Acyl Radical Cascade Reactions: The Synthesis of Azasteroids

A Thesis Submitted

by

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In Partial Fulfilment of the Requirements

for the Degree

of

Doctor of Philosophy

of the

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Declaration

The research described in this thesis is, to the best of my knowledge, original except where due reference is made to other authors, and has not been submitted in any part or form for a degree at this or any other university.

Dedicated to:

My Family

Acknowledgements

I would like to thank Professor Gerry Pattenden for his help and advice over the past three years. Also many thanks to Drs Shelley Bower and Graham Smith, my industrial collaborators, for their interest and advice. I would also like to thank Dr Bryon Gill, Dr Mark Searle and his group for their assistance in helping to identify a number of compounds using n.m.r.

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Abstract

Our work has been concerned with the synthesis of azasteroid ring systems, utilising acyl radical cascade reactions. Chapter 1 comprises an overview of published work relevant to our studies: an analysis of steroid biosynthesis and synthesis; a review of the use of azasteroids, their biological activity and current synthetic techniques in azasteroid formation. This initial chapter also includes an introduction to published work in the area of nitrogen heterocycle synthesis using radical reactions and finally the use of acyl radicals in synthesis, particularly cascade reactions.

Chapter 2 starts by describing the requirements of a reaction system for use in acyl radical cascades and then discusses the relevance of this to the synthesis of ring junction azasteroids. Our attempts to synthesise ring junction azasteroids and the problems that we encountered are then discussed.

Subsequent sections describe the disconnection of azasteroids where nitrogen is part of the body of the ring and the synthetic work that we performed in this area. Using cyclohexenyl enamides as the terminal electrophore in cascade reactions we were able to synthesise a 12-aza-D-homosteroid in nine steps. The final step was a cascade reaction involving three consecutive 6-*endo*-trig cyclisations starting from an acyl radical and terminating on an cyclohexenyl enamide electrophore. An extensive, though unsuccessful, study attempting to use linear enamides in cascade reactions is described showing routes towards the synthesis of steroid models.

Finally we reveal the work that was performed in the use of highly stabilised enamides as radical acceptors. This work resulted in the formation of a bicyclo[8.3.0]tridecene after a 10-*endo*-trig, 5-*exo*-trig cascade from a linear precursor designed to form a 7-azaandrostane skeleton.

Contents

Abbreviations

AIBN	azobis-*iso*-butyronitrile
Ar	aryl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
Bu	butyl
COSY	correlation spectroscopy
δ	chemical shift
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
de	diastereomeric excess
ee	enantiomeric excess
eq.	equivalents
Et	ethyl
EtOAc	ethyl acetate
Et_2O	diethyl ether
FT-IR	Fourier transform infrared
h	hours
HMQC	heteronuclear multiple quantum coherence
J	coupling constant
Me	methyl
MHz	megaHertz
min	minutes
m.p.	melting point
n.m.r.	nuclear magnetic resonance

nOe	nuclear Overhauser enhancement
NOSEY	nuclear Overhauser enhancement spectroscopy
Ph	phenyl
p.p.m.	parts per million
Pr	propyl
py	pyridine
rt	room temperature
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Ts	*para*-toluenesulfonyl
p-TsOH	*para*-toluenesulfonic acid
TTMSS	*tris*-trimethylsilylsilane
UV	ultraviolet

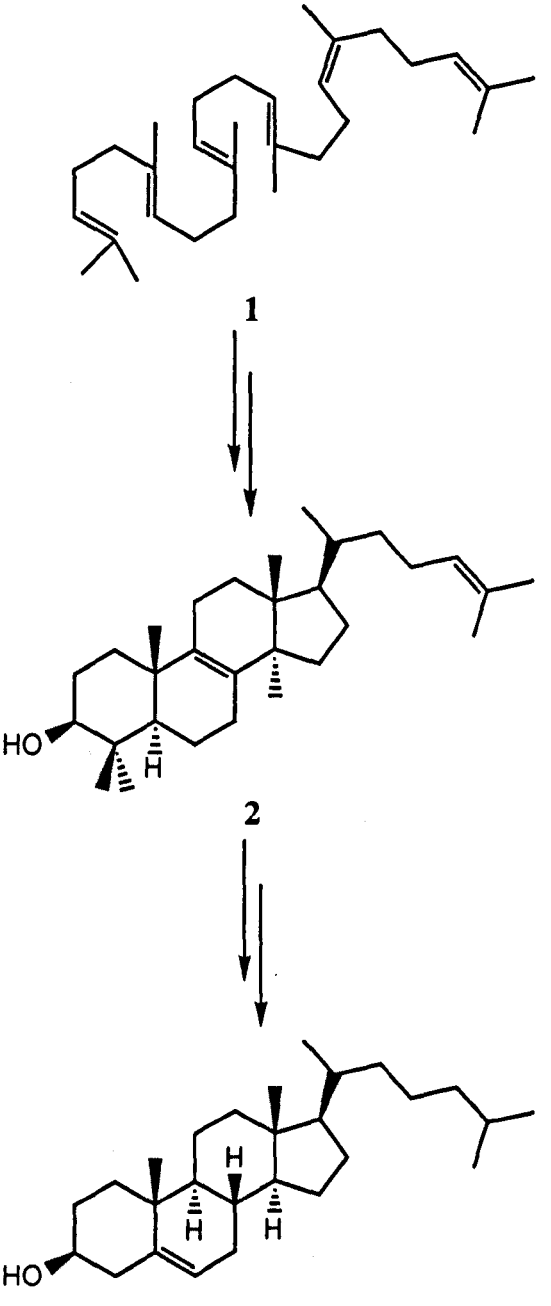
1. INTRODUCTION

1.1 STEROIDS

1.1.1 Biosynthesis of Steroids

Investigation into the biosynthesis of terpenoids and steroids has been a continuing theme in the chemical literature and this work has been reviewed extensively.[1] Revealing the full details of the story uncovering the mechanisms behind the remarkable biosynthesis of steroids, from squalene, has involved the work of many researchers. In 1953, Woodward and Bloch combined the groundbreaking work of Bloch,[2] Channon,[3] and Robinson [4] to hypothesise that squalene **1** was converted into lanosterol **2** as the key step in the cholesterol **3** biosynthetic pathway (Scheme 1).[5]
In 1955, Stork and Eschenmoser proposed that a prearranged squalene molecule could undergo an uninterrupted stereochemically controlled cascade cyclisation followed by 1,2-migrations to give lanosterol, as the key step in steroid biosynthesis.[6,7] Direct evidence for these proposals was uncovered by Bloch and Cornforth during their incorporation experiments, where deuterium and carbon-14 labelled malonates were fed to liver enzymes during the study of the biosynthesis of steroids.[8,9] Corey[10] and van Tamelen[11] demonstrated the intermediacy of 2,3-oxidosqualene in lanosterol **2** biosynthesis and Barton[12] verified that only (3*S*)-2,3-oxidosqualene **4** was accepted as a substrate by eukaryotic oxidosqualene cyclases. This led to the accepted cascade *via* the "chair-boat-chair" conformation of (3*S*)-2,3-oxidosqualene **5** initiated by an acid catalysed epoxide ring opening, with an anti-Markovnikov cyclisation in the formation of the C-ring to give the cationic intermediate tetracycle **6**. From **6**, 1,2-

methyl and 1,2-hydrogen migrations yielded lanosterol **2** to complete the biosynthesis of the steroidal core (Scheme 2).

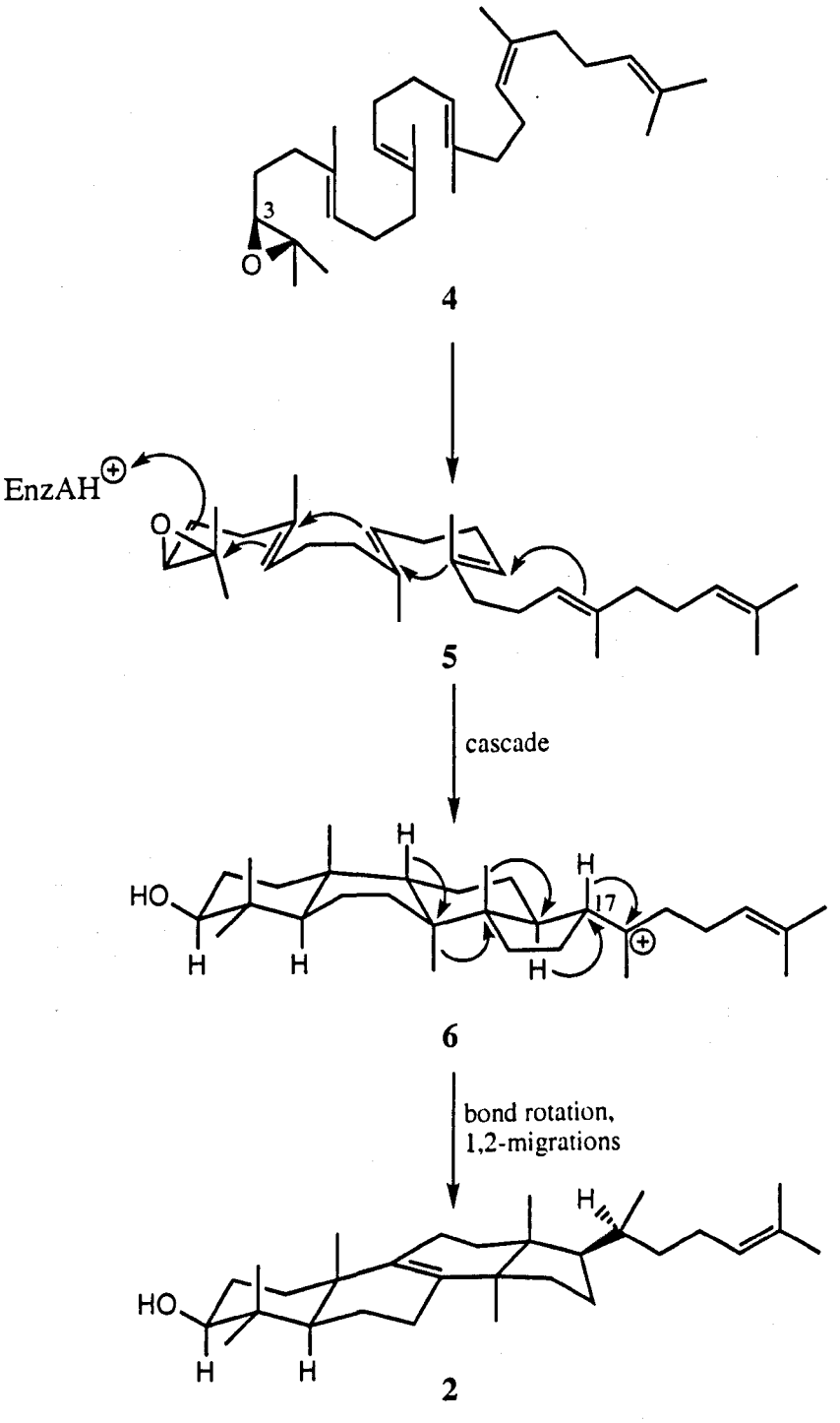


1

2

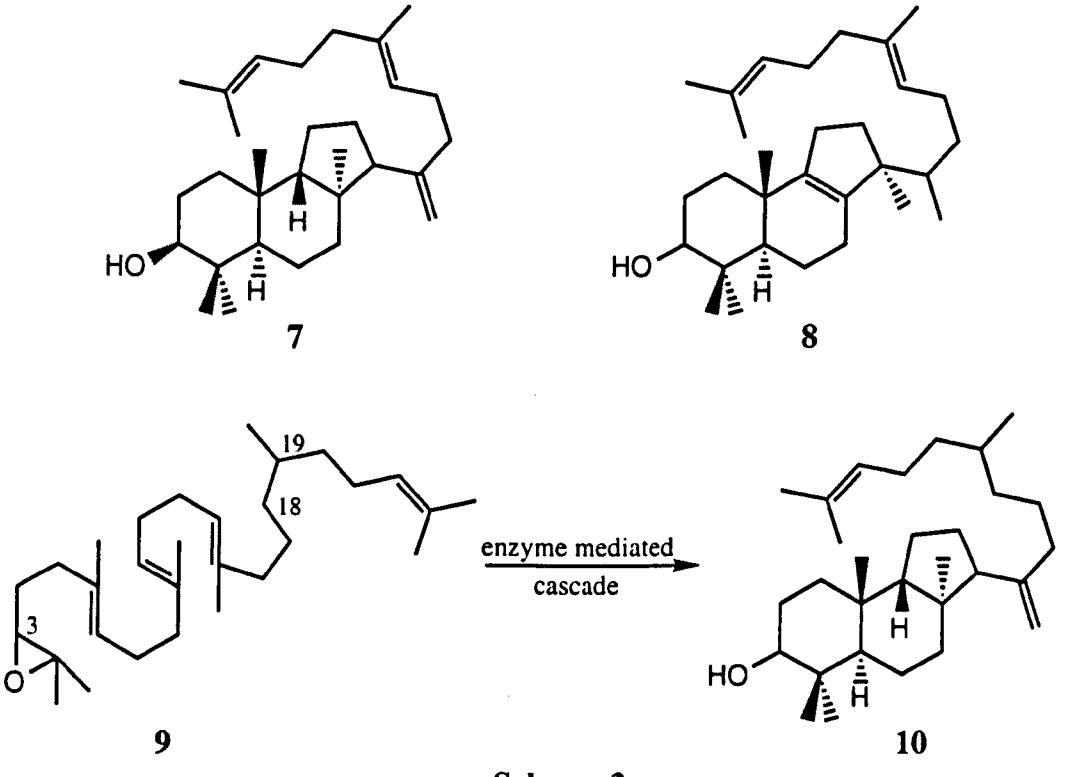
3

Scheme 1


3
O
4
EnzAH
O
5
cascade
HO
H
H
H
H
17
6
bond rotation,
1,2-migrations
HO
H
H
H
2

Scheme 2

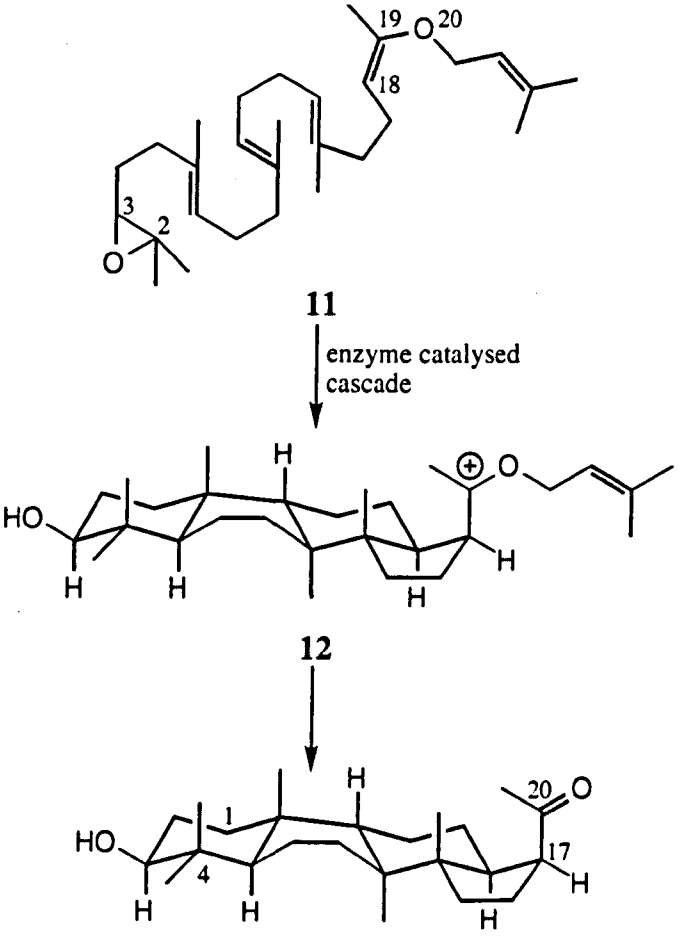
However, when 2,3-oxidosqualene **4** was submitted to non-enzymic cyclisation conditions the 6,6,5 fused tricyclic products, **7** and **8**, were isolated, resulting from the more favourable Markovnikov addition during the formation of the C-ring.[13] Further investigation into steroid biosynthesis, using 18,19-dihydro-2,3-oxidosqualene **9** as the enzyme substrate, resulted in the formation of the 6,6,5 fused tricycle **10** and highlighted the possibility of alternative sequences in the cascade leading to steroid formation (Scheme 3).[14,15]



Scheme 3

A recent in-depth reinvestigation of steroid biosynthesis, combining the ever developing arsenal of tools from chemistry, biochemistry and biological chemistry, has shown new and unexpected aspects of the cascade cyclisation. Corey and co-workers used 20-oxa-2,3-oxidosqualene **11** as a substrate in the enzyme catalysed cascade. They were able to trap the intermediate cation **12** which they isolated as the

ketone **13** (Scheme 4).[16] Stereochemical comparison to synthetic material revealed that the C-17 sidechain was in the β-configuration and not the α-configuration as previously assumed in the intermediate **6**.[6,7]



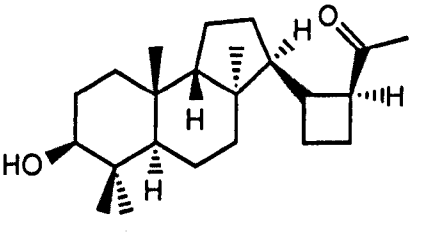
11

enzyme catalysed cascade

12

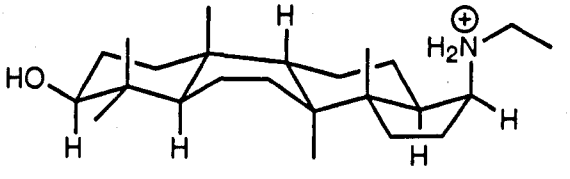
13

Scheme 4

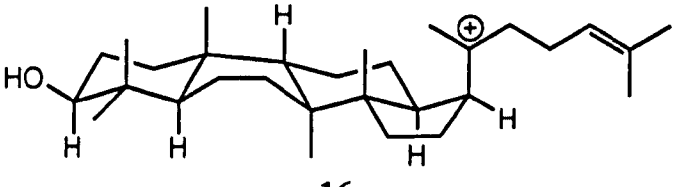


14

In the previously proposed biosynthesis (Scheme 2) the transformation from **6** into **2** involved a 120° bond rotation about the C-17/C-20 bond, which maintained the stereochemical integrity at C-20. However, with the C-17 side chain in the β orientation in intermediate **12** the required C-17/C-20 bond rotation was reduced to 60°. This change in the proposed pathway would lower the energy boundaries for the transformation. When this investigation was repeated on a larger scale small quantities of the 6,6,5,4 tetracycle **14** were isolated.[17] Trapping of the tetracycle **14** with its 5-membered C-ring pointed towards a Markovnikov cyclisation, which is favoured on steric grounds, rather than the previously proposed anti-Markovnikov cyclisation with its high steric constraints. This led to the hypothesis that the cationic cascade proceeded *via* a stepwise cyclisation pathway rather than a concerted cascade. Therefore, formation of the steroid ring system *via* this pathway would involve a ring expansion of a five membered C-ring, to the six membered ring found in steroids, from a discrete intermediate cation in the cyclisation pathway.



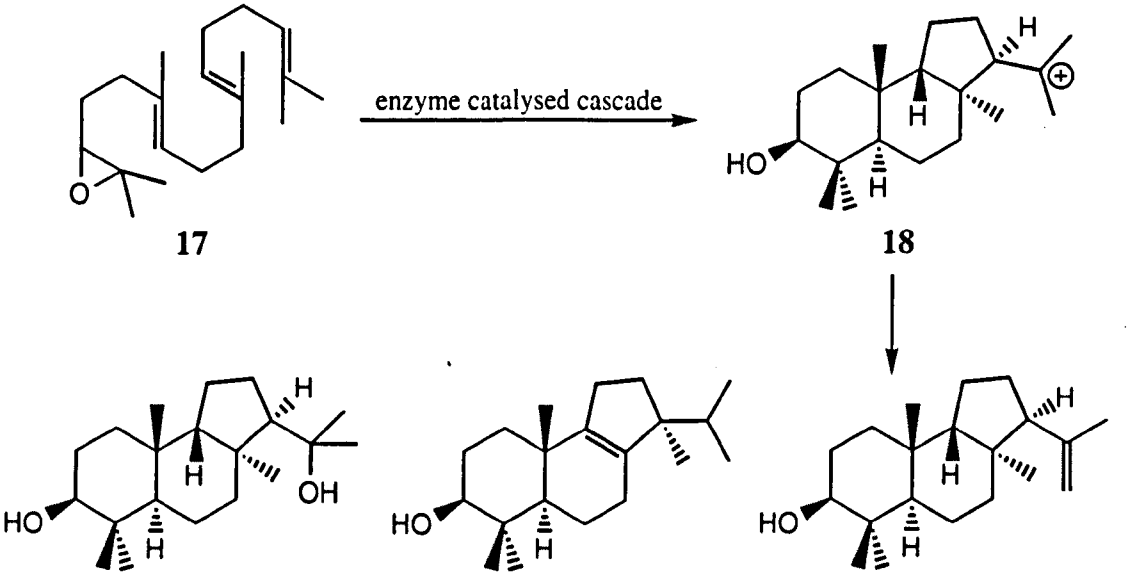
15



16

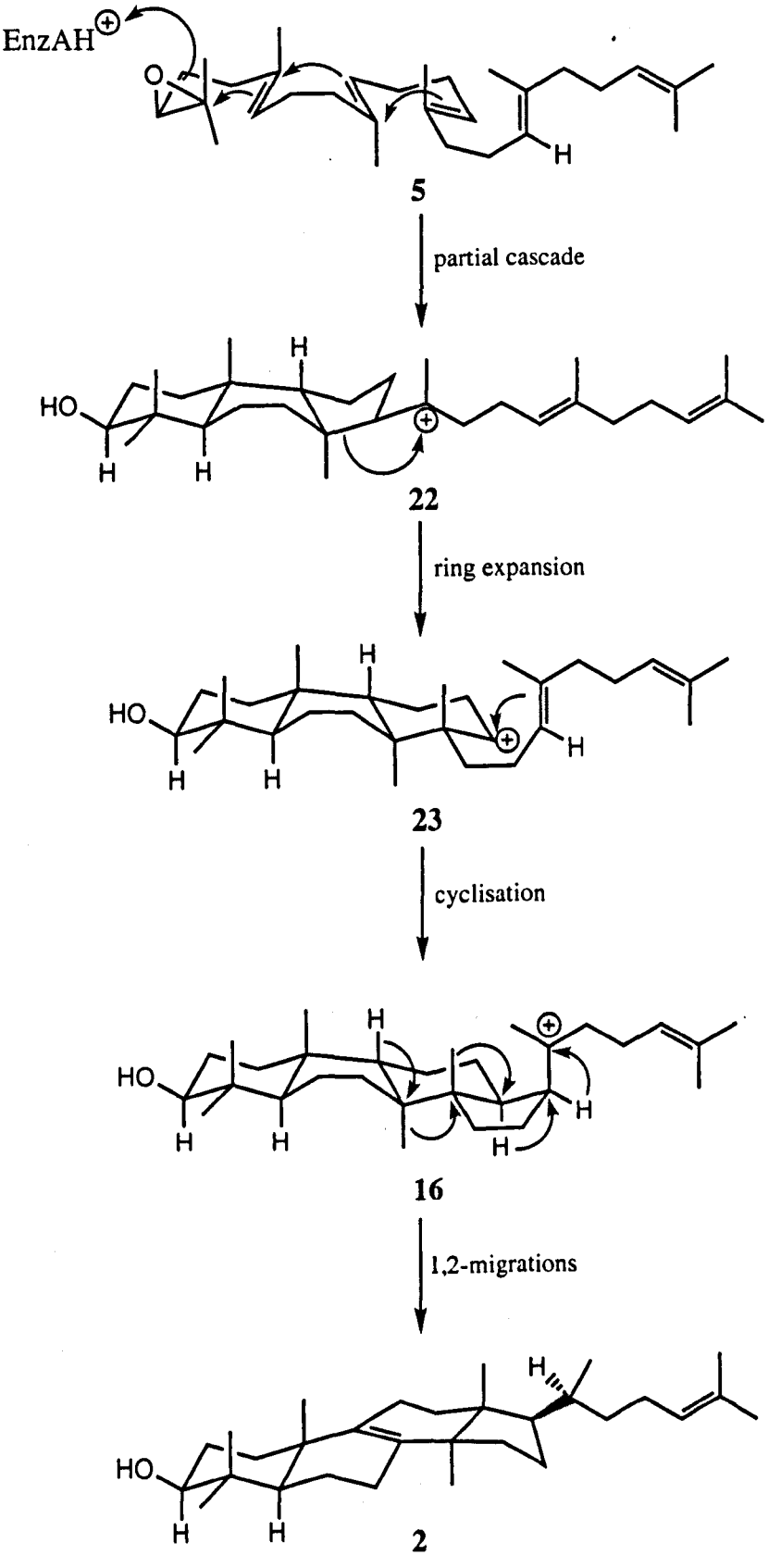
Further investigation by the Corey group also showed that the synthetic mimic **15** of the intermediate cation **16** did not block sterol biosynthesis implying that both the conformation of oxidosqualene and the shape of the enzyme site change during the

cyclisation.[18] Using the truncated analogue **17** of 2,3-oxidosqualene **4** Corey and Cheng were also able to show that the interrupted cascade of this substrate led entirely to the 6,6,5 tricyclic structures **19, 20** and **21** (Scheme 5).[19] The culmination of this work is a revised cationic cascade, with the intermediate tricyclic cation **22** undergoing ring expansion to form the cation **23**. The cascade continues, resulting initially in the formation of the tetracyclic system **16**, where 1,2-hydrogen and 1,2-methyl migrations on the protosterol **16** finally results in the biosynthesis of lanosterol **2** (Scheme 6).[18]



17 **18** **19** **20** **21**

Scheme 5

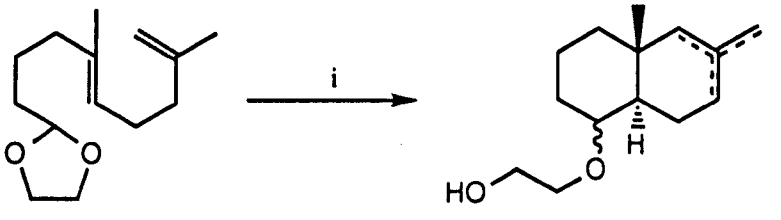

EnzAH
O
H
5
partial cascade
HO
H
H
H
22
ring expansion
HO
H
H
H
23
cyclisation
HO
H
H
H
H
16
1,2-migrations
HO
H
H
H
2

Scheme 6

1.1.2 Biomimetic Steroid Synthesis

Many synthetic approaches to steroids have been employed by chemists over the past six decades. These range from the synthetic modification of abundant steroid systems to their less abundant cousins[20] and annulation reactions,[21] such as the Diels-Alder and Robinson annulations for sequential ring formation. Perhaps one of the most elegant approaches is in the form of biomimetic cascade reactions. The synthesis of the tetracyclic ring system in one step in a fully stereoselective manner from polyolefinic precursors was the goal of these synthetic efforts. Ground-breaking work in this area was performed by the group of the late W. S. Johnson and has been extensively reviewed in recent literature.[22]

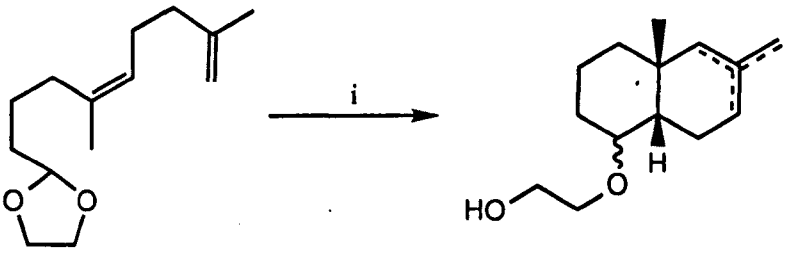
The stereoelectronic rationalisation of cationic cascades by Stork and Eschenmoser[6,7] led to a series of biomimetic synthetic approaches to steroids. A major advancement in this area was made with the introduction of acetals as initiators for the cationic cascades. Work by Johnson and co-workers[23] showed that bicyclic products **25** and **27** were formed in high yield and with high stereoselectivity under relatively mild conditions from the olefinic acetals **22** and **24** respectively, thus adhering to the Stork and Eschenmoser hypothesis (Scheme 7).



