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NEW SULFONE–ASSISTED STRATEGIES FOR ALKALOID SYNTHESIS

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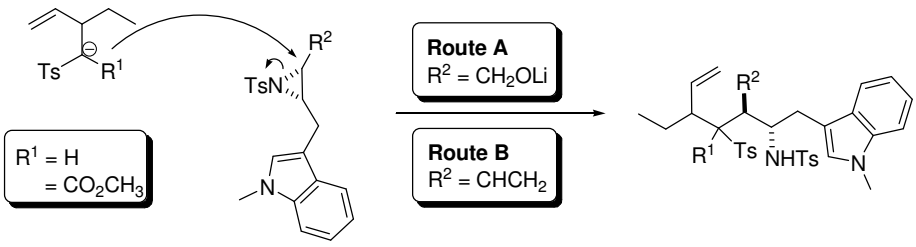
Abstract

This thesis is divided into three chapters.

Chapter 1 provides brief reviews on the subjects of previous total syntheses of suaveoline, alstonerine and cytisine. In addition, a review concerning the Pictet–Spengler reaction mechanism and its application to the total syntheses of isoquinoline containing natural products has been included as well.

Chapter 2 focuses on the research findings in the past three years. Two routes were investigated towards the total synthesis of (±)-suaveoline involving the decarboxylative Claisen rearrangement (dCr), *N*-sulfonylaziridine chemistry and subsequent nucleophilic ring-opening of the latter by various sulfone-anions. Route A focused on the use of oxo-lithio chelation during aziridine ring-opening while route B employed selective weakening of the aziridine C–N bond proximal to the olefin by $\pi_{C-C} \rightarrow \sigma^*_{C-N}$ overlap (Scheme 0.1).



Scheme 0.1

Attempts towards total synthesis of (±)-alstonerine involved the preparation and subsequent screening of various sulfone-anions against the indolic hydroxy aziridine, followed by an interesting E1cB / Michael addition, *cis*-Pictet–Spengler cyclization and an ambitious global reduction step.

Furthermore progress towards total synthesis of (–)-cytisine involved investigation towards the application of regioselective sulfone-anion hydroxy-aziridine opening mediated by oxo-lithio-chelation.

Chapter 3 provides the experimental details and characterization data.

Contents

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This thesis is dedicated to my parents Jean and Truus Tholen–Aarts for their unconditional love, support and dedication over all these years. Without you I would not be what and where I am today.

Thank you.

List of Abbreviations

Å	angstrom
Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Anh.	anhydrous
Ar	aromatic
aq.	aqueous
9-BBN	9-borabicyclo [3.3.1] nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium
bp	boiling point
Bu	butyl
Bz	benzoyl
˚C	degree Celsius
cat.	catalytic
CAN	ceric(IV)ammonium nitrate
Cbz	carbobenzyloxy
CDI	*N,N*'-carbonyldiimidazole
CI	chemical ionisation
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
d	doublet
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dCr	decarboxylative Claisen rearrangement
dd	doublet of doublet
DDC	*N*,*N*'-dicyclohexylcarbodiimide
ddd	doublet of doublet of doublet
DDQ	2,3-dicyano-5,6-dichloro-*para*-benzoquinone
ddt	doublet of doublet of triplet

d.e.	diastereoisomeric excess
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIBAL	diisobutylammonium hydride
DIC	diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppa	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'bis(diphenylphosphino)ferrocene
d.r	diastereomeric ratio
dt	doublet of triplet
dq	doublet of quartet
E1cB	elimination conjugate base
Ed.	edition
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
Fmoc	9-fluorenylmethyloxycarbonyl
h	hours
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	bis(trimethylsilyl)amide
HMPA	*N*,*N*,*N′*,*N′*,*N″*,*N″*-hexamethylphosphoric triamide
HOAt	1-hydroxy-7-azabenzotriazole
Hz	Hertz
IBX	*O*-iodoxybenzoic acid

^{i}Pr	*iso*-propyl
IR	infra red
La	lanthanide
LA	Lewis acid
LDA	lithium diisopropylamide
Ln	ligand
LTA	lead tetraacetate
lut.	lutidine
m	multiplet
M	molar
mCPBA	*meta*-chloroperoxybenxoic acid
Me	methyl
m-	*meta*
min	minutes
mmHg	millimeter of mercury
mL	milliliter
mol%	mole percentage
MOM	methoxymethyl ether
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
m/z	mass/charge ratio
^{n}	*normal*
Napht.	naphthalide
NBS	*N*-bromosuccinamide
^{n}BuLi	*n*-butyllithium
NMM	*N*-methyl morpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic rsonance
Nu	nucleophile
o-	*ortho*
p-	*para*
Ph	phenyl
phth	phthalimide

PMB	*para*-methoxybenzyl
ppm	parts per million
PTAB	phenyltrimethylammonium tribromide
py	pyridine
q	quartet
R_f	Retardation factor
rt	room temperature
s	singlet
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_NAr	nucleophilic aromatic substitution
t	triplet
TBAB	^{t}butylamineborane
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDMS / TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
^{t}Bu	*tert*-butyl
TEA	triethylamine
TES	triethylsilane
Tf	tetrafluoromethansulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
THPyr	tetrahydropyridine
tlc	thin-layer chromatography
TMA	trimethyl aluminum
TMEDA	*N,N,N',N'*-tetramethylethylenediamide
TMS	trimethylsilyl
Troc	2,2,2-trichloroethoxycarbonyl
Trp	tryptophan
Ts	*para*-toluenesulfonyl
tt	triplet of triplet
w/v	weight per volume

Stereochemical Notation

Throughout this report, to aid rapid visual identification of relative and absolute stereochemical configurations, the Maehr[1] convention has been adopted. Thus, solid and broken lines denote a racemate, while solid and broken wedges imply absolute configuration, as illustrated below.

Racemate Single enantiomer

Relative Stereochemistry Absolute Stereochemistry

Macroline skeletal numbering

A brief overview regarding the skeletal numbering of macroline according to LeMen and Taylor[2] has been depicted below (Figure 0.1) and will be used throughout this report.

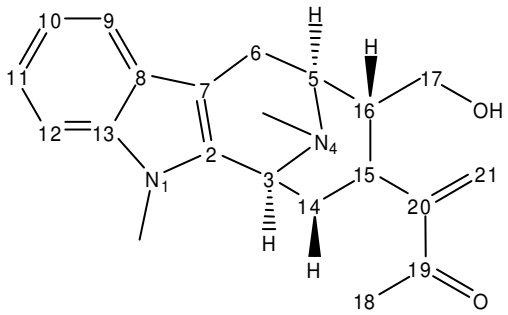


Figure 0.1

1. Maehr, H. *J. Chem. Ed.* 1985, *62*, 114.

2. LeMen, J.; Taylor, W. I. *Experientia* 1965, *21*, 508.

CHAPTER 1

Introduction

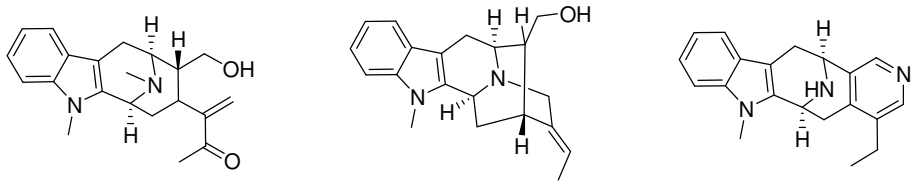
1. Introduction

This chapter provides brief reviews regarding the total syntheses of suaveoline, alstonerine and cytisine as represented in the literature. In addition, a review concerning the Pictet–Spengler reaction mechanism and application to the total syntheses of isoquinoline containing natural products has been included as well.

1.1. Suaveoline

1.1.1. Background

This report will cover the progress towards the total synthesis of the macroline-related natural products suaveoline **3** (Figure 1.1), alstonerine and the lupin alkaloid cytisine. The two former natural compounds are part of a much larger array of alkaloids isolated from the *Alstonia* genus of plants, commonly found in tropical regions. In these regions several species of *Alstonia* have found use in traditional medicine against malaria and dysentery.[1,2]



macroline **1** sarpagine **2** suaveoline **3**

Figure 1.1

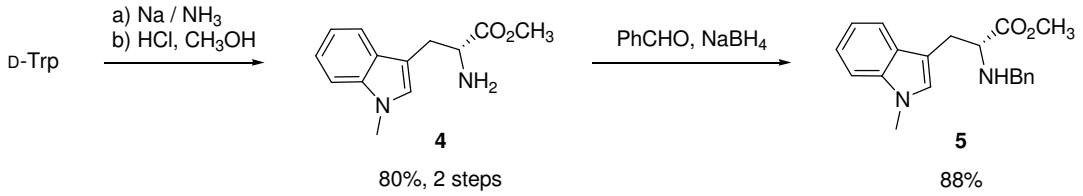
Suaveoline **3** was first isolated in 1972 by Potier[1] from the trunk bark of *Rauvolfia suaveolens*, and has since also been isolated from other species of the *Rauvolfia* family. Cook was the first to complete the total synthesis of racemic suaveoline in 1989.[2] Since then, three laboratories have reported total syntheses in either racemic or optically pure form. Structurally, suaveoline **3** and macroline **1** compounds are very alike, containing the characteristic azabicyclo [3.3.1] motif. Furthermore the absence of a N_4–C_{21} linkage, commonly found in the sarpagine-related compounds is a key feature, as is the 3,4,5-trisubstituted pyridine moiety.[3] In contrast to sarpagine **2**, macroline **1** has not been isolated from nature. It is widely believed that macroline is a common precursor to sarpagine alkaloids.[3]

1.1.2. Previous Total Syntheses of Suaveoline

1.1.2.1. Cook's Total Synthesis

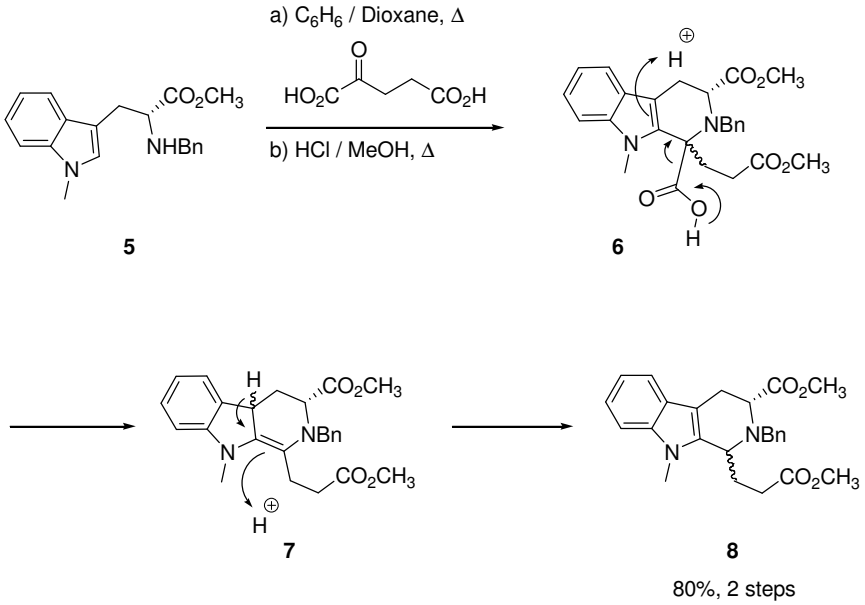
In 1989 Cook *et al.* reported the first total synthesis of (±)-suaveoline.[2] Subsequently the synthesis was refined, culminating in the enantioselective total synthesis of (–)-suaveoline.[4]

Key to Cook's synthesis was the use of the tetracyclic ketone intermediate **13**,[5] obtained from D-tryptophan using an improved modification of the Yoneda protocol[6] (Scheme 1.1). Protection of D-tryptophan gave **5**; care had to be taken during the reductive amination since prolonged reaction times resulted in erosion of enantiomeric excess.



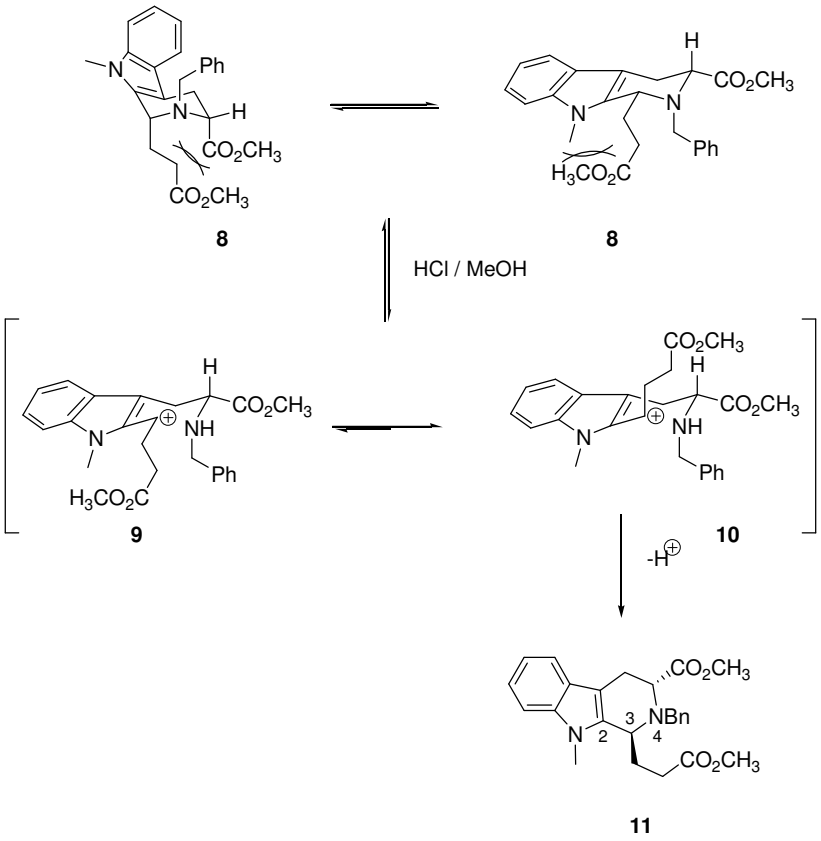
Scheme 1.1: Protection of D-tryptophan.

Synthesis of tetrahydro-β-carboline **8** had previously been achieved by Yoneda[6] in 59% yield using Pictet–Spengler condensation of the hydrochloride salt of **5** with methyl 3-formylpropionate in aqueous methanol. A 2 : 1 mixture of benzene and dioxane significantly improved the condensation reaction due to improved solubility of ketoglutaric acid. However, under these reaction conditions decarboxylation of **5** was observed and diester **8** obtained (Scheme 1.2). In this decarboxylation step, the diastereomeric ratio is determined by protonation of **7**, occurring after decarboxylation, thus resulting in formation of both *cis*- and *trans*-isomers of **8**.



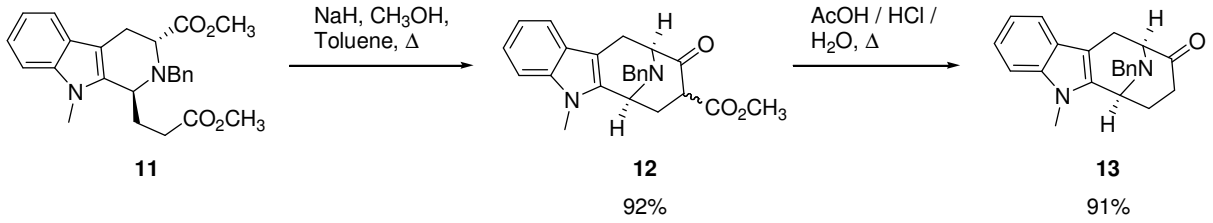
Scheme 1.2: Protonation of decarboxylated intermediate **8**.

Pure *trans*-isomer **11** was obtained by employing an acid-catalyzed isomerization step (**9** to **10**) in which the latter isomer is favored due to diminished steric buttressing between the ester groups (Scheme 1.3). The isomerization process is thought to occur *via* C_3–N_4 bond cleavage and C_3 cation formation due to delocalization of the positive charge over the indole ring.[7] Formation of **10** was proven through isolation of both a vinyloguous C_3–C_{14} intermediate of **10** and corresponding C_3 methyl ether of **10**. Both intermediates proved the C_3–C_4 bond fragmentation of *cis*-**8** due to 1,2-allylic strain to occur, therefore adopting a more relaxed *trans*-conformation **10**, resulting in formation of *trans*-**11**.[7]



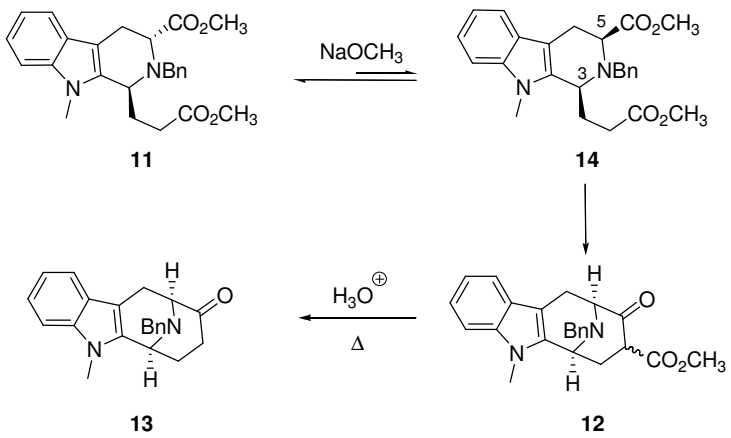
Scheme 1.3: Acid-induced epimerization to the 3,5-*trans* tetrahydro-β-carboline.

Dieckmann condensation of the diester **11** generated the β-keto ester **12** in 92% yield as reported by Yoneda.[6] Acid-catalyzed C_{15} decarboxylation subsequently gave the desired tetracyclic ketone **13** (Scheme 1.4).



Scheme 1.4: Tetracyclic ketone **13** formation.

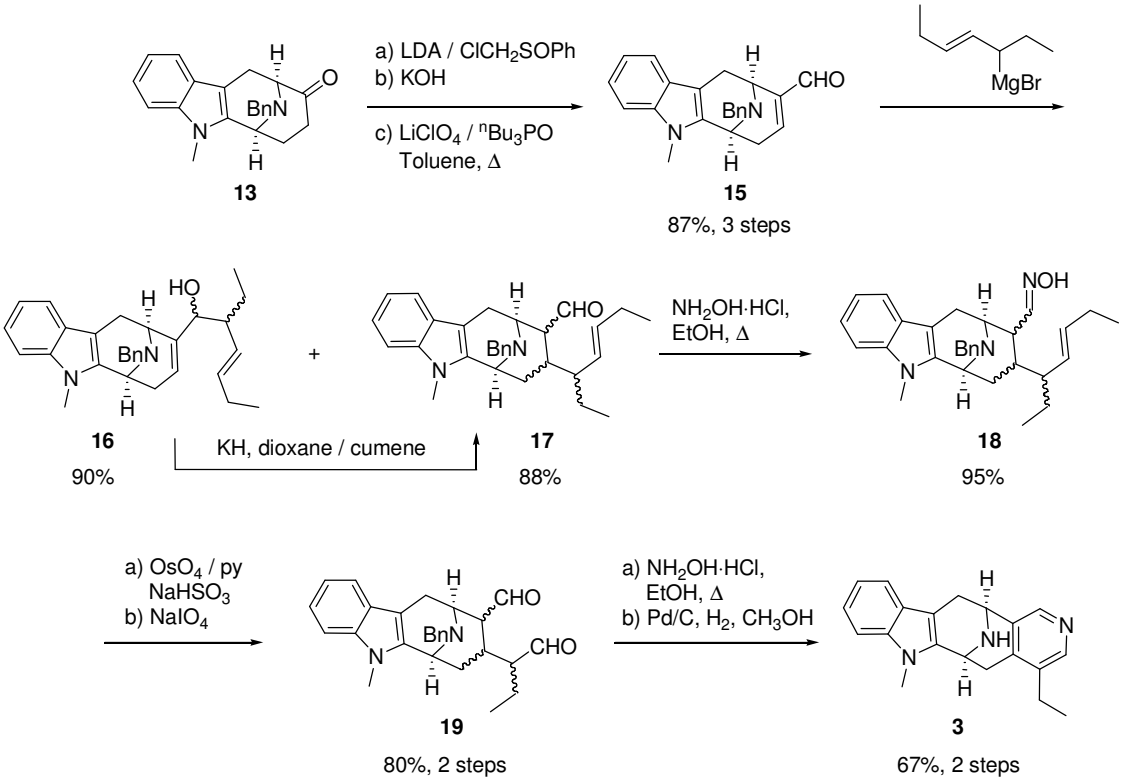
As the *trans*-isomer is unable to attain the configuration needed for cyclization, the base conditions involved in the Dieckmann condensation results in epimerization at the C_5 position prior to cyclization (Scheme 1.5). The initial incorrect configuration at C_5 induces the correct configuration at C_3 which in turn induces the correct and complete epimerization at C_5 and thus results in formation of **13**.



Scheme 1.5: Epimerization of **11**.

With tetracyclic ketone **13** in hand, the subsequent formation of α,β-unsaturated aldehyde **15** was achieved *via* rearrangement of the epoxide obtained from **13** and the anion of $ClCH_2SOPh$ (Scheme 1.6). Addition of the Grignard reagent generated from 1-bromo-2-pentene resulted in undesired alcohol formation due to allylic rearrangement. This problem was circumvented by the use of a pseudosymmetric secondary Grignard reagent which gave a mixture of 1 : 1, 1,2-**16** and 1,4-**17** addition products, after which **16** was converted into **17** by anionic oxy-Cope rearrangement.

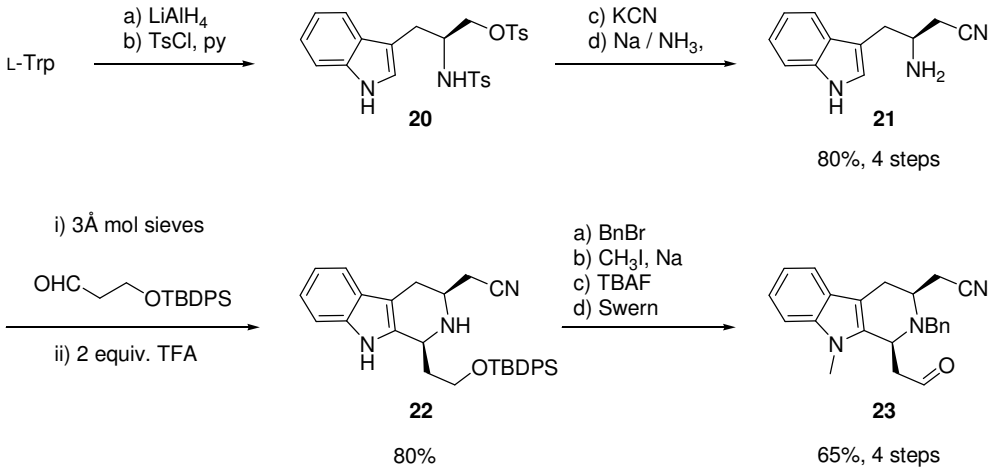
Attempts to cleave the olefinic bond oxidatively using ozone were unsuccessful; this was due to the reactivity of the 2,3-indole double bond. In order to prevent the formation of a hemiacetal, the aldehyde **17** was protected in the form of oxime **18**, osmylated and subsequently hydrolyzed reductively with $NaHSO_3$. The diol obtained was subjected to oxidative cleavage mediated by sodium periodate to provide **19**. Regeneration of the C_{16} aldehyde is believed to be induced by oxidative hydrolysis of the oxime function with sodium periodate.[4] Dialdehyde **19** was then exposed to hydroxylamine hydrochloride to furnish **3**. A change of protecting groups at the N_4-function was achieved by using Pd/C in methanol to give (–)-suaveoline **3** in seven steps.[4]



Scheme 1.6: Total synthesis of (–)-suaveoline **3** according to Cook.

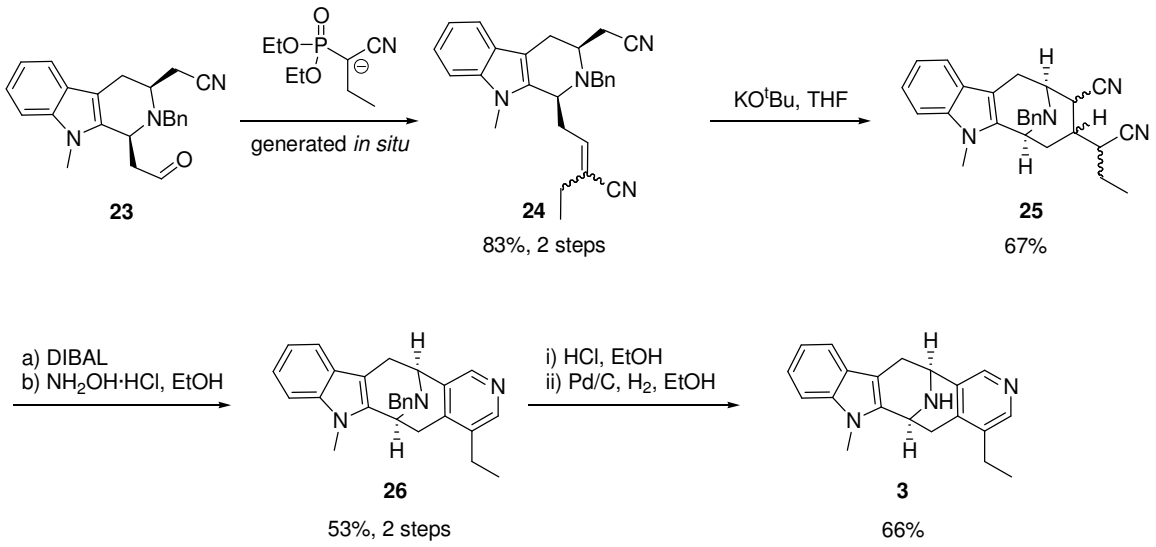
1.1.2.2. Bailey's Approach

Bailey and co-workers have made major contributions to the synthesis of indole alkaloids.[8] Their total synthesis of (–)-suaveoline used a Pictet–Spengler reaction, and began with the synthesis of cyanomethyltryptamine **21** from L-tryptophan (Scheme 1.7). Synthesis of **21** involved reduction of the carboxylic acid, tosylation of both terminal amine and newly formed alcohol, substitution of the *O*-tosyl by a cyano nucleophile and subsequent detosylation of the amine. Piperidine **22**, was obtained after the Pictet–Spengler cyclization gave only *cis*-C_3–C_5 tetrahydro-β-carboline. This was achieved after extensive optimization within the Bailey group as the need for a masked aldehyde was required at the C_3 position.[9] Incorporation of the hydroxyaldehyde in conjunction with the cyanomethyl substituent proved to be both synthetically useful and *cis*-specific. The absence of protecting groups at both nitrogen atoms might explain this selective outcome as Cook reported the presence of a bulky substituent at the N_4 position to enhance *trans*-C_3–C_5 selectivity.[10] In addition, both the reported use of kinetically controlled reaction conditions[8] and TBDPS instead of TBS might also provide an explanation regarding the observed *cis* specificity, the latter due to π-stacking. Deprotection of the alcohol and Swern oxidation gave the aldehyde **23**.



Scheme 1.7: Synthesis of cyano-aldehyde **23**.

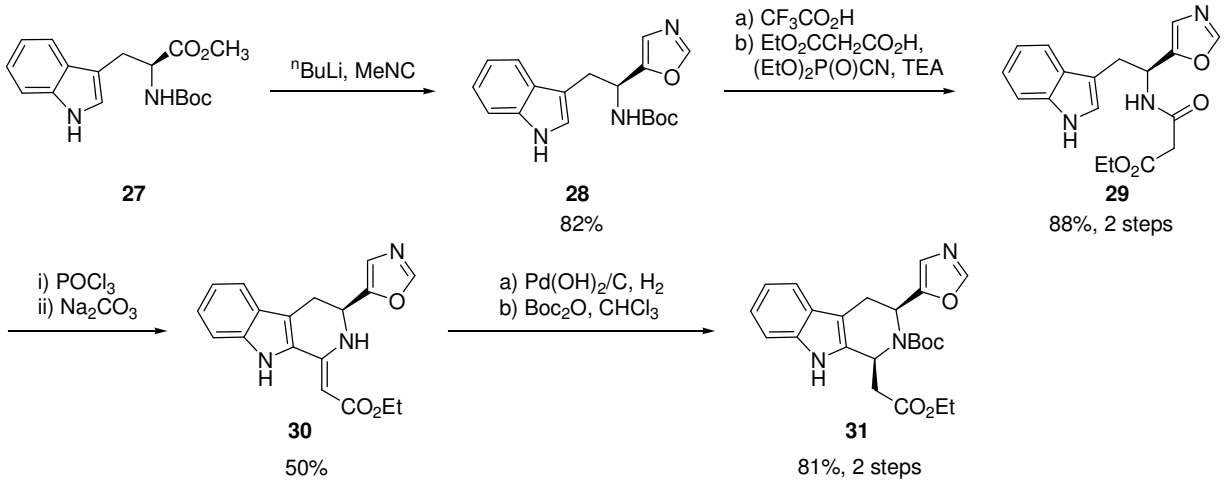
In more recent publications,[8] Bailey has employed the Horner–Wadsworth–Emmons reaction (**23**→**24**) followed by vinylogous Thorpe cyclization to give tetracyclic intermediate **25** (Scheme 1.8). The mixture of diastereoisomers was reduced using DIBAL and exposed to hydroxylamine hydrochloride to give 3,4,5-trisubstituted pyridine **26**. Results obtained later showed that an acid work-up after the DIBAL reduction was sufficient to form the pyridine ring. Debenzylation of N_4 finally resulted in (–)-suaveoline **3** formation in an overall yield of 14%.



Scheme 1.8: Total synthesis of (–)-suaveoline **3** according to Bailey.

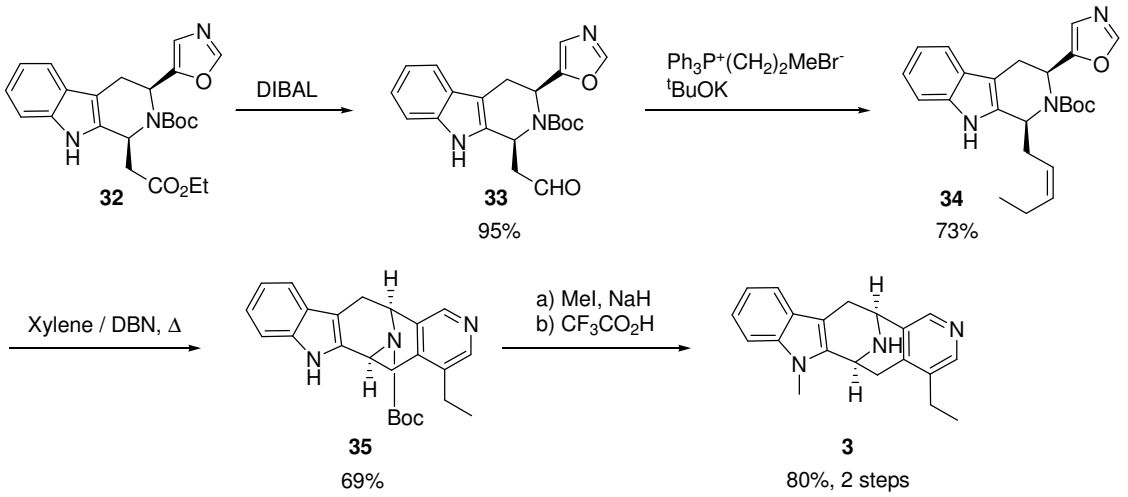
1.1.2.3. Ohba's Approach

Ohba's ongoing interest in annulated pyridine systems and exploitation of oxazole-olefin Diels–Alder reactions have recently culminated in the publication of a new total synthesis of (–)-suaveoline.[3,11] In this article Ohba and co-workers start from *N*-protected amino ester **27** which gave the oxazole **28** without erosion of *ee* according to their previously reported methodology.[12] Deprotection of the amine allowed amide formation **29** which was necessary for the formation of the C ring. A Bischler–Napieralski reaction,[13] initiated by $POCl_3$, gave **30**. Stereoselective hydrogenation using Pearlman's catalyst and hydrogen gave only the *cis*-1,3-disubstituted tetrahydro-β-carboline, which upon Boc-protection of the free amine provided **31** (Scheme 1.9).



Scheme 1.9: Synthesis of THBC **31**.

With the C-ring successfully constructed, employment of the oxazoline-olefin in an intramolecular Diels–Alder cyclization would result in simultaneous formation of rings D and E to provide **35** (Scheme 1.10). Reduction of the ester using DIBAL to provide aldehyde **33** and Wittig reaction gave olefin **34**. Finally, the intramolecular Diels–Alder reaction was performed in boiling xylene using DBN, which acted as a water scavenger and promoted the conversion of the Diels–Alder adduct into pyridine **35**. Methylation of the indole nitrogen resulted in the formation of (–)-suaveoline **3** in an overall yield of 10%.



Scheme 1.10: Total synthesis of (–)-suaveoline **3** by Ohba.

The total synthesis of (–)-suaveoline **3** as published by Ohba[11] is radically different from Bailey's[8] as it does not involve use of the Pictet–Spengler cyclization to yield the crucial tetrahydro-β-carboline, instead utilizing an intramolecular Diels–Alder reaction to form both D- and pyridine E-rings in **35**.

1.2 Alstonerine

1.2.1. Background

Alstonerine **36** was isolated in 1959 by Eldersfield and Gilman[14] as the major alkaloid in the bark of *Alstonia mycrophylla* and has since also been isolated from other family members.[15] Le Quesne *et al*.,[16] assigned the structure in 1969, yet the absolute configuration was uncertain until 1978 when the first biomimetic synthesis strongly suggested it to be similar to macroline. Biogenetic considerations suggest that (–)-alstonerine **36** may serve as a precursor to alstonine **37**, an oxindole alkaloid (Figure 1.2). However, as with suaveoline **3**, a full biological profile has not yet been established. In 1990 Cook and coworkers published the first total synthesis of alstonerine[17] starting from D-tryptophan.

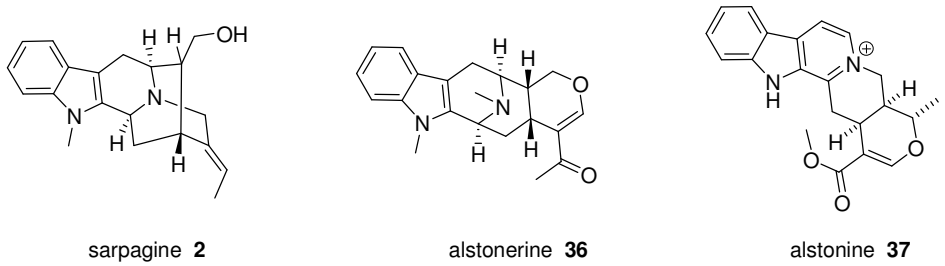


Figure 1.2

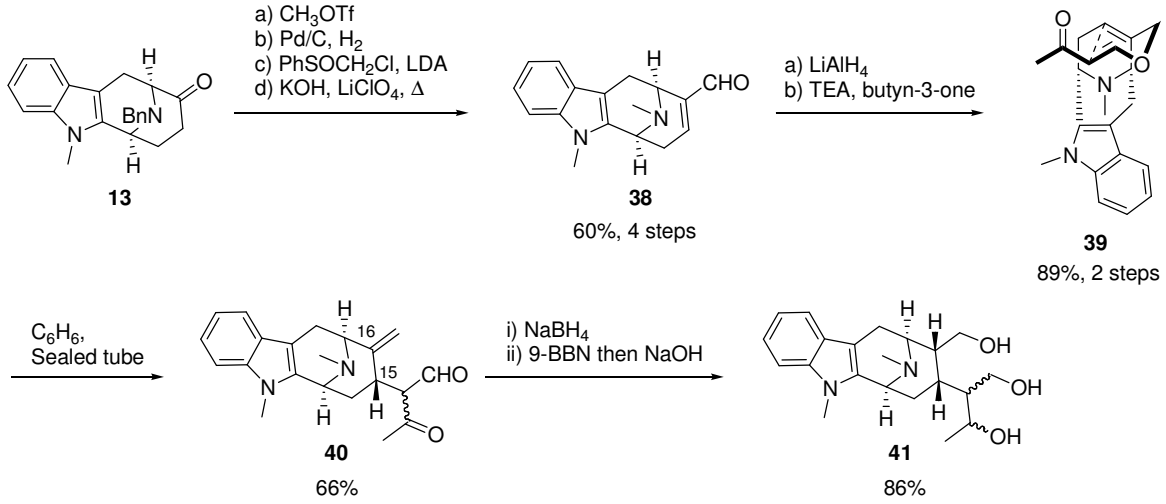
Structurally very similar to suaveoline, alstonerine contains the characteristic azabicyclo [3.3.1] core. In addition, the absence of the N_4–C_{21} linkage commonly found in the sarpagine-related compounds is a key feature.

1.2.2. Previous Total Syntheses of Alstonerine

1.2.2.1. Cook's Total Synthesis

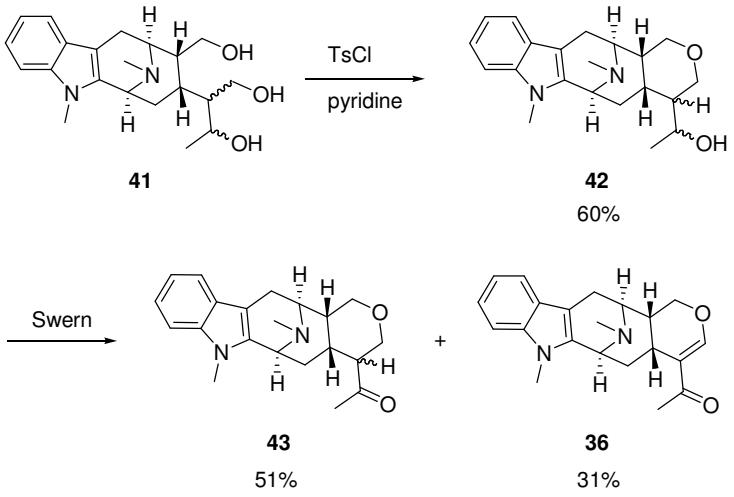
Cook *et al.*, reported the first total synthesis of (–)-alstonerine in 1990, using the tetracyclic ketone **13**.[17] The synthesis of the latter will not be discussed in this section, please see section 1.1.2.1.

Tetracyclic ketone **13** was prepared in seven steps from D-tryptophan, and converted into α,β-unsaturated aldehyde **38** *via* elimination of the spiroepoxide followed by oxidation[17] (Scheme 1.11). Chemoselective reduction of the aldehyde resulted in alcohol formation, which subsequently underwent oxo-Michael addition with butyn-3-one [18] to give desired enone **39**. Exposing the enol ether **39** to classical Claisen condensation conditions gave β-dicarbonyl **40** as a single diastereomer, probably due to α-face rearrangement of the double bond *via* a chair-like transition state.[19] This method had important implications since the correct C_{15} stereochemistry would induce the absolute configuration needed for the macroline / sarpagine / ajmaline alkaloids. Reduction of the β-dicarbonyl with sodium borohydride gave the corresponding triol **41**. Stereoselective hydroboration at the β-face of the exocyclic methylene function (C_{16}) with 9-BBN followed by oxidative work-up gave triol **41** stereoselectivity as a result of 1,3-steric repulsion between axial N_4-methyl function and the incoming borane.



Scheme 1.11: Synthesis of triol **41**.

Finally, cyclization of the triol **41** by tosylation and base treatment gave **42**, which after exposure to Swern oxidation conditions gave (–)-alstonerine **36** and the alstonerine derivative **43** (Scheme 1.12).



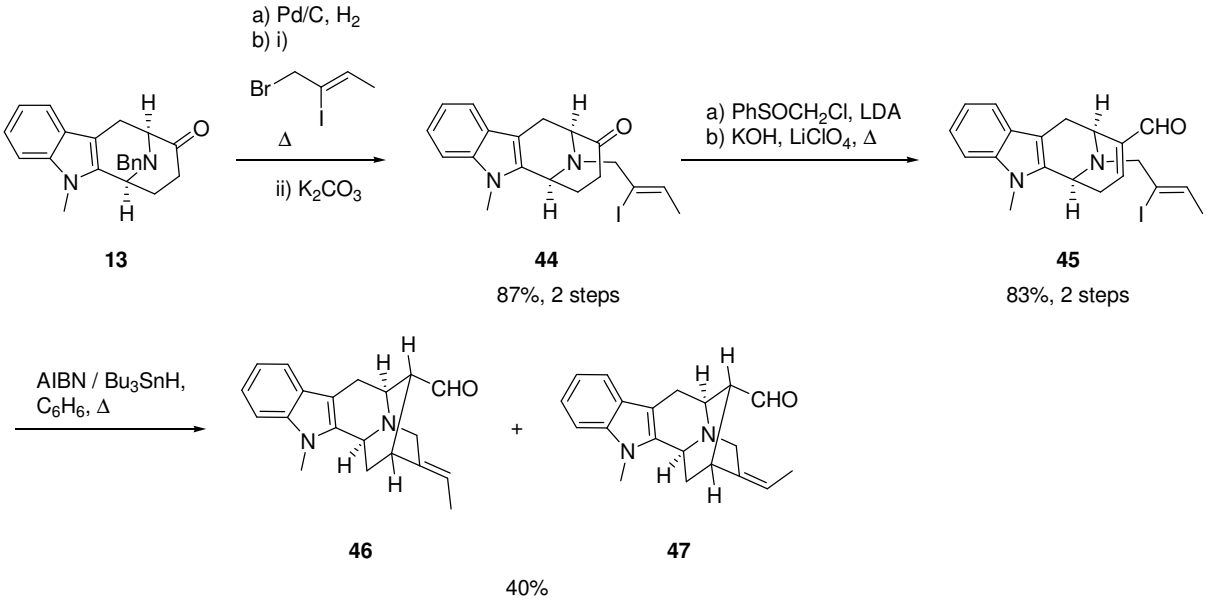
41 **42** 60%

43 51% **36** 31%

Scheme 1.12: First total synthesis of (–)-alstonerine **36** by Cook.

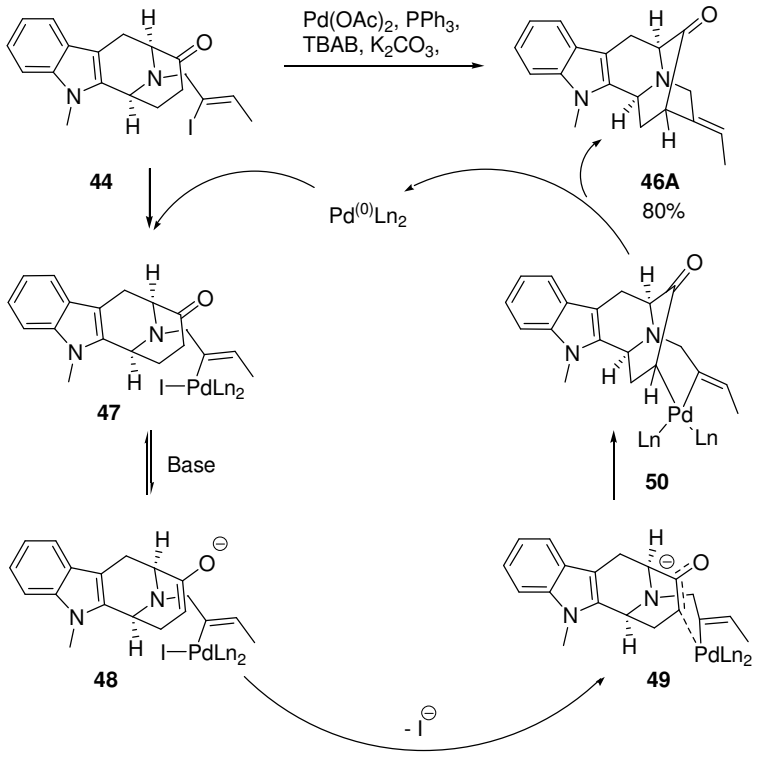
1.2.2.2. Cook's Second Approach

In 2005, Cook *et al.*[20] reported an improved total synthesis of (–)-alstonerine, once again using the tetracyclic ketone **13**[2] as their starting point (Scheme 1.13). Earlier attempts to provide the sarpagine skeleton *via* Michael addition had failed probably due to the relative acidity of the γ-position (C_{14}) of the α,β-unsaturated aldehyde system **45**.[21] Radical cyclization mediated by AIBN provided a mixture of **46** and **47**,[21] yet due to the moderate yield a Heck reaction was later employed, utilizing reaction conditions reported by Muratake and Natsume.[22]



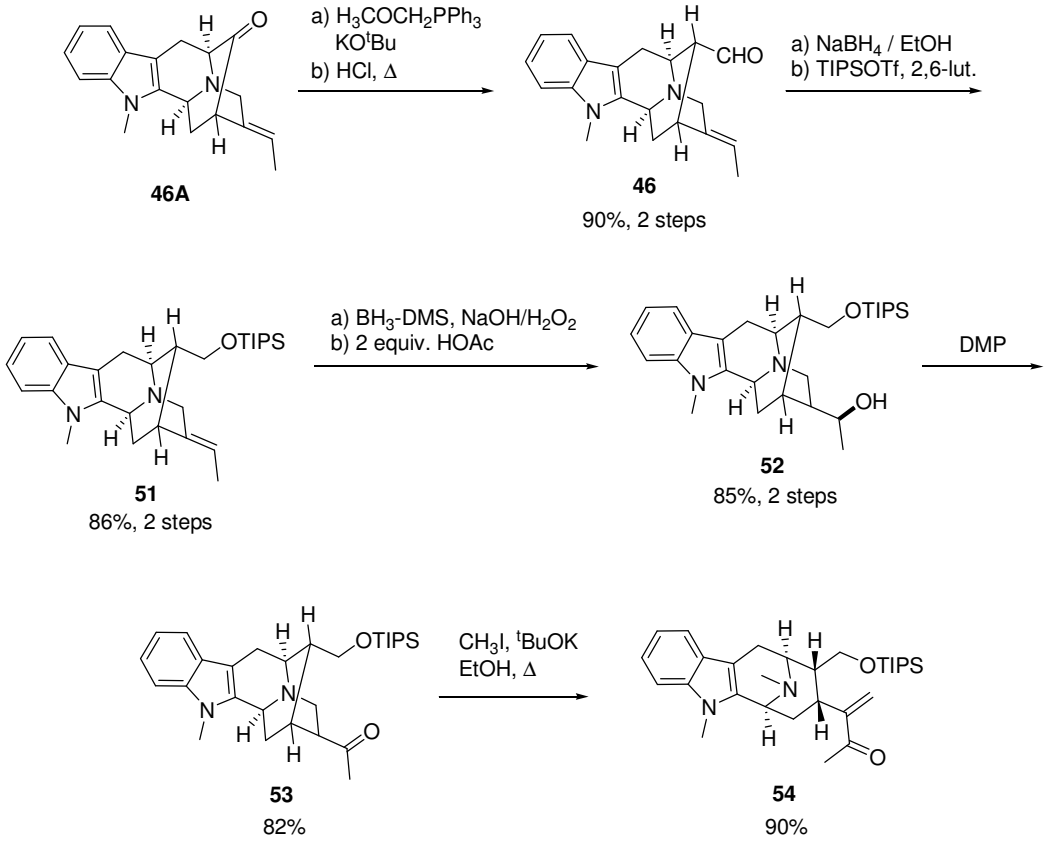
Scheme 1.13: Synthesis of the α,β-unsaturated aldehyde system **46** and **47**.

The Heck reaction is initiated by oxidative addition of the $Pd^{(0)}L_2$ to the vinyl iodide **47**, followed by an equilibrium between ketone **47** and its enolate **48** resulting in $Pd^{(II)}$ formation (Scheme 1.14). Enolate coordination with the Pd-complex gives **49** which finally undergoes reductive elimination to regenerate $Pd^{(0)}$ and provide **46A**.[21]



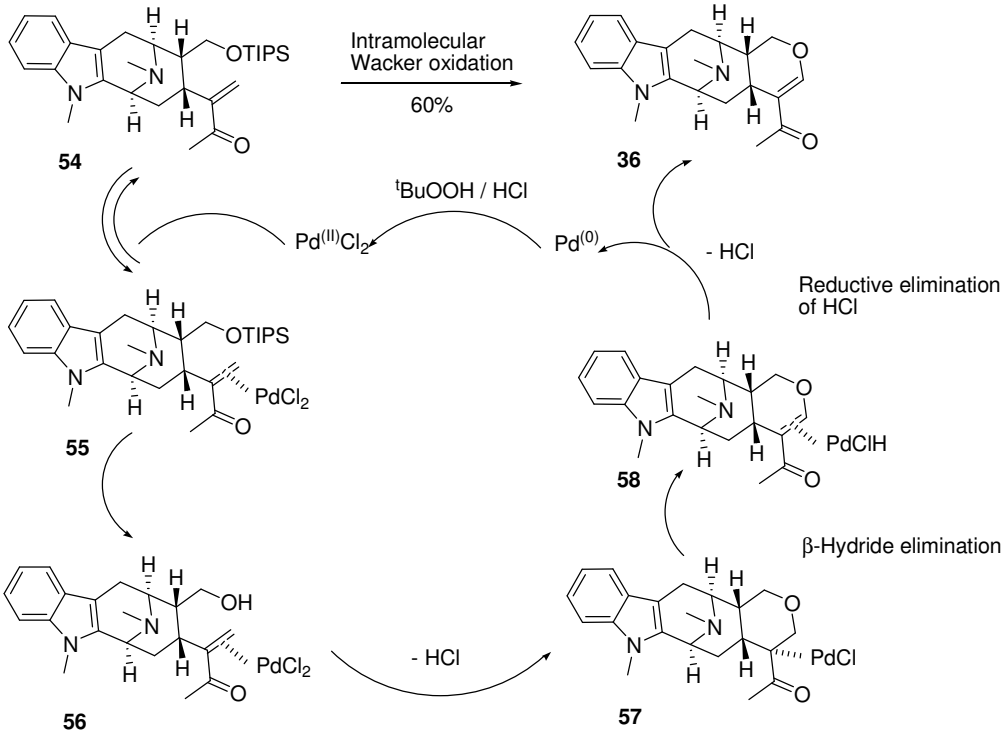
Scheme 1.14: Formation of **46A**.

When exchanging the vinyl iodide for the less reactive vinyl bromide only starting material was observed. This was probably due to the coordination of the palladium to the electron-rich indole which removes it from the reaction cycle. Subjecting ketone **46A** to Wittig reaction conditions provided the corresponding enol ether which was subsequently hydrolyzed to the corresponding aldehyde **46**. Reduction of **46** followed by silyl-ether formation gave protected alcohol **51**, (Scheme 1.15). This was followed by hydroboration–oxidation to provide alcohol **52**, which was oxidized to give ketone **53**. Subsequent *N*-methylation and spontaneous elimination of the quaternary ammonium salt gave **54**.[20]



Scheme 1.15: Synthesis of **54**.

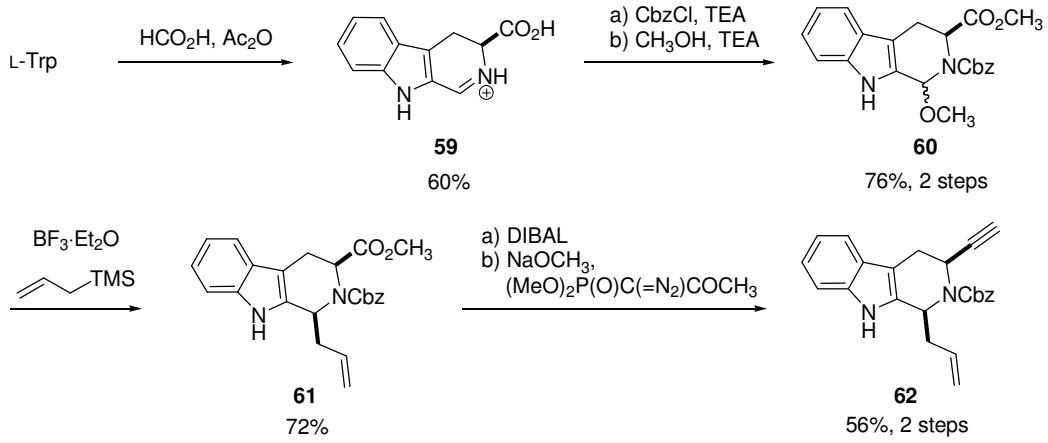
Finally, a modified intramolecular Tsuji–Wacker oxidation gave (–)-alstonerine **36** as a result of a one-pot domino process (Scheme 1.16). This process involves the deprotection of a silyl ether and carbon–oxygen bond formation under acidic conditions. The modified Wacker oxidation proved to be more successful than the traditional Wacker reaction in which case no reaction was observed due to the presence of a substituent adjacent to the carbonyl group. Carbon–oxygen bond formation is achieved *via* a palladium cycle, starting from $Pd^{(II)}$ coordination to the olefin as **55** in a reversible manner. This is followed by cleavage of the silyl ether **56** providing the nucleophilic oxygen, attacking the palladium and forming **57**. Then, β-hydride elimination **58**, followed by reductive elimination provides **36**; the $Pd^{(0)}$ is reoxidized by ^{t}BuOOH, re-entering the catalytic cycle.[20]



Scheme 1.16: Wacker Oxidation mechanism to produce (–)-alstonerine **36**.

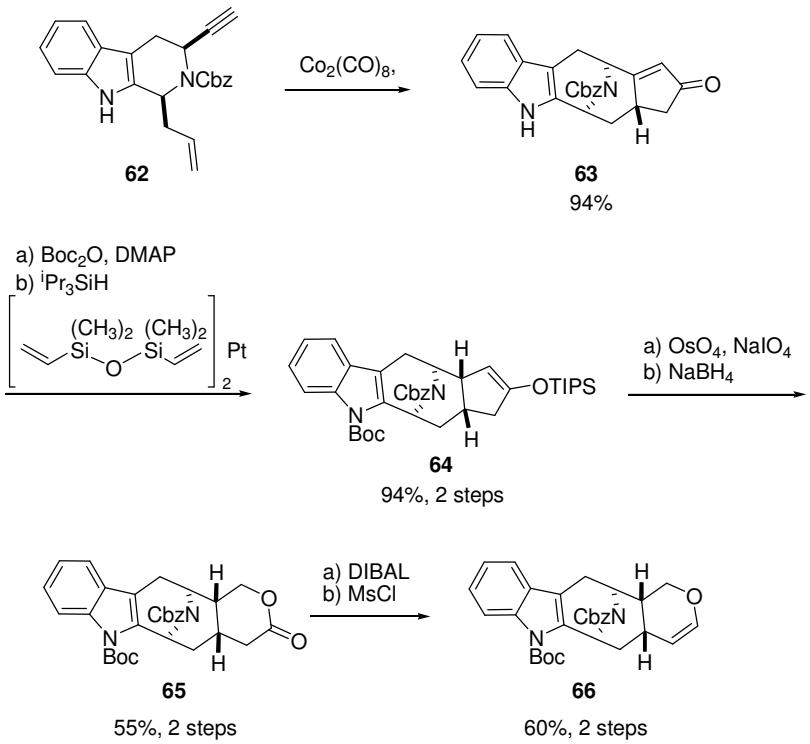
1.2.2.3. Martin's Approach

The Martin lab reported the first application of the Pauson–Khand reaction to the synthesis of azabridged bicyclic structures, culminating in the total synthesis of (–)-alstonerine.[23] Their route started with the conversion of L-tryptophan into the dihydrocarboline **59** *via* acetylation and cyclization as described by Previero *et al* (Scheme 1.17).[24,25] Further modification of carboline **59** into the diastereomeric mixture of aminal **60** was followed by installation of the terminal olefin by use of BF_3-mediated alkylation to give the adduct **61**. DIBAL reduction of the ester moiety in **61** resulted in the formation of the intermediate aldehyde, which was subsequently exposed to Ohira–Bestmann reagent, in the presence of $NaOCH_3$, to give enyne **62**.[26]



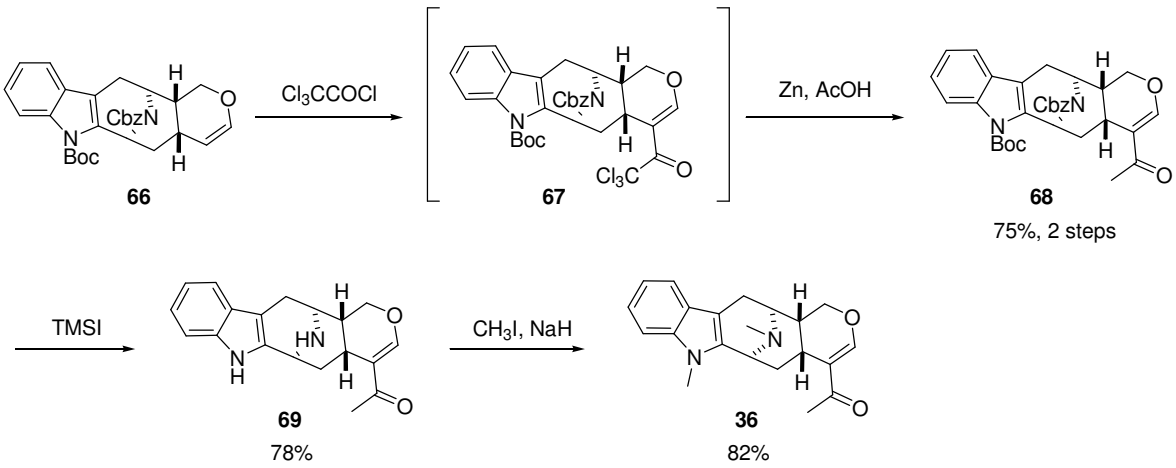
Scheme 1.17: Synthesis of enyne **62**.

Enyne **62** was exposed to Pauson–Khand reaction conditions to afford in excellent yield the cyclopentenone **63** as a single diastereomer (Scheme 1.18).[23] A stepwise approach was employed, in which cyclopentenol **63** was converted into the silyl-enol ether **64**, followed by oxidative cleavage, resulting in an aldehyde / carboxylic acid intermediate. Upon treatment with sodium borohydride followed by acid-induced cyclization lactone **65** was formed. With the δ-lactone in hand the next step involved the formation of tetrahydropyran **66** by use of DIBAL.[23]



Scheme 1.18: Synthesis of **66**.

Attempted conversion of both the *N*-Boc and *N*-Cbz moieties in **66** to *N*-methyl groups, followed by Friedel–Crafts acylation offered a complex mixture of products, probably due to the use of forcing conditions, in which competing C_5 acetylation of the indolic ring-system was observed (Scheme 1.19).[27] Further optimization of the acylation reaction involved use of milder reaction conditions; trichloroacetylation in the absence of a Lewis acid, similarly did not yield the required product. Applying the same trichloroacetylation reaction conditions to **66** showed ready acetylation towards **67**. Subsequent reduction of the latter using Zn / HOAc furnished **68**, this together with the removal of the protecting groups, followed by *N*-indole methyl installation gave (–)-alstonerine **36** *via* **69**.

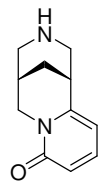


Scheme 1.19: Total synthesis of (–)-alstonerine **36** according to Martin.

1.3. Cytisine

1.3.1. Background

(–)-Cytisine (Figure 1.3) is a member of the lupin alkaloid family, and can be found in the seeds of the *Leguminosae* genus of plants.[28] After its isolation in 1862 it took another 70 years until the correct structure was elucidated by Ing in 1932.[29] Chemically, (–)-cytisine is a quinolizidine alkaloid with a tricyclic skeleton, consisting of a bicyclic piperidine fused to a 2-pyridone moiety. The two stereogenic centers were determined to be 7*R*,9*S*.



70

Figure 1.3: (–)-cytisine **70**

The first total synthesis of this molecule was achieved by van Tamelen in 1955, [30] closely followed by Bohlmann[31] and Govindachari.[32] Recently, after a 50 year gap, both academia and industry have renewed their mutual interest in cytisine and analogue synthesis due to its biological activity.[33] Multi-gram isolation of (–)-cytisine is easily obtained by simple extraction of the seeds of *Leguminosae anagyroides* using an aqueous mixture of ammonia in methanol and DCM, which provides a cheap resource of (–)-cytisine.

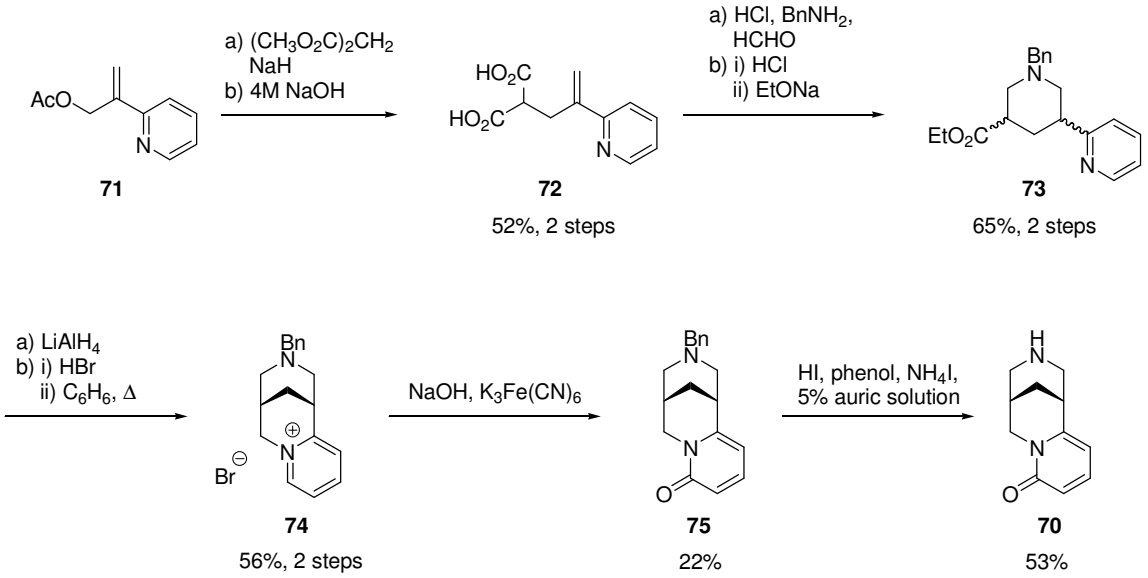
(–)-Cytisine has shown significant biological activity, specifically in the field of neuronal nicotine acetylcholine receptors. It has been shown to act as a partial agonist towards these receptors, resulting in the release of dopamine thus making it a useful starting point in the development of a smoking cessation drug. Despite its high affinity towards the nicotine binding receptors *in vitro*, *in vivo* tests showed poor efficacy due to its poor absorption and the inability to pass through the blood-brain barrier because of its protonated nitrogen atom at physiological pH.[33]

1.3.2. Previous Total Syntheses of Cytisine

Since the first successful total synthesis of (±)-cytisine by van Tamelen a total of 10 total syntheses have been reported; these are discussed in a recent review by O'Brien.[33] A summary of the first synthesis of (±)-cytisine by van Tamelen,[30] the O'Neill approach[34] and the only reported total synthesis of (–)-cytisine by Lesma[35] are highlighted due to their relevance to the project involved.

1.3.2.1. Van Tamelen's First Total Synthesis

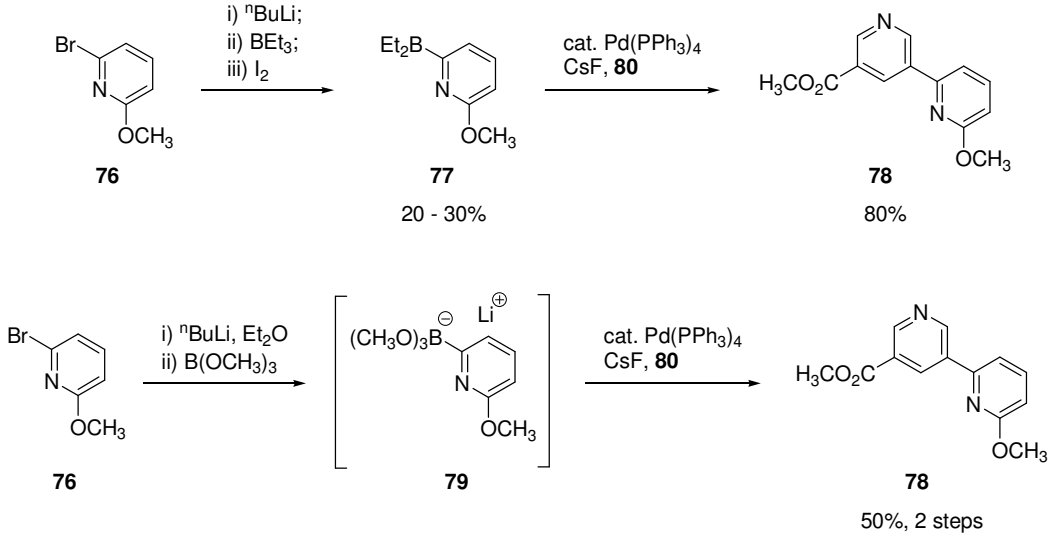
Van Tamelen published a seven-step route to (±)-cytisine in 1955 (Scheme 1.20). Formation of malonate **72** was achieved by substitution of acetate **71** with diethylmalonate, presumably *via* an allyl cation intermediate or a conjugate addition-elimination pathway.[33] A Mannich reaction between the enolate of **72** and the Mannich base of benzylamine and formaldehyde was followed by decarboxylation of one of the acid groups as indicated by the evolution of CO_2 which provided **73**. Intramolecular conjugate addition onto the vinylpyridine functionality in **72** to form the piperidine ring in **73** was reported to require at least 4 h. Isolation of ester **73** showed a high amount of *trans*-**73** instead of *cis*-**73**.[30] Thus the need for epimerization which gave the thermodynamically more stable *cis* isomer (both substituents in equatorial position) was required. Reduction of *cis*-**73** and cyclization using S_N2 displacement with bromine under thermal conditions gave biazocycle [3.3.1] **74**. Finally, low-yielding formation of pyridone **75**, followed by debenzylation furnished (±)-cytisine **70**.



Scheme 1.20: Total synthesis of (±)-cytisine **70** by van Tamelen.

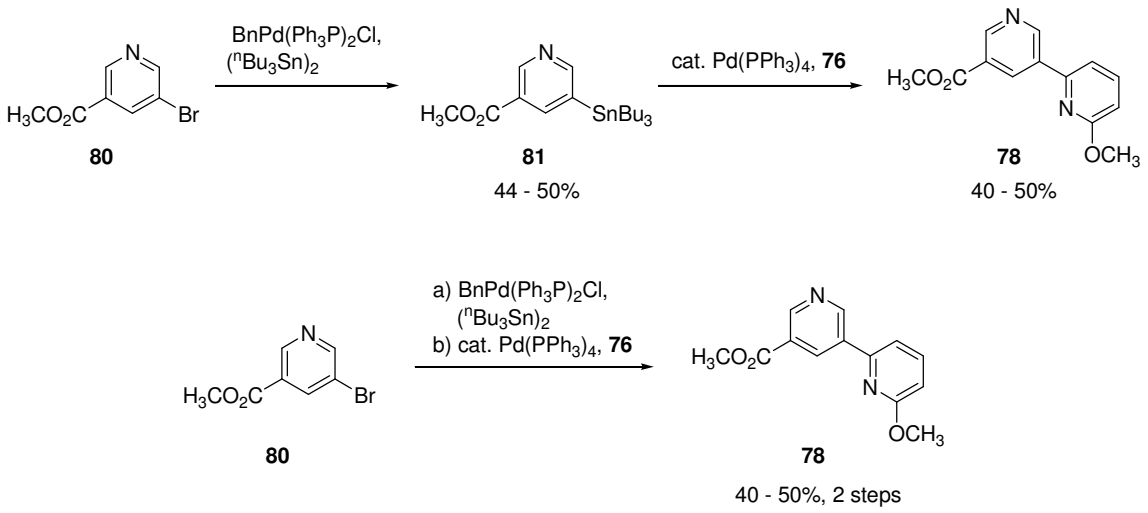
1.3.2.2. O'Neill's Approach

Recent publications by O'Neill have reported a shortened, five-step total synthesis of (±)-cytisine,[34] applying palladium chemistry. The presence of methoxypyridine **77** removed the need for late-stage oxidation of the pyridine to pyridone and was one of the key differences compared to the earlier van Tamelen approach. Aryl–aryl bond formation between **76** and **80** either *via* Suzuki or Stille cross-coupling reactions was investigated (Scheme 1.21). Although boranes **77** and **79** proved to be particularly efficient Suzuki-coupling partners (80%),[36] trapping of the latter proved difficult (20–30%). The *in situ* generation of the borate ester **79**,[37] followed by coupling with bromopyridine **76** gave a higher overall yield (50%).



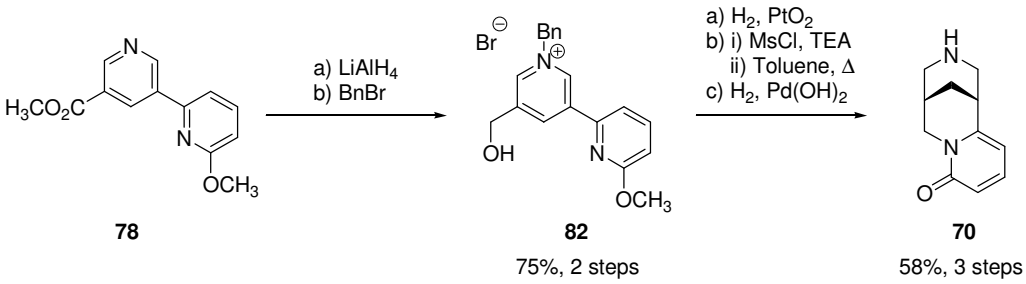
Scheme 1.21: Suzuki coupling reactions.

Stille coupling by preparation of stannane **81,**[38] followed by cross-coupling with **76** gave a similar low overall yield (Scheme 1.22). Application of the one-pot synthesis of stannane, prepared *in situ* and subsequently coupled to bromopyridine **76**, gave a similar yield compared to the Suzuki reaction mentioned earlier, without detection of the expected homodimers. Despite several optimization attempts, **78** could not be provided in a high yield. The one-pot strategy applied to both the Suzuki and Stille coupling reactions proved most successful.



Scheme 1.22: Stille coupling reactions.

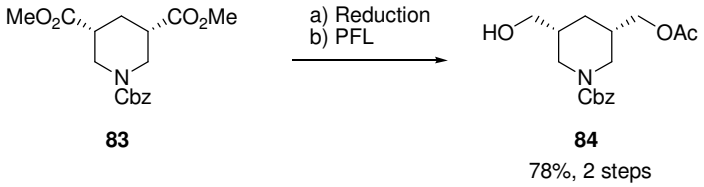
Reduction of ester moiety **78** was followed by chemoselective benzylation of the less hindered pyridine nitrogen to give pyridine salt **82** (Scheme 1.23). Selective reduction of the benzylpyridinium salt gave a mixture of *cis* / *trans* (85 : 15) regarding the 3,5-substituents. This selective reduction is believed to be linked to the oxidation level of the 3,5-substituents when compared to the inertness of the methoxypyridine. Cyclization of the biazacyclo [3.3.1] nonane ring was carried out by activation of the alcohol by mesylation and, subsequent chemoselective hydrogenolysis of the *N*-benzyl group to give (±)-cytisine **70**.



Scheme 1.23: Total synthesis of (±)-cytisine **70**.

1.3.2.3. Lesma's Approach

The Lesma approach to (–)-cytisine featured a ruthenium-catalyzed RCM, relying on the readily available *cis*-piperidine-3,5-dimethanol monoacetate **84** as the chiral building block (Scheme 1.24). This building block could be obtained in both enantiomeric forms by use of enzymatic asymmetrization of the appropriate σ-symmetrical dimethyl piperidine-3,5-dicarboxylate **83**.[39] Use of PFL (*Pseudomonas fluorescence* lipase) in combination with vinyl acetate gave **84** with >98 *ee*.

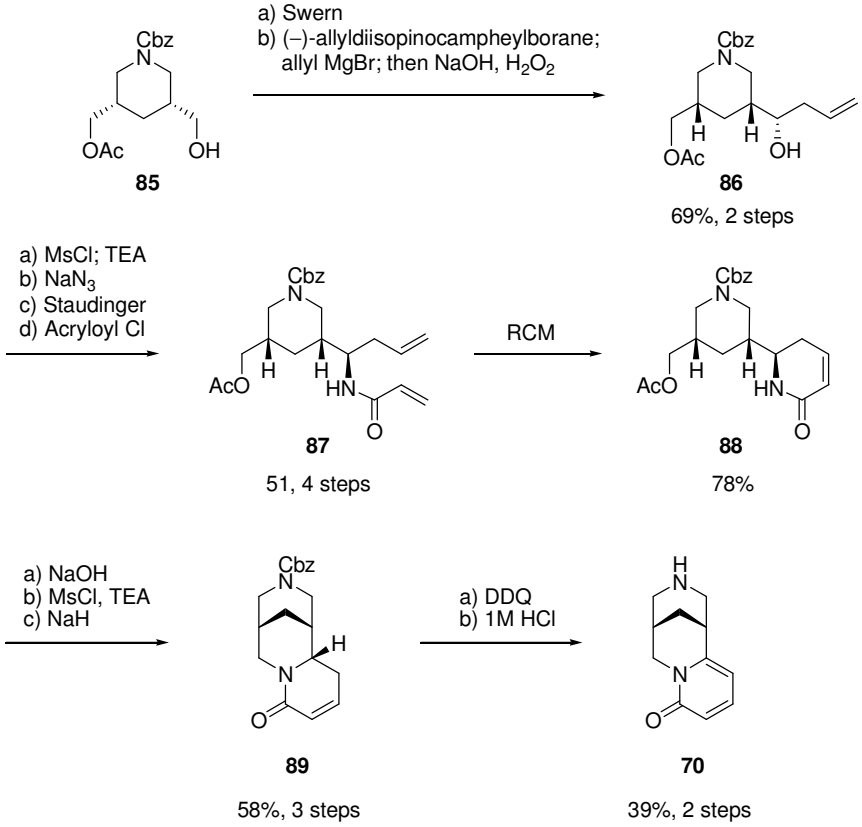


83 **84**

78%, 2 steps

Scheme 1.24: Synthesis of *cis*-piperidine-3,5-dimethanol monoacetate **84** building block.

Swern oxidation of **84** generated the corresponding aldehyde, which after allyl addition using Brown's (–)-allyldiisopinocampheylborane reagent gave a 10 : 1 mixture of alcohol **80** (Scheme 1.25). Although the stereogenic center at C_6 does not have any significant value in the total synthesis of (–)-cytisine, as it will be incorporated into the pyridone structure later on, the ease of working with a single diastereomer was advantageous. Formation of the mesylate was followed by azide displacement, which on exposure to Staudinger reduction conditions gave acryloyl amide **87** upon treatment with acryloyl chloride. Despite the presence of a free NH amide group, ring-closure of the diolefinic substructure **87** was achieved in high yield. It was rationalized that the neighboring piperidine ring sterically blocked the NH group, thus preventing formation of chelate complexes with ruthenium. Deprotection of the acetate in **88** was followed by mesylation after which base-induced intramolecular alkylation gave the tricyclic skeleton of (–)-cytisine, **89**. Dehydrogenation of dihydropyridone using DDQ provided the corresponding pyridine. Last, Cbz-deprotection furnished (–)-cytisine **70**.

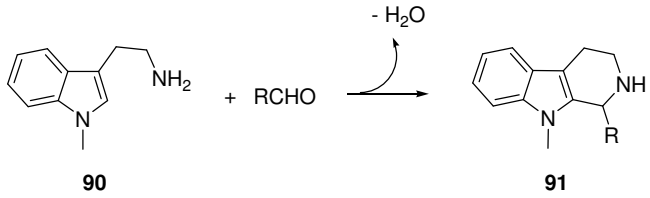


Scheme 1.25: Lesma's total synthesis of (–)-cytisine **70**.

1.4 The Pictet–Spengler Cyclization

The Pictet–Spengler reaction has proven to be a very powerful tool in indole and isoquinoline alkaloid synthesis. It was conceived in 1911 by Ame Pictet and Theodor Spengler, who successfully condensed β-arylethylamines with carbonyl compounds in an acidic environment as was already known to occur in plants.[40]

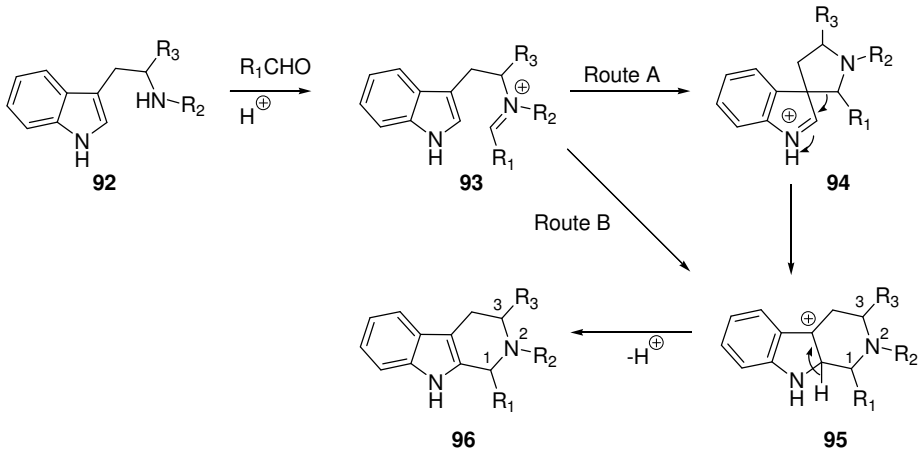
Increased interest in the synthesis of tetrahydro-β-carbolines, due to their biological activity,[41,42] provided the basis of further research into applying the Pictet–Spengler reaction towards the preparation of these substrates, this being a common motive in indole alkaloids.
Tatsui[43] was the first to report the successful application of this method to give tetrahydro-β-carbolines using indole bases instead of phenylethylamine (Scheme 1.26). These carbolines **91** were prepared by condensation of tryptamine derivatives **90** and aldehydes. In addition to aldehydes, other carbonyl containing compounds were tested, such as α-keto acids, that undergo facile decarboxylation, and β-keto-aldehydes both of which would yield carbolines.[44]



90 **91**

Scheme 1.26: Tetrahydro-β-carboline formation through Pictet–Spengler reaction.

Two mechanisms for the Pictet–Spengler cyclization reaction have been proposed and thoroughly investigated by Jackson and co-workers[45] (Scheme 1.27). However, regardless of which path is followed, it is the electrophilic nature of the imine double bond which is the driving force in this cyclization.
The first proposed mechanism involves formation of the spiroindolenine, as proposed by Woodward[46] in 1948, *via* electrophilic attack of the 3-position of the indole by the Schiff base (Route A). Subsequent 1,2-alkyl shift followed by deprotonation would give the carboline. The other mechanism would involve a much simpler route namely *via* direct attack at the 2-position of the indole, which would give rise to the cationic intermediate (Route B).[47]



Scheme 1.27: Two proposed mechanisms for the Pictet–Spengler reaction. Route A (*via* C_3) & route B (*via* C_2).

Jackson[45] illustrated the differences between both of the proposed mechanisms in an energy diagram (Figure 1.4 and Scheme 1.28). They reasoned that disruption of the π-electron system of the benzene ring (**I** → **IV**) would require more energy when compared to the indolenine (**I** → **II**), both of which would provide the same intermediate. Therefore, attack at the C_3-position would be favored over the C_2-position. The following step, which involves deprotonation to reform the indole ring (**V**), would not be affected by either pathway.

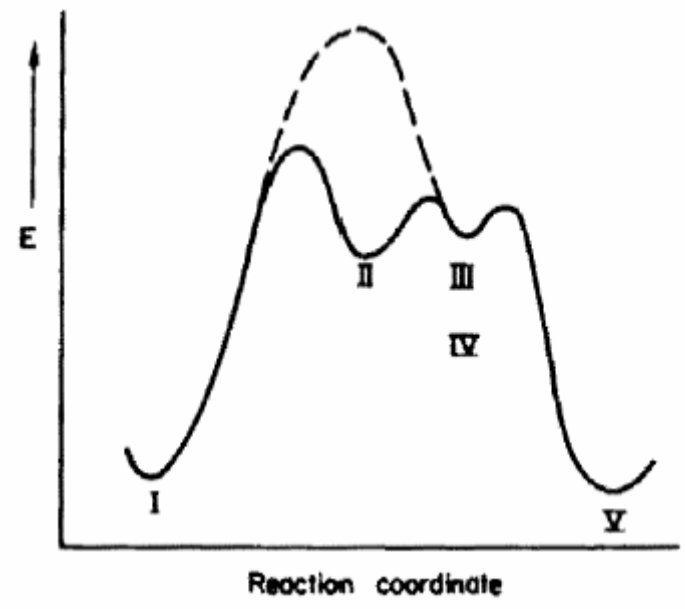
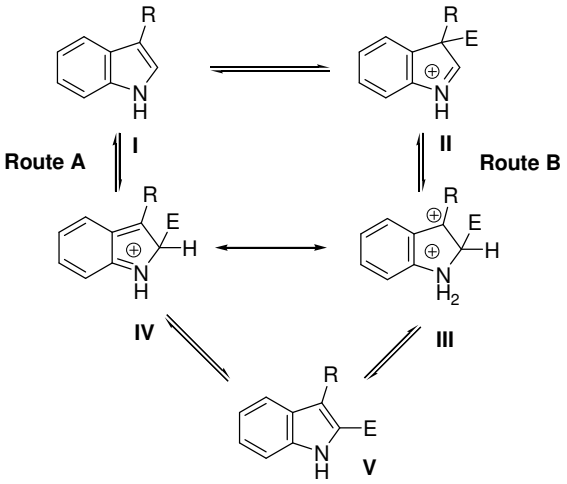
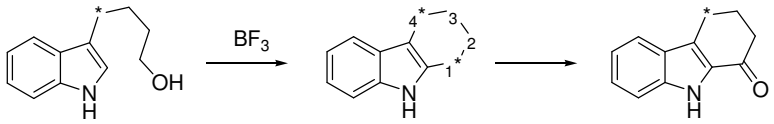


Figure 1.4: Energy diagram, route A and B.[45]



Scheme 1.28: Illustrated compounds belonging to Figure 1.4.

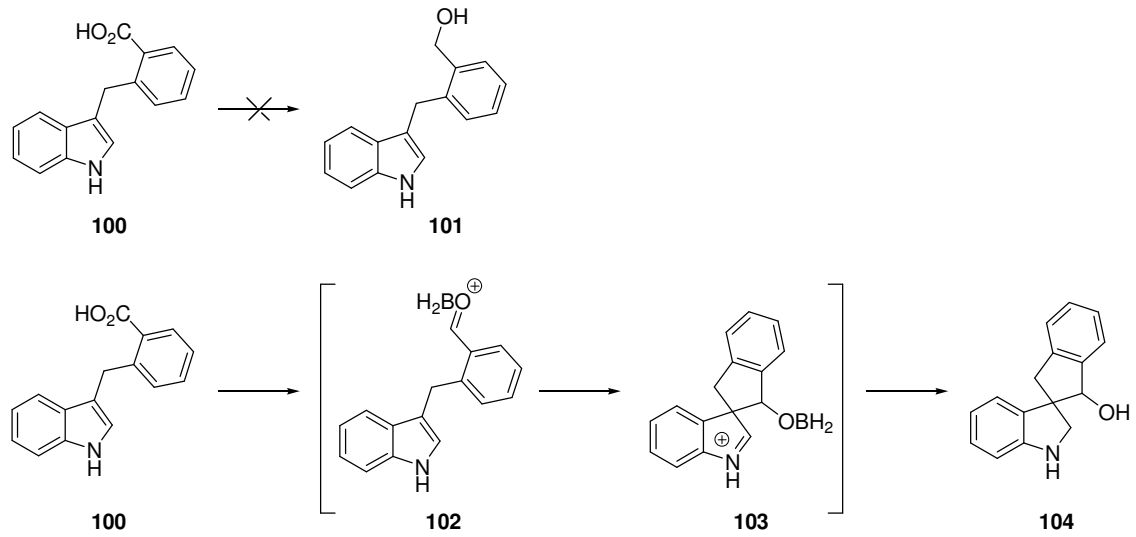
An interesting experiment in order to further investigate the viability of the proposed mechanisms involved labeling of indolyl-3-butanol **97** with tritium on the methylene group adjacent to the indole ring (Scheme 1.29). Treatment of the latter with BF_3 triggered cyclization (with all tritium labels in place) after which oxidation revealed loss of half of the labels which could only have occurred *via* spiroindolenine formation.[44]



97 **98** **99**

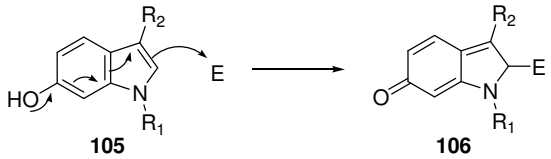
Scheme 1.29: Tritium (*) labeled experiment.

Another example[44] of strong evidence towards the former was obtained when an experiment to reduce the molecule's carboxylic acid functionality **100** to alcohol **101** instead resulted in spiroindolenine **104** formation (Scheme 1.30), probably through intermediates **102** and **103**.



