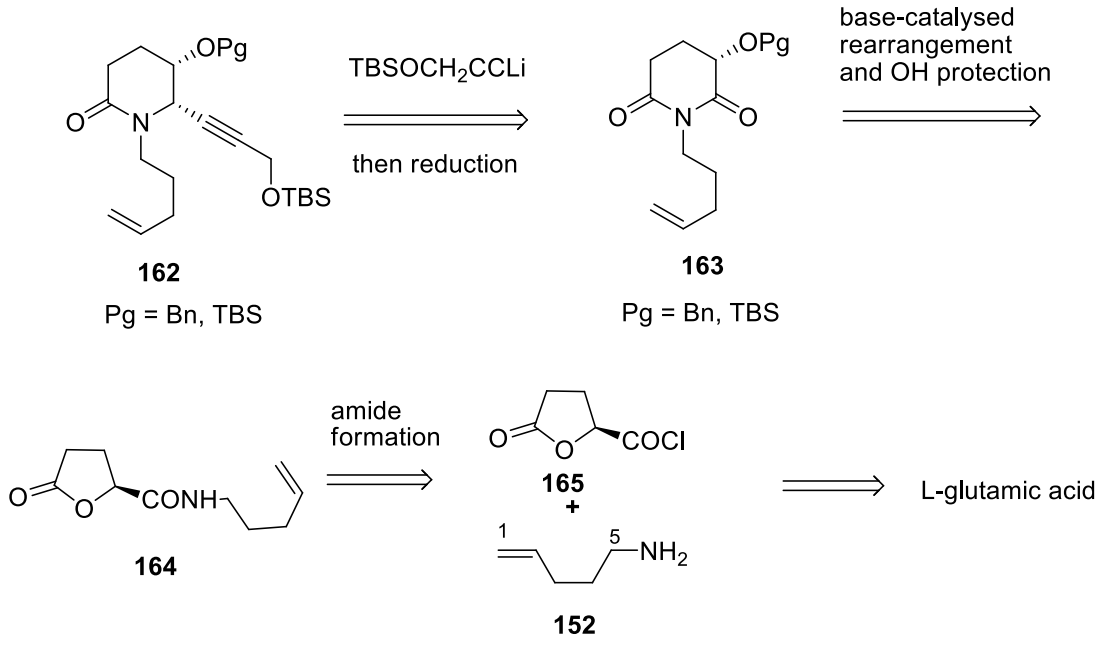
Reaction conditions: a) $PMBNH_2$, xylene, reflux, 3 h, 84%; b) Et_2O, BnBr (6.0 eq), Ag_2O (3.0 eq), 3d, 84%; c) CAN (5.0 eq), CH_3CN/H_2O (3:1), rt, 2 h, 82%; d) 4-penten-1-ol (1.0 eq), PPh_3 (1.0 eq), DIAD (1.0 eq),THF, 0 °C to rt, 4 h, 84%; e) $TBSOCH_2CCH$, *n*-BuLi, THF, -78 °C, then **158**, -78 °C, 1h (68%); (f) $NaCNBH_3$, AcOH, rt, (58%); (g) Jones' reagent, acetone, 0 °C; (h) DCC, DMAP, EtOH, CH_2Cl_2, (47%).

Scheme 2.1: The synthesis of lactam **161**[60]

Based on the success of this work, our retrosynthetic analysis of the *O*-protected piperidinone **162** (**142**, R= CH_2OTBS) is shown in **Scheme 2.2** starting from L-glutamic acid. It should be noted that if this route was successful it would produce the enantiomer of stemocurtisine. We chose to use L-glutamic acid rather than the D-form in our preliminary studies because of its cheaper cost.

Following this retrosynthetic analysis, compound **162** could be obtained from the imide **163** by the addition of the organolithium reagent $TBSOCH_2CCLi$ followed by reduction of the resulting hemiaminal. This imide could be prepared from the amide **164** via a base-catalysed rearrangement followed by a hydroxyl group protection

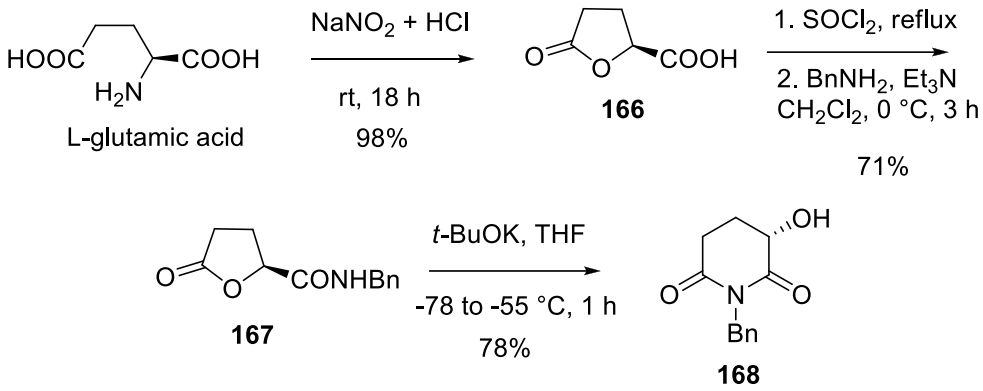
reaction. Amide **164** could be obtained from the reaction between 1-amino-4-pentene **152** and the acid chloride **165**, which could be synthesized from L-glutamic acid in two synthetic steps.[61]



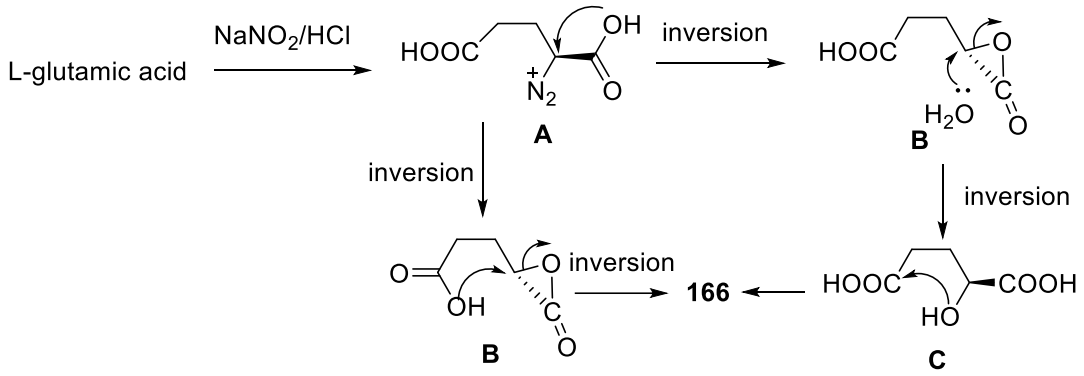
Scheme 2.2: Retrosynthesis of lactam **162**

In our initial model studies, L-glutamic acid was treated with $NaNO_2$ and HCl to give initially the corresponding α-hydroxy acid, which underwent lactonization to form the lactone **166** (**Scheme 2.3**).[61] A mechanistic scheme for the formation of the lactone **166** is shown in **Scheme 2.4**. The amino group of L-glutamic acid was converted to the unstable diazonium salt **A** by HNO_2 prepared *in situ* from HCl and $NaNO_2$. Nucleophilic displacement of N_2 from **A** via the α-carboxylic acid group formed the unstable 3-membered ring lactone **B**. Nucleophilic addition of H_2O to the α-carbon of **B** generated the hydroxyl-acid **C**, which upon lactonization would form the lactone acid **166**. Alternatively, the acid hydroxyl group of **B** can attack the α-carbon of the unstable 3-membered ring to form **166** directly. Either mechanism can account for the overall retention of configuration for this process. Acid **166** was converted to the corresponding acid chloride **165** by treatment with thionyl chloride at reflux temperature.[61] The acid chloride was then converted to the amide **167** in 71% overall yield by treatment with the model amine $BnNH_2$ and Et_3N in CH_2Cl_2 at

0 ºC. The relatively strong base *t*-BuOK (0.4 equiv) was employed to transform the amide **167** into the imide **168** at -78 ºC to -55 ºC using the method reported by Ruan[59] (**Scheme 2.3**).



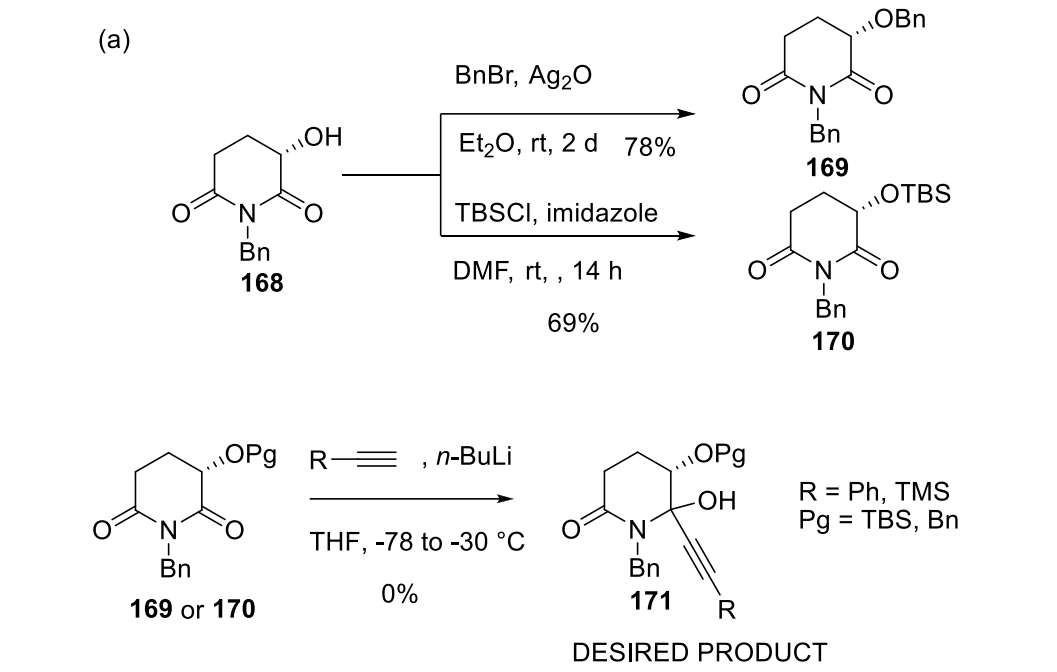
Scheme 2.3: Synthesis of the imide **168**

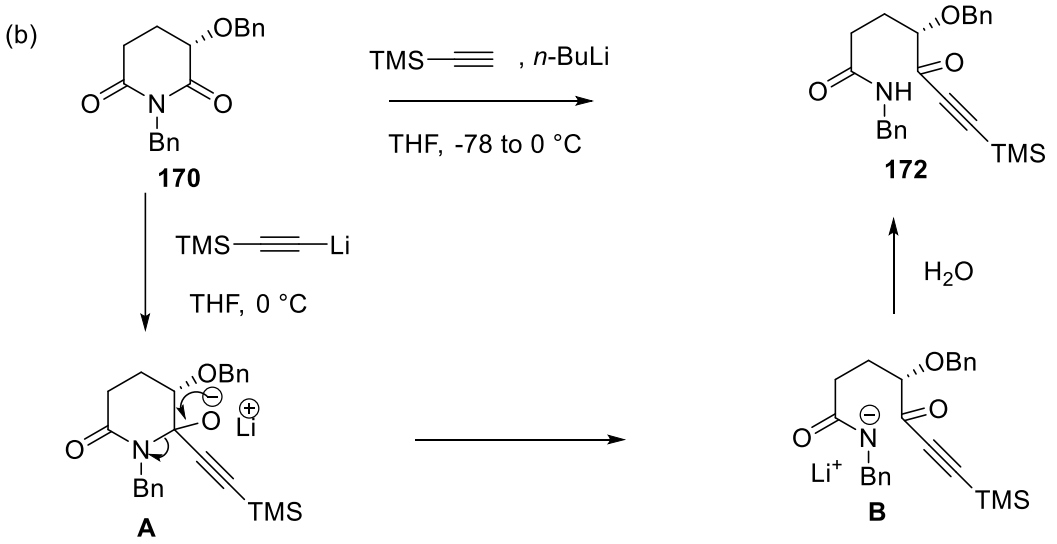


Scheme 2.4: Formation of lactone **166**

Protection of the hydroxy group of **168** by either Bn[62] or TBS[63] groups using standard reaction conditions produced compounds **169** and **170**, respectively (**Scheme 2.5**). The next step involved the nucleophilic addition of a lithium acetylide (RCCLi, R = Ph or TMS) to the carbonyl group of imides **169** or **170** to produce the desired adducts **171** (**Scheme 2.5**). The reactions using phenylacetylene were for model studies to develop the methodology. None of these desired products were formed at the reaction temperature of -78 ºC or when the reaction mixture was warmed to -30 ºC, only the starting imides were recovered. These results are in contrast to the conversion of **158** to **159** at -78 ºC (**Scheme 2.1**). When the reaction

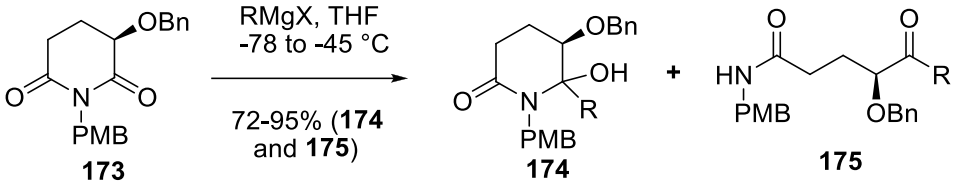
of **170** with TMSCCLi was warmed to 0 ºC the ring-opening product **172** was obtained instead of the desired one **171** (Pg = Bn, R = TMS) (**Scheme 2.5**).





Scheme 2.5: (a) Attempted addition of RCCLi to imides **169** and **170** and (b) the proposed mechanism for the formation of **172**

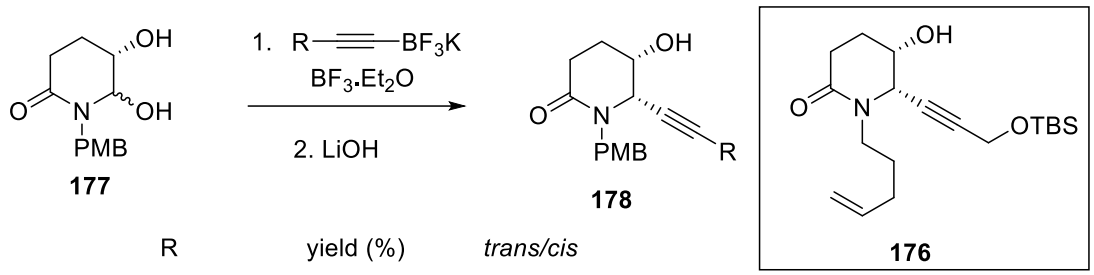
Presumably the addition of the organolithium to the more nucleophilic carbonyl group of **170** initially formed the intermediate **A**. This intermediate was then converted to the intermediate **B**. Protonation of **B** during work up process forms the ring opening product **172**. We did not attempt to purify this product, however the ^{1}H NMR spectrum of the crude reaction mixture showed a broad resonance for the amide NH group at δ 6.2. A similar problem was reported by Huang *et al*. [64] In their report, the addition of Grignard reagents to the imide **173** formed mixtures of the desired products **174** and the ring opened products **175** (**Scheme 2.6**). Clearly, the 5 and 6-membered ring imides behave differently upon nucleophilic addition, with the 5-membered ring imides favouring the ring closed products (**Scheme 2.1**).



(product ratios not given)

Scheme 2.6: Huang's study of the addition of Grignard reagents to **173**[64]

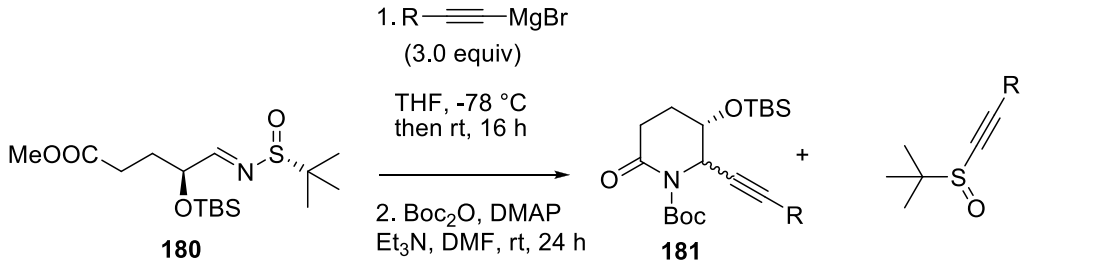
Another possible method for the synthesis of **176** (**142**; Pg = H, R = CH_2OTBS) was also considered but not pursued (**Scheme 2.7**). Pyne reported a method for the synthesis of *cis*-lactams **178** *via* the borono-Mannich reaction of the hemiaminal **177** with potassium alkynyltrifluoroborate salts (**Scheme 2.8**).[65] Although these reactions gave the desired products with good diasteroselectivities, the yields were not satisfactory (maximum yield of 36% with R = Ph) and therefore this procedure was not applied to the synthesis of the lactam **176**.



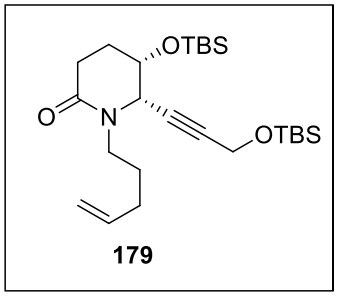
R	yield (%)	*trans/cis*
TMS	31	0:100
Ph	36	9:91

Scheme 2.7: Pyne's synthesis of *cis*-lactams **178**[65]

During the writing of this thesis, an alternative synthesis of *cis*-lactams **181**, which could be applied to synthesize the lactam **179** (**142**; Pg = OTBS, R = CH_2OTBS) (**Scheme 2.8**), was reported. Wei prepared lactams **181** by treatment of the chiral α-OTBS aldimine **180** with Grignard reagents followed by *N*-protection by the Boc group.[66] However, lactams **181** were prepared in low yields (maximum yield = 32%) and as mixtures of *cis* and *trans* isomers (**Scheme 2.8**).



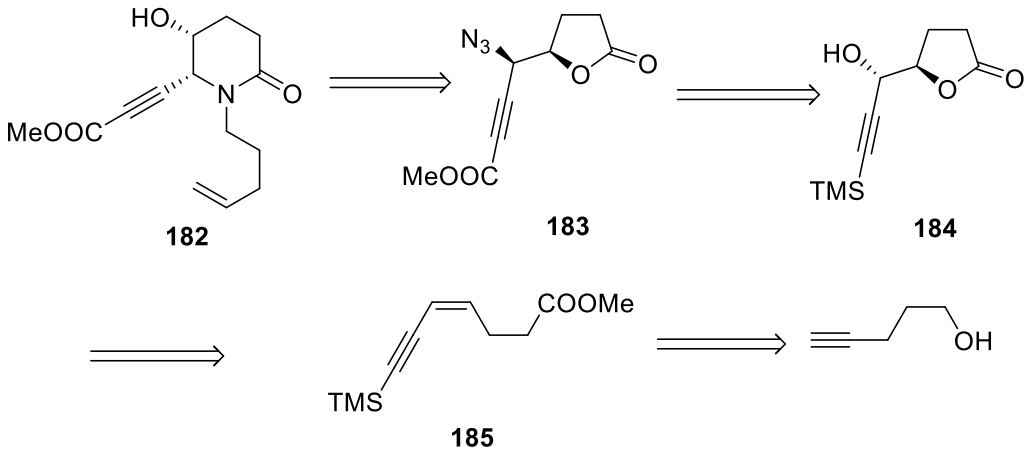
R	yield (%)	*trans/cis*
3-Me-C_6H_4-	32	15:85
4-Cl-C_6H_4-	28	13:87
$TBSOCH_2CH_2$-	23	5:95
$CH_3(CH_2)_3CH_2$-	27	22:78



Scheme 2.8: Wei's synthesis of *cis*-lactams **181**[66]

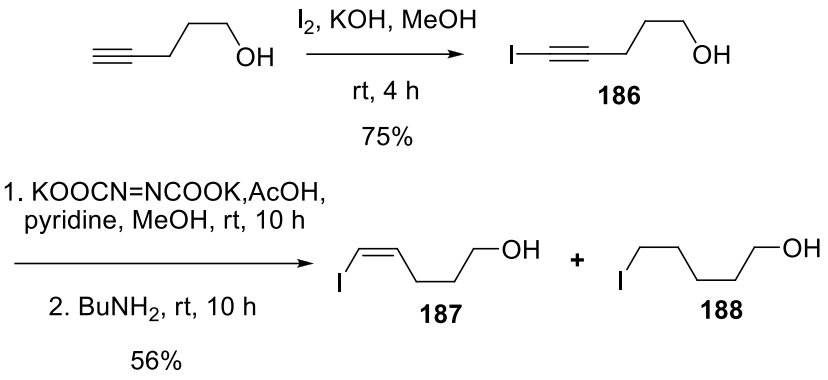
2.2 Second synthetic pathway, via an azido lactone (synthetic strategy 2)

Because of the aforementioned problems, we then investigated another synthetic route to prepare the ene-yne lactam **182** (**142**, Pg = H, R = COOMe) following the retrosynthetic analysis shown in **Scheme 2.9**. In principle, compound **182** could be prepared from the azido-lactone **183** via a Staudinger/aza-Wittig reaction of the azide group with 4-pentenal, followed by a base catalysed (*t*-BuOK) rearrangement of the corresponding amino-δ-lactone to the hydroxyl lactam **182**. Azido lactone **183** could be synthesized from the hydroxy lactone **184** via a functional group interconversion sequence. The lactone **184** could be prepared from the ene-yne **185** via *syn*-dihydroxylation of the alkene group and then lactonization. The ene-yne **185** could be obtained from 4-pentyn-ol in five synthetic steps.

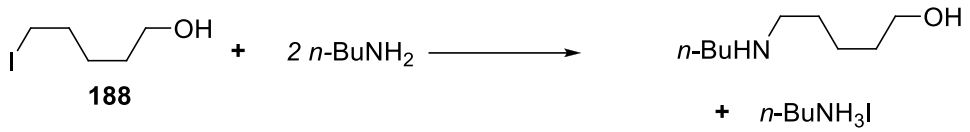


Scheme 2.9: Retrosynthetic analysis of the lactam **182**

For the synthesis of **185**, iodination of 4-pentyn-1-ol with I_2/KOH in MeOH led to the iodide **186**, which underwent *syn*-reduction of the alkyne by diimide (NH=NH), prepared *in situ* from potassium azodicarboxylate and AcOH, to give the known (*Z*)-vinyl iodide **187**[67] in 56% yield (**Scheme 2.10**). In fact, this reduction reaction gave two products, the desired vinyl iodide **187** and its saturated derivative **188**. The latter undesired product was removed by treatment of the reaction product mixture with $BuNH_2$ at rt for 10 h. This process converted **188** to its amine derivative, which could be separated from **187** by an acid extraction process (**Scheme 2.11**).

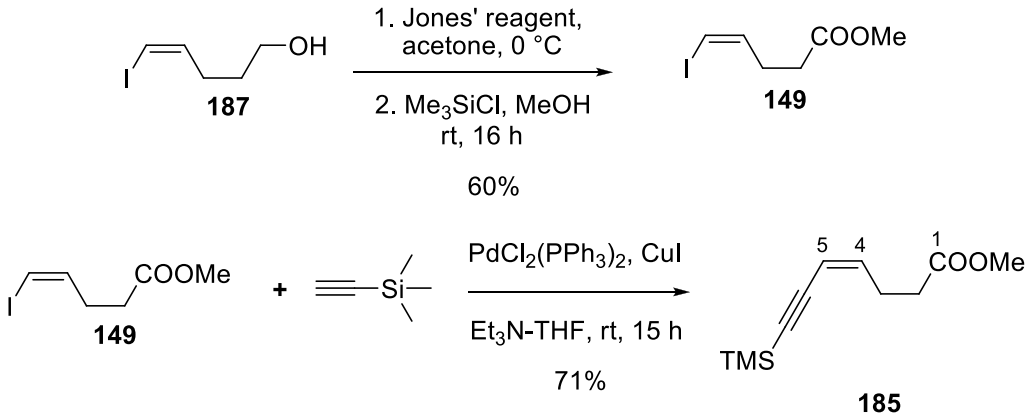


Scheme 2.10: Synthesis of *Z*-iodide **187**



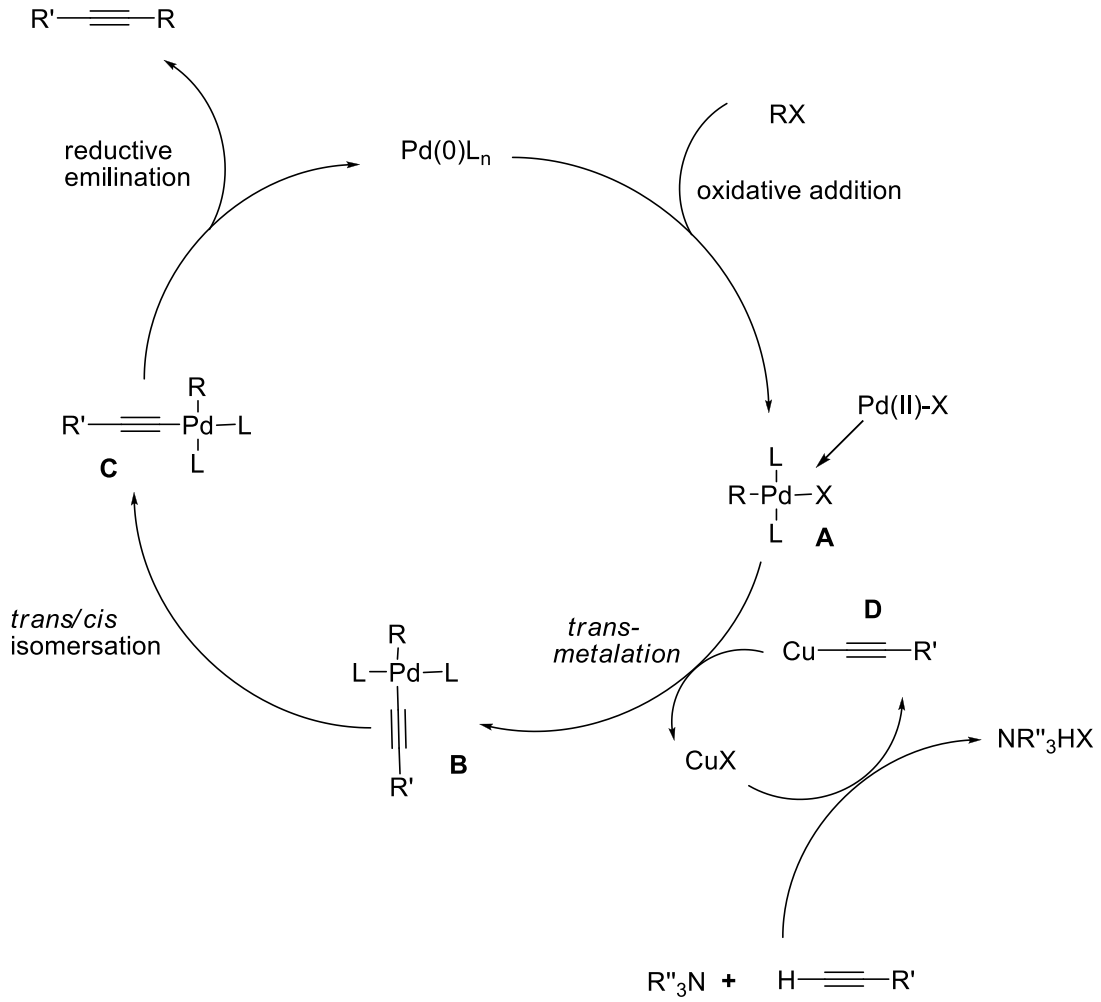
Scheme 2.11: Removal of the byproduct **188** by *n*-$BuNH_2$

Jones' oxidation of the primary alcohol **187** gave the known corresponding acid,[68] which was converted to the known methyl ester **149** by treatment with Me_3SiCl in MeOH (**Scheme 2.12**).[68] Sonogashira coupling of **149** with trimethylsilylacetylene catalysed by $PdCl_2(PPh_3)_2$/CuI[69] in a solvent mixture of THF-Et_3N under a N_2 atmosphere provided the novel ene-yne **185** in 71% yield (**Scheme 2.12**). The *Z*-configuration of **185** was confirmed by the magnitude of the coupling constant $J_{4,5}$ (10.5 Hz), which was a typical value for a *Z*-alkene.[70]



Scheme 2.12: Synthesis of *Z*-alkene **185**

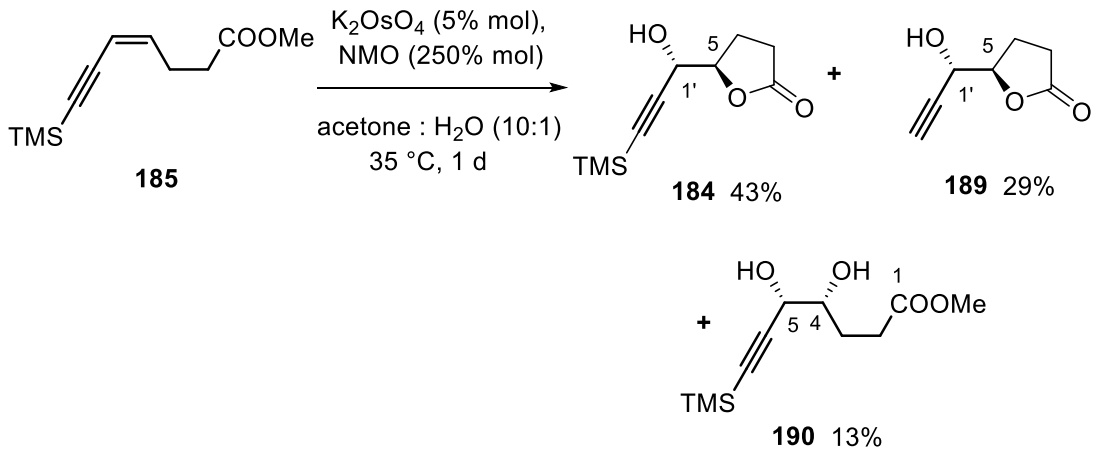
The accepted mechanism for the Sonogashira coupling reaction is shown in **Scheme 2.13**.[71] Initially, the catalyst reacts with a vinyl or aryl halide (RX) *via* an oxidative addition process to produce the Pd(II) complex **A**. This complex undergoes transmetalation with the copper acetylide **D**, which is formed from the reaction between the copper halide, the terminal alkyne and the tertiary amine (Et_3N), to give the Pd(II) complex **B**. Complex **B** undergoes a *trans/cis* isomerization of the two ligands L to form the complex **C**. In the final step, complex **C** undergoes reductive elimination to produce the substituted alkyne product, with regeneration of the Pd(0) catalyst.



Scheme 2.13: Accepted mechanism for the Sonogashira coupling reaction[71]

It should be noted that in the proceeding schemes all compounds are racemic, although only one enantiomer is shown for convenience with the desired configuration for the synthesis of stemocurtisine.

Syn-dihydroxylation of the alkene **185** with catalytic OsO_4, prepared *in situ* from K_2OsO_4 (0.05 equiv) and NMO (2.5 equiv), gave a chromatographically separable mixture of the racemic desired lactone **184**, the desilylated lactone **189** and the diol ester **190** (**Scheme 214**).[72] The undesired lactone **189**, which formed via loss of the terminal TMS group, accounted for 29% of the reaction product. Perhaps, this loss was due to the formation of the base *N*-methylmorpholine (from the reduction of NMO) which could generate a low concentration of hydroxide from water, which could cleave the TMS group.



Scheme 2.14: *Syn*-dihydroxylation reaction of **185**

The IR spectrum of **184** showed bands for a δ-lactone carbonyl at 1757 cm^{-1}, a hydroxyl group at 3402 cm^{-1} and an alkyne triple bond at 2170 cm^{-1}. In the ^1H NMR spectrum of **184**, the signals for the two oxymethine protons, H-5 and H-1', overlapped and resonated at δ 4.37-4.27 (m, 2H). The ^{13}C NMR spectrum of **184** showed diagnostic resonances for the carbonyl group at δ 174.9, the two oxymethine carbons C-5 and C-1' at δ 73.7 and 66.9, respectively and the CH_3-Si group at δ 0.12.

The IR spectrum of **189** showed bands for a δ-lactone carbonyl at 1763 cm^{-1}, a terminal alkyne C-H stretch at 2312 cm^{-1}, and an alkyne triple bond at 2180 cm^{-1}.

The ^{1}H NMR spectrum of **189** was similar to that of **184** except that the resonances for H-5 and H-1' overlapped and resonated at δ 4.66-4.56 (m, 2H). In addition, the alkynyl CH proton resonated at δ 2.49 (s, 1H, H3'). The ^{13}C NMR spectrum showed a resonance for the carbonyl group at δ 178.3. The lactone **189** was a known compound and its NMR spectroscopic data were consistent with those reported in the literature.[73]

In the ^{1}H NMR spectrum of compound **190**, the H-5 proton resonance appeared as a doublet at δ 4.32 with a coupling constant $J_{4.5}$ = 3.5 Hz, which is typical for this type of *anti*-1,2-diol. For example, in the ^{1}H NMR spectrum of compound **191 A**, H-3 resonated at δ 4.35 with the coupling constant $J_{2,3}$ = 3.5 Hz, while $J_{2,3}$ = 6.5 Hz in its *syn*-isomer **191 B** (**Figure 2.2**).[74] In addition, HRESIMS analysis (calcd. for $C_{11}H_{20}O_4SiNa$, $(M+Na)^+$ 267.1029, found 267.1026) confirmed the molecular formula of compound **190**.

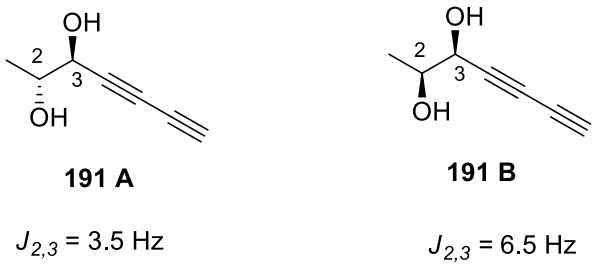
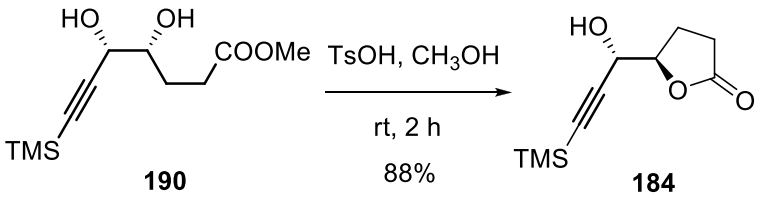


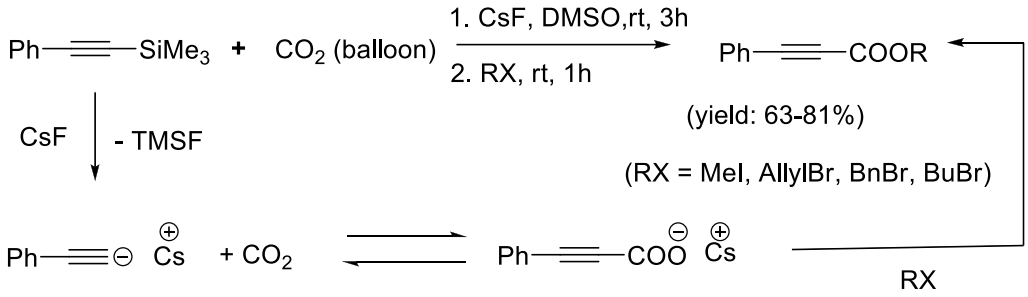
Figure 2.2: Structures and $J_{2,3}$ for the diols **191 A** and **191 B**[74]

The diol **190** could be converted to the hydroxy-lactone **184** in 88% yield by treatment with TsOH (1.5 equiv) in MeOH at rt for 2 h (**Scheme 2.15**).[75] This conversion also helped confirm the structures of these two compounds.



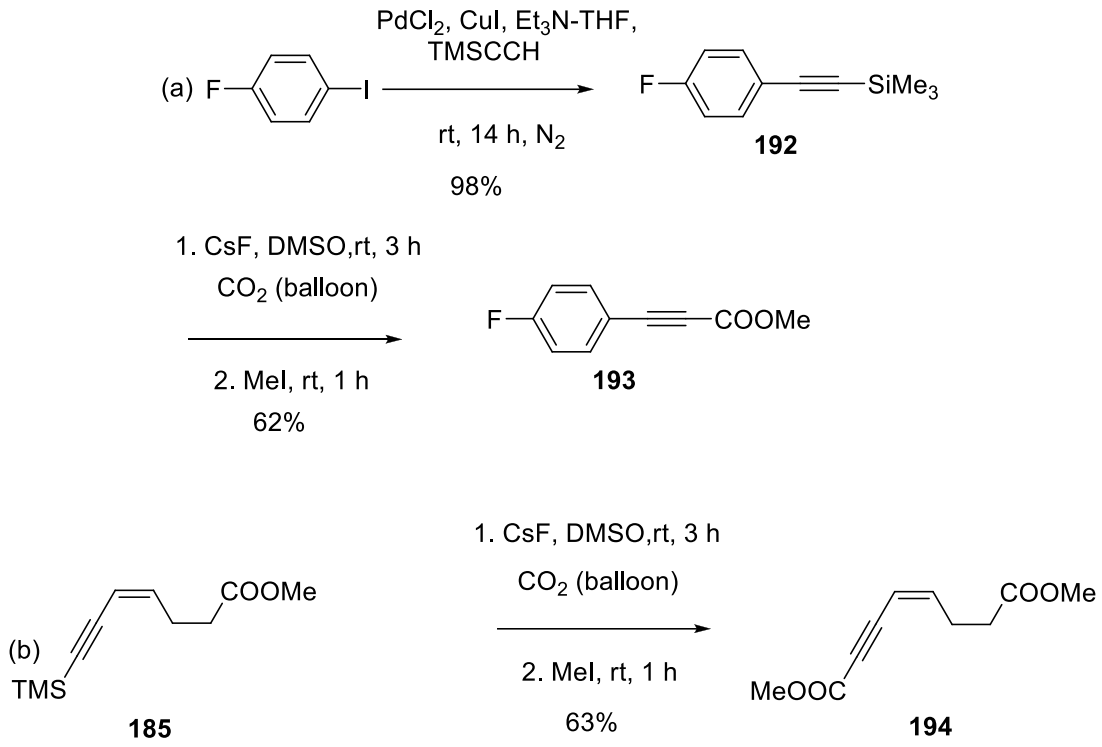
Scheme 2.15: Conversion of diol ester **190** to lactone **184**[75]

The next step in the synthesis was to replace the terminal TMS substituent of **184** with an ester group. Kondo reported a method of carboxylation of alkynyltrimethylsilanes to make the corresponding esters.[76] In this procedure, the silanes were treated with CsF and a primary halide (RX) in DMSO under a CO_2 atmosphere to provide the appropriate alkyne esters (yields = 63-81%). This reaction most likely proceeds via the ionic intermediates shown in **Scheme 2.16**, with the formation of $PhCCCO_2Cs$ *in situ* followed by its irreversible *O*-alkylation with RX to give the ester $PhCCCO_2R$.

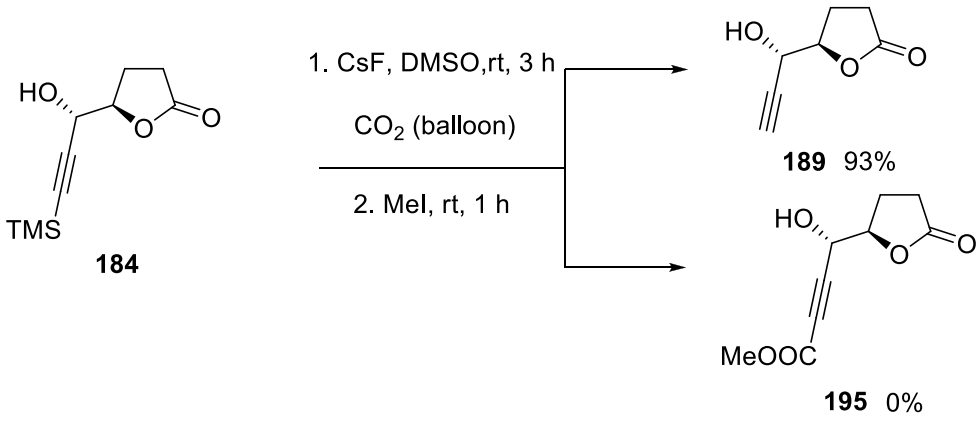


Scheme 2.16: Kondo's synthesis of alkyne esters from terminal alkyne silanes[76]

We first examined this method using the model compound **192**, which was obtained in 98% yield from 4-fluoro-iodobenzene and trimethylsilylacetylene via a Sonogashira coupling reaction.[69] Under the literature conditions, the methyl ester **193** was obtained in 62% yield from **192** (**Scheme 2.17** (a)). Using similar conditions we obtained the diester **194** in 63% yield from **185** (**Scheme 2.17** (b)). Unfortunately, the desired ester **195** was not formed when we applied the same conditions to **184**. Only the undesired terminal alkyne **189**, which we observed earlier in **Scheme 2.14**, was formed via a proto-desilylation reaction (**Scheme 2.18**). We suspect that the hydroxyl group ($pK_a \approx 16$)[77] in **184**, being more acidic than the terminal alkyne group ($pK_a \approx 25$),[77] protonates the initially formed cesium acetylide intermediate to give the terminal alkyne derivative **189**.

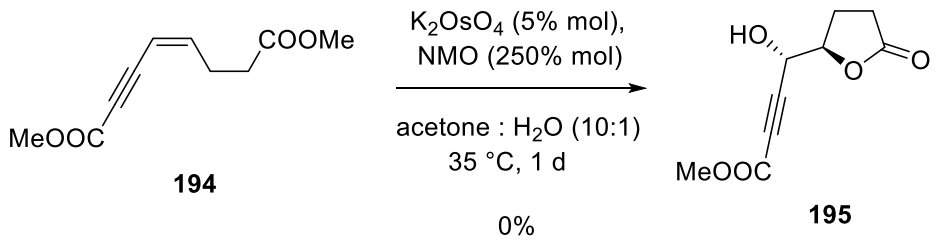


Scheme 2.17: Model work using Kondo's method



Scheme 2.18: Attempted synthesis of **195** using Kondo's protocol

We also attempted to prepare the lactone ester **195** directly from the diester **194** by a *syn*-dihydroxylation reaction. However this reaction failed to form the desired product **195** and only unreacted starting material was recovered (**Scheme 2.19**). The poor reactivity of **194** was due to the electron withdrawing effect of the alkyne ester substituent which made the alkene more electron deficient and therefore less relative towards electrophilic OsO_4.

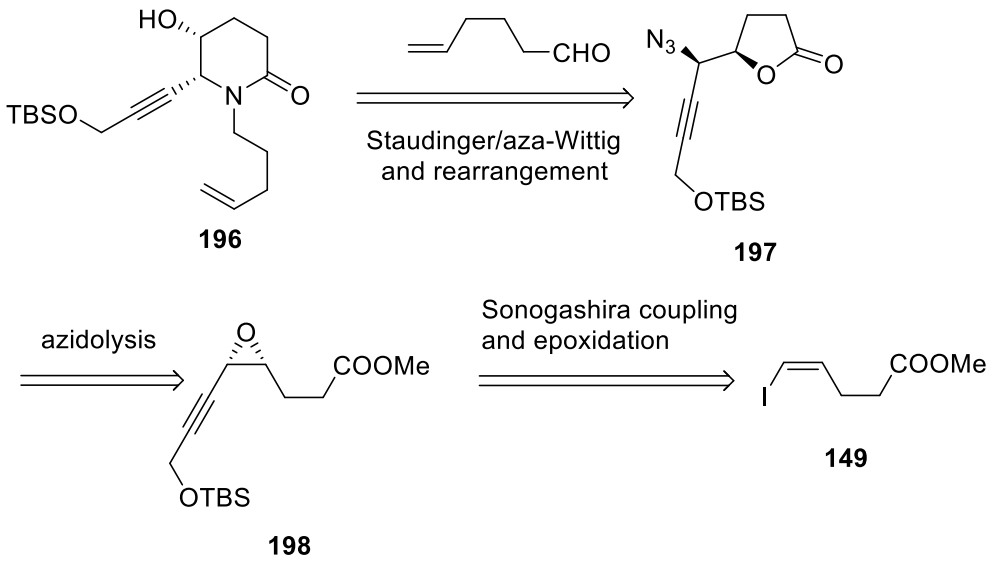


Scheme 2.19: Attempted dihydroxylation reaction of **194**

Due to the low overall yield in the preparation of **184** (8.5% over 5 steps) and its failure to be converted to its corresponding ester **195**, we next examined an alternative synthetic pathway to prepare the target ene-yne lactam **142**.

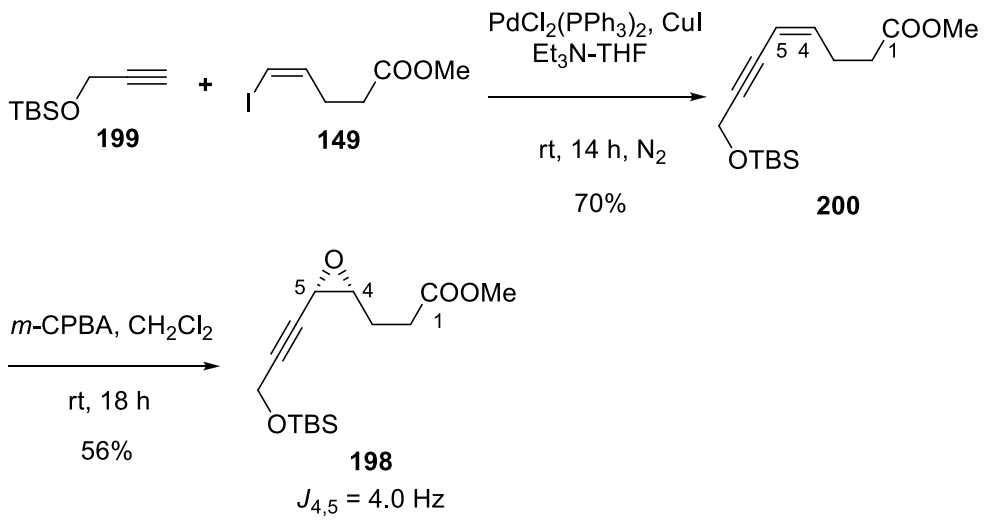
2.3 **The third synthetic pathway, via an epoxide** (synthetic strategy 3)

An alternative route to the synthesis of the lactam **196** (**142**, Pg = H, R = CH_2OTBS) was examined following the retrosynthetic analysis outlined in **Scheme 2.20**. Following this synthetic strategy, lactam **196** could be obtained from the azide **197** via a Staudinger/aza-Wittig reaction by treatment with 4-pentenal, followed by a base-catalysed rearrangement of the resulting 5-membered ring amino-lactone to a 6-membered ring hydroxy-lactam. The azide **197** could be prepared by an azidolysis reaction of the epoxide **198**, which could be obtained from **149** via a Sonogashira coupling reaction followed by an epoxidation process.

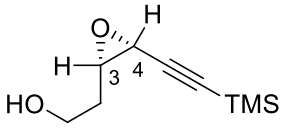


Scheme 2.20: An alternative retrosynthesis of **196** (**142**, Pg = H, R = CH_2OTBS)

Sonogashira coupling of the *Z*-vinyliodide **149** with the prepared alkyne **199** proceeded smoothly to provide the ene-yne **200** in good yield (75%) (**Scheme 2.21**). The *Z*-configuration of alkene **200** was confirmed by the coupling constant $J_{4,5}$ = 10.7 Hz (δ 5.53 (d, *J* = 10.7 Hz, 1H, H5)).[70] Epoxidation of **200** with *m*-CPBA in CH_2Cl_2 gave a chromatographically separable mixture of the racemic epoxide **198** (56% yield) and the starting material (24% recovered) (**Scheme 2.21**). The ^{1}H NMR coupling constant $J_{4,5}$ = 4.0 Hz (δ 3.48 (d, *J* = 4.0 Hz, 1H, H5) and δ 3.14 (ddd, *J* = 6.5, 5.5, 4.0 Hz, 1H, H4)) confirmed the *cis*-configuration of the epoxide **198** at C-4 and C-5. These chemical shifts and coupling constants for H-4 and H-5 were consistent with those for the related protons, H-3 and H-4, of compound **201** (**Figure 2.3**) in the reported literature (δ 3.48 (d, $J_{3,4}$ = 4.0 Hz, 1H, H4) and δ 3.26-3.22 (m, 1H, H3)).[78]



Scheme 2.21: Synthesis of the epoxide **198**

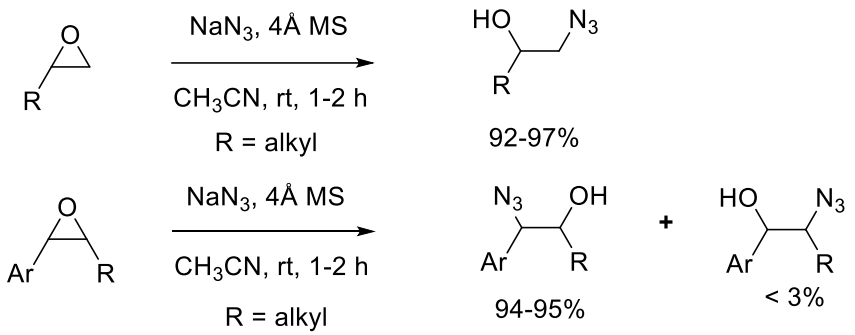


201

$J_{3,4}$ = 4.0 Hz

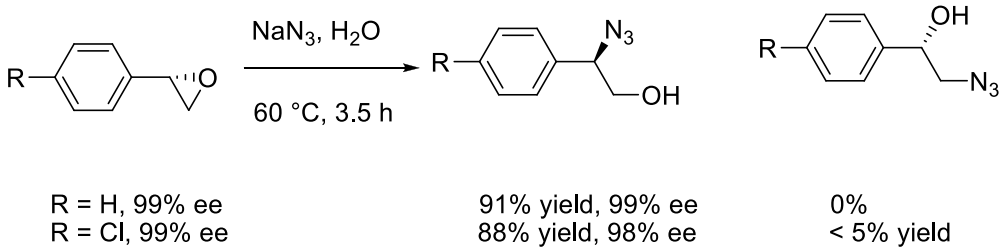
Figure 2.3: Structure and $J_{3,4}$ for the *cis*-epoxide **201**[78]

Barua reported a method for the azidolysis of epoxides using NaN_3 with 4Å molecular sieves in CH_3CN.[79] With monoalkyl substituted epoxides, the azide group attacked the less hindered carbon of the epoxide and gave β-hydroxy azide products in excellent yields (92-97%). Whereas with aryl epoxides the azide group mainly attacked the aryl (Ar) substituted carbon to give ring opened products in very good yields and with high regioselectivities (**Scheme 2.22**).



Scheme 2.22: Barua's synthesis of azides[79]

Margarita reported the synthesis of chiral azides from chiral 2-aryl epoxides using NaN_3 in hot water.[80] Azides were obtained in high yields and with excellent regioselectivities and enantiomeric purities (**Scheme 2.23**).



Scheme 2.23: Margarita's synthesis of chiral azides[80]

We tried both of these methods to make an azide from the ring opening of the epoxide **198** with NaN_3. However, both methods failed, and only the unreacted starting material was recovered (**Scheme 2.24**).

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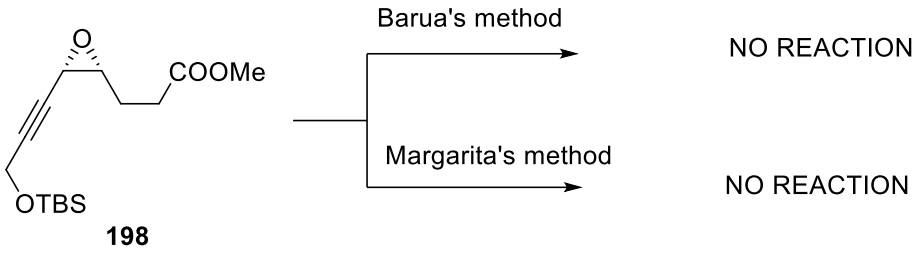
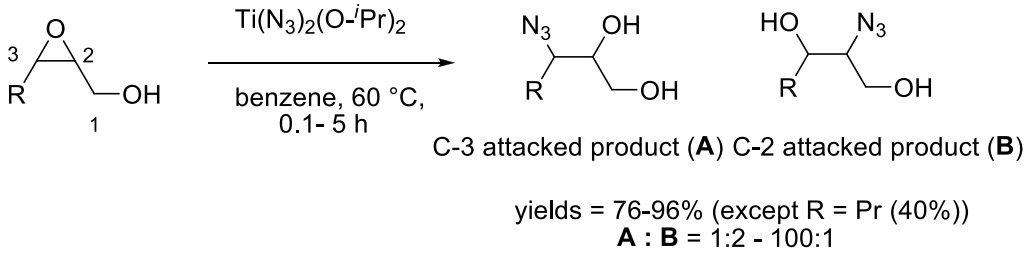
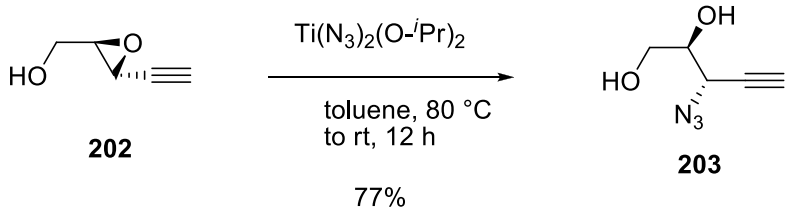


Scheme 2.24: Attempted epoxide ring opening of **198** under Buara's and Margarita's conditions

Kesselmayer reported a method of ring opening of 2-hydroxymethyl epoxides with $Ti(O\text{-}^{i}Pr)_2(N_3)_2$,[81] which was prepared *in situ* from the reaction of $Ti(O\text{-}^{i}Pr)_4$ and $TMSN_3$. Noticeably, with the phenyl epoxide (R = Ph) the reaction gave almost exclusively the products arising from attack at C3 (**A:B** > 100:1) (**Scheme 2.25**). McDonald employed the same reagent to prepare the azide **203** from the alkynyl epoxide **202** in 77% yield (**Scheme 2.26**).[82]

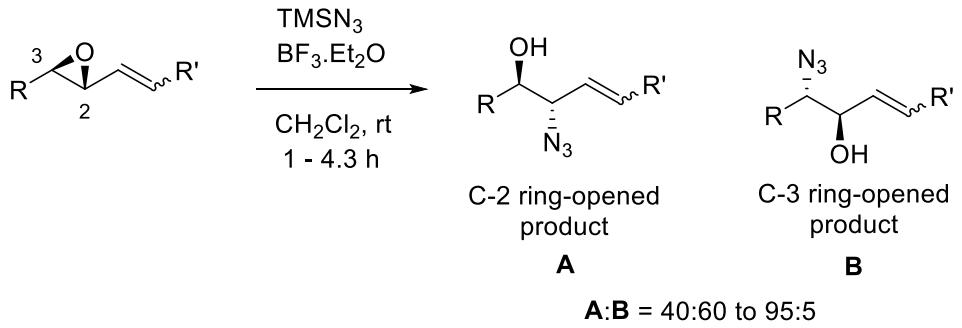


Scheme 2.25: Kesselmayer's synthesis of azides[81]



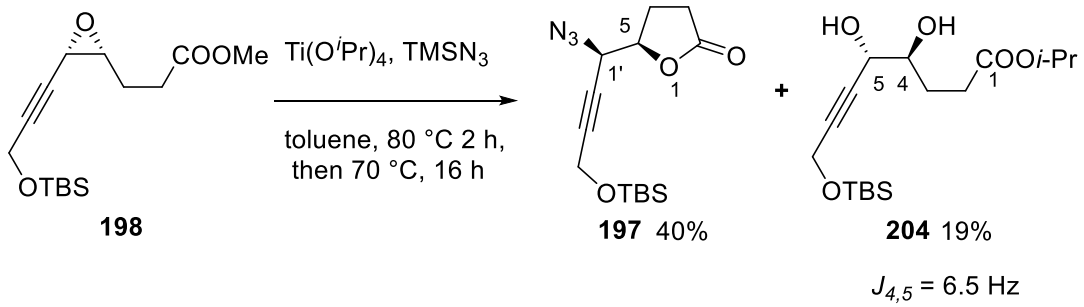
Scheme 2.26: McDonald's synthesis of azide **203**[82]

Righi reported that treatment of vinyl epoxides with $TMSN_3$ and $BF_3.Et_2O$ gave mixtures of C-2 and C-3 ring-opened products in moderate to excellent yields (48-96%) (**Scheme 2.27**).[83]



Scheme 2.27: Righi's azidolysis of chiral vinyl epoxide using $TMSN_3$[83]

The results from our attempts at the ring opening of epoxide **198** under Kesselmayer's conditions were not so impressive. The desired azide lactone **197** was obtained in a relatively low yield (40%). Surprisingly, the diol *i*-propyl ester **204** was also formed in 19% yield (**Scheme 2.28**).



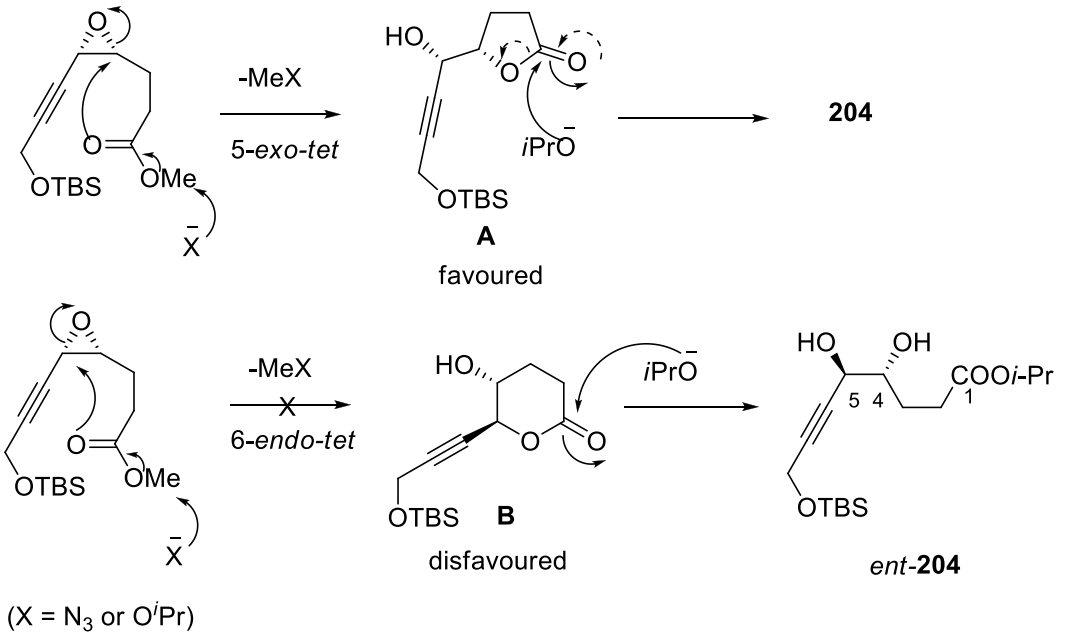
Scheme 2.28: Synthesis of azide **197**

In the IR spectrum of **197**, the δ-lactone carbonyl gave rise to a band at 1774 cm^{-1}, and the azide group gave rise to a band at 2140 cm^{-1}, while the alkyne triple bond appeared as a band at 2220 cm^{-1}. In the ^1H NMR spectrum of **197**, H-5 resonated downfield at δ 4.54 (dt, J = 7.0, 6.0 Hz, 1H, H5). These spectroscopic data were consistent with ring opening by azide at the activated propargyl carbon of the epoxide **198** and formation of a δ-lactone. The ^{13}C NMR spectrum of **197** showed a resonance for the carbonyl group at δ 176.2. The molecular formula of **197** was confirmed by HRESIMS (calcd. for $C_{14}H_{24}O_3N_3Si$, $(M+H)^+$ 310.1587, found: 310.1589).

In contrast to compound **190** (**Scheme 2.14**), H-5 in the ^1H NMR spectrum of **204** resonated at a more upfield position δ 4.20 (d, J = 6.5 Hz, 1H, H5). The chemical

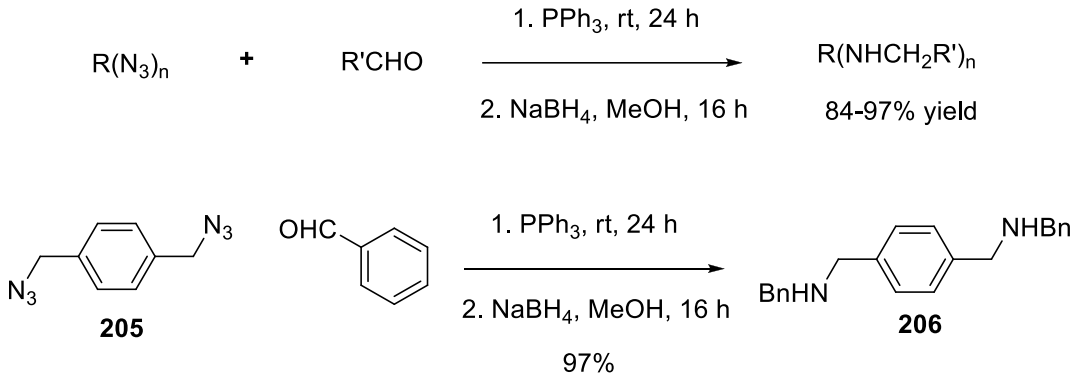
shift and the relatively large coupling constant $J_{4,5}$ = 6.5 Hz were consistent with those of the *syn*-isomer **191 B** (H3 δ 4.15, $J_{2.3}$ = 6.5 Hz) (**Figure 2.2**)[74] and allowed for the relative 4,5-*syn* configuration of **204** to be assigned at C-4 and C-5. Resonances for the isopropyl group occurred at δ 5.04 (heptet, *J* = 6.0 Hz, 1H, OC*H*$(CH_3)_2$) and δ 1.23 (d, *J* = 6.0 Hz, 6H, OCH(C*H*$_3)_2$). The molecular formula of **204** was confirmed by HRESIMS (calcd. for $C_{17}H_{32}O_5SiNa$, $(M+Na)^+$ 367.1918, found: 367.1917).

Since the diol ester **204** was formed under anhydrous conditions, the formation of **204** possibly involves an intramolecular epoxide ring opening of **198** by the ester carbonyl group to form the intermediate 5-membered ring lactone **A** via a 5-*exo-tet* process (**Scheme 2.29**). An alternative intermediate is the 6-membered ring lactone **B** formed via a 6-*endo-tet* process. According to Baldwin's rules[84] for the tetrahedral (*tet*) system, 5-*exo-tet* attack is favoured in this step and the intermediate 5-membered ring lactone **A** is predicted to be formed (3 to 7-*exo-tet* cyclizations are favoured, while 5 to 6-*endo-tet* cyclizations are disfavoured).[84] Addition of $^{i}PrO^-$ to the carbonyl group of lactone **A** produces diol **204** after protonolysis. The same racemic diol (drawn as *ent*-**204** in **Scheme 2.29**) could also possibly arise from the disfavoured 6-*endo-tet* process. These possibilities are summarized in **Scheme 2.29**.

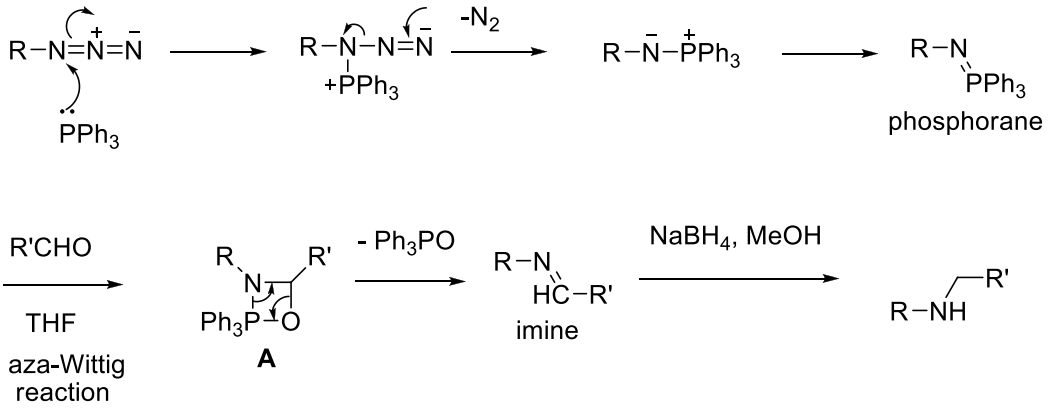


Scheme 2.29: Proposed mechanism for the formation of **204**

Lee reported a method for the preparation of polyamines from polyazides in excellent yields (84-98%) based on the Staudinger/aza-Wittig reaction (**Scheme 2.30**).[85] For example the bisamine **206** was obtained from the bisazide **205** in 97% yield. The Staudinger/aza-Wittig reaction starts with the addition of PPh_3 to the azide group to form a phosphorane intermediate (Staudinger reaction, **Scheme 2.31**). The phosphorane then reacts slowly with the aldehyde to give the unstable 4-membered ring azaphosphetane intermediate **A**, then the corresponding imine and Ph_3PO (aza-Wittig reaction). Reduction of this imine with $NaBH_4$/MeOH then gives the corresponding amine (**Scheme 2.31**).



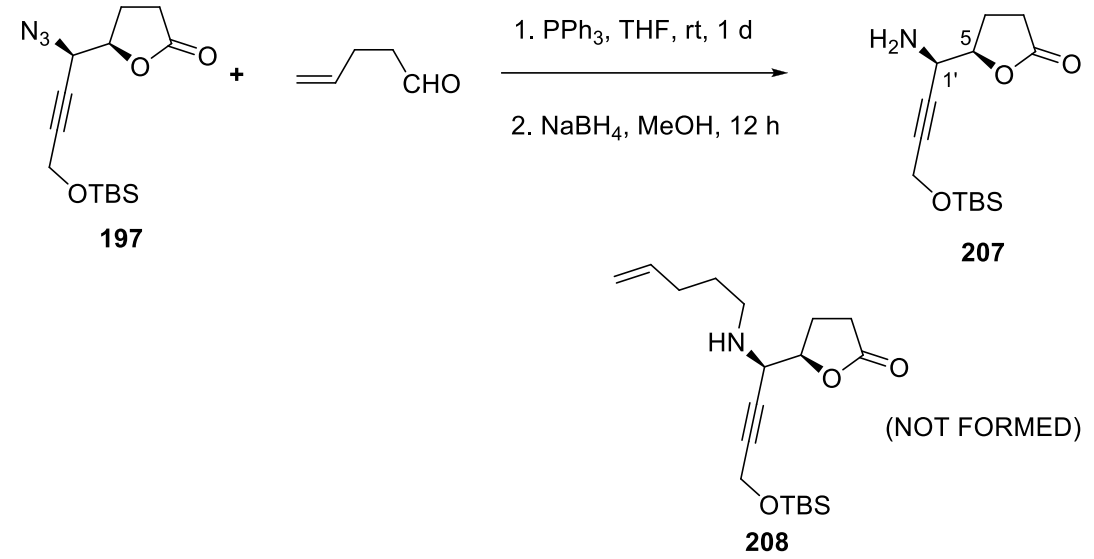
Scheme 2.30: Lee's synthesis of polyamines[85]



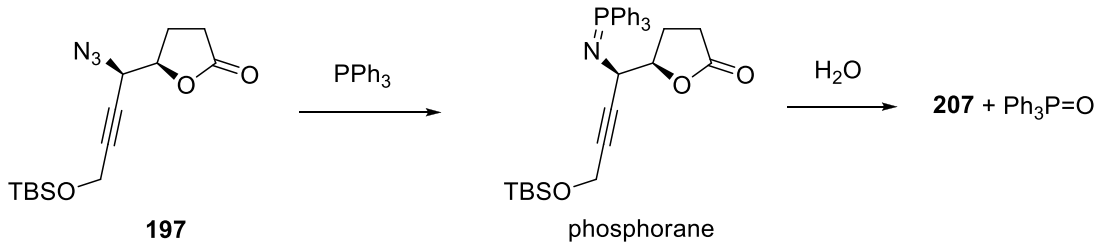
Scheme 2.31: Proposed mechanism for Staudinger/aza-Wittig reaction

Follow this method, azide **197** was treated with PPh_3 (1.1 equiv) and 4-pentenal (1.4 equiv) in THF for 1 d. $NaBH_4$ and MeOH were then added and the mixture was

stirred for 12 h. Unfortunately, only the primary amine **207** was formed instead of the desired product **208** (**Scheme 2.32**). Presumably, the quality of the aldehyde caused this deviation. 4-Pentenal is not commercially available, and was prepared from 4-penten-1-ol by oxidation with PCC. The aldehyde was very volatile and therefore we used it directly as a solution in CH_2Cl_2 and diethylether without purification. It appears that water in the aldehyde (perhaps as the hydrate) may have hydrolysed the intermediate phosphorane to the amine **207** (**Scheme 2.33**).



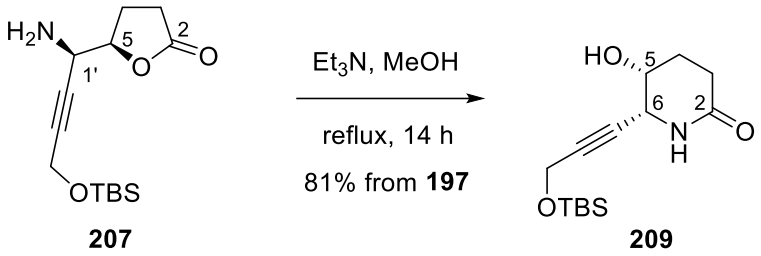
Scheme 2.32: Attempted Staudinger/aza-Wittig reaction of azide **197** with 4-pentenal



Scheme 2.33: Formation of the primary amine **207**

Amine **207** was obtained as a mixture with Ph_3PO. We did not isolate the amine **207** by column chromatography, however the ^1H NMR spectrum showed resonances for

the protons H-5 and H-1' at δ 4.46 (dd, J = 6.8, 6.8 Hz, 1H, H5) and δ 3.78 (d, J = 6.8 Hz, 1H, H1'), respectively. These resonances were consistent with the proposed structure **207**. This mixture then was heated with Et_3N in methanol at reflux temperature for 14 h to form the lactam **209** in 81% yield (over two steps from **197**) (**Scheme 2.34**).



Scheme 2.34: Synthesis of lactam **209**

The IR spectrum of **209** showed a lactam carbonyl band at 1638 cm^{-1}. The ^1H NMR and ^{13}C NMR spectra of **209** are shown in **Figures 2.5** and **2.6**, respectively. The NMR assignments of **209** were based on 2D NMR experiments (COSY, HSQC and HMBC). In the ^1H NMR spectrum of **209**, the lactam NH resonated at δ 5.75 (bs, 1H, NH). When compared to the chemical shift of H-1' (δ 3.78) in **207**, the corresponding proton H-6 in the ^1H NMR spectrum of lactam **209** appeared at lower field (δ 4.40, s) due to the deshielding and electron-withdrawing effects of the carbonyl group, while H-5 of **209** resonated at higher field (δ 4.10 (s, 1H, H5)) than H-5 (δ 4.46) in the ^1H NMR spectrum of **207**. These chemical shift differences between compounds **207** and **209** were therefore consistent with their assigned structures. The very small $J_{5,6}$ value of < 1 Hz in the ^1H NMR spectrum of **209** was consistent with the 5,6-*cis*-stereochemistry. For example, in the ^1H NMR spectrum of the *cis* compound **210 A**, the H-6 resonance appeared as a doublet at δ 4.66 with a coupling constant $J_{5,6}$ = 2.9 Hz, while in the ^1H NMR spectrum of **210 B**, the H-6 resonance appeared as a doublet at δ 4.48 with a coupling constant $J_{5,6}$ = 4.6 Hz (**Figure 2.4**).[86] Furthermore, the HRESIMS (calcd. for $C_{14}H_{26}O_3NSi$, $(M+H)^+$ 284.1678, found: 284.1682) confirmed the molecular formula of **209**.

210 A

$J_{5,6}$ = 2.9 Hz

210 B

$J_{5,6}$ = 4.6 Hz

Figure 2.4: Structures and $J_{5,6}$ coupling constants of **210 A** and **210 B**[86]

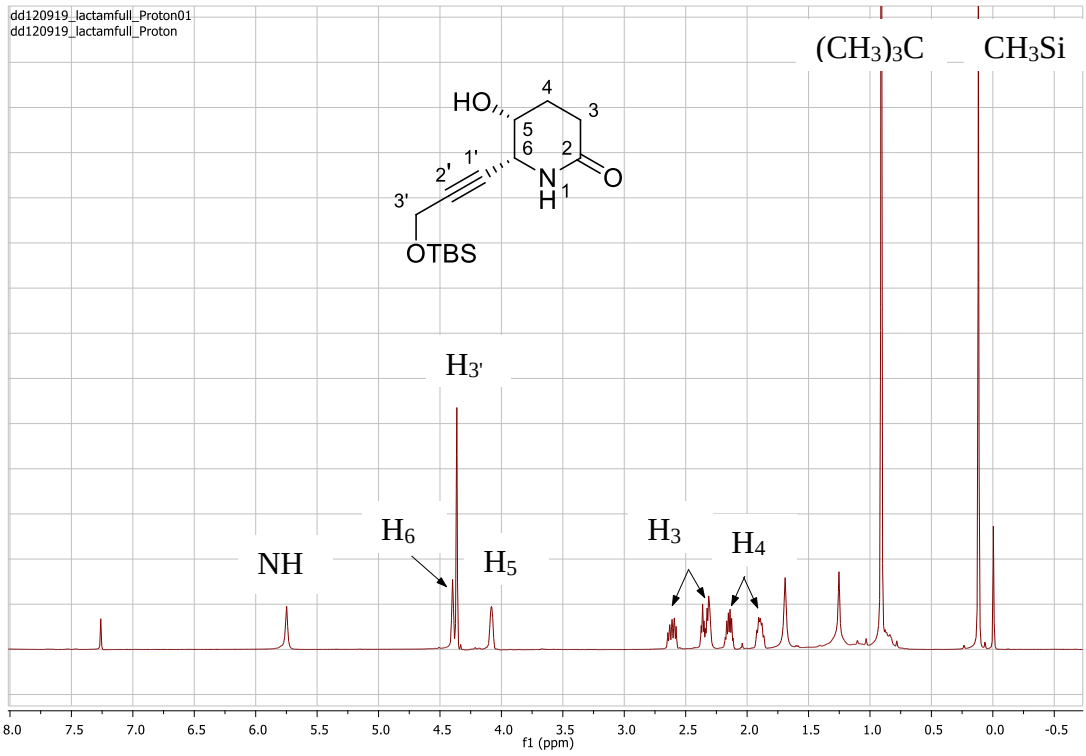


Figure 2.5: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **209**

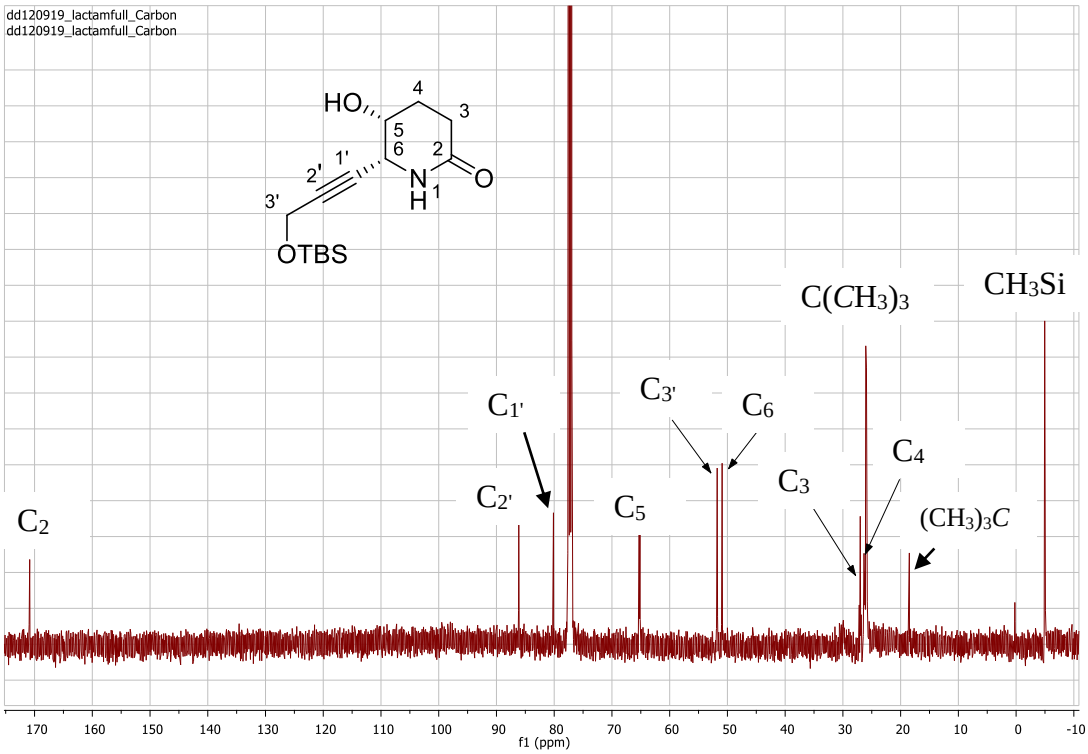
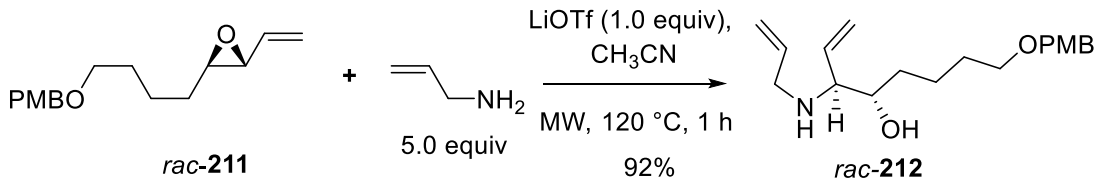


Figure 2.6: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **209**

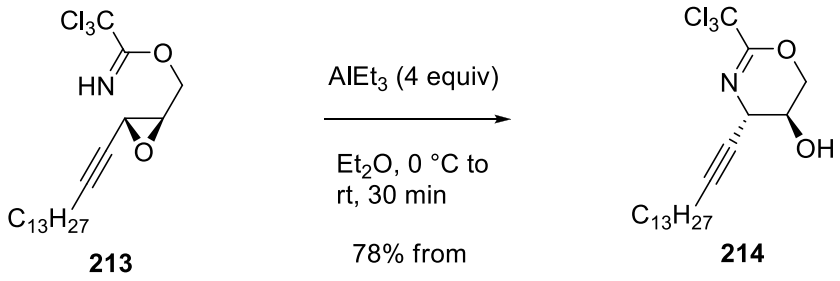
Due to the low yield of the azide **197** and the unsuccessful formation of **208**, we decided to modify the original route from the epoxide. The azidolysis step was replaced by an aminolysis reaction with the aim of developing a more efficient synthesis of **196**.

Pyne reported a method for aminolysis of a vinyl epoxide by heating the components in a microwave reactor using LiOTf (1.0 equiv) as a promoter.[87] The reactions proceeded well in high yield and with very good regioselectivity due to exclusive addition to the activated allylic carbon of the epoxide (**Scheme 2.35**).



