Studies Directed Toward the Total Synthesis of the Diterpene Alkaloids

A thesis submitted for the degree of Doctor of Philosophy
of the Australian National University

by

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by me during the period 2001-2005 and has not been presented for examination for any degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

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Abstract

The diterpene alkaloidsa are a diverse family of compounds that are becoming recognized for there potent interactions with the cardiac and central nervous system. The most complex of the C_{20} alkaloids is the polycyclic structure typified by hetisine (**3-1**), which provides a significant challenge from a synthetic standpoint. This thesis discusses and sets out strategies to enable the total synthesis of the heptacyclic diterpene moiety of hetisine. The development of these strategies led to the synthesis of key intermediate **6-50** from enone **3-50.**

Chapter One provides a brief overview of the structure of the diterpene alkaloids as well as their importance in relation to their cardiovascular activity. **Chapter Two** covers the total synthetic work carried out on this family of alkaloids to date and gives an account of the different strategies employed. In addition, important model studies are covered.

Chapter Three outlines the general end game strategy, to which all subsequent work is directed and outlines the first approach that was investigated. The first approach was aimed at accessing the lactam **3-9** through a modified Schmidt rearrangement of the azide **3-12.** It was intended that the azide **3-12** could be synthesised from the alkene **3-15**, which in turn could be accessed from cyclisation of the diazoketone **3-14**. In the event, cyclisation of **3-14** and its analogue **3-58** led to the formation of the rearranged products **3-40**, **3-59** and **3-61**, through unprecedented reaction pathways.

The strategy outlined in **Chapter Four** is an extension of that outlined in **Chapter Three.** The intention of installing the nitrogen early in the synthesis *via* functionalisation of the alkene **4-1**, is described. Displacement of the β-hydroxy function of **4-13** led to the tetrahydrofuran **4-18**, and while the reduction of oxime **4-30** led to the lactam **4-31**, this strategy was ultimately aborted due to its inefficiency.

Chapter Five discusses the entirely different strategy of forming the pyrrolidine **3-3** through a 1,6-addition of amine **5-3**, and lays the foundation for the synthetic sequence that was ultimately successful. Acylation of a preformed enolate **5-25** gave the β-keto ester **5-23**, which was elaborated with complete stereocontrol to the aldehyde **5-49**. However, attempts to install nitrogen were unsuccessful.

The strategy outlined in **Chapter Six** is analogous to that in **Chapter Five**, but addresses its shortcomings by employing the nitrile **6-9**, which gave access to the 1,6-addition precursor **6-33** and thus pyrolindine **6-50**. The future direction of this synthesis is discussed.

Chapter Seven provides a summary of the results obtained during the research for this PhD, and gives an overall conclusion.

Chapter Eight contains the experimental procedures conducted during this research as well as all the spectroscopic data.

Glossary

The following abbreviations have been used throughout this thesis:

AcCl	acetyl chloride
Ac_2O	acetic anhydride
AcOH	acetic acid
Ac	acetyl
Am	Amyl
aq.	Aqueous
atm	atmosphere
$BF_3 \cdot Et_2O$	boron trifluoride diethyl etherate
BH_3•DMS	borane dimethyl sulfide
Bu	butyl
^{t}Bu	*tertiary*-butyl
Bn	benzyl
Bz	benzoate
CCL	*Candidi cylindracea*
CAN	ceric ammonium nitrite
cat.	Catalyst
Cbz	benzyl carbamate
c.	concentrated
COSY	correlation spectroscopy
m-CPBA	*m*-chloroperbenzoic acid
δ	chemical shift (parts per million)
DBN	1,5-Diazabicyclo[4,3,0]non-5-ene
DBU	1,8-Diazobicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DIBALH	diisobutylaluminium hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
ED	effective dose
ee	enantiomeric excess
EI	electron impact

ether	diethyl ether
equiv. Or eq.	Equivalents
ESI	electrospray ionisation
Et	ethyl
Et_3N	triethylamine
EVK	ethyl vinyl ketone
g	gram
hr or hrs	hour(s)
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrum
Hv	light
Hz	Hertz
Im	imidazole
IR	infrared
i-Pr	*iso*-propyl
J	coupling constant (Hz)
LD	lethal dose
LDA	Lithium Diisopropylamine
$LiAlH_4$	lithium aluminium hydride
lit.	literature
$M^{+\bullet}$	molecular ion
m-CPBA	*meta*-chloro benzoic acid
Me	methyl
min	minute(s)
mol	mole
MOM	methoxymethyl
MEM	2-methoxyethoxymethyl
Mol Sieves	Molecular Sieves
MP	melting point (°C)
Ms	methanesulfonyl or mesyl
MS	mass spectrum
m/z	mass-to-charge ratio
NaOMe	sodium methoxide
NBS	*N*-bromo succimide
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
ν_{max}	infrared absorption maxima (cm^{-1})
p-Brosyl	*para*-bromosulfonyl
PDC	pryridinium dichromate
Ph	phenyl

Piv	Pival
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
pTol	*para*-tolulene
py	pyridine
Ra(Ni)	Rayney nickel
R_f	retardation factor
RT	room temperature (assumed to be ~18 °C)
sat.	saturated
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
Ts	*p*-toluenesulfonyl or tosyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TBDMS	*tertiary*-butyl dimethyl silyl
TMS	trimethylsilyl
p-TsOH	*p*-toluenesulfonic acid
vs.	*versus*
W	watt
wt	weight
Z	*zusammen* (together)
<	less than
>	greater than
°C	degrees Celsius
Δ	heat

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Chapter One

The Structure and Properties of the Diterpene Alkaloids

1.1 Introduction

The diterpene alkaloids (DAs) are constituted by a broad array of toxic compounds isolated from plants of the genera *Aconitum, Delphiunium, Thalictrum, Consolida* and *Rosera.*[1] Perhaps the most infamous of these plants is the species *Aconitum napellus* whose bell shaped flower earned it the common name Monkshood, and whose toxicity earned it the Greek name *lycotonum* - wolf's bane.[2] Similarly, *aconite* is derived from 'dart' in that darts or arrows dipped in preparations from the plant are lethal to wolves and humans.

However, these plants have also been used extensively in traditional medicine throughout Europe and Asia as painkillers and to reduce the increased heart rate associated with the onset of fever and anxiety.[3] However, being highly toxic and with the effective dose close to a lethal dose, a number of cases of poisoning have been reported. Overdose induces a sensation of crawling skin, laboured breathing, paralysis, nausea and vomiting; ultimately, the heart goes into shock and death results.

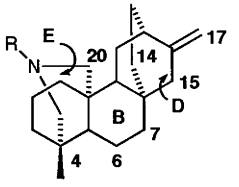
Disease associated with the heart and central nervous system are prevalent ailments of modern society. Although the diterpene alkaloids have been known for over 60 years they are only now becoming recognised for their activity and high selectivity within the above biological systems.[4] While the toxicity of the most active compounds limit there application, less toxic derivatives are emerging that could prove to be promising drug candidates.[5]

1.2 Structure

The structural elucidation of the diterpene alkaloids was initiated by Jacobs at the Rockerfeller Institute, early in the 20th Century. These studies were followed closely by the more sustained efforts of Weinser at the University of New Brunswick.[6] Between them and other researchers they produced a large number of papers which, through structural investigation, rationalisation, and correlation, produced a picture of the simple alkaloids. The structures of the more complex alkaloids were deduced through the use of the X-ray crystallography. From these initial studies over 400 aconite alkaloids have now been identified, with new alkaloids continuing to be isolated.[7]

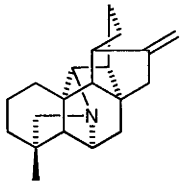
The alkaloids can be loosely divided into two main structural groups, the C_{20} diterpenoids (**Figure 1.1**) and the C_{19} *nor*-diterpenoids (**Figure 1.2**). The C_{20} DAs can be broken into two major groups based on the arrangement of the C and D-rings. Thus, the atisane

skeleton **1-1** possesses a bicyclo[2,2,2]octane CD-ring system, while the veatchane skeleton **1-2** has an *ent*-kaurene type bicyclo[3,2,1]octane arrangement. Further diversity is attributed to specific connections within the basic phenanthracene skeleton. These include a C20-C14 bond (delnudines **1-3**, hetidines **1-4**, hetisines **1-5,** anopterines **1-8**), a N-C6 bond (delnudines, hetidines), and a C20-C7 bond (denudatines **1-6**, napellines **1-7**). Delnudines also have the additional feature of a rearranged CD-ring system. Finally, the family is extended by different numbers of hydroxy groups and their derivatives - acetates, methyl ethers, and benzoates – that can occur on almost every carbon.



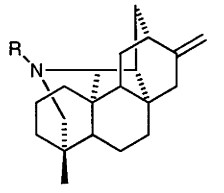
Atisines

1-1



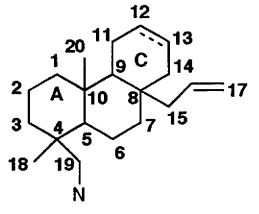
Delnudines

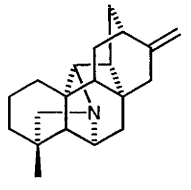
1-3



Hetidines

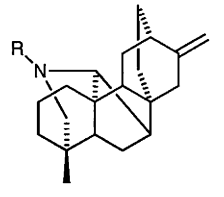
1-4





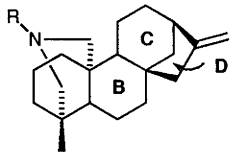
Hetisines

1-5



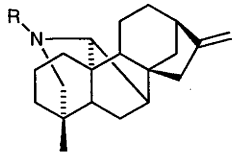
Denudatines

1-6



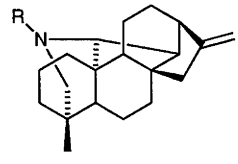
Veatchines

1-2



Napellines

1-7

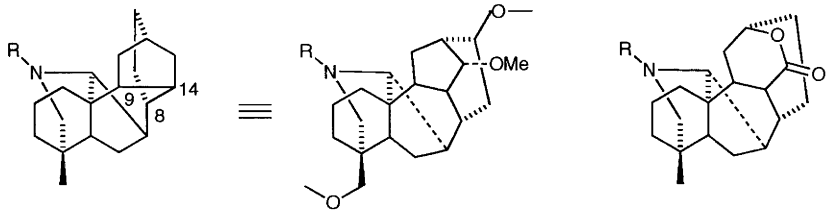


Anopterines

1-8

Figure 1.1. *The Skeletal Variation of the C_{20} Diterpene Alkaloids*

The *nor*-diterpenoids, which are related to the diterpenes *via* a 1,2-alkyl shift of the C8-C9 bond, can similarly be broken into two major groups, the lycoaconitines **1-9** and the heteratisines **1-10**. Again, the family of alkaloids is extended by different levels of oxidation of the parent skeleton.



Lycoctonines *Heteratisines*

1-9 **1-10**

Figure 1.2. *The Skeletal Variation of the C_{19} Diterpene Alkaloids*

1.3 Pharmacology

The diterpene alkaloids are extremely toxic, but have been successfully used in traditional medicine to alleviate a number of ailments. They are known to have analgesic and anti-inflammatory properties, and are also effective in treating trachyacardia brought on by anxiety or fever. Aconitine, which is a member of the C_{19} DA family, is the most active known diterpene alkaloid to be isolated and is reported to relieve pain at ED_{50} 0.06 $mg.kg^{-1}$, but the LD_{50} is 0.12-0.2 $mg.kg^{-1}$ and therefore extreme care must be taken to avoid inducing an arrhythmogenic cardiovascular effect (irregular heart beat followed by death). Conversely, nappelline, hetisine, heteratisine, and lappaconitine have been shown to have anti-arrhythmic properties and more acceptable analgesic properties. Anti-inflammatory, anti-epileptic, hypotensive, and bradycardic effects have also been noted.[8]

The pharmacology for the less active analogues is still being unravelled, but the mode of action of aconitine has been investigated. It is thought to exert its activity by modifying voltage dependent sodium (Na^+) channels, which increases the threshold at which pain, or other stimuli, are registered. Work is emerging that suggests that aconitine also interacts with the noradrenergic and cholinergic systems.[8] The shear molecular diversity of the DAs makes it difficult to generalise the mode of action, but their potency has prompted a number of synthetic groups to model the pharmacophore.[4,5,9]

1.4 Proposal

The diversity of the diterpene alkaloids provides a fascinating range of challenging targets for the synthetic chemist. Since the initial elucidations of structure, a number of total syntheses of different family members have been achieved, including the very complex hetisane skeleton **1-5**.[10] Since the hetisane structure was discovered, over 100 different variations on its structure have been isolated[11] and continuing synthetic efforts are required to harness the full potential of these alkaloids.

With the exception of the *exo*-methylene group, the heptacyclic hetisane skeleton is completely saturated with nine stereogenic centres and therefore provides a platform to explore

synthetic methodologies and apply fundamental synthetic principles. It is the intention of this proposal to devise and implement a synthetic strategy that will lead to the total synthesis of the hetisane skeleton.

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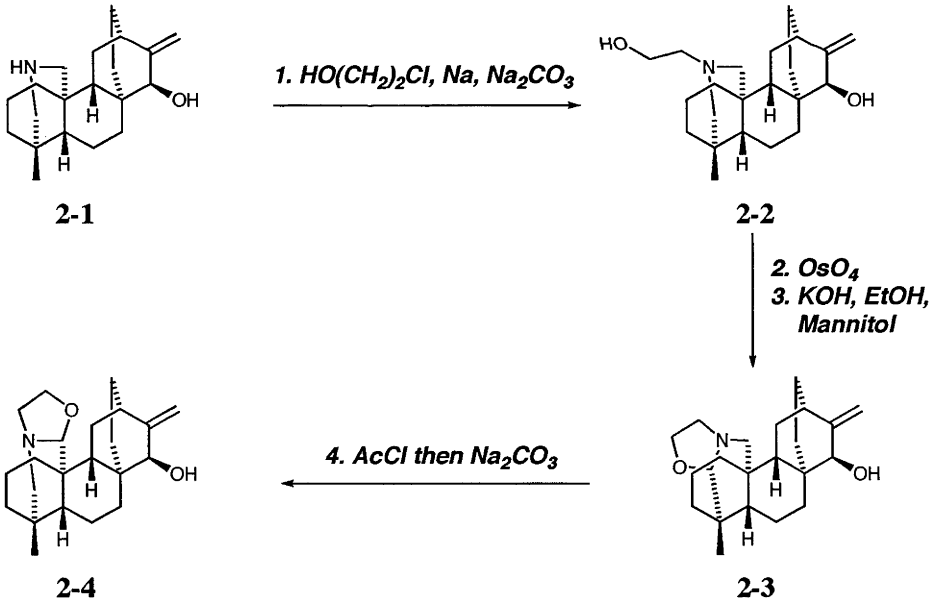
Chapter Two

Synthetic Effort Towards the Diterpene Alkaloids

2.1 Introduction

Most of the synthetic effort in the area of DA's has focused on the simpler alkaloids, and it is worthwhile to revise this work as these alkaloids share many structural features with the hetisane skeleton. The simpler alkaloids also possess an oxazolidine ring, which was removed and reinstalled in the early degradation studies (**Scheme 2.1**). The early synthetic work was vital in confirming the putatively assigned skeletal structures and typically converges with amine **2-1**, which could then converted to the natural products *via* protocols developed by Wiesner[1] and Pelletier.[2] Hence, alkylation of the amine **2-1** with ethylene chlorohydrin and base[†] gave dihydroatisine **2-2**, which on treatment with osmium tetroxide underwent a novel oxidation to give, after hydrolysis of the osmate ester, isoatisine **2-3**. Treatment of isoatisine **2-3** with AcCl followed by base initiates an isomerisation, *via* the acetate salt, to give the natural product atisine **2-4**. This sequence was also applied successfully to the isomeric veatchane skeleton.[1]



Scheme 2.1. *Conversion of Degradation Products to Natural Products*

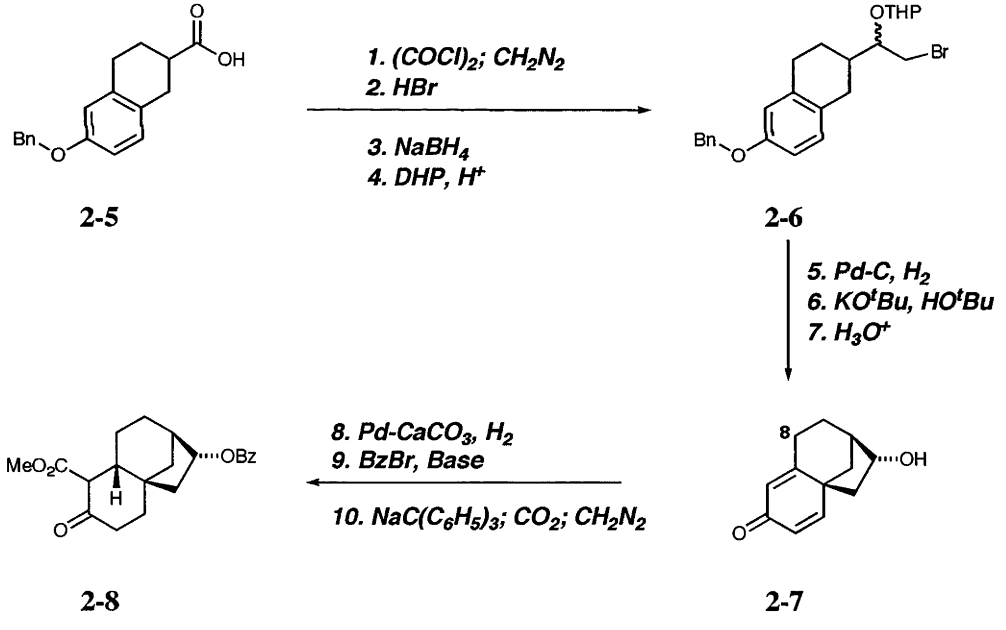
[†] Reaction conditions are indicative of conversions.

2.2 Total Syntheses of Diterpene Alkaloids

2.2.1 Masamune's Synthesis of Garryine

Masamune's strategy for the synthesis of garryine was to start with tetralone **2-5**, which would ultimately form the B and C-rings. The D-ring was constructed next, followed by the addition of the *trans*-fused A-ring system[3,4] and finally the piperidine ring.[5] Thus, the tetralone carboxylic acid **2-5** was converted to the corresponding diazoketone. The diazoketone was then treated with HBr to give the α-bromo ketone. Reduction of the ketone with $NaBH_4$ gave a mixture of alcohols, which were protected as THP ethers **2-6**. The bromide **2-6** could now act as an internal electrophile to form the D-ring. Accordingly, the benzyl ether was hydrogenolysed to yield the phenol, which on treatment with base underwent smooth cyclisation to furnish, after deprotection of the *exo*-hydroxy group, the bicyclo[3,2,1]octane **2-7**. The *endo* isomer failed to cyclise, presumably due to severe steric buttressing from the hydrogen on C8.

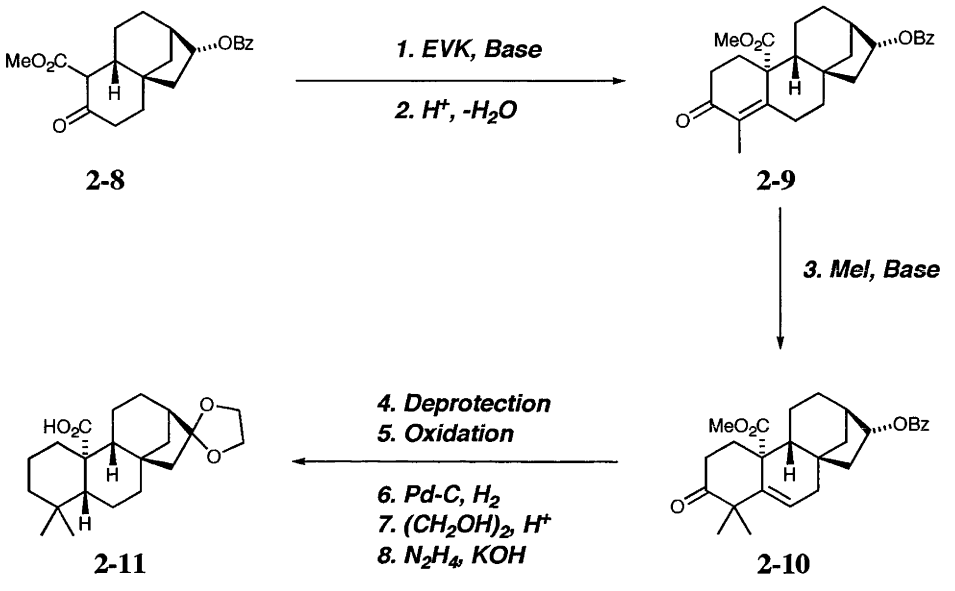
Hydrogenation of the dienone **2-7** gave the desired saturated *cis*-fused decalin in a 7:3 ratio with the corresponding *trans* isomer. The *exo* alcohol was then protected as the benzoate and the ketone acylated by treating the sodium enolate with carbon dioxide. Treatment of the β-keto acid with diazomethane then afforded the β-keto ester **2-8** (**Scheme 2.2**).



Scheme 2.2. *Masamume's Strategy for CD-Ring Construction*

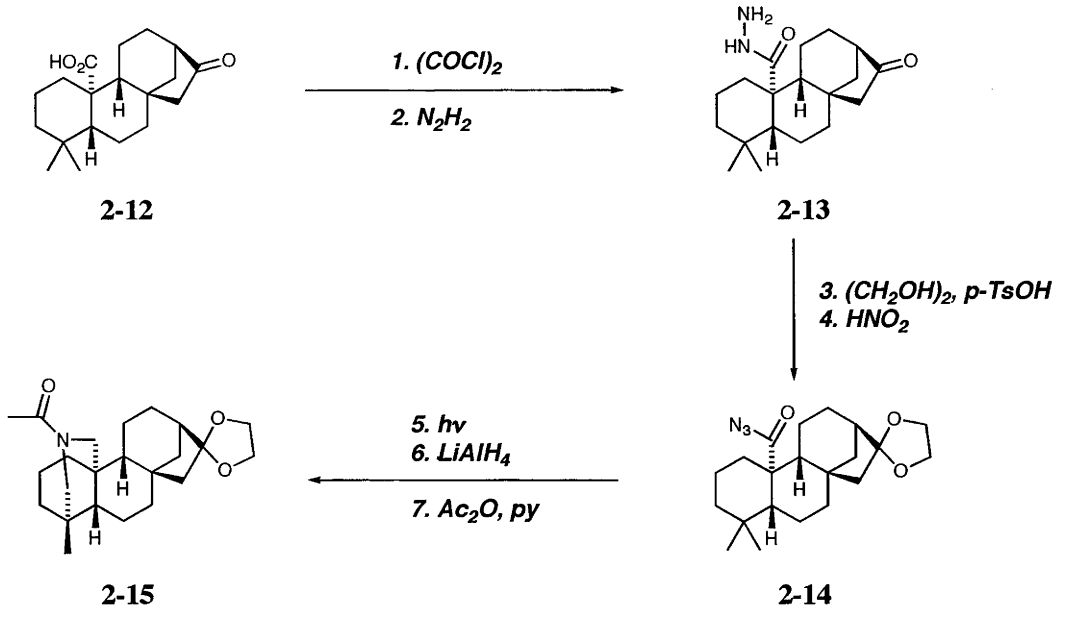
The β-keto ester **2-8** provided a departure point to elaborate the A-ring. Accordingly, the β-keto ester **2-8** was converted to the enone **2-9** *via* Robinson annulation. Treatment of the enone **2-9** with base and iodomethane then gave the *gem*-dimethyl ketone **2-10**. Deprotection, followed by

oxidation of the D-ring hydroxyl was undertaken and the alkene bond hydrogenated to give the desired *trans*-fused decalin in 60% yield. The D-ring ketone group was then selectively protected as the acetal and the A-ring carbonyl function removed *via* a Wolff-Kishner deoxygenation, which also saponified the ester to give the acid **2-11** (**Scheme 2.3**).[4] Acid **2-11** was correlated to one of the degradation products of the Garrya alkaloids, thereby confirming the putative structural assignments through direct synthesis. Acid **2-11** was also used to complete a synthesis of kaurene.[6]



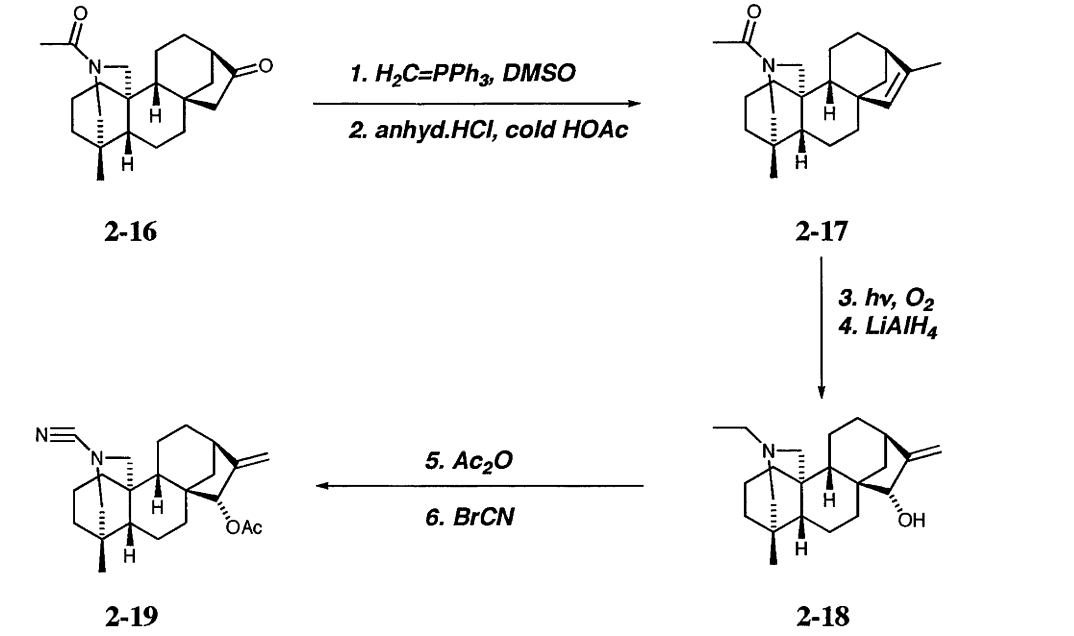
Scheme 2.3. *Masamume's Strategy for the Elaboration of the A-Ring*

With the structure confirmed, the ketal **2-11** was elaborated to the natural product. Accordingly, the corresponding acid **2-12** was converted to the acid chloride which, when treated with hydrazine, gave the acyl hydrazide **2-13**. The D-ring ketone of hydrazide **2-13** was then protected as the cyclic ketal and subsequently treated with nitrous acid to give the acyl azide **2-14**. The azide was photolysed to give a cyclic amide, which was reduced to the amine and protected to give the acetamide **2-15** in 5% yield from **2-14** (**Scheme 2.4**).



Scheme 2.4. *Formation of the Piperidine Ring*

The *exo*-methylene moiety was introduced by a Wittig reaction on the ketone **2-16**, and was then isomerised to the *endo*-alkene **2-17** by treatment with anhydrous HCl in cold acetic acid. The alkene **2-17** was then oxygenated in the presence of a photosensitiser (hematoporphorin), and the resulting peroxide reduced with $LiAlH_4$ to install the D-ring allylic alcohol. Reduction of the acetamide with $LiAlH_4$ gave the *N*-ethyl compound **2-18** which, on treatment with cyanogen bromide, underwent a von Braun reaction to yield the N-cyano compound **2-19** (**Scheme 2.5**).

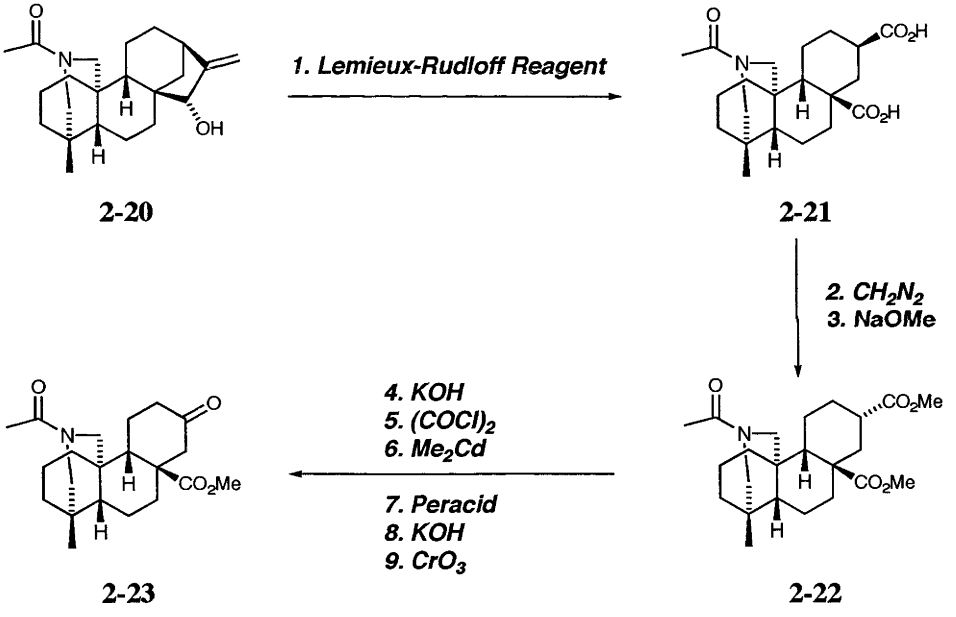


Scheme 2.5. *Functionalisation of the D-Ring*

The nitrile **2-19** was subsequently reduced to give an amine, which was identical to compounds derived from the degradation of the Garrya alkaloids.[5] As outlined above, Wiesner and co-workers had previously taken such alkaloids and rebuilt the natural products (**Scheme 2.1**). Thus, this work constituted a formal synthesis of garryine.

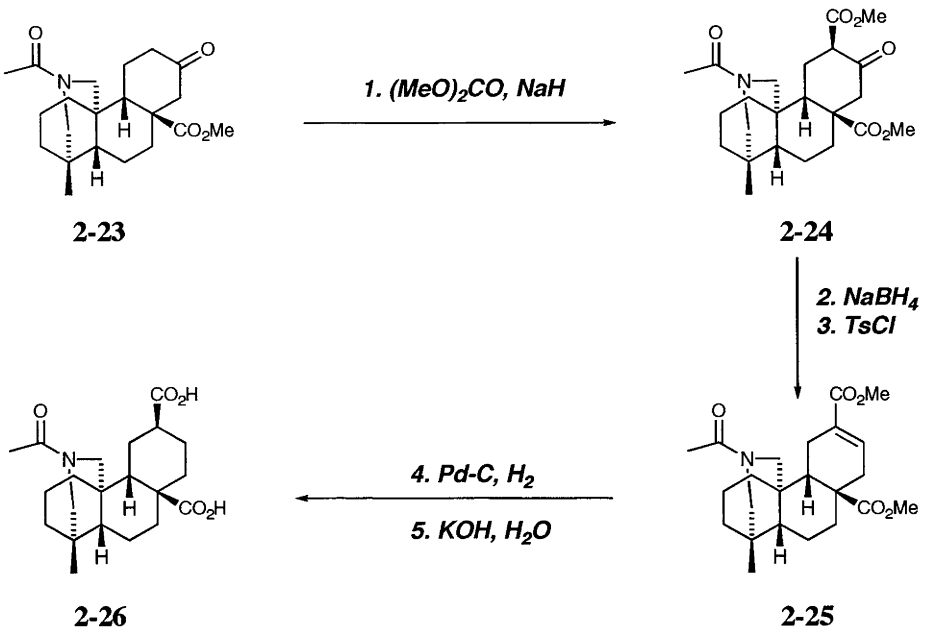
2.2.2 Masamune's Synthesis of Atisine

Exploiting intermediate **2-20**, albeit derived from the degradation of veatchine[6] rather than as described above, the synthesis of the atisine degradation products were also undertaken.[7] Subjecting the acetate **2-20** to a forcing oxidation yielded the diacid **2-21**, which after methylation and epimerisation yielded the diester **2-22**. The secondary ester was selectively saponified and converted to the methyl ketone by treatment of the corresponding acid chloride with dimethyl cadmium. Subsequent Baeyer-Villiger oxidation of the methyl ketone yielded the acetate which, after hydrolysis, was oxidised to the ketone **2-23** (**Scheme 2.6**).



Scheme 2.6. *Cleavage of the Veatchane D-Ring*

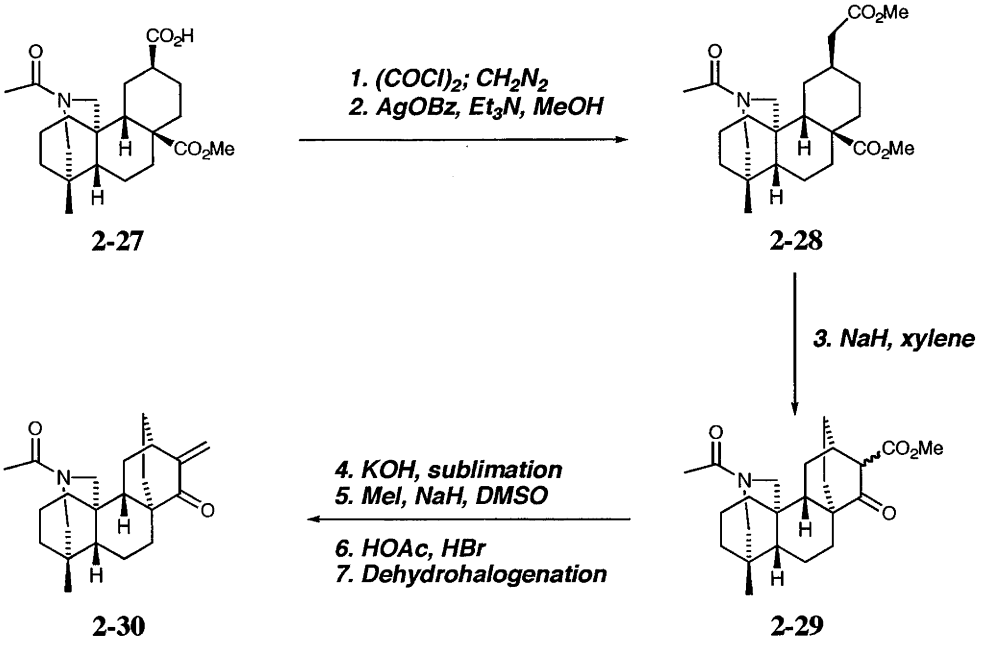
C-acylation of ketone **2-23** was carried out with dimethyl carbonate and sodium hydride to give the diester **2-24**. The ketone was then reduced to the alcohol and converted to the mesylate, elimination of which gave alkene **2-25**. Hydrogenation of the double bond and saponification gave diacid **2-26** (**Scheme 2.7**), which was identical to degradation products reported by Pelletier. As this intermediate had been carried through in a partial synthesis of atisine (**see Section 2.2.3**), this result constituted a formal total synthesis of atisine.



Scheme 2.7. *Elaboration to Pelletier's Intermediate*

2.2.3 Pelletier's Reconstitution of the Atisane Skeleton

The diacid **2-26** was one of the many degradation products of the atisine series that came out of the Jacobs and Pelletier laboratories. In order to confirm the assignment of the proposed structure of the natural product, a synthesis to reconstitute the bicyclo[2,2,2]octane ring was undertaken (**Scheme 2.8**).[8]



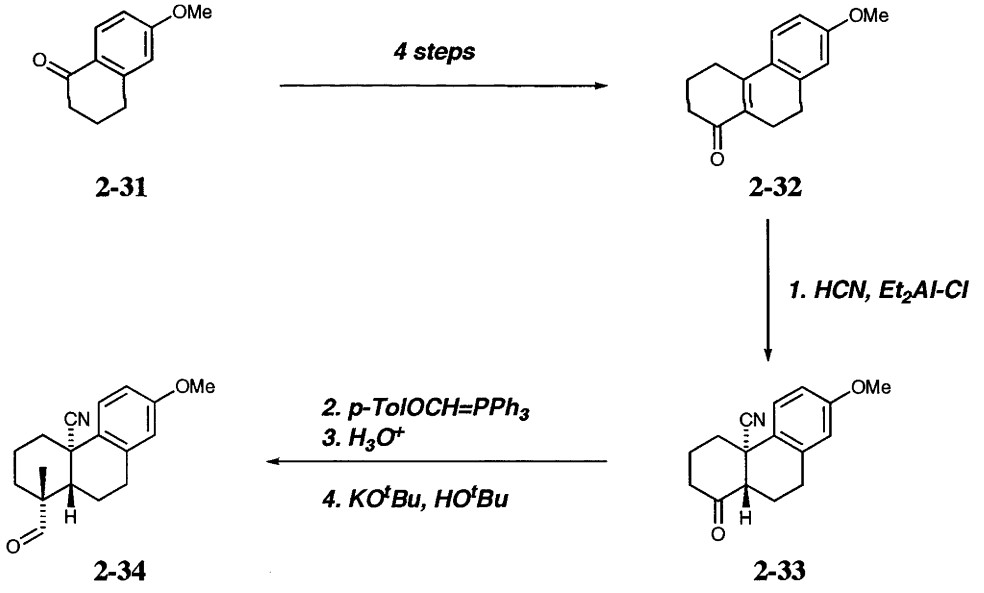
Scheme 2.8. *Pelletier's Partial Synthesis of Atisine*

The acid **2-27** was converted to the corresponding diazoketone and treated with silver benzoate and triethylamine, initiating a Wolff rearrangement, to give the diester **2-28**. A Dieckmann cyclisation was effected on treatment of the ester **2-28** with sodium hydride in xylene to give the ketone **2-29** as a mixture of epimers. The β-keto ester **2-29** was decarboxylated and the resulting ketone sequentially alkylated then brominated. Elimination of the bromide gave the enone **2-30**, which upon reduction gave a mixture of alcohols that could be easily separated and correlated with the natural products (**Scheme 2.8**).

2.2.4 Nagata's Synthesis of Atisine

Nagata's synthesis starts with the tetralone **2-31**, which was converted in 4 steps to the enone **2-32** using a modification of the method developed by Stork.[9,10] The enone **2-32** was then treated with HCN and diethyl aluminum chloride effecting a 1,4-cyano addition to deliver a mixture of *cis* and *trans*-decalins in 70% yield. The *trans*-ketone **2-33** was crystallised and after successive equilibration and crystallisation the *trans*-ketone was obtained in 95% yield.

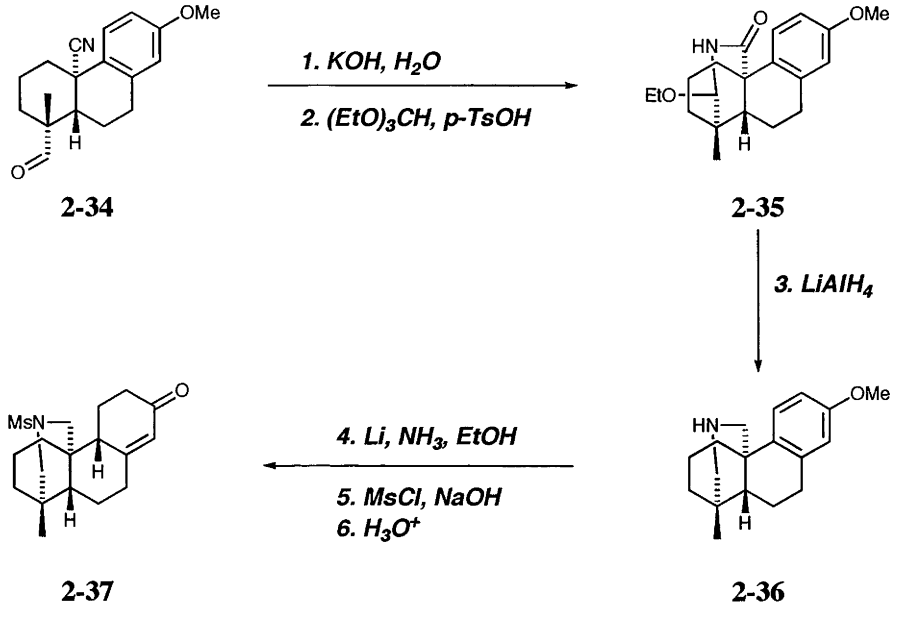
Construction of the quaternary centre at C4 was then undertaken. Thus, the ketone was elaborated, *via* a Wittig reaction and subsequent hydrolysis, to the aldehyde. The aldehyde was then alkylated with potassium *tert*-butoxide and MeI to afford **2-34** (**Scheme 2.9**).



Scheme 2.9. *A-Ring Elaboration and 1,4-Addition*

The stereochemistry of the alkylation was confirmed by partial hydrolysis of the nitrile group of **2-34** to the amide, which was accompanied by spontaneous cyclisation with the aldehyde function. The resulting hemi-aminal was subsequently captured on treatment with ethyl

orthoformate to give the aminal **2-35**, which was reduced with $LiAlH_4$ to the secondary amine **2-36**. With the ABE-rings secure, the synthesis now focused on the CD-rings. Accordingly, the anisole ring was reduced under Birch conditions and the resulting dihydroanisole isomerised to the enone **2-37** on treatment with acid (**Scheme 2.10**).

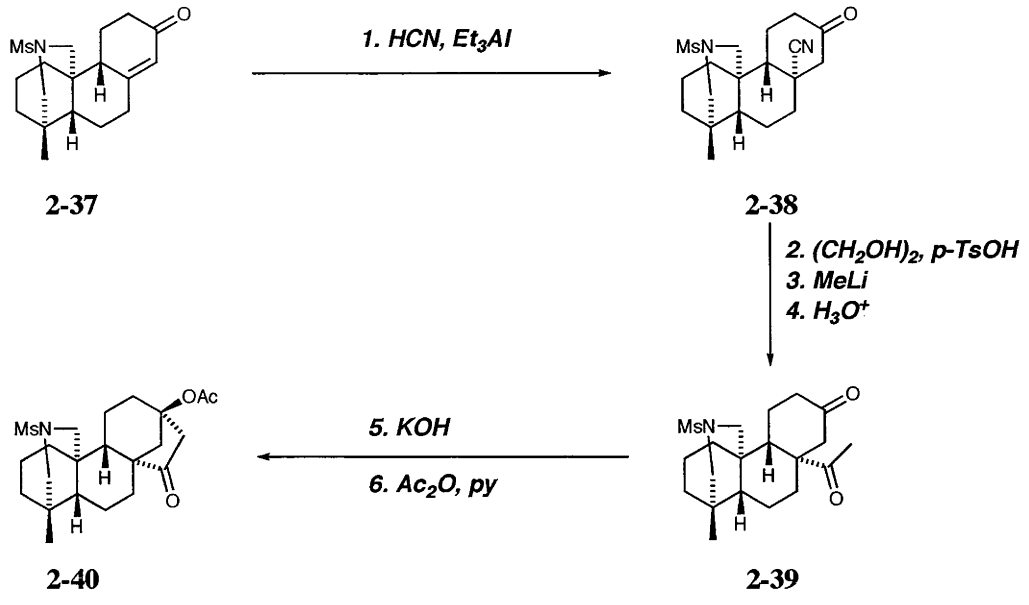


2-34 **2-35** **2-36** **2-37**

Scheme 2.10. *Nagata's Formation of the Piperidine Ring*

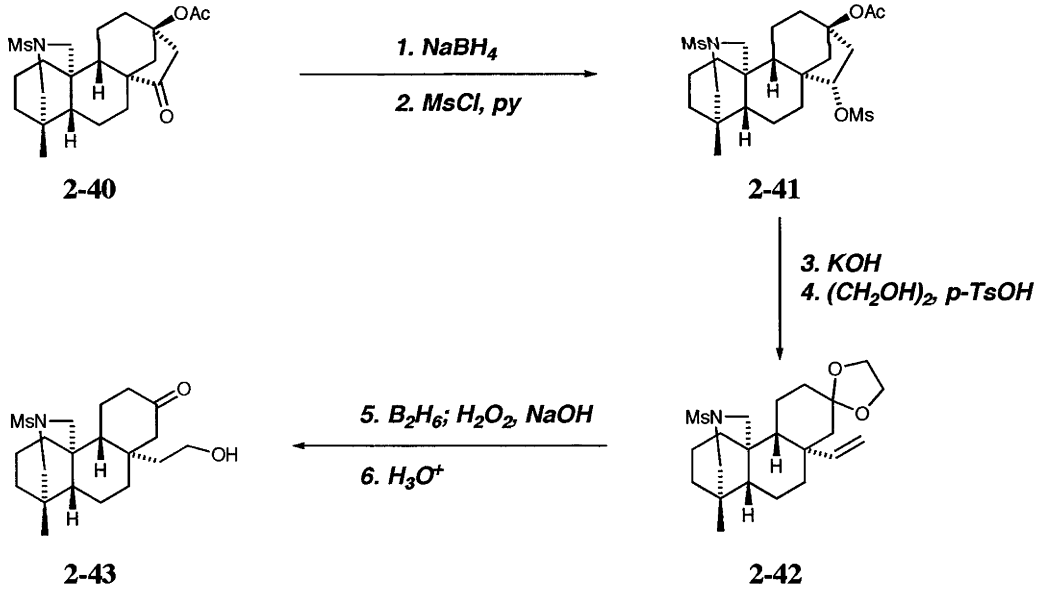
Another 1,4-cyano addition was used to start the construction of the D-ring, delivering the *trans* BC-ring junction **2-38**. Due to the difficulty encountered in converting the cyano group directly to a functionalised ethyl side chain - namely an Arndt-Eistert or Wittig reaction on the corresponding carboxylic acid or aldehyde, respectively - an indirect method was undertaken. Thus, the ketone **2-38** was protected as the acetal and the cyano group treated with methyl lithium to give a methyl imine, which on treatment with acid hydrolysed both the imine and the acetal functions to give the methyl ketone **2-39**.

It had been planned to carry out a 1,2-transposition of the carbonyl group in anticipation of the coming cyclisation of the D-ring, but the intramolecular cyclisation of the methyl ketone to the cyclopentanone **2-40** proved to be a very facile reaction, and all other intermolecular conversions proved troublesome. Therefore, the cyclopentanone was exploited for the desired transposition (**Scheme 2.11**).



Scheme 2.11. *D-Ring Formation*

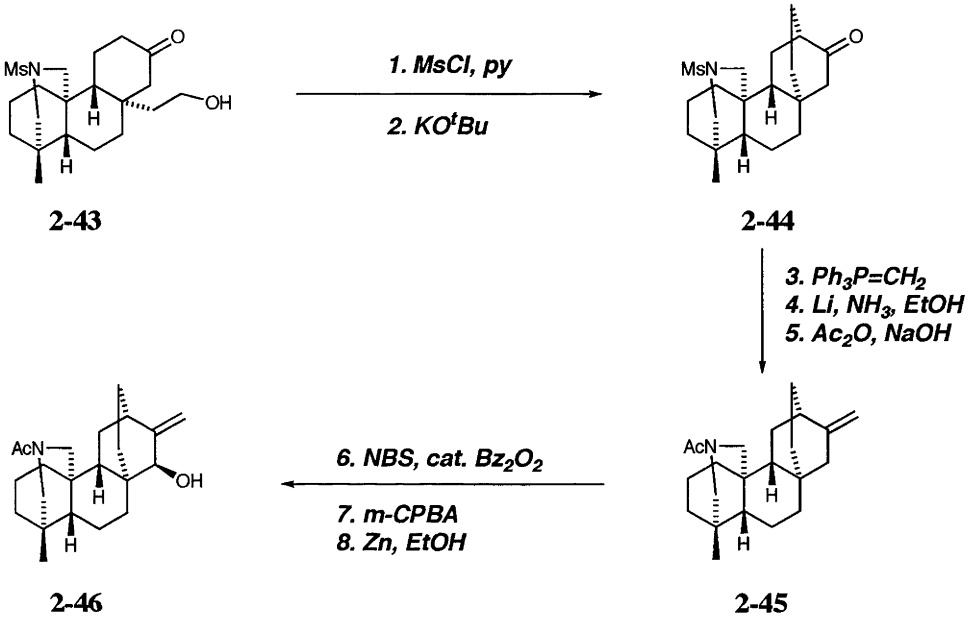
Reduction of the ketone **2-40** with $NaBH_4$ delivered exclusively the *endo* alcohol, which was converted to the mesylate **2-41**. On treatment with base the mesylate **2-41** underwent a Grob fragmentation to deliver, after protection of the ketone, the alkene **2-42**. The alkene **2-42** was hydroborated, and ketal removed to give the alcohol **2-43** (**Scheme 2.12**).



Scheme 2.12. *Grob Fragmentation of the D-Ring*

The stage was now set to investigate the cyclisation that would form the D-ring. The alcohol function of **2-43** was converted to the mesylate derivative, and on treatment with KO^{t}Bu the

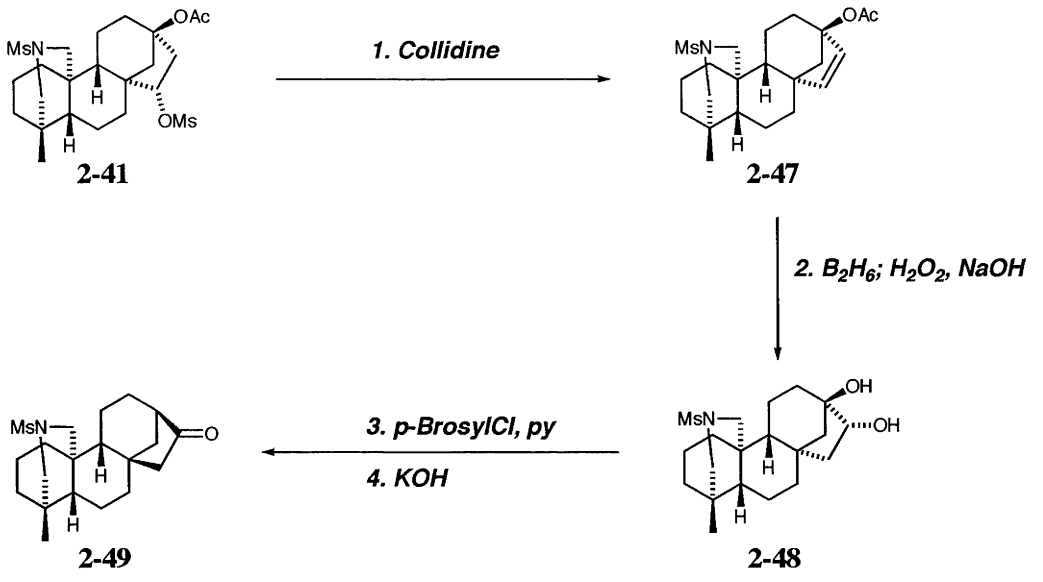
ketone underwent cyclisation to form the bicyclo[2,2,2]octane of the atisane skeleton **2-44**. The synthesis was completed by a Wittig reaction of the ketone to install the *exo*-methylene function. The amino protecting group was exchanged for acetyl and the *exo*-methylene **2-45** treated with NBS and benzoyl peroxide to give the primary allylic bromide, which was accompanied by isomerisation of the alkene. Subsequent epoxidation of the *endo* olefin bond gave a mixture of α and β-epoxides which, when treated with Zn in boiling ethanol, gave the desired allylic alcohol **2-46** (**Scheme 2.13**). The allylic alcohol **2-46** was identical to degradation products and its preparation constituted a formal synthesis of atisine.[10,11]



Scheme 2.13. *Formation of the Atisane Skeleton*

2.2.5 Nagata's Synthesis of Veatchine and Garryine

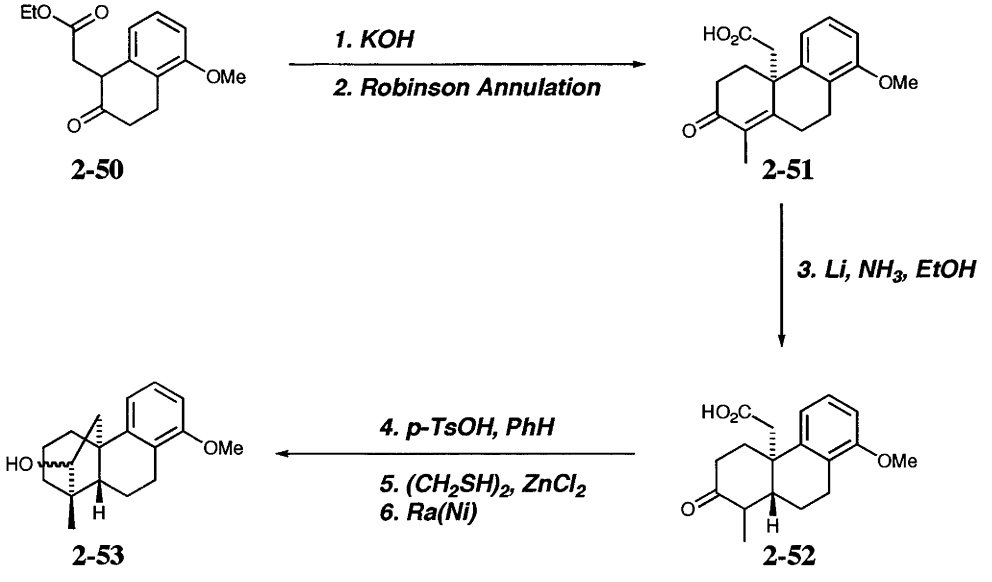
Nagata's synthesis of veatchine and garryine utilised the key intermediate **2-41**.[12,13] Elimination of the mesylate was effected to yield the alkene **2-47**, which was then hydroborated to deliver exclusively the *exo* alcohol **2-48**. Treatment of **2-48** with *p*-bromosulfonyl chloride followed by base initiated a Wagner-Meerwin rearrangement to give the desired bicycle **2-49**, which could then be elaborated to the natural products (**Scheme 2.14**).



Scheme 2.14. *Wagner-Meerwin Rearrangement Strategy for Veatchine CD-Ring Formation*

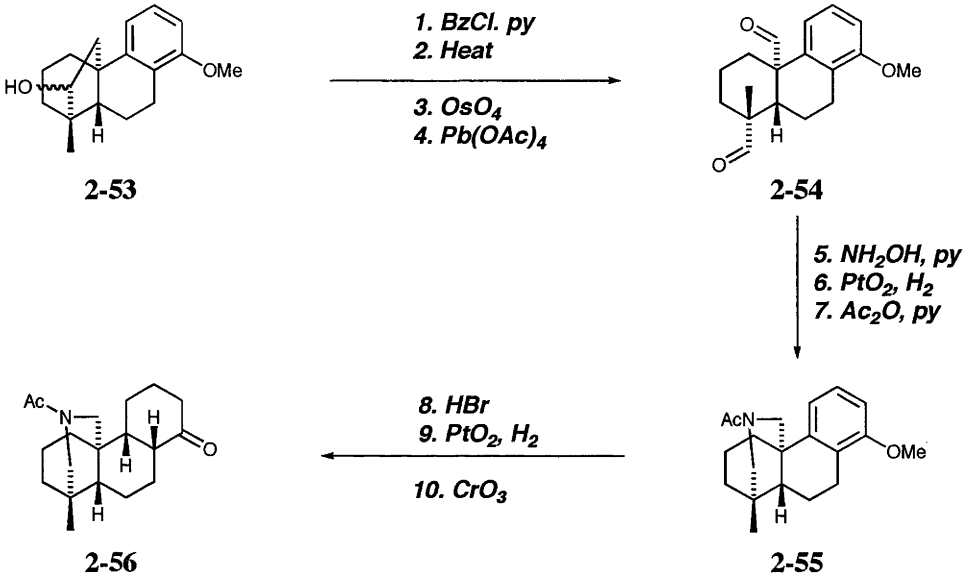
2.2.6 Wiesner's Synthesis of Veatchine and Garryine

Wiesner's synthesis begins with the ester **2-50**, which is derived from alkylation of the parent tetralone with ethyl bromoacetate. Following saponification of the ester **2-50**, a Robinson annulation gave enone **2-51**. A dissolving metal reduction then provided the desired *trans*-fused decalin **2-52**. Heating the acid **2-52** in benzene in the presence of *p*-TsOH initiated a Dieckmann cyclisation to give the diketone. The A-ring ketone was selectively deoxygenated by preferential formation of the 3-dithioketal. Subsequent reduction of the dithioketal with Raney Nickel also reduced E-ring ketone function to give the alcohols **2-53** (**Scheme 2.15**).[14]



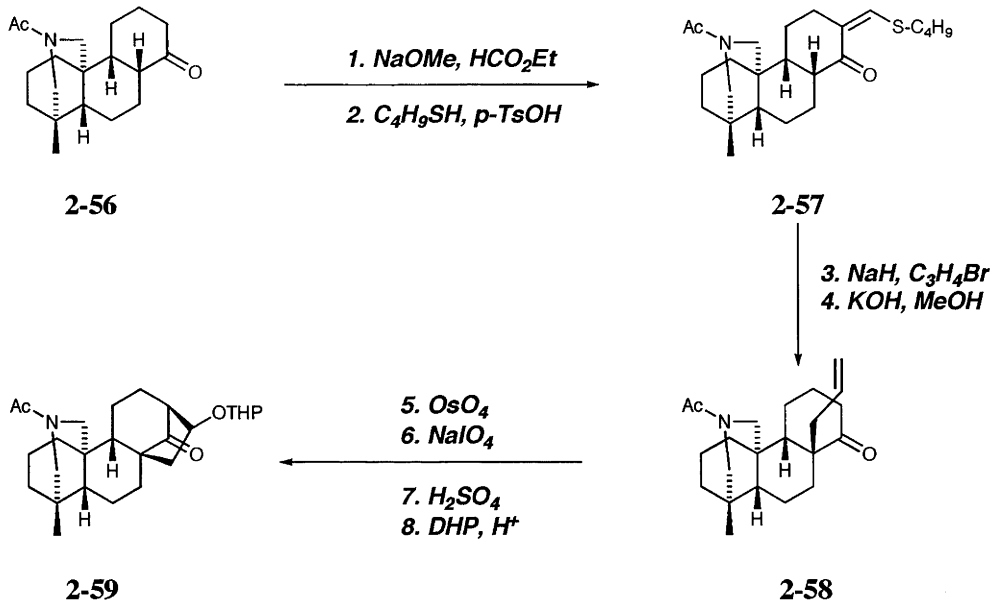
Scheme 2.15. *Formation of the Cyclopentanol* ***2-53***

The alcohols **2-53** were converted to benzoates and pyrolysed to give the bridged alkene. The alkene was subsequently dihydroxylated with OsO_4 and the resulting diol oxidised with $Pb(OAc)_4$ to afford the dialdehyde **2-54**. The dialdehyde **2-54** was treated with hydroxylamine to give the dioxime, which on reduction with PtO_2 gave the amine **2-55**. The amine **2-55** was acetylated and the anisole demethylated with HBr to give the corresponding phenol. The phenol was then hydrogenated and the resulting alcohol function oxidised to give the ketone **2-56** (**Scheme 2.16**).[15]



Scheme 2.16. *Formation of the Piperidine Ring*

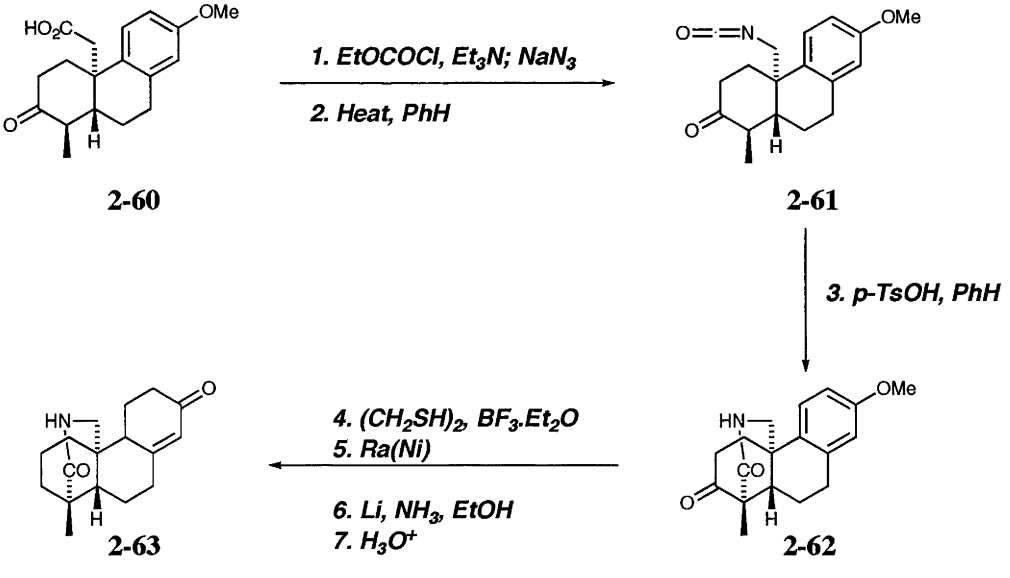
Alkylation at C13 in ketone **2-56** was blocked by treatment with ethyl formate and base followed by butylmercaptan to give the hydroxymethyleneketone and the thiomethyleneketone **2-57**, respectively. The more substituted position could then be alkylated at C8 with allyl bromide. Finally, the thiomethylene function was removed by treatment with base to give the allyl substituted ketone **2-58**. The alkene **2-58** was oxidatively cleaved to the aldehyde, which underwent an intramolecular Aldol reaction to give, after protection on the hydroxyl, the cyclopentanone **2-59** (**Scheme 2.17**). The ketone **2-59** was then elaborated to compounds that could be correlated to degradation products.



Scheme 2.17. Alkylation of the BC-Ring Fusion

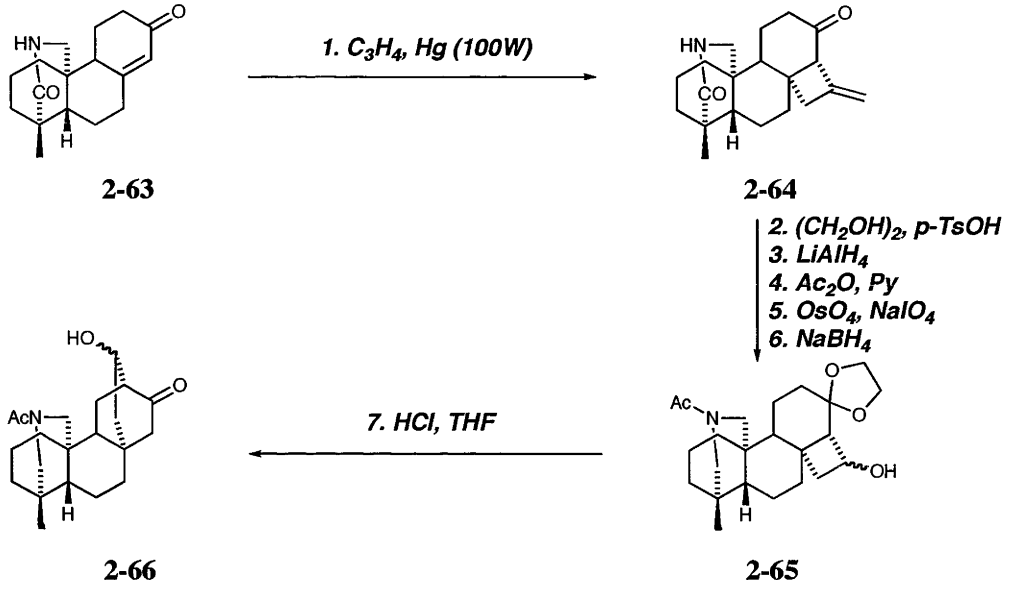
2.2.7 Wiesner's Synthesis of Atisine

Exploiting a similar intermediate to **2-52**, Wiesner's synthesis of atisine is more elegant than that described above, in that the nitrogen bridge is constructed in a more direct fashion. Treatment of the acid **2-60** with ethyl chloroformate followed by sodium azide gave the acyl azide, which underwent a Curtius rearrangement on heating to yield the isocyanate **2-61**. Treatment of the isocyanate with *p*-TsOH in benzene then gave the amide **2-62** through an isocyanate-type Dieckmann cyclisation. Deoxygenation of the A-ring ketone, as previously described, followed by a Birch reduction and subsequent isomerisation gave the enone **2-63** (**Scheme 2.18**).[16]



Scheme 2.18. Formation of the Piperidine Ring

The C and D-rings were elaborated utilising a novel cycloaddition approach to install the angular group at the ring junction. Thus, irradiation of the enone **2-63** in the presence of allene gave the [2+2]-cycloaddition product **2-64**. Following protection of the ketone group, the lactam function was reduced and the resulting amine acetylated. The alkene bond was oxidised with OsO_4 and $NaIO_4$ to give the cyclobutanone, which was reduced to afford the epimeric alcohols **2-65**. The synthesis of the atisane skeleton was completed by deprotection of the ketal, which induced a retro-aldol/aldol reaction to give the less strained bicyclo[2,2,2]octane **2.66** (**Scheme 2.19**). Following similar conversions to those described earlier, the synthesis converged with degradation products that could then be converted into the natural product. The [2+2]-cycloaddition approach was also later used to access the veatchane skeleton.[17]



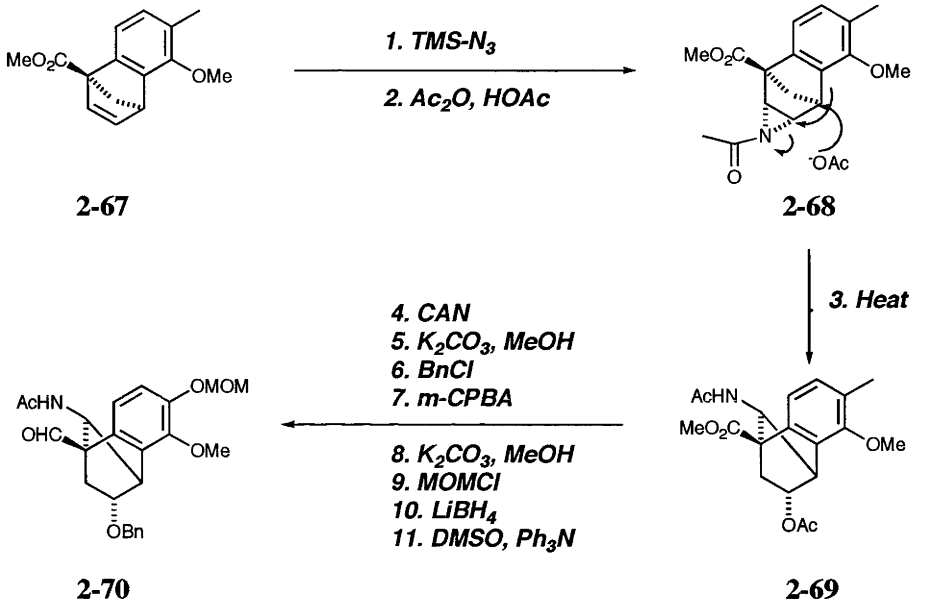
Scheme 2.19. *Retro-Aldol/Aldol CD-Ring Formation*

2.2.8 Weisner's Synthesis of Delphinine

Weisner produced many publications describing the synthesis of the extremely complex alkaloid delphine[18], and although the work ultimately converges on a *nor*-diterpenoid type skeleton (**Chapter 1, Figure 1.2**), it proceeds *via* the approach that was also used to construct the napellane structure **1-7**.[19-21] The synthesis that is described below is the fourth generation approach and a full account of the studies leading up to this work is covered extensively.[22] The beauty of this final synthesis is that it not only tackles the carbon backbone, but also elegantly installs the required oxygenation.

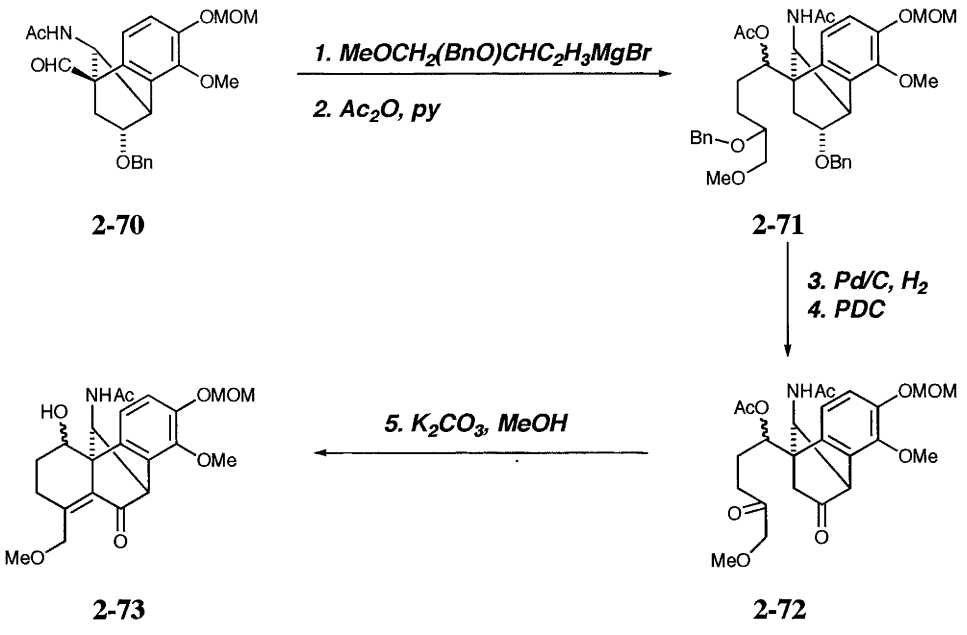
The alkene **2-67**, which was synthesised in 11 steps from *o*-cresol, was converted to the aziridine on treatment with TMS-N_3, and subsequently protected as the acetate **2-68**. Upon mild heating the aromatic ring underwent a 1,2-alkyl shift to give the acetamide **2-69** (**Scheme 2.20**).

