THE ATTEMPTED SYNTHESIS OF INDOLIZIDINE AND PYRROLIZIDINE NATURAL PRODUCTS

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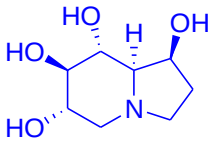
I would like to dedicate this thesis to my lovely wife Ramani Kondakal, my beautiful daughter Diya Reddy Kondakal and my parents Narsimha Reddy Kondakal and Lakshmi Kondakal for their constant love and support during this work and their sacrifices.

Abstract:

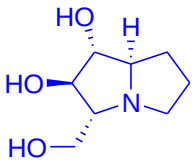
Aza-sugars are naturally occurring polyhydroxylated alkaloids in which the ring oxygen is replaced by nitrogen. They are reported to have a wide range of biological properties, most importantly as glycosidase inhibitors; these glycosidases play a key role in various diseases like HIV, cancer and lysosomal storage disorders.

This thesis will describe an approach to the synthesis of analogues and precursors of aza-sugar natural products in the indolizidine (for example castanospermine) and pyrrolizidine (for example hyacinthacine) using cyclopropenones and cyclic imines as key intermediates.



castanospermine

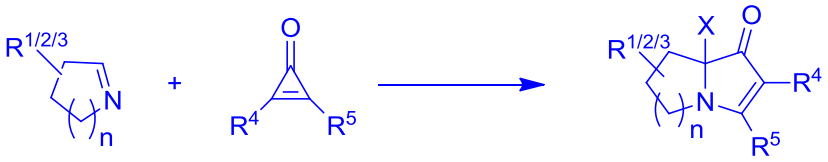
(indolizidine)



hyacinthacine A_2

(pyrrolizidine)

This thesis contains work that is an extension of the work pioneered by Eicher and Heimgartner and followed by our group for the reaction of cyclic imines with diphenylcyclopropenone. The methodology was extended towards the synthesis of more complex bicyclic heterocycles like indolizidine and pyrrolizidine aza-sugars and is summarised by the following Scheme. In this thesis, cyclopropenones other than diphenylcyclopropenone were used.



n = 1/2

X = H or OH
n = 1 (pyrrolizidine)
n = 2 (indolizidine)

This work also extended the range of cyclic imines that can be reacted by using for the first time, the parent aldimines, polyhydroxylated cyclic aldimines synthesised from sugars and other substituted cyclic imines. The reactions gave bicyclic products but always with an extra oxygen at the bridge head postion (X= OH) via aerial oxidation of the initial product (X= H).

Overview of thesis:

Chapter 1: gives a brief description of aza-sugars, their classification, their occurrence in nature and some of the recent literature syntheses of indolizidines like castanospermine and pyrrolizidines like the hyacinthacines and australine.

Chapter 2: contains the discussion of the experimental results and includes discussion about the various methods used for the synthesis of cyclic imines and cyclopropenones including a brief introduction of the structure and reactivity of cyclopropenones.
The reactions of these cyclic imines with cyclopropenones are discussed leading to the synthesis of indolizidine and pyrrolizidine systems. The chemistry behind the the addition reaction and the unexpected aerial oxidation of the addition products is also presented.

Chapter 3: concerns the presentation of the experimental techniques, results and data starting with the six membered cyclic imines then five membered cyclic imines, cyclopropenones and lastly the experimental data of the new cycloaddition products.

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Acknowledgements

Firstly, I would like to express my sincere gratitude to my supervisor Dr. Karl Hemming for a great opportunity to work with him. It was a great time working with such enthusiastic, immensely supportive and knowledgeable supervisor. I appreciate all his time, ideas and funding to make to my PhD experience productive and stimulating.

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I would like to thank my family members brother Ram Chandra Reddy Kondakal, sisters Vajram, Vanaja and Jaya for their constant love and encouragement to carry out this PhD. Thank you very much. Love you all.

I would like to thank The University of Huddersfield for the funding.

List of abbreviations

Ac	acyl
ACN	acetonitrile
AIBN	azobisisobutyronitrile
App t.	apparent triplet
Aq.	aqueous
Ar.	aryl
b	broad (NMR)
bd	broad doublet
Bn	benzyl
Boc	Di-tert-butyl dicarbonate
b.p.	boiling point
br	broad (IR)
bs	broad singlet
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
conc.	concentrated
d	days, doublet (NMR)
Davy reagent	2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane-2,4-disulfide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublets of doublets
ddd	doublets of doublets of doublets
DEPT	distortionless enhancement though polarization transfer
DMAP	4-*N,N*-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DPP	diphenylcyclopropenone
dq	doublet of quartets
dt	doublet of triplets
eq.	equivalent(s)
ER	endoplasmic reticuclum
EWG	electron-withdrawing group
FMO	frontier molecular orbital

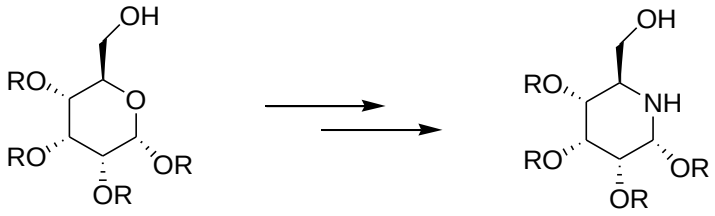
glu	glutamic acid
h	hour(s)
Heimgartner reagent	2,4-Bis(p-tolylthio)-1,3-dithia-2,4-diphosphetane-2,4-disulfide
HMBC	hetero nuclear multiple bond connectivity
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chomatography
HMS	high resolution mass spectrometry
HQC	heteronuclear single quantum coherence
Im	imidazole
LDA	lithium diisopropylamide
Lawesson reagent	2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide
lit.	literature
LITMP	lithium tetramethylpiperidide
LUMO	lowest unoccupied molecular orbital
m	multiplet (NMR)
min	minute(s)
m.p.	melting point
Ms	mesylate
MS	mass spectrometry
MW	molecular weight
NMO	4-methylmorpholine 4-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhause effect
Nu	nucleophile
PE	petroleum ether
Ph	phenyl
PIFA	phenyliodine(III)bis(trifluroacetate)
ppm	parts per million
PPTS	Pyridinium-*P*-toluenesulfonate
q	quartet
RCM	ring closing metathesis
RT	room temperature
s	strong (IR), singlet (NMR)
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilane

TCICA	trichlorocyanuric acid
TCDI	thionocarbonyl-1,1-diimidazole
Td	triplet of doublets
TEMPO	2,2,6,6-tetramethyl-1-piperidnyloxy, free radical
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin later chromatography
TMEDA	tetramethylethylenediamine
TMSOTf	trimethylsilyl trifluromethanesulfonate
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
TSA	transition state analogues
tt	triplet of triplets
UV	ultraviolet
Vs	very strong (IR)
W	weak (IR)

1-Introduction:

1.1 Overview of aza-sugar natural products

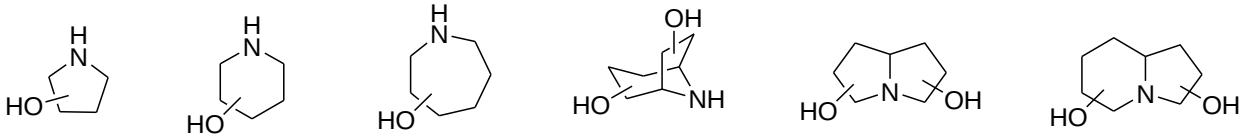
Aza-sugars as the name implies are the analogues of carbohydrates in which the ring oxygen is replaced by nitrogen.[1-3] These systems are observed widespread in plants and microorganisms. They are reported to be biologically important, due to the inhibition of carbohydrate processing enzymes.[1, 4]



Scheme-1.1

Fleet, Linda and Nash undertook pioneering working on the isolation and synthesis of aza-sugars.[5] aza-sugars are classified according to their structure as polyhydroxylated systems by Naoki, Fleet and Storer[6] as

1. Pyrrolidines
2. Piperidines
3. Azepanes
4. Nortropanes
5. Pyrrolizidines
6. Indolizidines



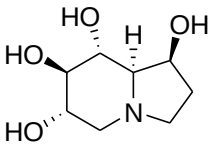
Pyrrolidine 1 | Piperidine 2 | Azepane 3 | Nortropane 4 | Pyrrolizidine 5 | Indolizidine 6

In this thesis we focussed on the synthesis of indolizidine and pyrrolizidine alkaloids with an emphasis on castanospermine (indolizidine) and hyacinthacines (pyrrolizidine).

1.2 Biological importance:[3-5]

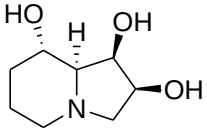
Glycosidases and glycosyltransferases are carbohydrate processing enzymes that play vital roles in a number of important cellular processes across various biological systems like cell-cell, cell-virus recognitions, synthesis of complex and essential carbohydrates and N-linked glycoprotein processing.[7-10] This makes the study of glycosidases and glycosyltransferases an important tool in drug design. As a result of this, the synthesis and design of glycosidase inhibitors has become an important area of research. Inhibitors of glycosidases are reported as potential theraupeutic agents for diseases like viral infections, lysosomal diseases and tumor metathesis. Iminosugars/azasugars are reported to be potent glycosidase inhibitors.[3, 4, 7, 9] Due to their similarity to the structure of sugars, they mimic the sugars in transition-states of sugar processing enzymes and thus inhibit the processing. Piperidine analogues mimic the monosaccharide sugars, whereas the bicyclic systems like indolizidines and pyrrolizidines have been reported as inhibitors of glycosidases.

Thus, as shown in the figure-1 below, castanospermine (7), swainsonine (8) and N-butyl-DNJ (10) have been shown to inhibit glycosidases in the endoplasmic reticulum (ER) and Golgi apparatus and affect the cellular repertoire of N-linked glycans of glycoproteins. They have been used to investigate the processes involved with various glycosidases and exploited for drug development for cancer therapy, immune response and antiviral activity.[11-13]



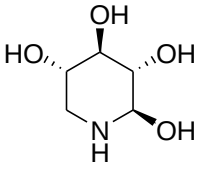
castanospermine

7



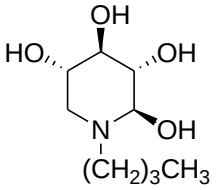
swainsonine

8



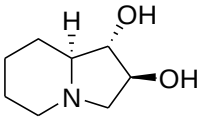
1-Deoxynojirimycin (DNJ)

9



N-butyl-DNJ

10



(+)-Lentiginosine

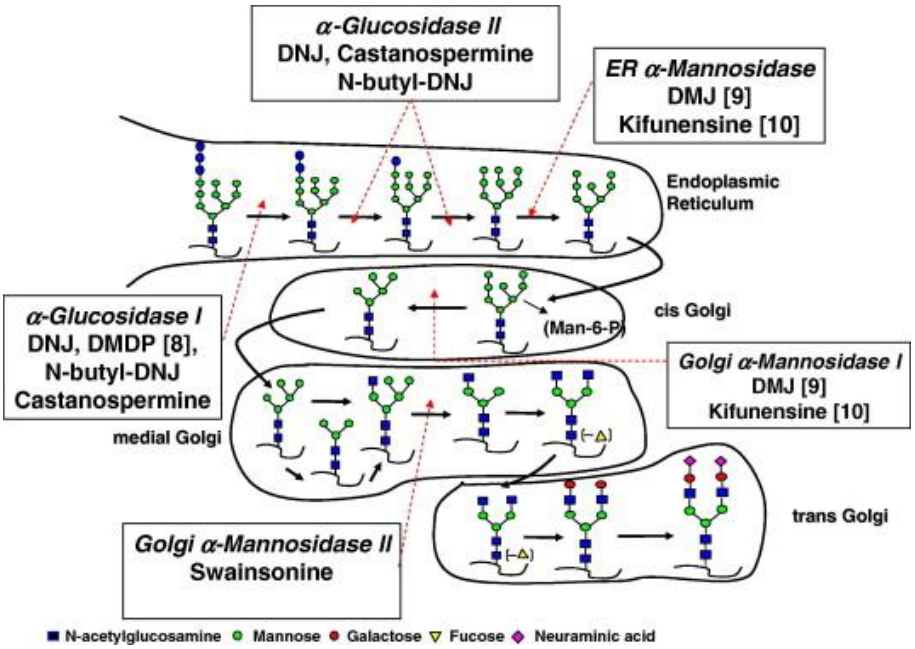
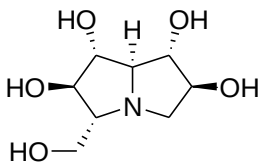


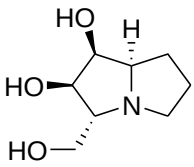
figure-1: Inhibition of processing glycosidases[5]

Between glycosyltransferase and glycosidase inhibitors, the latter have attracted more attention due to their potential as drug candidates. Some of the glycosidase inhibitors marketed as drugs are acarbose, miglitol, tamiflu or oseltamivir etc.[4] Castanospermine (7), swainsonine (8) and lentiginosine are indolizidine glycosidase inhibitors. Casuarine (11), hyacinthacine (12), australine (13), alexine (14) and uniflorine (15) are some of the pyrrolizidines reported as glycosidase inhibitors. Many of these indolizidines and pyrrolizidines are studied at clinical level[14-16] but, due to limitations like specificity, dose and extent of inhibition none of them are approved as drugs.[4] Attempts are being made by synthetic chemists to address the issues of selectivity and raise the efficiency and remove side effects,[7, 17-19] and this means that the synthesis of indolizidine and pyrrolizidine aza-sugar analogues is an area of active interest.[20-22]



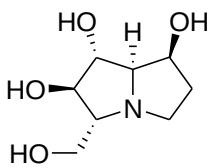
(+)-casuarine

11



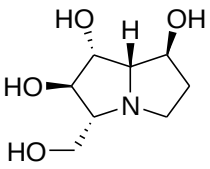
(+)-hyacinthacine A_1

12



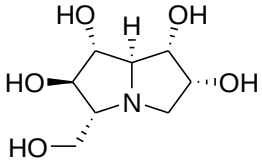
(+)-australine

13



(+)-alexine

14



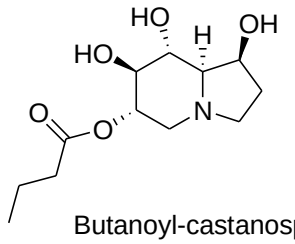
(-)-uniflorine

15

Indolizidine based azasugars

One of the important areas of organic synthesis is focussed on the synthesis of the six-five membered bicyclic systems (indolizidines), with a strong emphasis on swainsonine (8) and castanospermine (7) analogues, due to their theraupetic potential[23] and synthetic challenge. We focused on castanospermine analogues. A number of analogues of castanospermine have been reported and their biological activity has been tested.[23-25]

α-glucosidase inhibitors 1-deoxynorjirimycin (DNJ)(9) and castanospermine (CAST)(7) are the promising inhibitors demonstrated by many research groups to inhibit the morphogenesis of many enveloped viruses.[9] Derivatives of castanospermine have been reported to reduce viremia and dengue virus (DENV).[26, 27]



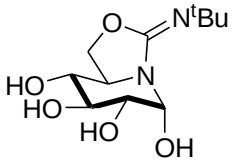
Butanoyl-castanospermine
(Bu-CAST)

16

Bu-CAST(16) has been tested in human clinical trials for antiviral activity aganist human immunodeficiency virus (HIV) and hepatitis C virus (HCV), where modest reduction in virus titer in the serum of some of the treated patients was observed.[26, 27]

Garcia et al[28] synthesised and studied anlogues of castanospermine bearing additional exocyclic nitrogen, an alkyl chain (17),(19) and sugar molecule (18) attached to nitrogen for the inhibitory activity towards glycosidases. The presence of the exocyclic nitrogen was

found to cause high anomeric specificity of inhibitors, whereas attaching a sugar molecule (18) was found to reverse the inhibitory acitivty towards α and β glucosidases when compared to castanospermine (7), indicating the influence of exocyclic substituent. The *N*-alkyl substituents were studied and it was found that the *N*-octyl derivative (19) was more potent towards β-glucosidase than N-pentyl derivative.[28] This interesting results resulted in further design and synthesis by other research groups.[29]



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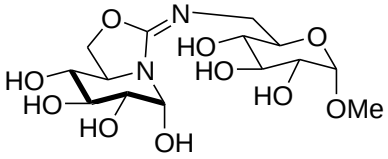

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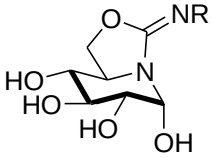
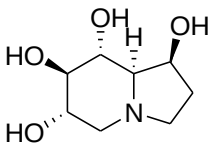


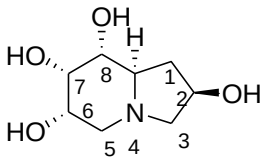
19 R = n-octyl
20 R = Ph

Gomez-Gullien et al[30] studied the glycosidase inhibitory activity of castanospermine analogues by changing the hydroxyl group position from C-1 to C-2 (21). It was concluded that 2R and 8aR configurations were essential for inhibitory activity towards amyloglucosidase.[30] Amyloglycosidases are enzymes used to catalyse the breakdown of oligosaccharides to glucose.



Castanospermine

7

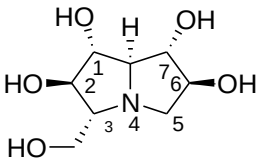


C1-C2 Hydroxy analogue

21

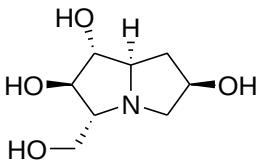
Pyrrolizidine based azasugars

Two main classes of pyrrolizidine analogues in the limelight for a long time are casuarine (11) analogues and hyacinthacine (12). Casuarine is a pyrrolizidine aza-sugar with the highest known number of hydroxyl groups. Its activity has been studied for the potential treatment of cancer and AIDS. Carmona et al[31] studied the biological activity of 7-deoxycasuarine (22) and concluded that loss of hydroxyl at C-7 results in loss of inhibitory activity towards glucosidase and improves selectivity towards amyloglucosidase.[31]



(+)-casuarine

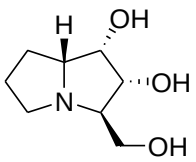
11



7-deoxycasurine

22

Hyacinthacines A1(12) and A2(23) are reported as very good inhibitors of amyloglucosidase from aspergillus niger, rat intestinal lactase and rat epididymis α-L-fucoside.



Hyacinthacine A1

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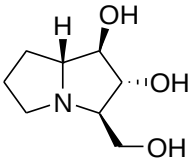
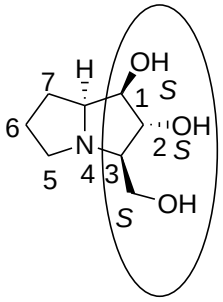


Hyacinthacine A2

23

Calvers and co-workers[32] studied the glycosidase inhibition activity of analogues of hyacinthacine A1 and A2 synthesised using chemoenzymatic methodology and observed that only compounds with S configuration at C1, C2, C3 (24&25) were active and that these compounds were the first reported inhibitors that displayed activity against rhamnosidase. They reported the need for more variation in structural design of glycosidase inhibitors.



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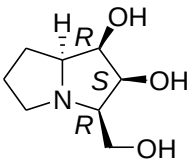

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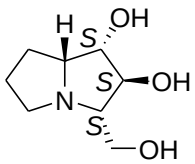

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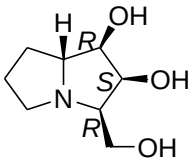
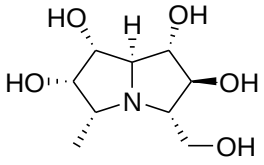


27

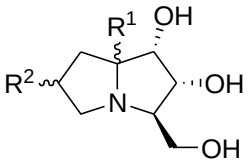
Hyacinthacines which are fully substituted are reported in very few numbers. Zhang et al[33] synthesised and studied some fully protected analogues of (+)-hyacinthacine and found that only one analogueue (28) was selective for α-glycosidase inhibition compared to natural (+)-hyacithacine A_2 (23).[33]



6-*epi*-(-)-hyacinthacine C_5

28

D'Adamino et al[34] studied the analogues of hyacinthacine A_1(12) and found that the presence of a β-hydroxy at C-6 (29) was found to diminish the activity, whereas compound (30) with an α-hydroxy resulted in a strong activity against amyloglucosodase and β-glucosidase suggesting the importance of the stereochemistry of the hydroxyl groups.



R^1 = α–H
R^2 = β–OH
29

R^1 = β–H
R^2 = α–OH
30

1.3 Natural occurrence:

1.3.1 Indolizidines:

Indolizidine systems have some structural relationship with the sugars whereby in each template the configuration of hydroxyls is related to the sugars.[4] In nature other functional groups like amides and carboxylic acids are also observed. The toxicity of legumes such as *Swainsonacanescens* and *Castanospermumaustrale* in Australia towards livestock, led to the isolation of the toxic principles swainsonine (8)[35] and castanospermine (7).[36] This created an interest in sugars containing nitrogen and their therapeutic potential. Later on, castanospermine (7) was also isolated from the dried pods of *Alexa leiopetala*.[37] It is a good

inhibitor of human neutral α-mannosidase.[38] Later, a number of structurally related natural analogues of castanospermine were reported. A diverse array of indolizidine and pyrrolizidine alkaloids were reported to be discovered from amphibian skin.[39] Major amounts of 5,8-disubstituted indolizidine 217B and trace quantities of 3,5-disubstitued indolizidines and pyrrolizidines were reported to be present in brightly coloured frogs of the genus *Mantella* found in the rain forests of Madagascar.[40] These systems are usually alkyl substituted rather than polyhydroxylated.

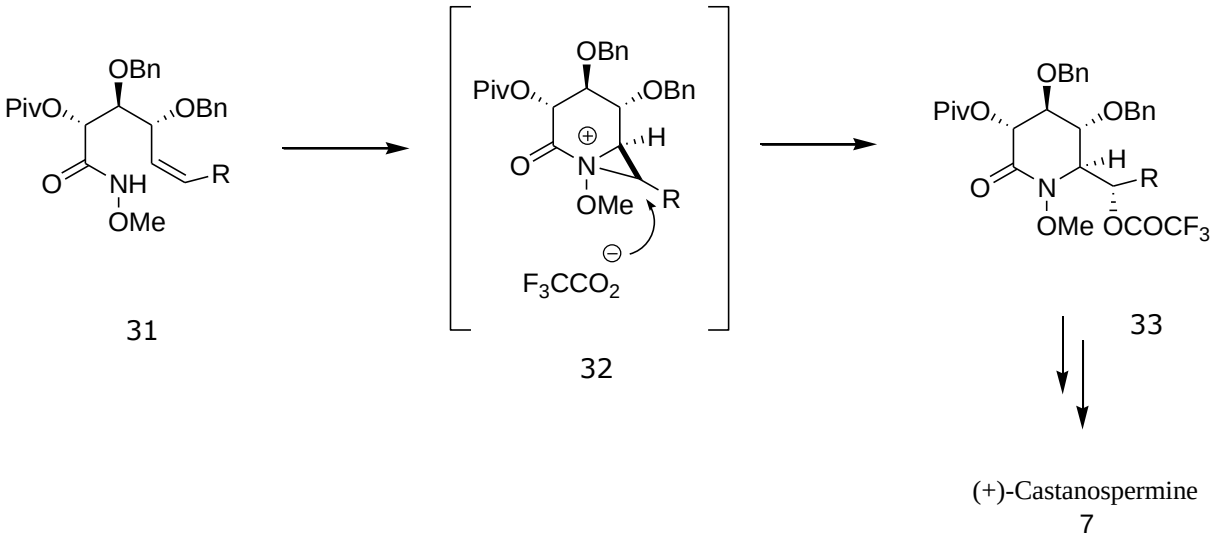
1.3.2 Pyrrolizidines:

There are many pyrrolizidine alkaloids reported and these alkaloids are produced by plants as defence systems against insects.

We were interested in hyacinthacines due to the interest in their therapeutic potential and due to ready routes through to the necessary precursor (see later). In 1999, polyhydroxylated pyrrolizidines different from the previously isolated alexines (14) and australines (13) were isolated from *Hyacinthoidesnon-scripta* and *Scillacampanulata* both of which are hyacinthacea family and so these compounds were named as hyacinthacines[41] the structures of which are given above (12 & 23). Two compound classes related to the hyacinthacines, the alexines (14) and australines (13) were isolated in the late 1980s. A brief review of methods for the synthesis of hyacinthacines, alexines and australines plus castanospermine (7) now follows.

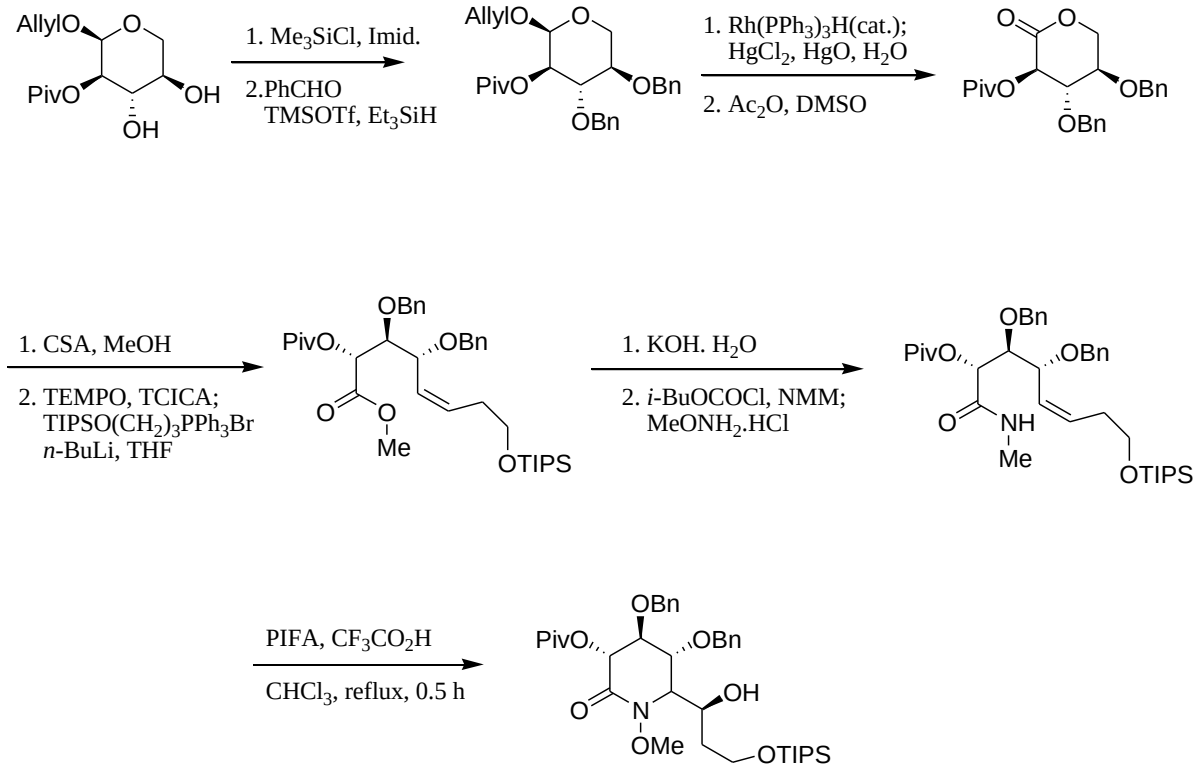
1.4 Literature synthesis of castanospermine*:*

Duncan et al reported the total synthesis of (+)-castanospermine (7) via diastereoselective nitrenium ion (32) mediated cyclofunctionalisation,[42] as summarised below in Scheme 1.2.



Scheme-1.2

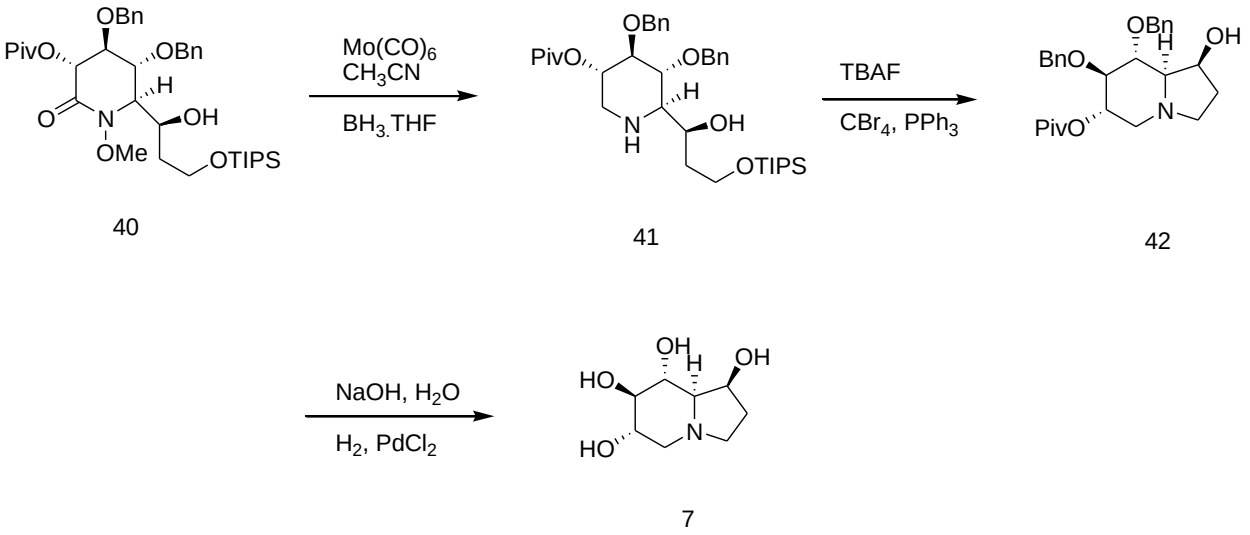
In Duncan's work α-D-xylopyranoside (34)[42] was used as the starting material and was converted to a dibenzyl ether (35) via reductive etherification of a (bis)trimethylsilyl ether intermediate using benzaldehyde.[43] The challenging deallylation of the dibenzyl ether was achieved using catalytic $HRh(PPh_3)_3$ in THF which resulted in the corresponding enol ether. This was hydrolysed with $HgCl_2$-HgO in a step-wise manner to yield a mixture of lactol anomers, which was converted to lactone (36) using Albright and Goldman conditions (DMSO, Ac_2O),[44] as shown in Scheme below 1.3, below:



Scheme-1.3

The side chain alkene was attached by methanolysis of the lactone in the presence of camphor sulfonic acid resulting in the δ-hydroxy ester in good yield. The primary alcohol was oxidised using TEMPO and TCICA and Wittig reaction of the resulting aldehyde with the ylide generated from 3-isopropylsiloxypropyltriphenylphosphonium bromide[45] resulted in the alkene (37). Saponification of methyl ester group was accomplished by treatment with aq KOH, THF and MeOH, which was then subjected to oxamidation by conversion to the corresponding anhydride (38) by treatment with methoxylamine hydrochloride.

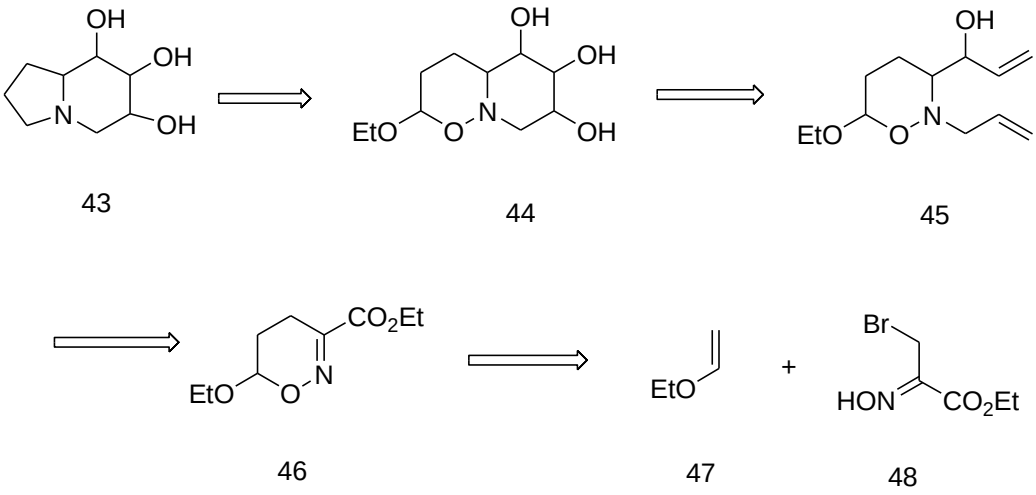
Exposure of the amidate (38) to PIFA and trifluoroacetic acid under reflux temperature resulted in the target intermediate (39), which was isolated as a single diastereoisomer after *in situ* amonolysis of the initial trifluoroacetate adduct.



Scheme-1.4

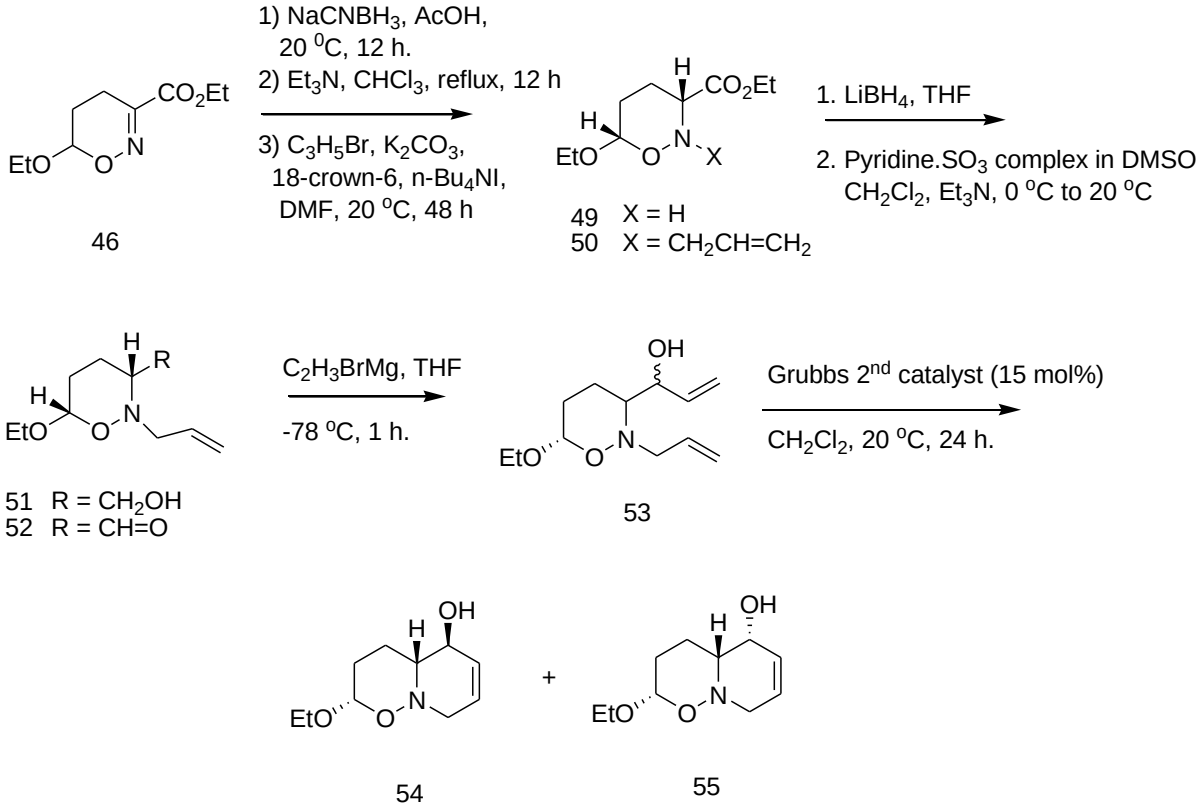
Treatment of the resulting adduct with $Mo(CO)_6$ in aq acetonitrile cleaved the N-O bond resulting in the NH lactam which was reduced with borane THF to give the corresponding piperidene (41). The TIPS protection was removed to give the amino-2,4-diol using fluoride ion and selectively brominated using Appel conditions[46] (CBr_4, PPh_3). The intermediate cyclised *in situ* and deprotection of the benzyl ethers and pivoloyl group gave the target indolizidine castanospermine (7) as shown above in Scheme 1.4.

A protection-free synthesis of analogues of castanospermine (7) was reported recently by Gallos et al[21] from readily accessible cheap starting materials using hetero-Diels-Alder cycloadditions and RCM (ring closing metathesis). The retrosynthetic approach as shown below in Scheme 1.5 involved construction of the pyrrolidine ring by N-O bond scission using hydrogenation (44 to 45), the precursor for which was prepared from hetero-Diels-Alder-reaction, followed by additions of appropriate terminal alkenes. Intermediate (45) was then subjected to RCM, resulting in the bicyclic system and an alkene which was dihydroxylated in a stereoselective manner and hydrogenated leading to the target analogue of castanospermine.



Scheme-1.5

An example is shown in Scheme 1.6 The starting material (46) was synthesised in high yield using a literature procedure[47] by a hetero-Diels-Alder reaction of the nitrosoalkene with ethyl vinyl ether. The imine was reduced selectively to give the *cis* isomer[47] of the adduct, this adduct (49) was allylated with allyl bromide and K_2CO_3 to give allyl substituted compound (50) in good yield. The ester in compound (50) was reduced to an aldehyde (52) in two steps using reduction by $LiBH_4$ followed by oxidation using Pyridine.SO_3 complex. This aldehyde (52) was subjected to Grignard reaction using vinylmagnesium bromide to give the terminal alkene (53), which was subjected to RCM using Grubbs 2nd generation catalyst to give the bicyclic compound as a mixture of two compounds (54 & 55) due to lack of selectivity in the Grignard reaction. The mixture of both allylic alcohols was dihydroxylated by osmylation and then subjected to N-O bond cleavage by Raney Ni to afford 1-deoxy-6-*epi*-castanospermine (57) and 1-deoxy-6,8a-di-*epi*-castanospermine (59) as shown below in Scheme 1.6.



46

49 X = H
50 X = $CH_2CH{=}CH_2$

51 R = CH_2OH
52 R = CH=O

53

54

55

54

56

1-deoxy-6-*epi*-castanospermine

57

55

58

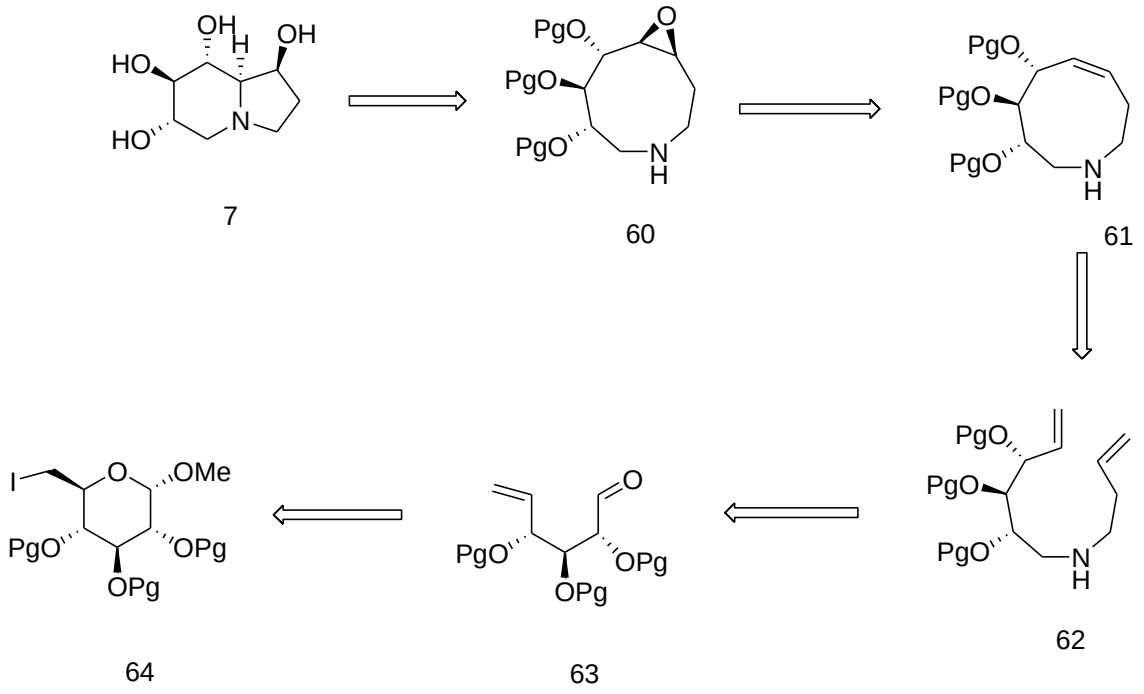
1-deoxy-6,8a-di-*epi*-castanospermine

59

Scheme-1.6

Another interesting synthesis of castanospermine was reported by Madsen[48] using ring-closing olefin metathesis (Scheme 1.7) and strain release transannular cyclisation as key

transformations.[49-52] Retrosynthetic analysis involved transannular cyclisation from an epoxide (60) which resulted in turn from an alkene formed via olefin metathesis, which originated from reductive amination of an aldehyde. This nine step synthesis of (+)-castanospermine from methyl-α-D-glucopyranside was accomplished in 22% yield.



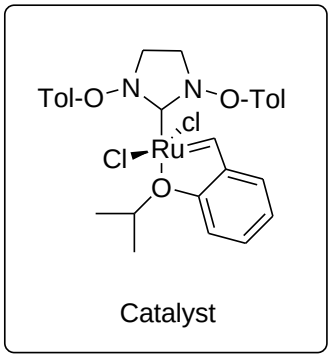
Scheme-1.7

The starting material, methyl 6-deoxy-6-iodo-α-D-glucopyranoside (64), was prepared in two steps from commercially available methyl-α-D-glucopyranoside by treatment with iodine and triphenyl phosphine,[53] followed by protection of the hydroxyl groups using an excess of benzyl trichloroacetamide under acidic conditions. The tribenzyl ether (64) was sonicated in the presence of activated Zn powder to result in the unsaturated aldehyde (63).

The crude aldehyde was subjected to reductive amination immediately, due to the epimerisation of the α-stereocenter on standing. The optimised conditions for the reductive amination were reported to be $NaCNBH_3$[54] in the presence of excess homo-allylamine and powdered 4 Å molecular sieves in THF. The resulting amine was protected using trifluoroacetamide by reacting with trifluroacetic anhydride and triethylamine.

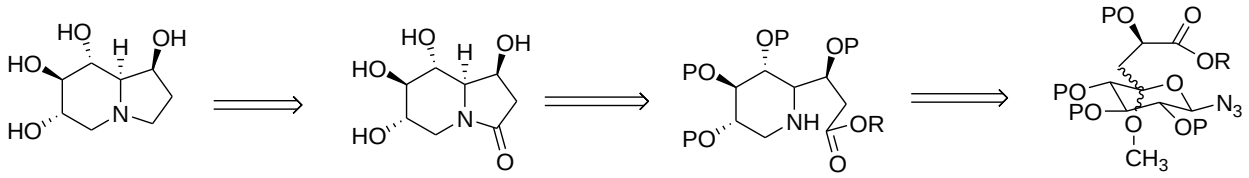
With this diene (62) in hand the authors found that Grubbs catalyst was best when compared to ruthenium indylidene catalyst (65).[55, 56] The optimised conditions for epoxide

generation used the *in situ* generated dioxirane of 1,1,1-trifluroacetone with good yield of 70%. The epoxide was used directly for the transannular cylisation step, to avoid the acid labile decomposition. Deprotection then resulted in the indolizidine castanospermine (7) in 22% overall yield.



65

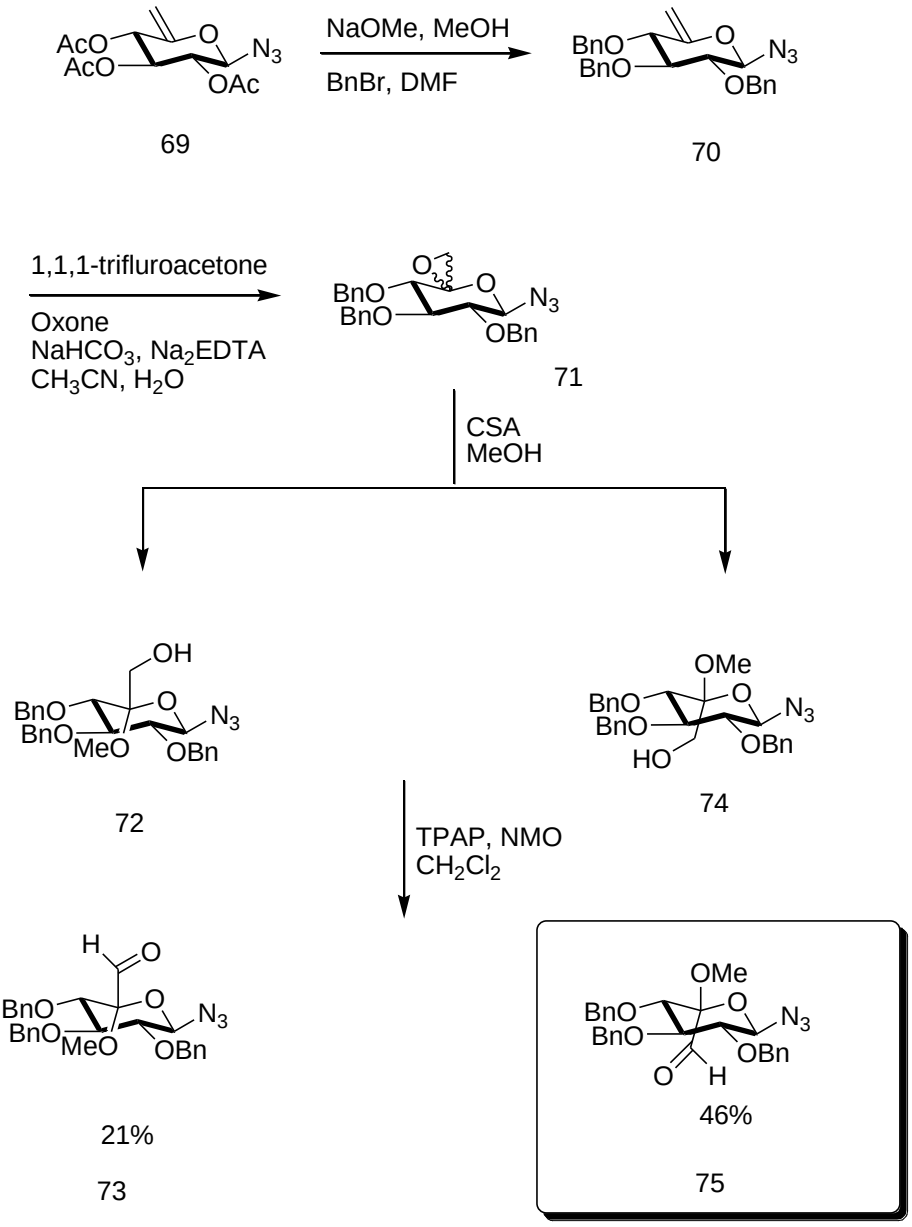
Another interesting synthesis of castanospermine was reported by Murphy in 2005,[57] using a novel catalytic reductive amination cascade and aldol reaction tactic, as shown below in Scheme 1.8. It was envisioned that 5-C-methoxypyranosyl azide (68) would undergo a reduction cascade to yield the indolizidine lactam (66) via the pyranosylamine (67).[58, 59]



Scheme-1.8

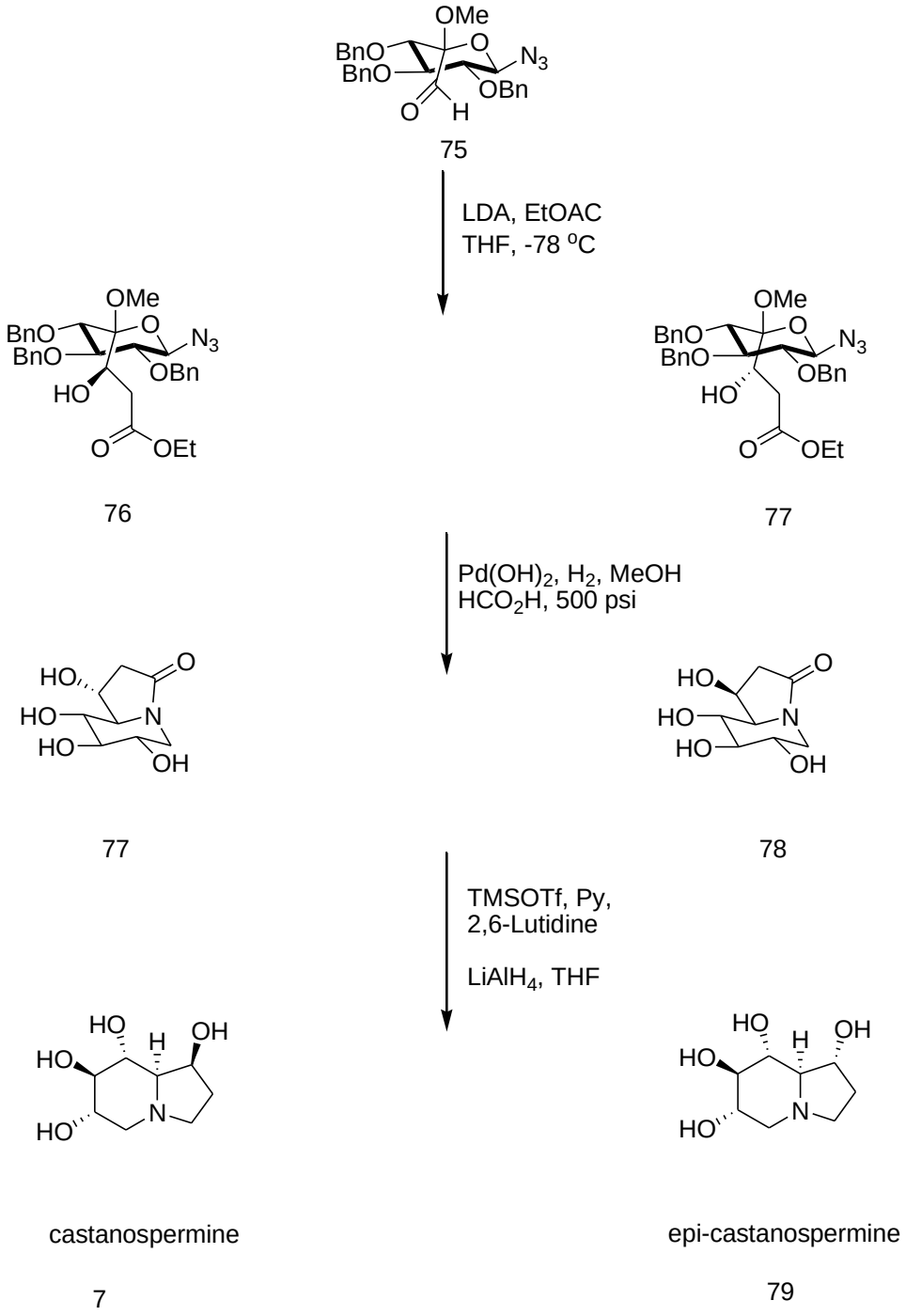
The forward synthesis is shown below.

The synthesis started with the 6-deoxyhex-5-enopyranoside (69), which was prepared from methyl α-D-glucopyranoside in five steps.[59]



Scheme-1.9

The acetate groups were exchanged with benzyl groups using benzyl bromide and sodium methoxide as base. In the next stage the epoxide (71) was generated from the alkene by oxidation using *in situ* generated methyl(trifluromethyl) dioxirane.[60] The ring opening of the epoxide using camphor sulfonic acid and methanol which resulted in a mixture of two isomers (72 & 74).[61] The mixture of isomeric alcohols was oxidised to aldehydes by the Ley and Griffith method[62] (TPAP, NMO). The resulting two aldehydes (73 & 75) were isolated using chomatography and characterised by NOE. Only one isomeric aldehyde (75), was taken further with aldol reaction using LDA and ethyl acetate at -78°C, resulting in a mixture of diastereomers (76 & 77), as shown below in Scheme-1.10;

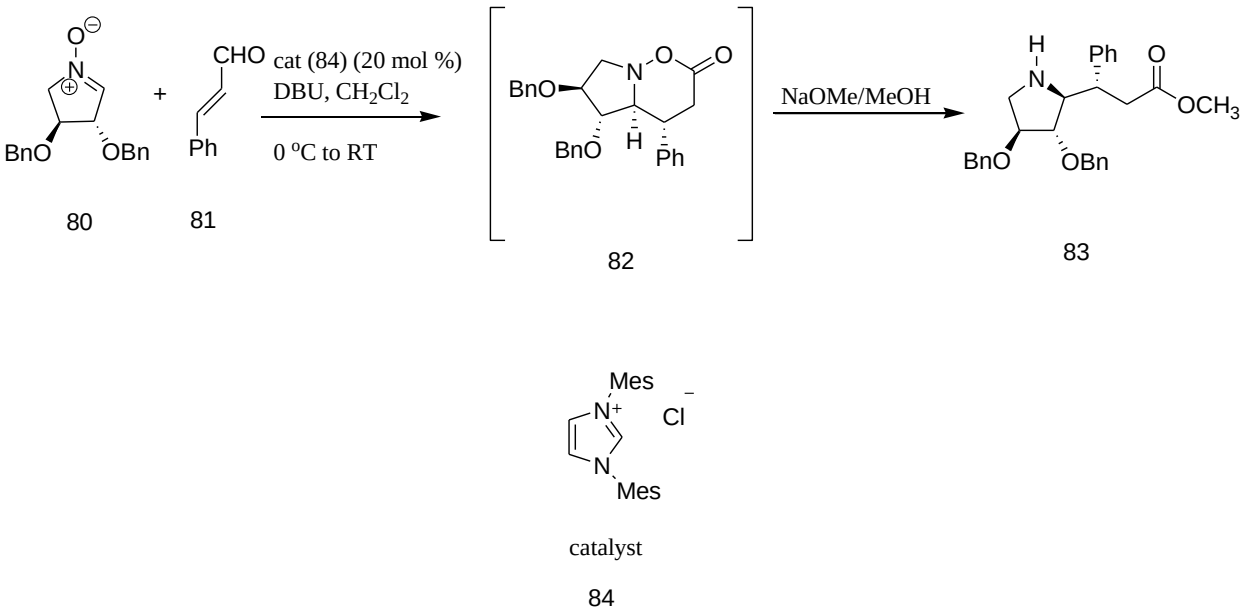


Scheme-1.10

The mixture of diastereomers (76 & 77) was subjected to a cascade of reductions using palladium hydroxide to yield the bicyclic lactam in a stereoselective manner. Conversion of the amide into the amine was via trimethyl silyl ether formation and $LiAlH_4$ reduction. The starting mixture of diastereomers gave both castanospermine (7) and epi-castanospermine (79) (Scheme 1.10).

1.5 Literature Synthesis of Hyacinthacines, Australines and Alexines*:*

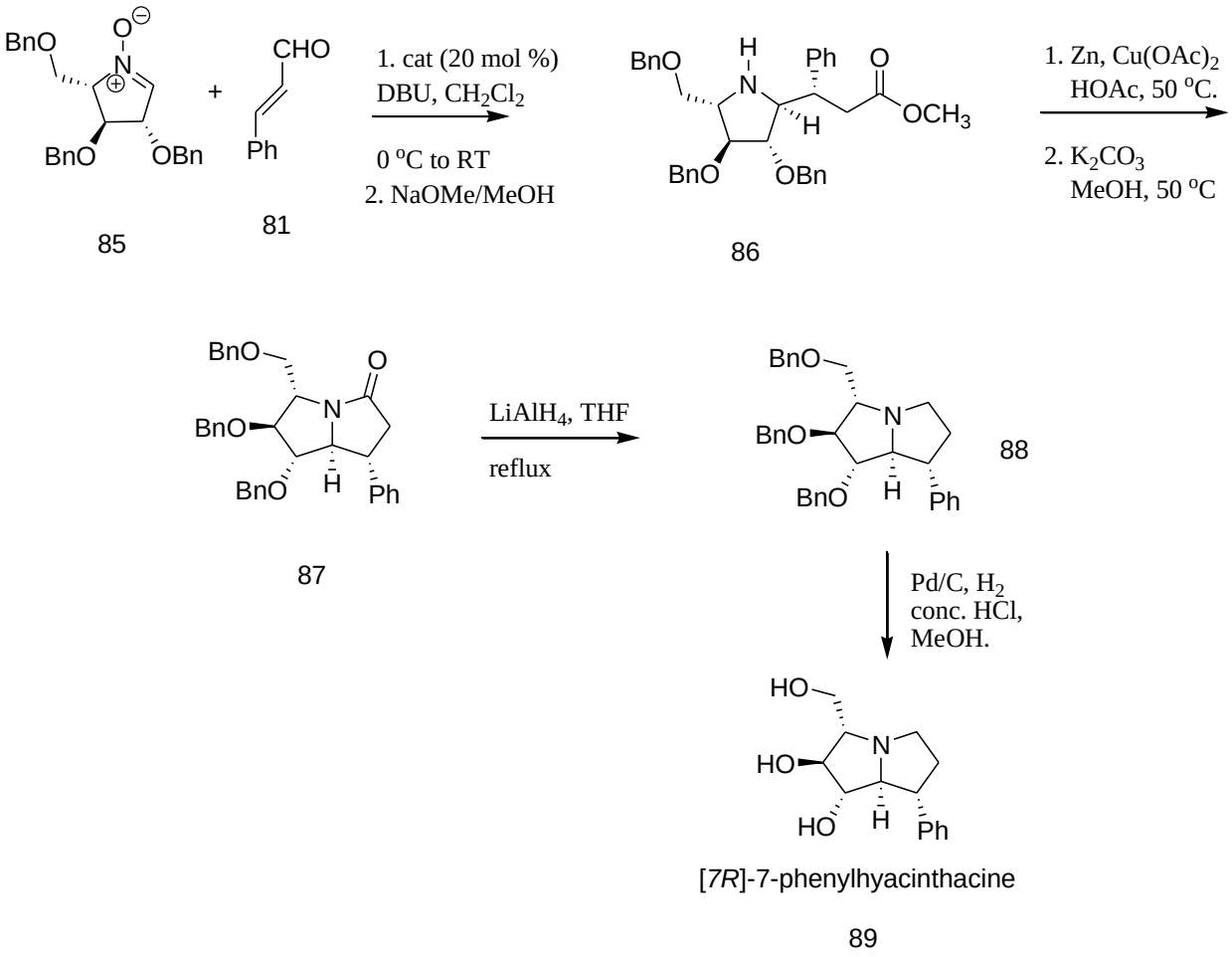
A general synthesis of polyhydroxylated pyrrolizidines and indolizidines has been reported recently by Yi Yu et al[63] using (*N*-heterocyclic carbine) NHC-mediated cross coupling of sugar derived cyclic nitrones (80) with enals (81),[64] using imidazole (84) as catalyst.



Scheme-1.11

The authors synthesised the nitrones[65-69] using literature routes. The reaction was studied using the nitrone (80) with cinnamaldehye (81) initially forming the six-membered ring (82) which was transformed into γ-hydroxyl amino ester (83) in one pot.

For the synthesis of phenylhyacinthacine (89), the nitrone (85) was coupled with cinnamaldehyde (81) to give the ester (86), which was reduced using Zn-Cu$(OAc)_2$-AcOH[70] to give the γ-amino ester, then treated with K_2CO_3/MeOH to give lactam (87). Hydrogenolysis of lactam (87) by $LiAlH_4$ gave the corresponding tertiary amine (88), which was further hydrogenated to give the required [*7R*]-7-phenylhyacinthacine (89) as shown below in Scheme 1.12. The authors reported the synthesis of a number of polyhydroxylated pyrrolizidines and indolizidines by this methodology.