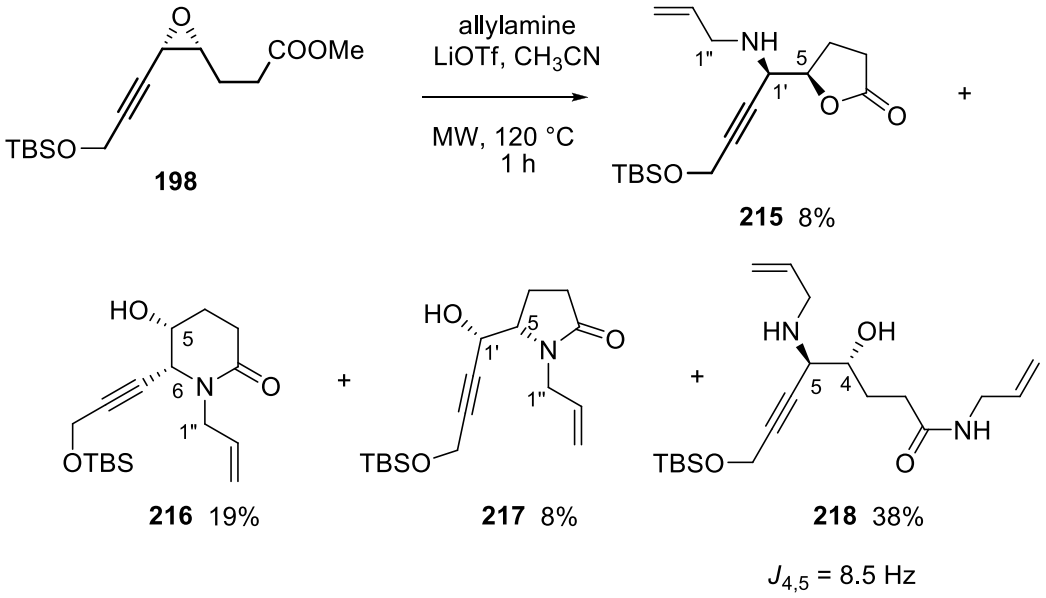
Scheme 2.35: Pyne's method of aminolysis of vinyl epoxide in microwave reactor[87]

Vasella reported an intramolecular aminolysis of the alkynyl epoxide **213** by the nitrogen of a trichloroimidate. Treatment of the trichloroimidate **213** with $AlEt_3$ in Et_2O provided cyclised compound **214** in 78% yield (**Scheme 2.36**) formed via a 6-*endo-tet* process.[88] The regiochemistry of this ring opening reaction is clearly assisted by the stabilizing alkynyl group.



Scheme 2.36: Vasella's aminolysis of alkynyl epoxide **213**[88]

We decided to try Pyne's aminolysis method using commercially available allylamine first to optimize the reaction conditions. When a solution of the epoxide **198**, allylamine (2 equiv) and LiOTf (1 equiv) in CH_3CN was heated in a microwave reactor at 120 ºC for 20 min, four compounds **215**-**218** (**Scheme 2.37**) were formed and separated by column chromatography.



Scheme 2.37: Aminolysis of **198** with allylamine

Compounds **215-217** are isomers and their respective HRESIMS (calcd. for $C_{17}H_{29}O_3NSiNa$, $(M+Na)^+$ 346.1814, found: 346.1818; calcd. for $C_{17}H_{29}O_3NSiNa$, $(M+Na)^+$ 346.1814, found 346.1811; calcd. for $C_{17}H_{30}O_3NSi$, $(M+H)^+$ 324.1985, found: 324.1995, respectively) confirmed their identical formulae.

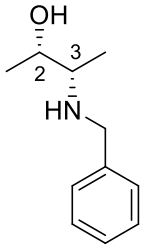
The δ-lactone carbonyl of **215** gave rise to a characteristic stretching band at 1776 cm^{-1} in its IR spectrum. In the ^1H NMR spectrum, H-5 and H-1' resonated at δ 4.59-4.53 (m) and δ 3.58 (s), respectively. The two diastereotopic protons H-1" resonated at δ 3.48 (dd, *J* = 13.5, 4.5 Hz, 1H, H1") and δ 3.25 (dd, *J* = 13.5, 6.5 Hz, 1H, H1"). These chemical shifts were consistent with the proposed structure of **215**. The conversion of **215** to lactam **216** (**Scheme 2.39**) further supported the structural assignments made to these compounds.

The IR spectrum of **216** showed bands for the lactam carbonyl at 1621 cm^{-1} and for the hydroxyl group at 3352 cm^{-1}. The ^1H NMR spectrum of **216** was similar to that of the lactam **209**. For example H-6 and H-5 resonated at δ 4.41-4.32 (m) and δ 4.02-3.96 (m), respectively. However unlike the ^1H NMR spectrum of **209**, no NH resonance was observed. The two diasterotopic H-1" protons resonated at lower field (δ 4.71 (dd, *J* = 15.0, 2.5 Hz) and δ 3.50 (dd, *J* = 15.0, 8.0 Hz)) in comparison to those of **215**, consistent with the structures of **215** and **216** and the stronger electron withdrawing effect of the lactam nitrogen and the deshielding effect of the carbonyl group in **216**.

The IR spectrum of **217** showed a band for the lactam carbonyl at 1689 cm^{-1}. In the ^1H NMR spectrum of **217**, the H-1' proton appeared as a doublet at δ 4.57 (d, *J* = 3.0 Hz, 1H, H6)), while the two diasterotopic H-1" protons resonated at δ 4.36 – 4.28 (m, 1H) and δ 3.79 – 3.69 (m, 1H), respectively. These methylene chemical shifts are similar to those of lactam **216** and downfield in comparison to H1" found in the ^1H NMR spectrum of lactone **215**. These methylene chemical shifts also supported the structure assigned to **217**.

The molecular formula of amide **218** was confirmed by it HRESIMS (calcd. for $C_{20}H_{37}O_3N_2Si$, $(M+H)^+$ 381.2581, found: 381.2573). In the ^1H NMR spectrum, the

amide proton CONH appeared at δ 6.03 (br, s, 1H), while H-5 resonated at δ 3.19 (d, J = 8.5 Hz, 1H, H5). The coupling constant $J_{4,5}$ = 8.5 Hz was similar to $J_{2,3}$ = 8.3 Hz found in the ^{1}H NMR spectrum of the *syn*-1,2-amino alcohol **219** (**Figure 2.7**)[89] and confirmed the relative *syn*-configuration of **218** at C-4 and C-5.



219

$J_{2,3}$ = 8.3 Hz

Figure 2.7: Structure and $J_{2,3}$ coupling constant for the *syn*- amino alcohol **219**[89]

The desired products in this reaction were the lactone **215** and the lactam **216**. We tried to optimize the reaction conditions by changing the reaction time and the molar equivalents of the amine to obtained high yields of these compounds. In the first reaction, we used a large excess of allylamine (5.5 equiv) and heated the reaction mixture in a microwave reactor for 1 h. This led, as would be expected, to a high yield of the undesired amide **218** (79%) (**Table 3.1.1**; entry 1). In the second attempt, we reduced the reaction time and equivalents of allylamine (20 min, 2.0 equiv) and this resulted in formation of four products but resulted in a low combined yield of **215** and **216** (27%), although the yield of amide **218** had reduced by a factor of nearly 50% (**Table 3.1.1**; entry 2). In the third attempt, we used 1.2 equivalents of allylamine and heated the reaction mixture for 20 min, then added an extra 0.8 equivalent of the amine and heated the reaction mixture for an additional 40 min after checking the progress of the reaction by TLC analysis. Under these conditions, the desired lactam **216** was formed in 40% yield while the yield of the amide **218** was reduced remarkably to 20% (**Table 3.1.1**; entry 3). We then increased the reaction time and reduced the equivalents of allylamine, however this variation did not improve the combined yield of **215** and **216** (**Table 2.3.1**; entries 4 and 5). The maximum combined yield of **215** and **216** was 40% (**Table 3.1.1**; entry 3).

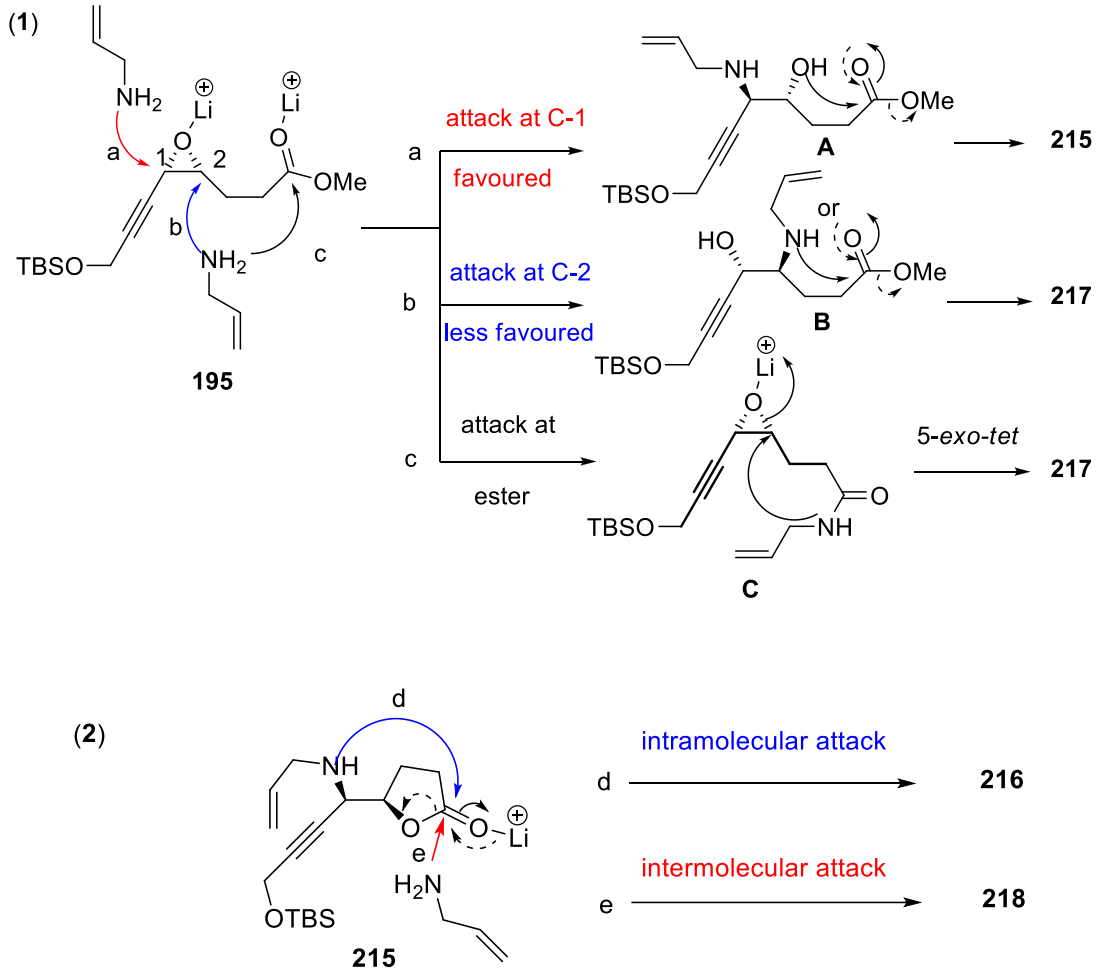
Entry	Time	Equivalents of amine	Starting recovered (%)	Isolated Yield (%)			
				215	**216**	**217**	**218**
1	1 h	5.5	0	2	0	11	79
2	20 min	2.0	21	8	19	8	38
3	20 min 40 min	1.2 0.8	20	0	40	9	20
4	1.5 h	2.0	11	5	32	8	27
5	3 h	1.5	3	9	23	8	31

Table 2.1: Reaction conditions and yields of products (**215**-**218**) formed from the aminolysis reactions of epoxide **198** with allylamine at 120 ºC in a microwave reactor

A scheme to explain the formation of this mixture of four products from the aminolysis reaction of **198** is provided in **Scheme 2.38**. The allylamine can attack at C-1 or C-2 of the epoxide moiety of **198** (**Scheme 2.38** (**1**), routes a and b, respectively) to form the regioisomeric amino alcohols **A** and **B**, respectively. Attack at the propargylic C-1 is favoured since the alkynyl group can stabilise any incipient positive charge formed at C-1 upon epoxide ring opening. Cyclization of **A** through the hydroxyl group and **B** through the amino group then gives the 5-membered ring lactone **215** and the lactam **217**, respectively. The lactam **217** could also be formed from the reaction of the ester carbonyl of **198** with allylamine, which initially forms the amide epoxide intermediate **C**. Then a favoured 5-*exo*-*tet* attack (in contrast to a less favourable 6-*endo*-*tet* attack)[84] of the amide nitrogen onto the epoxide ring of **C** could also give lactam **217** (**Scheme 2.38** (**1**), route c). Based on the highly regioselective outcomes of the later epoxide aminolysis described in this Chapter on substrate **234** (**Scheme 2.43**), which lacks the methyl ester group, we suggest that pathway c in **Scheme 2.38** (**1**) is followed to form the 5-membered ring lactam **217**.

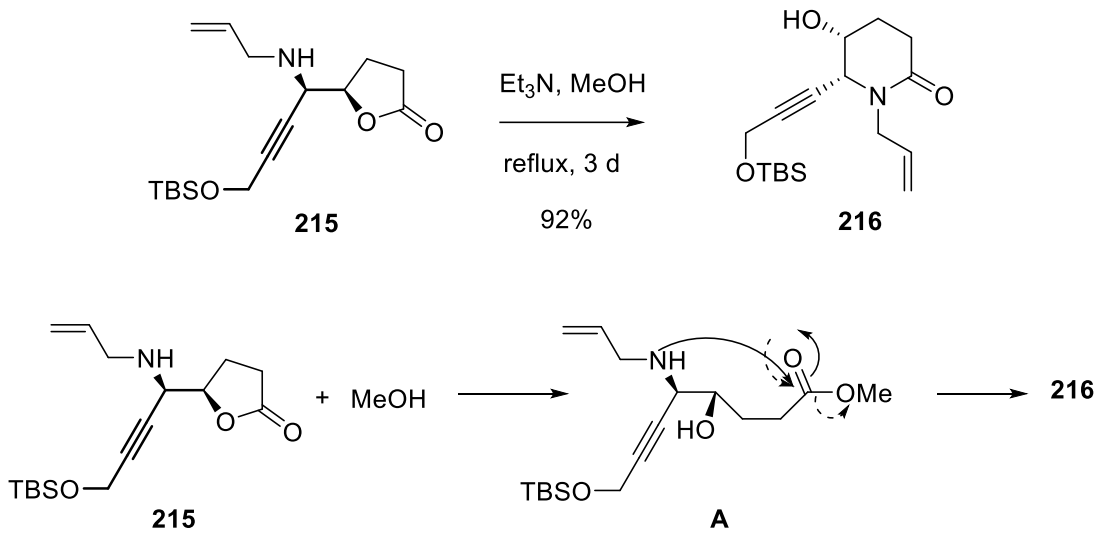
The 5-membered ring lactone of **215** is quite vulnerable to ring opening by amine. Intramolecular attack of the amine group in **215** to the lactone moiety would produce the lactam **216** (**Scheme 2.38** (**2**), route d). Intermolecular attack of allylamine to the

lactone of **215** would form the amide **218** (**Scheme 2.38** (**2**), route e). The major product from these competing reactions is dependent upon the molar equivalents of allylamine used, with an excess amount of allylamine favouring formation of **218** via an intermolecular reaction on **215** (**Scheme 2.38**).



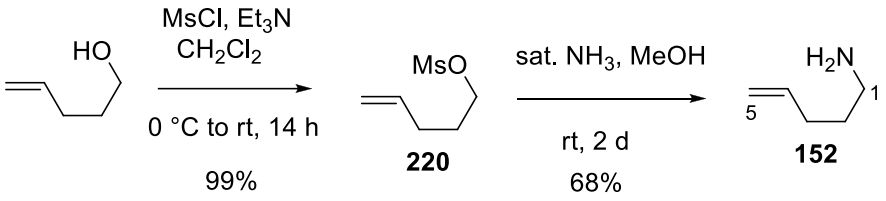
Scheme 2.38: Scheme for the formation of products **215-218** from the aminolysis reaction of **198**

Lactone **215** was converted to the lactam **216** in 92% yield by heating a solution of **215** and Et_3N (10 equiv) at reflux temperature in MeOH for 3 d. We assume that this reaction involves Et_3N assisted attack of MeOH to the lactone carbonyl to give the corresponding methyl ester **A**, which then cyclises to the lactam by attack of the amino group on the ester carbonyl (**Scheme 2.39**).



Scheme 2.39: Synthesis of **216** and the proposed mechanism for the conversion of amino lactone **215** to the lactam **216**

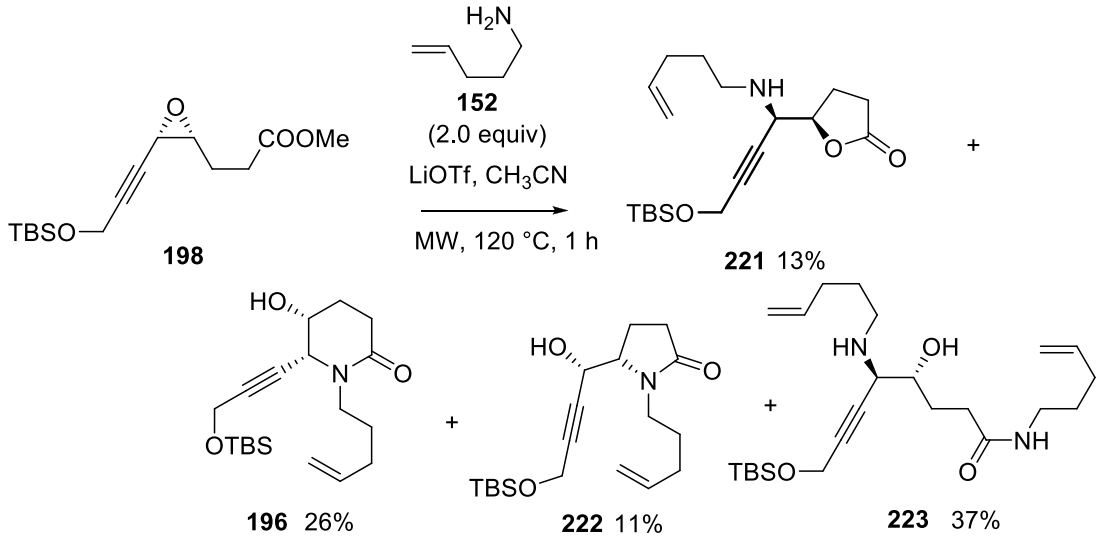
The aminolysis reaction of the epoxide **198** was next examined using the more relevant amine, 1-amino-4-pentene (**152**). This amine was prepared from commercially available 4-penten-1-ol in two synthetic steps. Treatment of this alcohol with MsCl, Et_3N in CH_2Cl_2 gave the expected mesylate **220**, which was converted to the amine **152** by stirring with a mixture of MeOH and saturated NH_3 solution for 2 d (**Scheme 2.40**).[90]



Scheme 2.40: Synthesis of amine **152**

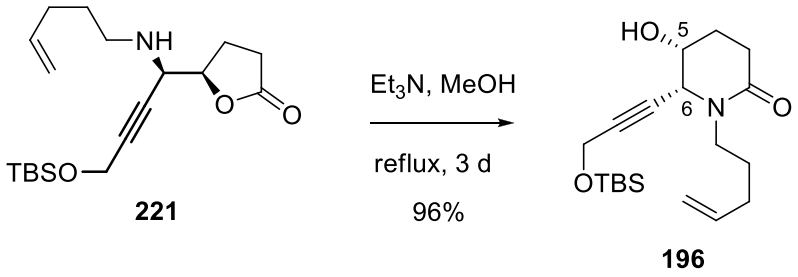
The aminolysis reaction of the epoxide **198** with the amine **152** using the best conditions from the model work (the only difference was the addition 2.0 equiv of amine **152** in one portion at the beginning of the reaction) gave a mixture of four products, compounds **196** and **221**-**223** (**Scheme 2.41**). The structure elucidation of these compounds was based on NMR and IR spectroscopic and MS spectrometric

analysis and from comparisons made with the spectroscopic data of the related compounds **215-218**.



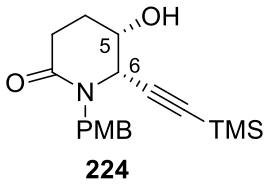
Scheme 2.41: Ring opening of the epoxide **198** with the amine **152**

Under similar reaction conditions developed for the conversion of the lactone **215** to the lactam **216**, lactone **221** was converted to the lactam **196** in 96% yield by heating at reflux with Et_3N in MeOH (**Scheme 2.42**). The ^1H and ^{13}C NMR spectra of the lactam **196** are displayed in **Figures 2.9** and **2.10**, respectively. The NMR resonance assignments made to **196** were based on 2D NMR experiments (COSY, HSQC and HMBC). In the ^1H NMR spectrum, H-5 and H-6 resonated at δ 4.32 (d, J = 4.5 Hz, 1H, H6) and δ 3.99 (dt, J = 10.0, 4.5 Hz, 1H, H5), respectively. These chemical shifts and $J_{5,6}$ coupling constant were consistent with those of H-5 and H-6 in the *cis* compound **224 (Figure 2.8**) reported in the literature (δ 4.14 (d, J = 4.6 Hz, 1H, H6) and δ 3.90-3.84 (m, 1H, H5).[65]



$J_{5,6}$ = 4.5 Hz

Scheme 2.42: Conversion of lactone **221** to lactam **196**



$J_{5,6}$ = 4.6 Hz

Figure 2.8: Structure and coupling constant $J_{5,6}$ of lactam **224**[65]

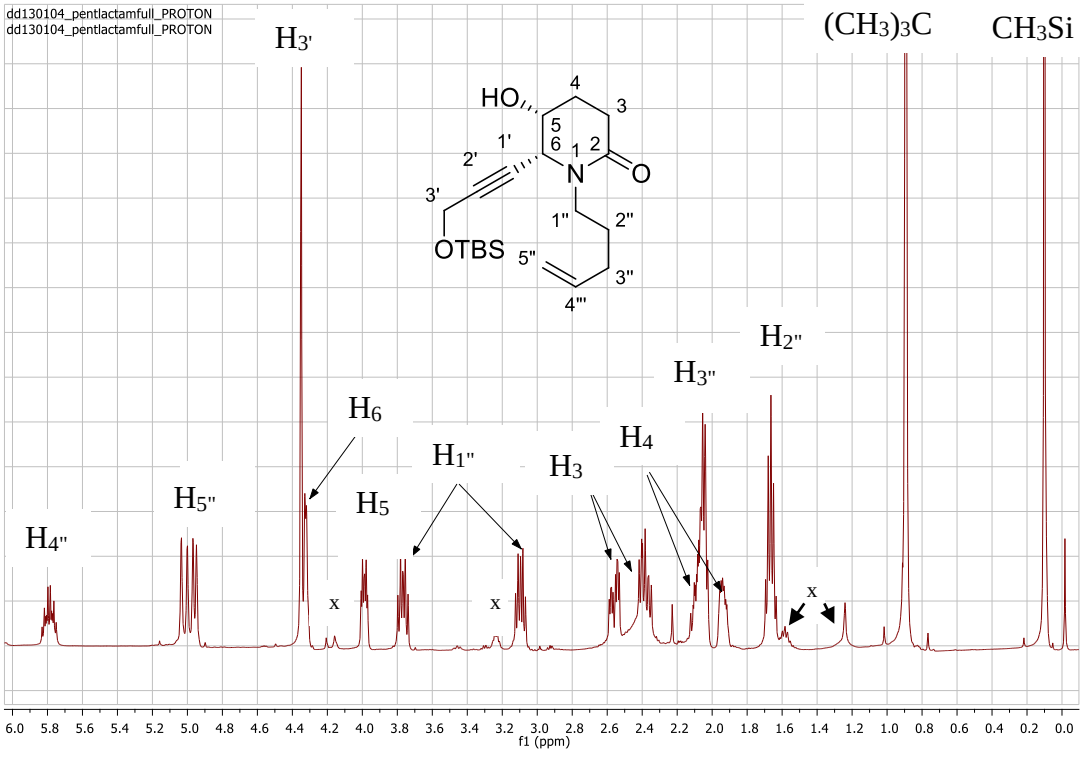


Figure 2.9: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **196** (x: impurities)

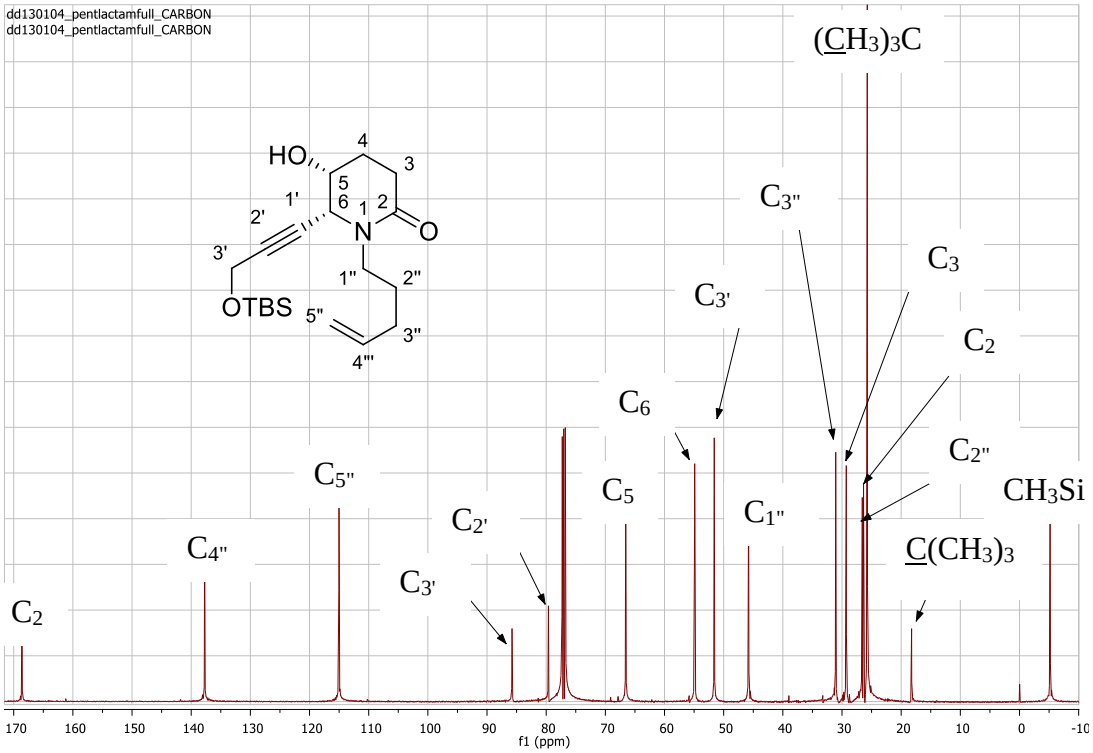
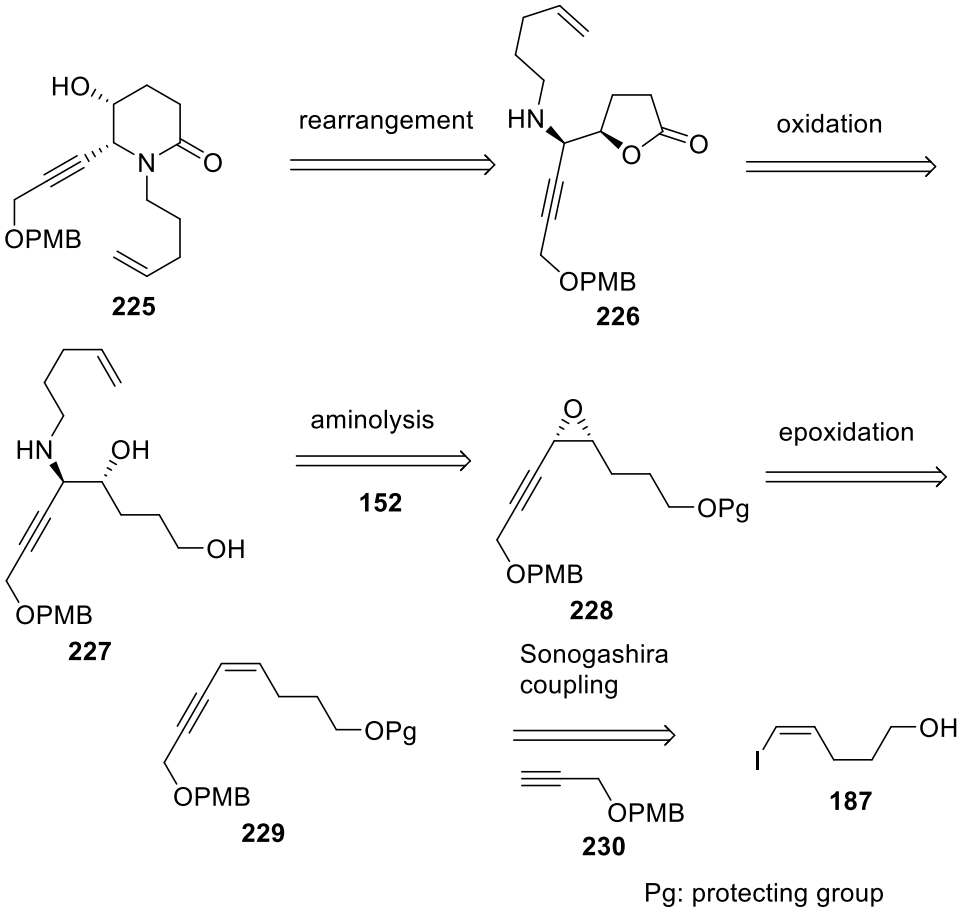


Figure 2.10: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **196**

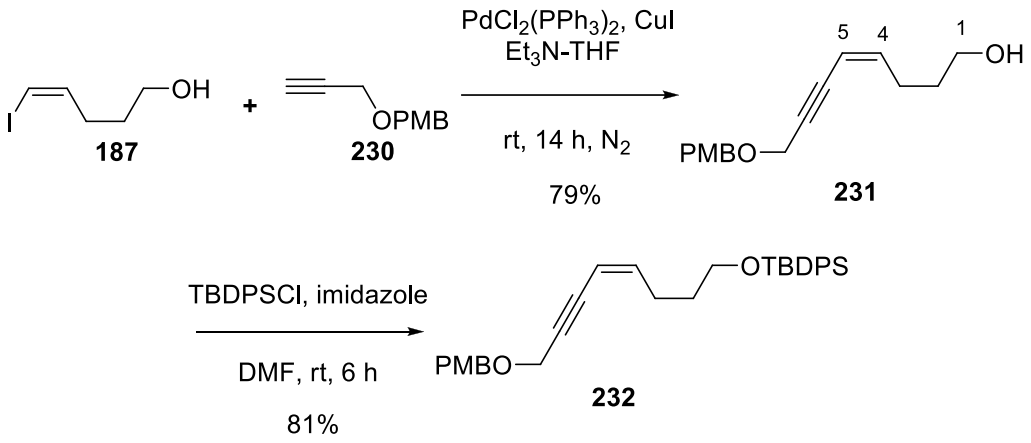
2.4 The successful synthesis of the ene-yne lactam 225 (synthetic strategy 3)

In this section, we report the main and most effective pathway to synthesize the ene-yne lactam **225** (**142**, Pg = H, R = CH_2OPMB) using the retrosynthetic analysis outlined in **Scheme 2.43**. Follow this scheme, **225** could be obtained from **226** via a base-catalysed-lactone to lactam rearrangement. This lactone could be prepared from the diol **227** by selective oxidation. The diol **227** could be obtained from epoxide **228** by an epoxide aminolysis reaction with the amine **152**, after deprotection of the primary hydroxy group. Epoxide **228** could be obtained from the *Z*-alkene **229** via epoxidation. The ene-yne **229** could be prepared from the iodide **187** via a Sonogashira coupling reaction with the alkyne **230**, followed by hydroxyl group protection. The potential advantage of this synthetic route was the absence of the methyl ester group in the epoxide **228**, which had caused problems in our earlier aminolysis reactions (**Scheme 2.37** and **2.41**).

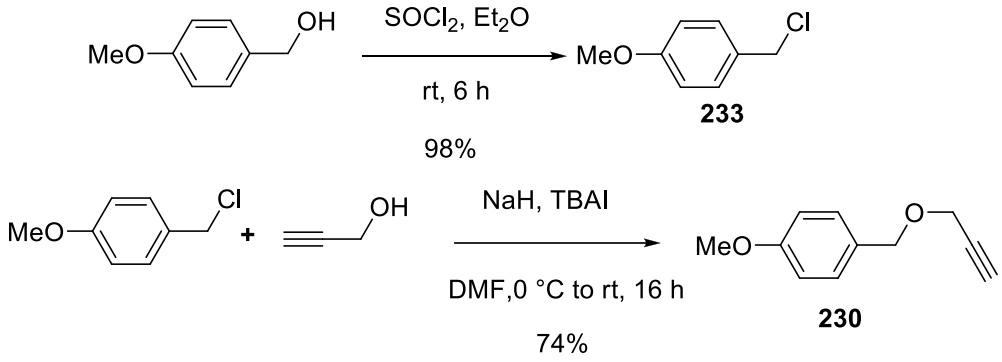


Scheme 2.43: Retrosynthetic analysis of lactam **225**

We first examined this method using allylamine. The Sonogashira coupling reaction between iodide **187** and the alkyne **230** worked smoothly with a favourable yield (79%) to provide the ene-yne **231**. The coupling constant $J_{4,5}$ = 10.5 Hz in the ^{1}H NMR spectrum of **231** (δ 5.57 (d, *J* = 10.5 Hz, 1H, H5)) confirmed its *Z*-configuration.[70] The alcohol **231** then was protected as the TBDPS ether **232** in 81% yield (**Scheme 2.44**). The alkyne **230** was obtained from the reaction of commercially available propargyl alcohol with PMBCl (**233**), which was prepared from commercially available 4-methoxybenzyl alcohol (**Scheme 2.45**).[91]



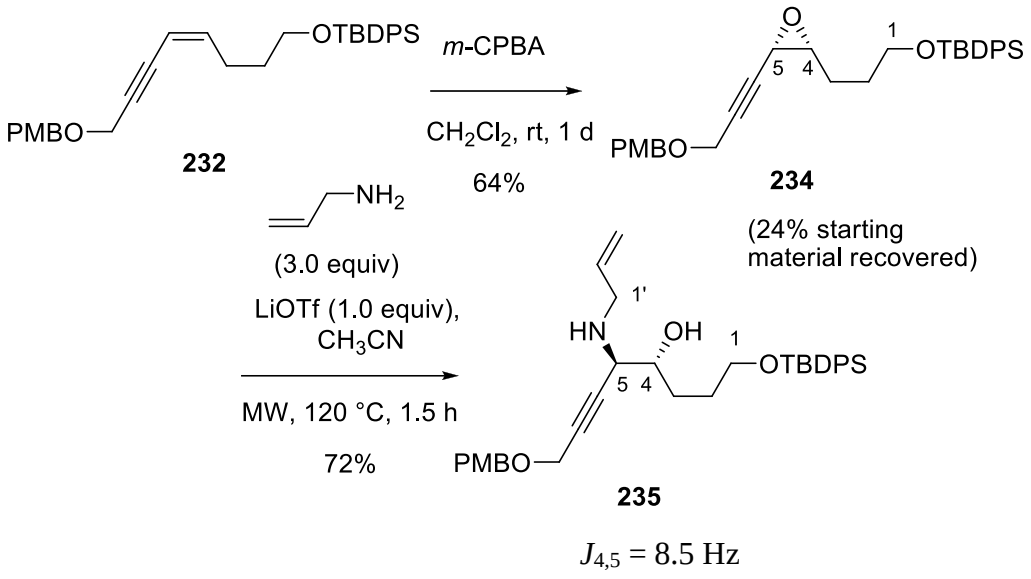
Scheme 2.44: Synthesis of ene-yne **232**



Scheme 2.45: Synthesis of alkyne **230**

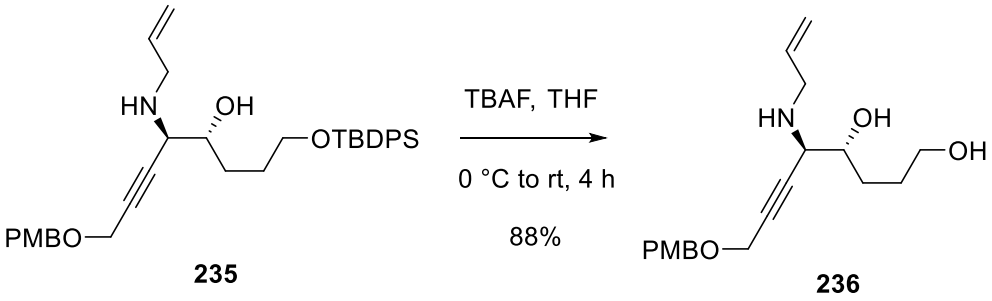
Epoxidation of **232** using *m*-CPBA in CH_2Cl_2 gave the racemic epoxide **234** in 64% yield (**Scheme 2.46**). The *cis*-configuration of the epoxide **234** was confirmed by the coupling constant $J_{4,5}$ = 3.5 Hz (δ 3.50 (d, *J* = 3.5 Hz, 1H, H5)) in its ^{1}H NMR spectrum (similar to epoxides **198** (**Scheme 2.21**) and **201** (**Figure 2.3**)).[77] The aminolysis reaction of **234** with allylamine (3.0 equiv) and LiOTf (1.0 equiv) with microwave heating at 120 ºC for 1.5 h afforded the racemic amine **235** in 72% yield (**Scheme 2.46**). The molecular formula of **235** was confirmed from its HRESIMS (calcd. for $C_{35}H_{46}O_4NSiNa$, $(M+Na)^+$ 572.3196, found: 572.3224). In the ^{1}H NMR spectrum of **235**, the H-5 resonance appeared as a doublet at δ 3.19 with a coupling constant $J_{4,5}$ = 8.5 Hz (δ 3.19 (d, *J* = 8.5 Hz, 1H, H5)). This coupling constant was the same as that found in the amino alcohol **218** (**Scheme 2.38**) and was similar to that found in the *syn*-2,3 amino alcohol **219** (**Figure 2.7**) ($J_{2,3}$ = 8.3 Hz).[89] The two

diasterotopic H-1' protons resonated at δ 3.53-3.45 (m, H1') and δ 3.29 (dd, *J* = 13.5, 6.0 Hz, 1H, H1').



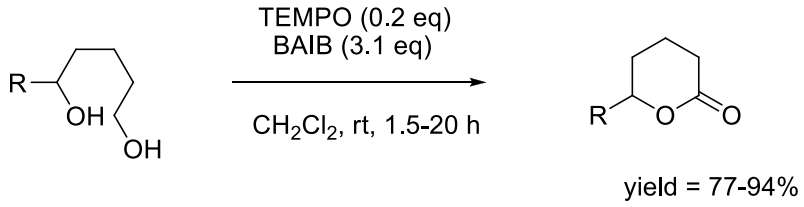
Scheme 2.46: Synthesis of amine **235**

Removal of the TBDPS group of **235** by treatment with TBAF in THF produced the diol **236** in 88% yield, ready for oxidation to the corresponding lactone (**Scheme 2.47**).

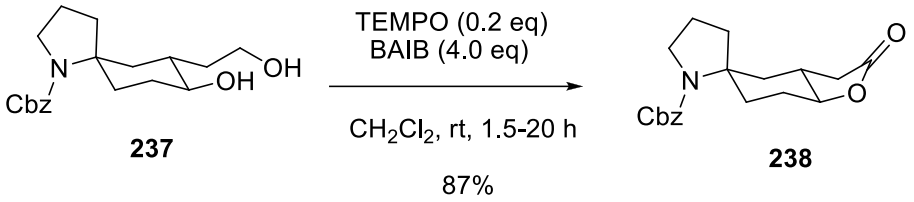


Scheme 2.47: Synthesis of diol **236**

Forsyth reported the oxidation of 1,5-diols to δ-lactones in very good yields (77-94%) using TEMPO/BAIB (**Scheme 2.48**).[92] Martin applied this method to construct the tricyclic lactone **238** from the bicyclic 1,4-diol **237** (**Scheme 2.49**).[93]

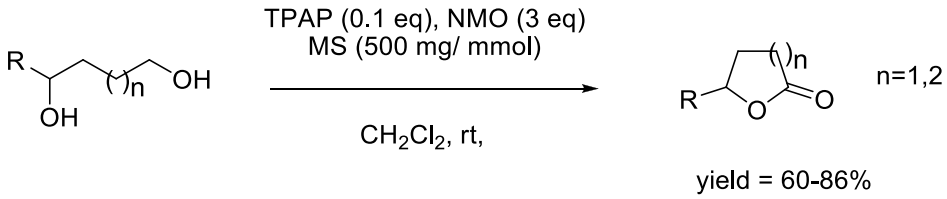


Scheme 2.48: Forsyth's oxidation of 1,5 diols to δ-lactones[92]



Scheme 2.49: Martin's synthesis of lactone **238**[93]

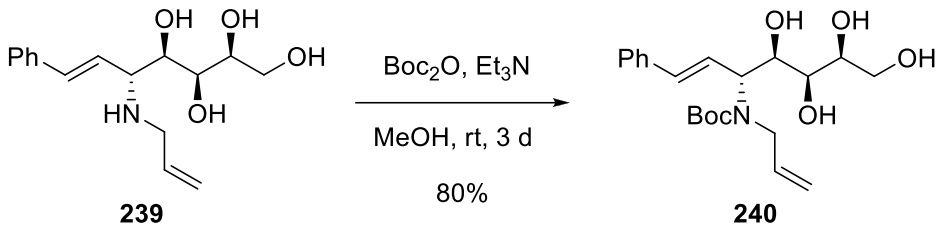
Oxidation of the diol **236** under Forsyth's conditions gave a complex mixture of inseparable products. An alternative method for oxidation of 1,4-diols and 1,5-diols to their corresponding lactones was reported by Brillet using TPAP/NMO (**Scheme 2.50**).[94]



Scheme 2.50: Brillet's synthesis of lactones from the corresponding diols[94]

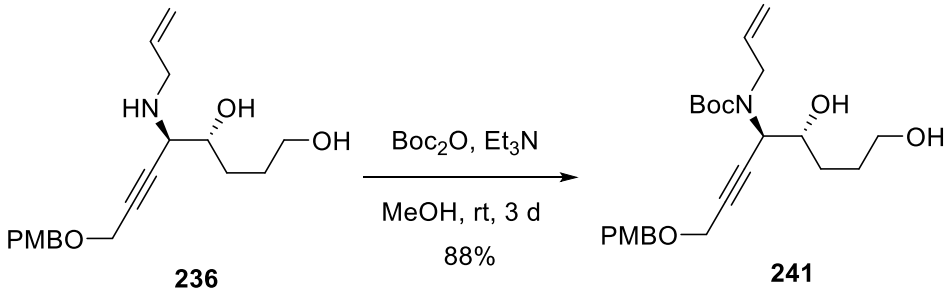
However, our attempts to oxidize the diol **236** to the desired lactone under Brillet's conditions also gave a complex mixture of products. Presumably, these reagents oxidized the amine group together with the primary hydroxyl group. To avoid this problem, we decided to protect the amine group of **236** before oxidation.

Initially, we chose a Boc group as the amine protecting group for the amino alcohol **236**. Pyne reported *N*-protection of the amino alcohol **239** by the Boc group to prepare **240** in 80% yield (**Scheme 2.51**)[95]



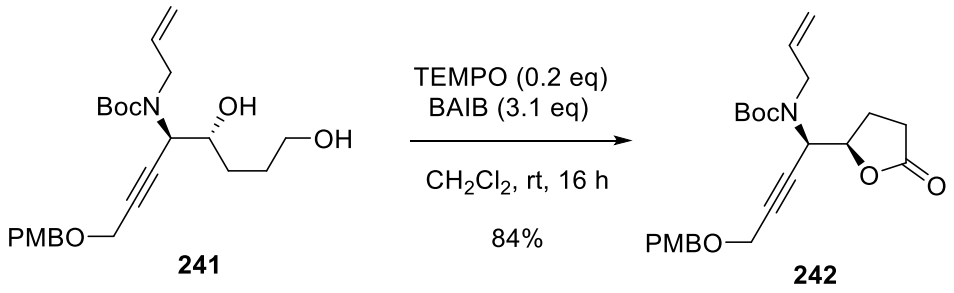
Scheme 2.51: Pyne's synthesis of **240**[95]

This procedure worked well with diol **236**. The Boc-diol **241** was obtained in better yield (88%) and shorter reaction time (18 h) in comparison with Pynes' report (**Scheme 2.52**).



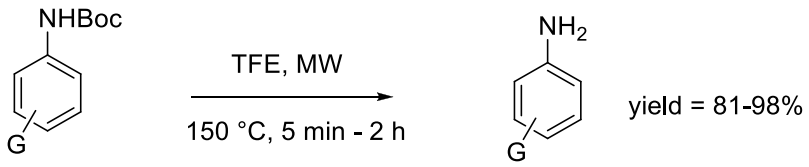
Scheme 2.52: Synthesis of Boc-diol **241**

To our delight, the oxidation of **241** with TEMPO/BAIB proceeded smoothly and the corresponding lactone **242** was obtained in good yield (84%) (**Scheme 2.53**). The presence of the Boc group made some resonances in the ^{1}H NMR and ^{13}C NMR spectra of **242** broad and difficult to interpret. However, the IR spectrum showed a band at 1754 cm^{-1} for the δ-lactone group and the HRESIMS (calcd. for $C_{24}H_{31}O_6NNa$, $(M+Na)^+$ 452.2037, found: 452.2049) further helped confirm the structure of **242**.

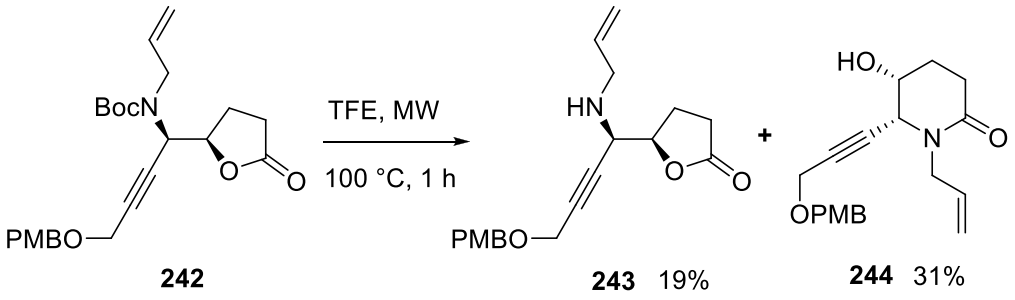


Scheme 2.53: Synthesis of Boc-lactone **242**

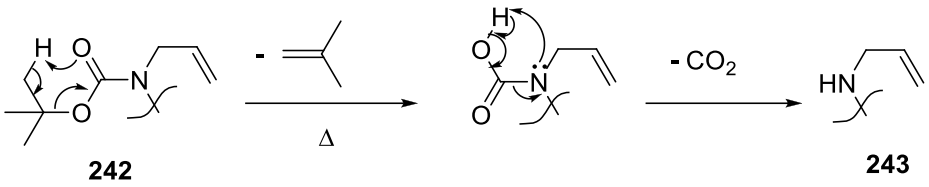
When searching the literature for a method to remove the Boc group of **242**, we found that many reagents used for *N*-Boc deprotection, for example TFA, also cleave the PMB protecting group. Therefore we tried Choy's method for removal of the Boc group (**Scheme 2.54**).[96] Compound **242** was dissolved in trifluoroethanol (TFE) and heated in microwave reactor at 150 ºC for 1 h. This reaction gave a separable mixture of the lactone **243** and the lactam **244** in low yields (19% and 31%, respectively). The starting material was also recovered in 30% yield (**Scheme 2.55**). A proposed mechanism for this Boc deprotection method is shown in **Scheme 2.56** and involves fragmentation of the *t*-butyl group assisted by the carbonyl group of the carbamate. A possible mechanism for the formation of the lactam **244** is shown in **Scheme 2.57** and is similar to the mechanism for the conversion of **215** to **216** (**Scheme 2.39**) involving first formation of the ester intermediate **A**.



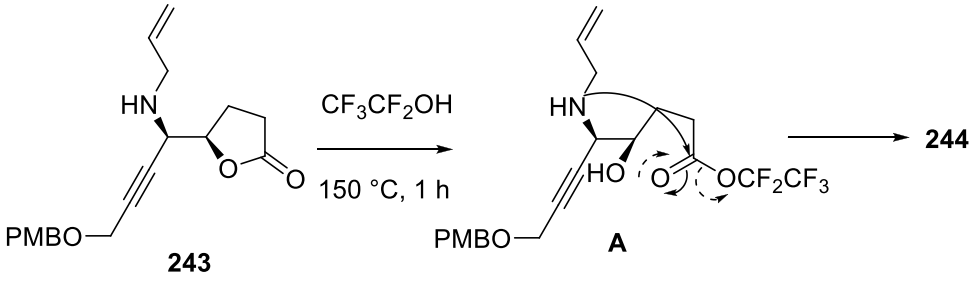
Scheme 2.54: Choy's Boc deprotection method[96]



Scheme 2.55: *N*-Boc group removal by heating in TFE in a microwave reactor

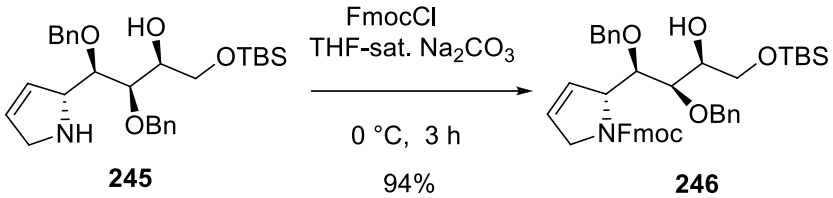


Scheme 2.56: Proposed mechanism for Boc deprotection of **242**



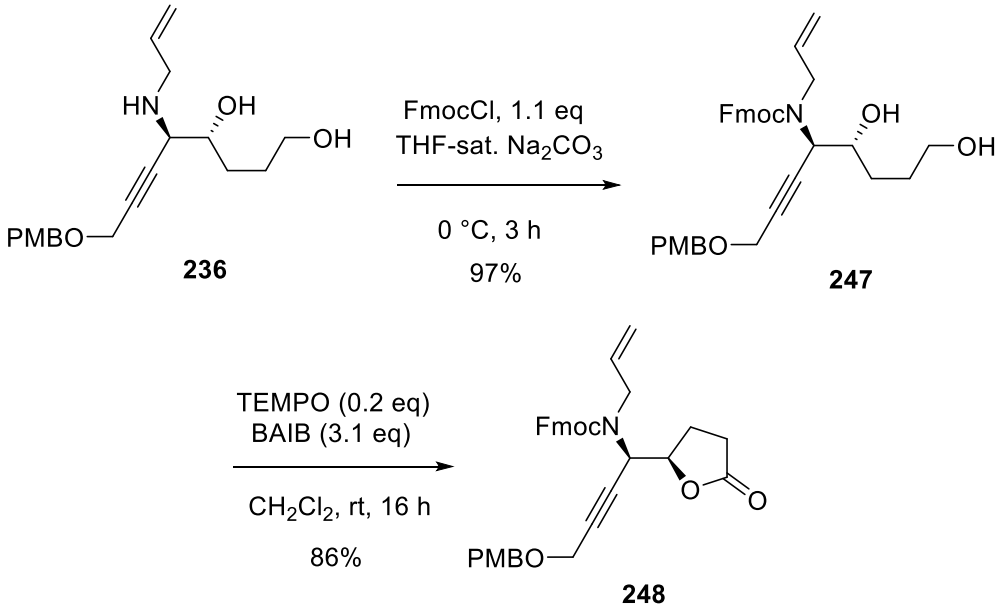
Scheme 2.57: Proposed mechanism for the formation of lactam **244**

While a longer reaction time may have improved the yields of **243** and **244**, the Fmoc group was also examined as an amine protecting group for **236**. Fmoc protection of amines has been widely used in the synthesis of peptides because of its ease of formation as well as its cleavage. For example, to protect the amine group of the amino alcohol **245**, Pyne prepared **246** via Fmoc protection in excellent yield (94%) (**Scheme 2.58**).[95]



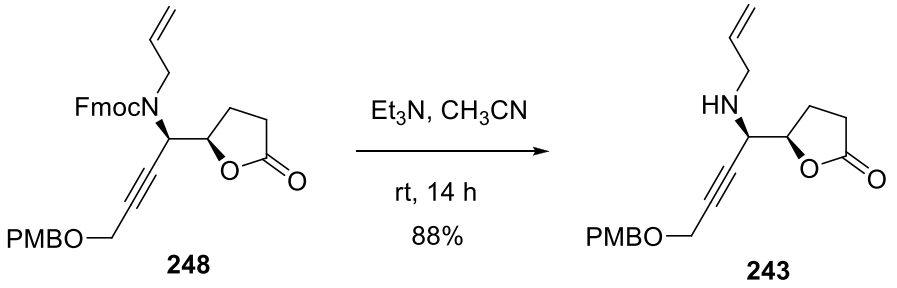
Scheme 2.58: Pyne's synthesis of **246**[95]

This procedure worked perfectly well with the amino alcohol **236**. The Fmoc-diol **247** was achieved in excellent yield (97%). The Fmoc-diol **247** then was oxidised to the expected Fmoc-lactone **248** in 86% yield (**Scheme 2.59**). Similar to the Boc protecting group, the Fmoc group caused almost all of the resonances in the ^{1}H NMR spectra and some those in the ^{13}C NMR spectra of **247** and **248** to be broad and obstructed NMR data analysis. However the HRESIMS of **247** and **248** (calcd. for $C_{34}H_{37}O_6NNa$, $(M+Na)^+$ 578.2519, found: 5782526 and $C_{34}H_{37}O_6NNa$, $(M+Na)^+$ 552.2386, found: 552.2397, respectively) confirmed their molecular formulae, while the IR spectrum of **248** showed bands for the carbonyl group of the δ-lactone at 1779 cm^{-1} and the carbamate at 1697 cm^{-1}.

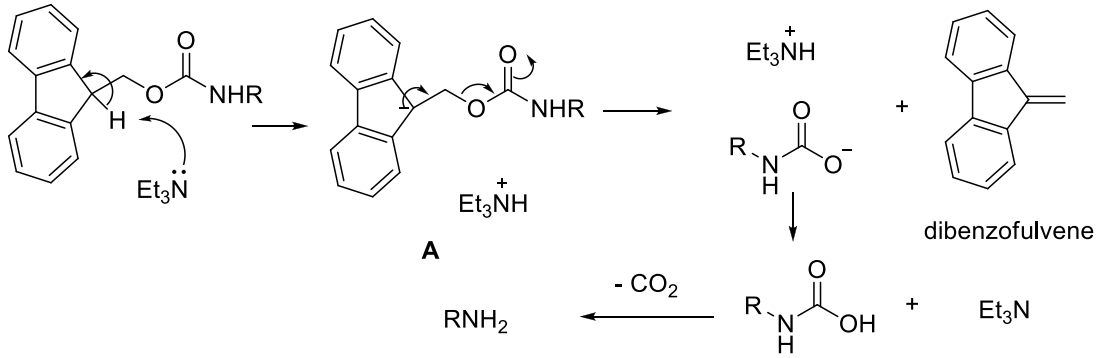


Scheme 2.59: Synthesis of Fmoc-lactone **248**

The Fmoc group can be easily removed by treatment with base in CH_3CN. DBU, piperidine, and morpholine are usually employed for Fmoc deprotection.[97,98] However, treatment of the Fmoc-lactone **248** with piperidine in CH_3CN led to the lactone **243** in only 40% yield due to a reaction between **243** and piperidine occuring when evaporating the solvent at the end of the reaction giving rise to a morpholino-amide by-product. Alternatively, treatment of **248** with Et_3N (20% volume in CH_3CN) gave the expected lactone **243** in 88% yield (**Scheme 2.60**). The accepted mechanism for the general Fmoc deprotection reaction is shown in **Scheme 2.61**.[99] Initially, deprotonation of the fluorene group, which is greatly facilitated by the aromatic nature of the resultant dibenzocyclopentadienide anion **A**, is accomplished with Et_3N. Subsequently, an elimination reaction of **A** generates dibenzofulvene and a carbamate residue, which then decomposes with loss of CO_2 to release the free amine.



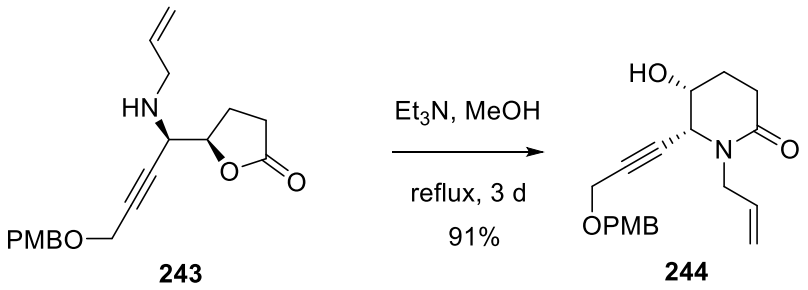
Scheme 2.60: Formation of the lactone **243**



Scheme 2.61: Accepted mechanism for the Fmoc deprotection reaction[99]

Previously, we successfully converted the amino lactones **215** and **221** to the corresponding lactams **216** and **196**, respectively, by heating in MeOH at reflux temperature for 3 d. We tried several conditions to optimize the yield as well as to

reduce the reaction time to convert lactone **243** to lactam **244**. The results are summarised in **Table 2.4.1**. Heating **243** with Et_3N in MeOH in a microwave reactor for 3 h or 8 h gave conversions of 49% and 70%, respectively, by ^1H NMR analysis (**Table 2.4.1**, entries 1 and 2). The stronger base DBU did not help improve the yield of lactam **244** (**Table 2.4.1**, entry 4). Heating **243** with DBU in CH_3CN in a microwave reactor gave no reaction (**Table 2.4.1**, entry 5). This result provided important evidence of the mechanism for the conversion of lactone **215** to lactam **216**, which involves ring opening of the lactone with MeOH and then cyclization of the resulting δ-amino ester (**Scheme 2.39**). The best conditions found were heating **243** and Et_3N in MeOH at reflux temperature for 3 d (**Table 2.4.1**, entry 3) (**Scheme 2.62**). These conditions were used before for the synthesis of the lactams **216** and **196**.



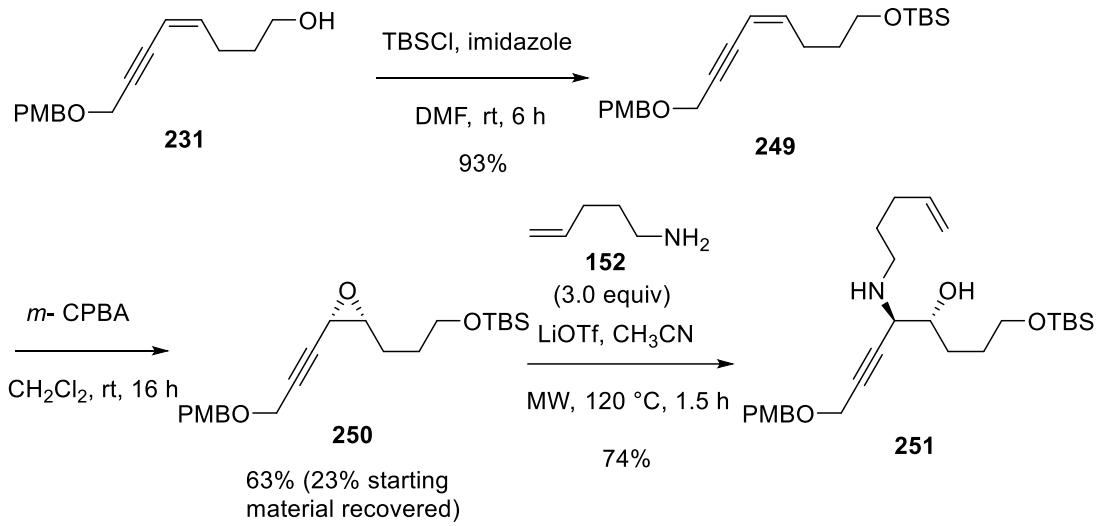
243 **244**

Scheme 2.62: Synthesis of lactam **244**

Entry	Base (equiv)	Solvent	Temperature	Time	Yield of **244**
1	Et_3N (10)	MeOH	110 ºC (MW)	3 h	49% (by NMR)
2	Et_3N (10)	MeOH	110 ºC (MW)	8 h	70% (by NMR)
3	Et_3N (10)	MeOH	reflux	3 d	91% (isolated)
4	DBU (1)	MeOH	110 ºC (MW)	3 h	52% (by NMR)
5	DBU (1)	CH_3CN	110 ºC (MW)	3 h	0%

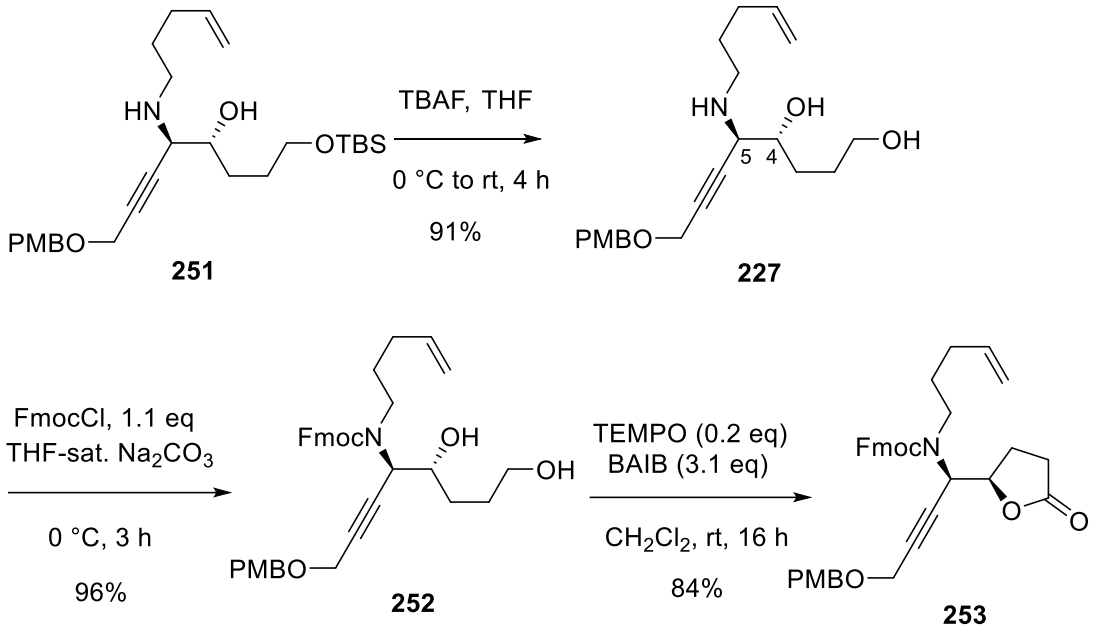
Table 2.2: Conditions and yields of the reactions to convert lactone **243** to lactam **244**

With the model work with allylamine proceeding efficiently, we then proceeded to prepare the ene-yne lactam **225**. TBSCl, a less expensive protecting reagent, was employed rather than TBDPCl, and the TBS ether **249** was obtained from alcohol **231** in 93% yield. Epoxidation of **249** using *m*-CPBA in CH_2Cl_2 led to the racemic epoxide **250** in 63% yield, which underwent ring opening upon aminolysis with the amine **152** to provide the amino alcohol **251** in 74% yield (**Scheme 2.63**).



Scheme 2.63: Synthesis of amine **251**

Removal the TBS group of **251** by treatment with TBAF in THF provided the diol **227** in 91% yield, which was converted to the Fmoc derivative **252** in excellent yield (96%) by treatment with FmocCl in THF-sat. Na_2CO_3 at 0 ºC for 4 h. Oxidation of the Fmoc-diol **252** with TEMPO/BAIB in CH_2Cl_2 led to the corresponding δ-lactone **253** in good yield (84%) (**Scheme 2.64**). The IR spectrum of **253** showed a band for the δ-lactone carbonyl group at 1773 cm^{-1}. In the ^1H NMR spectrum of diol **227**, the protons H-4 and H-5 resonated at δ 3.48 – 3.43 (m, 1H, H4) and δ 3.15 (d, J = 9.0 Hz, 1H, H5), respectively. The relative *syn*-configuration of **227** at C-4 and C-5 was consistent with the coupling constant $J_{4,5}$ = 9.0 Hz. This coupling constant is similar to that found in the 1,2-amino alcohol **219** (**Figure 2.7**).[89]

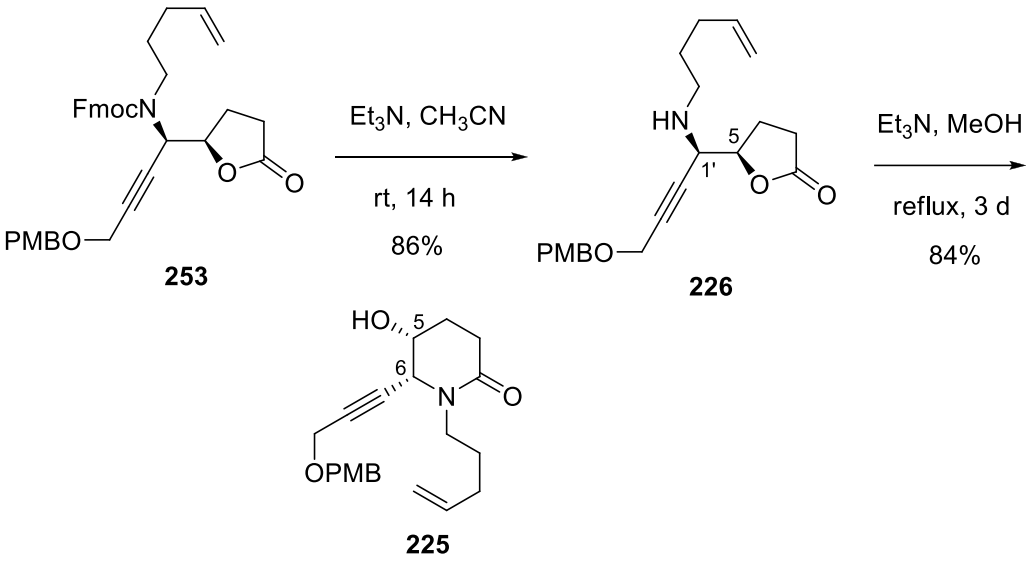


Scheme 2.64: Formation of Fmoc-lactone **253**

Finally the Fmoc group of **253** was removed by treatment with Et_3N in CH_3CN in 86% yield and the resulting lactone **226** was converted to the expected lactam **225** by heating with Et_3N in MeOH at reflux temperature in 84% yield (**Scheme 2.65**). The ^1H NMR and ^{13}C NMR spectra of the lactone **226** are displayed in **Figures 2.11** and **2.12**, respectively. The NMR resonance assignments of **226** are based on 2D NMR experiments (COSY, HSQC and HMBC). The ^1H NMR spectrum showed resonances for H-5 and H-1' at δ 4.60 (dd, *J* = 7.0, 5.5 Hz, 1H, H5) and δ 3.59 (d, *J* = 5.5 Hz, 1H, H1'), respectively. The two diasterotopic protons H1" resonated at δ 2.92 (dt, *J* = 11.5, 7.0 Hz, 1H, H1") and δ 2.67 – 2.59 (m, H1"). The ^1H NMR chemical shifts are consistent with the structure of the expected compound (**226**). In the ^{13}C NMR spectrum, the resonances for C-2, C-4" and C-5" appeared in the expected chemical shift regions at δ 177.1, 138.5 and 115.1, respectively.

The ^1H NMR and ^{13}C NMR spectra of the lactam **225** are displayed in **Figures 2.13** and **2.14**, respectively. The ^1H NMR spectrum shows resonances for the H" protons at δ 3.81 – 3.71 (m, 1H, H1") and δ 3.12 (dt, *J* = 14.0, 7.0 Hz 1H, H1"), downfield in comparison to the corresponding ones in the lactone **226**. In the ^{13}C NMR spectrum

of **225**, C-5 resonated at δ 66.8 (C5), an expected upfield chemical shift compared to C-5 (81.4 (C5)) in the ^{13}C NMR spectrum of the lactone **226**.



Scheme 2.65: Synthesis of lactam **225**

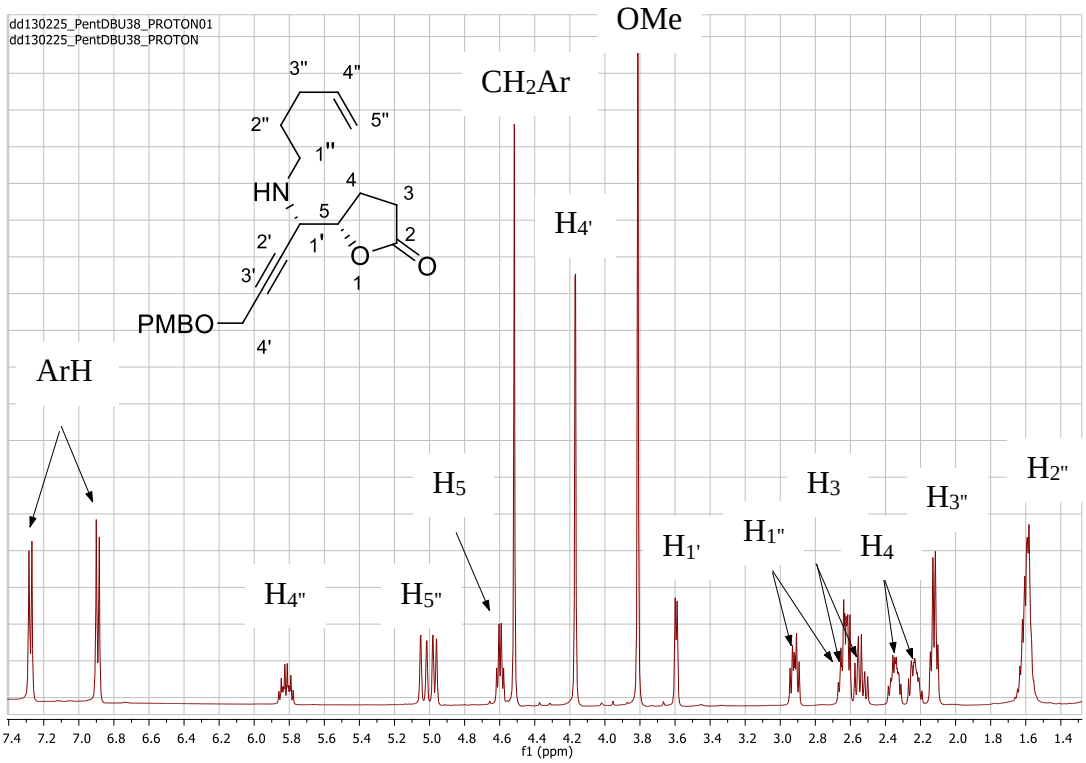


Figure 2.11: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **226**

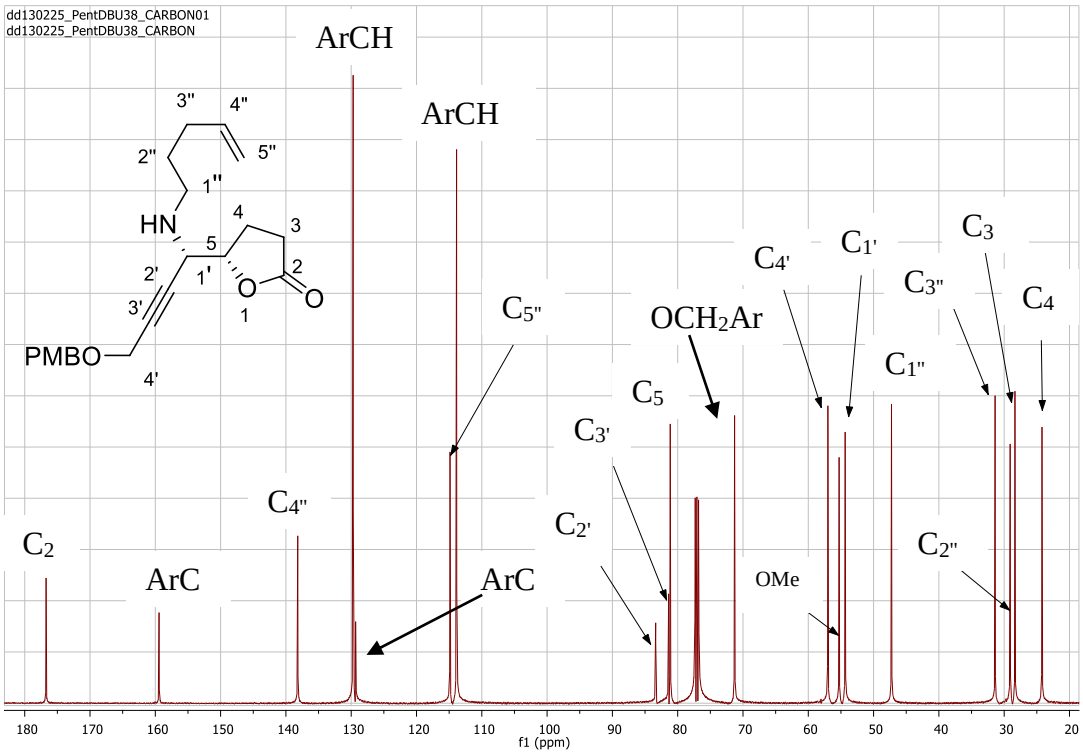


Figure 2.12: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **226**

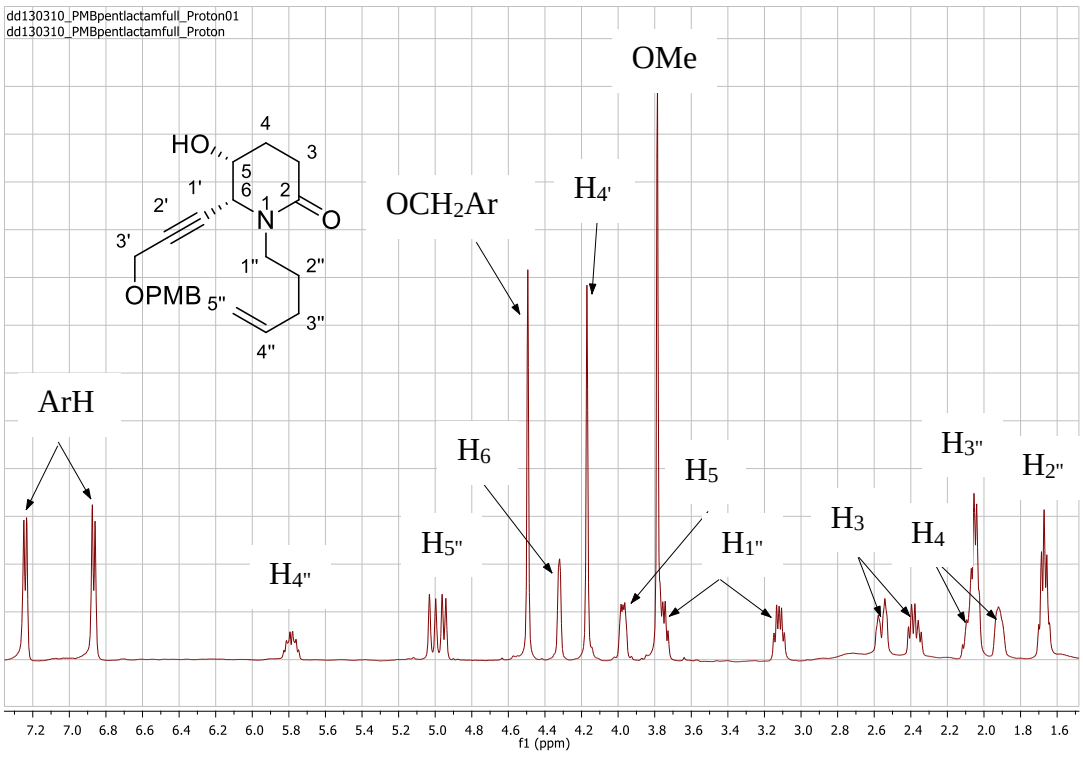


Figure 2.13: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **225**

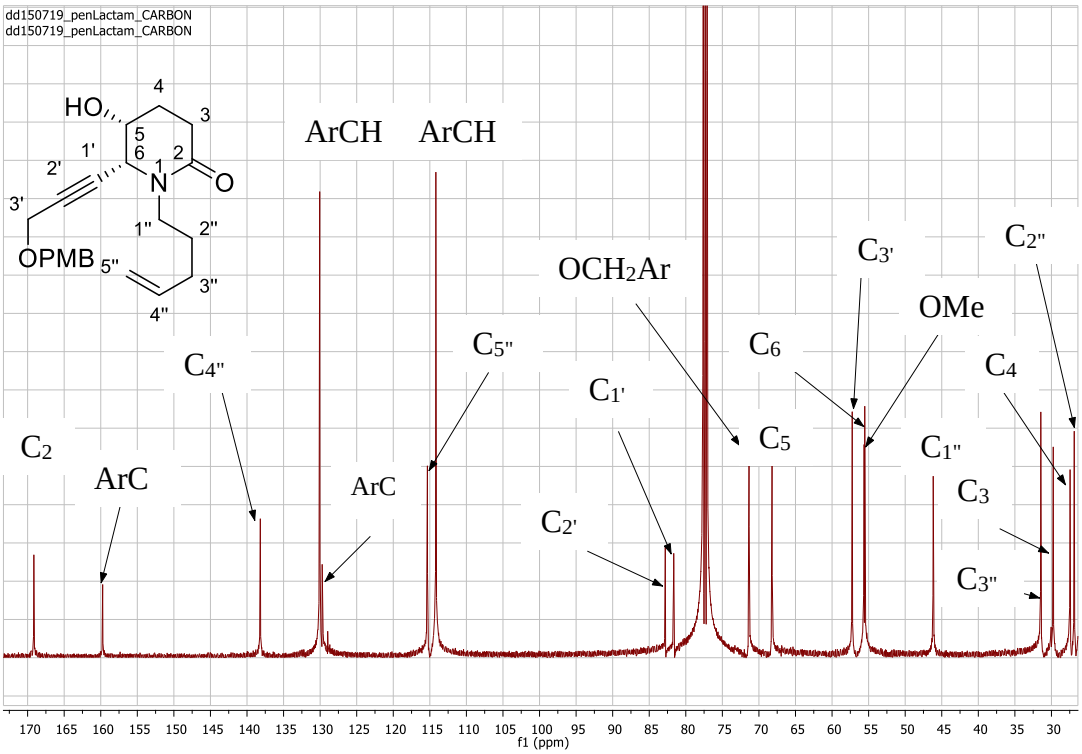
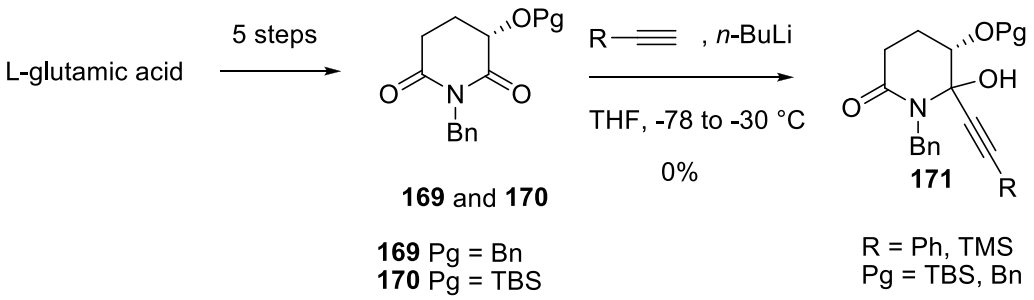


Figure 2.14: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **225**

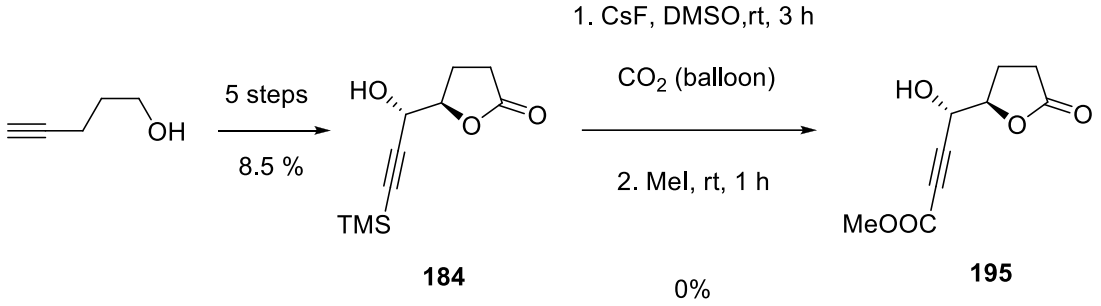
2.5 Conclusions

In conclusion, we have examined three different synthetic strategies to synthesize an ene-yne lactam similar to **142**. The first strategy failed due to the ring opening of the hemiaminal formed upon the nucleophilic addition of RCCLi to the imides **169** or **170**.