The aromatic methyl was integral to the success of the above rearrangement, but was subsequently converted to the corresponding protected hydroxyl. Accordingly, the aromatic methyl was oxidised to the aldehyde on treatment with ceric ammonium nitrate. The acetoxy group was then removed, and the free hydroxyl reprotected as a benzyl ether. The aromatic aldehyde was treated with *m*-CPBA, which induced a Baeyer-Villiger rearrangement. The resulting formate was subsequently hydrolysed to the phenol, which was protected as the MOM ether. Finally, in preparation for the construction of the A-ring, the ester function was reduced and then oxidised to afford aldehyde **2-70** (**Scheme 2.20**).



Scheme 2.20. *Synthesis of the Heterocyclic Core*

To construct the A-ring, the aldehyde **2-70** was first treated with 3-benzyloxy-4-methoxy-*n*-butyl magnesuim bromide to afford the epimeric alcohols, which were subsequently acetylated to give **2-71**. The benzyl groups were removed and the free hydroxyls oxidised to give the diketone complex **2-72**. Treatment of **2-72** with base closed the A-ring and also removed the acetate function to give enone **2-73** (**Scheme 2.21**).



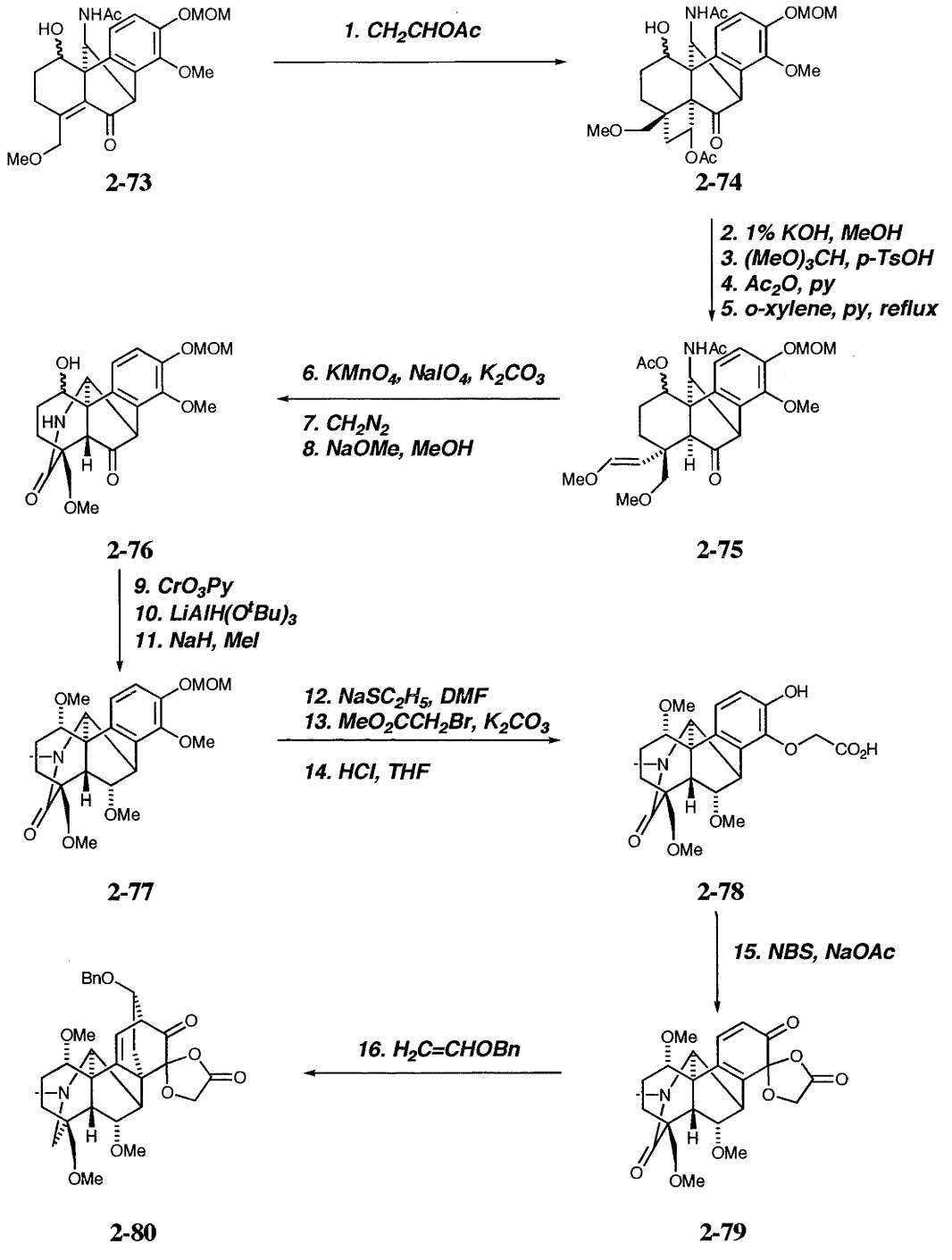
2-70 **2-71** **2-72** **2-73**

Scheme 2.21. *Formation of the A-Ring*

A [2+2]-cycloaddition of enone **2-73** with vinyl acetate delivered the protected cyclobutanol **2-74**. Hydrolysis of the acetate led to a spontaneous retro-aldol process and the resulting aldehyde was converted to the methyl enol ether **2-75** through formation of the methyl ketal followed by elimination of MeOH in boiling xylene. The methyl enol ether **2-75** was oxidatively cleaved and the resulting acid converted to the corresponding ester. Treatment of the ester with mild base initiated cyclisation with the amine function to give the lactam **2-76** with the correct A,B-*trans*-fusion. The free hydroxyl function of **2-76** was oxidised, and the resulting diketone reduced to the corresponding diol with the correct stereochemistry. To complete the A and B-ring the hydroxyls and amide were methylated to give **2-77**.

With correct A and B-ring functionality in place, the stage was now set to initiate the work on the C and D-rings. First, the methoxy group on the aromatic ring was selectively deprotected with thiolate ion, and the liberated phenol treated with methyl bromoacetate. The resulting ester and MOM group where then hydrolysed to give the acid **2-78**. Subsequent oxidation with NBS yielded the spirolactone **2-79**, which was immediately treated with benzyl vinyl ether to smoothly deliver the [4+2]-cycloaddition product **2-80** (**Scheme 2.22**).

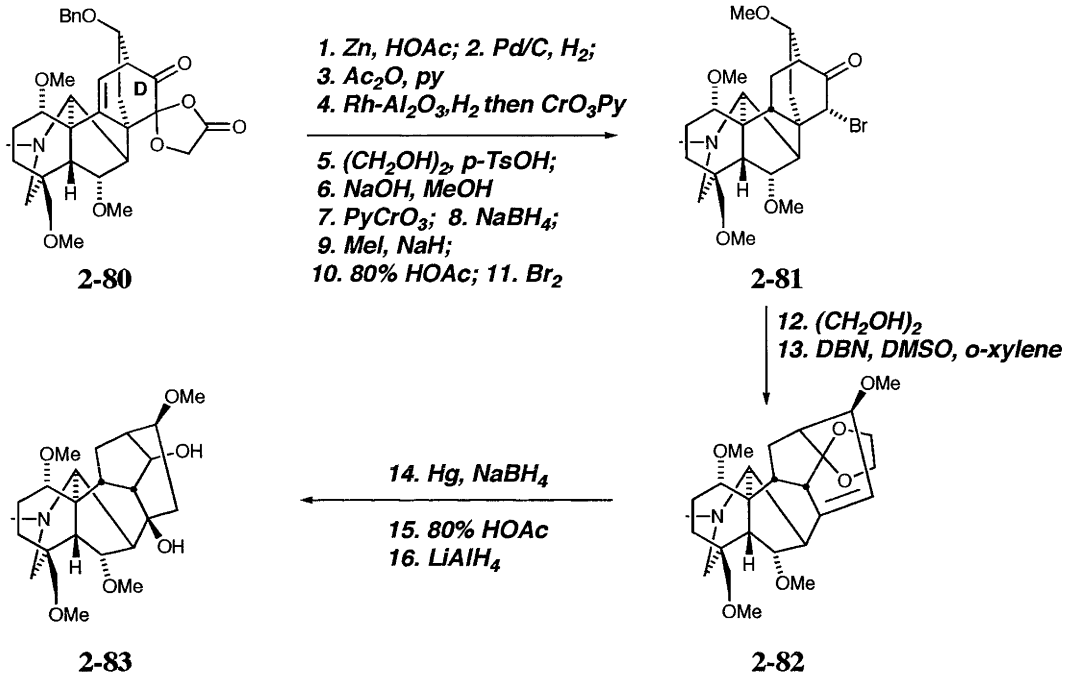
As mentioned earlier (**Chapter 1, Figure 1.2**), the *nor*-diterpene alkaloids are related to the diterpenes through a formal 1,2-alkyl shift of the C8-C9 bond. Wiesner's plan was to exploit such a rearrangement to complete the synthesis. The spirolactone function of **2-80** was reductively cleaved on treatment with zinc–acetic acid, and the benzyl ether was removed to give a mixture of epimeric alcohols, which were acetylated (**Scheme 2.23**). It became clear that the equilibration of the C-ring alcohol function had occurred through a retro-Aldol-Aldol reaction and needed to be corrected.



Scheme 2.22. *Formation of the E&CD-Rings*

First, the alkene was hydrogenated, which also reduced the D-ring ketone function and as such, oxidation back to the ketone was required. The stereochemistry for the C-ring alcohol was then addressed. The D-ring ketone function was protected and the C-ring acetate group cleaved with base. The alcohol group was converted to the ketone function and subsequently reduced to give, after protection, the desired methyl ether. Finally, the D-ring ketal was removed and the α-carbon brominated to give **2-81** in preparation for the planned rearrangement. The ketone function of **2-81**

was reprotected and on heating to 180 ^{0}C the desired the rearrangement took place to afford **2-82**. In order to complete the synthesis, the alkene bond was hydroxylated by oxymercuration and the acetal removed. The lactam and ketone group were then reduced with $LiAlH_4$ to deliver the target 13-deoxy-delphonine **2-83** (**Scheme 2.23**). This was a mammoth effort totalling 58 steps from *o*-cresol. The remaining challenge among the *nor*-diterpenoids is the synthesis of aconitine, which has an additional 4 oxygens!

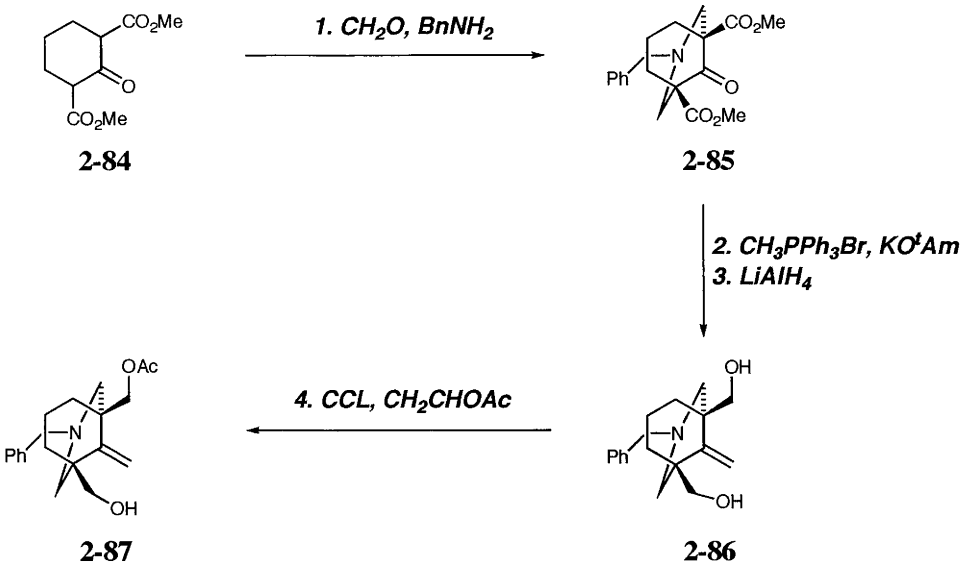


Scheme 2.23. *CD-Ring Rearrangement*

2.2.9 Ihara's Synthesis of Atisine

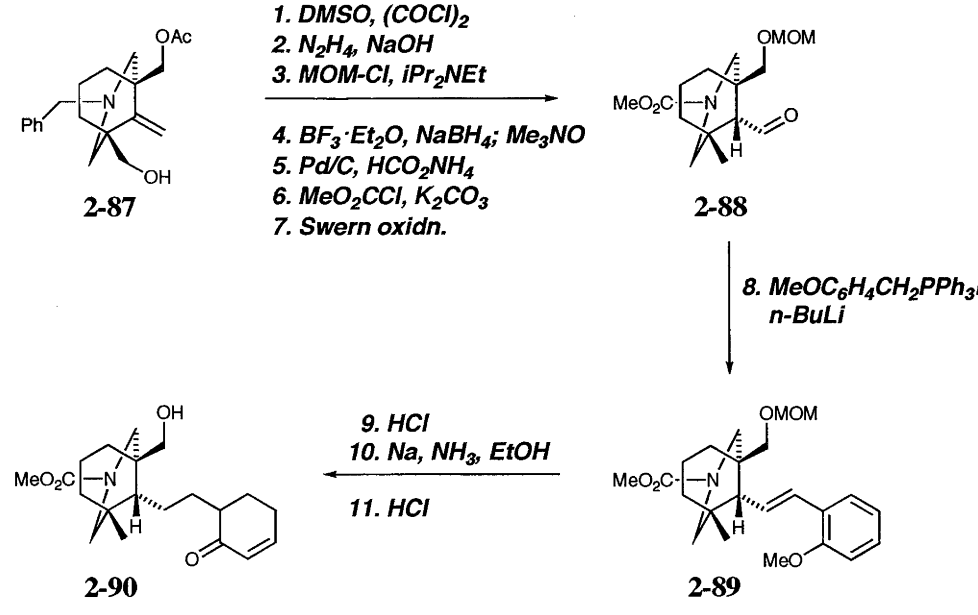
Ihara and co-workers have produced a number of elegant explorations towards the rapid construction of the phenanthrene backbone of the diterpene alkaloids, culminating in the enantioselective[23,24] total synthesis of atisine *via* a double Michael reaction strategy.[25-27]

The sequence started with a double Mannich reaction on the diester **2-84** to deliver the benzylamine **2-85**. The ketone **2-85** was then converted to the methylene derivative by a Wittig reaction and the ester functions reduced to afford the corresponding diol **2-86**. Resolution was achieved by a *Candidi cylindracea* lipase-catalysed irreversible transesterifiction in vinyl acetate to give the optically pure (100% ee) acetate **2-87** (**Scheme 2.24**).



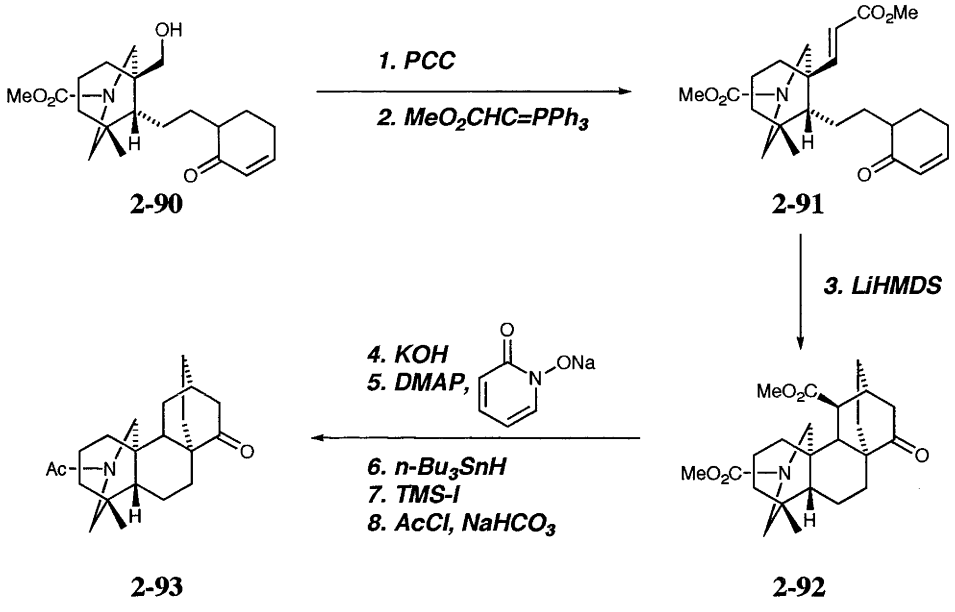
Scheme 2.24. *Synthesis of a Chiral A/E Precursor*

With enantiopure **2-87** in hand, the free hydroxyl was oxidised and the resulting aldehyde deoxygenated by a Wolff-Kishner reduction. Under the deoxygenation conditions the acetate group was also removed so the free hydroxyl was reprotected as the MOM ether. The methylene group was then hydroxylated, *via* hydroboration, with excellent diastereoselectivity. The *N*-benzyl group was removed and the free amine reprotected as the methyl carbamate. The alcohol was oxidised to afford the aldehyde **2-88** and the C-ring introduced by means of a Wittig reaction to give the styrene **2-89**. The styrene **2-89** was then subjected to a Birch reduction to give, after hydrolysis, the enone **2-90** **(Scheme 2.25)**.



Scheme 2.25. *Attachment of the C-Ring*

The second partner for the double Micheal reaction was then introduced by oxidation of the alcohol **2-90** and Wittig reaction to give the ester **2-91**. On treating ester **2-91** with base the expected tandem reaction took place to give the atisine skeleton **2-92**. The superfluous ester group was removed by way of the Barton free-radical decarboxylation procedure to give, following replacement of the carbamate function, acetamide **2-93**. This synthesis arrived at similar degradation intermediates to those that had been prepared by other groups and thereby achieved the first enantioselective synthesis of atisine (**Scheme 2.26**).

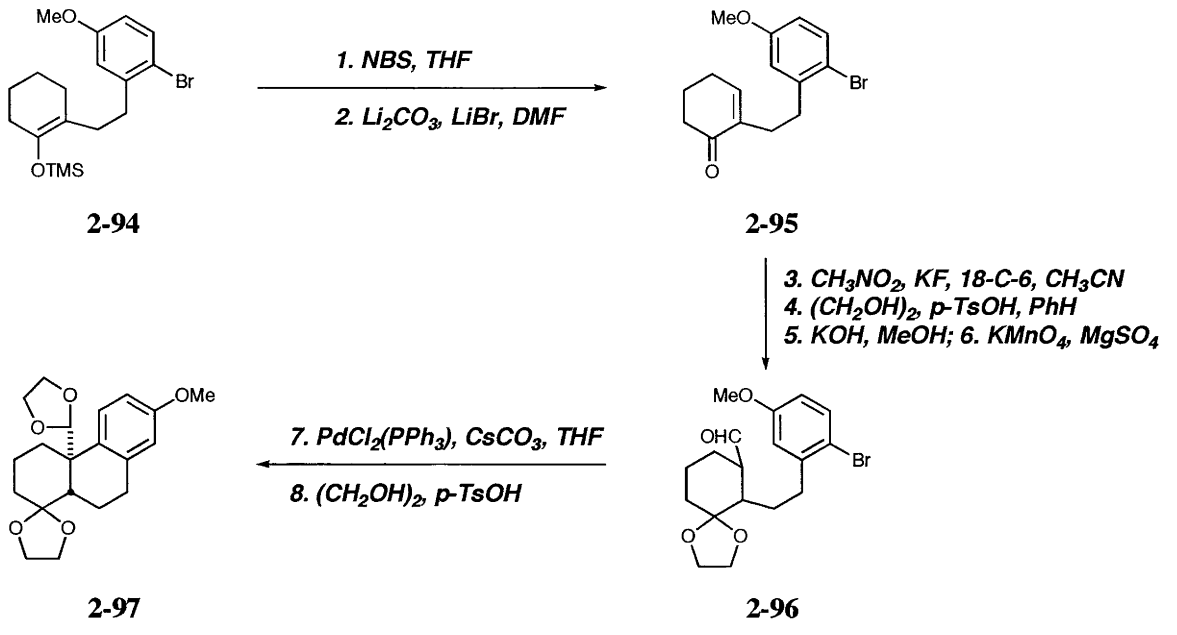


Scheme 2.26. *Double Michael Reaction for CD-Ring Formation*

2.2.10 Total Synthesis of Nominine

The hetisane skeleton has been the last diterpene alkaloid to be successfully targeted by total synthesis and has only recently been achieved.[28,29] The synthesis starts with the silyl enol ether **2-94**, which is derived from the alkylation of *N*-cyclohexylidenecyclohexylamine with 2-bromo-5-methoxyphenethyl iodide. The enol ether **2-94** was brominated and the resulting bromide substituent eliminated to give the enone **2-95**. 1,4-Addition of nitromethane to enone **2-95** was effected, ultimately affording aldehyde **2-96**. Treatment of **2-96** with a palladium complex then initiated cyclisation and gave, after protection of the aldehyde function, the diacetal **2-97** (**Scheme 2.27**).

The diacetal **2-97** provided the phenanthracene backbone on which to build the rest the molecule. The strategy involved elaboration the C and D-rings first, which is in contrast to all other diterpene alkaloid syntheses, bar that of Masamune's, which have focused on establishment of the A and B-ring functionality first.



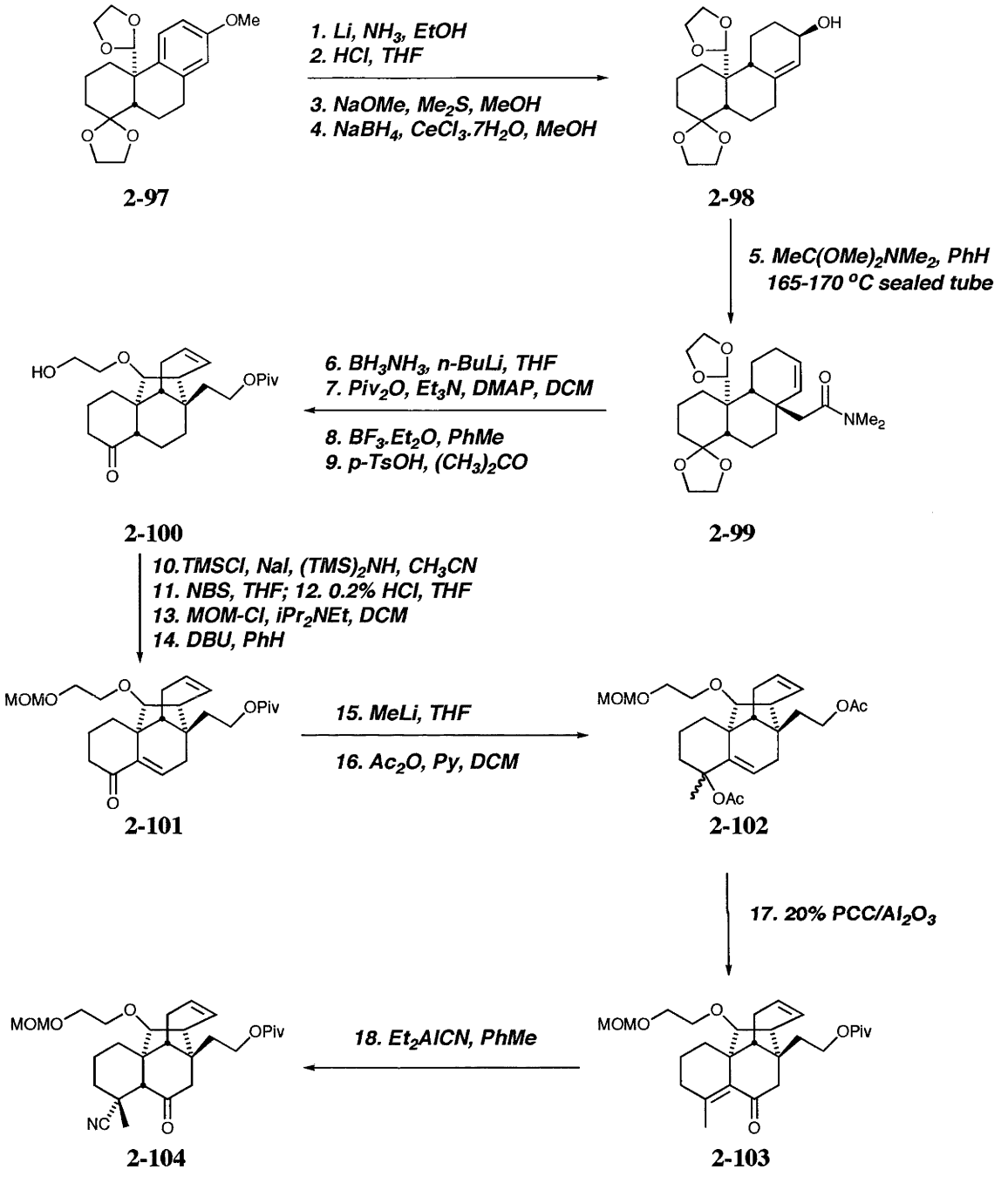
2-94 **2-95** **2-96** **2-97**

Scheme 2.27. *Formation of ABC-Rings*

The aromatic ring in **2-97** was reduced in the normal way and the product β,γ-enone isomerised to the αβ-enone. The enone was reduced to the allylic alcohol **2-98**, treated with *N, N*-dimethylacetamide dimethyl acetal, and heated in a sealed tube to induce an Eschenmoser-Claisen rearrangement to afford the amide **2-99**. The amide **2-99** was reduced to the alcohol and protected, and upon treatment with $BF_3 \cdot Et_2O$ an acetal-ene reaction was effected to afford **2-100**.

The focus of the synthesis then moved to the A and B rings. The thermodynamic silyl enol ether of **2-100** was brominated and the resulting bromide subsequently eliminated to give the enone **2-101**. The installation of the ketone functionality into the B-ring was then undertaken *via* a [3,3]-sigmatropic rearrangement followed by oxidation. Thus, methyl lithium was added to the ketone to give a mixture of hydroxy methyl compounds, which were acetylated to give the protected allylic alcohols **2-102**. On treatment with PCC the acetates **2-102** underwent the desired rearrangement and subsequent oxidation to give the enone **2-103**.

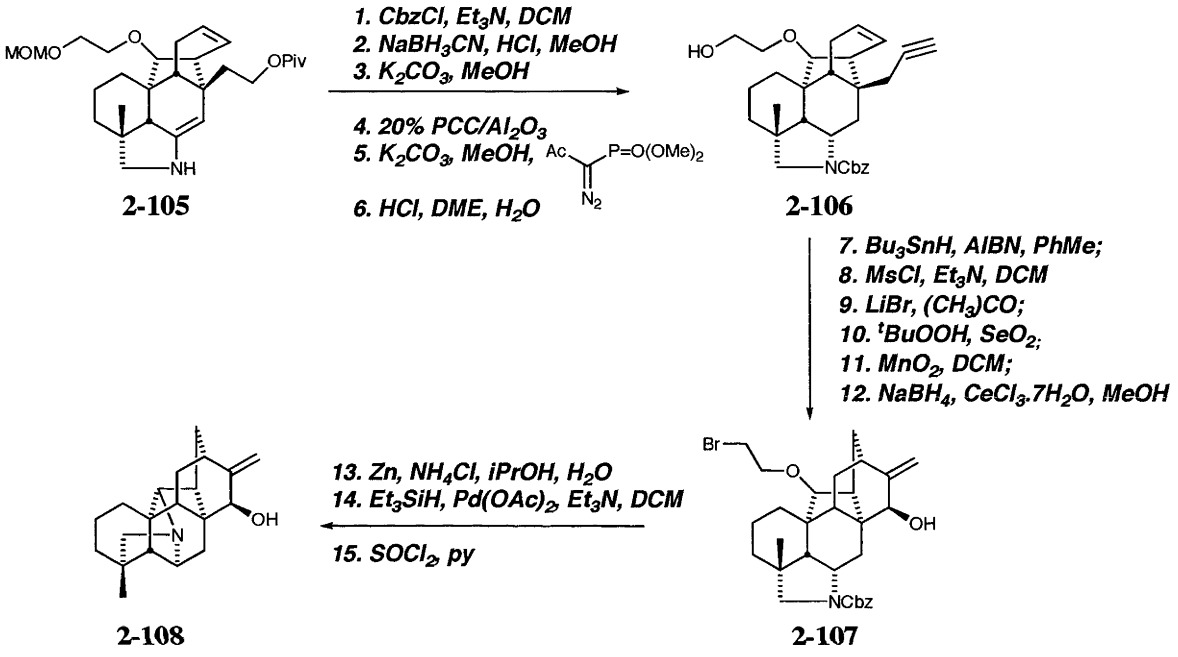
A 1,4-cyano addition was then carried out on enone **2-103**, not dissimilar to Overman's strategy for scopadulcic acid[30] and Tanaka's strategy for scopadulin[31], using diethyl aluminum cyanide to give the nitrile **2-104** (**Scheme 2.28**). As with other reported additions, the cyanide ion was directed exclusively to the α-face in spite of the steric hindrance involved.



Scheme 2.28. *Linking the C-Ring to C20*

The ketone **2-104** was then protected as the silyl enol ether in preparation for the nitrile reduction. The nitrile was reduced to the amine, which simultaneously cyclised on to the liberated ketone to give the enamine **2-105**. The enamine **2-105** was protected and reduced with $NaBH_3CN$ to give the cyclic amine. The angular alcohol function was then deprotected and further elaboration afforded the terminal alkyne **2-106**.

This compound was then used to complete the bicyclo[2,2,2]octane of the CD-rings through a radical cyclisation with the olefin group in the C-ring. The glycol moiety was converted to the bromo hydrin function and the *exo*-methylene group oxidised first to the C15 allylic alcohol, and then to the C15 oxo function. This compound was subsequently reduced to afford the allylic alcohol **2-107** with the correct stereochemistry. Finally, reductive elimination of the bromo ether function liberated the C20 alcohol and, after the Cbz group was removed, cyclisation was effected on treatment with thionyl chloride and pyridine to give nominine **2-108** (**Scheme 2.29**).

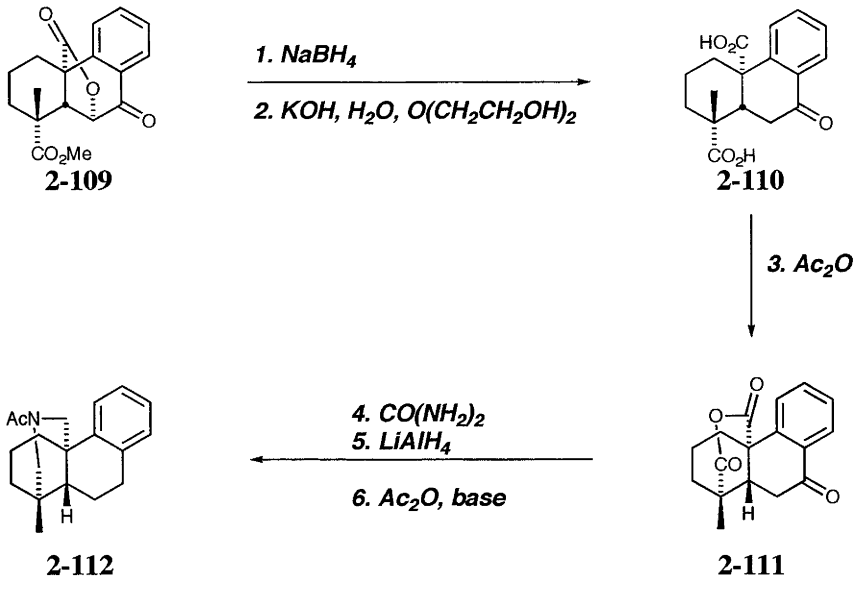


Scheme 2.29. *End Game*

2.3 Synthesis of Key Intermediates

2.3.1 Tahara's Synthesis from Abietic Acid

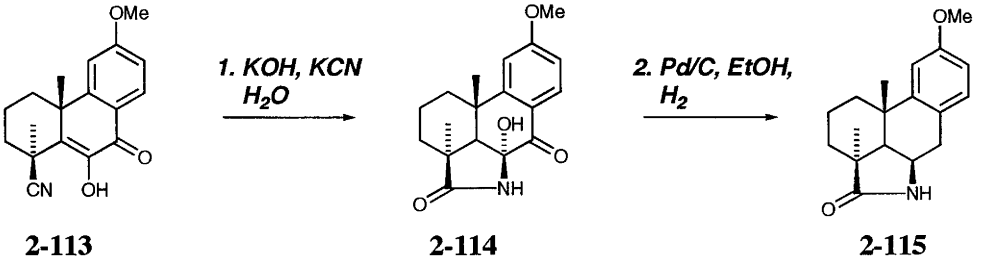
Tahara produced exhaustive publications on the chemical conversion of abietic acid to intermediates that could be used for the synthesis of a number of diterpenoid structures.[32] One such intermediate was exploited to gain access to the diterpene alkaloids.[33] Thus, intermediate **2-109** was reduced and hydrolysed to give the diacid **2-110**. Dehydration of **2-110** formed the cyclic anhydride **2-111**. Treatment of the anhydride with urea lead to the equivalent lactam, which on reduction and protection lead to the acetamide **2-112**. Acetamide **2-112** could then be elaborated to intersect with Nagata's intermediates (**Scheme 2.30**).



Scheme 2.30. *Synthesis of the E-Ring*

2.3.2 Mander's Synthesis of the Hetisane Pyrrolidine from Podacarpic Acid

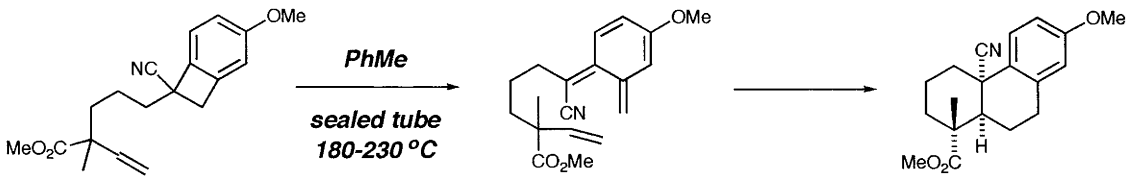
Mander *et al.* exploited the readily available podocarpic acid[34] derived intermediate **2-113** to synthesise the lactam **2-115**, which could potentially be used to gain entry into the *ent*-hetisine skeleton. Hydrolysis of the nitrile **2-113** in the presence of cyanide lead to the *hemi*-aminal **2-114** which, when hydrogenated, led to the lactam **2-115** (**Scheme 2.31**).



Scheme 2.31. *Pyrrolidine Formation*

2.3.3 The Model Studies of Kametani

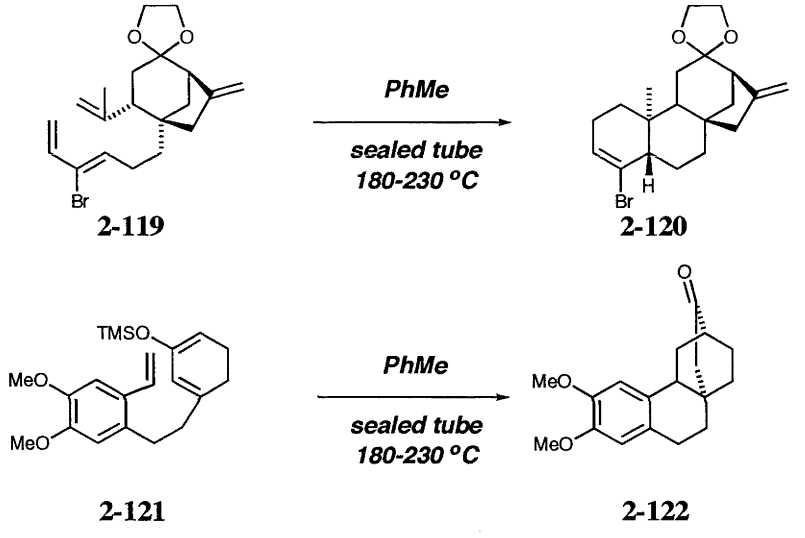
An elegant way to gain entry into the phenanthrene back-bone was developed by Kametani through the intramolecular cycloaddition of **2-117**.[35] On heating the cyclobutanone **2-116**, intermediate **2-117** is formed, which undergoes cycloaddition to give **2-118** (**Scheme 2.32**).



2-116 **2-117** **2-118**

Scheme 2.32. *Diels-Alder Approach to the Phenanthrene Backbone.*

Other cycloadditions have also been reported by the above workers[36] and by Ihara *et al*,[37] with intermediates **2-119** and **2-121** undergoing cycloadditions to give **2-120** and **2-122,** respectively. These intermediates could potentially be elaborated to the diterpene alkaloids (**Scheme 2.33**).



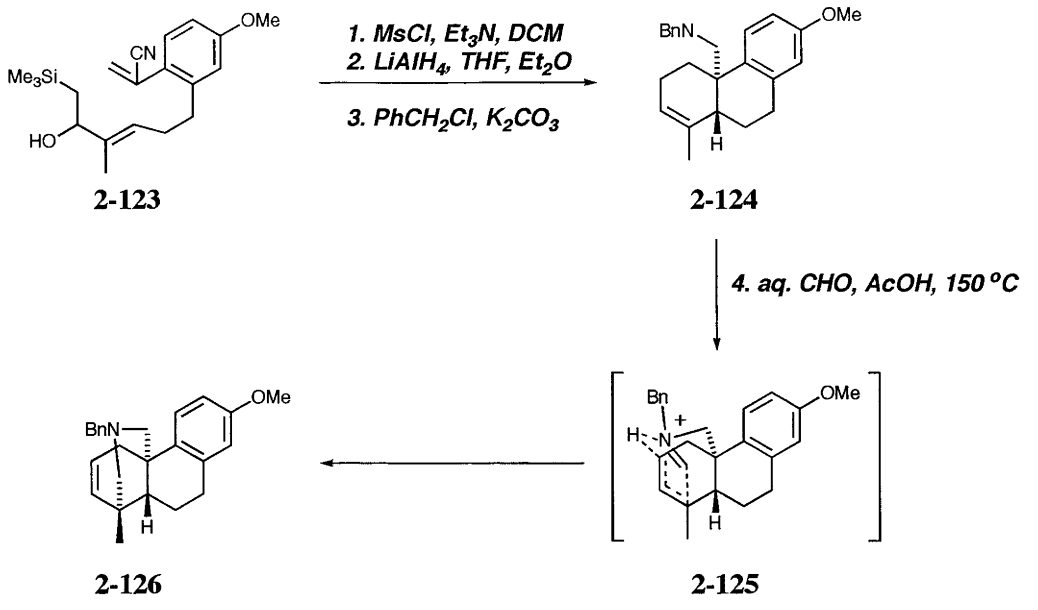
2-119 **2-120**

2-121 **2-122**

Scheme 2.33. *Diels-Alder Approaches*

2.3.4 Novel Piperidine Ring Formation

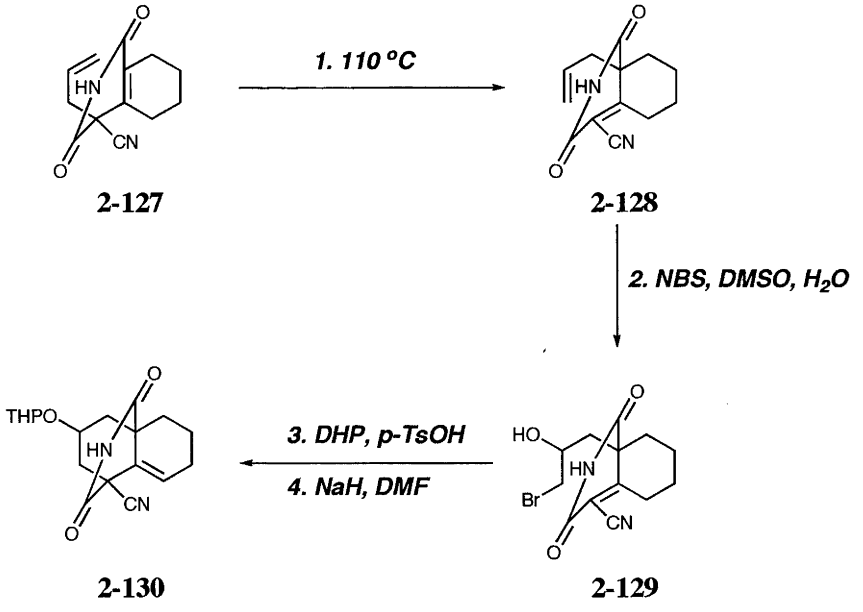
Fukumoto *et al.* have developed a novel *aza*-Prins type cyclisation[38] to generate the amine **2-126**. Conversion of the alcohol **2-123** to the corresponding mesylate was accompanied by spontaneous cyclisation to give, after conversion of the nitrile to the N-benzyl derivative, alkene **2-124**. The amine **2-124** was treated with formaldehyde and heated to give a cyclic amine **2-126**, presumably through a transition such as **2-125** (**Scheme 2.34**).



Scheme 2.34. *Aza-Prins Reaction*

2.3.5 Sigmatropic Rearrangement of AE-Ring Formation

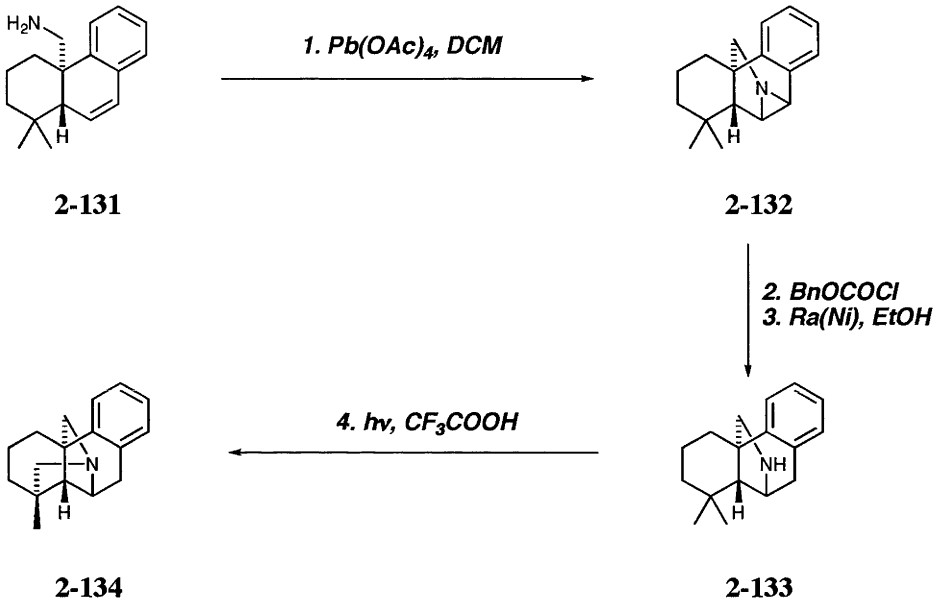
Another interesting route to the piperidine ring system has been developed *via* a [3,3] sigmatropic rearrangement on intermediate **2-127** to give the alkene **2-128.**[39] Functionalisation of the alkene to the bromo hydrin **2-129** followed by intramolecular alkylation led to the target piperidine **2-130** (**Scheme 2.35**).



Scheme 2.35. *Sigmatropic Rearrangment*

2.3.6 Aziridine for N-C20 Ring Formation

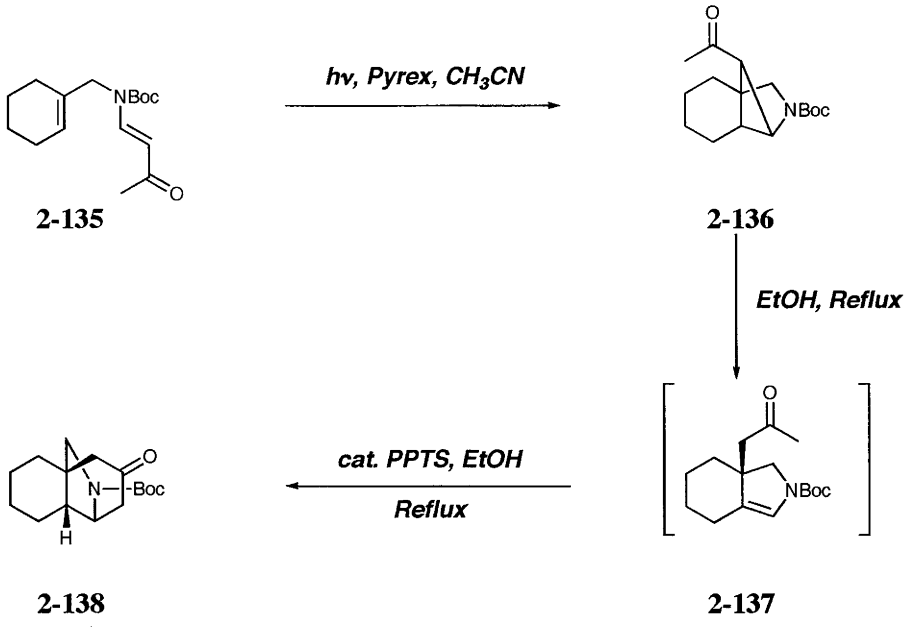
Following work initially developed by Nagata,[40] the authors were able to gain entry to the hetisane skeleton *via* aziridine formation.[41] Hence, treatment of **2-131** with lead tetraacetate led to the aziridine **2-132** which, when treated with benzyl chloroformate, gave a benzylic chloro compound. Reduction of the chloro compound with Raney nickel then gave the amine **2-133**. Photolysis of the *N*-chloro compound gave the azabicycle **2-134** (**Scheme 2.36**).



Scheme 2.36. *Aziridine Entry into the Hetisane Structure*

2.3.7 Winkler's Vinylogous Imide Photochemical Approach

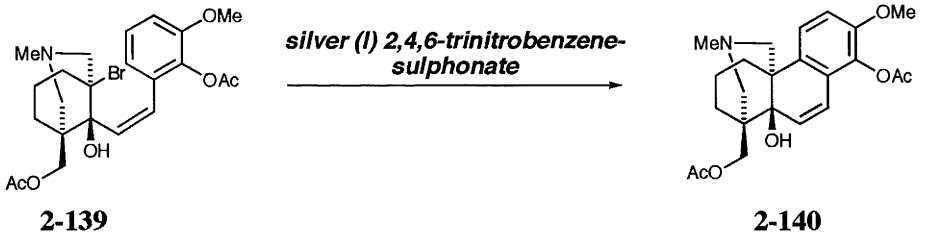
Entry into the *aza*-bicycle of hetisine was also developed by Winkler,[42] whereby irradiation of the vinylogous amide **2-135** led to a photocycloaddition product **2-136**. On heating, this product fragmented to give the enamine function **2-137**. Treatment of **2-137** with catalytic acid then afforded **2-138** (**Scheme 2.37**).



Scheme 2.37. Photocycloaddition Approach

2.3.8 The Williams Bridgehead Arylation

Williams was able to rapidly construct the functionalised tetracycle **2-140** from the bromide **2-139** through development of a silver (I) promoted intramolecular Friedel-Craft bridgehead arylation (**Scheme 2.38**).[43]



2-139 **2-140**

Scheme 2.38. Bridgehead Arylation Approach

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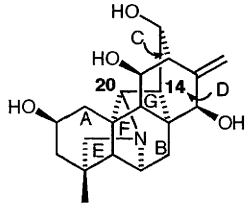
Chapter Three

α-Diazoketone Cyclisations for Entry into the Hetisane Skeleton

3.1 Synthetic Strategy

Hetisine **3-1** is an extremely complex diterpene alkaloid that was isolated as a minor constituent of *Aconitum heterophyllum* (**Figure 3.1**). Targeting the skeletal back bone, it was considered to be advantageous to construct the molecule around a benzenoid synthon as a precursor to the C and D-rings (**Figure 3.2**).[1] Pivotal to this strategy was the attachment of C14 to the angular C20 methyl late in the synthesis. This strategy is in contrast to the synthesis of *nominine* described by Muratake and Natsume, where the C14-C20 bond was one of the first to be installed (**Chapter 2.2.10, Scheme 2.28**).[2]



3-1

Figure 3.1. *Hetisine*

On partial completion of the A and B-ring functionality, it was envisaged that the aromatic ring **3-2** would be reduced using Birch conditions and the resulting dihydroanisole converted to the enone **3-3**. The elements of the D-ring would then be installed by a titanium (IV) catalysed 1,4-addition of allyl silane to give the adduct **3-4**. Allyl silane is known to add to a number of functionalities in the presence of titanium (IV) catalysts, but has a strong preference for 1,4 over 1,2-addition to enones.[3]

With the requisite number of carbons in place, the ketone **3-4** would be converted to the kinetically favoured silyl enol ether **3-5** and cyclised onto the propenyl residue on treatment with a palladium (II) catalyst, thereby delivering βγ-enone **3-6**. Palladium catalysed cycloalkenylations have become a powerful tool in the synthesis of bicycles and the resulting 13-one function would provide activation for linkage to C20.[4-6]

The 1,4-addition could reasonably be expected to be delivered to the β-face of the molecule, *anti* to the angular substituent on the α-face. However, if the allyl group is delivered to the α-face (**cf. Nagata's addition of cyanide; Chapter 2.2.4, Scheme 2.11**), resulting ultimately in the ketone and alkene functions being interchanged, the alkene bond could be ozonolysed and

the ketone group converted to the alkene by a Wittig reaction. This would obviously take more steps but ultimately would be acceptable.

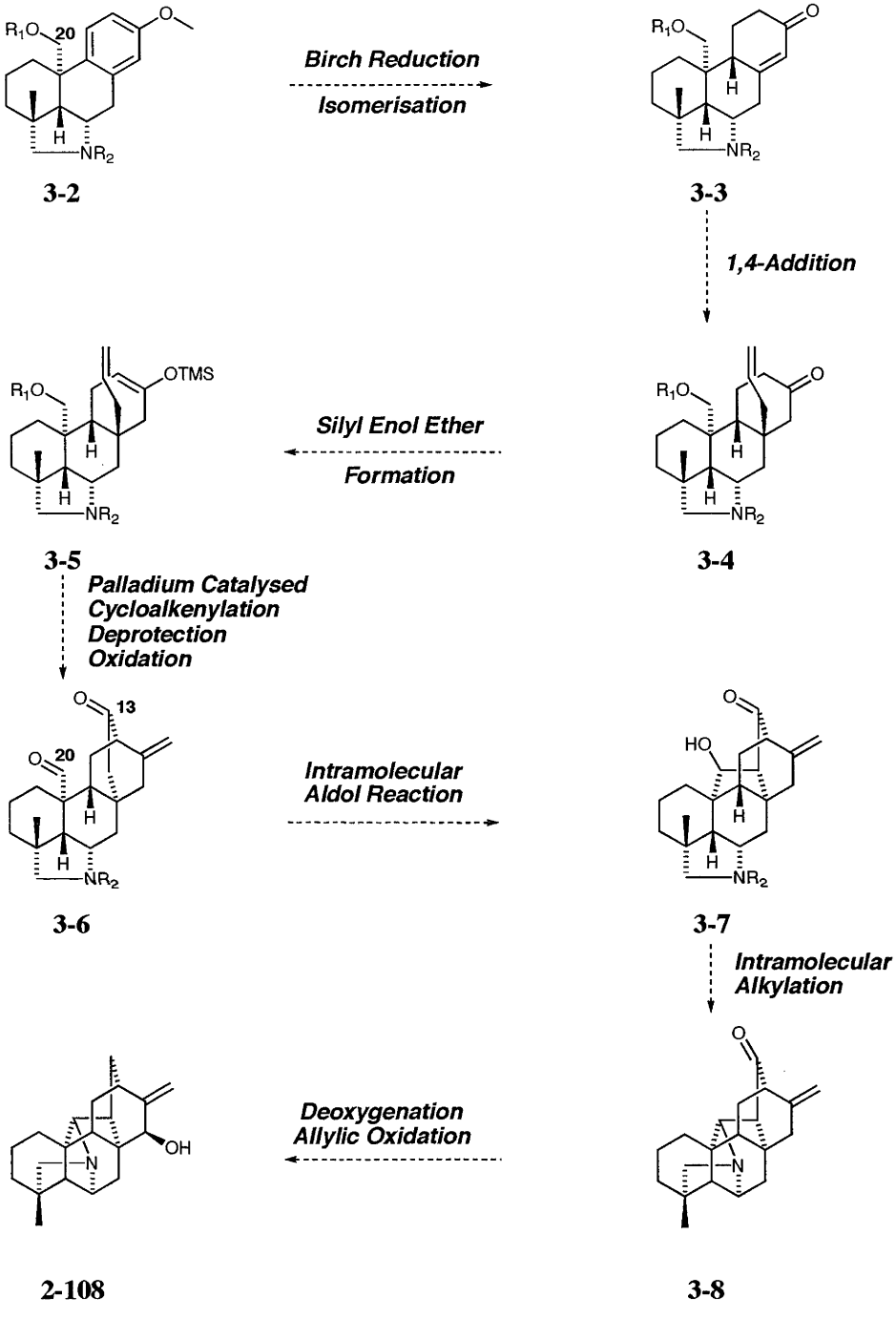
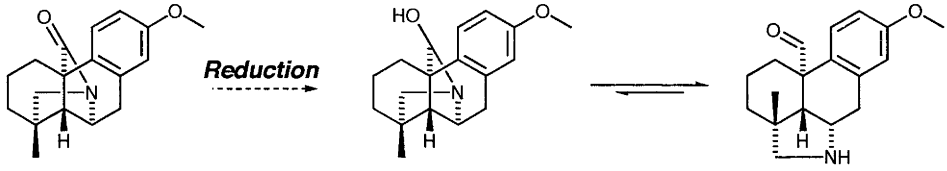


Figure 3.2. *End Game Strategy for Linking the C-Ring to C20*

Regardless, the positioning of the carbonyl function in the C-ring is crucial to the formation of the C14-C20 bond. It was envisaged that this step would be achieved by virtue of an intramolecular aldol reaction with the C20 aldehyde **3-6** to give the β-hydroxy ketone **3-7**. Thermodynamic control of the aldol reaction should ensure that the *exo*-20-ol would ensue. In this way the alcohol would be ideally positioned for the formation of the N-C20 bond through an intramolecular alkylation, thereby delivering the parent hetisane skeleton **3-8**. Deoxygenation

of the 13-one function followed by an allylic oxidation of the *exo*-17-ene function would then deliver the natural product *nominine* **2-108** (**Figure 3.2**).

The end game of the synthesis relies on the efficient construction of the A and B-ring functionality, with the prerequisite that the aldehyde be poised when required for the aldol reaction. The aldehyde **3-11** could be established in any number of ways, most simply by substituting an alkoxy function early in the synthesis. However, a novel way of arriving at a suitable intermediate is *via* liberation of an aldehyde from *hemi*-aminal **3-10**, which could be derived from the reduction of lactam **3-9**. It was thought that the *hemi*-aminal could not be reduced to the saturated amine, since elimination to the iminium species would not be possible (i.e. anti-Bredt).[7] Furthermore, the relief of strain could be expected to favour the aldehyde **3-11** (**Figure 3.3**) which, if reduced, would intersect with intermediate **3-2** (**Figure 3.2**).



3-9 **3-10** **3-11**

Figure 3.3. *Lactam Reduction Strategy for Liberating the Angular Aldehyde*

In pursuing this line of reasoning, it was conceivable that the lactam **3-9** could be obtained directly *via* a variant of the Schmidt rearrangement. Recently, this reaction has been shown to be useful for the construction of cyclic amides (**Figure 3.4**).[8,9]

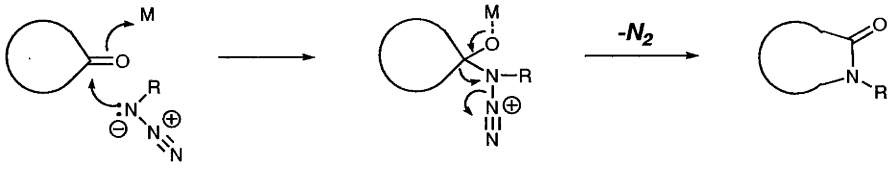


Figure 3.4. *Modified Schmidt Rearrangement*

Applying an intramolecular variation of this transformation to the preparation of lactam **3-9** in a retrosynthetic sense, identifies azide **3-12** as a possible precursor. In the forward direction, attack of the azide onto the carbonyl group of **3-12** would result in the formation of an unstable intermediate that would rearrange with expulsion of nitrogen. The alternative rearrangement can be ruled out as this would require the formation of the highly strained azetidine **3-13** (**Scheme 3.5**).

The synthesis of azide **3-12** is by no means trivial, but it appeared that the C4-C10 bridge could be accessed by acid catalysed cyclisation of diazo ketone **3-14**, which on protonation in the absence of good external nucleophiles could be expected to deliver the alkene **3-15**.[10,11] As with the Schmidt rearrangement, an alternate pathway was possible, but it was

reasoned that the formation of a cyclopentanone moiety would be favoured over the formation of a higher energy cyclobutanone (**Figure 3.6**).

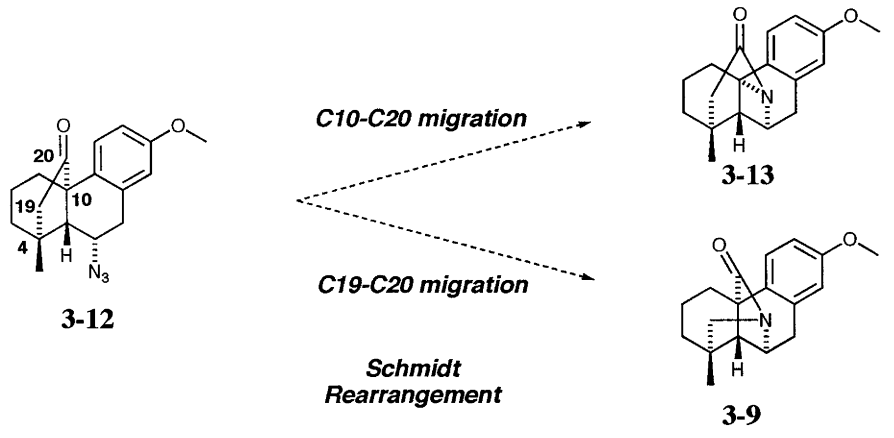


Figure 3.5. *Schmidt Rearrangement Approach to the Lactam* ***3-9***

Following protection of the ketone group of **3-15**, the B-ring alkene bond could then be elaborated, via hydroboration, to the β-hydroxy derivative **3-16**. This transformation would be critical, as it would have the dual purpose of the establishing the required *trans*-fused decalin moiety and providing a substituent that could be elaborated to the azide function. The borane would presumably be delivered to the less hindered β-face, and the resulting β-hydroxy alcohol could be derivatised – mesylate, triflate, etc – and then displaced by azide ion to give the desired azide **3-12** (**Figure 3.6**).[12]

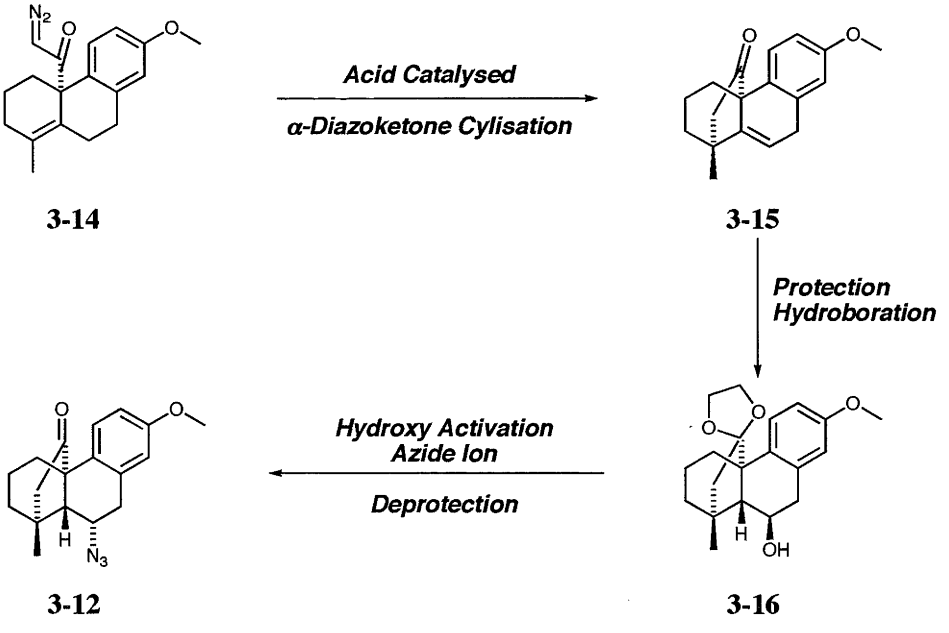


Figure 3.6. *Acid-Catalysed α-Diazoketone Cyclisation to Cyclopentanone*

The diazoketone **3-14** was expected to be a relatively simple target and should be readily obtained from the acid **3-19** by treating the corresponding acid chloride with diazomethane. Therefore, the task was reduced to the efficient construction of the acid **3-19**. An

ideal entry point to this intermediate was the enone **3-18**, which was expected to be available from the Robinson annulation of **3-17**. The angular ester could conceivably be converted to the acid through saponification and the alkene derived by deoxygenation of the enone (**Figure 3.7**).

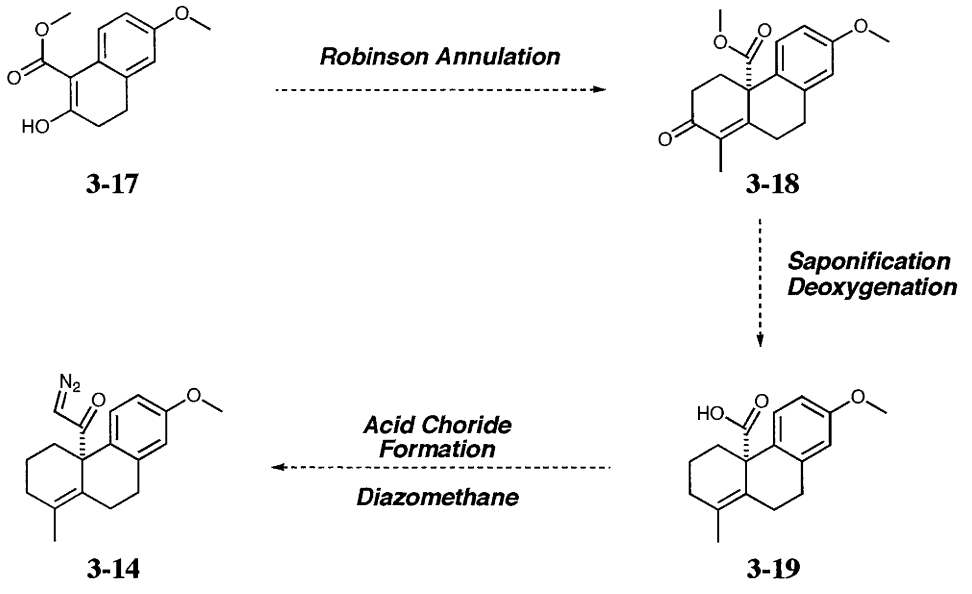
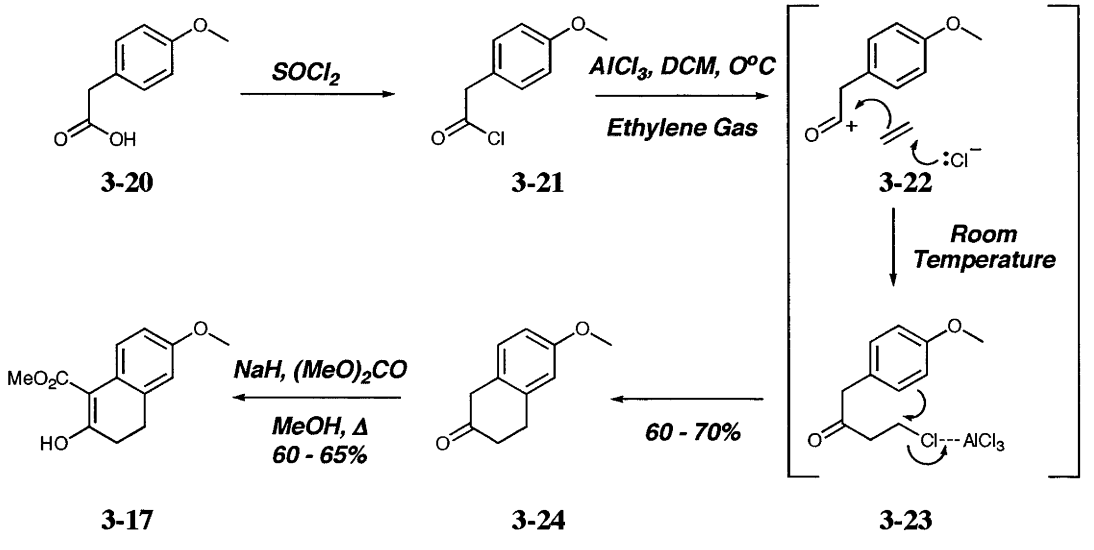


Figure 3.7. *Synthetic Plan for Synthesis of Diazoketone* ***3-14***

3.2 Synthesis of Enone 3-18

3.2.1 Synthesis of β-Keto Ester 3-17

The chemistry of β-tetralones has been well studied and they are versatile intermediates for total synthesis. As a result, there are a number of synthetic approaches, but the synthesis of Cadogan[13] is the most straightforward and amenable to large scale (**Scheme 3.1**). In addition, the starting material, 4-methoxy phenyl acetic acid **3-20**, is readily available and affordable.



Scheme 3.1. *Synthesis of β-Keto Ester* ***3-17***

Accordingly, the acid **3-20** was treated with thionyl chloride to give the acid chloride **3-21**. On treatment with aluminum chloride the acyl cation **3-22** is generated, and when ethylene gas is passed through the reaction mixture the ethylene is acylated, resulting in alkyl chloride **3-23**. As the reaction is warmed, a Friedel-Crafts alkylation ensues, evident by the formation of green aluminum salts, to give the β-tetralone **3-24** in 60-70% yield. Tetralone **3-24** was then acylated by treatment with sodium hydride in dimethyl carbonate to furnish the β-keto ester **3-17** in 60-70% yield (**Scheme 3.1**).[14]

3.2.2 Robinson Annulation of β-Keto Ester 3-17

The Robinson annulation has a reputation as a reliable work-horse in the synthesis of steroidal and terpenoid compounds, and is an obvious choice for the construction of the A-ring of acid **3-19**.[15] Formally, a Robinson annulation involves a 1,4-addition of an enolate **3-25** to an alkyl vinyl ketone to give the adduct **3-26**, which then equilibrates to the terminal enolate **3-27**. An intramolecular aldol reaction then ensues to afford the cyclic product **3-28**. Subsequent protonation gives the β-hydroxy ketone **3-29**, which then undergoes elimination to furnish the enone **3-30** (**Figure 3.8**).

Although the sequence is general and can be carried out on a number of cyclic enolates, a major drawback of Robinson annulations is the low yield of some enones. This has been attributed to the polymerisation of the vinyl ketone. Therefore, in addition to alkyl vinyl ethers, β-halo ketones and β-amino ketones are employed, the latter two forming the vinyl ketone *in situ*. Judicious choice of the base is therefore important to ensure both deprotonation of the β-keto ester and of the vinyl ketone precursor.