24 **25**; 80 %

Reagents: i, $SnCl_4$, CH_3NO_2, 0°C.

Scheme 7

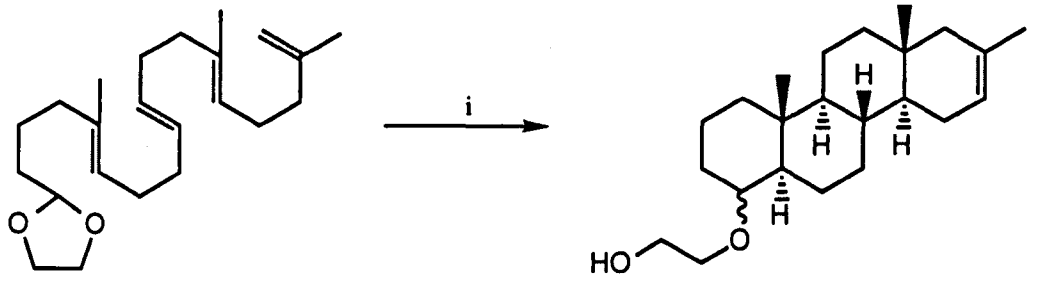


26 **27**; 88 %

Reagents: i, $SnCl_4$, CH_3NO_2, 0°C.

Scheme 7

The work was developed further for the formation of tetracyclic systems from tetraene acetals. Thus, cyclisation of the tetraene acetal **28**, under Lewis acidic conditions, led to the tetracycle **29** in 30 % yield and with high stereoselectivity (Scheme 8).[24] This was the first synthesis of a steroid ring system in one step from a linear precursor.

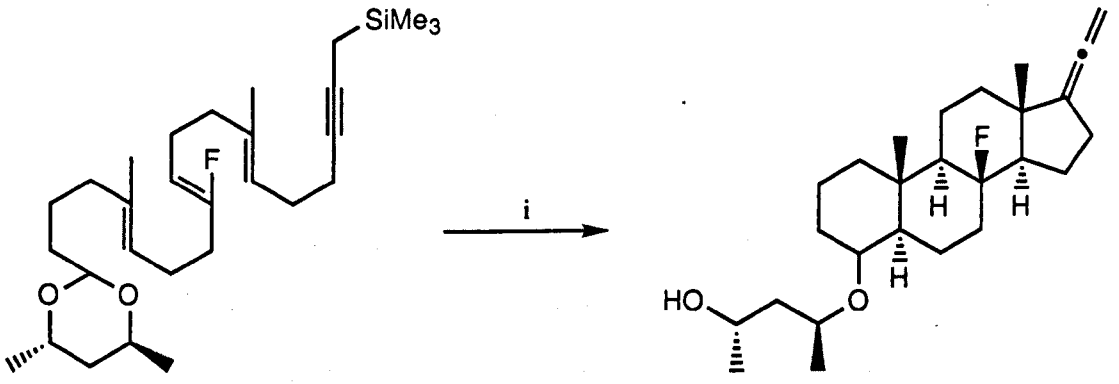


28 **29**; 30 %

Reagents: i, $SnCl_4$, pentane, 0°C.

Scheme 8

With the use of chiral acetals, the work has undergone a further metamorphosis, allowing the use of this methodology in the enantioselective synthesis of steroids.[25] For example, the fluorine substituted trieneyne acetal **30** underwent a Lewis acid initiated cascade to give the steroid **31** in 38 % yield and 93 %de (Scheme 9).[26] The use of cationic cascades in the synthesis of natural and unnatural steroids represents one of the most impressive stories in organic synthesis.



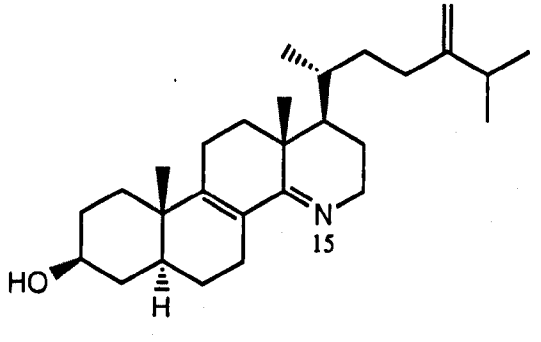
30 **31**; 38 %, 93 %de

Reagents: i, $SnCl_4$, $(Me_3Si)_2O$, -78°C.

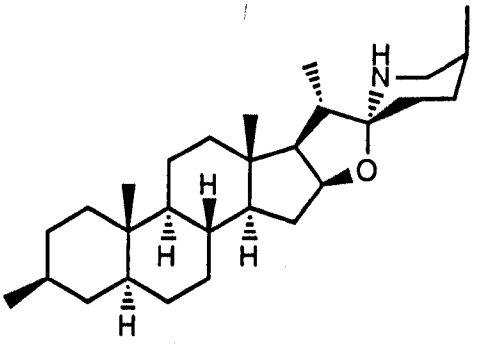
Scheme 9

1.2 AZASTEROIDS

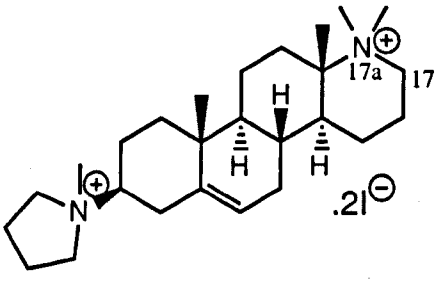
Azasteroids are a group of natural and unnatural products that contain nitrogen either in the tetracyclic steroidal core (nuclear azasteroids), or as part of an extra ring system or sidechain, apart from the tetracyclic core (extranuclear azasteroids), which show a wide and interesting variety of biological activity.[27] One of the few examples of a nuclear azasteroid natural product is A25822B **32**, a 15-azasteroid, where nitrogen is incorporated as part of an α,β-unsaturated imine in a homo-D-ring. An example of the more common class of extranuclear azasteroid natural products is the hexacyclic androstane-tomatidine **33**, isolated from tomato plants, where the nitrogen atom is incorporated as part of a spirofused hemiaminal. Extensive research as been conducted into nuclear azasteroids during the exploration of the biological activity of these functionally flexible molecules. Therefore, unnatural nuclear azasteroids predominate in the literature in this area and an example of this type of molecule is the neuromuscular blocking agent chandonium iodide **34**, where the nitrogen containing functionality is a quaternary iodide salt in the homo-D-ring.



32; A25822B



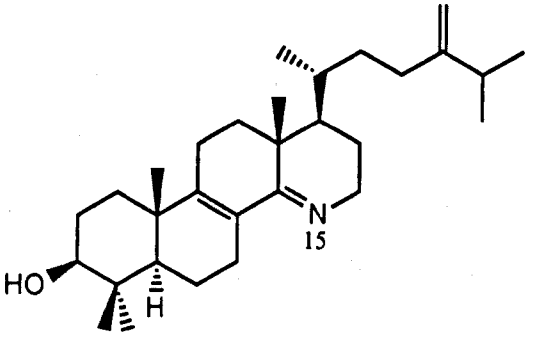
33; tomatidine



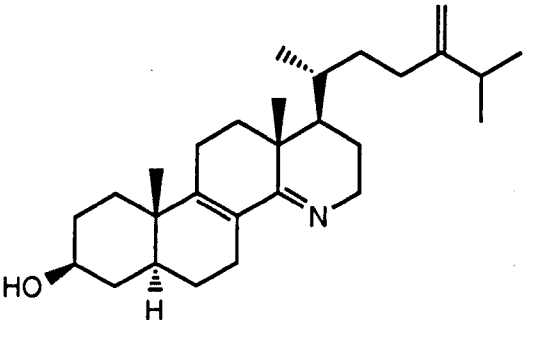
34; chandonium iodide

1.2.1 A25822

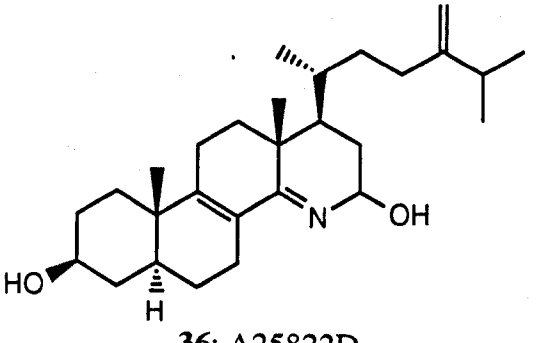
The range of natural products known as A25822 were isolated by chemists working at Eli Lilly in 1975 from the mould *Geotrichum flavo-brunneum*.[28] This mixture was subsequently identified as seven diverse structures all related to a central D-homo-15-azasteroidal ring structure.[29] These compounds became known as factors A **35**, B **32**, D **36**, H, L **37**, M **38**, N **39**, where the factor A25822H was unstable and had an undefinable structure.



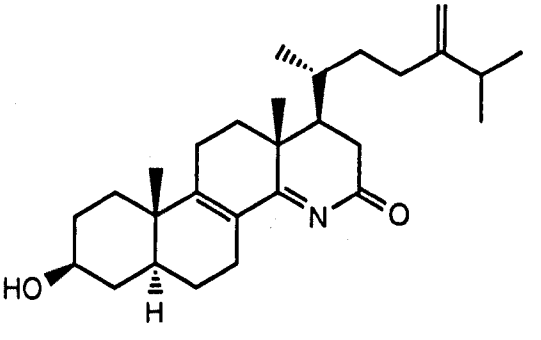
35; A25822A



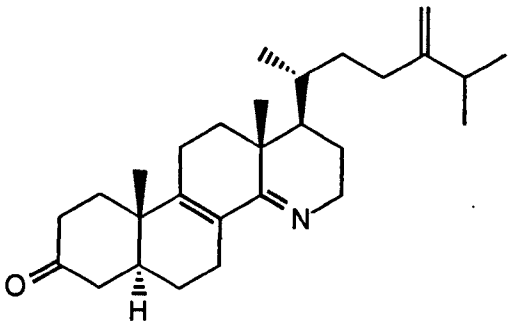
32; A25822B



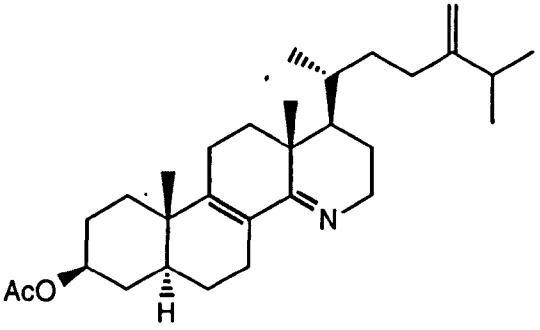
36; A25822D



37; A25822L

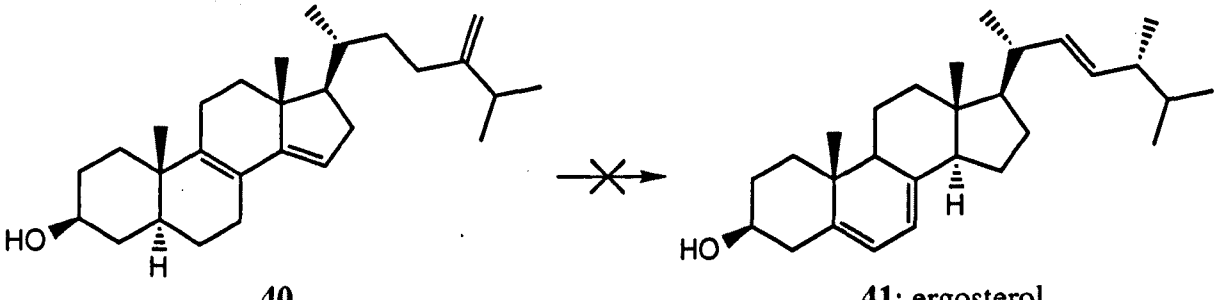


38; A25822M



39; A25822N

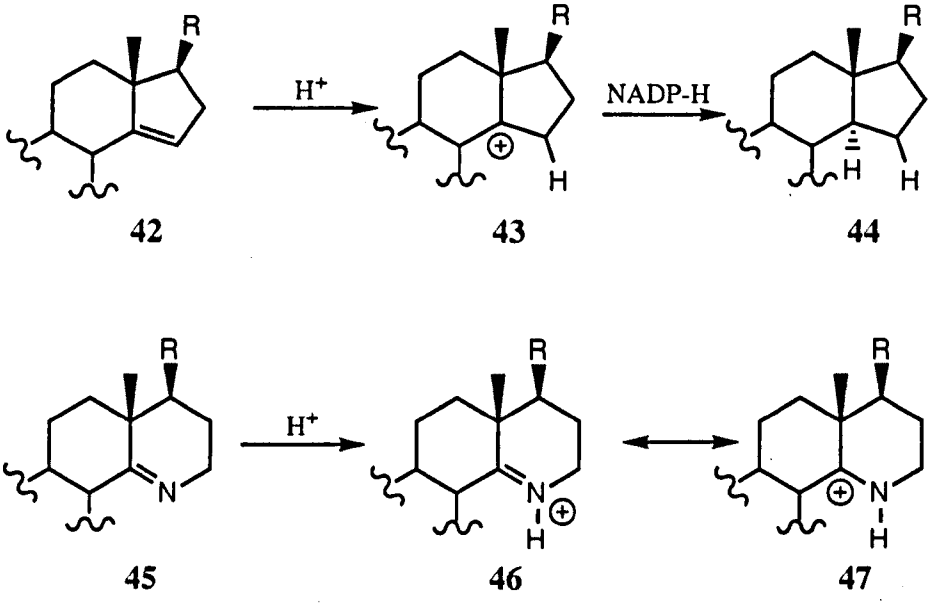
An investigation into their biosynthesis showed that increasing the amount of L-tryptophan in the fungal broth increased the yield of the azasteroids, but that racemic and D-tryptophan were not as active, implying this amino acid is the source of nitrogen during the biosynthesis.[30] Also it was shown that squalene and *iso*-valeric acid increased the yield of the azasteroids implying that the squalene oxide cascade is performed, unusually, in the bacterial cells.[30] Subsequent investigation into the biological activity of these compounds showed that A25822B **32**, by far the most abundant metabolite, also possessed the strongest antifungal activity.[31] A25822B **32** was shown to deactivate fungal cell proliferation by blocking ergosterol **41** synthesis at the NADP-H mediated $\Delta^{14\text{-}15}$ reductase stage from the triene **40** (Scheme 10).[32] It has been shown that treatment of fungal systems with A25822B **32** results in a build-up of the $\Delta^{14\text{-}15}$ precursor **40** in the fungal broth and loss of ergosterol **41**, consumed during cell proliferation.



40 **41**; ergosterol

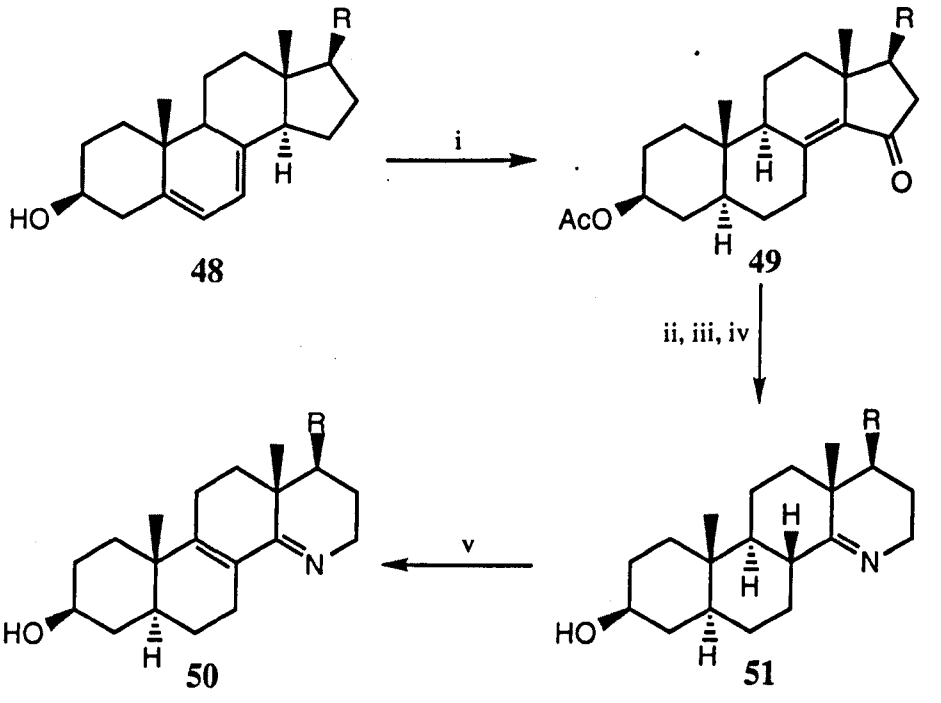
Scheme 10

It has been proposed that the conjugate acid of A25822B, **46**, binds competitively to the NADP-H site in the reductase enzyme, thus inhibiting this pathway by blocking the availability of these sites to the natural enzyme substrate **40**. There is clear congruence between the intermediate of reduction **43** in the biosynthetic pathway and the conjugate acids **46** and **47** (Scheme 11).[34] A25822B **32** has also been seen to be a potent plant growth regulator, again by blocking phytosterol biosynthesis at the $\Delta^{14\text{-}15}$ reduction stage.[35]



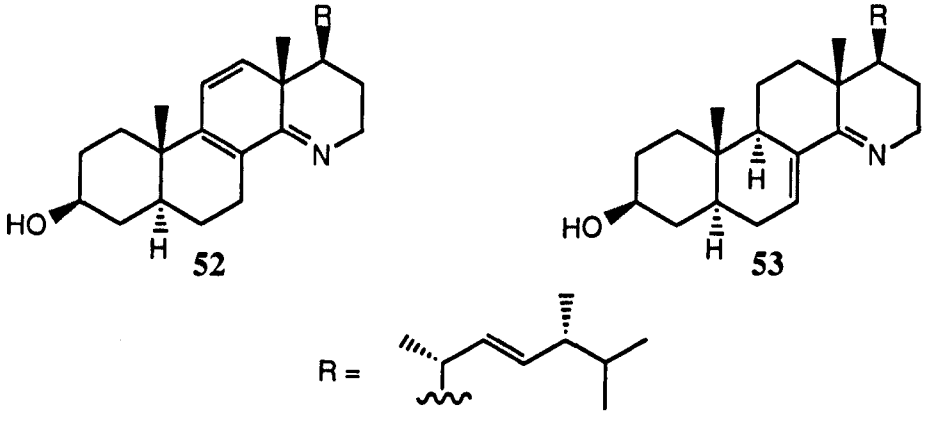
Scheme 11

This powerful and broad ranging *in vivo* biological activity has naturally spawned many partial and total synthetic efforts from the chemical community. In 1983 Barton *et al.*[36] synthesised derivatives of A25822B **32** using ergosterol **41** as the starting material. Conversion of **41** into the known ketone **49** progressed *via* literature procedures.[37] Generation of an oxime and then Beckmann rearrangement followed by reduction installed the imine into the homo-D-ring of **51**. Dehydrogenation of the steroid using DDQ afforded the A25822B analogue **50** and other unsaturated products **52** and **53** (Scheme 12).



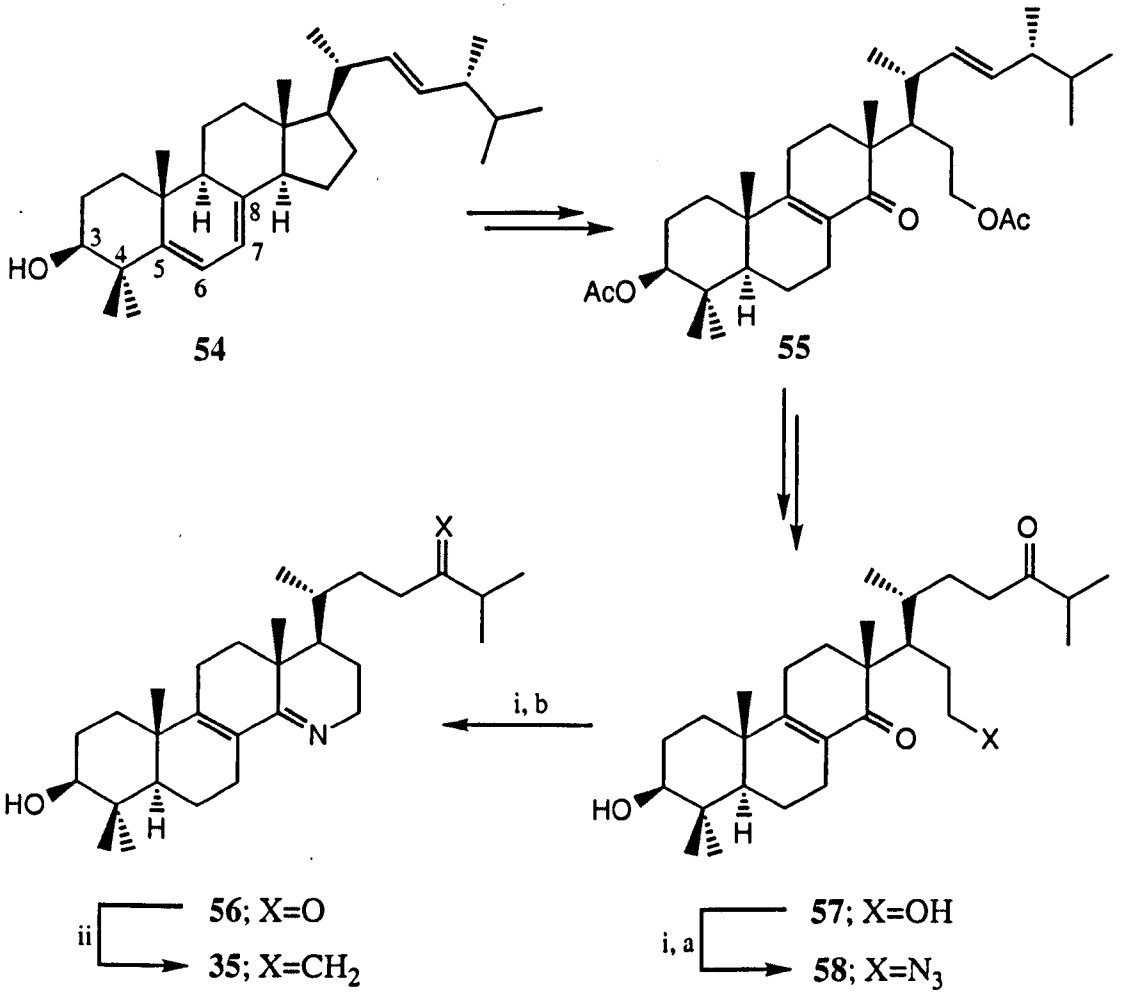
Reagents: i, reference 37; ii, ClNHOH, pyridine, MeOH, reflux; iii, *p*-toluenesulfonyl chloride, pyridine then HCl, MeOH; iv, $LiAlH_4$, THF, reflux; v, DDQ, C_6H_6, reflux.

Scheme 12



Workers at Smith-Kline and French undertook the total synthesis of A25822A **35**, again starting from a suitable steroid, in this case the diene (3β, 22*E*)-4,4-dimethyl ergosta-5,7,2-trien-3-ol **54**.[38,39] Isomerisation of **54** followed by oxidative ring opening and protection of the resulting functional groups gave the tricycle **55**. The side chain was removed by ozonolyisis and then replaced to give the key intermediate

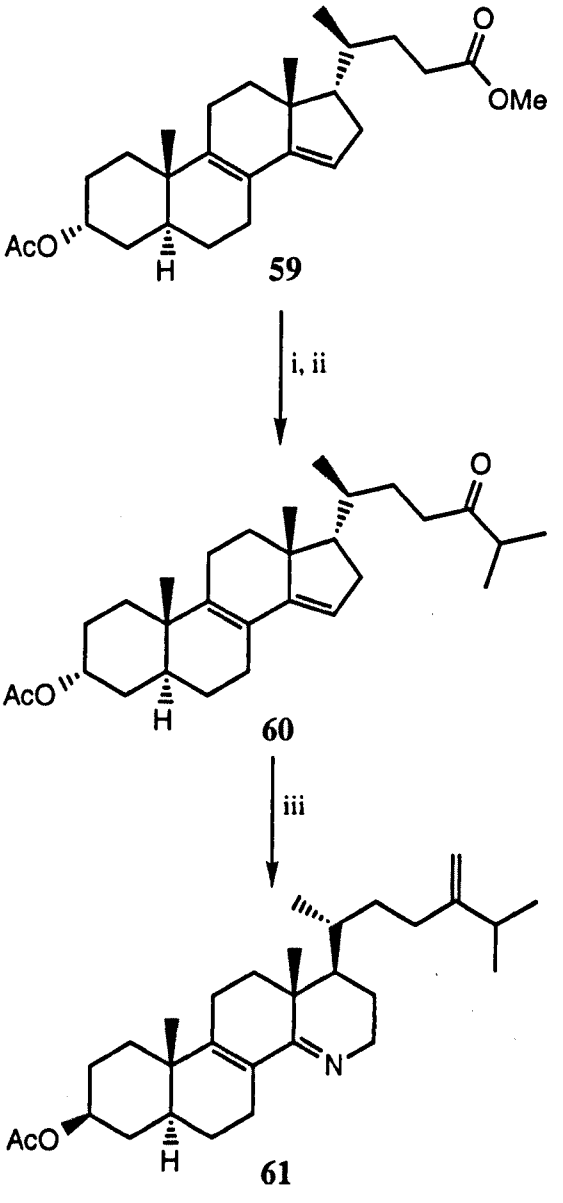
57. Highlighting the method used for the formation of the azasteroidal core, cyclisation of the tricycle **57** using an aza-Wittig protocol proceeded smoothly *via* the intermediate azide **58**, installed using a Mitsunobu reaction.[40] This sequence of reactions gave the azasteroid ring system **56** which was converted to A25822A **35** using a Wittig olefination reaction (Scheme 13). These workers progressed to synthesise a number of analogues of A25822A and A25822B. They employed the Beckmann rearrangement strategy, previously used by Barton,[36] to install the imine in the D-ring, again starting from steroidal starting materials.[41]



Reagents: i, a) DPPA, DEAD, PPh_3, THF; b) PPh_3, 70°C; ii, Ph_3PMeBr, $KOC(Me)_2Et$, toluene, 60°C.

Scheme 13

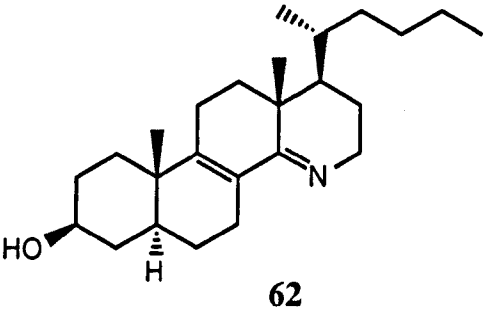
Workers from ICI Agrochemicals at Jealott's Hill were also interested in the fungicidal properties of the A25822 series of compounds and undertook the synthesis of an acetate protected version of A25822B using the same ring formation methodology as Dolle and Kruse.[38,42] However, they started from Cholic acid derivatives such as **59** and introduced the side chain using Grignard methodology, *via* an acid chloride, resulting in a synthesis of the ketone **60**. This was then converted into the protected version of A25822B **61** (Scheme 14).