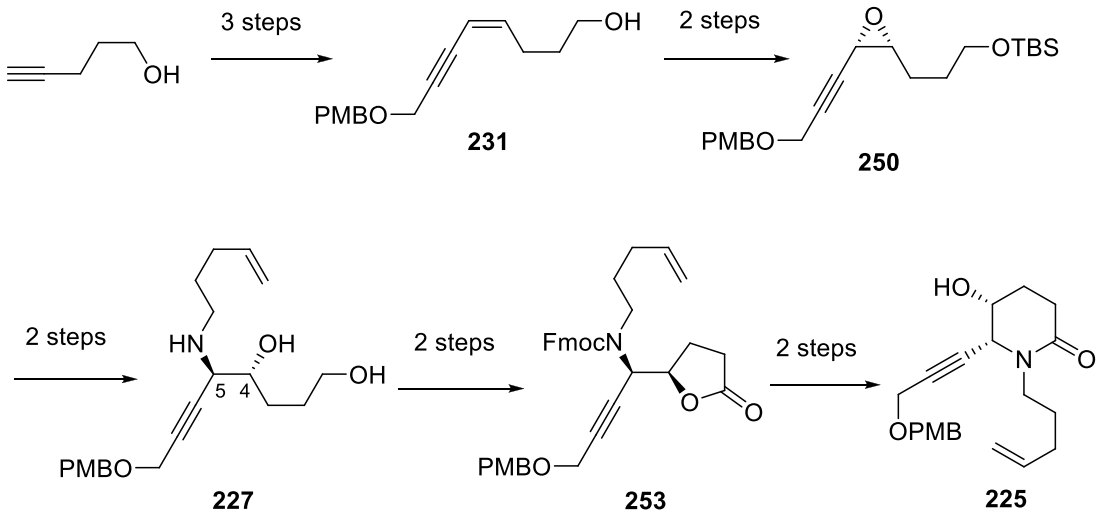
Scheme 2.66: Summary of outcomes from synthetic strategy 1

The second synthetic strategy failed because of the low yield of the lactone **184** and its unsuccessful conversion to the ester derivative **195** due to a competing proto-desilylation process.



Scheme 2.67: Summary of outcomes from synthetic strategy 2

Using synthetic strategy three, we achieved the synthesis of the ene-yne lactam **196** via the aminolysis ring opening reaction of the epoxide **198**, however we could not improve the yield of the desired products (**196** and **221**) over 40% due to competing reactions of the reactive ester group. Finally, we have successfully synthesized the ene-yne lactam **225** via the epoxide **250** (**228**; Pg = TBS), in which the problematic ester group was replaced with a CH_2OTBS group. Lactam **225** was obtained in 11 synthetic steps and 12.1% overall yield from 4-pentyne-1-ol. Construction of the A-B and A-B-C ring systems and attempts to make the ether linkage of stemocurtisine from the lactam **225** will be discussed in Chapter 3.



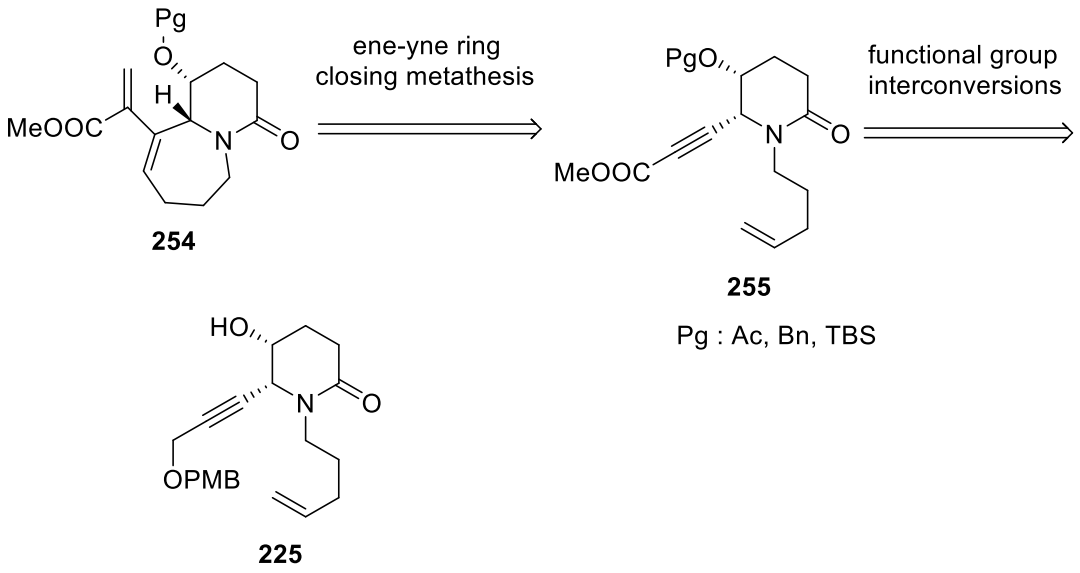
Scheme 2.68: Summary of the successful synthesis of lactam **225**

CHAPTER 3: CONSTRUCTION OF THE A-B AND A-B-C RING SYSTEMS OF STEMOCURTISINE

3.1 Construction of the A-B ring system of stemocurtisine

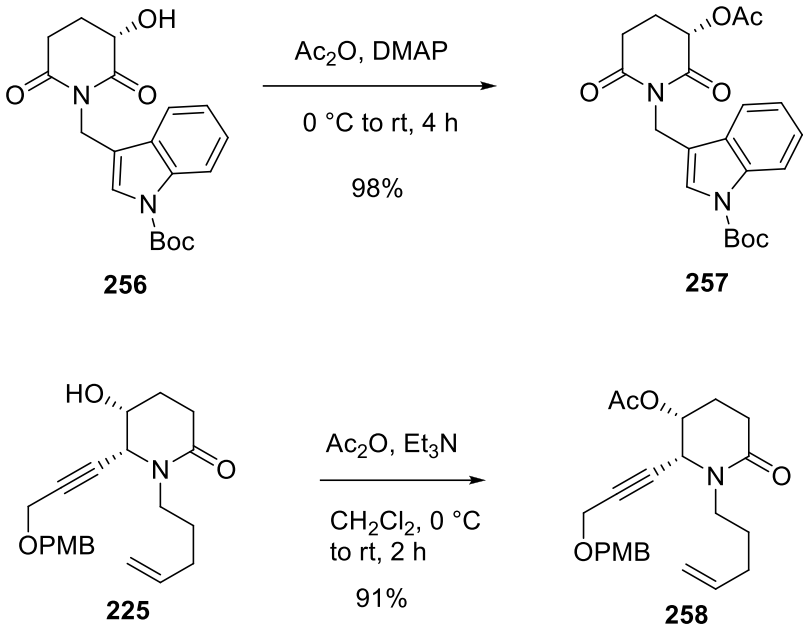
3.1.1 With an *O*-acetyl protecting group

With the ene-yne lactam **225** in hand, we then examined the construction of the A-B ring system of stemocurtisine, following the retrosynthestic analysis shown at **Scheme 3.1**. The bicyclic compound **254** could be obtained from the ene-yne **255** (**142**, R = COOMe) following the ene-yne ring closing metathesis procedure described by Mori.[27] Compound **255** could be obtained from **225** via hydroxyl group protection and a sequence of functional group interconversions.



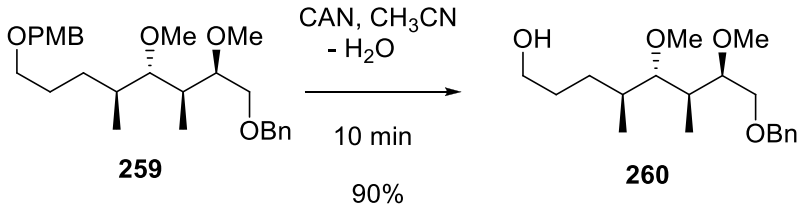
Scheme 3.1: Retrosynthestic analysis of **254**

Initially, the acetyl group was chosen to protect the hydroxyl of **225** due to its ease formation and subsequent cleavage. Follow Argade's procedure (preparation of **257** from **256**),[100] treatment of the alcohol **225** with Ac_2O and Et_3N in CH_2Cl_2 afforded the acetate **258** in 91% yield (**Scheme 3.2**).

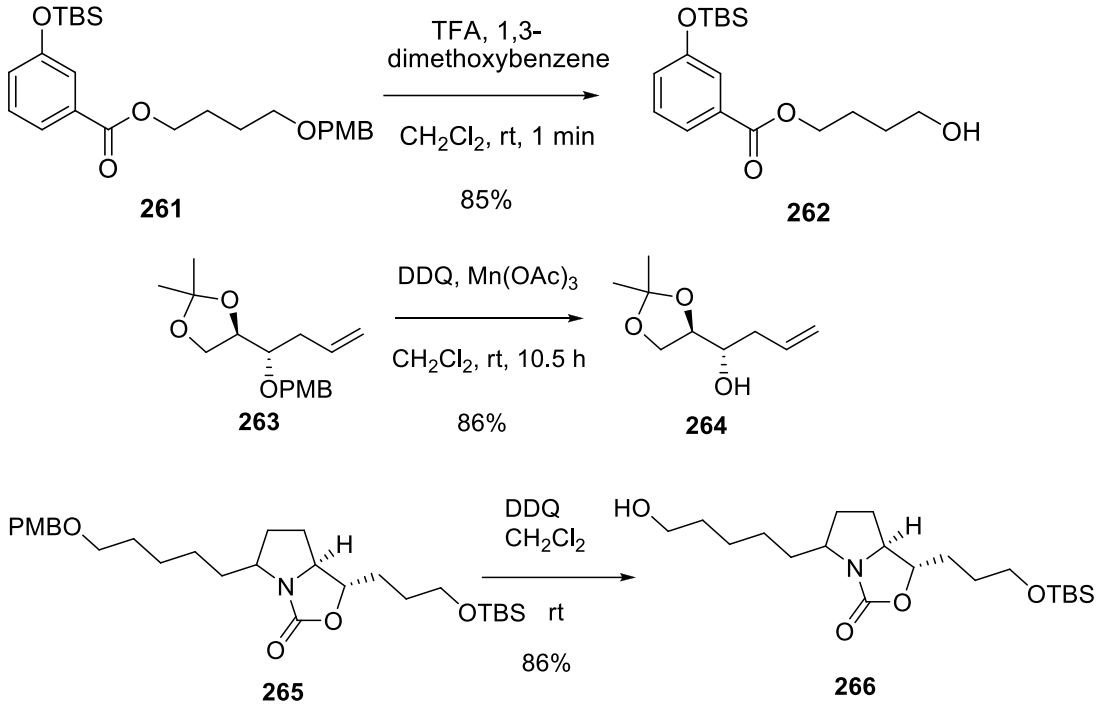


Scheme 3.2: Acetylation of **256** and **225** under Argade's conditions[100]

The next step involved the removal of the PMB protecting group of **258**. There are many methods to achieve this (**Scheme 3.3**). Enders reported the oxidative removal of the PMB ether group in **259** using CAN to prepare the primary alcohol **260** in 90% yield.[101] Jung used TFA and 1,3-dimethoxybenzene to cleave the PMB group of **261** to produce the corresponding primary alcohol **262** in 85% yield.[102] The PMB deprotection of **263** was carried out in CH_2Cl_2 using DDQ and $Mn(OAc)_3$ to provide the secondary alcohol **264** in 86%.[103] Tang used DDQ in CH_2Cl_2 and H_2O (15:1) to remove the PMB group of **265** in good yield (86%) (**Scheme 3.3**).[104]



Scheme 3.3: Literature methods for PMB deprotection[101-104]

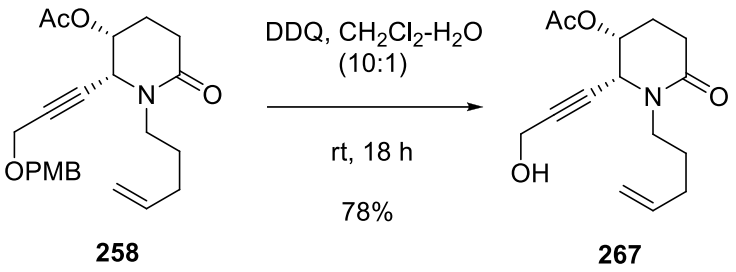


Scheme 3.3 (continued): Literature methods for PMB deprotection[101-104]

In order to maximize the yield of the PMB deprotection reaction of compound **258**, the four methods described above for PMB removal were examined. The results are summarized in the **Table 3.1**. Treatment of the PMB ether **258** with DDQ in CH_2Cl_2 and H_2O (10:1) gave the best yield (78%) of the corresponding alcohol **267** (**Table 3.1**, entry 4) (**Scheme 3.4**).

Entry	Reagent	Solvent	Time	Yield of **267**
1	CAN	CH_3CN-H_2O (4:1)	16 h	66%
2	TFA and 1,3-dimethoxybenzene	CH_2Cl_2	14 h	54%
3	DDQ and $Mn(OAc)_3$	CH_2Cl_2	16 h	77%
4	DDQ	CH_2Cl_2-H_2O (10:1)	18 h	78%

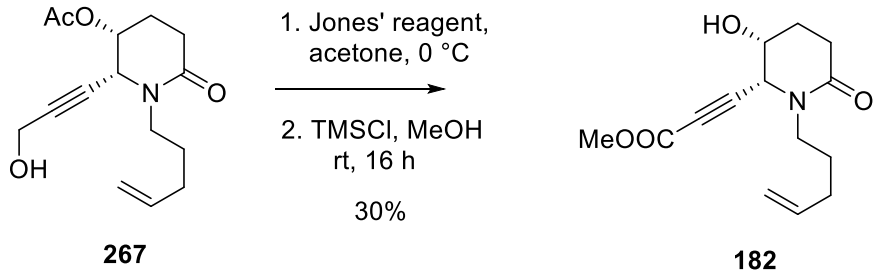
Table 3.1: Reaction conditions and yields for the PMB deprotection reactions of **258**



258 **267**

Scheme 3.4: Optimal conditions for PMB deprotection of **258**

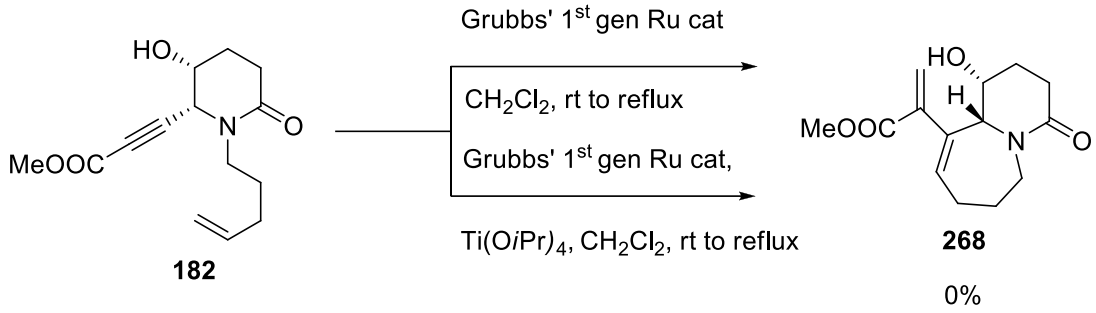
Jones' oxidation (acetone, 0 ºC) of **267** gave the corresponding acid. Treatment of this acid with TMSCl/MeOH provided the methyl ester **182**, with loss of the acetate group. Unfortunately the overall yield of these two steps was very low. The ester **182** was obtained in only 30% yield (**Scheme 3.5**).



267 **182**

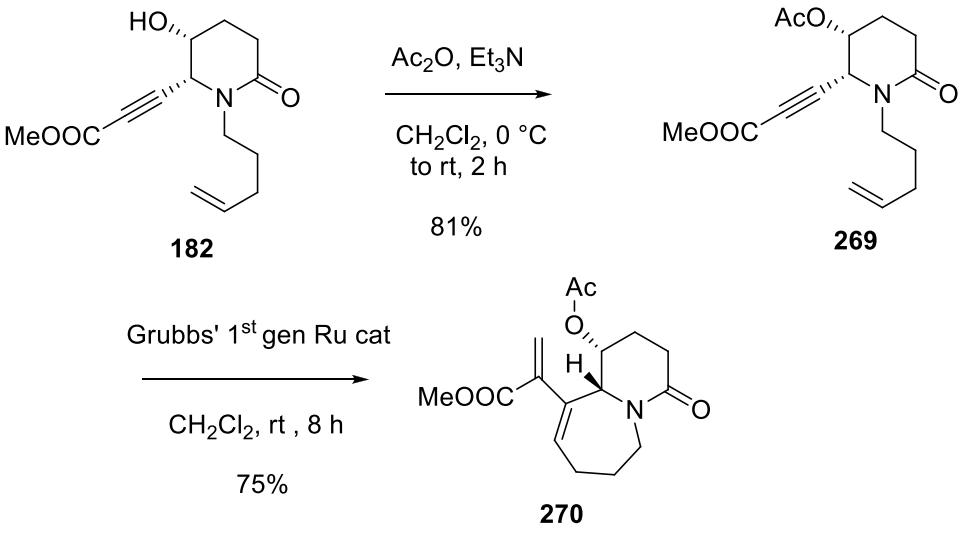
Scheme 3.5: Synthesis of ester **182**

To our surprise, treatment of the ene-yne **182** with Grubbs' 1st generation Ru catalyst in CH_2Cl_2 gave no product. Heating the reaction mixture at reflux did not help the reaction occur. We thought that perhaps the OH group could co-ordinate to the catalyst and then deactivate it. To prevent this co-ordination, Ti(O*i*Pr)$_4$ was added to the reaction mixture before heating at reflux temperature.[105] It was anticipated that the Ti(O*i*Pr)$_4$ would prevent deactivation of the catalyst by coordination to the OH group of **182**. However, this modifiation failed to form the desired product **268** and only unreacted ene-yne **182** was recovered (**Scheme 3.6**).



Scheme 3.6: Attempted RCM reactions of **182**

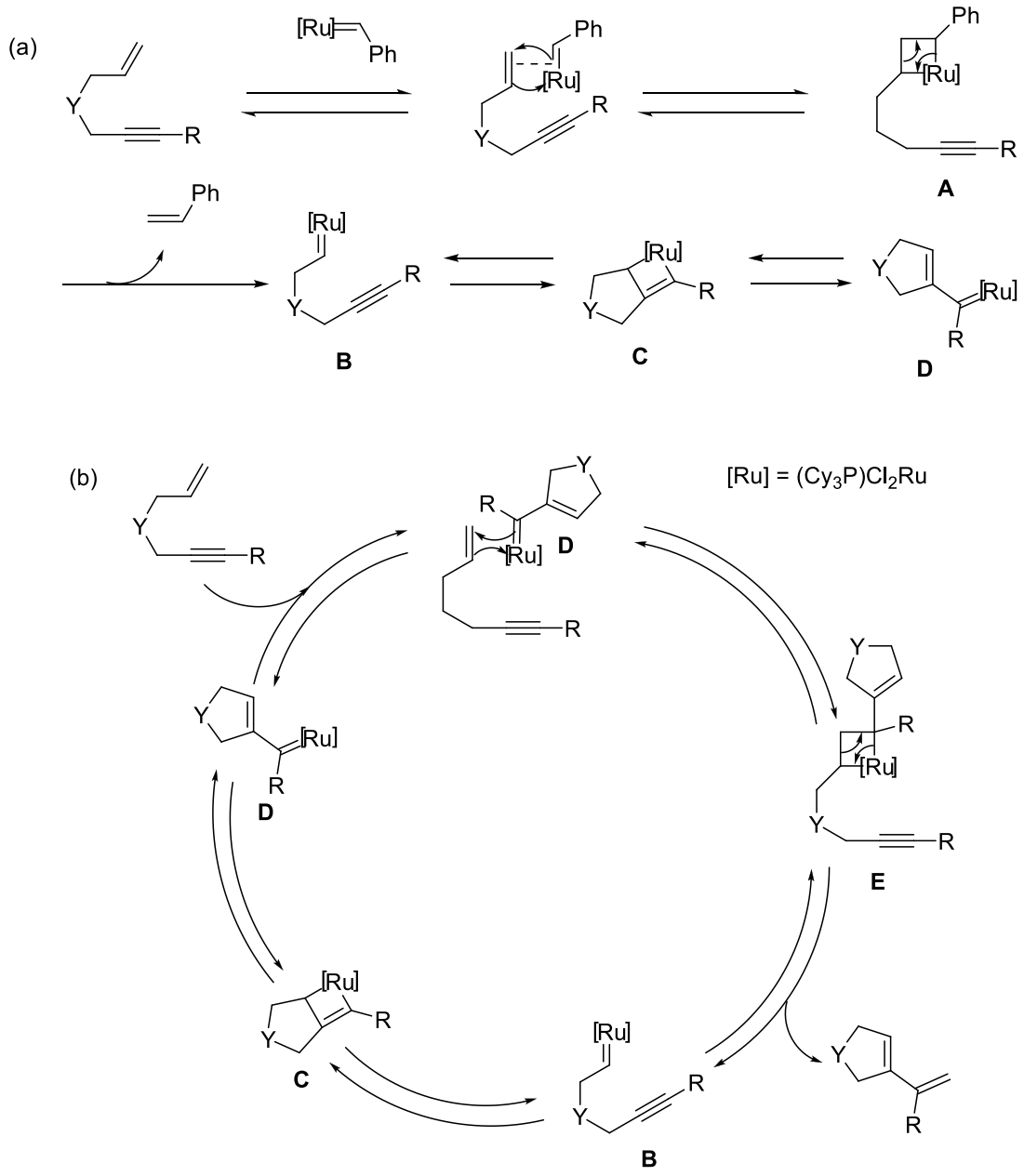
We then decided to protect the hydroxyl group of **182** before trying the RCM reaction. Treatment of **182** with Ac_2O and Et_3N in CH_2Cl_2 produced compound **269** in 81% yield. Finally, RCM of **269** catalysed by Grubbs' 1st generation Ru catalyst in CH_2Cl_2 at rt afforded the bicyclic compound **270** in 75% yield (**Scheme 3.7**).



Scheme 3.7: Preparation of the bicycle **270**

The proposed mechanism for the ene-yne ring closing metathesis reaction is shown at **Scheme 3.8**.[106] In the initiation step (a), the initial Ru complex undergoes loss of Cy_3P to generate an active catalyst abbreviated as [Ru]=CHPh. This undergoes a cycloaddition reaction with the alkene group of the substrate forming the ruthenacyclobutane **A**. A subsequent cycloelimination reaction then releases styrene and generates the Ru-carbene catalyst **B**, which reacts intramolecularly with the

triple bond to yield the bicyclic ruthenacyclobutene **C**. After cycloelimination the vinyl carbene catalyst **D** is generated. In the catalytic cycle (b), the vinyl carbene **D** first adds to the double bond of the substrate forming the ruthenacyclobutane **E**. Cycloelimination then gives the product and the ruthenium carbene intermediate **B** which undergoes a subsequent intramolecular cycloaddition with the alkyne give the bicyclic ruthenacyclobutene **C**. After cycloelimination, the vinyl carbene **D** is regenerated and the catalytic cycle is continued.



Scheme 3.8: Proposed mechanism for the ene-yne RCM reaction[106]

The structure of **270** was clearly evident from an analysis of its ^{1}H NMR spectrum (**Figure 3.1**). The H-9 and H-10a protons resonated at δ 5.83 (t, *J* = 6.0 Hz, 1H, H9) and 4.46 (s, 1H, H10a), respectively. In addition, the two H-4' protons appeared at δ 6.20 (s, 1H, H4', *Z*) and 5.60 (s, 1H, H4', *E*). The ^{13}C NMR spectrum showed resonances for the correct number and types of carbons. Furthermore, the HRESIMS (calcd. for $C_{16}H_{21}O_5NNa$, $(M+Na)^+$ 330.1317, found: 330.1302) analysis confirmed the molecular formula of compound **270**. The ^{1}H and ^{13}C NMR spectroscopic assignments are shown in **Figures 3.1** and **3.2**. These were based on 2D NMR experiments (COSY, HSQC and HMBC).

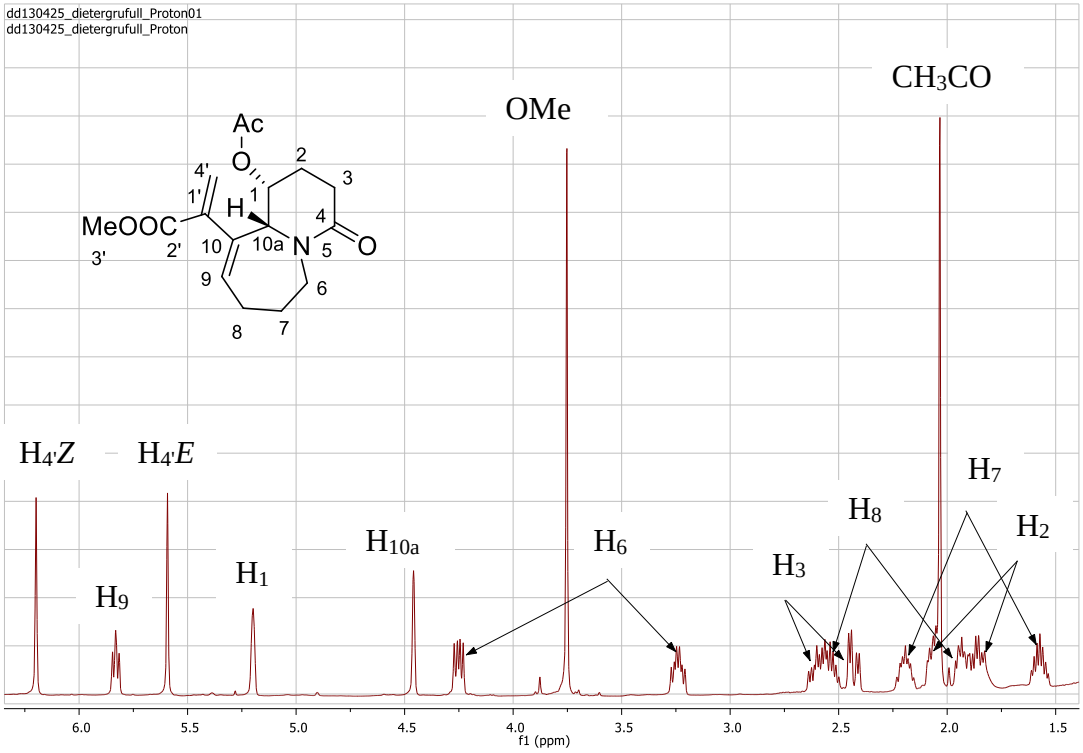


Figure 3.1: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **270**

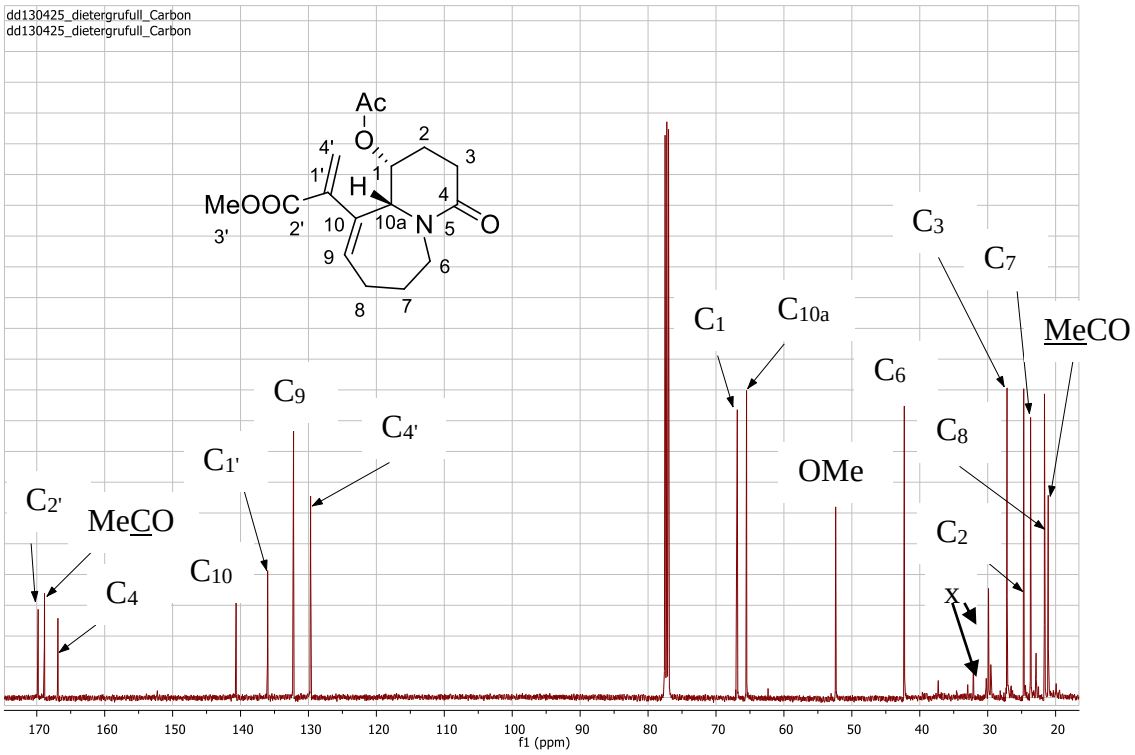
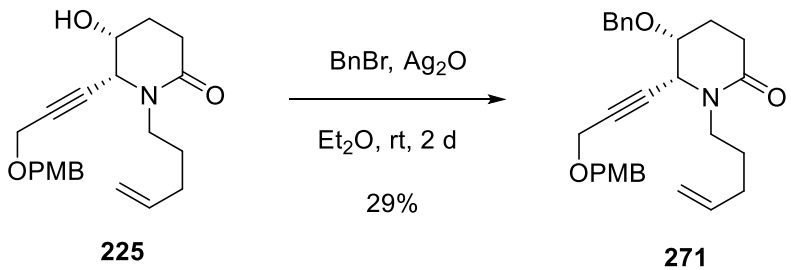


Figure 3.2: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **270** (x: impurities)

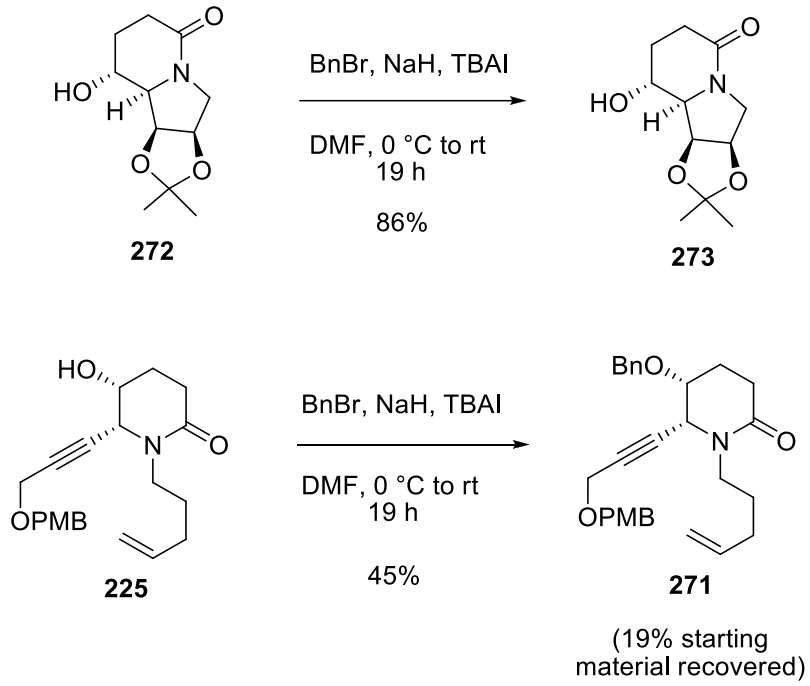
3.1.2 Using an *O*-benzyl protecting group

Due to the unsatisfactory overall yield of **182** (30%), the benzyl group was next examined as a hydroxyl protecting group for **225**. In contrast to the benzylation reaction of the imide **168** (**Scheme 2.6**), benzylation of the lactam **225** with BnBr, Ag_2O in Et_2O gave the corresponding benzyl ether **271** in very poor yield (29%) (**Scheme 3.9**). A slight improvement was achieved (45% yield and 19% starting material recovered) under William's type conditions used for the synthesis of **273** from **272** (**Scheme 3.10**).[107]



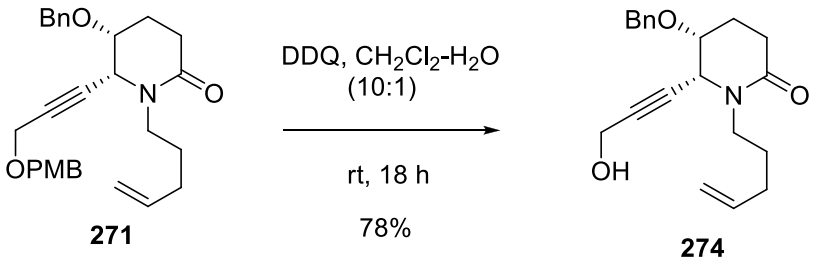
225 **271**

Scheme 3.9: *O*-benzylation of **225** with BnBr, Ag_2O



Scheme 3.10: *O*-benzylation of **272** and **225** under William's conditions[107]

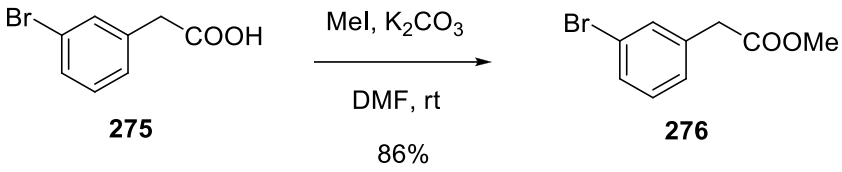
PMB deprotection of compound **271** was carried out using DDQ in CH_2Cl_2-H_2O at rt for 18 h to give the desired product **274** in 78% yield (**Scheme 3.11**).



Scheme 3.11: Removal the PMB group of **271** by DDQ

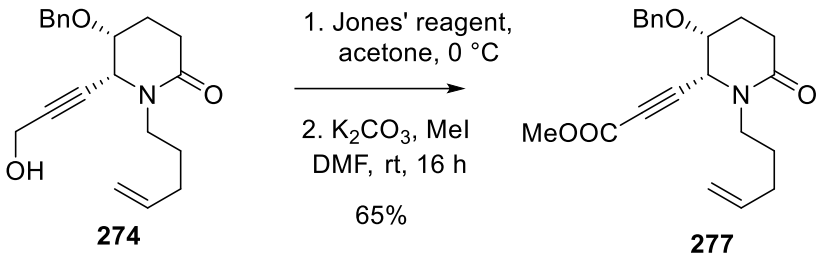
The primary alcohol group of **274** was oxidized to the corresponding acid by Jones' reagent in acetone at 0 ºC. We did not employ TMSCl/MeOH for the esterification of this acid because of our concerns for the benzyl protecting group, which may have been cleaved under the strong acid conditions (HCl is generated *in situ* from the reaction of TMSCl and MeOH). Kambe reported the synthesis of the ester **276** by treatment of the acid **275** with K_2CO_3/MeI in DMF in 86% yield (**Scheme 3.12**).[108]

Under these conditions, we obtained the ester **277** in 65% yield over the two steps from the alcohol **274** (**Scheme 3.13**).



275 **276**

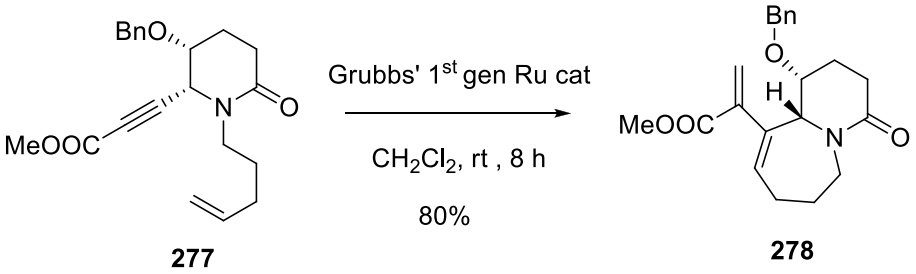
Scheme 3.12: Kambe's methylation of acid **276**[108]



274 **277**

Scheme 3.13: Synthesis of ester **277**

The bicyclic compound **278** was achieved in 80% yield via an ene-yne RCM reaction by treatment of **277** with Grubbs' 1st generation Ru catalyst in CH_2Cl_2 for 8 h under a N_2 atmosphere (**Scheme 3.14**).



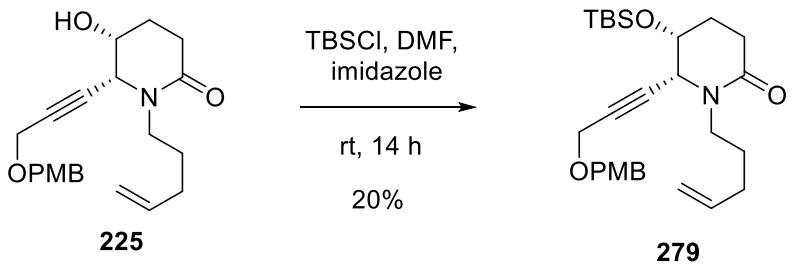
277 **278**

Scheme 3.14: Formation of bicycle **278**

3.1.3 Using an *O*-TBS protecting group

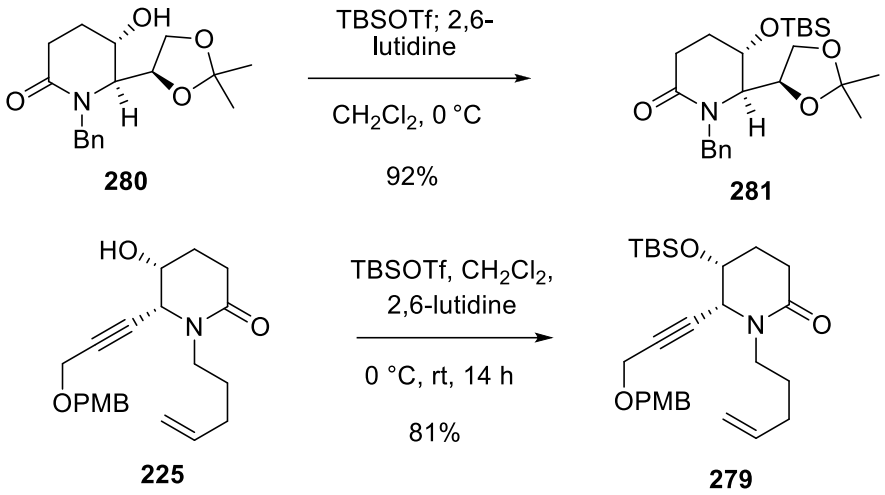
Because of the low yields in the conversion of the alcohol **267** to the ester **182** and *O*-benzylation reaction of **225**, we next examined the use of the TBS protecting group.

TBS protection of the hydroxyl group of the lactam **225** was quite a challenging process. Treatment of compound **225** with TBSCl and imidazole in DMF (under similar conditions that were used to prepare the TBS ether **170** shown in **Scheme 2.6**) gave only 20% yield of the expected product **279** (**Scheme 3.15**). Casiraghi reported the TBS-protection of **280** in 92% yield using TBSOTf and 2,6-lutidine in CH_2Cl_2.[109] Our first attempt using these conditions gave the desired TBS ether **279** in 30% yield (61% starting material recovered). Finally, with a slight modification we increased the yield of **279** to 81% (**Scheme 3.16**). TBSOTf (0.67 equiv) and 2,6-lutidine (1.0 equiv) were added dropwise to a solution of **22** at 0 ºC then the mixture was warmed to rt and stirred for 1 h. This process was repeated three times and then the reaction mixture was stirred at rt for 14 h. TLC analysis then showed complete disappearance of the starting alcohol. The TBS ether **279** was obtained in 81% yield after purification by column chromatography.



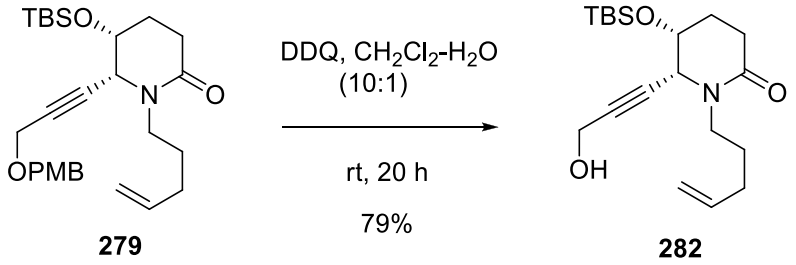
225 **279**

Scheme 3.15: TBS protection of **225** using standard conditions (TBSCl, imidazole in DMF)



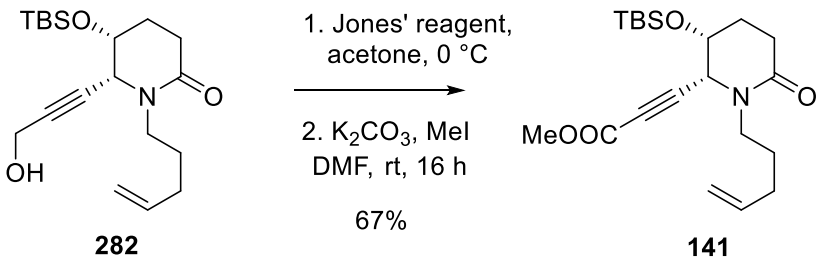
Scheme 3.16: TBS protection of **225** and **280** under Casiraghi's conditions[109] with modification

The PMB group of **279** was removed by treatment with DDQ to provide the corresponding alcohol **282** in 79% yield (**Scheme 3.17**).



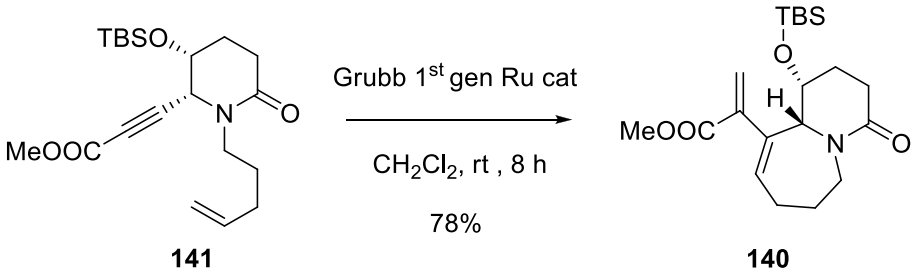
Scheme 3.17: Synthesis of the primary alcohol **282**

Jones' oxidation of **282**, followed by methylation (K_2CO_3/MeI in DMF) provided the ester **141** in 67% yield (over two steps from **282**) (**Scheme 3.18**).



Scheme 3.18: Synthesis of ester **141**

Treatment of the ene-yne **141** with Grubbs' 1st generation Ru catalyst in CH_2Cl_2 under a N_2 atmosphere provided the expected bicyclic compound **140** in 78% yield (**Scheme 3.19**).



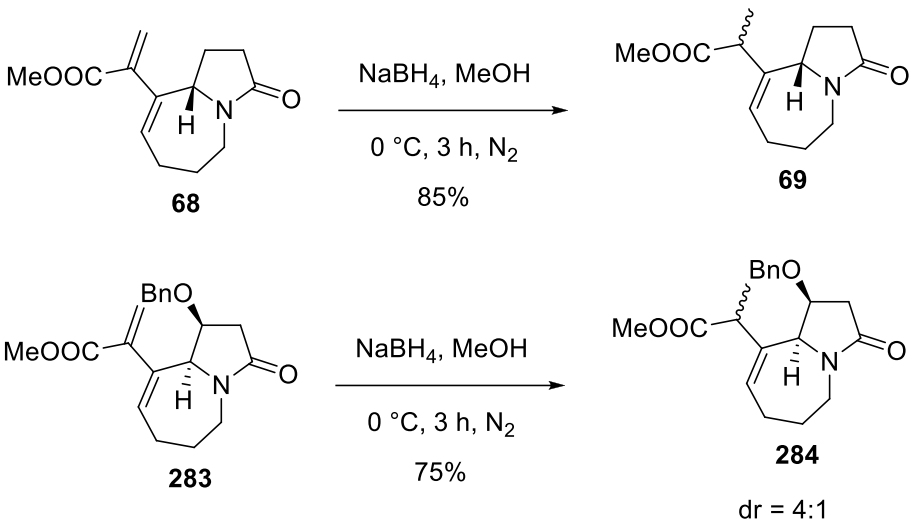
141 **140**

Scheme 3.19: Preparation of the bicycle **140**

3.2 Synthesis of the A-B-C ring system of stemocurtisine

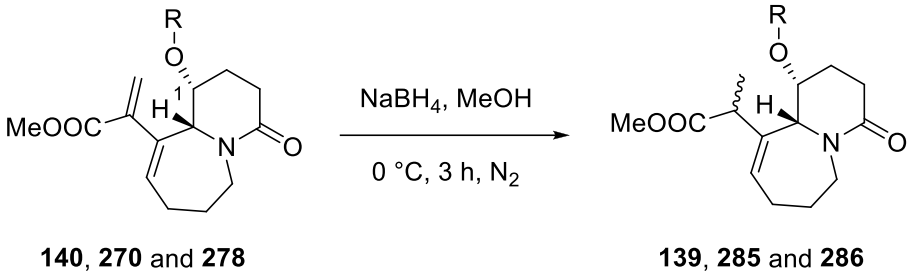
With the three bicyclic compounds, **140**, **270** and **278** in hand, we continued to follow Mori's procedures[27] to construct the corresponding tricyclic compounds possessing the core A-B-C ring structure of stemocurtisine **2**.

Mori[27] reported the synthesis of the saturated ester **69** from the reduction of α,β-unsaturated ester **68** with $NaBH_4$/MeOH via a 1,4-"hydride" reduction reaction. This reaction gave **69** as an inseparable mixture of diasteromers in 85% yield (**Scheme 1.1.1**). Swamy[60] successfully applied this procedure to prepare a diasteromeric mixture of **284** in good yield (75%, dr = 4:1) from the reduction of the α,β-unsaturated ester **283** (**Scheme 3.20**).



Scheme 3.20: Mori's[27] and Swamy's[60] reduction of α,β-unsaturated esters **68** and **283**

This procedure proceeded smoothly with our compounds **140**, **270** and **278**. We obtained the corresponding saturated esters **139**, **285** and **286**, in 75-78% yields as mixtures of two diastereomers (**Scheme 3.21** and **Table 3.2**). Noticeably, in all three reactions, the products and the starting materials had the same R_f values (by TLC analysis). So the success of these reactions was indicated by ^{1}H NMR analysis of the crude reaction mixture before purification by column chromatography.

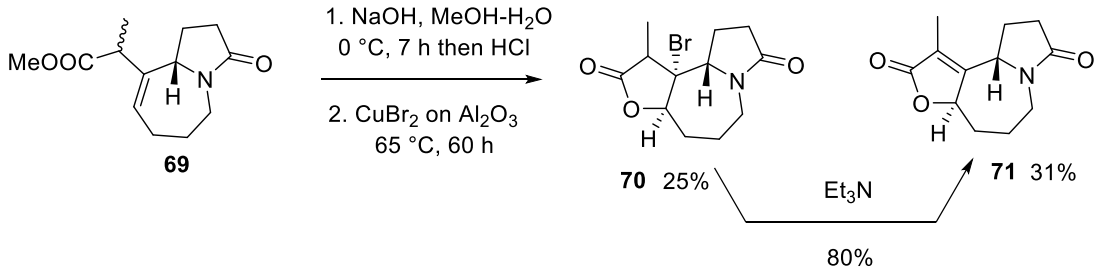


Scheme 3.21: Synthesis of saturated esters **139**, **285** and **286**

Starting material	R	Product	Yield	dr
140	TBS	**139**	78%	3:1
270	Ac	**285**	75%	2.5:1
278	Bn	**286**	77%	4:1

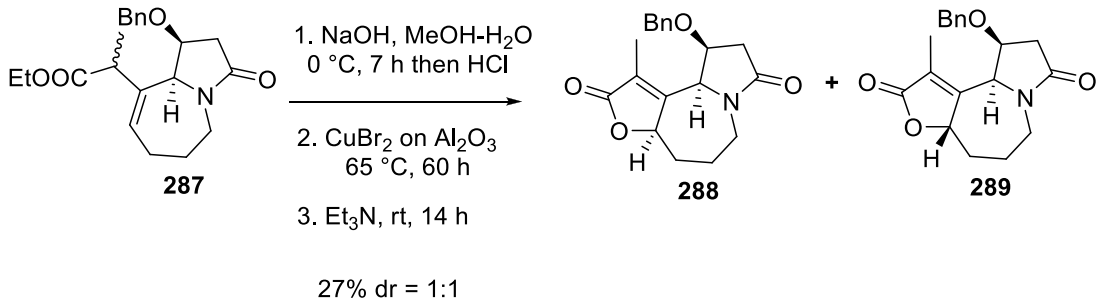
Table 3.2: Yields and dr of the reduction of **140**, **270** and **278** by $NaBH_4$/MeOH

Mori in his total synthesis of stemoamide **72** (**Scheme 3.21**),[27] hydrolysed the ester **69** using NaOH/MeOH-H_2O at 0 ºC for 7 h to furnish the corresponding acid. Then bromolactonization of this acid by treatment with $CuBr_2$ on alumina proceeded smoothly via a *5-endo-trig* cyclization, and two products **70** and **71** were obtained in 25% and 31% yields, respectively. Treatment of the bromide **70** with Et_3N in EtOAc converted it to compound **71** (total yield of **71** = 51%) (**Scheme 3.22**).



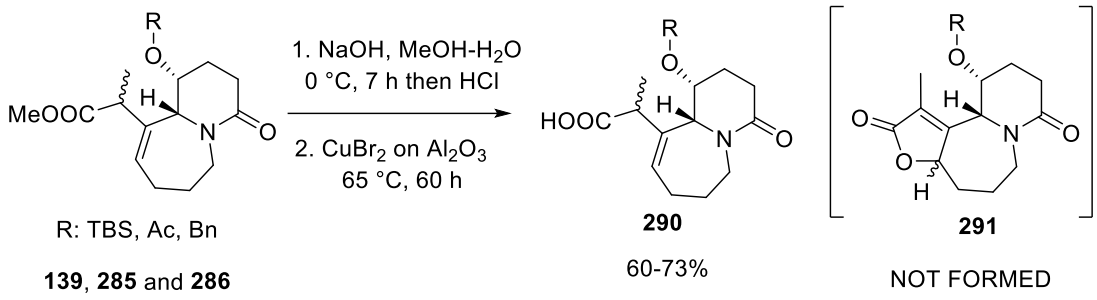
Scheme 3.22: Mori's synthesis of the tricyclic compound **71**

Swamy applied Mori's procedure to the compound **287**.[60] This reaction resulted in the synthesis of desired tricyclic compound **288** and its diasteromer **289** (dr = 1:1) in a combined yield of only 27% (**Scheme 3.23**).



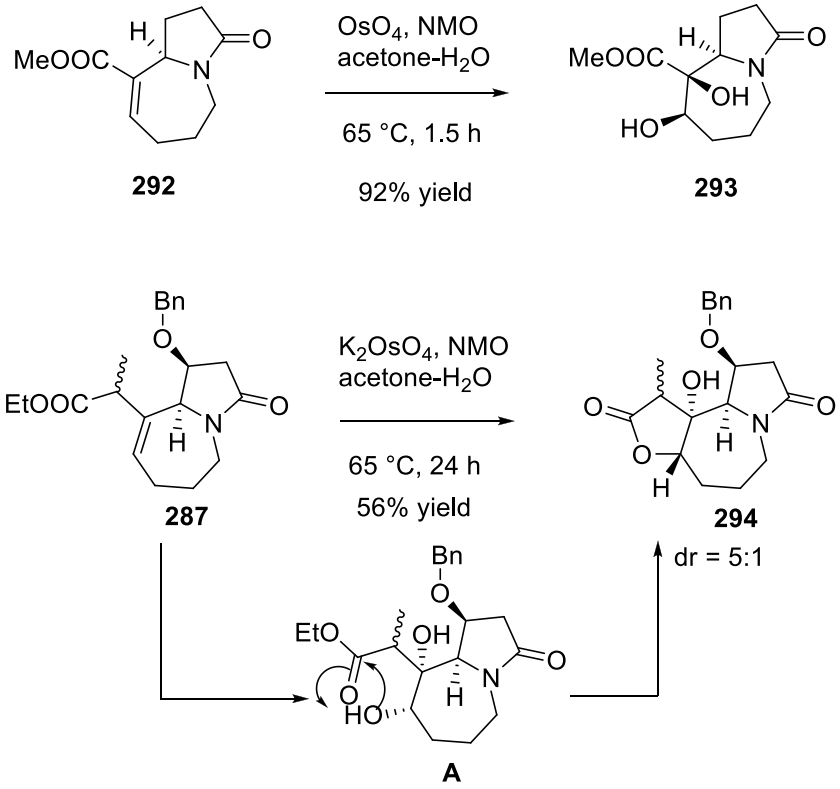
Scheme 3.23: Swamy's bromolactonization of **287**

We tried this method of bromolactonization on our compounds **139**, **285** and **286**. Unfortunately, these reactions failed to form the desired tricyclic lactone products **291** (**Scheme 3.24**) and only the corresponding acids **290** were isolated in 60-73% yields.



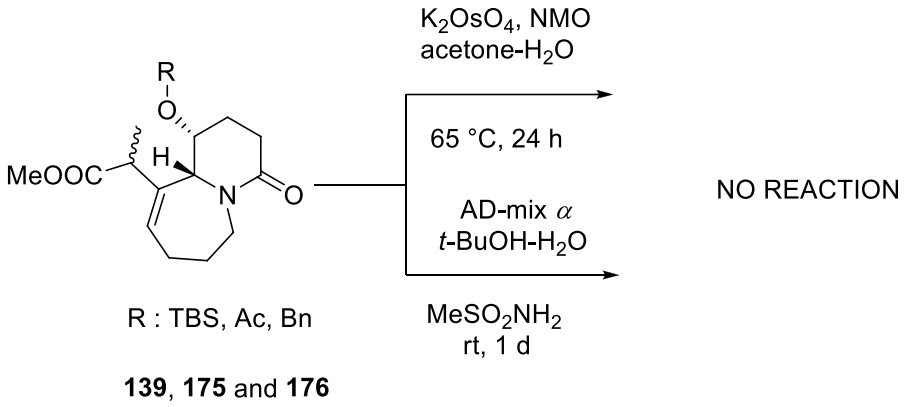
Scheme 3.24: Attempted bromolactonization of compounds **139**, **175** and **176**

Figueredo reported that the dihydroxylation reaction of the alkene **292** with OsO_4/NMO in acetone-H_2O at 65 ºC for 1.5 h provided the desired dihydroxylated product **293**[110] in an excellent yield of 92% (**Scheme 3.25**). Swamy[60] successfully synthesized the tricyclic lactone **294** from **287** following this dihydroxylation method with some modifications. Lactone **294** was obtained in moderate yield (56%) and relatively high diasteroselectivity (dr = 5:1) (**Scheme 3.25**).



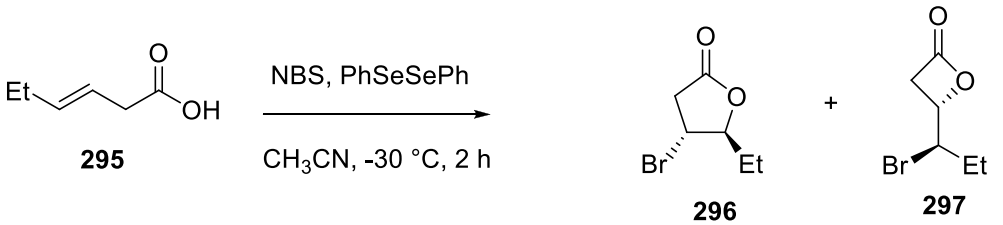
Scheme 3.25: Diastereoselective dihydroxylation reactions of **287**[60] and **292**[110]

Our attempts at the dihydroxylation reactions of compounds **139**, **185** and **186** under Swamy's conditions were not successful. We also tried to dihydroxylate these compounds using AD-mix-α and $MeSO_2NH_2$ using a co-solvent system of *t*-BuOH-H_2O, but these reactions also failed to form the desired products. Only the starting materials were recovered (**Scheme 3.26**). We are not sure why compounds **139**, **185** and **186** were so unreactive towards these bromolactonization and dihydroxylation reaction conditions, when compared to the pyrrolidine analogues **287** and **292**.



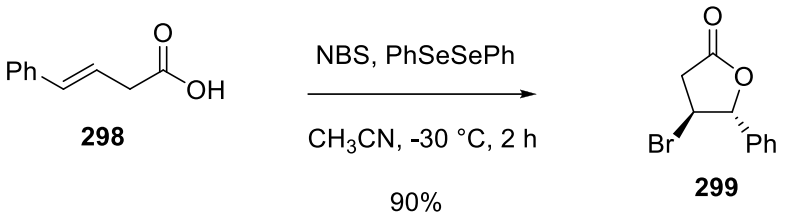
Scheme 3.26: Attempted dihydroxylation reactions of **139**, **185** and **186**

Tunge reported a method of halolactonization of β,γ-unsaturated carboxylic acids using NBS or NCS.[111] These reactions gave mixtures of β-lactones and γ-lactones (**Scheme 3.27**). With the substrate **295**, the yield of the latter (compound **296**) was maximised by using diphenyldiselenide as a catalyst. For example, γ-lactone **299** was obtained in excellent yield (90%) from 4-phenyl-3-butenoic acid (**Scheme 3.27**).



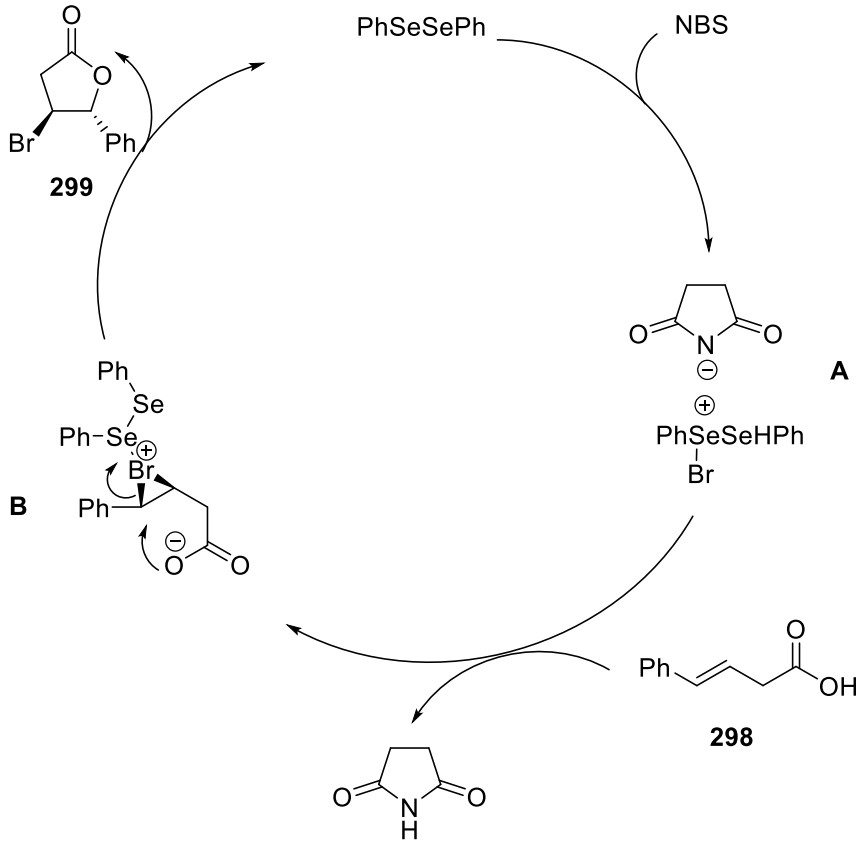
	296	:	**297**
no catalyst	2		1
5% mol PhSeSePh	17		1
5% mol PhSeBr	4		1
5% mol PhSe(phthalimide	2		1

Scheme 3.27: Tunge's halolactonization[111]



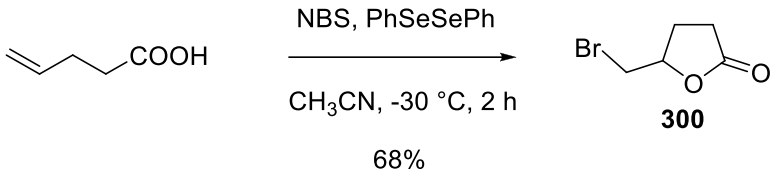
Scheme 3.27 (continued): Tunge's halolactonization[111]

The proposed mechanism[111] of this halolactonization reaction is shown in **Scheme 3.28**. Initially, the electrophilic NBS is activated via nucleophilic attack by PhSeSePh to form the ionic intermediate **A**. This intermediate then converts the alkene **298** to the bromonium ion intermediate **B**, where the selenium derivative remains coordinated to the bromine. Intramolecular attack by the carboxylate anion on to the 3-membered ring, via an S_N2 process, results in the *trans*-lactone product **299**.



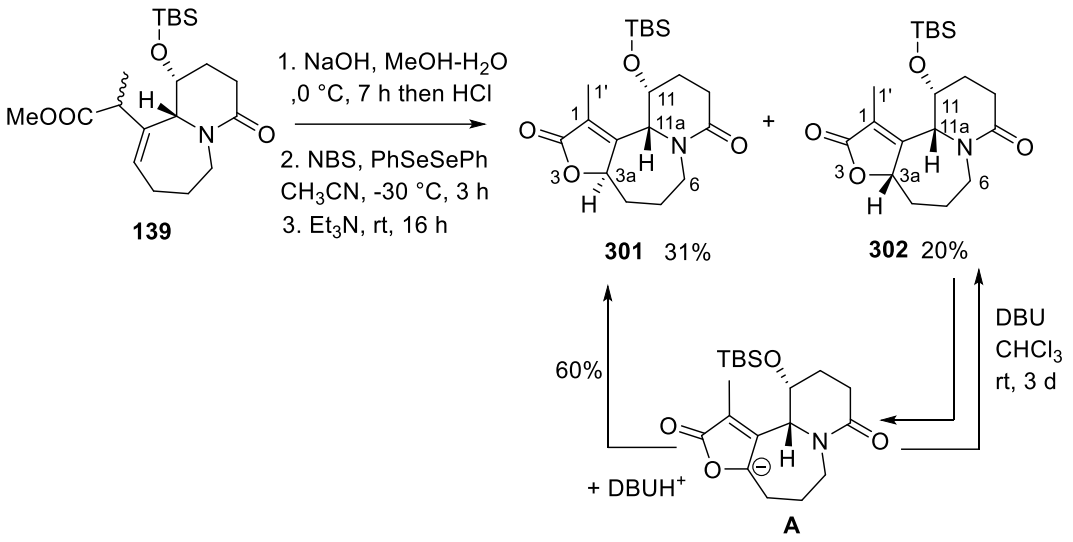
Scheme 3.28: Proposed mechanism for bromolactonization by NBS and PhSeSePh[111]

Our model work with this bromolactonization method proceeded well. Treatment of 4-pentenoic acid with PhSeSePh and NBS in CH_3CN at -30 ºC gave the corresponding lactone **300** in 68% yield, which had NMR spectroscopic data identical to those reported for this compound (**Scheme 3.30**).[112]



Scheme 3.30: Synthesis of lactone **300**

We then applied this procedure to compound **139** with some modifications. First, the ester **139** was hydrolysed to the corresponding acid by treatment with NaOH/MeOH-H_2O at 0 ºC for 8 h followed by acidification with HCl. The crude acid was then treated with NBS and PhSeSePh in CH_3CN at -30 ºC for 3 h. Instead of attempting to isolate the intermediate bromolactone, the crude reaction mixture was treated with Et_3N in EtOAc to promote elimination of hydrogenbromide. Purification of the reaction mixture by column chromatography gave the two bicyclic lactones **301** and **302** in yields of 31% and 20%, respectively (**Scheme 3.30**). Treatment of the minor product **302** with DBU in $CHCl_3$ converted it to the desired compound **301** in 60% yield. This interconversion most likely proceeds via the resonance stabilized intermediate anion **A** generated by deprotonation of **302** by the base DBU (**Scheme 3.30**).



Scheme 3.30: Synthesis of the tricyclic compound **301** via Tunge's halolactonization method

The identical molecular formulae of compounds **301** and **302** was confirmed by HRESIMS analysis (calcd. for $C_{19}H_{32}NO_4Si$, $(M+H)^+$ 366.2101, found: 366.2099 and calcd. for $C_{19}H_{32}NO_4Si$, $(M+H)^+$ 366.2101, found: 366.2110). In their ^1H NMR spectra, the H-11a protons of **301** and **302** resonated as singlets at δ 4.71 and δ 4.27, respectively, while the H-3a protons resonated at δ 4.97 (d, *J* = 9.5 Hz, 1H, H3a) and δ 4.80 (d, *J* = 11.0 Hz, 1H, H3a), respectively. The H-1' proton resonances of **301** and **302** appeared, as expected, as singlets at δ 1.90 (s, 3H, H1') and 2.10 (s, 3H, H1'), respectively. The ^1H and ^{13}C NMR spectroscopic assignments of the desired diasteromeric product **301** are shown in **Figures 3.3** and **3.4**, respectively.

Evidence for the relative configuration of **302** was obtained from NOESY NMR experiments, which showed a significant correlation between resonances for H3a and H11a ((**Figure 3.6**). In compound **301** however, no NOESY correlation between these corresponding resonances was observed (**Figure 3.5**). NOESY correlations between the resonances for H-11 and H-11a and H-6β and H-11a were also observed in both compounds (**Figures 3.5** and **3.6**).

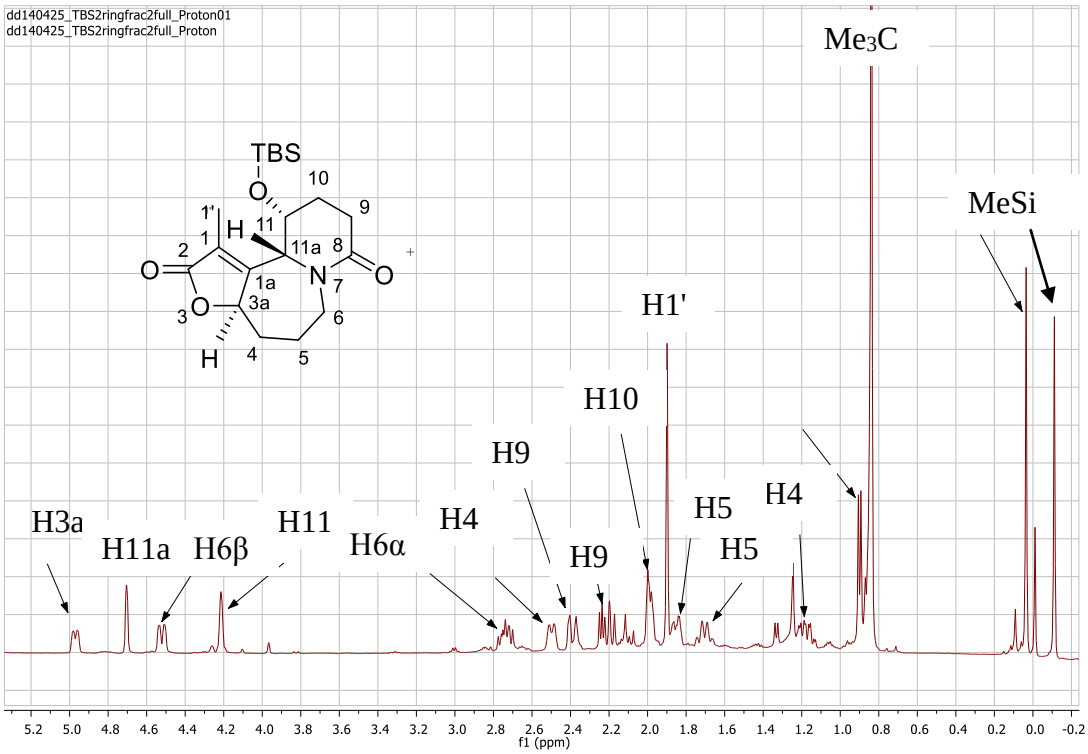


Figure 3.3: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **301**

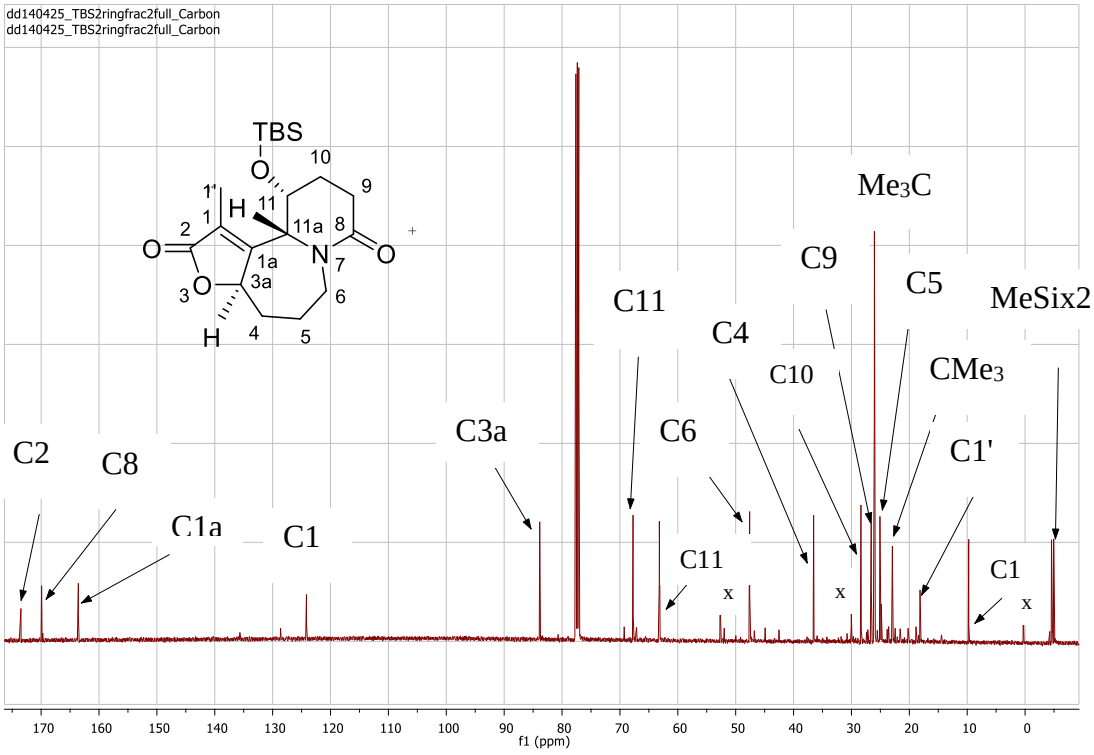


Figure 3.4: ^{13}C NMR spectrum ($CDCl_3$, 500 MHz) of **301** (x: impurities)

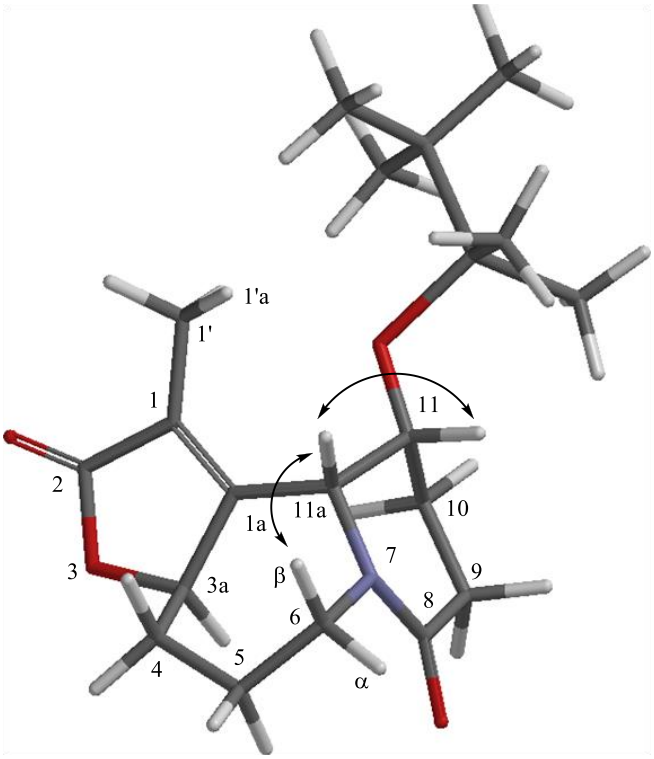


Figure 3.5: Spartan model (AM1) of **301** with atomic labelling and NOESY correlations shown by double-headed arrows

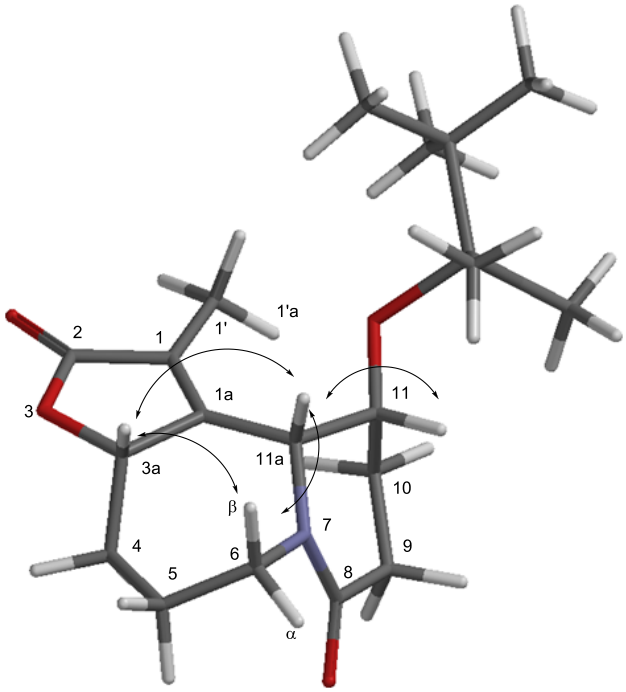
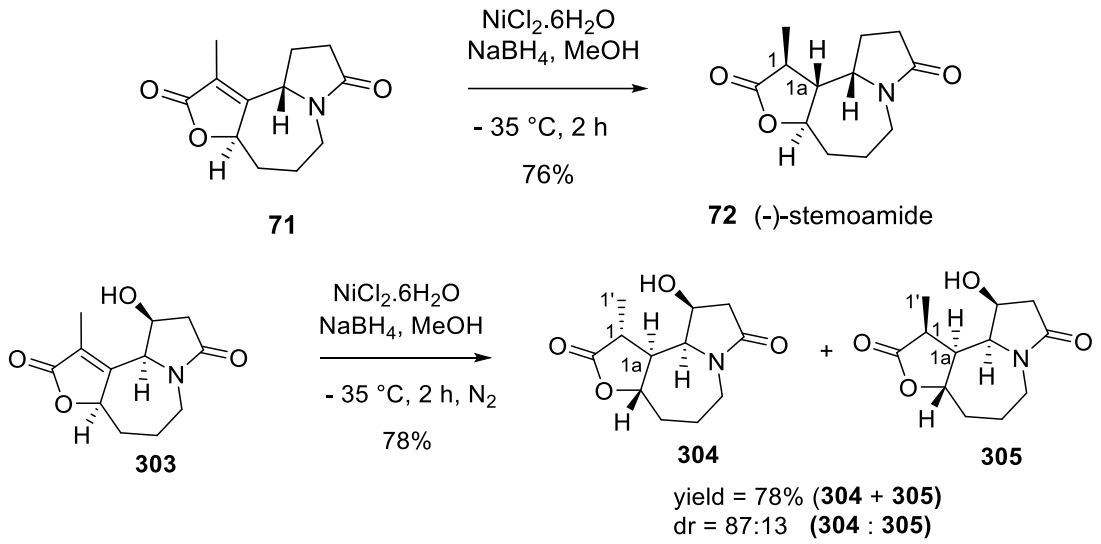


Figure 3.6: Spartan model (AM1) of **302** with atomic labelling and NOESY correlations shown by double-headed arrows

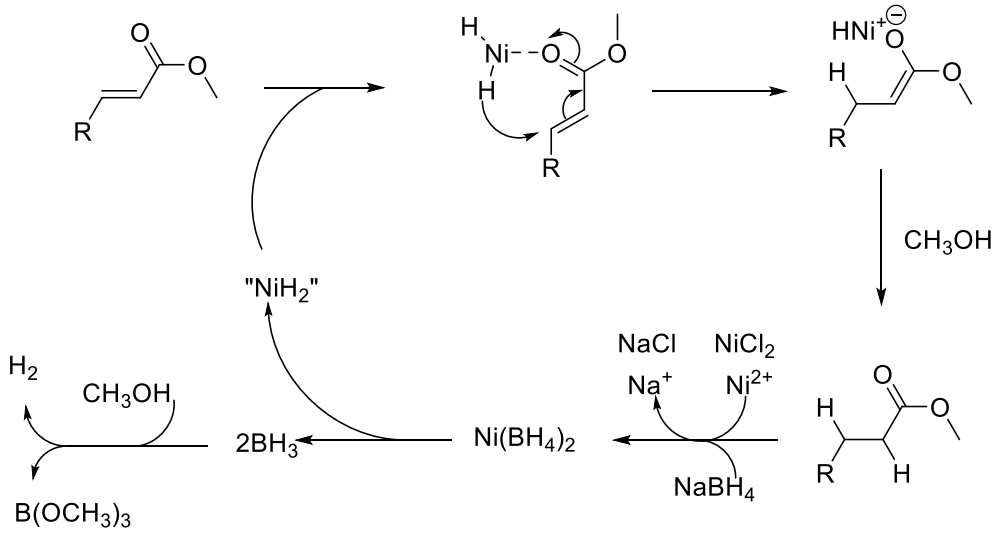
The major product of the bromolactonization of **139** (compound **301**) and the conversion of compound **302** to compound **301** under basic conditions suggest that compound **301** is thermodynamically more stable than compound **320**. Initially these structures were drawn in Spartan and a conformationed library was generated using molecular mechanics (MM force field). The lowest energy conformation was then geometry optimized using Semi-Empirical calculations (AM1). The AM1 heats of formation calculated for compound **301** and **302** were -863.2 kJ/mol and -851.5 kJ/mol, respectively, indicating **301** was thermodynamically more stable than **302** in the gas phase by about 12 kJ/mol. The calculated distances between H-3a and H-11a, H-3a and H-6β, and H-1 and H-11a in compound **302** were 2.73 Å, 2.45 Å and 2.39 Å, respectively, while for compound **301** the distances between H-3a and H-6α and H-11and H-11a were 2.79 Å and 2.45 Å, respectively. These interproton distances (< 3.0 Å**)** are consistent with the proposed structures of **301** and **302** and the observed NOESY correlations. The difference in energy between **301** and **302** was attributed to the sterically unfavourable pseudo-1,3-diaxial interactions between H-3a and H-6β and H-3a and H-11a in **302** and the closer distance between Me-1'a and the OTBS group in **302** (2.30 Å) compared to that in **301** (2.73 Å) (**Figures 3.5** and **3.6**).