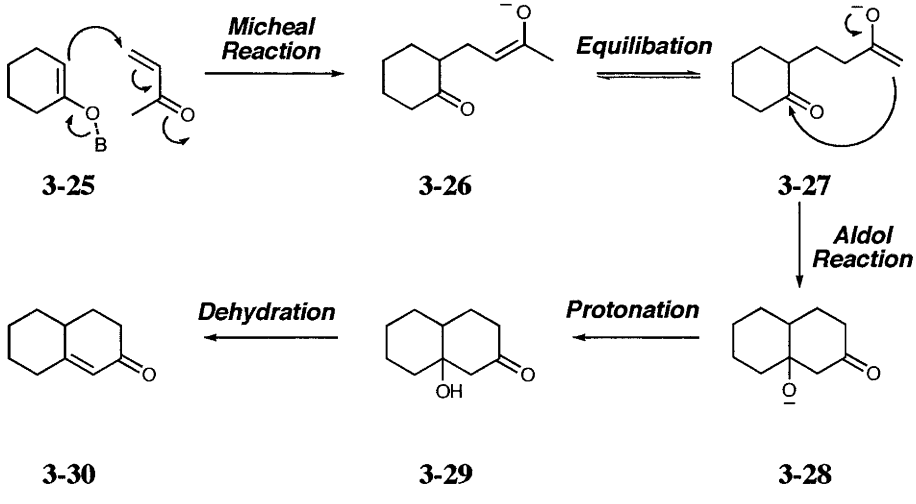
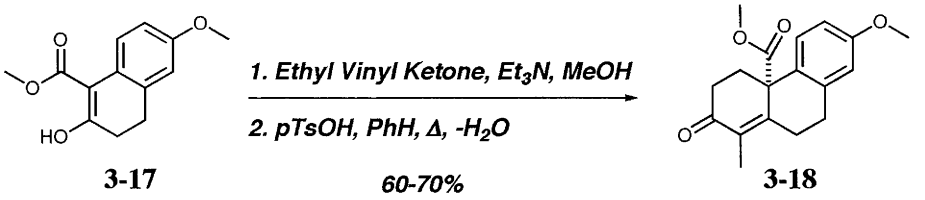


Figure 3.8. *Robinson Annulations*

In the event, *in situ* formation of the vinyl ketone was found to be unnecessary. Treatment of the β-keto ester **3-17** with a catalytic amount of triethyl amine in MeOH in the presence of ethyl vinyl ketone afforded the Michael adduct, which was immediately taken up in

benzene containing a catalytic amount of *para*-toluene sulfonic acid. Heating to reflux resulted in dehydration to afford the enone **3-18** in 60-70% yield over the two steps (**Scheme 3.2**).[16]

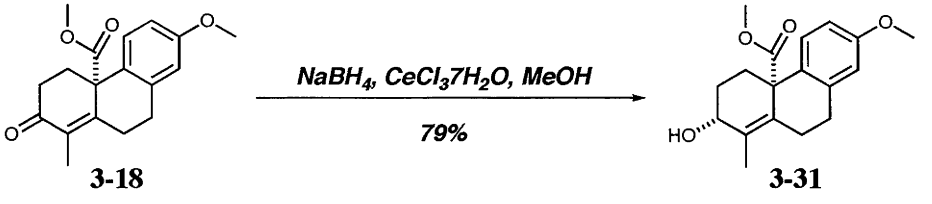


Scheme 3.2. *Synthesis of Enone* ***3-18*** *via Robinson Annulation*

3.3 Synthesis of Acid 3-19

With multi-gram quantities of the enone **3-18** in hand, the platform was set to allow exploration of the synthesis of acid **3-19**. Classical deoxygenation procedures – Clemmenson and Wolff-Kishner – were thought to be too harsh. A Barton-McCombie deoxygenation was considered, but it has been established that allylic thiocarbonates undergo Claisen-type [3,3] sigmatropic rearrangements.[17] It was thought unlikely that an allylic thiocarbonate would remain stable at the elevated temperatures required to initiate the subsequent radical reduction. The reduction of a thioketal with Raney nickel was a possibility, but again it was thought that the Lewis acid catalysis and subsequent reduction would be insufficiently mild.[18]

Hence, the seemingly simple task of deoxygenating the enone and saponifying the ester appeared to be more difficult than first thought, but ultimately, serendipidity prevailed. Reduction of the enone **3-18** with $NaBH_4$, $CeCl_37H_2O$ – Luche conditions[19] – yielded the allylic α-alcohol **3-31** in 79% yield (**Scheme 3.3**), as evident from the large axial-axial coupling on the axial allylic proton (4.01 ppm, J = 8.2 Hz). In addition, the IR spectrum showed the characteristic broad peak at 3456 cm^{-1} for the hydroxyl.



Scheme 3.3. *1,2-Reduction of Enone* ***3-18***

The Luche conditions are the conditions of choice for the 1,2-reduction of enones as in many instances 1,4-reduction competes with 1,2 reduction. Using Luche conditions, the chemoselectivity of the reduction is governed by the $CeCl_3$ which, through co-ordination to the enone prevents 1,4-reduction. This process is also helped by the fact that the β-carbon of the enone is at the junction of a decalin ring system and is consequently hindered.

The stereochemistry of the reduction is governed by the torsional strain of developing transition states. The axial approach of hydride leads to the lower energy *staggered* conformation. In contrast, equatorial approached leads to an *eclipsed* transition state.[20] For small

nucleophiles, it has been demonstrated that torsional steering is more significant than the steric hindrance imposed by the hydrogen at C1, but circumstances change as the steric bulk of nucleophile varies. In addition to the torsional effects may be the electrostatic effect imposed on the nucleophile by the angular ester group, which interferes with the approach of the borohydride to the α-face (**Figure 3.9**).[21]

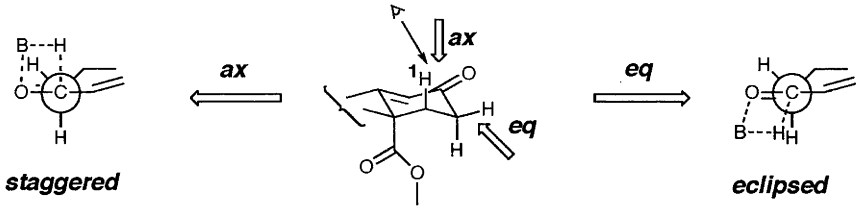
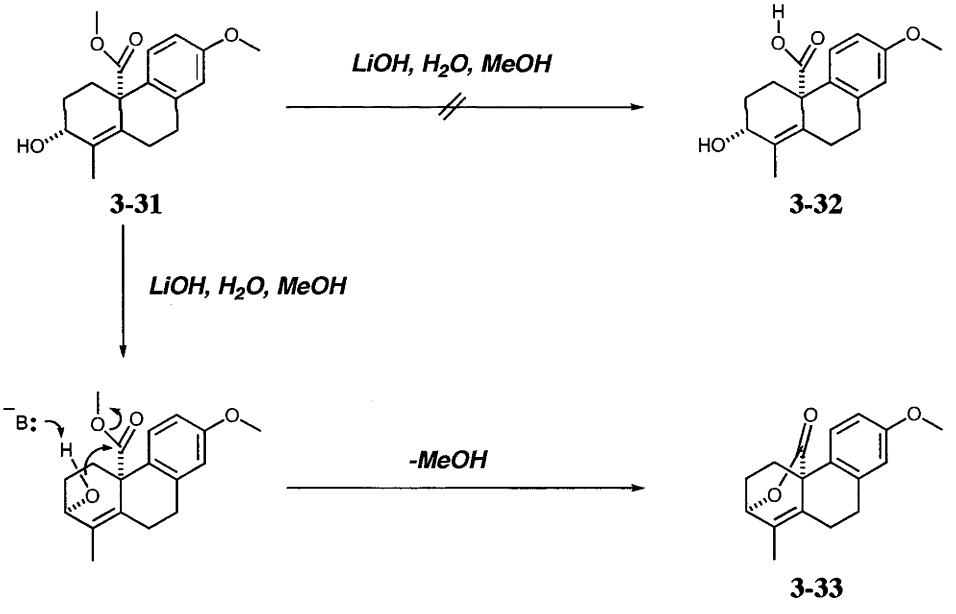


Figure 3.9. *Torsional Steering in the 1,2-Reduction of Enone* ***3-18***

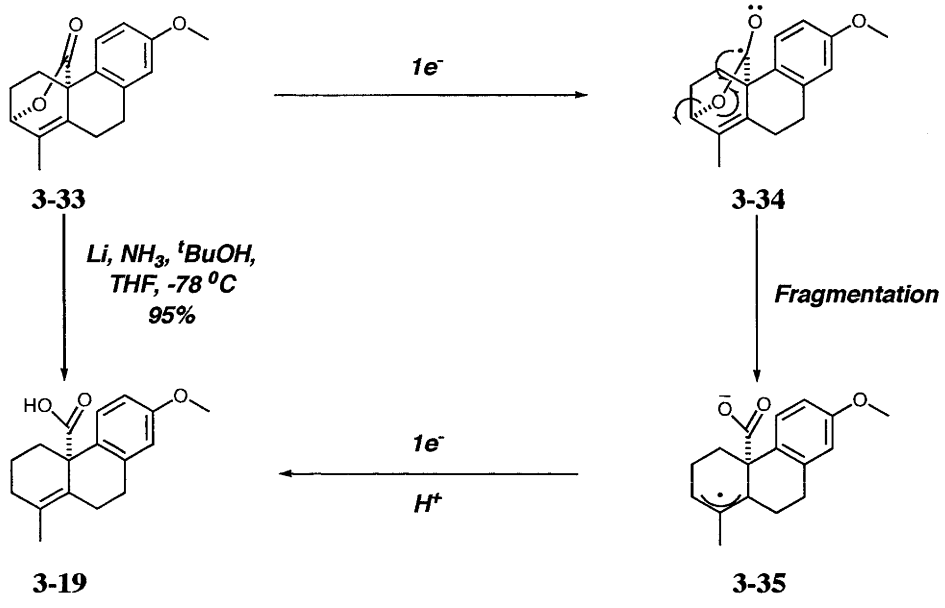
With the allylic alcohol in hand, saponification was attempted by treating alcohol **3-31** with aqueous LiOH in methanol. Surprisingly, no acid **3-32** was isolated; instead, the ester underwent cyclisation to give the lactone **3-33**. This result was evident from the absence of the ester methoxyl and the downfield shift to 4.99 ppm of the allylic proton. The broadening of the peak due to smaller couplings also indicating that the allylic proton was *pseudo*-equatorial as a consequence of the boat-like geometry adopted by the A-ring. In addition, the EI mass spectrum showed a strong ion of 226 as a result of the expulsion of CO_2 (**Scheme 3.4**).



Scheme 3.4. *Lactonisation of the Allylic Alcohol*

This result was initially disheartening, but ultimately provided the solution to the deoxygenation problem as it was considered that the allylic lactone could be reduced directly to the alkene *via* hydrogenolysis. The dissolving metal reduction of allylic ethers and acetates to the corresponding alkene is a well established reaction.[22,23] In this instance the alcohol was activated internally, through cyclisation with the ester, and it was hoped that hydrogenolysis would deoxygenate the allylic system and deliver the desired acid in the one transformation.

Pursuing this line of reasoning, the lactone **3-33** was reduced with lithium in liquid ammonia in the presence of ^{t}BuOH and smoothly delivered the desired acid **3-19** in a 70% yield (**Scheme 3.5**). The acid was characterised by the presence of an allylic methyl at 1.73 ppm. The ^{13}C NMR spectrum showed two tetrasubstituted olefinic carbons at 129.2 and 131.2 ppm, while IR indicated the acid carbonyl stretch at 1690 cm^{-1}. The EI mass spectrum was also consistent with a strong ion at 227 as a result of the ejection of CO_2H.



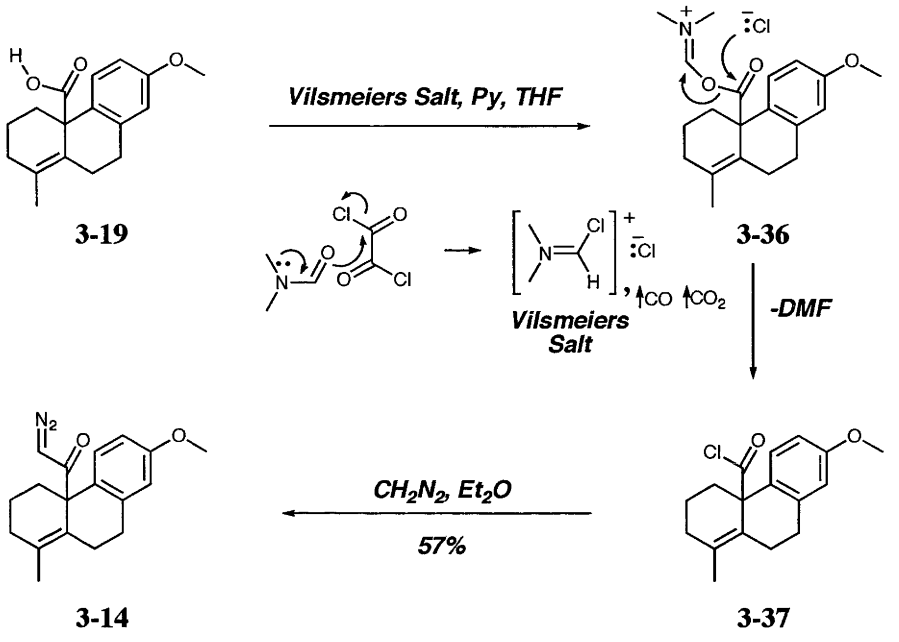
Scheme 3.5. *Reduction of Lactone* ***3-33***

The reaction most likely proceeds through the acceptance of an electron into the π*orbital of lactone function resulting in the formation of the radical anion **3-34**, which subsequently fragments the carbon-oxygen bond to give the delocalised radical **3-35**. The electron-rich carboxylate is resistant to further reduction, but the addition of another electron into the delocalised radical results in the formation of the corresponding anion. The formation of the tetrasubstituted alkene is most likely derived from quenching of the anion at the less hindered carbon. This was a excellent result as it perfectly balanced deoxygenation and saponification in one step.

3.4 α-Diazoketone Formation

Having achieved the synthesis of acid **3-19**, our attention turned to the synthesis of the diazoketone **3-14**. There are a number of methods for forming diazoketones, the most straightforward being the acylation of diazomethane with an acid chloride. Therefore, the first challenge was to form the acid chloride in anticipation of a subsequent reaction with diazomethane. Attempts to form the acid chloride directly with oxalyl chloride in the presence of pyridine gave a large a number of products. Even employing a catalytic amount of dimethyl formamide (DMF), which forms Vilsmeier's salt *in situ* – (*vide infra*), did not improve the reaction outcome. Due to the reactivity of acid chlorides, no attempts were made to try to isolate

any of the products, but it is likely that the acidic conditions promoted protonation of the alkene in conjunction with decarboxylation of the carboxylic acid. The acid **3-19** is sterically hindered, accounting for the lack of reactivity and associated side reactions. However, Vilsmeier's salt has been used successfully in a number of instances when direct acid chloride formation has failed.[24] On treatment with a carboxylic acid an acyl formimide **3-36** is formed, which readily reacts with chloride ion to give the acid chloride **3-37**.



Scheme 3.6. *Acid Chloride and Diazoketone Formation*

Treating acid **3-19** with Vilsmeier salt in the presence of pyridine indeed produced a clean reaction. The cleaner reaction could be associated with the increased electrophilicity of the Vilsmeier salt and resulting acyl imide to attack by acid and chloride ion respectively. The acyl imide is presumably a more reactive intermediate than the corresponding oxalyl anhydride. With acceptable results for acid chloride formation, the reaction mixture was cannulated directly into an excess of ethereal diazomethane to give the diazoketone **3-14** in 57% overall yield (**Scheme 3.6**). The diazoketone was identified by a singlet at 5.28 ppm in the ^{1}H NMR spectrum, attributed to the diazomethine proton, and the characteristic diazo-stretching band at 2100 cm^{-1} in the IR spectrum. It should be noted that it is neccessary to use an excess of diazomethane in order to deprotonate the initially formed diazonium intermediate. In the absence of an excess diazomethane deprotonation is in competition with the displacement of the diazonium ion by chloride ion, which affords the corresponding α-chloro ketone (**Figure 3.10**).

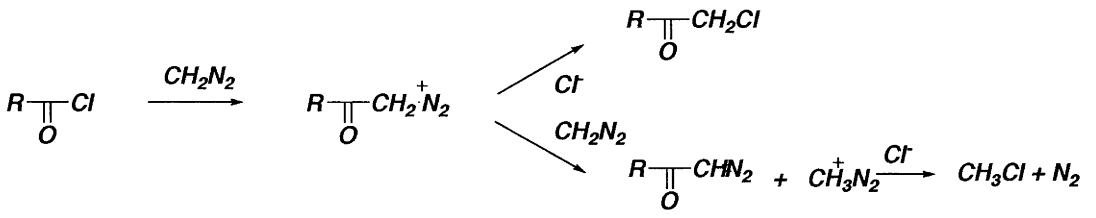


Figure 3.10. *Deprotonation Versus Displacement of the Diazonium Intermediates*

3.5 α-Diazoketone Cyclisations

3.5.1 Introduction

With the diazoketone **3-14** in hand, exploration of the cyclisation could begin. Diazoketones can be activated in two ways. Complexation with certain metal complexes creates a metal carbenoid which, depending on the metal and ligand system, can be used in a number of transformations including cyclopropanation, C-H, N-H, and OH insertions, and various reactions involving the formation of ylides.[11,25,26]

A second method, which we hoped to exploit, involves protonation of the diazoketone to give a diazonium ion, an extremely reactive leaving group, which can be displaced by any number of nucleophiles. Provided that external nucleophiles are excluded, it is possible to effect carbon-carbon bond formation with neighbouring alkene groups.

Extensive study of alkene participation in acid promoted diazoketone cyclisations has identified three main determining factors that govern the outcome: nucleophilicity of the alkene bond; strain effects in relation to ring size; and the stability of the incipient carbonium ions. The net outcome of these effects has been illustrated by Smith in a series of simple models (**Figure 3.11**). In the first example (**Entry 1**), the low yield can be attributed to the low nucleophilicity of the alkene and the relative instability of the intermediate secondary carbocation. In **Entry 2** and **3** the improved yield can be attributed to the fact that alkene is trisubstituted and as a consequence more nucleophilic. Furthermore, the resulting carbocation is tertiary and therefore more stabilised than the preceding secondary carbocation of **Entry 1**.

Entry 4 demonstrates this trend further, whereby the tetrasubstituted alkene gives an excellent yield of the corresponding cyclopentanone. Although the mechanism has been of much interest, it is difficult to determine whether the cyclisation to the cyclopentanone proceeds initially through the four member transition state or if the cyclisation proceeds directly to the cyclopentanone intermediate.

Very possibly both pathways are followed as in the example provided in **Entry 5**. The cyclisation of **Entry 5**, which is a trisubstituted alkene, would be expected to give a good yield of the corresponding cyclopentenone, but instead only proceeds in a 12% yield. The remainder of the material is a cyclobutanone (31%) and a cyclopentenone (28%) that results from a 1,2-alkyl shift. This outcome has been rationalised based on the relative stability of the transient carbocations, whereby the preferred cyclisation pathway is that which leads to a more stable

tertiary carbon cation and a 4-member ring despite the increased ring strain. Similarly, the product that results from a 1,2-alkyl shift does so through the formation of a more stable tertiary carbocation.

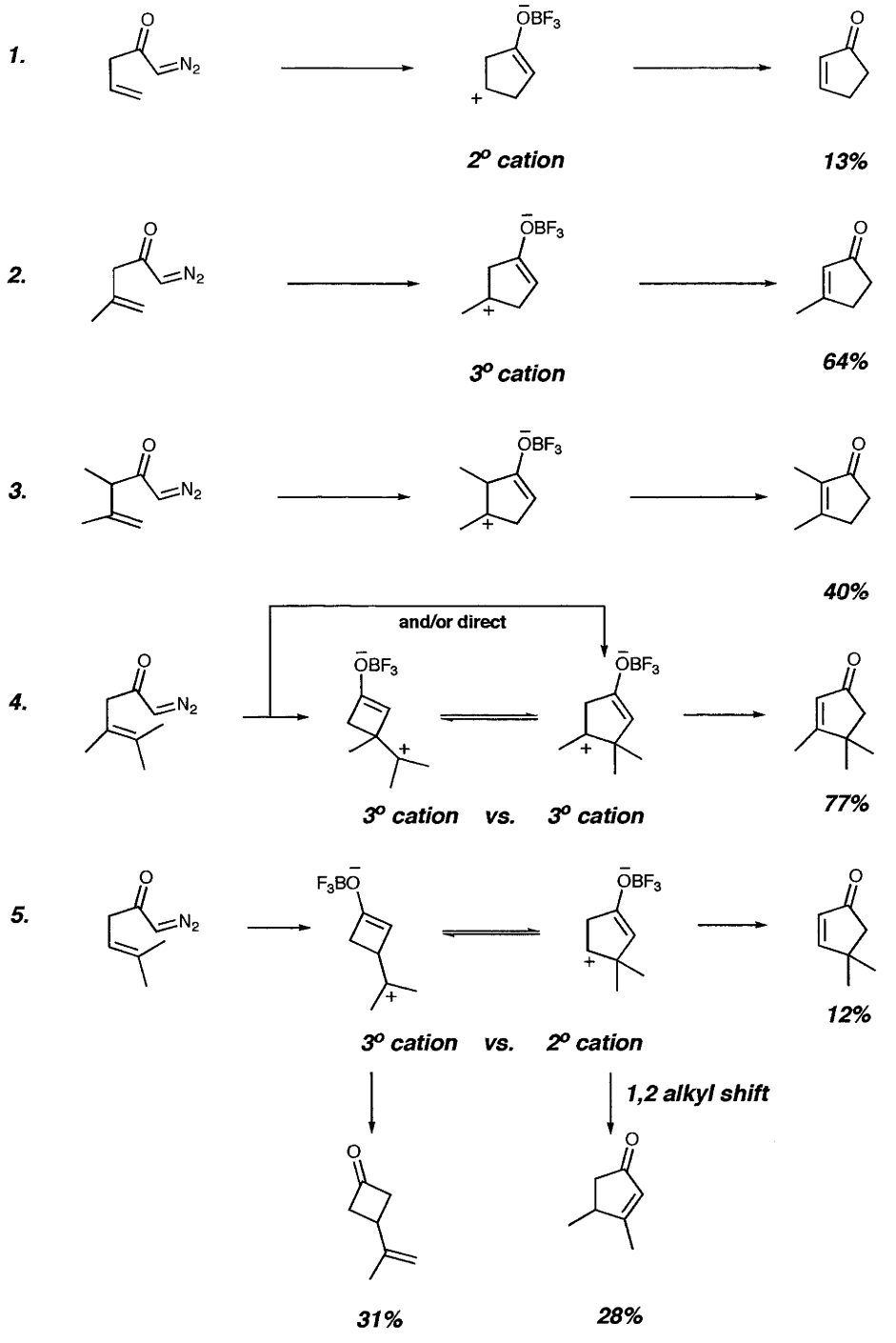


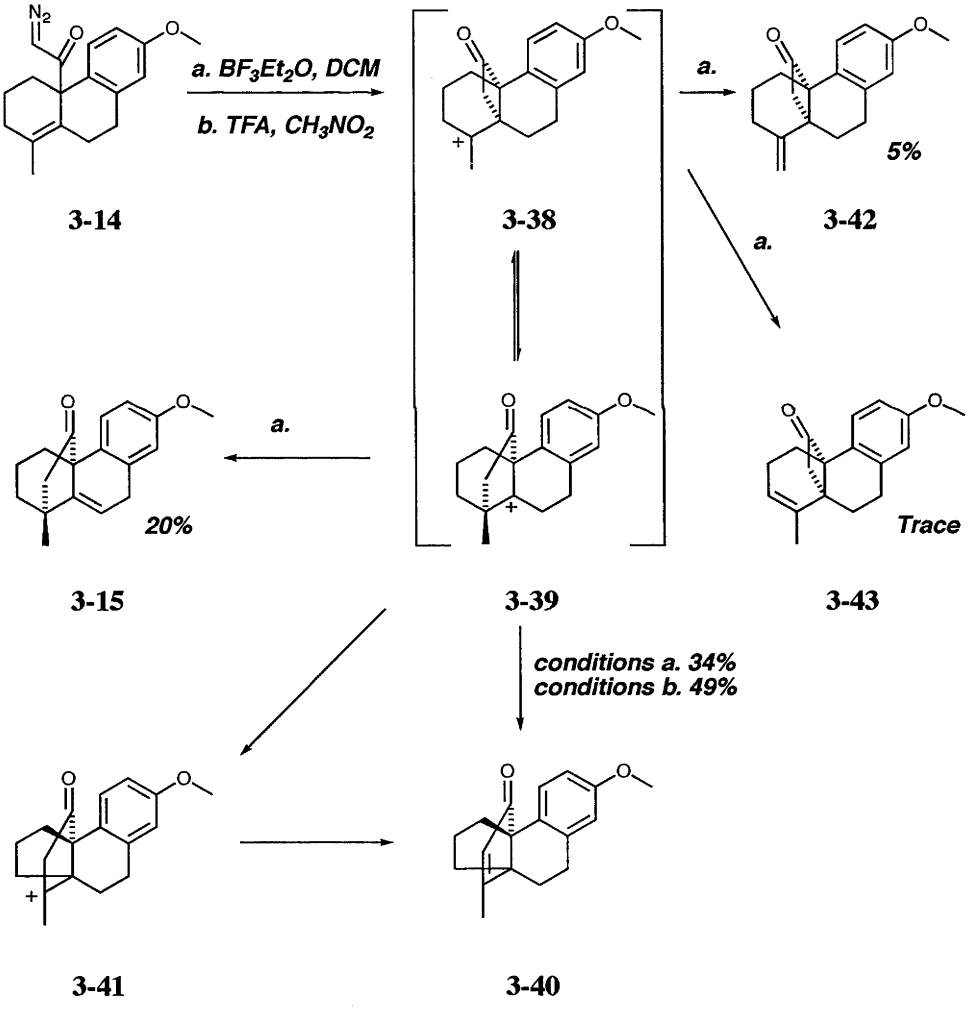
Figure 3.11. *Cation Stability and Ring Strain Factors Determining Cyclisation Outcomes*

The product that results from direct cyclopentanone cyclisation is isolated in yields comparable to **Entry 1**, presumably as a consequence of the relative instability of the secondary carbocation. For cyclobutanone formation to occur in **Entries 1-3** the cyclisation would have to balance the effects of an unstable primary cation. In **Entry 4** a cyclobutanone cyclisation could proceed through a tertiary cation, but clearly ring strain is the dominant control element.

3.5.2 Cyclisation of α-Diazoketone 3-14

Although the diazoketone **3-14** represents a more rigid system, it was hoped that as both possible cyclisation pathways led to a tertiary carbocation that the additional ring strain of the cyclobutanone transition state **3-38** would be less favoured than that for the cyclopentanone **3-39** formation.

In the event, treatment of the diazoketone **3-14** with $BF_3 \cdot Et_2O$ in DCM at -20 ^{0}C afforded the desired product **3-15**, albeit in a small yield of approximately 20%, as a mixture with other products. The main product formed was the enone **3-40**, which occurs through a 1,2-alkyl shift of the intermediate **3-39** to **3-41**. The other products included two unstable compounds that were tentatively assigned as the isomeric cyclobutanones **3-42** and **3-43**, which are derived from elimination of a proton from intermediate **3-38**, *vide infra* (**Scheme 3.7**).



Scheme 3.7. Diazoketone Cyclisation

Although integration of the crude ^{1}H NMR spectrum indicated the products to be roughly 4:3:3:2 **3-40**: **3-15**: **3-42**: **3-43**, and the isolated yields after chromatography generally reflected this in regard to enone **3-40** (30-40%) and **3-15** (20%), significant amounts of material

was lost and the cyclobutanones **3-42** and **3-43** were isolated in low yields (~5%) and would rapidly decompose.

Interestingly, the rearranged enone **3-40** could be formed exclusively using TFA in nitromethane. This suggests that the polar conditions stabilised the cation sufficiently to allow complete equilibration to the lower energy enone.

The formation of the cyclopentanone **3-15** was evident from the clear coupling of the alkene proton to the benzylic position in the ^{1}H NMR spectrum. The equatorial benzylic proton was down field and had a smaller coupling of 2.3 Hz, while the axial proton had a coupling of 4.4 Hz. The geminal coupling was large, but not as big as the geminal coupling of the protons on the cyclopentanone, J = 17 Hz; H19b was assigned to the more down field doublet which is presumably more shielded by the alkene bond. The IR spectrum showed a strong band at 1746 cm^{-1} indicative of a cyclopentanone. The aromatic region was standard for the substitution pattern, H12 coupled strongly to H11, and weakly to H14 (**Figure 3.12**).

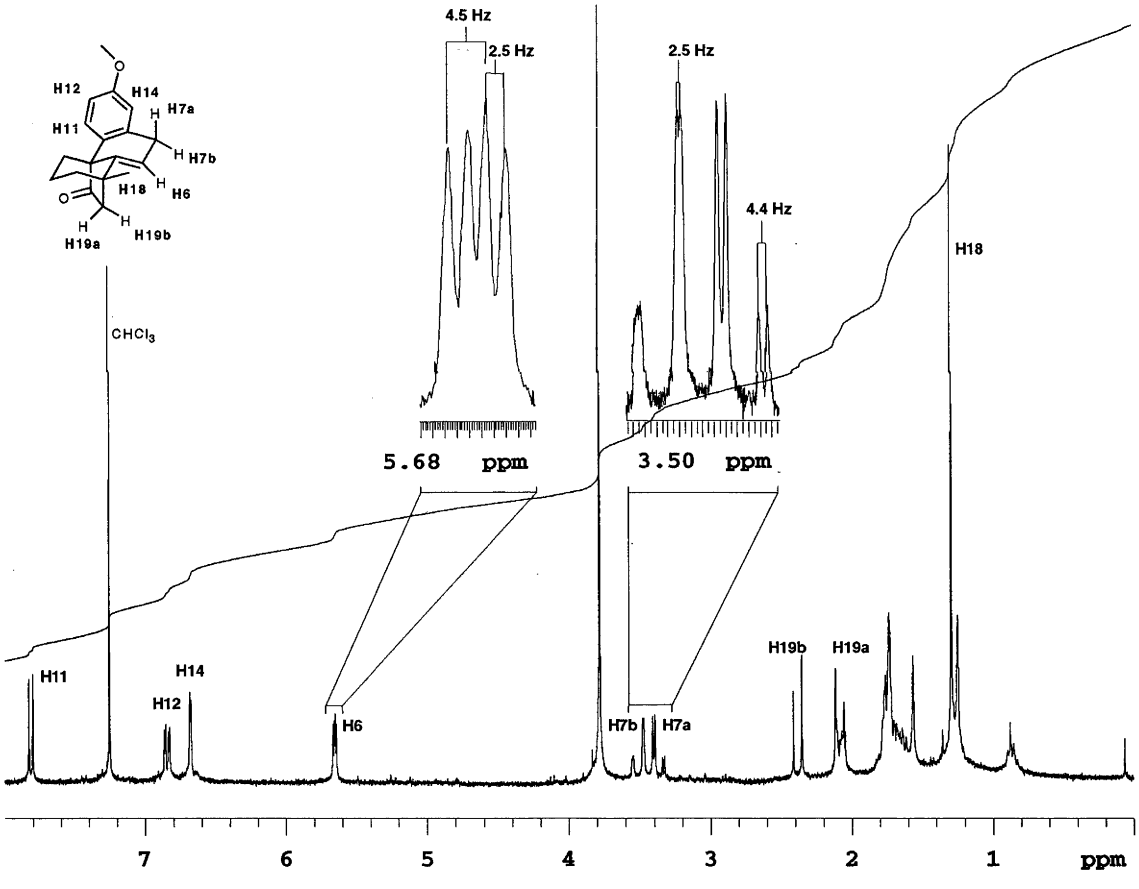


Figure 3.12. *^{1}H NMR Spectrum ($CDCl_3$) of Cyclopentanone **3-15***

The enone **3-40** was eventually characterised by the ^{1}H NMR spectrum, which had a signal at 6 ppm indicative of an enone proton and which also showed a small coupling of J = 1.3 ppm to the allylic methyl at 2.1 ppm. The IR spectrum had a lower frequency carbonyl stretching band at 1697 cm^{-1} characteristic of an enone (**Figure 3.13**).

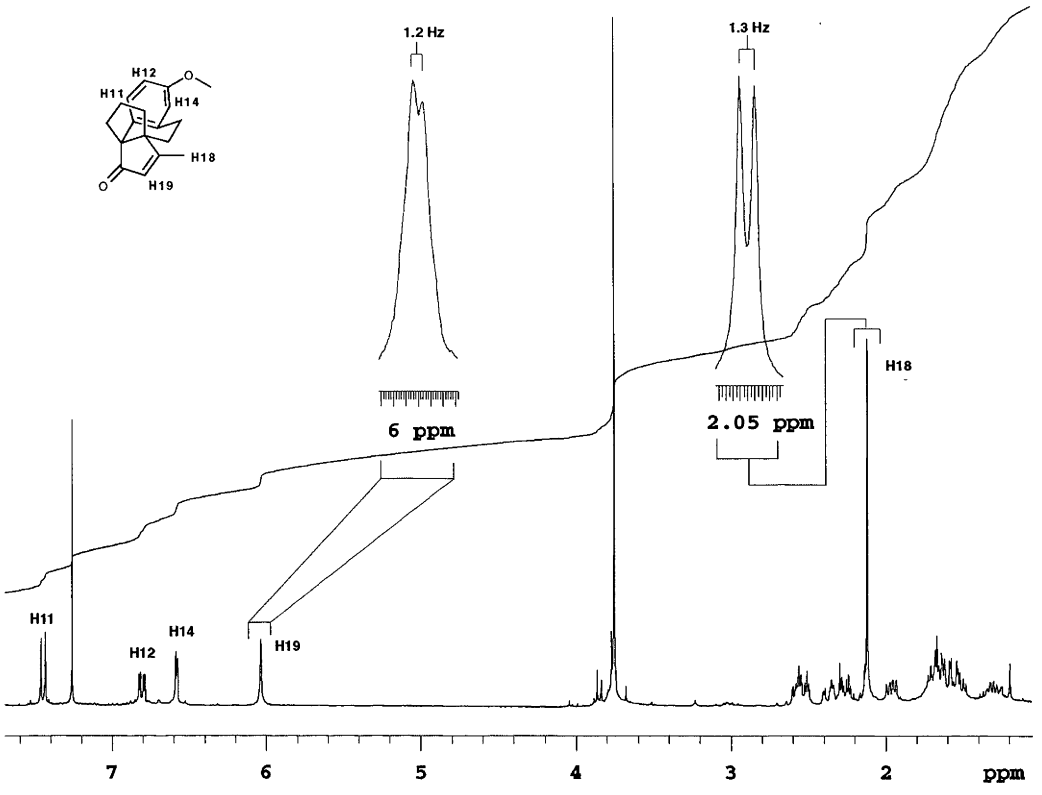


Figure 3.13. ^{1}*H NMR Spectrum (CDCl$_3$) of Cycolpentenone* ***3-40***

3.6 Discussion

It would appear that the cyclopentanone was indeed the favoured intermediate, but that it preferred to rearrange to the conjugated ketone. Although Baldwins's rules apply to anionic systems, the principles denoting to orbital overlap can also be applied to cationic systems and provide an explanation for the formation of cyclobutanone products. Baldwin's rules point to the fact that the bond forming process of a 4-*exo* cyclisation tends to be preferred over 5-*endo* cyclisation.

It is likely that the cyclopentanones are actually derived from **3-38** through 1,2-shifts. Unfortunately, the elimination of hydrogen to give the desired alkene **3-15** did not occur at a rate comparable to the 1,2-alkyl shift (**3-39→3-41**). The rearrangement also results in a lower energy conjugated alkene, which could also be a driving force for this rearrangement.

In contrast, Ghatak and co-workers observed the preferential formation of the cyclobutanones, and products arising from the rearrangement of intermediate cation **3-45** depending on the polarity of the medium (**Figure 3.14**).[27-32]

Treatment of the diazoketone **3-44** with 70% perchloric acid in chloroform gave exclusively the cyclobutanone **3-46** *via* elimination of a proton from intermediate **3-45**. However, when nitromethane was use as the solvent, which presumably stabilises the cationic centre, a cascade of 1,2-alkyl shifts predominates with formation of cations **3-47** and **3-48**. The latter is then quenched by nitromethane to give an adduct that hydrolyses to the alcohol on work up, to give the rearranged product **3-49**. Interestingly, they observed that the corresponding

para-methoxyphenyl analogue does not rearrange and that the cyclobutanone is the major product regardless of conditions, indicating that the benzylic cation is significantly more stable than the rearranged cationic intermediates.

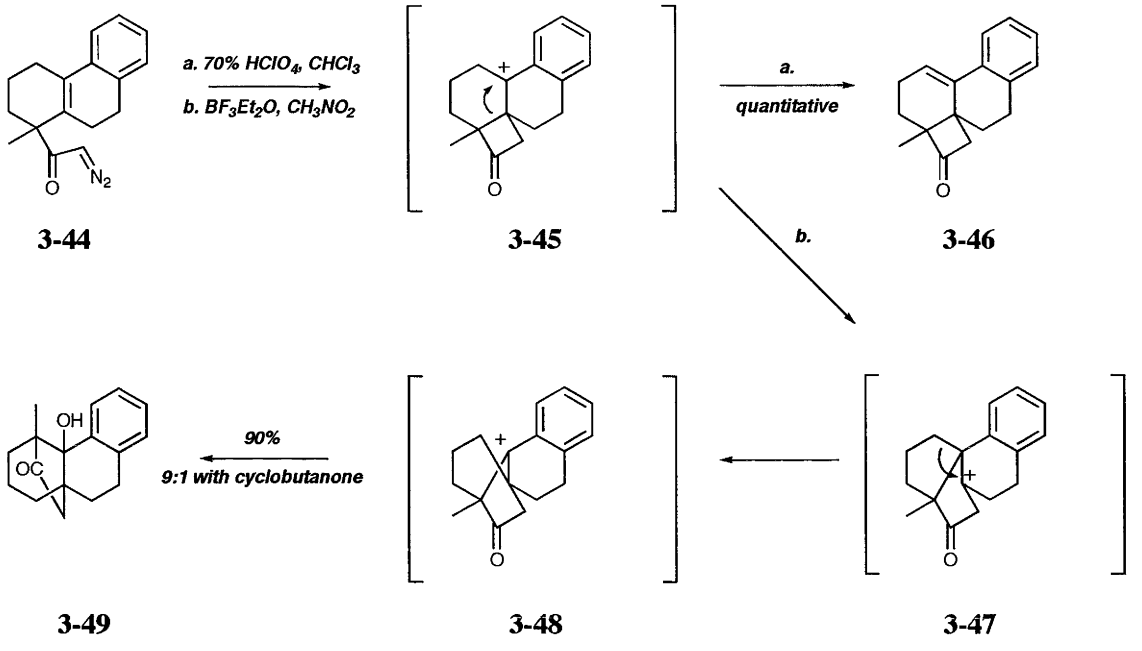


Figure 3.14. *Preferential Cyclobutanone Formation*

3.7 Attempt to Avoid Rearrangement

3.7.1 Introduction

In the above example, the predisposition towards cyclobutanone formation is not unexpected as the benzylic cation is clearly more stabilised than the alternative cation. However, the formation of the rearranged product **3-40** suggests that the cyclopentanone cation **3-39** is the lower energy intermediate in this instance, but that the barrier to the subsequent 1,2-alkyl shift is equally low. In light of this finding, it was considered that an alkene derivative lacking the C4 methyl could mitigate this process, as the 1,2-alkyl shift equilibration would require the formation of a higher energy secondary carbocation (**Figure 3.15**).

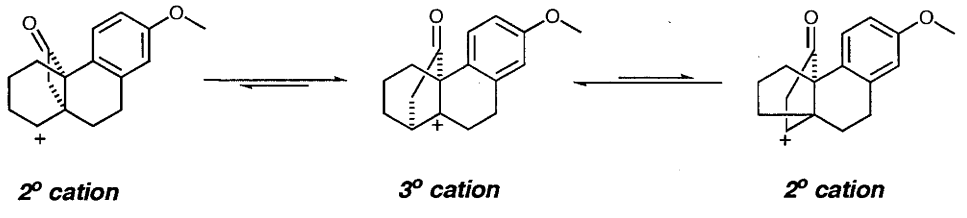
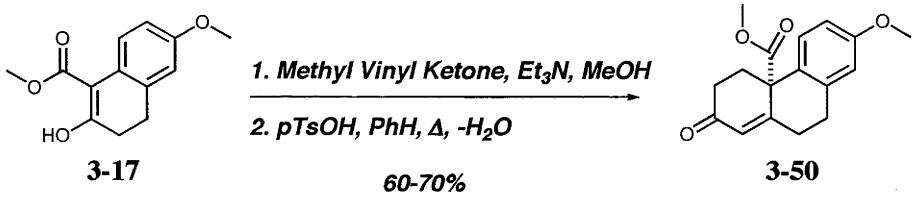


Figure 3.15. *Attenuation of the 1,2-Rearrangement*

Obviously, the resulting cyclopentanone would not be suitable for the synthesis of the desired lactam by the plan outlined earlier, but it could be used to test the viability of the Schimdt rearrangement. Alternatively, oxidative cleavage of the cyclopentanone could afford a valuable intermediate.

3.7.2 Synthesis of α-Diazoketone 3-58

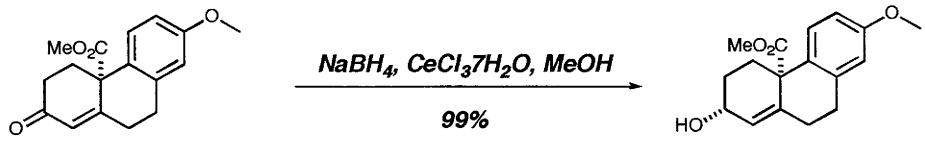
The attainment of the desmethyl diazoketone could easy be achieved by replacing ethyl vinyl ketone by methyl vinyl ketone in the Robinson annulation. Treatment of β-keto ester **3-17** with methyl vinyl ketone in MeOH with Et_3N followed by dehydration indeed gave the desired enone **3-50** in 60-70% yield (**Scheme 3.8**). The ^1H NMR spectrum showed a broad singlet at 6.0 ppm, indicative of the α proton of an enone.



3-17 **3-50**

Scheme 3.8. *Robinson Annulation*

With the intention of repeating the sequence as for the previous diazoketone, the enone **3-50** was reduced. Reduction of the enone **3-50** with $NaBH_4/CeCl_37H_2O$ again delivered the allylic alcohol **3-51** in an excellent yield of 99% (**Scheme 3.9**). The nature of the stereochemistry was evident from the couplings of the allylic proton.

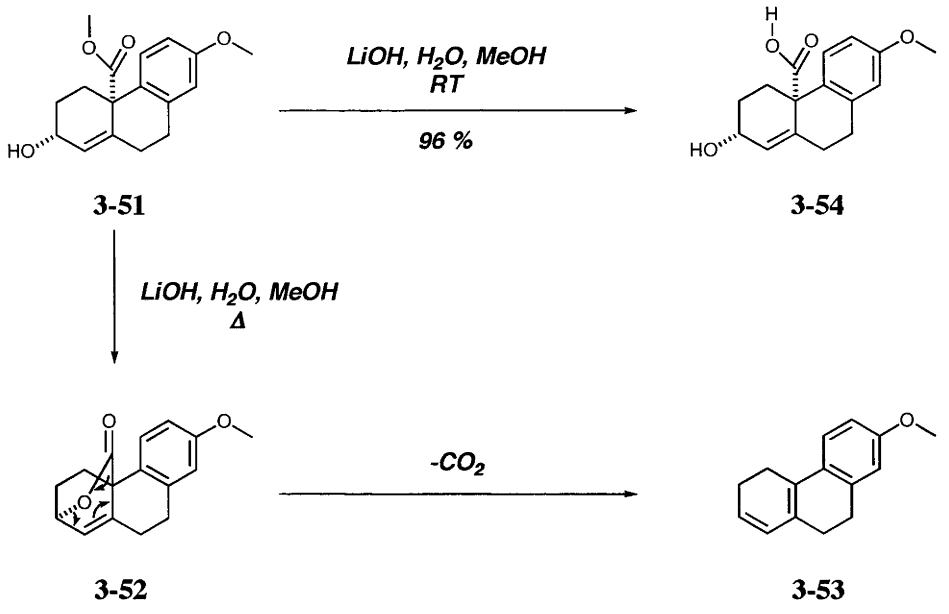


3-50 **3-51**

Scheme 3.9. *Reduction of Enone* ***3-50***

Hoping to form the lactone **3-52**, the allylic alcohol **3-51** was treated with base, but no lactonised products formed. An attempt to drive lactone formation by heating the allylic alcohol **3-51** in aqueous lithium hydroxide in methanol at reflux formed the diene **3-53**, presumably *via* the expulsion of CO_2 from lactone **3-52** (**Scheme 3.10**).

The differences in reactivity towards lactone formation between the two allylic alcohols **3-31** and **3-51** is unclear, but a possible explanation can be derived from the degree of eclipsing that occurs between the hydroxyl and the alkene substituent (**Figure 3.16**). Hence, the allylic methyl group of **3-31** has severe eclipsing interactions, which are relieved by lactone formation.



Scheme 3.10. *Saponification of the Ester*

Despite the failure of the lactonisation, the original intention of this reaction had been to saponify the ester. Employing a little patience and milder base conditions resulted in the slow saponification of the ester to give the acid **3-54** in 96% yield (**Scheme 3.10**).

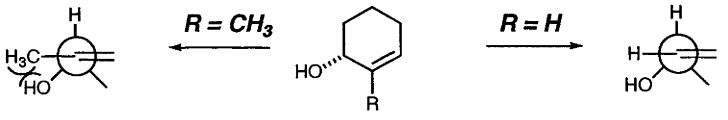
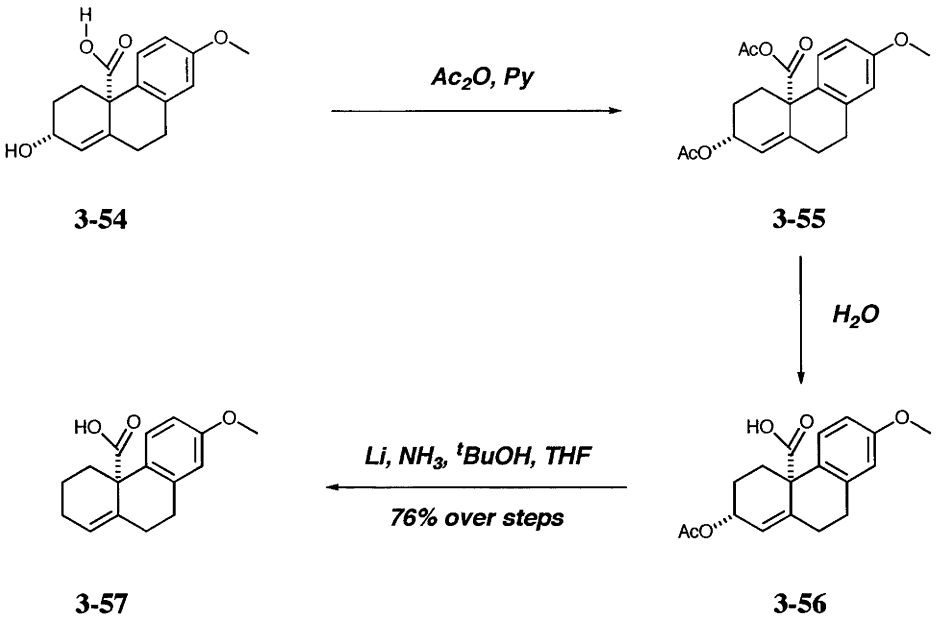


Figure 3.16. *Eclipsing Interactions*

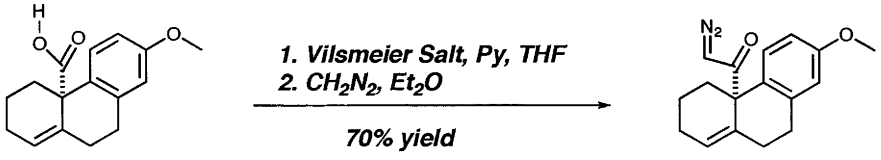
As the alcohol **3-54** had not lactonised, it was thought that it could be activated for deoxygenation by protection as the acetate. Treatment of the alcohol **3-54** with acetic anhydride and pyridine gave quite a number of products by TLC, presumably derived from mixed anhydride products **3-55**. However, stirring with water for 30 mins before work up cleanly delivered the allylic acetate **3-56** as the sole product. The characteristic chemical shift of the acetate function at 2.03 ppm in the ^{1}H NMR spectrum was accompanied by a downfield shift of the allylic alkoxy methine at 5.32 ppm. Gratefully, the reduction of the allylic acetate **3-56** with lithium in liquid ammonia gave the alkene **3-57** in a 76% yield from **3-54** (**Scheme 3.11**). The yield is somewhat lower than the previous example as some of the acetate was hydrolysed during the reduction, but the alcohol **3-54** could be recovered. Again, characterisation was based on the expulsion of CO_2H on mass spectrum, as well as IR and ^{1}H NMR spectra indicating the acetate had been removed. The mechanism for the reduction is analogous to that described earlier, except that in this instance acetate ion is expelled.



3-54 3-55 3-56 3-57

Scheme 3.11. Synthesis of the Acid 3-57

With the acid **3-57** in hand, it was possible to start the synthesis of the diazoketone. Hence, employing the same condition developed earlier, the acid **3-57** was treated with Vilsmeier's salt, which cleanly formed the acid chloride. The acid chloride was then cannulated into ethereal diazomethane to give the diazoketone **3-58** in 70% yield (**Scheme 3.12**). The ^1H NMR spectrum clearly showed the diazomethine at 5.4 ppm, as well as the alkene proton at 5.8 ppm. The IR spectrum showed a strong peak at 2102 cm^{-1} of the diazostretch.

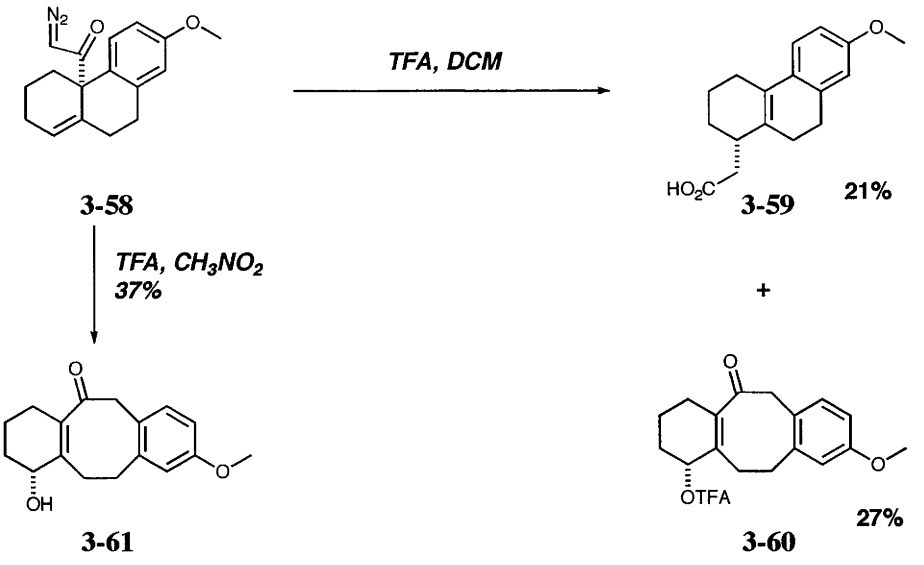


3-57 3-58

Scheme 3.12. Formation of Diazoketone 3-58

3.7.3 Cyclisation of α-Diazoketone 3-58

With the diazoketone **3-58** in hand, exploration of the cyclisation could begin. Treatment of diazoketone **3-58** with $BF_3{\cdot}Et_3O$ in DCM gave an inseparable mixture of products, but the ^1H NMR spectrum indicated that no olefinic products were present. However, TFA in DCM gave the acid **3-59** and the cyclooctane **3-60** in roughly a 1:1 ratio. Similarly, employing $BF_3{\cdot}Et_3O$ in nitromethane gave no identifiable products, but TFA in nitromethane delivered the alcohol **3-61** as the sole product (**Scheme 3.13**). As observed earlier, the alcohol group presumably arises through capture of the cation with nitromethane and subsequent hydrolysis.



Scheme 3.13. *Diazoketone Cyclisations of the Trisubstituted Alkene* ***3-58***

The cyclooctanes **3-60** and **3-61** were difficult to characterise by NMR spectra, but the structures were eventually solved by X-ray crystal structure of **3-61** (**Figure 3.17**). The structure of acid **3-59** was similarly difficult to solve, but the strong ion at 226 in the mass spectrum, which pertained to the loss off 59 ($-CH_2CO_2H$) from the molecular ion, was indicative.

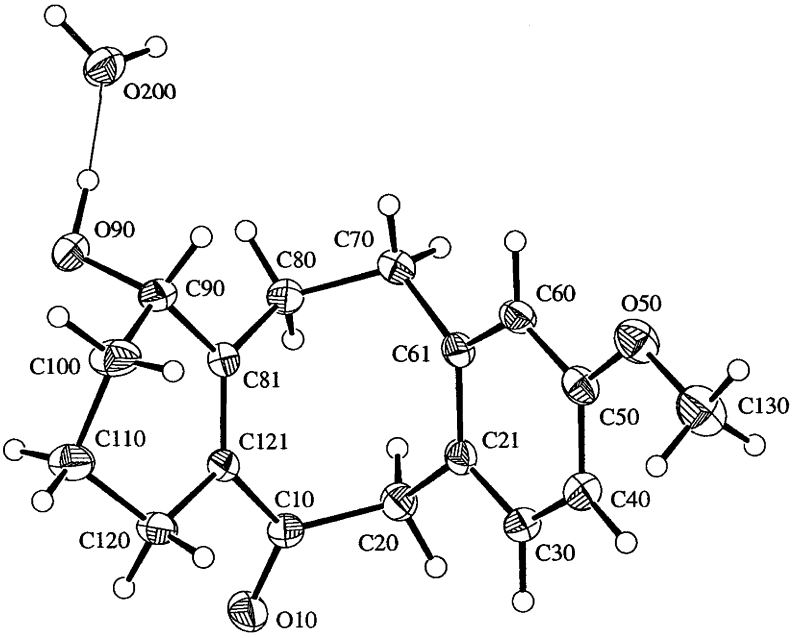
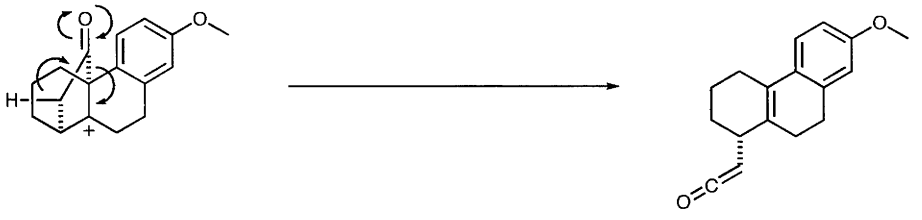


Figure 3.17. *X-Ray Crystal Structure of Cyclooctanone* ***3-61***

The acid **3-59** presumably forms through the formation of the cyclopentanone intermediate **3-62**. However, instead of the elimination of a proton to give the desired B-ring alkene, an alternate pathway occurs through fragmentation of the C10-C20 bond to give the ketene intermediate **3-63**. The ketene is then presumably captured by TFA and the resulting anhydride is subsequently hydrolysed on work up to give the acid **3-59**. This process has

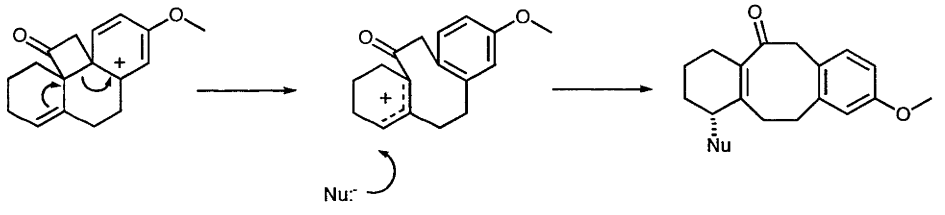
precedents and has been likened to the equivalent of a vinylogous Wolff rearrangement (**Figure 3.18**).[10]



3-62 **3-63**

Figure 3.18. *Formation of Acid* ***3-59*** *via Ketene* ***3-63***

The formation of the octanone **3-60** and **3-61** presumably arises from the ring expansion of the intermediate **3-64**, which is derived from a Ar_1-4 cyclisation with the aromatic ring (**Figure 3.19**). In previous studies on similar substrates (*vide infra*), this process is usually followed by one or more alkyl shifts, but in this instance, the positive charge developing adjacent the carbonyl group can be delocalised (**3-65**) by the double bond during fragmentation of the cyclobutanone ring. This pathway then becomes more favoured over the alkyl shifts that lead to less strained cyclopentanone moieties.



3-64 **3-65** **3-66**

Figure 3.19. *Reaction Pathway for the Formation of* ***3-66***

The derivation of the structures **3-60** and **3-61** led us to re-examine the two minor products of the cyclisation of diazoketone **3-14**, which were initially thought to be cyclobutanones **3-42** and **3-43** (**Scheme 3.7**). From the ^1H NMR spectrum we were able to deduce the structures of products to be **3-67** and **3-68** (**Figure 3.20**).

3-67 **3-68**

Figure 3.20. *Reassignment of* ***3-42*** *and* ***3-43***

3.8 Conclusion

In light of the above results it would appear that the assumption that 5-membered cyclisation would be preferred for both diazoketones **3-14** and **3-58** was correct, but that in the former case the outcome was a 1,2-alkyl shift resulting in enone **3-40**, while the latter resulted in a fragmenation to give acid **3-59**. Furthermore, the formation of **3-59** demonstrates that the 1,2-alkyl shift pathway in the cyclisation of **3-58** was deactivated by removing the olefinic methyl. However, this deactivation also increased competition of the Ar_1-4 cyclisation pathway as a result of reducing the nucleophilicity of the olefinic bond.

It is of interest that in both cases of olefinic cyclisation, the outcomes, a 1,2-alkyl shift to give enone **3-40** and fragmentation to acid **3-59**, were preferred over the elimination of a proton to give the B-ring alkene.

Finally, the formation of the octanones **3-60** and **3-61** inadvertently provides evidence for the mechanism of the reactions of diazoketone **3-69** to form **3-71** and **3-73**. In the case of the cyclisation of **3-69** the major product is **3-73**, which is thought to arise due to greater stabilisation of the intermediate cation **3-72** over that of **3-70** (**Figure 3.21**).[1] However, it is difficult to quantify this assumption as the intermediates cannot not isolated. In the case of the cyclisation of **3-58**, however, the initial intermediate is clearly **3-64** as is it captured indirectly through addition of a nucleophile followed by fragmentation to give the octalones **3-60** and **3-61**. This result by inference suggests that the initial intermediate in the olefinic cyclisation is the cyclobutanone, which rapidly rearranges to the corresponding cyclopentanone cation.

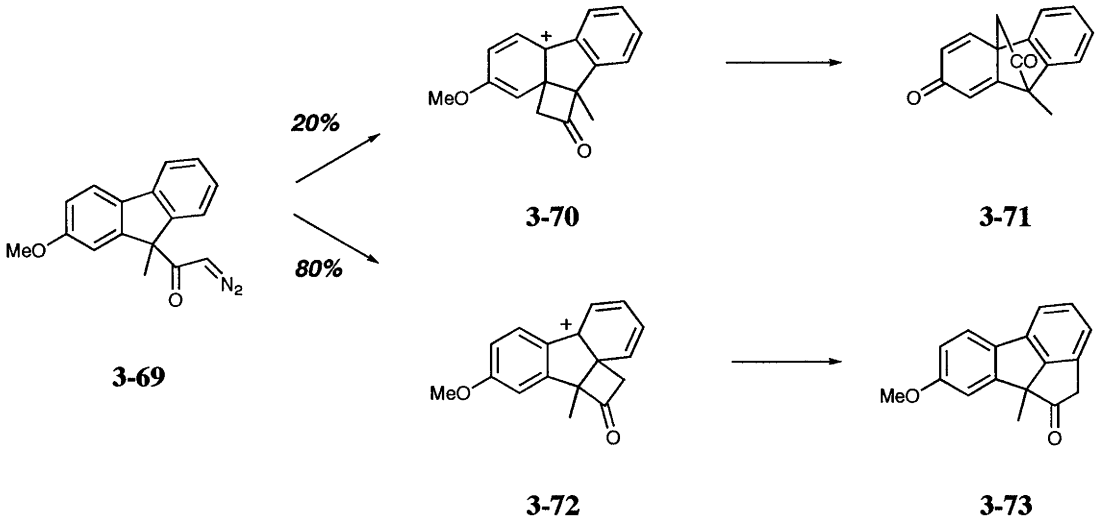


Figure 3.21. *Initial Ar_1-4 Cyclisation Pathways*

Even though the compounds **3-67** and **3-68** (**Figure 3.20**) were prone to rapid decomposition and were difficult to isolate, the crude ^1H NMR spectrum indicated that they represented a major proportion of the products. In light of this, it becomes clear that in both examples aromatic participation was a major reaction pathway that occurred at a similar rate to reaction with the olefin; although this pathway becomes more prominent in the case of the

trisubstituted example. Although the cyclopentanone **3-15** could be obtained the low yield was unsatisfactory and therefore alternative pathways to advanced intermediate were devised.

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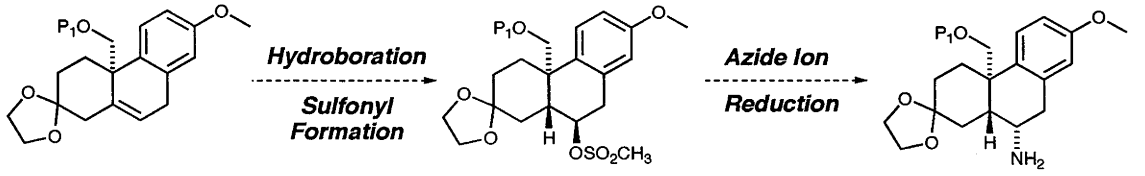
Chapter Four

Formation of the N-C6 Bond for Early Entry to the Hetisane Skeleton

4.1 Introduction

Despite the unprecedented outcome of the α-diazoketone cyclisations, it was thought that the general strategy of installing the C6 nitrogen *via* displacement of a suitably positioned sulfonyloxyl derivative with azide ion provided sufficient scope to warrant further investigation.

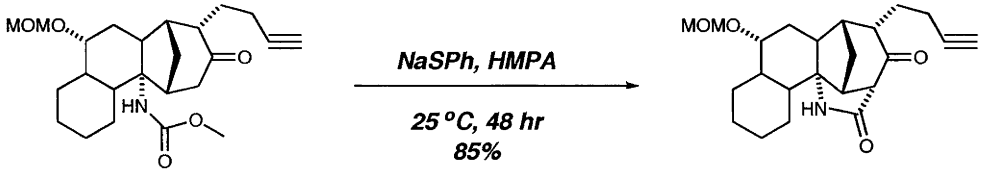
Similar to the strategy outlined in **Chapter 3.1** (**Figure 3.6**), it was conceived that the desired β-hydroxy function could be installed by the hydroboration of the alkene function of the ketal **4-1**. It is well established that the ketalisation of the α,β unsaturated ketones, where the β-carbon is at the junction of a decalin system, can induce isomerisation of the double bond.[1] The hydroboration of the alkene **4-1** could reasonably be expected to deliver the borane to the β-face, *anti* to the angular function on the α-face. The alcohol function could then be converted to a sulfonyloxy derivate **4-2** and subsequently displaced with azide[2] which, on reduction, would give access to the amine **4-3** (**Figure 4.1**).



4-1 **4-2** **4-3**

Figure 4.1. *Displacement of a β-Sulfonyl Derivative with Azide Ion*

Our interest in this strategy was prompted by the observation of O'Connor and Mander during the synthesis of the *himandrine* skeleton, whereby treatment of the carbamate function of **4-4** with base led to the lactam **4-5** in excellent yield (**Figure 4.1**).[3, 4]



4-4 **4-5**

Figure 4.2. *Carbamic Dieckmann-Type Cyclisation*

It was conceived that if an amine like **4-3** could be accessed, then treatment of the corresponding carbamate **4-6** with base would deliver the lactam **4-7** (**Figure 4.3**), which could be elaborated to converge with the intermediate **3-2** (**Figure 3.2**), and thus the end game strategy.

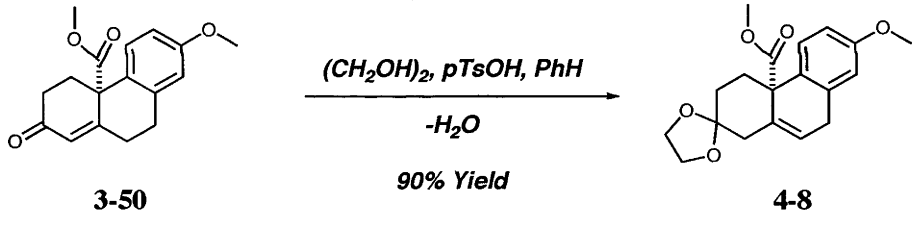
4-6 **4-7**

Figure 4.3. *Intramolecular Carbamic-Dieckmann Cyclisation Strategy*

4.2 Hydroboration of Δ^5 Derivatives

4.2.1 Synthesis of the Ester Δ^5 Ketal 4-8

With enone **3-50** already in hand, ketalisation was undertaken. Treatment of the enone **3-50** with ethylene glycol in benzene at reflux, with a catalytic amount of *p*-TsOH, under Dean-Stark conditions, gave the ketal **4-8** in 90% yield (**Scheme 4.1**).

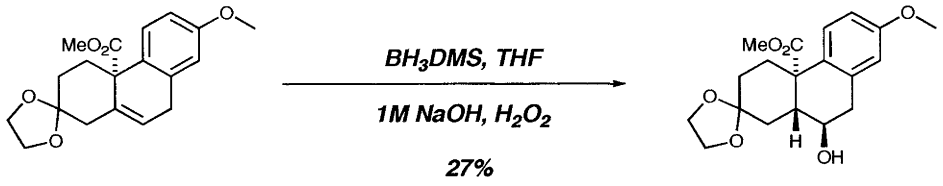


3-50 **4-8**

Scheme 4.1 *Formation of the Acetal* ***4-8***

The isomerisation of the alkene into the B-ring was evident by analysis of a 2D NMR COSY spectrum that indicated coupling of the alkene proton (5.82 ppm) to the benzylic methylene (3.48 ppm) and the appearance of a broad singlet at 2.40 ppm from the two hydrogens at C4.

Although ultimately it was thought an azide function might react with the an angular ester group it was considered worthwhile to attempt a hydroboration on the ester **4-8**. Accordingly, the alkene **4-8** was treated with BH_3DMS for 24 hrs, followed by NaOH and H_2O_2, to give the desired *trans*-fused compound **4-9**, but as an inseparable mixture with a minor product in approximately 27% yield (**Scheme 4.2**). The formation of the β-alcohol function was evident from the large diaxial coupling (J = 8.3 Hz) between the hydroxy methine (4.62 ppm) and the axial benzylic proton (2.68 ppm).



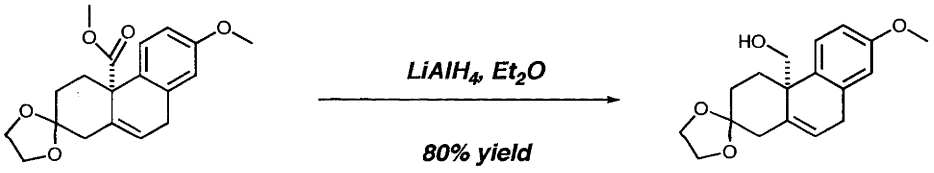
4-8 **4-9**

Scheme 4.2. *Hydorboration of the Ester Alkene* ***4-8***

Encouraged by the isolation of the desired product, it was postulated that the low yield could be attributed to the slow reduction of the ester group, which prompted us to continue our investigation on a corresponding protected hydroxymethyl derivative.

4.2.2 Synthesis of the Protected Hydroxy Methylene Δ^5 Ketal 4-11

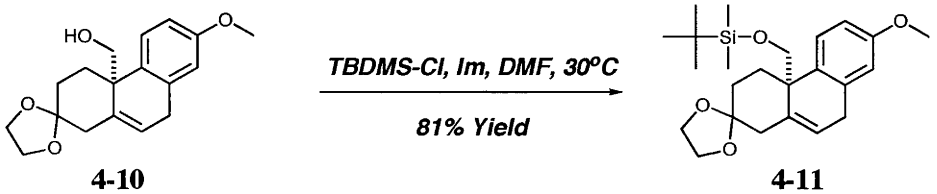
Treatment of ester **4-8** with $LiAlH_4$ in diethyl ether at 0 ^{0}C, and then stirring at RT for 1 hr, delivered the alcohol **4-10** in 80% yield (**Scheme 4.3**). The indicative O-H stretch at 3468 cm^{-1} in the IR spectrum and the assignment of a peak at 67 ppm, in the ^{13}C NMR spectrum, to the hydroxy methylene confirming the identity of alcohol **4-10**.



4-8 **4-10**

Scheme 4.3. *Reduction of the Ester Function*

With the angular alcohol **4-10** in hand, protection was next undertaken and the tert-butyl dimethyl silyl derivative provided acceptable protection. Accordingly, the alcohol **4-10** was treated with TBDMS-Cl and imidazole in DMF at 30 ^{0}C to give the corresponding silyl enol ether **4-11** (**Scheme 4.4**).[1]

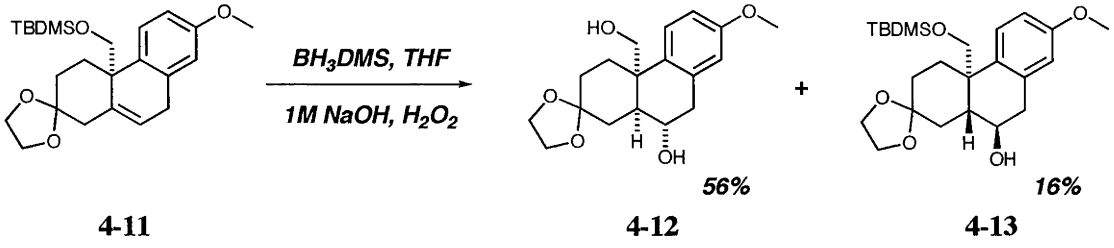


4-10 **4-11**

Scheme 4.4. *Protection of the Alcohol Function*

Hydroboration of the acetal **4-11** on treatment with borane dimethyl sulfide for 24 hrs, followed by oxidation with NaOH and H_2O_2 yielded a 4:1 mixture of *cis:trans*-fused decalin **4-12** and **4-13** in a combined 72% yield (**Scheme 4.5**). In addition, the silyl protecting group was

absent in the *cis*-fused compound, which was presumably a consequence of the proximity of the borane to the silane.



