Towards the total synthesis of vinigrol

Lisa Johnstone

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TOWARDS THE TOTAL SYNTHESIS OF VINIGROL

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PhD THESIS

UNIVERSITY OF DURHAM

DEPARTMENT OF CHEMISTRY

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In Loving Memory of

Papa Charlie

(Charles Johnstone 1935-2004)

and

Uncle Wull

(William John Johnstone 1962-2006)

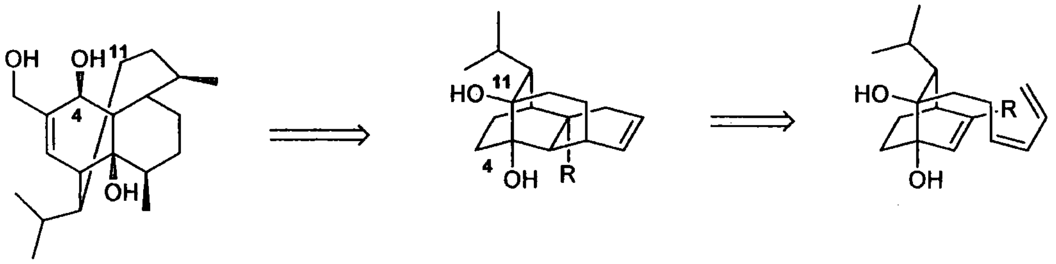
Abstract

Towards the Synthesis of Vinigrol

Lisa Johnstone PhD 2006

Vinigrol is a unique tricyclic diterpene containing the unprecedented decahydro-1, 5-butanonapathalene framework and with these unusual structural features it also has varied biological activity, making it a challenging synthetic target. Despite various groups working in this area, there has been no total synthesis published to date.

The thesis begins by discussing the challenging aspect of the total synthesis, construction of the 8-membered ring. Three distinct strategies exist for the construction of 8-membered carbocycles. C-C-bond forming reactions and ring expansion approaches have been utilised in the syntheses towards Vinigrol to date. However neither method has yet yielded a total synthesis. Ring fragmentation has not been exploited in the synthesis of Vinigrol to date and is a useful synthetic tool since smaller ring systems are easier to construct than their medium ring counterparts. It was envisaged that the 8-membered ring could be installed in a masked form as a series of 6-membered rings and thereby avoiding the normal difficulties associated with medium ring synthesis, Scheme 1. The key reaction of the synthesis was an intramolecular Diels Alder reaction. This thesis describes three related strategies which were utilised in order to afford the masked 8-membered ring which would then enable the tricyclic skeleton of Vinigrol to be obtained.



Scheme 1

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Declaration

This work was conducted in the Department of Chemistry at the University of Durham between October 2003 and September 2006. A three month CASE placement was undertaken at AstraZeneca, Alderley Park, Macclesfield between May 2005 and August 2005. This work has not been submitted in this, or any other university. It is my own work, unless otherwise stated.

Acknowledgments

Firstly I would like to thank my supervisor Patrick Steel, without whom none of this would have been possible. His continued enthusiasm throughout the last three years has truly been an inspiration.

Rob Davies, thanks for making feel welcome during my stay at Alderley Edge, the 'business lunches' and his contribution to this project.

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The past and present members of CG1/CY1 (too many of you to mention but you know who you are!), it was a pleasure to work with you all, I think! An apology for the numerous smells that I've had to subject you too, I'm assured it was all in the name of science!

Special mentions go to Liz, Marie and the Evil Twin for their advice and proof reading of this doorstop!

To my mam and dad, I promise I'll leave university soon, honest! Thanks for all the sacrifices that you've made over the years to make sure I've been able to get this far. I am truly indebted to you.

Vic, aka the Evil Twin. The bestest blister anyone could ever have. I know I might have the appropriate letters but still won't be able to give you a plaster!

Andrew, my other half, ta fir being there for the last four years, but now I'm no longer a 'dodgy student' you'll have to find some other nickname!

Thanks to Elaine (and Morgan) and Janet and the rest of my former team-mates of Gradstaff WFC and Valley Vixens and everyone I've had the pleasure of playing hockey with at both Durham City and Ustinov HC's. Weekends would have never been the same!

If there is anyone after reading this, feeling hard done by because they didn't get a mention then I'm sorry but I've only got limited space!!

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SECTION C EXPERIMENTAL

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Abbreviations

Ac – Acetyl
Acac - Acetylacetonate
AcOH – Acetic Acid
AcONa – Sodium Acetate
AIBN – Azo-*bis*-isobutyronitrile
AIDS – Acquired immune deficiency syndrome
Ar – Aryl
$BaSO_4$ – Barium Sulfate
BHT - Butylated Hydroxytoleune
BH_3.THF – Borane-Tetrahydrofuran Complex
Bn - Benzyl
Boc - ^{t}Butoxycarbonyl
b.p. – Boiling Point
br. - Broad
BuLi – Butyl lithium
Bu_3SnH – Tributyl tin hydride
$CaCO_3$ – Calcium Carbonate
CCl_4 – Carbon tetrachloride
$CHCl_3$ - Chloroform
CH_2Cl_2 - Dichloromethane
CI – Chemical Ionisation
CuI – Copper Iodide
m-CPBA – m-Chloroperbenzoic Acid
CSA – Camphorsulfonic Acid
CS_2 – Carbon disulfide
d – Doublet
DAIB – Diacetoxyiodobenzene
DBU – 1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCM - Dichloromethane
Dess-Martin - 2,2,2-Triacetyl-1,2-dihydro-2-ioda-3-oxa-naphthalen-4-one
DIBAL – Diisobutylaluminium hydride
DIPEA - Diisopropylethylamine

DMAP - 4-Dimethylaminopyridine

DME – 1,2-Dimethoxyethane

DMF – Dimethylformamide

DMSO – Dimethylsulfoxide

DPS - ^{t}Butyldiphenylsilane

d.s. - Diastereoselectivity

E – Entgegen (*trans* double bond)

EI - Electron Impact Ionisation

ES - Electrospray

Et - Ethyl

Et_3N – Triethylamine

Et_2O – Diethyl ether

EtOH – Ethyl Alcohol

EtONa – Sodium Ethoxide

EVE - Ethyl Vinyl Ether

GC - Gas chromatography

h - Hour

HCl - Hydrochloric Acid

$HClO_4$ – Perchloric Acid

HIV - Human immunodeficiency virus

H_2O_2 – Hydrogen peroxide

HMPA – Hexamethylphosphoramide

HMDS - 1,1,1,3,3,3-Hexamethyldisilazide

Imid. - Imidazole

^{i}Pr - Isopropyl

IR – Infrared Spectroscopy

KBr – Potassium Bromide

KH – Potassium Hydride

KHMDS – Potassium Hexamethyldisilazide

KOH – Potassium Hydroxide

LDA - Lithium Diisopropylamide

$LiAlH_4$ – Lithium Aluminium Hydride

$LiBH_4$ – Lithium Borohydride

LiHMDS – Lithium Hexamethyldisilazide

m – Multiplet

Me – Methyl

MeCN – Acetonitrile

MeLi – Methyl Lithium

MeOH – Methyl Alcohol

MOM – Methoxy methyl ether

m.p. – Melting point

MPM – Methoxyphenyl-methoxy

ml – Millilitre

MW – Microwave irridiation

N – Normal (concentration)

NCS - *N*-Chlorosuccinimide

Na_2CO_3 – Sodium Carbonate

NaCl – Sodium chloride

NaH – Sodium Hydride

$NaHCO_3$ – Sodium Hydrogen Carbonate

NaI – Sodium Iodide

$NaIO_4$ – Sodium Periodate

NaOH – Sodium Hydroxide

NBS – *N*-Bromosuccinimide

NIS - *N*-Iodosuccinimide

NMR – Nuclear Magnetic Resonance

NOESY – Nuclear Overhauser Enhancement Spectroscopy

PCC – Pyrdinium Chlorochromate

PG – Protecting group

Ph – Phenyl

$PhI(OAc)_2$ - Diacetoxyiodobenzene

PhMe - Toluene

Piv – Trimethylacetyl

PMB – *p*-Methoxybenzyl

$POCl_3$ – Phosphorus Oxychloride

PPTS – Pyridinium *p*-toluenesulfonate

q – Quartet

RCM – Ring Closing Metathesis

rt – Room temperature

'Ru' - Grubbs 2nd Generation RCM Catalyst

RuO_2 – Ruthenium Dioxide

s – Singlet

SmI_2 – Samarium Iodide

$SnCl_4$ – Tin (IV) Chloride

t – Triplet

^{t}BuOH - 2-Methyl-propan-2-ol

^{t}BuOK – Potassium *tert*-butoxide

TBAF – Tetrabutylammonium Fluoride

TBAI – Tetrabutylammonium Iodide

TFA – Trifluoroacetic Acid

TFMSA – Trifluoromethylsulfonic Acid

THF - Tetrahydrofuran

T.L.C – Thin Layer Chromatography

TNF – Tumour Necrosis Factor

p-TSA – *p*-Toluenesulfonic acid

TBDMS (TBS) – ^{t}Butyldimethylsilane

TBDPS – ^{t}Butyldiphenylsilane

TESCl - Chlorotriethylsilane

TMSCl – Chlorotrimethylsilane

v/v – volume/volume

Z – Zusammen (*cis* double bond)

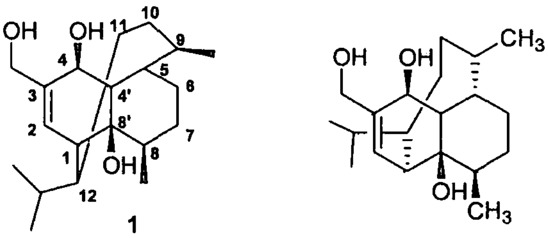
$ZnCl_2$ – Zinc Chloride

SECTION A : INTRODUCTION

Chapter 1 : Introduction

1.1 *General Introduction*

The aim of the project was to develop a strategy towards the total synthesis of the natural product Vinigrol **1** (Figure 1).[1] Vinigrol is a unique tricyclic diterpene containing the unprecedented decahydro-1, 5-butanonapothalene framework and with these unusual structural features it also has varied biological activity, making it a challenging synthetic target. Despite various groups working in this area, there has been no total synthesis published to date.[2,3,4,5,6]



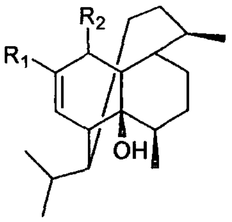
1

Figure 1

This chapter provides an overview of published strategies towards 8-membered rings and the total synthesis of Vinigrol and outlines the key reactions in the distinct approaches. Chapters 2 to 4 describe the approaches towards the total synthesis made in this project and Chapter 5 details the experimental procedures.

1.2 *Vinigrol : Discovery and Isolation*

Vinigrol **1** was first isolated from the culture broth of the fungal strain identified as *Virgaria nigra* by the Fujisawa Pharmaceutical Company in 1987.[1] 445 milligrams of Vinigrol were isolated from 140 litres fermentation broth. Ando *et al* attempted a range of derivatisation techniques to deduce the structure; however these were impractical for structure determination, Figure 2. To this end the oxidation product C, **5** was found to possess optimal crystals and these were submitted for X-ray analysis, this gave the structure as that shown in Figure 1. Stereochemistry at C4 was assigned with the help of NOESY NMR spectroscopy and absolute stereochemsitry was identified utilising circular dichorism. Vinigrol possesses eight chiral centres and a unique tricyclic skeleton containing a bridging 8-membered ring. The biosynthesis of Vinigrol has not been reported although it can be speculated that it may arise from a complex series of oxidative coupling reactions from mevalonate. Vinigrol **1** has shown activity as an antihypertensive and a platelet and TNF inhibitory agent and also slows the progression of AIDS-related complex (ARC) to AIDS.[1,7]



Ac$_2$O/py

$R_1 = CH_2OAc$
$R_2 = $ ◀OAc
2

Jones Oxidation

A $R_1 = CH_2OH$ **3**
$R_2 = (=O)$
B $R_1 = CHO$ **4**
$R_2 = $ ◀OH
C $R_1 = CHO$ **5**
$R_2 = (=O)$

Figure 2

1.3 Synthetic Approaches to 8-Membered Carbocycles

1.3.1 Introduction

One of the major challenges in this total synthesis is construction of the 8-membered ring due to the high degree of ring strain and transannular interactions[8] that need to be overcome during the synthesis. Ring expansion and fragmentation strategies from more readily available carbocycles can provide efficient access to medium sized rings to overcome the entropic factors that may impede ring closure. This section outlines possible approaches to their synthesis.

The conformation of 8-membered rings has been extensively studied and it has been shown that there are three major conformational families: the boat chair (BC), crown (CR) and boat-boat (BB) (Figure 3)[9]. The most stable conformation is usually the boat chair, which minimises transannular interactions and has a lower torsional strain. The parent cyclooctane exists predominately (>94 %) in one of the boat-chair **6** conformation and the remainder in the crown family **11** (Figure 4) but the addition of substituents will change this conformational equilibrium.

Boat-Chair (BC)
6

Twist Boat-Chair (TBC)
7

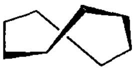
Chair (C)
8

Twist Chair (TC)
9

Twist Boat-Boat (TBB)
10

Crown (CR)
11

Chair-Chair (CC)
12



Twist Chair-Chair (TCC)
13

Boat-Boat (BB)
14

Boat (B)
15

Figure 3

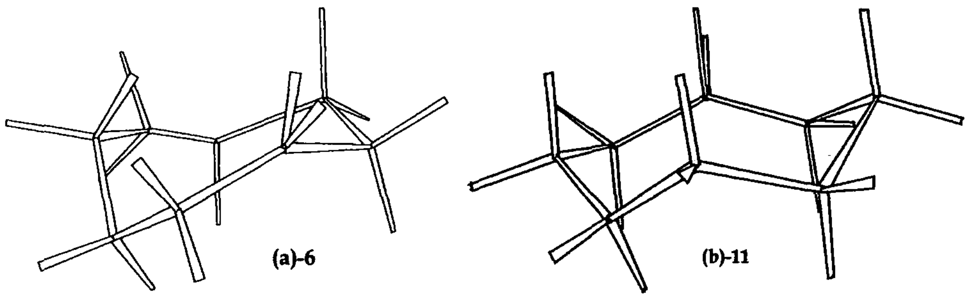
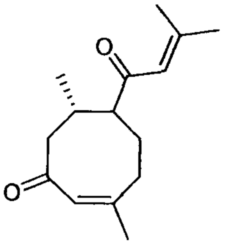
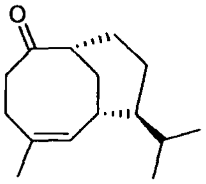


Figure 4 - Lowest Energy Conformations of Cyclooctanes (a) boat-chair 6, (b) crown 11

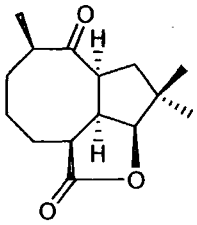
Syntheses of 8-membered rings are often not possible by the methods which are effective for smaller (3-7) or larger (10-16) ring systems.[10] However, the discovery of an increasing number of natural products containing an 8-membered ring has prompted significant synthetic attention in this area (Figure 5).[11]



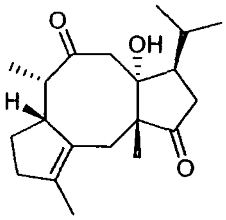
Spartidieneone
16



Salsoleneketone
17

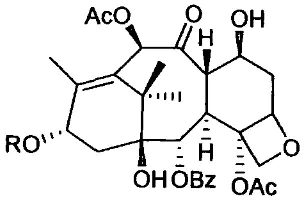


Asteriscanolide
18

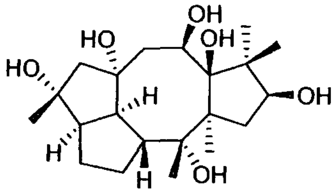


Roseadione

19

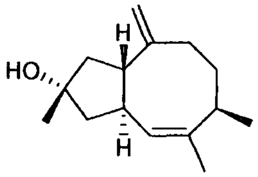


Taxol
R = PhCONH(Ph)CH(OH)CO
20

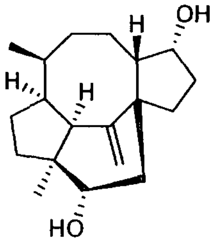


Kalmanol

21



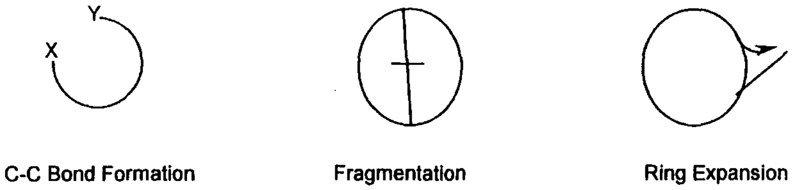
Dumortenol
22



Longipenol
23

Figure 5

There are three main strategies for building up 8-membered carbocycles: intramolecular C-C bond formation (including cycloadditions), ring fragmentation or ring expansion (Figure 6)[10] and these are described in more detail in the following sections.



C-C Bond Formation

Fragmentation

Ring Expansion

Figure 6

1.3.2 Carbon-Carbon Bond Formation

Intramolecular carbon-carbon-bond formation can be accomplished by several types of ring closures at C_1-C_8 (Figure 7). The formation of 8-membered rings by this method is often most difficult due to intrinsic conformational and entropic problems. The usual carbon-carbon-bond forming reactions (*e.g.* S_N2) normally give low yields or do not proceed at all.

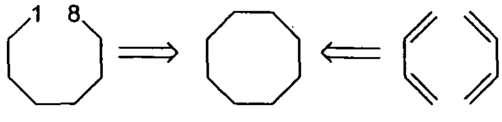


Figure 7

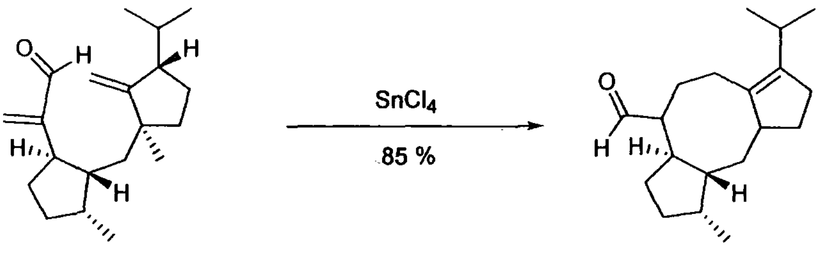
However, a number of reactions are viable for certain suitably functionalised 8-membered rings (Figure 8).[10,11] Variations of the aldol reaction have been used successfully for the synthesis of 8-membered rings and the intramolecular addition of a lactone enolate to an aryl aldehyde was utilised in the synthesis of steganone (Figure 8).[12]

24

25

Figure 8

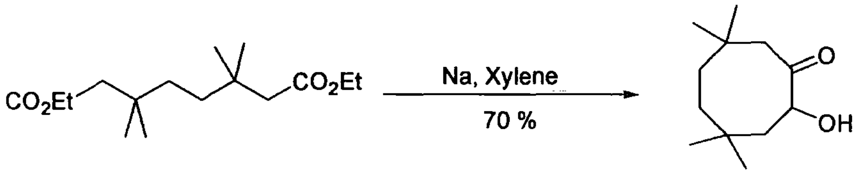
Conjugate additions have also been used successfully in synthesis and an efficient intramolecular ene-type reaction mediated by $SnCl_4$ was reported by Kato *et al* (Figure 9).[13]



26 **27**

Figure 9

Also a wide variety of carbonyl coupling reactions have been used successfully in 8-membered ring synthesis. Cyclooctanes may be produced by an acyloin reaction mediated by sodium metal (Figure 10), where the metal allows a degree of pre-organisation to allow the appropriate reacting centres to be in close proximity to allow coupling to occur.



28 **29**

Figure 10

Also, the simultaneous formation of two C-C bonds has been accomplished with a [4+4] cycloaddition under thermal or photochemical conditions (Figure 11)[14], however there are a number of other cycloadditions ([6π+2π][15], [4π+2π][16], [4π+2π+2π][17], Figure 11) which can also produce cyclooctanes in good yields.[11(d)]

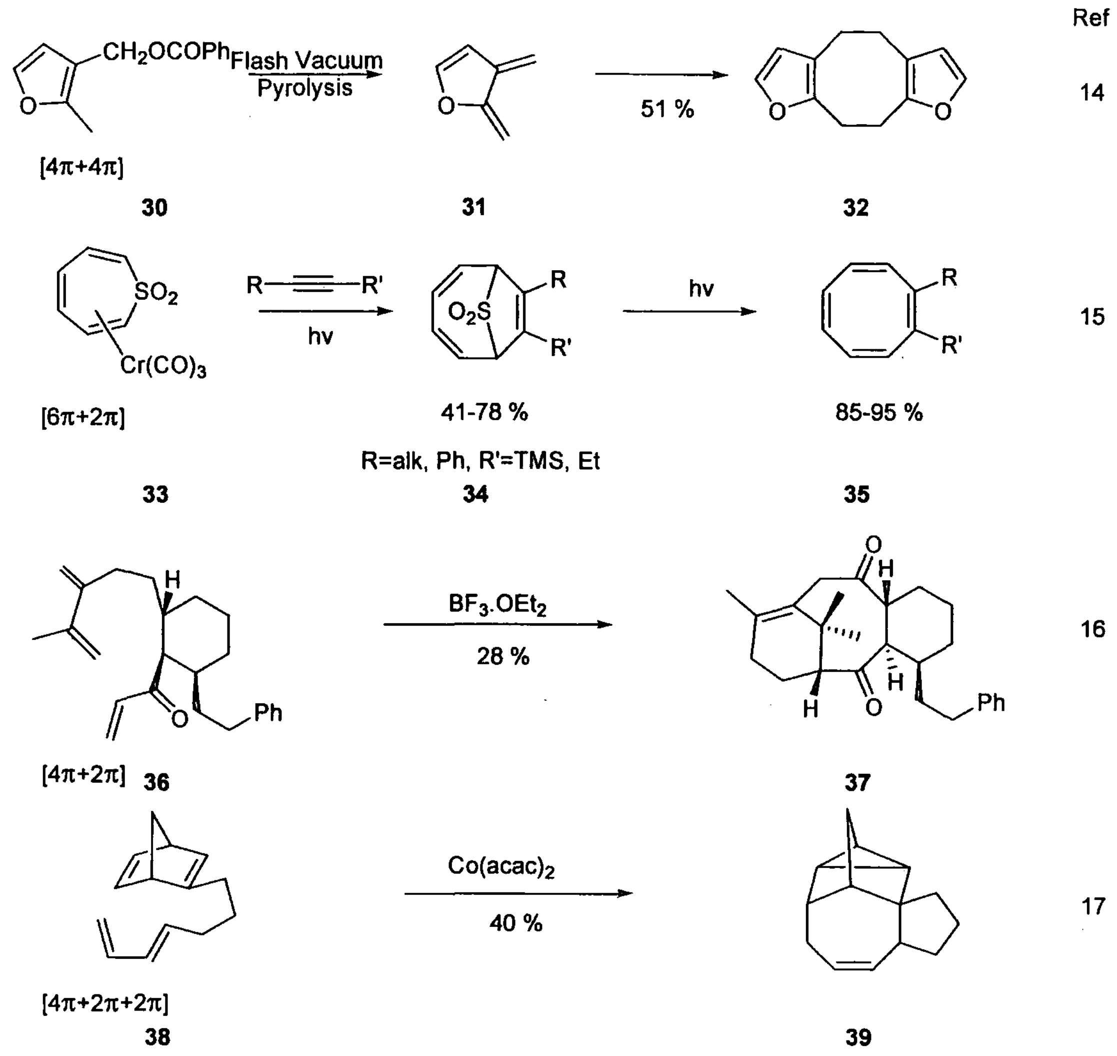


Figure 11

Recently ring closing metathesis (RCM) has become a powerful method of assembling such rings, however its success requires the presence of some conformational restraint, such as a pre-existing ring which bias the intra- versus the inter-molecular process (Figure 12).[18, 19]

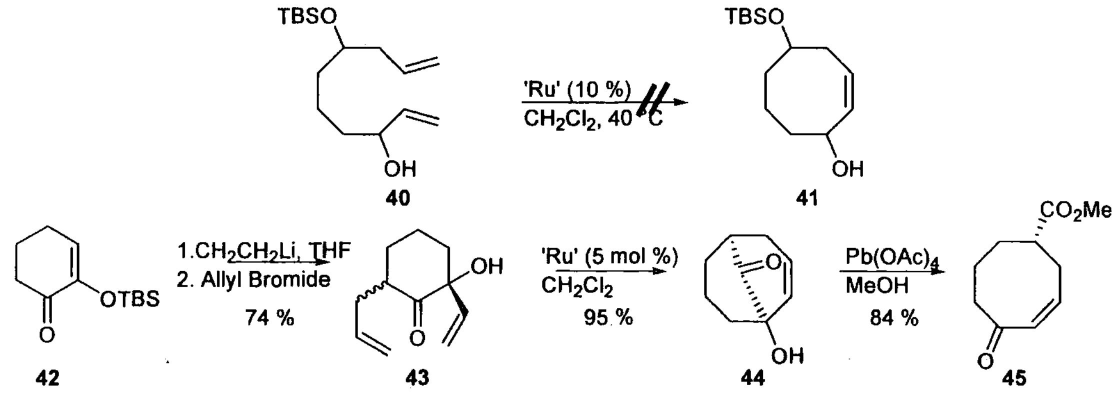
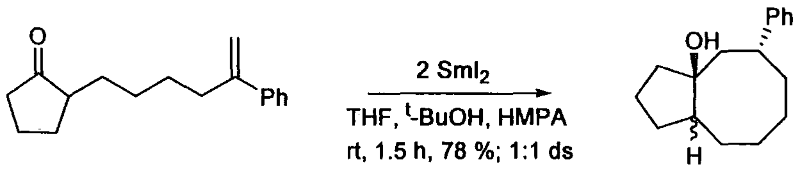


Figure 12

Simple routes to medium sized rings prove difficult because the coupling of two reactive termini are often spaced long distances apart. However it has been shown that reductive radical cyclisation techniques using samarium iodide can give good to moderate yields of 7-9 membered rings.[20] A similar approach utilising dissolving metal conditions had previously been explored but the yields of cyclooctanes were very low.[21] Molander *et al* have developed a general technique using an intramolecular ketyl-olefin coupling reaction to provide cyclooctanols in good yields (Figure 13).[10(c)] However, still no general technique exists for the synthesis of 8-membered rings by intramolecular bond formation and the precursors often have to be conformationally pre-organised to give the correct geometry to allow the reacting centres to come into the correct alignment.



46 **47**

Figure 13

1.3.3 Ring Expansion

The ring expansion of cyclic compounds has been an effective strategy for the synthesis of 8-membered rings and these include one-(a), two-(b), three-(c) or, four-atom-(d) ring expansions (Figure 14).[22]

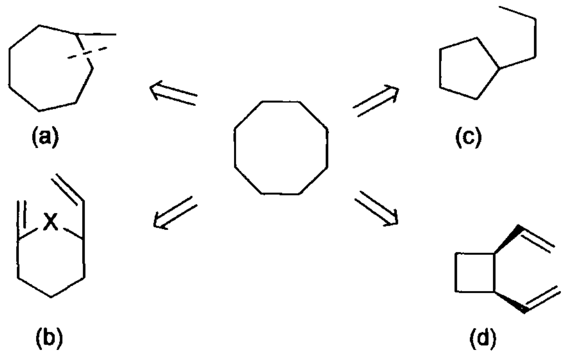


Figure 14

Ring expansion to larger rings has long been utilised for the formation of medium sized rings due to the ease of smaller ring synthesis and can be accomplished in a number of ways. 1-carbon ring expansion such as the Tiffeneau-Demyanov ring expansion (Figure 15)[23] and 2-carbon ring expansion such as [3, 3] sigmatropic rearrangements (*e.g.* oxy-Cope rearrangements, Figure 15)[24] are some of the reactions which have been exploited in synthesis of 8-membered rings.

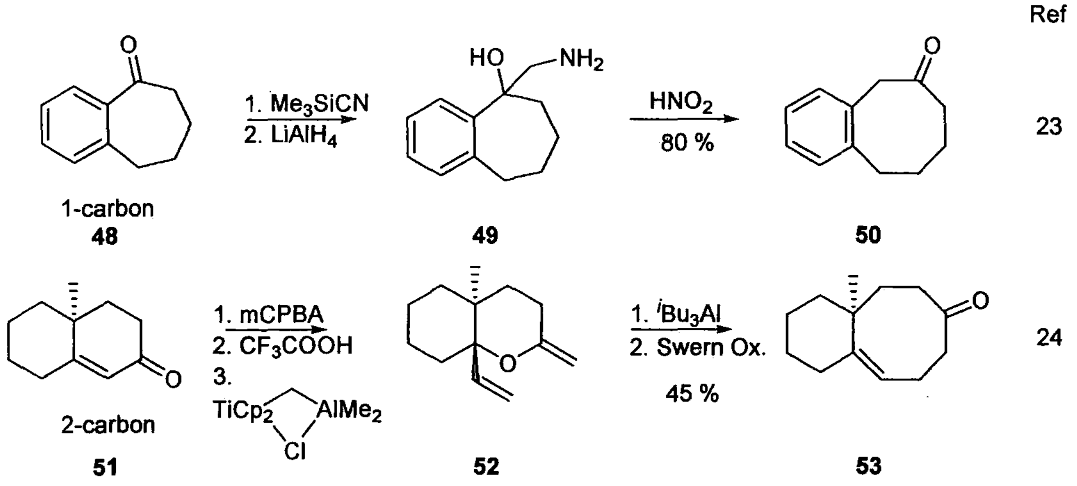


Figure 15

4-carbon ring expansions of divinyl cyclobutanes *via* Cope rearrangement to produce cyclooctadienes have been reported as an efficient process under mild conditions (Figure 16).[25]

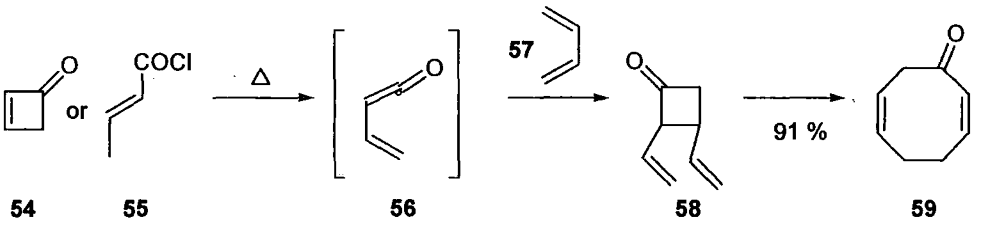


Figure 16

In contrast to the examples described above, 3-carbon ring expansions have only been reported in relatively few cases and have not generally been utilised in cyclooctane synthesis (Figure 17).[10,26] Ring expansion approaches appear to be widely utilised in total synthesis and have been widely developed into useful tools for the preparation of 8-membered rings due to the ease of which their precursors can be prepared.

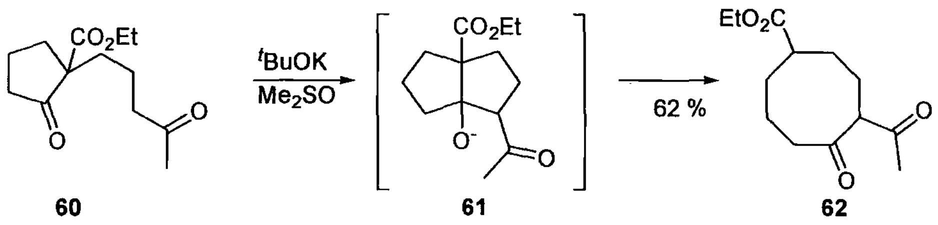


Figure 17

1.3.4 Ring Fragmentation

Ring fragmentation offers another useful method with which to prepare 8-membered rings involving the cleavage of the appropriate bond (Figure 18).[10] In a bicyclic system, the cleavage of a bond bridging two atoms of an 8-membered ring is a very effective method in the synthesis of these rings that has been exploited in a range of total syntheses (*vide infra*). There are three general modes of this type of process and involve fragmentation at C_1-C_7, C_1-C_6 and C_1-C_5. All of these bicyclic precursors have been used in the synthesis of 8-membered rings and, since the rings present in the molecules are smaller, they are much easier to construct. The conditions for the key fragmentation step are varied and include acid and base promoted reactions as well as redox methods. Several examples are described below.

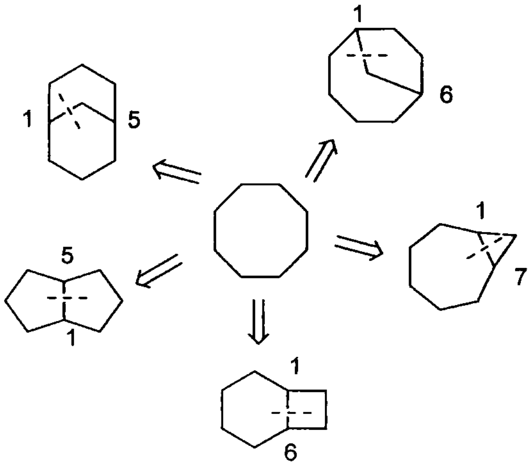
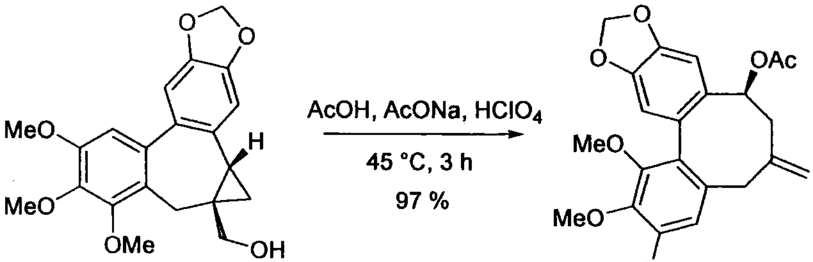


Figure 18

Magnus *et al* utilised fragmentation of [5.1.0]octane systems (C_1-C_7 fragmentation) in the synthesis of steganone natural products based on the expansion of fused biaryl cyclopropylmethanolcycloheptane derivatives (Figure 19).[27]



63 **64**

Figure 19

The photochemical [2+2] cycloaddition of an olefin to the enol form of 1,3 dicarbonyl derivatives followed by fragmentation of the resulting cyclobutane ring has been used extensively in synthesis (C_1-C_6 fragmentation).[28] The process is known as the deMayo[29] reaction and has been adapted for eight membered ring systems by utilising cyclohexane-1,3-dione derivatives. In an approach to fusicoccon H aglycone, Grayson *et al* used an intermolecular [2+2] photocycloaddition followed by a base-initiated retroaldol reaction (Figure 20).[30]

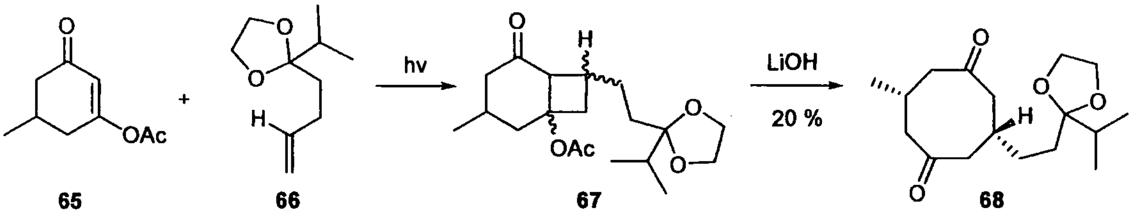


Figure 20

The cleavage of the C_1-C_5 bridging bond of fused 5-5 ring systems provides a general method for the construction of 8-membered rings. Mehta *et al* have used oxidative cleavage of a bridging olefinic bond providing 1,5 cyclooctadiones in the construction of the fusicoccin nucleus (Figure 21).[31]

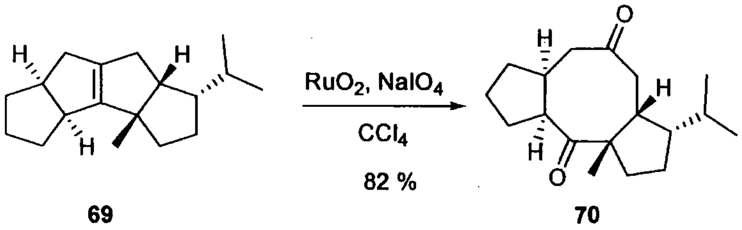


Figure 21

The Wharton fragmentation (Grob fragmentation variant) provides entry to 8-membered rings from bicyclo[3.3.1] nonane systems and Dutta has explored this in synthetic studies towards ophiobolins (Figure 22).[32]

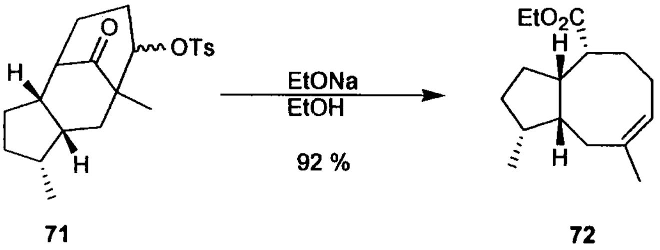


Figure 22

There are many strategies which are synthetically useful and permit access to a wide variety of structural motifs and substitution patterns. However, to date there remains no single synthetic approach to medium ring compounds comparable to that of the Diels Alder reaction for 6-membered systems.

1.4 Progress towards the Synthesis of Vinigrol

1.4.1 Introduction

Despite the obvious difficulties associated with a total synthesis of a natural product containing an 8-membered ring, the synthesis of Vinigrol has been attempted by a number of groups.[2,3,4,5,6] The efforts towards the total synthesis will be described in the following sections with particular emphasis on the efforts to develop strategies with which to introduce the 8-membered ring. Hanna *et al* have synthesised the full carbocyclic skeleton[2] and Matsuda's[4] and Barriaults's[6] groups have synthesised the partial carbocyclic skeleton containing the 8-membered ring (Figure 23). Only two different strategies have been published to date to facilitate construction of the 8-membered ring - ring expansion approach *via* oxy-Cope rearrangement and C-C bond formation utilising samarium iodide promoted Barbier coupling (Figure 23). These approaches towards the synthesis of the 8-membered ring and the efforts made towards the total synthesis will now be described concentrating on the strategies and key reactions involved.

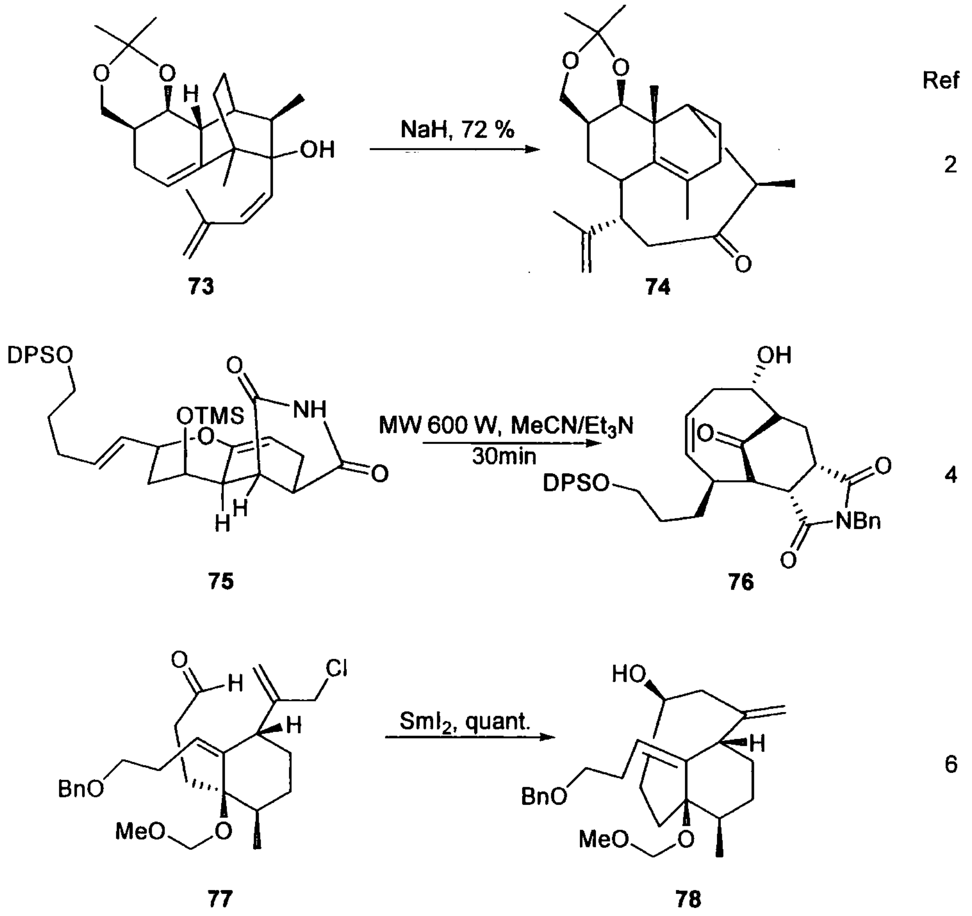
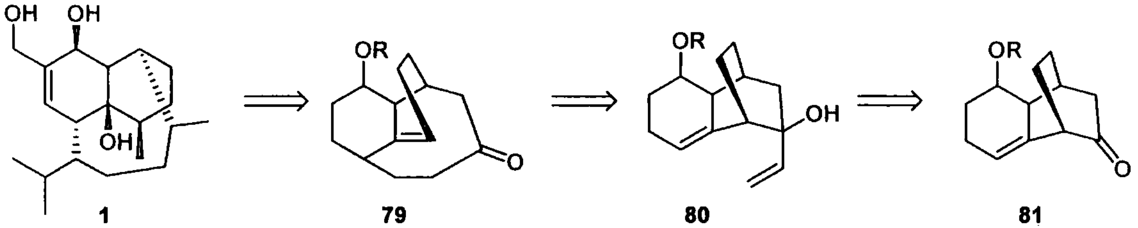


Figure 23

1.4.2 Synthesis of Tricyclic Skeleton of Vinigrol

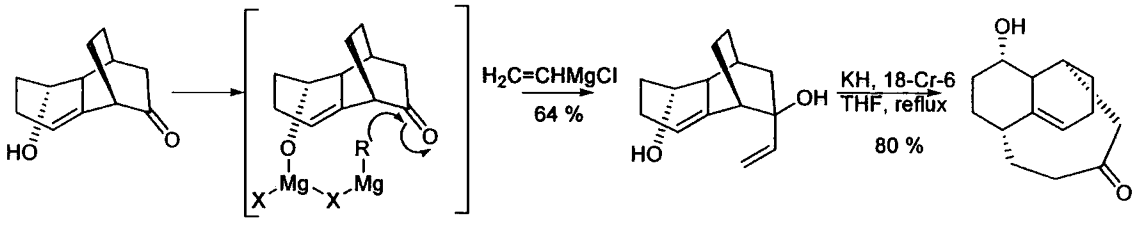
The first significant step towards the total synthesis of Vinigrol was the successful development of a method to complete the unusual decahydro-1,5-butanonaphthalene ring system.[2] The strategy of Hanna *et al* was based on the recognition that the oxygenated tricyclic skeleton of Vinigrol could be quickly elaborated *via* an anionic oxy-Cope rearrangement of tricyclic carbinol **80**, Figure 24.



1 **79** **80** **81**

Figure 24

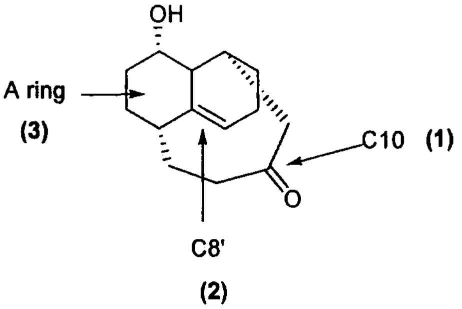
Chelation-controlled addition of vinyl magnesium bromide to ketone **82** gave exclusive formation of the desired *endo*-vinyl carbinol **83**, Figure 25. The resultant diol **83** was then treated with KH to initiate the anionic oxy-Cope rearrangement affording the desired tricyclic skeleton **84** after just 30 minutes, as a crystalline solid in good yield and very few synthetic steps.



82 **82‡** **83** **84**

Figure 25

Having achieved the synthesis of tricyclic skeleton **84**, attention was then focussed on efforts to elaborate on the functionality contained on the decahydro-1,5-butanonaphthalene ring system.[2] Three main areas of work were undertaken: removal of the carbonyl at C10 and introduction of the tertiary alcohol at C8′ and functionalisation of the A ring, Figure 26.



84

Figure 26

Thus, taking the tricyclic skeleton **84** methods were investigated to transform the C10 carbonyl to a methylene unit. Attempts utilising traditional methods (Huang-Minlon reduction, tosyl hydrazone, diethyl phosphate or dithioacetal) and the Barton deoxygenation were wholly unsuccessful and caused transannular cyclisation, Figure 27.

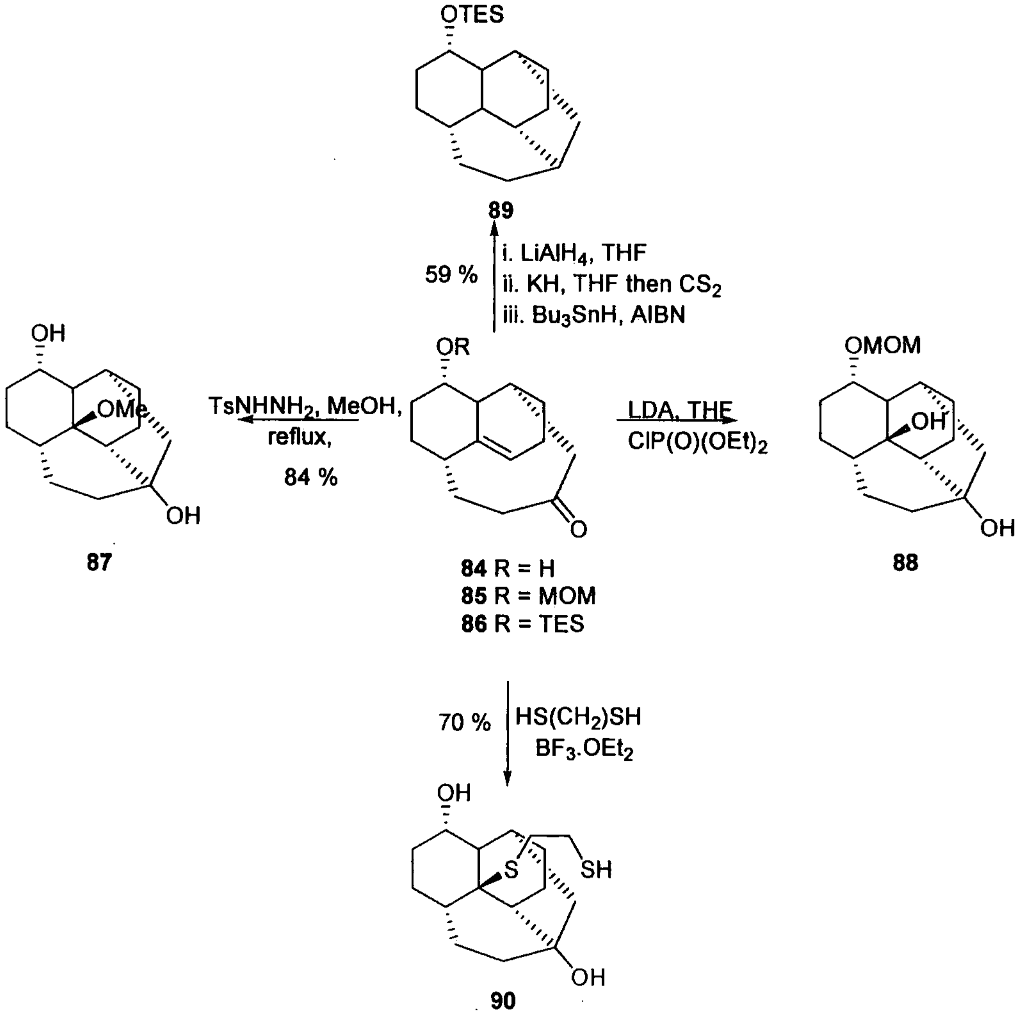


Figure 27

However, the solution to the problematic reductive removal of the carbonyl came from an unexpected observation when the group treated the intermediate with aqueous TFA in efforts to install the C8 hydroxy unit. Mono-protected triol **92** was obtained as a single isomer presumably through regio- and stereoselective hydration of the double bond after treatment with TESCl. This transformation reduced the propensity of the skeleton to undergo transannular cyclisation and subsequent protection allowed Barton deoxygenation to remove the functionality at C10 to give alcohol **93**, Figure 28.

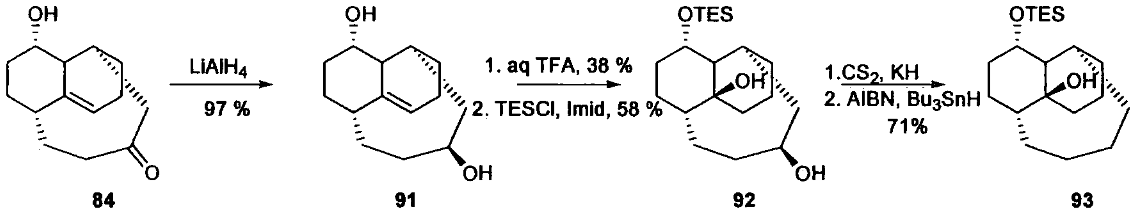


Figure 28

Functionalisation of the A ring was then attempted. Deprotection and oxidation gave ketone **94**. The hydroxymethyl unit was then introduced utilising Kobayashi's procedure[33] to give the desired alcohol **95**. However all attempts to prepare the α,β-unsaturated ketone **96** were unsuccessful giving complex mixtures of products, Figure 29.

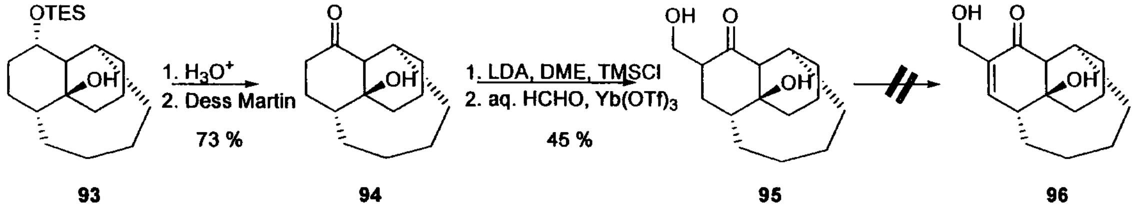


Figure 29

Hanna *et al* then redeveloped their strategy to include more functionality earlier in the synthesis as they had previously demonstrated that late-stage functionalisation of the tricyclic skeleton proved somewhat problematic.[2] This led to the reporting of the fully elaborated Vinigrol carbocyclic skeleton with methyl groups at C8 and C9 and stereoselective induction of the isopropyl group at C12, Figure 30.

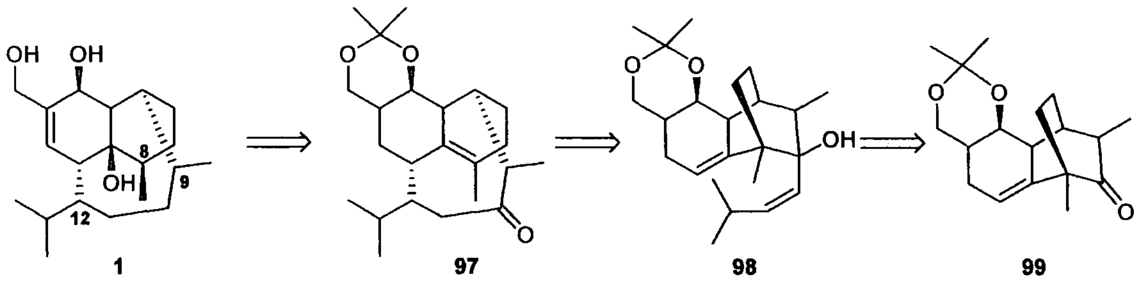


Figure 30

Cyclic acetal **101** was produced utilising previously established chemistry and inversion of the C4 hydroxyl group was achieved using the Mitsunobu procedure.[34,35] This stereocentre would then direct the introduction of the hydroxymethyl unit by the Stork procedure[36] on to the correct face of the molecule, Figure 31. Thus, acetal **101** was silylated to give bromomethyldimethylsilyl ether **102** and was then subjected to standard high dilution, radical-generating conditions followed by Tamao oxidation[37] to afford diol **103**, Figure 31.

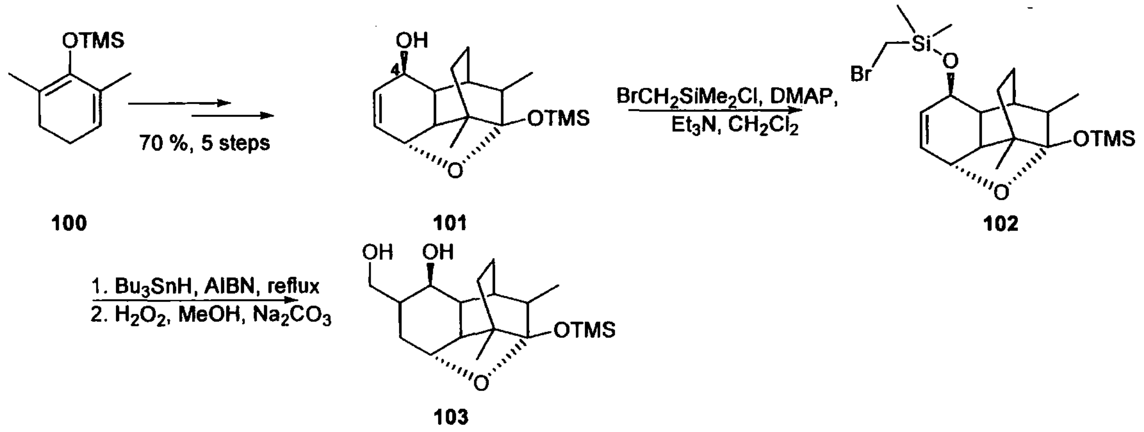


Figure 31

Acetonide protection and dehydration gave the desired ketone **99** and treatment with 3-methylbutynylmagnesium gave a mixture of alcohols (*endo*:*exo* = 4.2:1), Figure 32. Subsequent Lindlar reduction gave the oxy-Cope precursor **98**. However all attempts to induce this rearrangement resulted in recovered starting material or gave decomposition products. It is thought that steric crowding generated in the transition state impedes the rearrangement and stops it from taking place.

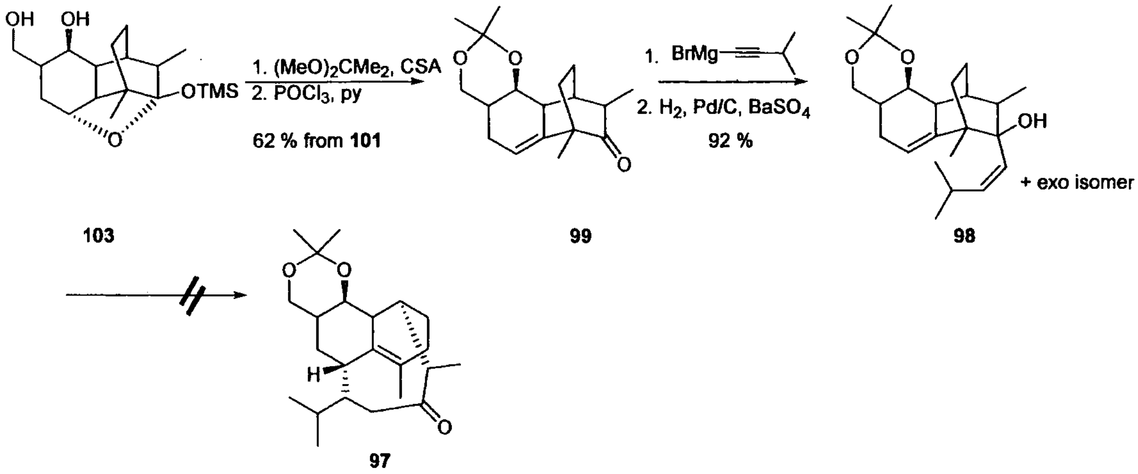


Figure 32

After considerable experimentation the isopropyl group was replaced by an isoprenyl group and the desired oxy-Cope reaction could be implemented, Figure 33. Thus, using the same chemistry as previously described alcohol **73** could be obtained and the rearrangement could be initiated by treatment of **73** with KH. Tricyclic skeleton **97** was obtained in good yields after hydrogenation.

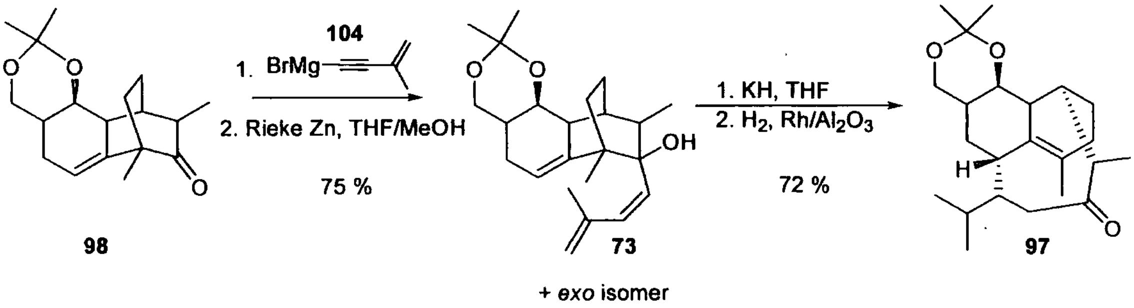


Figure 33

With **97** in hand, two further structural modifications were required to give the fully elaborated carbocyclic skeleton: removal of the carbonyl at C10 and installation of the tertiary alcohol at C4. These structural modifications were carried out with standard transformations to give tricyclic epoxide **106**, Figure 34.

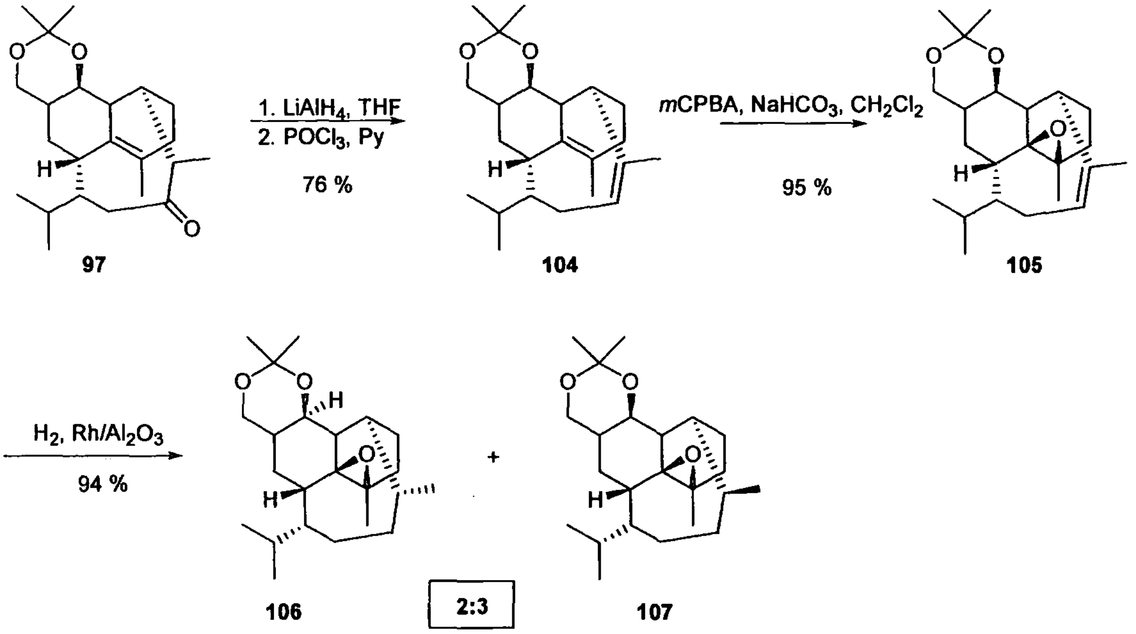


Figure 34

In summary, Hanna *et al* have elegantly and efficiently produced a highly advanced precursor of Vinigrol utilising an anionic oxy-Cope rearrangement as a key reaction to produce the 8-membered ring and have developed a strategy to fully elaborate the carbocyclic skeleton.

1.4.3 Functionalised Bicyclo[5.3.1]undecane Ring Systems

The functionalised bicyclo[5.3.1]undecane ring system **108** is contained in the structure of Vinigrol, Figure 35. Rapid and efficient construction of suitably fuctionalised derivatives of bicyclo[5.3.1]undecane have attracted much attention due to the number of groups working on the total synthesis of taxol and other natural products containing this system.[38]

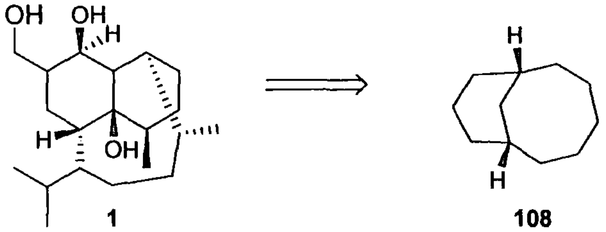
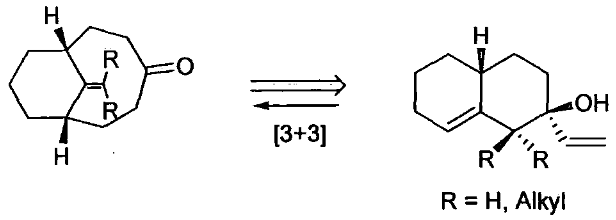


Figure 35

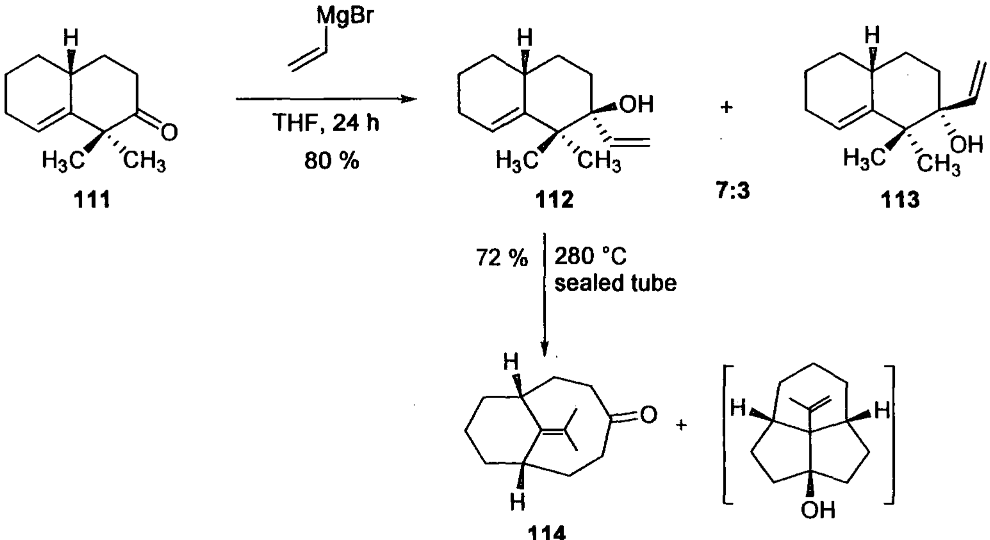
Computer generation allowed Mehta *et al* to recognise that they could gain entry to the bicyclo[5.3.1]undecane ring system **109** from the readily accessible bicyclo[4.4.0]decane precursor **110** (Figure 36).[3] This generic strategy employs the oxy-Cope rearrangement as the pivotal step in the synthesis as an aid to functionalisation of this ring system.



109 **110**

Figure 36

Thus, synthesis of the bicyclo[4.4.0]decane precursor **112** began from the readily available 1,1-dimethyl-8-octal-2-one **111** (Figure 37). Upon treatment with vinyl magnesium chloride, diastereomeric carbinols **112** and **113** were obtained (Figure 37). Alcohol **112** was heated in a sealed tube (280 °C) to give the oxy-Cope rearranged product **114** (and a by-product **115** which can arise from the tandem [3,3] sigmatropic rearrangement and an intramolecular carbonyl-ene reaction) (Figure 37).



111 **112** **113** **114** **115**

Figure 37

This synthesis was short and high yielding, however it has a low degree of functionalisation on the ring system and further studies are needed to demonstrate functional group tolerance to this strategy.

1.4.4 Tandem Pericyclic reactions and synthesis of the octalin ring

Barriault *et al* envisaged that the 8-membered ring of Vinigrol could be created by an intramolecular S_N2 displacement of a cyclic sulfate, **116** at C5 by a sulfone anion (Figure 38).[6] The desired *cis*-decalin would be obtained in one step utilising a tandem oxy-Cope/Claisen/ene reaction of allyl ether **118**.

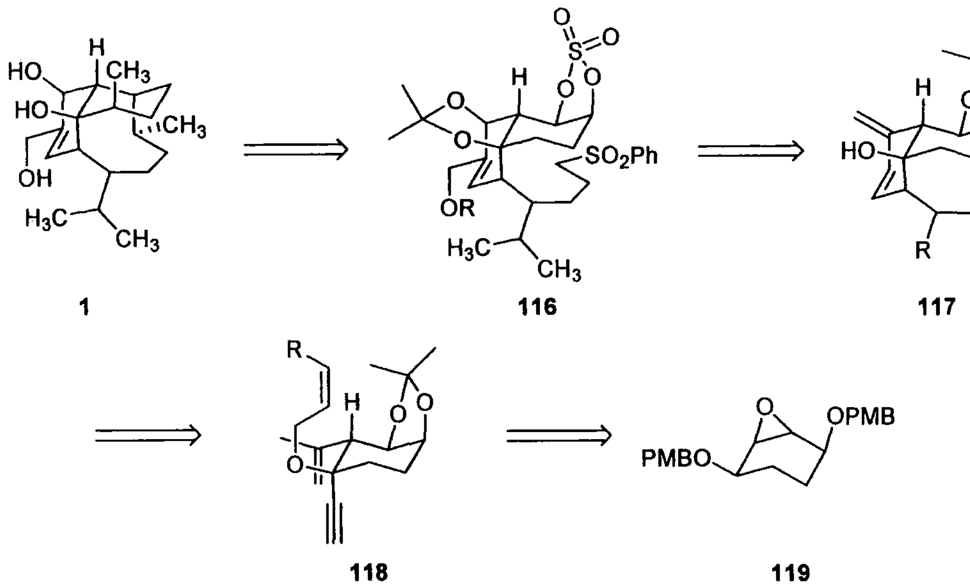


Figure 38

The desired allyl ether **121** can be prepared in a few steps (Figure 39) from known epoxide **119** and the tandem three-step reaction can be induced by microwave irradiation to give the desired *cis*-decalin in good yields with excellent diastereoselectivity.

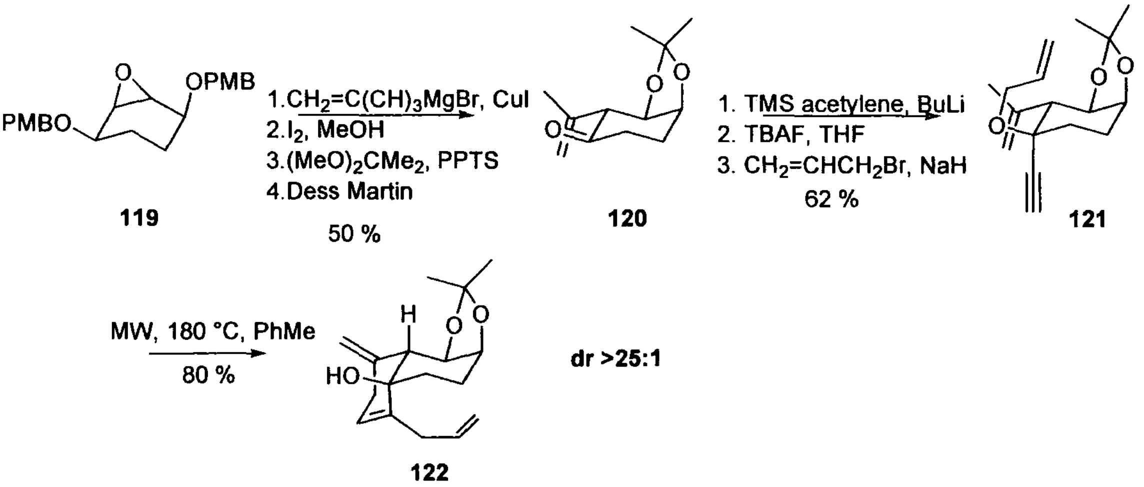


Figure 39

The high diastereoselectivity of the tandem process can be rationalised by the proposed mechanism (Figure 40). Allyl ether **121** can undergo an oxy-Cope rearrangement *via* two possible transition states **123** and **124**. Transition state **124** has severe 1,3 diaxial interactions and is therefore disfavoured. This is also supported by the fact that no *trans*-decalins are isolated from the reaction mixture. Thus, highly strained macrocyclic allene **125** undergoes a Claisen [3,3] shift to generate the enone

126 and subsequent transannular cyclisation by carbonyl/ene reaction gives the desired *cis*-decalin **122** in high diastereoselectivity.

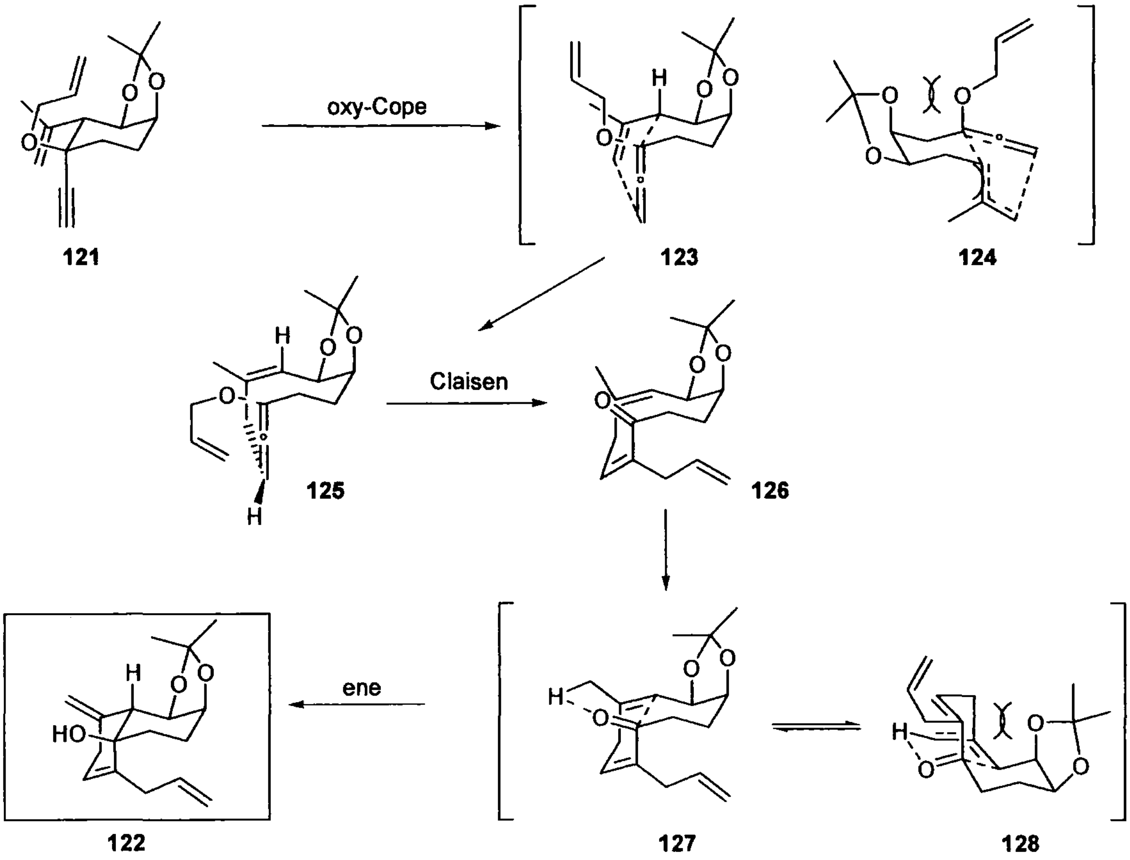


Figure 40

With the strategy to produce the desired decalin in hand, the group set about investigating the functional group tolerance of their approach. Synthesis of allyl ethers **129** and **130** with a terminal isopropyl group was undertaken utilising similar chemistry as previously described (Figure 39). However, *trans*-allyl ethers **129** and **130** gave no desired product when treated with microwave irradiation and it appears that large substituents are not tolerated in the terminal position, Figure 41.

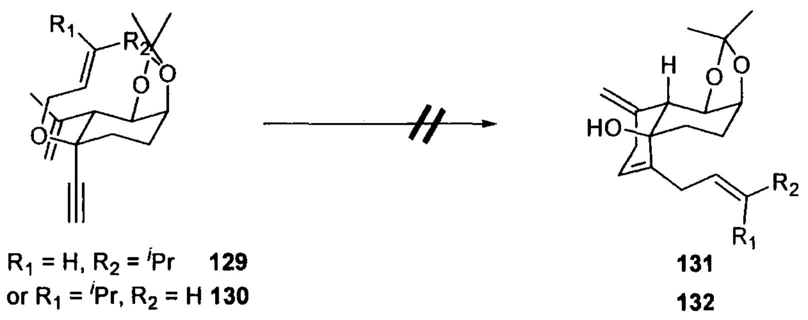


Figure 41

With this disappointing result, Barriault *et al* set about redeveloping their strategy towards Vinigrol and decided to concentrate on installing the 8-membered ring *via* three synthetic pathways: (a) ring expansion by Claisen rearrangement, (b) ring-closing metathesis, and (c) sequential hydroxy-Diels Alder/Clasien reaction (Figure 42).

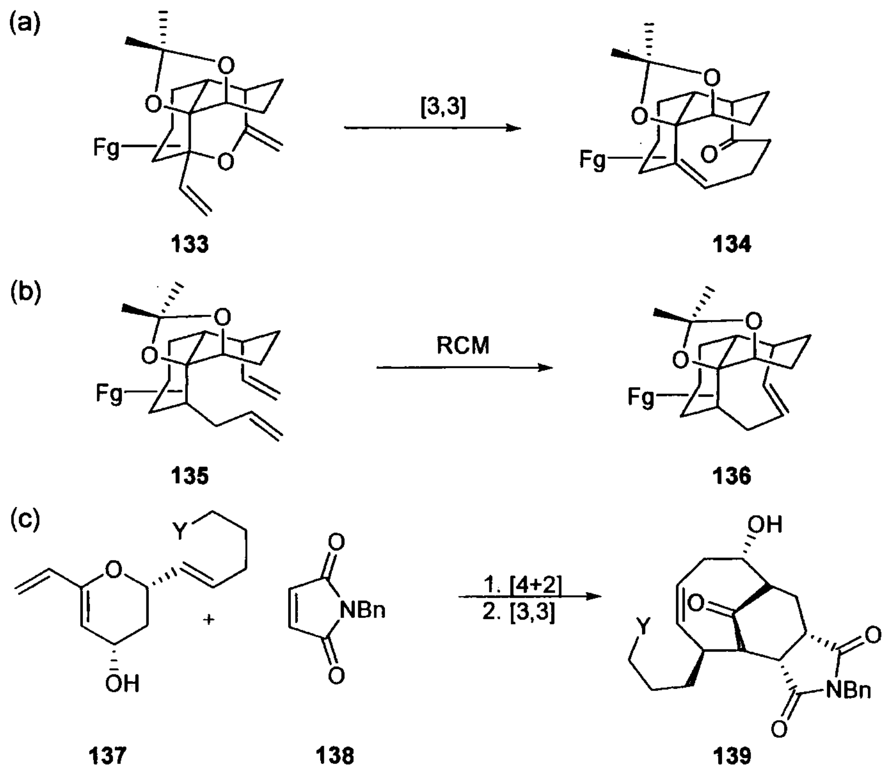


Figure 42

Attempts to generate the 8-membered ring by combining the alkyl chains present on the *cis*-decalin *via* [3,3] rearrangement or RCM were not successful.[6] Presumably this was because the installed pre-organisation could not bring the reacting centres in close enough proximity with which to react and overcome the entropic factors involved in the synthesis of 8-membered rings.

Thus, another strategy was investigated and the tricyclic skeleton was to be installed by an intramolecular alkylation (Figure 43). The desired 8-membered ring could be prepared from a sequential hydroxyl-directed Diels Alder reaction/Claisen rearrangement between diene **143** to afford bicyclic intermediate **142**.

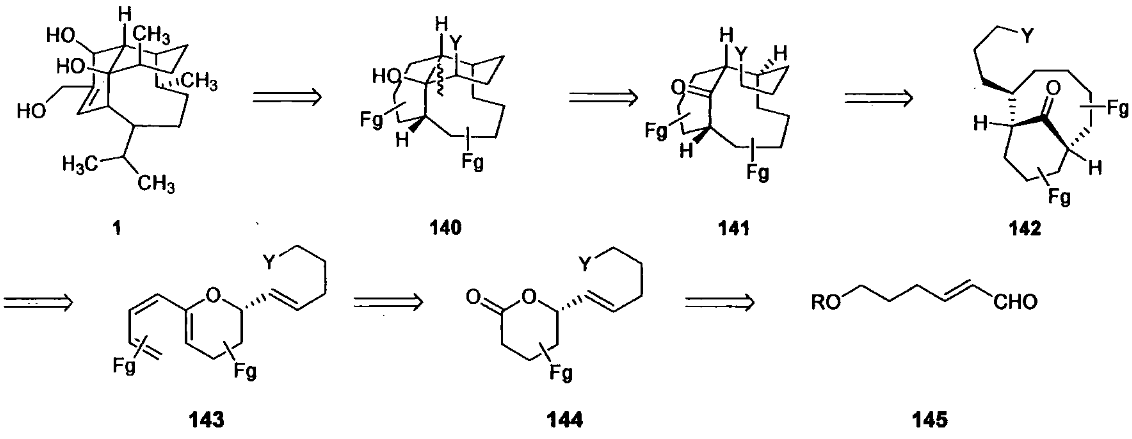


Figure 43

To this end, Diels Alder precursor **146** or **147** can be obtained from known aldehydes **145a** or **145b** in moderate yields (Figure 44). Subsequent cycloaddition of **146** or **147** with N-benzyl maleimide **138** gave the bicyclo[4.4.0]decanes **148** or **149** as single diastereomers and the system was then poised to undergo a Claisen [3,3] shift. However only the [1,3] hydrogen shift products **150** and **151** were detected on heating in a sealed tube at 170 °C for 15 h.

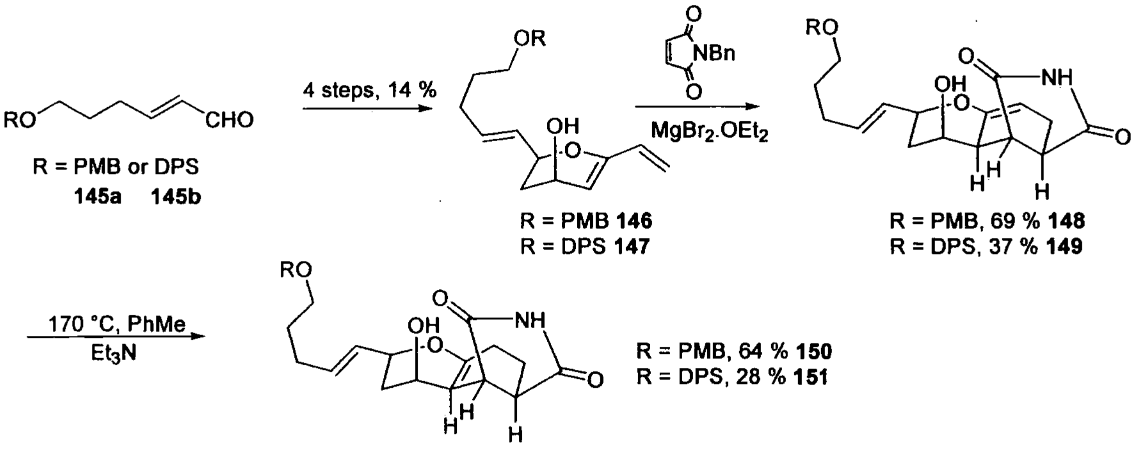
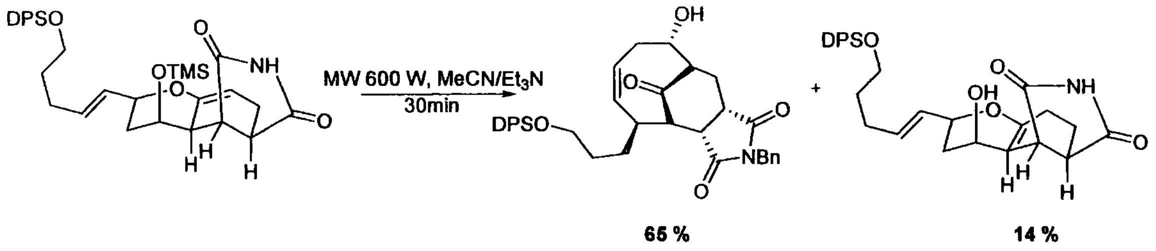


Figure 44

Protection of the free hydroxyl provided the solution to the H-shift problem and the desired bicyclo[5.3.1]undecanone could now be prepared in 25-35 % yield dependent on protecting group, Figure 45. The low yield is possibly due to the harsh reaction conditions (sealed tube, 170 °C, 15 h) to which the system was subjected and optimisation was subsequently investigated. Changing the thermal conditions to utilising microwave irradiation gave a dramatic improvement. The desired bicyclic *e.g.* **76** could now routinely be prepared in 65 % yield, Figure 45.



75 **76** **151**

Figure 45

In conclusion, Barriault *et al* have developed a highly diastereoselective route to *cis*-decalins and the problematic 8-membered ring can be installed *via* a sequential hydroxyl-directed Diels Alder reaction/Claisen rearrangement. Completion of the tricyclic skeleton ring of Vinigrol *via* an intramolecular alkylation upon the bridgehead ketone is currently under investigation.

1.4.5 Towards the Convergent Enantioselective Synthesis of Vinigrol

Paquette *et al*, in attempts to produce an enantioselective route towards the total synthesis of Vinigrol, hypothesised that the introduction of six neighbouring stereocenters could be brought about by an anionic oxy-Cope rearrangement, Figure 46.[5] Also, the problematic 8-membered ring was to be installed by an intramolecular S_N2 reaction, Figure 46.

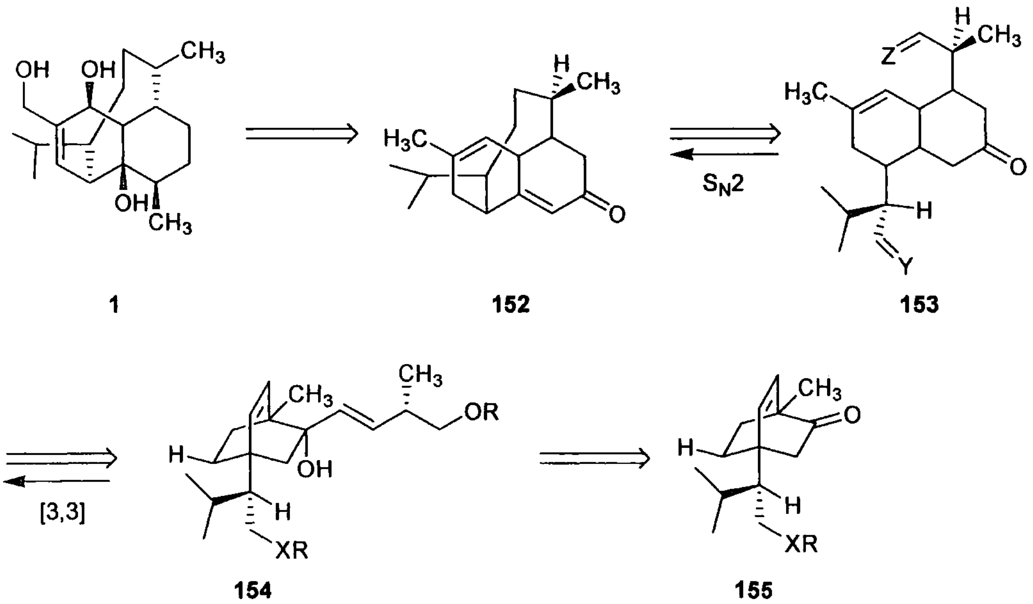


Figure 46

β,γ-Unsaturated ketone **158** was produced through a multi-step protocol, in which the key step was a double Michael addition, Figure 47. A mixture of diastereomers **158** and **159** were obtained but they were easily separable by column chromatography.

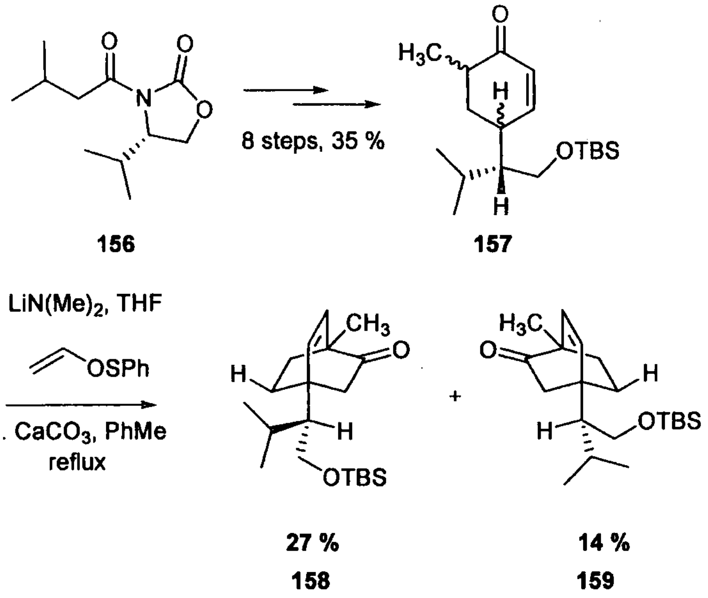


Figure 47

Following successful conversion to ketone **158** attention focussed on the facial selectivity of nucleophilic addition. After considerable experimentation and optimisation, the desired *exo*-carbinol **161** could be obtained in excellent yields with moderate selectivity, Figure 48.

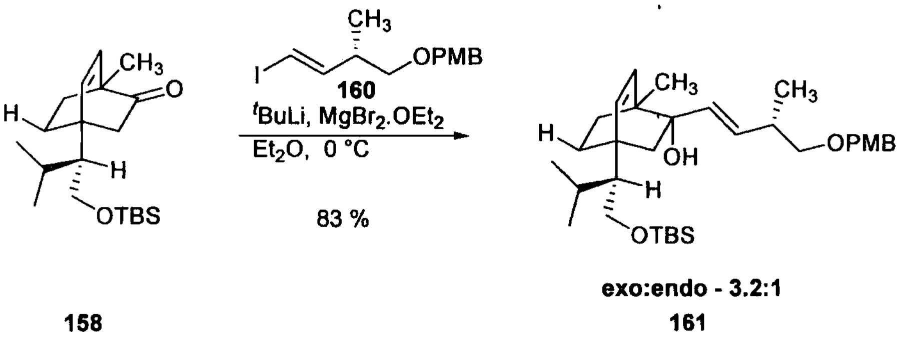


Figure 48

Carbinol **161** was then subjected to traditional anionic oxy-Cope conditions (refluxing KH in THF) however, this only induced gradual decomposition. The oxy-Cope rearrangement was finally induced by carrying out sealed tube experiments which afforded the desired *cis*-decalin in good yields, Figure 49. The stereochemistry was unambiguously assigned by X-ray crystallography after several functional group interconversions gave the crystalline iodide **163**, Figure 49.

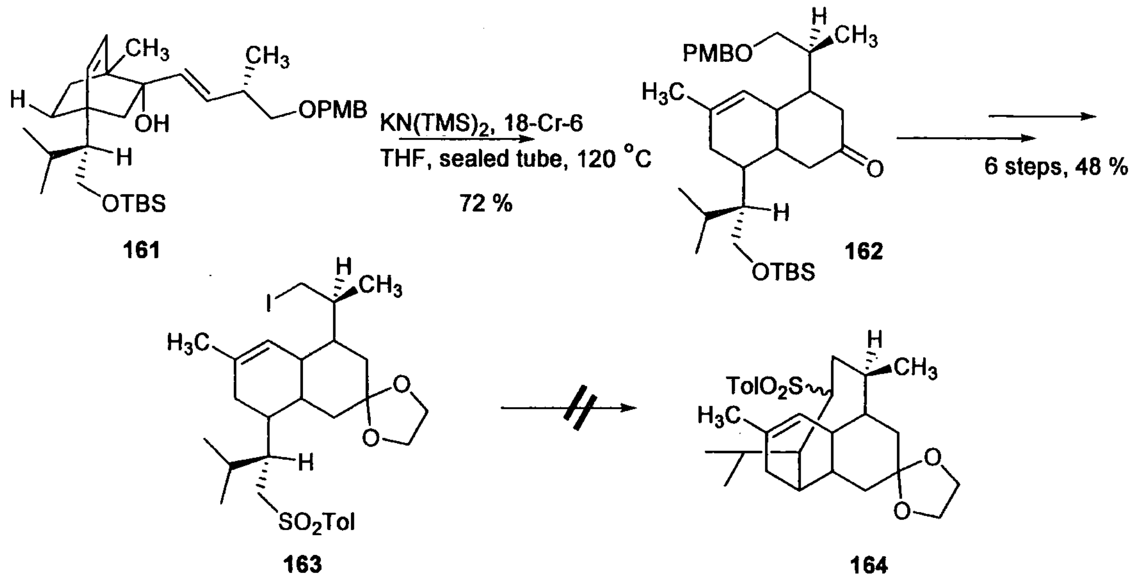
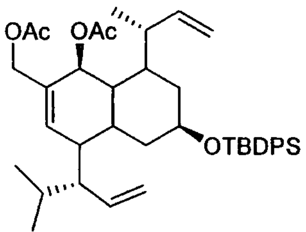


Figure 49

Attempts to initiate ring closure on iodide **163** with various bases resulted in no formation of the desired tricyclic skeleton **164**, only starting iodide **163** was recovered or elimination of HI was observed. The group conclude that ring closure brought about by nucleophilic attack did not occur as it was not possible for the reacting centres to align themselves correctly.

Subsequent attempts including structural modifications to utilise this skeleton to enable the synthesis of the 8-membered ring by RCM have also proved unsuccessful, Figure 50.[5]



165
No cyclisation observed

Figure 50

1.4.6 Construction of the 8-Membered Ring of Vinigrol *via* Samarium-Iodide promoted Barbier Coupling

The first synthesis to date of the 8-membered ring of Vinigrol **1** that does not involve an oxy-Cope rearrangement was reported in 1997.[4] An intramolecular reductive coupling induced by samarium iodide was used by Matsuda *et al*. The Barbier coupling precursors, aldehydes **77** and **175** were generated from (+)-chlorodihydrocarvone **166** in five relatively simple steps (Figure 51). Stereoselective aldol reaction of the Li-derived enolate generated from **166** with 3-benzyloxypropanal **167** or 3-(4-methoxyphenylmethoxy)propanal **168** gave the ketones **169** and **170** in good *e.e.* after dehydration. Stereoselective Grignard addition (β:α - 5:1) and protection gave the carbinols **171** and **172**. The desired β-epimer was then protected to allow regioselective hydroboration-oxidation of the terminal olefin followed by Dess Martin oxidation to give the aldehydes **77** and **175**.