Reagents: i, LiOH, MeOH, H_2O; ii, Ac_2O, pyridine, CH_2Cl_2; $(COCl)_2$ toluene; *i*-PrMgCl, CuCN, THF; iii, reference 38.

Scheme 14

Back and co-workers became interested in the synthesis of the A25822 class of compounds and developed new methodology for both the synthesis of the side chains and the ring system. Introduction of a side chain was achieved using a stereoselective conjugate addition to an α,β-unsaturated epoxide. Subsequent Baeyer-Villiger ring expansion and introduction of nitrogen gave the unnatural product **62**.[43] This methodology was then used in the first total synthesis of the natural product A25822B **32**.

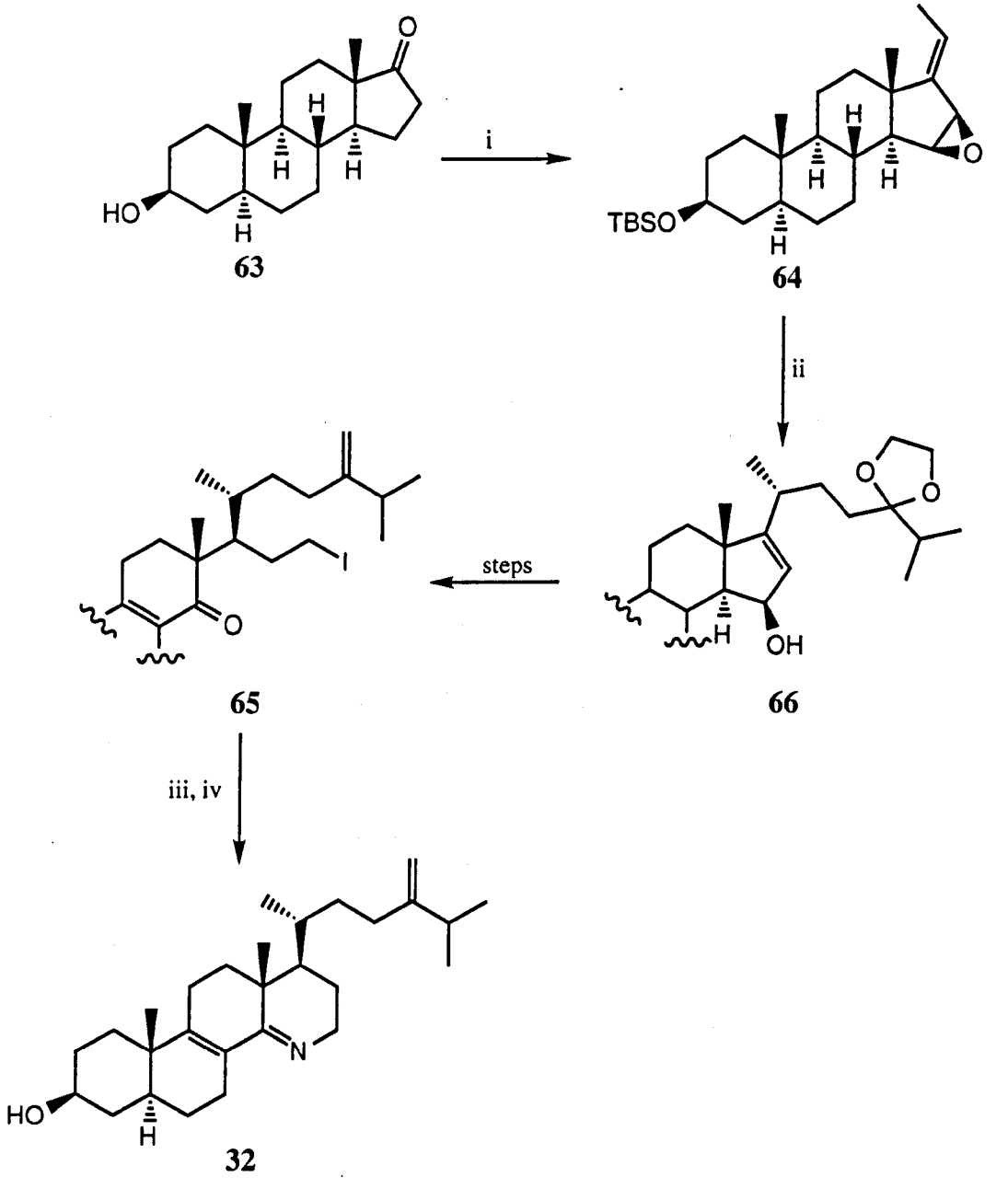


62

Following literature procedures they synthesised the α,β-unsaturated epoxide **64** from epiandrostane **63**.[44] A highly stereoselective addition of an organocuprate to the α,β unsaturated epoxide introduced the side chain in the form of the acetal **66**.[44c] Again, a Baeyer-Villiger ring expansion generated a six membered D-ring and subsequent functional group manipulations gave the key iodoketone **65**. Amination and acid catalysed cyclisation gave the natural product **32** (Scheme 15).[45]

Interest continues in this range of natural products with recent work being published by chemists from Jealott's Hill on the synthesis of C,D-ring analogues of A25822B.[46] These authors investigated a range of compounds with various side chains at C-17, also exploring the effects on biological activity of heteroatom substitutions into the

ring system. A number of different systems have been synthesised, but no data about the effect on the biological activity have been published.



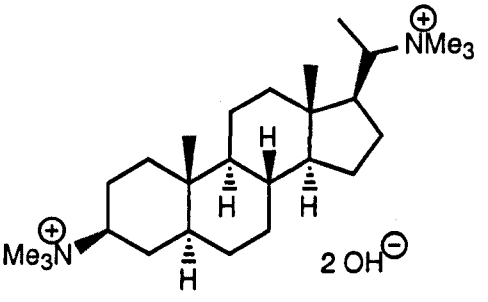
63 64 65 66 32

Reagents: i, reference 44; ii, $(CH_3)_2CHC(OCH_2CH_2O)CH_2CH_2I$, *t*-BuLi, Et_2O, -78°C; CuCN, Et_2O, -78°C; **64**, Et_2O, -78°C; iii, NH_3, MeOH, NH_4Cl; iv, H_3O^+, THF.

Scheme 15

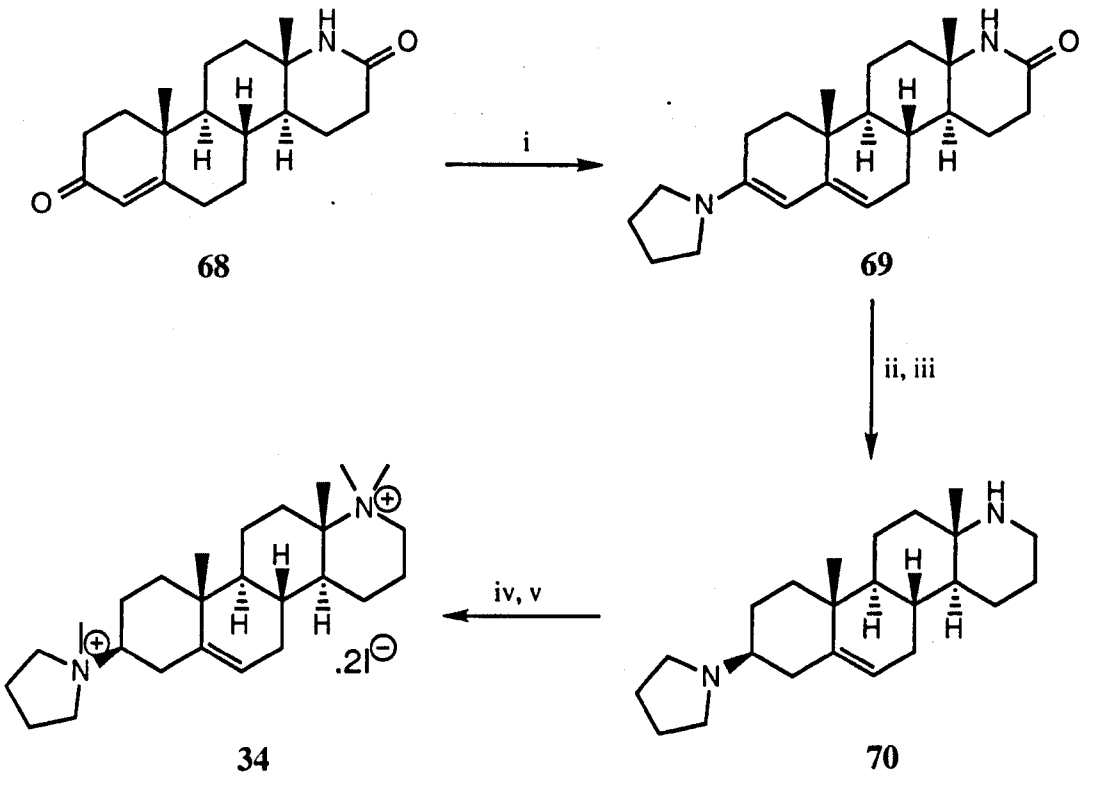
1.2.2 Neuromuscular Blocking Agents

Following the discovery of the steroidal alkaloid malouetine **67** and synthesis of some of its stereoisomers, which exhibit potent neuromuscular blocking activity, many other steroidal based bisonium compounds have been synthesised.[47,48] The rigid skeleton of the steroidal system allows the prediction of the interonium distance, which is a very important aspect of neuromuscular blocking activity,[49] and has led to successful development of pharmaceutical products based on these compounds.



67; malouetine

Synthetic work by the group of Singh resulted in the discovery of chandonium iodide **34** as a potent and selective neuromuscular blocking agent with minor ganglion blocking activity and little effect on blood presure.[50] The synthesis of chandonium iodide **34** started from the dione-D-homo-17a-azasteroid **68** which had previously been prepared by Reagan and Hayes.[51] Condensation with pyrrolidine led to the enamine **69** and subsequent reduction of the enamine and amide gave the diamine **70**. Methylation followed by conversion into the dimethiodide derivative realised the target **34** (Scheme 16). Continuation of synthetic studies in this area by Singh and co-workers failed to uncover a more potent agent than chandonium iodide which has been marketed as an effective nondepolarizing neuromuscular blocking agent.[52,53]

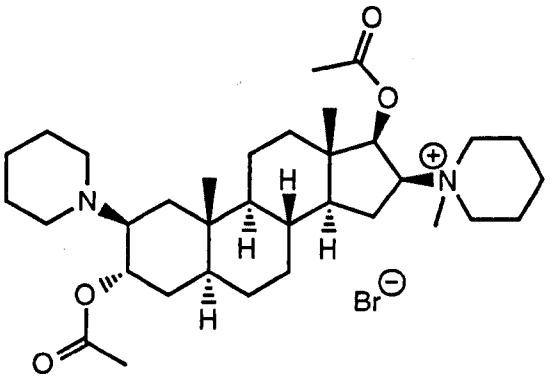


68 **69** **70** **34**

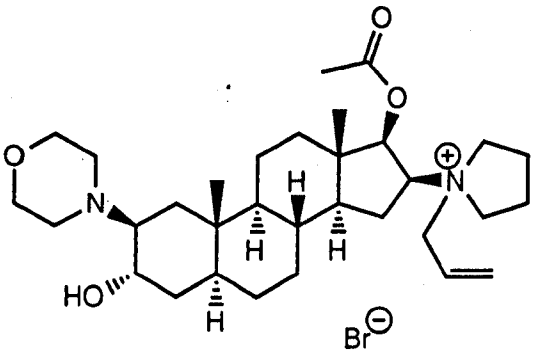
Reagents: i, pyrrolidine, MeOH, reflux; ii, $NaBH_4$, MeOH, reflux; iii, Na, *n*-pentanol, reflux; iv, formic acid, formalin, reflux; v, MeI, ethanol, reflux.

Scheme 16

This work has been developed in the area of extranuclear azasteroids by Akzo Nobel. Using maloutine **67** as a lead compound in a pharmaceutical study, they were able to develop three therapeutic agents as neuromuscular blocking agents for use in surgery. These are pancuronium bromide, vecuronium bromide **71**, a hexacyclic steroid with a single quaternized nitrogen and rocurnium bromide **72**, a structurally related compound.[54,55]



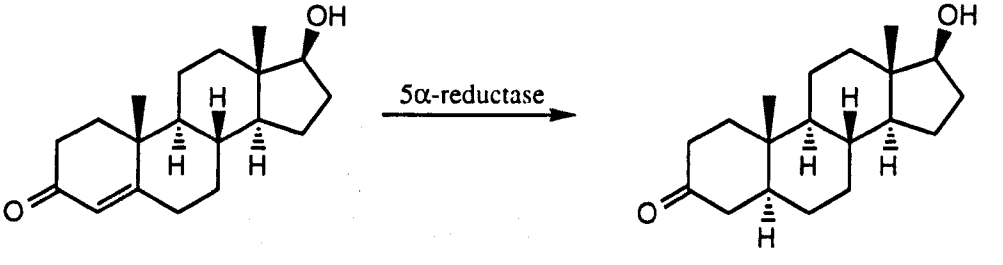
71; vercuronium bromide



72; rocurnium bromide

1.2.3 5α-Reductase Inhibitors

Numerous 4 and 6-azasteroids have shown activity as 5α-reductase inhibitors. This important area of research has been driven by the implication of 5α-dihydrotestosterone **74** as an intracellular androgenic in a number of conditions such as acne, benign prostatic hyperplasia and male pattern baldness.[56] Many 4 and 6-azasteroids have been shown to block both type I, expressed in the skin, and type II, expressed in the prostate, 5α-reductases and thus, the biosynthesis of 5α-dihydrotestosterone **74** from testosterone **73** (Scheme 17).



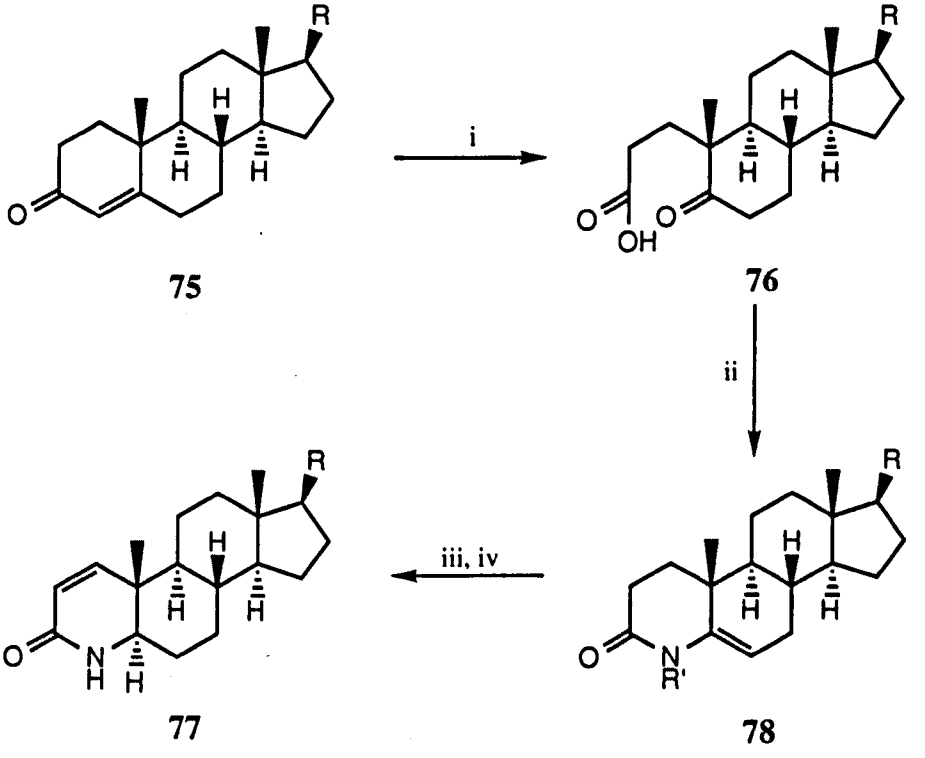
73; testosterone

74; 5α-dihydrotestosterone

Scheme 17

Rasmusson and co-workers have had a deep interest in the use of 4-azasteroids as 5α-reductase inhibitors and have synthesised a wide range of these compounds for biological testing on rat, dog and human 5α-reductase enzymes.[56] Starting from

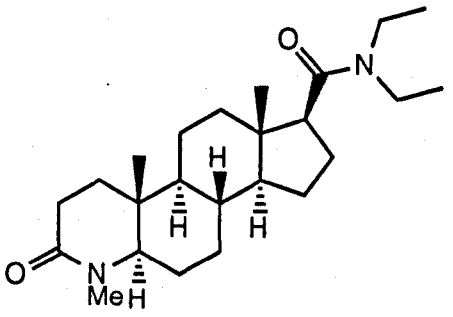
suitably substituted Δ^4-androstan-3-ones **75**, oxidative ring opening yielded **76**. A range of 4-aza-androstanes **78** were synthesised by condensation with a selection of amines. Hydrogenation of the Δ^5 bond, in the case where R'=H, and then oxidation in the Δ^1 position, using benzene selenic anhydride, led to a series of highly active reductase inhibitors **77** (Scheme 18).[57] Further modification of **77** and **78** gave a selection of structurally diverse steroids which were used for testing against 5-α reductases. A key lead compound, on which this study was based, was the 4-aza-androstane (4-MA) **79**, which showed high activity against rat and human 5α-reductase.[56c,58] Merck have since taken finasteride (MK-906) **80**, a compound from these studies, onto clinical trials although the results did not show the expected therapeutic activity.[59] A related series of compounds have also been synthesised by Labrie *et al.* and their biological activity has been assessed against both Type I and Type II Human 5α-reductases.[60]



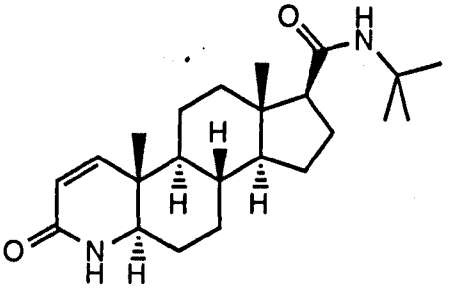
75 **76** **77** **78**

Reagents; i, $KMnO_4/NaIO_4$, *t*-BuOH, reflux; ii, $R'NH_2$, reflux; iii, H_2, Pt, CH_3CO_2H; iv, $(C_6H_5SeO)_2O$, C_6H_5Cl.

Scheme 18

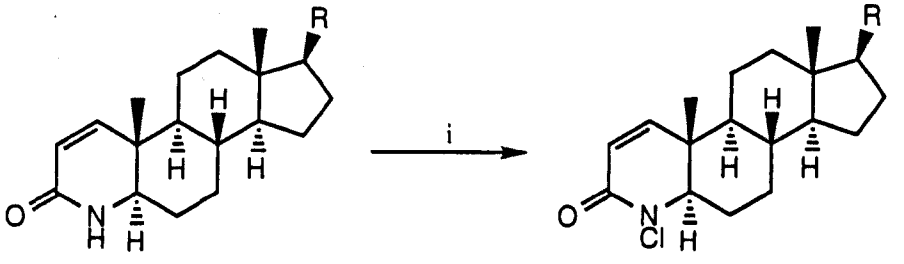


79; 4-MA



80; MK-906

Back and co-workers have published much work on azasteroids and they synthesised a range of *N*-chloro derivatives containing the α,β-unsaturated amide found in MK-906 **80**.[61] Treatment of the azasteroid **81** with trichloroisocyanuric acid (TCIA) gave the target *N*-chloro compounds **82** in excellent yields (Scheme 19).[61a] It has been hypothesised that these compounds may be irreversible inhibitors of 5α-reductases, with displacement of chloride resulting in covalent bond formation between the nitrogen and a cystine residue.



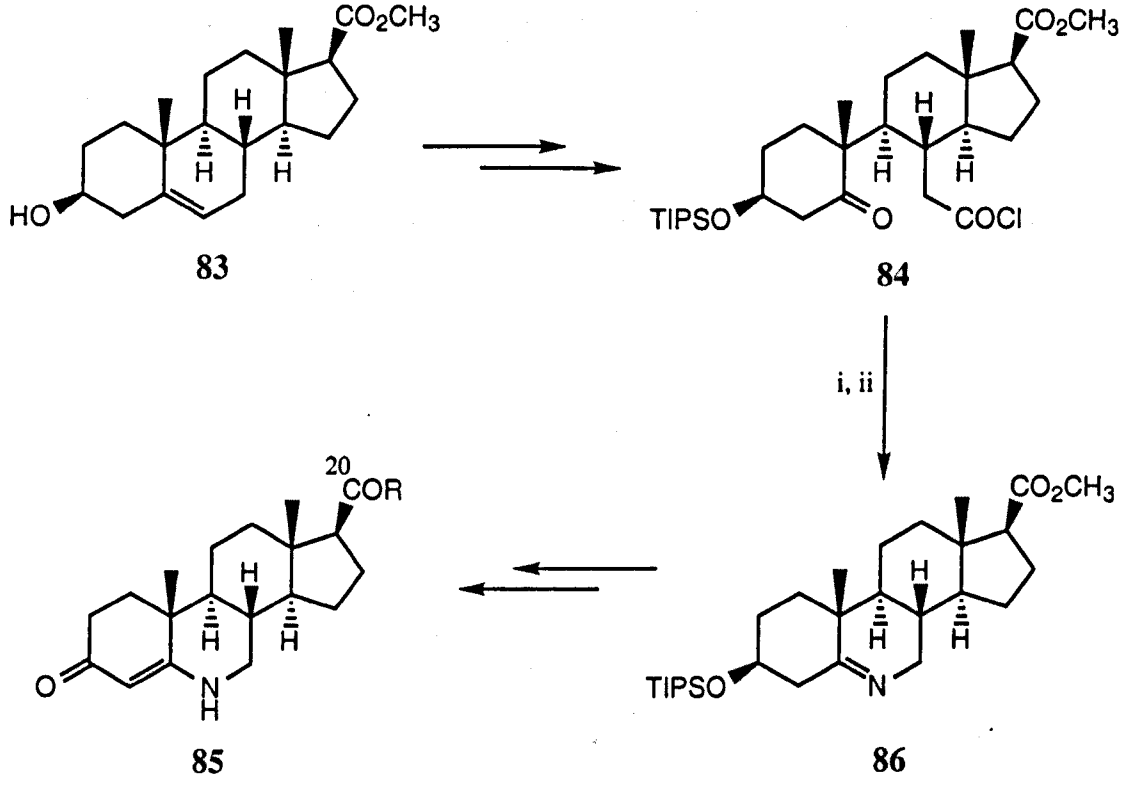
81 **82**

Reagents: i, TCIA, $CHCl_3$, reflux.

Scheme 19

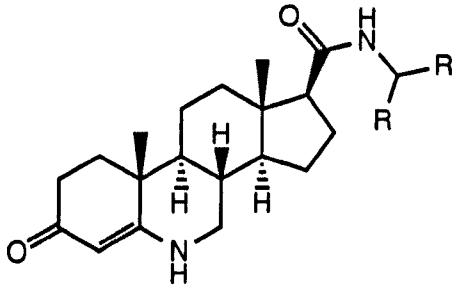
There has also been extensive interest in 6-azasteroids as 5α-reductase inhibitors and a range of these molecules have undergone *in vivo* testing by a group from Glaxo.[62,63] Synthesis of the key steroid nucleus followed a nine step route based on the original work performed by Lettré and co-workers.[64] Thus, starting from the known androstane **83**,[56c] oxidative ring opening followed by acyl chloride formation gave the

tricyclic compound **84**. Introduction of azide and silica catalysed Curtius rearrangement generated the key aza-B-ring in **86**. Functional group manipulation gave structural variations at the C-20 position which led to a range of 6-aza-androstanes **85**. These were further modified to give a huge variety of compounds for biological evaluation. Results from this investigation highlighted a number of compounds such as the azasteroids **87** and **88** with good *in vivo* efficacy and pharmacokinetics.



Reagents: i, NaN_3, THF; ii, SiO_2, Δ.

Scheme 20

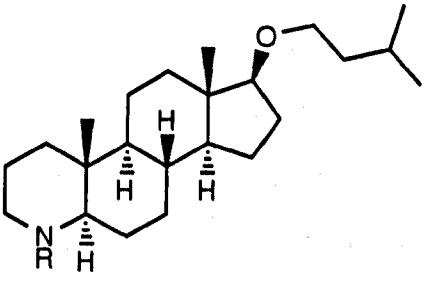


87; R=cyclohexyl
88; R=4-chlorophenyl

1.2.4 Other Biological Uses

Aside from the three main areas of biological activity already highlighted, azasteroids have been used for a range of other functions. 4-Azasteroids showed potency as antimicrobial agents in a study performed by Doorenbos and co-workers.[65] They synthesised a variety of 4-azasteroids using Curtius rearrangement methodology resulting in the identification of the androstane **89** and the methyl derivative **90** as having antimicrobial activity against Gram-positive bacteria, yeasts and moulds.

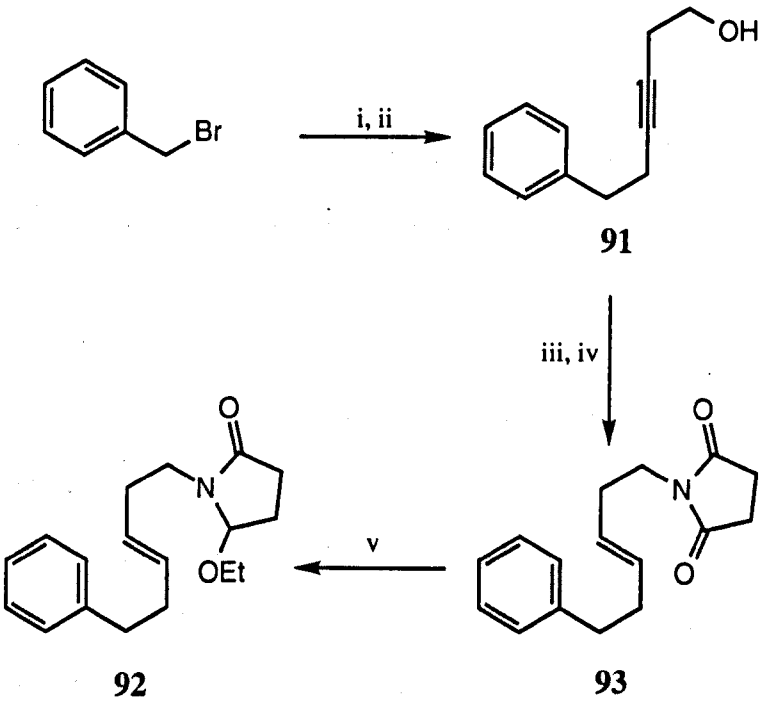
Azasteroids have also been used as probes for the mechanisms of cholesterol metabolism,[66] as antifertility compounds in a study on rats,[67] and in various synthetic studies investigating a number of biological areas.[68]



89; R=H
90; R=CH_3

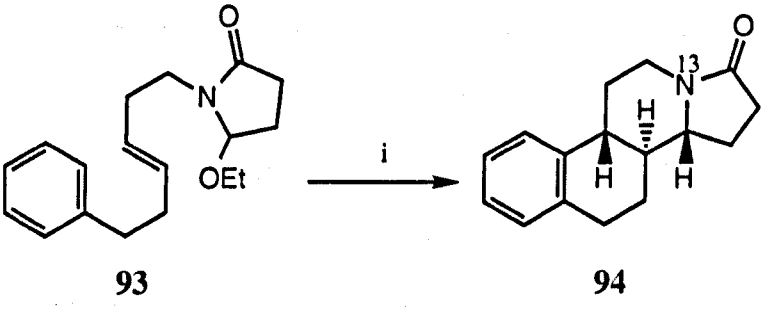
1.2.5 Total Synthesis of Azasteroids

The review above demonstrates that nuclear azasteroids exhibit a wide range of biological activity representing a variety of applications. This has led the development of a number of synthetic efforts in this area. However, most of this work concentrates on partial syntheses starting from readily available steroid materials and there have only been a few reported total synthesis of azasteroids.[27,69] We have seen that this is in contrast to carbocyclic steroids where biomimetic cascades are a major area of research. The main use of azasteroid total synthesis is in the incorporation of nitrogen into a ring junction position in the tetracyclic nucleus. This method has been exemplified by the work of Speckamp and co-workers who have specialised in pseudo-biomimetic acyl iminum ion cyclisations to give 13-azasteroids.[70] Synthesis of the precursor **92** started from benzyl bromide. Wurtz coupling with propargyl magnesium bromide followed by alkylation with ethylene oxide gave the key intermediate **91**. Sodium/ammonia reduction and introduction of succinimide using a Mitsunobu coupling yielded **93**. Subsequent reduction gave the desired precursor **92** (Scheme 21). Treatment of the precursor **92** with formic acid resulted in a highly stereoselective cyclisation to yield the 13-azasteroid **94** in 89 % yield (Scheme 22). This methodology has been used recently in the synthesis of 10-chloro-13-azasteroids for investigation into their biological activity.[71]



Reagents: i, propargyl magnesium bromide, Et_2O, 10°C; ii, Li/NH_3, ethylene oxide, DMSO 0°C; iii, Na/NH_3; iv, succinimde, DMAD, PPh_3, THF; v, $NaBH_4$, EtOH, 5°C.