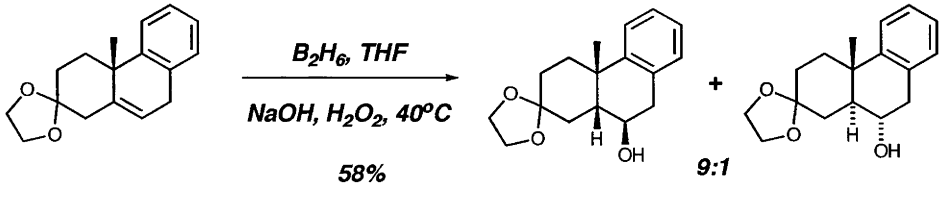
4-11 **4-12** **4-13**

Scheme 4.5. *Hydroboration of Acetal* ***4-11***

The stereochemical assignments were clear from the coupling between the H6 hydroxy methine proton and H7 benzylic protons. Thus, the *trans*-fused **4-13** compound had a large axial-axial coupling $J = 8.9$ Hz, and a smaller axial-equatorial coupling $J = 6.7$ Hz. In contrast, the cis-fused compound **4-12** had a equatorial-equatorial coupling of 6.3 Hz and an equatorial-axial coupling of 2.2 Hz.

The reason for the stereochemical outcome is unclear. It had been hoped that the steric restraint imposed by the angular silyl ether function would favour delivery to the upper face. It is unlikely that the borane was *directed* to the lower face as prior co-ordination to the oxygen lone-pair would deactivate the borane. It is more plausible that the upper face is hindered as a consequence of the concave conformation that the molecule must adopt in order to minimise interactions between the angular function and the acetal.

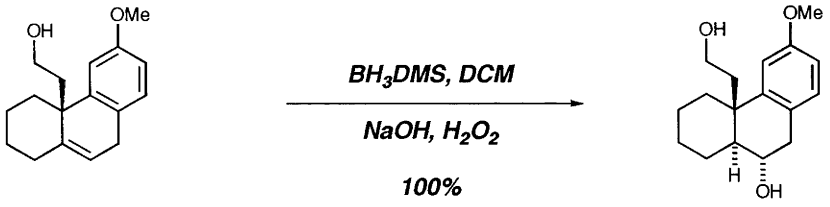
There is a clear difference in selectively between compounds that have an A-ring acetal and those that do not. For example, the hydroboration of the analogous angular methyl compound **4-14** affords mainly the *cis* compound **4-15**.[5]



4-14 **4-15**

Figure 4.4. *Analogous Hydroboration of an A-Ring Acetal*

In contrast, hydroboration of the compound **4-16**, which lacks the A-ring acetal, proceeds with excellent *trans* selectivity to give the alcohol **4-17** (**Figure 4.5**).[6]



4-16 **4-17**

Figure 4.5. *Hydroboration without a A-Ring Acetal*

The above results would suggest that the low yield of the *trans*-fused alcohol **4-9** (**Scheme 4.2**) could, in some part, be attributed to preference for the formation of *cis*-fused products in those compounds with an A-ring decalin.

4.3 Displacement of β-alcohol 4-13 with Azide Ion

Despite the low stereoselectivity, a quantity of the desired *trans*-fused decalin **4-13** was obtained, which provided an opportunity to test the installation of an azide group. A number of methods have been reported in the literature for such transformations, including the displacement of a sulfonyl derivative and the Mitsunobu reaction.[2,7] An excellent modification of the Mitsunobu reaction uses carbon tetrabromide as the oxidant and is reported to be the most efficient method for the installation of azide (**Figure 4.6**). [8, 9]

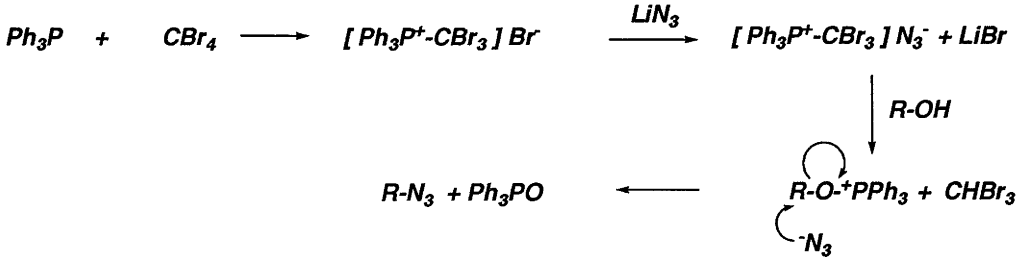
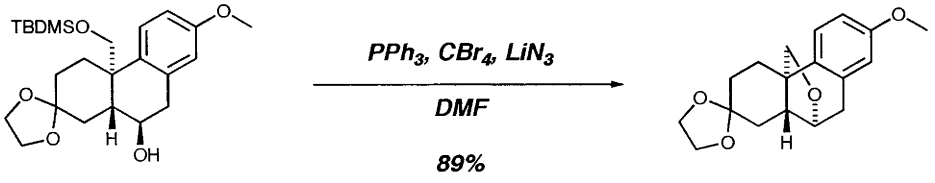


Figure 4.6. *Modified Mitsunobu Reaction*

The alcohol **4-13** was accordingly treated with carbon tetrabromide, triphenyl phosphine and sodium azide in DMF for 24 hrs. Unfortunately, instead of obtaining the desired azide, the cyclic ether **4-18** was obtained in a 71% yield (**Scheme 4.6**). This cyclisation was evident from the ^{1}H NMR spectrum, which showed a broad singlet resonance at 4.24 ppm attributed to the equatorial methine of the cyclic ether. A COSY 2D NMR spectrum confirmed that this proton was coupled to the benzylic protons, which afforded a resonance at 3.01 ppm.



4-13 **4-18**

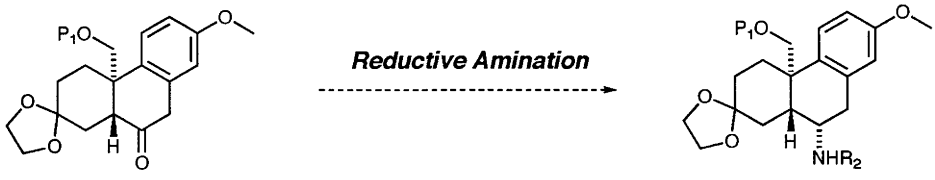
Scheme 4.6. *Attempted Azide Formation*

The high yield of **4-18** suggests that cyclisation is a relatively facile reaction. The bromide ion could be responsible for cleaving the silyl ether, but the steric environment would ensure that this would be a slow reaction. Therefore, the cyclisation most likely occurs as a consequence of the silyl ethers' proximity to the activated hydroxyl through a concerted mechanism, which would also account for the lack of any α-azide compounds.

4.4 Alternate Strategy for the Installation of the C6 α-Amino Function

4.4.1 Introduction

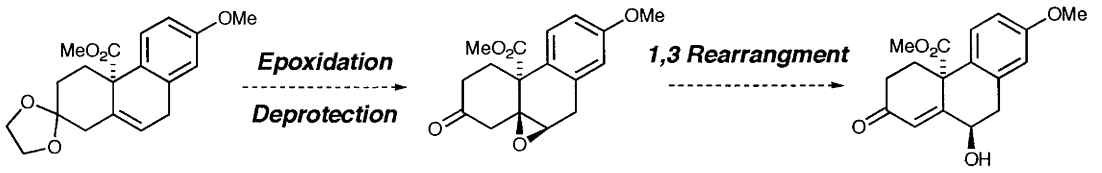
The undesired stereoselectivity of the hydroboration and the equally disappointing formation of the cyclic ether **4-18** compelled us to consider an alternative strategy for installing an α-amino function at C6. It was conceived that the reductive amination of the C6 oxo function of a compound like **4-19** could deliver the desired amine **4-3** (**Figure 4.7**). It was rationalised that the nature of a reductive amination would reduce the competitive S_N2 pathways that led to the formation of the cyclic ether **4-18**. In addition, targeting **4-19** would provide an opportunity to find a more selective method of introducing oxygen at the C6 position.



4-19 **4-3**

Figure 4.7. *Reductive Amination of the C6 Ketone*

An alternative method for oxidising the Δ^5 function of the acetal derivatives would be to carry out an epoxidation on ketal **4-8**. Deprotection of the ketal would then give ketone **4-20**, which would be poised to undergo a 1,3-rearrangement to give the γ-hydroxy enone **4-21** that could then be elaborated to the desired 6-oxo function (**Figure 4.8**).

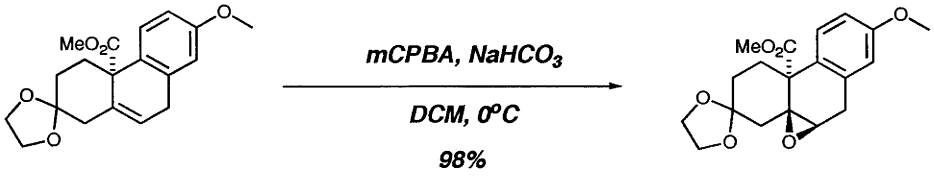


4-8 **4-20** **4-21**

Figure 4.8. 1,3-Rearrangement Strategy for γ-Hydroxy Enone Formation

4.4.2 Synthesis of γ-Hydroxy Enone 4-23

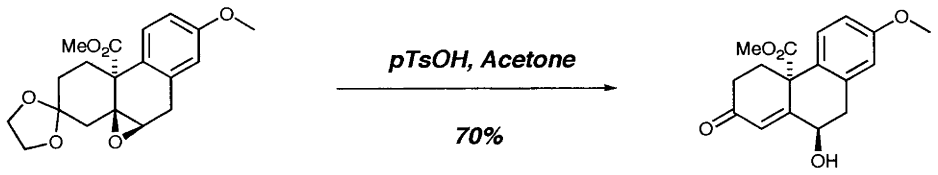
The ketal **4-8** was chosen to test this strategy and was treated with *m*-CPBA to give the epoxide **4-22** in 98% yield(**Scheme 4.7**). The epoxide was characterised by the ^{1}H NMR spectrum, which showed the benzylic methylene protons at 3.16 ppm as a doublet of doublets (J = 2.6 Hz, J = 17 Hz), and at 3.31 ppm as a broad doublet (J = 17 Hz). The former resonance was coupled to a doublet at 3.29 ppm (J = 2.6 Hz), which was assigned to the C6 proton. The stereochemistry was difficult to determine, but the analysis of simple CS Chem3D Pro™ models showed the epoxide *anti* to the ester had dihedral angles of $\angle\theta = 37^0$ and $\angle\theta = 61^0$ between the H6 proton and the H7β and H7α protons, respectively. Approximating the coupling constants for the dihedral angles pertains to 2-4 Hz for the former, which is consistent with the resonance at 3.16 ppm, and 0-2 Hz for the latter, which is consistent with the broad doublet at 3.31 ppm. Differences in the stereochemical outcome between the hydroboration and epoxidation is unclear, but it is postulated that selectivity of the latter is due to the increased steric bulk of the peracid in conjunction with minor directing effects from the acetal function.



4-8 **4-22**

***Scheme 4.7.** Epoxidation of the Alkene Function*

Removal of the ketal function on treatment of the epoxide **4-22** with catalytic *p*-TsOH in acetone for 24 hrs gave the desired **4-23** in 70% yield (**Scheme 4.8**). The stereochemistry of the hydroxyl was confirmed by the large diaxial coupling of 11.7 Hz between the axial benzylic proton (2.82 ppm) and the axial hydroxy methine proton (5.04 ppm). The γ-methine proton was also coupled to the equatorial benzylic proton (J = 5.9 Hz), as well as the enone methine (J = 1.8 Hz).



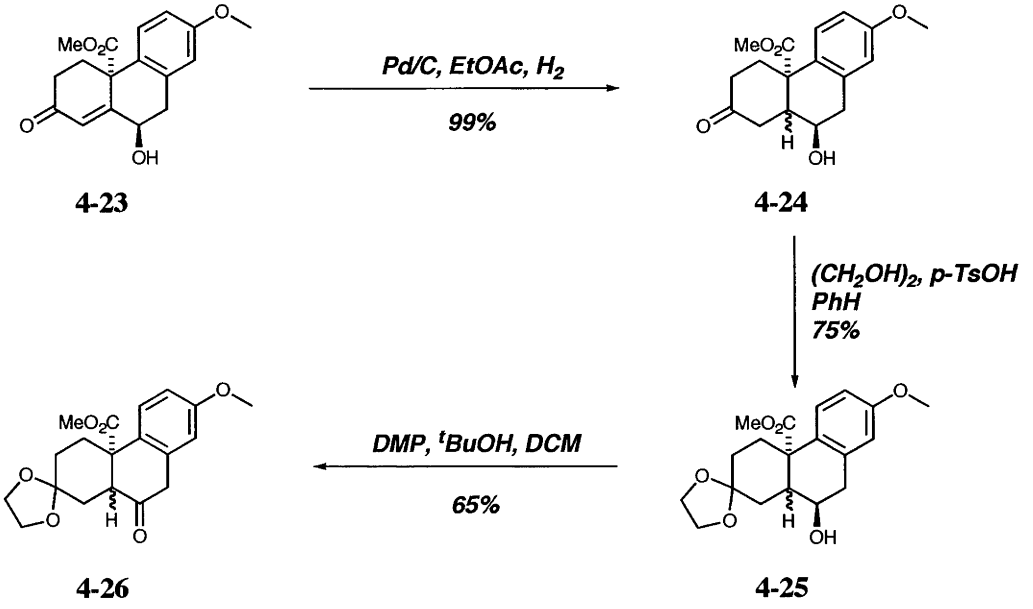
4-22 **4-23**

Scheme 4.8. *Formation of the γ-Hydroxy Enone* ***4-23***

4.4.3 Synthesis of Ketone 4-27

With the desired γ-hydroxy enone **4-23** in hand, elaboration to the C6 oxo function was undertaken. The most direct way to access the desired ketone function is a direct acid-catalysed isomerisation of the γ-hydroxy enone. This type of process has been reported to be of some utility, but was found to be ineffective in the present instance.[10,11] All attempts resulted in either recovered starting material or complex mixtures. The oxidation of the γ-hydroxyl to afford the endione, followed by hydrogenation was investigated, but the oxidation of the benzylic position was too facile to control. Therefore, the most secure route was to hydrogenate the double bond. Following protection of the ketone, the C6 hydroxyl could then be oxidised to the desired ketone.

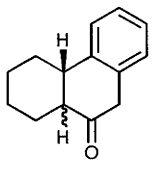
Hydrogenation of γ-hydroxyl **4-23** with Pd/C in AcOEt or PtO_2 in MeOH yielded a 1:1 mixture of *cis*:*trans* fused decalins **4-24** in 99% yield. The lack of stereochemical induction was considered to be of little consequence, as it could presumably be corrected *via* equilibration of the ketone function of **4-26**. Protection of the A-ring ketone was carried out by treatment of **4-24** with ethylene glycol under acid catalysed dehydrating conditions to the yield the ketal **4-25** in 75% yield. Oxidation of the alcohol function of **4-25** was next carried out with Dess-Martin periodane to give the ketone mixture **4-26** in 60% yield (**Scheme 4.9**).



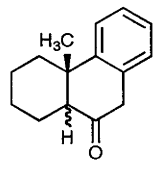
4-23 **4-24** **4-25** **4-26**

Scheme 4.9. *Conversion of the γ-Hydroxy Enone* ***4-23*** *to Ketones* ***4-26***

With the desired functionality in hand, the only remaining task was to equilibrate the ketone to the more stable *trans*-fused decalin. An excellent study has been conducted that analyses the stereochemical equilibrium in a number of benzooctalones[12] and has shown that when the angular substituent at the ring junction is a proton then the equilibrium favours the *trans*-fusion. However, this preference is reversed when the substituent is a methyl group, presumably as a consequence of increased 1,3-diaxial interactions in the *trans*-conformation **(Figure 4.9)**.



trans:cis 61:39

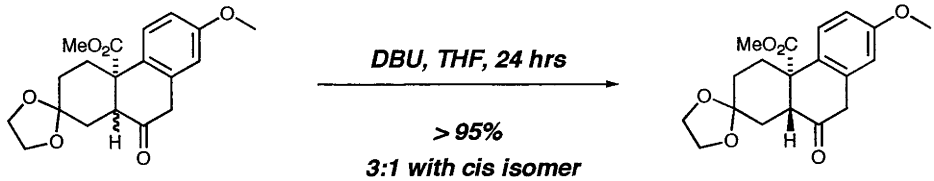


trans:cis 37:63

Figure 4.9. *Differences in Stereochemical Equilibrium*

The above results did not bode well for the equilibration of the ketone **4-26**, but we considered it worthwhile to attempt the equilibration on the premise that if we could obtain an amount of the desired ketone then we could test the viability of the reductive amination.

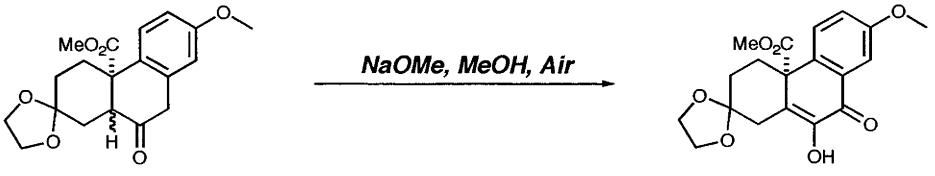
The ketone **4-26** was equilibrated using DBU in degassed THF under an atmosphere of argon to yield a 3:1 mixture of products **(Scheme 4.10)**. With no clear method for determining the stereochemistry, this mixture was assumed to be mainly the *trans*-isomer, and as it could not be separated was used to test the reductive amination approach.



4-26 **4-27**

Scheme 4.10. *Equilibration of the Ketone* ***4-26***

It was necessary to work under an inert atmosphere as the benzylic position was prone to oxidation to disophenol **4-28**.[12] Despite attempts to avoid oxidation, a small amount of the disophenol inevitably formed in this equilibration. Indeed, if the ketones **4-26** were treated with base and exposed to air, then complete conversion to the disophenol **4-28** was observed **(Scheme 4.11)**.

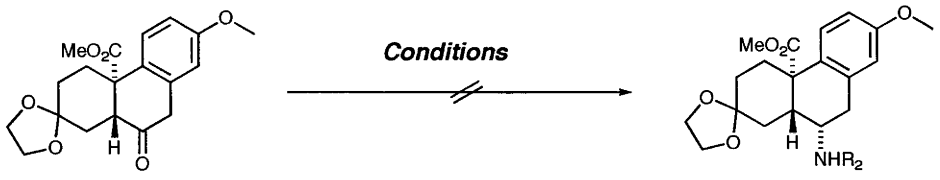


4-26 **4-28**

Scheme 4.11. *Disophenol Formation*

4.5 Attempted Reductive Amination of 4-27

Reductive amination is a well established methodology that has been covered extensively in the literature.[13] However, attempts at carrying out a reductive amination on ketone **4-27** gave none of the desired amine **4-29** (**Table 4.1**). The standard one pot procedure, which involves treating the ketone with ammonium acetate and sodium cyanoborohydride, yielded no amino products. Attempts to drive the imine formation with $Ti(OiPr)_4$ and $TiCl_4$ were also unsuccessful (**Scheme 4.12, Table 4.1**).



4-27 **4-29**

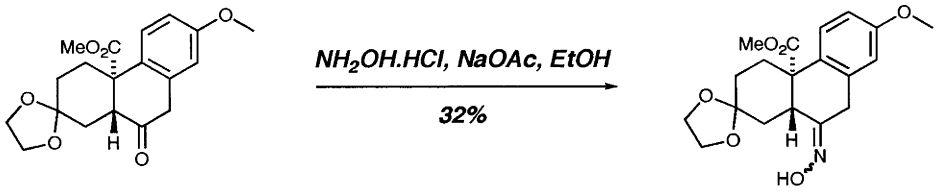
Scheme 4.12. *Attempted Reductive Amination*

Table 4.1. Attempted Reductive Aminations.

Entry	*Conditions*	*Result*
1.	NH_4OAc, $NaBH_3CN$, MeOH, THF	*No Reaction*
2.	NH_2Bn, $Ti(OiPr)_4$, $NaBH_3CN$, DCM	*No Reaction*
3.	NH_2Bn, Et_3N, $TiCl_4$, $NaBH_3CN$, DCM, MeOH	*No Reaction*

4.6 Oxime Formation and Reduction

In light of the above difficulties, it was thought that nitrogen could alternatively be introduced *via* the analogous oxime. Hydroxylamines are known to be more nucleophilic because of the α-hetereoatom.[14] It was hoped that the increased nucleophilicity of the hydroxylamine would overcome the steric barrier that the analogous amines were experiencing. Accordingly, the ketone **4-27** was treated with hydroxylamine hydrochloride and sodium acetate in EtOH at reflux to deliver the an oxime **4-30** in 32% yield (**Scheme 4.13**). The oxime **4-30** was characterised based on the mass spectrum with a strong molecular ion of 361. In addition, the IR spectrum showed a broad OH stretching band at 3410 cm^{-1}, and the ^{13}C NMR spectrum showed a resonance at 159.9 ppm. The remainder of the material was accounted for by a number of unidentifiable products, but which had the characteristics of the disophenol.



4-27 **4-30**

Scheme 4.13. *Oxime Formation*

It was still difficult to determine the stereochemistry, but it was reasoned that the stereochemistry would become obvious upon reduction. Accordingly, attention turned to reducing the oxime **4-30** to the amino function. Several attempts were made in an effort to reduce the amine function with a hydride source, but none were successful. With the exception of $LiAlH_4$, all of the standard reagents known to reduce oximes yielded only starting material **(Table 4.2)**.

Table 4.2. Attempted Hydride Reductions of Oxime 4-30

Entry	*Conditions*	*Result*
1.	$LiAlH_4$, THF, Reflux	*Decomposition*
2.	$ZrCl_4$, $NaBH_4$, THF	*No Reaction*
3.	$TiCl_4$, $NaBH_4$, THF	*No Reaction*
4.	$NaBH_3CN$, MeOH, HCl	*No Reaction*

Treatment of the oxime **4-30** with $LiAlH_4$ in THF at reflux consumed the starting material but yielded a complex mixture of products. This was not surprising as the reduction of homo-allylic oximes has been shown to result in aziridine formation **(Figure 4.10)**. The reaction is thought to proceed through an unsaturated nitrene, leading to the unsaturated aziridine that is then further reduced. Beckmann rearrangement products have also been isolated from related reductions.[15]

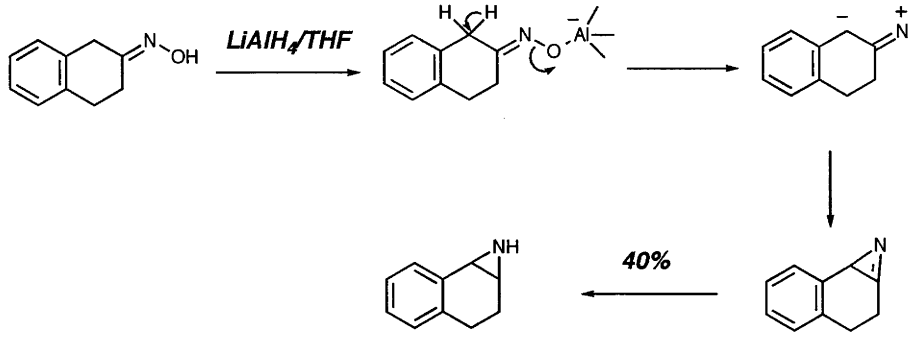
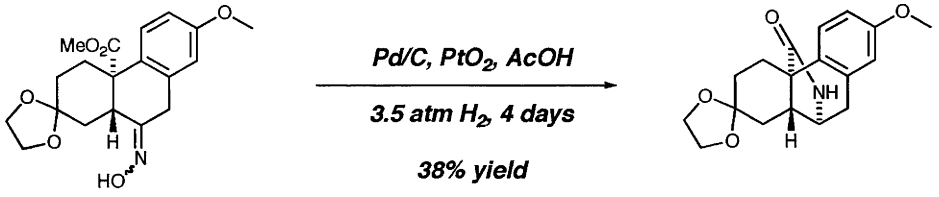


Figure 4.10. *Oxime Reduction with $LiAlH_4$*

It was clear that a hydride reduction was not going to effect the desired reduction. The remaining method for the reduction of oximes was catalytic hydrogenation.[16] Initial attempts to effect such a hydrogenation at atmospheric pressure yielded only starting material. However, treating the oxime **4-30** with Pd/C and PtO_2 in AcOH under 3.4 atmospheres of hydrogen for 4

days indeed delivered the cyclic amide **4-31** in a modest 38% yield (**Scheme 4.14**). The amide was characterised by the ^{1}H NMR spectrum, which showed benzylic hydrogens as a broad pair of AB doublets at 2.86 ppm and 3.06 ppm (J = 17 Hz), the latter had a additional coupling of 3.0 Hz. A broad singlet at 5.87 ppm could be assigned to the amide proton. COSY 2D NMR analysis show the benzylic protons to be coupled to a broad singlet at 3.6 ppm, which was assigned to the H6 amino methine proton. The stereochemistry of the ring junction was assigned *trans* as the H6 proton did not couple to H5. Analysis of a model indicated that the dihedral angle H5-H6 was approximately 90^0.



4-30 **4-31**

Scheme 4.14. *Successful Hydrogenation of Oxime* ***4-30***

Despite the feasibility of the reduction, the above approach clearly has serious pitfalls in terms of obtaining the α-amino function. Presumably, the low yields of the oxidation and oxime formation, which can be attributed to the modest equilibrium position and the predispostion of benzylic position towards oxidation, are unavoidable. In light of these pitfalls this approach was aborted and a new synthetic strategy was developed.

4.7 References

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Chapter Five

Pyrrolidine Ring Formation via 1,6-Amino Addition First Generation Approach

5.1 Introduction

The strategy outlined in **Chapter 3** focused on installing the C4 substituent in an intramolecular fashion followed by the installation the C6 nitrogen function. Unfortunately, the axial C4 substituent could not be introduced effectively as the intramolecular alkylation was followed by a facile rearrangement. Subsequent attempts to install the amine function first, as outlined in **Chapter 4**, were also problematic and as a result a new approach had to be developed. It was conceived that on establishing the quaternary centre at C4 and the N-C19 bond, the N-C6 bond of pyrrolidine **3-3** could be formed by an intramolecular 1,6-amino addition on the dienone **5-3**.[1,2] The dienone **5-3** in turn could be established by oxidation of enone **5-2**, which could be derived from the Birch reduction of the aromatic amine derivative **5-1** (**Figure 5.1**). Upon reaching the pyrrolidine **3-3**, the sequence would converge with the plan described earlier (**Figure 3.1**).

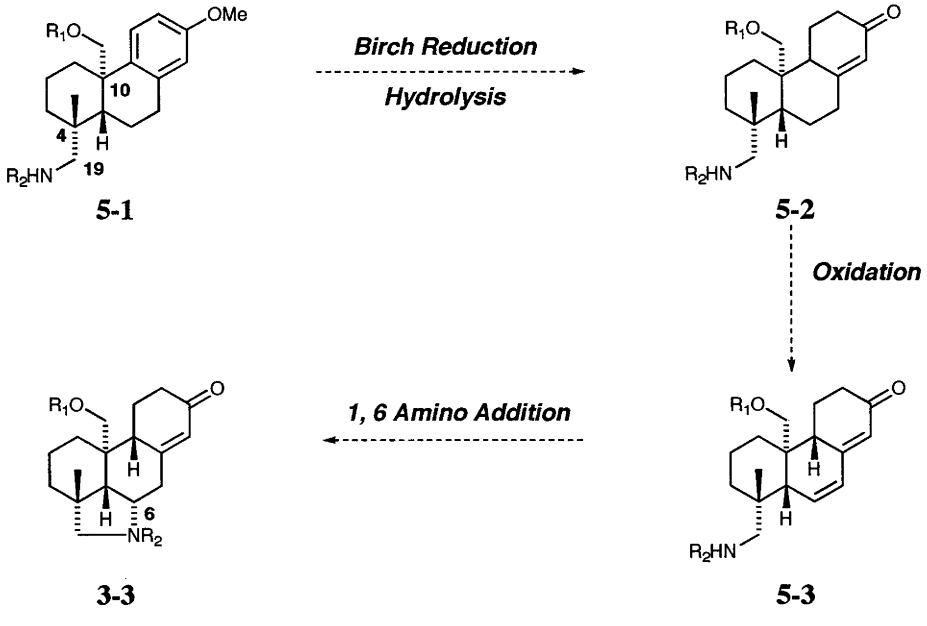


Figure 5.1. *1,6-Addition Strategy for Pyrrolidine Formation*

With this strategy in mind, a viable route to the aromatic amine **5-1** was undertaken. This target posed the challenge of establishing the two quaternary centres at C4 and C10, as well as the required *trans*-fused decalin, with the correct stereochemistry. It was thought that a

dissolving metal reduction of enone **5-4** in liquid ammonia, which could be accessed from the previously synthesised enone **3-50**, would establish the required *trans*-fusion and that the ensuing enolate could be acylated *in situ*. The resulting β-keto ester **5-5** could then be used to construct the quaternary centre at C4 by effecting a diastereoselective alkylation to give the functionalised derivative **5-6** (**Figure 5.2**).

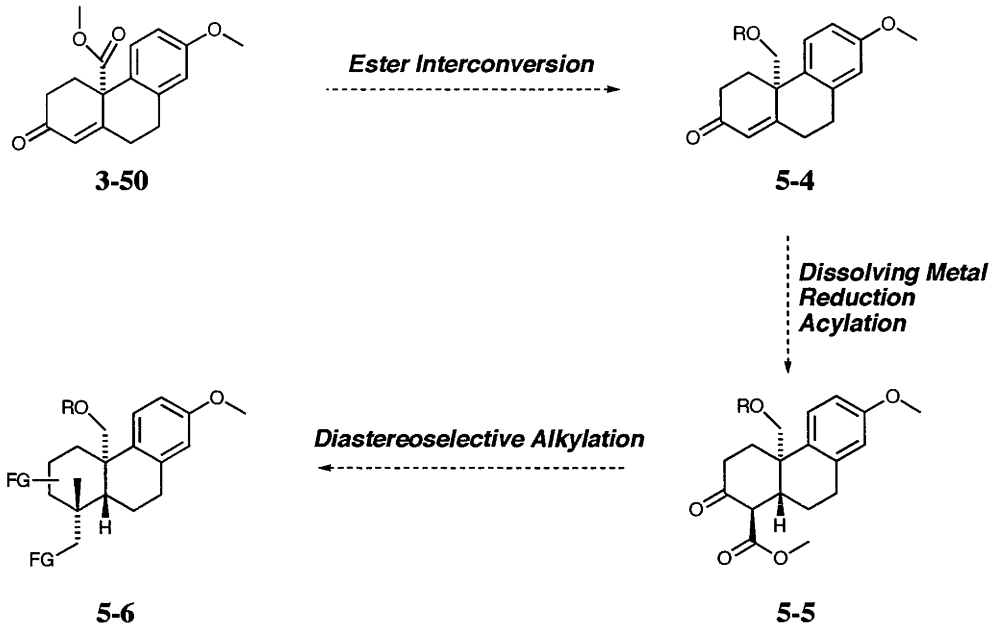
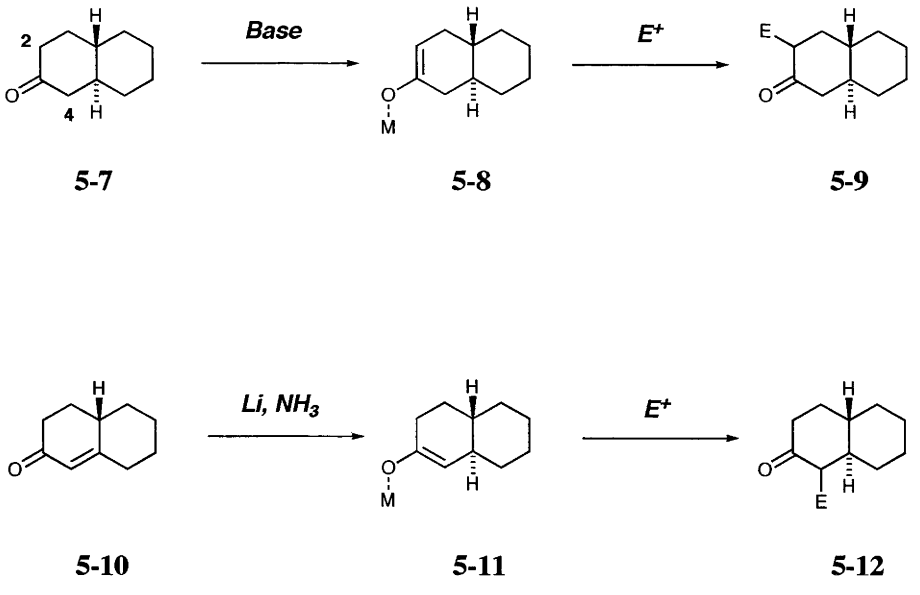


Figure 5.2. *Establishing the Quaternary Centre at C4*

Functionalisation at the C4 position is a longstanding challenge in synthesis due to the steric crowding. Thus, the deprotonation of ketone function **5-7** affords predominantly enolate **5-8**, and as such, acylation/alkylation occurs primarily at C2[†] affording **5-9**.[3] Therefore, in order to achieve activation at C4 it is essential that the enolate **5-11** be generated and trapped from the reduction of enone **5-10**. By its nature, the dissolving metal reduction ensures that the C4 enolate is formed and therefore has the dual propose of establishing the desired ring fusion stereochemistry and controlling the enolate geometry (**Figure 5.3**).[4] It should be noted that the dissolving metal reduction is unique in affording the *trans*-fusion as hydride reagents are known to give predominately the opposite *cis*-fusion.

Finally, the *C*-acylation of enolates has become a viable synthetic method through the development of methyl cyanoformate as an acylating agent.[5,6] Thus, it was intended that the β-keto ester **5-5**, derived from the treatment of the C4 enolate with methyl cyano formate, would be elaborated to the desired quaternary centre by alkylation of the β-keto ester or a derivative. The alkylation would need to deliver the methyl group along the equatorial vector; the resulting axial ester substituent could then be transformed into an amino function.

[†] A numbering system analogous to the diterpene alkaloids has been used for the decalin system.



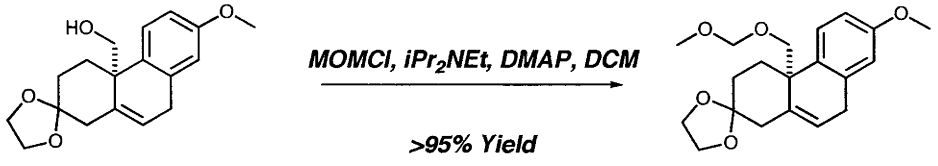
5-7 5-8 5-9

5-10 5-11 5-12

Figure 5.3. *Regiocontrol of Enolates and Stereocontrol of Decalin Fusion*

5.2 Preparation of MOM Ether 5-14

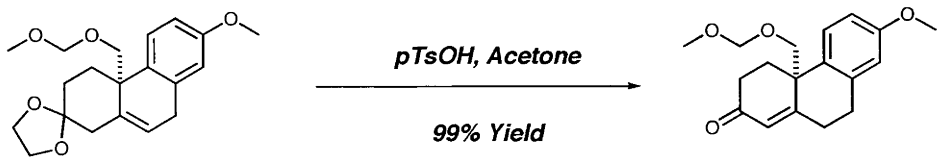
With the alcohol **4-10** already in hand, the selection of a alcohol protecting group was the first task and the MOM group appeared to be a good choice due to its robust nature. In this regard, its resistance to base hydrolysis and reduction, which would be important in the coming dissolving metal reduction, was an attractive characteristic. The alcohol **4-10** was treated with MOM-Cl in dichloromethane in the presence of diisopropylethylamine and a catalytic amount of DMAP to give the desired methoxy methyl ether **5-13** in 80% yield (**Scheme 5.1**).[7] This assignment was clear from the ^{1}H NMR spectrum that displayed the distinctive AB system of the methoxy methylene at 4.48 ppm and 4.51 ppm, the methoxy singlet at 3.22 ppm, and the resolved pair of AB doublets from the hydroxy methylene at 3.80 ppm and 3.83 ppm with a coupling constant of 9.5 Hz.



4-10 5-13

Scheme 5.1. *Protection of Alcohol* ***4-10***

All that now remained, prior to the dissolving metal reduction, was removal of the ketal. To this end, the ketal **5-13** was taken up in acetone and treated with *p*-TsOH, which effected a ketal transfer to deliver the enone **5-14** in 80% yield (**Scheme 5.2**). As expected, the alkene isomerised back into conjugation, this conclusion being evident from the singlet at 6.04 ppm in the ^{1}H NMR spectrum, indicative of an αβ-enone.



5-13 5-14

Scheme 5.2. Deprotection of Ketal ***5-13***

5.3 Dissolving Metal Reduction of Enones

5.3.1 Introduction

The dissolving metal reduction of enones in liquid ammonia is a well-established methodology and it has been demonstrated that when the β-carbon is at the fusion of a decalin ring system such as **5-15**, the *trans*-fused decalin **5-17** is the major product. It is rationalised that this outcome is derived from the relative stability of the transient radical anion **5-16**. The transition state of the radical anion can adopt three different all *chair* conformations **5-18**, **5-19**, and **5-20**. In order for bond formation to occur, the electrophile must meet the *stereoelectronic* requirement of approaching the radical anion from an axial trajectory. Furthermore, the π-system of the enone must fully delocalised, therefore, **5-18** may be disregarded because overlap is not maintained within this substrate. Of the two remaining geometries, the transition state that leads to the *cis*-fused product **5-19** is of higher energy, and is therefore disfavoured, due to butane-gauche interactions. Accordingly, the transition state that leads to the *trans*-fused product **5-20** is favoured (**Figure 5.4**).[4]

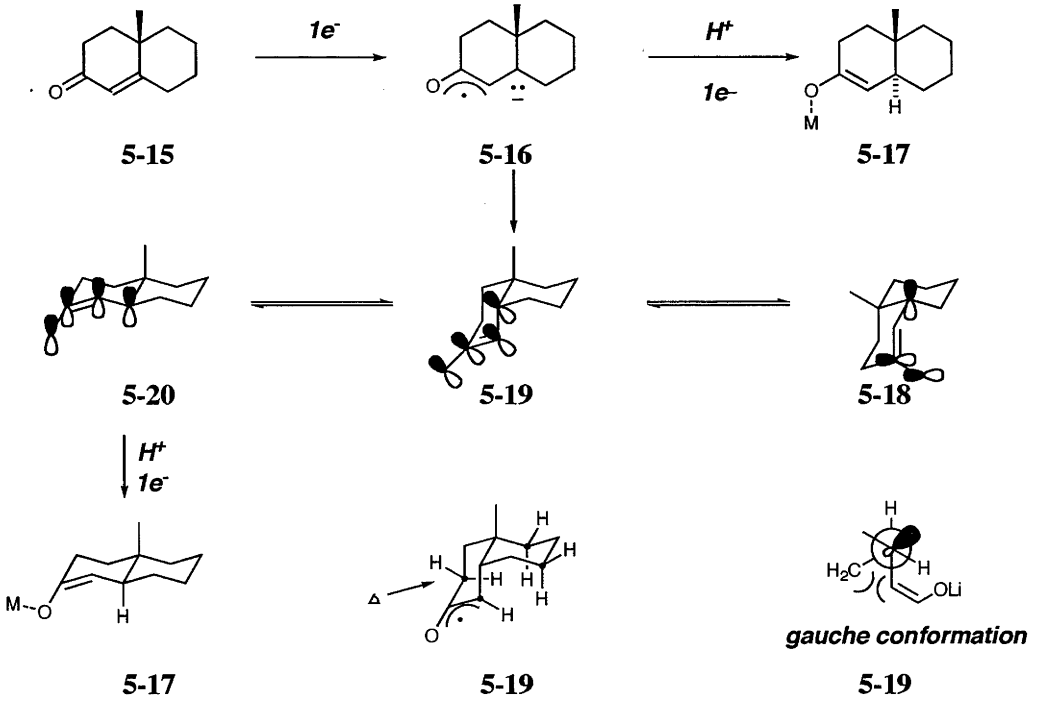


Figure 5.4. *Preference for Trans-Fused Products Based on Transition State Energies*

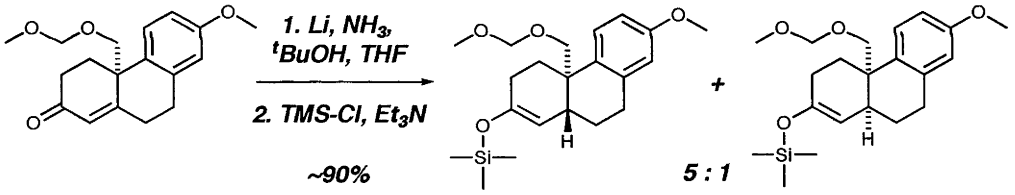
Once the stereochemistry of the β-carbon is set, an additional electron is added to the delocalised radical and an enolate is formed. The enolate can then be used in further synthetic procedures, but it is often important to remove the ammonia first to prevent unwanted side reactions between the ammonia and the electrophile.

5.3.2 Reduction of Enone 5-14

In order to confirm that the desired enolate was being formed, it was thought prudent to trap the enolate as a silyl enol ether first before adding any acylating agents. Thus, the enone **5-14**, in THF and liquid ammonia, was treated with lithium. Following the removal of ammonia, TMS-Cl and Et_3N were added to afford the trimethyl silyl enol ethers **5-21** and **5-22** as an inseparable mixture in a 5:1 ratio (**Scheme 5.3**).

The *cis* and *trans*-fused compounds could be differentiated based on the chemical shift of the β-carbon at the decalin ring fusion in the ^{13}C NMR spectrum. In the *trans*-fused compound **5-21**, this carbon appeared at 38.2 ppm, whereas it was substantially upfield in the *cis*-fused compound **5-22** at 34.4 ppm. This difference presumably arises due to *gauche* interactions between the methine hydrogen and the angular hydroxy methyl.

The *trans*:*cis* ratio is lower than the reduction of analogous enones,[4] but it is conceivable that the axial alkoxymethyl group provides significant steric buttressing, thus reducing the energy difference between the two chair conformations.



Scheme 5.3. *Reduction of Enone* ***5-14***

5.4 Acylation of the C4 Enolate

5.4.1 Introduction

To meet the requirements of our synthetic plan, the electrophile used to quench the enolate would provide a substituent that could be used to effect both a diastereoselective alkylation and ultimately be transformed into an amine function. Towards these ends, it was thought that a β-keto ester would suffice.

The acylation of enolates to give β-keto aldehydes, β-diketones, and β-keto esters can be divided into reversible and irreversible processes. Acylations with formates, oxalates, alkanoates, and carbonates all proceed with the expulsion of alkoxide and are reversible as the alkoxide can attack the product. Thus, the major product is the one with the more stable anion.

In unsymmetrical ketones this typically results in acylation of the less hindered site. Although *O*-acylation may compete kinetically, the reversibility of the reaction leads to the thermodynamically more stable *C*-acylation product.

In contrast, kinetic acylations carried out using acyl halides, acyl anhydrides or cyano formates are irreversible as the expelled anion is not sufficiently basic to attack the products formed. As a result the *O*-acylation product becomes more of an issue. The *O*-acylation/*C*-acylation ratio is dependent on a number of factors including: the metal cation; the solvent; enolate structure; and the electrophile.

Based on experimental evidence, *O*-acylation is favoured with metal enolates that exist as *solvent-separated* ion-pairs, while *C*-acylation is preferred with metal enolates that exist as *tight* ion-pairs (**Figure 5.5**). Hence, alkali metal cations in polar solvents give more *O*-acylated material, while cations, such as Mg^{2+}, in non-polar solvents lead to more *C*-acylated material.

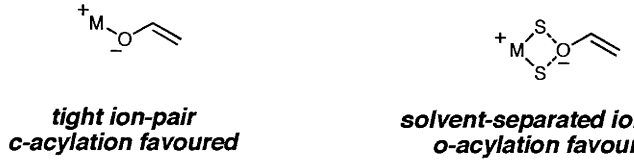


Figure 5.5. *Tight and Solvent-Separated Ion-Pairs*

However, the enolate structure also determines the nature of the ion pairs, as illustrated in **Figure 5.6**. Under the same conditions the *Z*-enolate has a more *solvent-separated* ion-pair character, as a requirement to decrease interaction with the adjacent butyl group, and affords predominately the *O*-acylated product.

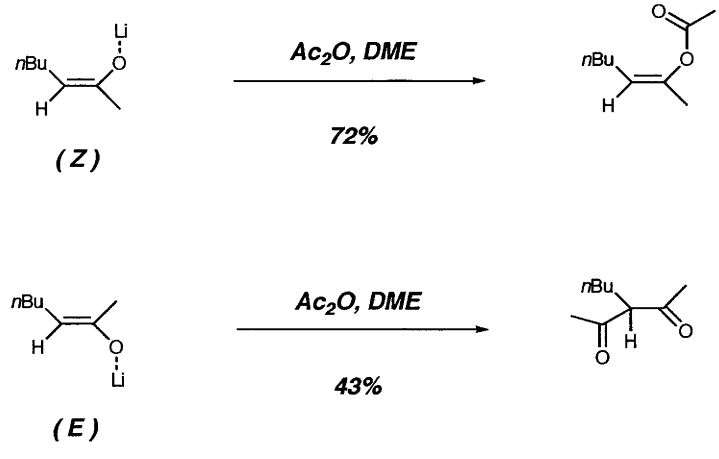


Figure 5.6. *Effect of Enolate Structure of Acylation Outcome*

The degree of shielding that the cation provides to the oxygen is thought to be a major factor for determining the amount of *O*-acylation and *C*-acylation. Hence, a *tight* ion-pair could be expected to shield the oxygen from the electrophile, and the electrophile would have a greater tendency to attack the carbon centre. This argument is strengthened by the observation that the acylation of α-metalated ketones, such as α-mercuricyclohexanone, which can be

thought of as a very *tight* ion-pair on carbon, leads to predominately *O*-acylation. In addition, it has been suggested that the metal could play a role in the transition state, directing the acylating agent to either carbon or oxygen (**Figure 5.7**).[8]

Figure 5.7. *Anion Shielding and Metal Participation*

Despite the influence of the above factors, it is the nature of the electrophile that appears to have the most profound effect. While methyl chloroformate and carbon dioxide have found some utility, their use is not general, and in more hindered instances either the yields obtained are unsatisfactory or significant amounts of *O*-acylated product are formed. In constrast, cyanoformates provide not only excellent yields, but also excellent chemoselectivity towards *C*-acylation. The reason for increased *C*-acylation is thought to revolve around the formation and subsequent collapse of tetrahedral cyano complexes (**Figure 5.8**). The initial reaction between the enolate and the cyano formate is thought to result in the formation of two isomeric tetrahedral cyano complexes; an *O*-complex and a *C*-complex. These complexes are thought to be in equilibrium, and of the two, the C-complex is the more stable due to chelation with the ketone. Therefore, regardless of the nature of the *ion-pair* the *O*-complex rapidly equilibrates in favour of the *C*-complex. Furthermore, the stability of the *C*-complex is such that its collapse to the β-keto ester product is slow and therefore allows all of the enolate to be consumed before proton transfer can occur between the product and the enolate. In a practical sense, the increased stability of the *C*-complex provides access to *C*-acylated products when analysis of the enolate structure would suggest that *C*-acylation would be unfavoured (e.g. in sterically crowded environments c.f. **Figure 5.6**).[9]

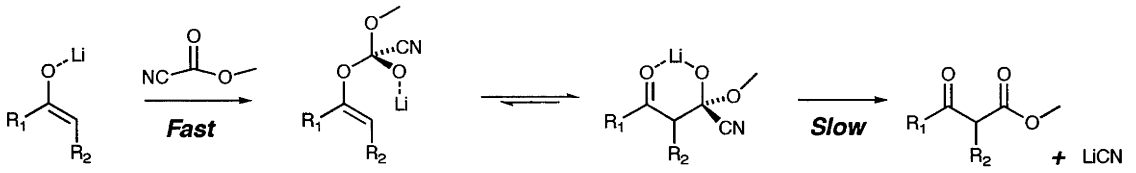
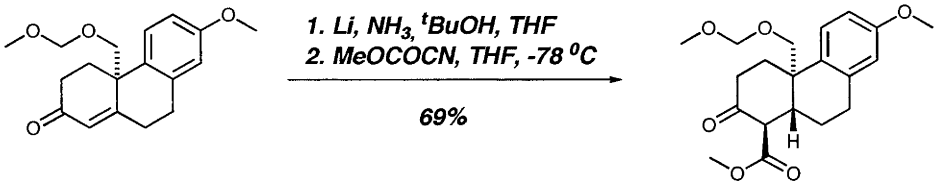


Figure 5.8. *Acylation with Methyl Cyanoformate*

5.4.2 Formation of β-Keto Ester 5-23

Treatment of the enolate, derived either by liberating it from the silyl enol ether **5-21** with methyl lithium, or from the reduction of the enone **5-14** directly, with methyl cyanoformate at –78 °C in either Et_2O or THF delivered the desired β-keto ester **5-23** in 65-75% yield (**Scheme 5.4**). The formation of the β-keto ester was clear from the ^1H NMR spectrum, which showed an additional methoxy peak at 3.74 ppm due to the newly installed ester, as well as a doublet at 3.80 ppm with a coupling constant of 11.0 Hz, pertaining to the α-proton and consistent with a

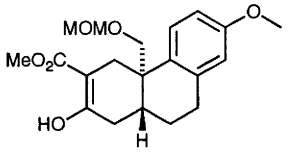
1,2-diaxial coupling to H5. The IR spectrum showed two carbonyl stretching bands at 1744 cm^{-1} and 1711 cm^{-1} corresponding to the ester and the ketone functions.



5-14 **5-23**

Scheme 5.4. *Formation of β-Keto Ester* ***5-23***

However, upon scale up of the reaction only 20% of the desired β-keto ester **5-23** was formed and a significant amount of an enol isomer was isolated in up to 60% yield. Characterisation indicated that this was a β-keto ester in the enol form, and was confirmed by X-ray crystallography, indicating structure **5-24** (**Figure 5.9**). On first inspection, the isolation of the regioisomer **5-24** would suggest that the cyano complex is unstable and can collapse to the β-keto ester **5-23** at a rate comparable to the acylation and therefore proton transfer can occur.



5-24

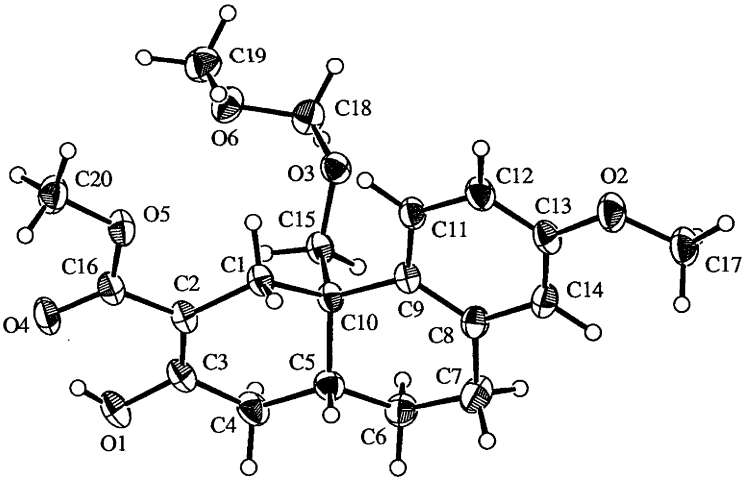


Figure 5.9. *Ortep Diagram of Regioisomer* ***5-24***

Fortunately, further experimentation demonstrated that the reaction was complete after 5 mins at –78 °C, and if quenched at –78 °C, then equilibration could be avoided. The original synthetic procedure[10] allows the reaction to warm to 0 °C for 30 mins before quenching, but employing this regime resulted in equilibration in this instance. The fact that the desired product **5-23** is formed after 5 mins, but that the isomer **5-24** is formed on warming, suggests that the reaction is reversible. This reversibility presumably arises due to the instability of the cyano complex at elevated temperatures, which results in the reverse reaction to give the starting enolate **5-25** in addition to the formation of the desired β-keto ester **5-23**. The equilibration then

occurs as a consequence of proton transfer between the enolate **5-25** and the β-keto ester **5-23**, to give **5-27** and **5-28**, respectively. Given the product ratios favour the regioisomer at higher temperatures, it is assumed that the reverse reaction is favoured under these conditions (**Figure 5.10**).

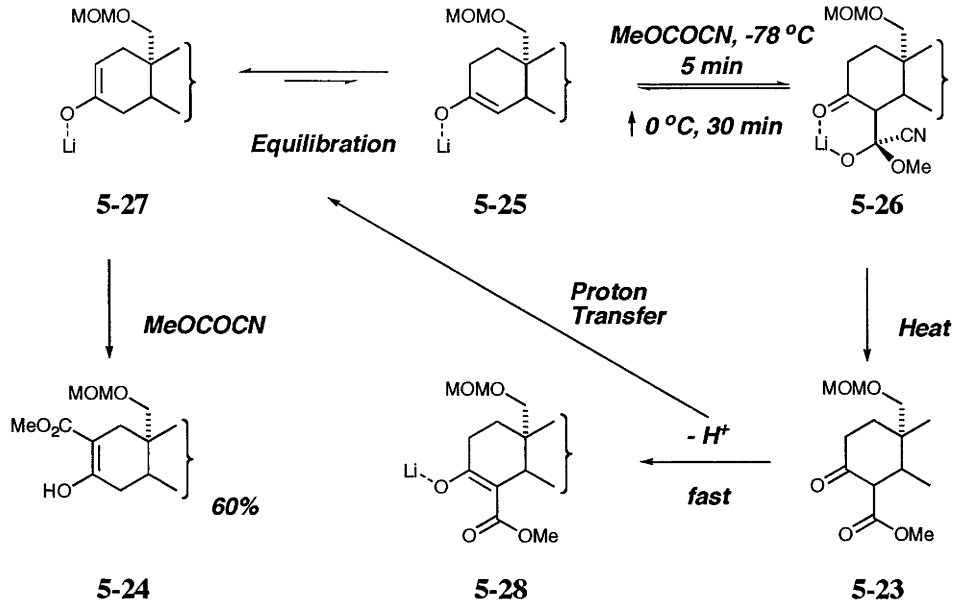


Figure 5.10. *Proton Transfer and Equilibration*

In the event, this rearrangement was of no consequence as it could be avoided by quenching at low temperatures. However, it is does suggest that the stability of the cyano complex is substrate dependent and therefore care must be taken in some cases to avoid equilibration of the enolate.

5.5 Diastereoselective Alkylation of β-Keto Esters

5.5.1 Introduction

The alkylation of β-keto esters is a venerable reaction that has been extensively studied and as such one may predict the diastereoselectivity with reasonable confidence.[11] The stereochemical outcome of an alkylation of an *endo*-cyclic enolate – an enolate within a ring – is governed by a number of factors. The fundamental requirement is that the electrophile must approach the enolate from an *axial*, or perpendicular, trajectory in order to maximise orbital overlap in the transition state. As a consequence, the alkylation of the conformationally locked 4-*tert*-butyl cyclohexanone **5-29** proceeds through two different ring geometries. The pathway that leads to the installation of an *axial* substituent **5-31** proceeds though a chair like transition state **5-30**. However, in order to alkylate along the *equatorial vector*, to deliver the *equatorial* alkyl group product **5-33**, the ring must obtain a twist-boat conformation **5-32** to maintain maximum orbital overlap. It should be noted that although alkylation proceeds through an *axial* transition state, this process is termed *equatorial* alkylation (**Figure 5.11**).

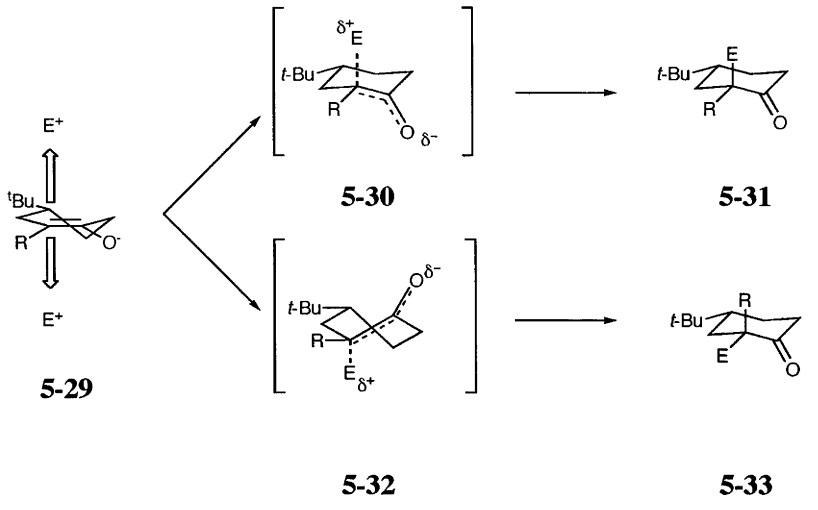


*Figure 5.11. Alkylation of **5-29***

In the above example, where R = H, there is little discrimination observed experimentally between the two pathways and therefore the reaction is considered to be going through an 'early' *substrate-like* transition state. However, when R = alkyl group, the *axial* product is more favoured, which is accounted for by an increase in eclipsing interactions between the methyl group and the *syn* β-hydrogen as the ring adopts the boat conformation.

This trend is similarly observed in the bicyclic system **5-34** (R =H), which gives a 95:5 ratio in favour of the *axial* alkylation product **5-35**. In contrast, **5-34** (R = Me) delivers a 5:95 ratio in favour of the *equatorial* alkylation product **5-36**. This outcome is attributed to the steric restrictions imposed by the angular methyl group on the trajectory of the electrophile along the *axial* vector, which outweighs the eclipsing interactions (**Figure 5.12**).

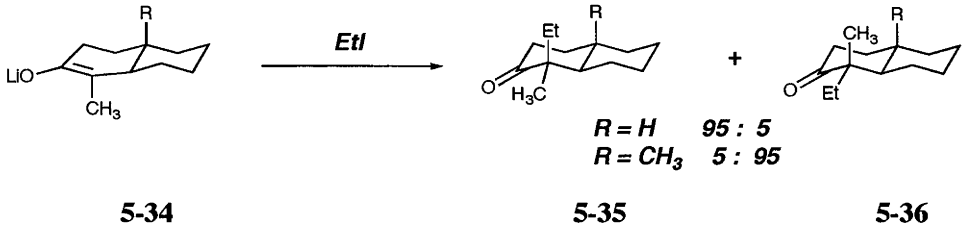
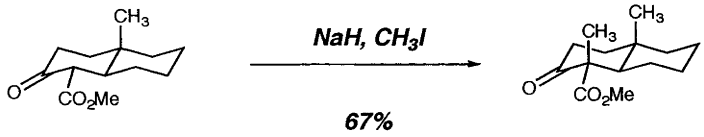


Figure 5.12. Steric Effects on Alkylation Outcome

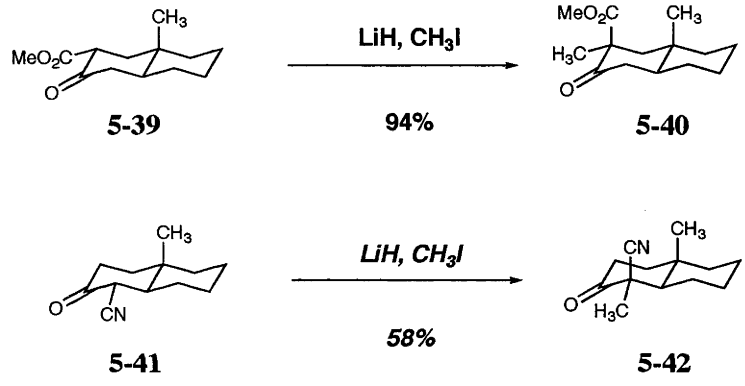
For less reactive enolates such as the β-keto ester **5-37**, where the α-ester function stabilises the enolate, the steric factor is not dominant and the alkylation product is derived from *axial* alkylation to give **5-38**. The less reactive enolate can be considered to proceed through a 'late' *product-like* transition state. Consequently, *equatorial* alkylation is more unfavoured due to eclipsing interactions in the transition state between the ester function and adjacent substituents as the ring adopts the boat conformation (**Figure 5.13**).



5-37 **5-38**

Figure 5.13. *Alkylation of Stabilised Enolates*

However, the alkylation of the regioisomer **5-39** proceeds along the *equatorial vector* to give **5-40** because the eclipsing interactions are relatively less severe and steric factors dominate. Similarly, the alkylation of the β-keto nitrile **5-41**, which could be expected to give a similar outcome to **5-37**, proceeds along the *equatorial vector* to give **5-42**. This result is attributed to the reduced steric bulk of the nitrile group relative to the ester function (**Figure 5.14**).



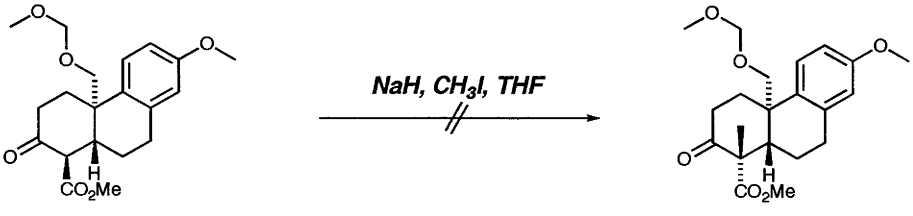
5-39 **5-40**

5-41 **5-42**

Figure 5.14. *Differences in Eclipsing Interactions*

5.5.2 Alkylation of β-Keto Ester 5-23

It was considered that the alkylation of β-keto ester **5-23** would predominantly give the *equatorial* methyl product **5-43**. Although precedent indicates that the alkylation of β-keto ester **5-23** would behave similar to that of **5-37**, and therefore deliver the *axial* product, it was reasonable to investigate this reaction on the basis that the additional steric demand imposed by the protected angular hydroxy methyl would outweigh the eclipsing interactions. In the event, carrying out the alkylation of β-keto ester **5-23** with sodium hydride in THF yielded a number of unidentifiable products (**Scheme 5.5**).



5-23 **5-43**

Scheme 5.5. *Attempted Alkylation of β-keto ester **5-23***

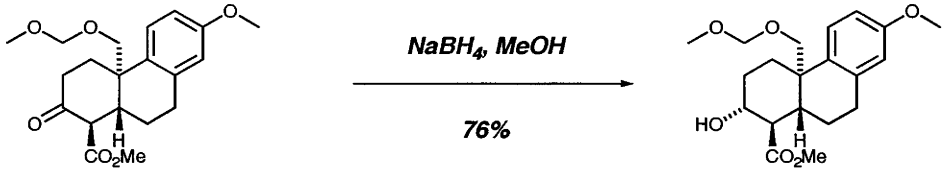
It was concluded that neither *axial* or *equatorial* vectors were acceptable as the steric demand of the former, and the eclipsing interactions of the latter, imposed too high an energy demand on the transition states, thereby rendering the enolate unreactive.

5.6 Revision of synthetic plan

Clearly, the alkylation of the β-keto ester **5-23** was unsatisfactory and an alternate pathway needed to be considered. The obvious course of action was to make a derivative of the β-keto ester in an attempt to procure a more reactive intermediate to deliver the desired stereochemical outcome. To this end, the removal of the ketone group seemed to be the most direct method of accessing such an intermediate. As the hetisine structure has a hydroxyl at C2, it was considered desirable to try to keep a 'handle' within the A-ring that could be elaborated at a later stage to this function. With this requirement in mind, reduction of the ketone, followed by subsequent elimination to the alkene, appeared to be a straight forward approach with which to meet this objective.

5.6.1 Reduction of Ketone 5-23

The β-keto ester **5-23** was treated with sodium borohydride in MeOH to deliver the α-alcohol **5-44** in upwards of 70% yield (**Scheme 5.6**). This stereochemistry was expected based on the plethora of data pertaining to similar reductions. As was discussed in the reduction of enone **3-18** (**Chapter 3.3**), it is well established that small nucleophiles with low steric demand deliver equatorial alcohols due to the torsional effects imposed on the transition state of the addition. The stereochemistry was determined from the ^{1}H NMR spectrum, which displayed a triplet of doublets at 3.80 ppm with two large *axial-axial* couplings of 10.8 Hz and a smaller *axial-equatorial* coupling of 4.4 Hz.

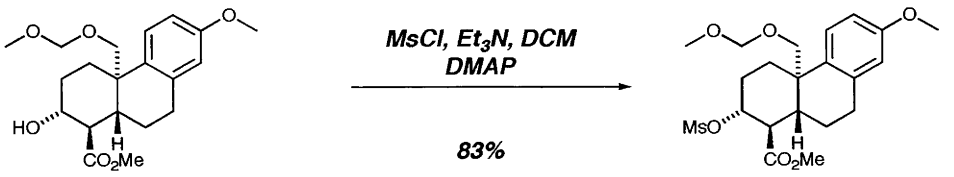


5-23 **5-44**

Scheme 5.6. *Reduction of* ***5-23***

5.6.2 Formation of the Mesylate and Elimination

Having acquired the alcohol, it was considered that a mesylate would provide adequate activation to enable elimination to the alkene. Accordingly, the alcohol **5-44** was treated with methanesulfonyl chloride and triethylamine in DCM with a catalytic amount of DMAP to give the desired mesylate **5-45** in 83% yield (**Scheme 5.7**).

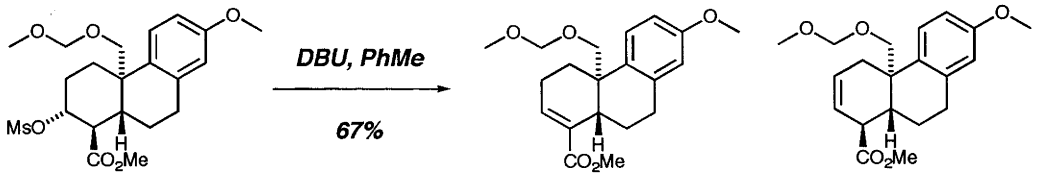


5-44 **5-45**

Scheme 5.7. *Formation of Mesylate* ***5-45***

The formation was evident from the ^{1}H NMR spectrum where the sulfonyloxy methine proton was observed at 4.76 ppm, again with indicative couplings of 11.4 Hz and 5.1 Hz.

With the mesylate in hand, all that was now required was to effect elimination to give the desired alkene. The preferred choice for such eliminations is DBU or DBN, which provide the required basicity without the nucleophilicity that can yield side reactions. Treatment of the mesylate **5-45** with DBU in toluene at reflux for 3 days yielded the alkene as a 1:2 mixture of the two isomers **5-46** and **5-47** in 67% yield, along with a 8% yield of a mixture of unidentified products (**Scheme 5.8**). The formation of the alkenes was clear from the mass spectrum, which clearly showed a fragment due to the molecular ion. The ^{1}H NMR spectrum displayed a resonance at 6.80 ppm assigned to C3 of the conjugated alkene **5-46**, while the double bond of **5-47** gave rise resonances at 5.64 ppm and 5.86 ppm. The IR spectrum was also indicative with two carbonyl stretches at 1738 cm^{-1} and 1715 cm^{-1} assigned to the conjugate and non-conjugated esters, respectively.



5-45 **5-46** **5-47**

Scheme 5.8. *Mesylate Elimination*

For a seemingly simple transformation, the relatively low yield (typically 38-46% over the 3 steps) was disappointing and was attributed to the equatorial nature of the alcohol substituent. Due to the *stereo-electronic* requirement, elimination must occur *anti-peri*-planar and therefore the mesylate **5-45** must adopt a boat conformation. It should be noted that in both geometries the more acidic proton, α to the ester function, does not meet this requirement. In hindsight, a possible solution to this problem would have been to firstly displace the mesylate with iodide. The iodo substituent would then be ideally positioned to eliminate with the α-proton of the ester (**Figure 5.15**).