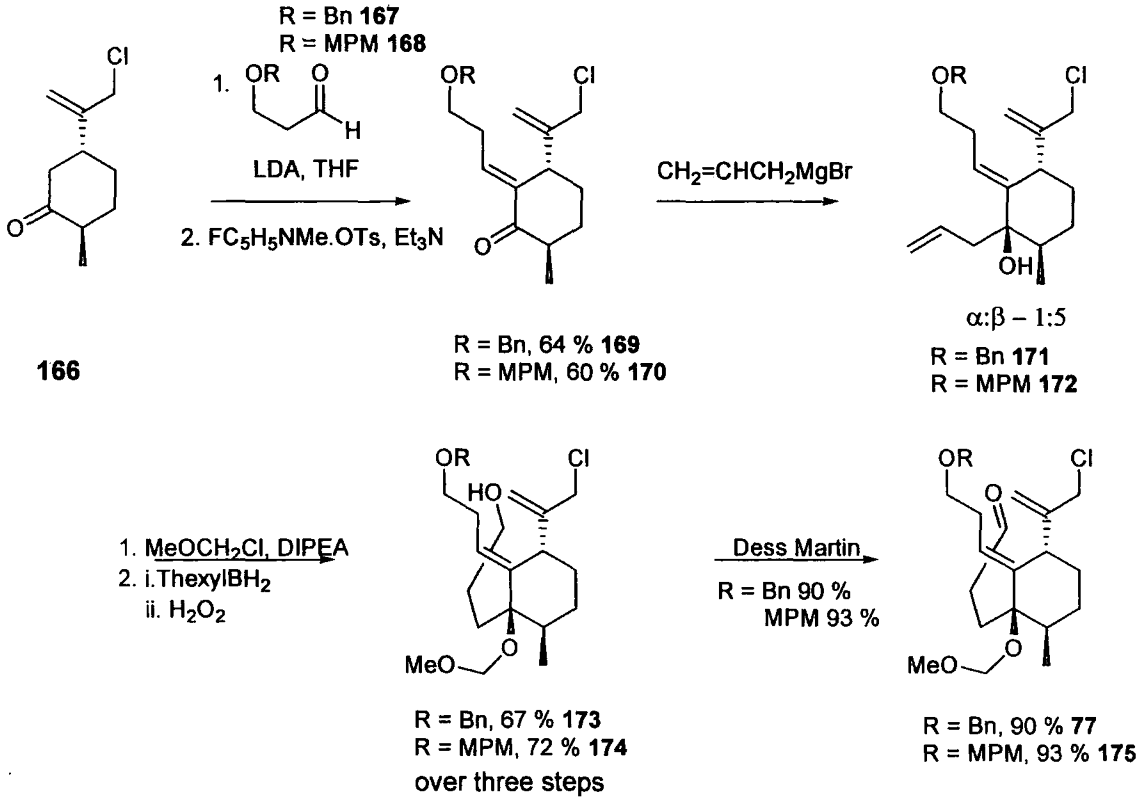
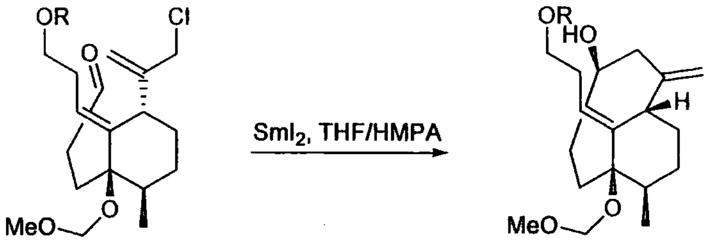


Figure 51

Aldehydes **77** and **175** were then treated with samarium iodide in the presence of HMPA under non-high-dilution conditions and the 8-membered ring closure took place instantaneously between the allyl chloride and aldehyde groups, Figure 52. The cyclooctanols **78** and **176** relevant to the 8,6 fused ring system of Vinigrol were the only detectable products from the reaction.



R = Bn **77**
R = MPM **175**

R = Bn, 99 % **78**
R = MPM, 98 % **176**

Figure 52

This synthesis produced quantitative conversion of the desired 8-membered carbocycle and may be applicable to the construction of various medium sized rings in other natural products.

1.4.7 Summary of Syntheses to Date

Relatively few academic groups have undertaken the synthetic challenge posed by the unprecedented decahydro-1,5-butanonaphthalene skeleton contained within the natural product Vinigrol. However, the literature approaches described in the above sections have made significant contributions towards achieving the total synthesis.

The bridging 8-membered ring created a considerable synthetic task, although 4 out of the 5 groups working in this area have successfully incorporated this problematic unit into their synthetic efforts. Ring expansion approaches from easily obtainable bicyclic systems have been particularly fruitful providing Hanna *et al* with the fully elaborated tricyclic skeleton of Vinigrol in relatively few synthetic steps. On the other-hand carbon-carbon bond forming approaches towards the total synthesis have been utilised with varying degrees of success, Matsuda *et al* successfully afforded the 8,6-fused system by SmI_2 initiated ring closure. The aldehyde precursor **77** or **175** was presumably in close enough proximity and in the correct orientation to enable closure to take place. However, Paquette *et al*'s numerous attempts to utilise a carbon-carbon forming reaction to install the 8-membered ring have proved disappointing. Intermediate **163** was hypothesised to be unable to adopt the correct geometry to allow an intramolecular S_N2 reaction to occur.

The various approaches towards the total synthesis of Vinigrol have attempted to install the tricyclic skeleton early in the synthesis however, these intermdiates then lack the necessary functionalisation to allow further elaboration. Therefore, it became increasingly difficult to incorporate the required functional groups regioselectively in later synthetic steps and caused the significant redevelopment of respective retrosynthetic strategies. Hanna *et al* were able to adjust their existing strategy; however Barriault *et al* had to abandon their initial strategy to enable further work towards Vinigrol to be investigated. Although there has been no total synthesis of Vinigrol to date significant synthetic contributions have been made in this area

1.5 Proposed Work

Three distinct strategies exist for the construction of 8-membered carbocycles. C-C-bond forming reactions and ring expansion approaches have been utilised in the syntheses towards Vinigrol to date. However neither method has yet yielded a total synthesis. Ring fragmentation has not been exploited in the synthesis of Vinigrol to date and is a useful synthetic tool since smaller ring systems are easier to construct than their medium ring counterparts.

Thus employing a ring fragmentation approach towards the total synthesis of Vinigrol, it was envisaged that the molecule could be disconnected according to the scheme shown in Figure 53. Reconnection of the bond between C4 and C11 yields diol **177** which can undergo oxidative ring fragmentation to give the tricyclic structure of Vinigrol. This approach allows construction of the 8-membered ring in a masked form, thus avoiding the normal difficulties associated with the formation of medium sized rings.

Further analysis suggested that key diol **177** could be accessed through an intramolecular Diels Alder cycloaddition with a Z,E diene contained in bicyclic intermediate **178**. Bicyclic intermediate **178** can then be envisaged to come from a functionalised bicyclic ketone **179** which can be further disconnected to a ketene equivalent **183** or **184** and an appropriately functionalised cyclic diene **182**. In model studies carried out on ketone **181**, where R = H, alkylation and nucleophilic additions were found to be essentially non-selective. This suggested that the early introduction of the C12 isopropyl group with absolute stereocontrol would be essential to an efficient synthesis.

Intramolecular Diels Alder cycloaddition is the key reaction in the retrosynthetic strategy described above and a review of the synthetic utility of this reaction is given in the next section.

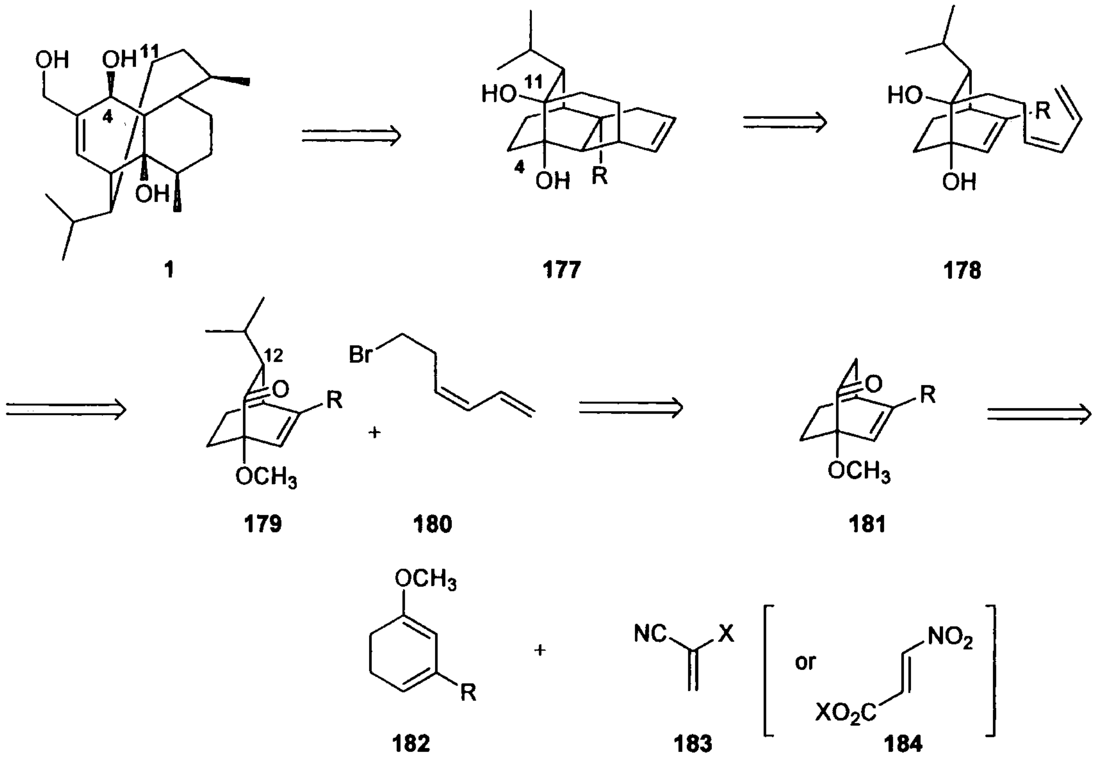


Figure 53

1.6 Intramolecular Diels Alder

1.6.1 Introduction

The key reaction in our retrosynthetic strategy was an intermolecular Diels Alder (IMDA) reaction of highly functionalised intermediate **178**, Figure 53. It is widely recognised that Diels Alder reactions are the most useful pericyclic reactions for the formation of six membered functionalised compounds and as a consequence has been widely utilised in natural product synthesis.[39]

1.6.2 Types of IMDA

There are two types of connectivity available to the intramolecular variant of the Diels Alder reaction. When diene and dienophile are joined at position 1 of the diene (type 1), cycloaddition usually gives rise to a fused bicyclic, Figure 54. This reaction has been widely used in organic synthesis.[40] However, a second variant involves the union of diene and dienophile at position 2 of the diene (type 2). Cycloaddition in this case results in the formation of a bridged ring system, Figure 54. The reaction has substantial synthetic potential as there are few methods that yield a bridged bicyclic in a single step form an acyclic precursor.

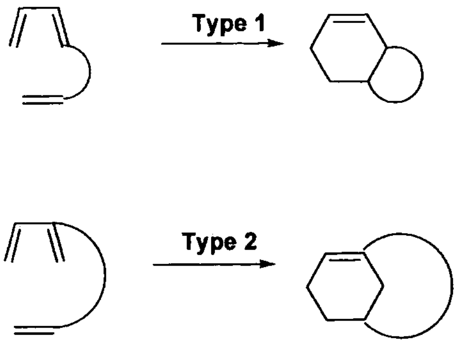


Figure 54

Also, there is a third variant of the IMDA reaction, a transannular Diels Alder (TADA) reaction, Figure 55. It usually involves the construction of a macrocyclic molecule containing the diene and dienophile, in which the conformational mobility allows the units into close proximity to produce highly complex polycyclic structures. These are produced with complete control of chemo-, regio- and stereoselectivity. However, the major synthetic challenge is the construction of the requisite macrocyclic precursor including correct diene and dieneophile geometries. TADA has been frequently used in the synthesis of 13-, 14- and 15-membered macrocycles.

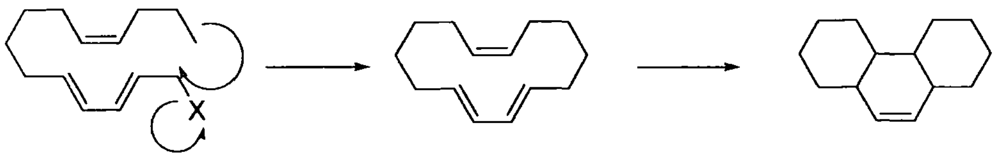


Figure 55

A number of classes of natural products (*e.g.* terpenoids, alkaloids, polyketides) have recently been synthesised utilising an intramolecular Diels Alder reaction as a key step in the construction of their basic frameworks. The use of the IMDA in complex natural product synthesis is described, illustrated with examples emphasising the synthesis of the precursor and the IMDA reaction.[39]

1.6.3 Applications in Natural Product synthesis

1.6.4 Type 1 IMDA - Trans Fused Systems

1.6.4.1 (-)-Chlorothricolide

Polyketide (-)-Chlorothricolide, an aglycon of chlorothricin, which was isolated from *Streptomyces antibioticus* was synthesised enantioselectively by Roush *et al.*[41] The route involved simultaneous inter- and intra-molecular Diels Alder reactions of a 21-carbon linear substrate with six carbon-carbon double bonds **188** and an enolate-protected form of pyruvate **189** as a dienophile, Figure 56. The linear substrate **188** was produced by the Suzuki coupling of (E)-vinyl boronic acid **185** and highly functionalised trimethylsilyl vinyl iodide **186**. This diene was then subjected to sequential Horner-Wadsworth-Emmons type olefinations to produce the IMDA substrate **188** and this was then heated in the presence of the dienophile **189** to produce the desired doubly cyclised product **190** along with IMDA adduct **191**. Adduct **191** could subsequently be converted to **190** by heating it again in the presence of the dienophile **189** and produced the octahydronaphthalene derivative **190** in moderate overall yields (55-59 %).

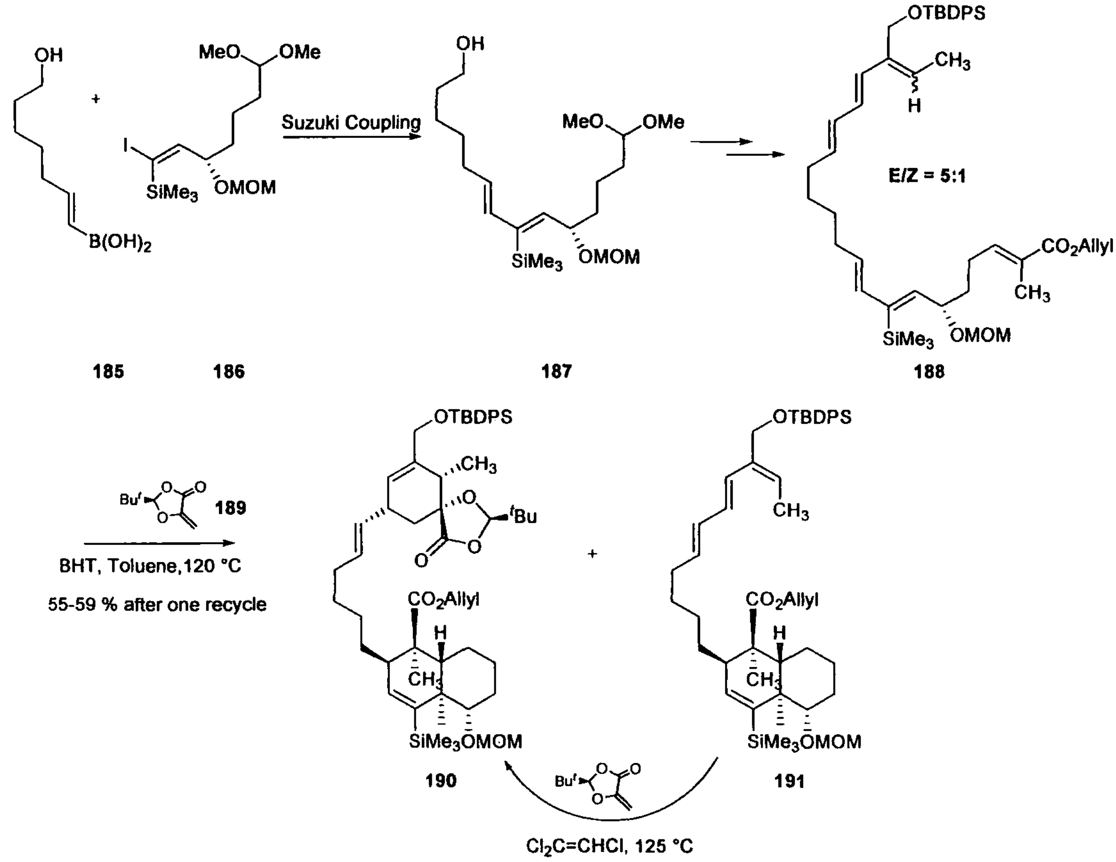


Figure 56

1.6.4.2 (+)-Tubelactimicin A

(+)-Tubelactimicin A was isolated from the culture broth of an antinomycete strain which showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.[42] The structure is characterised by *trans*-fused octahydronaphthalene with 6 stereocentres and a 16-membered lactone containing an (E),(E)-conjugate diene, Figure 57. Synthetic work in this area by Tadano *et al*[43] and their subsequent disconnection gave the lower half segment, a highly functionalised octahydronaphthalene. This could be synthesised through the *endo* and π-facial selective IMDA cyclisation of a β-substituted (E)-methacrolein derivative **197** possessing a carbon tether incorporating an (E),(E)-dienyne terminal, Figure 58. Diethyl

(R)-malate **192** can be transformed into aldehyde **194** in 9 steps with Seebach *et al*'s[44] regioselective and diasteroselective allylation of the lithium enolate of **192**, being an early key reaction to give **194**. Aldehyde **194** was then reacted with highly functionalised phosphonate **195** in a *E*-selective Horner-Wadsworth-Emmons reaction to give conjugated (E),(E)-dienyne **196**.

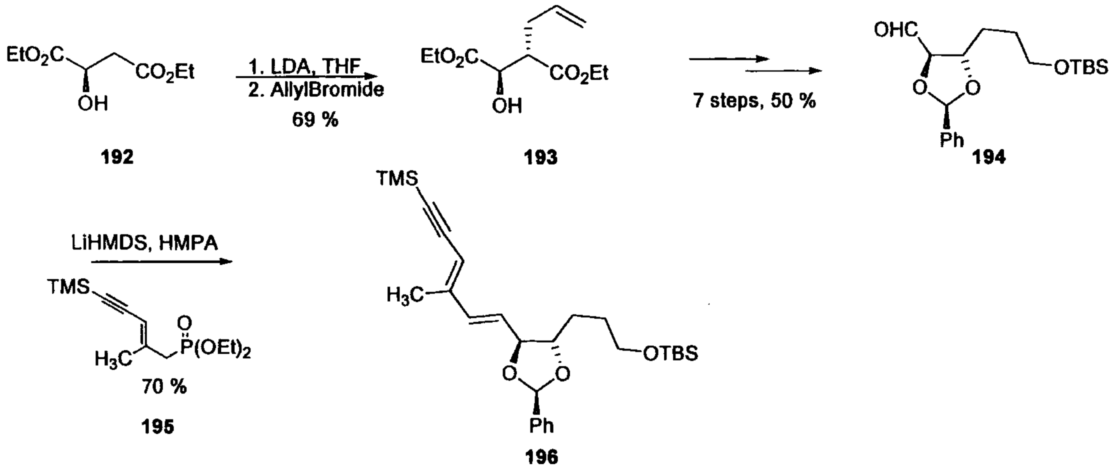


Figure 57

A further series of deprotection and oxidation/reduction steps gave the desired IMDA precursor **197** and the IMDA cyclisation proceeded stereoselectively to provide the desired *trans*-fused cycloadduct **198** in an excellent 93 % yield, Figure 58.

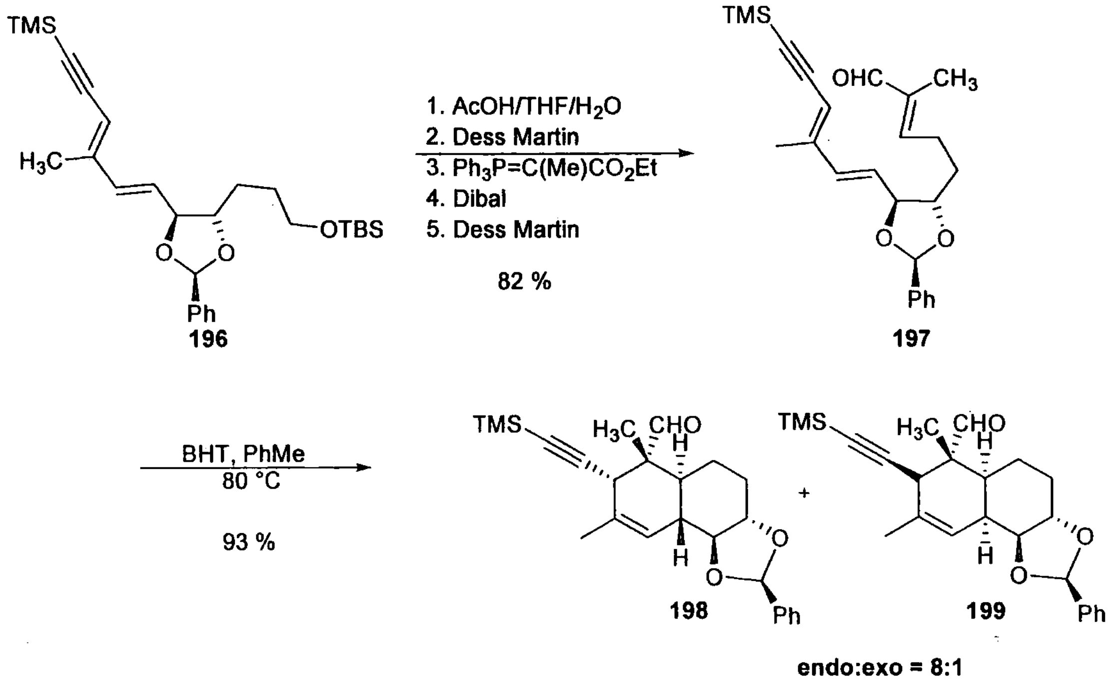


Figure 58

1.6.5 Type 1 IMDA - *cis*-Fused Systems

1.6.5.1 Bilosespenes A and B

Cis-fused systems are more difficult to achieve stereoselectively since an E-diene possesses two relatively accessible transition states (*endo, exo*) which in many instances can afford mixtures of *cis*- and *trans*-fused products, *vide infra*.[45] However, Liao and co-workers have developed IMDA reactions of masked *o*-benzoquinones and utilised them in the synthesis of cytotoxic marine sesterpenic acids (+/-)-bilosespenes A **206** and B **207**.[46] A combination of IMDA reaction of *o*-benzoquinones and the anionic oxy-Cope rearrangement of a synthetic intermediate derived from the IMDA reaction were used in the stereoselective construction of a *cis*-octahydronaphthalene skeleton of advanced intermediate **205**, Figure 59. The tricyclic intermediate **202** was obtained from the IMDA reaction of masked *o*-benzoquinone with an allyloxy group **201**. This was prepared *in-situ* from 2-methoxy-4-methyl phenol **200** by oxidation with DAIB in the presence of allyl alcohol. Further treatment of this IMDA with a vinylcerium reagent **203** provided alcohol **204** and resulting [3,3] sigmatropic rearrangement gave the desired *cis*-octahydronaphthalene structure, **205**. **205** was then transformed into bilosespenes A **206** and B **207** through further functional group interconversions, Figure 59.

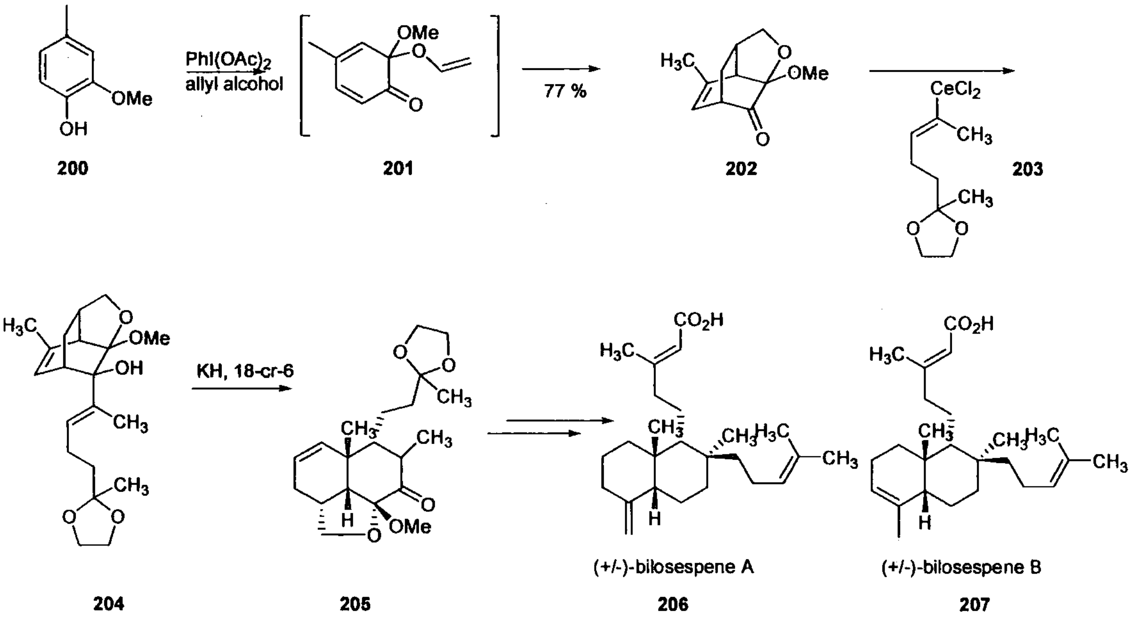


Figure 59

1.6.5.2 Total Synthesis of Ophirin B

(-)-Ophirin B **213** is a cladiellane diterpenoid which contains a unique oxatricyclic ring system with seven stereocentres.[47] Crimmins *et al* recently reported the total synthesis of this natural product utilising an IMDA strategy.[48] The group envisaged that the requisite Diels Alder intermediate could be tethered to an unsaturated medium ring ether, Figure 60. Furthermore, the corresponding unsaturated cyclic ether could be constructed utilising methodology recently developed within the Crimmins group using RCM and taking advantage of acyclic conformational restraints.[49]

Firstly, an oxygen-containing 9-membered cyclic intermediate was prepared *via* RCM and the functionalised oxazolidinone imide **208** was reduced to the long chain ether, **209** containing both required olefin terminals. On exposure to Grubbs 2nd generation catalyst the desired oxonene **210** was obtained as a single isomer. Further functional group interconversions gave the IMDA substrate **211** which on standing at room temperature gave the oxatricyclic ring system **212** as a single isomer quantitatively, Figure 60.

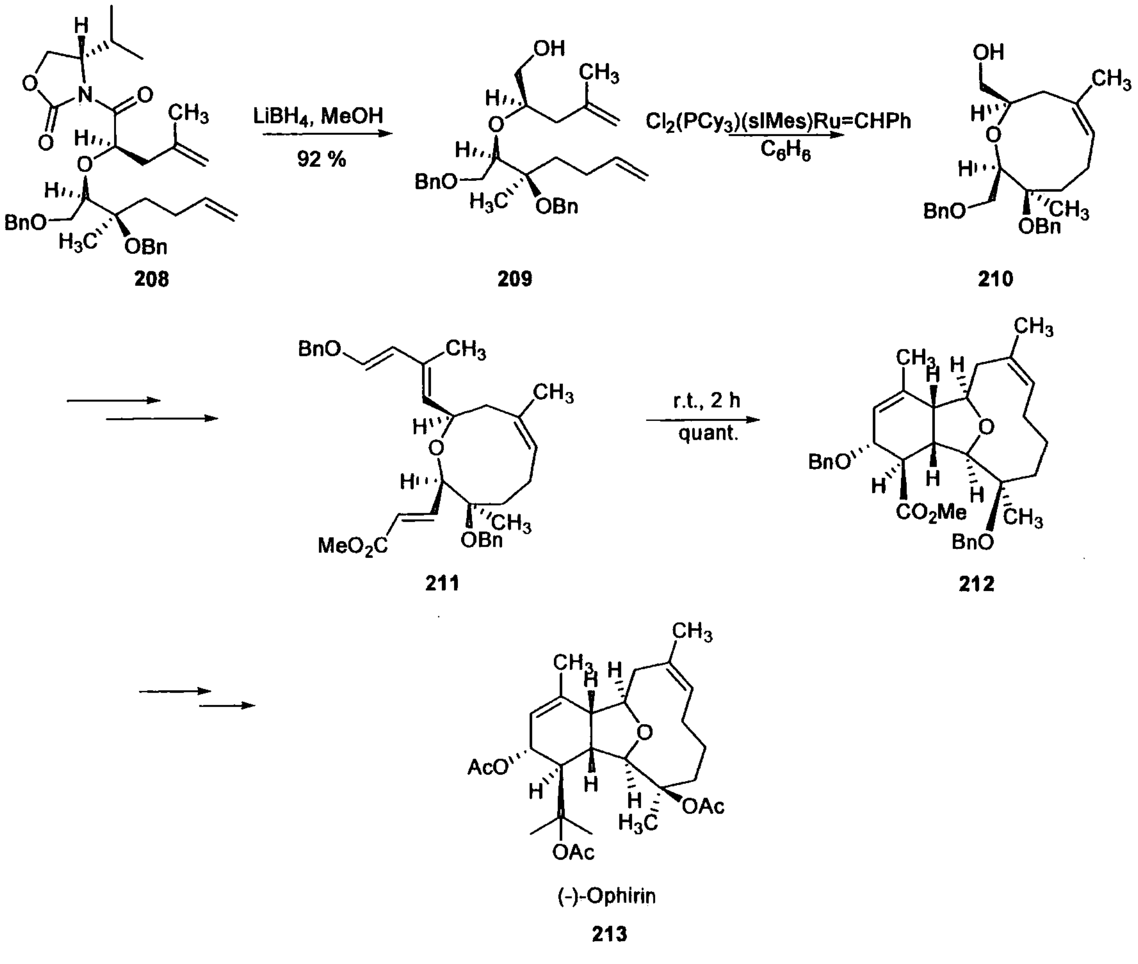


Figure 60

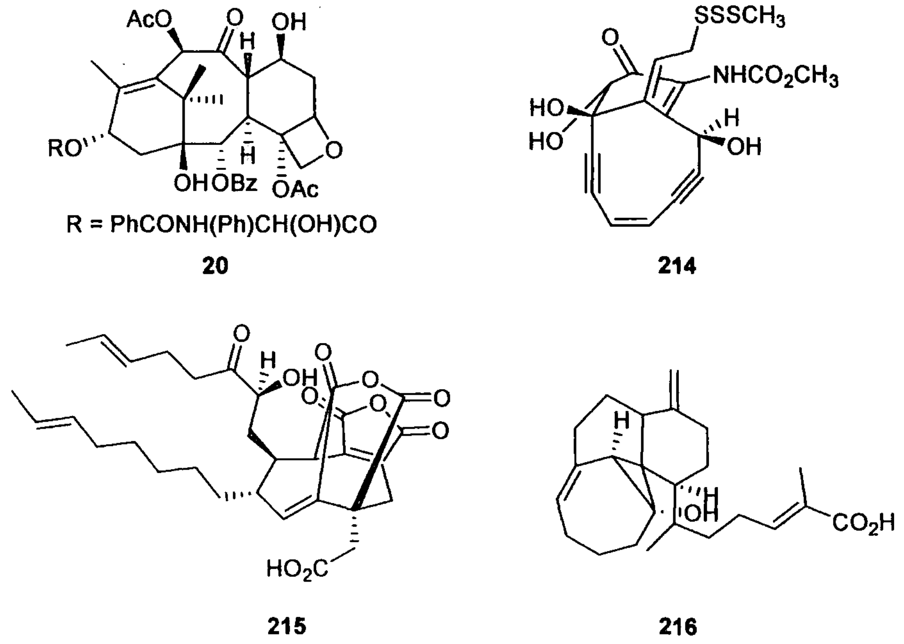
1.6.6 Summary of Type 1 -IMDA

Type 1 IMDA cycloaddition is a powerful tool in organic synthesis and can yield highly functionalised intermediates or natural products in high yields. *Cis-* or *trans-*fused systems are easily constructed through careful consideration of the geometries of the diene and dienophile.

1.6.7 Type 2 - IMDA

1.6.7.1 Introduction

The assembly of a bridged bicyclic skeleton in a single step from an acyclic precursor is a powerful synthetic tool.[50] The direct application of this reaction is a key step in the synthesis of naturally occurring bridged bicyclic compounds. A number of biologically important natural products contain bridged bicyclic rings, *e.g.* Taxol **20**[51], esperamicin A1 aglycone **214**[52], CP-263,114 **215**[53] and cerorubenic acid **216**[54] have used the type 2 IMDA reaction as the key step in the construction of the bridged bicyclic skeleton, Figure 61.



R = PhCONH(Ph)CH(OH)CO

20 **214**

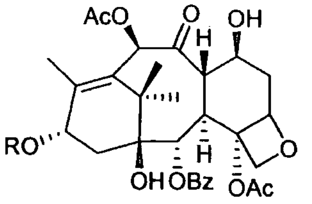
215 **216**

Figure 61

1.6.8 Type 2 - IMDA in Synthesis

1.6.8.1 Taxanes

Taxol was approved for the treatment of ovarian cancer in 1992[51,55] and prior to solving the availability problems, there was an enormous synthetic effort towards the total synthesis, Figure 62.[51] Within its complex structural core is contained a bridged tricyclo[9.3.1.0]pentadecene ring system with 11 stereocentres and a variety of differently functionalised oxygen substituents.



20

Taxol

R = PhCONH(Ph)CH(OH)CO

Figure 62

The type 2 IMDA reaction was employed in one of the first attempts to synthesise this natural product, a C-aromatic taxane skeleton, Figure 63.[56] Cycloaddition precursor **222** was synthesised by reaction of Grignard reagent **219**, prepared directly from the dibromide, with butadiene derivative **218**. The dieneophile moiety was introduced in two steps affording the IMDA precursor **222**. Trienone **222** underwent a thermally induced type 2 intramolecular Diels Alder reaction to give the desired tricycle **223** in excellent yield, Figure 63.

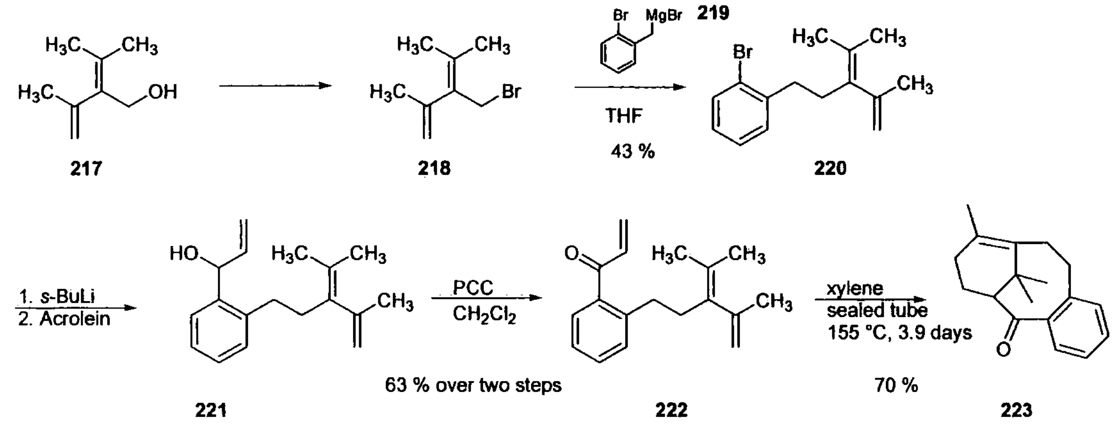
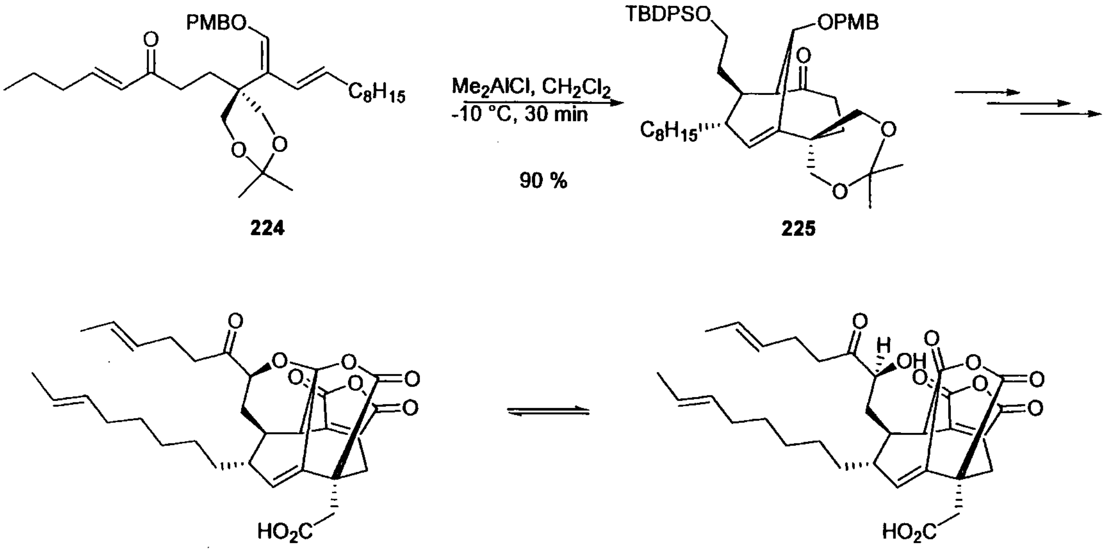


Figure 63

1.6.8.2 CP-263,114 and CP-255,917

The CP family of natural products has received considerable attention because of their biological activity as leads for cholesterol-lowering and anticancer agents. The core of the CP molecules consists of a bicyclo[4.3.1]decene ring system, Figure 64.

A number of syntheses of this ring system utilising the type 2 intramolecular Diels Alder reaction have been reported.[57,58] Nicolaou *et al* reported a highly elaborated Diels Alder precursor in the total synthesis of racemic CP-255,917 **224** and CP-263,114 **215**, Figure 64.[59] Lewis-acid-catalysed IMDA cycloaddition of **224** provided the bridged bicyclic intermediate which was then converted into the CP molecules **215** and **224**. Enantioselective syntheses have since been reported employing the use of BINOL-aluminium derivatives as chiral Lewis acids.[60]



224

225

CP-263,114

215

CP-225, 917

226

Figure 64

1.6.9 Summary of Type 2 IMDA cycloadditions

The type 2 IMDA reaction, a simple intramolecular variant of the Diels Alder reaction provides a direct route to bridged polycyclic compounds from simple to elaborate acyclic precursors in a single step. Products can range from strained isolable anti-Bredt alkenes to the core of Taxol. Furthermore, the type 2 IMDA cycloaddition has served as a key step in the construction of many complex polycyclic rings that make up the core of a number of important natural products.

1.6.10 Transannular Diels Alder (TADA) Cycloadditions

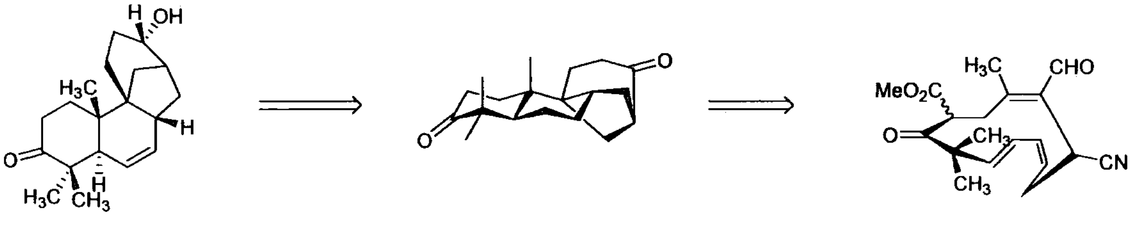
1.6.10.1 Introduction

The TADA reaction has been most frequently studied with 13-, 14- and 15-membered macrocycles under thermolytic reaction conditions but also with studies on the effects of Lewis acids and high pressures. The vigorous thermolytic conditions (200 °C to over 300 °C) sometimes used provoke competitive [1,5] hydrogen shifts, producing new dienes which can also undergo the TADA reaction, thus creating complex mixtures of cycloadducts. The use of Lewis acid catalysis is rewarding as the much lower temperatures inhibit the hydrogen shifts, and do not induce Alder-ene rearrangements of the C=C enophiles.[61,62]

1.6.11 Applications in Synthesis

1.6.11.1 (+)-Maritimol

(+)-Maritimol **227**, a member of the stemodane diterpenoids, was isolated from *Stemodia maritima* L. (Scrophulariaceae) and used as a Caribbean folk medicine for the treatment of venereal diseases, Figure 65.[63] It represented a long-standing synthetic challenge with its unique tetracyclic stemodane framework and 10 stereocentres. Deslongchamps *et al* reported the first asymmetric synthesis utilising a TADA as a key step in the retrosynthetic analysis.[64] Utilising the group's previous expertise in this area it was envisaged that the synthesis of maritimol would involve stereospecific transformation of a 13-membered *trans-cis-cis*-(TCC)-macrocyclic triene **229**. Triene **229** was expected to undergo cyclisation to produce the *trans-syn-cis*-(TSC)-ring system found in the natural product.



(+)-Maritimol
227

228

229

Figure 65

The Stille coupling of vinylstannane **230** with vinyl iodide **231**, followed by allylic chlorination, affords the 14-carbon β-keto ester with the 1-,3-,8-triene unit **232**, Figure 66. The intramolecular macroallylation of **232** was achieved with caesium carbonate under high dilution conditions to give aldehyde **229** after oxidation. The 13-membered TADA precursor **229** was then treated with Me_2AlCl to induce cyclisation to the TSC-fused tricyclic system **233** as a single isomer. Subsequent dimethoxycarbonylation under thermal conditions gave the highly functionalised core of (+)-maritimol **234**. Further functionalisation of this intermediate to install the fourth ring gave the first reported enantioselective synthesis of this natural product.[64]

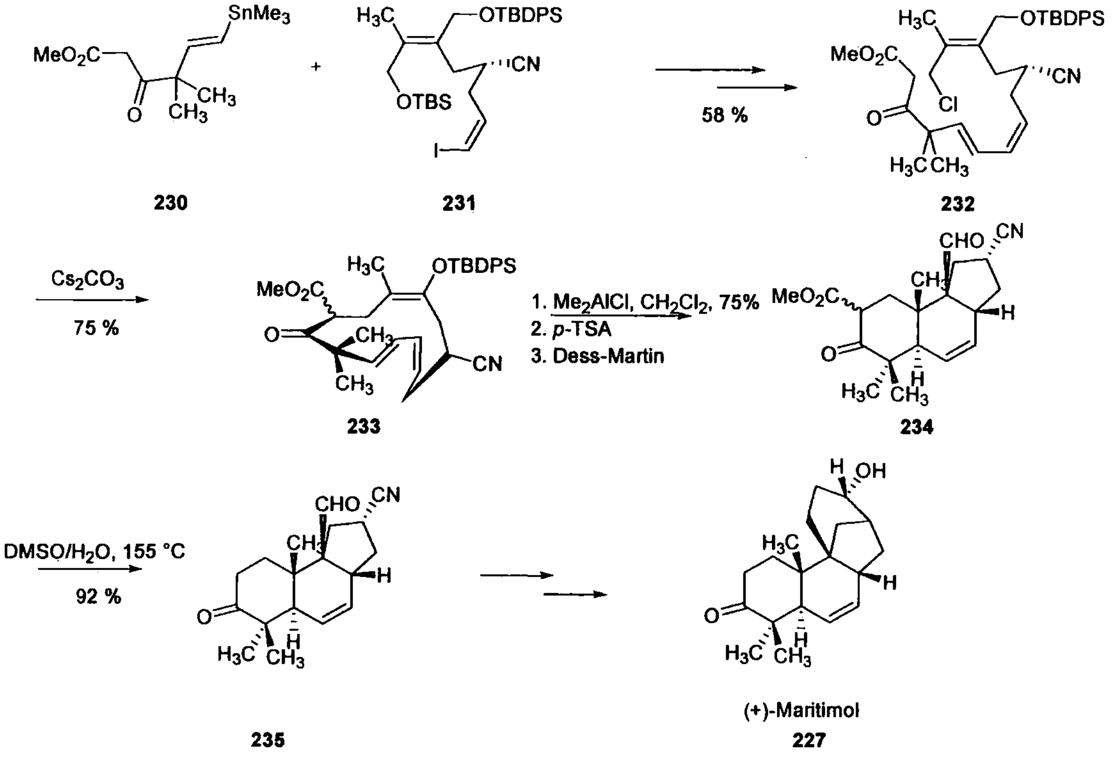


Figure 66

1.6.11.2 FR182877

FR182877 **241** exhibits microtubule-stabilising activity similar to the mode of action studied for paclitaxel and shows cytotoxcity towards multiple cell lines.[65] The highly carbon- and oxygen-functionalised hexacyclic core comprises of 12 stereogenic centres and a strained double bond at the bridgehead position, Figure 67. Sorensen and co-workers proposed that FR182877 might arise from a polyunsaturated linear biosynthetic intermediate by a cascade of intramolecular Diels Alder reactions.[66] To this end, a long chain polyketide-like intermediate with a conjugate diene, **237**, was synthesised through a Stille coupling and subsequent allylic alkylative 19-membered ring formation was achieved on exposure of **237** to $Pd_2(dba)_3$ to give the macrocycle **238**.[67] Further structural modifications on intermediate **238** gave the (E)-α-,β-,γ-,δ-unsaturated ester as the desired TADA precursor **239**. Upon warming **239** (40 °C) the desired pentacylic skeleton was obtained *via* sequential TADA and hetero-Diels-Alder reactions, Figure 67, and in a single reaction 7 new stereogenic centres and a pentacyclic skeleton have been produced.

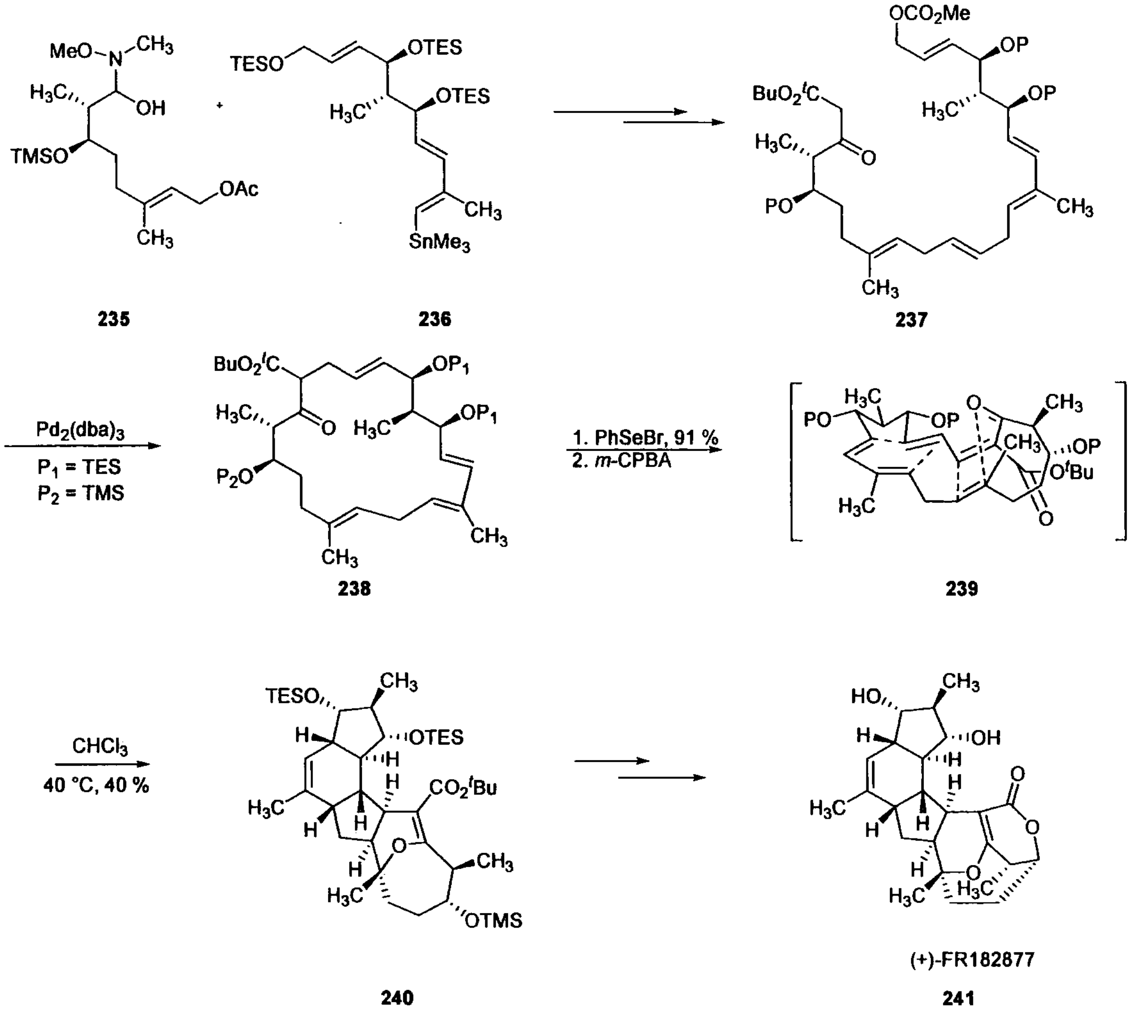


Figure 67

1.6.12 Summary of TADA

It is clear that the TADA approach permits a very high increase in molecular complexity during the macrocyclisation and subsequent cycloaddition, and depends only upon the ease of stereoselective triene macrocycle synthesis.

1.6.13 Summary of IMDA

The intermolecular Diels Alder reaction is now routinely performed at the highest selectivity levels by way of chiral and enantiopure dienes and/or dienophiles, or on chiral auxiliaries, or by enantiopure Lewis acid catalysis. The same strategies are being applied to the IMDA reaction, as well as the use of chiral and enantiopure chain tethers. The level of control now available for the Diels Alder reaction is demonstrated, suggesting that we can now choose our diene and dienophile components with great predictability as to the results of the cyclisation. With the diene and dienophiles being contained within the same molecule, the use of unactivated diene/dienophile systems may be utilised. The required reactive conformation has already been pre-organised and therefore the energies required can be reduced.

SECTION B :
RESULTS AND DISCUSSION

Chapter 2
Nitroacrylates

Chapter 2 : Nitroacrylates

2.1 Introduction

The focus of this project was to develop an approach to the total synthesis of Vinigrol, according to the retrosynthetic analysis shown in Figure 53, Page 29. Disconnection of the Vinigrol ring structure **1** identified bicyclic ketone **243** as a key intermediate establishing the stereochemistry of the ⁱPr substituent at C12 at an early stage. Further analysis suggested that this could be accessed through the cycloaddition of diene **244** and a functionalised ketene equivalent **245**, Figure 68.

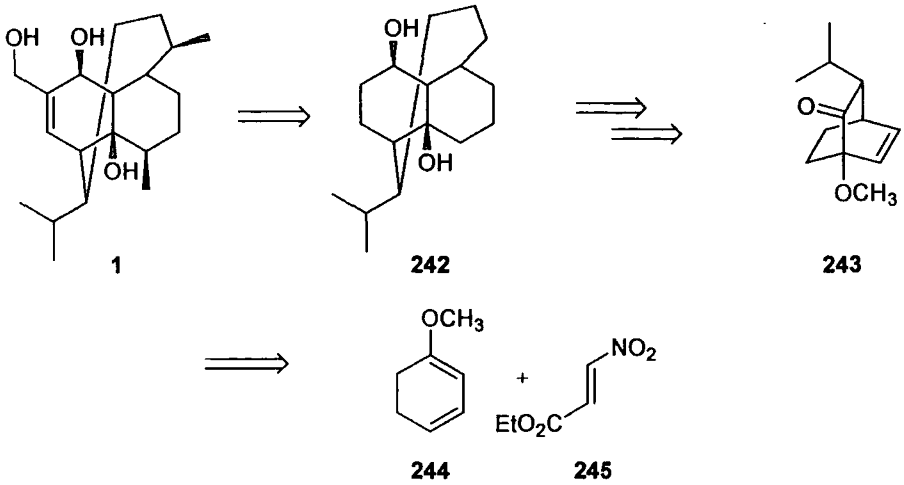
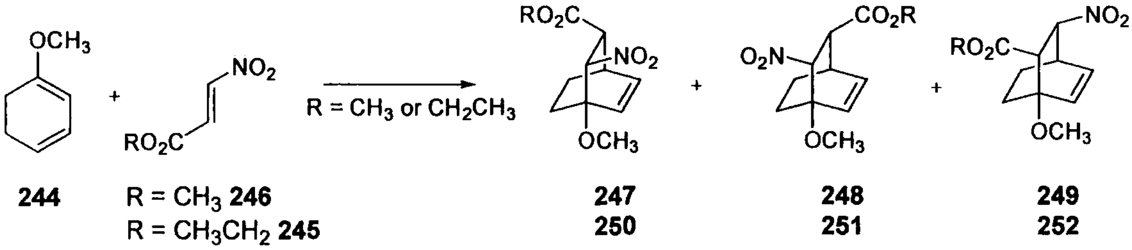


Figure 68

Previous work within the group investigated nitroacrylates as substituted ketene equivalents and their reactivity in Diels Alder cycloadditions. It was demonstrated that excellent regio-selectivity could be obtained on the addition of catalytic quantities of Lewis acids, Figure 69.[68] Cycloadduct **250** possessed the correct regiochemistry at C12 to enable introduction of the ⁱPr group on the correct face of bicyclic ketone **250** and the desired carbonyl functionality could be revealed by Nef chemistry.



R = CH3	Ph, 80 °C	50 :	37 :	13
R = CH2CH3	ZnCl2, CH2Cl2, 0 °C	97 :	3 :	0

Figure 69

The initial focus of the project was to investigate the synthesis of ketone **243** from bicyclic nitro ester **250**, Figure 70. Conversion of the C12 ester group attached to bicyclic intermediate **250** into an ⁱPr group and generation of the ketone functionality from the nitro group were to be initially investigated, Figure 70.

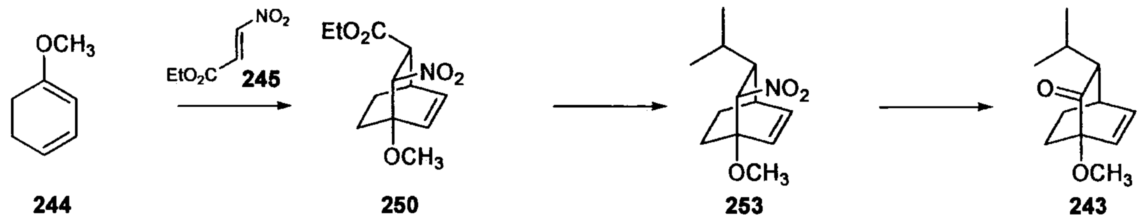


Figure 70

2.2 Nitroacrylates

2.2.1 Introduction

β-nitroacrylates were first reported by Shechter *et al* in 1952[69] in an investigation into the addition of nitryl chloride or dinitrogen tetroxide to a variety of unsaturated substrates, including acrylates, Figure 71. Nitroacrylates have been well exploited in synthetic chemistry. For example, they have been used as low energy dienophiles in Diels Alder reactions and as intermediates in β-amino acid synthesis.

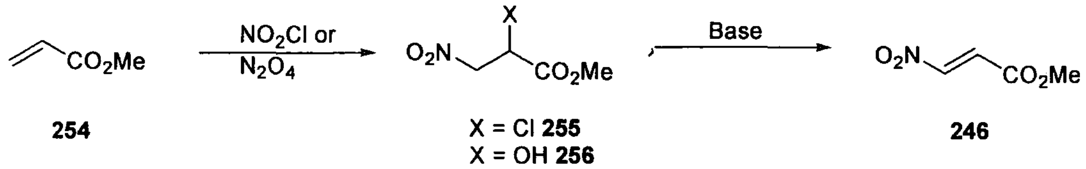


Figure 71

The remainder of this section reviews the literature where β-nitroacrylates have been utilised in the synthesis of natural products.

2.2.2 Literature Synthesis of Nitroacrylates

Following the pioneering work of Schechter *et al*, Emmons and Stevens[70] showed that the synthesis of nitroacrylates from methyl acrylate and N_2O_4 involved a radical mechanism. Excess iodine could be used to trap the intermediate radical **257** and afford iodo-ester **258** in good yields, Figure 72. The intermediate iodo compound **258** could be used without purification and following dehydrohalogenation gave methyl β-nitroacrylate **246**. This approach was later refined by Husser and McMurry who observed that yields could be increased by introducing N_2O_4 to an excess of acrylate.[74] This procedure is now the accepted method for the synthesis of nitroacrylates from acrylates.

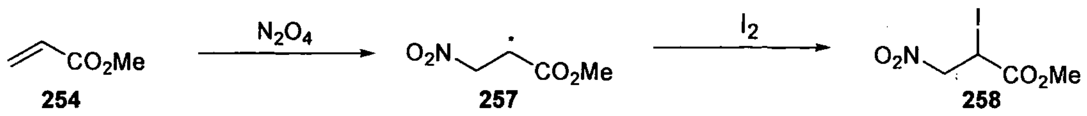


Figure 72

2.2.3 Synthetic Uses of Nitroacylates

The combination of the electron withdrawing effects of the nitro and ester groups in this system produces a very electron deficient double bond, which functions as an excellent dienophile in Diels Alder reactions. Nitroacrylates can also act as propiolate equivalents in Diels Alder reactions, Figure 73. Using conventional methodology with alkyl propiolates, the Diels Alder reaction gives exclusively the 1,2 regioisomer **262**, Figure 73. However, the reaction with methyl β-nitroacrylate **246** gives the 1,3 product **259** as a single regioisomer.

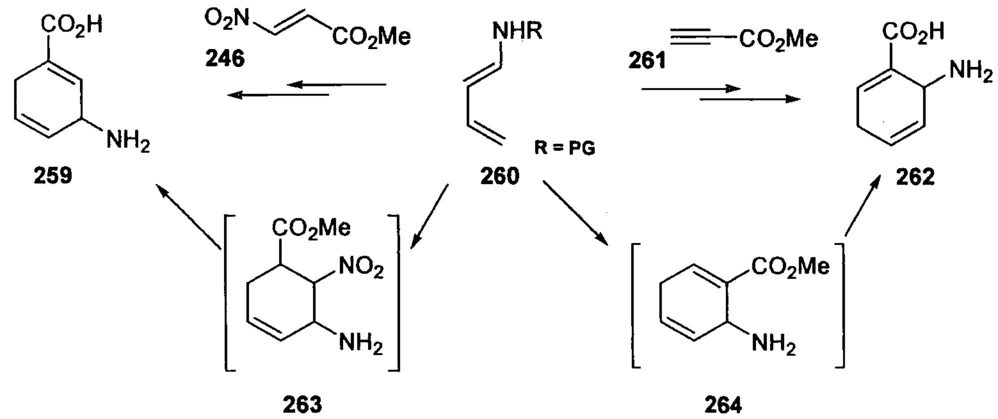


Figure 73

This observation was exploited by Danishefsky[71] *et al* in the synthesis of γ-aminobutyrate aminotransferase (GABA-T) inhibitor, isogabaculine **259**, Figure 74, utilising nitroacrylates as an alkyl propiolate equivalent. Reacting methyl β-nitroacrylate **246** and the 1-substitued diene **265** gave intermediate **266** as a single regioisomer. Elimination of nitrous acid, hydrolysis and protecting group removal affords isogabaculine **259**.

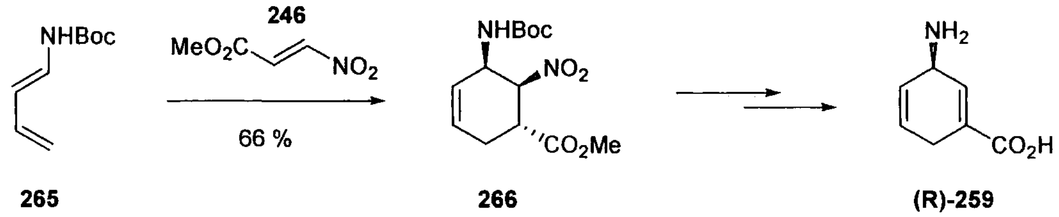


Figure 74

This approach has been further exploited through the use of chiral nitroacrylates, for example, in the synthesis of (-)-calicheamicinone **270** by Clive *et al*, Figure 75.[72] Chiral nitroacrylate derived from 8-phenylmenthyl **268** undergoes a Diels Alder reaction with the ketene acetal **267** to give ketone **269** as a single stereoisomer after crystallisation. Further elaboration of **269** gives (-)-calicheamicinone **270**.

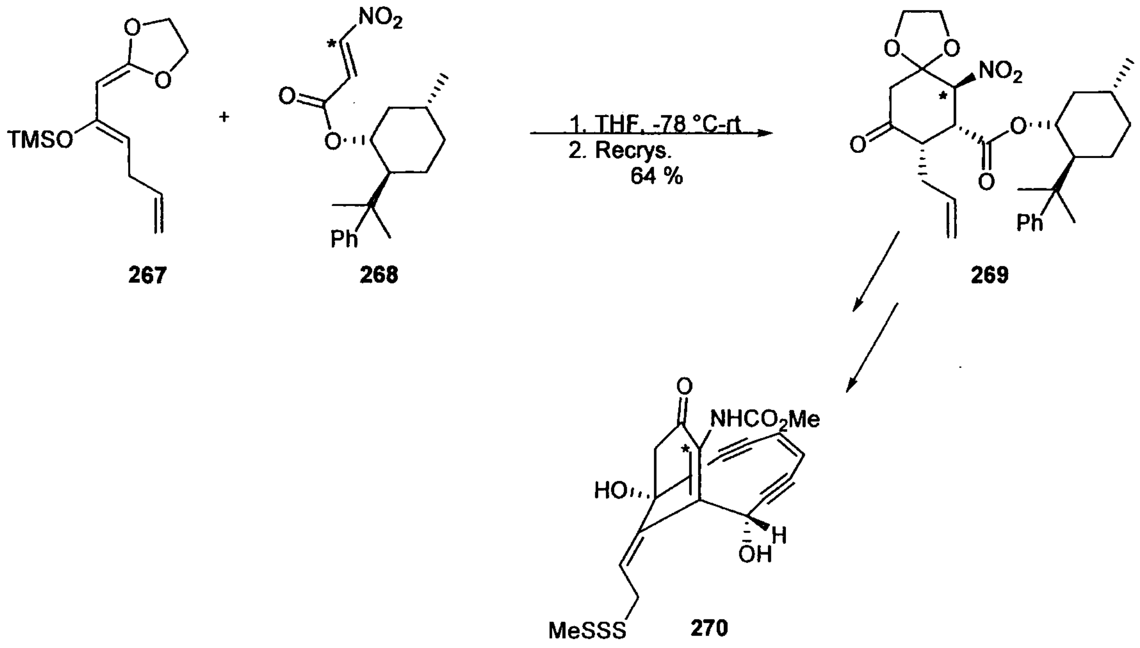


Figure 75

The use of nitroacrylates as versatile synthetic intermediates for β-amino acids has been well exploited by this laboratory in the total synthesis of oryzoxymycin **274**, Figure 76.[73] Diels Alder adduct **272** was obtained as the major isomer, in excellent yield from the cycloaddition of furan **271** and nitroacrylate **245**. Subsequent elaboration of adduct **272** yielded oryzoxymycin **274**.

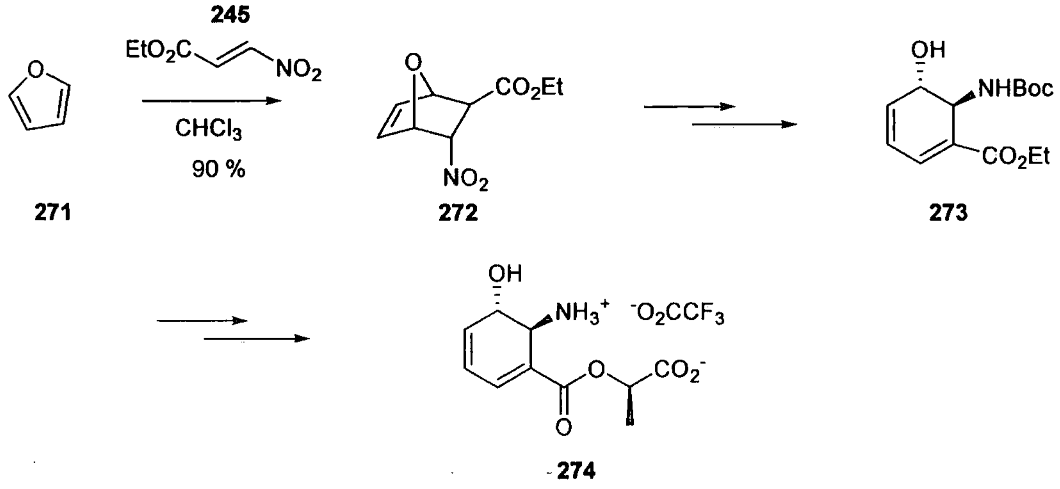


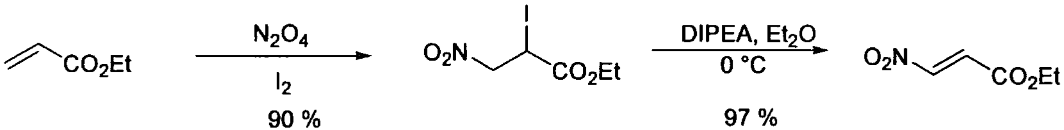
Figure 76

2.2.4 Summary of the use of Nitroacrylates in Organic Synthesis

Nitroacrylates have found widespread use in organic synthesis, particularly in the Diels Alder reaction. The highly functionalised adducts are easily prepared and can be utilised as key intermediates in natural product synthesis.

2.3 Synthesis of *endo*-nitro bicyclic ester

With the synthetic strategy outlined in Figure 70 (Page 43), the initial objective was to prepare ethyl β-nitroacrylate **245** in significant quantities. McMurry *et al*[74] reported large scale synthesis of **245** which involved the treatment of ethyl acrylate **275** with iodine and dinitrogen tetroxide to give iodo-nitro compound **276,** Figure 77. Subsequent dehydrohalogenation using sodium acetate should afford the nitroacrylate **245**. Following this procedure gave the intermediate iodo-nitro compound **276** in 90 % yield, Figure 77. However, attempts to achieve dehydrohalogenation using sodium acetate gave extensive decomposition. Subsequently, the literature procedure was modified to use 1.1 eq of ^{i}Pr$_2$NEt in ether at 0 °C. Crucially the base must be added dropwise, in order to avoid decomposition. Nitroacrylate **245** was obtained in 97 % yield as a bright yellow oil, which solidified on cooling. The exclusive product was the E-isomer characterised by a large 13 Hz (*trans*) coupling in the ^{1}H NMR spectrum.



275 **276** **245**

Figure 77

In order to continue the synthetic sequence outlined in Figure 53 and Figure 68, it was necessary to produce multigram-quantities of the diene 1-methoxy-1,3-cyclohexadiene **278**. Birch reduction of anisole **277** gave a mixture of 1,3 and 1,4 dienes.[75] However, the mixture was carried through to the next step as it is well documented that 1,4-dienes undergo isomerisation by heating on glass, Figure 78.[76]

With large quantities of nitroacylate **245** and diene **278** in hand, the Lewis-acid-catalysed Diels Alder reaction was attempted. Following this established precedence the desired *endo*-nitro-bicyclic adduct **250** was isolated as the major component of a 95:5 (GC) mixture of isomers on a 10 g scale, Figure 78. Purification by flash chromatography gave the desired product, confirmed by MS (CI, MH^+ = 256). ^{1}H and ^{13}C NMR spectra were also in excellent agreement with published data.[68,73]

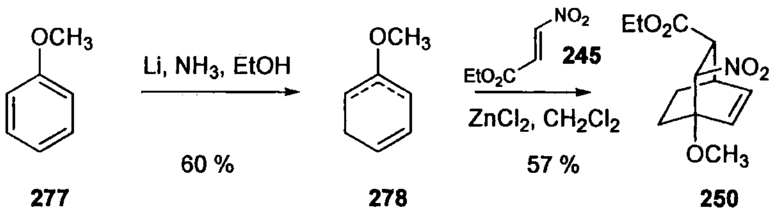


Figure 78

2.4 Introduction of the C12 ⁱPr group

2.4.1 Manipulation of Ester Group

With gram quantities of bicyclic intermediate **250** available, conversion of the ester functionality on nitro-bicyclic **250** into the desired C12 ⁱPr group was investigated, Figure 79. This was a high priority as this group was anticipated to provide facial selectivity over the organometallic addition to ketone **243** to allow the correct orientation for the intramolecular Diels Alder cycloaddition to occur.

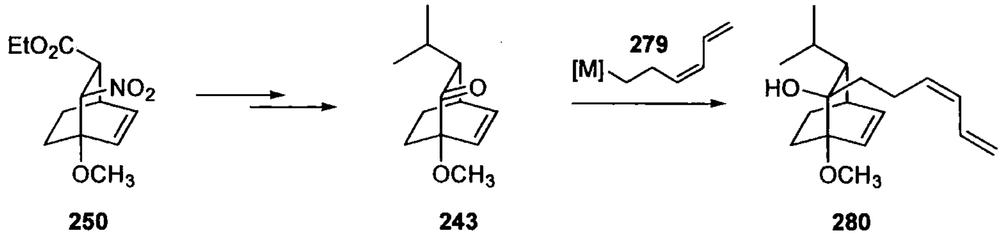


Figure 79

Bunnelle *et al*[77] have shown that direct conversion of an ester into an ⁱPr group can be achieved by the addition of 2 molar equivalents of trimethylsilylmethylmagnesium chloride to an ester **281**, Figure 80. Subsequent treatment of intermediate **282** promotes a Peterson olefination reaction to give the corresponding allylsilane **283**. Protodesilylation afforded the isopropenyl group and subsequent hydrogenation gave the desired ⁱPr group **284**.

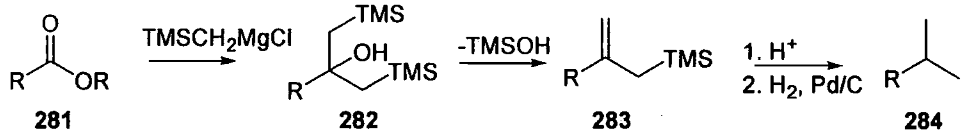


Figure 80

Bicyclic ester **250** was treated with a range of simple organometallic reagents to examine its behaviour during addition, Figure 81. However, in all cases, when a single equivalent of the organometallic reagent was used this returned starting material and disappointingly excess reagent led to significant decomposition.

It was hypothesised that the electron withdrawing nature of the nitro group and the adjacent ester on bicyclic intermediate **250** make the alpha protons extremely acidic. Therefore, the organometallic reagent may be acting as base, deprotonating and on work-up returning starting material or causing elimination. As a potential solution to this problem, organocerium reagents are reported to be more nucleophilic and less basic than their organolithium and Grignard counterparts. 'MeCeCl$_2$' was prepared and the effect of the addition on bicyclic ester **250** was observed. Disappointingly this method gave quantitative recovery of starting material.[78]

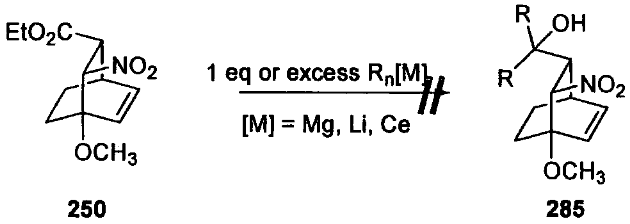


Figure 81

2.4.2 Addition to Bicyclic Ester 250

An alternative strategy to allow direct incorporation of the ^{i}Pr group was to reduce the acidity of the bicyclic ester **250** by conversion to the mono-Boc amino bicyclic ester **286**. The desired reduction and protection was carried out in a one pot procedure to minimise difficulties in the isolation of the free amine, Figure 82. After careful column chromatography to remove excess Boc anhydride, protected amine **286** was obtained in good yield and was characterised by the appearance of a ^{t}Bu [9 H] singlet at 1.46 ppm in the ^{1}H NMR spectrum.[1]

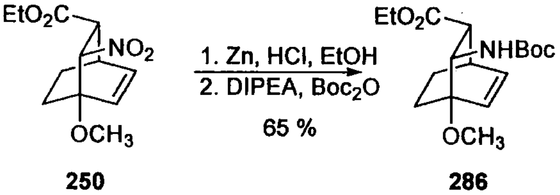


Figure 82

Boc-amino ester **286** was then treated with methyllithium to observe its reactivity, Figure 83. Encouragingly, this resulted in the desired tertiary alcohol **287** and was characterised by loss of the ester signals at 1.21 and 4.22 ppm in the ^{1}H NMR spectrum.

---

[1] Attempted purification by Kugelrohr distillation resulted in decomposition of the bicyclic structure.

No attempt to optimise this addition was made at this stage and attention was focused on the addition of silyl reagent $TMSCH_2Li$ (or MgCl) to directly introduce the ^iPr group, see Figure 80. However, disappointingly all variants of this silyl reagent (Grignard, lithium or cerium) did not add to the ester group and it is not obvious as to the unreactivity of the carbonyl group at this stage, Figure 83. Alternative strategies to utilise the nitro-bicyclic-ester **250** were then considered and these are discussed in the following sections.

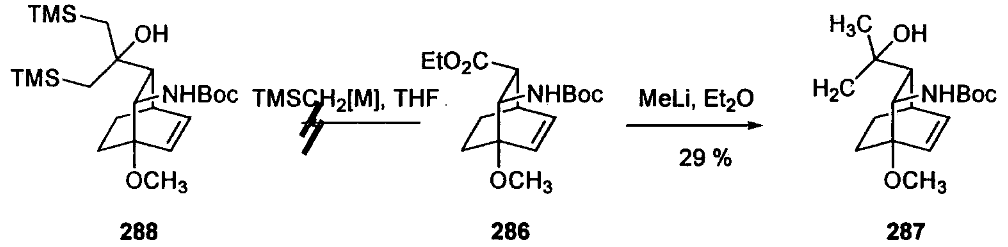


Figure 83

2.5 Manipulation of the Nitro Group

2.5.1 Introduction

In a parallel approach to the chemistry detailed in the previous section, an alternative strategy was investigated for the synthesis of Vinigrol utilising nitronate alkylation, Figure 84. In this approach we envisaged alkylation of a nitronate intermediate **289**, thus producing an sp^2 centre at C1 which may allow approach of a suitable electrophile. Nucleophilic reactions of nitroalkanes are powerful tools in the formation of C-C bonds. These reactions proceed under mild conditions and are known to tolerate a wide variety of functional groups.

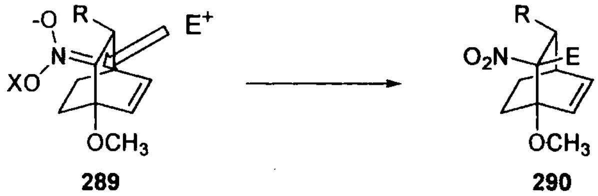


Figure 84

To incorporate this methodology into the retrosynthetic analysis, the route would include homologation of a side chain into the required diene **292**, Figure 85. Subsequent intramolecular Diels Alder reaction to give **293** followed by reduction of the nitro group and removal of the methyl ether would give the amino alcohol **294**. Oxidative cleavage would then give the keto-imine **295** with the 6,8,6-fused skeleton of Vinigrol.

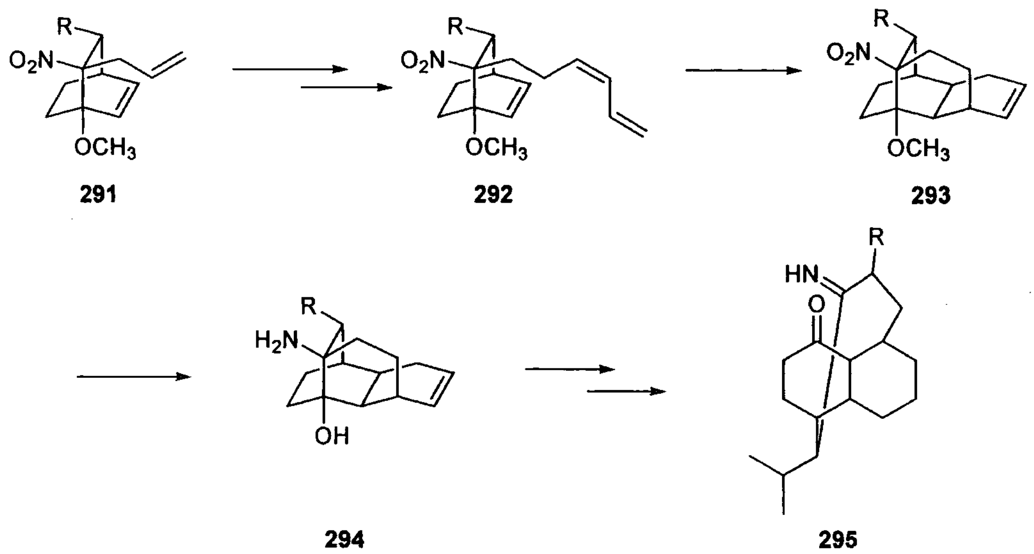


Figure 85

Initial investigations previously undertaken within the group had shown that the use of allyl bromide as the electrophile gave complex mixtures of products, Figure 86. This was attributed to hard-hard interaction of the bromide with the nitronate oxygen. Hence, this study was to involve the use of acrylates as the electrophile.

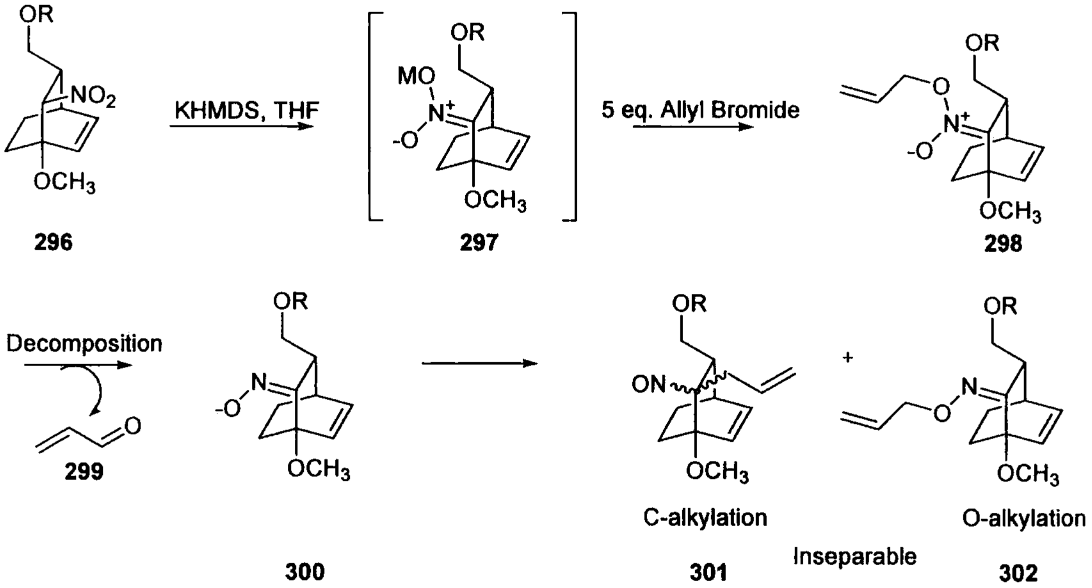
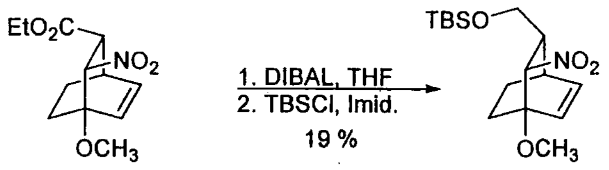


Figure 86

In order to remove complications due to elimination and competing sites of alkylation, it proved necessary to reduce the ester and protect the resultant alcohol. To this end, bicyclic ester **250** was treated with DIBAL and the resultant alcohol was treated with TBSCl and afforded silyl ether **303**, Figure 87. Ether **303** was characterised by the loss of the carbonyl signal at 1734 cm^{-1} in the IR spectrum and appearance of a [2H] multiplet at 3.66-3.68 ppm in the ^{1}H NMR spectrum.



250 **303**

Figure 87

2.6 Michael Addition Chemistry

Conjugate additions of secondary nitronate groups are well documented and various bases can be used as coupling agents. Guanidine bases are known to specifically hydrogen bond to increase the reactivity of the nitro group.[79] Michael addition of the nitronate derived from 2-nitro-octane **304** in the presence of tetramethyl guanidine to but-3-en-2-one **305** proceeds in excellent yield, Figure 88.[80]

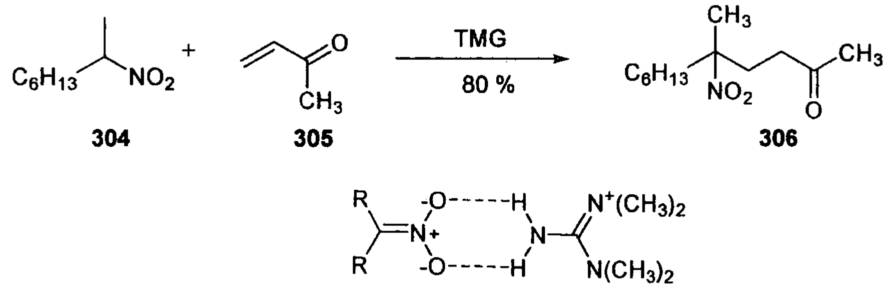


Figure 88

The nitronate alkylation chemistry was first examined on a model system as this gave simpler analytical data which was easier to interpret, Figure 89. Heating a mixture of diene **307** and nitroacrylate **245** afforded a single diastereoisomer **308** by NMR, which was in excellent agreement with literature data.[68] The ester group was then reduced by $LiAlH_4$ to give corresponding alcohol **309**, which was immediately protected as silyl ethers to afford **310** (TMS) or **311** (TBS), Figure 89. Ethers **310** and **311** were identified by the disappearance of the ester carbonyl stretch at 1735 cm^{-1} in the IR spectrum and the appearance of a double doublet (J = 10, 4 Hz) or multiplet at 3.45 ppm in the ^1H NMR spectrum corresponding to the new methylene group.

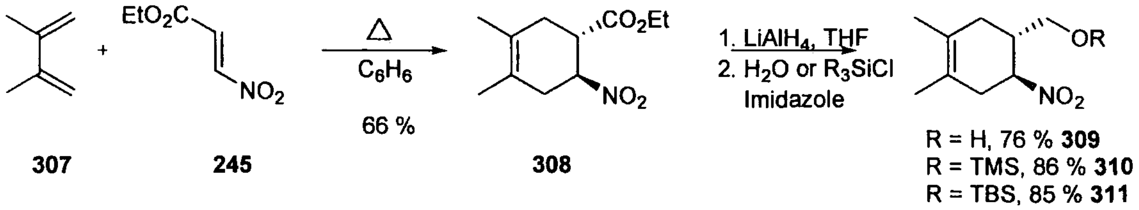


Figure 89

With large quantities of nitro alcohol **309** and TMS ether **310** in hand, the required Michael addition reactions were investigated. Nitro alcohol **309** and TMS ether **310** were reacted under optimised conditions from initial studies within the group,[68] Figure 90. This yielded a surprising result, in that the major product of the reaction was lactone **314**, characterised by the MS data (CI^+ 253 MH^+) and lack of an ester methyl by ^1H NMR spectra at ~ 4 ppm. However, using the less labile TBS protection **311** gave poor incorporation of the electrophile, Figure 90.

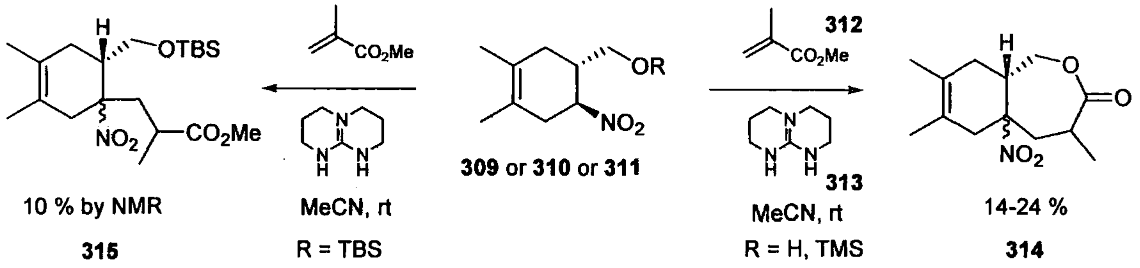


Figure 90

However, having demonstrated the desired carbon-carbon formation, no optimisation was carried out on this system and attention returned to the bicyclic intermediate **250**. An initial investigation into Michael chemistry was undertaken using the nitro alcohol **316** as the substrate and this revealed that protection of the alcohol functionality was required, as the Michael acceptor was added *via* a transesterification process to afford ester **317**, Figure 91. Ester **317** was characterised by the appearance of two olefinic signals at 5.60 and 6.07 ppm and the lack of a [3H] singlet at ~ 3.5 ppm in the ^1H NMR spectrum.

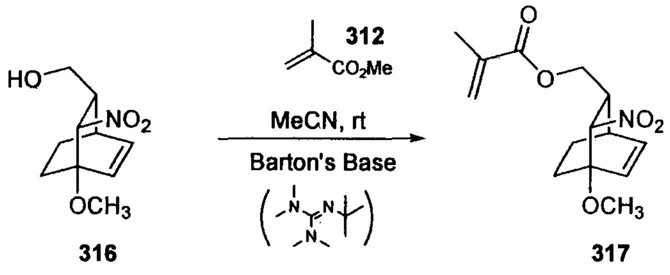


Figure 91

With significant quantities of silyl ether **303** in hand, it was decided that in order to achieve maximum results and efficiency an array would be developed, Figure 92. 24 separate reactions were carried out in a single operation using a Radleys Greenhouse™ parallel synthesiser allowing the reactions to be monitored easily and permitting an optimum solvent and base to be identified quickly. The yields obtained on the model system were moderate and it was hypothesised that methyl methacrylate was not sufficiently reactive. Thus, highly reactive 2-(dimethoxyphosphoryl)-acrylic acid methyl ester was selected as the Michael acceptor **318**, Figure 92. The Greenhouse apparatus allowed the screening of 4 bases (Et_3N, DBU, Barton's Base (2-tert-Butyl-1,1,3,3-tetramethylguanidine) and triazabicyclo [4.4.0] dec-5-ene) and 6 different solvents (DCM, MeCN, THF, dimethylformamide, DMSO, THF/^{t}BuOH).

Due to the reversible nature of Michael additions it was hypothesised that the use of stoichiometric base could promote the reverse reaction and other side reactions. To this end, the array chemistry was carried out with the use of both greater than stoichiometric (1.3 eq.) and catalytic (10 mol %) quantities of base to enable these potential side reactions to be investigated.

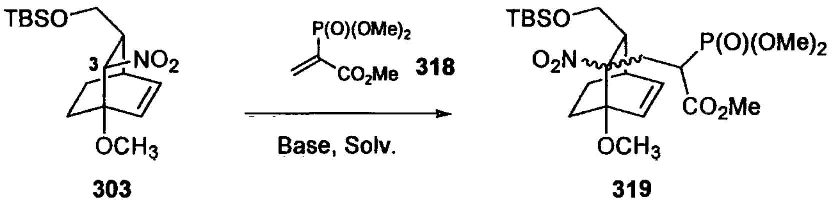


Figure 92

To this end bicyclic intermediate **303**, the base and solvent were added to the Greenhouse vials and the Michael acceptor **318** was added. The reaction mixtures were stirred at room temperature and monitored by TLC at various intervals; however, all reactions showed starting material present even after 7 days. Further analysis by LC-MS after 14 days showed that starting material was still present, together with polymerised Michael acceptor. No evidence of the coupled product was observed. The extensive investigation carried out to optimise the nitronate alkylation with guanidine bases had failed and it became evident that this chemistry would not yield the required bond formation at C3.

Continuing the nitronate strategy in Figure 84, investigations into the use of their silyl nitronate counterparts as an alternative approach was examined. The following section outlines the attempts made in this area.

2.7 Silyl Nitronate Chemistry

2.7.1 Introduction

Since the late 1970's, silylated nitronates have been well documented in the literature.[81] Silyl nitronates, *e.g.* **321**, are obtained by the reaction of a nitroalkane with a silyl chloride in the presence of a base, Figure 93. Simple alkyl silyl nitronates have been isolated and distilled and possess several modes of reactivity and these are shown in Figure 93.

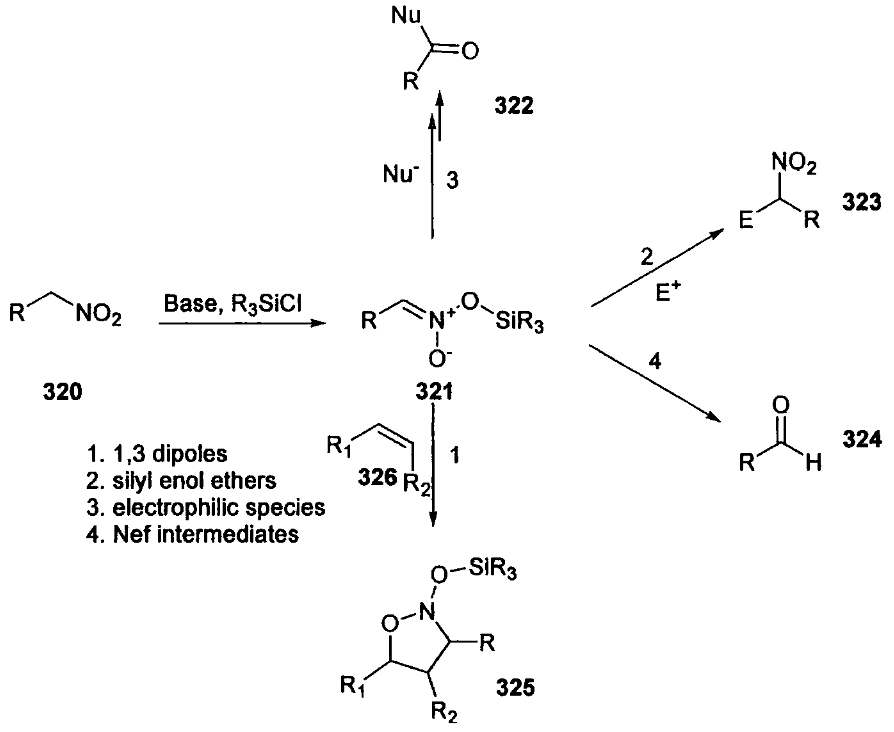


Figure 93

However, this project was interested in the observation that the chemistry of silyl nitronates can be compared to that of silyl enol ethers, pathway 2, Figure 93.

2.7.2 Silyl Nitronates as Enol Ether Equivalents

Seebach *et al* utilised silyl nitronates to improve the nitro aldol reaction.[82] Deprotonation of a nitroalkane **320** and quenching the resultant anion with TMSCl furnished silyl nitronate **327**. Addition of an aldehyde in the presence of TBAF gave the corresponding nitroalcohol **329**, Figure 94.

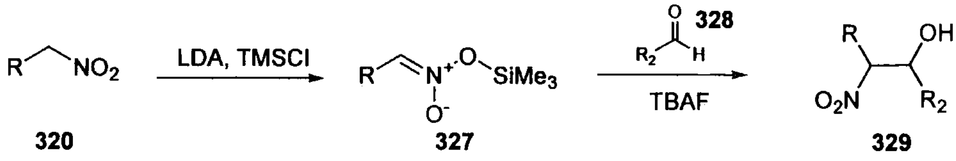


Figure 94

The work of Seebach *et al* suggested that this approach could be used to achieve the overall aims of the project. Previous work in the group had examined the formation and trapping of the silyl nitronate species **330** *in-situ* using a procedure based on a report by Palomo *et al.*[83] This involved the treatment of nitro compound **303** with Barton's Base and TBSCl, Figure 95.

Formation of silyl nitronate **330** was firstly confirmed by a CD_3OD quench, since attempts to isolate or detect **330** spectroscopically proved unsuccessful. Pleasingly 50 %

deuterium incorporation was measured by ^{1}H NMR and ^{2}H NMR (at 4.64 ppm) confirming that **330** had formed (also 50 % **303** returned), Figure 95. Therefore, this result suggested that the addition of an electrophile to a pre-formed nitronate species would allow an alternative strategy for carbon-carbon bond formation at C3 to be investigated, Figure 95.