Scheme 21



Reagents: i, HCO_2H.

Scheme 22

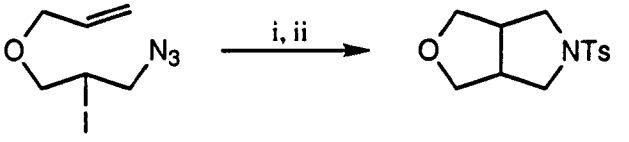
1.3 THE USE OF NITROGEN ELECTROPHORES IN HETEROCYCLE SYNTHESIS

The synthesis of ring systems *via* radical mediated cyclisation reactions is an ever expanding area in organic chemistry. Many carbon ring systems have been synthesised over the past decades and this research has been applied to natural product total synthesis.[72] Until recently however, the use of radical cyclisations in the synthesis of nitrogen heterocycles was a relatively under explored area, but there has now been an explosion of work investigating the possibilities of this methodology.[73] Two strategies towards nitrogen heterocycles have been developed, the use of nitrogen containing electrophores and the use of nitrogen centred radicals. For example, the generation of aminyl radicals from many different precursors has been explored by a number of researchers.[74] Iminyl radicals have also been used to good effect in the synthesis of heterocycles by Zard.[74d,75] Nitrogen can be incorporated into many different functional groups containing unsaturation suitable for accepting radical additions. The combination of these groups and the different nitrogen centred radicals has allowed researchers to explore many different avenues in the synthesis of heterocycles.

1.3.1 Azides

Azides, as well as being used as precursors to aminyl radicals *via* their reaction with tributyltin hydride, have been used widely as radical acceptors. In this case TTMSS has to be used as the initiator in the reactions, homolytically cleaving a halide-carbon

bond to generate radicals in the presence of azides. Kim and co-workers[76] have developed the use of azides as radical acceptors in the formation of 5 membered rings. For example, generation of an alkyl radical by TTMSS from the iodide **95** followed by two 5-*exo*-trig cyclisations resulted in the formation of the fused THF/pyrrolidinone **96** in 56 % yield (Scheme 23). The initial ring closure generated the tetrahydrofuran and subsequent cyclisation onto the azide, with loss of nitrogen, gave the product **96** after tosylation.

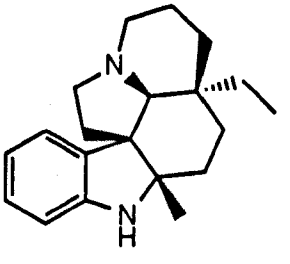


95 **96**

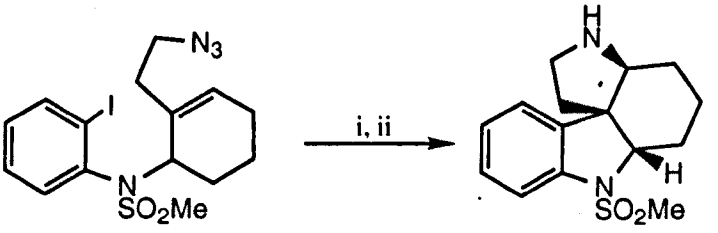
Reagents: i, $(TMS)_3SiH$, AIBN, C_6H_6, 80°C; ii, tosylation

Scheme 23

Murphy and co-workers[77] have used azides as radical acceptors in the key step of a synthetic approach towards aspidospermidine **97**. The tetracyclic core **99** was synthesised from the aryl iodide **98** with high diastereoselectivity and in an excellent yield of 95 % after TTMSS induced radical generation followed by two 5-*exo*-trig cyclisations, the second one terminating on the azide (Scheme 24).



97



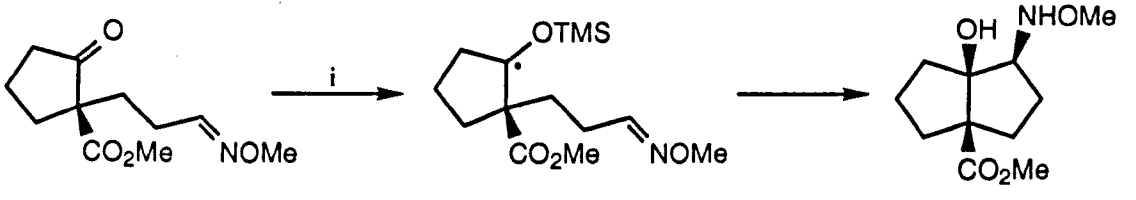
98 **99**

Reagents: i, $(TMS)_3SiH$, AIBN, C_6H_6, 80°C; ii, H_2O.

Scheme 24

1.3.2 Oximes

Oxime ethers are the most explored of the unsaturated nitrogen containing electrophores and they were the first system to be developed for synthesis. Even though they have not been applied to the synthesis of nitrogen containing heterocycles, this work represents an historically important development in radical chemistry. A large number of systems have been explored for many different purposes and the work has been extensively reviewed in the recent literature.[73] One of the first uses of this functional group was by Corey in 1983.[78] Generation of the trimethylsilyl protected ketyl radical **101** from the ketone **100**, followed by a 5-*exo*-trig cyclisation onto the oxime resulted in the formation of the bicyclic system **102** (Scheme 25).

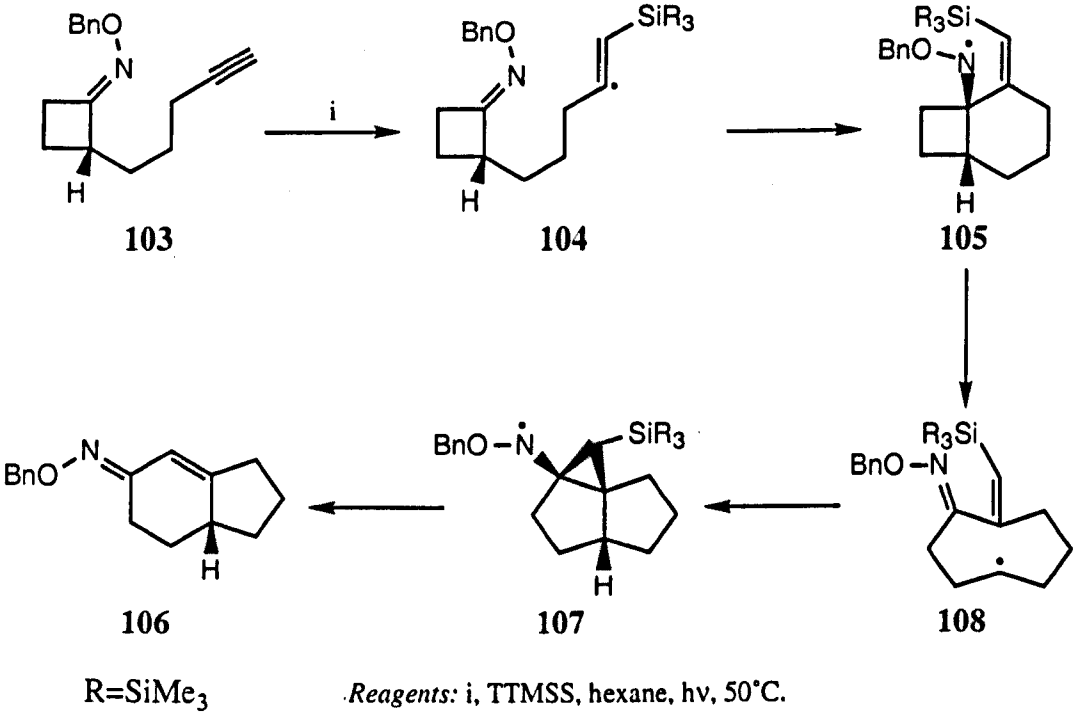


100 **101** **102**

Reagents: i, Zn, TMSCl, lutidine, THF, reflux.

Scheme 25

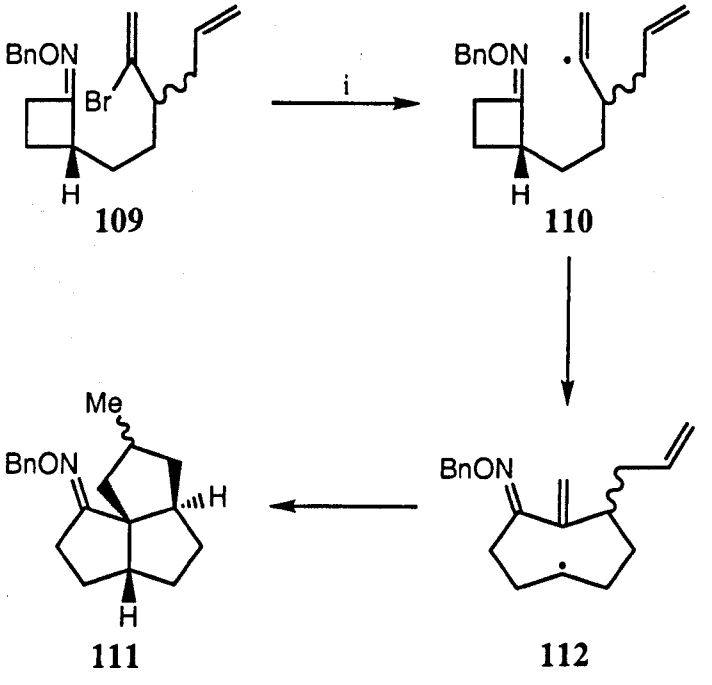
More recent work by Pattenden and co-workers has shown some of the flexibility that oximes exhibit.[79] The discovery of a novel double ring expansion cyclisation process led to the synthesis of the bicyclic system **106** in 70 % yield from the cyclobutane oxime **103**. Thus, **103** was subjected to radical generating conditions, *viz:* TTMSS, hexane, 50°C, hν; which resulted in the formation of the vinyl radical **104**. Upon 6-*exo*-trig cyclisation the resulting nitrogen centred radical **105** underwent β-fission to leave the 8 membered ring **108**. Transannulation of this radical **108** followed by 3-*exo*-trig cyclisation gave another nitrogen centred radical **107**, which also underwent β-fission and elimination of the silyl group to yield the bicyclic compound **106** (Scheme 26).



Scheme 26

This work was then taken to an extra dimension with the synthesis of the angular fused triquinane **111** from the vinyl bromide **109**.[80] Thus, generation of the vinyl radical **110**, which underwent a similar cyclisation/fragmentation sequence to the one which resulted in the formation of the eight membered ring **108** from **104**, led to the

intermediate radical **112**. This radical **112** then transannulated and underwent a 5-*exo*-trig cyclisation to give the triquinane **111** in 38 % as a 1:1 mixture of diastereoisomers (Scheme 27).

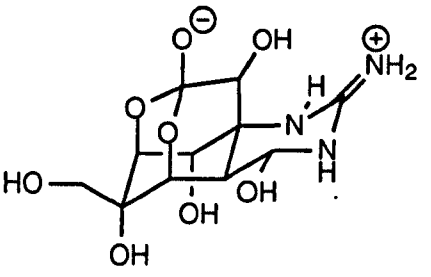


109 **110** **111** **112**

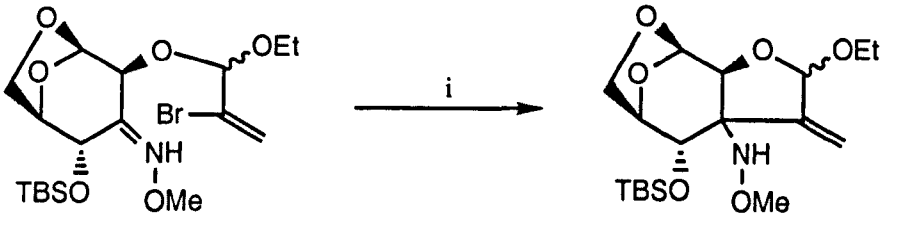
Reagents: i, TTMSS, C_6H_6, hν, reflux.

Scheme 27

Recently Alsono and Noya used oximes as radical acceptors in their synthetic approaches towards the puffer fish toxin tetrodotoxin **113**.[81] Choosing the oxime ether containing anhydromannose derivative **114** as a precursor and treating it with $Bu_3SnCl/NaBH_3CN$ (an *in situ* generator of Bu_3SnH) and AIBN in *tert*-butanol at 80°C, they found that it underwent a 5-*exo*-trig cyclisation reaction to give the desired tricycle **115** in a modest 29 % yield (Scheme 28).



113



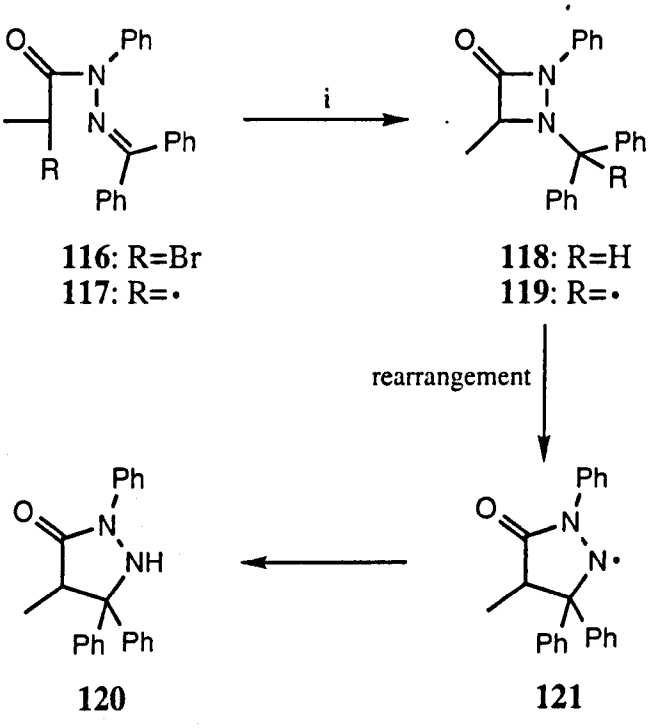
114 **115**

Reagents: i, Bu_3SnCl, $NaBH_3CN$, AIBN, *t*-BuOH, 90°C.

Scheme 28

1.3.3 Hydrazones

Radical reactions of hydrazones have not been explored to the same extent as oximes. Kim and co-workers have performed numerous studies into hydrazones as radical acceptors and generators but they have not used them in the synthesis of nitrogen heterocycles.[82] This work was extended by a variety of other authors who investigated hydrazones as radical acceptors and as radical clocks.[83] However, it was left to the group of Belletire to use hydrazones in the synthesis of heterocycles, albeit in a reaction designed to give a different product from the one isolated.[84] Taking the α-bromoacylphenyl hydrazone **116** and submitting it to standard radical conditions they were able to isolate pyrazolidinone **120** instead of the anticipated β-lactam product **118**. The authors proposed that the intermediate radical **117** underwent a 4-*exo*-trig cyclisation to give the intermediate radical **119**. Rearrangement of **119** gave radical **121** which was then quenched to give the isolated product **120** in 96 % yield, though a 5-*endo*-trig cyclisation would leave the same material (Scheme 29).



116: R=Br
117: R=•

118: R=H
119: R=•

120

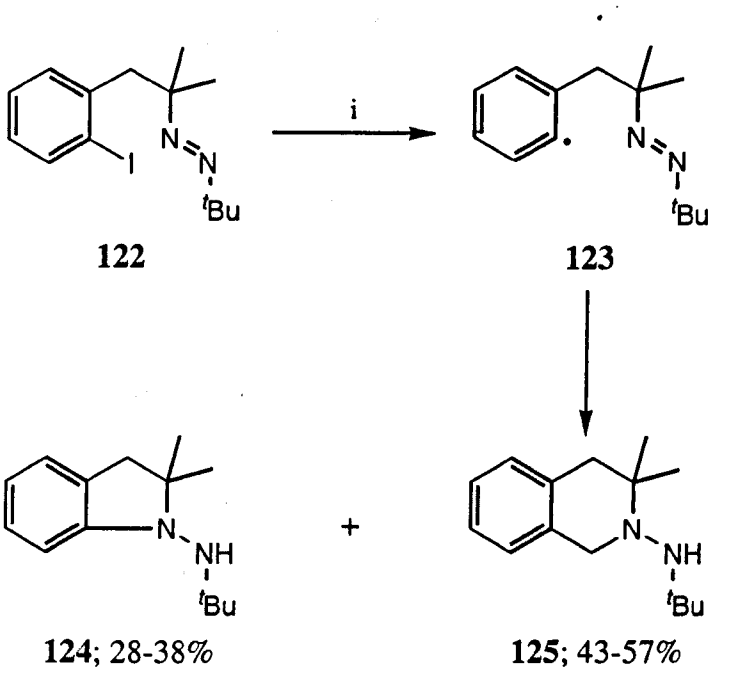
121

Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 29

1.3.4 Azo systems

In contrast to oximes, azo containing precursors have been used in the synthesis of nitrogen heterocycles. As part of a kinetic study into radical cyclisations Warkentin *et al.*[85] synthesised the aryl radical precursor **122** and measured rate constants for the intramolecular reactions of the corresponding radical **123**. They found that the radical species **123** underwent both 5-*exo* and 6-*endo*-trig cyclisation to yield the two products, **124** and **125**, respectively (Scheme 30). The ratio of the products depended on the concentration of tributyltin hydride in the reaction mixture.

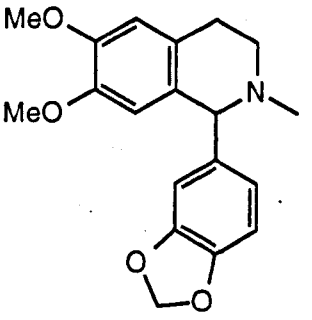


Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

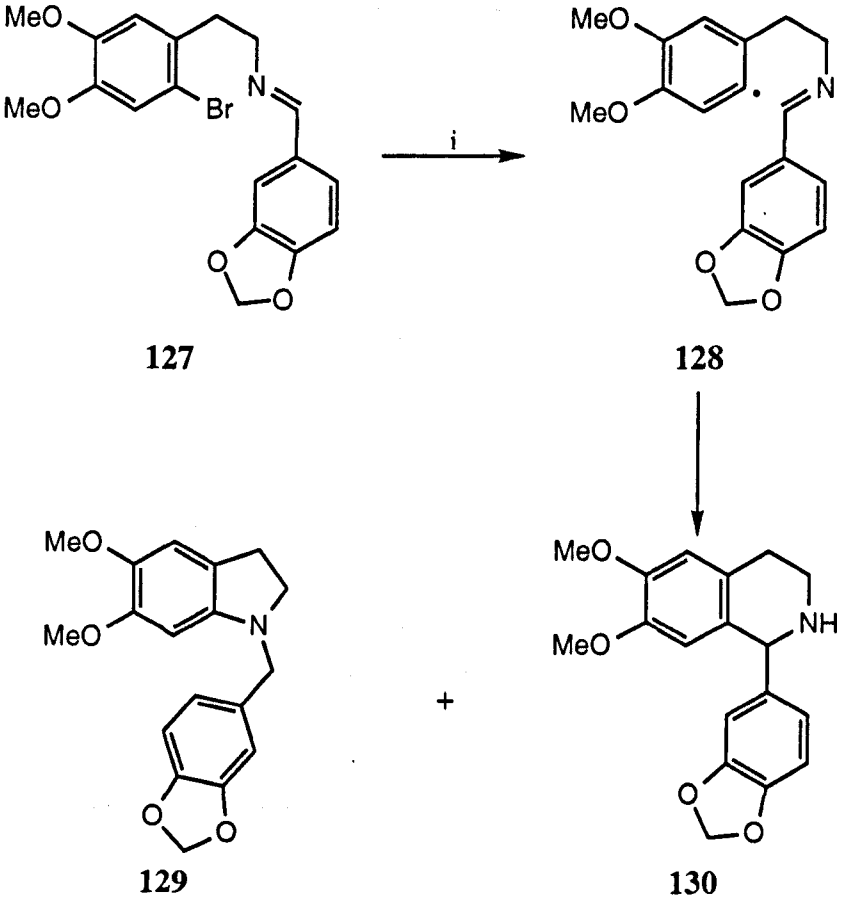
Scheme 30

1.3.5 Imines

During the 1990s imines have been investigated as radical acceptors and used to perform monocyclisations and as part of cascade sequences. In 1990, Takano reported a radical cyclisation onto an aryl imine as the key step in the synthesis of cryptostyline I **126**.[86] Generation of the aryl radical **128** from the bromide **127** resulted in a predominantly 6-*endo*-trig cyclisation to give the tetrahydro-*iso*-quinoline **130** in 56 % yield. The dihydroindole **129** was also isolated in 10 % yield following 5-*exo*-trig cyclisation from **128**.



126



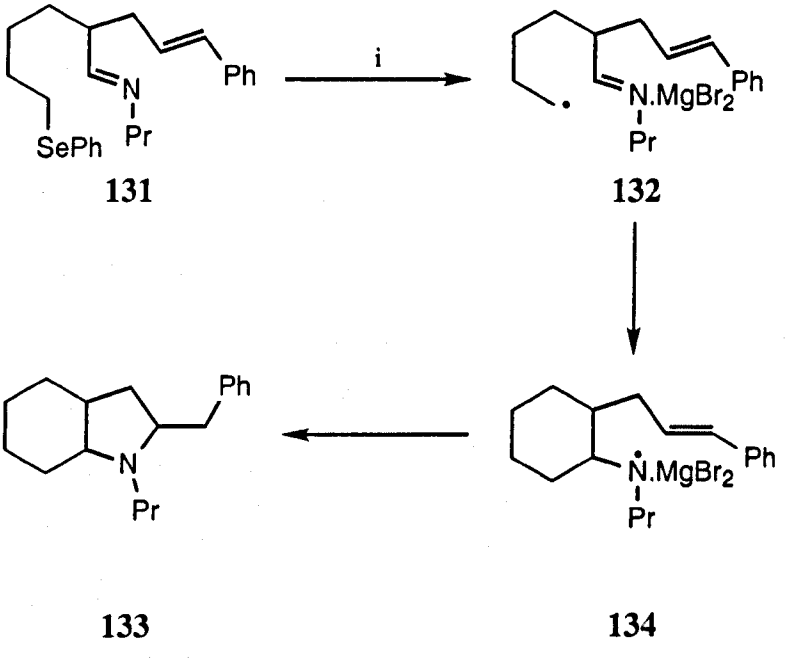
127 **128** **129** **130**

Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 31

Bowman and co-workers have concentrated their work in the area of alkyl radical cyclisation onto alkyl imines. Initial studies investigated the use of alkyl radicals in the formation of one ring by radical addition onto a variety of different imine systems.[83a] However, this work has been applied successfully to the synthesis of

bicyclic compounds *via* cascade processes.[87] For example, using the alkylselenoate **131** as a precursor, they were able to generate the alkyl radical **132**. A 6-*exo*-trig cyclisation and then a Lewis acid activated 5-*exo*-trig cyclisation of the intermediate aminyl radical **134**, resulted in the isolation of the bicycle **133** in 57 % yield as a mixture of diastereoisomers (Scheme 32).



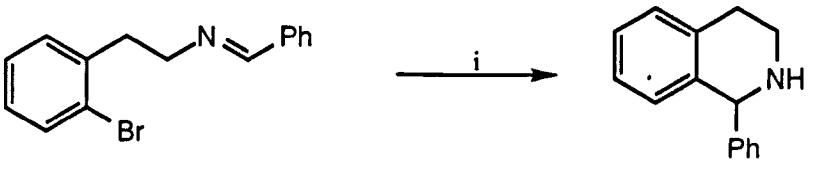
131 **132**

133 **134**

Reagents: i, Bu_3SnH, AIBN, $MgBr_2.Et_2O$, C_6H_6, 80°C.

Scheme 32

Bowman *et al.* found that precursors such as **131** could not be isolated due to the instability of the imine. Therefore, the condensation reaction to form the imine was performed in the same pot as the radical cyclisation reaction. Warkentin and co-workers approached the problem of imine instability by using highly reactive aryl radicals in cyclisations onto stabilised imines.[88] Thus, the aryl bromide **135**, when treated with tributyltin hydride and AIBN in benzene gave the tetrahydro-*iso*-quinoline **136** in 70 % yield (Scheme 33).



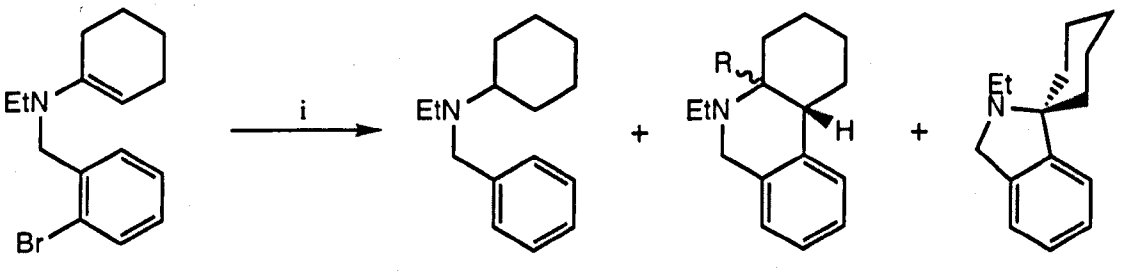
135 **136**

Reagents: i, Bu_3SnH, AIBN, C_6H_6, 80°C.

Scheme 33

1.3.6. Enamines

Glover *et al.*[89] have shown an interest in the cyclisation of aryl radicals onto enamines for the formation of tricyclic systems. They investigated the use of cyclohexenyl enamines as radical acceptors in a number of precursors and were able to show that systems of this type suffer from regioselectivity and stereoselectivity problems. For example, the ethyl substituted system **137**, upon treatment with tributyltin hydride/AIBN in toluene at 80°C gave a complex mixture of products. The fully reduced system **138** was isolated in 12 % yield. Both the *cis* and *trans* angular fused tricycles **139** and **140**, resulting from 6-*endo*-trig cyclisations, were isolated in 31 % and 13 % yields, respectively. Also the spirocycle **141** resulting from 5-*exo*-trig cyclisation was isolated in 28 % yield (Scheme 34). This result has probably hindered the development of the use of enamines in synthesis but has aided the development of the use of their structurally related cousins, enamides.



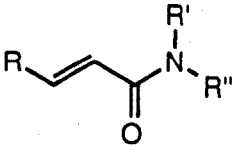
137 **138** **139**; R=β–H **140**; R=α–H **141**

Reagents: i, Bu_3SnH, AIBN, toluene, 80°C.

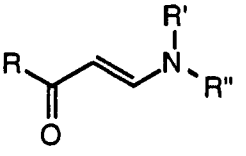
Scheme 34

1.3.7 Enamides

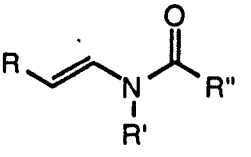
Using enamines and imines as electrophores in the synthesis of nitrogen heterocycles has resulted in problems with the stability of these functional groups in their preparation and in their radical reactions.[73,89] These problems have been overcome by the use of stabilised systems such as aromatic substituted imines,[88] oximes[80] and enamides.[90-93] Enamides can take a number of guises depending on the arrangement of the carbon-carbon double bond and the amide. For example, the three systems **142**, **143** and **144** have been used in the synthesis of heterocycles.