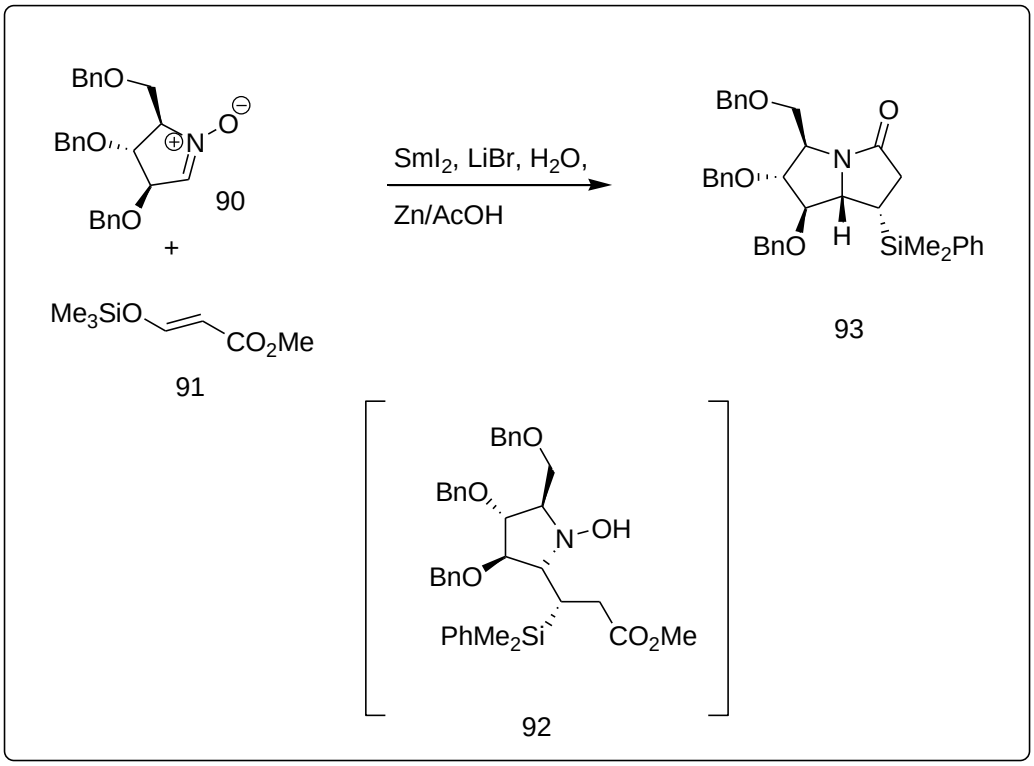


85 81 86 87 88 89

Scheme-1.12

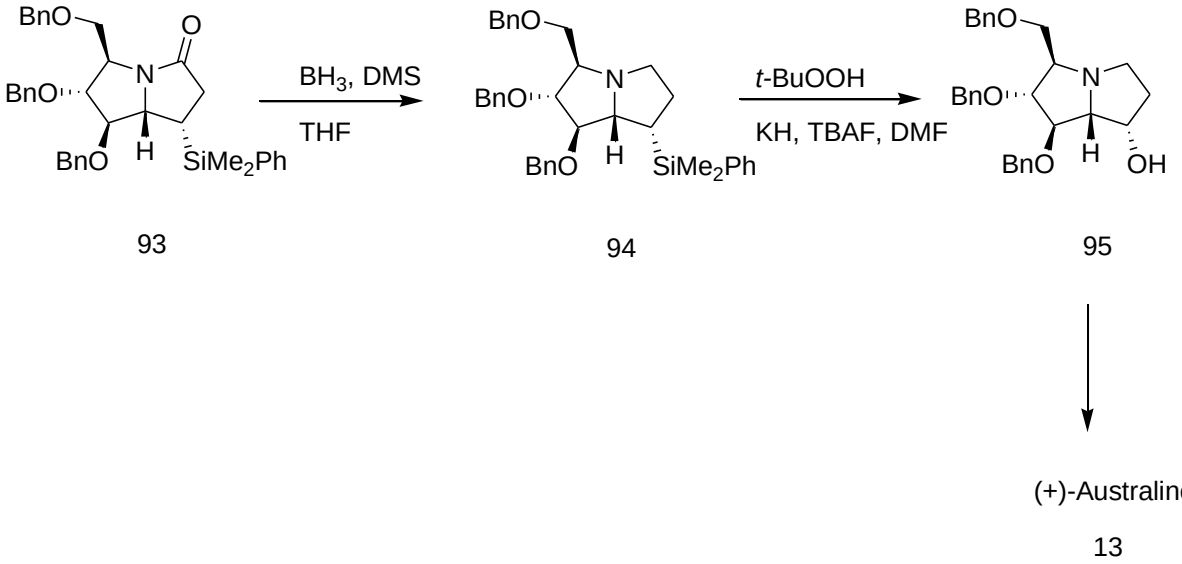
Py[71] reported on the construction of pyrrolizidines using SmI_2 cross coupling reactions utilising nitrones as starting materials, probably the most commonly used key intermediate for the construction of indolizidines or pyrrolizidines as shown in Scheme- 1.13.

The synthesis of (+)-australine (13) using SmI_2 mediated cross coupling is a typical example of Py's work. Thus treatment of nitrone (90) (Scheme-1.13) with β-silyl-α,β-unsaturated ester (91) followed by reduction using Zn,[71] gave the advanced intermediate (93). The reaction proceeded via species (92) and the nitrone was made from L-xylose.[72]



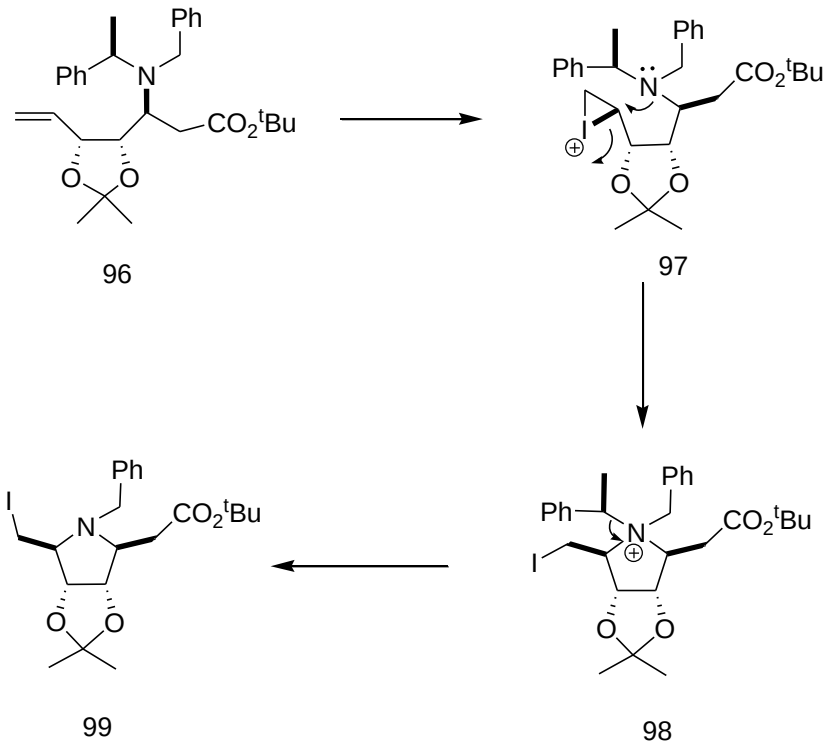
Scheme-1.13

Reduction of the pyrrolizidinone (93) to the pyrrolizidine (94) and oxidative desilylation using Tamao-Fleming conditions resulted in australine (13) as shown in Scheme 1.14.[72-74]



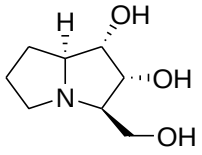
Scheme-1.14

Davis reported the synthesis of polyhydroxylated pyrrolizidines via transannular iodoamination of alkene (96) with concomitant N-debenzylation in an asymmetric route (Scheme-1.15).[75] This process gave the pyrrolidine (99)[76, 77] and also involved the preferential S_N1 type loss of the α-methyl benzyl group from the sterically congested nitrogen.



Scheme-1.15

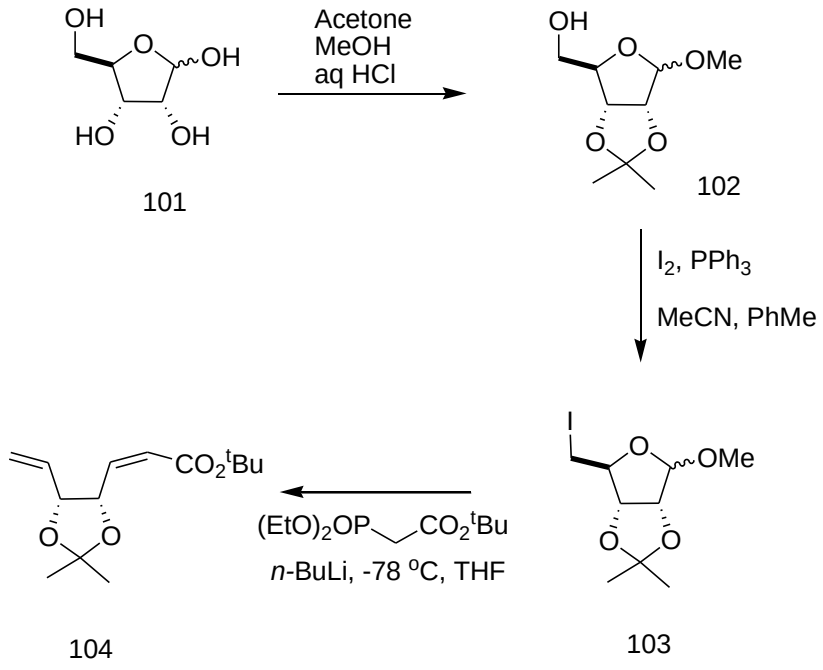
The authors used the methodology for the synthesis of (-)-7a-epi-hyacinthacine (100).



(-)-7a-epi-hyacinthacine.

100

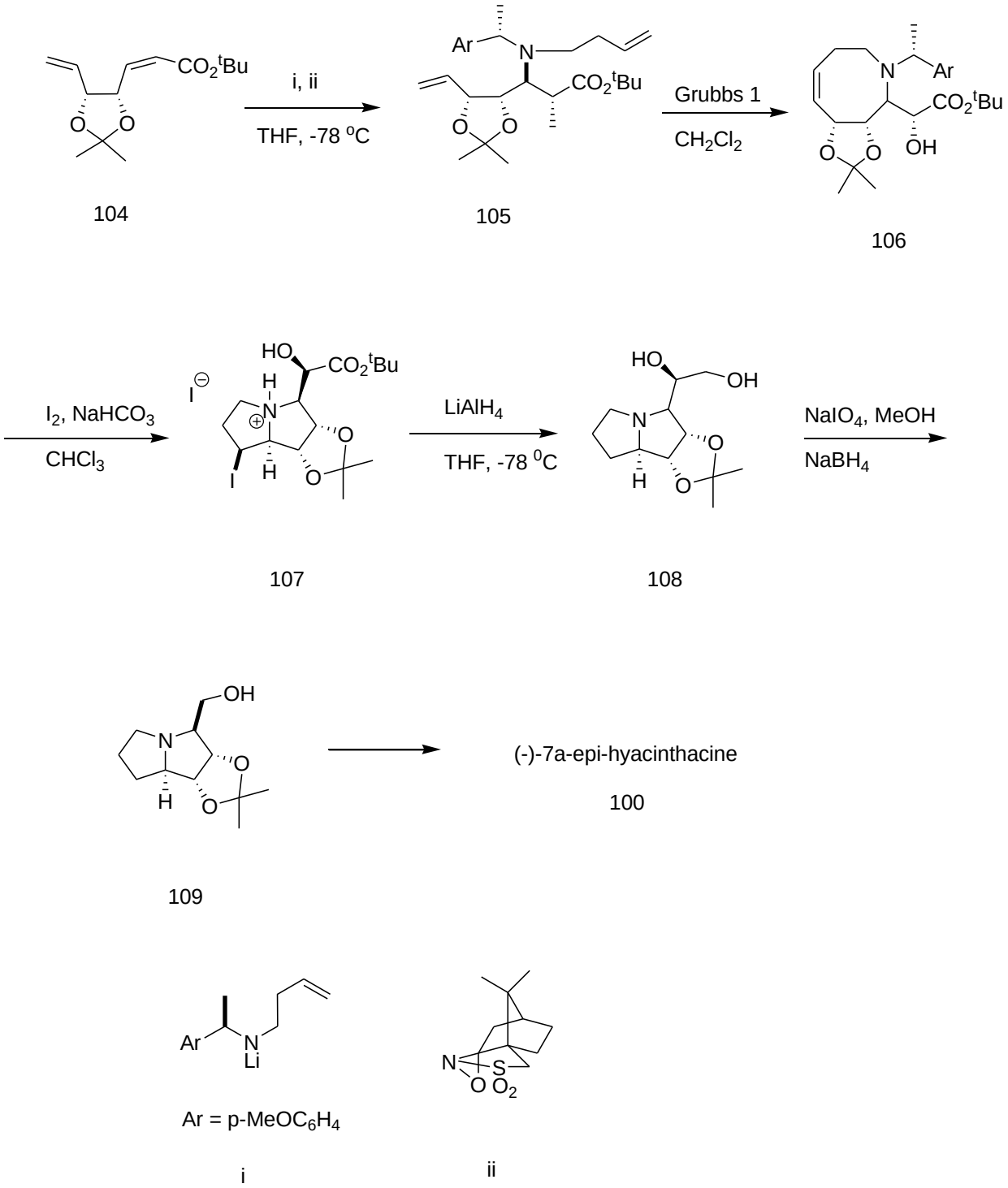
They started the synthesis (Scheme 1.16) with the construction of *tert*-butyl (4S,5R,E)-4,5-*O*-isopropylidene-2,7-dienoate (104) using D-ribose (101) as starting material.[78] Treatment of D-ribose with acetone and methanol in the presence of an acid gave the acetonide (102) which on treatment with iodine and triphenylphosphine gave the iodide (103).[79] The iodofuranose was subjected to ring opening and treated with diethylphosphonacetate in THF with *n*-BuLi[80] which promoted a tandem transmetalation/ring-opening/Wadswoth-Emmon olefination sequence to give the olefin (104).



Scheme-1.16

Doubly diastereoselective matched[81] conjugate addition of lithium compound (i) to α,β-unsaturated ester (104)[78] followed by *in situ* enolate oxidation with camphor sulfonylaziridine (ii) resulted in the hydroxy-β-amino ester (105) as a single diastereomer (Scheme 1.17). Grubbs I catalyst was used to cyclise by ring closing metathesis,[82, 83] and the product subjected to transannular iodoamination by using I_2 and $NaHCO_3$ in $CHCl_3$ giving the bicyclic core structure (107).

Reduction of the hydroiodide bicyclic core (107) with $LiAlH_4$ resulted in the diol (108). Oxidative cleavage of the diol using sodium periodate in MeOH and water and subsequent treatment of the reaction mass with sodium borohydride and hydrolysis of the resultant product (109) gave the final target (-)-7a-epi-hyacinthacine.[75]



104 105 106

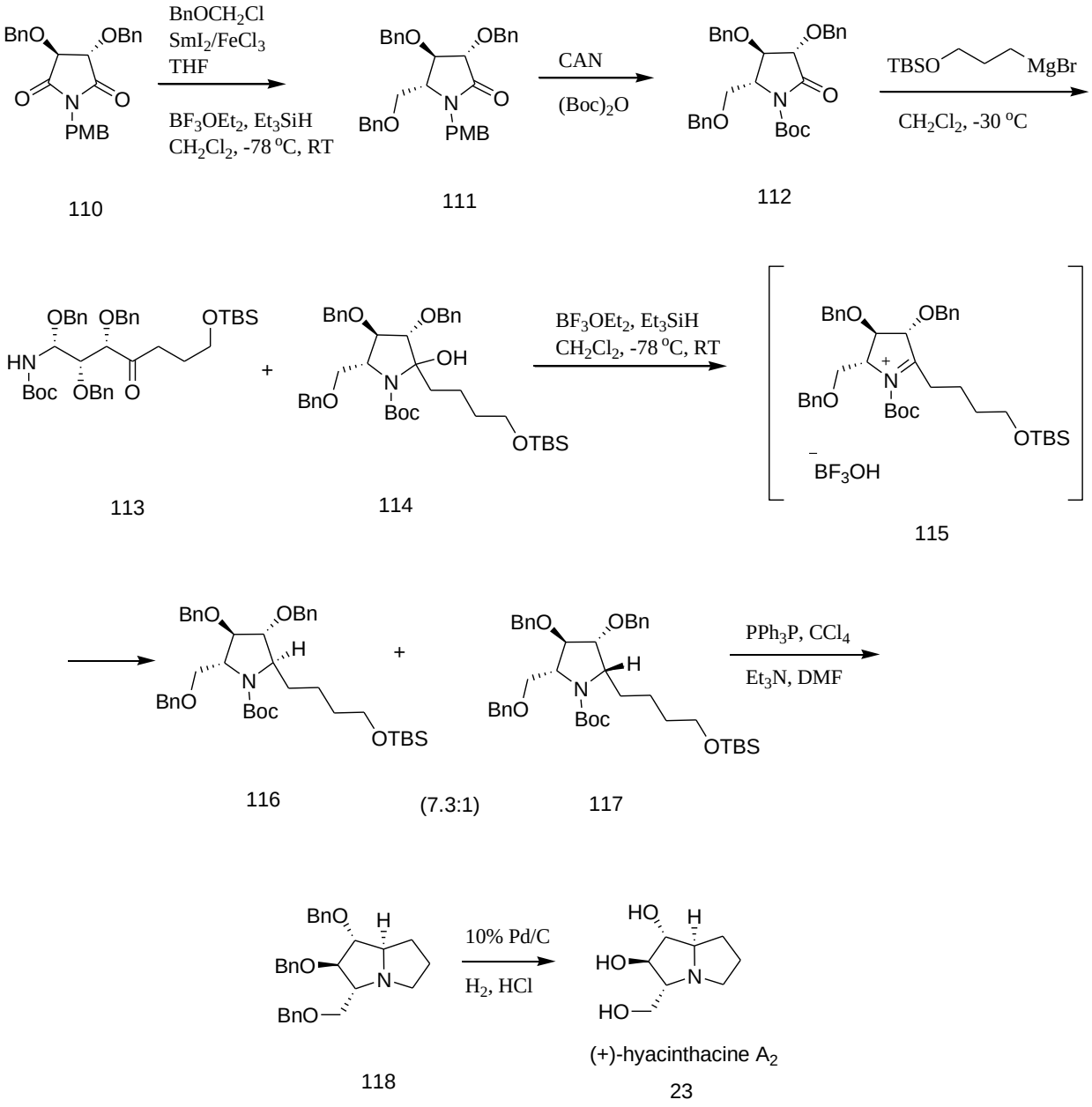
107 108

109 100

i ii

Scheme-1.17

A simple and flexible method for the synthesis of hyacinthacine A_2 and A_3 (Scheme 1.18) was reported by Huang et al (2010),[84] using an asymmetric route starting with reductive alkylation of O,O-dibenzyltartarimide as the key transformation (110 to 111).[85]



Scheme-1.18

Intermediate (111) was subjected to Grignard reaction after a protecting group switch,[86] resulting in a mixture of the open chain system (113) and the required cyclic tautomeric enol form (114).[87]

A second reduction step resulted in two aminols (116 & 117) in diastereomeric ratio of 7.3:1, with the advantage of cleaving the BOC protecting group in the one pot. Treatment of the major diastereomer (116) with triphenylphosphine in triethylamine and carbon

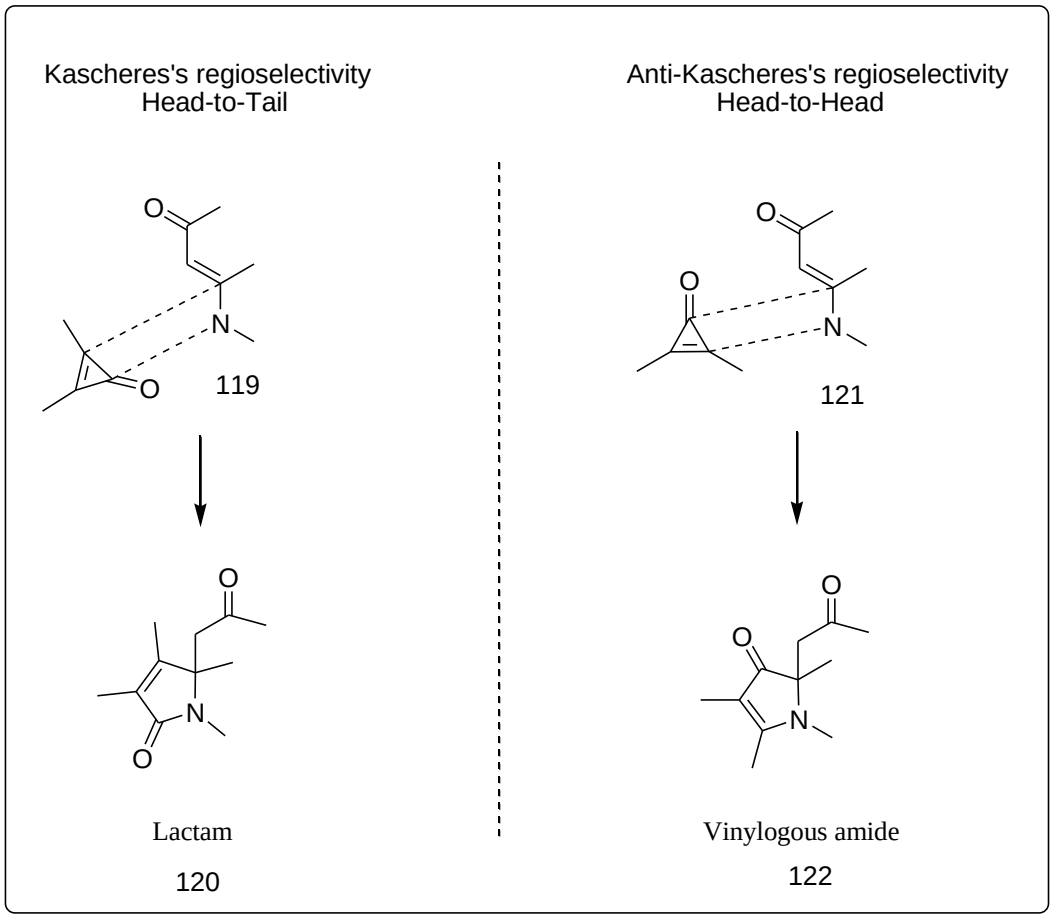
tetrachloride resulted in cyclisation.[46, 88-90] Further reduction with palladium on carbon gave the final target hyacinthacine A_2 (23).

This thesis will later be concerned with the development of a cyclic imine and cyclopropenone cycloaddition based route to indolizidines and pyrrolizidines. A survey of other cyclopropenone or imine cycloaddition methods is therefore included.

Other cyclopropenone or imine cycloaddition routes to indolizidines and pyrrolizidines.

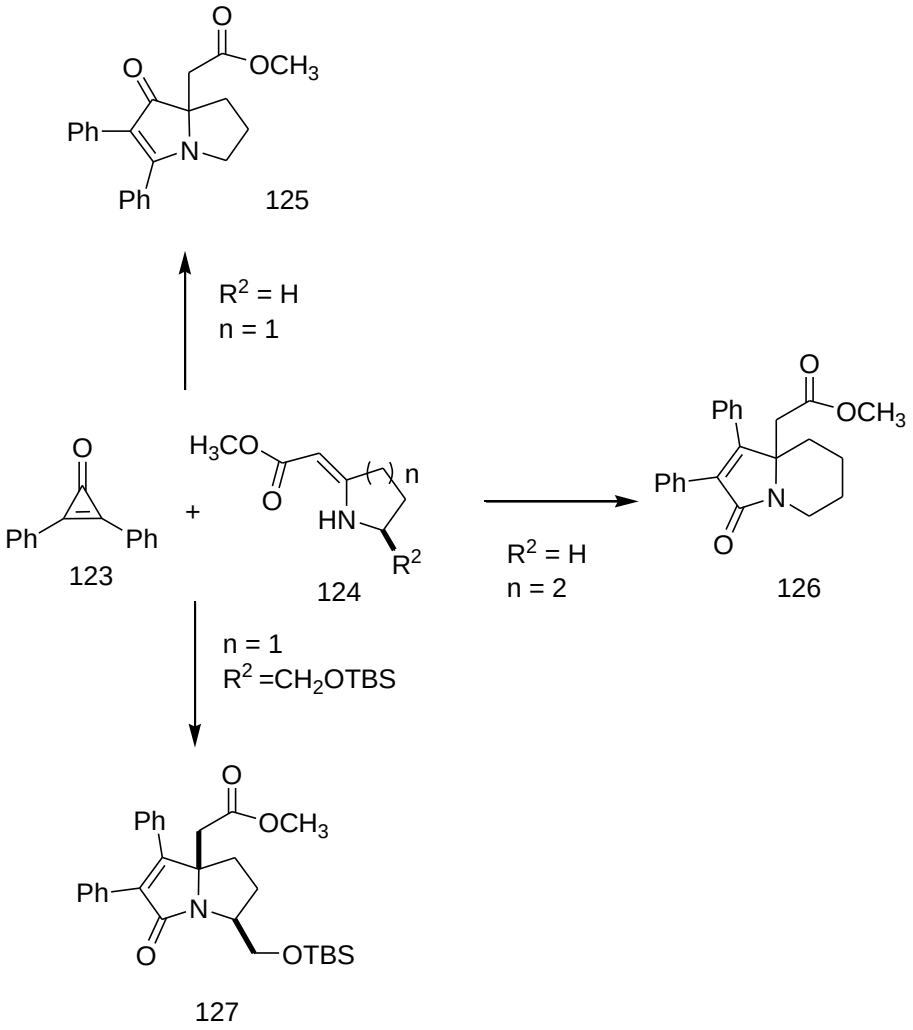
A cycloaddition strategy was reported for the construction of bicylcic systems by Cunha et al (2007).[91] They used cyclopropenones and cyclic enaminones in an aza-[3+2] cycloaddition reaction for the construction of indolizidine and pyrrolizidine bicyclic systems.[92-94]

The work of Cunha built upon previous literature reports by Kascheres for the reaction of diphenyl cyclopropenone with primary and secondary acyclic enaminones [95, 96] for the synthesis of functionalised head to tail and head to head regiochemistry, a process that is summarised in Scheme 1.19.[96-98]



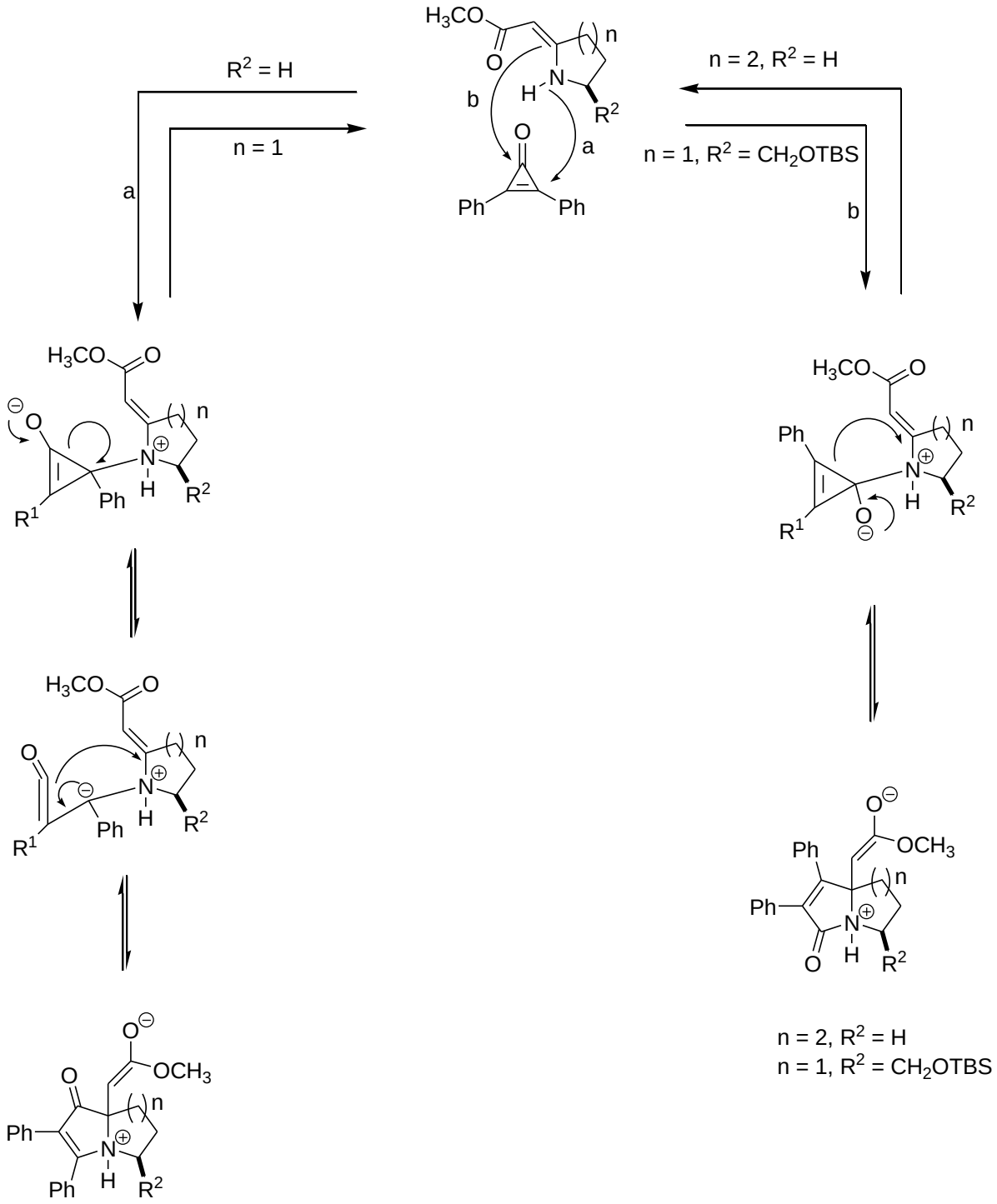
Scheme-1.19

Cunha et al (Scheme 1.20) started with the reaction of five and six membered systems (124) with commercially available diphenyl cyclopropenone (123). The pyrrolizidine bicyclic core was formed in very good yields. The regiochemistry of the addition product was assigned based on NMR studies and the correlation involving the α-methylene of $CH_2CO_2CH_3$ and the carbonyl from the cyclopropenone and indicated the opposite to the expected[96-100] regioisomer, giving the *anti* Kascheres head to head vinylogous amide structure (125), in the case of R^2 = H and the expected[99, 100] head–to–tail lactam product with R^2= CH_2OTBS (127). Once the regiochemistry was confirmed the authors tried to extend the chemistry towards indolizidine bicyclics, where they saw the regiochemistry leading again to a lactam (126).[99, 100]



Scheme-1.20

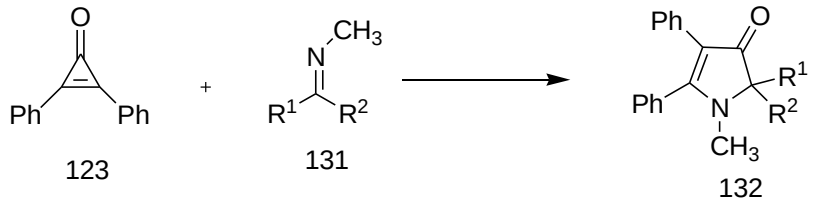
The suggested mechanistic details allowing for the formation of different regioisomers is shown below in Scheme-1.21. The reaction for formation of 125 was rationalised as ionic step-wise process, as shown by pathway (a) in Scheme 1.21, initiated by the attack of nucleophilic nitrogen in the enaminone at the vinylic carbon (see pathway a scheme 1.21). In pathway (a), attack at the vinylic carbon followed by 5-exo-trig cyclisation via Micheal reaction resulted via the head to head approach for the enolate of (125), with n=1. The second pathway (b) (favoured by the presence of more flexible six membered ring where n=2 or a C-5 substituent) causes a sterically hindered environment around the nucleophilic nitrogen of the cyclic enaminone, which favoured the attack at carbonyl carbon via head to tail approach shown in pathway (b) of scheme 1.21 for the formation of products (126) and (127).[91]



Scheme-1.21

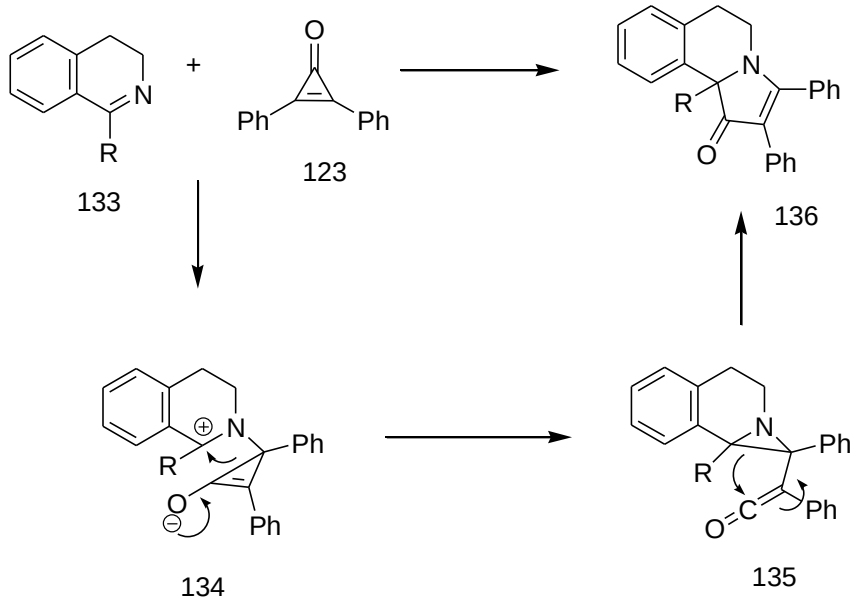
Reactivity of Imines with cyclopropenones:

Eicher et al, did the pioneering work on the reactivity of imines with diphenylcyclopropenone (123). Diphenyl cyclopropenone (DPP) (123) was reacted with an acyclic ketamine (131) which resulted in substituted pyrrolines (132) in very good yields. The reaction was presumed to be a [3+2] cycloaddition, at least in the formal sense.



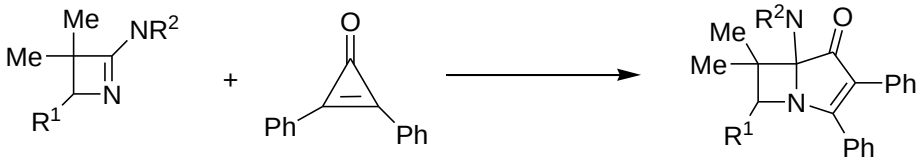
Scheme-1.22

This work was further developed by Eicher himself with the study of reactivity of DPP with cyclic imines (133). This is further discussed in later sections concerned with the reactivity of cyclopropenones (chapter-2, section 2.6 and section 2.15).



Scheme-1.23

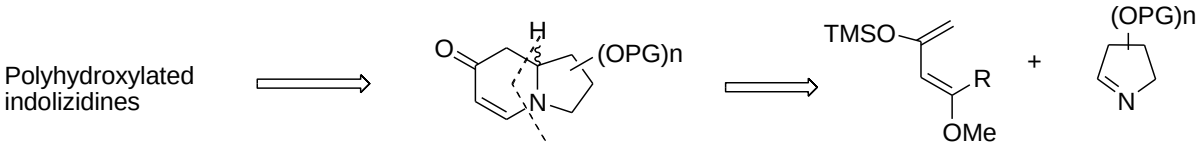
Heimgartner[101] showed that 2-amino-1-azetines (137) react with DPP (123) to give bicyclic pyrrolines (138) (Scheme-1-24).



Scheme-1.24

Whilst cyclic imines have, as discussed above, been used in [3+2] approaches to alkaloids, they have also been used in [4+2] approaches where the imine is added to a diene.

Retrosynthetic strategy:



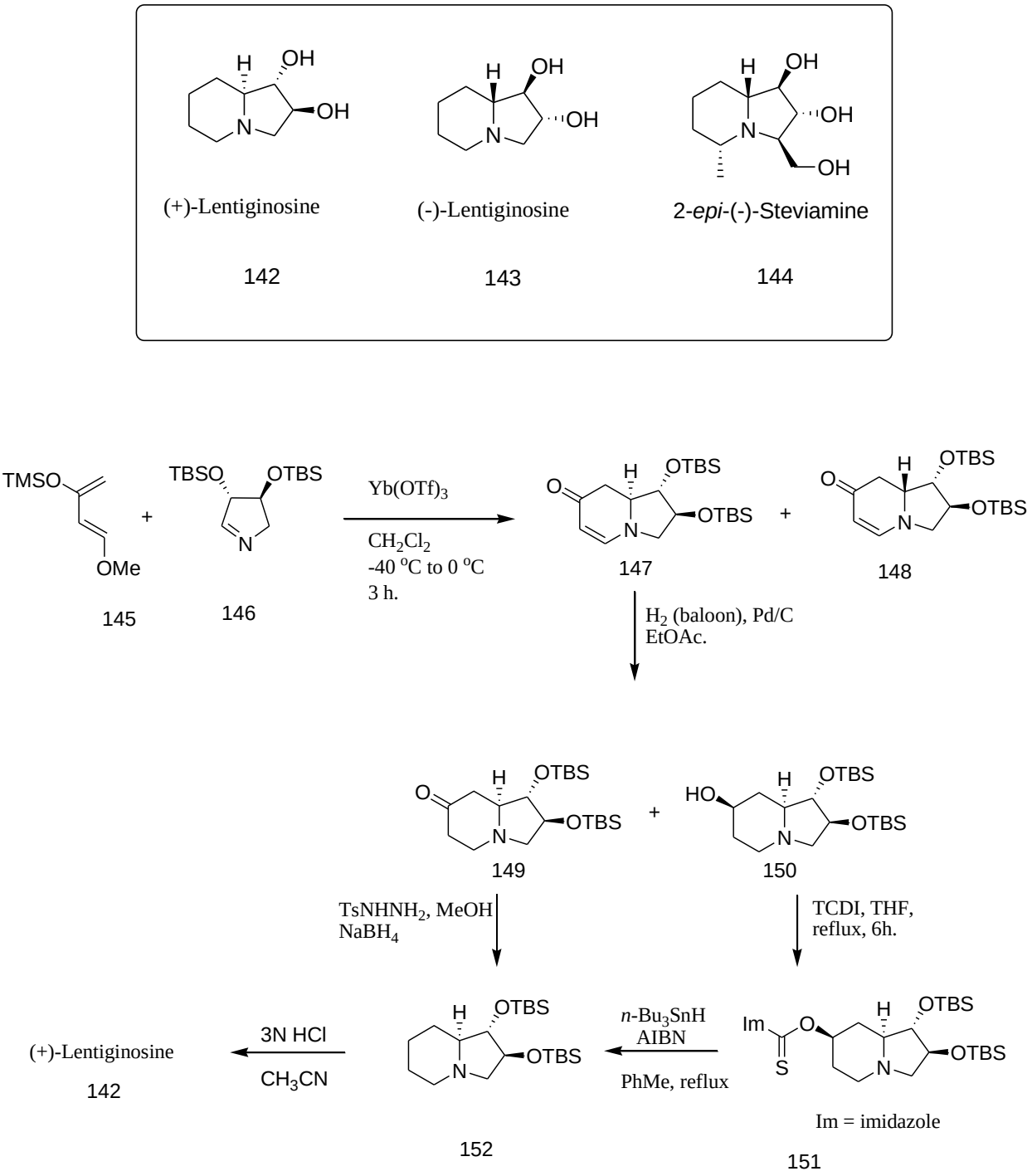
aza-Diels-Alder rxn

139 140 141

Scheme-1.25

In this strategy, intermolecular [4+2] aza-Diels-Alder reaction of an electron rich Danishefsky type siloxydiene and polyhydroxylated cyclic aldimines would lead to enaminones (139) which would then lead to the target indolizidine (Scheme-1.25), the stereochemistry of which could be controlled, leading to the technically challenging indolizidine system in single operation.[102-105]

The potential of this methodology is shown by a synthesis of the polyhydroxylated indolizidines (+)-/(-)-lentiginosine (142 & 143) and (-)-2-epi-steviamine (144).[106-109] as detailed below in Scheme-1.26.



Scheme-1.26

Trans-(3S,4S)-di-*O*-TBS protected pyrrolidine imine (146)[110] was reacted with a siloxy diene (145) in the presence of $Yb(OTf)_3$ catalyst. A range of cyclic imines were studied for the stereochemistry of the resulting enaminone bicyclic system. The imines were varied using different protecting groups on hydroxyl, including silyl (TBS) ether, benzyl ether and (MOM) methoxy methyl acetal and it was noted that all afforded *trans* H1 and H8a adducts with

high diastereomeric ratios. The bulkiness of the oxygen protection close to the imine carbon-nitrogen double bond was found to have a significant effect on the stereochemical outcome.

The vinolgous amide moiety (enaminone 147) was subjected to hydrogenation over palladium-carbon to yield a mixture of keto (149) and secondary alcohol compounds (150). The keto compound (149) was converted to TBS protected lentiginisone (152) by reduction via its tosyl hydrazine using sodium borohydride. The C7 hydroxy of the secondary alcohol (150) was eliminated through a Barton-McCombie radical deoxygenation method,[111, 112] which involved etherification with thionocarbonyl-1,1-diimidazole (TCDI) followed by radical reduction using tributyl tin hydride and AIBN as radical initiator. The resulting products were deprotected using 3N HCl resulting in the target lentiginosine (142).

Aims*:*

The brief introduction about aza-sugars, indolizidine and pyrrolizidine alkaloids and their biological importance clearly gives the importance of these natural products and their analogues in the study of various glycosidases inhibitors which in turn play a key role in various diseases like HIV, cancer and lysosomal storage disorders. This provides the evidence for exploring new and versatile methods for the synthesis of these materials.

With the previous work of the group on the reactivity of diphenylcyclopropenone with simple cyclic imines, we sought to extend the methodology towards the synthesis of aza-sugar natural products like castanospermine (indolizidine) and hyacinthacine (pyrrolizidine). Our methodology as shown in the above section involves the use of two key intermediates: cyclic imines and cyclopropenones. With this our aim was:

1) Synthesise a range of cyclic aldimines from sugars with appropriate stereochemistry.

2) To synthesise the second key intermediate, the cyclopropenones with and without substitution.

3) Study the reactivity of the above synthesised cyclic imines with the cyclopropenones and the further reactions of the products towards the synthesis of indolizidine and pyrrolizidine alkaloids like castanospermine and hyacinthacine.

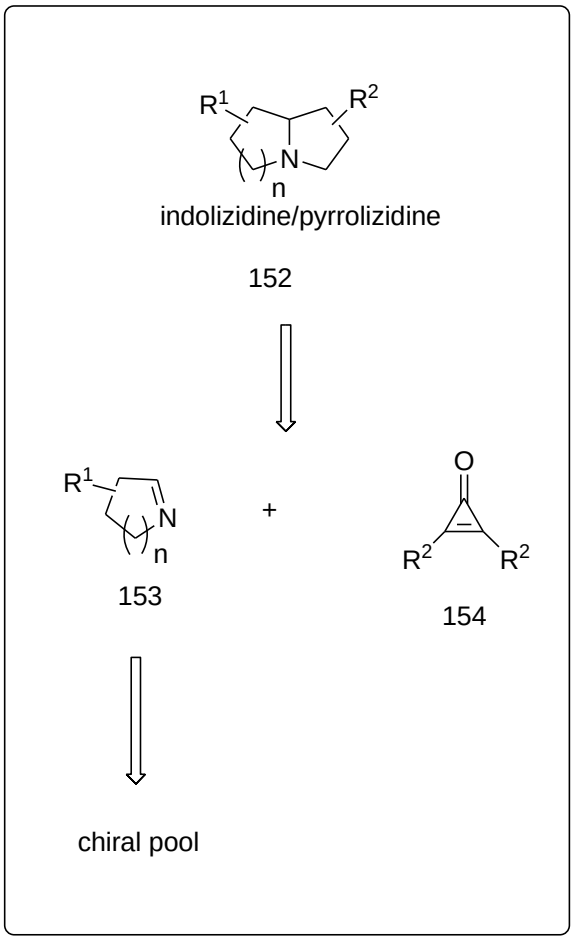
2-Discussion.

2.1 Studies towards the construction of azabicyclic systems leading to indolizidine and pyrrolizidine alkaloids.

Imino sugars/aza-sugars are reported to inhibit the activity of wide range of carbohydrate processing enzymes and affect the function of carbohydrate-recognising proteins.[113] These inhibition properties can be exploited to modify glycosylation of eukaryotic cells. Imino sugars are now being tested as potential therapeutic agents for lysosomal storage diseases and other related diseases.[1, 4] Iminosugars have enormous therapeutic potential in the treatment of a number of diseases such as cancer, viral diseases and diabetes.[4, 114] The most valuable property of iminosugars is their ability to inhibit glycosidase enzymes. This makes this area a very active area of research in both academia and industry.

There are many methods for the synthesis of indolizidine and pyrrolizidine alkaloids in the literature[7, 19, 115] as was briefly reviewed in the introduction. In this thesis the focus will be on the synthesis of indolizidine and pyrrolizidine alkaloids using a methodology based on the previous reported reactivity of electron rich imines with diphenylcyclopropenone.[116-120] The methodology[117, 121-124] (Scheme 2.1) was developed in our lab but much of the work done prior to this thesis used commercially available diphenylcyclopropenone (DPP) and simple imines.[125-127] This thesis has the aim of extending the methodology (scheme 2.1) towards the synthesis of aza-sugar natural products and so includes more complex imines and cyclopropenones other than DPP.

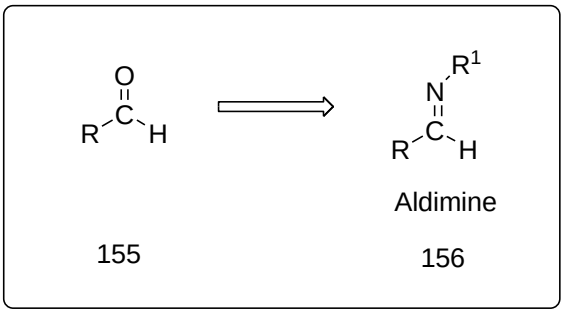
By varying the size of the heterocyclic ring (153) and by using substituents with appropriate stereochemistry on the imine ring and an appropriately substituted cyclopropenone ring this would lead us to the basic structure of the targeted indolizidine/pyrrolizidine alkaloids. The key strength of the methodology is the ability to alter the groups on the five membered ring contributed by the cyclopropenone, which are easy to synthesise from literature procedures,[95, 128, 129] and hence offer flexibility in the R^2 groupings.



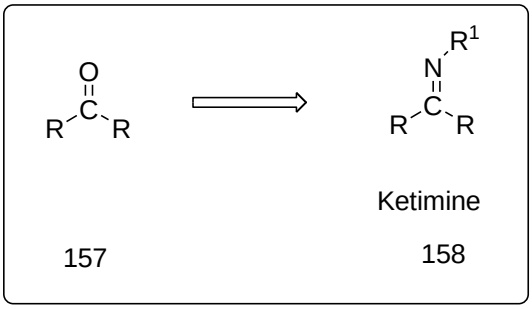
Scheme-2.1

The cyclic imines required are often sugar-like and thus we could utilize carbohydrates as starting materials and as sources of chirality. The next section focuses on the synthesis of six and five membered cyclic imines and has a particular focus on carbohydrates, although other imines will also be discussed.

Imines[130] are chemical compounds or functional groups containing a carbon-nitrogen double bond. Imines are related to carbonyl compounds (aldehyde or ketone) via replacement of the oxygen with an NR^1 group, shown in Schemes 2.2 and 2.3 below. We focussed upon the synthesis of cyclic aldimines and the synthesis of these is discussed next.



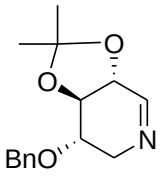
Scheme-2.2



Scheme-2.3

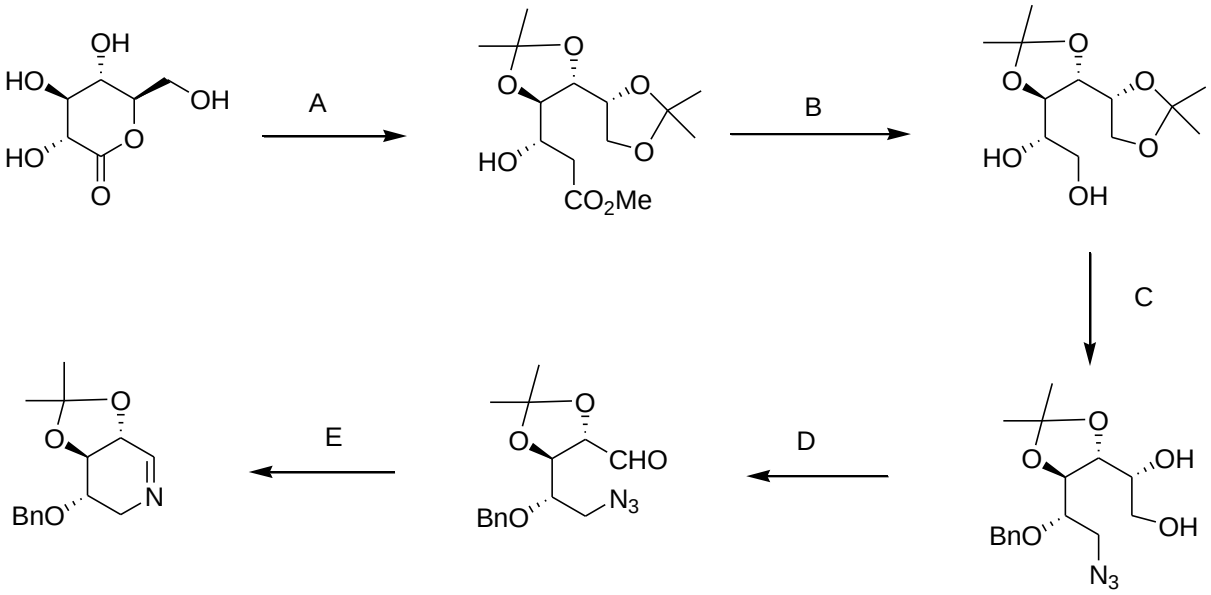
2.2 Synthesis of six- membered cyclic aldimines:

2.2.1 Synthesis of (3aR,7S,7aR)-7-(benzyloxy)-2,2-dimethyl-3a,6,7,7a-tetrahydro[1,3]dioxolo[4,5-*c*]pyridine:



159

Scheme 2.4 shows the synthesis of the imine:[57]

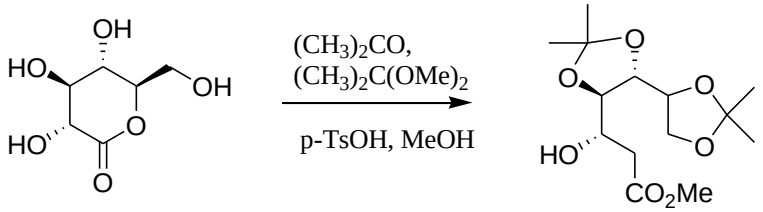


A: acetone, $(CH_3)_2C(OMe)_2$, p-TsOH, MeOH; B: $NaBH_4$, C_2H_5OH; C(i) 1.0 M MsCl, 2,4,6-lutidine, CH_2Cl_2, 0°C. (ii) NaN_3, DMF, 85°C. (iii) NaH, BnBr, THF. (iv) 80% AcOH, 20°C. D: $NaIO_4$, CH_2Cl_2-H_2O, 20°C. (E): PPh_3, THF, 55°C.

Scheme-2.4

Step A:

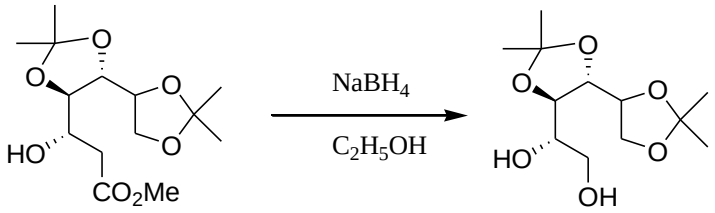
Acetonides are very common protecting groups for 1,2- and 1,3-diols, due to their great stability to a range of basic, nucleophilic and redox conditions making them excellent protecting groups in multistep synthesis with sensitive groups.[131] Under kinetic control glucanolactone (160) underwent selective acetonation at the primary alcohol to give the 1,3-acetonide and later with acetone to give the fully protected acetonide.The carboxylate was methylated with the methanol used as solvent under acidic conditions. The reaction took 48 hours for completion and gave a 73% yield of compound (161). The product obtained was fully consistent with that reported in the literature.[132]



160 161

The stereochemistry can be controlled by maintaining anhydrous conditions, as the glucanolactone converts to gluconic acid in the presence of water, changing to the *syn*-diol. The stereochemistry of the hydroxyls are retained in this reaction, as reported in the literature.[59]

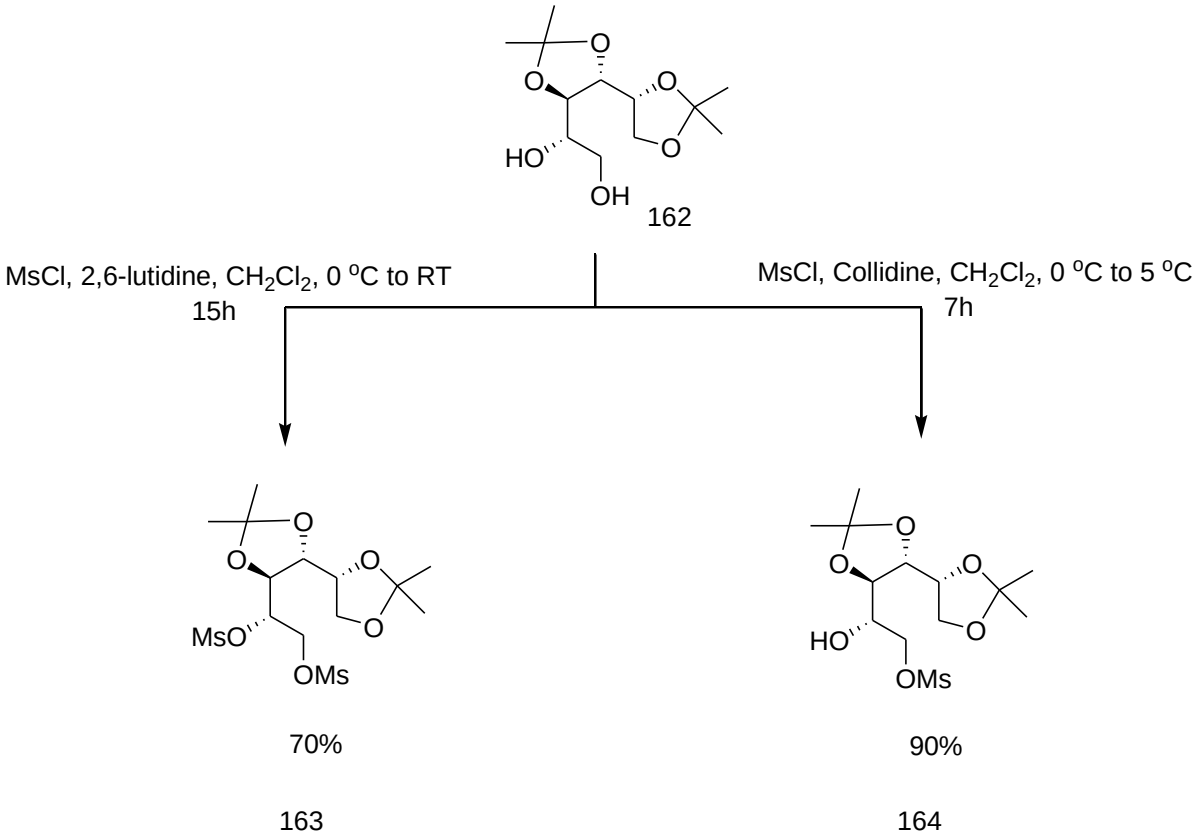
Step B:



161 162

The diacetonide (161) was reduced using sodium borohydride, during which the ester was reduced to primary alcohol (162). The reaction was clean and the procedure was exactly as reported in the literature.[132] The structure of the product (162) was confirmed by ^{1}H NMR spectroscopy which confirmed the loss of ester methyl at 3.84 ppm. The reaction proceeded with a good yield of 82%.

Step C:



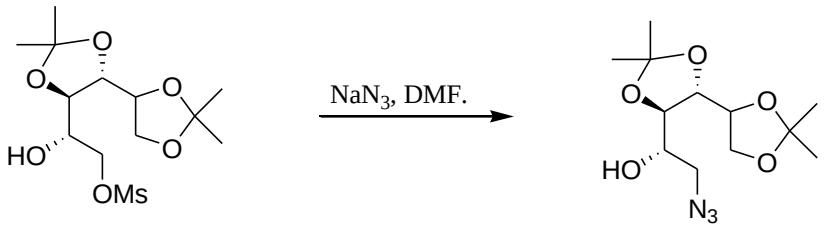
Scheme-2.5

This reaction was reported to be regioselective for the mesylation of the primary alcohol over the secondary,[59] but when the diol (162) was subjected to mesylation under conditions reported in the literature,[133] we found the dimesylate (163) as the major product. Thus a milder base was selected and the reaction mixture was left in the fridge after the addition of mesyl chloride and 2,4,6-lutidine.[134-136] It was observed that time was crucial factor; dimesylate formation increasing after 7 hours reaction. The product (164) was confirmed by ^{1}H NMR spectroscopy, the presence of monomesylate being confirmed by the presence of mesylate methyl at 3.11 ppm as a singlet. The rest of the molecule was intact with the four methyls of the acetonides and an alcohol group. The data obtained was consistent with the literature.[133]

Step D:

The monomesylate compound (164) obtained from the above step was substituted with an azide, using sodium azide in DMF. The reaction was clean and went smoothly. The product (165) was obtained in good yield (90%) and the data was consistent with the literature.[133] The presence of the product was confirmed by both IR and ^{1}H NMR spectroscopy. The NMR

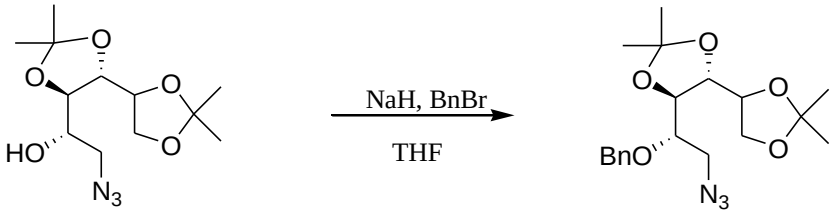
spectrum indicates the clear loss of the mesylate methyl group at 3.11 ppm. The IR spectrum confirms the presence of azide with a strong peak at 2200 cm^{-1}.[59]



164 165

Step E:

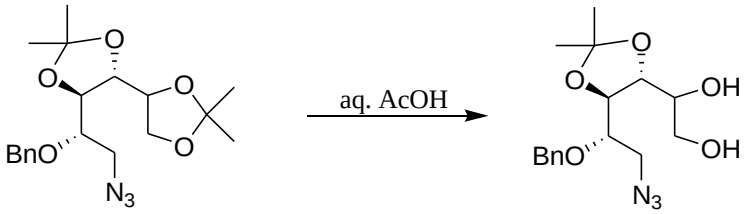
The free hydroxyl was benzyl protected using benzyl bromide and sodium hydride as base. Sodium hydride is reported to be the best base for the deprotonation of alcohols in sugar moieties.[131] The product (166) was obtained in good yield and the ^{1}H NMR data was consistent with the literature.[133] Five aromatic protons in the range of 7.38 to 7.30 ppm and two benzylic protons at 4.65 ppm in the ^{1}H NMR spectrum confirmed the benzylation. The four acetonide methyls were observed at 1.43, 1.42, 1.38, 1.35 ppm.[59, 133]



165 166

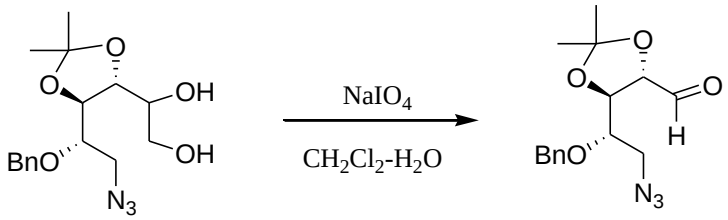
Step F:

The benzylated compound (166) obtained was subjected to hydrolysis which was intended to be regioselective for hydrolysis of the acetonide involving the primary alcohol. The compound was hydrolysed using 80 % acetic acid in water and the required product (167) was obtained after 5 h of stirring at room temperature. A raise in temperature or excess time lead to complete hydrolysis resulting in four free hydroxyl groups. The reaction mass was purified immediately by column chomatography to stop further hydrolysis. The product (167) was characterised by ^{1}H NMR spectroscopy, where the loss of two methyl groups of this acetonide indicated the deprotection of one acetonide group. The product was obtained in 48% yield.[59, 133]



166 167

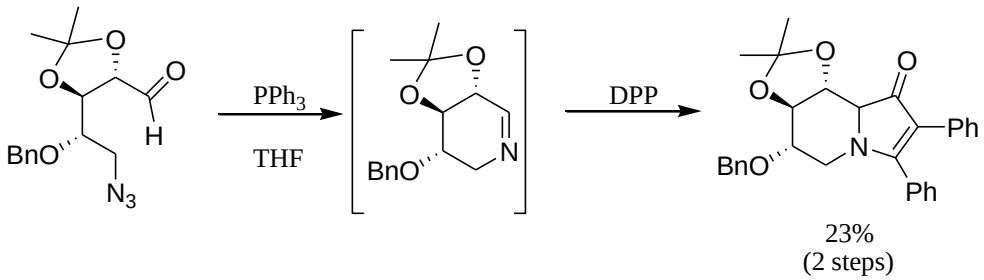
Step G:



167 168

Oxidative cleavage of the vicinal diol (167) with sodium periodate in dichloromethane and water resulted in the required aldehyde (168). The reaction was clean and went smoothly. The product (168) was isolated in good yield (70%) and was characterised by ^{1}H and ^{13}C NMR, IR, spectroscopy. IR spectroscopy showed strong peaks for carbonyl at 1733 cm^{-1}, characteristic of an aliphatic aldehyde and C-H bending at 2987 cm^{-1}. The ^{1}H NMR spectrum confirmed the aldehyde proton at δ 9.76 ppm. The rest of the molecule was intact with a clear acetonide group and benzyl ether.[59, 133]

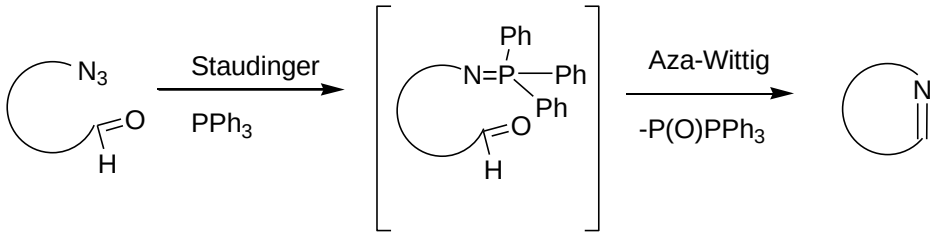
Step H:



168 159 169

Scheme-2.6

The azido aldehyde (168) compound synthesized as described above was subjected to cyclisation using a Staudinger aza-Wittig reaction (Scheme 2.6). The Wittig ylide, an iminophosphorane (see Scheme-2.7), was generated by a Staudinger reaction. Aza-Wittig cyclisation[137-140] of the ylide resulted in the cyclic aldimine (159). Attempts to isolate the imine were unsuccessful, so the imine was reacted with diphenylcyclopropenone *in situ* to give the desired product as shown in the Scheme above. Careful monitoring of the reaction showed loss of azide, indicating successful Staudinger reaction and loss of aldehyde, indicating successful aza-Wittig reaction.