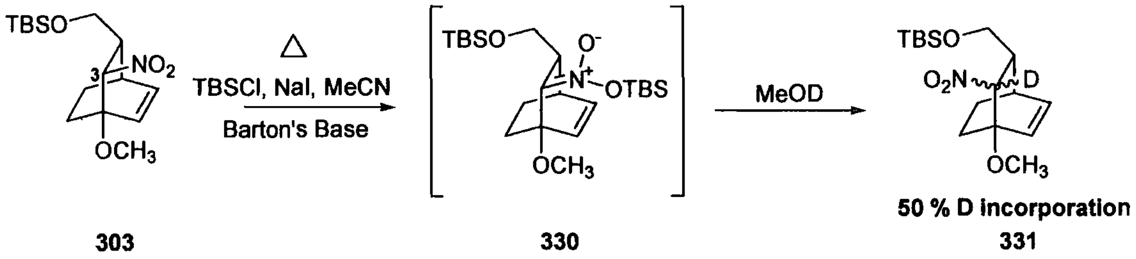


Figure 95

Encouraged by this result, an investigation into the addition of a range of electrophiles (NIS, NBS, NCS, dimethylformamide, Allyl bromide, butyraldehyde) to silyl nitronate **330** was investigated. Nitro compound **303** was treated with TBDMSCl, NaI and Barton's base and refluxed for 15 hours to generate the silyl nitronate **330**, Figure 96. The electrophiles were then added to the preformed silyl nitronate and stirred at room temperature for 4 hours. Crude ^{1}H NMR spectroscopy indicated that iodide, chloride and bromide had been added to **330** which was quantified measuring the reduction in integration for 3-H at ~ 4.6 ppm in the ^{1}H NMR spectrum. However upon column chromatography only the brominated species **332** could be isolated. α-bromo-bicyclic **332** was characterised by the loss of the C3 proton at 4.64 ppm and the correct bromine isotope splitting pattern obtained from mass spectrum data (CI^+ 406/408 MH^+).

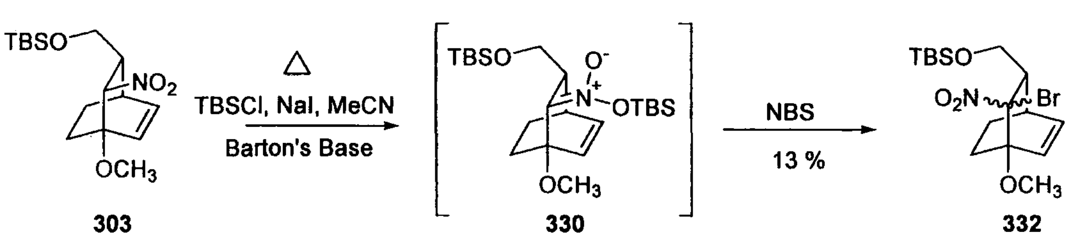


Figure 96

From the poor results obtained from the initial electrophile addition investigation, optimisation was clearly required. In an attempt to increase yields trapping the silyl nitronate in a cyclic fashion was attempted by treating the alcohol **316** with 1,2-dichloro-1,1,2,2-tetramethyldisilane, Figure 97. However, on CD_3OD quench no deuterium was incorporated, Figure 97, implying that the cyclic silyl nitronate **333** was not formed under the reaction conditions.

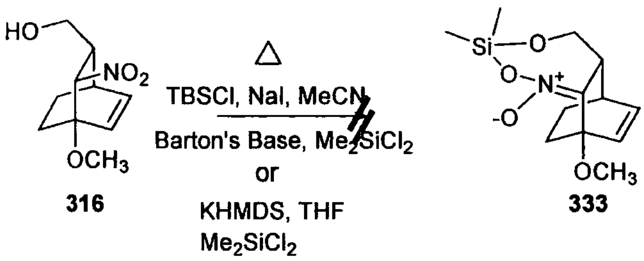


Figure 97

A further attempt to optimise the reaction involved attempting to force complete deprotonation with a strong base to give a metallated nitronate. However, the use of KHMDS and subsequent quenching with NBS gave identical isolated yields to that obtained by the silyl nitronate method, Figure 98.

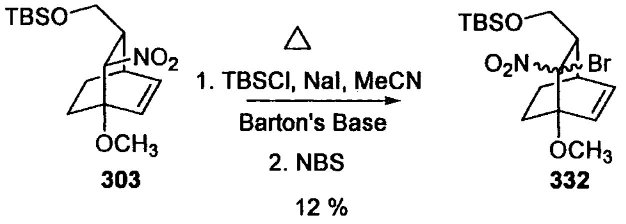


Figure 98

The yields from this work were disappointing after an initial encouraging result. The brominated compound **332** could have been of use in radical coupling reactions to furnish the desired carbon-carbon bond formation. However, due to poor yields obtained with this synthetic methodology even after attempted optimisation meant that this route had to be abandoned. It remains unclear at this time as to why poor yields were obtained from this reaction despite attempted optimisation.

However, the nitro group on bicyclic intermediates **250**/**303** remains a useful functional group, and can be converted into a variety of different functional groups. Applications of these towards a total synthesis of Vinigrol are discussed in the following section.

2.8 Direct Conversion of the Nitro Group - Nef Chemistry

In accordance with the overall goal, to develop an approach to the total synthesis of Vinigrol, the intermediate target was the synthesis of the Vinigrol tricyclic ring structure **242**. Therefore, the initial target in the synthesis was the formation of ketone **243** from the nitro bicyclic **250**, Figure 99. Conversion of the nitro group by Nef chemistry would give the desired ketone **243** in few synthetic steps, but extensive attempts to afford conversion had been carried out within the group[68,84] and had given disappointing results. The bicyclic nitro ester **250** did not undergo any Nef reactions under a variety of different conditions.

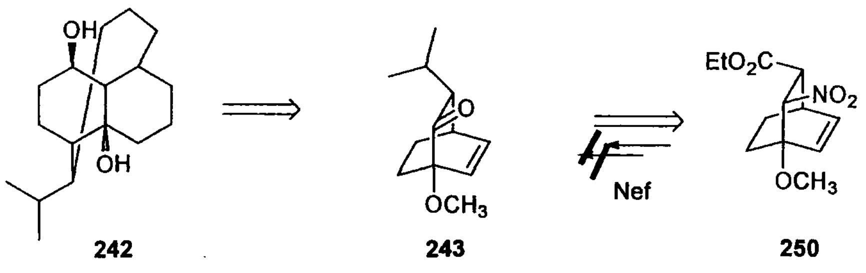


Figure 99

2.9 Amines

2.9.1 Introduction

Nef chemistry had been unsuccessful to reveal bicyclic ketone **243**, however with the correct regiochemistry present other methods to achieve carbon-carbon formation at C3 were investigated. The nitro group can be easily converted to a primary amine under reductive conditions and the corresponding amine may be synthetically useful in a variety of transformations, Figure 100. It was envisaged that amine oxidation and imine formation could facilitate the desired bond forming reaction and are discussed in the following section.

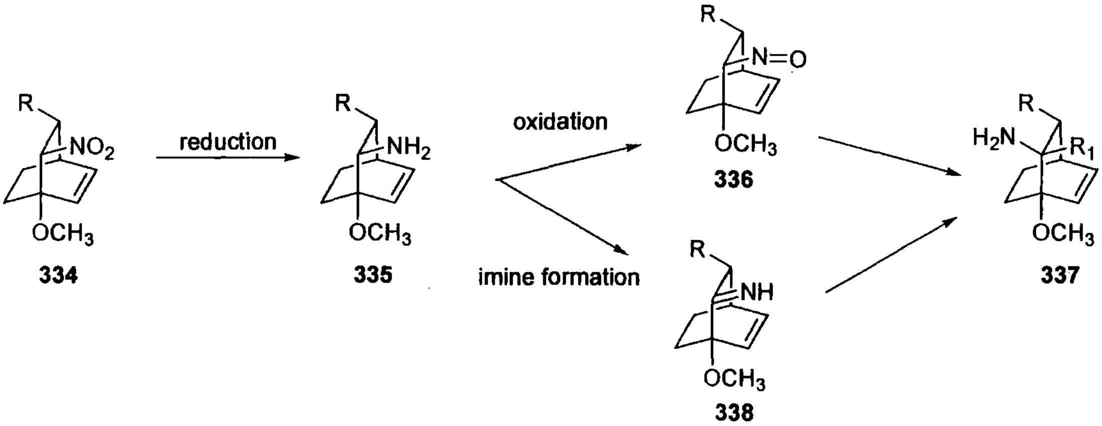


Figure 100

2.9.2 Amine Formation

To enable the investigation of carbon-carbon formation from functionalisation of amines, bicyclic intermediate **250** was doubly reduced, Figure 101. The ester group was removed by treatment with lithium aluminium hydride to afford alcohol **316** in moderate yield. Alcohol **316** was then treated pivaloyl chloride[85] or benzyl-2,2,2-trichloroacetimidate[86] to afford **339** or **340** which were characterised by the appearance of [9H] singlet at 1.17 ppm for the ^{t}Bu group and a [5H] multiplet at 7.29 ppm for the benzyl group respectively.

Reduction of the nitro group was afforded by Zn in HCl to give amines **341** and **342** in modest, unoptimised yields, and these were identified by the upfield shift of C3 in the ^{13}C NMR spectra from 90 to 57 ppm and a positive ninhydrin test. The amines were obtained by direct isolation and were comparable in yields to the one-pot reduction/protection strategy described earlier (Page 48).

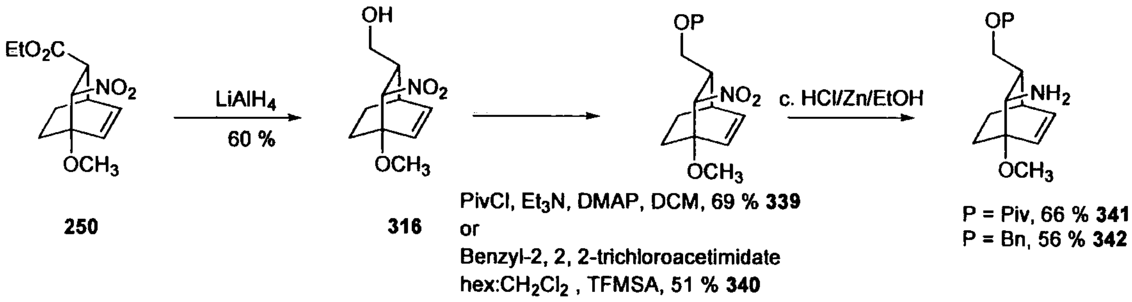


Figure 101

With amines **341** and **342** in hand, investigations began to implement the strategy outlined in Figure 100. The following sections describe the efforts made in this area.

2.10 Oxidation

Amines are reported to be easily oxidisable with reagents such as hydrogen peroxide, *m*-CPBA and even air. However, limited reports exist for this transformation. Corey *et al*[87] and Gilbert *et al*[88] observed that primary amines could be easily N-oxidised by treating with peracids. More recently milder processes for the N-oxidation have been developed which include a catalytic method using methyltrioxoruthenium (MTO) in hydrogen peroxide[89] and also the use of sodium perborate.[90]

Oxidation of an amine should afford the nitroso species which can subsequently tautomerise to the oxime, Figure 102. The oxime could then allow us to reveal the carbonyl group upon basic hydrolysis and addition of an organometallic species would give the desired carbon-carbon bond directly.

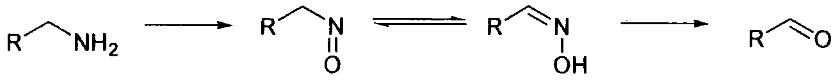
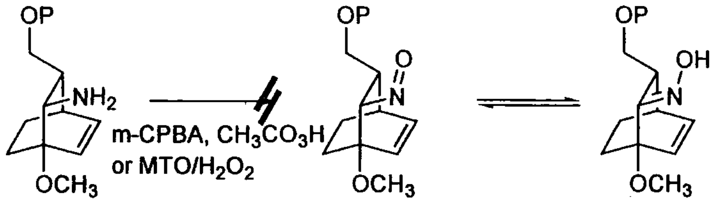


Figure 102

With the literature precedence for the required transformation in hand, amines **341** and **342** were treated with *m*-CPBA, peracetic acid and MTO, Figure 103. However, NMR and mass spectral analysis of the reaction mixtures indicated that significant decomposition had taken place. It is hypothesised that the double bond of the bicyclo[2.2.2] system was oxidised at a faster rate than the desired amine thus causing competing decomposition pathways.



P = Piv **341**
P = Bn **342**

P = Piv **343**
P = Bn **344**

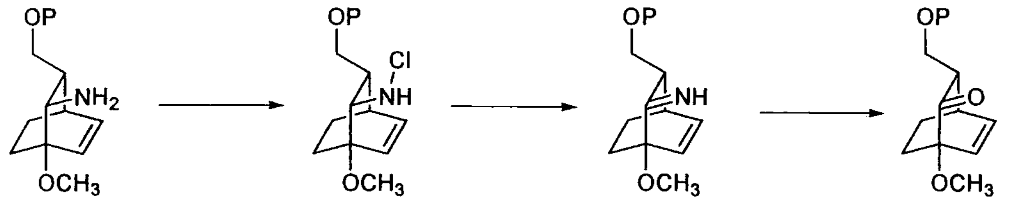
P = Piv **345**
P = Bn **346**

Figure 103

Thus it became evident from this small investigation that amine oxidation would not afford the desired carbon-carbon bond formation. It appears that the amine oxidation conditions are not compatible with the other functionality present on the bicyclic intermediates. Consequently we examined a further method to introduce this connection *via* imine chemistry and this is described in the next section.

2.11 Imine Formation by N-Chlorination

Generation of the oxime was unsuccessful, however it was hypothesised that the sp^2 C=N unit could be generated by N-chlorination and subsequent elimination. Hydrolysis of the resulting amine should give access to the required ketones **351** or **352**, Figure 104.



P = Piv **341**
P = Bn **342**

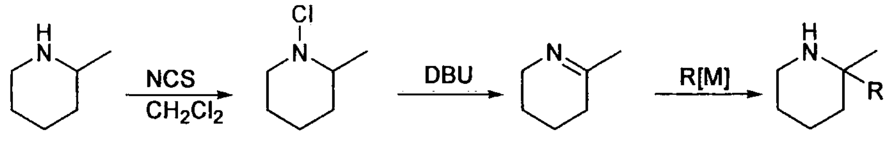
P = Piv **347**
P = Bn **348**

P = Piv **349**
P = Bn **350**

P = Piv **351**
P = Bn **352**

Figure 104

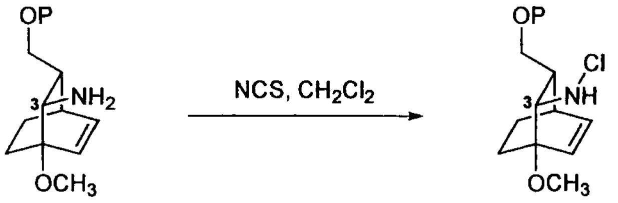
This transformation had been shown to proceed in good yields utilising cyclic piperidines.[91] N-chlorination and elimination of HCl with the hindered base DBU provided imine **355** which was successfully subjected to attack by a range of organometallic reagents, Figure 105.



353 **354** **355** **356**

Figure 105

Thus, based on this precedent amines **341** and **342** were treated with N-chlorosuccinimide[92] and analysis by TLC showed that the N-chlorinated amines possessed a significantly higher R_f value in comparison to the starting amines, Figure 106. The N-chlorinated amines **347** and **348** were produced in 10 minutes in moderate but unoptimised yields and the products were identified by an downfield shift of the 3-H proton from 3.5 to 3.9 ppm in the ^{1}H NMR spectra and C3 in the ^{13}C NMR spectra from 54 to 68 ppm.



P = Piv **341**
P = Bn **342**

P = Piv 41 % **347**
P = Bn 53 % **348**

Figure 106

With the N-chlorinated amines **347** and **348** in hand it was hypothesised that the addition of two molar equivalents of an organometallic species would give the desired carbon-carbon bond formation, Figure 107. The first equivalent would act as a base to produce imines **349** and **350** and the second equivalent would act as a nucleophile to install the alkyl group, Figure 107. Also the use of base (LDA or DBU) to generate the imine directly and then addition of an organometallic reagent was considered. However, laborious attempts under various reaction conditions to utilise this chemistry have been unsuccessful. It was noted that the precedented chemistry had been developed on secondary amines and we consequently attempted to alkylate amine **342** to examine this.

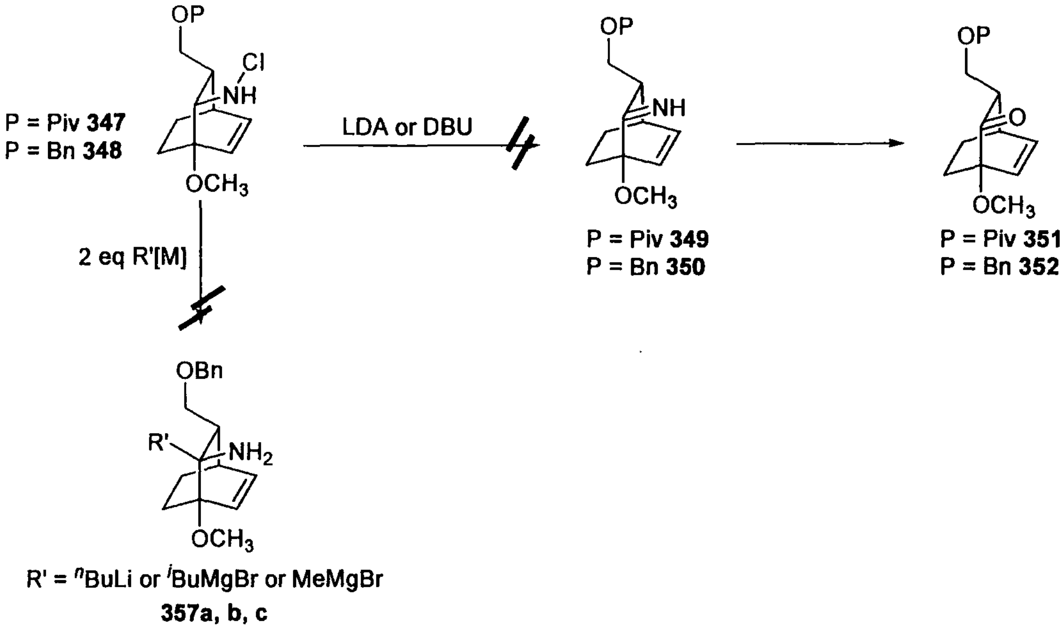


Figure 107

Derivatisation of primary amine **342** was attempted utilising reductive amination techniques so as to avoid the over alkylation pathway often observed with alkylating agents, however this method was unsuccessful. Amine **342** was then treated with benzyl bromide/sodium hydride and surprisingly only the monoalkylated amine was recovered and was identified with the appearance of a multiplet at ~ 7.3 ppm in the ^{1}H NMR spectra, Figure 109. With secondary amine **359** in hand it was treated with NCS but the desired N-chlorinated product **360** could not be isolated and reasons for this failure are unclear at this time.

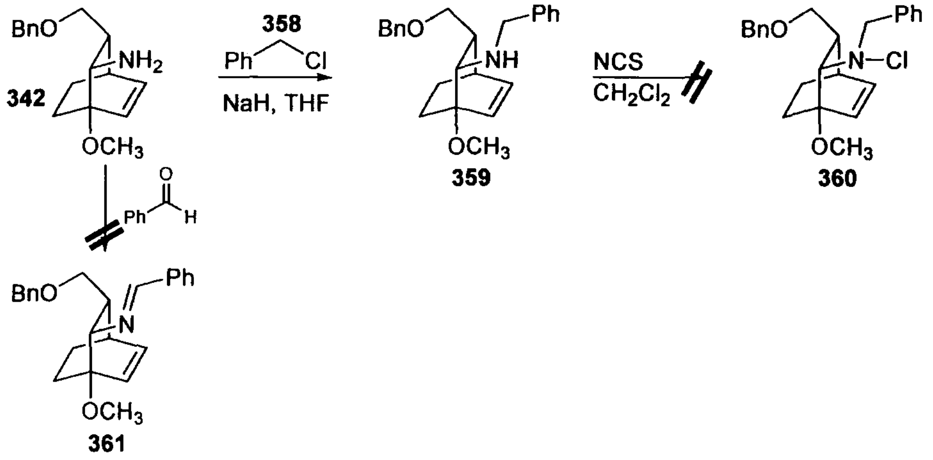


Figure 108

2.13 Conclusions

In initial studies towards the total synthesis this project has demonstrated that the initial goals in the strategy towards the total synthesis of Vinigrol have been unsuccessful. Attempts to elaborate the Diels Alder adduct using Michael addition and Nef chemistry have failed. Although no explanation is forthcoming for this failure, we speculate that the reaction fails due to the increase in strain involved in the formation of a sp^2 centre at C3 (C1) in the rigid bicyclic ring system since the reaction proceeds through an imine intermediate. Promisingly, nitronate alkylation was successful albeit in low yield; attempts to date to optimise this chemistry have been unsuccessful. Also, attempts to introduce the ^{i}Pr at C12 early in the synthesis have not succeeded due to the apparent lack of reactivity of the ester carbonyl.

Towards this end a parallel strategy was developed and the efforts made in this area are described in detail in the following chapter.

Chapter 3
Z,E Dienes and IMDA Cycloadditions

Chapter 3 : Z, E dienes and IMDA Cycloadditions

3.1 Introduction

Bicyclic intermediate **250** formed in the nitroacrylate strategy possessed the correct regiochemistry to allow the regioselective installation of the ^{i}Pr group, Figure 109. However, attempts to utilise this functionalised intermediate have been unsuccessful, thus an alternative strategy involving a related [2.2.2] system was developed towards the total synthesis, Figure 109. Bicyclic ketone **362** was identified as an alternative intermediate to the nitro-ester **250**, Figure 109. Alkylation and further manipulation will allow ^{i}Pr group to be introduced so that the direction of organometallic attack can be controlled.

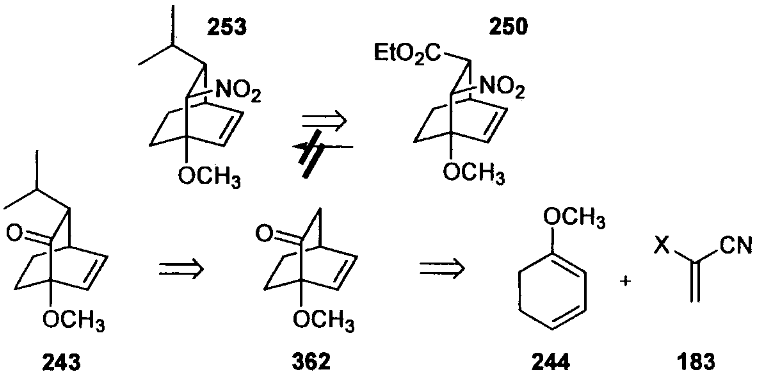


Figure 109

Ketone **362** would allow the retrosynthetic approach already described to be continued towards the total synthesis of Vinigrol. However, a model study was first investigated to test the intramolecular Diels Alder methodology and oxidative ring fragmentation approach to yield the tricyclic diketone **363**, Figure 110.

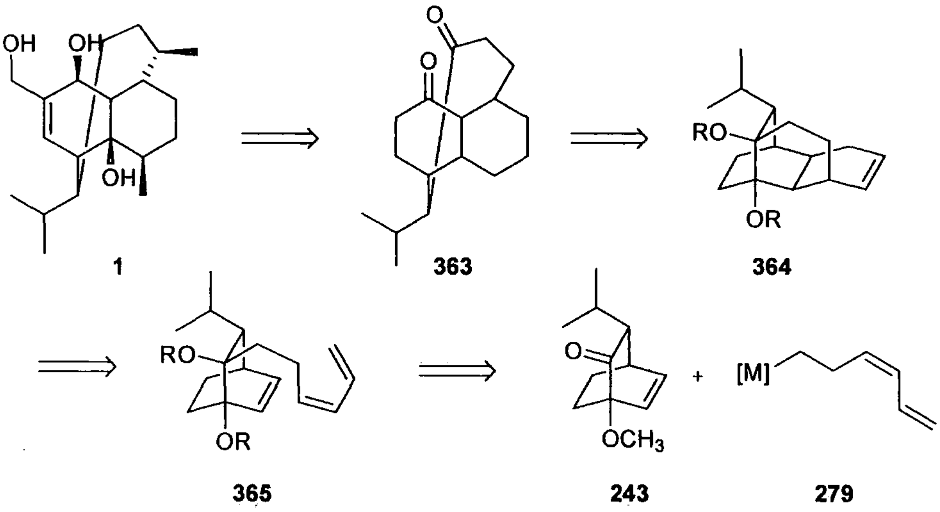


Figure 110

3.2 Introduction of the C12 ^{i}Pr Group

Early introduction of the C12 ^{i}Pr should allow control of the direction of organometallic addition to ketone **243** in the desired direction to allow an overall efficient synthesis towards Vinigrol, Figure 111.

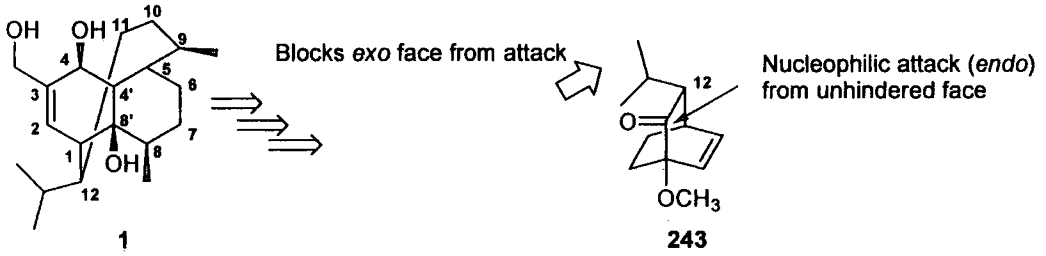


Figure 111

However, initial attempts to install the ^{i}Pr group directly *via* alkylation were unsuccessful due to the steric congestion around C12, Figure 112.

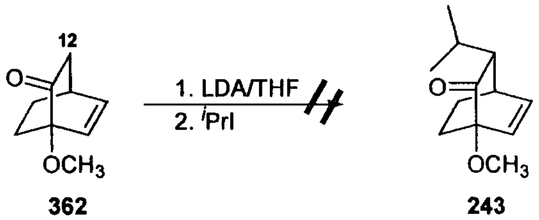


Figure 112

Thus, an alternative route to install the C12 ^{i}Pr group had to be devised, Figure 113. It was envisaged that an aldol condensation and subsequent activation/elimination would allow the required methyl group to be introduced by conjugate addition.

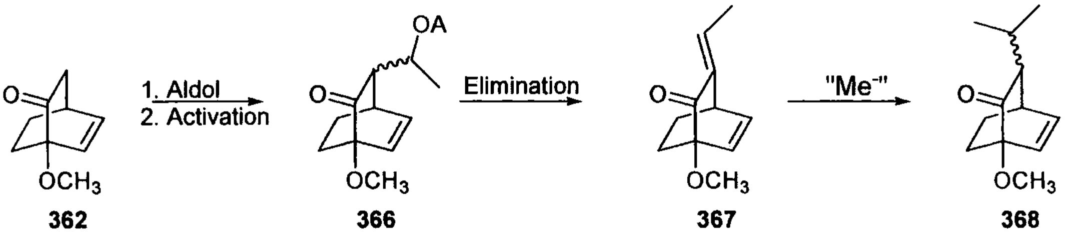


Figure 113

3.3 Synthesis of bicyclic ketone 362

In order to initiate the efforts towards the total synthesis, it was necessary to produce multigram quantities of ketone **362**. Previous work within the group had identified an optimal route utilising a Diels Alder cycloaddition with 1-methoxy-1,3-cyclohexadiene **278** and ketene equivalent **369**, Figure 114.[93] Diene **278** was prepared by Birch reduction of anisole **277** and provides a mixture of 1,3 and 1,4 dienes.[75] However, this mixture was used without purification since it is well documented that 1,4 dienes undergo isomerisation by heating on glass.[76]

Thus, with large quantities of diene **278** and the commercially available 2-chloroacryonitrile **369** in hand, cycloaddition was attempted. Heating **278** and **369** in benzene for 15 h pleasingly afforded the desired cycloadduct **370** after distillation. Prolonged alkaline hydrolysis over 7-10 days afforded bicyclic ketone **362** in moderate yield identified by the strong signal at 1733 cm^{-1} in the IR spectrum, Figure 114.

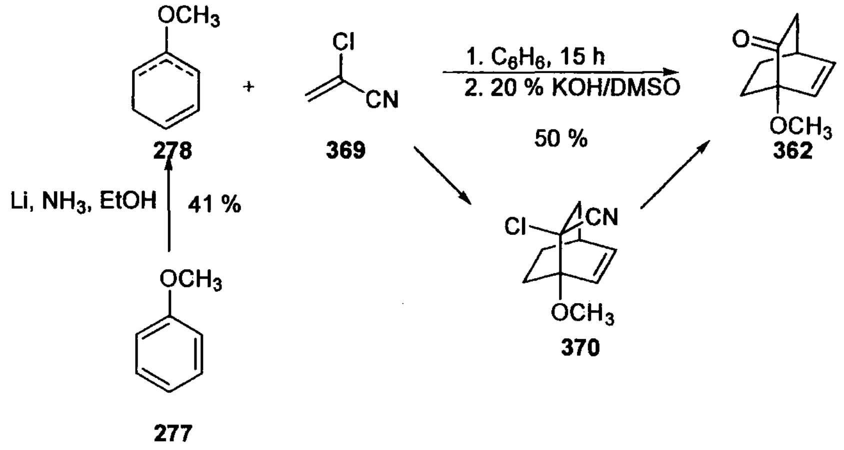


Figure 114

With gram quantities of unsubstituted ketone **362** in hand, the aldol reaction with acetaldehyde was investigated. β-hydroxy-ketone **371** could be obtained in good yields as a single diastereoisomer, Figure 115. Mesylation of the resulting alcohol **371** gave a crystalline solid which allowed the stereochemistry of the initial aldol reaction to be confirmed. The 1RS, 3SR, 4SR isomer was identified and is consistent with attack of the ketone **362** at the less hindered *endo*-face.

Mesylate **372** was treated with excess DBU and the desired elimination was completed after 2 h. The frequency of the IR (C=O) stretch changed from 1729 cm^{-1} for **372** to 1714 cm^{-1} for **367** indicating an α,β unsaturated ketone had been formed. Subsequent treatment of enone **367** with dimethylcopperlithium gave ^{i}Pr ketone **373**. Installation of the ^{i}Pr group could be completed by the linear sequence as described above in a moderate 43 % yield, Figure 115. However, analysis of the NOESY NMR spectrum of **373** revealed that the undesired *endo*- ^{i}Pr ketone **373** had exclusively been formed, Figure 115.

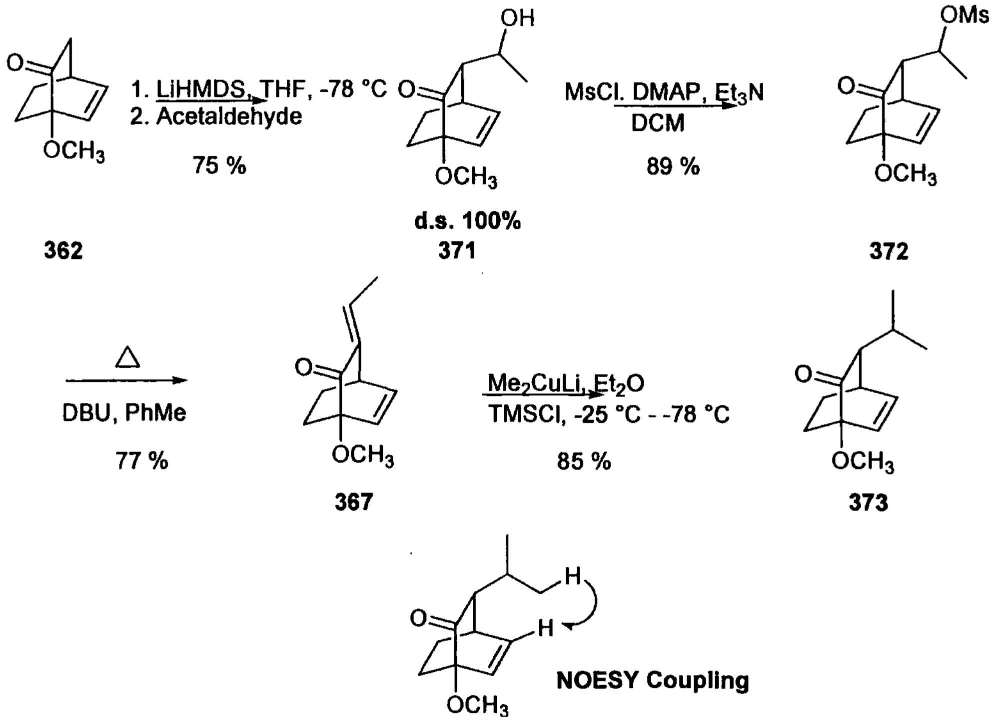


Figure 115

The *endo*- ^{i}Pr ketone contains an alpha acidic proton and this would allow base induced epimerisation to be investigated as a means of achieving the desired stereochemistry.

3.4 Epimersiation of ^{i}Pr-Ketone

Kim *et al* had utilised epimerisation methodology during the synthesis of (+/-)-perhydrohistrionicotoxin on a structurally related [2.2.2] bicyclic intermediate, Figure 116.[94] Alkylation of ketone **374** with ^{n}butyl iodide gave the *endo*-isomer stereospecifically. Epimerisation of the *endo*-isomer **375** was induced with methanolic sodium hydroxide and gave a chromatographically separable 73:27 equilibrium mixture of *endo:exo* in quantitative yield. Large quantities of the desired *exo*-isomer **376** were secured by recycling of the equilibrium mixture.

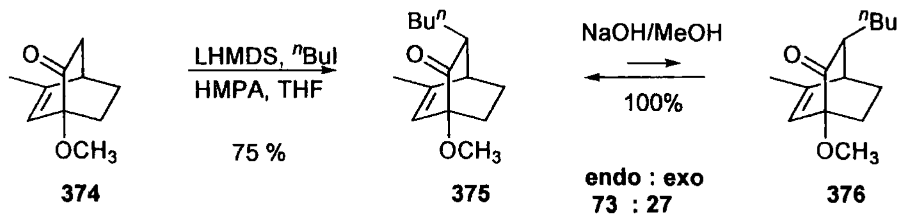


Figure 116

The literature precedence gave us confidence that the *exo*-^{i}Pr ketone **343** could be secured and investigations into this transformation began. Initial studies to identify optimal epimerisation conditions were undertaken using the C12 Me-analogue **377** since this could be prepared by a simple alkylation reaction, Figure 117. Thus, subsequent treatment of ketone **362** with methyl iodide provided *endo*-methyl ketone **377** as a single isomer in good yield, Figure 117. Epimerisation of *endo*-methyl ketone **377** was attempted using a range of bases, proton donors, modes of quenching and temperature. After considerable experimentation, we identified optimal kinetic epimerisation conditions as 2.1 eq of LHMDS/HMPA, *p*-NO$_2$ phenol, inverse quench and - 78 °C which gave a moderate 1:2 *endo*:*exo* ratio.

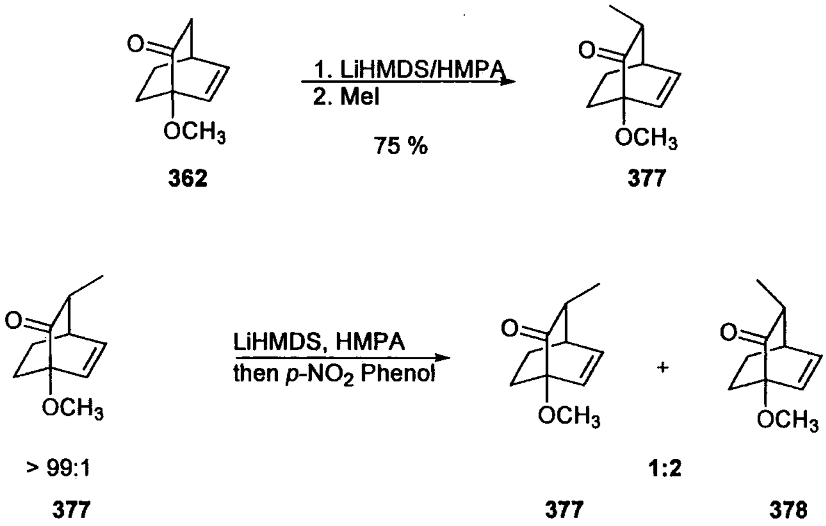


Figure 117

However, application of these optimised epimerisation conditions to the C12 ^{i}Pr **373** system gave no observed change in the *endo*:*exo* ratio by ^{1}H NMR spectroscopy, Figure 118. Further attempts to afford the desired change by kinetic and thermodynamic epimerisation by examining the base (LDA, KO^{t}Bu, NaH, KHMDS, LHMDS, DBU, NaOH) and proton donor (acetic acid, ^{i}PrOH, H$_2$O) also proved unsuccessful.

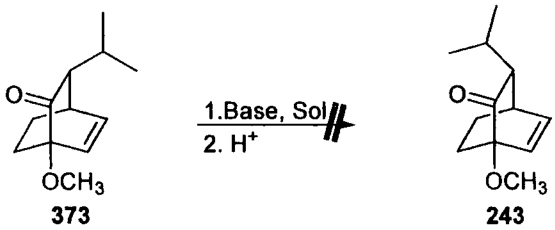
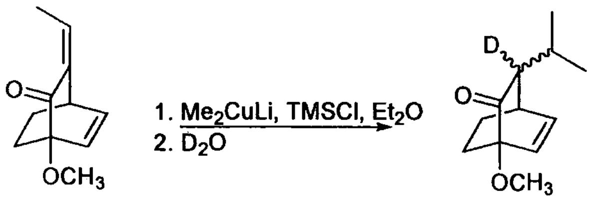


Figure 118

Attempts to alter the *endo*:*exo* ratio in our favour utilising kinetic or thermodynamic epimerisation were unsuccessful and it was hypothesised that the C12 *endo*-^{i}Pr ketone is the kinetic and thermodynamically most stable product. Undeterred by this initial set back, the possibility of intercepting the formation of the ^{i}Pr group at an earlier stage was investigated. The next section details the progress made in utilising cuprate addition as a method to yield the desired C12 *exo*-^{i}Pr ketone.

3.5 Investigations in Cuprate Addition

During cuprate addition to an α,β-unsaturated system an enolate is formed as an intermediate and we hypothesised that by changing the proton source and mode of quench, the *endo:exo* ratio could be altered in our favour. An initial reaction was carried out to test the aforementioned hypothesis and incorporation of deuterium would suggest that the enolate could be intercepted. Enone **367** was subjected to standard conjugate addition conditions and quenched with D_2O and deutero-ketone **379** was obtained and identified by the appearance of a singlet at 1.87 ppm in the ^{2}H NMR spectrum, Figure 119. With this promising result in hand we set about investigating what effect the proton source, mode of quench and temperature had on the *endo:exo* ratio obtained from the cuprate addition step.

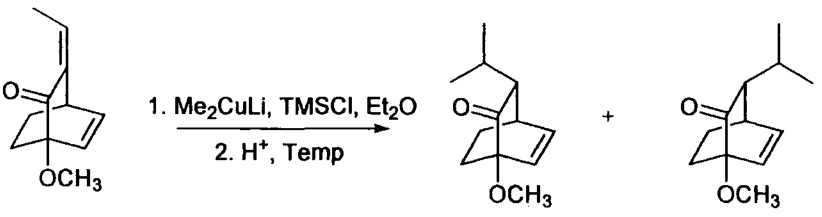


267 **379**

Figure 119

Enone **367** was treated under our standard cuprate addition conditions, Figure 120 and adding the yellow reaction mixture *via* cannula to the proton source, gave the ratios shown in Table 1. Entry 1 shows the result that was obtained when the reaction was quenched by pouring ammonium chloride into the reaction mixture. However, altering the proton donor to *p*-nitrophenol gave a complete reversal in the observed ratio. Disappointingly this result has been unreproducible to date and entry **4** shows that a ratio of 1:1 can now be routinely obtained. Also, the rate of addition of the enolate appears critical as pouring the reaction mixture into the proton source is detrimental to the quantity of the *exo*-isomer observed. Increasing the sterics around the proton donor (entry 11) appears to have little effect on the quantity of *exo*-isomer formed (*cf.* with NH_4Cl result, entry 1) and reaction temperature appears to have a less pronounced effect with the results obtained at 25 °C (entry 7) and -78 °C (entry 4) being very similar.

The optimisation of this reaction proved problematic with results proving unreproducible. However, alternative proton sources have enabled us to alter the *endo:exo* ratio from 100 % *endo* to 1:1 *endo:exo*. This ratio would give non-selective nucleophilic addition and thus not allow an efficient synthesis to be developed. There would be an opportunity to install the ^{i}Pr group later in the synthesis and thus the unsubstituted bicyclic ketone **362** was utilised to enable rapid continuation of the model synthesis.



exo endo

367 243 373

Figure 120

Table 1 - Effect of Proton Source on *Endo*:*Exo* Ratio obtained in Cuprate Addition

Entry	Temperature (°C)	Proton Source	*Endo*:*Exo* Ratio
1	-78	NH_4Cl	99:1[a]
2	-78	*p*-NO_2 Phenol	1:99[b]
3	-78	*p*-NO_2 Phenol	1:2[c]
4	-78	*p*-NO_2 Phenol	1:1[d]
5	-78	*p*-NO_2 Phenol	2:1[e]
6	-25	*p*-NO_2 Phenol	4:1
7	25	*p*-NO_2 Phenol	3:2
8	-78	Acetic Acid	4:1
9	-78	Benzoic Acid	9:1
10	-78	*p*-NO_2 Benzoic Acid	3:1
11	-78	di-tert-butylphenol	>15:1

Key : [a]standard conditions, [b]initial attempt, [c]second attempt, [d]mean of 5 attempts, [e]reaction mixture poured into proton source (instead of using cannula)

3.6 Summary of ^{i}Pr Ketone Synthesis

Direct addition of the ^{i}Pr group was not possible due to steric congestion and sequential attachment of the ^{i}Pr group by a linear sequence can be routinely carried out in good yields. However, the undesired stereochemistry was obtained and efforts to alter the ratio in our favour by epimerisation have been unsuccessful and we hypothesise that the *endo*-^{i}Pr ketone **373** is both the kinetic and thermodynamic product. Further attempts to obtain the *exo*-^{i}Pr by intercepting the enolate formed during the cuprate addition initially proved successful but this result has proved unreproducible. Further attempts to optimise this reaction by changing the proton source and temperature have proved disappointing.

3.7 Synthesis of the Carbocyclic Skeleton of Vinigrol

3.7.1 Introduction

The retrosynthetic strategy (Figure 110) shows that organometallic addition of diene fragment **180** to ketone **362** would give the desired precursor for the intramolecular Diels Alder reaction, Figure 121. However, previous attempts within the group to form the organometallic reagent of the diene fragment **180** resulted in Wurtz coupling and decomposition.[93(a)] Consequently, the diene must be sequentially built up as to avoid the difficulties associated with the direct attachment. To this end, it was envisaged that aldehyde **381** possessed the functionality required in order to build the diene rapidly by olefination techniques in few synthetic steps. The next section documents the work undertaken in the synthesis of the desired aldehyde **381**.

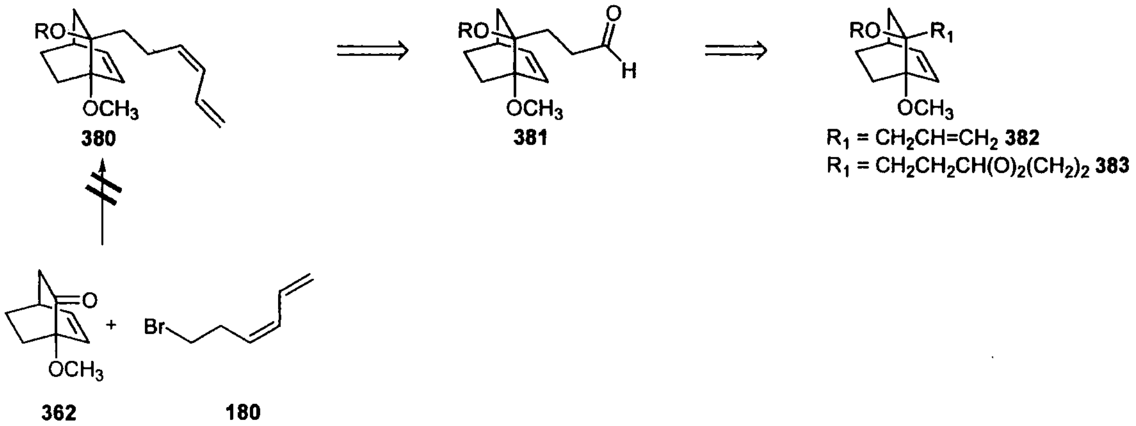
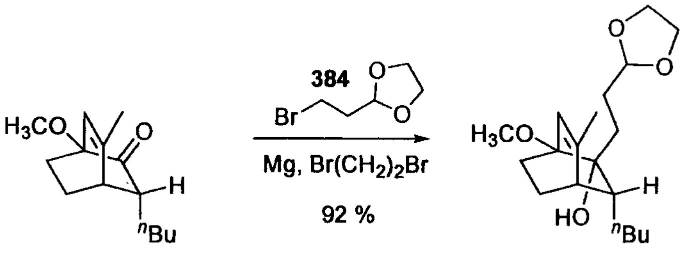


Figure 121

3.8 Aldehyde Synthesis

3.8.1 Dioxolane Attachment

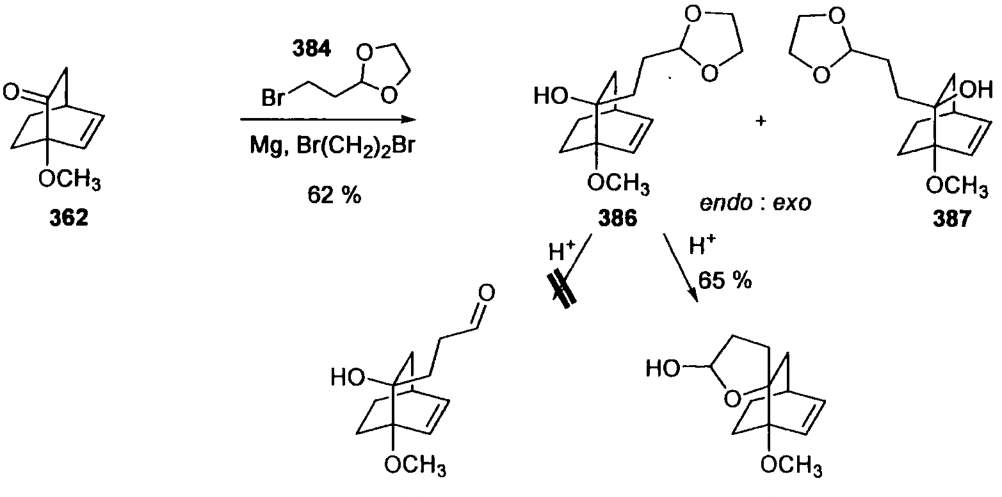
The dioxolane functionality allows aldehydes or ketones to be used directly in Grignard reactions only revealing the desired carbonyl group after hydrolysis. Kim *et al* utilised this approach in their synthesis of (±)-Perhydrohistrionicotoxin and, utilising Barbier type conditions, 2-(2-bromoethyl)-[1,3]dioxolane **384** was added in very good yield to the structurally related ketone **376**, Figure 122.[94]



376 **385**

Figure 122

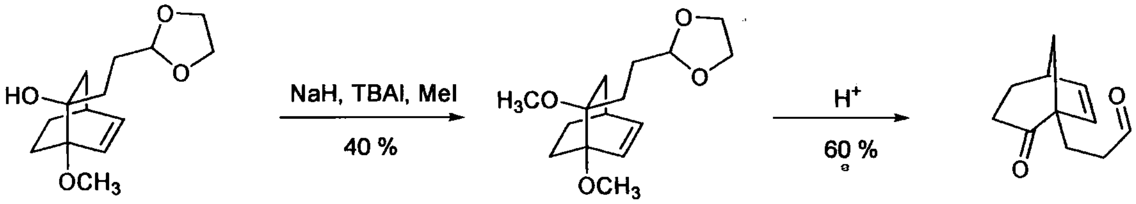
With significant quantities of the unsubstituted ketone **362** and the literature precedent in hand, an investigation of the direct attachment of the aldehyde side chain was initiated, Figure 123. Ketone **362** was treated under the conditions described by Kim *et al* and, following purification by column chromatography, to afford the desired protected aldehydes **386** and **387** in 62 % yield, as a 3:1 mixture of *endo:exo* isomers. The products were characterised by the loss of the carbonyl stretch (1712 cm^{-1}) and gain of OH (3200 cm^{-1}) stretches in the IR spectra. Aldehyde **388** was to be obtained upon acidic hydrolysis of *endo*-dioxolane **386**. However, attempts to carry out this transformation with various acid sources did not afford the aldehyde **388**. A single product was obtained from the reaction mixture and was identified as the unstable lactol **389** attached at the bridgehead position, Figure 123. Lactol **389** was characterised by the presence of a highly deshielded proton at 5.31 ppm in the ^{1}H NMR spectrum and the lack of a signal around 210 ppm for an aldehyde carbon in the ^{13}C NMR spectrum. It was hypothesised that under the acidic conditions the aldehyde is protonated and the hydroxyl group completes cyclisation to afford lactol **389**.



362 **386** **387** **388** **389**

Figure 123

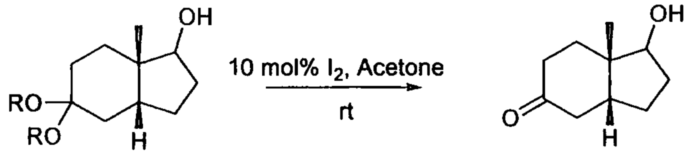
To this end, it was hypothesised that the nucleophilic hydroxyl group was preventing the isolation of the aldehyde and consequently alcohol **386** was protected as the methyl ether **390**, Figure 124. Dimethyl ether **390** was then subjected to acidic hydrolysis and a single product was also isolated from the reaction mixture. Subsequent spectroscopic analysis revealed that no methoxy signals were present in the ^{1}H NMR spectrum and it was hypothesised that the bicyclic intermediate **390** undergoes a pinacol rearrangement to afford aldehyde **391**. Aldehyde **391** was characterised by the appearance of two carbonyl signals at 202 and 210 ppm in the ^{13}C NMR spectrum and the aldehyde was confirmed by the presence of a one proton signal at 9.71 ppm in the ^{1}H NMR spectrum.



386 **390** **391**

Figure 124

Literature searches revealed that non-acidic methods could also be utilised to reveal the aldehyde functionality, thereby reducing the propensity of the intermediate to undergo rearrangement. Hu *et al* reported a highly chemoselective deprotection procedure of acetals and ketals catalysed by molecular iodine in acetone, which deprotects acyclic or cyclic acetals and ketals in excellent yields within a few minutes under neutral conditions, Figure 125.[95]

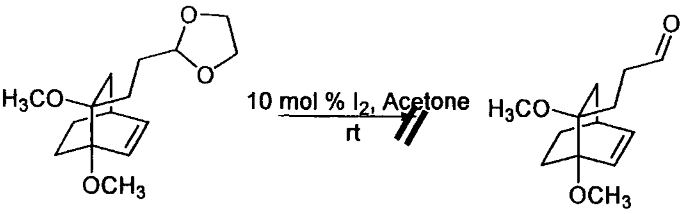


R = CH_3, 5 mins, 98 % **392**
R = $-CH_2CH_2-$, 45 mins, 98 % **393**

394

Figure 125

To this end dioxolane **390** was treated with catalytic iodine in acetone and NMR analysis after aqueous workup could not identify the desired aldehyde, Figure 126. Further examination of the NMR data revealed that the two methoxy groups were not present and the isolated product could not be identified on further spectroscopic analysis. In summary, the masked aldehyde strategy does not give the desired aldehyde to allow for subsequent functionalisation due to propensity of the bicyclic system to rearrange under acidic conditions. The following section will discuss another approach in the attempted synthesis of the carbocyclic skeleton.

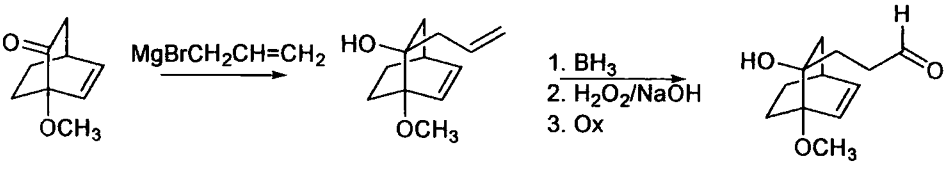


390 **395**

Figure 126

3.8.2 Allyl Group Attachment

The approach to introduce the aldehyde group directly was unsuccessful and a further strategy was necessary to enable sequential diene synthesis, Figure 127. It was envisaged that incorporation of an allyl side chain would allow the synthesis of the desired tethered aldehyde by robust synthetic techniques, Figure 127. Selective hydroboration of the terminal double bond and subsequent oxidation would allow the aldehyde to be introduced under non-acidic conditions thereby reducing the tendency of the [2.2.2] system to undergo rearrangement, Figure 127.



362 **396** **388**

Figure 127

Addition of allylmagnesium bromide to ketone **362** yielded the individual isomers **396** and **397** in a 45:55 *endo:exo* ratio after chromatography and were identified by NOESY ^1H NMR spectroscopy, Figure 128. At this point it was decided to accept the low selectivity and verify the intramolecular Diels Alder approach. If this proved successful the addition would be revisited for optimisation.

The *endo* alcohol **396** was then protected as the methyl ether by treating with methyl iodide/sodium hydride to inhibit lactol formation when the aldehyde functionality was installed later in the synthesis, Figure 128.

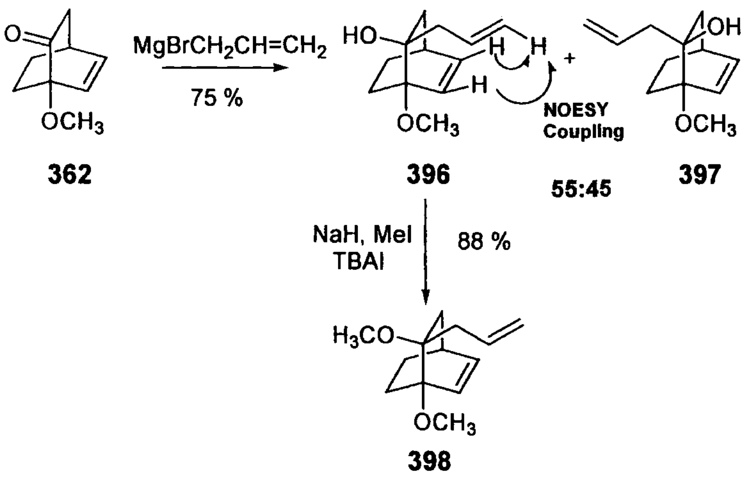


Figure 128

Dimethyl ether **398** was then treated with 0.5 equivalents of borane and subsequent oxidative work-up gave the desired primary alcohol **399** selectively in excellent yield, Figure 129. No evidence of hydroboration products relating to the oxidation of the bicyclic double bond could be identified by ^1H NMR spectroscopy and bulky borane reagents did not need to be utilised. Alcohol **399** was characterised by the appearance of a CH_2O signal at 3.61-3.64 ppm in the ^1H NMR spectrum and was oxidised utilising traditional Swern conditions[96] to produce the desired aldehyde **395**. Aldehyde **395** was identified by the appearance of a carbonyl stretch in the IR spectrum at 1723 cm^{-1} and a further single proton signal at 9.79 ppm in the ^1H NMR spectrum.

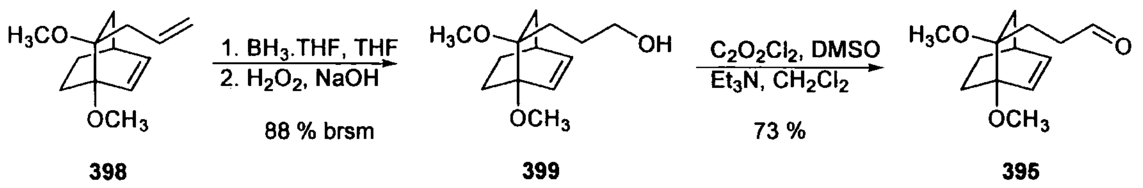
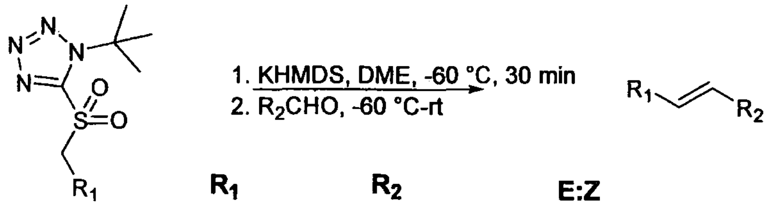


Figure 129

The desired aldehyde had been obtained and strategies towards selectively producing the Z,E diene had to be investigated. The proceeding section discusses methods towards this transformation.

3.9 Z,E Diene Synthesis

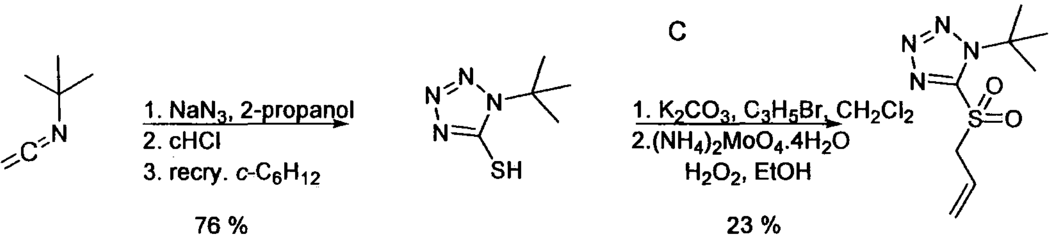
Successful synthesis of the tethered aldehyde **395** had been completed and the intermediate was at the correct oxidation level to be converted easily into the required *cis*-diene by olefination techniques, Figure 130. Many techniques are available for the synthesis of conjugated dienes including Wittig[97], Peterson[98] and Julia[99] olefinations. Wittig reactions, even under salt-free conditions, often yield poor Z,E ratios of conjugated dienes. Kocienski *et al*[100] has reported that modified Julia reagents, 1-tert-butyl-1H-tetrazol-5-yl sulfones, gave excellent Z selectivities when stabilised by allylic or benzylic conjugation, Figure 130.



R$_1$	R$_2$	E:Z
n-C_4H_9	*c*-C_6H_{11}	89:11
n-C_4H_9	Ph	79:21
Ph	*n*-C_9H_{19}	>1:99
$H_2C{=}CH$	*n*-C_9H_{19}	4:96

Figure 130

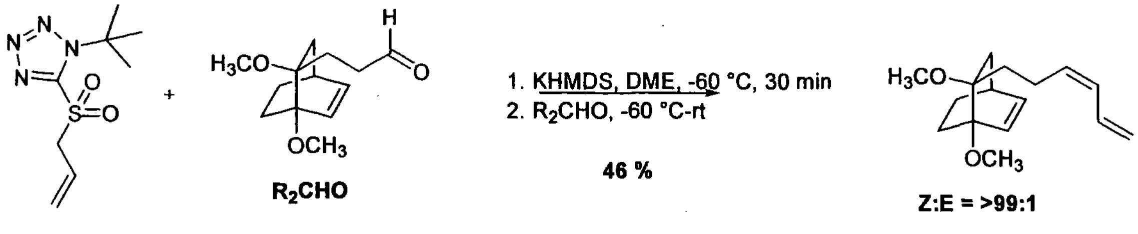
To this end, the Julia reagent 1-tert-Butyl-5-(prop-2-ene-1-sulfonyl)-1H-tetrazole **402** was prepared in 5 steps from ^{t}butylisothiocyanate **400**, Figure 131, following the procedure of Quast and Bieber.[101]



400 **401** **402**

Figure 131

With the Julia reagent **402** and aldehyde **395** in hand, the Julia olefination reaction was initiated, utilising the procedure of Kocienski *et al*, Figure 132. Pleasingly the tethered diene **403** was obtained as a single geometrical isomer after chromatography in a moderate 46 % yield, which was comparable to the literature results obtained on less complex aldehydes[100], Figure 130. The Z,E diene was characterised by the appearance of a further 5 olefinic protons at 4.99, 5.08, 5.36, 5.88 and 6.55 ppm in the ^{1}H NMR spectrum and a J = 6 Hz coupling constant in the ^{1}H NMR spectrum was observed which confirmed the desired *cis*-double bond had been obtained.



402 395 403

Figure 132

The modified Julia reaction had provided the desired Z,E diene in >99:1 selectivity and the key reaction, intramolecular Diels Alder reaction (IMDA), within the retrosynthetic analysis could now be investigated, Figure 133. However, the use of Z,E dienes have only rarely been utilised in organic synthesis to date and the next section gives a brief review of these dienes in IMDA reactions and their associated advantages and disadvantages.

404 405

Figure 133

3.10 Intramolecular Diels Alder reactions with Z,E Dienes

3.10.1 Introduction

The intramolecular Diels Alder reactions of E-dienes are valuable and often used strategies in organic synthesis. A limitation with the E-diene is however, that they possess two relatively accessible transition states (*endo*, *exo*) which in many instances can afford mixtures of *cis*- and *trans*-fused products, Figure 134.[102]

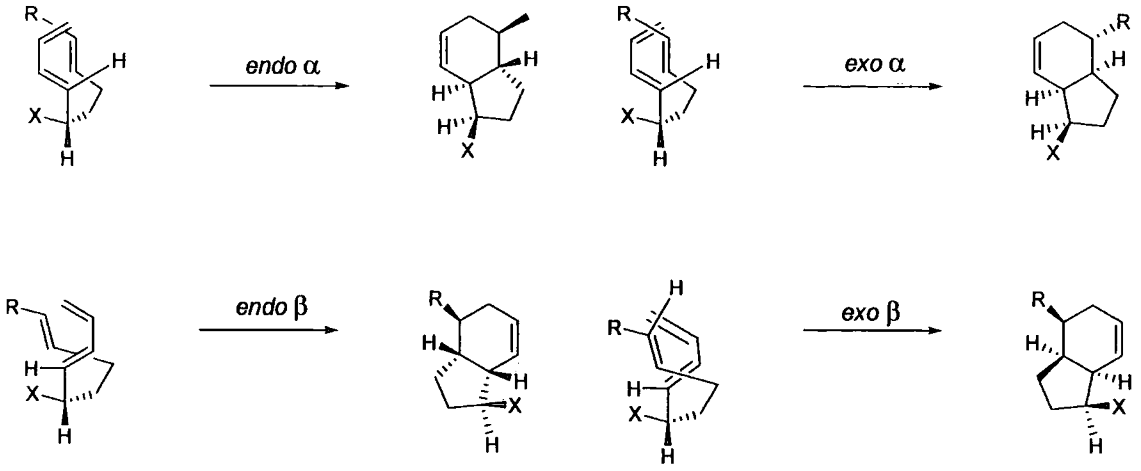


Figure 134

Dienes of Z-configuration lend themselves more readily to predictions about product stereochemistry since the geometry allows attainment of a single transition state, Figure 135. It is possible, however, that the strategy of utilising the Z-diene for total stereocontrol could be limited since side reactions such as 1,5 hydrogen migrations can give an isomeric diene before the cycloaddition has occurred.[103]

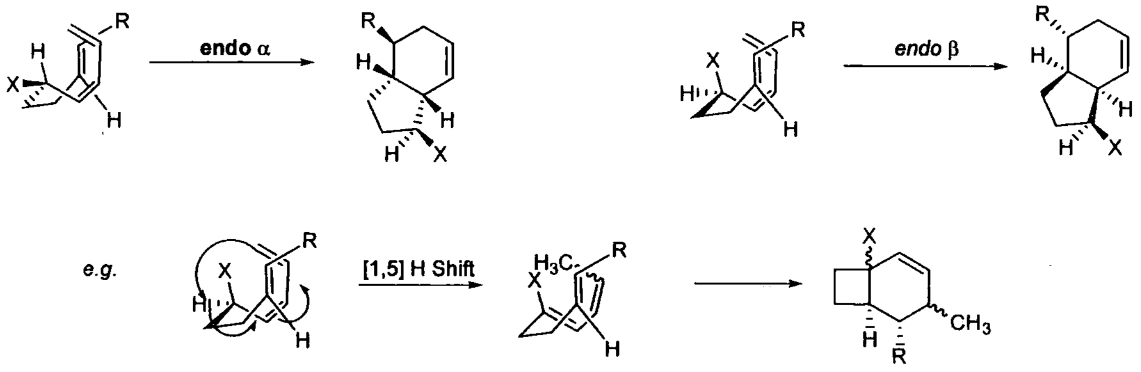


Figure 135

Whilst many examples of intramolecular Diels Alder cycloaddition are found in synthesis, relatively few examples exist of intramolecular Diels Alder reactions utilising a Z-diene. In a recent review of IMDA reactions in natural product synthesis only 3 from 48 reported utilised a Z-diene as a key reaction directly in the synthesis or a route to a key intermediate.[104]

3.11 E,Z dienes in IMDA

3.11.1 Applications in Synthesis - Hydroisoquinolines

The first general method for the construction of *cis*-fused hydroisoquinolines with complete stereocontrol *via* an intramolecular Diels Alder reaction was reported by Wattanasia *et al* only in 1985.[105]

During their synthetic investigations involving the synthesis of structural modifications of the naturally occurring fungal metabolites Compactin **408a** (R=H) and Mevinolin **408b** ($R=CH_3$), they identified **407** as a key intermediate, Figure 136. Complete stereocontrol by the use of an intramolecular Diels Alder reaction utilising a Z-diene was envisaged. To this end, triene **406** was identified as the IMDA precursor and the synthesis was completed utilising literature methods, Figure 136.

Triene **406** was heated to 160 °C (sealed tube for 48 h) and this afforded the desired *cis*-cycloadduct **407** as a single stereoisomer in 71 % yield, Figure 136. Cyclisation of the Z-diene occurs with complete stereoselectivity through the expected single transition state, Figure 136. Also [1,5]-hydrogen shifts, which would result in the loss of geometric integrity of the diene, apparently do not present a limitation for this unactivated system.

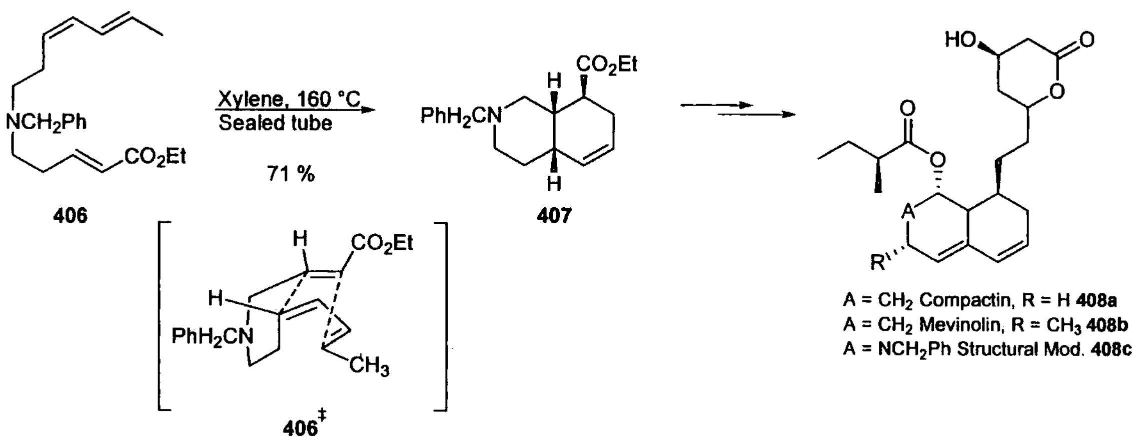


Figure 136

3.11.2 Applications in Synthesis - Castasterone

Uguen *et al* successfully utilised high-temperature cyclisation techniques to afford the *cis*-decalin of Castasterone **409** using an E,Z diene in good yields, Figure 137.[106]

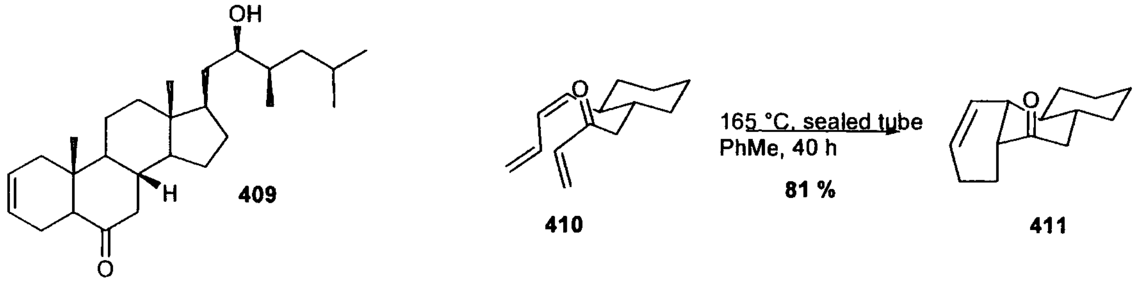


Figure 137

3.11.3 Control of Fused Ring Stereochemistry

Back *et al* also demonstrated that Z-dienes can be used in more complex natural product synthesis. During the total synthesis of (+/-)-Bakkenolide A **412**, the stereochemistry of the hydrindane ring system (*cis*- v *trans*-fused) was controlled by appropriate choice of E- or Z-geometry of the diene fragment, Figure 138.[107]

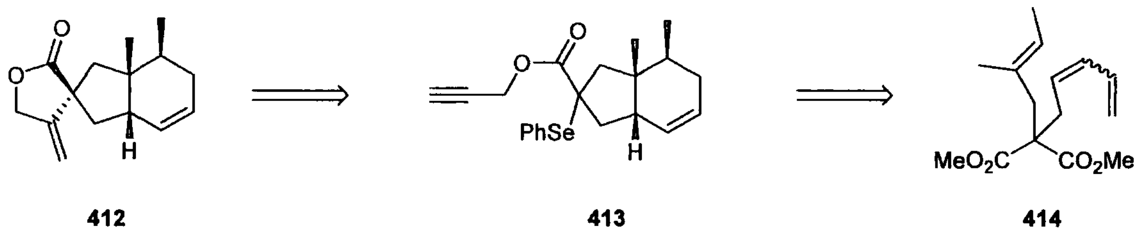


Figure 138

Previous studies of IMDA reactions of other 1,3,8-nonatrienes have revealed that compounds containing a (3Z)-diene moiety favour the formation of cis-hydrindanes, whereas the corresponding (3E)-dienes afforded poorer stereoselectivity favouring the trans-fused cycloadducts, Figure 139.

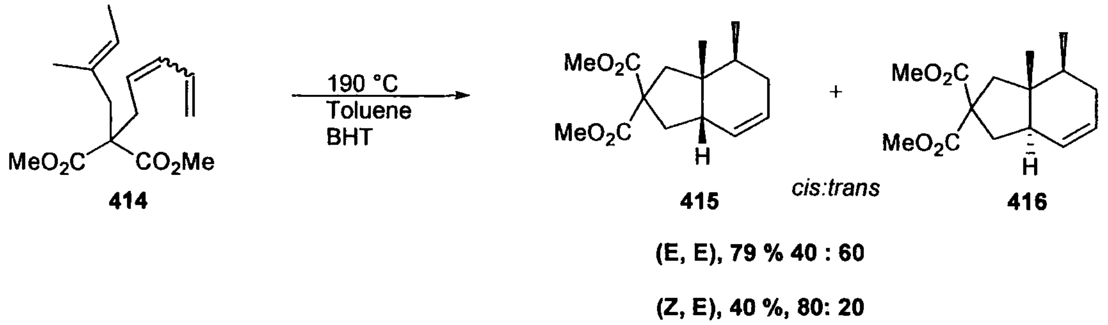


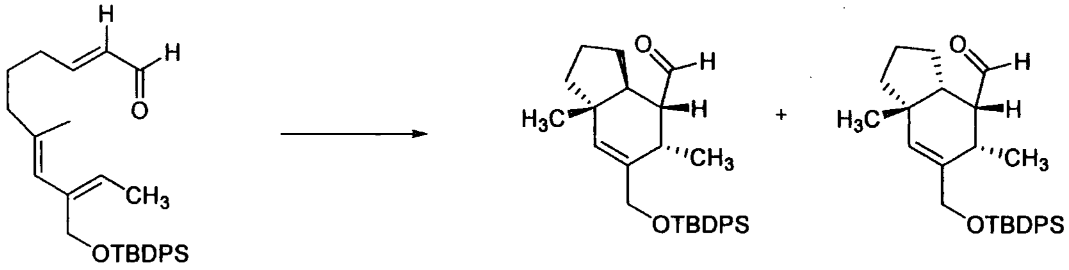
Figure 139

The mixture of cyclodducts were separated by reverse phase HPLC and the (+/-)-Bakkenolide A and its C-7, C-10 and C-7, C-10 epimers were completed after considerable experimentation.

3.11.4 Lewis-acid-catalysed IMDA

The use of acyclic Z-1,3-dienes or dienes with Z-substituents as substrates for IMDA cycloadditions has been limited due to their substantially diminished reactivity and propensity for olefin isomerisation under thermal conditions. However, the use of Lewis acid catalysts to circumvent the harsh conditions required for the thermal IMDA reactions of acyclic dienes with Z-dienes has largely been restricted to Type II IMDA cyclisations in the taxoid series.[108]

However, methodology by Roush *et al* has recently shown that Type I IMDA reactions can also utilise Lewis acids to circumvent the problems associated with thermal reaction conditions.[108] Triene **417** was subjected to both Lewis acid catalysis and traditional thermal techniques and the catalysed reaction gave both an excellent yield and stereoselectivity at low temperature, Figure 140. The Lewis acid catalysis also decreases the reaction time.



417 **418** **419**

A. 0.4 eq. $MeAlCl_2$, -78 °C-25 °C, 2 h, 62 % 99 : 1
B. 184 °C, PhMe, sealed tube, 45 h, 23 % 37 : 63

Figure 140

Activated triene **417** with 1,1,4-trisubstitution patterns in the diene unit can undergo efficient and highly stereoselective Lewis-acid-catalysed IMDA reactions in the presence of catalytic quantities of Lewis acids at low temperatures.

3.12 IMDA Conclusions

IMDA reactions of Z,E dienes can allow good predictions regarding fused ring junction stereochemistry and thus can be a key reaction in organic synthesis. The cycloadditions described above demonstrate the utility of Z-dienes in IMDA cycloadditions and Z-dienes can be used to give superior *cis*-fused yields of products as key intermediates in synthesis. The use of Lewis acids for these cycloadditions has recently been developed and can allow reduced reaction temperatures and times.

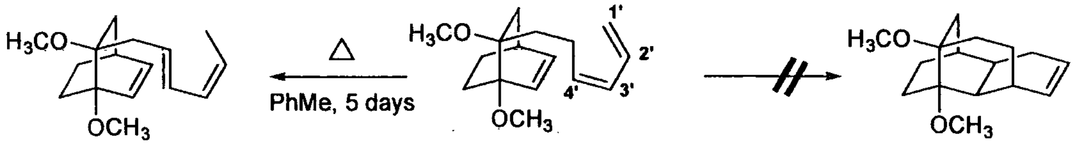
3.13 IMDA of Z,E dienes : Applications towards the Carbocyclic skeleton of Vinigrol

3.13.1 Introduction

The IMDA precursor **403** had been successfully prepared and methods of intramolecular ring closure to give the tricyclic structure **421** were investigated. The diene and dienophile contained within substrate **403** are relatively unactivated and factors such as temperature and pressure were important reaction variables which required consideration.

3.13.2 Thermal Closure

The thermal reaction was initially examined. IMDA substrate **403** was heated in toluene at reflux and was monitored by ^{1}H NMR spectroscopy. After 5 days, full consumption of the starting material was observed. However on examination of spectroscopic data, the desired product had not been formed and isomerisation of the double bond had occurred *via* a [1,5] hydrogen shift to give diene **420** with an internal double bond, Figure 141. Diene **420** was identified by the appearance of a [3H] multiplet at 1.73 ppm in the ^{1}H NMR spectrum for the vinylic methyl group and loss of the protons 1'-H$_2$ at 5.01 and 5.08.

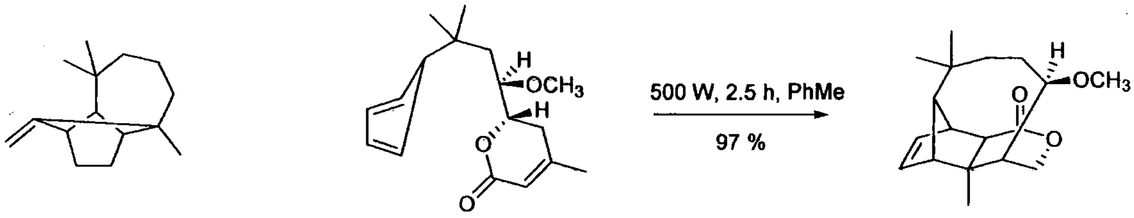


420 **403** **421**

Figure 141

3.13.3 Microwave Closure

Following the failure of standard thermal conditions, it was evident that another approach would have to be explored. Microwave reactors can cause superheating of organic liquids allowing higher temperatures and shorter reaction times to be obtained and may reduce the propensity of the system to undergo [H]-shifts.[109] Lei and Fallis[110] utilised microwave irradiation in the total synthesis of longifolene **422** to induce an IMDA cycloaddition, Figure 142.



422 **423** **424**

Figure 142

With this literature precedent in hand, this method for inducing the ring closure was examined. Substrate **403** was heated for 1, 3, and 5 hours at 150 °C under 5 psi pressure and subsequent analysis by NMR spectroscopy revealed no reaction had taken place with only starting material being recovered, Figure 143. Unfortunately, the IMDA substrate **403** proved to be unreactive to ring closure by this method.

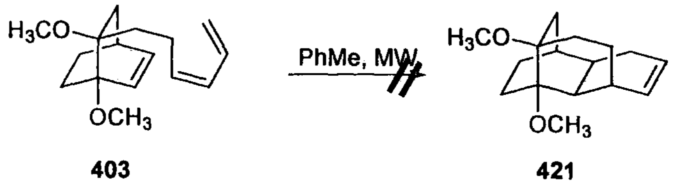


Figure 143

3.13.4 Carius Tube Closure

Undeterred by the apparent unreactivity of the Diels Alder precursor towards microwaves, the behaviour of substrate **403** was further investigated in a Carius oven where high temperatures in sealed tubes can be maintained. However, under various conditions this method also proved unsuccessful to induce the IMDA reaction on substrate **403**, Figure 144.

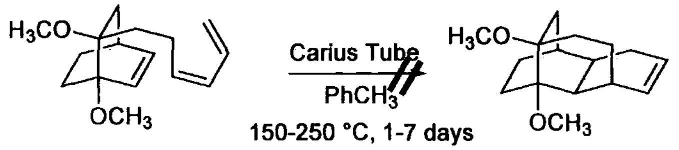


Figure 144

The cause for the unreactivity of the IMDA intermediate **403** is unclear at this point. However, the substrate **403** can be structurally modified to allow an activated intramolecular dienophile to be prepared, Figure 145. This would allow for the use of Lewis acids to aid ring closure at lower temperatures to be investigated.

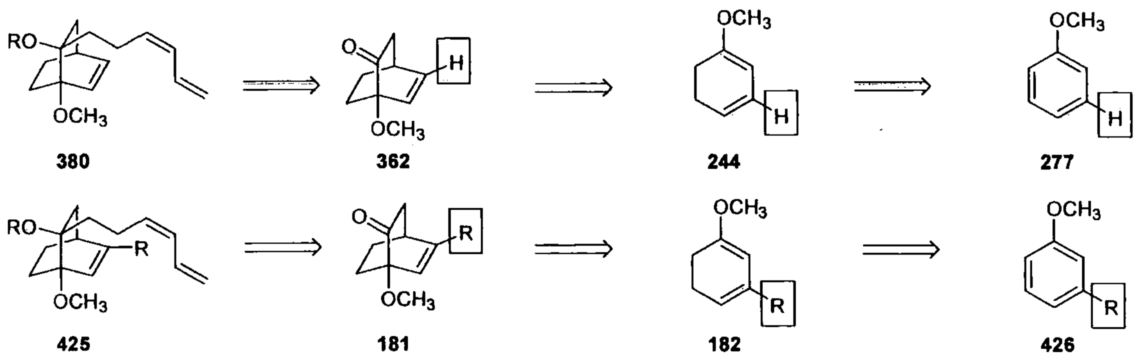


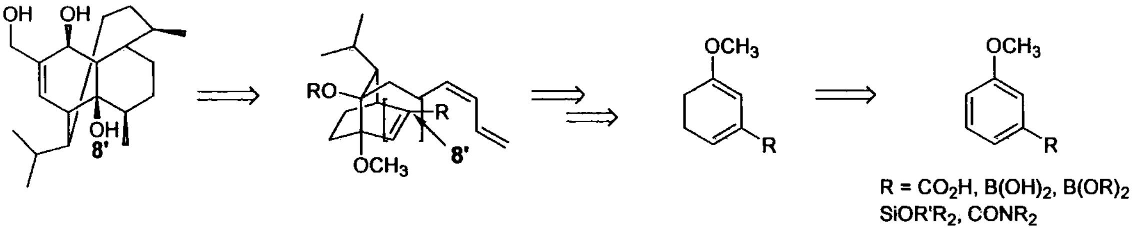
Figure 145

3.14 Approaches to C8′ OH

3.14.1 Introduction and Strategy

Vinigrol can be derived from a suitably substituted diene **182** and a ketene equivalent from our retrosynthetic analysis, Figure 146. The studies undertaken to date have utilised model substrates where C8′, R = H, however in Vinigrol, R = OH. In our synthetic scheme the role of the group on C8′ would be two-fold. Firstly it must be a group that can be converted to an OH group later in the synthetic scheme and, secondly it must be electron-withdrawing, as it becomes the dienophile in the intramolecular Diels Alder reaction.

Consequently, we require 3-(EWG)-1-methoxy-cyclohexa-1,3-dienes, which can be synthesised from the Birch reduction of *m*-functionalised anisoles **426**. This section details the work carried out in this area.



1 **427** **182** **426a,b,c,d,e,f**

Figure 146

3.15 Birch Reduction Methodology

3.15.1 Introduction

From our retrosynthetic analysis, Figure 53 (Page 29), we require appropriately functionalised cyclic dienes and, since these are not commercially available, methods towards their synthesis had to be investigated. To this end, Birch reductions of aromatic compounds have been well documented and utilised in organic synthesis for the production of dienes, Figure 147.[111]

277 **278** **428** **429**

Figure 147

This synthetic precedence would allow the investigation of the functional group tolerance towards dissolving metal reduction and subsequently identify groups which would allow appropriately functionalised dienes to be produced for use in our synthesis. Thus, we identified that ester, boronic acid (ester) and silyl functional groups possessed the properties that we required.

3.15.2 Reduction of *m*-substituted anisoles

Silverstein and Webster in synthetic approaches towards the pheromone grandisol required large quantities of 3-oxo-1-cyclohexenecarboxylic acid methyl ester **430**, which is obtained from Birch reduction of *m*-anisic acid, Figure 148.[112] The diene **431** required in our synthesis is formed as a precursor in the synthesis of this key intermediate.

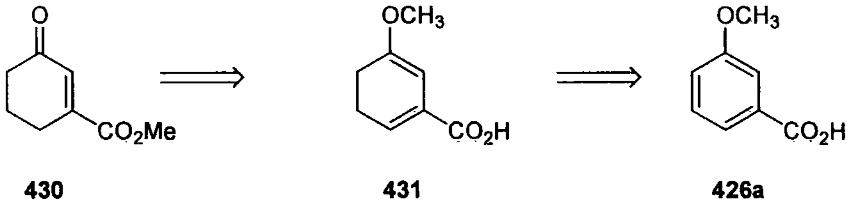


Figure 148

To this end, *m*-anisic acid was treated under the Birch reduction conditions described by Silverstein and Webster and afforded the unconjugated 2,5 diene **432**. Diene **432** was then treated with base to induce isomerisation to the desired conjugated diene **431**. After careful adjustment of the pH (approx 5) with concentrated HCl, 1,3 diene **431** was isolated in yields comparable to those reported, Figure 149. To aid purification at the cycloaddition stage diene **431** was subjected to standard methylation protocols. However, all attempts (diazomethane, methyl sulfate, MeI/Base) to afford this transformation have been unsuccessful and it is unclear why acid **431** is unreactive towards methylation, Figure 149.

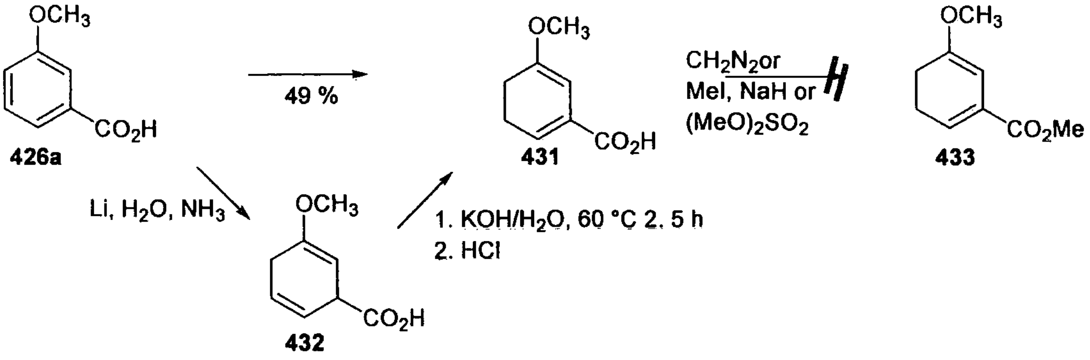


Figure 149

Attempts to carry out a Birch reduction on boronic acid (ester) and silyl dervatives also proved problematic, Figure 150. The incompatibility of the functional groups towards dissolving metal reduction was attributed to inability to form stable silyl and boronic acid derived dienes.

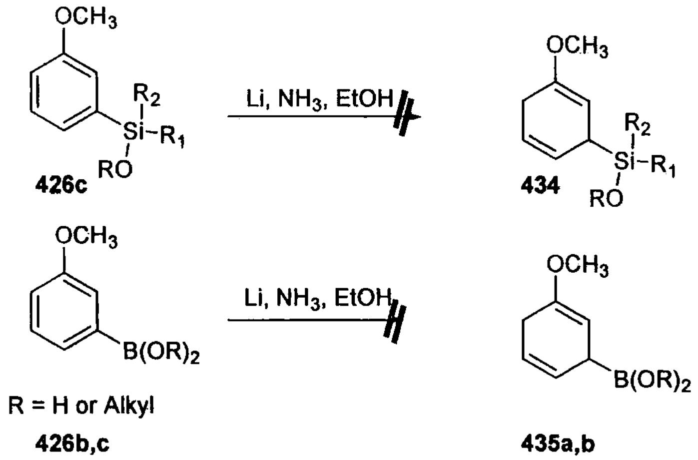


Figure 150

As discussed, the desired boronic acid/ester, silyl and carboxylic acid functionalities proved problematic when subjected to Birch reduction conditions, so focus turned towards the tertiary amide functional group. It was hypothesised that this group would be more robust and stable to dissolving metal reduction. Also, this group can undergo conversion to an aldehyde, which has the desired pre-requisites required for the *meta*-group. It is electron withdrawing and can undergo a Baeyer-Villiger type oxidation and subsequent hydrolysis to furnish the desired OH, Figure 151.

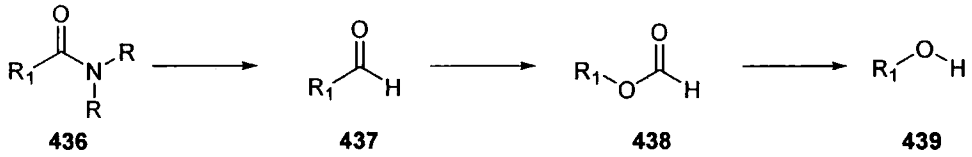


Figure 151

3.15.3 Tertiary Amide Synthesis

To enable the investigations into the tolerance of the tertiary amide derivatives towards Birch reduction to begin, synthesis of the required tertiary amide had to be initiated. Treatment of *m*-anisic with oxalyl chloride in the presence of catalytic dimethylformamide produced acid chloride **440** which was identified by the strong signal at 1790 cm^{-1} in the IR spectrum, Figure 152. Subsequent treatment of acid chloride **440** with excess diethylamine provided tertiary diethylamide derivative **441** in excellent yields and was characterised by the appearance of the [6H] multiplet at 1.13 ppm and [4H] multiplet at 3.28 ppm in ^{1}H NMR spectrum corresponding to the alkyl amide groups, Figure 152.

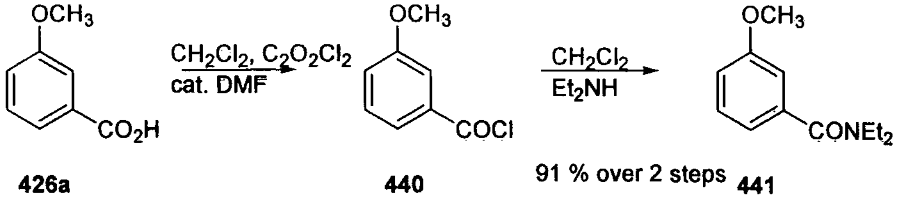


Figure 152

The Birch reduction of 3-methoxy benzamide **442** had been shown to proceed in moderate yields, Figure 153 and with this literature precedence in hand the dissolving metal reduction of tertiary amide **441** was examined, Figure 153.[113]

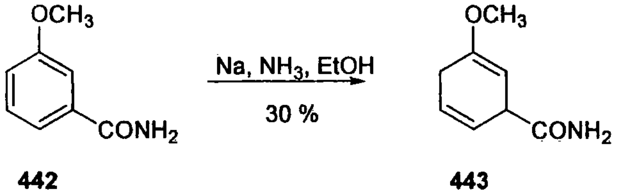


Figure 153

Numerous attempts to utilise ethanol as the proton source in the Birch reduction proved unsuccessful and gave incomplete reduction in all cases, Figure 154. Literature searches revealed that ^{t}butanol had also been utilised as a less acidic alternative to ethanol. Thus, the Birch reduction was attempted using ^{t}butanol and pleasingly diene **444** was obtained as a single product, Figure 154. Diene **444** was characterised by the loss of aromatic protons in the ^{1}H NMR spectrum at 7.3 ppm and appearance of alkyl protons at 2.24-2.31 ppm.

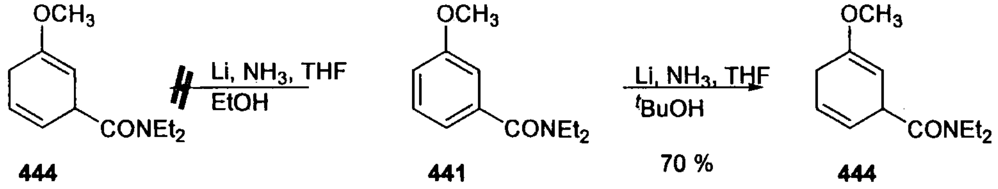


Figure 154

Following the successful diene formation, the required Diels Alder reaction with chloroacrylonitrile **369** was then attempted, Figure 155. It was expected that the diene would isomerise under the reaction conditions to give the conjugated 1,3 diene as before, Figure 114, Page 65. However, the sole product isolated from the reaction was not the desired bicyclic **446**. Examination of ^{1}H NMR and mass spectroscopic data suggested that the diene had undergone an undesired isomerisation to give diene **445**, Figure 155. The ^{1}H NMR data showed that three olefinic protons were still present at 4.87, 5.13, 5.43 ppm instead of only one required for the cycloaddition product **446** and they possessed greatly different chemical shifts from the starting diene (4.53, 5.59, 5.79

ppm). Also the mass data (ES+ = 210) was consistent with no observed incorporation of chloroacrylonitrile. The resultant diene is electron poor and this explains why the cycloaddition fails to be observed.

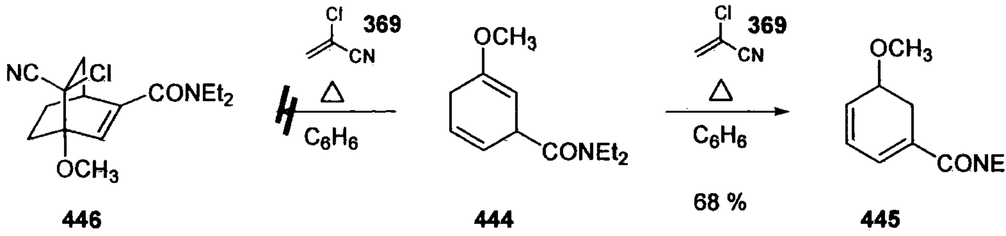
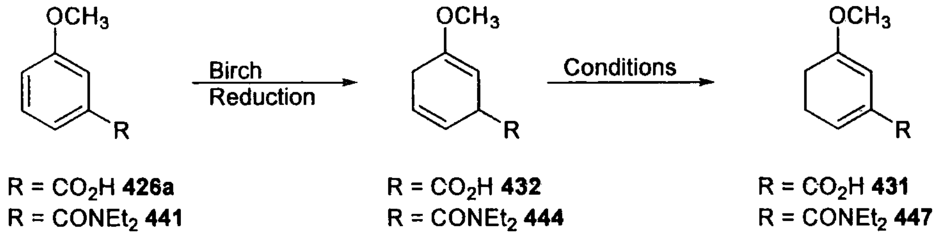


Figure 155

Undeterred by this setback, we utilised experience gained from the synthesis of the diene **431**, Figure 149, Page 81. The product of the Birch reduction of *m*-anisic acid was the unconjugated diene **432** and subsequent base-induced isomerisation gave the desired conjugated diene **431** in good yields, Figure 149. Thus, utilising the literature conditions of heating the 2,5-diene **444** in 1M KOH at 60 °C for 1 hour resulted in only 10 % conversion by ^{1}H NMR spectroscopy, Figure 156. Optimisation of these conditions was clearly required and after considerable experimentation, the temperature (reflux) and time (20 hours) were adjusted and desired diene **447** was obtained in a reasonable 64 % yield. Conjugated diene **447** was characterised by the reduction of the number of olefinic protons from [3H] to [2H] in the ^{1}H NMR spectrum. Also on scale-up of the isomerisation, the reaction time increased considerably to 4 days for 5 g of diene and to allow for a rapid accumulation of diene **447** the isomerisation conditions were optimised further. Thus, utilising microwave heating allowed the reduction of the reaction time to 45 minutes with a slight increase in yield obtained, Figure 156. Thus, with a rapid, reproducible and reliable method to afford the desired diene **447**, its behaviour in the Diels Alder cycloaddition was investigated.