Mori[27] reported that treatment of the α,β-unsaturated lactone **71** with $NaBH_4$ in the presence of $NiCl_2.6H_2O$ in MeOH furnished (-)-stemoamide **72** in 76% yield. Following this procedure, Swamy[60] obtained an inseparable mixture of lactones **304** and **305** in 78% yield from the reduction of the α,β-unsaturated lactone **303** (dr = 87: 13) (**Scheme 3.32**). The ^{1}H NMR spectrum of the major product **304** showed resonances for the H-1' proton as a doublet at δ 1.32 (d, J = 7.2 Hz, 3H, H1') and the H-1 proton as a dq at δ 3.30 (dq, J = 12.3, 7.2 Hz, 1H, H1). The coupling constant $J_{1,1a}$ = 12.3 Hz was consistent with that of stemoamide **72** reported in the isolation paper by Xu ($J_{1,1a}$ = 12.4 Hz).[113]



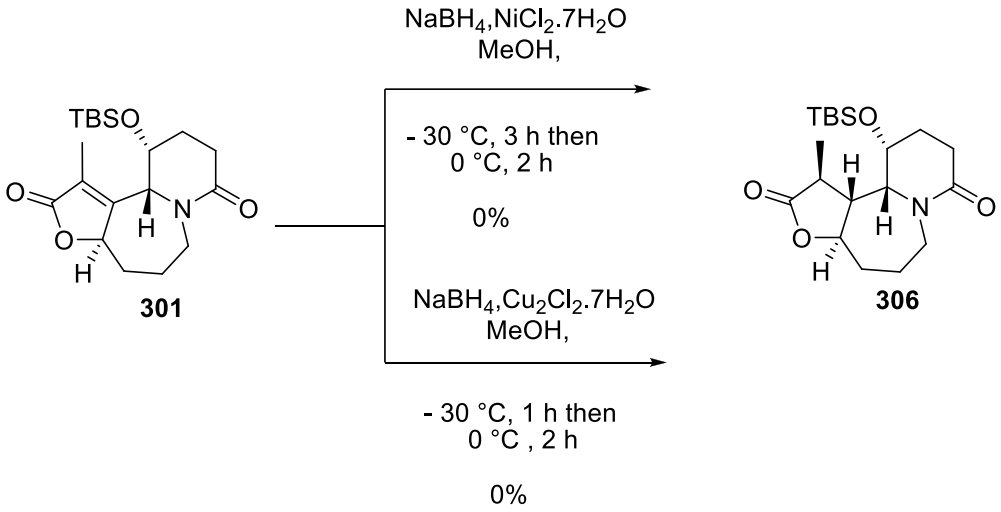
Scheme 3.32: Reduction of α,β-unsaturated lactones **71**[27] and **303**[60]

A proposed mechanism for this reduction reaction is shown in **Scheme 3.33**. This is based on the proposed mechanism for a related reduction using $Cu_2Cl_2/NaBH_4$,[114] it is postulated that a nickel "hydride" species is formed *in situ*, which is responsible for the observed 1,4-hydride reduction product.



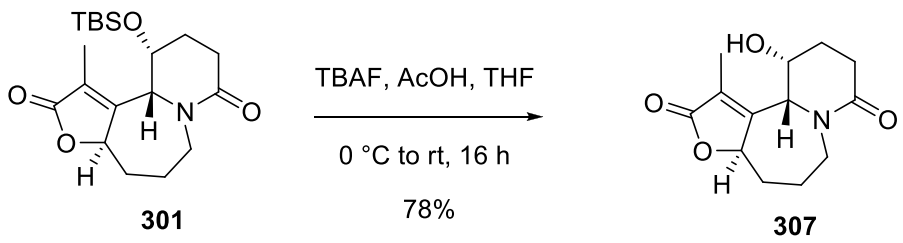
Scheme 3.33: Proposed mechanism for enone reduction by $NaBH_4$ and $NiCl_2$[114]

However, compound **301** was not reduced under these conditions. Treatment of **301** with $NaBH_4$ and $NiCl_2$ in MeOH at -30 ºC gave no product. This reaction did not occur when it was warmed to 0 ºC or rt. We also replaced the $NiCl_2$ by Cu_2Cl_2 as the catalyst (following Takeda's procedure)[114] but again the reduction reaction did not occur (**Scheme 3.34**).

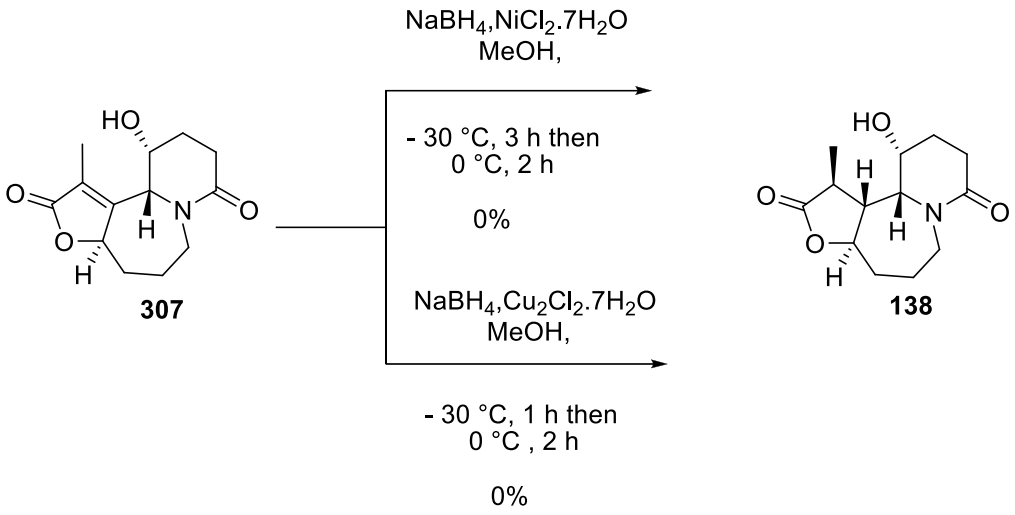


Scheme 3.34: Attempted reduction reactions of the α,β-unsaturated lactones **301**

We thought that the bulky TBS protecting group may have hindered these reactions. Therefore the TBS group of **301** was removed by treatment with TBAF in THF buffered by AcOH to provide the alcohol **307** in 78% yield (**Scheme 3.35**). However compound **307** was also unreactive under the aforementioned reduction conditions. We have no good explanation as to why these α,β-unsaturated lactones (**301** and **307**) were so unreactive in comparison to compounds **71** and **303** (**Scheme 3.36**). Perhaps the double bond in these compounds is less conjugated with the lactone carbonyl group because of the larger A-ring making it less electron deficient and more difficult to reduce.

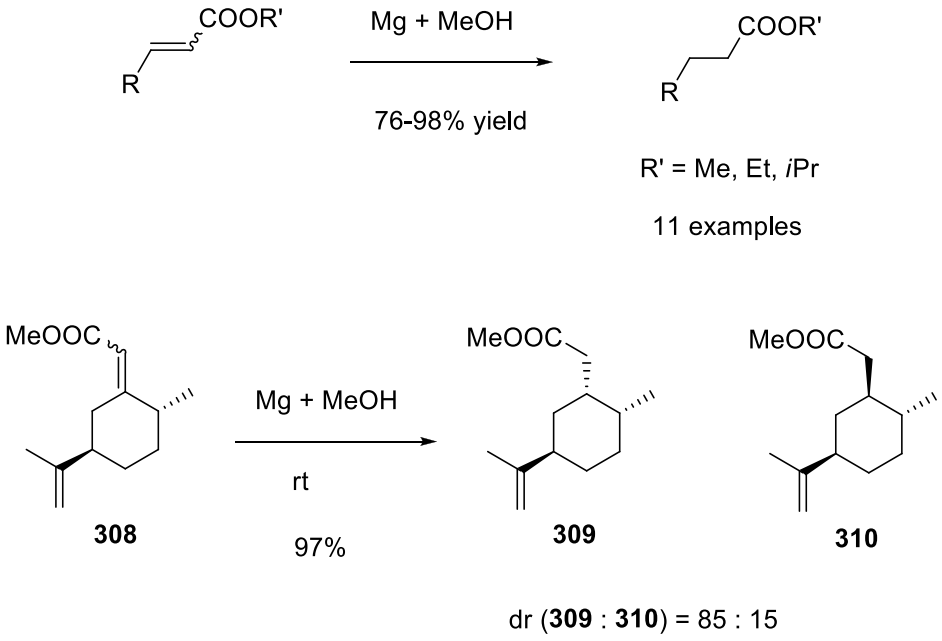


Scheme 3.35: TBS removal of **301**



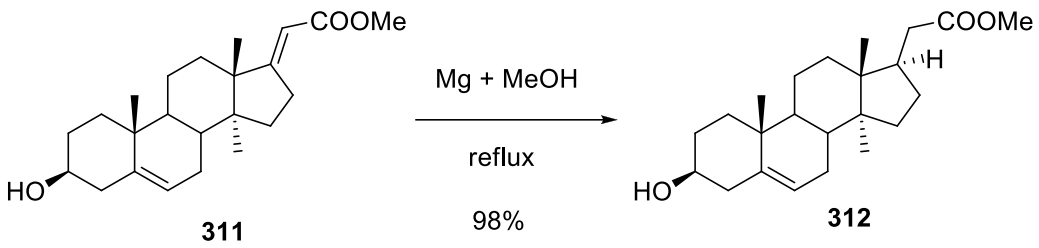
Scheme 3.36: Attempted synthesis of **138**

Pak reported that α,β-unsaturated esters could be reduced to the corresponding saturated esters in high yields (76-98%) using Mg/MeOH (**Scheme 3.37**).[115] Viterbo followed this method to prepare compounds **309** and **310** from the enone **308** in good yield and with some degree of diastereoselectivity (dr = 85:15) (**Scheme 3.37**).[116]



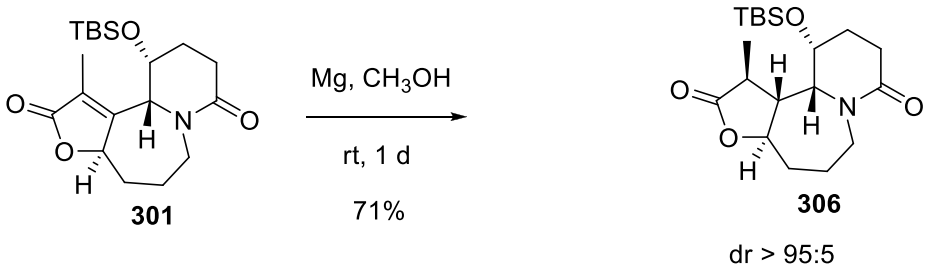
Scheme 3.37: Reduction of C=C bonds of α,β-unsaturated esters by Mg/MeOH[115,116]

More impressively, Zarecki applied this method to reduce the conjugated unsaturated ester **311** to the ester **312** in excellent yield (98%) as a single isomer (**Scheme 3.38**).[117]

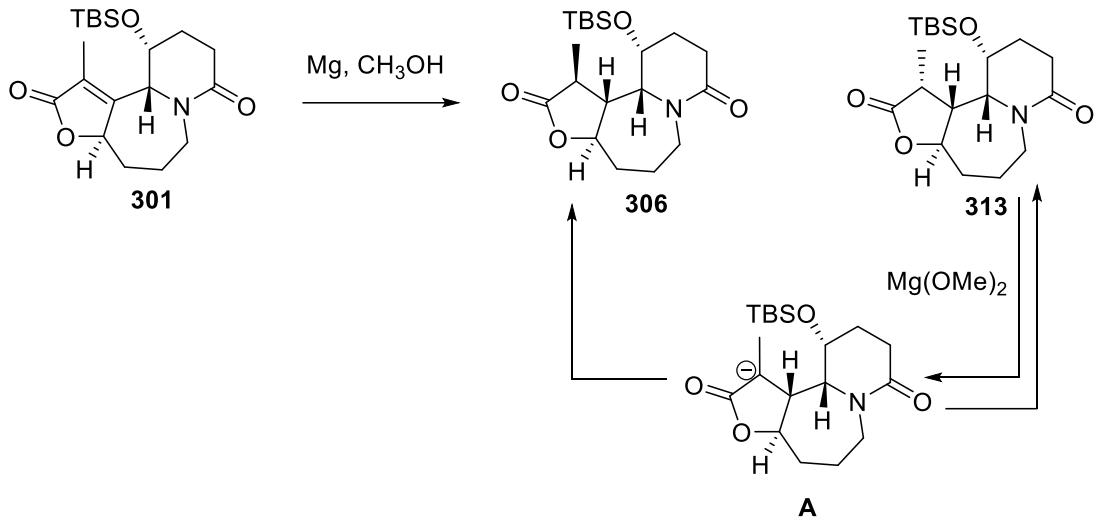


Scheme 3.38: Zarecki's synthesis of **312**[117]

We decided to examine this procedure on the α,β-unsaturated lactone **301**. Compound **301** was treated with Mg turnings (10 equiv) in MeOH for 1 d at rt. To our delight, the desired product **306** was obtained in good yield (71%) and excellent diasteroselectivity (dr > 95:5) (**Scheme 3.39**). This was the most impressive result of our synthesis. Presumably, the reduction of **301** led to a mixture of diastereomers **306** and **313**. However **313** is the thermodynamically less stable isomer due to an unfavourable steric repulsion between the CH_3 group and the bulky TBS group. Under the basic conditions of $Mg(OMe)_2$, we assume that if **313** was formed it would be converted to the more stable isomer **306** via the intermediate enolate anion **A** (**Scheme 3.39**).



Scheme 3.39: Reduction of **301** by Mg/MeOH



Scheme 3.39 (continued): Reduction of **301** by Mg/MeOH

The structure of **306** was confirmed by NMR, IR, MS and single crystal X-ray crystallographic analyses. The molecular formula of **306** was also confirmed by HRESIMS analysis (calcd. for $C_{19}H_{34}O_4NSi$, $(M+H)^+$ 368.2257, found: 368.2256). In the ^1H NMR spectrum of **306**, H-3a and H-6β resonated at δ 4.79 (td, *J* = 11.5, 2.5 Hz, IH, H3a) and δ 4.48 (d, *J* = 13.5 Hz, IH, H6β), respectively. The resonances for the H-11 and H-11a protons appeared at δ 4.25 (s, 1H, H11) and δ 3.73 (d, *J* = 7 Hz, 1H, H11a), respectively. H-1 and H-1' resonated typically at δ 2.86 (dq, *J* = 14.0, 7.0 Hz, 1H, H1) and 1.30 (d, *J* = 7.0 Hz, 3H, H1'). The coupling constant $J_{1,11b}$ = 14.0 Hz was quite close to the corresponding coupling constant of stemoamide[113] and is consistent with the 1,2-diaxial like relationship between H-1 and H-11b in the X-ray structure (ϕ1,11b = -156.1º). The ^1H and ^{13}C NMR spectroscopic assignments of the tricyclic compound **306** are shown in **Figures 3.7** and **3.8**, respectively and are based on 2D NMR experiments (COSY, HSQC, HMBC).

Evidence for the configuration of **306** was obtained from NOESY NMR experiments (**Figure 3.9**). Strong NOESY correlations were observed between H-11 and H-11a, H-11 and H-11b, H-11a and H-11b, H-11b and H-6β, H-11a and H-6β, H-1 and H-3a and H-3a and H-1' (**Figure 3.9**). No correlations were observed between H3a and H11b or between H1 and H11b, which further confirmed the relative configurations at C-1 and C-11b.

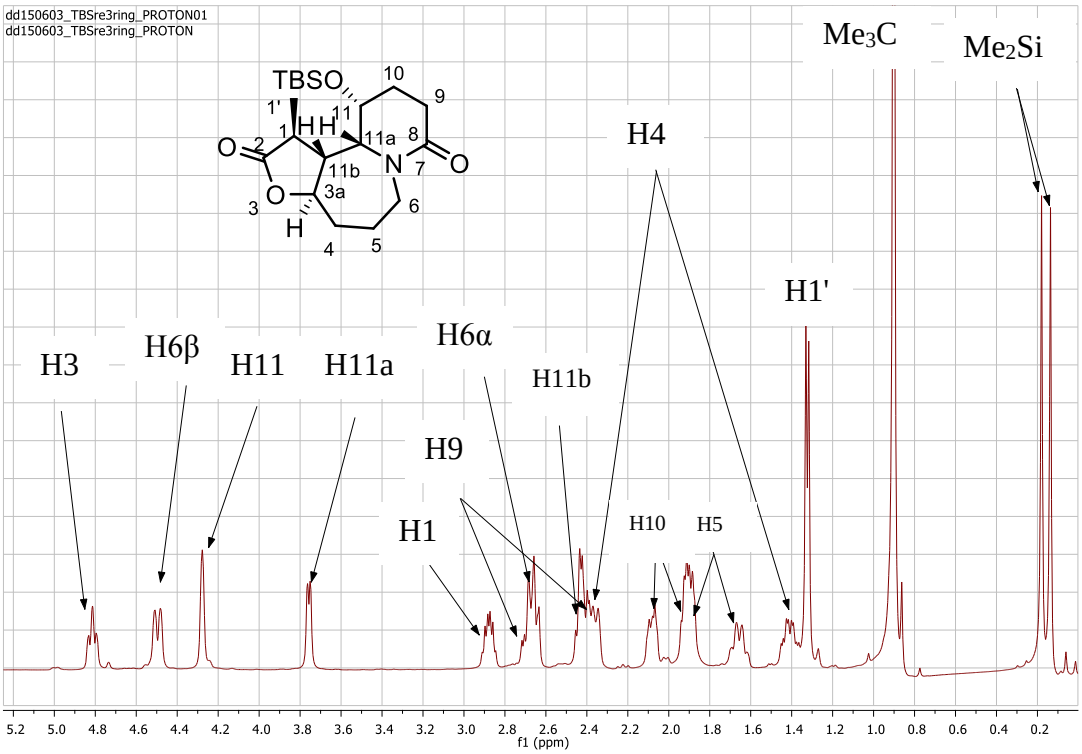


Figure 3.7: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **306**

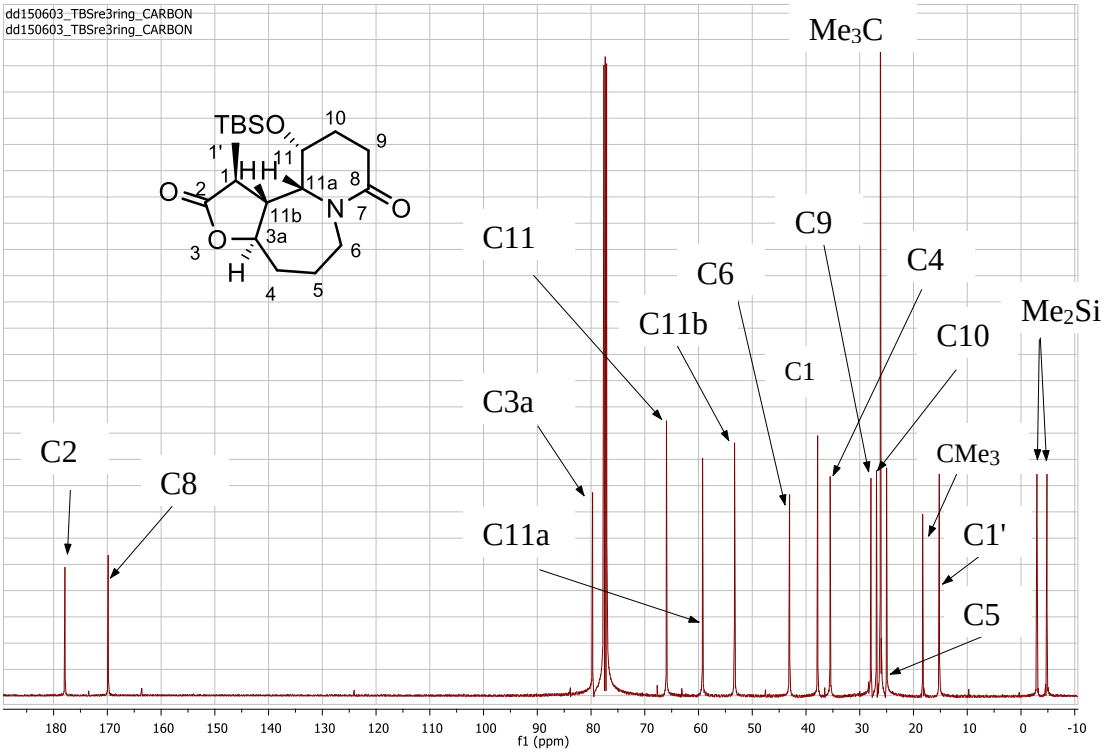


Figure 3.8: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **306**

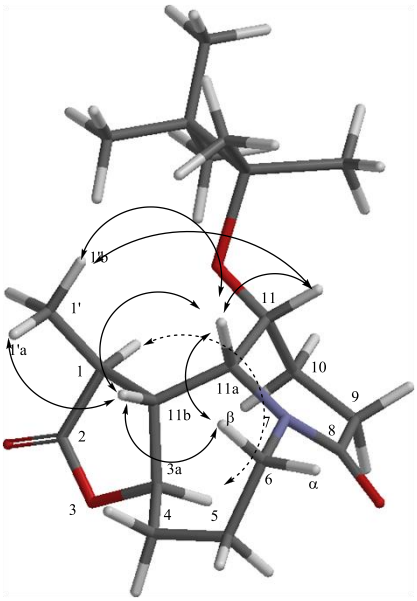


Figure 3.9: Spartan model (AM1) of **306** with atomic labeling and NOESY correlations shown by double-headed arrows.

Finally, the relative configuration of **306** was confirmed by its single crystal X-ray crystallography structure (**Figure 3.10**).

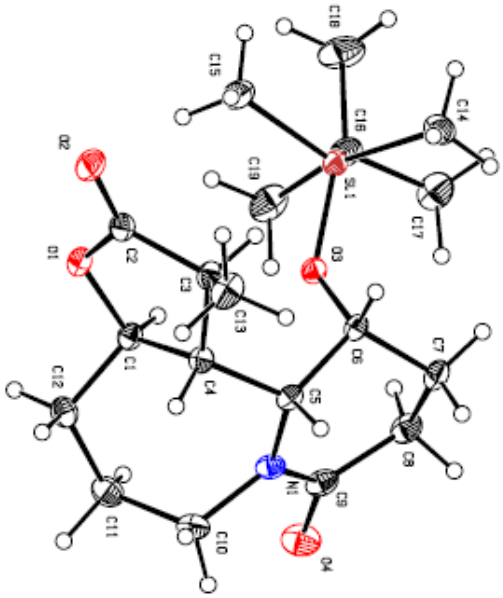


Figure 3.10: ORTEP X-ray crystal structure **306** with atomic labeling

We also used the Mercury software to visualise the X-ray structure of compound **306** and to measure some important distances between atoms (**Figure 3.11**). The results are given in **Table 4.2** with a comparison made with the corresponding distances calculated using Spartan modeling. Atomic labeling is shown in **Figure 3.9** (Spartan model).

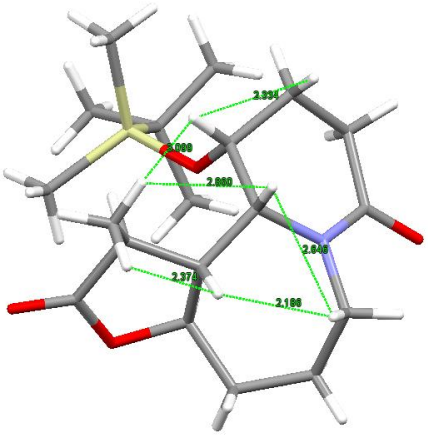


Figure 3.11: Mercury displayed X-ray crystal structure **306** with atomic distances (Å) displayed

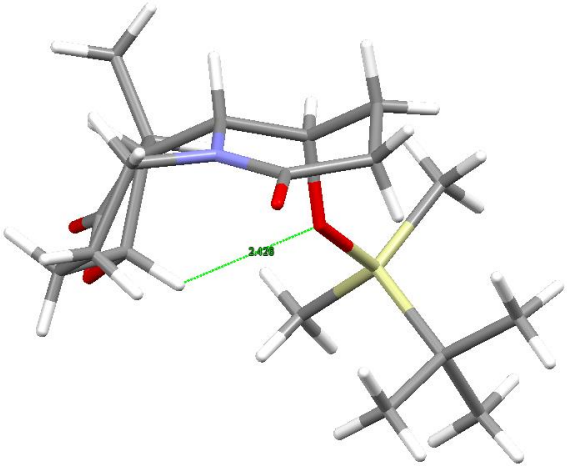


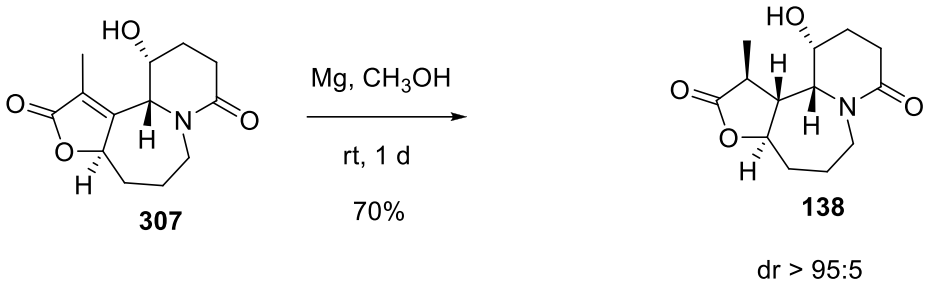
Figure 3.11 (continued): Mercury displayed X-ray crystal structure **306** with atomic distances (Å) displayed.

Entry	Selected atom pairs	Distances (Å)	
		Spartan model	X-ray
1	H-11-H-11a	2.39	2.33
2	H-11a-H-1'b	3.02	2.36
3	H-11-H-1'b	4.27	3.09
4	H-11b-H-6β	2.43	2.14
5	H-11a-H-6β	2.34	2.65
6	H-3a-OTBS	3.43	2.43
7	H-11b-H-1'a	2.34	2.37

Table 3.3: Comparison of the calculated distances between selected atoms in **306** from X-ray analysis with calculations using Spartan (AM1)

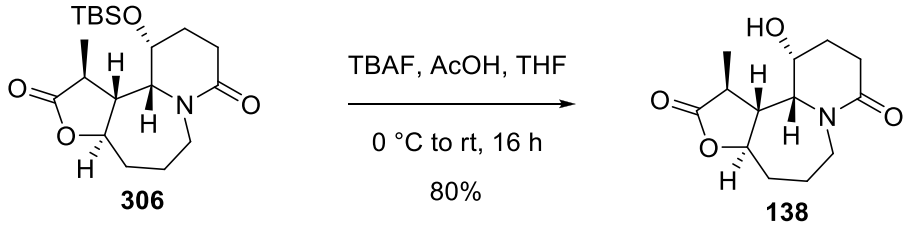
While the Spartan calculations were made with a low level of theory and in the gas phase, there is a reasonable agreement between the modeled distances and those in the solid state for four of the seven distances shown in the **Table 3.3** (entries 1, 4, 5 and 7). These four distances are for protons in the ridged tricyclic structure. Major differences are seen between the gas-phase and solid state distances between the C-1 methyl proton (H-1b') and H-11a and H-11; and H-3a and the oxygen at C-11 **(Table 3.3**, entries 2, 3, and 6). The modeling predicts these distances to be significant longer. This could be due to crystal-packing effects in the solid state in which these large ring substituents are forced into a position to minimize interactions with neighboring molecules in the crystal lattice.

Similar to the α,β-unsaturated lactone **301**, the α,β-unsaturated lactone **307** was reduced to compound **138** in good yield (75%) and high diaselectivity (dr > 95:5) (**Scheme 3.40**).



Scheme 3.40: Reduction of **307** by Mg/MeOH

Treatment of **306** with TBAF buffered with AcOH in THF also provided compound **138** in 80% yield, which was ready for attempts to prepare the ether linkage between C-11 and C-3a (**Scheme 3.41**). The ^{1}H and ^{13}C NMR spectroscopic assignments of compound **138** are shown in **Figures 3.12** and **3.13**, respectively.



Scheme 3.41: Synthesis of **138**

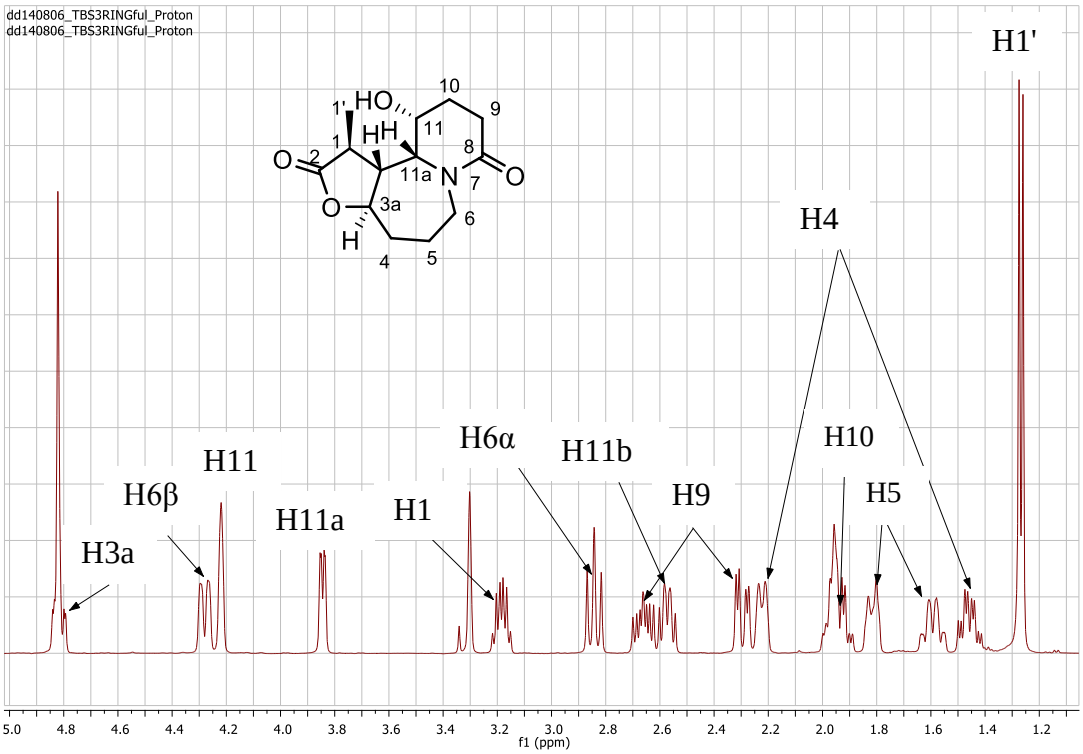


Figure 3.12: ^{1}H NMR spectrum (CD_3OD, 500 MHz) of **138**

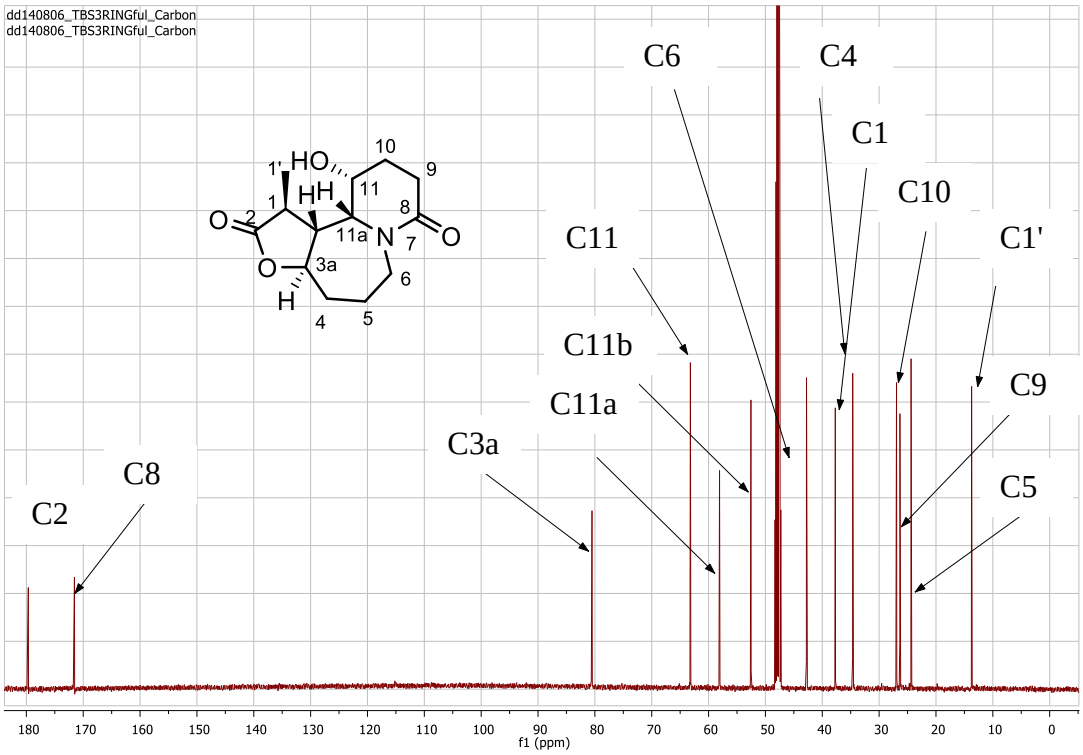
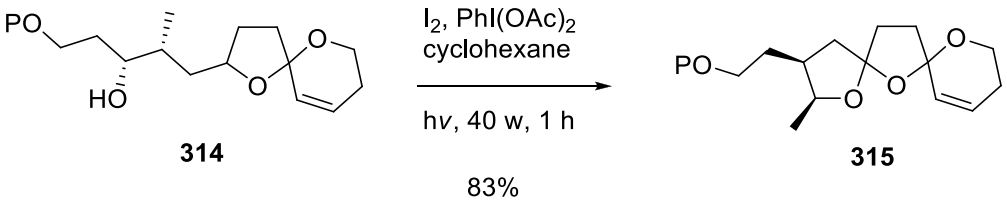


Figure 3.13: ^{13}C NMR spectrum (CD_3OD, 125 MHz) of **138**

3.3 Attempts to make the C-3a-C-11 ether linkage

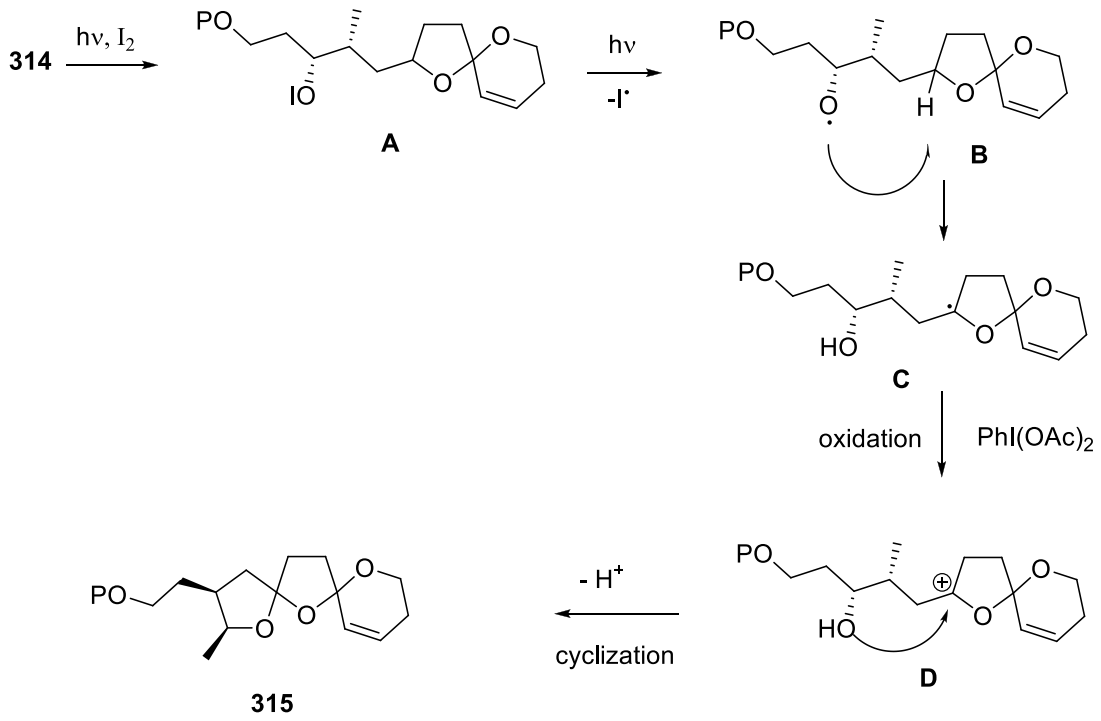
Making the ether linkage between C-3a and C-11 of **138** was a very challenging and crucial step in our synthesis. The literature indicated that this might be achieved under photochemical oxidative conditions.

Brimble reported a successful photochemically induced cyclization reaction of the spirocyclic compound **314**. Compound **314** was irradiated in the presence of I_2 and $PhI(OAc)_2$ at rt for 1 h to give the bis-spirocyclic ether **315** in 83% yield (**Scheme 3.42**).[118]



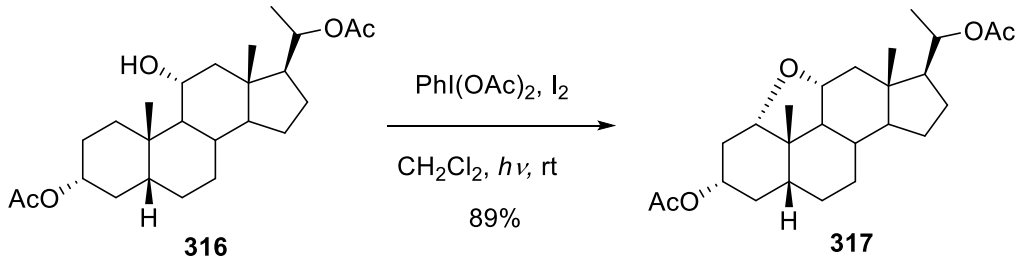
Scheme 3.42: The photochemical oxidative cyclization of **314**[118]

A possible mechanism of this reaction is shown in **Scheme 3.43**. Compound **314** reacts with I_2 to form the corresponding hypoiodite **A**, which undergoes homolytic cleavage (in the presence of light) to form the free radical **B**. The radical **B** is then transformed to the radical **C** by intramolecular H-atom abstraction. This radical is oxidized to the cation **D** by $PhI(OAc)_2$. Finally, intramolecular attack of the hydroxyl group on to the electrophilic carbon in **D** furnishes the product **315**.



Scheme 3.43: Proposed mechanism for the formation of **315**[118]

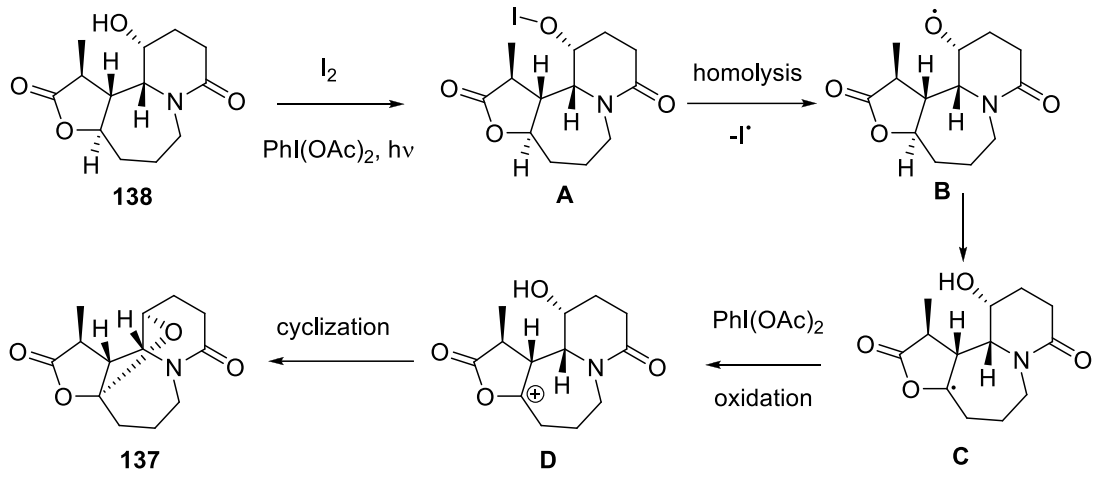
In a related process, Burton reported the photosynthesis of the *O*-bridge steroid **317**. Irradiation of compound **316** in the presence $PhI(OAc)_2$ and I_2 in CH_2Cl_2 resulted in compound **317** in excellent yield (89%) (**Scheme 3.44**).[58] These reactions favour H-atom abstraction by the RO• radical from a CH or CH_2 five atoms away (through a six-atom transition state) from the oxygen radical centre.



Scheme 3.44: Burton's synthesis of **317**[58]

These procedures could in principle be applied to make the ether linkage in **137** from the tricyclic compound **138**. A possible mechanism for the formation of **137** is shown

in **Scheme 3.45**. Compound **138** can react with I_2 to form the hypoiodite **A**, which can undergo homolytic cleavage (in the presence of light) to form the free radical **B**. The radical **B** can then be transformed to the radical **C** by intramolecular H-atom abstraction. As stated above, the distance between the oxygen at C-11 and H-3a is 2.43 Å in the X-ray structure (**Table 3.3**, entry 6), which would seem to be sufficiently close enough for this method to be successful. Further, the radical **C** can be resonance stabilize by the neighbouring lactone oxygen substituent. This radical then can be oxidized to the resonance stabilized cation **D** by $PhI(OAc)_2$. Finally, intramolecular attack of the hydroxyl group to the electrophilic carbon in **D** can furnish the desired product **137**.

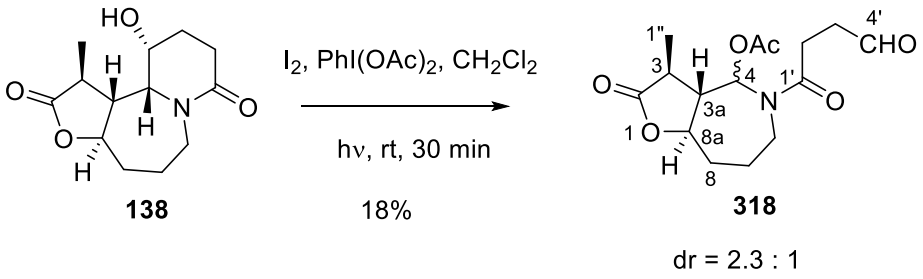


Scheme 3.45: Anticipated synthesis of the cyclic ether **137**

Thus, compound **138** was dissolved in CH_2Cl_2 then irradiated in the presence of I_2 and $PhI(OAc)_2$. Compound **138** was very reactive under these reaction conditions. TLC analysis showed the disappearance of the starting material after 30 min of irradiation. However, after workup we obtained a very complex mixture of products, from which the major product tentatively assigned as structure **318** was isolated in 18% yield (**Scheme 3.46**). The ^1H NMR spectrum of this compound indicated the presence of two isomeric compounds (A: major isomer, B: minor isomer) in a ratio of 2.5:1. Both products had an aldehyde resonance (δ 9.81 (s, H4'B); δ 9.79 (s, H4'A)), an acetoxy resonance (δ 2.11 (s, CH_3COA); δ 2.03 (s, CH_3COB)), a resonance for a hemiaminal proton (δ 7.06 (d, *J* = 9.0 Hz, H4B); δ 6.66 (d, *J* = 8.0 Hz, H4A)), and a resonance for a methyl group attached to a CH δ 1.25 (d, *J* = 6.5 Hz, H1"A); δ 1.21 (d, *J* = 6.5 Hz, H1"B)). The hemiaminal proton H-4 correlated to

H-3a in the COSY spectrum (observed in both isomers). COSY correlations were also observed between H-3 and H-1" and H-3 and H3a (weak) (**Figure 3.14 A**). Other proton assignments were deduced from 2D NMR spectra (COSY, HSQC, HMBC) (**Figure 3.15**). Similarly, the ^{13}C NMR spectrum showed resonances for an aldehyde group (δ 200.9 C4'A; 200.6 C4'B), a lactone carbonyl group (δ 177.4 C2B; 177.0 C2A), an amide carbonyl group (δ 171.8 C1'A; 171.5 C1'B), an acetoxy carbonyl group (δ 170.0 COMeA; 169.0 COMeB), a hemiaminal carbon (δ 82.6 C4A; 78.2 C4B), a methyl (δ 21.0, C1'A; 20.8, C1' B) and an acetyl methyl group (δ 15.0 COMeB; 14.7 COMeA). HMBC correlations were observed between H-3 and C-2; H-1' and C-2 ; H-4' and C-2' and C-3'; and H-4 and the acetoxy carbonyl group (**Figure 3.14 B**). The ^{13}C NMR carbon assignment resonances were deduced from 2D NMR spectra (COSY, HSQC, HMBC) (**Figure 3.16)**.

From the analysis of this spectroscopic data, the structure of the major compound was deduced as structure **318** (**Scheme 3.46)** despite being unable to assign all the proton and carbon resonances for the minor isomer. However, both the low and high resolution mass spectra showed that the molecular formula of this compound was $C_{15}H_{21}O_8N$ (HRESIMS calcd. for $C_{15}H_{21}O_8NNa$, $(M+Na)^+$ 366.1165, found 366.1158) indicating that this molecule had two more oxygen atoms compared to the proposed structure **318**. Clearly, the NMR data and MS data are at odds with each other and the structure assigned to **318** remains uncertain as it is difficult to accommodate two more oxygen atoms into structure **318** without significant changes in the NMR spectra.



Scheme 3.46: Photochemical reaction of **138**

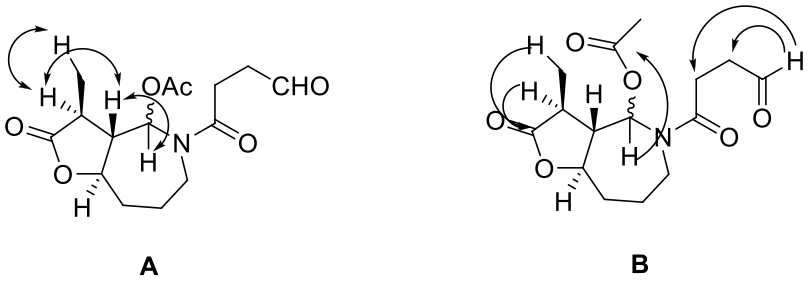


Figure 3.14: Observed COSY correlations (**A**) and HMBC correlations (**B**) of **318**

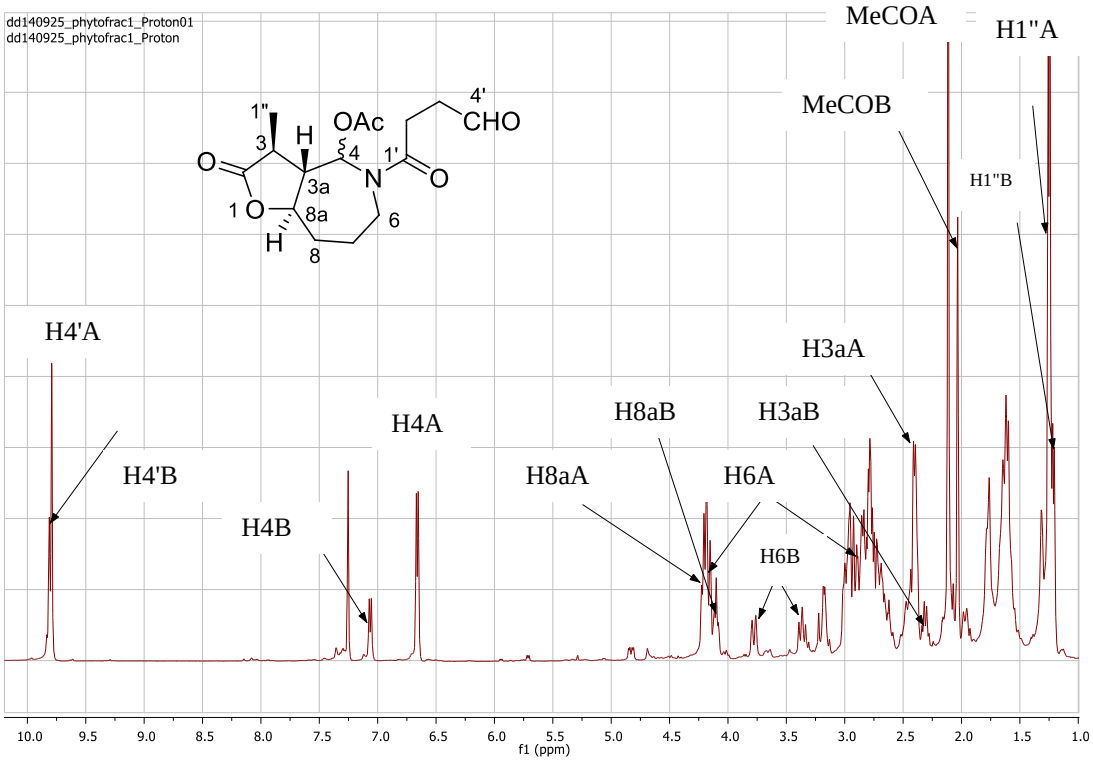


Figure 3.15: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **318** (A refers to the major isomer; B to the minor isomer)

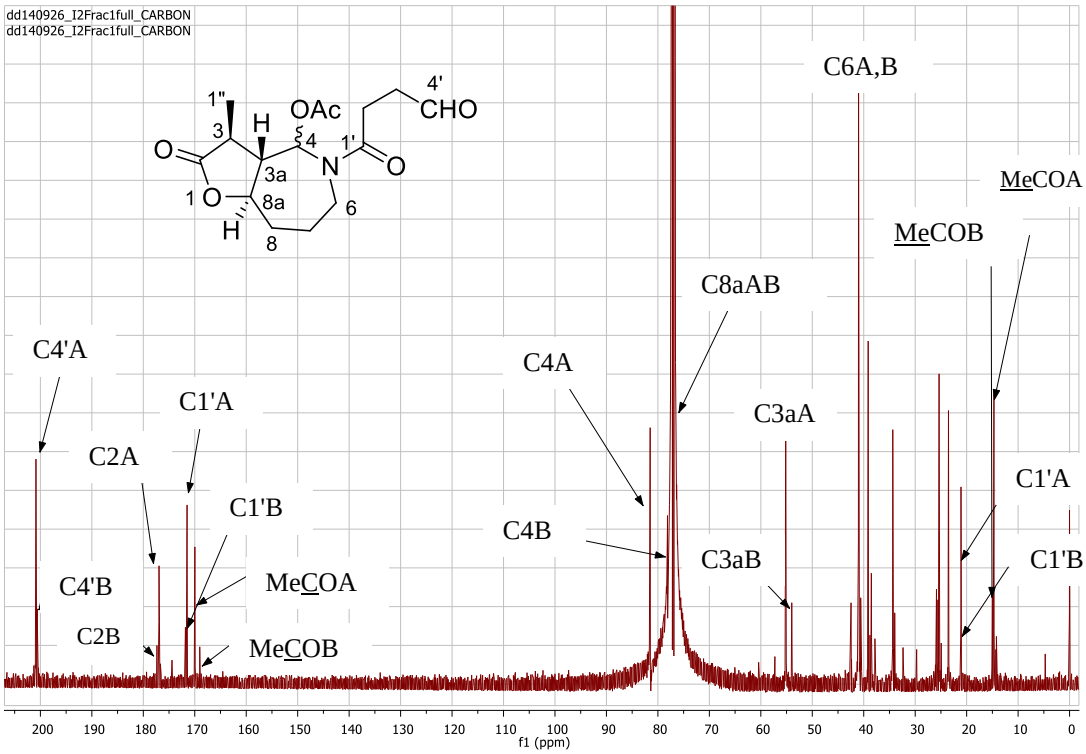


Figure 3.16: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **318**

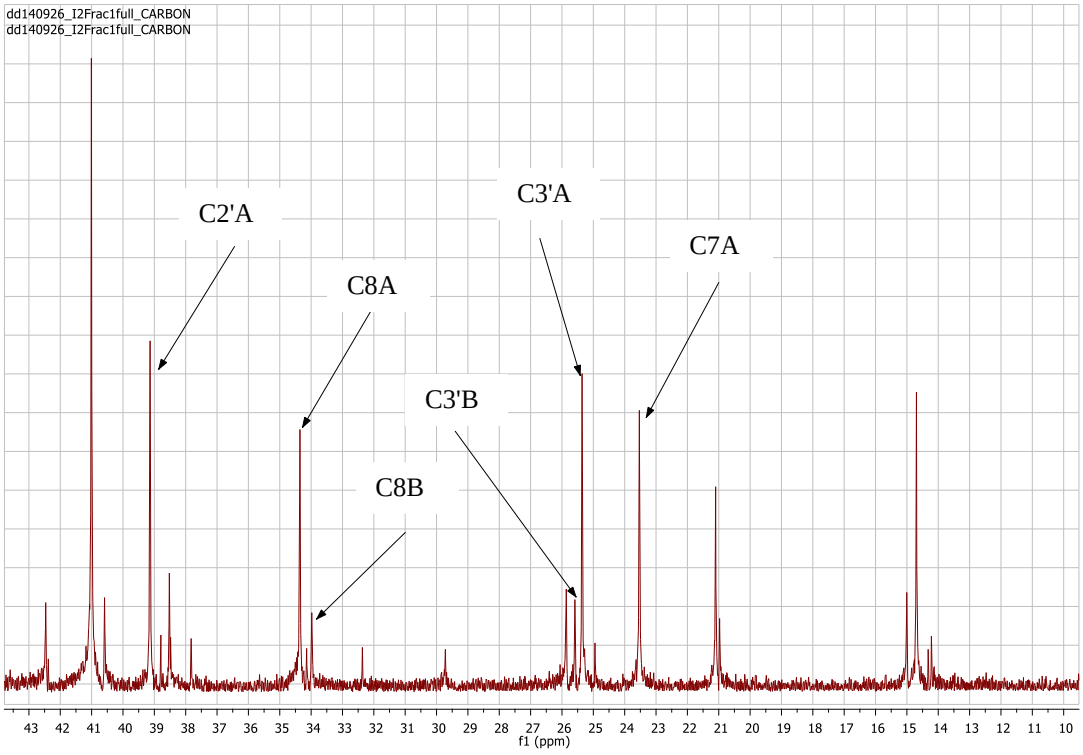
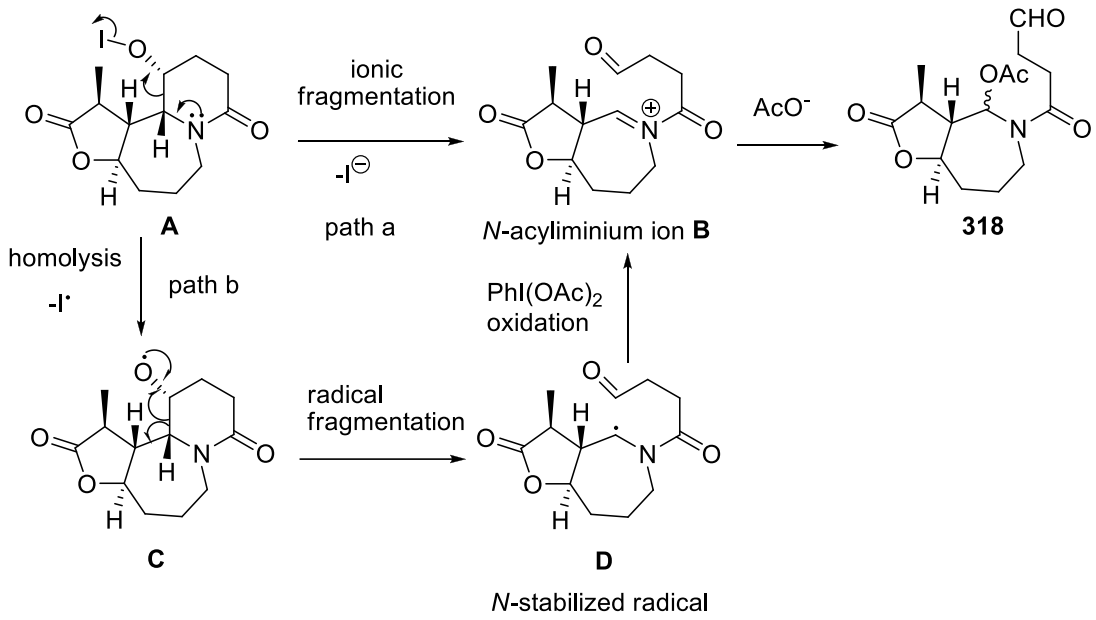


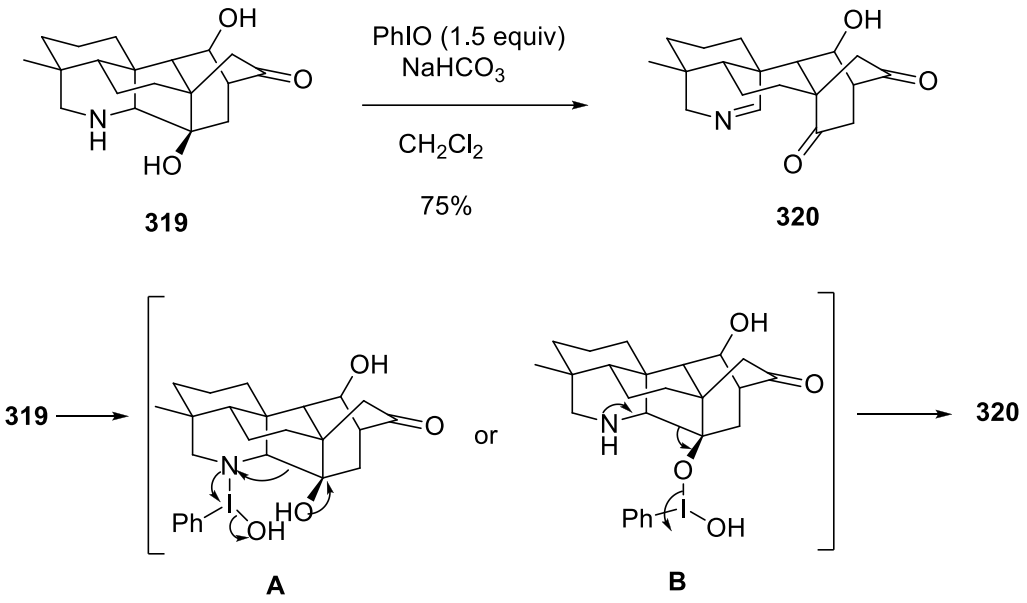
Figure 3.16: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **318**

A proposed a mechanism for the formation of the tentative structure **318** as shown in **Scheme 3.47**. The hypoiodite **A**, which forms from the reaction of **138** with I_2 (**Scheme 3.45**), can undergo an ionic-fragmentation to form the *N*-acyliminium ion **B** (**Scheme 3.47**, path a). Alternatively, the intermediate **A** can undergo homolytic cleavage of the hypoiodite to form the free radical **C** (**Scheme 3.47**, path b), which can undergo radical fragmentation to form the radical intermediate **D**. This intermediate then can be oxidized to the *N*-acyliminium ion **B** by $PhI(OAc)_2$. Addition of acetate to this acyliminium ion (from both faces of the iminium ion) can provide hemiaminal **318** as a mixture of diastereomers.



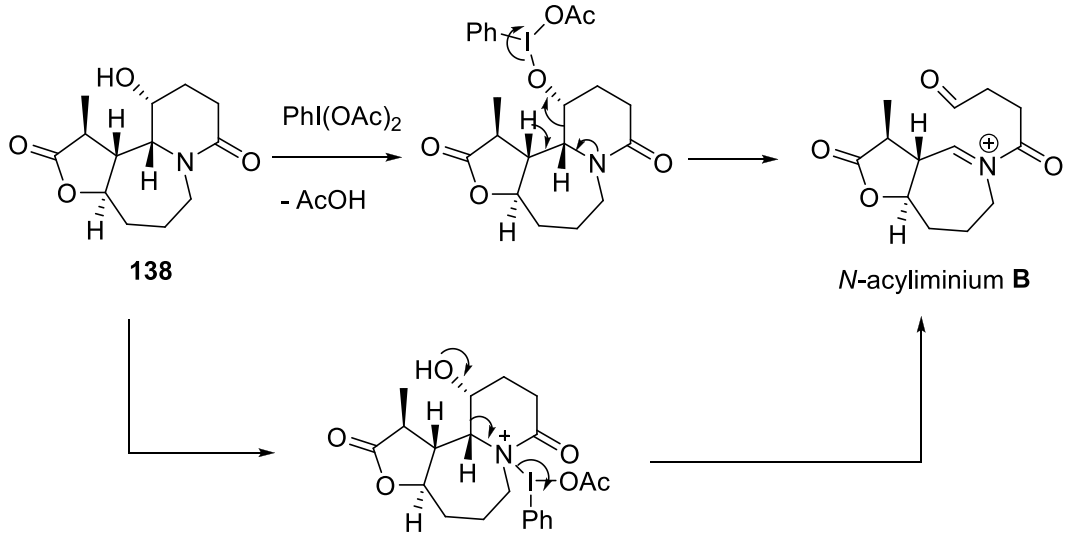
Scheme 3.47: Proposed mechanism for the formation of the tentative structure **318**

A related oxidative fragmentation was reported by Sarpong. Treatment of compound **319** with PhIO gave compound **320** in 75% yield (**Scheme 3.48**).[119] The reaction was thought to proceed via the intermediates **A** or **B**, the latter intermediate being similar to the intermediate **A** shown in **Scheme 3.47**.



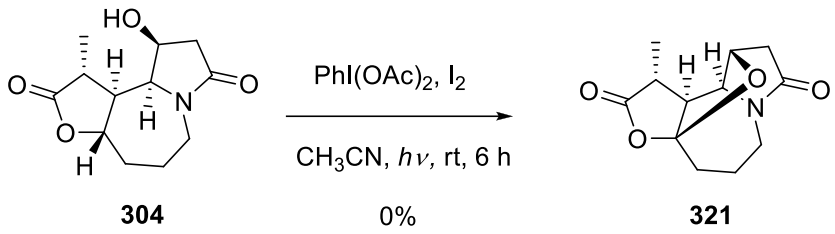
Scheme 3.48: Sarpong's synthesis of **320**[119]

Based on the Sarpong mechanism, other possible mechanisms for the formation of the *N*-acyliminium ion **B** are shown **Scheme 3.49**. These mechanisms however do not involve I_2.



Scheme 3.49: An alternative mechanism for formation of the *N*-acyliminium ion **B**

Earlier, Swamy attempted to make the ether **321** from the tricyclic compound **304** using a similar photochemical synthetic procedure.[60] A mixture of compound **304**, $PhI(OAc)_2$ and I_2 in CH_3CN were irradiated at 40W for 6 h. However, no desired product was formed, only the unreactive starting material was recovered (**Scheme 3.50**). In this case, the alcohol **342** was not soluble in CH_2Cl_2 and the photolysis was attempted in CH_3CN. This change in solvent may have been detrimental to the reaction.

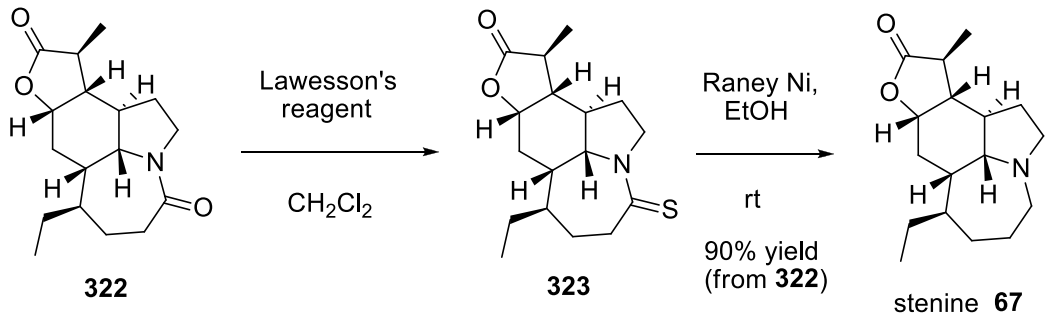


304 **321**

Scheme 3.50: Swamy's attempted photosynthesis of **321**

Because of the aforementioned fragmentation process, which was possibly related to the formation of a *N*-acyliminium ion, we decided to reduce the lactam carbonyl group of **138** to avoid the formation of such an *N*-acyliminium ion intermediate in these reactions.

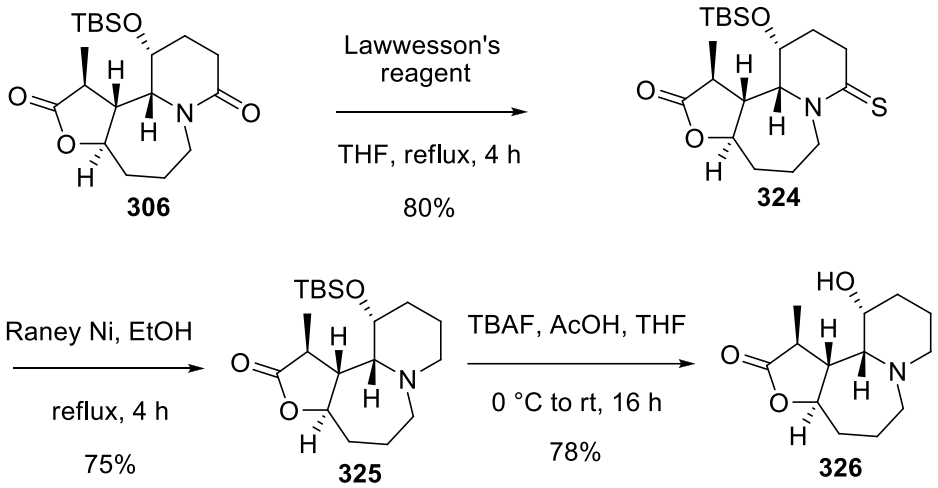
In the total synthesis of (-)-stenine, Zhang reported the conversion of lactam **322** to (-)-stenine **67**.[25] Treatment of the lactam **322** with Lawesson's reagent in CH_2Cl_2 gave the corresponding thiolactam **323**. Reduction of thiocarbonyl group by treatment with Raney Ni in EtOH afforded stenine **67** in 90% yield over the two steps (**Scheme 3.51**).[25]



322 **323** stenine **67**

Scheme 3.51: Zhang's synthesis of (-)-stenine **67**[25]

This procedure proceeded smoothly with lactam **306** after some modifications. Thio-lactam **324** was obtained in 80% yield from **306** by treatment with Lawesson's reagent in THF at reflux temperature (**Scheme 3.52**). The molecular formula of thio-lactam **324** was confirmed by HRESIMS analysis (calcd. for $C_{19}H_{34}O_3NSiS$, $(M+H)^+$ 384.2029, found: 384.2036). The IR spectrum of **324** showed a band for the thio-lactam C=S group at 1154 cm^{-1}. In the ^{13}C NMR spectrum of **324** the C=S resonance appeared at δ 201.1. Reduction of this thio-lactam by treatment with Raney Ni in ethanol at reflux temperature resulted in the corresponding amine **325** in 75% yield (**Scheme 3.52**). The molecular formula of amine **325** was also confirmed by HRESIMS analysis (calcd. for $C_{19}H_{36}O_3NSi$, $(M+H)^+$ 354.2452, found: 354.2464). Removal of the TBS group of **325** by treatment with TBAF in THF buffered with AcOH gave the alcohol **326** in 78% yield (**Scheme 3.52**).



Scheme 3.52: Synthesis of amine **326**

In the ^1H NMR spectrum of **326**, H-3a and H-11 resonated at δ 4.77 (td, *J* = 11.0, 3.5 Hz, 1H, H3a) and 3.86 (s, 1H, H11), respectively, while resonances for H-11a and H-11b protons appeared at δ 2.46 – 2.42 (m, 1H, H11a) and δ 2.20 (ddd, *J* = 12.5, 10.0, 8.0 Hz, 1H, H11b), significantly upfield in comparison to the corresponding resonances of H-3a and H-11 of the lactam **138** (δ 3.85 (m, H11a) and 2.61-2.54 (m, 1H, H11b)). The H-6 protons resonances appeared at 2.62 (dd, *J* = 19.0, 8.0 Hz, 1H, H6) and 2.48-2.40 (m, 2H, H6 and H8) and there were new regions for H-8 protons resonances at 2.88 (d, *J* = 11.0 Hz, 1H, H8) and 2.48-2.40 (m, H6 and H8). The ^1H

and ^{13}C NMR spectroscopic assignments of **326** were shown in **Figure 3.17** and **3.18**, respectively and based on 2D NMR experiments (COSY, HSQC, HMBC).

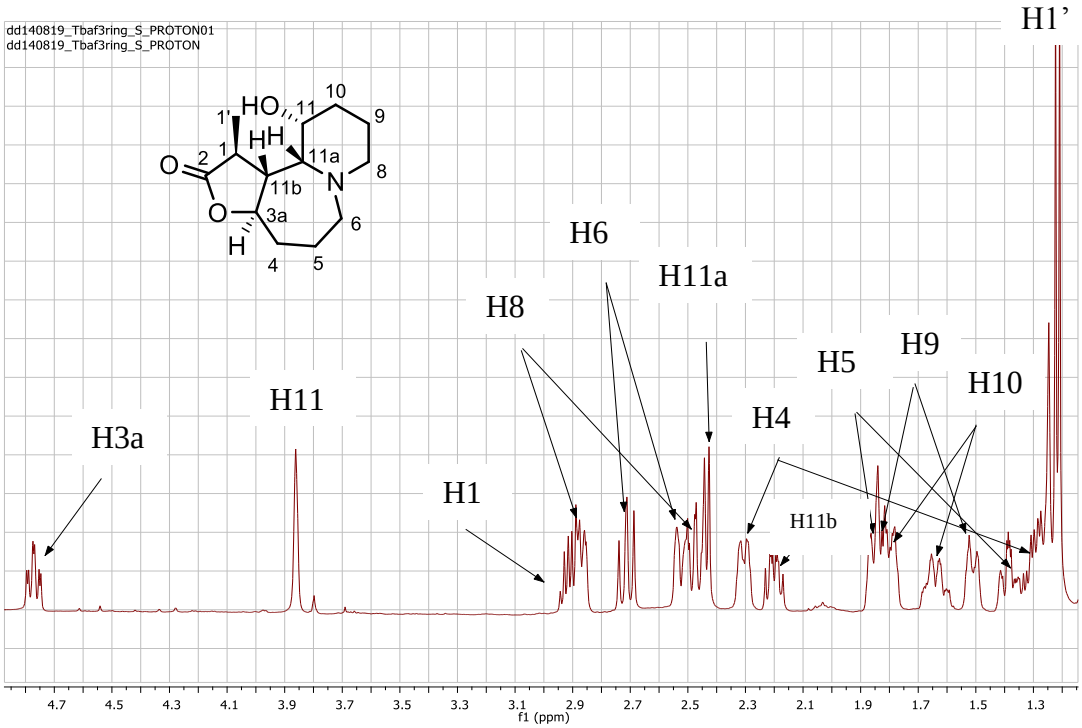


Figure 3.17: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **326**

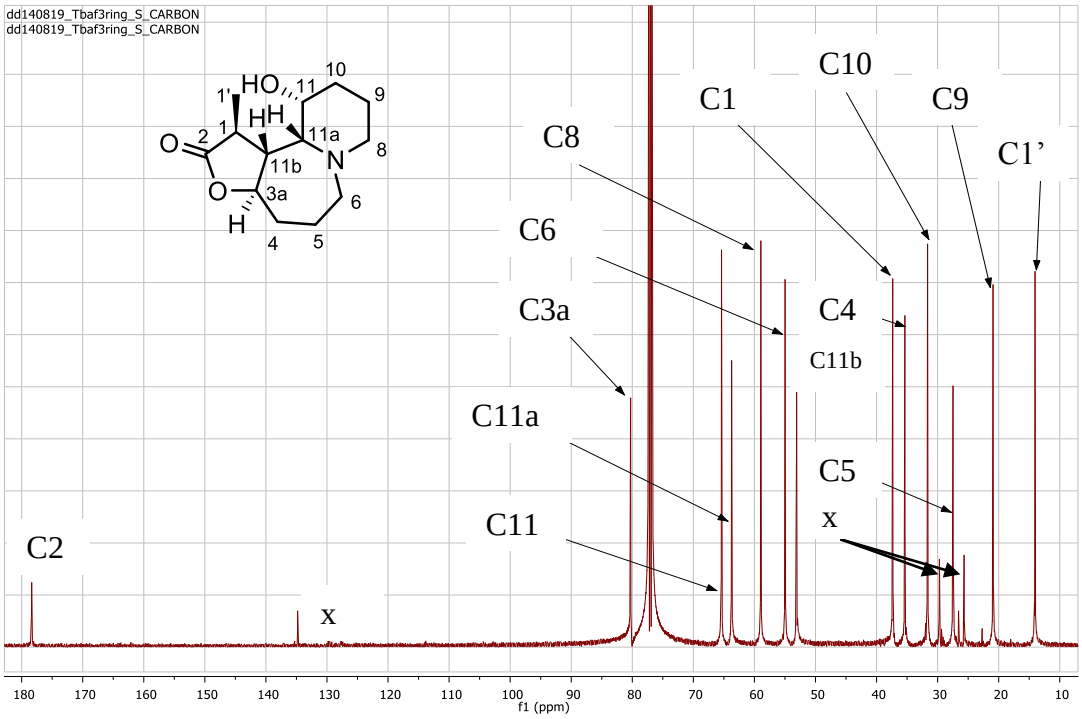
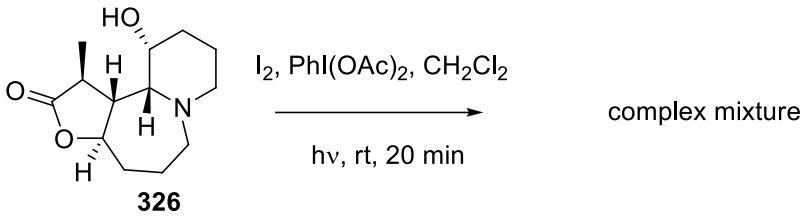


Figure 3.18: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **326** (x: impurities)

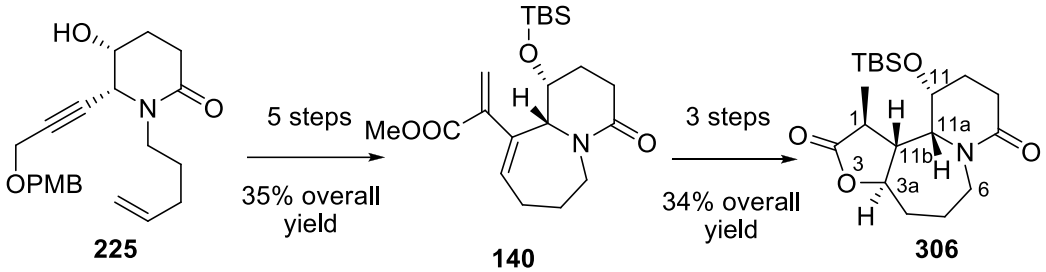
Similar to the lactam **138**, amine **326** was very reactive under the aforementioned photochemical reaction conditions. The reaction was complete in 20 min (by TLC analysis) when irradiating a solution of **326**, $PhI(OAc)_2$ and I_2 in CH_2Cl_2. However, again we obtained a very complex mixture of products. Due to the small amount of amine **326** available, as well as the multiple products by TLC analysis, we could not isolate any pure product in sufficient quantity to enable its characterization (**Scheme 3.53**). The more nucleophilic amino group may have interfered adversely in this reaction.



Scheme 3.53: Attempted photochemical synthesis with amine **326**

3.4 Conclusions

Towards the synthesis of stemocurtisine, we have successfully employed the ene-yne RCM reaction to the synthesis of an A-B ring precursor **140**. Compound **140** was synthesized in 35% overall yield over five synthetic steps from the lactam **225**.



Scheme 3.50: Synthesis of tricyclic compound **306**

The bicyclic compound **140** was then converted to the tricyclic compound **306** in 34% overall yield over three synthetic steps. The synthesis of **306** involved the

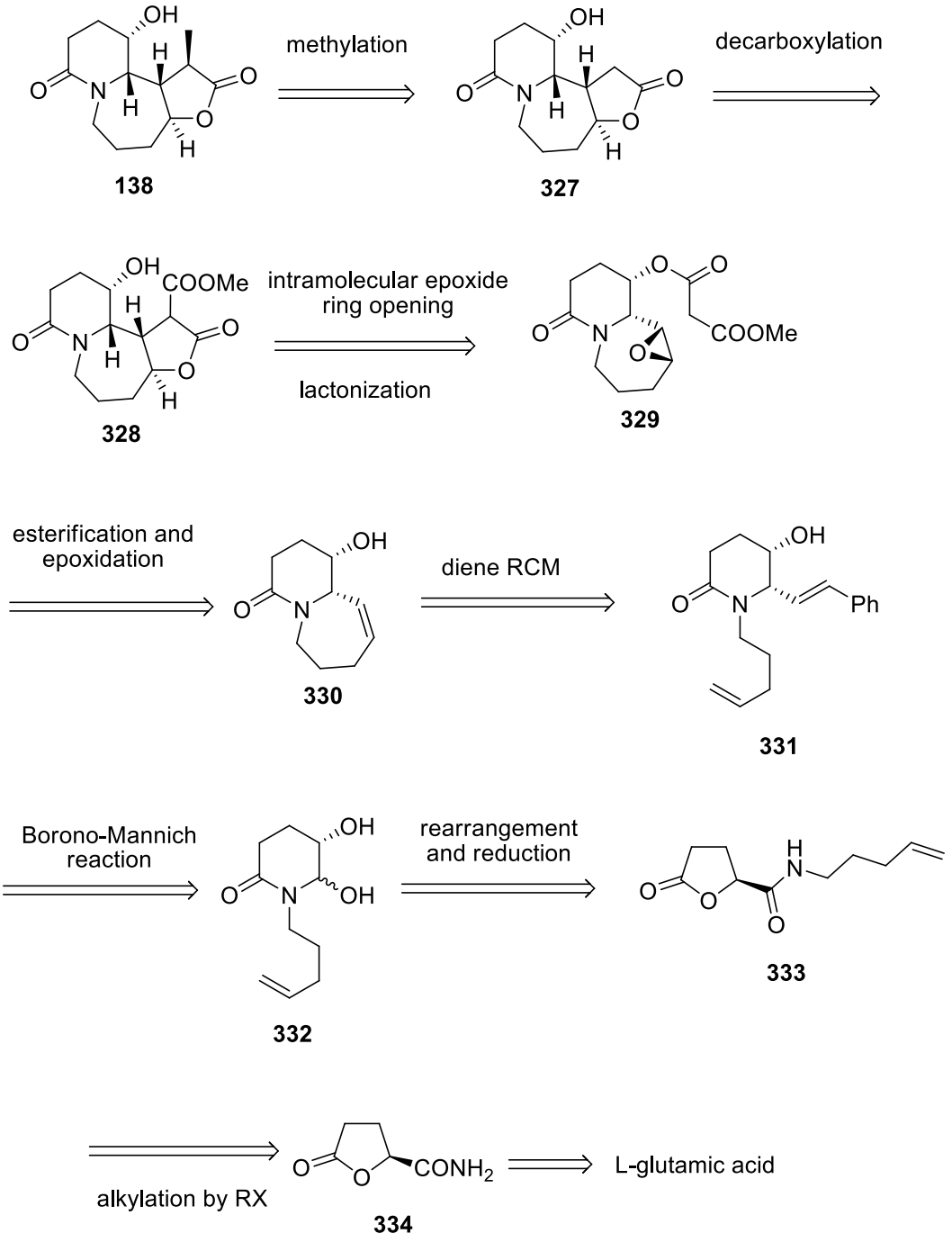
bromolactonization (PhSeSePh, NBS) of the corresponding acid of **139** to construct the ring C of stemocurtisine with the desired configuration at C-3a in the tricyclic lactone **301**. More impressively, reduction of the α,β-unsaturated lactone moiety of **301** by Mg/MeOH furnished the tricyclic compound **306** in 71% yield as a single diastereomer with the same relative configuration at C-1, C-3a, C-11, C-11a and C-11b as stemocurtisine. The structure of **306** was confirmed by NMR, IR, MS and single crystal X-ray crystallographic analyses.

We attempted to make the ether linkage between C-11 and C-3a in the alcohol **138** and it C-8 reduced piperidine derivative **326** via a photochemical oxidative process using I_2/PhI(OAc)$_2$. The reactions of both substrates led to the formation of fragmentation products. From the reaction of **138**, we isolated a main product, which had NMR spectroscopic data consistent with the aldehyde **318**, formed from the fragmentation of the piperidinone ring. However MS analysis of this compound indicated that the isolated compound had two more oxygen atoms than the proposed structure. The photochemical oxidation reaction of **326** gave a complex mixture of products, which could not be separated or characterized due to the small amount of starting material used as well as the close R_f values of the products formed. Time constraints prevented us from examining other reaction conditions or methods to make the ether bridge required for the total synthesis of stemocurtisine.

CHAPTER 4: AN ALTERNATIVE METHOD TO CONSTRUCT THE A-B-C RING SYSTEM OF STEMOCURTISISNE

4.1 Retrosynthetic analysis

This chapter reports the results of a study on an alternative pathway to prepare a tricyclic compound possessing the A-B-C ring system of stemocurtisine following the retrosynthetic analysis shown in **Scheme 4.1** starting from L-glutamic acid rather than the more expensive D-glutamic acid. If this method were successful, we would obtain the enantiomer of stemocurtisine. In principle, compound **138** could be prepared from compound **327** by a methylation process (MeI, LiHMDS) following the method reported by Morimoto.[24] The tricyclic lactone-ester **327** could be obtained from compound **328** via a decarboxylation process. Compound **328** could be prepared from the ester-epoxide **329** via a base catalysed intramolecular epoxide ring opening reaction followed by cyclization of the resulting hydroxyl ester intermediate. This ester epoxide could be obtained from the alkene **330** via an esterification and epoxidation process. The alkene **330** could be formed from compound **331** via a diene RCM reaction. Diene **331** could be synthesized from the hemiaminal **332** via a borono-Mannich reaction with β-styrenylboronic acid. The hemiaminal **332** could be prepared from the lactone amide **333** by a base-catalyzed rearrangement process followed by reduction. Alkylation of the primary amide **334** by the corresponding alkyl halide should provide amide **333**. The amide **334** could be obtained from L-glutamic acid in three synthetic steps. The synthesis of compound **330** was developed earlier in our group[121] but was not published and **330** and ít precusors were not fully characterized.