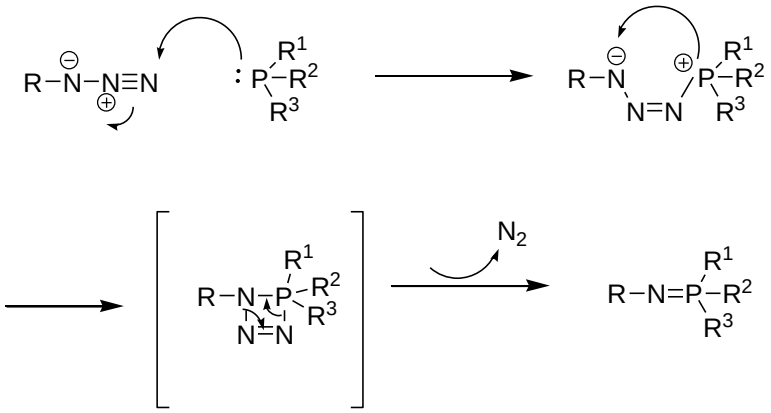


(iminophosphorane)

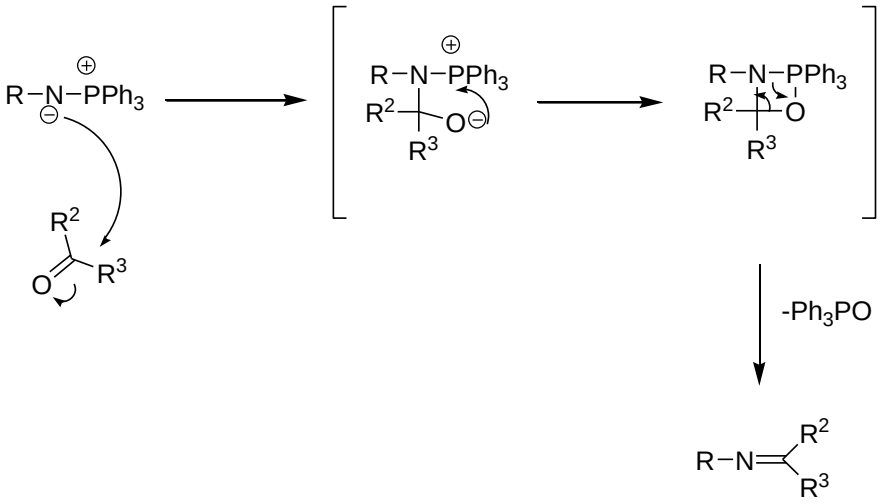
Scheme 2.7

Mechanisms:

Staudinger Reaction:[141, 142]

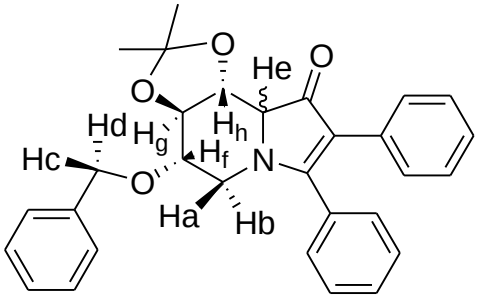


Aza-Wittig mechanism:[143]



Attempts were made to optimise the reaction conditions for the imine synthesis, but these were mostly unsuccessful. The reaction mixture after the consumption of triphenylphosphine (indicated by IR spectroscopy for loss of azide) was heated at 55 °C, overnight in the presence of diphenylcyclopropenone, resulting in the 23% yield of addition product.

The product (169) was characterised by ^{1}H and ^{13}C NMR spectroscopy and IR spectroscopy. The characteristic α,β-unsaturated keto group carbonyl was observed at 1704 cm^{-1}.



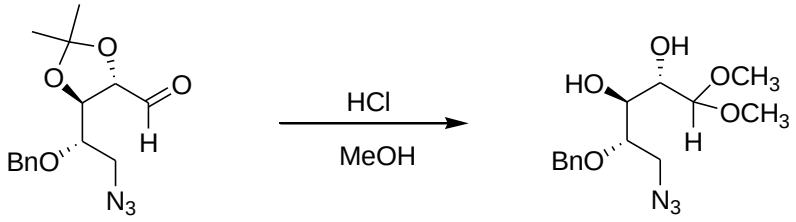
169

In the ^{1}HNMR spectrum the 15 aromatic protons of the 3 phenyl rings were in the range of 7.24-7.46 ppm, which suggests the addition product. The acetonide methyls were observed at 1.54 and 1.37 ppm. The two protons Ha and Hb next to nitrogen were an AX system with one proton appearing at 4.81(1H, dd, *J* =13.3, 5.8 Hz) and another at 2.88 ppm (1H, dd, *J* =13.4, 5.8 Hz), whereas the benzylic protons Hc and Hd were an AM system with one proton at 4.89 (1H, d, *J* =11.8 Hz) and the second at 4.75 ppm (1H, d, *J* =11.8 Hz). This structural assignment was further supported by the ^{13}C NMR spectrum with 3 quaternary

carbons and 9 CH of the phenyl rings. The carbonyl was observed at 168 ppm. Two CH_2 groups in the DEPT 135 appeared at 72 ppm (benzylic methylene) and 41.6 ppm (methylene connected to nitrogen). The two acetonide methyls appeared at 28.8, 28.6 ppm and the two alkene carbons were observed at 151.3 and 111.5 ppm

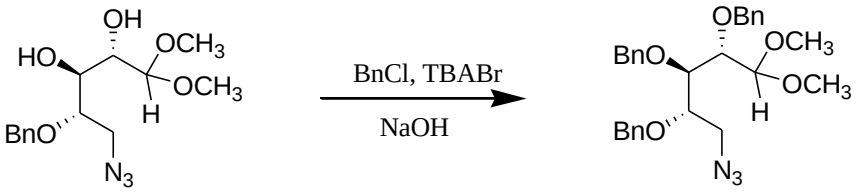
The desired product (169) was formed in only 23% yield and the main problem would seem to be the multistep nature of the transformation - Staudinger, aza-Wittig and cyclopropenone addition all in one. For this reason, other cyclisations were investigated.[144, 145]

It is possible that the *trans* protection of the azido aldehyde compound was one of the barriers to the cyclisation, so we tried to swap the acetonide for benzyl protection. Thus the acetonide (168) was deprotected and the aldehyde protected as the acetalin in one pot, by heating in 2M HCl in methanol.[146] IR spectroscopy indicated the clear loss of the aldehyde peak at 1733 cm^{-1}. The ^1H NMR spectrum indicated the loss of the aldehyde proton at 9.76 ppm, the loss of the two methyls of acetonide at 1.48 and 1.39 ppm and the presence of two additional methyl peaks at 3.95 and 4.10 ppm, was supported by ^{13}C NMR spectroscopy which showed the loss of the carbonyl and the presence of two OCH_3 peaks at 56 and 54 ppm. The mass spectral data further supported the structure.



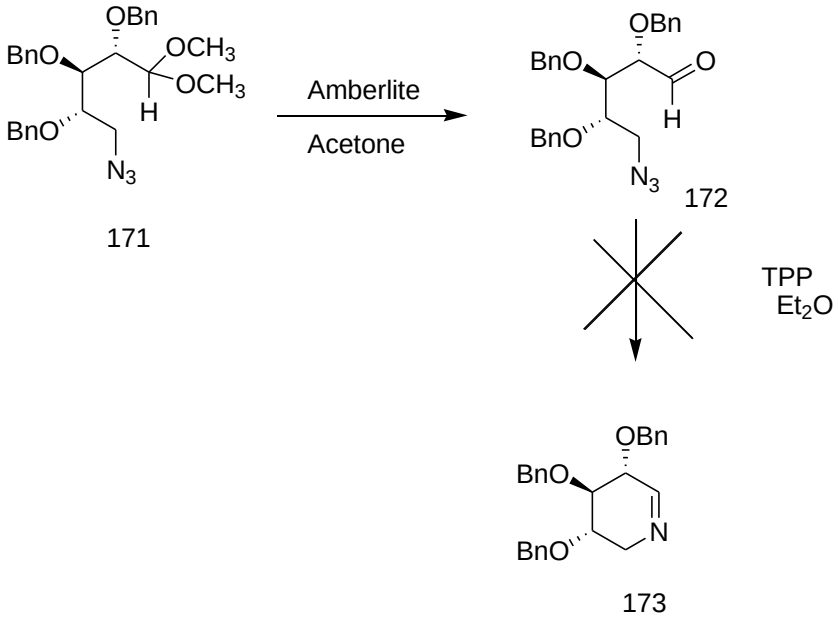
168 170

The diol compound (170) obtained above was subjected to benzylation, using benzyl chloride, aq. NaOH and TBABr as a phase transfer catalyst.[146] The purified compound (171) was characterised by ^1H NMR spectroscopy which showed the presence of three benzyl Ph groups in the range of 7.38-7.29 ppm for 15 H and two extra methylene groups in the range of 4.89 – 4.45 ppm, further supported by ^{13}C NMR spectroscopy in which three benzylic methylene groups appeared at 74.78, 73.63 and 73.36 ppm and the three quaternary carbons of the phenyls at 138.3, 138.2 and 138.0 ppm.



170 171

The final steps in the attempted synthesis of the tribenzylated tetrahydropyridine (173), as shown in Scheme 2.8 below, were acetal deprotection followed by Staudinger / aza-Wittig reactions.[137, 140]



171 173

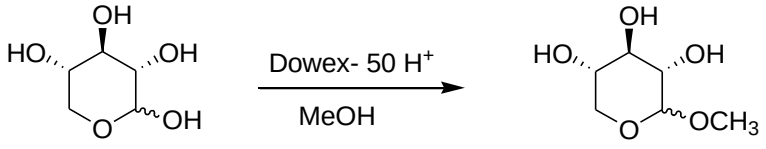
Scheme 2.8

The tribenzylated compound (171) was therefore subjected to hydrolysis to deprotect the aldehyde and subjected to cyclisation using Staudinger and aza-Wittig conditions (Scheme-2.8). The acetal was hydrolysed using Amberlyst (15) H^+ in acetone and the presence of the resultant aldehyde was confirmed by IR spectroscopy, with the carbonyl at 1730 cm^{-1}. The resultant mixture was treated with PPh_3. The reaction was stirred for 3 h and monitored by TLC and IR spectroscopy; this implied that the Staudinger reaction had occurred via the consumption of the azido group. The reaction mixture was then heated at reflux and although only a very weak aldehyde peak was seen, no imine could be detected or isolated after attempted purification by chomatography. Attempts to trap the imine (173) with DPP were unsuccessful, thus other routes to this imine (173) were investigated, as discussed below.

2.2.2 The synthesis of 3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine via a nitrone.[147]

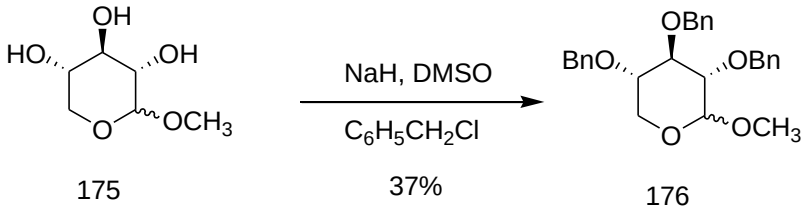
Deoxygenation of nitrones is an important method in organic synthesis for the synthesis of imines. There are various reagents reported for this process in the literature, for example, low valency Ti, P and S species, tributyltin hydride and Pd/C,[148-151] but all have unwanted side reactions, low yields or lack of selectivity. Some reagents were optimised for selectivity like triphenyl phosphine with catalytic Mo which was reported to be chemoselective under mild conditions.[152, 153] Recent literature reports the use of Lewis acids like $InCl_3$, $RuCl_3.xH_2O$, Zn-$AlCl_3$, $Zn(OTf)_2$, $Cu(OTf)_2$,[152-155] with mild conditions and good yields. We were particularly attracted by the method reported by Cividino et al[156] using a sugar based nitrone and tributylphosphine, due to the similarity of the sugar molecules to our ones, the availability of the reagents and the easy to handle reaction conditions. The reported mechanistic investigation of deoxygenation of nitrones to their corresponding imines by Cividino et al using tributylphosphine was limited to five membered cyclic nitrones.[156] We extended this methodology to a six membered system. We synthesized the six membered nitrone (178) based upon a method reported in the literature with some changes as discussed below.[147]

In the first step, the anomeric hydroxy of D-xylose (174) was methylated by heating D-xylose under reflux in anhydrous methanol in the presence of Dowex-50 (H^+) cation resin as shown below.[157] The product (175) was obtained easily by filtering the Dowex resin and distilling off the excess MeOH. The purified product was characterised using ^1H and ^{13}C NMR spectroscopy. The data was not reported in the literature,[157] and thus we attempted to elucidate the ^1H and ^{13}C NMR spectra. The proton NMR spectrum confirmed the presence of both α and β anomeric protons at 5.06 ppm and 4.95 ppm, the presence of two methoxy groups at 3.25-3.23 with the rest of the proton count matching. The ^{13}C NMR spectrum was supportive to the above structure, with α and β carbons at 105 and 100 ppm and two methoxy groups at 56 and 55 ppm. The mass spectrometry confirmed the addition of methoxy with m/z 187 for the sodium adduct of the product. The reaction worked in 61% yield.



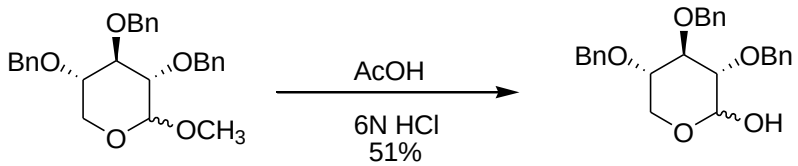
174 175

The tribenzylation of the methyl D-xylopyranoside (175) was achieved as shown below by using dimsyl carbanion as base (generated *in situ* from DMSO and NaH) and benzyl chloride in DMSO.[157] This avoids the side reactions that result from hydrolysis of the methoxy anomeric protection. The reaction was clean and went smoothly, but in only 37% yield. The reaction was exothermic during the addition of the pyranoside material and the crude material after workup was purified by column chomatography to yield a mixture of anomers as expected. The presence of the three phenyl groups was confirmed by the 30 aromatic protons in the ^{1}H NMR spectrum in the range of 7.43-7.31 ppm, for the mixture of anomers and the six benzylic methylene groups in the range of 4.98-4.48 ppm. Mass spectrometry supported the above structure with m/z 457 as the sodium adduct of the product (176).



175 176

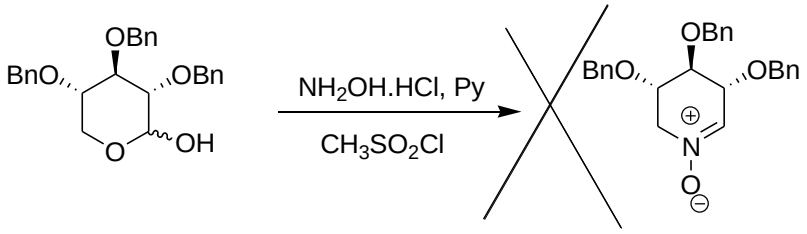
Next, as shown below, the methyl glycoside (176) was subjected to hydrolysis for selective deprotection of the methoxy acetal by acid catalysed hydroxylation using 6N HCl in acetic acid,[158] at 65 °C. The benzyl ether group was stable under these conditions, but if the temperature was increased and reaction times longer than 1.25 h used then a significant reduction in the yield was observed. The reaction was cooled to room temperature, the excess acetic acid was removed by distillation, the reaction mass washed with a base and the resultant crude mixture purified by chomatography to afford pure lactol (177) as a colourless solid. The proton NMR spectrum confirmed the loss of the methoxy group at 3.25 ppm and this was supported by ^{13}C NMR spectroscopy which showed loss of the peak of the anomeric methoxy acetal methyl signals at 56 and 55 ppm. The product was obtained was in 51% yield.



176 177

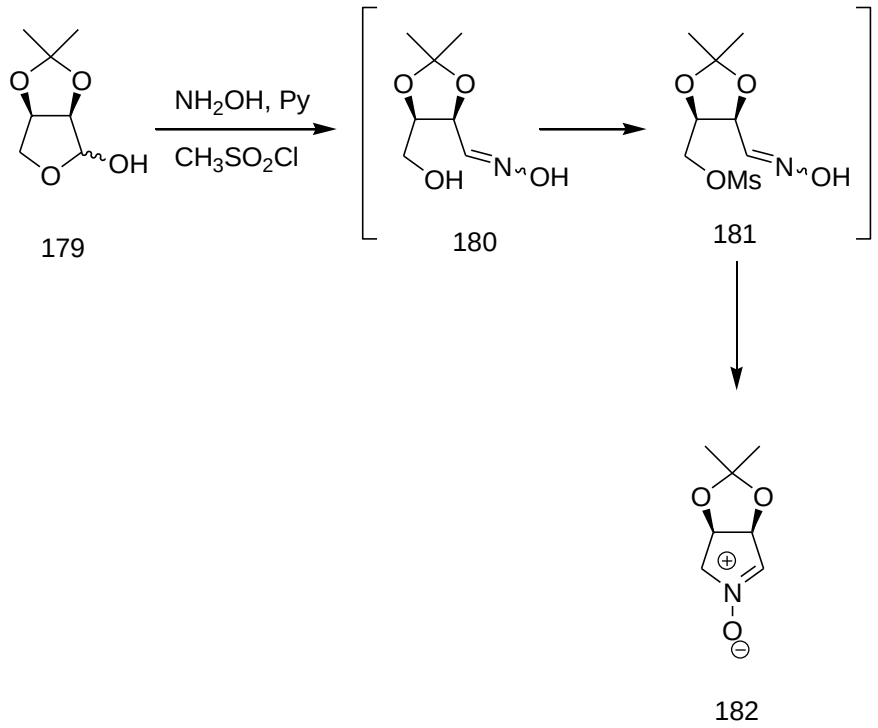
The next step was the crucial nitrogen insertion reaction.

The one-pot procedure reported in the literature by Cicchi et al[144] for the preparation of cyclic nitrones from the corresponding lactols was attempted on the six membered lactol (177) from above. Cicchi et al had limited their study to 5-membered rings. Attempts to synthesize the six membered cyclic nitrone failed (178) when we applied the conditions of Cicchi to our system. Unidentified products were isolated.



177 178

The reported one pot method process used by Cicchi[144] and followed by us is shown in Scheme-2.9.



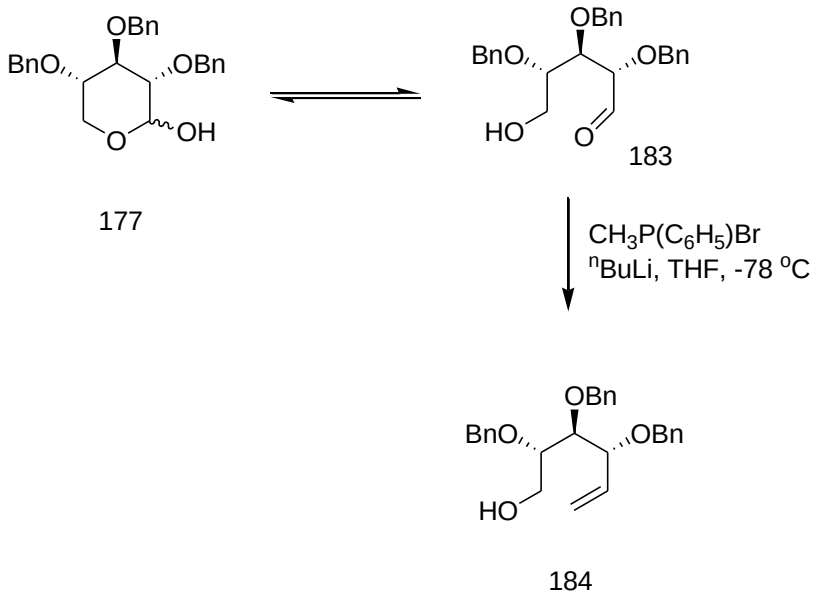
179 180 181 182

Scheme-2.9

Mesylation on the oxime hydroxyl is often a competing process and so we looked at a route which avoids this competitive C-O vs N-O mesylation.

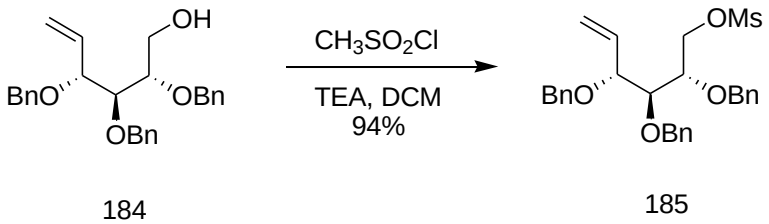
The idea was to convert the hydroxyl to a good leaving group first and then to convert the carbonyl to oxime and use subsequent ring closure to obtain the target nitrone.

For this reason, the aldehyde form of the carbohydrate was converted to an alkene by a Wittig reaction and the alkene reconverted into the aldehyde by oxidation using ozone following a literature procedure,[147] as shown below in Scheme-2.10

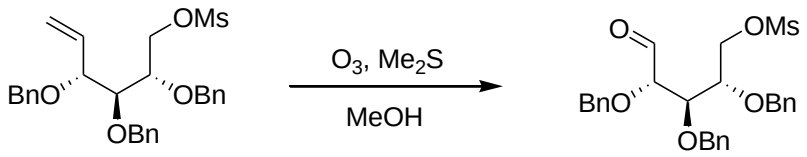


Scheme-2.10

The presence of the alkene (184) was characterised by ^{1}H NMR spectroscopy by the two multiplets in the range of 5.96-5.87 ppm for one H and 5.39-5.31 ppm for the two terminal hydrogens. The presence of the alcohol was confirmed by a peak at 2.27 ppm as a triplet. All of the data was consistent with that reported in the literature.[147] The yield was very dependent upon the purity of the lactol, but yields of 36% were obtained with good purity lactol.

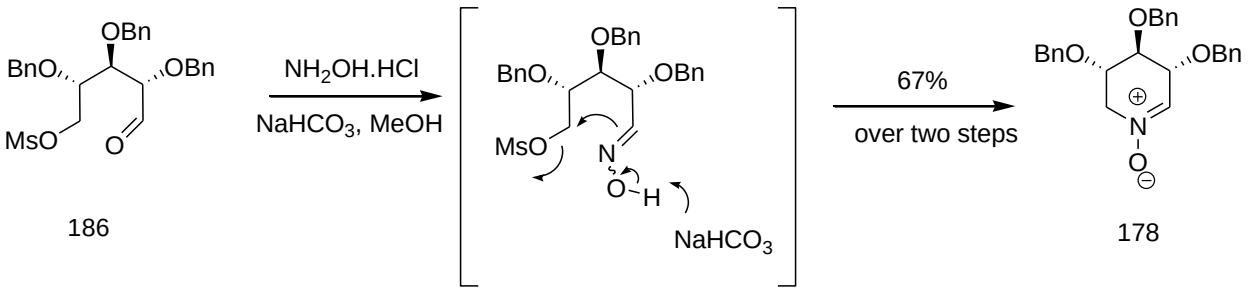


The next step was protection of the hydroxy group with mesyl which was clean and went smoothly, using methanesulfonyl chloride and triethylamine in DCM. The proton NMR spectrum confirmed the product (185) by the new methyl peak at 2.73 ppm and the disappearance of the triplet at 2.27 ppm for the OH group, consistent with the literature.[147]



185 186

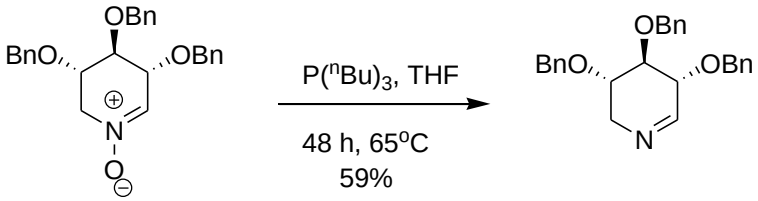
The alkene (185) was next converted back to aldehyde (186) by oxidation using ozone. The crude aldehyde was then treated with hydroxylamine to give the nitrone (178) as shown below.[159-161]



186 187 178

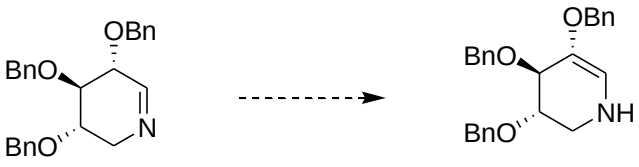
Scheme-2.11

The aldehyde (186), as shown above was reacted with hydroxylamine hydrochloride to give the corresponding oxime (187), which was cyclised in the presence of a mild base to afford the nitrone (178). The key step involves the basic abstraction of the hydroxyl proton and the attack of the lone pair of nitrogen with the subsequent removal of the leaving group mesylate (187). The product was obtained in 67% overall yield and was characterised by ^{1}H and ^{13}C NMR spectroscopy, which showed the presence of the proton connected to the imine at 6.89 ppm in the ^{1}H NMR spectrum, as well as a new CH peak at 137.66 ppm for the nitrone carbon in the ^{13}C NMR spectrum. The final step was to de-oxygenate the nitrone (178) and to do this, the method developed by Cividino[156] was used:



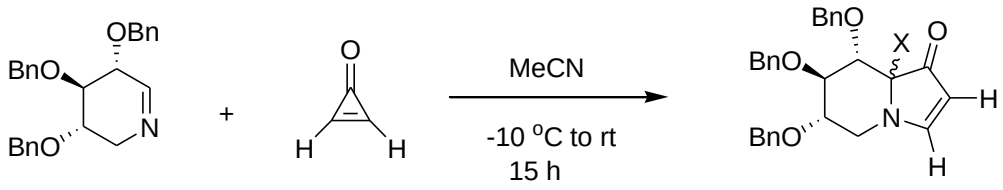
178 173

The reaction mixture was heated at 55 °C, for 24 h and the imine (173) was purified by column chomatography and characterised by ^{1}H and ^{13}C NMR spectroscopy. The imine was not stable for a prolonged period at RT and needed to be reacted as soon as possible. It was observed to be converting to the enamine form (188). The ^{1}H NMR spectrum of the compound indicated the imine proton at 8.07 ppm, 15 aromatic protons in the range of 7.36-7.14 ppm and the protons on the CH_2 next to nitrogen at 3.71 and 3.54 ppm. The assignment of structure (173) was further supported by the ^{13}C NMR spectrum, with the imine carbon of C=N at 161 ppm and the presence of the CH_2 carbon next to the nitrogen observed at 60.9 ppm, plus the expected benzyl CH_2s and three further CH signals. The data supports the formation of the imine. We also ended up with a probable enamine product (188) in cases where the imine was kept for prolonged periods, or where the imine (173) was left unreacted.



173 188

With a protected tri-hydroxyl-substituted imine now formed, the next step was to react it with a cyclopropenone to form indolizidines.



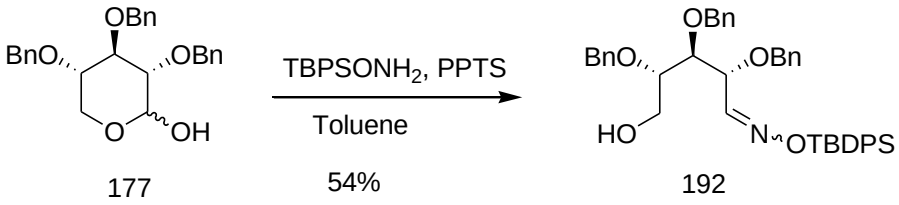
173 189

190 X = H (desired)
191 X = OH (observed)

The imine (173) synthesised as described in the above steps was reacted with the parent cyclopropenone (189) generated *in situ* from the corresponding acetal. The addition of the cyclopropenone was carried out at –10 °C and the mixture allowed to warm to room temperature overnight, resulting in a yellow coloured solution. The reaction mixture was purified by column chomatography and the main product characterised. The ^{1}H NMR spectrum showed the characteristic doublets of the vinylogous amide at 7.78 and 5.28 ppm (J = 3.6 Hz), the presence of the 15 aromatic protons in the range of 7.76 to 7.18 ppm, and the two protons on the methylene next to nitrogen as a multiplet at 3.60-3.52 ppm. Notably, the bridgehead C-H could not be seen. In the IR spectrum, the presence of the carbonyl was seen at 1693 cm^{-1}, as well as an unexpected broad band at 3377 cm^{-1}. The presence of the carbonyl at 202 ppm and the vinylogous amide carbons of the pyrrolidinone ring were observed at 169.21 and 102.5 ppm in the ^{13}C NMR spectrum. The presence of an extra quaternary C at 92.44 ppm gives evidence for the hydoxyl at the bridge head and inferred the above structure (191, X=OH). This was supported by the high resolution mass spectral data which showed an extra 16 mass units. The exact mechanism of the oxidation is unknown. A suggested mechanism is shown in the next section which deals with five membered pyrrolizidine systems, in which this same oxygen insertion process was observed. The product was formed in 20% yield.

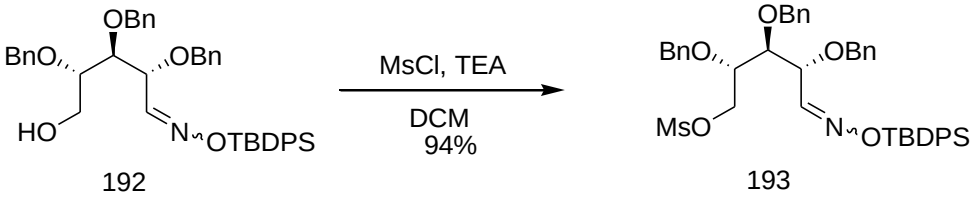
With a successful approach to the polyhydroxylated indolizidine now a possibility, we next attempted to optimise the yield of the nitrone. When looked closely into, the material was being lost in the Wittig reaction, as well as in the cyclisation of the nitrone.[147] The ozonolysis step was also unreliable. We aimed to look into an alternative process that would be more robust and easy. Thus the Wittig reaction was eliminated and instead of transforming aldehyde to alkene and reconverting it via an unreliable ozonolysis, we explored the use of a protected hydroxylamine and subsequent mesylation of the alcohol. Cyclisation to the oxime would then occur where the protection was easy to remove *in situ*.[162] For this purpose we prepared TBPSONH$_2$ by a literature[163] method and it should be noted that the

success of the subsequent reaction depended upon having high purity freshly prepared $TBPSONH_2$.



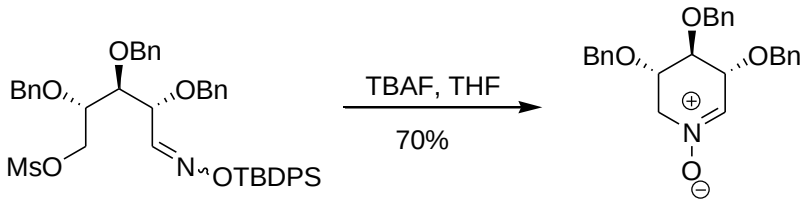
177 192

The lactol (177) was heated under reflux with O-(tert-butyldiphenylsilyl)hydroxylamine and a catalytic amount of PPTS in dry toluene in a Dean-Stark apparatus,[162] the reaction was clean and unreacted starting materials (20%) were recovered, with the product obtained in 54% yield, as a solid. ^{1}H NMR spectroscopy indicated the presence of the extra 10 protons from the phenyl groups in the silyl protecting group in the range of 7.72-7.13 ppm; the new imine proton was in the same region 7.72-7.13 ppm and the tertiary butyl group was present at 1.1 ppm as a singlet for 9 protons. The data was consistent with the literature.[162]



192 193

The mesylation of the alcohol (192) proceeded exactly as described previously, with 94% conversion of alcohol to the expected mesylate (193). The product was characterised by ^{1}H NMR spectroscopy which showed the methyl group of the sulfonyl at 2.83 ppm as a singlet integrating for 3 protons, with the rest of the data mostly unchanged and consistent with the literature.[147, 162]



193 178

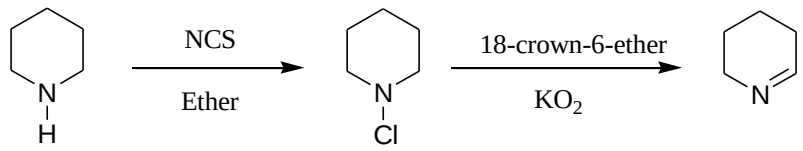
The cleavage of the silyl protection and cyclisation sequence was clean and proceeded smoothly in a short time (30 min). The silyl group was deprotected using TBAF (1M solution

in THF)[162] and the cyclisation occurred as soon as the deprotection was complete. The product (178) was isolated as a white solid (70% yield) and could be stored in the dessicator over a period of weeks at room temperature.

This method has 3 steps less than the Wittig process and is very easy with good reliable yields. The obtained nitrone (178) was deoxygenated as described earlier for the synthesis of the imine and subsequent addition reactions.

2.2.3 Synthesis of 2,3,4,5-tetrahydropyridine

Previous workers in the group had never utilised the parent six-membered ring cyclic imine (196), piperideine so we sought to make it due to its potential use for the synthesis of simple indolizidine alkaloids.



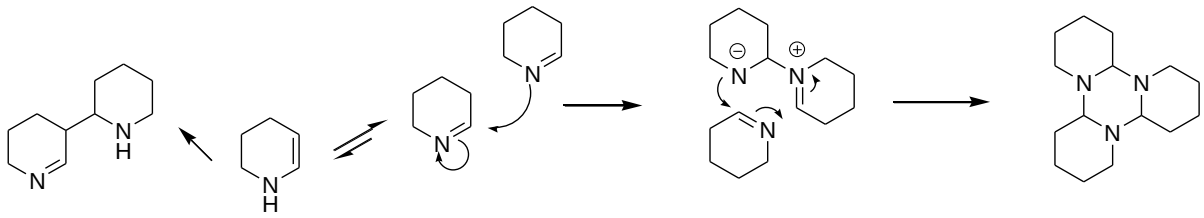
194 195 196

Scheme-2.12

Bachman et al in 1954,[164] reported the synthesis of carbonyl compounds from primary amines, via the conversion of the amine to chloroamine and dehydrohalogenation of the chloramines, to yield the imine which was hydrolysed to give the carbonyl compound.[164] Since then, many methods have been reported for the synthesis of imines by dehydrohalogenation.[165-168] Thus, piperidene (194), shown in Scheme 2.12 was stirred in anhydrous ether solution with n-chlorosuccinimide for 24 h at room temperature,[164, 165] the resulting solution was washed with water and dried over $MgSO_4$. The reaction mixture containing compound (195) in ether was used in the next step without purification.

The synthesis of tetrahydropyridines over the years 1970-1998 has been reviewed by Shvekhgeimer[169] and the most commonly employed method for the synthesis of piperideines was through dehydrohalogenation of the respective chlorinated precursors. We found that the commonly employed conditions of base in protic solvent like KOH/NaOH in ethanol, favoured trimerisiation (Scheme-2.13) of the piperideine (196) together with the formation of unidentified products.[169] We used potassium superoxide which has been found

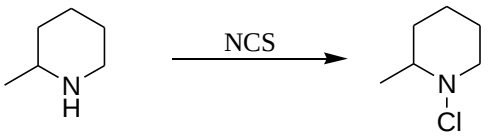
to be a mild and efficient method for the synthesis of piperideine.[165] In our hands, attempts to isolate the imine were unsuccessful, but it was prepared as a solution in diethyl ether and used without incident. Attempts at isolation may well have failed due to the well known trimerisation process (Scheme-2.13), discussed above.



Scheme-2.13

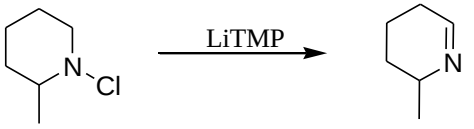
2.2.4 Synthesis of 2-methyl-2,3,4,5-tetrahydropyridine

The formation of imines via this route was also explored with the 2-methyl analogue:



197 198

The method used for the synthesis of n-chloro-2-methyl piperidine (198) was similar to that used for n-chloro piperidine.[165] This material was also unstable for isolation and less stable when compared to N-chloropiperidine; the material turned dark very rapidly when exposed to air.[165] Dehydrohalogenation was performed in a regioselective manner to give the novel cyclic aldimine (199) rather than the alternative ketimine.



198 199

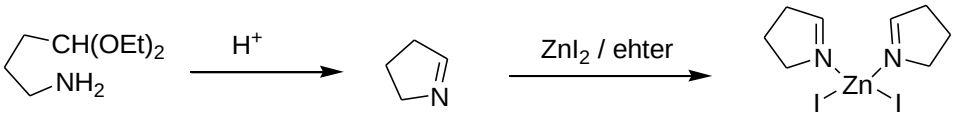
The inspiration for the synthesis of this imine was from the work of Davis on novel imino sugars,[137] which made use of the strong base LiTMP. Elimination of HCl from N-chloro-2-methyl piperidine (198) with hydroxide base would result in the ketimine, which is the more stable, more substituted system. Using a strong and bulkier base like LiTMP resulted in elimination of HCl regioselectively. Attempts to isolate the imine resulted in unidentified

products. The imine was generated at -78 ºC and used immediately in the next step. The elimination occurs by an E2 mechanism. The isolation of a cyclopropenone addition product of the imine confirmed the formation of the imine (see later sections).

Prior to discussing the synthesis of indolizidines from the above simple imines and prior to discussing pyrrolizidine synthesis, the synthesis of 5-membered imines will be discussed.

2.3 Synthesis of 5-membered cyclic imines:

2.3.1 Synthesis of bis (3,4-dihydro-2*H*-pyrrolo-1-yl)di-iodozinc.[170]

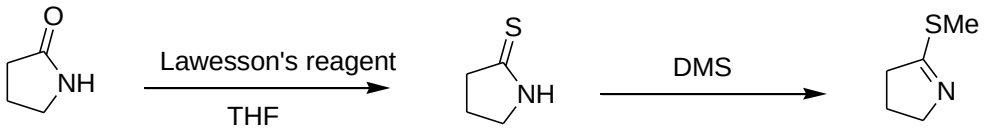


200 201 202

Scheme 2.14

3,4-Dihydro-2*H*-pyrrole (1-pyrroline, (201)) is the parent five membered cyclic aldimine and is reported to be highly unstable and volatile. 1-Pyrroline tends to trimerise in neutral or basic solutions.[171] There are methods reported in the literature for its synthesis such as dehydrohalogenation of n-chloropyrrolidine,[172] similar to the method used for the simple six-membered cyclic imine above, by treatment of ornithine with n-bromosuccinimide[173] and the use of various bases for this dehydrohalogenation have been reported.[110] The reaction of diamine oxidase on 1,4-diaminobutane has also been reported.[174] We attempted to follow a method where the imine is stabilised as a Zn complex and regenerated by a simple basic wash. The methodology is as shown in the above Scheme 2.14. Acid hydrolysis of 4-amino butanal diethylacetal (200) with 2M HCl in dry diethyl ether resulted in 1-pyrroline.[170] The generated 1-pyrroline (201) was complexed with zinc iodide. Metal co-ordination of the imine occurred at the nucleophilic nitrogen and resulted in a grey solid (202), which was crystallised from a chloroform and hexane mixture. 1-Pyrroline (201) was liberated using a base in chloroform or a catalytic amount of base in the reaction mixture for the slow release of the imine. The reactions of this and other cyclic imines with cyclopropenones will be discussed in a separate section later as many common features are shared.

2.3.2 Synthesis of 5-(methylthio)-3,4-dihydro-2*H*-pyrrole



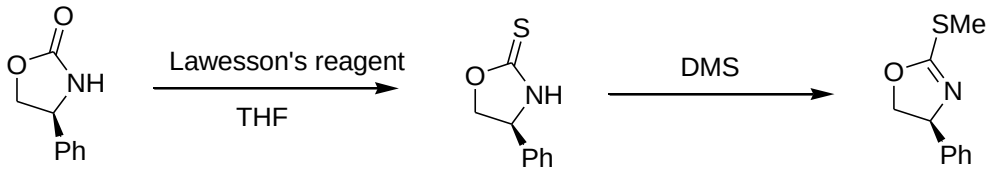
203 204 205

Scheme 2.15

The thiolactam[127] (204) was generated by thionation of pyrrolidine-2-one (203) using Lawesson's reagent in anhydrous THF. Lawesson's reagent[175] was used in preference to other thionating reagents like Davy's reagent, Heimgartner's reagent, phosphorus pentasulfide combined with sodium carbonate due to the availability of the reagent,[175-178] high yields of the product, easy handling and easy workup of the reaction mixture and mild reaction conditions. The reaction was monitored by TLC and the product[127, 179] was obtained in 90 % yield.

Alkylation of the thiolactam using dimethyl sulphate (DMS)[180] gave the corresponding imine[181] (205) in 32% yield. DMS was used for the alkylation in DCM with potassium carbonate as the base. The resulting solution was dried and concentrated to yield the desired product (205) as shown in Scheme 2.15, above. This imine has been used many times in the group before, but we hoped to react it with cyclopropenones not previously used before.

2.3.3 Synthesis of (S)-4-benzyl-2-(methylthio)-4,5-dihydrooxazole:



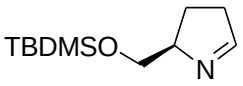
206 207 208

Scheme 2.16

The same approach was applied to the synthesis of an oxazolidinone derived imine (208). Lawesson's reagent was used as the thionating agent.[175] Attempts to isolate the imine (208) were unsuccessful and the imine (208) was used in subsequent reactions (see later) in crude form.

2.3.4 (R)-2-((tert-*butyldimethylsilyloxy*)methyl)-3,4-dihydro-2H-pyrrole:

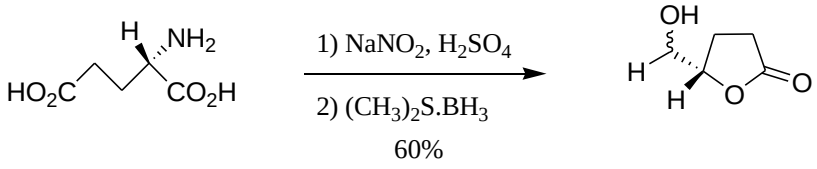
Imine (209) was targeted due to its synthesis in asymmetric form being known[182, 183] and because it would provide the CH_2OH group present in many natural products with biological activity.



209

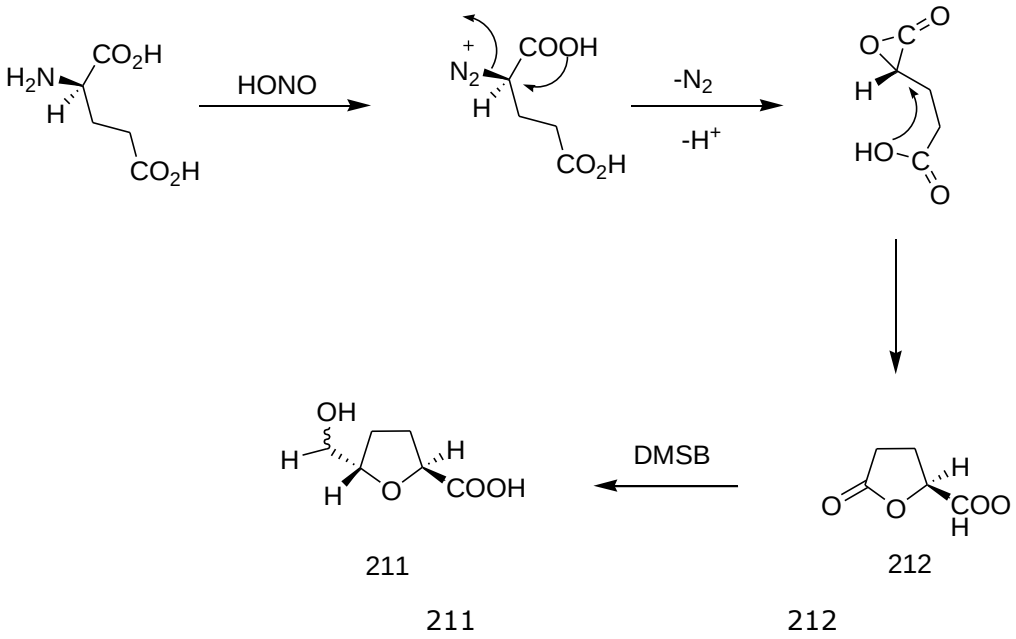
The strategy used for the synthesis of this imine (209) was the generation of aldehyde and azide functional groups and their subsequent cyclisation by Staudinger and aza-Wittig reaction. The multistep synthesis started with L-glutamic acid (210) to generate the R-enantiomer selectively. The imine thus generated was stable for two weeks when stored under nitrogen below -18 °C. The reactivity of the imine with cyclopropenones is discussed later in section 2.16. The multi step synthesis of the imine is discussed below, but largely followed a published literature[182, 183] procedure over 8 steps;

Step 1:



210 211

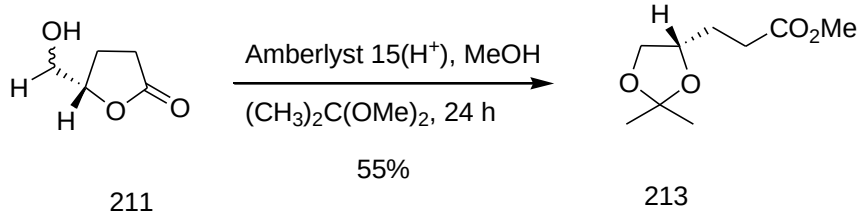
The hydroxymethyl dihydrofuranone (211) was prepared starting from L-glutamic acid.[184] The method involved lactonisation of glutamic acid and further reduction of the lactone using borane dimethylsulfide complex. The mechanism involved is shown below in Scheme-2.17.



Scheme 2.17

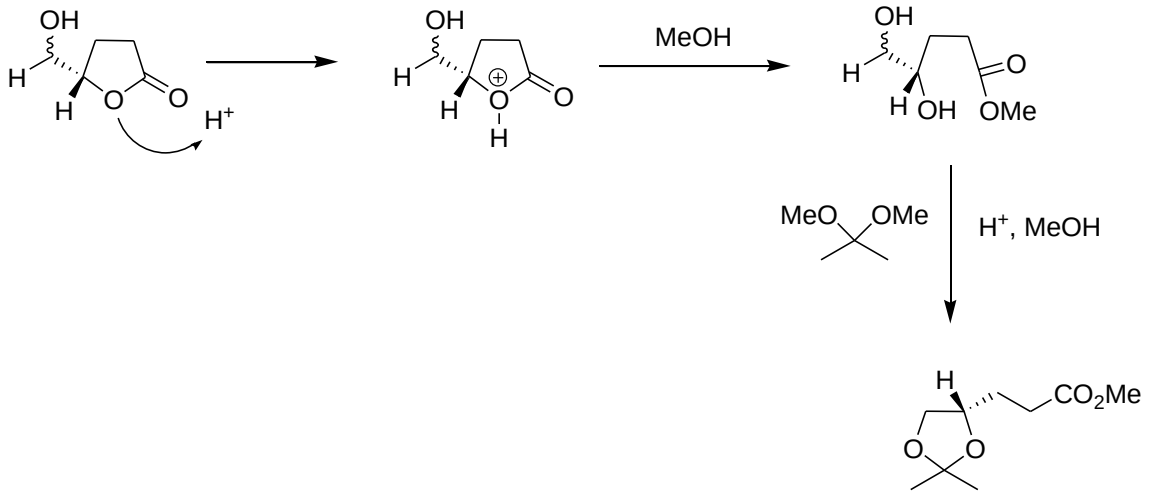
The amino group is converted to a diazonium group which leaves leading to a labile α-lactone, which reacts with the second carboxylic acid leading to a stable five membered lactone (212) with full retention of stereochemistry at the chiral centre. This was subjected to reduction of the carboxylic acid using borane dimethyl sulfide complex in THF resulting in the target hydroxymethyldihydrofuranone (211). IR spectroscopy showed the lactone carbonyl at 1770 cm^{-1} and the proton NMR spectrum confirms this with ring protons at 3.70-3.68 ppm and 3.60 ppm. The data was consistent with the reported literature.[184]

Step 2:



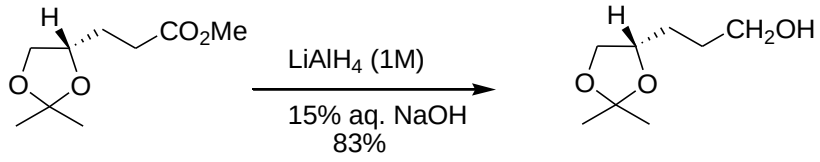
The lactone (211) was cleaved using Amberlyst 15 (H^+). The resulting diol was protected using 2,2-dimethoxy propane as described earlier in the synthesis of six membered imines. Use of Amberlyst 15 (H^+) was convenient as it can be removed easily by filtration and reduces the risk by otherwise using a base to quench the reaction mass. The product (213) was formed in a yield of 55%. The presence of the dimethyl group of the acetal was observed at 1.32 and 1.26 ppm in the ^1H NMR spectrum. The methyl of the ester was

observed at 3.60 ppm. The data obtained was consistent with the literature.[184] The mechanism involved is shown below in Scheme 2.18.



Scheme 2.18

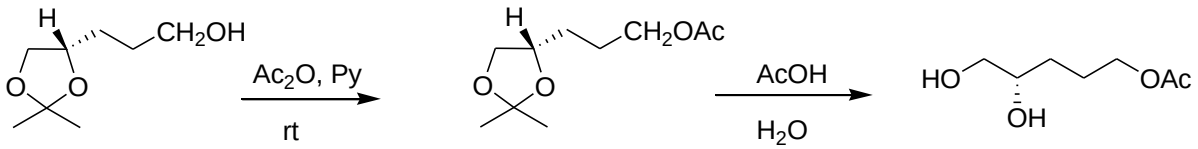
Step 3;



213 214

The ester (213) generated in the above step was subjected to reduction using lithium aluminium hydride in ether. The acetal group was stable under the reaction conditions. The aluminium salts were hydrolysed with water and 15 % NaOH. The successful reduction of the ester was identified by the loss of the carbonyl in the IR spectrum and further supported by the loss of the methyl signal at 3.60 ppm in the ^{1}H NMR spectrum. The data generated was consistent with the literature,[183, 184] the product (214) was obtained in 83% yield.

Step 4;

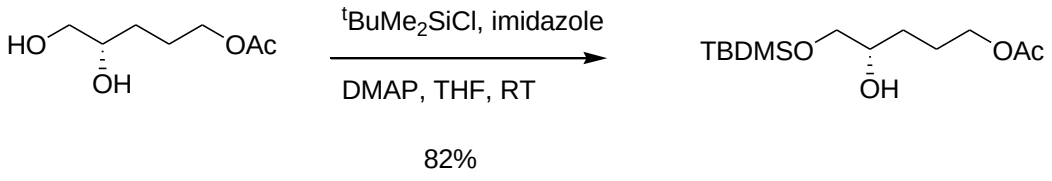


214 215 216

Scheme 2.19

The alcohol of the acetal (214) was protected as acetate (215), using acetic anhydride in pyridine. The alcohol is protected so that it could be easily cleaved without affecting the other protecting group in subsequent reactions and can finally be transformed into an aldehyde. The product (215) was isolated in 82 % yield. The acetal was subjected to hydrolysis with aqueous acetic acid, thus forming a polar diol compound (216), for further functional group transformation (see Scheme 2.19). The product (216) was isolated in 83% yield. The loss of the dimethyl group of the acetal in the ^{1}H NMR spectrum and the presence of broad peaks at 2.43 and 2.67 ppm for one proton each indicated the presence of two hydroxyl groups as reported in the literature.[182] The presence of acetate methyl was confirmed at 2.06 ppm in the proton NMR spectrum.

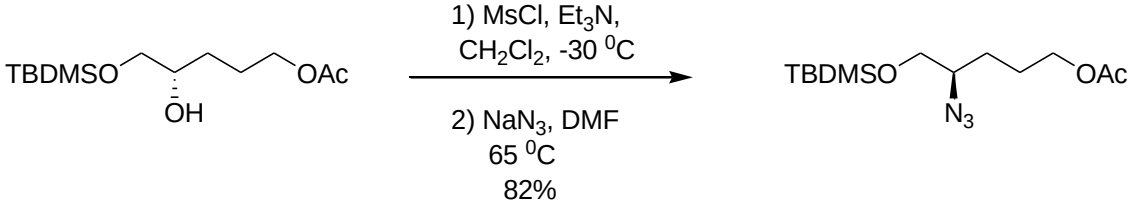
Step 5;



216 217

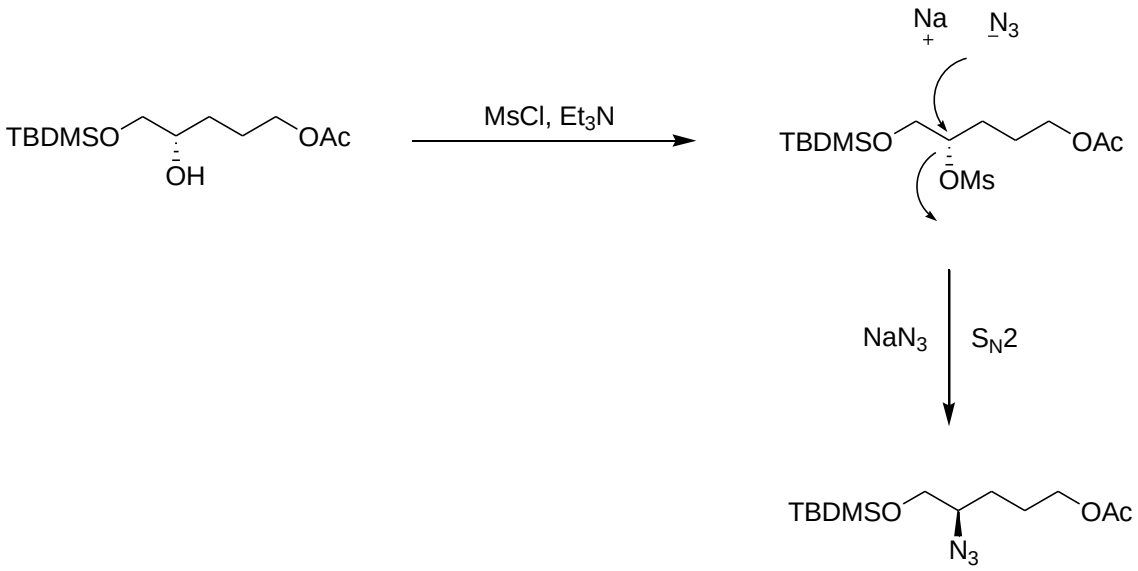
The diol (216) generated above has both a primary and a secondary alcohol. The primary alcohol was selectively protected using *tert*-butyldimethylsilyl chloride (TBDMSCl) and a weak base at 0 °C. The product (217) was purified over silica in 82 % yield as a pale yellow oil. The structure of the product was confirmed using ^{1}H NMR spectroscopy with the *tert*-butyl group integrating for 9H at 0.91ppm and two methyl groups at 0.09 ppm for 6 protons; again consistent with the literature.[182]

Step 6;



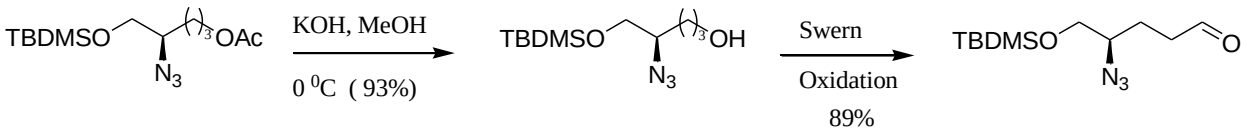
217 218

The secondary alcohol in 217 was converted into an azide. For this the alcohol was converted to a better leaving group and then substituted with an azide, with the overall inversion of configuration. In the first step the alcohol is converted into a better leaving group as mesylate. The mesylate was synthesised using mesyl chloride and triethylamine as base. TLC showed clear conversion in 1h. The reaction was quenched with ammonium chloride and washed with water, which resulted in the isolation of the mesylate intermediate. The mesylate was subjected to substitution using sodium azide in dry DMF at 65 °C (as shown in Scheme 2.20 below). The product (218) was purified over silica with a yield of 80% over two steps. IR spectroscopy showed a strong peak at 2108 cm^{-1} characteristic of the azide. All other data was consistent with that reported in the literature.[182]



Scheme 2.20

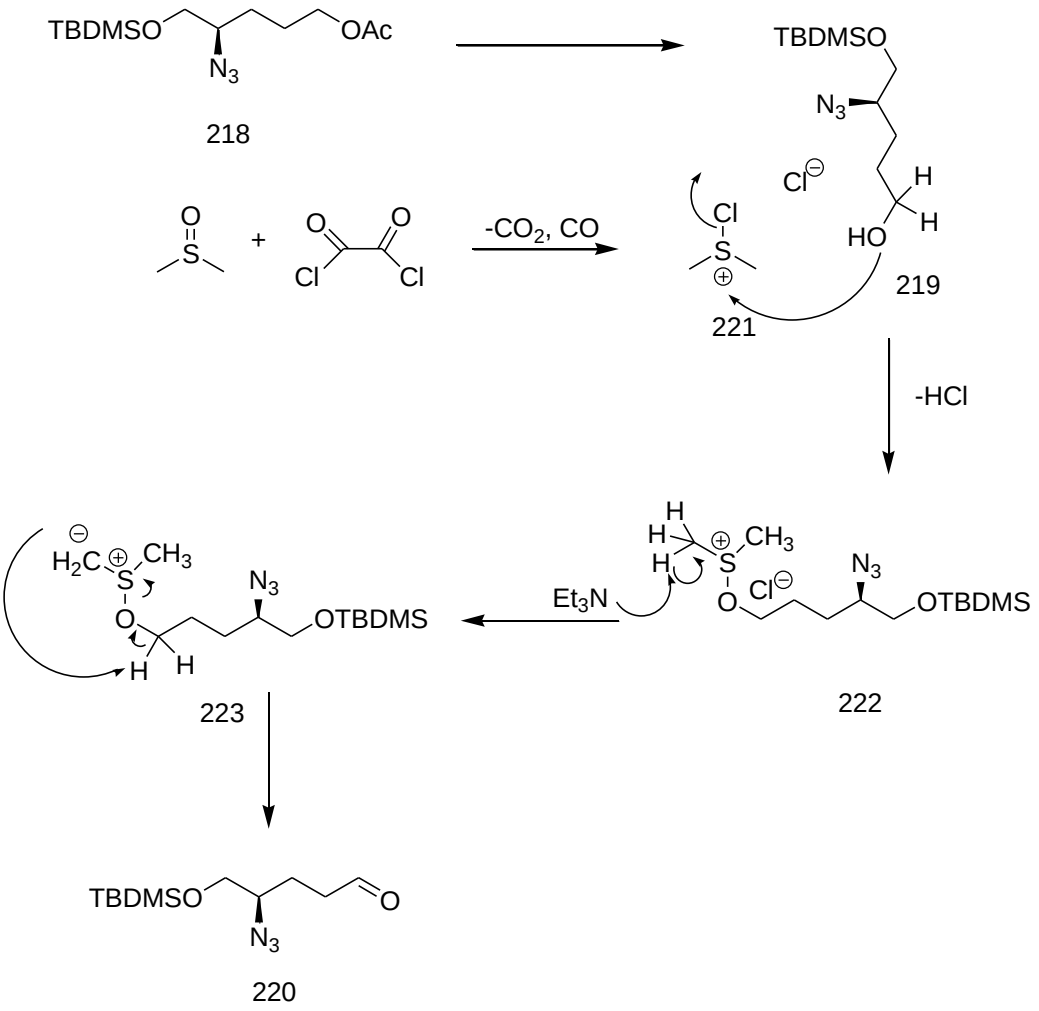
Step 7;



218 219 220

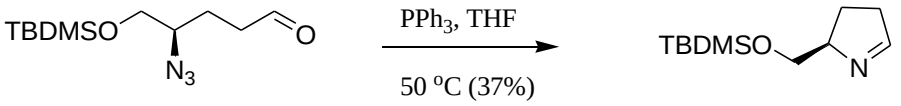
Scheme 2.21

The acetate was hydrolysed under mild conditions using methanolic potassium hydroxide (1M) at 0 °C leading to the alcohol (219) and leaving the TBDMS group untouched. The product (219) was obtained in 93 % yield and its structure was confirmed by the loss of the acetate methyl at 2.07 ppm in the ^{1}H NMR spectrum. The alcohol was subjected to Swern oxidation conditions. The mechanism (see below in Scheme 2.22) involved generation of dimethylchlorosulfonium chloride (221) from dimethyl sulfoxide and oxalyl chloride releasing CO_2 and CO. The resulting dimethylchlorosulfonium chloride (221) reacts with the alcohol to generate the key intermediate alkoxysulfonium ion. The organic base then deprotonates the alkoxysulfonium ion (222) and the resultant sulfur ylide (223) decomposes resulting in the formation of an aldehyde (220) and dimethyl sulfide. The IR spectrum of the purified product indicated the characteristic carbonyl of the aldehyde at 1726 cm^{-1} and the CH bending of the aldehyde at 2858 cm^{-1}. The ^{1}H NMR spectrum further supported the presence of the aldehyde with a peak at 9.82 ppm. The product (220) was obtained in 83% yield over two steps.