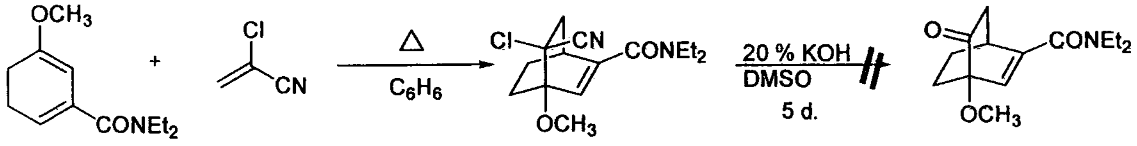


1. 1 M KOH, 60 °C, 1 h, R = CO_2H, 49 %
2. 1 M KOH, 60 °C, 1 h, R = $CONEt_2$, 10 % conv.
3. 2 M KOH, 100 °C, 20 h, R = $CONEt_2$, 63 %
4. 2 M KOH/THF, MW, 45 min, R = $CONEt_2$, 75 %

Figure 156

3.16 Attempted Synthesis of Substituted Ketone 448

Diene **447** and dienophile **369** were subjected to our standard cycloaddition conditions (Figure 114), Figure 157. Removal of the solvent and subsequent chromatography yielded the desired cycloadduct **446,** Figure 157. Cycloadduct **446** was characterised by the presence of a single proton in the ^{1}H NMR spectrum at 6.18 ppm, also demonstrating that a single regioisomer had been obtained. The cycloadduct **446** was then hydrolysed in 20 % aqueous KOH/DMSO for 5 days, however on work-up ketone **448** was not obtained, Figure 157. A further attempt was also unsuccessful and the hydrolysis conditions were clearly causing decomposition of chloronitrile **446** at this stage. However, attempts to reduce the hydrolysis time also proved unsuccessful and this caused a re-evaluation of the ketene equivalent.

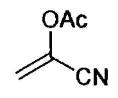


447 **369** **446** **448**

Figure 157

3.16.1 Other Ketene Equivalents

Optimisation of this synthetic route was examined, and investigations began to identify the variables which would allow a rapid solution to be given. Firstly, the prolonged hydrolysis time was identified as a major problem; 7-10 days was almost certainly causing amide decomposition. Thus, the investigation of identifying different ketene equivalents was initiated. A recent review of the uses of ketene equivalents in organic synthesis gave a wide range of different substrates which could be investigated.[114] However, a large number of these are not commercially available and require multistep synthesis, Figure 158. Surprisingly, 2-cyanovinyl acetate **449**, the first reported ketene equivalent was commercially available and was known to require significantly shorter hydrolysis conditions following cycloaddition, Figure 158.



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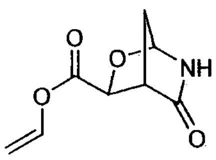

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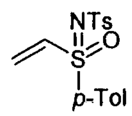

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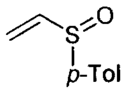

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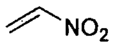


453

Figure 158

2-cyanovinyl acetate **449** was used in the synthesis of a range of 16-functionalised 14α 17α-ethano-19-norsteroids **456.**[115] Cycloaddition and alkaline hydrolysis over 24 h gave the desired products in excellent yields, Figure 159.

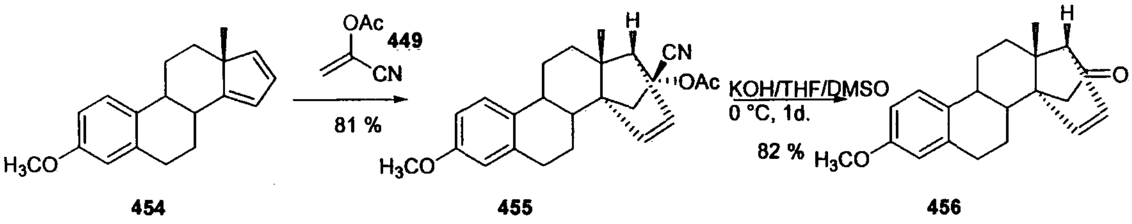


Figure 159

The literature also suggested that the 2-cyanovinyl acetate should behave similarly to 2-chloroacrylonitrile as a dienophile. However, it was less reactive and required higher reaction temperatures and prolonged reaction times.

3.16.2 Synthesis of Diethylamide Substituted Ketone 448

With significant quantities of diene **447** available, the cycloaddition with ketene equivalent **449** was investigated. Diethylamide diene **447** was added to a solution of ketene equivalent **449** in toluene and heated for 4 days, Figure 160. Subsequent work-up and column chromatography yielded the required cycloadduct **457**. Cyanoacetate **457** was characterised by the appearance of [3H] singlet at ~ 2.00 ppm in the ^{1}H NMR corresponding to the acetate group and correct mass data (MH^+ = 320). Subsequent alkaline hydrolysis of the cyanoacetate **457** over 24 hours afforded ketone **448**, identified by loss of the acetate [3H] singlet from the ^{1}H NMR spectrum.

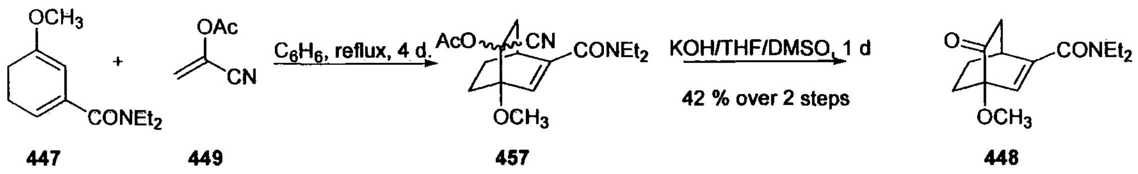


Figure 160

Hence a robust route had been identified to afford the required substituted [2.2.2] bicyclic ketone **448**, but further optimisation was still required. The initial cycloaddition took 4-5 days and this was stalling investigations into the synthesis of the required Diels Alder precursor. Therefore, it was investigated how the initial cycloaddition would behave under microwave heating. 2-cyanovinyl acetate **449** and diene **447** in toluene were sealed in a microwave tube and heated at 150 °C for 105 minutes. Subsequent solvent removal and column chromatography gave the desired adduct **457**, considerably reducing the reaction time (Table 2) but disappointingly giving no increase in isolated yield in comparison to the thermal route. Hydrolysis was carried out using the same conditions as previously described.

Table 2 - Optimisation Results for Synthesis of 448

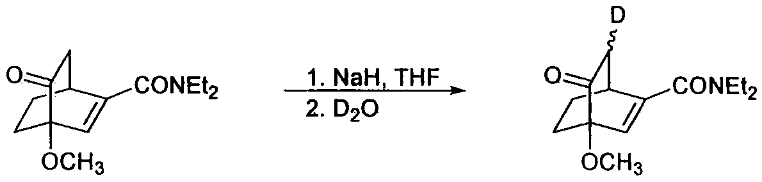
Conditions	*Cycloaddition, h*	*Yield, %*
Thermal (Reflux)	120	57
MW	1.75	50

With optimisation of the route to the starting material complete, significant quantities of ketone **448** were amassed to allow further functionalisation. Installation of the ^{i}Pr group at this point would allow the control of nucleophilic addition over the double bond and allow the use of the methodology previously discussed. The next sections describe in detail the synthetic efforts in these areas.

3.17 C12 ^{i}Pr Synthesis : Substituted Ketone

Direct attachment of the ^{i}Pr group was not possible due to steric hindrance and thus had to be introduced sequentially, Figure 149. With this in mind we were required to metallate C12 and utilised the experience gained with the unsubstituted bicyclic ketone system **362**.

Thus, treating ketone **448** with sodium hydride and quenching the resultant anion with D_2O, we were pleased to find after work-up and column chromatography that the desired deuterated ketone **458** was obtained and could be identified by the presence of a singlet at 2.43 ppm in the ^{2}H NMR spectrum, Figure 161.



448 **458**

Figure 161

Thus, with this result, we were confident that ketone **448** could be manipulated to give the desired C12-substituted ketone by the method described previously, Figure 115, Page 66. To this end ketone **448** was treated under our standard aldol conditions. However analysis by LC-MS showed that no reaction had occurred, Figure 162. Undeterred by this disappointing result, we investigated a range of bases, temperature and additives, however none of these allowed the isolation of the desired aldol adduct

460, Figure 162. Similarly, attempted alkylation at the C12 position was also unsuccessful, Figure 162. At this time it is unclear why ketone **448** will not undergo substitution at C12 with anything larger than deuterium.

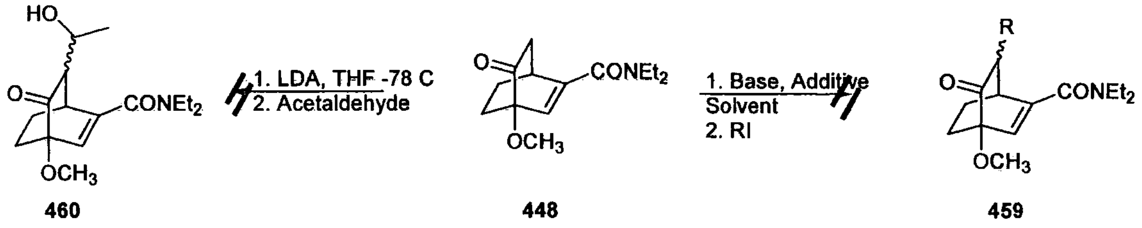


Figure 162

With the disappointing metallation results in hand we turned our focus towards the synthesis of the IMDA precursor. This intermediate would allow us to test the initial hypothesis involving our key intramolecular Diels Alder reaction with a more activated dienophile present. The next section describes in detail the efforts made in this area.

3.18 Synthesis of the Z,E diene : Substituted Ketone

Synthesis of IMDA precursor **403** in the unsubstituted ketone series has previously been described (Figure 128) and ketone **448** was subjected to identical conditions, Figure 163. Thus, nucleophilic addition to ketone **448** with allylmagnesium bromide and subsequent chromatography afforded an inseparable *endo:exo* (1:2) mixture of alcohols **461/462** identified by the OH stretch at 3200-3623 cm^{-1} in the IR spectrum. The *endo:exo* mixture was carried through the rest of the synthesis to observe the effect of dienophile activation on the closure of the IMDA precursor.

The mixture of alcohols **461/462** were then converted into the corresponding mixture of dimethyl ethers by alkylation with methyl iodide and were characterised by the appearance of a further CH_3O signal at ~ 3.5 ppm in the ^1H NMR spectrum.

Dimethylated bicyclics **461a/462a** were subsequently converted into the terminal alcohols by treatment with 0.5 equivalents of borane.THF complex followed by oxidative work-up. The desired primary alcohols **463** were obtained in a moderate 40 % yield and were characterised by the appearance of a CH_2O signal at 3.61 ppm in the ^1H NMR spectrum. Oxidation by the Swern protocol yielded the aldehydes **464** which were identified by the appearance of the aldehyde protons in the ^1H NMR spectra at 9.78 and 9.83 ppm and a carbonyl stretch at 1720 cm^{-1} in the IR spectra.

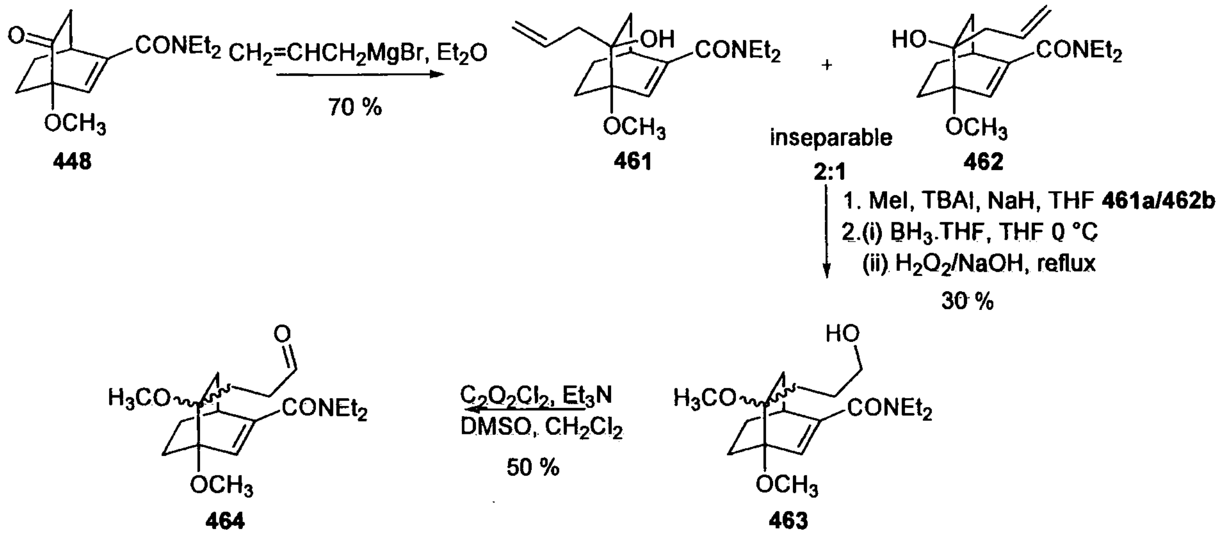


Figure 163

Following the successful oxidation, the intermediate aldehydes **464** were converted into the desired Z,E dienes **465** following the modified Julia protocol. Good selectivity was again achieved and gave the desired Z,E diene with an activating group present on the dienophile component, Figure 164. The desired IMDA intermediate **465** had successfully been obtained and investigations into achieving ring closure to give the tricyclic ring fragmentation precursor were initiated.

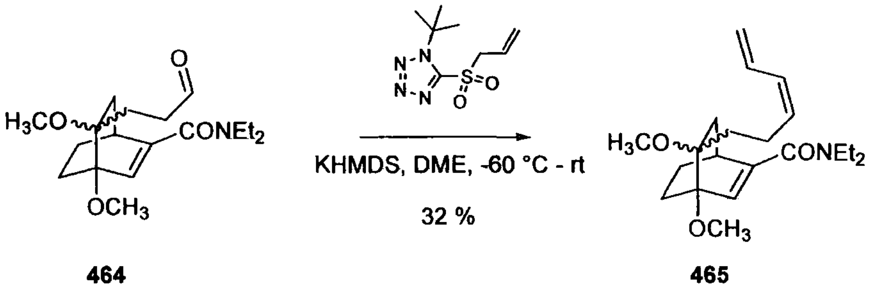


Figure 164

3.19 Intramolecular Diels Alder Cycloaddition : Substituted Ketone

Ring closure was attempted with IMDA precursor **465** and the use of thermal, microwave and the use of Lewis acids were thoroughly investigated as previously described. However under these conditions, Figure 165, the IMDA precursor **465** proved unreactive and substrate **465** was recovered or decomposition occurred, Figure 165.

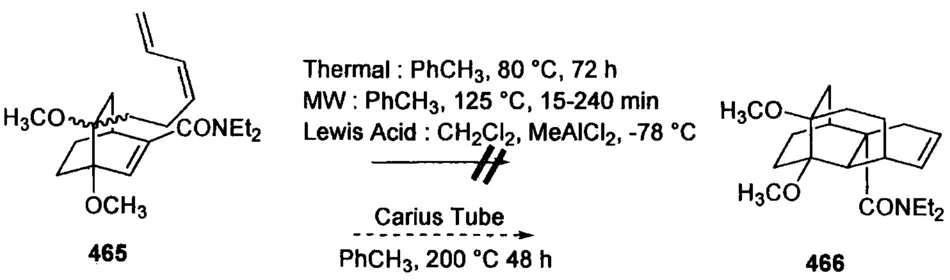


Figure 165

However, further attempts to induce ring closure by utilising sealed tube experiments proved more successful. Diene **465** was dissolved in toluene and degassed thoroughly by the freeze-pump-thaw method before sealing in a Carius tube. The reaction was then heated at 200 °C for 48 h in a Carius oven and after this time was analysed by mass spectrometry, Figure 116. It appears that one of the products present in the reaction mixture had the desired mass ion (bottom spectrum) but a different fragmentation pattern to the starting material (top spectrum). The reaction was carried out on 10 mg scale and did not allow isolation for further analytical analysis to be carried out. The additional activation present on the dienophile appears to aid the cycloaddition, but poor isolated yields have hampered this investigation.

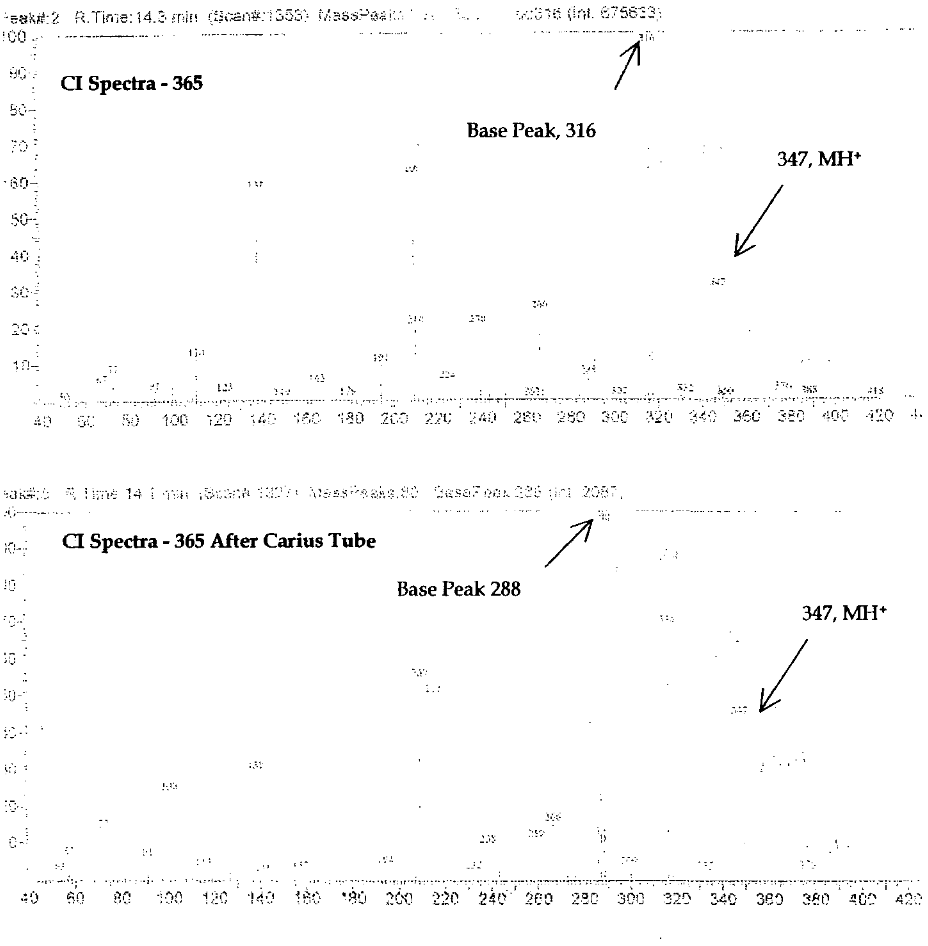


Figure 166

3.20 Dimethylamide Substituted Ketone 470

It was hypothesised that the steric bulk of the diethyl groups attached to the dienophile fragment of IMDA precursor **365** may be causing significant non-bonded interactions and not allowing the diene to come into close enough proximity in which to react. To this end the sterically less demanding dimethyl substituted ketone **470** was synthesised using the protocol previously described, Figure 167.

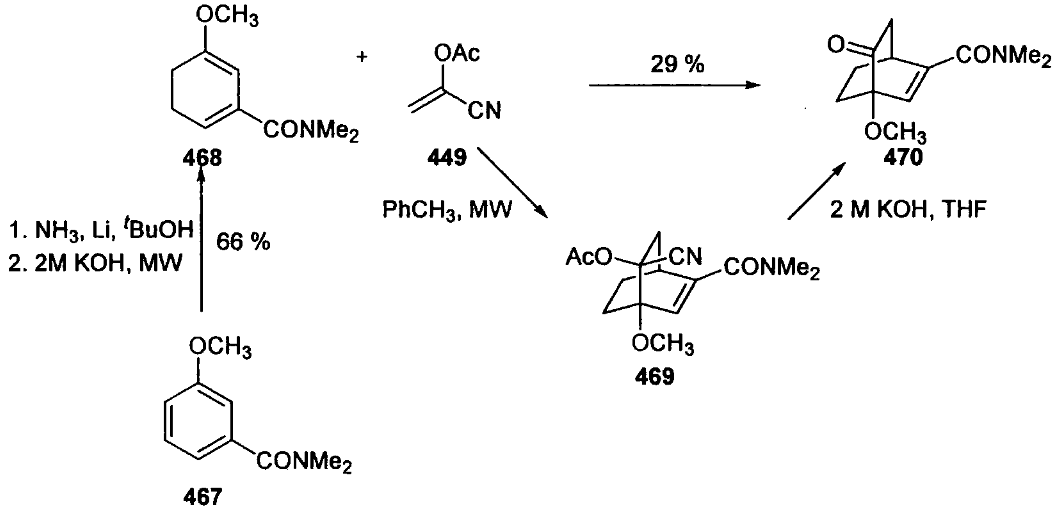


Figure 167

With ketone **470** in hand it was treated with allylmagnesium bromide and yielded an inseparable 2:1 *exo:endo* mixture of alcohols **471/472**, Figure 168. The ratio was calculated by examination of the ^{1}H NMR spectrum and comparing the values of integration present for 6-H. The mixture of alcohols were then converted to the desired aldehydes in 3 steps utilising previously described chemistry, Figure 168. Aldehydes **474** were subsequently transformed to dienes **474** on exposure to the KHMDS and Julia reagent **402**. Diene **475** was obtained as a mixture of *endo:exo* isomers but these were single geometrical isomers and were characterised by the appearance of a further 5 protons at 5.07, 5.17, 5.42, 5.97 and 6.62 ppm in the ^{1}H NMR spectrum.

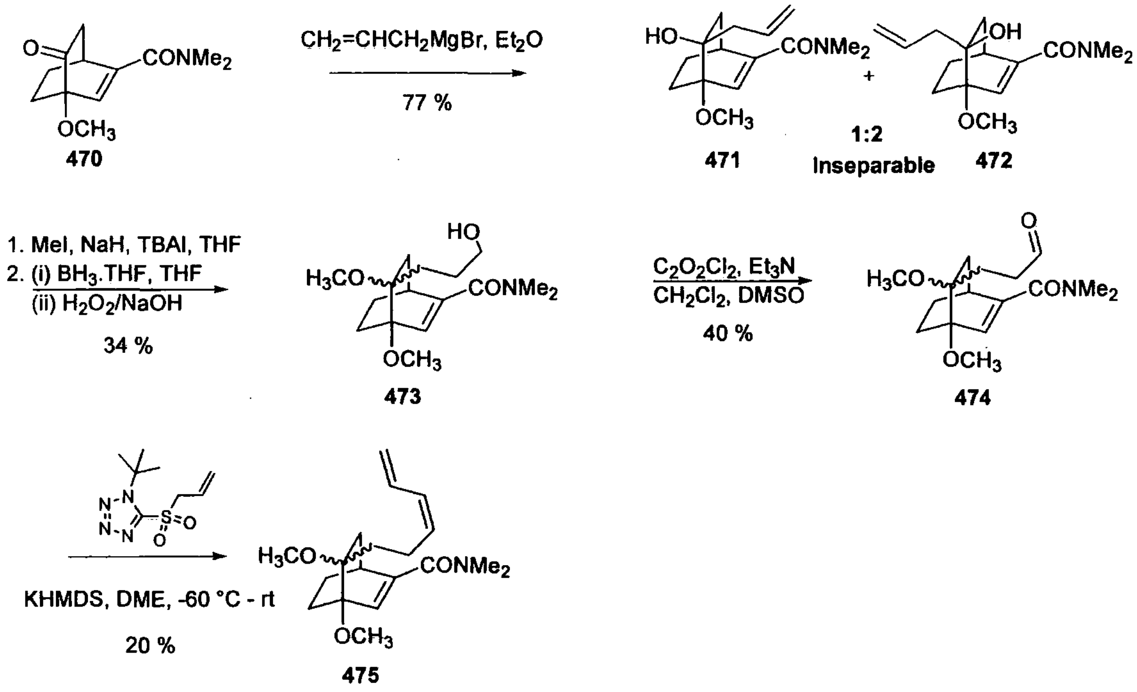
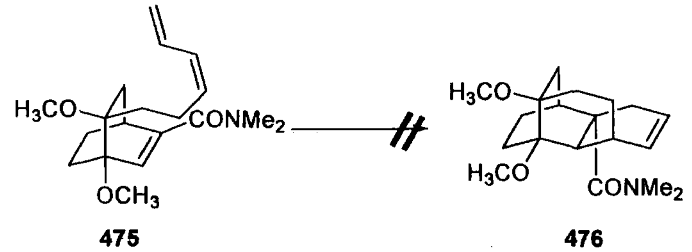


Figure 168

Diene **475** was then investigated under the IMDA reaction conditions previously described, Figure 169. However, all attempts to induce the IMDA reaction on dimethylamide IMDA intermediate **475**, utilising the aforementioned techniques have also proved unsuccessful, Figure 169. Decomposition products were only identifiable products on analysis by ^{1}H NMR spectroscopy and the dimethyl analogue appears to be less thermodynamically stable when compare to its diethyl analogue.



Thermal : $PhCH_3$, 80 °C, 72 h
MW : $PhCH_3$, 125 °C, 15-240 min
Carius Tubes : $PhCH_3$, 200 °C, 4-52 h
Lewis Acid : CH_2Cl_2, $MeAlCl_2$, -78 °C

Figure 169

3.21 Molecular Modelling

In collaboration with the molecular modelling department at AstraZeneca, Alderly Edge we obtained transition state energy calculations to help us understand the unreactivity of our substrates towards IMDA cycloaddition, Figure 170. The energies that were calculated do not appear to be significantly high to impede closure and it remains unclear at this time as to the inability to induce the IMDA reaction.

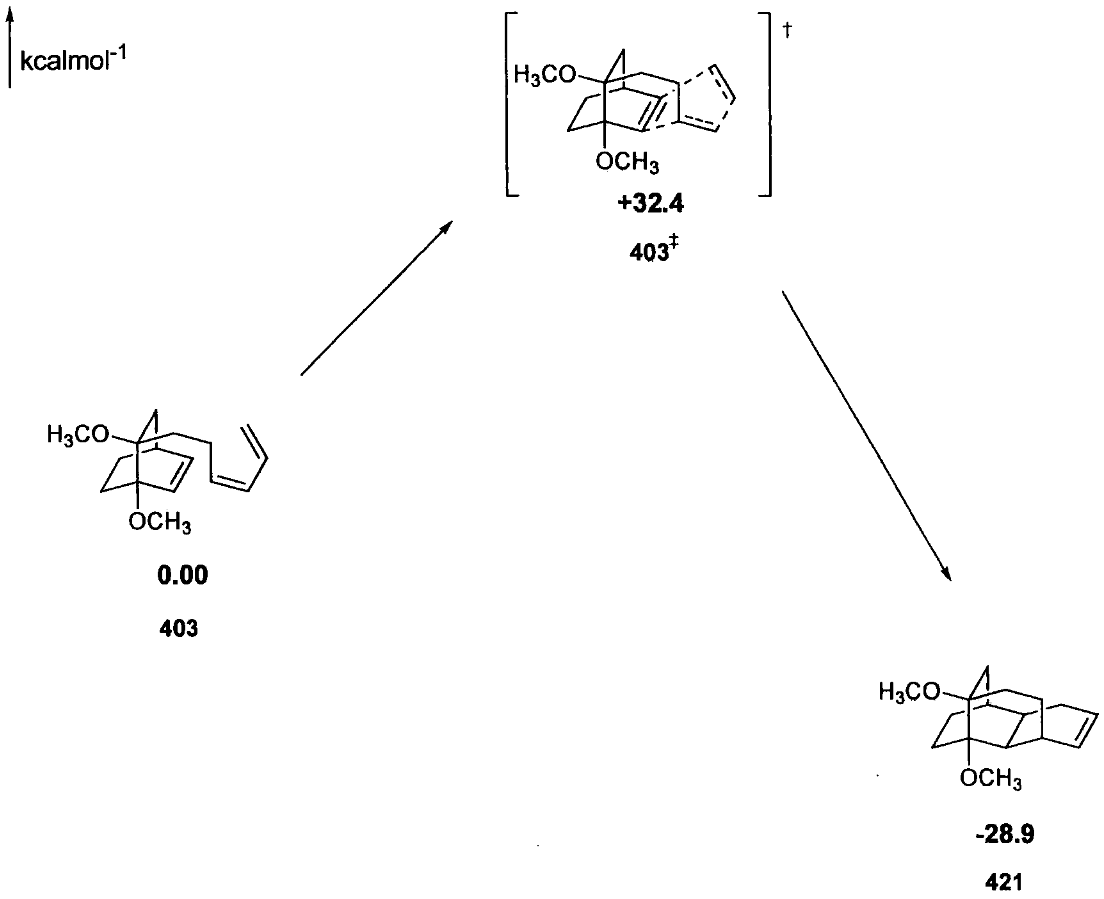


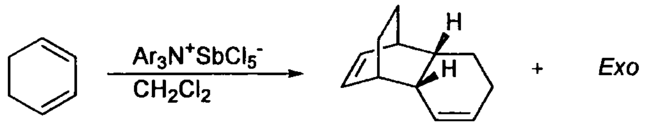
Figure 170

3.22 Conclusions of IMDA of the Z,E diene Approach

The direct attachment of the diene fragment **180** was not possible and this had to be sequentially built on to bicyclic ketones (**362**, **448** and **470**). We identified that tethered aldehyde *e.g.* **388** would allow the diene to be introduced by olefination techniques. Initial investigations utilising the dioxolane unit to produce aldehyde **388** gave good *endo:exo* selectivity. However formation of the aldehyde was hampered by the propensity of the system to rearrange under acidic reaction conditions. Addition of allylmagnesium bromide proved to be non-selective but allowed aldehyde **388** to be easily synthesised and the modified Julia reaction gave the IMDA precursor with excellent E:Z ratios. However in all cases we failed to induce ring closure even after further dienophile activation. Development of the desired late-stage intermediates allowed the investigation of the proposed IMDA strategy. However the oxidative ring fragmentation could not be tested due to the inability to induce ring closure. At present we are unsure of the unreactivity of the Z,E diene derivatives to under-go Diels Alder cycloaddition. However, we hypothesise that the energy required for the reacting groups to come into close enough proximity to react was too high to be obtained under the reaction conditions examined and at this time it is unclear why the tricyclic structure does not form easily.

3.23 Future Work

Bauld *et al*[116] have demonstrated the use of cation radicals in the dimerisation of 1,3-cyclohexadiene **477**, Figure 171. Under standard thermal conditions 30 % yield of the cycloadduct can be obtained in 20 h at 200 C, however under cation radical conditions the cycloaddition was completed in 15 minutes at 0 °C giving 70 % of cycloadduct **478**. The reaction requires (or prefers) ionisable dienophilic units to allow the reaction to proceed and this procedure may allow us to induce the IMDA.

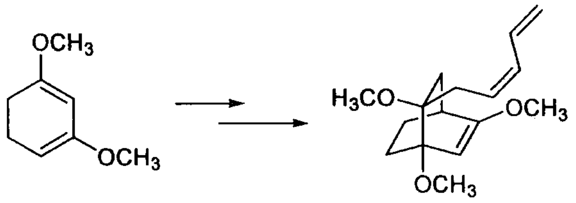


477 **478** 5:1

Ar = *p*-bromophenyl

Figure 171

Thus, future work in this area could focus on the synthesis of IMDA precursor **480** with an electron rich dienophile component, Figure 172 and this would then allow us to exploit cation radical catalysed Diels Alder reactions. Conversion of dienophiles to their corresponding cation radicals (highly electron deficient) may allow rapid addition to the desired diene.



479 **480**

Figure 172

3.24 Further Approaches to Vinigrol

We have so far been unable to test the IMDA cycloaddition and oxidative ring fragmentation approach and to this end a further strategy was developed in parallel, **Error! Reference source not found.**. The main structural features of Vinigrol are the 8-membered ring and the *cis*-decalin framework. We had initially focussed on installing the 8-membered ring early in the synthesis and we therefore decided to focus on early installation of the *cis*-decalin. It was hypothesised that a substituted decalin would allow the introduction of the 8-membered ring *via* an alternative intramolecular Diels Alder reaction, **Error! Reference source not found.**. The 8-membered ring would again be installed in a masked form to negate usual problems associated with their synthesis and also allow our ring fragmentation approach to be realised.

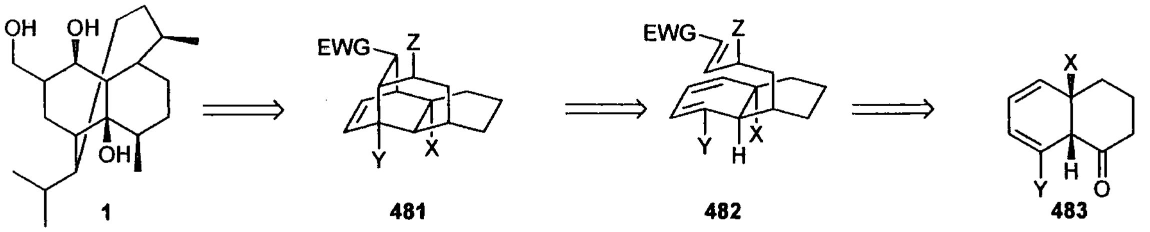


Figure 173

Chapter 4
Synthesis of Functionalised *cis*-Decalins

Chapter 4 : Synthesis of Functionalised *cis*-Decalins

4.1 *cis*-Decalins and Vinigrol

4.1.1 Introduction

An integral skeletal component of the carbocyclic framework of Vinigrol is a functionalised *cis*-decalin and many ways have been developed to synthesise the desired framework. The *cis*-decalin of Vinigrol requires a specific substitution pattern to allow us to exploit a ring fragmentation approach, Figure 174. Thus, investigations began in order to identify a technique that would afford an appropriately functionalised *cis*-decalin framework.

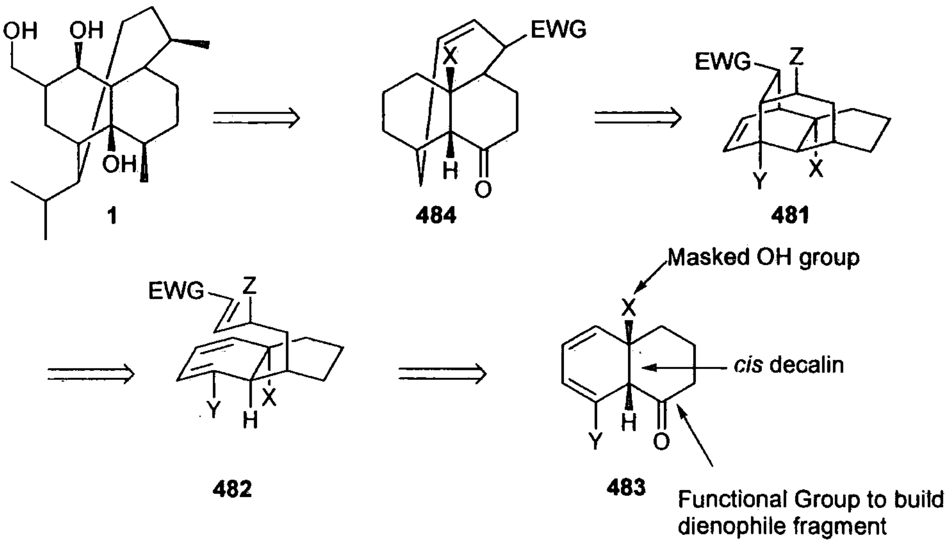
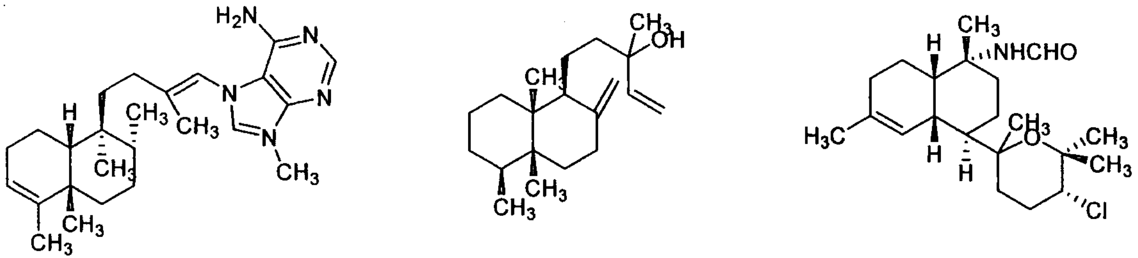


Figure 174

4.2 *cis*-Decalins in Synthesis

4.2.1 Introduction

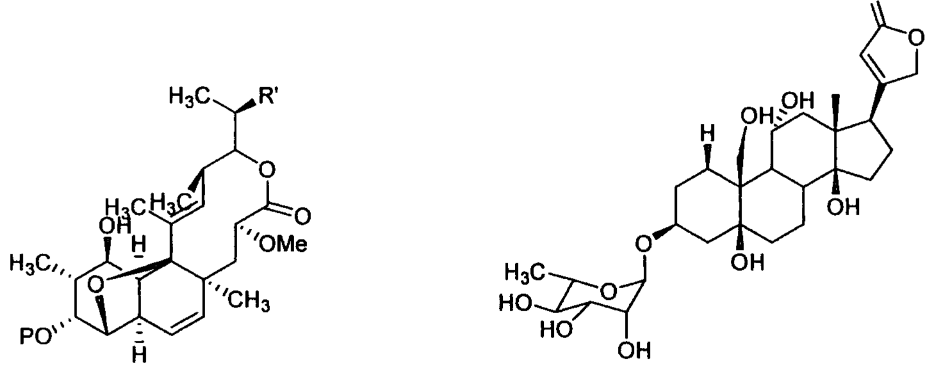
The *cis*-decalin component is present in the molecular structure of various classes of natural products such as *cis*-clerodanes[117], kalihinenes[118], thelepoganes[119], cadinanes[120], eremorphilanes[121] and valeranones, Figure 175.[122,123] Many of these *cis*-decalin-based natural products exhibit wide ranging and interesting biological activities. It is therefore evident that many of these natural products have varying degrees of substitution patterns and four or more continuous stereocentres on the decalin skeleton thus posing a considerable synthetic challenge. The structural complexity of these natural products coupled with their interesting biological properties have led to significant interest in the development of new and efficient methods for the synthesis of *cis*-decalins.



Agelasine A **485**

Nakamurol A **486**

Kakihinene X **487**



R = H, R' = OH Nodusmicin **488**
R = R' = H Deoxynodusmicin **489**

Ouabain **490**

Figure 175

4.3 Synthesis of *cis*-Decalins

Efforts towards the synthesis of *cis*-decalins were initially made within the context of the requisite natural product. Of the various strategies for the synthesis of the *cis*-decalin framework there are two main methods which have been extensively utilised; Robinson annulation[124] and the Diels Alder reaction. As the number of natural products containing *cis*-decalins has increased, the interest in developing new methods for their synthesis has intensified. However, most of the strategies which have been developed can be grouped into one of four catergories: (1) syntheses starting with Wieland-Miescher ketones, (2) cyclisation techniques, (3) Diels Alder reactions and (4) Cope rearrangements, which will now be described and shown with a related application in total synthesis.

4.3.1 *cis*-Decalins from Wieland-Miescher Ketones

In many syntheses, the key step in the formation of *cis*-decalins involves the saturation of the double bond of the ring junction in the decalenes, Figure 176. The decalins are synthesised by various methods but mainly utilise the Robinson annulation or Diels Alder reaction.[123] The ketones of type **492** have been widely used as starting materials for the synthesis of *cis*- and *trans*-decalin frameworks, Figure 176. The Birch reduction of **492** affords the *trans*-decalin **491** whereas catalytic reduction occurs from the least hindered face to give the *cis*-decalin **493** and the stereoselectivity of both reactions is usually good.[125]

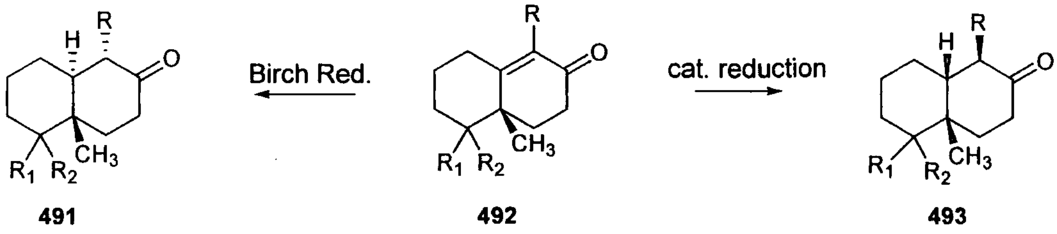


Figure 176

Ando *et al* synthesised *cis*-decalin-based eudesmanes **497A** and **497B**, Figure 177 and suggested a revised structure of a natural eudesmane-4,11-diol isolated from a Pakistani medicinal plant, *Pluchea arguta Bioss.*[126,127] The precursor **495** was prepared from α-santonin **494** and following their methodology, santonin was transformed to 6-episantonin. Zinc reduction and catalytic hydrogenation afforded the desired *cis*-decalin **496** which was subsequently elaborated to the eudesmanes **497A** and **497B**.

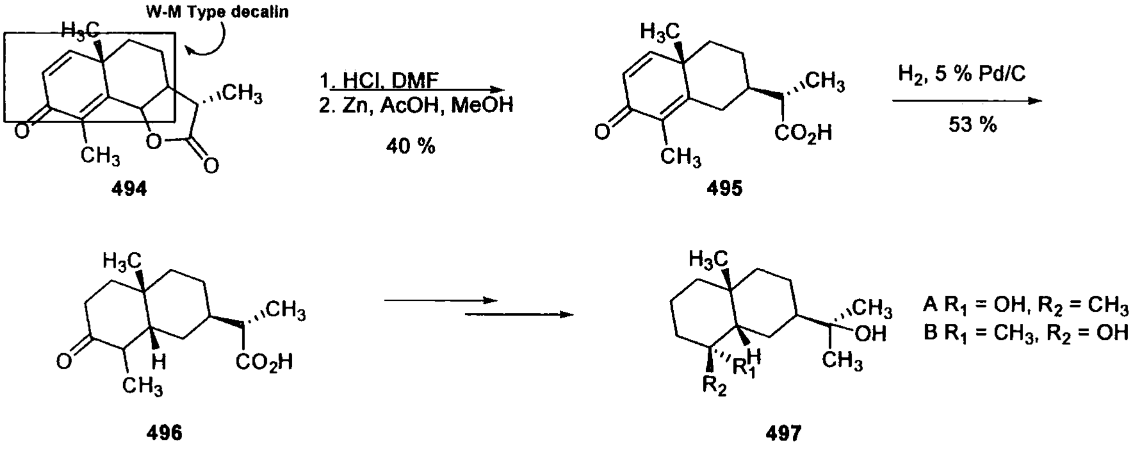


Figure 177

4.3.2 Cyclisation Techniques

Among the various cyclisation strategies the Robinson annulation has been extensively utilised for the synthesis of *cis*-decalin ring systems. The Robinson annulation, however, has various problems associated with the efficiency and the regio- and stereo-control of both steps of the annulation. Recently new methods of cyclisation have been developed.[123]

Ley *et al* synthesised the *cis*-fused decalin derivative **499** containing epoxydiacetate functionality (potential anti-feedant) by a stereospecific route, which can also be utilised to synthesise other similar analogues, Figure 178.[128] The β-keto ester **498** was prepared from 4,4-dimethylcyclohexanone and upon treatment with a Lewis acid undergoes *ene*-type cyclisation to give the desired *cis*-decalin. Subsequent reduction with lithium aluminium hydride followed by epoxidation and acetylation provides the desired *cis*-decalin **500**.

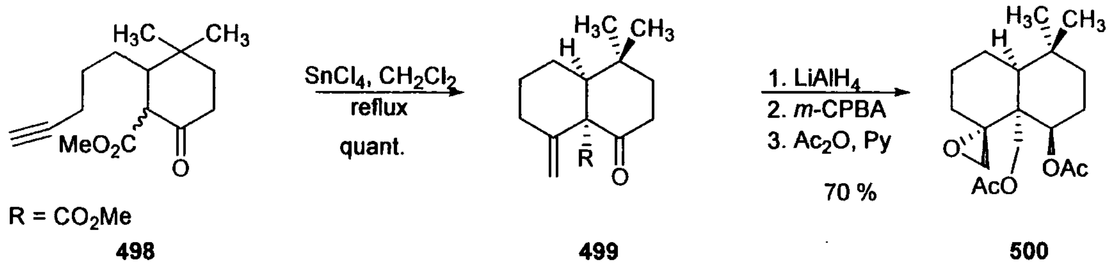


Figure 178

4.3.3 Diels Alder Cyclisation - Intermolecular

The intermolecular Diels Alder cycloaddition has been applied extensively for the construction of *cis*-decalins and in general two types of Diels Alder reaction have been employed, Figure 179. In the first type, 1-vinyl cyclohexene derivatives *e.g.* **501** are used as the diene component. A decalin whose double bond appears at the ring junction which has to be manipulated has been discussed, *e.g.* Figure 176. In the second type of Diels Alder reaction a cyclic enone **506** is utilised as the dienophile and its Diels Alder reaction with a diene **505** afforded a *cis*-decalin directly. Most often, the products are formed in a regio- and stereo-selective manner.

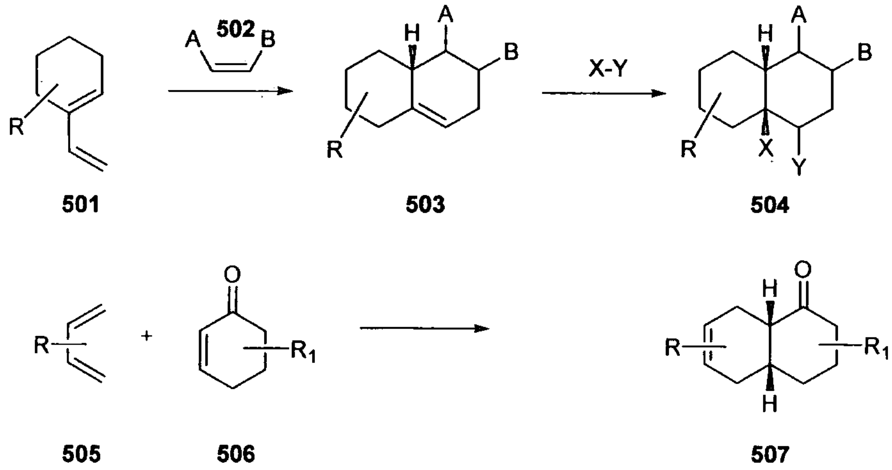
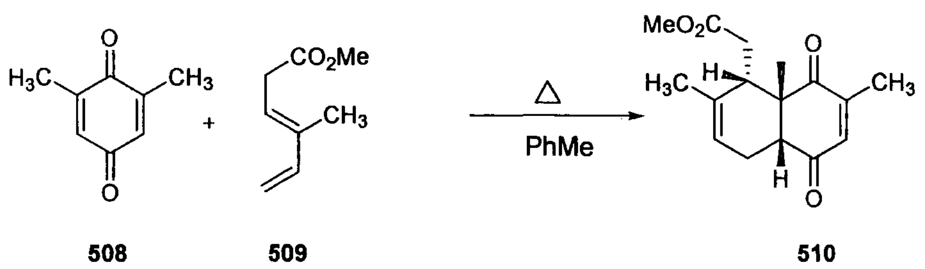


Figure 179

Fetizon *et al*, in approaches towards the AB ring system of Taxol reported the Diels Alder reaction between 2,6-dimethylbenzoquinone **508** and diene **509**.[129] The desired *cis*-fused cycloadduct **510** was prepared as a single regio- and stereo-isomer in good yields, Figure 180.



508 **509** **510**

Figure 180

4.3.4 Diels Alder Cyclisation - Intramolecular

The intramolecular Diels Alder reaction has also been employed to construct the decalin framework. A triene may undergo an IMDA cycloaddition to give either a *trans-* or *cis-*fused decalin framework depending on the transition state, Figure 181.

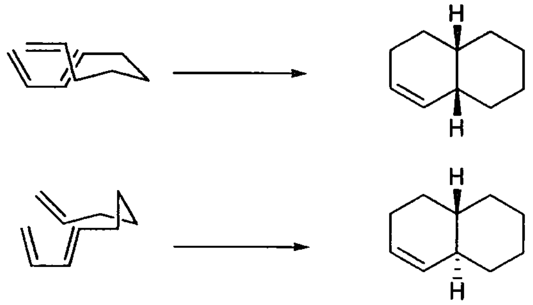
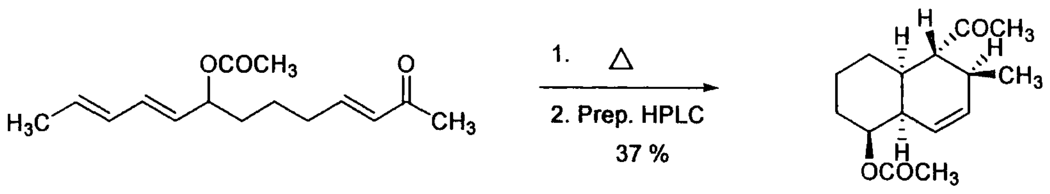


Figure 181

However, it is not always easy to predict the stereochemistry, as it depends on the cumulative effects of various factors, such as the competing conformational, steric and electronic effects in the transition states. It appears that the stereochemistry of the ring fusion is largely dependent on the diene and dienophile moieties. Unlike intermolecular Diels Alder reactions, intramolecular Diels Alder reactions are carried out at a later stage of the synthesis and one limitation of this methodology is that the preparation of the requisite precursor becomes a considerable synthetic task. This type of cycloaddition in applications towards total synthesis is discussed in detail in Section 4.13.

During the synthesis of nargenicin antibiotics, the framework of which contains a *cis-*decalin, Jones *et al* reported an IMDA with trienone **511**, Figure 182.[130] Thermal closure in oxygen-free xylene gave a stereoisomeric mixture of decalins from which the major *cis-*isomer **512** was obtained by preparative HPLC, Figure 182.

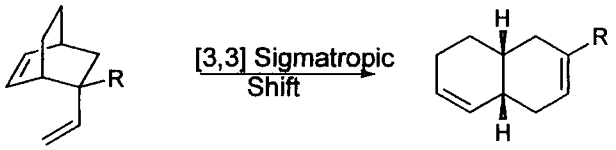


511 512

Figure 182

4.4.5 Cope Rearrangement

Another interesting route to *cis*-decalins is the Cope rearrangement, where bicyclo[2.2.2]octenones **513** can be directly transformed into the desired framework, Figure 183. There are many variations including the oxy-Cope (R = OMe or OH) and the anionic oxy-Cope (see Hanna *et al*, Section 1.4.2) rearrangements (R = O^-M^+). Oxy-Cope and anionic oxy-Cope rearrangements have found greater utility than the parent reaction since generally the rearrangements occur at lower temperatures and the precursors are easily prepared by a Grignard type addition of a vinyl metallic reagent to a carbonyl group in the bridged bicyclic systems.



513 514

Figure 183

Rigby *et al* reported a novel entry into the tricyclic ring systems of aristolanes that involved an oxy-Cope reaction in bicyclooctanes as the key step.[131] To this end the readily available tricyclic ketone **515** was treated with vinylmagnesium bromide to furnish *endo* and *exo* carbinols **516** and **517**, Figure 184. The desired *endo*-alcohol **516** was then treated potassium hydride to induce the [3.3]-sigmatropic shift to afford the desired tricyclic system **518**.

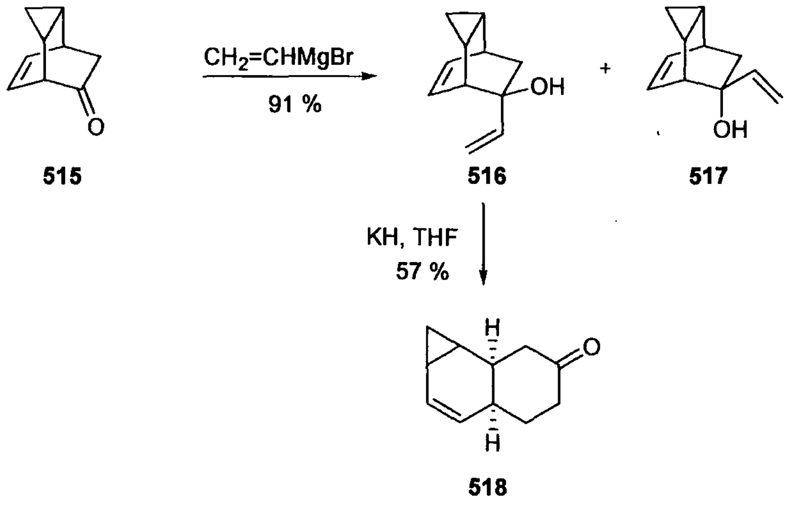


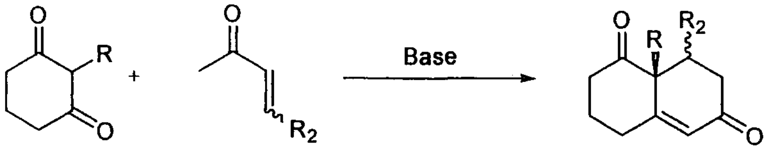
Figure 184

4.4 Summary of cis-Decalins in Synthesis

The continued emergence of natural products containing the *cis*-decalin framework has allowed the development of many new strategies for their formation. However, many natural products containing this framework have yet to be completed due to the specific substitution patterns required in key intermediates. Thus, there is a great need for the continued development of methodologies in this area.

4.5 *cis*-Decalins and Vinigrol

The formation of *cis*-decalins by Cope-type rearrangements in relation to Vingrol have already been exploited by various groups involved in the synthesis towards Vinigrol. Thus, these were not investigated as a ring fragmentation precursor was required in order to exploit a *de novo* approach towards the synthesis. Also, although Robinson annulation can be used to give functionalised decalins, the substitution pattern that is formed during their synthesis is very specific due to the reactants that are utilised, Figure 185. Also there are various problems associated with the efficiency and the regio- and stereo-control of both steps in the annulation. However these can be overcome and are discussed in detailed reviews by Jung[132] and Gawley.[133] The decalins obtained from a Robinson annulation would require significant manipulation to give the desired substitution so it was decided to investigate other available methods. The methods already described did not have the required substitution pattern to allow the desired ring fragmentation approach to be utilised. Consequently an alternative strategy would have to be developed to allow this and work undertaken in this area is described in the following sections.



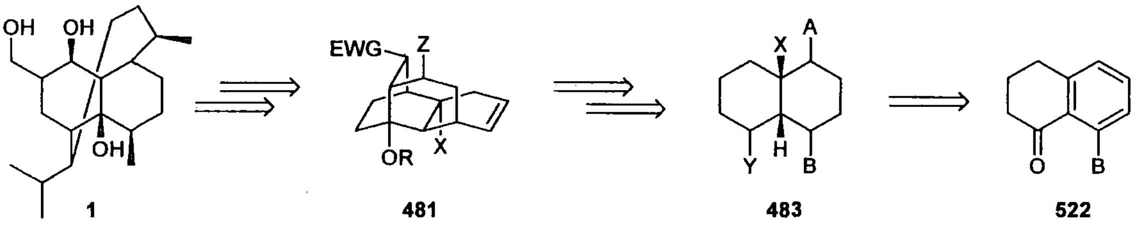
519 **520** **521**

Figure 185

4.6 Tetralone Derivatives

4.6.1 Introduction

Utilising a ring fragmentation approach, we envisaged that a Grob-type fragmentation precursor **481** could allow the formation of the problematic eight membered ring in a masked form. To enable access to this precursor an appropriately functionalised *cis*-decalin was required and it was envisaged that this could be accessed through the Birch reduction of a tetralone-type molecule **522**, Figure 186. Thus, to investigate the aforementioned strategy, the synthesis and reactivity of 8-substituted tetralones was to be examined.

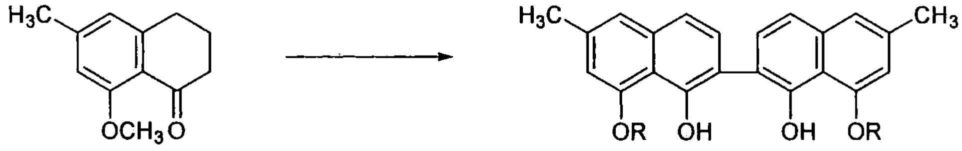


1 **481** **483** **522**

Figure 186

4.6.2 Birch Reduction of 8-substituted Tetralones

8-substituted tetralones were identified as the desired *cis*-decalin precursors following the retrosynthetic strategy shown in Figure 186. 5-, 6- and 7-methoxy-1-tetralones are easily accessible whereas 8-methoxy-1-tetralones are not. 8-methoxy-1-tetralones have great potential as starting materials for the synthesis of many natural compounds *e.g.* tetralone **523** could provide easy access to Diospyrol **525**, a potent anthelmintic agent, Figure 187. Thebtaranonth *et al*[134] developed a large scale synthesis of 8-methoxy-1-tetralones to allow the preparation of various aromatic and heterocyclic compounds that are otherwise difficult to obtain by conventional methods.

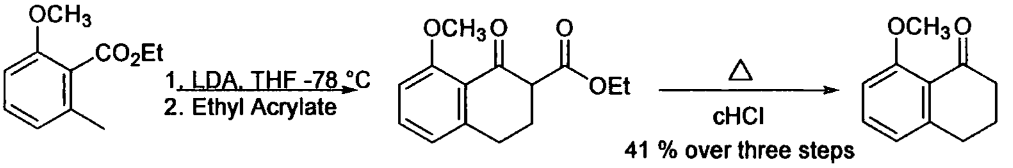


523

R = H **524**
R = Glu **525**

Figure 187

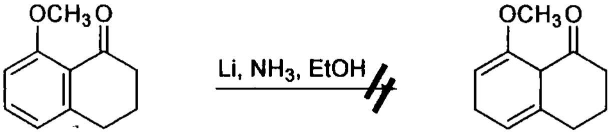
Thus, 8-methoxy-1-tetralone **528** was synthesised following the literature procedure described by Thebtaranonth *et al* to allow derivatives of substituted tetralones to be investigated under Birch reduction conditions, Figure 188. The key transformation in this synthesis employed a Michael-Dieckmann type cyclisation to afford large quantities of tetralone **528**, Figure 188.



526 **527** **528**

Figure 188

The Birch reduction of 8-methoxy-1-tetralone has not been previously reported in the literature and thus exploiting the experience gained from the dissolving metal reduction of substituted anisoles (Figure 149), the reaction was investigated. Tetralone **528** was treated under our standard conditions, but on work-up no evidence of reduction was observed by NMR spectroscopy, Figure 189. Thus, an investigation examining the reaction conditions was undertaken. However, increasing the reaction time, number of equivalents of alkali metal and reaction temperature (-78 °C to -33 °C) failed to give the desired diene. The failure of the reduction is not fully understood at this point.



528 **529**

Figure 189

However, to allow the Birch reduction to be investigated further, tetralone **528** was derivatised to examine the effect of changing the electronic nature of the system. Tetralone **528** was converted into alkene **530** after reaction with methyltriphenylphosphorane, Figure 190. Subsequent treatment under standard hydroboration conditions yielded alcohol **531** and this was characterised by the OH stretches at 3154 cm^{-1} present in the IR spectrum. Alcohol **531** was also converted into methyl ether **532** on treatment with methyl iodide to allow further functional group tolerance to be observed under the reduction conditions. Alcohol **531** and methyl ether **532** were treated separately under various conditions, Table 3. However, in both cases the desired reduction products could not be isolated and the starting tetralones were returned in each case.

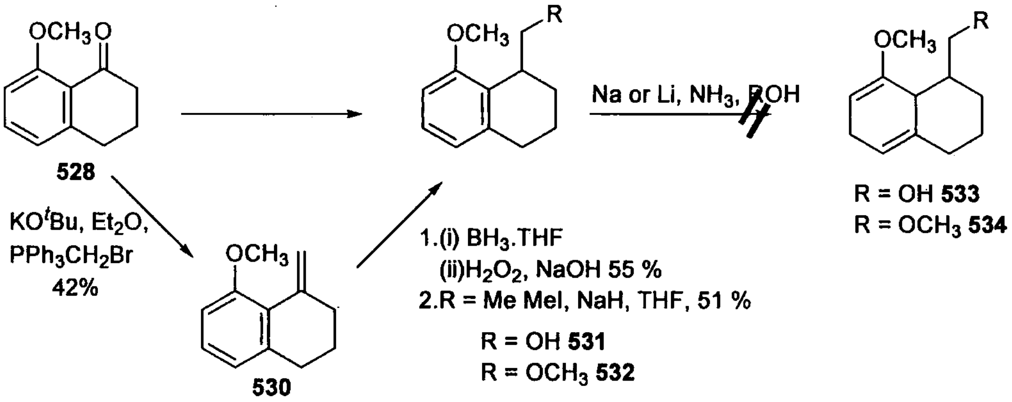


Figure 190

Table 3 - Birch Reduction of 8-substituted tetralones

Metal (eq)	R	Temperature	ROH	Reduction?
Lithium (3)	H	-78	EtOH	no
Lithium (6)	H	-78	EtOH	no
Sodium (8)	H	-78	EtOH	no
Sodium (20)	H	-78	EtOH	no
Lithium (5)	CH_3	-78	EtOH	no
Lithium (5)	CH_3	-78	ᵗBuOH	no

At this time it is not clear as to the lack of reactivity of 8-substituted tetralones under the Birch reduction conditions. However, it was hypothesised that the electron-donating nature of the methyl ether **532** and alcohol **531** were causing the substrates to be too electron rich to undergo reduction. Therefore, alkene **530** was converted into methyl derivative **535** by hydrogenation and was characterised by the loss of olefinic protons at 5.82-5.85 ppm in ^{1}H NMR spectrum, Figure 191. However, this substrate also proved to be inert to the reduction conditions, Figure 191.

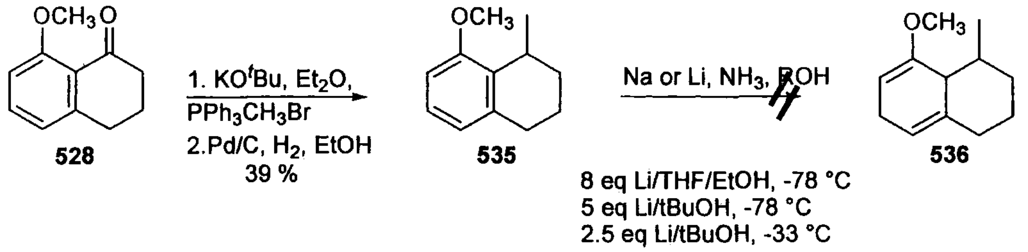


Figure 191

4.6.3 Birch Reduction of α-Tetralone

The ability to carry out reduction on the 8-methoxytetralone proved problematic, so attention was turned towards the unsubstituted tetralone **537**, Figure 192. It was envisaged that α-tetralone would allow the installation of the desired functionalisation at position 8 at a later stage in the synthesis.

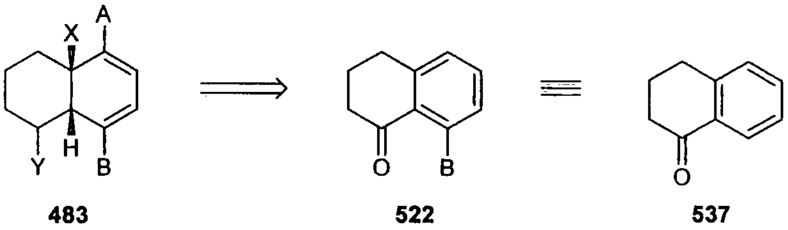


Figure 192

Rabideau *et al*[135] reported that the Birch reduction of α-tetralone could give up to 7 different compounds due to the incorporation of additional unsaturation present, since reduction can occur at either the aromatic ring or the carbonyl group, Figure 193.

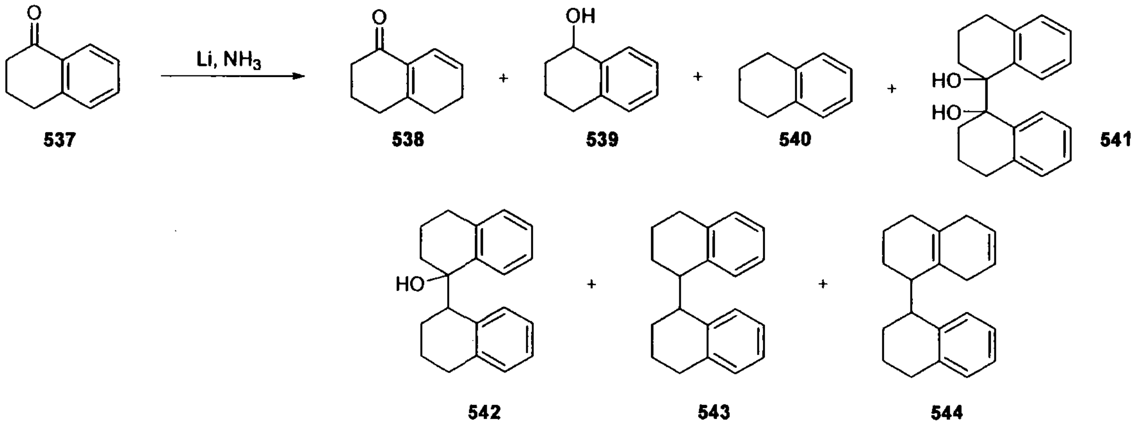


Figure 193

However, more encouragingly, Watanabe *et al*[136] carried out the reductive methylation affording the methyl dihydro product **545**, with no significant dimerisation observed, Figure 194.

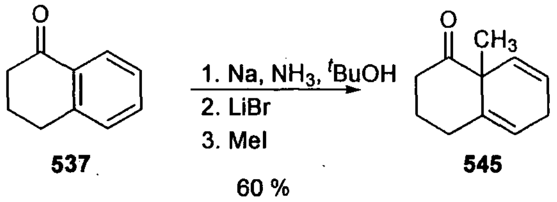


Figure 194

Thus, with the literature precedence and the commercially available tetralone in hand investigations began to determine which products could be obtained from the Birch reduction. Tetralone **537** was reduced under the standard literature conditions utilising ^{t}butanol as the proton source, however on work-up only partial reduction to diene **538** was observed.

Optimisation of this reaction was undertaken and after considerable experimentation complete reduction could be obtained after adapting the literature conditions to include THF as a co-solvent to aid solubility during the reaction, Figure 195. Pleasingly, diene **538** was the sole product of the reaction and was characterised by the appearance of two olefinic protons at 5.79 and 6.51 ppm in the ^{1}H NMR spectrum. Also no other reduction products observed by Rabideau *et al* could be detected by NMR spectroscopy.

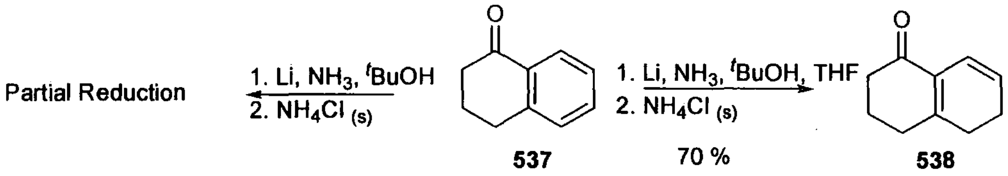
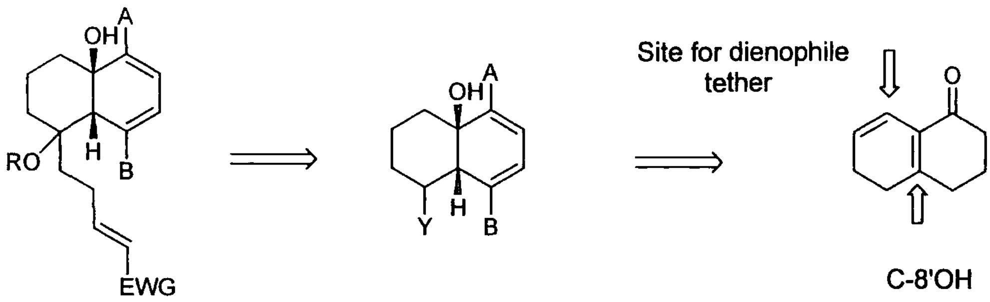


Figure 195

With considerable quantities of diene **538** available, methods to obtain the required substituted *cis*-decalin were undertaken. Installation of the tertiary alcohol functionality at C8′ and ring functionalisation to allow synthesis of the tethered dienophile were two areas that were given significant attention, Figure 196. Firstly, investigations began to try to install the tertiary alcohol and efforts towards this are described in the next section.



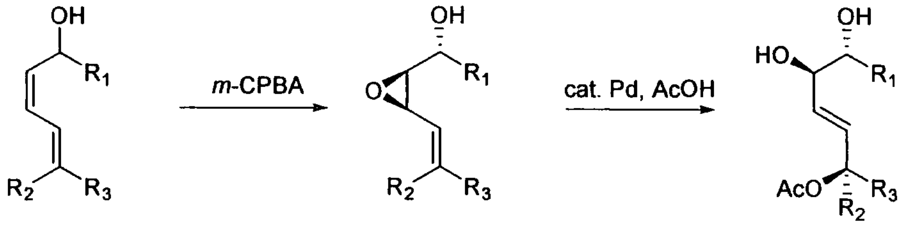
546 **547** **538**

Figure 196

4.7 C8′ OH Synthesis

4.7.1 Stereoselective Palladium catalysed Opening of Vinyl Epoxides

Stereoselective transformation of allylic epoxides into triol dervatives can be achieved through the stereocontrolled formation of π-allyl palladium intermediate from epoxide **550** or **551**.[137] The required triol derivative can be produced after the reaction with acetate anion, Figure 197.



$R_1 = R_3 = C_5H_{11}$, R_2 = H **548**
$R_1 = R_2 = C_5H_{11}$, R_3 = H **549**

77 %, > 95 % ds **550**
6 %, > 95 % ds **551**

71 %, 93 % ds **552**
88 %, 93 % ds **553**

Figure 197

Allylic epoxides such as 557 (Figure 198) were of the same substitution pattern that could be obtained upon epoxidation of the cyclic diene 556. Epoxide opening as described by Kobayashi *et al* would allow efficient and stereoselective access to the C8′ OH functionality, Figure 198.

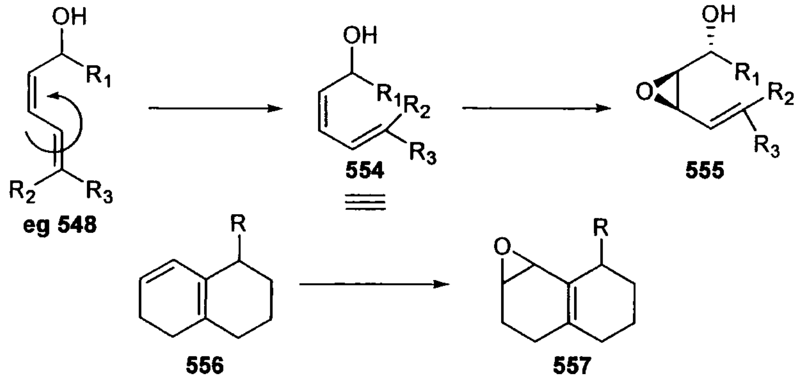


Figure 198

Thus, with gram quantities of ketone **538** in hand investigations began to examine the epoxidation and the tolerance of the stereoselective opening strategy to a cyclic system, Figure 199. Unsaturated ketone **538** was treated with *m*-CPBA and mono-epoxide **558** was obtained in moderate yields, Figure 199. **558** was identified by the loss of vinyl protons at 5.79 and 6.51 ppm. The poor yield may be attributed to Baeyer-Villiger type background reactions causing decomposition of the starting ketone and/or products formed.

With the vinyl oxirane **558** in hand it was treated with $Pd(PPh_3)_4$ and acetic acid under literature conditions. However attempts to yield the desired tertiary alcohol **559** were unsuccessful. Analysis of the reaction mixture by mass spectroscopy suggested that decomposition due to epoxide ring opening under the acidic reaction conditions had occurred.

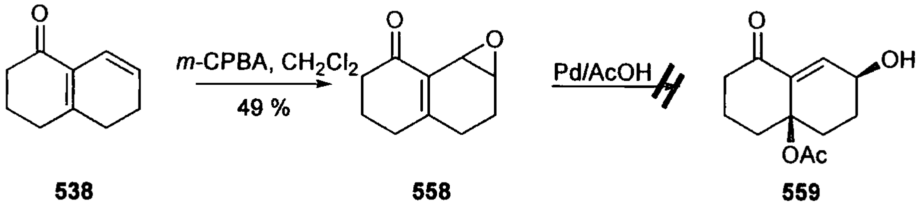


Figure 199

Kobayashi *et al* had successfully utilised palladium-induced stereoselective epoxide ring opening to give allylic alcohols and we observed that the ring opening could not be induced on allylic ketoepoxide **558**. To this end, **558** was reduced under standard Luche conditions.[138] However, the desired alcohol **560** could not be isolated and decomposition was detected by NMR spectroscopy, Figure 200. The instability of the epoxide to the reduction conditions caused the reinvestigation of the available intermediates to allow the isolation of allylic epoxy alcohol **560** and Pd-catalysed ring opening to be attempted.

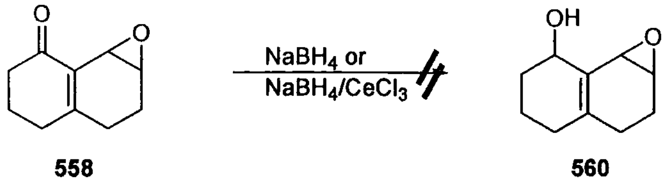


Figure 200

4.7.2 Reduction of Ketone 538

An alternative route to the vinyl oxirane **560** was therefore developed. Luche reduction of ketone **538** produced allylic alcohol **561** and was identified by the appearance of an OH stretch at 3090-3567 cm^{-1} in the IR spectrum coupled with the loss of the corresponding carbonyl signal, Figure 201. Subsequent formation of epoxy alcohol **562** was initiated by treating allylic alcohol **561** with *m*-CPBA and this proceeded smoothly affording a single product on TLC analysis. However, examination of the NMR spectral data showed that the external epoxide **562** had not been formed, Figure 201. Epoxidation of the more nucleophilic tetrasubstituted double bond had occurred to give the alternative vinyl oxirane **563** and was identified by the presence of the olefinic protons at 6.51 and 6.66 ppm, Figure 201.

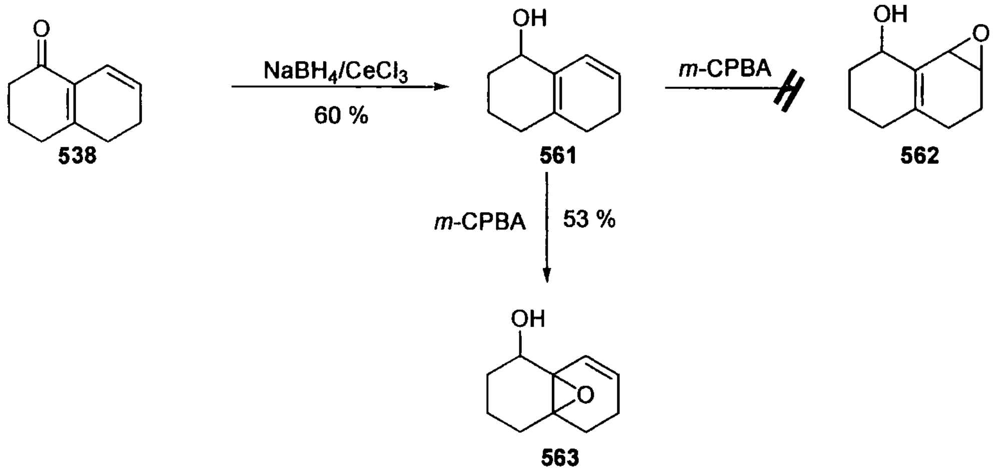
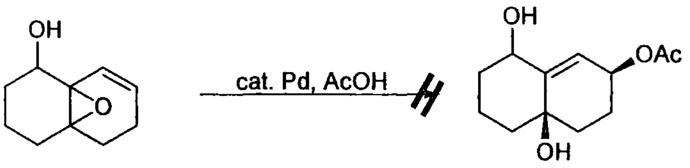


Figure 201

Internal vinyl oxirane **563** still had the correct attributes to allow palladium-catalysed ring opening and this was examined. Treatment of intermediate **563** under the literature conditions, however, did not yield the desired ring-opened product **564** and analysis by NMR and mass spectroscopy revealed that complex mixtures of products had been obtained, Figure 202.



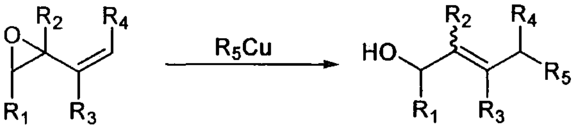
563 **564**

Figure 202

The methodology developed by Kobayashi *et al* does not appear to tolerate the rigid cyclic ring systems present in keto- and hydroxy-epoxides **558** and **563**. Undeterred by this disappointing result, examination of other methods to utilise vinyl oxirane **563** were undertaken to install the tertiary alcohol at C8′.

4.7.3 S_N2' Organocuprate Opening of Vinyl Oxiranes

On re-evaluation of the unexpected epoxide **563** obtained on treatment of cyclic allyl alcohol with *m*-CPBA, it was expected that the resultant allylic epoxide could still be utilised in order to furnish the desired tertiary alcohol. The S_N2' addition of organocopper reagents to vinyl oxiranes represents a versatile route to a variety of allylic alcohols. The addition was first observed by Anderson[139] and Johnson[140] with butadiene epoxide and isoprene epoxide and subsequently explored by others using cyclic vinyloxiranes, Figure 203.



565 **566**

Figure 203

The stereochemistry of S_N2' additions to cyclic vinyl oxiranes has been studied by various groups and it has been reported that allylic alcohol substituents were excellent S_N2' directors.[141] Cuprate additions are expected to preferentially occur *anti* to the epoxide oxygen *via* the s-*trans* and/or s-*cis* coplanar conformation of the vinyl oxirane, Figure 204.[141]

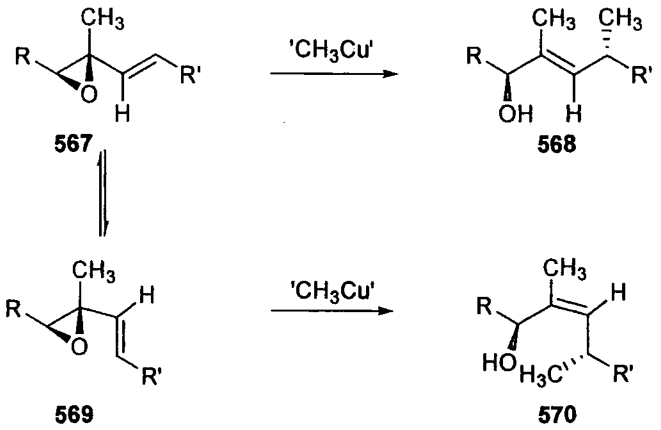


Figure 204

Thus, with the rigid cyclic vinyl oxirane the stereoselectivity of the S_N2' addition should be predictable and selective due to the inability of the cyclic vinyl epoxide to allow bond rotation.

4.8 Addition to Vinyl Oxirane 563

Organocuprates are soft nucleophiles and it was envisaged that S_N2' ring opening with a sulfur anion would also be a viable process since additional functionalisation around the ring was not required. The unwanted sulfur group could be removed later in the synthesis. However, attempted ring opening with a sulfur nucleophile proved unsuccessful, Figure 205.

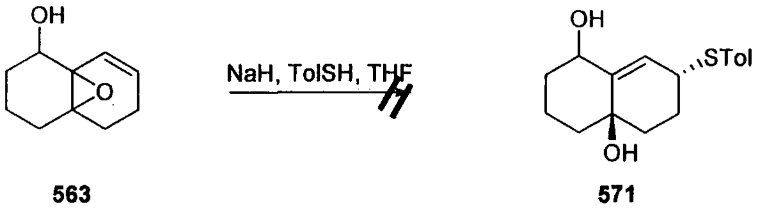
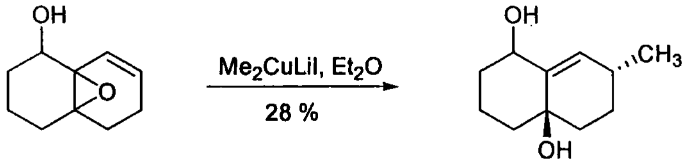


Figure 205

Thus we utilised the methyl analogue as a model system to allow the application of the desired reconnection strategy, *vide infra*. To this end, vinyl epoxide **563** was treated with 4.4 equivalents of dimethylcopperlithium iodide and upon work-up and subsequent chromatography yielded diol **572** as single diastereomer, Figure 206.[142] Attempts to identify the relative stereochemistry by X-ray crystallography have been unsuccessful to date.

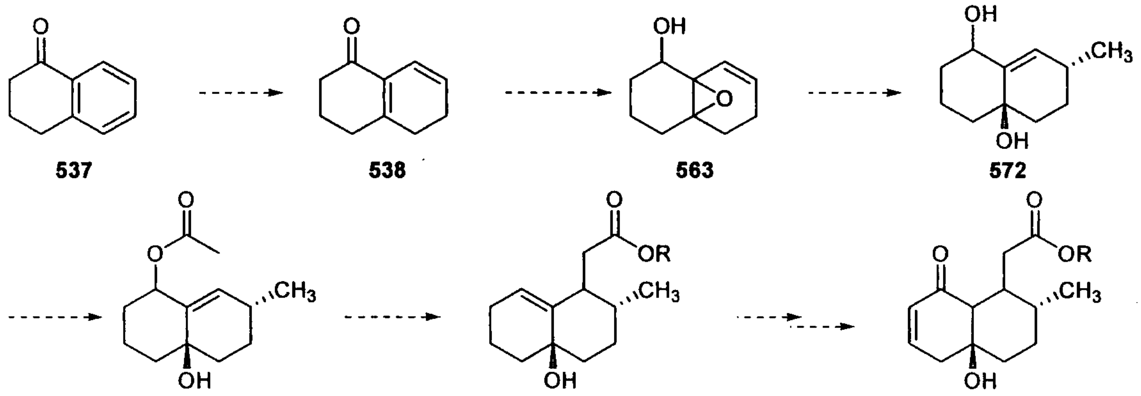


563 **572**

Figure 206

4.9 Tetralone Reconnection Strategy

Installation of the C8′ tertiary alcohol had been successfully completed and attention turned to further functionalisation of the diol **572**, Figure 207. The key reaction of this strategy hinged on an Ireland-Claisen-type rearrangement to functionalise the right hand ring to allow the dienophile tether to be incorporated. Also, the *cis*-decalin and functionalisation of the left hand ring would be revealed on hydroboration of the double bond present at the ring junction, Figure 207.



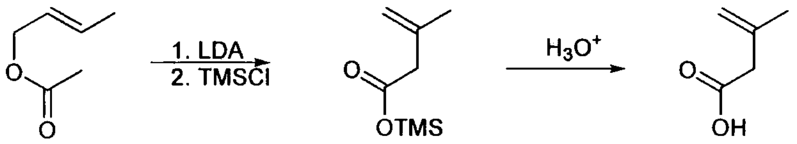
537 **538** **563** **572** **573** **574** **575**

Figure 207

4.10 Claisen Rearrangement approach

4.10.1 Ireland-Claisen Modification

Dialkylamide bases can generate ester enolates and Ireland *et al* reported the Claisen rearrangement of acetylated allylic alcohols at ambient temperature, Figure 208.[143]



576 **577** **578**

Figure 208

To initiate the reconnection strategy diol **572** had to be selectively monoacetylated. Therefore, taking advantage of the increased reactivity of the secondary alcohol over the more sterically encumbered tertiary alcohol should allow this transformation to be realised. Also, we envisaged that the tertiary alcohol should not be protected since the addition of any protecting group would result in its activation and increase the propensity to cause elimination.

Treating diol **572** with acetyl chloride in the presence of catalytic DMAP did not give the desired acetate but instead induced extensive decomposition which was evident on analysis by TLC, Figure 209. This result seems to suggest that diol **572** is unstable to the strong acid generated as a by-product even under a vast excess of amine. However, more pleasingly, treatment of diol **572** with acetic anhydride under standard conditions gave the desired monoacetate **573** which was identified by IR spectroscopy showing an OH bond stretch at 3336-3644 cm^{-1} and a strong carbonyl stretch at 1731 cm^{-1}, Figure 209.

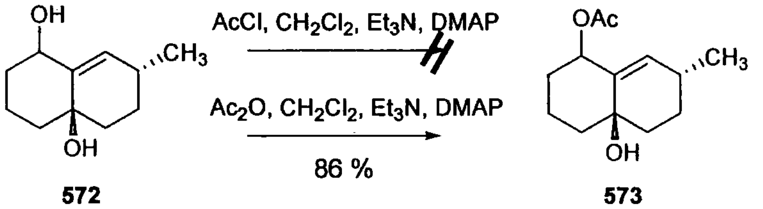
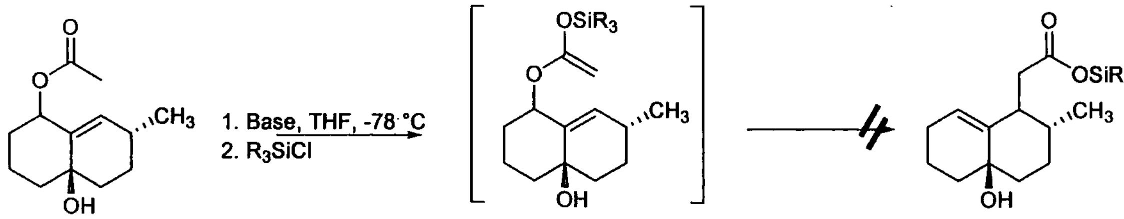


Figure 209

Thus, with monoacetate **573** in hand, an Ireland-Claisen type rearrangement was investigated. The silyl enol ether of the acetate group had to be formed to allow the sigmatropic rearrangement to occur.

Firstly, we tried to establish that the formation of silyl enol ether **579** was possible under the reaction conditions and set about trying to isolate **579**, Figure 210. Treatment of monoacetate **573** with LDA in the presence of TMSCl and subsequent non-aqueous work-up did not afford the desired intermediate. Extensive decomposition was observed on analysis of the reaction mixture, suggesting that the enol ether was highly unstable and must be generated *in-situ*. Further attempts to form the silyl enol ether *in-situ* and induce the desired sigmatropic rearrangement under various conditions were also unsuccessful, Figure 210. In each case the silyl enol formation appears to be complete by TLC analysis, however on further manipulation only decomposition products can be detected by spectroscopic methods.



573 **579** **580**

Conditions
1. 2.2 eq. LDA, TBSCl - aq w/u
2. 2.2 eq. LDA, TBSCl, HMPA - non aq w/u
3. 2.2 eq. LDA, TBSCl - non aq w/u
4. 2.2 eq. LDA, TMSCl - non aq w/u
5. 4.2 eq. LDA, TMSCl - 1 h reflux, non aq w/u

Figure 210

With the Ireland-Claisen type rearrangements proving unsuccessful, attention focussed on the traditional variant, the Claisen rearrangement[144] of the requisite vinyl ether or orthoester.

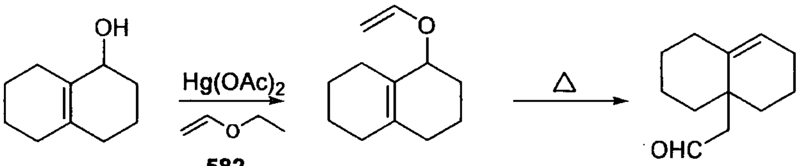
4.10.2 Claisen Rearrangement

The Clasien rearrangement has been extensively utilised in synthesis to date and there are two main methods with which to carry out the desired reaction through the formation of orthoesters or by direct formation of a vinyl ether followed by subsequent rearrangement.

The formation of orthoesters requires the use of acid and high temperatures.[145] However, vinylation occurs at relatively low temperatures without the need for acid[146] and therefore the Clasien rearrangement was firstly investigated involving this less harsh technique.

4.10.3 Claisen Reaction in Synthesis

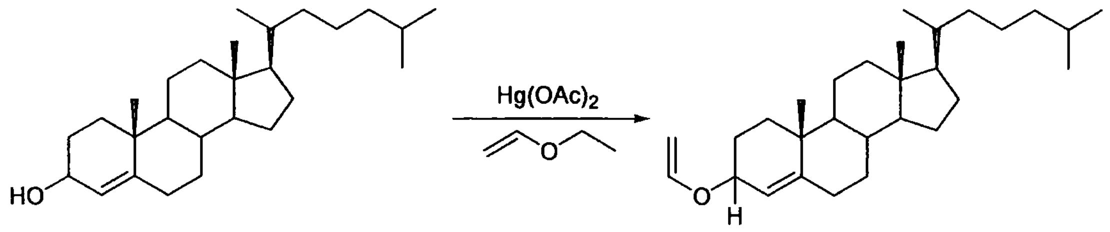
Burgsthaler and Nordin demonstrated that the desired Claisen rearrangement was successful in systems wherein at least one of the double bonds was contained in a ring system, Figure 211.[147]



581 **582** **583** **584**

Figure 211

Lesuisse *et al* also utilised [3,3] Claisen rearrangements as a key reaction during the synthesis of 19 nor-steriods.[148] However, it was reported that alkenylation can be challenging depending on the orientation of the hydroxyl group and vinyl ethers **587** and **588** could only be isolated in moderate or poor yields, Figure 212.[149]

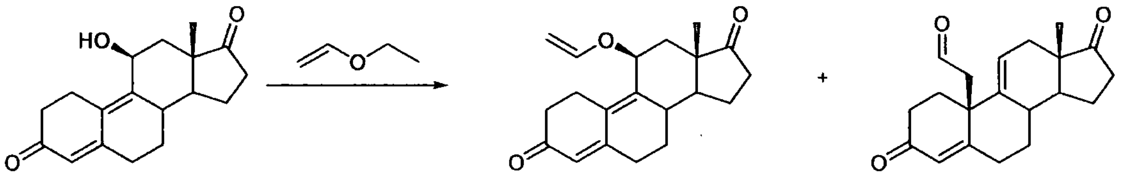


α-OH **585**
β-OH **586**

α-H, 65 % **587**
β-H, 5% **588**

Figure 212

However, similar studies with a related molecule, 11-β hydroxynordienedione, have shown that the Claisen rearrangement with ethyl vinyl ether in the presence of catalytic mercury (II) acetate can be carried out in a one-pot reaction at relatively low temperatures, Figure 213.[148] This was an unexpected result as Dauben *et al* reported that a similar system required temperatures of up to 200 °C to induce the desired rearrangement.[150]



589 **590** **591**

$Hg(OAc)_2$, rt 9 % 3 % + 72 % SM
$Hg(OAc)_2$,12 h reflux 77 %

Figure 213

Thus, with the literature precedence in hand, diol **572** was treated with catalytic mercury (II) acetate in refluxing ethyl vinyl ether and pleasingly the desired vinyl ether **592** could be isolated, albeit in poor yield, Figure 214. Optimisation of this reaction was required and subsequent attempts resulted in no increase in yield, even on doubling the reaction time. Also, further attempts at optimisation by utilising a microwave reactor also proved unsuccessful and this disappointing yield was similar observations reported by Burgstahler, Figure 212.