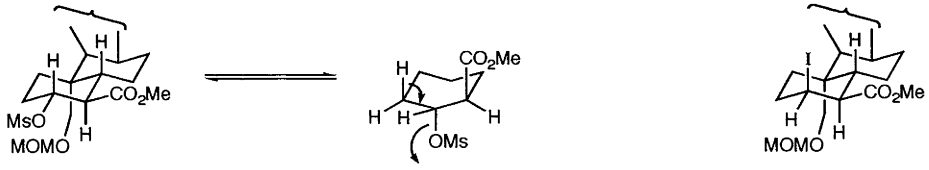
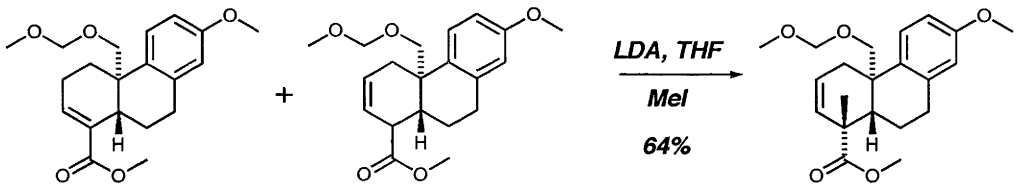


Figure 5.15. Elimination Conformation

5.7 Alkylation of the Alkene-Esters 5-46 and 5-47

With the desired alkenes in hand, exploration into the alkylation began in earnest. Gratefully, treatment of the alkenes **5-46** and **5-47** with LDA and iodomethane in THF smoothly delivered the desired alkylated product **5-48** in 64% yield as a single product (**Scheme 5.9**). The introduction of a methyl substituent was clear from the ^{1}H NMR spectrum exhibiting a singlet resonance at 1.39 ppm.



5-46 **5-47** **5-48**

Scheme 5.9. *Alkylation of the Alkene Ester*

The stereochemistry was assigned by a nOe difference experiment, whereby irradiation of the methyl group showed through space interactions with the protons at C3, C5, and C6 confirming the assigned stereochemistry (**Figure 5.16**). If an axial methyl had been installed, then it would have been reasonable to expect an interaction with the angular alkoxy methylene group.

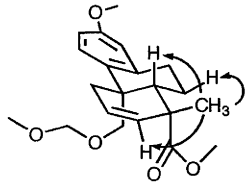


Figure 5.16. *nOe Difference Experiments to Determine the Stereochemistry*

The alkylation of esters **5-46** and **5-47** still constitutes the alkylation of an *endo*-cyclic enolate and therefore requires adopting the boat geometry in order to achieve *equatorial* alkylation. As the eclipsing interactions did not govern the outcome of the reaction, as in other stabilised *endo*-cyclic enolates, it is proposed that the alkylation occurs through an 'earlier'

more *substrate-like* transition state. Accordingly, the dominant control element is steric and as a result, the alkylation proceeds to the less sterically encumbered β-face. The transition state of the alkylation of **5-46** and **5-47** could be expected to be 'earlier' as the enolate would not be as effectively stabilised as in the ketone (**Figure 5.17**). However, it should be noted that a cyclohexene boat conformation incurs a smaller penalty due to reduced 1,3-diaxial and eclipsing interactions. Therefore, the outcome of this alkylation could simply be a result of reducing the energy required for the cyclohexene to adopt the boat conformation.

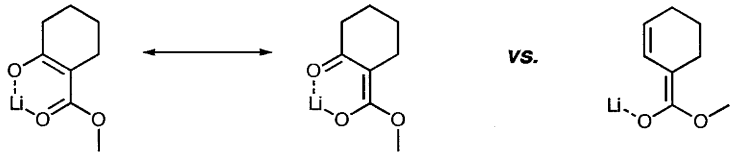


Figure 5.17. *Comparison in Stabilisation Between Endo-Cyclic Enolates*

5.8 Elaboration of Ester 5-48 to an Amino Derivative

5.8.1 Introduction

With all the requirements met, it was possible to go about installing nitrogen into the skeleton and then investigate the formation of the pyrrolidine ring. There were three possible ways to install nitrogen into this system *via* the ester **5-48** (**Figure 5.18**). The first was to saponify the ester to the acid, then convert the acid to the amide with an amide coupling agent such as DCC, or *via* the acid chloride. The amide could then be reduced to the desired amine.[12] The second approach would be to reduce the ester **5-48** to the alcohol and then displace it, or a sulfonoxyl derivative, with azide ion.[13,14] The amine could then be obtained by reduction of the azide group. The third option was to convert the ester to the aldehyde and then carry out a reductive amination to give the amine.[15]

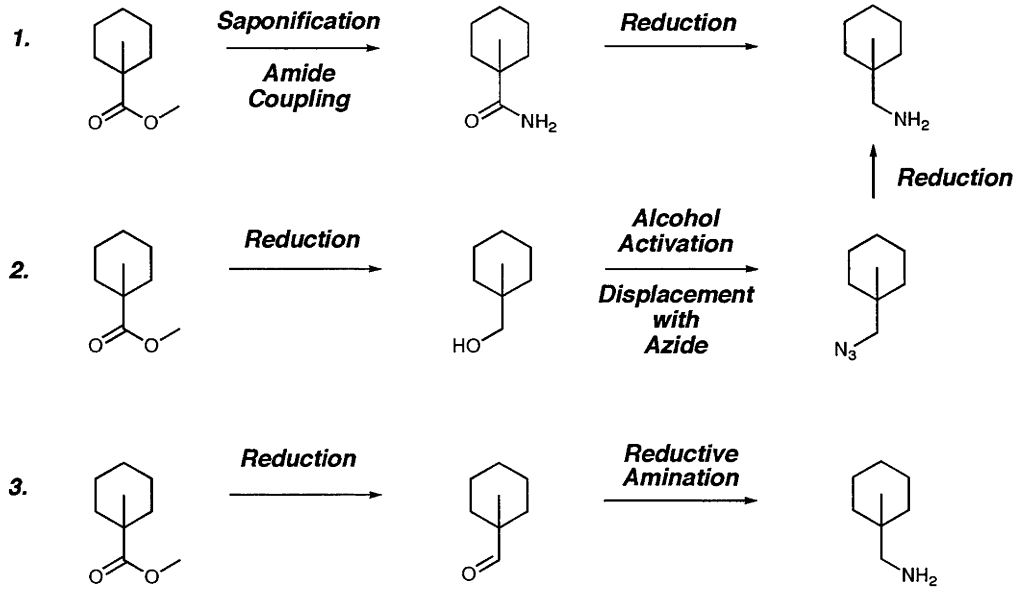
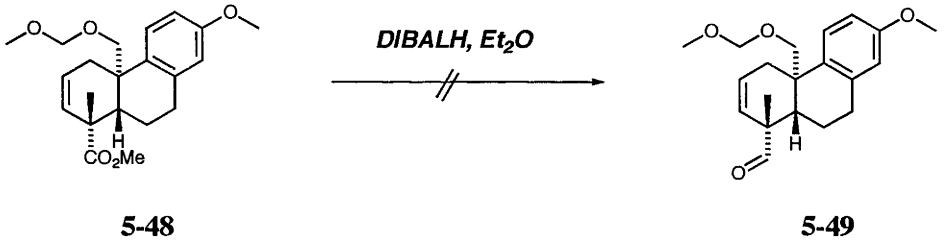


Figure 5.18. *Methods for Elaborating the Ester to an Amine Function*

A major obstacle to the success of this approach was the proximity of the angular alkoxy methyl function. For this reason it was important that the method used to install the amine be sufficiently mild as to prevent any unwanted side reactions between the two angular substituents. Previous work had shown that both lactones **3-33** and cyclic ethers **4-18** formed readily in this molecule. In the latter case, ether formation had occurred over azide ion displacement despite the hydroxy protecting group. In light of these concerns, the reductive amination was the only method that did not require initial activation of the angular substituent and was considered sufficiently mild to prevent hydrolysis of the MOM ether.

5.8.2 Conversion of the Ester 5-48 to the Aldehyde 5-49

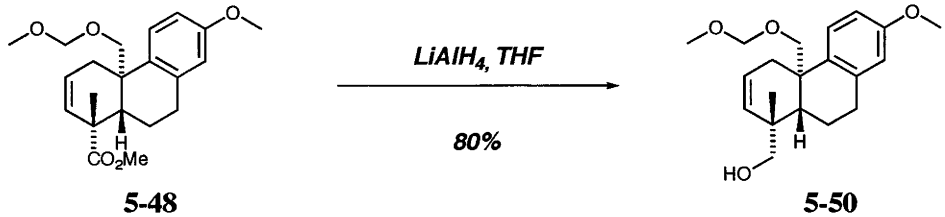
Reduction of the ester **5-48** to the aldehyde **5-49** was attempted with diisobutylaluminum hydride without success (**Scheme 5.10**), but excellent yields of the alcohol **5-50** were obtained.



5-48 **5-49**

Scheme 5.10. *Attempted Direct Reduction to Aldehyde* ***5-49***

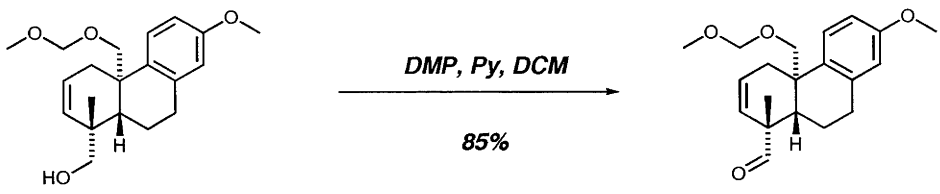
It was therefore obvious that a two step procedure would be required to access the aldehyde. Substituting $LiAlH_4$ for DIBALH gave the desired alcohol **5-50** in 80% yield (**Scheme 5.11**).



5-48 **5-50**

Scheme 5.11. *Reduction of the Ester* ***5-48*** *to the Alcohol* ***5-50***

With the alcohol **5-50** in hand, oxidation was carried out using Dess-Martin periodane (DMP). Treating the alcohol **5-50** with DMP in DCM gave yields of approximately 50-60%. The low yield was attributed to acidic residues in the reaction leading to lactol and lactone products. In fact, decomposition occurred if care was not taken. For this reason it was best to buffer the oxidation with pyridine, which resulted in excellent yields of the aldehyde **5-49** as the sole product in 85% yield (**Scheme 5.12**). The formation of aldehyde was clear from the ^1H NMR spectrum, which showed a characteristic resonance at 9.80 ppm.



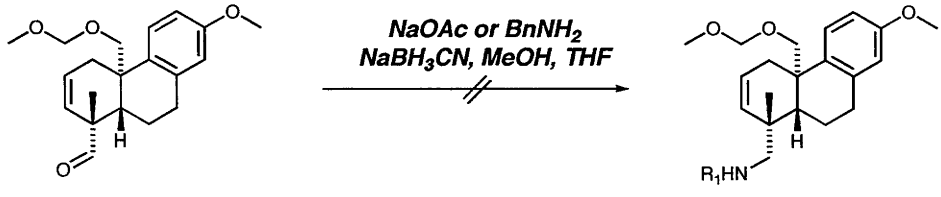
5-50 **5-49**

*Scheme 5.12. Oxidation of Alcohol **5-50***

5.8.3 Reductive Amination of Aldehyde 5-49

With aldehyde **5-49** in hand, elaboration to **5-51** could be attempted. Reductive amination has been extensively reviewed and is formally the formation of an iminium species followed by reduction to the amine. A major advancement to this reaction was the discovery of the pH dependent reducing agent, sodium cyanoborohydride, which at pH 5-7 will not reduce aldehydes and ketones but effectively reduces imine species. This reagent enables a one-pot procedure whereby the imine is reduced as it forms. Alternatively, the imine can be preformed and reduced with a number of other reducing agents.

Treatment of the aldehyde **5-49** with ammonium acetate, or benzyl amine, and sodium cyanoborohydride gave unsatisfactory results. Typically, decomposition ensued with trace amounts of suspected amine products isolated. Despite attempts to alter the reaction conditions, employing different solvent systems, trying to preform the imine, and driving its formation by acid catalysis no acceptable outcomes were discovered (**Scheme 5.13**).

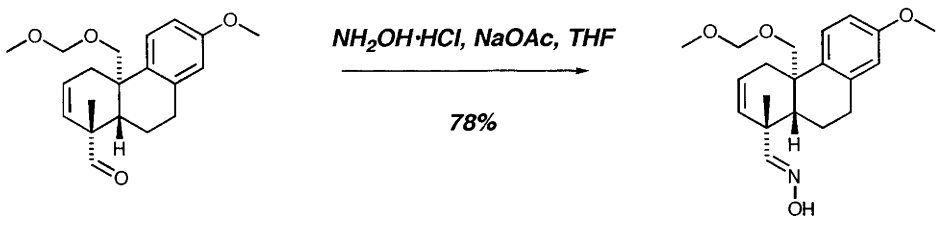


5-49 **5-51**

*Scheme 5.13. Attempted Reductive Amination of **5-49***

5.8.4 Oxime Formation

The reductive amination described above obviously required the initial formation of the imine and it was conceivable that the amine species were not nucleophilic enough to overcome the severe steric hindrance around the neopentyl aldehyde **5-49**. Work outlined in **Chapter 4** had shown that oximes formed more readily. Pursuing this line of reasoning, the aldehyde **5-49** was treated with hydroxylamine and sodium acetate in THF to give the oxime **5-52** in 78% yield (**Scheme 5.14**) The reaction was very rapid and it was clear the oxime had formed by the upfield shift of the oxime proton to 7.59 ppm in the ^{1}H NMR spectrum, and the broad OH stretch at 3367 cm^{-1} in the IR spectrum.

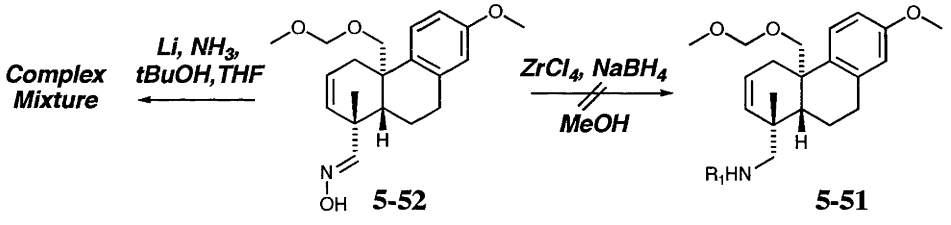


5-49 5-52

Scheme 5.14. Oxime Formation

5.8.5 Reduction of Oxime 5-52

With acceptable introduction of nitrogen into the skeleton, reduction of the oxime to **5-51** could be investigated. Reaction with $NaBH_4/ZrCl_4$ is a well known method for reducing oximes,[16] but in this instance returned only starting material. It was considered that reduction in liquid ammonia could reduce the oxime and aromatic ring simultaneously, but these conditions gave only a complex mixture of products (**Scheme 5.15**).



Scheme 5.15. Attempted Reduction of the Oxime

5.9 Redirection

It was thought that through further experimentation the oxime could be reduced to the amine by employing other hydride reagents or by catalytic hydrogenation. However, initial experiments to install the amine were frustrating. It was conceivable that the oxime could be dehydrated to the nitrile, which could then be reduced to the amine, as demonstrated in Mukatake and Natusme synthesis of *nominine*. However, if this strategy was to be implemented, it was thought that the nitrile could be obtained in a more direct fashion.

5.10 References

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Chapter Six

Successful Synthesis of Amine Derivatives

6.1 Introduction

The previous chapter described the alkylation of the ester **5-46** and **5-47** which, under good stereocontrol, delivered the methyl substituent exclusively to the β–face. However, subsequent attempts to install nitrogen were problematic, presumably due to the steric environment of the neopentyl angular aldehyde and interference from the adjacent MOM protected hydroxy methyl. Consequently, it was conceived that the desired amine derivative **6-4** could be derived through reduction of the nitrile **6-3**. To this end, a plan to access the nitrile **6-3** directly was developed, and it was thought that this could be achieved by initially converting the β–keto ester **6-1** to the nitrile **6-2**. The nitrile **6-2** could then be alkylated diastereoselectively and the alkylated nitrile **6-3** reduced to give the amine **6-4** (**Figure 6.1**). This strategy enabled an opportunity to address the deoxygenation of the β–keto ester **6-1**, which had previously been found to be low yielding, but had the drawback of removing the functionality from the A-ring. Nevertheless, it was important to establish a satisfactory procedure for amine formation. Functionalisation of the A-ring could be addressed later.

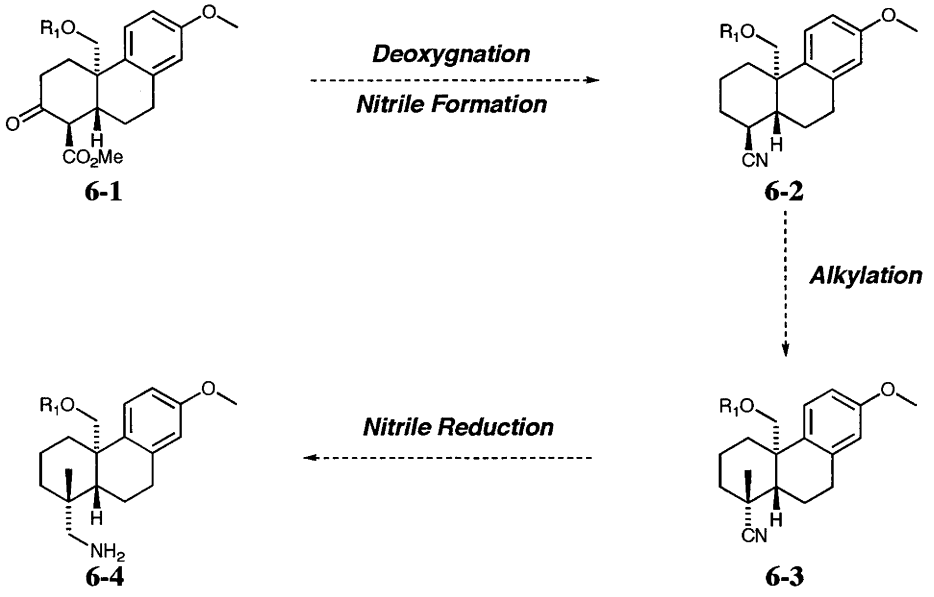


Figure 6.1. Revised Synthetic Strategy

6.2 Synthesis of Enone 6-5

It was thought that some of the problems observed in the reductive amination (**Chapter 5.8.3**) were due to the proximity of the MOM protected hydroxymethyl function to the angular aldehyde group **5-49**, which resulted in hydrolysis processes *via* anchimeric assistance. Conceivably, similar assistance could occur between the nitrile and an adjacent methoxy methyl function. Furthermore, concurrent work by Fairweather[1] has demonstrated that similar difficulties occur during the acid catalysed conversion of 1,4-dihydroanisoles to enones, post Birch reduction (**Figure 6.2**).

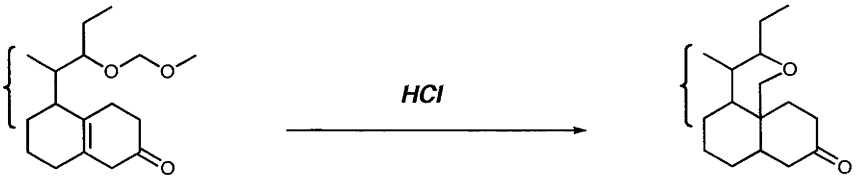
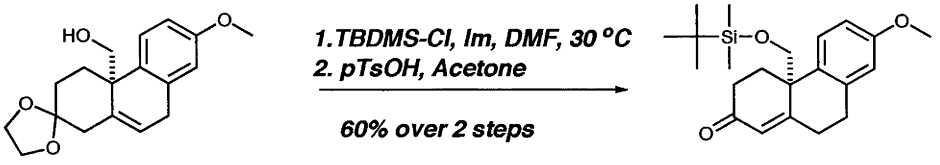


Figure 6.2. *Acid Catalysed Displacement of Methanol from MOM Ethers*

In light of these concerns, an alternate protection strategy was devised. It has been shown that the analogous *tert*-butyl dimethyl silyl ether is stable towards Birch reduction and subsequent acid isomerisation.[2] Accordingly, the previously synthesised silyl enol ether **4-11** was employed and the ketal converted into the desired enone **6-5** in 60% yield over the two steps from **4-10** (**Scheme 6.1**).

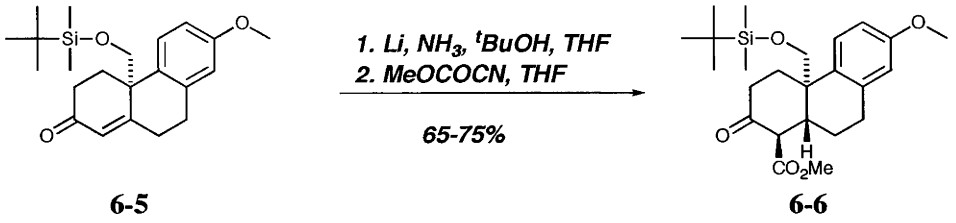


4-10 **6-5**

Scheme 6.1. *Synthesis of Enone* ***6-5***

6.3 Acylation of Enone 6-5

As with the previous series, the enone **6-5** was reduced with lithium in ammonia and then treated with methyl cyanoformate to afford the β-keto ester **6-6** in 69% yield. Again, equilibration was observed on scale up, but acceptable yields could be reproduced on a small scale. The formation of the correct isomer was clear from the ^{1}H NMR spectrum, which showed a doublet resonance at 3.9 ppm for H4 with a large diaxial coupling of 13.2 Hz to the proton of the decalin ring fusion (**Scheme 6.2**).



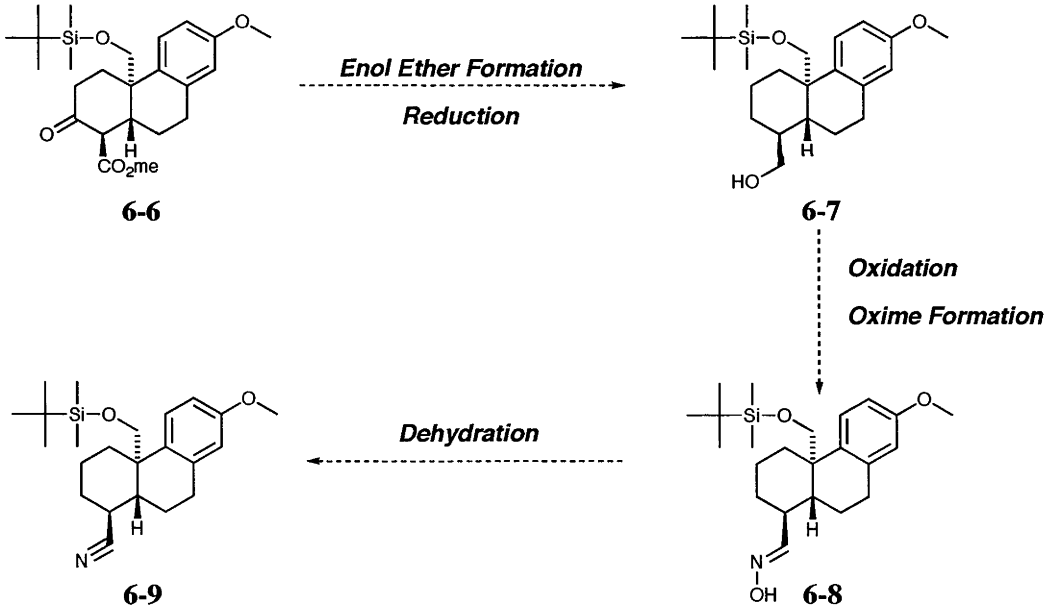
6-5 **6-6**

Scheme 6.2. Synthesis of β-Keto Ester ***6-6***

6.4 Synthesis of Nitrile 6-9

6.4.1 Introduction

The β-keto ester **6-6** provided the required starting point to elaborate the nitrile **6-9** (**Figure 6.3**). It was intended that the β-keto ester **6-6** would first be reduced to the alcohol **6-7** *via* reduction of the methoxyl methyl enol ether. With the ketone function removed, the alcohol **6-7** could then been oxidised to the aldehyde and converted to the oxime **6-8**. Finally, the oxime function could be dehydrated to the nitrile **6-9**, in preparation for the alkylation.



6-6 **6-7** **6-8** **6-9**

Figure 6.3. *Plan to Convert the β-Keto Ester* ***6-6*** *to Nitrile* ***6-9***

6.4.2 Synthesis of Alcohol 6-7

An excellent two step procedure for the deoxygenation of β-keto esters has been developed by Coates and Shaw[3] (**Figure 6.4**), whereby the conversion of β-keto ester **6-10** to the corresponding methoxymethyl enol ether **6-11**, followed by a dissolving metal reduction in liquid ammonia, delivers the corresponding ester **6-15**. The reduction of the enol ether **6-11** proceeds through the sequential addition of electrons to give the radical anion **6-12**, which on

protonation and the addition of another electron gives the intermediate enolate **6-13**. Finally, the enolate quenches through elimination of the methoxymethoxy function to give unsaturated ester **6-14**, which is subsequently reduced through the same process to give the ester **6-15**. The primary literature on this reaction points out the necessity of limiting the amount of lithium and proton source in order to minimise further reduction of the ester to the alcohol, but for the current purpose it was considered advantageous to access the alcohol directly.

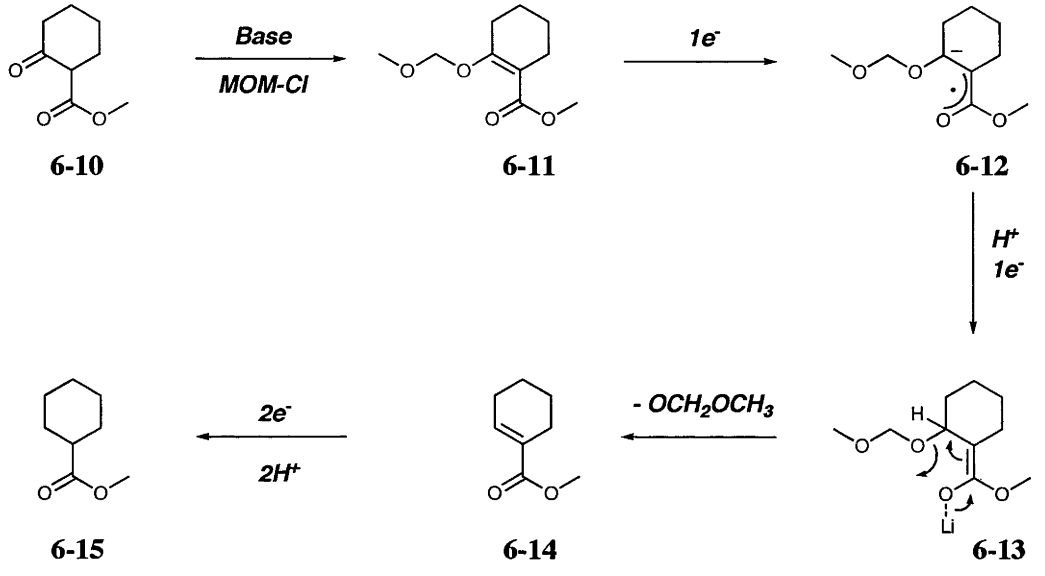
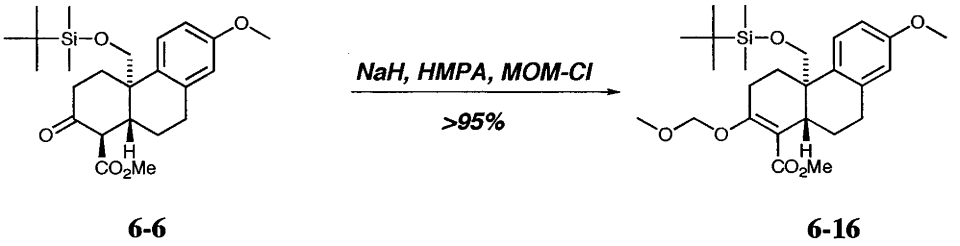


Figure 6.4. *Dissolving Metal Reduction of MOM Enol Esters*

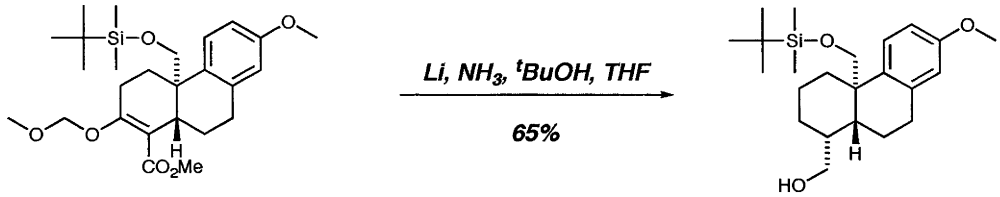
Accordingly, the β-keto ester **6-6** was treated with sodium hydride in HMPA, and on formation of the enolate, methoxymethyl chloride was added to give a quantitative yield of the desired methoxymethyl enol ether **6-16** (**Scheme 6.3**). The enol ether formation was evident from the ^{1}H NMR spectrum, which showed a pair of AB doublets at 4.91 ppm and 4.97 ppm (J = 6.7 Hz), and 3.46 ppm from the methoxymethylene and methoxymethyl, respectively. Both of these resonances were significantly downfield from the standard MOM resonances due to the additional shielding from the conjugated ester. Changes in the IR spectrum were also observed with the disappearance of the ketone carbonyl stretching band and the shift of the ester carbonyl stretching band from 1747 cm^{-1} to 1728 cm^{-1}.



Scheme 6.3. *Formation of Methoxymethyl Enol Ether* ***6-16***

The *O*-acylation of the β–keto ester **6-6** is consistent with comments made earlier (**Chapter 5.4**) in that the co-ordination of the HMPA to the ion-pair results in *solvent-separated* ion-pairs to such an extent that exclusive *O*-alkylation ensues. In fact, no *C*-alkylation products were observed from this reaction.

With the enol ether **6-16** in hand, the reduction was carried out (**Scheme 6.4**). Initial conditions employing 2 equivalents of tBuOH as a proton source gave roughly a 2:1 mixture of the alcohol **6-7** and the corresponding ester in a combined yield of approximately 70%. However, increasing the amount of proton source to 8 equivalents gave exclusively the alcohol **6-7**. The alcohol was identified by the IR spectrum, which had a characteristic large broad OH band at 3356 cm^{-1}, and the ^{13}C NMR spectrum, which displayed an additional resonance at 67.5 ppm indicative of a hydroxymethyl group.



6-16 **6-7**

Scheme 6.4. *Dissolving Metal Reduction of Methoxymethyl Enol Ether* ***6-16***

Although it was difficult to assign the stereochemistry of the hydroxy methylene further experimentation – *vida infra* – showed the substituent to be on the α–face. This stereochemistry is to be expected based on the kinetic protonation of the enolate derived from the reduction of the unsaturated enolate along the less hindered equatorial vector (**Figure 6.5**).

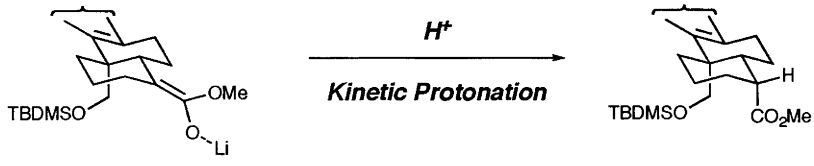
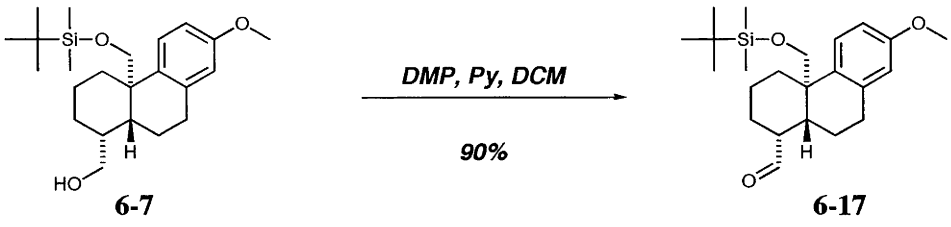


Figure 6.5. *Kinetic Protonation of Intermediate Enolate*

6.4.3 Oxidation of Alcohol 6-7 and Oxime Formation

Having acquired the desired alcohol **6-7**, oxidation was carried out next. The analogous oxidation in the previous series (**Chapter 5.8.2**) was shown to be acid sensitive and therefore buffered conditions were employed. Accordingly, alcohol **6-7** was treated with Dess-Martin periodane in DCM with pyridine as a buffer to give the aldehyde **6-17** in an excellent yield of 80% (**Scheme 6.5**). Formation of the aldehyde was evident from the ^{1}H NMR spectrum, with a key signal at 10 ppm due to the aldehyde proton. In addition, the ^{13}C NMR spectrum showed a resonance at 204.7 ppm, and the IR spectrum showed a carbonyl stretch at 1718 cm^{-1}, also indicative of an aldehyde.

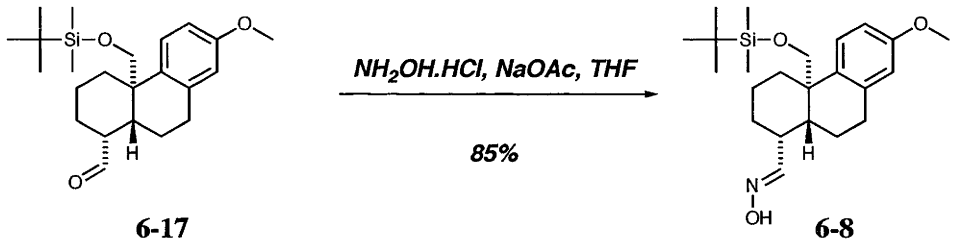


6-7 6-17

*Scheme 6.5. Oxidation of Alcohol **6-7***

The formation of an oxime had also been previously explored and was shown to be very successful. Accordingly, the aldehyde **6-17** was treated with hydroxylamine hydrochloride and sodium acetate in THF at reflux to afford the desired oxime **6-8** in 80% yield (**Scheme 6.6**).

The formation of the oxime was evident from the ^{1}H NMR spectrum, which had a doublet resonance at 7.68 ppm, indicative of the CH of the oxime. In addition, the IR spectrum showed a broad OH stretch at 3326 cm^{-1}, while the ^{13}C NMR spectrum showed an oxime carbon at 153 ppm.

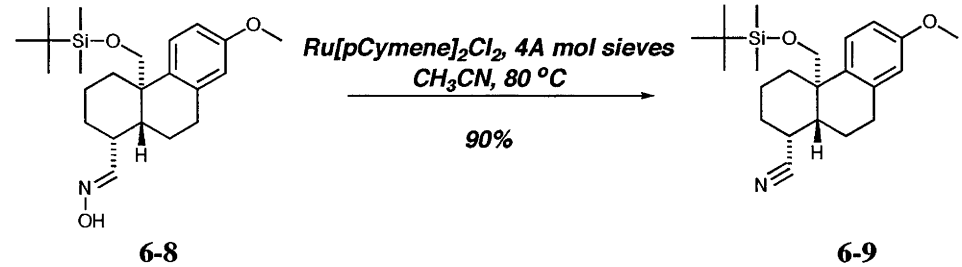


6-17 6-8

*Scheme 6.6. Formation of Oxime **6-8***

6.4.4 Dehydration of Oxime 6-8

The dehydration of oximes to form nitriles is a standard conversion that is classically carried out using acetic anhydride, but this procedure is known to suffer from poor yields and require forcing conditions. However, recent advances in Lewis acid catalysis have greatly improved the viability of this transformation. Treatment of the oxime **6-8** with $RuCl_2$[*p*-cymene] and 4Å molecular sieves in acetonitrile at 80 ^{0}C for 10 mins afforded the nitrile **6-9** in an excellent 80% yield (**Scheme 6.7**).[4]



6-8 6-9

*Scheme 6.7. Dehydration of Oxime **6-8***

The formation of nitrile **6-9** was evident from the ^{13}C NMR spectrum, which displayed a resonance at 122.4 ppm, and the IR spectrum which had a weak CN stretching band at 2233 cm^{-1}. The initial assignment of the stereochemistry of the alcohol **6-7** was confirmed by the chemical non-equivalence of the two protons on the adjacent silyl protected hydroxy methyl group, which were observed as an AB system at 4.2 ppm and 3.7 ppm, with a coupling of 10 Hz (**cf. Figure 6.6**). Presumably, shielding provided by the π-system of the nitrile accounted for the downfield shift of one of the protons.

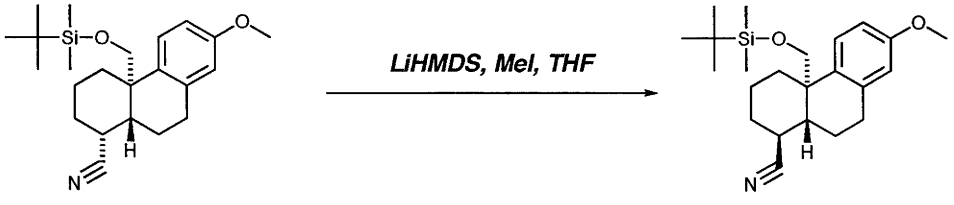
6.5 Alkylation of Nitrile 6-9

6.5.1 Introduction

The alkylation of *exo*-cyclic enolates is not restricted by *stereo-electronic* factors, as both *equatorial* and *axial* alkylation can occur without the need to adopt different ring geometries.[5] Consequently, the outcome of the reaction is governed by *steric* constraints imposed on the trajectory of the incoming electrophile. Therefore, it was expected that the electrophile would approach from the upper face, *anti* to the angular protected hydroxymethylene group, to deliver the equatorial methyl group.

6.5.2 Epimerisation of the Nitrile

The nitrile **6-9** was treated with LiHMDS/MeI in THF and HMPA to initiate an alkylation, but this only resulted in epimerisation to give the corresponding equatorial epimer **6-18** (**Scheme 6.8**). This was evident from the shifts of the angular silyl protected hydroxymethyl substituent, which moved upfield (**Figure 6.6**).



6-9 **6-18**

Scheme 6.8. *Epimerisation of the Nitrile* ***6-9***

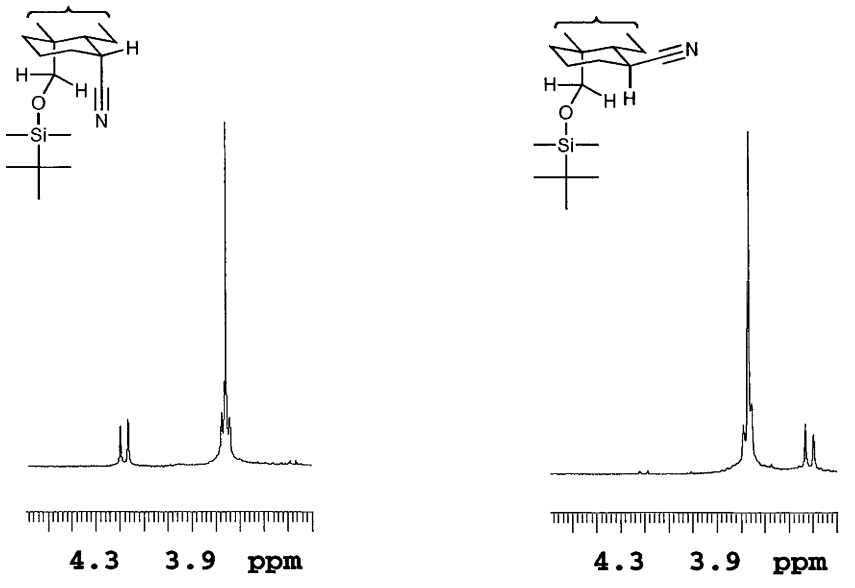
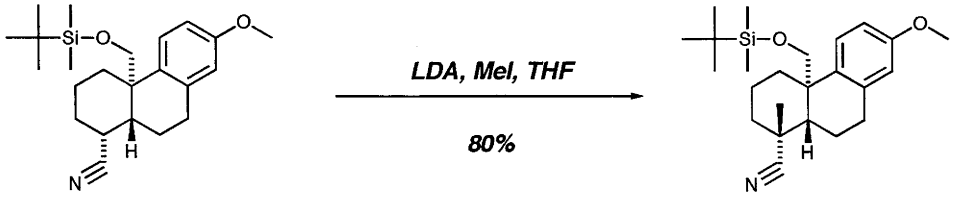


Figure 6.6. ^1H NMR Shifts of the Axial and Equatorial Nitrile

6.5.3 Successful Alkylation of the Nitrile 6-9

Due to the lack of success with LiHMDS, it was considered that a stronger base would be more effective. Accordingly, the nitrile **6-9** was treated with LDA in THF followed by methyl iodide to give a single alkylated product **6-19** in 80% yield (**Scheme 6.9**). The stereochemistry was based on the similarity of the chemical shifts of the angular hydroxymethyl protons observed earlier for **6-9** and was confirmed by subsequent experiments.



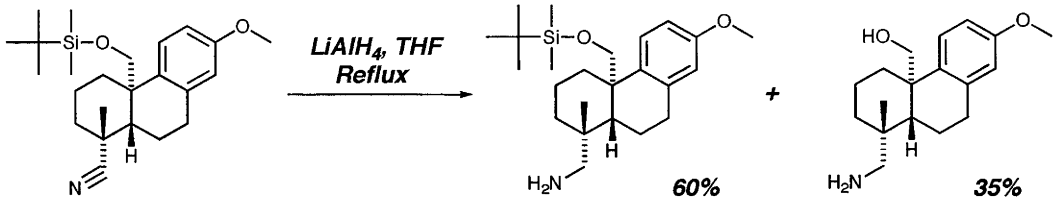
6-9 **6-19**

Scheme 6.9. Alkylation of Nitrile 6-9

Interestingly, the yield between alkylation of the ester **5-46** and the nitrile **6-9** were quite different. Although the ester **5-46** gave excellent diastereoselectivity, the lower yield could be accounted for by the later transition state, and hence complications arising from eclipsing interactions. The effective charge of carbonyl groups is spread over a larger area due to their triangular nature. In constrast, nitriles are very small electron-withdrawing groups and this property, along with their linear rod-like nature, minimises any steric interactions.[6]

6.6 Reduction of the Nitrile 6-19

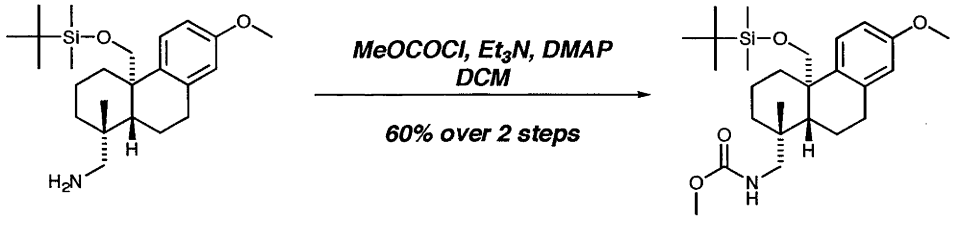
The next challenge was to elaborate the nitrile **6-19** to the desired amine. Attempts to hydrogenate the nitrile were unsuccessful and typically starting material was recovered. However, treatment of the nitrile **6-19** with $LiAlH_4$ in THF at reflux for 2-3 hrs gave the amine **6-20** in 60% yield along with 35% of the deprotected alcohol **6-21** (**Scheme 6.10**).



6-19 **6-20** **6-21**

Scheme 6.10. *Reduction of Nitrile* ***6-19***

With the amine in hand, it was considered best to protect it first before purification. Previous work within the Mander group has shown that methyl carbamates are stable to Birch conditions. Treatment of the amine **6-20** with methyl chloroformate and triethylamine in DCM yielded the carbamate **6-22** in 60% yield over the two steps (**Scheme 6.11**).



6-20 **6-22**

Scheme 6.11. *Protection of Amine* ***6-20***

The carbamate **6-22** was characterised by the ^1H NMR spectrum, which showed a pair of doublets of doublets at 3.1 ppm and 3.5 ppm attributed to the amino methylene. Both resonances had a large geminal coupling of 13.9 Hz and a smaller coupling to the NH proton of 5.4 Hz and 7.5 Hz, respectively (**Figure 6.7**). Irradiation of the singlet at 3.81 ppm, assigned to the protected hydroxy methylene, showed an nOe to the more downfield amino methylene proton, which supported the stereochemical assignment of the nitrile alkylation.

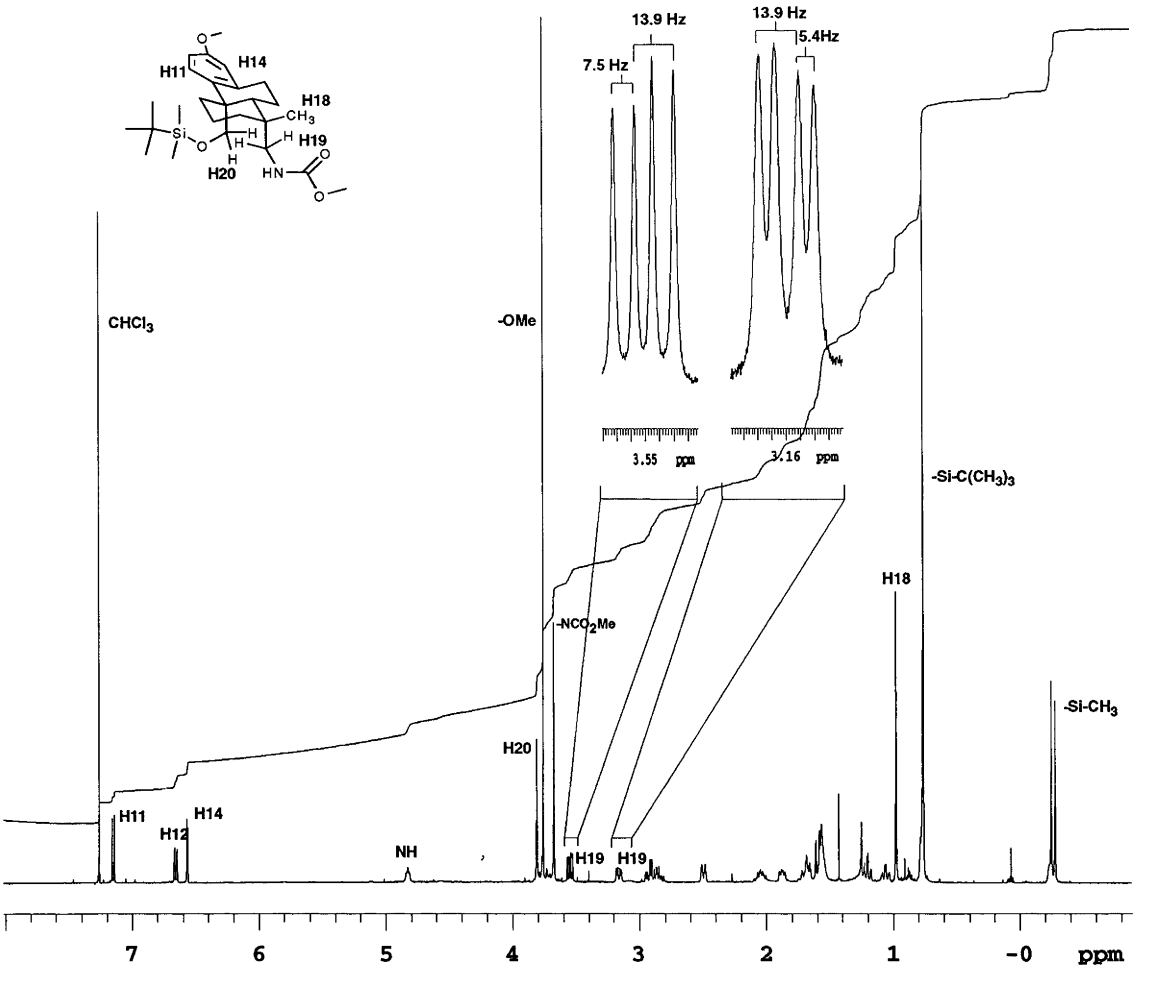


Figure 6.7. ^{1}*H NMR Spectrum of Carbamate* ***6-22***

6.7 Birch Reduction of the C-Ring

6.7.1 Introduction

With an acceptable route to the carbamate **6-22**, elaboration to the 1,6-addition precursor could be investigated (see **Figure 3.1**). The Birch reduction is the technique of choice for the reduction of aromatic species and like the dissolving metal reduction of other π-systems involves the sequential feeding of electrons into the π*-orbital of the aromatic ring **6-23**. Addition of the first electron results in the formation of a radical anion **6-24**, which is then protonated to give the delocalised radical **6-25**. The addition of another electron and subsequent protonation then gives the 1,4-dihydroanisole **6-26** (**Figure 6.8**).[7]

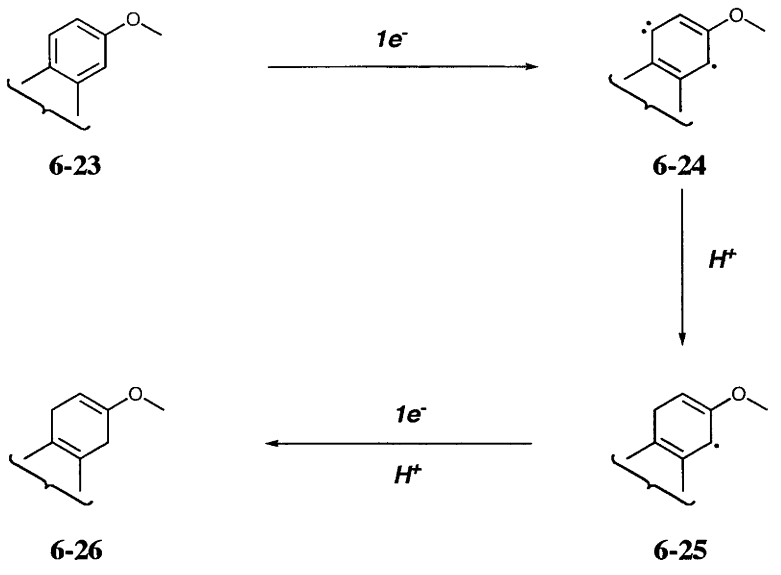
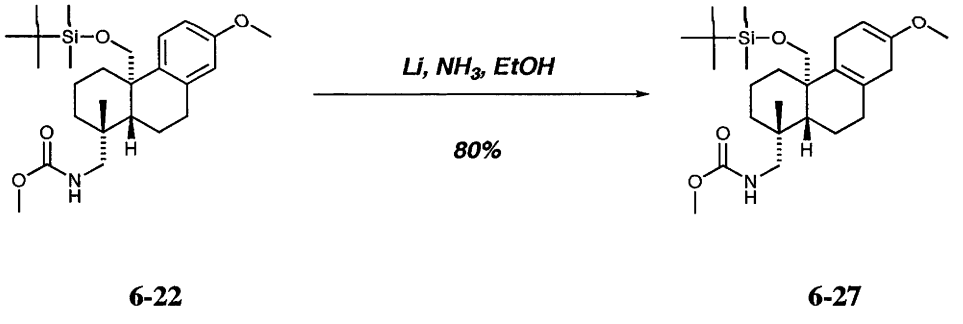


Figure 6.8. The Birch Reduction

6.7.2 Birch Reduction of Carbamate 6-22

The reduction of carbamate **6-22** was carried out using lithium in ammonia with ethanol as a proton source to give the dihydroanisole **6-27**, along with starting material in a yield of 80% (**Scheme 6.12**).



Scheme 6.12. Birch Reduction of Carbamate 6-22

The formation of the 1,4-dihydroanisole was evident from the ^{1}H NMR spectrum, which showed the disappearance of the aromatic signals and the appearance of the methyl enol ether proton at 4.49 ppm. In addition, the methyl ether signal had moved upfield to 3.53 ppm.

Although most carbonyls are reduced under dissolving metal reduction conditions, it is assumed that *in situ* deprotonation of the carbamate deactivates it towards reduction.

6.8 Isomerisation and Oxidation of the Dihydroanisole 6-27

6.8.1 Introduction

The hydrolysis and isomerisation of 1,4-dihydroanisole compounds to the corresponding enone is a classical conversion, and the Birch reduction followed by isomerisation has been used extensively in steroid chemistry. Fuchs has demonstrated how the dihydroanisole **6-28** can be isomerised under anhydrous acidic conditions to the linear dienol ether **6-29** and then this can be treated with Oxone to give the γ-hydroxy enone **6-31**.[8] Alternatively, treatment of the linear dienol ether with aqueous acid gave the αβ-enone **6-30** (**Figure 6.9**).

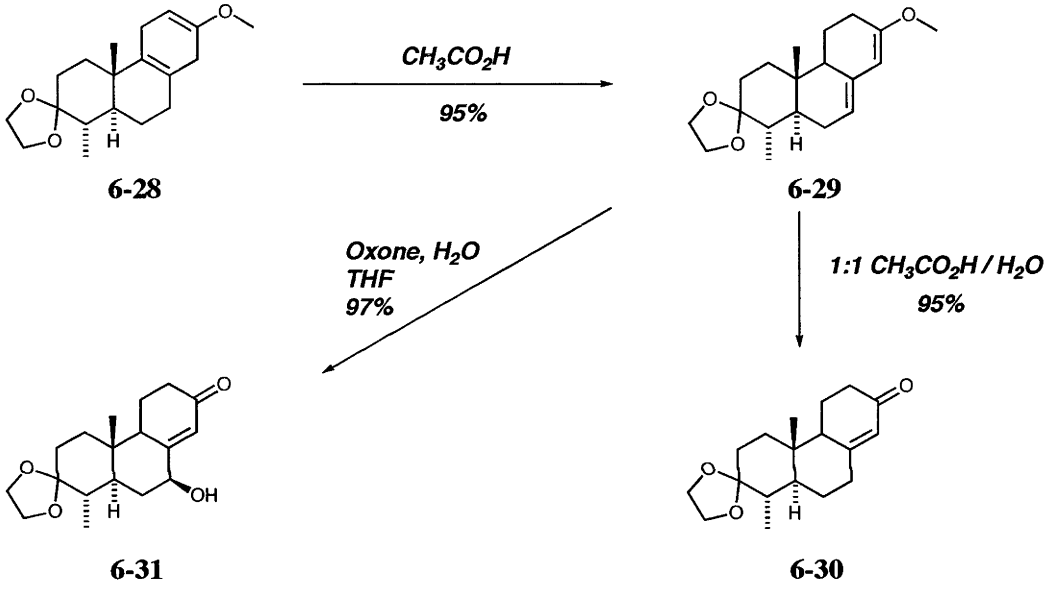


Figure 6.9. Fuchs Isomerisation to the Linear Dienol Ether

For the current purposes, a γ-hydroxy enone of the type **6-31** would be an ideal target for the dienone **6-33**. Conceivably, the analogous γ-hydroxyl could be converted to a sulfonyloxy derivative **6-32** and subsequently eliminated to give the desired dienone **6-33** in anticipation of 1,6-amino addition (**Figure 6.10**).

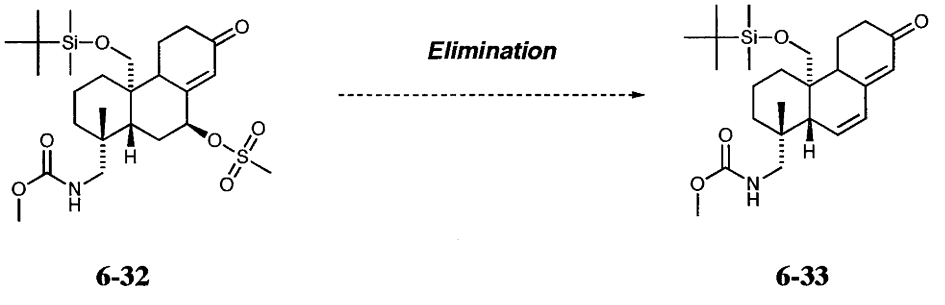
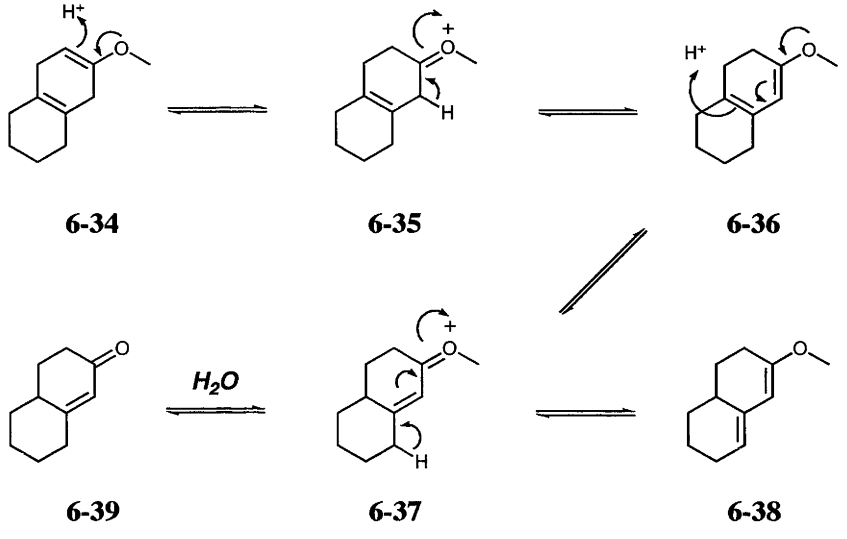


*Figure 6.10. Entry to the 1,6-Addition Precursor **6-33***

The isomerisation of the 1,4-dihydro anisole **6-34** to **6-38** proceeds through the protonation to give oxonium ion **6-35**, which can then be deprotonated to give the *cisoid* dienol ether **6-36**. Further equilibrium through the unsaturated oxonium ion **6-37** then proceeds to the lower energy *transoid* linear dienol ether **6-38**. Alternatively, the oxonium ions **6-35** and **6-37** can be attacked by water to give intermediate hemiacetals that collapse to the βγ-enone and αβ-enone **6-39**, respectively (**Figure 6.11**).



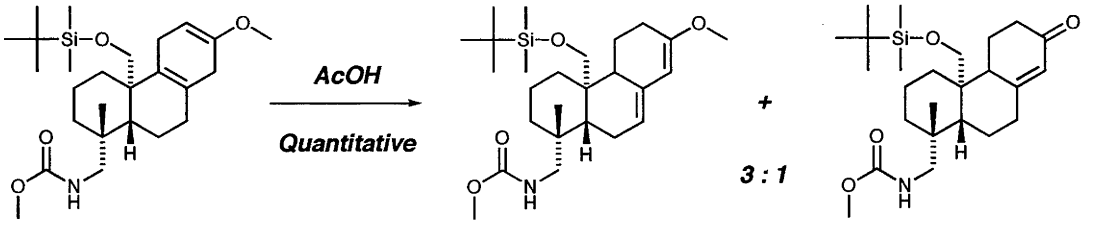
6-34 **6-35** **6-36**

6-39 **6-37** **6-38**

Figure 6.11. *Acid Catalysed Isomerisation of 1,4-Dihydroanisoles*

6.8.2 Isomerisation and Oxidation of the Linear Dienol Ether 6-40

In light of the above, the 1,4-dihydroanisole **6-27** was treated with anhydrous acetic acid to give approximately a 3:1 ratio of the linear dienol ether **6-40** and the corresponding αβ–enone **6-41** in quantitative yield (**Scheme 6.13**). The isomerisation to the linear dienol ether was evident from the ^{1}H NMR spectrum showing a sharp singlet a 5.19 ppm and a broad singlet at 5.32 ppm, which were assigned to the enol proton and the trisubstituted alkene proton, respectively. The presence of the enone **6-41** in the mixture was clear from the characteristic enone proton signal at 5.80 ppm.



6-27 **6-40** **6-41**

Scheme 6.13. *Attempted Isomerisation of the Dihydroanisole*

Even though the acetic acid used was freshly distilled from acetic anhydride to remove water, it is clear that the sensitive nature of this equilibrium results in the smallest amount of water interfering with the outcome by quenching the oxonium ion resulting in hydrolysis to the enone **6-41**. Similarly, attempts to make the γ-hydroxy enone by treating the mixture with Oxone, as described by Fuchs, were unsuccessful.

6.9 Successful Formation of the Dienone via DDQ Oxidations

6.9.1 Introduction

The Oxone oxidation procedure was clearly not going to be a viable pathway to the dienone **6-33**. Therefore, we began investigating alternate routes to this intermediate. An excellent one-pot direct conversion of linear dienol ethers, and enones, to the corresponding dienone *via* oxidation with DDQ is a well established reaction (**Figure 6.12**).[9] In the case of the DDQ oxidation of linear dienol ethers **6-42**, it is essential to use aqueous solvent in order to hydrolyse the intermediate oxonium ion **6-45**. Under anhydrous conditions further oxidation can occur *via* the enol ether **6-46** leading to aromatisation. The typical DDQ oxidation of enones **6-44** leads to the rearomatised phenol, but in the presence of acid, the equilibrium occurs to give the linear dienol **6-47**, which in the presence of DDQ is then oxidised to the dienone **6-43**.

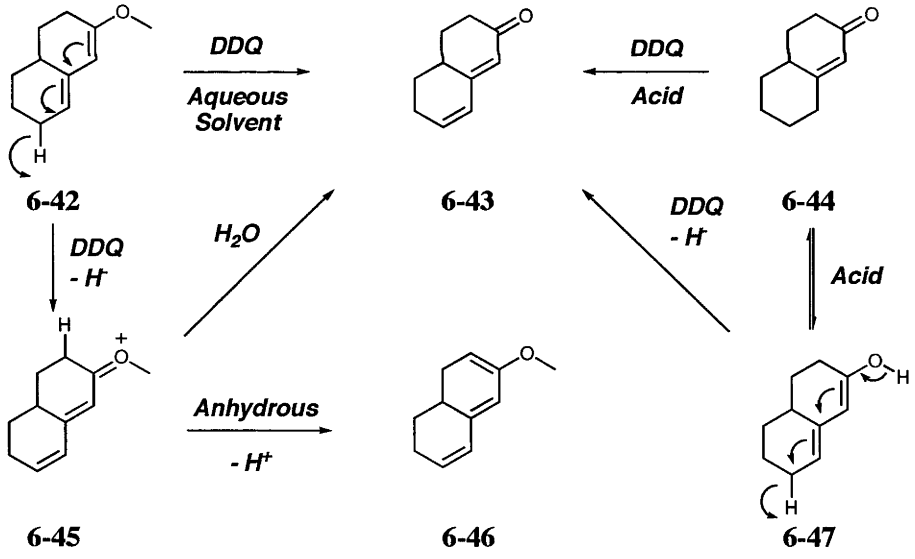
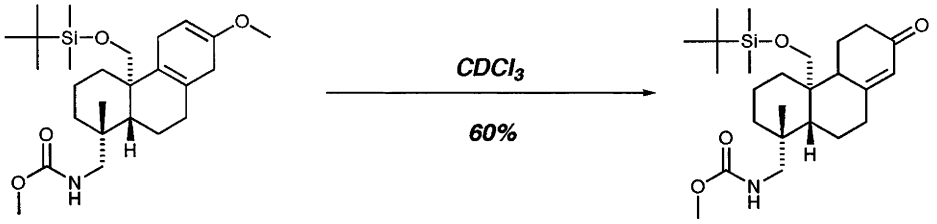


Figure 6.12. Synthesis of Dienones via Oxidation with DDQ

6.9.2 Successful Oxidation of the Enone 6-41

In light of the sensitivity of linear dienol ether **6-40** towards hydrolysis, it was considered best to hydrolyse the 1,4-dihydroanisole **6-27** directly to the enone **6-41** and investigate the acid catalysed oxidation. The hydrolysis of the dihydroanisole could be achieved in two ways. By treatment with aqueous AcOH in THF, or more simply by treatment in

deuterated chloroform. Presumably, the free HCl in the chloroform was responsible for the hydrolysis. Hence, treatment of the dihydroanisole **6-27** with $CDCl_3$ for 30 secs then pouring onto ether and washing with base yielded the desired aβ-enone **6-41** in 60% yield, along with 18% of starting aromatic compound **6-22** (**Scheme 6.14**). The αβ-enone was characterised based on the ^1H NMR spectrum, which displayed a resonance at 5.80 ppm, which is indicative of an enone methine. In addition, the IR spectrum had a carbonyl stretch at 1666 cm^{-1}.



6-27 **6-41**

Scheme 6.14. *Hydrolysis of the 1,4-Dihydroanisole*

The acid catalysed isomerisation, in this instance, sets up an equilibrium with the dienol. Even though protonation occurs preferentially at the α-carbon, the unsaturated ketone is a lower energy product due to the stability derived from conjugation, and ultimately is the preferred product of the equilibrium (**Figure 6.13**).

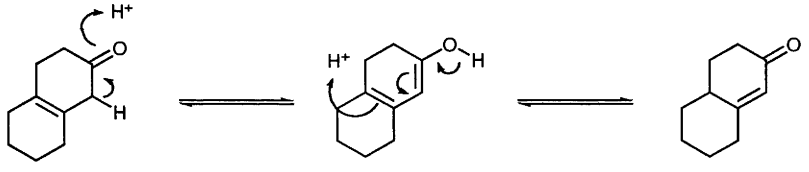
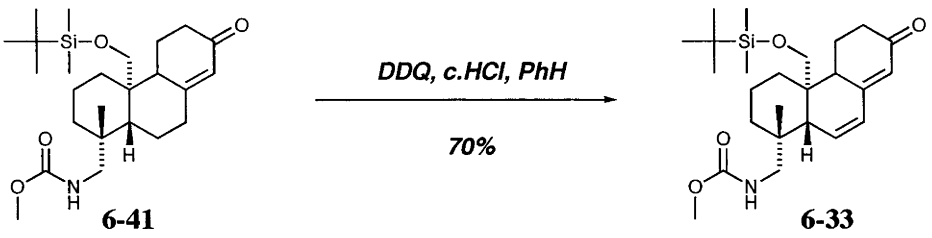


Figure 6.13. *Isomerisation*

With the enone **6-41** in hand, the acid catalysed DDQ oxidation could be attempted. The oxidation was carried out by treating the enone **6-41**, in benzene with a drop of concentrated HCl, with DDQ delivering the desired dienone **6-33** in 70% yield (**Scheme 6.15**). The dienone was characterised based on the ^1H NMR spectrum, which showed a pair of doublets at 6.32 ppm and 6.21 ppm, both with a vicinal coupling of 9.6 Hz, assigned to the two γ and ε protons. The ^{13}C NMR spectrum confirmed this finding with the appearance of two resonances at 111.7 ppm and 129.7 ppm.

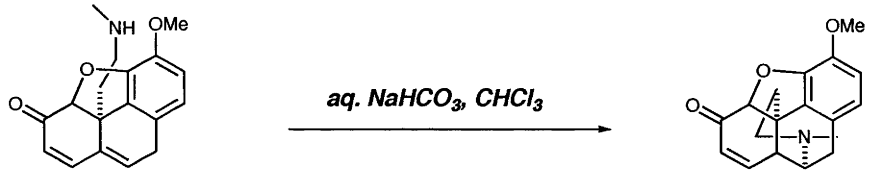


6-41 6-33

Scheme 6.15. *Oxidation of the Enone* ***6-41*** *to Dienone* ***6-33***

6.10 Pyrrolidine Formation

Having achieved the synthesis of the dienone **6-33**, our attention was turned to cyclising the carbamate function onto the dienone. A survey of literature revealed that intramolecular cyclisations of amino functions onto 1,4-enones are typically carried out using amides or amines. Fuchs synthesis of morphine employed a 1,6-addition, whereby treatment of the N-methyl amine **6-48** with base led to the cyclised product **6-49** (**Figure 6.14**). [10]

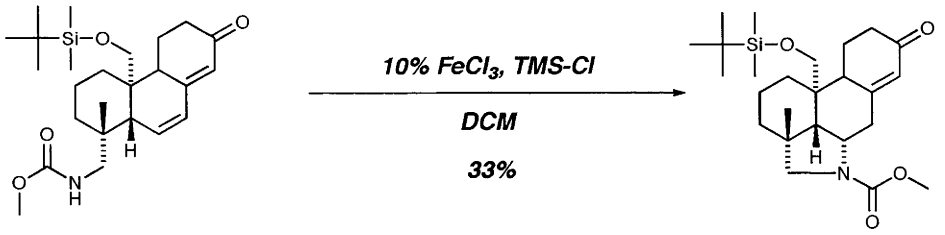


6-48 **6-49**

Figure 6.14. *Fuchs 1,6-Addition of N-Methyl Amine* ***6-49***

A number of papers have recently been published demonstrating the successful intermolecular 1,4-addition of carbamates under Lewis acid catalysed conditions. Under basic conditions it was considered that the reverse reaction, elimination of a carbamate group, would be facile and therefore it would be best to carry out the cyclisation under acidic conditions. Indeed, treatment of the carbamate **6-33** with DBU at room temperature or at reflux returned only starting material. Treatment under acidic conditions, employing *p*-TsOH, resulted in decomposition to a number of unidentified products, presumably as a consequence of cleavage of the silyl ether. In light of this outcome, the conditions needed to be sufficiently mild so as to prevent any unwanted side reactions.

A recent paper describes the intermolecular 1,4-addition of carbamates to enones catalysed by $FeCl_3$ and TMS-Cl.[11] We reasoned that an intramolecular process would be more favourable and so the carbamate **6-33** was treated with $FeCl_3$. After 2 hrs no reaction had occurred, but on the addition of 1 equivalent of TMS-Cl a rapid reaction took place to yield, to our delight, the desired 1,6-addition product **6-50** in 33% yield based on recovered starting material. Another product was also isolated in 12% that was tentatively assigned as the corresponding βγ-enone (**Scheme 6.16**).