Scheme 1.30: Unexpected spiroindolinene formation.

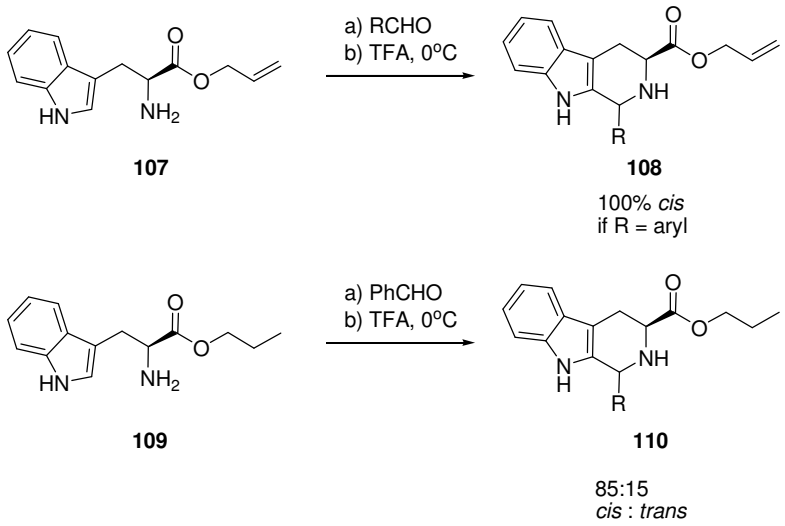
Casnati[47] has shown that changes in reaction conditions and / or substituents might induce attack at the C_2-position in competition with the indolenine mechanism (Scheme 1.31).



Scheme 1.31: C_2 favoring conditions.

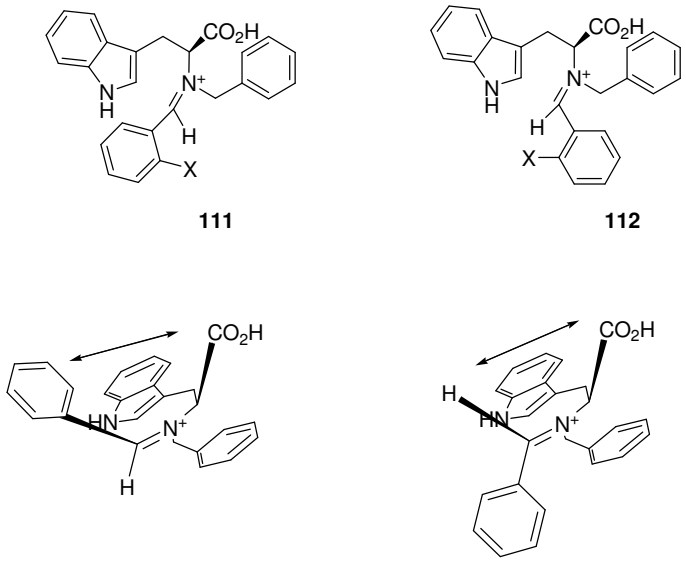
It seems reasonable that formation of the indolenine is kinetically controlled while the rearranged 2,3-disubstituted indole requires more energy to rearrange to a tetrahydro-β-carboline thus being thermodynamically controlled. While the spiroindolinene mechanism has been widely accepted, the direct C_2 coupling cannot be ruled out and both mechanisms result in general poor *cis* / *trans* selectivity.[9]

Pitchard[9] reported the *cis*-specific Pictet–Spengler reaction of benzaldehyde and an allyl ester of tryptophan (Scheme 1.32). Complete *cis* selectivity was observed when allyl esters **107** were used, using propyl esters **109** usually yielded 4 : 1 *cis* / *trans* mixtures as previously reported by this group. In addition to this finding, only aryl aldehydes were able to condense in a *cis*-specific way. This was explained by the possibility of π-stacking between the allyl / aryl groups, which would allow cyclization to proceed through a diaxial intermediate.



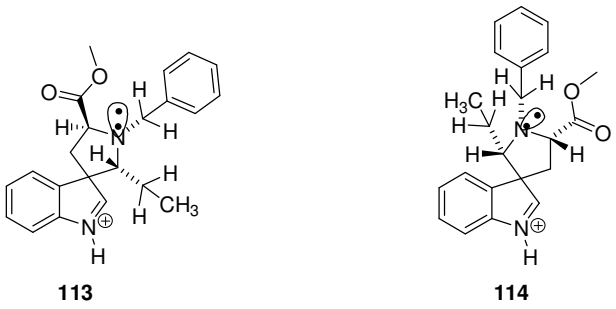
Scheme 1.32: *Cis*-specific Pictet–Spengler when using allyl esters.

The *trans*-specific Pictet–Spengler reaction was reported in detail by Cook *et al.*[10] They first looked at the possibility of both stereoisomers and concluded that one would clearly be favored (*E* isomer **111**) over the other (*Z* isomer **112**), due to steric interference between the 1,3-substituents during the transition state (Scheme 1.33). Initial attack of the indole double bond whether *via* the C_2 or C_3-position would be under stereoelectronic control, similar to attack of a hydroxide ion on imidate salt (periplanar) reported by Delongchamps.[48]



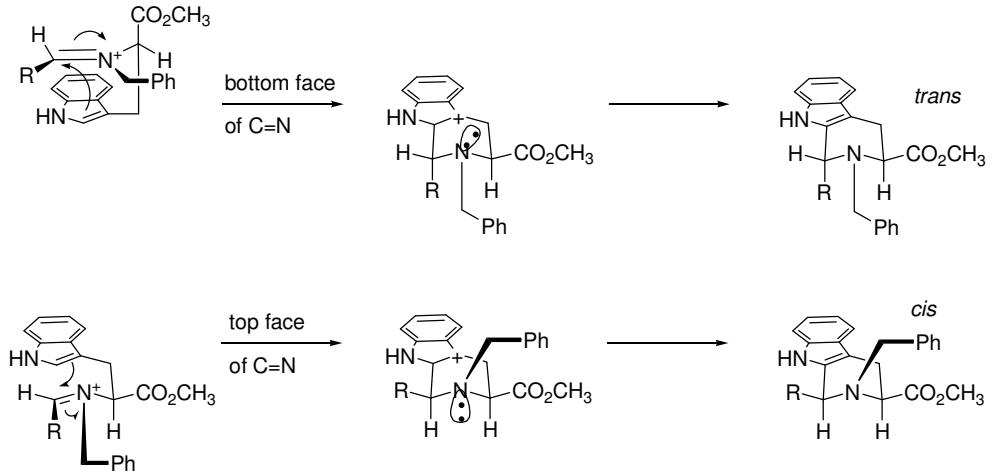
Scheme 1.33: Steric interference in the *Z* isomer **111** when compared to the *E* isomer **112**.

When considering the spiroindolenine (C_3) mechanism, the indole double bond could either attack at the bottom **113** or top face **114** of the imine. Bond formation *via* the top face addition would result in *cis* configuration with substituents C_1, C_2 and C_3 very close to each other (eclipsed) when compared to *trans*. In the case of structure **113** attack has taken place opposite to the ester function, which has also minimized interactions of these groups. The stereospecificity becomes more obvious when illustrated in Scheme 1.34.[10]



Scheme 1.34: Bottom (left, less crowded) and top face (right, crowded) after nucleophilic attack from the C_3 indole, **113** being less crowded due to the eclipsed conformation of the substituents in **114**.

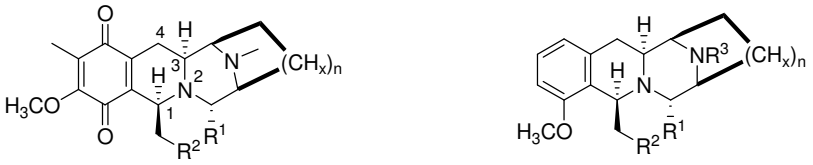
Even though the spiroindolenine is the most accepted mechanism, as stated before, one cannot rule out direct attack at C_2 (Scheme 1.34). When considering this mechanism, attack from the bottom face of $C=N^+$ gives the benzyl group in an equatorial position while the phenyl at C_1 occupies an axial position. The product of this attack yields a molecule with two equatorial and one C_1-axial position. In a similar sense attack at the top face would give a more crowded *cis*-molecule, giving rise to a less favorable equatorial 1-substituent along with the NH of the indole, and an axial 2-benzyl position during the transition state. In both mechanisms the *trans*-molecule is favored, which can be confirmed by NMR analysis.[49]



Scheme 1.35: Nucleophilic attack from the C_2-position of the indole from the top or bottom face.

1.5. Recent Progress in Pictet–Spengler Mediated Total Syntheses of Isoquinoline Alkaloids.

The tetrahydroisoquinoline (THIQ) ring system forms the core of a vast array of biologically active natural and unnatural products (Figure 1.5). These alkaloids have sparked the interest of both academic as well as industrial communities due to their exhibited medicinal bioactivities, physiological and pharmaceutical effects.[50] Recent methods applied towards the synthesis of these isoquinolines involve stereochemical modifications of sequential Bischler–Napieralski cyclization / reduction, the Pictet–Spengler and various Pomeranz–Fritsch cyclizations. In addition, the introduction of electrophilic / nucleophilic carbon units at the C_1 position *via* the C_1–C_α connectivity approach provides an alternative in regard to the more classical approaches that have been reported.[51] The overwhelming amount of reviews published in regard to Pictet–Spengler[52] / oxa-Pictet–Spengler cyclizations,[53] total syntheses of indole alkaloids[54] and recent progress towards β-carbolines[55] revealed the absence of an updated review regarding the progress in Pictet–Spengler mediated total syntheses of THIQ alkaloids. As such this review provides an updated overview from 2004 onwards[51] and has been organized into the alkaloid families of the THIQ natural products involved. In addition, besides highlighting the application of the Pictet–Spengler cyclization in the synthesis of the core scaffolds, key conversions in the total syntheses of these natural products will be examined as well.



115 n = 1 or 2 **116**

Figure 1.5: General THIQ structure.

1.5.1. Small THIQ-derived Natural-occuring Alkaloids

The THIQ structure is a common core structure in biologically active natural compounds (Figure 1.6). In addition to the complicated natural compounds, smaller congeners are known and relatively common. Jung,[56] Cuny[58] and Ruchirawat[61] have recently reported the total synthesis of a couple of these structurally simple THIQ natural products in order to show the general applicability of their methodologies.

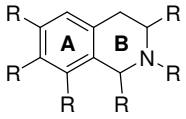
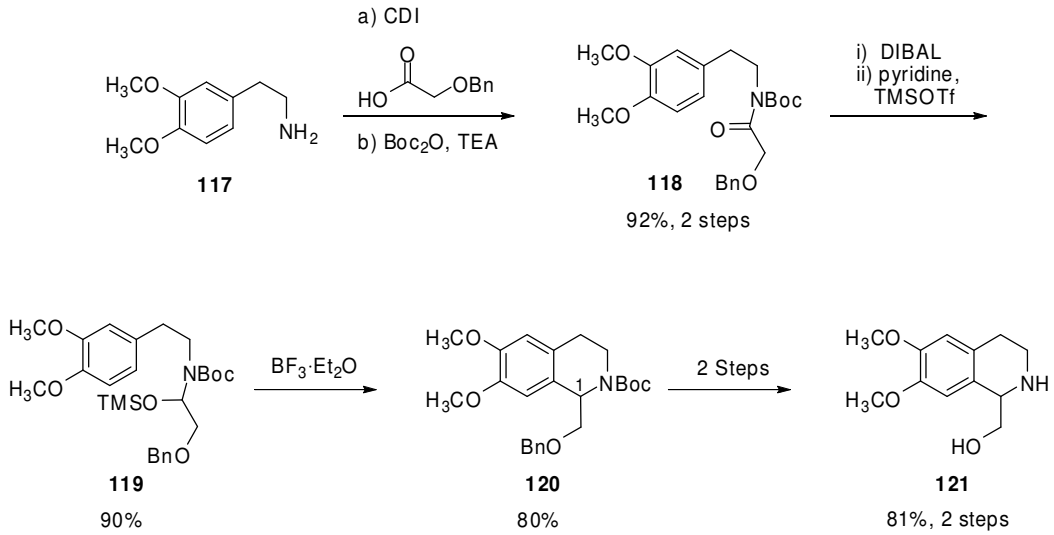


Figure 1.6: Characteristic THIQ core structure.

1.5.1.1. (±)-Calycotomine

Jung[56] reported a total synthesis of (±)-calycotomine **121** in 2007 that utilized their *N,O*-acetal TMS ether methodology[57] as an excellent means of generating acyliminium ions which are susceptible to various electrophilic reactions. The chief aim of their study was gaining rapid access to 1-substituted THIQs using the *N,O*-acetal TMS ether approach. This method proved to be superior to most other *N*-acyliminium ion precursors in terms of preparation, functional group compatibility and facile conversion.[56]

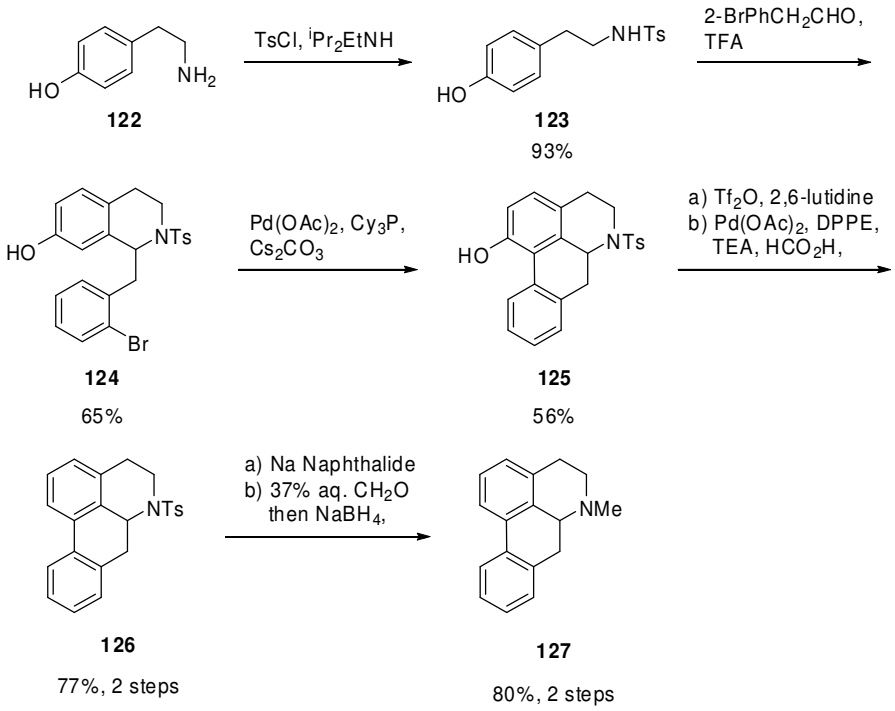
Condensation of phenylethyl amine **117** with (benzyloxy)acetic acid gave amide **118** (Scheme 1.36). Amide protection followed by reductive silylation gave the *N,O*-acetal TMS ether[57] **119**. Various reaction conditions were investigated to facilitate the intramolecular amido-alkylation of **119** *via* Pictet–Spengler cyclization, of which BF_3 proved to be the most effective, giving **120** in an 80% yield. Full deprotection of THIQ **120** furnished calycotomine **121**. Due to the lack of a set stereocenter in the THIQ, the Pictet–Spengler gives a diastereomeric C_1 mixture of (±)-calycotomine **121** after removal of both *N*- and *O*-protecting groups. Despite this drawback a fast and versatile route to small THIQ libraries had been achieved.



Scheme 1.36: Jung's total synthesis of (±)-calycotomine **121**.

1.5.1.2. (±)-Aporphine

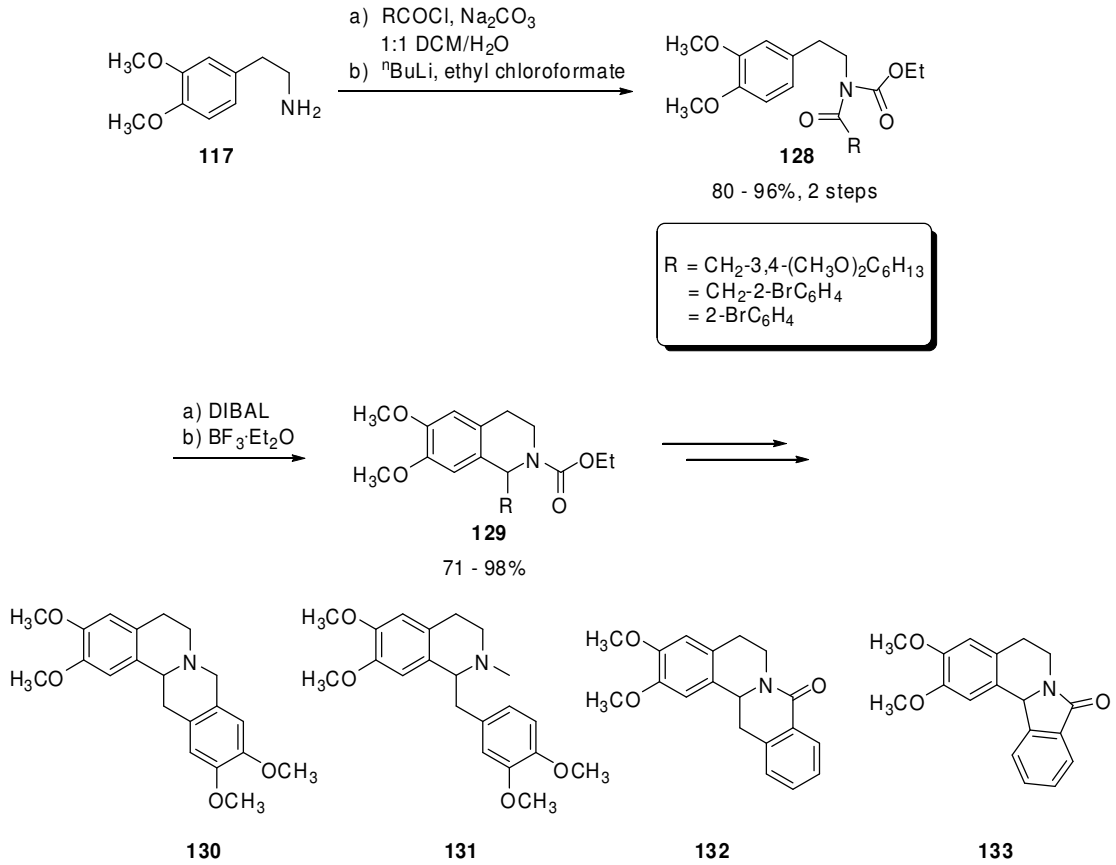
Cuny[58] reported the synthesis of (±)-aporphine **127** utilizing a Pictet–Spengler cyclization, followed by an *ortho*-arylation and an unusual dehydroxylation step (Scheme 1.37). Initially application of the Bischler–Napieralski cyclization was proposed yet the absence of an alkoxy moiety *para* to the site of cyclization caused this reaction to fail.[58] Barn[59] had reported the possibility of a Pictet–Spengler cyclization despite the absence of an electron-donating moiety in the aryl-ring. Therefore, synthesis starting with 4-methoxyphenylethylamine **122** would utilize a tosylamide. **122** was readily converted into **123**, which upon treatment with TFA and an aldehyde prepared Pictet-Spengler adduct **124** *via* iminium formation. Intramolecular *ortho*-arylation was attempted using previously developed palladium-catalyzed coupling conditions to give **125** in a moderate yield of 56%.[60] Next, phenol activation by triflic anhydride was followed by palladium-induced dehydroxylation, providing intermediate **126**.[58] Subsequent *N*-detosylation by sodium naphthalide followed by reductive amination provided (±)-aporphine **127** in seven steps. While successfully applying transition-metal mediated intramolecular *ortho*-arylation to aporphine class alkaloids, the moderate yields obtained severely limits the general applicability of this strategy.



Scheme 1.37: Cuny's total synthesis of (±)-aporphine **127**.

1.5.1.3. General Strategy Towards THIQ Synthesis

A simple but effective use of the Pictet–Spengler reaction was reported by Ruchirawat,[61] in which they developed a general procedure to synthesize a common intermediate **129**. From **129**; (+)-xylopinine **130**, (+)-laudanosine **131**, (+)-8-oxo-*O*-methylbharatamine **132** and (+)-isoindoloisoquinoline **133** were prepared. Treatment of 2-(3,4-dimethoxyphenyl)ethylamine **117** with the corresponding acid chloride provided the mono-amide using a biphasic system (Scheme 1.38). Subsequently, *N*-acylcarbamates **128** were obtained by ^{n}BuLi deprotonation followed by treatment with ethyl chloroformate. Diamides **128** were next reduced using DIBAL and Lewis acid-induced Pictet–Spengler cyclization using BF_3 gave THIQs **129** in good to excellent yields. However, when a non-activated aryl system was employed Pictet–Spengler cyclization did not take place, showing the limitation of this method in regard to THIQ formation.[61] Further manipulations of intermediates **129** were required to provide all four natural products **130 / 133**.



Scheme 1.38: Ruchirawat's total syntheses *via* common intermediate **129**.

1.5.1.4. Summary

When comparing all three methodologies described above, several limitations became apparent in terms of stereoselectivity (due to the lack of a set stereocenter), general reactivity and overall yield. Jungs's *N,O*-acetal TMS ether method, aside from the lack of stereoselectivity, provided a useful tool towards fast and high yielding synthesis of THIQ libraries. Cuny's intramolecular *ortho*-arylation for THIQ scaffold synthesis gave only moderate yields. Ruchirawat's syntheses subsequently failed to facilitate similar Pictet–Spengler cyclizations when using non-activated aryl systems, therefore severely limiting the general application of this strategy.

1.5.2. Asclepiadaceae Alkaloids

A structurally more interesting class of THIQs are the phenanthroindolizidine alkaloids (Figure 1.7). Part of the *Asclepiadaceae* family, these pentacyclic THIQs can be easily distinguished from other THIQ alkaloids by the phenanthrene core (C, A, D-rings). Synthesis of the C-A-D-core was first described by Pschorr[62] in 1896 *via* an arenediazonium salt, but a low yield and long linear sequence severely restricted this approach. Wang[64] and Fürstner[65] recently published alternatives to overcome these problems.

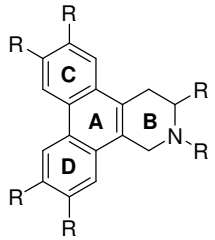


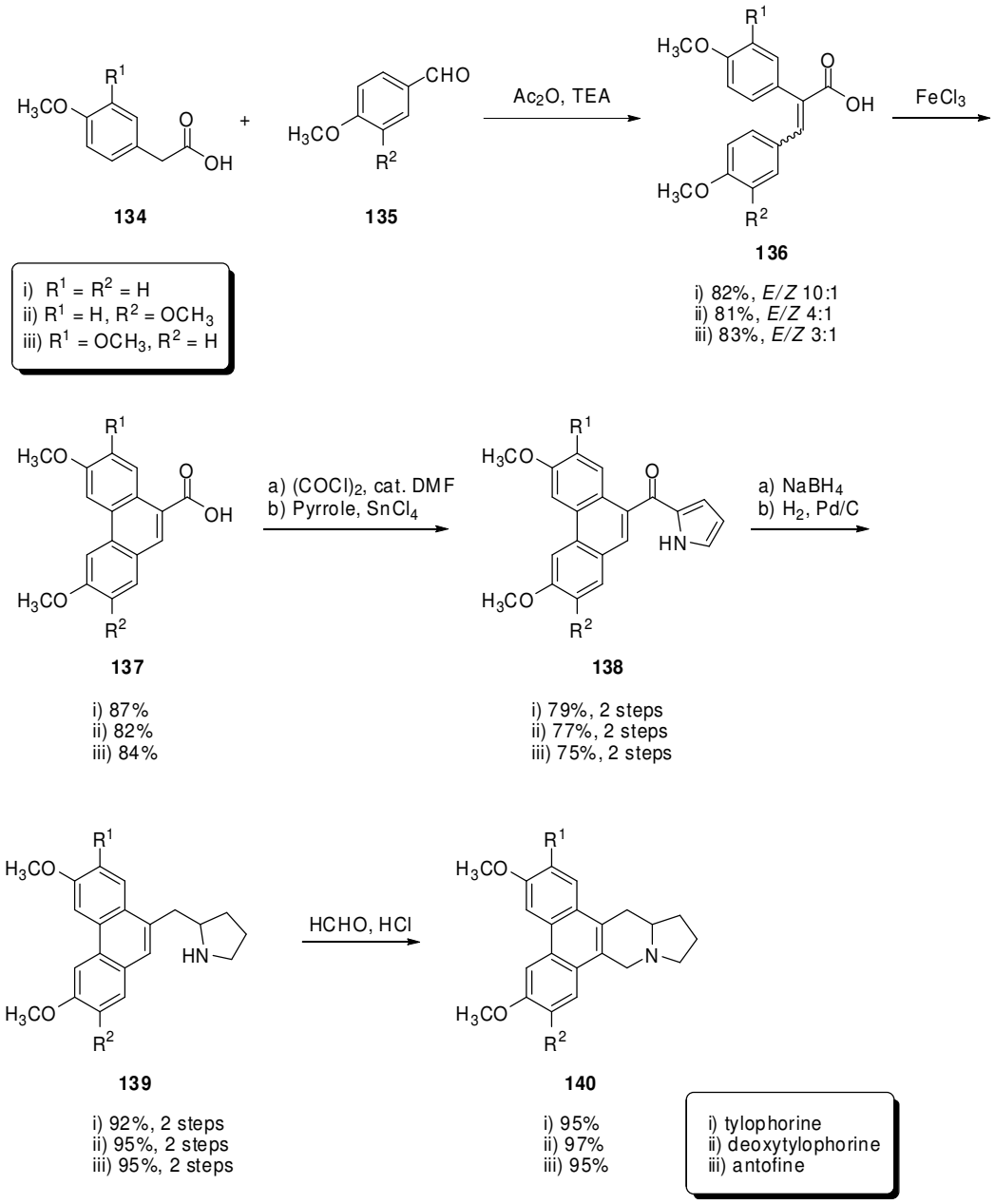
Figure 1.7: Phenanthroindolizidine-core of asclepiadaceae alkaloids.

1.5.2.1. Iron (III)-mediated Phenanthrene Synthesis

Various modifications of the Pschorr method have been reported but never broadly applied due to toxicity issues and low yields.[64] Iron (III) chloride, on the other hand, has been widely used in organic chemistry due to its inexpensive nature, environmentally benign and strong oxidizing character. Aryl–aryl coupling reactions using iron (III) have been reported, but have found limited application due to unwanted side-reactions.[63]

The total syntheses of tylophorine, deoxytylophorinine and antofine have been reported by Wang.[64] The Perkin condensation of benzeneacetic acid **134** and corresponding aromatic aldehydes **135** gave products **136** in good yields (Scheme 1.39).[64] A preference for the *E*-isomer was observed. Both *E*- and *Z*-isomers of **136** could be obtained separately by precipitation at different pH. The *para-para* coupling reaction was performed by treatment with iron (III), which gave the phenanthrene core **137**. Interestingly, in contrast to the Pschorr reaction, both the *E*- and *Z*-isomers were fully consumed to give corresponding **137**. Intermolecular tin tetrachloride-catalyzed Friedel–Crafts acylation of electron-rich pyrrole and the acid chloride corresponding to **137**, furnished **138**. Carbonyl reduction and pyrrole hydrogenation provided **139**, which upon acid-catalyzed Pictet–Spengler cyclization gave

THIQ **140**. Tylophorine, deoxytylophorinine and antofine were thus synthesized in 48%, 44% and 46% overall yield over six steps, utilizing mild and simple reaction conditions.

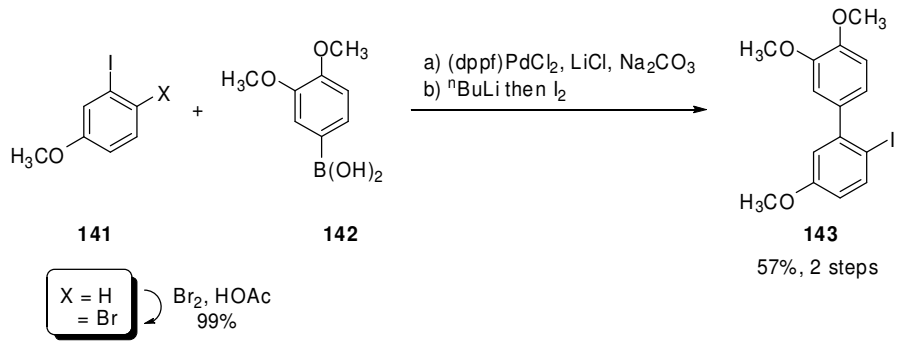


Scheme 1.39: Wang's total syntheses of tylophorine, deoxytolyphorine and antofine.

1.5.2.2. Phenanthrene Synthesis by Cycloisomerization

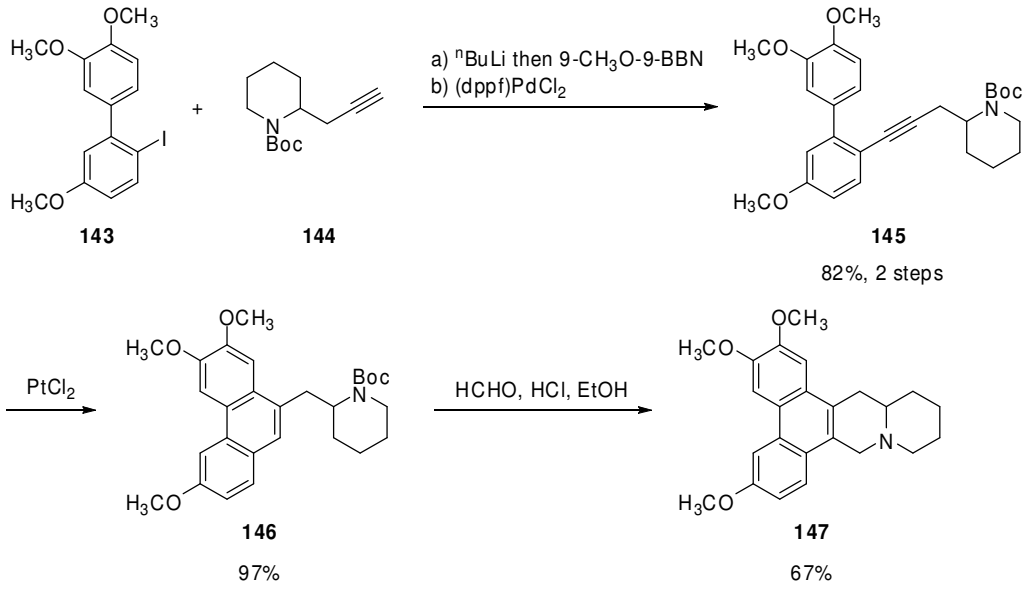
A different approach was reported by Fürstner[65] in the synthesis of phenanthrene-related alkaloids. Biaryl derivatives bearing an *ortho*-alkyne-substituent were observed to undergo cycloisomerization when exposed to various carbophilic Lewis acids.[66] Synthesis of biaryl **143** could easily be achieved *via* cross-coupling techniques, which are tolerant to various functional groups.

The total synthesis of cryptopleurin **147** would be the prototype required for the total syntheses of the three other phenanthrene-containing alkaloids. Bromination of arene **141** gave the dihalide as the Suzuki electrophile (Scheme 1.40). Subsequently, a Suzuki cross-coupling reaction of **141** with the boronic acid of **142** furnished **143**.



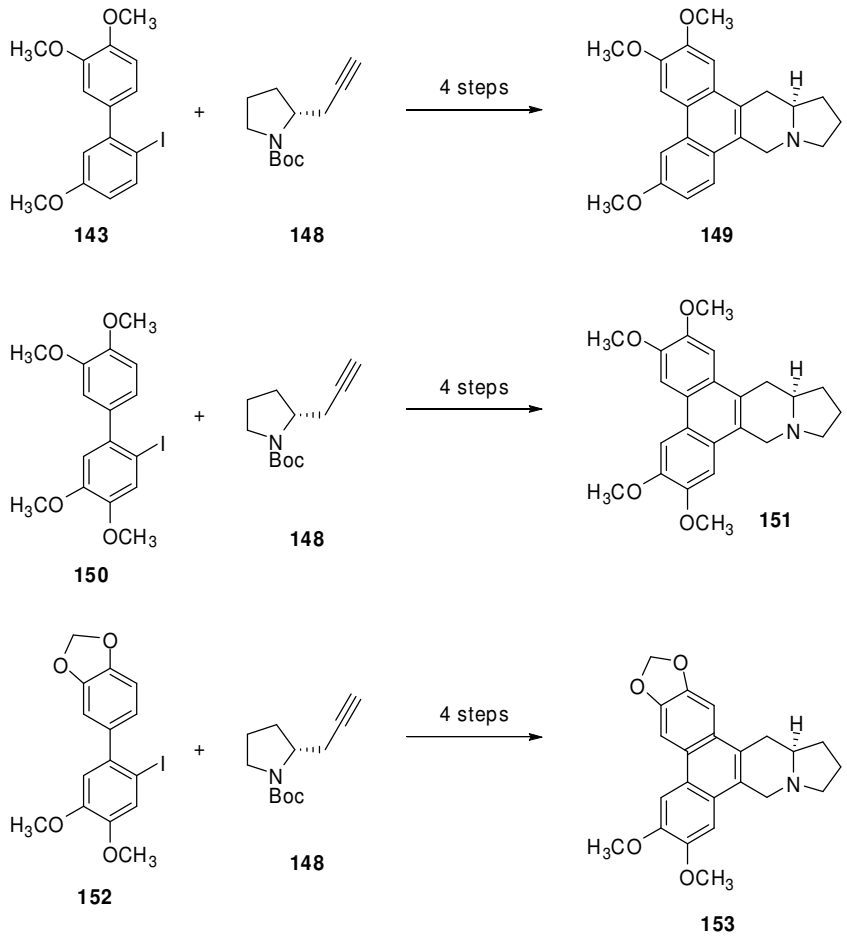
Scheme 1.40: Synthesis of phenanthrene precursor **143**.

Suzuki reaction conditions were once again employed, this time by reacting 9-CH_3O-9-BBN[67] with the alkynylmetal species of alkyne **144** (Scheme 1.41). The coupling strategy involved showed the ready transfer of alkynyl from the borate-complex to aryl halides or triflates under palladium catalysis.[67] With the aryl–alkyne adduct set for cycloisomerization, exposure to $PtCl_2$ gave the phenanthrene scaffold **146**.[66] Key to the success of this reaction proved to be the correct dilution due to competing oligomerization reactions of the substrate. Finally, one-pot deprotection and Pictet–Spengler cyclization provided cryptopleurin **147** in six steps.



Scheme 1.41: Total synthesis of cryptopleurin **147**.

A similar reaction sequence was applied in the syntheses of (–)-antofine **149**, (–)-tylophorine **151** and (–)-ficuseptine C **153** (Scheme 1.42). In contrast to cryptopleurin **147**, all three latter compounds were constructed using a proline-derived alkyne **148**; all gave comparable overall yields.



Scheme 1.42: Total synthesis of (–)-antofine **149**, (–)-tylophorine **151** and (–)-ficuseptine **153**.

1.5.2.3. Summary

Wang's strategy provided the phenanthrene ring-system in an overall higher yield but did not proceed with any stereoselectivity when compared to Fürstner's protocol. Both strategies approached the phenanthrene ring synthesis using transition metal catalysis, either by using iron (III)-mediated cyclization in which both *E*- and *Z*-isomers are consumed, or by platinum-induced cycloisomerization.

1.5.3. Amarylidaceae Alkaloids

Originally isolated from the *Amaryllidaceae* plant family, multiple synthetic studies have been reported since the first total synthesis by Brossi[68] in 1970, although this early work involved multiple steps and gave generally low yields. The amarylidaceae alkaloids are structurally more complex than the THIQ-scaffolds discussed earlier, possessing a common α-C_2 bridge embedded in an azabicyclo [4.3.0] nonane skeleton (Figure 1.8). Cho,[71] Chida,[78] Sha[79] and Banwell[82] have all recently reported total syntheses of amarylidaceae natural products.

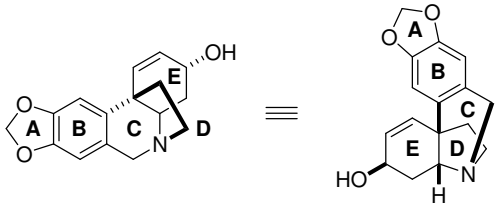


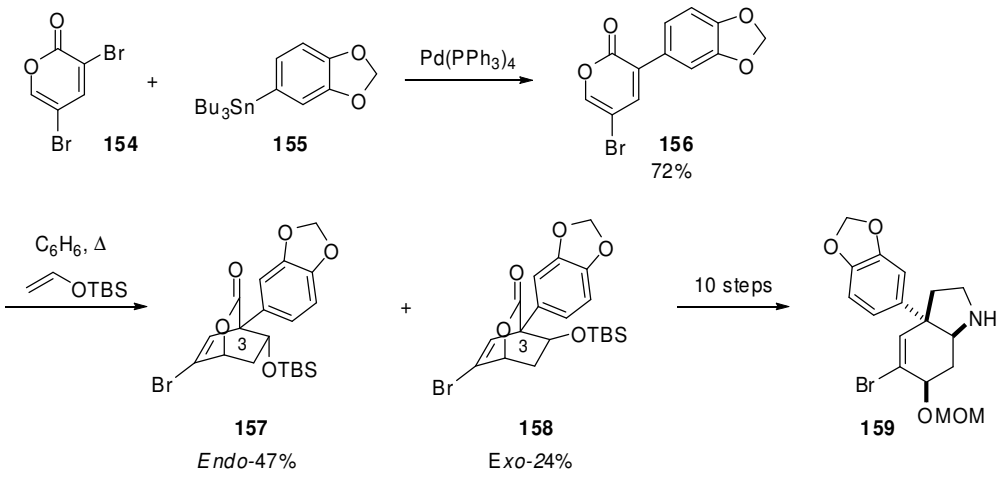
Figure 1.8: Amarylidaceae alkaloid structure.

1.5.3.1. (±)-Crinine and (±)-Crinamine by Diels–Alder

Crinine alkaloids are closely related to lycorane- and galanthamine-type alkaloids due to a common precursor, norbelladine.[69] As part of their continuing interest in applying 3,5-dibromo-2-pyrone **154**[70] and its derivatives as novel enophile synthons, Cho *et al.* reported the total synthesis of (±)-crinine and (±)-crinamine.[71] Previous efforts to incorporate the pyrone methodology had already culminated in the total synthesis of (±)–*trans*-dihydroarciclasine and (±)-joubertinamine,[72] though not including the Pictet–Spengler cyclization.

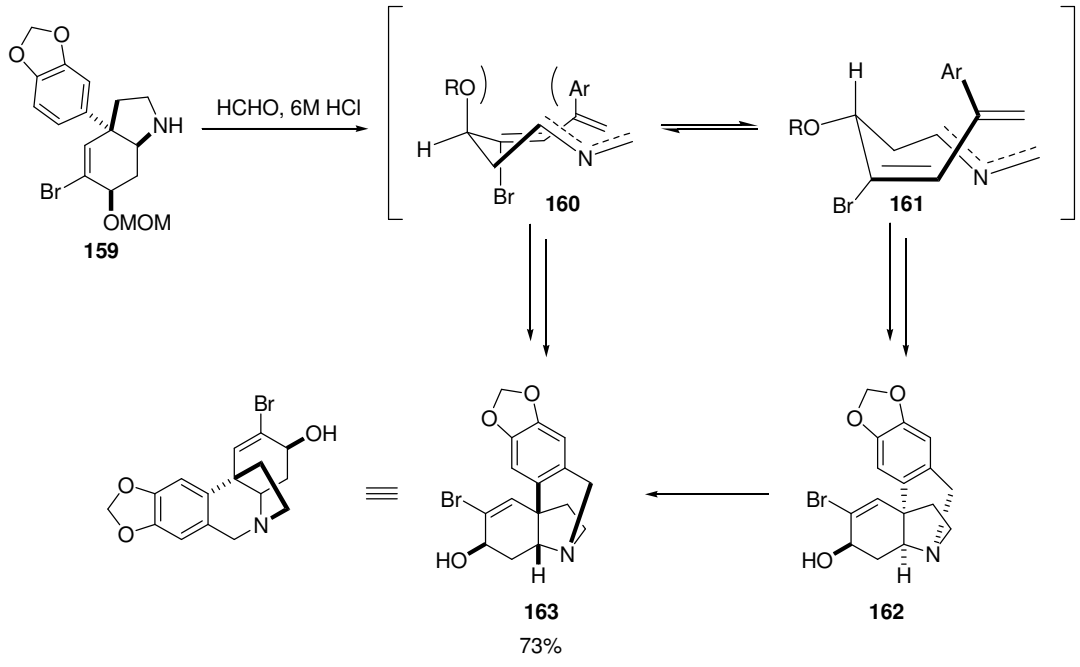
3,5-Dibromo-2-pyrone **154** was obtained from a Hunsdiecker reaction of 2-pyrone-carboxylic acid[73] (Scheme 1.43). Diene **154** proved to be more reactive than its mono-brominated counterpart in both normal- and inverse-electron-demand Diels–Alder reaction conditions applied to a series of electronically and sterically distinct dienophiles.[70] C_3 selective Stille coupling of pyrone **154** with aryltin substrate **155** gave **156**. Diels–Alder cycloaddition with TBS-protected vinyl ether produced the bicyclolactone **157** and **158** with moderate *endo*-selectivity due to the bulky C_3 substituent. Earlier studies had shown a high *endo*-preference when using **156** and other dienophiles as the steric bulk destabilizes the *endo*-transition

state.[70] Resolution gave the *endo*-compound **157**, which was further manipulated for the synthesis of **159** over 10 steps.



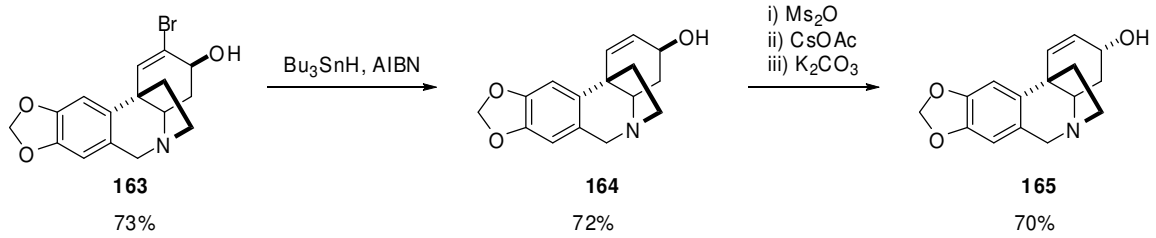
Scheme 1.43: Synthesis towards Pictet–Spengler precursor **159**.

The Pictet–Spengler cyclization was achieved upon heating **159** with paraformaldehyde in the presence of HCl as reported by Pearson (Scheme 1.44).[74] Molecular modeling had shown the *Z*-conformation of the diene to exert a strong influence on the reactivity of the cyclization precursors. Steric interactions between the alkoxy group and the aromatic moiety become evident in **160**. However, **161** does not exhibit such a clash being therefore preferred and resulting in **162** formation. Epimerization of the latter provides **163**. The analysis assumed a concerted [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] cycloaddition to take place thus providing a *cis*-conformation, Pearson had already observed similar results in earlier cycloadditions.[74]



Scheme 1.44: 2-Aza-allyl anion cycloaddition according to Pearson.

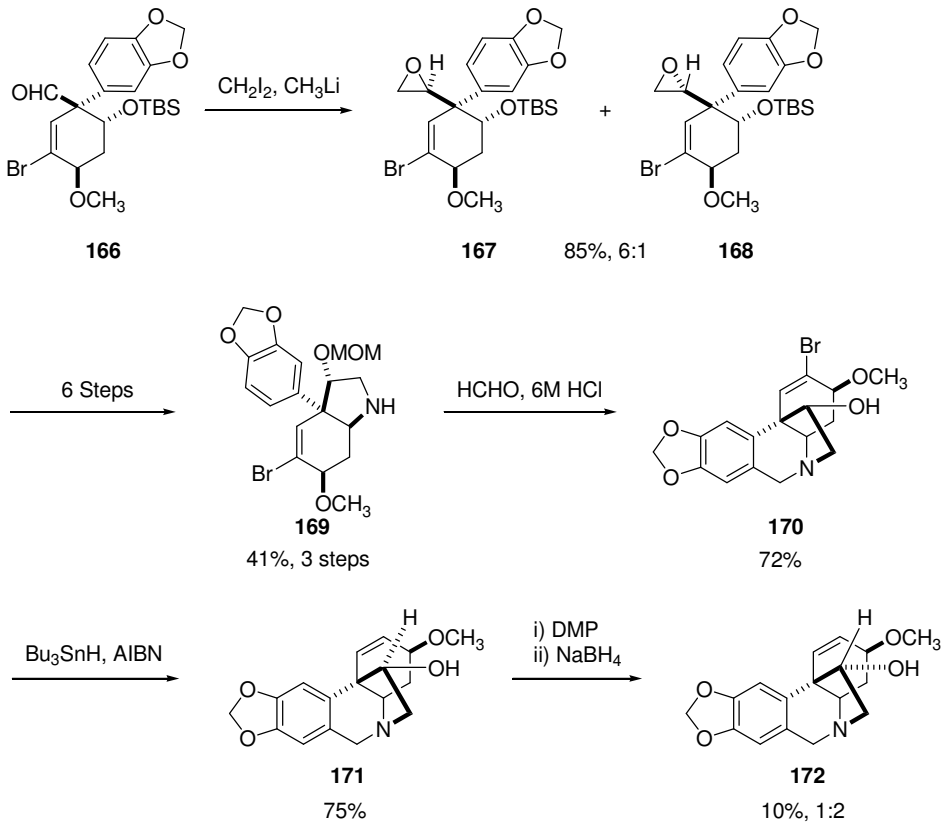
Reductive removal of the vinylogous bromide (**164**) was followed by a one-pot process as described by Pearson[74] to give (±)-crinine **165** (Scheme 1.45).



Scheme 1.45: Total synthesis of (±)-crinine **165**.

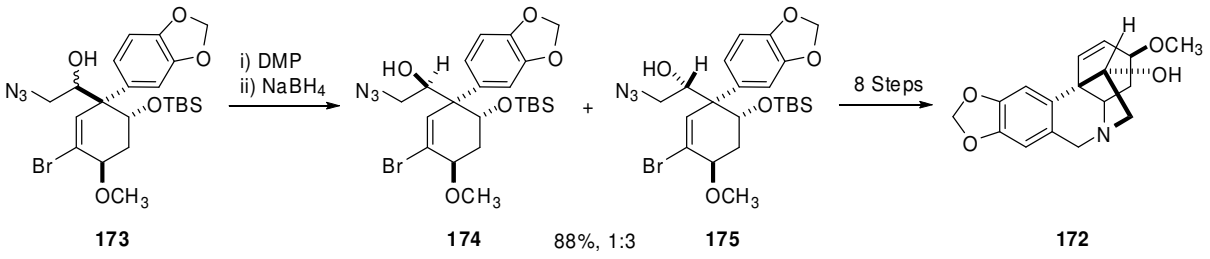
The same Diels–Alder strategy was also applied to the total synthesis of (±)-crinamine **172** and structurally related (±)-6a-*epi*-crinamine **171**. The stereoselective α-C_2 hydroxide moiety present in both compounds, in contrast to (±)-crinine **165**, would require a slightly different approach.

Formation of epoxides **167** and **168** was achieved by treating aldehyde **166** (obtained from *endo*-**157**) with diiodomethane and methyllithium to give a 6 : 1 mixture of two diastereomers **167** and **168** (Scheme 1.46).[75] Earlier attempts using Wittig olefination of aldehyde **166** followed by osmium-mediated dihydroxylation had been non-selective, probably due to the sterically-congested environment. Resolution of both diastereomers *via* column chromatography was possible after ring-opening of the epoxides **167** and **168** with sodium azide. **169** Was obtained from **167** after six steps and exposed to Pictet–Spengler reaction conditions. THIQ **170** was treated with paraformaldehyde in the presence of HCl. Finally, debromination of **170** resulted in formation of (±)-6a-*epi*-crinamine **171**. Unfortunately, the conversion of **171** into (±)-crinamine **172** proved to be low yielding even after optimization attempts.



Scheme 1.46: Synthesis of 6a-*epi*-crinamine **171**.

In light of these problems, (±)-crinamine was prepared using epoxide mixture **167** and **168** followed by azide-mediated ring-opening to provide the corresponding azido-alcohol **173**. Exposure to Dess–Martin / $NaBH_4$ prior to the formation of the THIQ resulted in isolation of the correct isomer **175**. The same reaction procedure ultimately gave (±)-crinamine **172** (Scheme 1.47). The reaction sequence as described by Cho revealed an interesting, albeit moderately successful Diels–Alder cycloaddition in combination with a very efficient Pictet–Spengler cyclization providing both crinine and crinamine in moderate overall yields.[71]

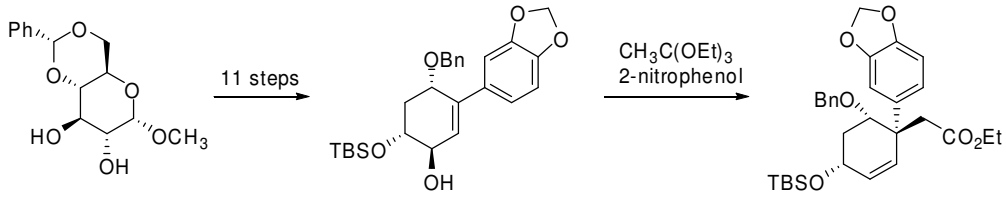


Scheme 1.47: Total synthesis (±)-crinamine **172**.

1.5.3.2. (+)-Vittatine and (+)-Haemanthamine by Claisen Rearrangement

Compared to their relatives, both crinine-type family members vittatine and haemanthamine have received only limited attention. Harboring the same ethanophenanthridine core skeleton as observed in all family members, Chida reported in 2007 the first enantioselective total synthesis of both (+)-vittatine and (+)-haemanthamine, starting from D-glucose.[76] Their approach included a stereoselective Claisen rearrangement, intramolecular aminomercuration-demercuration and Chugaev reaction as key-features.

Both natural compounds were constructed using a common intermediate **178**. Commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **176** was converted into chiral cyclohexenol **177** in 11 steps (Scheme 1.48). The conventional Johnson–Claisen rearrangement gave the rearranged product **178**. In order to improve the irreproducible result during this rearrangement 2-nitrophenol was added as an acid catalyst as described by Fukazawa.[77] Interestingly, application of 2,4-dinitrophenol instead of 2-nitrophenol resulted in substrate decomposition.

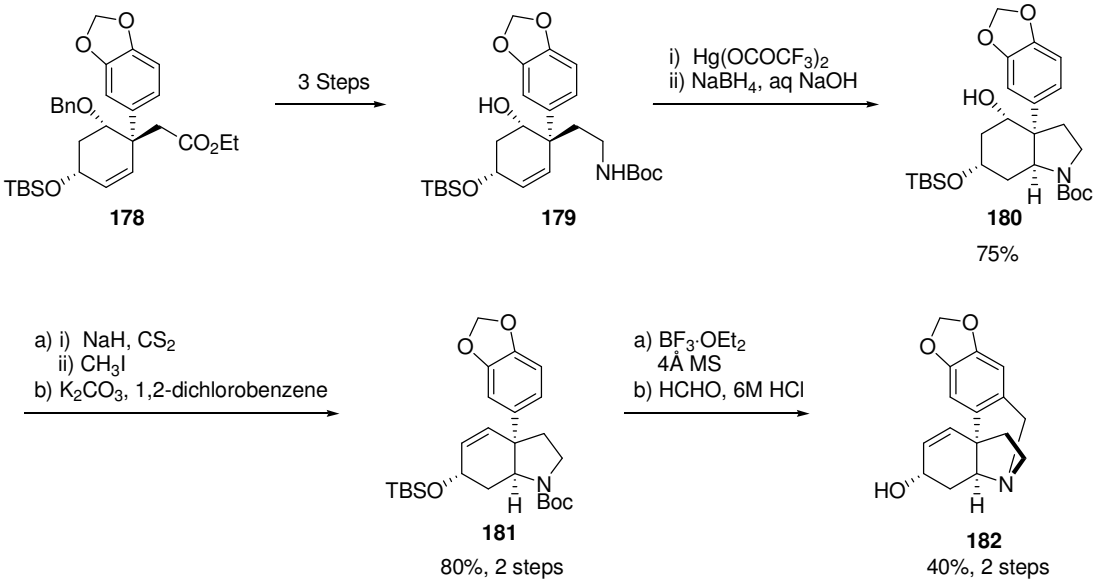


176 **177** **178**

71%

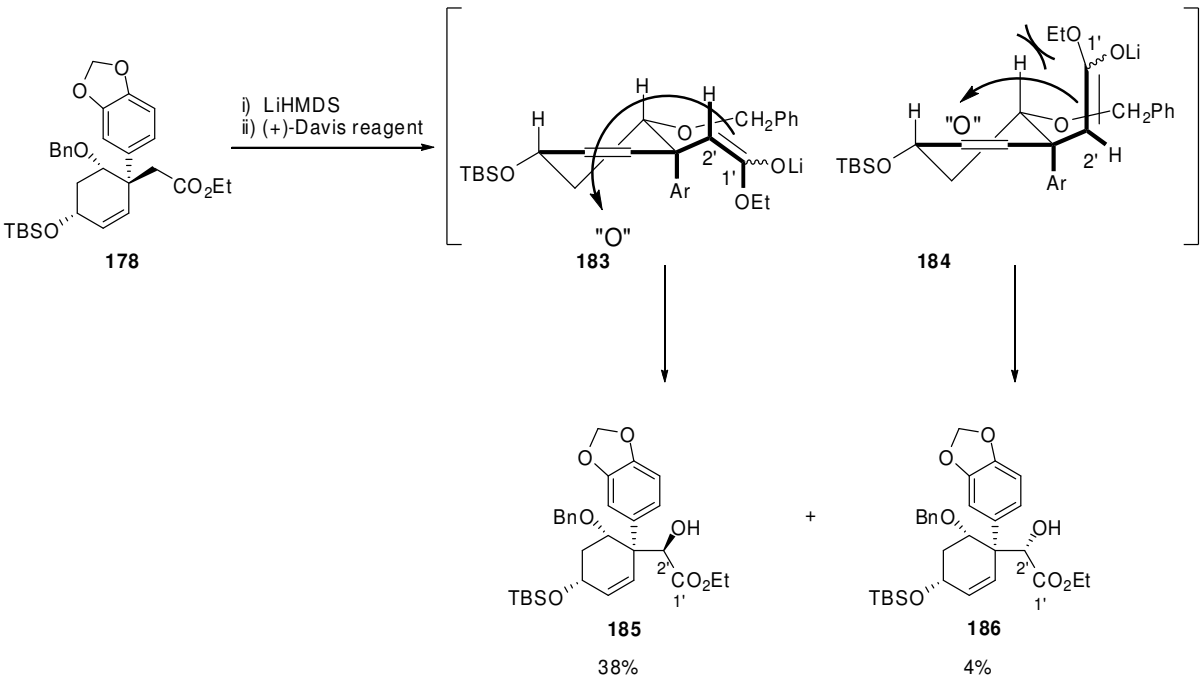
Scheme 1.48: Johnson–Claisen rearrangement of **177** into **178**.

The *N*-Boc protection was found to be necessary for the mercury-induced intramolecular perhydroindole skeleton formation (**180**), since use of the free amine did not result in cyclization. Chugaev reaction provided the xanthate ester from perhydroindole **180** which was removed under base conditions to provide hexene **181** (Scheme 1.49). Similar sulfone-induced eliminations proved to be unsuccessful and decomposition of the starting material was observed.[76] Finally, BF_3-induced deprotection was followed by Pictet–Spengler cyclization using acidified formalin, providing (+)-vittatine **182**.



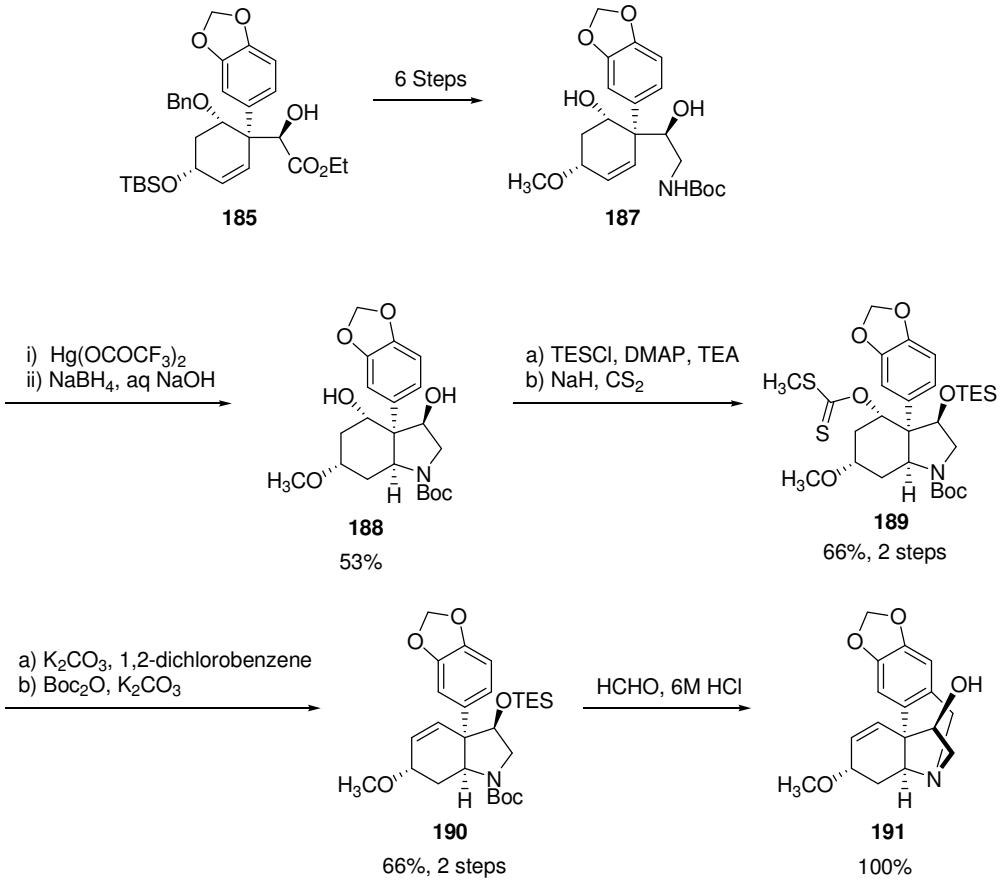
Scheme 1.49: Total synthesis of (+)-vittatine **182**.

In the same article,[76] the total synthesis of (+)-haemanthamine was reported using common intermediate **178**. The key difference between the target alkaloid and (+)-vittatine is the introduction of a hydroxy moiety at the C_2' position (Scheme 1.50). The Davis reagent was effective in this transformation and gave the corresponding hydroxy moiety **185**. A study revealed the need for LiHMDS at 0 ^{o}C in order to form the ester enolate in combination with the Davis reagent.[78] Regardless of the oxidant used, a diastereomeric mixture was obtained in all cases. Preferential formation of **185** was thought to be induced by steric factors. In the transition structures illustrated (Scheme 1.50), three out of four substituents are in an equatorial position therefore electrophilic attack would occur at the upper face of the enolate as the back face is hindered by the presence of the benzyloxy moiety. In **184** a non-bonding interaction between an axial C_6 hydrogen and enolate oxygen C_1' would be unfavourable, thus resulting in **183** (**185**) being the major product.



Scheme 1.50: Transition state structures for **185** and **186**.

After converting ester **185** into Boc-protected amine **187**, mercuration was applied to provide perhydroindole **188** (Scheme 1.51). Selective TES protection of the less sterically hindered hydroxy was followed by xanthate formation and Chugaev elimination to give xanthate ester **189**. As due to the removal of the Boc-group during the Chugaev reaction, the amine of **189** had to be Boc-protected in order to solve purification issues. Finally, treatment with paraformaldehyde in an acidic environment effected quantitative Pictet–Spengler cyclization to give (+)-haemanthamine **191**.



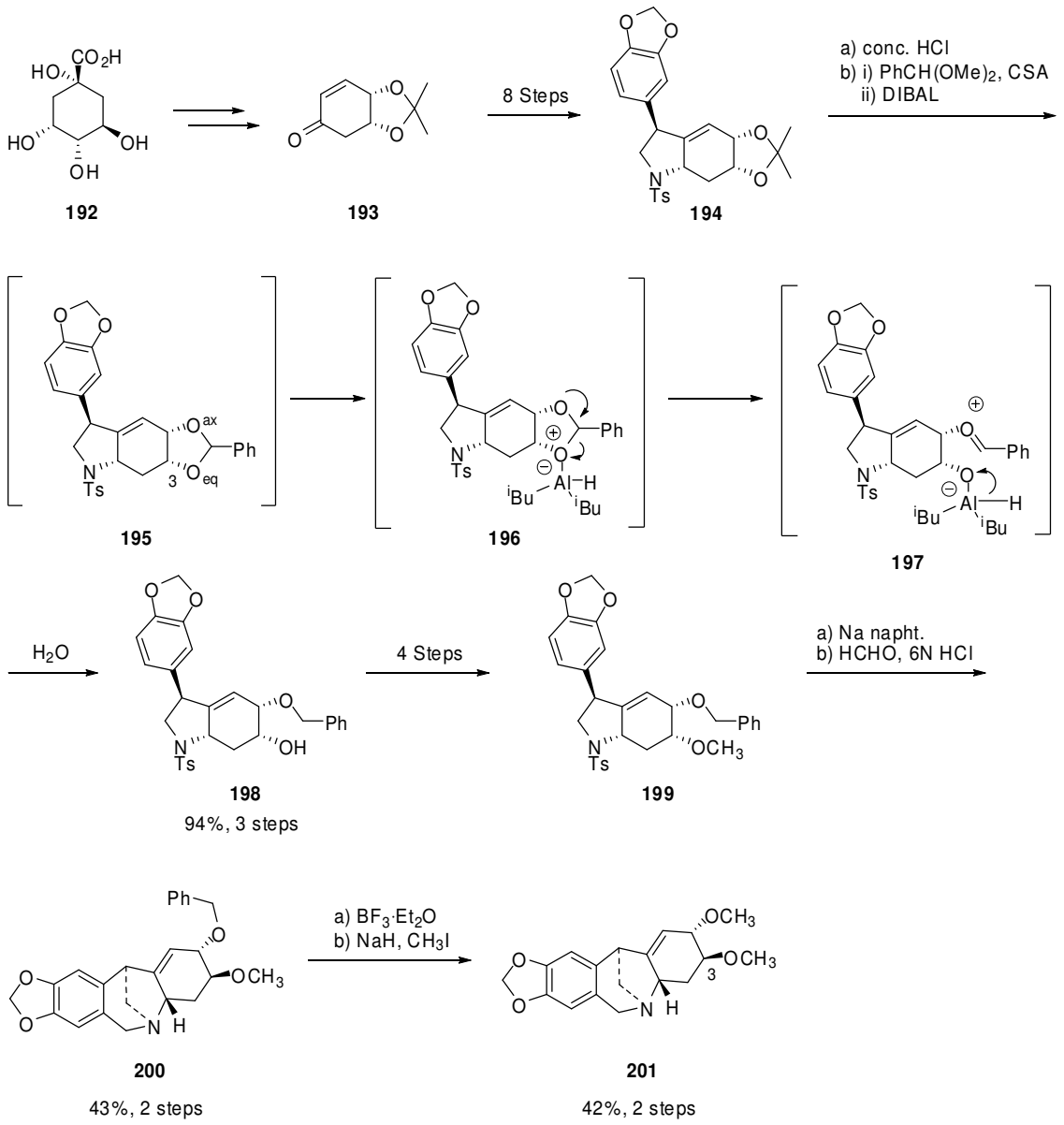
Scheme 1.51: Total synthesis of (+)-haemanthamine **191**.

Application of the Claisen rearrangement successfully provided rearranged product **178** in a moderately high yield when exposed to 2-nitrophenol. This in combination with mercury-induced cyclization and a Chugaev elimination step provided both (+)-vittatine and (+)-haemanthamine.

1.5.3.3. (–)-Manthine

(–)-Manthine **201** contains a core skeleton similar to that in the natural products described earlier with the key difference being the inversion of the C_3 configuration.[79] The total synthesis was initiated by converting (–)-quinic acid **192** into enone **193** by applying a protocol according to Elliott[80] (Scheme 1.52). **194** Was subsequently obtained in eight steps from enone **193**. **194** Underwent protecting group exchange give ketal intermediate **195**. Selective protection of the axial hydroxy-moiety would allow manipulation of the stereocenter at the C_3 C–O bond. Complexation of DIBAL gave **198** due to steric hindrance at the axial hydro-moiety, thus preferably coordinating to the equatorial oxygen.[81] **199**

Underwent Pictet–Spengler cyclization resulting in formation of the core structure **200**. Further manipulation of this structure by treatment with BF_3 followed by methylation finally provided (–)-mantine **201**.



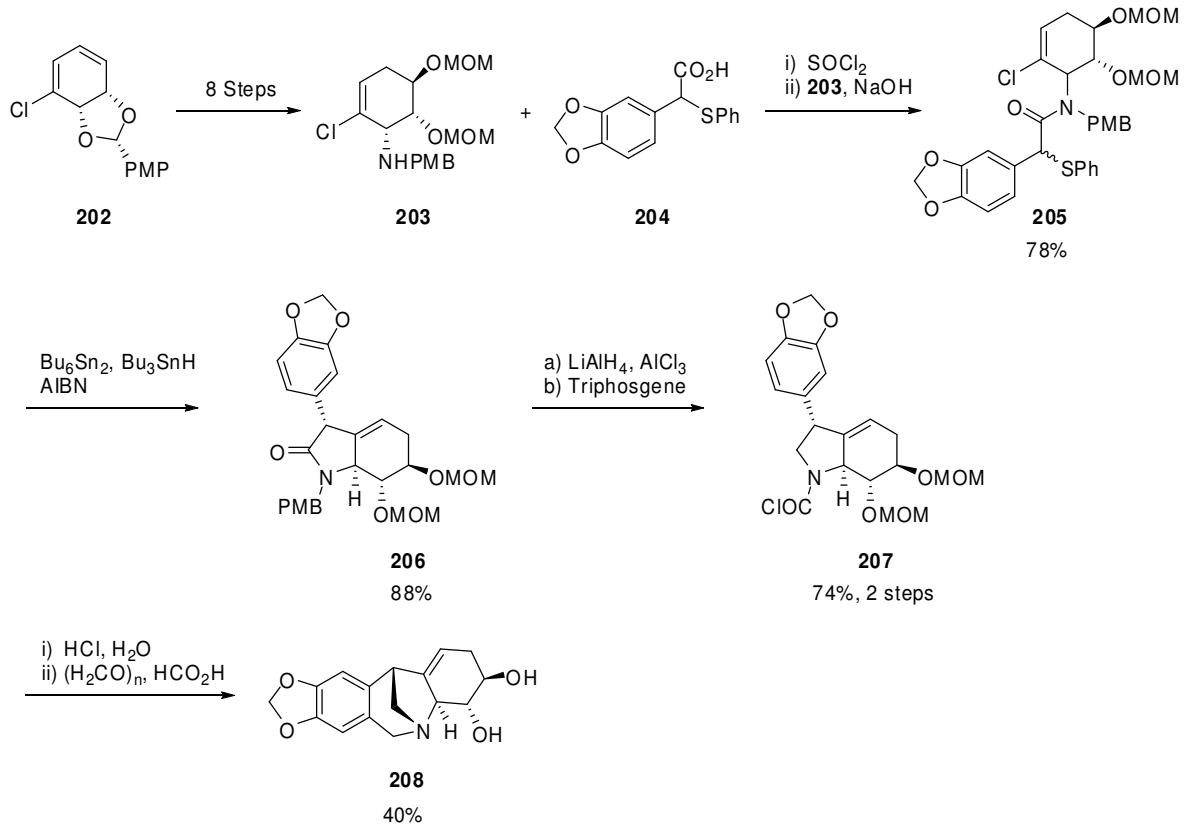
Scheme 1.52: Total synthesis of (–)-mantine **201**.

Although the subtlety in converting the C_3 position in mantine from a *cis* to a *trans* relationship by use of DIBAL is noteworthy, the low Pictet–Spengler cyclization yields severely limits the reaction sequence.

1.5.3.4. (+)-Nangustine

(+)-Nangustine was completed by Banwell[82] in order to exploit the enantiomerically pure *cis*-1,2-dihydrocatechol derivative **202**. Synthesis of this compound involved whole cell-mediated transformation starting from chlorobenzene, using genetically engineered organisms that over-express toluene dioxygenase.[83]

Having successfully obtained **203** after 8 steps from catechol acetal **202**, Schotten–Baumann conditions were applied to couple **203** with **204** (Scheme 1.53). Tin-mediated radical addition / elimination reaction resulted in the formation of the tetrahydro-oxindole **206**. A study on the mechanism in this cyclization is ongoing.[82] Reduction of the oxindole to the corresponding amine was followed by triphosgene cleavage of *N*-PMB. **207** Underwent acid-hydrolysis and was immediately exposed to conventional acid catalyzed Pictet–Spengler reaction conditions which gave (+)-nangustine **208**.



Scheme 1.53: Total synthesis of (+)-nangustine **208**.

1.5.3.5. Summary

Cho's total synthesis of crinine and crinamine provides an excellent example of using the Pictet–Spengler cyclization to obtain the corresponding THIQ in a highly stereoselective manner and high yield. Their sequence, applying a Diels–Alder approach provides an interesting reaction sequence although hampered by the moderate selectivity and yield.

Chida's approach towards vittatine and haemanthamine by Claisen rearrangement, mercuration and classic Pictet–Spengler conditions yielded both natural products in very high yields. The only drawback to this sequence was the inherent toxicity of mercury.

Sha's DIBAL-mediated conversion of the C_3 conformation of molecule **194**, from *cis* to *trans* using steric factors within manthine, provided an interesting example of simple yet effective conformational changes.

The synthesis of nangustine by Bandwell involved the use of catechol acetal **202** which was derived from chlorobenzene and converted into **202** by use of genetically engineered micro-organisms. Subsequent straight forward synthesis provided the natural compound in a good overall yield.

1.5.4. Schulzeine A, B and C

Schulzeine A, B and C belong to the schulzei class of THIQ alkaloids. These marine alkaloids were isolated from the sponge *Penares schulzei* by Fusetani;[84] they exhibit intriguing bioactivity and contain a unique chemical structure (Figure 1.9). This has led two research groups to explore the total synthesis of these natural compounds.

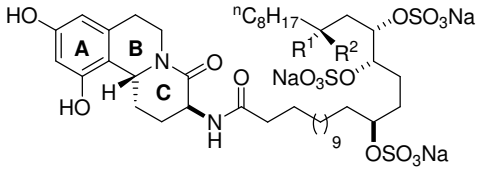
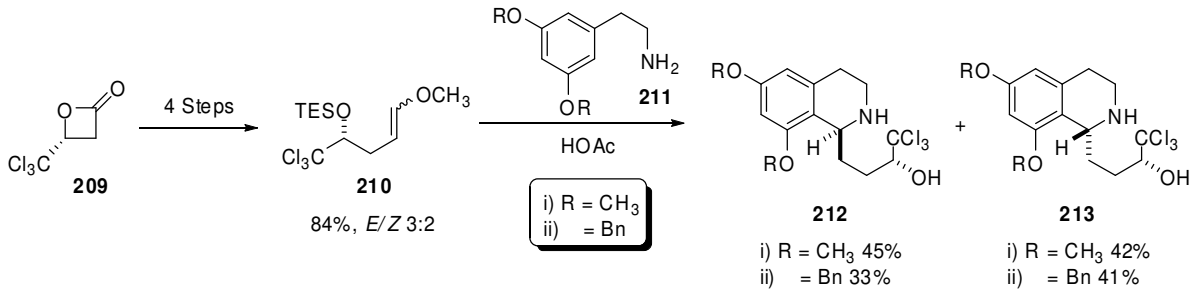


Figure 1.9: Schulzeine-class of alkaloids.

1.5.4.1. Corey–Link in Schulzeine B, C

Romo[85] reported the total synthesis of schulzeines B and C due to his interest into utilization of optically active trichloromethyl-β-lactone **209**, which was previously reported[86] to serve as a useful masked α-azido acid *via* the Corey–Link process.[87]

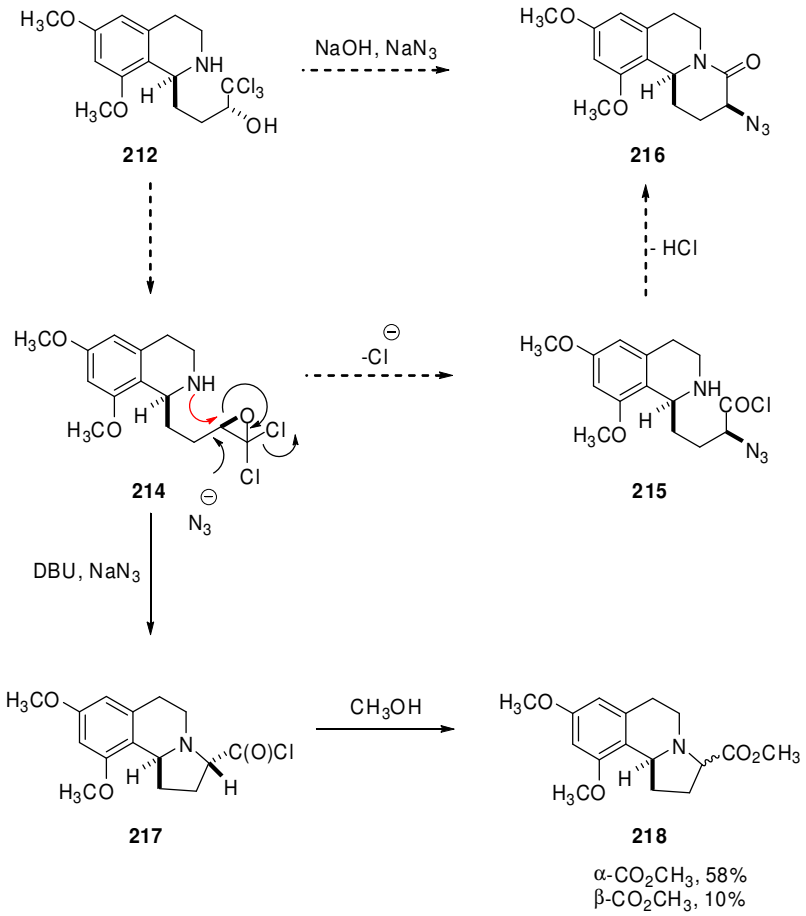
Commercially available β-lactone **209** was converted into enol ether **210** in four steps which gave a 3 : 2 mixture of *E / Z*-isomers of **210** (Scheme 1.54). A 1 : 1 mixture of diastereomers was obtained by treating **210** and **211** with glacial acetic acid facilitating *in situ* hydrolysis of the vinyl ether and simultaneously triggering Pictet–Spengler cyclization to give **212** and **213**.



Scheme 1.54: Synthesis of masked THIQ **212** and **213**.

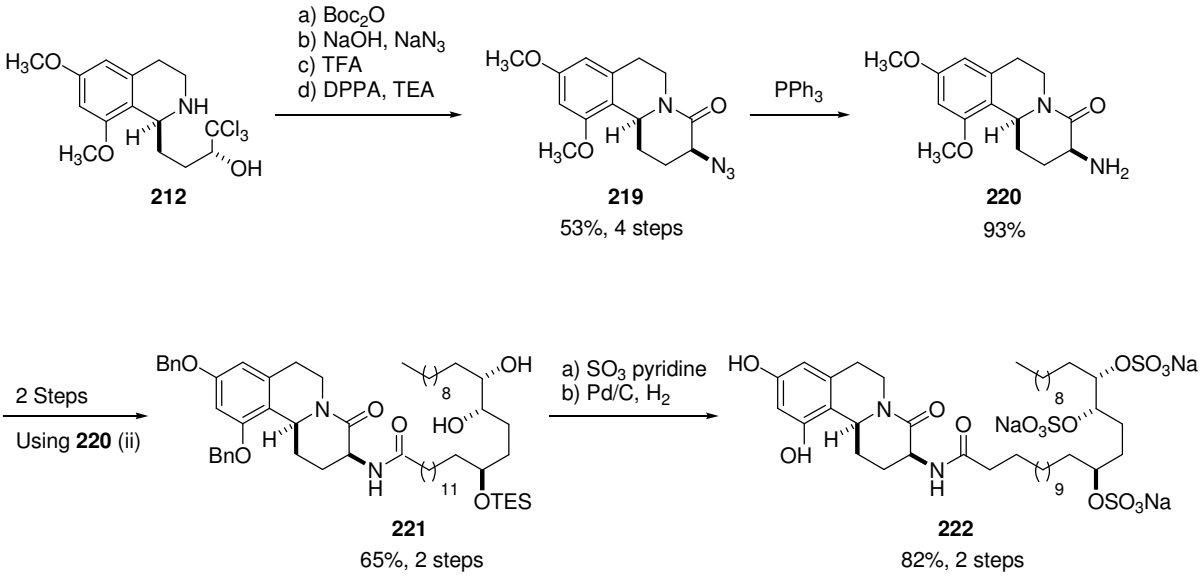
Initial attempts to utilize the Corey–Link process to obtain δ-lactam **216** were unsuccessful.[85] Although Corey–Link processes have rarely been described for amino-containing substrates, the expected formation of dichlorooxirane intermediate **214** has been reported (Scheme 1.55).[88] Oxirane **214** cleavage by azide would have yielded azide intermediate **215** which

would cyclize to δ-lactam **216**. When DBU was used as base, premature epoxide ring-opening / cyclization of **214** gave **217**.



Scheme 1.55: One-pot tricyclic core synthesis attempt.

In order to avoid the unwanted cyclization the THIQ amine **212** was Boc-protected and subjected to Corey–Link conditions, which upon Boc-deprotection and DPPA-induced δ-lactam formation provided **219**. Staudinger azide reduction furnished amine **220** (Scheme 1.56).



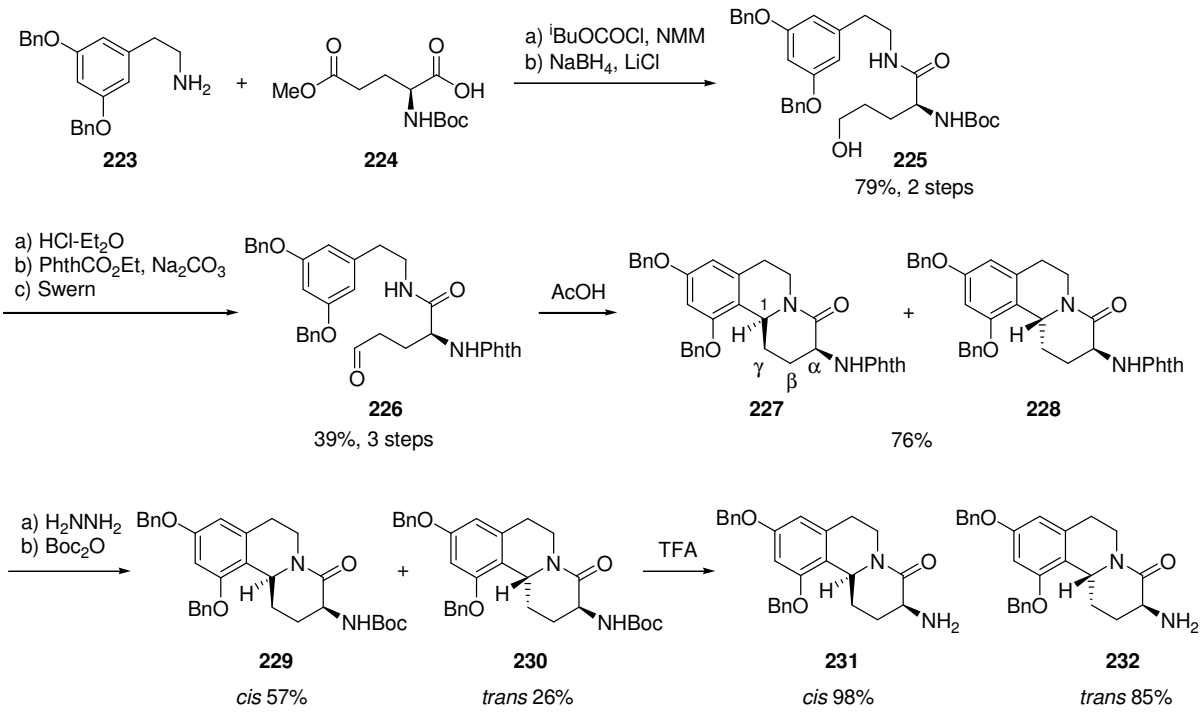
Scheme 1.56: Core structure synthesis and total synthesis of schulzeine B using **220** (ii).

A modified strategy in order to simplify the final catechol deprotection utilized a benzyl protected catechol **212** (ii, R = Bn, Scheme 1.56), which underwent a similar reaction sequence to give a benzyl protected catechol **220** (ii). Lowering of the reaction concentration solved initial solubility issues due to the increased hydrophobic nature of the substrate during Corey–Link transformation and **220** (ii) (CH_3O = BnO) was obtained in a high yield.[85] Subsequent peptide coupling of the corresponding fragments gave **221** which, after protecting group conversion provided schulzeine B **222**. Similarly, schulzeine C was prepared following the same reaction sequence starting from the other diastereomer **213** in order to obtain the correct stereochemistry. This reaction sequence utilized an α-amino acid aldehyde synthon derived from β-lactone **209** and a Corey–Link process in order to obtain both natural products thus showing the applicability of α-amino acid aldehyde synthons to natural product synthesis.[85]

1.5.4.2. Pictet–Spengler Issues Towards Schulzeine A, B, C

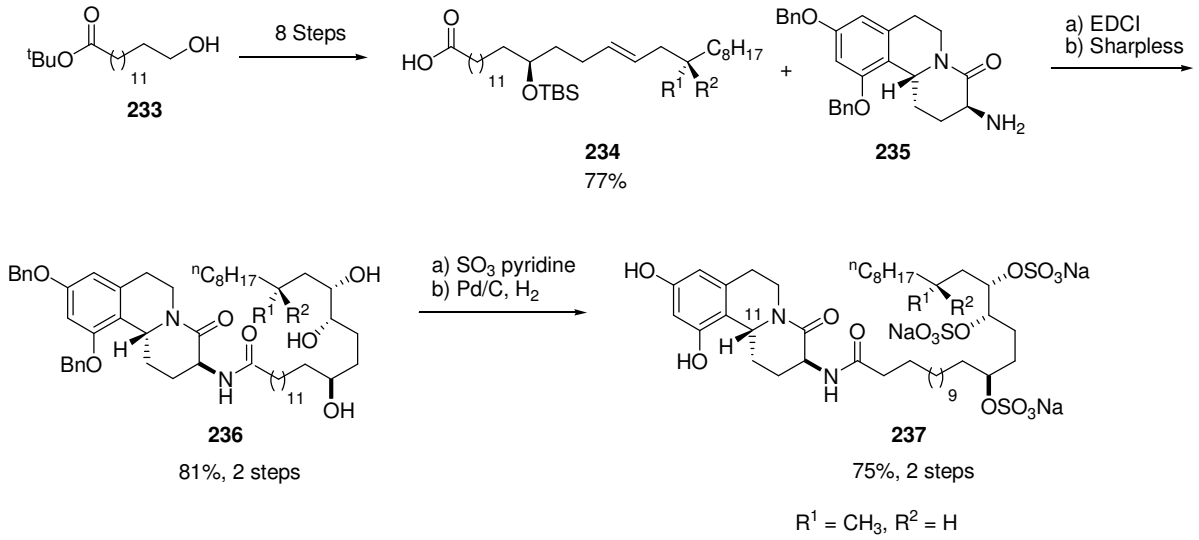
Wardrop[89] recently reported the synthesis of schulzeines A, B and C using L-glutamic acid γ-methyl ester **224** (Scheme 1.57). **224** Was first coupled with **223** *via* the mixed anhydride followed by chemoselective reduction of the methyl ester to the corresponding alcohol **225**. The Pictet–Spengler condensation could not be performed due to Boc-group interference; therefore, conversion of the carbamate into the more robust phthalamide was required.[90] Swern oxidation provided **226**, followed by treatment with acetic acid, gave lactams **227** and **228** were isolated. Exposure of **226** to BF_3, TFA or acetic acid facilitated the Pictet–Spengler

cyclization in varying degrees of *cis / trans* selectivity. Lee[91] and others[92] had already demonstrated the γ- and β-substituents of hydroxy lactams to be able to affect stereoselectivity at the C_1 ring conjunction. While both *cis* and *trans* products could not be separated, subsequent hydrazinolysis of the phthalimide group followed by carbamate formation made separation of both *cis* and *trans* products **229** and **230** possible, and thus provided the core substrates for the formation of schulzeine A, C and B respectively.