Scheme 2.22

Step 8;

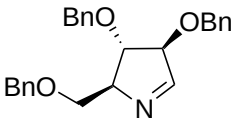


220 209

The azido aldehyde (220) was subjected to Staudinger aza-Wittig type cyclisation[185, 186] which led to the target five membered cyclic imine (209). The reaction was carried out in anhydrous conditions using triphenyl phosphine and freshly activated molecular sieves to remove any moisture which could hydrolyse the Staudinger product, the intermediate iminophosphorane. The ylide thus generated underwent aza-Wittig reaction with the aldehyde resulting in the imine (209), in 37% yield over the two steps.

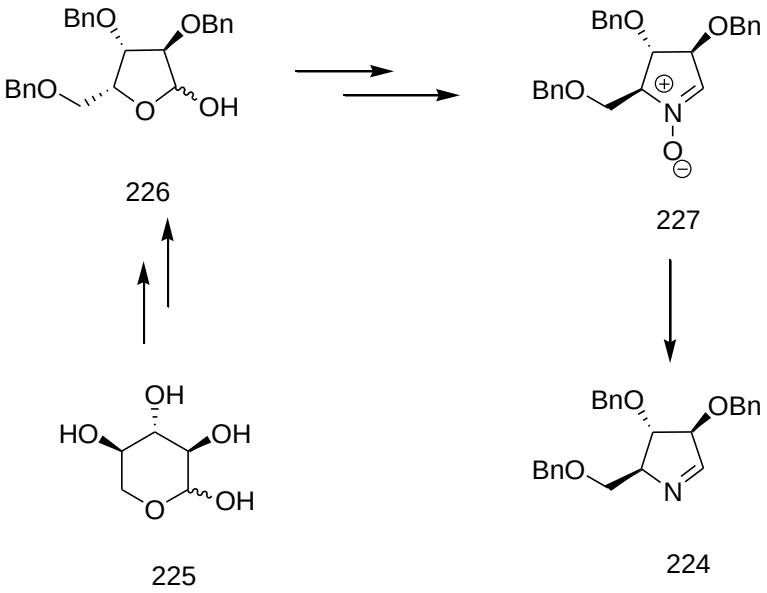
IR spectroscopy showed the loss of the strong azide and aldehyde peaks at 2113 and 1726 cm^{-1}, respectively. The ^{1}H NMR spectrum supports the above structure, with the imino hydrogen observed at 7.61 ppm. The protons on the side chain CH_2 behaved as an ABX system and the ring protons appeared as a multiplet in the range of 2.57-1.68 ppm. The 9 protons of the tertiary butyl group of the silyl protection were observed at 0.88 ppm. The data obtained was fully consistent with the literature,[182] including $[\alpha]_D^{20}$ -73.3 (*c* 1.98, CH_2Cl_2).

2.4 Synthesis of (2S,3S,4S)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyrrole:



224

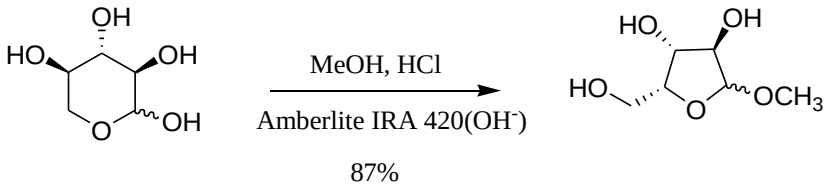
The methodology used here was to synthesise the corresponding protected lactol[187] (226) (see Scheme 2.23) with appropriate stereochemistry and then insertion of nitrogen to yield the corresponding nitrone[144] (227) and finally de-oxygenation[156] of the nitrone to yield the target imine (224), a tactic similar to that used with six-membered rings above.



Scheme 2.23

The synthesis was achieved in 4 steps as described below.

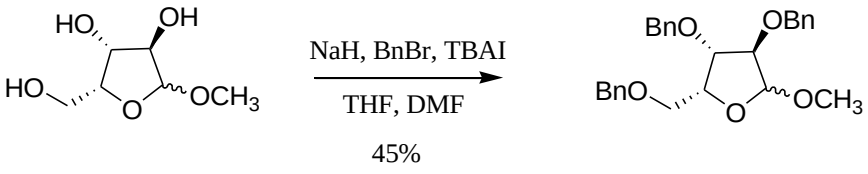
Step 1:



225 228

The anomeric hydroxyl of L-xylose (225) was selectively glycosylated using anhydrous MeOH under acidic conditions with a catalytic amount of conc. HCl. The resulting compound was quenched by passing through Amberlyst IRA 420 (OH^-) resin to neutralise the reaction mass thus avoiding basic workup and further exothermic reactions. The product was purified over silica with a highly polar methanol/chloroform system to give the methyl-L-xylofuranoside (228) as a mixture of anomers in 87% yield.[187, 188] The furanoside (228) was identified by ^1H NMR and ^{13}C NMR spectroscopy with the anomeric carbon observed at 109 and 102 ppm in the ^{13}C NMR spectrum.

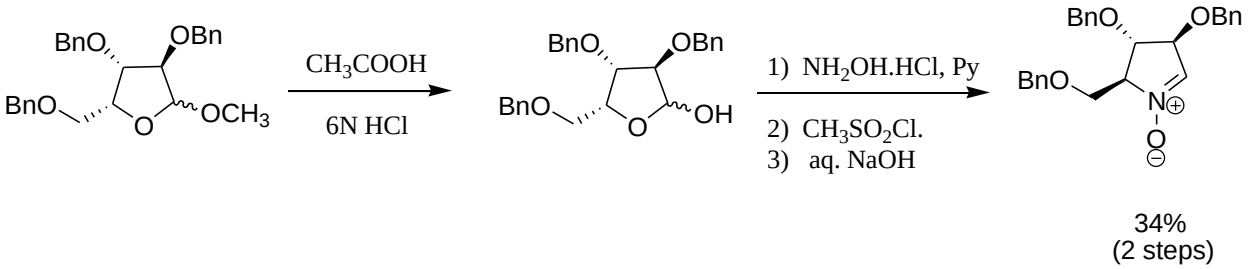
Step 2;



228 229

The methyl furanoglycoside (228) synthesised in the previous stage was benzylated using sodium hydride and benzyl bromide. Tetrabutyl ammonium bromide was used to enhance the reactivity of benzyl bromide. This helped to improve the yield and the product (229) was obtained in 45% yield after purification as a mixture of anomers.[188] The proton and carbon NMR spectra of the compound were too complex to analyse the complete structure, but the characteristic benzyl groups could be identified. Six benzyl protons in the range of 4.72-4.50 ppm and 15 aromatic protons in the range of 7.38-7.27 ppm in the ^1H NMR spectrum were further supported by ^{13}C NMR spectroscopy. Mass spectrometry gave further evidence for tribenzylation with a peak at 457.2 as a sodium adduct.

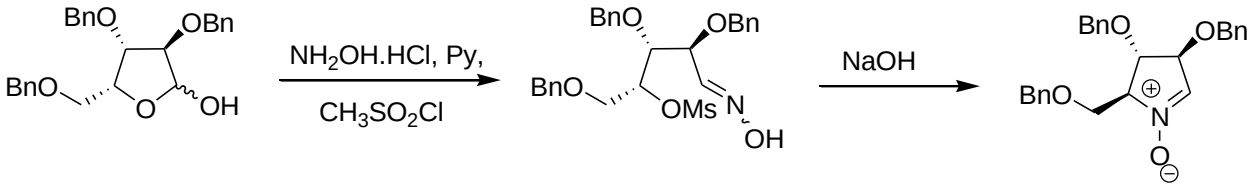
Step 3;



229 226 227

Scheme 2.24

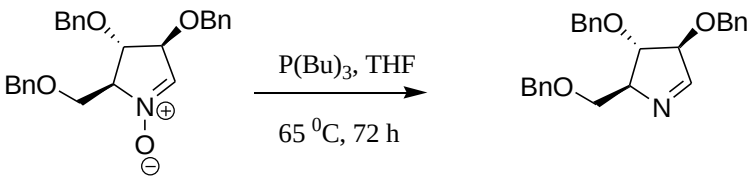
The benzylated methyl glycoside (229) was cleaved under acid conditions using a catalytic amount of 6N HCl in acetic acid at 65 °C.[158, 189] The excess acetic acid was distilled off and the product purified by column chomatography and treated with 0.5 M NaOH to yield the lactol (226) (Scheme 2.24). The product was characterised by ^{1}H NMR spectroscopy, which showed the loss of the anomeric methyl group at 3.44 ppm. The lactol (226) was treated with hydroxylamine hydrochloride in pyridine and methanesulfonyl chloride. The resulting reaction mixture was treated with aqueous NaOH to give the nitrone (227). The mechanism of the formation of nitrone (227) was discussed in section 2.9 of this thesis and the process is summarised below (Scheme 2.25). The data generated was consistent with the literature:[144] for example the iminium CH was seen at 6.91 ppm in the ^{1}H NMR spectrum.



226 230 227

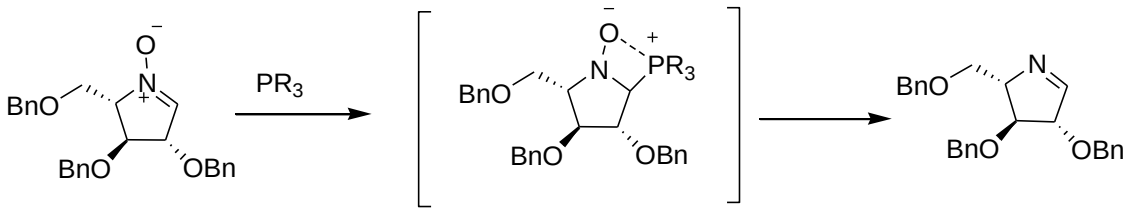
Scheme 2.25

Step 4;



227 224

Several methods are reported for the conversion of nitrones to imines via de-oxygenation. Fleet and co-workers used $TiCl_4$, NaI in acetonitrile with 53 % yield.[155] We used the tributyl phosphine mediated nitrone deoxygenation method (231) reported by Cividino et al[156] due to the similarity of the molecule used and due to our previous familiarity with this method. The advantage was to avoid the aqueous work up as the imine was likely to be sensitive to hydrolysis. The mechanism involves the nucleophilic attack on the electrophilic iminyl carbon of nitrone (231) as shown below in Scheme 2.26;

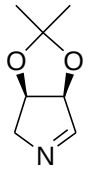


227 231 224

Scheme 2.26

The product (224) was isolated in 67% yield as a pale yellow oil. In the ^1H NMR spectrum the imine proton was observed at 7.5 ppm and this was further confirmed by ^{13}C NMR spectroscopy which showed the imino carbon at 165 ppm, the three ring CH at 89.9, 83.7 and 76.1 ppm and all other data was consistent with the literature,[156] including mass spectrometry, which confirmed loss of oxygen.

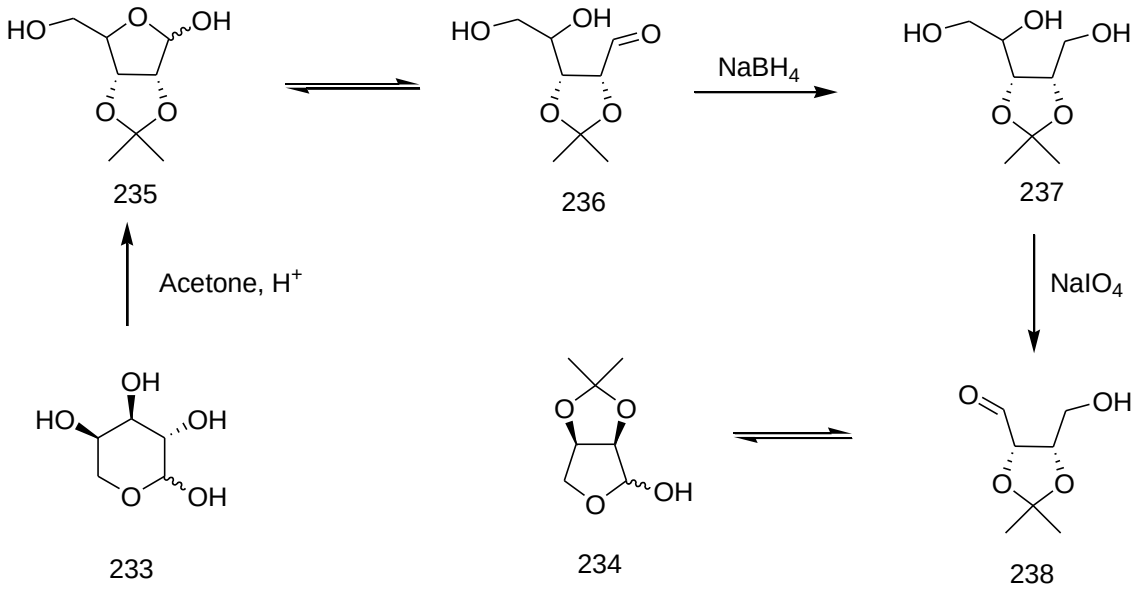
2.5 Synthesis of (3aR,6aS)-2,2-dimethyl-4,6a-dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrole



232

Step 1;

The same method for the de-oxygenation of nitrones (Civindo et al) was applied to the synthesis of the above imine (232). The lactol (234) was generated from the sugar D-ribose (233). The lactol was transformed into the nitrone and subjected to nitrone deoxygenation using tributylphosphine. The synthesis started with the acetone protection of D-ribose, followed by reduction with sodium borohydride and oxidative cleavage. The method used was a one pot procedure for the formation of the lactol from D-ribose.[190]
The key stages are shown below in Scheme 2.27.

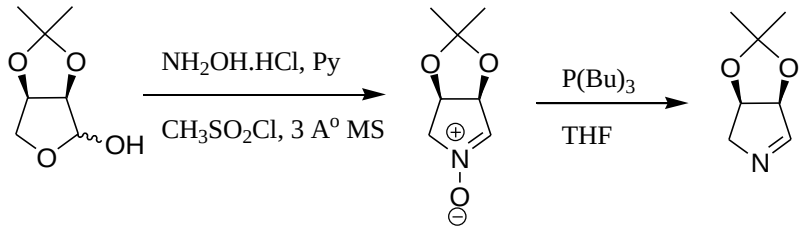


Scheme 2.27

The lactol (234) was purified over silica and identified by ^{1}H NMR spectroscopy. The acetal protection was identified with two singlets for three protons at 1.45 and 1.30 ppm, the anomeric OH was observed as a broad peak at 5.39 ppm for one proton. This was further

supported by the ^{13}C NMR spectrum, which showed the quaternary carbon at 112 ppm and the presence of 3 CH at 101, 85.1 and 80.3 ppm and one CH_2 carbon at 71.77 ppm.

Step 2;
The lactol (234) was next converted to the cyclic imine as summarised below:



234 239 232

Scheme 2.28

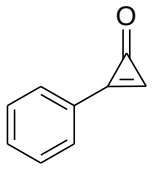
The method was similar to the process used for the synthesis of nitrones discussed in the previous stages.[144] The nitrone (239) was purified over silica to give a pure white solid. The nitrone was identified using ^{1}H NMR spectroscopy, the characteristic imino proton was observed at 6.84 ppm. The acetal group was observed at 1.41 and 1.33 ppm as two singlets for 3H each. The CH_2 shifted from 4.06 to 4.20 ppm to indicate the increase of polarity of the group.

Deoxygenation using tributyl phosphine[156] was complete after 77 h according to the TLC analysis. Attempts to isolate the imine (232) were unsuccessful. This imine (232) was subjected to attempted addition without purification. This is detailed in a later section of the thesis (Section 2.16).

With a range of cyclic imines now ready, we next needed a range of cyclopropenones in order to do a full investigation of the scope of the cyclic imine-cyclopropenone cycloaddition as a route to complex natural product-like indolizidines and pyrrolizidines. The next section looks at cyclopropenone synthesis.

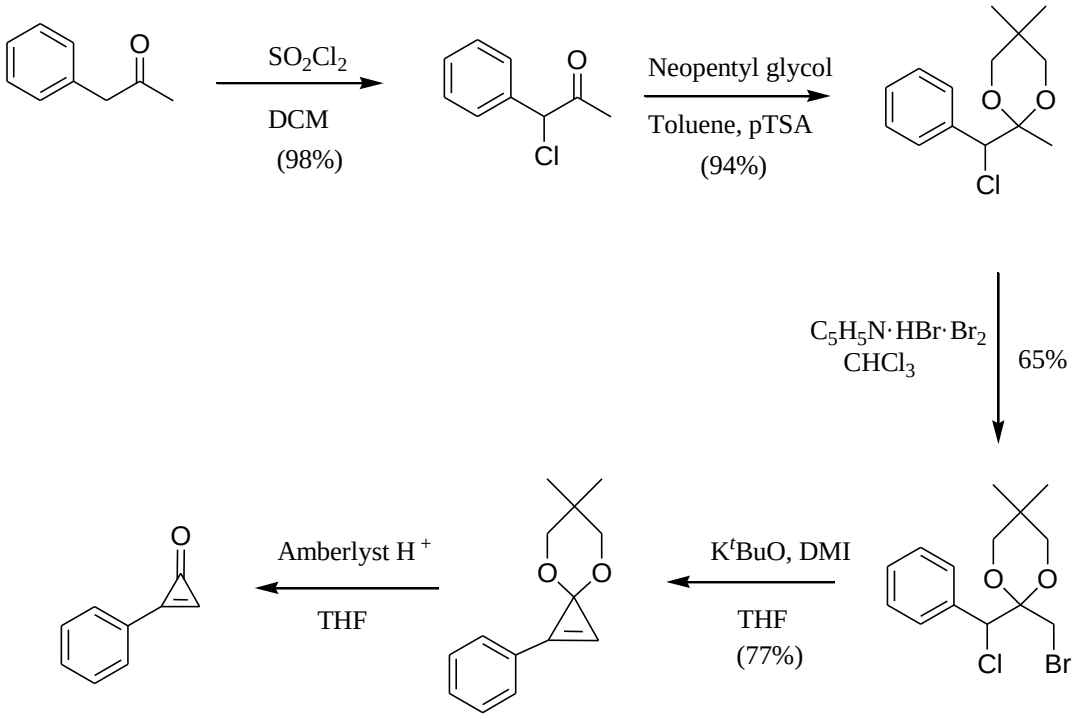
2.6 The synthesis of cyclopropenones

2.7 Synthesis of 2-phenylcycloprop-2-enone:



247

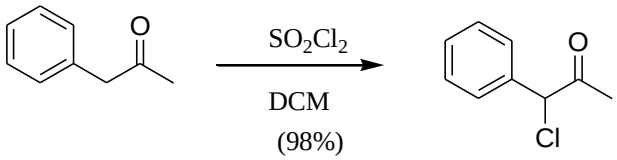
Phenylcyclopropenone (247) was obtained by the hydrolysis of phenylcyclopropenone acetal[191] (244), which was synthesised by the intramolecular cyclisation via dehydrohalogenation of a dihalo phenyl acetal compound, which was in turn prepared by halogenation and acetalation of phenyl acetone. The process is shown in Scheme 2.29. The key reaction is the cyclisation of the dihalo compound. The details of these reactions are discussed in the sections below. The process was an adaptation of a literature[191] method that needed some modification.



Scheme 2.29

Step 1;

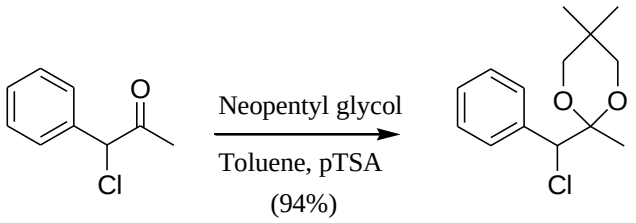
The first step was halogenation of phenyl acetone (240). Phenyl acetone was chlorinated at the benzylic position; the experimental procedure was repeated as reported in the literature, using sulfuryl chloride. The product (241) was isolated in good yield with data which was consistent with the literature.[191]



240 241

Step 2;

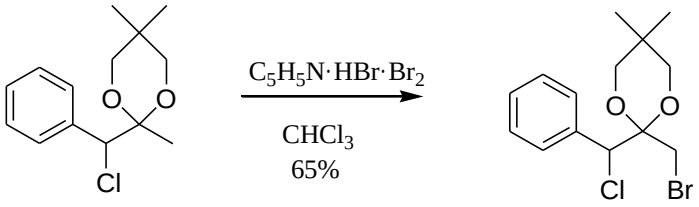
The α-chlorinated compound (241) was acetylated with neopentyl glycol and a catalytic amount of *p*-toluenesulfonic acid by azeotropic removal of water in a Dean-Stark apparatus using toluene as solvent. The product (242) was used in the next step without purification. The product was pure by TLC after workup for the removal of excess glycol and acid by sodium bicarbonate and hexane wash. The compound was characterised using ^{1}H NMR spectroscopy and the data generated was consistent with the literature.[191]



241 242

Step 3:

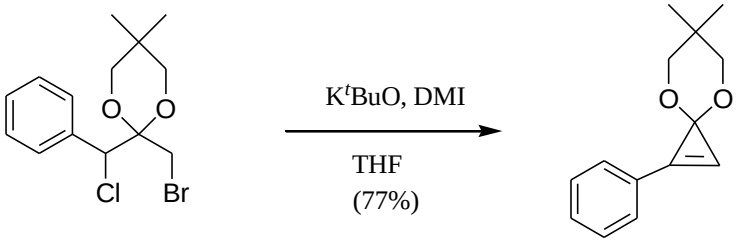
The chlorinated acetal (242) was subjected to bromination using pyridinium hydrobromide perbromide in refluxing chloroform. The reagent pyridinium hydrobromide perbromide was an easy to handle solid source of bromine. The HBr released in the reaction evaporated from the refluxing chloroform and the acetal group was unaffected, resulting in the bromination of the the methyl group. The reaction is thought to be a free radical reaction. The resulting dihalide was purified by recrystalisation from n-hexane to give a pure crystalline compound (243) in 65% yield. The compound gave spectroscopic data that was consistent with that reported in the literature.[191] For example, the ^{13}C NMR spectrum showed 3 CH_2 groups at 27.7, 70.1 and 71.0 ppm, confirming the bromination of a methyl group.



242 243

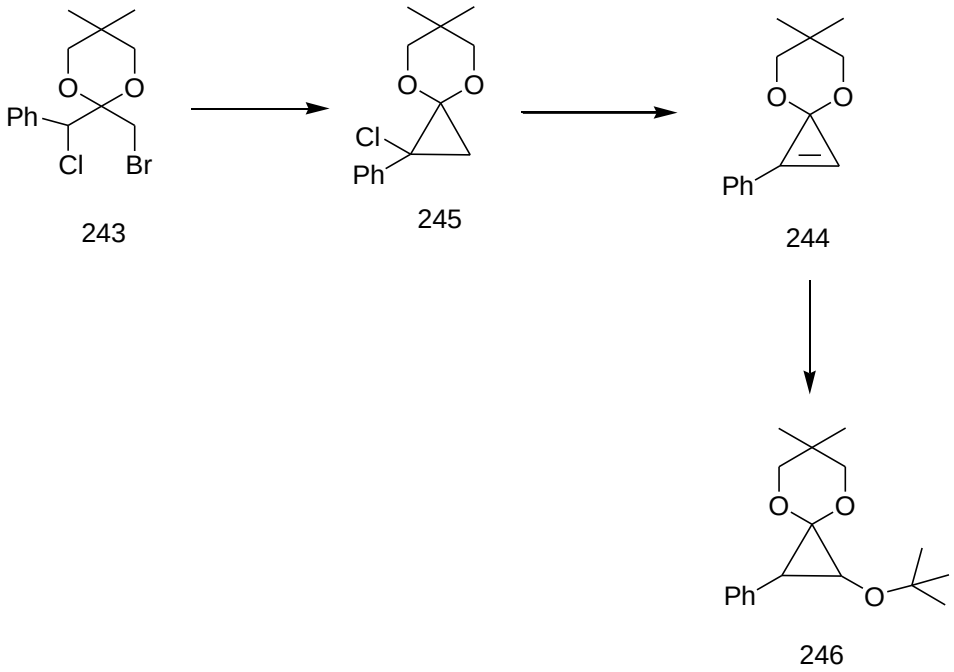
Step 4;

The dihalo acetal (243) was cyclised by dehydrohalogenation using two equivalents of potassium tert-butoxide, with 1,3-dimethyl-2-imidazolidinone and THF as solvent:



243 244

The reaction process was reported as deprotonation of the benzylic position in the first stage by one equivalent of the base, followed by intramolecular cyclisation to yield an intermediate chlorocyclopropane (245) which undergoes dehydrochlorination using the second equivalent of the *tert*-butoxide to yield the phenyl cyclopropenone acetal (244). Use of excess base resulted in the formation of 2-tert-butoxy-3-phenylcyclopropanone acetal (246), as shown below, Scheme 2.30.

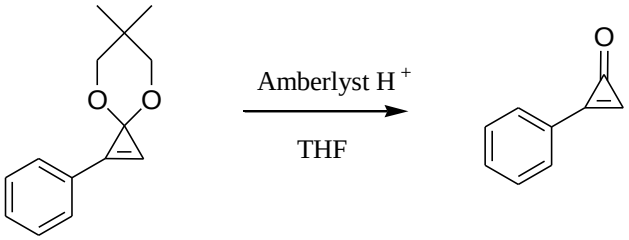


Scheme 2.30

The desired cyclopropenone product (244) was formed in 77% yield and the product was characterised by ^{1}H NMR spectroscopy. The methylene of the ring was observed at 7.71 ppm as a singlet for one proton, with aromatic protons in the range of 7.67-7.48 integrating for five protons. Confirmation that the acetal protection was intact was shown by the presence of the acetal methyls at 1.17 and 1.10 ppm as two singlets for three protons each. The structural assignment was supported by the ^{13}C NMR spectrum which showed the alkene quaternary carbon at 135 ppm and the alkene CH at 114.61 ppm. The data was consistent with the literature;[191] although it should be noted that considerable experimentation was necessary to optimise this reaction.

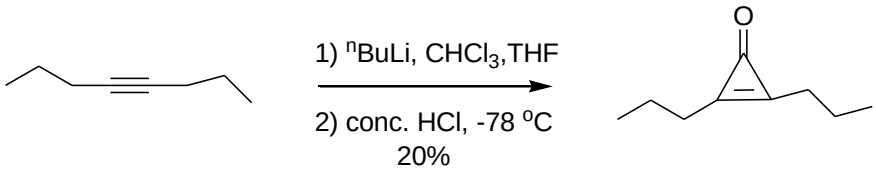
Step 5;

In the final step, shown below, the acetal (244) was subjected to hydrolysis using Amberlyst H^{+}, in THF/Acetone, with a few drops of water.[129] The use of Amberlyst over other acids gave the advantage of easy work up and mild conditions. The acid catalyst was filtered to give the pure compound (247). The compound was characterised by IR spectroscopy, for the presence of carbonyl and the alkene groups, with the carbonyl of the cyclopropenone being observed at 1790 cm^{-1} and the alkene stretching at 1550 cm^{-1}. The structure was further confirmed by ^{1}H NMR spectroscopy. With the deprotection of the acetal the carbonyl group contributed to the shift of the alkene proton from 7.71 to 8.47 ppm. The five aromatic protons were observed in the range of 7.72-7.50 ppm.[124, 129]



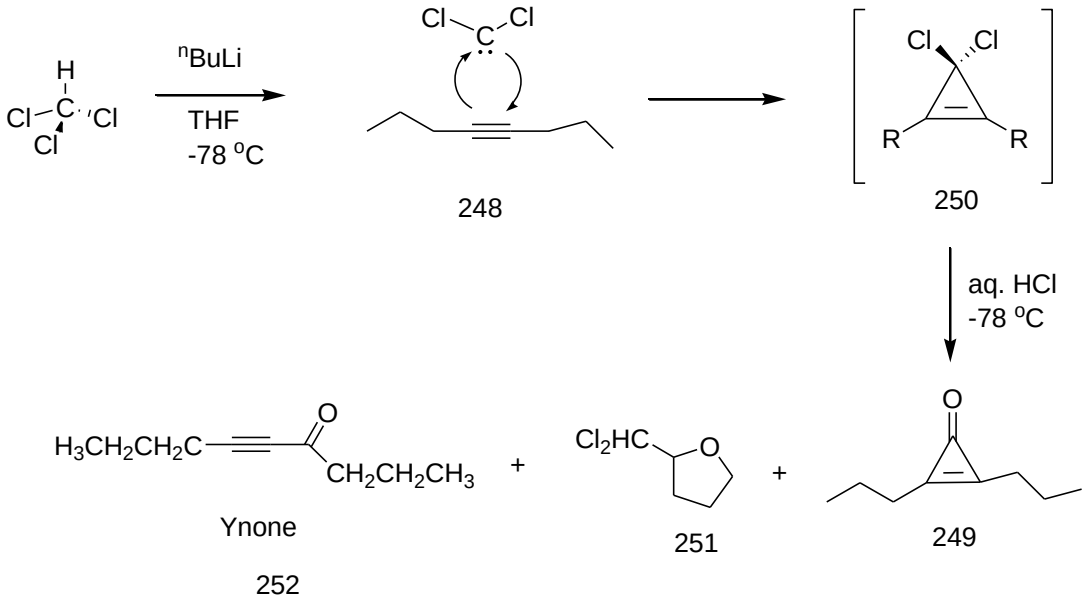
244 247

2.8 Synthesis of 2,3-dipropylcycloprop-2-enone:



248 249

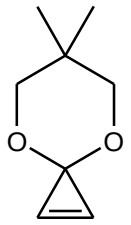
Dialkyl cyclopropenones were synthesised by the addition of the dihalocarbenoid reagent to suitable alkynes. Hydrolysis of the initial addition product results in the formation of alkyl cyclopropenones.[192] This method is reported to be more efficient than other methods like a modified Favorskii reaction[193] on dibromoketones or metallation of cyclopropenone acetals,[194] which will be described in further sections. We used the method reported for high yields of dialkyl cyclopropenones. Dichlorocarbene was generated using n-butyllithium and chloroform in THF at -78°C. Dichlorocarbenes generated from sodium trichloroacetate, $CHCl_3$ and NaOH under phase transfer catalysts gave low yields.[195, 196] The addition of dichlorocarbene generated *in situ* to the alkyne resulted in the formation of a dichlorocyclopropene intermediate (250). This was hydrolysed carefully to yield the target cyclopropenone (249). The use of water or aqueous base favoured the formation of ynones (252) as the major product, whereas acidic hydrolysis favoured cyclopropenone formation. The Scheme is shown below:



Scheme 2.31

The product cyclopropenone (249) obtained from dec-5-yne (248) was characterised by ^{1}H NMR spectroscopy which showed the presence of the two methyl groups of the chains at 1.03 ppm as a triplet integrating for 6 protons. The two methylenes attached to the cyclopropenone ring were observed at 2.56 ppm as a triplet integrating for four protons and the rest of methylenes were observed as a multiplet in the range of 1.75-1.66 ppm. The data generated was consistent with the literature.[192]

2.9 Attempted Synthesis of cyclopropenone acetal:

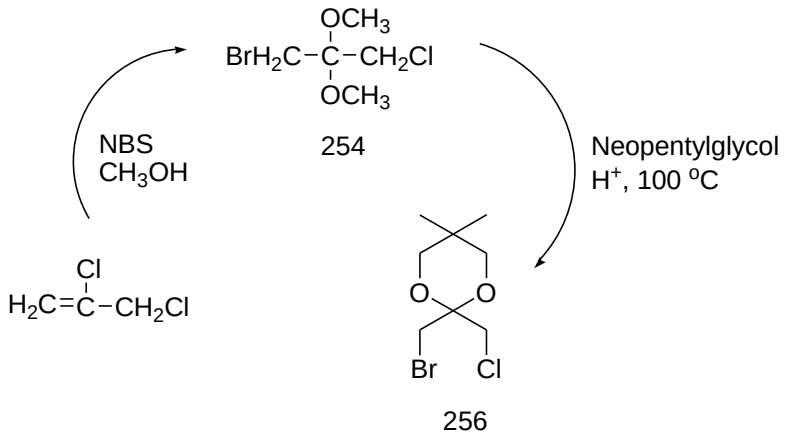


253

The unsubstituted cyclopropenone (189) was an important key intermediate for our synthesis of indolizidine and pyrrolizidine aza-sugars. The reported method in the literature for the synthesis of the precursor cyclopropeneone acetal (253) was cyclisation of a dihaloacetal in liquid ammonia using Na/K amide as the base.[129] We attempted the cyclisation under different conditions to avoid the use of liq NH_3. Various bases like

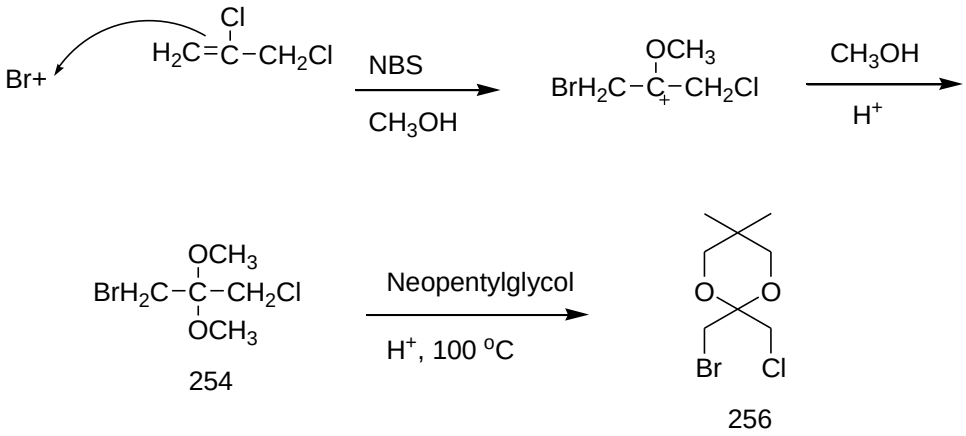
potassium tert-butoxide, LDA and butyllithium and numerous solvents were tried and were all unsuccessful.

Prior to cyclisation studies, the first step was to produce the dihaloacetal (256) and this was done as shown below:



Scheme 2.32

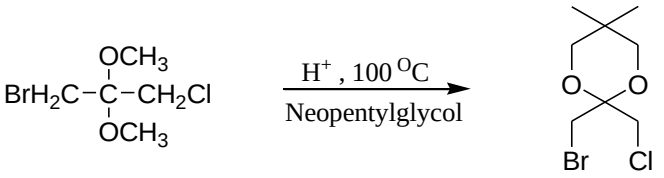
The method for the synthesis of the dihaloneopentyl glycol acetal (256) was as reported in the literature.[197, 198] 2,3-Dichloropropene was subjected electrophilic addition of bromine using N-bromosuccinimide as the brominating agent in the presence of a catalytic amount of acid and anhydrous methanol as the solvent, which facilitates the nucleophilic addition and substitution of the methoxy group, giving dimethoxy acetal protection in one pot forming compound (254), as shown below in Scheme 2.33:



Scheme 2.33

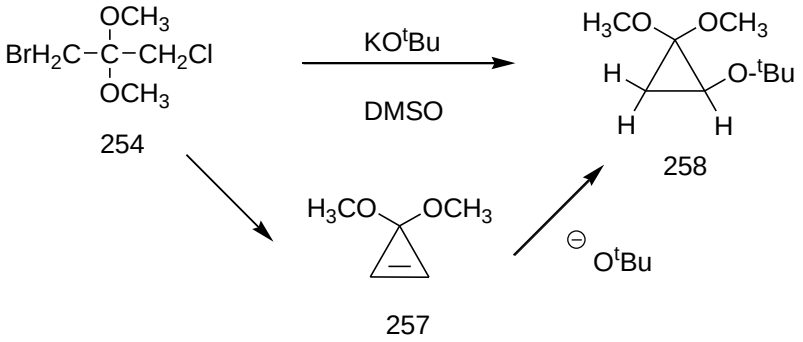
The product was purified by recrystalisation and gave data that was consistent with the literature.[197, 198]

The dimethoxy acetal (254) was next exchanged for the more stable neopentyl glycol protection. The reaction was simple to carry out as a neat reaction in a Dean-Stark apparatus. The dimethoxy acetal was hydrolysed producing methanol and the methoxy groups were exchanged for the more stable neopentyl acetal. The reaction was favoured by the removal of methanol. The target compound (256) was obtained in 86% yield without need for purification and was characterised by ^{1}H NMR spectroscopy. The dimethoxy acetal methyl groups were lost with new peaks for the acetal at 1.01 and 0.98 ppm as two singlets for 3 protons each. The acetal CH_2 resonances were observed at 3.55 ppm as a broad doublet for 4 protons. The data was consistent with the literature.[197, 198]



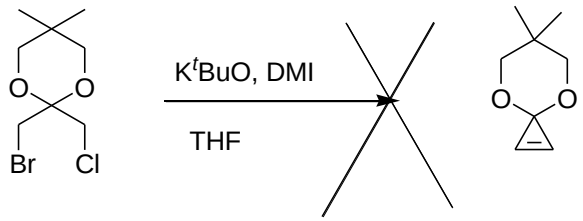
254 256

Next, a series of reactions were explored to convert the dihaloacetals (254) and (256) into cyclopropenone acetal. The formation of 1,1-dimethoxy-2-*tert*-butoxycyclopropane (258) (see Scheme 2.34 below) during the reaction of 1-bromo-3-chloro-2,2-dimethoxypropane with KO-^{t}Bu in DMSO,[198] was postulated as the result of the addition of *t*-butoxide to the desired 3,3-dimethoxycyclopropene product (257), which seemed to be a similar process to that of the *tert*-butyl phenyl cyclopropane acetal seen above (Scheme 2.30).[198] We attempted to see if we could control the reaction, but were unsuccessful and further attempts were stopped due to time limitations and a successful alternative route (see below Scheme 2.35). This route uses liquid ammonia as solvent and sodium amide as base, as reported in the literature.[129] The use of liquid ammonia, whilst successful (see below Scheme 2.35) was tedious. If attempts were made with different additives and solvents, there is the possibility to avoid the hazardous and laborious use of liquid ammonia, enhancing the use of cyclopropenones as intermediates.



Scheme 2.34

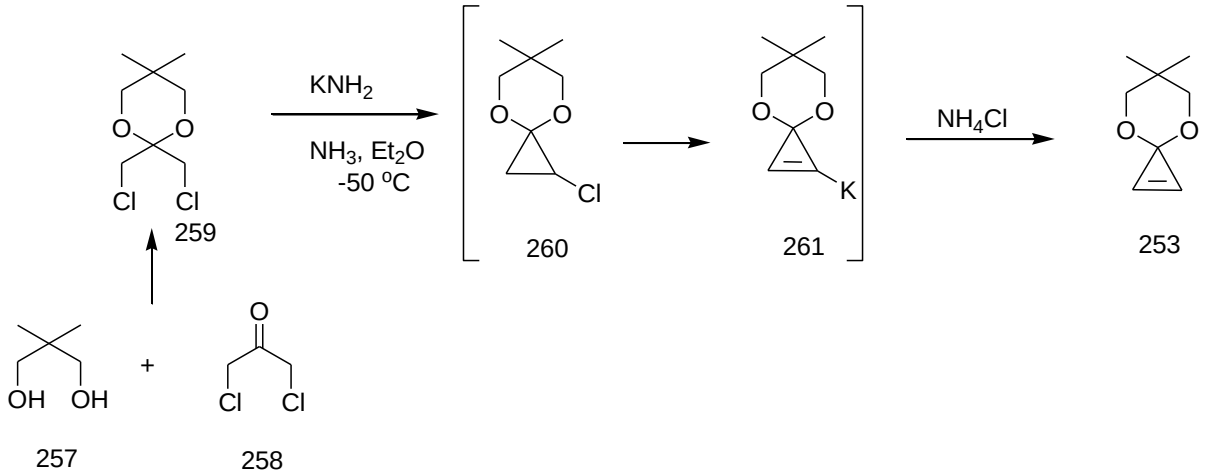
The butoxide route was also attempted with the neopentyl system as shown below:



All the attempts showed that this reaction did not work and we were able to isolate only DMI from the reaction mixture. It is suspected that the aqueous work up procedure may have destroyed the cyclopropenone, but the availability of an alternative (and successful) route and time limitations prevented a more thorough study.

2.10 Synthesis of cyclopropenone acetal:

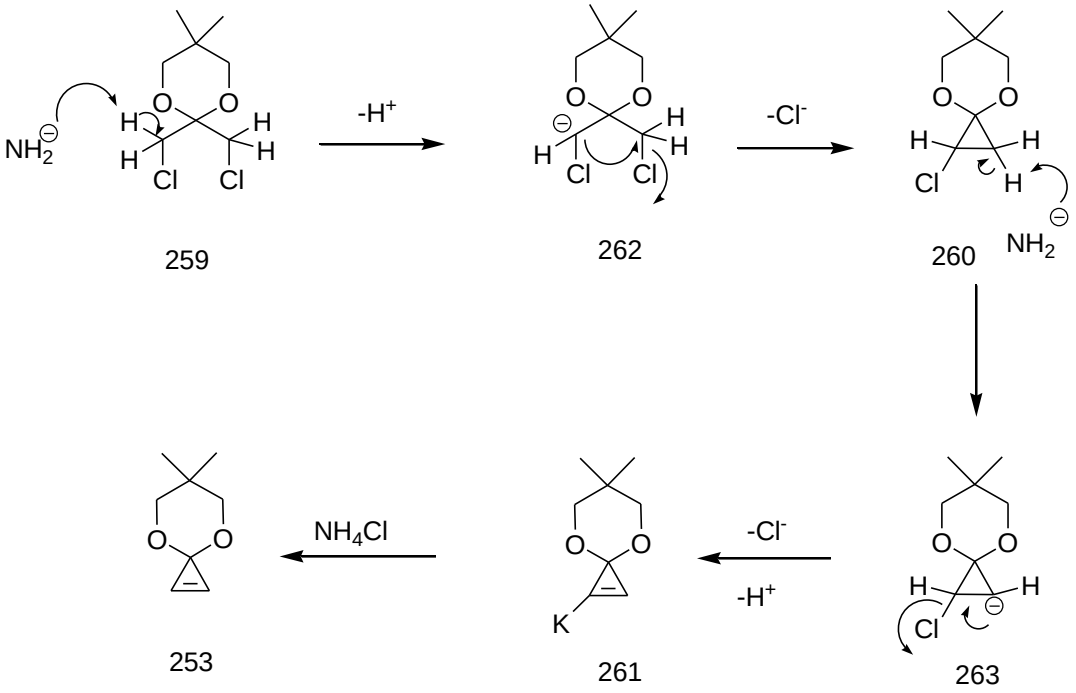
The route used to make compound (253) is shown below.



Scheme 2.35

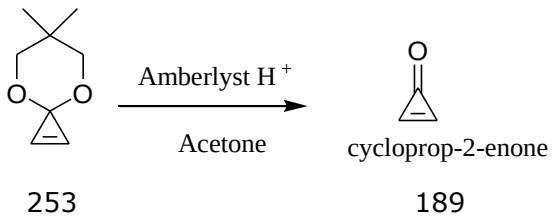
Rather than start with the bromo, chloro compound (256) as above which had been all used up, we started with the dichloro compound (259) as this was easy to make and had been used by Nakamura[129] to make the cyclopropenones. The method for making compound (259) was simple and worked in 97% yield, with data that was consistent with the literature.[129]

In the next step potassium amide was generated *in situ* in liquid ammonia by the addition of potassium metal. The dichloro acetal (259) was added and the reaction was quenched with ammonium chloride and the ammonia was allowed to evaporate. The crude cyclopropenone acetal (253) obtained was purified by vacuum distillation and was obtained as a pure colourless liquid which could be stored under nitrogen at -18°C for 4 weeks. The acetal was noted to decompose slowly after 2 weeks and the colour changed to yellow. The compound was characterised by ^{1}H NMR spectroscopy which showed the vinylic protons at 7.84 ppm and the acetal protons at 1.03 ppm as a singlet for 6 protons. The data was consistent with the literature.[128, 129, 199] The mechanism of the cyclisation is shown below in Scheme 2.36.

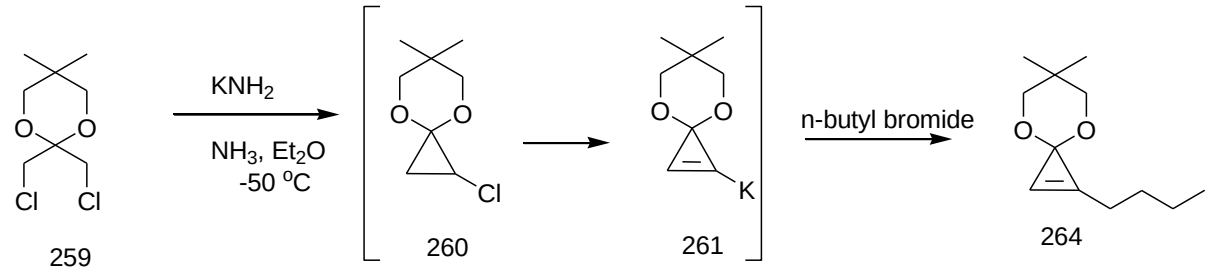


Scheme 2.36

The final step involved a method that was simple to use. The acid hydrolysis of cyclopropeneacetal in the presence of Amberlyst 15 (H^+) in acetone for 20 min, resulted in the removal of the acetal. The reaction was monitored by IR spectroscopy for the appearance of the carbonyl and hence for acetal cleavage. After 20 min we could clearly observe a strong peak at 1800 cm^{-1} for the carbonyl of the cyclopropenone (189), at which point the reaction was filtered and subjected to addition with the appropriate imine.



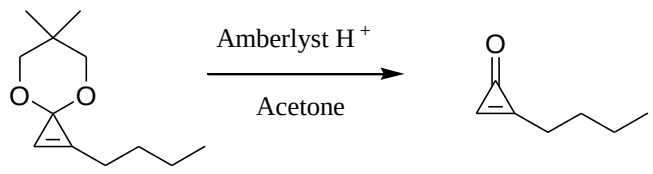
2.11 Synthesis of butyl cyclopropenone acetal:



Scheme 2.37

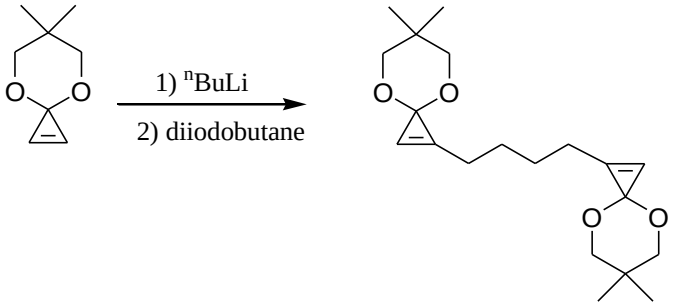
The method[129] for the synthesis of butylcyclopropene acetal, was similar to that of the synthesis of the cyclopropene acetal (Scheme 2.37). 3.5 Equivalents of potassium amide were used in the reaction, the third equivalent of the base allows the formation of potassium salt (261). Slow controlled addition of a primary alkyl iodide or bromide at -78°C, resulted in the monosubstituted alkyl cyclopropenone acetal (264). The resulting acetal was purified by vacuum distillation to give a colourless oil in 75% yield. The compound was characterised by ^{1}H NMR spectroscopy. The characteristic vinylic proton was observed at 7.31 ppm, the acetal methyls were distinct due to change in the symmetry of the acetal and were observed at 1.06 and 0.99 ppm as singlets integrating for 3 protons each. The butyl chain was observed with a characteristic triplet for the terminal methyl group at 0.9 ppm integrating for 3 protons, the rest of the chain appearing as multiplet, multiplet and triplet as expected. The data was consistent with the literature.[129] The method was adopted from the work of Nakamura.[129]

The acetal (264) was cleaved using the same procedure as for cyclopropenone (189). The hydrolysis was complete in 30 min and the reaction was followed by IR spectroscopy, which indicated the presence of the cyclopropenone carbonyl at 1800 cm^{-1}. Cyclopropenone (265) was formed in 75% yield from the acetal (264).



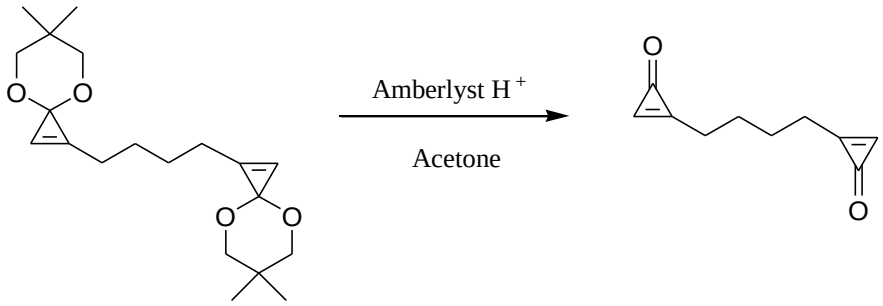
The same method, as per Nakamura,[129] was used to make some other cyclopropenones, as discussed below.

2.12 Synthesis of bis-cyclopropenone acetal:



253 266

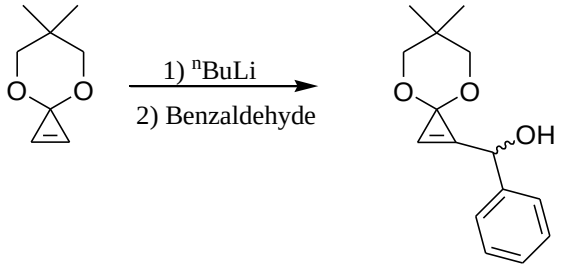
The bis-cyclopropene acetal (266) was synthesized from cyclopropene acetal (253) with two equivalents of n-BuLi and 0.5 equivalents of diiodobutane. The product (266) was observed to be unusually stable and could be purified over silica. The product was characterised by ^{1}H NMR spectroscopy, with the characteristic vinylic proton observed at 7.36 ppm as a singlet integrating for 2 protons. The methyls of the acetal were observed at 1.07 and 0.98 ppm as singlets integrating for 6 protons each, with two sets of signals as broad peaks at 2.56 and 1.74 ppm as reported by Nakamura.[129] Deprotection with Amberlyst was performed as before:



266 267

The cyclopropenone (267) was purified by chomatography over silica and was obtained in 94% yield as a pure white solid which could be stored on the bench. The compound (267) was characterised by ^{1}H NMR spectroscopy. The vinylic protons were shifted downfield by the removal of the acetal to 8.3 ppm. As with the other cyclopropenones in this section, the compound had data which was consistent with the literature.[129]

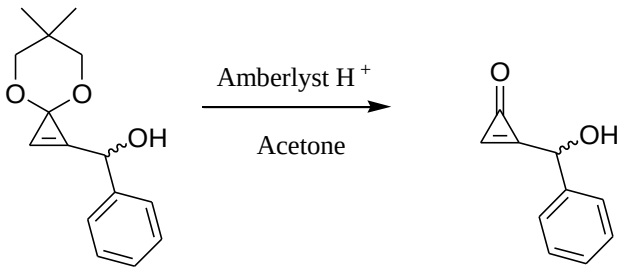
2.13 Synthesis of 2-(α-hydroxybenzyl)cyclopropenone acetal:



253 268

With the aim of synthesising a wide range of cyclopropenones to study the addition reactions of imines, we targeted hydroxyl phenyl cyclopropenone acetal (268). For the synthesis of the alcohol, the method used was the addition of benzaldehyde, after the addition of *n*-BuLi and TMEDA to the cyclopropenone acetal (253). The compound was characterised by ^{1}H NMR spectroscopy. This time the characteristic vinylic proton was merged with the aromatic protons with signals in the range of 7.53-7.29 ppm for 6 protons as a series of multiplets. The acetal group was observed at 1.08 and 0.83 ppm as two singlets integrating for 3 protons each. The proton on the chiral carbon was observed at 5.80-5.75 ppm as a multiplet integrating for one proton. The OH was observed at 3.3 ppm. The data was consistent with the literature.[129]

Synthesis of 2-(α-hydroxybenzyl)cyclopropenone:



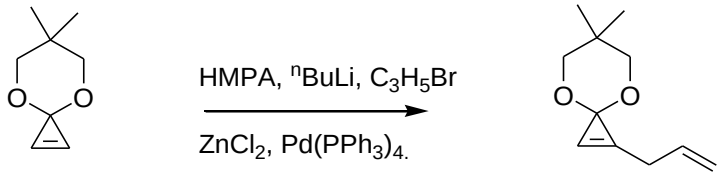
268 269

The method used was as above, the hydrolysis took one hour for completion. The reaction was monitored by TLC for completion and the desired compound (269) was obtained as an oil. The ^{1}H NMR spectrum clearly indicated the shifting of the vinylic proton to 8.51 ppm as

a singlet. Five aromatic protons were observed in the range of 7.58-7.41 ppm, the proton at the chiral centre was observed at 5.85 ppm as a broad singlet.

2.14 Synthesis of Allylcyclopropenone:

Allyl cyclopropenone acetal (270) is not reported in the literature. Intial attempts to add allyl bromide to the potassium cyclopropene acetal were unsuccessful. We tried with the lithiated cyclopropene acetal in the presence and absence of TMEDA and HMPA additives and were unsuccessful. We adopted the method for the synthesis of vinyl and aryl cyclopropene acetals by Nakamura and co workers,[129] whereby they swapped the lithium for zinc and used tetrakis(triphenylphosphine)palladium(0) for reaction with the alkyl halide. With this procedure, we were successful in isolating the desired compound (270), but in very low yield.



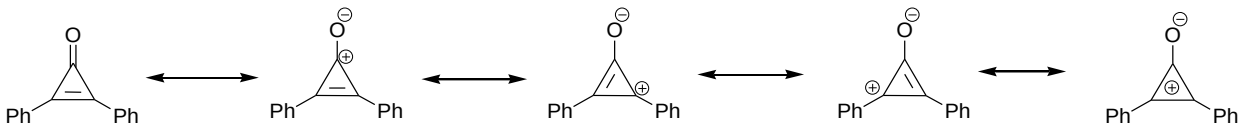
253 270

The compound (270) was characterised by ^{1}H NMR spectroscopy. The characteristic vinylic proton was observed at 7.41 ppm as a singlet integrating for one proton, the allyl group alkene was observed at 5.97 ppm for the CH and at 5.26 ppm for CH_2 as multiplets for one and two protons respectively. Compound (270) was deprotected using Amberlyst as described previously.

2.15 Reactivity of cyclic imines with cyclopropenones

In the methodology we used for the synthesis of indolizidines and pyrrolizidines, cyclopropenones are used as key intermediates. Cyclopropenones act as a building block for the five membered ring in each of the products. A short introduction to cyclopropenone chemistry is included at this point.

Cyclopropenones are three membered cyclic systems with a carbonyl and a double bond in the ring and are the smallest aromatic systems with Hückel aromaticity.[95, 125, 129] The cyclopropenium ion is known to have considerable thermodynamic stability despite its strain due to the small three membered ring having two ∏ electrons delocalised over 3 sp^2 orbitals. The resonance stabilised structure is shown below for diphenyl cyclopropenone (Scheme 2.38).



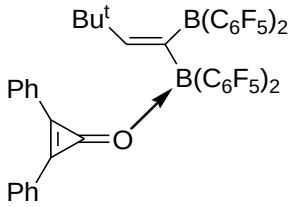
Scheme 2.38

Breslow et al synthesised the first cyclopropenone in 1959, diphenylcyclopropenone (123), which is now a commercially available stable cyclopropenone.[200] Many cyclopropenones are reported in the literature with a range of substituents from halogens, amino, alkyl, hydroxyl etc. The reactivity of cyclopropenones is mainly due to the polarized structure and large strain in the three membered ring. Cyclopropenone is an amphiphilic molecule taking part in both nucleophilic and eletrophilic reactions.[95]

The reactions of cyclopropenones are very well classified in a review by Komatsu et al as follows:[95]

1) Reaction with electrophiles.

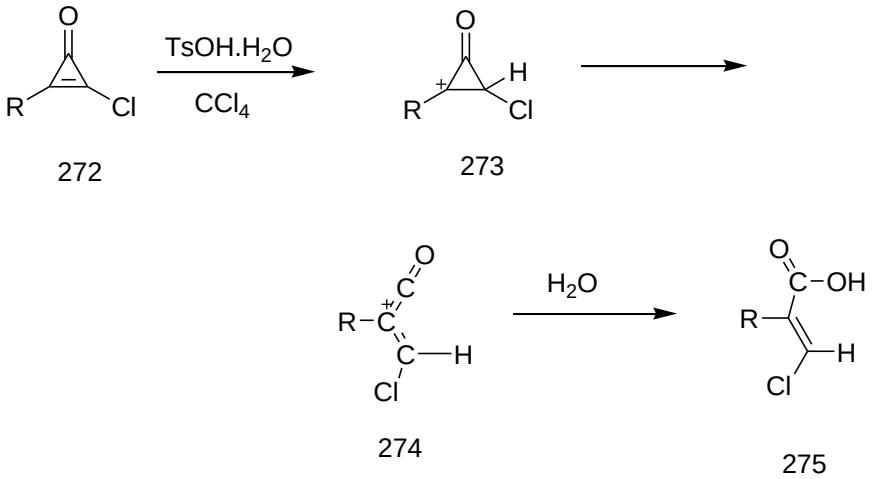
The carbonyl of cyclopropenones readily coordinate with strong electrophiles like boron-centered Lewis acids to form stable adducts (271), which are stabilised by delocalisation of the positive charge over the three membered ∏ system. For example, diphenylcyclopropenone and diborane $Bu^tCH=C[B(C_6F_5)_2]_2$ form a 1:1 adduct.[201] (271)



271

Alkylchlorocylopropenones, (272) however, react with $TsOH.H_2O$ in CCl_4 to give a ring opening product (275), due to the initial protonation on the vinylic carbon rather than carbonyl oxygen.[202] (Scheme 2.39)

The study of cyclopropenones in organometallic chemistry and their mode of ∏ complexation with metals centers has been a study for a long time. More recently quantum chemical calculations using DFT have been reported by Werz *et al*[203] for CpCo-capped *p*-benzoquinone complexes.[203]



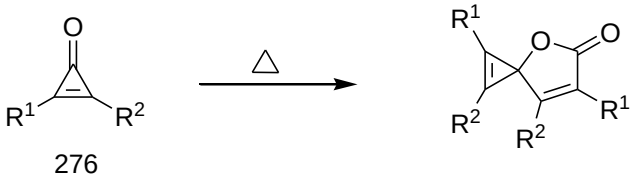
272 273 274 275

Scheme 2.39

2) Reaction at the C=O double bond

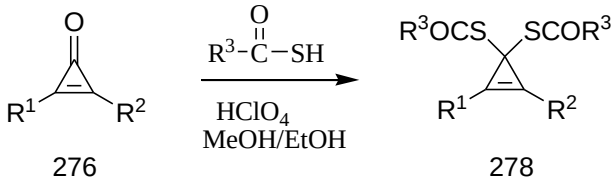
A number of reactions have been reported under this category. Cyclopropenones undergo reactions at the C=O bond and the cyclopropene moiety is reported to be retained with no loss of the C-C double bond. The exchange of the carbonyl oxygen of cyclopropenone with labelled water $H_2\,^{17}O$ has been reported.[204]

Thermal dimerisation resulting in spirolactones (277) using formal [3+2] cycloaddition between the carbonyl of one cyclopropenone molecule and the C-C single bond of another cyclopropenone was reported. Depending upon the nature of cyclopropenones, the reaction can be accompanied by decarbonylation.[205-210]



276 277

Acetalation at the carbonyl of cyclopropenone was reported with Et_3O^+ and subsequent treatment with an alcohol.[211] Replacement of the cyclopropenone oxygen with sulfur has been reported,[221] as shown in following example:



276 278

Another series of reactions reported at the carbonyl of cyclopropenone involve replacement of the carbonyl oxygen with silicon. For example, heteroanalogues (280) of di-tert-butylcyclopropenone and $(Bu^tMe_2Si)_3SiLi$.[212]

279 280

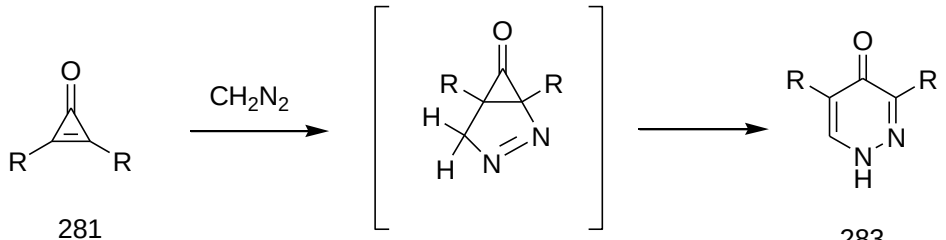
3) Cycloaddition to the three membered ring of cyclopropenone.