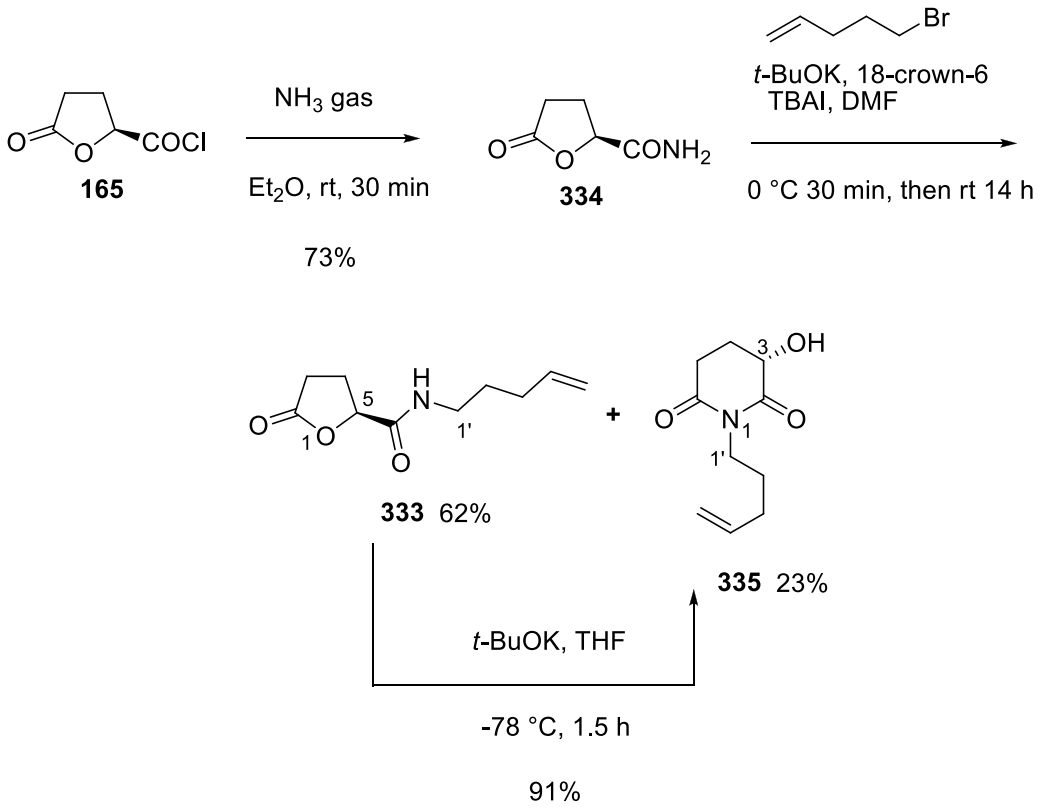


Scheme 4.1: Retrosynthsis of the pyrido-azepine **138**

4.2 Construction of the A-B ring system

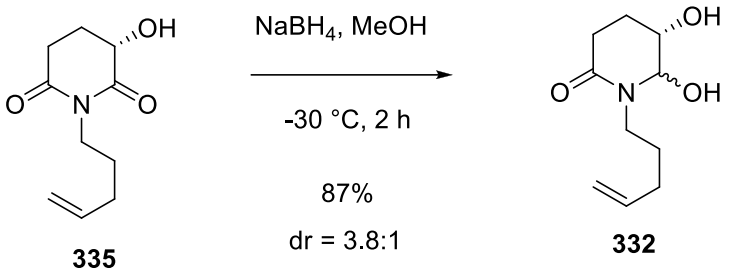
The amide **334** was prepared by bubbling NH_3 gas through a solution of acid chloride **165** (prepared from L-glutamic acid in **Scheme 2.3**) in anhydrous Et_2O in 73% yield (**Scheme 3.21**). Treatment of the primary amide **334** with 5-bromo-pent-1-

ene, *t*-BuOK, TBAI and 18-crown-6 gave a mixture of the secondary amide **333** (62% yield) and the imide **335** (23% yield). The IR spectrum of **333** showed bands for the lactone and amide carbonyl groups at 1743 cm^{-1} and 1665 cm^{-1}, respectively. In the ^1H NMR spectrum of **333**, the resonances for H-5 and H1' appeared at δ 4.84 (t, *J* = 7.5 Hz, 1H, H5) and 3.39 – 3.23 (m, 2H, H1'). The lactone amide **333** was then converted to the imide **335** by treatment with *t*-BuOK in THF at – 78 ºC in 91% yield (**Scheme 4.2**). In the ^1H NMR spectrum of **335**, resonances for the H-3 and H-1' protons appeared at δ 4.20 (dd, *J* = 12.5, 5.5 Hz, 1H, H3), 3.83 – 3.75 (m, 1H, H1'), and 3.75 – 3.68 (m, 1H, H1'), respectively.



Scheme 4.2: Synthesis of lactam **335**

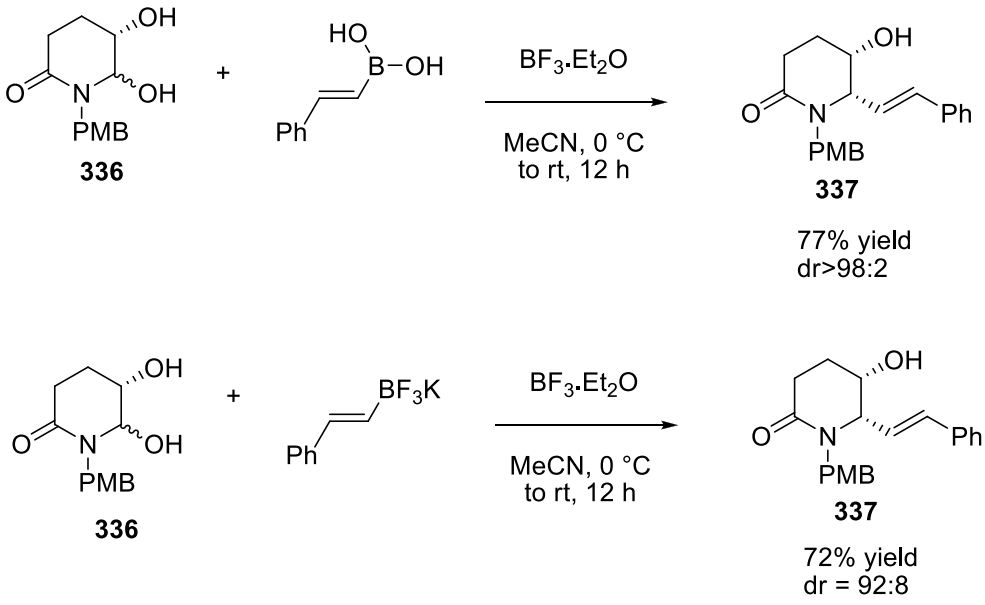
Reduction of the more nucleophilic carbonyl group of **335** by $NaBH_4$ in MeOH at -30 ºC led to an inseparable mixture of hemiaminal diastereoisomers **332** in 87% yield (**Scheme 4.3**).



335 **332**

Scheme 4.3: Synthesis of the diol **332**

Pyne reported the synthesis of the compound **337** from the hemiaminal **336** using *trans*-β-styrylboronic acid and the Lewis acid $BF_3.Et_2O$ in CH_3CN. The *cis* product was obtained in good yield and high diasteroselectivity.[120] When potassium β-styryltrifluoroborate was employed the yield and the diasteroselectivity were slightly reduced (**Scheme 4.4**). In unpublished work,[121] Morgan in our laboratory found that using a mixture (1:1) of *trans*-β-styrylboronic acid and potassium-β-styryltrifluoroborate gave the most reliable result.

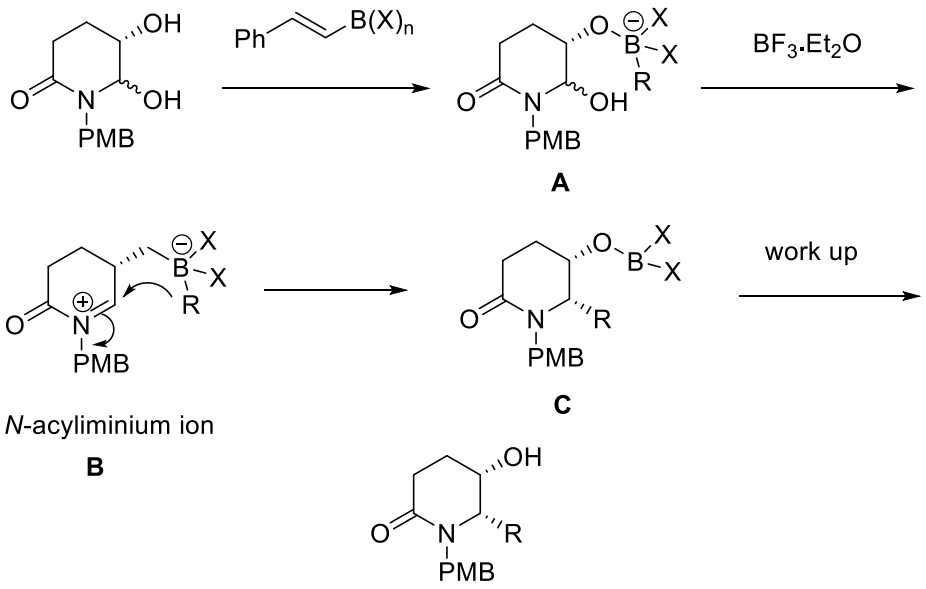


336 **337** **336** **337**

Scheme 4.4: Pyne's synthesis of **337**[120]

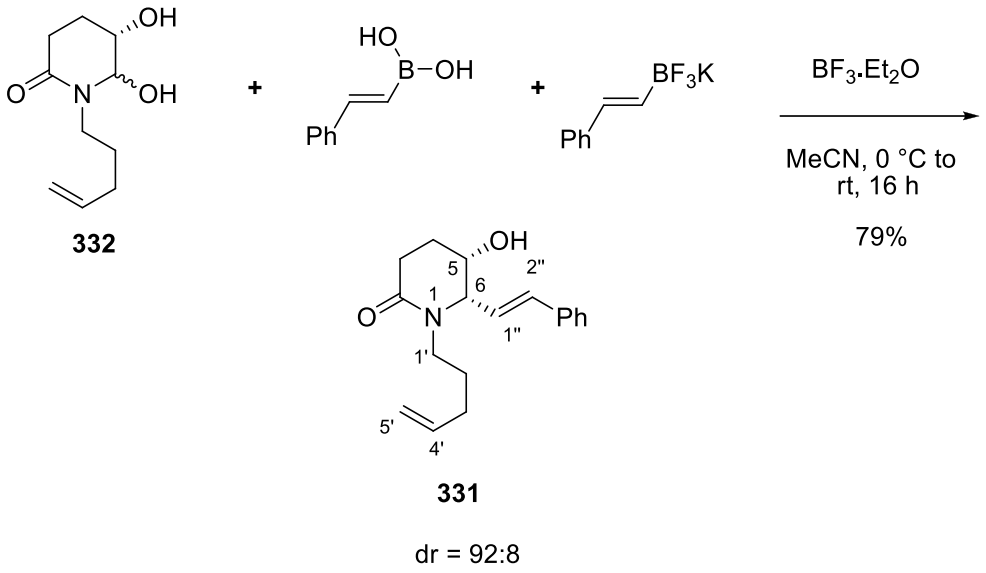
The proposed mechanism of this borono-Mannich reaction is shown at **Scheme 4.5**. The first step involves the co-ordination of the boron with the OH group to form the

"ate" intermediate **A**. The Lewis acid ($BF_3.Et_2O$) promoted the removal of the hemiaminal OH group to form the *N*-acyliminium ion **B**. The R group then migrates from the boron centre to the sp^2 carbon of the iminium ion from the same face to form the *cis*-intermediate **C**. Hydrolysis of **C** (during the work up process) gives the observed product.



Scheme 4.5: The proposed mechanism of the borono-Mannich reaction

In our study, treatment of the diol **332** with *trans*-β-styryl boronic acid (0.55 equiv), *trans*-β-styrylpotassiumtrifluoroborate (0.55 equiv) and $BF_3.Et_2O$ (3.0 equiv) in MeCN led to the diene **331** in 79% yield and high diasteroselectivity (dr 92:8) (**Scheme 4.6**).



Scheme 4.6: Synthesis of the diene **331**

The structure of the diene **331** was clearly evident from an analysis of its ^{1}H NMR spectrum. The H-1" and H-2" protons resonated at δ 6.25 (dd, *J* = 16.0, 7.0 Hz, 1H, H1") and δ 6.51 (d, *J* = 16.0 Hz, 1H, H2"). While H-6 and H-5 resonated at δ 4.14 (dd, *J* = 7.0, 5.0 Hz, 1H, H6) and 4.08 (dt, *J* = 10.0, 5.0 Hz, 1H, H5). The coupling constant $J_{1",2"}$ = 16.0 Hz confirmed the *trans* configuration of the alkene.[65] The coupling constant $J_{5,6}$ = 5.0 Hz was similar those of *cis* compounds **196** and **224** (**Scheme 2.42** and **Figure 2.7**, Chapter 2). The relative *cis*-configuration at C-5 and C-6 was further confirmed by the NOESY correlation between H-5 and H-6. The ^{1}H and ^{13}C NMR spectra of **321** are shown in **Figures 4.1** and **4.2**. The assignments are based on 2D experiments (COSY, HSQC, HMBC).

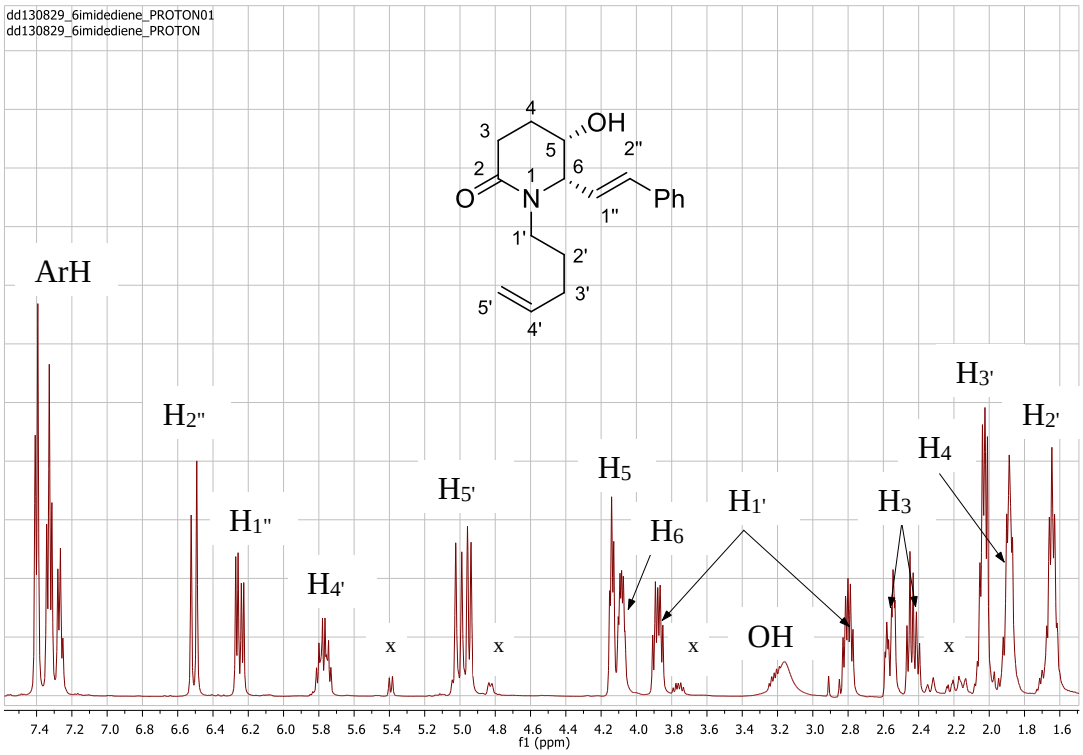


Figure 4.1: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **331** (x: minor diastereomer)

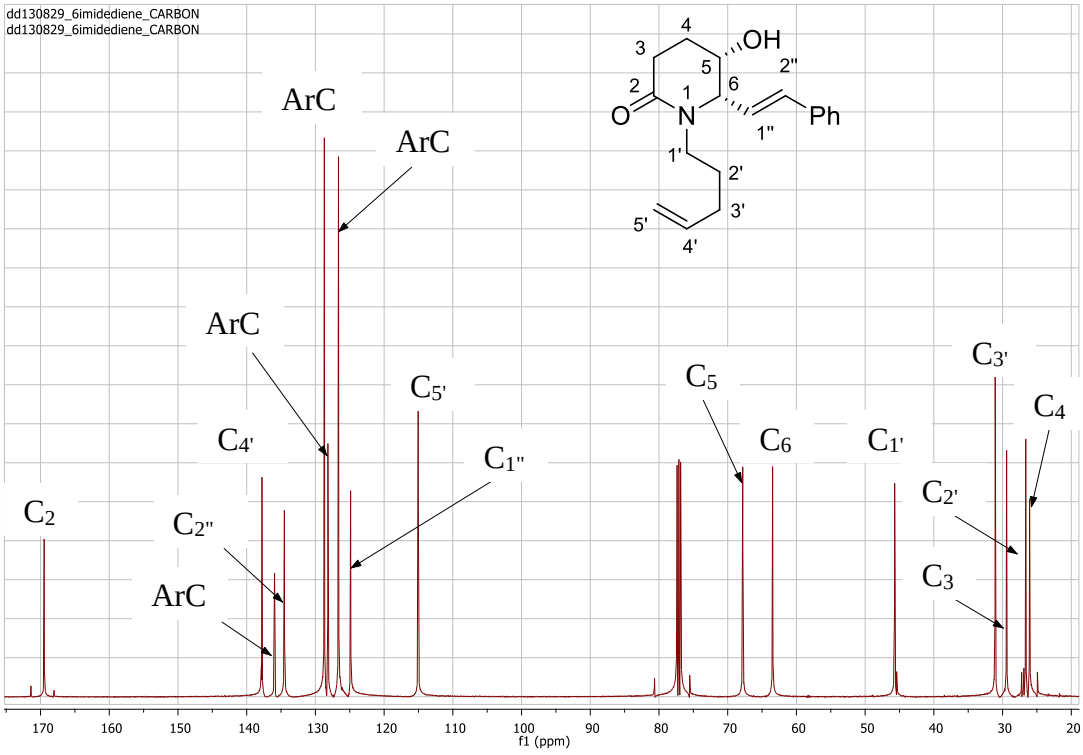
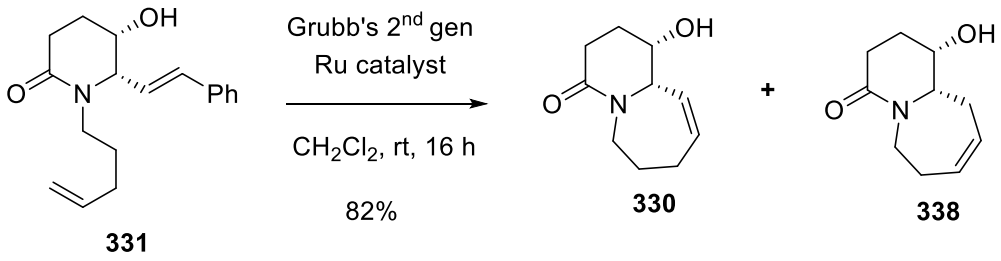


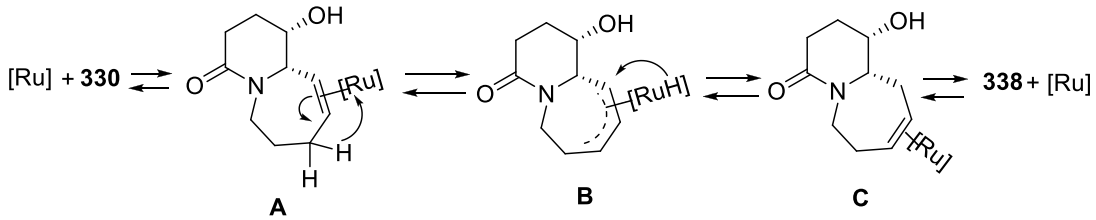
Figure 4.2: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **331**

Treatment of the diene **331** with Grubb's 2nd generation Ru catalyst (0.2 equiv) in CH_2Cl_2 at reflux temperature led to an inseparable mixture of desired product **330** and its isomer **338** (**330** : **338** = 87:13, as determined by ^{1}H NMR) due to the migration of the carbon-carbon double bond (**Scheme 4.7**). In the ^{1}H NMR spectrum of **330**, H-9 and H-10 resonated at δ 6.00 (dt, *J* = 10.8, 5.0 Hz, 1H, H9) and 5.73 (d, *J* = 10.8 Hz, 1H, H10), respectively, while in the ^{1}H NMR spectrum of mixture of **330** and **338**, resonances for H-8 and H-9 protons overlapped and appeared as multiplet at δ 6.85-6.79.



Scheme 4.7: Ring closing metathesis of diene **331** without an additive

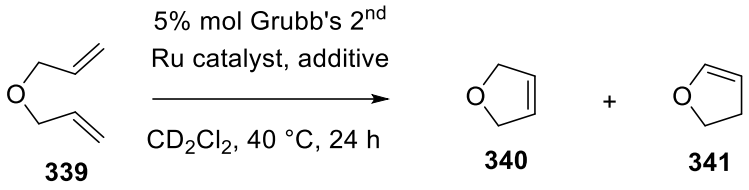
A proposed mechanism for the formation of **338** is shown in **Scheme 4.8**. The Ru catalyst can coordinate with the desired product **330** to form the Ru-alkene complex **A**. This complex can be converted to the allyl cation$^+$-[RuH]$^-$, from which the hydride on the Ru can add back to the allyl system to give the Ru-alkene complex **C**. Decomplexation of **C** then gives **338** (**Scheme 4.8**).



Scheme 4.8: Proposed mechanism for the formation of **338**

This phenomenon is not uncommon in diene RCM reactions and ene-ene cross metathesis reactions. Grubbs reported a study of the RCM reaction of diallylether **339** catalysed by Grubbs' 2nd generation Ru catalyst (**Scheme 4.9**).[122] The results are

shown in **Table 4.1**. With this substrate, acetic acid and 1,4-benzoquinone were found to be ideal to suppress the double bond migration process and stop the formation of **341**. These additives presumably convert the $[RuH]^-$ intermediate back to [Ru].

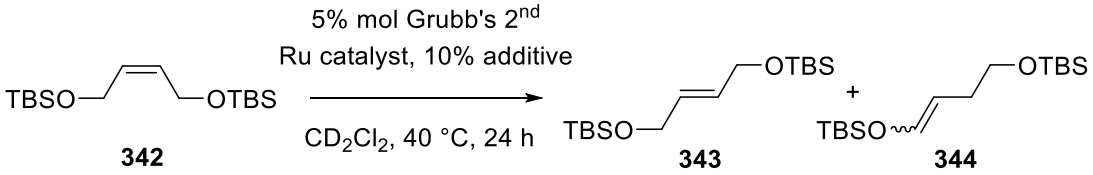


Scheme 4.9: Ring closing metathesis of diene **339** with additive[122]

Additive	Equiv (relative to **339**)	Product distribution (by ^{1}H NMR)	
		340	**341**
none	none	< 5%	> 95%
acetic acid	0.1	>95%	none
1,4-benzoquinone	0.1	> 95%	none
galvinoxyl	0.2	80%	20%
TEMPO	0.5	7%	93%
4-methoxyphenol	0.5	17%	83%
BHT	0.5	4%	93%

Table 4.1: Ratio of **340** and **341** under RCM of **339** with different additives[122]

In another study of the diene cross metathesis of compound **342** (**Scheme 4.10**), Grubbs showed that 1,4-benzophenone was a better reagent than acetic acid for suppressing double bond isomerisation (**Table 4.2**).[122]

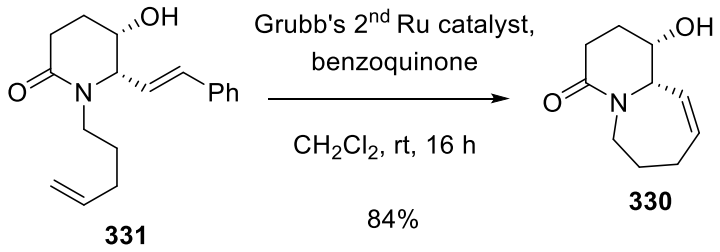


Scheme 4.10: Cross alkene metathesis of compound **342** with additive[122]

Additive	Product distribution (by ^{1}H NMR)	
	343	**344**
none	none	> 95%
1,4-benzoquinone	92%	none
acetic acid	none	> 95%

Table 4.2: Ratio of **343** and **344** under alkene cross metathesis of **342** with different additives[122]

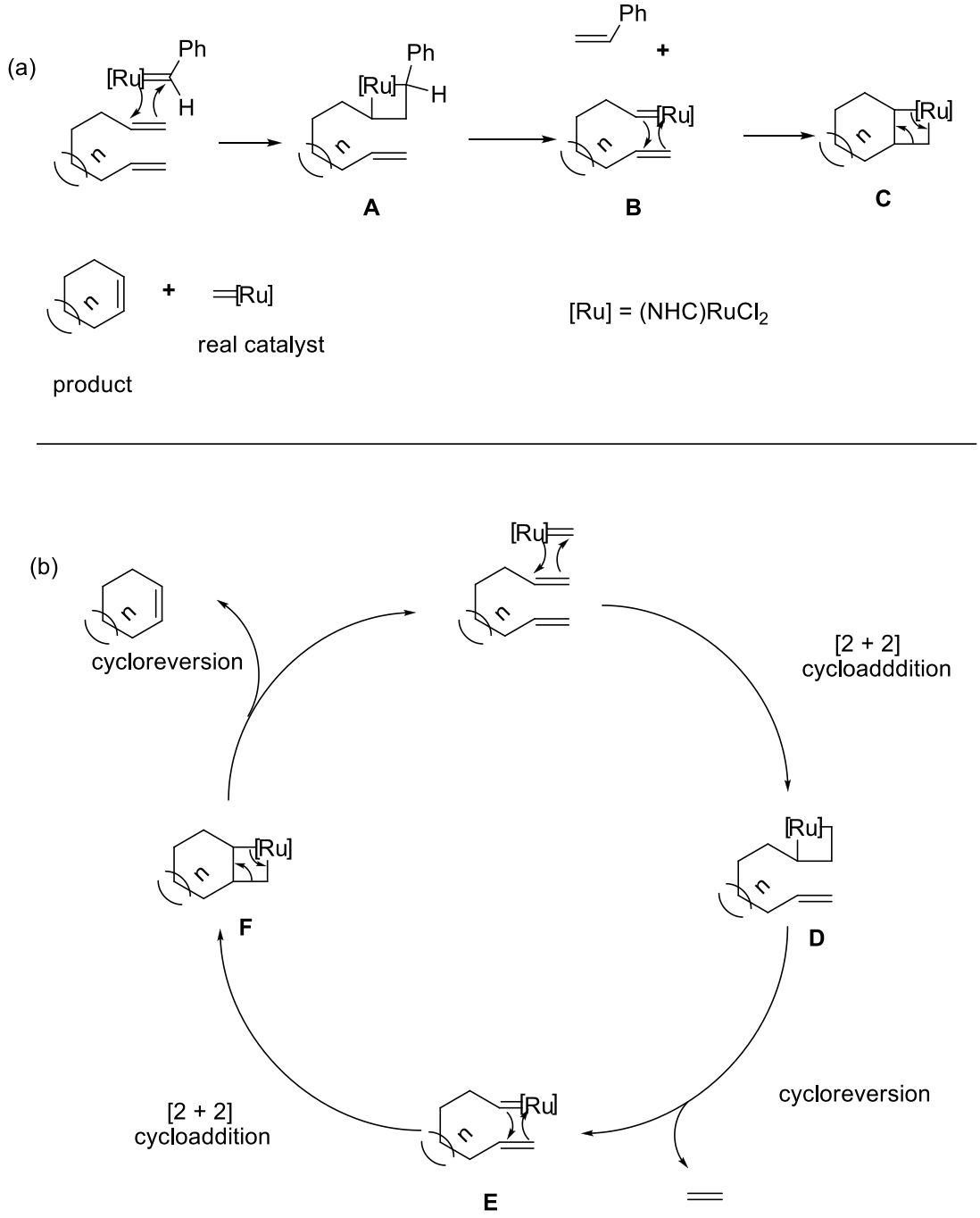
From these results, we chose 1,4-benzoquinone as the additive to avoid the by product **338**. Treatment of diene **331** with Grubbs' 2nd generation Ru catalyst in the presence of 1,4-benzoquinone (0.2 equiv) followed by separation of the minor diastereomer by column chromatography provided the pure bicyclic compound **330** in 84% yield (**Scheme 4.11**).



Scheme 4.11: Synthesis of the diene **330**

The proposed mechanism of the diene ring closing metathesis reaction is shown at **Scheme 4.12**.[123] In the initiation step ((a) in **Scheme 4.12**), the stable catalyst undergoes cycloaddition to the substrate forming the ruthenacyclobutane **A**. Subsequent cycloelimination releases styrene. The catalyst is then bound to the substrate in the form of the metal carbene **B**, which reacts intramolecularly with the double bond to yield the cyclobutane derivative **C**. This adduct undergoes a cycloreversion to form the cycloalkane product and the real catalyst (CH_2=[Ru]). In the catalytic cycle (b), this catalyst adds to the double bond of the substrate forming the ruthenacyclobutane **D**. Cycloelimination at this stage gives the ruthenium carbene

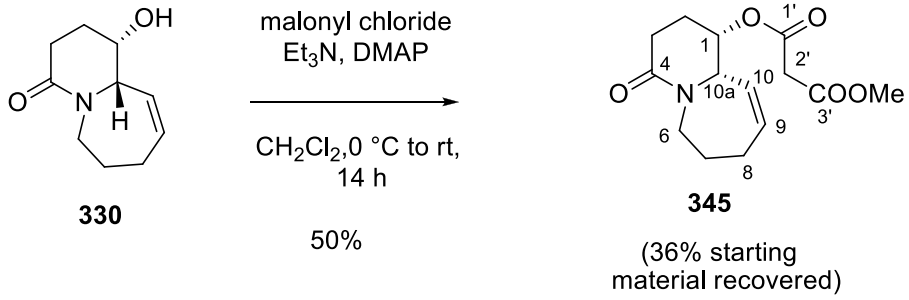
E with the release of ethylene. Subsequent intramolecular cycloaddition with the alkene gives the ruthenacyclobutane **F**. A cycloreversion gives the product cycloalkene and the catalyst is then regenerated; this reacts with another substrate molecule to give the product via methylene transfer, and the catalytic cycle is continued.



Scheme 4.12: Proposed mechanism for diene RCM reaction[123]

4.3 Attempts to make the C-ring

Treatment of alcohol **330** with malonyl chloride (MeO_2CCH_2COCl) and Et_3N in CH_2Cl_2 gave the corresponding ester **345** in 50% yield (with 36% starting material recovered) (**Scheme 4.13**). In the ^1H NMR spectrum of **345**, the OMe and H-2' protons resonated at δ 3.72 (s, 3H, OMe) and δ 3.37 (s, 2H, H2''), while the H-9 and H-10 protons resonated at δ 5.90 (dt, *J* = 10.0, 5.0 Hz, 1H, H9), 5.54 (d, *J* = 10.0 Hz, 1H, H10). The H-10a resonance appeared as a singlet at δ 4.31 (s, 1H, H10a).

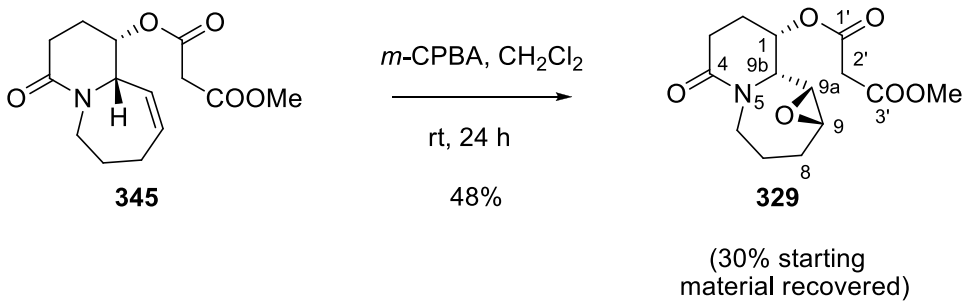


330 **345**

(36% starting material recovered)

Scheme 4.13: Synthesis of ester **345**

Treatment of alkene **345** with *m*-CPBA in CH_2Cl_2 for 24 h provided the epoxide **329** in 48% yield and the starting alkene was also recovered in 30% yield (**Scheme 4.14**).



345 **329**

(30% starting material recovered)

Scheme 4.14: Synthesis of epoxide **329**

The molecular formula of the epoxide **329** was confirmed by HRESIMS (calcd. for $C_{14}H_{19}O_6NNa$, $(M+Na)^+$ 320.1110, found: 320.1098) analysis. In the ^1H NMR

spectrum of **329**, H-9a and H-9 resonated at δ 3.21 (dd, *J* = 5.5, 4.5 Hz, 1H, H9a) and 3.12 (apparent q, *J* = 5.5 Hz, 1H, H9), respectively, while H-9b resonated at δ 3.64 (apparent t, *J* = 6.5 Hz, 1H). The ^{1}H and ^{13}C NMR assignments are shown in **Figure 4.3** and **4.4**, respectively and are based on 2D NMR experiments (COSY, HSQC, HMBC). The relative configuration of **329** was tentatively based on the NOESY correlations between H-1 and H-9b, and H-9 and H-9a. However no NOESY correlations were observed between H-9a and H-9b or H-1, or between H-9b and H-9 (**Figure 4.5**). If the alternative α-epoxide had been formed we would have expected to observe NOESY correlations between H-9a and H-9b.

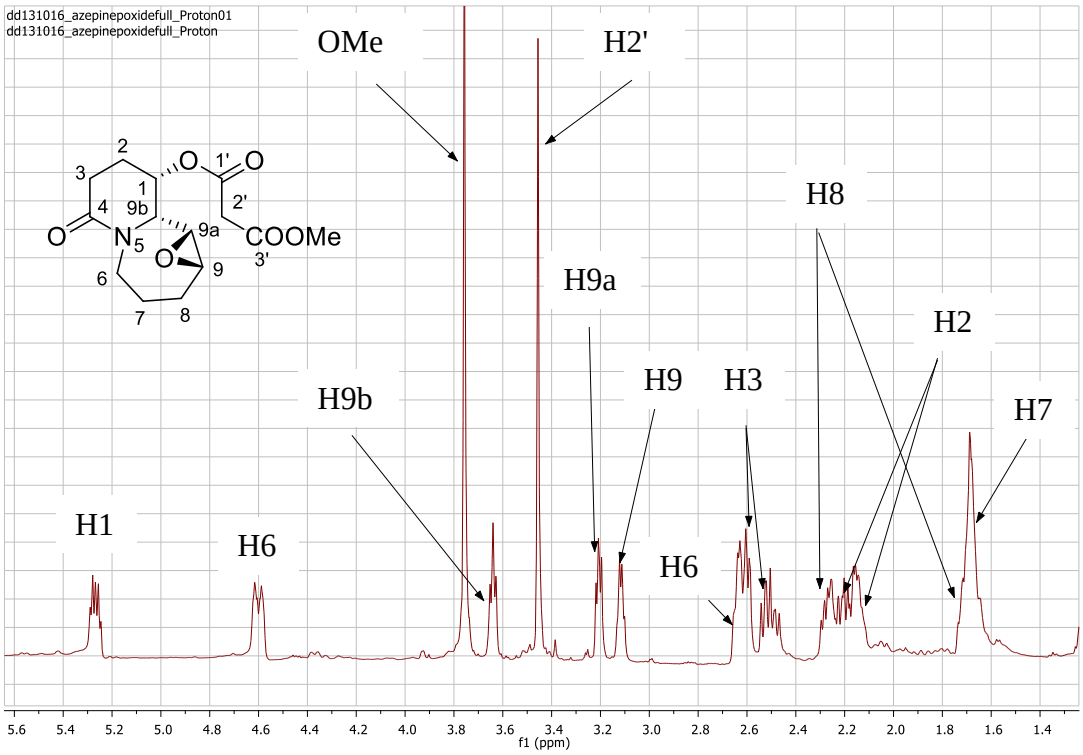


Figure 4.3: ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **329**

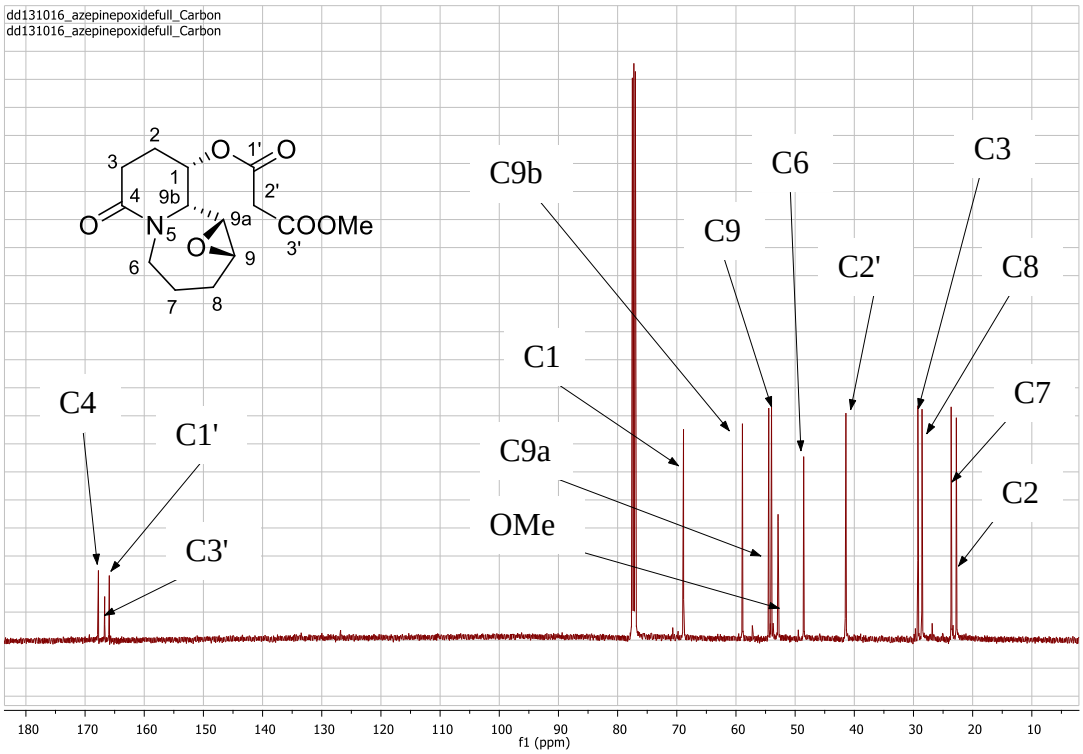


Figure 4.4: ^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of **329**

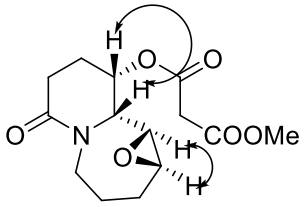
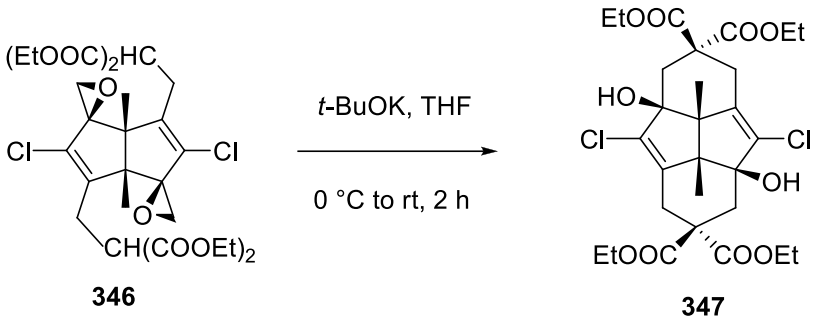


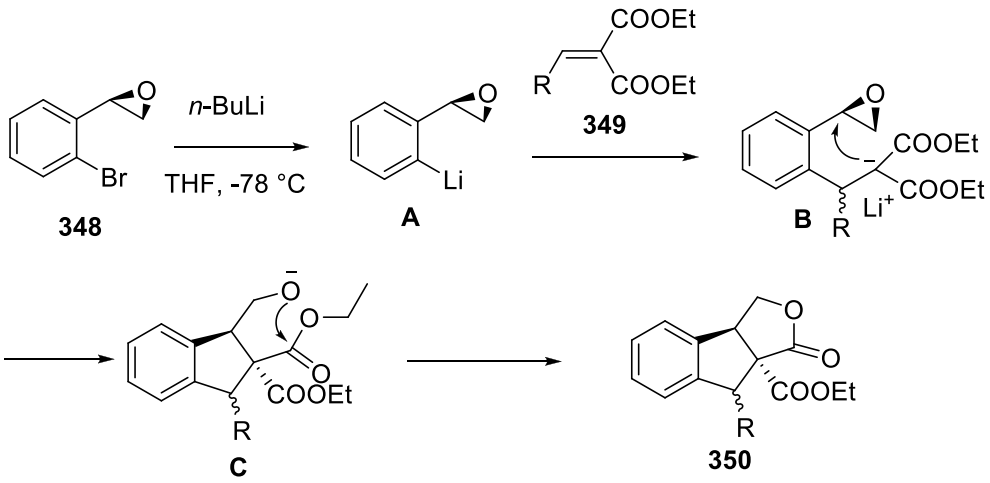
Figure 4.5: NOESY correlations of **329**

Kohnz reported the synthesis of the compound **347** by the intramolecular epoxide ring opening with the potassium malonate ester derivative of **346** (generated from the corresponding ester and *t*-BuOK) in THF (**Scheme 4.15**).[124]



Scheme 4.15: Kohnz's synthesis of **347**[124]

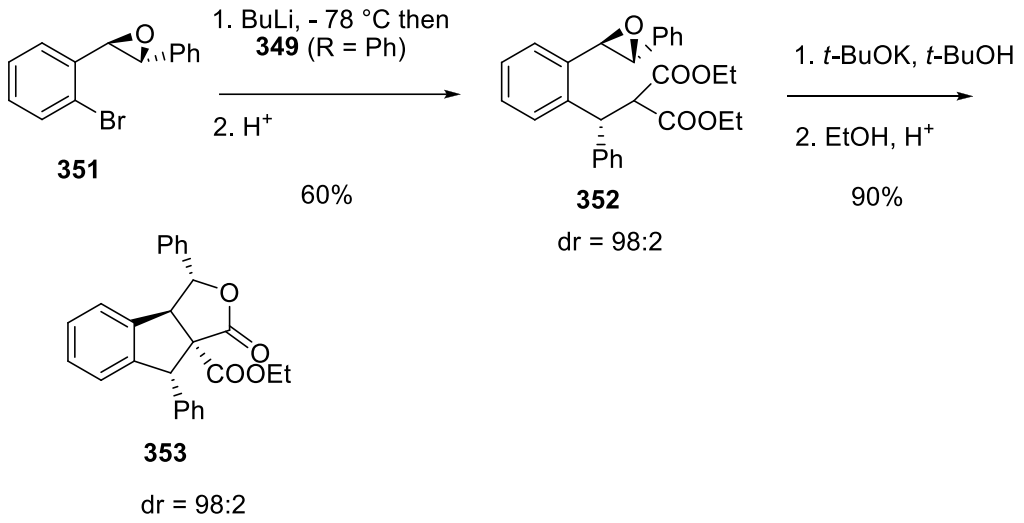
Florio reported the one-pot synthesis of compound **350** from oxirane **348** and diester **349**.[125] Treatment of the bromide-oxirane **348** with *n*-BuLi in THF at -78 ºC led to the aryllithium **A**. Michael addition of this aryllithium to the α,β-unsaturated malonate ester **349** formed the intermediate **B**. This adduct then cyclized onto the oxirane via a sterospecific intramolecular S_N2 reaction (5-*exo*-tet mode reaction) forming the intermediate **C**, which underwent lactonization to furnish **350** (**Scheme 4.16**).



R	yield (%)	dr
Ph	60%	50/50
n-Pr	50%	67/33
1,3,5-$(MeO)_3C_6H_2$	50%	60/40

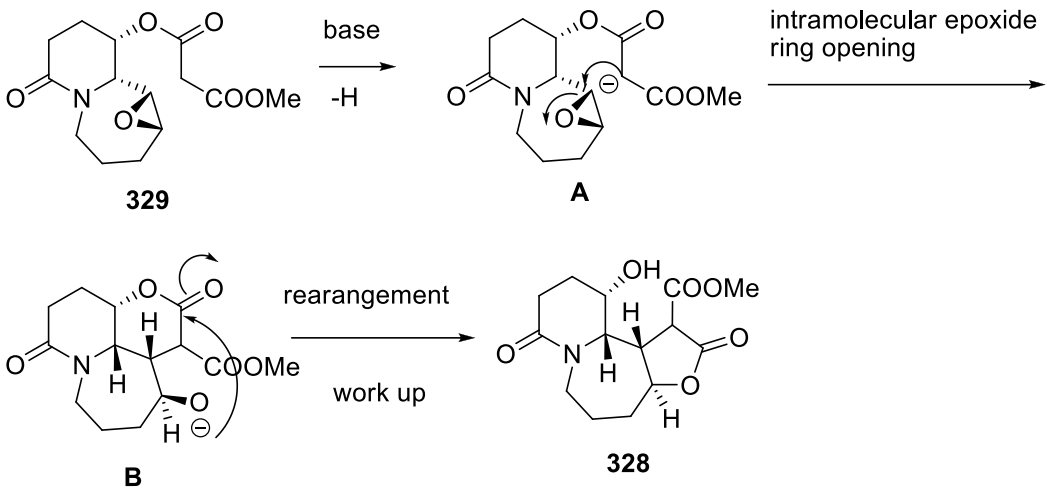
Scheme 4.16: Florio's synthesis of **350**[125]

The reaction of the oxirane **351** with the diester **349** (R = Ph) gave the corresponding diester **352** (dr = 98:2). Treatment of this compound with *t*-BuOK/*t*-BuOH resulted in the tricyclic compound **353** (**Scheme 4.17**).[125]



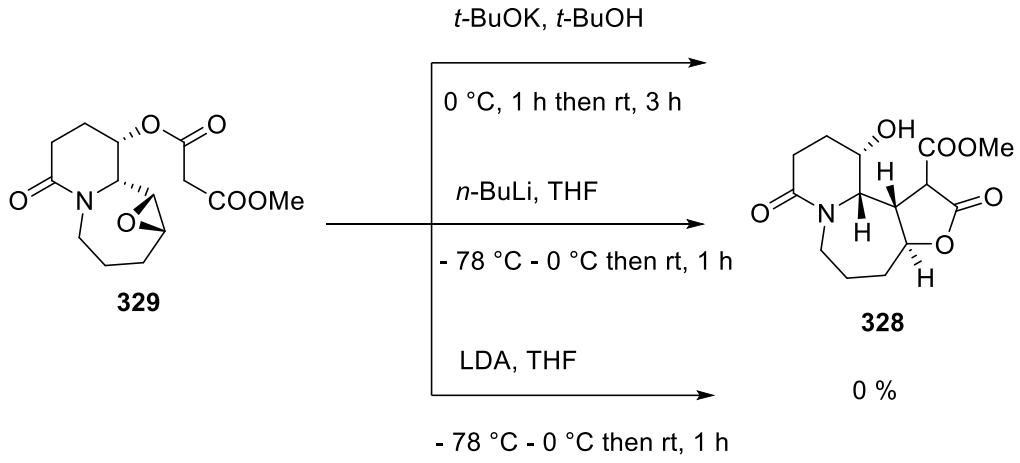
Scheme 4.17: Florio's synthesis of **353**[125]

From Kohnz's and Florio's results, we proposed that the bicyclic epoxide ester **329** could be converted to the tricyclic compound **328** under similar reaction conditions (**Scheme 4.18**). Treatment of **329** with a strong base could form the intermediate anion **A** by deprotonation. Intramolecular epoxide ring opening of the intermediate **A** by the malonate anion (6 – *exo*-tet mode) could result in the intermediate **B**. An intramolecular rearrangement could transform the 6-membered ring lactone of **B** to more stable form, the 5-membered ring lactone compound **328**, as is illustrated in **Scheme 4.18**.



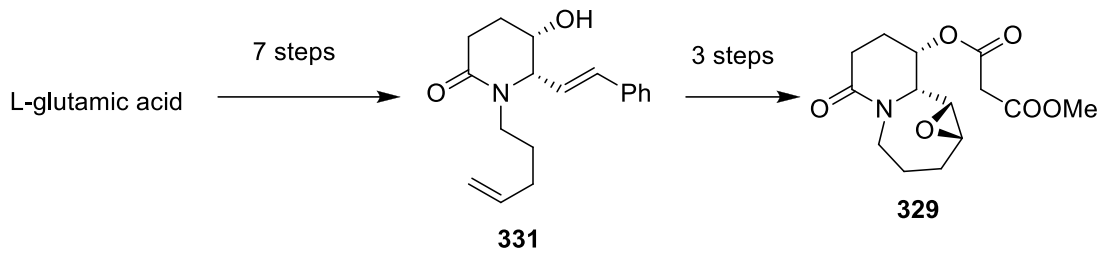
Scheme 4.18: The proposed formation of **328**

However, treatment of the epoxide **329** with base (*t*-BuOK in *t*-BuOH; or LDA in THF; or *n*-BuLi in THF) at rt gave none of the desired product **328**. Only the starting material **329** was recovered **(Scheme 4.18**). The failure of this cyclization reaction may indicate that **329** was the α-epoxide rather than the desired one. If this step had proceeded we could have synthesized the targeted tricyclic compound **139** (two steps more from **328**) in 13 overall synthetic steps from L-glutamic acid and possibly in better overall yield than the route originated from 4-pentyn1-ol (20 synthetic steps) (Chapter 3).



Scheme 4.18: Attemped preparation of lactone **328**

4.4 Conclusions



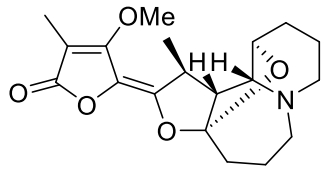
Scheme 4.19: Summarized synthesis of **329**

In conclusion, we have synthesized the diene **331** from L-glutamic acid in seven synthetic steps. The key step involved a borono-Mannich reaction between the hemiaminal **322** and *trans*-β-styryl boronic acid and *trans*-β-styrylpotassiumtrifluoroborate to prepare the *cis* diene **331**. From this diene, we obtained the epoxide **329** in three synthetic steps via a diene RCM reaction, esterification and epoxidation sequence. Epoxide **329** was synthesized in 6% overall yield from L-glutamic acid. We have attempted to prepare compound **328** from the ester-epoxide **329** via an intramolecular epoxide ring opening reaction followed by cyclization of the resulting hydroxyl ester intermediate. Different bases (*t*-BuOK in *t*-BuOH, LDA in THF, BuLi in THF) were examined. However all reactions failed to form the desired product **328** and only unreacted epoxide **329** was recovered. Further studies, including using higher reaction temperatures and the use of Lewis acid catalysts (for example, LiOTf) are warrented however time restraints did not allow these variations to be examined.

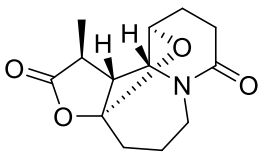
CHAPTER 5: CONCLUSIONS AND FUTURE DIRECTION

5.1 Conclusions

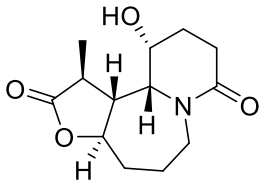
The main aim of this project was to develop a new synthetic methodology towards the total synthesis of stemocurtisine **2** as shown in **Figure 5.1**. In order to synthesize **2**, we planned to synthesize the racemic compound **138** and then the tetracyclic compound **137**.



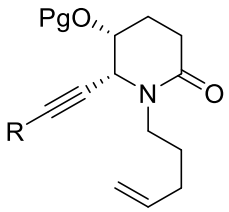
stemocurtisine **2**



137



138



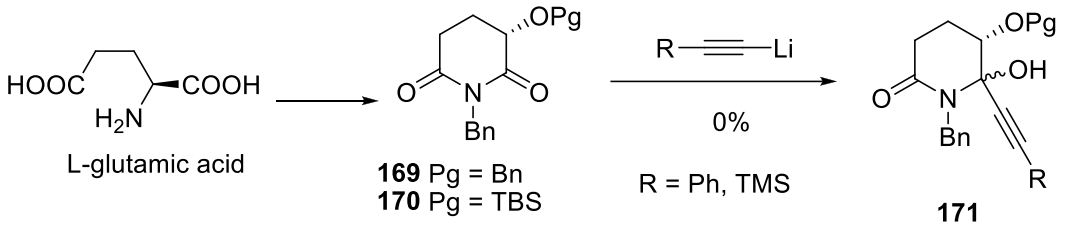
142

X = CH_2OPg, COOMe

Pg : protecting group

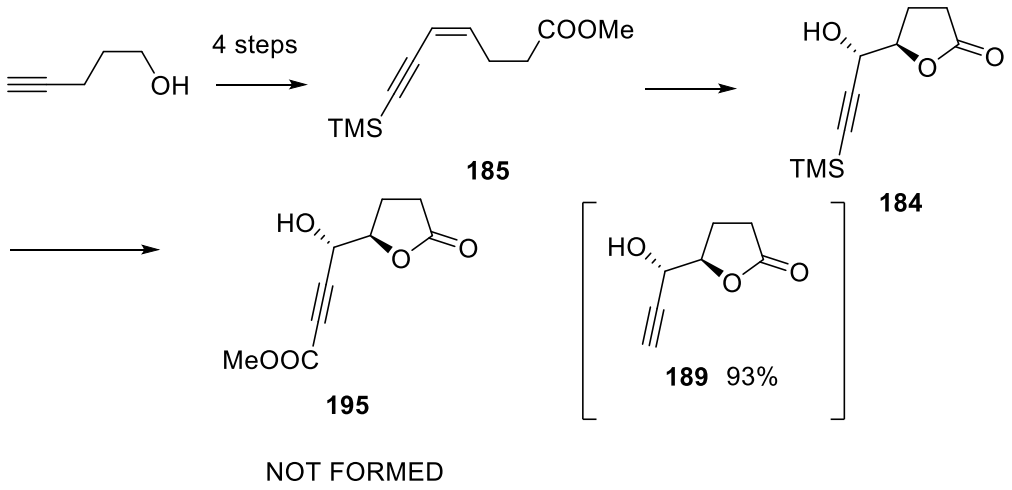
Figure 5.1: Stemocurtisine **2** and targeted compounds **137**, **138** and **142**

In Chapter 2 we examined three different synthetic strategies to construct an ene-yne lactam of the general structure **142**, which possessed the A-ring structure of the target compound **138** and an ene-yne moiety, which was necessary for synthesis of the azepine ring (B-ring). Following our synthetic strategy 1, we conducted model work to make imides **169** and **170**. However our attempts at nucleophilic additions of alkynyl Grignard reagents to **169** or **170** led to the ring opening of the desired hemiaminal products **171** (**Scheme 5.1**).



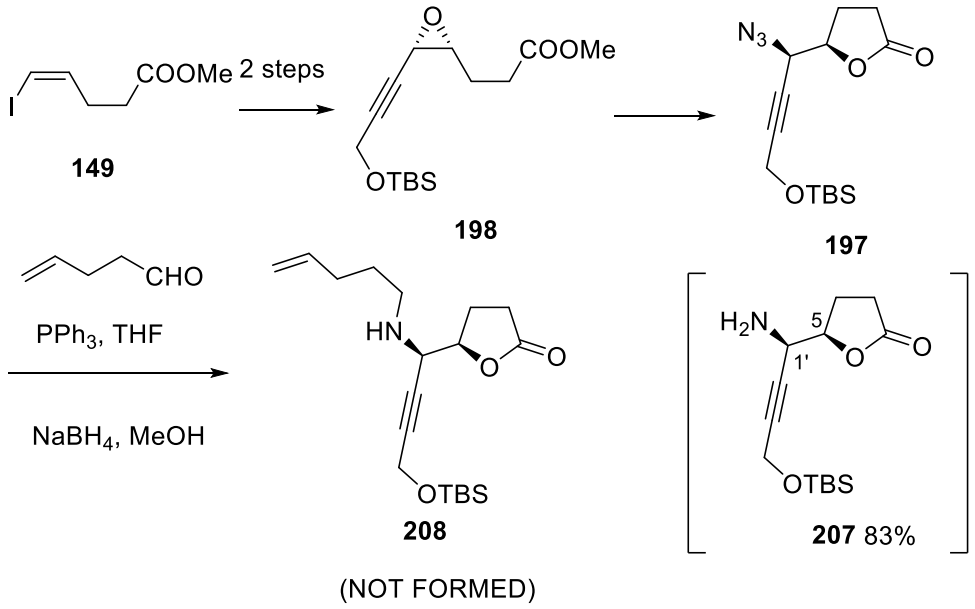
Scheme 5.1: Summary of synthetic strategy 1

Following synthetic strategy 2, we prepared the lactone **184**. However, the next step, which involved conversion of the TMS group of **184** to an ester group, failed to form the desired product **195** (**Scheme 5.2**), which in principle could be converted to **142** in three synthetic steps. Instead, the undesired terminal alkyne **189** was formed.



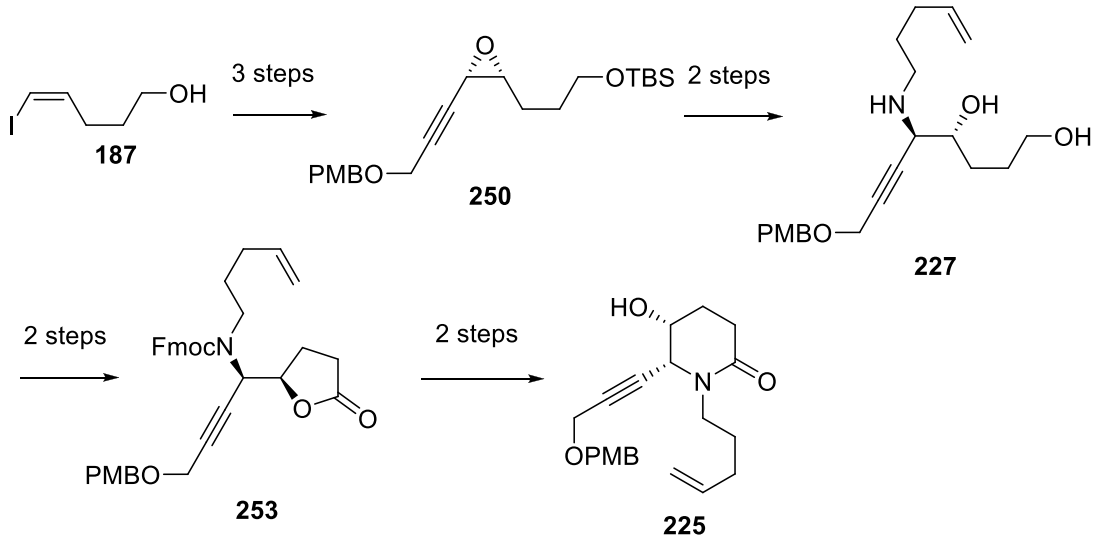
Scheme 5.2: Summary of synthetic strategy 2

We then examined the synthetic strategy 3. Initially, from the *Z*-iodide **149** we prepared the epoxide **198** in two synthetic steps. Azidolysis of this epoxide led to the azide **197**. However the Staudinger/aza-Wittig reaction between this azide and 4-pentenal did not give the desired product **208**, only the Staudinger product **207** was formed in 83% yield.



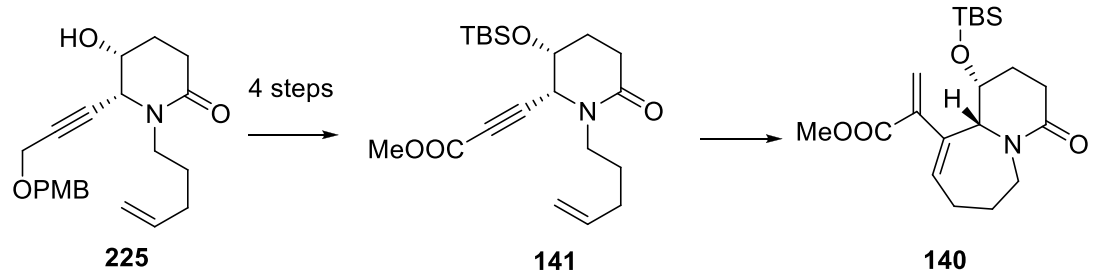
Scheme 5.3: Outcomes from our first attempts at synthetic strategy 3

Finally continuing this synthetic strategy with modifications, we successfully synthesized the ene-yne lactam **225** in 11 synthetic steps and 12.1% overall yield from 4-pentyne-1-ol. The key steps here involved an aminolysis reaction of the epoxide **250** with 4-pentene-1-amine and the oxidation of the *N*-Fmoc derivative of the 1,4-diol **227** to the lactone **253**. After Fmoc deprotection of **253**, the resulting lactone was then converted to the lactam **225** via a base catalysed rearrangement process. An alternative method to prepare the propiolate ester analogue of **227** was unsuccessful due to competing aminolysis of the terminal ester group (**Scheme 5.4**).



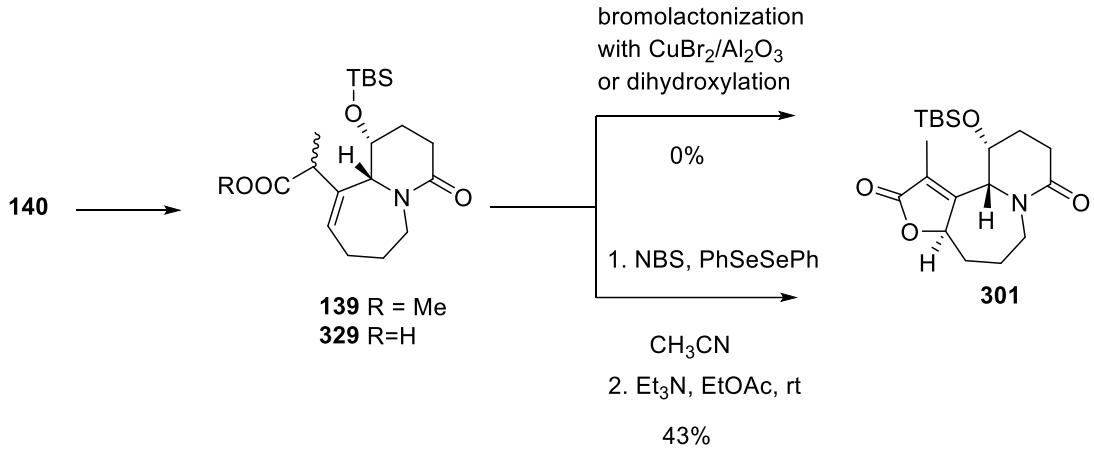
Scheme 5.4: Summary of the synthesis of **225**

In Chapter 3, we described synthesis of the A-B, A-B-C ring systems and attempts to make the ether linkage of stemocurtisine **2**. The bicyclic compound **140** was obtained from the lactam **225** in five synthetic steps and in 35% overall yield. The key step involved an ene-yne RCM reaction of **141** to form the 7-membered ring (the B-ring) of stemocurtisisne **2** (**Scheme 5.5**).



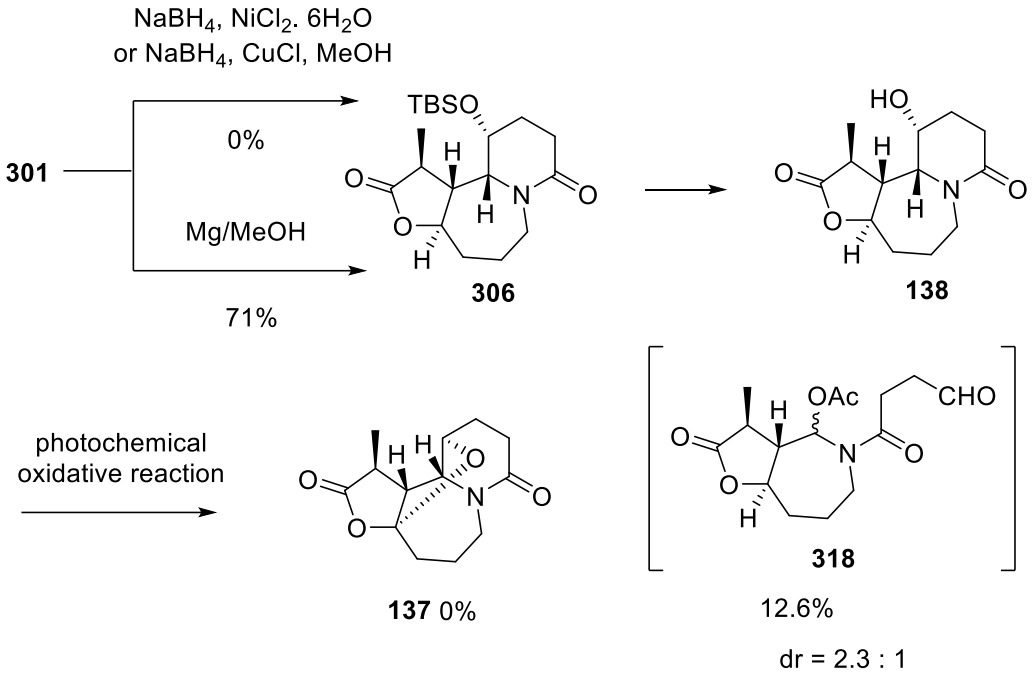
Scheme 5.5: Construction of the A-B ring of stemocurtisine

Compound **140** was then converted to a diastereomeric mixture of esters **139** via an 1,4-"hydride" reduction reaction using $NaBH_4$/MeOH. Attempts to prepare **301** from the corresponding acid **329** via bromolactonization with $CuBr_2$ on alumina or *syn* dihydroxylation with OsO_4 failed. Finally compound **301** was obtained from the mixture of **139** via bromolactonization of its corresponding acid derivative **329** using NBS/PhSeSePh followed by a base-catalysed elimination of the resulting bromolactone (**Scheme 5.6**). This process also produced the C-3a epimer of **301** (compound **302**), which could be converted to **301** by treatment with DBU in $CHCl_3$.

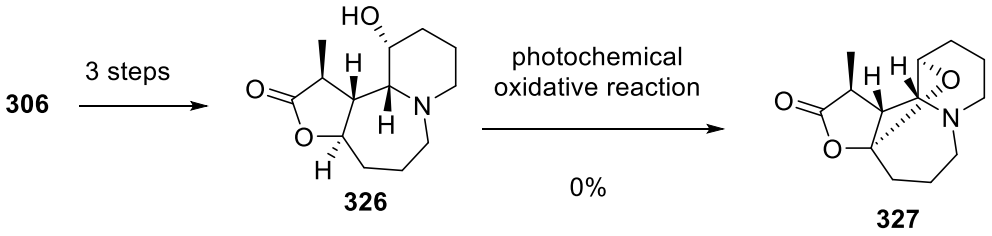


Scheme 5.6: Construction of the A-B-C ring of stemocurtisine

Reduction of the C-C double bond of the α,β-unsaturated lactone **301** using $NaBH_4/NiCl_2.6H_2O$ or $NaBH_4$/CuCl did not proceed at 0 ºC or rt. Surprisingly, treatment of **301** with Mg/MeOH led to the corresponding the tricylic lactone **306** as a single diastereomer in 71% yield. The relative configurations at C-1, C-3a, C-11, C-11a and C-11b in **306** were the same as those of stemocurtisine and were confirmed by NMR and single crystal X-ray crystallographic analyses. Finally, we attempted the photochemical oxidative cyclization reactions on compound **138** with the aim of preparing the ether linkage of **137**. This reaction resulted in a mixture of products and we could only isolate the major product, whose structure was proposed as **318**, as a 2.3:1 mixture of diastereomers (**Scheme 5.7**). NMR analysis of this compound indicated thet the piperidinone ring had undergone a cleavage reaction to give an aldehyde-*O*-aetyl hemiaminal. The proposed structure of this compound could not be confirmed from MS analysis, which indicated that the product had two extra oxygens. A similar photochemical oxidative cyclization process was attempted on the piperidine **328**. This reaction led to a complex mixture of products (**Scheme 5.8**). We could not isolate any pure compound due to the small amount of starting material used and the close R_f values of the products found (by TLC analysis). Time constrains prevented us to examine other variations or methods to make the ether linkage of stemocurtisine **2**.

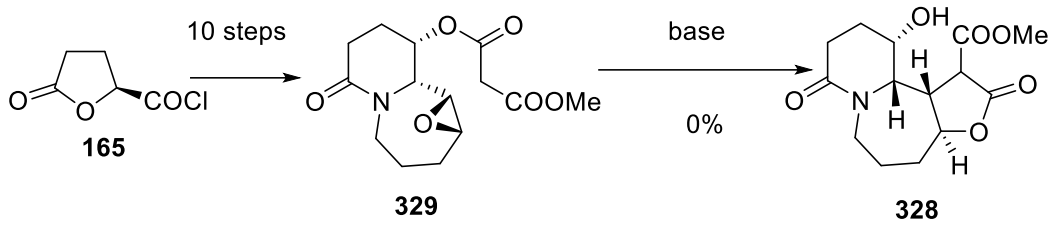


Scheme 5.7: Attempted synthesis of **137**



Scheme 5.8: Synthesis of **326** and attempts with photochemical oxidative reaction on this compound

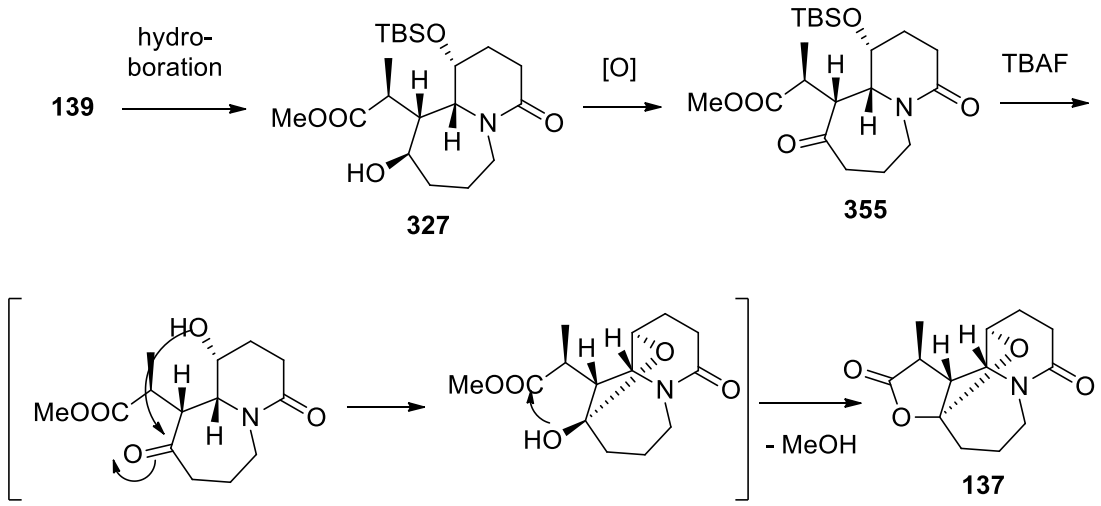
In Chapter 4 we discussed an alternative method to construct an A-B ring system of stemocurtisine as well as attempt to build the C-ring from L-glutamic acid. We synthesized the epoxide ester **329** in 10 synthetic steps. However attempts to prepare compound **328** from the ester-epoxide **329** via a base-catalysed intramolecular epoxide ring opening reaction followed by cyclization of the resulting hydroxyl ester intermediate failed to form the desired product **328** (**Scheme 5.9**).



Scheme 5.9: Synthesis of **329** from L-glutamic acid

5.2 Future directions

In the future we will continue to examine other methods to make the ether linkage to prepare the tetracyclic compound **137**. One possible method involves the hydroboration of the alkene of **139** followed by oxidation to the ketone **328**. Deprotection of the TBS ether of **328** may the provide access to the desired tetracyclic compound **137** via a series of two intramolecular cyclization reactions (**Scheme 5.10**). Introduction of the D-ring onto **137** would then be examined following method described Olivo[57] to prepare the A-B-C-D ring system of stemocurtisine **2**. We will also try to make an enantiomerically enriched version of the epoxide **250** using the Shi epoxidation reaction (instead of the racemic epoxide **250** in this thesis).[78] This method should lead to **138** in high enantiomeric purity with the same absolute configuration as stemocurtisine **2** at C-1, C-3a, C-11, C-11a and C-11b.



Scheme 5.10: A possible alternative synthesis of **137**

CHAPTER 6: EXPERIMENTAL SECTION

6.1 General experimental

6.1.1 Reaction conditions

All reactions were performed in oven dried glassware under an atmosphere of dry nitrogen, unless otherwise stated. Reactions were monitored by thin-layer chromatography analysis.

Anhydrous MeOH, EtOH, DMSO and dioxane were purchased form Sigma-Aldrich Chemical Co.

Anhydrous THF was obtained by distillation from sodium wire/benzophenone.

Anhydrous CH_2Cl_2, Et_2O, DMF and toluene were obtained from a Johnson Morris anhydrous solvent dispenser.

6.1.2 Nuclear Magnetic Resonance (NMR) Spectroscopy

^1H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^1H NMR running at 500 MHz and ^{13}C NMR running at 125 MHz) instrument. $CDCl_3$ was used as the NMR solvent unless otherwise stated. NMR assignments were based on COSY, HSQC, HMBC, NOESY and DEPT experiments.

^1H NMR chemical shifts are quoted in δ values in ppm and are referenced relative to the chemical shift of $CDCl_3$ (7.26 ppm) unless otherwise noted. Some spectra were acquired on a Varian Inova NMR Spectrometer (300 MHz). Coupling constants (*J*) are reported in Hz, with signal multiplicities designated at singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), quartet (q), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of triplets (ddt), multiplet (m), broad singlet (bs), broad multiplet (bm), quintet (quin), doublet of quartets (dq). The order in which the signal was described in the text is mulplicity, number of protons (integration), coupling constant (*J*), and assignment.

^{13}C NMR chemical shifts are quoted in δ values in ppm and are referenced relative to the chemical shift of $CDCl_3$ (77.36 ppm) unless otherwise noted. Some spectra were

acquired on a Varian Inova NMR Spectrometer (75 MHz). Resonances were assigned as follows: Chemical shift (assignment). In some cases carbon resonances appeared broad (b).

6.1.3 Mass Spectrometry

Low-resolution mass spectra were obtained on a Shimadu GC spectrometer (EI) or Water LCZ single quadropole (ESI). High resolution spectra were obtained on a VG Autospec mass spectrometer (EI) or Waters QTOF (ESI). HRMS were obtained in lieu of elemental analysis and ^{1}H and ^{13}C NMR spectroscopy and TLC analysis were used as the criteria for purity.

6.1.4 Melting point

The melting points were recorded on a Gallenhamp MF-370 carpillary tube, melting point apparatus and are uncorrected. The values are expressed in degree Celcius (ºC). Uncertanties in the quoted values are ±2 ºC.

6.1.5 Infrared spectroscopy

Infrared spectra were obtained as neat samples on a Smart Omni-Sampler Avator ESP Nicolet-Brand.

6.1.6 Polarimetry

Optical rotations were measured using a 1 cm cell, in a Jasco DIP-370 digital polarimeter. Specific rotations were calculated by using the average value of 10 optical rotation measurements.

6.1.7 Chromatography

TLC analyses were performed using aluminium backed Merck silica gel TLC plates. Compounds were detected under a 254 nm ultraviolet lamp, if applicable, or by a staining with acidified aqueous solution of ammonium molybdate and cerium(IV) sulphate, followed by heating with a 1400 W heat gun. Column chromatography was

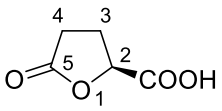
performed using Meck silica gel (40-63 μm) packed by the slurry method, under a positive pressure of air.

6.1.8 Microwave reactor

Microwave reactions were performed in a CEM microwave reactor at 120 ºC, 60 W using CH_3CN as a solvent in a 3 mL capped vial.

6.2 Experimental

(*S*)-5-Oxotetrahydrofuran-2-carboxylic acid (166)[126]

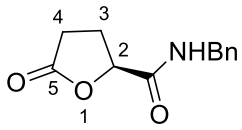


166

To the suspension of glutamic acid (10.0 g, 68 mmol) and $NaNO_2$ (7.5 g, 108.7 mmol, 1.6 equiv) in water (100 mL) was added HCl (10 mL concentrated diluted to 50 mL) dropwise via an addition funnel at 0 ºC with vigorous stirring for 1 h. The mixture was warmed to rt and stirred for 18 h.[61] The water was evaporated and then EtOAc (200 mL) was added. The mixture was stirred for 30 min and filtered. The solid cake was washed with EtOAc (2 x 75 mL). The organic extracts were combined and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was left under high vacuum for 12 h to give the lactone acid **166** (8.67 g, 98% yield) as a solid syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 – 4.97 (m, 1H, H2), 2.68 – 2.53 (m, 3H, 2H4 and H3), 2.44 – 2.35 (m, 1H, H3).
NMR spectroscopic data matched with the published data.[126]

(*S*)-*N*-Benzyl-tetrahydro-5-oxo-2-furaneamide (**167**)[59]



167

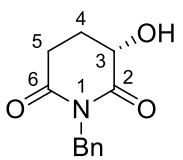
A mixture of (*S*)-γ-butyrolactone-γ-carboxylic acid **166** (5.5 g, 42.3 mmol) and thionyl chloride (26 mL, 127 mmol, 3 equiv) was heated and stirred at 60 ºC for 6 h under a N_2 atmosphere. The excess thionyl chloride was removed under vacuum, and the residue was dissolved in dry CH_2Cl_2 (80 mL). To the resulting solution was added, under a N_2 atmosphere, a mixture of benzylamine (8.3 mL, 76 mmol) and triethylamine (11.7 mL, 80 mmol) at 0 ºC. After 3 h stirring at 0 ºC, water (35 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography (2:3, EtOAc/petroleum spirit) to give the lactone amide **167** (7.25 g, 71% yield) as a white solid.

R_f = 0.69 (1:1, EtOAc/petroleum spirit).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 5H, ArH), 6.92 (bs, 1H, NH), 4.82 (dd, *J* = 9.5, 5.5 Hz, 1H, H2), 4.51 – 4.33 (m, 2H, CH_2-Ar), 2.58 (ddd, *J* = 12.5, 9.5, 6.5 Hz, 1H, H4), 2.50 (dd, *J* = 9.5, 6.5 Hz, 2H, H3), 2.33 (ddt, *J* = 15.5, 12.5, 6.5 Hz, 1H, H4).

NMR spectroscopic data matched with the published data.[59]

(*S*)-1-Benzyl-3-hydroxy-2,6-piperidinedione (**168**)[59]

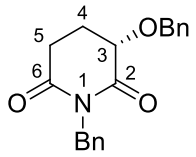


168

To a cooled solution (-78 ºC) of the lactone amide **167** (1.25 g, 5.7 mmol) in dry THF (120 mL) was added portionwise potassium *t*-butoxide (351 mg, 3.14 mmol, 0.55 equiv) under a N_2 atmosphere. The mixture was stirred for 10 min at the same temperature and then allowed to warm to -55 ºC and stirred for about 30 min. The reaction was quenched with water (30 mL) at -55 ºC. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with water (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the imide **168** (4.94 g, 78% yield) as a white solid.