Scheme 1.57: Synthesis of THIQ core.

Having prepared the core THIQ structures **231** and **232**, the synthesis of the aliphatic chain **234** starting with hydroxy ester **233**[93] was achieved in eight steps. A peptide coupling reagent afforded amide **236** from **234** and **235**. A 4 : 1 mixture of **236** was obtained from the Sharpless dihydroxylation in the presence of $(DHQ)_2PHAL$ ligand. Finally, installation of the sulfates using SO_3-pyridine complex and deprotection,[94] provided schulzeine A, B or C depending on the R^1 and R^2 substituents **237** (Scheme 1.58). Schulzeine A: C_{11} = **237**, R^1 = CH_3, R^2 = H. Schulzeine B: C_{11} = **237** diastereomer, R^1 = R^2 = H. Schulzeine C: C_{11} = **237**, R^1 = H, R^2 = H.



Scheme 1.58: Total syntheses of schulzeine A, B and C **237**.

1.5.4.3. Summary

Romo's approach towards schulzeine B and C using a Corey–Link process together with Noyori hydrogenation and Sharpless dihydroxylation shows the applicability of α-amino acid aldehyde synthons starting from β-lactone **209**. Similar to Wardrop's synthesis of schulzeine A, B and C, the Pictet–Spengler reaction proved complicated, unable to significantly distinguish between *cis*- and *trans*-conformations. This is probably due to the α- and β-substituents at the hydroxy lactam affecting C_1 stereocontrol.

1.5.5. Quinocarcin Family

Quinocarcin was originally isolated from a *Streptomyces melunovinuceus* culture broth by Takahashi and Tomita in 1983.[95] Recently Zhu reported a 22-step total synthesis of enantiomerically pure (–)-quinocarcin in 16% overall yield.[96] Quinocarcin family members incorporate a pentacyclic structure containing a bridge bicycle D / E as depicted in Figure 1.10.

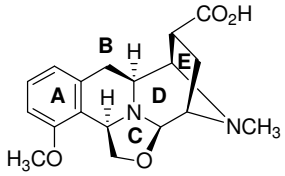
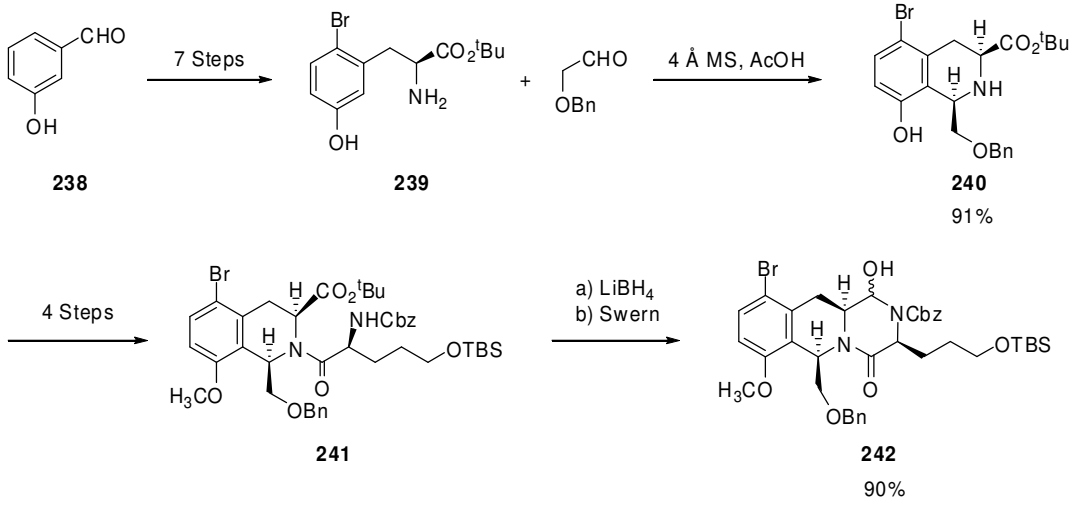


Figure 1.10: Quinocarcin alkaloids

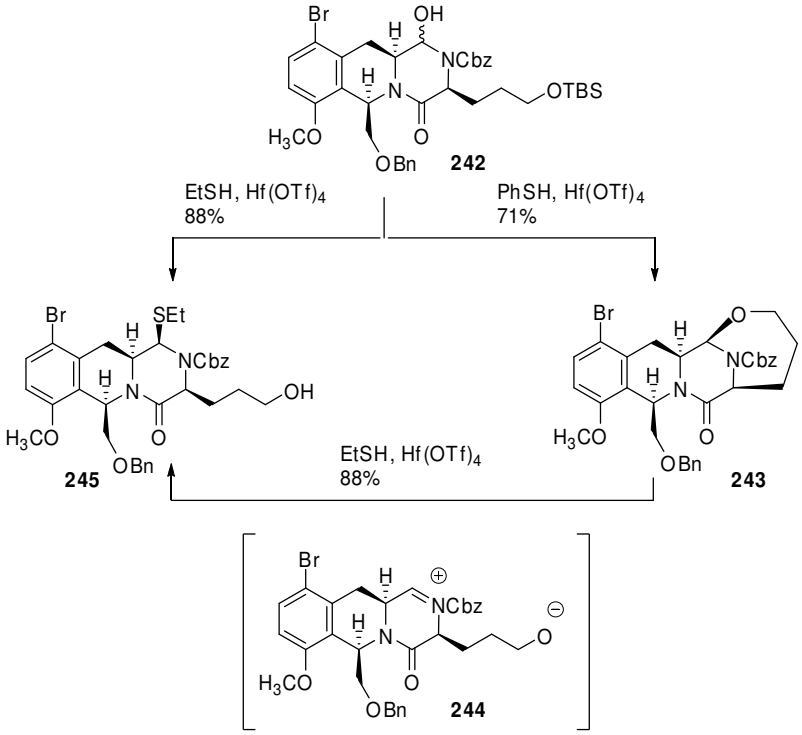
1.5.5.1. Mannich Reaction in (–)-Quinocarcin

Pictet–Spengler precursor **239** was obtained in seven steps by, among other conversions, applying an enantioselective alkylation using Corey's procedure in the presence of Corey–Lygo's phase transfer catalyst[97] starting from **238** (Scheme 1.59). Application of **239** to Pictet–Spengler cyclization provided THIQ **240**, and it was observed that slow addition of the aminoester to the acidic solution containing molecular sieves was pivotal to ensure a good yield.[96] Reduction of ester **241** and Swern oxidation furnished tricyclic hemiaminal **242**.



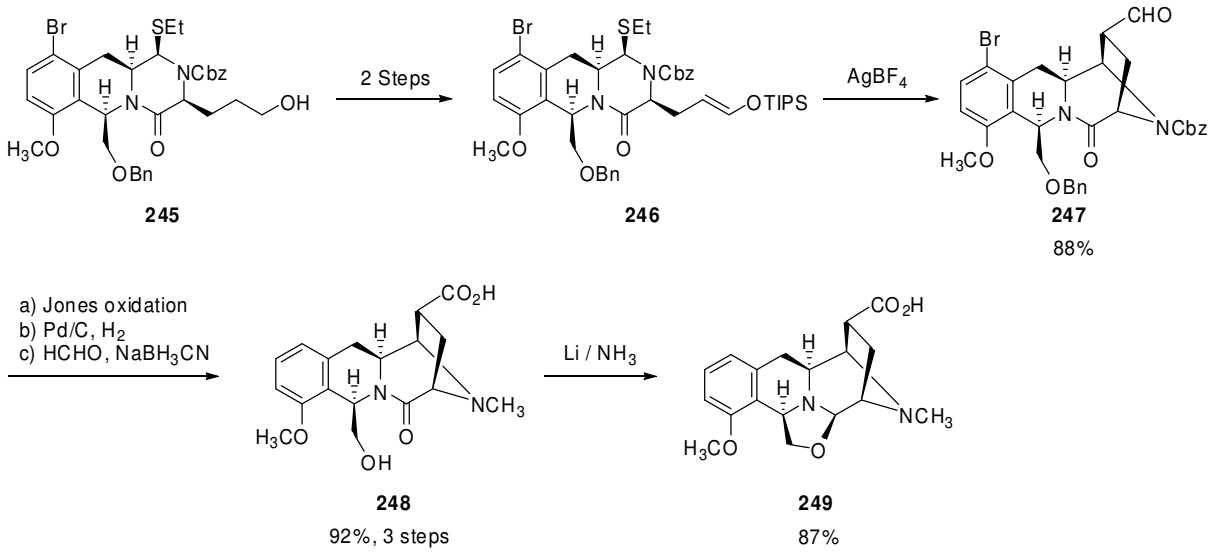
Scheme 1.59: Synthesis of tricyclic **242**.

In order to provide **245**, attempts to convert the hemiaminal **242** into either an amino ether or aminonitrile using methanol or TMSCN in the presence of various Lewis and Brønsted acids either gave no product or resulted in decomposition. Oxophilic hafnium[98] in combination with ethanethiol provided the solution to this problem and furnished amino thioether **245**. Removal of the silyl ether during this step prepared the molecule for the subsequent oxidation step (Scheme 1.60). Ethanethiol is crucial to the success of this conversion due to the formation of cyclic aminoether **243** when applying benzenethiol. A strong external nucleophile is needed to trap the *N*-acyliminium intermediate **244**. When a weaker nucleophile is used formation of **243** is observed due to nucleophilic attack of the tethered alcohol prevailing over the nucleophile. Although this side-reaction was observed using benzenethiol, the intermediate could be converted into the correct cyclic aminoether **245** by exposure to the same reaction conditions applied to **243** to give **245** in a single step. It is hypothesized that the equilibrium between *N*-acyliminium **244** and 1,3-oxazepine **243** was disturbed by use of the poorly thiophilic hafnium, thus forming the stable amino thioether **245**. When applying different Lewis and Brønsted acids, amino thioether **245** underwent rapid equilibrium with *N*-acyliminium **244**. This can be explained by looking at the structural conformation of *N*-acyliminium, adopting a pseudoaxial position and therefore favoring the formation of 1,3-oxazepine due to $A^{1,3}$ allylic interaction.[99]



Scheme 1.60: Synthesis of amino thioether **245**.

Oxidation was followed by silyl protection of the enolate, providing silyl enol ether **246** (Scheme 1.61). The silver tetrafluoroborate-mediated Mannich reaction furnished the tetracycle **247** containing an *exo*-oriented aldehyde function.[100] Silver activates both electrophile and nucleophile in this reaction enabling a disfavored 5-*endo-trig* cyclization. Jones oxidation furnished the carboxylic acid and was followed by a Pd/C-induced one-pot removal of the aryl-bromide, benzyl and Cbz moieties. Subsequent reductive amination provided quinocarciamide **248**. Partial lactam reduction in liquid ammonia was followed by slow sequential addition of methanol and ammonium chloride to provide (–)-quinocarcin **249**.



Scheme 1.61: Total synthesis of (–)-quinocarcin **249**.

1.5.5.2. Summary

The synthetic sequence towards the total synthesis of quinocarcin by Zhu[96] contains some very interesting chemical conversions, such as use of hafnium and ethanethiol in order to produce the Mannich precursor. Subsequently, application of the silver-mediated Mannich reaction provides ring-cyclization and giving rise to an *exo*-oriented aldehyde functionality.

1.5.6. Ecteinascidin Alkaloids

The ecteinascidins were first isolated from *Ecteinascidia turbinate* and are structurally composed out of two THIQs and an additional two bridged ring systems, to give in total a six membered ring-system (Figure 1.11).[101] Total synthesis of ecteinascidin 743 have recently been described by Danishefsky[102] and Zhu.[103]

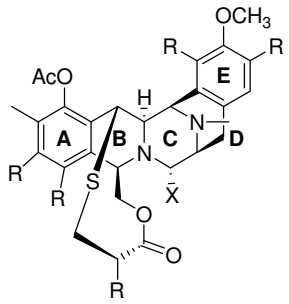
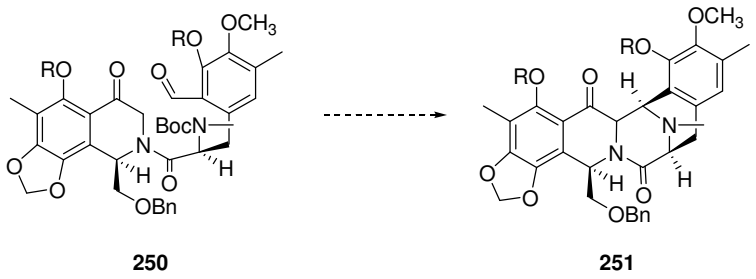


Figure 1.11: Ecteinascidin alkaloids.

1.5.6.1. Pictet–Spengler Cyclization Towards Et-743

Danishefsky had earlier reported his intention towards the use of a cascade-like reaction initiated by cleavage of a urethane function of the type **250** yet proven utilization of a linchpin Mannich cyclization (**250** to **251**) to be unattainable (Scheme 1.62).[104]

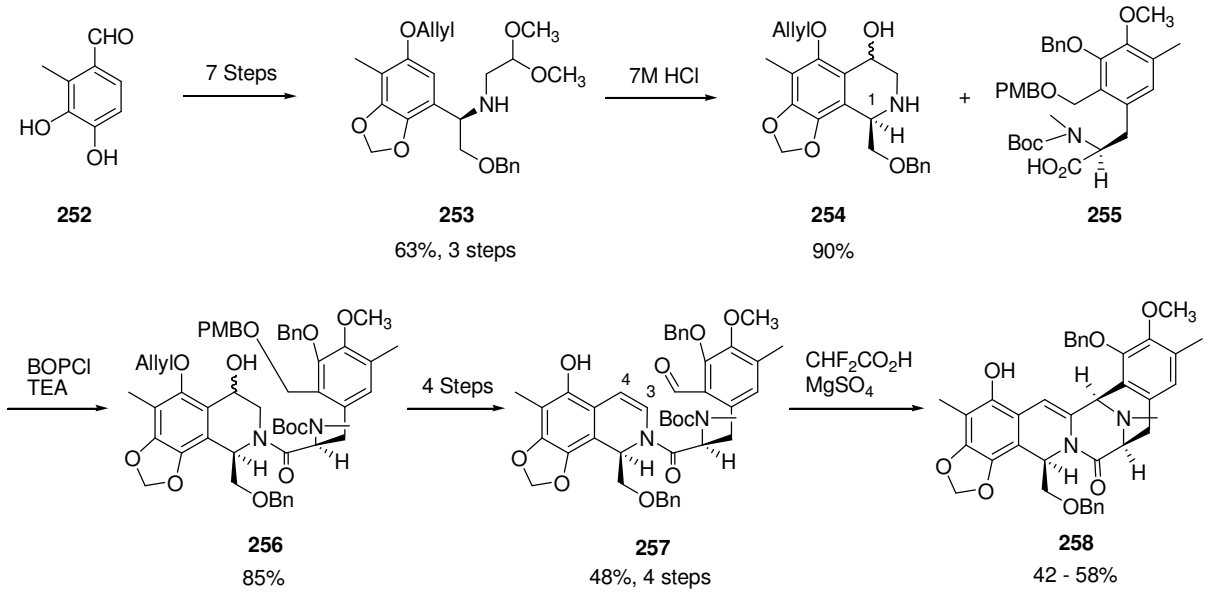


Scheme 1.62: Proposed Mannich reaction.

This cyclization would have been readily incorporated into the total synthesis of Et-743. However, this route was abandoned due to formation of the wrong *anti*-isomer of **254** and the need for a difficult late stage epimerization at the C_1 position. Therefore a new pathway was devised in which key intermediate **254** would be obtained *via* a 3,4-dehydro system. In an attempt to simplify the latter approach and gain access to a broad range of THIQ-related alkaloids, direct cyclization of *ortho*-hydroxystyrene **257** was proposed due to a sense of regiochemical discrimination by the hydroxy phenol (Scheme 1.63).

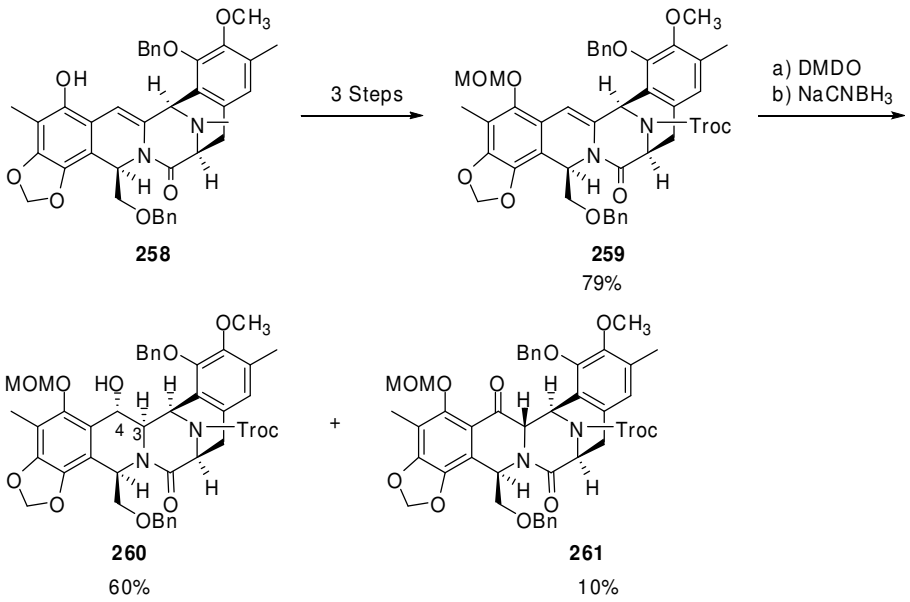
Key-steps in the formal total synthesis of Et-743 are: 1) the application of the aforementioned *ortho*-hydroxystyrene moiety to Pictet–Spengler cyclization, 2) Exploitation of an unusual enamide epoxide for hydration at the C_3–C_4 double bond through reductive treatment of **262** (Scheme 1.65, next page).

Danishefsky started his proposed route towards the total synthesis of Et-743 with the regio-stereospecific bromination of Borchardt catechol **252**[105] to provide **253**. Bobbitt-modified Pomeranz–Fritsch reaction conditions[106] subsequently furnished the THIQ core **254** (Scheme 1.63). Coupling of THIQ **254** with L-tyrosine derivative **255**[107] afforded amide **256** after which the Pictet–Spengler precursor **257** was obtained in 4 steps. Condensation with various acids provided **258** in moderate yields.



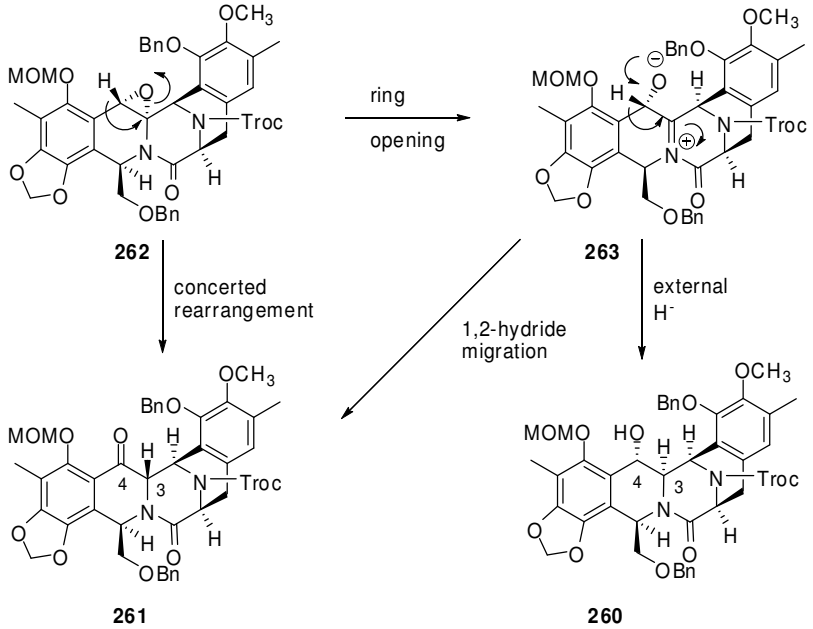
Scheme 1.63: Synthesis of **258**.

Selective functionalization of the C_3–C_4 double bond in **258** by epoxide formation proved to be rather complicated. A large variety of reagents were investigated but only dihydroxylation of **259** could be obtained (Scheme 1.64). The need of a strong oxidizing agent in combination with a more reactive double bond led to *N*-protecting group exchange using McCluskey reaction conditions[108] to afford the *N*-Troc urethane. Only DMDO was able to facilitate the epoxide formation. Selective epoxide opening using $NaCNBH_3$ afforded **260** and **261**.[102]



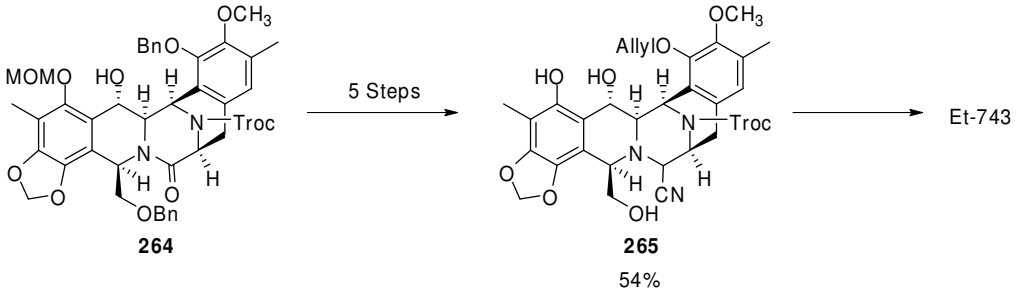
Scheme 1.64: DMDO / $NaCNBH_3$ mediated epoxide formation and selective opening.

A small amount of ketone **261** was obtained during the epoxide ring-cleavage which led to the proposal of a new mechanism involved in the ring-cleavage. Formation of ketone **261** could be induced due to a concerted rearrangement of epoxide **262**, providing the ketone and hydride shift from C_4 to C_3 (Scheme 1.65). Formation of imine **263** could also be followed by external hydride donation to give **260**. **263** can either undergo the aforementioned external hydride addition pathway or 1,2-hydride migration to **262**.



Scheme 1.65: Mechanistic proposal for the reduction of the epoxide of **262** into **260** and **261**.

The advanced Fukayama intermediate **265**[109] was obtained after several deprotection / protection steps and could be converted into Et-743 by following the latters procedure (Scheme 1.66).

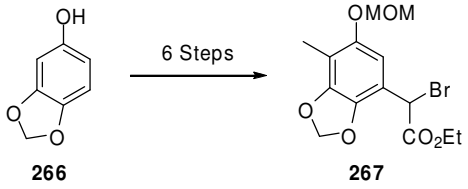


Scheme 1.66: Advanced intermediate towards Et-743.

1.5.6.2. Zhu's Approach Towards Et-743

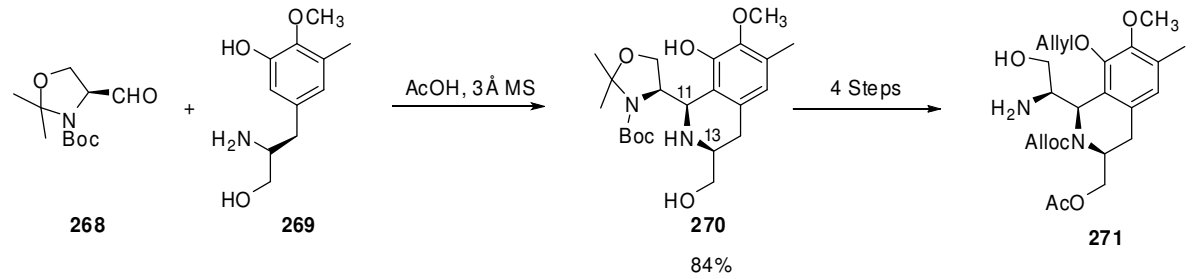
Zhu reported another total synthesis regarding Et-743 in 31 steps using simple reaction conditions.[103] Three key steps are; 1) the rapid and diastereoselective construction of the D-E segments by Pictet–Spengler cyclization of phenylalanol **269** and Garner's aldehyde **268**, 2) diastereoselective *N*-alkylation of racemic benzyl bromide **267** by use of enantiomerically pure **271** and 3) an one-pot deprotection / cyclization leading to formation of a 1,4-bridged 10-membered ring.

The synthesis started by converting sesamol **266** into α-bromo-α-aryl substituted ethyl acetate **267** (Scheme 1.67).



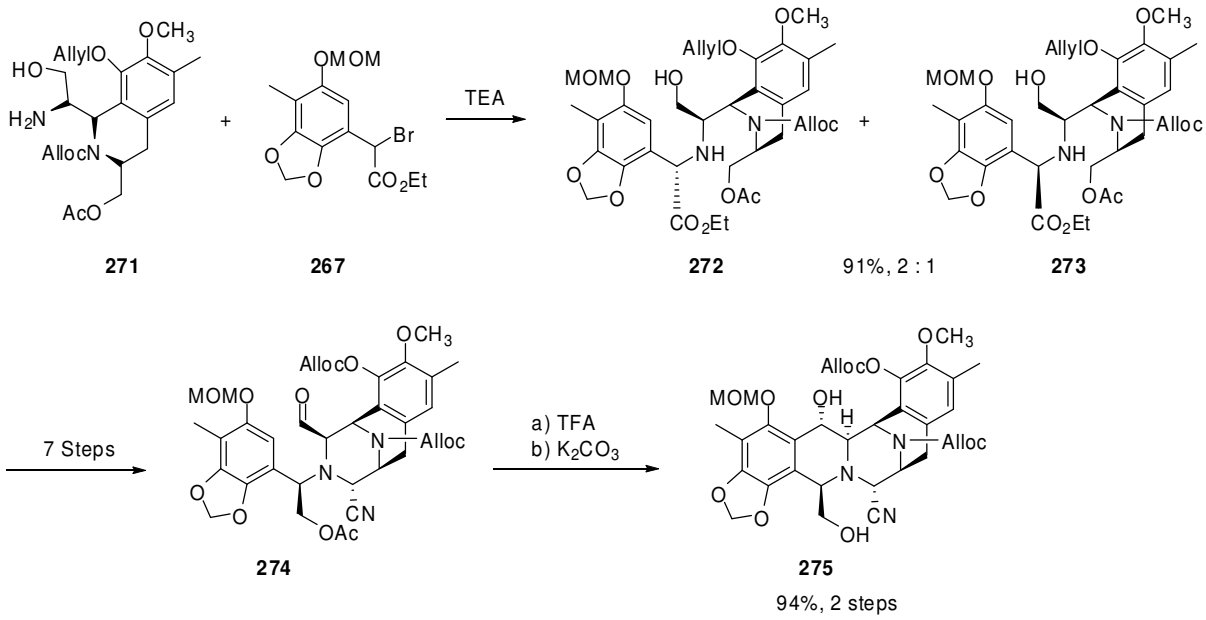
Scheme 1.67: Ethyl acetate **267** synthesis.

Intermolecular Pictet–Spengler condensation of Garner's aldehyde **268**, obtained in 8 steps from catechol,[110] and amine **269** gave **270** (Scheme 1.68). Interestingly, C_{11} stereochemistry during the Pictet–Spengler is solely controlled by the configuration of amino alcohol **269**, providing *cis*-C_{11}–C_{13}. Pseudoequatorial positioning of both C_{11} and C_{13} is presumed and results in *cis*-**270** formation after ring-closure.[103]



Scheme 1.68: Synthesis of the THIQ **271**.

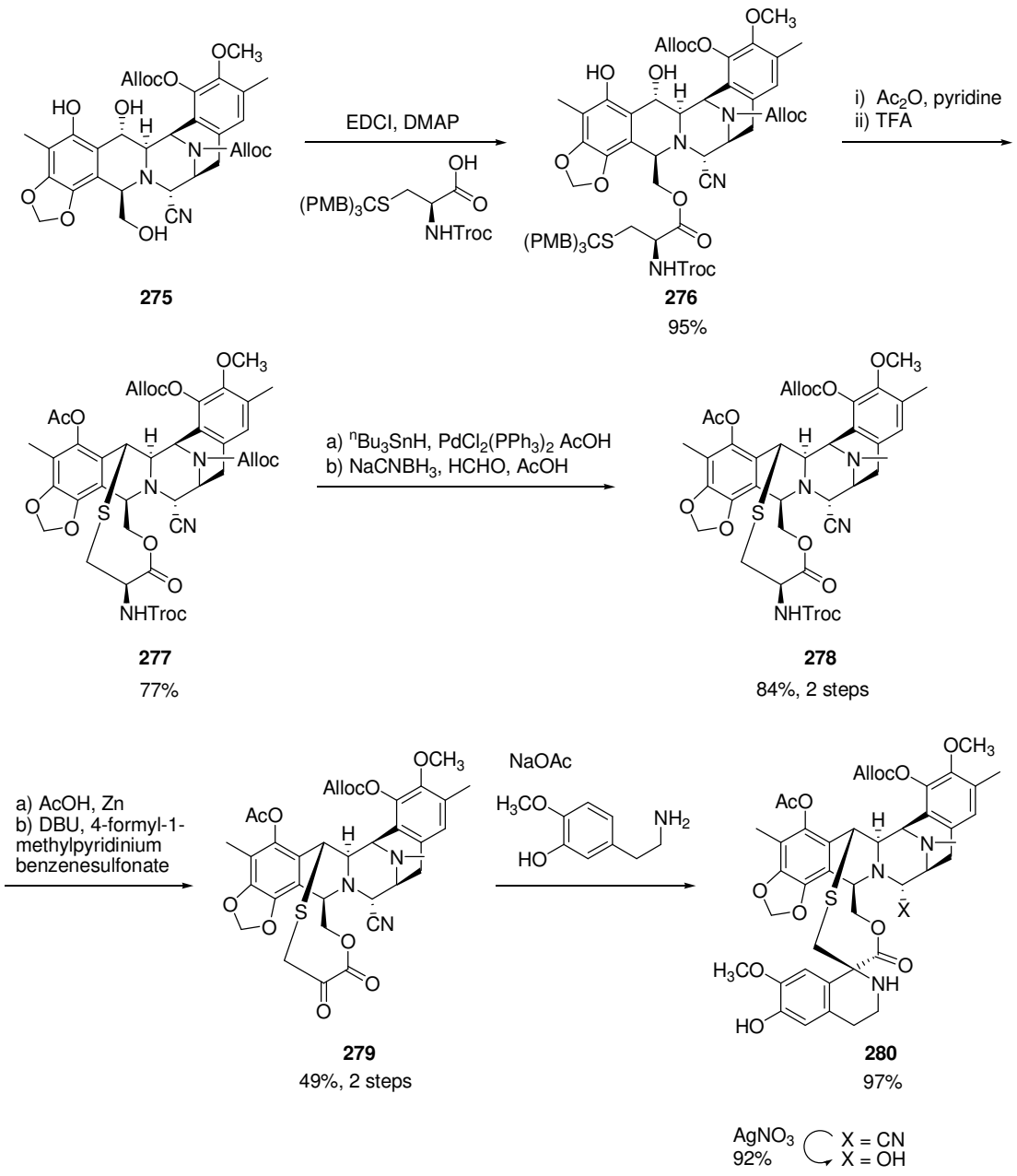
Coupling of amino alcohol **271** was achieved by use of TEA in combination with bromobenzene **267** to furnish amines **272** and **273** (Scheme 1.69). A 2 : 1 stereoselectivity was observed. The S_N1 mechanism involved in the coupling reaction forms a tentative explanation to the lack of stereochemical control in the formation of **272** and **273** *via ortho*-quinone methide intermediate.[111] After 7 steps, aldehyde **274** was obtained and applied to Pomerantz–Fritsch-type cyclization[106] affording alcohol **275**. The A-B-C-D-E ring system was constructed under mildly acid conditions.



Scheme 1.69: Synthesis of **275**.

Synthesis of the bridged ring-system in **277** involved selective ester formation of **276** after deprotection of the primary alcohol and phenol acetate formation using standard acid conditions (Scheme 1.70). This transformation involved a $(PMB)_3CS$ deprotection / cyclization to form the 1,4-bridged 10-membered ring *via* C–S formation, 1,4-β-elimination to an *ortho*-quinone methide and macrocyclization. Guibé's conditions[112] simultaneously removed the *N*-Alloc and *O*-allyl functional groups and subsequent reductive *N*-methylation

provided intermediate **278**. Lastly, Corey's protocol provided Et-743 in four steps starting with removal of *N*-Troc group by reductive conditions followed by amino ester oxidation to ketoester **279**. Pictet–Spengler reaction gave **280**, which upon treatment with $AgNO_3$ provided Et-743 **280**.[103]

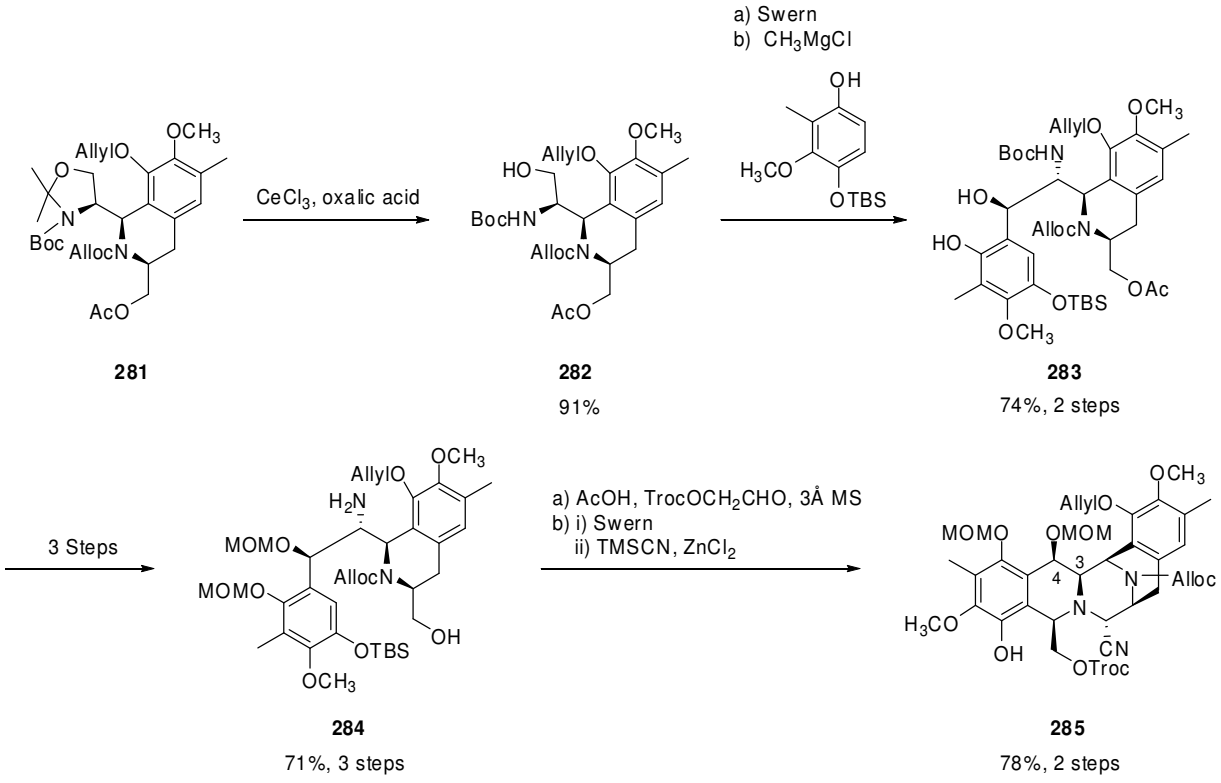


Scheme 1.70: Total synthesis of Et770 and Et743.

1.5.6.3. Stereoselective Aldol Applied to Et-583 and Et-597

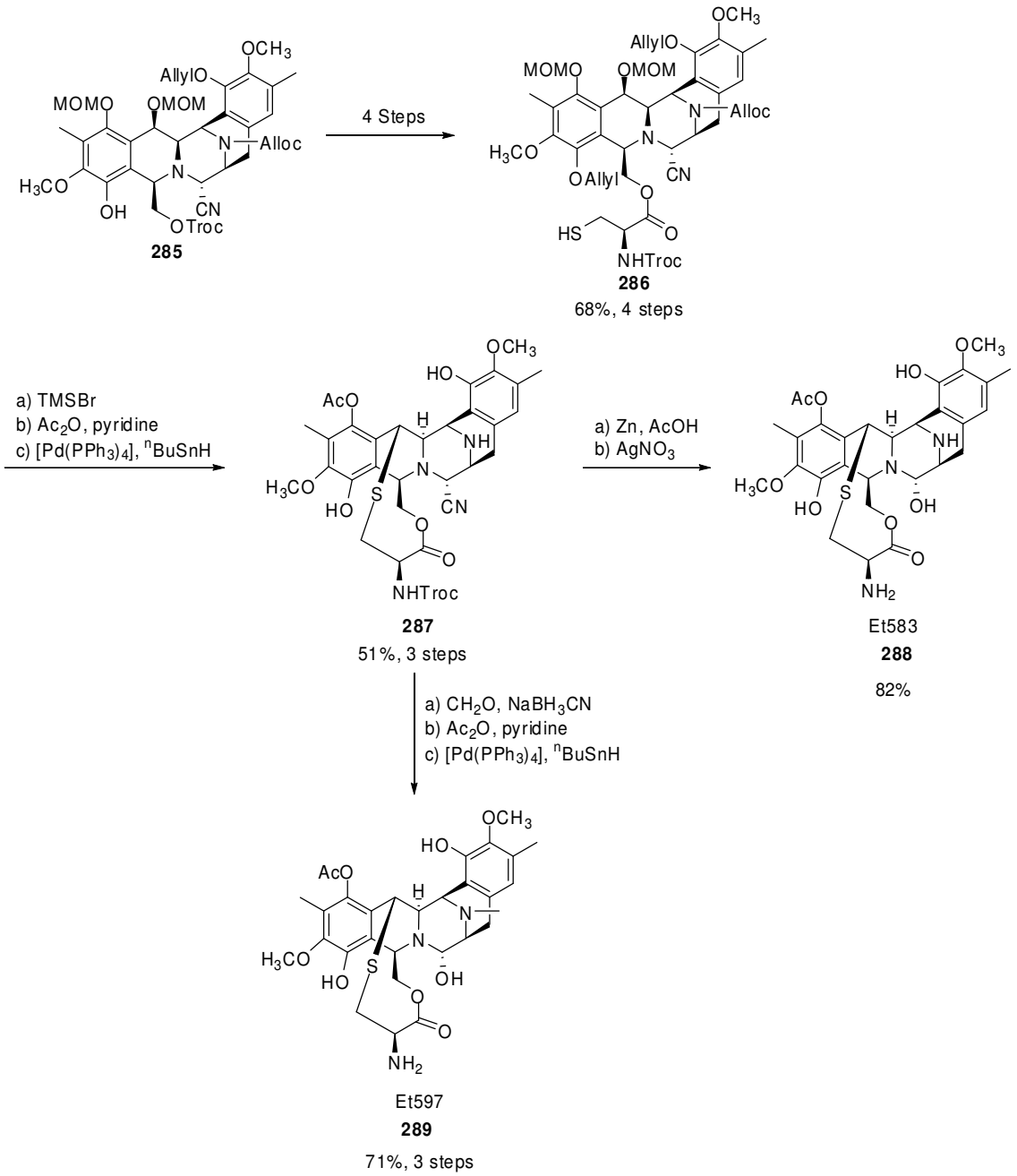
Total syntheses of different relatives of Et-743, namely Et-597 and Et-583 were reported by Zhu.[113] Their syntheses featured; 1) a stereoselective aldol reaction to couple the A-ring with the D-E unit, 2) highly stereoselective Pictet–Spengler B-ring formation and 3) TMSBr-promoted macrocyclization of thiol **287** to afford the 1,4-bridged 10 membered ring system.

In order to obtain pentacyclic **285**, a highly diastereoselective Pictet–Spengler condensation was applied between **268** and the Garner aldehyde (synthesis of **281** has already been discussed on page 79 regarding the total synthesis of Et-743). Selective hydrolysis of oxazolidine **281** afforded alcohol **282** which *via* Swern oxidation provided the corresponding aminoaldehyde (Scheme 1.71). Aldol condensation with magnesium phenolate provided *syn*-**283** exclusively.[114] Protecting group manipulation gave mono-THIQ **284** which underwent a second Pictet–Spengler cyclization when exposed to $TrocOCH_2CHO$ affording bis-THIQ **285** as a single enantiomer in a high yield. Swern oxidation followed by a zinc-mediated catalytic intramolecular Strecker reaction provided the adduct as a single diastereomer. The selectivity observed during the reaction sequence shows a highly efficient route towards construction of the pentacycle **285**.



Scheme 1.71: Synthesis of **285**.

The *trans*-configuration of the iminium intermediate of **285** with regard to the pseudoequatorial C_3 and C_4 substituents, explains the diastereoselectivity observed (Scheme 1.72).[113] Mechanistically however, an alternative phenolic aldol condensation and β-elimination resulting in orthoquinone methide and intramolecular Michael addition of the tethered amine cannot be disregarded. Protecting group manipulation was followed by ester formation to provide **286**. Removal of the S-protecting group resulted in formation of a thiol which upon exposure to TMSBr afforded the bridged macrocycle. C–S formation had been achieved in a single step which involved *O*-MOM deprotection, 1,4-elimination to provide the orthoquinone methide intermediate and macrocyclization *via* Michael addition. Guibe's procedure[112] removed the allyl and alloc moieties and this provided intermediate **287**. *N*-Troc deprotection and conversion of aminonitrile **287** into a secondary alcohol gave hemiaminal Et-583 **288**. Similar manipulations provided Et-597 **289**.



Scheme 1.72: Total synthesis of Et 583 **288** and Et 597 **289**.

1.5.6.4. Summary

Danishefsky's[104] and Zhu's[103] research in the field of Ecteinascidin alkaloids has revealed some very interesting complex chemical conversions. Danishefsky utilized an *ortho*-hydroxy styrene moiety to undergo Pictet–Spengler cyclization. Albeit progressing in a relative moderate yield, this ambitious cyclization provided the desired THIQ intermediate. Further manipulation involved formation of an unusual enamide epoxide **262** obtained from **259** C_3–C_4 double bond epoxidation, which through reductive treatment provided alcohol **260** in moderate yield.

Zhu's[103] reaction sequence involved a more straightforward approach and was able to obtain higher yields, providing a more preferable strategy towards total synthesis of Et-743. The D-E segments were constructed in a rapid and diastereoselective manner by Pictet–Spengler cyclization of phenylalanol **269** and Garner's aldehyde **268**. Diastereoselective *N*-alkylation of racemic benzyl bromide **267** by use of enantiomerically pure **271** and finally a one-pot deprotection / cyclization led to the formation of an 1,4-bridged 10-membered ring required for Et-743 in high yield.
In addition to Zhu's synthesis of Et-743,[113] the same intermediate was applied to the construction of Et-583 and Et-597. A stereoselective aldol reaction was utilized to couple the A-ring with the D-E unit together with a highly stereoselective Pictet–Spengler B-ring formation and TMSBr-promoted macrocyclization of thiol **287** to afford the 1,4-bridged 10 membered ring system.

Although Danishefsky developed some interesting chemistry, the relatively low yield of his synthesis hampers any scale-up endeavors when compared to Zhu's approach which utilizes more robust and higher-yielding chemical conversions.

1.5.7. Renieramycin Family

Four members of the renieramycin family of alkaloids were first isolated from the *Reniera* sponge by Frincke and Faulkner in 1982.[50] Over the years more family members were isolated from different sponges yet proved to be unstable.[50] Although structurally closely related to saframycins, the main difference can be observed when looking at the side chain revealing the presence of an angelic ester side chain in renieramycins in contrast to the pyruvamide in saframycins (Figure 1.12). Recently Williams,[115,124] Liao[119] and Zhu[121] have reported the total synthesis of renieramycin related natural products.

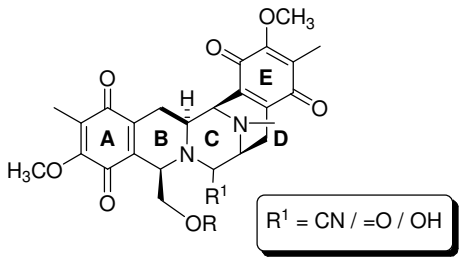
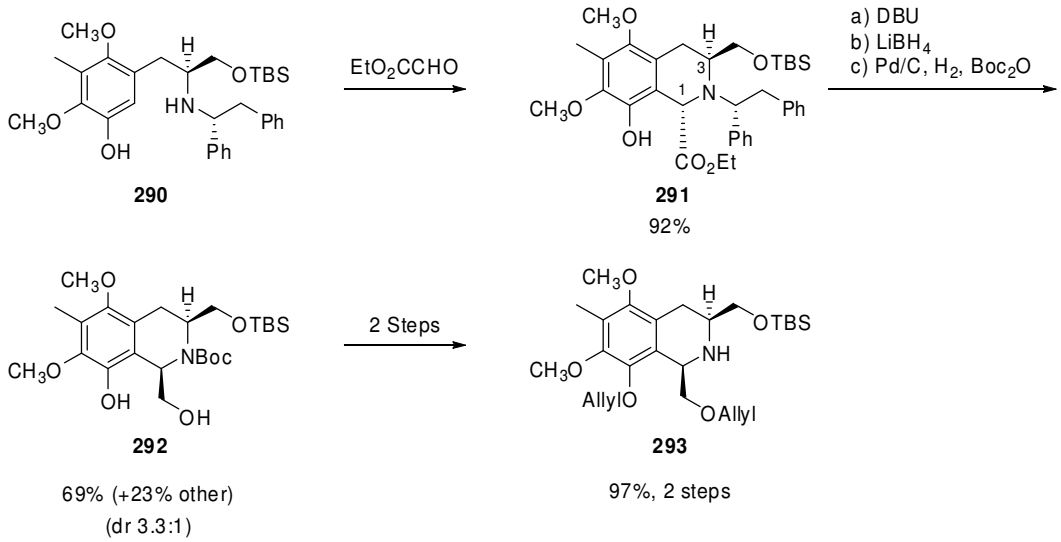


Figure 1.12: Renieramycin alkaloid general structure.

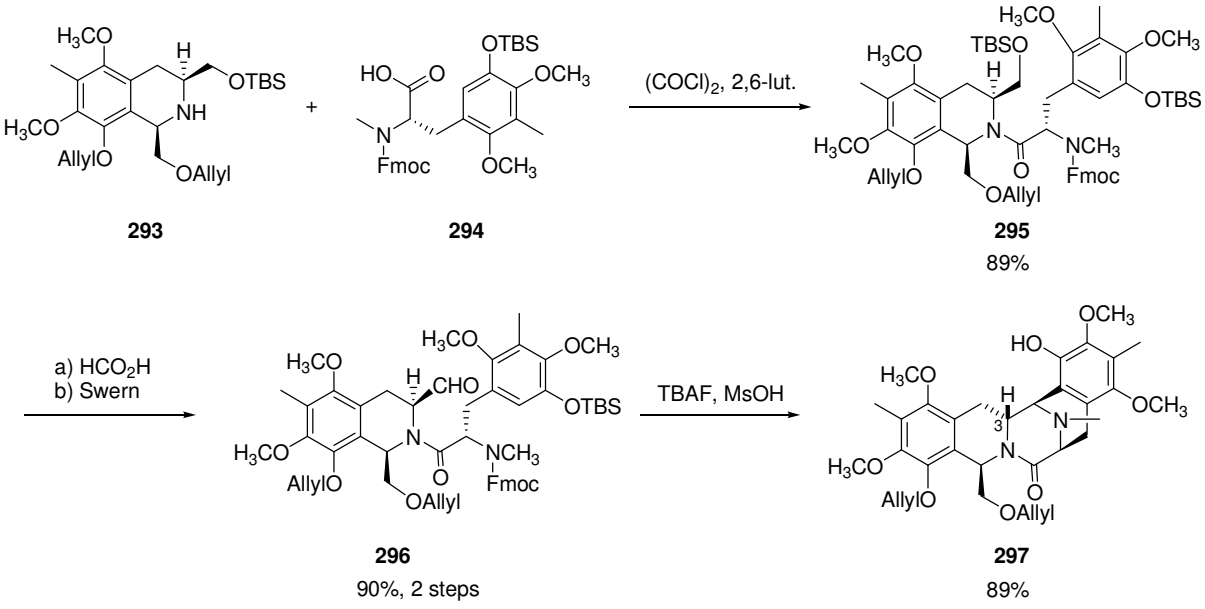
1.5.7.1. Total Syntheses of (–)-Jorumycin and (–)-Renieramycin G

Williams[115] reported the total synthesis of (–)-jorumycin and (–)-renieramycin G in 25 and 23 steps respectively. During their attempt to prepare both natural compounds stereoselectivity issues were encountered when applying the Pictet–Spengler cyclization to **290** providing an *anti*-relationship between the C_1–C_3 moieties in **291**. This problem was solved by treating the substrate with DBU,[116] providing a 3.3 : 1 relationship in favour of the *syn*-conformation (Scheme 1.73).



Scheme 1.73: Synthesis of THIQ **293**.

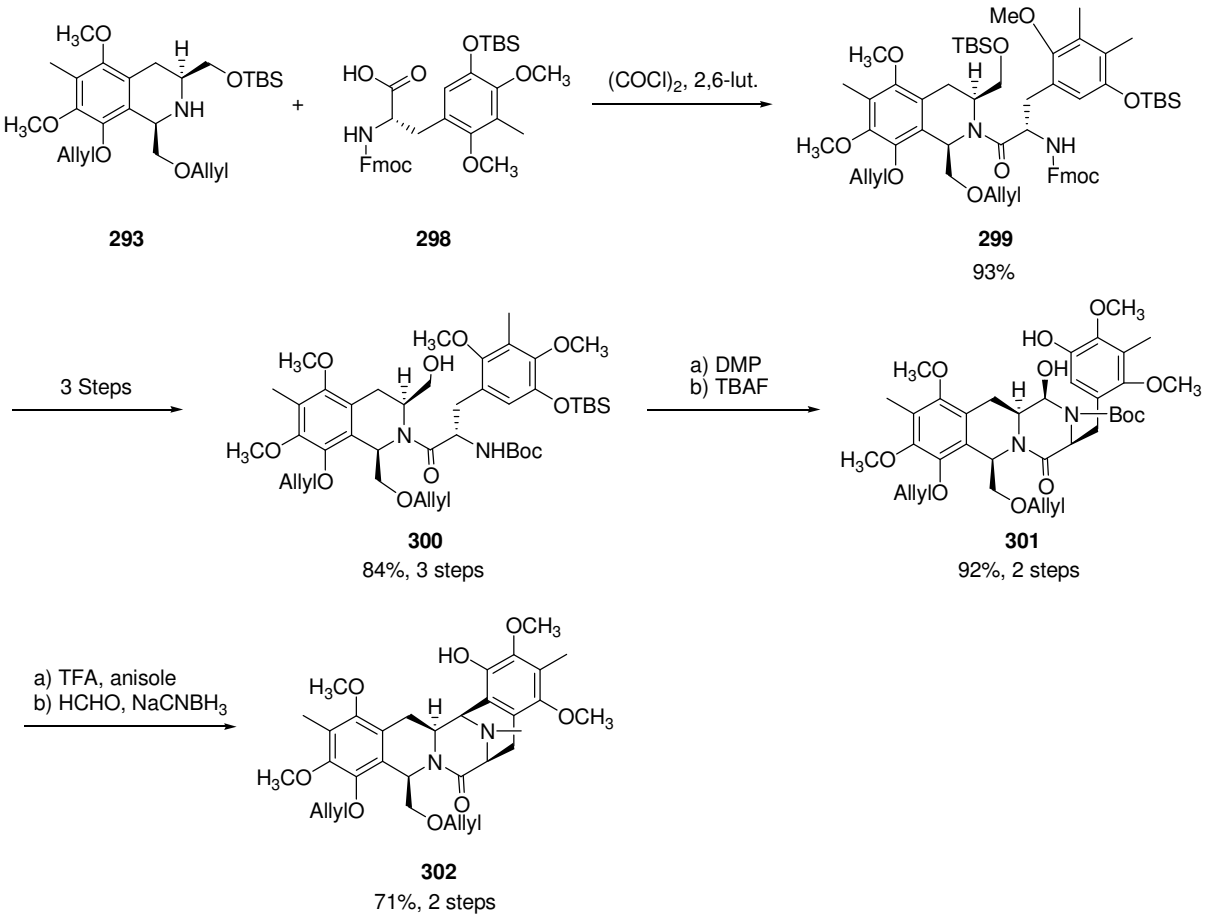
After isolating the *syn*-product **292**, further conversions yielded **297** which interestingly provided C_3-epimerized **297** (Scheme 1.74). Such observations had already been reported by Danishefky[117] and were reported to complicate the total syntheses of both natural products.



Scheme 1.74: Unwanted epimerization of **297**.

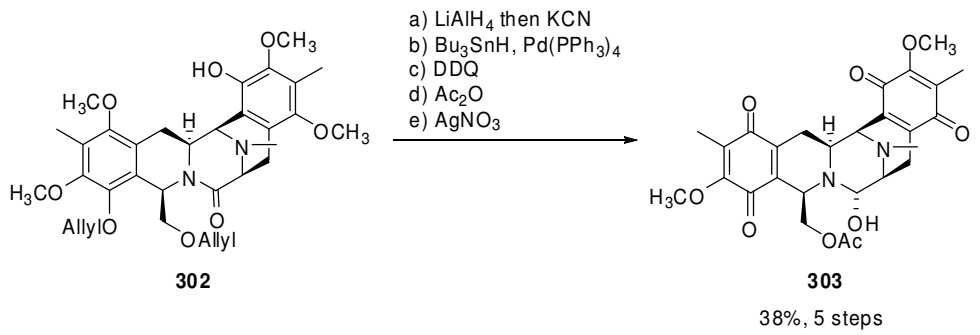
A hypothesis based upon earlier research by Corey[118] in which acidic conditions were used in the synthesis of the second THIQ **297** suggested that the unwanted epimerization is induced under basic conditions. Therefore, acidic conditions were applied and **297** obtained which contained the correct C_3 stereoconfiguration (Scheme 1.75). Protecting group manipulation

followed by oxidation and base-induced cyclization furnished **301** from **300**. Removal of the Boc-protecting group and reductive amination resulted in the formation of the THIQ core system **NC** of (–)-jorumycin and (–)-renieramycin **304**.



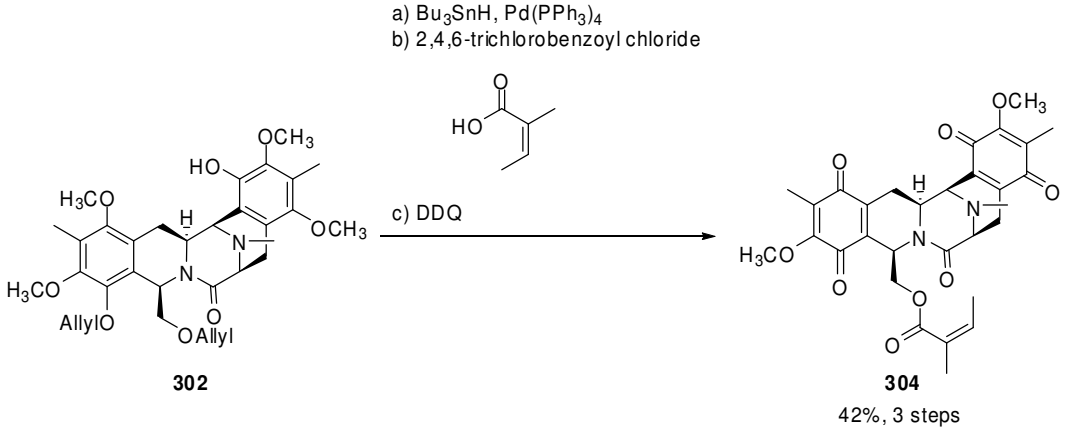
Scheme 1.75: Synthesis of pentacycle **302**.

(–)-Jorumycin **303** was obtained by installation of a cyanide moiety followed by protecting group manipulation, oxidation and cyanide reduction (Scheme 1.76).



Scheme 1.76: Total synthesis of (–)-jorumycin **303**.

(–)-Renieramycin G **304** utilized the same advanced intermediate **302**, in which protecting group manipulation and esterification provided the latter in three steps (Scheme 1.77).

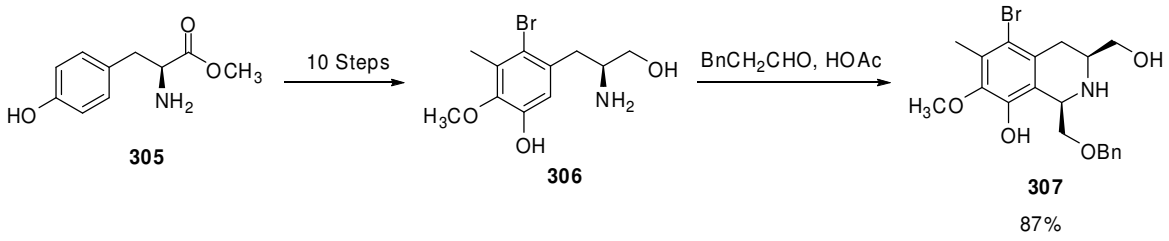


Scheme 1.77: Total synthesis of (–)-renieramycin G **304**.

1.5.7.2. (–)-Renieramycin G by Liao

Total synthesis of (–)-renieramycin G was reported by Liao[119] in 21 steps with an overall yield of 8.5% starting from L-tyrosine. This reaction sequence would involve a highly selective Pictet–Spengler cyclization for the construction of the pentacyclic ring-system.

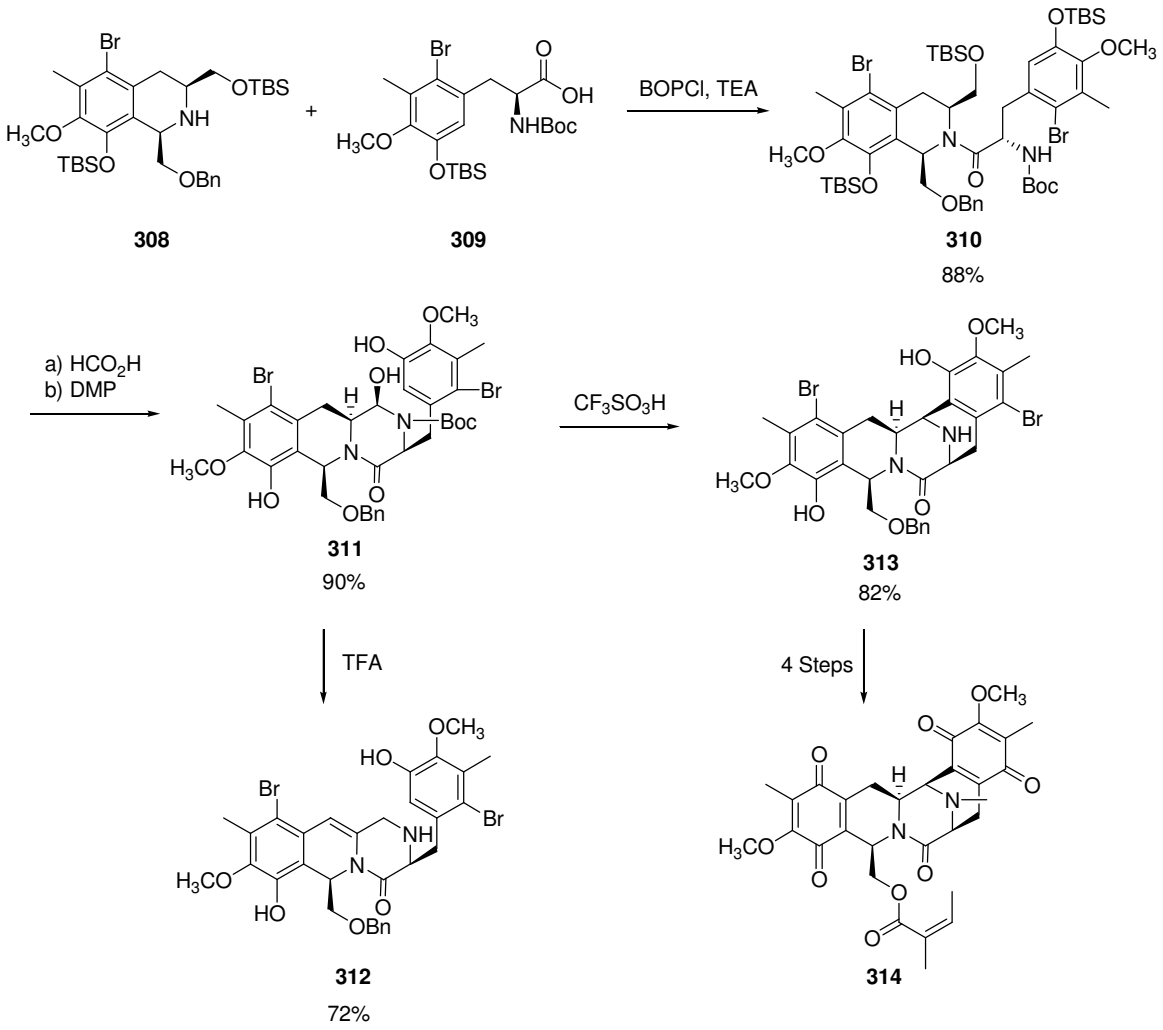
The synthesis started from L-tyrosine[120] **305** which after manipulation and Pictet–Spengler cyclization furnished THIQ **307** diastereoselectively (Scheme 1.78). This cyclization was extremely susceptible to temperature change; at rt a 5 : 4 *cis* : *trans* ratio of **307** was observed while at 0 °C the reaction proceeded selectively and only the *cis*-isomer was obtained. The same reaction did not facilitate any THIQ **307** formation at –10 °C.[119]



Scheme 1.78: THIQ western core synthesis.

After silyl protecting **307**, peptide coupling of both **308** and **309** fragments gave **310** without racemization. Hemiaminal **311** was subsequently obtained as a single diastereomer (Scheme 1.79). Removal of the secondary silyl ether moiety prior to DMP oxidation resulted in decomposition of the starting material, and therefore the latter was removed after oxidation.[119] Attempts to effect intramolecular Pictet–Spengler cyclization with HCOOH and TFA, BF_3 or

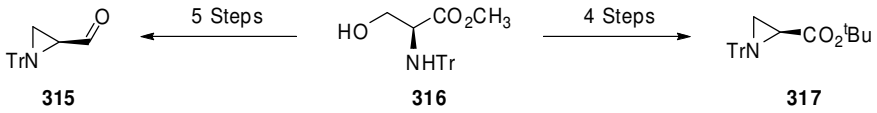
$MeSO_3H$ did not provide the pentacyclic product **313**. Fortunately exposure to CF_3SO_3H at room temperature provided the pentacyclic core and simultaneously removed both Boc and benzyl protecting groups. It was suggested that the presence of a bromide atom *para* to the phenolic hydroxyl group would retard electrophilic aromatic substitution. When TFA was used cyclic enamine **312** was obtained, being favored over electrophilic aromatic substitution.[119] Formation of a dication in the formation of **313** from **311** acted as a stronger electrophile in the intramolecular electrophilic substitution when compared to formation of **312**. The latter involved formation of a single monocationic enamine by favoring elimination over electrophilic substitution.[116] Finally, total synthesis of (–)-renieramycin G **314** was achieved in four steps from **313**.



Scheme 1.79: Synthesis of (–)-renieramycin G **314**.

1.5.7.3. Aziridine-Mediated Total Syntheses of (–)-Renieramycin M, G and (–)-Jorumycin

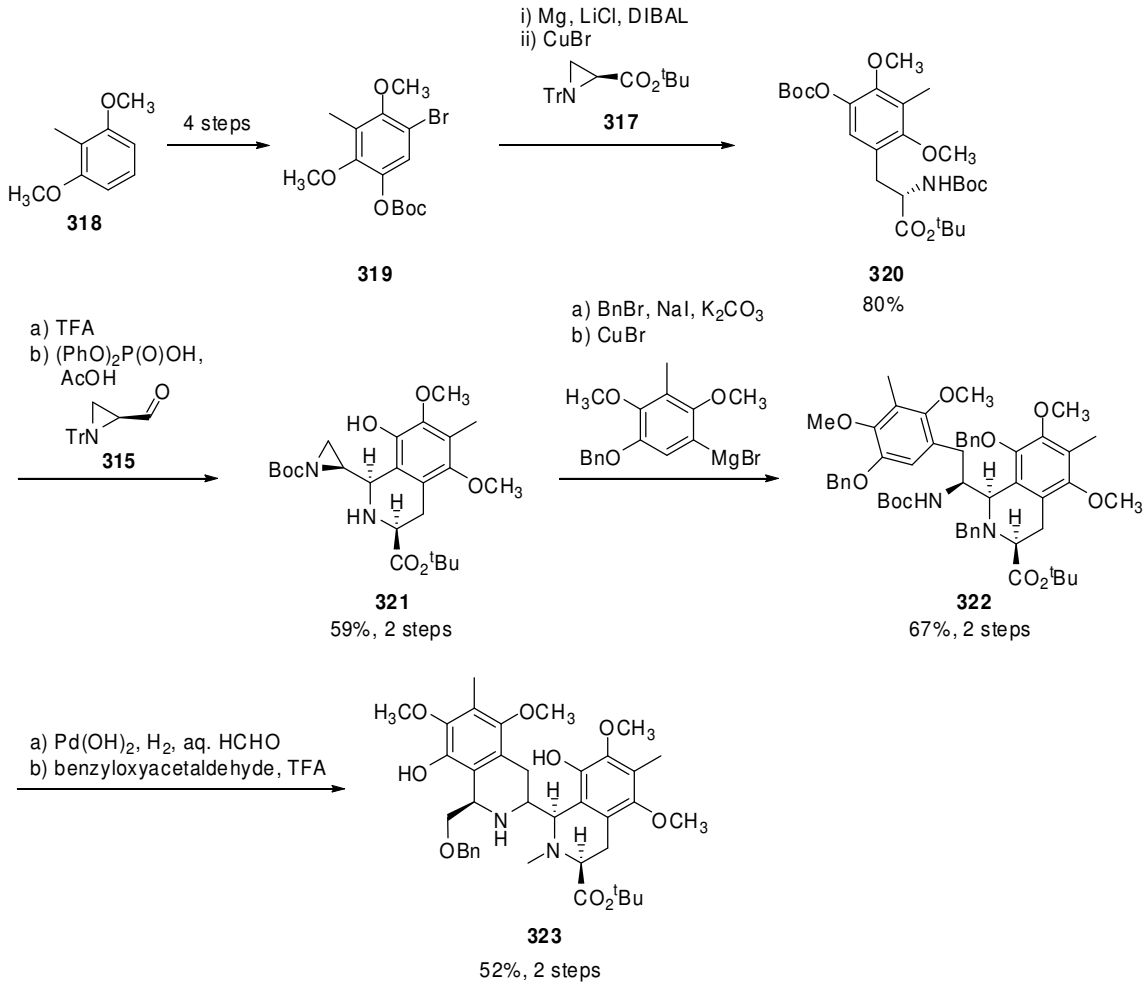
Zhu reported the total synthesis of (–)-renieramycin M, G and (–)-jorumycin using aziridine chemistry as the linchpin in their total synthesis.[121] The aziridines **315** and **317** were derived from *N*-trityl-L-serine methyl ester **316** (Scheme 1.80).



315 **316** **317**

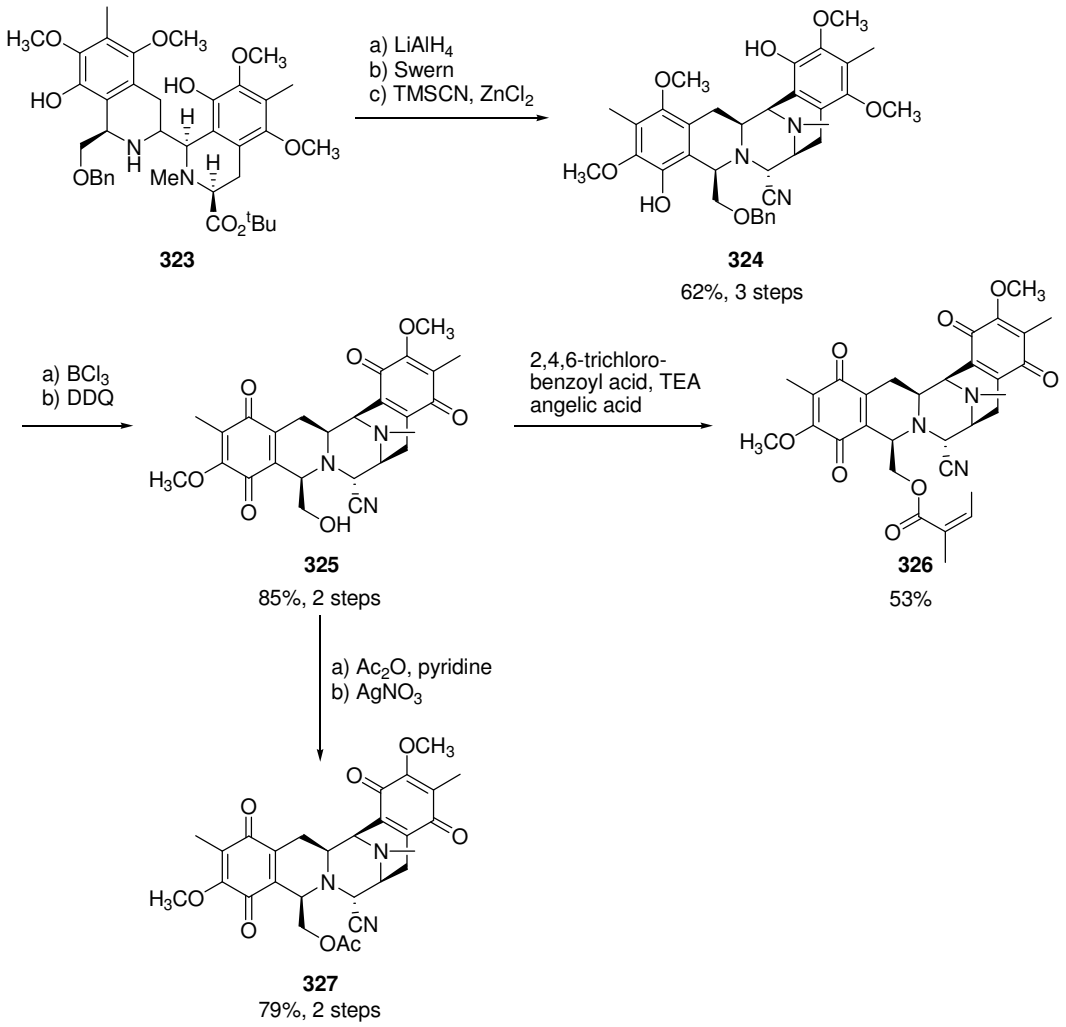
Scheme 1.80: Aziridine synthesis.

Synthesis of the core structure **323** would involve application of the aziridine moieties and started with the conversion of **318** into **319**. Arylmagnesium formation was achieved utilizing Knochel's conditions[122] and **320** was obtained by reacting the Grignard reagent of **319** with aziridine **317** (Scheme 1.81). *O*- and *N*-deprotection using acid conditions was followed by an intermolecular Pictet–Spengler reaction between aziridinal **315** and **320**. Classic reaction conditions proved complicated in inducing Pictet–Spengler cyclization, a catalytic amount of diphenylphosphoric acid was needed in order to provide THIQ **321**.[121] Benzylation of **321** was followed by exposure to aryl Grignard which fascilitated ring-opening of the aziridine providing amine **322**. Tandem Boc-deprotection and exposure to benzyloxyacetaldehyde furnished the Pictet–Spengler cyclized bisTHIQ **323**. Having constructed the core for all three natural products, separate manipulation of the bisTHIQ **323** would provide all three alkaloids.



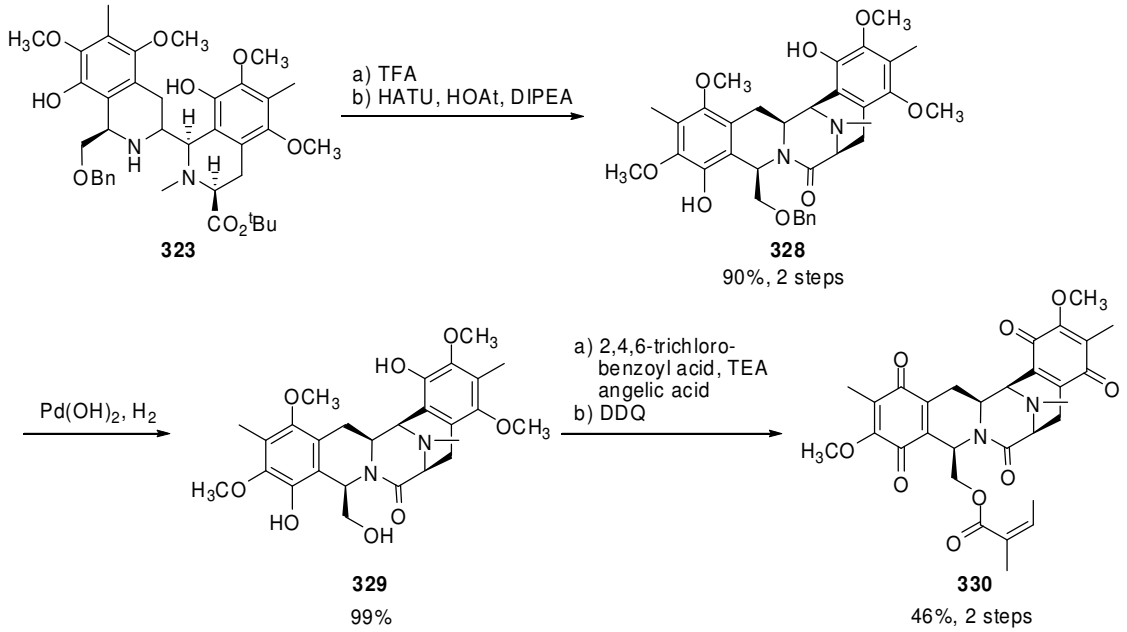
Scheme 1.81: Synthesis of core THIQ **323**.

(–)-Renieramycin M and (–)-jorumycin were prepared using a similar route which involved ester reduction, alcohol oxidation (providing the cyclized product) and cyanide installment by a Strecker reaction to furnish pentacyclic **324** (Scheme 1.82). *O*-Debenzylation by BCl_3 followed by oxidation provided (–)-jorunnamycin A **325**. This alkaloid could either provide (–)-renieramycin M **326** *via* angelic acid[123] installment or by acetylation and cyanide hydrolysis to provide (–)-jorumycin **327**.



Scheme 1.82: Total syntheses of (–)-renieramycin M **326** and (–)-jorumycin **327**.

Finally, total synthesis of (–)-renieramycin G **330** was achieved by ester saponification and peptide coupling to give pentacyclic **328** (Scheme 1.83). Debenzylation, esterification with angelic acid and phenol oxidation gave (–)-renieramycin G **330**.

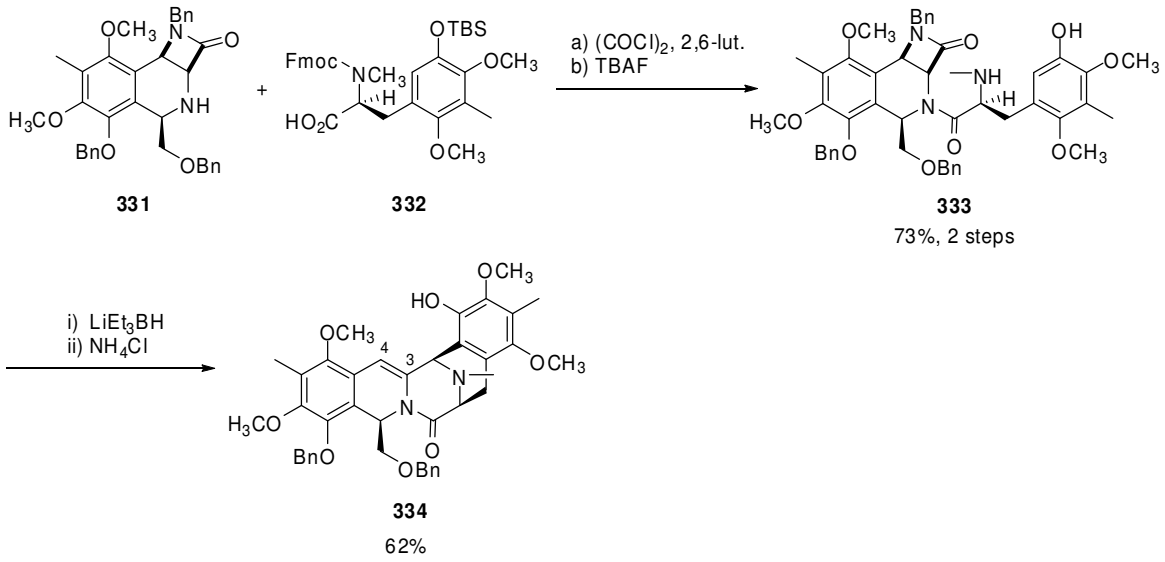


Scheme 1.83: Total synthesis of (–)-renieramycin G **330**.

1.5.7.4. (–)-Cribostatin 4

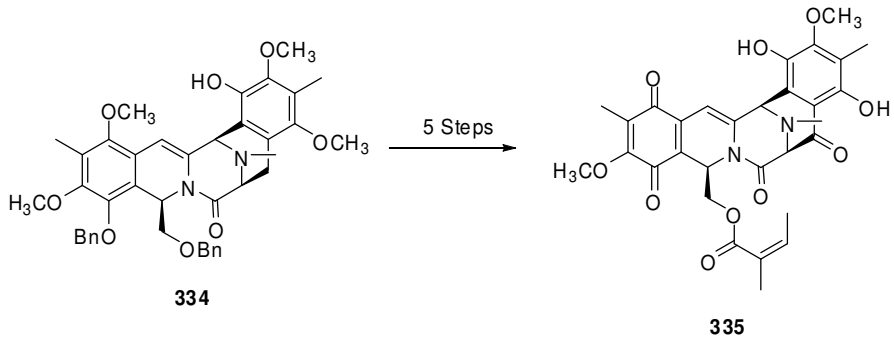
The Williams group[124] reported the total synthesis of (–)-cribostatin 4 (renieramycin H) utilizing previously reported strategies[126] for formation of the THIQ core and the eastern half of the molecule. The strategy involved built on methodology developed for the formation of the THIQ **334** C_3=C_4 present in cribostatin 4.[125] Key elements in the total synthesis of this compound being the reductive opening / elimination of the C_3–C_4 β-lactam present in **333**, and the Pictet–Spengler cyclization in order to obtain the pentacyclic skeleton.

The synthesis was initiated by acid chloride formation of **332** which subsequently afforded **333** following Fmoc-deprotection. Reduction of the β-lactam into the C_3=C_4 alkene was achieved by use of $LiEt_3BH$ to provide **334** (Scheme 1.84).



Scheme 1.84: Synthesis of pentacyclic **334**.

Two pathways towards formation of this benzylic alkene in **334** were proposed. The first of these involved β-elimination of the benzylamine residue at C_4 *via* the incipient aldehyde which would undergo Pictet–Spengler cyclization by an α,β-unsaturated iminium intermediate. An alternative pathway involved C_4 elimination of the benzylic amine after formation of the pentacyclic core *via* an *ortho*-quinone methide intermediate. Preliminary investigations support the latter.[124] Debenzylation of **334** was followed by oxidation to form the phenol moieties while preventing hydrogenation of the C_3–C_4 moiety (Scheme 1.85). Installation of the angelic acid chloride at the primary alcohol was followed by selenium induced oxidation of the C_{14} position to furnish the alcohol precursor of **334** in a chemo-, regio- and diastereoselective manner. Subsequent use of DMP oxidized this alcohol while addition of sodium thiosulfate reduced the quinine into hydroquinone thus concluding the total synthesis of (–)-cribostatin 4 **335**.



Scheme 1.85: Total synthesis of (–)-cribrostatin 4.

1.5.7.5. Summary

All four articles discussed regarding the total syntheses of renieramycin natural alkaloids provided an interesting view on the use of recently developed methodology / different strategies in the field of complex natural compounds synthesis.

Williams[115] reported the total syntheses of (–)-jorumycin and (–)-renieramycin G after successfully solving a base induced C_3-epimerization of one of the advanced intermediates. Application of acidic conditions prevented this unwanted conversion from taking place, thus allowing the reaction sequence to continue towards completion using a rather straightforward approach.

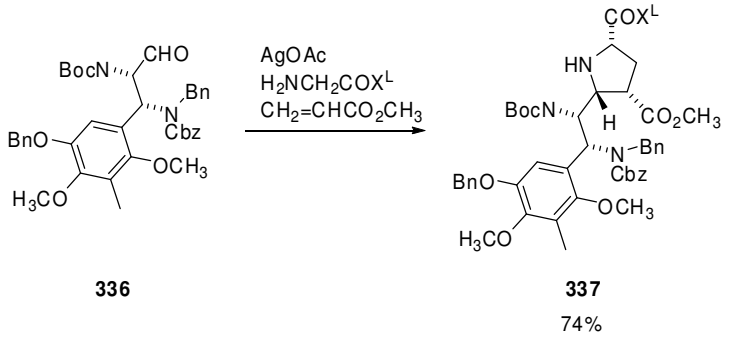
Liao[119] never observed any epimerization in his total synthesis and was able to report a very highly selective Pictet–Spengler cyclization using commercially available L-tyrosine as the starting material. This Pictet–Spengler cyclization was achieved by using superacidic conditions and relying on the *p*-bromine substituent on retarding electrophilic aromatic substitution.

Aziridine-mediated total synthesis by Zhu[121] described an interesting use of these moieties in the field of natural product synthesis. Successful application of these aziridines combined with two highly selective Pictet–Spengler cyclizations and no observed epimerization provides a very straightforward and efficient strategy.

Lastly, the second approach by Williams[124] utilized a very interesting β-lactam intermediate in order to construct the C_3=C_4 alkene, this in combination with a chemo-, regio- and diastereoselective manner of constructing this alkaloid makes for a very interesting approach.

1.5.8. Cyanocycline A and Bioxalomycin-β2

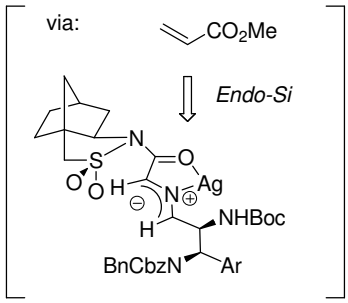
In order to utilize their [C+NC+CC] coupling reactions on a more complex scale, Garner[126] reported the total synthesis of cyanocycline A and bioxalomycin-β2. This methodology provided the formation of a highly functionalized pyrrolidine by means of a metal-mediated, multicomponent [3+2] cycloaddition. Previous total syntheses by both Evans (35 linear steps) and Fukuyama (32 linear steps) had already been reported.[126] In order to test Garner's methodology, aldehyde **336** was constructed, combined with L-glycylsultam by using AgOAc thus furnishing *syn*-pyrrolidine **337** (Scheme 1.86).



336 **337** 74%

Scheme 1.86: Key [C+NC+CC] coupling reaction.