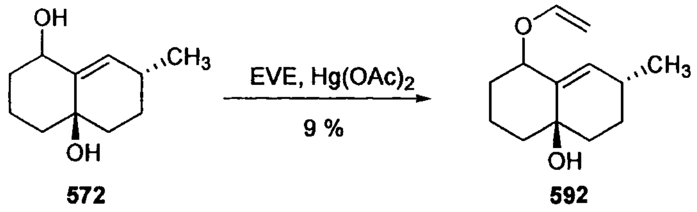


Figure 214

However, with a limited quantity of vinyl ether **592** available, the Claisen rearrangement was attempted. Vinyl ether **592** was dissolved in toluene and sealed in an NMR tube and heated at 120 °C for 60 h. Subsequent analysis by NMR spectroscopy showed that an aldehyde proton at 9.80 ppm was present, however significant decomposition had also occurred, Figure 215.

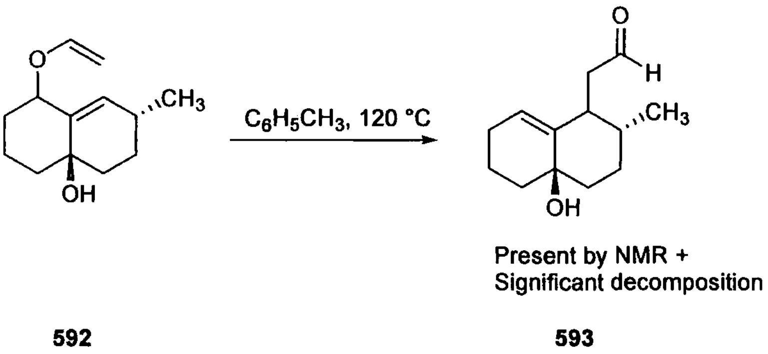
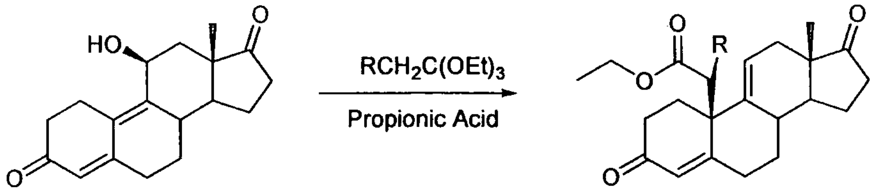


Figure 215

It became clear that the vinylation method was not going to yield the desired right hand ring functionality by rearrangement techniques. Poor incorporation of the vinyl group and the thermal instability of the Claisen precursor make this route non-viable for our studies towards Vinigrol. Thus, it was decided to investigate the orthoester method as a route to the sigmatropic rearrangement. This method would also allow us to examine the stability of diol **572** under the acidic reaction conditions.

4.10.4 Claisen Rearrangement *via* Orthoesters

Lesuisse *et al*[148] also showed the use of orthoesters to produce substituted esters by the Claisen rearrangement, Figure 216. However, the harsh reaction conditions cause competing side reactions, such as aromatisation and decomposition.

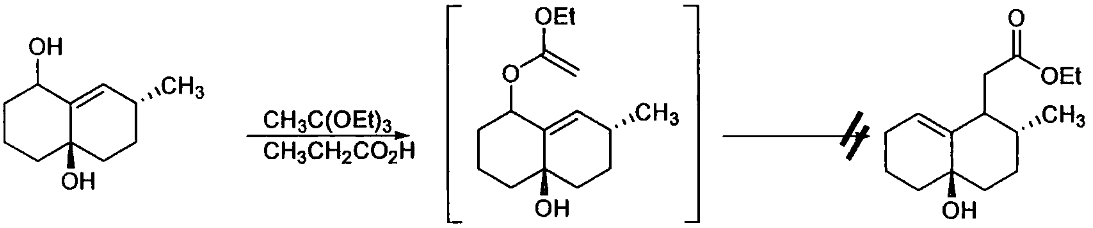


589

R = H, 81 % **594**
R = Cl, 43% **595**
R = COOEt, 81 % **596**

Figure 216

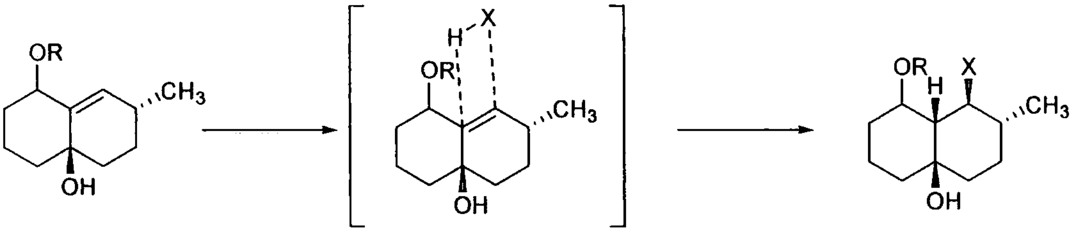
Diol **572** was heated in neat triethyl orthoacetate with catalytic propionic acid at 150 °C for 2 h, after which time analysis by TLC showed full consumption of the starting material, Figure 217. However, on analysis of the reaction mixture the desired ester could not be identified and significant decomposition was observed by ^{1}H NMR spectroscopy.



572 **597** **598**

Figure 217

The Claisen rearrangement strategy to further functionalise diol **572** had been unsuccessful due to the thermal instability of diol **572** resulting in significant decomposition. Attention was then focused on direct functionalisation of intermediate **599** and it was envisaged that formation of *cis*-decalin and functionalisation of the left hand ring could be accomplished a single synthetic step by *syn*-addition to the double bond, Figure 218.



599 **600** **601**

R = H or PG

Figure 218

4.11 Hydroboration of Intermediates 572/573

Hydroboration of **573** would reveal *cis*-decalin **602** on top-face attack of the least hindered end of the double bond and also allowing a hydroxyl group to be introduced on the unfunctionalised ring. Monoacetate **573** was to be utilised as it would allow selective manipulation of the two secondary alcohols that would be obtained. To this end, monoacetate **573** was treated with up to 4 equivalents of $BH_3.Me_2S$ complex and even after 24 h there was no observed reaction by TLC, Figure 219.

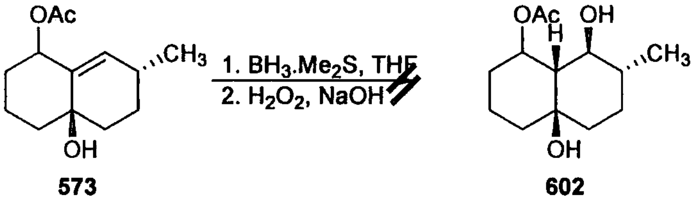


Figure 219

It was subsequently hypothesised that the protecting group was inhibiting hydroboration and thus the acetate should be replaced by a silyl group. To this end, diol **572** was treated with TBSCl in the presence of imidazole and afforded the TBS ether **603** in moderate yields, Figure 220. The ether **603** was identified by the appearance of the [9H] singlet at 0.88 ppm in the ^1H NMR spectrum. The TBS derivative was subjected to $BH_3.Me_2S$ complex as previously described. Again there was no observed reaction and starting material was recovered quantitatively on work-up, Figure 220. Subsequent efforts to carry out the hydroboration on free diol **572** were also unsuccessful, Figure 220. The unreactivity of **572**, **573** and **603** towards hydroboration is unclear.

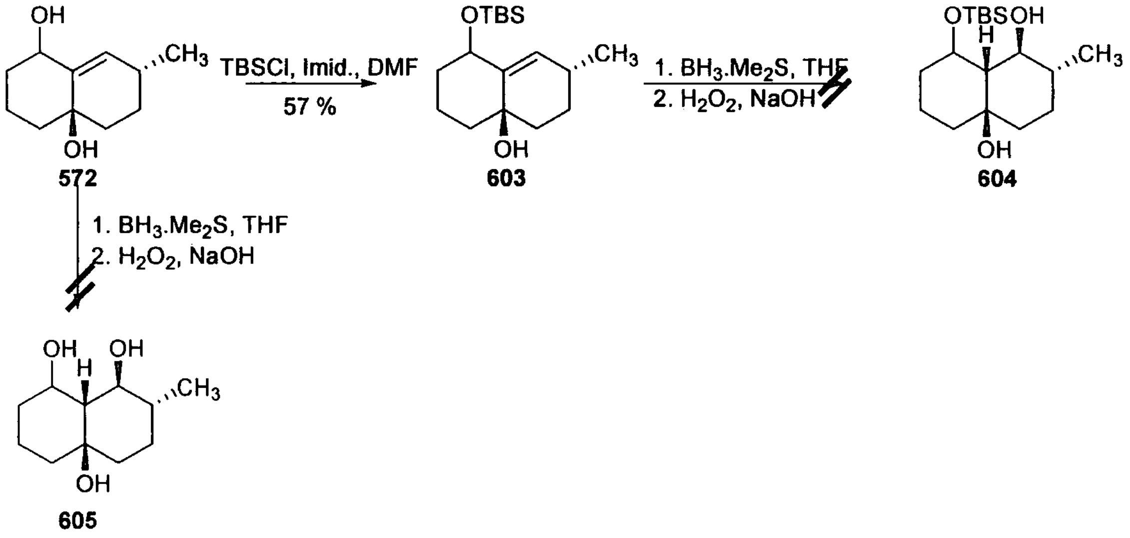


Figure 220

4.12 Conclusions

During this investigation it was identified that substituted tetralones could yield the appropriate substitution pattern after functional group interconversion. Palladium-catalysed stereoselective ring-opening of the vinyl epoxide did not allow installation of the desired tertiary alcohol group at C8′ due to the intolerance of the methodology to the rigid cyclic system. However, more encouragingly investigations utilising S_N2'-ring opening of vinyl oxiranes proved successful, yielding diol **572** as a single diastereomer. Diol **572** was identified as a key intermediate which would allow the necessary functionalisation to be built on to the existing ring. Attempted [3,3]-sigmatropic rearrangements proved to be an ineffective tool for effecting functionalisation of the acetate **573** or vinyl alcohol **592** due to the intolerance of the precursors to strong heating or mild acids. Thus, recognising that derivatives of diol **572** could be functionalised directly offered a solution to the problem. However, attempted hydroboration did not provide the desired diol (or triol) due to steric /electronic factors surrounding the trisubstituted double bond. Tetralone derivatives offer an alternative route to *cis*-decalins, though this was an ineffective method to provide the desired subsitution pattern in this case. The next section details an alternative approach to synthesising the desired *cis*-decalin by a Diels Alder cycloaddition.

4.13 Diels Alder Cycloaddtions : Synthesis of *cis*-Decalins

4.13.1 Introduction

Diels Alder cycloadditions have been utilised extensively in the synthesis of *cis*-decalins (see Section 4.4). In approaches to the synthesis of Vinigrol it was envisaged that the *cis*-decalin contained within the carbocyclic skeleton could be installed using an intermolecular Diels Alder reaction, Figure 221. The 8-membered ring would be revealed on Grob-type ring fragmentation of intermediate **606**, Figure 221. Further functional group conversion identifies bicyclic α,β-unsaturated ketone **608**, which could in turn be disconnected to come from diene **609** and cyclic dienophile **430**.

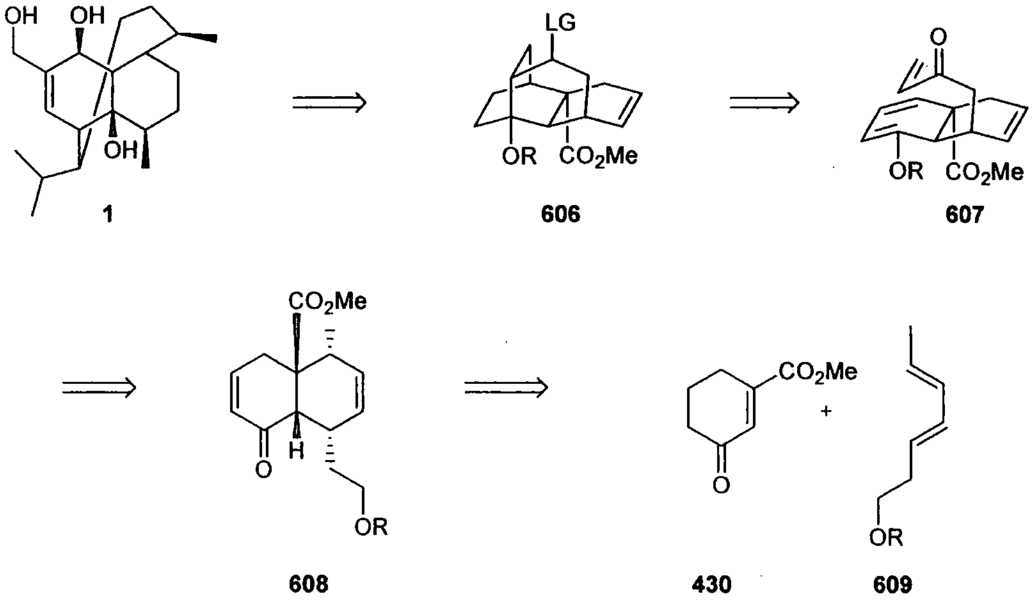


Figure 221

However, initial attempts to induce this cycloaddition with α,β-unsaturated ester **430** with simple dienes, *e.g.* isoprene and 1-methoxybuta-1,3-diene were unsuccessful, even under forcing conditions (sealed tube, 150 °C, 12 h), Figure 222. This result is consistent with that observed in the literature.[151] This suggested that the dienophile required additional activation to allow the desired cycloaddition to occur, Figure 222.

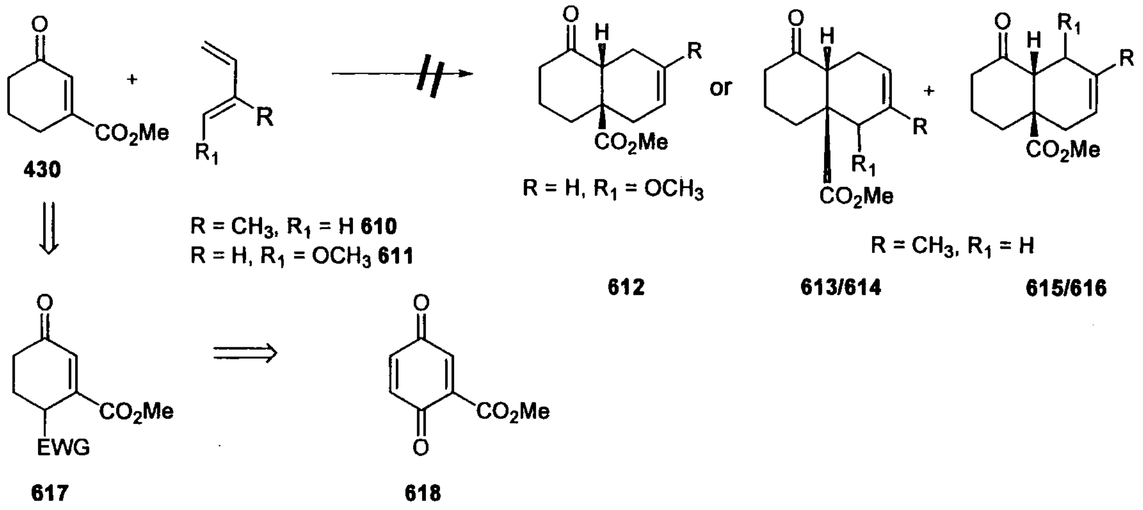


Figure 222

Thus, on revisiting the retrosynthetic strategy it suggested that the desired *cis*-decalin could be obtained from an alternative Diels Alder cycloaddition between quinone **618**[152] and appropriately functionalised diene **609**, Figure 223. Four of the stereocentres required for Vinigrol can be installed in a single synthetic step. Also, the ester group attached to the quinone **618** would be installed at position C8′, where we require an OH group. Reduction of the ester to the aldehyde, Baeyer-Villiger oxidation and hydrolysis of the formate ester would produce the desired tertiary alcohol. Thus, to continue with the retrosynthetic analysis shown below, it was necessary to prepare bicyclic systems such as **619**.

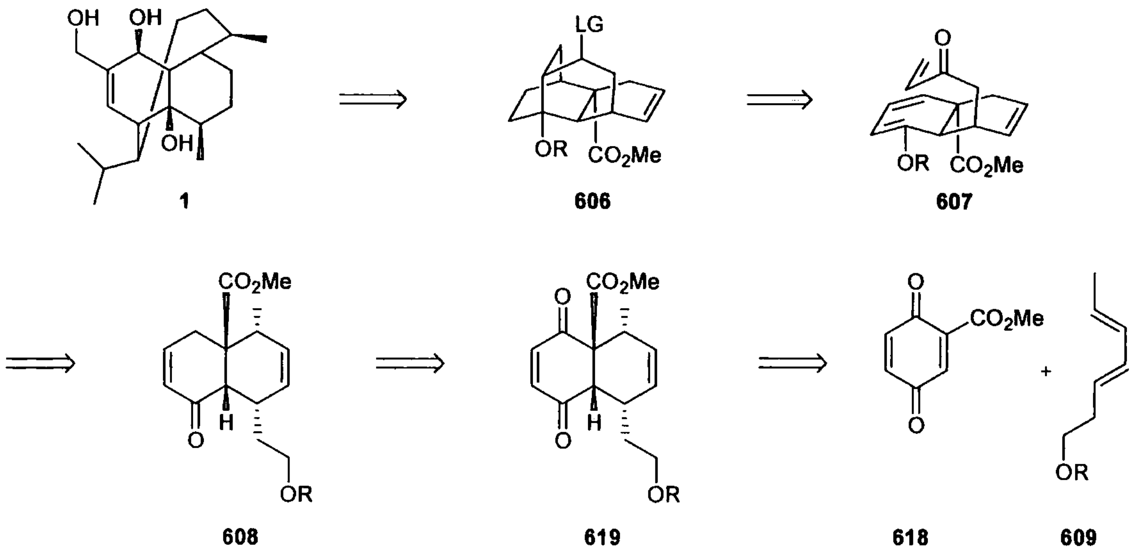


Figure 223

Limited reports exist on the reaction of quinones with unsymmetrical dienes. However, excellent regioselectivity can be obtained by utilising 1-substituted buta-1,3-dienes and we initially envisaged a selective alkylation approach to install the dienophile tether, Figure 224.

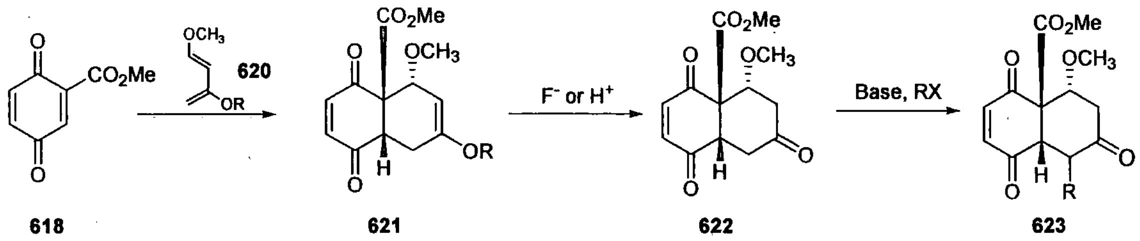


Figure 224

4.14 Diels Alder Cycloadditions of Activated quinones

4.14.1 Selective Alkylation Approach

To allow the selective alkylation strategy to be implemented, bicyclic structures such as **628** were required. Thomas *et al*,[153] in efforts towards the dihydroagrofuran framework, identified that the Diels Alder adduct of activated 1,4-benzoquinones and oxygenated buta-1,3-dienes could provide access to the bicyclo[4.4.0]decanes of use in the synthesis of polyhydroxylated dihydroagarofurans, Figure 225.

Thus, by treating quinone **618** with diene **627** at 5 °C for 2 h, cycloadduct **628** was obtained in almost quantitative yield as a single regio- and stereo-isomer, Figure 225. Further elaboration of adduct **628** gave ketones **629** and **630** which can be utilised as intermediates in the synthesis of polyhydroxylated dihydroagarofurans.

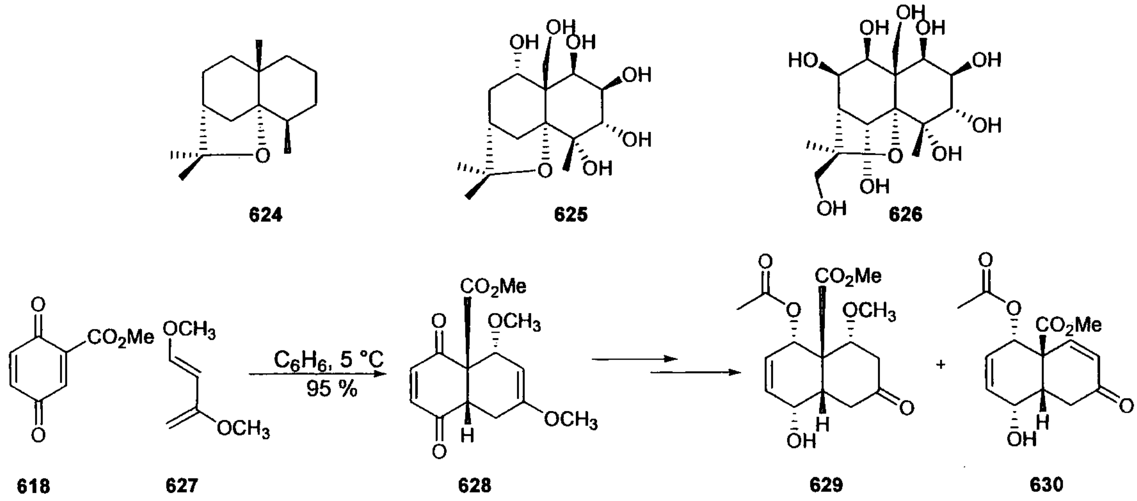


Figure 225

With the synthetic strategy outlined in Figure 223 and Figure 224, the initial objective was to prepare cycloadduct **628**. 1,3-dimethoxybuta-1,3-diene was not commercially available and is prepared *via* a multi-step and low-yielding synthesis. Thus, Danishefsky's diene **632** was identified as a commercially available alternative. It was hoped that this would allow rapid investigation of derivatives of cycloadduct **633** to be explored, Figure 226.

Oxidation of commercially available 2,5-dihydroxybenzoic acid methyl ester **631** with manganese dioxide under standard literature conditions afforded the desired activated quinone **618**.[152] Thus, with the diene **632** and quinone **618** in hand, the cycloaddition was attempted. Pleasingly, bicyclic intermediate **633** was obtained as a single stereo- and regio-isomer on stirring **618** with **632** at room temperature. Cycloadduct **633** was identified by the reduction in the number of olefinic protons from [6H] to [3H] in the ^{1}H NMR spectrum and the appearance of a proton at 5.17 ppm corresponding to the enol ether functionality.

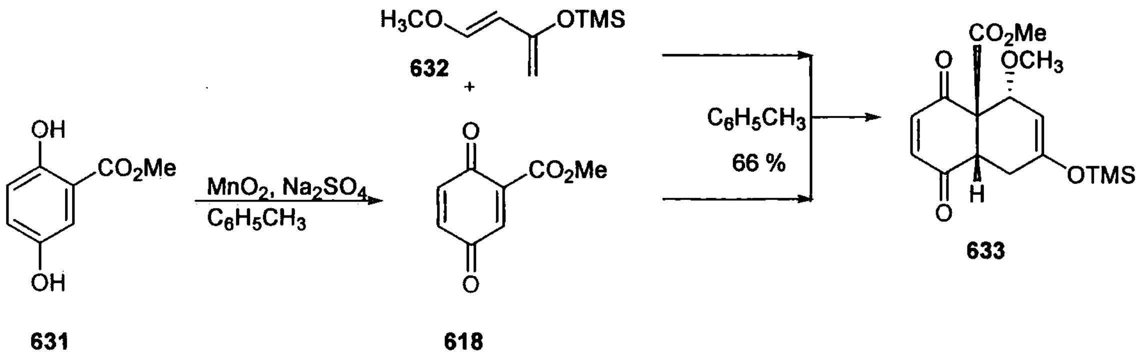


Figure 226

Cycloadduct **633** was then subjected to catalytic *p*-toluenesulfonic acid in order to reveal the desired ketone **622**. However on analysis of the crude reaction mixture by ^{1}H NMR spectroscopy it was revealed that extensive decomposition occurred, Figure 227.

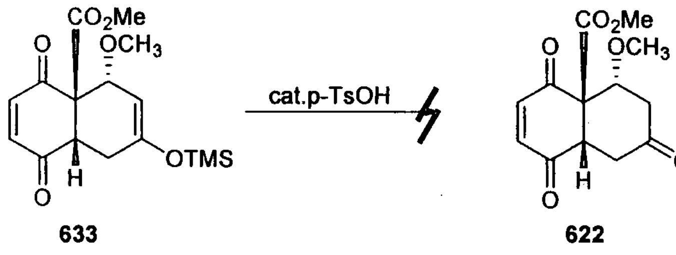
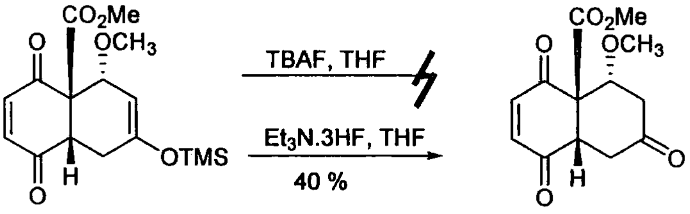


Figure 227

Undeterred by this disappointing result, alternative and basic deprotection methods were investigated. The use of TBAF also resulted in decomposition of silyl enol ether **633**. However more pleasingly, Et$_3$N.3HF afforded the desired ketone **622**, albeit, in poor yield and was identified by the disappearance of the TMS singlet at 0.00 ppm, Figure 228. Optimisation of this deprotection step was required and despite considerable experimentation, this remained precarious resulting in considerable decomposition on scale up.

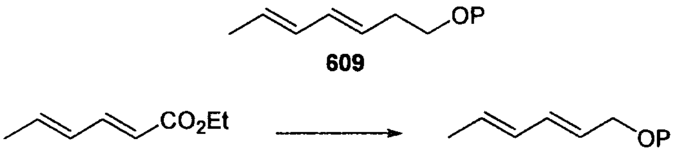


633 622

Figure 228

The route towards selective alkylation proved capricious and thus methods to directly install the desired alkyl group were examined. Since the dienophile fragment was deemed as optimal for reactivity in Diels Alder cycloaddition, the effect of changing the diene fragment was examined.

The retrosynthetic strategy had identified an unsymmetrical diene **609** as the required coupling partner for the Diels Alder reaction, Figure 223. Heptadiene derivatives are not commercially available and a model study was initiated employing derivatives of the readily available ethyl sorbate to test the Diels Alder methodology, Figure 229.



609

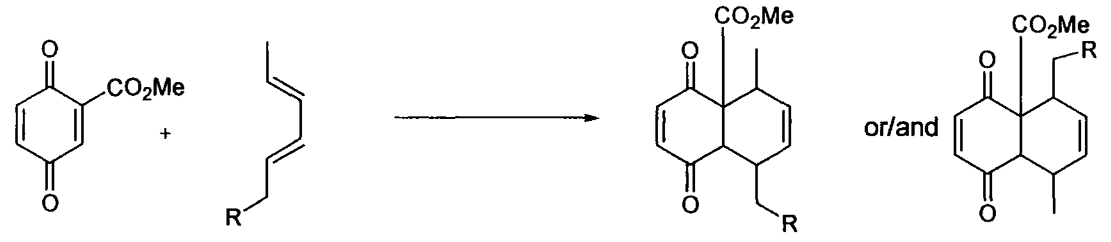
634 635

Figure 229

4.15 Dienes derived from Ethyl Sorbate and a Model Study

4.15.1 Introduction

The dienes identified as synthons from the retrosynthetic strategy were unsymmetrical in nature and two possible regioisomers can be formed in the cycloaddition, Figure 230. Thus, we needed to investigate the selectivity that could be obtained and examine the effect of the diene on the regioisomeric ratio.



618 **636** **637** **638**

Figure 230

4.15.2 Diels Alder and Regioselectivity

Kraus *et al*[154] investigated methods towards a regioselective Diels Alder reaction in their efforts towards CC-1065 and studied the effect exerted by substituents not directly attached to the diene. Dienes **639** and **640** exhibit synthetically useful regioselectivity when tested with a variety of dienophiles, Figure 231. When reacted with quinone **618**, diene **639** yields a 60:40 ratio of isomers whereas diene **640** affords a 20:1 ratio of isomers, Figure 231. Thus, by tuning the electronic and steric effects of the oxygen protecting group, the Diels Alder reaction can essentially be made regioselective.

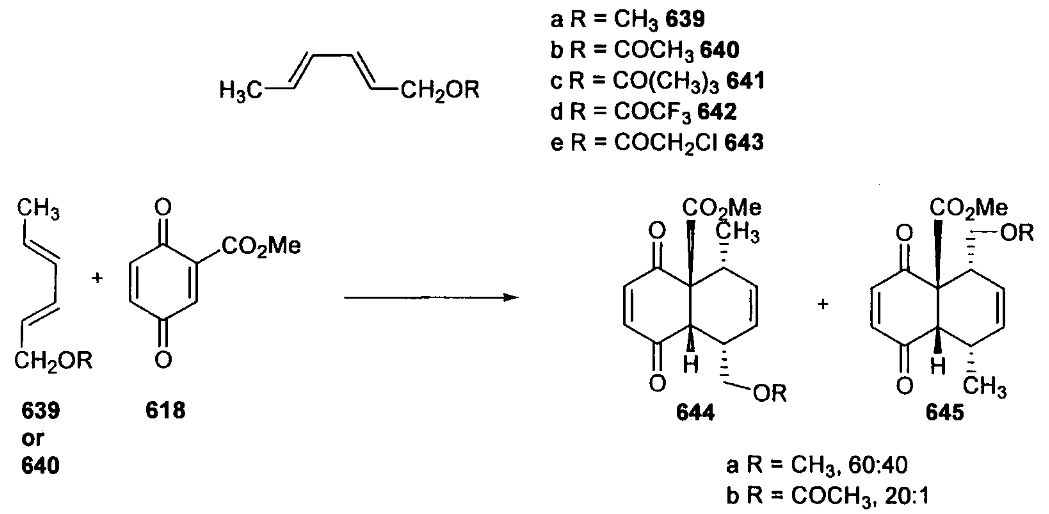


Figure 231

The desired cycloaddition had been carried out in the presence of mild Lewis acids. Suryawanshim *et al,*[155] in investigations examining Diels Alder reactions of electron deficient dienes, observed a rate acceleration effect when quinone **618** and diene **646** were reacted in the presence of LPDE (lithium perchlorate in diethyl ether) *versus* the thermal process, Figure 232. Cycloadduct **647** was obtained in moderate yield as a single regioisomer.

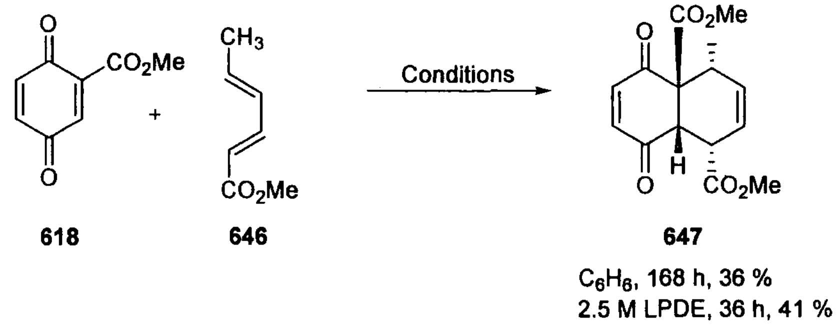


Figure 232

Thus, pleasingly the desired cycloaddition could be made regioselectively. However, neither the acetate **644** nor ester **647** functionality on the diene were optimal for the manipulation to install the dienophile fragment. Easy protecting group removal or functional group conversion was required without any significant effect on the bicyclic system **644/647**. Removal of acetate groups is traditionally carried out in basic media and the acidic proton on bicyclic intermediate **644/647** may lead to epimerisation and give rise to mixtures of *cis*- and *trans*-decalins **648/649**, Figure 233. Also, the selective reduction of a single ester in the presence of the other desired carbonyl functionality would be problematic.

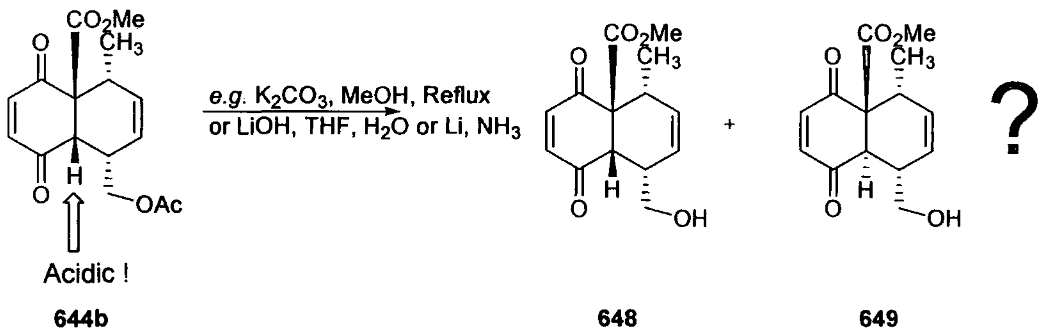


Figure 233

To this end silyl protecting groups were identified as a solution to avoid possible epimerisation and selectivity problems. To test this hypothesis a small range of derivatives of ethyl sorbate **634** were synthesised. Consequently, ethyl sorbate **634** was treated with lithium aluminium hydride to give alcohol **650**, which subsequently produced two different sterically demanding dienes on reaction with TBSCl or TBDPSCl. Silyl ethers **651** and **652** were identified by the appearance of the ^{t}Bu signal at 0.92 and 1.09 ppm respectively in the ^{1}H NMR spectrum, Figure 234. It is hypothesised that the two different protecting groups would allow the steric tolerance of the cycloaddition to be investigated and might allow us to obtain good regiocontrol. Also, ethyl sorbate was deconjugated with LDA and subsequent acidic quench to examine the effect of an unsubstituted double bond on the regioselectivity obtained,

Figure 234. Deconjugated diene **653** was characterised by the appearance of [2H] doublet (J = 7 Hz) at 3.09 ppm in the ^{1}H NMR spectrum. Diene **653** was then treated with lithium aluminium hydride and the alcohol that was produced was immediately treated with TBSCl to yield silyl ether **654**. **654** was identified by the loss of the ester signals at 1.22 and 4.12 ppm and the appearance of a [2H] triplet (J = 7 Hz) corresponding to 1-H_2 at 3.64 ppm in the ^{1}H NMR spectrum and the IR spectrum showed the loss of the carbonyl stretch at 1737 cm^{-1}.

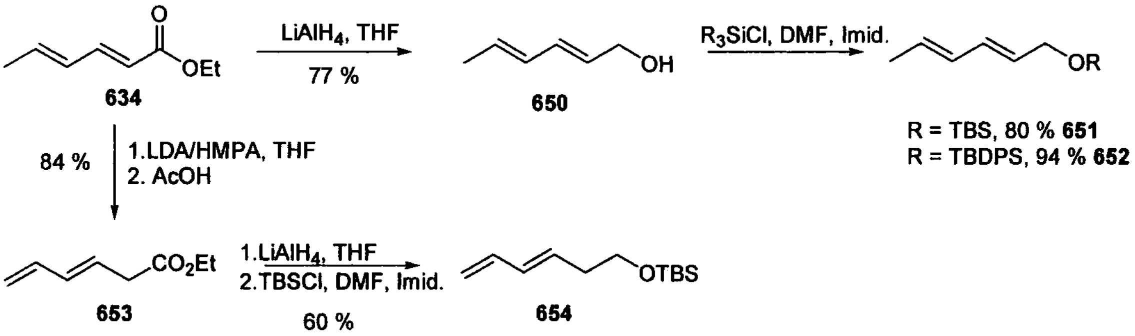


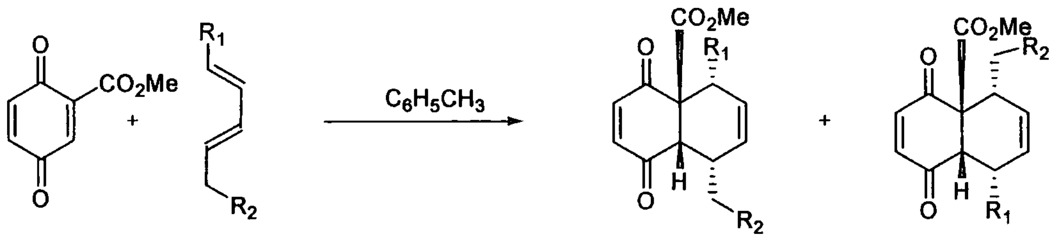
Figure 234

Thus to observe the effect on the regioselectivity obtained, dienes **651**, **652** and **654** were then treated with quinone **618** at room temperature and the results obtained are shown in Table 4. A single regioisomer was obtained from the deconjugated diene **654**. However, this result was not unexpected since it can be rationalised on electronic arguments.

The methyl-TBS diene **651** however gives a moderate regioselectivity of 2:1 (desired : undesired isomer). Also, on increasing the steric bulk of the protecting group on oxygen, TBDPS ether **652** disappointingly gave an identical ratio. Thus, it appears that in the case of silyl protecting group's steric bulk, is not important in obtaining a regioselective cycloaddition. Thus, comparing the results obtained below with that of Kraus *et al*, it appears that not only was steric bulk important, but the associated electronic nature of the diene are extremely significant.

Thus, investigations to increase the regioselectivity of the Diels Alder cycloaddition were undertaken. The Diels Alder reaction has incorporated the use of Lewis acids to promote rate acceleration, and coordination of the dienophile can allow regioselectivity to be observed.

Table 4 - Regioselectivity obtained with activated quinone 618 with a range of dienes

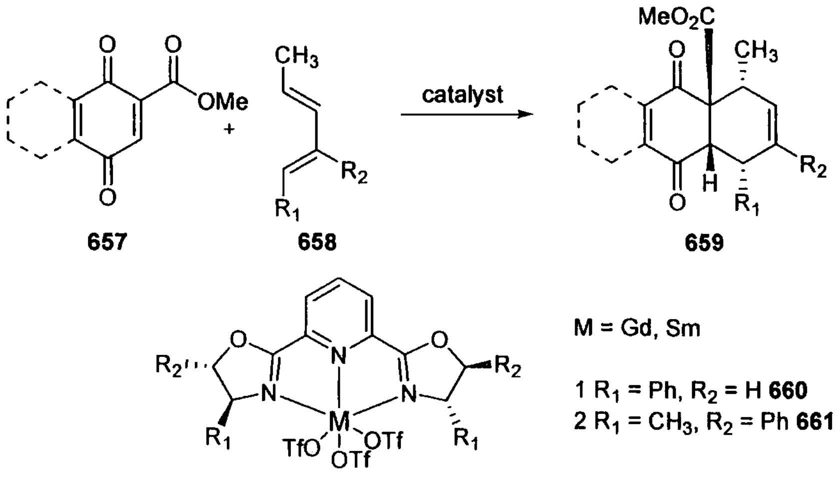


618 + **651** / **652** / **654** → **655** (A) + **656** (B)

R_1	R_2	Regioselectivity (A:B)
H	CH_2OTBS	0:100
CH_3	OTBS	67:33
CH_3	OTBDPS	67:33

4.15.3 Lewis Acid Catalysis

Enantioselective Diels Alder reactions have been achieved through the use of both chiral auxiliaries and chiral Lewis acids. However only a handful of chiral catalysts effectively mediate selected quinone Diels Alder reactions in moderate to good enantioselectivities.[156] Evans *et al*[157] report chiral Lewis acid complexes **660/661** derived from pyridyl-bis(oxazoline) (pybox) ligands and samarium and gadolinium triflates that are effective catalysts in quinone Diels Alder reactions, Figure 235.



657 **658** **659**

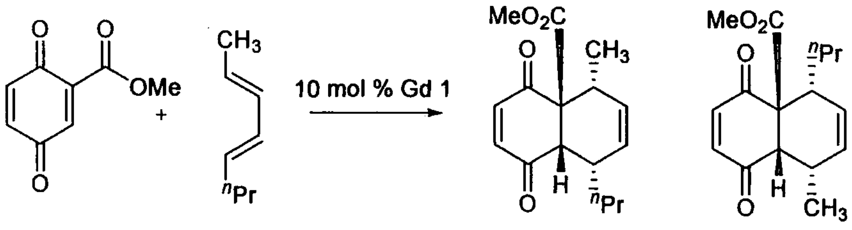
M = Gd, Sm

1 R_1 = Ph, R_2 = H **660**

2 R_1 = CH_3, R_2 = Ph **661**

Figure 235

Thus, the chiral complexes were used with a variety of quinones and dienes and high regioselectivities and enantioselectivites of >84 % were obtained in every case, eg Figure 236.



98 % ee, 15 : 1

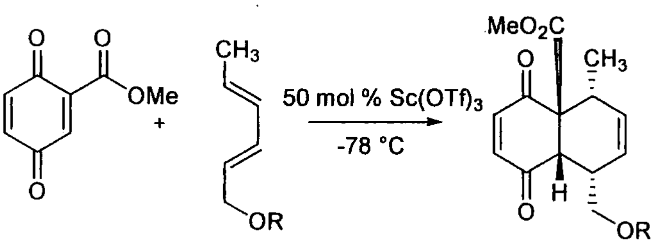
618 **662** **663** **664**

Figure 236

Thus, as good regioselectivities can obtained with the chiral lanthanide complexes, we hypothesised that the mild Lewis acids alone should allow good regioselectivity to be obtained in our model system.

To this end TBDPS diene **652** and quinone **618** were treated in the presence of 50 mol % of Sc(OTf)$_3$ at -78 °C and after 16 h the reaction was quenched with sodium hydrogen carbonate. Subsequent purification of the residue pleasingly yielded a single regioisomer, **665**. **665** was identified by the appearance of a single set of quinone olefinic signals at 6.64 and 6.73 ppm in the ^{1}H NMR spectrum, Figure 237. Subsequent X-ray crystallography identified that bicyclic qunione **665** possessed the desired regio- and stereo-chemistry (see Appendix and Figure 238). The Diels Alder cycloaddition had allowed four of the stereocentres of Vinigrol to be installed in a single step.

TBS diene **651** was also treated with quinone **618** in the presence of Sc(OTf)$_3$ and gratifyingly a single regioisomer could also be obtained with the sterically smaller protecting group.



618 **651 TBS** or **652 TBDPS**

R = TBDPS, 29 % **665**
R = TBS, 27 % **666**

Figure 237

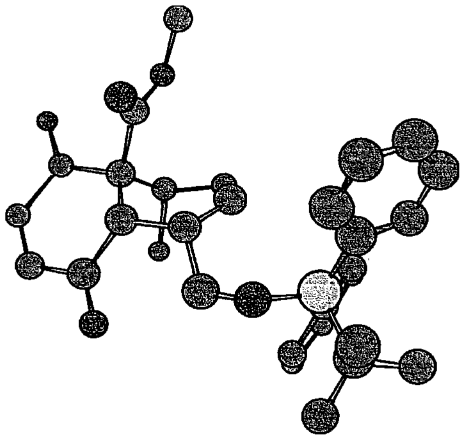


Figure 238 - X-ray Structure of 665 (shown without H's for clarity)

Thus, the extra activation of the dienophile by Lewis acid catalysis allows unsymmetrical dienes to show excellent regioselectivity. It was hypothesised that the coordination of the Lewis acid favours approach of the least hindered end of the diene towards the site of complexation yielding the desired bicyclic compound, Figure 239.

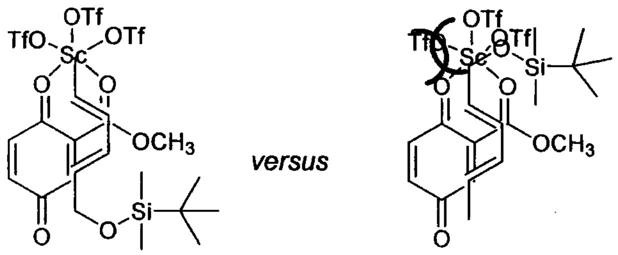


Figure 239

The yields of the cycloaddition were poor and it was clear that if this route was to be investigated, further optimisation of the Diels Alder cycloaddition conditions would have to be examined.

To this end a variety of reaction variables were investigated and the results are shown in Table 5.

Diels Alder cycloaddition of *in-situ* generated quinone with diene **651** gives a considerable increase in yield, however the observed regioselectivity is still poor. Decreasing the temperature of the *in-situ* method causes no reaction to be observed. This is attributed to the phenol oxidation not occurring at low temperature. Also, silver oxide is a relatively expensive reagent and efforts began on utilising manganese dioxide as the oxidant and this allowed the large scale preparation of quinone **618**. Subsequent investigation of the reaction temperature revealed that it has a significant impact on the observed yield of the reaction since complete decomposition of the diene was detected with temperatures above -25 °C. It was hypothesised that this was due to incompatibility of the silyl protecting group with the Lewis acid. The breakthrough of the optimisation was observed when the quantity of Lewis acid was studied and a simple 10-fold reduction causes a 2-fold increase in isolated yield with no loss of regiochemical integrity over the same reaction time. This result appears to be consistent with the temperature study in that the cycloadduct **666** and/or diene **651** are unstable in contact with high concentrations of Lewis acid even at low temperatures.

The limitation in this procedure is that less than 5 mol % of the Lewis acid requires a considerable increase in reaction time of up to 5 days and after which time the reaction was still not complete. This was not a viable time scale to allow rapid investigation of this synthetic route.

Table 5 - Optimisation of the Synthesis of 666

Oxidant	Temperature (°C)	Lewis Acid (mol %)	Yield (%)	Regioselectivity
Ag_2O	0	-	67	72:28
Ag_2O	-10	50	34	>99:1
Ag_2O	-25	-	68	70:30
Ag_2O	-78	-	no reaction	-
Ag_2O	-78	10	41	>99:1
MnO_2	25	10	decomp.	-
MnO_2	0	10	decomp.	-
MnO_2	-25	10	decomp.	-
MnO_2	-78	50	27	>99:1
MnO_2	-78	10	52	>99:1
MnO_2	**-78**	**5**	**67**	**>99:1**

With the significant increase in yield observed, major investigations could begin in order to eliminate the undesired ketone functionality present on the bicyclic intermediate **666**, Figure 240 (Also see retrosynthetic analysis, Figure 223).

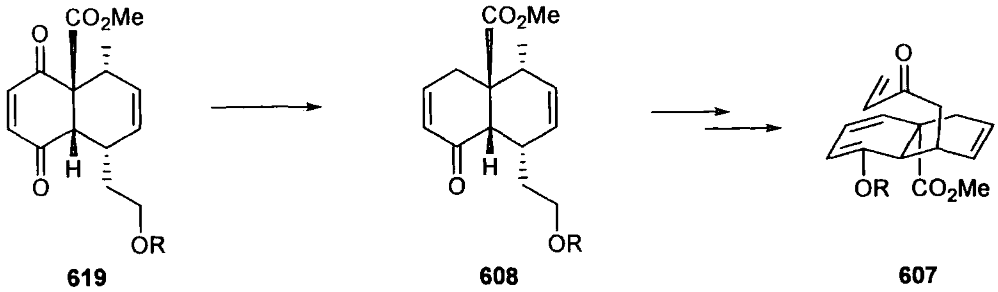


Figure 240

4.16 Ketone Differentiation

4.16.1 Introduction

Bicyclic intermediate **666** has two ketone functionalities and conversion of the ketone adjacent to the ester into a methylene group was required, Figure 241. It was envisaged that internal acetal formation would act as a protecting group to allow selective manipulation of the undesired ketone by the scheme shown in Figure 241. Thus, subsequent ketone reduction and conversion into the bromide would allow installation of the diene unit by radical techniques.

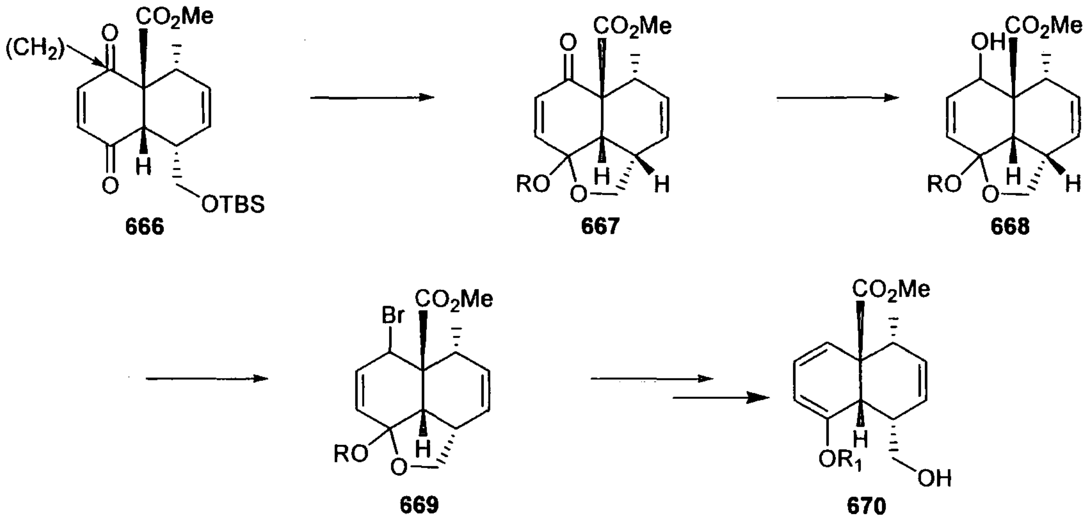
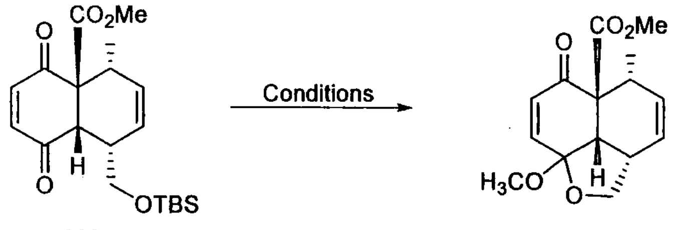


Figure 241

4.16.2 Internal Acetal Formation

As a result of the reconnection strategy shown in Figure 241, alcohol deprotection and internal acetal formation were to be examined. It was envisaged that this process could be carried out in a one pot process and consequently this was investigated, Figure 242. The results shown in Table 6, demonstrate that after minimal optimisation the desired ketone differentiation can be carried out in excellent and reproducible yields. Acetal **671** was identified by the appearance of a second OCH_3 signal at 3.45 ppm in the ^1H NMR spectrum.



666

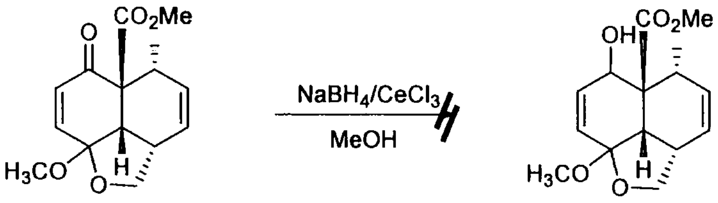
671

Figure 242

Table 6 - Optimisation of the Formation of Acetal 671

Acid	Solvent	Eq.	Yield (%)
5M HCl	THF	5	-
5M HCl	MeOH	5	<15
p-TSA	MeOH	1	50
p-TSA	MeOH	0.25	74

Thus, with significant quantities of internal acetal intermediate **671** in hand, conversion to bromide **670** *via* allylic alcohol **669** was examined. Due to the presence of the ester, selective ketone reduction was required. However, the use of Luche reduction conditions would easily allow this transformation to be carried out, Figure 243. Consequently ketone **671** was treated with $CeCl_3/NaBH_4$ in MeOH and TLC analysis after 5 minutes showed that the reaction was complete. However, on examination of the crude ^1H NMR spectrum significant decomposition was evident. Despite this, considerable efforts to isolate alcohol **672** by reducing the reaction temperature, equivalents of borohydride and reaction time and even *in-situ* trapping of alcohol **672** were all unsuccessful. We hypothesise that the instability of the allylic alcohol causes fragmentation of the bicyclic system resulting in decomposition.



671

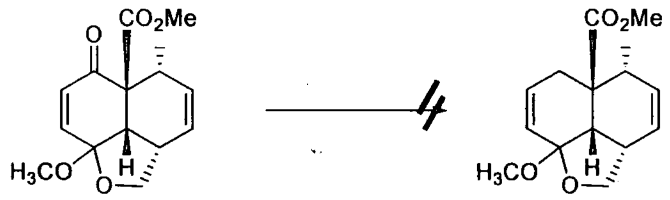
672

Figure 243

The instability of alcohol **672** indicated that an alternative strategy to install the diene fragment would have to be developed and direct conversion of ketone **671** to unsaturated acetal **673** was examined, Figure 244. Methods such as Wolff Kishner[158] and Clemmensen reductions,[159] reduction of tosyl hydrazones[160] and reduction of thioacetals[161] can effect this transformation directly. Clemmensen reduction is carried out in acidic media which would cause decomposition of the acetal. Addition of a thiol to an α,β-unsaturated system may cause Michael addition, thus these reactions were not utilised in this initial study.

To this end ketone **671** was treated under Huang Minlon modification[162] of the traditional Wolff-Kishner reduction and after 2 h at reflux TLC analysis showed complete consumption of the starting acetal. However on work-up and purification, analysis by NMR spectroscopy showed no evidence of the acetal functionality. The delicate nature of the acetal appears not to tolerate these harsh reaction conditions.

Undeterred by this disappointing result, an investigation began to test the compatibility of acetal **671** with the tosyl hydrazone reduction method, Figure 244. The reduction of tosyl hydrazones with boron hydrides offers a mild alternative to the Wolff-Kishner and Clemmensen reductions. Acetal **671** was treated with tosyl hydrazide in refluxing ethanol, but even after 24 h the starting material was still present by TLC analysis. Initial investigations in this area have not been examined further due to time constraints.



671 1. Hydrazine, KOH, Ethylene Glycol or, **673**
2.(a) Tosyl Hydrazide, (b)$NaCNBH_3$

Figure 244

4.17 Saturated Acetal System

4.17.1 Strategy

The inability to form alcohol **672** or induce a ketone reduction caused a re-evaluation of the reconnection strategy to that shown in Figure 241. The decomposition pathway observed in hydride reduction of ketone **671** was to be minimised by removal of the unsaturation present in the molecule. The undesired ketone functionality was to be removed by conversion to the enol triflate **675** and subsequent hydride reduction, Figure 245.

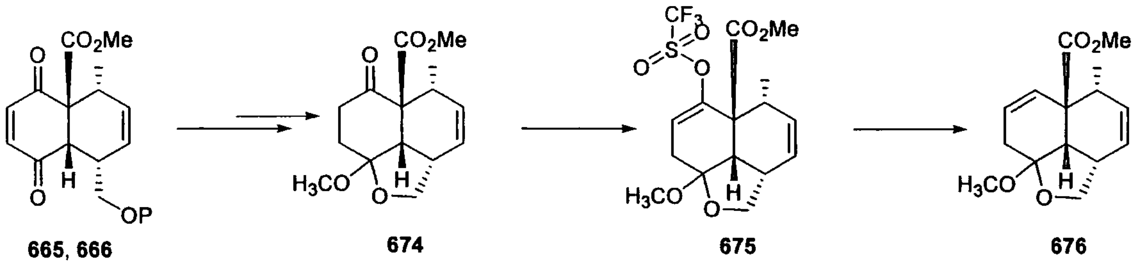
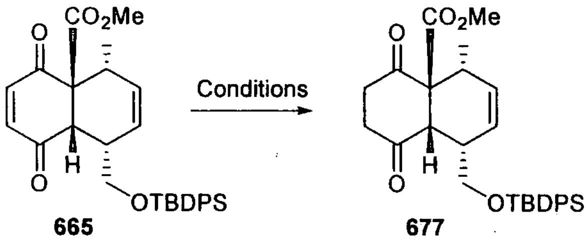


Figure 245

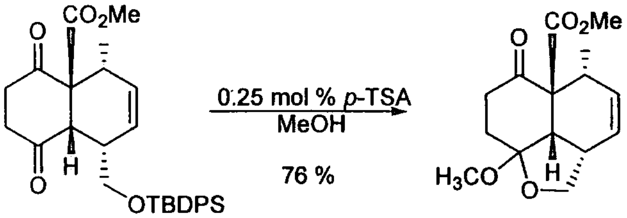
With gram quantities of unsaturated bicyclic diketone **665** available, the hydrogenation reaction was studied. Ketone **665** was subjected to standard hydrogenation conditions (5 % w/w Pd/C, ethanol, $H_{2(g)}$). However on analysis of the reaction mixture the desired product could not be isolated. It appears that the starting material or the products are incompatible to prolonged exposure to the hydrogenation conditions, Figure 246. Thus to decrease the propensity of **665** towards decomposition under the traditional conditions, ketone **665** was dissolved in a 1:1 mixture of ethyl acetate and ethanol and passed through the flow system of the H-Cube™ with a Pd/C catalyst cartridge. Removal of the reaction solvent and analysis of the residue gave a surprising result. Only the quinone double bond had been reduced, Figure 246. Diketone **677** was identified by the loss of olefinic signals at 5.54 (124) and 5.59 (130) ppm in the ^{1}H and ^{13}C NMR spectra. The hydrogenation was repeated under more forcing conditions (40 °C, 50 bar) to investigate if complete reduction could be observed, however only the mono-saturated ketone **677** could be recovered.



H_2, Pd/C - decomp.
H-Cube - Pd/C, rt quan.
- Pd/C, 40 °C, 50 bar - quan.

Figure 246

Thus, to continue the reconnection strategy outlined in Figure 245, diketone **677** was to be converted to the internal acetal **674** to again allow differentiation of the two ketone functionalities. Pleasingly, when ketone **677** was treated under the optimised acetal formation conditions the yield obtained was comparable to that observed on the unsaturated system, Figure 247. Internal acetal **674** was identified by the appearance of a [3H] singlet at 3.25 ppm in the ^1H NMR spectrum and loss of one carbonyl signal at ~206 ppm in the ^{13}C NMR spectrum.

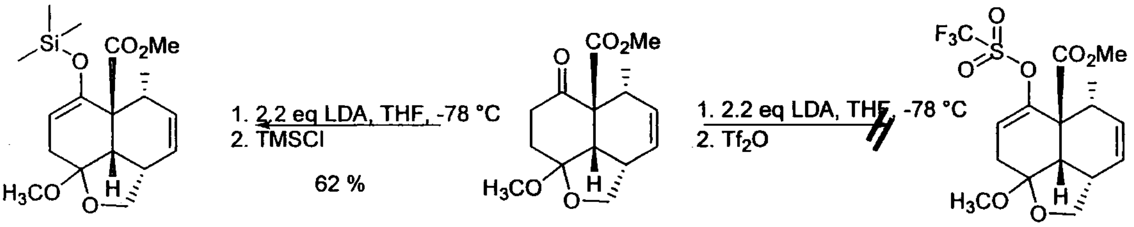


677 **674**

Figure 247

4.17.2 Enol Triflate Formation

Ketone **674** was treated with freshly prepared LDA at -78 °C and then with triflic anhydride, Figure 248. TLC analysis of the reaction mixture showed that no reaction had taken place. It was hypothesised that the desired deprotonation had not taken place. To this end, ketone **674** was again treated with LDA but was quenched with TMSCl. Pleasingly, silyl enol ether **678** was isolated as the major component of the reaction mixture and was characterised by the appearance an olefinic proton at 4.78 ppm in the ^1H NMR spectrum, Figure 248. The instability of the silyl enol ether **678** did not allow any further analysis or characterisation.



678 **674** **675**

Figure 248

With the confidence that metallation could be induced, ketone **677** was once again treated with LDA and quenched with triflic anhydride. Subsequent TLC analysis showed that no reaction had taken place and the reaction conditions were then subjected to optimisation. The number of equivalents of base (2.2-4.2), triflate agent (Tf_2O, $PhNTf_2$) and the use of additives (HMPA) were investigated but on application of these the desired enol triflate could not be isolated. The reasons for the lack of reactivity of the enolate towards triflate formation is unclear at this time.

4.18 Elimination Approach

As formation of enol triflate proved unsuccessful, an alternative route utilising ketone **674** to allow removal of the unwanted ketone functionality was proposed, Figure 249.

Reduction and activation of the C6 ketone should allow base-induced elimination to yield the desired methylene group.

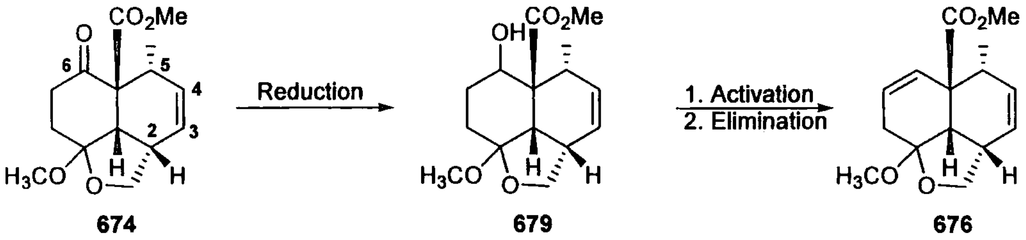


Figure 249

Sodium borohydride reduction of ketone **674** gave alcohol **679** in moderate yield characterised by the appearance of the C(H)OH proton at 4.48 ppm in the ^{1}H NMR spectrum, Figure 250. However, for reasons that are not clear this reaction was somewhat capricious, often affording complex mixtures of products. Alcohol **679** was treated with mesyl chloride in the presence of catalytic DMAP and the reaction was followed by TLC. No reaction could be observed even after 24 h and the starting material was recovered quantitatively. A subsequent attempt also proved unsuccessful. In spite of this, alcohol **679** was treated with acetic anhydride to examine its reactivity and pleasingly acetate **681** was obtained, albeit in low and unoptimised yield. Acetate **681** was identified by the loss of the OH stretch at 3576-3686 cm^{-1} in the IR spectrum and appearance of a [3H] singlet at 1.93 ppm corresponding to the acetate group in the 1H NMR spectrum. Treatment of acetate **681** with excess DBU did not result in the desired elimination and investigations into the activation of alcohol **679** with other groups are currently underway. It is not clear to the apparent lack of reactivity of alcohol **679** towards mesyl chloride.

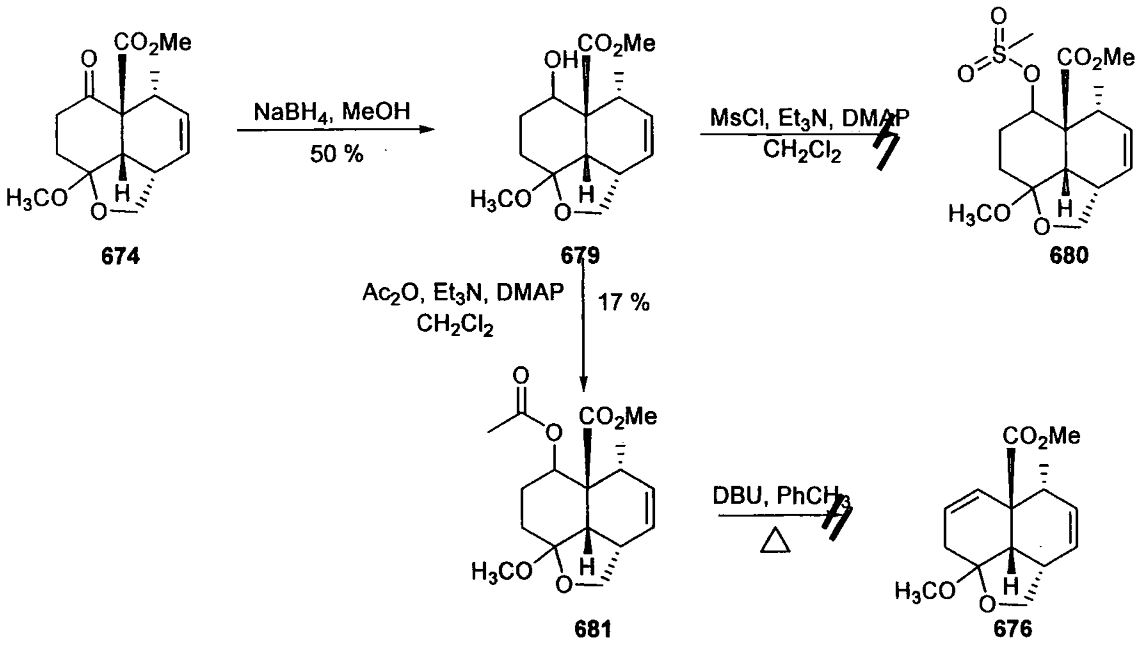


Figure 250

4.19 Conclusions

The initial reconnection strategy allowed good regioselectivity to be obtained through the use of highly oxygenated 1,3-butadienes. However attempts to utilise a selective alkylation approach proved unsuccessful due to the irreproducible results obtained on silyl enol ether deprotection. Fortuitously, this allowed development of a highly regioselective Lewis-acid-catalysed Diels Alder cycloaddition. The adducts obtained were identified by X-ray crystallography to possess 4 of the 8 stereocentres in the correct relative arrangement required for Vinigrol. Further derivatisation of bicyclic intermediate **665/666** allowed us to investigate a rapid method to install the desired cyclic diene. However the instability of allylic alcohol **672** hampered this study. Further investigations to install the diene fragment by selective ketone removal have to date been unsuccessful. However, a comprehensive study to effect this transformation has been hampered by time constraints. Also, attempts to utilise the saturated bicyclic compound **674** to remove the unwanted ketone functionality by enol triflate formation proved problematic due to the apparent unreactivity of the enolate towards electrophilic triflate sources. This model study has allowed the regioselective formation of bicyclic intermediate **665/666** with 4 of the desired stereocentres required for Vinigrol and initial investigations towards installation of the cyclic diene have been disappointing but remain a promising synthetic route in our studies towards Vinigrol.

4.20 Synthesis of Functionalised Heptadienes

4.20.1 Introduction/Strategy

In parallel with the model study utilising ethyl sorbate derivatives, the synthesis of the required heptadiene **609** was also investigated. From the retrosynthetic analysis a one-carbon homologue of ethyl sorbate was required, Figure 251. Dienes of this type are not commercially available and there was little methodology available in the literature for their preparation. It was envisaged however, that they could be synthesised relatively quickly and easily by the synthetic scheme shown in Figure 251. Stabilised Wittig reaction with *trans*-pentenal can give diene **682**. Subsequent base-induced deconjugation, reduction and protection should afford the appropriately functionalised diene.

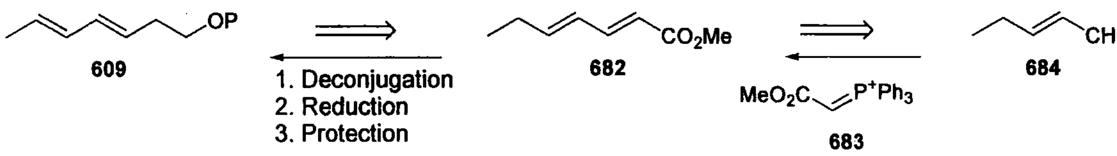


Figure 251

4.20.2 Synthesis

Thus, to initiate the synthetic pathway shown in Figure 251, coupling of stabilised Wittig reagent **683** with aldehyde **684** had to be examined. Pleasingly, Wittig reaction of the commercially available phosphonium salt **683** and aldehyde **684** afforded the desired diene after purification by Kugelrohr distillation, Figure 252. Diene **682** was identified by the appearance of a further two olefinic signals in the ^{1}H NMR spectrum together with the disappearance of the corresponding aldehyde proton at 9.72 ppm. To allow the terminal methyl substituent to be revealed, diene **682** was subjected to base-induced deconjugation, Figure 252. The shift of the ester carbonyl stretch from 1739 to 1702 cm^{-1} in the IR spectrum revealed that the desired diene **685** had been obtained. However, on detailed examination of the ^{1}H NMR spectrum, 6-H was found to possess coupling constants (J = 7, 11 Hz) that were too low to be consistent with a *trans*-double bond. Double bond isomerisation had also taken place yielding Z, E diene **686** instead of the desired E, E diene **685** required for cycloaddition.

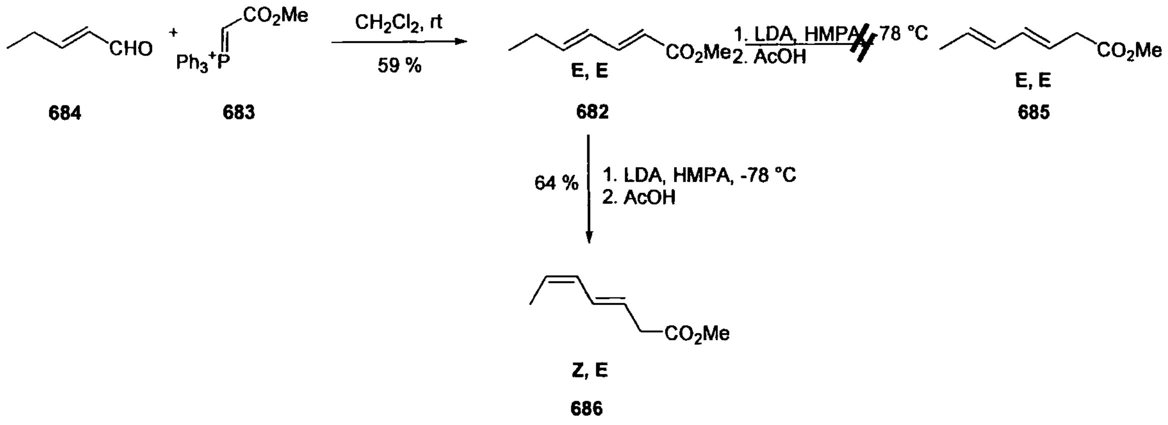


Figure 252

Unexpectedly the Z, E diene **686** had been obtained and methods to secure the desired E, E diene were examined. Simply treating the Z, E diene with a single crystal of iodine induced the desired double bond isomerisation which was identified by the amalgamation of the olefinic signals. Z, E diene **686** possesses 4 discrete olefinic signals at 5.32, 5.56, 5.89 and 6.29 ppm whereas the E, E diene **685** only shows 2 multiplets at 5.23-5.63 and 5.99-6.01 ppm for the same signals in the ^{1}H NMR spectrum, Figure 253.

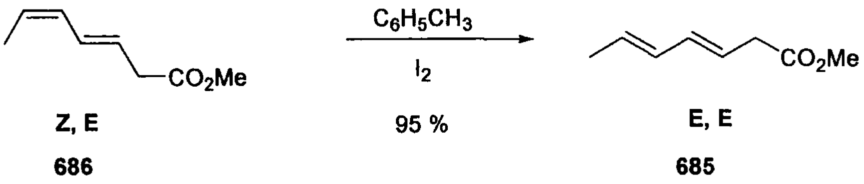


Figure 253

With diene **685** in hand, the Diels Alder cycloaddition was attempted. Diene **685** was treated with quinone **618** under our previously optimised conditions but this failed to yield the desired cycloadduct, Figure 254. At this time it is unclear why the ester fails to undergo cyclisation. With this result in hand, diene **685** was reduced with lithium aluminium hydride to give an alcohol, which was immediately protected as the silyl ether after treatment with TBSCl, Figure 254. Silyl ether **687** was identified by the loss of the carbonyl stretch at 1702 cm^{-1} in the IR spectrum and the appearance of the CH_2O protons at 3.66 ppm in the ^{1}H NMR spectrum.

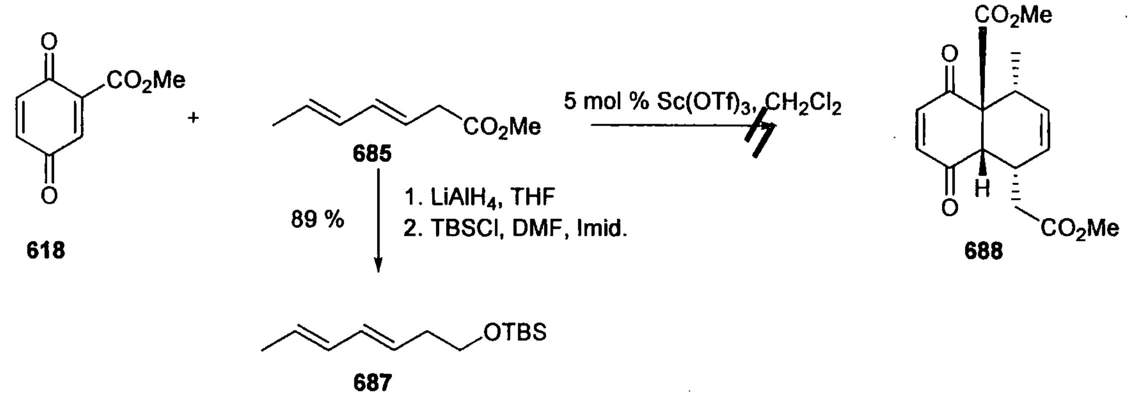


Figure 254

Thus, with silyl diene **687** in hand, the Diels Alder cycloaddition was investigated. Reacting **687** with quinone **618** under the optimised conditions, pleasingly the desired cycloaddition could be carried out, Figure 255. However, on examination of the ^{1}H NMR spectrum, a 1:1 mixture of regioisomers was identified, Figure 255. One carbon homologation of the diene results in a non-regioselective Diels Alder reaction. We hypothesise that there is little steric differentiation between the different functional groups present on the unsymmetrical diene (CH_3 v CH_2CH_2) resulting in the loss of regioselectivity.

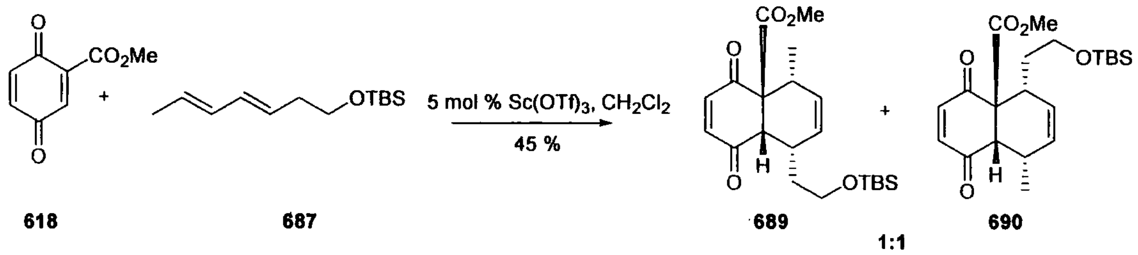


Figure 255

Therefore investigations began to enable the previously good regioselectivity to be obtained once again. It was hypothesised that increasing the steric bulk at the CH_2CH_2 end of the unsymmetrical diene should allow significant differentiation to allow a regioselective reaction to be achieved, Figure 256.

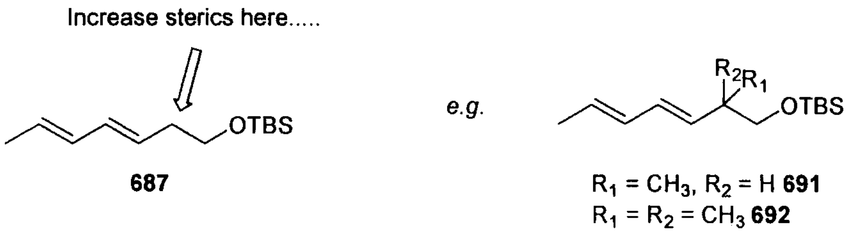


Figure 256

4.21 Achieving Regioselectivity

With a strategy in hand to gain back the regioselectivity previously observed, monomethyl diene **691** was to be synthesised, Figure 257. Coupling of commercially available Wittig salt **693** and known aldehyde **684** gave conjugated diene **694a** which was characterised by the presence of a CH_3 singlet at 1.93 ppm in the ^1H NMR spectrum. Diene **694a** was then deconjugated and again the Z,E isomerised product was obtained which was identified by the appearance of [1H] quintet (J = 7 Hz) at 3.19 ppm corresponding to 2-H. Diene **694** also possessed a low coupling constant between 5-H and 6-H (5-H J = 11 Hz) which is consistent with a *cis*-double bond. Subsequent reduction, TBS protection and iodine-induced isomerisation afforded the methyl substituted diene **691**. Diene **691** was identified by amalgamation of the olefinic signals at 5.39, 5.57, 5.96 and 6.36 ppm characteristic of the Z,E diene **694** to 2 [2H] multiplets at 5.47-5.58 and 5.99-6.05 ppm in the ^1H NMR spectrum for the E,E diene **691**.

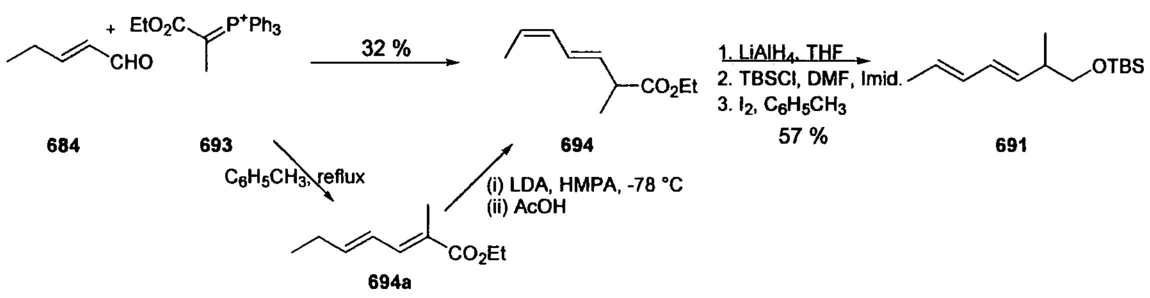


Figure 257

With the sterically differentiated unsymmetrical diene **691** in hand its behaviour in the Diels Alder cycloaddition was examined. Diene **691** was treated with activated quinone **618** under our optimised conditions and disappointingly cycloadduct **696** could not be isolated, Figure 258. The steric effects surrounding the introduction of the methyl group appears to have a detrimental effect on the rate of reaction, even under the influence of Lewis acid catalysis.

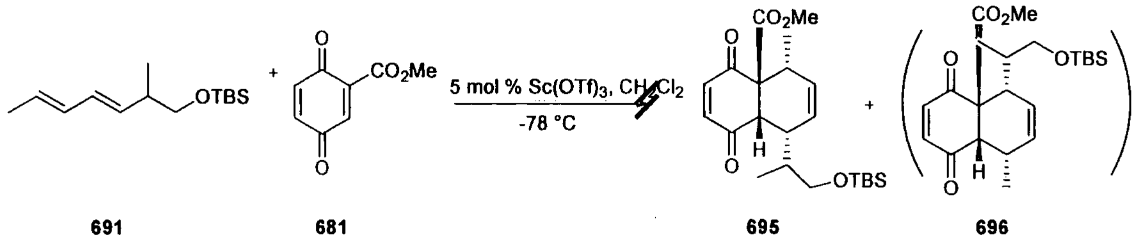


Figure 258

Undeterred by this disappointing result, work began to explore the reactivity of diene **691** towards Diels Alder cycloaddition. Thus, initial reactions focussed on forming the desired adduct **695** and to this end diene **691** was reacted at room temperature with *in-situ* generated 1,4 quinone. Gratifyingly, the cycloaddition could be initiated and on examination of the reaction mixture by ^{1}H NMR spectroscopy a 2:1 mixture of regioisomers was obtained, Figure 259. Thus, diene **691** can be used in Diels Alder cycloaddition and can increase the level of regioselectivity even at room temperature. Adduct **695** was the major component of the reaction mixture and could be isolated as a single isomer after careful chromatography and was characterised by examination of the COSY NMR spectrum. Distinct couplings between (1-8a) and (1-1'CH) could be identified Figure 259. The minor adduct was also identified by examining the COSY NMR spectrum of the mixture that remained after column chromatography, couplings between (1-8a) and (1-1'CH_3) were also observed. The major product appears to be a 3:1 mixture of diastereomers on analysis of the ^{1}H NMR spectrum. Due to time constraints further optimisation of this excellent result has not been undertaken.

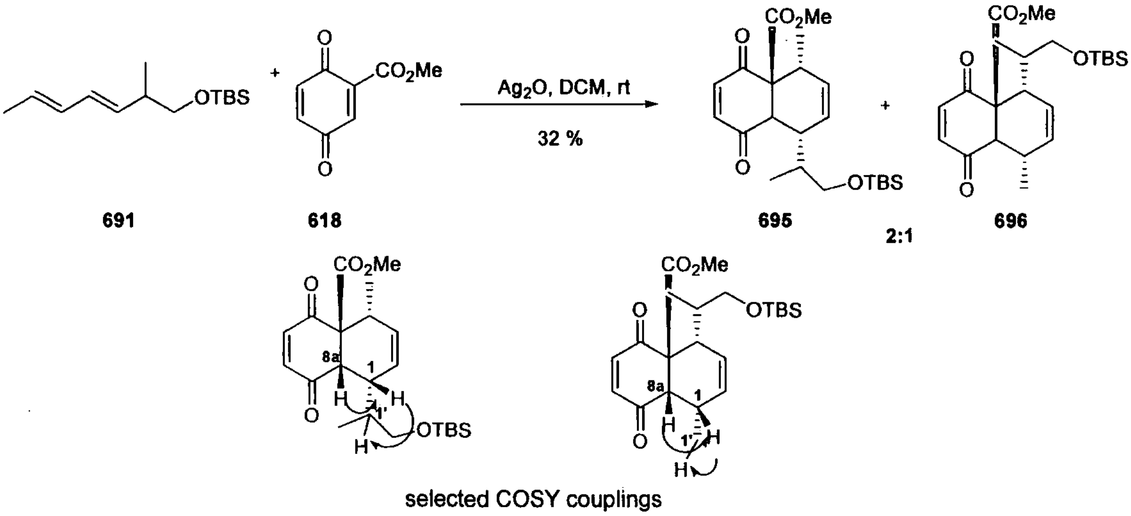


Figure 259

4.22 Conclusions of Diels Alder Approach to the Synthesis of Vinigrol

Syntheses of functionalised E, E-heptadienes were complicated due to the unexpected isomerisation during deconjugation but this was overcome by iodine-induced isomerisation. Subsequent cycloaddition of diene **687** with activated quinone **618** resulted in a non-regioselective cycloaddition under the optimised conditions. Simply increasing the steric bulk at one end of end of the diene **691** allows regioselectivity to be re-established; however optimisation in this area has not been investigated due to time constraints. Incorporation of the monomethyl diene produces a cycloadduct with 5 of the 8 desired stereocentres required for Vinigrol. The initial results obtained with this synthetic route have been promising and further investigations are required to test the viability of the alternative intramolecular Diels Alder reaction.

4.23 Future Work

4.23.1 Ketone Removal

Due to time constraints, there are several areas which require further investigation. Firstly, selective C6 ketone removal on bicyclic acetal **671** under less harsh reaction conditions requires to be given further consideration as this will allow rapid removal of the undesired ketone functionality and allow the desired diene to be formed in few synthetic steps.

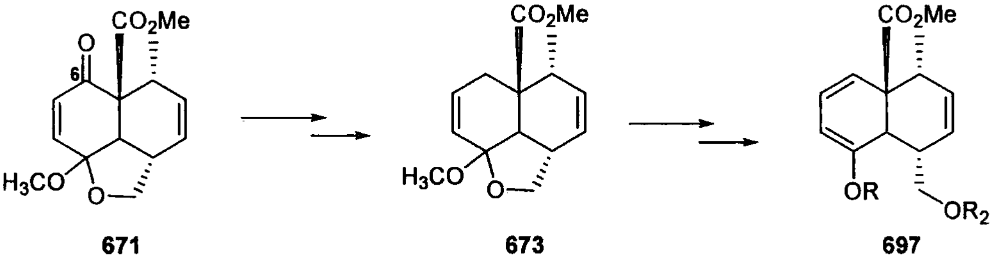


Figure 260

4.23.2 Enantio- and diastereo-selective Synthesis

Secondly, Evans *et al* have demonstrated that activated quinone Diels Alder reactions can be made enantioselectively with the use of chiral Lewis acids (see Figure 235, Page 131) and the application of pybox chiral ligands to our proposed synthesis may allow an enantioselective synthesis of Vinigrol with 5 of the desired stereocentres installed in the first synthetic step, Figure 261.

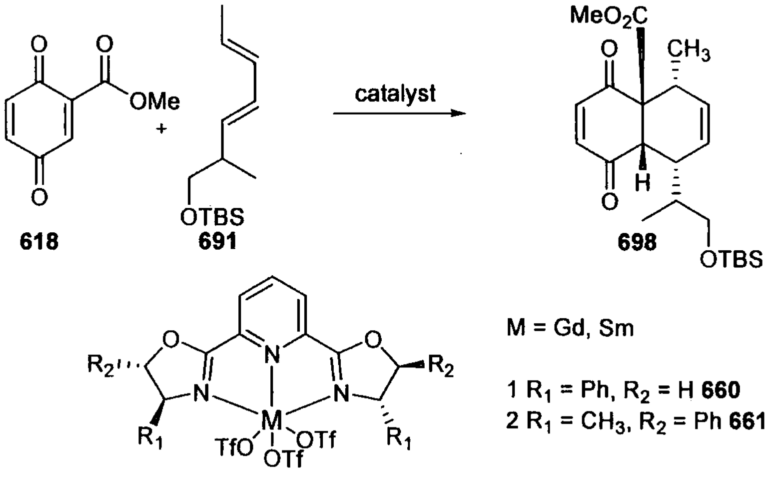


Figure 261

SECTION C :
EXPERIMENTAL

Chapter 5 : Experimental Procedures

5. 1 Introduction

General Procedures

All reactions were carried out under an argon atmosphere in glassware dried under high vacuum by a heat-gun unless otherwise stated.

Solvents

Petroleum ether refers to the fraction of petroleum ether boiling between 40-60°C and was redistilled before use. All solvents were distilled (dried) under a nitrogen atmosphere prior to use, using standard procedures or obtained from Innovative Technology Solvent Purification System. Hexanes and toluene were dried and deoxygenated by passing through two BASF Cu columns, dimethylformamide was dried over two molecular sieve columns and THF, DCM, Diethylether, $CHCl_3$, Methanol and acetonitrile were dried using two alumina columns.

Reagents

Reagents were used as supplied unless otherwise stated.

Chromatography

Flash column chromatography was carried out using silica gel 40-63µ 60A. Analytical thin layer chromatography (TLC) was performed using Merck aluminium backed silica gel 60 F_{254} plates and visualised by UV radiation at 254 nm, phosphomolybdic acid in ethanol and potassium permanganate in water.

IR Spectroscopy

Infra-red spectra were recorded *via* use of a Diamond ATR (attenuated total reflection) accessory (Golden Gate) on a Perkin Elmer Paragon 1000 FT-IR spectrometer, or recorded as a solution in chloroform *via* transmission IR cells on a Perkin Elmer Series 1600 FT-IR spectrometer.

NMR Spectroscopy

^1H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 200, Varian Unity-300, Brucker Advance 400 or Varian Inova-500 and reported as follows; chemical shift δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded at 126 MHz on Varian Inova-500 or at 101 MHz on Brucker Advance 400, using the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm) and coupling constants given in Hertz (Hz). Assignment of spectra was carried out using COSY, HSQC, HMBC and NOESY experiments.

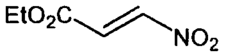
Mass Spectrometry

Low resolution mass spectra (EI or CI) were obtained on VG Analytical 7070E or VG Autospec Organic mass spectrometers. Gas chromatography was obtained using a Hewlett Packard 5890 Series II gas chromatograph with a 25 m column. Gas chromatography mass spectra (EI or CI) were obtained using a Thermo TRACE mass spectrometer or using a Hewlett Packard 5890 Series II GC equipped with a 25 m column connected to a VG Trio-1000. Electrospray mass spectra (ES) were obtained on a Micromass LCT mass spectrometer. High resolution mass spectra were obtained using a Thermo LTQ mass spectrometer (ES) at the University of Durham, or performed by the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea.

N.B. Where HRMS data is not stated, this data was unobtainable even after repeated submission to the M.S. department at the University of Durham.