These are the most commonly observed reactions of the cyclopropenone ring due to the reactive delocalised ∏ system. Reactions are observed at C=C and C-C, with a further transformation observed frequently, such as rearrangement and fragmentation. These reactions are discussed in two subsections below.[95]

a) Addition to C=C double bond;

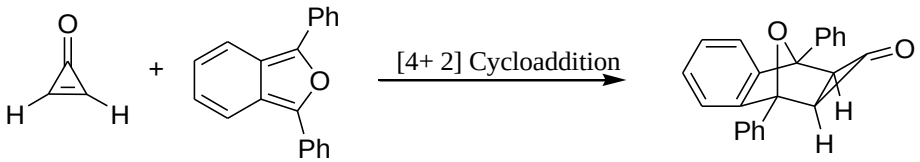
Cyclopropenones are known to react with 1,3-dipoles and activated dienes to form [3+2] and [4+2] cycloaddition products respectively.

An example of a [3+2] cycloaddition is the reaction of diazomethane as a 1,3-dipole adding across C=C of cyclopropenone, to give an adduct (282), which further rearranges to give a 3,5-disubstituted 4-pyridazone (283).[205]

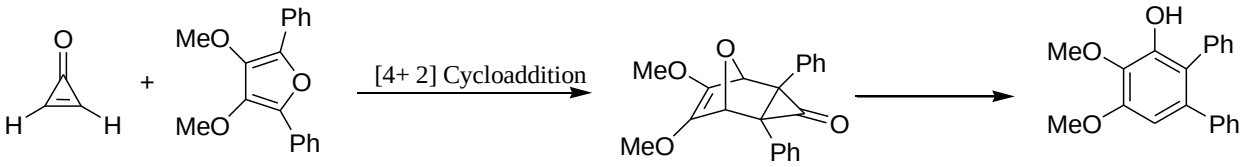


281 282 283

As an example of a [4+2] process, reaction with activated furans (284 and 286) and gave adducts (285 and 287), some of which reacted further as shown below:[213, 214]



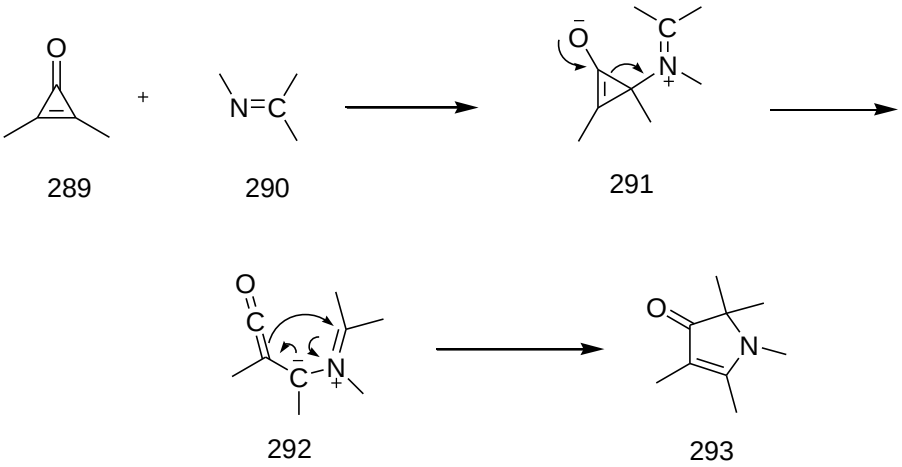
189 284 285



189 286 287 288

b) Addition with cleavage of C-C bond cleavage.

Addition of cyclopropenones to polarised ∏ bonds C=X (X= N, S, N=N) is a reaction reported in literature which is of direct interest to this thesis. In this reaction the C-C bond of the cyclopropenone is cleaved due to the ring strain and due to this the three carbons can become part of a five membered ring resulting in a [3+2] type addition product (293), as shown below (Scheme 2.40) with the case of an imine.

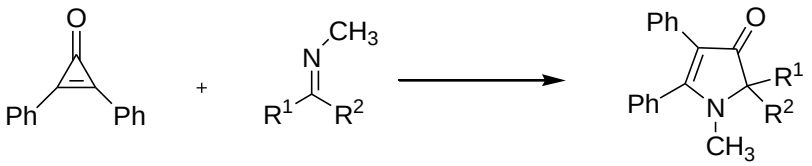


289 290 291 292 293

Scheme 2.40

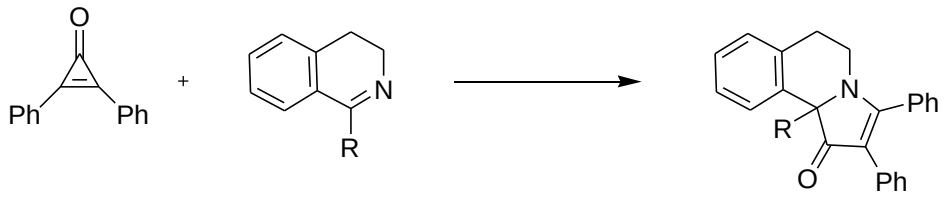
Diphenylcyclopropenone (123) undergoes cycloaddition with compounds containing imine structure such as guanidines[215] and other similar structures as described in the literature.[95]

Eicher et al in 1974 reported the first reaction of diphenylcyclopropenone (123) with an acyclic imine (131) to give a substituted 2-pyrrolinone (132), via a [3+2] cycloaddition.[119]



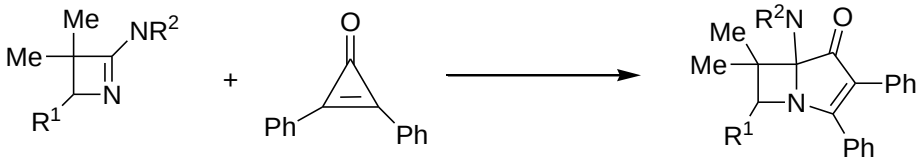
123 131 132

This work was further extended to a cyclic system (133) and diphenylcyclopropenone by Eicher et al, giving the benzo-fused system (136).[99]



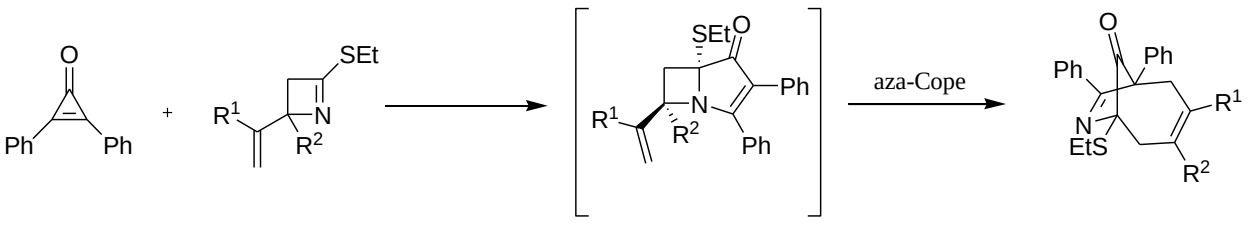
123 133 136

Heimgartner[101] showed that 2-amino-1-azetines (137) react with DPP (123) to give bicyclic pyrrolines (138).



137 123 138

Later, in 2006 based on the above Heimgartner work, the reaction of 1-azetines (294) with diphenylcyclopropenone (123) was explored by Hemming et al, resulting in azabicyclononanes (296), a result of an aza-Cope [3,3]-sigmatropic rearrangement of the initial cycloaddition product (295).[121]

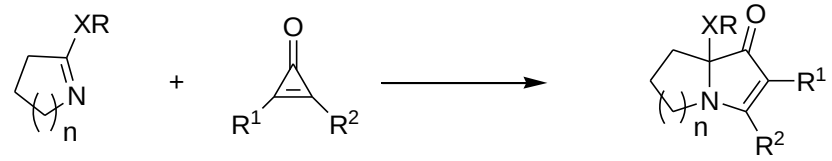


123 294 295 296

Scheme 2.41

The reactivity of five- and six-membered ketimines was further explored for the construction of indolizidine, pyrrolizidine (Scheme 2.42) and pyrroloazepines by Hemming et

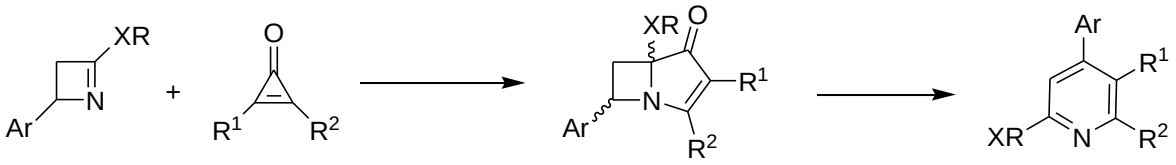
al in 2012 and the work extended to 4-aryl-1-azetines which were shown to produce pyridines (301), as shown below (Scheme 2.43).[122, 124]



n = 1, 2, 3
X= O,S
R = Me, Et

297 276 298

Scheme 2.42

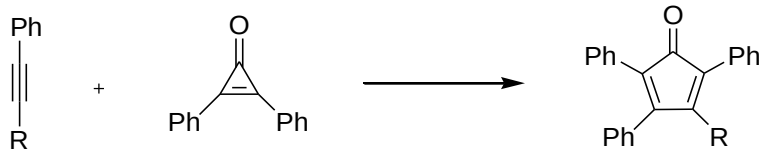


299 276 300 301

Scheme 2.43

The work presented in this thesis extends the work discussed above.

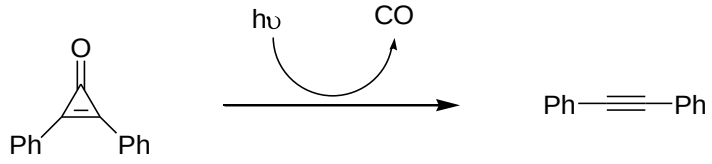
The Wender group has reported an elegant methodology for synthesis of cyclopentadienes (303) by Rh catalysed [3+2] cycloaddition of alkynes (302) with (123) cyclopropenones.[216]



302 123 303

4) Decarbonylation.

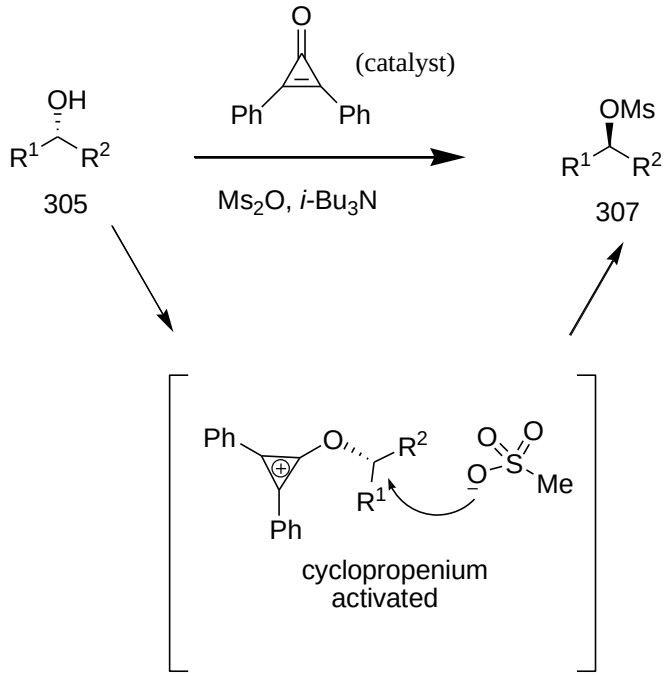
The photo decarbonylation of cyclopropenones has been studied recently by Popik et al. [217] High strain and the remarkably efficient photochemical activity of cyclopropenones has been utilised for the generation of the corresponding alkynes (304). The photodecarbonylation was used by Popik for the *in situ* generation of enediynes,[218] and selective labelling of living cells by a phototriggered click reaction,[219] whereby the alkyne reacts with an azide.



123 304

5) Cyclopropenones as catalysts.

Recently cyclopropenones have been used as catalysts (Scheme 2.44), for example, in the nucleophilic substitution of alcohols (305) by methanesulsulfonate ion, work that has been pioneered by the group of Lambert.[220]



Scheme 2.44

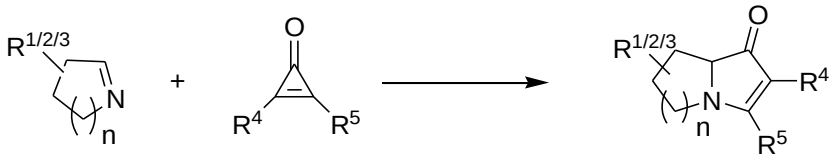
2.16 New reactions of cyclopropenones with imines:

This thesis will now describe the reactions of the imines whose synthesis was discussed in sections 2.1 to 2.4 with the cyclopropenones whose synthesis was also discussed in sections 2.6 to 2.15.

The imines (both six and five membered) were reacted the various cyclopropenones and with commercially available diphenylcyclopropenone (DPP). In some of the cases the imines and cylopropenones were generated *in situ* and reacted immediately due to stability factors.

No additional reagents were used in the reactions. All the reactions were conducted at room temperature, or started at -10°C and allowed to warm to room temperature.

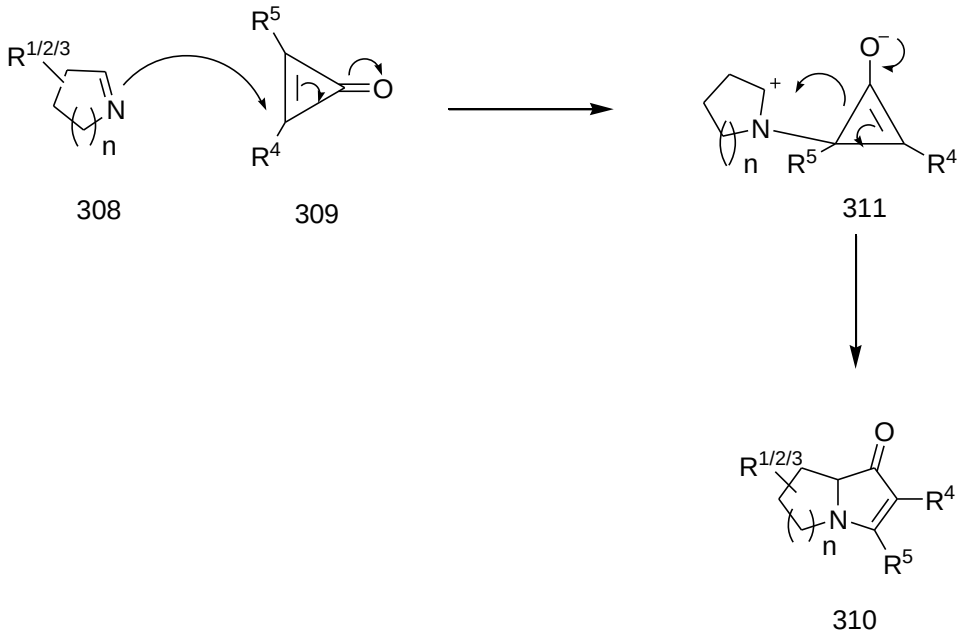
The general addition reaction is shown below (Scheme 2.45), together with a suggested mechanism.[117, 121-124] (Scheme 2.46)



308 309 310

Scheme 2.45

Proposed Mechanism:



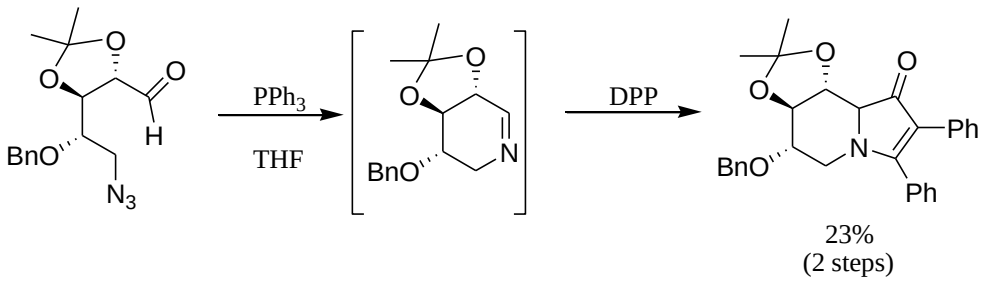
308 309 311 310

Scheme 2.46

The nucleophilic attack of the imino nitrogen on the eletrophilic cyclopropenone ring gives an intermediate (311) which undergoes electrocylisation leading to the bicyclic product (310).

2.17 Reaction of cyclopropenones with six- membered ring imines

The first reaction in this section is the attempted synthesis of indolizidines from aza-sugar based imines (159 & 173) with oxygen substituents arranged as per castanospermine (7).



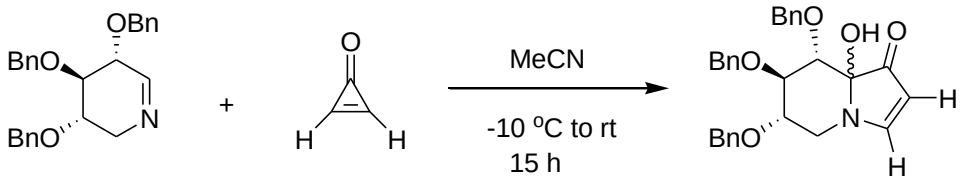
168 159 169

With imine (159), as shown above, the desired product (169) was isolated as a single diastereomer. The structural confirmation of the bicyclic core can be explained as follows. The five membered ring has a carbonyl conjugated with a double bond which is in conjugation with a tertiary amine and two phenyls. The vibrational stretching frequency of the conjugated carbonyl was observed at 1704 cm^{-1}, which was at a higher frequency than expected (1680 cm^{-1}), possibly due to the fused ring system. The structural assignment was further supported by the ^{13}C NMR spectrum, where the conjugated carbon of the keto was observed at 168.9 ppm. The presence of the conjugated double bond was observed as a strong band at 1583 cm^{-1} in the infrared spectrum. The presence of fifteen aromatic protons of the three different phenyl rings was observed in the range of 7.46-7.24 ppm in the ^{1}H NMR spectrum. The presence of the benzyl group was confirmed by the two benzylic protons at 4.89 and 4.75 ppm as doublets with a coupling constant of 11.8 Hz. The presence of the CH_2 next to the tertiary nitrogen was observed at 4.81 and 2.88 ppm as two doublets of doublets with coupling constants of 13.4 and 5.8 Hz. The proton on the bridge head was observed at 4.55ppm as a doublet. The three CH protons in the six-membered ring were observed at 3.87 (app t), 3.78 (m) and 3.09 (app t) ppm. The dimethyls of the acetonide were observed at 1.54 and 1.37 ppm as two singlets. The ^{13}C NMR spectrum offers more evidence for this structure. The carbonyl appeared at 168.9 ppm, along with two quaternary carbons for the alkene, three quaternary carbons from the aromatic rings and one from the acetonide. The presence of 2 CH_2 groups was observed in the DEPT 135, accounting for the benzyl and the methylene attached to nitrogen. The presence of two

methyls was observed at 26.8 and 26.6 ppm. The four non aromatic CH were confirmed by the DEPT spectra.

Attempts to react imine (159) with cyclopropenone itself were unsuccessful.

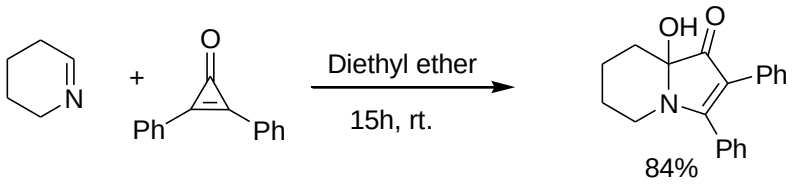
A second cyclic imine (173) with castanospermine oriented oxygen substituents (7) was also synthesised and reacted with cyclopropenone (189):



173 189 312

In the reaction, it was immediately obvious that the product obtained (312) was not what we expected. There was no bridgehead C-H, but there was an extra sp^3 quaternary carbon and mass spectral analysis showed an extra oxygen was present. The product was isolated as a single diastereomer. In the infrared spectrum, the carbonyl was observed at 1693 cm^{-1}, whereas the carbonyl in the cyclopropenone was observed at 1815 cm^{-1}. A hydroxyl group was observed as a broad peak at 3377 cm^{-1}. The presence of an alkene was clearly seen at 1538 cm^{-1}. The ^1H NMR spectrum clearly shows the diagnostic doublets for the two alkene CH protons, with one observed at 7.78 ppm and the other at 5.28 ppm with a coupling constant of 3.6 Hz. The three benzyl groups were clear with the 15 aromatic protons in the range of 7.76-7.18 ppm and six benzyl CH_2 protons observed at 5.27 ppm and in the range 4.69-4.48 ppm. The three CH protons connected to the three benzyloxy groups were observed at 4.19, 3.85 and 3.52 ppm, with the final ring CH_2 observed as a multiplet at 3.60-3.52 for two protons. This structural assignment was further supported by ^{13}C spectroscopy. The diagnostic carbonyl was observed at 202.16 ppm, the two CHs of the conjugated alkene were observed at 169 and 102.5 ppm. The number of quaternary carbons was 5 in total with 3 for the phenyls and 1 for the carbonyl and the fifth for the bridge-head hydroxyl at 92.44 ppm distinctive for C_q-O. DEPT analysis confirmed the presence of 4 CH_2 groups, three from the benzyls and one from the ring CH_2. The five non-aromatic CH were clearly assigned in the DEPT 90 with three sp^3 signals in a 6-membered ring and two sp^2 signals from the five-membered ring. The high resolution mass spectral data was the final confirmation of the proposed structure with observed mass of 494.1948 versus expected mass of 494.1937.

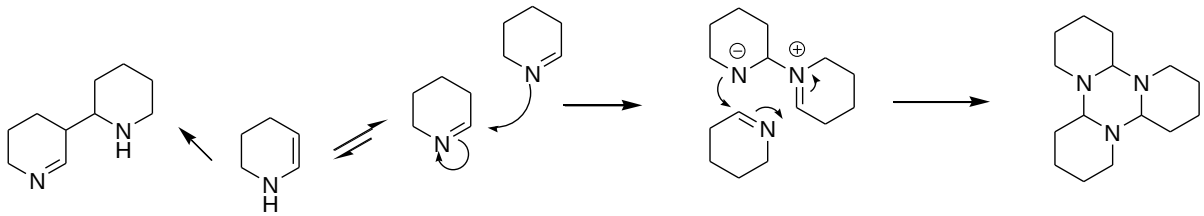
The next reaction was that of the parent piperideine (196) with diphenylcyclopropenone (123):



196 123 313

In this reaction, it was also noted that the expected indolizidine product had gained an extra oxygen and had a bridgehead C-OH rather than C-H hence forming compound (313).

As discussed in the imine synthesis section and shown below in Scheme 2.13, 2,3,4,5-tertrahydropiperideine was observed to be highly reactive and trimerises on standing:[221]

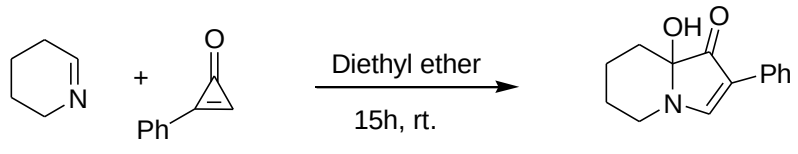


Scheme 2.13

The piperideine was thus generated *in situ* and diphenylcyclopropenone (123) was added to the piperideine solution. The product was isolated in 84% yield as a yellow solid. The carbonyl was observed at 1628 cm^{-1}, which was in the expected range. The hydroxyl peak stretching was observed at 3155 cm^{-1} as a broad peak. The proton arrangement was assigned from ^{1}H NMR, ^{13}C NMR and HMBC spectroscopic analysis. The six-membered ring has 4 methylene groups which appeared in the range of 1.29-3.62 ppm in the ^{1}H NMR spectrum. The protons in the aromatic region integrated to 10 H for the two phenyl rings. The CH_2 next to nitrogen appeared with one proton at 3.62 ppm as a dd with coupling constants *J*= 13.5, 4.7 with the other at 3.45 ppm as a td. The remaining protons appeared as multiplets, but the count was equal to 7H including the hydroxy proton. The ^{13}C NMR spectrum was more informative, with the carbonyl observed at 200.27 ppm, two phenyl quaternary carbons at 131.64 and 130.3 pm and the two alkene quaternary carbons at 172.07 and 107.4 ppm. The DEPT 135 showed clearly the presence of 4 CH_2. The hydroxy quaternary carbon was observed at 86.45 ppm, inferring the presence of the hydroxyl C-O.

The mass spectral evidence showed the gain of 16 mass units for the extra oxygen. The mechanism for oxygen uptake will be discussed later.

The next reaction was to use the same imine, the parent piperideine (196), but react it with phenylcyclopropenone (247). Again an extra oxygen appeared in the product (314).

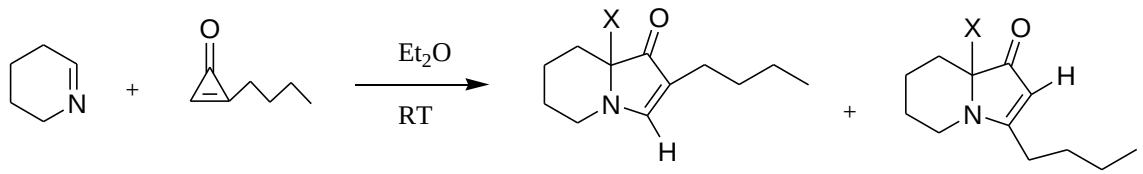


196 247 57% 314

The piperideine (196) was generated in-situ and was reacted with phenylcyclopropenone (247) synthesised as described above. The product (314) was a yellow gummy solid. The IR spectrum showed the characteristic carbonyl and hydroxy at 1614 and 3272 cm^{-1} where both peaks were strong and the hydroxy was broad. The proton NMR spectrum clearly indicated the formation of adduct (314). The presence of the phenyl ring was confirmed by 5 aromatic protons at 7.72, 7.25 and 7.02 ppm and the presence of the proton β to the carbonyl was observed at 8.76 ppm, as a singlet. The hydroxy was observed at 6.45 ppm as a broad singlet for one proton. The piperidine ring protons appeared as broad multiplets accounting for 8 protons. The ^{13}C NMR spectrum was more informative showing four quaternary carbons, the carbonyl at 199.81 ppm, the alkene at 133.59 ppm, the aromatic quaternary carbon at 128 ppm and the hydroxy substituted carbon at 86.14 ppm. The piperidine CH_2 carbons were observed at 44.94, 33.08, 27.13 and 18.63 ppm. The DEPT 90 showed the presence of one CH alkene carbon at 103.63 ppm, plus the three aromatic CH carbons.

There is a possibility of the formation of regioisomers, but we could isolate only one single regioisomer from the reaction mixture. The presence of the phenyl group next to the carbonyl was confirmed by the carbon correlations from HQC and HMBC. One of the reasons for regioselectivity could be the sterically free carbon of the cyclopropenone makes the nucleophilic attack easier than the carbon attached to the phenyl group. The mass spectral data further supported the proposed structure by showing m/z at 16 mass units higher than that expected, confirming the presence of the extra oxygen. The mechanism for the uptake of oxygen is discussed later in this section.

Next, the parent piperideine (196) system was reacted with butyl cyclopropenone (265):

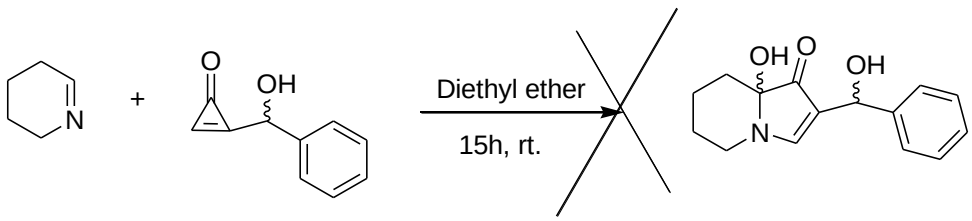


X= H / OH

196 265 315 316

The reaction led to a mixture of products believed to be regioisomers (315 & 316). The IR spectrum showed the presence of a strong carbonyl at 1633 and alkene at 1557 cm^{-1}. The hydroxy peak was observed at 3100cm^{-1} as a broad signal. The ^{1}H NMR spectrum clearly indicated the presence of a mixture. The distinctive peak of the alkene was observed for the two products as two singlets at 7.64 and 4.96 ppm. The region between 3.0 to 0.5 ppm was very complex due to the mixture of isomers giving overlapping signals. The ^{13}C NMR spectrum was equally complex, implying a mixture. The presence of two products was observed with two carbonyls at 205.7 ppm (A) and 189.7 ppm (B). The distinctive alkene CH were observed at 162.23 and 109.08. The presence of more than one product was confirmed using DEPT analysis which showed at least 14 CH_2s. The exact nature of the mixture remains uncertain and requires further work.

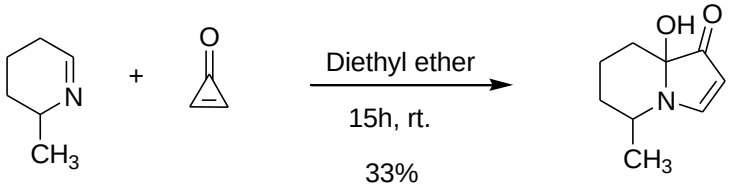
We also attempted to react the parent six membered ring piperideine (196) with 2(α-hydroxybenzyl)cyclopropenone (269):



196 269 317

The attempted reaction resulted in a yellow oily mass, from which no identifiable product could be isolated, although interestingly the starting cyclopropenone was consumed. This reaction needs further investigation.

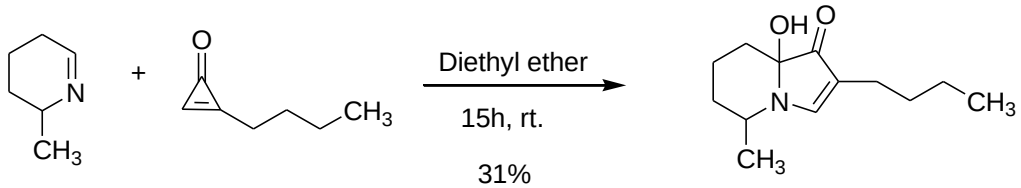
As discussed in the imine section we also had access to a methyl substituted piperideine. The thus generated imine (199) was subjected to addition to the in-situ generated unsubstituted cyclopropenone (189).



199 189 318

The reaction was sluggish and gave 33% yield; the product (318) was obtained as a single diastereomer. The IR spectrum of the product showed the presence of the α, β-unsaturated carbonyl at 1644 and 1538 cm^{-1}. The hydroxy was again observed as a broad peak at 3290 cm^{-1}. The ^{1}H NMR spectrum showed the distinct alkene protons of the five membered ring as two doublets at 7.85 and 5.00 ppm for one proton each (*J*= 3.4 Hz). The six membered ring had a distinctive doublet for the methyl observed at 1.37 ppm integrating for 3 protons. The N**CH**CH_3 was observed as a multiplet at 3.8-3.72 ppm for one proton. The remaining 6 protons of the ring were observed as multiplets in the range of 3.1 to 1.42 ppm. The carbon NMR spectrum showed the carbonyl at 204 ppm and the two alkene carbons were observed at 159.5 and 92.7 ppm, respectively. The bridgehead carbon attached to the hydroxy was observed at 86.8 ppm. The **CH-**CH_3 was observed at 50.0 ppm (CH) and the methyl at 17.70 ppm. The presence of 3 methylenes was confirmed with signals at 36.6, 33.43 and 19.30 ppm. Mass spectroscopic analysis confirmed the extra oxygen.

The same methyl substituted piperideine (199) was also reacted with butyl cyclopropenone (265):

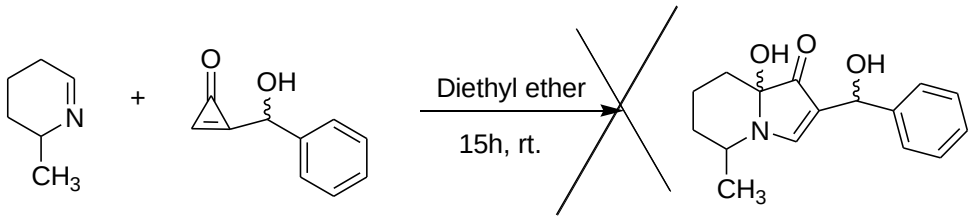


199 265 319

The infrared spectrum showed a peak for the carbonyl at 1661 cm^{-1} and the alkene stretching at 1583 cm^{-1}. The hydroxyl group stretching was observed at 3300 cm^{-1} as a broad peak. ^{1}H NMR analysis of the compound showed the alkene H at 7.61 ppm as a singlet for one proton. Only one isomer was isolated from the reaction mixture. The second

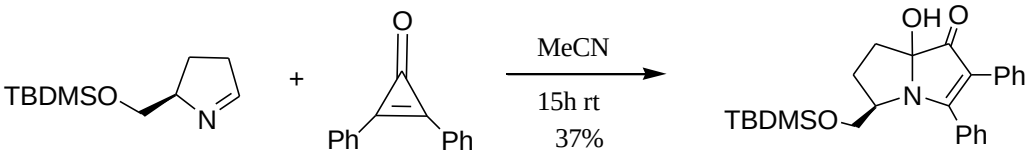
characteristic in the ^{1}H NMR spectrum was the presence of the butyl chain, the pattern for which was clearly observed as a triplet at 0.9 ppm for the methyl with the three methylenes as multiplets, at 1.50, 1.68 and 1.87 ppm. The methyl group on the six-membered ring was observed as a doublet for 3 protons and the CH connected to the methyl as a multiplet at 3.62-3.53 ppm. In the ^{13}C NMR spectrum, the carbonyl appeared at 203 ppm and the alkene CH at 158.26 ppm and the alkyl substituted alkene carbon at 117.28 ppm. Dept 135 showed the presence of the 6 methylenes. The methyl on the ring was observed at 18.53 ppm and the second methyl appeared at 13.95 ppm. The presence of the CH carbon was observed at 50.44 ppm and the bridgehead C-OH was seen at 73.06 ppm. Mass spectral evidence for the structure further confirmed the proposed structure, with a peak at 246.1 for the expected mass plus the extra atom of oxygen.

Attempts were made to study the reactivity of the same imine (199) towards hydroxy benzyl cyclopropenone (269). There was no reactivity between the two materials and no addition products were isolated from the reaction mixture.



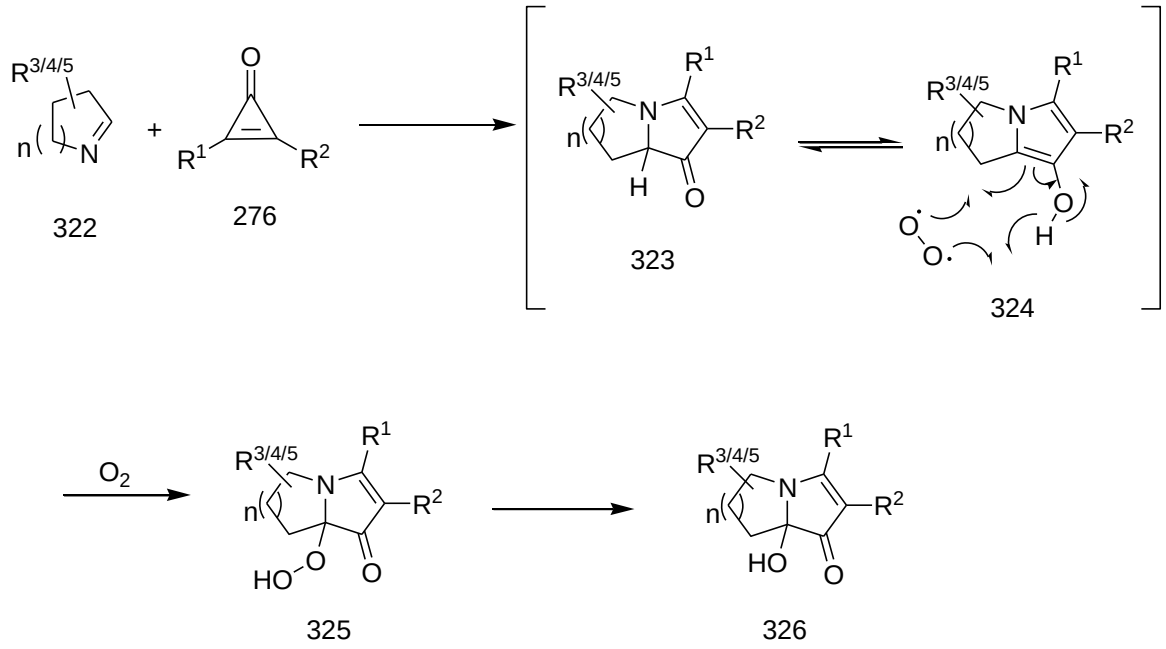
199 269 320

2.18 Reactions of 5-membered cyclic imines towards cyclopropenones:



209 123 321

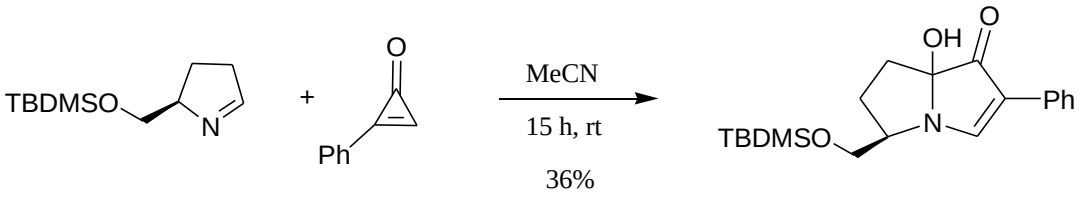
The cyclic imine (209) was synthesised as described in Section 2.3 above. This imine (209) was then reacted with commercially available diphenyl cyclopropenone (123), both the materials being stable at RT. In common with the reactions discussed above an extra oxygen in the final product. A mechanism for this oxygen uptake is now proposed; we believe that reaction initially leads to the predicted bicyclic product (323) with H on the bridgehead as shown below Scheme 2.47. Keto-enol tautomerism is then favoured by gaining pyrrole aromaticity to form (324). At this stage oxygen is picked up (324), to give a hydroperoxide (325), the initial product of oxidation. The hydroperoxide (325) undergoes O-O cleavage to give the isolated alcohol (326). It is reported in the literature that enols and their derivatives can undergo oxidation resulting in α-hydroxy ketones, without any catalyst, photosensitiser or photoinducer.[222] Likewise 3-hydroxypyrroles are also reported to undergo photooxidation resulting in highly reactive hydroperoxides.[223-225] The complete mechanistic details of this oxygen uptake (and those discussed above) are not clearly understood. It has been observed in some studies[222] that free radical traps failed to stop the reaction or that ESR signals could not be observed. In our catalyst free systems, it is possible that the intermediates are acting as oxidising agents or that the cyclopropenone acts as a photoinducer. A proposed reaction mechanism is shown below (Scheme 2.47), for a general imine and general cyclopropenone.



Scheme 2.47

The final product (321), the hydroxy ketone, was fully characterised. The infrared spectrum showed the hydroxy as a broad peak at 3342 cm^{-1} and the alpha, beta unsaturated ketone at 1679 and 1551 cm^{-1}. The ^{1}H NMR spectrum showed the two phenyls at 7.50-7.38 and 7.21-7.11 ppm as two separate multiplets for five protons each. The hydroxy group on the bridgehead was clearly observed at 4.1 ppm as a broad peak for one proton. The CH_2 connected to the TBDMS was seen as a multiplet at 3.85-3.79 ppm. The ring CH_2 groups appeared as multiplets at 3.50 and 2.24 ppm. The methyl groups of the TBDMS were observed as two singlets at 0.96 ppm for 9 protons and 0.17 ppm for 6 protons.
The ^{13}C NMR spectrum showed the carbonyl at 199.08 ppm, the alkene quaternary carbons at 176.1 and 113.76 ppm, the bridgehead C-OH at 96.57 ppm. NOESY analysis showed the hydroxy was *cis* to the TBDMS group. DEPT analysis showed the presence of the three methylenes at 66.7, 33.32 and 29.03 ppm and one CH at 60.9 ppm. The mass spectral data showed m/z 458.2 for the hydroxy ketone (M+Na), confirming the molecular weight.
A second as yet unidentified product was also isolated from this reaction which was clearly an imine-DPP addition product, but could not be fully characterised.

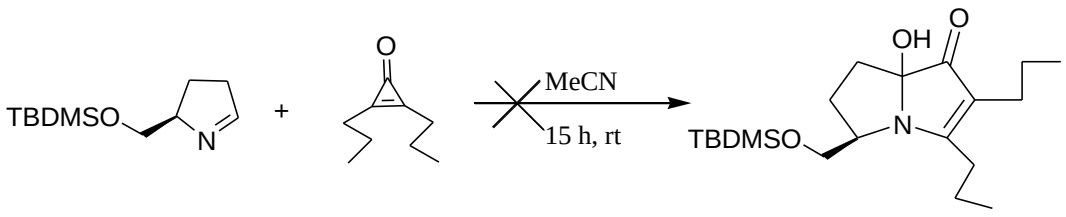
Next, the siloxymethyl substituted pyrroline (209) was reacted with phenyl cyclopropenone (247):



209 247 327

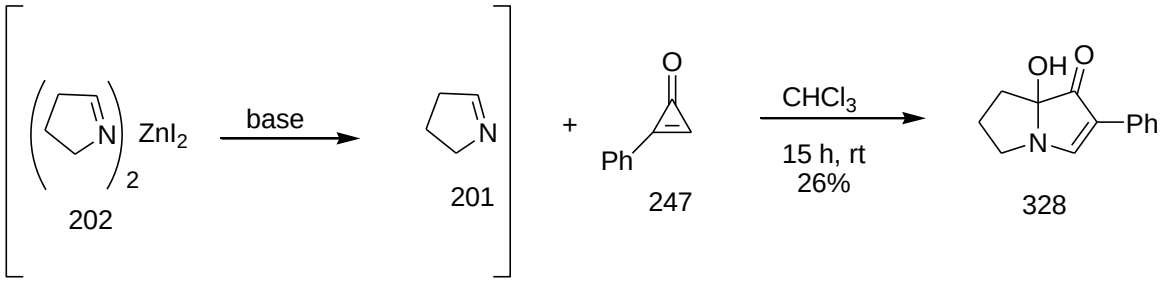
Only the oxidised hydroxy ketone (327) was isolated from the reaction mixture. The IR spectrum showed the carbonyl at 1667 cm^{-1} and the alkene at 1568 cm^{-1} for the α,β-unsaturated carbonyl system. The hydroxy was observed as a broad peak at 3366 cm^{-1}. ^{1}H NMR spectroscopy showed the CH of the alkene at 8.04 ppm as a singlet for one proton and the five aromatic protons as three multiplets in the range of 7.65-7.19 ppm. The CH_2 connected to TBDMS was observed as a multiplet at 3.82-3.74 ppm. The sp^3 CH in the 5-membered ring was a multiplet at 3.59 ppm and the two CH_2s of the ring were seen as 4 multiplets integrating for one proton each. The methyls of the TBDMS group were observed at 0.96 ppm as a singlet for 9H and at 0.15 ppm as a singlet for 6H.
The ^{13}C NMR spectrum provided further evidence for the above structural assignment. The carbonyl appeared at 199.34 ppm, the phenyl substituted alkene carbon at 114.23 ppm and the alkene CH at 165.25 ppm. The aromatic quaternary carbon was observed at 130.94 ppm, with three aromatic CH carbons between 128.47 and 124.14 ppm. The presence of the bridgehead carbon as a quaternary signal was observed at 96.91 ppm. DEPT 135 showed 3 CH_2 groups at 66.89, 33.26 and 29.60 ppm and DEPT 90 analysis confirmed the ring CH group at 63.2 ppm. The silyl methyls were observed at 25.88 ppm and -5.56 and the ^{t}Bu quaternary carbon was seen at 18.31 ppm. The structure was confirmed by mass spectral analysis with a peak at 382.2 as the sodium adduct of the oxygenated product.

The siloxymethyl substituted 1-pyrroline (209) failed to react with dibutylcyclopropenone (249);



209 249 328

Reactions of the parent 1-pyrroline:



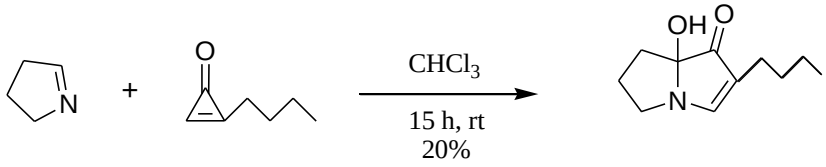
The simple parent imine 1-pyrroline (201) and its reaction with diphenylcyclopropenone (123) had been studied in our group previously. We extended these studies to phenylcyclopropenone (247), alkyl and other substituted cyclopropenones. This study started with phenylcyclopropenone (247). As observed in earlier cases we could isolate only one regioisomer. The imine (201) was highly reactive and was generated *in situ* from its stable zinc complex (202), using base. The product was again isolated as the bridgehead oxidised system (329). The IR spectra showed the presence of a carbonyl at 1602 cm^{-1} and the alkene unsaturation at 1553 cm^{-1}. The hydroxy group was observed at 3332 cm^{-1}.

The CH of the alkene was observed at 7.98 ppm in the ^{1}H NMR spectrum as a singlet for one proton and the five aromatic protons were observed at 7.63-7.16 ppm as multiplets. The second part of the ring derived from the imine was complex and the methylenes were multiplets, accounting for 6H. The protons on the carbon next to nitrogen were higher field in the ^{1}H NMR spectrum at 3.66 and 3.26 ppm. The ^{13}C NMR spectrum was more informative with the carbonyl carbon at 200.19 ppm and the methylene CH of the alkene at 165.39 ppm. The second alkene carbon (quaternary) was observed at 115 ppm. The bridgehead quaternary carbon appeared at 97.16 ppm. 3 CH_2 groups were seen at 49.12, 33.69 and 27.04 ppm. The mass spectrum showed a peak at 238.08 as the sodium adduct of the expected oxygenated structure.

The reactivity of the five membered parent cyclic imine (201) was also studied towards butyl cyclopropenone (265). This was found to react in the same fashion as monophenyl cyclopropenone (247), i.e. at the less hindered position as we were able to isolate only one regioisomer. The IR data showed the presence of the hydroxy group at 3350 cm^{-1} and the α,β-unsaturated carbonyl system at 1666 cm^{-1} and 1580 cm^{-1}.

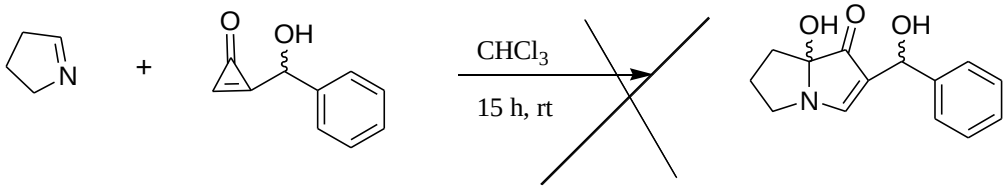
The ^{1}H NMR data showed further evidence for a single regioisomer, with the presence of only a single CH peak at 7.41ppm as a singlet. The CH_2 of the alkyl chain next to the ring was observed as a triplet at 2.08 ppm, with J= 7.6 Hz. Multiplets were observed for two

methylenes at 1.45 and 1.37 ppm with a triplet for the terminal methyl at 0.89 ppm with *J*=7.3 Hz. The ring methylenes 3 signals observed at 3.51-3.45 ppm for N-CH_2, with the second two methylenes at 2.02, 3.08 and 2.31 ppm as multiplets. The hydroxy proton was observed at 3.50 ppm as a broad peak. The ^{13}C NMR spectrum showed the presence of a carbonyl at 203 ppm, the alkene quaternary carbon at 117.71 ppm and the alkene CH at 166.40 ppm. The distinctive quaternary carbon to hydroxy was at 96.42 ppm consistent with a hydroxyl group at the bridgehead position. The second ring CH_2 groups and the alkyl chain methylenes were observed in the DEPT 135 spectrum. The terminal methyl carbon was observed at 13.79 ppm. The mass spectral data was in full accordance with the proposed structure and again confirmed the uptake of the additional oxygen atom.



201 265 330

The same cyclic imine (201) was subjected to potential reaction with hydroxy benzyl cyclopropenone (269). The attempt yielded unidentified products and showed no evidence for the formation of the desired product (331).

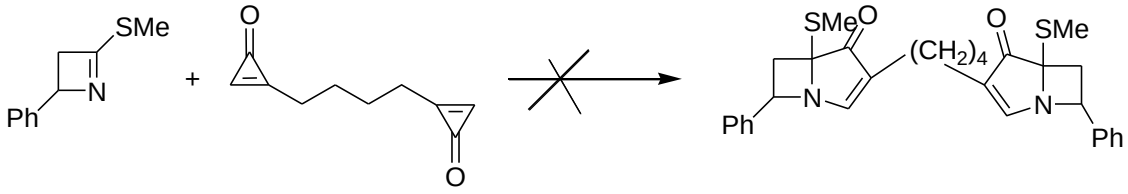


201 269 331

The reactivity of the same imine (201) towards butylbiscyclopropenone (267) was studied. The imine was generated *in situ* from the metal complex. The reaction mass was purified after 15 hours to recover the unreacted butylbiscyclopropenone (267). The reaction failed under various other conditions.

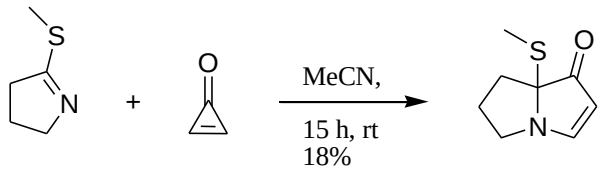
201 267 332

The reactivity of the biscyclopropenone (267) towards a 1-azetine (333) was also explored. The reaction was studied at room temperature to no effect and was then attempted at 65°C for 72 h with continuous monitoring. The imine (333) started decomposing but there was no change in the biscyclopropenone spot when monitored by TLC and IR spectroscopy. The reaction mass was purified to recover the unreacted biscyclopropenone (267).



333 267 334

Next a short series of reactions with the parent cyclopropenone and 1-pyrrolines was conducted, the first of which is shown below:

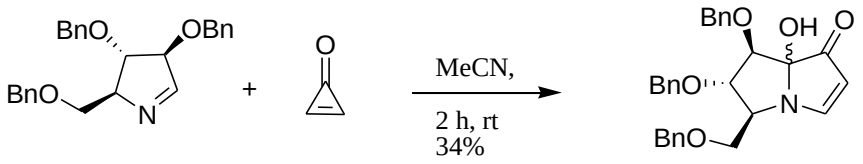


205 189 335

The imine (205) was synthesised as reported. This imine (205) has been widely studied in our group.[122] The new reaction with cyclopropenone (189) was successful and gave the desired product (335). The α,β-unsaturated carbonyl was observed in the IR spectrum at 1681 and 1533 cm^{-1}. The hydroxyl was observed at 2980 cm^{-1} as a broad peak. The proton NMR spectrum showed the characteristic two doublets for the alkene protons at 7.77 and 5.35 ppm. The three methylenes appeared at 3.56, 3.36 and 2.22 ppm for 6 H as three multiplets and the S methyl appeared at 1.96 ppm as a singlet. The carbon NMR spectrum showed the presence of the carbonyl at 203.54 ppm and the alkene CH at 169 and 105 ppm. The three CH_2 groups were observed at 48.46, 32.86 and 27.07 ppm. The bridgehead quaternary was seen at 79.46 ppm. The methyl was observed at 11.84 ppm. The mass

spectral data was in agreement with the proposed structure with m/z 192.04 for the sodium adduct of the product.

With a good protocol established for the use of the parent cyclopropenone, the next reaction explored with the parent cyclopropenone (189) was with the hyacinthacine-targeted imine (224) as shown below:



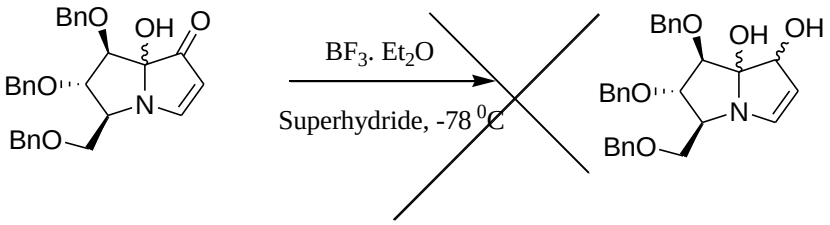
224 189 336

The imine (224) was synthesised as reported above in this thesis as a single enantiomer and reacted with the cyclopropenone (189). A clear new product was formed which was observed to be unstable and reacted further. The initial product slowly underwent transformation to the stable product (336) over 48 h in an NMR tube. The final product was analysed and gave spectral data consistent with the above structure (336). The IR spectra clearly showed the presence of a carbonyl at 1688 cm^{-1} and the alpha, beta unsaturation at 1538 cm^{-1}. The hydroxy group was observed as a broad signal at 3359 cm^{-1}.

The proton NMR spectrum showed the distinctive two doublets at 7.76 and 5.23 ppm for the alkene. The fifteen aromatic protons were observed in the range of 7.37-7.17 ppm as two multiplets. The proton on the carbon next to nitrogen was at 3.44-3.47 ppm as a ddd. The CH_2 connected to this CH was observed at 5.53 ppm as two dd. The bridgehead OH was observed at 3.89 ppm as a broad singlet for one proton. The remaining two CH of the ring were observed at 3.53 ppm for the CH next to the bridgehead at 4.17 ppm (dd). The benzyl CH_2s were observed in the range of 4.97-4.49 ppm. The structure was further confirmed by the ^{13}C NMR spectrum with the carbonyl observed at 201 ppm and the alkene CH at 168.75 and 102.24 ppm. The bridgehead carbon with the hydroxyl was observed at 92.02ppm and the three quaternary carbons for the phenyls of the benzyls were at 137.3, 137.1 and 136.6 ppm. The four CH_2 groups were observed at 71.5, 72.5, 73.06 and 73.2 ppm. The mass spectral data was in agreement with the proposed structure with a peak at 494.1 for the sodium adduct of the product, thus confirming the extra oxygen.

Attempted reactions of the adducts:

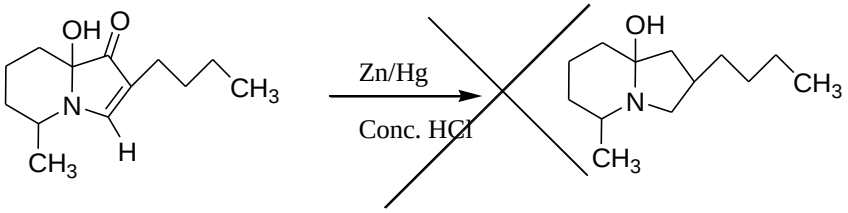
Attempted superhydride reduction of the enone (337) was unsuccessful.



337 338

We had anticipated that this would provide a route through to some interesting polyhydroxylated pyrrolizidines with substitution patterns similar to the hyacinthacines.

Similarly, Clemenson reduction[226] proved unsuccessful:



319 339

It was hoped that this reaction would give some indolizidines with alkyl substituent - a class of compounds that has attracted a lot of interest and include the so called poison-dart alkaloids found in several species of neotropical frog.
The reactions of castanospermine based imines (159 and 173) have already been discussed in a previous section (see Section 2.2).

159 173

Conclusion

The methodology of the reaction of cyclic imines with cyclopropenones was extended towards the synthesis of indolizidine and pyrrolizidine alkaloids, as an example analogues of benzylated castanospermine and hyacinthacines were presented.

Cyclic imines were synthesied using different methodologies like aza-Wittig reaction, dehydrohalogenation of N-halogentated systems and in some cases regioselective dehydrohalogenation was used. Another interesting methodology used was deoxygenation of nitrones, which resulted in the corresponding imines including some novel six membered cyclic imines. Nitrones were synthesised from different sugars with appropriate substitution patterns for the corresponding natural products like castanospermine and hyacinthacine.

A range of cyclopropenones with different substitution patterns like phenyl, butyl, diisopropyl, unsubstituted, hydroxyphenyl and biscyclopropenone were synthesised using the literature procedure in very good yields, although in some cases a slight modification of the procedure was needed. Attempts to synthesise allyl cyclopropenone were made but more experimentation is needed.

With these imines and cyclopropenones synthesised, their cycloaddition resulted in the bicyclic systems having the substitution patterns similar to that of castanospermine and hyacinthacine. A number of different analogues were made with parent cyclic imines and their reaction with phenyl and alkyl substituted cyclopropenones were made which are interesting as potential precursors to alkaloids such as those found in the Madagascan frogs *Mantella aurantiaca* for example.

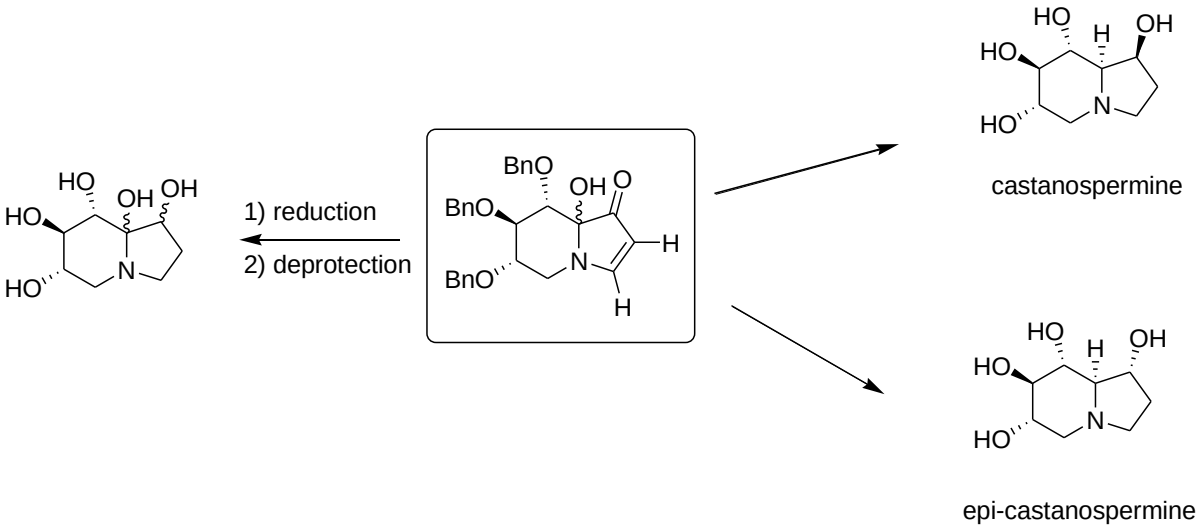
In the process of this study surprisingly we found an extra 16 mass units, on almost all addition products indicating an extra hydoxyl group at the bridge head position. This may have been due to aerial oxidation of the cycloaddition products.

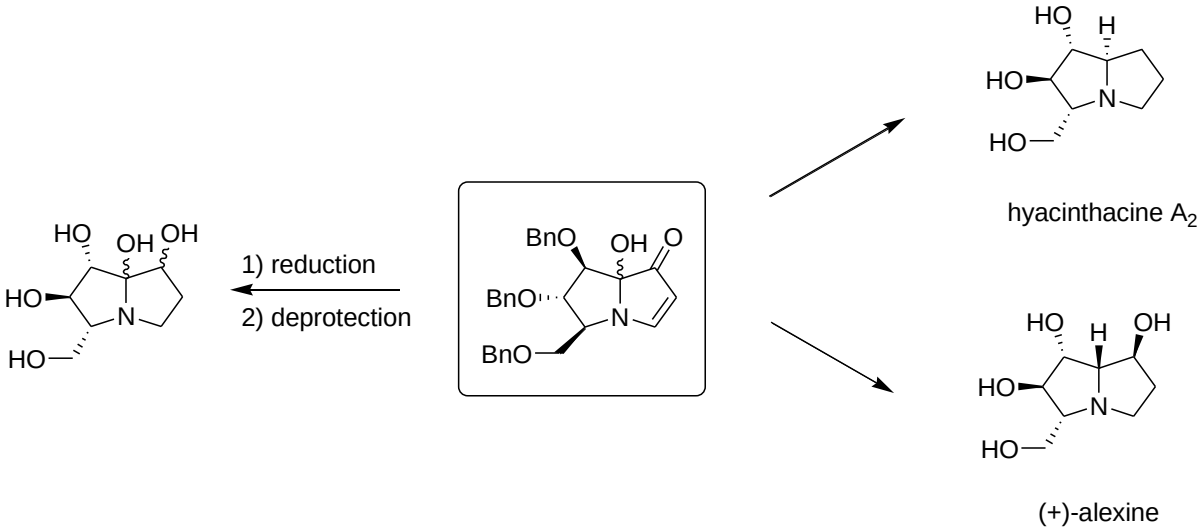
This work has shown that cyclopropenones can be reacted with complex and simple cyclic imines to give indolizidines and pyrrolizidines which have substitution patterns present in natural products such as hyacinthacines and castanospermine.