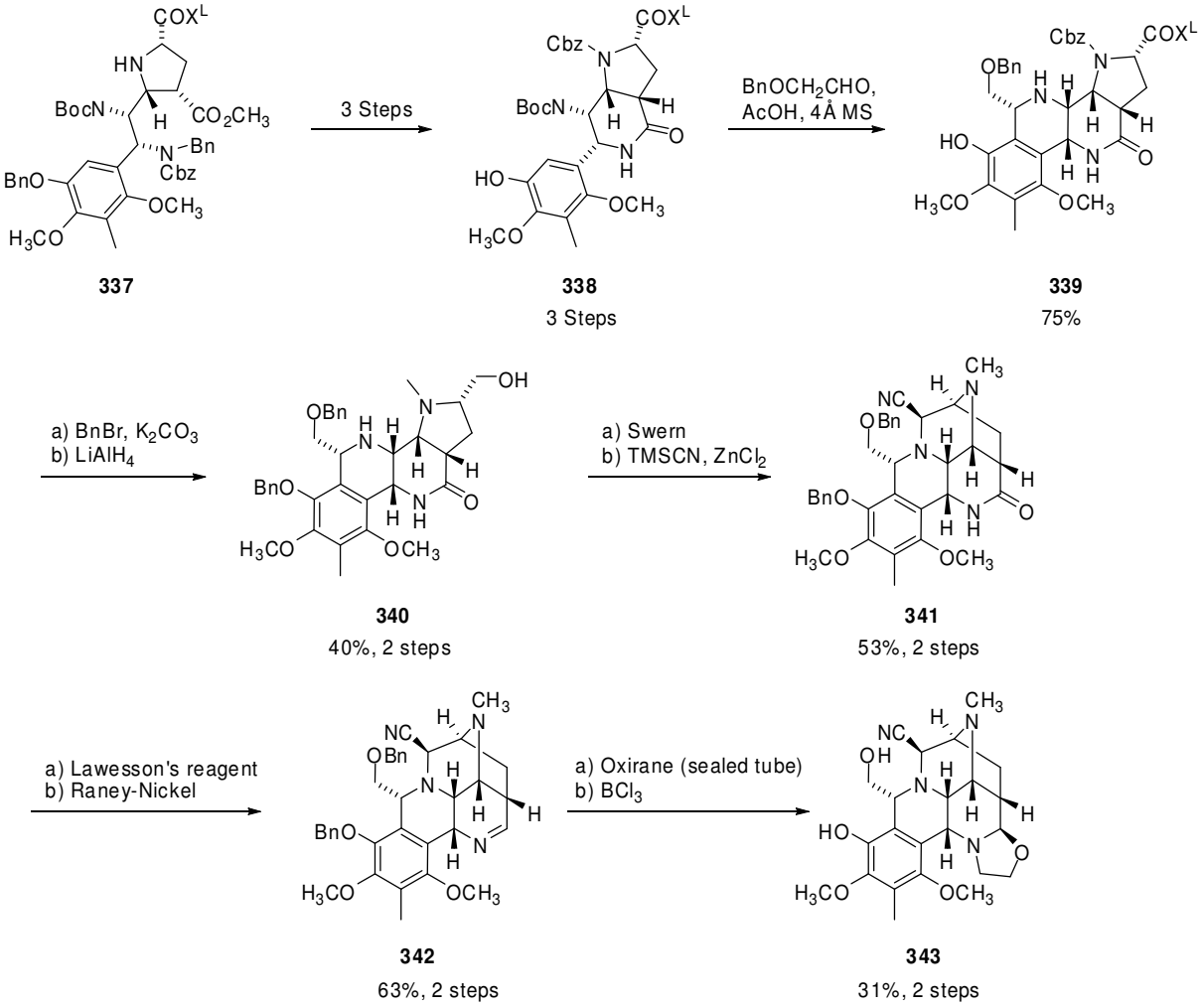
On the basis of earlier studies revealing the *endo-si* preference for this [3+2] cycloaddition it was assumed the latter had been formed due to the steric hindrance created by urethane functionalities, NMR observation would later prove this assumption to be correct (Scheme 1.87).[126]



Scheme 1.87 Key [C+NC+CC] coupling reaction approach hypothesis.

After the successful synthesis of **337,** the latter was converted into **338** which underwent Pictet–Spengler cyclization to afford THIQ **339** in a stereoselective manner (Scheme 1.88). Benzyl protection was followed by $LiAlH_4$ reduction to give primary alcohol **340**. This reaction involved cleavage of the chiral auxiliary together with the conversion of the urethane

moiety to *N*-methyl. Swern oxidation and aminonitrile exposure furnished **341**. Formation of the F-oxazilidine **343** was obtained by use of Pelletier's process[127] *via* imine **342**. Debenzylation using BCl_3 finally gave **343**, which is an advanced intermediate reported by Fukayama.[128] In addition, as cyanocycline A can readily be converted into bioxalomycin-β2 through the use of $Ag^{(I)}$,[129] both natural compounds could be prepared using this advanced intermediate.



337 → **338** (3 Steps) → **339** (75%)

340 (40%, 2 steps) → **341** (53%, 2 steps)

342 (63%, 2 steps) → **343** (31%, 2 steps)

Scheme 1.88: Garners total synthesis towards cyanocycline A.

1.5.8.1. Summary

The formal total synthesis of cyanocycline A and bioxalomycin-β2 involved utilization of a [3+2] cycloaddition providing a highly functionalized pyrrolidine *via* [C+NC+CC]-methodology. Application of their methodology to these complex molecules reduced the amount of steps involved from 35 or 32 steps to 22. The methodology described therefore provided an interesting application to the field of natural product total synthesis due to the fast, efficient and stereoselective manner in which it allows [3+2] cycloadditions to take place starting from small molecules.

1.6. References

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CHAPTER 2

Results and Discussion

2. Results and Discussion

In this part of the report our efforts towards the total synthesis of (±)-suaveoline, (±)-alstonerine, and (–)-cytisine will be discussed. A summary of earlier studies conducted within the Craig group will be included in order to provide a more detailed background to our work.

2.1. Suaveoline

2.1.1. Prior Work within the Craig Group

The total synthesis of (–)-suaveoline was proposed[1] with the aim of incorporating the newly developed decarboxylative Claisen rearrangement (dCr)[2] as well as the *de novo* pyridine[3] methodology.

In addition to both the dCr and *de novo* pyridine methodologies, synthesis of 1,3-*cis*-bridged piperidine **3** *via* Pictet–Spengler cyclization was to be employed (Figure 2.1). Previous research had shown that when the cyclization occurred intramolecularly, complete selectivity for the 1,3-*cis*-bridged piperidine ring was observed.[4] Preparation of the 3,4,5-trisubstituted pyridine ring would involve oxidative cleavage of cyclopentene **346** followed by treatment with an ammonia source. The use of cyclopentene **346** instead of the bis-olefin was proposed to aid both α-alkylation at the tosyl-C_4 position as well as increase the yield of the 1,5-dicarbonyl-containing product of oxidative cleavage.[5] Dual-dCr of **349** would provide 4-tosyl-1,6-heptadiene **348**.

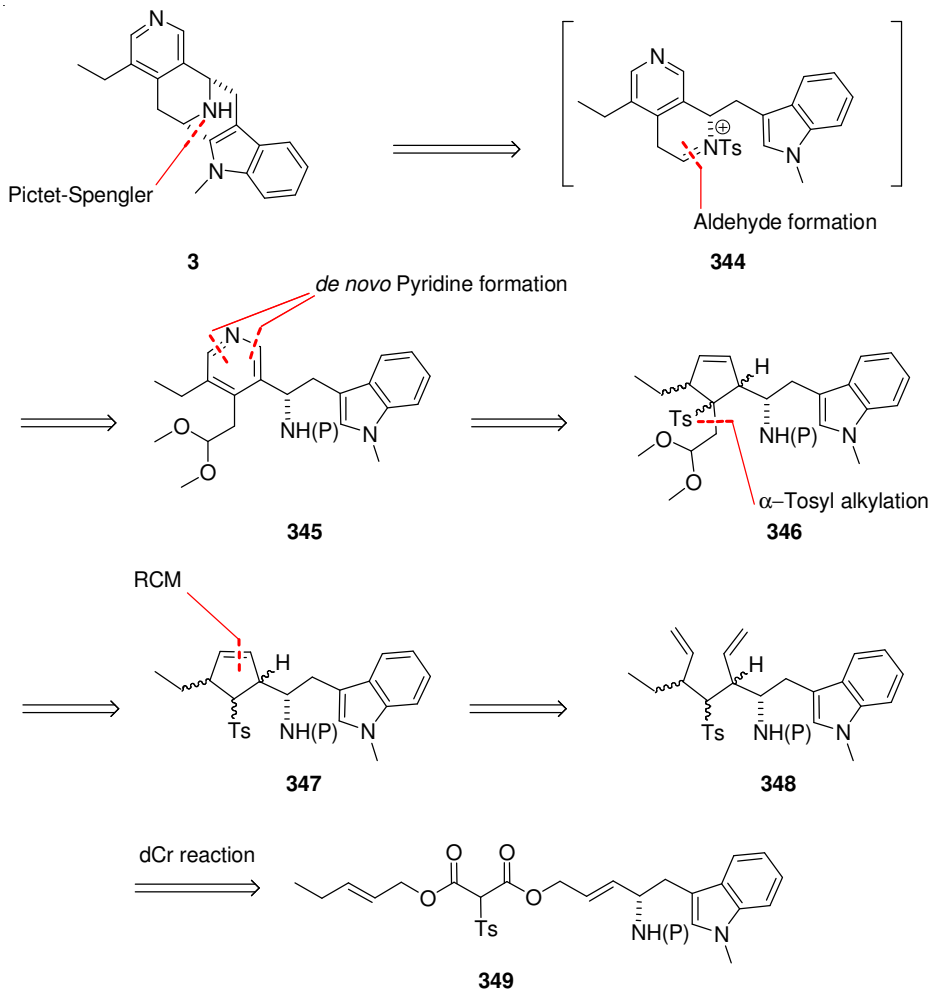
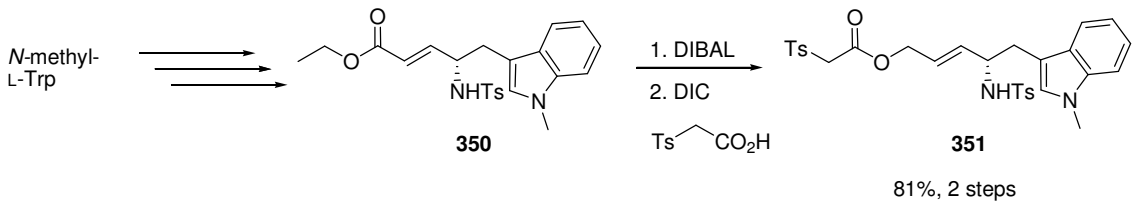


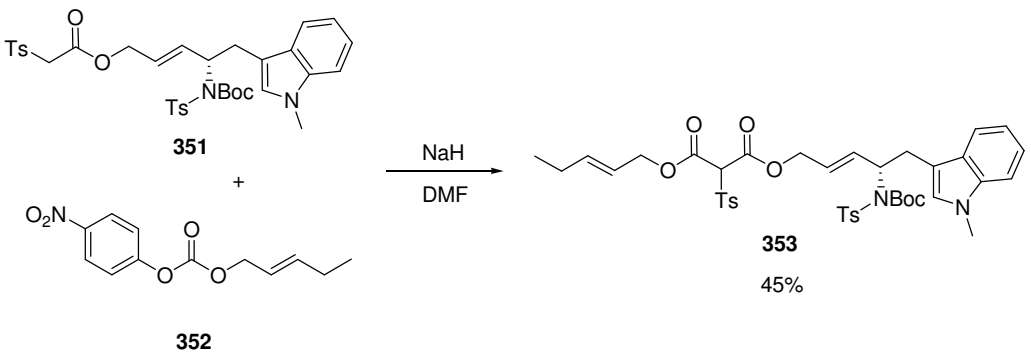
Figure 2.1: Retrosynthesis of (–)-suaveoline.

Synthesis of malonate **349** started from *N*-methyl-L-tryptophan and involved Weinreb amide synthesis, ester reduction and Horner–Wadsworth–Emmons olefination to provide vinylogous ester **350** (Scheme 2.1). Subsequent DIBAL reduction of the α,β-unsaturated ester **350** gave the corresponding alcohol, which upon esterification with tosylacetic acid gave **351**.



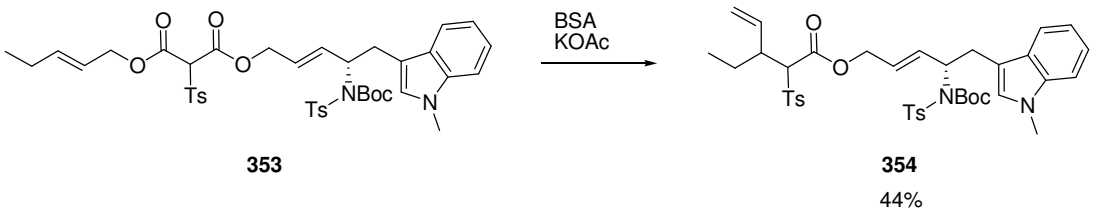
Scheme 2.1: Synthesis of dCr intermediate **351**.

Amine protection was necessary due to competition between the highly acidic amine proton and the desired α-tosyl position in the carboxylation step. Malonate **353** was subsequently obtained in moderate yield (Scheme 2.2).



Scheme 2.2: Synthesis of malonate **353**.

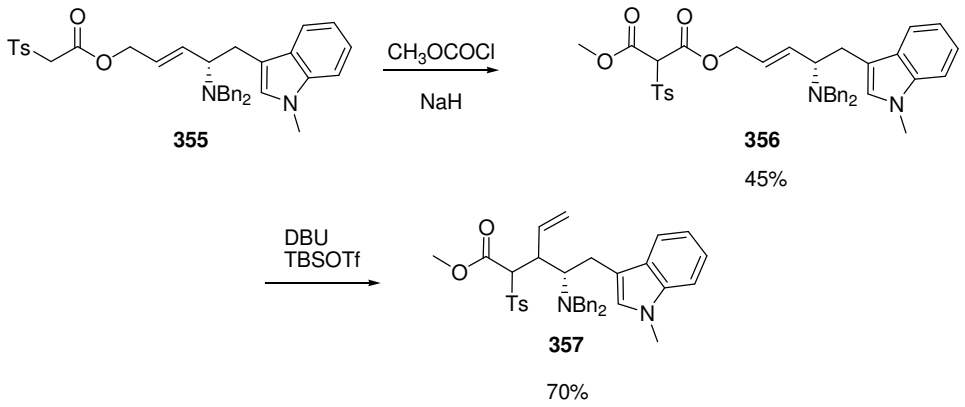
Malonate **353** underwent dCr reaction (discussed in detail on page 117) to give terminal olefin **354** regioselectively (Scheme 2.3). However, the desired dual-dCr rearrangement was not observed and thought to be inhibited by the electron-withdrawing, sterically demanding tosamide moiety next to the more substituted end of the diene.



Scheme 2.3: Regioselective dCr product **354**.

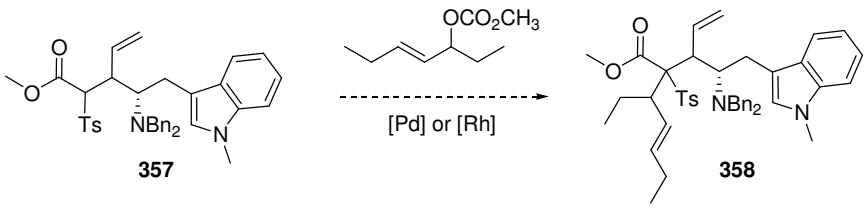
The analogous substrate possessing the less electron-withdrawing PMB moiety similarly gave only the mono-dCr product. It was therefore hypothesized that even the tosyl-protecting group might also be too electron-withdrawing and so both protecting groups were to be converted to furnish the corresponding chemically inert, electron-rich, dibenzyl amine. However, subsequent microwave-assisted dCr of the dibenzyl amine malonate failed to furnish the dual-dCr rearranged product. Installation of a second ester moiety at the α-tosyl position of malonate **355** simultaneously provided a more reactive dCr substrate and an activating group which it was hoped would enable incorporation of the second olefin α to the tosylate. In addition, this could potentially be used in chain homologation / piperidinium formation

required to form *cis*-bridged piperidine **3** at a later stage. Olefin **357** was subsequently obtained in a high yield under dCr conditions (Scheme 2.4).



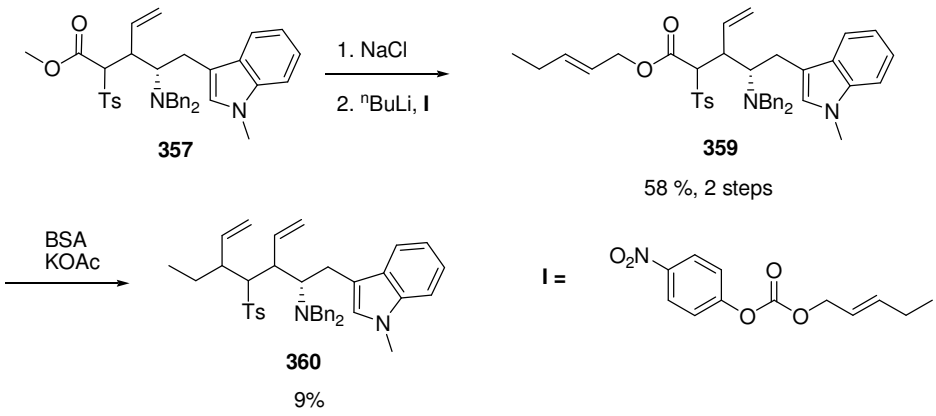
Scheme 2.4: Synthesis of **357**.

With mono-olefin **357** in hand, two strategies were investigated for the insertion of the second olefinic moiety (Scheme 2.5). π-Allyl palladium chemistry was to be employed as, besides being highly demanding, formation of a quaternary center with α-branching on two of the substituents would vastly simplify the final approach towards (–)-suaveoline.



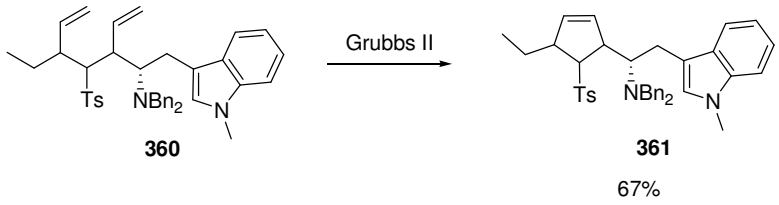
Scheme 2.5: Transition-metal approach.

The use of rhodium, as described by Evans[6], was also investigated for the required allylation reaction. Unfortunately, no product formation was observed using either palladium or rhodium catalysts. In addition to the unsuccessful transition-metal induced α-tosyl alkylation, transesterification of **357** proved equally disappointing. Therefore, removal of the methyl ester moiety was followed by ^{n}BuLi-induced deprotonation and carboxylation to give **359** (Scheme 2.6). Subsequent microwave-assisted dCr gave diene **360** in low yield, together with starting material **360**. Attempts to preserve the α-ester moiety in **360** by inhibiting the decarboxylation step proved ineffective.



Scheme 2.6: Stepwise access to 2nd dCr substrate.

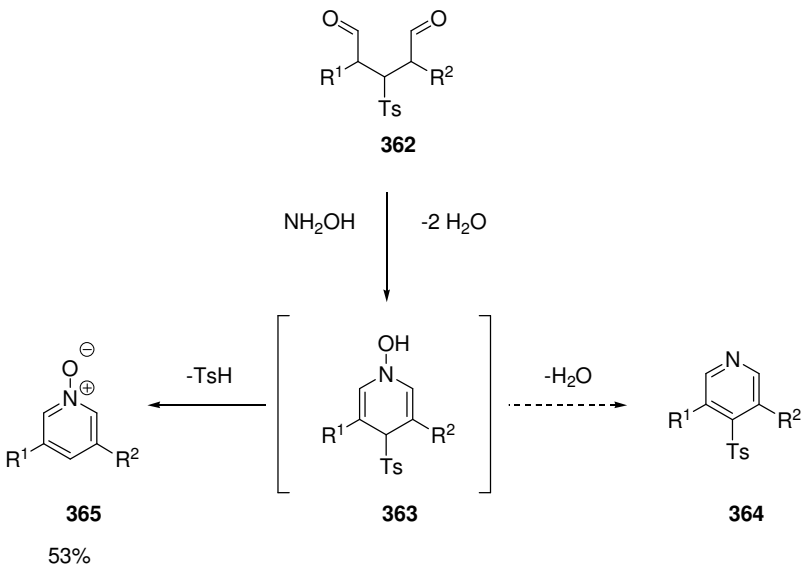
With the desired dual dCr product in hand, the following Grubbs II-mediated RCM met with little complications and the corresponding cyclopentene **361** was isolated in moderate yield (Scheme 2.7).



Scheme 2.7: RCM.

Attempts to alkylate the α-tosyl position proved unsuccessful. It was suggested that although formation of the anion was a viable process, alkylation at that same position with anything more sterically hindered than a proton was not and only epimerization was observed.[1] Furthermore, reductive α-desulfonylation followed by attempted *in situ* alkylation using a variety of electrophiles provided only α-desulfonylated product.

It was therefore necessary to find an alternative method for cyclopentene alkylation, and the use of tosyl pyridine *N*-oxide **365** was investigated (Scheme 2.8). It was thought that the 4-position of the pyridyl moiety would be susceptible to S_NAr reaction *via* a Birch intermediate[7] **363**, through reductive desulfonylation–alkylation. S_NAr reactions of 4-sulfonylpyridine **364** with cyanide are known.[8]

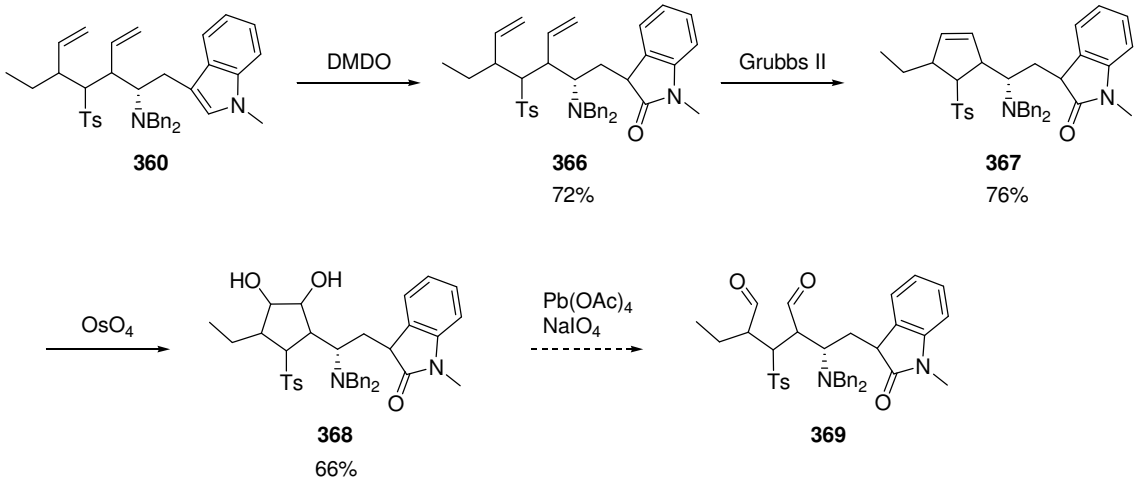


Scheme 2.8: Possible products from use of hydroxylamine.

Formation of a pyridine *N*-oxide model system showed loss of the C_4 tosyl-moiety, resulting in a 53 % yield of pyridine-*N*-oxide **365** ($R^{1,2}$ = H). A better leaving group at the *N*-position, formed by treating diketene with hydroxylamine-*O*-sulfonic acid was speculated to prevent the loss of the tosyl moiety, to no avail. However, selective C_4 functionalization of the pyridine-*N*-oxide **365** could still be achieved, as described by Saito[9i] and Taylor.[9ii]

Attempting to utilize the pyridine-*N*-oxide method in the total synthesis approach towards (–)-suaveoline required mild oxidative cleavage of the cyclopentene *via* the vicinal diol.[4] This is due to the oxidatively sensitive electron-rich indole 2,3-π system which undergoes facile cleavage, especially under ozonolytic conditions.[10] Several attempts to cleave the cyclopentene oxidatively *via* the vicinal diol proved unsuccessful.

The failure to dihydroxylate the cyclopentene was thought to be caused by competing oxidation of the indole, and therefore attempts were made to convert the electron-rich 2,3-π system into an oxindole (Scheme 2.9). Use of DMDO as reported by Zhang,[11] provided oxindole **366** in moderate yield. Subsequent RCM using Grubbs II catalyst gave cyclopentene **367** and OsO_4 mediated Upjohn dihydroxylation[12] provided the vicinal diol **368**. However, oxidative cleavage of the diol **368** did not result in the isolation of the corresponding dialdehyde **369** due to the instability of the latter. A similar result was observed when attempting direct ozonolytic cleavage of **367**. Although one-pot treatment of the crude dialdehyde mixture with $NH_2OH{\cdot}HCl$ gave some pyridine-*N*-oxide according to mass spectrometric analysis, no product was isolated.



360 → **366** (72%) → **367** (76%)

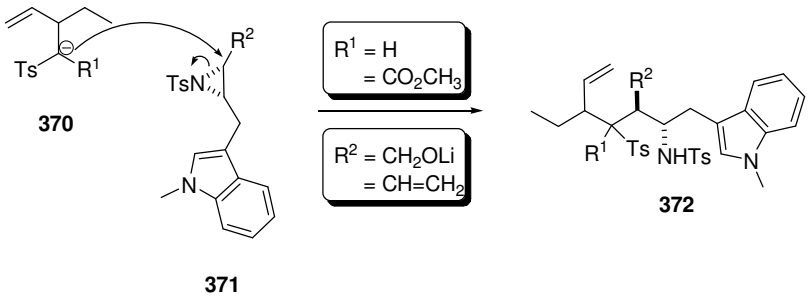
368 (66%) → **369**

Scheme 2.9: Oxidative cleavage of **367**.

2.1.2. Current Progress Towards (±)-Suaveoline

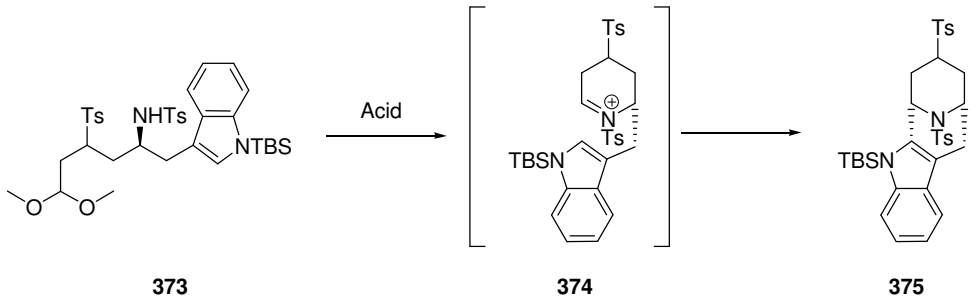
The retrosynthesis of (±)-suaveoline was based upon previous research involving attempts to facilitate a double intramolecular dCr, as discussed in section 2.1.1. Problems arose due to the application of a dual-dCr to a system which already contained a sterically demanding tosamide moiety positioned adjacent to a significantly electron-depleted alkene.[3]

In order to circumvent these chemically demanding rearrangements, the proposed key step in this project involved the installment of dCr adducts **370** as sulfone-stabilized anions, which nucleophilically ring-open *N*-sulfonylaziridines **371** (Scheme 2.10). Results from the alkylation of aziridines **371** with the nucleophiles of type **370** would then be assessed in order to identify the best outcome with respect to yield and regioselectivity. Recent studies[13,14] carried out in our group have shown that vinylaziridines related to **371** are attacked by sulfone-stabilized carbanions at the ring carbon adjacent to the double bond if the nucleophile is not excessively hindered. We interpret the observed selectivity in terms of selective weakening of the aziridine C–*N* bond proximal to the olefin by $\pi_{C=C} \rightarrow \sigma^*_{C-N}$ overlap.[15,16] Sterically more demanding nucleophiles were found to attack these vinyl aziridines at the terminus of the double bond, where this would be the case, utilizing the directing effect of the hydroxy moiety would ensure the correct regioselectivity through lithium chelation.[17]



Scheme 2.10: Sulfone-anion mediated *N*-sulfonylaziridine opening.

Retrosynthetic analysis revealed the synthesis of the characteristic azabicyclo [3.3.1] substructure in suaveoline **3**, prevalent in all ajmaline / sarpagine related alkaloids,[18] *via* pyridine C_4 side chain homologation (Scheme 2.11). Reducing the ester functionality at this newly expanded carbon chain to an aldehyde followed by acid treatment would trigger the formation of tetrahydropyridinium **374**, which in turn would undergo intramolecular Pictet–Spengler cyclization. Reactions of this type have been thoroughly investigated within our group and have been proven to be highly regio- and stereoselective.[4] In the example outlined below, deprotection of protected aldehyde **373** with an acid catalyst gave the tetrahydropyridinium intermediate **374**, which was converted spontaneously into **375** *via* Pictet–Spengler cyclization.



373 **374** **375**

Scheme 2.11: Lewis acid mediated Pictet–Spengler cyclization.

The proposed synthesis of the 3,4,5-trisubstituted pyridine motif in **3** involved our recently developed method for the synthesis of polysubstituted pyridines from dicarbonyls,[2] such as dialdehyde **377** (Figure 2.2). Obtaining this dialdehyde containing compound would either be achieved *via* oxidative cleavage of the corresponding terminal olefins (R^2 = $CH{=}CH_2$) or involve a combination of oxidative cleavage and alcohol oxidation (where R^1 = CH_2OH) depending on the type of aziridine used.

As stated earlier, adduct **378** would, be obtained by combination of lithiated dCr products **380** with the *N*-sulfonylaziridine **379**. Use of the less substituted congener would require an additional α-tosyl carboxylation step to ensure pyridine C_4 alkylation. Synthesis of the dCr products **380** would involve exposure of sulfonyl esters **382** to established dCr reaction conditions,[2] the synthesis of the requisite *N*-sulfonylaziridine electrophiles would start from *cis*-2-butene-1,4-diol **381**.[19]

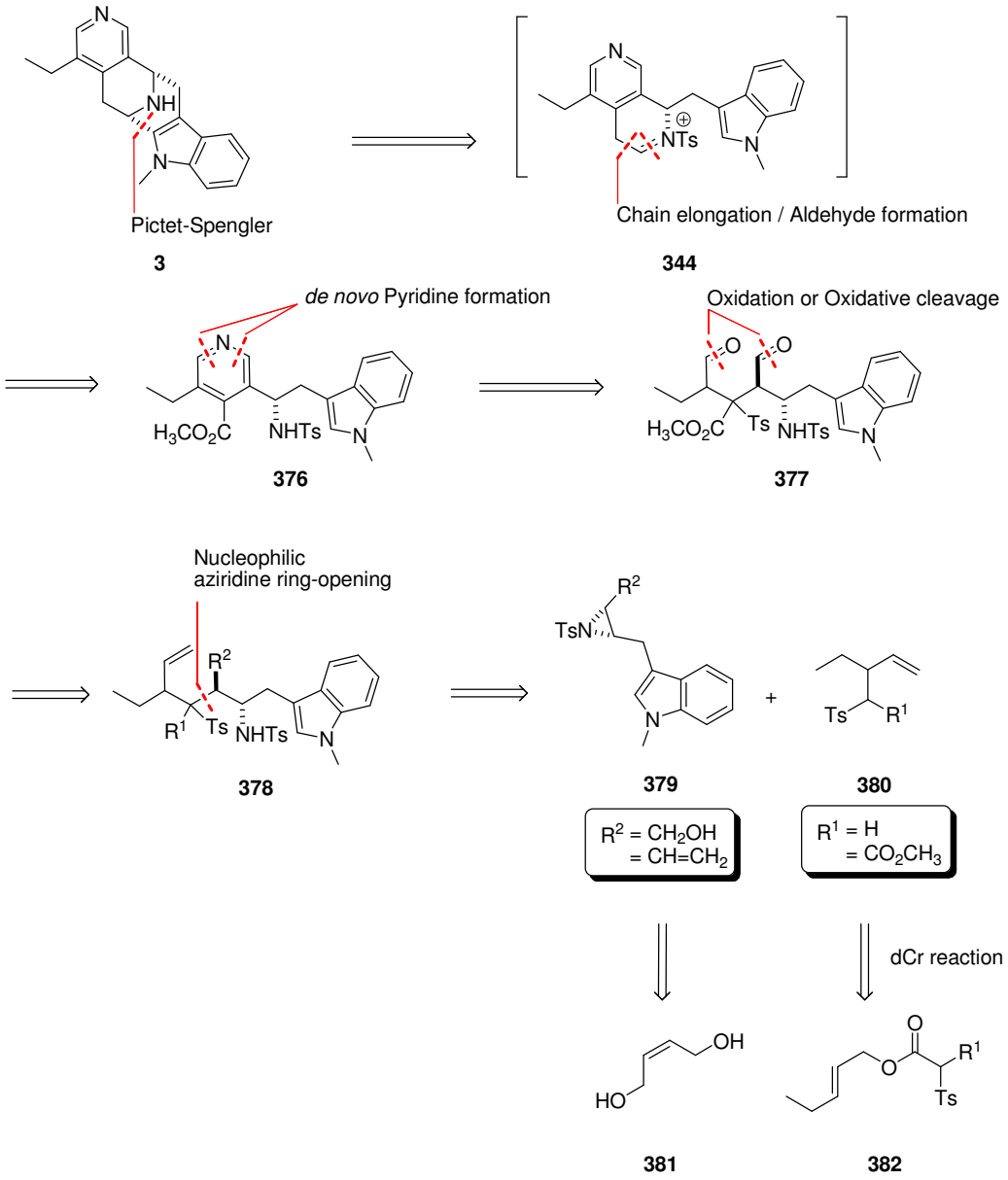
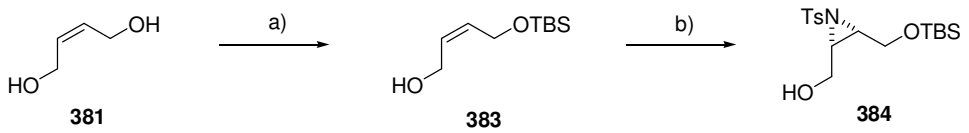


Figure 2.2: Retrosynthesis of (±)-suaveoline **3**.

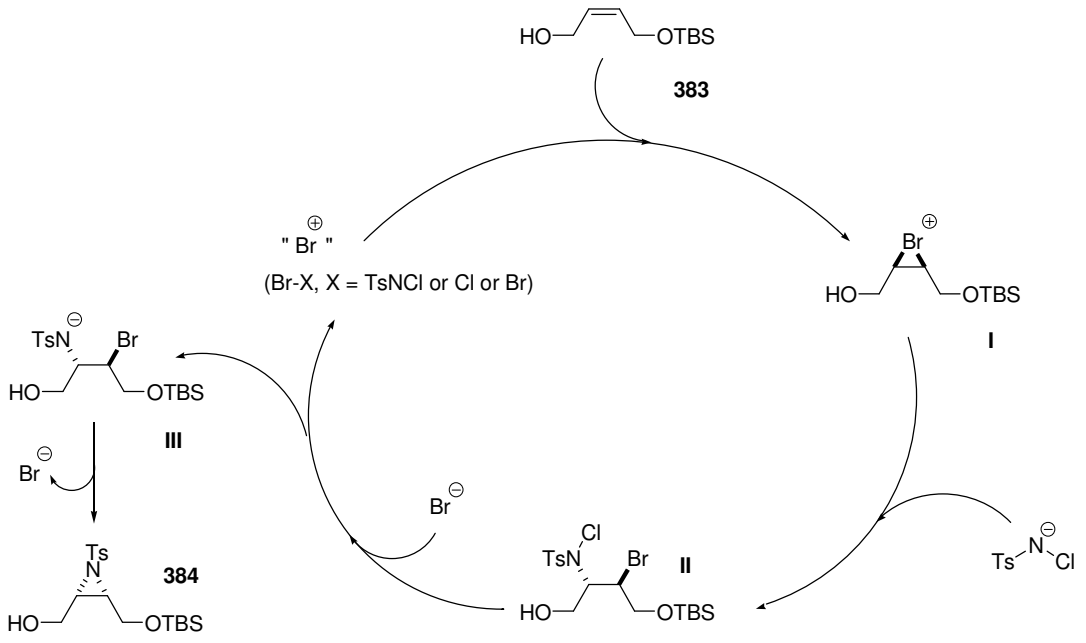
2.1.2.1. Preparation of Hydroxy Aziridine 388

The synthetic routes towards (±)-suaveoline and (±)-alstonerine were initiated by mono protection of *cis*-2-butene-1,4-diol **381** using TBSCl to give **383**. Subsequent hydroxy-assisted aziridination[20] of the alkene *via* the Sharpless method provided the corresponding hydroxy aziridine **384** (Scheme 2.12).



Scheme 2.12: a) i) NaH, THF, rt, 16 h; ii) TBSCl, rt, 15 min, 90%; b) Chloramine-T, PTAB, CH_3CN, rt, 72 h, 93%.

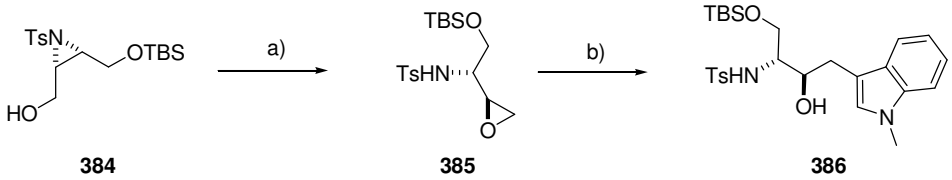
The proposed mechanism, depicted in Scheme 2.13, is initiated by insertion of a bromonium species following treatment of alkene **383** with PTAB to give **I**. Nucleophilic ring opening mediated by ionic chloramine-T results in formation of **II**, after which chloride displacement by either a bromide ion or another chloramine-T anion generates a Br–X species and forms **III**. Aziridine formation and subsequent bromide expulsion gives rise to **384** and a bromide ion which in turn can re-enter the catalytic cycle by regenerating a new Br–X species.



Scheme 2.13: Sharpless aziridination mechanism.

Following the Sharpless aziridination of **383** the corresponding epoxide **385** was obtained following a base-induced aza-Payne rearrangement (Scheme 2.14). Studies by Fuji *et al.*[21] have shown that NaH as well as KH can be used in order to trigger inversion of the configuration at the C_2 carbon *via* a S_N2 mechanism. Use of other bases such as ^nBuLi, LDA or DBU were ineffective. Furthermore, the substrate used needs to be an "activated" aziridine (such as the electronically deficient *N*-tosyl aziridine **384**) in order to facilitate this rearrangement due to failure when utilizing non-activating protecting groups. The solvent of choice was found to be THF, alternatives such as toluene, dimethoxyethane and DCM either would not facilitate complete product formation or required excessively long reaction times. The ideal temperature for complete aza-Payne rearrangement was determined to be between 0 °C and room temperature. Below 0 °C the equilibrium is pushed towards the aziridine due to the fact that the aza-anion formed after rearrangement is slightly higher in energy when compared to its oxa-counterpart.[21]

Lewis-acid mediated Friedel–Crafts type alkylation of *N*-methylindole using epoxide **385**[19] resulted in the formation of indolic amino-alcohol **386** in a moderate yield of 50%.



384 **385** **386**

Scheme 2.14: a) NaH, THF, 0 °C, 4 h, 93%; b) *N*-methyl indole, anh. $NaHCO_3$, $BF_3{\cdot}Et_2O$, DCM, rt, 16 h, 50%.

Ring-opening of epoxides using indoles and pyrroles has been reported using different methods such as acid catalysis,[22] application of high pressure,[23] lanthanides[24] and HBF_4-SiO_2.[25] The yields reported are usually unsatisfactory, especially with aliphatic epoxides.

Due to the low yield of the initial nucleophilic ring-opening of epoxide **385**, attempts were made to optimize this reaction (Table 2.1) using different "mild" Lewis acids.

Table 2.1: Lewis acid mediated Friedel–Crafts indole alkylation.

Entry	Lewis Acid	Conditions	Yield
1	$Yb(OTf)_3$	DCE, 1.5 M, rt, 2.5 h	0%
2	$Yb(OTf)_3$	DCE, 1.5 M, μW, 80 °C, 2 x 0.5 h	0%
3	$Yb(OTf)_3$	DCE, 1.5 M, μW, 100 °C, 2 x 0.5 h	0%
4	$In(OTf)_3$	DCE, 1.5 M, rt, 16 h	0%
5	$In(OTf)_3$	DCE, 1.5 M, μW, 100 °C, 2 x 0.5 h	0%
6	$Cu(BF_4)_2$	DCM, 1.0 M, rt, 16 h	65%
7	$Cu(BF_4)_2$	DCM, 1.0 M, μW, 80 °C, 2 x 0.5 h	84%
8	$ZnCl_2$	DCM, 1.0 M, rt, 16 h	66%
9	$ZnCl_2$	DCM, 1.0 M, μW, 80 °C, 2 x 0.5 h	92%

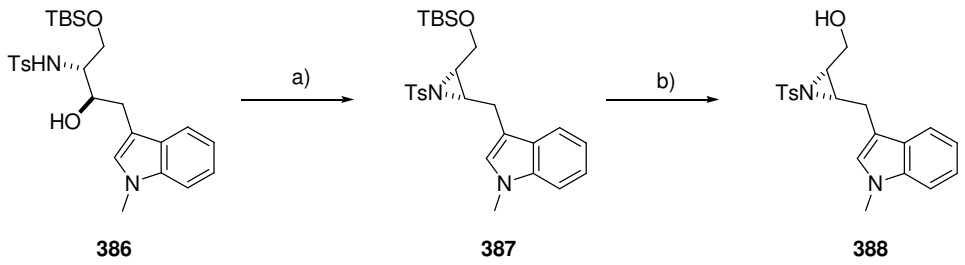
Although rare, the use of lanthanides as Lewis acids in epoxide ring-opening reactions has been documented.[23] Ytterbium (III) is reported to facilitate epoxide ring-opening when using primary amines, resulting in high yields of aminoalcohols.[23] Applying ytterbium (III) to a mixture of our epoxide **385** and *N*-methylindole at rt in DCE (to increase overall solubility) did not yield any product (entry 1, 2 and 3). Umani-Ronchi[26] reported that indium (III), facilitated Friedel–Crafts type addition of indole to optically active styrene oxide. Various mild Lewis acids were applied, giving the following order of reactivity: In (III) > Zn (II) > BF_3 > Sc (III) > Cu (II). Indium (III) was found to be the most reactive without significant erosion of *ee*. Application of indium (III) to our structurally more complex epoxide **385** in combination with the less reactive *N*-methylindole resulted in the recovery of starting material (entry 4 and 5).

Despite being reported to be less reactive than indium (III) in promoting Friedel–Crafts-type addition of indole to 2-phenyloxirane, the use of zinc (II)[27] and copper (II)[28] gave promising results. Consumption of starting material was observed together with product formation (entry 6). No further conversion was detected after 16 hours and attempts to further increase the consumption of starting material resulted in application of the microwave[29] (entry 7). High yields of the amino alcohol **386** were obtained when applying the microwave irradiation at

10 mol% catalyst loading, but the use of increased catalyst loadings did not improve the overall conversion. Friedel–Crafts addition of *N*-methylindole to epoxide **385** using sub-stoichiometirc zinc(II) chloride gave amino alcohol **386** in 92% yield (entry 9). No ring-opening of the epoxide by chloride nor any other side products were observed; this clean method seems limited only by the size of the microwave reactor.

Due to the restriction on reaction scale imposed by use of the microwave, several attempts to optimize the initial BF_3-mediated reaction were investigated concurrently with the screen of alternative Lewis acidic additives. Earlier results had shown that reaction at rt reached completion within 30 min, and it was considered that this rapid formation and subsequent decomposition of material was likely to be reduced by lowering the reaction temperature. It was hoped that slowing the reaction down would subsequently inhibit the decomposition. Lowering the temperature to –40 °C gave an increase in isolated product while the reaction time slowed down to 2.5 h. A further decrease in temperature to –78 °C showed total conversion of starting material **385** to amine alcohol **386** with no sign of decomposition with the reaction reaching completion after 4 h (95% yield). Large scale reactions (17 g-scale) could be carried out without erosion of the yield, this in combination with the high increase in yield (50% → 95%) turned this reaction from being a chocking-point into a very successful indole-mediated epoxide alkylation.

Mitsunobu-type reaction conditions were applied in order to facilitate ring closure of amino-alcohol adduct **386**, resulting in formation of aziridine **387** (Scheme 2.15). Subsequent fluoride-mediated desilylation using TBAF resulted in an 80% yield of hydroxy aziridine **388**.[19]



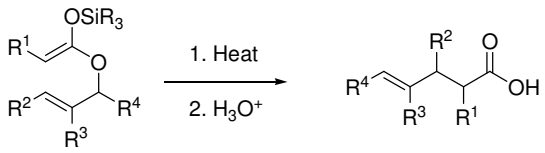
386 **387** **388**

Scheme 2.15: a) DIAD, PPh_3, THF, rt, 1 h, 86%; b) TBAF, THF, 0 °C, 15 min, 80%.

2.1.2.2. Decarboxylative Claisen Rearrangement

The discovery of the Claisen rearrangement[30] in 1912 provided a new chemical tool to generate highly stereoselective products *via* [3,3]-sigmatropic rearrangements. Its frequent use is due to various factors, such as the ease of substrate synthesis, high levels of stereoselectivity based on well-established trends, compatibility with a wide range of functionalities and the ability to form new carbon–carbon bonds with regioselective transposition from simple derivatives of alcohol precursors.[31]

Various adaptations of this type of rearrangement have been developed, further enhancing it as a powerful carbon–carbon bond-forming tool in organic synthesis. One of these adaptations is the Ireland–Claisen rearrangement (Scheme 2.16)[32] in which silyl ketene acetals **389** derived from allylic carboxylic esters yield carboxylic acids **390** upon hydrolysis of the initial silyl ester products.



389 **390**

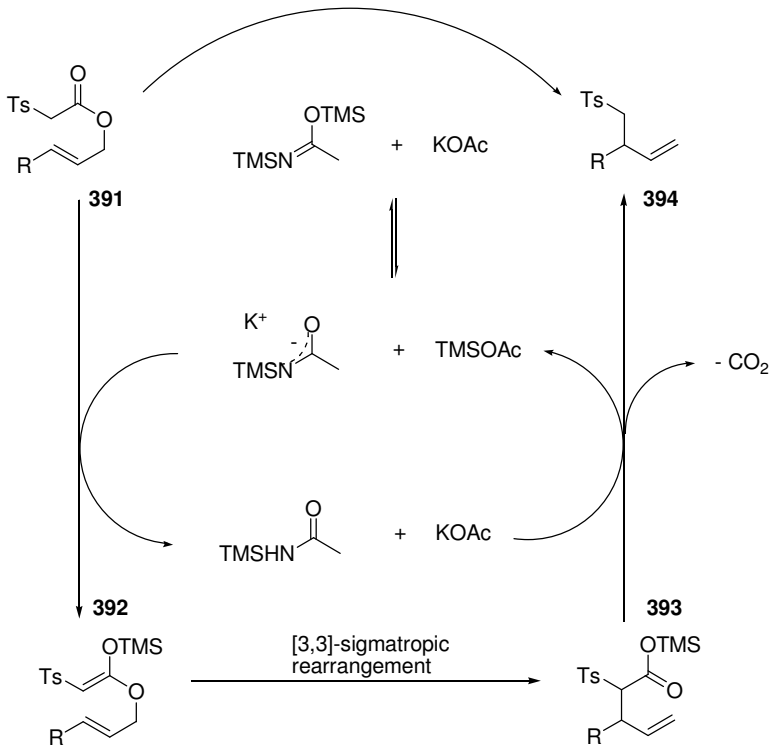
Scheme 2.16: The Ireland–Claisen rearrangement

The failure in our own laboratory of Ireland–Claisen type rearrangements previously reported by Davidson and co-workers, involving tosylacetate substrates, lithium diisopropylamide and chlorosilanes resulted in the development of milder conditions in which a weak base and a silylating agent were used.[2(i)] This provided an intermediate silyl ketene acetal which underwent [3,3] sigmatropic rearrangement followed by spontaneous decarboxylation, leading to the term decarboxylative Claisen rearrangement (dCr).

Over time several important features of the dCr reaction have become apparent; the tolerance towards oxygen and nitrogen substituents, provided that they are fully masked; complete regioselectivity; transformation takes place regardless of the substrate structure (ester derived from primary or secondary alcohols), and irrespective of the level of substitution on the olefinic carbon.[2(iv)]

The proposed mechanism for the dCr reaction (Scheme 2.17) starts with the reversible combination of KOAc and BSA to give the conjugate base of *N*-trimethylsilylacetamide and

TMSOAc. Deprotonation of **391** by the former results in enolate formation, which is silylated to generate the silyl ketene acetal **392** and potassium acetate. [3,3] Sigmatropic rearrangement of **392** yields the γ,δ unsaturated silyl ester **393**, followed by reversible desilylation mediated by the acetate ion which regenerates TMSOAc. Spontaneous decarboxylation of the desilylated product gives the conjugate base of **394** which abstracts a proton from *N*-trimethylsilylacetamide formed in the initial deprotonation. The regenerated conjugate base of *N*-trimethylsilylacetamide re-enters the cycle, thus generating new nucleophilic enolates.[2 (iv)]



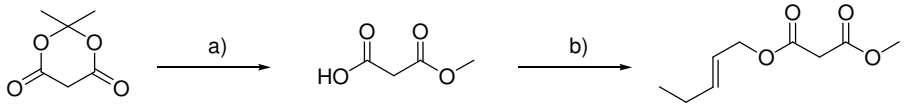
Scheme 2.17: Proposed mechanism of the dCr.

Support for the proposed mechanism was provided by the following observations:[2(i)] heating of toluene solutions of substrate with potassium acetate alone led to full recovery of starting material; substitution of BSA with other silylating agents, such as TMSOAc, TMSOTMS or $(TMS)_2NH$, likewise resulted in complete starting material recovery. Reactions in which KOAc was substituted with TEA, DBU or pyrrolidine together with BSA resulted in rearrangement not decarboxylation, giving carboxylic acid products. Treatment of the substrate with BSA alone in toluene at reflux likewise resulted in the formation of rearranged product, which again did not decarboxylate. This indicated the key, catalytic role of the acetate ion in the silyl transfer step.

Finally, exposure to a mixture of ^{t}BuLi, *N*-trimethylacetamide and TMSOAc gave a moderate yield of dCr product, and when ^{t}BuLi was substituted with KH the same result was observed.

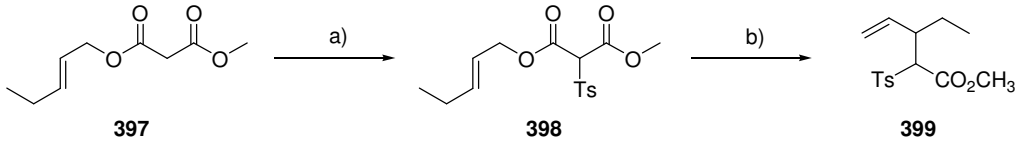
These results suggesting that despite the key catalytic role it fulfills, the mode of generation of acetate ion is of less importance.

The synthesis of malonate **397** was initiated by treating Meldrum's acid **395** with methanol at reflux, to yield methyl malonate **396** quantitatively (Scheme 2.18). Esterification of **396** using a standard DCC / DMAP condensation reaction with *trans*-2-penten-1-ol gave compound **397**.



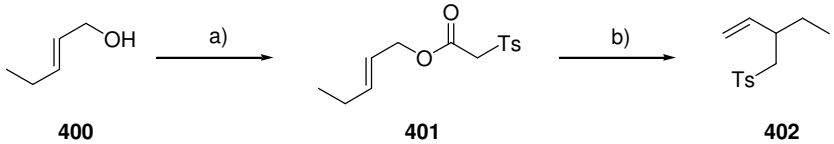
Scheme 2.18: a) CH_3OH, Δ, 16 h, 92%; b) *trans*-2-penten-1-ol, DCC, DMAP, DCM, rt, 16h, 65%.

Subsequent tosylation using ^{t}BuOK–TsF in DMSO gave **398**. Four equivalents of the anion of **397** were generally required to gain acceptable levels of conversion; unconsumed malonate was usually recovered in good yields. Exposing **398** to dCr reaction conditions gave in modest yield the product of formal regiospecific allylation of methyl tosylacetate **399** [2(ii)] (Scheme 2.19).



Scheme 2.19: a) ^{t}BuOK, TsF, DMSO, rt, 16h, 64%; b) DBU, TBDMSOTf, DCM, rt, 1.5h, 64%.

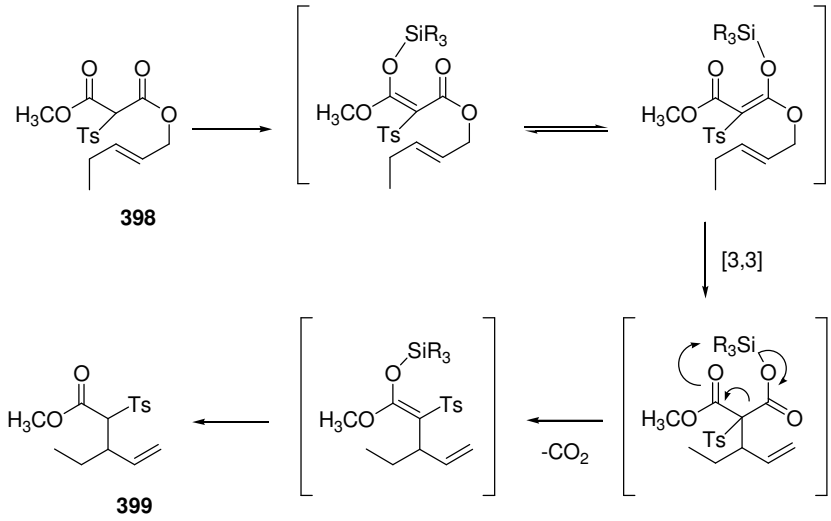
The tosylacetate ester **401** was prepared in a similar manner, by DCC / DMAP-mediated esterification of commercially available tosyl acetic acid with allyl alcohol. Exposure of **401** to dCr reaction conditions gave **402** in good yield (Scheme 2.20).



Scheme 2.20: a) DCC, DMAP, tosyl acetic acid, DCM, rt, 16 h, 92%; b) BSA, KOAc, toluene, Δ, 16 h, 91%.

As discussed earlier, the dCr reaction was attempted using DBU and TBDMSOTf (as in the case of formation of **399**). However, this did not result in any product formation and clean starting material **401** was recovered (Scheme 2.21). Therefore the original dCr procedure was used, involving BSA as the silylating agent and KOAc as the base.[2 (i)] The inability of the DBU–TBDMSOTf procedure to successfully rearrange **401** to **402**, when compared to BSA–KOAc, is because acetate ion is required in order to facilitate the silyl transfer step, resulting

in decarboxylation of **401**.[2(i)] However, when using DBU in the dCr of **398** an alternative dCr mechanism becomes apparent (Scheme 33), which does not require acetate assisted desilylation-decarboxylation. In this case, after [3,3]-sigmatropic rearrangement, decarboxylation is achieved *via* silatropic rearrangement in a formal retro-ene reaction.[2(iv)]



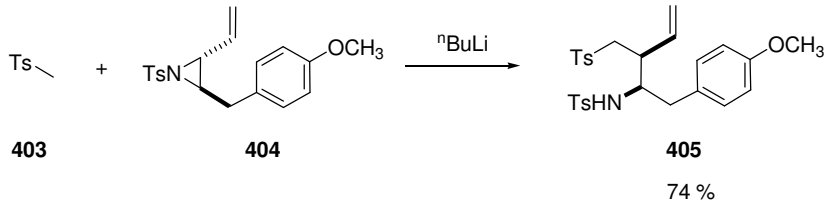
Scheme 2.21: Proposed alternative dCr reaction.

Alternatively, treating **402** with 2 equivalents of ^{n}BuLi followed by methyl formate treatment provided **399** in a high (81%) yield. Excess base is needed due to the high acidity of the newly formed α-proton in **399**, which results in the consumption of one equivalent of additional base in the carboxylation reaction.

2.1.2.3. Regioselective Ring-Opening of Aziridines

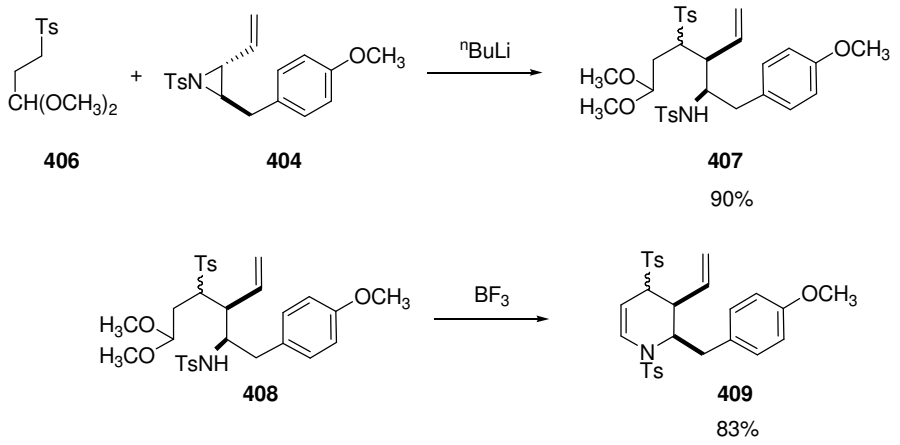
Aziridines are invaluable intermediates for nitrogen-containing molecules and have become increasingly popular in recent decades with respect to their use as building blocks in synthetic chemistry,[33,34] especially for nitrogen-containing bioactive natural compounds.[35] Regioselective ring-opening depends on the nature of both the aziridine and incoming nucleophile. In general, 1,2-disubstituted aziridines mirror similarly substituted epoxides, in that they suffer attack at the less substituted end. Where both carbon atoms are substituted, competing steric and electronic effects may be such that regioselectivity of nucleophilic ring-opening is eroded. For example, this changes when the C–*N* bonds are polarized unequally, thus favoring one over the other by the increased formation of a positive charge at the more substituted carbon atom.[16] It is widely accepted that aziridines containing an electron-withdrawing group at the *N*-position, such as sulfonyl, phosphoryl and carbonyl, are more reactive with regard to ring-opening than their *N*-alkyl or *N*-unsubstituted counterparts.[36]

Previous studies have demonstrated regioselective ring-opening of 1,2,3-trisubstituted aziridines by use of sulfone-stabilized carbanions using both terminal lithiated methylhydroxy and vinyl moieties at the ring carbon adjacent to the double bond if the nucleophile is not excessively hindered.[14,16,17] For example, initial test reactions with (2*R*,3*R*) aziridine **404** and the lithio anion of **403** gave a single regioselective product **405** (Scheme 2.22).[16]



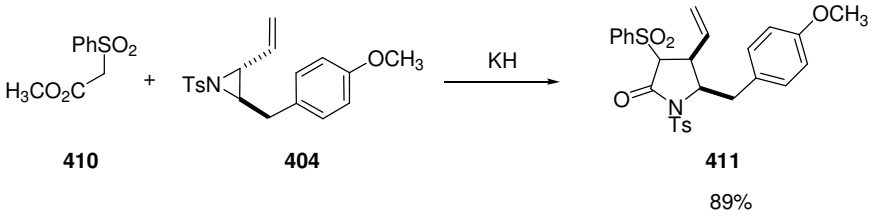
Scheme 2.22: Regioselective sulfone-aziridine ring-opening.

In a similar fashion, the conjugate base of acetal **406** gave a single regioisomer which could be cyclized into tetrahydropyridine **409** upon treatment with BF_3 (Scheme 2.23).[37]



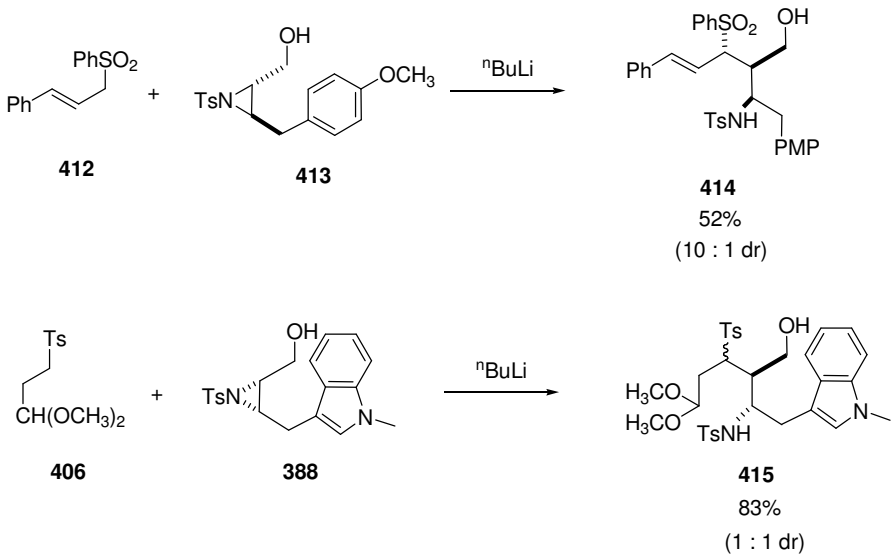
Scheme 2.23: Regioselective opening of sulfone-aziridine **404** with acetal **406**, and subsequent cyclization.

More complex sulfone-stabilized anions showed a similar trend upon exposure to comparable reaction conditions. Treatment of methyl 2-phenylsulfonylacetate **410** with KH formed the potassium enolate of **410**. Upon nucleophilic aziridine ring-opening of **404** at the less hindered carbon, γ-lactam **411** was isolated following *in situ* cyclization (Scheme 2.24).[16]



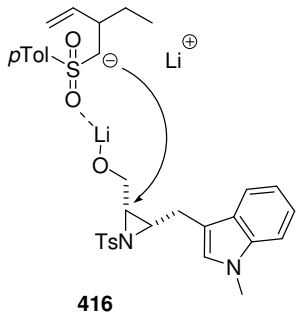
Scheme 2.24: KH induced γ-lactam formation.

These results show a powerful directing effect of the vinyl moiety towards regioselective aziridine ring-opening. This may be attributed to selective weakening of the aziridine C–*N* bond proximal to the olefin by $\pi_{C-C} \rightarrow \sigma^*_{C-N}$ overlap. Exposure of vinyl aziridines to organomagnesium[38] and organocopper[39] reagents predominantly give the S_N2' products, as do the more sterically hindered organolithium reagents.[16] In addition, ring-opening experiments were carried out using both hydroxy aziridine **413** and **388** in order to probe regioselectivity. Exposure of these hydroxyaziridines to the lithio-anions of **412** and **406** gave the corresponding regiochemical adducts **414** and **415**. It seems likely that the lithiated oxygen moiety interacts with both the electrophile and the nucleophile, thus directing the incoming nucleophile towards the proximal aziridine carbon (Scheme 2.25).[15,16] Protection of the hydroxy moiety by MOM gave a mixture of regioisomers as expected, further supporting this assumption.



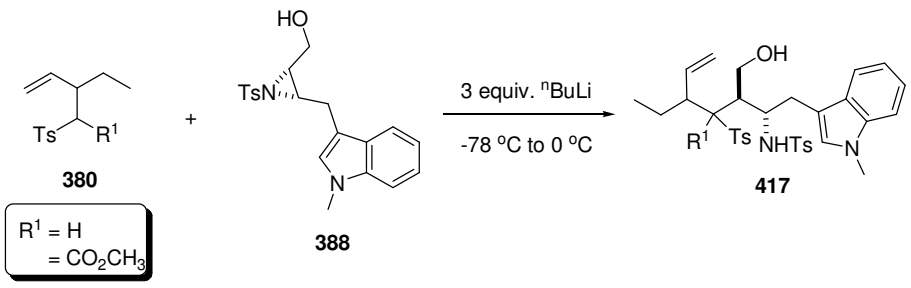
Scheme 2.25: Regioselective sulfone-aziridine opening using sulfone-anions of **412** and **406**.

Alkylation reactions[40,41] of this type have been known to work by deprotonating the α-acidic proton of sulfone-anions with ^{n}BuLi prior to addition to the *O*-lithiated hydroxyaziridine. As discussed earlier, lithium-chelation control should enable correct regioselectivity regarding the aziridine ring-opening (Scheme 2.26). When considering lithium chelation between the *N*-aziridine hydroxy and sulfone-stabilized anion intermolecular ring-opening at the less hindered carbon is induced as illustrated in model **416**.



Scheme 2.26: Sulfone-anion mediated opening of hydroxy-aziridine.

Following the successful preparation of dCr adducts **380** and indolic hydroxy aziridine **388**, attempts to regioselectively ring-open **388** to provide **417** were investigated (Scheme 2.27).



Scheme 2.27: Sulfone-anion mediated aziridine ring-opening reactions.

Experiments involving the nucleophilic ring-opening of aziridine **388** with the sulfone-stabilized lithio-enolate of **380** ($R^1 = CO_2CH_3$) did not result in the formation of the desired product **417**. The prospect of producing a quaternary center, together with the high level of steric interference already present within this nucleophile might have proved too demanding for reaction of the subsequent lithio-enolate.

In light of the unsuccessful attempts described above, application of the lower homologue to the nucleophilic ring-opening of aziridinol **388** was investigated ($R^1 = H$). As stated earlier, the use of secondary sulfone-stabilized lithio-anions in aziridine ring-opening reactions proven had to be reliable.[16] Addition of ^{n}BuLi to **380** ($R^1 = H$) showed an immediate colour change, which has previously been reported as evidence for the formation of the sulfone-stabilized lithio-anion.[13,14] However, in none of the experiments was the aziridine ring-opened product **417** obtained, or consumption of hydroxyaziridine **388** observed. TMEDA, a well known ^{n}BuLi co-solvent responsible for increasing the nucleophilicity of lithio-anions by complexation with the lithium counter-ion, was also used, yet proved equally unsuccessful. Increased concentrations, variations of temperature, reversal of addition, application of ^{n}BuLi to both reagents and use of an excess of ^{n}BuLi all failed to contribute to the formation of **417**. Interestingly no consumption of hydroxyaziridine nor the sulfone-stabilized anion was observed.

Use of 1,10-phenanthroline[42] (^{n}BuLi indicator) did detect an excess of ^{n}BuLi in the reaction mixture. The carbanion used simply did not seem to be sufficiently nucleophilic to react with the *N*-sulfonyl activated aziridine.

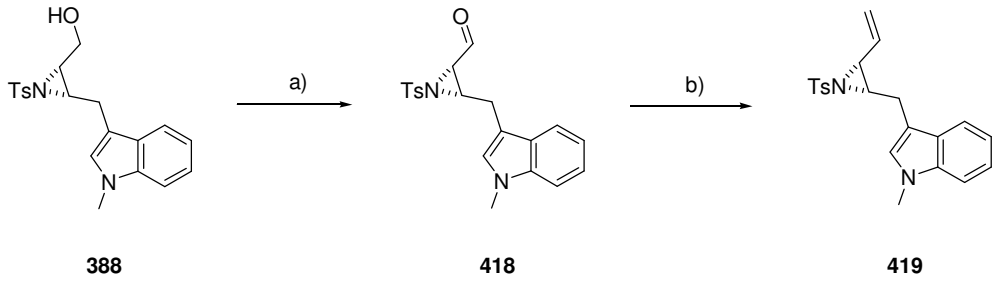
More demanding reaction conditions were therefore required in order to facilitate the ring-opening of aziridine **388**. It was thought that conversion of the hydroxy moiety into the

corresponding terminal olefin, as suggested in the retrosynthesis, would allow harsher reaction conditions to be employed without risk of aza-Payne rearrangement (occurs at rt when utilizing ^{n}Buli and 0 ^{o}C for NaH).

2.1.2.4. Towards Vinylogous Aziridine 419

Conversion of alcohol **388** into the corresponding olefinic aziridine **419** could be achieved by conversion of the alcohol into the aldehyde followed by Wittig olefination.[43] Prolonged exposure to air resulted in extensive decomposition of the unstable aldehyde, and therefore the oxidation method used had to deliver a quantitative yield of the aldehyde following facile work-up.

From four different oxidation techniques, IBX, Dess–Martin, Parikh–Doering and Swern oxidation, IBX was selected due to its ease of application and subsequent work-up in combination with a high yield of crude aldehyde **418** (Scheme 2.28).

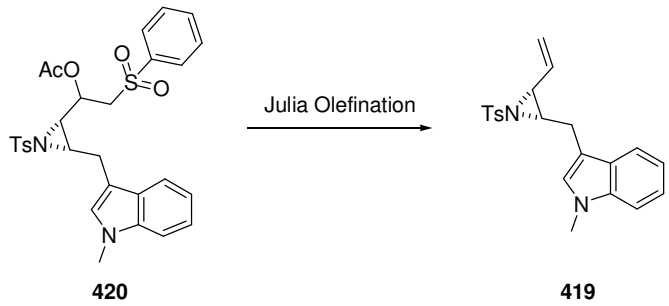


388 **418** **419**

Scheme 2.28: a) IBX, DMSO, rt,16 h, 75%; b) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, rt, 1.5 h, 12%.

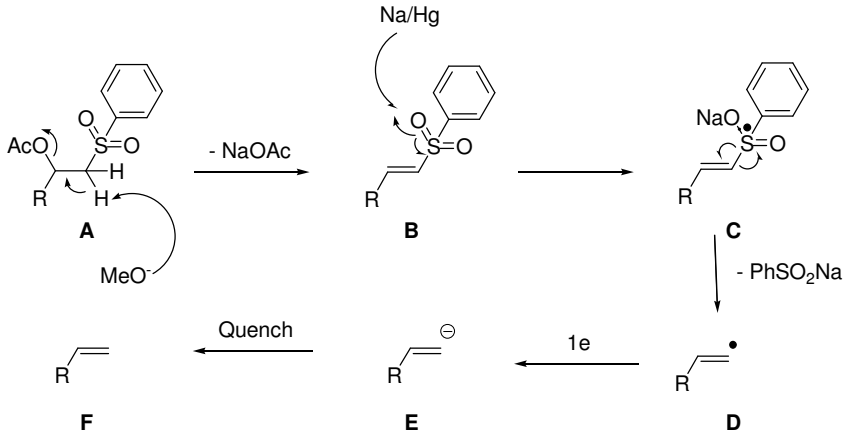
Subsequent olefination of the aldehyde using the Wittig reaction[43] gave **419** in low yield on a small scale but decreased even more dramatically when on a larger scale with the olefin being isolated in only 12% yield[13,44] in contrast to earlier results published by Hyland.[14] Changes in the phosphonium species (iodide instead of bromide) and the base used to generate methylenetriphenylphosphorane (commercially available sodium hexadimethylsilazide was more concentrated than the potassium analogue: 2 M vs 0.1 M) did not increase the yield.[44] These conversions had already been described by previous group members who had shown the ready decomposition of α,β-aziridinoaldehydes to give complex mixtures.[16]

Alternative pathways for the synthesis of the vinyl aziridine **419** using hydroxy aziridine **388** were therefore investigated. It was considered that Julia–Lythgoe olefination could provide the vinyl aziridine **419** *via* sulfone-aziridine acetate **420** (Scheme 2.29).



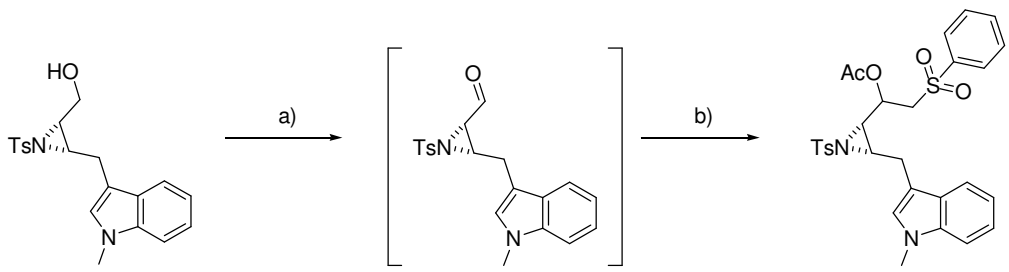
Scheme 2.29: Proposed Julia–Lythgoe olefination of **420**.

The Julia–Lythgoe olefination incorporates the use of methanol and sodium amalgam in order to facilitate the formation of an alkene.[45] This procedure was first reported by Julia[46] in 1973 and has since proven to be a valuable tool in the synthesis of alkenes. In most cases sodium phosphate buffers are used in order to control the pH of the reaction and prevent any unwanted alkoxide-induced side-reactions from taking place.[47] The reaction is believed to be initiated by the formation of methoxide, from reaction of sodium and methanol (Scheme 2.30). Deprotonation at the α-carbon to the sulfone in **A** results in alkene formation and acetate expulsion to give **B**. A radical reaction then reduces the vinyl sulfone to a vinyl radical **D** and subsequent single electron donation gives the ionic species **E** with sodium acting as the counterion. Quenching of the ionic species finally results in formation of the desired terminal olefin **F**.



Scheme 2.30: Julia-Lythgoe mechanism.

Synthesis of **420** from **388** involved use of IBX oxidation to give the aldehyde **418** (Scheme 2.31). Nucleophilic attack of the lithio-anion of methyl phenyl sulfone at the aldehyde and subsequent acetic anhydride quench of the oxanion adduct gave **420**.

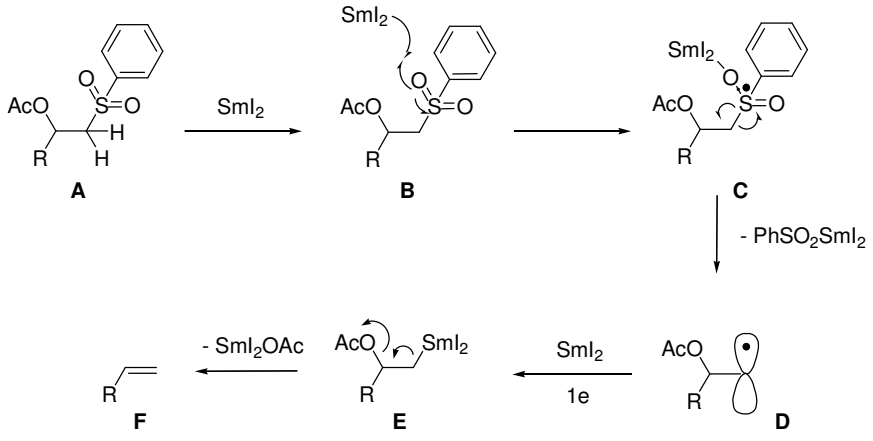


388 **418** **420**

Scheme 2.31: a) IBX, DMSO, rt, 16 h; b) i) Phenylsulfonyl methane, ^{n}BuLi, THF, –78 °C → –40 °C, over 3 h; ii) Ac_2O, rt, 15 min, 74%.

Julia olefination of **420** using the classic Na/Hg reagent would inevitably produce a methoxide-mediated aziridine ring-opened side product. This in combination with the use of substantial amounts of mercury severely limited this conversion. On the other hand, Julia olefination mediated by SmI_2[47] provided an attractive alternative, since no alkoxides are involved, thereby providing a different pathway compared to sodium amalgam (Scheme 2.32).

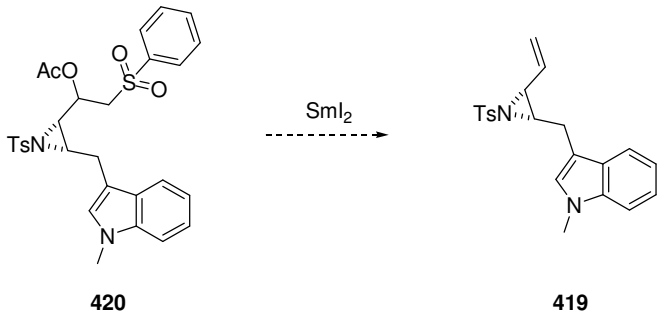
This pathway is initiated by a radical reaction at the aromatic sulfone **A**. This is followed by expulsion of the phenylsulfinate ion, resulting in formation of alkyl radical **D**. Donation of a second electron from SmI_2 to radical **D** then affords the intermediate organosamarium derivate **E**, which undergoes β-elimination to yield the olefin **F.**



Scheme 2.32: Alternative Julia–Lythgoe mechanism.

Use of freshly prepared SmI_2 was vital to the success of this reaction and therefore was prepared *in situ*.[48] Addition of HMPA or DMPU has commonly been reported to increase the overall reactivity of the reagent in these processes.[49]

Experiments involving **420**, SmI_2 and DMPU did not result in any product formation and only starting material was observed (Scheme 2.33).

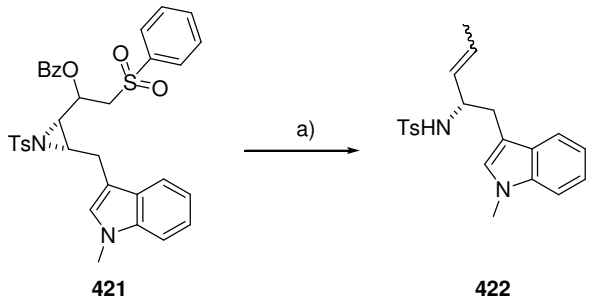


420 **419**

Scheme 2.33: SmI_2 mediated Julia olefination attempt.

During the experiment a color change was observed from purple to grey indicating decomposition of the SmI_2 reagent.

Examples of both acetate and benzoate esters used in the Julia olefination are known in the literature.[50] Using a similar reaction pattern to that of the Julia acetate substrate, but quenching the sulfone-alkoxide intermediate with benzoyl chloride instead of acetic anhydride, resulted in formation of the benzoate ester in 40% yield. Subsequent experiments involving **421**, SmI_2 and DMPU resulted in formation of **422** (Scheme 2.34).

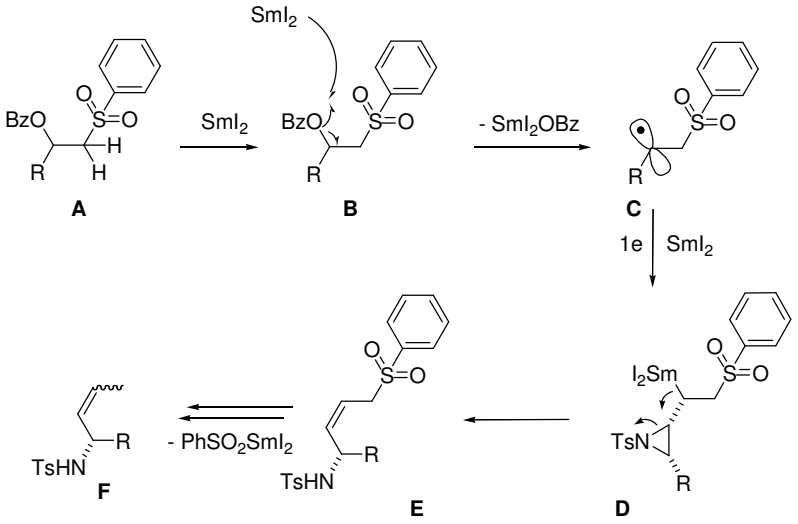


421 **422**

Scheme 2.34: a) SmI_2, DMPU, THF, rt, 30 min, 40%.

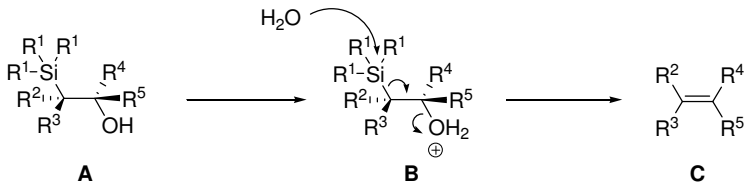
An explanation for the formation of this unusual side-product can be found when examining the radical reaction involved. Markó reported a similar observation when using β-benzyloxy sulfone esters instead of the corresponding β-hydroxy sulfones.[51] He reported a change in mechanism when applying the SmI_2 protocol to benzyloxy containing compounds (Scheme 2.35). When applying this protocol to benzyloxy sulfone ester **A**, single electron transfer takes place at the benzoate moiety **B**. A process described as being much easier and taking place

very rapidly even at very low temperatures (–84 °C), when compared to the β-hydroxy sulfones. Expulsion of the benzoate to give **C**, followed by donation of a second electron from SmI_2 to radical **C** then affords the intermediate organosamarium derivate **D**, which undergoes elimination towards the tosyl-activated aziridine. Subsequent removal of the aromatic sulfone in **E** takes place as described earlier and ultimately results in the formation of olefin **F.**



Scheme 2.35: Alternative Julia–Lythgoe mechanism.

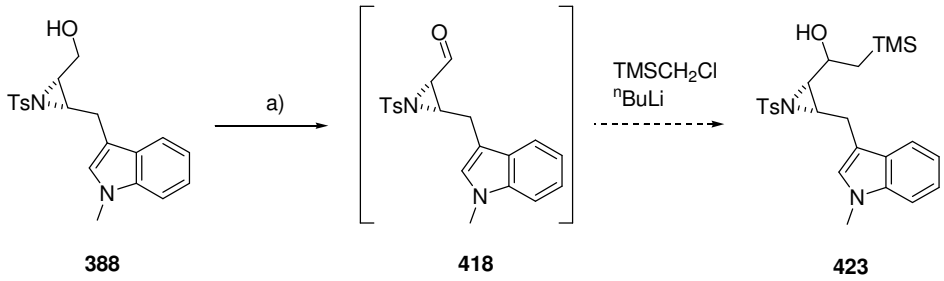
A different olefination reaction, the Peterson reaction[52] (Scheme 2.36), was investigated in order to gain access to vinyl aziridine **419**. The intermediate β-hydroxy silane **A** can be isolated from the corresponding aldehyde, and the subsequent Peterson elimination step, can be performed separately. Both acid and base conditions can be used to trigger the elimination step, yet the outcome results in different stereoisomers. In our case, base was believed to lead to aza-Payne rearrangement prior to elimination and thus was not an option. Aqueous acid treatment of the hydroxysilane would trigger a similar β-elimination to that described for the Julia–Lythgoe olefination and should result in the formation of olefin **C**.



Scheme 2.36: Acid-induced Peterson olefination.

Attempts to isolate Peterson precursor **423** proved unsuccessful due to the unstable nature of the product (Scheme 2.37). An one-pot strategy towards vinyl aziridine **419** involved

exposing crude **423** to acid, to no effect and only decomposition was observed. Further investigations into this type of olefination reaction were abandoned.

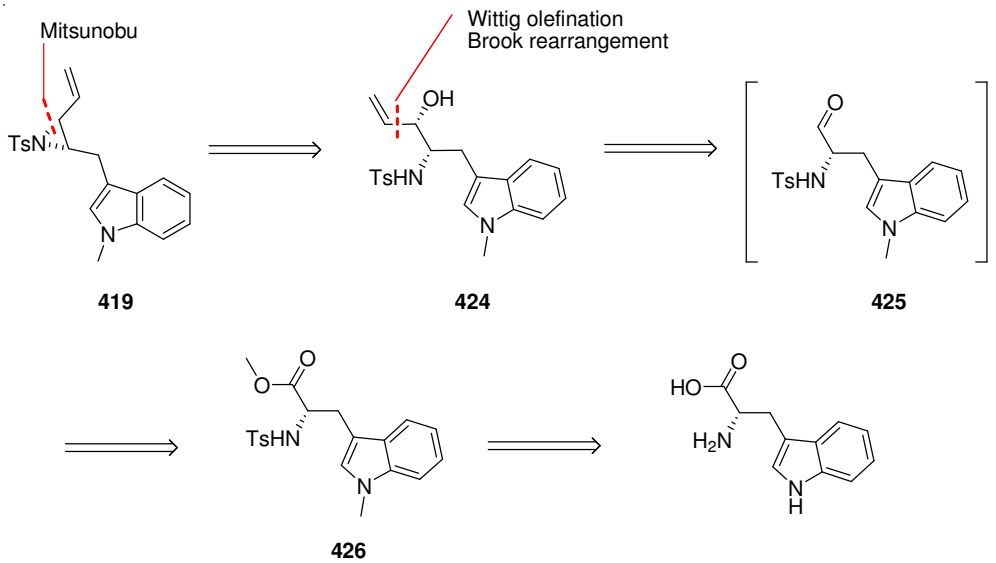


388 **418** **423**

Scheme 2.37: a) IBX, DMSO, rt, 16 h.

2.1.2.5. Tryptophan-Based Approach Towards 419

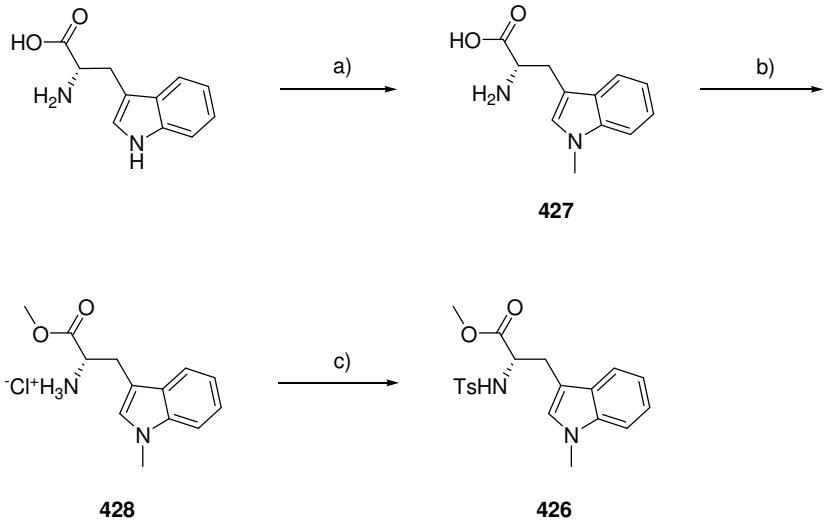
All α,β-aziridinoaldehyde-based olefination approaches had proven to be unsuccessful in providing the vinyl aziridine, and a major factor had been the instability of the aldehyde involved.[16] Therefore, a new strategy using L-tryptophan was proposed. In this strategy, we envisaged the successful synthesis of vinyl aziridine **419** by application of the Mitsunobu condensation of tosylamino-alcohol **424** (Figure 2.3). This compound would be constructed using a Wittig reaction followed by an *in situ* Brook rearrangement[53] to give the corresponding *syn*-vinylogous hydroxy-amine **424** upon desilylation. Direct addition of vinyl Grignard to **425** was suspected to provide a mixture of *syn*- / *anti*-vinylogous **424**. Synthesis of the presumed unstable aldehyde **425** would involve selective DIBAL ester reduction of the fully protected L-tryptophan derivative **426**.



419 **424** **425** **426**

Figure 2.3: Revised synthesis of vinyl aziridine **419**.