5. 2 Experimental Details

Ethyl (E)-3-nitropropenoate[68,70]



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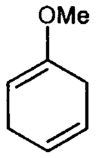
To a solution of iodo-ester **276** (10.00 g, 36.8 mmol) in diethyl ether (700 ml) at 0 °C was added a solution of $^{i}Pr_2NEt$ (5.80 g, 40.5 mmol) dropwise over 15 minutes. The resultant suspension was immediately passed through two separate 100 g plugs of silica and flushed with 10 % diethyl ether in petroleum ether (100 ml). The solution was concentrated under reduced pressure and the residue purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to yield the title compound as a yellow solid (7.8 g, 97 %). ν_{max} (NaCl) 1754 (C=O), 1659, 1645, 1532 (NO_2), 1468, 1447, 1260, 1301, 1176, 1096, 1033, 950, 560, 766, 655 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, J =7 Hz, OCH_2CH_3), 4.22 (2H, q, J =7 Hz, OCH_2CH_3), 7.00 (H, d, J = 13 Hz, 2-*H*), 7.61 (H, d, J = 13 Hz, 3-*H*); δ_c (100 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 62.9 ($CO_2CH_2CH_3$), 128.8 (C-2), 148.9 (C-3), 162.6 (C=O); *m/z* (ES+) 146 $(MH)^+$

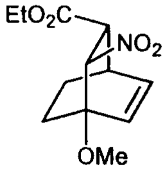
1-Methoxy-1,4-cyclohexadiene[75]



244

To a solution of methoxybenzene (25.00 g, 157.5 mmol) in diethyl ether (100 ml) at -78 °C was added liquid ammonia (300 ml) followed by portionwise addition of lithium metal (7.50 g) over 10 minutes with stirring. The resultant blue solution was stirred for 3 h and ethanol (77 ml) was added. The reaction mixture was stirred for a further 3 h at -78 °C. The reaction was then quenched by the addition of saturated ammonium chloride (200 ml) and the reaction was allowed to warm to room temperature over 12 h. To the colourless solution was added water (400 ml) and extracted with diethyl ether (3 x 200 ml). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was distilled to yield the title compound as a colourless oil (10.5 g, 41 %, bp 148 °C, literature reference : 148-150 °C). ν_{max} (NaCl, $CHCl_3$) 1704, 1560, 1464, 1386, 1342, 1210, 1166, 1024 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.60-2.81 (4H, m, 3-H_2, 6-H_2), 3.52 (3H, s, OCH_3), 4.62 (1H, s, 2-*H*), 5.65 (2H, br s, 4-*H*, 5-*H*); δ_c (100 MHz, $CDCl_3$) 26.8, 27.7 (*C*-3, *C*-6), 53.7 (OCH_3), 92.3 (*C*-2), 123.2, 124.57 (*C*-4, *C*-5), 152.9 (*C*-1); *m/z* (ES+) 110 $(MH)^+$

(2SR,3RS,4SR)-4-Methoxy-3-nitrobicyclo[2.2.2]oct-5-ene-2-carboxylic acid ethyl ester[68]

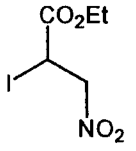


250

Nitroacrylate **245** (2.00 g, 13.8 mmol) was dissolved in DCM (50 ml) and was cooled to 0 °C and $ZnCl_2$ (1M in diethylether, 1.4 ml, 1.4 mmol) was added, followed by diene **244** (3.8 ml, 27.6 mmol). The reaction mixture was stirred at 0 °C until GC analysis showed that the ethyl (E)-3-nitropropenoate had been consumed (14 h). The resulting solution was quenched with 50 ml of water before transferring to a separating funnel. The organic layer was obtained and the aqueous layer was further extracted with 30 ml of DCM. The organic layers were combined and dried over magnesium sulfate and concentrated under reduced pressure. The dark orange oil that remained was purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to yield the title compound as a colourless oil (2.04 g, 57 %). ν_{max} (NaCl) 1734 (C=O), 1556

(NO_2), 1464, 1375, 1277, 1200, 1037, 1019, 951, 860, 676 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, J = 7 Hz, OCH_2CH_3), 1.29-1.75 (4H, m, 7-H_2, 8-H_2), 3.05-3.18 (2H, m, 1-*H*, 2-*H*), 3.41 (3H, s, OCH_3), 4.22 (2H, q, J = 7 Hz, OCH_2CH_3), 5.39 (H, d, J = 7 Hz, 3-*H*), 6.12 (H, d, J = 9 Hz, 5-*H*), 6.42 (H, dd, J = 9, 7 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 14.4 ($CO_2CH_2CH_3$), 21.1 (C-7), 25.7 (C-8), 31.9 (C-1), 50.2 (C-2), 51.1 (OCH_3), 61.7 ($CO_2CH_2CH_3$), 78.8 (C-4), 86.8 (C-3), 132.0 (C-5), 132.2 (C-6), 170.9 (C=O); *m/z* (CI, NH_3) 273 $(MNH_4)^+$(55 %), 256 (100 %), 22 (90 %), 110 (30 %)

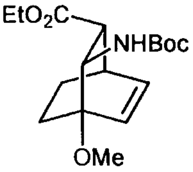
2-Iodo-3-nitropropionic acid ethyl ester[68,70]



276

N_2O_4 (9.5 ml, 166 mmol) was added to a stirred and cooled (0 °C) solution of ethyl acrylate (44.5 ml, 410.0 mmol) and iodine (31.00 g, 122.0 mmol) in diethyl ether (400 ml). The reaction mixture was stirred for 1 h at 0 °C and then at 25 °C for 4 h. The resultant dark solution was washed with saturated sodium thiosulfate solution until the aqueous layer ran clear (~ 1.2 L) leaving the organic layer light yellow in colour. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The excess ethyl acrylate was distilled off under reduced pressure at room temperature to give the title compound as a bright yellow oil (30 g, 90 %). ν_{max} (NaCl, $CHCl_3$) 2978, 1744 (C=O), 1584 (NO_2), 1376, 1245, 1193, 1120, 1018, 866 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, J = 7 Hz, OCH_2CH_3), 4.22 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.68 (1H, dd, J = 15, 4 Hz, 2-*H*), 4.89 (1H, dd, J = 11, 4 Hz, 3-H_a), 5.07 (1H, dd, J = 15, 11 Hz, 3-H_b); δ_C (100 MHz, $CDCl_3$) 8.0 (C-2), 13.8 ($CO_2CH_2CH_3$), 64.7 ($CO_2CH_2CH_3$), 76.9 (C-3), 169.0 (C-1); *m/z* (EI) 273 $(MH)^+$(12 %), 226 (96 %), 180 (32 %), 55 (100 %)

(2SR,3RS,4SR)-3-^{t}Butoxycarbonylamino-4-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylicacid-ethyl ester

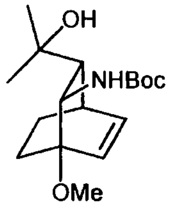


286

To a solution of nitro-ester **250** (1.70 g, 7.0 mmol) in ethanol (200 ml) was added concentrated HCl (13.6 ml, 119.0 mmol) followed by portionwise addition of zinc powder (9.80 g, 175.0 mmol). The reaction mixture was stirred at room temperature for

12 h. Excess zinc was removed by filtration, and added to the resulting colourless solution was $^{i}Pr_2NEt$ (15.4 g, 119.0 mmol) and di-tert-butyl dicarbonate (3.05 g, 14 mmol). The suspension that was produced was stirred at room temperature for 20 h. The reaction mixture was then reduced to 100 ml by concentration under reduced pressure, and was then partitioned between ethyl acetate (2 x 400 ml) and 1 : 1 mixture of water : sat. sodium hydrogen carbonate (400 ml) and the layers separated. The aqueous layer was reextracted with ethyl acetate (3 x 200 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was then purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to yield the title compound as a colourless oil (1.37 g, 63 %). ν_{max} (ATR) 1725 (C=O), 1503, 1390, 1367, 1280, 1245, 1158, 1012, 858, 841, 787, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.43 (3H, t, J = 7 Hz, OCH_2CH_3), 1.46 (9H, s, $C(CH_3)_3$),1.62-2.05 (5H, m, 2-*H*, 7-H_2, 8-H_2), 2.50 (1H, br s, 1-*H*), 2.91 (1H, br s, 3-*H*), 3.48 (3H, s, OCH_3), 4.36 (2H, q, J = 7 Hz, OCH_2CH_3), 6.23 (1H, d, J = 9 Hz, 5-*H*), 6.52 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 14.5 (CH_3CH_2), 21.9, 22.3 (C-7, C-8), 28.6 ($C(CH_3)_3$), 50.4 ($C(CH_3)_3$), 51.7 (OCH_3), 59.3 (C-4), 61.1 (CH_3CH_2), 63.6 (C-1), 78.6 (C-3), 83.8 (C-2), 132.3 (C-5), 133.1 (C-6), 154.9 ($C=O_{Boc}$), 173.4 (C=O); *m/z* (CI, NH_3) 342 $(MNH_4)^+$ (23 %), 326 (100 %), 180 (32 %), 55 (100 %)

(1SR,2RS,3SR)N-[3-(1′-Hydroxy-1′-methylethyl)-1-methoxy-bicyclo[2.2.2]oct-5-en-2-yl]-2,2-dimethyl propionamide

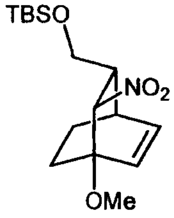


287

To a stirred, cooled (-78 °C) solution of ester **286** (0.10 g, 0.3 mmol) in diethyl ether (10 ml) was added MeLi (0.7 ml, 1.6 M in diethyl ether) dropwise. The resulting suspension was stirred at -78 °C for 1 h before warming to room temperature over 2 h. The reaction mixture was then quenched with sat. ammonium chloride (10 ml). The mixture was then extracted with ethyl acetate (2 x 10 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was then purified by column chromatography eluting with 30 % diethyl ether in petroleum ether to yield the title compound as a colourless film (0.02 g, 29 %). ν_{max} (NaCl) 3436 (OH), 2979, 2253, 1702, 1505 (NO_2), 1368, 1167, 920, 896, 757, 649 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.30-1.33 (6H, br d, 1″-CH_3, 2″-CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.73-2.61 (4H, m, 7-H_2, 8-H_2), 3.33 (3H, s, OCH_3), 3.65 (1H, m, 2-*H*), 4.01 (1H, m, 3-*H*), 4.48 (1H, br d, O*H*), 5.99 (1H, d, J = 9 Hz, 5-*H*), 6.44 (1H, m, 6-*H*); δ_c (100 MHz,

$CDCl_3$) 22.2, 25.8 (*C*-1″, *C*-2″), 28.0 (*C*-7), 28.6 ($C(CH_3)_3$), 30.2 (*C*-3), 32.1 (*C*-1), 50.4 ($C(CH_3)_3$), 51.7 (OCH_3), 59.3 (*C*-4), 71.3 (*C*-1′), 79.1 (*C*-2), 79.7 (*C*-3), 132.8, 137.5 (*C*-5, *C*-6), 150.2 (C=O); *m/z* (CI, NH_3) 312 $(MH)^+$(83 %), 256 (58), 212 (38 %), 110 (100 %)

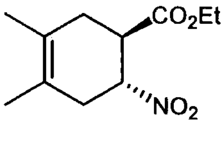
(2SR,3RS,4SR)-^{t}Butyl-4-methoxy-3-nitro-bicyclo[2.2.2]oct-5-en-2-ylmethoxy dimethyl silane[68]



303

To a solution of alcohol **316** (0.50 g, 2.5 mmol) in dimethylformamide (15 ml) was added TBSCl (0.57 g, 3.8 mmol) and imidazole (0.43 g, 6.3 mmol) and the solution was stirred at room temperature for 12 h. The reaction mixture was partitioned between ethyl acetate (15 ml) and water (15 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (2 x 10 ml) and the combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether to yield the title compound as a white solid (0.25 g, 32 %). m.p. 48-50 °C; ν_{max} (ATR) 1555 (NO_2), 1470, 1373, 1255, 1108, 1085, 836, 777 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, 2 x $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.20-1.85 (4H, m, 7-H_2, 8-H_2), 2.33 (1H, m, 1-*H*), 2.60 (1H, m, 2-*H*), 3.40 (3H, s, OCH_3), 3.66 (2H, m, CH_2O), 4.64 (1H, d, J = 7 Hz, 3-*H*), 6.17 (1H, d, J = 9 Hz, 5-*H*), 6.48 (1H, dd, J = 9, 6 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) -5.3 (2 x $SiCH_3$), 18.4 ($SiC(CH_3)_3$), 20.2, 26.8 (C-7, C-8), 28.0 ($SiC(CH_3)_3$), 31.5 (C-1), 48.2 (C-2), 51.3 (OCH_3), 64.0 (CH_2O), 79.2 (C-4), 90.1 (C-3), 131.5 (C-5), 134.4 (C-6); *m/z* (CI, NH_3) 328 $(MH)^+$ (100 %), 310 (87 %), 270 (83 %), 209 (12 %), 110 (57 %)

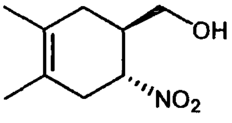
(1RS, 6RS)-3,4-Dimethyl-6-nitrocyclohex-3-ene carboxylic acid ethyl ester[68]



308

To a solution of nitroacrylate **245** (2.00 g, 14.0 mol) in benzene (40 ml) was added 2,3-di-methyl-1,3-butadiene (2.30 g, 28.0 mol). The reaction mixture was stirred at 80 °C for 6 h, after which time analysis by GC showed consumption of ethyl (E)-3-nitropropenoate. The resulting light orange solution was concentrated under reduced pressure and purified by column chromatography eluting with 5 % diethyl ether in petroleum ether to yield the title compound as an orange oil (2.01 g, 66 %). ν_{max} (ATR) 1735 (C=O), 1558 (NO_2), 1444, 1384, 1308, 1235, 1189, 1030 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J = 7 Hz, OCH_2CH_3), 1.63 (6H, s, 2 x CH_3), 2.17-2.76 (4H, m, 2-H_2, 5-H_2), 3.20 (1H, ddd, J = 12, 12, 6 Hz, 1-*H*), 4.15 (2H, q, J = 7 Hz, OCH_2CH_3), 4.85 (1H, ddd, J = 12, 12, 6 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 18.3, 25.7 (2 x CH_3), 33.8 (C-2), 36.2 (C-5), 43.2 (C-1), 61.2 ($CO_2CH_2CH_3$), 82.2 (C-6), 122.4, 124.3 (C-3, C-4), 172.3 (C=O); *m/z* (CI, NH_3) 228 $(MH)^+$ (2 %), 245 $(MNH_4)^+$ (100 %), 198 (90 %)

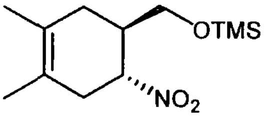
(1RS, 6RS)-3,4-Dimethyl-6-nitrocyclohex-3-enylmethanol[68]



309

To a solution of ester **308** (2.00 g, 8.8 mmol) in THF (150 ml) at - 78 °C was added DIBAL (30.8 ml, 1 M in DCM) dropwise over 10 minutes. The reaction mixture was then allowed to warm to room temperature over 12 h. Methanol (7 ml) was added dropwise and the resultant slurry was diluted with ethyl acetate (400 ml) and water (400 ml). This mixture was then filtered through a pad of Celite© and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 75 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 3:2 petroleum ether : diethyl ether to yield the title compound as a colourless oil (1.25 g, 76 %). ν_{max} (NaCl, $CHCl_3$) 3392 (OH), 1547 (NO_2), 1442, 1371, 1296, 1115, 1055, 912, 757 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.61 (6H, s, 2 x CH_3), 2.09-2.12 (2H, m, 2-H_2), 2.29-2.81 (3H, m, 1-*H*, 5-H_2), 3.59 (2H, m, CH_2O), 4.67 (1H, dd, J = 10, 6 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 18.5, 18.6 (2 x CH_3), 33.2, 35.8, 39.9 (C-1, C-2, C-5), 63.0 (CH_2O), 84.4 (C-6), 121.6 (C-3), 124.3 (C-4); *m/z* (CI, NH_3) 203 $(MNH_4)^+$ (15 %), 136 (100 %), 122 (98 %)

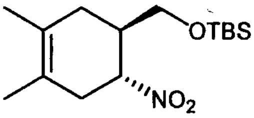
(1RS, 6RS)-3,4-Dimethyl-6-nitrocyclohex-3-enylmethoxytrimethylsilane



310

To a solution of alcohol **309** (0.20 g, 1.1 mmol) in dimethylformamide (10 ml) was added TMSCl (0.23 g, 1.6 mmol) and imidazole (0.15 g, 2.2 mmol) and the solution was stirred at room temperature for 14 h. The reaction mixture was partitioned between ethyl acetate (20 ml) and water (20 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 15 ml) and the combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether to yield the title compound as a colourless oil (0.24 g, 86 %). ν_{max} (NaCl, $CHCl_3$) 1549 (NO_2), 1471, 1387, 1257, 1116, 1086, 839, 777 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.09 (9H, s, 3 x $SiCH_3$), 1.56 (6H, s, 2 x CH_3), 2.07-2.09 (2H, m, 2-H_2), 2.41-2.50 (2H, m, 5-H_2), 2.63-2.66 (1H, m, 1-*H*), 3.47-3.57 (2H, dd, J = 10, 4 Hz, CH_2O), 4.67-4.73 (1H, dt, J =10, 6 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 0.00 (3 x $SiCH_3$), 19.3, 19.4 (2 x CH_3), 33.7, 36.8, 39.7 (C-1, C-2, C-5), 63.3 (CH_2O), 85.0 (C-6), 122.2, 125.85 (C-3, C-4); *m/z* (ES+) 280 $(MNa)^+$, 242 $(MMeCN)^+$

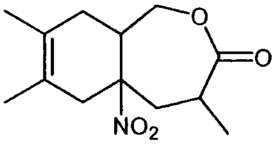
(1RS, 6RS)-^{t}Butyl-3,4-dimethyl-6-nitrocyclohex-3-enylmethoxydimethylsilane[68]



311

To a solution of alcohol **309** (0.25 g, 1.4 mmol) in dimethylformamide (5 ml) was added TBSCl (0.30 g, 2.0 mmol) and imidazole (0.23 g, 3.4 mmol) and the solution was stirred at room temperature for 12 h. The reaction mixture was partitioned between ethyl acetate (15 ml) and water (15 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 10 ml) and the combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether affording the title compound as a colourless oil (0.35 g, 85 %). ν_{max} (ATR) 1549 (NO_2), 1471, 1387, 1257, 1116, 1086, 839, 777 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.03 (6H, s, 2 x CH_3), 0.88 (9H, s, $SiC(CH_3)_3$), 1.64 (6H, s, 2 x CH_3), 2.09-2.65 (5H, m, 1-H, 2-H_2, 5-H_2), 3.46-3.62 (2H, m, CH_2O), 4.96 (1H, dt, J = 10, 6 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) -5.5 (2 x $SiCH_3$), 18.5 ($SiC(CH_3)_3$), 18.6, 18.8 (2 x CH_3), 26.8 ($SiC(CH_3)_3$) 33.0, 36.2, 39.4 (C-1, C-2, C-5), 63.0 (CH_2O), 84.2 (C-6), 121.5 (C-3), 125.2 (C-4); *m/z* (CI, NH_3) 300 $(MH)^+$ (8%), 317 $(MNH_4)^+$ (8 %), 270 (20 %), 136 (100 %)

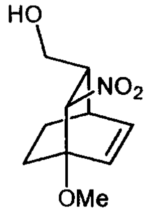
4,7,8-Trimethyl-5a-nitro-4,5,5a,6,9,9a-hexahydro-1H-benzo[c]oxepin-3-one



314

To a solution of silyl ether **310** (0.50 g, 27.0 mmol) and triazabicyclo [4.4.0] dec-5-ene (0.40 g, 35.1 mmol) in acetonitrile (15 ml) was added methyl methacrylate (0.47 ml, 54.3 mmol). The reaction mixture was stirred for 12 h at room temperature and was then partitioned between ethyl acetate (50 ml) and water (50 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (2 x 30 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40 % diethyl ether in petroleum ether to give the title compound as a colourless oil (0.10 g, 24 %). ν_{max} (NaCl, $CHCl_3$) 1740 (C=O), 1540, 1185, 919, 754, 650 cm^{-1}; δ_H (400 MHz, $MeOD_6$) 1.09 (3H, d, J = 7 Hz, $CHCH_3$), 1.60 (6H, s, 2 x CCH_3), 2.01-2.28 (4H, m 6-H_2, 9-H_2), 2.43-2.47 (2H, m, 4-*H*, 9a-*H*), 2.73-2.78 (1H, m, 5-H_a), 2.91-2.99 (1H, m, 5-H_b), 4.01-4.05 (1H, m, 1-H_a), 5.03-5.10 (1H, m, 1-H_b); δ_C (100 MHz, $CDCl_3$) 18.1, 18.5, 18.9 ($CHCH_3$, 2 x CCH_3), 32.2, 32.7 (C-6, C-9), 42.2, 42.4, 43.9 (C-4, C-5, C-9a), 67.7 (C-1), 90.2 (C-5a), 122.1, 125.4 (C-7, C-8), 176.9 (C-3); *m/z* (CI, NH_3) 254 $(MH)^+$ (20 %), 271 $(MNH_4)^+$ (100 %), 191 (18 %)

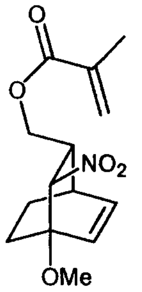
(2SR, 3RS, 4SR)-4-Methoxy-3-nitrobicyclo[2.2.2]oct-5-en-2-ylmethanol[68]



316

To a solution of nitro-ester **250** (2.80 g, 11.1 mol) in THF (125 ml) at - 78 °C was added DIBAL (35 ml, 1 M in DCM) was added dropwise over 10 minutes and the reaction mixture was then allowed to warm to room temperature over 12 h. Methanol (7 ml) was added dropwise and the resultant slurry was diluted with ethyl acetate (300 ml) and water (400 ml) and this mixture was then filtered through a pad of Celite© and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 200 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 50 % diethyl ether in petroleum ether to 100 % diethyl ether to give the title compound as a yellow oil (1.38 g, 59%). ν_{max} (ATR) 3467-3095 (OH), 1550 (NO_2), 1510, 1443, 1321, 1220, 824, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.27-1.87 (5H, m, 7-H_2, 8-H_2, O*H*), 2.39 (1H, m, 2-*H*), 2.64 (1H, m, 1-*H*), 3.95 (3H, s, OCH_3), 3.71-3.75 (2H, m, CH_2O), 4.63 (1H, d, J = 5 Hz, 3-*H*), 6.23 (1H, d, J = 9 Hz, 5-*H*), 6.49 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_C (100 MHz, $CDCl_3$) 20.3, 26.7 (C-7, C-8), 31.0 (C-1), 48.2 (C-2), 51.4 (OCH_3), 63.9 (CH_2O), 79.1 (C-4), 90.4 (C-2), 131.2, 134.2 (C-5, C-6); *m/z* (CI, NH_3) 231 (MH)+ (100 %), 214 (50 %), 170 (20 %), 110 (12 %)

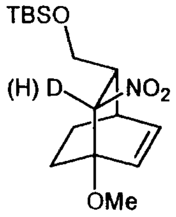
(2SR,3RS,4SR)-2-Methylacrylic acid 4-methoxy-3-nitrobicyclo[2.2.2]oct-5-en-2-yl methyl ester



317

To a solution of alcohol **316** (0.30 g, 0.01 mmol) and (0.31 g, 0.02 mmol) in acetonitrile (7 ml) was added methyl methacrylate (0.30 ml, 0.03 mmol). The reaction mixture was allowed to stir for 48 h at room temperature and was then partitioned between ethyl acetate (20 ml) and water (20 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (2 x 15 ml) and the organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (0.07 g, 19 %). ν_{max} (NaCl) 1774 (C=O), 1636, 1560, 1458, 1374, 1294, 1156, 1064, 1026, 946, 814 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 1.26-1.53 (3H, m, 7-H_2, 8-H_2), 1.92 (3H, s, CH_3), 2.58-2.63 (2H, m, 2-H_2), 3.42 (3H, s, OCH_3), 4.22 (2H, m, CH_2O), 4.68 (1H, d, J = 5 Hz, 3-*H*), 5.60 (1H, br t, C=CH$_a$), 6.07 (1H, s, C=CH$_b$), 6.21 (1H, d, J = 9 Hz, 5-*H*), 6.51 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_c (125 MHz, CDCl$_3$) 18.4 (*C*H$_3$), 20.2, 26.7 (*C*-7, *C*-8), 31.2 (*C*-1), 45.1 (*C*-2), 51.4 (O*C*H$_3$), 65.6 (CH$_2$O), 79.1 (*C*-4), 90.6 (*C*-3), 126.9 (C=*C*H$_2$), 131.4 (*C*-5), 133.9 (*C*-6), 135.8 (*C*=CH$_2$), 167.3 (*C*=O); *m/z* (CI, NH$_3$) 282 (MH)$^+$ (62 %), 299 (MNH$_4$)$^+$ (100 %), 110 (68 %)

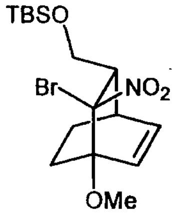
(2SR,3RS,4SR)-^{t}Butyl-4-methoxy-3-nitrobicyclo[2.2.2]oct-5-en-2-ylmethoxy dimethylsilane



331

To a stirred solution of nitro-bicyclic intermediate **303** (0.20 g, 0.6 mmol) in acetonitrile (6 ml) was added 2-tert-butyl-1, 1, 3, 3-tetramethylguanidine (0.21 g, 1.2 mmol), TBDMSCl (0.12 g, 0.8 mmol) and sodium iodide (0.04 g, 0.5 mol %) and the suspension was stirred at reflux for 15 h. The mixture was then allowed to cool and deuterated methanol (2 ml) was added and stirred at room temperature for 30 minutes before being partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was re-extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified using column chromatography eluting with 10 % diethyl ether in petroleum ether to yield the title compound as a colourless oil (0.17 g, 87 %). ν_{max} (ATR) 1555 (NO_2), 1470, 1373, 1255, 1108, 1085, 836, 777 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, 2 x $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.20-1.85 (4H, m, 7-H_2, 8-H_2), 2.33 (1H, m, 1-*H*), 2.60 (1H, m, 2-*H*), 3.40 (3H, s, OCH_3), 3.66 (2H, m, CH_2O), 4.64 (1H, d, J = 7 Hz, 3-*H*), 6.17 (1H, d, J = 9 Hz, 5-*H*), 6.48 (1H, dd, J = 9, 6 Hz, 6-*H*); δ_{2H} (500 MHz, $CHCl_3$) 4.64 (H, s, 3-*D*); δ_c (100 MHz, $CDCl_3$) -5.3 (2 x $SiCH_3$), 18.4 ($SiC(CH_3)_3$), 20.2, 26.8 (*C*-7, *C*-8), 28.0 ($SiC(CH_3)_3$), 31.5 (*C*-1), 48.2 (*C*-2), 51.3 (OCH_3), 64.0 (CH_2O), 79.2 (*C*-4), 90.1 (*C*-3), 131.5 (*C*-5), 134.4 (*C*-6); *m/z* (CI, NH_3) 346/347 $(NH_4)^+$ (7 %), 328/329 $(MH)^+$ (72 %), 310 (100 %), 271 (82 %), 110 (71 %)

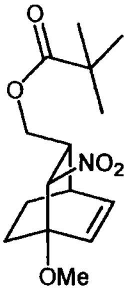
(2SR,3RS,4SR)-3-Bromo-4-methoxy-3-nitrobicyclo[2.2.2]oct-5-en-2-lmethoxy ^{t}butyldimethylsilane



332

To a stirred solution of nitro-bicyclic intermediate **303** (0.10 g, 0.3 mmol) in acetonitrile (5 ml) was added 2-tert-butyl-1, 1, 3, 3-tetramethylguanidine (0.11 g, 0.6 mmol), TBDMSCl (0.06 g, 0.4 mmol) and sodium iodide (0.02 g, 0.5 mol %) and the suspension was stirred at reflux for 15 h. The mixture was then allowed to cool and the acetonitrile was removed under reduced pressure and the residue re-dissolved in THF (5 ml). N-bromosuccinimide (0.2 g, 1.24 mmol) was added in THF (2 ml) and the reaction mixture was stirred at room temperature for a further 4 h. The reaction mixture was then partitioned between ethyl acetate (10 ml) and water (10 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 10 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified using column chromatography eluting with 5 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (0.01 g, 13 %). ν_{max} (ATR) 1564 (NO_2) 1472, 1390, 1258, 1096, 936, 673 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, 2 x $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.19-1.87 (4H, m, 7-H_2, 8-H_2), 2.56 (1H, m, 1-*H*), 2.88 (1H, m, 2-*H*), 3.40 (3H, s, OCH_3), 3.97 (2H, m, CH_2O), 6.45 (2H, m, 5-*H*, 6-*H*); δ_c (100 MHz, $CDCl_3$) -5.3 (2 x $SiCH_3$), 18.4 ($SiC(CH_3)_3$), 31.3 (C-1), 31.4 ($SiC(CH_3)_3$), 34.6, 36.7 (C-7, C-8), 57.4 (OCH_3), 57.8 (C-4), 69.3 (CH_2O), 87.8 (C-2), 115.1 (C-3), 136.7, 139.3 (C-5, C-6); *m/z* (ES+) 406/408 (MH)+

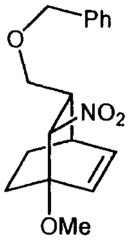
(2SR, 3RS, 4SR)-2,2-Dimethylpropionic acid 4-methoxy-3-nitrobicyclo[2.2.2]oct-5-en-2-ylmethylester



339

To a solution of alcohol **316** (1.25 g, 5.9 mmol), DMAP (0.14 g, 1.2 mmol) and triethylamine (2.38 g, 23.5 mmol) in DCM (15 ml) was added PivCl (1.42 g, 11.7 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h before warming to room temperature and after this time the mixture was quenched with saturated aqueous sodium bicarbonate (20 ml) and diluted with ethyl acetate (50 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 35 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 20 % diethyl ether in petroleum ether to yield a clear oil (1.20 g, 69 %). CHN : Found : C, 60.61 %; H, 7.89; N, 4.40 % $C_{15}H_{24}NO_5$ requires C, 60.61 %, H, 7.74, N, 4.40 %; ν_{max} (ATR) 1718 (C=O), 1500 (NO_2), 1479, 1380, 1285, 1165, 1095, 820, 754, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (9H, s, $C(CH_3)_3$), 1.25-1.83 (4H, m, 7-H_2, 8-H_2), 2.51-2.63 (2H, m, 1-*H*, 2-*H*), 3.41 (3H, s, OCH_3), 4.05-4.15 (2H, m, CH_2O), 4.64 (1H, d, J = 5 Hz, 3-*H*), 6.18 (1H, d, J = 9Hz, 5-*H*), 6.48 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 20.0, 26.4 (C-7, C-8), 26.5 ($C(CH_3)_3$), 31.1 (C-1), 38.8 ($C(CH_3)_3$), 44.8 (C-2), 51.2 (OCH_3), 65.3 (CH_2O), 78.9 (C-4), 90.4 (C-3), 131.0 (C-5), 133.6 (C-6), 178.3 (C=O); *m/z* (ES+) 251 $(M-NO_2)^+$

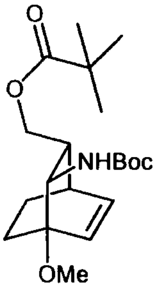
(1SR, 5SR, 6RS)-Benzyloxymethyl-1-methoxy-6-nitrobicyclo[2.2.2]oct-2-ene



340

To a solution of alcohol **316** (1.25 g, 5.9 mmol) and benzyl-2, 2, 2-trichloroacetimidate (1.77 g, 7.0 mmol) in mixture of hexane (20 ml) and DCM (10 ml) at room temperature was added trifluoromethanesulfonic acid (0.2 ml). The mixture was then stirred at room temperature for 30 minutes and the crystalline trichlororacetamide was removed by filtration and the filtrate washed with saturated aqueous sodium bicarbonate (50 ml) and water (50 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to yield the title compound as a light yellow oil (1.00 g, 51 %). ν_{max} (ATR) 3060, 3028, 2940, 2872, 1552 (NO_2), 1373, 1302, 1216, 1198, 1113, 1091, 911, 735, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22-1.81 (4H, m, 7-H_2, 8-H_2), 2.49-2.51 (1H, m, 5-*H*), 2.64-2.66 (1H, m, 4-*H*) 3.40 (3H, s, OCH_3), 3.45-3.57 (2H, m, CH_2O), 4.52 (2H, s, $ArCH_2O$), 4.43 (1H, d, J = 5 Hz, 6-*H*), 6.18 (1H, d, J = 9Hz, 2-*H*), 6.48 (H, dd, J = 9, 7 Hz, 3-*H*), 7.29-7.39 (5H, m, Ar-*H*); δ_c (100 MHz, $CDCl_3$) 19.9, 26.5 (C-7, C-8), 31.2 (C-4), 45.6 (C-5), 51.1 (OCH_3), 70.7, 73.2 (2 x CH_2O), 78.9 (C-1), 90.1 (C-6), 127.5, 127.8, 128.5, 130.9, 134.0 (C-Ar, C-2, C-3), 137.8 (C-Ar); *m/z* (ES^+) 326 $(MNa)^+$

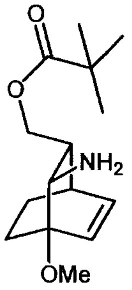
(2SR, 3RS, 4SR)-2,2-Dimethylpropionic acid 3-^{t}butoxycarbonylamino-4-methoxybicyclo[2.2.2]oct-5-en-2-yl methyl ester



341a

To a solution of nitro-bicyclic intermediate **339** (1.20 g, 4.3 mmol) in ethanol (250 ml) was added concentrated HCl (7.64 ml, 76.4 mmol) followed by portionwise addition of zinc powder (9.3 g, 143.2 mmol). The reaction mixture was stirred at room temperature for 12 h. Excess zinc was removed by filtration, and added to the resulting colourless solution was $^iPr_2NEt$ (18.50 g, 143.2 mmol) and di-tert-butyl dicarbonate (1.89 g, 8.7 mmol). The suspension that was produced was stirred at room temperature for 20 h. The reaction mixture was then reduced to 100 ml by concentration under reduced pressure and then partitioned between ethyl acetate (400 ml) and 1:1 mixture of water : sat. sodium hydrogen carbonate (400 ml) and the layers were separated. The aqueous layer was re-extracted with ethyl acetate (2 x 200 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was the purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to yield the title compound as clear oil (0.92 g, 58 %). CHN (Found : C, 64.14 %; H, 9.10; N, 3.69 % $C_{20}H_{34}NO_5$ requires C, 65.21 %, H, 9.24, N, 3.80 %); ν_{max} (ATR) 1718 (C=O), 1498, 1390, 1365, 1283, 1244, 1160, 1026, 974, 770, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.21 (9H, s, C(C*H*$_3$)$_3$), 1.43 (9H, s, OC(C*H*$_3$)$_3$), 1.47-1.84 (5H, m, 2-*H*, 7-*H*$_2$, 8-*H*$_2$), 2.25-2.46 (2H, m, 1-*H*, 3-*H*), 3.31 (3H, s, OC*H*$_3$), 3.55 (1H, br s, NH), 4.06-4.35 (2H, m, C*H*$_2$O), 6.05 (1H, d, J = 9Hz, 5-*H*), 6.40 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 20.5, 25.6 (*C*-7, *C*-8), 27.2, 28.4 (C(CH$_3$)$_3$,OC(CH$_3$)$_3$), 30.9 (*C*-1), 38.8 (OC(CH$_3$)$_3$), 38.8 (*C*(CH$_3$)$_3$), 47.7 (*C*-3), 50.4 (OCH$_3$), 53.6 (*C*-2), 65.6 (CH$_2$O), 78.4 (*C*-4), 133.3 (*C*-5), 135.5 (*C*-6), 155.5 (NC=O), 178.3 (C=O); *m/z* (ES+) 390 (MNa)$^+$, 268 (M-Boc)$^+$

(2SR, 3RS, 4SR)-2,2-Dimethylpropionic acid 3-amino-4-methoxybicyclo[2.2.2]oct-5-en-2-yl methyl ester

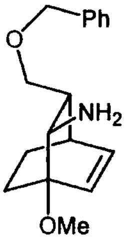


341

Method 1 To a solution of Boc protected amine **341a** (0.92 g, 2.5 mmol) in DCM (75 ml) cooled to 0°C was added trifluoroacetic acid (19 ml). The mixture was stirred at 0 °C for 2 h before removing the DCM/TFA under reduced pressure to give the TFA salt. The amine was re-dissolved in ethyl acetate (20 ml) and was washed with 3 M NaOH (2 x 25 ml). The organic layer was the dried over magnesium sulfate and then concentrated under reduced pressure to yield the title compound as a light brown oil (0.44 g, 66 %).

Method 2 To a solution of nitro-bicyclic intermediate **339** (1.38 g, 4.66 mmol) in ethanol (150 ml) was added concentrated HCl (7.92 ml, 79.2 mmol) followed by portionwise addition of zinc powder (7.57 g, 116.5 mmol). The reaction mixture was stirred at room temperature for 12 h. Excess zinc was removed by filtration and solution was concentrated under reduced pressure. The resultant clear liquid was partitioned between 200 ml ethyl acetate and 200 ml of water. The organic layer was obtained and the pH of the aqueous was adjusted to 12 by dropwise addition of 3 M NaOH. The suspension was then filtered through Celite© and further extracted with 2 x 200 ml ethyl acetate. The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was the purified by column chromatography eluting with 100 % ethyl acetate to 5 % methanol in chloroform to yield the title compound as a light brown oil (0.87 g, 72 %). ν_{max} (ATR) 1728 (C=O), 1479, 1459, 1396, 1301, 1283, 1158, 1125, 1033, 975, 908, 843, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.21 (9H, s, C(C*H*$_3$)$_3$), 1.16-1.83 (5H, m, 2-*H*, 7-*H*$_2$, 8-*H*$_2$), 2.42-2.44 (1H, m, 1-*H*), 2.50-2.51 (1H, m, 3-*H*), 3.36 (3H, s, OC*H*$_3$), 4.02-4.24 (2H, m, C*H*$_2$O), 6.14 (1H, d, J = 9Hz, 5-*H*), 6.38 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 20.5, 25.5 (*C*-7, *C*-8), 27.2 ($C(CH_3)_3$), 31.1 (C-1), 38.8 ($C(CH_3)_3$), 47.5 (C-2), 50.6 (OCH_3), 56.9 (C-3), 65.4 (CH_2O), 80.6 (C-4), 131.2 (C-5), 134.8 (C-6), 178.3 (C=O); *m/z* (ES) 268 (MH)$^+$

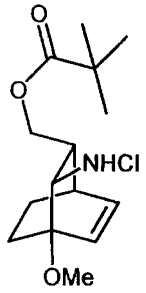
(1SR, 2RS, 3SR)-3-Benzyloxymethyl-1-methoxybicyclo[2.2.2]oct-5-en-2-ylamine



342

To a solution of nitro-bicyclic intermediate **340** (1.00 g, 3.30 mmol) in ethanol (250 ml) was added concentrated HCl (7.64 ml, 76.4 mmol) followed by portionwise addition of zinc powder (9.3 g, 143.2 mmol). The reaction mixture was stirred at room temperature for 12 h. Excess zinc was removed by filtration and the suspension that was produced was stirred at room temperature for 20 h. The reaction mixture was then reduced to 100 ml by concentration under reduced pressure and then partitioned between ethyl acetate (400 ml) and 1:1 mixture of water : sat. sodium hydrogen carbonate (400 ml) and the layers separated. The aqueous layer was re-extracted with ethyl acetate (2 x 200 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was the purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to yield the title compound as clear oil (0.35 g, 39 %). ν_{max} (ATR) 3031-2939 (NH_2), 1453, 1367, 1195, 1117, 737, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34-1.78 (7H, m, 5-*H*, 7-*H*$_2$, 8-*H*$_2$, 2 x N-*H*), 2.41-2.49 (1H, m, 6-*H*), 2.58-2.63 (1H, m, 4-*H*) 3.34 (3H, s, OC*H*$_3$), 3.36-3.41 (1H, m, C*H*$_a$O), 3.66-3.70 (1H, m, C*H*$_b$O), 4.45-4.60 (2H, m, ArC*H*$_2$O), 6.01 (1H, d, J = 9Hz, 2-*H*), 6.38 (H, dd, J = 9, 7 Hz, 3-*H*), 7.30-7.36 (5H, m, Ar-*H*); δ_c (100 MHz, $CDCl_3$) 20.7, 25.8 (C-7, C-8), 31.3 (C-4), 48.4 (C-5), 50.8 (OCH_3), 57.4 (C-6), 72.0 (CH_2O), 73.4 ($ArCH_2O$), 80.1 (C-1), 127.8, 127.9, 128.6, 131.8, 135.7 (C-Ar, C-2, C-3), 138.8 (C-Ar); *m/z* (ES+) 274 (MH)$^+$

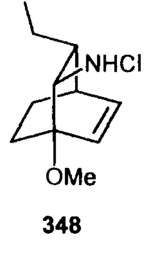
(2SR, 3RS, 4SR)-2,2-Dimethylpropionic acid N-chloro-3-amino-4-methoxybicyclo [2.2.2]oct-5-en-2-yl methyl ester



347

To a stirred solution of N-chlorosuccinimide (0.09 g, 0.1 mmol) in DCM (12 ml) at room temperature was added amine **341** (0.24 g, 0.1 mmol) in DCM quickly dropwise. The resulting solution was stirred at room temperature for 10 minutes. The reaction mixture was the filtered and then partitioned between DCM (10 ml) and 0.40 M sodium hydrogen carbonate (2 x 10 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography eluting with 10 % methanol in DCM to give the title compound as orange oil (0.24 g, 83 %). v_{max} (ATR) 1727 (C=O), 1479, 1459, 1368, 1284, 1158, 1033, 679 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15 (9H, s, C(CH_3)$_3$), 1.49-1.86 (5H, m, 7-H_2, 8-H_2, N*H*), 2.50-2.58 (1H, m, 2-*H*), 2.80-2.91 (1H, m, 3-*H*), 3.28 (3H, s, OCH_3), 3.94-3.99 (1H, m, CH_aO), 4.22-4.27 (1H, m, CH_bO), 4.84 (1H, m, 3-*H*), 6.10 (1H, d, J = 9Hz, 5-*H*), 6.27 (1H, dd, J = 9, 7 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 20.4, 25.7 (C-7, C-8), 27.2 (C(CH_3)$_3$), 31.0 (C-1), 38.8 (C(CH_3)$_3$), 43.2 (C-2), 50.9 (OCH_3), 65.7 (CH_2O), 69.7 (C-3), 80.1 (C-4), 131.0 (C-5), 134.0 (C-6), 178.4 (C=O); *m/z* (ES+) 268 (MH-Cl)$^+$

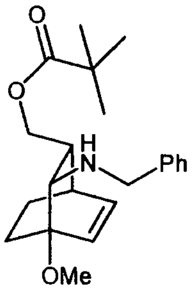
(1SR,2RS,3SR)-*N*-Chloro-3-benzyloxymethyl-1-methoxy-bicyclo[2.2.2]oct-5-en-2-ylamine



348

To a stirred solution of N-chlorosuccinimide (0.13 g, 1.3 mmol) in DCM (10 ml) at room temperature was added amine **342** (0.35 g, 1.3 mmol) in DCM quickly dropwise. The resulting solution was stirred at room temperature for 10 minutes. The reaction mixture was the filtered and then partitioned between DCM (10 ml) and 0.40 M sodium hydrogen carbonate (2 x 10 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography eluting with 10 % methanol in DCM to yield the title compound as orange oil (0.28 g, 70 %). ν_{max} (ATR) 1736 (C=O), 1453, 1370, 1111, 736, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.28-1.94 (5H, m, 2-*H*, 7-*H*$_2$, 8-*H*$_2$), 2.78-2.81 (2H, m, 1-*H*, N*H*), 3.36 (3H, s, OC*H*$_3$), 3.42-3.45 (1H, m, C*H*$_a$O), 3.82-3.85 (1H, m, C*H*$_b$O), 4.45-4.63 (2H, m, ArC*H*$_2$O), 4.86 (1H, m, 3-*H*), 6.18 (1H, d, J = 10 Hz, 5-*H*), 6.38 (1H, dd, J = 12, 10 Hz, 6-*H*) and 7.37-7.40 (5H, m, Ar-*H*), δ_c (100 MHz, $CDCl_3$) 20.3, 25.9 (C-7, C-8), 30.8 (C-1), 44.0 (C-2), 50.9 (OCH_3), 69.6 (C-3), 71.9 (CH_2O), 73.0 ($ArCH_2O$), 80.2 (C-4), 127.6, 124.6, 130.7, 134.3 (C-*Ar*, C-5, C-6), 138.4 (C-Ar), *m/z* (ES+) 276 (MH-Cl)$^+$

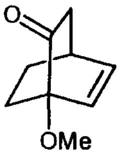
(2SR,3RS,4SR)-2,2-Dimethylpropionicacid-3-benzylamino-4-methoxybicyclo[2.2.2] oct-5-en-2-yl methyl ester



359

To a stirred suspension of sodium hydride (0.01 g, 0.4 mmol) in THF (3 ml) was added amine **342** (0.05 g, 0.2 mmol) in THF (0.5 ml). The mixture was stirred at room temperature for 17 h before addition of ammonium chloride (5 ml) and ethyl acetate (5 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 5 ml) and the combined organic layers were dried over magnesium sulfate before concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with diethyl ether affording the title compound as light yellow oil (0.06 g, 83 %). ν_{max} (ATR) 1664, 1453, 1367, 1195, 1117, 737 and 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.14 (9H, s, C(C*H*$_3$)$_3$), 1.30-1.75 (4H, m, 7-*H*$_2$, 8-*H*$_2$), 1.89 (1H, br s, N*H*), 2.39-2.44 (2H, m, 1-*H*, 2-*H*), 3.20 (3H, s, OC*H*$_3$), 3.59-3.62 (H, m, C*H*$_a$O), 3.79-3.85 (2H, m, ArC*H*$_2$O), 4.14-4.15 (1H, m, C*H*$_{2b}$O), 6.01 (1H, d, J = 9 Hz, 5-*H*), 6.19 (1H, dd, J = 9, 7 Hz, 6-*H*), 7.28-7.32 (5H, m, Ar-*H*); δ_c (100 MHz, $CDCl_3$) 20.8, 25.6 (C-7, C-8), 27.5 ($C(CH_3)_3$), 31.2 (C-1), 39.0 ($C(CH_3)_3$), 44.8 (C-2), 50.6 (OCH_3), 51.3 (CH_2O), 62.4 (C-3), 66.3 ($ArCH_2O$), 80.1 (C-4), 127.1, 127.2, 128.3, 128.4, 128.5 (C-Ar), 133.1 (C-5), 133.4 (C-6), 140.4 (C-Ar), 178.7 (C=O) *m/z* (ES+) 358 (MH)$^+$

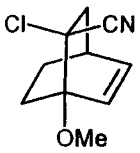
[1RS, 4SR]-1-Methoxybicyclo[2.2.2.]oct-5-ene-2-one[93]



362

To a solution of chloronitriles **370** (11.30 g, 56.6 mmol) in dimethylsulfoxide (200 ml) was added a 20 % aqueous solution of KOH (335 ml) and the reaction was stirred at room temperature for 7 days. The reaction was diluted with water, extracted into diethyl ether (3 x 300 ml) and the layers separated. The organic layers were combined, washed with brine (500 ml) and then dried over magnesium sulfate. The solvent was then removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 5 % - 10 % diethyl ether in petroleum ether to give the title compound as a colorless liquid (7.0 g, 79 %). ν_{max} (NaCl) 1733 (C=O), 1610, 1464, 1405, 1365, 1089, 851, 657 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.48-1.89 (4H, m, 7-H_2, 8-H_2), 2.05-2.06 (2H, m, 3-H_2), 2.87-2.89 (1H, m, 4-*H*), 3.45 (3H, s, OCH_3), 6.17 (1H, d, J = 8 Hz, 6-*H*), 6.37 (1H, dd, J = 8, 6 Hz, 5-*H*); δ_c (100 MHz, $CDCl_3$) 25.3, 27.3 (*C*-7, *C*-8), 31.5 (*C*-4), 40.3 (*C*-2), 53.2 (OCH_3), 84.7 (*C*-1), 128.3 (*C*-5), 135.9 (*C*-6), 211.2 (C=O); *m/z* (ES+) 152 (M^+)

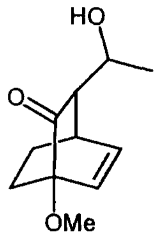
[1RS,6RS,4SR]-6-Chloro-6-cyano-1-methoxybicyclo[2.2.2]oct-2-ene[93]



370

Diene **244** (10.00 g, 90.9 mmol) was added dropwise to a solution of 2-chloroacrylonitrile **369** (15.88 g, 181.5 mmol) and phenothiazine (0.09 g, 0.5 mmol) in benzene (85 ml). The resulting mixture was heated at reflux for 9 h and after which time the solvent was removed under reduced pressure. The residue was then purified by Kugelrohr distillation (80 °C/0.8 mbar) to give the title compound as a colourless oil (11.3 g, 63 %), Literature b.p. 116-119/0.1 mmHg; IR (NaCl) ν_{max} 2240 (C=N), 1610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.41-2.74 (7H, m, 4-*H*, 5-H_2, 7-H_2, 8-H_2), 3.51 (3H, s, OCH_3), 6.22 (1H, d, J = 10 Hz, 2-*H*), 6.37 (1H, dd, J = 10, 8 Hz, 3-*H*); δ_c (100 MHz, $CDCl_3$) 24.6 (*C*-7, *C*-8), 29.5 (*C*-5), 46.9 (*C*-4), 52.5 (OCH_3), 61.6 (*C*-6), 80.7 (*C*-1), 120.0 (CN), 130.1, 134.0 (*C*-2, *C*-3); *m/z* (ES+) 216 $(MOH_2)^+$

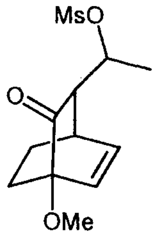
[1RS, 3SR, 4SR]-3-(1'-Hydroxyethyl)-1-methoxybicyclo[2.2.2]oct-5-en-2-one[93]



371

To a solution of diisopropylamine (3.33 ml, 23.7 mmol) in THF (30 ml) at - 78 °C was added ^{n}BuLi (13 ml, 2.0 M solution in hexanes, 25.7 mmol) dropwise over 20 minutes. The reaction was allowed to stir for 20 minutes after which time ketone **362** (3.00 g, 20.0 mmol) in THF (10 ml) was added dropwise *via* a cannula at - 78 °C and stirred for 1 h to allow complete metallation. Acetaldehyde (2.24 ml, 40.0 mmol) in THF (10 ml) was then added dropwise to the reaction mixture and after 3 h the reaction was quenched with saturated ammonium chloride (50 ml) and allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (3 x 75 ml) and the combined organic extracts were washed with brine (100 ml) before drying over magnesium sulfate. The solvent was then removed under reduced pressure and the residue that remained purified by column chromatography eluting with 50 % diethyl ether in petroleum ether to give the title compound as a colourless oil (2.89 g, 74 %). ν_{max} (NaCl) 3154-3056 (OH), 1712 (C=O), 1466, 1379, 1293, 920, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, J = 6 Hz, 2'-H_3), 1.42-1.81 (5H, m, 3-*H*, 7-H_2, 8-H_2), 2.81 (1H, m, 4-*H*), 3.46 (3H, s, OCH_3), 3.53 (1H, m, 1'-*H*), 3.86 (1H, br s, O*H*), 6.11 (1H, d, J = 8 Hz, 6-*H*), 6.32 (1H, dd, J = 6, 8 Hz, 5-*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (C-1'), 25.4, 25.5 (C-7, C-8), 33.7 (C-4), 53.1 (OCH_3), 55.5 (C-3), 69.5 (C-2'), 84.3 (C-1), 128.9, 135.8 (C-5, C-6), 213.1 (C-2); *m/z* (ES+) 219 $(MNa)^+$; HRMS (ES+) MNa^+; Found 219.1015; $C_{11}H_{16}O_3Na$ requires 219.0997

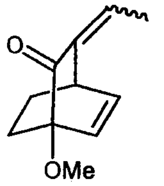
[1RS, 3SR, 4SR]-Methanesulfonic acid 1-(4-methoxy-3-oxobicyclo[2.2.2]oct-5-en-2-yl)ethyl ester[93]



372

To a stirred solution of alcohol **371** (2.89 g, 14.7 mmol), triethylamine (5.12 ml, 36.8 mmol) and DMAP (0.18 g, 1.5 mmol) in DCM (200 ml) at 0 °C was added methane sulfonyl chloride (1.71 ml, 2.1 mmol) The mixture was allowed to warm to room temperature and stirred for 2 h after which time ^{1}H NMR showed the reaction to be complete. The reaction mixture was diluted with DCM (100 ml) and washed with water (200 ml), 5 % HCl (200 ml) and brine (200 ml). The resulting solution was dried over magnesium sulfate and the residue that remained was purified by column chromatography eluting with 50 % ethyl acetate in petroleum ether to afford the title compound as a white solid (3.58 g, 89 %). mp 54-56 °C; Found : C, 52.50 %; H, 6.57 % $C_{12}H_{18}O_5S$ requires C, 52.50 %, H, 6.56 %; ν_{max} (NaCl) 1729 (C=O), 1462, 1352 (SO_2), 1174 (SO_2), 1041, 918, 710, 531 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, J = 6 Hz, CH_3), 1.48-2.01 (5H, m, 2-*H*, 7-H_2, 8-H_2), 2.57 (1H, m, 7-*H*), 2.97 (3H, s, SO_2CH_3), 3.44 (3H, s, OCH_3), 5.05 (1H, m, 1-*H*), 5.99 (1H, d, J = 9 Hz, 6-*H*), 6.37-6.41 (1H, dd, J = 7, 9 Hz, 5-*H*); δ_c (100 MHz, $CDCl_3$) 18.7 (CH_3), 24.7, 25.7 (C-8, C-9), 32.1 (7-C), 38.4 (SO_2CH_3), 53.1, 53.2 (OCH_3, C-1), 78.1 (C-2), 84.3 (C-4), 127.5, 135.0 (C-5, C-6), 205.3 (C-3); *m/z* (ES+) 297 (MNa)$^+$; HRMS (ES+) MNa$^+$; Found 297.0758; $C_{12}H_{18}O_5NaS$ requires 297.0773

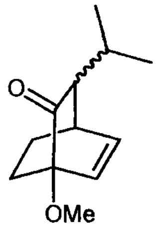
[1RS, 4SR]-3-(E, Z)-Ethylidene-1-methoxybicyclo[2.2.2]oct-5-en-2-one



367

To a solution of mesylate **372** (3.50 g, 14.0 mmol) in toluene (75 ml) was added 1, 8-diazabicylo[5.4.0]undec-7-ene (10.5 ml, 70 mmol) dropwise with stirring. The reaction was heated to reflux and followed by TLC (2:1 petroleum ether:ethyl acetate) which showed removal of starting material after 2 h. The reaction was diluted with DCM (150 ml), poured into 0.1 M HCl (150 ml) and exhaustively extracted with DCM. The combined organic extracts were washed with brine (200 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with eluting with 20 % diethyl ether in petroleum ether to give the title enone as a mixture of isomers (*E*:*Z*, 95:5) as a light yellow oil (1.93 g, 78 %). ν_{max} (NaCl) 1714 (C=O), 1649, 1462, 1360, 110, 787 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **Major** 1.49-1.82 (7H, m, 7-H_2, 8-H_2, 3′-CH_3), 3.52 (3H, s, OCH_3), 3.64 (1H, m, 4-*H*), 6.22 (1H, d, J = 8 Hz, 6-*H*), 6.24-6.38 (1H, dd, J = 6, 8 Hz, 5-*H*), 6.41-6.47 (1H, q, J = 7 Hz, 3′-*H*); **Minor** 1.55-1.82 (4H, m, 7-H_2, 8-H_2), 2.03 (3H, d, J = 7 Hz, 3′-H_3), 3.32 (1H, m, 4-*H*), 3.52 (3H, s, OCH_3), 5.85-5.91 (1H, q, J = 7 Hz, 3′-*H*), 6.17 (1H, d, J = 9 Hz, 6-*H*), 6.37-6.41 (1H, dd, J = 7, 9 Hz, 5-*H*); δ_c (100 MHz, $CDCl_3$) **Major** 13.1 (C-2′), 25.3, 26.4 (C-7, C-8), 33.4 (C-4), 53.4 (OCH_3), 84.6 (C-1), 128.4, 130.9 (C-5, C-6), 134.3 (C-1′), 135.0 (3-C), 197.4 (2-C); **Minor** 14.6 (C-2′), 26.0, 26.3 (C-7, C-8), 41.5 (C-4), 53.4 (OCH_3), 58.4 (C-*1*), 130.1, 133.36 (C-5, C-6), 134.4 (C-1′), 134.9 (C-3), 199.5 (C-2); *m/z* (ES+) 201 (MNa)$^+$; HRMS (ES+) MNa$^+$; Found 201.0903; $C_{11}H_{14}O_2Na$ requires 201.0891

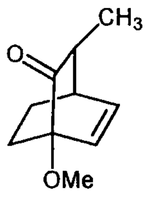
[1RS, 3SR/RS, 4SR]-3-Prop-2′-yl-1-methoxybicyclo[2.2.2]oct-5-en-2-one



373

To a suspension of copper iodide (0.28 g, 1.5 mmol) in diethyl ether (20 ml) cooled to - 25 °C was added chlorotrimethylsilane (0.35 ml, 2.7 mmol). Methyl lithium (2.70 ml, 1.1 M solution in diethyl ether, 2.97 mmol) was then added dropwise immediately turned the suspension bright yellow, on complete addition, there remained a colourless solution. The solution that remained was cooled to - 78 °C and the enone **367** (0.24 g, 1.4 mmol) in diethyl ether (5 ml) was added *via* cannula at - 78 °C, turning the solution bright yellow. The reaction mixture was stirred at - 78 °C for 10 minutes and TLC analysis (3:1 petroleum ether : diethyl ether) showed the reaction to be complete. Saturated ammonium chloride (20 ml), brine (10 ml) and ethyl acetate (20 ml) was added and the reaction mixture was warmed to room temperature or the reaction mixture was added by cannula to a range of proton sources (see Table 1, Page 68). The aqueous layer was extracted with ethyl acetate (3 x 40 ml). The organic layers were combined, dried and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 9:1 petroleum ether:diethyl ether yielding the title compound as a 90:10 *endo* : *exo* mixtute of isomers as a colourless oil (0.25 g, 94 %). ν_{max} (NaCl) 1727 (C=O), 1462, 1366, 1196, 1079, 912, 849, 704 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1RS, 3SR, 4SR]** 0.65 (3H, d, J = 7 Hz, CH(C*H*$_3$)$_2$), 0.94 (3H, d, J = 7 Hz, CH(C*H*$_3$)$_2$), 1.51-1.90 (5H, m, 3-*H*, 7-*H*$_2$, 8-*H*$_2$), 1.99-2.07 (1H, m, C*H*(CH$_3$)$_2$), 2.79-2.81 (1H, m, 4-*H*), 3.45 (3H, s, OCH$_3$), 5.99 (1H, d, J = 8 Hz, 6-*H*), 6.31 (1H, dd, J = 6, 8 Hz, 5-*H*); **[1RS, 3RS, 4SR]** 0.89 (3H, d, J = 7 Hz, CH(C*H*$_3$)$_2$), 1.10 (3H, d, J = 7 Hz, CH(C*H*$_3$)$_2$), 1.51-1.90 (5H, m, 3-*H*, 7-*H*$_2$, 8-*H*$_2$), 1.99-2.07 (1H, m, C*H*(CH$_3$)$_2$), 2.85-2.88 (1H, m, 4-*H*), 3.44 (3H, s, OCH$_3$), 6.16 (1H, d, J = 8 Hz, 6-*H*), 6.41 (1H, dd, J = 6, 8 Hz, 5-*H*); δ_c (100 MHz, $CDCl_3$) **[1RS, 3SR, 4SR]** 20.3, 20.9 (2 x CH$_3$), 25.6 (C-7, C-8), 28.7 (C-4), 33.1 (CH(CH$_3$)$_2$), 52.6 (C-3), 53.1 (OCH$_3$), 84.5 (C-1), 135.2, 137.1 (C-5, C-6), 209.8 (C-2); **[1RS, 3RS, 4SR]** 20.9, 21.3 (2 x CH$_3$), 25.6 (C-7, C-8), 29.1 (C-4), 34.0 (CH(CH$_3$)$_2$), 52.6 (C-3), 52.5 (OCH$_3$), 84.5 (C-1), 130.3, 137.1 (C-5, C-6), 210.8 (C-2); *m/z* (ES+) 217 (MNa)$^+$; HRMS (ES+) Found MNa$^+$; 217.1214; $C_{12}H_{18}O_2Na$ requires 217.1204

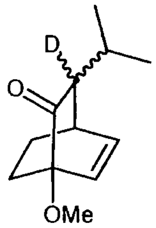
[1RS, 3RS, 4SR]-1-Methoxy-3-methylbicyclo[2.2.2]oct-5-en-2-one[94]



377

To a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.82 ml, 3.94 mmol) in THF (10 ml) at - 78 °C was added ^{n}BuLi (2.6 ml, 4.14 mmol, 1.4 M solution in hexanes) dropwise over 5 minutes. The reaction was allowed to stir for 20 minutes after which time ketone **362** (0.30 g, 2.0 mmol) and HMPA (2.5 ml) in THF (5 ml) was added dropwise *via* a cannula at - 78 °C. The reaction was stirred for 1 h to generate the enolate. After which time MeI (0.49 ml, 7.88 mmol) in THF (2 ml) was added *via* cannula at - 78 °C and the reaction mixture was stirred for a further 2 h at - 78 °C. The mixture was then warmed to - 20 °C and stirred for a further 3 h. The reaction was then treated with saturated ammonium chloride (10 ml) and allowed to warm to room temperature. The mixture was transferred to a separating funnel and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 9:1 petroleum ether : diethyl ether affording the title compound as a light orange oil (0.25 g, 75 %). ν_{max} (NaCl) 1728 (C=O), 1453, 1366, 1172, 968, 923 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, J = 8 Hz, CH_3), 1.65-1.72 (2H, m, 7-H_a, 8-H_a), 1.84-1.96 (2H, m, 7-H_b, 8-H_b), 2.09-2.12 (1H, q, J = 8 Hz, 5-*H*), 2.75-2.76 (1H, m, 4-*H*), 3.53 (3H, s, OCH_3), 6.19 (1H, d, J = 8 Hz, 6-*H*), 6.38 (1H, dd, J = 8, 6 Hz, 5-*H*); δ_c (100 MHz, $CDCl_3$) 17.5 (CH_3), 25.2 (C-7), 25.8 (C-8), 32.3 (C-4), 44.3 (C-2), 53.1 (OCH_3), 84.4 (C-1), 128.6 (C-5), 134.9 (C-6), 211.6 (C=O); *m/z* (CI, NH_3) 184 (MNH_4^+) (100 %), 167 (MH^+) (67 %)

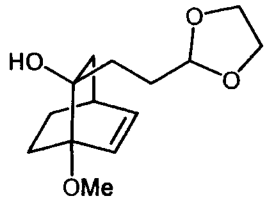
[1RS, 3SR/RS, 4SR]-3-deutero-3-Prop-2′-yl-1-methoxybicyclo[2.2.2]oct-5-en-2-one



379

Prepared in the same manner except a D_2O quench was employed as above to afford the title compound as colourless oil (0.05 g, 84 %). ^{2}H NMR (500MHz, $CHCl_3$) 1.87 (s, 3-*D*)

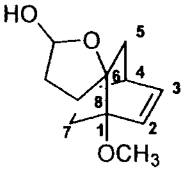
[1RS, 2SR, 4SR]-2-(2′-(1″, 3″-dioxolane-2″-yleth-1′-yl))-1-methoxybicyclo[2.2.2]oct-5-en-2-ol[3]



386

A solution of ketone **362** (0.50 g, 3.3 mmol) in dry THF (40 ml) was slowly added dropwise onto a solution of magnesium turnings (0.28 g, 11.5 mmol). To the mixture was added 2-(2-bromoethyl)-1,3-dioxolane (1.98 ml, 16.5 mmol) and a catalytic amount of 1,2-dibromoethane. After 1 ½ h, the reaction was quenched slowly with saturated ammonium chloride solution (75 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine (150 ml) before drying over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with petroleum ether : diethyl ether (3:1). The title compound was obtained as colourless oil (0.52 g, 62 %). ν_{max} (NaCl) 3620-3354 (OH), 1452, 1408, 1371, 1144, 1040, 988, 944, 696 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.16-1.96 (11H, m, 3-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, O-*H*, 1′-*H*$_2$, 2′-*H*$_2$), 2.44 (1H, m, 4-*H*), 3.27 (3H, s, OCH_3), 3.73-3.78 (2H, m, 1″-*H*$_2$), 3.85-3.91 (2H, m, 3″-*H*$_2$), 4.76-4.78 (1H, m, 2″-*H*), 6.09 (1H, dd, J = 6, 9 Hz, 5-*H*), 6.17 (1H, d, J = 9 Hz, 6-*H*); δ_c (125 MHz, $CDCl_3$) 22.1, 25.3 (C-7, C-8), 27.3 (C-3), 30.7 (C-4), 32.6 (*C-1′*), 39.7 (2′-C), 51.8 (OCH_3), 65.1 (C-1″, C-3″), 78.2 (C-2), 83.0 (C-1), 105.3 (*C-2″*), 132.8, 133.7 (C-5, C-6); *m/z* (ES+) 277 (MNa)$^+$; HRMS (ES+) Found MNa$^+$; 277.1413; $C_{14}H_{22}O_4Na$ requires 277.1410

1-methoxy-4′,5′-dihydro-3′H-spiro-bicyclo-[2.2.2]-oct-2-ene-6-2′-furan-5-ol

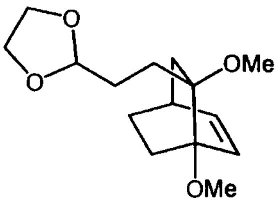


389

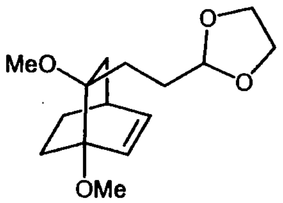
Acetic Acid (2 µl, 0.04 mmol) was added to a stirred solution of dioxolane **386** (0.10 g, 0.4 mmol) in THF/water (1:1, 8 ml) and stirred at room temperature for 2 h. After which time sodium hydrogen carbonate (3 ml) and diethyl ether (8 ml) were added.

The layers were separated and the aqueous layer was re-extracted with diethyl ether (3 x 7 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure and the title compound was obtained as a colourless oil (0.08 g, 65 %). ν_{max} (NaCl) 1456, 1369, 1072, 996, 960, 693 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 1.29-1.78 (7H, m), 1.89-2.31 (3H, m), 2.34-2.47 (1H, br s, 1-*H*), 3.37 (3H,s, OCH$_3$), 4.48 (1H, d, J = 11 Hz, 2′-*H*), 5.31 (1H, dd, J = 5, x Hz, 3′-*H*), 6.12-6.27 (2H, m, 2-*H*, 3-*H*); δ_c (100 MHz, CDCl$_3$) 21.8, 25.7, 30.7, 34.1, 35.5, 45.8 (C-5, C-7, C-8, C-1′, C-2′), 51.5 (OCH$_3$), 81.6, 89.7 (C-1, C-6), 99.1 (C-3′), 131.6, 136.0 (C-2, C-3), *m/z* (ES+) 193 (M-OH)$^+$; HRMS (ES+) Found (M-OH)$^+$; 193.1225; $C_{12}H_{17}O_2$ requires 193.1223

[1RS,2RS/SR,4SR]-2-(2′-(1″,3″-dioxolane-2″-yleth-1′-yl))-1,2-dimethoxybicyclo[2.2.2] oct-5-ene



390b

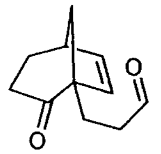


390

To a stirred solution of alcohol **386** (1.13 g, 4.5 mmol) in THF (10 ml) was added sodium hydride (0.43 g, 17.8 mmol). The solution was stirred at room temperature for 30 minutes. After which time methyl iodide (0.30 ml, 4.9 mmol) was added dropwise and then tetrabutylammonium iodide (0.17 g, 10 mol %). The mixture was stirred at room temperature for 4 h. Water (20 ml) was added slowly and the solution was transferred to a separating funnel and ethyl acetate (40 ml) was added. The aqueous layer was further extracted with ethyl acetate (2 x 30 ml). The organic extracts were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 9:1 petroleum ether : diethyl ether to afford the title compound as light yellow oil (0.32 g). [1RS, 2SR, 4SR] - ν_{max} (NaCl) 1464, 1408, 1368, 1117, 1063, 1037, 690 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 1.13-2.01 (9H, m, 1′-*H*$_2$, 2′-*H*$_2$, 3-*H*$_2$, 7-*H*$_a$, 8-*H*$_2$), 2.22-2.28 (1H, m, 7-*H*$_b$), 2.50 (1H, m, 4-*H*), 3.34 (3H, s, OCH$_3$), 3.36 (3H, s, OCH$_3$), 3.85-3.87 (2H, m, 1″-*H*$_2$), 3.98-4.00 (2H, m, 3″-*H*$_2$), 4.85-4.87 (1H, m, 2″-*H*), 6.16 (1H, dd, J = 7, 9 Hz, 5-*H*), 6.21 (1H, d, J = 9 Hz, 6-*H*); δ_c (125 MHz, CDCl$_3$) 22.8, 24.5 (C-7, C-8), 27.0, 27.4 (C-1″, C-3″), 30.4 (C-4), 42.2 (C-2′), 51.0 (OCH$_3$), 52.7 (OCH$_3$), 65.3 (C-2″, C-3″), 82.0, 84.5 (C-1, C-2), 105.3 (C-2″), 133.8, 134.4 (C-5, C-6); *m/z* (ES+) 277 (MNa)$^+$; HRMS (ES+) Found MNa$^+$; 277.1413; $C_{14}H_{22}O_4Na$ requires 277.1410) Further elution with gave a light yellow oil (0.14 g, 40 % overall). [1RS, 2RS, 4SR]- ν_{max} (NaCl) 1466, 1373, 1191, 1115 1037, 975, 690 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 1.35-1.75 (8H, m, 3-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, 1′-*H*$_2$), 1.90-1.92 (1H, m, 2′-*H*$_2$), 1.95-2.21 (1H, m, 2′-*H*$_2$), 2.53 (1H, m, 4-*H*), 3.23 (3H, s, OC*H*$_3$), 3.28 (3H,s, OC*H*$_3$), 3.87-3.89 (2H, m, 1″-

H$_2$), 4.00-4.02 (2H, m, 3″-*H*$_2$), 4.90 (1H, t, J = 5 Hz, 2″-*H*), 6.24 (1H, dd, J = 7, 9 Hz, 5-*H*), 6.38 (1H, d, J = 9 Hz, 6-H); δ_c (125 MHz, $CDCl_3$) 24.1, 25.6 (*C*-7, *C*-8), 26.0 (C-3), 28.7 (C-1″), 30.2 (C-4), 41.9 (C-2′), 51.3, 51.8 (OCH_3), 65.1 (*C*-2″, *C*-3″), 81.9, 83.8 (C-1, C-2), 105.3 (C-2″), 132.2, 132.8 (*C*-5, *C*-6); *m/z* (ES+) 277 $(MNa)^+$

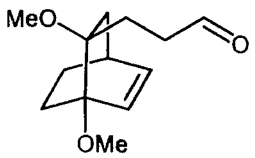
3-(2-Oxo-bicyclo[3.2.1]oct-6-en-1-yl)propionaldehyde



391

To a stirred solution of dioxolane **390** (0.05 g, 0.2 mmol) was dissolved in THF (1 ml) and distilled water (1 ml) and 10 mol % of CSA, AcOH, *p*-TSA or 1 M HCl were added. The mixtures were then stirred at room temperature and monitored by TLC. On completion the reaction mixture was poured into sodium hydrogenate carbonate (5 ml) and ethyl acetate (7 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 7 ml) and the organic layers were combined washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with 4:1 petroleum ether : diethyl ether to yield the title compound as a colourless oil (0.02 g, 60 %). ν_{max} (KBr) 1720 (C=O), 1701 (C=O), 1216, 920, 790 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.70-1.92 (5H, m, 4-*H*$_2$, CH_2CH_aCHO, CH_2CH_2CHO), 2.01-2.22 (1H, m, CH_2CH_bCHO), 2.23 (1H, dd, J = 8, 18 Hz, 8-*H*), 2.36-2.43 (2H, m, 1-*H*$_2$), 2.57-2.63 (1H, m, 8-*H*), 2.85-2.87 (1H, m, 5-H), 5.64 (1H, d, J = 6 Hz, 7-*H*), 6.12-6.14 (1H, m, 6-*H*), 9.71 (1H, s, C*H*O); δ_c (100 MHz, $CDCl_3$) 23.5 (CH_2CH_2CHO), 26.4 (C-4), 35.2 (C-8), 39.9 (C-5), 40.0 (C-1), 45.8 (CH_2CH_2CHO), 61.2 (C-3), 135.6 (C-7), 138.4 (C-6), 202.3 (C-2), 210.7 (CHO); *m/z* (ES+) 194 $(MOH_2)^+$

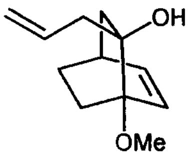
[1RS, 5SR, 6SR]-3′-(1,2-Dimethoxy-bicyclo[2.2.2]oct-5-en-2-yl)propionaldehyde



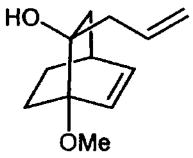
395

To a stirred solution of oxalyl chloride (0.18 ml, 2.0 mmol) in DCM (5 ml) at - 78 °C was added dimethylsulfoxide (0.19 ml, 2.7 mmol) *via* cannula at - 78 °C and stirred for 5 minutes. After which time alcohol **399** (0.30 g, 1.4 mmol) in DCM (3 ml) was added dropwise and was stirred for 15 minutes before adding triethylamine (0.93 ml, 6.8 mmol) and the mixture was warmed to room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then the mixture was partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous layer was then re-extracted with diethyl ether (2 x 50 ml). The combined organic layers were washed with brine and dried over magnesium sulfate before concentrating under pressure. The resulting residue was purified by column chromatography eluting with 1:3 petroleum ether : ethyl acetate to afford the title compound as a yellow oil (0.22 g, 73 %). IR (NaCl) v_{max} 1723 (C=O), 1463, 1084, 1061, 699 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 1.29-2.01 (8H, m, 3-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, 1′-*H*$_2$), 2.33-2.43 (1H, m, 2′-H_a), 2.52 (1H, br s, 4-*H*), 2.62-2.68 (1H, m, 2′-H_b), 3.30 (3H, s, OC*H*$_3$), 3.34 (3H, s, OC*H*$_3$), 6.20-6.25 (2H, m, 5-*H*, 6-*H*), 9.79 (1H, s, C*H*O); δ_c (100 MHz, $CDCl_3$) 22.3, 24.9 (C-7, C-8), 26.1 (C-3), 30.3 (C-4), 38.7 (C-1′), 41.2 (C-2′), 51.2 (OCH_3), 52.2 (OCH_3), 81.7, 84.4 (C-1, C-2), 133.9, 134.1 (C-5, C-6) 203.3 (C=O); *m/z* (ES+) 247 (MNa)$^+$; HRMS (ES+) Found MNa$^+$; 247.1303; $C_{13}H_{20}O_3Na$ requires 247.1305

[1RS, 2SR/RS 4SR]-1-methoxy-2-prop-2′-ylbicyclo[2.2.2]oct-5-en-2-ol



397

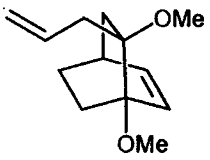


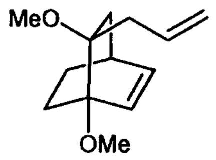
396

To a suspension of magnesium turnings (1.52 g, 63.2 mmol) in diethyl ether (10 ml) was added one drop of 1,2-dibromoethane. Freshly distilled allyl bromide (2.49 ml, 29.2 mmol) in diethyl ether (20 ml) was then added dropwise. The suspension was stirred for 20 minutes and added *via* cannula to a cooled (-78 °C) solution of ketone **362** (1.20 g, 7.9 mmol) in diethyl ether (30 ml). The solution was allowed to warm to room temperature and stirred at room temperature for 2 h. The solution was re-cooled to 0 °C and aqueous ammonium chloride (60 ml) was added slowly. The solution was then transferred to a separating funnel and the aqueous layer was further extracted with ethyl acetate (2 x 100 ml). The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 6:1 petroleum ether : diethyl ether to yield [1RS, 2SR, 4SR] isomer as a clear oil (0.49 g) and further elution gave [1RS, 2RS, 4-SR] isomer also as clear oil (0.61 g, 72 % overall). **[1RS, 2SR, 4SR]** - v_{max} (NaCl) 3567-3211 (OH), 1637, 1370, 1121, 1000, 909, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.40-1.77 (6H, m, 3-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$),1.96-2.05 (1H, m, O*H*), 2.52-2.56 (3H, m, 4-*H*, 1′-*H*$_2$), 3.39 (3H, s, OCH_3), 5.03-5.11 (1H, m, 2′-*H*), 5.81-5.94 (2H, m, 3′-*H*$_2$), 6.18 (1H, dd, J = 5, 7 Hz, 6-*H*), 6.25 (1H, d, J = 7 Hz, 5-*H*); δ_c (100 MHz, $CDCl_3$) 22.1, 25.4 (C-7, C-8), 30.8 (C-4), 39.9, 43.9 (C-3, C-1′), 51.8 (OCH_3), 78.0 (C-2), 82. 9 (C-1), 118.1 (C-3′), 132.7, 133.9 (C-5, C-6), 134.8 (C-2′); *m/z* (ES+) 217 (MH)$^+$; HRMS (ES+) Found MNa$^+$; 217.1203; $C_{12}H_{18}O_2Na$ requires

217.1199; **[1RS, 2RS, 4SR]** - ν_{max} (NaCl) 3567-3489 (OH), 1637, 1371, 1110, 908, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.38-1.48 (2H, m, 3-*H*, 7-H_a), 1.53-1.66 (3H, m, 7-H_b, 8-H_2), 1.74-1.77 (1H, m, 3-*H*), 2.03 (1H, br s, O*H*), 2.15-2.19 (1H, m, 1′-*H*), 2.54 (1H, m, 4-*H*), 2.66-2.70 (1H, m, 1′-*H*), 3.47 (3H, s, OCH_3), 5.10-5.14 (1H, m, 2′-*H*), 5.97-6.02 (2H, m, 3′-H_2), 6.34 (2H, d, J = 4 Hz, 5-*H*, 6-*H*). δ_c (100 MHz, $CDCl_3$) 21.9, 24.5 (*C*-7, *C*-8), 30.3 (*C*-4), 39.7 (*C*-3), 43.7 (*C*-1′), 51.6 (OCH_3), 77.8 (*C*-2), 82.7 (*C*-1), 117.8 (*C*-3′), 132.6, 133.6 (*C*-5, *C*-6), 134.6 (*C*-2′); *m/z* (ES+) 217 (MH)$^+$; HRMS (ES+) Found MNa$^+$; 217.1199; $C_{12}H_{18}O_2Na$ requires 217.1199

[1RS, 2RS/SR, 4SR]-6-allyl-1,6-dimethoxy-bicyclo[2.2.2]oct-2-ene


397a

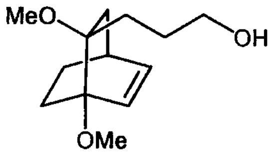

396a

To a stirred solution of alcohols **396/397** (0.49 g, 2.5 mmol) in THF (15 ml) was added sodium hydride (0.08 g, 3.3 mmol). The solution was stirred at room temperature for 1 h. After which time methyl iodide (0.32 ml, 5.1 mmol) was added dropwise. The mixture was stirred at room temperature for 15 h. Water (20 ml) was added slowly and the solution was transferred to a separating funnel and ethyl acetate (40 ml) was added. The aqueous layer was further extracted with ethyl acetate (2 x 30 ml). The organic extracts were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 9:1 petroleum ether:diethyl ether affording the title compound as light yellow oil (0.10 g, 27 % based on recovery of starting material).

Method 2 o a stirred solution of alcohols **396/397** (0.05 g, 0.3 mmol) in THF (10 ml) was added sodium hydride (0.02 g, 1.0 mmol). The solution was stirred at room temperature for 30 minutes. After which time methyl iodide (0.02 ml, 0.3 mmol) was added dropwise and then tetrabutylammonium iodide (0.09 g, 10 mol %). The mixture was stirred at room temperature for 4 h. Water (20 ml) was added slowly and the solution was transferred to a separating funnel and ethyl acetate (40 ml) was added. The aqueous layer was further extracted with ethyl acetate (2 x 30 ml). The organic extracts were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 9:1 petroleum ether : diethyl ether to yield the title compound as light yellow oil (0.05 g, 88 %). [1RS, 2RS, 4RS] - ν_{max} (NaCl) 1638, 1446, 1372, 1107, 1075, 908, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.39-1.59 (4H, m, 7-H_2, 8-H_2), 1.72-1.79 (1H, m, 5-*H*), 1.89 (1H, dd, J = 7, 15 Hz, 1′-H_a), 1.97-2.02 (1H, m, 5-*H*), 2.48-2.54 (1H, br s, 4-*H*), 2.92-2.96 (1H, dd, J = 7, 15

Hz, 1'-H_b), 3.35 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 5.04-5.07 (2H, m, 3'-H_2), 5.82-5.92 (1H, m, 2'-*H*), 6.15-6.20 (2H, m, 2-*H*, 3-*H*); δ_c (100 MHz, $CDCl_3$) 22.8, 24.5 (*C*-7, *C*-8), 30.4 (*C*-4), 37.7 (C-5), 41.5 (C-1'), 51.1 (OCH_3), 52.8 (OCH_3), 82.1, 84.5 (C-1, C-6), 117.1 (C-3'), 133.9, 134.3 (C-2, C-3), 135.0 (C-2'); *m/z* (ES+) 231 $(MNa)^+$; HRMS (ES+) Found MNa^+; 231.1361; $C_{13}H_{20}O_2Na$ requires 231.1356. [1RS, 2RS, 4-SR]-1-methoxy-2-prop-2'-ylbicyclo[2.2.2]oct-5-en-2-ol was treated to the same procedure as above to yield the title compound as a light yellow oil. [1RS, 2SR, 4SR] -v_{max} (NaCl) 1638, 1446, 1372, 1107, 1075, 908, 688 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.36-1.64 (6H, m, 5-H_2, 7-H_2, 8-H_2), 2.22 (1H, dd, J = 7, 15 Hz, 1'-H_a), 2.54 (1H, m, 4-*H*), 2.93 (1H, dd, J = 7, 15 Hz, 1'-H_b), 3.28 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 5.07-5.15 (2H, m, 3'-H_2), 6.26 (1H, dd, J = 7, 9 Hz, 3-*H*), 6.39 (1H, d, J = 9 Hz, 2-*H*); δ_c (125 MHz, $CDCl_3$) 24.7, 25.4 (C-7, *C*-8), 30.0 (C-4), 36.4 (C-5), 41.1 (*C-1'*), 51.1, 52.0 (2 x OCH_3), 81.9, 83.5 (*C*-1, *C*-6), 116.4 (C-3'), 132.1, 132.4 (*C*-2, *C*-3), 135.6 (*C*-2'); *m/z* (ES+) 231 $(MNa)^+$

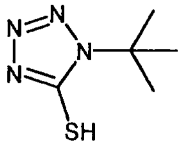
[1RS, 5SR, 6SR] -3-(1,2-Dimethoxybicyclo[2.2.2]oct-5-en-2-yl)-propan-1-ol



399

To a cooled (0 °C) stirred solution of allyl intermediate **396** (0.50 g, 2.4 mmol) in THF (5 ml) was added BH_3.THF (1.2 ml, 1.2 mmol, 1 M in THF) and the reaction mixture was stirred at 0 °C for 1 h. Then NaOH (0.07 ml) and H_2O_2 (35 % w/w in water, 0.07 ml) were added and the mixture was warmed to room temperature before stirring at reflux for 1 h. After which time the mixture was poured into ammonium chloride (15 ml) and ethyl acetate (20 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 20 ml). The organic layers were combined and washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The resulting residue was purified by column chromatography eluting with 1:3 petroluem ether : ethyl acetate to yield the title compound as a colourless oil (0.23 g, 82 % based on recovery of starting material). v_{max} (KBr) 3413-3250 (OH), 1630, 1463, 1369, 1210, 1057, 787, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15-1.60 (7H, m, 5-H_2, 7-H_2, 8-H_2, 1'-H_a), 1.72-1.78 (1H, m, 2'-H_a), 1.87 (1H, br s, O*H*), 1.95-1.99 (1H, m, 2'-H_b), 2.12-2.15 (1H, m, 1'-H_b), 2.48 (1H, m, 4-*H*), 3.34 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.61-3.64 (2H, m, 3'-*H*), 6.15-6.20 (2H, m, 2-*H*, 3-*H*); δ_c (100 MHz, $CDCl_3$) 22.9, 24.4 (C-7, C-8), 26.3 (C-1'), 29.2 (C-5), 30.4 (C-2'), 42.2 (C-4), 50.9, 52.8 (OCH_3), 63.8 (C-3'), 82.2 (C-1), 84.6 (C-6), 133.6, 134.5 (C-2, C-3); *m/z* (ES+) 195 $(M(2CH_3))^-$, 209.5 $(MCH_3)^-$, 249.5 $(MNa)^+$; HRMS (ES+) Found MNa^+; 249.1458; $C_{13}H_{22}O_3Na$ requires 249.1461

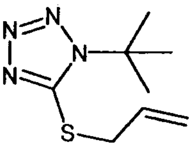
1-^{t}Butyl-1H-tetrazole-5-thiol[101]



401

To a stirred solution of sodium azide (14.1 g, 217.0 mmol) in boiling water (67 ml) was added a solution of ^{t}-butylisothiocyanate (25 g, 217.0 mmol) in propan-2-ol (53 ml) and was stirred at reflux for 16 h. The reaction was cooled to 0 °C and concentrated HCl (33 ml) was added dropwise and the volume reduced to by half under reduced pressure. The suspension that remained was cooled to 0 °C and stirred for 12 h after which time, the suspension was then filtered yielding a pale yellow solid which was then recrystallised from cyclohexane to afford the title compound as a white solid (21.1 g, 62 %). mp 92-94 °C (Lit 94 °C); ν_{max} (NaCl) 3348-2116 (S-H), 1519, 1300, 1254, 1094, 802, 673, 555 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.85 (9H, s, $C(CH_3)_3$); δ_c (100 MHz, $CDCl_3$) 27.6 ($C(CH_3)_3$), 63.6 ($C(CH_3)_3$), 163.0 (C=N); *m/z* (ES+) 159 (MH^+)

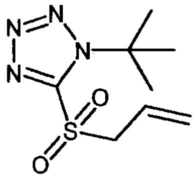
5-Allylsulfanyl-1-^{t}butyl-1H-tetrazole[101]



402a

To a stirred suspension of thiol **401** (1.00 g, 6.3 mmol) and potassium carbonate (0.69 g, 7.0 mmol) in DCM (10 ml) was added allylbromide (0.59 ml, 7.0 mmol) dropwise. The mixture was stirred at room temperature for 16 h. Once this time had elapsed the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resultant oil was purified by Kugelrohr distillation (55 °C, 0.8 mbar) to yield a colourless oil (1.01 g, 81 %). Literature b.p 26-27 °C.10^{-2} Torr; ν_{max} (NaCl) 1636, 1474, 1372, 1362, 1224, 132, 1096, 990, 927, 729, 595 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.73 (9H, s, $C(CH_3)_3$), 3.95 (2H, d, J = 15 Hz, CH_2), 5.12 (1H, br d, C=CH_2), 5.35 (1H, br d, C=CH_2), 5.82 (1H, m, CH=CH_2); δ_c (100 MHz, $CDCl_3$) 28.8 ($C(CH_3)_3$), 36.6 (CH_2CH=CH_2), 61.0 ($C(CH_3)_3$), 119.8 (CH=CH_2), 131.7 (CH=CH_2), 152.1 (C=N); *m/z* (ES+) 198 (MH^+), 155 ($MC_4H_8^-$)

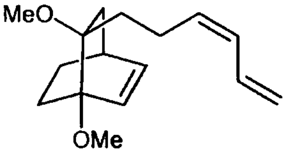
1-^{t}Butyl-5-(prop-2-ene-1-sulfonyl)-1H-tetrazole[100]



402

To a cooled (0 °C) stirred solution of thioether **402a** (0.50 g, 2.5 mmol) in ethanol (30 ml) was added ammonium molybdate (0.05 g, 0.3 mmol) in H_2O_2 (1.43 g, 12.7 mmol). The resultant suspension was warmed to room temperature and stirred for 16 h. After which time a further portion of ammonium molybdate was added and this was stirred for a further 24 h. The mixture was then diluted with diethyl ether (40 ml) and water (40 ml) and transferred to a separating funnel. The aqueous layer was further extracted with diethyl ether (2 x 40 ml). The organic layers were combined and washed with brine, then dried over magnesium sulfate before concentrating under reduced pressure. The resulting residue was purified by column chromatography eluting with 3:1 petroleum ether : ethyl acetate to afford the title compound as a pale yellow solid (0.15 g, 25 %). mp 40-42 °C (Lit 41 °C); ν_{max} (KBr) 1736, 1340 (SO_2), 1158 (SO_2), 941, 663 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.78 (9H, s, $C(CH_3)_3$), 4.46-4.48 (2H, d, J = 7 Hz, $CH_2CH{=}CH_2$), 5.50-5.58 (2H, m, $CH{=}CH_2$), 5.84-5.93 (1H, m, $CH{=}CH_2$); δ_c (100 MHz, $CDCl_3$) 39.7 ($C(CH_3)_3$), 60.9 (CH_2), 65.4 ($C(CH_3)_3$), 122.4, 127.5 ($CH{=}CH_2$); *m/z* (ES+) 253 $(MNa)^+$

[1RS, 5-SR, 6SR]-1,6-Dimethoxy-6′-((E)-penta-2′,4′-dienyl)bicyclo[2.2.2]oct-2-ene

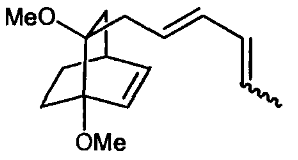


403

To a cooled (-60 °C) stirred solution of sulfone **402** (0.10 g, 1.4 mmol) in DME (20 ml) was added KHMDS (0.10 g, 0.5 mmol). The yellow solution was stirred at -60 °C for 30 minutes before addition of aldehyde **395** (0.11 g, 0.5 mmol) in DME (2 ml). The mixture was stirred at -60 °C for a further 3 h before warming to room temperature and stirring for a further 16 h. After which time the reaction mixture was poured into diethyl ether (40 ml) and ammonium chloride (40 ml). The aqueous layer was re-extracted with diethyl ether (2 x 40 ml). The combined organic layers were washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The resulting residue was purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to yield the title compound as light yellow oil (0.04 g, 31 %).

ν_{max} (KBr) 1459, 1368, 1114, 1081, 900, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.11-1.46 (5H, m, 7-H_a, 8-H_a, 6′-H_a, 5′-H_2), 1.62-1.70 (1H, m, 7-H_b), 1.88-1.93 (1H, m, 8-H_b), 2.09-2.14 (3H, m, 5-H_2, 6′-H_b), 2.42 (1H, br s, 4-*H*), 3.26 (3H, s, O CH_3), 3.28 (3H, s OCH_3), 4.99-5.01 (1H, d, J = 12 Hz, 1′-H_a), 5.08 (1H, d, J = 12 Hz, 1′-H_b), 5.36-5.40 (1H, m, 3′-*H*), 5.88 (1H, t, J = 11 Hz, 4′-*H*), 6.08-6.13 (2H, m, 2-*H*, 3-*H*), 6.55-6.63 (1H, m, 2′-*H*); δ_c (100 MHz, $CDCl_3$) 21.5 (C-5), 22.9, 24.5 (C-7, C-8), 30.4 (C-4), 32.9 (C-6′), 42.2 (C-5′), 51.0, 52.8 (2 x OCH_3), 82.2, 84.6 (C-1, C-6), 116.9 (C-1′), 129.1 (C-3′), 132.6 (C-2′), 133.6 (C-4′), 133.8, 134.4 (C-2, C-3); *m/z* (ES+) 271 $(MNa)^+$; HRMS (ES+) Found MNa^+; 271.1668; $C_{16}H_{24}O_2Na$ requires 271.1669

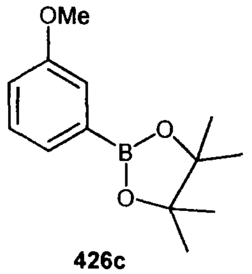
6-Hexa-2′,4′-dienyl-1,6-dimethoxy-bicyclo[2.2.2]oct-2-ene



420

Diene **403** (0.01 g, 0.04 mmol) in benzene (0.5 ml) was sealed in an NMR tube and heated at 120 C for 5 days. After which time the solvent was removed under reduced pressure to afford the title compound as a light yellow oil (0.01 g, 100 %). ν_{max} (KBr) 1447, 1382, 1261, 1109 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.39-1.47 (6H, 5-H_2, 7-H_2, 8-H_2), 1.73-1.77 (3H, m, 6′-CH_3) , 1.98-2.01 (1H, m, 1′-H_a), 2.48-2.49 (1H, br s, 4-*H*), 2.96 (1H, dd, J = 7, 9 Hz, 1′-H_b), 3.36 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 5.34-5.40 (1H, m, 5′-*H*), 5.65-5.71 (1H, m, 2′-*H*), 5.98 (1H, t, J = 11 Hz, 4′-*H*), 6.16-6.21 (2H, m, 2-*H*, 3-*H*), 6.32 (1H, m, 3′H); δ_c (100 MHz, $CDCl_3$) 13.5 (C-6′), 22.8, 24.5 (C-7, C-8), 30.4 (C-6′), 36.8 (C-2′), 41.5 (C-5), 51.1 (OCH_3), 52.8 (OCH_3), 82.4, 84.5 (C-1, C-6), 123.9 (C-5′), 127.9 (C-3′), 129.9 (C-4′), 130.4 (C-2′), 133.8, 134.3 (C-2, C-3); *m/z* (ES+) 271 $(MNa)^+$.