142

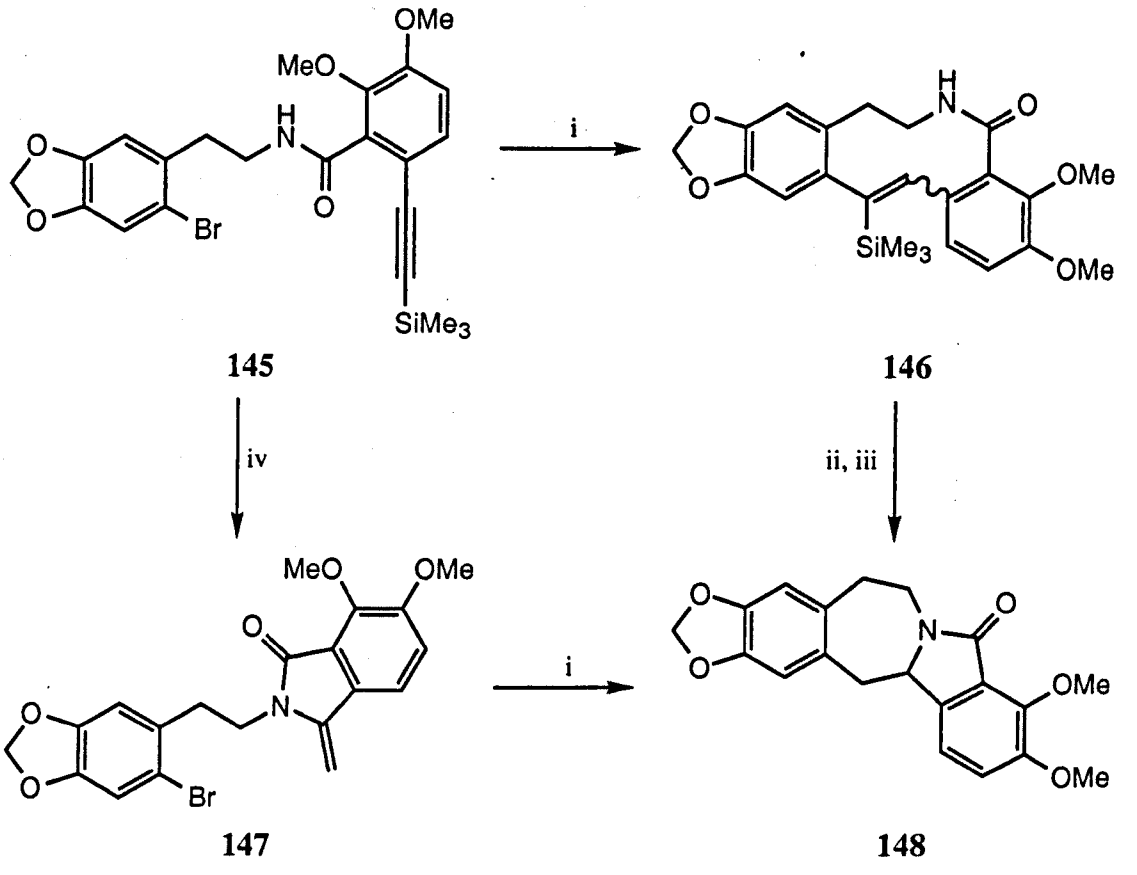


143



144

The enamide functional group has been used in the synthesis of many natural products by radical cyclisation due to its flexibility, stability and predictable regioselectivity. This was exemplified by the work of Castedo and Dominguez.[90] Using the common intermediate **145** they were able to synthesise the natural product lennoxamine **148** by two routes (Scheme 35). Radical cyclisation of **145** gave the 10-membered heterocycle **146** which after base catalysed cyclisation and desilyation yielded the natural product **148**. The alternative approach was to facilitate the base catalysed cyclisation/desilyation first to give the tetracycle **147** and then follow that with a 7-*endo*-trig radical cyclisation to again yield the natural product lennoxamine **148**. This synthetic effort shows the flexibility of enamides as radical acceptors in synthesis. There have been many other natural product synthesis using similar methodology.[73,91]

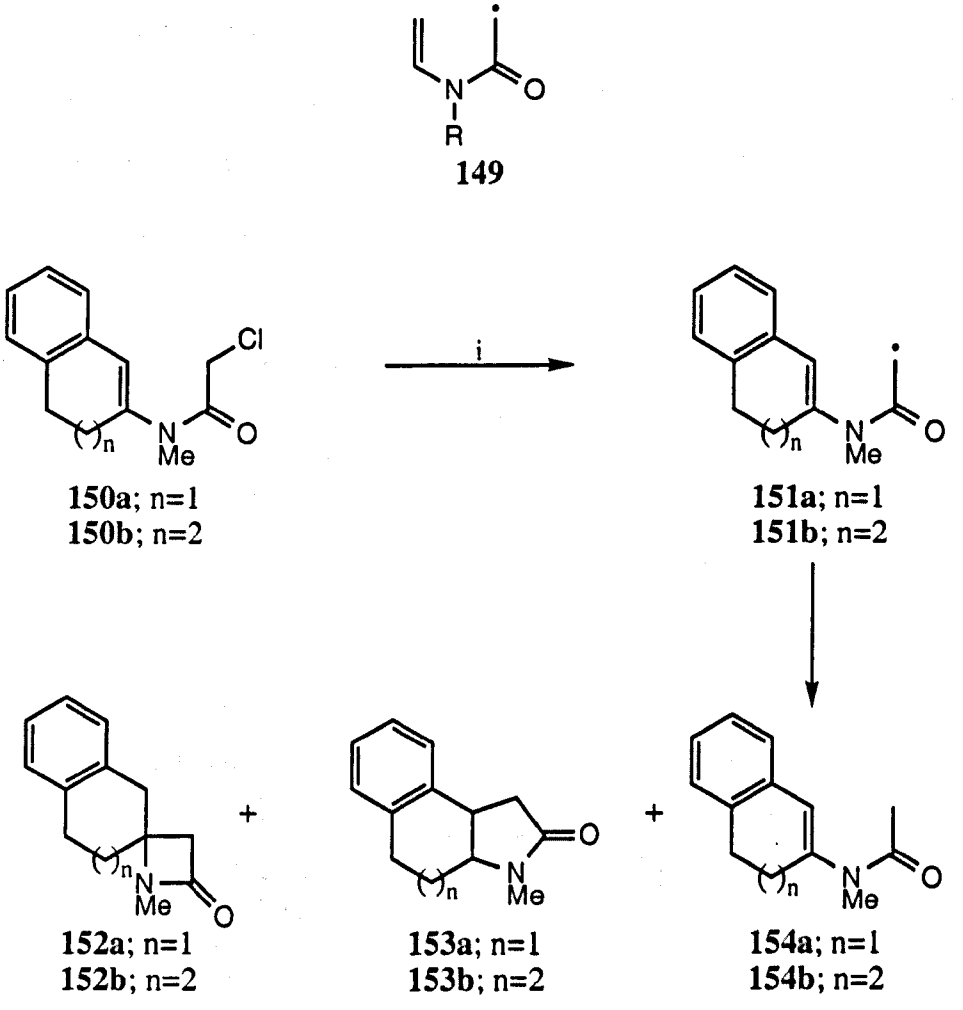


Reagents: i, Bu_3SnH, AIBN, C_6H_6, 80°C; ii, *t*-BuOK, THF; iii, TBAF, THF; iv, K_2CO_3, MeOH.

Scheme 35

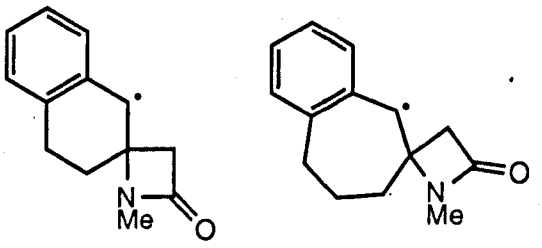
As well as the use of enamides in natural product synthesis there have been many methodology orientated investigations into their synthetic potential. Ikeda and co-workers demonstrated the use of enamides as radical acceptors in 1991 when they investigated the cyclisation of various systems based on the enamide radical **149**.[92a] For example, the α-chloroenamides **150a** and **150b**, when reacted under standard radical generating conditions gave a varying mixture of products (Scheme 36). The 6,6 ring system **150a** gave the α-amidyl radical **151a** which underwent 4-*exo*-trig cyclisation to give the β-lactam **152a** in 50 % yield. None of the product **153a** from the 5-*endo*-trig cyclisation was isolated, but there was some of the reduced product **154a** (32 %). In contrast the 6,7 ring system **150b** gave a very different mixture of

products. The corresponding radical **151b** cyclised in a 5-*endo*-trig manor to yield 41 % of the γ-lactam **153b**, with none of the β-lactam **152b** isolated. Again there was some of the reduced starting material **154b** (20 %) resulting from direct quenching of the radical **151b**. Using molecular modelling in an attempt to explain these results Ikeda postulated that the p-orbital of the intermediate radical **155** overlapped with the neighbouring aromatic π-orbitals stabilising the system. However, in the intermediate **156** the p- and π-orbitals were perpendicular resulting in the formation of the observed 6,7,5 ring system **153b**.



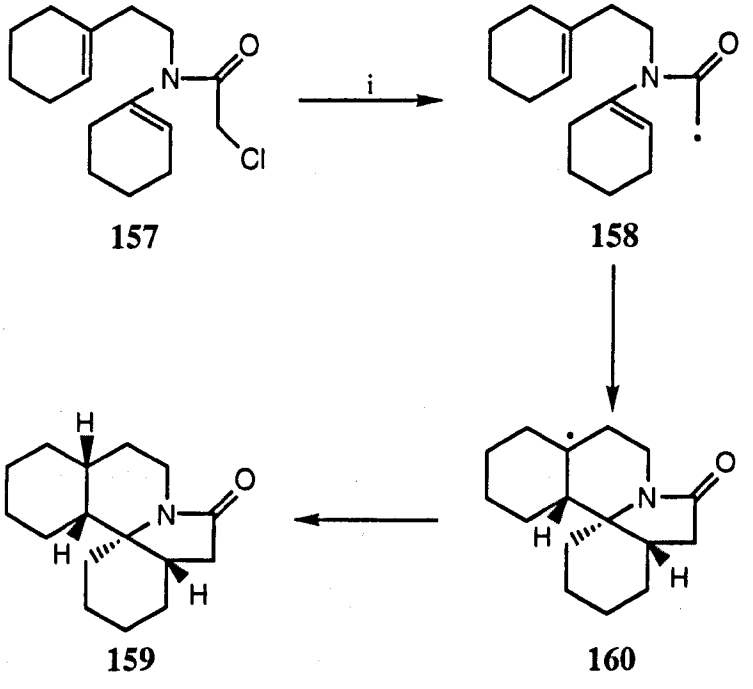
Reagents: i, Bu_3SnH, AIBN, C_6H_5Me, reflux.

Scheme 36



155 **156**

Ikeda then used this methodology to generate the perhydroerythrinane skeleton **159** in a tandem radical reaction from the α-chloroenamide **157**.[92c] Generation of the radical species **158** followed by 5-*endo*-trig and then 6-*endo*-trig cyclisations gave the tetracyclic radical **160** which was quenched exclusively from the β-face to give the perhydroerythrinane skeleton **159** in 44 % yield (Scheme 37). Also isolated was the product resulting from the reduction of the intermediate radical **158** (4 %) and the monocyclised product in 9 % yield.

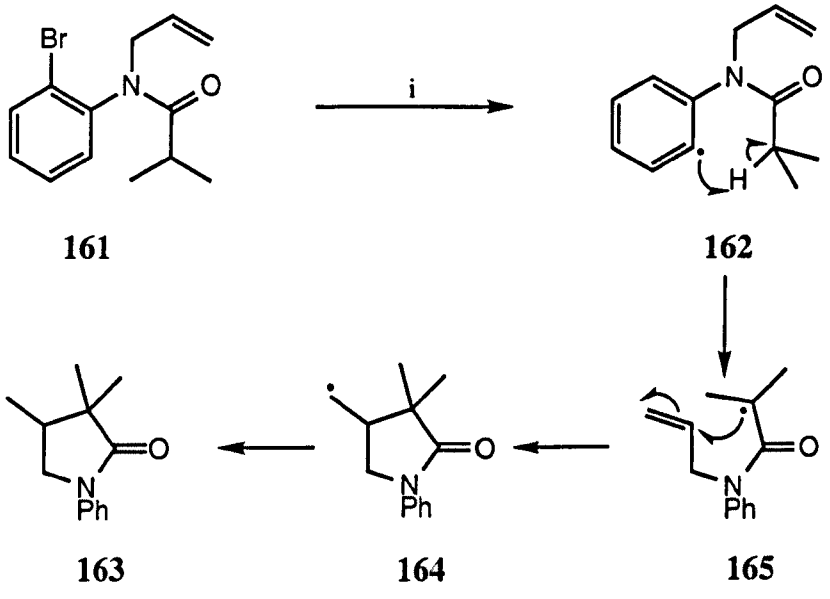


157 **158** **159** **160**

Reagents: i, Bu_3SnH, AIBN, C_6H_5Me, reflux.

Scheme 37

As part of their studies into enamides as radical acceptors, Beckwith and co-workers employed an imaginative approach to the generation of tertiary radicals for 5-*exo*-trig cyclisation onto enamides.[93b] Treatment of the bromobenzene **161** with tributyltin hydride gave the aryl radical **162**. Then, 1,5 hydrogen abstraction generated the intermediate tertiary radical **165** which cyclised onto the enamide double bond to yield the pyrrolidinone **163** (Scheme 38).

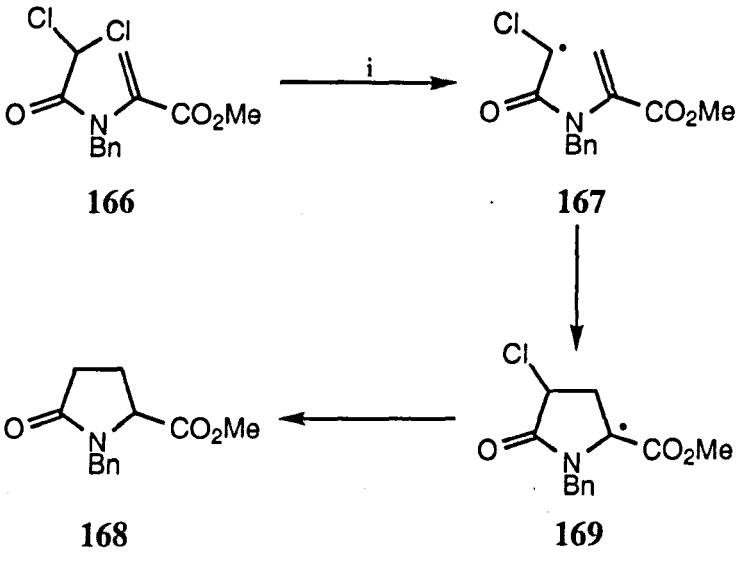


161 **162** **163** **164** **165**

Reagents: i, Bu_3SnH, AIBN, C_6H_6, 80°C.

Scheme 38

Goodall and Parsons investigated methodology for the synthesis pyroglutamates.[94] For example, taking the dichloro substituted enamide **166** and treating this with 2.2 equivalents of tributyltin hydride, in benzene, with catalytic AIBN they were able to generate the radical **167** which underwent 5-*endo*-trig cyclisation to give the captodative radical **169**. Quenching of the radical **169** followed by a radical reduction of the remaining chloride then gave the pyroglutamate **168** in 70 % yield (Scheme 39).



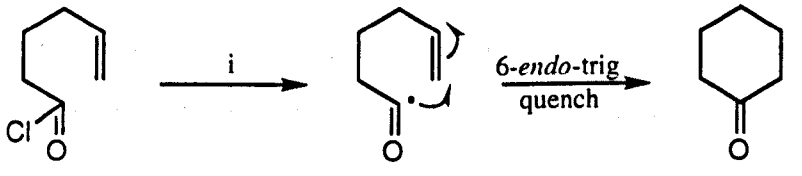
Reagents: i, Bu_3SnH, AIBN, C_6H_6, 80°C.

Scheme 39

1.4 ACYL RADICALS

1.4.1 History

Acyl radicals are centred on the carbon of a carbonyl group and it has become apparent that this structure imparts different reactive properties upon them when compared with alkyl radicals. Acyl radicals generated from aldehydes by reaction with peroxides and by photochemistry were used in addition reactions to double bonds by Kharasch[95] and Patrick[96] as early as 1948. Tributyltin hydride reactions with acyl chlorides were identified in 1966 by Kuivila and he proposed that they proceeded *via* a radical mechanism.[97] However, it was not until 1972 that Cekovic used this methodology to synthesise cyclohexanones.[98] Taking 5-hexenoyl chloride **170** and generating the acyl radical **171**, he isolated cyclochexanone in 36 % yield, after an unprecedented 6-*endo*-trig cyclisation onto the double bond (Scheme 40).



170 **171**

Reagents: i, Bu_3SnH, AIBN.

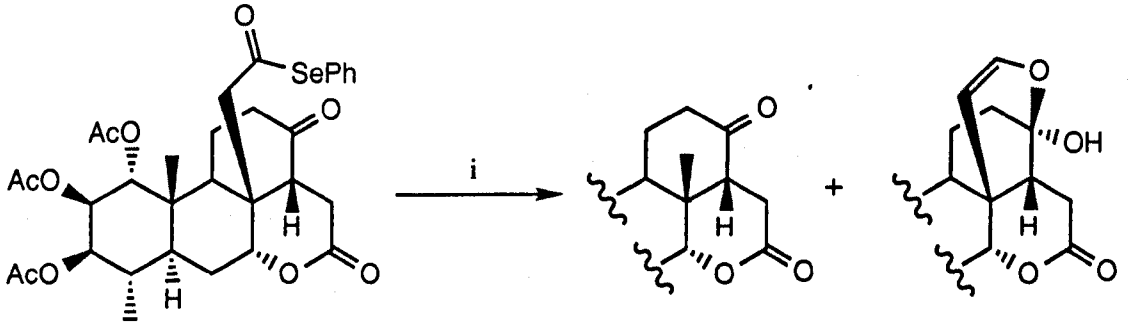
Scheme 40

Since the ground breaking work of Cekovic there have been many methods devised for the formation of acyl radicals from a variety of precursors. The use of acyl

selenium, germanium and tellurium compounds has been well documented,[99] as well as acyl xanthates[100] and acyl colbalts.[101]

1.4.2 Generation of Acyl Radicals

During the development and utilisation of acyl radicals in synthesis many techniques have been used to generate them. The initial generation methods of aldehyde and acid chloride homolysis soon went out of vogue when new milder techniques were developed. In 1980, Pfenninger and co-workers identified a radical induced decarbonylation from a selenyl ester precursor.[102] Taking the tetracyclic compound **172** and treating it with tributyltin hydride they isolated the decarbonylated product **173** along with the expected aldehyde **174** in its hemiacetal form (Scheme 41). In a subsequent investigation into the effect of solvent and temperature on this reaction the authors found that increasing the temperature caused a decrease in the yield of the hemiacetal product **174**.[103] Despite this early investigation into the use of selenyl esters as precursors to acyl radicals, it was not until 1988 that Boger and Mathvink started synthetic work with selenyl esters. Since then they have become the group of choice for the generation of acyl radicals under mild conditions.[99,104]

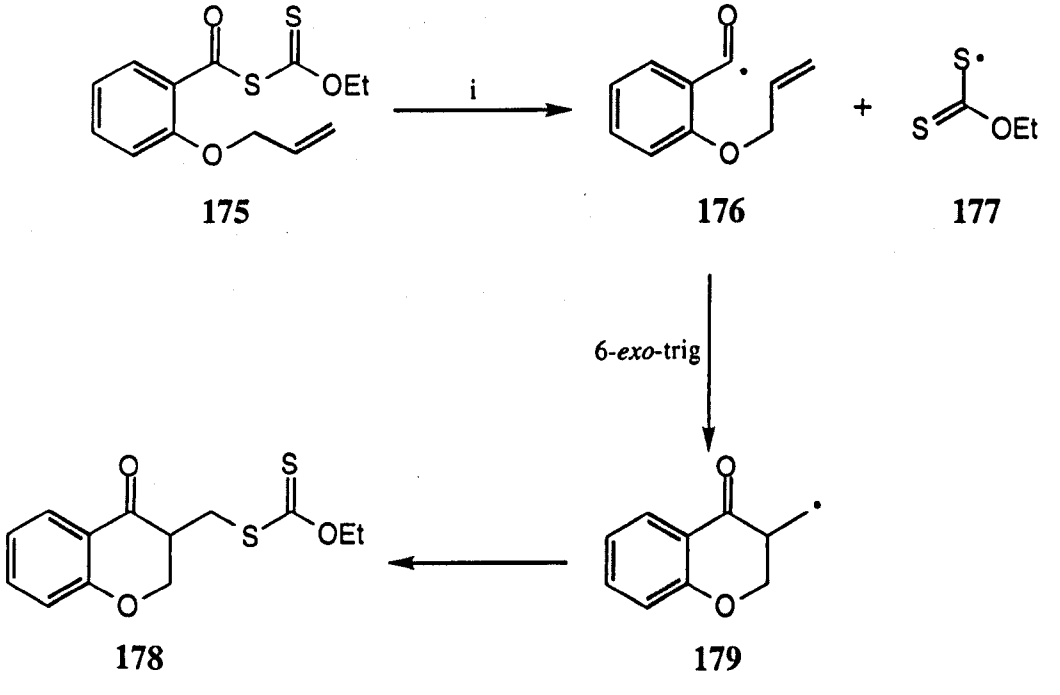


172 **173** **174**

Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 41

Barton and co-workers initiated the use of acyl xanthates as precursors to acyl radicals for decarbonylation reactions.[105] However, Zard and co-workers have applied this methodology in intramolecular cyclisation reactions.[100] Thus, exposing the acyl xanthate precursor **175** to ultraviolet light formed the carbon and sulfur centred radicals **176** and **177**, respectively. Cyclisation of **176** and trapping of the resulting radical **179** by the sulfur radical **177** gave the chromanone **178** in 70 % yield (Scheme 42).



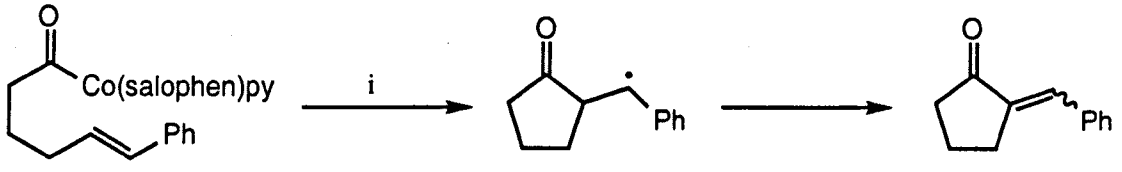
175 **176** **177**

178 **179**

Reagents: i, hν, C_6H_5Me, reflux.

Scheme 42

Pattenden and co-workers have used acylcobalt salophens for the addition of acyl radicals to activated carbon-carbon double bonds in the synthesis of enones and functionalised ring systems.[101] For example, exposing the acylcobalt salophen **180** to ultraviolet light generated an acyl radical which underwent a 5-*exo*-trig cyclisation. Trapping of the intermediate radical **181** with cobalt followed by dehydrocobaltation gave the five membered ring **182** (Scheme 43).

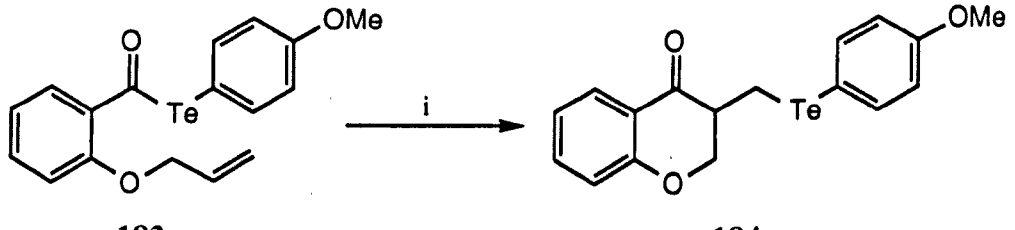


180 **181** **182**

Reagents: i, hν, CH_2Cl_2, reflux.

Scheme 43

Acyl tellurides have recently been used for the generation of acyl radicals and employed in the synthesis of bicyclic molecules by Crich and co-workers.[106] Using a system analogous to that described by Zard (Scheme 42),[100] Crich *et al.* exposed the telluryl ester **183** to ultraviolet light which resulted in cyclisation *via* the two radicals **176** and **179** (Scheme 42) to give the bicyclic compound **184** in 80 % yield (Scheme 44). A number of other systems such as thioesters,[107] and acyl germanes[108] have been employed in the generation of acyl radicals but by far the majority of synthetic work has used selenyl esters as precursors in reductive cyclisations with tributyltin hydride.



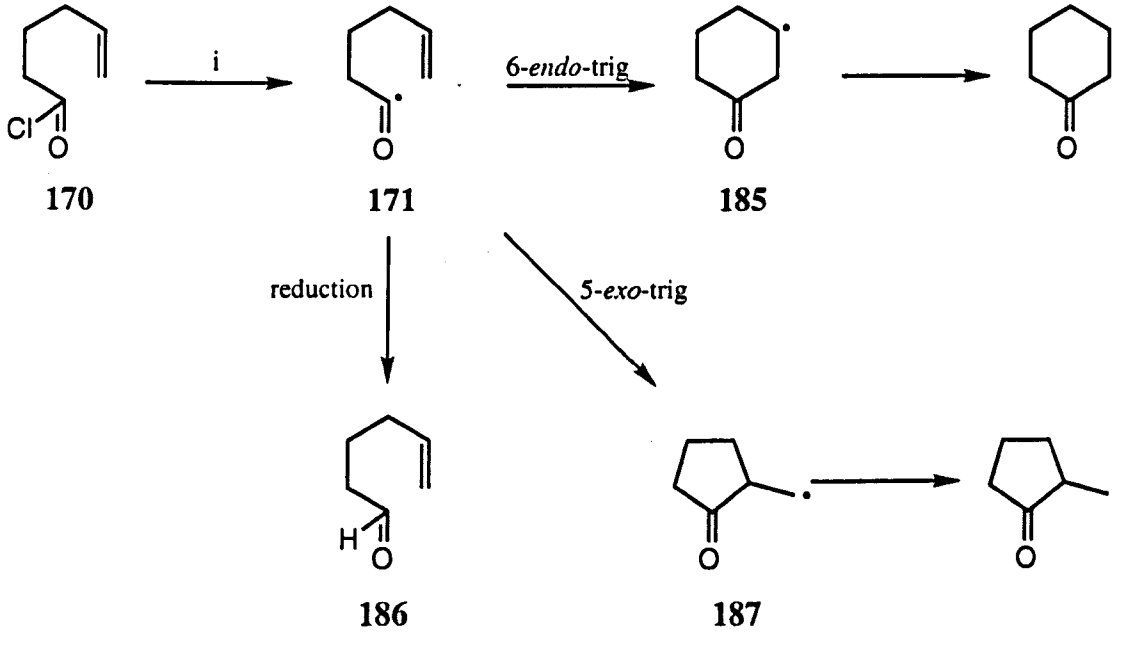
183 **184**

Reagents: i, hν, $CDCl_3$, 8°C.