Attempts to optimize the full protection of L-tryptophan had already been thoroughly investigated by previous group members Ioannidis and Rahn.[54] Methylation of the indole amine was achieved by use of $NaNH_2$–CH_3I in liquid ammonia (Scheme 2.38). Initial addition of excess CH_3I severely complicated the work-up of the reaction and proved to be unnecessary. Equally, a decrease in reaction concentration from 0.5 M to 0.1 M further increased the yield and simplified the purification of the product considerably. Esterification of the *N*-methylindole **427** with methanol in the presence of $SOCl_2$ afforded **428** and was followed by N_4-tosylation to furnish **426** as reported.[54]

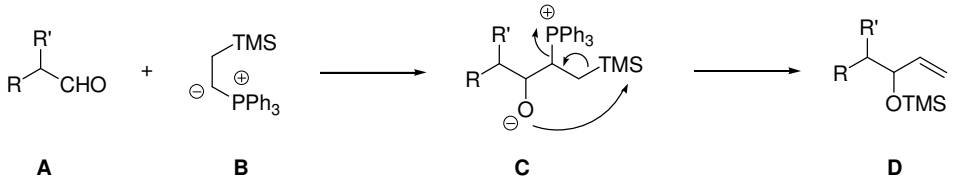


Scheme 2.38: a) CH_3I, cat. $FeCl_3$, NH_3, –78 °C, 5 h, 91 %; b) $SOCl_2$, CH_3OH, Δ, 4 h, 99 %; c) TsCl, TEA, DCM, rt, 16 h, 80%.

Synthesis of *syn*-vinylogous amino alcohol **424** was more desirable as earlier investigations using similar systems revealed the difficulty of ring-opening *trans*-vinyl aziridines, with a preference for S_N2' at the vinyl-position instead. When comparing both conformations of *cis*- and *trans*-vinyl aziridines, it becomes obvious that the *cis*-product is more strained due to steric hindrance at both aziridine positions, making it more susceptible to ring-opening. In contrast the *trans*-isomer is less constrained and as a result far less reactive.[13]

Depending on the stability of aldehyde **425**, DIBAL reduction of ester **426** would either be exposed immediately to the Wittig reaction and Brook rearrangement or, purified prior to exposure. The application of the required Wittig reagent has been reported by Taddei *et al*,[53] whereby simple α-amino aldehydes are used in order to obtain high quantities of *syn*-

vinylogous amino alcohols in a Cram-selective fashion. Based upon the work of Tokoroyama,[55] β-silylphosphorous ylides **B** prepared *in situ* react with α-alkyl- or α-alkoxy aldehydes **A** to give the vinylogous products **D** *via* silyl group migration towards the oxygen with expulsion of triphenylphosphine (**C**) (Scheme 2.39).



Scheme 2.39: Wittig reaction followed by Brook rearrangement.

The transition state during these reactions favors chelation-controlled *si* attack (Figure 2.4). In the same article a substantial reduction of selectivity was observed when using compounds with a trisubstituted amine in which case undesired *re* attack is significantly increased (Figure 2.4).[53,55]

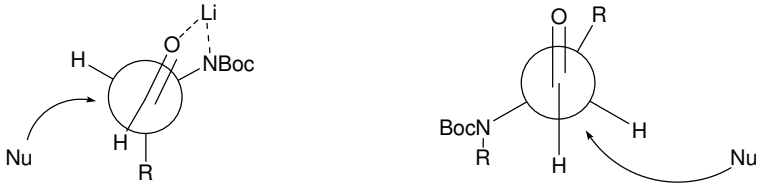
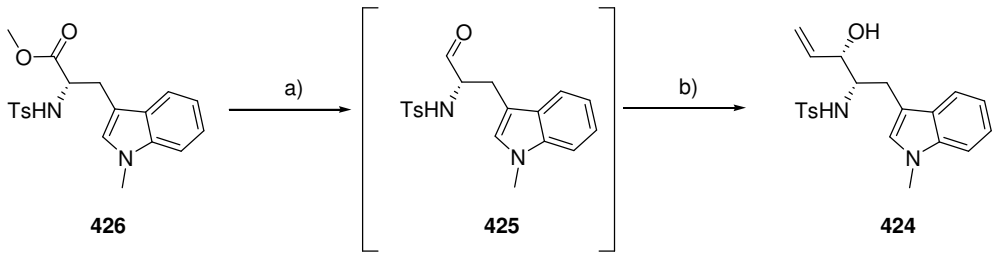


Figure 2.4: Chelation control, *si* versus non-chelation control, *re* attack.

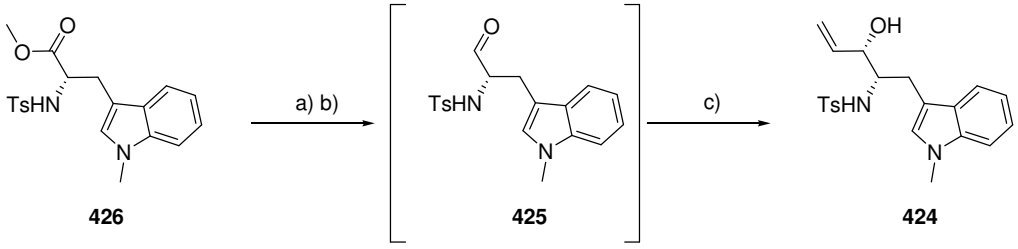
Optimization of the *in situ* ester reduction followed by the one pot Wittig / Brook rearrangement proved to be impossible (Scheme 2.40). Over-reduction of **426** by DIBAL to the corresponding alcohol (80% yield) severely hampered the reaction. Lowering the amount of the reducing agent to one equivalents from two equivalents did not result in any aldehyde **425** formation at –78 ^{o}C, instead resulting in partial alcohol formation as soon as the temperature reached –40 ^{o}C. In order to circumvent this problem, a new route was proposed which involved the re-oxidation of the alcohol to aldehyde **425** prior to the Wittig treatment.



426 **425** **424**

Scheme 2.40: a) DIBAL, THF, 0 °C, 30 min; b) i) $Ph_3P{=}CHCH_2Si(CH_3)_3$, ^{n}BuLi, THF, –78 °C; ii) TBAF, THF, rt, 30 min, 23% (3 steps).

Although the reduction of ester **426** to the corresponding alcohol was achieved in high yield using $LiAlH_4$, aldehyde **425** proved to be unstable during work-up and would start to readily decompose, resulting in a low yield (Scheme 2.41). Although NMR analysis showed complete selectivity towards the *syn*-diastereomer of the alcohol this route was deemed unviable due to the low yield of **424**.

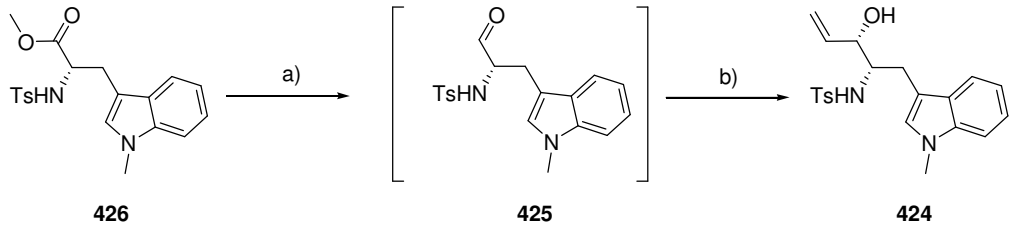


426 **425** **424**

Scheme 2.41: a) $LiAlH_4$, THF, 0 °C, 16 h, 80%; b) IBX, DMSO, rt, 16 h, 95%; c) i) $Ph_3P{=}CHCH_2Si(CH_3)_3$, ^{n}BuLi, THF; ii) TBAF, THF, rt, 30 min, 33% (2 steps).

An article by Jurczak *et al.*[56] reports a DIBAL reduction of an *N*-monoprotected α-amino ester followed by *in situ* treatment with vinyl Grignard to obtain the corresponding vinylogous amino alcohol. Initial reactions involving the addition of vinyl Grignard to amino aldehydes at room temperature showed moderate selectivity (3 : 2) towards the *syn*-product. Reduction of the temperature to –78 °C showed a preference towards *anti* (30 : 70). As in the case of the Wittig / Brook protocol, the same Cram chelation-control model is proposed. A similar preference for *syn*-selectivity was observed by Ibuka,[57] and this was ascribed to the enhanced chelation of the aldehyde by aluminium (ratio *syn* : *anti* 90 : 10). Both groups reported problems regarding the reproducibility of the yields involved (30 – 50%).

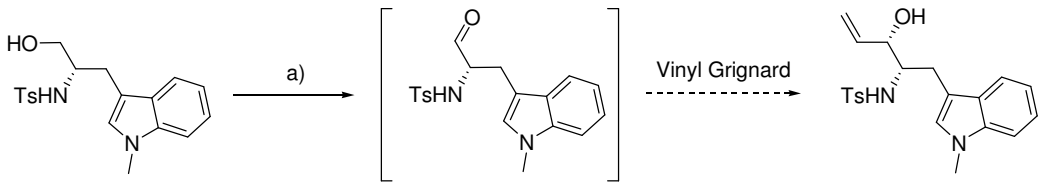
When using this protocol for the olefination of **425**, a mixture of both diastereomers of **424** (41%; 80 : 20 in favor of *syn*) together with the corresponding alcohol of **426** (40%) was obtained. Attempts to optimize this reaction failed to give increased yield or selectivity (Scheme 2.42).



426 **425** **424**

Scheme 2.42: a) DIBAL, THF, 0 °C; b) vinyl Grignard, THF, 0 °C → rt, 2 h, 41% (2 steps).

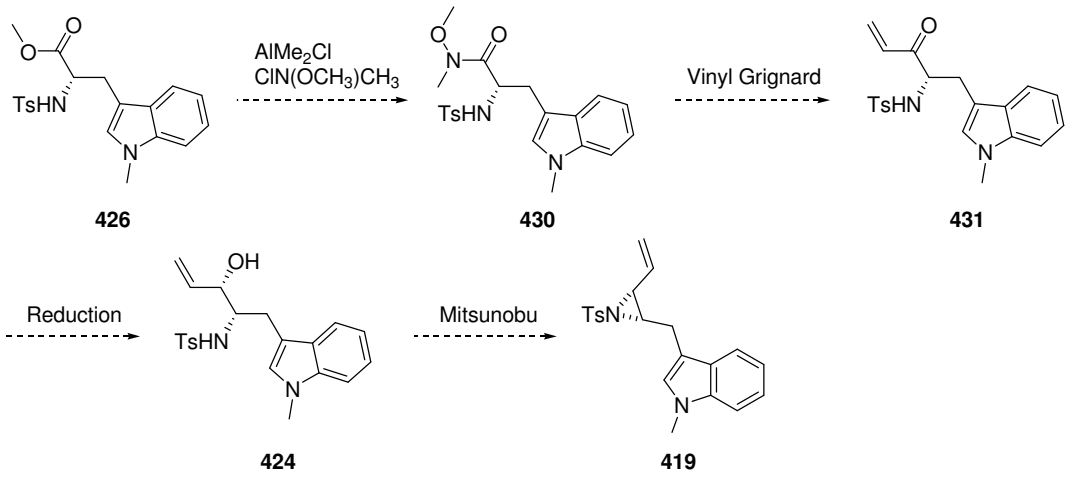
In a similar article by Ali,[58] using the Ireland–Norbeck protocol,[59] Swern oxidation of an α-amino alcohol was followed by *in situ* treatment with vinyl Grignard to give the corresponding vinylogous *syn*-α-amino alcohol as a single isomer. However, applying the same oxidation protocol to our amino alcohol **429** followed by vinyl Grignard treatment resulted in complete decomposition (Scheme 2.43).



429 **425** **424**

Scheme 2.43: a) IBX, DMSO, rt, 16 h.

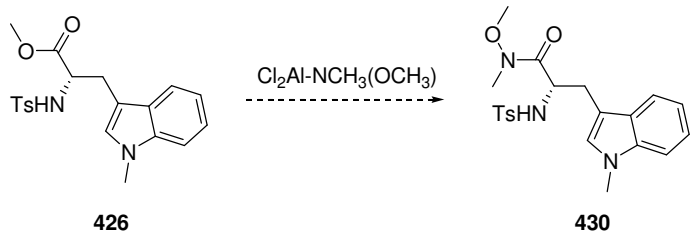
As conversion of ester **426** into the corresponding vinylogous amino alcohol **424** *via* aldehyde **425** had been unsuccessful, we envisaged an alternative route from **426** which would include the use of Weinreb amide **430** (Scheme 2.44). Treatment with vinyl Grignard would result in the formation of vinyl ketone **431**,[60] which *via* selective reduction of the vinyl ketone to the *syn*-amino alcohol **424**, followed by Mitsunobu condensation would provide diastereoselective vinyl aziridine **419**.



Scheme 2.44: Anticipated route towards vinyl aziridine **419**.

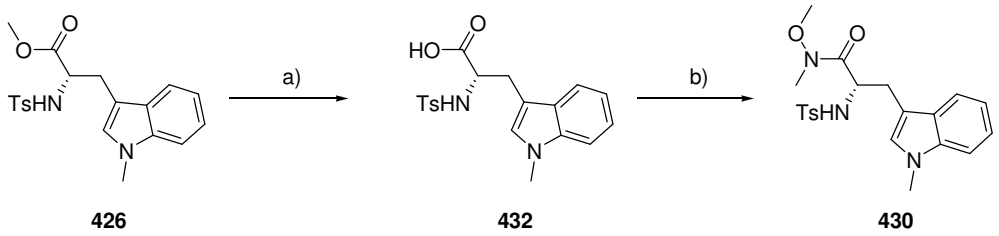
Following the original Weinreb amide synthesis route using amidation of a carboxylic acid with the hydrochloric salt of (methoxy)methyl amine, an alternative was reported by Shimizu[61] using Me_2AlCl. While this procedure, using Me_2AlCl, had already been reported by Weinreb, Shimizu observed unsatisfactory results in the case of sterically crowded lactones. The reactive species formed *in situ* during this process is $Cl_2Al\text{-}NCH_3(OCH_3)$ with the evolution of two equivalents of methane using 2–5 equivalents of the aluminium source. A number of variations have since been reported, all using strong Lewis acid / nucleophilic reagents such as $(OCH_3)NCH_3\text{-}MgCl$[62] and $(OCH_3)NCH_3\text{-}SnCl$.[63]

Application of the Shimizu protocol to our ester **426** did not provide the corresponding Weinreb amide **430**, with decomposition being observed. Failure of this reaction might be due to the presence of a tosamide moiety in close proximity to the carbonyl group (Scheme 2.45).



Scheme 2.45: Application of Shimizu protocol to **426**.

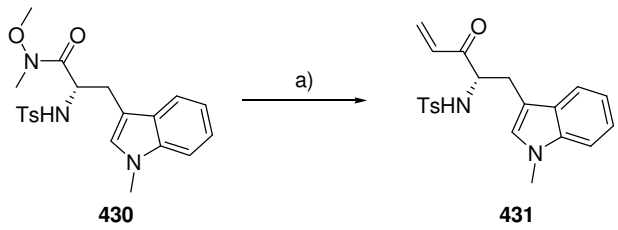
Synthesis of the Weinreb amide was achieved by saponification of ester **426** with LiOH, followed by amidation using a peptide coupling agent and the hydrochloride salt of (methoxy)methyl amine (Scheme 2.46). Use of EDCI as the coupling agent led to moderate conversion of carboxylic acid **432**; changing the coupling agent to DIC in combination with TEA and a catalytic amount of DMAP increased the yield to 95% of Weinreb amide **430**.



426 **432** **430**

Scheme 2.46: a) LiOH, DME, H_2O, rt, 2 h, 95%; b) (Methoxy)methyl amine, DIC, DMAP, TEA, DCM, rt, 16 h, 95%.

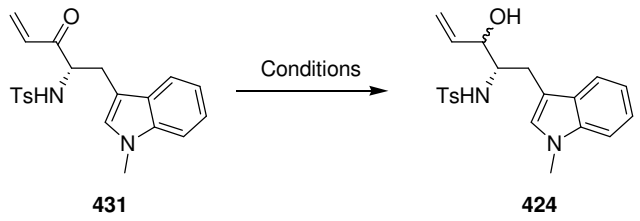
Exposure of the Weinreb amide **430** to vinyl Grignard gave the corresponding vinyl ketone **431** after acidic work-up (Scheme 2.47).[60] With the vinyl ketone in hand, subsequent selective reduction experiments were carried out in order to generate the desired *syn*-stereoselective vinylogous amino alcohol.



430 **431**

Scheme 2.47: a) Vinyl Grignard, THF, rt , 16 h, 95%.

Several methods for the stereoselective reduction of ketones into alcohols have been reported in the literature. A selection was made and applied to our vinyl ketone **431**; the results are collected in Table 2.2.



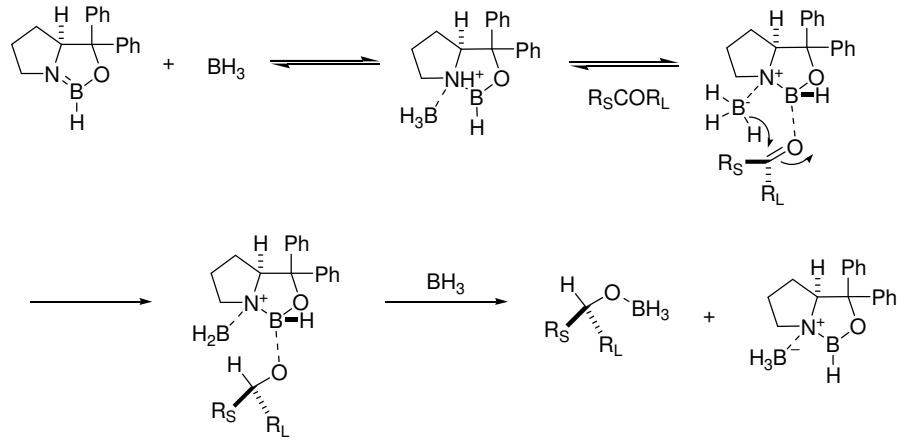
431 **424**

Scheme 2.48 and **Table 2.2**. Attempts to stereoselectively reduce ketone **431** to amino alcohol **424**.

Entry	Conditions	Ratio (*syn* : *anti*)	Yield
1	$CeCl_3$ / $NaBH_4$, rt, 5 min	1 : 1	95%
2	CBS / BH_3·THF, rt, 16 h	n / a	SM
3	$TiCl_4$ / BH_3·pyridine, –78 °C, 2 h	n / a	Decomposition
4	Selectride / $CeCl_3$, –78 °C, 2 h	n / a	Decomposition
5	$NaBH_4$ / LiCl, rt, 5 min	1 : 1	80%
6	$LiBH_4$, rt, 30 min	1 : 1	90%
7	$Zn(BH_4)_2$, rt, 16 h	n / a	SM
8	DIBAL, –78 °C → rt, 30 min	1 : 2.8	96%

The Luche reduction has been reported by Spaltenstein[64] to give the vinylogous *syn*-α-amino alcohol with moderate stereoselectivity when applied to its vinylogous ketone counterpart (3 : 1, *syn* : *anti)*. While this method can be applied without the requirement for moisture / air exclusion and includes easy work-up, high yields and fast reaction times, no selectivity was observed either at rt or at T = –78 °C (entry 1).

Stereoselective reduction of vinylogous alcohols has been thoroughly described by Corey *et al*.[65] and has led to the development of the Corey–Bakshi–Shibata catalyst.
Prepared *in situ* from (*S*)-diphenylprolinol and BH_3·THF, the CBS catalyst is reported to react rapidly with a large variety of ketones, with easy recovery of the dipenylprolinol ligand. The method uses very low catalyst loadings (typical 0.6 equivalents BH_3 : 0.05 equivalents diphenylprolinol) (Scheme 2.49).



Scheme 2.49: CBS-catalyst activation and mechanism.

Surprisingly, the CBS catalyst proved to be inert (entry 2). In order to ascertain the quality of our catalyst, a small test reaction was conducted with cyclohexanone which showed rapid reduction to cyclohexanol.

Marcantoni[66] published an article describing the use of $TiCl_4$ / BH_3 and $LiEt_3BH$ (L-selectride) / $CeCl_3$ on α-alkyl-β-keto sulfones. While the strongly chelating $TiCl_4$ was reported to lead to the *syn*-product, application of L-selectride / $CeCl_3$ protocol showed a strong preference for the Felkin–Ahn model resulting in *anti*-formation. It is unclear whether cerium, as stated by the author, is non-chelating.[66] Use of both methods resulted in decomposition, probably due to the harsh reaction conditions employed in these reductions (entry 3 and 4).

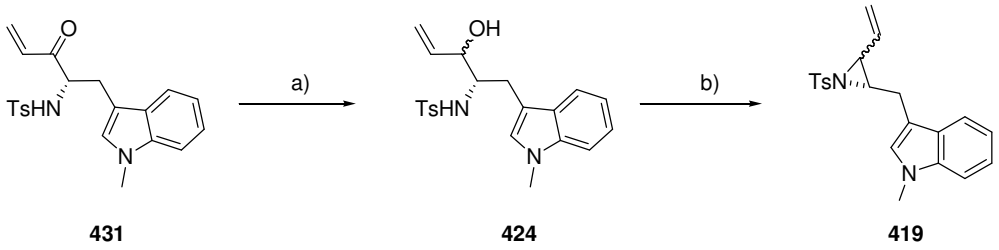
Hoping to induce some form of metal-chelation control, and thus a more stereoselective outcome, application of $NaBH_4$ and $LiBH_4$ was proposed. In both cases no stereoselectivity was observed, yet use of $LiBH_4$ in contrast to $NaBH_4$ / LiCl took considerably longer (entry 5 and 6).

Narasimhan[67] reported the use of $Zn(BH_4)_2$ in reducing carboxylic acids to their corresponding alcohols. Experiments involving this reagent did not give the vinyl ketone, and further attempts were aborted (entry 7).

As a last attempt to facilitate stereoselective ketone reduction, the use of DIBAL was proposed. Katsumura[68] reported a 14 : 1 *anti* : *syn* ratio when applying DIBAL to his vinyl

ketone. Interestingly we observed a significantly lower stereoselectivity, though still in favor of the *anti*-product (1 : 2.8, *syn* : *anti*, entry 8).

Previous research had shown a lack of reactivity when using *trans*-vinyl aziridines in combination with sulfone-anions.[13] The different composition of vinylaziridine **419** in regard to earlier aziridine substrates would hopefully prove to increase general reactivity. Therefore, use of a $CeCl_3$ / $NaBH_4$ procedure, incorporating an easy work-up and robust application was used in the reduction of vinyl ketone **431** into diastereomeric vinyl amino alcohol **424**. A high yield of the aforementioned racemate was obtained (Scheme 2.50). Subsequent Mitsunobu reaction gave a 1 : 1 mixture of *cis* and *trans* vinyl aziridines **419**. Separation of the diastereomers of **424** had previously been described by S. Carballares in which he utilized TBSCl, significantly improving separation by column chromatography.[13] However, no attempt to separate the aziridine mixture was undertaken in this report.

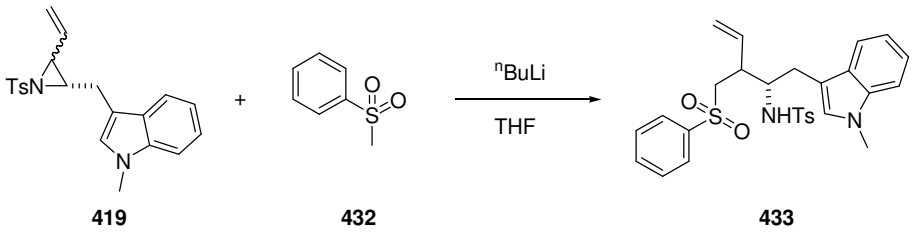


431 **424** **419**

Scheme 2.50: a) $CeCl_3$, $NaBH_4$, CH_3OH, rt, 5 min, 95%, b) DIAD, PPh_3, THF, rt, 30 min, 96%.

2.1.2.6. Ring-Opening of Aziridine 419

To ascertain the reactivity of diastereomeric vinyl aziridine **419**, test reactions were carried out using the sulfone-anion of **432**, in order to facilitate aziridine **419** ring-opening (Scheme 2.51, Table 2.3). Throughout these optimization attempts, the amount of base being used equaled the amount of pre-nucleophile + 1 extra equivalent.



419 **432** **433**

Scheme 2.51 and **Table 2.3**: Attempts to ring-open aziridine **419** using tosyl nucleophile **432**.

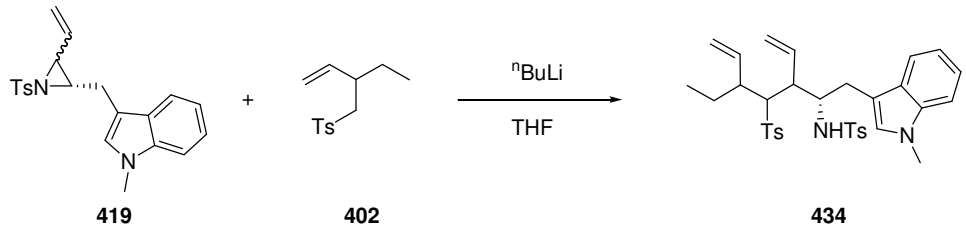
Entry	Ratio 432 : 419	Reaction Concentration	Reaction Conditions	Yield
1	1 : 1	0.5 M	–78 °C → rt, 16 h	0%
2	1 : 1	0.5 M	–40 °C → rt,16 h	0%
3	1 : 1	1.0 M	–40 °C → rt, 16 h	48%[1]
4	1 : 1	2.0 M	–40 °C → rt, 16 h	47%[1]
5	2 : 1	2.0 M	–40 °C → rt, 16 h	48%[1]
6	3 : 1	2.0 M	–40 °C → rt, 16 h	89%
7	1 : 1	3.0 M	–40 °C → rt, 16 h	47%[1]
8	2 : 1	3.0 M	–40 °C → rt, 16 h	87%
9	3 : 1	3.6 M	–40 °C → rt, 16 h	90%
10	1 : 1	4.0 M	–40 °C → rt, 16 h	0%[2]

[1] = only *cis* opening of aziridine **419**

[2] = decreased solubility inhibited the reaction from taking place.

Initial results revealed the ineffectiveness of the nucleophile when using standard reaction conditions due to insolubility of the newly formed sulfone-anion (entry 1). Increasing the temperature did increase the solubility, but did not facilitate aziridine ring-opening (entry 2). Concentrating the reaction mixture indicated product formation; only the *cis*-diastereomer was consumed (entries 3, 4 and 5). Complete conversion of diastereomeric vinyl aziridine was achieved following further optimization; using three equivalents of sulfone anion at a concentration of 3.6 M gave the highest-yielding reaction (entry 8). A concentration of 3.6 M proved to be the upper limit, as higher concentrations (entry 10) resulted in insolubility of the reagents.

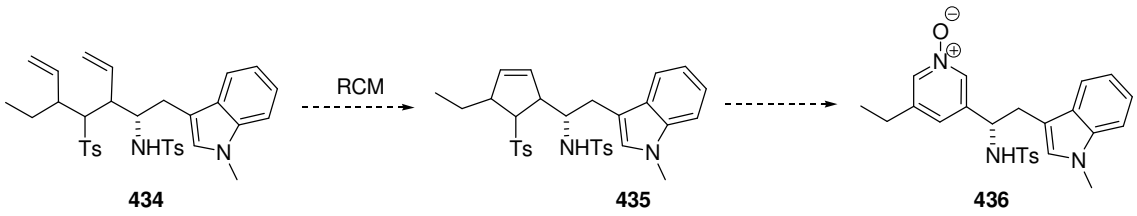
Applying mild reaction conditions to vinyl aziridine **419** using the more sterically demanding sulfone **402** revealed the same lack of reactivity as that described earlier. Use of the optimized reaction conditions resulted in total consumption of the starting material, and diolefinic amine **434** was obtained in high yield (Scheme 2.52, Table 2.4).



Scheme 2.52 and **Table 2.4**: Attempts to ring-open aziridine **419** using tosyl nucleophile **402**.

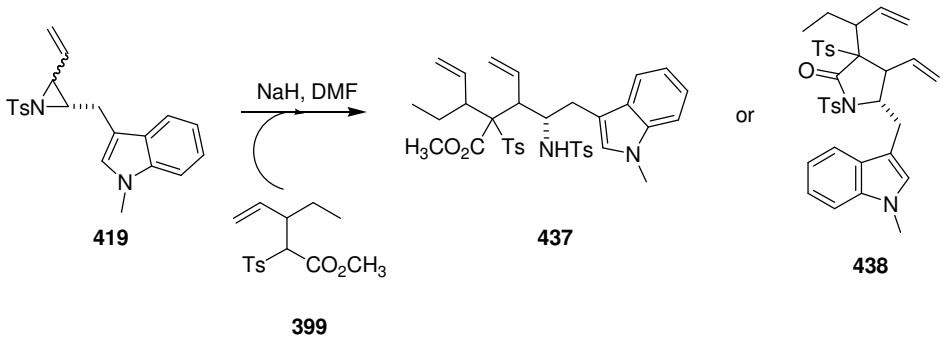
Entry	Ratio 402 : 419	Reaction Concentration	Reaction Conditions	Yield
1	1 : 1	0.5 M	–40 °C → rt, 16 h	0%
2	1 : 1	2.0 M	–40 °C → rt, 16 h	0%
3	3 : 1	3.6 M	–40 °C → rt, 16 h	94%

Having successfully obtained **434**, Grubbs II mediated RCM reaction could provide cyclopentene **435** (Scheme 2.53). Lewis had already utilized a similar cyclopentene, and had observed pyridine-*N*-oxide formation as evidenced by mass spectrometry, after several unsuccessful attempts at alkylation α- to the cyclopentene tosyl group (section 2.1.1, page 103).



Scheme 2.53: Route towards cyclopentene **436**.

Attempts to open the same diastereomeric vinyl aziridine **419** with the higher homologue **399** using the sodium enolate were investigated. A similar protocol had previously been developed regarding the synthesis of γ-lactams from the sulfone-enolate assisted ring-opening of vinyl aziridines followed by intramolecular condensation (Scheme 2.54, Table 2.5).[14,16]

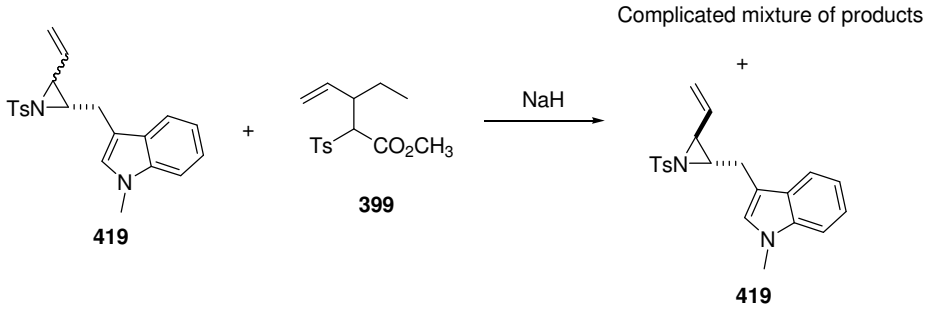


Scheme 2.54 and **Table 2.5**: Attempts to ring–open aziridine **419** using tosyl nucleophile **399**.

Entry	Ratio 399 : 419	Reaction Concentration	Reaction Conditions	Yield[1]
1	1 : 1	0.3 M	60 °C, 16 h	0%
2	1 : 1	1.0 M	rt, 16 h	45%
3	1 : 1	2.0 M	rt, 16 h	42%
4	1 : 1	3.0 M	rt, 16 h	44%
5	1 : 1	3.6 M	rt, 16 h	46%

[1] = yield of *trans*-isomer regained.

Initially, there was no evidence of product formation using standard reaction conditions, with complete decomposition being observed (entry 1). Decreasing the reaction temperature to room temperature did improve the reaction (entry 2). Further optimization led to the consumption of the *cis*-isomer, resulting in the formation of a complex mixture of products and isolation of the unreacted *trans*-diastereomer (Scheme 2.55). This trend of selective *cis*-aziridine opening has been observed in previous research,[13] and is thought to be due to the closer proximity of functional groups, and the more sterically strained nature of the aziridine when compared to its *trans*-counterpart.



Scheme 2.55: NaH-induced nucleophilic ring-opening of aziridine **419** using sodium enolate nucleophiles of **399**.

A strategy involving utilization of a less complex, therefore more reactive sulfone-anion related to **399** was proposed.

2.1.3. Second Generation Approach

In light of the problematic nucleophilic ring-opening of vinyl aziridine **419** with the sodium enolate of **399** described above, a second route towards the total synthesis of (±)-suaveoline was proposed. This strategy would utilize similar transformations, but would involve the aziridine ring-opening of **419** with the structurally less complex ester **443**. Retrosynthetically, formation of the pyridine, together with the construction of the azabicyclo [3.3.1] core would involve chemistry already discussed in section 2.1.2, page 111, involving *de novo* pyridine synthesis[3] together with *cis*-Pictet–Spengler cyclization (Figure 2.5).[4] Pictet–Spengler adduct **439** would be obtained by substitution of the OP functional group in **440** with a cyanide moiety, thus providing a masked aldehyde and simultaneously allowing C–C homologation.

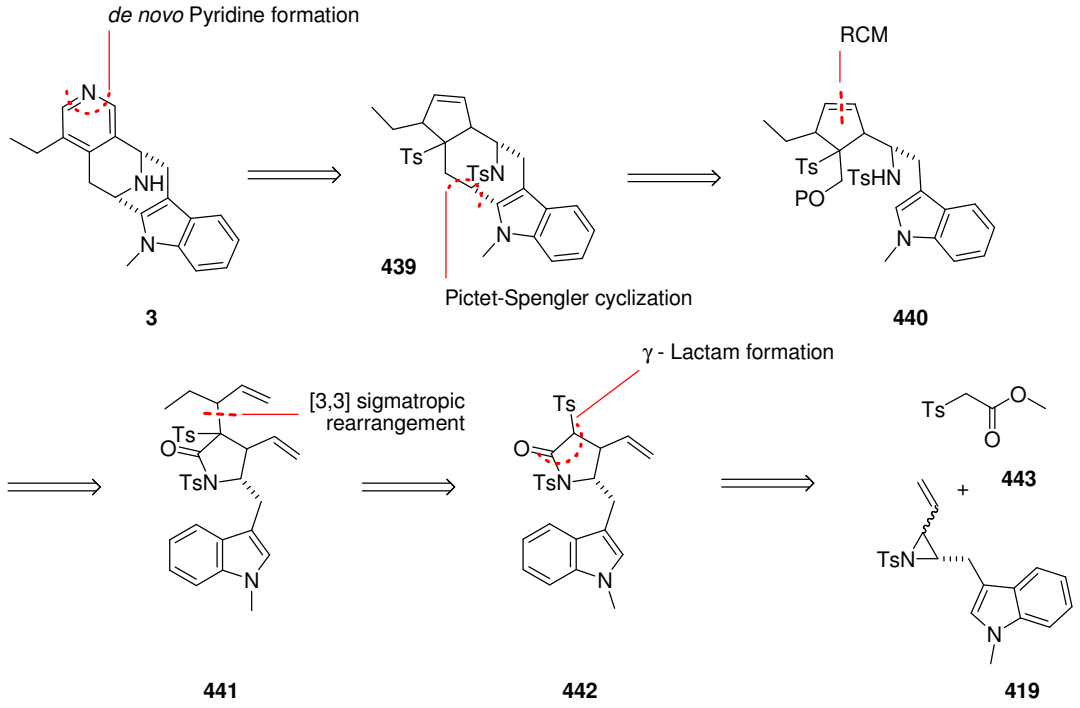
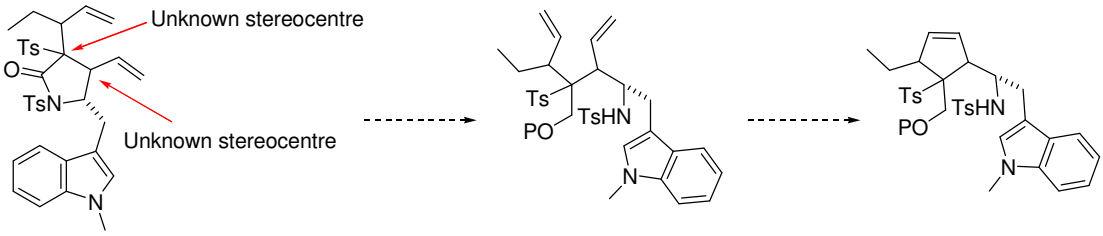


Figure 2.5: Second route towards suaveoline.

Disconnection of the cyclopentene in **440** revealed diolefin **441**, which we anticipated to complicate RCM due to the lack of guaranteed *syn*-stereochemistry of the olefinic moieties. In our view the *syn*-diastereomer of **441** would undergo RCM, while the *anti*-diastereomer would not due to conformational constraints.[13,44] Therefore, γ-lactam **441** would undergo *N*-carbonyl cleavage facilitated by Superhydride or $NaBH_4$ to provide a more flexible **444** product (Scheme 2.56).



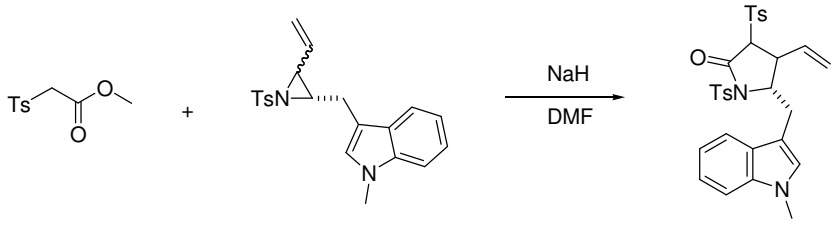
441 **444** **440**

Scheme 2.56: Forward synthesis of cyclopentene **440**.

In contrast to the structurally more complex olefinic ester **399**, sulfone-ester **443** does not contain an olefinic moiety, and therefore this had to be installed after the initial γ-lactam formation from vinyl aziridine **419** and the sulfone-nucleophile of **443** (Scheme 2.57). Enolization of lactam **443** using NaH would be followed by subsequent addition of 3-iodopentene (prepared *in situ* by treatment of 3-bromopentene and TBAI). Claisen rearrangement would then give the corresponding [3,3]-sigmatropically rearranged diolefin **441**.[2] Similar reactions on γ-lactams were previously reported to proceed in high yields.[14,44]

2.1.3.1. γ-Lactam Formation

Attempts to obtain γ-lactam **442** from the sulfone-stabilized ring-opening of vinyl aziridine **419** with methyl phenylsulfonyl acetate **443** are listed in Table 2.6.



443 **419** **442**

Scheme 2.57 and **Table 2.6:** Attempts to ring-open aziridine **419** using tosyl nucleophile **443**.

Entry	Ratio 443 : 419	Reaction Concentration	Reaction Conditions	Yield[1]
1	1 : 1	0.3 M	60 °C, 16 h	Decomposition
2	1 : 1	1.0 M	rt, 16 h	49%
3	1 : 1	2.0 M	rt, 16 h	23%
4	1 : 1	3.0 M	rt, 16 h	0%
5	1 : 1	3.6 M	rt, 16 h	Decomposition

[1] = yield of *trans*-isomer regained.

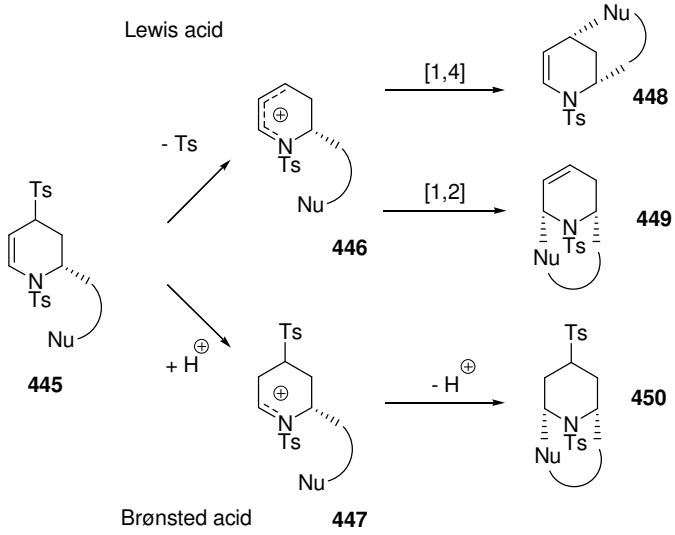
The nucleophilic ring-opening / intramolecular condensation reaction failed to give **442**. Initial application of the Hyland protocol[14] led to the decomposition of the vinyl aziridine **419** (entry 1). Reactions at room temperature proved to be more successful (entries 2 to 5); with partial consumption of the *cis*-diastereomer observed at 1 M. Although a subsequent increase in concentration led to a total consumption of vinyl aziridine **419**, mass spectrometry indicated no product to be present in the complex mixture of products. Further increase in concentration led to total decomposition (entry 5).

Optimization of the aziridine ring-opening reaction of **419** using the sodium enolate of **443** might be effected by using KH as the base. This would provide a more reactive enolate species and therefore hopefully be more successful in forming γ-lactam **442**. Due to time constraints, further optimization was not carried out.

2.2. Alstonerine

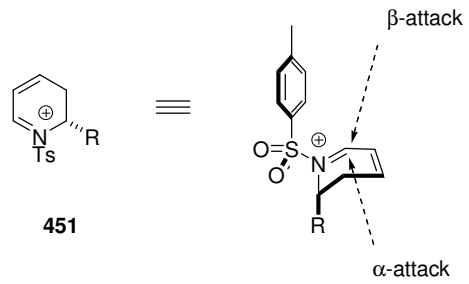
2.2.1. Prior Work within the Craig Group

The basis of the Craig group's attempts towards alstonerine involved a previously developed synthetic route towards the preparation of 2,6-*syn*-piperidines **450** as well as 2,4-*syn*-THPyr (tetrahydropyridine) **448** from **445** (Scheme 2.57).[37,69] Exposure of THPyr **445** to Lewis acidic conditions provided the conjugated iminium species **446**, which could be attacked by a nucleophile at the C_4 position to afford **448** or at C_6 generating **449**. Protonation of **445** under Brønsted acidic conditions generated iminium species **447** which gave **450** *via* nucleophilic attack at the C_2 position.[37]



Scheme 2.57: Lewis acid / Brønsted acid conditions applied to **445**.

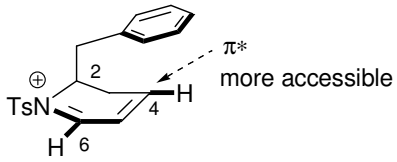
Analysis by X-ray crystallography showed the conformation of **451** to be as depicted in Figure 2.6. In this chair-like conformation, steric repulsion between the tosyl group and the C_2–R moiety is minimized, and due to the *N*-tosyl moiety blocking β-face attack, cyclization (as depicted in Scheme 2.57, compound **449**) can only occur on the α-face.[117]



451

Figure 2.6: α- and β-attack possibilities.

The observed stereochemistry when using Lewis acid conditions can be attributed to the more accessible π* orbital at C_4 rather than C_6. A model depicted as **452** shows the π* orbital at C_4 to allow maximal overlap with the reacting π-system in contrast to C_6 (Figure 2.7).[4,69]



452

Figure 2.7: Accessibility of the C_4 π*-orbital.

2.2.1.1. The Diels–Alder Approach

A key synthetic intermediate in the first strategy for the total synthesis of (–)-alstonerine **36**, by Ioannidis,[69] was ketone **455** (Figure 2.8). It was anticipated that the fifth ring would be formed *via* a regioselective aldol reaction with formaldehyde to provide β-hydroxyketone **454**. Conversion into β-ketoester **453** and subsequent Knoevenagel reaction would establish the fifth ring, after which oxidation level adjustment would give (–)-alstonerine **36**.[69]

The application of homochiral lithium amide bases would discriminate between both α-positions of ketone **455** because of their quasi-enantiotopic nature.[70] Furthermore, the approach of the formaldehyde should take place on the β-face for stereoelectronic reasons. In the cyclohexanone moiety the axial proton is lost due to its greater acidity as a result of maximum σ_{C-H} orbital overlap with the carbonyl π^*.[71] It appears that attack along the α-trajectory is both sterically hindered and stereoelectronically disfavored, leading to axial C–C bond formation.

Ketone **455** would subsequently be formed from sulfone **456** *via* oxidative desulfonylation. **456** in turn would be obtained from acid-mediated Pictet–Spengler cyclization of **457**.

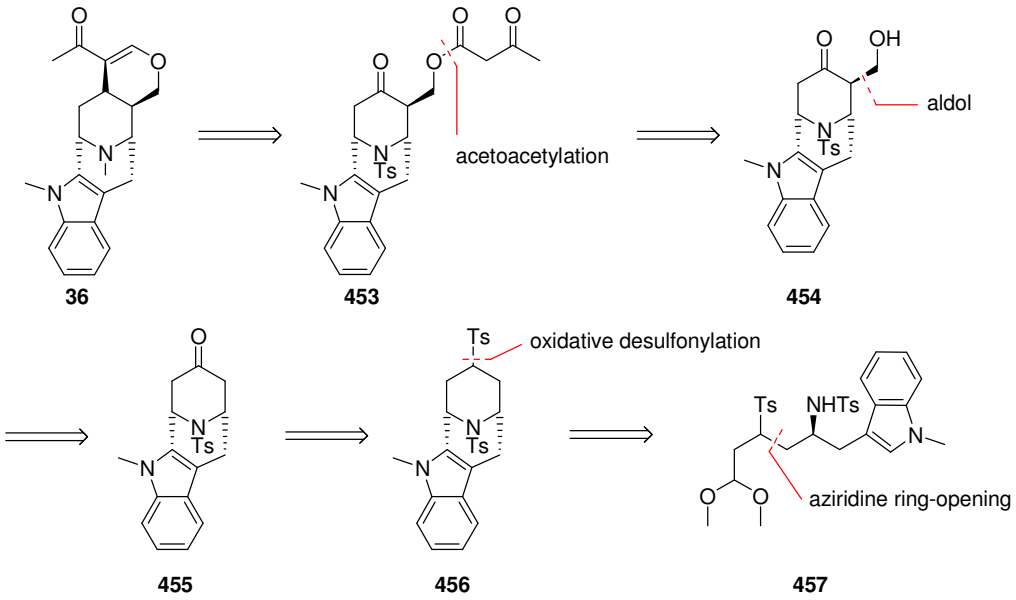
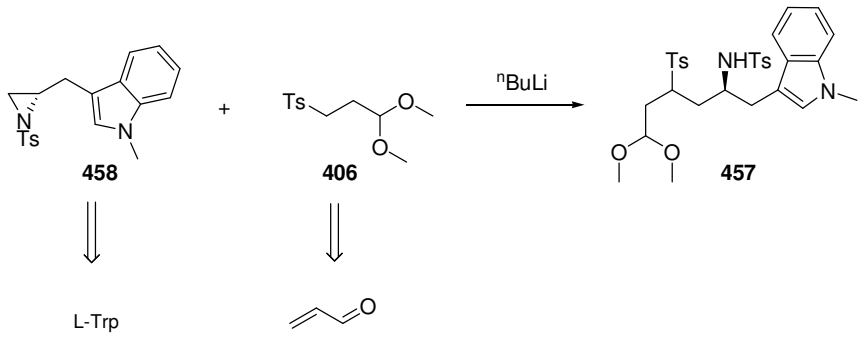


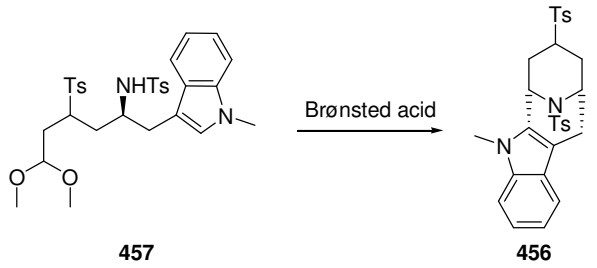
Figure 2.8: Retrosynthetic analysis of (–)-alstonerine.

The strategy was initiated by ring-opening of L-tryptophan-derived aziridine **458**, with the lithio-sulfone acetal **406**, obtained from acrolein (discussed in detail on page 182, Scheme 2.117).



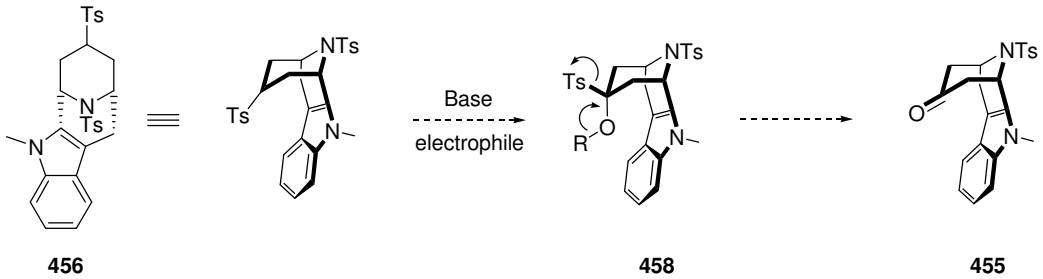
Scheme 2.58: Sulfone-anion mediated aziridine ring-opening.

The diastereomeric mixture of **457** was treated with either (±)-CSA or *p*-TsOH to give the Pictet–Spengler tetracyclic product **456** (Scheme 2.59).



Scheme 2.59: *cis*-Pictet–Spengler bicyclization.

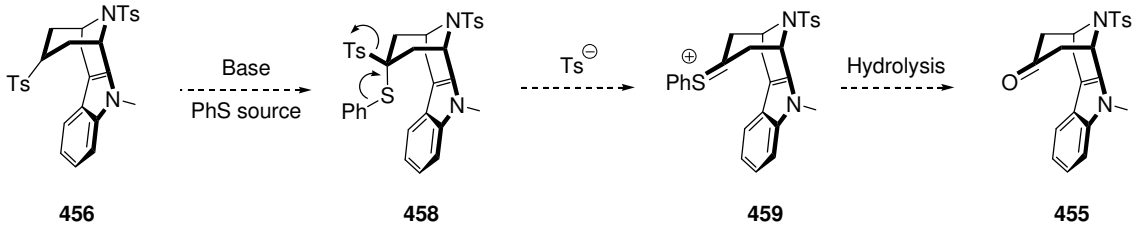
Having successfully prepared the diastereomeric tetracyclic structure **456**, the next step would involve oxidative desulfonylation (Scheme 2.60). Published reports[69,72,73,74] describe these procedures to progress initially *via* α-deprotonation of the sulfone followed by reaction with an oxygen electrophile (peroxide), which in turn promotes the departure of the sulfonyl group as sulfinate anion, to form the carbonyl functionality **455**.



Scheme 2.60: Oxidative desulfonylation mechanism.

In order to facilitate oxidative desulfonylation, several reagents were evaluated in combination with ^{n}BuLi. The molybdenum(V) reagent MoOPH[72] was not tried due to its toxicity and instability. Despite several attempts, involving BTSP,[73] chlorodimethoxyborane[74] and anhydrous lithium ^{t}butylhydroperoxide, none of the desired ketone **455** was isolated.

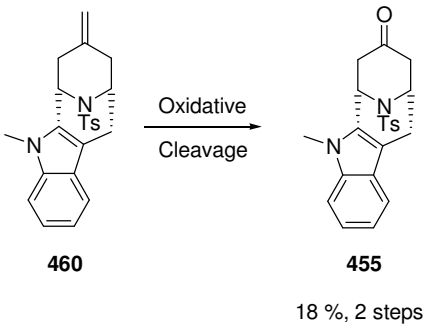
An alternative strategy for ketone formation involved the introduction of a thiophenyl group at the α-position. It was anticipated that exposure of **458** to Lewis acid would yield thionium ion **459**, which would give ketone **455** on hydrolysis (Scheme 2.61). However, no product was obtained, and this was attributed to steric interference between the nucleophile and the indole ring, which blocks the α-face approach.



Scheme 2.61: Thiophenyl induced detosylation followed by α-oxidation.

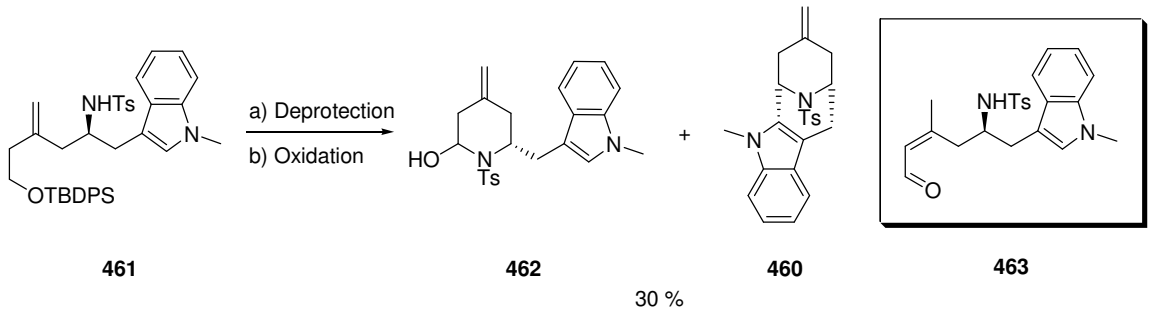
Following several unsuccessful attempts to obtain α-thiophenyl intermediate **458**, a thioacetal analogue was finally obtained in unacceptably low yield.[54,69]

A new approach to the synthesis of ketone **455** involving oxidative cleavage of terminal olefin **460** (Scheme 2.62) proved successful when using OsO_4 and $NaIO_4$, as reported by Cook.[75]



Scheme 2.62: Oxidative cleavage of **460**.

However, the synthesis of **460** proved low yielding in part due to the formation of an inseparable mixture during alcohol oxidation and Pictet–Spengler cyclization (Scheme 2.63). In most cases migration of the terminal olefin into conjugation with the aldehyde was observed, forming conjugated enal **463**.

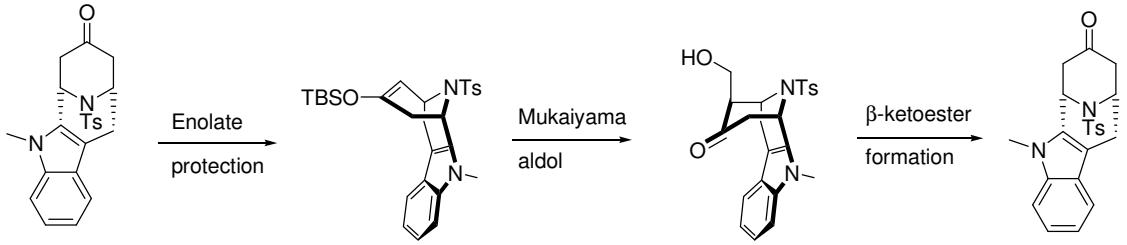


461 **462** **460** **463**

30 %

Scheme 2.63: Pictet–Spengler bicyclization.

Exposure of ketone **455** to Mukaiyama aldol reaction conditions[76] furnished **464**. However, attempted β-ketoester formation from **464** resulted in substrate decomposition, with regeneration of ketone **455** (Scheme 2.64). Earlier attempts to install the α-methanol substituent at ketone **455** using LDA and paraformaldehyde had revealed a *retro*-aldol reaction to take place. It was hoped that reducing the amount of base to catalytic amounts in the β-ketoester formation step would retard the *retro*-aldol reaction, to no avail.[69]



455 **464** **465** **455**

99 % 54%

Scheme 2.64: Mukaiyama aldol reaction followed by β-ketoester formation.

In light of the unsuccessful attempts described above, a second approach was pursued. The new strategy involved hetero-Diels–Alder reaction of diene **467** with formaldehyde to construct the fifth ring in **466** (Figure 2.9). The diene would be prepared from aziridine ring-opening of **458** with the desulfonylated sulfone-anion of **471**. This cyclopentene would provide a 1,5-dialdehyde *via* oxidative cleavage. Dialdehyde **469** could be used in the *cis*-Pictet–Spengler cyclization *via* cyclic iminium formation, and subsequent desulfonylation would provide enal **468**, which upon enolate *O*-silylation would provide the conjugated diene **467**.[54]

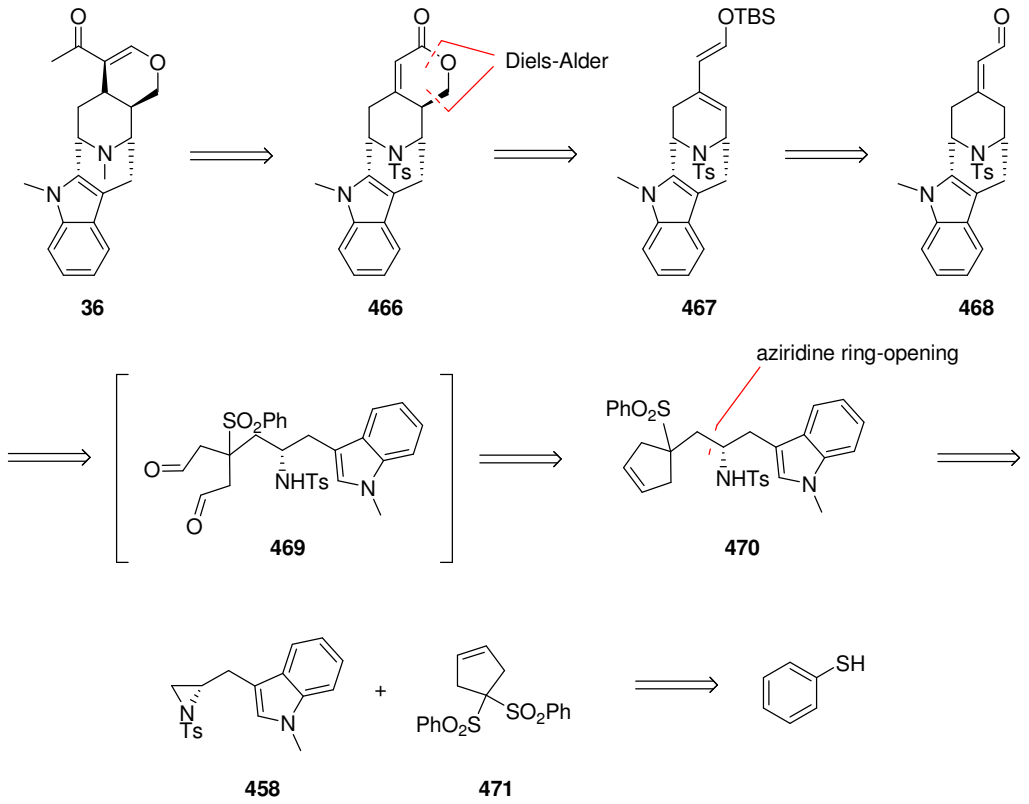
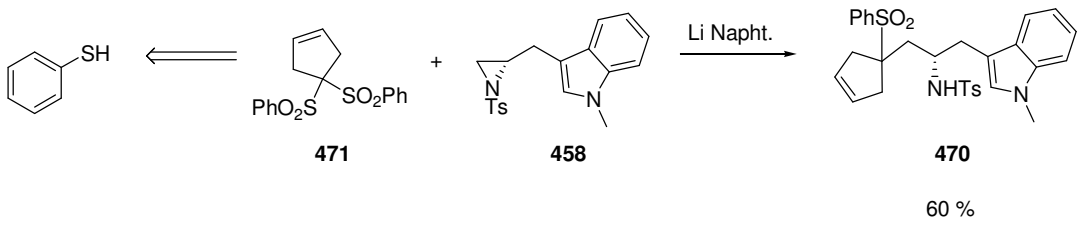


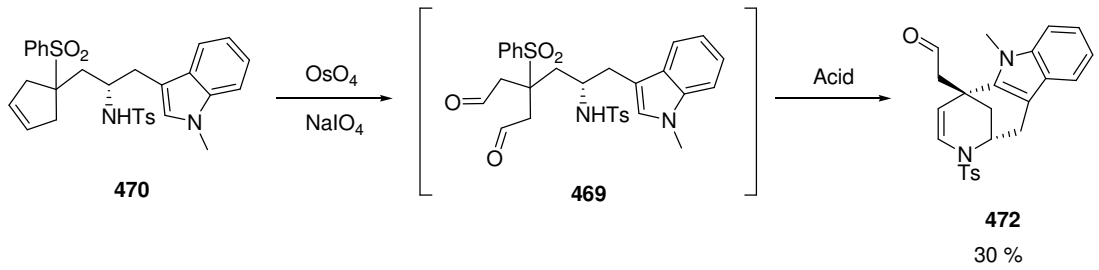
Figure 2.9: Second retrosynthetic analysis of (–)-alstonerine **36**.

Bis(phenylsulfonyl)cyclopentene **471** was made from thiophenol and could be prepared in large quantities in three steps (Scheme 2.65).[69] Aziridine ring-opening of **458** was carried out using lithium naphthalide-mediated desulfonylation of **471**, giving **470**.[54,77]



Scheme 2.65: Aziridine ring-opening by desulfonylated **471**.

In initial studies, oxidative cleavage of the cyclopentene double bond with OsO_4 and $NaIO_4$ gave compound **472** instead of the desired aldehyde intermediate (Scheme 2.66).

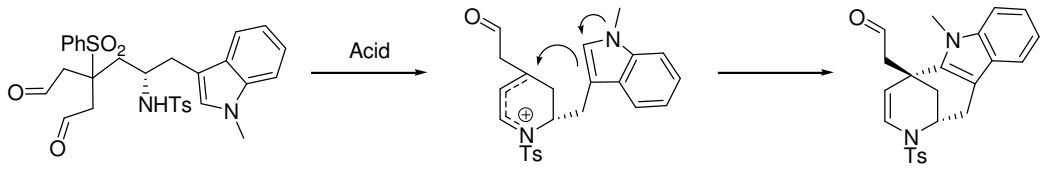


470 **469** **472**

30 %

Scheme 2.66: Oxidative cleavage followed by acid induced Pictet–Spengler cyclization.

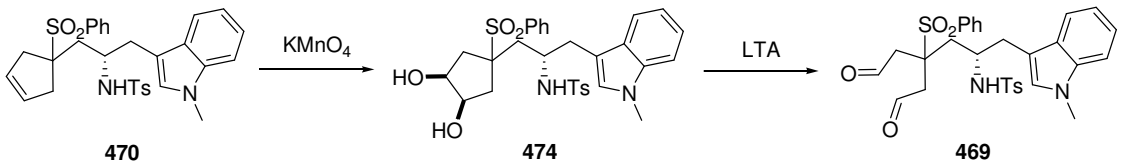
The acidic conditions used in the reaction resulted in formation of cyclic iminium **473** in which the C_4-sulfonyl moiety had been removed. As such an allylic carbocation **473** was formed which underwent Pictet–Spengler cyclization at the C_4 position (Scheme 2.67).



469 **473** **472**

Scheme 2.67: Side-product formation due to Pictet-Spengler cyclization.

An alternative two-step approach involved permanganate-induced dihydroxylation[78] of **470** followed by LTA (lead tetraacetate) mediated oxidative cleavage[79] afforded the unstable dialdehyde **469** in high yield (Scheme 2.68).

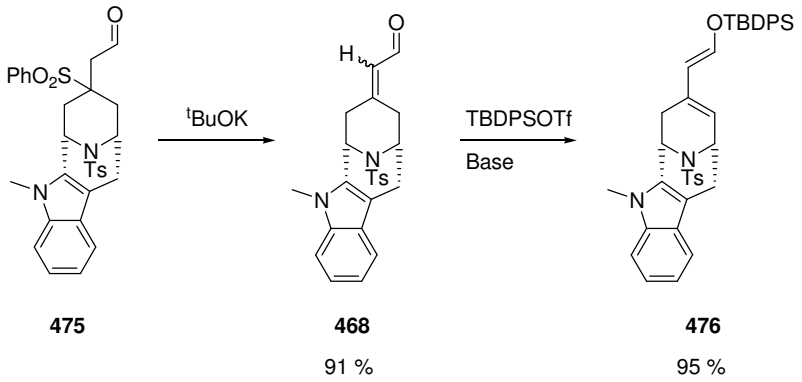


470 **474** **469**

50 % > 95 %

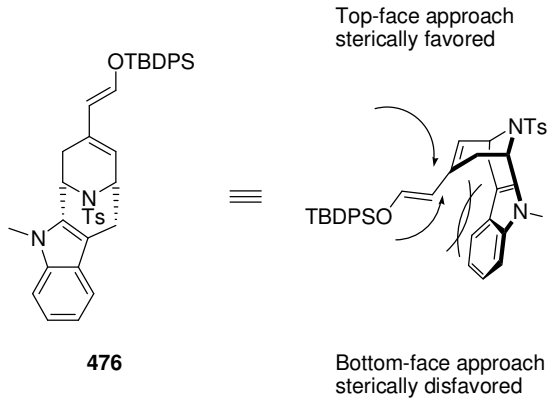
Scheme 2.68: Dihydroxylation / oxidative cleavage of cyclopentene.

Optimization of the Pictet–Spengler cyclization by treating intermediate **469** with TFA finally gave cyclic aldehyde **475** in 80 % yield, which was converted into the unsaturated aldehyde **468** using mild basic conditions (Scheme 2.69). Diene formation was achieved in high yield using TBDPS which was found to be hydrolytically less sensitive than the TIPS and TBS derivatives.[54]



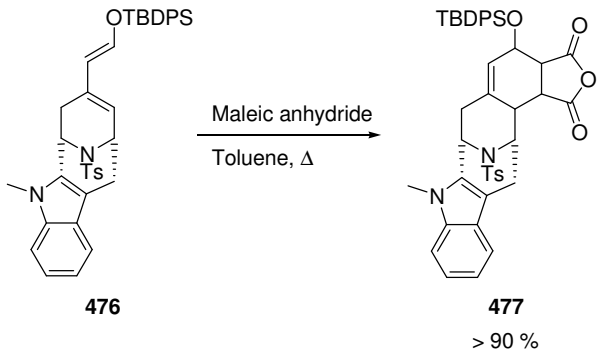
Scheme 2.69: Vinyl aldehyde formation, followed by trapping of silyl enolate trapping.

As in the case of the aldol-type reactions attempted earlier, it was anticipated that the required stereochemistry at C_{13} would be obtained by the preferred approach of the formaldehyde from the top face of the diene (Scheme 2.70). Top-face attack would give a chair-like conformation of the piperidine ring, while bottom face approach would give a twisted-boat conformation; in addition, top-face attack appears to be sterically favored.[69,80]



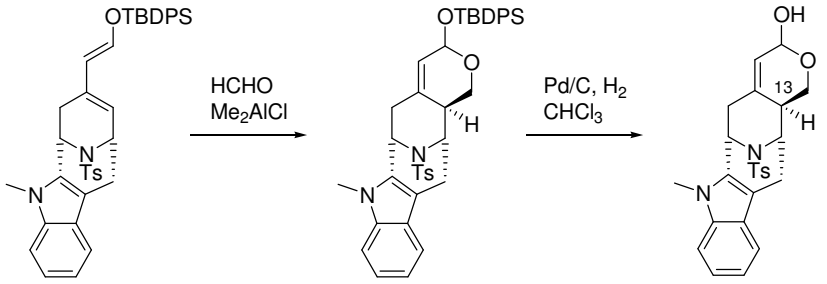
Scheme 2.70: Conformation analysis of **476**.

A test reaction using maleic anhydride as dienophile gave **477**, demonstrating the reactivity of the diene in the Diels–Alder cycloaddition (Scheme 2.71).[80]



Scheme 2.71: Diels-Alder cycloaddition of maleic anhydride.

Following the successful formation of adduct **477**, **476** was exposed to oligomeric/polymeric sources of formaldehyde (paraformaldehyde, 1,3,5-trioxane) in conjunction with a range of Lewis acids ($BF_3{\cdot}Et_2O$, lanthanide triflates, $TiCl_4$, Me_3Al, Me_2AlCl), all to no avail.[54,80] Use of monomeric formaldehyde, obtained by a modified Schlosser treatment,[80,81] in combination with Me_2AlCl provided the pentacycle **478**, but in low yield; this was due to facile retro-Diels–Alder reaction of **478**, regenerating **476** (Scheme 2.72).



476 **478** 36 % **479** 66%

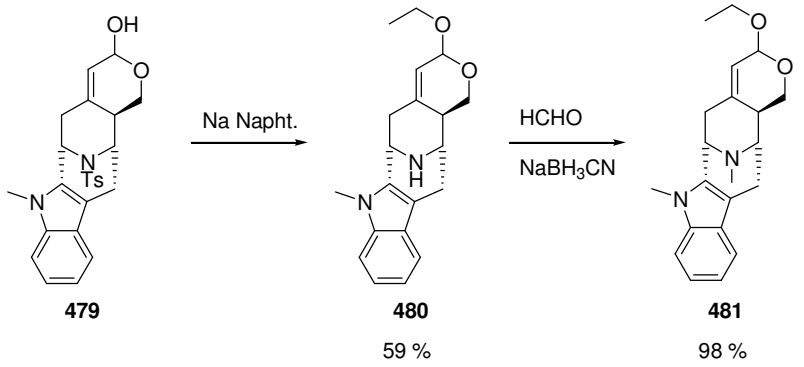
Scheme 2.72: Successful hetero-Diels–Alder cyclization using monomeric formaldehyde.

In order to prevent retro-Diels–Alder reaction and establish the *syn*-C_{13}–C_{18} relationship *via* hydrogen addition at the less sterically hindered bottom-face of **478**, attempts to hydrogenate the existing double bond were made using several homo- as well as heterogeneous catalysts.[80,82] Deprotection of the silyl-ether in **478** provided **479** after exposure to Pd/C, which although undesired would provide evidence regarding the nature of the C_{13} stereochemistry by use of X-ray crystallography (Scheme 2.72). Analysis showed the Diels–Alder reaction to have taken place at top face of the indole, therefore providing the correct C_{13} stereochemistry.

In all, no hydrogenation attempts led to the formation of hydrogenated **478**, instead resulting in lactol formation due to silyl deprotection in most cases. Simultaneous efforts to oxidize the lactol to the corresponding lactone, using several oxidizing agents, as well as isomerization of the double bond, were equally unsuccessful.[80]

It was considered that the piperidine *N*-tosyl group might be reducing the overall reactivity of **478**, and changing the *N*-piperidine substituent from tosyl to methyl was therefore proposed; this was a required structural feature in the target molecule

Sodium naphthalide-induced detosylation gave **480**, possibly due to the slightly acidic conditions while purifying by column chromatography using EtOAc–MeOH. Reductive amination[83] using formaldehyde gave **481** (Scheme 2.73).



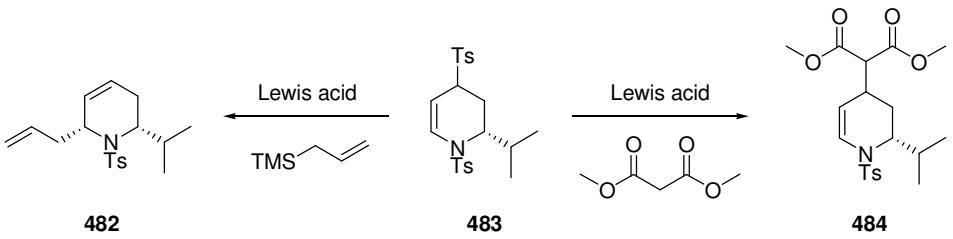
479 **480** 59 % **481** 98 %

Scheme 2.73: *N*-piperidine protecting group conversion.

A number of Pd/C-mediated hydrogenation attempts were made with **481**, but these were unsuccessful. Due to lack of time, further studies into the hydrogenation / oxidation / isomerization of **481** were not conducted.[80]

2.2.1.2. The Conjugated Iminium Approach

A different approach towards the total synthesis of (±)-alstonerine **36** was based upon previous work conducted in the Craig group with regard to THPyr. These 1,4-bis(tosyl)THPyrs readily undergo loss of the tosyl moiety to form conjugated iminium species,[117] which may be intercepted at C_6 (**482**) or at C_4 (**484**), the latter generally by bulkier nucleophiles (Scheme 2.74).



Scheme 2.74: Soft nucleophile C_4 attack (left); Hard nucleophile C_6 attack (right).

Intramolecular substitutions are also possible, as described earlier on page 146. Retrosynthetic analysis of (±)-alstonerine **36** reveals the reduction of a lactone which will allow the fifth alstonerine ring to be constructed from corresponding cyclic silyl-enol ether **485** (Figure 2.10).

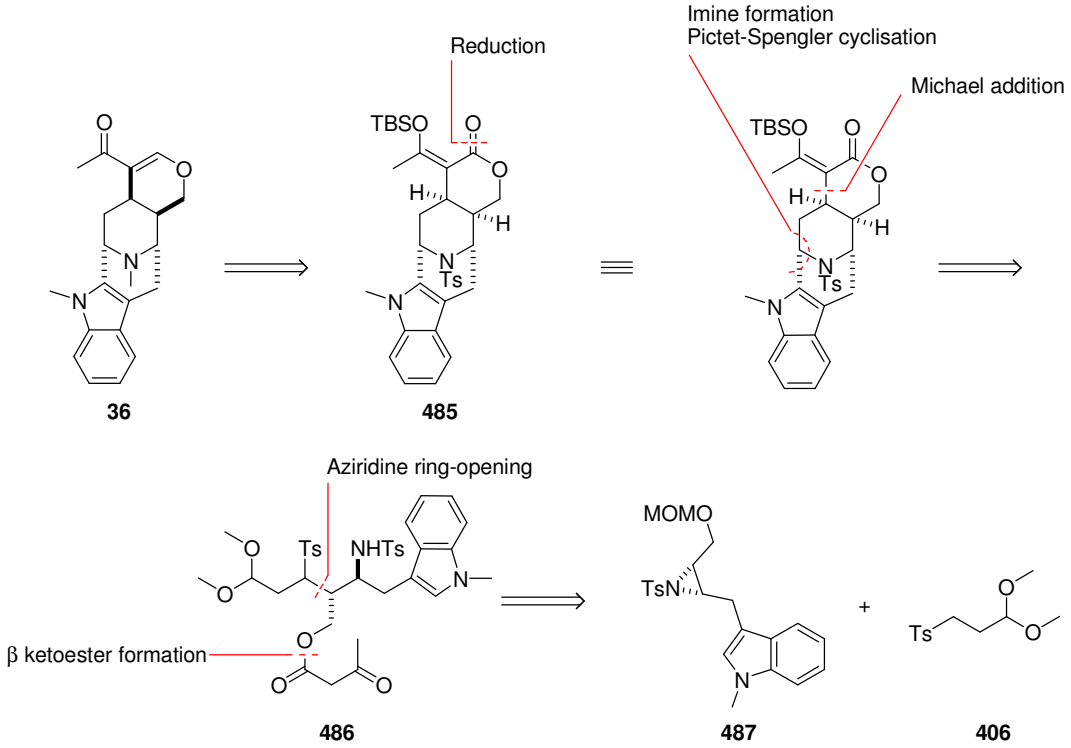
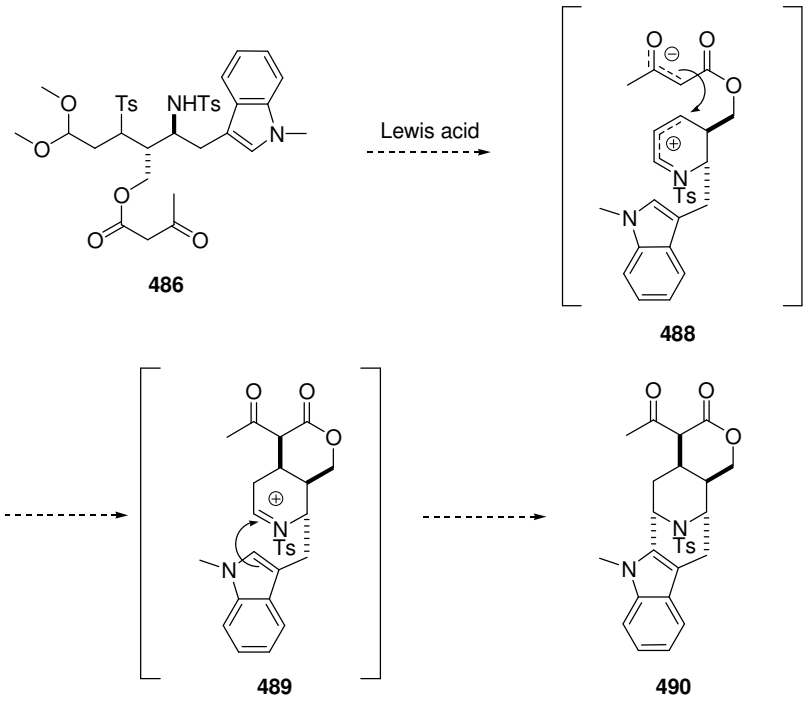


Figure 2.10: Retrosynthetic analysis of (±)-alstonerine **36**.

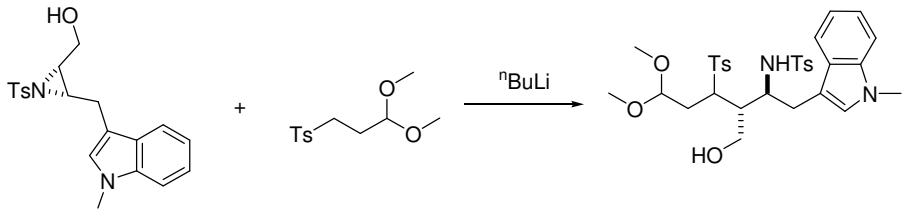
Silyl ether **485** would be formed by three sequential cyclizations (Scheme 2.75). Treating **486** with Lewis acid would, according to previous studies,[37,69] form cyclic iminium **488** *via* E1cB desulfonylation. Michael-type addition of the β-ketoenolate forms **489**[19] after which addition of a catalytic amount of acid would be sufficient to trigger Pictet–Spengler cyclization to give **490**.



486 **488** **489** **490**

Scheme 2.75: Triple cyclization cascade.

Although a mixture of regioisomers was obtained from the ring-opening reaction of MOM-protected aziridine **487** with the sulfone-anion **406**, combination of lithio-**406** with *O*-lithio **388** resulted in successful formation of **415**. This marked change in selectivity is attributed to the directing effect of the alkoxylithium group in the conjugate base of **388** as discussed on page 123 (Scheme 2.76).

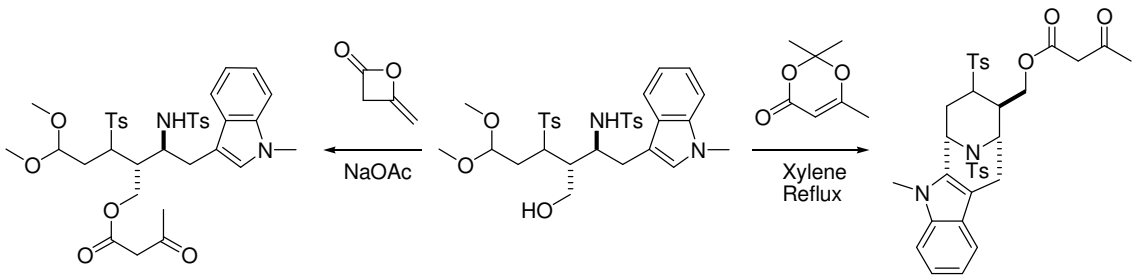


388 **406** **415**

75 %

Scheme 2.76: Aziridine ring-opening by tosyl acetal **406**.

Subsequent functionalization of the alcohol to the corresponding β-ketoester **486** gave unexpected results. Use of trimethyldioxinone resulted in premature Pictet–Spengler cyclization, thus preventing the desired sequence of sulfinate elimination and subsequent Michael-type addition at the iminium C_4 (Scheme 2.77). Use of diketene gave **486** without formation of cyclized side-product **491**.[19]



486 54 % **415** **491** 86 %

Scheme 2.77: β-Ketoester formation.

Treatment of β-ketoester **486** with several Lewis acids gave **491**, again due to premature Pictet–Spengler cyclization. Attempts to decrease the overall acidity of the reaction mixture by adding base were made as this would increase the rate of tetrahydropyridine formation and allow formation the β-ketoester enolate. Unfortunately, no cyclisation product was observed other than **491**, that of Pictet–Spengler reaction.

2.2.2. Current Progress Towards (±)-Alstonerine

As with our proposal for the total synthesis of (±)-suaveoline, the key step in the final strategy evaluated for the total synthesis of (±)-alstonerine **36** involved the regioselective opening of hydroxyaziridine **388**. In order to prevent the premature Pictet–Spengler cyclisation described earlier, δ-lactam **493** was identified as a key intermediate. This necessitated the use of a more highly oxidized sulfone anion as the key nucleophilic reactant.[19]

Our proposal towards the total synthesis of (±)-alstonerine **36** involved a *cis*-selective Pictet–Spengler cyclization in order to construct the characteristic [3.3.1]-azabicyclic system **36** from **492**. This bicyclic core would be formed by a global reduction step, which would convert the vinylogous carbonate into the transposed vinylogous ester and reduce the δ-lactam to the labile *N*-tosyl hemiaminal, which on acidification would undergo spontaneous Pictet–Spengler cyclization to give **36** (Figure 2.11).

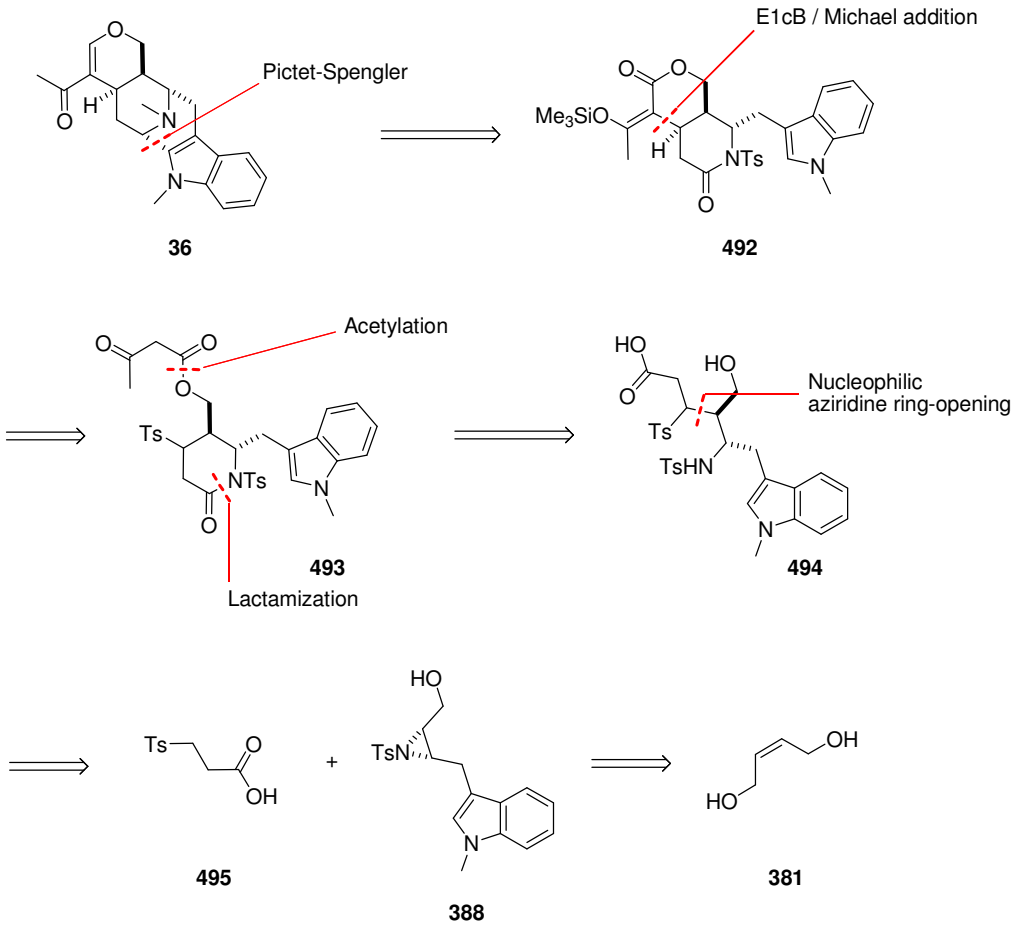
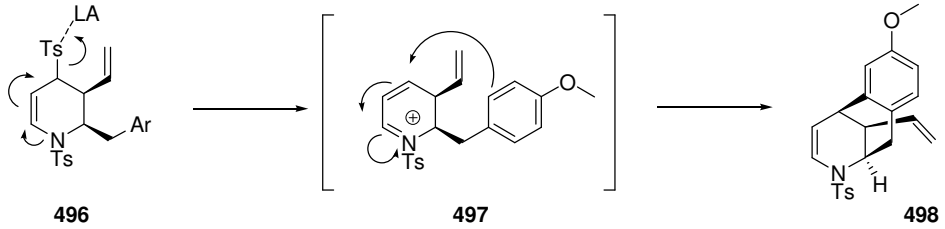


Figure 2.11: Retrosynthetic analysis of (±)-alstonerine **36**.

Construction of **494** will be achieved *via* nucleophilic ring-opening reaction of *N*-sulfonylaziridine **388** using the dianion of **495**, followed by lactamization and acylation of the primary alcohol to furnish **493** (Figure 2.11). E1cB elimination of the tosyl moiety would be followed by a Michael-type addition providing tetracycle **492**.