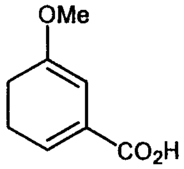
2-(3-Methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane



426c

To a stirred solution of pinnacol (3.66 g, 30.0 mmol) in DCM (150 ml) was added 3-methoxyphenylboronic acid (5.00 g, 33.0 mmol) and 4Å molecular sieves (1.5 g). The suspension was stirred at room temperature for 15 h and magnesium sulfate was added. The resultant suspension was filtered and concentrated under reduced pressure to yield the title compound as clear oil which solidified on cooling to a white solid (6.9g, 90 %). m.p 27-28 °C; ν_{max} (KBr) 1634, 1575, 1420, 1352, 1142, 1042, 850, 706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.37 (12H, s, 4 x CH_3), 3.56 (3H, s, OCH_3), 7.02-7.05 (1H, m, Ar-*H*), 7.30-7.44 (3H, m, Ar-*H*); δ_c (100 MHz, $CDCl_3$) 25.1 (4 x CH_3), 55.5 (OCH_3), 84.1 ($C(CH_3)_2O_2$), 118.2, 118.6 (C-2, C-4), 127.4 (C-3), 129.1, 129.3 (C-1, C-5), 159.2 (C-3); *m/z* (ES+) 234 $(MH)^+$, 148 $(M-(C_6H_{18}O_2))^+$

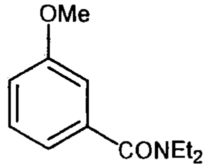
5-Methoxycyclohexa-1,5-dienecarboxylic acid methyl ester



431

To a slurry of m-anisic acid (3.00 g, 19.7 mmol) in water (5 ml) was condensed ammonia (67 ml). The yellow solution that remained was added lithium pieces (0.46g, 59.8 mmol) over 20 minutes, the blue solution that remained was stirred until the colour dissipated. The cooling finger was removed and the ammonia was allowed to evaporate under a constant stream of nitrogen over 15 h. The light yellow solution that remained was slowly added to 1 N KOH (150 ml) and heated to 60 °C for 2.5 h. The solution that remained was then treated dropwise with concentrated HCl to adjust the pH to 5 with frequent extractions into chloroform. The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure to yield the title compound as an off white solid (1.49 g, 49 %). mp 62-63 °C; ν_{max} (ATR) 3050-2541 (OH), 1693 (C=O), 1598, 1442, 1367, 1297, 1233, 1096, 888, 808, 517 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.26-2.32 (2H, m, 3-H_2), 2.46-2.48 (2H, m, 4-H_2), 3.68 (3H, s, OCH_3), 5.43 (1H, m, 6-H), 6.74 (1H, s, 2-H); δ_c (100 MHz, $CDCl_3$) 24.2, 25.6 (C-3, C-4), 54.9 (OCH_3), 90.1 (C-6), 128.7 (C-2), 131.1 (C-1), 159.4 (C-5), 170.4 (CO_2H); *m/z* (ES-) 153 $(MH)^-$; HRMS (ES-) Found MH^-; 153.0547; $C_8H_9O_3$ requires 153.0546

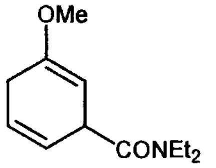
N,N-Diethyl-3-methoxybenzamide



441

To a stirred solution of m-anisic acid (5.00 g, 33.0 mmol) and a drop of dimethylformamide in DCM (150 ml) was added oxalyl chloride (3.38 ml, 39 mmol) dropwise. Evolution of gas was observed for 20 minutes and after which time a small aliquot was removed and concentrated under reduced pressure. Acid chloride formation was observed by IR spectroscopy (1790 cm^{-1}). The resultant reaction mixture was concentrated under reduced pressure and re-dissolved in DCM (50 ml) and added dropwise to a cooled solution (0 °C) of diethyl amine in DCM (100 ml). The solution was then warmed to room temperature and stirred for 1 h. The reaction mixture was then poured into 5 % aqueous HCl (150 ml). The aqueous layer was then re-extracted with DCM (2 x 150 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The resultant residue was purified by column chromatography eluting with 1:1 petroleum ether : ethyl acetate to yield the title compound as a light yellow oil (5.85 g, 86 %). ν_{max} (NaCl) 1626 (C=O), 1578, 1427, 1287, 1042, 821, 789, 749 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.13-1.26 (6H, br d, 2 x NCH_2CH_3), 3.28-3.55 (4H, m, 2 x NCH_2), 3.82 (3H, s, OCH_3), 6.91-6.95 (3H, m, 4-*H*, 5-*H*, 6-*H*), 7.29-7.33 (1H, m, 2-*H*); δ_c (100 MHz, $CDCl_3$) 14.2 (2 x NCH_2CH_3), 55.3 (OCH_3), 60.4 (2 x NCH_2), 111.7, 115.0, 118.4 (C-4, C-5, C-6), 129.5 (C-2), 138.6 (C-3), 159.6 (C-1), 171.1 (C=O); *m/z* (ES+) 208 $(MH)^+$; HRMS (ES+) Found MNa^+; 230.1153; $C_{12}H_{17}O_2NNa$ requires 230.1152

3-Methoxycyclohexa-2,5-dienecarboxylic acid diethylamide

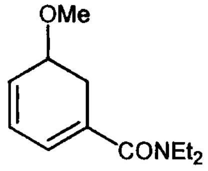


444

To a stirred solution of N,N-diethyl-3-methoxybenzamide (1.20 g, 5.8 mmol) in THF (20 ml) was added 2-methylpropan-2-ol (13.7 ml, 145.0 mmol) and the solution was cooled to -78 °C. Liquid ammonia (60 ml) was added and lithium ribbon (0.11 g, 14.5 mmol) was added in small pieces and after the blue colour dissipated, ammonium chloride (5 g) was added and the ammonia was allowed to evaporate. The resultant slurry was diluted with water (75 ml) and ethyl acetate (75 ml) and the aqueous layer was re-extracted with ethyl acetate (2 x 75 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 2:1 diethyl ether : petroleum ether to afford the title compound as a light orange oil (0.86 g, 70 %). ν_{max} (NaCl) 1688, 1645 (C=O), 1458, 1425, 1216, 856, 800 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, t, J = 9 Hz, NCH_2CH_3), 1.24 (3H, t, J = 9 Hz, NCH_2CH_3), 2.59-2.81 (2H, m, 4-H_2), 3.28-3.37 (4H, m, 2 x NCH_2), 3.51 (3H, s, OCH_3), 4.00-4.08 (1H, m, 1-*H*), 4.53 (1H, m, 2-*H*), 5.59 (1H, m, 6-*H*), 5.79 (1H, m, 5-*H*); δ_c (100 MHz, $CDCl_3$) 12.9, 14.8 (2 x NCH_2CH_3), 28.5 (C-4), 40.5, 41.7 (2 x NCH_2CH_3), 42.1 (C-1), 53.9 (OCH_3), 90.8 (C-2), 123.5, 125.2 (C-5, C-6), 154.6 (C-3), 172.4

(C=O); *m/z* (ES+) 211 $(MH)^+$; HRMS (ES+) Found MNa^+; 232.1308; $C_{12}H_{19}O_2NNa$ requires 232.1308

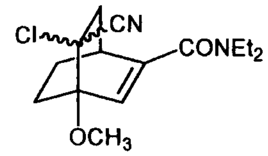
5-Methoxycyclohexa-1,3-dienecarboxylic acid diethylamide



445

Diene **444** (0.50 g, 2.3 mmol) was added dropwise to a solution of 2-chloroacrylonitrile (0.41 g, 4.7 mmol) and phenothiazine (0.01 g, 0.01 mmol) in benzene (10 ml). The resulting mixture was heated at reflux for 9 h and then the solvent was removed under reduced pressure. The residue was then purified by column chromatography eluting with 3:1 petroleum ether : ethyl acetate to give the uncyclised product as the title compound as a light brown oil (0.34 g, 68 %). ν_{max} (NaCl) 1643 (C=O), 1578, 1430, 1218, 1031, 801, 747, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, t, J = 9 Hz, NCH_2CH_3), 1.09-1.13 (3H, t, J = 9 Hz, NCH_2CH_3), 2.03-2.10 (1H, m, 6-H_a), 2.80-2.92 (1H, m, 6-H_b), 3.15-3.44 (4H, m, 2 x NCH_2), 3.54 (3H, s, OCH_3), 3.57-3.62 (1H, m, 5-*H*), 4.87 (1H, dd J = 3, 10 Hz, 4-*H*), 5.13 (1H, dd, J = 3, 10 Hz, 3-*H*), 5.93 (1H, m, 2-*H*); δ_c (100 MHz, $CDCl_3$) 13.0, 14.7 (2 x NCH_2CH_3), 30.0 (*C*-6), 38.8 (*C*-5), 40.1, 41.8 (2 x NCH_2), 54.7 (OCH_3), 91.6 (*C*-2), 116.0, 125.9 (*C*-3, *C*-4), 159.4 (*C*-1), 172.8 (C=O); *m/z* (ES+) 210 (M^+)

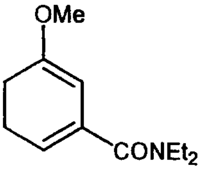
[1SR,4RS,5SR/RS]-5-Chloro-5-cyano-4-methoxy-bicyclo[2.2.2]oct-2-ene-2-carboxylic acid diethylamide



446

2-chloroacryonitrile **369** (1.06 g, 12.2 mmol) was added to a stirred solution of diene **447** (1.28 g, 6.11 mmol) in toluene (30 ml) and the mixture was heated to reflux and stirred for 5 h. After which time the solvent was removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 3:1 ethyl acetate : petroleum ether to afford the title compound as an orange oil (0.50 g, 28 %). ν_{max} (NaCl) 2245 (C=N), 1655 (C=O), 1615 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.09-1.15 (6H, m, 2 x NCH_2CH_3), 1.60-1.97 (4H, m, 7-H_2, 8-H_2), 2.23-2.28 (1H, m, 5-H_b), 2.62-2.63 (1H, m, 5-H_b), 2.85-2.87 (1H, br s, 1-*H*), 3.36-3.40 (4H, m, 2 x NCH_2), 3.47 (3H, s, OCH_3), 6.18 (1H, s, 3-*H*); δ_c (100 MHz, $CDCl_3$) 13.1, 13.9 (2 x NCH_2CH_3), 24.6, 25.0 (*C*-7, *C*-8), 26.0 (*C*-6), 40.3, 41.6 (2 x NCH_2), 46.4 (C-1), 51.9 (OCH_3), 62.5 (C-5), 81.3 (C-4), 119.0 (CN), 127.5 (C-3) 134.0 (C-2), 174.2 ($CONEt_2$); *m/z* (ES+) 319 $(MNa)^+$

5-Methoxycyclohexa-1,5-dienecarboxylic acid diethylamide

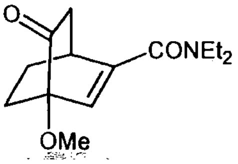


447

Method 1 To a stirred solution of diene **444** (2.00 g, 9.6 mmol) in THF (30 ml) and 2M KOH (90 ml) was heated at reflux for 96 h. The mixture was cooled and diluted with water (60 ml) and ethyl acetate (80 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 75 ml) and the combined organic layers were washed with brine before drying over magnesium sulfate. The solvent was removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 1:1 ethyl acetate : petroleum ether to afford the title compound as orange oil (1.25 g, 63 %).

Method 2 To a solution of diene **444** (1.00 g, 4.8 mmol) in toluene (1 ml) was added 2 M KOH (2 ml). This solution was sealed in a microwave tube and heated at 150 °C for 45 minutes. The mixture was then poured into water (30 ml) and ethyl acetate (30 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The residue was purified by column chromatography eluting with 1:1 petroleum ether : ethyl acetate to giving the title compound as a orange oil (0.75 g, 75 %). ν_{max} (NaCl) 1649 (C=O), 1380, 1280, 1237, 1154, 1092, 1009, 800, 740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.07 (6H, t, J = 7 Hz, 2 x NCH_2CH_3), 2.24-2.31 (4H, m, 3-H_2, 4-H_2), 3.31-3.41 (4H, m, 2 x NCH_2), 3.57 (3H, s, OCH_3), 4.96 (1H, s, 6-*H*) , 5.45-5.49 (1H, s, 2-*H*); δ_c (100 MHz, $CDCl_3$) 13.2, 14.5 (2 x NCH_2CH_3), 23.4, 26.5 (C-4, C-5), 40.0, 41.7 (2 x NCH_2), 54.9 (OCH_3), 92.3 (C-2), 116.7 (C-6), 134.1 (C-1), 159.7 (C-3), 171.6 (C=O); *m/z* (ES+) 182 $(MH)^+$, 204 $(MNa)^+$; HRMS (ES+) Found MNa^+; 204.0995; $C_{10}H_{15}O_2NNa$ requires 204.0995

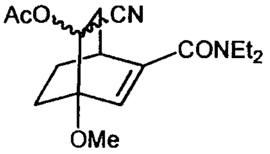
[1SR, 4RS]-4-Methoxy-5-oxo-bicyclo[2.2.2]oct-2-ene-2-carboxylic acid diethylamide



448

To a cooled (0 °C) stirred solution of cyano-acetates **457** (1.09 g, 3.1 mmol) in THF (40 ml) and dimethylsulfoxide (40 ml) was added 2M KOH dropwise (40 ml) and stirred for 30 minutes before warming to room temperature. The reaction mixture was then stirred at room temperature for 1 h. Ammonium chloride (100ml) was then added and the aqueous layer was extracted with chloroform (3 x 125 ml). The organic layers were combined and washed with brine (2 x 150 ml) and dried over magnesium sulfate before concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with ethyl acetate to afford an orange oil (0.58 g, 74 %). ν_{max} (NaCl) 1733 (C=O), 1611 (C=O amide), 1432, 1281, 1063 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.18-1.21 (6H, t, J = 8 Hz, 2 x NCH_2CH_3), 1.87-2.01 (4H, m, 7-H_2, 8-H_2), 2.36-2.48 (2H, m, 3-H_2), 3.22 (1H, br s, 4-*H*), 3.56 (3H, s, OCH_3), 3.33-3.42 (4H, m, 2 x NCH_2), 6.31 (1H, s, 6-*H*); δ_c (125 MHz, $CDCl_3$) 18.2, 19.3 (2 x NCH_2CH_3), 26.2, 27.1 (*C*-7, *C*-8), 34.8 (*C*-4), 40.6 (*C*-3), 39.3, 42.1 (2 x NCH_2), 53.7 (OCH_3), 85.0 (*C*-1), 127.7 (*C*-6), 142.9 (*C*-5), 168.4 (NC=O), 208.9 (*C*-2); *m/z* (ES+) 252 (MH)$^+$, 293 (MCH_3CN)$^+$, 315 (MNa)$^+$; HRMS (ES+) Found M$^+$; 252.1596; $C_{14}H_{22}NO_3$ requires 252.1600

[1RS,2RS/SR,4SR]-2-Cyano-5-diethylaminomethyl-1-methoxy-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester



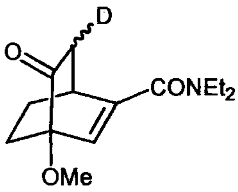
457

Method 1 To a stirred solution of 1-cyanovinyl acetate (1.15 ml, 10.8 mmol) in toluene (21 ml) was added diene **447** (1.25 g, 6.0 mmol) in toluene (4 ml) dropwise. The mixture was stirred at reflux for 120 h. After this time had elapsed the solvent was removed under reduced pressure and the residue was purified by column chromatography eluting with 1:1 ethyl acetate : petroleum ether to give the title compound 5:1 mixture of *endo:exo* CN isomers as a pale yellow oil (1.09 g, 57 %)

Method 2 To a solution of diene **447** (1.00 g, 4.8 mmol) in toluene (1 ml) was added 1-cyanovinyl acetate (0.70 ml, 7.2 mmol). This mixture was sealed in a microwave tube and heated for 1 h 45 minutes at 150 °C. The solvent was then removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 1:1 ethyl acetate : petroleum ether to yield the title compound as a 5:1 mixture of *endo* : *exo* CN isomers as a pale yellow oil (0.73 g, 50 %). IR (NaCl) ν_{max} 2246 (C=N), 1751 (C=O), 1611(C=O amide), 1435, 1242, 920, 723 cm^{-1}; **Major** δ_H (400 MHz, $CDCl_3$) 1.10-1.27 (6H, m, 2 x NCH_2CH_3), 1.65-2.08 (8H, m, 3-H_a, 7-H_2, 8-H_2, CH_3C=O), 2.78 (1H, br d, 3-H_b), 2.92 (1H, br s, 4-*H*), 3.39-3.45 (4H, m, 2 x NCH_2), 3.54 (3H, s,

$\mathrm{OC}\mathit{H}_3$), 6.31 (1H, s, 6-*H*); **Minor** δ_H (400 MHz, $\mathrm{CDCl_3}$) 1.10-1.27 (6H, m, $\mathrm{NCH_2C}\mathit{H}_3$), 1.65-2.08 (8H, m, 3-$\mathit{H}_a$, 7-$\mathrm{H_2}$, 8-$\mathit{H}_2$, $\mathrm{C}\mathit{H}_3\mathrm{C{=}O}$), 2.78 (1H, br d, 3-$\mathit{H}_b$), 2.92 (1H, br s, 4-*H*), 3.39-3.45 (4H, m, $\mathrm{NC}\mathit{H}_2$), 3.59 (3H, s, $\mathrm{OC}\mathit{H}_3$), 6.32 (1H, s, 6-*H*), δ_c (100 MHz, $\mathrm{CDCl_3}$) **Major** 12.1, 14.6 (br d, 2 x $\mathrm{NCH_2CH_3}$), 21.3 ($\mathrm{CH_3C{=}O}$), 24.1, 25.1 (C-7, C-8), 32.2 (C-3), 40.2, 43.9 (br d, 2 x $\mathrm{NCH_2}$), 44.1 (C-4), 53.9 ($\mathrm{OCH_3}$), 77.6 (C-2), 80.6 (C-1), 117.8 (C=N), 127.7 (C-6), 141.9 (C-5), 168.4 , 168.9 ($\mathrm{CH_3C{=}O}$, Amide C=O), **Minor** 12.1, 14.6 (br, $\mathrm{NCH_2CH_3}$), 20.7 ($\mathrm{CH_3C{=}O}$), 24.1, 26.3 (C-7, C-8), 32.3 (C-3), 40.2, 43.9 (br, 2 x $\mathrm{NCH_2}$), 41.9 (C-4), 52.9 ($\mathrm{OC}\mathit{H}_3$), 76.2 (C-2), 80.9 (C-1), 118.7 (C=N), 128.3 (C-6), 143.1 (C-5), 168.2, 169.5 ($\mathrm{CH_3C{=}O}$, Amide C=O); *m/z* (ES+) 343 $(\mathrm{MH})^+$, 663 $(\mathrm{2MNa})^+$

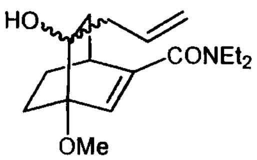
6-Deutero-4-Methoxy-5-oxo-bicyclo[2.2.2]oct-2-ene-2-carboxylic acid diethyl amide



458

Ketone **448** (0.05 g, 0.2 mmol) in THF (0.5 ml) was added dropwise to a suspension of sodium hydride (0.01 g, 0.5 mmol) in THF (3 ml) at room temperature and the mixture stirred for 2 h. After which time ammonium chloride (3 ml) and ethyl acetate (4 ml) were added and the layers separated. The aqueous layer was re-extracted with ethyl acetate (3 x 5 ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with ethyl acetate to afford the title compound as an orange oil (0.03 g, 60 %). ^{2}H NMR (500 MHz, $\mathrm{CHCl_3}$) 2.43 ppm

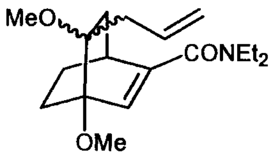
[1SR, 5RS/SR, 4RS]-5-Allyl-5-hydroxy-4-methoxy-bicyclo[2.2.2]oct-2-ene-2-carboxylic acid diethylamide



461/462

To a suspension of magnesium turnings (0.12 g, 5.0 mmol) in diethyl ether (5 ml) was added one drop of 1,2-dibromoethane. Freshly distilled allyl bromide (0.22 ml, 2.5 mmol) in diethyl ether (1 ml) was then added dropwise. The suspension was stirred for 20 minutes and added *via* cannula to a cooled (-78 °C) solution of ketone **448** (0.25 g, 1.0 mmol) in diethyl ether (30 ml). The solution was allowed to warm to room temperature and stirred at room temperature for 2 h. The solution was cooled to 0 °C and aqueous ammonium chloride (15 ml) was added slowly. The solution was transferred to a separating funnel and the aqueous layer was further extracted with ethyl acetate (2 x 25 ml). The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with ethyl acetate yielding the title compound as a 2:1 *exo:endo* mixture as a colourless oil (0.20 g, 70 %). ν_{max} (NaCl) 3623-3200 (OH), 1608, 1433, 1347, 1282, 1219, 1064, 741 cm^{-1}; δ_H (500 MHz, $CDCl_3$) **Major** 1.13-1.15 (6H, m, 2 x CH_2CH_3), 1.54-2.23 (8H, m, 6-H_2, 7-H_2, 8-H_2, 1'-H_a), 2.51-2.58 (1H, m, 1'-H_b), 2.71 (1H, m, 1-*H*), 3.35-3.38 (7H, m, 2 X NCH_2, OCH_3), 4.97-5.10 (2H, m, 3'-H_2), 5.83-5.90 (1H, m, 2'-*H*), 6.25 (1H, s, 3-*H*); **Minor** 1.13-1.15 (6H, m, 2 x CH_2CH_3), 1.54-2.23 (8H, m, 6-H_2, 7-H_2, 8-H_2, 1'-H_a), 2.61-2.65 (1H, m, 1'-H_b), 2.71 (1H, m, 1-*H*), 3.35-3.38 (4H, m, 2 X NCH_2), 3.61 93H, s, OCH_3), 4.97-5.10 (2H, m, 3'-H_2), 5.83-5.90 (1H, m, 2'-*H*), 6.30 (1H, s, 3-*H*); δ_c (125 MHz, $CDCl_3$) **Major** 13, 15 (br 2 x NCH_2CH_3), 25.8, 26.1 (C-7, C-8), 27.0 (C-5), 33.6 (C-1), 39 (br NCH_2), 40.6 ($CH_2CH=CH_2$), 43 (br NCH_2), 53.6 (OCH_3), 83.2 (C-4), 84.4 (C-5), 118.4 ($CH_2CH=CH_2$), 130.9 (C-2), 134.3 ($CH_2CH=CH_2$), 141.1 (C-3), 168.4 (C=O); **Minor** 13, 15 (br 2 x NCH_2CH_3), 25.8, 26.1 (C-7, C-8), 27.0 (C-5), 34.8 (C-1), 39 (br NCH_2), 39.9 ($CH_2CH=CH_2$), 43 (br NCH_2), 52.4 (OCH_3), 83.2 (C-4), 84.4 (C-5), 118.1 ($CH_2CH=CH_2$), 127.7 (C-2), 135.1 ($CH_2CH=CH_2$), 142.9 (C-3), 169.6 (C=O); *m/z* (ES+) 357 (MMeCN)$^+$, 316 (MNa)$^+$, 294 (MH)$^+$; HRMS (EI) Found M$^+$; 294.2095; $C_{17}H_{28}NO_3$ requires 294.2069

[1SR,5RS/SR,4RS]-5-Allyl-4,5-dimethoxybicyclo[2.2.2]oct-2-ene-2-carboxylicacid diethyl amide

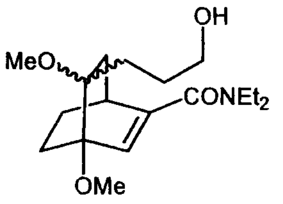


461a/462a

To a stirred solution of alcohols **461/462** (0.20 g, 0.7 mmol) in THF (10 ml) was added sodium hydride (0.07 g, 2.7 mmol). The solution was stirred at room temperature for 30 minutes. After which time methyl iodide (0.05 ml, 0.8 mmol) was added dropwise and then tetrabutylammonium iodide (0.03 g, 10 mol %s). The mixture was stirred at room temperature for 4 h. Water (20 ml) was added slowly and the solution was transferred to a separating funnel and ethyl acetate (40 ml) was added. The aqueous layer was further extracted with ethyl acetate (2 x 30 ml). The organic extracts were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate, yielding the title compound as a 2:1 *exo:endo* mixture as light yellow oil (0.13 g, 60 %). ν_{max} (KBr) 1599 (C=O), 1434, 1120, 922, 897, 713 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1SR,5RS,4RS]** 1.04-1.18

(6H, m, 2 x NCH$_2$CH$_3$), 1.42-1.61 (4H, m, 6-H$_a$, 7-H$_a$, 8-H$_2$), 1.65-2.11 (2H, m, 6-H$_b$, 7-H$_b$), 2.17-2.23 (1H, m, 1′-H$_a$), 2.71 (1H, br s, 1-H), 2.91-2.97 (1H, m, 1′-H$_b$), 3.35-3.47 (10H, m, 2 x OCH$_3$, 2 x NCH$_2$), 4.96-5.15 (2H, m, 3′-H$_2$), 5.75-5.96 (1H, m, 2′-H), 6.43 (1H, s, 3-H); **[1SR,5SR,4RS]** 1.04-1.18 (6H, m, 2 x NCH$_2$CH$_3$), 1.42-1.61 (5H, m, 6-H$_2$, 7-H$_a$, 8-H$_2$), 1.65-2.11 (2H, m, 1′-H$_a$ 7-H$_b$), 2.52-2.54 (1H, m, 1′-H$_b$) 2.71 (1H, br s, 1-H), 3.24 (3H, s, OCH$_3$), 3.35-3.47 (7H, m, OCH$_3$, 2 x NCH$_2$), 4.96-5.15 (2H, m, 3′-H$_2$), 5.75-5.96 (1H, m, 2′-H), 6.37 (1H, s, 3-H); δ_C (100 MHz, CDCl$_3$) **[1SR,5RS,4RS]** 13.1, 14.0 (2 x NCH$_2$CH$_3$), 22.7, 27.1 (C-7, C-8), 32.5 (C-1), 35.2 (C-1′), 38.0 (NCH$_2$), 40.7 (C-6), 42.7 (NCH$_2$), 51.1, 51.7 (2 x OCH$_3$), 82.5, 83.1 (C-4, C-5), 116.8 (C-3′), 129.6 (C-3), 139.5 (C-2′), 140.7 (C-2), 170.1 (C=O); **[1SR,5SR,4RS]** 13.1, 14.0 (2 x NCH$_2$CH$_3$), 22.0, 25.6 (C-7, C-8), 33.4 (C-1), 38.0 (NCH$_2$), 39.7 (C-6), 42.7 (NCH$_2$), 44.2 (C-1′), 51.2, 51.8 (2 x OCH$_3$), 81.8, 84.6 (C-4, C-5), 117.3 (C-2′), 130.7 (C-3), 134.3 (C-3′), 141.4 (C-2), 169.4 (C=O); *m/z* (ES+) 371 (MMeCN)$^+$, 330 (MNa)$^+$, 308 (MH)$^+$; HRMS (EI) Found M$^+$; 308.2226; C18H30NO3 requires 308.2215

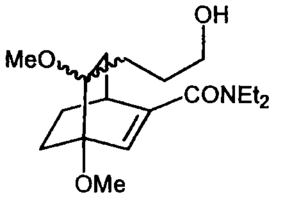
[1SR,5RS/SR,4RS]-5-(3′-Hydroxypropyl)-4,5-dimethoxybicyclo[2.2.2]oct-2-ene-2-carboxylic acid diethyl amide



463

To a cooled (0 °C) stirred solution of allyl intermediates **461a/462a** (0.20 g, 1.0 mmol) in THF (20 ml) was added BH$_3$.THF (0.73 ml, 0.7 mmol, 1 M in THF) and the reaction mixture was stirred at 0 °C for 1 h. Then NaOH (0.24 ml) and H$_2$O$_2$ (35 % w/w in water, 0.24 ml) were added and the mixture was warmed to room temperature before stirring at reflux for 1 h. After which time the mixture was poured into ammonium chloride (25 ml) and ethyl acetate (35 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 25 ml). The organic layers were combined and washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The resulting residue was purified by column chromatography eluting with 70-100 % isohexane : ethyl acetate to yield the title compounds as a as a 2:1 *exo:endo* mixture as a colourless oil (0.04 g, 18 %). ν_{max} (KBr) 1598 (C=O), 1434, 1118, 1062, 910 cm^{-1}; δ_H (400 MHz, CDCl$_3$) **[1SR,5RS,4RS]** 1.61 (6H, t, J = 7 Hz, 2 x NCH$_2$CH$_3$), 1.47-1.70 (9H, m, 6-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, 1′-*H*$_2$, 2′-*H*$_a$), 2.02-2.21 (2H, m, O-*H*, 2′-*H*$_b$), 2.95 (1H, br s, 1-*H*), 3.23 (3H, s, OC*H*$_3$), 3.37 (3H, s, OC*H*$_3$), 3.39-3.48 (4H, m, 2 x NCH$_2$), 3.69-3.73 (2H, m, 3′-*H*$_2$), 6.38 (1H, s, 3-*H*); **[1SR,5SR,4RS]** 1.61 (6H, t, J = 7 Hz, 2 x NCH$_2$CH$_3$), 1.47-1.70 (9H, m, 6-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, 1′-*H*$_2$, 2′-*H*$_a$), 2.02-2.21 (2H, m, O-*H*, 2′-*H*$_b$), 2.95 (1H, br s, 1-*H*), 3.23 (3H, s, (6H, m, 2 x NCH_2CH_3), 1.42-1.61 (4H, m, 6-H_a, 7-H_a, 8-H_2), 1.65-2.11 (2H, m, 6-H_b, 7-H_b), 2.17-2.23 (1H, m, 1'-H_a), 2.71 (1H, br s, 1-H), 2.91-2.97 (1H, m, 1'-H_b), 3.35-3.47 (10H, m, 2 x OCH_3, 2 x NCH_2), 4.96-5.15 (2H, m, 3'-H_2), 5.75-5.96 (1H, m, 2'-H), 6.43 (1H, s, 3-H); **[1SR,5SR,4RS]** 1.04-1.18 (6H, m, 2 x NCH_2CH_3), 1.42-1.61 (5H, m, 6-H_2, 7-H_a, 8-H_2), 1.65-2.11 (2H, m, 1'-H_a 7-H_b), 2.52-2.54 (1H, m, 1'-H_b) 2.71 (1H, br s, 1-H), 3.24 (3H, s, OCH_3), 3.35-3.47 (7H, m, OCH_3, 2 x NCH_2), 4.96-5.15 (2H, m, 3'-H_2), 5.75-5.96 (1H, m, 2'-H), 6.37 (1H, s, 3-H); δ_C (100 MHz, $CDCl_3$) **[1SR,5RS,4RS]** 13.1, 14.0 (2 x NCH_2CH_3), 22.7, 27.1 (C-7, C-8), 32.5 (C-1), 35.2 (C-1'), 38.0 (NCH_2), 40.7 (C-6), 42.7 (NCH_2), 51.1, 51.7 (2 x OCH_3), 82.5, 83.1 (C-4, C-5), 116.8 (C-3'), 129.6 (C-3), 139.5 (C-2'), 140.7 (C-2), 170.1 (C=O); **[1SR,5SR,4RS]** 13.1, 14.0 (2 x NCH_2CH_3), 22.0, 25.6 (C-7, C-8), 33.4 (C-1), 38.0 (NCH_2), 39.7 (C-6), 42.7 (NCH_2), 44.2 (C-1'), 51.2, 51.8 (2 x OCH_3), 81.8, 84.6 (C-4, C-5), 117.3 (C-2'), 130.7 (C-3), 134.3 (C-3'), 141.4 (C-2), 169.4 (C=O); *m/z* (ES+) 371 $(MMeCN)^+$, 330 $(MNa)^+$, 308 $(MH)^+$; HRMS (EI) Found M^+; 308.2226; C18H30NO3 requires 308.2215

[1SR,5RS/SR,4RS]-5-(3'-Hydroxypropyl)-4,5-dimethoxybicyclo[2.2.2]oct-2-ene-2-carboxylic acid diethyl amide

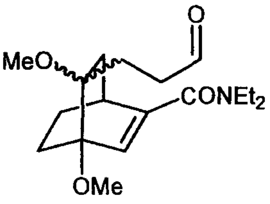


463

To a cooled (0 °C) stirred solution of allyl intermediates **461a/462a** (0.20 g, 1.0 mmol) in THF (20 ml) was added BH_3.THF (0.73 ml, 0.7 mmol, 1 M in THF) and the reaction mixture was stirred at 0 °C for 1 h. Then NaOH (0.24 ml) and H_2O_2 (35 % w/w in water, 0.24 ml) were added and the mixture was warmed to room temperature before stirring at reflux for 1 h. After which time the mixture was poured into ammonium chloride (25 ml) and ethyl acetate (35 ml). The aqueous layer was re-extracted with ethyl acetate (2 x 25 ml). The organic layers were combined and washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The resulting residue was purified by column chromatography eluting with 70-100 % isohexane : ethyl acetate to yield the title compounds as a as a 2:1 *exo:endo* mixture as a colourless oil (0.04 g, 18 %). ν_{max} (KBr) 1598 (C=O), 1434, 1118, 1062, 910 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1SR,5RS,4RS]** 1.61 (6H, t, J = 7 Hz, 2 x NCH_2CH_3), 1.47-1.70 (9H, m, 6-H_2, 7-H_2, 8-H_2, 1'-H_2, 2'-H_a), 2.02-2.21 (2H, m, O-*H*, 2'-H_b), 2.95 (1H, br s, 1-*H*), 3.23 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.39-3.48 (4H, m, 2 x NCH_2), 3.69-3.73 (2H, m, 3'-H_2), 6.38 (1H, s, 3-*H*); **[1SR,5SR,4RS]** 1.61 (6H, t, J = 7 Hz, 2 x NCH_2CH_3), 1.47-1.70 (9H, m, 6-H_2, 7-H_2, 8-H_2, 1'-H_2, 2'-H_a), 2.02-2.21 (2H, m, O-*H*, 2'-H_b), 2.95 (1H, br s, 1-*H*), 3.23 (3H, s,

OCH_3), 3.35 (3H, s, OCH_3), 3.39-3.48 (4H, m, 2 x NCH_2), 3.61-3.65 (2H, m, 3′-H_2), 6.29 (1H, s, 3-*H*); δ_c (100 MHz, $CDCl_3$) **[1SR,5RS,4RS]** 15.0, 15.2 (br 2 x NCH_2CH_3), 23.4, 24.7, 26.2, 29.6 (C-6, C-7, C-8, C-1′), 32.8 (C-1), 39.5 (br NCH_2), 41.4 (C-2′), 43.0 (br NCH_2), 51.4, 51.9 (2 x OCH_3), 63.8 (C-3′), 82.9, 84.3 (C-4, C-5), 130.0 (C-3), 139.5 (C-2), 170.3 (NC=O); **[1SR,5SR,4RS]** 15.0, 15.2 (br 2 x NCH_2CH_3), 23.0, 24.7, 26.2, 30.1 (C-6, C-7, C-8, C-1′), 33.2 (C-1), 39.5 (br NCH_2), 42.5 (C-2′), 43.0 (br NCH_2), 51.3, 52.8 (2 x OCH_3), 63.6 (C-3′), 82.2, 85.0 (C-4, C-5), 133.1 (C-3), 140.9 (C-2), 169.8 (NC=O); *m/z* (ES+) 348 (MNa^+), 326 (MH^+), 294 $(M\text{-}MeOH)^+$; HRMS (EI+) Found M^+; 326.2307; $C_{18}H_{32}NO_4$ requires 326.2331

[1SR,5RS/SR,4RS]-4,5-Dimethoxy-5-(3-oxo-propyl-bicyclo[2.2.2]oct-2-ene-2-carboxylicacid diethylamide

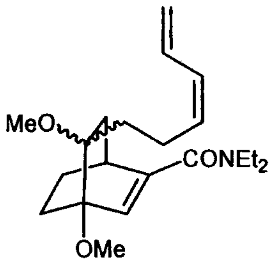


464

To a stirred solution of oxalyl chloride (0.15 ml, 1.7 mmol) in DCM (5 ml) at - 78 °C was added dimethylsulfoxide (0.16 ml, 2.2 mmol) *via* cannula at - 78 °C and stirred for 5 minutes. After which time alcohols **463** (0.36 g, 1.1 mmol) in DCM (3 ml) was added dropwise and was stirred for 15 minutes before adding triethylamine (0.79 ml, 5.6 mmol) and the mixture was warmed to room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then the mixture was partitioned between diethyl ether (50 ml) and water (50 ml). The aqueous layer was then re-extracted with diethyl ether (2 x 50 ml). The combined organic layers were washed with brine and dried over magnesium sulfate before concentrating under pressure. The resulting residue was purified by column chromatography eluting with ethyl acetate to yield a mixture of 2:1 *exo:endo* isomers as a yellow oil (0.18 g, 52 %). ν_{max} (KBr) 1720 (C=O), 1599 (C=O amide), 1434, 1118, 1064, 801 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1SR,5RS,4RS]** -1.16 (6H, t, J = 11 Hz, 2 x NCH_2CH_3), 1.41-1.75 (7H, 6-H_2, 7-H_2, 8-H_a, 1′-H_2), 1.87-1.97 (1H, m, 8-H_b), 2.76 (1H, br s, 1-*H*), 3.15 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.40-3.44 (6H, m, 2′-H_2, 2 x NCH_2), 6.30 (1H, s, 3-*H*), 9.83 (1H, s, C*H*O); **[1SR,5SR,4RS]** 1.16 (6H, t, J = 11 Hz, 2 x NCH_2CH_3), 1.41-1.75 (5H, 6-H_2, 7-H_a, 1′-H_2), 2.36-2.52 (2H, m, 7-H_b, 8-H_2), 2.76 (1H, br s, 1-*H*), 3.30 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.36-3.40 (H, m, 2′-H_2), 3.41-3.44 (4H, m, 2 x NCH_2), 6.36 (1H, s, 3-*H*), 9.78 (1H, s, C*H*O); δ_c (100 MHz, $CDCl_3$) **[1SR,5RS,4RS]** 14.1, 15.3 (br 2 x NCH_2CH_3), 23.5, 24.3 (C-7, C-8), 26.8 (C-6), 32.7 (C-1), 39.2 (br NCH_2), 39.4 (C-1′), 40.6 (C-2′), 43.6 (br NCH_2), 50.9, 51.9 (2 x OCH_3), 82.4 (C-4), 84.1 (C-5), 130.6 (C-3), 139.3 (C-2), 170.0 (NC=O), 202.9 (C=O); **[1SR,5SR,4RS]**

14.1, 15.3 (br 2 x NCH_2CH_3), 22.5, 24.3 (C-7, C-8), 26.8 (C-6), 33.1 (C-1), 39.4 (br NCH_2), 38.4 (C-1′), 41.5 (C-2′), 43.6 (br NCH_2), 51.4, 52.3 (2 x OCH_3), 81.6 (C-4), 84.8 (C-5), 132.3 (C-3), 140.9 (C-2), 169.4 (NC=O), 202.7 (C=O); *m/z* (ES+) 387 $(MCH_3CN)^+$, 362 $(MK)^+$, 346 $(MNa)^+$, 324 $(MH)^+$; HRMS (ES+) Found M^+; 324.2202; $C_{18}H_{30}NO_4$ requires 324.2175

[1SR,5RS/SR,4RS]-5-((Z)-Hexa-3,5-dienyl)-4,5-dihydroxybicyclo[2.2.2]oct-2-ene-2-carboxylicacid diethylamide

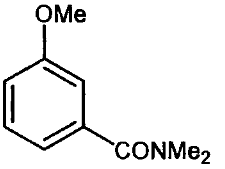


465

To a cooled (-60 °C) stirred solution of 1-tert-butyl-5-(prop-2-ene-1-sulfonyl)-1H-tetrazole (0.18 g, 0.8 mmol) in DME (20 ml) was added KHMDS (0.16 g, 0.8 mmol). The yellow solution was stirred at -60 °C for 30 minutes before addition of aldehydes **464** (0.18 g, 0.5 mmol) in DME (2 ml). The mixture was stirred at -60 °C for a further 3 h before warming to room temperature and stirring for a further 16 h. After which time the reaction mixture was poured into diethyl ether (40 ml) and ammonium chloride (40 ml). The aqueous layer was re-extracted with diethyl ether (2 x 40 ml). The organic layers were combined, washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The resulting residue was purified by column chromatography eluting with ethyl acetate yielding the title compound as a 2:1 mixture of *exo:endo* isomers as colourless film (0.06 g, 34 %). ν_{max} (KBr) 1598 (C=O), 1469, 1381, 1093, 916, 740, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1SR,5RS,4RS]** - 1.16-1.20 (6H, m, 2 x NCH_2CH_3), 1.50-1.88 (8H, m, 6-H_2, 7-H_2, 8-H_2, 1′-H_2), 2.18-2.23 (2H, m, 2′-H_2), 2.75 (1H, br s, 1-*H*), 3.24 (3H, s, OCH_3), 3.35-3.41 (7H, m, OCH_3, 2 x NCH_2), 5.04-5.11 (1H, d, J = 11 Hz, 6′-H_a), 5.19-5.22 (1H, d, J = 11 Hz, 6′-H_b), 5.43-5.53 (1H, m, 3′-H), 5.96-6.04 (1H, m, 4′-*H*), 6.38 (1H, s, 6-*H*), 6.63-6.73 (1H, m, 5′-*H*); **[1SR,5SR,4RS]** 1.16-1.20 (6H, m, 2 x NCH_2CH_3), 1.50-1.88 (7H, m, 6-H_2, 7-H_2, 8-H_2, 1′-H_a), 2.08-2.10 (1H, m, 1′-H_b), 2.31-2.42 (2H, m, 2′-H_2), 2.75 (1H, br s, 1-*H*), 3.24 (3H, s, OCH_3), 3.35-3.41 (7H, m, OCH_3, 2 x NCH_2), 5.04-5.11 (1H, m, 6′-H_a), 5.16-5.22 (1H, m, 6′-H_b), 5.43-5.53 (1H, m, 3′-H), 5.96-6.04 (1H, m, 4′-*H*), 6.28 (1H, s, 6-*H*), 6.63-6.73 (1H, m, 5′-*H*); δ_c (100 MHz, $CDCl_3$) **[1SR,5RS,4RS]** 12.1, 14.2 (2 x NCH_2CH_3), 22.7, 23.4 (C-7, C-8), 27.3 (C-1′), 31.2 (C-6), 32.8 (C-1), 41.5 (C-2′), 51.4, 51.9 (2 x OCH_3), 82.7 (C-4), 84.3 (C-5), 117.2 (C-6′), 129.4 (C-4′), 130.2 (C-3′), 132.4 (C-3), 133.2 (C-5′), 139.4 (C-2), 170.3 (NC=O); **[1SR,5SR,4RS]** 12.1, 14.2 (2 x NCH_2CH_3), 21.3, 22.9 (C-7, C-8), 24.8 (C-1′), 33.3 (C-6), 33.4 (C-1), 42.5 (C-2′), 51.3, 52.9 (2 x OCH_3), 82.1 (C-4), 84.9 (C-5), 117.1 (C-6′), 129.3 (C-4′), 132.4 (C-3′), 132.8

(C-3), 133.1 (C-5′), 140.9 (C-2), 169.6 (NC=O); *m/z* (ES+) 370 (MNa^+), 348 (MH^+), 316 (M-$MeOH^+$); HRMS (ES+) Found M^+; 348.2546; $C_{21}H_{34}NO_3$ requires 348.2439

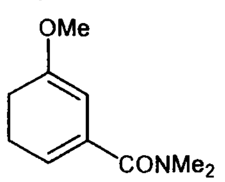
3-Methoxy-N,N-dimethylbenzamide



467

To a stirred solution of *m*-anisic acid (10.00 g, 65.8 mmol) and a drop of dimethylformamide in DCM (250 ml) was added oxalyl chloride (78.9 ml, 78.9 mmol, 2 M in DCM) dropwise. Evolution of gas was observed for 20 minutes and after which time a small aliquot was removed and concentrated under reduced pressure. Acid chloride formation was observed by IR spectroscopy. The resultant reaction mixture was concentrated under reduced pressure and re-dissolved in DCM (50 ml) and added dropwise to a cooled solution (0 °C) of dimethyl amine (90 ml, 151.3 mmol, 2 M in THF) in DCM (250 ml). The solution was then warmed to room temperature and stirred for 1 h. The reaction mixture was then poured into 5 % aqueous HCl (250 ml) in a separating funnel and the layers separated. The aqueous layer was then re-extracted with DCM (2 x 250 ml). The organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 1 : 1 petroleum ether:ethyl acetate to yield a light yellow oil (10.00 g, 85 %). ν_{max} (NaCl) 1640 (C=O), 1480, 1393, 1288, 1043, 795, 751, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.04 (6H, br s, 2 x NCH_2CH_3), 3.82 (3H, s, OCH_3), 6.95-6.98 (2H, m, 4-H, 6-*H*), 7.30 (1H, t, J = 7 Hz, 5-*H*); δ_c (100 MHz, D_6MSO) 55.2 (OCH_3), 112.2 (C-5), 114.9 (C-6), 118.84 (C-4), 129.4 (C-2), 137.9 (C-1), 158.9 (C-3), 169.8 (C=O); *m/z* (EI) 179 $(M)^+$, 135 $(M\text{-}NMe_2^+)^+$; HRMS (EI) Found M^+; 179.0942; $C_{10}H_{13}NO_2$ requires 179.0946

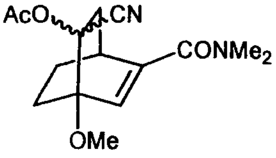
5-Methoxycyclohexa-1,5-dienecarboxylic acid dimethylamide



468

The title compound was prepared by the same procedure as 5-methoxycyclohexa-1,5-dienecarboxylic acid diethylamide and was obtained as a light yellow oil (66 % over two steps). ν_{max} (NaCl) ν_{max} 1655 (C=O), 1495, 1450, 1379, 1263, 1174, 1052, 739 cm^{-1}, δ_H (400 MHz, $CDCl_3$) 2.28-2.38 (4H, m, 3-H_2, 4-H_2), 2.97-3.02 (6H, m, 2 x NCH_3), 3.62 (3H, s, O*C*H_3), 5.05 (1H, s, 6-*H*), 5.56-5.58 (1H, m, 2-*H*); δ_c (100 MHz, $CDCl_3$) 23.3, 26.2 (*C*-3, *C*-4), 34.8, 35.3 (2 x NCH_3), 55.1 (OCH_3), 92.0 (*C*-2), 102.1 (*C*-6), 118.5 (*C*-1), 159.5 (*C*-5), 171.7 (C=O); *m/z* (ES+) 182 $(MH)^+$, 204 $(MNa)^+$; HRMS (ES+) Found MNa^+; 204.0995; $C_{10}H_{15}O_2NNa$ requires 204.0995

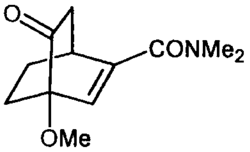
Acetic acid 2-cyano-5-dimethylcarbamoyl-1-methoxybicyclo[2.2.2]oct-5-en-2-yl ester



469

Prepared in the same manner as chloroacetate **457** and the title compound was obtained as a 2:1 mixture of *exo:endo* isomers as an orange oil (7.16 g, 62 %). ν_{max} (NaCl) 1751 (C=O), 1614, 1243, 1047, 922, 897 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **Major** 1.70-2.20 (9H, m, 3-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, CO(C*H*$_3$), 2.63 (1H, m, 4-*H*), 2.95-3.16 (6H, m, 2 x NC*H*$_3$), 3.55 (3H, s, OC*H*$_3$), 6.38 (1H, s, 6-*H*); **Minor** 1.70-2.20 (9H, m, 3-*H*$_2$, 7-*H*$_2$, 8-*H*$_2$, CO(C*H*$_3$), 2.63 (1H, m, 4-*H*), 2.95-3.16 (6H, m, 2 x NC*H*$_3$), 3.53 (3H, s, OC*H*$_3$), 6.39 (1H, s, 6-*H*); δ_c (100 MHz, $CDCl_3$) **Major** 21.3 ($CO(CH_3)$), 24.1, 24.9, 31.9 (*C*-3, *C*-7, *C*-8), 35.4, 39.1 (2 x NCH_3), 44.1 (*C*-4), 53.1 (OCH_3), 77.0 (*C*-2), 80.7 (*C*-1), 117.8 (CN), 130.4 (*C*-6), 140.9 (*C*-5), 168.3 (C=O), 168.9 (C=O); **Minor** 20.8 ($CO(CH_3)$), 21.3, 26.0, 32.0 (*C*-3, *C*-7, *C*-8), 35.4, 39.1 (2 x NCH_3), 41.9 (*C*-4), 52.9 (OCH_3), 76.2 (*C*-2), 81.0 (*C*-1), 118.9 (CN), 130.9 (*C*-6), 142.2 (*C*-5), 168.2 (C=O), 169.5 (C=O); m/z (ES+) 315 $(MNa)^+$, 606 $(2MNa)^+$; HRMS (ES+) Found MNa^+; 315.1315; $C_{15}H_{20}O_4N_2Na$ requires 315.1315

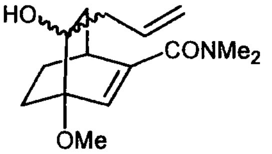
[1SR, 4RS]-4-Methoxy-5-oxo-*bicyclo*[2.2.2]oct-2-ene-2-carboxylic acid dimethylamide



470

Chloroacetate **469** was subjected to identical procedure as cyanoacetate **457** to afford the title compound as an orange oil (2.61 g, 46%). ν_{max} (NaCl) 1745, 1598, 1454, 1394, 1325, 1085, 866, 745 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.83-2.04 (4H, m, 7-*H*$_2$, 8-*H*$_2$), 2.16-2.25 (2H, m, 6-*H*$_2$), 3.01-3.07 (6H, m, 2 x NC*H*$_3$), 3.25 (1H, m, 1-*H*), 3.54 (3H, s, OCH_3), 6.35 (H, s, 3-H); δ_c (100 MHz, $CDCl_3$) 25.9, 27.0 (C-7, C-8), 34.5 (C-6), 36.0, 39.2 (2 x NCH_3), 40.5 (C-1), 53.7 (OCH_3), 85.1 (C-4), 130.2 (C-3), 142.1 (C-2), 168.4 (C=O), 208.9 (C-5); (ES+) 224 $(MH)^+$

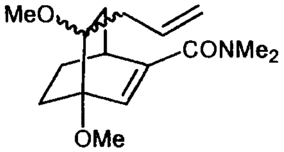
[1SR,5RS/SR,4RS]-5-Allyl-5-hydroxy-4-methoxybicyclo[2.2.2]oct-2-ene-2-carboxylic acid dimethyl amide



471/472

Ketone **470** (2.61 g, 11.8 mmol) was subjected to identical conditions as ketone **448** to afford the title compound as a 2:1 mixture of exo:endo isomers as an orange oil (2.39 g, 77 %). ν_{max} (NaCl) 3560-3155 (OH), 1636, 1609, 1399, 910, 899, 712, 650 cm^{-1}; δ_H (400 MHz, CDCl$_3$) **[1SR, 5RS, 4RS]** 1.62-2.04 (6H, m, 6-H_2, 7-H_2, 8-H_2), 2.17-2.25 (H, m, 1'-H_a), 2.63-2.68 (H, m, 1'-H_b), 2.79 (H, m, 1-*H*), 2.97-3.12 (6H, m, 2 x NCH_3), 3.40 (3H, s, OCH$_3$), 5.10-5.13 (2H, m, 3'-H_2), 5.91-5.99 (H, m, 2'-*H*), 6.38 (H, m, 3-*H*); **[1SR, 5SR, 4RS]** 1.62-2.04 (6H, m, 6-H_2, 7-H_2, 8-H_2), 2.17-2.25 (H, m, 1'-H_2), 2.79 (H, m, 1-*H*), 2.97-3.12 (6H, m, 2 x NCH_3), 3.54 (3H, s, OCH$_3$), 5.10-5.13 (2H, m, 3'-H_2), 5.91-5.99 (H, m, 2'-*H*), 6.35 (H, m, 3-*H*); δ_c (100 MHz, CDCl$_3$) **[1SR, 5SR, 4RS]** 23.3, 26.2 (C-7, C-8), 32.7 (C-1), 35.1, 39.4 (2 x NCH$_3$), 40.9 (C-1'), 42.0 (C-6), 51.9 (OCH$_3$), 83.1, 85.1 (C-4, C-5), 118.2 (C-3'), 133.4 (C-3), 134.9 (C-2'), 139.2 (C-2), 169.9 (C=O); **[1SR, 5SR, 4RS]** 25.9, 27.0 (C-7, C-8), 34.4 (C- 1), 35.1, 39.4 (2 x NCH$_3$), 40.5 (C-1'), 42.0 (C-6), 53.7 (OCH$_3$), 83.1, 85.1 (C-4, C-5), 118.2 (C-3'), 130.1 (C-3), 134.9 (C-2'), 142.1 (C-2), 168.4 (C=O); *m/z* (ES+) 288 (MNa)$^+$; HRMS (ES+) Found MNa$^+$; 288.1568; $C_{15}H_{23}O_3NNa$ requires 288.1570

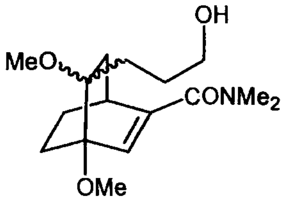
[1SR, 5(RS/SR), 4RS]-5-Allyl-4,5-dimethoxy-bicyclo[2.2.2]oct-2-ene-2-carboxylic acid dimethylamide



471a/472a

Allyl alcohols **471/472** (2.39 g, 9.02 mmol) was subjected to identical conditions as allyl alcohols **461/462** to afford the title compound as a 2:1 mixture of exo:endo isomers as a colourless oil (0.85 g, 34 %). ν_{max} (NaCl) 1643, 1503, 1393, 1048, 750 cm^{-1}; δ_H (400 MHz, CDCl$_3$) **[1SR, 5RS, 4RS]** 1.56-1.83 (5H, m, 6-H_2, 7-H_a, 8-H_2), 1.93 (1H, m, 1'-H_a), 2.06 (1H, m, 7-H_a), 2.80 (1H, m, 1-*H*), 2.92-3.12 (7H, m, 2 x NCH_3, 1'-H_b), 3.37 (3H, s, OCH_3), 3.39 (3H, s, OCH$_3$), 5.05-5.08 (2H, m, 3'-H_2), 5.79 (H, m, 2'-*H*), 6.35 (H, s, 3-*H*); **[1SR, 5SR, 4RS]** 1.53-1.74 (6H, m, 6-H_2, 7-H_2, 8-H_2), 2.24 (1H, m, 1'-H_a), 2.81 (1H, m, 1-*H*), 2.93-3.14 (7H, m, 2 x NCH_3, 1'-H_b), 3.26 (3H, s, OCH$_3$), 3.38 (3H, s, OCH$_3$), 5.09-5.16 (2H, m, 3'-H_2), 5.95 (1H, m, 2'-*H*), 6.44 (1H, s, 3-*H*); δ_c (100 MHz, CDCl$_3$) **[1SR, 5RS, 4RS]** 22.9, 24.7 (C-7, C-8), 32.9 (C-1), 38.3 (C-1'), 41.3 (C-6), 51.4, 52.7 (2 x OCH$_3$), 82.1, 84.9 (C-4, C-5), 117.6 (C-3′), 134.5 (C-2′), 135.5 (C-3), 140.1 (C-2), 171.6 (C=O); **[1SR, 5SR, 4RS]** 23.4, 27.1 (C-7, C-8), 32.5 (C-1), 35.7 (C-1′), 40.8 (C-6), 51.5, 51.9 (2 x OCH_3), 82.8, 84.4 (C-4, C-5), 117.2 (C-3′), 132.8 (C-2′), 135.2 (C-3), 138.9 (C-2), 170.3 (C=O); *m/z* (ES+) 302 $(MNa)^+$; HRMS (ES+) Found MNa^+; 302.1723; $C_{16}H_{25}O_3NNa$ requires 302.1726

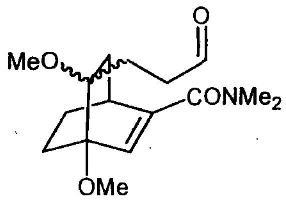
[1SR,5(RS/SR),4RS]-5-3′-Hydroxypropyl-4,5-dimethoxybicyclo[2.2.2]oct-2-ene-2-carboxylic acid dimethyl amide



473

Allyl ethers **471a/472a** (0.85 g, 2.9 mmol) was subjected to identical conditions as allyl ethers **461a/462a** to afford the title compound as a 2:1 mixture of exo:endo isomers as a colourless oil (0.30 g, 35 %). ν_{max} (NaCl) 3154 (OH), 1639, 1603, 1468, 1382, 910, 752, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1SR, 5RS, 4RS]** 1.52-1.93 (10H, m, 6-H_2, 7-H_2, 8-H_2, 1′-H_2, 2′-H_2), 2.80 (1H, m, 1-*H*), 2.99-3.14 (6H, m, 2 x NCH_3), 3.22 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.67-3.71 (2H, m, 3′-H_2), 6.44 (H, s, 2-*H*); **[1SR, 5SR, 4RS]** 1.52-1.93 (10H, m, 6-H_2, 7-H_2, 8-H_2, 1′-H_2, 2′-H_2), 2.80 (H, m, 1-*H*), 2.99-3.14 (6H, m, 2 x NCH_3), 3.35 (3H,s, OCH_3), 3.36 (3H, s, OCH_3), 3.61-3.64 (2H, m, 3′-H_2), 6.37 (1H, s, 2-*H*); δ_c (100 MHz, $CDCl_3$) **[1SR, 5RS, 4RS]** 23.5, 27.1, 27.6, 27.7, (C-6, C-7, C-8, C-1′), 32.5 (C-1), 35.2, 39.2 (2 x NCH_3), 41.3 (C-2′), 51.5, 51.8 (2 x OCH_3), 63.8 (C-3′), 82.9, 84.5 (C-4, C-5), 132.9 (C-3), 138.7 (C-2), 170.2 (C=O); **[1SR, 5SR, 4RS]** 22.9, 24.5, 29.7, 30.1 (C-6, C-7, C-8, C-1′), 32.5 (C-1), 35.2, 39.2 (2 x NCH_3), 42.4 (C-2′), 51.4, 52.8 (2 x OCH_3), 63.6 (C-3′), 82.2, 85.1 (C-4, C-5), 135.9 (C-3), 140.2 (C-2), 169.6 (C=O); *m/z* (ES+) 320 $(MNa)^+$; HRMS (ES+) Found MNa^+; 320.1832; $C_{16}H_{27}O_4NNa$ requires 320.1832

[1SR,5(RS/SR),4RS]-4,5-Dimethoxy-5-(3-oxo-propyl)bicyclo[2.2.2]oct-2-ene-2-carboxylic acid dimethyl amide

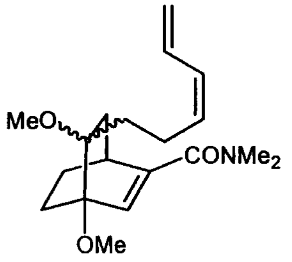


474

Alcohols **473** (0.30 g, 1.0 mmol) was subjected to identical conditions as alcohol **463** to afford the title compound as a 2:1 mixture of exo:endo isomers as a colourless oil (0.13 g, 43 %). ν_{max} (NaCl) 1720 (C=O), 1605 (C=O), 1498, 1454, 1399, 1117, 901, 752 cm^{-1}; δ_H

(400 MHz, $CDCl_3$) **[1SR, 5RS, 4RS]** 1.37-1.93 (5H, m, 6-*H*, 7-*H*, 1′-H_a), 2.08-2.51(3H, m, 8-H_a, 1′-H_2), 2.82 (1H, m, 1-*H*), 2.99-3.13 (8H, m, 2′-H_2, 2x NCH_3), 3.14 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 6.43 (1H, s, 3-H), 9.82 (1H, s, CHO); **[1SR, 5SR, 4RS]** 1.37-1.93 (5H, m, 6-H_2, 7-H_2, 1′-H_a), 2.08-2.51 (3H, m, 8-H_a, 1′-H_b), 2.82 (1H, m, 1-*H*), 2.99-3.13 (8H, m, 2′-H_2, 2x NCH_3), 3.30 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 6.37 (1H, s, 3-H), 9.78 (1H, s, CHO); δ_c (100 MHz, $CDCl_3$) **[1SR, 5RS, 4RS]** 22.5, 24.8 (C-7, C-8), 26.3 (C-6), 32.8 (C-1), 35.2 (NCH_3), 38.0 (NCH_3), 38.4 (C-1′), 41.4 (C-2′), 51.5 (OCH_3), 52.2 (OCH_3), 81.6, 84.9 (C-4, C-5), 138.4 (C-3), 149.7 (C-2), 169.6 (NCO), 202.7 (C=O); **[1SR, 5SR, 4RS]** 23.8, 24.4 (C-7, C-8), 26.3 (C-6), 32.4 (C-1), 35.2 (NCH_3), 38.0 (NCH_3), 39.4 (C-1′), 40.4 (C-2′), 50.8 (OCH_3), 51.7 (OCH_3), 82.5, 84.2 (C-4, C-5), 133.6 (C-3), 135.1 (C-2), 169.9 (NCO), 202.8 (C=O); *m/z* (ES+) 318 $(MNa)^+$; HRMS (ES+) Found MNa^+; 318.1674; $C_{16}H_{25}NO_4Na$ requires 318.1676

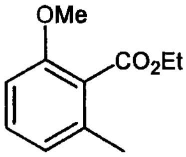
[1SR, 5(RS/SR), 4RS]-5-((Z)-Hexa-3′,5′-dienyl)-4,5-dimethoxy-bicyclo[2.2.2]oct-2-ene-2-carboxylic acid dimethyl amide



475

Aldehyde **474** (0.30 g, 0.4 mmol) was subjected to identical conditions as aldehyde **464** to afford the title compound as a 2:1 mixture of exo:endo isomers as a yellow oil (0.03 g, 19 %). ν_{max} (NaCl) 1638, 1398, 1383, 1216, 1111, 924, 917 cm^{-1}; δ_H (400 MHz, $CDCl_3$) **[1SR, 5RS, 4RS]** 1.52-1.63 (6H, m, 6-H_2, 7-H_2, 8-H_2), 1.80-2.24 (2H, m, 1′-H_2), 2.35-2.40 (2H, m, 2′-H_2), 2.80 (1H, m, 1-*H*), 2.99-3.15 (6H, m, 2x NCH_3), 3.36 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 5.07 (1H, t, J = 12 Hz, 6′-H_a), 5.17 (1H, t, J = 16 Hz, 6′-H_b), 5.49-5.51 (1H, m, 3′-*H*), 5.97 (1H, t, 11 Hz, 4′-*H*), 6.44 (1H, s, 3-*H*), 6.62-6.70 (1H, m, 5′-*H*); **[1SR, 5SR, 4RS]** 1.52-1.63 (6H, m, 6-H_2, 7-H_2, 8-H_2), 1.80-2.24 (2H, m, 1′-H_2), 2.35-2.40 (2H, m, 2′-H_2), 2.80 (1H, m, 1-*H*), 2.99-3.15 (6H, m, 2x NCH_3), 3.24 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 5.07 (1H, t, J = 12 Hz, 6′-H_a), 5.17 (1H, t, J = 16 Hz, 6′-H_b), 5.42-5.44 (1H, m, 3′-*H*), 5.97 (1H, t, J = 11 Hz, 4′-*H*), 6.36 (1H, s, 3-*H*), 6.62-6.70 (1H, m, 5′-*H*) δ_c (100 MHz, $CDCl_3$); **[1SR, 5RS, 4RS]** 22.7, 23.4 (C-7, C-8), 27.1 (C-1′), 31.4 (C-1), 32.5 (C-6), 35.2, 39.2 (2 x NCH_3), 41.4 (C-2′), 51.4 (OCH_3), 51.5 (OCH_3), 82.8, 84.4 (C-4, C-5), 117.3 (C-6′), 129.4 (C-4′), 132.4 (C-3′), 133.1 (C-5′), 133.2 (C-3), 138.6 (C-2), 170.2 (C=O); **[1SR, 5SR, 4RS]** 21.3, 23.0 (C-7, C-8), 27.1 (C-1′), 30.0 (C-1), 32.9 (C-6), 35.2, 39.2 (2 x NCH_3), 42.4 (C-2′) 51.4 (OCH_3), 51.5 (OCH_3), 82.8, 84.4 (C-4, C-5), 117.2 (C-6′), 129.3 (C-4′), 132.4 (C-3′), 133.1 (C-5′), 135.2 (C-3), 140.1 (C-2), 169.5 (C=O); *m/z* (ES+) 342 $(MNa)^+$; HRMS (ES+) Found MNa^+; 342.2037; $C_{19}H_{29}NO_3Na$ requires 342.2040

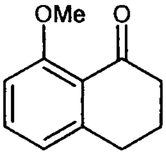
2-Methoxy-6-methylbenzoic acid ethyl ester[163]



526

To a stirred suspension of 2-methoxy-6-methylbenzoic acid ethyl ester (8.00 g, 47.6 mmol) and potassium carbonate (14.5 g, 90.5 mmol) in acetone (50 ml) was added dimethylsulfate (6.96 ml, 57.1 mmol). This mixture was then stirred at reflux for 16 h. Once this had elapsed it was filtered and the acetone was removed under reduced pressure. Excess dimethylsulfate was removed by dissolving the residue in diethyl ether (100 ml) and adding triethylamine (15 ml). The diethyl ether solution became opaque and an oily precipitate of the quaternary salt was formed and after 1 h the solution was transferred to a separating funnel and washed with water (2 x 20 ml), 10 % HCl (1 x 20 ml) and brine (1 x 20 ml). The organic layer was then dried over magnesium sulfate before concentrating under reduced pressure and used without further purification. The title compound was obtained as a light yellow oil (7.20 g, 83 %). ν_{max} (NaCl) 1736 (C=O), 1585, 1472, 1260, 1072, 779, 620 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34 (2H, t, J = 7 Hz, $CH_2C\mathit{H}_3$), 2.29 (3H, s, $ArC\mathit{H}_3$), 3.81 (3H, s, OCH_3), 4.34 (2H, q, J = 7 Hz, $C\mathit{H}_2CH_3$), 6.73 (1H, d, J = 8 Hz, 3-*H*), 7.19 (1H, m, 5-*H*), 7.23 (2H, m, 4-*H*); δ_c (100 MHz, $CDCl_3$) 14.3 (CH_2CH_3), 19.1 ($ArCH_3$), 55.9 (OCH_3), 61.5 (CH_2CH_3), 108.6 (C-3), 122.4 (C-4), 124.1 (C-5), 130.1 (C-2), 136.3 (C-6), 156.4 (C-8), 168.5 (C=O); *m/z* (EI+) 194 $(M)^+$, 149 $(M\text{-}OEt)^+$; HRMS (EI+) Found M^+; 194.0946; $C_{11}H_{14}O_3$ requires 194.0930

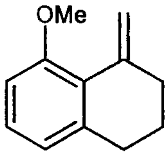
8-Methoxy-3,4-dihydro-2H-naphthalen-1-one[134]



528

To a cooled (-78 °C), stirred solution of lithium diisopropylamine (30.29 ml, 23.3 mmol, 1M in THF) in THF (70 ml) was added a solution of ester **526** (3.50 g, 18.0 mmol) dropwise in THF (15 ml) over 15 minutes. Ethyl acrylate (4.44 ml, 44.9 mmol) was the added dropwise, turning the solution bright red and subsequently light yellow on complete addition. The reaction was warmed to 0 °C and stirred for 5 h. After this time had elapsed saturated ammonium chloride (50 ml) and ethyl acetate (80 ml) were added and the aqueous layer was further extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine before drying over magnesium sulfate. The solvent was removed under reduced pressure and the residue that remained was dissolved in methanol : HCl (4:1) (120 ml) and heated at reflux for 15 h. The reaction mixture was then reduced to 100 ml under reduced pressure. The solution that remained was diluted with water (75 ml) and ethyl acetate (75 ml). The aqueous layer was reextracted with ethyl acetate (3 x 70 ml). The combined organic layers were washed with brine before drying over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 1 : 1 ethyl acetate:petroleum ether to afford the title compound as bright yellow oil (1.28 g, 41 %). ν_{max} (NaCl) 1670 (C=O), 1469, 1271, 909, 712, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.02-2.10 (2H, m, 4-H_2), 2.61 (2H, t, J = 13 Hz, 3-H_2), 2.89 (2H, t, J = 13 Hz, 2-H_2), 3.91 (3H, s, OCH_3), 6.81 (2H, br d, 5-*H*, 7-*H*), 7.35 (1H, br t, 6-*H*); δ_c (100 MHz, $CDCl_3$) 23.1 (C-3), 31.1 (C-4), 41.2 (C-2), 56.2 (OCH_3), 110.2 (C-5), 120.9 (C-6), 122.4 (C-5a), 134.2 (C-7), 147.4 (C-8a), 160.6 (C-8), 198.0 (C=O), *m/z* (EI+) 176 (M$^{\cdot+}$), 148 (M-CO$^+$), HRMS (EI+) Found M$^+$; 176.0844; $C_{11}H_{12}O_2$ requires 176.0837

8-Methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene

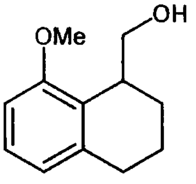


530

To a stirred suspension of potassium ^{t}butoxide (0.80 g, 7.2 mmol) in diethyl ether (30 ml) was added methyltriphenylphosphonium bromide (2.56 g, 7.2 mmol) and was heated at reflux for 15 minutes. After this time had elapsed ketone **528** (1.20 g, 6.8 mmol) in diethyl ether (10 ml) was added and the mixture stirred for a further 20 minutes at reflux. The mixture was then allowed to cool and ammonium chloride (25 ml) was added slowly dropwise and the reaction was then diluted with diethyl ether and the aqueous was re-extracted with diethyl ether (2 x 30 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10 % diethyl ether in petrol to yield the title compound as a light yellow oil (0.50 g, 42 %). ν_{max} (NaCl) 1615, 1593, 1571, 1467, 1252, 1087, 756 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.07-2.12 (2H, m, 3-H_2), 2.20-2.22 (2H, m, 4-H_2), 2.63 (2H, t, J = 16 Hz, 2-H_2), 3.80 (3H, s, OCH_3), 5.82-5.85 (2H, m, CH=CH_2), 6.78-6.80 (2H, m, 5-*H*, 7-*H*), 7.08 (1H, t, J = 8 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 23.1 (C-3), 23.5 (C-4), 30.0 (C-2), 55.7 (OCH_3), 110.6 (C-5), 120.6 (C-7), 125.3 (C-

5′), 126.7 (C=CH2), 127.4 (C-6), 133.0 (C-1′), 140.0 (C-8′), 156.8 (C-8); *m/z* (EI) 174 $(M)^+$ (76 %), 159 (100 %), 144 (40 %), 115 (32 %)

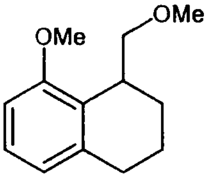
(8-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl) methanol



531

To a cooled (0 °C), stirred solution of alkene **530** (0.50 g, 2.8 mmol) in THF (30 ml) was added BH_3.THF complex (1M solution in THF, 1.99 ml) dropwise. The mixture was stirred at 0 °C for 45 minutes and after this time had elapsed NaOH (3M, 0.66 ml) and H_2O_2 (35 % w/w in water, 0.66 ml) was added. The reaction mixture was then stirred at reflux for 1 h and was then diluted with ammonium chloride (30 ml) and diethyl ether (15 ml). The layers were separted and the aqueous was re-extracted with diethyl ether (2 x 30 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 25 % ethyl acetate in petroleum ether to yield the title compound as colourless oil (0.29 g, 55 %). ν_{max} (NaCl) 3154 (OH), 1466, 1382, 1096, 919, 711, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.64-1.83 (3H, m, 2-H_a, 3-H_2), 2.09-2.21 (1H, m, 2-H_b), 2.73-2.78 (2H, m, 4-H_2), 3.24-3.28 (1H, m, 1-*H*), 3.64 (1H, dd, J = 2, 8 Hz, CH_aOH), 3.81-3.85 (4H, m, CH_bOH, OCH_3), 6.68 (1H, d, J = 8 Hz, 5-*H*), 6.74 (1H, d, J = 8 Hz, 7-*H*), 7.09 (1H, t, J = 8 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 18.5 (C-3), 24.7 (C-2), 29.7 (C-4), 35.5 (C-1), 55.5 (OCH_3), 65.9 (CH_2OH), 107.6 (C-5), 122.1 (C-7), 125.9 (C-5′), 126.9 (C-6), 139.4 (C-1′), 157.7 (C-*8*); *m/z* (EI) 192 $(M)^+$ (15 %), 161 (100 %), 115 (25 %), 91 (26 %)

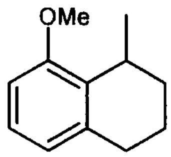
8-Methoxy-1-methoxymethyl-1,2,3,4-tetrahydronaphthalene



532

A solution of alcohol **531** (0.62 g, 3.2 mmol) in THF (5 ml) was added dropwise to a suspension of sodium hydride (0.31 g, 12.9 mmol) in THF (25 ml). The mixture was then stirred at room temperature for 1 h before tertbutylammonium iodide (0.12 g, 0.32 mmol) and methyl iodide (0.23 ml, 3.65 mmol) was added. The resultant suspension was stirred for a further 8 h at room temperature before dilution with ammonium chloride (20 ml) and ethyl acetate (30 ml). The layers were separated and the aqueous layer was re-extracted with ethyl acetate (2 x 30 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 25 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (0.34 g, 51 %). ν_{max} (NaCl) 1583, 1466, 1253, 1102, 769, 735 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.38-1.66 (4H, m, 3-H_2, 4-H_2), 1.97-2.01 (1H, m, 1-*H*), 3.13-3.15 (1H, m, CH_aOCH_3), 3.21 (3H, s, OCH_3), 3.37-3.39 (1H, m, CH_bOCH_3), 3.65 (3H, s, OCH_3), 6.48-6.53 (2H, m, 5-*H*, 7-*H*), 6.90 (1H, t, J = 8 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 17.8 (C-3), 23.7 (C-2), 29.5 (C-4), 32.2 (C-1), 55.2 (OCH_3), 58.4 (OCH_3), 73.7 (CH_2OCH_3), 107.3 (C-5), 121.6 (C-7), 125.6 (C-5′), 126.6 (C-6), 139.3 (C-8′), 157.6 (C-8); *m/z* (EI) 206 (M)$^+$ (25 %), 160 (100 %), 115 (28 %), 90 (24 %)

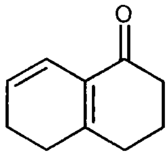
8-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthalene



535

To palladium on carbon (0.15 g, 10 % w/w) under argon was added alkene **530** (1.20 g, 6.9 mmol) in absolute ethanol (25 ml) *via* cannula. The system was charged with hydrogen and stirred at room temperature for 16 h, after which time the reaction was filtered through Celite© and the solvent was removed under reduced pressure. The title compound was obtained as colourless oil and was used without further purification (1.10 g, 93 %). ν_{max} (NaCl) 1583, 1469, 1251, 1096, 1070, 764, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, J = 7 Hz, CH_3), 1.70-1.89 (3H, m, 2-H_a, 3-H_2), 2.66-2.80 (2H, m, 4-H_2), 3.16-3.19 (1H, m, 2-H_b), 3.44 (1H, q, J = 7 Hz, 1-*H*), 3.85 (3H, s, OCH_3), 6.64 (1H, d, J = 8 Hz, 5-*H*), 6.65 (1H, d, J = 8 Hz, 7-*H*), 7.03 (1H, t, J = 8 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) 18.0 (C-3), 20.9 (CH_3), 26.9 ($CHCH_3$), 29.7 (C-2), 29.9 (C-4), 55.9 (OCH_3), 107.3 (C-5), 121.5 (C-7), 125.8 (C-6), 131.1 (C-5′), 137.8 (C-8′), 157.4 (C-8); *m/z* (ES+) 177 (MH)$^+$

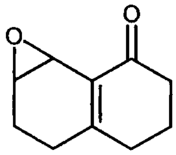
3,4,5,6-Tetrahydro-2H-naphthalen-1-one[135]



538

To a solution of α-tetralone (20.00 g, 140.0 mmol), ^{t}butanol (130 ml, 1400.0 mmol) and THF (50 ml) at -78 °C was condensed ammonia (400 ml) and lithium ribbon (3.80 g, 550.0 mmol) was added slowly. The reaction mixture was stirred at -78 °C until the blue colour disappeared (between 5-15 minutes) and solid ammonium chloride (10 g) was added. The mixture was then allowed to warm to room temperature and the ammonia evaporated under a stream of nitrogen. After this time water (100 ml) and diethyl ether (300 ml) were added and the layers separated. The aqueous layer was further extracted with diethyl ether (3 x 250 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purfied by Kugelrohr distillation (85 °C, 0.8 mbar) to afford the title compound as a colourless oil (14 g, 70 %). ν_{max} (NaCl) 1658, 1401, 1287, 751 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.97-2.03 (2H, m, 4-H_2), 2.20-2.25 (2H, m, 6-H_2), 2.33-2.36 (2H, m, 5-H_2), 2.45-2.39 (4H, m, 2-H_2, 3-H_2), 5.79-5.83 (1H, m, 7-*H*), 6.49-6.51 (1H, d, J = 11 Hz, 8-*H*); δ_c (100 MHz, $CDCl_3$) 21.9 (C-4), 22.6 (C-6), 29.3 (C-5), 31.3 (C-3), 37.9 (C-2), 120.0 (C-8), 125.3 (C-7), 129.8 (C-4a), 156.3 (C-8a), 196.6 (C-1); *m/z* (ES+) 149 $(M)^+$; HRMS (ES+) Found M^+; 149.0961 $C_{10}H_{13}O$ requires 149.061

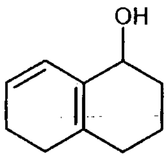
2,3,4,5,6,7b-Hexahydro-1aH-1-oxa-cyclopropa[a]naphthalen-7-one



558

To a stirred solution of diene **538** (0.50 g, 2.8 mmol) in DCM (30 ml) at 0 °C was added sodium hydrogen carbonate (0.72 g, 8.5 mmol) and *m*-CPBA (0.83 g, 3.7 mmol). The reaction mixture was stirred at 0 °C for 1 h before quenching with saturated sodium thiosulfate solution (30 ml). The layers were separated and the aqueous layer was further extracted with DCM (3 x 25 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 10-20 % ethyl acetate in petroleum ether to afford the title compound as a colourless oil (0.23 g, 49 %). ν_{max} (NaCl) 1662, 1379, 1278, 1191, 897, 831, 681 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.61-1.64 (1H, m, 3-H_a), 1.84-2.00 (3H, m, 3-H_b, 6-H_2), 2.20-2.40 (6H, m, 2-H_2, 4-H_2, 5-H_2), 3.44-3.51 (1H, m, 7-*H*), 4.02 (1H, d, J = 5 Hz, 8-*H*); δ_c (100 MHz, $CDCl_3$) 20.7 (C-3), 21.9 (C-5), 26.5 (C-6), 31.6 (C-4), 37.5 (C-2), 44.2 (C-7), 54.2 (C-8), 128.9 (C-8a), 160.8 (C-4a), 197.5 (C-1); *m/z* (ES+) 165 $(MH)^+$

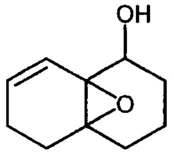
1,2,3,4,5,6-Hexahydronaphthalen-1-ol



561

$CeCl_3.4H_2O$ (50.30 g, 135.0 mmol) and sodium borohydride (2.55 g, 67.5 mmol) were added to a cooled (-78 °C) solution of ketone **538** (2.00 g, 13.5 mmol) in dry methanol (50 ml). The reaction mixture was stirred at -78 °C for 1 h before quenching with acetone (1 ml) and allowed to warm to room temperature. Water (50 ml) and ethyl acetate (100 ml) were added and the layers separated. The aqueous layer was further extracted with ethyl acetate (3 x 100 ml) and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purifed by column chromatography eluting with 10-20 % ethyl acetate in petroleum ether to yield the title compound as a colourless oil (1.25 g, 60 %). ν_{max} (NaCl) 3567-3090 (OH), 1453, 1040, 940 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.60-1.61 (1H, m, 3-H_a), 1.70-1.76 (3H, m, 2-H_2, 3-H_b), 2.02-2.08 (4H, m, 4-H_2, 5-H_2), 2.14-2.17 (2H, m, 6-H_2), 4.08 (1H, m, 1-*H*), 5.72 (1H, m, 7-*H*), 5.98 (1H, m, 8-*H*); δ_c (100 MHz, $CDCl_3$) 18.4 (C-3), 22.8 (C-4), 28.3 (C-5), 30.5 (C-6), 32.2 (C-2), 67.2 (C-1), 124.6 (C-7), 126.1 (C-8), 129.2, 134.3 (C-4a, C-8a); *m/z* (EI) 150 $(M)^+$(60 %), 116 (60 %), 103 (82 %), 90 (80 %), 78 (100 %)

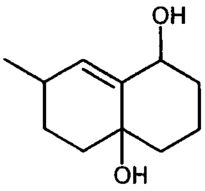
11-Oxatricyclo[4.4.1.0*1,6*]undec-9-en-2-ol



563

To a stirred solution of alcohol **561** (1.00 g, 6.7 mmol) in DCM (150 ml) at 0 °C was added sodium hydrogen carbonate (1.68 g, 20.0 mmol) and *m*-CPBA (1.49 g, 8.7 mmol). The reaction mixture was stirred at 0 °C for 1 h before quenching with saturated sodium thiosulfate solution (100 ml). The layers were separted and the aqueous layer was further extracted with DCM (3 x 75 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 10-30 % ethyl acetate in petroleum to yield the title compound as a white solid (0.58 g, 53 %). mp 69-71 °C; ν_{max} (NaCl) 3656-3516 (OH), 1254, 916, 900, 752, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.90-1.93 (1H, m, 4-H_a), 2.07-2.14 (1H, m, 3-H_a), 2.20-2.24 (4H, m, 3-H_b, 4-H_b, 5-H_2), 2.40-2.41 (2H, m, 7-H_a, O*H*), 2.36-2.45 (1H, m, 7-H_b), 2.55-2.69 (2H, m, 8-H_2), 4.50 (1H, dd, J = 5, 9 Hz, 2-*H*), 6.51-6.54 (1H, m, 9-*H*), 6.66-6.67 (1H, m, 10-*H*); δ_c (100 MHz, $CDCl_3$) 18.9 (C-4), 21.2 (C-3), 27.5, 27.6 (C-5, C-7), 28.7 (C-8), 60.6 (C-2), 67.7, 69.9 (C-1, C-6), 125.6 (C-9), 133.1 (C-10); *m/z* (EI) 166 $(M)^+$ (6 %), 109 (22 %). 81 (100 %), 78 (76 %), 65 (30 %)

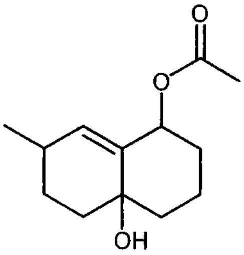
7-Methyl-1,2,3,4,4a,5,6,7-octahydro-2H-naphthalene-1,4a-diol



572

To a suspension of copper iodide (3.05 g, 16.0 mmol) in THF (50 ml) at 0 °C was added methyl lithium (11.73 ml, 1.42 M in diethyl ether, 16.7 mmol) to give a clear solution. Vinyl oxirane **563** (0.60 g, 3.6 mmol) in THF (2 ml) was to then added dropwise immediately yielding a bright yellow suspension and was stirred for 1 h at 0 °C. After this time had elapsed the reaction mixture was carefully quenched with saturated ammonium chloride (30 ml) and diluted with ethyl acetate (75 ml). The layers were separated and the aqueous layer was further extracted with ethyl acetate (3 x 75 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 20-40 % ethyl acetate in petroleum ether to afford the title compound as a colourless oil (0.18 g, 28 %). ν_{max} (NaCl) 3622-3316 (OH), 1442, 1245, 936, 838, 767 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, J = 8 Hz, CHCH_3), 1.27-1.31 (1H, m, 6-H_a), 1.43-1.57 (3H, m, 2-H_a, 3-H_a, 4-H_a), 1.65-1.72 (2H, m, 5-H_2), 1.81-1.84 (1H, m, 3-H_a), 1.86-1.92 (1H, m, 6-H_b), 1.97-2.00 (1H, m, 2-H_b), 2.10-2.14 (1H, m, 4-H_b), 2.28-2.32 (1H, m, 7-*H*), 3.14 (1H, br s, OH), 3.38 (1H, m, br s, OH), 4.25 (1H, br s, 1-*H*), 5.63 (1H, d, J = 4 Hz, 9-*H*); δ_C (100 MHz, $CDCl_3$) 16.1 (C-3), 20.1 ($CHCH_3$), 27.1 (C-6), 29.9 (C-7), 34.4 (C-2), 35.8 (C-5), 40.4 (C-4), 70.9 (C-4$_a$), 74.8 (C-1), 133.1 (C-9), 138.6 (C-8$_a$); *m/z* (EI) 178 (55%) 163 (M-OH)$^+$ (45 %), 136 (100 %), 104 (60 %), 91 (70 %)

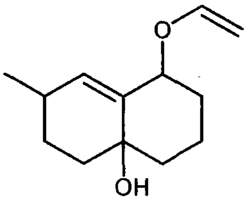
1-Acetoxy-4a-hydroxy-7-methyl-1,2,3,4,4a,5,6,7-octahydronaphthalene



573

Acetic anhydride (0.11 ml, 1.4 mmol) was added dropwise to a cooled (0 °C) solution of diol **572** (0.20 g, 1.10 mmol), triethylamine (0.54 ml, 3.8 mmol) and DMAP (0.01 g, 0.1 mmol) in DCM (15 ml). The mixture was stirred at 0 °C for 1 h and was quenched with water (10 ml). The organic layer was then washed with 10 % aq HCl and the layers separated. The aqueous layer was further extracted with DCM (3 x 15 ml) and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to yield the title compound as a colourless oil (0.20 g, 86 %). ν_{max} (NaCl) 3644-3336 (OH), 1731, 1454, 1371, 1233, 900, 866 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 0.97 (3H, d, J = 8 Hz, CHCH$_3$), 1.27-1.35 (1H, m, 6-H_a), 1.39-1.42 (1H, m, 2-*H*), 1.50-1.63 (3H, m, 3-H_a, 4-H_a, 5-H_a), 1.70-1.72 (1H, m, 4-H_b), 1.87-2.03 (4H, m, 2-H_b, 3-H_b, 5-H_b, 6-H_b), 2.08 (3H, s, C=OCH_3), 2.29-2.38 (1H, m, 7-*H*), 5.40 (1H, m, 1-*H*), 5.82 (1H, d, J = 4 Hz, 8-*H*); δ_C (100 MHz, CDCl$_3$) 16.5 (C-3), 19.5 (CHCH$_3$), 21.9 (C=OCH$_3$), 25.9 (C-6), 29.8 (C-7), 31.6 (C-5), 34.5 (C-4), 40.1 (C-2), 69.1 (C-4$_a$), 78.2 (C-1), 134.9 (C-8), 137.7 (C-8$_a$), 169.9 (C=OCH$_3$); *m/z* (ES+) 247 (MNa)$^+$, 288 (MNaMeCN)$^+$; HRMS (ES+) Found MNaMeCN$^+$; 288.1572 ; $C_{15}H_{23}O_3NNa$ requires 288.1570

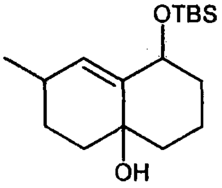
7-Methyl-1-vinyloxy-1,2,3,4,4a,5,6,7-octahydro-2H-naphthalen-4a-ol



592

To a stirred solution of diol **572** (0.20 g, 1.1 mmol) in ethyl vinyl ether (5 ml) was added mercury acetate (0.23 g, 0.7 mmol). After stirring for 15 h at reflux the reaction mixture was diluted with ethyl acetate (15 ml) and washed with 5 % NaOH (10 ml). The layers were separated and the aqueous was re-extracted with ethyl acetate (2 x 15 ml). The combined organic extracts were washed with brine, dried over magnesium sulphate and the solvent removed under reduced pressure. The residue was purified by column chromatography eluting with 10 % ethyl acetate in petroleum ether to yield the title compound as a colourless oil (0.02 g, 9 %). ν_{max} (NaCl) 3599-3198 (OH), 1470, 1247, 989, 836, 777 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 0.97 (3H, d, J = 7 Hz, 7′-CH_3), 1.37-1.62 (2H, m, 4-H_2), 1.48-1.49 (H, m, 2-H_a), 1.67-1.75 (2H, m, 6-H_2), 1.82-1.86 (2H, m, 3-H_2), 1.89-2.00 (2H, m, 7-H_2), 2.01-2.13 (1H, m, 2-H_b), 2.32-2.38 (1H, m, 7-*H*), 4.07 (1H, m, 1-H), 4.24 (1H, dd, J = 2, 6 Hz, OCH=CH_a), 4.36 (1H, dd, J = 2, 14 Hz, OCH=CH_b), 5.66 (1H, d, J = 4 Hz, 8-*H*), 5.24 (1H, dd, J = 6, 14 Hz, OC*H*=CH$_2$); δ_C (100 MHz, CDCl$_3$) 16.3 (C-3), 18.8 (CHCH$_3$), 26.4 (C-4), 29.9 (C-7), 31.7 (C-2), 34.7 (C-5), 40.4 (C-6), 69.5 (C-4$_a$), 82.9 (C-1), 90.5 (CH=CH$_2$), 135.7 (C-8), 135.8 (C-8$_a$), 149.8 (CH=CH$_2$); *m/z* (EI) 208 (M-OH)$^+$ (10 %), 164 (58 %),, 104 (76 %), 91 (96 %), 81 (100 %), 78 (98 %)

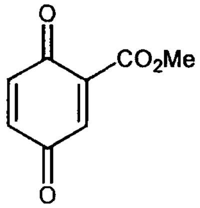
1-(^{t}Butyldimethylsilanyloxy)-7-methyl-1,2,3,4,4a,5,6,7-octahydro-2H-naphthalen-4a-ol



603

To a stirred solution of diol **572** (0.20 g, 1.1 mmol) in dimethylformamide (3 ml) was added imidazole (0.30 g, 4.4 mmol) and TBSCl (0.19 g, 1.4 mmol) and the reaction stirred at room temperature for 15 h. After which time ammonium chloride (5 ml) and diethyl ether (20 ml) were added. The layers were separated and the aqueous layer was further extracted with diethyl ether (2 x 15 ml). The combined organic layers were washed with brine (2 x 20 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (0.19 g, 57 %). ν_{max} (NaCl) 3606-3266 (OH), 1471, 1253, 1047, 836, 777 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, 2 x $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.92 (3H, d, J = 7 Hz, $CHCH_3$), 1.17-1.24 (1H, m, 6-H_a), 1.34-1.49 (4H, m, 3-H_2, 4-H_2), 1.57-1.72 (1H, m, 2-H_a), 1.75-1.89 (3H, m, 5-H_2, 6-H_b), 2.11-2.16 (1H, m, 2-H_b), 2.24-2.27 (1H, m, 7-*H*), 4.24 (1H, m, 1-*H*), 4.49 (1H, br s, O*H*), 5.47 (1H, d, J = 4 Hz, 8-*H*); δ_C (100 MHz, $CDCl_3$) -4.6 (2 x $SiCH_3$), 16.3 (C-3), 18.2 (C-5), 20.2 ($CHCH_3$), 25.9 ($SiC(CH_3)_3$), 27.2 (C-6) 30.0 ($SiC(CH_3)_3$), 35.1 (C-4), 35.3 (C-5), 40.9 (C-2), 70.3 (C-4_a), 76.1 (C-1), 131.5 (C-8), 138.6 (C-8_a); *m/z* (ES+) 296 $(MH)^+$; HRMS (ES+) Found MNa^+; 319.2065; $C_{17}H_{32}O_2SiNa$ requires 319.2064

3,6-Dioxocyclohexa-1,4-dienecarboxylic acid methyl ester[152]

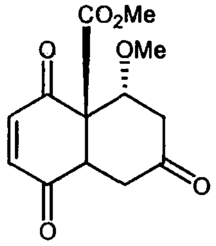


618

To a stirred solution of 2,5-dihydroxybenzoic acid methyl ester (1.00 g, 6.0 mmol) and sodium sulfate (1.50 g, 10.6 mmol) was added manganese dioxide (5.24 g, 60.0 mmol) and was stirred at room temperature for 2 h. The reaction mixture was then filtered through a pad of Celite© and concentrated under reduced pressure. The title compound was obtained as an orange oil which was used without subsequent purification (0.53 g, 53 %). ν_{max} 1744, 1667, 1438, 1267, 1248, 1047, 898 cm^{-1}; δ_H (400

MHz, $CDCl_3$) 3.92 (3H, s, OMe), 6.83 (2H, d, J = 1 Hz), 7.12 (1H, t, J = 1 Hz); δ_c (100 MHz, $CDsCl_3$) 53.1 (OCH_3), 136.5, 136.9, 137.1 (C-2, C-4, C-5), 163.1 (C-1), 182.9, 186.8 (C-3, C-6)

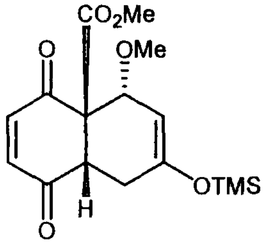
(4aRS,5RS,8aSR)-4-Methoxy-2,5,8-trioxo-1,3,4,5,8,8a-hexahydro-2H-naphthalene-4a-carboxylic acid methyl ester



622

$Et_3N.3HF$ (0.34 ml, 2.09 mmol) was added to a stirred solution of silyl enol ether **633** (0.10 g, 0.3 mmol) in THF (5 ml) at 0 °C for 30 minutes. After which time the reaction mixture was passed through a plug of silica gel and the filtrate was concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 50 % ethyl acetate in petroleum ether to yield the title compound as an off white solid (0.03 g, 40 %). m.p. 68-69 °C; v_{max} (NaCl) 1746 (C=O), 1382, 1218, 1110, 898, 845 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.17-2.22 (1H, m, 3-*H*a), 2.77-2.80 (2H, m, 1-*H*2), 3.14 (3H, s, OCH_3), 3.23 (1H, dt, J = 2, 15 Hz, 3-*H*b) 3.88 (3H, s, OCH_3), 3.97 (1H, dd, J = 2, 6 Hz, 8a-*H*), 4.34 (1H, m, 4-*H*), 6.73 (1H, d, J = 10 Hz), 6.89 (1H, d, J = 10 Hz); δ_c (100 MHz, $CDCl_3$) 36.7 (C-3), 41.9 (C-1), 48.5 (C-8a), 53.9 (OCH_3), 57.1 (OCH_3), 63.7 (C-4a), 82.2 (C-4), 139.5, 142.6 (C-6, C-7), 168.5 (CO_2Me), 193.8, 194.4 (C-5, C-8), 204.3 (C-2); *m/z* (ES+) 284 $(MNa)^+$

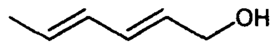
(4aRS,5RS,8aSR)-5-Methoxy-1,4-dioxo-7-trimethylsilanyloxy-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester



633

To cooled (0 °C), stirred solution of quinone **618** (0.30 g, 1.8 mmol) in toluene (10 ml) was added Danishefsky's diene (0.45 g, 2.3 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1h before warming to room temperature and concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with 10 % ethyl acetate in petroleum ether to yield the title compound as a colourless oil (0.39 g, 66 %). ν_{max} (NaCl) 1746 (C=O), 1684 (C=O), 1375, 1212, 1089, 878, 845 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.23 (9H, s, Si(CH_3)$_3$), 2.03-2.08 (1H, dd, J = 8, 18 Hz, 8-H_a), 3.00 (1H, d, J = 18 Hz, 8-H_b), 3.10 (3H, s, OCH_3), 3.79 (3H, s, CO_2CH_3), 3.80 (1H, m, 8a-*H*), 4.46 (1H, d, J = 6 Hz, 5-*H*), 5.17 (1H, dt, J = 2, 6 Hz, 6-*H*), 6.67 (1H, d, J = 11 Hz), 6.85 (1H, d,J = 11 Hz); δ_c (100 MHz, $CDCl_3$) 0.4 (Si(CH_3)$_3$), 25.3 (C-8), 46.2 (C-8a), 53.3 (OCH_3), 55.8 (OCH_3), 63.6 (C-4a), 76.3 (C-5), 101.9 (C-6), 139.5 (C-7), 142.3, 153.3 (C-2, C-3), 168.5 (CO_2Et), 195.2, 195.8 (C-1, C-4); *m/z* (ES+) 699 (2MNa)$^+$

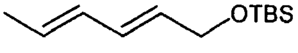
(2E,4E)-Hexa-2,4-dien-1-ol[164]



650

Ethyl sorbate (5.00 g, 35.7 mmol) in THF (20 ml) was added dropwise to a cooled (0 °C) suspension of lithium aluminium hydride (1.36 g, 35.7 mmol) in THF (110 ml). The reaction mixture was then warmed to room temperature and stirred for 1 h. The suspension was then cooled to 0 °C and water (2 ml), 1 M NaOH (1 ml) and water (2 ml) were added sequentially and the solution was filtered through a plug of Celite©. The filtrate was then diluted with diethyl ether (50 ml) and the layers separated and the aqueous layer was further extracted with diethyl ether (2 x 75 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to afford the title compound as a colourless oil (2.70 g, 77 %). ν_{max} (NaCl) 3556-3196 (OH), 1447, 1382, 990 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.76 (3H, d, J = 7 Hz, 6-H_3), 4.14 (1H, d, J = 6 Hz, 1-H_2), 5.68-5.74 (2H, m, 2-*H*, 5-*H*), 6.04 (1H, dd, J = 11, 15 Hz, 4-*H*), 6.16 (1H, dd, J = 11, 15 Hz, 3-*H*); δ_c (100 MHz, $CDCl_3$) 18.4 (C-6), 63.9 (C-1), 129.4, 130.1 (C-2, C-5), 130.9 (C-4), 131.1 (C-3), *m/z* (EI) 98 (M)$^+$,(50 %), 83 (60 %), 55 (100 %), 41 (92 %)

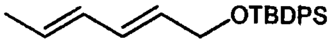
^{t}Butyl-[((2E,4E)-hexa-2,4-dienyl)oxy] dimethylsilane[165]



651

To a stirred solution of alcohol **650** (2.70 g, 27.6 mmol) in dimethylformamide (15 ml) was added imidazole (7.30 g, 109.0 mmol) and TBSCl (4.45 g, 33.0 mmol). The reaction was stirred at room temperature for 15 h and after which time ammonium chloride (25 ml) and diethyl ether (50 ml) were added. The aqueous layer was re-extracted with diethyl ether (2 x 40 ml) and the combined organic layers were washed with brine (2 x 100 ml) and dried over magnesium sulfate before concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether affording the title compound as clear oil (4.67 g, 80 %). ν_{max} (NaCl) 1471, 1259, 987, 836, 755 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 0.08 (6H, s, 2 x SiCH_3), 0.92 (9H, s, SiC(CH_3)$_3$), 1.76 (3H, d, J = 7 Hz, 6-H_3), 4.20 (1H, d, J = 6 Hz, 1-H_2), 5.62-5.71 (2H, m, 2-*H*, 5-*H*), 6.04 (1H, dd, J = 11, 15 Hz, 4-*H*), 6.16 (1H, dd, J = 11, 15 Hz, 3-*H*); δ_c (100 MHz, CDCl$_3$) -3.3 (SiCH$_3$), -4.9 (SiCH$_3$), 18.7 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 26.2 (C-6), 63.9 (C-1), 129.3, 130.1 (C-2, C-5), 130.5 (C-4), 131.2 (C-3), *m/z* (EI) 212 (M)$^+$ (3 %), 155 (73 %), 74 (100 %)

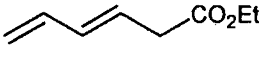
^{t}Butyl-[((2E,4E)-hexa-2,4-dienyl)oxy] diphenylsilane



652

To a stirred solution of alcohol **650** (3.20 g, 33.0 mmol) in dimethylformamide (30 ml) was added imidazole (9.00 g, 132.0 mmol) and TBDPSCl (9.84 g, 36.0 mmol). The reaction mixture was stirred at room temperature for 15 h and after which time ammonium chloride (30 ml) and diethyl ether (60 ml) were added. The layers were separated and the aqueous layer was re-extracted with diethyl ether (2 x 40 ml). The combined organic layers were washed with brine (2 x 100 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether to yield the title compound as colourless oil (10.5 g, 94 %). ν_{max} (NaCl) 1471, 1427, 1380, 1111, 988 cm^{-1}, δ_H (400 MHz, CDCl$_3$) 1.09 (9H, s, Si(CH_3)$_3$), 1.76 (3H, d, J = 7 Hz, 6-H_3), 4.24 (1H, d, J = 6 Hz, 1-H_2), 5.61-5.75 (2H, m, 2-*H*, 5-*H*), 6.02-6.32 (2H, m, 4-*H*, 3-*H*), 7.39-7.43 (6H, m, Ar-H), 7.6-7.73 (4H, m, Ar-H); δ_c (100 MHz, CDCl$_3$) 18.1 (C-6), 19.3 (SiC(CH$_3$)$_3$), 26.9 (SiC(CH$_3$)$_3$), 64.3 (C-1), 127.6 (C-Ar), 128.9, 129.5 (C-2, C-5), 129.6 (C-Ar), 130.3 (C-4), 131.1 (C-3), 133.8 (C-Ar), 135.6 (C-Ar); *m/z* (ES+) 377 (MMeCN)$^+$, 400 (MMeCNNa)$^+$

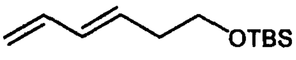
(Z)-Hexa-3,5-dienoic acid ethyl ester[166]



653

To a cooled (-78 °C) stirred solution of diisopropylamine (2.70 ml, 20.0 mmol) in THF (20 ml) was added ^{n}butyl lithium (13.0 ml, 1.4 M solution in hexanes, 18.0 mmol) and HMPA (4.32 ml, 25.0 mmol) and the resulting solution was stirred at -78 °C for 20 minutes. After this time had elapsed a solution of ethyl sorbate (1.85 g, 12.0 mmol) in THF (12 ml) was added dropwise and the mixture was stirred at -78 °C for 4 h. The reaction was quenched at -78 °C with 25 ml of 10 % (v/v) acetic acid in 1:1 THF : water and then warmed to room temperature in a water bath. The THF was removed under reduced pressure and the remaining aqueous layer was extracted with diethyl ether (3 x 40 ml).The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The oil that remained was purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (1.55 g, 84 %). ν_{max} (NaCl) 1737, 1368, 1181, 1139, 1003, 904 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 1.22 (3H, t, J = 7 Hz, OCH$_2$CH_3), 3.09 (2H, d, J = 7 Hz, 2-H_2), 4.12 (2H, q, J = 7Hz, OCH_2CH$_3$), 5.03 (1H, d, J = 10 Hz, 6-H_a), 5.13 (1H, d, J = 10 Hz, 6-H_b), 5.77 (1H, m, 3-*H*), 6.12 (1H, m, 4-*H*), 6.34 (1H, m, 5-*H*); δ_C (100 MHz, CDCl$_3$) 14.4 (OCH$_2$CH$_3$), 38.2 (C-2), 60.9 (OCH$_2$CH$_3$), 117.1 (C-6), 125.9 (C-3), 134.5 (C-4), 136.6 (C-5), 171.7 (C=O), *m/z* (EI) 141 (M)$^+$ (12 %), 112 (65 %), 86 (100 %)

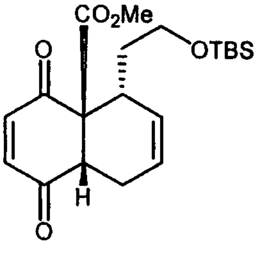
^{t}Butyl-[((E)-hexa-3,5-dienyl)oxy]-dimethylsilane[167]



654

Ester **653** (1.20 g, 8.6 mmol) in diethyl ether (7 ml) was added dropwise to a cooled (0 °C) suspension of lithium aluminium hydride (0.32 g, 8.6 mmol) in dry diethyl ether (60 ml) and the resulting mixture was stirred at room temperature for 1 h. After cooling to 0 °C, water (1 ml), 3 M NaOH (0.5 ml), water (1 ml) were added sequentially. The resulting suspension was filtered through a pad of Celite© and washed with diethyl ether. The diethyl ether extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue (0.37 g) that remained was dissolved in dimethylformamide (8 ml) and imidazole (1.19 g, 4.4 mmol) and chloro^{t}butyl dimethylsilane (0.76 g, 5.7 mmol) were added. The mixture was stirred at room temperature for 15 h. After which time diethyl ether (20 ml) and saturated ammonium chloride (10 ml) were added. The layers were separated and aqueous layer was re-extracted with diethyl ether (2 x 20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The residue that remained was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (0.48 g, 60 %). ν_{max} (NaCl) 1463, 1255, 105, 836, 755 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 0.05 (6H, s, Si(CH_3)$_2$), 0.91 (9H, s, SiC(CH_3)$_3$), 2.15 (2H, q, J = 7 Hz, 2-H_2), 3.64 (2H, t, J = 7 Hz, 1-H_2), 4.96 (1H, d, J = 10 Hz, 6-H_a), 5.08 (1H, d, 17 Hz, 6-H$_b$), 5.67-5.72 (1H, m, 3-*H*), 6.01-6.09 (1H, m, 4-*H*), 6.26-6.33 (1H, dt, J = 10, 17 Hz, 5-H); δ_c (100 MHz, CDCl$_3$) -4.9 (SiCH$_3$), -5.0 (SiCH$_3$), 18.5 (C(CH$_3$)$_3$), 26.2 (SiC(CH$_3$)$_3$), 36.4 (C-2), 63.0 (C-1), 115.5 (C-6), 131.6 (C-3), 132.9 (C-4), 137.4 (C-5); *m/z* (EI) 212 (M)$^+$ (5%), 189 (65 %), 147 (100 %), 73 (60 %)

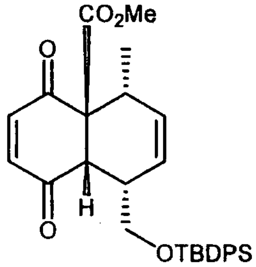
(4aSR,5RS,8aSR)-5-[2-(^{t}Butyldimethylsilanyloxy)-ethyl]-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester



655B

Diene **654** (0.20 g, 0.9 mmol) was dropwise to cooled (0 °C), stirred solution of quinone **618** (0.12 g, 0.7 mmol) in toluene (5 ml) was added. The reaction mixture was stirred at 0 °C for 2 h before warming to room temperature and concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with 15 % ethyl acetate in petroleum ether to yield the title compound as a colourless oil (0.13 g, 46 %). ν_{max} (NaCl) 1685 (C=O), 1437, 1258, 897, 753, 650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.02 (6H, s, 2 x $SiCH_3$), 0.09 (9H, s, $SiC(CH_3)_3$), 1.67-1.71 (2H, m, 1'-H_2), 2.22-2.28 (1H, m, 8-H_a), 2.46-2.53 (1H, m, 8-H_b), 2.96-2.99 (1H, m, 5-*H*), 3.58-3.63 (1H, m, 2'-*H*a), 3.64-3.68 (1H, m, 2'-H_b), 3.72 (1H, t, J = 8Hz, 8a-*H*), 3.77 (3H, s, OCH_3), 5.62-5.65 (1H, m, 6-*H*), 5.79-5.82 (1H, m, 7-*H*), 6.66 (1H, d, J = 10Hz, 2-*H*), 6.73 (1H, d, J = 10 Hz, 3-*H*); δ_c (100 MHz, $CDCl_3$) -5.10 (2 x $SiCH_3$), 18.5 ($SiC(CH_3)_3$), 23.9 (C-8), 26.1 ($SiC(CH_3)_3$), 35.1 (CH_2CH_2O), 36.5 (C-5), 49.8 (C-8a), 53.4 (OCH_3), 60.8 (CH_2CH_2O), 63.4 (C-4a), 123.2 (C-6), 128.6 (C-7), 138.9 (C-2), 140.9 (C-3), 171.1 (CO_2Me), 195.9 (C-1), 198.3 (C-4), (ES+) 378 $(M)^+$; HRMS Found M^+; 379.1935; $C_{20}H_{30}O_5Si$ requires 379.1935

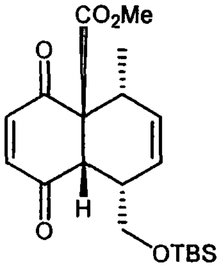
(1SR,4RS,4aSR,8aSR)-1-(^{t}Butyldiphenylsilanyloxymethyl)-4-methyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester



665

Diene **652** (0.49 g, 1.5 mmol) in DCM (0.75 ml) was added dropwise to a cooled (-78 °C) stirred solution of quinone **618** (0.20 g, 1.2 mmol) and ytterbium triflate (0.29 g, 0.6 mmol) in DCM (15 ml). The mixture was stirred at -78 °C for 16 h and was then quenched with saturated sodium hydrogen carbonate (15 ml). The layers were separated and the aqueous layer was re extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The residue that remained was purified by column chromotagraphy eluting with 10 % ethyl acetate in petroleum ether to yield title compound as light yellow oil (0.16 g, 27 %). ν_{max} (NaCl) 1747 (C=O), 1682 (C=O), 1074, 902, 729 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, J = 8 Hz, $CHCH_3$), 1.04 (9H, s, $SiC(CH_3)_3$), 2.43-2.47 (1H, m 1-*H*), 3.18-3.21 (1H, m, 4-*H*), 3.80 (3H, s, OCH_3), 3.93-3.96 (1H, dd, J = 3, 8 Hz, CH_aO), 3.99 (1H, d, J = 5 Hz, 8a-*H*), 4.08-4.12 (1H, dd, J = 3, 8 Hz, CH_bO), 5.54-5.56 (1H, m, 2-*H*), 5.59-5.63 (1H, dt, J = 3, 11 Hz, 3-*H*), 6.64 (1H, d, J = 11 Hz, 7-*H*), 6.3 (1H, d, J = 11 Hz, 6-*H*), 7.38-7.44 (6H, m, Ar-*H*), 7.62-7.64 (4H, m, Ar-H); δ_c (100 MHz, $CDCl_3$) 18.9 ($CHCH_3$), 19.5 ($SiC(CH_3)_3$), 27.0 ($SiC(CH_3)_3$), 24.7 (C-4), 38.7 (C-1), 49.2 (C-8a), 53.5 (OCH_3), 64.1 (CH_2O), 64.3 (C-4a), 124.3 (C-2), 127.9 (C-Ar), 128.0 (C-Ar), 129.9 (C-Ar), 130.0 (C-3), 130.6 (C-Ar), 135.7 (C-Ar), 135.8 (C-Ar), 139.1 (C-6), 142.7 (C-7), 170.7 (CO_2Me), 196.8 (C-5), 197.9 (C-8); *m/z* (ES+) 503 $(MH)^+$, 520 $(MOH_2)^+$, 1029$(2MNa)^+$; HRMS (ES+) Found MH^+; 503.2242; $C_{30}H_{32}O_5Si$ requires 503.2248

(1SR,4RS,4aSR,8aSR)-1-(^{t}Butyldimethysilanyloxymethyl)-4-methyl-5,8-dioxo-1,5,8,8a-tetra hydro-4H-naphthalene-4a-carboxylic acid methyl ester

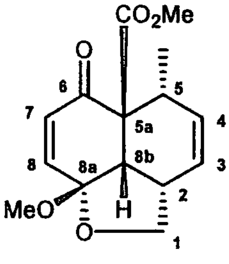


666

Diene **651** (3.18 g, 14.9 mmol) in DCM (2 ml) was added dropwise to a cooled (-78 °C) stirred solution of quinone **618** (2.23 g, 13.4 mmol) and ytterbium triflate (0.42 g, 0.7 mmol) in DCM (120 ml). The mixture was stirred at -78 °C for 16 h and was then quenched with saturated sodium hydrogen carbonate (40 ml). The layers were separated and the aqueous layer was re-extracted with DCM (3 x 70 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The residue that remained was purified by column chromotagraphy eluting with 10 % ethyl acetate in petroleum ether to afford the title compound as light yellow oil (3.46 g, 68 %). ν_{max} (NaCl) 1747 (C=O), 1682 (C=O), 1258, 943, 837 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.02 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, d, J = 8 Hz, $CHCH_3$), 2.37-2.41 (1H, m 1-*H*), 3.13-3.16 (1H, m, 4-*H*), 3.79 (3H, s, OCH_3), 3.85-3.94 (3H, m, CH_2O, 8a-*H*), 5.57-5.59 (1H, m, 2-*H*), 5.63 (1H, dt, J = 3, 10 Hz, 3-*H*), 6.66 (1H, d, J = 10 Hz, 7-*H*), 6.74 (1H, d, J = 10 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) -5.2 (2 x $SiCH_3$), 18.4 ($SiC(CH_3)_3$), 18.7 ($CHCH_3$), 26.1 ($SiC(CH_3)_3$), 34.8 (C-4), 38.8 (C-1), 49.6 (C-8a), 53.5 (OCH_3), 63.5 (CH_2O), 63.9 (C-4a), 124.5 (C-2), 130.7 (C-3), 139.2

(C-7), 142.6 (C-6), 170.8 (CO_2Me), 197.4 (C-5), 197.9 (C-8); *m/z* (ES+) 378 $(M)^+$; HRMS Found MH^+; 379.1932; $C_{20}H_{30}O_5Si$ requires 379.1935

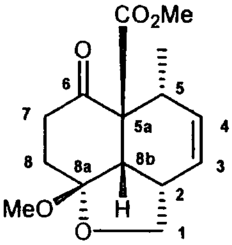
(2aSR,5RS,5aSR,8aRS,8bSR)-8a-Methoxy-5-methyl-6-oxo-2a,6,8a,8b-tetrahydro-2H,5H-naphtho[1,8-bc]furan-5a-carboxylic acid methyl ester



671

p-Toluenesulfonic acid (0.09 g, 0.5 mmol) was added to a stirred solution of silyl ether **666** (0.50 g, 1.8 mmol) in methanol (10 ml) and stirred at room temperature for 15 h. After which time saturated sodium hydrogen carbonate (10 ml) and ethyl acetate (15 ml) were added. The layers were separated and the aqueous later was further extracted with ethyl acetate (3 x 15 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The remaining residue was purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to yield the title compound as bright yellow oil (0.27 g, 74 %). ν_{max} (NaCl) 1708 (C=O), 1498, 1383, 1105, 922, 905, 728 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30-1.31 (3H, d, J= 7 Hz, $CHCH_3$), 2.56-2.58 (1H, m, 5-*H*) 3.08-3.09 (2H, m, 1-H_a, 2-*H*), 3.45 (3H, s, OCH_3), 3.59-3.62 (1H, m, 8b-*H*), 3.75 (3H, s, OCH_3), 4.12-4.17 (1H, m, 1-H_b), 5.49-5.56 (1H, dt, J = 2, 10 Hz, 3-*H*), 5.82-5.85 (1H, dt, J = 2, 10 Hz, 4-*H*), 6.16-6.18 (1H, d, J= 10 Hz, 7-*H*), 6.45-6.74 (1H, d, J= 10 Hz, 8-*H*), δ_c (100 MHz, $CDCl_3$) 16.8 ($CHCH_3$), 37.3 (C-5), 37.8 (C-2), 46.7 (C-8b), 49.7 (OCH_3), 53.0 (OCH_3), 58.1 (C-5a), 69.4 (C-1), 103.7 (C-8a), 124.5 (C-3), 132.1 (C-7), 134.9 (C-4), 140.9 (C-8), 172.6 (CO_2CH_3), 196.3 (C-6), *m/z* (ES+) 301 $(MNa)^+$, HRMS (ES+) Found MNa^+; 301.1049; $C_{15}H_{18}O_5Na$ requires 301.1047

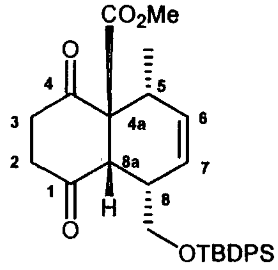
(2aSR,5RS,5aSR,8aRS,8bSR)-8a-Methoxy-5-methyl-6-oxo-2a,6,7,8,8a,8b-hexahydro-2H,5H-naphtho[1,8-bc]furan-5a-carboxylic acid methyl ester



674

To a stirred solution of silyl ether **677** (0.55 g, 1.5 mmol) in methanol (30 ml) was added p-toluenesulfonic acid (0.07 g, 0.4 mmol). The reaction mixture was stirred at room temperature for 15 h before the addition of saturated sodium hydrogen carbonate (10 ml) and ethyl acetate (30 ml). The layers were separated and the aqueous later was further extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The remaining residue was purified by column chromatography eluting with 25 % ethyl acetate in petroleum ether to give the title compound as an off white solid (0.33 g, 76 %). m.p. 97-99 °C; ν_{max} (NaCl) 1751 (C=O), 1715 (C=O), 1470, 1256, 1216, 1096, 907, 837 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, J = 8 Hz, 5-CH_3), 1.78-1.83 (1H, m, 7-H_a), 2.22-2.37 (3H, m, 5-*H*, 7-H_b, 8-H_a), 2.54-2.59 (1H, dd, J = 8, 12 Hz, 8-H_b), 3.10-3.14 (1H, m, 2-*H*), 3.25 (3H, s, OCH_3), 3.54-3.58 (2H, m, 1-H_a, 8b-*H*), 3.82 (3H, s, OCH_3), 4.11-4.13 (1H, t, J = 9 Hz, 1-H_b), 5.50-5.52 (1H, dt, J = 3, 10 Hz, 4-*H*), 5.76-5.78 (1H, dt, J = 3, 10 Hz, 3-*H*); δ_c (100 MHz, $CDCl_3$) 16.2 (5-CH_3), 26.4 (C-5), 35.7, 35.9, 38.0 (*C*-2, *C*-7, *C*-8), 48.9 (OCH_3), 53.0 (OCH_3), 53.4 (C-5b), 61.8 (C-5a), 72.7 (C-1), 108.7 (C-8a), 126.4, 134.0 (C-3, C-4), 173.2 (CO_2CH_3), 206.7 (C-6); *m/z* (ES)+ 303 $(MNa)^+$, 345 $(MNaMeCN)^+$

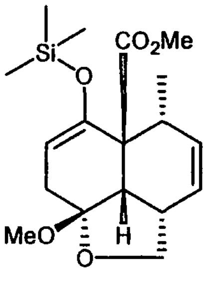
(4aSR,5RS,8SR,8aSR)-8-(^{t}Butyldiphenylsilanyloxymethyl)-5-methyl-1,4-dioxo-1,3,4,5,8,8a-hexahydro-2H-naphthalene-4a-carboxylic acid methyl ester



677

A solution of diene **665** (2.00 g, 4.0 mmol) in ethyl acetate : ethanol (1:1) (80 ml) was passed through the H-Cube™ (Pd/C cat cart at 0.05 mmol/1mlmin^{-1} flow rate) and then concentrated under reduced pressure. The title compound was obtained without further purification as white solid (2 g, 99 %). m.p. 82-84 °C; IR (NaCl) 1751 (C=O), 1715 (C=O), 1470, 1256, 1216, 1096, 907, 837 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, J = 8 Hz, CHCH_3), 1.06 (9H, s, SiC(CH_3)$_3$), 2.18-2.40 (1H, m, 8-*H*), 2.45-2.52 (1H, m, 2-H_a), 2.66-2.74 (2H, m, 3-H_2), 3.24-3.31 (2H, m, 2-H_b, 5-*H*), 3.79 (3H, s, OCH_3), 3.95 (1H, d, J = 6 Hz, 8a-*H*), 3.99-4.03 (1H, dd, J = 2, 7 Hz, CH_aO), 4.11-4.12 (1H, m, CH_bO), 5.52-5.60 (2H, m, 2-H_2, 3-H_2), 7.33-7.44 (6H, m, Ar-*H*), 7.63-7.66 (4H, m, Ar-H); δ_c (100 MHz, $CDCl_3$) 17.4 ($CHCH_3$), 19.5 (SiC(CH_3)$_3$), 27.1 (SiC(CH_3)$_3$), 34.0, 35.4 (C-2, C-3), 37.7 (C-5), 37.9 (C-8), 47.4 (C-8a), 53.6 (OCH_3), 62.7 (C-4a), 64.5 (CH_2O), 123.9 (C-6), 127.9 (C-Ar), 128.0 (C-Ar), 129.9 (C-Ar), 130.0 (C-7), 133.8 (C-Ar), 133.9 (C-Ar), 135.7 (C-Ar), 135.8 (C-Ar), 170.2 (CO_2CH_3), 206.8, 207.3 (C-1, C-4); *m/z* (ES+) 505 $(MH)^+$

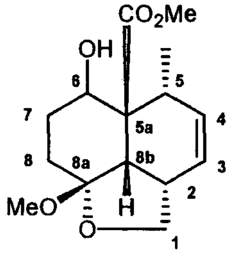
(2aSR,5RS,5aSR,8aRS,8bSR)-8a-Methoxy-5-methyl-6-trimethylsilanyloxy-2a,8,8a,8b-tetrahydro-2H,5H-naphtho[1,8-bc]furan-5a-carboxylic acid methyl ester



678

Ketone **674** (0.10 g, 0.4 mmol) in THF (0.5 ml) was added dropwise to a stirred solution of lithium diisopropylamine (1.4 ml, 1.4 mmol, 1 M in THF) in THF (3 ml) at -78 °C and stirred for 1½ h. After which time chlorotrimethylsilane (0.05 ml, 0.44 mmol) was added dropwise and the reaction mixture was stirred for a further 20 mins. After which time petroleum diethyl ether (5 ml) was added and the reaction was warmed to room temperature. The suspension that remained was filtered through a plug of Celite© and the filtrate was concentrated under reduced pressure to afford the title compound as a colourless oil (0.08 g, 62 %). δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, J = 8 Hz, 5-CH_3), 2.22-2.37 (2H, m, 5-*H*, 8-H_a), 2.54-2.59 (1H, dd, J = 8, 12 Hz, 8-H_b), 3.10-3.14 (1H, m, 2-*H*), 3.25 (3H, s, OCH_3), 3.54-3.58 (2H, m, 1-H_a, 8b-*H*), 3.82 (3H, s, OCH_3), 4.11-4.13 (1H, t, J = 9 Hz, 1-H_b), 4.78 (1H, m, 7-*H*), 5.50-5.52 (1H, dt, J = 3, 10 Hz, 4-*H*), 5.76-5.78 (1H, dt, J = 3, 10 Hz, 3-*H*)

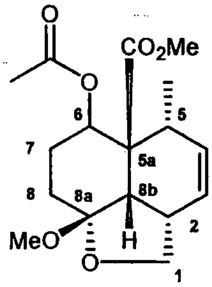
(2aSR,5RS,5aSR,8aRS,8bSR)-6-Hydroxy-8a-methoxy-5-methyl-2a,6,7,8,8a,8b-hexahydro-2H,5H-naphtho[1,8-bc]furan-5a-carboxylic acid methyl ester



679

To a stirred solution of ketone **674** (0.05 g, 0.2 mmol) in methanol (3 ml) was added sodium borohydride (0.01 g, 0.4 mmol) and the mixture was stirred for 2h. Additional sodium borohydride (0.01 g, 0.4 mmol) was then added and the mixture stirred at room temperature for a 2 h. The reaction was then quenched with water (1 ml) and diluted with ethyl acetate (7 ml). The layers were separated and the aqueous layer was re-extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with brine and concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 30 % ethyl acetate in petroleum ether yielded the title compound as a light yellow oil (0.02 g, 42 %). ν_{max} (NaCl) 3686-3576 (OH), 1724 (C=O), 1653, 1251, 1001, 927 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, J = 7 Hz, 5-CH_3), 1.48-1.54 (1H, m, 8-H_b), 1.61-1.67 (1H, dt, J = 5, 13 Hz, 8-H_a), 1.72-1.79 (1H, dt, J = 5, 13 Hz, 7-H_a), 1.85-1.91 (1H, m, 7-H_b), 2.27-2.34 (1H, m, 5-*H*), 2.71-2.77 (1H, m, 8-*H*), 3.09-3.12 (1H, d, J = 10 Hz, 8b-*H*), 3.15 (3H, s, OCH_3), 3.65-3.66 (1H, m, O*H*), 3.67 (3H, s, OCH_3), 4.03-4.06 (1H, dd, J = 4, 9 Hz, 1-H_a), 4.38-4.42 (1H, t, J = 8 Hz, 1-H_b), 4.48-4.49 (1H, d, J = 4 Hz, 6-*H*), 5.44-5.48 (1H, dt, J = 3, 10 Hz, 3-*H*), 5.57-5.61 (1H, dt, J = 3, 10 Hz, 4-*H*); δ_c (100 MHz, $CDCl_3$) 18.0 ($CHCH_3$), 27.6, 28.3 (C-7, C-8), 32.9, 34.8 (C-2, C-5), 49.9 (OCH_3), 50.8 (C-8b), 52.1 (OCH_3), 58.7 (C-5a), 74.8 (C-1), 79.4 (C-6), 119.1 (C-8a), 127.9, 131.5 (C-3, C-4), 175.8 (CO_2CH_3), *m/z* (ES+) 305 $(MNa)^+$, 346 $(MNaMeCN)^+$

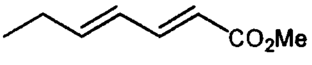
(2SR,5RS,5aSR,8aRS,8bSR)-6-Acetoxy-8a-methoxy-5-methyl-2a,6,7,8,8a,8b-hexahydro-2H,5H-naphtho[1,8-bc]furan-5a-carboxylic acid methyl ester



681

Acetic anhydride (19 µl, 0.19 mmol) was added dropwise to a solution of alcohol 679 (0.05 g, 0.17 mmol), triethylamine (122 µl, 0.88 mmol) and DMAP (2 mg) in DCM (3 ml) at 0 °C was added. The mixture was stirred at 0 °C for 1 h and was quenched with water (7 ml). The organic layer was then washed with 10 % aq HCl and the aqueous layer was further extracted with DCM (3 x 8 ml). The combined organic layers were washed with brine and dried over magnesium sulfate before concentrating under reduced pressure. The residue that remained was purified by column chromatography eluting with 20 % ethyl acetate in petroleum ether to give the title compound as colourless oil (0.01 g, 17 %). ν_{max} (NaCl) 1726 (C=O), 1231, 1038, 926 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, J = 7 Hz, 5-CH_3), 1.16-1.22 (1H, m, 7-H_a), 1.52-1.61 (1H, m, 7-H_b), 1.93 (3H, s, COCH_3), 2.10-2.18 (1H, m, 8-H_a), 2.29-2.34 (1H, m, 8-H_b), 2.46-2.52 (1H, m, 5-*H*), 3.22 (3H, s, OCH_3), 3.30-3.32 (2H, m, 2-*H*, 8b-*H*), 3.66-3.70 (1H, m, 1-H_a), 3.74 (3H, s, OCH_3), 4.16-4.20 (1H, m, 1-H_b), 5.40-5.42 (1H, m, 3-*H*), 5.58-5.64 (2H, m, 4-*H*, 6-*H*); δ_c (100 MHz, $CDCl_3$) 15.9 ($CHCH_3$), 21.8 ($COCH_3$), 24.7 (C-8), 26.9 (C-7), 35.3 (C-5), 37.4 (C-2), 46.2 (C-8b), 48.6 (OCH_3), 50.3 (C-5a), 53.0 (OCH_3), 67.8 (C-6), 73.0 (C-1), 109.7 (C-8a), 125.3, 129.8 (C-3, C-4), 169.9 (CH_3C=O), 176.2 (CO_2Me); *m/z* (ES+) 347 $(MNa)^+$

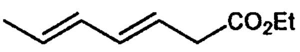
(2E,4E)-Hepta-2,4-dienoic acid methyl ester[168]



682

To a stirred solution of carboxymethyl phosphonium bromide (20.70 g, 59.5 mmol) in DCM (125 ml) was added (E)-pent-2-enal (4.40 g, 59.5 mmol) dropwise. The solution was stirred at room temperature for 6 h and then the solvent was removed under reduced pressure. The residue that remained was washed with petroleum ether and filtered, the filtrate was then concentrated and the oil that remained was purified by Kugelrohr distillation (125 °C, 0.8 mbar) to afford a colourless oil (4.91 g, 59 %). ν_{max} (NaCl) 1739 (C=O), 1185, 1030, 950 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.02-1.05 (3H, t, J = 7 Hz, 7-CH_3), 2.15-2.21 (2H, m, 6-H_2), 3.72 (3H, s, OCH_3), 5.76-5.80 (1H, d, J = 15 Hz, 5-*H*), 6.15-6.17 (2H, m, 3-*H*, 4-*H*), 7.23-7.29 (1H, m, 2-*H*); δ_c (100 MHz, $CDCl_3$) 13.1 (CH_2CH_3), 26.3 (CH_2CH_3), 51.7 (OCH_3), 118.9 (C-5), 127.6 (C-4), 145.7 (C-2), 146.4 (C-3), 167.9 (CO_2CH_3); *m/z* (EI) 140 (M)$^+$ (85 %), 110 (100 %), 79 (90 %), 53 (70 %)

(3E, 5E)-Hepta-3,5-dienoic acid ethyl ester[169]



685

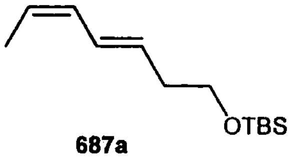
To diene **686** (0.20 g, 1.4 mmol) in toluene (4 ml) was added a single crystal of iodine. The mixture was exposed to artificial light for 36 h. After this time had elapsed the solvent was removed under reduced pressure and the title compound was afforded as light yellow oil (0.19 g, 95 %). ν_{max} (NaCl) 1706 (C=O), 1638, 1436, 1309, 1271, 1146, 999, 747 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, J = 7 Hz, OCH_2CH_3), 1.74 (3H, d, J = 7 Hz, 7-H_3), 3.08 (2H, q, J = 7 Hz, OCH_2CH_3), 4.13-4.17 (2H, d, J = 8 Hz, 1-H_2), 5.61-5.70 (2H, m, 3-*H*, 5-*H*), 6.03-6.17 (2H, m, 4-*H*, 6-*H*), δ_c (100 MHz, $CDCl_3$) 14.4 (*C*-7), 18.3 (OCH_2CH_3), 60.9 (OCH_2CH_3), 122.5, 129.4 (C-4, C-6), 131.1, 134.1 (C-3, C-5), 172.1 (CO_2Et), *m/z* (EI) 226 (M)$^+$ (9 %), 211 (22 %), 169 (100 %), 74 (89 %)

(3E, 5Z)-Hepta-3,5-dienoic acid methyl ester[169]

686

Diene **682** (2.50 g, 17.9 mmol) in THF (12 ml) was added dropwise to a cooled (-78 °C) stirred solution of sodium hexamethyldisilazide (6.20 g, 36.7 mmol) in THF (90 ml) and the mixture was stirred at -78 °C for 4 h. The reaction was quenched at -78 °C with 30 ml of 10 % (v/v) acetic acid in 1:1 THF : water and then warmed to room temperature in a water bath. The THF was removed under reduced pressure and the remaining aqueous layer was extracted with diethyl ether (3 x 40 ml).The combined organic layers were washed with brine before drying over magnesium sulfate. The solvent was removed under reduced pressure and the oil that remained was purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to yield the title compound as a colourless oil (1.59, 64 %). ν_{max} (NaCl) 1702 (C=O), 1643, 1436, 1305, 1271, 1146, 1001, 747 cm^{-1}, δ_H (400 MHz, CDCl$_3$) 1.17 (3H, dd, J = 2, 7 Hz, 7-C*H*$_3$), 3.14 (2H, d, J = 8 Hz, 6-*H*$_2$), 3.68 (3H, s, OC*H*$_3$), 5.50 (1H, dq, J = 7, 11 Hz, 6-*H*), 5.76 (1H, dt, J = 7, 15 Hz, 3-*H*), 5.97-6.03 (1H, m, 5-*H*), 6.44 (1H, dd, J = 11, 15 Hz, 4-*H*); δ_c (100 MHz, CDCl$_3$) 13.6 (C-7), 38.3 (C-2), 52.1 (OCH$_3$), 124.6 (C-3), 126.5 (C-6), 128.8 (C-5), 129.2 (C-4), 172.4 (C-1); *m/z* (EI) 140 (M)$^+$ (90 %), 98 (81 %), 81 (100 %), 79 (95 %), 53 (81 %)

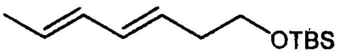
^{t}Butyl-[((3E,5Z)-hepta-3,5-dienyl)oxy] dimethylsilane



687a

Ester **686** (1.3 g, 8.6 mmol) in diethyl ether (10 ml) was added dropwise to cooled (0 °C) suspension of lithium aluminium hydride (0.32 g, 8.6 mmol) in diethyl ether (60 ml) and the resulting mixture was stirred at room temperature for 1 h. After cooling to 0 °C, water (1 ml), 3 M NaOH (0.5 ml), water (1 ml) were added sequentially. The resulting suspension was filtered through a pad of Celite© and washed with diethyl ether. The diethyl ether extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue (0.82 g) that remained was dissolved in dimethylformamide (10 ml) and imidazole (2.06 g, 30.24 mmol) and chloro^{t}butyl dimethylsilane (1.36 g, 7.56 mmol) and the mixture was stirred at room temperature for 15 h. To the mixture was added diethyl ether (20 ml) and saturated ammonium chloride (10 ml). The aqueous layer was re-extracted with diethyl ether (2 X 20 ml). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether and afforded the title compound as a colourless oil (1.38 g, 80 %). ν_{max} (NaCl) 1383, 1255, 1102, 835 cm^{-1}; δ_H (400 MHz, CDCl$_3$) -0.00 (6H, s, 2 x SiC*H*$_3$), 0.842 (9H, s, SiC(C*H*$_3$)$_3$), 1.67-1.69 (3H, dd, J = 2, 7 Hz, 7-*H*$_3$), 2.25 (2H, q, J = 7 Hz, 2-*H*$_2$), 3.59-3.62 (2H, t, J = 7 Hz, 1-*H*$_2$), 5.32-5.37 (1H, dq, J = 7, 11 Hz, 6-*H*), 5.56-5.63 (1H, dt, J = 7, 15 Hz, 3-*H*), 5.89-5.95 (1H, m, 5-*H*), 6.29-6.37 (1H, ddq, J = 1, 11, 15 Hz, 4-*H*); δ_c (100 MHz, CDCl$_3$) -3.6 (2 x SiCH$_3$), 13.2 (C-7), 18.4 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 36.3 (C-2), 63.1 (C-1), 124.5 (C-6), 127.3 (C-4), 129.4 (C-5), 130.3 (C-3); *m/z* (EI) 226 (M)$^+$ (2 %), 211 (22 %), 169 (100 %), 74 (85 %)

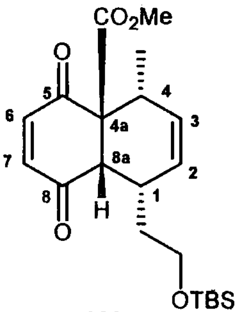
^{t}Butyl-[((3E,5E)-hepta-3,5-dienyl)oxy] dimethylsilane



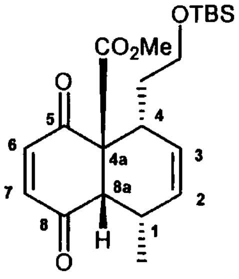
687

To diene **687a** (1.38 g, 6.1 mmol) in toluene (4 ml) was added a single crystal of iodine. The mixture was exposed to artificial light for 36 h. After this time had elapsed the solvent was removed under reduced pressure and the title compound was afforded as light yellow oil which was used without further purification (1.23 g, 89 %). ν_{max} (NaCl) 1385, 1258, 1123, 839 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 0.07 (6H, s, Si(C*H*$_3$)$_2$), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 1.74 (3H, d, J = 7 Hz, 7-C*H*$_3$), 2.30 (2H, q, J = 7 Hz, 2-*H*$_2$), 3.66 (2H, t, J = 7 Hz, 1-*H*$_2$), 5.23-5.63 (2H, m, 4-*H*, 6-*H*), 5.99-6.01 (2H, m, 3-*H*, 6-*H*), δ_c (100 MHz, CDCl$_3$) -5.0 (Si(CH$_3$)$_2$), 18.4 (SiC(CH$_3$)$_3$), 18.6 (SiC(CH$_3$)$_3$), 26.2 (C-7), 36.5 (C-2), 63.3 (C-1), 127.6, 128.1 (C-4, C-6), 131.8, 132.4 (C-3, C-6); *m/z* (EI) 226 (M)$^+$ (5 %), 211 (36 %), 169 (100 %), 74 (75 %)

(1SR,4RS,4aSR,8aSR)-1-[2-(^{t}Butyldimethylsilanyloxy)-ethyl]-4-methyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester and (1SR,4RS,4aSR,8aSR)-4-[2-(^{t}Butyldimethylsilanyloxy)-ethyl]-1-methyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester



689

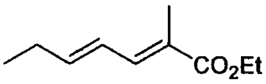


690

Diene **687** (0.13 g, 0.8 mmol) in DCM (0.75 ml) was added dropwise to a cooled (-78 °C) stirred solution of quinone **618** (0.20 g, 0.9 mmol) and ytterbium triflate (0.03 g, 5 mol %) in DCM (15 ml). The mixture was stirred at -78 °C for 16 h and was then quenched with saturated sodium hydrogen carbonate (15 ml). The layers were separated and the aqueous layer was re-extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 10 % ethyl acetate in petroleum ether to afford the title compound as a 1:1 mixtures of isomers as light yellow oil (0.14 g, 45 %). ν_{max} (NaCl)

1747 (C=O), 1703 (C=O), 1257, 1101, 899, 717 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.02 (12 H, s, 4 x $SiCH_3$), 0.87 (18 H, s, 2 x $SiC(CH_3)_3$), 0.90 (3H, d, J = 7 Hz, $CHCH_3$), 0.92 (3H, d, J = 7 Hz, $CHCH_3$), 1.76-1.81 (1H, m, 1'-H_a), 1.94-2.02 (3H, 1'-H_b, 1'-H_2), 2.33-2.36 (1H, m, 1-*H*), 2.66-2.67 (1H, m, 4-*H*), 2.71-2.75 (1H, dt, J = 3, 11 Hz, 1-*H*), 3.65-3.69 (5H, m, 2 x 2'-H_2, 8a-*H*), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.89-3.91 (1H, m, 8a-*H*), 5.58-5.73 (4H, m, 2-*H*, 3-*H*), 6.62 (1H, d, J =10 Hz, 7-*H*), 6.66 (1H, d, J =10 Hz, 7-*H*), 6.77 (1H, d, J =10 Hz, 6-*H*), 6.79 (1H, d, J =10 Hz, 6-*H*); δ_c (100 MHz, $CDCl_3$) -5.2 ($SiCH_3$), 18.4 ($SiC(CH_3)_3$), 18.5 ($CHCH_3$), 19.1 ($CHCH_3$), 26.1 ($SiC(CH_3)_3$), 30.7 (C-4), 31.5 (C-1), 33.9 (2 x C-1'), 34.2 (C-4), 34.7 (CH_2CH_2O), 36.2 (C-1), 51.1 (C-8a), 53.4 (OCH_3), 53.5 (OCH_3), 54.4 (C-8a), 60.9 (C-2'), 61.1 (C-2'), 62.3 (C-4a), 64.8 (C-4a), 127.1, 127.7, 129.3, 129.5 (2 x C-2, 2 x C-3), 139.0, 140.4, 142.9, 143.1 (2 x C-6, 2 x C-7), 170.7 (CO_2CH_3), 170.9 (CO_2CH_3), 195.7, 197.8, 198.5, 199.2 (2 x C-5, 2 x C-8); *m/z* (ES+) 329 $(MH)^+$, 415 $(MNa)^+$; HRMS (ES+) Found MH^+; 393.2094; $C_{21}H_{33}O_5Si$ requires 393.2092

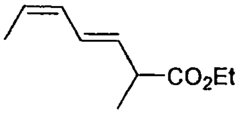
(2E, 4E)-2-Methylhepta-2,4-dienoic acid ethyl ester[170]



694a

To a stirred solution of phosphonium bromide **693** (21.50 g, 59.5 mmol) in toluene (150 ml) was added (E)-pent-2-enal (5 g, 59.5 mmol) dropwise. The solution was stirred at reflux for 16 h and then the solvent removed under reduced pressure. The residue that remained was washed with petroleum ether and filtered. The filtrate was then concentrated and the oil that remained was purified by Kugelrohr distillation (95 °C, 0.8 mbar) to afford a colourless oil (7.48 g, 76 %). ν_{max} (NaCl) 1705 (C=O), 1640, 1228, 1104, 971 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.04-1.07 (3H, t, J = 8 Hz, 7-H_3), 1.29-1.31 (3H, t, J = 7 Hz, OCH_2CH_3), 1.93 (3H, s, $CH_3C=C$), 2.19-2.23 (2H, quin, J = 7 Hz, 6-H_2), 4.19 (2H, q, J = 7 Hz, CH_2O), 6.09-6.14 (1H, m, 5-*H*), 6.31-6.36 (1H, m, 4-*H*), 7.16 (1H, d, J = 10 Hz, 3-*H*); δ_C (100 MHz, $CDCl_3$) 13.6 (CH_3CH) 14.4 (C-7), 17.6 (CH_3CH_2O), 43.4 (C-6), 60.5 (CH_2O), 125.3 (C-4), 125.3 (C-2), 138.8 (C-3), 144.7 (C-5), 168.9 (C-1); *m/z* (ES+) 169 $(MH)^+$; HRMS (ES+) Found MH^+; 169.1224; $C_{10}H_{17}O_2$ requires 169.1223

(3E, 5Z)-2-Methylhepta-3,5-dienoic acid ethyl ester

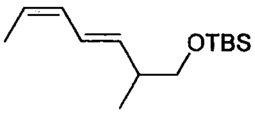


694

To a cooled solution of diisopropylamine (3.78 g, 37.4 mmol) in THF (25 ml) at -78 °C was added ^{n}butyl lithium (26.00 ml, 39.1 mmol, 1.5 M in hexanes) and after 5 minutes

HMPA (4 ml) was added. The mixture was stirred at -78 °C for 25 minutes before diene **694a** (3 g, 17.8 mmol) in THF (12 ml) was added dropwise and stirred at -78 °C for 4 h. After which time 15 ml of 10 % (v/v) acetic acid in 1:1 THF : water was added and the mixture warmed to room temperature in a water bath. The THF was removed under reduced pressure and the remaining aqueous layer was extracted with diethyl ether (3 x 40 ml).The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the oil that remained purified by column chromatography eluting with 10 % diethyl ether in petroleum ether to afford the title compound as a colourless oil (1.67 g, 42 %). ν_{max} (NaCl) 1735 (C=O), 1456, 1373, 1177 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 1.28 (3H, t, J = 7 Hz, C*H*$_3$CH$_2$), 1.29-1.31 (3H, d, J = 7 Hz, 7-*H*$_3$), 1.75-1.78 (3H, dd, J = 2, 7 Hz, CH$_3$CH), 3.19 (1H, quin, J = 7 Hz, 2-*H*), 4.14 (2H, q, J = 7 Hz, CH$_3$CH$_2$), 5.47-5.51 (1H, m, 6-*H*), 5.70-5.75 (1H, dd, J = 7, 8 Hz, 3-*H*), 5.98-6.01 (1H, t, J = 12 Hz, 5-*H*), 6.41-6.46 (1H, dd, J = 4, 10 Hz, 4-*H*); δ_c (100 MHz, CDCl$_3$) 13.6 (CH$_3$CH$_2$), 14.4 (C-7), 17.6 (CH$_3$CH), 43.4 (CH$_3$CH), 60.9 (CH$_2$O), 126.4 (C-6), 126.6 (C-4), 129.0 (C-5), 132.1 (C-3), 174.9 (C-1); *m/z* (ES+) 169 (MH)$^+$; HRMS (ES+) Found MH$^+$; 169.1223; $C_{10}H_{17}O_2$ requires 169.1221

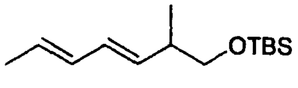
(3E, 5Z)-^{t}Butyldimethyl-(2-methyl-hepta-3,5-dienyloxy)-silane



691a

Ester **694** (1.66 g, 9.8 mmol) in diethyl ether (4 ml) was added dropwise to cooled (0 °C) suspension of lithium aluminium hydride (0.37 g, 9.8 mmol) in diethyl ether (40 ml) and the resulting mixture was stirred at room temperature for 1 h. After cooling to 0 °C, water (1 ml), 3 M NaOH (0.5 ml), water (1 ml) were added sequentially. The resulting suspension was filtered through a pad of Celite© and washed with diethyl ether. The diethyl ether extracts were dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue that remained was dissolved in dimethylformamide (7 ml) and imidazole (2.90 g, 39.2 mmol) and chloro^{t}butyl dimethylsilane (1.91 g, 12.7 mmol) and the mixture was stirred at room temperature for 3 h. To the mixture was added diethyl ether (15 ml) and saturated ammonium chloride (10 ml). The aqueous layer was re-extracted with diethyl ether (2 x 25 ml). The combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue that remained was purified by column chromatography eluting with 5 % diethyl ether in petroleum ether and afforded the title compound as a colourless oil (1.44 g, 60 %). ν_{max} (NaCl) 1471, 1255, 1112, 838, 775 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 0.06 (6H, s, 2 x SiC*H*$_3$), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 1.04 (3H, d, J = 7 Hz, CHC*H*$_3$), 1.75 (3H, dd, J = 2, 6 Hz, 7-H$_3$), 2.39 (1H, quin, J = 7 Hz, 2-H), 3.42 (1H, dd, J = 3, 7 Hz, 1-H_a), 3.52 (1H, dd, J = 3, 7 Hz, 1-H_b), 5.39-5.44 (1H, m, 6-*H*), 5.57 (1H, dd, J = 7, 7, Hz, 3-*H*), 5.96-6.01 (1H, m, 5-*H*), 6.36 (1H,dd, J = 4, 11 Hz, 4-*H*); δ_c (100 MHz, $CDCl_3$) -5.0 (2 x $SiCH_3$), 15.5 (C-7), 16.8 ($CHCH_3$), 18.3 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 39.5 (C-2), 68.2 (C-1), 124.7 (C-6), 125.2 (C-4), 129.8 (C-5), 136.8 (C-3); *m/z* (EI) 225 $(M-CH_3)^+$ (18 %), 183 (94 %), 141 (64 %), 114 (86 %), 72 (100 %), 67 (60 %)

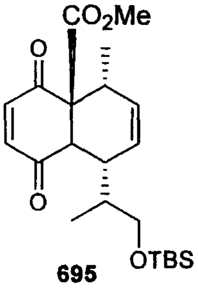
(3E, 5E)-^{t}Butyldimethyl-(2-methyl-hepta-3,5-dienyloxy)-silane[171]



691

To diene **691a** (1.44 g, 6.0 mmol) in toluene (10 ml) was added a single crystal of iodine. The mixture was exposed to artificial light for 36 h. After this time had elapsed the solvent was removed under reduced pressure and the title compound was afforded as light yellow oil which was used without further purification (1.36 g, 95 %). ν_{max} (NaCl) 1471, 1256, 1112, 839, 775cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, 2 x $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.01 (3H, d, J = 7 Hz, 2-CH_3), 1.74-1.75 (3H, m, 7-H_3), 2.33-2.41 (1H, m, 2-H), 3.47 (2H, q, J = 7 Hz, 1-H_2), 5.47-5.58 (2H, m, 3-*H*, 6-*H*), 5.99-6.05 (2H, m, 4-*H*, 5-*H*), δ_c (100 MHz, $CDCl_3$) -5.1 (2 x $SiCH_3$), 13.5 (C-7), 16.8 ($CHCH_3$), 18.6 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 39.9 (C-2), 68.2 (C-1), 124.7, 125.2, 129.8, 136.8 (C-3, C-4, C-5, C-6); *m/z* (EI) 225 $(M-CH_3)^+$ (6 %), 183 (100 %), 115 (80 %), 89 (86 %), 73 (98 %)

(1RS,4SR,4aSR,8aSR)-1-[2-(^{t}Butyldimethylsilanyloxy)-1-methyl-ethyl]-4-methyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester



695

Silver oxide (8.4 mmol) was added to a stirred solution of phenol **631** (0.20 g, 1.2 mmol) and diene **691** (0.35 g, 1.45 mmol) in DCM (7 ml) and stirred at room temperature for 18 h. After which time the mixture was filtered through a plug of Celite© and the filtrate was concentrated under reduced pressure. The residue that remained was purified by column chromatography eluting with 2.5 % diethyl ether in petroleum ether to afford the title compound as a light yellow oil (0.16 g, 32 %). ν_{max} (NaCl) 1742, 1685, 1471, 1258, 1090, 837 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.01 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.87

(9H, s, SiC(C*H*$_3$)$_3$), 0.91 (3H, d, J = 7 Hz, 4-C*H*$_3$), 1.06 (3H, d, J = 7 Hz, CHC*H*$_3$), 2.04-2.64 (1H, m, C*H*CH$_3$), 2.62-2.64 (1H, m, 4-*H*), 2.82-2.84 (1H, m, 8a-*H*), 3.29-3.63 (2H, m, C*H*$_2$O), 3.77 (3H, s, OC*H*$_3$), 5.63-5.65 (2H, m, 2-*H*, 3-*H*), 6.60 (1H, d, J = 10 Hz), 6.78 (1H, d, J = 10 Hz); δ_c (125 MHz, CDCl$_3$) -5.2 (2 x SiCH$_3$), 14.6 (CH$_3$CHCH$_2$), 16.5 (CH$_3$C-4), 18.6 (Si*C*(CH$_3$)$_3$), 26.2 (SiC(CH$_3$)$_3$), 31.1 (*C*-4), 34.0 (*C*-1), 39.9 (CH$_3$CHCH$_2$), 53.6 (*C*-8a), 54.9 (OCH$_3$), 62.9 (*C*-4a), 68.2 (CH$_2$O), 124.9, 129.6 (*C*-2, *C*-3), 140.4, 143.1 (*C*-6, *C*-7), 172.0 (CO$_2$Me), 195.7, 199.4 (*C*-5, *C*-8); *m/z* (ES+) 407 (MH)$^+$, 429 (MNa)$^+$

SECTION D :
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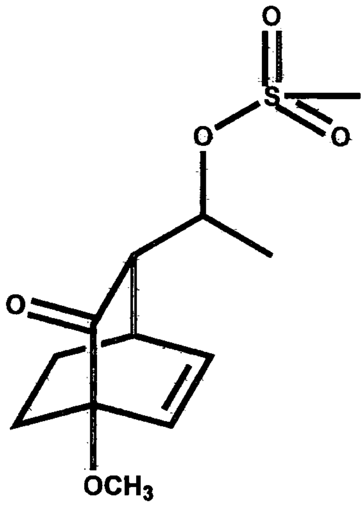
SECTION E :
APPENDIX
X-ray Crystallography Data



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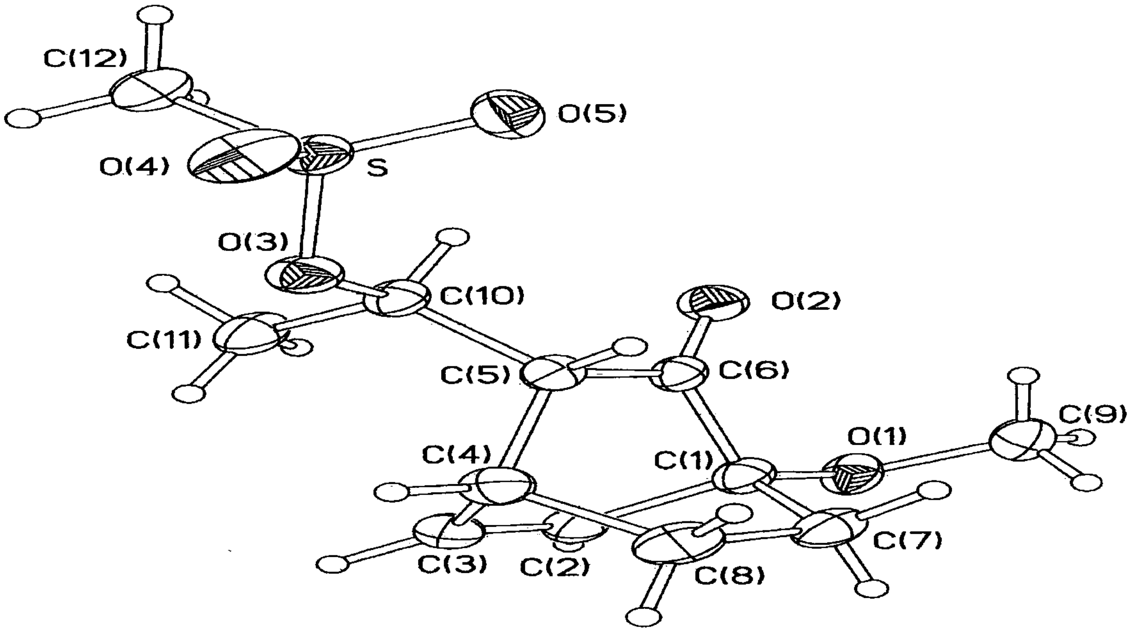


U4 SPV 337

Table 1. Crystal data and structure refinement for **372**.

Identification code	**372**	
Empirical formula	C12 H18 O5 S	
Formula weight	274.32	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 11.937(1) Å	α= 90°.
	b = 11.203(1) Å	β= 90°.
	c = 20.058(2) Å	γ = 90°.
Volume	2682.4(4) Å^3	
Z	8	
Density (calculated)	1.359 Mg/m^3	
Absorption coefficient	0.252 mm^{-1}	
F(000)	1168	
Crystal size	0.35 x 0.30 x 0.18 mm^3	
Theta range for data collection	2.03 to 30.00°.	
Index ranges	-16<=h<=16, -15<=k<=15, -28<=l<=28	
Reflections collected	35788	
Independent reflections	3911 [R(int) = 0.0528]	
Completeness to theta = 30.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3911 / 0 / 235	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.1113	
R indices (all data)	R1 = 0.0500, wR2 = 0.1193	
Largest diff. peak and hole	0.395 and -0.355 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **372**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S	7325(1)	5439(1)	3701(1)	26(1)
O(1)	3494(1)	495(1)	3454(1)	31(1)
O(2)	5089(1)	2061(1)	2940(1)	29(1)
O(3)	6103(1)	5152(1)	3953(1)	28(1)
O(4)	7864(1)	5982(1)	4260(1)	40(1)
O(5)	7804(1)	4392(1)	3414(1)	43(1)
C(1)	3872(1)	1459(1)	3852(1)	25(1)
C(2)	2922(1)	2335(1)	3940(1)	29(1)
C(3)	3174(1)	3303(1)	4289(1)	32(1)
C(4)	4363(1)	3347(1)	4545(1)	29(1)
C(5)	5182(1)	3240(1)	3951(1)	23(1)
C(6)	4769(1)	2221(1)	3508(1)	23(1)
C(7)	4324(1)	1097(1)	4547(1)	32(1)
C(8)	4535(1)	2211(1)	4977(1)	36(1)
C(9)	4258(1)	-479(1)	3383(1)	37(1)
C(10)	5387(1)	4366(1)	3543(1)	25(1)
C(11)	4362(1)	5077(1)	3352(1)	37(1)
C(12)	7127(1)	6507(1)	3079(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for **372**.

S-O(5)	1.4273(11)
S-O(4)	1.4286(10)
S-O(3)	1.5760(9)
S-C(12)	1.7456(14)
O(1)-C(1)	1.4152(15)
O(1)-C(9)	1.4300(18)
O(2)-C(6)	1.2146(15)
O(3)-C(10)	1.4773(15)
C(1)-C(2)	1.5101(18)
C(1)-C(6)	1.5337(16)
C(1)-C(7)	1.5494(18)
C(2)-C(3)	1.326(2)
C(2)-H(2)	0.935(19)
C(3)-C(4)	1.5103(19)
C(3)-H(3)	0.996(18)
C(4)-C(5)	1.5465(17)
C(4)-C(8)	1.553(2)
C(4)-H(4)	0.955(18)
C(5)-C(10)	1.5231(17)
C(5)-C(6)	1.5271(17)
C(5)-H(5)	0.946(18)
C(7)-C(8)	1.537(2)
C(7)-H(71)	0.916(19)
C(7)-H(72)	0.963(19)
C(8)-H(81)	1.01(2)
C(8)-H(82)	0.97(2)
C(9)-H(91)	0.940(19)
C(9)-H(92)	0.962(17)
C(9)-H(93)	0.97(2)
C(10)-C(11)	1.5103(18)
C(10)-H(10)	0.970(15)
C(11)-H(111)	0.99(2)
C(11)-H(112)	0.975(19)
C(11)-H(113)	0.92(2)
C(12)-H(121)	0.914(18)
C(12)-H(122)	0.97(2)

C(12)-H(123)	0.96(2)
O(5)-S-O(4)	119.10(8)
O(5)-S-O(3)	109.43(6)
O(4)-S-O(3)	104.64(6)
O(5)-S-C(12)	109.13(8)
O(4)-S-C(12)	109.30(7)
O(3)-S-C(12)	104.15(6)
C(1)-O(1)-C(9)	115.78(11)
C(10)-O(3)-S	118.60(8)
O(1)-C(1)-C(2)	108.81(10)
O(1)-C(1)-C(6)	113.23(10)
C(2)-C(1)-C(6)	102.40(10)
O(1)-C(1)-C(7)	114.76(10)
C(2)-C(1)-C(7)	108.99(11)
C(6)-C(1)-C(7)	107.88(10)
C(3)-C(2)-C(1)	115.09(12)
C(3)-C(2)-H(2)	127.9(11)
C(1)-C(2)-H(2)	116.9(11)
C(2)-C(3)-C(4)	114.78(12)
C(2)-C(3)-H(3)	123.0(10)
C(4)-C(3)-H(3)	122.1(10)
C(3)-C(4)-C(5)	109.22(10)
C(3)-C(4)-C(8)	106.72(11)
C(5)-C(4)-C(8)	106.39(11)
C(3)-C(4)-H(4)	110.5(10)
C(5)-C(4)-H(4)	111.3(10)
C(8)-C(4)-H(4)	112.5(10)
C(10)-C(5)-C(6)	111.02(10)
C(10)-C(5)-C(4)	116.80(11)
C(6)-C(5)-C(4)	107.61(10)
C(10)-C(5)-H(5)	106.9(10)
C(6)-C(5)-H(5)	103.7(10)
C(4)-C(5)-H(5)	110.0(9)
O(2)-C(6)-C(5)	123.65(11)
O(2)-C(6)-C(1)	123.96(11)
C(5)-C(6)-C(1)	112.35(10)
C(8)-C(7)-C(1)	110.47(11)

C(8)-C(7)-H(71)	110.4(11)
C(1)-C(7)-H(71)	107.0(12)
C(8)-C(7)-H(72)	109.1(10)
C(1)-C(7)-H(72)	111.5(10)
H(71)-C(7)-H(72)	108.4(15)
C(7)-C(8)-C(4)	109.34(11)
C(7)-C(8)-H(81)	106.5(11)
C(4)-C(8)-H(81)	111.6(11)
C(7)-C(8)-H(82)	112.4(12)
C(4)-C(8)-H(82)	106.1(11)
H(81)-C(8)-H(82)	111.0(17)
O(1)-C(9)-H(91)	113.4(11)
O(1)-C(9)-H(92)	107.5(10)
H(91)-C(9)-H(92)	106.5(15)
O(1)-C(9)-H(93)	111.1(11)
H(91)-C(9)-H(93)	108.6(15)
H(92)-C(9)-H(93)	109.5(14)
O(3)-C(10)-C(11)	107.22(11)
O(3)-C(10)-C(5)	106.76(10)
C(11)-C(10)-C(5)	116.29(11)
O(3)-C(10)-H(10)	107.5(9)
C(11)-C(10)-H(10)	111.5(9)
C(5)-C(10)-H(10)	107.2(9)
C(10)-C(11)-H(111)	110.8(12)
C(10)-C(11)-H(112)	111.7(11)
H(111)-C(11)-H(112)	108.9(15)
C(10)-C(11)-H(113)	113.2(12)
H(111)-C(11)-H(113)	107.6(17)
H(112)-C(11)-H(113)	104.4(16)
S-C(12)-H(121)	108.1(11)
S-C(12)-H(122)	108.7(12)
H(121)-C(12)-H(122)	112.3(17)
S-C(12)-H(123)	104.6(12)
H(121)-C(12)-H(123)	112.1(15)
H(122)-C(12)-H(123)	110.6(17)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å^{2}x 10^3) for **372**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2}U^{11} + ... + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S	22(1)	23(1)	33(1)	1(1)	-2(1)	-3(1)
O(1)	27(1)	23(1)	41(1)	2(1)	-4(1)	-4(1)
O(2)	30(1)	29(1)	29(1)	-1(1)	2(1)	-3(1)
O(3)	26(1)	29(1)	31(1)	-4(1)	4(1)	-7(1)
O(4)	40(1)	46(1)	35(1)	6(1)	-12(1)	-17(1)
O(5)	28(1)	28(1)	73(1)	-3(1)	7(1)	3(1)
C(1)	21(1)	23(1)	32(1)	5(1)	-2(1)	-2(1)
C(2)	20(1)	29(1)	38(1)	8(1)	2(1)	0(1)
C(3)	26(1)	31(1)	38(1)	4(1)	7(1)	1(1)
C(4)	30(1)	31(1)	26(1)	0(1)	3(1)	-2(1)
C(5)	21(1)	24(1)	24(1)	2(1)	-2(1)	-1(1)
C(6)	20(1)	21(1)	29(1)	4(1)	-2(1)	1(1)
C(7)	29(1)	33(1)	33(1)	13(1)	-2(1)	-2(1)
C(8)	41(1)	41(1)	26(1)	7(1)	-2(1)	-5(1)
C(9)	39(1)	26(1)	45(1)	2(1)	3(1)	-1(1)
C(10)	22(1)	23(1)	29(1)	2(1)	-2(1)	-4(1)
C(11)	28(1)	32(1)	51(1)	15(1)	-3(1)	0(1)
C(12)	32(1)	31(1)	32(1)	4(1)	-4(1)	-8(1)

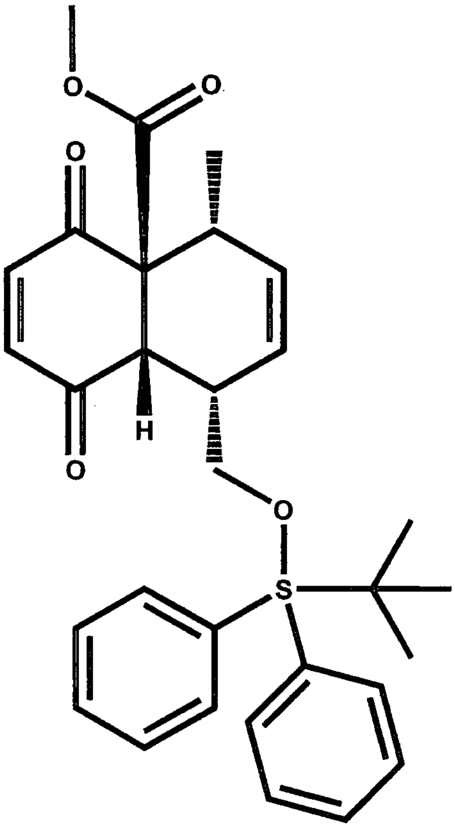
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **372**.

	x	y	z	U(eq)
H(2)	2250(16)	2160(16)	3721(9)	37(5)
H(3)	2617(15)	3937(16)	4395(8)	35(4)
H(4)	4488(14)	4065(16)	4791(8)	36(4)
H(5)	5889(15)	2971(15)	4101(8)	32(4)
H(71)	3791(16)	622(17)	4741(9)	43(5)
H(72)	5009(16)	647(15)	4512(8)	34(4)
H(81)	5329(18)	2148(18)	5144(10)	51(5)
H(82)	4011(18)	2276(17)	5344(9)	51(5)
H(91)	3993(16)	-1087(17)	3101(9)	43(5)
H(92)	4354(14)	-834(16)	3816(8)	31(4)
H(93)	4980(17)	-207(17)	3218(9)	40(5)
H(10)	5818(13)	4135(14)	3154(7)	25(4)
H(111)	3952(19)	5351(17)	3756(10)	46(5)
H(112)	4555(15)	5770(18)	3082(9)	42(5)
H(113)	3864(17)	4653(16)	3092(10)	45(5)
H(121)	6699(16)	6173(16)	2750(9)	43(5)
H(122)	6776(19)	7204(18)	3274(10)	54(6)
H(123)	7871(17)	6694(18)	2926(9)	48(5)

Table 6. Torsion angles [°] for **372**.

C(7)-C(1)-O(1)-C(9)	-51.06(15)
C(4)-C(5)-C(10)-C(11)	-45.87(16)
C(4)-C(5)-C(10)-O(3)	73.71(13)
C(5)-C(10)-O(3)-S	114.76(9)
C(10)-O(3)-S-C(12)	77.45(10)
C(10)-O(3)-S-O(5)	-39.13(11)

Symmetry transformations used to generate equivalent atoms:



365

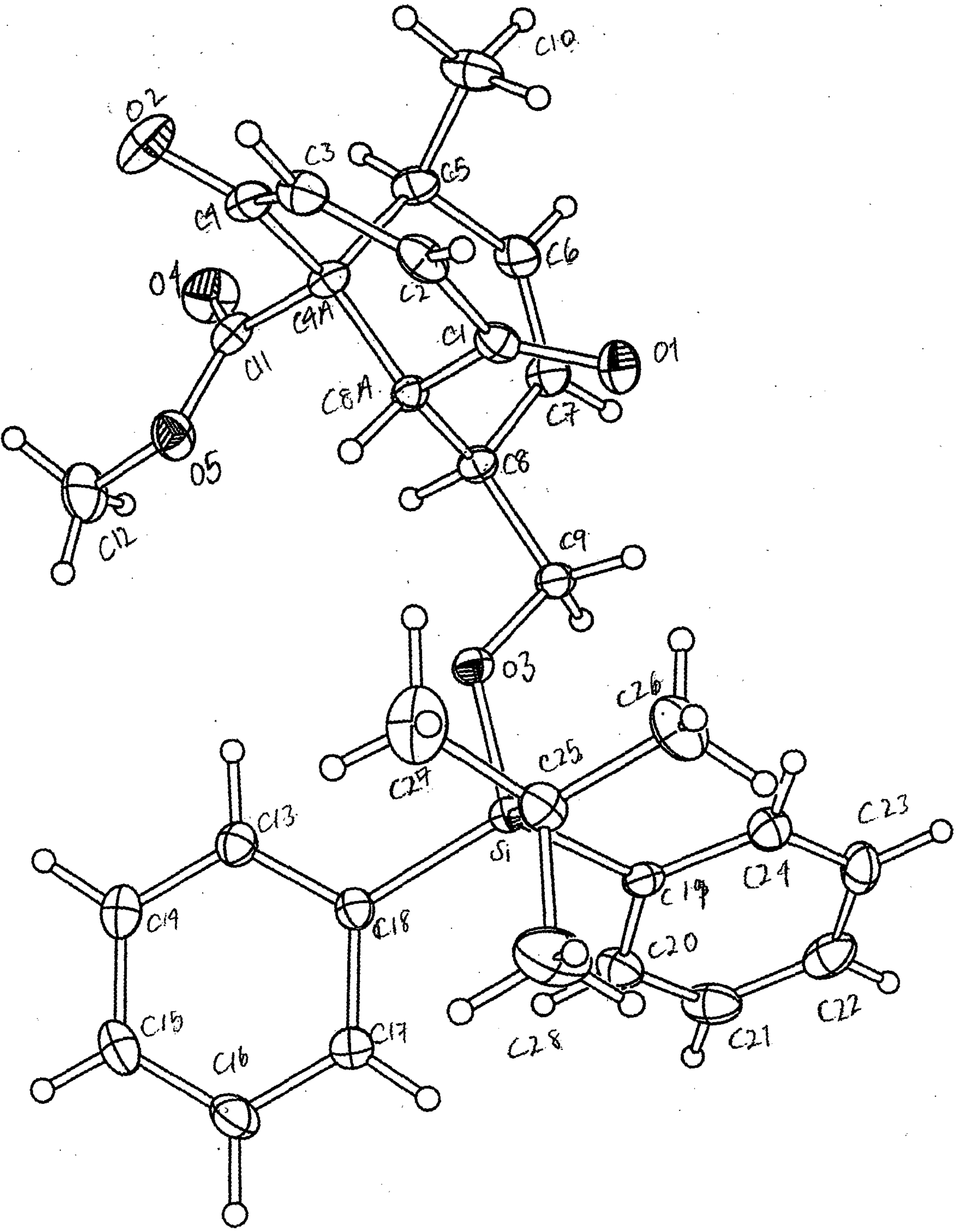

C10
O2
C3
C5
C4
C6
O4
C2
C4A
C1
O1
C11
C8A
C7
C8
O5
C12
C9
O3
C26
C27
C25
C23
C13
Si
C24
C19
C14
C18
C20
C15
C17
C22
C16
C28
C21

Table 1. Crystal data and structure refinement for **365**.

Identification code	**365**	
Empirical formula	C30 H34 O5 Si	
Formula weight	502.66	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 12.5675(10) Å	α= 90°.
	b = 11.7223(10) Å	β= 90°.
	c = 17.9516(15) Å	γ = 90°.
Volume	2644.6(4) $Å^3$	
Z	4	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	0.127 mm^{-1}	
F(000)	1072	
Crystal size	0.20 x 0.20 x 0.14 mm^3	
Theta range for data collection	2.07 to 28.99°.	
Index ranges	-17<=h<=17, -15<=k<=15, -24<=l<=24	
Reflections collected	29522	
Independent reflections	6999 [R(int) = 0.0480]	
Completeness to theta = 28.99°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6999 / 1 / 461	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0751	
R indices (all data)	R1 = 0.0481, wR2 = 0.0792	
Absolute structure parameter	0.07(9)	
Largest diff. peak and hole	0.295 and -0.195 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **365**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	4514(1)	4673(1)	4568(1)	15(1)
O(1)	3891(1)	3977(1)	7104(1)	24(1)
O(2)	-306(1)	3798(1)	7113(1)	33(1)
O(3)	3676(1)	5073(1)	5223(1)	20(1)
O(4)	-36(1)	6420(1)	6536(1)	33(1)
O(5)	532(1)	5170(1)	5681(1)	24(1)
C(1)	2960(1)	3862(1)	6941(1)	18(1)
C(2)	2368(1)	2807(2)	7142(1)	21(1)
C(3)	1310(1)	2792(1)	7192(1)	22(1)
C(4A)	1239(1)	4946(1)	6894(1)	17(1)
C(4)	657(1)	3825(2)	7064(1)	21(1)
C(5)	1396(1)	5644(2)	7631(1)	21(1)
C(6)	2270(2)	6514(2)	7547(1)	22(1)
C(7)	2936(1)	6596(2)	6980(1)	21(1)
C(8A)	2314(1)	4714(1)	6492(1)	14(1)
C(8)	2849(1)	5846(1)	6301(1)	17(1)
C(9)	3892(1)	5718(2)	5877(1)	18(1)
C(10)	1597(2)	4929(2)	8333(1)	30(1)
C(11)	502(1)	5617(1)	6369(1)	21(1)
C(12)	-113(2)	5741(2)	5128(1)	33(1)
C(13)	4943(1)	3155(2)	4767(1)	22(1)
C(14)	5548(2)	2650(2)	4108(1)	40(1)
C(15)	5628(2)	3051(2)	5469(1)	31(1)
C(16)	3923(2)	2464(2)	4895(2)	37(1)
C(17)	3716(1)	4676(1)	3688(1)	17(1)
C(18)	4191(2)	4579(2)	2985(1)	22(1)
C(19)	3585(2)	4536(2)	2340(1)	26(1)
C(20)	2483(2)	4600(2)	2381(1)	26(1)
C(21)	1992(2)	4692(2)	3070(1)	25(1)
C(22)	2602(1)	4723(2)	3717(1)	20(1)
C(23)	5619(1)	5745(1)	4520(1)	19(1)
C(24)	6360(1)	5856(2)	5101(1)	23(1)
C(25)	7125(2)	6716(2)	5100(1)	27(1)

C(26)	7173(1)	7481(2)	4515(1)	30(1)
C(27)	6450(2)	7398(2)	3937(1)	30(1)
C(28)	5686(2)	6541(2)	3943(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for **365**.

Si-O(3)	1.6473(13)
Si-C(17)	1.8703(17)
Si-C(23)	1.8749(16)
Si-C(13)	1.8933(18)
O(1)-C(1)	1.214(2)
O(2)-C(4)	1.214(2)
O(3)-C(9)	1.423(2)
O(4)-C(11)	1.197(2)
O(5)-C(11)	1.343(2)
O(5)-C(12)	1.445(2)
C(1)-C(2)	1.488(2)
C(1)-C(8A)	1.519(2)
C(2)-C(3)	1.333(2)
C(2)-H(2)	0.93(2)
C(3)-C(4)	1.480(2)
C(3)-H(3)	0.975(19)
C(4A)-C(4)	1.535(2)
C(4A)-C(11)	1.537(2)
C(4A)-C(8A)	1.556(2)
C(4A)-C(5)	1.568(2)
C(5)-C(6)	1.506(3)
C(5)-C(10)	1.535(3)
C(5)-H(5)	0.972(19)
C(6)-C(7)	1.322(3)
C(6)-H(6)	0.93(2)
C(7)-C(8)	1.506(2)
C(7)-H(7)	0.953(17)
C(8A)-C(8)	1.528(2)
C(8A)-H(8A)	0.962(18)
C(8)-C(9)	1.523(2)
C(8)-H(8)	0.986(18)
C(9)-H(91)	0.98(2)
C(9)-H(92)	1.01(2)
C(10)-H(101)	1.00(2)
C(10)-H(102)	0.96(2)
C(10)-H(103)	0.95(2)

C(12)-H(121)	0.99(3)
C(12)-H(122)	0.99(2)
C(12)-H(123)	0.95(2)
C(13)-C(14)	1.527(3)
C(13)-C(15)	1.530(3)
C(13)-C(16)	1.534(3)
C(14)-H(141)	1.02(2)
C(14)-H(142)	0.97(2)
C(14)-H(143)	1.02(3)
C(15)-H(151)	0.96(2)
C(15)-H(152)	0.93(2)
C(15)-H(153)	1.00(2)
C(16)-H(161)	0.93(3)
C(16)-H(162)	0.93(3)
C(16)-H(163)	1.07(3)
C(17)-C(18)	1.401(2)
C(17)-C(22)	1.402(2)
C(18)-C(19)	1.387(3)
C(18)-H(18)	0.95(2)
C(19)-C(20)	1.388(3)
C(19)-H(19)	1.01(2)
C(20)-C(21)	1.387(3)
C(20)-H(20)	0.91(2)
C(21)-C(22)	1.392(3)
C(21)-H(21)	1.00(2)
C(22)-H(22)	0.96(2)
C(23)-C(28)	1.398(3)
C(23)-C(24)	1.404(2)
C(24)-C(25)	1.393(3)
C(24)-H(24)	0.96(2)
C(25)-C(26)	1.381(3)
C(25)-H(25)	0.97(2)
C(26)-C(27)	1.383(3)
C(26)-H(26)	0.94(2)
C(27)-C(28)	1.389(3)
C(27)-H(27)	0.93(2)
C(28)-H(28)	0.93(2)

O(3)-Si-C(17)	105.05(7)
O(3)-Si-C(23)	108.38(7)
C(17)-Si-C(23)	110.98(8)
O(3)-Si-C(13)	108.28(7)
C(17)-Si-C(13)	108.33(8)
C(23)-Si-C(13)	115.30(7)
C(9)-O(3)-Si	128.26(11)
C(11)-O(5)-C(12)	115.84(15)
O(1)-C(1)-C(2)	121.11(15)
O(1)-C(1)-C(8A)	124.78(15)
C(2)-C(1)-C(8A)	114.03(14)
C(3)-C(2)-C(1)	121.76(16)
C(3)-C(2)-H(2)	121.0(14)
C(1)-C(2)-H(2)	117.3(14)
C(2)-C(3)-C(4)	122.12(16)
C(2)-C(3)-H(3)	121.7(11)
C(4)-C(3)-H(3)	116.2(11)
C(4)-C(4A)-C(11)	105.85(13)
C(4)-C(4A)-C(8A)	110.83(13)
C(11)-C(4A)-C(8A)	109.20(13)
C(4)-C(4A)-C(5)	109.84(14)
C(11)-C(4A)-C(5)	109.03(13)
C(8A)-C(4A)-C(5)	111.90(13)
O(2)-C(4)-C(3)	121.34(16)
O(2)-C(4)-C(4A)	120.74(16)
C(3)-C(4)-C(4A)	117.88(14)
C(6)-C(5)-C(10)	109.36(16)
C(6)-C(5)-C(4A)	111.22(14)
C(10)-C(5)-C(4A)	115.41(14)
C(6)-C(5)-H(5)	106.1(11)
C(10)-C(5)-H(5)	109.1(11)
C(4A)-C(5)-H(5)	105.2(11)
C(7)-C(6)-C(5)	125.92(16)
C(7)-C(6)-H(6)	120.1(14)
C(5)-C(6)-H(6)	113.5(14)
C(6)-C(7)-C(8)	122.38(16)
C(6)-C(7)-H(7)	121.5(11)
C(8)-C(7)-H(7)	115.9(11)

C(1)-C(8A)-C(8)	117.06(13)
C(1)-C(8A)-C(4A)	109.48(13)
C(8)-C(8A)-C(4A)	109.52(13)
C(1)-C(8A)-H(8A)	102.9(10)
C(8)-C(8A)-H(8A)	109.7(11)
C(4A)-C(8A)-H(8A)	107.6(11)
C(7)-C(8)-C(9)	113.54(14)
C(7)-C(8)-C(8A)	110.94(14)
C(9)-C(8)-C(8A)	113.88(13)
C(7)-C(8)-H(8)	107.7(10)
C(9)-C(8)-H(8)	103.5(10)
C(8A)-C(8)-H(8)	106.5(10)
O(3)-C(9)-C(8)	107.51(13)
O(3)-C(9)-H(91)	108.2(11)
C(8)-C(9)-H(91)	107.9(11)
O(3)-C(9)-H(92)	110.5(11)
C(8)-C(9)-H(92)	110.8(11)
H(91)-C(9)-H(92)	111.7(16)
C(5)-C(10)-H(101)	108.3(14)
C(5)-C(10)-H(102)	111.9(14)
H(101)-C(10)-H(102)	103.3(19)
C(5)-C(10)-H(103)	110.1(14)
H(101)-C(10)-H(103)	111(2)
H(102)-C(10)-H(103)	111.8(19)
O(4)-C(11)-O(5)	123.56(17)
O(4)-C(11)-C(4A)	126.10(17)
O(5)-C(11)-C(4A)	110.33(14)
O(5)-C(12)-H(121)	103.5(13)
O(5)-C(12)-H(122)	109.8(13)
H(121)-C(12)-H(122)	112.9(18)
O(5)-C(12)-H(123)	108.5(14)
H(121)-C(12)-H(123)	112.6(19)
H(122)-C(12)-H(123)	109.4(19)
C(14)-C(13)-C(15)	109.09(16)
C(14)-C(13)-C(16)	109.12(19)
C(15)-C(13)-C(16)	107.74(17)
C(14)-C(13)-Si	111.07(13)
C(15)-C(13)-Si	113.02(13)

C(16)-C(13)-Si	106.66(13)
C(13)-C(14)-H(141)	109.4(13)
C(13)-C(14)-H(142)	107.8(13)
H(141)-C(14)-H(142)	105.8(18)
C(13)-C(14)-H(143)	114.1(15)
H(141)-C(14)-H(143)	106.9(19)
H(142)-C(14)-H(143)	113(2)
C(13)-C(15)-H(151)	109.4(13)
C(13)-C(15)-H(152)	113.1(14)
H(151)-C(15)-H(152)	110(2)
C(13)-C(15)-H(153)	111.1(13)
H(151)-C(15)-H(153)	103.4(18)
H(152)-C(15)-H(153)	110(2)
C(13)-C(16)-H(161)	107.4(17)
C(13)-C(16)-H(162)	111.7(15)
H(161)-C(16)-H(162)	108(2)
C(13)-C(16)-H(163)	112.3(16)
H(161)-C(16)-H(163)	107(2)
H(162)-C(16)-H(163)	111(2)
C(18)-C(17)-C(22)	117.49(16)
C(18)-C(17)-Si	122.13(13)
C(22)-C(17)-Si	120.32(13)
C(19)-C(18)-C(17)	121.43(17)
C(19)-C(18)-H(18)	117.4(13)
C(17)-C(18)-H(18)	121.0(13)
C(18)-C(19)-C(20)	120.04(17)
C(18)-C(19)-H(19)	120.0(13)
C(20)-C(19)-H(19)	119.9(13)
C(21)-C(20)-C(19)	119.77(17)
C(21)-C(20)-H(20)	118.5(12)
C(19)-C(20)-H(20)	121.7(12)
C(20)-C(21)-C(22)	120.03(17)
C(20)-C(21)-H(21)	122.7(12)
C(22)-C(21)-H(21)	117.2(12)
C(21)-C(22)-C(17)	121.24(17)
C(21)-C(22)-H(22)	116.8(12)
C(17)-C(22)-H(22)	122.0(12)
C(28)-C(23)-C(24)	116.71(15)

C(28)-C(23)-Si	121.68(13)
C(24)-C(23)-Si	121.33(13)
C(25)-C(24)-C(23)	121.56(18)
C(25)-C(24)-H(24)	117.5(12)
C(23)-C(24)-H(24)	120.9(12)
C(26)-C(25)-C(24)	120.12(18)
C(26)-C(25)-H(25)	120.6(14)
C(24)-C(25)-H(25)	119.3(14)
C(25)-C(26)-C(27)	119.67(17)
C(25)-C(26)-H(26)	120.6(15)
C(27)-C(26)-H(26)	119.8(15)
C(26)-C(27)-C(28)	120.00(19)
C(26)-C(27)-H(27)	119.4(16)
C(28)-C(27)-H(27)	120.6(16)
C(27)-C(28)-C(23)	121.94(18)
C(27)-C(28)-H(28)	117.6(13)
C(23)-C(28)-H(28)	120.5(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for **365**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2}U^{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si	14(1)	18(1)	14(1)	0(1)	1(1)	0(1)
O(1)	20(1)	26(1)	25(1)	1(1)	-5(1)	3(1)
O(2)	22(1)	27(1)	50(1)	-3(1)	13(1)	-5(1)
O(3)	18(1)	25(1)	18(1)	-5(1)	3(1)	-3(1)
O(4)	30(1)	30(1)	40(1)	-2(1)	4(1)	15(1)
O(5)	21(1)	26(1)	25(1)	0(1)	-5(1)	6(1)
C(1)	22(1)	17(1)	15(1)	-4(1)	2(1)	4(1)
C(2)	30(1)	18(1)	17(1)	-1(1)	-3(1)	4(1)
C(3)	31(1)	16(1)	18(1)	-1(1)	2(1)	-5(1)
C(4A)	16(1)	16(1)	19(1)	-1(1)	4(1)	0(1)
C(4)	22(1)	21(1)	20(1)	-2(1)	6(1)	-4(1)
C(5)	24(1)	19(1)	20(1)	-3(1)	7(1)	1(1)
C(6)	28(1)	19(1)	20(1)	-7(1)	1(1)	-1(1)
C(7)	23(1)	17(1)	23(1)	-2(1)	1(1)	-4(1)
C(8A)	13(1)	15(1)	15(1)	-3(1)	2(1)	0(1)
C(8)	17(1)	15(1)	17(1)	-1(1)	2(1)	1(1)
C(9)	19(1)	20(1)	16(1)	-2(1)	3(1)	-3(1)
C(10)	46(1)	26(1)	17(1)	-2(1)	7(1)	-3(1)
C(11)	15(1)	21(1)	26(1)	2(1)	4(1)	-2(1)
C(12)	28(1)	34(1)	37(1)	6(1)	-12(1)	4(1)
C(13)	24(1)	21(1)	22(1)	0(1)	-1(1)	5(1)
C(14)	52(1)	35(1)	32(1)	-3(1)	5(1)	20(1)
C(15)	40(1)	24(1)	29(1)	4(1)	-10(1)	5(1)
C(16)	39(1)	20(1)	54(1)	5(1)	-8(1)	-4(1)
C(17)	19(1)	15(1)	18(1)	1(1)	-1(1)	-1(1)
C(18)	20(1)	28(1)	19(1)	1(1)	1(1)	-2(1)
C(19)	31(1)	32(1)	16(1)	2(1)	-2(1)	-6(1)
C(20)	29(1)	25(1)	23(1)	1(1)	-11(1)	-4(1)
C(21)	20(1)	23(1)	31(1)	2(1)	-6(1)	-1(1)
C(22)	20(1)	20(1)	21(1)	2(1)	0(1)	0(1)
C(23)	17(1)	23(1)	17(1)	-3(1)	4(1)	-1(1)
C(24)	21(1)	26(1)	22(1)	-2(1)	1(1)	1(1)
C(25)	20(1)	29(1)	31(1)	-11(1)	-4(1)	-1(1)

C(26)	26(1)	26(1)	38(1)	-10(1)	10(1)	-9(1)
C(27)	42(1)	23(1)	25(1)	-4(1)	10(1)	-8(1)
C(28)	28(1)	24(1)	18(1)	-3(1)	0(1)	-2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for **365**.

	x	y	z	U(eq)
H(2)	2765(17)	2160(20)	7237(13)	35(6)
H(3)	923(15)	2100(16)	7324(10)	17(5)
H(5)	742(16)	6074(15)	7693(10)	15(5)
H(6)	2375(17)	6953(19)	7971(12)	29(6)
H(7)	3464(13)	7179(15)	6959(10)	9(4)
H(8A)	2158(14)	4301(15)	6042(10)	10(4)
H(8)	2379(14)	6234(15)	5941(10)	11(4)
H(91)	4128(15)	6483(17)	5725(10)	14(4)
H(92)	4442(15)	5321(17)	6193(11)	17(5)
H(101)	1667(18)	5460(20)	8765(14)	38(6)
H(102)	2275(19)	4554(19)	8318(13)	34(6)
H(103)	1030(19)	4400(20)	8405(13)	37(6)
H(121)	109(17)	5377(19)	4654(15)	37(6)
H(122)	31(17)	6570(20)	5140(13)	33(6)
H(123)	-844(18)	5608(19)	5242(13)	32(6)
H(141)	5786(17)	1850(20)	4235(12)	34(6)
H(142)	6195(18)	3087(19)	4043(12)	28(6)
H(143)	5110(20)	2600(20)	3631(15)	47(7)
H(151)	5775(17)	2261(19)	5564(11)	26(5)
H(152)	5313(18)	3380(20)	5888(14)	36(6)
H(153)	6350(18)	3390(20)	5388(12)	33(6)
H(161)	4120(20)	1710(30)	4963(14)	55(8)
H(162)	3473(19)	2500(20)	4487(15)	44(7)
H(163)	3510(20)	2720(30)	5393(17)	66(9)
H(18)	4938(19)	4483(19)	2935(12)	33(6)
H(19)	3944(18)	4499(18)	1839(13)	34(6)
H(20)	2065(15)	4553(16)	1965(12)	19(5)
H(21)	1199(17)	4745(18)	3129(12)	27(5)
H(22)	2224(16)	4783(18)	4179(12)	27(5)
H(24)	6333(15)	5364(18)	5526(11)	20(5)
H(25)	7608(19)	6780(20)	5518(13)	38(6)
H(26)	7702(18)	8049(19)	4503(14)	40(6)

H(27)	6470(20)	7940(20)	3553(14)	43(7)
H(28)	5225(16)	6501(17)	3540(12)	22(5)