Future work:

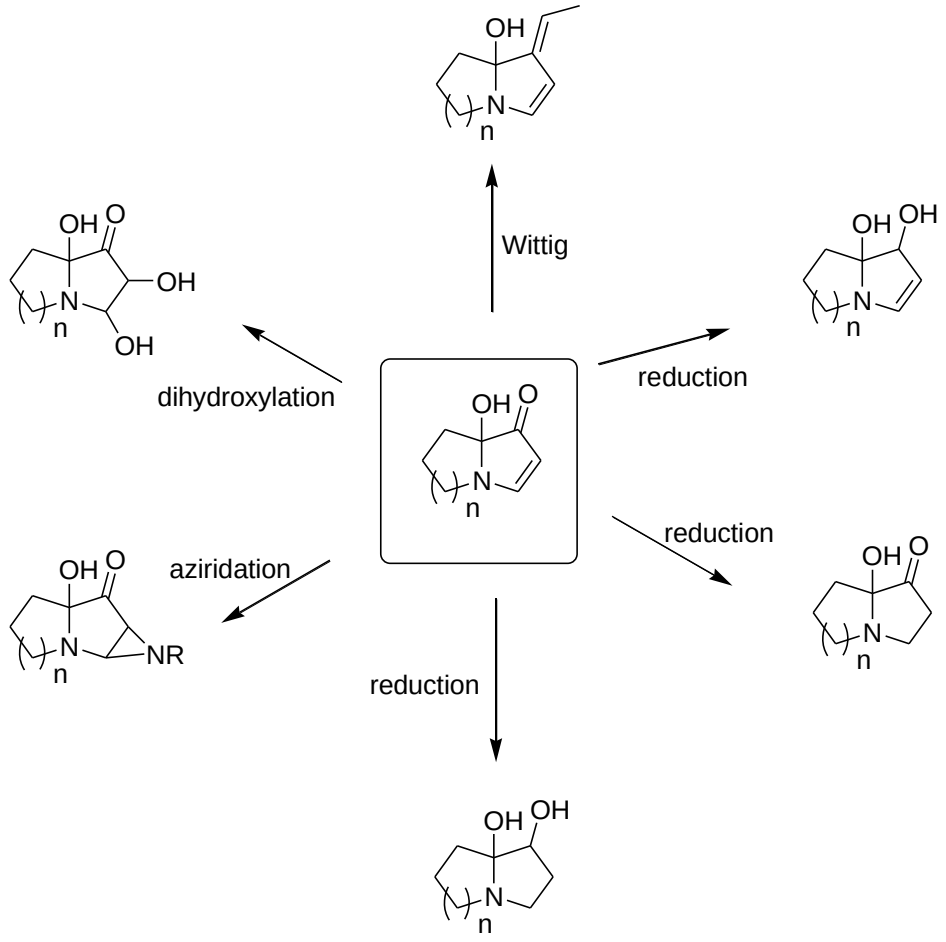
Further work is needed to synthesise the natural products castanospermine and hyacinthacine. A few reactions were conducted for the reduction of the vinylogous amide bond in the anlogues of alkaloids synthesised so far, like reduction using superhydride, $NaCNBH_3$ and Clemenson reduction. Similar work was carried out by the Sarpong group[227] for the reduction of simple indolizidine systems using $BF_3.OEt_2$ superhydride. These conditions were used in our systems, but resulted in unidentified products. Clemenson reduction seemed to give global reduction. More work is needed on this, the product of which can then further be subjected to removal of benzyl groups to result in the hydroxyl analogues of castanospermine and hyacinthacine. Removal of the hydroxyl group at the bridge head would result in the natural products castanospermine, hyacinthacine and alexine as shown below. This may be possible by OH derivatisation, elimination and reduction followed by deprotection.

Further mechanistic investigation of the oxidation of addition products would help to improve the yields and provide a route to avoid oxidation and synthesise natural prodcuts.





Secondly the vinylogous amide group could be used as a potential handle for further chemistry as shown below.

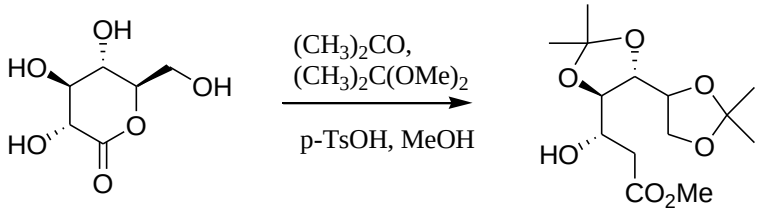


3. Experimental:

Indolizidines:

3.1 Synthesis of (3aR,7S,7aR)-7-(benzyloxy)-2,2-dimethyl-3a,6,7,7a-tetrahydro-[1,3]dioxolo[4,5-c]pyridine:

3.1.1 Synthesis of (S)-methyl 3-hydroxy-3-((4R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)propanoate:

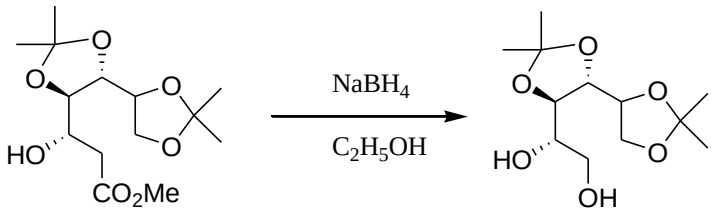


160 161

To glucanolactone (160) (20 g, 112.2 mmol), methanol (4 mL), acetone (12 mL) and 2,2-dimethoxy propane (40 mL, 325.3 mmol) and p-TsOH (300 mg, 1.57 mmol) were added. The resulting mixture was left stirring at RT for 48 h. The suspension turned into a clear solution after few hours, the mixture was stirred at RT for 2 days. A saturated solution of aqueous $NaHCO_3$ (4 mL) was added to the mixture and the resulting solution was distilled to remove the excess 2,2-dimethoxy propane to give a residue which was dissolved in CH_2Cl_2 and washed with brine. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined layers were dried over $MgSO_4$. Filtration and removal of solvent gave the acetonide (161) (32 g), as a colourless oil. TLC 30% EtOAc / P.E. TLC plate charred with 20% H_2SO_4 in ethanol. The oil was subjected to column chomatography over silica, EtOAc / P.E 30:70. to yield the product (161) as oil (24 g, 73%).
Data as per reported in the literature.[58, 59] key assignments are listed below:

^{1}H NMR δ (400 MHz, $CDCl_3$) 4.35 (1H, dd, *J*= 1.4, 9.1 Hz, C**H**$_2$(CO_2Me)), 4.22 (1H, dd, *J* = 1.4, 7.5 Hz, C**H** (OH)), 4.17-3.99 (4H, br m, 4 × **CH** (OC(CH_3)), 3.84 (3H, s, CO_2**CH_3**), 3.04 (1H, d, *J* = 9.1, **OH**), 1.43, 1.39, 1.37, 1.35 (12H, 4 × s, **2** × C(**CH_3**)$_2$).

3.1.2 Synthesis of (S)-1-((4R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)ethane-1,2-diol:

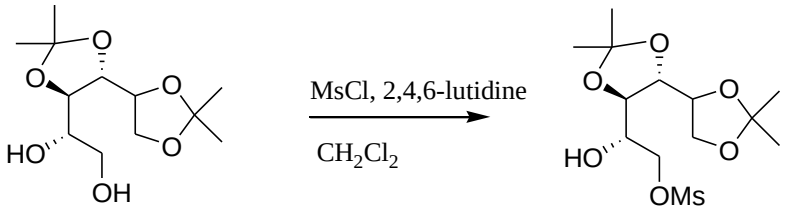


161 162

The acetonide (161) (10 g, 32.6 mmol) was dissolved in ethanol (50 mL) and the solution was cooled to 0 ^{o}C, $NaBH_4$ (5 g, 132.17 mmol) was added portion-wise, the reaction mixture was heated at reflux for 1h and ethanol was distilled off, to yield a gummy residue, which was dissolved in DCM (75 mL) and washed with water (75 mL). The organic washings were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the diol (9 g) as an oil. The resulting crude was subjected to chomatography over silica (EtOAc / PE: 50:50, R_f 0.3) to yield the product (162) as a colourless oil (7 g, 82%).

^{1}H NMR δ (400 MHz, $CDCl_3$) 4.19-4.15 (1H, m, **CH**$_2$ (OH)), 4.13-3.95 (4H, br m, 4 × CH $OC(CH_3)_2$), 3.86-3.67 (3H, br, m), 2.68 (1H, d, *J* = 8.3, **OH**), 2.51 (1H, m, **OH**), 1.43, 1.42, 1.39, 1.35 (12H, 4 × s, 2 × C(**CH$_3$**)$_2$), as reported in the literature.[58, 59]

3.1.3 Synthesis of (S)-2-hydroxy-2-((4R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)ethyl methanesulfonate:



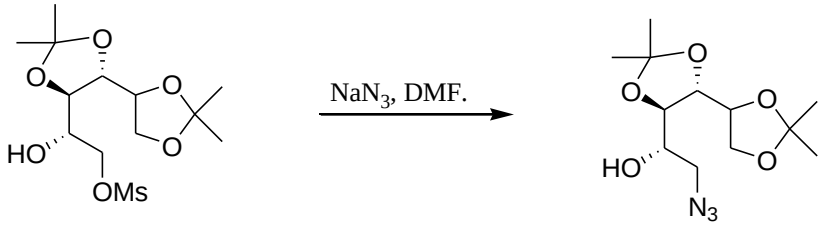
162 164

2,4,6-Lutidine (17.97 mL, 13.6 mmol) and methane sulfonyl chloride (1.0M in DCM, 11.5 mL, 14.96 mmol) were added to an ice cooled solution of diol (162) (4.0 g, 13.60 mmol) in dry CH_2Cl_2 (150 mL) and the mixture was stirred at 0 ^{0}C for 2 h. The sealed RB flask was left in the fridge overnight at 5-7 ^{0}C, whereupon the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with sat aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over ($MgSO_4$), filtered and the solvent removed under reduced pressure. Chomatography of

the residue on silica, (EtOAc / toluene: 50:50, R_f 0.3) yielded the product (164) as a white solid (3.6 g, 90%).

^{1}H NMR δ (400 MHz, $CDCl_3$) 4.38-4.30 (2H, m, **CH**, **CH$_2$**(**OMs**)), 4.20-4.16 (1H, m), 4.12-4.04 (2H, m), 4.01-3.91 (3H, m), 3.11 (3H, s, **CH$_3$**(**OMs**)), 2.53 (1H, d, *J* = 9.1 Hz, **OH**), 1.44, 1.43, 1.39, 1.36 (12H, 4 × s, 2 × **C**(**CH$_3$**)$_2$), as reported in the literature.[58, 59]

3.1.4 Synthesis of (S)-2-azido-1-((4R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)ethanol:



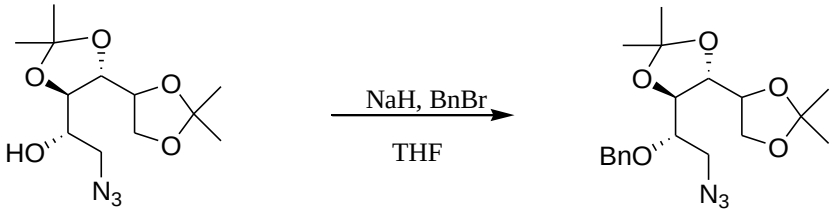
164 165

Sodium azide (1.1 g, 17.2 mmol) was added to the mesylate (164) (4.5 g, 13.23 mmol) in DMF (35 mL) and the mixture stirred at 100 ^{0}C for 3.5 h. The mixture was cooled to room temperature, diluted with EtOAc (50 mL) and then washed with water (50 mL). The aqueous layers were washed with EtOAc (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$) to give the desired compound.[58, 59] Chomatography of the residue on silica, (EtOAc / toluene: 30:70, R_f 0.4) yielded the product (165) (3.6 g, 90%) as a colourless oil, with data consistent with that reported. [58, 59]

^{1}H NMR δ (400 MHz, $CDCl_3$) 4.18-4.14 (1H, m, **CHN$_3$**, 4.07-4.02 (1H, m), 3.99-3.88 (4H, m), 3.50-3.45 (1H, m,), 3.39-3.35 (1H, m), 2.51 (1H, d, *J* = 9.1 Hz, **OH**), 1.43, 1.42, 1.38, 1.35 (12H, 4 × s, 2 × **C**(**CH$_3$**)$_2$).

IR: u_{max} (cm^{-1}): 3422, 2105, 1369, 1250, 1068, 850.

3.1.5 Synthesis of (4R,5R)-5-((S)-2-azido-1-(benzyloxy)ethyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane):

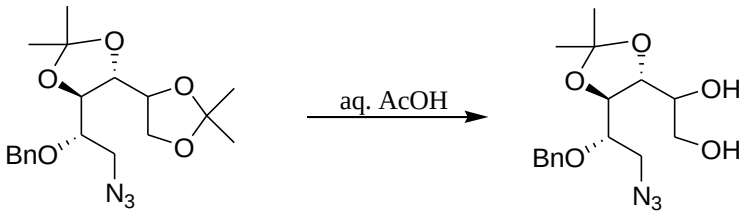


165 166

To a stirred solution of the azide (165) (1.54 g, 5.365 mmol) at 0 ^{0}C in THF (40 mL) was added NaH (167 mg, 6.975 mmol, 1.3 eq, 60% dispersion in mineral oil). The suspension was stirred for 1 h at room temperature. Benzyl bromide (0.83 mL, 6.975 mmol) was added dropwise and the mixture was stirred overnight at room temperature. The mixture was filtered though celite, concentrated and EtOAc (40 mL) was added. The organic layer was washed with water (40 mL) and dried ($MgSO_4$). Filtration and removal of solvent gave the benzyl protected compound[58, 59] (166) as a yellow oil, which was purified by chomatography over silica (eluent 5:95 EtOAc/PE) in 76 % yield, giving data consistent with that reported previously. [58, 59]

^{1}H NMR δ (400 MHz, $CDCl_3$) 7.38-7.30 (5H, m, **CH**(Ph)), 4.65 (2H, q, *J* = 11.4 Hz, CH_2 (Ph) 4.18-4.14 (1H, m, **CH**N_3), 4.07-4.02 (1H, m), 3.99-3.88 (4H, m), 3.50-3.45 (1H, m,), 3.39-3.35 (1H, m), 1.43, 1.42, 1.38, 1.35 (12H, 4 × s, 2 × **C**(**CH_3**)$_2$).

3.1.6 Synthesis of 1-((4R,5R)-5-((S)-2-azido-1-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol



166 167

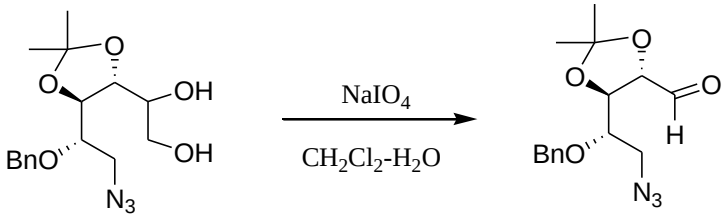
The benzylated intermediate (3.5 g) (166) was dissolved in 80% aq acetic acid and the mixture stirred at room temperature for 5 h and monitored by TLC for rxn completion. The

solvent was removed under vacuum. Chomatography on silica (eluent 50:50 EtOAc/PE) yielded the desired compound (167) as yellow oil, in 48 % yield

^{1}H NMR δ (400 MHz, $CDCl_3$) 7.40-7.33 (5H, m, **CH**(Ph)), 4.76 (2H, q, *J* = 11.4 Hz, **CH_2** (Ph) , 4.03 (1H, dd, *J* = 8, 3.5 Hz), 3.93-3.84 (2H, m), 3.78-3.71 (1H, m), 3.66-3.63 (2H, m), 3.56-3.47 (2H, m), 3.11 (1H, d, *J* = 2.7, **OH**), 2.14 (1H, m, **OH**), 1.41, 1.38 (6H, 2 × s, **C**(**CH_3**)$_2$).

The data was consistent with the literature.[58, 59]

3.1.7 Synthesis of (4S,5R)-5-(S)-2-azido-1-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde



167 168

The diol (167) (3.5 g, 10.38 mmol) was dissolved in CH_2Cl_2 (50 mL) and water (50 mL). The reaction mixture was cooled to 0 ^{0}C and then $NaIO_4$ (2.88 g, 13.50 mmol) was added and stirring was continued for 2 h allowing the mixture to attain room temperature. Water (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. Chomatography of the residue (EtOAc / PE; 25:75) gave the aldehyde (168) (2.2 g, 70%) as a colourless oil, data consistent with that reported.[58, 59]

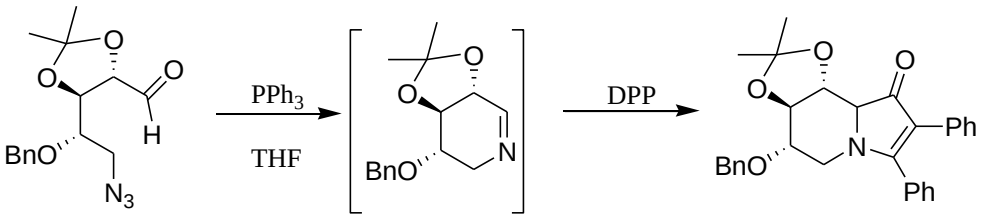
IR: υ_{max} (cm^{-1})3428, 2987, 2103 (N_3), 1733(C=O), 1455, 1372, 1254, 1215, 1164, 1084, 870, 737, 698.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.76 (1H, d, *J* = 1.5 Hz **HC**=O), 7.39-7.30 (5H, m, **CH** (Ph)), 4.76 (2H, q *J* = 11.5 Hz, **CH_2** (Ph), 4.30 (1H, m), 3.73 (1H, m), 3.49 (1H, m), 1.48, 1.39 (6H, 2 × s, **C**(**CH_3**)$_2$).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 201.1 (**CH**), 137.71 (**C**), 128.55 (**CH**), 128.11 (**CH**), 111.7 (**C**), 80.87 (**CH**), 77.39 (**CH**), 77.08 (**CH**), 73.56 (**CH_2**), 51.2 (**CH_2**), 26.52 (**CH_3**), 26.07 (**CH_3**).

ESI/MS (m/z): 328.1($M+Na^+$).

3.1.8 Synthesis of (3aR,4S,9bR)-4-(benzyloxy)-2,2-dimethyl-7,8-diphenyl-4,5-dihydro-[1,3]dioxolo[4,5-g]indolizin-9(3a*H*,9a*H*,9b*H*)-one.



168 159 169

In an oven dried three neck RBF, the azido aldehyde (168) (140 mg, 0.459 mmol) was weighed, dry THF (10 mL) was added under N_2 and freshly activated powdered molecular sieves were added and the mixture stirred at RT for 15 min. PPh_3 (144 mg, 0.550 mmol) was added, under N_2 flow. The mixture was stirred again for 15 min until the evolution of N_2 was complete. The resultant solution was transferred to an oil bath at 55 ^{0}C and stirred for 5 h and the rxn monitored by IR for disappearance of azido and aldehyde peaks. To this hot solution, diphenylcyclopropenone (144 mg, 0.55 mmol) was added and the mixture was stirred at 55 ^{0}C overnight. The solution turned yellow. The THF was removed by distillation under rotary evaporation. The residue was purified by chomatography, eluting with EtOAc/PE (15:85 to 30:70) to give the final product (169) 50 mg (23%), as bright yellow oil. R_f 0.5 (EtOAc/PE 30:70).

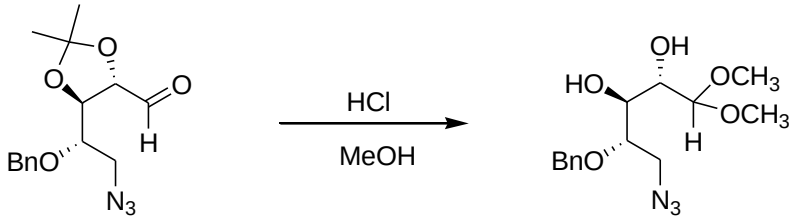
IR: u_{max} (cm^{-1}): 2951, 2855, 1704 (C=O), 1461, 1386, 1251, 1111, 835, 777, 698.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.46 (15H, m, **CH**(Ph), 4.89 (1H, d, *J* =11.8 Hz, **CH_2**O), 4.81 (1H, dd, *J* =13.3, 5.8 Hz, **CH_2**N), 4.75 (1H, d, *J* =11.8 Hz, **CH_2** (Ph)), 4.55 (1H, d, *J* = 9.6 Hz, **CH**C=O, bridge), 3.87 (1H, app t, *J* =18.3 Hz, CH (**CH**OCCH_3), 3.78-3.73 (1H, m, **CH** (OBn)), 3.09 (1H, app t, *J* =18.3 Hz, **CH**OCCH_3), 2.88 (1H, dd, *J* =13.4, 5.8 Hz, **CH_2**N), 1.54 (3H, s, **CH_3**CCH_3), 1.37 (3H, s, **CH_3**CCH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 168.9 (**C**=O), 151.3 (**C**), 137.8 (**C**), 132.7 (**C**), 132.2 (**C**), 131.4 (**C**), 129.5 (**CH** (Ph)), 129.0 (**CH** (Ph)), 128.8 (**CH** (Ph)), 128.4 (**CH** (Ph)), 128.2 (**CH** (Ph)), 128.1 (**CH** (Ph)), 128.0 (**CH** (Ph)), 127.7 (**CH** (Ph)), 127.4 (**CH** (Ph)), 111.5 (**C**), 83.2 (**CH**), 78.8 (**CH**), 74.7(**CH**), 72.0 (**CH_2**), 63.0 (**CH**), 41.6 (**CH_2**), 26.8 (**CH_3**), 26.6 (**CH_3**).

Mass: M/z required 490.1988 observed 490.1945 (M^+Na).

3.1.9 Synthesis of (2S,3S,4S)-5-azido-4-(benzyloxy)-1,1-dimethoxypentane-2,3-diol:



168 170

To a 50 mL RBF, fitted with a condenser, the azido aldehyde (168) (186 mg) was added. To this methanol (10 mL) was added and aqueous HCl (1 M, 2mL) was added and the whole heated at reflux for 2h, whilst being monitored by TLC. The solvent was distilled off under vacum and column chomatographed EtOAc/PE 50:50 to obtain the deprotected acetal (170) (160 mg, 96%). R_f 0.3, EtOAC/PE 50:50.

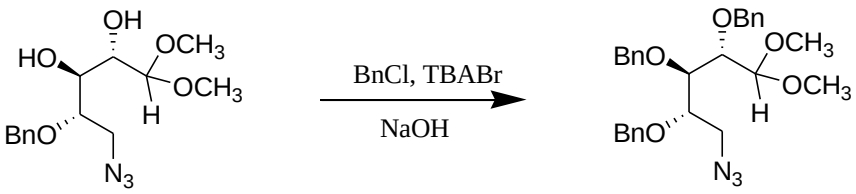
IR: u_{max} (cm^{-1}): 3449, 2926, 2089, 1453, 1282, 1114, 1069, 744.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.31 (5H, m, **CH** (Ph)), 4.77 (1H, d, *J* = 11.2 Hz, **CH_2**(Ph)), 4.65 (1H, d, *J* = 11.2 Hz, **CH_2**(Ph)), 4.43 (1H, d, *J* = 6 Hz, **CH** $(OCH_3)_2$), 3.94 (1H, t, *J* = 5 Hz, **CH** (OH)), 3.77 (1H, m, **CH**(OBn)), 3.68 (1H, t, *J* = 4.5 Hz, (**CH**(OH)), 3.62-3.52 (2H, m,2 × **OH**), 3.84 (3H, s, O**CH_3**), 3.46 (3H, s, O**CH_3**) 2.79-2.75 (2H, m, **CH_2N_3**).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 137.4 (**C** (Ph)), 128.5 (**CH** (Ph)), 128.11(**CH** (Ph)), 128.05(**CH** (Ph)), 105.12 (**CH**), 79.74 (**CH**), 73.13 (**CH_2**), 70.09(**CH**), 68.99(**CH**), 56.22 (O**CH_3)**, 54.86 (O**CH_3)**, 51.09 (**CH2**N_3)

Mass : m/z 334.1

3.1.10 Synthesis of (2S,3S,4S)-5-azido-(2,3,4)–tris(benzyloxy)-1,1-dimethoxypentane:



170 171

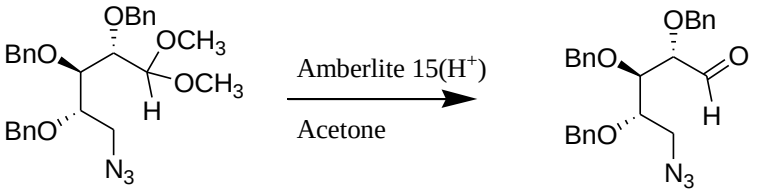
In a 50 mL RBF was weighed the deprotected compound (170) from above (220 mg, 0.707 mmol). To this 33% aq NaOH (10 mL), tetrabutyl ammonium bromide (200 mg) and BnCl (2.4 mL, 2.12 mmol) were added and the whole stirred at RT for 15 h and monitored by TLC. To this solution toluene (10 mL) was added and the phases were separated and the organic phase was washed with water until neutral, dried over anhydrous $MgSO_4$ and solvent evaporated under vacuum. The residue was chomatographed with EtOAc / PE 10:90 to afford the benzyl protected compound (171) (245 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.29 (15H, m, **CH** (Ph)), 4.89 (1H, d, *J* = 11.5 Hz, **CH**$_2$(Ph)), 4.74 (1H, d, *J* = 11.5Hz, **CH**$_2$(Ph)), 4.67-4.63 (3H, m, **CH$_2$**(Ph) **CH**$_2$(Ph)), 4.45 (1H, d, *J* = 6.5 Hz, **CH**$_2$(Ph)), 3.84 (1H, dd, *J* = 6.9, 2.9Hz, **CH** $(OCH_3)_2$), 3.76 (1H, td, *J* = 6.6, 2.9 Hz, **CH** (OBn)), 3.61 (1H, dd, *J* = 6.6, 2.9 Hz **CH** (OBn)), 3.52 (3H, s, O**CH$_3$**), 3.37-3.34 (1H, m, **CH**(OBn)), 3.31 (3H, s, O**CH$_3$**), 3.1-3.05 (2H, m, **CH$_2$**N_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.34(**C** (Ph)), 138.22 (**C** (Ph)), 138.05 (**C** (Ph)), 128.46 (**CH** (Ph)), 128.42 (**CH** (Ph)), 128.39 (**CH** (Ph)), 128.35 (**CH** (Ph)), 128.07 (**CH** (Ph)), 127.79 (**CH** (Ph)), 105.56 (**CH** (OCH_3)), 78.94 (**CH**(OBn)), 77.93 (**CH**(OBn)), 77.30 (**CH**(OBn)), 74.78 (**CH$_2$**(Ph)) , 73.63 (**CH$_2$**(Ph)), 73.36 (**CH$_2$**(Ph)), 56.43 (O**CH$_3$**), 54.33(O**CH$_3$**), 51.72(**CH$_2$**N_3).

Previously unreported.

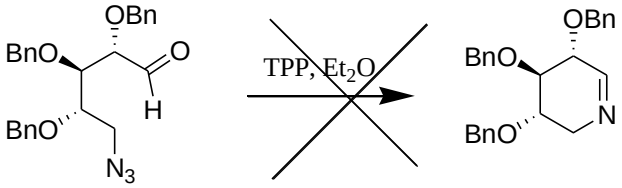
3.1.11 Synthesis of (2S,3R,4S)-5-azido-2,3,4-tris(benzyloxy)pentanal:



171 172

The benzylated compound (171) (50 mg) was weighed into a 25 mL RBF. To this, acetone (15 mL) and Amberlite-15 (50 mg) were added and the mixture stirred for 15h and the reaction monitored by TLC. The Amberlite was filtered off and the acetone was distilled off to obtain the crude carbonyl (40 mg) which was used in the next step without further purification.

3.1.12 Attempted Synthesis of (3S,4R,5R)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine:

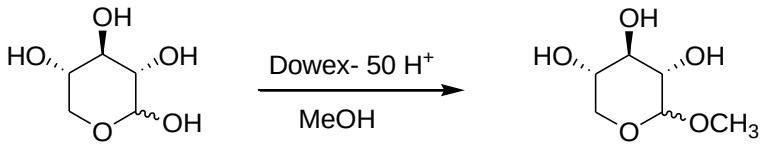


172 173

The crude azidoaldehyde (172) (40 mg, 0.10 mmol) obtained in the above step was placed in a clean oven dried RBF. To this Et_2O (8 mL) and TPP (triphenylphosphine) (79 mg, 0.30 mmol) were added under nitrogen and the rxn mixture was stirred at RT for 3 h and monitored by IR. This showed disappearance of the azide group, after which the mixture was heated to reflux. Infrared monitoring showed no further reaction and neither starting material, intermediate iminophosphorane or product imine could be recovered from the reaction mass. The only material recovered was triphenylphosphine oxide.

3.2 Synthesis of (3R,4S,5S)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine 1-oxide.

3.2.1 Synthesis of (3R,4S,5R)-2-methoxy-tetrahydro-2*H*-pyran-3,4,5-triol



174 175

D-xylose (174) (30 g, 199.8 mmol) and Dowex-50 (H^+) (10 g) in dry MeOH (200 mL) were heated under reflux for 6 h, after which the reaction mass was filtered concentrated to leave a residue which was chomatographed on silica to yield the product (175) (20.1g, 63%) as an oily mass (MeOH / $CHCl_3$, 10:90, R_f = 0.35), as mixture of anomers.

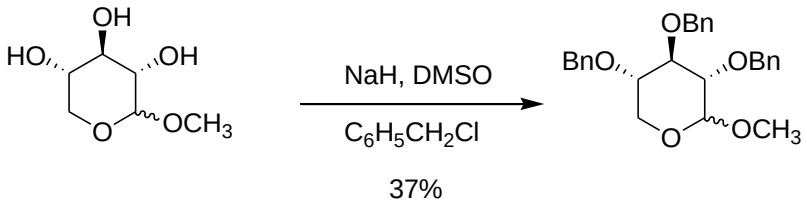
^{1}H NMR (500 MHz, DMSO) δ : (mixture of *α and β* anomers.) 5.06 (1H, d, *J*= 5.0 Hz, **CH**), 4.95 (2H, dd, *J*= 5.0, 1.8, Hz), 4.90 (1H, d, *J*= 4.9 Hz, **CH**), 4.78 (1H, d, *J*= 4.6 Hz), 4.76-4.70 (2H, m), 4.48 (1H, d, *J*=3.6 Hz), 4.02-3.94 (2H, m), 3.71-3.68 (2H, m), 3.50-3.39 (2H, m), 3.25-3.23 (6H, m, 2 × (**CH_3**)), 3.21-3.16 (1H, m), 3.10-3.0 (2H,), 2.95-2.91 (1H, m).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 105.17 (**CH**), 100.63 (**CH**), 76.99 (**CH**), 75.6 (**CH**), 73.88 (**CH**), 73.68 (**CH**), 70.42 (**CH**), 70.04 (**CH**), 66.13 (**CH_2**), 62.14 (**CH_2**), 56.42 (**CH_3**), 55.01(**CH_3**).

Mass: M/z 187.1 ($M+Na^+$).

As reported in the literature.[157]

3.2.2 Synthesis of (3R,4S,5R)-3,4,5-tris(benzyloxy)-2-methoxy-tetrahydro-2*H*-pyran.



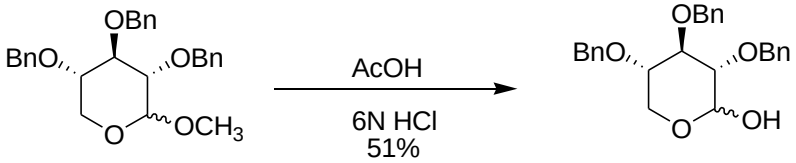
175 176

Methyl D-xylopyranoside (175) (20 g) in DMSO (60 mL) was added drop-wise to a stirred solution of dimsyl carbanion (prepared from 13 g of NaH and 40 mL of DMSO). After stirring for 1 h, benzyl chloride (70 g) in DMSO was added drop-wise to the reaction mixture. After stirring for 3 h at room temperature, the mixture was poured into ice water and extracted with Et_2O. The extract was concentrated to dryness. The residue was purified by column chomatography (eluent EtOAC / PE 30:70 R_f= 0.5). To give 20 g of the product[157] (176) in 37% yield, with data consistent with that reported. [157]

^{1}H NMR (500MHz, $CDCl_3$) δ : (mixture of α,β anomers.) 7.43-7.31 (30 H, m, **CH** (Ph)), 4.98-4.48 (m, 14H), 4.02-3.93 (m, 2H), 3.85-3.75 (m, 1H), 3.68-59 (m 2H), 3.59-3.57 (m, 3H), 3.56-3.52 (m, 1H), 3.50-3.48 (m, 1H), 3.44 (s, 1H), 3.41 (s, 3H), 3.40-3.38 (m, 1H), 3.30-3.24 (1H).

Mass: found M/z 457.19 (M+Na).

3.2.3 Synthesis of (3R,4S,5R)-3,4,5-tris(benzyloxy)-tetrahydro-2*H*-pyran-2-ol



176 177

Methyl 2,3,4-tri-o-benzyl-D-xylopyranoside (176) (15.5 g) was dissolved in acetic acid (100 mL) and to this 6N HCl (25mL) was added,[158] and the solution was stirred at 65 °C for 1.25 h. The reaction was followed by TLC. The resultant mixture was evaporated *in vacuo* and the resultant black residue was purified under column chomatography on silica to yield

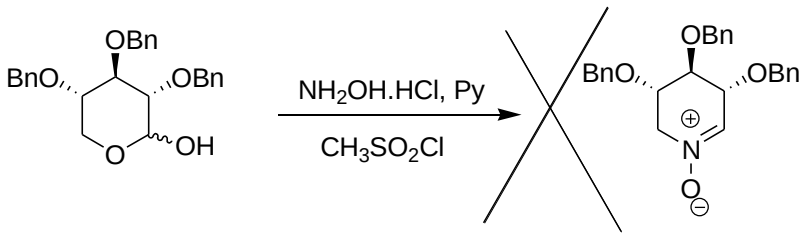
a white gummy solid (177) (7.71 g, 51% yield); (eluent, EtOAc / PE 30:70, R_f= 0.3); which gave data as reported in the literature. [158]

^{1}H NMR (500 MHz, $CDCl_3$) δ : 7.42-7.280 (m, 30H), 5.52(dd, 1H, J= 9.6, 4.2 Hz), 5.32-5.28 (m, 1H), 4.68-4.49 (m, 12H), 4.45-4.41 (m, 2H), 4.15-4.14 (m, 2H), 4.08-4.06 (m, 1H), 4.0 (d, 1H, J= 2.7 Hz), 4.0-3.96 (m, 2H), 3.82-3.68 (m, 4H).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ; 101.65, 96.17, 86.55, 81.25, 79.29, 73.64, 73.43, 72.99, 72.63, 72.28, 71.83, 68.64, 68.23.

Mass: m/z 443.2 (M+Na).

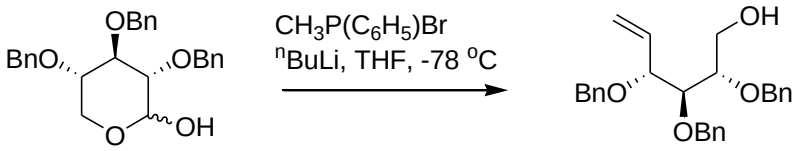
3.2.4 Attempted Synthesis of (3R,4S,5S)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine 1-oxide.



177 178

To a 0.5 M solution of lactol (177) (5 g) in dry pyridine (23.8 mL) was added 3 Å molecular sieves (3 g) and hydroxylamine hydrochloride (992 mg). The mixture was stirred overnight at room temperature and then a 0.6 M solution of methanesulfonyl chloride in dry pyridine (23.8 mL) was added. The reaction mixture was stirred overnight at room temperature and then filtered though Celite. The filtrate washed with dioxane (10 mL). The crude product was checked by TLC which showed no products or starting material. Column chomatography lead to decomposition products and a black residue.

3.2.5 Synthesis of (2R,3R,4S)-2,3,4-tris(benzyloxy)hex-5-en-1-ol.



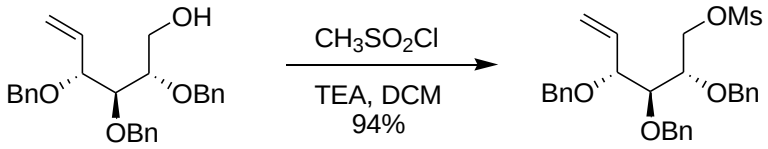
177 184

To a stirred solution of methyl triphenylphosphonium bromide (7.655 g) in dry THF (30 mL) was added *n*BuLi (13.39 mLof a 2.5 M solution in hexane) at -78 °C. The mixture was stirred at this temperature under nitrogen for 1 h and then 2,3,4-tri-o-benzyl-D-pyranoside (177) (3 g) in THF (25 mL) was added to the reaction mixture slowly at 0 °C. The reaction mixture was stirred at room temperature for 8 h and then quenched by adding saturated NH_4Cl and extracted with ether (3 x 50 mL). The organic layers were combined, washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chomatography to give the alcohol (184) as a colourless oil (eluent, EtOAc / PE, 20:80, R_f = 0.3) in 36% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.46-7.29 (15H, m, **CH** (Ph)), 5.96-5.87 (1H, m, **CH**=C), 5.39-5.31 (2H, m, **CH$_2$**=C), 4.77 (2H, s, **CH$_2$** (Ph)), 4.7-4.65 (4H, m, 2 × **CH$_2$**(Ph)), 4.16-4.12 (1H, m, **CH** (OH)), 3.76-3.56 (3H, m, 3 × **CH**), 3.48-3.46 (1H, m, **CH** (OH)), 2.27 (1H, t, J = 5.6 Hz, **OH**).
^{13}C NMR (100 MHz, $CDCl_3$) δ; 138.1 (**C**H=C), 137.73 (**C**H=C), 137.57 (**C**), 137.28 (**C**), 127.89 (**CH** (Ph)), 127.81 (**CH** (Ph)), 127.75 (**CH** (Ph)), 127.40 (**CH** (Ph)), 127.26 (**CH** (Ph)), 127.15 (**CH** (Ph)), 127.07 (**CH** (Ph)), 127.06 (**CH** (Ph)), 126.96 (**CH** (Ph)), 126.31 (**CH** (Ph)), 118.32 (**CH$_2$**=C)), 81.00 (**CH** (OBn)), 79.74 (**CH** (OBn)), 78.84 (**CH** (OBn)), 74.17 (**CH$_2$** (Ph)), 72.14 (**CH$_2$** (Ph)), 70.02 (**CH$_2$** (Ph)), 60.77 (**CH$_2$** (OH)).

The data was consistent with the literature.[147]

3.2.6 Synthesis of (2R,3R,4S)-2,3,4-tris(benzyloxy)hex-5-enyl methanesulfonate.



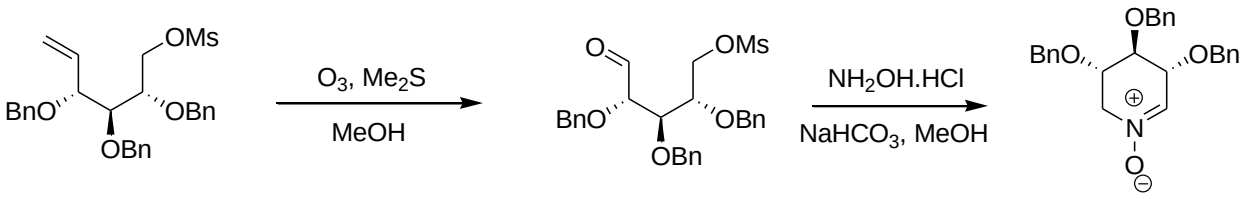
184 185

To a stirred solution of the alcohol (184) (500 mg) in dry DCM (20 mL) was added triethylamine (0.5 mL) followed by the addition of methanesulfonyl chloride, (0.138 mL) at 0 °C. The mixture was stirred for 3 h at RT. The reaction was quenched by the addition of water (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give the mesylated compound (185) (500 mg) as a colourless oil, in 84% yield.
The data obtained was consistent with the reported literature:[147]

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.35-7.17 (15H, m, **CH** (Ph)), 5.82-5.74 (1H, m, **CH**=C), 5.25-5.17 (2H, m, **CH_2**=C)), 4.70-4.46 (6H, m, 3 × **CH_2** (Ph)), 4.31-4.26 (2H, m, 2 × **CH** (OBn)), 4.13 (1H, dd, *J* = 11.0, 6.2 Hz, **CH** (OBn)), 4.01 (1H, dd, *J* = 7.5, 4.6 Hz, **CH_2** (OMs), 3.80-3.75 (1H, m, **CH_2** (OMs)), 2.73 (3H, s, **CH_3** (SO_2)).

^{13}C NMR (100 MHz, $CDCl_3$) δ; 138.2 (**CH**=C), 137.24 (**C**), 137.2 (**C**), 137.1 (**C**), 134.3 (**C**), 128.78 (**CH** (Ph)), 128.27 (**CH** (Ph)), 127.80 (**CH** (Ph)), 127.76 (**CH** (Ph)), 127.72 (**CH** (Ph)), 127.54 (**CH** (Ph)), 127.32 (**CH** (Ph)), 127.23 (**CH** (Ph)), 127.20 (**CH** (Ph)), 118.67 (**CH_2**=C), 79.53 (**CH** (OBn)), 79.07 (**CH** (OBn)), 74.10 (**CH** (OBn)), 72.83 (**CH_2** (Ph)), 69.93 (**CH_2** (Ph)), 69.48 (**CH_2** (Ph)), 36.40 (**CH_3SO_2O**).

3.2.7Synthesis of (3R, 4S, 5S)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine 1-oxide.



185 186 178

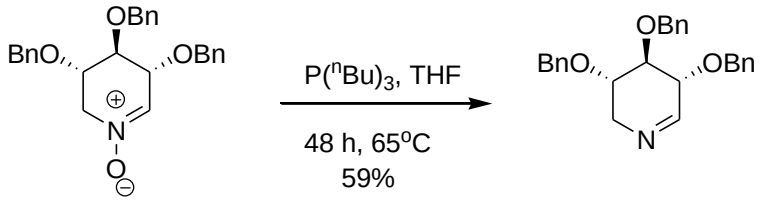
The crude mesylate (185) (2.2 g) was dissolved in dry methanol and O_3 gas was bubbled into the solution at -78 °C, until the solution turned blue. The reaction was quenched with Me_2S (3 mL) and the solvent evaporated to give the aldehyde intermediate (186), as an oil. The whole of the crude residue was used directly without further purification. To a solution of the crude aldehyde (186) (1.43 g), in MeOH (30 mL) was added $NH_2OH.HCl$ (1.59 g) and $NaHCO_3$ (1.92 g). The mixture was stirred at reflux overnight. After removal of the solvent, the residue was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried over $MgSO_4$ and concentrated and then purified by column chomatography on silica to give 800 mg (47 %) as of oily mass.[147] (178) (Eluent, MeOH / EtOAc, 5:95, R_f = 0.3). This was used directly in the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51-7.06 (15H, m, **CH** (Ph)), 6.89 (1H, br, s, **CH**=N), 4.66-4.49 (6H, m, 3 × **CH_2** (Ph)), 4.38-4.36 (1H, m, **CH** (OBn)), 4.06-4.00 (3H, m, 2 × **CH** (OBn), **CH_2**-N), 3.76 (1H, q, J = 2.6 Hz, **CH_2**-N).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.66 (**CH**=N), 137.20 (**C**), 137.10 (**C**), 132.90 (**C**), 128.62 (**CH** (Ph)), 128.57 (**CH** (Ph)), 128.40 (**CH** (Ph)), 128.18 (**CH** (Ph)), 128.15 (**CH** (Ph)), 127.96 (**CH** (Ph)), 127.93 (**CH** (Ph)), 127.77 (**CH** (Ph)), 127.72 (**CH** (Ph)), 82.77 (**CH** (OBn)), 80.33 (**CH** (OBn)), 73.49 (**CH** (OBn)), 72.1 (**CH_2** (Ph)), 71.93 (**CH_2** (Ph)), 71.68 (**CH_2** (Ph)), 66.08 (**CH_2**-N).

As reported in the literature.[147]

3.2.8 Synthesis of (3R,4S,5S)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine.



178 173

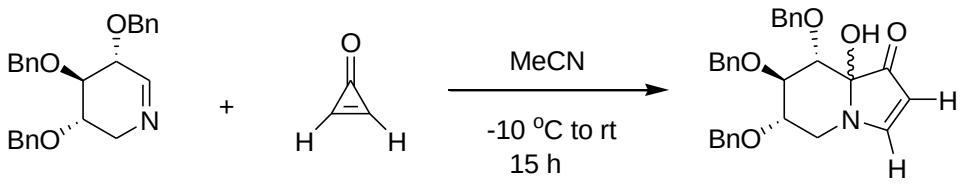
To a solution of nitrone (178) (350 mg) dissolved in 20 mL of dry THF was added n-tributylphosphine (419 µl, 2 eq) and the solution was stirred at 65°C for 48 h. The rxn was followed by TLC for completion. The solvent was removed under vaccum and the residue was purified by column chomatography with 1% MeOH in ethyl acetate to afford the imine (173) (198 mg, 59% yield) as an oily mass, which was used immediately, after analysis.

IR: u_{max} (cm^{-1}); 3100, 2863, 1724 (HC=N), 1496, 1454, 1361, 1242, 1098, 737, 698.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (1H, s, **HC**=N), 7.36-7.14 (15H, m, **CH** (Ph)), 4.62-4.52 (4H, m, 2 × **CH_2** (Ph)), 4.32 (2H, t, J = 6.2Hz, **CH_2** (Ph)), 4.11 (1H, t, J = 3.7Hz, **CH** (OBn)), 3.77-3.74 (1H, m, **CH** (OBn)), 3.71 (2H, dd, J = 6.05Hz, **CH** (OBn), **CH_2**N), 3.54 (1H, dd, J = 9.7, 6.3Hz, **CH_2**N).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 161.31 (**HC**=N), 138.13 (**C**), 137.87 (**C**), 137.49 (**C**), 128.62 (**CH** (Ph)), 128.57 (**CH** (Ph)), 128.40 (**CH** (Ph)), 128.18 (**CH** (Ph)), 128.15 (**CH** (Ph)), 127.96 (**CH** (Ph)), 127.93 (**CH** (Ph)), 127.77 (**CH** (Ph)), 127.72 (**CH** (Ph)), 90.62 (**CH** (OBn)), 84.39 (**CH** (OBn)), 76.77 (**CH** (OBn)), 73.34 (**CH_2** (Ph)), 72.33 (**CH_2** (Ph)), 71.98 (**CH_2** (Ph)), 60.98 (**CH_2**-N).

3.2.9Synthesis of (6R,7S,8R)-6,7,8-tris(benzyloxy)-8a-hydroxy-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one.



173 189 191

To a solution of the imine (173) (188 mg) dissolved in acetonitrile (15 mL) cooled to -10°C was added cyclopropenone (~65.3 mg) generated *in-situ* from the acetal, in acetone, dropwise over a period of 10 min. The solution was stirred overnight at room temperature. The rxn mass was distilled under vacuum and the crude residue was purified using column chomatography with 30:70 EtOAc: Petrol, R_f 0.3, yielding 50 mg of pure cycloaddition product (191) in 20% yield.

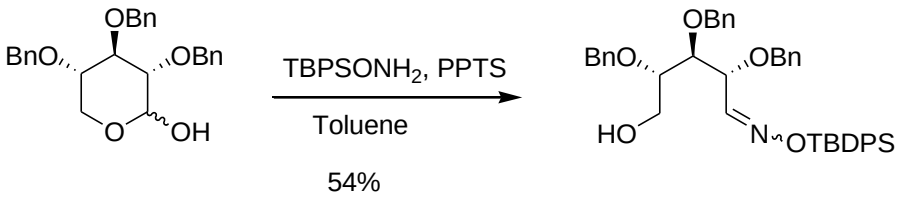
IR: $u_{max:}$ 3377 (br, OH), 3064, 3031, 2927, 2871, 1693 (C=O), 1538, 1454, 1114, 735.

^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.78 (1H, d, *J* = 3.6 Hz, N**CH**=CH), 7.76-7.18 (15H, m, **CH** (Ph)), 5.28 (1H, d, *J* = 3.6 Hz, C=**CH**C=O), 5.27 (d, 1H, *J*= 11.6 Hz, **CH_2** (Ph)), 4.69-4.48 (5H, m, **CH_2** (Ph)), 4.19 (dd, 1H, *J*= 6.4 Hz, **CH** (OBn)), 3.85 (d, 1H, *J*= 6.8 Hz, **CH**, (OBn)), 3.60-3.52 (m, 2H, N**CH_2**), 3.52-3.44 (m, 1H, **CH** (OBn)).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 202.16 (**C**), 169.21(**CH**), 137.58 (**C**), 137.45 (**C**), 136.97 (**C**), 128.56, 128.47, 128.41, 128.40, 128.08, 127.91, 127.85, 127.82, 127.70 (9 × **CH** (Ph)), 102.52 (**CH**), 92.44 (**C**), 87.37 (**CH**), 82.26 (**CH**), 73.57 (**CH_2**), 73.33 (**CH_2**), 72.82 (**CH_2**), 71.86 (**CH_2**), 63.14 (**CH**).

Mass: M/z required 494.1937 observed 494.1948 (M^+Na).

3.2.10Synthesis of (2S,3R,4R)-2,3,4-tris(benzyloxy)-5-hydroxypentanal O-tert-butyldiphenylsilyl oxime.



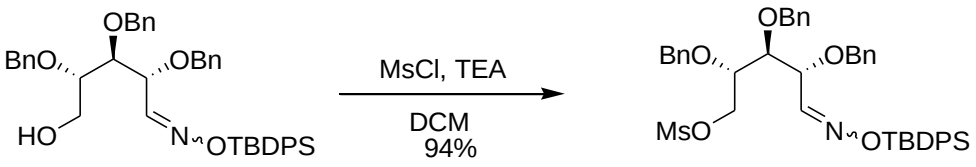
177 192

To the tribenzylated pyranose (177) (2.5g, 5.95 mmol) in dry toluene (50 mL), was added $TBPSONH_2$ (2.42g, 8.93 mmol), PPTS (46 mg, catalytic amount) and the reaction was heated at reflux with Dean-Stark apparatus for 3 h. The rxn mass was cooled to room temperature and toluene removed under vacuum and the resulting crude product was purified by column chomatography using 10:90 EtOAc / PE, to give the silyl protected alcohol (192) (2.17g, 50%) as a mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.72-7.13 (26H, m, **CH** (Ph), **CH**=N),4.74-4.62 (1H, bm, **OH**) 4.45-4.35 (2H, m, $\mathbf{CH_2}$ (Ph)), 4.24-4.14 (4H, m, $\mathbf{CH_2}$ (Ph)), 3.99-3.3.80 (1H, m, **CH** (OBn)), 3.70 (1H, dd, *J* = 5.6, 3.0 Hz, **CH** (OBn)), 3.42-3.37 (2H, m, CH_2OH), 2.39 (1H, d, *J* = 6.5 Hz CH_2OBn) 1.1 (9H, s, C($\mathbf{CH_3}$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.2 (**HC=N**), 137.94, 137.92, 137.4, 135.58, 135.5, 133.42, 133.31, 129.93, 129.76, 128.52, 78.57 (**CHOH**), 76.75 (**CHOH**), 74.25 ($\mathbf{CH_2}$), 73.29 ($\mathbf{CH_2}$), 72.90 ($\mathbf{CH_2}$), 70.85 ($\mathbf{CH_2}$), 69.62(**CHOH**), 27.10 ($\mathbf{CH_3}$)$_3$, 19.29 (**C**).
Consistent with literature.[147, 162]

3.2.11 Synthesis of (2R,3R,4S)-2,3,4-tris(benzyloxy)-5-(tert-butyldiphenylsilyloxyimino) pentyl methanesulfonate.



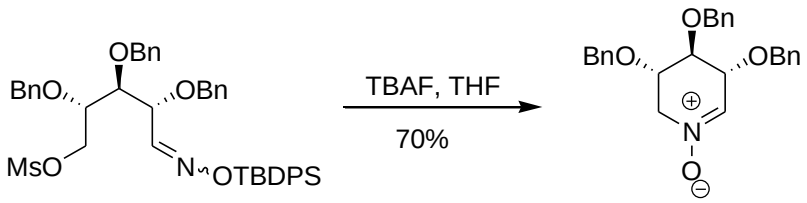
192 193

To a solution of silyl protected alcohol (192) (2 g, 2.96 mmol) in dry CH_2Cl_2 (30 mL) was added triethylamine (1.24 mL, 8.9 mmol) followed by addition of methanesulfonyl chloride (0.34 mL, 4.45 mmol) at 0 ºC. The mixture was stirred for 3 h at r.t. The reaction was quenched by addition of water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under vaccum to afford an oily mass, which upon chomatography over silica (20:80 EtOAc / PE) afforded the mesylated compound (193) (2.0 g, 90%).
The data was consistent with the literature.[147]

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.72-7.10 (26H, m, **CH** (Ph), **CH**=N), 4.93-4.08 (6H, m, **CH_2** (Ph)), 4.11-4.08 (1H, m, CHOBn), 4.0 (1H, dd, *J* = 7.8, 4.24 Hz CHOBn), 3.90 (1H,dd, *J*= 6.3, 4.24 Hz, CHOBn), 3.63 (1H, dd, *J* = 11.2, 3.1 Hz), 3.36 (1H, dd, *J* = 11.2, 5.3 Hz, CH_2OMs), 2.83 (3H, s, **CH_3**SO_2), 1.12 (9H, s, C(**CH_3**)**$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.70 (**CH**=N), 137.29 (**C**, Ph), 136.60 (**C**, Ph), 135,59 (**C**, Ph), 133.25 (**C**, Ph), 129.99 (**C**, Ph), 128.64, 128.55, 128.47, 128.41, 128.22, 128.16, 128.01, 127.90, 127.77, 127.67(**10** × **CH** (Ph)), 81.27 (**CH**) 78.67 (**CH**), 75.16 (**CH_2**), 74.50 (**CH**), 73.26 (**CH_2**), 70.68 (**CH_2**), 68.53 (**CH_2**), 38.24(**CH_3**), 27.04 **3** × (**CH_3**), 19.23 (**C**).

3.2.12Synthesis of (3R,4S, 5S)-3,4,5-tris(benzyloxy)-2,3,4,5-tetrahydropyridine 1-oxide.



193 178

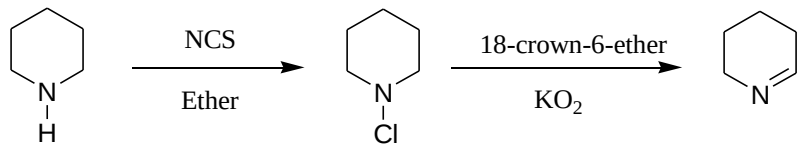
To the mesylate (193) (2.3 g) dissolved in THF (30 mL), was added molecular sieves (2 g), followed by TBAF (3.36 mL). The mixture was heated at reflux for 30 min, the crude residue was concentrated under vacuum and purified by chomatography over silica (5:95, MeOH/EtOAc), to afford the nitrone (178) (900 mg, 70% yield) as white solid.[147]

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.51-7.06 (15H, m, **CH** (Ph)), 6.89 (1H, br, s, **CH**=N), 4.66-4.49 (6H, m, 3 × **CH_2** (Ph)), 4.38-4.36 (1H, m, **CH** (OBn), 4.06-4.00 (3H, m, 2 × **CH** (OBn), **CH_2**-N), 3.76 (1H, q, *J* = 2.6 Hz, **CH_2**-N).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.66 (**CH**=N), 137.20 (**C**), 137.10 (**C**), 132.90 (**C**), 128.62 (**CH** (Ph)), 128.57 (**CH** (Ph)), 128.40 (**CH** (Ph)), 128.18 (**CH** (Ph)), 128.15 (**CH** (Ph)), 127.96 (**CH** (Ph)), 127.93 (**CH** (Ph)), 127.77 (**CH** (Ph)), 127.72 (**CH** (Ph)), 82.77 (**CH** (OBn)), 80.33 (**CH** (OBn)), 73.49 (**CH** (OBn)), 72.1 (**CH_2** (Ph)), 71.93 (**CH_2** (Ph)), 71.68 (**CH_2** (Ph)), 66.08 (**CH_2**-N)

Consistent with the literature.[147]

3.3 Synthesis of 2,3,4,5-tetrahydropyridine

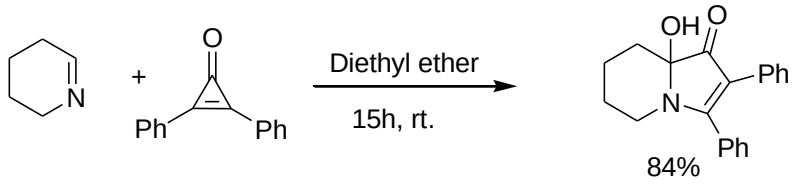


194 195 196

In a 500 mL oven dried RBF, a mixture of piperidene (194) (10 g, 0.1174 mmol), NCS (15.68 g, 0.1174 mmol) and dry ether (250 mL) was stirred under nitrogen for 24 h, at 0°C. This solution was concentrated to approximately 215 mL under vaccum at RT, to give an approximately (195) 0.3 M solution,[165] which was used directly in the next step.

To 100 mL of the above 0.3 M solution, (195) (28.57 mmol) was added KO_2 (4.26 g, 60 mmol) and 18-crown-6-ether. The mixture was slurried for 15 h at RT, during which the yellow colour of KO_2 faded to a beige. The solution (196) was filtered and used directly for cycloaddition in the next step.

3.3.1 Synthesis of 8a-hydroxy-2,3-diphenyl-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one



196 123 313

To a 250 mL oven dried RBF, containing the above obtained ethereal cyclic imine solution (0.3M, 20 mL) (196) was added DPP (123) (150 mg, 0.72 mmol) and the mixture was stirred at RT for 15 h and the rxn monitored by TLC. The solvent was distilled off and the residue purified by column chomatography with PE / EtOAc 60:40 to 30:70 to yield 186 mg (84%) of yellow gummy solid (313).

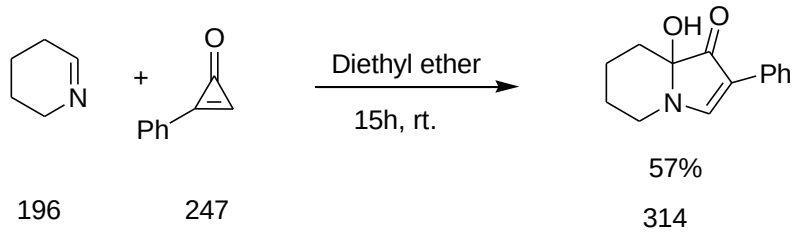
IR: υ_{max} 3155, 2981, 1628, 1527, 1438, 1378, 1280, 1188, 779, 719.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-6.99 (10H, m, **CH** (Ph)), 3.62 (1H, dd, J = 13.5, 4.7 Hz, **CH**$_2$N), 3.45 (1H, td, J=13.5, 3.4 Hz, **CH**$_2$N), 2.19 (1H, m, **CH$_2$**), 2.08-1.99 (1H, m, **CH**$_2$), 1.76-1.64 (4H, m, 3 × **CH**$_2$, **OH**), 1.32-1.29 (1H, m, **CH**$_2$),

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 200.27 (**C**=O), 172.07 (N**C**=C), 131.64 (**C** (Ph)), 130.31 (**C** (Ph)), 130.23 (**CH** (Ph)), 129.04 (**CH** (Ph)), 128.43 (**CH** (Ph)), 128.30 (**CH** (Ph)), 127.78 (**CH** (Ph)), 125.22 (**CH** (Ph)), 107.42 (NC=**C**CO), 86.45 (**C** (OH)), 41.95 (**CH$_2$**), 34.23 (**CH$_2$**), 27.38 (**CH$_2$**), 19.14 (**CH$_2$**).