Previous research had already shown the formation of a conjugated cationic system **497** following the departure of the tosyl-moiety triggers cyclization by the aromatic ring providing **498** (Scheme 2.78).[16,37]

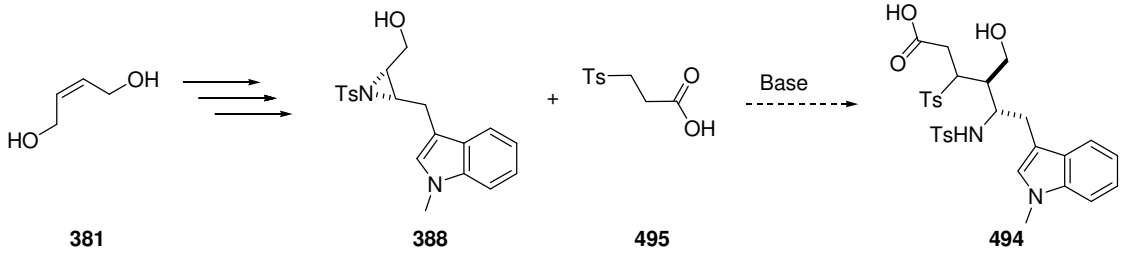


496 **497** **498**

Scheme 2.78: Lewis acid mediated C_6 cyclization.

2.2.2.1. Dianion-Mediated Aziridine Ring-Opening

Preparation of hydroxyaziridine **388** involved the same sequence as described earlier, starting from *cis*-2-butene-1,4-diol **381** (page 113). The key step once again involved the aziridine ring-opening of **388** by the sulfone-anion mediated dianion of **495** (Scheme 2.79).

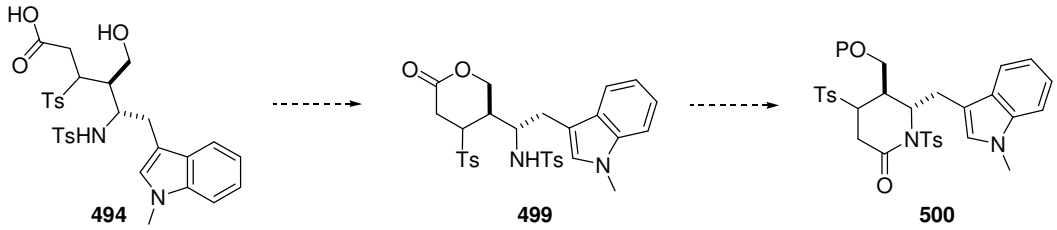


381 **388** **495** **494**

Scheme 2.79: Proposed aziridine ring-opening by tosyl carboxylic acid.

In the event that formation of the protected-ether **500** proved inefficient, alternative peptide coupling conditions could be employed to form δ-lactam **500** or δ-lactone **499** prior to alcohol protection. In this reaction formation of the δ-lactone is probably favored due to the higher reactivity of the alcohol when compared to the electron-deficient tosamide. Conversion of the δ-lactone **499** into the silyl protected δ-lactam **500** would be achieved by using acid-mediated δ-lactone cleavage followed by silyl protection of the alcohol, forming the acid-silyl ether

precursor of **500** as described by Hanquet *et al* (Scheme 2.80).[84] Having protected the alcohol, peptide coupling reactions would provide lactam **500**.

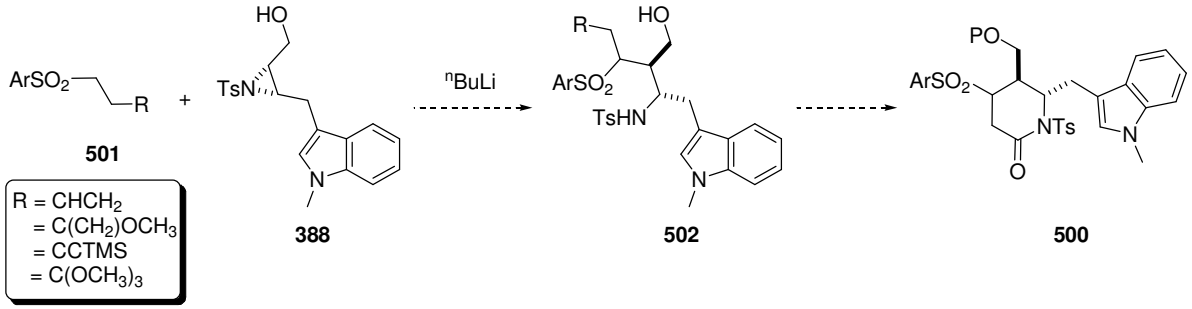


Scheme 2.80: Proposed δ-lactone formation followed by the Hanquet protocol towards silyl-protected δ-lactam.

Disappointingly, no aziridine ring-opening was observed when combining the dianion of **495** with aziridine **388**. Carrying out the reaction at different temperatures, as well as using different modes of addition and different bases (NaH or ^{n}BuLi) failed to yield the desired product.

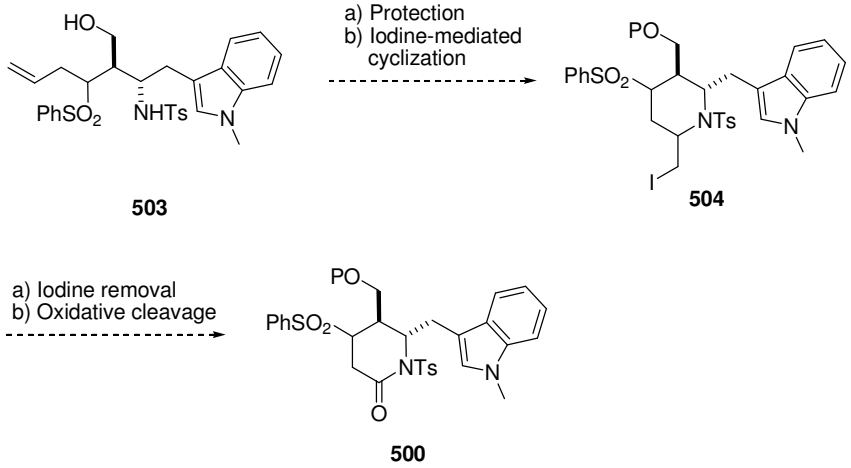
2.2.2.2. Alternative Tosyl-containing Nucleophiles

Due to the lack of success using the dianion of **495**, four alternative strategies were proposed in regard to the preparation of δ-lactam **500** (Scheme 2.81).



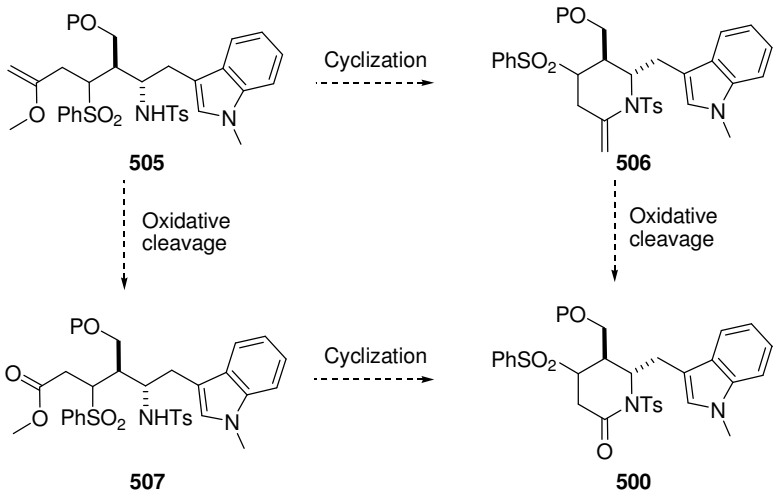
Scheme 2.81: Proposed sulfone-nucleophiles for aziridine ring-opening.

One of these alternatives involved a terminal olefin (R = $CHCH_2$), which would provide halogen piperidine **504** *via* iodine-induced cyclization (Scheme 2.82). Subsequent removal of the halogen followed by oxidative cleavage of the cyclic enamine would furnish δ-lactam **500.** Cyclizations similar to that of **504** have been reported in the literature by Minakata *et al.*[86] and utilize a strategy not dissimilar to that of the Sharpless aziridination.[20]



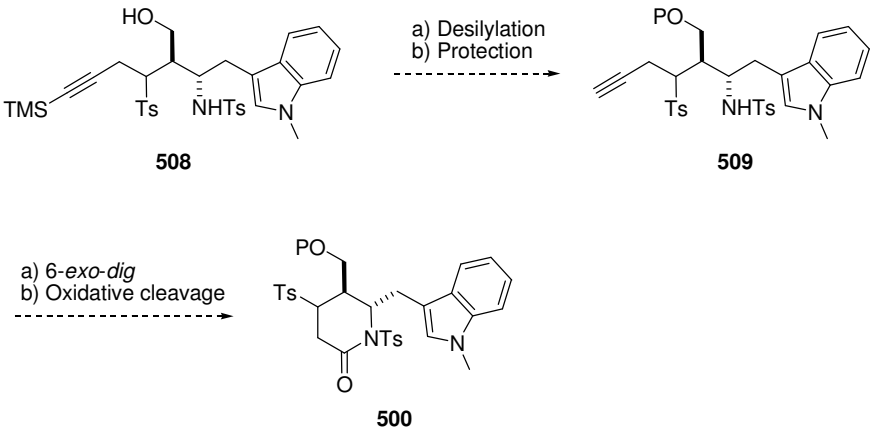
Scheme 2.82: Olefin-mediated δ-lactam formation.

Another alternative would utilize a rather unstable enol-ether approach (R = $C(CH_2)OCH_3$) which we hoped to utilize in order to obtain δ-lactam **500** (Scheme 2.83). Enol-ether **505** would therefore either undergo cyclization followed by oxidative cleavage or subjected to the reverse sequence of reactions.



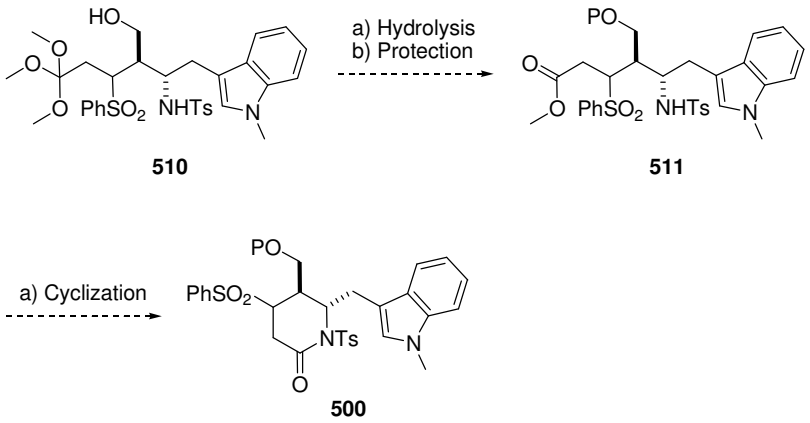
Scheme 2.83: Enol-ether approach towards lactam **500**.

An interesting approach towards preparation of **500** could also involve a 6-*exo-dig* cyclization of a deprotected acetylene with tosamide **509** (R = CCTMS, Scheme 2.84). Oxidative cleavage of this enamine would form the lactam **500**. However, according to Baldwin's rules, no special preference is observed when considering 6-*exo-dig versus 7-endo-dig* cyclisation.



Scheme 2.84: 6-*Exo-dig* approach utilizing acetylene **508**.

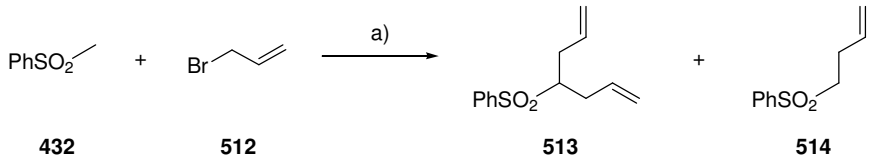
A last alternative was based upon the earlier success of tosyl acetal-induced aziridine ring-opening (as reported on page 157). Formation of ortho-ester **510** (R = $C(OCH_3)_3$) would involve a similar nucleophilicity as compared to the tosyl acetal and provide a higher oxidation state therefore preventing any unwanted Pictet–Spengler cyclization upon deprotection (Scheme 2.85).



Scheme 2.85: Ortho-ester hydrolysis followed by δ-lactam formation.

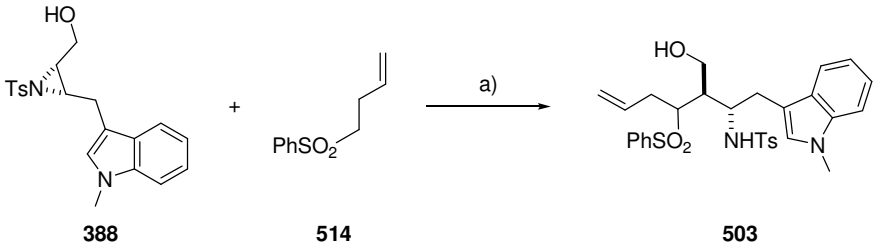
2.2.2.2.1. Sulfonyl-Olefin 514

Synthesis of sulfonyl-olefin **514** was described by Takahata *et al.*[85] using 1-bromo-2-propene **512** as electrophile and the lithio-anion of phenyl methyl sulfone **432** to give **514**, **513** and unreacted starting material (Scheme 2.86). Deprotonation of the secondary acidic α-sulfone proton of **514** resulted in additional alkylation at this position by another equivalent of 1-bromo-2-pentene to provide **513**. Thus both mono-, dialkylated product and starting material were obtained.



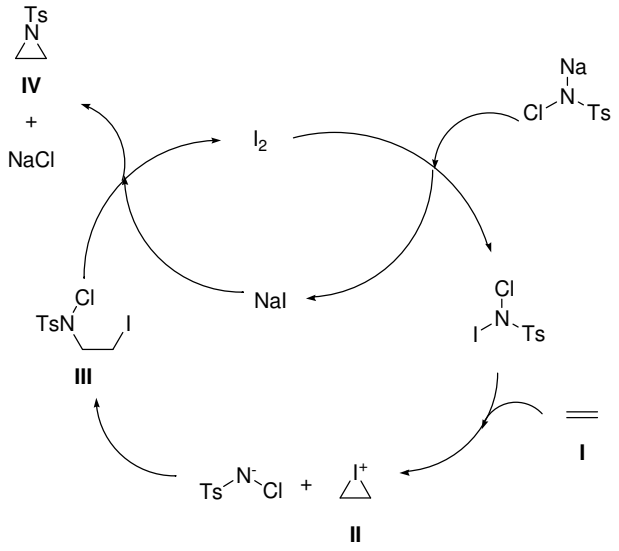
Scheme 2.86: a) LDA, **432**, THF, –78 °C, 1 h then addition of **512**, –78 °C, 30 min, 31% **513**, 48% **514**.

Sulfonyl olefin **514** was subsequently utilized in the sulfone-aziridine ring-opening, giving the olefinic amino alcohol **503** in moderate yield (Scheme 2.87).



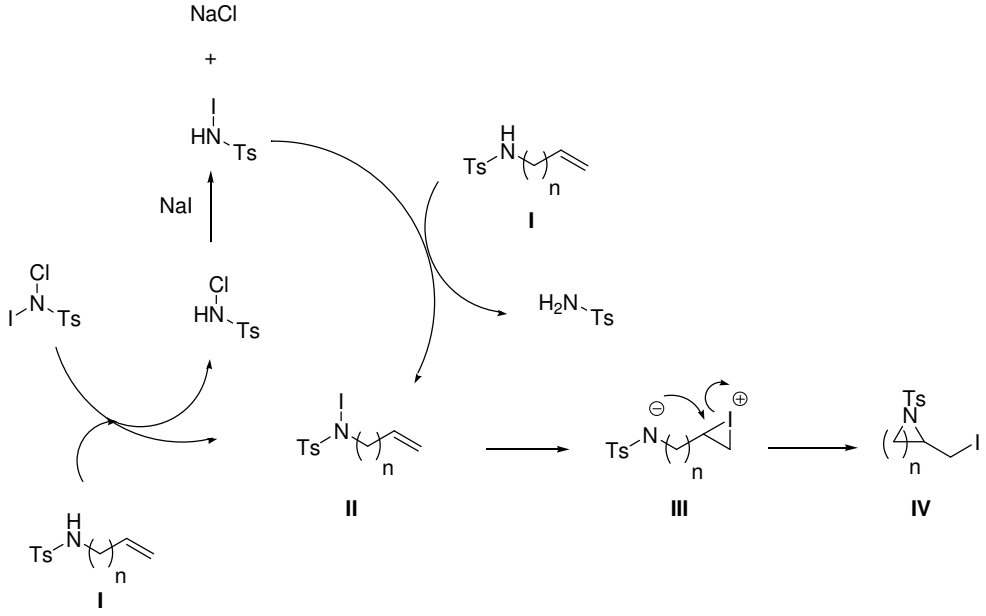
Scheme 2.87: a) ^{n}BuLi, **514**, THF, –78 °C, 30 min, then addition of **388**, –78 °C → rt, 16 h, 60%.

After the aziridine ring-opening, silylether formation would be followed by iodide-mediated cyclization as described by Minakata *et al.*[86] In this article electrophilic cyclization is achieved by use of a chloramine-T–I_2 system to produce *N*-tosylaziridines and *N*-tosylheterocycles from the corresponding *N*-alkenylamides (Scheme 2.88). Similar to the Sharpless aziridination,[20] formation of an iodinium species **II** from olefin **I** is followed by nucleophilic ring-opening using nucleophilic chloramine-T, thus forming **III**. Formation of the aziridine **IV** regenerates the iodine.



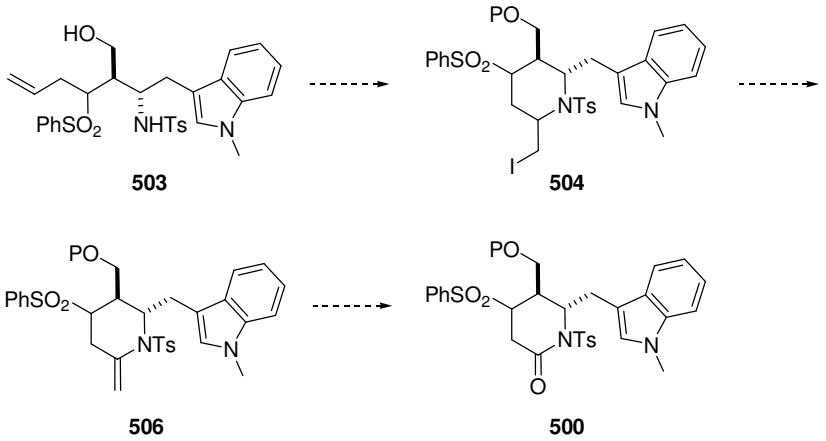
Scheme 2.88: Proposed pathway for the I_2-catalyzed aziridination of olefins using chloramine-T.

Applying this general reaction mechanism to *N*-alkenylamides, a slightly different mechanism was proposed regarding iodine transfer from iodinated chloramine-T to *N*-alkenylamide **I** (Scheme 2.89).[86] Cyclization was assumed to proceed *via* a three-membered iodonium ion **III**, generated from iodine transfer from the *N*-iodinated alkenylsulfonamide **II**. Subsequent iodonium ring-opening by the amine induces the formation of the *N*-heterocycle **IV**. Experiments using different *N*-protecting groups such as Boc and benzoyl did not generate any product, pointing to the importance of the tosylamides acidity to perform the iodination of **II**.



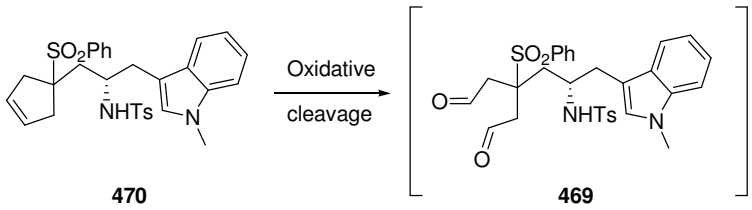
Scheme 2.89: Proposed reaction pathway to formation of *N*-heterocycles.

Following the formation of cyclic iodide **504**, removal of the halogen, either by use of crown ether[87(i)] or under base conditions,[87(ii)] would produce the corresponding ene–sulfonamide **506** (Scheme 2.90). The stability of this enamine requires evaluation, as the terminal olefin might move into conjugation, forming a more highly substituted ene–sulfonamide. Careful oxidative cleavage of enamine **506** would give lactam **500**.



Scheme 2.90: Proposed route towards δ-lactam **500** *via* enamine **506** using I_2-catalyzed cyclization.

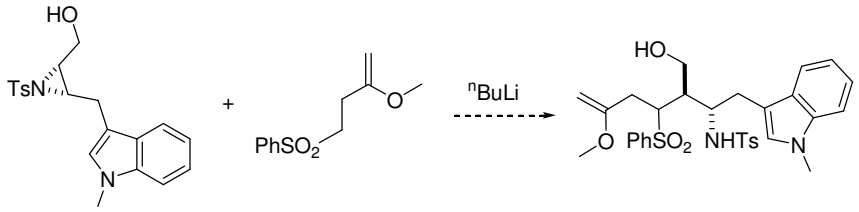
Similar studies had already been conducted by Ioannidis[69] and Rahn[80] in regard to oxidative cleavage of the cyclopentene in proximity of the electron rich indolic C_2–C_3 π-system (Scheme 2.91).



Scheme 2.91: Oxidative cleavage of the cyclopentene in proximity of an electron rich indolic C_2–C_3 π-system.

2.2.2.2.2. Sulfonic Enol-Ether 515

Using a sulfonic enol-ether strategy would apply a similar sequence as for the sulfone-olefin yet circumvent the iodine mediated cyclization and subsequent halogen removal reactions. Synthesis of sulfonyl enol-ether **515** would give, upon aziridine ring-opening, enol-ether tosamide **505** (Scheme 2.92).

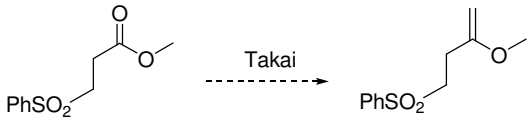


388 **515** **505**

Scheme 2.92: Aziridine ring-opening mediated by the sulfone-anion of **515**.

This sulfonyl enol-ether is produced from the corresponding tosyl ester under Takai reaction conditions. The Takai reaction has proven to be a useful tool in converting carbonyl compounds into terminal olefins / enol ethers.[88] When compared to other classical $Ti^{(IV)}$ alkylidene reagents, the Takai reagent has proven to be applicable to a wide range of carbonyl compounds.[89] In contrast, the titanium reagents developed by Tebbe[90] and Grubbs,[91] are limited to methylenation, while those developed by Petasis[92] may only be utilized if there is no possibility of β-elimination.

Application of the Takai olefination protocol to ester **516** gave irreproducible results (Scheme 2.93). Enol-ether **515** was suspected to be unstable, since complete decomposition was detected. This route was subsequently abandoned.

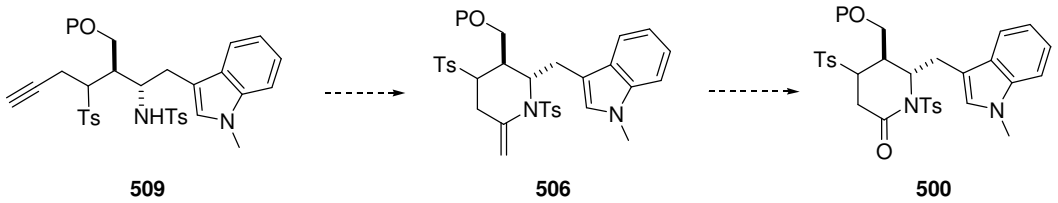


516 **515**

Scheme 2.93: Takai protocol regarding ester, enol ether conversion.

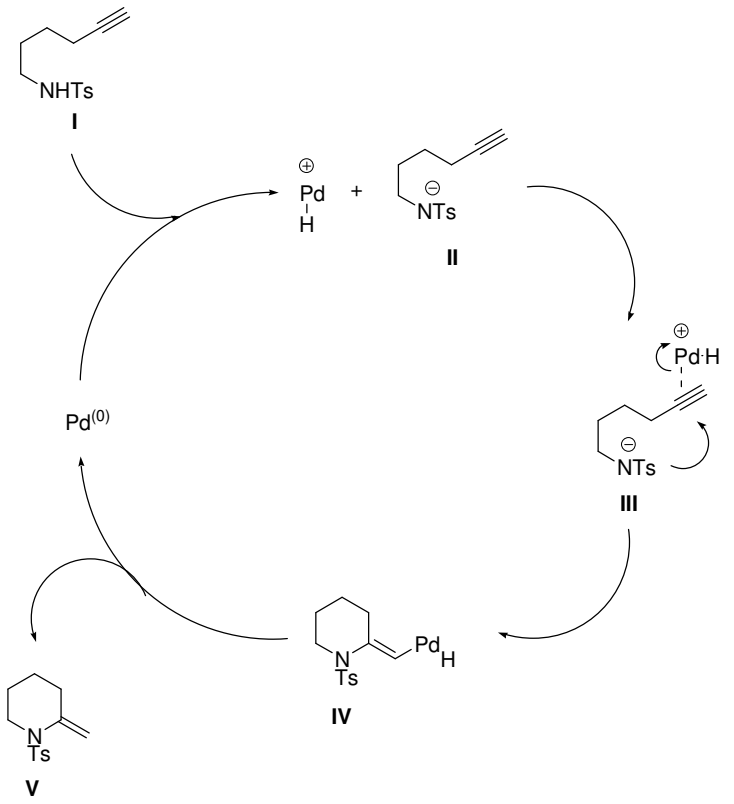
2.2.2.2.3. Tosyl-Alkyne 519

Intramolecular 6-*exo-dig* cyclization between the sulfonamide and alkyne in **509** was also investigated (Scheme 2.94).



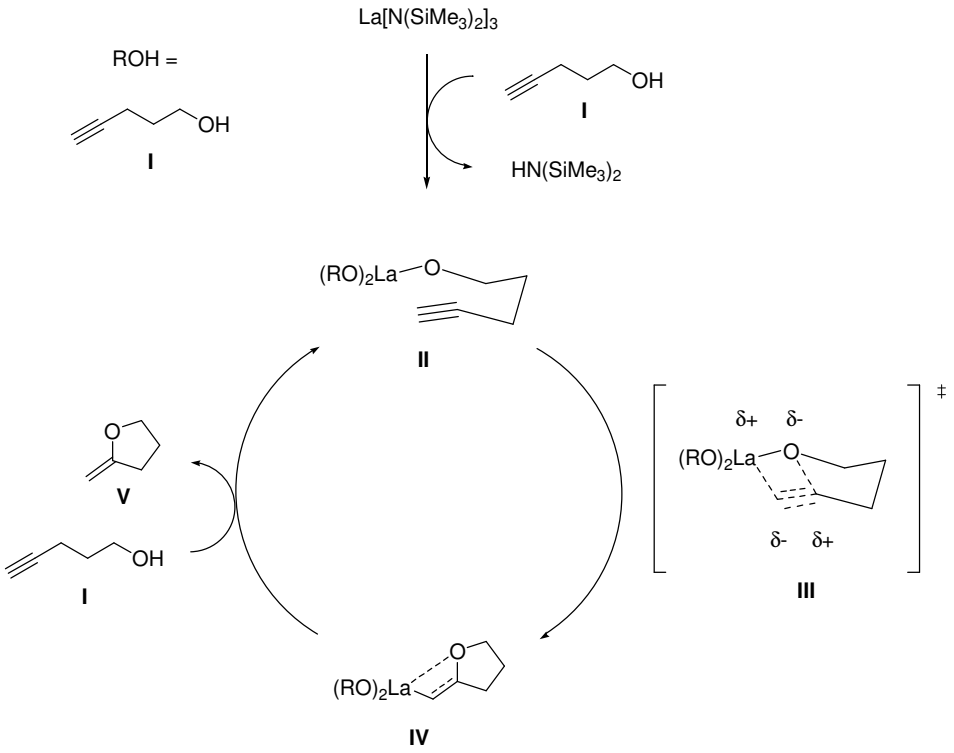
Scheme 2.94: Proposed route towards δ-lactam **500** *via* 6-*exo-dig* cyclization.

As stated earlier, according to Baldwin's rules[93] no strong preference exists between 6-*exo-dig* and 7-*endo-dig* cyclization. In the context of the development of regiocontrolled synthesis of complex functionalized hetero- and carbocycles, catalytic organometallic chemistry has proven to be a powerful tool. Besides Hg, Pd salts and lanthanides,[94] the later transition metals Pt, Au and Ag[95] have shown excellent applicability in the promotion of a variety of organic transformations.[96] The Lewis acidic nature of these metals promotes the intra- and intermolecular attack of a nucleophile by π-acid activation of unsaturated groups. With regard to Pt, Ag and Au, lack of toxicity is a significant advantage. In addition, the high affinity towards the π-system, together with easy removal due to the kinetically labile carbon–metal bond allows efficient turnover.[97] The proposed mechanism involves initiation of **I** by hydride extraction, forming a cationic palladium-hydride and **II** (Scheme 2.95). Next, PdH^+ coordinates to the triple bond of **III** followed by intramolecular cyclization affording vinylpalladium **IV**. Reductive elimination of **IV** delivers the $Pd^{(0)}$ species back into the cycle and forms the enamine **V**.[98]



Scheme 2.95: Proposed palladium-mediated catalytic cycle.

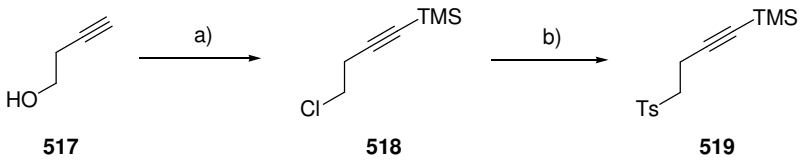
When comparing commonly used metal-based catalysts to rare lanthanides (La), a different mechanism is proposed (Scheme 2.96).[94] Liberation of the active catalyst by complexation of the lanthanide complex to the alkynol **I**, thus forming **II**, is followed by insertion of the alkyne triple bond into La–O **III**. Subsequent La–C protonolysis reforms the lanthanide-alkynol complex **II** and generates the methylene-containing heterocycle **V**.



Scheme 2.96: Proposed lanthanide catalytic cycle.

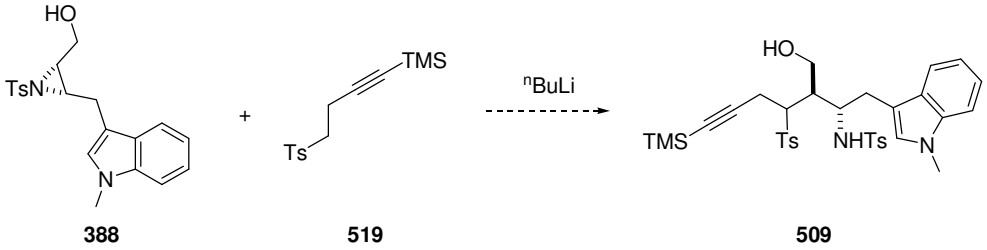
While the large majority of articles concerning cyclic enamines describe 5-*exo-dig* and 6-*endo-dig* cyclizations, the analogous 6-*exo-dig* reactions are rare. Rutjes *et al.*[99] reported the use of palladium catalysts to trigger tosamide 6-*exo-dig* cyclization, albeit in low yield (7%). Application of the latter to corresponding alcohols gave slightly higher yields (24 – 32%), presumably due to the higher nucleophilicity of the oxanion compared to the electron-deficient tosamide. A higher yield of enamine (58%) was obtained by Luo,[100] in a process in which intramolecular aminopalladation was followed by cross-coupling.

Following literature procedures, 3-butyn-1-ol **517** was chlorinated using $SOCl_2$ and subsequently TMS protected to give silyl protected alkyne **518** in good yield (Scheme 2.97).[101] Substituting the halogen for a tosyl moiety *via* substitution gave the tosyl nucleophile **519**.[102]



Scheme 2.97: a) i) EtMgBr, TMSCl, THF, rt, 1.5 h; ii) $SOCl_2$, pyridine, Δ, 7 h, 65%; b) Anh. Na *p*-toluenesulfinate, anh. NaI, DMF, 80 °C, 12 h, 40 °C, 12 h, 62%.

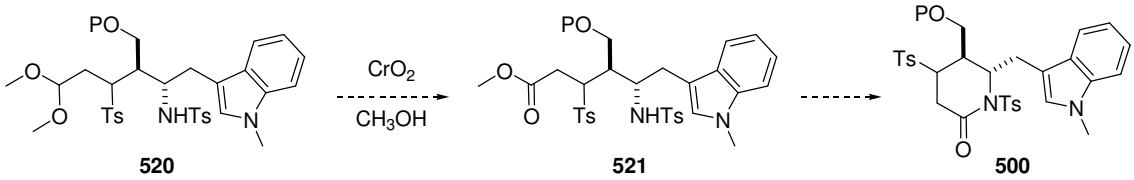
TMS protection was deemed important in this step due to the acidity of the alkyne (Scheme 2.98). Initial experiments involving combination of the lithio-anion of sulfone **519** to aziridinol **388** returned only starting material. This was disappointing in view of reported aziridine ring-opening reactions involving **519-**like sulfone-nucleophiles.[16] A possible explanation was thought to be the dilution used for this reaction, which was 0.24 M, as reported by Wenkert,[102] in contrast to the more typical values of 0.50–1.0 M used in previous studies.[15,69,80] This approach was not pursued further due to advances elsewhere.



Scheme 2.98: Sulfone-nucleophile **519** mediated aziridine ring-opening.

2.2.2.2.4. Tosyl Acetal Hydrolysis

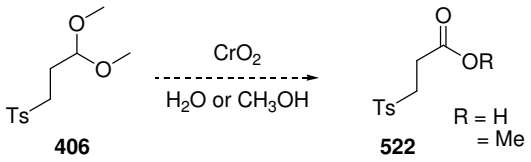
In a recently published article it was reported that acetals could be easily converted into their corresponding acids *via* the aldehydes using CrO_2 under mild, aerobic conditions.[103] If successful, the deprotection and subsequent oxidation of the aldehyde into the ester moiety would give **521**; ring-closure would then give lactam **500** (Scheme 2.99).



Scheme 2.99: Proposed synthesis towards δ-lactam **500**.

In order to test the viability of the protocol reported, experiments involving the chromium catalyst were carried out using the readily available tosyl acetal. Using various reaction

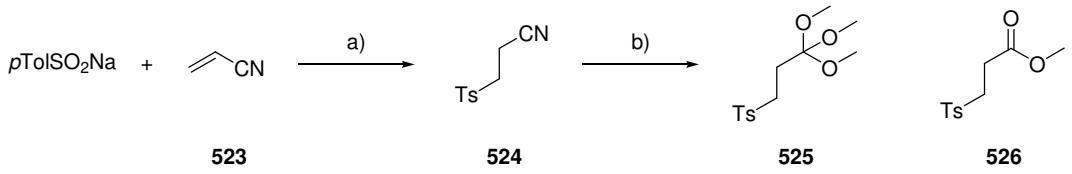
conditions, it was reported that either the methyl ester (when using methanol as solvent), or the free acid (in aqueous media) could be obtained.[103] In the event, no conversion was observed, and pure starting material was recovered (Scheme 2.100).



Scheme 2.100: CrO_2 mediated acetal conversion.

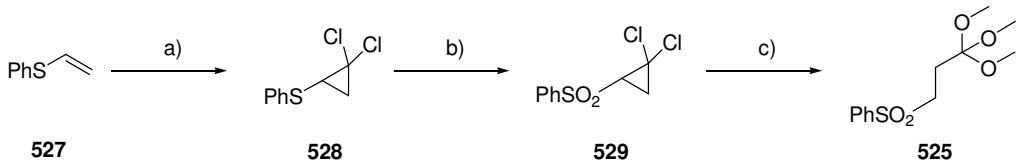
2.2.2.2.5. Orthoester 525

Following the failure of attempts to oxidize the acetal group in adduct **520** and analogues, it was considered that the masked ester **525** might be a suitable alternative. Initial attempts to prepare **525** followed the method described by Ghosez.[104] Condensation of *p*-toluenesulfinic acid with acrylonitrile gave **526** in an excellent yield (Scheme 2.101). However, conversion of the tosyl nitrile into the orthoester *via* the imine methoxide was not realized, despite being reported in the literature. Several attempts to reduce the amount of acid present by base-wash to form the orthoester *via* imidate alcoholysis[105] yielded ester **526** exclusively.[19,106]



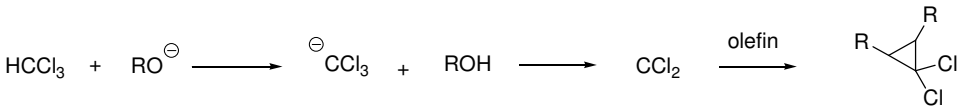
Scheme 2.101: a) AcOH, Δ, 16 h, 95%; b) i) CH_3OH, AcCl, DCM, 5 °C, 45 h; ii) CH_3OH, 20 °C, 72 h, 85% **526**.

An alternative route towards the synthesis of the phenylsulfonyl orthoester has been reported by Parham *et al.*[107] α,β-Unsaturated sulfide **527** was treated with dichlorocarbene, generated from methoxide and ethyl trichloroacetate, to give corresponding dichlorocyclopropane **528** (Scheme 2.102).



Scheme 2.102: a) Ethyl trichloroacetate, $NaOCH_3$, petrol, 0 °C → rt, 16 h, 60%; b) AcOH, H_2O_2, 100 °C, 3 h, 90%; c) $NaOCH_3$, CH_3OH, Δ, 2 h, 95%.

These reactions generally yield 60% of product due to a side-reaction involving the dichlorocarbene and the alcohol formed in these formation reactions (Scheme 2.103).[108]

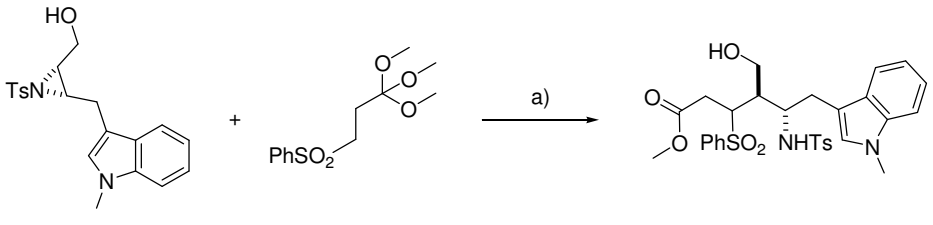


Scheme 2.103: Carbene reaction mechanism.

Although ^{t}butoxide is considered superior to sodium methoxide because of its decreased reactivity towards the carbene, no significant yield increase was observed when comparing potassium ^{t}butoxide, sodium methoxide and sodium ethoxide. Pivotal to the success of the carbene reaction was the use of carefully purified petrol, as olefinic impurities caused significant reductions in product purity and ease of isolation.[107]

Oxidation of **528** involved *in situ* formation of peracetic acid from peroxide and acetic acid and gave **529** as a white solid (Scheme 2.102). Purification of the latter involved base-wash and column chromatography in order to remove any traces of phenylsulfonylethene (oxidized unreacted starting material) and acetic acid; since the acid caused hydrolysis of the orthoester to the corresponding methyl ester. Treatment of **529** with freshly prepared sodium methoxide gave **525** in excellent yield.[109]

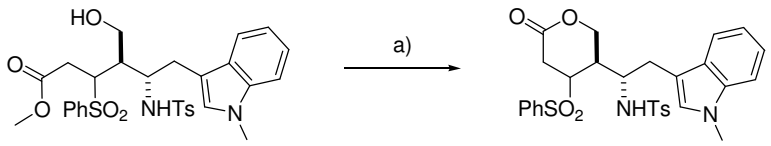
Applying our sulfone-stabilized nucleophile methodology to aziridinol **388** gave **526** upon mild-acidic work-up, similar to that of the tosylacetal utilization (Scheme 2.104).



388 **526** **527**

Scheme 2.104: a) ^{n}BuLi, 2.0 equiv. **526**, THF, –78 ^{o}C, 30 min, then addition of **388**, –78 ^{o}C → rt, 16 h, 90%.

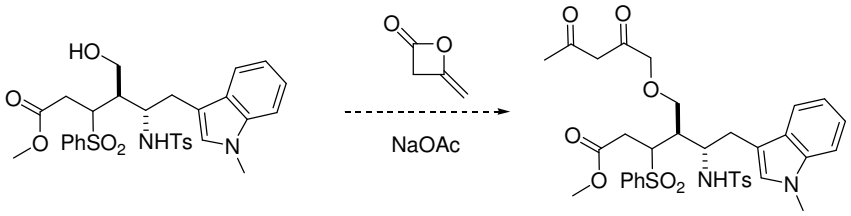
It was found subsequently that if left standing, hydroxyester **527** was converted into lactone **528**. Treatment of **527** with TFA gave a similar result (Scheme 2.105).[110]



527 **528**

Scheme 2.105: a) TFA, DCM, rt, 5 min, 65%.

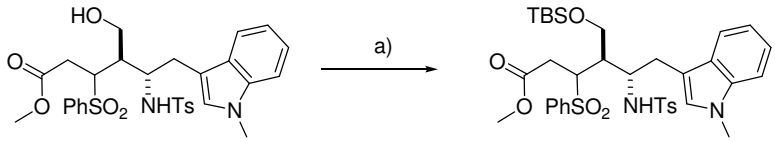
Having prepared **527**, protection of the alcohol was important, since it was anticipated that any attempt at cyclization would lead to the formation of lactone rather than lactam products. Attempted formation of β-ketoester **528** by treatment of **527** with sodium acetate and diketene was unsuccessful (Scheme 2.106).[111] This is probably due to the presence of the amine which could interfere in this reaction. Starting material decomposition was observed.



527 **528**

Scheme 2.106: Attempted β-ketoester formation.

It was found subsequently that hydroxyl protection was necessary prior to cyclization. This was achieved using standard silylating conditions to give **529** in high yield (Scheme 2.107).



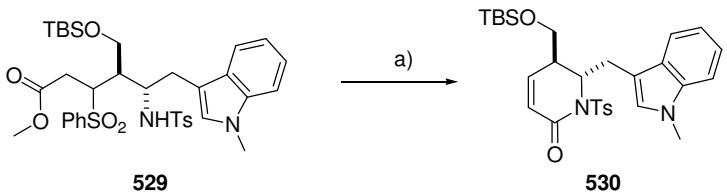
527 **529**

Scheme 2.107: a) TBSCl, imidazole, DMF, rt, 30 min, 91%.

Thermal as well as Lewis acid conditions were investigated to promote the cyclization. Scott *et al.*[112] reported the use of thermal reaction conditions to facilitate intramolecular δ-lactam formation from the corresponding secondary amine and ester moieties. Exposing **529** to high temperatures (refluxing toluene) did not result in any product formation, and starting material was recovered cleanly.

In an article by Dake,[113] deprotection of a Boc-*N*-tosyl substrate was followed by treatment with trimethylaluminium (TMA) at room temperature which provided an effective route to δ-

lactams. Initial experiments at room temperature did not generate the product and only starting material was obtained. When increasing the reaction temperature to 80 °C exceptionally clean conversion of **529** into **530** was observed (Scheme 2.108).



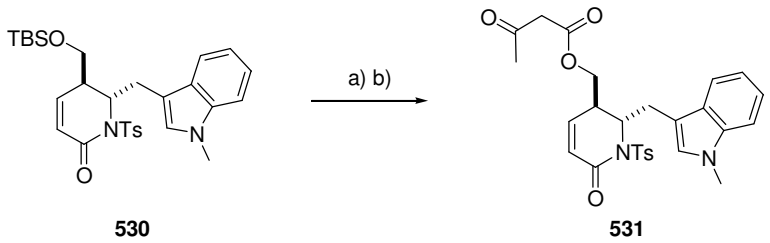
529 **530**

Scheme 2.108: a) TMA, toluene, rt → 80 °C, 3 h, 99%.

In this cyclization reaction, the TMA-species binds to the amide, forming an aluminium-amide complex similar to that reported for Weinreb amide formation using TMA. This complex increases the nucleophilicity of the amide, resulting in cyclization through an addition–elimination process.[114] In a later step TMA also activates the sulfone which is removed to give unsaturated lactam **530**, presumably *via* an E1cB mechanism.

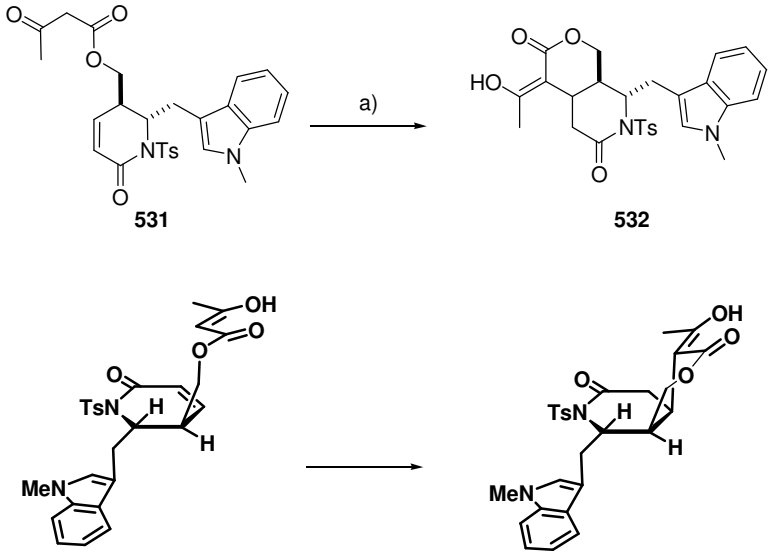
2.2.2.3. Towards (±)-Alstonerine

Removal of the TBS group was achieved using standard conditions.[15] Installation of the β-ketoester through the use of potassium acetate and diketene[111] (the acetate forming an activated β-keto anhydride) at elevated temperatures gave β-ketoester lactam **531** (Scheme 2.109).



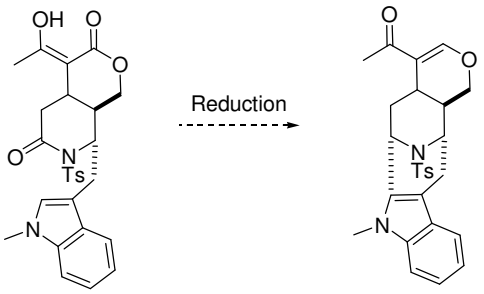
Scheme 2.109: a) HOAc : H_2O : THF (3 : 1 : 1), rt, 16 h, 99%; b) KOAc, diketene, THF, Δ, 1 h, 93%.

Following successful installation of the β-ketoester, treatment of **531** with DBU would trigger a Michael-type addition of the *in situ* formed enolate to the vinylogous lactam forming the final ring structure of alstonerine. This reaction gave a pure conversion of **531** to **532** in which **532** exhibits a singlet proton at 14 ppm due to intramolecular hydrogen bonding within the enol tautomer (Scheme 2.110).



Scheme 2.110: a) DBU, THF, rt, 6 h, 91%.

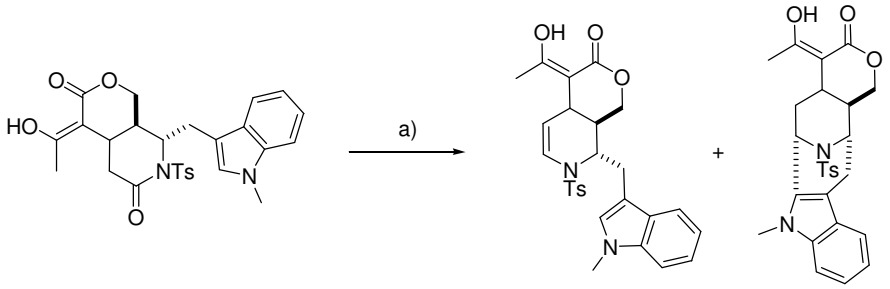
With all ring-systems now incorporated we hoped to simultaneously perform a Pictet–Spengler cyclization and reduce the β-ketolactone into the vinylogous carbonate. DIBAL was chosen to perform this ambitious sequence of reactions (Scheme 2.111).



532 **36**

Scheme 2.111: Global reduction.

The global reduction step was followed by an acid quench which gave a mixture of 2 products, **533** and **534**. The acid quench (containing 6 M HCl) was too acidic therefore removing the alcohol in the aminol intermediate resulting in THPyr **533** formation (Scheme 2.112). **533** Could easily be converted into **534** by treatment with a catalytic amount of TFA. This minor issue was circumvented by the addition of catalytic TFA at the end of the DIBAL reduction, reaction providing **534** as a single product.

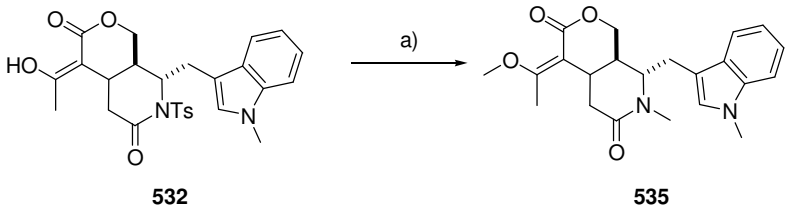


532 **533** **534**

Scheme 2.112: a) i) DIBAL, THF, 1 h, –78 °C; ii) 6M HCl (cat.), rt, 15% **533**, 75% **534**.

DIBAL, Superhydride and L-Selectride all failed to effect conversion of **532** into alstonerine **36** and **534** was obtained. Subsequent attempts to further reduce **534** using the aforementioned reagents failed and pure **534** was recovered. A modification would involve conversion of the *N*-Ts lactam into the *N*-Me lactam prior to the global reduction step, thus obtaining the correct piperidine structure needed and obviating the need for subsequent deprotection–protection. It was hoped also that such conversion would provide a more reactive substrate for vinylogous carbonate reduction. Rahn had already examined the sulfonamide detosylation, using sodium naphthalide followed by reductive amination with formaldehyde, in which the *N*-Me piperidine was obtained in moderate yield.[80] Lactam desulfonylation by use of a mild reduction step employing samarium diiodide[115] was unsuccessful. A final attempt to access alstonerine **36**, bis-methylation[116] to gain **535** (of both *N*-piperidine as well as enolic OH) was

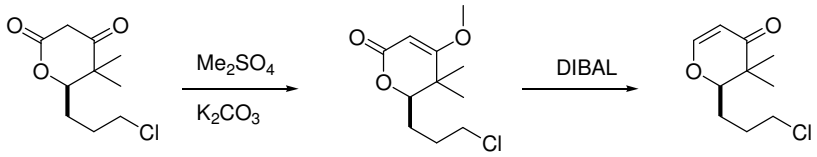
attempted, after which it was hoped that global reduction would yield the natural product. Extensive decomposition during the dimethylation reaction towards **535** was observed (Scheme 2.113). However, NMR analysis revealed the absence of the enolic hydroxy and tosyl moiety and the presence of two new methyl functionalities.



532 **535**

Scheme 2.113: a) i) Na napthalide, THF, –78 °C, 1 h; ii) CH_3I, rt, 30 min.

Kocienski previously reported[116] such a transformation involving conversion of β-ketolactone **536** into enol ether **537** followed by reduction using DIBAL to provide **538** (Scheme 2.114).

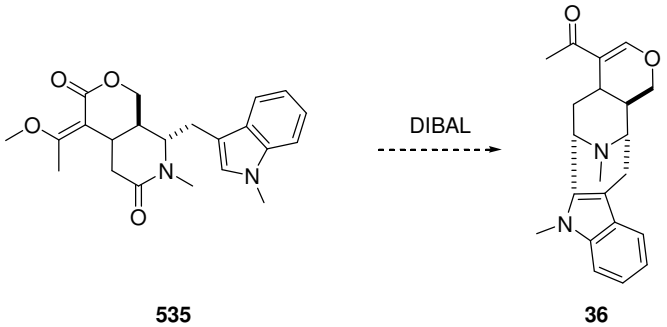


536 **537** **538**

99 % 85 %

Scheme 2.114: Koscienski approach to the formation of vinylogous ester **538**.

A last attempt towards DIBAL induced global reduction of **535** to obtain alstonerine **36** was attempted yet proved unsuccessful (Scheme 2.115).



535 **36**

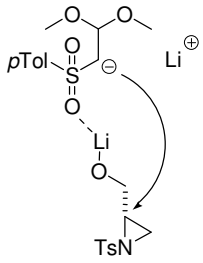
Scheme 2.115: Attempted global reduction of **535**.

Despite this setback a new strategy towards the total synthesis of (±)-alstonerine has been developed and is presented in this thesis. As such, optimalization of the final global reduction steps is required in order to successfully conclude the total synthesis of (±)-alstonerine.

2.3. Cytisine

2.3.1. Current Progress Towards (–)-Cytisine

Key to the viability of the cytisine project was the regioselective opening of the aziridinol by the tosyl acetal anion nucleophile (Scheme 2.116). Lithium-chelation control was expected to assist the nucleophile towards attack at the more substituted end (**539**).[16,17] In addition to the application of the aziridine ring-opening mediated by sulfone-anions, synthesis and chemical manipulation of THPyrs would be a major component in the synthesis of this natural product. The latter has been thoroughly investigated within the Craig group for the last decade, initiated by the work of Williams.[117]



539

Scheme 2.116: Regioselective aziridine ring-opening.

Retrosynthetic analysis of (–)-cytisine **70** reveals a disconnection between the *N*-pyridone and the piperidine side chain (Figure 2.12). Construction of the tricycle would involve deprotection of the pyridone amine **540** followed by displacement of the OR-moiety to intramolecularly construct the bridged tricyclic structure within **70**, followed by detosylation of the piperidine. Debenzylation of the pyridone, probably by use of hydrogenation, would simultaneously deprotect the latter and saturate the double bond within the THPyr of **542**. Further analysis of the fused pyridone and THPyr reveals a Suzuki or Stille coupling reaction, not unlike that used by O'Neil and co-workers[118] in order to form the C_3–C_6 bond.

Iodination of THPyr[119] would provide the Suzuki nucleophile **542** from **543** using NIS, while using the O'Neil protocol would provide the electrophile **541**. Access to **542** follows from Lewis acid treatment of **544**.[37]

As stated earlier, the key step involved the sulfone-anion mediated ring-opening of azridinol **545**, which it was hoped would result in the regioselective opening of the latter at the more substituted end, providing **544**.

The tosyl diacetal nucleophile **406**[13] would be prepared in two steps from tolylsulfinic acid and acrolein, while the aziridinol **545** would be prepared either as a racemate from 2-propen-1-ol (one step) *via* Sharpless aziridination,[20] or in enantiomerically pure from L-serine (six steps).[120]

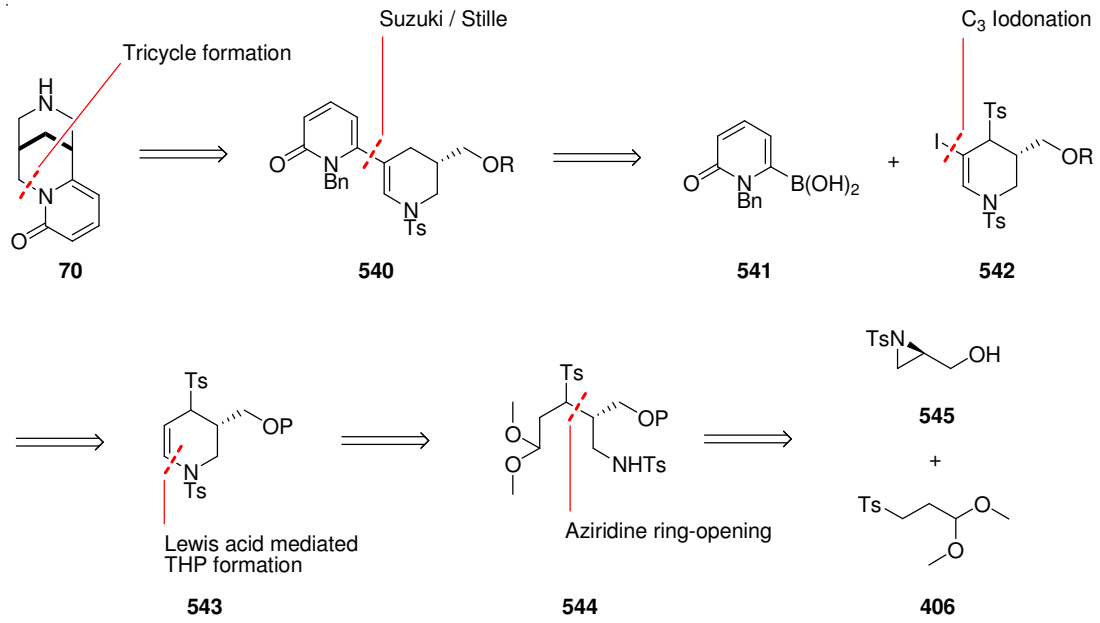
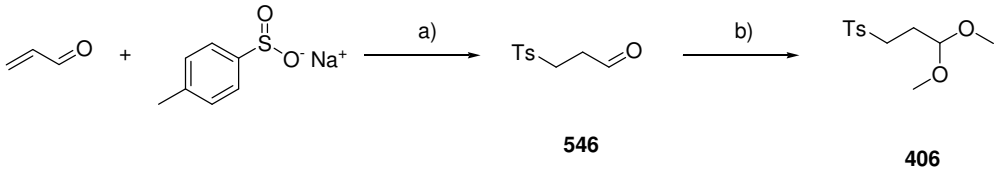


Figure 2.12: Retrosynthesis of cytisine **70**.

2.3.2.1. Tosyl Acetal 406

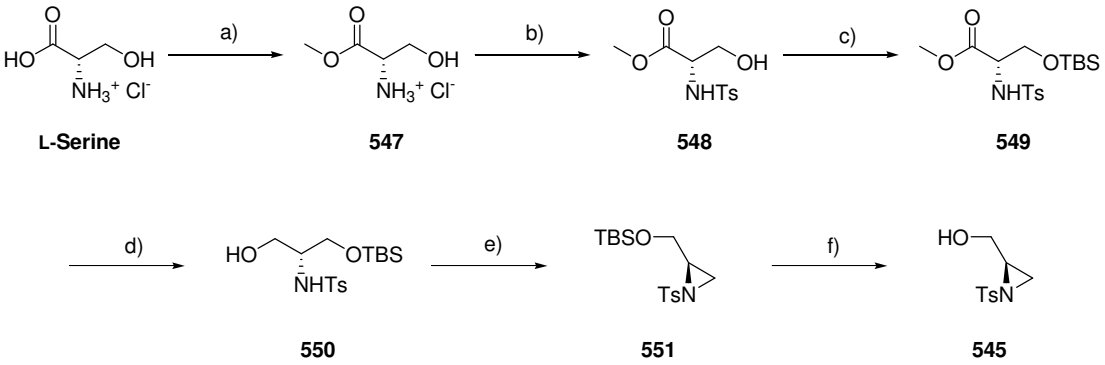
Acetal **406** (Scheme 2.117) was prepared using a standard procedure developed in our group,[13] which included the use of *p*-toluene sulfinic acid sodium salt and acrolein in an acidic THF / H_2O solution (1 : 1). The resulting 3-tosylpropanal **546** was subjected to a catalytic amount of tosic acid in methanol in the presence of trimethyl orthoformate to give acetal **406** in 83% yield.



Scheme 2.117: a) HOAc, THF / H_2O, rt, 16 h, 99%; b) *p*-TsOH, CH_3OH, trimethyl orthoformate, 50 °C, 16 h, 83%.

2.3.2.2. Enantiomerically Pure Aziridinol 545

L-Serine was chosen as the starting material for the synthesis of the enantiomerically pure aziridinol **545** (Scheme 2.118). Following the Bergmeier synthesis route[120(ii)] towards **545**, the initial step involved the $SOCl_2$ mediated esterification of serine to provide the corresponding methyl ester as a HCl salt **547**. Neutralization followed by treatment with tosyl chloride gave tosyl ester **548**. Protection of the alcohol as a silyl ether gave fully protected L-serine **549**. Reduction of the ester moiety by use of $LiBH_4$, either prepared from $NaBH_4$ and LiCl or used as commercially available reagent, furnished amino alcohol **550**. Application of Mitsunobu condensation reaction conditions resulted in aziridine silyl-ether **551**. TBAF desilylation gave **545** in six steps with an overall yield of 44% as described by Bergmeier.[120(ii)]

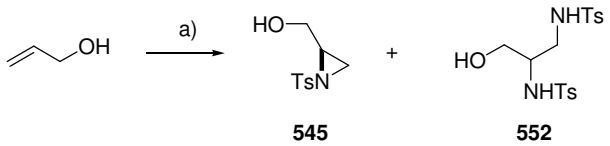


Scheme 2.118: a) $SOCl_2$, CH_3OH, Δ, 4 h, 99%; b) TsCl, TEA, DCM, 0 °C, 16 h, 85%; c) TBSCl, Imidazole, DCM, rt, 16 h, 97%; d) $LiBH_4$, THF, rt, 16 h, 80%; e) DIAD, PPh_3, THF, 0 °C → rt, 16 h, 97%; f) TBAF, THF, 0 °C, 1 h, 90%.

2.3.2.3. Racemic Aziridinol 545

An alternative route towards racemic aziridinol **545** was investigated, thus circumventing the six-step approach towards the enantiomerically pure material. Utilization of the Sharpless aziridination[20] would provide a quick and steady supply of the latter to screen the aziridine ring-opening experiments.

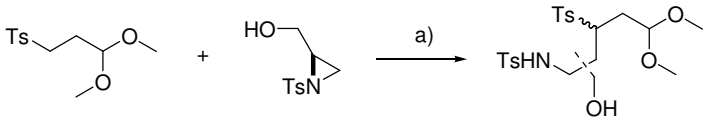
Applying the Sharpless aziridination protocol to 1-propenol would produce the corresponding racemic azirdin-1-ol in a single step (Scheme 2.119). Treatment of 1-propenol with PTAB and chloramine-T gave racemic aziridinol **545** and diamine **552**. This phenomenon occurs due to the electrophilicity of the newly formed aziridinol, which in the presence of nucleophilic $TsNCl^-$, results in the ring-opening of aziridinol **545**.[20]



Scheme 2.119: a) Chloramine-T, PTAB, CH_3CN, rt, 16 h, 52%; 40% diamine.

2.3.2.4. Aziridine Ring-Opening

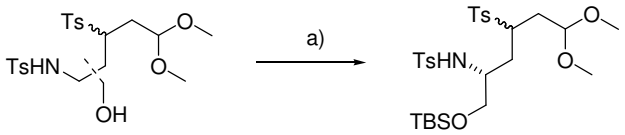
Nucleophilic sulfone-anion mediated ring-opening reactions of **406** were attempted using the standard ^{n}BuLi treatment,[117] in which product **553** was obtained (Scheme 2.120). No significant changes were observed when applying different methods of addition. NMR data obtained from product **553** proved inconclusive in ascertaining the precise regioselective outcome.



406 **545** **553**

Scheme 2.120: a) ^{n}BuLi, THF, –78 °C → rt, 3 h, 95%.

TBS-protection of the alcohol-moiety had previously facilitated the separation of diastereomers, as in the case of racemic vinyl aziridine precursor described by Carballares.[13] This same method improved separation significantly, NMR data obtained showed a 3 : 1 ratio between both diastereomers **554** (Scheme 2.121). The regioselectivity observed showed a total preference towards opening at the least hindered end.

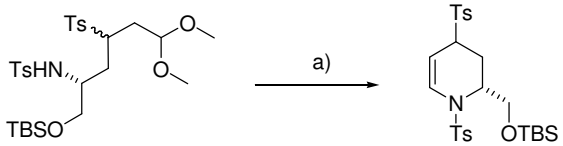


553 **554**

3 : 1

Scheme 2.121: a) DMAP, TEA, TBSCl, DCM, 1.5 h, rt, 91%.

BF_3 treatment provided corresponding silyl-protected THPyr **555** which showed no sign of a branched structure further adding proof to the regioselective outcome of the previous aziridine ring-opening reaction (Scheme 2.122).



554 **555**

3 : 1

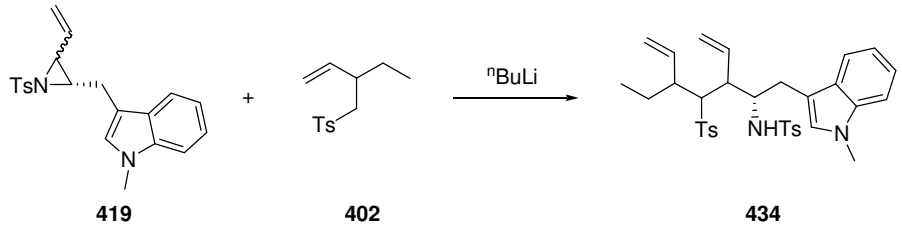
Scheme 2.122: a) $BF_3{\cdot}Et_2O$, DCM, 30 min, –78 °C → –20 °C, 59%.

Due to the regioselective outcome observed during aziridine ring-opening, no further attempts were made towards the total synthesis of cytisine using the route described.

2.4. Conclusion and Future Work

2.4.1. (±)-Suaveoline

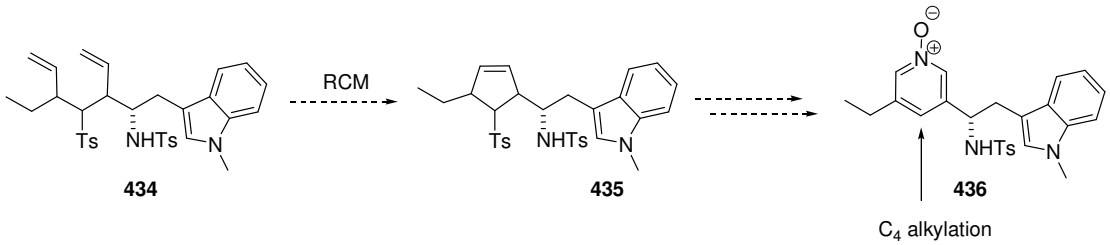
Our endeavours into the nucleophilic aziridine ring-opening reaction using sulfone-stabilized anions, have led to the synthesis of *cis / trans*-vinyl aziridine **419** in 8 steps from L-tryptophan due to observed inreactivity of the corresponding hydroxy-aziridine **388** (Scheme 2.123). No pure *cis*-vinyl aziridine was obtained in a sufficient yield and reactions continued using the diastereomeric mixture of **419**.



419 **402** **434**

Scheme 2.123: Sulfone-mediated aziridine ring-opening.

Of the three nucleophiles evaluated for nucleophilic aziridine ring-opening, the secondary sulfone-stabilized anion of **402** was most able to successfully ring-open vinyl aziridine **419** to give the diolefin **434** (Scheme 2.124). In other cases complex mixtures of products were obtained. Failed α-tosyl alkylations, reported by Lewis,[1] led to investigations towards the synthesis of pyridine-*N*-oxide; this strategy would enable the functionalization at the C_4 position in suaveoline. Similar cases have been reported in literature regarding the insertion of cyanide at pyridine C_4.[121]



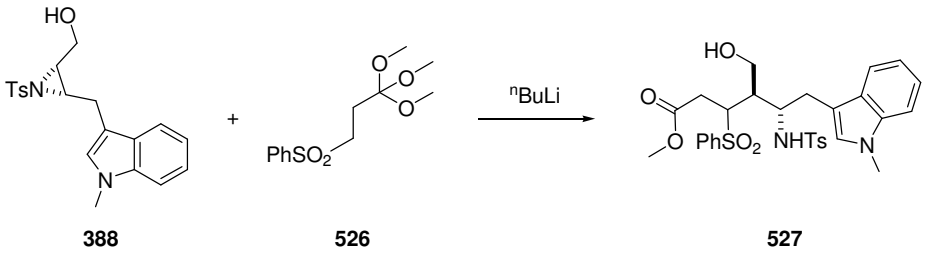
434 **435** **436**

Scheme 2.124: Proposed pyridine-*N*-oxide formation.

Hydrolyzing this cyanide moiety to the ester-functionality would, as described on page 111, provide a handle for chain homologation and subsequent Pictet–Spengler bicyclization.

2.4.2. (±)-Alstonerine

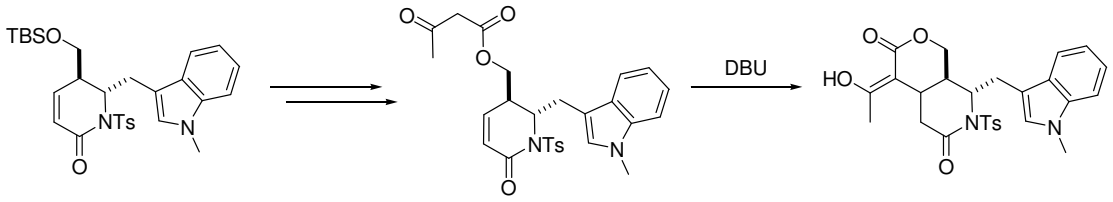
Following the successful optimization of epoxide **385** ring-opening by *N*-methylindole and subsequent synthesis of indole aziridinol **388**, a range of sulfone-nucleophiles were tested each involving a different strategy towards the synthesis of δ-lactam **500**. Formation of tosyl orthoester **526** proved to be the most successful approach and as such was carried through towards the total synthesis of (±)-alstonerine (Scheme 2.125).



388 **526** **527**

Scheme 2.125: Nucleophilic ring-opening of aziridine **388** using the lithio-anion of **526**.

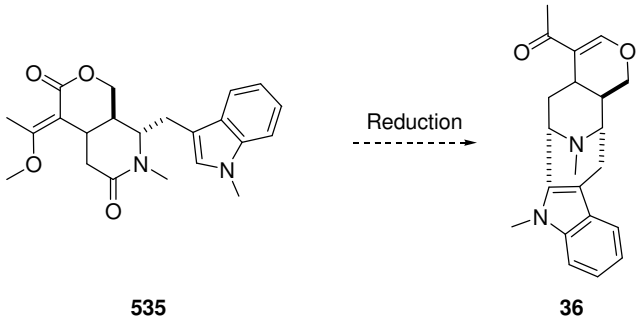
Application of TMA to the corresponding silyl-ether of **527** facilitated formation of δ-lactam **530** *via* E1cB (Scheme 2.126). Michael-type addition of the β-ketoester at the vinyl moiety of the δ-lactam C_4 position also progressed at a very high yield. Investigations into global reduction of both carbonyl moieties in **532** did not lead to alstonerine formation. Pictet–Spengler cyclization was observed, forming the piperidine pentacyclic system while not affecting the lactone ring, showing the ease of this cyclization to occur.



530 **531** **532**

Scheme 2.126: Synthesis of **532**.

A last attempt towards reduction of the lactone carbonyl involved methylation of the enolate together with conversion of the *N*-tosyl protecting group into *N*-methyl **535** (Scheme 2.127). Global reduction was unsuccessful and due to the lack of material and time, no further optimization of this conversion could be carried out.



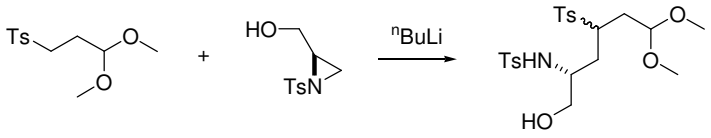
535 **36**

Scheme 2.127: Attempted global reduction of **535**.

With the successful completion of the total synthesis of (±)-alstonerine **36** just two steps away, a more efficient dimethylation reaction to give **535,** and a method for its reduction requires further investigation. Recent articles have described the conversion of lactones into transposed vinyloguous esters in high yield, applying DIBAL reduction on methyl enolate lactones.[116]

2.4.3. (–)-Cytisine

Aziridine **545** could be prepared either enantiomerically pure in six steps or in its racemic form utilizing Sharpless aziridination of propene-1-ol in a single step. The ring-opening reaction using tosyl acetal **406** only furnished unwanted regioselective product **552** (Scheme 2.128). Our attempt to regioselectively ring-open **545** by use of the aforementioned lithio-oxygen chelation control proved to be unsuccessful, and as such this project has been abandoned.



406 **545** **552**

Scheme 2.128: Synthesis of **552**.

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CHAPTER 3

Experimental

3. Experimental

All experiments were performed under a nitrogen atmosphere unless stated otherwise, with standard laboratory techniques used when handling water-sensitive reagents.

Solvents and reagents: Solvents were distilled under nitrogen prior to use; MeCN and CH_2Cl_2 from calcium hydride, toluene from sodium, Et_2O, THF and DME from sodium-benzophenone ketyl, MeOH from magnesium turnings and iodine, DCE from calcium chloride water using a Stuart Merit Water Still W4000. Petrol refers to the fraction of light petroleum ether that boils at 40–60 ^oC. All solvents were dry reagent grade unless otherwise stated. All chemical reagents used were commercially available from Fischer and Sigma Aldrich. ^nBuLi (2.5 M in hexanes) was titrated prior to each use using diphenyl acetic acid.

Melting points: Determined on Stuart Scientific SMP1 melting point apparatus.

Infrared Spectroscopy: Spectra were recorded by a PerkinElmer Spectrum 100 series FT-IR Spectrometer.

Optical rotation: Measured on an Optical Activity Ltd. Instrument.

Microwave: Performed in a Biotage Initiator upgraded to version 2.5 and cooled using compressed air (4 bar).

NMR spectroscopy: ^1H NMR recorded on Bruker Ultra-Shield AV400 and DRX-400 at 400 MHz. ^{13}C NMR recorded on Bruker Ultra-Shield AV400 and DRX-400 at 100 MHz. Chemical shifts are in parts per million (ppm) and are referenced relative to the residual proton-containing solvent ($CDCl_3$; ^1H NMR = 7.27 ppm, ^{13}C = 77.0 ppm, CD_3OD; ^1H NMR 4.87, 3.31 ppm, ^{13}C = 49.1 ppm).

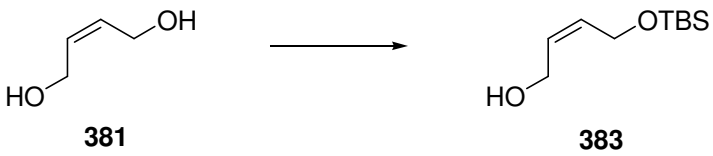
Mass Spectroscopy (CI, ESI): Low and high resolution mass spectra recorded on Micromass Autospec Premier spectrometer.

Elemental Analysis: Performed by Dr. Stephen Boyer at the microanalytical laboratory, London Metropolitan University.

Chromatography: Thin layer chromatography (TLC) performed on aluminium-backed 0.2 mm Merck 60 F_{254} plates with visualisation effected with ultraviolet light, potassium permanganate or vanillin. Flash chromatography with BDH (40–63 μm) silica gel performed according to the method employed by Still.[1]

3.1. (±)-Suaveoline

Cis-4-[(ᵗbutyldimethylsylil)oxy]-but-2-en-1-ol 383



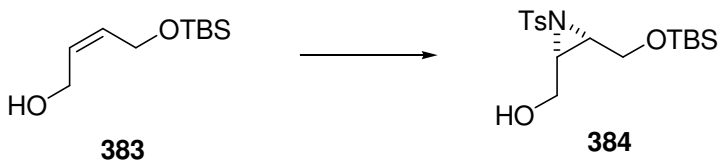
381 **383**

To a suspension of NaH (2.80 g, 70.0 mmol, 1.0 equiv.) in THF (140 ml) at rt was added *cis*-but-2-ene-1,4-diol **381** (6.20 g, 5.80 mL, 70.0 mmol, 1.0 equiv.) and the mixture stirred for 16 h. TBDMSCl (10.4 g, 69.3 mmol, 1.0 equiv.) was then added and vigorous stirring continued for 45 min. The reaction mixture was poured onto Et_2O (500 mL) and the resulting solution washed with 10% aqueous K_2CO_3 (2 x 200 mL) and brine (200 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (10% → 50% EtOAc–petrol) gave **383** as a pale yellow oil (13.9 g, 98%).

R_f = 0.15 (40% Et_2O–petrol); ν_{max} (film) 3400, 2929, 2961, 2857, 1474, 1465, 1253, 1082, 1029, 833, 774 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.68 (2H, m, CH_2CH=$CHCH_2$), 4.26 (2H, d, *J* 5.0 Hz, CH_2OH), 4.20 (2H, d, *J* 5.5 Hz, CH_2OTBS), 2.46 (1H, broad s, O*H*), 0.91 (9H, s, $(CH_3)_3C$), 0.09 (6H, s, $(CH_3)_2Si$); δ_C (100 MHz, $CDCl_3$) 131.2 (CH=*C*HCH_2OH), 130.1 (CH=*C*HCH_2OTBS), 59.4 (*C*H_2OH), 58.4 (*C*H_2OTBS), 25.8 (3 x *C*H_3C), –5.3 (2 x *C*H_2Si); M/z (CI) 220 $[M+NH_4]^+$, 203 $[M+H]^+$, 170, 153, 132 (Found $[M+H]^+$, 203.1465. $C_{10}H_{22}SiO_2$ requires $[M+H]^+$, 203.1467).

The data are in agreement with the reported compound.[2]

***Cis*-((2R,3S)-3-((ᵗbutyldimethylsilyloxy)methyl)-1-tosylaziridin-2-yl)methanol 384**



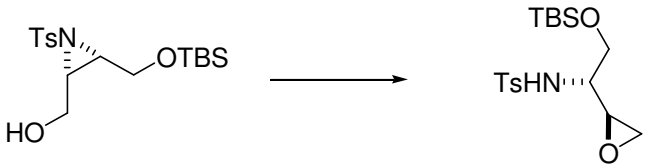
383 **384**

To a mixture of olefin **383** (9.50 g, 47.0 mmol, 1.0 equiv.) and anhydrous chloramine T (12.8 g, 56.4 mmol, 1.2 equiv.) in CH_3CN (240 mL) at rt was added PTAB (1.80 g, 4.70 mmol, 10 mol %). The reaction mixture was stirred at rt for 48 h, partially concentrated under reduced pressure and filtered through a pad of silica (washing with Et_2O). Concentration of the filtrate under reduced pressure and column chromatography (25% → 50% EtOAc–petrol) gave **384** as a pale yellow oil (15.7 g, 90%).

R_f = 0.25 (66% petrol–EtOAc); ν_{max} (film) 3500, 2933, 2861, 1601, 1466, 1324, 1264, 1159, 1089, 948, 834, 669 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.35 (2H, d, *J* 8.5 Hz, *meta*-Ts), 3.88 (3H, dd, *J* 6.0, 11.5 Hz, NC*H*CH_2OH), 3.76 (1H, dd, *J* 6.5, 13.0 Hz, NC*H*CH_2OTBS), 3.69 (2H, m, NCHC*H*$_2$OH), 3.10 (2H, m, NCHC*H*$_2$OTBS) 2.45 (3H, s, TsC*H*$_3$), 2.33 (1H, t, *J* 6.5, O*H*), 0.82 (9H, s, (C*H*$_3$)$_3$C), 0.04 (6H, s, (C*H*$_3$)$_2$Si); δ_C (100 MHz, $CDCl_3$) 145.0 (SO_2C), 134.5 (CH_3CTs), 130 (*ortho*-Ts), 128 (*meta*-Ts), 60.5 (CH_2OH), 59.5 (CH_2OTBS), 44.0 (CCH_2OH), 43.5 (CCH_2OTBS), 26.0 ((*C*H$_3$)$_3$), 21.5 (Ts*C*H$_3$), 18.0 ((CH$_3$)$_3$*C*), –5.5 ((CH$_3$)$_2$Si). M/z (CI) 389, 372 $[M+H]^+$, 218, 189, 174 (Found $[M+H]^+$ 371.1431, $C_{17}H_{29}NO_4SSi$ requires $[M+H]^+$ 371.1587). (Found: C, 55.00; H, 7.79; N, 3.79. $C_{17}H_{29}NO_4SSi$ requires C, 54.95; H, 7.87; N, 3.77%).

The data are in agreement with the reported compound.[2]

_N_-((R)-2-(^t^Butyldimethylsilyloxy)-1-((S)-oxiran-2-yl)ethyl)-4-methylbenzenesulfonamide 385



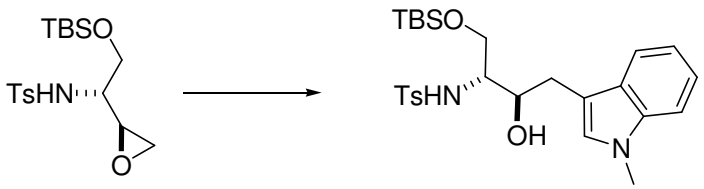
384 **385**

To a 60% w/t suspension of NaH in mineral oil (7.30 g, 183 mmol, 4.0 equiv.) in THF (360 mL) at 0 °C was dropwise added a solution of aziridine **384** (17.0 g, 45.7 mmol, 1.0 equiv.) in THF (140 mL). The reaction mixture was stirred for 3 h at 0 °C after which it was cooled to –78 °C and saturated aqueous NH_4Cl (100 mL) was added dropwise. After warming to rt, the aqueous layer was extracted with Et_2O (3 x 100 mL), and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield compound **385** as a colorless oil (15.8 g, 93%).

R_f = 0.75 (50% petrol–EtOAc); ν_{max} (film) 2929, 2860, 1600, 1475, 1336, 1255, 1163, 1092, 899, 836, 814 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.5 Hz, *ortho*-Ts), 7.32 (2H, d, *J* 8.0 Hz, *meta*-Ts), 4.73 (1H, d, *J* 8.0 Hz, N*H*Ts), 3.59 (1H, m, NHC*H*), 3.52 (2H, m, CH_2OTBS), 3.17 (1H, dd, *J* 2.5, 6.5, C*H*OCH_3), 2.69 (1H, dd, *J* 3.0, 4.5 Hz, C$H_A$$H_B$OCH), 2.57 (1H, dd, *J* 3.0, 5.0 Hz, CH_AH_BOCH), 2.44 (3H, s, TsCH_3), 0.86 (9H, s, (CH_3)$_3$C), 0.00 (6H, s, (CH_3)$_2$Si); δ_C (100 MHz, $CDCl_3$) 143.5 (SO_2C), 138.0 (CH_3CTs), 129.7 (*ortho*-Ts), 127.0 (*meta*-Ts), 63.2 (CH$_2$OTBS), 53.7 (NH*C*H), 51.1 (NHCH*C*HO), 43.8 (CH$_2$OCH), 25.8 ((*C*H$_3$)$_3$), 18.2 (TsCH_3), 14.1 ((CH$_3$)$_3$*C*), –5.9 ((*C*H$_3$)$_2$Si); M/z (CI) 389 $[M+NH_4]^+$, 372, 314, 218, 174, 116, 108, 91 (Found: $[M+H]^+$, 372.1667. $C_{17}H_{29}NO_4SSi$ requires $[M+H]^+$, 372.1587) (Found: C, 55.02; H, 7.91; N, 3.77. $C_{17}H_{29}NO_4SSi$ requires C, 54.95; H, 7.87; N, 3.77%).

The data are in agreement with the reported compound.[2]

***N*-((2R,3R)-1-(ᵗButyldimethylsilyloxy)-3-hydroxy-4-(1-methyl-1H-indol-3-yl)butan-2-yl)-4-methylbenzenesulfonamide 386**



385 **386**

Classic Approach

To a suspension of epoxide **385** (17.0 g, 45.7 mmol, 1.0 equiv.), *N*-methylindole (23.4 ml, 183 mmol, 4.0 equiv.) and anhydrous $NaHCO_3$ (15.5 g, 183 mmol, 4.0 equiv.) in DCM (30 mL) at –78 °C was dropwise added $BF_3{\cdot}Et_2O$ (5.80 ml, 45.7 mmol, 1.0 equiv.). The reaction mixture was stirred at this temperature for 3 h. H_2O (60 mL) was added and the solution allowed to heat up to rt. The aqueous layer was extracted using Et_2O (3 x 200 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography (25% → 50% EtOAc–petrol) gave compound **386** as a pale yellow oil (22.8 g, 95%).

Microwave Application

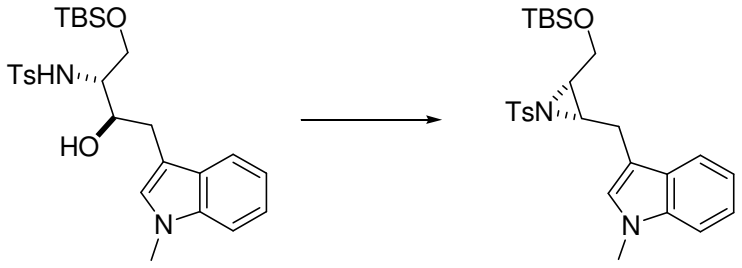
Epoxide **385** (900 mg, 2.40 mmol, 1.0 equiv.), *N*-methylindole (383 µl, 3.00 mmol, 1.3 equiv.) and $ZnCl_2$ (100 mg, 1.20 mmol, 0.5 equiv.) were dissolved in DCM (5 mL) and heated 2 x 30 min at 80 °C using the microwave. The reaction mixture was poured into H_2O (30 mL) and extracted using DCM (3 x 20 mL). The combined organic layers were dried (Mg_2SO_4), filtered and concentrated under reduced pressure. Chromatography (25% → 50% EtOAc–petrol) gave compound **386** as a pale yellow oil (1.12 g, 92%).