6-33 **6-50**

Scheme 6.16. *Lewis Acid Catalysed Cyclisation*

The ^{1}H NMR spectrum of **6-50** was initially deceptive until it was realised that the carbamate existed as a pair of E/Z isomers. Upon heating a sample of **6-50** to 100 ^{0}C (D_6-DMSO) the rotamers coalesced to a single compound with an indicative amino methine proton at 4.09 ppm. From COSY analysis this resonance could be correlated to the two allylic C7 protons, at 2.75 ppm (J = 6.3 Hz, J = 19.5) and 3.12 ppm (J = 8.8 Hz), and H5 at 1.68 ppm (J = 8.3 Hz) (**Figure 6.15**). The methine at 4.09 ppm is a quartet with a 1:3:3:1 weighting and is therefore an unresolved with doublet of doublets of doublets with couplings to the C7 axial proton, C7 equatorial proton, and H5 proton of 6.3 Hz, 8.8 Hz, and 8.3 Hz, respectively. The ^{13}C NMR (75 ^{0}C, D_6-benzene) displayed three carbons at 59.5 ppm, 55.7 ppm, 53.5 ppm, which are characteristic of a pyrrolidine and could be assigned to C19, C5, and C6, respectively

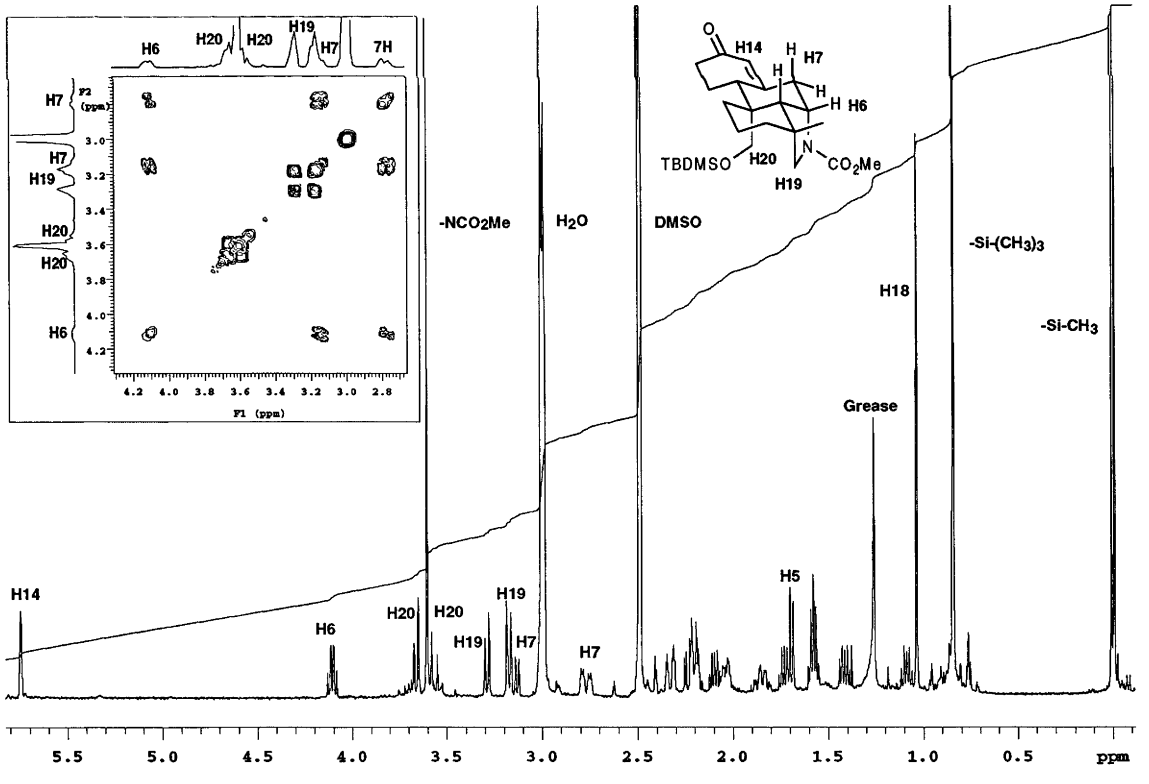


Figure 6.15. *^{1}H NMR (500 MHz, 100 ^{0}C, D_6-DMSO) spectrum and COSY spectrum of* ***6-50***

The product that was tentatively assigned as βγ-enone gave a similar ^{1}H NMR spectrum, with a broad peak at 4 ppm, but lacked the H14 methine proton of the conjugated enone, which was reflected in the IR spectrum with a carbonyl stretching band at 1683 cm^{-1} (cf. 1675 cm^{-1} for the αβ-enone). The IR spectrum was also informative wtih regard to the nature of the carbamate, which displayed a carbonyl stretching band at 1714 cm^{-1} in precursor **6-33**, but at 1700 cm^{-1} in the cyclised products, reflecting 2^0 and 3^0 carbamates, respectively.

The formation of **6-50** was an excellent result as it is the first reported case of an intramolecular conjugate of a carbamate. It establishes that the 1,6-addition is a viable route to access an advanced intermediate.

6.11 Future Directions

Pyrrolidine **6-50** intersects cleanly with the sequence outlined in **Chapter 3** and the next step will involve elaboration to allyl function **6-51**. As the reaction is catalysed by $TiCl_4$, it is conceivable that a βγ-enone would be enolised under the reaction conditions and deliver the same outcome as the addition to the αβ-enone. The stereochemistry of the 1,4-addition is uncertain and the outcome will determine the direction of the synthesis. Assuming the allyl substituent is delivered to the upper face of the molecule, the synthesis will lead directly to the bicyclooctane **6-52**. If the isomeric adduct is obtained as a result of the allyl substituent being delivered to the lower face, the synthesis will have to digress to interconvert the functionality. Regardless, on obtaining the bicycle **6-52** the silyl ether would be cleaved and the resulting alcohol group oxidised. The C14-C20 bond could then be constructed through an aldol reaction. The synthesis of the core structure **6-53** could then be completed on removal the carbamate group and activation of the hydroxyl group followed by an intramolecular alkylation (**Figure 6.12**).

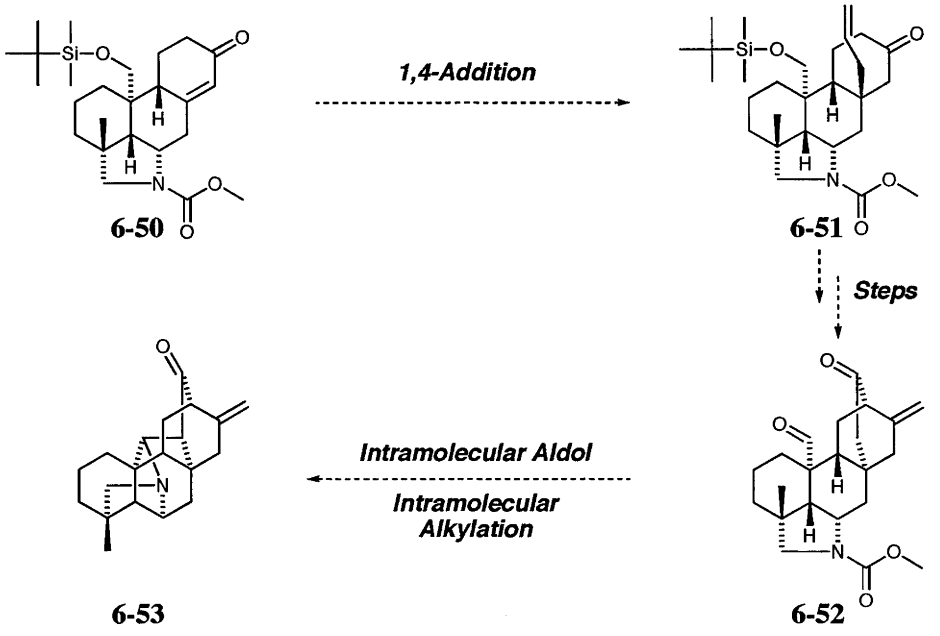


Figure 6.12. Future Directions

6.12 References

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Chapter Seven

Summary and Conclusions

7.1 Summary

The focus of this thesis was to devise a synthesis that would allow the construction of the hetisane skeleton, which is the most complex parent structure of the C_{20} family of diterpene alkaloids. The diterpene alkaloids are becoming increasingly important in the study of the central nervous system and this interest has sparked a resurgence in synthetic studies, with a view to discovering analogues with potent and specific biological activities.

Overall, two main approaches were explored. The first was outlined in **Chapter Three** and **Four**, whereby the plan was to install nitrogen at C6. In **Chapter Three** the installation of nitrogen was to be followed by an intramolecular variant of the Schmidt rearrangement, which would provide a concise entry point into the hetisane skeleton. Unfortunately, attempts to construct the precursor *via* the cyclisation of diazoketones resulted in unprecedented rearrangements. Thus, the synthetic strategy outlined in **Chapter Four** was devised, whereby the installation of nitrogen at C6 would be followed by a carbamate variant of the Dieckmann cyclisation. However, this strategy similarly met with difficulties and was ultimately aborted.

The second approach was outlined in **Chapters Five** and **Six**, and relied on the initial construction of the C4 quaternary centre complete with the N-C19 bond. The strategy was to use the stereochemistry invested in the C4 quaternary centre to direct the formation of the N-C6 bond by virtue of a 1,6-amino addition. The research conducted in **Chapter Five** proved the viability of constructing the C4 quaternary centre, but fell short of installing nitrogen into this system. This obstacle was overcome in **Chapter Six** whereby nitrogen was introduced early in the sequence as a nitrile, and the latent amino function being later liberated through reduction. The success of this strategy enable the preparation of the desired 1,6-dienone and thus the target pyrrolidine, which completed the synthesis of the A and B-ring functionality.

7.2 Conclusions

The overall focus of these studies was to grasp the complexity of total synthesis through the development of a strategy directed toward the synthesis of the diterpene alkaloids. Therefore, what the research outlined in **Chapter Three** did not provide towards these ends, was made up for by some fascinating chemistry that increased our understanding of diazoketone cyclisations. Similarly, **Chapter Four** was valuable in demonstrating the fine line on which a successful strategy rests, and then how the inherent properties of a chemical system can conspire against any efforts to achieve the desired outcome.

In contrast, **Chapter Five** exploited these properties to construct a system that was invaluable in laying the foundation for **Chapter Six**. In conclusion, this research has led to the successful synthesis of an advanced intermediate and in its entirety, this thesis will give researchers a solid platform on which to plan future efforts.

Chapter Eight

Experimental

8.1 General Experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In addition, selected experiments were run on an Inova 500 spectrometer operating at 500 MHz for proton and 125 MHz for carbon nuclei. Variable temperature experiments were run on the Inova 500 spectrometer. Chemical shifts were recorded as δ values in parts per million (ppm). Most spectra were acquired at 300 MHz, in deuterochloroform ($CDCl_3$), at 20 ^{0}C unless otherwise stated. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ7.26) was used as the internal reference; in CD_3OD the peak a due to residue D_3-MeOH (δ4.79); in D_6-acetone the central peak (δ2.05) of the pentet due to residual D_5-acetone; in D_6-benzene the peak due residual benzene at 7.15 ppm; in D_6-DMSO the central peak (δ2.49) of the pentet due to residual D_5-DMSO. The ^{1}H NMR spectra are reported as follows: chemical shift (δ) [relative integral, multiplicity (where multiplicity is defined as, AB = AB doublet, br = broad, d = doublet, t = triplet, m = multiplet, or combination thereof), coupling constant(s) *J* (Hz), and assignment (if significant) where H*a* = axial proton and H*e* = equatorial proton]. Selected ^{13}C NMR spectra were conducted using the attached proton test (APT) and the central peak (δ77.0) of the $CDCl_3$ triplet was used as an internal reference; in CD_3OD the central peak (δ49.0) of the CD_3OD septet; in D_6-benzene the central peak (δ128.0) of the D_6-benzene triplet. For ^{13}C NMR spectra, the data was reported as: chemical shift (δ) [protonicity (where protonicity is defined as: q = quartenary, t = tertiary, s = secondary, p = primary), assignment (where possible)]. The assignments of various NMR spectra were often assisted by homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY) and nuclear Overhauser effect (nOe, 1D NOSEY).

Infrared (IR) spectra (ν_{max}) were recorded on a Perkin-Elmer Spectrum One spectrometer. Samples were analysed as thin films on NaCl discs. The IR data is recorded as follows: wavenumber (cm^{-1}) [intensity defined as s = strong, m = medium, w = weak].

Low and high resolution mass spectra were recorded on a VG Fisions AutoSpec three sector (E/B/E) double focusing mass spectrometer, using positive ion electron impact techniques. Mass spectra data are listed as follows: mass-to-charge ratio (assignment [where possible]), intensity as relative % of base peak).

Melting points were recorded on a Gallenkamp Melting Point Apparatus and are uncorrected.

Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia.

Analytical thin layer chromatography (TLC) was conducted on aluminium backed 0.2 mm thick silica gel 60 F_{254} plates (Merck), visualised under a 254 nm UV lamp and/or by treatment with a poly molylidic acid (PMA) dip, followed by heating. Flash chromatography was conducted according to the method of Still and co-workers using silica gel 60 (mesh size 0.040-0.063) or alumina oxide 60 (mesh size 0.063-0.200) as the stationary phase and the analytic (AR) grade solvent indicated. Petroleum spirits refers to petroleum spirits 60-80 ^{0}C.

Materials and reagents were obtained from the Aldrich Chemical Company and were used as supplied or simply dried and/or distilled. Magnesium sulfate ($MgSO_4$) for drying was purchased from the Aldrich Chemical Company. Reactions employing air and moisture sensitive reagents and intermediates were conducted under an atmosphere of argon (that had been passed through a Alltech Associates Oxy-Trap and a column of Dierlite and calcium chloride) in a flame-dried apparatus.

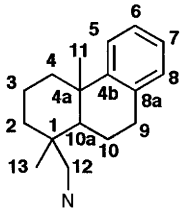
RT is assumed to be ca. 18 ^{0}C.

THF, Et_2O, benzene, and toluene were dried using sodium metal and then distilled, as required, from sodium benxophoneone ketyl. DCM was distilled from calcium hydride. Ammonia was dried with sodium metal and $FeNO_3$ and then distilled under an inert atmosphere as required. HMPA was dried over 4Å molecular sieves.

Organic solutions obtained from the work-up of reaction mixtures were dried with $MgSO_4$. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator with the water bath generally not exceeding 40 ^{0}C. Samples were then subjected to high vacuum to remove any remaining solvent.

8.2 Notes on Nomenclature

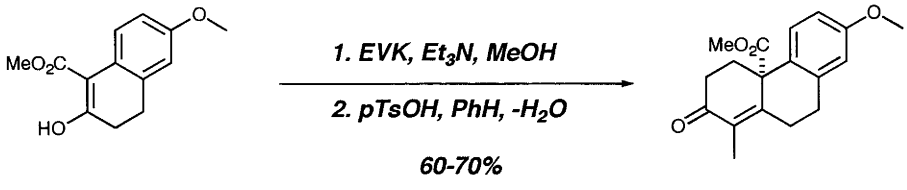
Throughout this thesis the carbon skeleton has been referred to using the established number system of the diterpene alkaloids (**Chapter 1, Figure 1.1**). However, in the following experimental section the compounds are named as phenanthrene derivatives. The common ring system of compounds synthesised during the course of this research is indicated below:



1,2,3,4,4a,9,10,10a-octahydro-4a-methylphenanthrene

8.3 Chapter Three Experimental

(±)-Methyl 2,3,4,4a,9,10-Hexahydro-7-methoxy-1-methyl-2-oxophenanthrene-4a-carboxylate (3-18)



3-17 **3-18**

The β-keto ester[1, 2] **3-17** (600 mg, 2.6 mmol) was taken up in MeOH (5 mL) in a 25 mL RB-flask. The flask was flushed with N_2 and triethylamine (0.8 mmol, 120 mL) and ethyl vinyl ketone (5.2 mmol, 520 mL) were added. After stirring at RT for 24 hrs, TLC indicated that the starting material had been consumed. The reaction mixture was diluted with EtOAc (30 mL) and was washed successively with 10% HCl (30 mL), H_2O (30 mL), and brine (30 mL). The aqueous layers were then re-extracted with EtOAc (2x, 30 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The brown residue was immediately taken up in toluene (30 mL) in a 50 mL RB-flask and *p*-TsOH (0.39 mmol, 77 mg) added. The flask was then fitted with a Dean-Stark apparatus and condenser, flushed with N_2 and then heated to reflux for 18 hrs. The reaction was allowed to cool and most of the toluene removed under reduced pressure. The reaction mixture was then diluted with EtOAc (30 mL) and washed successively with sat. $NaHCO_3$ and brine. The aqueous layers were re-extracted with EtOAc (2x, 30 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The brown residue was chromatographed on silica gel (Pet. Sp : EtOAc 4:1) to yield enone **3-18** (468mg, 62%).

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

MP: 108 °C (Lit. 102-103 °C)[3]

MICROANALYSIS: Found C 72.1, H 6.9, $C_{18}H_{20}O_4$ requires C 72.0, H 6.7.

HRMS: Found: M+ 300.1363. $C_{18}H_{20}O_4$ requires 300.1362.

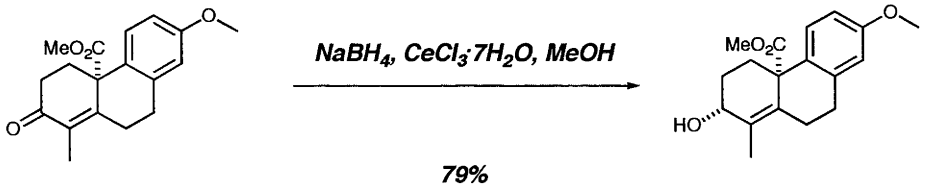
IR υ_{max} 2951 (l), 1724 (l), 1666 (l), 1499 (m), 1229 (m), 753 (m) cm^{-1}.

^{1}H NMR: δ 7.38 (1H, d, J = 8.8 Hz), 6.80 (1H, dd, J = 2.7 Hz, J = 8.7 Hz), 6.69 (1H, d, J = 2.6 Hz), 3.80 (3H, s), 3.65 (3H, s), 2.75-3.01 (5H, m), 2.57 (2H, m), 2.07 (1H, m), 1.87 (3H, s).

^{13}C NMR: δ 197.0 (q, C2), 172.4 (q, C11), 158.3 (t, C17), 155.0 (q, C10a), 138.6, 131.1. 129.2 (q, C8a, C4b, C1), 127.1 (t, C5), 112.9, 112.5 (t, C6, C8), 55.0, 52.6 (p, -O<u>C</u>H$_3$), 50.6 (q. C4a), 34.9, 33.8, 29.1, 28.8 (s, C9, C10, C3, C4), 11.2 (p, C12).

MS: *m/z* 300 (M+, 20%), 241 (100), 213 (37), 198 (12), 115 (22).

Methyl (2RS,4aSR)-2,3,4,4a,9,10-Hexahydro-2-hydroxy-7-methoxy-1-methylphenanthrene-4a-carboxylate (3-21)



3-18 **3-21**

A 150 mL RB-flask was charged with enone **3-18** (2.4 g, 8 mmol) and MeOH (80 mL), the flask was then flushed with N_2 and cooled to 0 ^{0}C (H_2O, ice). $CeCl_3$•$7H_2O$ (12 mmol, 2.9 g) was then added followed by the gradual addition of $NaBH_4$ (12 mmol, 460 mg). After addition was complete the ice bath was removed and the reaction allowed to stir for 90 mins, after which time TLC indicated the reaction to be complete. The flask was cooled to 0 ^{0}C (H_2O, ice) and H_2O (10 mL) slowly added. The quenched reaction was diluted with EtOAc (200 mL) and then washed with H_2O (100 mL) and brine (100 mL). The aqueous layers were re-extracted with EtOAc (100 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel (Pet.Sp.:EtOAc 1:2) to yield the alcohol **3-21** (1.9 g. 79%) as a clear oil.

R_f: 0.32 (1:1 Pet.Sp:EtOAc).

HRMS: Found: M+ 302.1519. $C_{18}H_{22}O_4$ requires 302.1518.

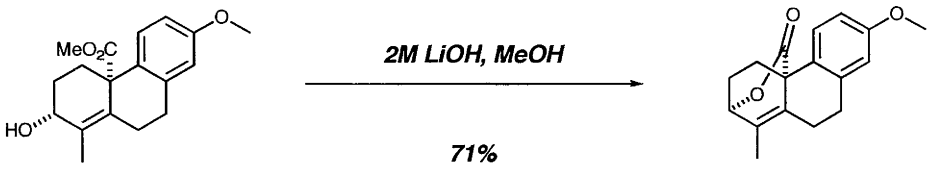
IR: 3456 (bm), 2947 (l), 1722 (l), 1608 (l), 1579 (m), 1498 (l), 1248 (l), 754 (l) cm^{-1}.

^{1}H NMR: δ 7.36 (1H, d, J = 8.8 Hz), 6.76 (1H, dd, J = 2.8 Hz, J = 8.6 Hz), 6.64 (1H, d, J = 2.8 Hz), 4.01 (1H, dd, J = 6.7 Hz, J = 8.2 Hz, H2), 3.78 (3H, s), 3.62 (3H, s), 2.59-2.82 (5H, m), 2.28 (1H, s), 2.12 (1H, m), 1.81 (3H, s), 1.56-1.79 (2H, m).

^{13}C NMR:δ 175.1 (q, C11), 157.9 (t, C7), 139.3, 132.1, 131.4, 131.2 (q, C1, C10a, C8a, C4b), 127.4 (t, C5), 112.9, 112.0 (t, C6, C8), 70.5 (t, C2), 55.1, 52.4 (p, -O<u>C</u>H$_3$), 50.3 (q. C4a), 32.6, 30.2, 29.6, 26.8 (s, C3, C4, C9, C10), 15.1 (p, C12).

MS *m/z* 302 (M+, 4%), 243 (100), 225 (71), 211 (38), 165 (28), 115 (18).

(2RS,4aSR)-2,3,4,4a,9,10-Hexahydro-2-hydroxy-7-methoxy-1-methylphenanthrene-2,4a-carbolactone (3-33)



3-31 **3-33**

A 100 mL RB-flask was charged with alcohol **3-31** (1.2 g, 4 mmol), MeOH (40 mL), and 2M LiOH (20 mL). The resulting mixture was stirred for 24 hrs. After this time the reaction was then diluted with EtOAc (150 mL) and washed with H_2O (2x, 100 mL), and brine (100 mL). The aqueous layers were further extracted with EtOAc (2x, 100 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The oily residue was chromatographed (Pet.Sp:EtOAc 3:1) to yield lactone **3-33** (770 mg, 71%) as awhite solid.

R_f: 0.50 (1:1 Pet.Sp:EtOAc).

MP: 109-110 ^{0}C

HRMS: Found: M+ 270.1258. $C_{17}H_{18}O_3$ requires 270.1256

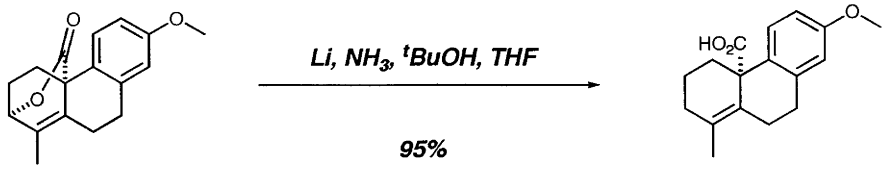
IR: υ_{max} 2939 (bm). 1744 (l), 1611 (m), 1578 (l), 1505 (l), 1248 (l), 1120 (l) cm^{-1}.

^{1}H NMR: δ 7.41 (1H, d, J = 8.6 Hz), 6.85 (1H, dd, J = 2.6 Hz, J = 8.6 Hz), 6.73 (1H, d, J = 2.3 Hz), 4.99 (1H, brs, H2), 3.81 (3H, s), 2.73 (2H, m), 2.55 (1H, s), 2.26-2.43 (3H, m), 1.90 (3H, s), 1.74 (1H, m), 1.55 (1H, m).

^{13}C NMR: δ 174.8 (q, C11), 158.1 (t, C7), 139.3, 135.4, 131.1, 125.6 (q, C1, C10a, C8a, C4b), 129.5 (t, C5), 113.2, 112.2 (t, C6, C8), 78.4 (t, C2), 55.1 (p, -O<u>C</u>H$_3$), 48.3 (q. C4a), 29.3, 28.8, 26.5, 23.7 (s, C3, C4, C9, C10), 14.5 (p, C12).

MS: *m/z* 270 (M+, 3%), 243 (8), 226 (100), 211 (67), 165 (24)

(±)-2,3,4,4a,9,10-Hexahydro-7-methoxy-1-methylphenanthrene-4a-carboxylic acid (3-19)



3-33 **3-19**

The lactone **3-33** (230 mg, 0.85 mmol), in dry THF (9 mL), containing ^{t}BuOH (90 μL, 0.85 mmol), was added to freshly distilled ammonia (200 mL) at –78 ^{0}C (acetone/dry ice), under an atmosphere of nitrogen, in a 3-necked RB-flask fitted with a dry ice condenser. Lithium (10 mg) was added and the resulting blue solution stirred for 30 mins. At this point the excess lithium was quenched with ammonium chloride (NH_4Cl) and the ammonia removed under a stream of nitrogen. Removal of the THF under reduced pressure yielded a white residue that was taken up in EtOAc (20 mL) and washed with H_2O (20 mL). The aqueous phase was then acidified (pH 2) with 5M HCl reaction and the organic layer washed with water (20 mL) and brine (20 mL). The aqueous layers were re-extracted with EtOAc (2x, 20 mL) and the combined organic layers dried over magnesium sulphate ($MgSO_4$). Removal of the solvent under reduced pressure yielded the acid **3-19** (220 mg, 95%) as a white solid.

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

MP: 182 ^{0}C

MICROANALYSIS: Found C 75.2, H 7.6, $C_{17}H_{20}O_2$ requires C 75.0, H 7.4

HRMS: Found: M+, 272.1414. $C_{17}H_{20}O_3$ requires 272.1412.

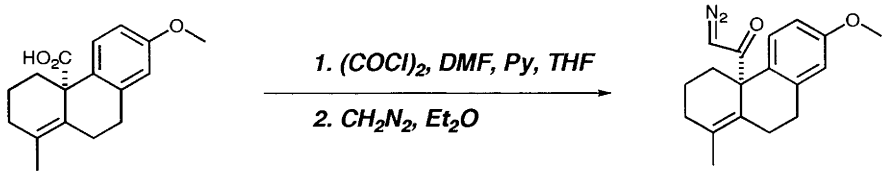
IR: υ_{max} 2916 (s), 1690 (s), 1607 (m), 1498 (m), 1247 (m) cm^{-1}.

^{1}H NMR: δ 7.43 (1H, d, J = 8.8 Hz), 6.76 (1H, dd, J = 2.8 Hz, J = 8.6 Hz), 6.64 (1H, d, J = 2.8 Hz), 3.8 (3H, s, O-CH_3), 2.59-8.88 (5H, brm), 2.06 (1H, brs), 1.73 (3H, s) 1.64-1.81 (3H, m).

^{13}C NMR: δ 181.8 (q, C11), 157.9 (q, C7), 139.6, 131.2 (q, C4b, C8a), 129.2, 127.9 (q, C10a, C1), 128.2 (t, C11), 113.0, 112.0 (t, C8, C8), 55.2 (p, -O$\underline{C}H_3$), 49.6 (q, C4a), 35.1, 31.9, 30.2, 26.2, 20.0 (s, C2, C3, C4, C9, C10), 19.6 (p, C12).

MS: *m/z* 272 (M^+, 6%), 227 (M^+ -CO_2H, 100), 198 (7), 171 (9), 115 (7).

(±)-4a-Diazoacetyl-2,3,4,4a,9,10-hexahydro-7-methoxy-1-methylphenanthrene (3-14)



3-19 **3-14**

Oxalyl chloride (350 μL, 4 mmol) was added to a solution of DMF (310 μL, 4 mmol) in dry THF (5 mL), under N_2, at 0 ^{0}C and the resulting suspension stirred for 1 hr. The acid **3-19** (100 mg, 0.4 mmol), in dry THF (5 mL) containing pyridine (100 μL, 1.2 mmol), was transferred into the DMF solution by canular. The mixture was stirred for 2 hrs at RT before heating to reflux for an additional 2 hr. The reaction was then cooled and carefully cannulated into an excess of diazomethane being stirred at 0 ^{0}C. The reaction was allowed to warm to RT and stirred for 2 hr. The solvent was removed under reduced pressure and the residue chromatographed on silica gel (9:1 EtOAc:Pet. Sp.) to yield the diazoketone **3-14** (70 mg, 59%) as a yellow oil.

R_f: 0.67, (2:1 Pet.Sp:EtOAc).

HRMS: Found: M+ -N_2, 268.1467, $C_{18}H_{20}O_2$ requires 268.1463.

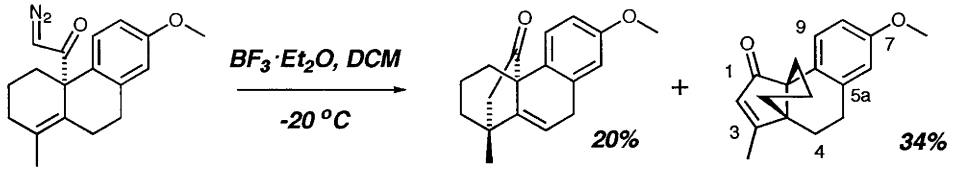
IR: υ_{max} 2934 (m), 2100 (s), 1723 (m), 1609 (m), 1497 (m), 1337 (m) cm^{-1}.

^{1}H NMR: δ 7.37 (1H, d, J = 8.6 Hz), 6.78 (1H, dd, J = 2.8 Hz, J = 8.6 Hz), 6.67 (1H, d, J = 2.8 Hz), 5.18 (1H, s, -C<u>H</u>N_2), 3.79 (s), 2.68-2.73 (2H, m), 2.48-2.53 (2H, m), 2.07 (2H, brs), 1.72-1.88, (3H, m), 1.7 (3H, s, -C<u>H</u>$_3$).

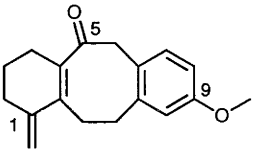
^{13}C NMR: δ 198.0 (q, C11), 158.2 (q, C7), 140.5, 132.3, 130.7, 127.6 (q, C1, C4b, C8a, C10a), 127.0 (t, C5), 113.1, 111.7 (t, C6, C8), 55.2 (p, -O<u>C</u>H_3) , 54.6 (q, C4a), 53.4 (t, -<u>C</u>HN_2), 34.1, 31.9, 29.4, 27.0 (s, C2, C4, C9, C10), 19.8 (s, C3), 19.1 (p, C12).

MS: *m/z* 268 (M+ –N_2, 7%) 227 (100), 211 (7), 167 (7), 115 (6).

(1SR, 4aSR) 1,2,3,4,4a,9-Hexahydro-1,4a-ethano-7-methoxy-1-methylphenanthren-11(12H)-one (3-15), 1,2,3,4,11,12-Hexahydro-1-methylene-9-methoxy-dibenzo[a,e]cyclooctene-5(6H)-one (3-67) & (3aRS,9bSR)-4,5-Dihydro-7-methoxy-3-methyl-3a,9b-propano-3aH-cyclopenta[a]naphthalen-1(9bH)-one (3-40)



3-14 **3-15** **3-40**



5%

3-67

The diazoketone **3-14** (20mg, 0.07 mmol) in dry DCM (7 mL) was cooled to –20 °C (acetone, dry ice) under an atmosphere of argon. BF_3•Et_2O (0.33 mmol, 42 μL) was then added and the reaction stirred for 10 mins. H_2O (2 mL) was added and the ice bath removed and the reaction stirred at RT for 30 mins. The organic layer was separated and washed with H_2O (5 mL) and brine (5 mL). The aqueous layers were re-extracted wit EtOAc (2x, 5 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a oily residue. The residue was then chromatographed on silica gel (Pet.Sp:EA 9:1 – 1:1) to give in order of elution, cyclopentanone **3-15** (3.9 mg, 20%), octalone **3-67** (1 mg, 5%), and cyclopentanone **3-40** (6.5 mg, 34 %).

(1SR, 4aSR) 1,2,3,4,4a,9-Hexahydro-1,4a-ethano-7-methoxy-1-methylphenanthren-11(12H)-one (3-15)

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

HRMS: Found: $M^{+\cdot}$, 268.1465, $C_{18}H_{20}O_2$ requires 268.1463.

IR: υ_{max} 2932 (s), 1746 (s), 1610 (m), 1503 (m), 1278 (m) cm^{-1}.

^{1}H NMR: δ 7.80 (1H, d, *J* = 8.5 Hz), 6.83 (IH, dd, *J* = 2.9 Hz, *J* = 8.8 Hz), 6.78 (IH, d, *J* = 2.9 Hz), 5.64 (IH, dd, *J* = 2.5 Hz, *J* = 4.7 Hz, H10), 3.78 (3H, s), 3.47 (1H, brd, *J* = 2.5 Hz, *J* = 21.3 Hz, H9*e*), 3.32 (1H, dd, *J* = 4.7 Hz, *J* = 21.7 Hz, H9*a*), 2.36 (1H, d, *J* = 17.9 Hz), 2.06 (2H, d&m, *J* = 17.9 Hz), 1.6 – 1.8 (6H, m).

^{13}C NMR: δ 216.1 (q, C11), 158.0 (q, C7), 147.5, 134.8 (q, C4b, C8a), 128.8, 127.1 (C5, C10a), 112.6, 112.3 (t, C6, C8), 110.4 (t, C10), 55.2 (-O$\underline{C}$H$_3$), 53.5, 51.3 (C12, C4a), 43.0 (C1), 40.1, 39.6 (C2, C9), 30.0, 22.6, 20.7 (C3, C4, C13).

MS: *m/z* 268 ($M^{+\cdot}$, 85%), 240 (50), 225 (100), 184 (72), 165 (30).

1,2,3,4,11,12-Hexahydro-1-methylene-9-methoxy-dibenzo[a,e]cyclooctene-5(6H)-one (3-67)

^{1}H NMR: δ 6.93 (1H, d, J = 8.1 Hz), 6.61 (2H, m), 5.24 (1H, s, H12), 4.93 (1H, s, H12`), 3.85 (2H, s), 3.76 (3H, s), 3.01 (2H, t, J = 7.5 Hz), 2.87 (2H, d, J = 7.5 Hz), 2.06 (4H, m), 1.44 (2H, m)

(3aRS,9bSR)-4,5-Dihydro-7-methoxy-3-methyl-3a,9b-propano-3aH-cyclopenta[a]naphthalen-1(9bH)-one (3-40)

R_f: 0.64 (1:1 Pet. Sp.:EtOAc).

HRMS: Found: M+., 268.1465, $C_{18}H_{20}O_2$ requires 268.1463.

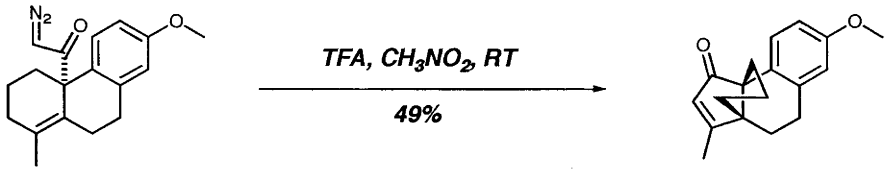
IR: υ_{max} 2947 (m), 1697 (s), 1619 (m), 1498 (m), 1248 (m) cm^{-1}.

^{1}H NMR: δ 7.43 (1H, d, *J* = 8.5 Hz), 6.79 (IH, dd, *J* = 2.8 Hz, *J* = 8.6 Hz), 6.58 (IH, d, *J* = 2.6 Hz), 6.03 (IH, d, *J* = 1.2 Hz), 3.76 (3H, s, -OCH$_3$), 2.50-2.62 (2H, m), 2.12-2.41 (2H, m), 2.12 (3H, d, *J* = 1.3 Hz), 1.94-2.00 (1H, m), 1.50-1.73 (4H, m), 1.22-1.46 (1H, m).

^{13}C NMR: δ 209.5 (q, C12), 180.6 (q, C14), 157.8 (q, C4), 138.6, 130.3 (q, C8a, C4b), 132.7 (t, C13), 129.7 (t, C2), 113.0, 112.8 (t, C3, C5), 61.7, 58.8 (q, C1a, C8), 55.5 (p, -O$\underline{C}$H$_3$) 38.6, 37.0, 32.1, 27.9, 23.8 (s, C6, C7, C9, C10, C11), 15.6 (p, C15).

MS: *m/z* 268 (M+, 100%), 253 (29), 240 (20), 225 (32), 200 (30), 165 (20), 115 (19).

(3aRS,9bSR)-4,5-Dihydro-7-methoxy-3-methyl-3a,9b-propano-3aH-cyclopenta[a]naphthalen-1(9bH)-one (3-40)

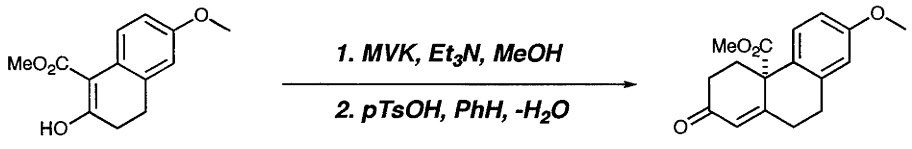


3-14 **3-40**

The diazoketone **3-14** (10 mg, 0.03 mmol) in nitromethane (2 mL)was added dropwise, over 15 mins, to a solution of nitromethane containing TFA (10 μL, 0.09 mmol) at RT. The reaction mixture was then poured onto EtOAc (20 mL) and washed with sat. $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL). The aqueous layers were back extracted with EtOAc (2x, 5 mL) and the combined organic layers dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure gave a brown oil. Flash chromatography (silica gel, 1:4 EtOAc:Pet.Sp.) yielded the cyclopentanone **3-40** (4 mg, 49%) as a yellow oil.

As characterised above.

(±)-Methyl 2,3,4,4a,9,10-Hexahydro-7-methoxy-2-oxophenanthrene-4a-carboxylate (3-50)



3-17 **3-50**

The β-keto ester **3-17** (12.2 g, 52 mmol) was taken up in MeOH (100 mL) in a 250 mL RB-flask. The flask was flushed with N_2 then triethylamine (17 mmol, 2.4 mL) and ethyl vinyl kentone (104 mmol, 8.8 mL) were added. After stirring at RT for 72 hrs TLC indicated that the starting material had been consumed. The reaction mixture was diluted with EtOAc (500 mL) and was washed successively with 10% phosphoric acid (500 mL), sat. $NaHCO_3$ (500 mL), and brine (500 mL). The aqueous layers were re-extracted with EtOAc (2x, 500 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The brown residue was immediately taken up in benzene (140 mL) in a 250 mL RB-flask and *p*-TsOH (1 g) added. The flask was then fitted with a Dean-Stark apparatus and condenser, flushed with N_2, and then heated to reflux for 18 hrs. The reaction was allowed to cool and most of the toluene removed under reduced pressure. The reaction mixture was diluted with EtOAc (200 mL) and washed successively with sat. $NaHCO_3$ (200 mL) and brine (200 mL). The aqueous layers were re-extracted with EtOAc (2x, 200 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The brown residue was chromatographed on silica gel (Pet. Sp : EtOAc 4:1) to yield enone **3-50** (10.2 g, 67%), which gave yellow crystals from MeOH.

R_f: 0.42 (EA: Pet.Sp. 1:1)

MP: 81-83 °C

MICROANALYSIS: Found C 71.0, H 6.4, $C_{17}H_{18}O_4$ requires C 71.3, H 6.3.

HRMS: Found: M^+ 286.1205, $C_{17}H_{18}O_4$ requires 286.1205.

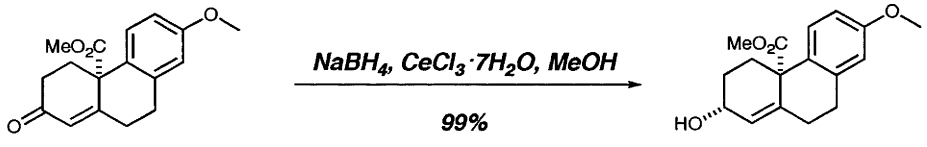
IR: υ_{max} 2952 (m), 1727 (l), 1671 (l), 1609 (l), 1501 (l), 1247 (l), 1040 (m) cm^{-1}.

^{1}H NMR: δ 7.37 (1H, d, J = 8.8 Hz), 6.78 (1H, dd, J = 2.8 Hz, J = 8.8 Hz), 6.65 (1H, d, J = 2.8 Hz), 6.02 (1H, s), 3.79 (3H, s), 3.68 (3H, s), 2.46-3.14 (7H, m), 1.96 (1H, td, J = 4.7 Hz, J = 13.9).

^{13}C NMR: δ 198.6 (q, C2), 171.9 (q, C11), 162.5 (q, C10a), 158.4 (t, C7), 137.4, 128.6 (q, C8a, C4a), 127.9, 126.2 (t, C1, C5), 113.4, 113.2 (t, C6, C8), 55.2, 52.9 (p, -O<u>C</u>H$_3$), 49.5 (q. C4a), 36.0, 35.9, 32.7, 30.4 (s, C9, C10, C4, C3).

MS: *m/z* 286 (M^+, 27%), 227 (100), 199 (25), 171 (13), 115 (17).

Methyl (2RS,4aSR)-2,3,4,4a,9,10-Hexahydro-2-hydroxy-7-methoxyphenanthrene-4a-carboxylate (3-51)



3-50 **3-51**

The enone **3-50** (5g, 17.5 mmol) was dissolved in MeOH (180 mL) and cooled to 0 °C (H_2O, ice). $CeCl_3$•$7H_2O$ (17.5 mmol, 4.3 g) was added followed by the slow addition of $NaBH_4$ (26 mmol, 990 mg). The flask was then flushed with nitrogen and allowed to warm to RT. After 1 hr TLC analysis indicated that the starting material had been consumed. The reaction was then cooled to 0 °C (H_2O, ice) and quenched with the slow addition of H_2O (5 mL). Most of the MeOH was removed under reduced pressure and EtOAc (100 mL) and H_2O (100 mL) added. The organic layer was washed with H_2O (100 mL) and brine (100 mL) and the aqueous layers re-extracted with EtOAc (2x, 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give alcohol **3-51** (5g, 99%) as a clear oil.

R_f: 0.16 (2:1 Pet. Sp.:EtOAc).

HRMS: Found: M^+ 288.1364, $C_{17}H_{20}O_4$ requires 288.1362.

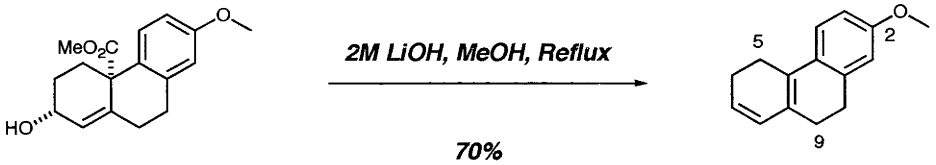
IR: υ_{max} 3401 (bs), 2933 (m), 1725 (s), 1608 (m), 1500 (m), 1227 (m) cm^{-1}.

^{1}H NMR: δ 7.36 (1H, d, J = 8.8 Hz), 6.74 (1H, dd, J = 2.6 Hz, J = 8.7 Hz), 6.59 (1H, d, J = 2.6 Hz), 5.70 (1H, s), 4.23 (1H, brt), 3.76 (3H, s), 3.64 (3H, s), 2.70 (4H, m), 2.40 (1H, m), 2.05 (1H, m), 1.6 (2H, m).

^{13}C NMR: δ 174.6 (q, C11), 158.1 (q, C7), 139.5, 138.2, 130.4 (q, C10a, C4b, C8a), 128.4, 127.7 (t, C1, C5), 113.2, 112.7 (t, C6, C8), 67.2 (t, C2), 55.1, 52.5 (p, -O<u>C</u>H$_3$), 49.0 (q, C4a), 34.8, 31.6, 31.4, 30.8 (s, C3, C4, C9, C10).

MS: *m/z* 288 (M$^{+\cdot}$, 22%), 229 (100), 211 (95), 179 (15)

5,6,9,10-tetrahydro-2-methoxyphenanthrene (3-53)



3-51 **3-53**

The alcohol **3-51** (1g, 3.47 mmol) was taken up in MeOH (30 mL) and treated with 2M LiOH (34 mmol, 17 mL) and heated to reflux for 18 hrs at which point TLC analysis indicated all the starting material was consumed. The reaction was then cooled to 0 ^{0}C (H_2O, ice) and EtOAc (50 mL) and H_2O (50 mL) added. The aqueous layer was extracted with EtOAc (2x, 100 mL) and the organic layers then washed with H_2O (100 mL) and brine (100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude phenanthrene **3-53** as a brown oil (520 mg, 70%), which was characterised without further purification.

HRMS: Found: M$^{+\cdot}$ 212.1202, $C_{15}H_{16}O$ requires 212.1201.

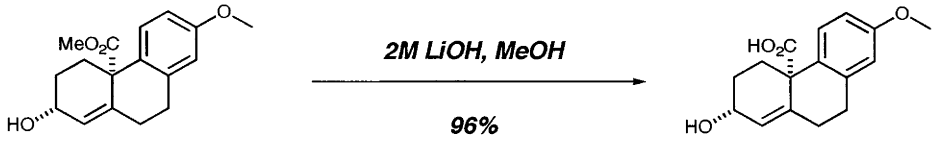
IR: υ_{max} 2930 (m), 2828 (m), 1605 (m), 1497 (m), 1251 (m) cm^{-1}.

^{1}H NMR: δ 7.15 (1H, d, J = 8.1 Hz), 6.70 (2H, m), 5.91 (1H, brd, J = 9.5 Hz), 5.81 (1H, m), 3.80 (3H, s), 2.74 (2H, t, J = 8.2 Hz), 2.48 (2H, m), 2.25 (4H, m).

^{13}C NMR: δ 158.0 (q, C2), 137.7, 128.9, 128.4, 126.9 (q, C4a, C4b, 8a, C10a), 128.6, 125.3, 122.7 (t, C4, C7, C8), 113.7, 110.9 (t, C1, C3), 55.3 (p, -O<u>C</u>H$_3$), 28.8, 27.2, 23.3, 23.0 (s, C5, C6, C9, C10).

MS: 212 (M$^{+\cdot}$, 50%), 147 (15).

(2RS,4aSR)-2,3,4,4a,9,10-Hexahydro-2-hydroxy-7-methoxyphenanthrene-4a-carboxylic acid (3-54)



3-51 **3-54**

The alcohol **3-51** (5g, 17.3 mmol) was taken up in MeOH (180 mL) and treated with LiOH (7g, 0.17 mol) and H_2O (20 mL) and heated at 30-40 ^{0}C for 18 hrs, at which point TLC analysis indicated all the starting material had been consumed. The reaction was cooled to 0 ^{0}C (H_2O, ice) and phosphoric acid added to adjust to pH 2. The aqueous layer was extracted with EtOAc (2x, 200 mL) and the organic layers washed with H_2O (200 mL) and brine (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the acid **3-54** (4.6g, 96% over 2 steps) as an off-white amorphous solid.

HRMS: Found: $M^{+\cdot}$ 274.1205, $C_{16}H_{18}O_4$ requires 274.1205.

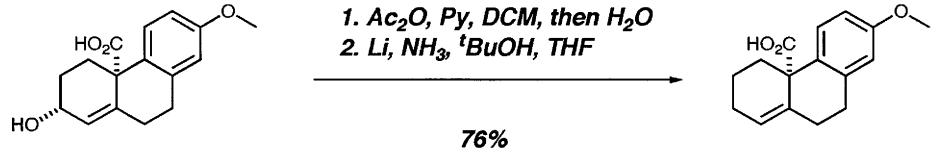
IR: υ_{max} 3401 (bs), 2935 (s), 1713 (s), 1608 (s), 1500 (s), 1243 (s) cm^{-1}.

^{1}H NMR: (CD_3OD) δ 7.20 (1H, d, J = 8.7 Hz), 6.57 (1H, d, J = 8.8 Hz), 6.59 (1H, s), 5.49 (1H, s), 4.02 (1H, brt), 3.59 (3H, s), 2.40-2.90 (4H, m), 2.20 (1H, m), 1.90 (1H, m), 1.3-1.6 (2H, m)

^{13}C NMR: (CD_3OD) δ 177.6 (q, C11), 159.6 (q, C7), 141.0, 139.4, 132.2 (q, C10a, C4b, C8a), 129.3, 128.6 (t, C1, C5), 114.2, 113.7 (t, C6, C8), 68.1 (t, C2), 55.6 (p, -O<u>C</u>H$_3$), 50.0 (q, C4a), 35.9, 32.7, 31.5 (s, C3, C4, C9, C10).

MS: *m/z* 274 ($M^{+\cdot}$, 3%), 229 ($M^{+\cdot}$ –CO_2H, 70), 212 (100), 197 (32), 165 (31).

(±)-2,3,4,4a,9,10-Hexahydro-7-methoxyphenanthrene-4a-carboxylic acid (3-57)



3-54 **3-57**

The acid **3-54** (4.6g, 1.7 mmol) was dissolved in pyridine (150 mL) and acetic anhyride (83.5 mmol, 7.8 mL). The reaction was stirred for 24 hrs and then ice (5g) was added and the reaction stirred for an additional 3 hr. After this time the reaction was poured onto H_2O (200 mL) and phosphoric acid added to adjust to pH 2. The aqueous layer was extracted with EtOAc (3x, 200 mL) and the organic layers washed with H_2O (100 mL) and brine (100 mL). The combined orgainic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the acetate **3-63** as crude solid (5.2 g, 98%). The crude acetate **3-63** (5.2 g, 16 mmol) was immediately taken up in dry THF (150 mL) containing ^tBuOH (16 mmol, 1.5 mL) and added to freshly distilled NH_3 (400 mL) at –78 ^0C (acetone/dry ice) under an atmosphere of N_2. Small pieces of lithium were added until the characteristic blue colour persisted for 2 mins. The reaction was then quenched by the addition of NH_4Cl, the ice bath removed and the ammonia removed under a stream of nitrogen to give a white residue. The residue was dissolved in H_2O (200 mL) and adjusted to pH 2. The aqueous layer was extracted with EtOAc (2x, 200 mL) and the organic layers washed with brine. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the acid **3-57** as a crude white solid. Successive crystallisation of the acid from MeOH then afforded the acid **3-57** as clear crystals (2.02 g, 45% over 2 steps). Removal of the mother liquor gave the crude acid (1.4g, 31% over 2 steps).

MP: 173 ^0C

EA: Found C 74.2, H 6.9, $C_{16}H_{18}O_3$ requires C 74.4, H 7.0.

HRMS: Found: $M^{+\cdot}$ 258.1257, $C_{16}H_{18}O_3$ requires 258.1256.

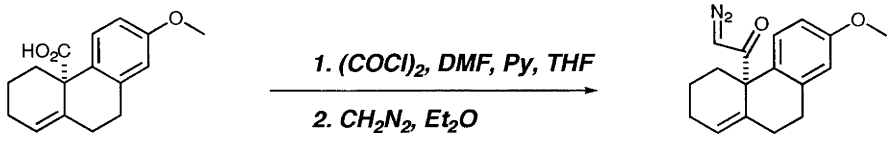
IR: υ_{max} 2927 (m), 1688 (m), 1606 (w),1497 (w) cm^{-1}.

^{1}H NMR: (CD_3OD) δ 7.24 (1H, d, J = 8.8 Hz), 6.56 (1H, d, J = 2.7 Hz, J = 8.8 Hz), 6.45 (1H, d, J = 2.6 Hz), 5.50 (1H, s), 3.59 (3H, s), 2.50-2.70 (4H, m), 2.18 (1H, m), 1.81 (2H, m), 1.55 (2H, m), 1.19 (1H, td, J = 5.4 Hz, J = 12.6 Hz).

^{13}C NMR: (CD_3OD) δ 178.4 (q, C11), 159.5 (q, C7), 139.7, 138.6, 132.6 (q, C10a, C4b, C8a), 129.6, 124.5 (t, C1, C5), 114.2, 113.5 (t, C6, C8), 55.5 (p, -O<u>C</u>H$_3$), 49.9 (q, C4a), 36.9, 33.0 (2x), 25.0, 21.5 (s, C2, C3, C4, C9, C10).

MS: *m/z* 258 ($M^{+\cdot}$, 3%), 213 ($M^{+\cdot}$ –CO_2H, 100), 171 (3), 128 (2).

(±)-4a-Diazoacetyl-2,3,4,4a,9,10-hexahydro-7-methoxy-phenanthrene (3-58)



3-57 *70%* **3-58**

Oxalyl chloride (19.3 mmol, 1.7 mL) was carefully added to a solution of DMF (19.3 mmol, 1.5 mL) in dry THF (40 mL), under nitrogen, at 0 ^{0}C (H_2O, ice). The ice bath was removed and the suspension stirred for 1 hr. The mixture was then cooled to 0 ^{0}C (H_2O, ice) and the acid **3-57** (500 mg, 1.9 mmol), in dry THF (20 mL) containing pyridine (5.8 mmol, 465 μL), was added *via* a cannular. The ice bath was removed and the mixture was stirred for 2 hrs at RT after which time TLC analysis indicated the stating material was consumed. The reaction was cooled and carefully cannulated into an excess of ethereal diazomethane at 0 ^{0}C (H_2O, ice). The reaction was allowed to warm to RT and stirred for 2 hrs. The solvent was slowly removed under reduced pressure and the residue chromatographed on silica gel (1:6 EtOAc:Pet. Sp.) to yield the diazoketone **3-58** (393 mg, 72%) as a yellow oil.

HRMS: Found: $M^{+\cdot}$ 282.1366 , $C_{17}H_{18}O_2N_2$ requires 282.1368.

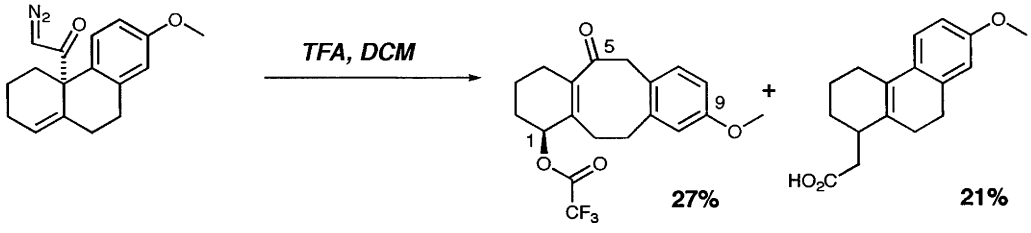
IR: υ_{max} 2931 (m), 2102 (s), 1609 (m), 1497 (m), 1329 (m) cm^{-1}.

^{1}H NMR: δ 7.51 (1H, d, J = 8.7 Hz), 6.78 (1H, d, J = 2.6 Hz, J = 8.8 Hz), 6.60 (1H, d, J = 2.7 Hz), 5.82 (1H, s), 5.44 (1H, s, -C<u>H</u>N$_2$), 3.77 (3H, s), 2.40-2.90 (5H, m), 1.6-2.12 (5H, m).

^{13}C NMR: δ 197.9 (q, C11), 158.0 (q, C7), 138.6, 136.0, 131.2 (q, C10a, C4b, C8a), 129.1, 125.9 (t, C1, C5), 113.0, 112.6 (t, C6, C8), 55.0 (p, -O<u>C</u>H$_3$), 54.1 (t, C12), 52.9 (q, C4a), 35.7, 31.3 (2x), 24.8, 19.4 (s, C2, C3, C4, C9, C10).

MS: *m/z* 282 ($M^{+\cdot}$, 1%), 213 (100), 171 (20), 165 (17), 115 (15).

(±)-1,2,3,4,5,6,11,12-Octahydro-9-methoxy-1-trifluoroacetoxy-dibenzo[a,e]cyclooctene-5(6H)-one (3-60) & (±)-2-(1,2,3,4,9,10-Hexahydro-7-methoxyphenanthren-1-yl)acetic acid (3-59).



3-58 **3-60** **3-59**

The diazoketone **3-58** (50 mg, 0.18 mmol) in dry DCM (1 mL) was added to TFA (0.18 mmol, 14 μL) in dry DCM (1 mL) at 0 ^{0}C (H_2O, ice) and stirred for 5 mins. After this time H_2O (5 mL) and EtOAc (5 mL) were added. The organic layer was washed with H_2O (2x, 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give an oil. Chromatography of the residue on silica gel (Pet.Sp: EtOAc 9:1) gave the cyclooctanone **3-60** (18 mg, 27 %) as a yellow oil and the acid **3-59** (10 mg, 21%) as a crude solid.

(±)-1,2,3,4,5,6,11,12-Octahydro-9-methoxy-1-trifluoroacetoxy-dibenzo[a,e]cyclooctene-5(6H)-one (3-60)

HRMS: Found: $M^{+\cdot}$ 368.1246 , $C_{19}H_{19}O_4F_3$ requires 369.1235.

IR: υ_{max} 2947 (m), 1779 (s), 1683 (m), 1609 (m), 1504 (m), 1150 (s) cm^{-1}.

^{1}H NMR: δ 6.96 (1H, d, *J* = 8.2 Hz), 6.67 (1H, d, *J* = 2.8 Hz, *J* = 8.2 Hz), 6.64 (1H, d, *J* = 2.6 Hz), 5.30 (1H, brt, *J* = 4.2 Hz), 3.80 (2H, s), 3.77 (3H, s), 2.93 (2H, pt, *J* = 7.4 Hz), 2.53 (2H, pt, *J* = 7.0 Hz), 2.02 (1H, m), 1.94 (1H, m), 1.4-1.8 (4H, m).

^{13}C NMR: δ 208.0 (q, C5), 161.5 (q, -O<u>C</u>OCF$_3$), 159.1 (q, C9), 140.7, 140.4, 131.2, 131.0, 126.6 (C4a, C6a, C7, C10a, C12a), 115.7, 111.9 (t, C8, C10), 75.7 (t, C1), 55.1 (p, -O<u>C</u>H$_3$), 50.0 (s, C6), 31.8, 31.3, 27.8, 26.1, 17.3 (s, C2, C3, C4, C11, C12).

MS: *m/z* 368 ($M^{+\cdot}$, 70%), 255 (20, -OCOCF$_3$), 226 (75), 134 (100).

(±)-2-(1,2,3,4,9,10-hexahydro-7-methoxyphenanthren-1-yl)acetic acid (3-59).

HRMS: Found: $M^{+\cdot}$ 272.1415, $C_{17}H_{20}O_3$ requires 272.1412.

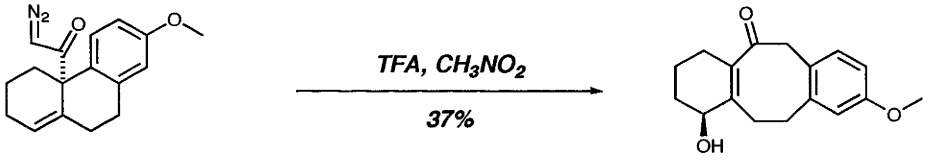
IR: υ_{max} 2929 (m), 1704 (s), 1607 (m), 1499 (m), 1254 (m) cm^{-1}.

^{1}H NMR: δ 7.12 (1H, d, J = 8.2 Hz), 6.69 (2H, s), 3.80 (3H, s), 2.60 (3H, m), 2.0-2.4 (6 H, m), 1.8 (3H, m), 1.6 (1H, m).

^{13}C NMR: δ 178.9 (q, $\underline{C}O_2H$), 158.0 (q, C7), 137.1, 132.4, 129.4, 128.4, 123.0 (C4a, C4b, C5, C8a, C10a), 113.2, 110.9 (t, C6, C8), 55.2 (p, -O$\underline{C}H_3$), 37.9, 36.1, 28.9, 27.8, 27.2, 25.6, 19.4 (C1, C2, C3, C4, C9, C10, -$\underline{C}H_2CO_2H$),

MS: *m/z* 272 ($M^{+\cdot}$, 23%), 213 ($M^{+\cdot}$ -CH_2CO_2H, 100).

(±)-1,2,3,4,5,6,11,12-Octahydro-9-methoxy-1-hydroxy-dibenzo[a,e]cyclooctene-5(6H)-one (3-68)



3-58 **3-61**

The diazoketone **3-58** (20 mg, 0.07 mmol) in CH_3NO_2 (2 mL) was added to TFA (0.35 mmol, 26 μL) in CH_3NO_2 (7 mL) at 0 °C (H_2O, ice) and stirred for 5 mins. EtOAc (5 mL) and H_2O (10 mL) were added and the organic layer was then washed with H_2O (2x, 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give an oily residue. Chromatography of the residue on silica gel (Pet.Sp: EA 9:1 – 4:1) gave the alcohol **3-61** (7 mg, 37%) as an off-white solid, which was re-crystallised from MeOH.

MP: 61-62 °C.

HRMS: Found: $M^{+\cdot}$ 272.1418, $C_{17}H_{20}O_3$ requires 272.1412.

IR: υ_{max} 3420 (bs), 1670 (s), 1606 (m), 1502 (s), 1256 (s) cm^{-1}.

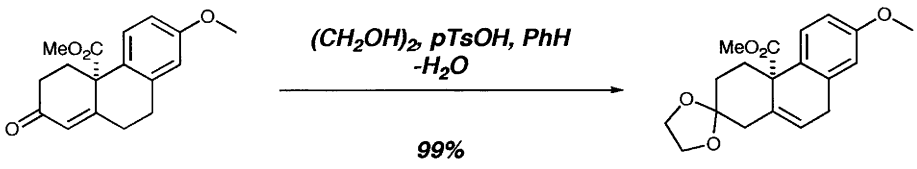
^{1}H NMR: δ 6.96 (1H, d, J = 8.7 Hz), 6.65 (2H, m), 3.90 (1H, bt), 3.80 (2H, s), 3.77 (3H, s), 2.90 (2H, m), 2.69 (2H, m), 1.99 (1H, m), 1.85 (1H, m), 1.4-1.6 (4H, m).

^{13}C NMR: δ 208.5 (q, C5), 158.7 (q, C9), 140.9, 138.9, 136.4, 131.1, 126.2 (C4a, C6a, C7, C10a, C12a), 115.7, 111.0 (t, C8, C10), 68.3 (t, C1), 55.0 (p, -O<u>C</u>H$_3$), 50.1 (s, C6), 32.4, 31.3, 31.0, 26.0, 17.3 (s, C2, C3, C4, C11, C12).

MS: *m/z* 272 ($M^{+\cdot}$, 50%), 226 (100), 134 (70).

8.4 Chapter Four Experimental

(±)-1,2,3,4,4a,9-Hexahydro-2,2-ethylenedioxy-4a-methoxycarbonyl-7-methoxyphenanthrene (4-8)



3-50 **4-8**

A 50 mL RB-flask was charged with enone **3-50** (1 g, 3.5 mmol), benzene (35 mL), ethylene diol (18 mmol, 1 mL) and *p*-TsOH (100 mg). The flask, fitted with a Dean-Stark apparatus and condenser, was flushed with N_2 and heated to reflux for 4 hrs, after which time TLC indicated that the reaction was complete. The reaction mixture was then allowed to cool and the majority of the benzene removed under reduced pressure. The remainder was diluted with EtOAc (50 mL) then washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL). The aqueous layers were re-extracted with EtOAc (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the ketal **4-8** (1.2 g, 99%) as a yellow oil. A small amount was crystallised from methanol for characterisation and the remainder was used without further purification.

MP: 111-113 °C.

R_f: 0.5 (Pet.Sp.:EtOAc 1:1).

HRMS: Found: M^+ 330.1468, $C_{19}H_{22}O_5$ requires 330.1467.

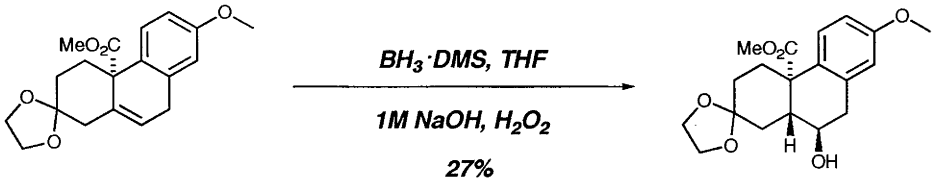
IR: υ_{max} 2952 (l), 1726 (l), 1610 (l), 1503 (l), 1241 (l), 1117 (l), 1042 (l) cm^{-1}.

^{1}H NMR: δ 7.31 (1H, d, J = 8.8 Hz), 6.72 (1H, dd, J = 2.8 Hz, J = 8.7 Hz), 6.62 (1H, d, J = 2.6 Hz), 5.82 (1H, bs, H10), 3.90 (4H, m), 3.77 (3H, s), 3.61 (3H, s), 3.48 (2H, bs), 2.75 (1H, ddd, J = 13 Hz, J = 4.1 Hz, J = 2.6 Hz), 2.40 (2H, bs), 1.90 (1H, td, J = 13.7 Hz, J = 4 Hz), 1.80 (1H, bd, J = 13.9 Hz), 1.62 (1H, td, J = 3.9 Hz, 13.7 Hz).

^{13}C NMR: δ 173.8 (q, C11), 158.1 (q, C7), 133.8, 132.3, 127.8 (q, C10a, C8a, C4a), 127.4 (t, C5), 121.4 (t, C10), 112.7, 112.5 (t, C6, C8), 108.0 (q, C2), 64.4, 64.3 (s, acetal), 55.0, 52.4 (p, -O<u>C</u>H$_3$), 49.6 (q, C4a), 43.5 (s, C9), 35.2, 33.0, 30.0 (s, C1, C3, C4).

MS: *m/z* 330 (M^+, 44%), 271 (100), 227 (78), 209 (40), 171 (36), 99 (85).

(4aSR,10RS,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-2,2-ethylenedioxy-10-hydroxy-4a-methoxycarbonyl-7-methoxyphenanthrene (4-9)



4-8 **4-9**

To a flame dried 25 mL RB-flask was added ketal **4-8** (200 mg, 0.60 mmol) and dry THF (5 mL). The flask was then flushed with argon and cooled to 0 ^{0}C (H_2O, ice). BH_3•DMS [2M in THF] (0.72 mmol, 363 μL) was then slowly added and the reaction allowed to warm to RT for 48 hrs, after which point TLC analysis indicated that most of starting material had been consumed. The flask was then cooled to 0 ^{0}C (H_2O, ice) and fitted with a condenser, 1M NaOH (5 mL) was slowly added and the reaction stirred for 3 mins before the careful addition of H_2O_2 [30% in H_2O] (5 mL). The ice bath was then removed and the reaction stirred for 3 hrs. After this time the reaction was partioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was re-extracted with EtOAc (2x, 20 mL) and the organic layer was washed with H_2O (20 mL) and brine (20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a clear oil. Chromatography of the residue on silica gel (Pet.Sp:EA 2:1) yielded the *trans*-fused alcohol **4-9** (64 mg, 27%) as a 5:1 mixture with an unidentified product.

HRMS: Found: $M^{+\cdot}$ 348.1574, $C_{19}H_{24}O_6$ requires 348.1573.

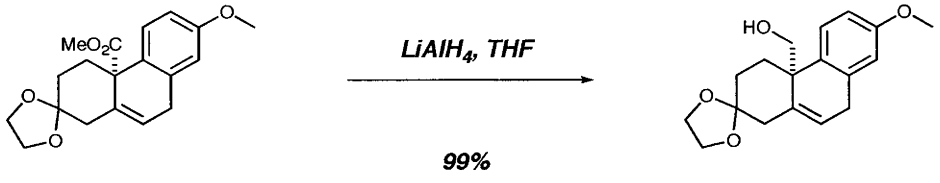
IR: υ_{max} 3431(bs), 2950 (s), 1721 (s), 1608 (m), 1500 (s), 1240 (m) cm^{-1}.

^{1}H NMR: Key Signals δ 7.52 (1H, d, *J* = 8.8 Hz), 6.71 (1H, dd, *J* = 2.9 Hz, *J* = 8.8 Hz), 6.60 (1H, d, *J* = 2.7 Hz), 4.62 (1H, brdd, *J* = 8.1 Hz, *J* = 16.4 Hz), 3.90 (4H, m), 3.77 (3H, s), 3.59 (3H, s), 3.21 (1H, dd, *J* = 6.6 Hz, *J* = 17.0 Hz), 2.68 (1H, dd, *J* = 8.2 Hz, *J* = 16.6 Hz).

^{13}C NMR: Key Signals δ 173.8 (q, C11), 158.6 (q, C7), 136.8, (q, C5), 129.4, 127.6 (q, C4b, C8a), 113.6, 112.5 (t, C6, C8), 108.8 (q, C2), 66.8 (t, C10), 66.6, 64.2 (s, -O-$\underline{C}H_2\underline{C}H_2$-O-).

MS: *m/z* 348 ($M^{+\cdot}$, 30%), 289 (32), 271 (36), 245 (50), 227 (100).

(±)-1,2,3,4,4a,9-Hexahydro-2,2-ethylenedioxy-4a-(hydroxymethyl)-7-methoxyphenanthrene (4-10)



4-8 **4-10**

A 50 mL RB-flask was charged with ketal **4-8** (1.2 g, 3.5 mmol) and dry THF (14 mL) then cooled to 0 ^{0}C (H_2O, ice). Freshly ground $LiAlH_4$ (3.5 mmol, 132 mg) was then slowly added. Once addition was complete the ice bath was removed and the mixture allowed to stir for 2 hrs. After this time TLC indicated the reaction to be complete. The mixture was then filtered through celite and the residue washed with Et_2O (2x, 20 mL). H_2O (10 mL) was then slowly added and the organic layer washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The aqueous layers were re-extracted with EtOAc (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford the alcohol **4-10** (1.05g, 99%) as a yellow oil.