MS: M/z required 306.1488 found 306.1485 (M^+ + H), $C_{20}H_{20}N_1O_2$.

3.3.2 Synthesis of 8a-hydroxy-2-phenyl-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one:



196 247 57% 314

To a 250 mL oven dried RBF, containing the above obtained ethereal cyclic imine solution (0.3M, 20 mL) (196) was added cyclopropenone (247) (150 mg, 1.15 mmol) and the mixture was stirred at RT for 15 h and monitored by TLC. The solvent was distilled off and the residue purified by column chomatography with PE/EtOAc 60:40 to 30:70 to yield 75 mg a of gummy solid, plus another gummy solid (314) (75 mg).

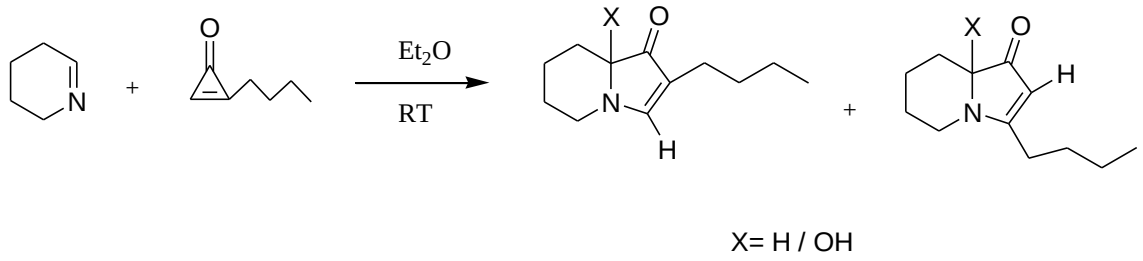
IR: u_{max} 3272, 2947, 1614, 1557, 1432, 1227, 1012.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (1H, s, **HC**=C), 7.72 (2H, d, J = 7.3 Hz. **CH** (Ph)), 7.25 (2H, t, J = 7.7 Hz, 2 × **CH** (Ph)), 7.02 (1H, t, J = 7.3 Hz, **CH** (Ph)), 6.45 (1H, s, br, O**H**), 3.75-3.67 (1H, m, **CH**$_2$), 3.5-3.49 (1H, m, **CH**$_2$), 1.81-1.72 (3H, m **CH**$_2$ and **CH$_2$**), 1.61-1.59 (1H, m, **CH**$_2$) 1.43-1.35 (1H, m, **CH**$_2$), 1.29-1.23 (1H, m, **CH**$_2$).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 199.81(**C**=O), 160.64 (**CH**), 133.59 (**C**), 128.07 (**CH** (Ph)), 123.85 (**CH** (Ph)), 122.75 (**CH** (Ph)), 103.63 (**C**), 86.14 (**C**OH), 44.94 (**CH$_2$**), 33.08 (**CH$_2$**), 27.13 (**CH$_2$**), 18.63 (**CH$_2$**).

MS: M/z required 252.0995 found 252.0994 (M^+ +Na)

3.3.3 Synthesis of 2-butyl-8a-hydroxy-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one.



X= H / OH

196 265 315 316

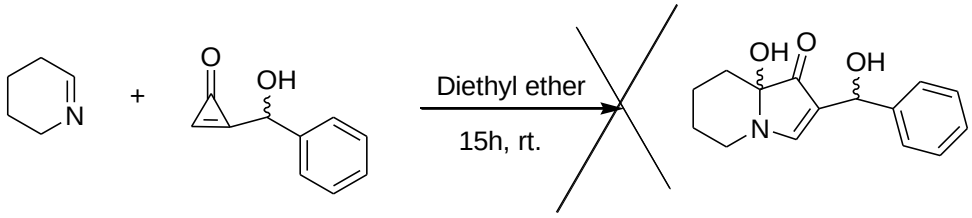
To a 250 mL oven dried RBF, containing the above obtained ethereal cyclic imine solution (0.3M, 20 mL) (196) was added butyl cyclopropenone (265) (160 mg, 1.45 mmol) and the mixture stirred at RT for 15 h, monitored by TLC. The solvent was distilled off and the residue purified by column chomatography with 2% methanol in ethyl acetate to yield 60 mg of a gummy solid as a mixture of regioisomers (315 & 316).

IR: u_{max}: 3100, 2956, 2870, 1633, 1557, 1455, 1365, 13357.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (1H, s, N**CH**=C), 4.96 (1H, s, NC=**CH**), 3.59-3.22 (2H, m, **CH_2**N), 2.80-2.70 (1H, m, CH_2N), 2.68-2.60 (1H, m, CH_2N), 2.58-2.36 (1H, m, CH_2), 2.32-2.30 (2H, m , br), 2.12-1.81 (9H, m, CH_2), 1.74-1.46 (4H, m, br, CH_2), 1.43-1.24 (9H, m, CH_2), 1.17-1.14 (1H, m, CH_2), 0.96-0.79 (6H, m 2 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.77 (**C**=O), 189.79 (**C**=O), 162.23 (N**CH**=C), 132.62 (N**C**=CH), 109.47 (**C**=CH), 95.45 (**C** (OH)), 84.18 (**C**H=CN), 83.07 (**C** (OH)), 45.60 (**CH_2**N), 43.11 (**CH_2**N), 37.87 (**CH_2**), 36.53 (**CH_2**), 34.61 (**CH_2**), 31.80 (**CH_2**), 31.49 (**CH_2**), 31.15 (**CH_2**), 28.62 (**CH_2**), 25.85 (**CH_2**), 23.32 (**CH_2**), 21.90 (**CH_2**), 21.80 (**CH_3**) 21.22 (**CH_2**), 19.00 (**CH_2**), 13.82 (**CH_3**).

3.3.4 Attempted synthesis of 8a-hydroxy-2-(hydroxy(phenyl)methyl)-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one

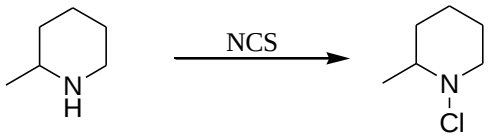


196 269 317

To a stirring solution of the imine (196) in dry diethyl ether (0.3 M, 100 mL) generated as above, cooled to -15 °C, was added dropwise a solution of hydroxyl phenyl cyclopropenone (100 mg, 0.62 mmol) (269) in acetone (15 mL), generated in-situ, by deprotection of the acetal form. The solution was stirred at RT and overnight the rxn was concentrated under vaccum and purified by chomatography over silica EtOAc / PE (50:50) and then MeOH / EtOAc (5:95), to yield the crude prodcut which showed some of the expected diagnostic signals but could not be purified further.

3.4 Synthesis of 2-methyl-2,3,4,5-tetrahydropyridine

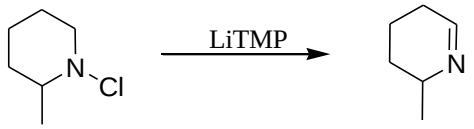
3.4.1 Synthesis of 1-chloro-2-methylpiperidine



197 198

To a solution of 2-methyl piperidine (197) (5 g, 51.01 mmol) in dry ether (250 mL), was added NCS (7.5 g, 56.11 mmol). The mixture was stirred under nitrogen for 20 h, at RT. The rxn was followed by TLC for consumption of starting material. The rxn mixture was washed with deionised water (3×50 mL), the ethereal layer dried over $MgSO_4$ and concentrated to yield 1-chloro-2-methylpiperidine (198) as an oily mass (5.5 g). The material was not stable and was used immediately in the next step.

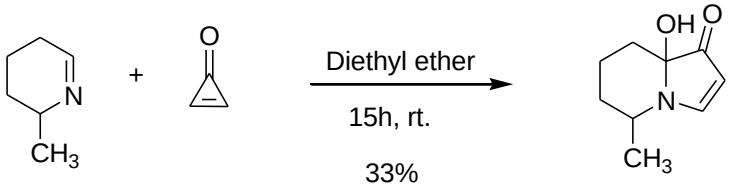
3.4.2 Synthesis of 2-methyl-2,3,4,5-tetrahydropyridine



198 199

To a solution of 1-chloro-2-methylpiperidine (198) (1 g, 7.480 mmoles) in dry Et_2O / PE (15 mL) cooled to -78 °C , was added LiTMP. (A solution of LiTMP was generated at 0 ^{0}C, from 2,2,6,6-tetramethylpiperidine (1.8 g, 12.74 mmol) and n-BuLi (5.6 mL, 2.5 M in hexanes) in 10 mL of anhydrous Et_2O)[228], slowly over a period of 15 min. The solution was stirred at this temperature for 3 h and the rxn was monitored by IR for the formation of imine peak at 1623 cm^{-1} and the rxn was quenched at the same temperature with 25 mL of deionised water and allowed to warm to RT. 15 mL of Et_2O was added and the mixture was washed with water (3×30 mL). The organic layer was dried over $MgSO_4$ and the solution (199) was used for the cycloaddition in the next step. Attempts to isolate the imine (199) resulted in degradation products.

3.4.3 Synthesis of 8a-hydroxy-5-methyl-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one



199 189 318

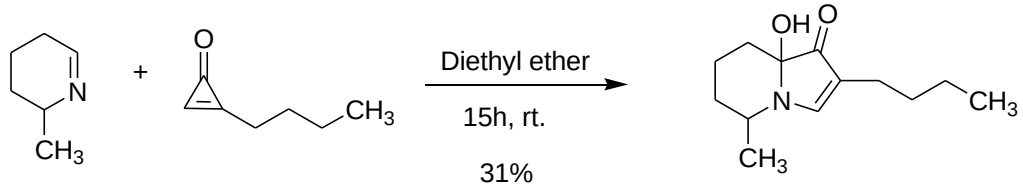
To the solution of imine (199) in ether (20 mL, 0.5M) was added cyclopropenone (189) (250 mg, generated *in situ*in acetone from its precursor cyclopropenone acetal), dropwise over 20 min at -10 °C and the solution was stirred overnight reaching RT. The crude mixture was concentrated and chomatographed on silica (eluent 30:70 EtOAc/PE) to yield 8a-hydroxy-5-methyl-6,7,8,8a-tetrahydroindolizin-1(5H)-one (318) (50 mg 33% yield).

IR: u_{max}: 3290, 2933, 1644, 1538.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.85 (1H, d, *J* = 3.4 Hz, N**CH**=CH), 5.0 (1H, d, *J* = 3.4 Hz, NCH=**CH**), 3.8-3.72 (1H, m, N**CH**CH_3), 3.13 (1H, q, *J* = 7.3 Hz, CHH), 2.11-1.97 (2H, m, CH_2), 1.88-1.84(1H, m, CHH), 1.73-1.67(1H, m, CHH), 1.42-1.40 (1H, m, CHH), 1.37 (3H, d, *J* = 6.6 Hz, **CH_3**).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.8 (**C**=O), 159.5 (N**CH**=CH), 92.7 (NCH=**CH**), 86.8 (**C**(OH)), 50.0 (**CH**), 36.6 (**CH_2**), 33.43 (**CH_2**), 19.30 (**CH_2**), 17.70 (**CH_3**).

3.4.4 Synthesis of 2-butyl-8a-hydroxy-5-methyl-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one



199 265 319

To a solution of the imine (199) in ether 25 mL was added butyl cyclopropenone (265) (250 mg, generated *in situ* in acetone from its precursor cyclopropenone acetal), dropwise over 20 min at -10 °C. The solution was stirred overnight reaching RT. The crude mixture was concentrated and chomatographed (eluent 30:70 EtOAc/PE) to give the product (319) in 31% yield

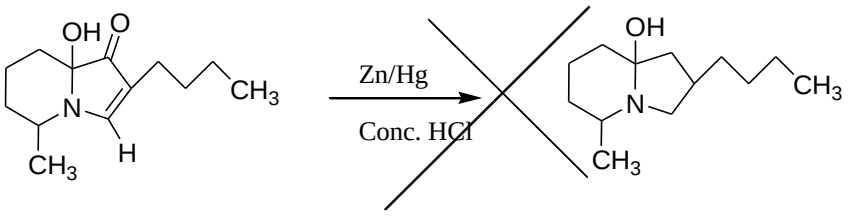
IR: u_{max}: 3300 (br), 2932, 2870, 1661, 1583.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.61 (1H, s, N**CH**=C), 3.62-3.53 (1H, m, N**CH**CH_3), 2.34-2.28 (1H, m, CH_2**CH_2**CH_2 (ring)), 2.15-2.08 (2H, m, CH=C**CH_2**), 1.87-1.77 (1H, m, CH_2**CH**$_2CH_2$ (ring)), 1.75-1.68 (1H, m, **CH**$_2$COH), 1.68-1.62 (2H, m, **CH_2**$CHCH_3$), 1.50-1.34 (2H, m, CH_2**CH**$_2CH_2$ (butyl chain)), 1.34-1.30 (2H, m, **CH_2**CH_3), 1.28 (3H, d, *J* = 6.7 Hz, **CH_3**CH (ring)), 1.14-1.10 (1H, m, **CH**$_2$COH), 0.90 (3H, t, *J* =7.2 Hz, **CH_3**CH_2 (butyl chain)).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 203.00 (C=O), 158.26 (C=**CH**), 117.28 (**C=Cq**), 73.06 (**C**OH), 50.44 (**CH**CH_3), 34.36 (**CH_2**), 31.32 (**CH_2**), 26.89 (**CH_2**), 22.54 (**CH_2**), 22.25 (**CH_2**), 18.77 (**CH_2**), 18.53 (**CH_3,** ring), 13.95 (**CH_3,** butyl chain).

Mass: m/z: 246.1.

3.4.5 Attempted synthesis of 2-butyl-5-methyl-octahydroindolizin-8a-ol



319 339

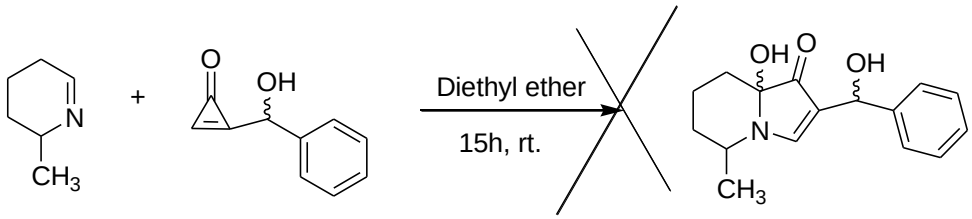
To a solution of 2-butyl-8a-hydroxy-5-methyl-6,7,8,8a-tetrahydroindolizin-1(5H)-one (319) (25 mg, 0.1mmol) in 5 mL of conc. HCl was added Zn/Hg (20 mg) in a 25 mL reaction flask fitted with a reflux condenser. The solution was heated at reflux for 4 h, whereupon the colour changed from pale yellow to colourless. The reaction mixture was allowed to cool to room temperature and followed by TLC which indicated complete consumption of starting material. The mixture was neutralised with NaOH until pH 8 and then extracted with ether (3 x 10 mL), the solution was dried with $MgSO_4$ and evaporated to yield 10 mg of a crude material which could not be fully charaterised.

IR: υ_{max} 3357, 2928, 2851, 1621, 1465, 1040

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.32 (1H, br), 1.66-082 (24 H, m, br).

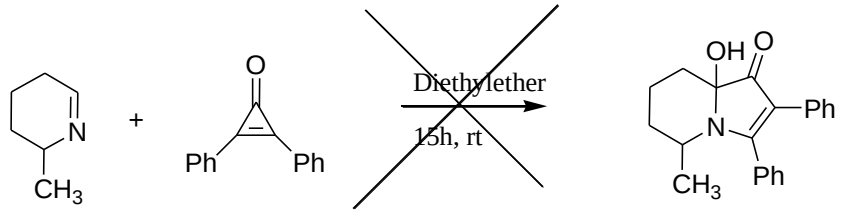
MS : m/z 198.2

3.4.6 Attempted synthesis of 8a-hydroxy-2-(hydroxy(phenyl)methyl)-5-methyl-6,7,8,8a-tetrahydroindolizin-1(5*H*)-one



199 269 320

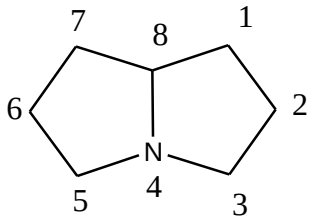
To a solution of imine (199) in ether (20 mL) added butyl cyclopropenone (269) (250 mg, generated *in situ* in acetone from its precursor cyclopropenone acetal), dropwise over 20 min at -10 °C. The solution was stirred overnight reaching RT. The crude mixture was concentrated and chomatographed to yield an unidentified mass from which no diagnostic signals could be seen.



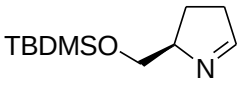
199 123 340

To a solution of imine (199) in ether (20 mL) was added diphenylcyclopropenone (123) (100 mg) at -10 °C and the solution was stirred overnight reaching RT. TLC showed no reaction. The resulting crude mixture was concentrated; the residue was subjected chomatography to recover the DPP (75 mg) and an unidentified oily mass (20 mg).

Pyrrolizidines

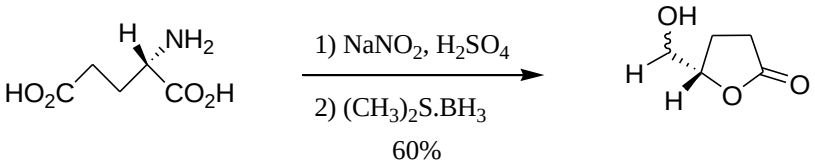


3.5 Synthesis of (R)-2-((tert-butyldimethylsilyloxy)methyl)-3,4-dihydro-2H-pyrrole:



209

3.5.1 Synthesis of (S)-5-(hydroxymethyl)-dihydrofuran-2(3*H*)-one:



210 211

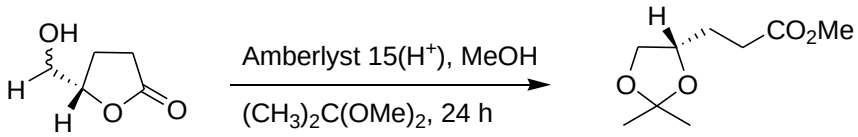
To a suspension of L-glutamic acid (210) (7.35 g, 50 mmol) in a 500 mL 3 neck RBF in water (65 mL) stirring vigourously, was added $NaNO_2$ (4.135 g, 60 mmol) in water (65 mL) and 2N H_2SO_4 (65 mL) simultaneously from separating funnels over about 30 min. During the additions the temperature was between 30 to 35°C and smooth evolution of NO_2 and N_2 was observed. The solution was stirred at RT overnight, water was removed by heating below 50° C under reduced pressure on the rotary evaporator and the resulting pasty solid was triturated with 500 mL of boiling ethylacetate and the hot solution filtered. The process was repeated four times and the organic layers set aside to cool. Removal of the solvent on the rotary evaporator afforded crude butyrolactone-γ-carboxylic acid as a slightly yellow oil. The resulting compound was dissolved in anhydrous THF (40 mL) and borane dimethyl sulfide complex (2 M, in ether, 17 mL) was added and the whole stirred for 1 hour. Anhydrous methanol (30 mL) was added and the resulting solution was stirred for 10 min

and the solvent was distilled off by rotary evaporation. The process was repeated twice with methanol to obtain the lactone (211) (4.5 g, 60%). The data was consistent with the literature.[184]

IR u_{max} (cm^{-1}): 3436, 2950, 1770, 1188, 1067.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70-3.68 (3H, m, OH, **CH_2CH**O,), 3.60 (2H, s), 1.97-1.91 (2H, m), 1.35 (1H, t, J = 7.1 Hz).

3.5.2 Synthesis of (S)-methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl) propanoate:

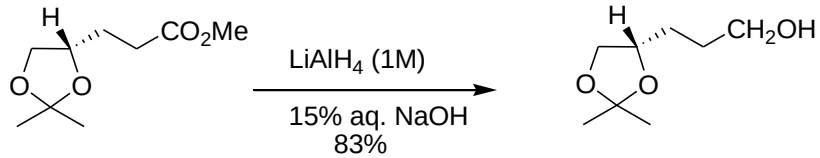


211 213

To a solution of the lactone (211) (3.48 g, 30 mmol) in methanol (10 mL) and 2, 2-dimethoxy propane (40 mL) was added Amberlyst-15 catalyst (500 mg) and the mixture stirred for 24 h. The rxn mixture was filtered to remove the Amberlyst. Removal of the solvents afforded the acetal protected ester. The crude product was purified by chomatography with EtOAc / PE 10:90 to give the pure ester (213) (3.38 g, 55%). The data was consistent with the literature.[184]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08-3.96 (2H, m), 3.60 (3H, s, CO_2**CH_3**), 3.49- 3.46 (1H, m), 2.44-2.29 (2H, m), 1.87-1.73 (2H, m), 1.32 (3H, s, C**CH_3**), 1.26 (3H, s, C**CH_3**).

3.5.3 Syntheis of (S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol



213 214

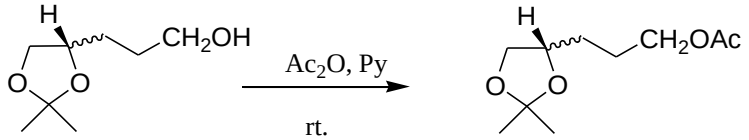
To a solution of the ester (213) (3.76 g, 21.36 mmol) in anhydrous ether (30 mL) previously cooled to -20^0 C, was added $LiAlH_4$ (1 M, in hexane, 11.5 mL, 11.54 mmol) and

stirring continued for 3 h. The mixture was hydrolysed with water (0.5 mL) and then NaOH (0.5 mL, 15%) was added, followed by water (1.5 mL). The resulting solution was filtered though celite to remove the aluminium salts and purified by flash column chromatography (eluent 1:99 MeOH/EtOAc) to give the alcohol (214) (2.86 g, 83%). The data was consistent with the literature.[184]

IR υ_{max} (cm^{-1}) : 3434, 2985, 2937, 2871, 1378, 1216, 1157, 1056.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16-4.04 (2H, m), 3.67 (2H, br), 3.53 (1H, t, J =7.52 Hz), 2.28 (1H, br), 1.72-1.61 (4H, m), 1.42 (3H, s, C**H$_3$**), 1.36 (3H, s, C**H$_3$**).

3.5.4 Synthesis of (S)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate



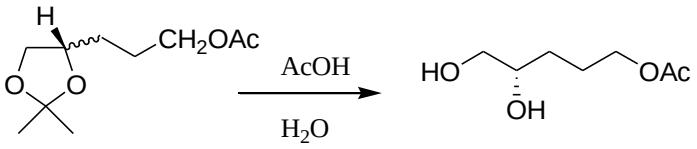
214 215

A solution of the above alcohol (214) (500 mg, 3.13 mol) in dry pyridine (5 mL) was treated with acetic anhydride (0.45 mL) and stirred at rt for 1.75 h. The solution was partitioned between water and Et_2O and extracted with Et_2O (3x30 mL). The combined organic layers were dried and the solvent was evaporated. Residual pyridine was azeotropically removed with heptanes. The crude product was purified by silica chomatography using Et_2O / PE, 50:50 to 70:30 to give the acetate (215) (520 mg, 82%) as pale yellow oil. R_f 0.36 (PE / Et_2O; 60:40). The data was consistent with the literature.[182]

IR: υ_{max} (cm^{-1}); 2980, 1725, 1370, 1190.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12-4.01 (4H, m, **CH$_2$**(OAc), **CH$_2$**($OC(CH_3)_2$)), 3.50 (1H, t, J= 7.5 Hz, **CH**($OC(CH_3)_2$)), 2.01 (3H, s, **CH$_3$**(C=O), 1.80-1.54 (4H, br, (**CH$_2$**)$_2$ CH_2OAc), 1.38, 1.33 (6H, 2 × s, **C**(**CH$_3$**)$_2$).

3.5.5 Synthesis of (S)-4,5-dihydroxypentyl acetate

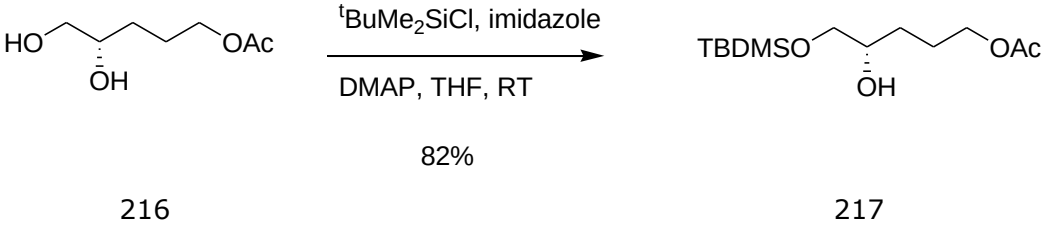


215 216

A solution of the acetate (215) (520 mg) in water (20 mL) was diluted with acetic acid (9 mL) and stirred at rt for 5 h. The solvent was evaporated *in vacuo* and acetic acid was azeotropically removed with heptane. The crude product was purified by column chomatography with AcOEt/MeOH (100:0 to 96:4) to afford the diol (216) (348 mg, 83%) as a pale yellow oil. R_f 0.34 (AcOEt/MeOH 98:2). The data was consistent with the literature.[182]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (2H, t, J = 6.6 Hz, **CH_2** (OAc)), 3.76- 3.71 (1H, br, **CH**OH), 3.69-3.63 (1H, br, CH_2OH), 3.49-3.43 (1H, br, part of ABX, CH_2OH), 2.67 (1H, br, **OH**CH_2), 2.43 (1H, br, **OH**CH), 2.06 (3H, s, **CH_3**CO), 1.90-1.48 (4H, m, **$(CH_2)_2$** (CH_2OAc)).

3.5.6 Synthesis of (S)-5-(tert-butyldimethylsilyloxy)-4-hydroxypentyl acetate



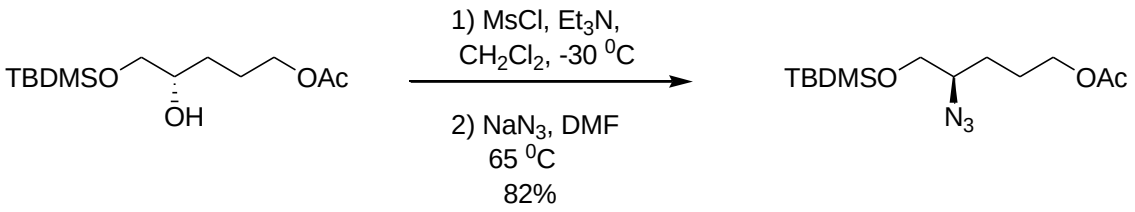
216 217

A solution of the diol (216) (335 mg, 2.06 mmol) in dry THF (10 mL) was treated with imidazole (154 mg, 2.27 mmol) and 4-dimethylamino pyridine (3.78 mg, 0.015 mmol) and then cooled to 0^0 C. A solution of *tert*-butyldimethylsilyl chloride (342 mg, 2.27 mmol) in dry THF (5 mL) was added via syringe and the mixture stirred for 2 h at 0 ^{0}C and then at RT for 3 h. After addition of water (5 mL) the solution was partially concentrated *in vacuo* and then partitioned between water (20 mL) and Et_2O (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried and the solvents were evaporated. The crude product was purified by chomatography with PE/Et_2O (90:10 to 1:1) to give the TBDMSO

protected compound (217) (360 mg, 65%) as pale yellow oil. The data was consistent with the literature.[182]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (td, J =6.6, 1.8 Hz, **CH_2**(OAc)), 3.68-3.65 (1H, m, **CH**O), 3.62, 3.39 (2H, m, **CH_2**OH), 2.47 (1H, d, J = 3.4 Hz, **OH**), 2.06 (3H, s, **CH_3**CO), 1.86-1.45(4H, m, **$(CH_2)_2$**(CH_2OAc)), 0.91 (9H, s, C(**CH_3**)$_3$), 0.09 (6H, s, Si(**CH_3**)$_2$).

3.5.7 Synthesis of (S)-4-azido-5-(tert-butyldimethylsilyloxy)pentyl acetate



217 218

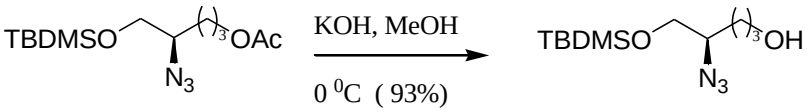
(a) Mesylate: a solution of the above compound (217) (360 mg, 1.3 mmol) in dry DCM (10 mL) was cooled to -30 ^{0}C and treated with Et_3N (0.23 mL 1.68 mmol) and MsCl (0.12 mL 1.55 mmol). After 1 h the reaction was quenched with aqueous saturated NH_4Cl (5 mL) and diluted with water (10 mL) and Et_2O (25 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude mesylate obtained was used directly in the following reaction. R_f 0.48 (PE/Et_2O/CH_2Cl_2 45:10:45).

(b) Substitution with NaN_3: to a solution of crude mesylate in dry DMF (10 mL) was added sodium azide and the suspension stirred at 65°C for 6 h. The crude product was partitioned between water (25 mL) and Et_2O (25 mL), separated and the aqueous layer extracted with ether (25 mL). The combined organic layers were dried and solvent was evaporated. The crude product was purified by chomatography with PE/Et_2O (95:5 to 80:20) to give the azide (218) (214 mg, 80%) as a pale yellow oil. R_f 0.82 (PE/Et_2O/CH_2Cl_2 45:10:45). The data was consistent with the literature.[182]

IR υ_{max} (cm^{-1}): 2955, 2930, 2858, 2108, 1742, 1248, 1115, 838, 778.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (2H, td, J = 6.4, 2.9 Hz, **CH_2**(OAc)), 3.75, 3.64 (2H, part of ABX system, **CH_2**OSi, J_{AB} = 10.4, J_{AX} = 6.8, J_{BX} = 4.0 Hz), 3.40-3.36 (1H, m, **CH**N_3), 2.07 (3H, s, **CH_3**CO), 1.82-1.46 (4H, brm, **$(CH_2)_2$**(CH_2OAc)), 0.92 (9H, s, C(**CH_3**)$_3$), 0.10 (6H, s, Si(**CH_3**)$_2$).

3.5.8 Synthesis of (S)-4-azido-5-(tert-butyldimethylsilyloxy) pentan-1-ol



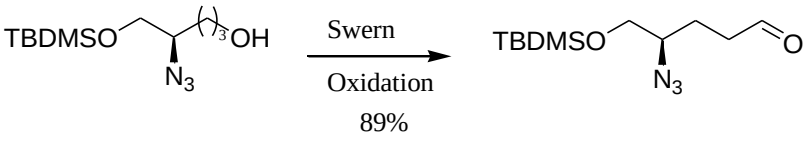
218 219

To a solution of the acetate (218) (230 mg, 0.76 mmol) in MeOH (5 mL) cooled to 0 °C was added KOH (1M solution in MeOH, 5 mL). After 45 min the reaction was quenched with NH_4Cl (aq saturated solution, 5 mL) and concentrated *in vacuo*. The residue was extracted with Et_2O (30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by chomatography with PE/Et_2O (8:2 to 1:1) to give the alcohol (219) (185 mg, 93%) as a pale yellow oil. R_f 0.45 (PE/Et_2O 1:1). The data was consistent with the literature.[182]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73-3.60 (4H, m, **CH_2**O, **CH_2**OSi), 3.42-3.38 (1H, m, **CH**N_3), 1.76-1.45 (4H, br, **$(CH_2)_2$** (CH_2OH)), 0.93 (s, 9H, C(**CH_3**)$_3$), 0.1 (6H, s, Si(**CH_3**)$_2$).

It was observed that the compound was not stable on prolonged standing (>24 h) and started decomposing.

3.5.9 Synthesis of (S)-4-azido-5-(tert-butyldimethylsilyloxy)pentanal



219 220

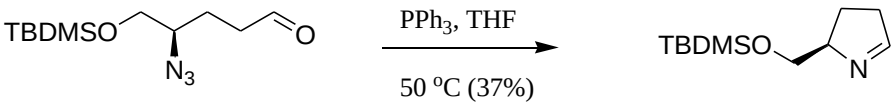
A solution of oxalyl chloride (0.5 mL, 0.98 mmol, 2.13 M solution in CH_2Cl_2) in dry DCM (5 mL) was cooled to -78 °C. Dry DMSO (0.15 mL 1.563 mmol) was added. After 10 min of stirring, a solution of starting material (219) (170 mg, 0.6513 mmol) in dry DCM (5 mL) was added followed by Et_3N (0.4 mL, 2.734 mmol). After 2 h at -78 °C the reaction was quenched with NH_4Cl (aq saturated solution, 5 mL) and extracted with Et_2O (30 mL x 2). The combined layers were dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by chomatography with PE/Et_2O (75:25 to1:1) to give the aldehyde (220) (150

mg, 89%) as a pale yellow oil. R_f 0.72 (PE/Et_2O 1:1). The data was consistent with the literature.[182]

IR: υ_{max} 2955, 2930, 2858, 2113, 1726, 1258, 1121, 838, 778.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (1H, t, J =1.1 Hz, **HC**=O), 3.78, 3.66 (2H, part of ABX system, **CH_2**OSi, J_{AB} = 10.4, J_{AX} = 6.8, J_{BX} = 4.0), 3.45-3.41 (1H, m, **CH**N_3), 2.65-2.60 (2H, m, **CH_2**CH_2CHO), 1.88-1.66 (2H, m, **CH_2**CHO), 0.92 (9H, s, C(**CH_3**)$_3$), 0.1 (6H, Si(**CH_3**)$_2$).

3.5.10 Synthesis of (R)-2-((tert-butyldimethylsilyloxy)methyl)-3,4-dihydro-2*H*-pyrrole



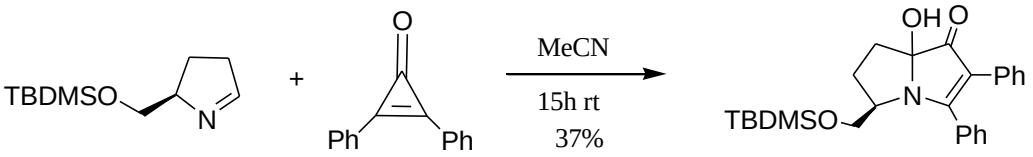
220 209

To a solution of the aldehyde (220) obtained in the above step (100 mg, 0.384 mmol) in dry THF (5 mL), freshly activated 4 Å powdered molecular sieves (20 mg) were added. After stirring for 15 min at rt, PPh_3 (121 mg, 0.461 mmol) was added in two portions. After evolution of nitrogen finished, the reaction was stirred at 50 °C for 5 h. The sieves were filtered and the resulting solution was concentrated and directly purified by chomatography with PE/Et_2O (1:1 to 3:7) to give the cyclic imine (209) (60 mg, 70%) as a pale yellow oil. R_f 0.52 (PE/Et_2O 2:8). The data was consistent with the literature.[182]

IR υ_{max} (cm^{-1}); 2951, 2928, 1190, 1113, 717.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, s, br, **CH**=N), 4.19-4.17 (1H, br, **CH**CH_2O), 3.84, 3.67 (2H, part of ABX system, **CH_2**OSi, J_{AB} = 10.1, J_{AX} = 5.3, J_{BX} = 4.1 Hz), 2.57-1.68 (4H, m, **CH_2CH_2**), 0.88 (9H, s, C(**CH_3**)$_3$), 0.06,0.05 (6H, 2 × s, Si(**CH_3**)$_2$).

3.5.11 Synthesis of (5R)-5-((tert-butyldimethylsilyloxy)methyl)-2,3-diphenyl-5,6,7,7a-tetrahydropyrrolizin-1-one.



209 123 321

To a solution of the cyclic imine (209) (70 mg, 0.3286 mmol) in dry acetonitrile (6 mL), was added diphenylcyclopropenone (123) (74 mg, 0.3615 mmol) and the mixture stirred at RT for 15 h under nitrogen. The resulting solution was concentrated and the mixture purified by chomatography (PE/Et_2O 3:7 to 4:6), with 21% yield of product (321) and an unidentified product which was clearly an imine-DPP addition product.

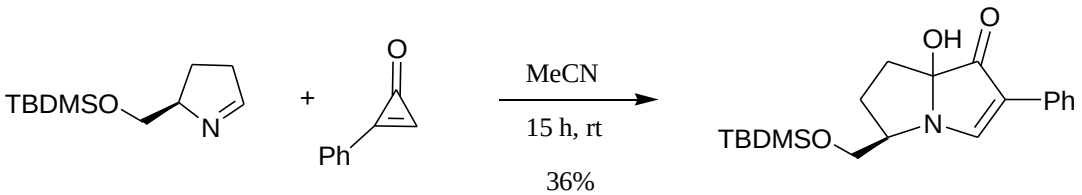
IR: υ_{max} 3342, 2928, 1679, 1551, 1471, 1390, 1255, 1104, 836, 779, 696.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.38(5H, m, **CH** (Ph)), 7.21-7.11(5H, m, **CH** (Ph)), 4.1(1H, broad, **OH**), 3.85-3.79 (2H, m, **CH_2**OTBDMs), 3.50-3.47 (1H, m, **CH**CH_2), 2.24-2.11 (4H, m, 2 × **CH_2**), 0.96 (9H, s, C(**CH_3**)$_3$), 0.17(6H, s, Si(**CH_3**)$_2$).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 199.08 (**C**=O), 176.10 (**C**), 133.38 (**C**, Ph), 131.19 (**C**, Ph), 131.05 (**CH**, Ph), 129.49 (**CH**, Ph), 128.88 (**CH**, Ph), 128.73 (**CH**, Ph), 127.99 (**CH**, Ph), 126.16 (**CH**, Ph), 113.76 (**C**), 96.57 (**C**), 66.70(**CH_2**), 60.91 ((**CH**), 33.32 (**CH_2**), 29.03 (**CH_2**), 25.79 (**3** × **CH_3**), 18.4 (**C** (CH_3)$_3$) -5.41(**2** × **CH_3**).

Mass: M/z $C_{26}H_{33}N_1NaO_3Si_1$ (M+ Na) required 458.2121 observed 458.2116.

3.5.12 Synthesis of (5R)-5-((tert-butyldimethylsilyloxy)methyl)-7a-hydroxy-2-phenyl-5,6,7,7a-tetrahydropyrrolizin-1-one



209 247 327

To a solution of the cyclic imine (209) (150 mg, 0.704 mmol) in dry acetonitrile (6 mL) was added phenylcyclopropenone (247) (100 mg, 0.7746 mmol). The solution was stirred at rt under nitrogen for 15 h. The resulting solution was concentrated and purified by chomatography with PE/Et_2O (4:6 to 6:4), to give the product (327) (87 mg, 30%), R_f 0.7 (PE/Et_2O).

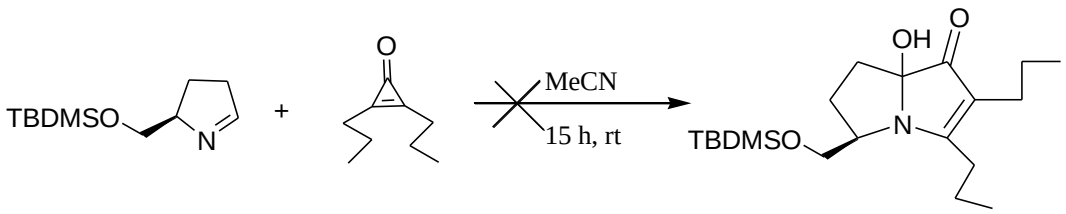
IR u_{max} (cm^{-1}):3366, 2953, 2856, 1667, 1568, 1361, 1256, 1100, 837, 778, 695.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (1H, s, N**CH**=CPh), 7.65-7.62 (2H, m, **CH** (Ph)), 7.35-7.31 (2H, m, **CH** (Ph)), 7.23-7.19 (1H, m, **CH** (Ph)), 3.82-3.74 (2H, m, **CH_2**OTBDMS), 3.59-3.57 (1H, m, **CH**CH_2), 2.32-3.28 (1H, m, **CH_2**CH), 2.24-2.20 (1H, m, **CH_2**CH), 2.14-2.09 (1H, m, **CH_2**COH), 1.85-1.78 (1H, m, **CH_2**COH), 0.96 (9H, s, C(**CH_3**)**$_3$**), 0.15 (6H, s, Si(**CH_3**)**$_2$**).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 199.34 (**C**=O), 165.25 (N**CH**=C), 130.94 (**C**, Ph), 128.47 (**CH**, Ph), 128.39 (**CH**, Ph), 124.14 (**CH**, Ph), 114.23 (**C**), 96.91 (**C**), 66.89 (**CH**), 63.47 (**CH**), 33.26 (**CH_2**), 29.60 (**CH_2**), 25.88 (**3** × **CH_3**), 18.31 (**C** $(CH_3)_3$)-5.56 (**2** × **CH_3**).

Mass: M/z 382.2 (M^+ Na).

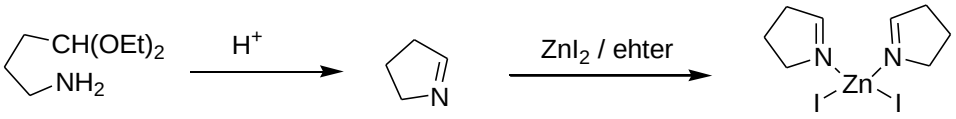
3.5.13 Attempted Synthesis of (5R)-2,3-dibutyl-5-((tert-butyldimethylsilyloxy)methyl)-7a-hydroxy-5,6,7,7a-tetrahydropyrrolizin-1-one



209 249 328

To a solution of the cyclic imine (209) (70 mg, 0.326 mmol) in dry acetonitrile (8 mL) in a 50 mL oven dried RBF, was added di-isopropylcyclopropenone (249) (45 mg, 0.3260 mmol). The solution was stirred at RT overnight, whilst the rxn was monitored by TLC. There was no change by TLC and so the rxn was heated at 50 ^{o}C for 5 h and monitored by TLC. There was still no change and so the rxn mass was heated at reflux overnight. TLC showed that the cyclic imine had decomposed but that the cyclopropenone was still not consumed.

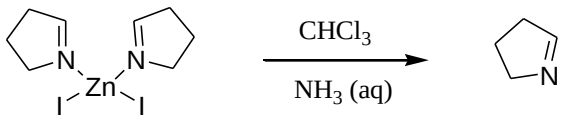
3.6 Synthesis of Bis (3, 4-dihydro-2H-pyrrolo-1-yl)di-iodozinc.



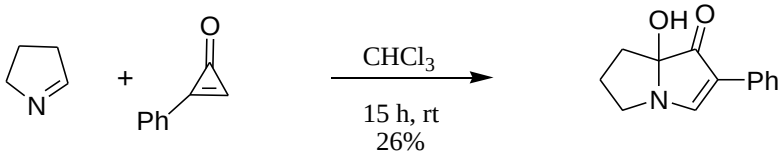
200 201 202

A solution of 4-aminobutanal diethylacetal (200) (2.3 g) in 2M HCl (20 mL) and dry ether (50 mL) in a 250 mL RBF under continuous flow of nitrogen, was cooled to 0 ºC and stirred at this temperature for 20 min. The resulting was basified with K_2CO_3. The mixture was taken into a separating funnel, the layers were separated and the aqueous layer was extracted with cold dry ether (3 × 40 mL). The combined ethereal extracts (201) were dried over $MgSO_4$ and filtered at 0 ºC. Anhydrous zinc iodide (2.08 g) was added and the mixture was stirred at 0 ºC under nitrogen for 30 min. The precipitate was filtered off and washed with ether (3 × 30 mL), to yield the zinc complex (202) (2.0 g) as a pale yellow solid.

3.6.1 Synthesis of 7a-hydroxy-2-phenyl-5,6,7,7a-tetrahydropyrrolizin-1-one:



202 201



201 247 329

To the zinc complex (202) (200 mg) was added $CHCl_3$ (10 mL) followed by 30%aq NH_3 (10 mL) in a separating funnel. The layers were separated and the organic layer was dried quickly over anhydrous $MgSO_4$. The organic layer was treated with phenylcyclopropenone (247) (50 mg) and stirred overnight, the rxn being monitored by TLC. $CHCl_3$ was distilled off by rotary evaporation and the crude product purified by column chomatography with (EtOAc / PE 45:55 to 50:50), R_f. 0.3, EtOAc / PE 50:50, to give 200 mg (26%) of the desired compound (329).

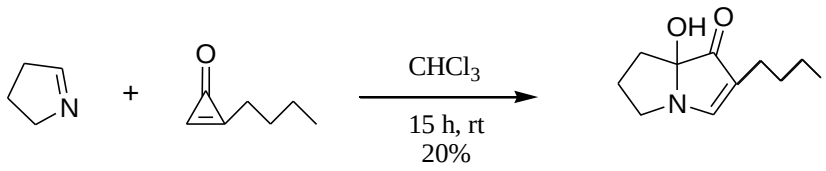
IR υ_{max} (cm^{-1}); 3332, 2969, 1602, 1553, 1392, 1255, 970.

^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.98 (1H, s, N**CH**=C), 7.63-7.16 (5H, m, **CH** (Ph)), 3.66-3.62 (1H, m, N**CH**$_2$), 3.26-3.21 (1H, m, N**CH**$_2$), 2.43-2.33 (1H, m,**CH**$_2$), 2.13-2.04 (2H, m,**CH$_2$**), 1.94-1.88 (1H, m, **CH**$_2$).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ 200.19 (**C**=O), 165.39 (N**C**H=C), 130.73 (**C** (Ph)), 128.54 (**CH** (Ph)), 126.62 (**CH** (Ph)), 124.99 (**CH** (Ph)), 115.01 (**C**=CH), 97.16 (**C**), 49.15 (**CH$_2$**), 33.69 (**CH$_2$**), 27.04 (**CH$_2$**).

Mass: M/z $C_{13}H_{13}NNaO_2$ (M+ Na) required 238.0849 observed 238.0838.

3.6.2 Synthesis of 7a-hydroxy-5,6,7,7a-tetrahydropyrrolizin-1-one:



201 265 330

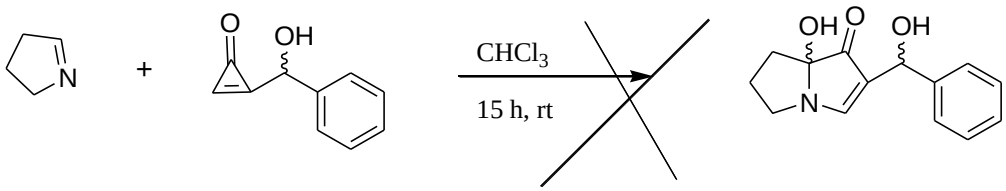
To the zinc complex (202) (200 mg) was added $CHCl_3$ (10 mL) followed by 30%aq NH_3 (10 mL) in a separating funnel. The layers were separated and the organic layer was dried quickly over anhydrous $MgSO_4$. The organic layer was treated with butylcyclopropenone (265) (50 mg) and stirred overnight, the rxn being monitored by TLC. $CHCl_3$ was distilled off by rotary evaporation and the crude product purified by column chomatography with (EtOAc / PE 40:60) R_f. 0.3, EtOAc / PE 50:50, to give 42 mg (20%) of the desired compound (330).

IR u_{max} (cm^{-1}); 3350, 2955, 2927, 1666, 1580, 1377, 1234, 1072, 800.

^{1}H NMR (500 MHz, $CDCl_3$) δ :7.41(1H, s, N**CH**=C), 3.51-3.45 (2H, m, **CH_2**), 3.08-3.02 (1H, m, **CH_2**), 2.31-2.23 (1H, m, **CH_2**), 2.08 (2H, t, J = 7.6 Hz, **CH_2**C=C), 2.02-1.95 (2H, m, **CH_2**) 1.87-1.86 (1H, m, O**H**), 1.45-1.39 (2H, m, **CH_2**), 1.34-1.27 (2H,m, **CH_2**), 0.89 (3H, t, J = 7.3, **CH_3**).
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 203.48 (**C**=O), 166.40 (**CH**), 117.71 (**C**), 96.42 (**C**OH), 49.23 (**CH_2**), 33.74 (**CH_2**), 30.53 (**CH_2**), 26.95 (**CH_2**), 22.31 (**CH_2**), 21.96 (**CH_2**), 13.79 (**CH_3**).

M/Z - [M^+ +Na]. $C_{11}H_{17}N_1Na_1O_2$: calc: 218.1151, obsd: 218.1157.

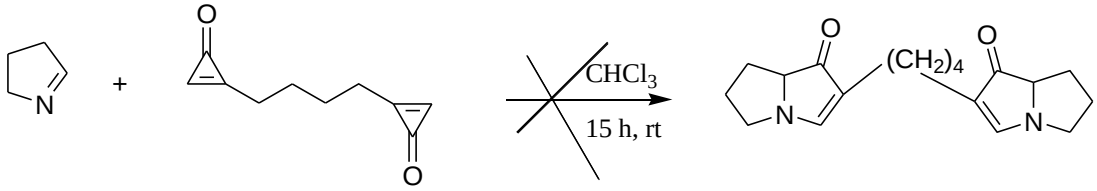
3.6.3 Attempted synthesis of 7a-hydroxy-2-(hydroxy(phenyl)methyl)-5,6,7,7a-tetrahydropyrrolizin-1-one:



201 269 331

To the zinc complex (202) (200 mg) was added $CHCl_3$ (10 mL) followed by 30% aq NH_3 (10 mL) in a separating funnel. The layers were separated and the organic layer was dried quickly over anhydrous $MgSO_4$. The organic layer was treated with hydroxyphenyl cyclopropenone (269) (50 mg) and stirred overnight, the rxn being monitored by TLC. $CHCl_3$ was distilled off by rota evaporation and the crude product purified by column chomatography with EtOAc/PE 45:55 to 50:50, R_f. 0.3, EtOAc/PE 50:50, to give 200 mg (26%) of an unidentified compound.

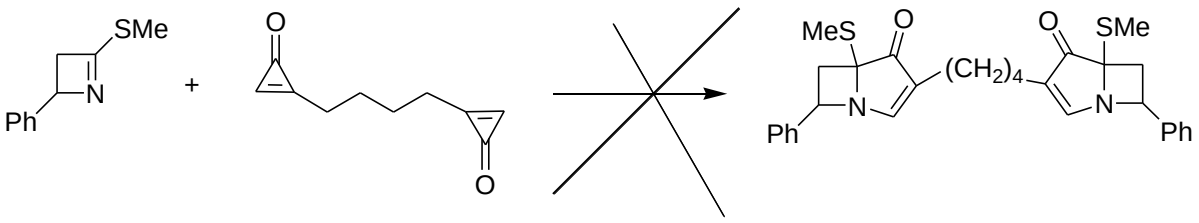
3.6.4 Attempted synthesis of bis- 2-butyl-5,6,7,7a-tetrahydropyrrolizin-1-one



201 267 332

To the zinc complex (202) (275 mg 0.60 mmol) was added $CHCl_3$ (10 mL) followed by 30%aq NH_3 (10 mL) in a separating funnel. The layers were separated and the organic layer was dried quickly over anhydrous $MgSO_4$. The organic layer was treated with tetramethylene-tethered-bis(cylopropenone) (267) (92 mg, 0.56 mmol) and stirred overnight, the rxn being monitored by TLC. $CHCl_3$ was distilled off under vaccum and the crude product purified by column chomatography with EtOAc/PE 80:20 R_f. 0.3, EtOAc/PE 50:50, to give 82 mg of unreacted tetramethylene-tethered-bis(cylopropenone) (267) and no other prodcuts.

3.6.5 Attempted synthesis of bis-3-butyl-5-(methylthio)-7-phenyl-1-aza-bicyclo[3.2.0]hept-2-en-4-one

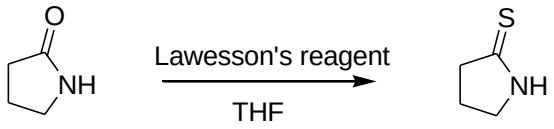


333 267 334

To a solution of 2-thiomethyl-4-phenyl-1-azetine (333) (250 mg, 1.55 mmol) in dry acetonitrile (10 mL) in a 50 mL oven dried RBF, was added tetramethylene-tethered-bis(cylopropenone) (267) (82 mg, 0.50 mmol). The solution was stirred at RT overnight, whilst the rxn was monitored by TLC. There was no change by TLC and so the rxn was heated at 60^{o}C for 72 h and monitored by TLC. The imine was consumed but cyclopropenone was not. The rxn mass was concentrated under reduced pressure and chomatography of the residue resulted in 60 mg of tetramethylene-tethered-bis(cylopropenone). No other products were isolated.

3.7 Synthesis of 5-(methylthio)-3,4-dihydro-2H-pyrrole

3.7.1 Synthesis of pyrrolidine-2-thione



203 204

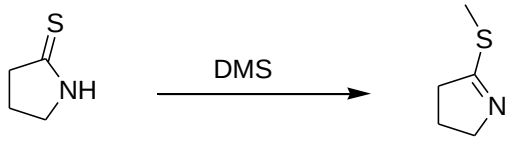
A solution of pyrrolidine-2-one (203) (1 g, 11.75 mmol, 1 eq) and Lawesson's reagent (2.37 g, 5.87 mmol, 0.5 eq.) in anhydrous tetrahydrofuran (15 mL) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC. Upon completion of the reaction (two hours) the mixture was left to cool to ambient temperature, concentrated and purified by column chomatography (eluent: hexane: EtOAc 3:1, Rf = 0.23) to yield pyrrolidine-2-thione (204) (532 mg, 90 %) as white crystals, m.p. 115-117 ^{0}C, as reported previously.

IR: υ_{max} (cm^{-1})3139 (br, **NH**), 2916 (w), 2884 (w), 1533 (m, **C=S**), 1469 (w), 1445 (m), 1291(s), 1214 (m).

^{1}H NMR δ(400.13 MHz, $CDCl_3$): 8.74 (1H, s, **NH**), 3.63 (2H, t, *J*= 7.3 Hz, N**CH_2**), 2.92 (2H, t, *J*= 8.0 Hz, SC**CH_2**), 2.21 (2H, m, CH_2**CH_2**CH_2).

^{13}C NMR δ(100 MHz, $CDCl_3$):206.07 (C=S), 49.86 (CH_2), 43.21 (CH_2), 22.87 (CH_2).

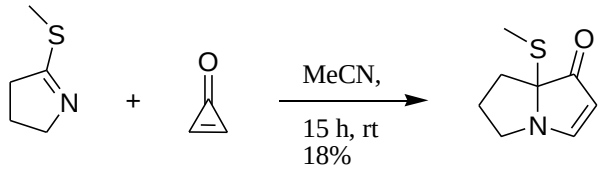
3.7.2 Synthesis of 5-(methylthio)-3,4-dihydro-2*H*-pyrrole



204 205

Dimethylsulfate (878.67 mg, 5.94 mmol, 1.2 eq.) was added in one portion to pyrrolidine-2-thione (204) (500 mg, 4.95 mmol, 1 eq) and the mixture was stirred for 16 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (15 mL). The solution was added dropwise to a 10% aqueous solution of potassium carbonate (10 mL) at -10^{0}C and extracted with DCM (2× 15 mL), the aqueous layer was washed with dichloromethane (2 × 10 mL) and the combined organic extracts were dried over magnesium sulfate. After filtration and solvent was evaporated *in vacuo,* to leave 2 mL of liquid product as a dark orange oil (205) which was used crude in the next step.

3.7.3 Synthesis of 7a-(methylthio)-5,6,7,7a-tetrahydro-pyrrolizin-1-one



205 189 335

Cyclopropenone (189) (140 mg, 2.60 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-pyrrolidine (205) (300 mg, 2.60 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for 12 hours, concentrated and purified by column chomatography (eluent: hexane:EtOAc, 4:1, Rf = 0.36) to yield 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one (335) (81 mg, 18 %) as a yellow oil.

IR: υ_{max} (cm^{-1}): 2980 (br), 1681, 1533.

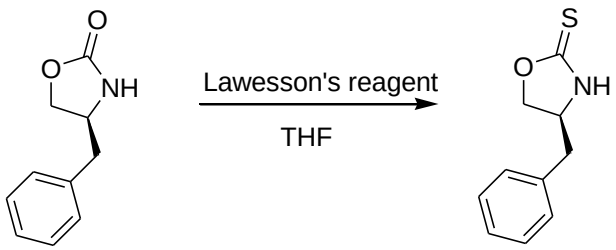
^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.77 (1H, d, *J*= 3.6 Hz, N**CH**=CH), 5.35 (1H, d, *J*= 3.6 Hz, NCH=**CH**), 3.56-3.49 (1H, m, **CH**$_2$), 3.36-3.30 (1H, m, **CH**$_2$), 2.22-2.05 (2H, m, **CH$_2$**), 1.96 (3H, s, S**CH$_3$**), 1.93-1.85 (2H, m, **CH$_2$**).

^{13}C NMR (100 MHz) ($CDCl_3$) δ: 203.54 (**C**=O), 169.00 (**CH**), 105.24 (**CH**), 79.46 (**C**), 48.46 (**CH_2**), 32.86 (**CH_2**), 27.07 (**CH_2**) 11.84 (**CH_3**).

HMS (ESI+): Found 192.0454, $C_8H_{11}NOSNa$, requires 192.0454.

3.8 Attempted Synthesis of (S)-4-benzyl-2-(methylthio)-4,5-dihydrooxazole

3.8.1 Synthesis of (S)-4-benzyloxazolidine-2-thione



206 207

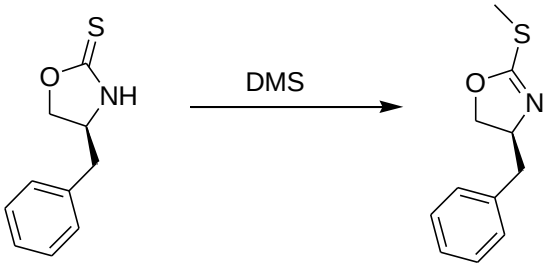
A mixture of 7a-(methylthio)-5,6,7,7a-tetrahydro-pyrrolizin-1-one (206) (260 mg, 1.46 mmol, 1 eq) and Lawesson's reagent (296 mg, 0.7 mmol) in anhydrous tetrahydrofuran (15 mL) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC and showed no product formation.The solvent was replaced with toluene, (8 mL) and the reaction mixture was heated to reflux for 2 h and monitored by TLC for completion. The mixture was left to cool, concentrated and purified by column chomatography (eluent: hexane: EtOAc, 50:50, R_f = 0.23) to yield 70% of the desired product (207) (200 mg), as a gummy solid.

IR: υ_{max} (neat, cm^{-1}): 3186 (b), 1521, 1327, 1269, 1175.

^{1}H NMR (400 MHz) ($CDCl_3$) δ:7.37-7.33 (2H, m,**CH** (Ph)), 7.31-7.26 (2H, m,**CH** (Ph)), 7.21-7.18 (1H, m, **CH** (Ph)), 5.99 (1H, s, **NH**), 4.49 (1H, t, *J* = 8.1 Hz, **CH**NH), 4.18-4.09 (2H, m, **CH_2**O), 2.95-2.84 (2H, **CH_2**Ph).

^{13}C NMR (100 MHz) ($CDCl_3$) δ: 189.55 (**C**=S), 135.94 (**C** (Ph)), 129.05 (**CH** (Ph)), 129.01 (**CH** (Ph)), 127.26 (**CH** (Ph)), 69.61 (**CH_2**), 53.81(**CH**), 41.42 (**CH_2**).

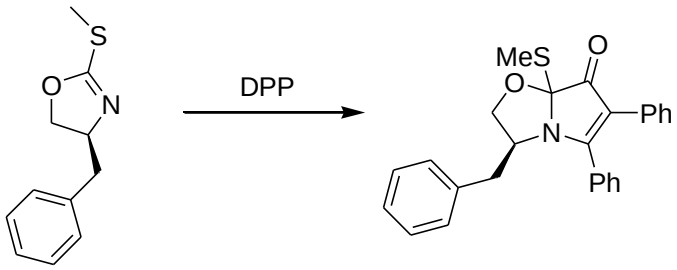
3.8.2 Attempted Synthesis of (S)-4-benzyl-2-(methylthio)-4,5-dihydrooxazole



207 208

Dimethyl sulfate (44 mg, 0.3 mmol) was added in one portion to the thione (207) (58 mg, 0.3 mmol) and the mixture was stirred for 16 hours at ambient temperature under an atmosphere of dry nitrogen. The solution was added dropwise to a 10% aqueous solution of potassium carbonate (5 mL) at -10 ^{0}C and extracted with DCM (2 × 15 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL) and the combined organic extracts were dried over magnesium sulfate. After filtration and solvent was evaporated *in vacuo,* to leave 2 mL of a crude product (208), which was used in the next step directly. TLC showed the completion of the reaction.

3.8.3 Attempted synthesis of (3S)-3-benzyl-7a-(methylthio)-5,6-diphenyl-2,3-dihydropyrrolo[2,1-b]oxazol-7(7aH)-one

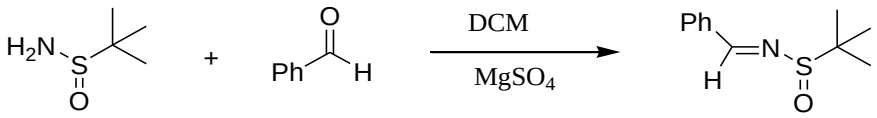


208 341

Diphenylcyclopropenone (123) (23 mg, 0.1 mmol,) was added in one portion to a stirring solution of the imine (208) (20 mg, 0.1 mmol) dissolved in anhydrous acetonitrile (5 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for 12 hours, monitored by TLC with no product formation. Heating at reflux similarly showed no reaction.