R_f = 0.33 (66% petrol–EtOAc); ν_{max} (film) 3507, 3288, 2954, 2929, 2857, 1616, 1473, 1327, 1157, 1092, 1073, 838, 734 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.5 Hz, *ortho*-Ts), 7.51 (1H, d, *J* 8.0 Hz, C-9), 7.30 (3H, m, *meta*-Ts + C-12), 7.23 (1H, t, *J* 7.5 Hz, C-11), 7.10 (1H, t, *J* 7.5 Hz, C-10), 6.67 (1H, s, C-2), 5.32 (1H, d, *J* 9.0 Hz, N*H*), 4.24 (1H, t, *J* 6.5 Hz, C*H*OH), 3.73 (3H, s, NCH_3), 3.68 (1H, dd, *J* 5.0, 10.5 Hz, CH_AH$_B$OTBS), 3.63 (1H, dd, *J* 5.0, 10.5 Hz, CH$_A$$H_B$OTBS), 3.39 (1H, m, C*H*N), 2.94 (1H, s, OH), 2.77 (2H, m, CH_2C), 2.45 (3H, s, TsCH_3) 0.88 (9H, s, (CH_3)$_3$C), -0.01 (6H, s, (CH_3)$_2$Si); δ_C (100 MHz, $CDCl_3$) 143.4 (SO_2C), 138.7 (CH_3CTs), 137.1 (C-13), 129.9 (*ortho*-Ts), 128.0 (C-2), 127.7 (C-8), 127.3 (*meta*-Ts), 121.8 (C-11), 119.0 (C-10), 119.0 (C-9), 110.0 (C-7), 109.3 (C-12), 72.1 (*C*HOH), 65.7 (*C*H$_2$OTBS), 55.4 (*C*HN), 32.6 (N*C*H$_3$), 29.5 (*C*H$_2$C), 25.8 ((*C*H$_3$)$_3$Si), 21.5 (Ts*C*H$_3$), 18.1 (SiC), -5.65 ((CH$_3$)$_2$Si) M/z (CI) 520 $[M+NH_4]^+$, 503 $[M+H]^+$, 349, 189, 174, 165, 148, 132 (Found $[M+H]^+$, 503.2322. $C_{26}H_{32}N_2O_4SSi$ requires $[M+H]^+$, 503.2415).

The data are in agreement with the reported compound.[2]

3-(((2S,3S)-3-((tButyldimethylsilyloxy)methyl)-1-tosylaziridin-2-yl)methyl)-1-methyl-1H-indole 387



386 **387**

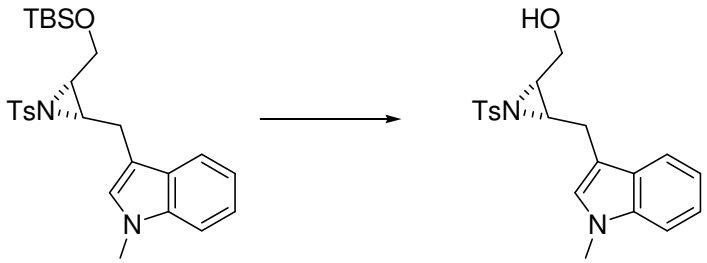
To a solution of aminoalcohol **386** (6.00 g, 12.0 mmol, 1.0 equiv.) and PPh_3 (3.80 g, 18.0 mmol, 1.2 equiv.) in THF (130 mL) at rt was added DIAD (3.60 mL, 18.0 mmol, 1.5 equiv.) dropwise over 15 min. The reaction mixture was stirred at rt for 1 h and concentrated under reduced pressure. Chromatography (10% → 40% EtOAc–petrol) gave compound **387** as a pale yellow oil (5.00 g, 86%).

R_f = 0.87 (50% petrol–EtOAc); ν_{max} (film) 2953, 2929, 2884, 1725, 1598, 1472, 1326, 1160, 1122, 838 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.48 (1H, d, *J* 8.0 Hz, C-9), 7.25 (2H, m, C-11 + C-12), 7.12 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.12-7.06 (1H, m, C-10), 6.85 (1H, s, C-2), 3.90 (1H, dd, *J* 11.0, 5.5 Hz, CH_AH_BOTBS), 3.78 (1H, dd, *J* 11.0, 6.5 Hz, CH_AH_BOTBS), 3.68 (3H, s, NCH_3), 3.18 (1H, m, $CHCH_2OTBS$), 3.11 (1H, m, $CHCH_2C$), 2.99 (1H, dd, *J* 15.5, 5.5 Hz, CH_AH_BC), 2.89 (1H, dd, *J* 15.5, 7.5 Hz, CH_AH_BC), 2.40 (3H, s, $TsCH_3$), 0.88 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $(CH_3)_2Si$); δ_C (100 MHz, $CDCl_3$) 144.1 (SO_2C), 136.6 (C-13), 129.4 (*ortho*-TsCH), 128.1 (*meta*-TsCH), 127.7 (C-8), 127.0 (C-2), 121.8 (C-11), 119.1 (C-10), 118.8 (C-9), 109.9 (C-7), 109.2 (C-12), 60.4 (CH_2OTBS), 44.9 ($CHCH_2OTBS$), 44.8 ($CHCH_2C$), 32.7 (NCH_3), 26.0 ($C(CH_3)_3$, 22.9 (CH_2C), 21.6 ($TsCH_3$), –5.2 ($Si(CH_3)_2$); M/z (CI) 485 $[M+H]^+$, 331, 214, 189, 174, 144, 132 (Found: $[M+H]^+$, 485.2309. $C_{26}H_{37}N_2O_3SSi$ requires $[M+H]^+$, 485.2294.).

The data are in agreement with the reported compound.[2]

((2S,3S)-3-((1-Methyl-1H-indol-3-yl)methyl)-1-tosylaziridin-2-yl)methanol 388



387 **388**

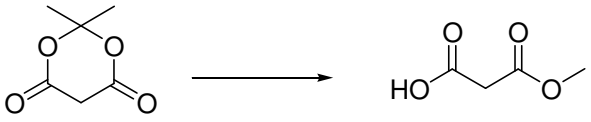
To a solution of aziridine **387** (5.00 g, 10.3 mmol, 1.0 equiv.) in THF (25 mL) at 0 °C was added a 1 M solution of TBAF in THF (11.3 mL, 11.3 mmol, 1.1 equiv.). The reaction mixture was stirred at 0 °C for 15 min. Saturated aqueous NH_4Cl (47 mL) was added and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography (50% → 100% EtOAc–petrol) gave compound **388** as a pale yellow oil (3.00 g, 80%).

R_f = 0.20 (50% petrol–EtOAc); ν_{max} (film) 3508, 3364, 2932, 1808, 1783, 1598, 1325, 1184, 1091, 739 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.48 (1H, d, *J* 8.0 Hz, C-9), 7.29-7.21 (2H, m, C-11 + C-12), 7.12 (2H, d, *J* 8.0, *meta*-Ts), 7.09 (1H, m C-10), 6.78 (1H, s, C-2), 3.89 (2H, m CH_2OH), 3.67 (3H, s, NCH_3), 3.21 (1H, q, *J* 7.0 Hz, C*H*CH_2C), 3.16 (1H, app. q, *J* 6.5 Hz, C*H*CH_2OH), 2.99 (1H, dd, *J* 15.5, 6.0 Hz, CH_AH$_B$C), 2.94 (1H, dd, *J* 15.5, 7.5 Hz, CH$_A$$H_B$C), 2.41 (3H, s, TsC$H_3$), 1.59 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 144.4 (SO_2C), 137.0 (CH_3*C*Ts), 134.7 (C-13), 129.5 (*ortho*-Ts), 128.1 (*meta*-Ts), 127.5 (C-8), 126.8 (C-2), 122.0 (C-11), 119.3 (C-10), 118.7 (C-9), 110.2 (C-7), 109.3 (C-12), 59.6 (*C*H_2OH), 45.6 (*C*HCH_2C), 44.6 (*C*HCH_2OH), 32.8 (N*C*H_3), 23.1 (*C*H_2C), 21.9 (TsCH_3); M/z (CI) 372 $[M+H]^+$, 217, 144 (Found: $[M+H]^+$, 371.1677. $C_{20}H_{22}N_2O_3S$ requires $[M+H]^+$, 371.1351.).

The data are in agreement with the reported compound.[2]

3-Methoxy-3-oxopropanoic acid 396

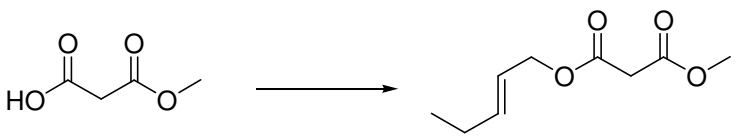


395 **396**

A solution of Meldrum's acid **395** (3.0 g, 21.1 mmol, 1.0 equiv.) in methanol (1.0 mL) was heated to 80 ^oC and stirred over 16 h. Evaporation of the residual acetone gave methyl malonate **396** (2.3 g, 92%). ν_{max} (film) 3515, 2960, 1713, 1440, 1328, 1154, 1015 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.9 (1H, s, CO_2*H*), 3.71 (3H, s, OCH_3), 3.43 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 171.8 (*C*O_2H) 167.1 (*C*O_2CH_3), 52.8 (CO_2*C*H_3), 10.8 (*C*H_2); M/z (CI) 136 $[M+NH_4]^+$ (Found: $[M+H]^+$, 136.0611. $C_4H_6O_4$ requires $[M+NH_4]^+$, 136.0266).

The data are in agreement with the reported compound.[3]

(E)-Methyl pent-2-enyl malonate 397



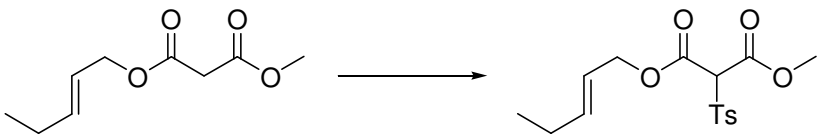
396 **397**

To a solution of methyl malonate **396** (2.21 g, 18.7 mmol, 1.0 equiv.) and *trans*-2-penten-1-ol (1.87 mL, 18.7 mmol, 1.0 equiv.) in DCM (50 mL), were added at 0 ^{o}C, DCC (3.90 g, 18.7 mmol, 1.0 equiv.) and DMAP (0.23 g, 18.7 mmol, 0.1 equiv.). After stirring 16 h at rt, the mixture was filtered through Celite (DCM washing). The filtrate was washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (25% → 50% EtOAc–petrol) gave compound **397** as a pale yellow oil (2.46g, 65%).

ν_{max} (film) 2962, 1733, 1332, 1199, 1146, 971 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.84 (1H, dt, *J* 15, 6.5 Hz, CH=C*H*CH_2O), 5.55 (1H, dt, *J* 15, 6.5 Hz, C*H*=$CHCH_2O$), 4.59 (2H, m, CH_2O), 3.75 (3H, s, CH_3O), 3.39 (2H, s, $COCH_2CO$), 2.12–2.01 (2H, m, CH_3CH_2), 1.00 (3H, t, *J* 7.5 Hz, CH_3CH_2); δ_C (100 MHz, $CDCl_3$) 167 (C=O), 166.3 (C=O), 138.7 (CH=*C*HCH_2O), 122.1 (*C*H=$CHCH_2O$), 66.3 (*C*H_2O), 52.4 (*C*H_3O), 41.3 (CO*C*H_2CO), 25.2 (CH_3*C*H_2), 13.0 (*C*H_3CH_2); M/z (CI) 236, 218, 204 $[M+NH_4]^+$, 136 (Found: $[M+NH_4]^+$, 204.1231. $C_9H_{14}O_4$ requires $[M+NH_4]^+$, 204.0892).

The data are in agreement with the reported compound.[3,4]

Methyl (2-pentenyl) (toluene-4-sulfonyl) malonate 398



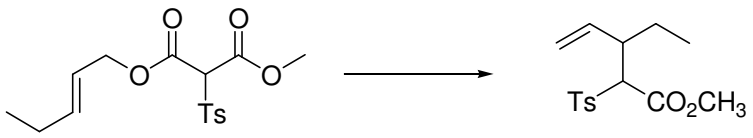
397 **398**

To a solution of **397** (6.80 g, 36.6 mmol, 2.0 equiv.) in DMSO (19 mL) was added at rt, very slowly, potassium ^{t}butoxide (4.10 g, 36.6 mmol, 2.0 equiv.). The reaction was then stirred for 15 min prior to addition of tosyl fluoride (3.20 g, 18.3 mmol, 1.0 equiv.). After stirring for 16 h the mixture was poured onto 10% aqueous HCl (50 mL), extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with brine (2 x 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (0% → 50% EtOAc–petrol) gave compound **398** as a pale yellow oil (7.90 g, 64%).

R_f = 0.55 (25% EtOAc–petrol); ν_{max} (film) 2925, 1742, 1436, 1336, 1266, 732 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.34 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.81 (1H, td, *J* 6.5, 15.0 Hz, OCH_2CH=CH), 5.47 (1H, app. ttd, *J* 1.5, 6.5, 15.0 Hz, CH=C*H*-CH_2), 4.96 (1H, s, C*H*Ts), 4.58 (2H, d, *J* 6.5 Hz, OCH_2), 3.77 (3H, s, OCH_3), 2.44 (3H, s, CH_3Ts), 2.05 (2H, quint, *J* 7.5 Hz, CH_2CH_3), 0.98 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 161.5, 160.7 (2 x CO), 146.0 (SO_2C), 139.6 (CH=*C*HCH_2O), 134.2 (*C*CH_3), 130.1 (*ortho*-Ts), 129.4 (*meta*-Ts), 121.3 (*C*H=$CHCH_2O$), 74.4 (*C*HTs), 67.7 (CH_2O), 53.6 (CH_3O), 25.2 (CH_3CH_2), 14.1 (CH_3CH_2); M/z (CI) 358 $[M+NH_4]^+$, 246, 204, 136, 52 (Found: $[M+NH_4]^+$, 358.1319. $C_{16}H_{20}O_6$ requires $[M+NH_4]^+$, 358.0981).

The data are in agreement with the reported compound.[3,4]

Methyl 3-ethyl-2-tosylpent-4-enoate 399

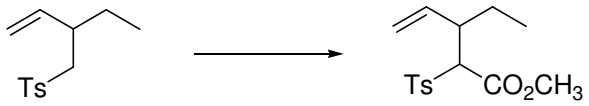


398 **399**

1 : 1

To a solution of **398** (2.80 g, 8.50 mmol, 1 equiv.) in DCM (28 mL) were added simultaneously, at rt, TBDMSOTf (4.11 ml, 17.9 mmol, 2.1 equiv.) and DBU (2.68 mL, 118 mmol, 2.1 equiv.). After 30 min of stirring, the reaction mixture was concentrated under reduced pressure. Chromatography (0% → 25% EtOAc–petrol) gave compound **399** as a colorless oil (1.61 g, 64%, 1 : 1 dr).

Deprotonation / carboxylation method



402 **399**

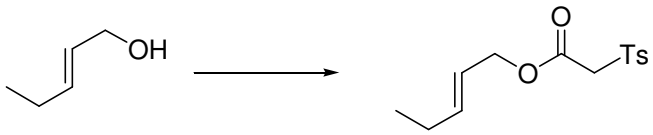
1 : 1

To a solution of **402** (500 mg, 1.90 mmol, 1.0 equiv.) in THF (25 mL) at –78 ^{o}C was added 2.5 M ^{n}BuLi (2.0 mL, 4.6 mmol, 2.4 equiv.) and the solution stirred for 30 min. The orange solution was allowed to heat up to –50 ^{o}C and methylchloroformate (210 µL, 2.70 mmol, 1.4 equiv.) was added dropwise. After stirring at –50 ^{o}C for 1 h, the mixture was allowed to heat up to rt and quenched using saturated aqueous NH_4Cl (75 mL). The aqueous layer was extracted using EtOAc (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified using column chromatography (75% petrol–EtOAc). **399** Was obtained in 486 mg as a colorless oil, 81% yield.

R_f = 0.74 (25% EtOAc–petrol); ν_{max} (film) 2925, 1740, 1597, 1323, 1139, 1083, 814 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz, *ortho*-Ts major), 7.77 (2H, d, *J* 8.0 Hz, *ortho*-Ts minor) 7.35 (2H, d, *J* 8.0 Hz, *meta*-Ts major), 7.34 (2H, d, *J* 8.0 Hz, *meta*-Ts minor) 5.58 (1H, m, C*H*=CH_2), 5.10 (2H, m, CH=CH_2), 4.03 (1H, d, *J* 9.0 Hz, C*H*-Ts minor), 4.01 (1H, d, *J* 9.0 Hz, C*H*Ts major), 3.66 (3H, s, OCH_3 minor), 3.52 (3H, s, OCH_3 major), 2.80 (1H, qd, *J* 4.0, 9.0 Hz, C*H*-CH=CH_2 major), 2.70 (1H, qd, *J* 4.0, 9.0 Hz, C*H*CH=CH_2 minor), 2.48 (3H, s, CH_3-Ts major), 2.46 (3H, s, CH_3-Ts minor), 1.45 (2H, m, C$H_2$$CH_3$ major), 1.25 (2H, m, C$H_2$$CH_3$ minor), 0.87 (3H, t, *J* 7.5 Hz, C$H_2$$CH_3$ major), 0.81 (3H, t, *J* 7.5 Hz, C$H_2$$CH_3$ minor); δ_C (100 MHz, $CDCl_3$) 166.4 (CO major), 166.0 (CO minor), 145.3 (SO_2C), 136.3 (CH_2=*C*HCH minor), 136.0 (CH_2=*C*HCH major), 134.1 (*C*CH_3), 129.6 (*ortho*-Ts), 129.4 (*meta*-Ts), 118.8 (*C*H_2=CHCH major), 118.6 (*C*H_2=CHCH minor), 75.1 (CHTs, major), 74.5 (CHTs minor), 52.7 (OCH_3 minor), 52.4 (OCH_3 major), 44.7 (CH_2=CH*C*H major), 44.5 (CH_2=CH*C*H minor), 25.1 (*C*$H_2$$CH_3$ minor), 21.7 (CH_2*C*H_3 major), 11.1 (CH_2*C*H_3 major), 10.9 (CH_2*C*H_3 major); M/z (CI) 314 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 314.1429. $C_{15}H_{20}O_4$ requires $[M+NH_4]^+$, 314.1426).

The data are in agreement with the reported compound.[3,4]

Pent-2-enyl 2-tosylacetate 401



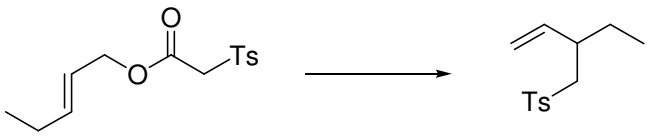
400 **401**

To a solution of tosyl acetic acid (9.00 g, 42.0 mmol, 1.0 equiv.) and 2-penten-1-ol **400** (4.20 mL, 42.0 mmol, 1.0 equiv.) in DCM (120 mL), were added at 0 °C, DCC (8.70 g, 42.0 mmol, 1.0 equiv.) and DMAP (0.52 g, 4.20 mmol, 0.1 equiv.). After stirring for 16 h at rt, the mixture was filtered through Celite (DCM washing). The filtrate was washed with brine (60 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (0% → 50% EtOAc–petrol) gave compound **401** as a pale yellow oil (10.9 g, 92%).

R_f = 0.50 (25% EtOAc–petrol); ν_{max} (film) 2968, 1738, 1597, 1457, 1400, 1327, 1275, 1150, 1085, 1018, 967, 813 cm^{-1};

δ_h (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.37 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.81 (1H, dt, *J* 6.5, 15.5 Hz, CH=C*H*CH_2O), 5.45 (1H, dtt, *J* 1.5, 6.5, 15.5 Hz, C*H*=$CHCH_2O$), 4.53 (2H, d, *J* 6.0 Hz, CH=CHC*H*$_2$O), 4.11 (2H, s, COC*H*$_2$Ts), 2.47 (3H, s, CH_3Ts), 2.07 (2H, m, CH_3C*H*$_2$), 1.00 (3H, t, *J* 7.0 Hz, C*H*$_3$$CH_2$);); δ_C (100 MHz, $CDCl_3$) 162.3 (CO), 145.4 (CSO_2), 139.4 (CH=*C*HCH_2O), 135.8 (*C*CH_3), 129.8 (*ortho*-Ts), 128.6 (*meta*-Ts), 121.6 (*C*H=$CHCH_2O$), 67.0 (CH=CH*C*H$_2$O), 61.1 (CO_2*C*H_2Ts), 25.2 (CH_3*C*H_2), 13.0 (*C*$H_3$$CH_2$); M/z (CI) 300 $[M+NH_4]^+$ (Found $[M+NH_4]^+$, 300.1274. $C_{14}H_{18}O_4S$ requires $[M+NH_4]^+$, 300.1270).

1-(2-Ethylbut-3-enylsulfonyl)-4-methylbenzene 402

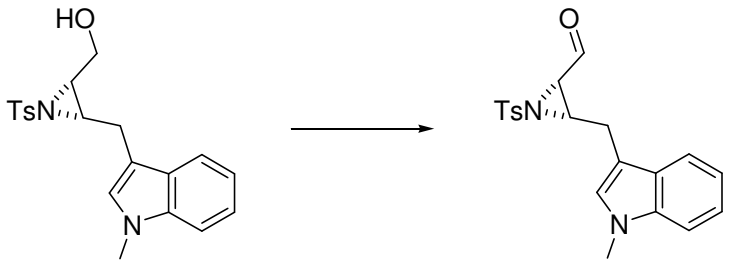


401 **402**

To a solution of compound **401** (10.0 g, 35.5 mmol, 1.0 equiv.) in toluene (200 mL) was added, at rt, BSA (8.80 ml, 35.5 mmol, 1.0 equiv.) and KOAc (350 mg, 3.55 mmol, 0.1 equiv.). After stirring for 16 h the reaction mixture was concentrated under reduced pressure. Chromatography (10% EtOAc–petrol) afforded compound **402** as a colorless oil (7.69 g, 91%).

R_f = 0.65 (25% EtOAc–petrol); ν_{max} (film) 2963, 2927, 1598, 1454, 1316, 1301, 1146, 1087, 817 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.33 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.55 (1H, ddd, *J* 8.5, 10.5, 17.0, C*H*=CH_2), 5.01 (2H, m, CH=C*H*$_2$), 3.13 (2H, d, *J* 6.5 Hz, C*H*$_2$-Ts), 2.55 (1H, m, CH=CHC*H*), 2.46 (3H, s, CH_3-Ts), 1.63 (2H, m, C*H*$_2$$CH_3$ major), 1.39 (2H, m, C*H*$_2$$CH_3$ minor), 0.85 (3H, t, *J* 7.5 Hz, C*H*$_2$$CH_3$); δ_C (100 MHz, $CDCl_3$) 144.5 (SO_2C), 138.9 (CH_2=*C*HCH), 137.1 (*C*CH_3), 129.8 (*ortho*-Ts), 128.0 (*meta*-Ts), 116.4 (*C*H_2=CHCH), 60.6 (*C*H_2Ts), 40.1 (CH_2=CH*C*H), 27.3 (*C*$H_2$$CH_3$ minor), 21.6 (CH_2*C*H_3 major), 10.9 (CH_2*C*H_3); M/z (CI) 256 $[M+NH_4]^+$, 239 $[M+H]^+$ (Found: $[M+NH_4]^+$, 256.1374. $C_{13}H_{18}O_2S$ requires $[M+NH_4]^+$, 256.1372) (Found: C, 65.60; H, 7.57. $C_{13}H_{18}O_2S$ requires C, 65.51; H, 7.61%).

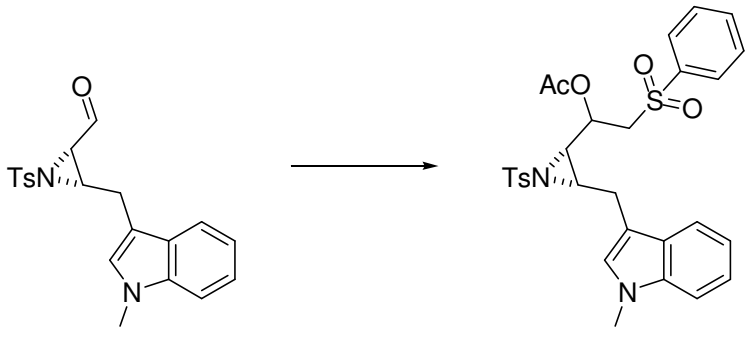
(2S,3S)-3-((1-Methyl-1H-indol-3-yl)methyl)-1-tosylaziridine-2-carbaldehyde 418



388 **418**

A solution of aziridinol **388** (230 mg, 0.62 mmol, 1.0 equiv.) and IBX (174 mg, 0.62 mmol, 1.0 equiv.) in DMSO (6 mL) was stirred at rt for 16 h. The solution was partitioned between H_2O (15 mL) and EtOAc (15 mL) and the aqueous layer extracted using EtOAc (3 x 10 mL). Combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Crude aldehyde **418** was used immediately (172 mg, 75%).

1-((2S,3S)-3-((1-Methyl-1H-indol-3-yl)methyl)-1-tosylaziridin-2-yl)-2-(phenylsulfonyl)ethyl acetate 420



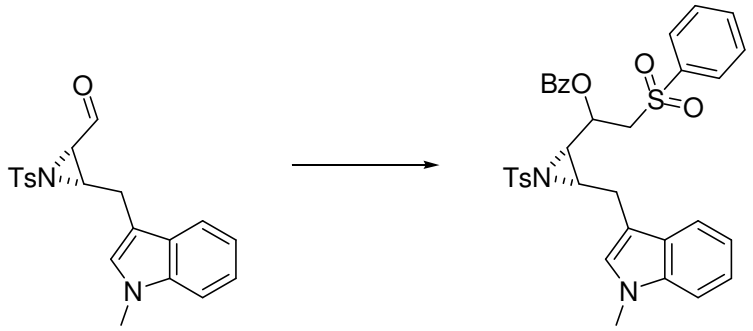
418 **420**

To a solution of methyl *p*-tolyl sulfone (4.52 mg, 29.0 mmol, 1.2 equiv.) in THF (125 mL) at –78 °C was added 1.95 M ^{n}BuLi (16 mL, 31 mmol, 1.3 equiv.) and stirred for 30 min. Aldehyde **418** (9.0 g, 24 mmol, 1.0 equiv.) was added in THF (100 + 25 mL) at –78 °C *via* cannula. The mixture was stirred for 3 h while heating up –40 °C. Acetic anhydride (6.0 mL, 62 mmol, 2.6 equiv.) was added and the mixture stirred for 15 min at rt, poured onto saturated aqueous $NaHCO_3$ (200 mL) and extracted using DCM (2 x 200 mL). The combined organic

layers were washed with H_2O (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (66% → 50% petrol–EtOAc) yielded **420** as a yellow foam (10.1 g, 74%).

R_f = 0.40 (66% Et_2O–petrol); m.p. = 88 °C; ν_{max} (film) 3494, 2980, 1747, 1614, 1598, 1470, 1447, 1373, 1321, 1305, 1224, 1151, 1087, 735 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 7.5 Hz, *ortho*-Ts), 7.63 (2H, m, *ortho*-Ts), 7.40 (2H, d, *J* 8.5 Hz, C-9), 7.21 (2H, d, *J* 3.5 Hz, C-12), 7.04 (1H, dd, *J* 4.0, 8.0 Hz, C-11), 6.99 (2H, d, *J* 8.0 Hz, C-10), 6.61 (1H, s, C-2), 5.29 (1H, td, *J* 4.0, 8.0 Hz, C*H*OAc), 3.63 (2H, m, C*H*$_2$$SO_2$Ph), 3.61 (3H, s, NCH_3), 3.15 (1H, m, CHOAcC*H*NTs), 3.09 (2H, m, C*H*$_2$CHNTs), 2.72 (1H, dd, *J* 9.0, 15.0 Hz, CH_2C*H*NTs), 2.39 (3H, s, CH_3Ts), 1.91 (3H, s, CH_3CO_2); δ_C (100 MHz, $CDCl_3$) 169.4 (C=O), 144.4 (CSO_2), 139.6 (CSO_2), 136.7 (CH_3*C*Ts), 133.3 (*para*-$PhSO_2$), 129.8 (C-13), 129.4 (*ortho*-Ts), 129.1 (*ortho*-$PhSO_2$), 128.4 (*meta*-Ts), 127.9 (C-8), 127.8 (*meta*-$PhSO_2$), 126.9 (C-2), 121.4 (C-11), 118.9 (C-10), 118.6 (C-9), 109.6 (C-12), 109.0 (C-7), 65.0 (*C*HOAc), 57.7 (*C*H_2SO_2Ph), 47.7 (*C*HCHOAc), 43.1 (CH_2*C*HNTs), 32.5 (NCH_3), 22.9 (*C*H_2CNTs), 21.7 (TsCH_3), 20.6 (CO_2CH_3). M/z (ESI) 605.1260, 589.1454 $[M+Na]^+$, 567.1639 $[M+H]^+$, 196.0197 (Found: $[M+H]^+$, 567.1639. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H]^+$, 567.1545) (Found: C, 61.37; H, 5.21; N, 4.89. $C_{29}H_{30}N_2O_6S_2$ requires C, 61.46; H, 5.34; N, 4.94%).

1-((2S,3S)-3-((1-Methyl-1H-indol-3-yl)methyl)-1-tosylaziridin-2-yl)-2-(phenylsulfonyl)ethyl benzoate 421

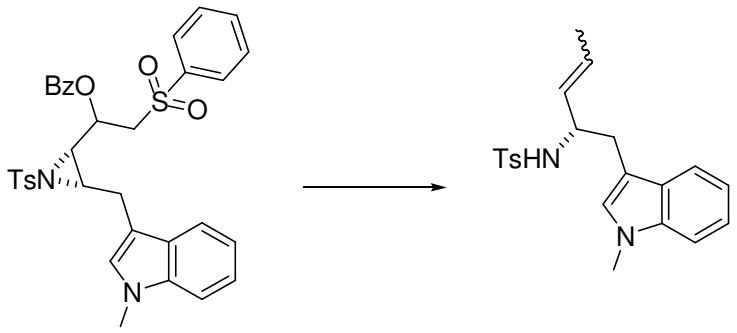


418 **421**

To a solution of methyl *p*-tolyl sulfone (114 mg, 0.73 mmol, 1.2 equiv.) in THF (3 mL) at –78 ^{o}C was added 2.5 M ^{n}BuLi (317 μL, 0.79 mmol, 1.2 equiv.) and stirred for 30 min. Aldehyde **418** (225 mg, 0.61 mmol, 1.0 equiv.) was added in THF (3 + 2 mL) at –78 ^{o}C *via* cannula. The mixture was stirred for 2 h while heating up to rt. Benzoyl chloride (90.0 μL, 0.79 mmol, 1.3 equiv.) was added and the mixture stirred for 1 h at rt, poured on saturated aqueous $NaHCO_3$ (100 mL), extracted using DCM (2 x 100 mL). The combined organic layers were washed with H_2O (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (66% → 50% petrol–EtOAc) yielded **421** as a yellow gum (269 mg, 70%).

R_f = 0.40 (66% Et_2O–petrol); ν_{max} (film) 3062, 2927, 1724, 1614, 1599, 1472, 1447, 1376, 1304, 1264, 1148, 1087, 1069, 956, 740 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.96 (2H, d, *J* 7.5 Hz, *ortho*-Ts), 7.75 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.58 (3H, m, C-9), 7.45–7.36 (4H, m, C-12), 7.17 (3H, m, C-11), 7.00 (2H, d, *J* 8.0 Hz, C-10), 6.58 (1H, s, C-2), 5.52 (1H, dt, *J* 2.5, 8.5 Hz, C*H*OBz), 3.83 (2H, m, C$H_2$$SO_2$Ph), 3.49 (3H, s, NCH_3), 3.23–3.20 (3H, m, CHOBzC*H*NTs + CH_2CHNTs), 2.86 (1H, dd, *J* 9.0, 15.0 Hz, CH_2C*H*NTs), 2.40 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 164.5 (CO), 164.2 (CO), 144.4 (CSO_2), 139.6 (CSO_2), 136.7 (CH_3*C*-Ts), 133.7 (*C*CO), 133.6 (*para*-PhSO_2), 133.5 (*para*-Bz), 129.8 (C-13), 129.4 (*ortho*-Ts), 129.3 (*ortho*-PhSO_2), 129.1 (*ortho*-Bz), 128.3 (*meta*-Ts), 128.0 (C-8), 127.9 (*meta*-PhSO_2), 127.8 (*ortho*-Bz), 127.4 (*meta*-Bz), 126.9 (C-2), 121.5 (C-11), 118.9 (C-10), 118.7 (C-9), 109.7 (C-7), 108.9 (C-12), 65.9 (*C*HOBz), 58.0 (*C*$H_2$$SO_2$Ph), 47.9 (*C*HCHOBz), 43.3 (CH_2*C*HNTs), 32.3 (NCH_3), 23.0 (*C*H_2CNTs), 21.8 (CH_3Ts); M/z (ESI) 196.0166, 629.1779 [M+H]$^+$, 651.1599 [M+Na]$^+$ (Found: [M+H]$^+$, 629.1779. $C_{34}H_{32}N_2O_6S_2$ requires [M+H]$^+$, 629.1702).

(S)-4-Methyl-*N*-(1-(1-methyl-1H-indol-3-yl)pent-3-en-2-yl)benzenesulfonamide 422

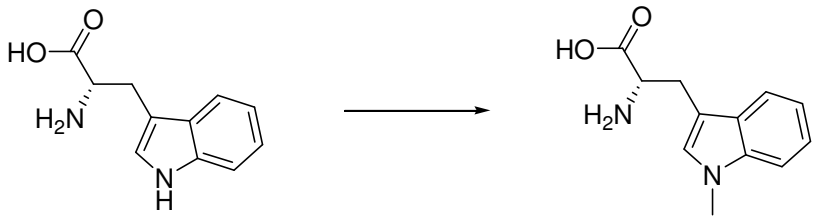


421 **422**

To a flame-dried flask containing Sm^0 (218 mg, 1.44 mmol, 9.0 equiv.) was slowly added diodoethane (360 mg, 1.28 mmol, 8.0 equiv.) in THF (15 mL) at 0 °C. After stirring at rt for 2 h, the aziridine benzoyl ester **421** (100 mg, 0.16 mmol, 1.0 equiv.) was added in THF (2 mL) together with DMPU (483 μL, 4.00 mmol, 25.0 equiv.) and stirred for 45 min at rt. The solution was concentrated under reduced pressure and dissolved using EtOAc (50 mL), the organic layer was washed with 1 M HCl (2 x 20 mL), H_2O (2 x 20 mL), saturated aqueous $Na_2S_2O_3$ (2 x 20 mL), H_2O (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (25% EtOAc–petrol) gave the amino olefin **422** as a yellow gum (23 mg, 40%).

R_f = 0.65 (50% EtOAc–petrol); δ_h (400 MHz, $CDCl_3$) 7.51 (2H, d, *J* 8.5 Hz, *ortho*-Ts), 7.35 (1H, d, *J* 8.0 Hz, C-9), 7.28 (1H, d, *J* 8.0 Hz, C-12), 7.23 (1H, dd, *J* C-11), 7.11 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.06 (1H, dd, *J* 4.0, 11.0 Hz, C-10), 6.82 (1H, s, C-2), 5.51 (1H, dt, *J* 6.5, 13.0 Hz, CHC*H*CH_3), 5.31 (1H, ddd, *J* 1.5, 7.0, 15.0 Hz, C*H*$CHCH_3$), 4.46 (1H, d, *J* 6.0 Hz, N*H*Ts), 3.99 (1H, m, C*H*NHTs), 3.74 (3H, s, NCH_3), 2.96 (1H, dd, *J* 5.5, 14.0 Hz, CH_AH_BCHNHTs), 2.86 (1H, dd, *J* 7.0, 14.0 Hz, CH_AH_BCHNHTs), 2.38 (3H, s, CH_3Ts), 1.57 (3H, d, *J* 6.0 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 142.8 (CCH_3), 137.4 (C-13), 137.0 (CSO_2), 131.1 (*C*$HCHCH_3$), 129.2 (*meta*-Ts), 128.6 (C-2), 127.8 (C-8), 127.4 (CH*C*HCH_3), 127.1 (*ortho*-Ts), 121.7 (C-11), 119.1 (C-10), 1191.0 (C-9), 109.0 (C-12), 108.9 (C-7), 55.8 (*C*HNHTs), 32.6 (NCH_3), 32.8 (*C*H_2CHNHTs), 21.5 CH_3Ts), 17.6 (CH_3).

(S)-2-Amino-3-(1-methyl-1H-indol-3-yl)propanoic acid 427



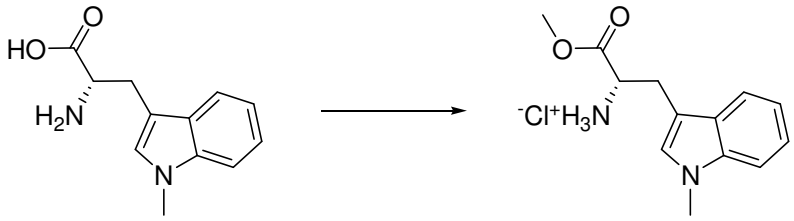
427

To a solution of sodium (1.20 g, 50.0 mmol, 2.0 equiv.) in liquid ammonia (~200 mL) at –78 °C in a three-neck flask equipped with a dry ice condenser was added $FeCl_3$ (cat.). The solution was stirred for 1 h while the colour changed from deep blue to dark grey. In the dark L-tryptophan (5.00 g, 25.0 mmol, 1.0 equiv.) was added in one portion. After 15 min CH_3I (2.00 mL, 27.5 mmol, 1.1 equiv.) was added dropwise *via* a syringe and the solution stirred for 1 h at –78 °C. After evaporation of the ammonia, the residue was dissolved in H_2O (20 mL, 65 °C) and filtered hot. Precipitation occurred while adjusting the pH of the filtrate to 5 by dropwise addition of HOAc (conc.) at 65 °C. After cooling to rt, the precipitate was filtered and washed (70% EtOH–H_2O). Recrystallization (70% EtOH–H_2O) gave **427** as a white solid (5.10 g, 91%).

R_f = 0.40 (100% CH_3OH); ν_{max} (film), 3010, 1663, 1589, 1409, 1350, 1280, 728 cm^{-1}; δ_H (400 MHz, CD_3COOD) 7.65 (1H, d, *J* 8.0 Hz, CH-9), 7.32 (1H, d, *J* 8.0 Hz, C-12), 7.22 (1H, t, *J* 7.5 Hz, C-11), 7.14 (1H, s, C-2), 7.10 (1H, t, *J* 7.5 Hz, C-10), 4.37 (1H, br s, NH_2CH), 3.74 (3H, s, NCH_3), 3.53 (1H, dd, *J* 6.0, 14.5 Hz, $CH_AH_BCHNH_2$), 3.40 (1H, dd, *J* 6.0, 14.5 Hz, $CH_AH_BCHNH_2$); δ_C (100 MHz, $CDCl_3$) 177.0 (CO), 137.2 (C-13), 129.0 (C-8), 127.7 (C-2), 121.7 (C-11), 119.2 (C-9), 118.6 (C-10), 109.2 (C-12), 106.2 (C-7), 57.4 ($CHNH_2$), 31.8 (CH_3N), 26.0 (CH_2CHNH); M/z (ESI) 219, 202 $[M+H]^+$.

The data are in agreement with the reported compound.[5]

(S)-1-Methoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-aminium chloride 428



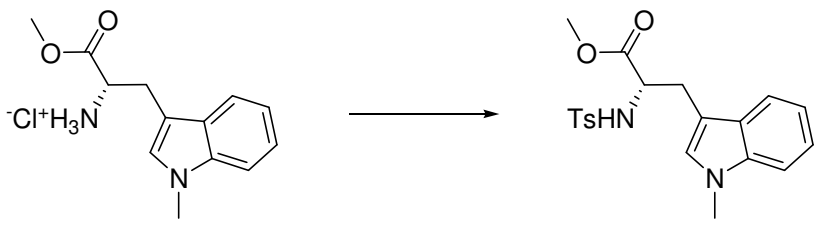
427 **428**

To a solution of **427** (4.00 g, 18.3 mmol, 1.0 equiv.) in CH_3OH (50 mL) at 0 ^oC was added thionyl chloride (2.00 mL, 27.5 mmol, 1.5 equiv.) dropwise. The solution was refluxed for 2 h, cooled to rt, and concentrated under reduced pressure. Azeotropic removal of H_2O using toluene provided **428** as a white solid (4.9 g, 99%).

R_f = 0.32 (20% CH_3OH–EtOAc); ν_{max} (film), 2840, 1747, 1506, 1474, 1448, 1327, 1232, 739 cm^{-1}; δ_H (400 MHz, D_2O) 7.46 (1H, d, *J* 8.0 Hz, CH-9), 7.36(1H, d, *J* 8.0 Hz, CH-12), 7.20 (1H, t, *J* 7.5 Hz, CH-11), 7.09 (1H, t, *J* 7.5 Hz, CH-10), 7.06 (1H, s, CH-2), 4.31 (1H, t, *J* 6.0 Hz, NH_2CH), 3.69 (3H, s, NCH_3), 3.64 (3H, s, OCH_3), 3.31 (2H, m, CH_2CHNH_2); δ_C (100 MHz, $CDCl_3$) 170.3 (CO), 136.9 (C-13), 129.6 (C-12), 126.8 (C-8), 122.0 (C-2), 119.4 (C-11), 118.2 (C-9), 110.1 (C-10), 104.8 (C-7), 53.5 ($CHNH_2$), 53.3 (OCH_3), 32.1 (NCH_3), 25.5 (CH_2CHNH_2); M/z (ESI) 216, 233 $[M+H]^+$.

The data are in agreement with the reported compound.[5]

(S)-Methyl 3-(1-methyl-1H-indol-3-yl)-2-(4-methylphenylsulfonamido)propanoate 426



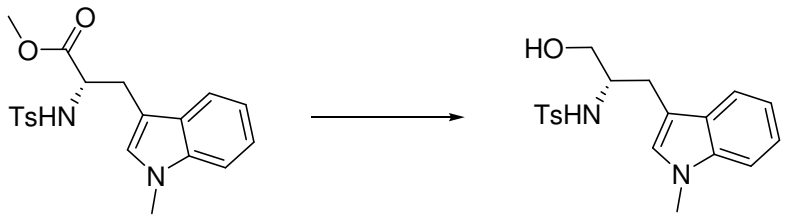
428 **426**

To a suspension of **428** (1.70 g, 6.3 mmol, 1.0 equiv.), DMAP (160 mg, 1.30 mmol, 0.2 equiv.) and TsCl (1.30 g, 6.90 mmol, 1.1 equiv.) in DCM (13 mL) at 0 ^{o}C was added TEA (1.80 mL, 14.0 mmol, 2.2 equiv.). After 30 min at 0 ^{o}C, the mixture was allowed to warm up to rt for 16 h. The mixture was partitioned between DCM (125 mL) and H_2O (100 mL). The aqueous layer was extracted using DCM (3 x 50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$). Concentration under reduced pressure and chromatography (50% petrol–EtOAc) gave **426** as a white solid (1.9 g, 80% yield).

R_f = 0.37 (50% EtOAc–petrol); ν_{max} (film), 3399, 3293, 2952, 1741, 1432, 1332, 1160, 1091, 814, 743, 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* 8.5 Hz, *ortho*-Ts), 7.43 (1H, d, *J* 8.0 Hz, C-9), 7.28 (1H, d, *J* 8.0 Hz, C-12), 7.21 (2H, m, *meta*-Ts + C-11), 7.08 (1H, dd, *J* 4.0, 11.0 Hz, C-10), 6.90 (1H, s, C-2), 5.15 (1H, d, *J* 9.0 Hz, NHTs), 4.26 (1H, dt, *J* 5.5, 9.0 Hz, C*H*NHTs), 3.74 (3H, s, NCH_3), 3.47 (3H, s, OCH_3), 3.25 (2H, d, *J* 5.5 Hz, CH_2CHNHTs), 2.39 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 171.6 (CO), 143.4 (CCH_3), 136.8 (C-13), 136.6 (CSO_2), 129.5 (*meta*-Ts), 128.1 (C-2), 127.7 (C-8), 127.1 (*ortho*-Ts), 121.7 (C-11), 119.2 (C-10), 118.6 (C-9), 109.3 (C-12), 107.3 (C-7), 56.0 (CHNHTs), 52.4 (OCH_3), 32.7 (NCH_3), 29.2 (*C*H_2CHNHTs), 21.5 (CH_3Ts); M/z (ESI) 450, 436, 425, 409, 395, 387 $[M+H]^+$, 373.

The data are in agreement with the reported compound.[5]

(S)-N-(1-Hydroxy-3-(1-methyl-1H-indol-3-yl)propan-2-yl)-4-methylbenzenesulfonamide 429



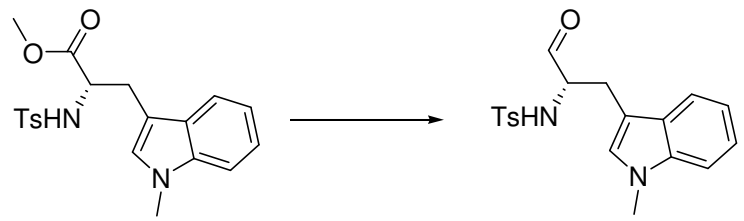
426 **429**

To a solution of $LiAlH_4$ (296 mg, 7.80 mmol, 2.0 equiv.) in THF (8.0 mL) at 0 °C was added **426** (1.50 g, 3.90 mmol, 1.0 equiv.) in THF (30 mL). After stirring at 0 °C for 1 h, the suspension was slowly heated to rt over 16 h and quenched using Rochelle's salt until evaporation of gas ended. Filtration through a Celite plug was followed by washing the residue with EtOAc. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (50% EtOAc–petrol) gave **429** as a yellow gum (1.30 g, 94%).

R_f = 0.40 (100% EtOAc); ν_{max} (film), 3530, 3280, 2924, 1600, 1471, 1320, 1250, 1090, 1040, 880, 739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.28–7.19 (3H, m, C-9 + C-12 + C-11), 7.07 (2H, d, *J* 8.0 Hz, *meta*-Ts), 6.99 (1H, dd, *J* 4.0, 11.0 Hz, C-10), 6.78 (1H, s, C-2), 5.00 (1H, m, NHTs), 3.73 (1H, m, CH_AH$_B$OH), 3.70 (3H, s, NCH_3), 3.62 (1H, m, CH$_A$$H_B$OH), 3.50 (1H, m, C*H*NHTs), 2.95 (1H, dd, *J* 6.5, 14.5 Hz, CH_AH$_B$CHNHTs), 2.83 (1H, dd, *J* 7.5, 14.5 Hz, CH$_A$$H_B$CHNHTs), 2.37 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 143.2 (CCH_3), 137.1 (C-13), 136.4 (CSO_2), 129.4 (*meta*-Ts), 128.6 (C-2), 127.7 (C-8), 126.8 (*ortho*-Ts), 121.7 (C-11), 119.2 (C-10), 118.6 (C-9), 109.2 (C-12), 108.9 (C-7), 64.7 (CH_2OH), 55.6 (CHNHTs), 32.6 (NCH_3), 27.3 (*C*H_2CHNHTs), 21.6 (CH_3Ts); M/z (ESI) 359 $[M+H]^+$.

The data are in agreement with the reported compound.[5]

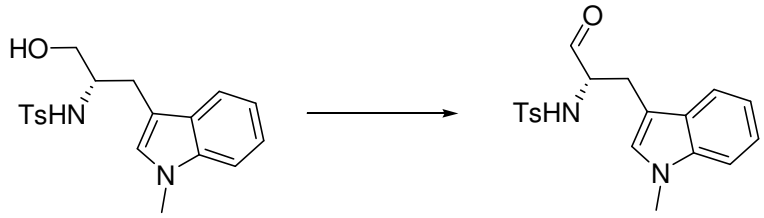
(S)-4-Methyl-N-(1-(1-methyl-1H-indol-3-yl)-3-oxopropan-2-yl)benzenesulfonamide 425



426 **425**

Procedure A

To a solution of **426** (100 mg, 0.26 mmol, 1.0 equiv.) in THF (2 mL) at –78 °C was added 1.2 M DIBAL (0.43 mL, 0.52 mmol, 2.0 equiv.) and stirred at –78 °C for 30 min. Quenching the reaction using Rochelle's salt (~5 mL) was followed by addition of EtOAc (10 mL). The aqueous layer was extracted using EtOAc (3 x 5 mL), the combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Crude aldehyde **425** was used immediately (91 mg, 98%).

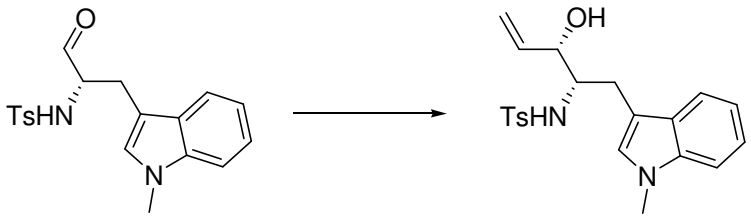


429 **425**

Procedure B

A solution of **429** (370 mg, 1.00 mmol, 1.0 equiv.) and IBX (310 mg, 1.10 mmol, 1.1 equiv.) in DMSO (6 mL) was stirred at rt for 16 h. The solution was partitioned between H_2O (10 mL) and EtOAc (10 mL) and the aqueous layer extracted using EtOAc (3 x 10 mL). Combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Crude aldehyde **425** was used immediately (300 mg, 81%).

***N*-((2S,3S)-3-Hydroxy-1-(1-methyl-1H-indol-3-yl)pent-4-en-2-yl)-4-methylbenzenesulfonamide 424**



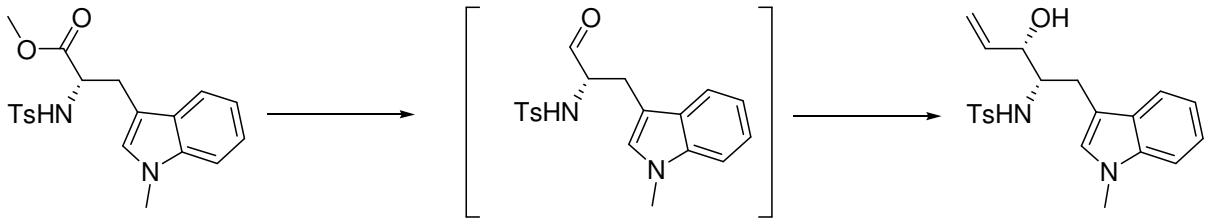
425 **424**

Procedure A

To a solution of Ph_3PCH_3Br (1.40 g, 4.00 mmol, 4.0 equiv.) in THF (20 mL) at 0 °C was added 1.66 M ^{n}BuLi (2.40 mL, 4.00 mmol, 4.0 equiv.). After stirring for 1 h at rt, the solution was cooled to 0 °C and $(CH_3)_3SiCH_2I$ (594 µL, 4.00 mmol, 4.0 equiv.) was dropwise added. Stirring at rt for 1 h was followed by addition of 1.66M ^{n}BuLi (2.40 mL, 4.00 mmol, 4.0 equiv.) at –78 °C. The solution was stirred at –78 °C for 1 h after which aldehyde **425** (370 mg, 1.00 mmol, 1.0 equiv.) in THF (20 mL) was added and the solution allowed to warm to rt over 16 h. Quenching the mixture using saturated aqueous NH_4Cl (30 mL) was followed by addition of EtOAc (30 mL). The layers were partitioned and the aqueous layer was extracted using EtOAc (3 x 40 mL), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude silylether was dissolved in THF (10 mL) at 0 °C and 1M TBAF (1.40 mL, 1.40 mmol, 1.4 equiv.) was added. After stirring for 30 min at 0 °C, the suspension was allowed to rt and diluted by addition of H_2O (10 mL). The aqueous layer was extracted using EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography gave **424** as a colorless gum (100 mg, 33% (2 steps)).

Procedure B

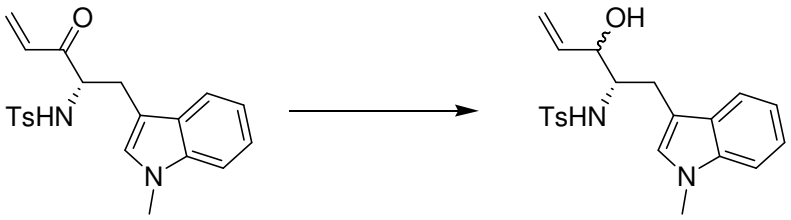
To a solution of aldehyde **425** (0.50 g, 4.20 mmol, 1.0 equiv.) in THF (6 mL) at –78 °C was added 1.0 M vinyl Grignard (5.60 mL, 5.60 mmol, 4.0 equiv.) dropwise. After 10 min stirring at –78 °C, the solution was allowed to warm up to rt over 2 h. The reaction was quenched using saturated aqueous NH_4Cl (20 mL) and DCM (40 mL) was added. After partitioning the layers, the aqueous layer was extracted with DCM (3 x 40 mL). The combined organic layers were washed with brine (70 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (50% EtOAc–petrol) gave **424** as a colorless gum (150 mg, 41% (2 steps)).



426 **425** **424**

Procedure C

To a solution of **426** (200 mg, 0.52 mmol, 1.0 equiv.) in DCM (1.0 mL) at –78 °C was added 1.0 M DIBAL (1.10 mL, 1.10 mmol, 2.0 equiv.). After stirring for 1 h at –78 °C, 1.0 M vinyl Grignard (1.56 mL, 1.56 mmol, 3.0 equiv.) was added and the solution allowed to warm up slowly to rt over 4 h. Quench with saturated aqueous NH_4Cl (5 mL) was followed by dilution using EtOAc (5 mL), partitioning the layers was followed by extraction of the aqueous layer using EtOAc (3 x 5 mL), the combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (50% EtOAc–petrol) gave **424** as a colorless gum (100mg, 51%) as well as alcohol **429** as a yellow gum (71mg, 41% (2 steps)).



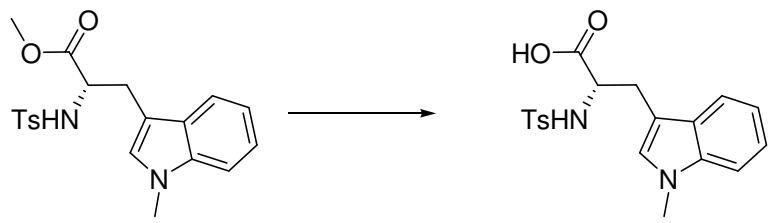
431 **424**

Procedure D

To a mixture of vinyl ketone **431** (60 mg, 0.17 mmol, 1.0 equiv.) and $CeCl_3 \cdot 7H_2O$ (63 mg, 0.17 mmol, 1.0 equiv.) in CH_3OH (2.5 mL) at rt was added $NaBH_4$ (6.0 mg, 0.17 mmol, 1.0 equiv.) and stirred for 10 min. The mixture was partitioned between saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL) and the aqueous layers extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (50% EtOAc–petrol) gave **424** as a colorless gum (58 mg, 95%).

R_f = 0.35 (50% EtOAc–petrol); ν_{max} (film), 3489, 3288, 2925, 1710, 1598, 1473, 1424, 1377, 1326, 1155, 1092, 812, 740, 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.46 (1H, m, C-9), 7.23 (2H, m, C-12 + C-11), 7.08 (2H, m, *meta*-Ts + C-10), 6.79 (1H, s, C-2), 5.73 (1H, ddd, *J* 5.5, 10.5, 17.0 Hz, C*H*=CH_2), 5.26 (1H, d, *J* 17.0 Hz, CH=C$H_A$$H_B$), 5.11 (1H, d, *J* 10.5 Hz, CH=$CH_A$$H_B$), 4.99 (1H, d, *J* 7.5 Hz, NHTs), 4.23 (1H, m, C*H*OH), 3.69 (3H, s, NCH_3), 3.52 (1H, m, C*H*NHTs), 3.12 (1H, dd, *J* 7.5, 14.5 Hz, C$H_A$$H_B$CHNHTs), 2.82 (1H, dd, *J* 6.5, 14.5 Hz, $CH_A$$H_B$CHNHTs), 2.37 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 142.9 (CCH_3), 137.5 (*C*H=CH_2), 137.3 (C-13), 136.9 (CSO_2), 129.2 (*meta*-Ts), 127.7 (C-2), 127.6 (C-8), 126.9 (*ortho*-Ts), 121.7 (C-11), 119.1 (C-10), 118.8 (C-9), 116.8 (CH=*C*H_2), 109.6 (C-7), 109.2 (C-12), 72.6 (*C*HOH), 58.1 (*C*HNHTs), 32.6 (NCH_3), 27.6 (*C*H_2CHNHTs), 21.1 (CH_3Ts); M/z (CI) 144, 385 $[M+H]^+$, 402 $[M+NH_4]^+$, 429, 528 (Found: $[M+H]^+$, 385.1581. $C_{21}H_{24}N_2O_3S$ requires $[M+H]^+$, 385.1508).

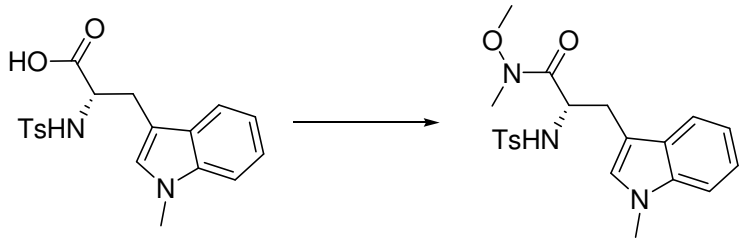
(S)-3-(1-Methyl-1H-indol-3-yl)-2-(4-methylphenylsulfonamido)propanoic acid 432



426 **432**

A solution of **426** (0.60 g, 1.70 mmol, 1.0 equiv.) and LiOH (80.0 mg, 1.90 mmol, 1.1 equiv.) in 1:1 DME–H_2O (2 + 2 mL) at rt was stirred for 16 h. Adjusting the pH to 4 using 10% citric acid was followed by extraction of the aqueous layer using EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide crude acid **432** as a yellow oil (550 mg, 95%).

(S)-*N*-Methoxy-N-methyl-3-(1-methyl-1H-indol-3-yl)-2-(4-methylphenylsulfonamido)propanamide 430



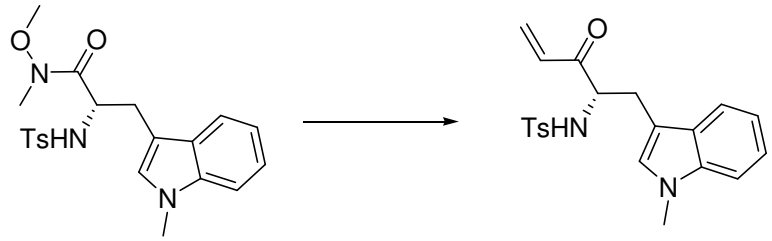
432 **430**

To a solution of **432** (550 mg, 1.60 mmol, 1.0 equiv.) and DMAP (20.0 mg, 0.16 mmol, 0.1 equiv.) in DCM (10 mL) at rt was added TEA (0.63 mL, 4.80 mmol, 3.0 equiv.). DIC (0.25 mL, 1.60 mmol, 1.0 equiv.) was added dropwise and the solution stirred for 16 h at rt. The mixture was extracted with 10% aqueous HCl (3 x 10 mL) and the organic layer was subsequently washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (50% EtOAc–petrol) gave Weinreb amide **430** as a yellow gum (620 mg, 95%).

R_f = 0.30 (50% EtOAc–petrol); ν_{max} (film), 3248, 2937, 1655, 1474, 1377, 1328, 1157, 1092, 987, 741 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.39 (1H, d, *J* 8.5 Hz, C-9), 7.21 (2H, m, C-12 + C-11), 7.09 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.05 (1H, dt, *J* 1.5, 8.5 Hz, C-10), 6.83 (1H, s, C-2), 5.59 (1H, d, *J* 7.0 Hz, NHTs), 4.15 (1H, m, C*H*NHTs), 3.66 (3H, s, NCH_3 Indole), 3.36 (3H, s, NCH_3 Weinreb amide), 3.19 (1H, dd, *J* 6.0, 15.0 Hz, $CH_AH_BCHNHTs$), 3.08 (1H, dd, 7.0, 15.0 Hz, $CH_AH_BCHNHTs$), 2.49 (3H,s , OCH_3), 2.34 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 207.8 (CO), 143.4 (CCH_3), 136.9 (CSO_2), 136.4 (C-13), 129.4 (*meta*-Ts), 128.2 (C-2), 127.9 (C-8), 126.9 (*ortho*-Ts), 121.8 (C-11), 119.2 (C-10), 118.5 (C-9), 109.3 (C-12), 107.5 (C-7), 61.6 (CHNHTs), 59.8 (NCH_3 Weinreb amide), 44.8 (OCH_3), 32.6 (NCH_3), 28.1 ($CH_2CHNHTs$), 21.5 (CH_3Ts); M/z (CI) 433 $[M+NH_4]^+$, 416 $[M+H]^+$ (Found: $[M+H]^+$, 416.1641. $C_{21}H_{25}N_3O_4S$ requires $[M+H]^+$, 416.1566) (Found: C, 60.70; H, 6.06; N, 10.11. $C_{21}H_{25}N_3O_4S$ requires C, 60.66; H, 5.98; N, 10.15%).

(S)-4-Methyl-N-(1-(1-methyl-1H-indol-3-yl)-3-oxopent-4-en-2-yl)benzenesulfonamide 431



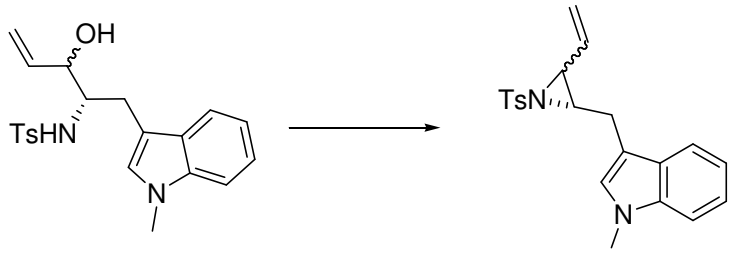
430 **431**

To a solution of Weinreb amide **430** (307 mg, 0.76 mmol, 1.0 equiv.) in THF (4 mL) at rt was added 1 M vinyl Grignard in THF (3.00 mL, 3.04 mmol, 4.0 equiv.). After stirring at rt for 16 h, the solution was quenched using saturated aqueous NH_4Cl (10 mL) and EtOAc (10 mL) was added. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (50% EtOAc–petrol) gave vinyl ketone **431** as a yellow gum (255 mg, 95%).

R_f = 0.51 (50% EtOAc–petrol); ν_{max} (film), 3292, 2926, 1701, 1612, 1701, 1473, 1403, 1376, 1331, 1158, 1091, 989, 740 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 7.57 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.40 (1H, d, *J* 8.5 Hz, C-9), 7.26 (1H, dd, *J* 1.0, 8.5 Hz, C-12), 7.22 (1H, dd, *J* 1.0, 8.5 Hz, C-11), 7.15 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.06 (1H, dt, *J* 1.0, 8.0 Hz, C-10), 6.82 (1H, s, C-2), 6.42 (1H, dd, *J* 10.5, 17.5 Hz, C*H*=CH_2), 6.22 (1H, dd, *J* 1.0, 17.5 Hz, CH=C$H_A$$H_B$), 5.78 (1H, dd, *J* 1.0, 10.5 Hz, CH=$CH_A$$H_B$), 5.39 (1H, d, *J* 7.5 Hz, NHTs), 4.49 (1H, dd, *J* 6.0, 13.5 Hz, C*H*NHTs), 3.72 (3H, s, CH_3N), 3.23 (1H, dd, *J* 6.0, 15.0 Hz, C$H_A$$H_B$CHNHTs), 3.13 (1H, dd, *J* 6.0, 15.0 Hz, C$H_A$$H_B$CHNHTs), 2.38 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 197.2 (CO), 143.4 (CCH_3), 136.9 (CSO_2), 136.6 (C-13), 132.3 (*C*H=CH_2), 130.3 (CH=*C*H_2), 129.5 (*meta*-Ts), 128.0 (C-2), 127.6 (C-8), 126.0 (*ortho*-Ts), 121.8 (C-11), 119.2 (C-10), 118.7 (C-9), 109.3 (C-12), 107.3 (C-7), 59.7 (CHNHTs), 32.7 (NCH_3), 28.9 (*C*H_2CHNHTs), 21.5 (CH_3Ts); M/z (ESI) 446.1525, 421.0988, 405.1249 $[M+Na]^+$, 383.1422 $[M+H]^+$, 196.0171 (Found: $[M+H]^+$, 383.1422. $C_{21}H_{22}N_2O_3S$ requires $[M+H]^+$, 383.1351).

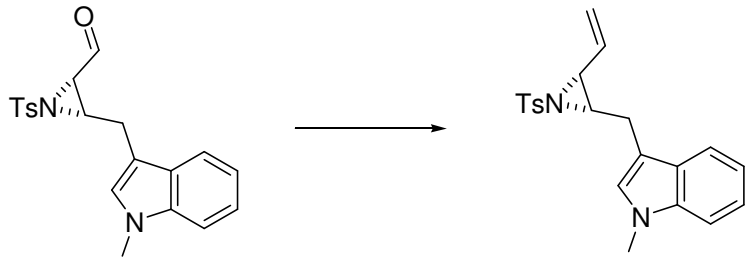
(S)-1-Methyl-3-((1-tosyl-3-vinylaziridin-2-yl)methyl)-1H-indole 419



424 **419**

To a solution of **424** (280 mg, 0.78 mmol, 1.0 equiv.) and PPh_3 (262 mg, 1.0 mmol, 1.2 equiv.) in THF (8 mL) at rt was dropwise added, in the dark, DIAD (232 μL, 1.17 mmol, 1.5 equiv.). After stirring at rt for 1.5 h the solution was concentrated under reduced pressure followed by column chromatography (66% petrol–EtOAc) gave **419** as a yellow gum (251 mg, 96%).

Wittig Reaction to provide 419

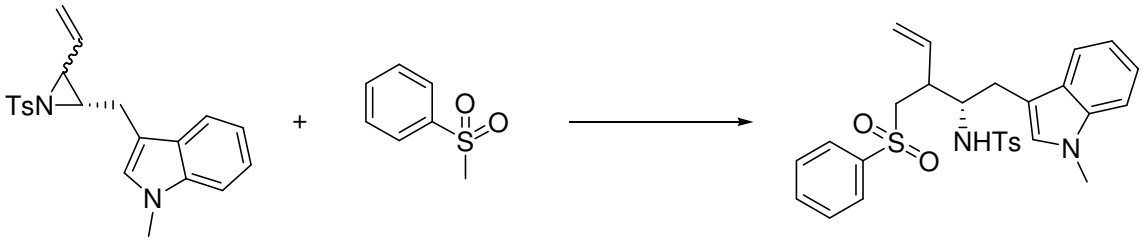


418 **419**

To a solution of PPh_3CH_3Br (343 mg, 0.95 mmol, 1.2 equiv.) in THF (11 mL) at –20 °C was added KHMDS (1.92 mL, 0.95 mmol, 1.2 equiv.). After stirring at –20 °C for 15 min, the solution was heated to rt and stirred for 10 min, cooled to –20 °C and aldehyde **418** (289 mg, 0.80 mmol, 1.0 equiv.) in THF (11 mL) was added. The solution was stirred for 30 min at –20 °C, poured on brine (100 mL) and extracted using Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure and purified using column chromatography (66% petrol–EtOAc) to give **419** (36 mg, 12%).

R_f = 0.81 (50% EtOAc–petrol); ν_{max} (film), 3301, 3055, 2935, 1716, 1598, 1475, 1437, 1376, 1323, 1265, 1154, 1013, 734 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.49 (1H, d, *J* 8.5 Hz, C-9), 7.28–7.20 (2H, m, C-12 + C11), 7.09 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.05 (1H, dt, *J* 1.0, 8.0 Hz, C-10), 6.77 (1H, s, C-2), 5.83 (1H, ddd, *J* 7.0, 10.5, 17.5 Hz, C*H*=CH_2), 5.55 (1H, dd, *J* 8.0, 17.0 Hz, CH=CH_AH_B), 5.42 (1H, dd, *J* 1.0, 10.5 Hz, CH=CH_AH_B), 3.67 (3H, s, NCH_3), 3.52 (1H, app t, *J* 7.5 Hz, NTsC*H*CH=CH_2), 3.25 (1H, dd, *J* .7.5, 13.5 Hz, CH_2C*H*NTs), 2.93 (1H, dd, *J* 6.0, 15.0 Hz, CH_AH_BCHNTs), 2.87 (1H, dd, *J* 6.0, 15.0 Hz, CH_AH_BCHNHTs), 2.41 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 143.9 (CCH_3), 136.8 (CSO_2), 134.9 (C-13), 129.9 (*C*H=CH_2), 129.2 (*meta*-Ts), 127.5 (*ortho*-Ts), 127.4 (C-8), 126.7 (C-2), 121.6 (*C*H_2=CH), 121.6 (C-11), 118.9 (C-10), 118.7 (C-9), 110.0 (C-7),109.0 (C-12), 46.2 (CH_2*C*HNTs), 45.3 (NTs*C*HCHCH_2), 32.6 (NCH_3), 22.8 (*C*H_2CNTs), 21.7 ($TsCH_3$); M/z (CI) 441, 423, 385 $[M+NH_4]^+$, 367 $[M+H]^+$, 189 (Found: $[M+H]^+$, 367.1484. $C_{21}H_{22}N_2O_2S$ requires $[M+H]^+$, 367.1402).

4-Methyl-*N*-((2S)-1-(1-methyl-1H-indol-3-yl)-3-(phenylsulfonylmethyl)pent-4-en-2-yl)benzenesulfonamide 433

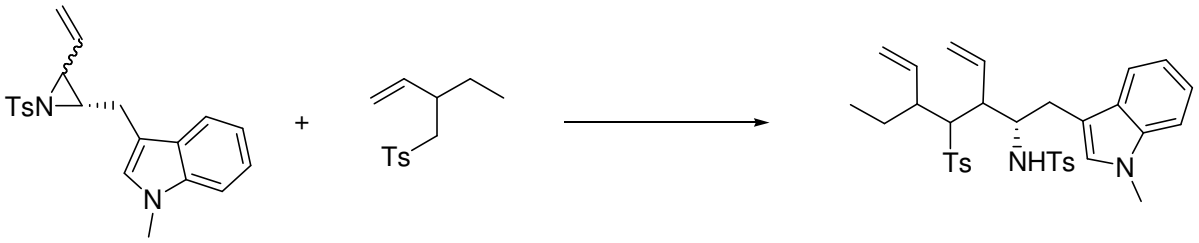


419 **432** **433**

To a solution of sulfone **432** (150.0 mg, 0.90 mmol, 3.0 equiv.) in THF (1.0 mL) was added 2.5 M ^{n}BuLi (588 μL, 1.35 mmol, 4.5 equiv.) at –40 ^{o}C,. After 30 min, aziridine **419** (100 mg, 0.30 mmol, 1.0 equiv.) in THF (0.5 mL) was added at –40 ^{o}C dropwise and stirred for 16 h while heating up to rt. The solution was quenched using saturated aqueous NH_4Cl (15 mL) and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (33% EtOAc–petrol) gave **433** as a yellow gum (133 mg, 90%).

R_f = 0.30 (33% EtOAc–petrol); ν_{max} (film), 3298, 2924, 2854, 1735, 1704, 1598, 1467, 1424, 1376, 1304, 1249, 1147, 1084, 925, 738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 7.5 Hz, *ortho*-Ts), 7.78 (1H, app. d, *J* 8.0 Hz, *para*-$PhSO_2$), 7.64 (2H, m, *ortho*-$PhSO_2$), 7.47 (2H, t, *J* 8.0 Hz, *meta*-$PhSO_2$), 7.35 (1H, d, *J* 7.5 Hz, C-9), 7.21 (1H, d, *J* 3.5 Hz, C-12), 7.02 (3H, m, *meta*-Ts + C-11), 6.95 (1H, m, C-10), 6.69 (1H, s, C-2), 5.80 (1H, m, C*H*=CH_2), 5.23 (1H, d, *J* 10.0 Hz, CH=CH_AH$_B$), 5.15 (1H, d, *J* 17.0 Hz, CH=C$H_A$$H_B$), 4.63 (1H, d, *J* 7.5 Hz, NHTs), 3.72 (1H, m, C*H*NHTs), 3.68 (3H, s, NCH_3), 3.50 (1H, dd, *J* 6.0, 14.5 Hz, CH_AH$_B$CHNHTs), 3.19 (1H, dd, *J* 6.5, 14.5 Hz, CH$_A$$H_B$CHNHTs), 3.11 (1H, m, C*H*CH=CH_2), 2.98 (1H, dd, *J* 4.5, 14.0 Hz, CH_AH$_B$$SO_2$Ph), 2.65 (1H, dd, *J* 8.5, 14.5 Hz, CH$_A$$H_B$$SO_2$Ph), 2.34 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 142.3 (CSO_2), 139.5 (CSO_2), 136.8 (CCH_3), 135.5 (*C*H=CH_2), 133.7 (C-13), 133.3 (*para*-$PhSO_2$), 129.3 (*meta*-Ts), 129.1 (*meta*-$PhSO_2$), 127.7 (*ortho*-Ts), 127.6 (*meta*-$PhSO_2$), 126.9 (C-8), 126.6 (C-2), 121.7 (*C*H_2=CH), 120.3 (C-11), 119.2 (C-10), 118.5 (C-9), 109.1 (C-12), 108.2 (C-7), 57.4 (*C*H_2CHNHTs), 56.0 (*C*HNHTs), 42.1 (*C*HCH=CH_2), 32.6 (NCH_3), 26.6 (*C*$H_2$$SO_2$Ph), 21.8 ($TsCH_3$); M/z (ESI) 586.1797, 561.1319, 545.1528 [M+Na]$^+$, 523.1721 [M+H]$^+$, 363.0991, 196.0160 (Found: [M+H]$^+$, 523.1721. $C_{28}H_{30}N_2O_4S_2$ requires [M+H]$^+$ 523.1647).

_N_-((2S)-5-Ethyl-1-(1-methyl-1H-indol-3-yl)-4-tosyl-3-vinylhept-6-en-2-yl)-4-methylbenzenesulfonamide 434

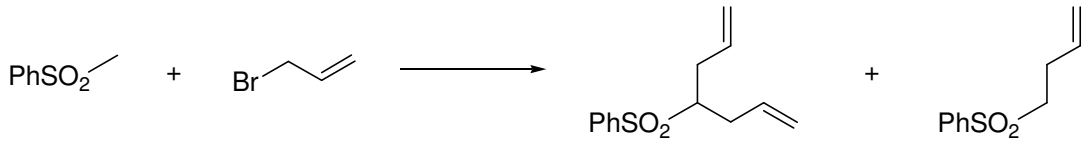


419 **402** **434**

To a solution of sulfone **402** (266 mg, 0.78 mmol, 3.0 equiv.) in THF (100 μL) was added 2.5 M ^{n}BuLi (480 μL, 1.04 mmol, 4.0 equiv.) at –40 ^{o}C. After 30 min, aziridine **419** (100 mg, 0.26 mmol, 1.0 equiv.) in THF (190 μL) was added at –40 ^{o}C dropwise and stirred for 16 h while heating up to rt. The solution was quenched using saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (80% Et_2O–petrol) gave **434** as a yellow gum (187 mg, 94%).

R_f = 0.50 (80% Et_2O–petrol); ν_{max} (film), 3060, 3025, 2948, 2926, 2874, 2853, 1590, 1490, 1454, 1370, 1140, 1086, 968, 910, 810 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, *J* 8.0 Hz, *ortho*-Ts), 7.75 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.71 (1H, dd, *J* 3.0, 8.5 Hz, ArH), 7.45 (1H, d, *J* 8.0 Hz, ArH), 7.34 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.24 (3H, m, *meta*-Ts + ArH), 7.11–7.07 (2H, m, ArH) 6.74 (1H, s, NC*H*), 6.16 (1H, dt, *J* 10.0, 17.0 Hz, C*H*=CH_2), 5.87 (1H, dt, *J* 7.0, 17.0 Hz, C*H*=CH_2'), 5.78 (1H, d, *J* 7.0 Hz, N*H*Ts), 5.46 (1H, m, CH=CH_AH$_B$), 5.24 (1H, m, CH=CH$_A$$H_B$), 4.99 (1H, m, CH=C$H_AH_B$'), 4.69 (1H, m, CH=CH$_A$$H_B$'), 3.82 (1H, m, C*H*NHTs), 3.72 (3H, s, NCH_3), 3.45 (1H, m, CHTs'), 3.42 (1H, m, CHTs), 2.97–2.83 (3H, m, CH_2CHNHTs + C*H*CH=CH_2), 2.45 (3H, s, CH_3Ts), 2.43 (3H, s, CH_3Ts'), 2.07 (1H, m, C*H*CH=CH_2'), 0.65 (2H, m, CH_2CH_3), 0.32 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 144.5, 143.3, 137.9, 137.2, 137.0, 136.5, 132.0, 129.7, 129.5, 129.3, 128.7, 128.6, 128.5, 127.4, 127.2, 122.4, 121.8, 118.9, 116.6, 109.9, 109.2, 67.9, 58.4, 46.6, 44.7, 44.0, 32.6, 29.3, 22.8, 21.6, 12.4, 11.3; M/z (ESI) 1232, 628, 627 $[M+Na]^+$, 605 $[M+H]^+$ (Found: $[M+H]^+$, 605.2505. $C_{34}H_{40}N_2O_4S_2$ requires $[M+H]^+$ 605.2429).

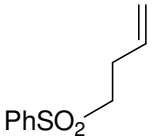
3.2. (±)-Alstonerine



432 **512** **513** **514**

To a solution of LDA (prepared from diisopropylamine (1.80 mL, 14.0 mmol, 2.2 equiv.) and 2.5 M ^{n}BuLi (3.20 mL, 7.00 mmol, 1.1 equiv.)) in THF (6 mL) at –78 ^{o}C was added a solution of methylphenylsulfone **432** (1.00 g, 6.40 mmol, 1.0 equiv.) in THF (3 mL). After stirring for 1 h at –78 ^{o}C, allyl bromide **512** (0.61 mL, 7.00 mmol, 1.1 equiv.) was added and the solution heated to rt. The reaction mixture was quenched using saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (20% Et_2O–petrol) afforded compound **514** as a colorless oil (610 mg, 48%) together with the bissubstituted adduct **513** (472 mg, 31%) and starting material **432** (218 mg, 22%).

(But-3-enylsulfonyl)benzene 514

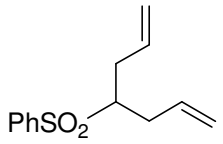


514

R_f = 0.51 (33% EtOAc–petrol); ν_{max} (film) 1642, 1446, 1305, 1233, 1142, 1085, 919 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 7.5 Hz, *ortho*-Ar), 7.70 (1H, t, *J* 7.5 Hz, *para*-Ar), 7.61 (2H, t, *J* 7.5 Hz, *meta*-Ar), 5.75 (1H, ddt, *J* 6.5, 10, 17.0 Hz, *C*H=CH_2); 5.08 (2H, t, *J* 8.0 Hz, CH=C*H*$_2$), 3.19 (2H, t, *J* 8.0 Hz, SO_2*C*H_2), 2.49 (2H, m, SO_2CH_2C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 139.0 (SO_2C), 133.8 (CH_2=*C*H), 129.3 (*ortho*-Ar + *para*-Ar), 128.1 (*meta*-Ar), 117.2 (*C*H_2=CHCH), 55.4 (SO_2*C*H_2), 26.9 (SO_2CH_2*C*H_2); M/z (CI) 214 $[M+NH_4]^+$, 197 $[M+H]^+$.

The data are in agreement with the reported compound.[6]

(Hepta-1,6-dien-4-ylsulfonyl)benzene 513

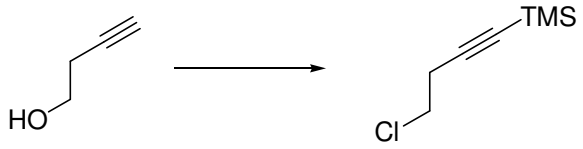


513

R_f = 0.65 (33% EtOAc–petrol); ν_{max} (film) 1641, 1446, 1303, 1143, 1084, 917 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.33 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.55 (1H, ddd, *J* 8.5, 10.5, 17.0, C*H*=CH_2), 5.01 (2H, m, CH=CH_2), 3.13 (2H, d, *J* 6.5 Hz, CH_2-Ts), 2.55 (1H, m, CH=CHC*H*), 2.46 (3H, s, CH_3-Ts), 1.63 (2H, m, CH_2CH_3 major), 1.39 (2H, m, CH_2CH_3 minor), 0.85 (3H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 137.9 (SO_2C), 133.7 (CH_2=*C*H), 129.3 (*ortho*-Ar + *para*-Ar), 128.9 (*meta*-Ar), 117.2 (*C*H_2=CHCH), 63.7 (SO_2*C*H), 31.7 (SO_2CH_2*C*H_2); M/z (CI) 254 $[M+NH_4]^+$, 237 $[M+H]^+$.

The data are in agreement with the reported compound.[6]

(4-Chlorobut-1-ynyl)trimethylsilane 518



517 **518**

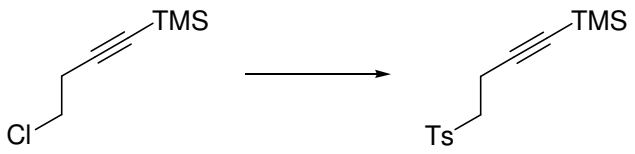
To a solution of EtMgBr (43.0 mL, 160 mmol, 2.5 equiv.) in THF (38 mL) was added 4-hydroxy-1-butyn **517** (5.00 mL, 64.0 mmol, 1.0 equiv.) at rt. After stirring for 20 min at rt, TMSCl (20.0 mL, 160 mmol, 2.5 equiv) in THF (38 mL) was added and stirred for 1.5 h. The solution was quenched with aqueous NH_4Cl (11.4 g in 44 mL H_2O), separated and the organic layer concentrated to ~38 mL. To the solution was added aqueous NH_4Cl (11.4 g in 44 mL water) and stirred at rt for 16 h. The aqueous mixture was extracted with Et_2O (3 x 50 mL), dried ($MgSO_4$) and concentrated. The liquid obtained was redissolved in $SOCl_2$ (15 mL) and pyridine (0.8 mL) and refluxed for 7 h. After cooling the solution to rt, the resulting mixture was poured into ice / H_2O and extracted using Et_2O (3 x 100 mL), the combined organic layers were washed with 10 M HCl (2 x 100 mL), dried ($MgSO_4$) and concentrated under

reduced pressure. Distillation (62 °C, 10 mmHg) gave **518** as a colorless liquid (6.66 g, 65% yield).

ν_{max} (film) 2961, 2179, 1250, 1004, 838 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.60 (2H, t, *J* 7.5, $ClCH_2CH_2$), 2.69 (2H, t, *J* 7.5, $ClCH_2CH_2$), 0.17 (9H, s, $(CH_3)_3Si$); δ_C (100 MHz, $CDCl_3$) 102.3 ($CCSi(CH_3)_3$), 87.0 ($CCSi(CH_3)_3$), 41.9 ($ClCH_2CH_2$), 24.2 ($ClCH_2CH_2$), -0.06 ($Si(CH_3)_3$); M/z (CI) Unable to ascertain mass, compound not detected.

The data are in agreement with the reported compound.[7]

Trimethyl(4-tosylbut-1-ynyl)silane 519



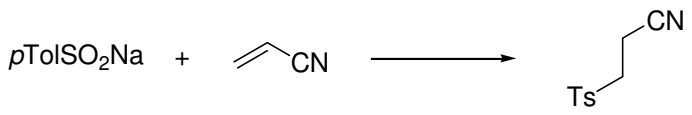
518 **519**

A mixture of **518** (0.30 g, 1.90 mmol, 1.0 equiv), anhydrous NaI (285 mg, 1.90 mmol, 1.0 equiv.) and anhydrous sodium *p*-toluenesulfinate (406 mg, 2.28 mmol, 1.2 equiv.) in DMF (2 mL) was heated to 80 °C and stirred for 12 h, after which it was cooled to 40 °C and stirred at this temperature for 12 h. The solution was cooled to rt and diluted with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure resulting in a yellow solid. Recrystilization from 50% petrol–Et_2O gave **519** as a colorless oil (330 mg, 62% yield).

ν_{max} (film) 2958, 2173, 1281, 1135, 759 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.38 (2H, d, *J* 8.0 Hz, *meta*-Ts), 3.30 (2H, t, *J* 8.0 Hz, $TsCH_2$), 2.47 (3H, s, CH_3Ts), 2.66 (2H, *J* 8.0 Hz, $TsCH_2CH_2$), 0.10 (9H, s, $(CH_3)_3Si$); δ_C (100 MHz, $CDCl_3$) 145.0 (CSO_2), 135.6 (CH_3C), 130.0 (*ortho*-Ts), 128.3 (*meta*-Ts), 101.4 (TMS*C*C), 87.1 (TMSC*C*), 54.8 ($TsCH_2$), 21.7 (CH_3Ts), 14.7 ($TsCH_2CH_2$), 0.10 ($(CH_3)_3Si$); M/z (CI) 298 $[M+NH_4]^+$, 281 $[M+H]^+$ (Found: $[M+NH_4]^+$, 298.1292. $C_{14}H_{20}O_2SSi$ requires $[M+NH_4]^+$, 298.1297.).