HRMS: Found: M^+ 302.1519, $C_{18}H_{22}O_3$ requires 302.1518.

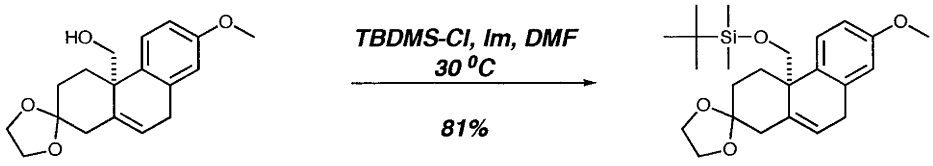
IR: υ_{max} 3468 (bs), 2944 (m), 1610 (m), 1502 (l), 1241 (m), 1117 (m), 1088 (m), 1048 (m) cm^{-1}.

^{1}H NMR: δ 7.17 (1H, d, J = 8.6 Hz), 6.70 (1H, dd, J = 2.9 Hz, J = 8.8 Hz), 6.58 (1H, d, J = 2.8 Hz), 5.83 (1H, bs), 3.80 (5H, m), 3.74(3H, s), 3.61 (3H, s), 3.57 (1H, d, J = 10.9 Hz, H11), 3.36 (2H, m), 2.59 (1H, m), 2.23-2.37 (2H, m), 1.70-1.91 (3H, m).

^{13}C NMR: δ 157.4 (q, C7), 135.7, 133.7, 131.30 (q, C10a, C8a, C4b), 126.6 (t, C5), 123.3 (t, C10), 112.7, 112.1 (t, C6, C8), 108.2 (q, C2), 67.1 (s, C11), 64.3, 64.2 (s, -O-$\underline{C}H_2\underline{C}H_2$-O-), 54.9 (p, -O$\underline{C}H_3$), 43.1, 41.6 (q, C4a, C9), 32.3, 31.6, 30.4 (s, C1, C3, C4).

MS: *m/z* 302 (M^+, 21%), 271 (97), 209 (52), 171 (47), 128 (28), 99 (52).

(±)-1,2,3,4,4a,9-Hexahydro-2,2-ethylenedioxy-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene (4-11)



4-10 **4-11**

To a 50 mL RB-flask was added the alcohol **4-10** (12.4 g, 41 mmol) and DMF (24 mL). The flask was then flushed with N_2, and Imidazole (102 mmol, 6.9 g) was added followed by TBDMS-Cl (4.9 mmol, 7.3g). The reaction was then heated to 30 ^{0}C and stirred for 18 hrs. After this time, the reaction was allowed to cool and Et_2O (100 mL) was added. The reaction was then washed with 1M HCl (100 mL), H_2O (3x, 100 mL), and brine (100 mL). The aqueous layers were then re-extracted with Et_2O (2x, 100 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give an oil, which solidified on standing to give the silane **4-11** (13.9 g, 81%) as a waxy white solid.

R_f: 0.34 (Pet.Sp.:EA 4:1)

HRMS: Found: M^+ 416.2383, $C_{24}H_{36}O_4Si$ requires 416.2383.

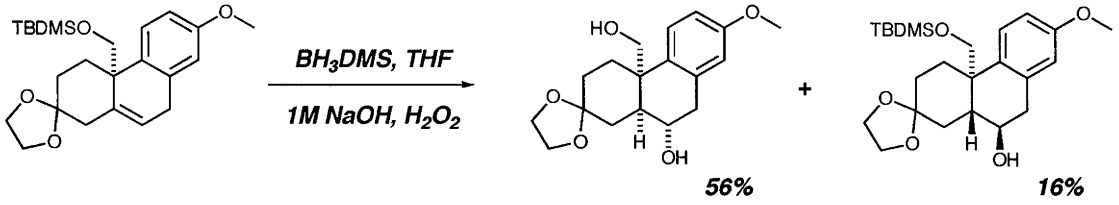
IR: υ_{max} 2952 (l), 1611 (m), 1502 (l), 1250 (l), 1002 (l), 838 (m) cm^{-1}.

^{1}H NMR: δ 7.26 (1H, d, J = 8.4 Hz), 6.70 (1H, dd, J = 2.6 Hz, J = 8.8 Hz), 6.66 (1H, d, J = 2.6 Hz), 5.7 (1H, s), 3.82 (4H, m), 3.73 (3H, s), 3.72 (1H, d, J = 9.1 Hz, H11), 3.62 (1H, d, J = 9.6 Hz, H11), 3.34 (2H, m), 2.67 (1H, d, 14 Hz), 2.4 (1H, m), 2.33 (1H, dd, J = 2.3 Hz, J = 14.3 Hz), 1.67-1.97 (3H, m), 0.80 (9H, s), –0.15 (3H, s), -0.19 (3H, s).

^{13}C NMR: δ 157.3 (q, C7), 135.1, 134.9, 133.2 (q, C10a, C8a, C4b), 127.6, 126.6 (t, C10, C5), 111.7, 111.6 (t, C6, C8), 108.5 (q, C2), 67.2 (s, C11), 64.2, 64.1 (s, acetal), 54.8 (p, -O$\underline{C}H_3$), 42.3, 41.9 (q, s, C9, C4a), 31.5, 31.1, 30.5 (s, C3, C4, C1), 25.6 (p, -Si-C($\underline{C}H_3)_3$), 17.9 (q, . -Si-$\underline{C}(CH_3)_3$), -5.1 (p, -Si-($\underline{C}H_3)_2$.

MS: *m/z* 416 (M^+, 23%), 271 (100), 227 (55), 184 (12), 73 (17).

(4aSR,10SR,10aSR)-4,4a,10,10a-Tetrahydro-2,2-ethylenedioxy-10-hydroxy-4a-(hydroxymethyl)-7-methoxy-phenanthrene (4-12) & (4aSR,10RS,10aRS)-4,4a,10,10a-Tetrahydro-2,2-ethylenedioxy-10-hydroxy-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene (4-13)



4-11 **4-12** **4-13**

To a flame dried 25 mL RB-flask was added ketal **4-11** (200 mg, 0.48 mmol) and dry THF (5 mL). The flask was then flushed with argon and cooled to 0 ^{0}C (H_2O, ice). BH_3•DMS [2M in THF] (0.48 mmol, 240 μL) was then slowly added and the reaction allowed to warm to RT for 48 hrs, at which point TLC analysis indicated that the starting material had been consumed. The flask was then cooled to 0 ^{0}C (H_2O, ice) and fitted with a condenser, 1M NaOH (5 mL) was slowly added and the reaction stirred for 3 mins, at which point H_2O_2 [30% in H_2O] (5 mL) was carefully added. The ice bath was then removed and the reaction stirred for 3 hrs, after which the reaction was partioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous layer was re-extracted with EtOAc (2x, 20 mL) and the organic layers washed with H_2O (20 mL) and brine (20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a clear oil. Chromatography of the residue on silica gel (Pet.Sp:EA 4:1→ 2:1) then gave, in order of elution, the *trans*-fused alcohol **4-13** (33 mg, 16%) and the *cis*-fused alcohol **4-12** (80 mg, 56%).

(4aSR,10RS,10aRS)-4,4a,10,10a-Tetrahydro-2,2-ethylenedioxy-10-hydroxy-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene (4-13)

R_f: 0.35 (Pet.Sp.:EtOAc 1:2).

HRMS: Found: M^+ 434.2490, $C_{24}H_{38}O_5Si$ requires 434.2489.

IR: υ_{max} 3432 (bs), 2953 (s), 1609 (m), 1502 (m), 1250 (m), 1082 (m) cm^{-1}.

^{1}H NMR: δ 7.17 (1H, d, J = 8.7 Hz), 6.66 (1H, dd, J = 2.8 Hz, J = 8.7 Hz), 6.58 (1H, d, J = 2.6 Hz), 4.12 (1H, m), 3.78 (4H, m), 3.77 (3H, s), 3.71 (1H, d, J = 9.9 Hz), 3.62 (1H, d, J = 9.8 Hz), 3.26 (1H, dd, J = 6.7 Hz, J = 16.9 Hz), 2.69 (1H, dd, J = 8.9 Hz, J = 16.6 Hz), 2.45 (1H, m), 2.14 (1H, m), 1.43-2.02 (4H, m), 0.76 (9H, s), -0.23 (3H, s), -0.25 (3H, s).

^{13}C NMR: δ 157.8 (q, C7), 136.0, 134.5, 127.4 (C8a, C5, C4b), 113.0, 111.4 (t, C6, C8), 108.8 (q, C2), 66.7, 65.0 (C10, C11), 64.3, 64.2 (s, acetal), 55.2 (p, -O$\underline{C}H_3$), 46.4, 41.7 (C10a, C4a), 40.4, 32.5, 31.3, 30.8 (s, C1, C3, C4, C9), 25.7 (p, -Si-C($\underline{C}H_3)_3$), 18.0 (q, -Si-$\underline{C}(CH_3)_3$), -5.9 (p, Si-$\underline{C}H_3$).

MS: *m/z* 434 ($M^{+\cdot}$, 1%), 337 (50), 289 (100), 271 (95), 227 (95), 209 (53), 171 (37).

(4aSR,10SR,10aSR)-4,4a,10,10a-Tetrahydro-2,2-ethylenedioxy-10-hydroxy-4a-(hydroxymethyl)-7-methoxy-phenanthrene (4-12)

R_f: 0.15 (Pet.Sp.:EtOAc 1:2)

HRMS: Found: M^+ 320.1621, $C_{18}H_{24}O_5$ requires 320.1624.

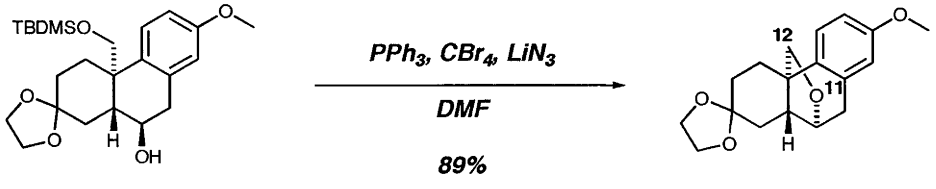
IR: υ_{max} 3402 (bm), 2947 (m), 1609 (m), 1502 (m), 1238 (m) cm^{-1}.

^{1}H NMR: δ 7.14 (1H, d, J = 8.8 Hz), 6.61 (1H, dd, J = 2.6 Hz, J = 8.7 Hz), 6.60 (1H, d, J = 2.6 Hz), 3.77-3.99 (4H, m), 3.75 (3H, s), 3.56 (2H, s), 3.10 (1H, dd, J = 6.3 Hz, J = 18.3 Hz), 2.76 (1H, dd, J = 2.2 Hz, J = 18.1 Hz), 2.20-2.25 (1H, m), 2.01-2.07 (1H, m), 1.36-1.84 (4H, m).

^{13}C NMR: δ 157.9 (q, C7), 136.7, 128.5, 126.5 (C5, C4b, C8a), 114.0, 112.9 (t, C6, C8), 108.6 (q, C3), 71.8, 68.7 (C11, C10), 64.2, 64.1 (s, -O$\underline{C}H_2\underline{C}H_2$O-), 55.1 (p, O$\underline{C}H_3$), 42.7, 41.9 (C4a, C10a), 36.2, 35.0, 30.7, 30.6 (s, C3, C4, C1, C9).

MS: *m/z* 320 ($M^{+\cdot}$, 8%), 289 (96), 271 (80), 227 (100), 209 (55), 171 (38).

(4aSR,10SR,10aRS)-4,4a,10,10a-Tetrahydro-2,2-ethylenedioxy-7-methoxy-10,4a-epoxymethano-phenanthrene (4-18)



4-13 **4-18**

The alcohol **4-13** (31 mg, 0.7 mmol) was dissolved in dry DMF (1 mL), and PPh_3 (0.1 mmol, 26mg) and CBr_4 (0.1 mmol, 33 mg) were then added, followed by LiN_3 (0.45 mmol, 22mg). The flask was then flushed with argon and the reaction allowed to stir at RT for 18 hrs. H_2O (5 mL) and Et_2O (5 mL) were then added and the reaction stirred for 3 mins. The organic

layer was washed with H_2O (2x, 5 mL), brine (5 mL), and dried over $MgSO_4$. Filtration, and removal of sovlent under reduced pressure to gave a residue, which was chromatographed on silica gel (Pet. Sp.:EA 9:1) to give the ether **4-18** (19 mg, 89%) as a clear oil.

HRMS: Found: $M^{+\cdot}$ 302.1519, $C_{18}H_{22}O_4$ requires 302.1519.

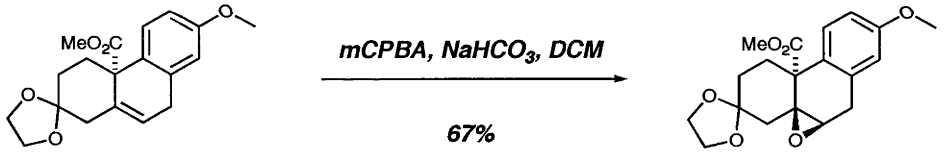
IR: υ_{max} 2925 (s), 1609 (m), 1498 (m), 1096 (m) cm^{-1}.

^{1}H NMR: δ 7.07 (1H, d, J = 8.5 Hz), 6.67 (1H, dd, J = 2.6 Hz, J = 8.5 Hz), 6.66 (1H, d, J = 2.6 Hz), 4.24 (1H, brs), 4.11 (1H, d, J = 7.6 hz), 3.90 (4H, m), 3.76 (3H, s), 3.66 (1H, d, J = 7.6 Hz), 3.01 (2H, bs), 2.05 (3H, m), 1.65 (4H, m).

^{13}C NMR: δ 158.0 (q, C7), 139.2, 135.1 (q, C4b, C8a), 123.6 (t, C5), 114.4, 111.3 (t, C6, C8), 108.5 (q, C2), 80.4 (t, C10), 76.5 (s, C11), 64.3 (s, -O<u>C</u>H$_2$<u>C</u>H$_2$O-), 55.2 (p, -O<u>C</u>H$_3$), 45.2, 42.7, 39.2, 34.8, 30.7, 24.8 (C1, C3, C4, C4a, C9, C10a).

MS: *m/z* 302 ($M^{+\cdot}$, 72%), 216 (15), 186 (100), 171 (20), 99 (45).

Methyl (4aRS,10SR,10aSR)-1,2,3,4,4a,9,10,10a-Octahydro-10,10a-epoxy-2,2-ethylenedioxy-4a-methoxycarbonyl-7-methoxy-phenanthrene (4-22)



4-8 **4-22**

The ketal **4-8** (200 mg, 0.6 mmol) was taken up in DCM (6 mL), cooled to 0 ^{0}C (H_2O, ice) then treated with $NaHCO_3$ (1.8 mmol, 151 mg) and *m*CPBA (0.9 mmol, 221 mg). The ice bath was then removed and the reaction allowed to stir for 1 hr at which point TLC analysis indicated that all the starting material had been consumed. 1M Na_2SO_3 (5 mL) was then added and the reaction stirred for an additional 30 mins. The reaction was then partioned between EtOAc (20 mL) and H_2O (20 mL). The organic layer was washed with 1M NaOH (20 mL) and brine (20 mL) and the aqueous layer re-extracted with EtOAc (2x, 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield the epoxide **4-22** (140 mg, 99%) as a clear oil.

HRMS: Found: M^+ 346.1415, $C_{19}H_{22}O_6$ requires 346.1416.

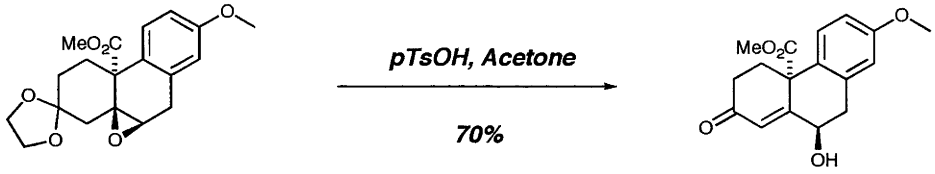
IR: υ_{max} 2954 (brs), 1727 (s), 1610 (m), 1503 9s), 1243 (brs) cm^{-1}.

^{1}H NMR: δ 7.23 (1H, d, *J* = 8.8 Hz), 6.68 (1H, dd, *J* = 2.7 Hz, *J* = 8.7 Hz), 6.54 (1H, d, *J* = 2.5 Hz), 3.80 (4H, m), 3.70 (3H, s), 3.58 (3H, s), 3.31 (1H, d, *J* = 17.2 Hz), 3.29 (1H, d, *J* = 2.6 Hz), 3.16 (1H, dd, *J* = 2.5 Hz, *J* = 17.0 Hz), 2.90 (1H, m), 2.36 (1H, d, 14.4 Hz), 1.92 (2H. m), 1.71 (1H, td, *J* = 3.7 Hz, *J* = 13.7 Hz), 1.49 (1H, dd, *J* = 2.8 Hz, *J* = 14.3 Hz).

^{13}C NMR: δ 172.7 (q, C11), 158.7 (q, C7), 134.0, 126.5 (q, C4b, C8a), 127.1 (t, C5), 114.2, 112.3 (t, C6, C8), 107.7 (q, C2), 64.5, 64.1 (s, -O$\underline{C}$H$_2\underline{C}$H$_2$O-), 60.3 (q, C10a), 56.7, 54.9 (p, O$\underline{C}$H$_3$), 52.2 (t, C10), 50.4 (q, C4a), 40.0, 32.3, 30.8, 28.5 (s, C1, C3, C4, C9).

MS: *m/z* 346 ($M^{+\cdot}$, 35%), 287 (25), 260 (15), 245 (30), 199 (20).

Methyl (4aRS,10RS)-2,3,4,4a,9,10-Hexahydro-10-hydroxy-7-methoxy-2-oxophenanthrene-4a-carboxylate (4-23)



4-22 **4-23**

The epoxide **4-22** (206 mg, 0.59 mmol) was taken up in acetone (20 mL), *p*TsOH (20 mg) was added and the reaction was stirred for 18 hrs under an atmosphere of argon. After this time the reaction was poured into Et_2O (50 mL), then the organic layer was washed with 1M NaOH (50 mL) and brine (50 mL). The aqueous layers were then re-extracted with Et_2O (50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give **4-23** (126 mg, 70 %) as a yellow oil.

R_f: 0.37 (Pet.Sp.:EtOAc 1:2)

HRMS: Found: $M^{+\cdot}$ 302.1148, $C_{17}H_{18}O_5$ requires 302.1154.

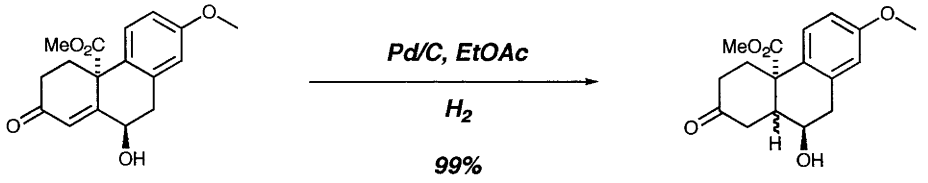
IR: υ_{max} 3419 (bm), 2954 (m), 1730 (s), 1662 (s), 1610 (m), 1502 (s), 1245 (m) cm^{-1}.

^{1}H NMR: δ 7.36 (1H, d, *J* = 8.8 Hz), 6.80 (1H, dd, *J* = 2.8 Hz, *J* = 8.8 Hz), 6.63 (1H, d, *J* = 2.6 Hz), 6.43 (1h, d, *J* = 1.8 Hz), 5.04 (1H, ddd, *J* = 1.8 Hz, *J* = 5.9 Hz, *J* = 11.7 Hz, H10), 3.79 (3H, s), 3.68 (3H, s), 3.20 (1H, dd, *J* = 5.9 Hz, *J* = 15.3 Hz, H9*e*), 2.93 (1H, ddd, *J* = 2.5 Hz, *J* = 4.8 Hz, *J* = 13.5 Hz), 2.82 (1H, dd, *J* = 11.8 Hz, *J* = 15.3 Hz, H9*a*), 2.62 (1H, dt, *J* = 4.7 Hz, *J* = 14.0 Hz), 2.47 (1H, m), 1.98 (1H, td, *J* = 4,7 Hz, *J* = 14 Hz).

^{13}C NMR: δ 199.2 (q, C3), 171.7 (q, C11), 164.9 (q, C10a), 158.7 (q, C7), 134.8, 127.9 (q, C4b, C8a), 127.6 (t, C5), 121.5 (t, C1), 113.7, 113.4 (t, C6, C8), 67.8 (t, C10), 55.1, 52.9 (p, O<u>C</u>H$_3$), 50.9 (q, C4a), 38.9, 36.5, 35.3 (s, C3, C4, C9).

MS: *m/z* 302 ($M^{+\cdot}$, 12%), 243 (100), 227 (7), 197 (5), 171 (6).

Methyl (4aS,10R,10aRS/SR)-1,2,3,4,4a,9,10,10a-Octahydro-10-hydroxy-7-methoxy-2-oxophenanthrene-4a-carboxylate (4-24)



4-23 **4-24**

The γ-hydroxy enone **4-23** (1.2 g, 3.9 mmol) was dissolved in EtOAc (250 mL) and 10% Pd/C (100 mg) added. A hydrogen ballon was fitted and the flask evacuated and flushed with hydrogen three times. The reaction was then left to stir at RT overnight. The reaction was then filtered through a pad of celite and the solvent removed under reduced pressure to give an oily residue, which was chromatographed on silica gel to give the alcohols **4-24** (1.2g, 99%) as a mixture.

R_f: 0.37 (Pet.Sp.:EtOAc 1:2)

HRMS: Found: $M^{+\cdot}$ 304.1310, $C_{17}H_{20}O_5$ requires 304.1311.

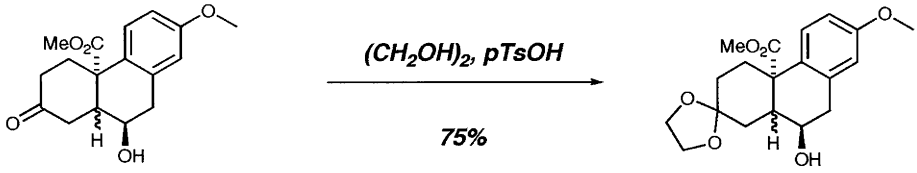
IR: υ_{max} 3428 (bs), 2953 (m), 1716 (s), 1610 (m), 1566 (s), 1502 (m), 1240 (m), 1041 (m) cm^{-1}.

^{1}H NMR: δ 7.28 (1H, d, *J* = 8.8 Hz), 7.16 (1H, d, *J* = 8.7 Hz), 6.65 (2H, m), 6.58 (1H, s), 4.54 (1H, dd, *J* = 9.5 Hz, *J* = 15.8 Hz), 4.24 (1H, s), 3.66 (6H, s), 3.59 (3H, s), 3.56 (3H, s), 1.6-3.21 (1H, m).

^{13}C NMR: δ 211.2, 210.2 9q, C2), 175.5, 173.2 (q, C11), 158.4, 158.1 (q, C7), 136.6, 135.0, 128.0, 127.8, 127.3, 126.2 (C5, C4b, C8a), 113.6, 113.3, 112.9, 112.4 (t, C6, C8), 66.5, 65.8 (t, C9), 54.7, 52.3, 51.9 (p, -O<u>C</u>H$_3$), 49.7, 49.2, 48.4, 43.2, 39.8. 39.1, 38.8, 38.4, 37.4, 35.4, 35.2, 34.1 (C1, C3, C4, C4a, C9, C10a).

MS: *m/z* 304 ($M^{+\cdot}$, 50%), 245 (100), 227 (46), 199 (72), 185 (57), 171 (22), 82 (62).

(4aSR,10RS,10aRS/SR)-1,2,3,4,4a,9,10,10a-Octahydro-2,2-ethylenedioxy -10-hydroxy-7-methoxy-4a-methoxycarbonyl-phenanthrene (4-25)



4-24 **4-25**

The alcohols **4-24** (1.2 g, 3.9 mmol) were taken up in benzene (70 mL), followed by the addition of *p*TsOH (62 mg) and ethylene glycol (11.8 mmol, 637 μL). The flask was fitted with a Dean-Stark apparatus and condenser, flushed with argon, and heated to reflux for 12 hrs. After this time the reaction was cooled and most of the benzene removed under reduced pressure. The residue was then poured into EtOAc (100 mL), and the organic layer was washed with 1M NaOH (50 mL) and brine (50 mL). The aqueous layers were then re-extracted with EtOAc (2x, 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a oil, which was chromatographed on silica gel (Pet. Sp.: EtOAc 2:1) to give the ketals **4-25** as a yellow oil (1.02 g, 75%).

HRMS: Found: M^+ 346.1419, $C_{19}H_{22}O_6$ requires 346.1416.

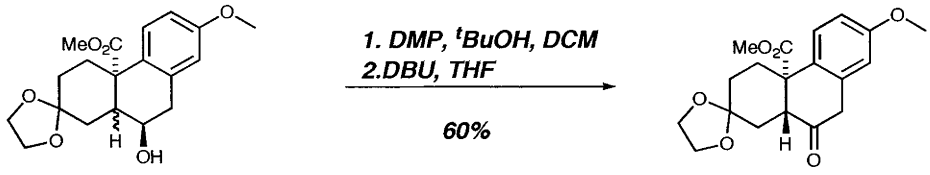
IR: υ_{max} 3436 (bm), 2952 (s), 1721 (s), 1609 (m), 1502 (m), 1237 (m) cm^{-1}.

^{1}H NMR: δ 7.33 (1H, d, *J* = 8.8 Hz), 7.27 (1H, d, *J* = 8.8 Hz), 6.69 (2H, m), 6.60 (1H, d, *J* = 2.6 Hz), 6,58 (1H, d, *J* = 2.6 Hz), 4.59 (1H, dd, *J* = 8.2 Hz, *J* = 16.2 Hz), 4.2 (1H, m), 3.94 (8H, m), 3.75, 3.74 (6H, m), 3.61, 3.57 (6H, m), 3.18 (1H, dd, *J* = 5.9 Hz, *J* = 16.6 Hz), 2.98 (1H, dd, *J* = 5.8 Hz, *J* = 16.8 Hz), 1.40 – 2.88 (16H, m).

^{13}C NMR: δ 176.2, 173.6 (q, C11), 158.3, 158.0 (q, C7), 136.9, 136.5 (t, C5), 129.0, 128.7, 127.3, 125.2 (q, C4b, C8a), 113.4, 113.3, 112.6, 112.1 (t, C6, C8), 108.2, 107.0 (q, C2), 66.4, 66.0 (t, C10), 64.0, 64.0, 63.8 (x2) (s, -O$\underline{C}$H$_2$$\underline{C}H_2$O), 54.6, 50.0 (p, -O$\underline{C}H_3$), 51.6, 50.0, 49.8, 47.0, 41.3, 39.3, 34.9, 33.8, 33.2, 32.7, 31.7, 30.8 (C1, C3, C4, C10a, C4a, C9).

MS: *m/z* 348 ($M^{+\cdot}$, 52%), 289 (57), 271 (59), 227 (100), 209 (34), 171 (32).

(4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-2,2-ethylenedioxy-4a-methoxycarbonyl-7-methoxy-10-oxophenanthrene (4-27)



4-25 **4-27**

The alcohol **4-25** (369 mg, 1.04 mmol) was taken up in dry DCM (10 mL), ^{t}BuOH (2.1 mmol, 198 μL), cooled to 0 ^{0}C and flushed with argon. DMP (2.1 mmol, 850 mg) was then added and the reaction allowed to warm to RT under an atmosphere of argon. After 30 mins TLC analysis indicated all the starting material had been consumed. The reaction was quenched by the addition of 1M NaOH (5 mL) and 1M $Na_2S_2O_5$ (5 mL). The reaction was stirred until the residue dissolved and then the organic layer removed and washed with brine (5 mL). The aqueous layers were re-extracted with EtOAc (2x, 10 mL) and the combined organic layers dried over $MgSO_4$. Filtration and the removal of solvent gave an oil, which was chromatographed on silica gel (Pet. Sp: EtOAc 2:1) to give the ketones **4-26** (235 mg, 65%).

The ketones **4-26** were immediately taken up in dry THF (10 mL), the flask evacuated and flushed with argon (5x) before the addition of DBU (200 μL). The reaction was then stirred under an atmosphere of argon for 18 hrs, at which point the reaction was poured into Et_2O (20 mL) and washed with 10% HCl (10 mL), H_2O (10 mL) and brine (10 mL). The aqueous layers were re-extracted with EtOAc (2x, 10 mL) and the combined organic layers dried over $MgSO_4$. Filteration followed by removal of the solvent under reduced pressure gave the ketone **4-27** as a 3:1 mixture of *trans*:*cis* **4-27** (215 mg, 91%)

Major Product

HRMS: Found: M^+ 346.1419, $C_{19}H_{22}O_6$ requires 346.1416.

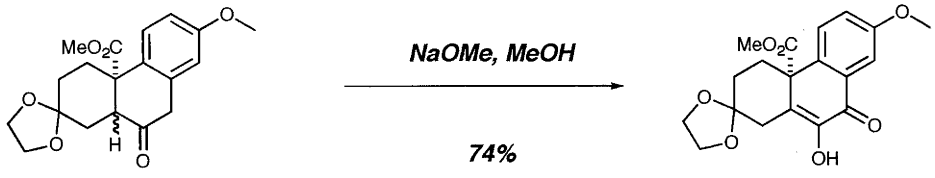
IR: υ_{max} 2954 (bs), 1723 (bs), 1608 (m), 1500 (s) cm^{-1}.

^{1}H NMR: δ 7.38 (1H, d, *J* = 8.8 Hz), 6.80 (1H, dd, *J* = 2.7 Hz, *J* = 8.8 Hz), 6.64 (1H, d, *J* = 2.6 Hz), 3.80 (4H, m), 3.78 (3H, s), 3.75 (1H, d, *J* = 21.7 Hz) 3.58 (1H, d, *J* = 21.7 Hz), 3.57 (3H, s), 2.99 (1H, dt, *J* = 4.1 Hz, *J* = 13.6 Hz), 2.54 (1H, dd, *J* = 3.4 Hz, *J* = 12.4 Hz), 2.31 (1H, dt, *J* = 3.3 Hz, *J* = 14.2 Hz), 1.2-2.2 (6H, m)

^{13}C NMR: δ 206.9 (q, C10), 172.7 (q, C11_, 159.0 (q, C7), 135.7, 129.2 (q, C4b, C8a), 126 (t, C5), 55.2, 52.3 (p, -O<u>C</u>H$_3$), 51.4 (t, C10a), 50.7 (q, C4a), 42.8 (s, C9), 32.3, 32.0, 30.9 (s, C1, C3, C4).

MS: *m/z* 346 ($M^{+\cdot}$, 72%), 287 (80), 243 (52), 232 (25), 187 (27).

(±) Methyl 1,2,3,4-Tetrahydro-2,2-ethylenedioxy-10-hydroxy-9-oxo-phenanthrene carboxylate (4-28)



4-26 **4-28**

The ketones **4-26** (40 mg, 0.12 mmol) were taken up in MeOH (2 mL) and NaOMe [1M in MeOH] (120 μL, 0.12 mmol) was added. The reaction was left to stir overnight while exposed to air. The reaction was then quenched with H_2O (5 mL) and EtOAc (5 mL) was added. The organic layer was washed with H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the disophenol **4-28** (31 mg, 74%), which was characterised without further purification.

HRMS: Found: M^+ 360.1208, $C_{19}H_{20}O_7$ requires 360.1209.

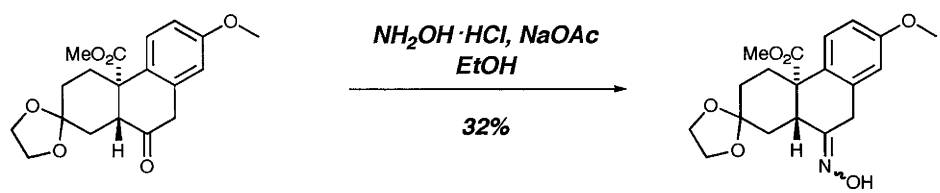
IR: υ_{max} 3399 (bm), 2965 (m), 1731 (s), 1642 (m), 1607 (m), 1497 (m), 1231 (m) cm^{-1}.

^{1}H NMR: δ 7.64 (1H, d, *J* = 2.9 Hz), 7.53 (1H, d, *J* = 8.8 Hz), 7.13 (1H, dd, *J* = 2.6 Hz, *J* = 8.7 Hz), 6.77 (1H, bs), 3.90 (4H, m), 3.87 (3H, s), 3.57 (3H, s), 3.38 (1H, dd, *J* = 2.8 Hz, *J* = 13.9 Hz), 2.93 (1H, bd, *J* = 12.6 Hz), 2.00 (1H, m), 1.8 (1H, m), 1.61 (2H, m).

^{13}C NMR: δ 179.6 (q, C9), 172.2 (q, C11), 159.2 (q, C7), 144.3 (q, C10), 135.1, 129.9, 126.2 (q, C4b, C8a, C10a), 127.7 (t, C5), 121.6, 108.9 (t, C6, C8), 108.7 (q, C2), 64.7, 64.6 (s, -O<u>C</u>H-$_2$<u>C</u>H_2O-), 55.2, 53.1 (p, -O<u>C</u>H_3), 50.9 (q, C4a), 35.2 (2x), 32.3 (s, C1, C3, C4).

MS: *m/z* 360 ($M^{+\cdot}$, 20%), 301 (37), 257 (20).

(4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-2,2-ethylenedioxy-10-(hydroxyimino)-7-methoxy-4a-methoxycarbonylphenanthrene (4-30)



4-27 **4-30**

The ketone **4-27** (440 mg, 1.26 mmol) was taken up in EtOH (25 mL), followed by the addition of NH_2OH•HCl (4.3 mmol, 229m mg) and NaOAc (4.3 mmol, 352 mg). The flask was flushed with argon and the reaction heated to reflux for 1 hr, at which point TLC analysis indicated all the starting material had been consumed. The reaction was allowed to cool, then poured onto EtOAc (50 mL) and washed with H_2O (2x, 50 mL) and brine (50 mL). The aqueous layers were re-extracted with EtOAc (2x, 50 mL), and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give an oil, which was chromatographed on silica gel to give the oxime **4-30** (146 mg, 32%).

HRMS: Found: M^+ 361.1515, $C_{19}H_{23}NO_6$ requires 361.1525.

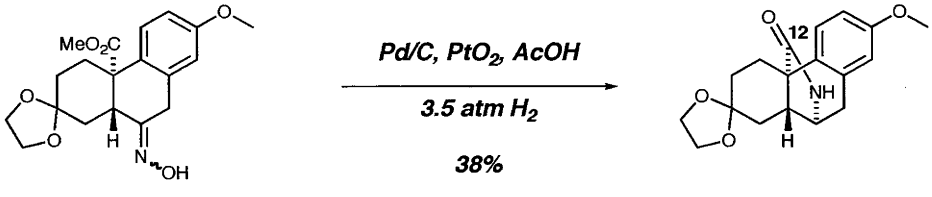
IR: υ_{max} 3413 (bs), 1727 (s), 1606 (m), 1501 (m), 1245 (m) cm^{-1}.

^{1}H NMR: (D_6-Acetone) δ 9.69 (1H, s), 7.37 (1H, d, 9.3 Hz), 6,8 (2H, m), 3.82 (4H, m), 3.79 (5H, s), 3.52 (3H, s), 2.97 (1H, m), 2.58 (1H, m), 2.27 (1H, dt, J = 3.1 Hz, J = 14.0 Hz), 1.6 (4H, m)

^{13}C NMR: δ 173.3 (q, C11), 159.9 (q, C10), 157.0 (q, C7), 136.6, 131.4 (q, C4b, C8a), 127.3 (t, C5), 114.6, 113.1 (t, C6, C8), 108.7 (q, C2), 65.0, 64.9 (s, -O<u>C</u>H_2<u>C</u>H_2O-), 55.4, 52.1 (p, -O<u>C</u>H_3), 49.8, 44.3 (C10a, C4a), 34.7, 33.0, 32.3, 30.4 (C3, C4, C9, C1).

MS: *m/z* 361 (M^+, 100%), 345 (17), 302 (42), 286 (40), 242 (17).

(4aSR,10SR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-11-aza-4a,10-ethano-7-methoxy-12-oxo-phenanthrene (4-31)



4-30 **4-31**

The oxime **4-30** (30 mg, 0.08 mmol) was dissolved in AcOH (5 mL) and Pd/C (5% on carbon) (10 mg) was added, followed by PtO_2 (5 mg). The reaction flask was evacuated and then exposed to 3.5 atm of hydrogen for 4 days. After this time the reaction was poured onto EtOAc (20 mL) and H_2O (10 mL), then saturated NaOH was carefully added until pH 10. The organic layer was washed with brine and the aqueous layer re-extracted EtOAc (3x, 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under

reduced pressure to give an oil, which was chromatographed on alumina (1% EtOAc in Pet.Sp to 10% EtOAc in Pet.Sp) to give the amide **3-31** (8 mg, 38%) as a yellow oil.

HRMS: Found: M^+ 315.1461, $C_{18}H_{21}NO_4$ requires 315.1471.

IR: υ_{max} 3242 (m), 2948 (m), 1706 (s), 1608 (m), 1497 (m) cm^{-1}.

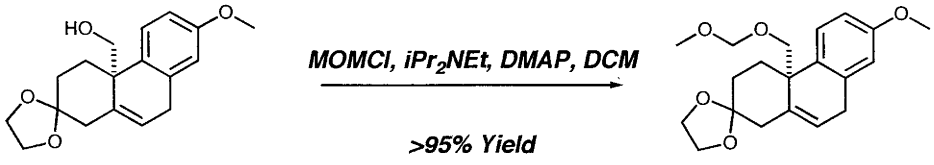
^{1}H NMR: δ 7.13 (1H, d, *J* = 8.7 Hz), 6.70 (1H, dd, *J* = 2.6 Hz, *J* = 8.5 Hz), 6.63 (1H, d, *J* = 2.7 Hz), 5.87 (1H, bs), 3.90 (4H, m), 3.75 (3H, s), 3.57 (1H, bs), 3.06 (1H, dd, *J* = 3.0 Hz, *J* = 17.2 Hz), 2.86 (1H, d, *J* = 16.9 Hz), 2.65 (1H, m), 2.73 (1H, dd, *J* = 5.8 Hz, *J* = 12.2), 1.60-2.00 (5H, m)

^{13}C NMR: δ 178.3 (q, C11), 158.8 (q, C7), 134.3, 132.3 (q, C4b, C8a), 125.3 (t, C5), 115.2, 11.8 (t, C6, C8), 108.1 (q, C2), 64.4, 64.3 (s, -O$\underline{C}H_2\underline{C}H_2$O-), 55.2 (p, O$\underline{C}H_3$), 53.0 (t, C10), 46.6, 44.9 (C4a, C10a), 35.5 (x2), 31.4, 23.9 (C2, C3, C9, C1)

MS: *m/z* 315 ($M^{+\cdot}$, 100%), 270 (25), 213 (24), 186 (35).

8.5 Chapter Five Experimental

(±)-1,2,3,4,4a,9-Hexahydro-2,2-ethylenedioxy-4a-[(methoxymethoxy)methyl]-7-methoxyphenanthrene (5-13)



4-10 **5-13**

A 50 mL RB-flask was charged with ketal **4-10** (1 g, 3.6 mmol) and dry DCM (35 mL). The flask was then flushed with N_2 and the reaction cooled to 0 ^{0}C (H_2O, ice). Diisopropylethylamine (35 mmol, 6.1 mL) was added followed by the slow addition of MOM-Cl (35 mmol, 2.7 mL). Once addition was complete, DMAP (50mg) was added, the ice bath was then removed and the reaction allowed to stir for 18 hrs. The reaction was then washed with 10% phosphoric acid, sat $NaHCO_3$, and brine. The aqueous layers were re-extracted with EtOAc (2x, 20 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give ether **5-13** (1.3 g, >95%) as brown oil. A small portion was chromatographed (Pet.Sp: EtOAc 4:1) for characterisation and the remainder used without further purification.

MP: 73-75 ^{0}C.

HRMS: Found: M^+ 346.1780, $C_{20}H_{26}O_5$ requires 346.1780

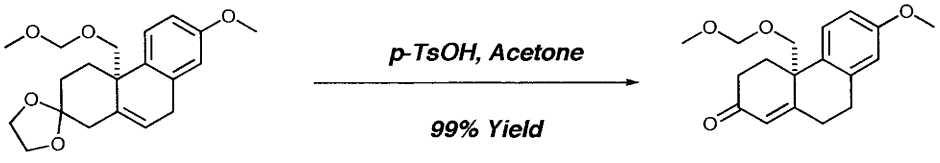
IR: υ_{max} 2946 (bs), 2883 (bs), 1611 (s), 1503 (s), 1243 (bm), 1110 (bm) cm^{-1}.

^{1}H NMR: δ 7.26 (1H, d, J = 8.8 Hz), 6.72 (1H, dd, J = 2.8 Hz, J = 8.6 Hz), 6.52 (1H, d, J = 2.8 Hz), 5.81 (1H, m), 4.37 (2H, AB, J = 6.6 Hz), 3.88-4.00 (4H, m), 3.79 (1H, d, J = 9.5 Hz), 3.75 (3H, s), 3.67 (1H, d, J = 9.5 Hz), 3.31 (2H, m), 3.09 (3H, s), 2.69 (1H, m), 2.3 (2H, m), 1.73-1.94 (3H, m).

^{13}C NMR: δ 157.3 (q, C7), 135.3, 134.4, 132.7 (q, C10a, C8a, C4b), 127.0 (t, C5), 122.8 (t, C10), 112.2, 111.8 (t, C6, C8), 108.4 (q, C2), 96.1 (s, -O-$\underline{C}H_2$-O-, 71.8 (s, C11), 64.4, 64.3 (s, -O-$\underline{C}H_2\underline{C}H_2$-O-), 55.0, 54.9 (p, -O$\underline{C}H_3$), 41.9, 41.4 (q,s, C4a, C9), 32.8, 31.8, 30.5 (s, C1, C3, C4).

MS: *m/z* 346 (M^+, 46%), 271 (100), 227 (67), 209 (38), 184 (26), 171 (33), 99 (33).

(±)-4,4a,9,10-Tetrahydro-7-methoxy-4a-(methoxymethoxymethyl)phenanthren-2(3H)-one (5-14)



5-13 **5-14**

A 50 mL RB-flask was charged with Ketal **5-13** (1.3 g, 3.5 mmol) and acetone (35 mL). *p*TsOH (500 mg) was added and the reaction stirred for 40 mins, after which time TLC indicated that the reaction was complete. The majority of the acetone was removed under reduced pressure and the remainder was diluted with EtOAc (100 mL), the washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL). The aqueous layers were then re-extracted with EtOAc (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed (Pet.Sp.:EtOAc 4:1) to yield the enone **5-14** (1.1 g, 99%) as a yellow oil.

HRMS: Found: M^+ 302.1512, $C_{18}H_{22}O_4$ requires 302.1518.

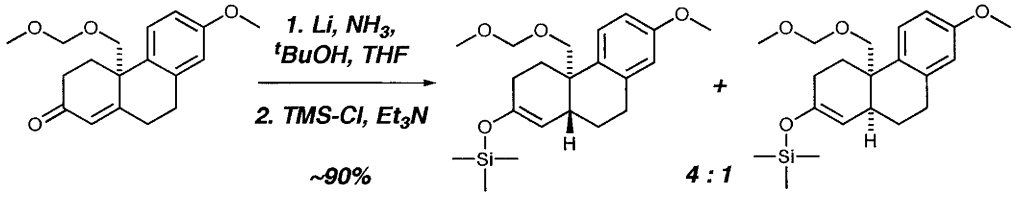
IR: υ_{max} 2930 (bl), 1669 (l), 1501 (l), 1245 (s), 1149 (m), 1107 (s), 1040 (s) cm^{-1}.

^{1}H NMR: δ 7.28 (1H, d, J = 8.8 Hz), 6.77 (1H, dd, J = 2.8 Hz, J = 8.8 Hz), 6.63 (1H, d, J = 2.8 Hz), 6.04 (1H, s), 4.48 (2H, AB, J = 6.7 Hz), 3.83 (2H, AB, J = 9.7 Hz), 3.79 (3H, s), 3.22 (3H, s), 2.78-3.00 (4H, m), 2.41-2.64 (3H, m), 1.99 (1H, td, J = 14.1 Hz, J = 5.3 Hz).

^{13}C NMR: δ 198.7 (q, C2), 165.7 (q, C10a), 157.5 (q, C7), 136.6, 131.9 (q, C8a, C4b), 127.4, 125.9 (t, C1, C5), 112.7, 112.6 (t, C6, C8), 96.0 (s, -O-$\underline{C}H_2$-O-), 74.5 (s, C11), 55.0, 54.8 (p, -O$\underline{C}H_3$), 42.4 (q, C4a), 34.7, 33.8, 31.4, 30.4 (s, C4, C3, C10, C9).

MS: *m/z* 302 (M^+, 6%), 272 (39), 227 (100), 199 (28), 171 (13).

(4aSR,10aRS)-3,4,4a,9,10,10a-Hexahydro-4b,5,6,8ab,9,10-hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-2-(trimethylsiloxy)phenanthrene (5-21) & (4aSR,10aSR)-3,4,4a,9,10,10a-Hexahydro-4b,5,6,8ab,9,10-hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-2-(trimethylsiloxy)phenanthrene (5-22).



5-14 **5-21** **5-22**

Freshly cleaned lithium wire (4 mmol, 28 mg) was added to freshly distilled ammonia (40 mL) in a 100 mL 3-necked round-bottomed flask at –78 °C (acetone/dry ice) under an atmosphere of argon. On dissolution of the lithium (approx. 10 min) enone **5-14** (290 mg, 0.96 mmol) in dry THF (4 mL) containing ^{t}BuOH (0.9 Equiv., 0.84 mmol, 80 μL), was added quickly, *via* syringe, to the rapidly stirred dark blue ammonia solution. After the addition was complete the syringe was rinsed with THF (2 mL) and this was then added to the solution. The dark blue solution was stirred for an additional 2-3 mins and then quenched by the addition of isoprene until the dark blue colour dissipated. The cold bath was then removed and the ammonia evaporated by gently heating the flask under a stream of argon. The THF was then removed under high vaccum and the resulting foam held under high vacuum for 1 hr. The flask was then recharged with argon and THF (20 mL) added. The reaction was cooled to –78 °C (acetone/dry Ice) and triethylamine (665 μL, 4.8 mmol) was added followed by trimethylsilyl chloride (609 μL, 4.8 mmol). The reaction was allowed to warm to RT for 4 hr. Hexane was then added and the washed with H_2O (2x, 20 mL) and brine (20 mL). The aqueous layers were then re-extracted with EtOAc (3x, 20 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the silyl ether **5-21** and **5-22** (280 mg, 80 %) as a yellow oil.

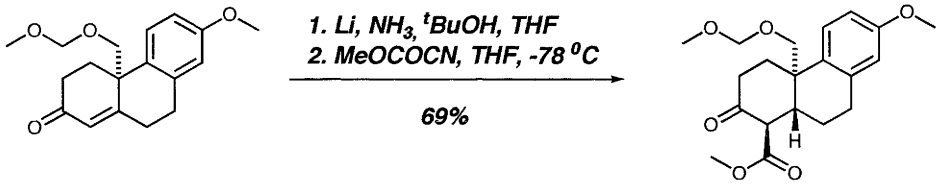
(4aSR,10aRS)-3,4,4a,9,10,10a-Hexahydro-4b,5,6,8ab,9,10-hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-2-(trimethylsiloxy)phenanthrene (5-21)

^{13}C **NMR:** MAJOR δ 157.5 (q, C7), 150.3 (q, C2), 137.2, 135.5 (q, C8a, C4b), 127.1 (t, C5), 113.7, 110.4 (t, C6, C8), 107.1 (t, C1), 96.6 (s, -O-$\underline{C}H_2$-O), 69.1 (s, C11), 54.9, 54.8 (p, O$\underline{C}H_3$), 40.1 (t, C4a), 38.2 (q, C10a), 28.8, 28.7, 27.8, 28.6 (s, C3, C4, C9, C10).

(4aSR,10aSR)-3,4,4a,9,10,10a-Hexahydro-4b,5,6,8ab,9,10-hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-2-(trimethylsiloxy)phenanthrene (5-22)

^{13}C NMR: MINOR δ 157.5 (q, C7), 150.6 (q, C2), 138.9, 130.8 (q, C8a, C4b), 128.0 (t, C5), 113.1, 112.1 (t, C6, C8), 107.8 (t, C1), 96.4 (s, -O-$\underline{C}H_2$-O), 74.7 (s, C11), 55.0 (p, O$\underline{C}H_3$), 39.3 (t, C4a), 34.3 (q, C10a), 30.3, 27.2, 26.8, 25.2 (s, C3, C4, C9, C10).

Methyl (1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(methoxymethoxymethyl)-2-oxophenanthrene-1-carboxylate (5-23)



5-14 **5-23**

Freshly cleaned lithium wire (17 mmol, 120 mg) was added to freshly distilled ammonia (150 mL) in a 250 mL 3-necked round-bottomed flask at –78 °C (acetone/dry ice) under an atmosphere of argon. On dissolution of the lithium (approx.10 min) enone **5-14** (500 mg, 1.7 mmol) in dry THF (13 mL), containing ^{t}BuOH (0.9 Equiv., 1.5 mmol, 140 μL), was added quickly, *via* syringe, to the rapidly stirring dark blue ammonia solution. After the addition was complete the syringe was rinsed with THF (2 mL) and this was then added to the solution. The dark blue solution was stirred for an additional 2-3 mins and then quenched by the addition of isoprene until the dark blue colour dissipated. The cold bath was then removed and the ammonia evaporated by gently heating the flask under a stream of argon. The THF was then pumped under high vacuum to ensure that the ammonia was removed. The flask was recharged with argon and additional THF (20 mL) added. The solution was then cooled to –78 °C (acetone/dry ice) and methyl cyanoformate (1.2 Equiv. 2 mmol, 160 μL) was added in a dropwise fashion. After 10 mins, TLC indicated that the reaction was complete. Cold H_2O (5 mL) was then added slowly and stirred for 2 mins. Cold diethyl ether (-78 °C, 100 mL) was then added followed by the addition of cold 10% K_2CO_3 (100 mL). The cold bath was then removed and the slurry stirred for 15 mins. The ether layer was partitioned and washed successively with 1M NaOH (100 mL), and brine (100 mL). The aqueous layers were re-extracted with ether and the combined organic layers dried over $MgSO_4$. Removal of the ether under reduced pressure gave an orange oil which was then chromatographed on silica gel (Pet Sp: EA 4:1) to yield **5-23** (424 mg, 69%) as a clear oil.

HRMS: Found: M^+ 362.1731, $C_{20}H_{26}O_6$ requires 362.1729.

IR: υ_{max} 2945 (bl), 1744 (l), 1711 (l), 1609 (m), 1500 (m), 1152 (m), 1042 (s) cm^{-1}.

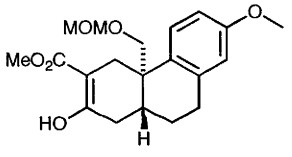
^{1}H NMR: δ 7.22 (1H, d, *J* = 8.7 Hz), 6.67 (1H, dd, *J* = 2.6 Hz, *J* = 8.5 Hz), 6.60 (1H, d, *J* = 2.6 Hz), 4.47 (2H, AB, *J* = 6.6 Hz), 3.92 (1H, d, *J* = 10.0 Hz, H1), 3.80 (1H, d, *J* = 11 Hz), 3.77 (3H, s), 3.74 (3H, s), 3.59 (1H, d, *J* = 10.2 Hz), 3.23 (3H, s), 2.81-3.05 (4H, m), 2.48-2.57 (2H, m), 1.82-1.98 (2H, m), 1.61 (1H, m).

^{13}C NMR: δ 205.9 (q, C2), 170.4 (q, C16), 158.0 (q, C7), 138.7, 133.5 (q, C8a, C4b), 127.2 (t, C5), 113.5, 111.7 (t, C6, C8), 96.3 (s, -O-$\underline{C}H_2$-O-), 72.1 (s, C11), 60.0 (t, C1), 55.6, 55.1, 52.1 (p, -O$\underline{C}H_3$), 43.9 (t, C10a), 38.9, 38.3, 33.7, 29.2, 23.7 (s, C3, C4, C10, C9, q, C4a).

MS: *m/z* 362 (M^+, 18%), 287 (100), 255 (75), 227 (100), 199 (26), 171 (31).

Methyl (4aSR,10aRS)-1,4,4a,9,10,10a-Hexahydro-2-hydroxy-7-methoxy-4a-(methoxymethoxymethyl)-2-oxophenanthrene-3-carboxylate (5-24)

The rearranged product **5-24** isolated on quenching the above reaction at RT.



5-24

MP: 76-77 °C.

HRMS: Found: M^+ 362.1730, $C_{20}H_{26}O_6$ requires 362.1729.

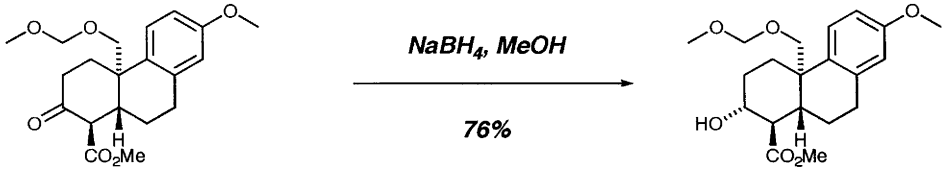
IR: υ_{max} 2930 (s), 1658 (s), 1616 (s), 1501 (s), 1442 (s), 1216 (s) cm^{-1}.

^{1}H NMR: δ 12.21 (1H, s), 7.34 (1H, d, *J* = 8.8 Hz), 6.71 (1H, dd, *J* = 2.8 Hz, *J* = 9 Hz), 6.61 (1H, d, *J* = 2.8 Hz), 4.34, 4.36 (2H, AB, *J* = 6.9 Hz), 3.78 (3H, s), 3.78 (3H, s), 3.57 (2H, s), 3.10 (1H, d, *J* = 15.0 Hz, H4*e*), 3.06 (3H, s), 2.87 (2H, s), 2.25 (2H, s), 2.07 (1H, brd, *J* = 15Hz, H4*a*), 1.96 (2H, m), 1.67 (1H, m).

^{13}C NMR: δ 172.9, 170.9 (q, C12, C2), 157.5 (q, C7), 137.2, 133.7 (q, 8a, 4b), 128.5 (t, C5), 112.9, 111.6 (t, C6, C8), 96.3, 96.2 (C3, -O-$\underline{C}H_2$-O-), 69.6 (s, C11), 54.9, 54.7, 51.3 (p, -O$\underline{C}H_3$), 38.2 (q, C4a), 37.4 (t, C10a), 33.2, 32.0, 29.5, 24.5 (s, C1, C4, C9, C10).

MS: *m/z* 362 (M^+, 25%), 287 (100), 255 (55), 227 (20).

Methyl (1RS,2RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-2-hydroxy-7-methoxy-4a-(methoxymethoxymethyl)phenanthrene-1-carboxylate (5-44)



5-23 **5-44**

A 50 mL RB-flask was charged with the β-keto ester **5-23** (1.8 g, 5 mmol) and MeOH (50 mL). The flask was then flushed with N_2, cooled to 0 °C (H_2O, ice), and $NaBH_4$ (5 mmol, 190 mg) was then slowly added. After the addition was complete the ice bath was removed and the reaction was allowed to stir at RT for 1 hr. The majority of the solvent was removed under reduced pressure and the remainder diluted with Et_2O (50 mL). H_2O (10 mL) was carefully added, followed by 3M HCl (10 mL). After stirring for 5 min the reaction mixture was washed successively with H_2O (50 mL), sat. $NaHCO_3$, and brine. The aqueous layers were re-extracted with EtOAc (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude alcohol **5-44** as white solid (1.4 g, 76%). A small portion of the residue was chromatographed on silica gel (Pet.Sp.:EtOAc 2:1) and then crystallised from MeOH, the remainder was used without further purification.

MP: 128 °C

EA: Found C 65.4, H 7.7, $C_{20}H_{28}O_6$ requires C 65.9, H 7.7.

HRMS: Found: M^+ 364.1887, $C_{20}H_{28}O_6$ requires 364.1886.

IR: υ_{max} 3267 (bl), 2934 (bl), 1725 (l), 1610 (m), 1499 (m), 1153 (m), 1051 (s) cm^{-1}.

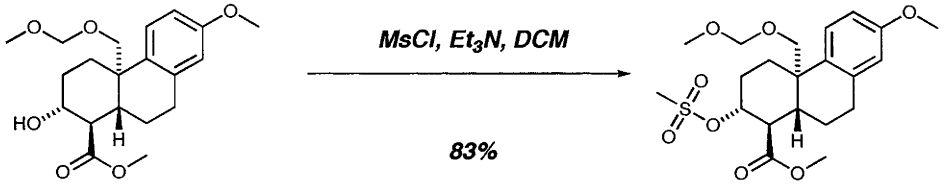
^{1}H NMR: δ 7.22 (1H, d, *J* = 8.8 Hz), 6.64 (1H, dd, *J* = 2.8 Hz, *J* = 8.6 Hz), 6.57 (1H, d, *J* = 2.8 Hz), 4.36 (2H, AB, *J* = 6.6 Hz), 3.82 (1H, dt, *J* = 4.4 Hz, *J* = 10.8 Hz), 3.77 (1H, d, *J* = 9.5 Hz), 3.74 (3H, s), 3.73 (3H, s), 3.46 (1H, d, *J* = 9.5 Hz), 3.14 (3H, s), 2.86 (2H, m), 2.62 (2H, m), 1.66 (4H, m), 1.34-1.52 (2H, m).

^{13}C NMR: δ 175.2 (q, C12), 157.5 (q, C7), 136.7, 134.8 (q, C8a, C4b), 127.4 (t, C5), 113.2, 111.0 (t, C6, C8), 96.4 (s, -O-$\underline{C}H_2$-O-), 72.3 (t, C2), 69.6 (s, C11), 55.1, 55.0 (p, -O$\underline{C}H_3$), 53.6

(t, C1), 51.6 (p, -O<u>C</u>H$_3$), 42.8 (t, C10a), 38.8 (q, C4a), 31.2, 30.5, 28.9, 22.4 (s, C4, C3, C10, C9).

MS: *m/z* 364 (M^+, 26%), 333 (8), 289 (97), 271 (100), 229 (28), 211 (87), 171 (28).

(1RS,2RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-1-methoxycarbonyl-4a-(methoxymethoxymethyl)-2-methanesulfoxy-phenanthrene (5-45)



5-44 **5-45**

A 50 mL RB-flask was charged with alcohol **5-44** (190 mg, 52 mmol) and dry DCM (5 mL), flushed with N_2, and cooled to 0 ^{0}C (H_2O, ice). Triethylamine (1.6 mmol, 216 μL) was then added followed by the careful addition of MsCl (1.6 mmol, 120 μL). A crystal of DMAP was added, the ice bath removed and the reaction allowed to stir for 4 hrs. The reaction was sequentially washed with H_2O (5 mL), 10% HCl (5 mL), sat. $NaHCO_3$ (5 mL), and brine (5 mL). The aqueous layers were then re-extracted with EtOAc (2x, 5 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel (Pet. Sp.:EtOAc 4:1 then 2:1) to yield mesylate **5-45** (192 mg, 83%) as a yellow oil.

R_f: 0.23 (Pet.Sp.:EtOAc 2:1).

HRMS: Found: M^+ 442.1664, $C_{21}H_{30}O_8S$ requires 442.1661.

IR: υ_{max} 2928 (bl), 1723 (l), 1614 (m), 1579 (m), 1502 (m), 1358 (l), 1212 (l), 1175 (l) cm^{-1}.

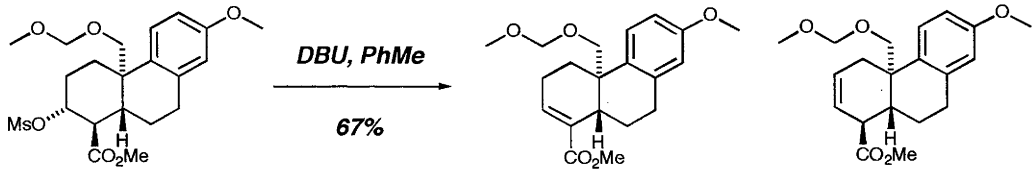
^{1}H NMR: δ 7.18 (1H, d, *J* = 8.6 Hz), 6.64 (1H, dd, *J* = 2.8 Hz, *J* = 8.6 Hz), 6.57 (1H, d, *J* = 2.6 Hz), 4.76 (1H, dt, *J* = 5.1 Hz, *J* = 11.4 Hz), 4.39 (2H, AB, *J* = 6.6 Hz), 3.73 (4H, bs), 3.73 (3H, s), 3.44 (1H, d, *J* = 9.8 Hz), 3.16 (3H, s), 2.96 (1H, t, *J* = 11.4 Hz), 2.94 (3H, s), 2.88 (2H, m), 2.66 (1H, m), 2.32 (1H, m), 1.81-2.12 (3H, m), 1.42-1.52 (2H, m).

^{13}C NMR: δ 173.8 (q, C12), 157.8 (q, C7), 136.2, 133.9 (q, C8a, C4b), 127.3 (t, C5), 113.3, 111.3 (t, C6, C8), 96.3 (s, -O-<u>C</u>H$_2$-O-), 82.7 (t, C2), 70.0 (s, C15), 55.2, 54.9, 51.9 (p, -O<u>C</u>H$_3$),

50.5 (t, C1), 43.2 (t, C10a), 38.5 (q, C4a), 37.9 (t, Ms), 31.2, 28.6, 28.3, 22.1 (s, C3, C4, C10, C9).

MS: *m/z* 442 (M^+, 7%), 367 (30), 271 (100). 211 (47), 197 (13), 171 (14).

Methyl (4aSR,10aSR)-3,4,4a,9,10,10a-Hexahydro-7-methoxy-4a-(methoxymethoxymethyl)phenanthrene-1-carboxylate (5-46) & Methyl (1SR,4aSR,10aRS)-1,4,4a,9,10,10a-Hexahydro-7-methoxy-4a-(methoxymethoxymethyl)phenanthrene-1-carboxylate (5-47)



5-45 **5-46** **5-47**

A 25 mL RB-flask was charged with mesylate **5-45** (1.3 g, 2.9 mmol), toluene (29 mL), and DBU (21 mmol, 3.1 mL). The flask was fitted with a condenser, flushed with N_2, heated to reflux, and stirred for 2 days. The reaction was then allowed to cool and Et_2O (100 mL) was then added. The mixture was washed successively with 10% phosphoric acid (50 mL), H_2O (50 mL), $NaHCO_3$ (50 mL), and brine (50 mL). The aqueous layers were then re-extracted with EtOAc (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel (Pet.Sp:EtOAc 4:1) to yield the isomeric alkenes **5-46** and **5-47** (670 mg, 67%) as an inseparable mixture.

R_f: 0.54 (Pet.Sp.:EtOAc 2:1).

HRMS: Found: M^+ 346.1781, $C_{20}H_{28}O_6$ requires 346.1780.

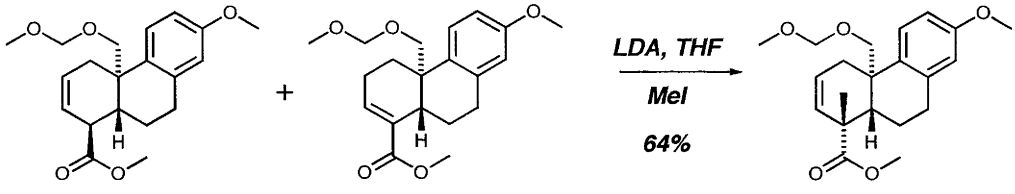
IR: υ_{max} 2928 (bs), 1738 (l), 1715 (l), 1609 (m), 1501 (m), 1241 (m), 1152 (l), 1043 (l) cm^{-1}.

^{1}H NMR: δ 7.31 (2/3H, d), 7.25 (1/3H, d, J = 8.8 Hz), 6.80 (1/3H, m, H3), 6.70 (2H, dd, J = 3.1 Hz, J = 8.9 Hz), 6.67 (1H, d, J = 0.3 Hz), 6.59 (1H, d, J = 2.6 Hz), 5.86 (2/3H, m), 5.64 (2/3H, m), 4.45 (1H, d, J = 6.4 Hz), 4.40 (1/3H, d, J = 6.4 Hz), 4.36 (2/3H, d, J = 6.6 Hz), 4.32 (2/3H, d, J = 6.6 Hz), 3.77 (3H, s), 3.74 (3H, s), 3.66 (2/3H, d, J = 9.2 Hz), 3.61 (2/3H, d, J = 9.4 Hz), 3.57 (1/3H, d, J = 9.5 Hz), 3.43 (1/3H, d, J = 9.1 Hz), 3.10 (3H, s), 3.08 (H, s), 2.66-3.05 (7H, m), 1.45-2.4 (10H, m).

^{13}C NMR: δ 177.4, 168.5 (q, C12), 157.8, 157.6 (q, C7), 138.5 (t, C2), 137.3, 137.0, 134.0, 133.2 (q, C8a, C4b), 135.5 (q, C1), 128.5, 128.4 (t, C5), 126.7, 124.1 (t, C2, C3), 113.8, 112.9, 111.7 110.6 (t, C6, C8), 96.6, 96.4 (s, -O-$\underline{C}H_2$-O-), 70.3, 69.0 (s, C11), 55.0, 55.0, 52.0, 51.4, (p, -O$\underline{C}H_3$), 46.0 (t, C1), 40.6, 40.1 (t, C10a), 38.7, 38.1 (q, C4a), 34.7, 29.7, 28.3, 27.2, 23.4, 23,2, 20.1 (s, C4, C10, C9, A, C4, C3, C10, C9, B).

MS: *m/z* 346 (M^+, 30%), 271 (71), 211 (100), 196 (6), 176 (7), 165 (6).

Methyl (1RS,4aSR,10aSR)-1,4,4a,9,10,10a-Hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-1-methylphenanthrene-1-carboxylate (5-48)



5-47 **5-46** **5-48**

A 50 mL RB-flask was charged with dry THF (15 mL) and diisopropylamine (3.2 mmol, 451 μL). The flask was then flushed with N_2 and cooled to 0 °C (H_2O, ice). *n*-BuLi [1.6 M in Hexanes] (3.2 mmol. 2 mL) was then added in a dropwise fashion. After 15 min the alkenes **5-46** and **5-47** (570 mg, 1.6 mmol) in dry THF (16 mL) were slowly added via syringe. The reaction was stirred at 0 °C for 30 mins and then iodomethane (8 mmol, 500 μL) was added. The ice bath was removed and the reaction was stirred for an additional 2 hrs. The reaction was then quenched by the careful addition of H_2O (2 mL). The reaction was diluted with EtOAc (20 mL) and then with H_2O (2x, 20 mL) and brine (20 mL). The aqueous layers were re-extracted with EtOAc (2x, 20 mL) and the combined organic layers then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed (Pet.Sp.:EA 4:1) on silica gel to give the ester **5-48** (370 mg, 64%) as a pale yellow oil.

R_f: 0.78 (Pet. Sp.: EtOAc 1:2).

HRMS: Found: M^+ 360.1940, $C_{20}H_{26}O_6$ requires 360.1937.

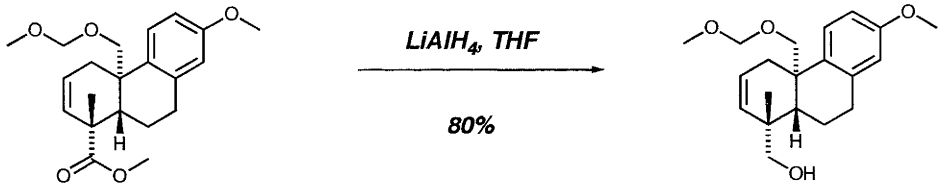
IR: υ_{max} 2948 (bl), 1728 (l), 1609 (m), 1501 (m), 1239 (m), 1044 (s) cm^{-1}.

^{1}H NMR: δ 7.25 (1H, d, *J* = 8.8 Hz), 6.69 (1H, dd, *J* = 2.8 Hz, *J* = 8.6 Hz), 6.60 (1H, d, *J* = 2.8 Hz), 5.74 (2H, m), 4.30 (2H, AB, *J* = 6.3 Hz), 3.76 (3H, s), 3.69 (1H, d, *J* = 9.7 Hz), 3.66 (3H, s), 3.61 (1H, d, *J* = 9.5 Hz), 3.00 (3H, s), 2.73-2.98 (3H, m), 2.11-2.2 (2H, m), 1.98 (1H, d, *J* = 17.6 Hz), 1.82 (1H, dd, *J* = 6.7 Hz, *J* = 8.2 Hz), 1.39 (3H, s).