R_f = 0.61 (1:1, EtOAc/petroleum spirit).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H, ArH), 4.95 (s, 2H, CH_2-Ar), 4.22 (dd, *J* = 12.5, 5.5 Hz, 1H, H3), 2.91 (d, *J* = 18.0 Hz, 1H, H5), 2.70 – 2.61 (m, 1H, H5), 2.36 – 2.30 (m, 1H, H4), 1.90 (qd, *J* = 13.0, 4.5 Hz, 1H, H4).
^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C2), 171.4 (C6), 136.8 (ArC), 129.2 (ArCH), 128.9 (ArCH), 128.1 (ArCH), 68.8 (C3), 44.0 (CH_2Ar), 31.2 (C5), 25.6 (C4).
NMR spectroscopic data matched with the published data.[59]

(*R*)-1,3-Dibenzylpiperidine-2,6-dione (**169**)[90]



169

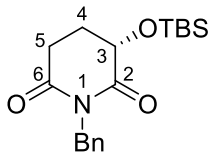
Silver oxide (1.39 g, 6 mmol, 3 equiv) and BnBr (1.43 mL, 12 mmol, 6 equiv) were added to a solution of the alcohol **168** (440 mg, 2 mmol) in anhydrous Et_2O (20 mL) and the mixture was stirred at rt for 2 d in the dark.[61] The mixture the filtered through a pad of celite and the solid cake was washed with Et_2O (2 x 50 mL). The solvent was *removed in vacuo* and the residue was purified by column chromatography (1:4, EtOAc/petroleum spirit) to provide the benzyl ether **169** (484 mg, 78% yield) as a white solid.

R_f = 0.67 (1:1, EtOAc/petroleum spirit).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 10H, ArH), 4.93 (s, 2H, $PhCH_2N$), 4.80 (d, *J* = 12.0 Hz, 1H, PhC*H*HO), 4.62 (d, *J* = 12.0 Hz, 1H, ArCH*H*O), 4.08 – 4.04 (m, 1H, H3), 2.91 (ddd, *J* = 18.0, 8.0, 6.0 Hz, 1H, H5), 2.57 (dt, *J* = 18.0, 6.0 Hz, 1H, H5), 2.06 (dt, *J* = 9.5, 6.0 Hz, 2H, H4).

NMR spectroscopic data matched with the published data.[90]

(*S*)-1-Benzyl-3-(*tert*-butyldimethylsilyloxy)piperidine-2,6-dione (**170**)



170

Imidazole (374 mg, 5.5 mmol, 2.5 equiv) and TBSCl (364 mg, 2.42 mmol, 1.1 equiv) were added to a solution of the alcohol **168** (482 mg, 2.2 mmol) in DMF (20 mL) and the mixture was stirred for 14 h at rt under a N_2 atmosphere.[63] Water (30 mL) was added and the aqueous phase was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:7, EtOAc/petroleum spirit) to afford the TBS ether **170** (506 mg, 69% yield) as a pale yellow oil. This is a known compound however its spectroscopic data was not published.[127]

R_f = 0.58 (2:3, EtOAc/petroleum spirit).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 5H, ArH), 4.94 (s, 2H, CH_2-Ar), 4.35 (dd, *J* = 7.5, 4.0 Hz, 1H, H3), 2.95 (ddd, *J* = 17.5, 8.5, 5.5 Hz, 1H, H5), 2.63 (ddd, *J* = 17.5, 7.5, 5.5 Hz, 1H, H5), 2.10 – 1.97 (m, 2H, H4), 0.90 (s, 9H, $(CH_3)_3C$), 0.13 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5 (C2), 172.1 (C6), 137.3 (ArC), 128.9 (ArC), 128.7 (ArC), 127.7 (ArC), 69.6 (C3), 43.23 (CH_2-Ar), 29.3 (C5), 26.7 (C4), 26.0 ($(CH_3)_3C$), 18.5 ($(CH_3)_3C$), -4.43 (CH_3-Si), -5.09 (CH_3-Si).

ESIMS *m/z* 356 [$(M+Na)^+$ 100%].

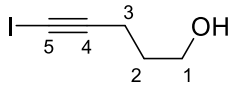
HRESIMS calcd. for $C_{18}H_{27}O_3N\,NaSi$, $(M+Na)^+$ 356.1658, found: 356.1654.

Attempted addition of lithium trimethylsilylacetylide to 170

To a solution of trimethylsilylacetylene (60 mg, 0.6 mmol, 2 equiv) in THF (4 mL) at -78 ºC under a N_2 atmosphere was added a solution of 1.6 M *n*-BuLi in THF (360 μL, 0.57 mmol, 1.9 equiv) and the mixture was stirred at -78 ºC for 15 min. To this mixture, was added dropwise a solution of **170** (92 mg, 0.3 mmol) in THF (0.5 mL). The reaction mixture was stirred at -78 ºC for 30 min, at -40 ºC for 1 h, and -0 ºC for 1 h (by TLC analysis).[60,61] The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was then evaporated. ^1H NMR analysis of the resulting residue showed signals of the ring opening product **172**

^1H NMR (500 MHz, $CDCl_3$) in part δ 6.20 (bs, 1H, NH), 4.03 (dd, *J* = 2.5, 4.5 Hz, 1H, C*H*OBn), 0.19 (s, 9H, $(CH_3)_3Si$).

5-Iodo-4-pentyn-1-ol (**186**)[67]



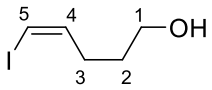
186

A solution of KOH (8.40 g, 150 mmol, 2.5 equiv) in H_2O (12 mL) was added to a solution of 4-pentyn-1-ol (5.04 g, 60 mmol). Then I_2 (16.76 g, 66 mmol, 1.1 equiv) was added portionwise to the resulting solution over a period of 30 min.[67] After being stirred 3 h at rt, a saturated solution of $Na_2S_2O_3$ (60 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were concentrated by rotary evaporation to give a brown residue. The residue was dissolved in CH_2Cl_2 (100 mL) which was washed with brine (50 mL) and then was dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporation to give the crude product which was purified by column chromatography (1:3,

EtOAc/petroleum spirit) to afford the iodide **186** (9.32g, 75% yield) as a colourless oil.

R_f = 0.57 (2:3, EtOAc/petroleum spirit).
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (t, *J* = 6.0 Hz, 2H, H1), 2.50 (t, *J* = 7.0 Hz, 2H, H3), 1.80 – 1.74 (m, 2H, H2).
^{13}C NMR (125 MHz, $CDCl_3$) δ 94.2 (C4), 61.8 (C1), 31.4 (C3), 17.7 (C2), -5.9 (C5).
NMR spectroscopic data matched with the published data.[67]

(*Z*)-5-Iodo-4-penten-1-ol (**187**)[67]



187

To a solution of alkene **186** (10.5 g, 50 mmol) in MeOH (80 mL) were added pyridine (22.9 mL, 300 mmol, 6.0 equiv) and potassium azodicarboxylate (5.82 g, 30 mmol, 0.6 equiv) sequentially at rt. Acetic acid (18.1 mL, 316 mmol, 6.3 equiv) was then added slowly via a syringe pump over 10 h at rt. During the addition of acetic acid, additional potassium azodicarboxylate (0.6 equiv) was added at 2 h, 4 h, 6 h, and 8 h, respectively. After complete addition of the acetic acid, the mixture was poured into a 1-L beaker together with Et_2O (150 mL) and aqueous HCl solution 1M (300 mL). The aqueous layer was extracted with Et_2O (3 x 150 mL) and the combined organic layers were concentrated by rotary evaporation to give a pale yellow residue. The residue was dissolved in Et_2O (150 mL) which was washed with aqueous 1M HCl solution (2 x 75 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL), then was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was treated with *n*-$BuNH_2$ (8 mL) and the solution was stirred at rt for 10 h to remove the over reduced product. The mixture was dissolved in Et_2O (150 mL) which was washed with aqueous 1M HCl solution (2 x 100 mL), saturated aqueous $NaHCO_3$ (100 mL) solution, and brine (100 mL), then was dried over Na_2SO_4 and filtered. After removal of the solvent, the residue was purified by

column chromatography (1:3, EtOAc/petroleum spirit) to give the (*Z*)-vinyl iodide **187** (5.94 g, 56% yield) as a colourless oil.[67]

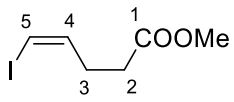
R_f = 0.61 (2:3, EtOAc/petroleum spirit).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25-6.17 (m, 2H, H4 and H5), 3.68 (t, *J* = 8.5 Hz, 2H, H1), 2.25 (q, *J* = 7.0 Hz, 2H, H3), 1.74 – 1.66 (m, 2H, H2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9 (C4), 83.4 (C5), 62.4 (C1), 31.5 (C3), 31.1 (C2).

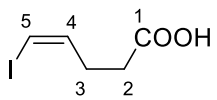
NMR spectroscopic data matched with the published data.[67]

Methyl (*Z*)-5-iodobut-4-en-1-oate (**149**)[128]



149

To a stirred solution of the primary alcohol **187** (3.18 g, 15 mmol) in acetone (90 mL) at 0 ºC was added dropwise Jones' reagent (21.4 mL) until an orange colour became permanent.[68] The reaction mixture was stirred for 30 min at 0 ºC. Methanol (10 mL) was added dropwise and the resulting mixture was stirred for additional 15 min at 0 ºC. Chromium salts were filtered off and the solvent was evaporated to give a pale yellow residue. Water (50 mL) was added to the residue and the aqueous phase was extracted with EtOAc (5 x 100 mL). The combined organic extract was dried over $MgSO_4$, filtered and evaporated to give the crude corresponding acid (3.02 g, 89% yield) which could be used without any further purification.



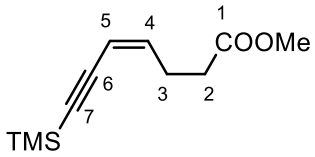
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (d, *J* = 7.5 Hz, 1H, H5), 6.28 – 6.22 (m, 1H, H4), 2.52 – 2.44 (m, 4H, H2 and H3).

To a stirred solution of the above acid (3.00 g, 13.3 mmol) in methanol (100 mL) was added chlorotrimethylsilane (3.4 mL, 26.6 mmol, 2 equiv).[67] The mixture was

stirred for 14 h at rt and the volatiles were evaporated. The crude product was dissolved in CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ solution (50 mL) and water (50 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (1:9, EtOAc/petroleum spirit) to give the ester **149** (2.13 g, 67% yield) as a pale yellow oil.

R_f = 0.68 (1:4, EtOAc/petroleum spirit).
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (d, *J* = 7.3 Hz, 1H, H5), 6.25 – 6.19 (m, 1H, H4), 3.69 (s, 3H, MeO), 2.44 (s, 4H, H2 and H3).
^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3 (C1), 139.5 (C4), 84.1 (C5), 52.0 (MeO), 32.6 (C3), 30.5 (C2).
NMR spectroscopic data matched with the published data.[128]

(*Z*)-Methyl 7-(trimethylsilyl)hept-4-en-6-ynoate (**185**)



185

To a solution of the vinyl iodide **149** (800 mg, 3.33 mmol) in Et_3N (12 mL), were added $PdCl_2(PPh_3)_2$ (47 mg, 0.067 mmol, 0.02 equiv) and CuI (128 mg, 0.67 mmol, 0.2 equiv) under an argon atmosphere.[69] The mixture was stirred for 15 min then a solution of trimethylsilylacetylene (1457 mg, 4.66 mmol. 1.4 equiv) in THF (6 mL) was added dropwise over period of 30 min. After being stirred for 16 h, the mixture was diluted with Et_2O (150 mL) then washed with saturated NH_4Cl solution (2x 30 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, Et_2O/petroleum spirit) to give the ene-yne **185** (496 mg, 71% yield) as a colourless oil.

R_f = 0.69 (1:4, EtOAc/petroleum spirit)

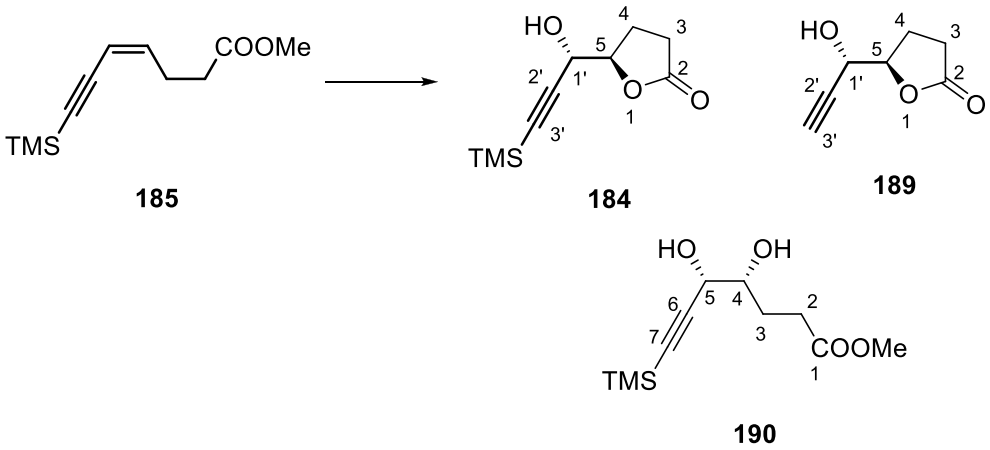
IR (neat, ν_{max}/cm^{-1}): 2958, 1734, 1507, 1249, 1168, 841.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (dt, *J* = 10.5, 7.5 Hz, 1H, H4), 5.52 (d, *J* = 10.5 Hz, 1H, H5), 3.67 (s, 3H, OMe), 2.62 (q, *J* = 7.5 Hz, 2H, H3), 2.43 (t, *J* = 7.5 Hz, 2H, H2), 0.18 (s, 9H, $(CH_3)_3Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5 (C1), 142.8 (C4), 111.0 (C5), 101.6 (C7), 100.0 (C6), 51.9 (OMe), 33.4 (C3) 25.9 (C2), 0.3 (CH_3Si).

Satisfactory EI or ESI MS data could not be obtained on this compound.

Dihydroxylation of alkene 185



185 **184** **189** **190**

Potassium osmate dihydrate (18.4 mg, 0.05 mmol, 0.05 equiv) and NMO (382 mg, 2.5 mmol, 2.5 equiv) were added to a solution of the alkene **185** (210 mg, 1 mmol) in acetone and water (10 mL, 3:2) and the mixtute was allowed to stir at 35 ºC for 1 d.[72] The organic phase was removed *in vacuo* and water (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 30 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:9 to 3:2, EtOAc/petroleum spirit) to give three compounds **184** (91 mg, 43% yield), **185** (41 mg, 29% yield) and **190** (30 mg, 13% yield).

(*R)-5-((*S**)-1-Hydroxy-3-(trimethylsilyl)prop-2-ynyl)dihydrofuran-2(3*H*)-one** (**184**)

White solid.

R_f = 0.63 (3:2, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 3402, 2957, 2170, 1757, 1181, 1060, 992, 838.

^1H NMR (500 MHz, $CDCl_3$) δ 4.32 (m, 2H, H5 and H1'), 2.52 (m, 2H, H3), 1.94 (m, 1H, H4), 1.84 (m, 1H, H4), 0.18 (s, 9H, $(CH_3)_3Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (C2), 103.1 (C2'), 92.5 (C3'), 73.7 (C5), 66.9 (C1'), 30.7 (C3), 27.6 (C4), 0.12 (CH_3Si).

ESIMS *m/z* 235 [$(M+Na)^+$ 100%].

HRESIMS calcd. For $C_{10}H_{16}O_3NaSi$, $(M+Na)^+$235.0766, found: 235.0757

(*R)-5-((*S**)-1-Hydroxyprop-2-ynyl)dihydrofuran-2(3*H*)-one** (**189**)

White solid.

Mp = 73-74 ºC

R_f = 0.63 (3:2, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 3280, 2921, 2312, 2180, 1763, 1184, 1054, 1015, 990, 938

^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (m, 2H, H5 and H1'), 2.70 – 2.59 (m, 1H, H3), 2.51 – 2.42 (m, 1H, H3), 2.49 (s, 1H, H3'), 2.39 – 2.24 (m, 2H, H4).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3 (C2), 81.7 (C2'), 80.3 (C3'), 75.5 (C5), 63.8 (C1'), 28.5 (C3), 22.0 (C4).

NMR spectroscopic data matched with the published data.[73]

(4*S,5*R**)-Methyl 4,5-dihydroxy-7-(trimethylsilyl)hept-6-ynoate** (**190**)

Colourless oil.

R_f = 0.63 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3431, 2960, 2179, 1763, 1249, 1180, 1016, 840, 759.

^1H NMR (500 MHz, $CDCl_3$) δ 4.32 (d, *J* = 3.5 Hz, 1H, H5), 3.67 (s, 4H, OMe and H4), 2.52 (dd, *J* = 6.6, 4.6 Hz, 2H, H2), 1.97-1.90 (m, 1H, H3), 1.88-1.80 (m, 1H, H3) 0.16 (s, 9H, $(CH_3)_3Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (C1), 103.1 (C7), 92.5 (C6), 73.7 (C4), 66.9 (5), 52.1 (OMe), 30.7 (C2), 27.6 (C3), 0.12 ($(CH_3)_3Si$).

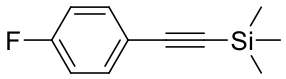
ESIMS *m/z* 245 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{14}H_{26}O_3NaSi$, $(M+Na)^+$ 267.1029, found: 267.1026.

Conversion of 190 to 184

Compound **190** (41 mg, 0.17 mmol) was dissolved in methanol (2 mL) and catalytic amount of *p*-TSA (3 mg, 0.17 mmol, 0.1 equiv) was added to this solution.[75] The reaction mixture was stirred at rt till completion of the reaction. Saturated sodium bicarbonate solution (3 mL) was added to the reaction mixture and stirred for 5 min. Methanol was removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 10 mL), washed with brine solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluant to give the lactone **184** (31 mg, 88% yield).

((4-Fluorophenyl)ethynyl)trimethylsilane (**192**)[129]



192

To a solution of 4-fluoro-iodobenzene (222 mg, 1 mmol) in Et_3N (3 mL), were added $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol, 0.01 equiv) and CuI (10 mg, 0.05 mmol, 0.05 equiv) under an argon atmosphere.[69] The mixture was stirred for 15 min then a solution of trimethylsillylacetylene (185 µL, 11.3 mmol. 1.3 equiv) in THF (1.5 mL) was added dropwise over a period of 15 min. After being stirred for 16 h, the mixture was diluted with Et_2O (50 mL) and washed with saturated NH_4Cl solution (2 x 20 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, Et_2O/petroleum spirit) to afford compound **192** (188 mg, 98% yield) as a yellow solid.

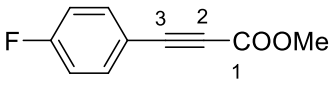
Mp = 57-59 ºC

R_f = 0.63 (2:3, Et_2O/petroleum spirit)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.5, 5.5 Hz, 2H, ArH), 7.02 (t, *J* = 8.5 Hz, 2H, ArH), 0.28 (s, 9H, $(CH)_3Si$).

The ^{1}H NMR spectroscopic data matched with the published data.[129]

Methyl 3-(4-fluorophenyl)propiolate (**193**)[130]



193

A dried and CO_2 (balloon) infused Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with CsF (182 mg, 1.2 mmol, 1.2 equiv) in DMSO (2.5 mL). Alkynylsilane **192** (192 mg, 1 mmol) was added via a syringe to the reaction mixture and the reaction was stirred at rt for 3 h. Methyl iodide (140 µL, 2.4 mmol, 2.4 equiv) was added to the reaction mixture and the reaction was stirred at rt for 1 h.[76] Saturated aqueous NH_4Cl (10 mL) was added and the whole mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (1:9, Et_2O/petroleum spirit) to afford the methyl ester **193** (110 mg, 62% yield) as a colourless oil.

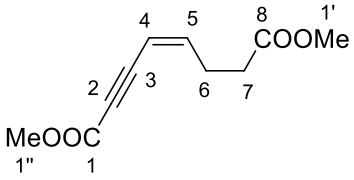
R_f = 0.56 (2:3, Et_2O/petroleum spirit).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.5, 5.5 Hz, 2H ArH), 7.05 (t, J = 8.5 Hz, 2H, ArH), 3.82 (s, 3H, OMe).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 (d, J = 254 Hz, ArC), 154.6 (C1), 135.5 (d, J = 9 Hz, ArCH), 116.4 (d, J = 10 Hz, ArCH), 115.9 (d, J = 4.0 Hz, ArC), 85.7 (C3), 80.6 (C2), 53.1 (OMe).

The ^{1}H NMR spectroscopic data matched with the published data.[130]

(*Z*)-Dimethyl oct-4-en-2-ynedioate (**194**)



194

A dried and CO_2 (balloon) infused Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with CsF (182 mg, 1.2 mmol, 1.2 equiv) in DMSO (2.5 mL). Alkynylsilane **185** (210 mg, 1 mmol) in DMSO (0.5 mL) was added to the reaction mixture and the reaction was stirred at rt for 3 h. Methyl iodide (140 µL, 2.4 mmol, 2.4 equiv) was added to the reaction mixture and the reaction was stirred at rt for 1 h.[76] Saturated aqueous NH_4Cl (10 mL) was added and the whole mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (1:9, EtOAc/petroleum spirit) to afford the diester **194** (123 mg, 63% yield) as a colourless oil.

R_f = 0.68 (1:4, Et_2O/petroleum spirit).
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.24 (dt, *J* = 10.8, 7.5 Hz, 1H, H5), 5.58 (d, *J* = 10.8 Hz, 1H, H4), 3.76 (s, 3H, OMe1), 3.66 (s, 3H, OMe2), 2.65 (q, *J* = 7.5 Hz, 2H, H6), 2.43 (t, *J* = 7.5 Hz, 2H, H7).
^{13}C NMR (1256 MHz, $CDCl_3$) δ 173.0 (C8), 154.6 (C1), 148.7 (C5), 108.2 (C4), 85.3 (C3), 83.0 (C2), 53.0 (OMe), 52.00 (OMe), 33.1 (C6), 26.4 (C7).
Satisfactory EI or ESI MS data could not be obtained on this compound.

Attempted to prepare 195 from 184

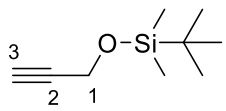
A dried and CO_2 (balloon) infused Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with CsF (182 mg, 1.2 mmol, 1.2 equiv) in DMSO (2.5 mL). Alkynylsilane **184** (212 mg, 1 mmol) in DMSO (0.5 mL) was added to the reaction mixture and the reaction was stirred at rt for 3 h. Methyl iodide (140 µL, 2.4

mmol, 2.4 equiv) was added to the reaction mixture and the reaction was stirred at rt for 1 h.[76] Saturated aqueous NH_4Cl (10 mL) was added and the whole mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the crude material was purified by silica gel column chromatography (1:9, EtOAc/petroleum spirit) to afford the terminal alkyne lactone **189** (130 mg, 03% yield) as a white solid. The desired product **195**was not form in this reaction.

Attempted with dihydroxylation of 194

Potassium osmate dihydrate (9.2 mg, 0.025 mmol, 0.05 equiv) and NMO (191 mg, 1.25 mmol, 2.5 equiv) were added to a solution of the alkene **194** (98 mg, 0.5 mmol) in acetone and water (5.0 mL, 3:2) and the mixtute was allowed to stir at 35 ºC for 1 d.[72] The organic phase was removed *in vacuo* and water (5 mL) was added. The aqueous phase was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. No desired product was formed (TLC and ^1H NMR analysis), only unreacted starting material was recovered.

3-(*tert*-Butyldimethylsilyloxy)-1-propyne (**199**)[131]



199

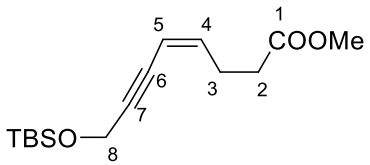
To a solution of propargyl alcohol (2.5 g, 44.5 mmol) in dichloromethane (70 mL) were added imidazole (7.6 g, 112 mmol, 2.5 equiv) and *tert*-butyldimethylsilyl chloride (8.1 g, 52.5 mmol, 1.2 equiv) at rt. The reaction mixture was stirred at rt for 4 h and quenched with water (100 mL).[131] The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give a colourless liquid. The crude product **199** (30.1 g, 99%) was used without purification for the next reaction.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, 2H, *J* = 2.5 Hz, H1), 2.39 (t, 1H, *J* = 2.5 Hz, H3), 0.91 (s, 9H, $(CH_3)_3C$), 0.12 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 81.7 (C3), 72.2 (C2), 50.8 (C1), 25.2 ($(CH_3)_3C$), 17.6 ($(CH_3)_3C$), -4.3 (CH_3Si).

NMR spectroscopic data matched with the published data.[131]

(*Z*)-Methyl 8-(*tert*-butyldimethylsilyloxy)oct-4-en-6-ynoate (**200**)



200

To a solution of the vinyl iodide **149** (1.182 g, 4.93 mmol) in Et_3N (12 mL) under an argon atmosphere were added $PdCl_2(PPh_3)_2$ (69 mg, 0.098 mmol, 0.02 equiv) and CuI (189 mg, 0.098 mmol, 0.2 equiv).[69] The mixture was stirred for 15 min then a solution of alkyne **199** (1.005 g, 5.91 mmol, 1.2 equiv) in THF (6 mL) was added dropwise over a period of 30 min. After being stirred for 16 h, the mixture was diluted with Et_2O (150 mL) and washed with saturated NH_4Cl solution (2 x 30 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, EtOAc/petroleum spirit) to give the ene-yne **200** (874 mg, 70% yield) as a colourless oil.

R_f = 0.62 (1:4, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2956, 1710, 1168, 1022, 919.

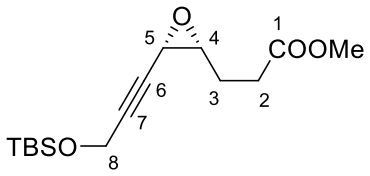
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 10.7, 7.3 Hz, 1H, H4), 5.53 (d, *J* = 10.7 Hz, 1H, H5), 4.46 (s, 2H, H8), 3.68 (s, 3H, MeO), 2.61 (dd, *J* = 14.8, 7.4 Hz, 2H, H3), 2.42 (t, *J* = 7.5 Hz, 2H, H2), 0.91 (s, 9H, $(CH_3)_3C$), 0.13 (s, 6H, CH_3Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (C1), 141.6 (C4), 110.6 (C5), 93.2 (C6), 81.4 (C7), 52.6 (C8), 52.0 (MeO), 33.6 (C3), 26.2 (C2), 25.9 ($(CH_3)_3C$), 18.7($(CH_3)_3C$), -4.8 (CH_3Si).

ESIMS *m/z* 305 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{15}H_{26}O_3SiNa$, $(M+H)^+$ 305.1563, found: 305.1544.

Methyl 3-((2*R,3*S**)-3-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)oxiran-2-yl)propanoate** (**198**)



198

m-Chloroperbenzoic acid, which was purified following the procedure descrbed by Perrin,[132] (743 mg, 4.2 mmol, 1.4 equiv) was added to a solution of the alkene **200** (846 mg, 3 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at rt for 14 h.[133] The reaction was quenched with saturated $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with Et_2O (3 x 75 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:8, EtOAc/petroleum spirit) to give the epoxide **198** (439 mg, 56% yield) as a colourless oil and the starting alkene (200 mg, 27%).

Rf = 0.58 (1:4, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2955, 2239, 1767, 1251, 1185, 1041.

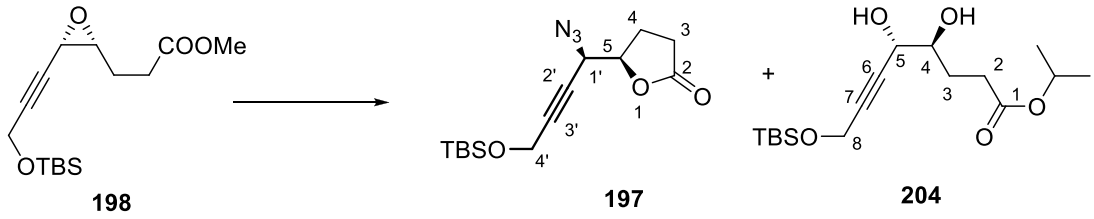
^1H NMR (500 MHz, $CDCl_3$) δ 4.34 (s, 2H, H8), 3.70 (s, 3H, MeO), 3.48 (d, *J* = 4.0 Hz, 1H, H5), 3.14 (ddd, *J* = 6.6, 5.5, 4.0 Hz, 1H, H4), 2.53 (t, *J* = 7.4 Hz, 2H, H2), 2.11 – 1.92 (m, 2H, H3), 0.90 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4 (C1), 85.0 (C7), 79.5 (C6) , 57.2 (C4), 52.1 (MeO), 52.0 (C8), 45.7 (C5), 30.7 (C2), 26.1 ($(CH_3)_3C$), 25.3 (C3), 18.6 ($(CH_3)_3C$), -4.9 (CH_3Si).

ESIMS *m/z* 321 $[(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{15}H_{26}O_4SiNa$, $(M+Na)^+$ 321.1498, found 321.1488

Azidolysis of epoxide 198



A solution of Me_3SiN_3 (243 mg, 2.11 mmol, 6 equiv) and Ti(O*i*-Pr)$_4$ (300 mg, 3 equiv) in toluene (5 mL) was stirred at 75-80 ºC for 2 h. The mixture then allowed to cool to rt and a solution of the epoxide **198** (105 mg, 0.35 mmol) in toluene (1 mL) was added. The reaction mixture was stirred at 40 ºC for 18 h. The solvent was removed *in vacuo* and the residue was dissolved into Et_2O (3 mL). To this solution, was added 5% H_2SO_4 solution (200 μL) and the mixture was stirred for 1 h at rt.[81] Water (10 mL) was added and the aqueous phase was extracted with EtOAc (4 x 20 mL). The organic extracts were combined, washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:4 to 1:1, EtOAc/petroleum spirit) to provide the azide **197** (43 mg, 40% yield) as a colourless oil and the diol **204** (31 mg, 19% yiled) as a colourless oil.

(*R)-5-((*R**)-1-Azido-4-(*tert*-butyldimethylsilyloxy)but-2-ynyl)dihydrofuran-2(3*H*)-one** (**197**)

Colourless oil.

R_f = 0.63 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2930, 2857, 2220, 2140, 1774, 1153, 1062, 814, 777.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (dt, *J* = 7.0, 6.0 Hz, 1H, H5), 4.41-4.37 (m, 1H, H1'), 4.39 (s, 1H, H4'), 2.67 (m, 1H, H3), 2.53 (m, 1H, H3), 2.35 (m, 1H, H4), 2.26 – 2.16 (m, 1H, H4), 0.91 (s, 9H, $(CH_3)_3C$), 0.12 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (C2), 88.9 (C3'), 79.6 (C5), 76.0 (C2'), 56.0 (C1'), 51.8 (C4'), 30.1 (C3), 26.0 ($(CH_3)_3C$), 23.7 (C4), 18.6 ($(CH_3)_3C$), -4.89 (CH_3Si) .

ESIMS *m/z* 310 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{14}H_{24}O_3N_3Si$, $(M+H)^+$ 310.1589, found: 310.1587.

(4*S,5*S**)-Isopropyl 8-(*tert*-butyldimethylsilyloxy)-4,5-dihydroxyoct-6-ynoate (**204**)**

Colourless oil.

R_f = 0.63 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3293, 2924, 2313, 1764, 1647, 1398, 1136, 1013.

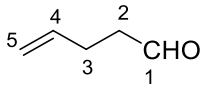
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 – 4.95 (m, 1H, CO_2CH), 4.34 (s, 2H, H8), 4.20 (d, *J* = 6.5 Hz, 1H, H5), 3.64 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H, H4), 2.53 – 2.40 (m, 2H, H2), 2.00 (dtd, *J* = 10.5, 7.5, 3.0 Hz, 1H, H3), 1.79 (qd, *J* = 14.5, 7.5 Hz, 1H, H4), 1.23 (d, *J* = 6.0 Hz, 6H, $(CH_3)_2CH$), 0.89 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (123 MHz, $CDCl_3$) δ 173.9 (C1), 85.5 (C7), 83.1 (C6), 74.5 (C4), 68.3 (CO_2CH), 66.5 (C5), 52.0 (C8), 31.4 (C2), 27.9 (C3), 26.1 ($(CH_3)_3C$), 22.1 ($(CH_3)_2CH$), 18.6 ($(CH_3)_3C$), -4.8 (CH_3Si).

ESIMS *m/z* 367 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{17}H_{32}O_5SiNa$, $(M+Na)^+$ 367.1918, found: 367.1917.

4-Penten-1-al

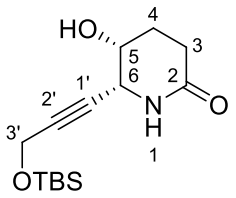


To a 100-mL flask were added PCC (1.9 g, 8.7 mmol) and dry CH_2Cl_2 (25 mL). 4-Penten-1-ol (0.5 g, 5.8 mmol) in CH_2Cl_2 (4 mL) was added dropwise to the PCC solution over 5 h. The mixture was stirred for an additional 2 h at room temperature. At that time the black mixture was diluted with ether (35 mL). The brown suspension was then filtered through Florisil. The black tar that remained in the flask was washed with ether (3 x 20 mL), the washings were filtered through Florisil, and the Florisil was washed with ether (35 mL). The ethereal solutions were combined, dried over $MgSO_4$, and filtered.[134] The solvent was carefully removed *in vacuo* to yield 4-penten-1-al (0.41 g, 44%) as a 21% solution in CH_2Cl_2 and Et_2O (yield and concentration was relatively determined by NMR analysis).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H, H1), 5.92 – 5.71 (m, 1H, H4), 5.09 – 5.03 (d, *J* = 17.0 Hz, 1H, H5), 5.02 (d, *J* = 10.5 Hz, 1H, H5), 2.53 (t, *J* = 7.5 Hz, 2H), 2.39 (q, *J* = 7.5 Hz, 2H).

NMR spectroscopic data matched with the published data.[135]

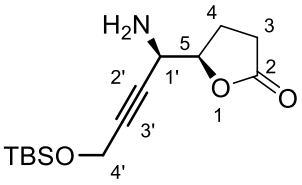
(5*R,6*R**)-6-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one** (**209**)



209

To a solution of the azide **197** (28 mg, 0.09 mmol) in anhydrous THF (1.5 mL) was added PPh_3 (26.2 mg, 0.1 mmol, 1.1 equiv) and the mixture was stirred at rt for 2 h. A solution of 5-pentenal (9.0 mg, 0.11 mmol, 1.2 equiv) in CH_2Cl_2 (0.5 mL) was then added and the mixture was allowed to stir at rt for 30 h. $NaBH_4$ (7 mg, 0.18 mmol, 2 equiv) and MeOH (200 µL) were then added sequentially. The mixture was stirred at rt for an additional 2 h.[85] The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a mixture of amine **207** and Ph_3PO, which was used in the next step without further purification.

(*R)-5-((*R**)-1-Amino-4-(*tert*-butyldimethylsilyloxy)but-2-ynyl)dihydrofuran-2(3H)-one** (**207**)



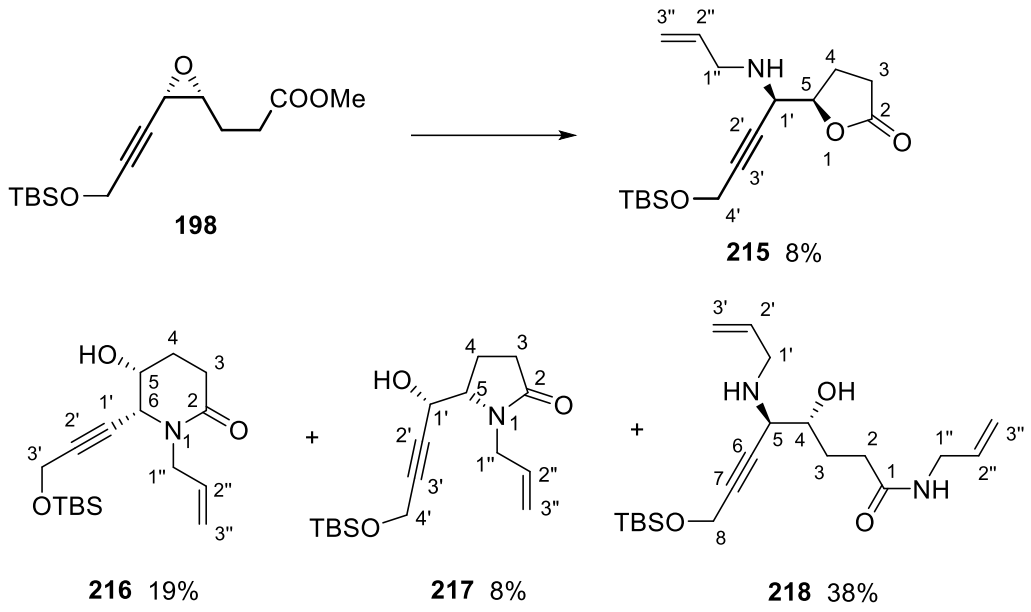
207

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (dd, *J* = 6.8, 6.8 Hz, 1H, H5), 4.32 (s, 2H, H4'), 3.78 (d, *J* = 6.8 Hz, 1H, H1'), 2.70 – 2.47 (m, 2H, H3), 2.42 – 2.29 (m, 1H, H4), 2.24 – 2.10 (m, 1H, H4), 0.91 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$).

To the above mixture of amine **207** and Ph_3PO were added MeOH (1 mL) and Et_3N (200 µL) and the reaction mixture was heated and stirred at reflux temperature for 14 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/MeOH) to provide the lactam **209** (21 mg, 81% yield from **197**) as a colourless oil.[136]

R_f = 0.59 (4:1, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 3242, 2927, 1638, 1329, 1250, 1195, 1060, 834, 776.
^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (bs, 1H, NH), 4.40 (s, 1H, H6), 4.36 (s, 2H, H3'), 4.12-3.07 (m, 1H, H5), 2.66 – 2.57 (m, 1H, H3), 2.38 – 2.29 (m, 1H, H3), 2.19 – 2.10 (m, 1H, H4), 1.93 – 1.85 (m, 1H, H4), 0.91 (s, 9H, $(CH_3)_3C$), 0.12 (s, 6H, $(CH_3)_2Si$).
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0 (C2), 86.3 (C2'), 80.3 (C1'), 65.4 (C5), 51.9 (C6), 51.1 (C3'), 27.1 (C3), 26.6 (C2), 26.2 ($(CH_3)C$), 18.6 ($(CH_3)_3C$), -4.82 (CH_3Si).
ESIMS *m/z* 284 [$(M+H)^+$ 100%]
HRESIMS calcd. for $C_{14}H_{26}O_3NSi$, $(M+H)^+$ 284.1682, found: 284.1678.

Aminolysis of epoxide 198 with allylamine



Lithium triflate (162 mg, 1 mmol, 1 equiv) and allylamine (114 mg, 2.0 mmol, 2.0 equiv) were added to a solution of the epoxide **198** (298 mg, 1 mmol) in CH_3CN (2 mL) in microwave reaction vial. The mixture was heated in a microwave reactor at

110 ºC and 200 W for 20 min.[87] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:3 to 100:0, EtOAc/petroleum spirit). Four compounds **215-218** were obtained.

(*R)-5-((*R**)-1-(Allylamino)-4-(*tert*-butyldimethylsilyloxy)but-2-ynyl)dihydrofuran-2(3*H*)-one** (**215**)

Colourless oil, 26 mg, 8% yield.

Rf = 0.55 (1:3, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3321, 2954, 2929, 1776, 1625, 1462, 1411, 1255, 1085, 814, 777.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 16.5, 10.0, 6.0 Hz, 1H, H2"), 5.20 (d, *J* = 17.0 Hz, 1H, H3"(*Z*)), 5.10 (d, *J* = 9.5 Hz, 1H, H3"(*E*)), 4.59 – 4.53 (m, 1H, H5), 4.31 (s, 2H, H4'), 3.58 (s, 1H, H1'), 3.48 (dd, *J* = 13.5, 4.5 Hz, 1H, H1"), 3.25 (dd, *J* = 13.5, 6.5 Hz, 1H, H1"), 2.65 – 2.57 (m, 1H, H3), 2.55 – 2.46 (m, 1H, H3), 2.36 – 2.28 (m, 1H, H4), 2.25 – 2.17 (m, 1H, H4), 0.89 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C1), 136.1 (C2"), 117.2 (C3"), 84.5 (C2'), 81.6 (C3'), 81.5 (C5), 53.7 (C1'), 52.0 (C4'), 50.3 (C1"), 28.6 (C3), 26.1 (C4), 24.5 ($(CH_3)_3C$), 18.6($(CH_3)_3C$), -4.9 (CH_3Si).

ESIMS *m/z* 346 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{17}H_{29}O_3NSiNa$, $(M+Na)^+$ 346.1814, found: 346.1818.

(5*R,6*R**)-1-Allyl-6-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxypiperidin-2-one** (**216**)

Colourless oil, 61 mg, 19% yield.

Rf = 0.65 (2:3, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3352, 2955, 2929, 1621, 1472, 1255, 1091, 1075, 834, 777.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H, H2"), 5.20 (d, *J* = 17.0 Hz, 1H, H3"), 5.14 (d, *J* = 10.5 Hz, 1H, H3"), 4.71 (dd, *J* = 15.0, 2.5 Hz, 1H, H1"), 4.41 – 4.32 (m, 3H, H6 and H3'), 4.02 – 3.96 (m, 1H, H5), 3.50 (dd, *J* = 15.0, 8.0 Hz, 1H, H1"), 2.61 (dt, *J* = 18.0, 5.0 Hz, 1H, H3), 2.43 (dt, *J* = 18.0, 9.0 Hz, 1H, H3), 2.14 – 2.08 (m, 1H, H4), 2.00 – 1.92 (m, 1H, H4), 0.91 (s, 9H, $(CH_3)_3C$), 0.12(s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (C2), 132.7 (C2''), 118.6 (C3''), 86.5 (C2'), 79.6 (C3'), 66.8 (C5), 54.1 (C4'), 51.9 (C1'), 47.9 (C1''), 29.6 (C3), 27.0 (C4), 26.1 ($CH_3)_3C$), (($CH_3)_3C$), -4.8 (CH_3Si).

ESIMS *m/z* 346 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{17}H_{29}O_3NSiNa$, $(M+Na)^+$ 346.1814, found 346.1811.

(5*S,6*S**)-5-(Allylamino)-6-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)tetrahydro-2H-pyran-2-one** (**217**)

Colourless oil, 26 mg, 8% yield.

Rf = 0.69 (1:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3312, 2928, 1689, 1635, 1452, 1418, 1260, 1128, 1074, 835.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.5, 10.5, 6.0 Hz, 1H, H2''), 5.22 (d, *J* = 17.5, 1H, H3''), 5.19 (d, *J* =10.5, 1H, H3'') 4.57 (d, *J* = 3.0 Hz, 1H, H1'), 4.36 – 4.28 (m, 3H, H4' and H1''), 3.82 – 3.76 (m, 2H, H1'' and H5), 2.61 – 2.52 (m, 1H, H3), 2.36 – 2.28 (m, 1H, H3), 2.19 – 2.07 (m, 2H, H4), 0.90 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0 (C2), 133.2 (C2''), 118.3 (C3''), 86.0 (C2'), 82.7 (C3'), 64.5 (C1'), 61.5 (C5), 51.9 (C4'), 44.8 (C1''), 30.4 (C3), 26.1 (($CH_3)_3C$), 21.2 (C4), 18.6(($CH_3)_3C$), -4.9 (CH_3Si).

ESIMS *m/z* 324 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{17}H_{30}O_3NSi$, $(M+H)^+$ 324.1995, found: 324.1985.

(4*R,5*R**)-*N*-Allyl-5-(allylamino)-8-(*tert*-butyldimethylsilyloxy)-4-hydroxyoct-6-ynamide** (**218**)

yellow solid, 144 mg, 38% yield.

Mp = 61-63 ºC

Rf = 0.58 (:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3267, 2930, 1633, 1550, 1250, 1093, 834, 777.

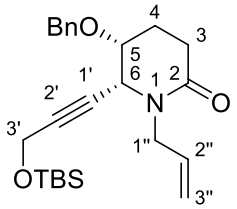
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (bs, 1H, NH amide), 5.93 – 5.78 (m, 2H, H2' and H2''), 5.26 – 5.09 (m, 4H, H3' and H3''), 4.33 (s, 2H, H8), 3.87 (t, *J* = 5.0 Hz, 2H, H1''), 3.58 – 3.45 (m, 2H, H1' and H4), 3.28 (dd, *J* = 13.5, 6.0 Hz, 1H, H1'), 3.19 (d, *J* = 8.5 Hz, 1H, H5), 2.48 – 2.36 (m, 2H, H3), 2.18 (dd, *J* = 13.0, 6.5 Hz, 1H, H2), 1.73 (td, *J* = 14.5, 6.5 Hz, 1H, H2), 0.90 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C1), 135.9 (C2''), 134.6 (C2'), 117.4 (C3''), 116.6 (C3'), 84.9 (C6), 82.7 (C7), 72.7 (C4), 55.4 (C5), 52.1 (C8), 50.0 (C1'), 42.3 (C1''), 33.4 (C2), 29.6 (C3), 26.1 ((CH_3)$_3$C), 18.6((CH_3)$_3$*C*), -4.8 (CH_3Si).
ESIMS *m/z* 381 [$(M+H)^+$ 100%].
HRESIMS calcd. for $C_{20}H_{37}O_3N_2Si$, $(M+H)^+$ 381.2581, found: 381.2573.

Preparation of lactam 216 from the amino-lactone 215

To solution of the amino-lactone **215** (24 mg, 0.07 mmol) in MeOH (1.0 mL) was added Et_3N (250 µL, 20% volume in MeOH) and the mixture was stirred at reflux temperature for 3 d.[136] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the lactam **216** (22 mg, 92% yield) as a pale yellow oil.

(5*R,6*R**)-1-Allyl-5-(benzyloxy)-6-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)piperidin-2-one** (**354**)



354

Silver oxide (97 mg, 0.42 mmol, 3 equiv) and BnBr (100 µL, 0.84 mmol, 6 equiv) were added to a solution of the alcohol **216** (45 mg, 0.14 mmol) in anhydrous Et_2O (5 mL) and the mixture was stirred at rt for 2 d in the dark. The mixture the filtered through a small pad of celite and the solid cake was washed with Et_2O (2 x 25 mL). The solvent was removed *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to provide compound **354** (19 mg, 32% yield) as a colourless oil.

R_f = 0.63 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2929, 1644, 1544, 1452, 1364, 1253, 1074, 919, 835, 734.

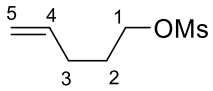
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H, ArH), 5.72 (ddt, *J* = 17.0, 10.0, 4.5 Hz, 1H, H2''), 5.20 (d, *J* = 17.0 Hz, 1H, H3''), 5.17 (d, *J* = 10.5 Hz, 1H, H3''), 4.76 – 4.69 (m, 1H, H1''), 4.66 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.59 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.40 (d, *J* = 4.4 Hz, 1H, H6), 4.38 (s, 2H, H3'), 3.72 (dt, *J* = 11.0, 4.0 Hz, 1H, H5), 3.49 (dd, *J* = 15.5, 8.0 Hz, 1H), 2.61 (ddd, *J* = 18.0, 7.0, 2.5 Hz, 1H, H3), 2.41 (ddd, *J* = 18.0, 10.5, 7.0 Hz, 1H, H3), 2.23 (qd, *J* = 11.0, 7.0 Hz, 1H, H4), 2.03 – 1.96 (m, 1H, H4), 0.92 (s, 9H, $(CH_3)_3C$), 0.13 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8 (C2), 137.9 (C2''), 132.7 (ArC), 128.8 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 118.5 (C3''), 84.9 (C6'), 80.1 (C7'), 73.6 (C5), 71.4 (CH_2-Ar), 52.1 (C3'), 51.1 (C6), 47.9 (C1''), 29.9 (C3), 26.10 ($(CH_3)_3C$), 24.4 (C4), 18.6 ($(CH_3)_3C$), -4.79 (CH_3Si).

ESIMS *m/z* 414 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{24}H_{36}O_3NSi$, $(M+H)^+$ 414.2464, found: 414.2482.

Pent-4-enyl methanesulfonate (**220**)[90]



220

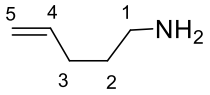
Mesyl chloride (6.7 mL, 87 mmol, 1.5 equiv) was added dropwise to a solution of 4-pentene-1-ol (5.0 g, 58 mmol) and Et_3N (12.2 mL, 87 mmol, 1.5 equiv) in CH_2Cl_2 (100 mL) in a period of 30 min at 0 ^{0}C under a N_2 atmosphere.[90] The mixture then allowed to warm to rt and stir for 14 h. CH_2Cl_2 (100 mL) was added and the mixture was washed with saturated $NaHCO_3$ solution (2 x 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent then was evaporated *in vacuo* to give the crude mesylate product **220** (9.24 g, 99% yield) as a pale yellow oil which was used for the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, H4), 5.08 (d, *J* = 17.0 Hz, 1H, H5), 5.04 (d, *J* = 10.5 Hz, 1H, H5), 4.23 (t, *J* = 6.0 Hz, 2H, H1), 3.00 (s, 3H, Me), 2.19 (q, *J* = 7.0 Hz, 2H, H3), 1.86 (p, *J* = 6.5 Hz, 2H, H2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9 (C4), 116.3 (C5), 69.6 (C1), 37.6 (Me), 29.7 (C3), 28.5 (C2).

NMR spectroscopic data matched with the published data.[90]

Pent-4-en-1-amine (**152**)[90]



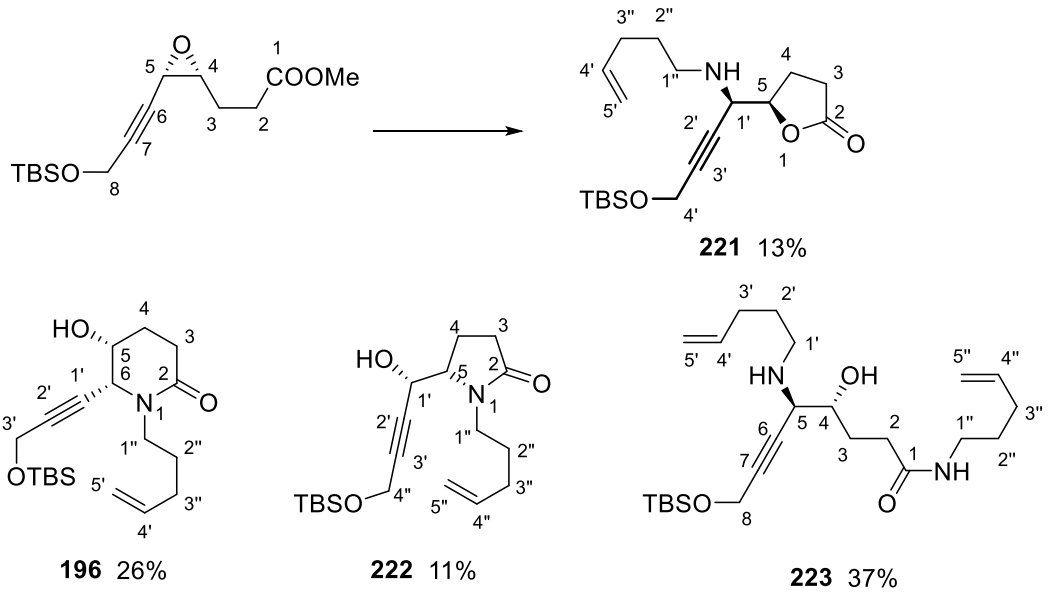
152

To a solution of the mesylate **220** (9.15 g, 55.8 mmol) in MeOH (100 mL) was added 28% NH_3 solution (150 mL) and the mixture was stirred at rt for 2 days.[89] The mixture then was extracted with CH_2Cl_2 (3x 100 mL). The organic layers were combined, dried over $MgSO_4$ and filtered. The solvent was carefully evaporated under reduced pressure (40 ^{0}C, 500 mbar) to afford 7.86 g of 41% solution of amine **152** (68% yield) in CH_2Cl_2 (yield and concentration were determined by NMR) as a pale yellow solution.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4), 4.96 (d, *J* = 17.0 Hz, 1H, H5), 4.90 (d, *J* = 10.0 Hz, 1H, H5), 2.64 (t, *J* = 7.0 Hz, 1H, H1), 2.07 – 2.00 (m, 2H, H3), 1.52 – 1.44 (m, 2H, H2).

^{1}H NMR spectroscopic data matched with the published data.[90]

Aminolysis of epoxide 198 with amine 152[87]



Lithium triflate (162 mg, 1 mmol, 1 equiv) and 4-penten-1-amine (170 mg, 2 mmol, 2 equiv) were added to a solution of epoxide **198** (298 mg, 1 mmol) in CH_3CN (2 mL) in a microwave reaction vial. The mixture was heated in a microwave reactor at 110 ºC, 200 W for 1 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:3 to 100:0, EtOAc/petroleum spirit). Four compounds **196** and **221**-**223** were obtained.

(*R)-5-((*R**)-4-(*tert*-Butyldimethylsilyloxy)-1-(pent-4-enylamino)but-2-ynyl)dihydrofuran-2(3*H*)-one** (**221**)

Colourless oil, 46 mg, 13% yield.

Rf = 0.58 (1:4, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3330, 2929, 1765, 1657, 1461, 1253, 1080, 814, 777.

^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 5.00 (d, *J* = 17.0 Hz, 1H, H5"), 4.94 (d, *J* = 10.0 Hz, 1H, H5"), 4.54 (dd, *J* = 12.5, 4.5 Hz, 1H, H5), 4.31 (s, 2H, H4'), 3.53 (d, *J* = 4.5 Hz, 1H, H1'), 2.88 (dt, *J* = 11.5, 7.0 Hz, 1H, H1"), 2.65 – 2.55 (m, 2H, H1" and H3), 2.51 (dt, *J* = 18.0, 9.0 Hz, 1H, H3), 2.36 – 2.27 (m, 1H, H4), 2.24 – 2.14 (m, 1H, H4), 2.09 (q, *J* = 7.0 Hz, 2H, H3"), 1.59 – 1.53 (m, 2H, H2"), 0.89 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1 (C2), 138.5 (C4"), 115.1 (C5"), 84.3 (C2'), 81.9 (C3'), 81.5 (C5), 54.7 (C1'), 52.0 (C4'), 47.5 (C1"), 31.7 (C3"), 29.4 (C2"), 28.7 (C3), 26.1 ((CH$_3$)$_3$C), 24.6 (C4), 18.6 ((CH$_3$)$_3$$C$), -4.8 ($CH_3Si$).

ESIMS *m/z* 374 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{33}O_3NNaSi$, $(M+H)^+$ 374.3127, found: 374.3137.

(5*R,6*R**)-6-(3-(*tert*-Butyldimethylsilyloxy)prop-1-ynyl)-5-hydroxy-1-(pent-4-enyl)piperidin-2-one** (**196**)

Colourless oil, 92 mg, 26% yield.

Rf = 0.58 (1:4, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3250, 2928, 2857, 2310, 1635, 1471, 1251, 834

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 5.02 (d, *J* = 17.0, 1H, H5"), 4.96 (d, *J* = 10.0 Hz, 1H, H5"), 4.35 (s, 2H, H3'), 4.32 (d, *J* = 4.5 Hz, 1H, H6), 3.99 (dt, *J* = 10.0, 4.5 Hz, 1H, H5), 3.77 (dt, *J* = 14.0, 8.0 Hz, 1H, H1"), 3.13 – 3.06 (m, 1H, H1"), 2.56 (ddd, *J* = 18.0, 6.5, 4.0 Hz, 1H, H3), 2.43 – 2.34 (ddd, *J* = 18.0, 10.0, 7.5 Hz, 1H, H3), 2.12 – 2.04 (m, 3H, H3" and H4), 1.97 – 1.90 (m, 1H, H4), 1.70 – 1.62 (m, 2H, H2"), 0.89 (s, 9H, (CH$_3$)$_3$C), 0.10 (s, 6H, (CH$_3$)$_2$Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9 (C2), 138.1 (C4"), 115.6 (C5"), 86.1 (C3'), 80.0 (C2'), 66.9 (C5), 55.2 (C6), 51.9 (C3'), 46.1 (C1"), 31.4 (C3"), 29.6 (C3), 27.1 (C4), 26.8 (C2"), 26.1 ((CH$_3$)$_3$C), 18.6 ((CH$_3$)$_3$$C$), -4.9 ($CH_3Si$).

ESIMS *m/z* 374 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{33}O_3NNaSi$, $(M+H)^+$ 374.3127, found: 374.3127.

(*S)-5-((*S**)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxybut-2-ynyl)-1-(pent-4-enyl)pyrrolidin-2-one** (**222**)

Colourless oil, 39 mg, 11% yield.

Rf = 0.58 (1:4, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3317, 2926, 1668, 1458, 1252, 1080, 1006, 998, 777.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 5.02 (d, *J* = 17.0 Hz, 1H, H5"), 4.97 (d, *J* = 10.0 Hz, 1H, H5"), 4.56 (d, *J* = 3.0 Hz, 1H, H1'), 4.31 (s, 2H, H4'), 3.80 – 3.64 (m, 1H, H5), 3.66 (ddd, *J* = 14.0, 9.0, 8.0 Hz, 1H, H1"), 3.15 (ddd, *J* = 14.0, 9.0, 5.5 Hz, 1H, H1"), 2.57 – 2.48 (m, 1H, H3), 2.34 – 2.25 (m,

1H, H3), 2.18 – 2.00 (m, 4H, H2" and H3"), 1.75 – 1.69 (m, H4), 1.64 – 1.60 (m, 1H, H4), 0.90 (s, 9H, $(CH_3)_3C$), 0.10 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1 (C2), 138.0 (C4"), 115.5 (C5"), 86.0 (C3'), 82.6 (C2'), 64.6 (C1'), 61.7 (C5), 51.9 (C4'), 41.8 (C1"), 31.4 (C3"), 30.5 (C3), 26.9 (C4), 26.1 ($(CH_3)_3C$), 21.2 (C2"), 18.6 ($(CH_3)_3C$), -4.9 (CH_3Si).

ESIMS *m/z* 374 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{33}O_3NNaSi$, $(M+H)^+$ 374.3127, found: 374.3115.

(4*R,5*R**)-8-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-*N*-(pent-4-enyl)-5-(pent-4-enylamino)oct-6-ynamide** (**223**)

Yellow solid, 161 mg, 37% yield.

Mp = 79-81 ºC

Rf = 0.58 (1:4, EtOAc/Petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3401, 2952, 2931, 1460, 1562, 1249, 1168, 1030, 835,

^1H NMR (500 MHz, $CDCl_3$) δ 6.63 (bs, 1H, NH amide), 5.82 – 5.72 (m, 2H, H4' and H4"), 5.00 (d, *J* = 17.0 Hz, 2H, H5' and H5"), 4.95 (d, *J* = 10.0 Hz, 2H, H5' and H5"), 4.31 (s, 2H, H8), 3.58 – 3.53 (m, 1H, H4), 3.25 (d, *J* = 9.0 Hz, 1H, H5), 3.20 (dd, *J* = 13.0, 6.5 Hz, 2H, H1'), 2.91 – 2.84 (m, 1H, H1"), 2.64 – 2.56 (m, 1H, H1"), 2.46 – 2.35 (m, 2H, H2), 2.14 – 2.02 (m, 5H, H3', H3" and H3), 1.75 (td, *J* = 14.5, 7.0 Hz, 1H, H3), 1.66 – 1.54 (m 4H, H2' and H2"), 0.89 (s, 9H, $(CH_3)_3C$), 0.09 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (C1), 138.2 (C4'), 138.0 (C4"), 115.4 (C5'),115.3 (C5"), 85.4 (C7), 81.9 (C6), 73.3 (C4), 55.8 (C5), 52.0 (C8), 46.9 (C1'), 39.7 (C1"), 32.9 (C2), 31.6 (C3'), 31.3 (C3"), 29.3 (C3), 28.7 (C2'), 28.6 (C2"), 26.1 ($(CH_3)_3C$), 18.6 ($(CH_3)_3C$), -4.9 (C-Si).

ESIMS *m/z* 437 [$(M+H)^+$ 100%].

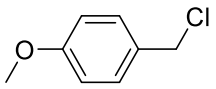
HRESIMS calcd. for $C_{24}H_{45}O_3N_2Si$, $(M+H)^+$ 437.3183, found: 437.3199.

Preparation of lactam 196 from the amino-lactone 221

To solution of the amino-lactone **221** (43 mg, 0.13 mmol) in MeOH (1.5 mL) was added Et_3N (337 μL, 25% volume in MeOH) and the mixture was stirred at reflux temperature for 3 d.[136] The solvent was evaporated *in vacuo* and the residue was

purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the lactam **196** (41 mg, 96% yield) as a pale yellow oil.

4-Methoxybenzyl chloride (**233**)[91]

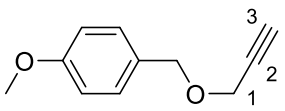


233

Thionylchloride (10.53 mL, 144.52 mmol, 2 equiv) was carefully added to a solution of 4-methoxybenzylalcohol (9.0 mL, 72.26 mmol, 1 equiv) in anhydrous diethyl ether (144 mL; 2 mL/mmol) and stirred for 5 h.[91] The reaction mixture was quenched with water (144 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic phases were washed with water (2 x 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. 4-Methoxybenzylchloride **233** (11.08 g, 98% yield) was obtained as a light yellow oil and used without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): 7.29 (d, *J* = 7.5 Hz, 2H, ArH), 6.86 (d, *J* = 7.5 Hz, 2H, ArH), 4.56 (s, 2H, CH_2Ar), 3.79 (s, 3H, OMe).
^{13}C NMR ($CDCl_3$, 125 MHz): 160.0 (ArC), 130.4 (ArCH), 130.0 (ArC), 114.5 (ArCH), 55.3 (OCH_3), 46.3 (CH_2Ar).
NMR spectroscopic data matched with the published data.[91]

1-(4-Methoxybenzyloxy)-2-propyne (**230**)[137]



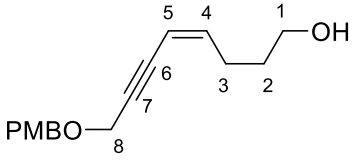
230

To a solution of propargyl alcohol (1.50 mL, 25.8 mmol) in anhydrous THF (70 mL) was added NaH (1.86 g, 60 wt% in oil, 46.4 mmol, 1.8 equiv) portionwise at 0 ºC and the mixture was stirred for 15 min. Then *p*-methoxybenzyl chloride **233** (5.20

mL, 38.7 mmol, 1.5 equiv) and TBAI (1.24 g, 3.35 mmol, 0.13 equiv) were added at 0 ºC.[130] The reaction mixture was warmed to rt and stirred for 16 h. Then the mixture was cooled to 0 ºC and diluted with Et_2O (50 mL) and saturated aqueous NH_4Cl solution (50 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography (1:9, Et_2O/petroleum spirit) to give the alkyne **230** (3.33 g, 74% yield) as a colorless oil.

Rf = 0.65(1:4, Et_2O/petroleum spirit).
^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 2H, ArH), 6.92 (d, *J* = 8.5 Hz, 2H, ArH), 4.58 (s, 2H, CH_2Ar), 4.17 (d, *J* = 2.5 Hz, 2H, H1), 3.84 (s, 3H, OMe), 2.49 (t, *J* = 2.5 Hz, 1H, H3).
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (ArC), 130.1 (ArCH), 129.7 (ArC), 114.2 (ArCH), 80.1 (CH_2Ar), 74.8 (C3), 71.5 (C2), 57.0 (C1), 55.6 (OMe).
NMR spectroscopic data matched with the published data.[137]

(*Z*)-8-(4-Methoxybenzyloxy)oct-4-en-6-yn-1-ol (**231**)



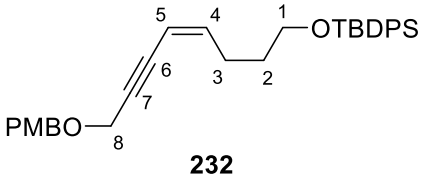
231

To a solution of the vinyl iodide **187** (1.484 g, 7 mmol) in Et_3N (50 mL), were added $PdCl_2(PPh_3)_2$ (112 mg, 0.154 mmol, 0.02 equiv) and CuI (267 mg, 1.54 mmol, 0.2 equiv) under a nitrogen atmosphere.[69] The mixture was stirred for 15 min then a solution of alkyne **230** (1.48 g, 8.4 mmol, 1.2 equiv) in THF (25 mL) was added dropwise over period of 30 min. After being stirred for 14 h, the mixture was diluted with Et_2O (150 mL) and washed with saturated NH_4Cl solution (2x 50 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:7,

EtOAc/petroleum spirit) to give the ene-yne **231** (1.438 g, 79% yield) as a colourless oil.

Rf = 0.61 (1:1, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 3412, 2937, 1713, 1608, 1512, 1246, 1173, 1029, 818.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 5.97 (dt, *J* = 10.5, 7.5 Hz, 1H, H4), 5.57 (d, *J* = 10.5 Hz, 1H, H5), 4.56 (s, 2H, OCH_2Ar), 4.30 (s, 2H, H8), 3.82 (s, 3H, OMe), 3.67 (t, *J* = 6.5 Hz, 2H, H1), 2.44 (q, *J* = 7.5 Hz, 2H, H3), 1.73 – 1.67 (m, 2H, H2).
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7 (ArC), 143.9 (C4), 130.1 (ArCH), 129.8 (ArC), 114.2 (ArCH), 109.7 (C5), 90.0 (C7), 83.4 (C6), 71.5 (OCH_2Ar), 62.4 (C1), 57.9 (C8), 55.6 (OMe), 31.9 (C2), 26.9 (C3).
ESIMS *m/z* 283 [$(M+Na)^+$ 100%].
HRESIMS calcd. for $C_{16}H_{20}O_3Na$, $(M+Na)^+$ 283.1316, found 283.1316.

(*Z*)-*tert*-Butyl(8-(4-methoxybenzyloxy)oct-4-en-6-ynyloxy)diphenylsilane (**232**)



232

Imidazole (1.087 g, 15.83 mmol, 2.5 equiv) and TBDPSCl (1.98 mL, 7.59 mmol, 1.2 equiv) were added to a solution of alcohol **231** (1.645 g, 6.33 mmol) in DMF (30 mL) at rt under a N_2 atmosphere and the mixture was stirred under the same conditions for 6 h.[63] The reaction mixture then was poured into a beaker containing water (60 mL) and then extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with water (2 x 100 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, EtOAc/petroleum spirit) to give the TBS ether **232** (2.554 g, 81% yield) as a colourless oil.

Rf = 0.63 (1:4, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 2931, 2856, 1513, 1426, 1248, 1107, 821, 739.

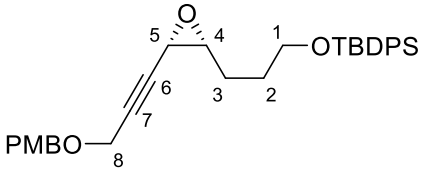
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.63 (m, 4H, ArH), 7.46 – 7.33 (m, 6H, ArH), 7.26 (d, *J* = 8.3 Hz, 2H, ArH), 6.86 (d, *J* = 8.3 Hz, 2H, ArH), 5.92 (dt, *J* = 10.7, 7.4 Hz, 1H, H4), 5.50 (d, *J* = 10.7 Hz, 1H, H5), 4.52 (s, 2H, CH_2Ph), 4.26 (s, 2H, H8), 3.79 (s, 3H, OMe), 3.69 (t, *J* = 6.3 Hz, 2H, H1), 2.45 – 2.41 (m, 2H, H3), 1.72 – 1.64 (m, 2H, H2), 1.04 (s, 9H, $(CH_3)_3C$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7 (Ar), 144.4 (C4), 135.9 (Ar), 134.3 (Ar), 130.2 (Ar), 130.1 (Ar), 130.0 (Ar), 129.9 (Ar), 128.0 (Ar), 127.9 (Ar), 109.1 (C5), 89.8 (C7), 83.5 (C6), 71.4 (CH_2Ar), 63.7 (C1), 57.9 (C8), 55.6 (OMe), 32.2 (C2), 27.3 (C3), 27.2 ((CH_3)$_3$C), 19.6 ((CH$_3$)$_3$*C*).

ESIMS *m/z* 521 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{32}H_{38}O_3SiNa$, $(M+Na)^+$ 521.2488, found 521.2478.

***tert*-Butyl(3-((2*R**,3*S**)-3-(3-(4-methoxybenzyloxy)prop-1-ynyl)oxiran-2-yl)propoxy)diphenylsilane** (**234**)



234

Purified *m*-chloroperbenzoic acid (1.283 g, 7.44 mmol, 1.3 equiv) was added to solution of the alkene **232** (2.85 g, 5.72 mmol) in CH_2Cl_2 (100 mL) and the mixture was stirred at rt for 14 h.[133] The reaction was quenched with saturated $NaHCO_3$ (60 mL) and the aqueous phase was extracted with Et_2O (3x 100 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered through a short column loaded with Al_2O_3. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:8, EtOAc/petroleum spirit) to give the epoxide **234** (2.44 g, 64% yield) as a colourless oil and the starting alkene (684 mg, 24% yield).

R_f = 0.60 (1:3, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3282, 2957, 2308, 1428, 1107, 818, 668.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72-7.64 (m, 4H, ArH), 7.43 – 7.34 (m, 6H, ArH), 7.24 (d, *J* = 8.4 Hz, 2H, ArH), 6.86 (d, *J* = 8.4 Hz, 2H, ArH), 4.49 (s, 2H, CH_2Ph), 4.14 (s, 2H, H8), 3.79 (s, 3H, OMe), 3.73 (t, *J* = 5.6 Hz, 2H, H1), 3.50 (d, *J* = 3.5 Hz,

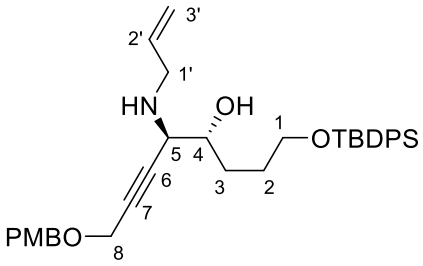
1H, H5), 3.09 (dd, *J* = 6.0, 3.5 Hz, 1H, H4), 1.86 – 1.75 (m, 4H, H2 and H3), 1.04 (s, 9H, $(CH_3)_3C$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (Ar), 135.9 (Ar), 135.1 (Ar), 134.2 (Ar), 130.1 (Ar), 130.0 (Ar), 129.9 (Ar), 129.6 (Ar), 128.1 (Ar), 128.0 (Ar), 114.2 (Ar), 82.0 (C6), 81.8 (C7), 71.6 (CH_2Ar), 63.8 (C1), 58.3 (C4), 57.3 (C8), 55.6 (OMe), 45.6 (C5), 29.3 (C3), 27.2 (($CH_3)_3C$) 26.9 (C2), 19.6 (($CH_3)_3C$).

ESIMS *m/z* 537 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{32}H_{38}O_4SiNa$, $(M+Na)^+$ 537.2439, found: 537.2437.

(4*R,5*R**)-5-(Allylamino)-1-(*tert*-butyldiphenylsilyloxy)-8-(4-methoxybenzyloxy)oct-6-yn-4-ol** (**235**)



235

Lithium triflate (162 mg, 1 mmol, 1 equiv) and allylamine (171 mg, 3 mmol, 3 equiv) were added to solution of the epoxide **234** (514 mg, 1 mmol) in CH_3CN (2 mL) in a microwave reactor vial. The mixture was heated in a microwave reactor at 110 ºC, 200 W for 1.5 h.[87] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:7, EtOAc/petroleum spirit) to give the amine **235** (411 mg, 72% yield) as a pale yellow oil.

R_f = 0.62 (1:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3332, 2930, 1611, 1513, 1248, 1103, 1035, 821, 701.

^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H, ArH), 7.43-7.33 (m, 6H, ArH), 7.25 (d, *J* = 8.0 Hz, 2H, ArH), 6.86 (d, *J* = 8.0 Hz, 2H, ArH), 5.95-5.85 (m, 1H, H2'), 5.23 (d, *J* = 17.0 Hz, 1H, H3'), 5.12 (d, *J* = 10.5 Hz, 1H, H3'), 4.50 (s, 2H, CH_2Ph), 4.15 (s, 2H, H8), 3.79 (s, 3H, OMe), 3.74-3.69 (m, 2H, H1), 3.53-3.45 (m, 2H, H4 and H1'), 3.29 (dd, *J* = 13.5, 6.0 Hz, 1H, H1'), 3.19 (d, *J* = 8.5 Hz, 1H, H5), 2.00 – 1.92

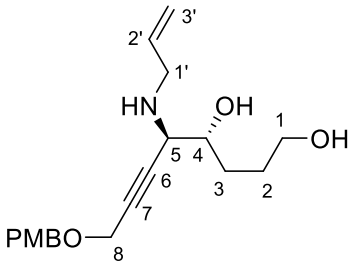
(m, 1H, H3), 1.87 – 1.77 (m, 1H, H2), 1.75 – 1.66 (m, 1H, H2) 1.57 – 1.46 (m, 1H, H3), 1.04 (s, 9H, $(CH_3)_3C$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8 (Ar), 136.5 (Ar), 135.9 (C2'), 134.3 (Ar), 130.1 (Ar), 129.9 (Ar), 129.8 (Ar). 128.0 (Ar), 116.9 (Ar), 114.2 (C3'), 85.4 (C6), 81.6 (C7), 73.1 (C4), 71.6 (CH_2-Ar) , 64.3 (C1), 57.5 (C8), 55.6 (OMe), 55.5 (C5), 50.1 (C1'), 30.5 (C3), 29.0 (C2), 27.2 ((*C*H_3)C) , 19.6 ((CH_3)$_3$*C*).

ESIMS *m/z* 572 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{35}H_{46}O_4NSiNa$, $(M+Na)^+$ 572.3224, found: 572.3196.

(4*R,5*R**)-5-(Allylamino)-8-(4-methoxybenzyloxy)oct-6-yne-1,4-diol** (**236**)



236

1M tetrabutylamonium fluoride (TBAF) solution in THF (1.8 mL, 1.8 mmol, 1.5 equiv) was added dropwise to a solution of the TBDPS ether **235** (685 mg, 1.2 mmol) in THF (15 mL) at 0 ^{0}C and the mixture was warmed to rt and stirred for 4 h.[138] Saturated $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with EtOAc (3x30 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (9:1 to 100:0, EtOAc/petroleum spirit) to give the diol **236** (352 mg, 88% yield) as a colourless oil.

R_f = 0.68 (1:9, MeOH/EtOAc).

IR (neat, ν_{max}/cm^{-1}): 3355, 2930, 2852, 1611, 1513, 1453, 1248, 1062, 1031, 818.

^1H NMR (500 MHz, $CDCl_3$,) δ 7.27 (d, *J* = 8.5 Hz, 2H, ArH), 6.89 (d, *J* = 8.5 Hz, 2H, ArH), 5.89 (ddt, *J* = 17.0, 10.5. 5.5 Hz 1H, H2'), 5.23 (d, *J* = 17.0, Hz, 1H, H3'), 5.13 (d, *J* = 10.5 Hz, 1H, H3'), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H8), 3.81 (s, 3H, OMe), 3.73-3.63 (m, 2H, H1), 3.55 – 3.44 (m, 2H, H4 and H1')), 3.28 (dd, *J* = 14.0,

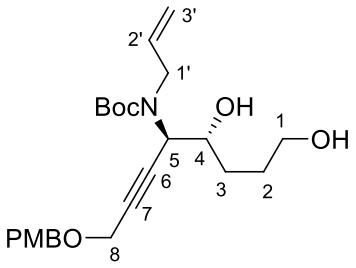
6.5 Hz, 1H, H1'), 3.20 (d, *J* = 9.0 Hz, 1H, H5), 2.02-1.95 (m, 1H, H3), 1.79 – 1.73 (m, 2H, H2), 1.58 – 1.49 (m, 1H, H3).

^{13}C NMR (125 MHz, $CDCl_3$,) δ 159.8 (ArC), 136.2 (C2'), 130.0 (ArCH), 129.6 (ArC) , 117.1 (C3'), 114.2 (ArCH), 85.1 (C6), 81.8 (C7), 73.1 (C4), 71.6 (OCH_2Ar), 63.2 (C1), 57.4 (C8), 55.6 (OMe), 55.3 (C5), 50.0 (C1'), 31.1 (C3), 29.6 (C2).

ESIMS *m/z* 334 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{28}O_4N$, $(M+H)^+$ 334.2018, found: 334.2010.

***tert*-Butyl allyl((4*R*,5*R*)-5,8-dihydroxy-1-(4-methoxybenzyloxy)oct-2-yn-4-yl)carbamate** (**241**)



236

To a solution of the amine **236** (165 mg, 0.5 mmol) and Et_3N (85 μL, 0.6 mmol, 1.2 eq) in CH_2Cl_2 (4 mL) was added a solution of $(Boc)_2O$ (116 mg, 0.53 mmol, 1.05 eq) in CH_2Cl_2 (1 mL) dropwise at rt. The reaction mixture was stirred at rt for 18 h and quenched with saturated aqueous $NaHCO_3$ solution (10 mL).[95] The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography (1:1, EtOAc/petroleum spirit) to give the Boc-diol **241** (190 mg, 88% yield) as a colourless oil.

R_f = 0.63 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3413, 2920, 1667, 1513, 1455, 1398, 1248, 1141, 1066, 1032, 819.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.2 Hz, 2H, ArH), 6.88 (d, *J* = 8.2 Hz, 2H, ArH), 6.01 – 5.87 (m, 1H, H2'), 5.22 (d, *J* = 17.0 Hz, 1H, H3'), 5.14 (d, *J* = 10.0 Hz, 1H, H3'), 4.51 (s, 2H, OCH_2Ph), 4.16 (s, 2H, H8), 4.02-3.95 (bm, 1H, H1'), 3.86

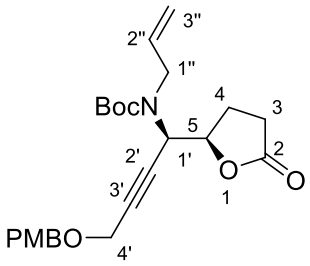
(dd, *J* = 16.0, 6.5 Hz, 1H, H1'), 3.81 (s, 3H, OMe), 3.76-3.65 (m, 4H, H1, H4 and H5), 1.95 (dt, *J* = 6.5, 6.0 Hz, 1H, H3), 1.80-1.72 (m, 2H, H2), 1.55 (m, 1H, H3), 1.46 (s, 9H, $(CH_3)_3C$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (ArC), 156.6 (b, C=O), 135.6 (C2'), 130.1 (ArCH), 129.6 (ArC), 117.0 (C3'), 114.2 (ArCH), 82.6 (C7), 81.3 (C6), 73.2 (b, C4), 71.7 (OCH_2Ar), 63.1 (C1), 57.3 (C8), 55.6 (OMe), 54.6 (b, C5), 48.1 (b, C1'), 31.3 (C3), 29.4 (C2), 28.7 ($(CH_3)_3C$), [$(CH_3)_3CO$) not observed].

ESIMS *m/z* 456 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{24}H_{35}O_6NNa$, $(M+Na)^+$ 456.2362, found: 456.2340.

tert-Butyl allyl((*R)-4-(4-methoxybenzyloxy)-1-((*R**)-5-oxotetrahydrofuran-2-yl)but-2-ynyl)carbamate** (**242**)



242

To a solution of the Boc-diol **241** (170 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (3 mL) were added TEMPO (13 mg, 0.078 mmol, 0.2 equiv) and BAIB (506 mg, 1.57 mmol, 4equiv) at rt and the mixture was stirred at rt for 18 h.[93] The reaction mixture was quenched by 0.1 M $Na_2S_2O_3$ solution (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the Boc-lactone **242** (141 mg, 84% yield) as a colourless oil.

R_f = 0.68 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2953, 1754, 1680, 1513, 1366, 1248, 1140, 1062, 1033.

^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5, 2H, ArH), 6.90 (d, *J* = 8.5, 2H, ArH),

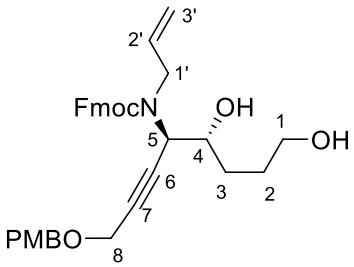
5.93-5.83 (bm, 1H, H2''), 5.22-5.10 (bm, 2H, H3'), 4.69-4.63 (bm, 1H, H5), 4.52 (s, 2H, OCH_2Ar), 4.18 (s, 2H, H4'), 4.03-3.87 (bm, 3H, H1'' and H1'), 3.82 (s, 3H, OMe), 2.61-2.49 (m, 2H, H3), 2.40-2.32 (m, 1H, H4), 2.18-2.10 (m, 1H, H4), 1.47 (s, 9H, $(CH_3)_3C$).