The data are in agreement with the reported compound.[8]

3-Tosylpropanenitrile 524



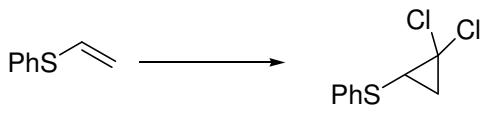
523 **524**

A solution of acrylonitrile **523** (4.0 mL, 60.0 mmol, 1.0 equiv.), *p*-toluenesulfinic acid (11.6 g, 65.0 mmol, 1.1 equiv.) and HOAc (4 mL) was heated to reflux for 16 h. After cooling down to rt, the mixture was extracted with DCM (3 x 30 mL) and the combined organic layers washed with saturated aqueous $NaHCO_3$ (3 x 30 mL), H_2O (3 x 30 mL) and brine (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide **524** (11.9 g, 95%).

R_f = 0.31 (50% EtOAc–petrol); m.p. = 94 °C (lit.[9] m.p. 94–95 °C); ν_{max} (film) 2991, 2927, 2248, 1791, 1596, 1422, 1302, 1139, 1084 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.43 (2H, d, *J* 8.0 Hz, *meta*-Ts), 3.38 (2H, t, *J* 7.5 Hz, Ts*C*$H_2$$CH_2$), 2.82 (2H, t, *J* 7.5 Hz, CH=C*H*$_2$), 2.49 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 146.0 (SO_2C), 134.5 (*C*CH_3), 130.4 (*ortho*-Ts), 128.3 (*meta*-Ts), 116.0 (CN), 51.2 (Ts*C*$H_2$$CH_2$), 21.7 ($CH_3$Ts), 12.1 (Ts$CH_2$*C*$H_2$); M/z (CI) 254 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 227.0852. $C_{10}H_{11}NO_2S$ requires $[M+NH_4]^+$, 227.0854.).

The data are in agreement with the reported compound.[9]

(2,2-Dichlorocyclopropyl)(phenyl)sulfane 528



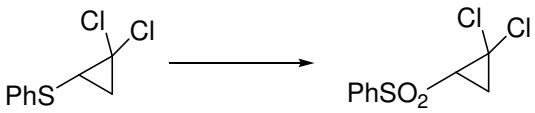
527 **528**

To a solution of NaOMe (0.47 g, 8.70 mmol, 1.5 equiv.) in petrol (5.5 mL) was added phenylvinylsulfide **527** (0.50 mL, 5.80 mmol, 1.0 equiv.) at 0 °C. Ethyl trichloroacetate (0.89 mL, 6.40 mmol, 1.1 equiv.) was added dropwise over 30 min and the solution was stirred for 6 h at 0 °C. After heating to rt for 16 h, water (3 mL) was added and the organic layer separated. The aqueous layer was extracted using DCM (3 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Distillation (95 °C, 1 mmHg) gave **528** as a pale yellow oil (76.0 mg, 60%).

ν_{max} (film) 3085, 3009, 1584, 1480, 1440, 1092, 1053, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40 (3H, m, *ortho*-, *para*-Ar), 7.27 (2H, m, *meta*-Ar), 2.98 (1H, dd, *J* 7.5, 10.5 Hz, PhSC*H*), 2.07 (1H, dd, *J* 7.5, 10.5 Hz, PhSCHCH_AH$_B$), 1.57 (1H, dd, *J* 6.5, 8.5 Hz, PhSCHCH$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 135.4 (CS), 129.2 (*ortho*-Ar), 127.6 (*meta*-Ar), 126.3 (*para*-Ar), 61.9 (CCl_2), 32.7 (PhSCH), 27.4 (PHSCH*C*H_2; M/z (CI) 218 $[M+H]^+$, 183, 147 (Found: $[M+H]^+$, 218.0228. $C_9H_8Cl_2S$ requires $[M+H]^+$, 218.9720.).

The data are in agreement with the reported compound.[10]

(2,2-Dichlorocyclopropylsulfonyl)benzene 529



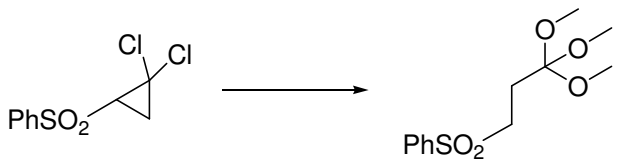
528 **529**

A solution of **528** (160 mg, 0.75 mmol, 1.0 equiv.) and 30% wt H_2O_2 (320 μL) in HOAc (1.1 mL) was heated to 100 °C for 3 h. After cooling to rt, water (10 mL) was added and the aqueous layer extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a white solid. Chromatography (30% Et_2O–petrol) gave **529** as a white solid (662 mg, 90%).

R_f = 0.40 (66% Et_2O–petrol); m.p. = 88 °C (lit.[11] m.p. 87–88 °C); ν_{max} (film) 3112, 3033, 1446, 1322, 1214, 1158, 1087, 723 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.04 (2H, dd, *J* 1.0, 8.0 Hz, *ortho*-Ar), 7.75 (1H, dd, *J* 1.0, 8.0 Hz, *para*-Ar), 7.65 (2H, dd, *J* 1.0, 8.0 Hz, *meta*-Ar), 3.32 (1H, dd, *J* 7.5, 10.0 Hz, PhSC*H*), 2.47 (1H, t, *J* 7.5 Hz, PhSCHCH_AH_b), 2.20 (1H, dd, *J* 7.5, 10.0 Hz, PhSCHCH_AH_B); δ_C (100 MHz, $CDCl_3$) 139.6 (CS), 134.3 ((*para*-Ar),129.5 (*ortho*-Ar), 128.0 (*meta*-Ar), 55.4 (CCl_2), 47.9 (PhSCH), 26.3 (PHSCH*C*H_2; M/z (CI) 268 $[M+NH_4]^+$ (Found: $[M+NH_4]^+$, 267.9970. $C_9H_8Cl_2O_2S$ requires $[M+NH_4]^+$, 267.9966.).

The data are in agreement with the reported compound.[11]

(3,3,3-Trimethoxypropylsulfonyl)benzene 525



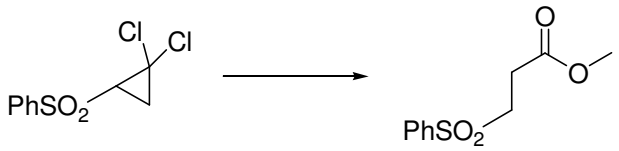
529 **525**

To a solution of NaOMe (110 mg, 2.04 mmol, 3.0 equiv.) in methanol (2 mL) was added **529** (167 mg, 0.68 mmol, 1.0 equiv.) in methanol (2 mL) and heated to reflux for 2 h. After cooling down to rt, the solution was poured into water (13 mL) and the aqueous layer extracted using Et_2O (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give **525** as a colorless oil (172 mg, 95%).

ν_{max} (film) 2947, 2840, 1446, 1284, 1240, 1143, 1076, 100 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.0 Hz, *ortho*-Ar), 7.68 (1H, m, *para*-Ar), 7.59 (2H, m, *meta*-Ar), 3.19 (9H, s, $(CH_3O)_3$), 3.14 (2H, dt, *J* 4.5, 9.0 Hz, $PhSO_2CH_2$) 2.18 (2H, dt, *J* 4.5, 9.0 Hz, $PhSO_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 139.0 (CSO_2), 139.0 (*para*-Ar), 129.4 (*ortho*-Ar), 127.9 (*meta*-Ar), 114.3 ($C(CH_3O)_3$), 51.3 ($PhSO_2CH_2$), 49.6 ($(OCH_3)_3$), 23.9 ($PhSO_2CH_2CH_2$); M/z (CI) 292 $[M+NH_4]^+$, 243, 214, 105 $[(M-OCH_3)+H]^+$ (Found: $[M+NH_4]^+$, 292.1219. $C_{12}H_{18}O_5S$ requires $[M+NH_4]^+$, 292.1219.) (Found: C, 52.63; H, 6.68; $C_{12}H_{18}O_2S$ requires C, 52.54; H, 6.61%).

The data are in agreement with the reported compound.[11]

Methyl 3-(phenylsulfonyl)propanoate 525

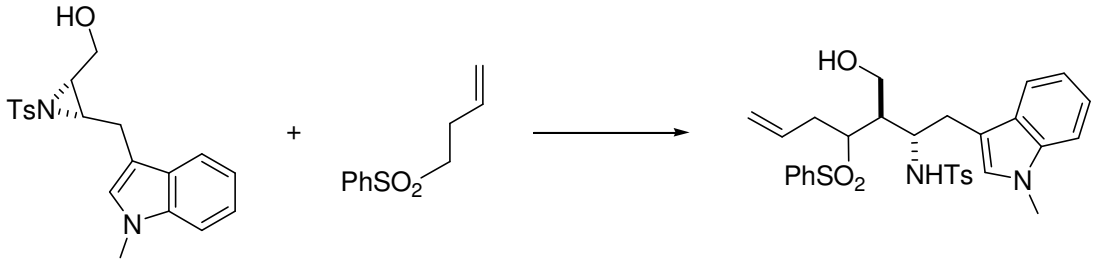


529 **525**

ν_{max} (film) 2955, 1736, 1586, 1586, 1447, 1439, 1308, 1251, 1148, 1132, 1086, 1071, 732, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, m, *ortho*-Ar), 7.69 (1H, *J* 1.0, 9.0 Hz, *para*-Ar), 7.58 (2H, dd, *J* 5.0, 9.0 Hz, *meta*-Ar), 3.64 (3H, s, OCH_3), 3.44 (2H, t, *J* 8.0 Hz, $PhSO_2CH_2$), 2.79 (2H, t, *J* 8.0 Hz, $PhSO_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 170.4 (CO), 138.4 (CSO_2), 134.1 (*para*-Ar), 129.5 (*ortho*-Ar), 128.2 (*meta*-Ar), 52.3 ($PhSO_2CH_2$), 51.5 (OCH_3), 27.6 ($PhSO_2CH_2CH_2$); M/z (CI) 246 $[M+NH_4]^+$, 229 $[M+H]^+$.

The data are in agreement with the reported compound.[12]

***N*-((2S,3R)-3-(Hydroxymethyl)-1-(1-methyl-1H-indol-3-yl)-4-(phenylsulfonyl)hept-6-en-2-yl)-4-methylbenzenesulfonamide 503**

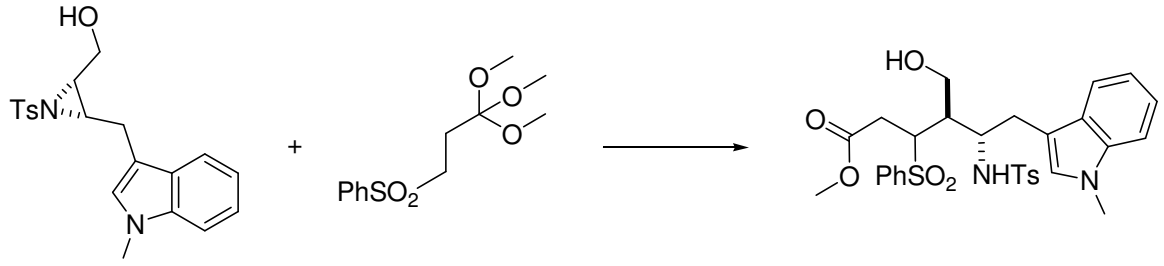


388 **514** **503**

To a solution of sulfone **514** (780 mg, 4.00 mmol, 2.0 equiv.) in THF (2.2 mL) and 2.5 M ^nBuLi (3.0 mL, 6.0 mmol, 3.0 equiv.) at –78 ^oC was added, after 30 min, aziridine **388** (742 mg, 2.00 mmol, 1.0 equiv.) in THF (2.2 mL). After stirring for 16 h while heating up to rt, the solution was quenched using brine (40 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (33% EtOAc–petrol) gave **503** as a pale yellow oil (663 mg, 60%).

R_f = 060 (66% EtOAc–petrol); ν_{max} (film) 3401, 2932, 1808, 1783, 1642, 1598, 1325, 1184, 1091, 919, 739 cm^{-1}; δ_h (400 MHz, Aceton D_6) 8.05 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.93 (2H, d, *J* 8.0 Hz, *ortho*-Ts'), 7.79 (2H, m, C-9 + ArH), 7.69 (3H, m, *meta*-Ts + C-10), 7.62 (2H, m, *meta*-Ts'), 7.46 (3H, 3 x ArH), 7.29 (2H,m , 2 x ArH), 7.24 (3H, m, 3 x ArH), 7.13 (2H, m, 2 x ArH), 7.01 (2H, m, 2 x ArH), 6.95 (3H, m, 3 x ArH), 6.93 (1H, s, C-2), 6.83 (1H, s, C-2'), 6.52 (1H, d, *J* 7.0 Hz, NHTs), 6.23 (1H, d, *J* 7.0 Hz, NHTs'), 5.76 (1H, m, C*H*=CH_2), 5.42 (1H, m, C*H*=CH_2), 5.04 (1H, dd, *J* 1.5, 17.0 Hz, C$H_A$$CH_B$=CH), 4.94 (1H, dd, *J* 1.5, 17.0 Hz, C$H_A$$CH_B$=CH'), 4.85 (1H, dd, *J* 1.0, 10.5 Hz, CH_ACH_B=CH'), 4.83 (1H, dd, *J* 1.5, 10.5 Hz, CH_ACH_B=CH), 4.31 (1H, m, C*H*NHTs), 4.11 (1H, m, C*H*NHTs'), 4.03-3.94 (1H, m, $CHSO_2$Ph'), 3.85 (1H, m, $CHSO_2$Ph), 3.68 (3H, s, NCH_3), 3.63 (3H, s, NCH_3'), 3.23 (1H, dd, *J* 5.5, 14.5 Hz, C$H_A$$H_B$CHNHTs), 3.01 (1H, dd, *J* 4.0, 14.5 Hz, C$H_A$$H_B$CHNHTs'), 2.94 (1H, dd, *J* 8.5, 14.5 Hz, $CH_A$$H_B$CHNHTs), 2.76 (1H, dd, *J* 8.5, 14.5 Hz, $CH_A$$H_B$CHNHTs'), 2.70-2.61 (4H, m, CH_2CH=CH_2 + CH_2CH=CH_2'), 2.55 (2H, C*H*CH_2OH + C*H*CH_2OH'), 2.55-2.45 (4H, m, CH_2OH + CH_2OH'), 2.34 (3H, s, CH_3Ts), 2.32 (3H, s, CH_3Ts'); δ_C (100 MHz, $CDCl_3$) 143.0 (CSO_2), 138.2 (CH_3*C*Ts, 138.0 (CSO_2), 137.5, 136.8, 136.7, 134.9, 134.1, 133.7, 132.6, 129.4, 129.3, 129.2, 128.8, 128.7, 127.7, 127.3, 126.8, 121.8, 119.1, 118.4, 117.8, 109.2, 108.5, 108.3, 62.8 (*C*H_2OH), 61.6 , 60.4, 60.2, 58.6, 54.3, 52.9, 45.3, 42.6, 33.5, 32.6, 29.9, 28.6, 28.1, 21.6 (CH_3Ts); M/z (CI) 584 $[M+NH_4]^+$, 567 $[M+H]^+$, 499, 425, 189, 174, 160 (Found: $[M+H]^+$, 567.1967. $C_{30}H_{34}N_2O_5S_2$ requires $[M+H]^+$, 567.1987).

4R,5S)-Methyl 4-(hydroxymethyl)-6-(1-methyl-1H-indol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate 527



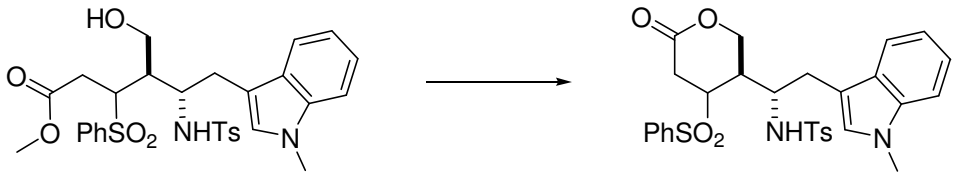
388 **526** **527**

To a solution of sulfone **526** (108 mg, 0.39 mmol, 1.5 equiv.) in THF (0.5 mL) was added, after 30 min, aziridine **388** (100 mg, 0.26 mmol, 1.0 equiv.) in THF (0.6 mL) at –78 ^oC dropwise. After stirring for 16 h while heating up to rt, the solution was quenched using saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 x 15

mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (50% EtOAc–petrol) gave **527** as an off-white solid (140 mg, 90%).

R_f = 0.35 (66% EtOAc–petrol); m.p. = 90–92 ^oC; ν_{max} (film) 3301, 2924, 1739, 1601, 1475, 1427, 1305, 1155, 1090, 1072, 954, 726 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.69 (1H, m, C-9), 7.59 (3H, m, *meta*-Ts + C-12), 7.25 (2H, m, 2 x ArH), 7.20, (2H, d, *J* 7.5 Hz, 2 x ArH) 7.10 (2H, d, *J* 7.5 Hz, C-11 + ArH), 7.04 (1H, m, C-10), 6.80 (1H, s, C-2), 5.84 (1H, d, *J* 9.0 Hz, N*H*Ts), 4.32 (1H, dt, *J* 3.0, 6.0 Hz, $PhSO_2CH$), 4.10 (1H, dt, *J* 8.5 Hz, TsNHC*H*), 4.01 (2H, ddd, *J* 6.5 Hz, CH_2OH), 3.64 (3H, s, NMe), 3.42 (3H, s, OMe), 3.10-2.90 (2H, dd, *J* 7.0 Hz, $CH_2CHNHTs$), 2.36 (2H, d, *J* 5.0 Hz, CH_2CO_2Me), 2.52 (1H, m, $CHCH_2OH$), 2.93 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 170.7 (CO), 142.9 (CSO_2), 137.8 (CSO_2), 137.6 (CH_3C-Ts), 134.2 (*para*-$PhSO_2$), 129.8 (C-13), 129.2 (*ortho*-Ts), 129.3 (*ortho*-$PhSO_2$), 129.0 (*meta*-Ts), 128.8 (Ar*C*), 127.7 (*meta*-$PhSO_2$), 126.8 (*meta*-$PhSO_2$), 121.7 (ArH), 119.1 (ArH), 118.5 (ArH), 109.0 (ArCH), 107.5 (C-7), 60.1 (CH_2OH), 59.2 (OCH_3), 53.2 ($PhSO_2CH$), 52.2 (TsNH*C*H), 46.8 ($CHCH_2OH$), 34.1 ($CH_2CO_2CH_3$), 32.5 (NCH_3), 29.0 (CH_2C), 21.6 ($TsCH_3$); M/z (ESI) 621.1710 $[M+Na]^+$, 589.1450 $[M+Na-OCH_3]^+$, 567.1626 $[M-OCH_3]^+$, 479.1616 $[M+Na-SO_2Ph]^+$, 457.1797 $[M-SO_2Ph]^+$ (Found: $[M+H]^+$, 599.1890. $C_{30}H_{34}O_7S_2$ requires $[M+H]^+$, 599.1870.) (Found: C, 60.20; H, 5.74; N, 4.64 $C_{30}H_{34}O_7S_2$ requires C, 60.18; H, 5.72; N, 4.68%).

4-Methyl-N-((1S)-2-(1-methyl-1H-indol-3-yl)-1-((3R)-6-oxo-4-(phenylsulfonyl)tetrahydro-2H-pyran-3-yl)ethyl)benzenesulfonamide 528



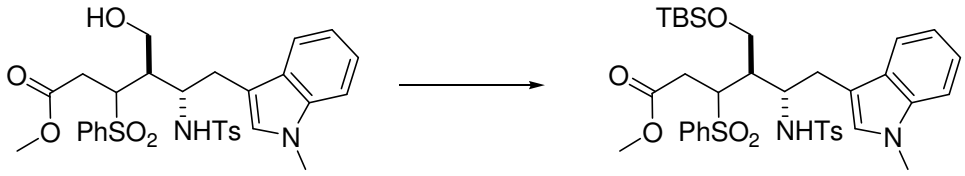
527 **528**

To a solution of **527** (100 mg, 0.17 mmol, 1.0 equiv.) in DCM (1.0 mL) at rt was added TFA (1 drop) and the solution stirred for 3 h at rt. The solution was diluted using DCM (10 mL) and neutralized by addition of saturated aqueous $NaHCO_3$ (2 x 7 mL). The combined organic layers were subsequently washed with brine (7 mL), dried ($MgSO_4$) and concentrated under

reduced pressure. Preparative TLC (66% EtOAc–petrol) provided lactone **528** as a gum (61 mg, 65%).

R_f = 0.40 (66% EtOAc–petrol); ν_{max} (film) 3301, 2928, 2851, 1759, 1749, 1600, 1447, 1314, 1155, 1084, 737, 667 cm^{-1}; δ_h (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.68 (1H, m, ArH), 7.55 (2H, t, *J* 8.5 Hz, *ortho*-$PhSO_2$), 7.47 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.25 (2H, m, 2 x ArH), 7.12–7.04 (4H, m, 4 x ArH), 6.74 (1H, s, C-2), 4.76 (1H, d, *J* 7.5 Hz, N*H*Ts) 4.50 (1H, dd, *J* 4.0, 12.5 Hz, CH_AH_BO)4.33 (1H, dd, *J* 4.0, 12.5 Hz, CH_AH_BO), 3.82 (1H, m, C*H*SO_2Ph), 3.70 (3H, s, NCH_3), 3.64 (1H, m, C*H*NHTs), 2.99 (1H, dd, *J* 5.0, 15.0 Hz, CH_AH_BCHNHTs) 2.92 (1H, m, CHNHTsC*H*), 2.80 (2H, m, $CH_AH_BCO_2$ + CH_AH_BCHNHTs), 2.64 (1H, dd, *J* 7.0, 15.5 Hz, $CH_AH_BCO_2$), 2.36 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 168.9 (CO), 137.0 (CSO_2), 136.2 (CSO_2), 134.5 (*para*-$PhSO_2$), 129.6 (*ortho*-Ts), 129.5 (*ortho*-$PhSO_2$), 129.1 (*meta*-Ts), 127.8 (*meta*-$PhSO_2$), 126.7 (*meta*-$PhSO_2$), 122.0 (ArH), 119.6 (ArH), 118.1 (ArH), 109.4 (ArCH), 107.3 (C-7), 66.5 (CH_2O), 56.8 (CH_2C=O), 53.7 ($PhSO_2CH$), 36.6 ($CHCH_2C$=O), 32.9 (NCH_3), 29.0 (CH_2CHNHTs), 21.9 ($TsCH_3$); M/z (ESI) 488.1618, 463.1095, 447.1363 $[M+Na-SO_2Ph]^+$, 425.1541 $[M-SO_2Ph]^+$ (Found $[M+H-SO_2Ph]^+$, 425.1541. $C_{29}H_{30}N_2O_6S_2$ requires $[M+H-SO_2Ph]^+$, 425.1613) (Found: C, 61.96; H, 5.55; N, 4.81. $C_{29}H_{30}N_2O_6S_2$ requires C, 62.05; H, 5.55; N, 4.82%).

(4R,5S)-Methyl-4-((tert-butyldimethylsilyloxy)methyl)-6-(1-methyl-1H-indol-3-yl)-5-(4-methylphenylsulfonamido)-3-(phenylsulfonyl)hexanoate 529



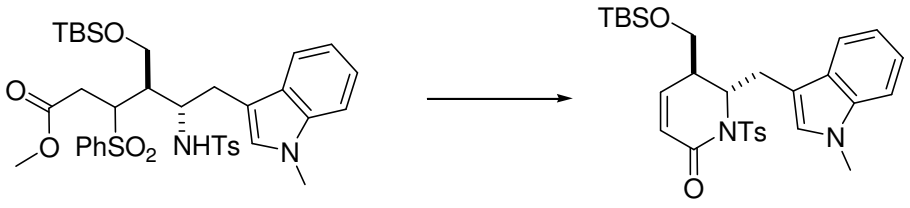
527 **529**

A solution of **527** (30 mg, 50 µmol, 1.0 equiv.), imidazole (5.0 mg, 75 µmol, 1.5 equiv.) and TBSCl (11 mg, 75 µmol, 1.5 equiv.) in DMF (0.3 mL) was stirred at rt for 30 min. The solution was poured onto H_2O / EtOAc (1 : 1, 10 mL) and the organic layer separated. The aqueous layer was washed using EtOAc (3 x 5 mL) and the combined organic layers washed with 10% citric acid (2 x 10 mL), brine (15 mL), dried ($MgSO_4$) and concentrated under

reduced pressure. Preparative TLC (50% EtOAc–petrol) provided **529** as a colorless gum (32 mg, 91%).

R_f = 0.85 (66% EtOAc–petrol); ν_{max} (film) 3294, 2957, 2928, 2862, 1742, 1472, 1331, 1305, 1262, 1159, 1089, 838, 777 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65 (4H, m, *ortho*-Ts + 2 x ArH), 7.58 (1H, m, ArH), 7.43 (2H, m, 2 x ArH), 7.29–7.21 (3H, m, 3 x ArH), 7.17 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.02 (1H, t, *J* 7.5 Hz, C-11), 6.84 (1H, s, C-2), 5.93 (1H, d, *J* 8.0 Hz, NHTs), 4.25 (1H, td, *J* 2.0, 8.5 Hz, C*H*SO_2Ph), 3.77 (1H, m, C*H*NHTs), 3.72 (3H, s, OCH_3), 3.68 (1H, m, C$H_A$$H_B$OTBS), 3.54 (1H, dd, *J* 5.5, 10.5 Hz, $CH_A$$H_B$OTBS), 3.47 (3H, s, NCH_3), 3.12 (1H, dd, *J* 6.5, 14.5 Hz, C$H_A$$H_B$CHNHTs), 3.00 (1H, dd, *J* 8.0, 18.0 Hz, C$H_A$$H_B$$CO_2CH_3$), 2.89 (1H, dd, *J* 6.0, 14.5 Hz, $CH_A$$H_B$CHNHTs), 2.78 (1H, dd, *J* 3.0, 18.0 Hz, $CH_A$$H_B$$CO_2CH_3$), 2.62 (1H, m, C*H*$CH_2$OTBS), 2.06 (3H, s, CH_3Ts), 0.93 (9H, s, $((CH_3)_3)$C), -0.08 (3H, s, CH_3Si), -0.09 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 171.0 (CO), 138.2 (CSO_2), 136.9 (CSO_2), 133.7 (*para*-$PhSO_2$), 129.4 (*ortho*-Ts), 129.1 (*ortho*-$PhSO_2$), 128.8 (*meta*-Ts), 128.2 (CH_3Ts), 126.8 (*meta*-$PhSO_2$), 121.6 (ArC), 119.2 (ArC), 118.6 (ArC), 109.2 (ArC), 108.9 (ArC), 109.2 (ArC), 108.8 (ArC), 64.0 (CH_2OTBS), 60.4 (*C*HSO_2Ph), 52.4 (OCH_3), 52.0 (TsNH*C*H), 42.9 (C*H*CH_2OTBS), 32.7 (NCH_3), 30.9 (*C*$H_2CO_2CH_3$), 29.7 (*C*H_2CHNHTs), 25.6 (*C*$H_3)_3$C), 21.0 (CH_3Ts), -3.6 ($(CH_3)_2$Si); M/z (ESI) 751.2312, 735.2578 $[M+Na]^+$, 713.2740 $[M+H]^+$, 593.2466 (Found $[M+H]^+$, 713.2740. $C_{36}H_{48}N_2O_7S_2Si$ requires $[M+H]^+$ 713.2672) (Found: C, 61.13; H, 7.00; N, 3.95. $C_{37}H_{50}N_2O_6S_2Si$ requires C, 61.13; H, 6.93; N, 3.85%).

(5R,6S)-5-((tButyldimethylsilyloxy)methyl)-6-((1-methyl-1H-indol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 530



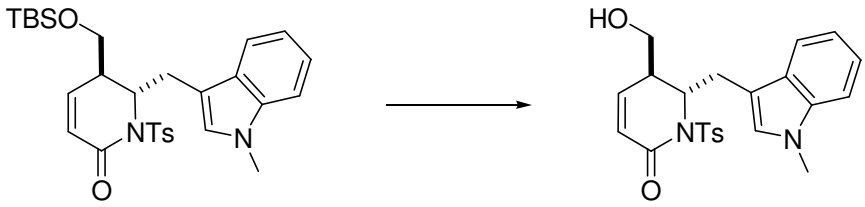
529 **530**

To a solution of **529** (25 mg, 40 µmol, 1.0 equiv.) in toluene (1.0 mL) was added at rt 1M $AlMe_3$ (40 µL, 40 µmol, 1.0 equiv.) and the solution stirred at rt for 30 min. The solution was heated to 80 °C and stirred for 3 h at this temperature. After cooling down to rt the solution

was quenched using saturated aqueous NH_4Cl (5 mL) and extracted using EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative TLC (66% petrol–EtOAc) gave **530** (21 mg, 99%).

R_f = 0.50 (75% petrol–EtOAc); ν_{max} (film) 3049, 2953, 2928, 2856, 1688, 1471, 1385, 1350, 1251, 1169, 1251, 1087, 814 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.04 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.86 (1H, d, *J* 7.5Hz, C-9), 7.71 (1H, d, *J* 8.0 Hz, C-12), 7.59 (1H, t, *J* 8.0 Hz, C-11), 7.32 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.17 (1H, t, *J* 7.5 Hz, C-10), 6.95 (1H, s, C-12), 6.53 (1H, ddd, *J* 1.5, 6.0, 8.0 Hz, C*H*=CHCO), 5.93 (1H, d, *J* 9.5 Hz, CH=C*H*CO), 5.23 (1H, dd, *J* 3.5, 11.5 Hz, CHNTs), 3.78 (3H, s, NCH_3), 3.46 (1H, dd, *J* 5.5, 10.5 Hz, CH_AH_BOTBS), 3.35 (1H, m, CH_AH_BCHNTs), 3.29 (1H, m, CH_AH_BOTBS), 3.19 (1H, m, CH_AH_BCHNTs), 2.67 (1H, m, C*H*CH_2OTBs), 2.45 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 161.6 (C=O lactam), 144.6 (CSO_2), 142.3 (*C*H=CHCO), 137.0 (CH_3*C*Ts), 136.6 (C-13), 129.7 (*meta*-Ts), 129.0 (*ortho*-Ts), 127.9 (C-8), 125.9 (C-2), 125.7 (CH=*C*HCO), 121.8 (C-11), 119.4 (C-10), 119.0 (C-9), 109.8 (C-12), 109.2 (C-7), 62.60 (*C*H_2OTBS), 56.6 (*C*HCH_2OTBS), 40.0 (*C*HNTs), 32.7 (NCH_3), 29.8 (*C*H_2CHNTs), 25.6 ((*C*H_3)$_3$C), 21.7 (CH_3Ts), 17.8 ((CH_3)$_3$*C*), -5.75 (CH_3Si), -5.56 (CH_3Si); M/z (ESI) 577.1982, 561.2199 $[M+Na]^+$, 539.2383 $[M+H]^+$, 224.0116, 196.0164 (Found $[M+H]^+$, 539.2383. $C_{29}H_{38}N_2O_4SSi$ requires $[M+H]^+$ 539.2322).

(5R,6S)-5-(Hydroxymethyl)-6-((1-methyl-1H-indol-3-yl)methyl)-1-tosyl-5,6-dihydropyridin-2(1H)-one 530A



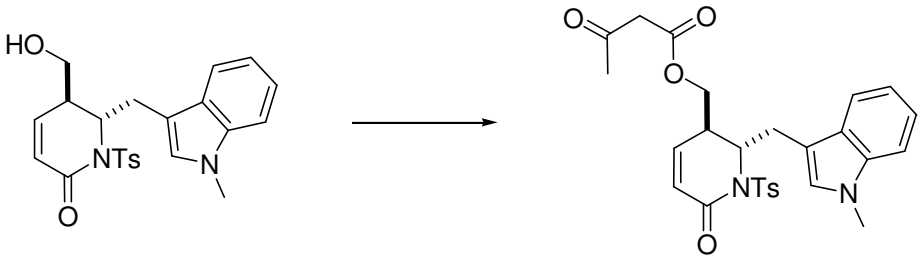
530 **530A**

A solution of **530** (25 mg, 47 μmol, 1.0 equiv.) in 3 : 1 : 1 AcOH : H_2O : THF (1.5 mL) was stirred at rt for 2 h. The solution was neutralized using saturated aqueous $NaHCO_3$ (5 mL) and extracted by EtOAc (3 x 5 mL), the combined organic layers were washed with brine (10

mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative TLC (66% EtOAc–petrol) gave **530A** (20 mg, 99%).

R_f = 0.45 (66% EtOAc–petrol); ν_{max} (film) 3434, 2924, 2859, 1689, 1477, 1388, 1347, 1253, 1168, 1088, 1065, 815, 744 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.01 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.69 (1H, d, *J* 8.0 Hz, C-9), 7.32 (3H, m, *meta*-Ts + C-12), 7.26 (1H, m, C-11), 7.17 (1H, dt, *J* 1.0, 7.5 Hz, C-10), 6.92 (1H, s, C-2), 6.59 (1H, ddd, *J* 1.5, 6.0, 8.0 Hz, C*H*=CHCO), 5.97 (1H, d, *J* 9.5 Hz, CH=C*H*CO), 5.18 (1H, dd, *J* 4.0, 10.0 Hz, CHNTs), 3.77 (3H, s, NCH_3), 3.60 (1H, m, CH_AH_BOH), 3.41 (1H, m, CH_AH_BOH), 3.33 (1H, dd, *J* 5.0, 14.0 Hz, CH_AH_BCHNTs), 3.16 (1H, dd, *J* 5.0, 10.0 Hz, CH_AH_BCHNTs), 2.72 (1H, dd, *J* 6.5, 9.5 Hz, C*H*CH_2OH), 2.44 (3H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 161.6 (C=O lactam), 144.7 (CSO_2), 142.3 (*C*H=CHCO), 137.0 (CH_3CTs), 136.4 (C-13), 129.3 (*meta*-Ts), 129.0 (*ortho*-Ts), 127.8 (C-8), 125.9 (C-2), 125.9 (CH=*C*HCO), 121.9 (C-11), 119.4 (C-10), 118.9 (C-9), 109.5 (C-7), 109.4 (C-12), 62.9 (CH_2OH), 56.9 (*C*HCH_2OH), 39.8 (*C*HNTs), 32.7 (NCH_3), 29.9 (*C*H_2CHNTs), 21.9 (CH_3Ts); M/z (ESI) 463.1100, 447.1357 $[M+Na]^+$, 425.1530 $[M+H]^+$, 196.0171 (Found $[M-SO_2Ph]^+$, 425.1530. $C_{23}H_{24}N_2O_4S_1$ requires $[M+H]^+$ 425.1457).

((2S,3R)-2-((1-Methyl-1H-indol-3-yl)methyl)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl 3-oxobutanoate 531

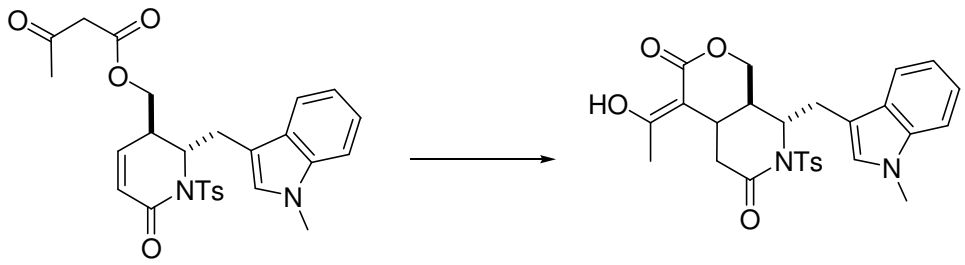


530A **531**

To a solution of **530A** (80 mg, 0.19 mmol, 1.0 equiv.) and KOAc (cat.) in THF (1.0 mL) was added freshly distilled diketene (21 μL, 0.25 mmol, 1.3 equiv.) in THF (0.5 mL) and the solution heated to reflux for 1 h. After cooling to rt, the solution was quenched with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative TLC (66% EtOAc–petrol) gave **531** in 90 mg, 93% yield.

R_f = 0.70 (66% EtOAc–petrol); ν_{max} (film) 2925, 1855, 2337, 1729, 1640, 1612, 1470, 1344, 1248, 1161, 1100, 745, 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.05 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.82 (1H, d, *J* 8.0 Hz, C-9), 7.35 (3H, m, *meta*-Ts + C-12), 7.29 (1H, m, C-11), 7.20 (1H, dt, *J* 1.0, 7.5 Hz, C-10), 6.90 (1H, s, C-2), 6.52 (1H, ddd, *J* 1.5, 6.0, 8.0 Hz, C*H*=CHCO), 6.00 (1H, d, *J* 9.5 Hz, CH=C*H*CO), 5.16 (1H, dd, *J* 4.0, 10.0 Hz, CHNTs), 4.09 (1H, dd, *J* 4.5, 11.0 Hz, C$H_A$$H_B$O), 3.87 (1H, dd, *J* 7.5, 11.0 Hz, CH$_A$$H_B$O), 3.79 (3H, s, NCH_3), 3.38 (1H, dd, *J* 4.0, 13.5 Hz, CH$_A$H$_B$CHNTs), 3.21-3.06 (3H, m, $COCH_2CO$ + CH$_A$$H_B$CHNTs), 2.84 (1H, m, C*H*CH_2O), 2.46 (3H, s, CH_3-Ts), 2.13 (3H, s, $COCH_3$); δ_C (100 MHz, $CDCl_3$) 166.6 (C=O lactam), 161.2 (C=O), 144.9 (CSO_2), 140.0 (*C*H=CHCO), 137.2 (CH_3*C*Ts), 136.3 (C-13), 129.4 (*meta*-Ts), 129.1 (*ortho*-Ts), 127.9 (C-2), 127.4 (C-8), 126.7 (CH=*C*HCO), 122.0 (C-11), 119.4 (C-10), 119.1 (C-9), 109.5 (C-12), 109.3 (C-7), 63.6 (*C*H_2CO), 56.9 (*C*HCH_2O), 49.2 (CO*C*H_2CO), 36.3 (*C*HNTs), 32.8 (NCH_3), 30.3 (*C*H_2CHNTs), 21.7 (CH_3Ts); M/z (ESI) 547.1292, 531.1712 $[M+Na]^+$, 509.1735 $[M+H]^+$ (Found $[M+H]^+$, 509.1735. $C_{27}H_{28}N_2O_6S$ requires $[M+H]^+$ 509.1668).

(8S,8aR,Z)-4-(1-Hydroxyethylidene)-8-((1-methyl-1H-indol-3-yl)methyl)-7-tosyltetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione 532

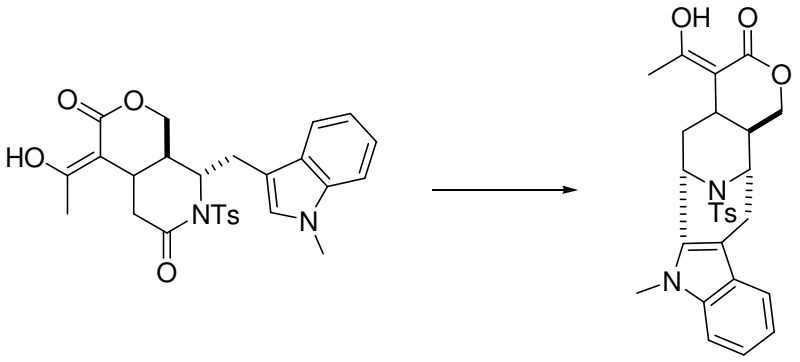


To a solution of **531** (90.0 mg, 0.18 mmol, 1.0 equiv.) in THF (1.0 mL) was added at rt DBU (5.0 µL, 36 µmol, 0.2 equiv.) and the solution stirred for 6 h at rt. The brown / red solution was quenched using saturated aqueous NH_4Cl (5 mL) and extrated by EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative TLC (66% EtOAc–petrol) gave **532** as a colorless gum in 82 mg, 91% yield.

R_f = 0.90 (66% EtOAc–petrol); ν_{max} (film) 3057, 2923, 2854, 1690, 1612, 1597, 1475, 1347, 1244, 1164, 1086, 907 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 13.74 (OH), 7.96 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.74 (1H, d, *J* 8.0 Hz, C-9), 7.36 (2H, d, *J* 8.0 Hz, *meta*-Ts), 7.30 (2H, m, C-11 + C-12), 7.20 (1H, dt, *J* 1.0, 7.5 Hz, C-10), 6.96 (1H, s, C-2), 4.80 (1H, m, CH_2CHNTs), 4.23 (1H, ddd, *J* 1.5, 4.5, 11.5 Hz, CH_AH_BO), 4.06 (1H, app. t, *J* 11.5 Hz, CH_AH_BO), 3.81 (3H, s, NCH_3), 3.56 (1H, dd, *J* 3.5, 14.5 Hz, CH_AH_BCHNTs), 3.23 (1H, dd, *J* 3.5, 14.5 Hz, CH_AH_BCHNTs), 3.14 (1H, $CHCH_2CO$), 2.69 (3H, s, CH_3Ts), 2.57 (2H, m, CH_AH_BCO + $CHCH_2O$), 2.30 (3H, s, $C(OH)CH_3$), 2.19 (1H, m, CH_AH_BCO); δ_C (100 MHz, $CDCl_3$) 177.2 (C=*C*OH), 170.9 (lactam C=O), 167.3 (lactone C=O), 145.4 (CH_3CTs), 137.1 (CSO_2), 135.7 (C-13), 129.4 (*ortho*-Ts), 128.2 (*meta*-Ts), 127.7 (C-8), 122.3 (C-2), 119.8 (C-11), 118.5 (C-10), 109.6 (C-12), 108.3 (C-7), 66.9 (CH_2CO), 57.3 ($CHCH_2CO$), 57.2 ($COCHCO$), 36.6 ($CHNTs$), 32.9 (NCH_3), 31.7 (CH_2CHNTs), 25.9 ($CHCH_2CONTs$), 21.7 (CH_3Ts), 17.9 (CH_3COH); M/z (ESI) 572.1885, 547.1374, 531.1563 $[M+Na]^+$, 509.1741 $[M+H]^+$ (Found $[M+H]^+$, 509.1741. $C_{27}H_{28}N_2O_6S$ requires $[M+H]^+$ 509.1668).

Alstonerine precursor 534



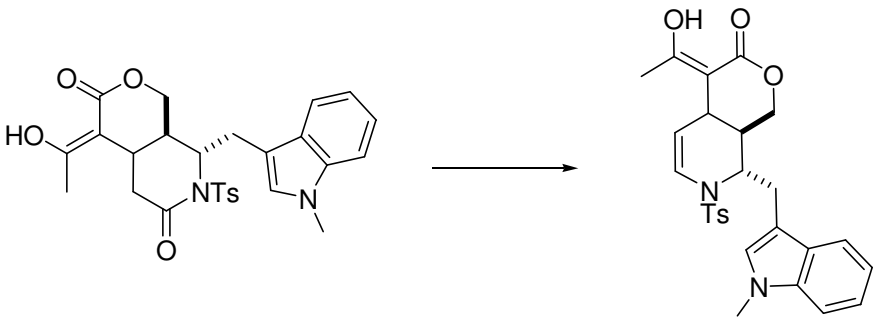
532 **534**

To a solution of **532** (20 mg, 30 μmol, 1.0 equiv.) in THF (1.0 mL) at –78 °C was added 1.2M DIBALH (50 μL, 60 μmol, 2.0 equiv.) and the mixture stirred for 2 h. After reacting for 2 h, the mixture was quenched using 6 M HCl (2.0 mL) and heated to rt. The organic layer was separated and the aqueous layers extrated using EtOAc (3 x 5mL), the combined organic layers were washed with brine (5.0 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Preparative TLC (66% petrol–EtOAc) gave **533** (2.7 mg, 15%) and **534** (15.0 mg, 75%).

Treatment of the DIBAL reaction mixture with TFA (drop) solely provided **534** in 18 mg, 96%.

R_f = 0.35 (66% petrol–EtOAc); δ_H (400 MHz, $CDCl_3$) 14.06 (1H, s,OH), 7.39 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.29 (2H, m, C-9), 7.21 (1H, m, C-11 + C-12), 7.06 (1H, t, *J* 6.0 Hz, C-10), 6.84 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.33 (1H, s, CC*H*NTs), 4.73 (1H, t, *J* 12.0 Hz, CH_AH_BO), 4.43 (1H, dd, *J* 1.5, 12.0 Hz, CH_AH_BO), 4.34 (1H, d, *J* 8.0 Hz, CH_2CHNTs), 3.70 (3H, s, NCH_3), 2.96 (1H, dd, *J* 8.0, 16.0 Hz, CH_AH_BCHNTs), 2.76 (1H, m, CCH(NTs)CH_2CH), 2.52 (1H, d, *J* 16.0 Hz, CH_AH_BCHNTs), 2.27 (1H, m, CH_2CH(NTs)C*H*), 2.23 (1H, m, CCH(NTs)CH_AH_B), 2.20 (3H, s, CH_3Ts), 2.06 (3H, s, C(OH)CH_3), 1.77 (1H, dq, *J* 3.0, 4.0, 14.0 Hz, CCH(NTs)CH_AH_B)

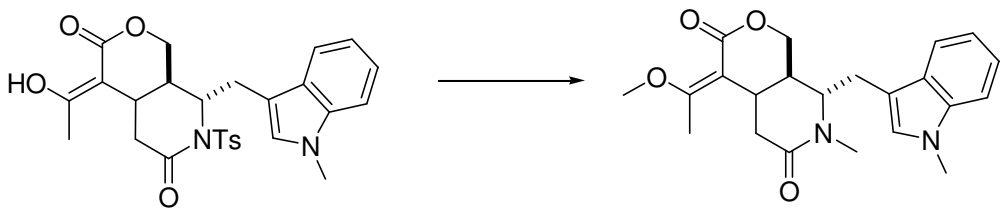
(8S,8aR,Z)-4-(1-Hydroxyethylidene)-8-((1-methyl-1H-indol-3-yl)methyl)-7-tosyl-4,4a,8,8a-tetrahydro-1H-pyrano[3,4-c]pyridin-3(7H)-one 533



532 **533**

R_f = 0.40 (66% petrol–EtOAc); δ_H (400 MHz, $CDCl_3$) 14.03 (1H, s,OH), 7.84 (1H, d, *J* 8.0 Hz, C-9), 7.73 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.33 (4H, m, *meta*-Ts + C-11 + C-12), 7.24 (1H, dt, *J* 1.5, 8.0 Hz, C-10), 6.88 (1H, s, C-2), 6.77 (1H, dd, *J* 1.5, 8.5 Hz, CH=C*H*NTs), 6.40 (1H, dt, *J* 1.5, 8.5 Hz, C*H*=CHNTs), 4.01 (1H, m, CH_2CHNTs), 3.80 (3H, s, NCH_3), 3.45 (1H, m, CH_AH_BCHNTs), 3.42 (1H, m, C*H*CH=CHNTs), 3.11 (2H, m, CHCH_2O), 3.02 (1H, m, CH_AH_BCHNTs), 2.44 (3H, s, CH_3Ts), 2.20 (3H, s, C(OH)CH_3), 2.18 (3H, s, C(OH)CH_3), 2.13 (1H, m, C*H*CH_2O)

(8S,8aR,Z)-4-(1-Methoxyethylidene)-7-methyl-8-((1-methyl-1H-indol-3-yl)methyl)tetrahydro-1H-pyrano[3,4-c]pyridine-3,6(4H,7H)-dione 535



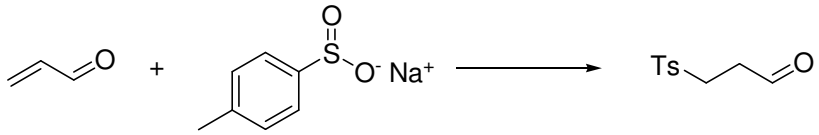
532 **535**

A solution of Na (7.50 mg, 0.31 mmol, 8.0 equiv.) and naphthalene (31.0 mg, 0.31 mmol, 8.0 equiv.) in THF (0.5 mL) was stirred for 45 min at –78 °C. **532** (20.0 mg, 0.04 mmol, 1.0 equiv.) in THF (0.5 mL) was added to the dark blue sodium naphthalide solution and stirred for 1 h at –78 °C. CH_3I (7.50 μL, 0.12 mmol, 3.0 equiv.) was added and the solution allowed to heat to rt. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (66% EtOAc–petrol) gave **535** (3.1 mg, 20%)

R_f = 0.65 (66% EtOAc–petrol); δ_H (400 MHz, $CDCl_3$) 3.75 (3H, s, Indole NCH_3), 3.47 (3H, s, NCH_3), 2.99 (3H, s, OCH_3). Tosyl-moiety missing in aromatic region (8.0–6.5 ppm), no NH peak (6.0–4.0 ppm) detected.

3.3. (–)-Cytisine

3-Tosylpropanal 546



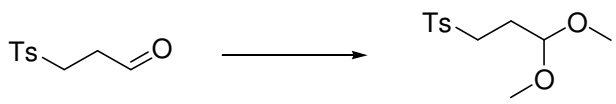
546

To a solution of *p*-toluenesulfinic acid sodium salt (10.0 g, 56.1 mmol, 1.0 equiv.) in THF (32 mL) and H_2O (64.5 mL) was dropwise added AcOH (3.21 mL, 56.1 mmol, 1.0 equiv.). The solution was cooled to 0 ^oC and acrolein (7.50 mL, 12.2 mmol, 2.0 equiv.) in THF (32 mL) added dropwise to form a white emulsion. This emulsion was allowed to warm to rt over 16 h, and diluted with EtOAc (160 mL) and H_2O (130 mL). The aqueous layer was then extracted with EtOAc (300 mL), and the combined organic layers washed with $NaHCO_3$ (3 x 200 mL), brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **546** (11.8 g, 99%) as a colorless gel.

R_f = 0.20 (70% petrol–EtOAc); ν_{max} (film) 3480, 2927, 1723, 1597, 1496, 1408, 1312, 1288, 1302, 1136, 1086, 1018 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.76 (1H, s, CO*H*), 7.80 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.39 (2H, d, *J* 8.0 Hz, *meta*-Ts), 3.40 (2H, m, TsCH_2), 2.97 (2H, m, CH_2CHO), 2.48 (3H, s, CH_3Ts); δ_C (100.6 MHz, $CDCl_3$) 197.0 (C=O), 145.2 (*ipso*-CH_3Ts), 135.7 (*ipso*-$ArSO_2$), 130.1 (*meta*-$ArSO_2$), 128.1 (*ortho*-$ArSO_2$), 49.2 (TsCH_2), 36.7 (CH_2CHO), 21.7 (CH_3Ts); M/z (CI) 230 $[M+NH_4]^+$, 213 $[M+H]^+$, 189, 174, 130 (Found: $[M+NH_4]^+$, 230.0851. $C_{10}H_{16}NO_3S$ requires: $[M+NH_4]^+$, 230.0851).

The data are in agreement with the reported compound.[13]

1-(3,3-Dimethoxypropylsulfonyl)-4-methylbenzene 406



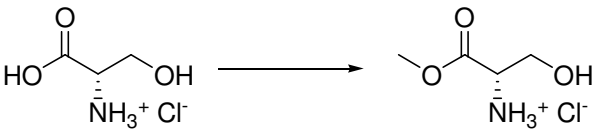
546 **406**

To a solution of **546** (12.8 g, 59.2 mmol, 1.0 equiv.) and *p*-toluenesulfonic acid (0.30 g, 1.59 mmol, 2.7 mol %) in methanol (103 mL) was dropwise added trimethylorthoformate (13.0 mL, 118.5 mmol, 2.0 equiv.) resulting in a pale yellow solution. The solution was heated to 50 ^{o}C for 16 h, concentrated under reduced pressure, redissolved in Et_2O (150 mL), and subsequently washed with $NaHCO_3$ (4 x 150 mL), H_2O (3 x 150 mL) and brine (1 x 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (66% Et_2O–petrol) gave **406** (13.9 g, 83%) as a pale yellow solid.

R_f = 0.19 (66% Et_2O–petrol); m.p. = 31–33 ^{o}C (lit.[13] m.p. 32–33 ^{o}C); ν_{max} (film) 3505, 3063, 3029, 2938, 2834, 2083, 2036, 1927, 1636, 1597, 1445, 1404, 1383, 1303, 1288, 1234, 1192, 1145, 1123, 1073 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz *ortho*-Ts), 7.35 (2H, d, *J* 8.0 Hz, *meta*-Ts), 4.40 (1H, t, *J* 5.0 Hz, $C(OMe)_2H$), 3.28 (6H, s, 2 x OCH_3), 3.13 (2H, m, $TsCH_2$), 2.44 (3H, s, CH_3), 1.99 (2H, m, CH_2C); δ_C (100.6 MHz, $CDCl_3$) 144.8 (*ipso*-CH_3Ts), 136.0 (*ipso*-$ArSO_2$), 129.9 (*meta*-$ArSO_2$), 128.0 (*ortho*-$ArSO_2$), 102.5 ($C(OMe)_2H$), 53.6 (OCH_3), 51.7 ($TsCH_2$), 26.2 (CH_2C), 21.6 (CH_3Ts); M/z (CI) 276 $[M+NH_4]^+$, 244 $[M+NH_4–CH_3OH]^+$, 227 $[M–OCH_3]^+$, 212 $[M+NH_4–C_2H_8O]^+$ (Found: $[M+NH_4]^+$, 276.1279. $C_{12}H_{22}NO_4S$ requires: $[M+NH_4]^+$, 276.1270).

The data are in agreement with the reported compound.[13]

(*S*)-Methyl 2-amino-3-hydroxypropanoate hydrochloride acid 547



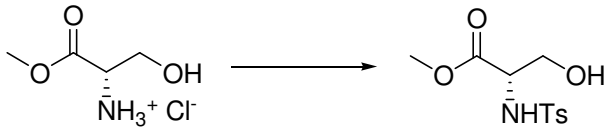
547

To a white suspension of L-serine (5.00 g, 47.6 mmol, 1.0 equiv.) in methanol (250 mL) stirred at 0 °C was dropwise added $SOCl_2$ (7.63 mL, 104.7 mmol, 2.2 equiv). The clear solution was refluxed at 80 °C for 4 h, cooled to rt and concentrated under reduced pressure. Azeotropic removal of H_2O by using toluene (2 x 100 mL) gave **547** (7.41 g, 99%) as a white solid.

R_f = 0.41 (66% CH_2Cl_2–MeOH + 1% TEA); m.p. = 163–165 °C (lit.[14] m.p. 162–165 °C); $[\alpha]_D^{23}$ + 15.1 (*c* 0.78, $CHCl_3$); ν_{max} (film) 3395, 2907, 2640, 1965, 1739, 1585, 1503, 1440, 1250, 1043, 973 cm^{-1}; δ_H (400 MHz, CD_3OD) 4.17 (1H, t, *J* 4.0 Hz, NH_3^+CH), 4.03 (1H, dd, *J* 4.5, 12.0 Hz, CH_2OH), 3.97 (1H, dd, *J* 3.5, 12.0 Hz, CH_2OH), 3.88 (3H, s, OCH_3); δ_C (100 MHz, CD_3OD) 168.0 (CO), 59.3 (CH_2OH), 54.7 (NH_3^+CH), 52.3 (OCH_3); M/z (ESI) 137 $[M+NH_4–HCl]^+$, 120 $[M+H–HCl]^+$ (Found: $[M+H–HCl]^+$, 120.0661. $C_4H_{10}NO_3$ requires: $[M+H–HCl]^+$, 120.0661).

The data are in agreement with the reported compound.[14]

(*S*)-Methyl 3-methyl-2-(4-methylphenylsulfonamido)butanoate 548



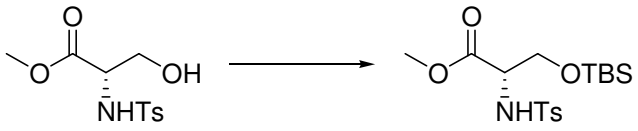
547 **548**

To a solution of **547** (7.00 g, 45.0 mmol, 1.0 equiv.) in CH_2Cl_2 (47.3 mL) at 0 °C was added dropwise TEA (12.6 mL, 90.0 mmol, 2.0 equiv.) causing effervescence. A solution of *p*-toluenesulfonyl chloride (8.58 g, 45.0 mmol, 1.0 equiv.) in DCM (47.3 mL) was added dropwise and the mixture was stirred for 16 h at 0 °C. The white precipitate was filtered off and the solution concentrated under reduced pressure. The residue was taken up in EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), 10 % aqueous citric acid (40 mL), brine (40 mL) and dried ($MgSO_4$). Concentrating the solution under reduced pressure gave **548** (10.4 g, 85 %) as a white solid.

R_f = 0.15 (50% EtOAc–petrol); m.p. = 87–89 °C (lit.[14] m.p. 87–89 °C); $[\alpha]_D^{23}$ + 19.1 (*c* 0.76, -$CHCl_3$); ν_{max} (film) 3507, 3272, 2940, 1748, 1602, 1436, 1333, 1229, 1162, 1063, 664 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz *ortho*-Ts), 7.32 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.83 (1H, d, *J* 8.0 Hz, TsN*H*), 4.01 (1H, dt, *J* 4.0, 8.0 Hz, TsNHC*H*), 3.89 (2H, m,, CH_2OH), 3.62 (3H, s, OCH_3), 2.43 (3H, s, CH_3 of Ts); δ_C (100 MHz, $CDCl_3$) 170.2 (CO), 143.9 (*ipso*-CH_3CTs), 136.5 (*ipso*-CSO_2), 130.3 (*ortho*-Ts), 127.2 (*meta*-Ts), 63.7 (CH_2OH), 57.6 (NHTs*C*H), 52.9 (OCH_3), 21.8 ($TsCH_3$); M/z (CI) 274 $[M+H]^+$, 291 $[M+NH_4]^+$.

The data are in agreement with the reported compound.[14]

(S)-Methyl-3-(^{t}butyldimethylsilyloxy)-2-(4-methylphenylsulfoneamido)propanoate 549



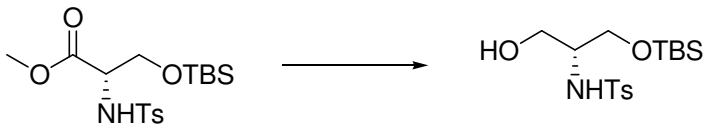
548 **549**

Imidazole (1.24 g, 18.2 mmol, 2.0 equiv.), 2.11 g of TBSCl (14.0 mmol, 1.5 equiv.) and **548** (12.5 g, 9.1 mmol, 1 equiv.) were dissolved in DCM (50 mL) and stirred at rt for 16 h. Poured on water (100 mL) and extracted with EtOAc (120 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (66% → 50% petrol–EtOAc) gave **549** as colorless crystals (3.45 g, 97%).

R_f = 0.42 (50% EtOAc–petrol); m.p. = 56–57 °C (lit.[14] m.p. 56 °C); $[\alpha]_D^{23}$ + 29.7 (*c* 0.01, $CHCl_3$); ν_{max} (film) 3492, 3270, 2952, 1742, 1599, 1497, 1434, 1329, 1210, 1158, 1125, 1090, 1062, 1021, 968, 819 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.30 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.38 (1H, d, *J* 9.0 Hz, TsN*H*), 4.04 (1H, dt, *J* 3.0, 9.0 Hz, TsNHC*H*), 3.96 (1H, dd, *J* 3.0, 10.0 Hz CH_AH$_B$OH), 3.78 (1H, dd, *J* 3.5, 10.0 Hz, CH$_A$$H_B$OH), 3.56 (3H, s, OCH_3), 2.46 (3H, s, CH_3Ts), 0.82 (9H, s, *(C*H_3)$_3$C), 0.02 (3H, s, *C*H_3Si), 0.00 (3H, s, *C*H_3Si); δ_C (100 MHz, $CDCl_3$) 170.1 (CO), 143.5 (*ipso*-CH_3*C*Ts), 137.2 (*ipso*-CSO_2), 129.6 (*ortho*-Ts), 127.1 (*meta*-Ts), 64.5 (*C*H_2OH), 57.6 (TsNH*C*H), 52.4 (OCH_3), 25.6 ((*C*H_3)$_3$C), 21.5 (TsCH_3), -5.6 ((CH_3)$_2$Si); M/z (CI) 405 $[M+NH_4]^+$, 388 $[M+H]^+$, 330.

The data are in agreement with the reported compound.[14]

(R)-N-(1-(tbutyldimethylsilyloxy)-3-hydroxypropan-2-yl)-4-methylbenzenesulfoneamide 550



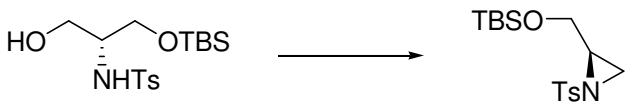
549 **550**

To a solution of **549** (3.40 g, 8.80 mmol, 1.0 equiv.) in THF (23 mL) was added 2.0 M $LiBH_4$ (13.2 mL, 26.4 mmol, 3 equiv.) at 0 ^oC and stirred for 30 min after which it was heated up to rt and reacted for a further 16 h. Dropwise addition of saturated aqueous NH_4Cl (7 mL) at 0 ^oC resulted in a white solid formation which was filtered off using THF. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure, taken up in EtOAc and washed with saturated aqueous NH_4Cl, H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (30% EtOAc–petrol) gave **550** as a colorless oil (2.49g, 80%).

R_f = 0.31 (30% EtOAc–petrol); $[\alpha]_D^{23}$ + 19.7 (*c* 0.76, $CHCl_3$); ν_{max} (film) 3408, 1433, 1318, 1152, 1046, 960, 813, 519 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.32 (2H, d, *J* 8.0 Hz, *meta*-Ts), 5.20 (1H, d, *J* 7.5 Hz, TsN*H*), 3.71–3.51 (4H, m, CH_2OH + CH_2OTBS), 3.29 (1H, m, TsNHC*H*), 2.44 (3H, s, CH_3Ts), 2.18 (1H, br s, OH), 0.85 (9H, s, (CH_3)$_3$C), 0.02 (3H, s, CH_3Si), 0.00 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 143.6 (*ipso*-CH_3*C*Ts), 137.5 (*ipso*-CSO_2), 129.8 (*ortho*-Ts), 127.1 (*meta*-Ts), 63.4 (CH_2OH), 62.9 (CH_2OTBS), 55.5 (TsNHCH), 25.8 ((*C*H_3)$_3$C), 21.5 (TsCH_3), 18.2 ((CH$_3$)$_3$*C*), -5.63 ((*C*H_3)$_2$Si); M/z (CI) 377 $[M+NH_4]^+$, 360 $[M+H]^+$.

The data are in agreement with the reported compound.[14]

(S)-2-((tButyldimethylsilyloxy)methyl)-1-tosylaziridine 551



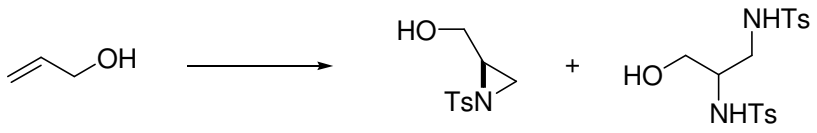
550 **551**

To a solution of **550** (2.49 g, 6.90 mmol, 1.0 equiv.) and PPh_3 (2.00 g, 7.61 mmol, 1.1 equiv.) in THF (44 mL) was added DEAD (1.40 mL, 7.60 mmol, 1.1 equiv.) at rt and stirred for 16 h. Concentration of the solution using reduced pressure was followed by column chromatography (20% EtOAc–petrol) and provided **551** as an yellow oil (2.43 g, 97%).

R_f = 0.45 (80% petrol–EtOAc); $[\alpha]_D^{23}$ + 40.4 (*c* 0.72, $CHCl_3$); ν_{max} (film) 3277, 2954, 2929, 2857, 1599, 1472, 1411, 1331, 1252, 1161, 1093, 980, 939, 832, 776, 663 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.35 (2H, d, *J* 8.0 Hz, *meta*-Ts), 3.72 (1H, dd, *J* 4.0, 11.5 Hz, CH_AH_BOTBS), 3.61 (1H, dd, *J* 5.5, 11.5 Hz, CH_AH_BOTBS), 2.95 (1H, ddd, *J* 4.5, 7.0, 9.5 Hz, TsNHCH), 2.67 (1H, d, *J* 7.0 Hz, $TsNCH_AH_B$), 2.46 (3H, s, CH_3Ts), 2.23(1H, d, *J* 4.5 Hz, $TsNCH_AH_B$), 0.83 (9H, s, $(CH_3)_3C$), 0.00 (3H, s, CH_3Si), -0.02 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 144.5 (CSO_2), 135.1 (CCH_3), 129.7 (*ortho*-Ts), 128.0 (*meta*-Ts), 62.4 (CH_2OTBS), 40.9 (TsNCH), 30.6 ($TsNHCH_2$), 25.8 ($(CH_3)_3C$), 21.7 (CH_3Ts), 18.3 ($(CH_3)_3C$), -5.5 (CH_3Si), -5.47; M/z (CI) 359 $[M+NH_4]^+$, 342 $[M+H]^+$, 284.

The data are in agreement with the reported compound.[14]

(S)-(1-Tosylaziridin-2-yl)methanol 545



545 **552**

To a solution of Chloramine-T trihydrate (3.91 g, 14.0 mmol, 0.93 equiv.) and PTAB (2.11 g, 5.61 mmol, 0.37 equiv.) in CH_3CN (60 mL) was added allyl alcohol (1.00 mL, 15.0 mmol, 1.0 equiv.) and the solution stirred for 2 h at rt. EtOAc was added and the organic layer was washed with H_2O, brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (50% EtOAc–petrol) gave **545** as a colorless oil (1.46 g, 52%) and **552** as an yellow oil (1.10 g, 40%).

551 **545**

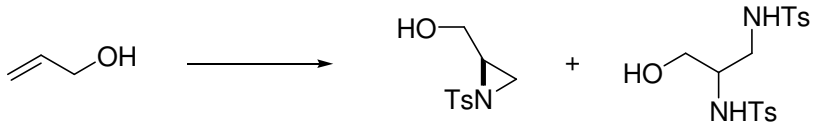
To a solution of TBS-aziridine **551** (22.3 g, 65.0 mmol, 1.0 equiv.) in THF (75 mL) at 0 ^oC was added TBAF (23.0 g, 72.0 mmol, 1.1 equiv.) in THF (75 mL). After 20 min stirring at 0 ^oC, the solution was heated to rt and diluted by addition of brine (150 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted using EtOAc (3 x 100 mL), combined, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (66% → 50% petrol–EtOAc) gave **545** as a colorless oil in a 14.6 g, 90% yield.

R_f = 0.30 (50% EtOAc–petrol); ν_{max} (film) 3515, 3287, 2928, 2889, 1598, 1450, 1322, 1290, 1266, 1155, 1089, 1042, 814, 732 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.35 (2H, d, *J* 8.0 Hz, *meta*-Ts), 3.82 (1H, dt, *J* 3.5, 12.0 Hz, CH_AH$_B$OH), 3.54 (1H, dt, *J* 5.0, 12.5 Hz, CH$_A$$H_B$OH), 3.01 (1H, m, TsNCH), 2.58 (1H, d, *J* 7.0 Hz, TsNCH_AH$_B$) 2.45 (3H, s, CH_3Ts), 2.30 (1H, d, *J* 4.5 Hz, TsNCH$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 144.9 (*C*SO_2), 134.4 (*C*CH_3), 129.8 (*ortho*-Ts), 128.0 (*meta*-Ts), 60.8 (*C*H_2OH), 40.5 (TsNCH), 31.0 (TsNCH_2), 21.7 (CH_3Ts); M/z (CI) 245 $[M+NH_4]^+$, 228 $[M+H]^+$.

$[\alpha]_D^{24}$ + 31.6 (*c* 1.23, $CHCl_3$), regarding enantiomerically pure material.[14]

The data are in agreement with the reported compound.[14,15]

2,3-Bis[[4-(methylphenyl)sulfonyl]amino]-1-propanol 552

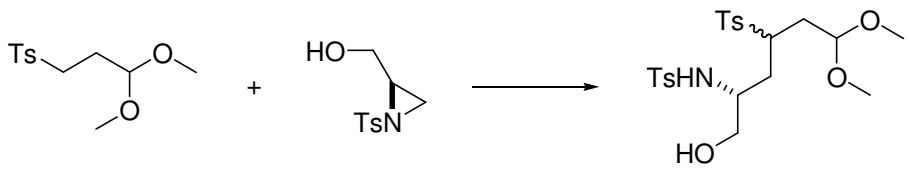


545 **552**

R_f = 0.61 (50% EtOAc–petrol); ν_{max} (film) 3513, 3273, 2927, 1708, 1598, 1494, 1423, 1322, 1305, 1266, 1154, 1090, 976, 733, 662 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.69 (2H, d, *J* 8.0 Hz, *ortho*-Ts), 7.35-7.29 (4H, m, *meta*-Ts), 5.60 (1H, d, *J* 8.0 Hz, TsN*H*CH), 5.43 (1H, t, *J* 7.5 Hz, TsN*H*CH_2), 3.66 (1H, dd, *J* 4.0, 11.5 Hz, CH_AH_BOH), 3.54 (1H, dd, *J* 5.0, 11.5 Hz, CH_AH_BOH), 3.30 (1H, m, TsNHC*H*), 3.05 (2H, m, TsNHCH_2), 2.78 (1H, br s, OH), 2.44 (6H, s, CH_3Ts); δ_C (100 MHz, $CDCl_3$) 143.8 (*C*SO_2), 136.9 (*C*CH_3), 136.3 (*C*CH_3), 129.9 (*ortho*-Ts), 127.1 (*meta*-Ts), 127.0 (*meta*-Ts), 61.8 (CH_2OH), 53.9 (TsNHCH), 43.8 (TsNHCH_2), 21.6 (CH_3Ts); M/z (CI) 263 $[M+NH_4\text{-Ts}]^+$, 245 $[M+H\text{-Ts}]^+$.

The data are in agreement with the reported compound.[15]

(R)-*N*-(1-Hydroxy-6,6-dimethoxy-4-tosylhexan-2-yl)-4-methylbenzenesulfonamide 553



406 **545** **553**

3 : 1

To a solution of sulfone **406** (1.24 g, 4.84 mmol, 1.1 equiv.) in THF (20 mL) was added 2.5M ^{n}BuLi (4.80 mL, 10.6 mmol, 2.4 equiv.) at –78 ^{o}C. After 30 min, a solution of hydroxyaziridine **545** (1.00 g, 4.41 mmol, 1.0 equiv.) in THF (20 mL) was added and the mixture, after stirring at –78 ^{o}C for 30 min, slowly heated to rt over 5 h. EtOAc (10 mL) and saturated aqueous NH_4Cl (20 mL) were added and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (50% → 33% petrol–EtOAc) gave **553** as a colorless gum (2.0 g, 95%, 3 : 1 dr).

R_f = 0.25 (minor), 0.20 (major) (66% EtOAc–petrol); ν_{max} (film) 3515, 3270, 2934, 1597, 1440, 1300, 1286, 1157, 1128, 1083, 1055, 971, 814 cm^{-1};

Minor

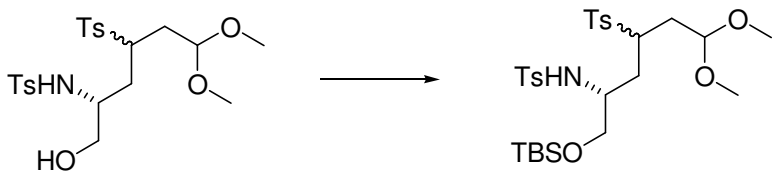
δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.0 Hz, *ortho*-TsCH), 7.71 (2H, d, *J* 8.0 Hz, *ortho*-TsN), 7.36 (2H, d, *J* 8.0 Hz, *meta*-TsCH), 7.33 (2H, d, *J* 8.0 Hz, *meta*-TsN), 5.51 (1H, d, *J* 7.5 Hz, N*H*Ts), 4.42 (1H, t, *J* 5.0 Hz, $(CH_3O)_2CH$), 3.58 (2H, m, C*H*NHTs + CH_AH_BOH), 3.46 (1H, m, CH_AH_BOH), 3.27 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.10 (1H, dd, *J* 4.0, 9.0 Hz, TsC*H*), 2.54 (1H, s, OH), 2.46 (3H, s, CH_3-TsCH), 2.44 (3H, s, CH_3-TsNH), 2.18 (1H, m, $CH_AH_BCHCH_2OH$), 2.07 (1H, m, $(CH_3O)_2CHCH_ACH_B$), 1.83 (1H, m, $CH_AH_BCHCH_2OH$), 1.64 (1H, m, $(CH_3O)_2CHCH_ACH_B$); δ_C (100 MHz, $CDCl_3$) 145.2 (CSO_2, TsCH), 144.9 (CSO_2, TsN), 137.8 (CH_3C, TsCH), 133.3 (CH_3C, TsN), 130.0 (*ortho*-TsCH), 129.8 (*ortho*-TsN), 129.2 (*meta*-TsCH),127.1 (*meta*-TsN), 102.2 ($(CH_3O)_2CH$), 63.8 ($NHTsCHCH_2OH$), 57.6 (Ts*C*H), 54.5 (CH_3O), 53.6 (TsNH*C*H), 52.9 (CH_3O), 32.8 ($TsCHCH_2CHCH_2OH$), 30.4 ($(CH_3O)_2CHCH_2$), 21.6 (2 x CH_3Ts);

Major

δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.0 Hz, *ortho*-TsCH), 7.62 (2H, d, *J* 8.0 Hz, *ortho*-TsN), 7.35 (2H, d, *J* 8.0 Hz, *meta*-TsCH), 7.33 (2H, d, *J* 8.0 Hz, *meta*-TsN), 5.62 (1H, d, *J* 7.5 Hz, N*H*Ts), 4.39 (1H, t, *J* 5.0 Hz, $(CH_3O)_2CH$), 3.51 (1H, m, CH_AH_BOH), 3.42 (2H, m, C*H*NHTs + CH_AH_BOH), 3.26 (6H, s, 2 x OCH_3), 3.15 (1H, dd, *J* 4.0, 9.0 Hz, TsC*H*), 2.51 (1H, s, OH), 2.47 (3H, s, CH_3-TsCH), 2.45 (3H, s, CH_3-TsNH), 2.23 (1H, m, $CH_AH_BCHCH_2OH$), 1.96 (1H, m, $(CH_3O)_2CHCH_ACH_B$), 1.82 (1H, m, $CH_AH_BCHCH_2OH$), 1.65 (1H, m, $(CH_3O)_2CHCH_ACH_B$); δ_C (100 MHz, $CDCl_3$) 145.0 (CSO_2, TsCH), 143.6 (CSO_2, TsN), 137.3 (CH_3C, TsCH), 133.3 (CH_3C, TsN), 130.0 (*ortho*-TsCH), 129.8 (*ortho*-TsN), 128.9 (*meta*-TsCH),127.1 (*meta*-TsN), 102.6 ($(CH_3O)_2CH$), 64.1 (NHTsCHCH_2OH), 57.6 (Ts*C*H), 54.4 (CH_3O), 53.4 (TsNH*C*H), 52.9 (CH_3O), 32.9 (TsCHCH_2CHCH_2OH), 30.8 ($(CH_3O)_2CHCH_2$), 21.7 (CH_3TsCH), 21.0 (CH_3TsNH);

M/z (CI) 503 $[M+NH_4]^+$, 348, 174 (Found: $[M+NH_4]^+$, 503.1873. $C_{22}H_{31}NO_7S_2$ requires: $[M+NH_4]^+$, 503.1886) (Found: C, 54.60; H, 6.57; N, 2.86. $C_{22}H_{31}NO_7S_2$ requires C, 54.41; H, 6.43; N, 2.88%).

(R)-*N*-(1-(^t^Butyldimethylsilyloxy)-6,6-dimethoxy-4-tosylhexan-2-yl)-4-methylbenzenesulfonamide 554



553 **554**

3 : 1

A mixture of acetal **553** (14.2 g, 29.0 mmol, 1.0 equiv.), DMAP (354 mg, 2.90 mmol, 0.1 equiv.), TEA (4.81 mL, 35.0 mmol, 1.2 equiv.) and TBSCl (6.70 g, 43.5 mmol, 1.5 equiv.) in DCM (140 mL) was stirred for 1.5 h at rt. The solution was diluted with saturated aqueous NH_4Cl (100 mL) and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (75% → 66% → 50% petrol–EtOAc) gave **554** as a colorless gum (16.0 g, 91% yield, 3 : 1 dr).

R_f = 0.90 (minor), 0.85 (major) (66% EtOAc–petrol); ν_{max} (film) 3350, 3054, 2954, 2858, 1725,1590, 1469, 1422, 1322, 1279, 1163, 1089, 838 cm^{-1};

Major

δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.0 Hz, *ortho*-TsCH), 7.71 (2H, d, *J* 8.0 Hz, *ortho*-TsN), 7.33 (2H, d, *J* 8.0 Hz, *meta*-TsCH), 7.31 (2H, d, *J* 8.0 Hz, *meta*-TsN), 5.12 (1H, d, *J* 8.5 Hz, TsNH), 4.37 (1H, t, *J* 5.0 Hz, $(CH_3O)_2CH$), 3.51 (1H, m, NHTsC*H*) 3.40 (1H, dd, *J* 2.0 Hz, TBSOCH_AH_B), 3.36 (1H, m, TsCH), 3.27 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 3.16 (1H, m, TBSOCH$_A$$H_B$), 2.45 (3H, s, CH_3Ts), 2.44 (3H, s, CH_3Ts), 2.15 (1H, m, CH_AH$_B$CHCH$_2$OTBS), 1.96 (1H, m, $(CH_3O)_2CHCH_ACH_B$), 1.87 (1H, m, CH_AH$_B$CHCH$_2$OH), 1.68 (1H, m, $(CH_3O)_2CHCH_ACH_B$), 0.84 (9H, s, $(CH_3)_3C$), 0.00 (3H, s, CH_3Si), -0.04 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 144.7(CSO_2, TsCH), 144.4(CSO_2, TsN), 137.7 (H_3C, TsCH), 134.4 (CH_3C, TsN), 129.8 (*ortho*-TsCH), 129.7 (*ortho*-TsN), 128.9 (*meta*-TsCH),128.7 (NTs*C*HCH), 127.0 (*meta*-TsN), 102.7 ($(CH_3O)_2CH$), 64.3 (NHTsCH*C*H$_2$OTBS), 56.5 (Ts*C*H), 54.2 (CH_3O), 53.8 (TsNH*C*H), 53.2 (CH_3O), 32.6 (TsCH*C*H$_2$CHCH$_2$OH), 32.3

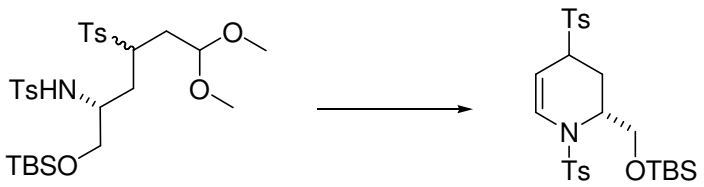
($(CH_3O)_2CHCH_2$), 25.8 ($(CH_3)_3C$), 21.6 (CH_3Ts), 21.5 (CH_3Ts), 18.2 ($CH_3)_3C$), -5.60 (CH_3)Si), -5.67 (CH_3)Si);

Minor

δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.0 Hz, *ortho*-TsCH), 7.70 (2H, d, *J* 8.0 Hz, *ortho*-TsN), 7.33 (2H, d, *J* 8.0 Hz, *meta*-TsCH), 7.29 (2H, d, *J* 8.0 Hz, *meta*-TsN), 4.92 (1H, d, *J* 8.5 Hz, TsNH), 4.51 (1H, t, *J* 5.0 Hz, $(CH_3O)_2CH$), 3.48 (1H, m, NHTsC*H*) 3.41 (1H, dd, *J* 2.0 Hz, TBSOCH_AH_B), 3.34 (1H, m, TsCH), 3.28 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.13 (1H, m, TBSOCH_AH_B), 2.44 (3H, s, CH_3Ts), 2.42 (3H, s, CH_3Ts), 2.12 (1H, m, CH_AH_BCHCH$_2$OTBS), 2.02 (1H, m, $(CH_3O)_2$CHCH_ACH_B), 1.85 (1H, m, CH_AH_BCHCH$_2$OH), 1.75 (1H, m, $(CH_3O)_2$CHCH_ACH_B), 0.83 (9H, s, $(CH_3)_3$C), -0.04 (3H, s, CH_3Si), -0.08 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 144.5 (CSO_2, TsCH), 144.3(CSO_2, TsN), 137.6 (H_3C, TsCH), 134.2 (CH_3C, TsN), 129.7 (*ortho*-TsCH), 128.9 (*ortho*-TsN), 128.5 (*meta*-TsCH),128.7 (NTs*C*HCH), 127.0 (*meta*-TsN), 102.7 ($(CH_3O)_2CH$), 64.3 (NHTsCH*C*H$_2$OTBS), 56.5 (Ts*C*H), 54.2 (CH_3O), 53.6 (TsNH*C*H), 53.0 (CH_3O), 32.6 (TsCH*C*H$_2$CHCH$_2$OH), 32.1 ($(CH_3O)_2CHCH_2$), 25.8 ($(CH_3)_3C$), 21.6 (CH_3Ts), 21.3 (CH_3Ts), 18.2 ($CH_3)_3C$), -5.60 (CH_3)Si), -5.67 (CH_3)Si);

M/z (CI) 617 $[M+NH_4]^+$, 553, 536 (Found: $[M+NH_4]^+$, 617.2747, $C_{28}H_{49}N_2O_7S_2Si$ requires: $[M+NH_4]^+$ 617.2750). (Found: C, 56.14; H, 7.62; N, 2.25. $C_{28}H_{49}O_7S_2Si$ requires C, 56.06; H, 7.56; N, 2.31%).

(S)-2-((tButyldimethylsilyloxy)methyl)-1,4-ditosyl-1,2,3,4-tetrahydropyridine 555



554 **555**

3 : 1

To a solution of acetal **554** (6.30 g, 11.0 mmol, 1.0 equiv.) in DCM (200 mL) at –78 °C was added $BF_3{\cdot}Et_2O$ (5.30 mL, 45.0 mmol, 4.0 equiv.). The solution was slowly warmed to –20 °C and stirred for 30 min. Saturated aqueous NH_4Cl (150 mL) was added and the suspension heated to rt. The layers were separated and the aqueous layer extracted with DCM (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (75% petrol–EtOAc) gave **555** as a pale-yellow solid (3.80 g, 59%).

R_f = 0.80 (50% petrol–EtOAc); m.p. = 98 °C; ν_{max} (film) 2957, 1720, 1596, 1493, 1445, 1401, 1343, 1266, 1144, 1087, 1042, 814 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.0 Hz, *ortho*-TsCH), 7.54 (2H, d, *J* 8.0 Hz, *ortho*-TsN), 7.31 (2H, d, *J* 8.0 Hz, *meta*-TsCH), 7.22 (2H, d, *J* 8.0 Hz, *meta*-TsN), 6.91 (1H, dd, *J* 1.5, 8.5 Hz, NTsC*H*CH), 5.18 (1H, dt, *J* 1.5, 8.5 Hz, NTsCHC*H*), 3.87 (1H, m, NTsC*H*CH_2), 3.75–3.65 (2H, m, NTsCHCH_AH_BOH + TsC*H*), 3.43 (1H, dd, *J* 6.5, 12.5 Hz, NTsCHCH_AH_BOH), 2.46 (3H, s, CH_3-TsCH), 2.42 (3H, s, CH_3-TsNH), 2.21 (1H, dd, *J* 6.0, 13.0 Hz, NTsCHCH_2C$H_A$$H_B$CHTs), 1.17 (1H, td, *J* 4.5, 16.0 Hz, , NTsCHCH_2C$H_A$$H_B$CHTs), 0.76 (9H, s, (C$H_3$)$_3$C), 0.00 (3H, s, CH_3Si), -0.03 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 144.8 (CSO_2, TsCH), 144.1 (CSO_2, TsN), 135.3 (CH_3C, TsCH), 133.6 (CH_3C, TsN), 129.9 (*ortho*-TsCH), 129.6 (*ortho*-TsN), 129.0 (*meta*-TsCH),128.7 (NTs*C*HCH), 126.7 (*meta*-TsN), 98.9 (NTSCH*C*H), 61.8 (NTSCH*C*H_2OH), 55.8 (Ts*C*H), 52.5 (NTs*C*HCH_2OH), 25.7 ((*C*H_3)$_3$C), 21.6 (2 x CH_3Ts + NTsCH*C*H_2CHTs), 17.9((CH_3)$_3$*C*), -5.5 ((CH_3)$_2$Si); M/z (CI) 553 $[M+NH_4]^+$, 536 $[M+H]^+$, 381, 174 (Found: $[M+NH_4]^+$, 553.2210.$C_{26}H_{41}N_2O_5S_2Si$ requires: $[M+NH_4]^+$, 553.2226).

3.4. References

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