Scheme 44

1.4.3 5-*Exo* versus 6-*endo* Cyclisation

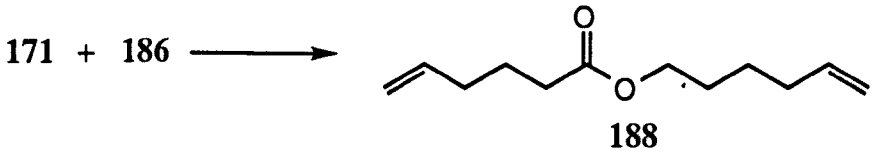
During the course of the many investigations into the synthesis of cyclic compounds with acyl radicals it has emerged that they have a synthetically useful tendency to favour 6-*endo* cyclisations over the usually preferred 5-*exo* cyclisations.[109] This was first highlighted in the work of Cekovic (Scheme 40) and reinvestigated by the group of Walsh in 1980.[110] A detailed study of the effects of temperature, solvent and concentration highlighted a number of different products from the reaction of the 5-hexenoyl radical **171** that Cekovic had not isolated. Walsh showed a different 1:5 ratio of cyclohexanone to 2-methylcyclopentanone in refluxing benzene (Scheme 45) when compared to Cekovic's results. Interestingly, they did not isolate any of the aldehyde **186** resulting from direct reduction of the acid chloride but found that this compound reacted with the acyl radical **171** to form the ester **188** (Scheme 46). Later, a study by Penn and Liu found similar results from the photo induced homolysis of 2-naphthyl thioesters giving a similar distribution of products.[111]



170 **171** **185** **186** **187**

Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

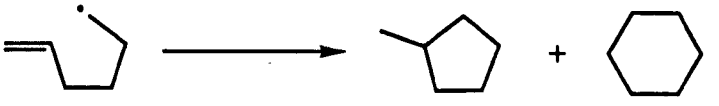
Scheme 45



188

Scheme 46

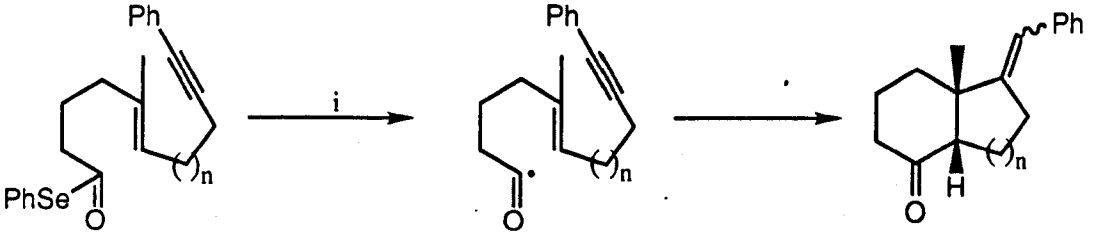
Even though the amount of 6-*endo*-trig cyclisation observed by Walsh was small, and did not compare to the ratios claimed by Cekovic, it was unusual when compared to the alkyl radical cyclisation of the same system. Beckwith's study of this reaction showed that the alkyl radical **181** underwent preferential 5-*exo*-trig cyclisation to give a 98:2 ratio of methylcyclopentane and cyclohexane (Scheme 47).[109b]



189 98 % 2 %

Scheme 47

These initial observations sparked a lot of research into the mode of the 6-*endo*-trig cyclisation. In 1990, Boger and Mathvink used acyl radical intermediates in the synthesis of 6/5 and 6/6 ring systems and concurrently investigated the mechanism of these radical cyclisations.[112] The initial cyclisation was directed exclusively in the 6-*endo*-trig mode by substitution of a methyl group on the carbon-carbon double bond. They suggested that this cyclisation mode resulted from kinetic deceleration of the 5-*exo*-trig cyclisation and kinetic acceleration of the 6-*endo*-trig mode by steric factors. Thus, for example, a solution of the ene/yne selenyl esters **190a** and **190b** in refluxing benzene gave the acyl radicals **191a** and **191b** respectively, after syringe pump addition of tributyltin hydride and AIBN over one hour. These radicals **191a** and **191b** underwent initial 6-*endo*-trig cyclisation followed by a 5-*exo*-dig process to give the bicycle **192a**, as a single diastereoisomer in 77 % yield, or a 6-*exo*-dig cyclisation to give **192b**, as a 58:42 mixture of *cis:trans* isomers in 82 % yield (Scheme 48).



190a; n=1
190b; n=2

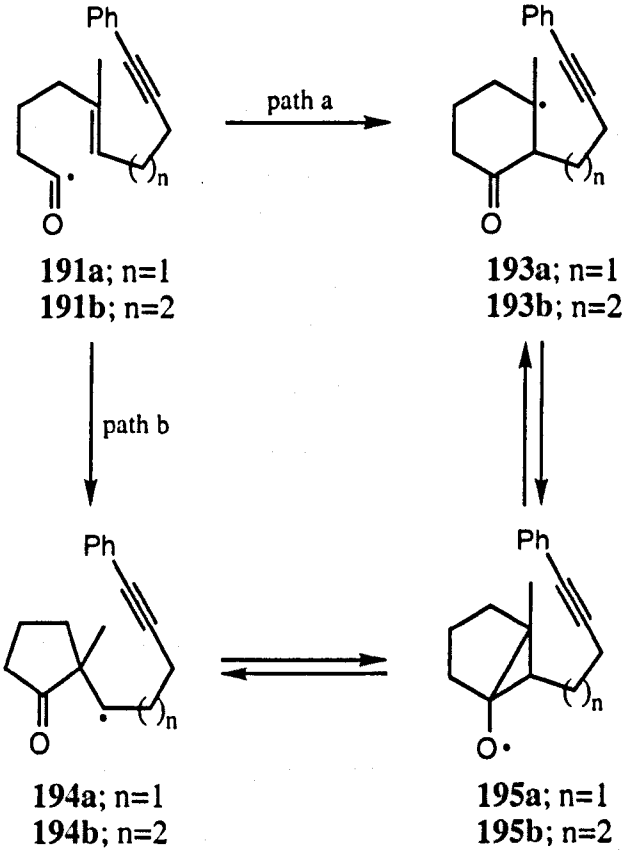
191a; n=1
191b; n=2

192a; n=1
192b; n=2

Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 48

In an attempt to explain the mode of radical cyclisation the authors synthesised precursors to some of the potential intermediate radicals from this pathway.[113] Thus, the radical **191** could undergo a direct 6-*endo*-trig cyclisation (path a) to the cyclic product **193**. It is also possible for **191** to undergo a 5-*exo*-trig cyclisation to give **194** (path b), followed by a 3-*exo*-trig cyclisation to give **195** and a subsequent ring expansion reaction to **193** (Scheme 49).



191a; n=1
191b; n=2

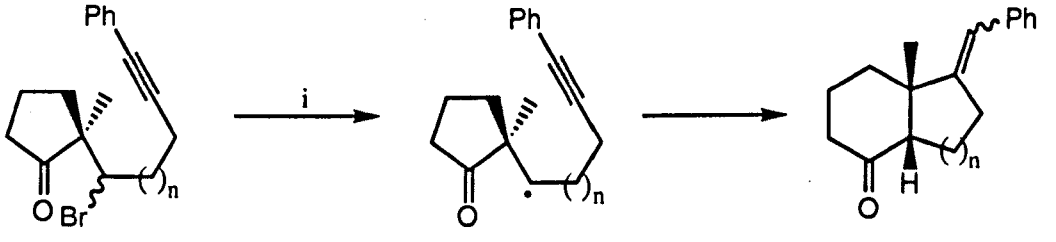
193a; n=1
193b; n=2

194a; n=1
194b; n=2

195a; n=1
195b; n=2

Scheme 49

They found that generation of the radical **194a** from the corresponding bromide **196a** resulted in the formation of the bicyclic compound **192a**. However, in a related series using **196b** as starting material none of the bicycle **192b** was isolated, though the authors did not say what the product of this reaction was (Scheme 50). From this significant result they concluded that even though the ring expansion route (Scheme 49) was a possible mechanism for the cyclisation of the radical it was not the route by which the cyclisation occurred, implying that direct 6-*endo*-trig cyclisation was the pathway that these reactions followed. Crich and co-workers have also hypothesised that a ring expansion pathway is a possible route for 7-*endo*-trig cyclisations and after a through investigation with a number of substrates they concluded that the mode of cyclisation was a result of a subtle interplay of conformation effects and the reversibility of the ring closure.[114]



196a; n=1
196b; n=2

194a; n=1
194b; n=2

192a; n=1
192b; n=2

Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 50

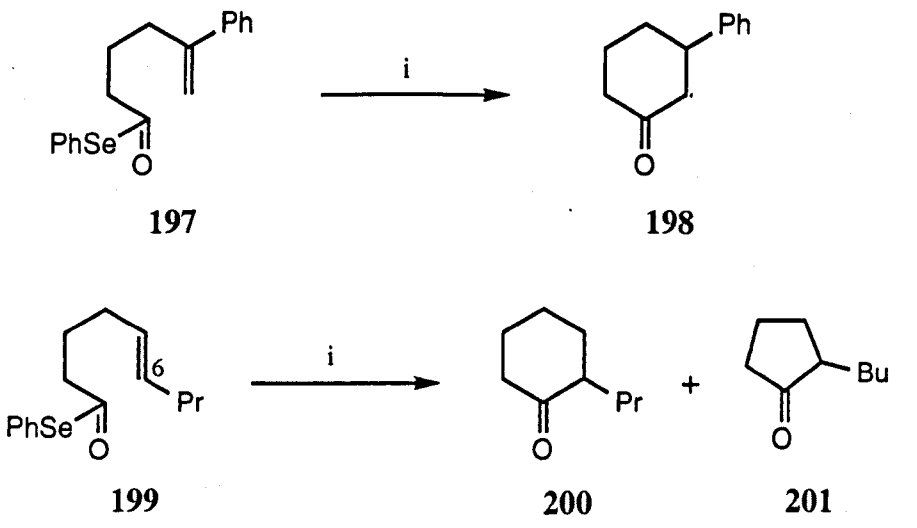
There have been some recent investigations into this cyclisation pathway using *ab initio* studies of the reactions involved in the transformation of radical **194** to **193** *via* the two possible intermediates **191** and **195** (Scheme 49).[115] These studies used a simplified model and demonstrated that the reaction of **194** to **191** was unfavourable when compared to the reaction **194** to **195**. However, they did not address the issue of whether the initial cyclisation **191** to **194** underwent a preferred 6-*endo*-trig or 5-

exo-trig cyclisation. Also, the effects of substitution patterns used by synthetic chemists in these reactions were not explored though these studies are apparently being performed. From these various investigations it seemed likely that 5-methyl substituted 5-hexenoyl radicals cyclise in a direct 6-*endo*-trig mode. It has become apparent that the reaction would follow the ring expansion mechanism rather than reverse if an initial 5-*exo*-trig cyclisation occurred.

1.4.4 Synthetic Applications of Acyl Radicals

Crich and co-workers have investigated the synthesis of (+)-1α,25-dihydroxyvitamin D_3 and initially used a stereochemically controlled acyl radical mediated cyclisation for the construction of the A-ring. However they found that the starting materials were difficult to synthesise and turned to a different approach.[116]

Most of the work in the synthetic exploitation of these results in cascade reactions has been left to the group of Pattenden. They performed extensive studies in this area as part of a synthetic effort towards a steroid nucleus using a cascade reaction.[117] Initial studies highlighted the effect of substitution patterns on the mode of cyclisation that the acyl radical prefers. Substituted 5-hexenyl acyl radicals undergo 6-*endo* and 5-*exo* cyclisation in varying ratios depending on the substituting group and its position in the molecule. For example phenyl 5-phenyhex-5-enselenoate (**197**) undergoes exclusive 6-*endo*-trig cyclisation to yield the 3-phenylcyclohexan-1-one (**198**). However, if the double bond is substituted in the C-6 position such as in the selenyl ester **199** then a 3:2 ratio of the 6 and 5 membered rings **200** and **201** are produced (Scheme 51).

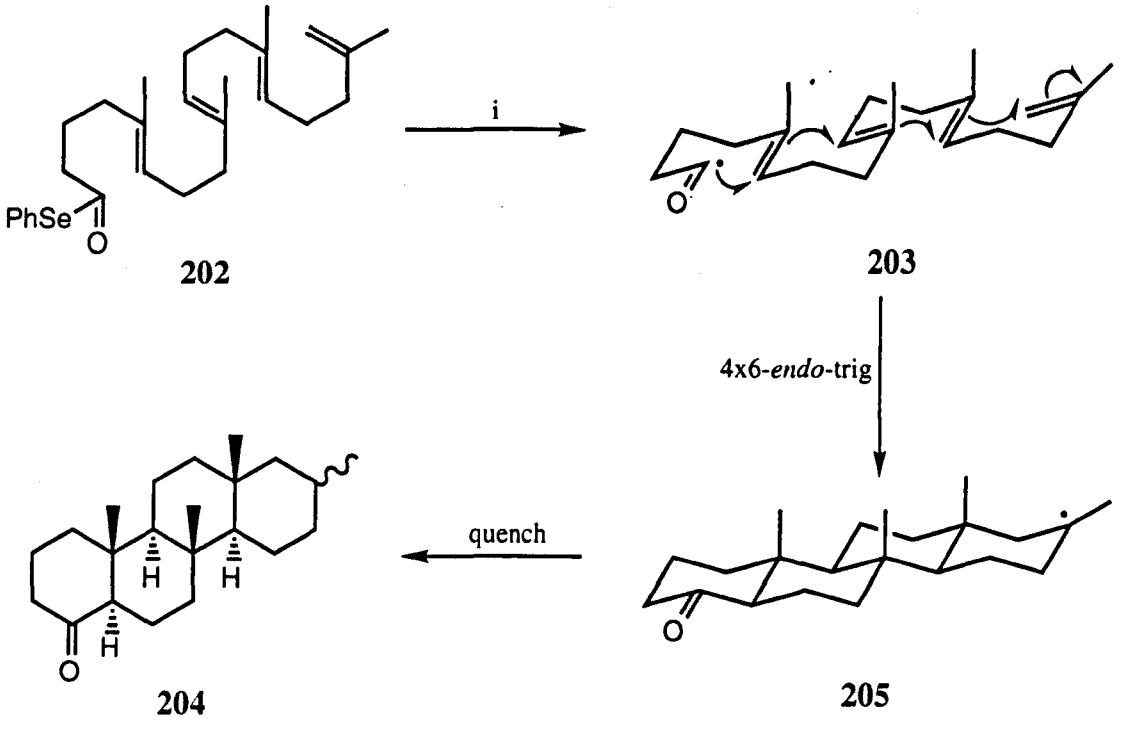


Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 51

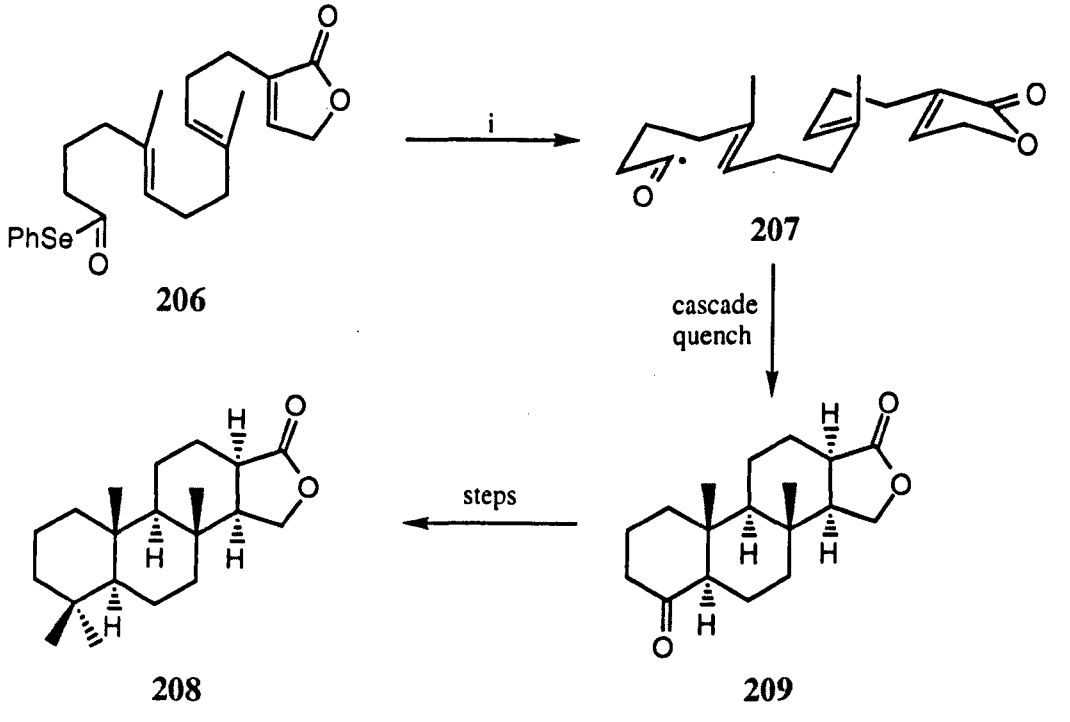
This observation was then used in the synthesis of a steroid ring system **204** from the tetraene selenyl ester **202** in 60-80 % yield (Scheme 52). The reaction involved four consecutive 6-*endo*-trig cyclisations from the acyl radical **203** to give the alkyl radical **205**. It has been proposed that the intermediate **203** adopts a highly ordered transition state leading to the isolation of just one diastereoisomer from this reaction. Other carbocyclic steroid ring systems were then synthesised using the same methodology.[117]

This strategy has been employed in the first total synthesis of the marine sponge diterpene spongian-16-one **208** isolated from *Dictyodendrilla cavernosa*.[118] Thus, generation of the acyl radical intermediate **207**, from the selenyl ester **206**, followed by serial 6-*endo*-trig cyclisations lead to the ketone **209** in 65 % yield. Subsequent functional group manipulations gave spongian-16-one **208** in three steps (Scheme 53).



Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

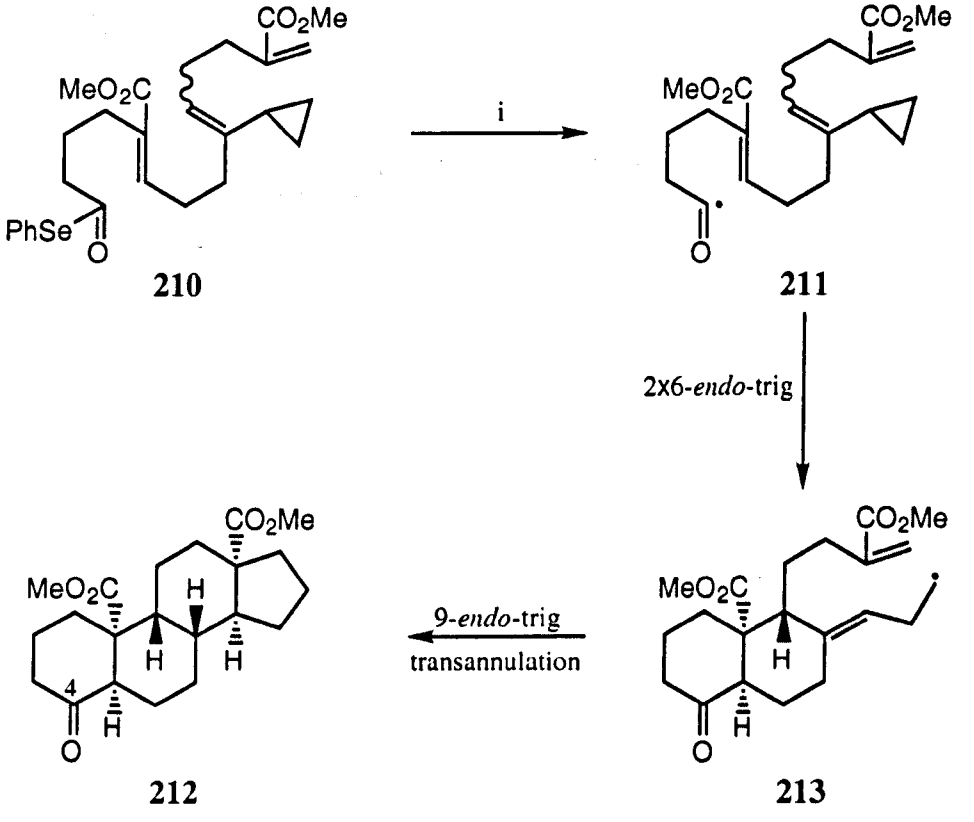
Scheme 52



Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 53

Recently, this strategy has been further elaborated for use as part of a cascade process followed by a macrocyclisation/transannulation reaction sequence for the synthesis of an unnatural steroid isomer **212**.[119] Thus, the cyclopropane-triene-selenyl ester **210** when treated with tributyltin hydride under standard conditions generated the acyl radical **211**. This radical underwent two 6-*endo*-trig cyclisations and a cyclopropane ring opening to give the alkyl radical **213**. A 9-*endo*-trig macrocyclisation followed by a transannulation gave the *cis, anti, cis, anti, cis* steroid **212** in 45 % yield (Scheme 54). The stereochemistry of this product was confirmed by X-ray analysis of the 4-hydroxy derivative of **212**.



Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 54

2. DISCUSSION

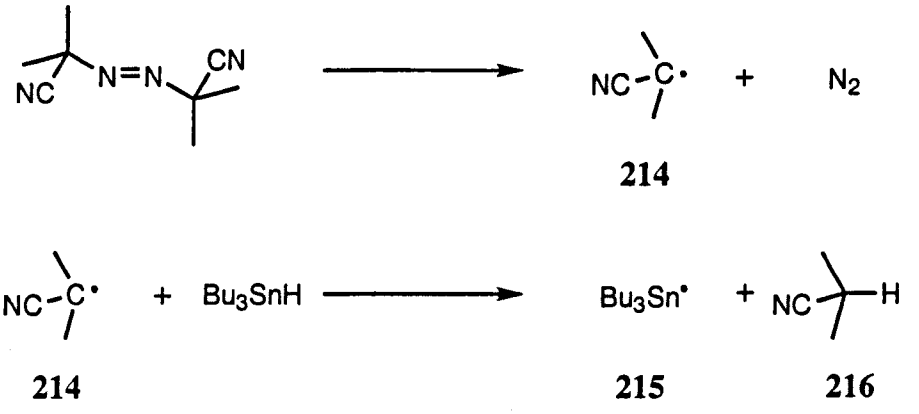
2.1 INTRODUCTION

Following the successful application of acyl radical cascade reactions to the "pseudo biomimetic" synthesis of carbocyclic steroids and related natural products,[117-119] we aimed to synthesise azasteroids using this methodology.[120] As we have highlighted earlier in Section 1.2 there have been many syntheses of azasteroids. Hitherto, work in this area has relied largely on the degradation of conveniently available steroids followed by reconstruction with simultaneous introduction of nitrogen functionality.[27] Therefore, application of acyl radical cascade reactions to the synthesis of nitrogen containing ring systems, in the form of azasteroids, opens up a complementary approach to these novel and biologically interesting molecules.

2.2 ACYL RADICALS IN SYNTHESIS

For the synthetic application of radicals to be successful a number of criteria have to be met. Thus, the radical has to be generated under mild conditions by homolytic cleavage of a suitable functional group, without interfering with other sensitive functional groups in the molecule. Then, reaction of this radical with the desired electrophore has to be competitive when compared to undesired side reactions. Finally, in the reaction sequence the resulting radical must quench with a hydrogen donating agent. We discussed earlier in Section 1.4 that most acyl radicals are currently generated from a selenyl ester in refluxing benzene by reaction with

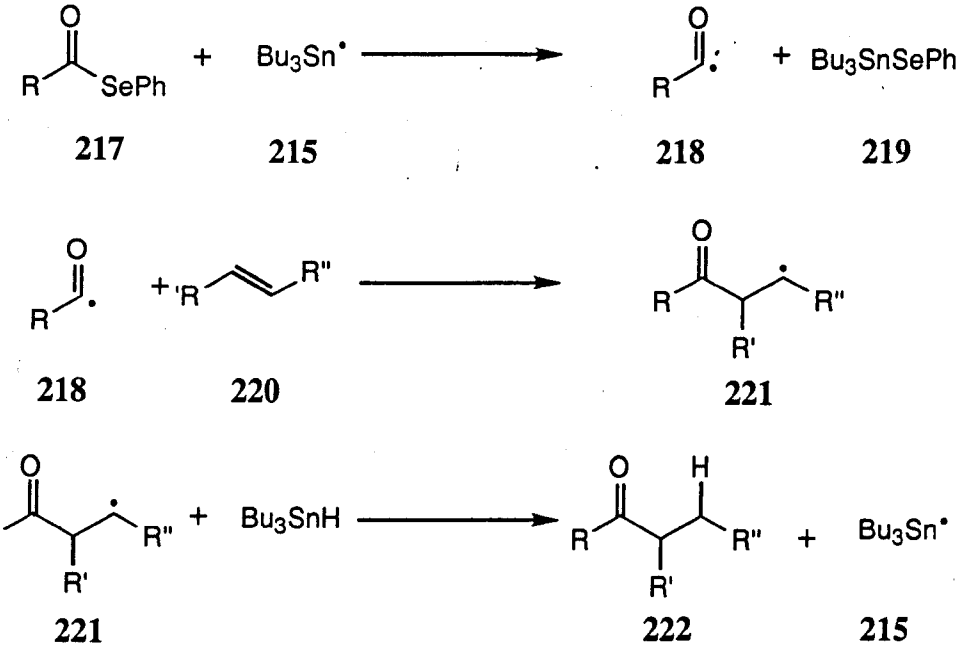
tributyltin radical **215** which in turn is generated by reaction with the radical **214** produced from decomposition of AIBN. As we used this system in our synthetic approach to azasteroids, only effects relating to it will be discussed here (Scheme 55).



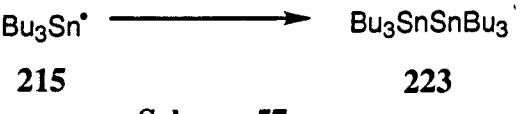
Scheme 55

The tributyltin radical **215** then propagates the sequence by homolytic cleavage of the carbon-selenium bond in the precursor **217** leading to the formation of the acyl radical **218** together with the stable tin-selenium by-product **219**. The acyl radical **218** then goes on to perform the synthetic transformations such as addition to the carbon-carbon double bond **220** which results in carbon-carbon bond formation and generation of the radical **221**. At the end of the reaction sequence the carbon centred radical **221** abstracts hydrogen from tributyltin hydride yielding the product **222** and regenerating tributyltin radical **215** which re-enters the cycle as the radical propagator (Scheme 56).

The reaction is terminated either by dimerisation of the carbon centred radicals **218** and **221** though these are not common, or by dimerisation of the tributyltin radical **215** to give hexabutylditin **223** (Scheme 57). Diphenyl diselenide is also formed in small quantities during these reaction sequences.