^{13}C NMR (125 MHz, $CDCl_3$) 176.1 (C2), 159.5 (ArC), 155.8 (b, C2''), 135.0 (ArCH), 129.7 (ArC), 116.3 (C3''), 113.9 (ArCH), 83.5 (b, $OC(CH_3)_3$), 81.4 (b, C3'), 81.0 (b, C2'), 79.8 (b, C5), 71.4 (b, OCH_2Ar), 56.9 (C4'), 56.3 (OMe), 51.8 (b, C1'), 48.1 (b, C1''), 28.3 ($(CH_3)_3C$), 28.0 (C3), 24.8 (C4).

ESIMS *m/z* 452 $[(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{24}H_{31}O_6NNa$, $(M+Na)^+$ 452.2049, found: 452.2037.

(9*H*)-Fluoren-9-yl)methyl allyl((4*R,5*R**)-5,8-dihydroxy-1-(4-methoxybenzyloxy) oct-2-yn-4-yl)carbamate** (**247**)



247

To a solution of the amine **236** (333 mg, 1 mmol) in THF (10 mL) was added a saturated solution of Na_2CO_3 (5 mL) and the mixture was allowed to cool to 0 ^{0}C. FmocCl (1.1 mmol, 1.1 equiv) was added portionwise at 0 ^{0}C and the reaction mixture was stirred at the same temperature for 4 h.[95] The organic phase was removed *in vacuo* and the aqueous layer was extracted with EtOAc (3 x 30 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give te Fmoc-diol **247** (539 mg 97% yield) as an waxy solid.

R_f = 0.60 (9:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3384, 2928, 1687, 1512, 1477, 1451, 1410, 1248, 1031, 741.

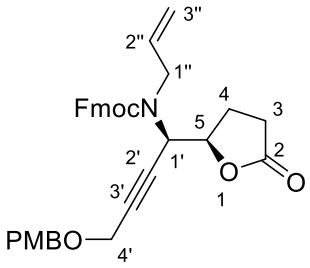
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H, ArH), 7.63 (d, *J* = 8.5 Hz, 2H, ArH), 7.43 (t, *J* = 8.5 Hz, 2H, ArH), 7.34 (t, *J* = 8.5 Hz, 2H, ArH), 7.28 (d, *J* = 9.0 Hz, 2H, ArH), 6.91 (d, *J* = 9.0 Hz, 2H, ArH), 5.80-5.73 (bm, 1H, H2'), 5.15-5.04 (bm, 2H, H3'), 4.62-4.57 (bm, 1H, FmocCH_2O), 4.52 (s, 2H, OCH_2Ar), 4.23 (t, *J* = 6.0 Hz. 1H, FmocCH), 4.19-4.16 (bm, 1H, H1'), 4.17 (s, 2H, H8), 3.90-3.86 (m, 1H, H1'), 3.83 (s, 3H, OMe), 3.72-3.67 (bm, 3H, H1 and H4), 1.92-1.86 (bm, 2H, H3), 1.79-1.71 (bm, 2H, H2), 1.60-1.52 (bm, 1H, H2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (ArC), 144.2 (ArC), 141.7 (ArC), 134.9 (C3'), 130.1 (ArC), 129.5 (ArC), 128.0 (ArC), 127.4 (ArC), 125.2 (ArC), 120.3 (ArC), 115.2 (C5''), 114.1 (ArC), 82.8 (C7), 82.3 (C6), 73.2 (b, C4), 71.7 (OCH_2Ph), 67.2 (FmocCH_2O), 63.1 (C1), 57.3 (C8), 55.6 (OMe), 55.0 (C5), 47.9 (C1''), 47.6 (FmocCH), 45.6 (C1''), 31.2 (C3), 29.2 (C2).

ESIMS *m/z* 578 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{34}H_{37}O_6NNa$, $(M+Na)^+$ 578.2526, found: 578.2519.

(9*H*)-Fluoren-9-yl)methyl allyl((*R)-4-(4-methoxybenzyloxy)-1-((*R**)-5-oxotetrahydrofuran-2-yl)but-2-ynyl)carbamate** (**248**)



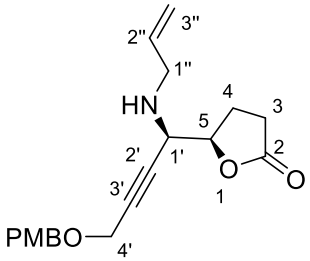
248

To solution of the diol **247** (510 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (10 mL) were added TEMPO (30 mg, 0.18 mmol, 0.2 equiv) and BAIB (1.1.8 g, 3.67 mmol, 4 equiv) at rt and the mixture was stirred at the same temperature for 18 h.[93] The reaction was quenched by 0.1 N $Na_2S_2O_3$ solution (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2,

EtOAc/petroleum spirit) to give the Fmoc-lactone **248** (435 mg, 86% yield) as an waxy solid.

R_f = 0.63 (3:2, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 2938, 1779, 1697, 1451, 1406, 1247, 1173, 1066, 917, 759, 741
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 2H, ArH), 7.62 (dd, *J* = 7.0, 3.0 Hz, 2H, ArH), 7.43 (t, *J* = 7.5 Hz, 2H, ArH), 7.35 (t, *J* = 7.5 Hz, 2H, ArH), 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 5.85-5.70 (bm, 1H, H2''), 5.15-5.05 (bm, 3H, H3'' and H1'), 4.75-4.66 (bm, 2H, H5 and FmocC*H*HO), 4.65-4.55 (bm, 1H, FmocCH*H*O), 4.55 (bs, 2H, OCH_2Ph), 4.27 (t, *J* = 6.5 Hz, 1H, FmocCH), 4.18 (bs, 2H, H8), 4.13-3.97 (bm, 1H, H1''), 3.94-3.84 (bm, 1H, H1''), 3.84 (s, 3H, OMe). 2.58-2.56 (bm, 1H, H2), 2.46-2.38 (bm, 1H, H2), 2.37-2.36 (bm, 1H, H3), 2.12-2.02 (bm, 1H, H3)
^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2 (C2), 159.5 (Ar), 156.3 (b, COOCH2), 143.8 (Ar), 141.4 (ArC), 134.2 (C2''), 129.7 (Ar), 129.1 (Ar), 127.7 (Ar), 127.1 (Ar), 124.9 (Ar), 120.0 (Ar), 116.8 (b, C3''), 113.9 (Ar), 83.2 (C3'), 79.4 (b, C5), 79.6 (b, O-$C(CH_3)_3$), 78.8 (b, C2'), 71.5 (OCH_2Ph), 68.1 (b, FmocCH_2O), 56.8 (C4'), 55.3 (OMe), 52.8 (b, C1''), 47.3 (FmocCH), 28.1 (C3), 24.9 (C4).
ESIMS *m/z* 552 [$(M+H)^+$ 100%].
HRESIMS calcd. for $C_{34}H_{37}O_6NNa$, $(M+Na)^+$ 552.2386, found: 552.2374.

(*R)-5-((*R**)-1-(Allylamino)-4-(4-methoxybenzyloxy)but-2-ynyl)dihydrofuran-2(3*H*)-one**



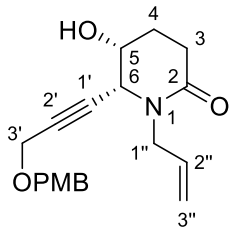
243

Triethylamine (2 mL) was added to a solution of the Fmoc-lactone **248** (716 mg, 1.3 mmol) in CH_3CN (8 mL) at rt and the mixture was allowed to stir at rt for 14 h. The solvent was evaporated *in vacuo* and the residue was purified by column

chromatography (4:1, EtOAc/petroleum spirit) to give the lactone **243** (377 mg, 88% yield) as a pale yellow oil.[96]

R_f = 0.57 (9:1, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 3352, 2931, 1741, 1610, 1513, 1248, 1172, 1065, 1030.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 6.89 (d, *J* = 8.5 Hz, 2H, ArH), 5.87 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H, H2''), 5.24 (d, *J* = 17 Hz 1H, H1''), 5.14 (d, *J* = 10.5 Hz, 1H, H1''), 4.61 (dd, *J* = 9.0, 5.5 Hz, 1H, H5), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H4'), 3.81 (s, 3H, OMe), 3.64 (d, *J* = 5.5 Hz, 1H, H1'), 3.53 (dd, *J* = 14.0, 5.5 Hz, 1H, H1''), 3.30 (dd, *J* = 14.0, 6.5 Hz, 1H, H1''), 2.64 (ddd, *J* = 17.5, 10.0, 5.5 Hz, 1H, H3), 2.52 (dt, *J* = 17.5, 5.5 Hz 1H, H3), 2.39 – 2.31 (m, 1H, H4), 2.26 – 2.19 (m, 1H, H4).
^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (C1), 159.7 (ArC), 136.1 (C2''), 130.0 (ArCH), 129.6 (ArC), 117.2 (C3''), 114.2 (ArCH), 83.4 (C2'), 81.9 (C3'), 81.5 (C5), 71.6 (OCH_2Ar), 57.3 (C4'), 55.6 (OMe), 53.7 (C1'), 50.4 (C1''), 28.6 (C3), 24.5 (C4).
ESIMS *m/z* 330 [$(M+H)^+$ 100%]
HRESIMS calcd. for $C_{19}H_{24}O_4N$, $(M+H)^+$ 330.1705, found: 330.1716.

(5*R,6*R**)-1-Allyl-5-hydroxy-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)piperidin-2-one** (**244**)



244

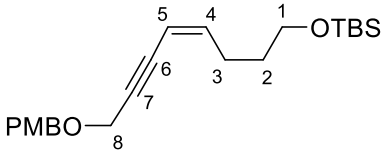
To solution of of the amino-lactone **243** (1.086 g, 3.3 mmol) in MeOH (12 mL) was added Et_3N (3 mL) and the mixture was stirred at reflux temperature for 3 d.[136] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the hydroxyl-lactam **244** (988 mg, 91% yield) as a pale yellow oil.
R_f = 0.66 (9:1, EtOAC/MeOH).

IR (neat, ν_{max}/cm^{-1}): 3370, 2952, 2361, 1623, 1465, 1410, 1255, 1087, 998, 933, 777.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H, ArH), 6.86 (d, *J* = 8.5 Hz, 2H, ArH), 5.71 (ddt, *J* = 17.0, 10.0, 4.5 Hz, 1H, H2"), 5.15 (d, *J* = 17.0 Hz, 1H, H3"), 5.08 (d, *J* = 10.0 Hz, 1H, H3") , 4.68 – 4.61 (m, 1H, H1"), 4.49 (s, 2H, OCH_2Ar), 4.32 (s, 2H, H3'), 4.16 (s, 1H, H6), 3.98 – 3.92 (m, 1H, H5), 3.77 (s, 3H, OMe), 3.51 (dd, *J* = 15.0, 7.5 Hz, 1H, H1"), 2.61 – 2.54 (m, 1H, H3), 2.44 – 2.35 (m, 1H, H3), 2.14 – 2.03 (m, 1H, H4), 1.94-1.87 (m, 1H, H4).
^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0 (C2), 159.8 (ArC), 132.6 (C2"), 130.0 (ArCH), 129.4 (ArC), 118.5 (ArCH), 114.2 (C3"), 83.2 (C2'), 81.6 (C1'), 71.9 (OCH_2Ar), 66.7 (C5), 57.2 (C3'), 55.5 (OMe), 54.1 (C6), 48.0 (C1"), 29.6 (C3), 26.8 (C4).
ESIMS *m/z* 330 $[(M+H)^+$ 100%].
HRESIMS calcd. for $C_{19}H_{24}O_4N$, $(M+H)^+$ 330.1705, found: 330.1698.

Microwave assisted Boc-deprotection of 242

A solution of the N-Boc protected amine **242** (135 mg, 0.31 mmol) in TFE (2 mL) was placed in a sealed microwave vial. The reaction mixture was heated at 100 ºC in a microwave reactor with stirring for 1 h. After cooling to room temperature, the mixture was evaporated to dryness under reduced pressure. The crude product was purified by flash-column chromatography (3:1 to 100:0, EtOAc/petroleum spirit) to give the lactone **243** (19 mg, 19% yield) and the lactam **244** (31 mg, 31% yield).[96]

(*Z*)-*tert*-Butyl(8-(4-methoxybenzyloxy)oct-4-en-6-ynyloxy)dimethylsilane (**249**)



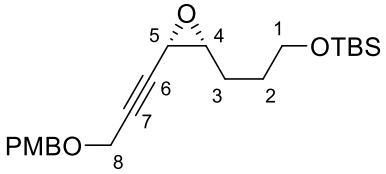
249

Imidazole (2.176 g, 32 mmol, 2.5 equiv) and TBSCl (2.215 g, 14.72 mmol, 1.15 equiv) were added to a solution of alcohol **231** (3.33 g, 12.8 mmol) in DMF (40 mL) at rt under a N_2 atmosphere and the mixture was stirred at rt for 6 h.[63] The mixture was then poured into a beaker containing water (70 mL) and then extracted with

EtOAc (3 x 100 mL). The organic extracts were combined, washed with water (2 x 100 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (1:9, EtOAc/petroleum spirit) to give the TBS ether **249** (4.453 g, 93% yield) as a colourless oil.

R_f = 0.61 (1:3, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 2931, 2856, 1512, 1426, 1248, 1107, 819, 741.
^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H, ArH), 6.88 (d, *J* = 8.6 Hz, 2H, ArH), 5.96 (dt, *J* = 10.7, 7.4 Hz, 1H, H4), 5.52 (d, *J* = 10.7 Hz, 1H, H5), 4.55 (s, 2H, OCH_2Ar), 4.29 (s, 2H, H8), 3.80 (s, 3H, OMe), 3.64 (t, *J* = 6.5 Hz, 2H, H1), 2.38 (q, *J* = 7.3 Hz, 2H, H3), 1.68 – 1.61 (m, 2H, H4), 0.89 (s, 9H, $(CH_3)_3C$), 0.05 (s, 6H, $(CH_3)_2Si$).
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7 (ArC), 144.4 (C4), 130.1 (ArCH), 130.0 (ArC), 114.2 (ArCH), 109.1 (C5), 89.8 (C7) , 83.5 (C6), 71.4 (OCH_2Ar), 63.0 (C1), 57.9 (C8), 55.6 (OMe), 32.4 (C2), 27.2 (C3), 26.3 ($(CH_3)_3C$), 18.7 ($(CH_3)_3C$), -4.9 (CH_3Si).
ESIMS *m/z* 397 $[(M+Na)^+]$.
HRESIMS calcd. for $C_{22}H_{34}O_3SiNa$, $(M+Na)^+$ 397.2175, found: 397.2156.

***tert*-Butyl(3-((2*R**,3*S**)-3-(3-(4-methoxybenzyloxy)prop-1-ynyl)oxiran-2-yl)propoxy)dimethylsilane (250)**



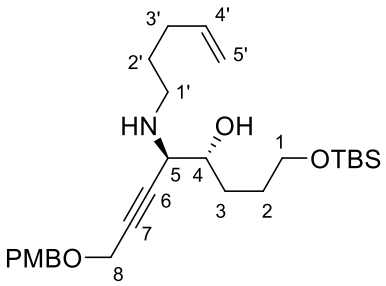
250

Purified m-chloroperbenzoic acid (2.38 g, 13.8 mmol, 1.2 equiv) was added to solution of the alkene **250** (4.3 g, 11.5 mmol) in CH_2Cl_2 (150 mL) and the mixture was stirred at rt for 14 h.[133] The reaction was quenched with saturated $NaHCO_3$ solution (100 mL) and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered through a short

column loaded with Al_2O_3. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:8, EtOAc/petroleum spirit) to give the epoxide **250** (2.825 g, 63% yield) as a colourless oil and the starting alkene **249** (0.989 g, 23%).

R_f = 0.59 (1:3, EtOAc/petroleum spirit).
IR (neat, ν_{max}/cm^{-1}): 3312, 2930, 2856, 1612, 1513, 1465, 1248, 1094, 834, 755.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H, ArH), 6.88 (d, *J* = 8.0 Hz, 2H, ArH), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H8), 3.80 (s, 3H, OMe), 3.72 – 3.64 (m, 2H, H1), 3.49 (d, *J* = 3.5 Hz, 1H, H5), 3.10 (dd, *J* = 7.0, 3.5 Hz, 1H, H4), 1.80-1.71 (m, 4H, H2 and H3), 0.89 (s, 9H, $(CH_3)_3C$), 0.05 (s, 6H, $(CH_3)_2Si$).
^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (ArC), 130.1 (ArCH), 129.6 (ArC), 114.2 (ArCH), 82.0 (C6), 81.8 (C7), 71.6 (OCH_2Ar), 63.0 (C1), 58.3 (C4), 57.3 (C8), 55.6 (OMe), 45.5 (C5), 29.5 (C3), 26.6 (C2), 26.3 ($(CH_3)_3C$), 18.6 ($(CH_3)_3C$), -5.0 (CH_3Si).
ESIMS *m/z* 413 [$(M+Na)^+$ 100%].
HRESIMS calcd. for $C_{22}H_{34}O_4SiNa$, $(M+Na)^+$ 413.2124, found: 413.2126.

(4*R,5*R**)-1-(*tert*-Butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-5-(pent-4-enylamino)oct-6-yn-4-ol** (**251**)



251

Lithium triflate (162 mg, 1 mmol, 1 equiv) and 4-penteneamine (340 mg, 3 mmol, 3 equiv) were added to solution of the epoxide **250** (390 mg, 1 mmol) in CH_3CN (2 mL) in a microwave reactor vial. The mixture was heated in a microwave reactor at 110 ºC, 200 W for 1.5 h.[87] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:7, EtOAc/petroleum spirit) to give the amine **251** (352 mg, 74% yield) as a pale yellow oil.

R_f = 0.60 (1:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3370, 2930, 2855, 1513, 1465, 1248, 1091, 833, 755.

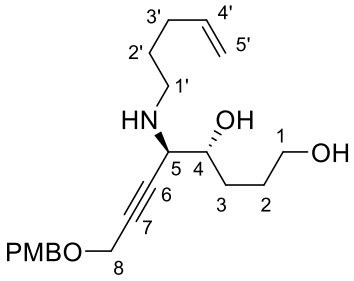
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H, ArH), 6.90 (d, *J* = 8.0 Hz, 2H, ArH), 5.83 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4'), 5.05 (d, *J* = 17.0 Hz, 1H, H5'), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.53 (s, 2H, OCH_2Ar), 4.18 (s, 2H, H8), 3.83 (s, 3H, OMe), 3.69 (t, *J* = 6.0 Hz, 2H, H1), 3.46 (dd, *J* = 8.5, 6.0 Hz, 1H, H4), 3.17 (d, *J* = 8.5 Hz, 1H, H5), 2.91 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.64 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.15 (q, *J* = 7.0 Hz, 2H, H3'), 1.97 – 1.88 (m, 1H, H3), 1.83-1.74 (m, 1H, H2), 1.73 – 1.67 (m, 1H, H2), 1.66-1.57 (m, 2H, H2'), 1.54 – 1.45 (m, 1H, H3), 0.91 (s, 9H, $(CH_3)_3C$), 0.07 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (ArC), 138.6 (C4'), 130.1 (ArCH), 129.8 (ArC), 115.2 (C5'), 114.2 (ArCH), 85.7 (C6), 81.3 (C7), 73.2 (C4), 71.6 (OCH_2Ar), 63.6 (C1), 57.5 (C8), 56.3 (C5), 55.6 (OMe), 47.0 (C1'), 31.8 (C3'), 30.7 (C3), 29.6 (C2), 29.3 (C2'), 26.3 ((CH_3)C), 18.7 ((CH_3)$_3$*C*), -4.9 (CH_3Si).

ESIMS *m/z* 476 [(M+H)$^+$ 100%].

HRESIMS calcd. for $C_{27}H_{46}O_4NSi$, (M+H)$^+$ 476.3196, found: 476.31983.

(4*R,5*R**)-8-(4-Methoxybenzyloxy)-5-(pent-4-enylamino)oct-6-yne-1,4-diol** (**227**)



227

1M tetrabutylamonium fluoride solution in THF (3.8 mL, 3.8 mmol, 1.5 equiv) was added dropwise to a solution of the TBS ether **251** (1.19 g, 2.5 mmol) in THF (30 mL) at 0 ^{0}C and the mixture was warmed to rt and stirred for 4 h.[138] Saturated $NaHCO_3$ (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column

chromatography (9:1 to 100:0, EtOAc/petroleum spirit) to give the diol **227** (890 mg, 91% yield) as a colourless oil.

R_f = 0.69 (1:9, MeOH/EtOAc).

IR (neat, ν_{max}/cm^{-1}): 3310, 2944, 1779, 1696, 1450, 1410, 1247, 1066, 1030, 740.

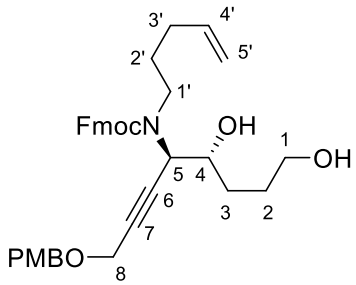
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4'), 5.04 (d, *J* = 17.0, 1H, H5'), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H8), 3.82 (s, 3H, OMe), 3.74-3.64 (m, 2H, H1), 3.48 – 3.43 (m, 1H, H4), 3.15 (d, *J* = 9.0 Hz, 1H, H5), 2.90 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.63 (dt, *J* = 11.5, 7.0 Hz, 1H, H1'), 2.14 (q, *J* = 7.0 Hz, 2H, H3'), 2.04 – 1.95 (m, 1H, H3), 1.83 – 1.74 (m, 2H, H2), 1.63-1.59 (m, 2H, H2'), 1.58 – 1.48 (m, 1H, H3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (ArC), 138.5 (C4'), 130.1 (ArCH), 129.7 (ArC), 115.3 (C5'), 114.2 (ArCH), 85.2 (C6), 81.7 (C7), 73.0 (C4), 71.6 (OCH_2Ar), 63.2 (C1), 57.4 (C8), 56.0 (C5), 55.6 (OMe), 46.9 (C1'), 31.7 (C3'), 31.1 (C3), 29.7 (C2), 29.6 (C2').

ESIMS *m/z* 362 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{21}H_{32}O_4N$, $(M+H)^+$ 362.2321, found: 362.2331.

(9*H*)-Fluoren-9-yl)methyl (4*R,5*R**)-5,8-dihydroxy-1-(4-methoxybenzyloxy)oct-2-yn-4-yl(pent-4-enyl)carbamate** (**252**)



252

To a solution of the amine **227** (975 mg, 2.7 mmol) in THF (40 mL), was added a saturated solution of Na_2CO_3 (20 mL) and the mixture was allowed to cool to 0 ^{0}C. FmocCl (768 mg. 2.97 mmol, 1.1 equiv) was added portionwise at 0 ^{0}C and the

reaction mixture was stirred at rt for 4 h.[95] The organic phase was removed *in vacuo* and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the Fmoc-diol **252** (1.511 g, 96% yield) as a waxy solid.

R_f = 0.60 (9:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3436, 2927, 1687, 1611, 1458, 1248, 1066, 1032, 739.

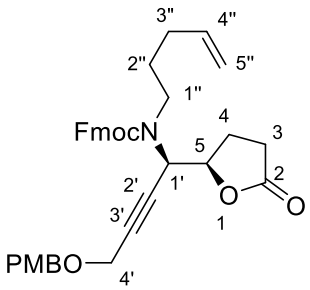
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (*J* = 8.5 Hz, 2H, ArH), 7.59 (*J* = 8.5 Hz, 2H, ArH), 7.39 (t, *J* = 8.5 Hz, 2H, ArH), 7.31 (t, *J* = 8.5 Hz, 2H, ArH), 7.23 (*J* = 9.0 Hz, 2H, ArH), 6.87 (*J* = 9.0 Hz, 2H, ArH), 5.72-5.62 (bm, 1H, H4"), 5.01-4.90 (bm, 2H, H5"), 4.77-4.72 (bm, 1H, FmocCH_2O), 4.67-4.57 (bm, 2H, FmocCH_2O and H1'), 4.47 (s, 2H, OCH_2Ar), 4.23 (t, *J* = 6.0 Hz. 1H, FmocCH), 4.12 (s, 2H, H4'), 3.80 (s, 3H, OMe), 3.67-3.58 (bm, 3H, H1 and H4), 3.12-2.97 (bm, 2H, H1'), 1.90-1.80 (bm, 2H, H3'), 1.75-1.65 (bm, 2H, H2'), 1.55-1.40 (bm, 4H, H2 and H3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7 (Ar), 144.1 (Ar), 141.6 (Ar), 138.0 (C4'), 129.9 (Ar), 129.5 (Ar), 127.9 (Ar), 127.3 (Ar), 124.9 (Ar), 120.2 (Ar), 115.2 (C5"), 114.1 (Ar), 82.5 (C7), 82.2 (C6), 73.0 (b, C4), 71.5 (OCH_2Ar), 67.2 (FmocCH_2O), 63.0 (C1), 57.2 (C8), 55.5 (OMe), 54.9 (b,C5), 47.7 (FmocCH), 45.6 (b, C1"), 31.4 (C3'), 31.2 (C2'), 29.4 (C3), 28.8 (b, C2).

ESIMS *m/z* 606 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{36}H_{41}O_6NNa$, $(M+Na)^+$ 606.2832, found: 606.2822.

(9*H*)-Fluoren-9-yl)methyl (*R)-4-(4-methoxybenzyloxy)-1-((*R**)-5-oxotetrahydrofuran-2-yl)but-2-ynyl(pent-4-enyl)carbamate** (**253**)



253

To a solution of of the diol **252** (1.28 g, 2.2 mmol) in anhydrous CH_2Cl_2 (30 mL) were added TEMPO (69 mg, 0.44 mmol, 0.2 equiv) and BAIB (2.83 g, 8.8 mmol, 4 eq) at rt and the mixture was stirred at rt for 18 h.[93] The reaction was quenched by 0.1 N $Na_2S_2O_3$ solution (20 mL) . The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the Fmoc-lactone **253** (813 mg, 84% yield) as a waxy solid.

R_f = 0.65 (3:2, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 3346, 2935, 1773, 1612, 1513, 1455, 1451, 1246, 1713, 1067, 1029, 919, 817.

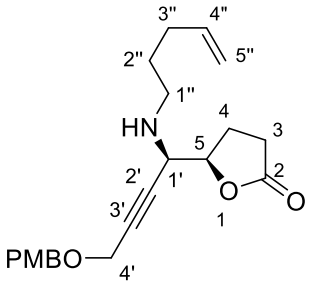
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 2H, ArH), 7.63 (t, *J* = 7.0 Hz, 2H, ArH), 7.43 (t, *J* = 7.5 Hz, 2H, ArH), 7.35 (t, *J* = 7.0 Hz, 2H, ArH), 7.27 (d, *J* = 8.5 Hz, 2H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 5.72-5.3 (bm, 1H, H4"), 5.15-5.05 (bm, 3H, H5" and H1'), 4.71-4.63 (bm, 2H, H5 and FmocCH_2O), 4.62-4.57 (bm, 1H, FmocCH_2O), 4.50 (bs, 2H, OCH_2Ar), 4.27 (t, *J* = 5.0 Hz, 1H, FmocCH), 4.16 (bs, 2H, H4'), 3.84 (s, 3H, OMe), 3.34-3.26 (bm, 1H, H1'), 3.13-3.07 (bm, 1H, H1"), 2.59-2.52 (bm, 1H, H3), 2.12-2.03 (bm, 3H, H3 and 2H3"), 1.89-1.83 (bm, 1H, H4), 1.58-1.52 (bm, 1H, H2"), 1.45-1.38 (bm, 1H, H2").

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2 (C2), 159.5 (Ar), 156.3 (b, FmocCO), 143.8 (Ar), 141.4 (Ar), 137.7 (C4"), 129.7 (Ar), 129.1 (Ar), 127.4 (Ar), 127.1 (Ar), 124.7 (Ar), 120.0 (Ar), 115.1 (b, C3"), 113.9 (Ar), 83.2 (C3'), 79.4 (b, C5), 78.8 (b, C2'), 71.4 (OCH_2Ar), 67.1 (b, FmocCH_2O), 56.8 (C4'), 55.3 (OMe), 52.4 (b, C1'), 47.3 (FmocCH), 31.1 (C3"), 28.2 (C2"), 28.1 (b,C3), 24.9 (C4).

ESIMS *m/z* 602 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{36}H_{37}O_6NNa$, $(M+Na)^+$ 602.25143, found: 602.2519.

(*R)-5-((*R**)-4-(4-Methoxybenzyloxy)-1-(pent-4-enylamino)but-2-ynyl)dihydrofuran-2(3*H*)-one** (**226**)



226

Triethyamine (5 mL) was added to a solution of the Fmoc-lactone **253** (2.432 g, 4.2 mmol) in CH_3CN (20 mL) at rt and the mixture was allowed to stir at rt for 14 h.[96] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the lactone **226** (1.289 g, 86% yield) as a pale yellow oil.

R_f = 0.63 (9:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 3343, 2935, 2841, 1773, 1611, 1512, 1247, 1067, 1029, 816.

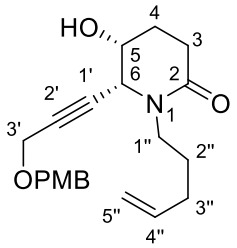
^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 6.89 (d, *J* = 8.5 Hz, 2H ArH), 5.82 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 5.03 (d, *J* = 17.0 Hz, 1H, H5"), 4.97 (d, *J* = 10.0 Hz, 1H, H5")), 4.60 (dd, *J* = 7.0, 5.5 Hz, 1H, H5), 4.52 (s, 2H, OCH_2Ar), 4.17 (s, 2H, H4'), 3.81 (s, 3H, OMe), 3.59 (d, *J* = 5.5 Hz, 1H, H1'), 2.92 (dt, *J* = 11.5, 7.0 Hz, 1H, H1"), 2.67 – 2.59 (m, 2H, H1" and H3), 2.54 (m, 1H, H3), 2.39 – 2.31 (m, 1H, H4), 2.27 – 2.19 (m, 1H, H4), 2.12 (q, *J* = 7.0 Hz, 2H, H3"), 1.64 – 1.55 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1 (C1), 159.7 (ArC), 138.5 (C4"), 130.0 (ArCH), 129.6 (ArC), 115.1 (C5"), 114.2 (ArCH), 83.7 (C2'), 81.7 (C3'), 81.4 (C5), 71.6 (OCH_2Ar), 57.3 (C4'), 55.6 (OMe), 54.7 (C1'), 47.6 (C1"), 31.7 (C3"), 29.4 (C2"), 28.7 (C3), 24.5 (C4).

ESIMS *m/z* 380 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{21}H_{27}O_4NSiNa$, $(M+Na)^+$ 380.1838, found: 380.1842.

(5*R,6*R**)-5-Hydroxy-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one** (**225**)



225

To solution of the amino-lactone **226** (1.086 g, 3.3 mmol) in MeOH (12 mL) was added Et_3N (3 mL) and the mixture was stirred at reflux temperature for 3 d.[136] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the lactam **225** (920 mg, 84% yield) as a pale yellow oil.

R_f = 0.63 (1:9, MeOH/EtOAc)

IR (neat, ν_{max}/cm^{-1}): 3361, 2930, 1614, 1513, 1438, 1413, 1247, 1067, 1031, 817

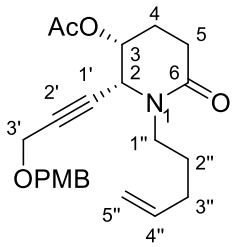
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.5 Hz, 2H, ArH), 6.87 (d, *J* = 7.5 Hz, 2H, ArH), 5.79 (ddt, *J* = 17.0, 10.0, 4.5 Hz, 1H, H4"), 5.01 (d, *J* = 17.0 Hz, 1H, H5"), 4.95 (d, *J* = 10.0 Hz, 1H, H5"), 4.49 (s, 2H, OCH_2Ar), 4.32 (s, 1H, H6), 4.17 (s, 2H, H3'), 4.01 – 3.95 (m, 1H, H5), 3.79 (s, 3H, OMe), 3.81 – 3.71 (m, 1H, H1"), 3.12 (dt, *J* = 14.0, 7.0 Hz 1H, H1"), 2.59-2.53 (m, 1H, H3), 2.38 (dt, *J* = 11.5, 7.0 Hz, 1H, H3), 2.14 – 2.02 (m, 3H, H4 and H3"), 1.95-1.88 (m, 1H, H4), 1.76 – 1.62 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C1), 159.8 (ArC), 138.0 (C4"), 130.2 (ArCH), 129.3 (ArC), 115.4 (C5"), 114.2 (ArCH), 83.2 (C2'), 81.8 (C1'), 71.9 (OCH_2Ar), 66.8 (C5), 57.3 (C3'), 55.6 (OMe), 55.2 (C6) 46.2 (C1"), 31.4 (C3"), 29.8 (C3), 29.5 (C4), 26.7 (C2").

ESIMS *m/z* 380 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{21}H_{27}O_4NSiNa$, $(M+Na)^+$ 380.1838, found: 380.1839.

(2*R,3*R**)-2-(3-(4-Methoxybenzyloxy)prop-1-ynyl)-6-oxo-1-(pent-4-enyl)piperidin-3-yl acetate** (**258**)



258

To an ice-bath cooled solution of the alcohol **225** (339 mg. 0.85 mmol) in CH_2Cl_2 (10 mL) were added successively DMAP (25 mg, 8.62 mmol, 0.17 equiv), Ac_2O (100 μL, 1.02 mmol, 1.2 equiv), and Et_3N (140 μL, 42.25 mmol, 1.2 equiv). The mixture was stirred at room temperature for 14 h.[100] The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ solution and 10 mL of water at 0 ^{0}C. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to afford the acetate **258** (345 mg, 91% yield) as a pale yellow oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 2936, 1743, 1640, 1513, 1369, 1235, 1031, 916, 819

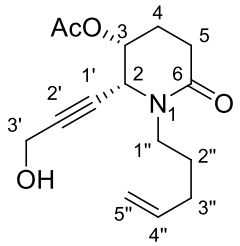
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.0 Hz, 2H, ArH), 6.89 (d, *J* = 7.0 Hz, 2H, ArH), 5.84 – 5.74 (m, 1H, H4"), 5.05- 4.94 (m, 3H, H5" and H3), 4.52 (d, *J* = 1.5 Hz, 1H, H2), 4.50 (s, 2H, OCH_2Ar), 4.16 (s, 2H, H3'), 3.82 – 3.73 (m, 1H, H1"), 3.79 (s, 3H, OMe), 3.12 (dt, *J* = 13.5, 7.0 Hz, 1H, H1"), 2.63-2.57 (m, 1H, H5), 2.51 – 2.42 (m, 1H, H5), 2.29-2.26 (td, *J* = m, 1H, H4), 2.10 (s, 3H, MeCO), 2.08 – 2.01 (m, 2H, H3"), 1.94-2.02 (m, 1H, H4), 1.73 – 1.65 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (ester *C*O), 168.5 (C6), 159.8 (ArC), 138.0 (C4"), 130.0 (ArCH), 129.4 (ArC), 115.4 (C5"), 114.2 (ArCH), 82.4 (C2'), 80.7 (C1'), 71.5 (OCH_2Ar), 68.5 (C3), 57.1 (C3'), 55.7 (OMe), 51.7 (C2), 46.2 (C1"), 31.4 (C3"), 29.5 (C5), 26.7 (C2"), 23.7 (C4), 21.3 (MeCO).

ESIMS *m/z* 422 [(M+Na)$^+$ 100%].

HRESIMS calcd. for $C_{23}H_{29}NO_5Na$, (M+H)$^+$ 422.1943, found: 422.1958.

(2*R,3*R**)-2-(3-Hydroxyprop-1-ynyl)-6-oxo-1-(pent-4-enyl)piperidin-3-yl acetate** (**267**)



267

To a mixture of the PMB ether **258** (620 mg, 1.55 mmol) in CH_2Cl_2 (50 mL) and water (5 mL), was added DDQ (633 mg, 2.79 mmol, 1.8 equiv) portionwise at 0 ^{0}C and the mixture was allowed to warm to rt and stirred for 18 h.[104] Then the mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 x 50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the primary alcohol **267** (339 mg, 78% yield) as a yellow oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3361, 2936, 1743, 1625, 1415, 1369, 1228, 1043, 1026, 913, 779.

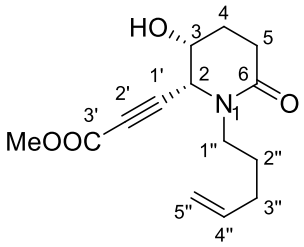
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 4.98 – 4.88 (m, 3H, H5" and H3), 4.44 (d, *J* = 3.0 Hz, 1H, H2), 4.21 (s, 2H, H3'), 3.69 (dt, *J* = 14.5, 7.0 Hz, 1H, H1"), 3.04 (dt, *J* = 14.5, 7.0 Hz, 1H, H1"), 2.54-2.48 (m, 1H, H5), 2.42-2.34 (m,1H, H5), 2.23 – 2.13 (m, 1H, H4), 2.05 (s, 3H, MeCO), 2.03-1.95 (m, 2H, H3"), 1.90 (dd, *J* = 8.5, 4.0 Hz, 1H, H4), 1.65 – 1.56 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (ester *C*O), 168.7 (C6), 137.7 (C4"), 115.3 (C5"), 85.1 (C2'), 79.3 (C1'), 68.2 (C3), 51.5 (C2), 50.5 (C3'), 45.9 (C1"), 31.1 (C3"), 29.1 (C5), 26.4 (C2"), 23.3 (C4), 21.1 (MeCO).

ESIMS *m/z* 302 [(M+H)$^+$ 100%]

HRESIMS calcd. for $C_{15}H_{21}O_4NNa$, (M+H)$^+$ 302.1368, found 302.1355.

Methyl 3-((2*R,3*R**)-3-hydroxy-6-oxo-1-(pent-4-enyl)piperidin-2-yl)propiolate (182)**



182

To a solution of the primary alcohol **267** (310 mg, 1.1 mmol) in acetone (10 mL) was added Jones' reagent (1.6 mL) dropwise at 0 ^{0}C. After being stirred for 30 min at 0 ^{0}C, CH_3OH (0.2 mL) was added and the reaction mixture was stirred for additional 10 min at 0 ^{0}C. Water (15 mL)) was added and the mixture was extracted with CH_2Cl_2 (4 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude acid (286 mg, 88% yield) as a yellow solid which was used in the next step without further purification. To a solution of the above acid (286 mg, 0.97 mmol) in anhydrous MeOH, was added TMSCl (250 µL, 1.95 mmol, 2 equiv) under a N_2 atmosphere and the mixture was stirred at rt for 12 h.[68] The volatiles were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (70 mL) and washed with $NaHCO_3$ (2 x 20 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the hydroxyl ester **182** (80 mg, 30% yield) as a yellow oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3455, 2924, 2953, 17331718, 1272, 1177, 1131.

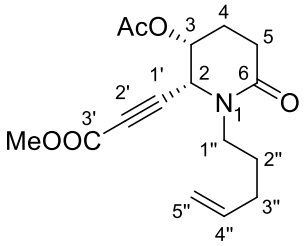
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.75 (m, 1H, H4"), 5.04 (d, *J* = 17.0 Hz, 1H, H5"), 4.98 (d, *J* = 10.0 Hz, 1H, H5"), 4.43 (d, *J* = 4.6 Hz, 1H, H2), 4.13 – 4.08 (m, 1H, H5), 3.78 (s, 3H, OMe), 3.81 – 3.70 (m, 1H, H1"), 3.13 (dt, *J* = 13.0, 6.5, 1H, H1"), 2.64 – 2.57 (m, 1H, H5), 2.48 – 2.39 (m, 1H, H5), 2.10-2.19 (m, 1H, H4), 1.97-2.10 (m, 3H, H4 and H3"), 1.72 – 1.65 (m, 2H, H2").

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2 (C6), 153.7 (C3'), 137.8 (C4"), 115.5 (C5"), 83.5 (C1'), 77.6 (C2'), 66.8 (C3), 55.2 (C2), 53.3 (OMe), 46.5 (C1"), 31.2 (C3"), 29.6 (C5), 26.8 (C2"), 26.6 (C4).

ESIMS *m/z* 288 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{14}H_{19}O_4NNa$, $(M+Na)^+$ 288.1212, found 288.1200.

Methyl 3-((2*R,3*R**)-3-acetoxy-6-oxo-1-(pent-4-enyl)piperidin-2-yl)propiolate (269)**



269

To an ice-bath cooled solution of the alcohol **182** (66 mg, 0. 25 mmol) in CH_2Cl_2 were added sequentially DMAP (7 mg, 0.043 mmol, 0.17 equiv), Ac_2O (28 μL, 0.3 mmol, 1.2 equiv), and Et_3N (42 μL, 0.3 mmol, 1.2 equiv).[100] The mixture was stirred at rt for 16 h. The reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ solution and 10 mL of water at 0 ^{0}C. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to afford the acetate **269** (62 mg, 81% yield) as a colourless oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2930, 2848, 2240, 1743, 1717, 1653, 1368, 1226, 1144, 909.

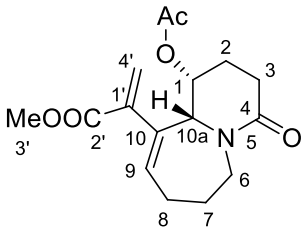
NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H, H4''), 5.08-4.97 (m, 3H, H5" and H3), 4.61 (d, *J* = 5.0 Hz, 1H, H2), 3.80 (s, 3H, OMe), 3.81-3.72 (m, 1H, H1"), 3.11 (dt, *J* = 14.0, 7.0 Hz, 1H, H1"), 2.65-2.59 (m, 1H, H5), 2.53-2.45 (m, 1H, H5), 2.30-2.22 (m, 1H, H4), 2.14 (s, 3H. CH_3CO), 2.09-2.01 (m, 2H, H3"), 1.91-1.85 (m, 3H , H4 and H3'), 1.72-1.66 (m , 2H, H2").

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 ($CH_3\underline{C}OO$), 168.2 (C6), 153.4 (C3'), 137.8 (C4''), 115.6 (C5''), 82.1 (C1'), 77.4 (C2'), 68.0 (C3), 53.3 (C2), 51.7 (OMe), 46.5 (C1''), 31.2 (C3'), 29.4 (C5), 26.6 (C4), 23.8 (C2''), 21.2 ($\underline{C}H_3CO$).

ESIMS *m/z* 308 [$(M+H)^+$ 100%]

HRESIMS calcd. for $C_{16}H_{22}O_5N$, $(M+H)^+$ 3308.1498, found: 308.1489.

Methyl 2-((1*R,10a*R**)-1-acetoxy-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)acrylate** (**270**)



270

To a solution of the ene-yne **269** (46 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (80 mL) was added Grubb's 1st generation Ru catalyst (12.3 mg, 0.015 mmol, 0.1 equiv) under a N_2 atmosphere and the mixture was stirred at rt for 8 h.[60] The reaction mixture then was exposed to the open air for 30 min. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the bicyclic compound **270** (34 mg, 75% yield) as a yellow oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2925, 2853, 1739, 1737, 1373, 1224, 1196, 1107, 1012.

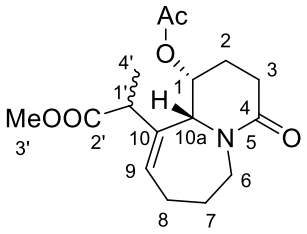
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H, H4 (*Z*)'), 5.83 (t, *J* = 8.0, 1H, H9), 5.60 (s, 1H, H4' (*E*)), 5.20 (s, 1H, H1), 4.46 (s, 1H, H10a), 4.25 (dd, *J* = 13.5, 7.5 Hz, 1H, H6), 3.76 (s, 3H, OMe), 3.24 (td, *J* = 12.3, 6.8 Hz, 1H, H6), 2.65-2.49 (m, 2H, H8 and H3), 2.46-2.40 (m, 1H, H3), 2.25 – 2.14 (m, 1H, H7), 2.11 – 2.02 (m, 1H, H2), 2.03 (s, 3H, COMe), 1.97 – 1.80 (m, 2H, H8 and H2), 1.62-1.54 (m, 1H, H7).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (C4), 169.0 ($CH_3\underline{C}OO$), 167.0 (C2'), 140.8 (C10), 136.1 (C1'), 132.3 (C9), 129.8 (C4'), 67.0 (C1), 65.6 (C10a), 52.5 (OMe), 42.4 (C6), 27.3 (C3), 24.8 (C2), 23.8 (C7), 21.8 (C8), 21.2 (CH_3CO).

ESIMS *m/z* 330 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{16}H_{21}O_5NNa$, $(M+Na)^+$ 330.1317, found: 330.1302.

Methyl 2-((1*R,10a*R**)-1-acetoxy-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)propanoate** (**285**)



285

To a solution of the enone **270** (36.8 mg, 0.12 mmol) in anhydrous MeOH (5 mL) was added $NaBH_4$ (41 mg, 1.1 mmol, 9 equiv) portionwise at 0 ^{0}C under a N_2 atmosphere and the mixture was stirred at the same condition for 3 h.[60] The reaction was quenched by adding saturated $NaHCO_3$ solution (10 mL) at 0 ^{0}C and the mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:1, EtOAc/petroleum spirit) to give **285** as an inseparable mixture of diasteroisomers (28 mg, 75% yield) as a pale yellow oil.

R_f = 0.59 (4:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 2921, 2918, 2848, 1739, 1616, 1452, 1324, 1157, 1092, 813.

^{1}H NMR (500 MHz, $CDCl_3$) *major diastereomer* δ 5.89-5.83 (m, 1H, H9), 5.40 (s, 1H, H1), 4.24 (d, *J* = 7.0 Hz, 1H, H10a), 4.24-4.18 (m, 1H, H6), 3.65 (m, 3H, OMe), 2.93 (q, *J* = 7 Hz, 1H, H1'), 2.85 (dt, *J* = 12.0, 6.0 Hz, 1H, H6), 2.62-2.55 (m, 1H, H3), 2.55-2.40 (m, 2H, H3 and H8), 2.27-2.15 (m, 2H H2 and H7), 2.03 (s, 3H, MeCO), 1.99-1.89 (m, 2H, H2 and H8), 1.58-1.49 (m, 1H, H7), 1.34 (d, *J* = 7.0 Hz, 3H, H4').

^{13}C NMR (126 MHz, $CDCl_3$) *major diastereomer* δ 174.7 (C2'), 170.1 (AcO), 169.0 (C4), 136.2 (C10), 128.2 (C9), 67.8 (C10a), 67.4 (C1), 52.3 (OMe), 44.0 (C11), 42.9 (C6), 27.4 (C2), 24.2 (C3), 23.6 (C7), 21.2 (C8), 21.1 (CH_3CO), 18.8 (C4').

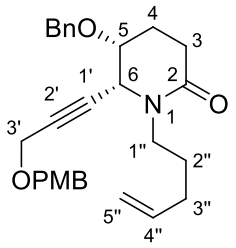
^{1}H NMR (500 MHz, $CDCl_3$) *minor diastereomer* δ 5.89-5.83 (m, 1H, H9), 5.47 (s, 1H, H1), 4.26 (d, *J* = 7.0 Hz, 1H, H10a), 4.24-4.18 (m, 1H, H6), 3.71 (m, 3H, OMe), 3.05 (q, *J* = 7 Hz, 1H, H1'), 2.85 (dt, *J* = 12.0, 6.0 Hz, 1H, H6), 2.73-2.64 (m, 1H, H3), 2.55-2.40 (m, 2H, H3 and H8), 2.27-2.15 (m, 1H H2), 2.14-2.08 (m, 1H, H7), 2.03 (s, 3H, MeCO), 1.99-1.89 (m, 2H, H2 and H8), 1.58-1.49 (m, 1H, H7), 1.34 (d, *J* = 7.0 Hz, 3H, H4').

^{13}C NMR (126 MHz, $CDCl_3$) *minor diastereomer* δ 175.2 (C2'), 170.0 (AcO), 168.9 (C4), 135.6 (C10), 127.4 (C9), 67.9 (C10a), 66.0 (C1), 52.5 (OMe), 43.0 (C11), 42.5 (C6), 27.2 (C2), 24.9 (C3), 23.6 (C7), 21.2 (C8), 21.1 (CH_3CO), 14.4 (C4').

ESIMS *m/z* 332 [$(M+Na)^+$ 100%]

HRESIMS calcd. for $C_{16}H_{23}O_5NNa$, $(M+Na)^+$ 332.1674, found: 332.1667

(5*R,6*R**)-5-(Benzyloxy)-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one** (**271)**



271

Sodium hydride in mineral oil (60%, 60 mg, 1.5 mmol, 1.5 equiv), BnBr (300 μL, 2.5 mmol, 2.5 equiv) and Bu_4NI (37 mg, 0.1 mmol, 0.1 equiv) were added to a solution of the alcohol **270** (358 mg, 1 mmol) in DMF (15 mL) at 0 ^{0}C and the resultant mixture was warmed to rt and stirred for 19 h.[107] The reaction mixture was diluted with EtOAc (15 mL), quenched with water (5 mL) and the aqueous layer extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. This was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the benzyl ether **271** (125 mg, 28%) as a colourless oil and the starting alcohol **270** (160 mg, 45%).

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2947, 2317, 1639, 1513, 1249, 1168, 1098, 1070, 1028, 698.

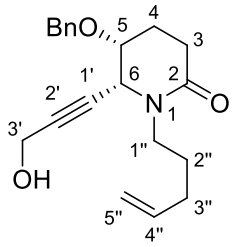
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, ArH), 7.24 (d, *J* = 8.2 Hz, 2H, ArH), 6.85 (d, *J* = 8.2 Hz, 2H, ArH), 5.80 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H, H4"), 5.02 (d, *J* = 17.1 Hz, 1H, H5"), 4.97 (d, *J* = 10.2 Hz, 1H, H5"), 4.67 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 4.63 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 4.52 (s, 2H, OCH_2Ar), 4.39 (d, *J* = 2.7 Hz, 1H, H5), 4.18 (s, 2H, H3'), 3.80 (s, 3H, OMe), 3.76 (dd, *J* = 14.8, 5.4 Hz, 2H, H1" and H5), 3.16 – 3.09 (m, 1H, H1"), 2.63 – 2.56 (m, 1H, H3), 2.42-2.34 (m, 1H, H3), 2.26 – 2.16 (m, 1H, H4), 2.07 – 2.00 (m, 3H, H4 and 2H3"), 1.69-1.63 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5 (C6), 159.6 (Ar), 142.0 (Ar), 137.8 (C4"), 130.5 (Ar), 129.6 (Ar), 129.1 (Ar), 128.5 (Ar), 128.1 (Ar), 115.5 (C5"), 114.1 (Ar), 85.2 (C2'), 79.0 (C1'), 73.5 (C5), 73.4 (OCH_2Ar), 71.5 (OCH_2Ph), 57.1 (C3'), 55.7 (OMe), 51.7 (C6), 46.2 (C1"), 31.4 (C3"), 29.5 (C3), 26.7 (C2"), 23.7 (C4).

ESIMS *m/z* 470 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{28}H_{33}O_4NNa$, $(M+Na)^+$ 470.2034, found 470.2032.

(5*R,6*R**)-5-(Benzyloxy)-6-(3-hydroxyprop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one** (**274**)



274

To a mixture of the PMB ether **271** (179 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) and water (1 mL) was added DDQ (163 mg, 0.72 mmol, 1.8 equiv) portionwise at 0 ^{0}C and the mixture was allowed to stirr at rt for 18 h.[104] Then the mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (2 x 2mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the primary alcohol **274** (103 mg, 78% yield) as a pale yellow oil.

R_f = 0.60 (9:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3320, 2926, 2313, 1697, 1620, 1453, 1411, 1270, 1163, 1095, 1070, 914, 740.

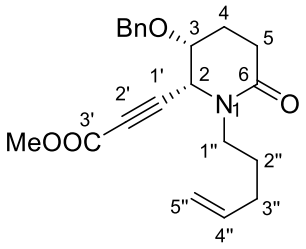
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H, ArH), 5.78 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, H4"), 5.02 (d, *J* = 17.0 Hz, 1H, H5"), 4.97 (d, *J* = 10.5 Hz, 1H, H5"), 4.64 (d, *J* = 17.0 Hz, 1H, OCH_2Ph), 4.61 (d, *J* = 17.0 Hz, 1H, OCH_2Ph), 4.33 (s, 1H, H6), 4.27 (s, 2H, H3'), 3.77 – 3.68 (m, 2H, H5 and H1"), 3.14 – 3.06 (m, 1H, H1"), 2.61-2.55 (m, 1H, H3), 2.42 – 2.32 (m, 1H, H3), 2.23 – 2.12 (m, H, H4), 2.06 – 1.99 (m, 2H, H3"), 1.99-1.93 (m, 1H, H4), 1.68 – 1.59 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8 (C2), 138.0 (C4"), 137.6 (ArC), 128.9 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 115.4 (C5"), 84.8 (C2'), 80.7 (C1'), 73.5 (C5), 71.5 (OCH_2Ph), 52.5 (C6), 51.1 (C3'), 46.5 (C1"), 31.3 (C3"), 29.5 (C3), 26.6 (C2"), 23.9 (C4).

ESIMS *m/z* 350 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{20}H_{25}O_3NNa$, $(M+Na)^+$ 350.1732, found: 350.1718.

Methyl 3-((2*R,3*R**)-3-(benzyloxy)-6-oxo-1-(pent-4-enyl)piperidin-2-yl)propiolate** (**277**)



277

To a solution of the primary alcohol **274** (95 mg, 0.29 mmol) in acetone (3 mL) was added Jones' reagent (420 µL) dropwise at 0 ^{0}C. After stirring for 30 min at 0 ^{0}C, CH_3OH (0.1 mL) was added at the same temperature and the reaction mixture was stirred for additional 10 min. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude acid (95 mg, 91% yield) as a yellow solid which was used in the next step without further purification. This acid was dissolved into anhydrous DMF (2 mL). Then K_2CO_3 (77

mg, 0.56 mmol, 2 equiv) was added at rt and the mixture was stirred for 15 min under a N_2 atmosphere. MeI (100 µL, 1.6 mmol, 6 equiv) was then added and the mixture was stirred at rt for 14 h.[108] Water (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the methyl ester **277** (63 mg, 65% yield) as a pale yellow oil.

R_f = 0.69 (3:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2916, 2376, 2313, 1718, 1620, 1272, 1099, 698.

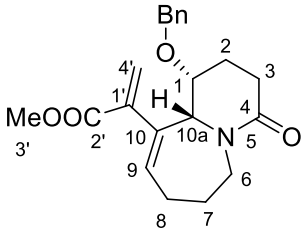
H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H, ArH), 5.72 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 4.95 (d, *J* = 17.0 Hz, 1H, H5"), 4.91 (d, *J* = 10.0 Hz, 1H, H5"), 4.58 (s, 2H, OCH_2Ph), 4.33 (d, *J* = 3.5 Hz, 1H, H2), 3.73 (s, 3H, OMe), 3.73-3.63 (m, 2H, H5 and H1"), 3.03 (dt, *J* = 13.5, 7.5 Hz, 1H, H1"), 2.57-2.51 (m, 1H, H5), 2.35-2.25 (m, 1H, H5), 2.15-2.06 (m, 1H, H4), 2.03-1.92 (m, 3H, H4 and 2H3"), 1.61-1.54 (m, 2H, H2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C6), 153.7 (C3'), 138.0 (C4"), 137.6 (ArC), 129 (ArCH), 128.9 (ArCH), 128.1 (ArCH), 115.5 (C5"), 83.3 (C1'), 77.2 (C2'), 73.4 (C3), 71.7 (OCH_2Ph), 53.2 (OMe), 52.8 (C2), 46.6 (C1"), 31.3 (C3"), 29.7 (C5), 26.7 (C2"), 24.5 (C4).

ESIMS *m/z* 378 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{21}H_{25}O_4NNa$, $(M+Na)^+$, 378.1681, found; 378.1674.

Methyl 2-((1*R,10a*R**)-1-(benzyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-a]azepin-10-yl)acrylate** (**278**)



278

To a solution of the ene-yne **277** (53 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (40 mL) was added Grubb's 1st generation Ru catalyst (12.4 mg, 0.015 mmol, 0.1 equiv) under a N_2 atmosphere and the mixture was stirred at rt for 8 h.[60] The reaction mixture then was exposed to open air for 30 min. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:1, EtOAc/petroleum spirit) to give the bicyclic compound **278** (42 mg, 80% yield) as a pale yellow oil.

R_f = 0.57 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2937, 1740, 1635, 1623, 1451, 1250, 1171, 1050, 726.

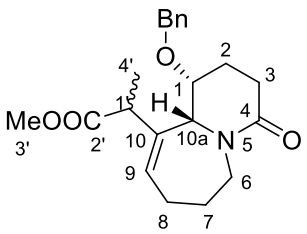
^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H, ArH), 6.10 (s, 1H, H4'), 5.88 (dd, *J* = 8.5, 6.5 Hz, 1H, H9), 5.54 (s, 1H, H4'), 4.60 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.36 (d, *J* = 12.5 Hz, 2H, OCH_2Ph and H1), 4.24 (dd, *J* = 12.7, 7.3 Hz, 1H, H6), 3.76 (s, 3H, OMe), 3.73 (s, 1H, H10a), 3.20 (td, *J* = 12.7, 6.8 Hz, 1H, H6), 2.72 – 2.61 (m, 1H, H8 and H3), 2.39-2.33 (m, 1H, H3), 2.24 – 2.14 (m, 1H, H7 and H2), 1.94 – 1.86 (m, 1H, H8), 1.77-1.69 (m, 1H, H2), 1.63 – 1.53 (m, 1H, H7).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6 (C4), 167.3 (C2'), 142.1 (C10), 138.6 (ArC), 136.4 (C1'), 132.2 (C9), 128.6 (C4'), 128.4 (ArC), 127.6 (ArC), 127.3 (ArC), 71.9 (C1), 70.9 (OCH_2Ph), 66.7 (C10a), 52.5 (OMe), 42.7 (C6), 27.2 (C3), 24.0 (C7), 23.5 (C2), 21.8 (C8).

ESIMS *m/z* 378 $[(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{21}H_{25}O_4NNa$, $(M+Na)^+$, 378.1697, found; 378.1681.

Methyl 2-((1*R,10a*R**)-1-(benzyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-a]azepin-10-yl)propanoate** (**286**)



286

Sodiumborohydride (34 mg, 0.9 mmol, 9 equiv) was added portionwise to a solution of the enone **278** (36 mg, 0.1 mmol) in anhydrous MeOH (3 mL) at 0 ^{0}C under a N_2 atmosphere and the mixture was stirred at 0 ^{0}C for 3 h.[60] Saturated aqueous $NaHCO_3$ solution (10 mL) was added at 0 ^{0}C and the mixture was extracted with EtOAc (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:1, EtOAc/petroleum spirit) to give **286** (28 mg, 77% yield) as a pale yellow oil as an inseparable mixture of diastereomers.

R_f = 0.62 (9:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 2940, 1730, 1626, 1454, 1276, 1246, 1173, 1108, 1098, 736, 717

^{1}H NMR (500 MHz, $CDCl_3$) *major diastereomer* δ 7.34 – 7.24 (m, 5H, ArH), 5.88 (t, *J* = 7.0 Hz, 1H, H9), 4.60 (d, *J* = 11.0 Hz, 1H, OCH_2Ph), 4.47 (d, *J* = 11.0 Hz, 1H, OCH_2Ph), 4.20 (dd, *J* = 13.2, 7.3 Hz, 1H, H6), 4.04 (s, 1H, H1), 3.99 (s, 1H, H10a), 3.67 (s, 3H, OMe), 2.95 (q, *J* = 7.0 Hz, 1H, H1'), 2.86-2.76 (m, 1H, H6), 2.74-2.64 (m, 1H, H3), 2.64-2.56 (m, 1H, H8), 2.37 (dd, *J* = 17.5, 5.5 Hz, 1H, H3), 2.27-2.20 (m, 1H, H2), 2.17-2.09 (m, 1H, H7), 1.91-1.73 (m, 2H, H8 and H2), 1.52-1.43 (m, 1H, H7), 1.32 (d, *J* = 7.0 Hz, 3H, H4').

^{13}C NMR (126 MHz, $CDCl_3$) *major diastereomer* δ 174.8 (C2'), 169.6 (C4), 138.8 (ArC), 136.8 (C10), 128.6 (ArC), 127.7 (ArC), 127.6 (ArC), 127.5 (C9), 72.4 (C1), 71.2 (OCH_2Ph), 69.2 (C10a), 52.3 (OMe), 44.3 (C1'), 43.0 (C6), 27.2 (C3), 24.0 (C2), 23.9 (C7), 21.2 (C8), 19.1 (C4').

^{1}H NMR (500 MHz, $CDCl_3$) *minor diastereomer* δ 7.34 – 7.24 (m, 5H, ArH), 5.88 (t, *J* = 7 Hz, 1H, H9), 4.60 (d, *J* = 11.0 Hz, 1H, OCH_2Ph), 4.40 (d, *J* = 11.0 Hz, 1H, OCH_2Ph), 4.18 (dd, *J* = 13.2, 7.3 Hz, 1H, H6), 4.11 (s, 1H, H10a), 3.86 (s, 1H, H1), 3.56 (s, 3H, OMe), 2.92-2.87 (m, 1H, H1'), 2.86-2.76 (m, 1H, H6), 2.74-2.64 (m, 1H, H3), 2.64-2.56 (m, 1H, H8), 2.37 (dd, *J* = 17.5, 5.5 Hz, 1H, H3), 2.27-2.20 (m, 1H, H2), 2.17-2.09 (m, 1H, H7), 1.91-1.73 (m, 2H, H8 and H2), 1.52-1.43 (m, 1H, H7), 1.29 (d, *J* = 7.0 Hz, 3H, H4').

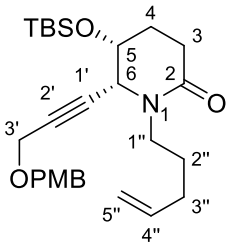
^{13}C NMR (126 MHz, $CDCl_3$) *minor diastereomer* δ 175.3 (C2'), 169.5 (C4), 138.4 (ArC), 134.4 (C10), 128.6 (ArC), 127.9 (ArC), 127.7 (ArC), 127.2 (C9), 72.4 (C1),

71.0 (OCH_2Ph), 69.1 (C10a), 52.4 (OMe), 44.3 (C1'), 42.8 (C6), 27.2 (C3), 24.0 (C2), 23.9 (C7), 21.3 (C8), 16.5 (C4').

ESIMS *m/z* 358 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{21}H_{28}O_4N$, $(M+H)^+$ 358.2018, found: 358.2001.

(5*R,6*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-(3-(4-methoxybenzyloxy)prop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one** (**279**)



279

To a solution of the alcohol **225** (990 mg, 2.77 mmol) in CH_2Cl_2 (30 mL) were added TBSOTf (10.43 mL, 1.85 mmol, 0.67 equiv) and 2,6-lutidine (0.32 mL, 2.77 mmol, 1 equiv) at 0 ^{0}C.[109] The mixture was warmed to rt and stirred for 1 h. This step was repeated three times and the reaction mixture was stirred at rt for 12 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give compound **279** (1.16 g, 81% yield) as a colourless oil.

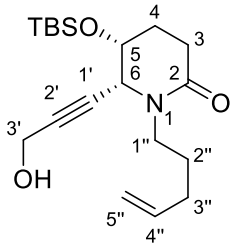
R_f = 0.62 (9:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2936, 1742, 1635, 1610, 1462, 1231, 1170, 1032.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 8.5 Hz, 2H, ArH), 5.84 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 5.06 (d, *J* = 17.0 Hz, 1H, H5"), 5.00 (d, *J* = 10.0 Hz, 1H, H5"), 4.55 (s, 2H, OCH_2Ar), 4.23 (d, *J* = 3.0 Hz, 1H, H6), 4.20 (s, 2H, H3'), 4.08 – 4.03 (m, 1H, H5), 3.83 (s, 3H, OMe), 3.79 (dt, *J* = 14.0, 7.0 Hz, 1H, H1"), 3.18 (dt, *J* = 14.0, 7.0 Hz, 1H, H1"), 2.64-2.58 (ddd, *J* = 18.0, 7.0, 3.5 Hz, 1H, H3), 2.61 (ddd, *J* = 18.0, 10.0, 7.0 Hz, 1H, H3), 2.25 – 2.15 (m, 1H, H4), 2.10 (q, *J* = 7.0 Hz, 2H, H3"), 1.89 – 1.83 (m, 1H, H4), 1.72 (quin, *J* = 7.5 Hz, 2H, H2"), 0.94 (s, 9H, $(CH_3)_3C$)), 0.15 (s, 6H, $(CH_3)_2Si$).).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0 (C2), 159.7 (ArC), 138.2 (C4"), 130.0 (ArCH), 129.7 (ArC), 115.3 (C5"), 114.2 (ArCH), 82.8 (C2'), 81.6 (C1'), 71.3 (OCH_2Ar), 68.2 (C5), 57.2 (C3'), 55.6 (OMe), 55,5 (C6), 46.1 (C1"), 31.4 (C3"), 29.7 (C3), 27.5 (C4), 27.0 (C2"), 26.0 ((CH_3)$_3$C), 18,4 ((CH_3)$_3$*C*), -4.2 (CH_3Si).
ESIMS *m/z* 494 [$(M+Na)^+$ 100%].
HRESIMS calcd. for $C_{27}H_{41}O_4NSiNa$, $(M+Na)^+$ 494.2708, found: 494.2703.

(5*R,6*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-(3-hydroxyprop-1-ynyl)-1-(pent-4-enyl)piperidin-2-one** (**282**)



282

To a mixture of the PMB ether **225** (1.178 g, 2.5 mmol) in CH_2Cl_2 (50 mL) and water (5 mL,) was added DDQ (1.022 g, 4.5 mmol, 1.8 equiv) portionwise at 0 ^{0}C and the mixture was allowed to stirred at rt for 18 h.[104] Then the mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 x 50 mL). The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the primary alcohol **282** (694 mg, 79% yield) as a yellow oil.

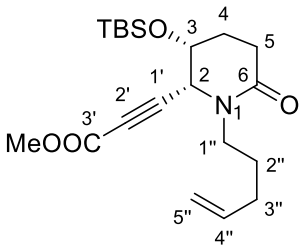
R_f = 0.57 (9:1, EtOAc/petroleum spirit)
IR (neat, ν_{max}/cm^{-1}): 3326, 2926, 2869, 2361, 1622, 1454, 1126, 1024, 913.
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4"), 5.03 (d, *J* = 17.0 Hz, 1H, H5"), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.34 (s, 1H, H6), 4.31 (s, 2H, H3'), 4.05-4.00 (m, 1H, H5), 3.77 (dt, *J* = 13.5, 8.0 Hz, 1H, H1"), 3.12 (dt, *J* = 13.5, 8.0 Hz, 1H, H1"), 2.59 (ddd, dt, *J* = 18.0, 6.5, 4.0 Hz 1H, H3), 2.40 (dt, *J* = 17.5, 7.5 Hz 1H, H3), 2.13-2.03 (m, 3H, H4 and 2H3"), 1.98-1.91 (m,1H, H4), 1.67 (quin, *J* = 7.5 Hz, 2H, H2"), 0.86 (s, 9H, (CH_3)$_3$C), 0.10 (s, 6H, (CH_3)$_2$Si).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0 (C2), 137.8 (C4''), 111.1 (C5''), 85.2 (C2'), 80.6 (C1'), 66.6 (C5), 54.9 (C6), 50.9 (C3'), 45.9 (C1''), 31.0 (C3), 29.7 (C3''), 29.2 (C2''), 26.1 ((CH_3)$_3$C), 26.0 (C4), 18.5 ((CH_3)$_3$*C*), -4.7 (CH_3Si).

ESIMS *m/z* 374 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{33}O_3NSiNa$, $(M+Na)^+$ 374.2127, found:374.2123.

Methyl 3-((2*R,3*R**)-3-(*tert*-butyldimethylsilyloxy)-6-oxo-1-(pent-4-enyl)piperidin-2-yl)propiolate** (**141**)



141

To a solution of the primary alcohol **282** (635 mg, 1.81 mmol) in acetone (20 mL) was added Jones' reagent (2.7 mL) dropwise at 0 ^{0}C. After stirring for 30 min at 0 ^{0}C, CH_3OH (0.5 mL) was added and the reaction mixture was stirred for additional 10 min at 0 ^{0}C. Water (40 mL) was added and the mixture then was extracted with CH_2Cl_2 (4 x 60 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude acid (594 mg, 90% yield) as a yellow solid, which was used in the next step without further purification. To a solution of this acid (594 mg, 1.63 mmol) in anhydrous DMF (20 mL), was added K_2CO_3 (450 mg, 3.26 mmol, 2 equiv) at rt and the mixture was stirred for 15 min under a N_2 atmosphere. Then MeI (610 μL, 9.8 mmol, 6 equiv) was added and the reaction mixture was allowed to stirred at rt for 14 h.[108] Water (40 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 60 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the ester **141** (413 mg, 67% yield) as a pale yellow oil.

R_f = 0.65 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2930, 1717, 1635, 1436, 1249, 858, 751.

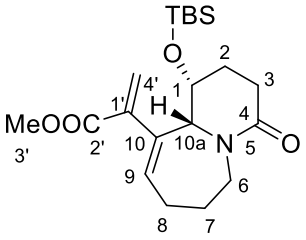
NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.5, 10.5, 6.0 Hz, 1H, H4''), 5.04 (d, *J* = 17.5 Hz, 1H, H5''), 4.98 (d, *J* = 10.0 Hz, 1H, H5'), 4.27 (d, *J* = 3.5 Hz, 1H, H2), 4.10-4.05 (m, 1H, H3), 3.78 (s, 3H, OMe), 3.74 (dt, *J* = 13.5, 8.0 Hz, 1H, H1''), 3.15 (dt, *J* = 13.5, 7.5 Hz, 1H, H1''), 2.63-2.57 (ddd, dt, *J* = 18.0, 7.0, 6.5, Hz 1H, H5), 2.38 (ddd, *J* = 18.0, 10.0, 7.0 Hz 1H, H5), 2.16-2.10 (m, 1H, H4), 2.07 (quin, *J* = 6.5 Hz, 2H, H3''), 1.91-1.85 (m, 1H , H4), 1.72-1.65 (m , 2H, H2''), 0.91 (s, 9H, $(CH_3)_3C$), 0.12 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8 (C6), 153.8 (C3'), 138.0 (C4''), 115.5 (C5''), 84.0 (C1'), 77.2 (C2'), 67.8 (C3), 55.7 (C5), 53.1 (OMe), 46.4 (C1''), 31.4 (C3''), 29.5 (C5), 27.7 (C4),26.8 (C2''), 25.9 ($(CH_3)_3C$), 18.3 ($(CH_3)_3C$), -4.2 (CH_3Si).

ESIMS *m/z* 402 $[(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{20}H_{33}O_4NSiNa$, $(M+Na)^+$ 402.2084, found: 402.2077.

Methyl 2-((1*R,10a*R**)-1-(*tert*-butyldimethylsilyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)acrylate** (**140**)



140

To a solution of the ene-yne **141** (872 mg, 2.3 mmol) in anhydrous CH_2Cl_2 (80 mL) was added Grubb's 1st generation Ru catalyst (189 mg, 0.23 mmol, 0.1 equiv) under a N_2 atmosphere and the mixture was stirred at rt for 8 h.[60] The reaction mixture then was exposed to open air for 30 min. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give the bicyclic compound **140** (680 mg, 78% yield) as a yellow oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2952, 2929, 1720, 1639, 1251, 1222, 1202, 1074, 990, 812, 774.

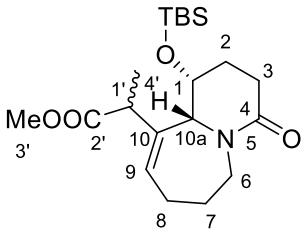
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (s, 1H, H4'), 5.94 – 5.87 (t, *J* = 8.0 Hz, 1H, H9), 5.73 (s, 1H, H4'), 4.27 (s, 1H, H10a), 4.23 (dd, *J* = 13.0, 7.5 Hz, 1H, H6), 4.00 (s, 1H, H1), 3.77 (s, 3H, OMe), 3.20 (td, *J* = 13.0, 6.5 Hz, 1H, H6), 2.75 – 2.64 (m, 2H, H3 and H8), 2.34 (dd, *J* = 17.7, 5.7 Hz, 1H, H3), 2.23 – 2.13 (m, 1H, H7), 1.96 – 1.90 (m, 1H, H2), 1.90 – 1.76 (m, 2H, H8 and H2), 1.58 – 1.49 (m, 1H, H7), 0.88 (s, 9H, $(CH_3)_3C$), 0.02 (s, 6H, $(CH_3)_2Si$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 (C4), 167.5 (C2'), 142.3 (C10), 136.1 (C1'), 132.8 (C9), 127.4 (C4'), 67.6 (C10a), 66.5 (C1), 52.5 (OMe), 42.3 (C6), 28.1 (C2), 27.1 (C3), 26.2 ($(CH_3)_3C$), 24.0 (C7), 22.1 (C8), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si).

ESIMS *m/z* 380 $[(M+H)^+$ 100%].

HRESIMS calcd. for $C_{20}H_{34}O_4NSi$, $(M+H)^+$ 380.2261, found: 380.2257.

Methyl 2-((1*R,10a*R**)-1-(*tert*-butyldimethylsilyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)propanoate** (**139**)



139

Sodiumborohydride (532 mg, 14 mmol, 8 equiv) was added portionwise to a solution of the enone **140** (663 mg, 1.75 mmol) in anhydrous MeOH (20 mL) at 0 ^{0}C under a N_2 atmosphere and the mixture was stirred at 0 ^{0}C for 3 h.[60] Saturated aqueous $NaHCO_3$ solution (30 mL) was added at 0 ^{0}C and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:2, EtOAc/petroleum spirit) to give an unseparable mixture of diasteroisomers **139** (517 mg, 78% yield) as a pale yellow oil.

R_f = 0.69 (4:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 2948, 2930, 1736, 1631, 1462, 1251, 1202, 1166, 1095, 993, 836.

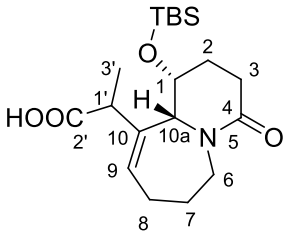
^{1}H NMR (500 MHz, $CDCl_3$) δ *major diastereomer* 5.86-5.79 (m, 1H, H9), 4.26-4.19 (m, H1 and H6), 3.93 (s, 1H, H10a), 3.69 (s, 3H, OMe), 3.04-2.96 (m, 1H, H1'), 2.85-2.69 (m, 2H, H6 and H3), 2.69-2.56 (m, 1H, H8), 2.41-2.32 (m, 1H, H3), 2.16-2.07 (m, 1H, H7), 2.02-1.94 (m, 1H, H2), 1.91-1.83 (m, 1H, H2), 1.83-1.75 (m, 1H, H8), 1.34 (d, *J* = 7.5 Hz, 3H, H4'), 0.86 (s, 9H, $(CH_3)_3C$), 0.11 (s, 6H, $(CH_3)_2Si$).
^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (C2'), 169.5 (C4), 135.9 (C10), 127.8 (C9), 69.2 (C1), 66.9 (C10a), 52.1 (OMe), 44.8 (C1'), 42.1 (C6), 28.4 (C2), 27.1 (C3), 26.1 ($(CH_3)_3C$), 23.9 (C7), 21.5 (C8), 19.0 (C4'), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si).
^{1}H NMR (500 MHz, $CDCl_3$) δ *minor diastereomer* (*in part*) 5.86-5.79 (m, 1H, H9), 4.19-4.13 (m, H1 and H6), 3.97 (s, 1H, H10a), 3.70 (s, 3H, OMe), 3.04-2.96 (m, 1H, H1'), 2.94-2.86 (m, 1H, H6), 2.85-2.69 (m, 1H, H3), 2.69-2.56 (m, 1H, H8), 2.41-2.32 (m, 1H, H3), 2.16-2.07 (m, 1H, H7), 2.02-1.94 (m, 1H, H2), 1.91-1.83 (m, 1H, H2), 1.83-1.75 (m, 1H, H8), 1.35 (d, *J* = 7.5 Hz, 3H, H4'), 0.86 (s, 9H, $(CH_3)_3C$), 0.1 (s, 6H, $(CH_3)_2Si$).
^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4 (C2'), 169.5 (C4),134.7 (C10), 127.5 (C9), 69.8 (C1), 65.8 (C10a), 52.4 (OMe), 43.2 (C1'), 42.1 (C6), 28.2 (C2), 27.0 (C3), 26.1 ($(CH_3)_3C$), 23.8 (C7), 21.5 (C8), 19.0 (C4'), 18.5 ($(CH_3)_3C$), -4.7 (CH_3Si).
ESIMS *m/z* 382 [$(M+H)^+$ 100%].
HRESIMS calcd. for $C_{20}H_{36}NO_4Si$, $(M+H)^+$ 382.2414, found: 382.2411.

Attempted bromolactonization of 139

To a solution of mixture **139** (57 mg, 0.15 mmol) in MeOH (12.5 mL), was added slowly aqueous 1M NaOH solution (1.6 mL) at 0 ^{0}C and the mixture was stirred at 0 ^{0}C for 8 h. The reaction mixture then was acidified with 1M HCl solution to pH = 5 and extracted with EtOAc (4 x 50 ml). Organic extracts were combined, dried over $MgSO_4$ and filtered. Solvent was evaporated in vacuo to afford a crude mixture of acids, which was used in the next step without further purification. The crude acid was dissolved in $CHCl_3$ (15 mL), and $CuBr_2$ on alumina (0.85 mg) was added. The mixture was heated at 65 ˚C for 60 h. After filteration, the solid was washed with MeOH, and the filterate was concentrated. Water (5 mL) was added to the residue, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine soluition, dried over $MgSO_4$, filtered and

concebtrated. The residue was dissolved in EtOAc (3.5 mL), and Et_3N (40 μL, 0.3 mmol) was added and the solution was stirred at rt for 16 h. EtOAc (20 mL) was added and the mixture was washed with 10% HCl solution, brine and saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered and concentrated. ^{1}H NMR analysis of the residue showed a diastereomeric mixture of acids. From this crude mixture the major diastereomer (**290**) was purely isolated by column chromatography (9:1, EtOAc/petroleum spirit).[60]

2-((1*R*,10a*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-10-yl)propanoic acid (**290**)



290

Mp = 207-209 ºC

R_f = 0.69 (4:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 2951, 1718, 1615, 1256, 1092, 1067, 988, 924, 838.

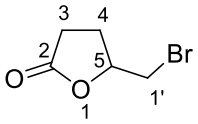
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (t, *J* = 7.5 Hz, 1H, H9), 4.22 (s, 1H, H1), 4.16 (dd, *J* = 13.1, 7.2 Hz, 1H, H6), 4.11 (s, 1H, H10a), 3.09 – 2.99 (m, 2H, H6 and H1'), 2.81 – 2.72 (m, 1H, H3), 2.61 (m, 1H, H8), 2.44 (dd, *J* = 17.7, 5.5 Hz, 1H, H3), 2.20 – 2.10 (m, 1H, H7), 2.02 – 1.96 (m, 1H, H2), 1.89 (m, 2H, H8 and H2), 1.51 (dt, *J* = 13.2, 6.4 Hz, 1H, H7), 1.40 (d, *J* = 7.1 Hz, 3H, H3'), 0.88 (s, 9H, $(CH_3)_3C$), 0.09 (s, 3H, CH_3Si), 0.03 (s, 2H), 0.03 (s, 3H, CH_3Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3 (C2'), 170.4 (C4), 134.7 (C10), 127.4 (C9), 69.8 (C1), 65.7 (C10a), 43.2 (C1'), 42.7 (C6), 28.1 (C2), 26.9 (C3), 26.1 ($(CH_3)_3C$), 23.9 (C7), 21.5 (C8), 18.4 ($(CH_3)_3C$), 15.8 (C3'), -4.2 (CH_3Si), -4.71 (CH_3Si).

ESIMS *m/z* 368 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{32}NO_4Si$, $(M+H)^+$ 368.2257, found: 368.2240.