3.9 Attempted synthesis of 1-(tert-butylsulfinyl)-2,4,5-triphenyl-1,2-dihydropyrrol-3-one

3.9.1 Synthesis of *N*-(benzylidene)-*t*-butanesulfinamide

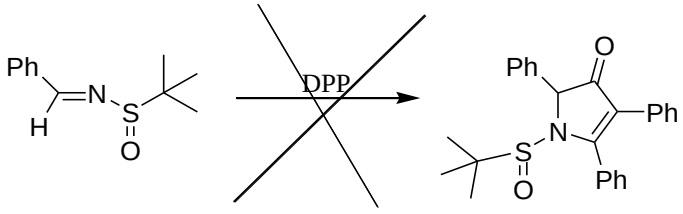


341 342 343

To a stirring solution of 2-methyl-2-propanesulfinamide (341) (1 g, 8.25 mmol) in anhydrous DCM (17 mL) was added magnesium sulfate (5 g, 41.25 mmol) and benzaldehyde (342) (2.62 g, 24.7 mmol) and the mixture stirred at ambient temperature under an atmosphere of dry nitrogen. Upon completion (24 hours) the reaction was filtered, concentrated and purified by column chomatography (hexane: EtOAc, 90:10) yielding *N*-(benzylidene)-*t*-butanesulfinamide (343) (846 mg, 50 %), as an off white oil.[229, 230]

^{1}H NMR δ(400.13 MHz, $CDCl_3$)**:** 8.63 (1H, s, N**C*H***), 7.86 (2H, dd, *J*= 1.7, 8.1, 2 × **CH** (Ar)) 7.50 7.45 (3H, m, 3 × **CH** (Ar)), 1.28 (9H, s (**C*H*$_3$**)$_3$**).** ^{13}C NMR δ(100 MHz, $CDCl_3$)**:** 163.29 (**CH**), 134.27 (q), 132.75 (**CH**), 129.19 (**CH**), 128.64(**CH**), 58.11 (**C**), 22.84 (**CH$_3$**).

3.9.2 Attempted synthesis of 1-(tert-butylsulfinyl)-2,4,5-triphenyl-1,2-dihydropyrrol-3-one

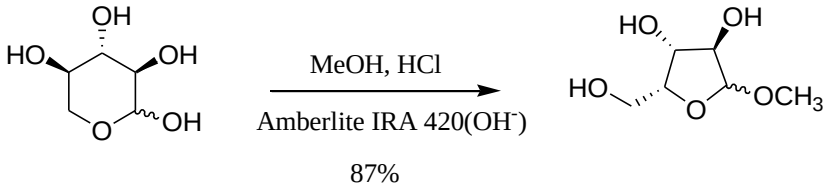


343 344

To a stirring solution of *N*-(benzylidene)-*t*-butanesulfinamide (343) (437 mg, 2.08 mmol) in anhydrous acetonitrile was added DPP (430 mg, 2.087 mmol) and the reaction was stirred at rt for 15 h monitored by TLC. There was no change in the starting materials, so the reaction was heated to reflux overnight after which there was no change in the starting materials. Further heating lead to decomposition products.

3.10 Synthesis of (2S,3S,4S)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyrrole:

3.10.1 Synthesis of (2S,3R,4R)-2-(hydroxymethyl)-5-methoxy-tetrahydrofuran-3,4-diol



225 228

To a solution of L-xylose (225) (10 g, 66.6 mmol) in anhydrous methanol (200 mL) was added concentrated HCl (1.4 mL) and the mixture was stirred for 4 hours at room temperature. The mixture was passed though Amberlyst IRA 420 (OH^-) resin (20 g), until at neutral pH and the resulting mixture was concentrated under reduced pressure. Flash chomatography on silica gel and elution with MeOH: $CHCl_3$ (10:90, R_f 0.3) resulted in methyl-L-xylofuranoside (228) as a mixture of anomers as an oil (9.5 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.31-5.30 (1H, d, *J* = 4.2 Hz, CH (anomeric), 5.02-5.01 (1H, d, *J* = 5.4 Hz, CH, (anomeric)), 4.78-4.77 (1H d, *J* = 6.44 Hz, **OH**), 4.72-4.71(2H, d, *J* = 4.8 Hz, 2 × **OH**), 4.60 (1H, S, **OH**), 4.44-4.41 (2H, m, 2 × **OH**), 4.03-3.86 (4H m, 2 × **CH** (OH), 2 × **CH**(CH_2)), 3.81-3.77 (2H, m, **CH_2**(OH)), 3.6-3.41 (4H, m, **CH_2**(OH), 2 × **CH**(OH)), 3.3 (3H, S, O**CH_3**), 3.23 (3H, S, **OCH_3**).

^{13}C NMR δ(100 MHz, $CDCl_3$)**:**109.84 **CH** (OCH_3), 102.58 **CH** (OCH_3), 82.97 **CH** (CH_2), 81.26 **CH** (CH_2), 79.26 **CH** (OH), 77.92 **CH** (OH), 76.06 **CH** (OH), 75.24 **CH** (OH), 61.10 **CH_2** (OH), 61.04 **CH_2** (OH), 55.26 **OCH_3**, 55.01 **OCH_3**.

The IRA 420 was prepared according to the literature procedure[231]

3.10.2 Synthesis of (2S,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-methoxy-tetrahydrofuran

228 229

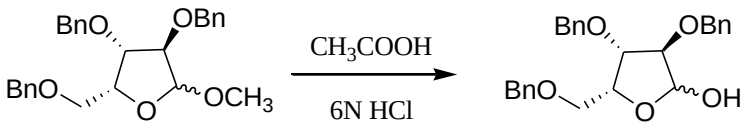
To a suspension of sodium hydride (14.3 g, 0.36 mol, 60% in mineral oil washed three times with pentane) in a mixture of tetrahydrofuran (125 mL) and dimethylformamide (250 mL) was added dropwise under stirring a mixture of benzylbromide (42.6 mL, 0.36 mol), methyl-L-xylofuranoside (228) (18.96 g, 0.116 mol) and tetra-n-butylammonium iodide (1.86 g) dissolved in tetrahydrofuran (125 mL) and dimethylformamide (250 mL). The mixture was stirred overnight at room temperature. Saturated aqueous ammonium sulphate (15 mL) was added. The mixture was dried under reduced pressure. The residue was taken up into water, extracted three times with ethyl acetate (3 × 50 mL). The organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an oil. Flash chomatography on silica gel and elution with a 8:2 mixture of cyclohexane and ethyl acetate yielded methyl 2,3,5-tri-O-benzyl-L-xylofuranoside (229) as a mixture of anomers as an oil (22.7 g, 45%). Data consistent with literature.[187]

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.38-7.27 (15H, m, **CH** (Ph)), 4.95 (1H, d, *J* = 1.4 Hz, **CH** (OCH_3)), 4.72-4.50 (7H, m, 3 × **CH_2** (Ph), **CH** (CH_2OBn)), 4.10-4.08 (1H, m, **CH_2**(OBn)), 4.02-4.01 (1H, m, **CH** (OBn)), 3.85-3.74 (2H, m, **CH_2** (OBn), **CH** (OBn)), 3.44 (3H, s, **OCH_3**).

^{13}C NMR δ(100 MHz, $CDCl_3$): 127.89, 127.75, 127.69, 127.66, 127.48, 127.25, 127.16, 127.11, 127.06, 126.97, 126.89, 126.31 (9 × **CH** (Ph), 3 × C_q), 99.82 **CH**OMe), 83.24 (**CH** OBn), 80.87 (**CH**OBn), 75.21 **CH** (OBn), 72.80 (**CH_2**), 71.94 (**CH_2**), 68.74 (**CH_2**), 64.67 (**CH_2**), 54.63 (**OCH_3**).

M/Z- 457.2 [M^+ +Na].

3.10.3 Synthesis of (3R,4S,5S)-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-ol



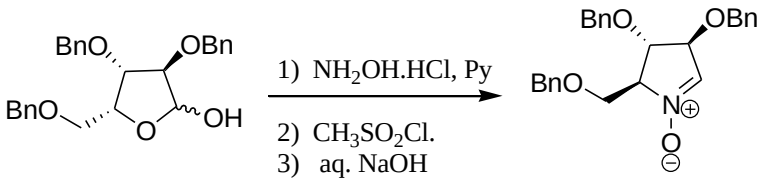
229 226

To a solution of 2,3,4-tri(benzyloxymethyl)-5-methoxy-tetrahydrofuran (229) (2.8 g) dissolved in acetic acid (40 mL), HCl (6 mL, 6N aq. HCl) was added and the mixture was stirred at 65 ^{0}C for 1.25 h, the rxn being monitored by TLC for completion. The acetic acid was distilled off under reduced pressure and column chomatographed on silica (12:88 to 30:70 EtOAc / PE) to afford the lactol (226) (1.77g 87%). Traces of acetic acid were removed by treatment with 0.5 N NaOH. (R_f 0.3, 30:70 EtOAc / PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.26 (15H, m, **CH** (Ph)), 5.52-5.26 (1H, m, **CH** (OH)), 4.66-4.51 (6H, m, 3 × **CH_2** (Bn)), 4.44-4.40 (1H, m, OH)), 4.14, 3.75 (3H, AMX system, **CH_2** (OBn), **CH** (CH_2OBn), J_{AM} = 10, J_{AX} = 5.4, J_{MX} = 3.1), 4.07- 3.96 (2H, m, 2 × **CH** (OBn).

Consistent with reported literaure.[187]

3.10.4 Synthesis of (2S,3S,4S)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide:



226 227

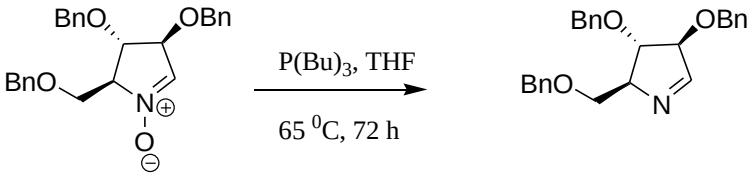
To 0.5 M solution of the lactol (226) (1.65 g, 3.92 mmol) in dry pyridine (7.86 mL) was added 3 Å molecular sieves (2 g) and hydroxylamine hydrochloride (327 mg, 4.71 mmol). The mixture was stirred overnight at room temperature and then a 0.6 M solution of methanesulfonyl chloride (7.86 mL) in dry pyridine was added. The reaction mixture was stirred overnight at room temperature and then filtered though Celite. The filter mass was washed with dioxane (10 mL) and the filtrate collected was cooled at 0 °C. An ice cooled 2

M NaOH solution was added dropwise until pH = 10 and the mixture was stirred at 0 °C for 2 h, maintaining the solution at pH > 9. Dioxane was removed *in vacuo* without heating. The solution was adjusted to pH = 7 by dropwise addition of a cooled 2 M aqueous HCl solution. The resulting mixture was extracted with dichloromethane (3 × 50 mL). The collected organic phases were dried with Na_2SO_4, filtered, concentrated and purified by column chomatography over silica DCM / EtOAc (30:70), R_f = 0.40. A white solid (227) was obtained in a 25% yield.

^{1}H NMR (400 MHz, $CDCl_3$) *δ:* 7.38-7.26, 15H, m, 15 ×**CH** (Ph)), 6.91 (1H, s, br, **CH**=N), 4.71- 4.70 (1H, t, *J* = 1.9 Hz, (**CH**OBn)), 4.67-4.52 (6H, m, 3 ×(CH_2Bn)), 4.37 (1H, dd, *J* = 3.5 Hz, 2.2 Hz, (**CH**OBn)), 4.11, 3.81 (2H, part of ABX system, J_{AB} = 9.9 Hz, J_{AX} = 5 Hz, JBX = 2.7 Hz, (**CH_2**OBn)), 4.07-4.06 (**1H**, m, br, CH (CH_2OBn)).

^{13}C NMR δ (100 MHz, $CDCl_3$)**:** 137.0(**C**, Ph), 136.6 (**C**, Ph), 136.4 (**C**, Ph), 132.3 (**C**=N), 129.97, 129.92, 127.76, 127.51, 127.50, 127.32, 127.28, 127.11, 127.07, (9 × **CH**, Ph), 82.11 (**CH**OBn), 79.65 (**CH**OBn), 76.80, (**CH**OBn), 72.81 (**CH_2**), 71.24 (**CH_2**), 70.99 (**CH_2**), 65.42 **CH_2** (OBn).

3.10.5 Synthesis of (2S,3S,4S)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole:



227 224

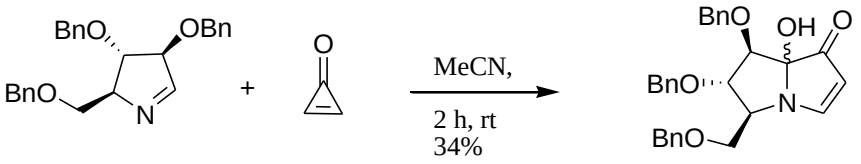
To a stirred solution of the nitrone (227) (268 mg, 0.64 mmol) in dry THF (10 mL) under nitrogen tributylphosphine (321 µL) was added in one portion. The reaction mixture was heated to 65 °C and stirred at this temperature for 72 h, after which the solvent was evaporated under reduced pressure. The resulting crude product was purified by column chomatography on silica (eluent 40:60 EtOAc / PE , R_f = 0.45). The imine (224) (173 mg, 67%) was obtained as a pale yellow oil[156]

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.50 (1H, d, *J* = 2.3 Hz, N=**CH**), 7.30-7.12 (15H, m, 15 × CH (Ph)), 4.55-4.41 (7H, m, (3 × **CH_2**), (**CH**OBn)), 4.11-4.0 (1H, m, **CH**CH_2), 4.05-4.01 (1H, m, (CHOBn)), 3.68(1H, dd, *J* = 9.7, 4.5 Hz, **CH_2**), 3.46 (1H, dd, *J* = 9.7, 6.3 Hz, **CH_2**).

^{13}C NMR δ (100 MHz, $CDCl_3$)**:** 165 (N=**CH),** 137.4, 137.1, 136.8 (3 × **C** (Ph)), 127.88, 127.75, 127.69, 127.39, 127.29, 127.17, 127.13, 127.05, 126.94, (9 × **CH** (Ph)), 89.9 (**CH**), 83.7 (**CH**), 76.13 (**CH**), 72.66 (**CH_2**), 71.64 (**CH_2**), 71.30 (**CH_2**), 70.29(**CH_2**).

Data consistent with reported literature[156]

3.10.6 Synthesis of 7a-Hydroxy-(5S,6S,7R)-6,7-bis(benzyloxy)-5-(benzyloxymethyl)-5,6,7,7a-tetrahydropyrrolizin-1-one:



224 189 337

The imine (224) was dissolved in 10 mL of anhydrous acetonitrile and cooled to -10 to -20 ° C. To this solution was added a cooled solution of deprotected unsubstituted cyclopropenone (189) (prepared from the hydrolysis of acetal cyclopropenone using Amberlyst (H^+) in acetone). The reaction mixture was stirred at this temperature for 2 hours, monitored by TLC and allowed to warm to room temperature. The solvent was removed under vacuum and purified by column chomatography on silica (eluent, EtOAc / PE 40:60, R_f = 0.5) to give yellow oily product (337) in 34% yield.

IR: υ_{max} (neat, cm^{-1}): 3359 (b, m), 3062 (w), 3031 (m), 2926 (m), 2867 (m), 1688 (s), 1538 (s), 1454 (m), 1362 (m), 1206 (m), 1111 (s), 738 (m), 699 (m);

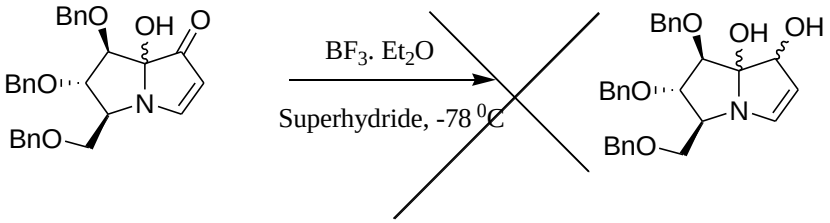
^{1}H NMR (500 MHz, $CDCl_3$), δ_H: 3.44 – 3.47 (1H, ddd, *J* 7.2, 5.9, 4.7, C*H*N), 3.53 (1H, dd, *J* 7.2, 9.4, CHCH_2OBn), 3.58 (1H, dd, *J* 4.7, 9.4, CHCH_2OBn), 3.82 (1H, d, *J* 6.8, C(OH)C*H*OBn), 3.89 (1H, br s, OH), 4.17 (1H, dd, *J* 5.9, 6.8, C*H*$(CHOBn)_2$), 4.49 (1H, d, *J* 11.7, OCH_2Ph), 4.51 (1H, d, *J* 11.9, OCH_2Ph), 4.55 (1H, d, *J* 11.9, OCH_2Ph), 4.61 (1H, d, *J* 11.7, OCH_2Ph), 4.66 (1H, d, *J* 11.7, OCH_2Ph), 4.97 (1H, d, *J* 11.7, OCH_2Ph), 5.23 (1H, d, *J* 3.7, C=C*H*), 7.17 – 7.19 (2H, m, ArH), 7.28 – 7.37 (13H, m, ArH), 7.76 (1H, d, *J* 3.7, *H*C=C);

^{13}C NMR: δ_c (125 MHz, $CDCl_3$): 62.90 (CH), 71.58 (CH_2), 72.50 (CH_2), 73.06 (CH_2), 73.28 (CH_2), 82.00 (CH), 87.07 (CH), 92.02 (C), 102.24 (CH), 127.36 (CH), 127.47 (CH), 127.51

(CH), 127.57 (CH), 127. 75 (CH), 128.05 (CH), 128.07 (CH), 128.13 (CH), 128.14 (CH), 136.68 (C), 137.18 (C), 137.30 (C), 168.75 (CH), 201.73 (C=O).

m/z (electrospray) HMS: calcd for $C_{29}H_{29}NO_5$ + Na^+ = 494.1938, found: 494.1947 [2 ppm error].

3.10.7 Attempted synthesis of (5S,6S,7R)-6,7-bis(benzyloxy)-5-(benzyloxymethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolizine-1,7a-diol:

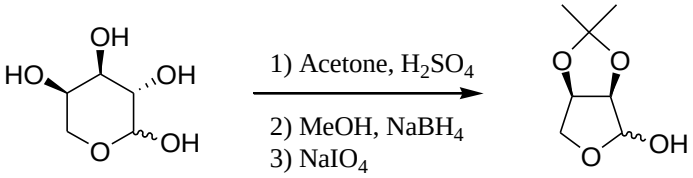


337 338

To a stirring solution of pyrrolizidine adduct (337) (120 mg, 0.25 mmol) dissolved in anhydrous THF (20 mL) cooled to -78 ºC, maintained under constant flow of nitrogen, was added $BF_3.Et_2O$ (42 µL, 0.33 mmol). After 10 min a 1.0 M solution of Super-Hydride® in THF (0.35 mL, 0.33 mmol) was added and the resulting mixture was stirred for 1 h at -78 °C. The solution changed from orange to yellow after addition, the reaction was quenched at the same temperature with brine (2 mL) and the mixture allowed to warm to -30 °C, where the colour changed back to orange. At this point saturated aq. $NaHCO_3$ (5 mL) was added and the solution was allowed to warm to RT. 10 mL of EtOAc was added and the layers were separated and the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, the solvent was removed under vacuum to afford 60 mg of residue. TLC indicated a range of spots, however, column chomatography on silica (EtOAc: PE 40:60 to 70:30), resulted in no identfiable products.

3.11 Synthesis of (3aR,6aS)-2,2-dimethyl-4,6a-dihydro-3aH-[1,3]dioxolo[4,5-c]pyrrole

3.11.1 Synthesis of (3aR,6aR)-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-ol:



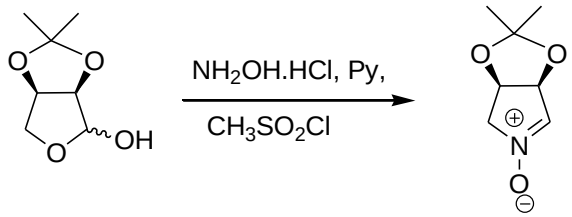
233 234

To a stirring solution of D-ribose (233) (10 g, 66.6 mmol), in anhydrous acetone (100 mL) was added conc. sulfuric acid (0.3 mL) at room temperature and the resulting solution was stirred at RT for 2 h. The reaction was monitored by TLC for completion. The reaction mixture was neutralised by the addition of solid $NaHCO_3$ and the mixture was filtered to remove the inorganic solids. The resulting solution was concentrated under vacuum to give D-ribose monoacetonide as colourless syrup (11g, 57.8 mmol), which was dissolved in anhydrous methanol (70 mL) and the solution was cooled to 0 °C. To this was added small portion of $NaBH_4$ (3.29 g, 86.8 mmol) and the resulting reaction mixture was stirred at RT for 1 h, monitored by TLC for completion, at which point the solvent was distilled off under vacuum. To the resulting residue was added $^tBuOH/H_2O$ (90/60 mL) and small portions of $NaIO_4$ (49.5 g, 231.5 mmol) at RT. The reaction mass was stirred at RT for 12 h monitored by TLC and the resulting mixture was diluted with DCM (150 mL) and neutralised with solid $NaHCO_3$. Inorganic solids were removed by filtration and the filtrate was extracted with DCM (2 × 50 mL) and dried over $MgSO_4$. The solution was concentrated under vacuum to obtain a residue which was subjected to chomatography on silica, using hexane:EtOAc; 70:30, R_f 0.4, to yield lactone (234) (6 g), a compound known in the literature.[190]

^{1}H NMR (400 MHz, $CDCl_3$): 5.39 (1H, br, **CH**OH), 4.82(1H, dd, *J* = 5.9, 3.4 Hz, **CH**CHOH), 4.54(1H, d, *J* =5.9 Hz, **CHCH$_2$**), 4.06-3.98 (2H, m, **CH$_2$**), 3.81(1H, d, *J* = 1.2 Hz, **OH**), 1.45 (3H, s, C**CH$_3$**), 1.30 (3H, s, C**CH$_3$**).

13C NMR (100 MHz, CDCl3)**:** 112.2 (**C**), 101.0 (**CH**), 85.1 (**CH**), 80.3 (**CH**), 71.77(**CH$_2$**), 26.1(**CH$_3$**), 24.66(**CH$_3$**).

3.11.2 Synthesis of (3aR,6aS)-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole 5-oxide

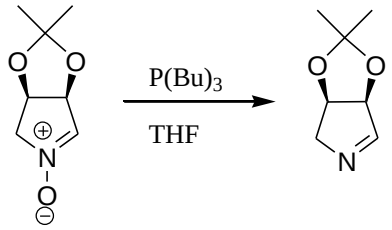


234 239

To a 0.5 M solution of lactol (234) (460 mg) in dry pyridine (5.75 mL) was added 3 Å molecular sieves (2 g) and hydroxylamine hydrochloride (239 mg). The mixture was stirred overnight at room temperature and then a 0.6 M solution of methanesulfonyl chloride (5.75 mL) in dry pyridine was added. The reaction mixture was stirred overnight at room temperature and then filtered though Celite. The filter was washed with dioxane (10 mL). The filtrate was concentrated and purified by column chomatography on silica to give a white solid (239) (180 mg) (eluent, DCM / EtOAc / MeOH, 66:30:4, R_f = 0.3). The data was consistent with reported literature.[144]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, q, J = 1.5 Hz, N=**CH**), 5.26 (1H, d, J = 6.2 Hz, **CH**COC), 4.87 (1H, ddd, J = 6.5, 5.1, 1.5, **CH**CH_2), 4.20-3.90 (2H, m, **CH_2**), 1.41 (3H, s, C**CH_3**), 1.33 (3H, s, C**CH_3**).

3.11.3 Synthesis of (3aR,6aS)-2,2-dimethyl-4,6a-dihydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole

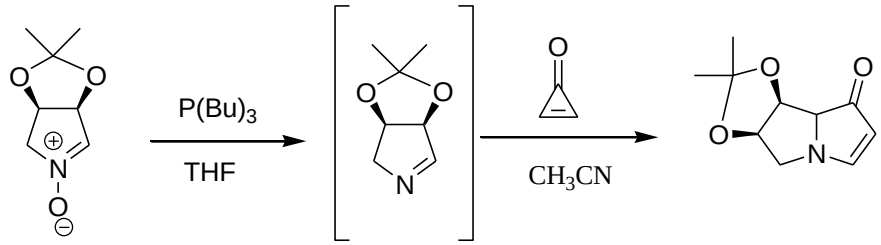


239 232

To a stirred solution of nitrone (239) (95 mg) in dry THF (10 mL) under nitrogen, tributylphosphine (300 µL) was added in one portion. The reaction mixture was heated to 65 °C and stirred at this temperature for 72 h, the reaction being monitored by TLC for completion. The solvent was evaporated under reduced pressure. Attempts to isolate the

imine were not fruitful, but the TLC indicated the complete consumption of starting material and formation of a new product assigned as the imine (232), which was used directly.

3.11.4 Attempted Synthesis of (3-R,8-S)-2,2-dimethyl-3a,4-dihydro-8a-[1,3]dioxolo[4,5-a]pyrrolizin-8-one



239 232 345

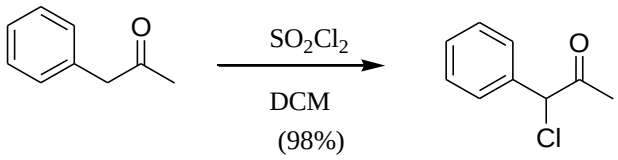
To a stirred solution of nitrone (239) (95 mg) in dry THF (10 mL) under nitrogen, tributylphosphine (300 µL) was added in one portion. The reaction mixture was heated to 65 °C and stirred at this temperature for 72 h and monitored by TLC for completion, after which the solvent was evaporated under reduced pressure. Anhydrous acetonitrile was added and the mixture was cooled to -5 ºC. Unsubstituted cylopropenone (189) (83 mg) [generated *in situ*] was added dropwise over a period of 10 min. The rxn was monitored by TLC, left stirring at RT for 12 h. The resulting mixture was concentrated under vacuum and subjected to chomatography from which a product was isolated, but which decomposedwithin hours of isolation.

^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (1H, d, *J* = 3.9 Hz, N**CH**=CH), 5.05 (1H, d, *J* = 3.9 Hz, NCH=**CH**), 4.93 (1H, dd, *J* = 5.5, 3.8 Hz, NC**H**$_2$), 4.71 (1H, d, J = 5.5 Hz, NCH), 3.72-3.67 (1H, m, NCH), 3.53-3.40 (2H, m, 2 × CH), 0.94 (3H, s, **CH$_3$**), 0.91 (3H, s, **CH$_3$**).

Cyclopropenones and their acetals:

3.12 Synthesis of 2-phenylcycloprop-2-enone:

3.12.1 Synthesis of 1-chloro-1-phenylpropan-2-one:

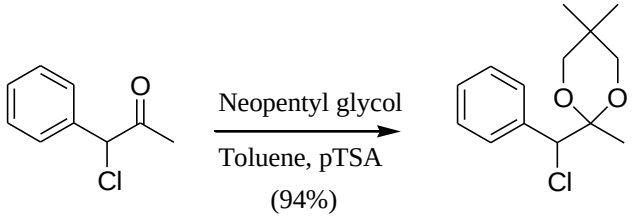


240 241

In a 1000 mL RBF, phenylacetone (240) (50 g, 372.63 mmol) was dissolved in DCM (300 mL). This solution was cooled to 0 °C and sulfuryl chloride (36.2 mL, 447.15 mmol) was added slowly. The resulting solution was stirred for 7 h at RT whilst the rxn was monitored by TLC. Water (200 mL) was added to the solution, the aqueous layer was separated and extracted with DCM (50 mL × 2) and the combined organic layers were washed with sat. aq. NaCl solution (50 mL), dried over anhydrous $MgSO_4$ and evaporated to give the crude α-chloroketone (241) (62 g, 98%) as a yellow oil, R_f. 0.5 (EtOAc / PE, 10:90).
Data consistent with the literature[191]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58-7.30 (5H, m, **CH** (Ph)), 5.30 (1H, s, **CH**Cl), 2.20 (3H, s, **CH_3**CO).

3.12.2 Synthesis of 2-[chloro(phenyl)methyl]-2,5,5-trimethyl-1,3-dioxane:



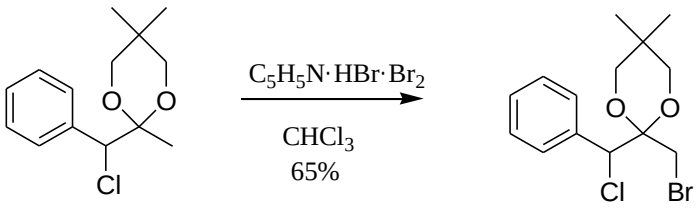
241 242

To a solution of the α-chloroketone (241) (62 g, 367.73 mmol) in toluene (350 mL) in a 1000 mL RBF was added neopentyl glycol (55.5 g) and *p*-toluenesulfonic acid (1.35 g). The resulting mixture was heated at reflux for 7 h in a Dean-Stark apparatus for continuous

removal of water. After cooling to RT, n-hexane (500 mL) was added and the resulting mixture was concentrated under reduced pressure and washed with n-hexane. The filtrate was washed successively with sat. aq. $NaHCO_3$ solution (200 mL), water (200 mL) and sat. aq. NaCl solution (200 mL) and dried over anhydrous $MgSO_4$. Removal of the drying agent and concentration afforded the crude acetal (242) (87.3 g), R_f. 0.7 (EtOAc / PE, 10:90) which was used in the next step without further purification.
Data consistent with the literature:[191]

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.63-7.51 (2H, m, **CH** (Ph)), 7.32-7.20 (3H, m, **CH** (Ph)), 5.21 (1H, s, **CH**Cl), 3.60 (1H, d, *J* =11.5 Hz, **CH**$_2$OC), 3.58 (1H, d, *J*= 11.2 Hz, **CH**$_2$OC), 3.50 (1H, dd, *J*=11.5, 1.6Hz, **CH**$_2$OC), 3.43 (1H, dd, *J*=11.2, 1.6 Hz, **CH**$_2$OC), 1.53 (3H, s, **CH$_3$**C), 0.95 (3H, s, C(**CH$_3$**)$_2$), 0.88 (3H, s, C(**CH$_3$**)$_2$).

3.12.3 Synthesis of 2-(bromomethyl)-2-[chloro(phenyl)methyl]-5,5-dimethyl-1,3-dioxane:



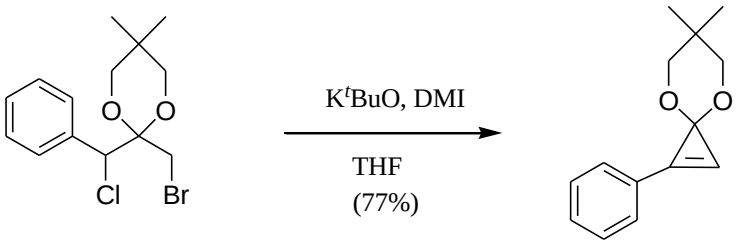
242 243

To a solution of crude acetal (242) (76.3 g, 300 mmol) in $CHCl_3$ (700 mL) in a 1000 mL RBF, was added pyridinium hydrobromide perbromide (100 g) and the mixture heated at reflux for 30 min, then cooled to RT. Water (500 mL) was added, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 100 mL) and the combined organic layers were washed with water, saturated $NaHCO_3$ solution (100 mL) and saturated NaCl solution (100 mL). The resulting solution was dried over $MgSO_4$. Evaporation of the solvent gave crude chloro bromo acetal (243).

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.61-7.54 (2H, m, **CH** (Ph)), 7.37-7.28 (3H, m, **CH** (Ph)), 5.32 (1H, s, **CH**Cl), 3.97 (1H, d, *J*= 11.7 Hz), 3.67-3.43 (5H, m), 0.83 (3H, s, C(**CH$_3$**)$_2$), 0.78 (3H, s, C(**CH$_3$**)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.39 (**C**, Ph), 129.74 (**CH**, Ph), 128.46 (**CH**, Ph), 127.74 (**CH**, Ph), 97.73 (HCCl-**C**-CHBr), 71.14 (O**CH$_2$**), 70.90 (O**CH$_2$**), 63.44 (**CH**Cl), 29.57(**C**$(CH_3)_2$), 27.71 (**CH$_2$**Br), 22.18 (**CH$_3$**), 22.15 (**CH$_3$**).

3.12.4 Synthesis of 2-phenylcyclopropenone 2,2-dimethyl-1,3-propanediyl acetal:



243 244

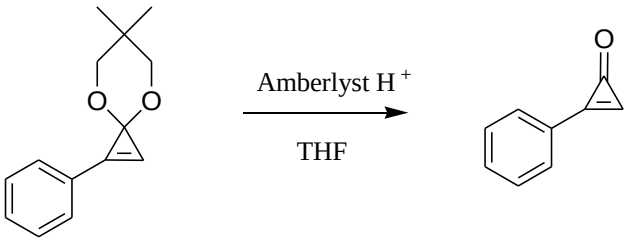
Into a 50 mL RBF the dihalide (243) (1 g, 2.994 mmol) was weighed, sealed under nitrogen and dry THF (1 mL) was added and the mixture cooled to 0 °C. In a separate oven dried RBF, K*t*BuO. (672 mg, 5.98 mmol) was weighed and dry THF (4 mL) and DMI (5 mL) were added under N_2. The solution of K*t*BuO was added dropwise over a period of 30 min to the dihalide and the resultant mixture stirred for 3 h, at 0 °C. Water (20 mL) was added and the aqueous solution was extracted with n-hexane (3 x 40 mL). The combined extracts were washed with saturated aq. NaCl (50 mL) and dried over anhydrous $MgSO_4$. Removal of the drying agent and concentration yielded the crude product (500 mg), which was purified over silica using flash chomatography (eluent 30:70 EtOAc/PE) as a yellow oily mass (244) (300 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.71 (1H, s, **CH**), 7.67-7.64 (2H, **CH** (Ph)), 7.48-7.39 (3H, m, **CH** (Ph)), 3.80 (4H, s, **CH_2** ($C(CH_3)_2$), 1.17 (3H, s, $C(\mathbf{CH_3})_2$), 1.10 (3H, s, $C(\mathbf{CH_3})_2$)).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.60 (Ph**C**=CH), 130.06 (**C** (Ph)), 129.65 (**CH** (Ph)), 128.32 (**CH** (Ph)), 125.85 (**CH** (Ph)), 114.61 (**CH**=C), 83.16 (**C**(OCH_2), 77.31 (**CH_2**(CCH_3), 30.47 (**C**$(CH_3)_2$), 21.95 (**CH_3**), 22.52 (**CH_3**).

Data consistent with the literature.[191]

3.12.5 Synthesis of 2-phenylcycloprop-2-enone:



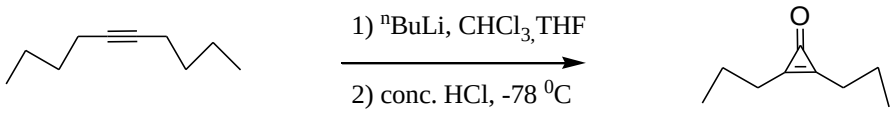
244 247

To the crude acetal (244) (500 mg) dissolved in THF (10 mL) was added water (3-4 drops) and, simultaneously Amberlyst-15 (100 mg) was added and the rxn was stirred at RT overnight. The Amberlyst was filtered off and the rxn mass was distilled to remove THF. The residue was purified by chomatography with EtOAc / PE 60:40 to give phenyl cyclopropenone (247) (300 mg, 77%).

IR: υ_{max} 3400, 2855, 1790, 1550, 1050, 700.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.47 (1H, s **CH**=CO), 7.72 (2H, d, 6.8 Hz, **CH** (Ph)), 7.50-7.38 (3H, m, **CH** (Ph)).
Data consitent with literature.[129]

3.13 Synthesis of 2,3-dipropylcycloprop-2-enone:



248 249

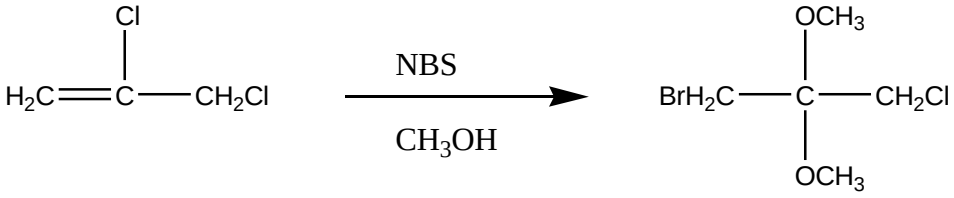
To a stirring solution of 4-octyne (248) (220 mg, 1.99 mmol) and $CHCl_3$ (0.4 mL, 4.99 mmol), in THF (30 mL) maintained at -78 ºC, was added dropwise *n*-butyllithium (2.74 mL, 1.6 M, 4.39 mmol), over a period of 5 min under continous flow of nitrogen. The reaction mixture was stirred at this temperature for 4 h, after which conc. HCl (1 mL) was added slowly dropwise over a period of 10 min. The cooling bath was removed and the mixture stirred at RT for 10 min. Water (20 mL) was added and the resulting mixture was extracted with DCM (5 × 20 mL). The organic layers were dried over $MgSO_4$ and the solvent removed

under reduced pressure to yield crude dipropyl cyclopropenone (249), whose data was consistent with that reported in the literature.[192]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.56 (4H, t, J = 7.2 Hz, 2 × **H_2**CC**=C**), 1.75-1.66 (4H, m, 2 × H_3C**CH_2**), 1.03 (6H, t, J = 7.4 Hz, 2 × **CH_3**CH_2).

3.14 Attempted synthesis of cyclopropenone acetal:

3.14.1 Synthesis of 1-bromo-3-chloro-2,2-dimethoxypropane:



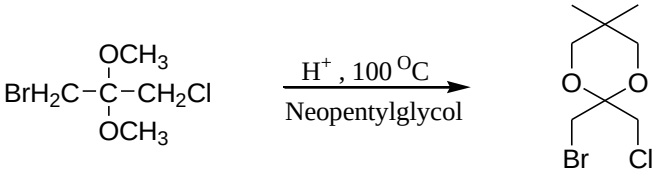
346 254

To a solution of 2,3-dichloropropene (346) (12 g, 0.10 mmol) in anhydrous methanol (32 mL), was added conc. H_2SO_4 (2 drops). To this was added *N*-bromosuccinimide (19.2 g, 0.1 mmol) in very small portions and the resulting reaction mixture was stirred for 1 h. Sodium carbonate (5 g) was added to neutralise the acid catalyst, the resulting solution was poured into water (50 mL), both the layers were separated and the aqueous layer was extracted with pentane (2 × 30 mL). The organic layers were combined and dried over $MgSO_4$. The solution was filtered into a 500 mL Erlenmeyer flask and closed with a rubber stopper. The flask was cooled in an ice bath for 30 min. The pentane solution was decanted to obtain colourless crystalline product (254) (4.7 g, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (2H, s, **CH_2**Cl), 3.56 (2H, s, **CH_2**Br), 3.31(6H, s, 2 × O**CH_3**).

Data consistent with literature.[197]

3.14.2 Synthesis of 2-(bromomethyl)-2-(chloromethyl)-5,5-dimethyl-1,3-dioxane.



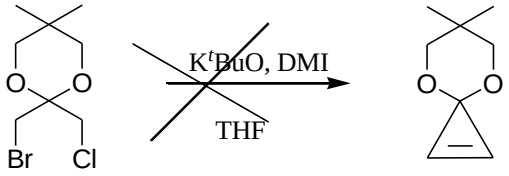
254 256

To a solution of 1-bromo-3-chloro-2,2-dimethoxypropane (254) (3.9 g, 17.93 mmol) in a 100 mL RBF fitted with a 10 mL Dean-Stark apparatus and a condenser was added neopentylglycol (2.24 g, 21.51 mmol) and conc. H_2SO_4 (2 drops). The resulting mixture was heated at reflux for 8 h. The mixture was allowed to cool to room temperature and partitioned between pentane (100 mL) and water (40 mL).The pentane layer was dried over $MgSO_4$ and the solvent was removed under vacuum, to yield the acetal (256) (4 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (2H, s, **CH_2**Cl), 3.69 (2H, s, **CH_2**Br), 3.55 (4H, d, br, J = 3Hz, 2 × **CH_2**C(CH_3)), 1.01 (3H, s, **CH_3**C), 0.98 (3H, s, **CH_3**C).

Consistent with the literature.[197]

3.14.3 Attempted synthesis of cyclopropenone acetal:

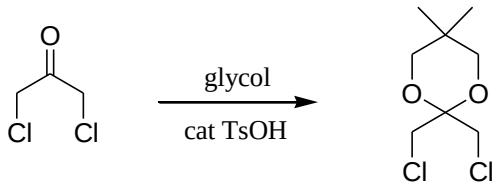


256 253

A solution of 2-(bromomethyl)-2-(chloromethyl)-5,5-dimethyl-1,3-dioxane (256) (1 g, 3.88 mmol) in anhydrous THF (2 mL) under continuous flow of nitrogen was cooled to 0 °C. To this was added mixture of potassium *tert*-butoxide (871 mg, 112.21), DMI (5 mL), anhydrous THF (5 mL) slowly over a period of 30 min. at 0 ^{0}C. The reaction was maintained at this temperature for 3 h. Water (20 mL) was added and the aqueous solution was extracted with n-hexane (3 × 40 mL). The combined extracts were washed with saturated aq. NaCl (50 mL) and dried over anhydrous $MgSO_4$. Removal of the drying agent and concentration yielded an unknown mass which seemed to be mainly DMI.

3.15 Synthesis of cyclopropenone:

3.15.1 Synthesis of 2,2-bis(chloromethyl)-5,5-dimethyl-1,3-dioxane:



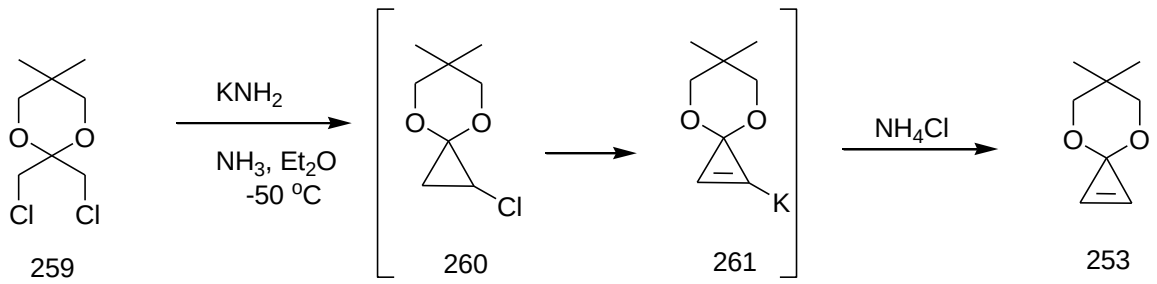
258 259

To 1,3-dichloroacetone (258) (25 g, 0.19 mmol) was added toluene (100 mL), in a 250 mL RBF equipped with a Dean-Stark apparatus and condensor. To this solution was added neopentylglycol (22g, 0.216 mmol) and para-toluene sulfonic acid (pTSA) (0.78 g, catalytic). The resulting solution was heated at 140 °C, for a period of 15 h, with the azeotropic removal of water. The resulting solution was cooled to room temperature, partitioned between hexane (200 mL) and sat. aq. $NaHCO_3$ (100 mL). The organic phase was washed with water and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Distillation under reduced pressure (98-100 °C), yielded 1,3-dichloroacetone acetal (259) (40 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (4H, s, 2 × **CH_2** C $(CH_3)_2$), 3.58 (4H, s, 2 × **CH_2**Cl), 1.01 (6H, s, (**CH_3**)$_2$C).

Consistent with that reported in the literature.[129]

3.15.2 Synthesis of cyclopropenone acetal:



259 260 261 253

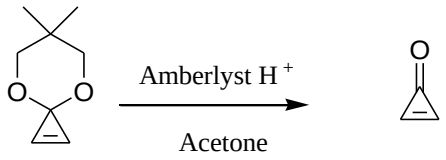
To a 3-neck 250 mL RBF equipped with an acetone-dry ice condenser, stopper, drying tube with potassium hydroxide pellets, gas inlet, magnetic stirring bar and a bubbler, under continuous flow of nitrogen in a acetone-dry ice bath (- 50 to - 60ºC), anhydrous ammonia

(~ 100 mL) was condensed. The bubbler was replaced with a stopper, a small piece of potassium metal (~50 mg of 2.75 g, 0.07 mmol) was added to the liquid ammonia and the solution turned blue in colour, at which point the cooling bath was removed and a catalytic amount of anhydrous ferric chloride (50 mg) was added and the solution allowed to warm to reflux temperature. At this point the blue colour turned gray. The remaining potassium metal (2.7 g) was added slowly in small pieces and stirred until the gray solution persisted (~10 min). The cooling bath was returned (- 50 to - 60 ºC), the stopper was replaced with an addition funnel containing 1,3-dichloroacetone acetal (259) (5g, 0.023 mmol) in 10 mL of anhydrous ether. This was added dropwise over a period of 10 min while the temperature was maintained at -50 ºC. The resulting solution was stirred at this temperature for 3 h and solid ammonium chloride (4 g) was added slowly to quench the excess potassium amide. The cooling bath was removed and ammonia was allowed to evaporate, whilst anhydrous ether was (75 mL) added dropwise though an addition funnel to replace the ammonia. When the solution reached 0 ºC, the reaction mass was filtered though a coarse fritted-glass filter by suction to remove the inorganic salts. The salts were washed twice with anhydrous ether (30 mL) and the combined ethereal layers were concentrated under reduced pressure (< 30ºC, 80-100 mm), to give a yellowish oily mass. This was transferred to a RBF (25 mL), purified by distillation (1-2 mm, 30-35ºC) using a water cooled short path distillation head and an ice cooled receiver. Cyclopropenone acetal (253) (2 g, 97%) was obtained as a colourless oil, which could be stored under nitrogen in the freezer for 4-6 weeks.

IR: υ_{max} : 2975, 2870, 1698, 1504, 1441, 1397, 1251, 1098, 1024.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (2H, **HC**=**CH**), 3.61 (4H, s, 2 × **CH_2**$C(CH_3)_2$), 1.03 (s, 6H, s, $C(\mathbf{CH_3})_2$).

The data is consistent with that reported in the literature.[129]

3.15.3 Synthesis of cycloprop-2-enone:

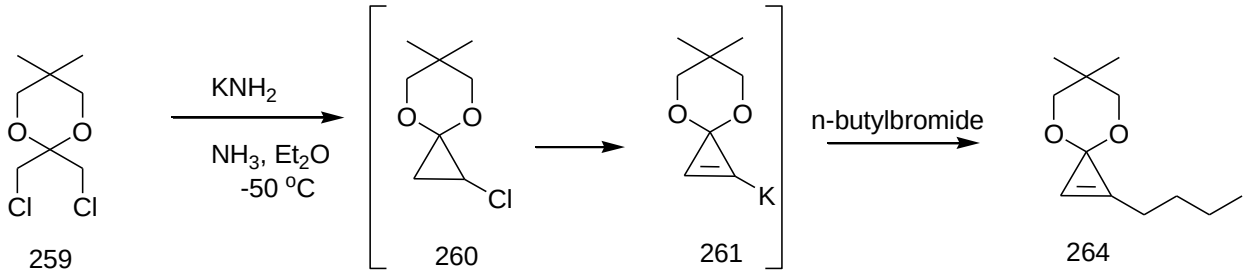


253 189

To the acetal (253) (500 mg) dissolved in acetone (10 mL), Amberlyst-15 (100 mg) was added and the rxn was stirred at RT for 20 min. The Amberlyst was filtered off and the rxn mass was added dropwise to the respective solution of imine. Due to the nature of the cyclopropenone (unstable and volatile) (189) was not purified. The rxn was monitored by IR for the removal of acetal. The characteristic carbonyl and alkene were observed at 1820 and 1584 cm^{-1},[129] with a clear loss of acetal alkene at 1698 cm^{-1}.

3.16 Synthesis of Butylcycloprop-2-enone:

3.16.1 Synthesis of butyl cyclopropenone acetal:



259 260 261 264

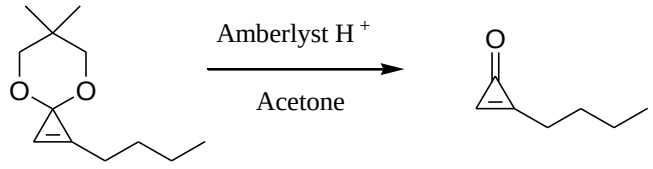
To a 3-neck 250 mL RBF equipped with an acetone-dry ice condenser, stopper, drying tube with potassium hydroxide pellets, gas inlet, magnetic stirring bar and a bubbler, under continuous flow of nitrogen in a acetone-dry ice bath (- 50 to - 60ºC), anhydrous ammonia (~ 100 mL) was condensed. The bubbler was replaced with a stopper, a small piece of potassium metal (~50 mg of 2.75 g, 0.07 mmol) was added to the liquid ammonia and the solution turned blue in colour, at which point the cooling bath was removed and a catalytic amount of anhydrous ferric chloride (50 mg) was added and the solution allowed to warm to reflux temperature. At this point the blue colour turned gray. The remaining potassium metal (2.7 g) was added slowly in small pieces and stirred until the gray solution persisted (~10 min). The cooling bath was returned (- 50 to - 60 ºC), the stopper was replaced with

an addition funnel containing 1,3-dichloroacetone acetal (259) (5g, 0.023 mmol) in 10 mL of anhydrous ether. This was added dropwise over a period of 10 min while the temperature was maintained at -50 ºC. The resulting solution was stirred at this temperature for 3 h and to this solution was added a solution of 1-bromobutane in Et_2O (2.77 mL, 0.025 mmol in 10 mL) dropwise over a period of 25 min. After stirring for 30 min, solid NH_4Cl (4 g) was added. The cooling bath was removed and ammonia was allowed to evaporate, during which time anhydrous Et_2O (100 mL) was added slowly. The ethereal solution was filtered though a coarse fritted-glass filter by suction to remove the inorganic salts. The salts were washed twice with anhydrous ether (30 mL) and the combined ethereal layers were concentrated under reduced pressure (< 30ºC, 80-100 mm), to give a yellowish oily mass. This was transferred to a RBF (25 mL), purified by vacuum distillation (1-2 mm, 54 ºC) resulting in pure butylcyclopropenone acetal (264) (3.44 g, 75%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (1H, s, br, **HC**=C), 3.60 (2H, S, **CH_2**OC), 3.56 (2H, s, **CH_2**OC), 2.52 (2H, t, J = 7.2Hz, C=C**CH_2**), 1.60 (2H, m, CH_2**CH_2**CH_2), 1.4 (2H, m, **CH_2**CH_3), 1.06 (3H, s, C**CH_3**), 0.99 (3H, s, C**CH_3**), 0.9 (3H, t, J = 7.4Hz, **CH_3**CH_2).

The data was consistent with the literature data.[129]

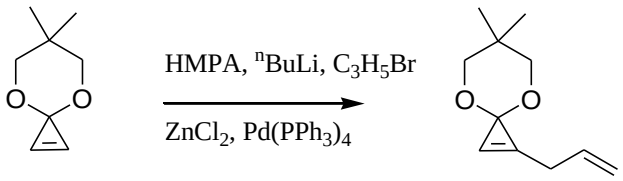
3.16.2 Synthesis of Butylcycloprop-2-enone:



264 265

To the acetal (264) (500 mg) dissolved in acetone (10 mL), Amberlyst-15 (100 mg) was added and the rxn was stirred at RT for 20 min. The Amberlyst was filtered off and the rxn mass was concentrated under reduced pressure. Attempts to isolate the cyclopropenone by chromatography resulted in degradation on the column. The rxn mass was instead purified by vaccum distillation (25 ^{o}C, at 0.2 mm Hg) as a colourless oil (242 mg, 95%)
IR: u_{max} cm^{-1}: 3045, 2959, 2872, 1830, 1590, 1037.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, s, br, **HC**=C), 2.65 (2H, t, J = 7.2Hz, C=C**CH_2**), 1.66 (2H, m, CH_2**CH_2**CH_2), 1.37 (2H, m, **CH_2**CH_3), 1.01 (3H, s, C**CH_3**).

3.17 Synthesis of allylcyclopropenone:



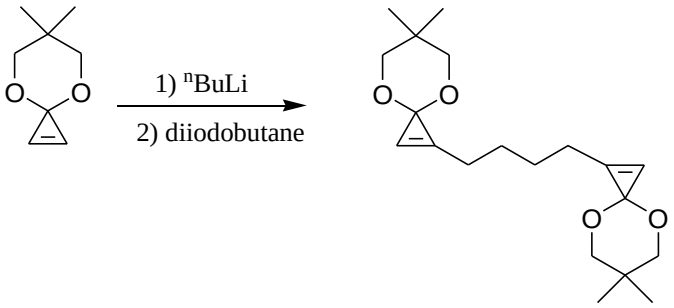
253 270

To a solution of cyclopropenone acetal (253) (1g, 7.14 mmol) and HMPA (4.13 mL, 23.78 mmol), in anhydrous THF (15 mL) at -78 ^{0}C, was added n-BuLi (2.85 mL, of 2.5M solution in hexane) over a period of 5 min. The resulting mixture was stirred for 30 min. Zinc chloride (3.5 mL of a 1M solution in THF) was added and the dry ice cooling bath was removed. $Pd(PPh_3)_4$ (0.27 mg, 0.23 mmol) and allyl bromide (0.61 mL, 7.14 mmol) were added and the mixture was stirred for 2 h. Triethylamine (0.5 mL) was added and the solution was diluted with hexane (20 mL) and evaporated under vacuum. The resulting crude product was subjected to column chomatography on silica (R_f0.3, EtOAc / PE, 10:90) to yield 75 mg, 10% yield, of the desired allyl substituted product (270).

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.41 (1H, s, **HC**=C), 5.97-5.87 (1H, m, **CH**=CH_2), 5.26-5.17 (2H, m, **CH_2**=CH), 3.79 (2H, s, **CH_2**OC), 3.62 (2H, m, **CH_2**OC), 1.04 (3H, s, **CH_3**C), 1.01 (3H, d, *J* = 5.2 Hz, **CH_3**C).

3.18 Synthesis of biscyclopropenone:

3.18.1 Synthesis of biscyclopropenone acetal:



253 266

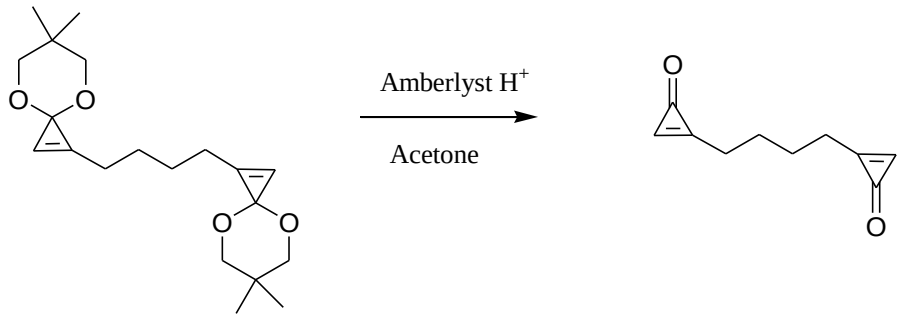
To a solution of unsubstituted cyclopropenone acetal (253) (600 mg, 4.28 mmol) in anhydrous THF (10 mL) under nitrogen was added HMPA (1.49 mL, 8.57 mmol). The resulting solution was cooled to – 78 ^{0}C, n-BuLi (1.7 mL, 2.5M) was added slowly over a period of 5 min and the resulting solution was stirred for 30 min. 1,4-Diiodobutane (0.22 mL, 1.71 mmol) was added slowly and the mixture stirred for 4 h at -78 ^{0}C. The reaction was quenched by pH 7.4 buffer (2 mL, pH buffer*: THF (1:5)). The reaction was allowed to warm to room temperature. THF was removed under reduced pressure and the resulting solution was dissolved in EtOAc (30 mL) and washed with water (30 mL). The aq. layer was washed with ethylacetate (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated to yield a brown coloured oily mass. $R_{f:}$ 0.3 (15:85 EtOAc/ PE). The crude material was subjected to chomatography over silica (25:75 EtOAc / PE, 0.5% Et_3N) to afford 230 mg (17%) of pure biscyclopropenone acetal (266).

*pH buffer used was 7.4 phosphate buffer in THF (1/5 v/v). (Purchased from Sigma Aldrich)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (2H, s, br, 2 × **HC**=C), 3.60 (8H, q, J = 10.6 Hz, 4 × **CH_2**OC), 2.56 (4H, s, br, C=C**CH_2**), 1.74 (4H, s, br, CH_2**CH_2CH_2** CH_2), 1.07 (6H, s, 2 × C**CH_3**), 0.98 (6H, s, 2 × C**CH_3**).

Data consistent with that reported in the literature.[129]

3.18.2 Synthesis of biscyclopropenone:



266 267

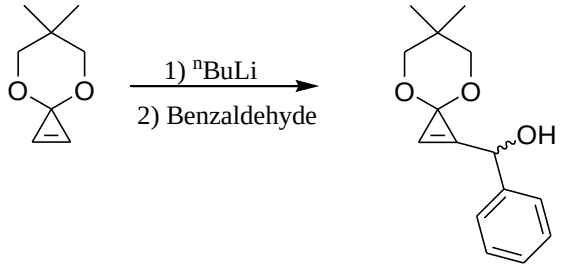
To the crude acetal (266) (200 mg) dissolved in acetone (20 mL) was added Amberlyst-15 (40 mg, 20% by weight) and the rxn was stirred at RT for one hour. The rxn was monitored by TLC. Amberlyst was filtered off and the rxn mass was distilled to remove acetone. The residue was purified by chomatography with EtOAc / PE 50:50 to 80:20 to give bis-cyclopropenone (267) (92 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.3 (2H, s, 2 × **HC**=C), 2.62 (4H, s, 2 × C=C**CH_2**), 1.2 (4H, m, CH_2**CH_2CH_2** CH_2).

The data was consistent the literature.[129]

3.19 Synthesis of 2-(α-hydroxybenzyl)cyclopropenone:

3.19.1 Synthesis of 2-(α-hydroxybenzyl)cyclopropenoneacetal:



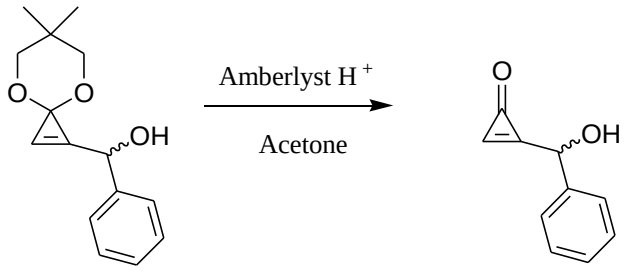
253 268

To a solution of the unsubstituted cyclopropenone acetal (253) (950 mg, 6.785 mmol) in anhydrous THF (15 mL) under nitrogen was added TMEDA (2.74 mL, 116.2 mmol). The resulting solution was cooled to – 78 ^{0}C, n-BuLi (2.74 mL, 2.5M) was added slowly over a period of 5 min and the resulting solution was stirred for 30 min at the same temperature. Benzaldehyde (0.66 mL, 6.78 mmol) was added slowly and the mixture stirred for 2 h at the same temperature. The reaction was quenched by pH 7.4 buffer (2 mL, pH buffer: THF (1:5)). The reaction was allowed to cool to room temperature, THF was removed under reduced pressure and the resulting solution was dissolved in EtOAc (30 mL) and washed with water (30 mL). The aqueous layer was washed with ethylacetate (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated to yield a brown coloured oily mass 1.41 g (268) (85%). R_f 0.3 (30:70 EtOAc / PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53-7.29 (6H, m, **CH**=C, 5 × **CH** (Ph)), 5.80-5.75 (1H, m, **CH** (OH)), 3.60 (2H, m, **CH_2** OC), 3.50 (2H, m, **CH_2** OC), 3.3 (1H, m, **OH**), 1.08 (3H, s, C**CH_3**), 0.83 (C**CH_3**).

The data was consistent with that reported in the literature.[129]

3.19.2 Synthesis of 2-(α-hydroxybenzyl)cyclopropenone:



268 269

To the crude acetal (268) (107 mg) dissolved in acetone (15 mL) was added Amberlyst-15 (22 mg, 20% by weight) and the rxn was stirred at RT for one hour and rxn monitored by TLC. Amberlyst was filtered off and the rxn mass was distilled to remove acetone. The residue was purified by chomatography with EtOAc / PE 50:50 to 80:20 to give hydroxy benzyl cyclopropenone (269) (60 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, s, br, **CH**=C), 7.58-7.41 (5H, m, 5 × **CH** (Ph)), 5.85 (1H, s, br, **CH** (OH)), 3.87 (1H, m, br, **OH**),

The data was consistent with that reported in the literature.[129]

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