Scheme 56



Scheme 57

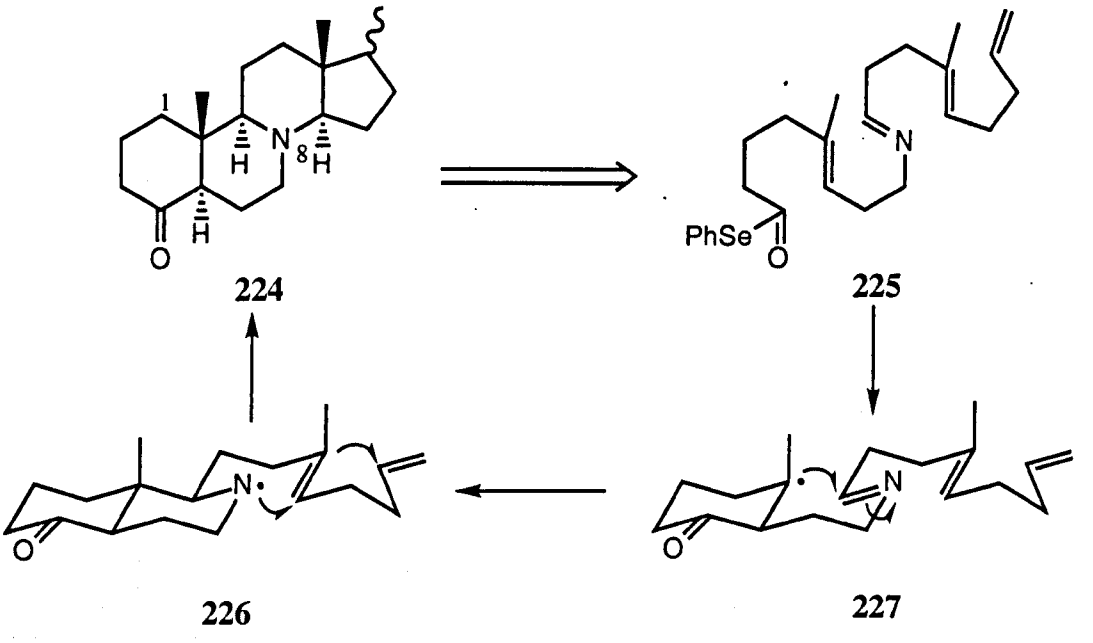
For the synthetic transformations to occur the lifetime of the intermediate radicals such as **218** and **221** have to be as long as possible. Therefore, to minimise side reactions high dilution conditions are employed to lower the concentration of radicals in the solution. However, this method is ineffective for the cascade synthesis of steroids in which sequences of three or four cyclisations are involved. Syringe pump addition of a solution of tributyltin hydride to the reaction over a number of hours has been used to keep the concentration of both tributyltin hydride and other radicals down. This methodology has resulted in the successful synthesis of a number of steroid systems (Schemes 52-54).[117-119]

2.3 CASCADE SYNTHESIS OF AZASTEROIDS

Approaches to azasteroids from linear molecules using acyl radical cascade cyclisations can give two different electrophore structures. To generate ring junction azasteroids a suitably positioned imine has to be present in the radical precursor. To synthesise azasteroids where nitrogen is in the body of the ring then an enamine or similar electrophore has to be present in the radical precursor.

2.4 IMINE PRECURSORS

To synthesise azasteroids with nitrogen at the ring junction it is necessary for the precursor to contain an imine electrophore. For example, the 8 and 9-azasteroids **224** and **230** can be disconnected to the imine containing selenyl esters **225** and **231** respectively. In the cascade sequence for the synthesis of **224** the carbon centred radical **227** has to cyclise onto the carbon of the imine giving the aminyl radical **226**, which in turn has to cyclise further to give the azasteroid **224** (Scheme 58). The retrosynthesis of 8-azasteroids is analogous to the disconnection for the 10 and 13-azasteroids **228** and **229**, when relating to the sequence of cyclisation reactions.

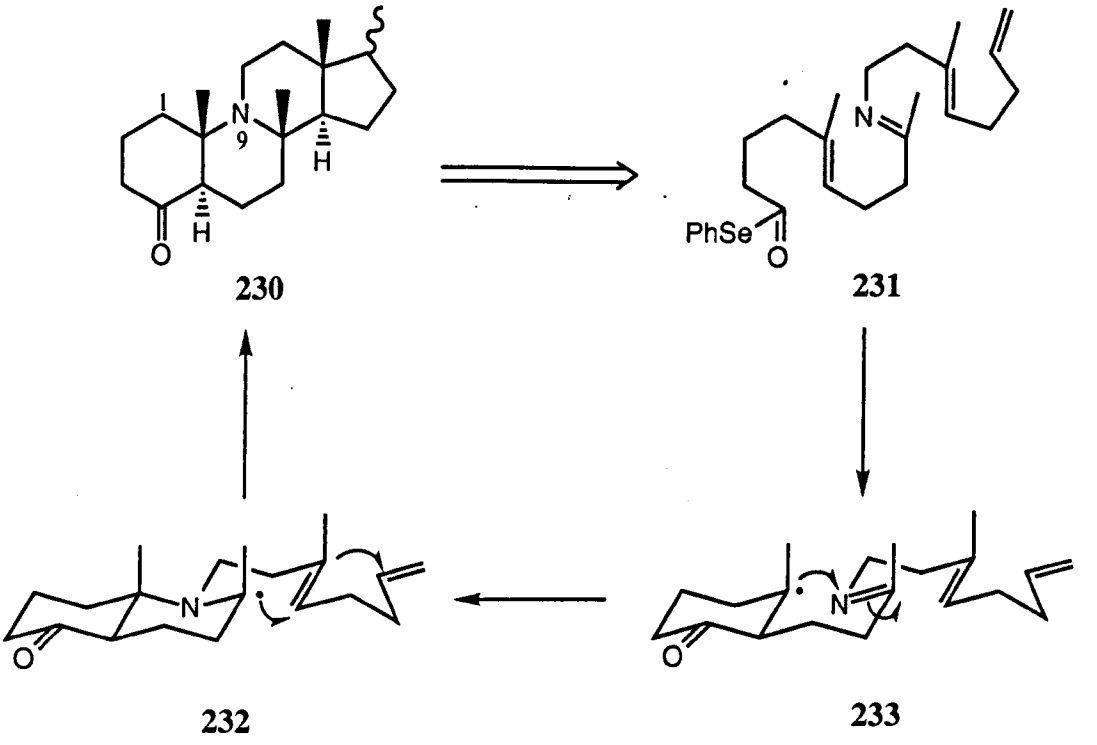


224 225 226 227

Scheme 58

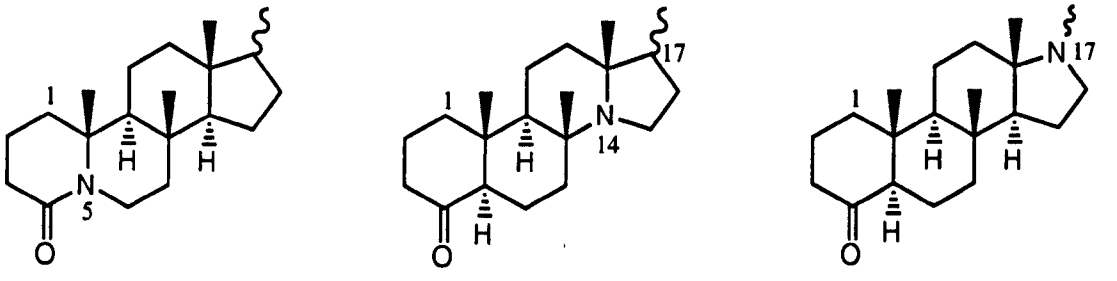
228 229

The 9-azasteroid **230** is analogous to 5, 14 and 17-azasteroids **234**, **235** and **236** respectively, when considering the type of radical cascade reaction required in their synthesis. In can be envisaged that the precursor **231**, upon treatment with tributyltin hydride and AIBN, gives the corresponding acyl radical which cyclises giving the tertiary carbon centred radical **233**. This, in turn would have to cyclise onto the nitrogen in the imine functionality resulting in the α-aminyl radical **232** which then gives the steroid **230** in the final cyclisations (Scheme 59).



230 231 232 233

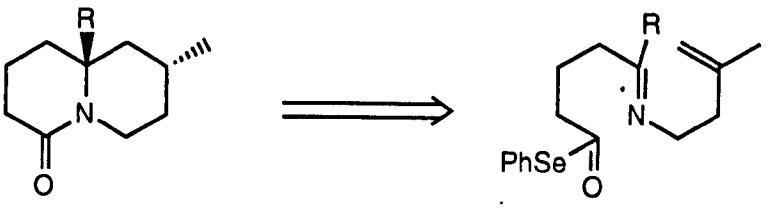
Scheme 59



234 235 236

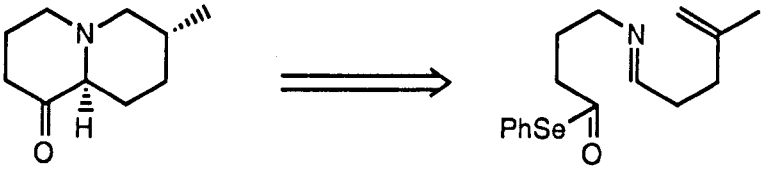
2.4.1 Synthetic Studies

Initial synthetic studies were directed towards the nitrogen containing heterocycles **237** and **239**. Both targets are fused bicycles with nitrogen situated on the ring junction and these molecules were chosen as simplified models for azasteroids. Retrosynthetic analysis of **237** and **239** led to the imine containing precursors **238** and **240** (Scheme 60).



237a; R=H
237b; R=Me

238a; R=H
238b; R=Me

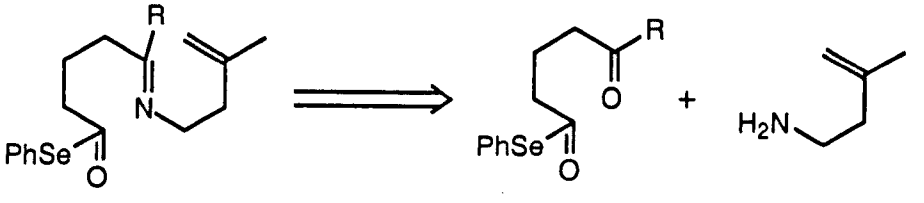


239

240

Scheme 60

Further disconnection of the precursors **238a** and **238b** led us to attempt the synthesis from the corresponding amine and aldehyde/ketone *via* a condensation protocol (Scheme 61). The ketone **241b** was readily synthesised from commercially available 5-oxohexanoic acid using diphenyl diselenide and tributylphosphine (Scheme 62). However, initial condensation reactions were attempted using aniline as we were unable to isolated the amine **242**. These reactions proved unsuccessful and we were never able to isolate the precursor **243**. We therefore investigated the alternative system **240**.

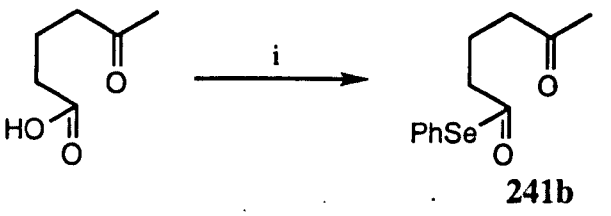


238a; R=H
238b; R=Me

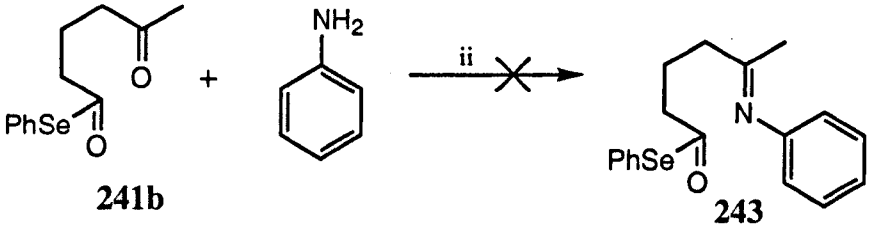
241a; R=H
241b; R=Me

242

Scheme 61



241b

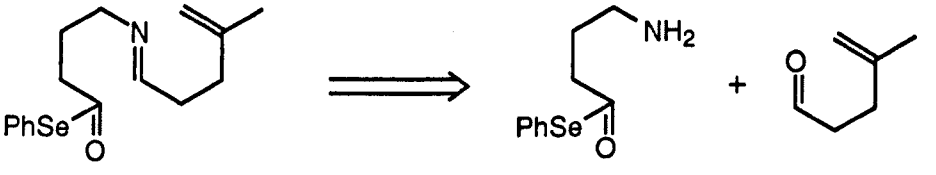


241b **243**

Reagents: i, Ph_2Se_2, Bu_3P, C_6H_6, rt, 85%; ii, molecular sieves, C_6H_6, rt, 0%

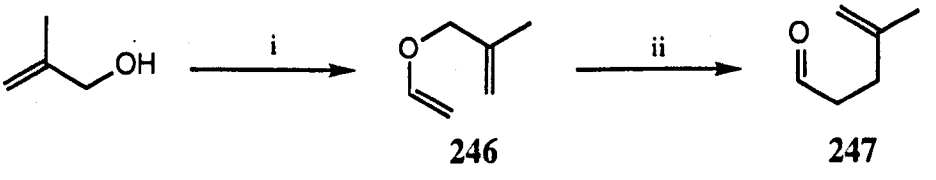
Scheme 62

Retrosynthetic analysis of the selenyl ester **240** gave the amine **244** and the aldehyde **245** as partners in a condensation reaction (Scheme 63). The aldehyde **245** was readily synthesised in two steps using a literature procedure from 2-methylprop-2-en-1-ol (Scheme 64).[117] However, synthesis of the amine **244** could not be effected and the coupling reaction was never attempted.



240 **244** **245**

Scheme 63



246 **247**

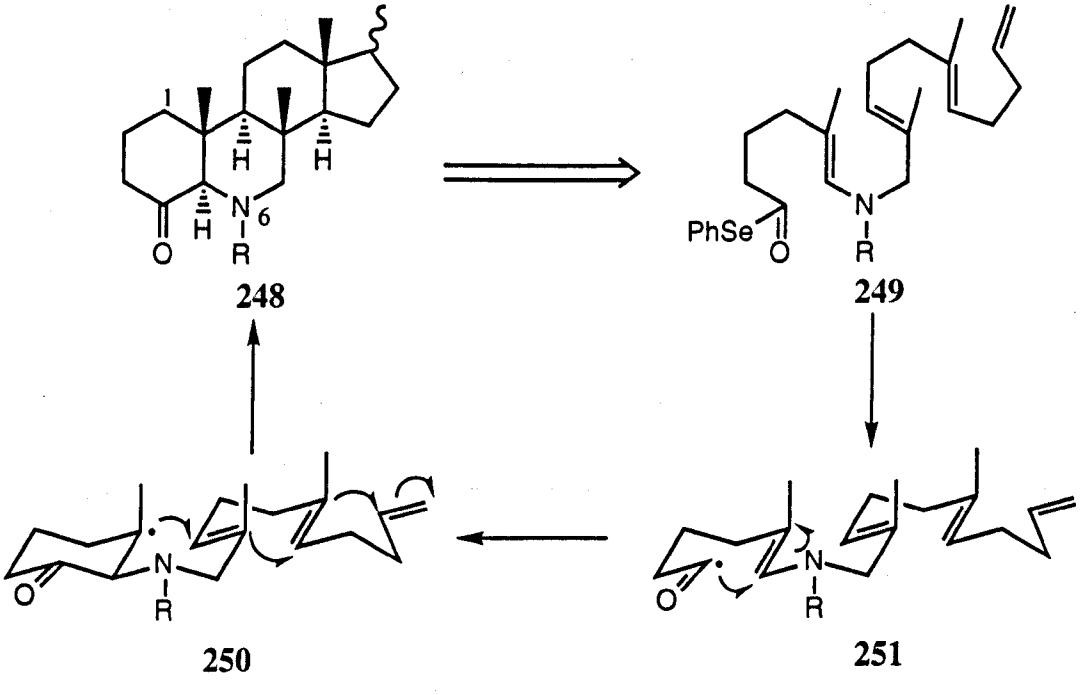
Reagents: i, $Hg(O_2CCF_3)$, ethylvinyl ether; ii, 120°C, 24 h, 56%-2 steps.

Scheme 64

The difficulties encountered in synthesising imines and their inherent instability led us to reconsider our approach to azasteroids. Disconnecting the steroidal core for azasteroids where nitrogen is not on the ring junction gives greater flexibility in the choice of electrophore and we therefore changed our approach to these systems.

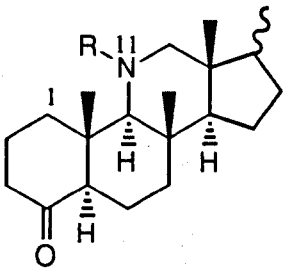
2.5 ENAMINE PRECURSORS

Disconnection of 6 and 7-azasteroids **248** and **255** gives the enamine containing selenyl esters **249** and **256**. Thus, synthesis of the 6-azasteroid **248** involves the cyclisation of the carbon centred radical **251** onto the carbon α to the nitrogen in the enamine and results in the formation of the β-aminyl radical **250**, which could continue the cascade to give the steroid **248** (Scheme 65). This cyclisation protocol is analogous to the mode of cyclisation required to form the 11, 15 and 16-azasteroids **252**, **253** and **254**, respectively.

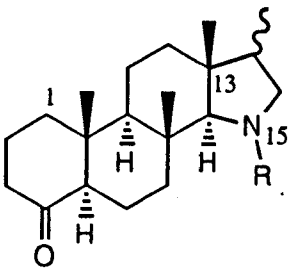


R=alkyl, acyl or aryl

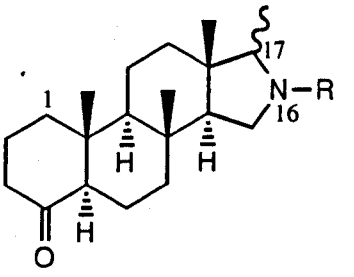
Scheme 65



252

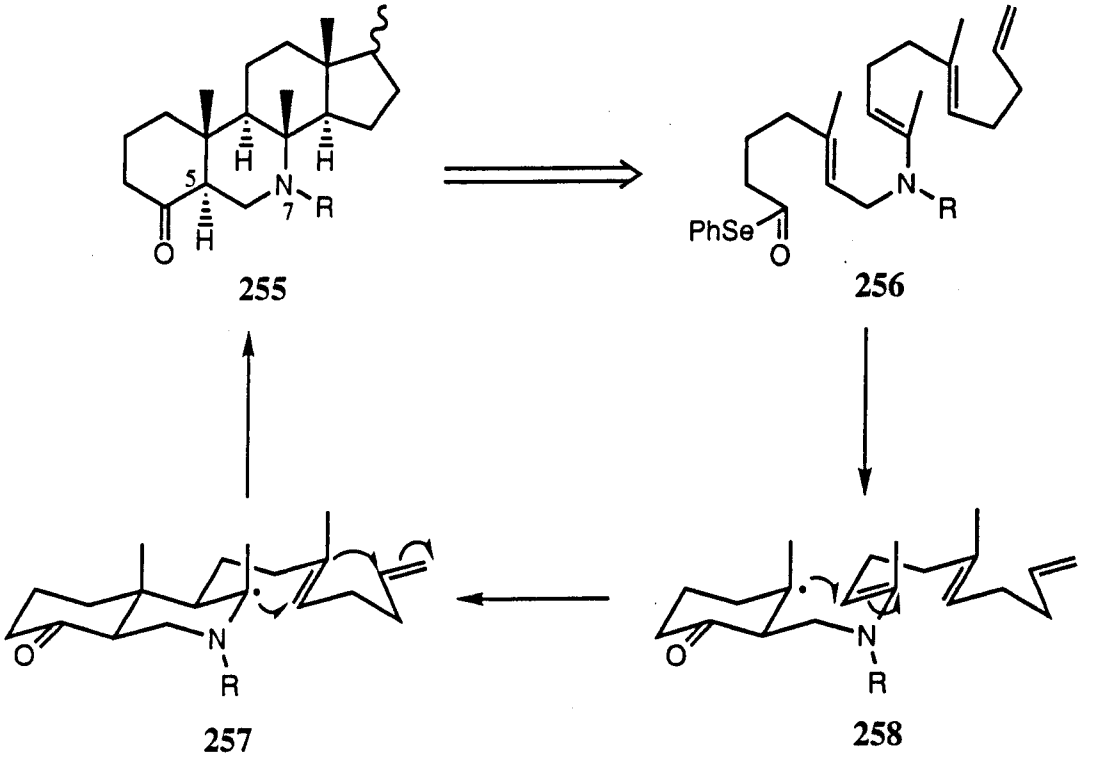


253



254

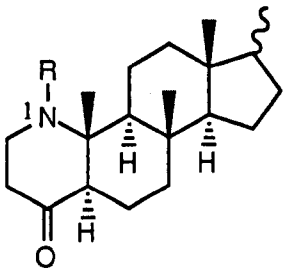
For the 7-aza system **255** the cyclisation from the carbon centred radical **258** would be required to react with the carbon β to nitrogen resulting in the formation of the α-aminyl radical **257** which could cascade further to give the steroid **255** (Scheme 66). This protocol is analogous to the cyclisations required to give 1 and 12-azasteroids **259** and **260**. With these different approaches in mind we started work on the synthesis of azasteroids using acyl radical cascades.



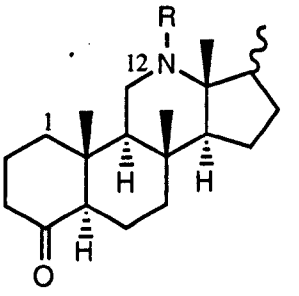
255 256 257 258

R=alkyl, acyl or aryl

Scheme 66



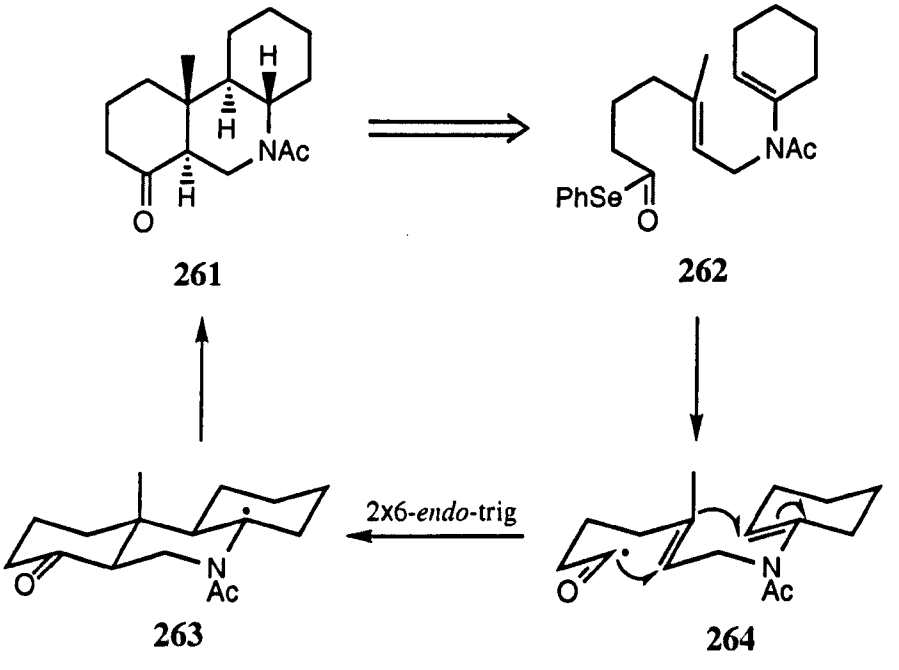
259



260

2.6 CYCLOHEXENYL ENAMIDE PRECURSORS

Imines and enamines such as **240** and **249** (R=alkyl) are inherently unstable to hydrolysis, difficult to synthesis, isolate and characterise. We therefore turned our attention to more stable nitrogen containing functional groups for cascade reactions. Looking at synthetic pathways to the tricyclic system **261**, as a simplified model for an azasteroid, we considered a strategy that involved disconnecting to the enamide containing precursor **262**. We chose the enamide functional group as it is stable to hydrolysis and its use in radical reactions has been well documented by other researchers.[90-94] This strategy involved two 6-*endo*-trig cyclisations from the acyl radical **264**, terminating with quenching of the α-aminyl radical **263** to give the tricycle **261** (Scheme 67).

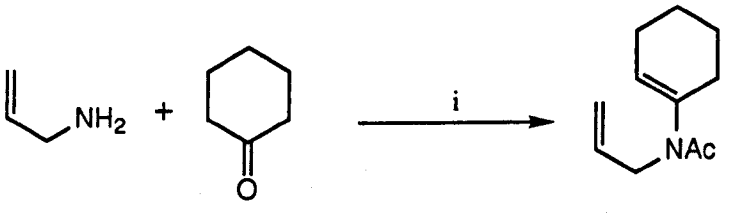


261 **262** **263** **264**

Scheme 67

2.6.1 Model Studies

Model studies were performed on the enamide **265** so that the stability of the system present in **262** towards hydrolysis and selenyl ester formation could be tested. Also an examination of the conformation of this functional group using n.m.r. experiments was performed. The enamide **265** was synthesised in one step using the methodology developed by Ikeda and co-workers in their studies into the radical reactions of enamides.[92a] Condensation of cyclohexanone and 1-aminoprop-2-ene in a sealed tube followed by acylation using acetyl chloride resulted in the isolation of the enamide **265** in 52 % yield (Scheme 68).



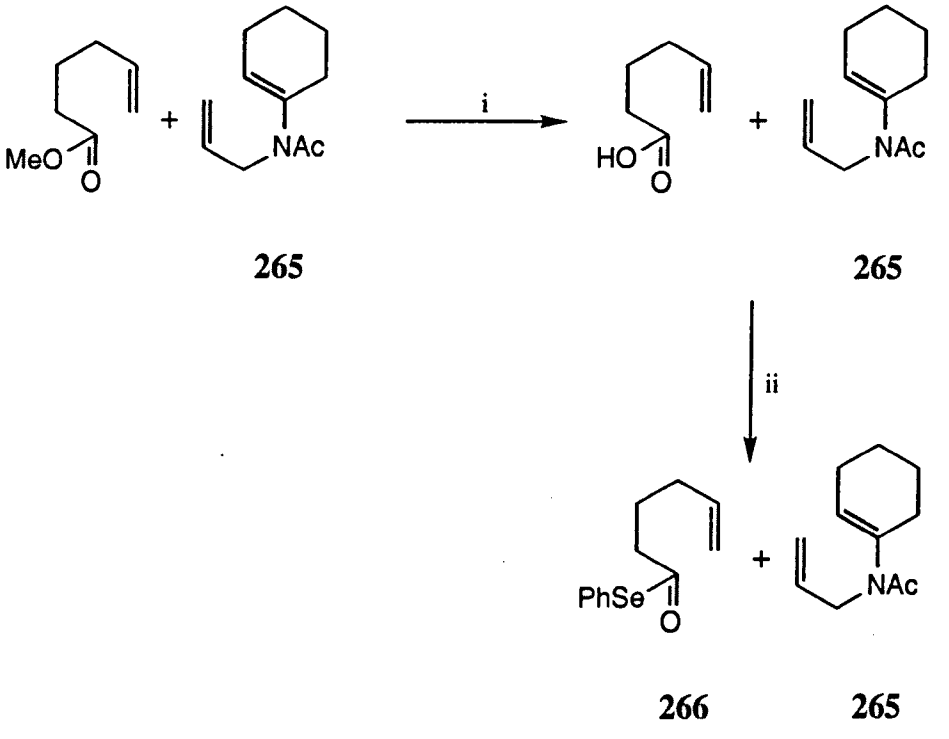
265

Reagents: i, C_6H_5Me, sealed tube, 100°C;
AcCl, Et_3N, DMAP, C_6H_5Me, 0°C, 52%.

Scheme 68

Using parallel reactions we were able to test the functional group present in **265** whilst synthesising both the acid and the selenyl ester required in the final synthetic steps towards the precursor **262**. Both the enamide **265** and methyl hex-5-enoate were submitted to ester hydrolysis conditions, *viz:* LiOH, THF, H_2O, and after complete hydrolysis of methyl hex-5-enoate to hex-5-enoic acid we were able to isolate the enamide **265** in near quantitative yield. Subsequently we were able to show that the enamide **265** was stable to the conditions that we planned to use for the formation of

our selenyl ester by using the same strategy. Hex-5-enoic acid was converted into the selenyl ester **266** in the presence of the enamide **265** using tributylphosphine and diphenyl diselenide (Scheme 69).



265 **265**

266 **265**

Reagents: i, LiOH, THF, H_2O, rt; ii, Ph_2Se_2, Bu_3P, C_6H_6, rt.