^{13}C NMR: δ 175.8 (q, C12), 157.4 (q, C7), 137.5, 135.0 (q, C8a, C4b), 131.5, 128.8, 124.6 (t, C2, C3, C5), 112.6, 111.8 (t, C6, C8), 96.0 (s, -O-$\underline{C}H_2$-O-), 71.0 (s, C11), 55.0, 54.8 (p, -O$\underline{C}H_3$), 51.6 (p, -O$\underline{C}H_3$), 49.6 (t, C10a), 45.6 (q, C1), 39.5 (q, C4a), 36.2, 31.6, 21.0 (s, C4, C10, C9), 27.9 (p, C13).

MS: *m/z* 360 (M^+, 1%), 285 (100), 239 (6), 225 (65), 210 (8).

[(1RS,4aSR,10aRS)-1,4,4a,9,10,10a-Hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-1-methylphenanthren-1-yl]methanol (5-50)



5-48 **5-50**

The ester **5-48** (145 mg, 0.4 mmol) was taken up in dry THF (4 mL) and cooled to 0 °C (H_2O/Ice). $LiAlH_4$ (1M soln in THF, 0.4 mmol, 400 μL) was added slowly and the reaction allowed to warm to RT over 30 mins. The reaction was then cooled and H_2O (10 mL) slowly added to quench the excess hydride. The aqueous layer was then extracted with EtOAc (3x10 mL) and the organic layers washed with 10% HCl (10 mL), 1M NaOH (10 mL), and brine (10 mL). The organic layer was then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the alcohol **5-50** (115 mg, 80%) as a white foam.

R_f: 0.5 (Pet. Sp.: EtOAc 1:2)

HRMS: Found: M^+ 332.1990, $C_{20}H_{28}O_4$ requires 332.1988.

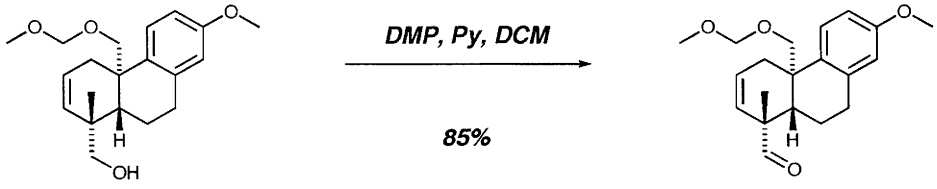
IR: υ_{max} 3341 (brm), 2933 (m), 1608 (m), 1500 (m), 1041 (m) cm^{-1}.

^{1}H NMR: δ 7.22 (1H, d, *J* = 8.8 Hz), 6.70 (1H, dd, *J* = 2.9 Hz, *J* = 8.8 Hz), 6.58 (1H, d, *J* = 2.8 Hz), 5.72 (1H, ddd, *J* = 1.5Hz, *J* = 4.7 Hz, *J* = 10.1 Hz), 5.65 (1H, dd, *J* = 2.5 Hz, *J* = 10.4 Hz), 4.31 (2H, AB, *J* = 4 Hz), 3.86 (1H, d, *J* = 9.8 Hz), 3.77 (3H, s), 3.53 (1H, m), 2.99 (3H, s), 2.81-2.98 (2H, m), 2.61 (1H, dd, *J* = 5.9 Hz, *J* = 17 Hz), 1.85-2.16 (4H, m), 1.21 (3H, s).

^{13}C NMR: δ 157.4 (q, C7), 137.7, 135.5 (q, C8a, C4b), 133.5, 128.2, 124.5 (t, C2, C3, C5), 112.7, 111.9 (t, C6, C8), 96.3 (s, -O-$\underline{C}H_2$-O-), 73.2 (s, C11), 67.5 (s, C12), 55.1, 55.0 (p, -O$\underline{C}H_3$), 48.4 (t, C10a), 40.2, 39.4 (q, C1, C4a), 36.4, 31.3, 19.4 (s, C4, C10, C9), 26.2 (p, C13).

MS: *m/z* 332 (M^+, 33%), 257 (100), 239 (15), 225 (7), 211 (15), 147 (17).

(1RS,4aSR,10aSR)-1,4,4a,9,10,10a-Hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-1-methylphenanthrene-1-carbaldehyde (5-49)



5-50 **5-49**

The alcohol **5-50** (115 mg, 0.35 mmol) was dissolved in dry DCM (5 mL), flushed with argon, and cooled to 0 ^{0}C (H_2O, ice). Pyridine (0.38 mmol, 30 μL) was then added, followed by DMP (0.38 mmol, 155 mg). The ice bath was then removed and the solution stirred for 3 hrs after which time TLC indicated that all the starting material had been consumed. H_2O (1 mL) was then added followed by 1M NaOH (1 mL) and 1M $Na_2S_2O_5$ (1 mL). The white suspension was stirred until all the solids had dissolved (~30 min). 1M NaOH (10 mL) was then added and the aqueous layer extracted with EtOAc (3x10 mL). The organic layers were washed with 10% phosphoric acid (10 mL), 1M NaOH (10 mL), and brine (10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the aldehyde **5-49** (99 mg, 85%) as a clear oil.

R_f: 0.46 (Pet. Sp.: EtOAc 2:1)

HRMS: Found: M^+ 330.1831, $C_{20}H_{26}O_4$ requires 330.1831.

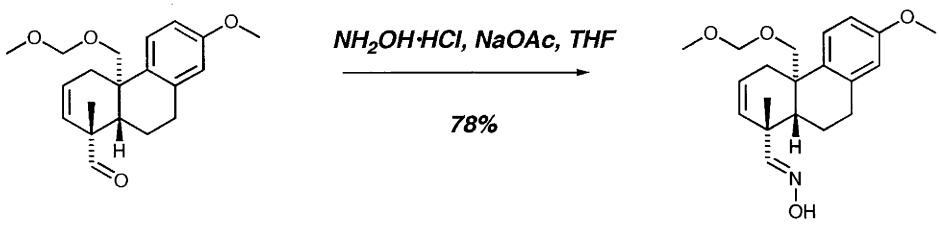
IR: υ_{max} 2932 (bs), 1718 (s), 1609 (m), 1501 (s), 1043 (s) cm^{-1}.

^{1}H NMR: δ 9.8 (1H, s), 7.21 (1H, d, *J* = 8.8 Hz), 6.71 (1H, dd, *J* = 2.7 Hz, *J* = 8.7 Hz), 6.59 (1H, d, *J* = 2.8 Hz), 5.85 (1H, ddd, *J* = 1.9 Hz, *J* = 5.8 Hz, *J* = 10 Hz), 5.64 (1H, dd, *J* = 1.8 Hz, *J* = 10.2 Hz), 4.29 (2H, s), 3.76 (3H, s), 3.59, 3.65 (2H, ABd, *J* = 9.8 Hz), 2.97 (3H, s), 2.73 (2H, m), 2.63 (1H, dd, *J* = 5.8 Hz, *J* = 17.7 Hz), 2.26, 2.35 (2H, ABdd, *J* = 5.9, *J* = 12.9), 2.04 (3H, m), 1.94 (1H, dd, *J* = 2.1 Hz, *J* = 13.3 Hz), 1.28 (3H, s).

^{13}C NMR: δ 206.6 (t, C12), 157.5 (q, C7), 137.3, 134.5 (q, C8a, C4b), 129.8, 127.9, 127.1 (t, C2, C3, C5), 112.7, 112.1 (t, C6, C8), 96.0 (s, -O-$\underline{C}H_2$-O-), 72.3 (s, C11), 55.0, 54.9 (p, -O$\underline{C}H_3$), 50.4, 48.4 (C1, C10a), 39.3 (q, C4a), 36.5, 31.3, 19.4 (s, C4, C10, C9), 23.4 (p, C13).

MS: *m/z* 330 (M^+, 5%), 285 (6), 255 (95), 227 (100), 211 (20), 147 (34).

(1RS,4aSR,10aSR)-1,4,4a,9,10,10a-Hexahydro-7-methoxy-4a-(methoxymethoxymethyl)-1-methylphenanthrene-1-carbaldoxime (5-52)



5-49 **5-52**

The aldehyde **5-49** (108 mg, 0.35 mmol) was dissolved in THF (5 mL) then hydroxylamine hydrochloride (1.8 mmol, 120 mg) and sodium acetate (3.5 mmol, 287 mg) were added. The flask was fitted with a condenser and the mixture heated to 70 ^{0}C for 1 hr, at which point TLC indicated that the starting material had been consumed. The reaction was then cooled to RT and EtOAc (10 mL) was added. The organic layer was washed with H_2O (10 mL) and brine (10 mL), then the aqueous layers were re-extracted with EtOAc (2x, 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the oxime **5-52** (95 mg, 78%) as a yellow foam.

R_f: 0.41 (Pet. Sp.: EtOAc 2:1)

HRMS: Found: M^+ 345.1941, $C_{20}H_{27}NO_4$ requires 345.1940

IR: υ_{max} 3367 (bs), 2931 (s), 1732 (w), 1609 (s), 1501 (s), 1043 (s) cm^{-1}.

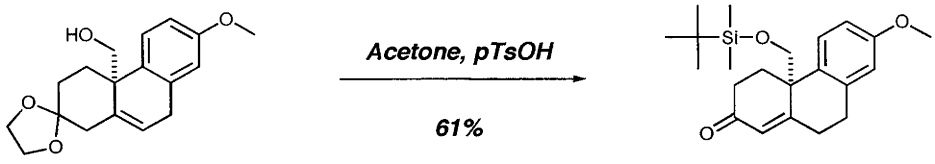
^{1}H NMR: δ 7.59 (1H, s), 7.22 (1H, d, J = 8.8 Hz), 6.71 (1H, dd, J = 2.8 Hz, J = 8.8 Hz), 6.60 (1H, d, J = 2.8 Hz), 5.77 (1H, ddd, J = 1.8 Hz, J = 5.6 Hz, J = 9.9 Hz), 5.66 (1H, dd, J = 1.9 Hz, J = 10.2 Hz), 4.34 (2H, s), 3.77 (3H, s), 3.68 (2H, AB, J = 9.8 Hz), 2.98 (3H, s), 2.80-2.97 (2H, m), 2.64 (1H, dd, J = 10.7 Hz, J = 16.9), 1.80-2.20 (6H, m), 1.29 (3H, s).

^{13}C NMR: δ 157.4 (q, C7), 155.8 (t, C12), 137.3, 135.0 (q, C8a, C4b), 131.0, 128.0, 125.1 (t, C2, C3, C5), 112.7, 111.9 (t, C6, C8), 96.1 (s, -O-$\underline{C}H_2$-O-), 71.5 (s, C11), 55.0, 54.7 (p, -O$\underline{C}H_3$), 48.9 (t, C10a), 40.9, 39.4 (q, C1, C4a), 36.2, 31.1, 27.2, 19.8 (C4, C10, C9, C13).

MS: *m/z* 345 (M^+, 1%), 313 (3), 270 (100), 252 (50), 225 (41), 211 (17).

8.6 Chapter Six Experimental

(±)-4,4a,9,10-Tetrahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-phenanthre-2(3H)-one (6-5)



4-10 **6-5**

A 500 mL RB-flask was charged with ketal **4-10** (11g, 26.4 mmol), acetone (250 mL), and *p*TsOH (2.6 mmol, 450 mg). The flask was then flushed with N_2 and stirred at RT for 1 hr, after which time TLC indicated the reaction was complete. The reaction was then poured into Et_2O (500 mL) before washing with 1M NaOH (200 mL), H_2O (200 mL), and brine (200 mL). The aqueous layers were then re-extracted with Et_2O (2x, 200 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel (Pet.Sp.:EtOAc 6:1) to give the enone **6-5** (6g, 61%) as a clear oil,. which solidified to give a wax on standing.

R_f: 0.24 (Pet.Sp.:EA 4:1).

HRMS: Found: M^+ 372.2122, $C_{22}H_{32}O_3Si$ requires 4372.2121.

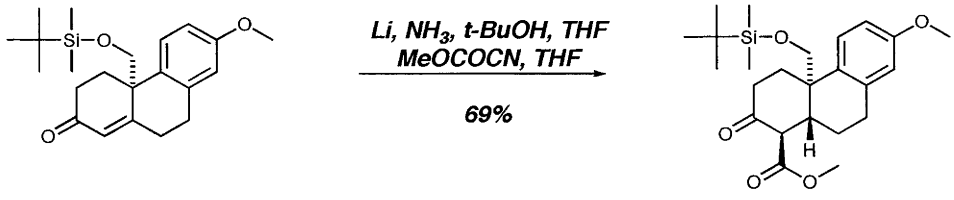
IR: υ_{max} 2930 (bs), 1669 (l), 1610 (m), 1502 (m), 1251 (m), 1098 (m) cm^{-1}.

^{1}H NMR: δ 7.23 (1H, d, J = 8.9 Hz), 6.73 (1H, dd, J = 2.7 Hz, J = 8.7 Hz), 6.59 (1H, d, J = 2.7 Hz), 6.02 (1H, s), 3.89 (1H, d, J = 9.9 Hz), 3.76 (1H, d, J = 9.8 Hz), 3.74 (3H, s), 2.33-2.99 (7H, m), 1.91 (1H, dt, J = 5.5 Hz, J = 14 Hz), 0.79 (9H, s), –0.07 (3H, s), -0.11 (3H, s).

^{13}C NMR: δ 199.2 (q, C2), 165.1 (q, C10a), 157.7 (q, C7), 136.7, 132.2 (q, C8a, C4b), 127.7, 126.4 (t, C1, C5), 112.8, 112.5 (t, C6, C8), 70.7 (s, C11), 54.9 (p, -O$\underline{C}H_3$), 43.9 (q, C4a), 35.0, 33.7, 31.3 30.9 (s, C3, C4, C9, C10), 25.54 (p, -Si-C($\underline{C}H_3)_3$), 17.9 (q, -Si-$\underline{C}(CH_3)_3$), -6.1 (p, -Si-($\underline{C}H_3)_2$.

MS: m/z 372 (M^+, 52%), 342 (100), 315 (45), 227 (87), 199 (36), 115 (41).

Methyl (1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-2-oxophenanthrene-1-carboxylate (6-6)



6-5 **6-6**

Freshly cleaned lithium wire (10 Equiv., 13.4 mmol, 93 mg) was added to 150 mL (0.01 M) of freshly distilled ammonia in a 250 mL 3-necked round-bottomed flash at –78 ^{0}C (acetone/dry ice) under an atmosphere of argon. On dissolution of the lithium (approx. 10 min), enone **6-5** (500 mg, 1.34 mmol) in 13 mL (0.1 M) of dry THF, containing ^{t}BuOH (0.9 Equiv., 1.2 mmol, 114 μL), was added quickly, *via* syringe, to the rapidly stirred dark blue ammonia solution. After the addition was complete the syringe was rinsed with THF (2 mL) and this was then added to the solution. The dark blue solution was stirred for an additional 2-3 mins and then quenched with the addition of isoprene until the dark blue colour dissipated. The cold bath was then removed and ammonia evaporated by gently the heating the flask under a stream of argon. The THF was pumped under high vacuum to ensure the ammonia was removed and then flask was recharged with argon and THF (20 mL) added. The solution was then cooled to –78 ^{0}C (acetone/dry ice) and methyl cyano formate (1.2 Equiv. 1.6 mmol, 130 μL) added in a dropwise fashion. After 40 mins TLC indicated that the reaction was complete. Cold H_2O (5 mL) was then added slowly and stirred for 2 mins. Cold diethyl ether (-78 ^{0}C, 100 mL) was added followed by the addition of cold 10% K_2CO_3 (100 mL). The cold bath was then removed and the slurry stirred for 15 mins. The ether layer was then partitioned and washed successively with 1M NaOH (50 mL) and brine (50 mL). The aqueous layers were then back extracted with ether and the combine organic layers dried over $MgSO_4$. Removal of the ether under reduced pressure gave a orange oil, which was then columned with on silica gel (Pet Sp: EA 6:1) to yield **6-6** (400 mg, 69%).

MP: 92-93 ^{0}C.

R_f: 0.2 (Pet.Sp.:EA 4:1).

MICROANALYSIS: Found C 66.6, H 8.5, $C_{24}H_{36}O_5Si$ requires C 66.6, H 8.4.

HRMS: Found: M^+ 432.2322, $C_{24}H_{36}O_5Si$ requires 432.2332.

Found: $M^{+\cdot}$ -C_4H_9, 375.1628, $C_{20}H_{27}O_5Si$ requires 375.1628.

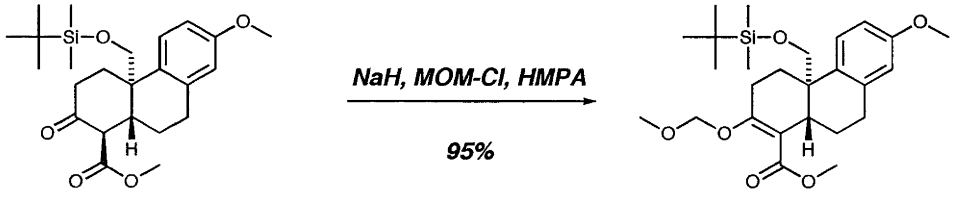
IR: υ_{max} 2652 (bs), 1747 (l), 1713 (l), 1609 (m), 1501 (m), 1256 (m), 1089 (m) cm^{-1}.

^{1}H NMR: δ 7.19 (1H, d, *J* = 8.8 Hz), 6.68 (1H, dd, *J* = 2.9 Hz, *J* = 8.8 Hz), 6.61 (1H, d, *J* = 2.7 Hz), 4.00 (1H, d, *J* = 10.5 Hz), 3.90 (1H, d, *J* = 13.2 Hz), 3.78 (3H, s), 3.76 (3H, s), 3.67 (1H, d, *J* = 10.5 Hz), 2.8-3.0 (4H, m), 2.49 (2H, m), 1.8 (2H, m), 1.63 (1H, m), 0.85 (9H, s), -0.52 (3H, s), -0.66 (3H, s).

^{13}C NMR: δ 206.5 (q, C2), 170.8 (q, C12), 158.8 (q, C7), 136.9, 133.7 (q, C8a, C4b), 127.3 (t, C5), 113.5, 111.6 (t, C6, C8), 68.0 (s, C11), 59.9 (t, C1), 55.1, 52.0 (p, -O$\underline{C}H_3$), 43.7 (t, C10a), 39.7, 38.4, 33.8, 29.3, 23.6 (q, s, C3, C4, C4a, C9, C10), 26.8 (p, -Si-C($\underline{C}H_3)_3$), 18.0 (q, -Si-$\underline{C}(CH_3)_3$), -5.9, -6.0 (p, -Si-($\underline{C}H_3)_2$).

MS: *m/z* 432 (M^+, 4%), 375 (52), 287 (87), 227 (100), 147 (22).

Methyl (4aSR,10aSR) 3,4,4a,9,10,10a-Hexahydro-7-methoxy-2-(methoxymethoxy) 4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene-1-carboxylate (6-16)



6-6 **6-16**

To a flame dried 50 mL RB-flask was added β-keto ester **6-6** (730 mg, 1.7 mmol) and HMPA (12 mL). NaH (45 mg, 1.9 mmol) was added to a separate 50 mL RB-flask and the flask flushed with N_2. The HMPA solution was then slowly added to the NaH and the resulting solution stirred for 4 hrs. MOM-Cl (154 μL, 2 mmol) was then slowly added and the solution stirred for an additional 4 hrs. At this point, H_2O (30 mL) was slowly added and the solution poured into Et_2O (50 mL) and washed with H_2O (3x, 50 mL) and brine (50 mL). The aqueous layers were re-extracted (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield the ether **6-16** (844 mg, >95 %).

R_f: 0.28 (Pet.Sp.:EA 4:1).

HRMS: Found: M^+ 476.2600, $C_{26}H_{40}O_6Si$ requires 476.2594.

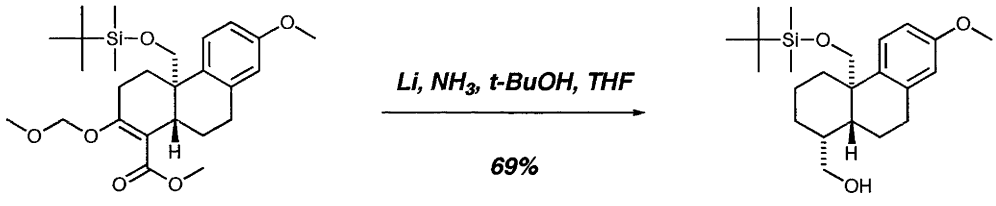
IR: υ_{max} 2951 (bs), 1728 (l), 1608 (m), 1501 (m), 1256 (m), 1152 (l), 1090 (m) cm^{-1}.

^{1}H NMR: δ 7.24 (1H, d, *J* = 8.4 Hz), 6.62 (2H, m), 4.91 (2H, AB, *J* = 6.7 Hz), 3.80 (1H, d, *J* = 9.5 Hz), 3.77 (6H, s), 3.46 (3H, s), 3.41 (1H, d, *J* = 9.5 Hz), 2.92 (2H, m), 2.76 (1H, m), 2.37 (2H, m), 1.60 (2H, m), 1.41 (1H, m), 0.81 (9H, s), -0.19 (3H, s), -0.27 (3H, s).

^{13}C NMR: δ 169.0 (q, C12), 157.7 (q, C7), 152.6 (q, C2), 136.5, 134.8 (q, C8a, C4b), 127.4 (t, C5), 114.6, 113.5 (t, C6, C8), 110.5 (q, C1), 92.9 (s, -O-$\underline{C}H_2$-O), 64.1 (s, C11), 56.2, 55.1, 51.4 (p, -O$\underline{C}H_3$), 40.4, 39.2 (q, t, C4a, C10a), 28.7, 27.5, 22.5, 21.4 (q, C3, C4, C9, C10), 25.7 (p, -Si-C($\underline{C}H_3$)$_3$), 18.1 (q, -Si-$\underline{C}$(CH$_3$)$_3$), -5.9, -6.1 (p, -Si-($\underline{C}H_3$)$_2$).

MS: *m/z* 476 (M^+, 1%), 419 (47), 255 (100), 2227 (13), 147 (12).

(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthren-1-yl)methanol (6-7)



6-16 **6-7**

Freshly cleaned lithium (36 mmol, 250 mg) was added to freshly distilled NH_3 (200 mL) at –78 °C (acetone/dry ice) under an atmosphere of argon. On dissolution of the lithium, the reaction was warmed to –40 °C and the ether **6-16** (1.6 g, 3.6 mmol) in dry THF, containing *t*-BuOH (21 mmol, 2 mL), was added in a dropwise fashion. The reaction was then allowed to reflux for 10 mins and then quenched by the addition of isoprene (200 μL). The ammonia was allowed to evaporate, H_2O (20 mL) was then added followed by EtOAc (20 mL). The organic layer was then wahed with H_2O (20 mL) and brine (20 mL). The aqueous layers were then re-extracted with EtOAc (2x, 20 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was chromatographed on silica gel (Pet.Sp: EtOAc 4:1) to give the alcohol **6-7** (980 mg, 69%) as a clear oil.

R_f: 0.21 (Pet.Sp.:EA 4:1)

HRMS: Found: M^+ 390.2590, $C_{23}H_{38}O_3Si$ requires 390.2590.

IR: υ_{max} 3356 (bm), 2928 (l), 1609 (m), 1499 (m), 1249 (m), 1093 (m) cm^{-1}.

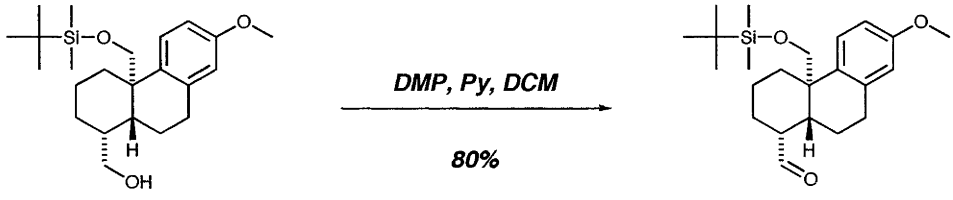
^{1}H NMR: δ 7.15 (1H, d, *J* = 8.7 Hz), 6.64 (1H, dd, *J* = 2.8 Hz, *J* = 8.7 Hz), 6.57 (1H, s, *J* = 2.8 Hz), 3.76 (4H, d, s), 3.54 (2H, AB, *J* = 9.9 Hz), 3.45 (1H, d, *J* = 10.3 Hz), 2.83-3.00 (2H, m),

2.45 (1H, d, J = 13.5 Hz), 2.13-2.27 (1H, m), 1.89-2.09 (2H, m), 1.11-1.64 (7H, m), 0.78 (9H, s), -0.25 (3H, s), -0.27 (3H, s).

^{13}C NMR: δ 157.4 (q, C7), 137.3, 136.9 (q, C8a, C4b), 128.0 (t, C5), 113.0, 110.9 (t, C6, C8), 67.5, 62.2 (s, C11, C12), 55.1 (p, -O$\underline{C}$H$_3$), 44.1, 43.7, 40.9 (q, t, C1, C4a, C10a), 33.8, 30.5, 27.7, 24.0, 18.2 (s, C2, C3, C4, C9, C10), 25.8 (p, -Si-C($\underline{C}$H$_3$)$_3$), 18.1 (q, -Si-$\underline{C}$(CH$_3$)$_3$), -5.9, -6.1 (p, -Si-($\underline{C}$H$_3$)$_2$).

MS: *m/z* 390.3 (M$^+$, 2%), 333 (112), 245 (100), 227 (15), 147 (17), 126 (32).

(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene-1-carbaldehyde (6-17)



6-7 **6-17**

The alcohol **6-7** (980 mg, 2.5 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C (H_2O/ice). Pyridine (4.1 mmol, 330 μL) was then added followed by DMP (4.1 mmol, 1.67 g). The reaction was then allowed to warm to RT for 3 hrs, at which point TLC indicated that the reaction was complete. The reaction was then quenched by the addition of 1M NaOH (5 mL) followed by 1M $Na_2S_2O_3$ (5 mL), and the reaction mixture stirred until the white precipitate had dissolved. At this point, EtOAc (30 mL) was added and the organic layer washed with 1M NaOH (20 mL), H_2O (20 mL), and brine. The aqueous layers were then re-extracted with EtOAc (2x, 20 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed to give the aldehyde **6-17** (920 mg, 94%) as a clear oil.

R_f: 0.49 (Pet.Sp.:EA 4:1).

HRMS: Found: M$^+$ 388.2433, $C_{23}H_{36}O_3Si$ requires 388.2434.

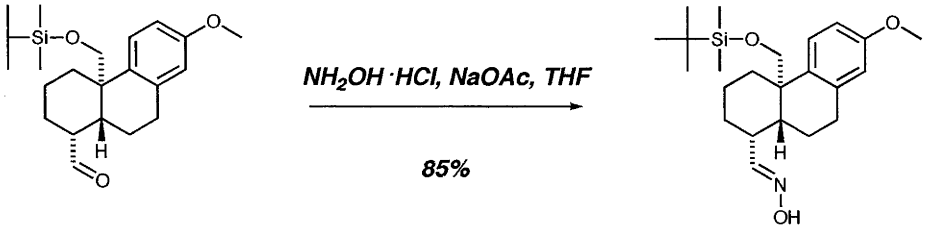
IR: υ_{max} 2928 (bs), 1718 (m), 1609 (w), 1500 (m), 1464 (m), 1251 (s), 1096 (m) cm^{-1}.

^{1}H NMRP: δ 10.05 (1H, s), 7.18 (1H, d, J = 8.8 Hz), 6.67 (1H, dd, J = 2.9 Hz, J = 8.7 Hz), 6.60 (1H, d, J = 2.8 Hz), 3.77 (3H, s), 3.60 (1H, d, J = 10.2 Hz), 3.50 (1H, d, J = 10.2 Hz), 2.9 (2H, m), 2.6 (1H, m), 2.34 (2H, m), 2.15 (1H, m), 1.90 (1H, m), 1.55 (2H, m), 1.20-1.40 (3H, m), 0.81 (9H, s), -0.19 (3H, s), -0.27 (3H, s).

^{13}C NMR: δ 204.7 (t, C12), 157.6 (q, C7), 137.3, 135.8 (q, C8a, C4b), 127.6 (t, C5), 113.1, 111.3 (t, C6, C8), 66.8 (s, C11), 55.1 (p, -O$\underline{C}$H$_3$), 52.1 (t, C1), 43.9, 41.1 (q, t, C4a, C10a), 34.0, 30.7, 29.7, 24.9, 19.2 (s, C2, C3, C4, C9, C10), 25.7 (p, -Si-C($\underline{C}$H$_3$)$_3$), 18.0 (q, -Si-$\underline{C}$(CH$_3$)$_3$), -5.9, -6.1 (p, -Si-($\underline{C}$H$_3$)$_2$).

MS: *m/z* 388 (M$^+$, 1%), 331 (30), 243 (100), 215 (30), 147 (22).

(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene-1-carbaldoxime (6-8)



6-17 **6-8**

The aldehyde **6-17** (920 mg, 2.4 mmol), in dry THF (24 mL), was treated with NH$_2$OH•HCl (11.5 mmol, 796 mg) and sodium acetate (23 mmol, 1.8 g) and heated at 70 °C (oil bath) for 30 mins. After this time, TLC indicated that the starting material had been consumed. The reaction was allowed to cool to RT and EtOAc (50 mL) was added and the organic layer was washed with H$_2$O (50 mL) and brine (50 mL). The aqueous layers were then re-extracted with EtOAc (2x, 50 mL) and the combined organic layers were then dried over MgSO$_4$, filtered, and the solvent removed under reduced pressure to give the crude oxime **6-8** (822 mg, 85%) as an oil that was used without further purification.

R$_f$: 0.14 (Pet.Sp.:EA 9:1).

HRMS: Found: M$^+$ 403.2527, $C_{23}H_{37}NO_3Si$ requires 403.2543.

IR: υ_{max} 3326 (bm), 2928 (s), 1725 (bw), 1609 (m), 1499 (m), 1249 (m), 1096 (m) cm^{-1}.

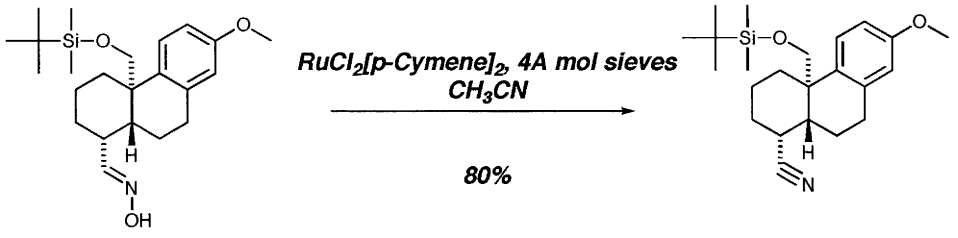
^{1}H NMR: δ 7.68 (1H, d, *J* = 4.7 Hz), 7.21 (1H, d, *J* = 8.7 Hz), 6.65 (1H, dd, *J* = 2.6 Hz, *J* = 8.9 Hz), 6.58 (1H, d, *J* = 2.2 Hz), 3.77 (3H, s), 3.63 (2H, AB, *J* = 9.9 Hz), 2.91 (2H, m), 2.66 (1H, m), 2.48 (1H, m), 2.16-2.29 (2H, m), 1.97 (1H, m), 1.43-1.78 (4H, m)), 1.15 (2H, m), 0.77 (9H, s), -0.22 (3H, s), -0.25 (3H, s).

^{13}C NMR: δ 157.4 (q, C7), 153.2 (t, C12), 137.1, 136.3 (q, C8a, C4b), 127.7 (t, C5), 113.0, 111.0 (t, C6, C8), 66.4 (s, C11), 55.0 (p, -O$\underline{C}$H$_3$), 44.2, 41.0, 39.7 (q, t, C1, C4a, C10a), 33.6,

30.0, 28.0, 23.8, 18.55(s, C2, C3, C4, C9, C10), 25.7 (p, -Si-C($\underline{C}H_3)_3$), 18.0 (q, -Si-$\underline{C}(CH_3)_3$), -6.0, -6.2 (p, -Si-($\underline{C}H_3)_2$).

MS: *m/z* 403 (M^+, 2%), 346 (13), 328 (60), 258 (62), 240 (100).

(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene-1-carbonitrile (6-9)



6-8 **6-9**

The crude oxime **6-8** (240 mg, 0.58 mmol) was taken up in acetonitrile (4 mL), treated with 4A molecular sieves (240 mg/mmol, 139 mg) and $RuCl_2[p\text{Cymene}]_2$ (2%, 7mg), and heated to 80 °C for 10 mins. After this time the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (Pet.Sp:EtOAc 9:1) to give the nitrile **6-9** (180 mg, 80%) as a clear oil.

R_f: 0.21 (Pet.Sp.:EA 9:1)

HRMS: Found: M^+ 385.2448, $C_{23}H_{37}NO_3Si$ requires 385.2437.
Found: M^+-CH_3, 370.2206, $C_{22}H_{32}NO_2Si$ requires 370.2202.

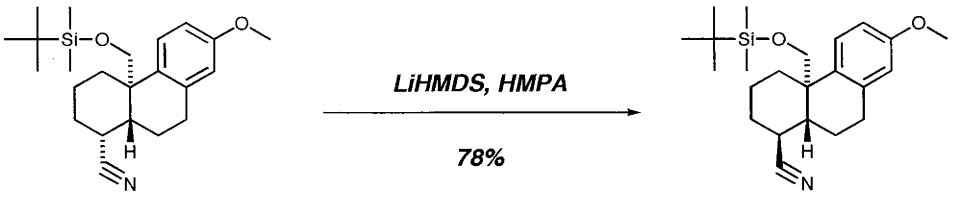
IR: υ_{max} 2931 (s), 2233 (w), 1609 (m), 1500 (m), 1470 (m), 1248 (m), 1099 (m) cm^{-1}.

^{1}H NMR: δ 7.16 (1H, d, *J* = 8.7 Hz), 6.65 (1H, dd, *J* = 2.2 Hz, *J* = 8.7 Hz), 6.60 (1H, d, *J* = 1.9 Hz), 4.19 (1H, d, *J* =10.0 Hz), 3.77 (4H, d&s), 2.95 (2H, dd, *J* = 5.1 Hz, *J* = 9.1 Hz), 2.89 (1H, t, *J* = 4.4 Hz), 2.67 (1H, d, *J* = 13.2 Hz), 2.45 (1H, m), 2.13 (1H, d, *J* = 13.5 Hz), 1.82 (1H, dt, *J* = 4.0 Hz, *J* = 13 Hz), 1.60-1.79 (4H, m), 1.09 (1H, td, *J* = 4.1 Hz, *J* = 13.0 Hz) 0.79 (9H, s), -0.19 (3H, s), -0.23 (3H, s).

^{13}C NMR: δ 157.7 (q, C7), 153.2 (t, C12), 136.5, 137.8 (q, C8a, C4b), 127.8 (t, C5), 122.3 (q, C12), 113.2, 110.8 (t, C6, C8), 63.8 (s, C11), 55.1 (p, -O$\underline{C}H_3$), 41.9, 41.0 (q, t, C4a, C10a), 31.8, 31.0, 29.2, 28.6, 23.9, 18.8 (s, C1, C2, C3, C4, C9, C10), 25.8 (p, -Si-C($\underline{C}H_3)_3$), 18.1 (q, -Si-$\underline{C}(CH_3)_3$), -5.9, -6.1 (p, -Si-($\underline{C}H_3)_2$).

MS: *m/z* 385 (M^+, 2%), 370 (3), 328 (85), 254 (17), 240 (100).

(1SR,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)phenanthrene-1-carbonitrile (6-18)



6-9 **6-18**

To a flame-dried 10 mL RB-flask was added the nitrile **6-9** (38 mg, 0.1 mmol), dry THF (1 mL) and dry HMPA (1 mL). The flask was then flushed with argon, cooled to 0 ^{0}C and treated with LiHMDS [1M in THF] (0.2 mmol, 200 μL). After stirring at this temperature for 30 mins MeI (0.2 mmol, 12 μL) was added and the reaction was allowed to warm to RT and stir overnight. The reaction was quenched by the careful addition of H_2O (1 mL) and then partitioned between Et_2O (5 mL) and H_2O (5 mL). The organic layer was washed with 10% HCl (5 mL), H_2O (3x, 5 mL), and brine. The aqueous layers were then re-extracted with Et_2O (5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the nitrile **6-18** (30 mg, 78%) as a yellow oil that was characterised without further purification.

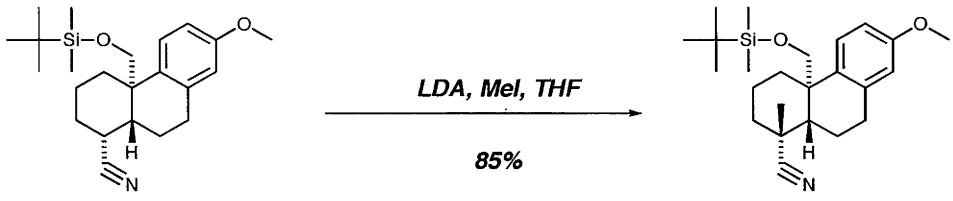
HRMS: Found: $M^{+\cdot}$ - ^{t}Bu 328.1731, $19_3H_{26}NO_2Si$ requires 328.1733.

^{1}H NMR: δ 7.14 (1H, d, *J* = 8.8 Hz), 6.65 (1H, dd, *J* = 2.6 Hz, *J* = 8.7 Hz), 6.61 (1H, d, *J* = 2.7 Hz), 3.77 (3H, s), 3.76 (1H, d, *J* = 9.9 Hz), 3.50 (1H, d, *J* = 10.2 Hz), 2.92 (2H, m), 2.54 (1H, m), 2.16 (2H, m), 1.57 (6H, m), 1.22 (1H, m), 0.82 (9H, s), -0.13, -0.14 (6H, s).

^{13}C NMR: δ 157.8 (q, C7), 136.8, 134.7 (q, C8a, C4b), 127.0 (t, C5), 122.6 (q, C12), 113.4, 111.3 (t, C6, C8), 67.0 (s, C11), 55.1 (p, -O$\underline{C}H_3$), 43.9, 40.1, 33.6 (q, t, C1, C4a, C10a), 31.1, 30.4, 28.9, 22.8, 21.2 (s, C2, C3, C4, C9, C10), 25.8 (p, -Si-C($\underline{C}H_3)_3$), 18.0 (q, -Si-$\underline{C}(CH_3)_3$), -5.9, -6.0 (p, -Si-($\underline{C}H_3)_2$).

MS: m/z 328 ($M^{+\cdot}$ - ^{t}Bu, 75%), 254 (23), 240 (100).

(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-1-methylphenanthrene-1-carbonitrile (6-19)



6-9 **6-19**

A flame-dried 25 mL RB-flask, containing dry THF (5 mL), was flushed with argon and cooled to 0 ^{0}C (H_2O/ice). Diisopylamine (1.23 mmol, 174 μL) was then added followed by the dropwise addition of *n*-BuLi (1.6M in hexane, 769 ul). The reaction was stirred for 15 mins and then cooled to –78 ^{0}C (acetone/dry ice). The nitrile **6-9** (190 mg, 0.49 mmol) and dry THF (5 mL) was then slowly added via syringe. Once addition was complete the syringe was rinsed with dry THF (2x, 500 μL), which was added to the reaction. The flask was allowed warm to RT over 1hr. After cooling to –78 ^{0}C (acetone/dry ice), MeI (1.9 mmol, 122 μL) added. The reaction was stirred at –78 ^{0}C for two hrs and then put in the freezer (-20 ^{0}C) overnight. Saturated NH_4Cl (5 mL) was then added, followed by EtOAc (20 mL). The organic layer was washed with H_2O (20 mL), 10% HCl (20 mL), and brine (20 mL). The aqueous layers where then re-extracted with EtOAc (2x, 20 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel (Pet.Sp: Et_2O 9:1) to give the nitrile **6-19** (170 mg, 85%) as a clear oil.

R_f: 0.60 (Pet.Sp.:EA 4:1).

HRMS: Found: M^+ -C_4H_9, 342.1887, $C_{20}H_{28}NO_2Si$ requires 342.1887.

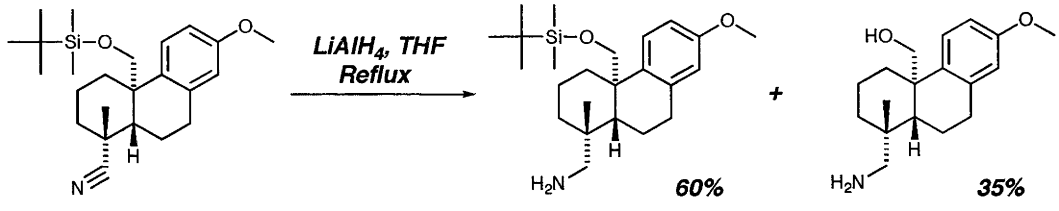
IR: υ_{max} 2930 (s), 2228 (w), 1609 (m), 1500 (m), 1470 (m), 1250 (s), 1096 (s) cm^{-1}.

^{1}H NMR: δ 7.16 (1H, d, J = 8.7 Hz), 6.65 (1H, dd, J = 2.7 Hz, J = 8.7 Hz), 6.60 (1H, d, J = 2.8 Hz), 4.27 (1H, d, J = 9.9 Hz), 3.77 (4H, d&s), 2.89-3.07 (2H, m), 2.74 (1H, m), 1.72-2.19 (5H, m), 1.44 (1H, m), 1.43 (3H, m), 1.05 (3H, m), 0.80 (9H, s), -0.17 (3H, s), -0.25 (3H, s).

^{13}C NMR: δ 157.7 (q, C7), 136.2, 136.2 (q, C8a, C4b), 127.8 (t, C5), 124.6 (q, C12), 113.0, 110.7 (t, C6, C8), 63.0 (s, C11), 55.1 (p, -O$\underline{C}H_3$), 49.2 (t, C10a), 41.5, 39.1 (q, t, C1, C4a), 35.4, 31.9, 28.4, 19.4, 19.4 (s, C2, C3, C4, C9, C10), 28.1 (p, C13), 25.7 (p, -Si-C($\underline{C}H_3$)$_3$), 18.1 (q, -Si-$\underline{C}$(CH$_3$)$_3$), -5.9, -6.1 (p, -Si-($\underline{C}H_3$)$_2$).

MS: m/z 342 (M^+ -C_4H_9, 52%), 315 (2), 268 (10), 254 (100).

[(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-1-methylphenanthren-1-yl]methanamine (6-20) & [(1RS,4aSR,10aRS)-1-(aminomethyl)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-1-methylphenanthren-4a-yl]methanol (6-21)



6-19 **6-20** **6-21**

To a flame-dried 50 mL RB-flask was added the nitrile **6-19** (544 mg, 1.4 mmol) and dry THF (15 mL). The flask was then fitted with a consdenser and flushed with argon. $LiAlH_4$ (8.2 mmol) was then slowly added and the reaction brought to reflux for 2 hrs. After this time, TLC analysis indicated that all the starting material had been consumed. The reaction was cooled to 0 ^{0}C (H_2O/ice) and quenched with a few drops of Rochelle salt, followed by 10% HCl (1 mL). H_2O (10 mL) was then added and the mixture extracted with Et_2O (20 mL). The organic layer was then washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude amine **6-20** (336 mg, 62%) as yellow solid that was used in the next step without further purification. The aqueous layer was then adjusted to pH 12 with 1M NaOH (30 mL) and the aqueous layer extracted with 10% propan-2-ol/EtOAc (x3, 20 mL). The organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the alcohol **6-21** as a white solid (135 mg, 35%).

[(1RS,4aSR,10aRS)-1-(aminomethyl)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-1-methylphenanthren-4a-yl]methanol (6-21)

HRMS: Found: M^+ -CH_2OH, 258.1854, $C_{17}H_{24}NO$ requires 258.1858.

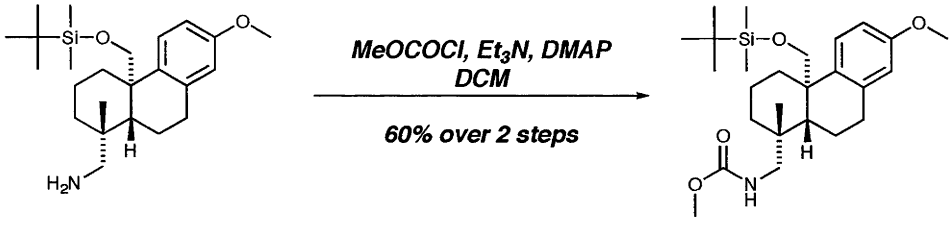
IR: υ_{max} 3376 (bs), 3310 (bs), 2924 (s), 1607 (m), 1575 (w), 1499 (m), 1242 (m) cm^{-1}.

^{1}H NMR: (D_6-Benzene) δ 7.17 (1H, d, J = 8.7 Hz), 6.67 (1H, dd, J = 2.8 Hz, J = 8.7 Hz), 6.60 (1H, d, J = 2.5 Hz), 3.73 (1H, d, J = 11.1 Hz), 3.64 (1H, d, J = 11.1 Hz), 3.38 (3H, s), 3.35 (2H, s), 2.40-2.80 (5H, m), 1.80-2.20 (5H, m), 1.35-1.60 (2H, m), 1.00-1.20 (1H, m), 0.97 (3H, s).

^{13}C NMR: (D_6-Benzene) δ 158.2 (q, C7), 137.6, 137.6 (q, C8a, C4b), 128.1 (t, C5), 113.9, 111.5 (t, C6, C8), 66.5 (s, C11), 54.7 (p, -O<u>C</u>H$_3$), 51.7 (t, C10a), 45.8, 42.4 (q, t, C1, C4a), 37.9, 36.7, 34.7, 31.2, 27.6, 19.2, 19.0 (s, C2, C3, C4, C12, C13, C9, C10).

MS: (ESI) *m/z* 290 ($M^+ + H^+$, 50%), 272 (100).

Methyl [(1RS,4aSR,10aRS)-1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-1-methylphenanthren-1-yl)methylcarbamate (6-22)



6-20 **6-22**

The crude amine **6-20** (54 mg, 0.12 mmol) was taken up in dry DCM (2 mL), the flask flushed with argon and cooled to 0 °C (H_2O, ice). Triethylamine (1.2 mmol, 96 μL) was then added followed by methyl chloroformate (1.2 mmol, 173 μL) and DMAP (5 mg). The reaction was then stirred for 18 hrs. After this time, H_2O (1 mL) was added, followed by EtOAc (5 mL). The organic layer was then washed with 10% HCl (5 mL), H_2O (5 mL), and brine (5 mL). The aqueous layers were then re-extracted with EtOAc (2x, 5 mL) and the combined organic layers then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed (Pet.Sp.:EA 6:1) to give the carbamate **6-22** (33mg, 60% over 2 steps from **6-20**) as a clear oil.

R_f: 0.25 (Pet.Sp.:EA 4:1)

HRMS: Found: M^+ (-tBu) 404.2253, $C_{20}H_{34}NO_4Si$ requires 404.2257.

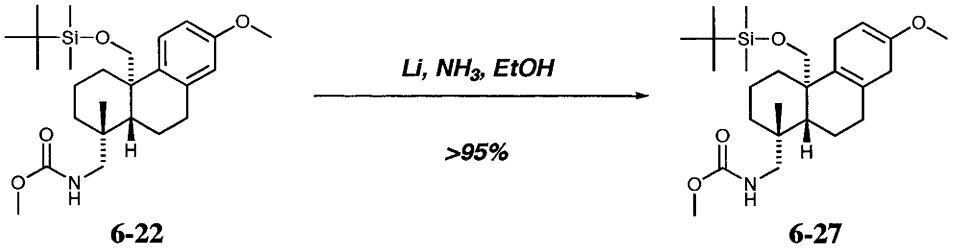
IR: υ_{max} 3350 (bm), 2927 (s), 1714 (m), 1608 (m), 1524 (m), 1500 (m), 1250 (m) cm^{-1}.

^{1}H NMR: (500MHz) δ 7.14 (1H, d, J = 8.8 Hz), 6.65 (1H, dd, J = 2.9 Hz, J = 8.7 Hz), 6.56 (1H, d, J = 2.9 Hz), 4.82 (1H, t, J = 5.4 Hz), 3.81 (2H, s), 3.76 (3H, s), 3.68 (3H, s), 3.53 (1H, dd, J = 7.5 Hz, 13.9 Hz), 3.14 (1H, dd, J = 5.4 Hz, J = 13.9 Hz), 2.90 (1H, dd, J = 6.1 Hz, J = 16.6 Hz), 2.81 (1H, ddd, J = 3.0 Hz, J = 7.7 Hz, J = 17.5 Hz), 2.48 (1H, d, J = 13.6 Hz), 2.00 (1H, m), 1.85 (1H, m), 1.50-1.76 (7H, m), 1.74 (1H, dt, J = 3.9 Hz, J = 13.0 Hz), 1.03 (1H, dt, J = 3.5 Hz, J = 13.3 Hz), 0.98 (3H, s), 0.77 (9H, s), -0.25, -0.28 (6H, s).

^{13}C NMR: δ 157.5, 157.3 (q, C7, -N-$\underline{C}O_2CH_3$), 137.8, 137.1 (q, C8a, C4b), 128.0 (t, C5), 112.8, 111.0 (t, C6, C8), 67.6 (s, C11), 55.1 (p, -O$\underline{C}H_3$), 52.0, 51.1 (C10a, -N-$CO_2\underline{C}H_3$), 44.5, 41.6, 37.7 (C1, C4a, C12), 36.4, 34.3, 30.7 (C2, C4, C9), 27.8 (p, C13), 25.8 (p, -Si-C($\underline{C}H_3)_3$), 18.8, 18.5, 18.1 (C3, C10, -Si-$\underline{C}(CH_3)_3$), -6.0 (p, -Si-($\underline{C}H_3)_2$).

MS: *m/z* 404 (M^+ -tBu, 57%), 316 (90), 284 (52), 241 (100).

Methyl [(1RS,4aSR,10aRS)-1,2,3,4,4a,5,8,9,10,10a-Decahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-1-methylphenanthren-1-yl]methylcarbamate (6-27)

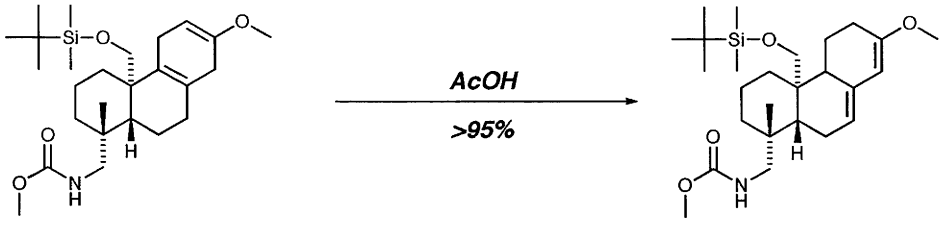


6-22 **6-27**

A 3-necked RB-flask was fitted with a dry ice condenser and flame dried under vaccum. The flask was then cooled to –78 °C (acetone, dry ice) and ammonia (25 mL) was then distilled into the flask. Lithium (7.5 mmol, 52 mg) was added and once the metal had dissolved the carbamate **6-22** (70 mg, 0.15 mmol), in dry THF (2 mL) and EtOH (1 mL), was added slowly by syringe. Once the addition was complete, the syringe was rinse with THF (1 mL) and this was then added to the flask. The temperature was then raised to –40 °C (acetone, dry ice) and stirred for 3 hrs at this temperature. If the blue colour dissipated during this time, then more small pieces of lithium were added. After 3 hrs MeOH (2 mL) was slowly added, and once the blue colour had dissipated the ice bath was removed and the ammonia allowed to evaporate under a stream of argon. H_2O (5 mL) was added, followed by Et_2O (5 mL), and the organic layer was then washed with H_2O and brine. The aqueous layers were then re-extracted with EtOAc (2x, 5 mL) and the combined organic layers then dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude 1,4 dihydroanisole **6-27** (70 mg, ~100%) as a white solid, which was then used immediately in the next reaction.

^{1}H NMR: Key Signals δ 4.86 (1H, bt, -N$\underline{H}CO_2Me$), 4.56 (1H, bt, H5), 3.65 (3H, s), 3.53 (3H, s), 3.08 (1H, 1H, dd, J = 5.1 Hz, J = 13.7 Hz), 0.93 (3H, s), 0.84 (9H, s), -.002, -0.03 (6H, s)

Methyl [(1RS,4aRS,10aRS)-1,2,3,4,4a,4b,5,6,10,10a-decahydro-7-methoxy-4a-(tert-butyl-dimethylsiloxymethyl)-1-methylphenanthren-1-yl]methylcarbamate (6-40)

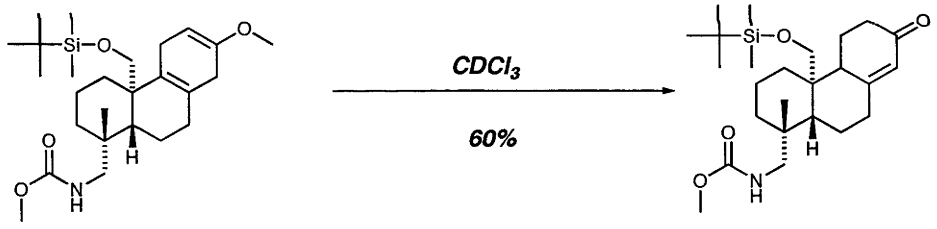


6-27 **6-40**

The crude 1,4 dihydroanisole **6-27** (33 mg, 0.07 mmol) was taken up in freshly dried AcOH (1 mL) and stirred for 4 hrs. After this time, the solvent was removed under reduced pressure to give a mixture ~3:1 of enone **6-41** and the linear dienol **6-40** (30 mg, >95%), which was used immediately.

^{1}H NMR: Key Signals for **6-40** δ 5.32 (1H, brs, H9), 5.19 (1, s, H8), 4.62 (1H, brs, -NH-), 3.66 (3H, s, -$NHCO_2CH_3$), 3.56 (3H, s, -OCH_3), 0.86 (9H, s), 0.06 (6H, s).

Methyl [(1R,4aR,10aR)-1,2,3,4,4a,4b,5,6,7,9,10,10a-Dodecahydro-4a-(tert-butyl-dimethylsiloxymethyl)-1-methyl-7-oxophenanthren-1-yl]methylcarbamate (6-41)



6-27 **6-41**

To the crude 1,4-dihydroanisole **6-27** (500 mg, 1.1 mmol) was added $CDCl_3$ (30 mL). The solution was stirred for 2 mins and then Et_2O (50 mL) and 1M NaOH (20 mL) were added. The organic layer was then washed with brine (50 mL). The aqueous layer was re-extracted with EtOAc (2x, 50 mL) and the combined organic layers dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give an oil. The oil was chromatographed on silica gel (Pet.Sp:EA 6:1 to 2:1) to give the aromatic compound **6-22** (80 mg, 16%) and the α,β-enone **6-41** (300 mg, 60%) as a clear oil.

R_f: 0.27 (Pet.Sp.:EA 2:1).

HRMS: Found: $M^{+\cdot}$ –^{t}Bu 392.2245, $C_{21}H_{34}NO_4Si$ requires 392.2257.

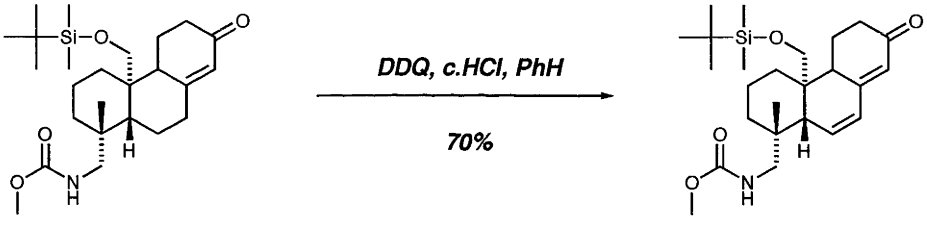
IR: υ_{max} 3342 (brs), 2929 (s), 1718 (s), 1666 (s), 1547 (m) cm^{-1}.

^{1}H NMR: δ 5.80 (1H, s, H8), 4.61 (1H, bs, -NHCO$_2$Me), 3.75 (1H, dd, J = 3.8 Hz, J = 15.4 Hz, H12), 3.66 (3H, s), 3.61 (2H, s), 3.01 (1H, dd, J = 5.6 Hz, J = 13.7 Hz), 1.40 – 2.60 (16H, m), 0.96 (3H, s), 0.83 (9H, s), 0.01 (6H, s).

^{13}C NMR: δ 199.6 (q, C7) 166.5 (q, -NHCO$_2$Me), 157.4 (q, C8a), 124.7 (t, C8), 63.9 (s, C11), 54.4 (p, -OCH$_3$), 51.9, 51.3 (t, C4b, C10a), 43.4 (s, C12, -CH$_2$N-), 42.5 (q, C4a), 37.9 (q, C1), 37.1, 35.9, 35.7, 34.9 (s, C2, C4, C6, C9), 27.7 (p, C13), 25.6 (p, -Si-C(CH$_3$)$_3$), 21.6, 20.8, 18.7 (s, C3, C5, C10), 17.8 (q, -Si-C(CH$_3$)$_3$, -5.9 (p, -Si-CH$_3$).

MS: *m/z* 392 (M^+ -tBu, 55%), 279 (20), 167 (30), 149 (89).

Methyl [(1R,4aR,10aR)-1,2,3,4,4a,4b,5,6,7,10a-Decahydro-4a-(tert-butyl-dimethylsiloxymethyl)-1-methyl-7-oxophenanthren-1-yl]methylcarbamate (6-33)



6-41 **6-33**

The enone **6-41** (66 mg, 0.15 mmol) was dissolved in benzene (5 mL) and c.HCl (3 drops) added. As the reaction was stirred rapidly, DDQ (0.16 mmol, 36 mg), dissolved in benzene (2 mL), was added in a dropwise fashion, allowing the yellow colour to dissipate between drops. Once the addition was complete, the reaction was allowed to stand for 1 min and then the benzene was removed by pipette taking care to avoid c.HCl drops at the bottom of the flask. Once the benzene was removed the c.HCl drops were washed with benzene (2x, 1 mL), and the reaction mixture was then loaded onto an alumina column (2 g) and the benzene eluted. The dienone was then eluted (by gradient of 1% EtOAc/Pet.Sp to 5% EtOAc/Pet.Sp) to afford dienone **6-33** (47 mg, 70%) as a clear oil.

R_f: 0.25 (Pet.Sp.:EA 2:1).

HRMS: Found: $M^{+\cdot}$ 447.2808, $C_{25}H_{41}NO_4Si$ requires 447.2805.

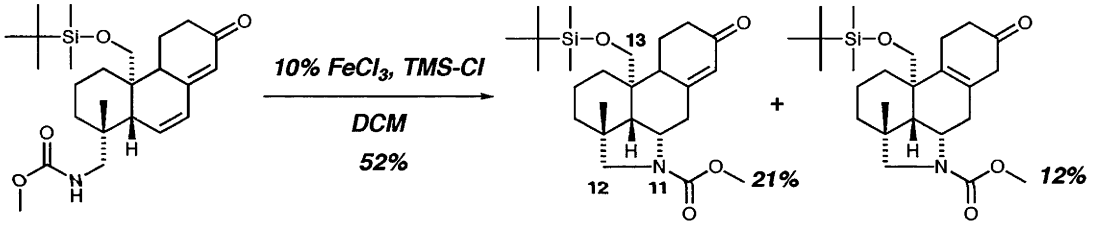
IR: υ_{max} 3362 (brs), 2928 (s), 1715 (s), 1660 (s) cm^{-1}.

^{1}H NMR: δ 6.32 (1H, d, *J* = 9.6 Hz, C9), 6.21 (1H, dd, *J* = 9.9 Hz, *J* = 3.2 Hz, C10), 5.81 (1H, s, C8), 4.81 (1H, brt, -NHCO$_2$Me), 3.67 (3H, s), 3.64 (2H, s), 3.46 (1H, dd, *J* = 8.1 Hz, *J* = 14 Hz, H12), 3.10 (1H, dd, *J* = 5.5 Hz, *J* = 14.1 Hz).

^{13}C NMR: δ 200.2 (q, C7), 157.6, 157, 4 (q, C8a, -N<u>C</u>O$_2$Me), 137.2 (t, C10), 129.7, 125.0 (t, C8, C9), 61.8 (s, C11), 54.9 (p, O<u>C</u>H$_3$), 52.1, 51.2 (t, C4b, C10a), 44.5 (s, C12), 42.7, 38.2 (q, C1, C4a), 37.4, 36.4, 32.9 (s, C2, C4, C6), 27.1 (p, C13), 25.8 (p, -Si-C(<u>C</u>H$_3$)$_3$), 22.9, 18.5 (s, C3, C5), 18.0 (q, -Si-<u>C</u>(CH$_3$)$_3$), -5.7 (p, -Si-<u>C</u>H$_3$)

MS: *m/z* 447 (M$^{+\cdot}$, 3%), 390 (100), 366 (22), 346 (20).

Methyl [(1R,4aR,10aR)-1,2,3,4,4a,4b,5,6,7,10a-Dodecahydro-11-aza-10,4-enthano 4a-(tert-butyl-dimethylsiloxymethyl)-1-methyl-7-oxophenanthren-11-carboxylate (6-50) & Methyl [(1R,4aR,10aR)-1,2,3,4,4a,5,6,7,8,10a-Dodecahydro-11-aza-10,4-enthano-4a-(tert-butyl-dimethylsiloxymethyl)-1-methyl-7-oxophenanthren-11-carboxylate (6-54)



6-33 **6-50** **6-54**

The dienone **6-33** (47 mg, 0.1 mmol) was taken up in dry DCM (1 mL) and treated with $FeCl_3$ (10%, 2 mg), following which the reaction when a deep green. TMS-Cl (0.1 mmol, 12 μL) was then slowly added and the reaction instantly changed to a yellow colour. After 10 mins, TLC indicated that most of the starting material hand been consumed. H_2O (1 mL) followed by EtOAc (5 mL) were added and the organic layer washed with 1M NaOH (5 mL) and brine (5 mL). The aqueous layers were re-extracted with EtOAc (2x, 5 mL) and the combined organic layer dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel (Pet.Sp: EA 6:1) to give the βγ-enone **6-54** (6 mg, 12%), the diene **6-33** (9 mg, 19 mg), and the αβ-enone **6-51** (10 mg, 21%).

R_f: 0.20 (Pet.Sp.:EA 2:1).

HRMS: Found: M$^{+\cdot}$ 447.2812, $C_{25}H_{41}NO_4Si$ requires 447.2805

IR: υ_{max} 2953 (s), 1701 (s), 1675 (s), 1449 (m), 1388 (m) cm^{-1}.

^{1}H NMR: (500 MHz) 5.91 (1H, s, H8), 4.17 ($^{11}/_{20}$H, dd, *J* = 7.8 Hz, *J* = 15.1 Hz, H6), 4.10 ($^{9}/_{20}$H, dd, *J* = 7.3, *J* = 14.6 Hz, H6'), 3.74 (2H, s), 3.70 (3H, s), 3.43 ($^{9}/_{20}$H, d, *J* = 11.8 Hz, H12'), 3.26 ($^{9}/_{20}$H, d, H12'), 3.16 ($^{9}/_{20}$H, dd, *J* = 9.3 Hz, *J* = 19.5 Hz, H7*e*'), 2.65 ($^{9}/_{20}$H, d, *J* = 20 Hz, H7*a*'), 3.33 ($^{11}/_{20}$H, dd, J= 8.8 Hz, *J* = 19.5 Hz, H7*e*), 3.27 ($^{11}/_{20}$H, d, *J* = 10.7 Hz, H12), 3.22 ($^{11}/_{20}$H, d, *J* = 11.2 Hz, H12), 2.74 ($^{11}/_{20}$H, brd, H7*a*), 2.50 (1H, m), 2.20 (m), 1.89 (m), 1.74 (m), 1.44 (m), 1.07 (3H, s), 0.85 (9H, s), 0.07, 0.01 (6H, s).

^{1}H NMR: (500MHz, 100 ^{0}C, D_6-DMSO) δ 5.75 (1H, s, H8), 4.09 (1H, ddd, *J* = 8.3 Hz, C10), 3.65 (1H, d, *J* = 11.2, H11), 3.60 (3H, s), 3.58 (1H, d), 3.28 (1H, d, *J* = 10.7, H12), 3.16 (1H, d, *J* = 11.2 Hz), 3.12 (1H, dd, *J* = 8.8 Hz), 2.75 (1H, dd, *J* = 6.5 Hz, *J* = 19.5 Hz), 2.32 (1H, m), 2.18 (2H, m), 2.02-2.13 (2H, m), 1.80 (1H, m), 1.70 (1H, m), 1.68 (1H, d, *J* = 8.3 Hz, H10a), 1.55 (1H, m), 1.38 (1H, m), 1.06 (1H, m), 1.04 (3H, s, H13), 0.85 (9H, s), 0.01, -0.01 (6H, s).

^{13}C NMR: (125 MHz, 75 ^{0}C, D_6-Benzene): δ 196.4 (q, C7), 162.6, 156.0 (q, C8a, -N$\underline{C}O_2$Me), 127.4 (t, C8), 63.3 (s, C11), 59.5, 55.7, 53.5, 5.20 (C12, C10a, C10, C4b), 52.1 (p, O$\underline{C}H_3$), 40.0, 39.3 (C1, C4a), 36.6 (s, C9), 31.7 (x2), 30.2, 29.3 (x2) (s, C2, C4, C6), 26.0 (p, -Si-C($\underline{C}H_3$)$_3$), 25.6 (p, C13), 18.3 (q, -Si-$\underline{C}$(CH$_3$)$_3$, -5.7, -5.8 (p, -Si- $\underline{C}H_3$)

MS: *m/z* 447 ($M^{+\cdot}$, 3%), 390 (100), 360 (5), 338 (5), 256 (12).

Methyl [(1R,4aR,10aR)-1,2,3,4,4a,5,6,7,8,10a-Dodecahydro-11-aza-10,4-enthano-4a-(tert-butyl-dimethylsiloxymethyl)-1-methyl-7-oxophenanthren-11-carboxylate (6-54)

HRMS: Found $M^{+\cdot}$ -^{t}Bu 392.2256, $C_{21}H_{34}NO_4Si$ requires 392.2257

IR: ν_{max} 2954 (s), 1700 (s), 1983 (s), 1459 (m), 1389 (w) cm^{-1}.

^{1}H NMR: 4.09-4.18 (1H, brm, H10), 3.73, 3.69 (3H, s), 3.35 ($^1/_2$H, d, *J* = 10.7 Hz), 3.21 ($^1/_2$H, D, *J* = 10.9 Hz), 3.11 ($^1/_2$H, d, *J* = 10.7 Hz), 2.20-2.80 (m), 1.03 (3H, s), 0.84 (9H, s), -0.02, -0.05 (6H, s).

MS: *m/z* 447 ($M^{+\cdot}$, >1%), 392 (50), 272 (100), 227 (50).

8.7 References

(1) Sims, J. J.; Selman, L. H.; Cadogan, M., 6-Methoxy-Beta-Tetralone, *Org. Synth.* **1988**, *50-9*, 744-746.

(2) Colvin, E. W.; Doyle, M.; Shroot, B.; Raphael, R. A.; Martin, J.; Parker, W., Bridged Ring-Systems .16. Synthetic Approach to Lycopodium Alkaloids, *J. Chem. Soc., Perkin Trans. 1* **1972**, 860.

(3) Hedstrand, D. M.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L., Bruceantin support studies. 10. Use of an axial b-face thiomethyl control element in intramolecular conjugate additions. Synthesis of a tricyclic bruceantin precursor, *J. Org. Chem.* **1987**, *52*, 592-8.

Appendix

The following compounds were crystallised from methanol. The data was collected and analysed by Anthony C. Willis at the Research School of Chemistry of the Australian National University.

Table 1. X-ray data for **3- 61** and **5-24**

	3-61 (Figure 3.17)	**5-24 (Figure 5.9)**
Formula	$C_{17}H_{20}O_7.H_2O$	$C_{20}H_{26}O_6$
Mass/g mol^{-1}	290.36	362.42
Crystal System	Monoclinic	Triclinic
Space Group	$P2_1/a$	P_1
a/Å	8.5529 (2)	9.2710 (7)
b/Å	20.3609 (5)	10.177 (2)
c/Å	8.9489 (2)	11/304 (1)
β/Å	96.8096 (14)	109.237 (7)
V/Å	1547.41 (6)	908.3 (2)
Z	4	2
T/K	200	296
μ (Mo Kα)/mm^{-1}	0.099 mm^{-1}	0.801
No. of reflections	21764	3451
Unique reflections	2732	2894
No. of measured reflections	1755 $I > 3u\ (I)$	2621
R	0.0324	0.0401
wR	0.0376	0.0540

Appendix Two

Errata

Page 12, **Scheme 2.9** – Step four should include MeI;

Page 31, **Scheme 2.34** – Step four *CHO* should be CH_2O;

Page 32, **Scheme 2.36** – Step four should include a N-chlorination step;

Page 68 & 139 – The correct yield of **4-22** is 67%;

Page 69 & 143 – The correct yield of **4-26** from **4-25** is 65%;

Page 77 – The correct yield of **5-13** is >95%;

Page 78 – The correct yield of **5-14** is 99%;

Page 99 – The correct yield of **6-8** is 85%;

Page 129 – The correct yield of **3-58** is 72%;

Page 99 & 163 – The correct yield of **6-17** is 94%.