5-(Bromomethyl)dihydrofuran-2(3*H*)-one (300)[139]

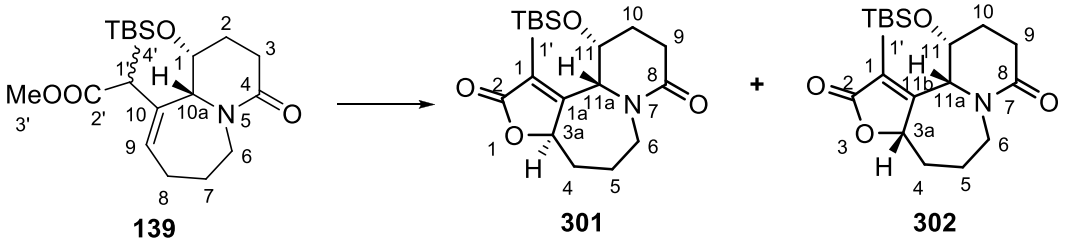


300

Diphenyl diselenide (16 mg, 0.05 mmol, 0.05 equiv) was added to a solution of 4-pentenoic acid (100 mg, 1.00 mmol) in CH_3CN (3 mL) and the resulting mixture was cooled to -30 ^{0}C. N-bromosuccinimide (231 mg, 1.3 mmol, 1.3 equiv) was added with stirring, and the resulting reaction mixture was stirred at -30 ^{0}C for 3 h.[111] The resulting solution was concentrated to <1 mL *in vacuo*, and EtOAc (60 mL) was added. The resulting organic layer was washed with water (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to afford a yellow residue, which was purified by silica gel column chromatography (1:3, EtOAc/petroleum spirit) to give compound **300** (152 mg, 68% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (ddd, *J* = 12.0, 6.8, 5.1 Hz, 1H), 3.54 (d, *J* = 4.9 Hz, 2H, H1'), 2.65 – 2.49 (m, 2H), 2.45 – 2.37 (m, 1H), 2.12 – 2.03 (m, 1H).
NMR spectroscopic data matched with the published data.[139]

Bromolactonization of 139



139 **301** **302**

To a solution of **139** (648 mg, 1.3 mmol) in MeOH (15 mL), was added slowly 1M aqueous NaOH solution (13.7 mL) at 0 ^{0}C and the mixture was stirred at 0 ^{0}C for 8 h. The mixture the was acidified to pH = 5 with 1M HCl solution and extracted with EtOAc (4 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ and

filtered. The solvent was evaporated *in vacuo* to afford a diasteromeric mixture of acids, which was used in the step without further purification.

To a solution of this acid in CH_3CN (4 mL) was added diphenyl diselenide (21 mg, 0.65 mmol, 0.05 equiv) and the resulting mixture was cooled to -30 ^{0}C. *N*-bromosuccinimide (277 mg, 1.69 mmol, 1.3 equiv) was added with stirring, and the resulting reaction mixture was stirred at -30 ^{0}C for 3 h.[111] The resulting solution was concentrated to <1 mL *in vacuo*, and EtOAc (60 mL) was added. The resulting organic layer was washed with water (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to afford a yellow residue, which then was dissolved in EtOAc (10 mL). Et_3N (0.2 mL) was added to the resulting solution and the mixture was stirred at rt for 18 h. The mixture was then diluted with EtOAc (40 mL), washed with water (2 x 10 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography (6:4 to 9:1, EtOAc/petroleum spirit) of the resulting residue gave the tricyclic compounds **301** (192 mg, 31% yield) and **302** (124 mg, 20% yield) as white solids.

(3a*R,11*R**,11a*R**)-11-(*tert*-Butyldimethylsilyloxy)-1,3a,11a-trimethyl-3a,4,5,6,9,10,11,11a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione** (**301**)

Mp = 137-139 ºC

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2951, 2930, 1751, 1630, 1253, 1196, 1148, 1082, 993, 835, 776.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (d, *J* = 9.5 Hz, 1H, H3a), 4.71 (s, 1H, H11a), 4.52 (d, *J* = 10.5 Hz, 1H, H6), 4.21 (s, 1H, H11), 2.79 – 2.69 (m, 1H, H9), 2.54 – 2.47 (m, 1H, H4), 2.42-2.36 (m, 1H, H9), 2.27 – 2.15 (m, 1H, H6), 2.02-1.96 (m, 2H, H10), 1.90 (s, 3H, CH_3), 1.88-1.81 (m, 1H, H5), 1.75-1.65 (m, 1H, H5), 1.22 – 1.14 (m, 1H, H4), 0.84 (s, 9H, $(CH_3)_3C$), 0.03 (s, 6H, $(CH_3)_2$ Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5 (C2), 169.9 (C8), 163.6 (C11b), 124.2 (C1), 83.9 (C3a) , 67.7 (C11), 63.2 (C11a), 47.6 (C6), 36.5 (C4) , 28.4 (C10), 26.6 (C9), 26.0 ((CH_3)$_3$C), 25.1 (C5), 18.2 ((CH_3)$_3$*C*), 9.74 (C1'), -4.6 (CH_3Si), -4.9 (CH_3Si).

ESIMS *m/z* 366 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{32}NO_4Si$, $(M+H)^+$ 366.2101, found: 366.2099.

(3a*S,11*R**,11a*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyl-3a,4,5,6,9,10,11,11a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione** (**302**)

Mp = 140-142 ºC

R_f = 0.69 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2954, 2930, 1749, 1628, 1254, 1160, 1103, 938, 834, 777.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (d, *J* = 11.0 Hz, 1H, H3a), 4.51 – 4.45 (m, 1H, H11), 4.37-4.30 (m, 1H, H6), 4.27 (d, *J* = 3.0 Hz, 1H, H11a), 2.94 – 2.87 (m, 1H, H6), 2.57 (dt, *J* = 17.5, 7.0 Hz, 1H, H9), 2.44 (dt, *J* = 17.5, 7.0 Hz 1H, H9), 2.33 – 2.26 (m, 1H, H4), 2.19 – 2.07 (m, 3H, H10 and H5), 2.10 (s, 3H, H1'), 1.74 – 1.63 (m, 1H, H5), 1.60-1.54 (m, 1H, H4), 0.86 (s, 9H, $(CH_3)_3C$), 0.12 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (C2), 170.1 (C8), 157.3 (C11b), 123.3 (C1), 83.4 (C3a), 68.3 (C11), 62.3 (C11a), 46.1 (C6), 29.3 (C9), 28.3 (C4), 27.9 (C10), 26.0 ($(CH_3)_3C$), 21.5 (C5), 18.3 ($(CH_3)_3C$), 12.6 (C1'), -4.2 (CH_3Si), -4.6 (CH_3Si).

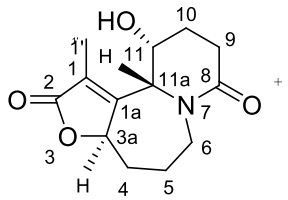
ESIMS *m/z* 366 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{32}NO_4Si$, $(M+H)^+$ 366.2101, found: 366.2110.

Synthesis of 301 from 302

To a solution of compound **302** (104 mg, 0.28 mmol) in $CHCl_3$ (2 mL), was added DBU (3 drops) and the mixture was stirred at rt for 2 d. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give compound **301** (61 mg, 60% yield).

(3a*R,11*R**,11a*R**)-11-Hydroxy-1,3a,11a-trimethyl-3a,4,5,6,9,10,11,11a-octahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione** (**307**)



307

To a solution of the TBS ether **301** (30 mg, 0.082 mmol) and acetic acid (12 μL, 0.206 mmol, 3 equiv) in anhydrous THF at 0 ºC was added a 1M solution of TBAF in THF (206 μL, 0.206 mmol, 3 equiv).[139] The mixture was then warmed to rt and stirred for 14 h. The reaction was quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to give the alcohol **307** (16 mg, 78% yield) as a pale yellow solid.

Mp = 137-139 ºC

R_f = 0.69 (9:1), EtOAc/MeOH)

IR (neat, ν_{max}/cm^{-1}): 3326, 2925, 1774, 1498, 1177, 1166, 1137, 1071, 1025, 769, 682.

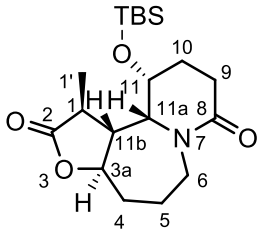
^{1}H NMR (500 MHz, CD_3OD) δ 5.10 (d, *J* = 7.1 Hz, 1H, H3a), 4.96 (d, *J* = 2.5 Hz, 1H, H11a), 4.42 (dd, *J* = 13.9, 4.7 Hz, 1H, H6), 4.22 (s, 1H, 11), 2.76 – 2.67 (m, 1H, H9), 2.49 – 2.41 (m, 1H, H4), 2.40 – 2.29 (m, 2H, H6 and H9), 2.11 – 1.96 (m, 2H, H10), 1.90 (s, 3H, H11'), 1.87 – 1.81 (m, 1H, H5), 1.73 – 1.62 (m, 1H, H5), 1.22 (tdd, *J* = 14.2, 10.1, 3.9 Hz, 1H, H4).

^{13}C NMR (125 MHz, CD_3OD) δ 176.0 (C2), 172.8 (C8), 165.5 (C1a), 125.2 C1), 85.6 (C3a), 66.7 (C11), 63.8 (C11a),48.4 (C6), 37.1 (C4), 28.4 (C9), 27.5 (C10), 26.0 (C5), 9.3 (C1').

ESIMS *m/z* 252 $[(M+H)^+$ 100%].

HRESIMS calcd. for $C_{13}H_{18}NO_4$, $(M+H)^+$ 252.1236, found: 252.1238.

(1*S,3a*R**,11*R**,11a*R**,11b*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyldecahydrofuro[3,2-c]pyrido[1,2-*a*]azepine-2,8-dione** (**306**)



306

Magnesium tunnings (39 mg, 1.64 mmol, 15 equiv) were added to a solution of the α,β-unsaturated lactone **301** (40 mg, 0.11 mmol) in MeOH (1.2 mL) at 0 ^{0}C. The mixture was warmed to rt and stirred for 1 d.[114] After cooling to 0 ^{0}C, acetic acid (12 µL, 0.22 mmol. 2 equiv) was added and the resulting mixture was stirred at rt for 30 min. Water (5 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (7:3, EtOAc/petroleum spirit) to provide compound **306** (29 mg, 71% yield) as a white solid. Recrystalization for X-ray structural analysis was performed using a solvent mixture of CH_2Cl_2 and *n*-hexane at rt.

Mp = 160-162 ºC

R_f = 0.65 (9:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3233, 2957, 2318, 1765, 1632, 1448, 1390, 1253, 1185, 1101, 1065, 1014, 774.

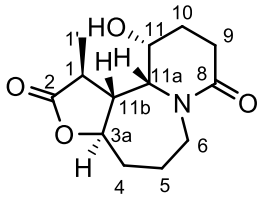
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (td, *J* = 11.5, 2.5 Hz, IH, H3a), 4.48 (d, *J* = 13.5 Hz, IH, H6), 4.25 (s, 1H, H11), 3.73 (d, *J* = 7 Hz, 1H, H11a), 2.86 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.71-2.60 (m, 2H, H6 and H9), 2.43-2.31 (m , 3H, H9, H4 and H11b), 2.09-2.03 (m, 1H, H10), 1.92-1.84 (m, 2H, H10 and H5), 1.68-1.58 (m, 1H, H5), 1.43-1.33 (m, 1H, H4), 1.30 (d, *J* = 7.0 Hz, 3H, H1'), 0.88 (s, 9H, $(CH_3)_3C$), 0.16 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9 (C2), 169.9 (C8), 79.7 (C3a), 66.0 (C11), 59.3 (C11a), 53.4 (C11b), 43.1 (C6), 37.9 (C1), 28.0 (C9), 26.8 (C10), 26.2 ($(CH_3)_3C$), 25.1 (C5), 18.3 ($(CH_3)_3C$), 15.2 (C1'), -2.9 (CH_3Si), -4.7 (CH_3Si).

ESIMS *m/z* 368 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{34}O_4NSi$, $(M+H)^+$ 368.2257, found: 368.2256.

(1*S,3a*R**,11*R**,11a*R**,11b**R*)-11-Hydroxy-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepine-2,8-dione (138)**[134]



138

To a solution of the TBS ether **306** (30 mg, 0.082 mmol) and acetic acid (12 µL, 0.206 mmol, 3 equiv) at 0 ºC was added a solution of 1M TBAF in THF (206 µL, 0.206 mmol, 3 equiv). The mixture then was warmed to rt and stirred for 14 h.[139] The reaction was quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the alcohol **138** (16 mg, 80% yield) as a pale yellow solid.

Mp = 254-256 ºC

R_f = 0.68 (9:1, EtOAc/MeOH)

IR (neat, ν_{max}/cm^{-1}): 3340, 2957, 2856, 1765, 1624, 1183, 1104, 1067, 1012, 870, 794.

^{1}H NMR (500 MHz, CD_3OD) δ 4.86 – 4.78 (m, 1H, H3a), 4.28 (d, *J* =13.5 Hz, 1H, H6β), 4.22 (s, 1H, H11), 3.85 (dd, *J* =7.5, 2.0 Hz 1H, H11a), 3.18 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.84 (t, *J* = 13.5 Hz, 1H, H6α), 2.71 – 2.61 (m, 1H, H9), 2.61-2.54 (m, 1H, H10), 2.30 (m, 1H, H9), 2.25-2.19 (m, 1H, H4), 2.01 – 1.88 (m, 1H, H10), 1.85-1.79 (m, 1H, H5), 1.59 (m, 1H, H5), 1.46 (m, 1H, H4), 1.27 (d, *J* = 7.0 Hz, 3H, H1').

^{13}C NMR (125 MHz, CD_3OD) δ 181.1 (C2), 172.9 (C8), 81.9 (C3a), 64.6 (C11), 59.5 (C11a), 53.90 (C11b), 44.2 (C6), 39.1 (C1), 36.0 (C4), 28.3 (C10), 27.7 (C9), 25.7 (C5), 15.0 (C1').

ESIMS *m/z* 354 [$(M+H)^+$ 100%].

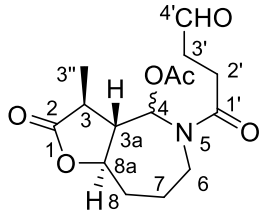
HRESIMS calcd. for $C_{13}H_{20}O_4N$, $(M+H)^+$ 254.1392, found: 254.1396.

Preparation of 138 from 307

Magnesium tunnings (36 mg, 1.5 mmol, 15 equiv) were added to a solution of the α,β-unsaturated lactone **307** (24 mg, 0.1 mmol) in MeOH (1.00 mL) at 0 ^{0}C. The mixture was warmed to rt and stirred for 1 d. After cooling to 0 ^{0}C, acetic acid (12 µL, 0.20 mmol. 2 equiv) was added and the resulting mixture was stirred at rt for 30 min.[114] Water (5 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (7:3, EtOAc/petroleum spirit) to provide compound **138** (17 mg, 70% yield).

Attempted synthesis of 137

To a solution of **138** (15.7 mg) in CH_2Cl_2 (3 mL) were added BIAB (24 mg, 0.07 mmol, 1.2 equiv) and I_2 (16.6 mg, 0.065 mmol, 1.05 equiv). The mixture the was irradiated with a UV lamp at rt, 500 W for 30 min.[58] The reaction was quenched with 1M $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2:3, EtOAc/petroleum spirit) to give the major product **318** (3.4 mg, 16% yield) as a pale yellow oil and as a mixture of diastereomers (dr = 2.3:1).



315

R_f = 0.69 (4:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 2924, 1764, 1640, 1501, 1448, 1397, 1244, 973.

^{1}H NMR (500 MHz, $CDCl_3$) *major isomer* δ 9.79 (s, 1H, CHO), 7.06 (d, *J* = 9.0 Hz, 1H, H4), 4.24-4.13 (m, 2H, H8a and H6), 3.02-2.80 (m, 3H, H2', H6 and H3'), 2.80-

2.62 (m, 3H, H3, H2' and H3'), 2.42-2.37 (m, 1H, H3a and H8), 2.11 (s, 3H, CH_3CO), 180-1.75 (m, 1H, H7), 1.68-1.56 (m, 2H, H8 and H7), 1.25 (d, *J* = 7.0 Hz, 3H, H3'').

^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 200.9 (C4'), 177.0 (C2), 171.5 (C1), 170.0 (CH_3CO), 82.6 (C4), 78.1 (C8a), 55.2 (C3a), 41.0 (C6), 39.1 (C2'), 34.4 (C8), 25.4 (C3'), 23.5 (C7), 21.0 (CH_3CO), 14.7 (C3'').

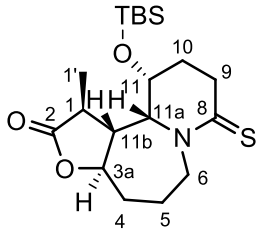
^{1}H NMR (500 MHz, $CDCl_3$) *minor isomer* (in part) δ 9.81 (s, 1H, CHO), 6.66 (d, *J* = 8.0 Hz, 1H, H4), 4.13-4.07 (m, 2H, H8a and H6), 2.34-2.27 (m, 1H, H3a), 2.03 (s, 3H, CH_3CO), 1.21 (d, *J* = 7.0 Hz, 3H, H3'').

^{13}C NMR (125 MHz, $CDCl_3$) *minor isomer* δ 200.6 (C4'), 177.4 (C2), 171.8 (C1), 169.0 (CH_3CO), 78.2 (C4), 77.3 (C8a), 54.0 (C3a), 41.0 (C6), 38.5 (C2'), 34.0 (C8), 25.9 (C3'), 23.5 (C7), 20.8 (CH_3CO), 15.0 (C3'').

ESIMS *m/z* 366 $[(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{15}H_{21}O_8NNa$, $(M+Na)^+$ 366.1158, found: 366.1165.

(1*S,3a*R**,11*R**,11a*R**,11b*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyl-8-thioxodecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-2(8*H*)-one** (**324**)



324

Lawessons' reagent (21.2 mg, 0.053 mmol, 0.055 equiv) was added to a solution of the lactam **306** (35 mg, 0.095 mmol) in THF (12 mL) and the reaction mixture was heated at reflux temperature for 3 h.[25] The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (3:1, EtOAc/petroleum spirit) to give the thio-lactam **324** (29 mg, 80% yield) as a white solid.

Mp = 154-156 ºC

R_f = 0.61 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2952, 1736, 1493, 1254, 1177, 1154, 1066, 1010, 980, 794.

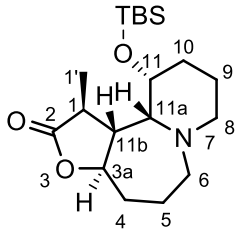
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (dd, *J* = 13.5, 4.0 Hz, 1H, H6β), 4.69 (dt, *J* = 11.5, 3.5 Hz, 1H, H3a), 4.34 (s, 1H, H11), 3.76 (dd, *J* = 7.5, 2.0 Hz 1H, H11a), 3.19-3.09 (m, 3H, H6 and H9), 2.88 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.60 – 2.52 (m, 1H, H11b), 2.40-2.33 (m, 1H, H4), 2.10 – 1.83 (m, 4H, H5 and H10), 1.47 (qd, *J* = 13.0, 5.5 Hz, 1H, H4), 1.31 (d, *J* = 7.0 Hz, 3H, H1'), 0.87 (s, 9H, $(CH_3)_3C$), 0.15 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1 (C8), 177.4 (C2), 79.3 (C3a), 66.1 (C11), 62.2 (C11a), 52.9 (C11b), 51.2 (C6), 38.0 (C1), 37.0 (C9), 35.4 (C4), 28.0 (C3), 26.2 ($(CH_3)_3C$), 23.1 (C5), 18.3 ($(CH_3)_3C$), 15.3 (C1'), -2.9 (CH_3Si), -4.8 (CH_3Si).

ESIMS *m/z* 384 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{34}O_3NSiS$, $(M+H)^+$ 384.2036, found: 384.2029.

(1*S,3a*R**,11*R**,11a*R**,11b*R**)-11-(*tert*-Butyldimethylsilyloxy)-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-2(8*H*)-one** (**325**)



325

An excess amount of Raney Ni (*ca* 20 mg) was added to a solution of the thio-lactam **324** (26.5 mg, 0.07 mmol) in EtOH (4 mL) and the mixture was heated at reflux temperature for 4 h.[25] The mixture was filtered through a small pad of celite and the filtered cake was washed with EtOH (60 mL). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the amine **325** (19 mg, 75% yield) as a pale yellow solid.

Mp = 117-119 ºC

R_f = 0.58 (4:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2946, 2927, 1762, 1465, 1325, 1209, 1165, 1025.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (dt, *J* = 10.5, 3.0, 1H, H3a), 3.94 (s, 1H, H11), 2.88 (d, *J* = 11.1 Hz, 1H, H8), 2.78 (dq, *J* = 14.0, 7.0 Hz, 1H, H1), 2.62 (dd, *J* = 19.0,

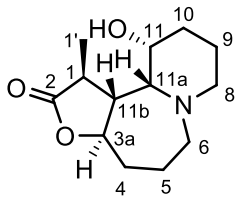
8.0 Hz, 1H, H6), 2.48-2.40 (m, 2H, H6 and H8), 2.36 (d, *J* = 7.5 Hz, 1H, H11a), 2.28 (dd, *J* = 10.0, 5.0 Hz, 1H, H4), 2.19 (apparent dt, *J* = 12.0, 9.0 Hz, 1H, H11b), 2.00 – 1.91 (m, 1H, H3), 1.91 – 1.83 (m, 1H, H3), 1.69 (dt, *J* = 16.0, 8.0 Hz, 2H, H5), 1.41 – 1.33 (m, 2H, H9), 1.31 – 1.21 (m, 1H, H4), 1.30 (d, *J* = 7.0 Hz, 3H, H1'), 0.89 (s, 9H, $(CH_3)_3C$), -0.11 (s, 6H $(CH_3)_2Si$,).

^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3 (C2), 80.5 (C3a), 67.7 (C11), 63.7 (C11a), 58.8 (C8), 55.0 (C6), 53.8 (C11b), 37.6 (C1), 36.1 (C4), 32.7 (C10), 27.7 (C5), 26.3 ($(CH_3)_3C$), 21.5 (C9), 18.5 ($(CH_3)_3C$) 15.2 (C1'), -3.0 (CH_3Si), -4.6 (CH_3Si).

ESIMS *m/z* 354 $[(M+H)^+$ 100%].

HRESIMS calcd. for $C_{19}H_{36}O_3NSi$, $(M+H)^+$ 354.24564, found: 354.2452.

(1*S,3a*R**,11*R**,11a*R**,11b*R**)-11-Hydroxy-1-methyldecahydrofuro[3,2-*c*]pyrido[1,2-*a*]azepin-2(8*H*)-one** (**326**)



326

To a solution of the TBS ether **325** (23 mg, 0.065 mmol) and acetic acid (11 μL, 0.195 mmol, 3 equiv) at 0 ºC was added a 1M solution of TBAF in THF (195 μl, 0.195 mmol, 3 equiv).[139] The mixture then was warmed to rt and stirred for 14 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the alcohol **326** (17 mg, 78% yield) as a pale yellow solid.

Mp = 210-212 ºC

R_f = 0.61 (9:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 3431, 2928, 1762, 1453, 1261, 1182, 1165, 1125, 1102, 1075, 1025, 769, 682.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (dt, *J* = 11.0, 3.5 Hz, 1H, H3a), 3.86 (s, 1H, H11), 2.96-2.84 (m, 2H, H1 and H8), 2.75 – 2.68 (m, 1H, H6), 2.56 – 2.46 (m, 2H, H6 and H8), 2.46 – 2.42 (m, 1H, H11a), 2.31 (d, *J* = 10.0 Hz, 1H, H4), 2.20 (apparent ddd, *J* = 12.5, 11.0, 8.0 Hz, 1H, H11b), 1.89 – 1.76 (m, 3H, H10, H9 and H5), 1.70 – 1.58 (m, 1H, H5), 1.54 – 1.48 (m, 1H, H9), 1.43 – 1.32 (m, 1H, H10), 1.32 – 1.23 (m, 1H, H4), 1.22 (d, *J* = 7.0 Hz, 3H, H1').

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7 (C2), 80.6 (C3a), 65.7 (C11), 64.1 (C11a), 59.3 (C8), 55.3 (C6), 53.4 (C11b), 37.7 (C1), 35.7 (C4), 32.0 (C10), 27.8 (C5), 21.2 (C9), 14.4 (C1').

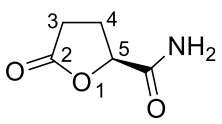
ESIMS *m/z* 240 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{13}H_{22}O_3N$, $(M+H)^+$ 240.1600, found: 240.1601.

Attempted photochemical cyclization reaction of 323

To a solution of **323** (14.4 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) were added BIAB (24 mg, 0.07 mmol, 1.2 equiv) and I_2 (16.6 mg, 0.065 mmol, 1.05 equiv). The mixture the was irradiated with a UV lamp at rt, 500 W for 15 min.[58] The reaction was quenched with 1M $Na_2S_2O_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo*. The ^{1}H NMR analysis of the crude reaction mixture and TLC analysis showed a complex mixture of products.

(*S*)-5-Oxotetrahydrofuran-2-carboxamide (**334**)



334

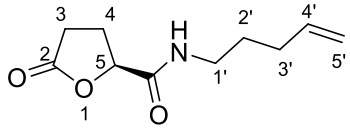
Thionyl chloride (38 mL, 189 mmol, 3 equiv) was added to the lactone acid **166** (8.19 g, 63 mmol) and the mixture was stirred at 60 ºC for 4 h. The excess thionyl chloride was removed *in vacuo*, and then under high vacuum at 55 ºC for 12 h. The

crude product (7.7 g, 82% yield) was used for the next step without further purification.[121]

A saturated NH_3 solution in Et_2O was prepared in a 2L 2-necked flask under a N_2 atmosphere by bubbling NH_3 gas through Et_2O (200 mL). The acid chloride (3.5 g, 23.6 mmol) then was added dropwide at rt via syringe to this solution (while still bubbling with NH_3) over a period of 20 min.[121] The mixture then was stirred for additional 20 min. The solid was filtered and put in a flask with $CHCl_3$ (300 mL) and stirred for 45 min. The solid was filtered and the solid cake was washed with hot $CHCl_3$ (100 mL). The washings were combine and the solvent was removed *in vacuo* to afford the lactone amide **334** (2.22 g, 73%) as a white solid, which had spectroscopic data consistent with those in the literature.[140]

^{1}H NMR (500 MHz, DMSO-D_6) δ 7.52 (bs, 2H, NH_2), 4.84 (m, 1H, H5), 2.76-1.72 (m, 4H, H3 and H4).

(*S*)-5-Oxo-*N*-(pent-4-enyl)tetrahydrofuran-2-carboxamide (**333**)



333

To a solution of the primary lactone amide **334** (1.7 g, 7.75 mmol) in DMF (120 mL) at 0 ºC were added 18-crown-6 (40 mg, 0.15 mmol, 0.2 eq), TBAI (200 mg, 0.54 mmol, 0.07 eq) and *t*-BuOK (955 mg, 8.53 mmol, 1.1 eq) under a N_2 atmosphere. The mixture was stirred at 0 ºC for 30 min then allowed to warm to rt and stirred for 14 h.[121] The reaction was quenched with water (150 mL) at 0 ºC and extracted with EtOAc (3 x 150 mL). The organic extracts were combined, wash with water (100 mL), dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (3:7, EtOAc/petroleum spirit) to provide the amide **333** (1.61 g, 62% yield) as a pale yellow oil and the imide **335** (597 mg, 23% yield) as a pale yellow oil.

$[\alpha]_D^{23}$ -36.2 (*c* 6.7, $CHCl_3$)

R_f = 0.68 (1:1, EtOAc/petroleum spirit)

IR (neat, ν_{max}/cm^{-1}): 3390, 2941, 1743, 1665, 1369, 1319, 1127, 997.

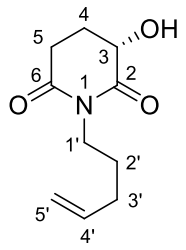
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (bs, 1H, NH), 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4'), 5.04 (d, *J* = 17.0 Hz, 1H, H5'), 5.00 (d, *J* = 10.0 Hz, 1H, H5'), 4.84 (t, *J* = 7.5 Hz, 1H, H5), 3.39 – 3.23 (m, 2H, H1'), 2.69 – 2.59 (m, 1H, H3), 2.59 – 2.53 (m, 2H, H4), 2.40-2.32 (m, 1H, H3), 2.09 (dd, *J* = 14.0, 7.0 Hz, 2H, H3'), 1.69 – 1.59 (m, 2H, H2').

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0 (C2), 169.5 (CO-NH), 137.7 (C4'), 115.9 (C5'), 77.8 (C5), 39.2 (C1'), 31.3 (C3'), 28.8 (C2'), 28.0 (C4), 26.2 (C3).

ESIMS *m/z* 198 [(M+H)$^+$ 100%].

HRESIMS calcd. for $C_{10}H_{16}O_3N$, (M+H)$^+$, 198.1051, found: 198.1051.

(*S*)-3-Hydroxy-1-(pent-4-enyl)piperidine-2,6-dione (**335**)



335

To a solution of the lactone amide **333** (887 mg, 4.5 mmol) in THF (50 mL) at -78 ºC was added *t*-BuOK (151 mg, 1.35 mg, 0.3 eq). The mixture was stirred at -78 ºC for 2 h and quenched with H_2O (50 mL).[121] The aqueous phase was extracted with EtOAc (3 x 75 mL). The organic extracts were combined, wash with H_2O (100 mL), dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:1, EtOAc/petroleum spirit) to provide the imide **335** (807 mg, 91% yield) as a pale yellow oil, which had spectroscopic data consistent with the literature.

$[\alpha]_D^{23}$ -67.2 (*c* 5.0, $CHCl_3$)

R_f = 0.68 (3:2, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3456, 2960, 1730, 1655, 1435, 1339, 1154, 1127,

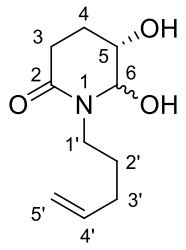
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, H4'), 5.02 (d, *J* = 17.0, Hz, 1H, H5'), 4.96 (d, *J* = 10.0 Hz, 1H, H5'), 4.20 (dd, *J* = 12.5, 5.5 Hz, 1H, H3), 3.83 – 3.75 (m, 1H, H1'), 3.75 – 3.68 (m, 1H, H1'), 2.90 – 2.83 (m, 1H, H5), 2.66 – 2.57 (m, 1H, H5), 2.35 – 2.28 (m, 1H, H4), 2.05 (q, *J* = 7.0 Hz, 2H, H3'), 1.88 (m, 1H, H4), 1.64 – 1.56 (m, 2H, H2').

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5 (C2), 171.5 (C6), 137.8 (C4'), 115.4 (C5'), 68.6 (C3), 40.4 (C1'), 31.3 (C5), 31.2 (C3'), 27.2 (C2'), 25.7 (C4).

ESIMS *m/z* 198 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{10}H_{16}O_3N$, $(M+H)^+$, 198.1051, found: 198.1051.

(*S*)-5,6-Dihydroxy-1-(pent-4-enyl)piperidin-2-one (**332**)



332

To a solution of compound **335** (600 mg, 3.2 mmol) in EtOH (20 mL) was added portionwise $NaBH_4$ (610 mg, 16 mmol, 5 equiv) at -30 ºC under a N_2 atmosphere and the mixture was stirred at -30 ºC for 2 h.[121] Saturated $NaHCO_3$ solution (20 mL) and saturated NaCl solution (70 mL) were added and the mixture was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (9:1, EtOAc/petroleum spirit) to provide the hemiaminal **332** (528 mg, 87% yield) as a colourless oil and as a mixture of diastereomers (dr = 3.8:1).

R_f = 0.53 (100:0, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 3292, 2930, 1635, 1611, 1278, 972, 911.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, H4'), 5.04 (d, *J* = 17.0 Hz, 1H, H5'), 4.98 (d, *J* = 10.5 Hz, 1H, H5'), 4.78 (dd, *J* = 6.0, 4.0 Hz, 1H, H6), 3.96 (d, *J* = 3.0 Hz, 1H, H5), 3.71 – 3.60 (m, 1H, H1'), 3.27 – 3.16 (m, 1H, H1'), 2.63 – 2.52 (m, 1H, H3), 2.39 (dt, *J* = 12.5, 5.5 Hz, 1H, H3), 2.22 – 2.14 (m, 1H,

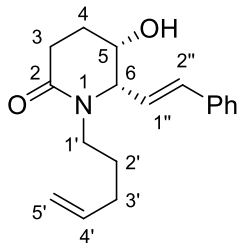
H4), 2.09 (dd, *J* = 14.5, 7.5 Hz, 2H, H7), 1.84 (dt, *J* = 12.5, 6.0 Hz, 1H, H4), 1.71 (m, 2H, H2').

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (C2), 138.3 (C4'), 115.4 (C5'), 84.5 (C6), 69.0 (C5), 44.8 (C1'), 31.4 (C3'), 28.0 (C3), 27.4 (C2'), 23.8 (C4).

ESIMS *m/z* 200 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{10}H_{18}O_3N$, $(M+H)^+$, 200.1295, found: 200.1287.

(5*S*,6*S*)-5-Hydroxy-1-(pent-4-enyl)-6-styrylpiperidin-2-one (**331**)



331

β-Styryl boronic acid (122 mg, 0.825 mmol, 0.55 equiv) and β-styryl potassiumtrifluoroborate (174 mg, 0.825 mmol. 0.55 equiv) were added to a solution of the diol **332** (300 mg, 1.5 mmol) in CH_3CN (25 mL) at rt. The mixture the was cooled to 0 ºC and $BF_3.Et_2O$ (15 mmol, 3.0 equiv) was added dropwise. The resulting reaction mixture was stirred at 0 ºC for 45 min then warmed to rt and stirred for 15 h.[121] The reaction mixture was cooled to 0 ºC and quenched with saturated NH_4Cl (10 mL) and saturated NaCl (10 mL) solutions. The mixture was extracted with EtOAc (3 x 70 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (9:1 to 100:0, EtOAc/petroleum spirit) to provide the the diene **331** (339 mg, 79% yield) as a colourless oil.

$[\alpha]_D^{23}$ -7.2 (*c* 2.97, $CHCl_3$).

R_f = 0.68 (90:10, EtOAc/MeOH).

IR (neat, ν_{max}/cm^{-1}): 3281, 2928, 1637, 1362, 1279, 972, 912, 694.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.24 (m, 5H, ArH), 6.51 (d, *J* = 16.0 Hz, 1H, H2''), 6.25 (dd, *J* = 16.0, 7.0 Hz, 1H, H1'), 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz 1H, H4'), 5.01 (d, *J* = 17.0 Hz, 1H, H5'), 4.95 (d, *J* = 10.0 Hz, 1H, H5'), 4.14 (dd, *J* = 7.0, 5.0

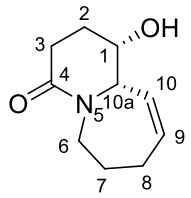
Hz, 1H, H6), 4.08 (dt, *J* = 10.0, 5.0 Hz, 1H, H5), 3.93 – 3.83 (m, 1H, H1'), 2.83 – 2.74 (m, 1H, H1'), 2.56 (dt, *J* = 18.0, 5.0 Hz 1H, H3), 2.43 (dt, *J* = 18.0, 9.0 Hz 1H, H3), 2.07-2.00 (m, 2H, H3'), 1.93-1.85 (m, 2H, H4), 1.69-1.61 (m, 2H, H2').

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (C2), 138.0 (C4'), 136.2 (ArC), 134.8 (C2''), 129.0 (ArC), 128.4 (ArC), 126.9 (ArC), 125.1 (C1''), 115.3 (C5'), 68.1 (C5), 63.7 (C6), 46.0 (C1''), 31.3 (C3''), 29.7 (C3), 26.9 (C2''), 26.3 (C4).

ESIMS *m/z* 286 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{18}H_{24}O_2N$, $(M+Na)^+$286.1812, found: 286.1807.

(1*S*,10a*S*)-1-Hydroxy-1,2,3,7,8,10a-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one (**330**)



330

To a solution of the diene **331** (286 mg, 1 mmol) in CH_2Cl_2 (80 mL) were added 1,4-benzoquinone (145 mg, 1.32 mmol, 1.32 equiv) and Grubbs' 2nd generation Ru catalyst (170 mg, 0.2 mmol, 0.2 equiv).[121] The reaction mixture was stirred at 35 ºC for 4 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1:9, MeOH/EtOAc) to provide the bicyclic compound **330** (151 mg, 84% yield) as a brown oil.

$[\alpha]_D^{23}$ +25.5 (*c* 1.43, $CHCl_3$)

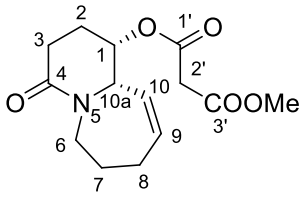
R_f = 0.68 (1:4, MeOH/EtOAc).

IR (neat, ν_{max}/cm^{-1}): 3317, 2930, 1606, 1457, 1271, 1077, 1038, 872.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (dt, *J* = 10.8, 5.0 Hz, 1H, H9), 5.73 (d, *J* = 10.8 Hz, 1H, H10), 4.48 – 4.39 (m, 1H, H6), 4.19 (s, 1H, H10a), 4.10 – 4.03 (m, 1H, H1), 2.87-2.80 (m, 1H, H6), 2.65-2.54 (m, 1H, H3), 2.43 – 2.34 (m, 1H, H3), 2.34 – 2.23 (m, 1H, H7), 2.17 – 2.08 (m, 1H, H7), 2.06 – 1.91 (m, 2H, H3 and H7), 1.91-1.83 (m, 1H, H3), 1.82 – 1.71 (m, 1H, H7).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (C4), 133.6 (C9), 127.6 (C10), 66.3 (C1), 62.4 (C10a), 45.9 (C6), 28.7 (C3), 25.8 (C2), 25.3 (C8), 25.1 (C7).
ESIMS *m/z* 182 [$(M+H)^+$ 100%].
HRESIMS calcd. For $C_{10}H_{16}O_2N$, $(M+H)^+$ 182.1181, found: 182.1179.

Methyl (1*S*,10a*S*)-4-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-*a*]azepin-1-yl malonate (**345**)



345

Triethyamine (80 μL, 0.59 mmol, 1.5 equiv) and methyl malonylchloride (51 μL, 0.47 mmol, 1.2 equiv) were added to a solution of the alcohol **330** (71 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at 0 ºC under a N_2 atmosphere.[100] The reaction mixture then was allowed to warm to rt and stirred for 14 h. Water (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to provide the ester **345** (91 mg, 50% yield) as a brown oil and the starting alcohol **330** (26 mg, 36%).

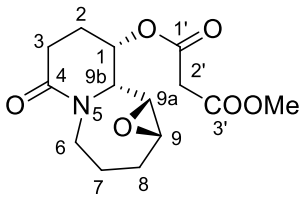
$[\alpha]_D^{23}$ -58.8 (*c* 1.93, $CHCl_3$).
R_f = 0.58 (9:1, EtOAc/petroleum spirit)
IR (neat, ν_{max}/cm^{-1}): 2954, 1730, 1604, 1272, 1204, 1044, 1016
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 10.0, 5.0 Hz, 1H, H9), 5.54 (d, *J* = 10.0 Hz, 1H, H10), 5.23 – 5.17 (m, 1H, H1), 4.46 – 4.39 (m, 1H, H6), 4.31 (s, 1H, H10a), 3.72 (s, 3H, OMe), 3.37 (s, 2H, H2'), 2.86 – 2.78 (m, 1H, H6), 2.54 (dt, *J* = 17.5, 6.5 Hz, 1H, H3), 2.44 (dt, *J* = 17.5, 7.5 Hz 1H, H3), 2.29 – 2.18 (m, 1H, H8), 2.12-2.03 (m, 2H, H8 and H2), 1.98 – 1.88 (m, 2H, H2 and H7), 1.77-1.68 (m, 1H, H7).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6 (C4), 166.8 (C3'), 165.8 (C1'), 133.5 (C9), 126.9 (C10), 69.8 (C1), 59.6 (C10a), 52.9 (OMe), 45.9 (C6), 41.6 (C2'), 28.6 (C3), 25.1 (C8), 25.0M (C7), 23.6 (C2).

ESIMS *m/z* 281 [$(M+H)^+$ 100%].

HRESIMS calcd. for $C_{14}H_{20}O_5N$, $(M+H)^+$282.1341, found: 282.1328.

Methyl (1a*S*,9*S*,9a*R*,9b*R*)-6-oxodecahydrooxireno[2,3-*c*]pyrido[1,2-*a*]azepin-9-yl malonate (**329**)



329

To a solution of the alkene **345** (54 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added purified *m*-CPBA (31.4 mg, 0.18 mmol, 1.4 equiv) and the mixture was stirred at rt for 14 h.[133] The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (4:1, EtOAc/petroleum spirit) to give the epoxide **329** (26 mg, 48% yield) as a colourless oil and the starting material **345** (16 mg, 30%).

$[\alpha]_D^{23}$ -71.7 (*c* 2.92, $CHCl_3$).

R_f = 0.53 (9:1, EtOAc/petroleum spirit).

IR (neat, ν_{max}/cm^{-1}): 2955, 1743, 1625, 1467, 1272, 1229, 1182, 1117, 1011.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 – 5.24 (m, 1H, H1), 4.64 – 4.57 (m, 1H, H6), 3.76 (s, 3H, OMe), 3.64 (t, *J* = 6.0 Hz, 1H, H9b), 3.46 (s, 2H, H2'), 3.21 (dd, *J* = 6.0, 4.5 Hz, H9a), 3.12 (q, *J* = 6.0 Hz, H9), 2.64-2.58 (m, 2H, H6 and H3), 2.55-2.46 (m, 1H, H3), 2.31 – 2.11 (m, 3H, 2 x H2 and H8), 1.74 – 1.63 (m, 3H, H8 and 2 x H7).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9 (C4), 166.8 (C1'), 166.0 (C3'), 69.0 (C1), 59.0 (C9b), 54.6 (C9a), 54.1 (C9), 53.0 (OMe), 48.7 (C6), 41.5 (C2'), 29.4 (C3), 28.7 (C8), 23.7 (C7), 22.9 (C2).

ESIMS *m/z* 320 [$(M+Na)^+$ 100%].

HRESIMS calcd. for $C_{14}H_{19}O_6NNa$, $(M+Na)^+$ 320.1110, found: 320.1098.

Attempted cyclization of 329

To a solution of **329** (10 mg, 0.034 mmol) in THF (0.6 mL) at 0 ºC was added *t*-BuOK (6 mg, 0.051 mmol, 1.5 equiv) and the solution was stirred for 1 h. The mixture was then warmed to rt and stirred for 1 h. The mixture was quenched with saturated NH_4Cl (2 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR analysis of the crude mixture indicated that no reaction occurred only the unreacted starting material remained in the crude mixture. Attempts with *n*-BuLi (1.5 equiv) in THF ºC (-78 ºC 1 h and to rt 1 h) and LDA (1.5 equiv) in THF (-78 ºC 1 h and to rt 1 h) gave the similar results.

IREFERENCES

(1) Greger, H. Structural Relationship, Distribution and Biological Activities of *Stemona* Alkaloids. *Planta. Med*. **2006**, *72*, 99-113.

(2) Pilli, R. A.; Rosso, G. B.; Ferreira de Olivera. M, d. C. (a) Recent Progress in the Chemistry of the *Stemona* Alkaloids. *Nat. Prod.Rep*. **2000**, *17*, 117-127. (b) Pilli, R. A.; Rosso, G. B.; Ferreira de Olivera. M, d. C. The Chemistry of Stemona Alkaloids: An update. *Nat. Prod.Rep*. **2010**, *27*, 1908-1937. (c) Yu, L. -X.; Peng, W. –F. Recent Advances in the Synthesis of *Stemona* Alkaloids. *Nat. Prod. Com.* **2015**, *10*, 1093-1102.

(3) https://en.wikipedia.org/wiki/Stemona#/media/File:ManShengBaiBu.JPG. (accessed April, **2015**).

(4) Chung, H. -S.; Hon, P. -M.; Lin, G.; But, P. P. -H.; Dong, H. Antitussive Activity of *Stemona* Alkaloids from *Stemona Tuberosa. Planta. Med*. **2003**, *69*, 914-920.

(5) Sekine, T.; Ikegami, F.; Fukasawa, N.; Kashiwagi, Y.; Aizawa, T.; Fujii, Y.; Ruangrungsi, N..; Murakoshi, I. Structure and Relative Stereochemistry of a New Polycyclic Alkaloid, Asparagamine A, Showing Anti-oxytocin Activity, Isolated from *Asparagus racernosus. J. Chem. Soc., Perkin Trans. 1*. **1995**, 391-393.

(6) Suzuki, K. *J. Pharm. Soc. Japan*. **1934**, *54*, 96 (Cited from reference number 7).

(7) Götz, M.; Bögri, T.; Gray, A. H.; Strunz, G. M. The Sructure of Tuberostemonine *Tetrahedron* **1967**, *24*, 2631-2643.

(8) Shinozaki, H.; Ishida, M. Inhibitory Actions of Tuberostemonine on the Excitatory Transmission at the Crayfish Neuromuscular Junction. *Brain. Res.* **1985**, *334*, 33-40.

(9) Brem, B.; Seger, C.; Pacher, T.; Hofer, O.; Vaijrodaya, S.; Greger, H. Feeding Deterrence and Contact Toxicity of *Stemona* Alkaloids A Source of Potent Natural Insecticides. *J. Agric. Food. Chem.* **2002,** *50,* 6383-6388.

(10) Mungkornasawakul, P.; Pyne, S. G.; Jatisatienr, A.; Supyen, D.; Lie, W.; Ung, A. T.; Skelton, B. W.; White, A. H. Stemocurtisine, the First Pyrido[1,2-*a*]azapine *Stemona* Alkaloid. *J. Nat. Prod.* **2003**, *66*, 980-982.

(11) Mungkornasawakul, P.; Pyne, S. G.; Jatisatienr, A.; Supyen, D.; Jatisatienr, C.; Lie, W.; Ung, A. T.; Skelton, B. W. White. A. H. Phytochemical and Larvicidal Studies on *Stemona curtisii*: Structure of a New Pyrido[1,2-*a*]azepine *Stemona* Alkaloid. *J. Nat. Prod.* **2004**, *67*, 675-677.

(12) Kalteneger, K.; Brem, B.; Mereiter, H.; Kalchhauser, H.; Kahlig, H.; Hofer. O.; Vajrodaya, S.; Greger, H. Insecticidal Pyrido[1,2-*a*]azepine Alkaloids and Related Derivatives from Stemona Rpecies. *Phytochemistry* **2003**, *63*, 803-816.

(13) Tang, C. -P.; Chen, T.; Velten, R.; Jeschke, P.; Ebbinghaus-Kintscher, U.; Geibel, S.; Ye, Y. Alkaloids from Stems and Leaves of *Stemona Japonica* and Their Insecticidal Activities. *J. Nat. Prod*. **2008**, *71*, 112-116.

(14) Lin, L. -G.; Zhong, Q. -X.; Cheng, T. -Y.; Tang, C. -P.; Ke, C. Q.; Lin, G.; and Ye, Y. Stemoninines from the Roots of *Stemona Tuberosa. J. Nat. Prod*. **2006**, *69*, 1051-1054.

(15) Lin, L. -G.; Leung, H. P. -H.; Zhu, J. Y.; Tang, C. -P.; Ke, C. -Q.; Rudd, J. A.; Ye, Y. Croomine- and Tuberostemonine-type Alkaloids from Roots of Stemona *Tuberosa* and Their Antitussive Activity. *Tetrahedron* **2008**, *64*, 10155-10161.

(16) Lin. L. -G.; Li, K. M.; Tang, C. -P.; Ke, C. -Q.; Rudd, J. A.; and Ye, Y. Antitussive Stemoninine Alkaloids from the Roots of *Stemona Tuberosa*. *J. Nat. Prod.* **2008**, *71*, 1107-1110.

(17) Wang, P.; Liu, A. -L.; An, Z.; Li, Z. -H.; Du, G. -H Qin, H. -L. Novel Alkaloids from the Roots of Stemona *Sessilifolia. Chem. & Biodiversity*, **2007**, *4*, 523-530.

(18) Ramli, R. A.; Lie. W; Pyne, S. G. Alkaloids from the Roots and Leaves of *Stichoneuron Halabalensis* and Their Acetylcholinesterase Inhibitory Activities. *Nat. Prod. Comm.* **2013**, *8*, 695-698.

(19) Ramli, R. A.; Pudjiastuti, P.; Tjahjandaric, T.; Lie, W.; Rattanajak, R.; Kamchonwongpaisan, S.; Pyne, S. G. Alkaloids from the Roots of Stemona *Javanica* (Kunth) Engl. (*Stemonaceae*) and their Anti-Malarial, Acetylcholinesterase Inhibitory and Cytotoxic Activities. *Phytochemistry Lett*. **2015**, *11*, 157-162.

(20) Hart, D. J.; Chen, C. Y. A Diels-Alder Approach to *Stemona* Alkaloids: Total

Synthesis of Stenine. *J. Org. Chem*. **1993**, *58*, 3840-3849.

(21) Wipf, P.; Kim, Y.; Goldstein, D. M. Asymmetric Total Synthesis of the *Stemona* Alkaloid (-)-Stenine. *J. Am. Chem. Soc*. **1995**, *117*, 11106-11112.

(22) Frankowsky, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. Syntheses of the *Stemona* Alkaloids (±)-Stenine, (±)-Neostenine, and (±)-13-Epineostenine Using a Stereodivergent Diels–Alder/Azido-Schmidt Reaction. *J. Am. Chem. Soc*. **2008**, *130*, 6018-6024.

(23) Padwa, A.; Ginn, J. D. Total Synthesis of (±)-Stenine Using the IMDAF Cycloaddition of a 2-Methylthio-5-amido-substituted Furan. *Org. Lett*. **2002**, *4*, 1015-1017.

(24) Morimoto, Y.; Iwahashi, M.; Kinoshita, T.; Nishida, K. Stereocontrolled Total Synthesis of the *Stemona* Alkaloid (-)-Stenine. *Chem. Eur. J*. **2001**, *7*, 4107-4116.

(25) Chen, J.. -B, Chen, J. -C.; Xia, Y.; Zhang, H. Enantioselective Total Synthesis of (-)-Stenine. *Angew. Chem. Int. Ed*. **2012**, *51*, 1024-1027.

(26) Fujioka, H.; Nakahara, K.; Kotoku, N.; Ohba, Y.; Nagatomi, Y.; Wang, T. -L.; Sawama, Y.; Murai, K.; Hirano, K.; Oki, T.; Wakamatsu S.; Kita, Y. Asymmetric Total Synthesis of (-)-Stenine and 9a-*epi*-Stenine. *Chem. Eur. J*. **2008**, *18*, 13861-13870.

(27) Kinoshita, A.; Mori, M. Total Synthesis of (-)-Stemoamide Using Ruthenium-Catalyzed Enyne Metathesis Reaction. *J. Org. Chem*. **1996**, *61*, 8356-8357.

(28) Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. Heterocyclic Prostaglandins V. Synthesis of (12*R*, 15*S*)-(-)-11-Deoxy-8-azaprostaglandin E1and Related Compounds. *Chem. Pharm. Bull*. **1980**, *25*, 1449-1458.

(29) Jacobi, P. A.; Lee, K. Total Synthesis of (±)-Stemoamide. *J. Am. Chem. Soc*. **1997**, *119*, 3409-3410.

(30) Jacobi, P. A.; Lee, K. Total Syntheses of (±)- and (-)-Stemoamide. *J. Am. Chem. Soc*. **2000**, *122*, 4295-4303.

(31) Gurjar, M. K.; Reddy, D. S. Carbohydrate Based Formal Synthesis of Stemoamide Using Ring-closing Metathesis. *Tetrahedron Lett*. **2002**, *43*, 295-298.

(32) Olivo, H. F.; Tovar-Miranda, R.; Barragan, E. Synthesis of (-)-Stemoamide Using a Stereoselective *anti*-Aldol Step. *J. Org. Chem*. **2006**, *71*, 3287-3290.

(33) Torssell, S.; Wanngren, E.; Somfai, P. Total Synthesis of (-)-Stemoamide. *J. Org. Chem*. **2007**, *71*, 4246-4249.

(34) Bogliotti, N.; Dalko, P. I.; Cossy, J. Desymmetrization of Substituted 1,3-Diketones: A Formal Synthesis of (+)-Stemoamide. *Synlett* **2006**, 2664-2666.

(35) Bates, R. W.; Sridhar, S. A Synthesis of (±)-Stemoamide Using the Intramolecular Propargylic Barbier Reaction. *Synlett* **2009**, 1979-1981.

(36) Honda, T.; Matsukawa, T.; Takahashi, K. Efficient Total Synthesis of (-)-Stemoamide. *Org. Biomol. Chem*. **2011**, *9*, 673-675.

(37) Sibi, M. P.; Subramanian, T. An Enantioselective Total Synthesis of (-)-Stemoamide. *Synlett* **2004**, 1211-1214.

(38) Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. Total Synthesis of (-)-Stemonine. *Org. Lett*. **2003**, *5*, 3361-3364.

(39) Williams, D. R.; Brown, D. L.; Benbow, J. W. Studies of *Stemona* Alkaloids. Total Synthesis of (+)-Croomine. *J. Am. Chem. Soc*. **1989**, *111*, 1923-1925.

(40) Williams, D. R.; Fromhold, M. G.; Earley, J. D. Total Synthesis of (-) Stemospironine. *Org. Lett*. **2011**, *3*, 2721-2724.

(41) Bardají, N.; Izquierdo, S. F.; Alibés, R.; Font, J.; Figueredo, M. Flexible Approach to Stemona Alkaloids: Total Syntheses of (-)-Stemospironine and Three New Diastereoisomeric Analogs. *Org. Lett*. **2012**, *14*, 4854-4857.

(42) Chen, Z. -H.; Zhang, Y. -Q.; Chen, Z. -M.; Tu, Y. -Q.; Zhang, F. -M. Total Synthesis of (±)-Maistemonine and (±)-Stemonamide. *Chem. Commun*. **2011**, *47*, 1836-1838.

(43) Aubé, J.; Milligan. G. L. Intramolecular Schmidt Reaction of Alkyl Azides. *J. Am. Chem. Soc*. **1989**, *113*, 8965-8966.

(44) Lindlar, H.; Dubuis, R. Palladium Catalyst for Partial Reduction of Acetylene. *Org. Synth*. **1966**, *46*, 89-91.

(45) Zhao, Y. -M.; Gu, P.; Tu, Y. -Q.; Fan, C. -A.; Zhang, Q. An Efficient Total Synthesis of (±)-Stemonamine. *Org. Lett*. **2008**, *10*, 1763-1766.

(46) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. J. Total Synthesis of (±) -Stemonamide and (±)-Isostemonamide. *Tetrahedron* **2002**, *58*, 61-74.

(47) Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. Total Synthesis of (±)-Stemonamide and (±)-Isostemonamide Using a Radical Cascade. *Org. Lett*. **2008**, *10*,197-199.

(48) Taniguchi, T.; Ishibashi, H. Total synthesis of (±)-Stemonamide, (±)-Isostemonamide, (±)-Stemonamine, and (±)-Isostemonamine Using a Radical Cascade. *Tetrahedron* **2008**, *64*, 8773-8779.

(49) Hoye, A. T.; Wipf, P. Total Synthesis of (-)-Sessilifoliamide C and (-)-8-*epi*-Stemoamide. *Org. Lett*. **2011**, *13*, 2634-2637.

(50) Schulte, M. L.; Turlington, M. L.; Phatak, S. S.; Harp, J. M.; Stauffer, S. R.; Lindsley, C. W. Total Synthesis of Stemaphylline N-Oxide and Related C9a-Epimeric Analogues. *Chem. Eur. J*. **2013**, *19*, 11847-11852.

(51) Kende, A. S.; Smalley, T. L.; Huang, H. Total Synthesis of (±)-Isostemofoline. *J. Am. Chem. Soc*. **1999**, *121*, 7431-7432.

(52) Brüggemann, M.; McDonald, A. I.; Oveman, L. E.; Rosen, M. D.; Schwink, L.; Scott. J.P. Total Synthesis of (±)-Didehydrostemofoline (Asparagamine A) and (±)-Isodidehydrostemofoline. *J. Am. Chem. Soc*. **2003**, *125*, 15284-15285.

(53) Huang, P. -Q.; Huang, S. -Y.; Gao, L. -H.; Mao, Z. -Y.; Chang, Z.; Wang, A.-E. Enantioselective Total Synthesis of (+)-Methoxystemofoline and (+)-Isomethoxystemofoline. *Chem. Commun*. **2015**, *51*, 4576-4578.

(54) Liu, X. -K.; Ye, J. -L.; Ruan, Y. -P.; Li, Y. -X.; Huang, P. -Q. Total Synthesis of (-)-Sessilifoliamide J. *J. Org. Chem*. **2013**, *78*, 35-41.

(55) a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. The Vinylogous Aldol Reaction: A Valuable, Yet Understated Carbon-Carbon Bond-Forming Maneuver. *Chem. Rev*. **2000**, *100*, 1929-1972. b) Bur, S. K.; Martin, S. F. Vinylogous Mannich Reactions: Selectivity and Synthetic Utility. *Tetrahedron* **2001**, *57*, 3221-3242. c) Martin, S. F. Evolution of the Vinylogous Mannich Reaction as a Key Construction for Alkaloid Synthesis. *Chem. Res*. **2002**, *35*, 895-904

(56) Corey, E. J.; Zheng, G. Z. Catalytions of Samarium(II) Iodide. *Tetrahedron Lett*. **1997**, *38*, 2045-2048.

(57) Valazquez, F.; Olivo, H.F. Synthesis of Bicyclic γ-Ylidenetetronates. *Org. Lett*. **2002**, *4*, 3175-3178.

(58) Veleiro, A. S.; Taich, P. J.; Alvarez, L. D.; Di Chenna, P. H.; Burton, G. Synthesis of C(1)–C(11) Oxygen-Bridged Pregnanes. *Tetrahedron Lett*. **2005**, *46*, 4235-4238.

(59) Huang, P. -Q.; Liu, L. -X.; Ruan, Y. -P. Asymmetric Synthesis of (+)-L-733,

060 and (+)-CP-99, 994 Based on a New Chiral 3-Piperidinol Synthon. *Org. Lett*. **2003**, *5*, 1927.

(60) Swamy, N. K.; Pyne, S.G. Model Studies Towards The Total Synthesis of The *Stemona* Alkaloids 1-Hydroxyprotostemonine: Synthesis of ent-1-Hydroxystemoamide. *Heterocycles* **2011**, *81*, 473-492.

(61) Ruan, Y. -P.; Wei, B. –G.; Xu, X. –Q.; Liu, G.; Yu, D. –S.; Liu, L. –X.; Huang, P. -Q. Detailed Studies on the Enantioselective Synthesis and HPLC Enantioseparation of *N*-Protected 3-Hydroxyglutarimides. *Chirality*. **2005**, *17*, 595-599.

(62) Fu, R.; Du, Y.; Li, Z. –Y.; Xu, W. –X.; Huang, P. –Q. Asymmetric Syntheses of 6-Deoxyfagomin, D-Deoxyrhamnojirimycin and D-Deoxyrhamnono-1,5 lactam. *Tetrahedron* **2009**, *65*, 9765-9771.

(63) Cleary, L.; Yoo, H.; Shea, K. J. Micowave Assisted Synthesis of Bridgehead Alkenes. *Org. Lett.* **2011**, *13*, 1781-1783.

(64) Liu, L. -X.; Ruan, Y. -P.; Guo, Z. -Q.; Huang, P. -Q. A General Approach to (5*S*,6*R*)-6-Alkyl-5-benzyloxy-2-piperidinones: Application to the Asymmetric Syntheses of Neurokinin Substance P Receptor Antagonist (-)-L-733,061 and (-)-Deoxocassine. *J. Org. Chem*. **2004**, *69*, 6001-6009.

(65) Jury, J. C.; Nalivera, K. S.; Yazici, A.; Willis, A. C.; Pyne, S. G. Metal-Catalyzed Cycloisomerization Reactions of *cis*-4-Hydroxy- 5-alkynylpyrrolidinones and *cis*-5-Hydroxy-6-alkynylpiperidinones: Synthesis of Furo[3,2-*b*]pyrroles and Furo[3,2-*b*]pyridines. *J. Org. Chem*. **2009**, *74*, 5523-5527.

(66) Si, C. -M.; Mao, Z. -Y.; Dong, H. -Q.; Zu, Z. -T.; Wei, B. -G. Divergent Method to *trans*-5-Hydroxy-6-alkynyl/alkenyl-2-piperidinones: Synthesis of (-)-Epiquinamide and (+)-Swainsonine. *J. Org. Chem*. **2015**, *80*, 5824-5833.

(67) Denmark, S. E.; Yang, S. -M.; Intramolecular Silicon-Assisted Cross-Coupling Reactions: General Synthesis of Medium-Sized Rings Containing a 1,3-*cis*-*cis* Diene Unit. *J. Am. Chem. Soc*. **2002**, *124*, 2102-2103.

(68) Germain, J.; Deslongchams, P. Total Synthesis of (±)-Momilactone A. *J. Org. Chem*. **2002**, *67*, 5269-5278.

(69) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. Highly Satisfactory Alkynylation of Alkenyl Halides via Pd-Catalyzed Cross-

Coupling with Alkynylzincs and Its Critical Comparison with the Sonogashira Alkynylation. *Org. Lett*. **2003**, *10*, 1597-1600.

(70) Hesse, M.; Meier, H.; Zeeh, B. *Spectroscopic Methods in Organic Chemistry*, **1997**. Thieme, New York.

(71) Mundi, B. P.; Ellerd, M. G.; Favaloro, F. G. *Name Reactions and Reagents in Organic Synthesis*, 2nd edition, **2005**, pp 612-613, New Jersey, Wiley.

(72) Fischer, R.; Stanko, B.; Prónayová, N. Diastereoselective Synthesis of Racemic 3,4-*cis* and 3,4-*trans* Isomers of Isoxazolidine-4,5-diols and Their Derivatives. *Synlett* **2013**, *24*, 2132-2136.

(73) Jian, A. J.; Wu, Y. The Enantioselective Total Synthesis of Nemotin. *Org. Biomol. Chem.* **2010**, *8*, 811-821.

(74) Wu, J.; Wu, Y.; Jian, Y.; Zhang, Y. Synthesis and Absolute Configuration of the Diynediol from *Psathyrella scobinacea*. *Chin. J. Chem.* **2009**, *27*, 13-15.

(75) Kandula, S. R. V.; Kumar, P. An Asymmetric Aminohydroxylation Route to *cis*-2,6-Disubstituted Piperidine-3-ol: Application to the Synthesis of (L)-Deoxocassine. *Tetrahedron* **2006**, *62*, 9942-9948.

(76) Kobayashi, M. Y.; Inamoto, K.; Tanaka, Y.; Kondo, Y. Carboxylation of Alkynylsilanes with Carbon Dioxide Mediated by Cesium Fluoride in DMSO *Org. Biomol. Chem.* **2013**, *11*, 3773-3775.

(77) Clayden. J; Greeves. N; Warren. S. Wothers. P. *Organic Chemistry*: **2005**, pp 191-194. Oxford University Press

(78) Burke, C. P.; Shi, Y. Enantioselective Epoxidation of Conjugated *cis*-Enynes by Chiral Dioxirane. *J. Org. Chem*. **2007**, *72*, 4093-4097.

(79) Boruwa, J.; Borah, J. C.; Kalita, B.; Barua, N. C. Highly Regioselective Ring Opening of Epoxides using NaN_3: A Short and Efficient Synthesis of (-)-Cytoxazone. *Tetrahedron Lett.* **2004**, *45*, 7355-7358.

(80) Huang, K.; Wang, H.; Stepanenko, V.; Jesús, M. D.; Torruellas, C.; Correa. W; Margarita, O. M. Chiral Epoxides via Borane Reduction of 2-Haloketones Catalyzed by Spiroborate Ester: Application to the Synthesis of Optically Pure 1,2-Hydroxy Ethers and 1,2-Azido Alcohols. *J. Org. Chem*. **2011**, *76*, 1883-1886.

(81) Paquette, L. A.; Kesselmayer, M. A.; Künzer, H. Regioselective Azide Opening of 2,3-Epoxy Alcohols by $[Ti(O\text{-}i\text{-}Pr)_2(N_3)_2]$: Synthesis of α-Amino

Acids. *J. Org. Chem*. **1988**, *53*, 5185-5187.

(82) McDonald, F. E.; Gleason, M. M. Asymmetric Synthesis of Nucleosides via Molybdenum-Catalyzed Alkynol Cycloisomerization Coupled with Stereoselective Glycosylations of Deoxyfurannose Glycals and 3-Amidofuranose Glycals. *J. Am. Chem. Soc*. **1996**, *118*, 6648-6659.

(83) Righi, G.; Manni, L. S.; Bovicelli, P.; Pelagalli, R. A New, Simple, and Mind Azidolysis of Vinylepoxides. *Tetrahedron Lett.* **2011**, *52*, 3895-3896.

(84) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. Rules for Ring Closure: Ring Formation by Conjugate Addition of Oxygen Nucleophiles. *J. Org. Chem*. **1977**, *42*, 3846-3852.

(85) Lee, J. W.; Han, S. C.; Kim. J. H.; Lee, K. S. Synthesis of Secondary Bis- and Tris(amines) Derivatives through Staudinger/aza-Wittig Reactions. *Bull. Korean. Chem. Soc*. **2006**, *27*, 1667-1670.

(86) Pansare, S. V.; Paul, E. K. Synthesis of (+)-L-733,060, (+)-CP-99,994 and (2*S*,3*R*)-3-Hydroxypipecolic Acid: Application of an Organocatalytic Direct Vinylogous Aldol Reaction. *Org. Biomol. Chem*. **2012**, *10*, 2119-2125.

(87) Lindsay, K. B.; Tang, M.; Pyne, S. G. Diastereoselective Synthesis of Polyfunctional-Pyrrolidines via Vinyl Epoxide Aminolysis/Ring-Closing Metathesis: Synthesis of Chiral 2,5-Dihydropyrroles and (1*R*,2*S*,7*R*,7a*R*)-1,2,7-Trihydroxypyrrolizidine. *Synlett* **2002**, 731-734.

(88) Bernet, B.; Vasella. A. Enantioselective Synthesis of D- *erythro*-Sphingosine. *Tetrahedron Lett.* **1983**, *24*, 5491-5494.

(89) Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Abika, K. Stereoselective Synthesis of 1,2-Amino Alcohols by Addition of Organocuprate.BF3 Complexes and Organolithium Reagents to an α-Silyloxyaldimine Derived from (S)-Ethyl Lactate. *Tetrahedron* **1996**, *52*, 13137-13144.

(90) Jury, J. C.; Swamy, N. K.; Yazici, A.; Willis, A. C.; Pyne, S. G. Metal-Catalyzed Cycloisomerization Reactions of *cis*-4-Hydroxy-5-alkynylpyrrolidinones and *cis*-5-Hydroxy-6-alkynylpiperidinones: Synthesis of Furo[3,2-b]pyrroles and Furo[3,2-b]pyridines. *J. Org. Chem*. **2009**, *74*, 5523-5527.

(91) Feng, X.; Sun, A.; Zhang, S.; Yu, X. Q.; Bao, M. Palladium-Catalyzed

Carboxylative Coupling of Benzyl Chlorides with Allyltributylstannane: Remarkable Effect of Palladium Nanoparticles. *Org. Lett*. **2013**, *15*, 108-111.

(92) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J.; Forsyth, C. J. Highly Chemoselective Oxidation of 1,5-Diols to δ-Lactones with TEMPO/BAIB. *Tetrahedron Lett.* **2003**, *44*, 57-59.

(93) Simila, S. T. M.; Martin, S. F. Toward the Total Synthesis of FR901483: Concise Synthesis of the Azatricyclic skeleton. *J. Org. Chem*. **2007**, *72*, 5342-5349.

(94) Bloch, R.; Brillet, C. Selective Oxidation of Primery-Secondary Diols to Lactones Catalyzed by Tetrapropylammonium Perruthenate. *Synlett* **1991**, 29-30.

(95) Ritthiwigrom, T.; Willis, A. C.; Pyne, S. G. Total Synthesis of Uniflorine A, Casuarine, Australine, 3-epi-Australine, and 3,7-Di-epi-australine from a Common Precursor *J. Org. Chem*. **2010**, *75*, 815-824.

(96) Choy, J.; Figueroa, S. J.; Jiang, L.; Wagner, P. Novel Practical Deprotection of N-Boc Compounds Using Fluorinated Alcohols. *Syn. Commun*. **2008**, *38*, 3840- 3853.

(97) Sheppeck II, J. E.; Kar. H.; Hong. H. A Convenient and Scaleable Procedure for Removing the Fmoc Group in Solution. *Tetrahedron Lett.* **2000**, *41*, 5329-5333.

(98) Daiber, R.; Ziegler, T.; Synthesis and Structure of a Bis-glycosylated Hexa-β-Peptide. *ARKIVOC* **2013**, *2*, 408-420.

(99) Kocieński, P. J. *Protecting Groups*, 3rd Edition, **2004**, pp 9. Georg Thieme Verlag.

(100) Mondal, P.; Argade, N. P. Enantioselective Total Synthesis of Desbromoarborescidines A−C and the Formal Synthesis of (S)-Deplancheine. *J. Org. Chem*. **2013**, *78*, 6802-6808.

(101) Enders, D.; Geibel, G.; Osborne, S. Diastereo- and Enantioselective Total Synthesis of Stigmatellin A. *Chem. Eur. J*. **2000**, *6*, 1302-1309.

(102) Jung, M. E.; Koch, P. Mild, Selective Deprotection of PMB Ethers with Triflic Acid/1,3-Dimethoxybenzene. *Tetrahedron Lett.* **2011**, *52*, 6051-6054.

(103) Sharma, G. V. L.; Lavanya, B.; Mahalingam, A. K.; Krishna, P. G. $Mn(OAc)_3$-an Efficient Oxidant for Regeneration of DDQ: Deprotection of *p*-

Methoxy Benzyl Ethers. *Tetrahedron Lett.* **2000**, *41*, 10323-10326.

(104) Tang, M. PhD Thesis: The Asymmetric Synthesis of Polyhdroxylated Pyrrolizidine Alkaloids. University of Wollongong, **2004**, pp 167-168.

(105) Yang, Q.; Xiao, W. -J.; Yu, Z. Lewis Acid Assisted Ring-Closing Metathesis of Chiral Diallylamines: An Efficient Approach to Enantiopure Pyrrolidine Derivatives. *Org. Lett*. **2005**, *7*, 871-874.

(106) Li, J. J. *Name Reactions*, 3rd edition. **2006**, pp 499-500,Springer. New York.

(107) Quach, T.; Tsegay, S.; Thompson, A. J.; Kukushkin, N. V.; Alonzi, D. S.; Butters, T. D.; Davies, G. J.; Williams, S. J. Fleetamine (3-O-α -D-Glucopyranosyl-Swainsonine): The Synthesis of a Hypothetical Inhibitor of endo-α-Mannosidase *Tetrahedron* **2012**, *23*, 992-997.

(108) Kambe, T.; Maruyama, T.; Nakano, M.; Yamaura, Y.; Shono, T.; Seki, A.; Sakata, A.; Maruyama, T.; Nakai, H.; Toda, M. Discovery of Orally Available 8-Aza-5-thia Prostaglandin E1 Analogs as Highly Selective EP4 Agonists. *Chem. Pharm. Bull*. **2011**, *59*, 1523-1534

(109) Rassu, G.; Auzzas, L.; Zambrano, V.; Burreddu, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Casiraghi, G. Variable Strategy toward Carbasugars and Relatives. 6. Diastereoselective Synthesis of 2-Deoxy-2-amino-5a-carba-*β*-L-Mannopyranuronic Acid and 2-Deoxy-2-amino-5a-carba-*β*-L-Mannopyranose *J. Org. Chem.* **2004**, *69*, 1625-1628.

(110) Sanchez-Izquierdo, F.; Blanco, P.; Busque, F.; Alibes, R.; Pedrpo de March; Figueredo, M.; Font, J.; Parella, J. Total Synthesis of the Putative Structure of Stemonidine: The Definitive Proof of Misassignment. *Org. Lett*. **2007**, *9*, 1769-1772.

(111) Mellegaard-Waetzig, S. R.; Wang, C.; Tunge, J. A. Selenium-catalyzed Oxidative Halogenation. *Tetrahedron* **2006**, *62*, 7191-7198.

(112) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y. Y. Efficient Medium Ring Size Bromolactonization Using a Sulfur-Based Zwitterionic Organocatalyst. *J. Am. Chem. Soc*. **2012**, *134*, 16492-16495.

(113) Lin, W. -H.; Ye, Y.; Xu, R. S. Chemical Studies on New *Stemona* Alkaloids, IV. Studies on New Alkaloids from *Stemona Tuberosa*. *J. Nat. Prod*. **1992**, *55*, 571-576.

(114) Narisada, M.; Horibe, I.; Wanatabe, F.; Takeda. K. Selective Reduction of

Aryl Halide and α,β-Unsaturated Esters with Sodium Borohydride-Cuprous Chloride in Methanol and its Application to Deuterium Labeling. *J. Org. Chem*. **1989**, *54*, 5308-5313.

(115) Youn, I. K.; Yon, G. H.; Pak, C. S. Magnegium-Methanol as a Simple Convenient Reducing Reagent for α,β -Unsaturated Esters. *Tetrahedron Lett.* **1986**, *27*, 2409-2410

(116) Gabriëls, S.; van Haver, D.; Vandewalle, M.; De Clercq, P.; Viterbo, D. On the Unexpected Stereochemical Outcome of the Magnesium in Methanol Conjugate Reduction of an Exocyclic α,β-Unsaturated Ester. *Eur. J. Org. Chem.* **1999**, *8*, 1803-1809.

(117) Zarecki, A.; Wicha, J. Magnesium in Methanol Selective Reduction of a Conjugate Double Bond in an α,β-Unsaturated Ester related to Pregnadiene. *Synthesis* **1996**, *4*, 455-456.

(118) Furkert, D. P.; Brimble, M. A.; Synthesis of the C10-C22 Bis-spiroacetal Domain of Spirolides B and D via Iterative Oxidative Radical Cyclization *Org. Lett*. **2002**, *4*, 3655-3658.

(119) Hamlin, A. M.; Lapointe, D.; Owens, K.; Sarpong, R. Studies on C_{20}-Diterpenoid Alkaloids: Synthesis of the Hetidine Framework and its Application to the Synthesis of Dihydronavirine and the Atisine Skeleton. *J. Org. Chem*. **2014**, *79*, 6783-6800.

(120) Morgan, I. R.; Yazici, A.; Pyne, S. G. Diastereoselective Borono-Mannich Reactions on Cyclic N-acyliminium ions. *Tetrahedron* **2008**, *64*, 1409-1419.

(121) Morgan. I, Pyne. S. G. Unpublished work. University of Wollongong, **2007**.

(122) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H.; Prevention of Undesirable Isomerization during Olefin Metathesis. *J. Am. Chem. Soc*. **2005**, *127*, 17160-17161.

(123) Murahashi, S. I. *Ruthenium in Organic Synthesis*: 6. Ruthenium-catalyzed Olefin Metathesis, **2004**, pp 153-176. Wiley-VCH.

(124) Kohnz, H.; Düll, B.; Müllen, K. From the Bicyclo[3,3,0]octane Framework to Multiply Bridge [12]Annulennes and Semibullvalenes. *Angew. Chem. Int. Ed. Engl*. **1989**, *10*, 1343-1354.

(125) Salomone, A.; Capriati, V.; Florio, S.; Luisi, R. Michael Addition of Ortho-Lithiated Aryloxiranes to α,β-Unsaturated Malonates: Synthesis of

Tetrahydroindenofuranones. *Org. Lett*. **2008**, *4*, 1947-1950.

(126) Singh, A. N.; Dakanali, M.; Hao, G.; Ramezani, S.; Kurma, A.; Sun, X. Enantiopure Bifunctional Chelators for Copper Radiopharmaceuticals- Does Chirality Matter in Radiotracer Design. *Eur. J. Med. Chem*. **2014**, *80*, 309-315.

(127) Huang, P. –Q.; Wei, B. –G.; Ruan, Y. –P. Asymmetric Synthesis of Antimalarial Alkaloids (+)-Febrifugine and (+)-Isofebrifugine. *Synlett* **2003**, 1163-1167.

(128) Marcel, A.; Pierre, D.; Daniel, F.; Catherine, G.; Samia, M.; Jean-Paul, M.; Laurent, M.; Roberto, P.; Michel, V. Derives Halogenes de 1-Phenoxy-3-*N* Alkylaminopropane-2-ol Utilisables Comme Marqueurs des Recepteurs β-Adrenergiques Myocarddiquers at Comme (β-Bloquant) Description. *PCT Int. Appl*. **1994**, 2721925.

(129) Xu, C.; Du, W.; Zeng, Y.; Dai, B.; Guo, H. Reactivity Switch Enabled by Counterion: Highly Chemoselective Dimerization and Hydration of Terminal Alkynes. *Org. Lett*. **2014**, *16*, 948-951.

(130) Cahiez, G.; Gager, O.; Buendia, J. Copper-Catalysed Cross Coupling of Alkyl and Aryl Grignard Reagents with Alkynyl Halides. *Angew. Chem. Int. Ed*. **2010**, *49*, 1278-1281.

(131) Hagashino, M.; Ikeda, N.; Shinada, T.; Sakaguchi, K.; Ohfune, J. Stereoselective anti-S_N2' Mitsunobu Reaction of α-Hydroxy-α-alkenylsilanes *Tetrahedron Lett.* **2011**, *52*, 422-425.

(132) Armarego, W. L. F.; Perrin, D. D.; *Purification of Laboratory Chemicals* (4th ed.). Oxford: Butterworth-Heinemann. 4th edition, **1996**, pp 145.

(133) Odedra, A.; Lush, S. F.; Liu, R. S. Dicobaltoctacarbonyl-Mediated Synthesis of Tricyclic 5,6-Diydropyran-2-one Derivatives via Tandem Cycloaddition Reaction between *cis*-Epoxyalkynes, a Tethered Olefin and CarbonMonoxide *J. Org. Chem.* **2007**, *72*, 567-573.

(134) Baldwin, J. E.; Burrell, R. C. Kinetics of Thermal Gas-Phase Isomerizations and Fragmentations of *cis*- and *trans*-1-(*E*)-Propenyl-2-methylcyclobutanes at 275 °C. *J. Org. Chem*. **2002**, *67*, 3249-3256.

(135) Siebum, A.; van Wijk, A.; Schoevaart, R.; Kieboom, T. Galactose Oxidase and Alcohol Oxidase: Scope and Limitations for the Enzymatic Synthesis of

Aldehydes. *J. Mol. Cat. B: Enzymatic*, **2006**, *41*, 141-145.

(136) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. Total Syntheses of (+)-2,8,8a-Tri-*epi*-Swainsonine and (-) - 1- *epi*-Swainsonine. *J. Org. Chem.* **1993**, *58*, 3397-3400.

(137) Takemura, A.; Fujiwara, K.; Shimawaki, K.; Murai, A.; Kawai, H.; Suzuki, T. Synthesis of the EF-ring Segment of Ciguatoxin CTX1B Based on Novel Regioselective Reduction of Unsaturated Cyanohydrins and Ring-closing Olefin Metathesis. *Tetrahedron* **2005**, *61*, 7392-7419.

(138) Schultz, E. E.; Sarpong, R. Application of In Situ-Generated Rh-Bound Trimethylenemethane Variants to the Synthesis of 3,4-Fused Pyrroles. *J. Am. Chem. Soc*. **2013**, *135*, 4696−4699.

(139) Paquette, L. A.; Collado, I.; Purdie, M. Total Synthesis of Spinosyn A. 2. Degradation Studies Involving the Pure Factor and Its Complete Reconstitution. *J. Am. Chem. Soc.* **1998**, *120*, 2553-2562.

(140) Schmidt, U.; Roland, U.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P. Amino Acids and Peptides; 59. Synthesis of Biologically Active Cyclopeptides; 9. Synthesis of 16 Isomers of Dolastatin; I. Synthesis of the 2-(1-aminoalkyl)-thiazol-4-carboxylic Acids. *Synthesis* **1987**, 233-236.