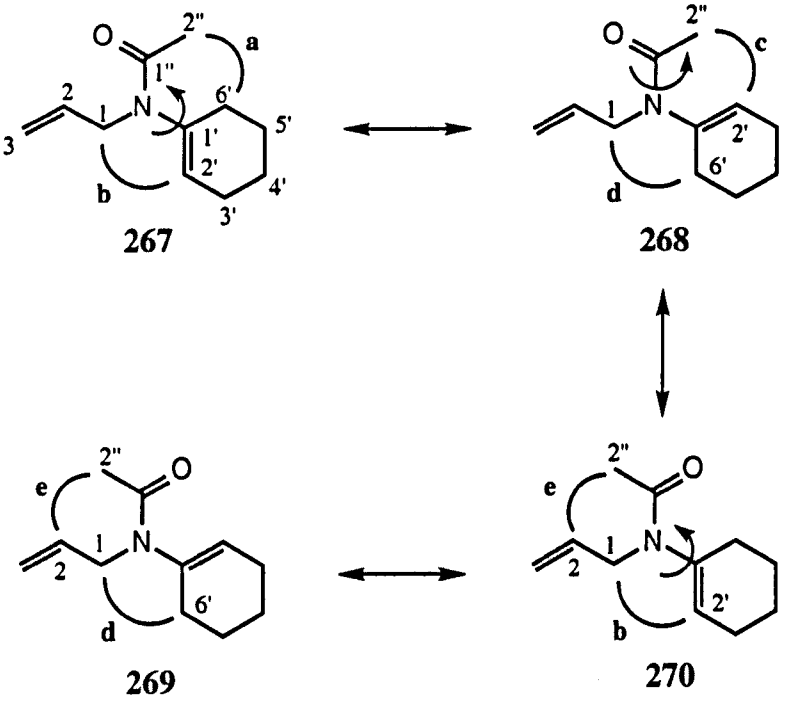
Scheme 69

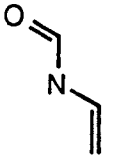
A conformational analysis of the enamide moiety present in the selenyl ester **262** was performed using extensive 2D n.m.r. techniques on the model system **265**. Studies were carried out on this system because both the ^1H and the ^{13}C n.m.r. spectra were fully assignable from ^1H-^1H COSY and ^1H-^{13}C COSY interactions. This leads to a simplification in nOe analysis that could not be achieved with the precursor **262**.

A 500 MHz NOESY experiment along with variable temperature experiments were performed to identify the lowest energy conformations of this system. Three through space nOes were clearly defined in the NOESY experiment. These correspond to the interactions **b**, between the protons in the 1 and 2' positions, **c**, between the protons in the 2' and 2" positions, and **d** between the protons in the 1 and 6' positions in

conformers **267** and **268**. The interaction **a** was not detectable due to the similar chemical shift of the two signals involved. No nOe was seen for the interaction **e** between the protons in the 2" and 1/2/3 positions of the allyl functionality from conformations **269** and **270**. Variable temperature n.m.r., -5°C to 80°C, showed no change in the ^1H spectra and titrating the sample with C_6D_6, along with other solvent changes, did not lead to a splitting of the signals required to visualise the nOe interaction **a**.

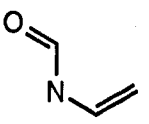
These collected data imply that the two conformations **267** and **268** are the most stable with an undetectable population of the conformations **269** and **270**. This relates well to electronic arguments which point to the form **267** having increased through bond conjugation, with the five bonds of the enamide system as the linear "W" conformation **271**. The enamides **268** and **270** exist as the more bent "sickle" form **272**, thus breaking down conjugation. The enamide **269** is in a "U" conformation **273** with low through bond conjugation. There appears to be relatively free rotation about the *N*-cyclohexenyl bond and very limited rotation about the *N*-acetyl bond. Rotation about the *N*-allyl bond appears to be unrestricted though analysis of this portion of the molecule is limited.[121]





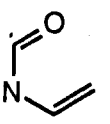
"W"

271



"sickle"

272

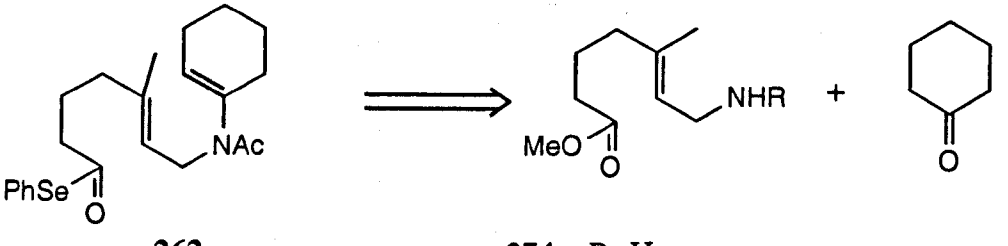


"U"

273

2.6.2 Tricycle Synthesis

After these initial studies we started the synthesis of the precursor **262**. Disconnection across the cyclohexenyl-nitrogen bond split the molecule into two halves (Scheme 70). This approach to the molecule gave cyclohexanone as the right hand side. However, in more complex systems where we would have to construct the right hand side it was envisaged that this disconnection would result in a convergent synthesis for any precursor. The left hand side could be seen to be a suitably oxidised amine **274a** which could be synthesised in a protected form **274b**. From the model studies that we had undertaken, we knew that the use of a methyl ester in this portion was appropriate. Therefore, our first synthetic target was the protected *E*-amine **274b**.



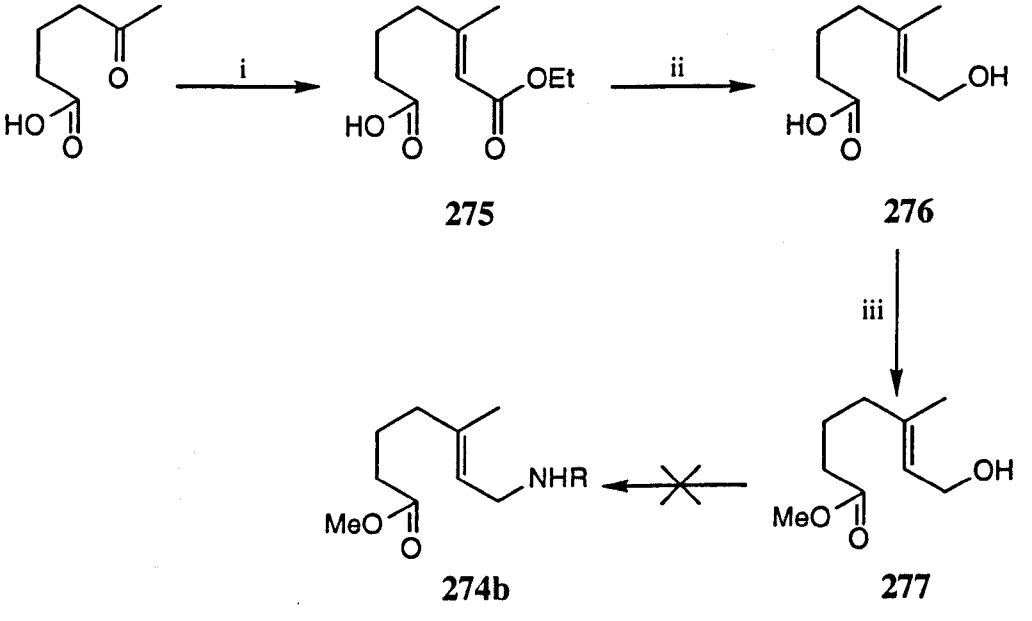
262

274a; R=H
274b; R=Protecting group

Scheme 70

The route of choice was *via* a Wadsworth-Emmons coupling reaction between 5-oxohexanoic acid and triethylphosphonoacetate to give the ester acid **275** as a 2:1

mixture of *Z:E* isomers. The geometry of the carbon-carbon double bond was assigned through comparison of the ^{1}H and ^{13}C n.m.r. spectra with known compounds of defined geometry.[217-219] The first double bond has been shown by others to have little effect on the mode and stereochemistry of the cyclisation reactions and so it was decided to carry the mixture of isomers through the synthetic route.[217-219] Selective reduction of the ester to the hydroxy acid **276** using DIBAL-H and subsequent conversion of the acid **276** to the hydroxy ester **277** gave the carbon skeleton and oxidation state required in our amine portion. However, the conversion of the alcohol **277** into the corresponding amine **274b** *via* various intermediates failed in the presence of the methyl ester and so other synthetic routes were investigated (Scheme 71).



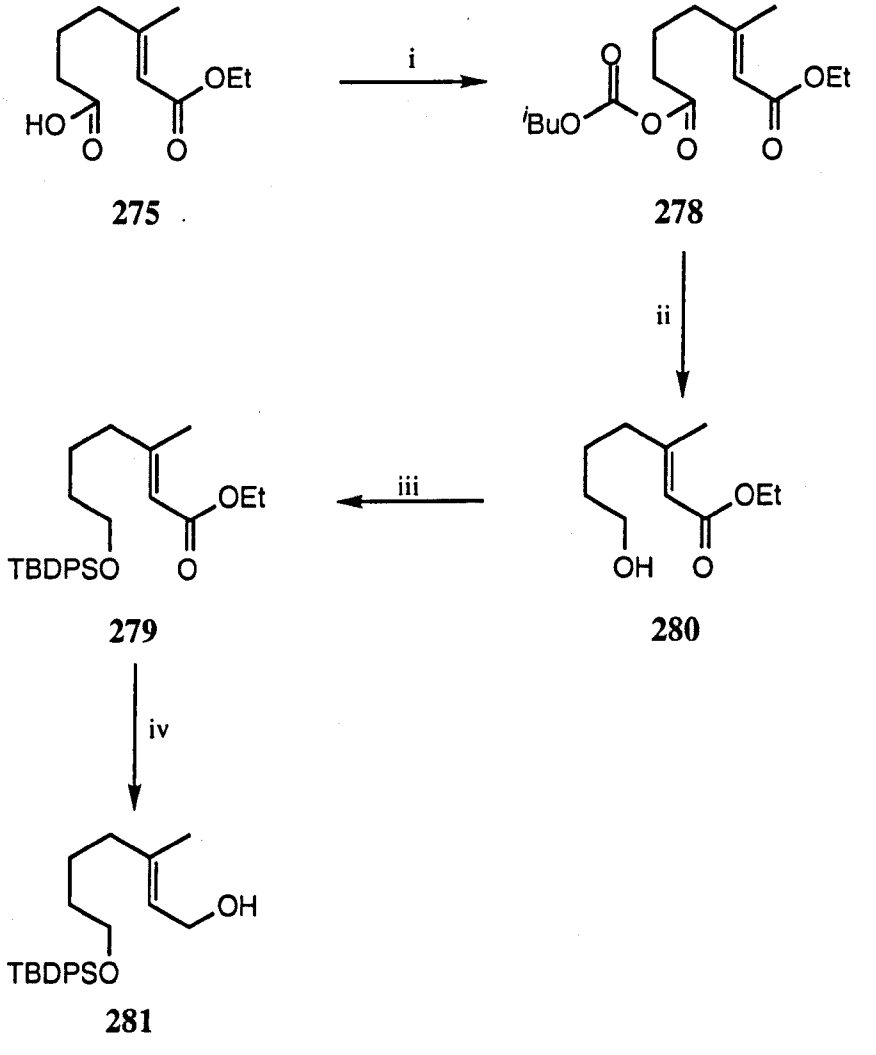
R=protecting group

Reagents: i, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0°C, 96%; ii, DIBAL-H, CH_2Cl_2, -78°C; iii, $TMSCHN_2$, MeOH, C_6H_6, rt, 81%-2 steps.

Scheme 71

Consequently, we were forced to perform a double reduction of both the ester and the acid present in **275** and carry the material through the amine formation stage as the

protected alcohol. Thus, starting from the Wandsworth-Emmons product **275**, we were able to synthesise the alcohol **280** by activation of the acid to the carbonic anhydride **278** followed by *in situ* reduction with sodium borohydride. Protection of the hydroxy group in **280** yielded **279** and reduction with DIBAL-H then gave the key intermediate alcohol **281** (Scheme 72).

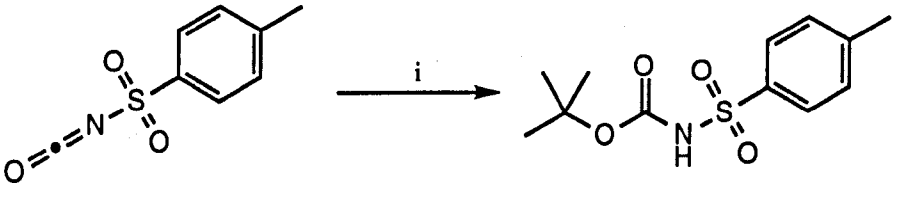


275 **278** **279** **280** **281**

Reagents: i, *i*-BuO_2CCl, Et_3N, CH_2Cl_2, rt; ii, $NaBH_4$, MeOH, 0°C 84%-2 steps; iii, TBDPSCl, Et_3N, CH_2Cl_2, rt, 100%; iv, DIBAL-H, CH_2Cl_2, -78°C, 92%.

Scheme 72

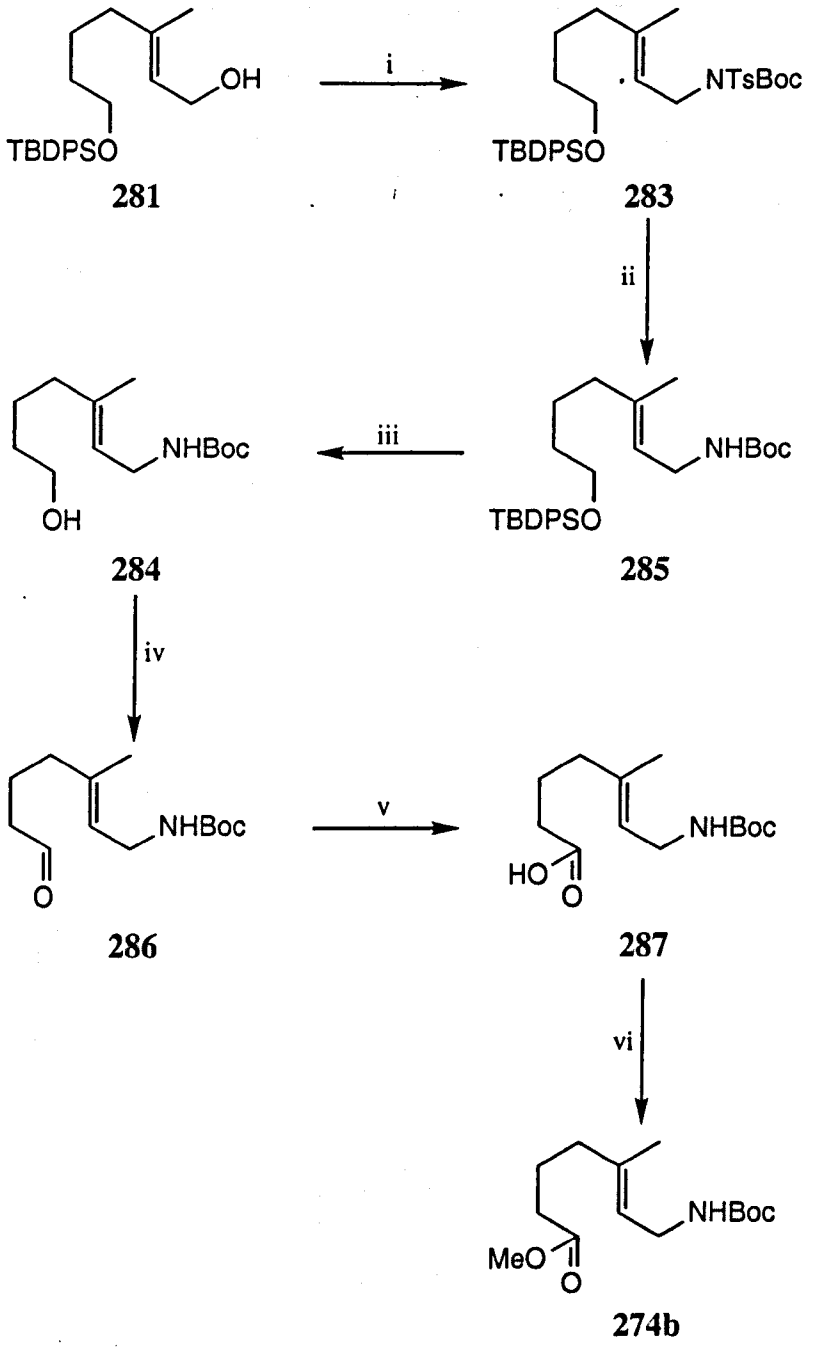
Introduction of the amine functionality into **281** required reagent **282**. This was synthesised in quantitative yield from *para*-toluenesulfonyl isocyanate and *tert*-butanol (Scheme 73) using the method of Weinreb.[122] A Mitsunobu reaction on **281** using the amine **282** gave the triprotected amine-diol **283** in nearly quantitative yield (99 %). Sequential deprotection first using sodium amalgam gave the Boc protected amine **285** and then using TBAF yielded the alcohol **284**. Oxidation of this alcohol using Dess-Martin periodinane gave the aldehyde **286** which was further oxidised to the acid **287**. Subsequent protection of **287** as the methyl ester with trimethylsilyl diazomethane to give our target **274b** in 11 steps and 40 % overall yield (Scheme 74).



282

Reagents: i, *t*-BuOH, rt, 100%.

Scheme 73

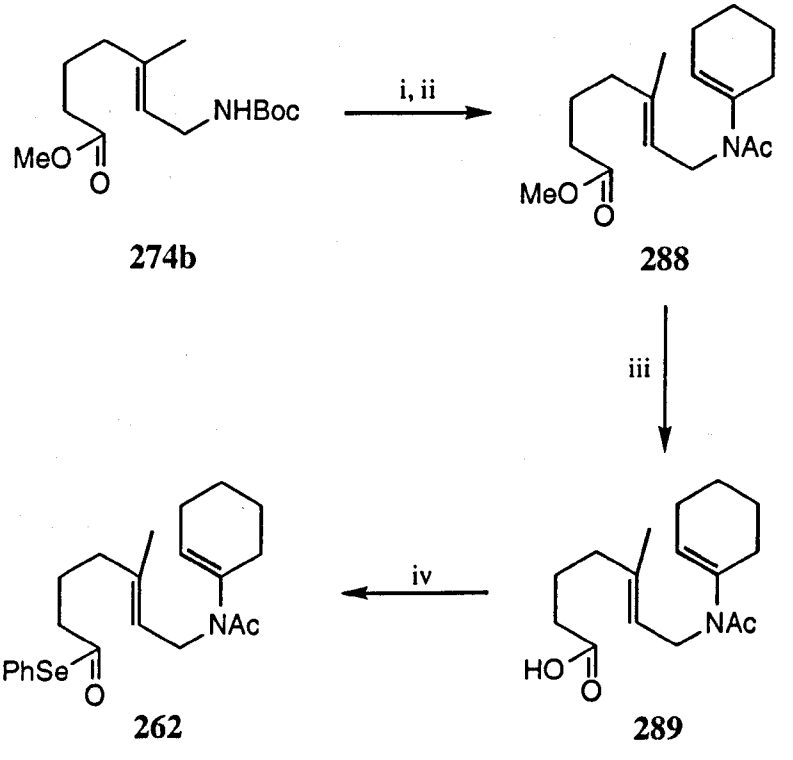


Reagents: i, **282**, DEAD, PPh_3, THF, rt, 99%; ii, NaHg (4.5% w/w), NaH_2PO_4, MeOH, rt, 85%; iii, TBAF, TsOH, THF, rt, 100%; iv, Dess Martin, CH_2Cl_2, rt, 70%; v, $NaCl_2O_4$, K_2HPO_4, 2-methyl-2-butene, H_2O, *t*-BuOH, rt; vi, $TMSCHN_2$, C_6H_6, MeOH, rt, 92%-2 steps.

Scheme 74

With the protected amine **274b** in hand, subsequent elaboration to the enamide **288** proceeded smoothly *via* deprotection with TFA to give the amine salt, followed by

condensation with cyclohexanone and acylation of the intermediate imine to give the product **288**. Hydrolysis of the ester in **288** generated the acid **289** which was used without further purification to synthesise the selenyl ester **262** (Scheme 75). These reactions worked well and we were able to isolate **262** in 35 % yield from the protected amine **274b**.



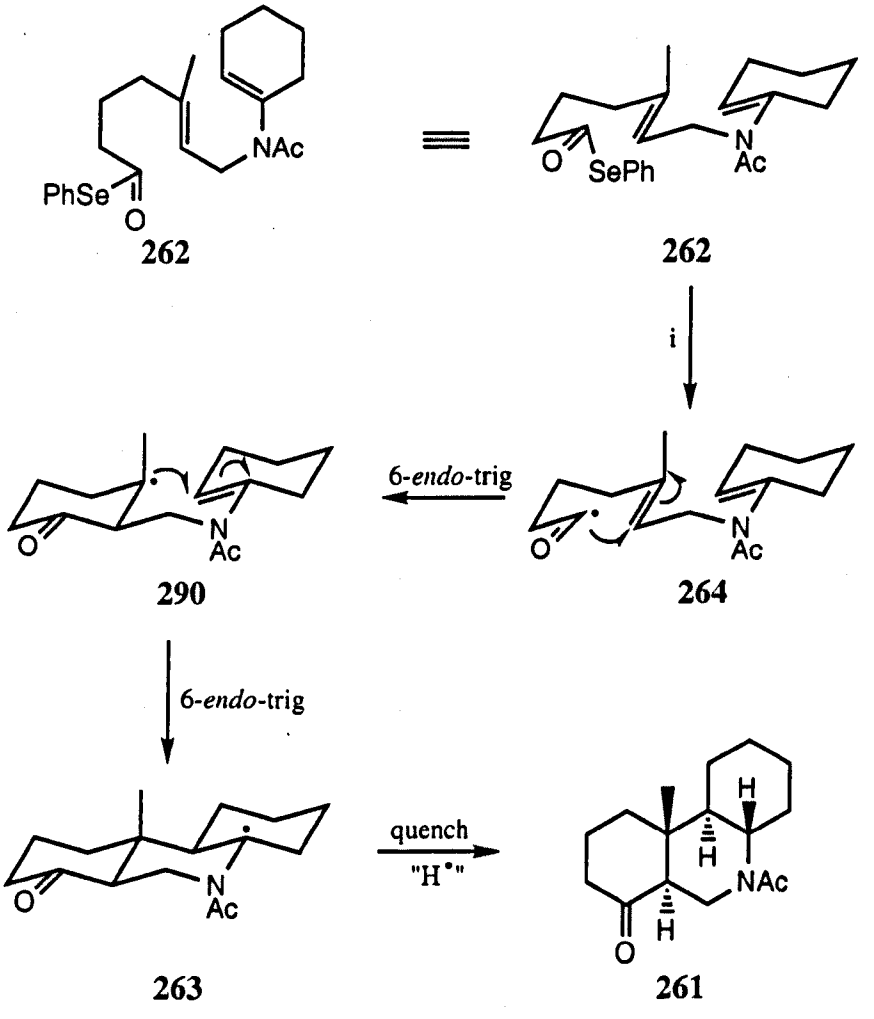
274b **288** **289** **262**

Reagents: i, TFA, rt; ii, Et_3N, C_6H_6; cyclohexanone, molecular sieves, C_6H_6, rt; AcCl, Et_3N, DMAP, C_6H_6, rt, 56%-2 steps; iii, LiOH, THF, H_2O, rt; iv, Ph_2Se_2, Bu_3P, C_6H_6, rt, 62%-2 steps.

Scheme 75

Following this synthetic route we were able to access enough of the selenyl ester **262** to study the radical chemistry of this system in some depth. Treatment of the selenyl ester **262** under radical generating conditions resulted in the formation of the reduced azaphenanthridine **261** in 65 % yield (Scheme 76). We used high dilution conditions and syringe pump addition to help prolong the life of the intermediate radicals in solution. After investigating a number of addition times we found that this optimised

yield was obtained from a two hour addition of a solution of 1.25 equivalents of tributyltin hydride and catalytic AIBN in degassed benzene to a refluxing 5 mM solution of the selenyl ester **262** and AIBN in degassed benzene. After a further two hours at reflux t.l.c. showed that there was no starting material remaining. Purification using column chromatography allowed us to isolate the tricycle **261** in 65 % yield as a single rotamer of one diastereoisomer (Scheme 76). This product was formed after the initial acyl radical **264** cyclised in a 6-*endo*-trig manner to give the tertiary alkyl radical **290**. This radical **290** subsequently underwent 6-*endo*-trig cyclisation to form the α-amidyl radical **263**, which in turn was quenched with tributyltin hydride, to yield the isolated product **261**.

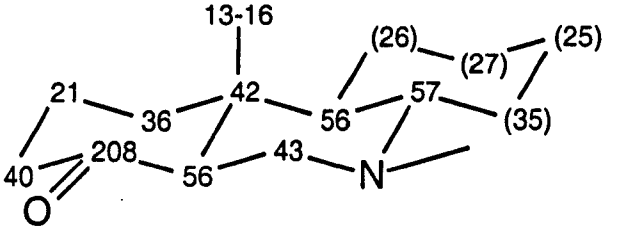


Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux, 65%.

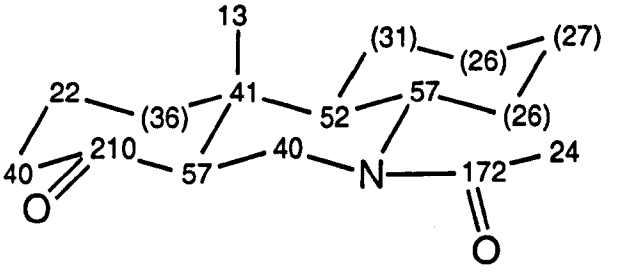
Scheme 76

Identification of the product followed from extensive analysis of one and two dimensional 500 MHz n.m.r. spectra. Initially from the ^{1}H n.m.r. spectra we were able to see that cyclisation had occurred and that we had isolated a tricyclic structure as there were no olefinic protons in the spectra. Analysis of the ^{13}C n.m.r spectra showed us that there were two carbonyl carbons, one at δ 209 p.p.m. corresponding to a cyclic ketone and at δ 172 p.p.m. corresponding to the amide. In the aliphatic region of the ^{13}C n.m.r. spectra there were 14 signals which, from the DEPT, we were able to assign as one quaternary centre, three CH, eight CH_2 and two methyl groups. Analysing the different reaction pathways available to our system during the radical reaction we were able to show that the most likely routes to this pattern of carbons in the DEPT was either two sequential 6-*endo*-trig cyclisations or a 5-*exo*-trig followed by a 5-*endo*-trig cyclisation. Of these two, by far the most probable cyclisation pathway would be the tandem 6-*endo*-trig cyclisation. We were able to confirm the 6, 6, 6 angular fused structure by looking at the ^{1}H-^{1}H and ^{1}H-^{13}C COSY n.m.r. spectra. From this it was possible to verify that the nitrogen was adjacent to both a CH at C-8 (using steroid numbering) (δ 3.37 p.p.m. in the ^{1}H n.m.r. spectra and δ 57.4 p.p.m. in the ^{13}C n.m.r spectra) and a CH_2 at C-6 (δ 3.73 and δ 3.43 p.p.m. in the ^{1}H n.m.r. spectra and δ 40.1 p.p.m. in the ^{13}C n.m.r. spectra) which was adjacent to the CH at C-5 (δ 2.51 p.p.m. in the ^{1}H n.m.r. spectra and δ 57.1 p.p.m. in the ^{13}C n.m.r. spectra). This pattern would not be possible in the 5 and 5,6 tricyclic molecule obtained from the other possible cyclisation pathway. With conclusive evidence that the 6, 6, 6 angular fused tricycle was the skeleton that we had generated from our studies we then attempted to assign the stereochemistry by comparing our n.m.r. results to those published in the literature.[117] Very little information could be obtained from the ^{1}H n.m.r. spectra as the signals are concentrated in the aliphatic region of the spectra between δ 2.5 and δ 0.5 p.p.m. and the coupling constants are masked. However, H-8 appeared as an apparent triple doublet with vicinal coupling

constants to H-9 and H-14(α) of 10.7 Hz and to H-14(β) of 2.8 Hz. Also, the protons at C-6 had vicinal couplings of 8.3 and 7.1 Hz to the proton at C-5. These coupling constants are consistent with a slightly flattened chair, chair, chair conformation that we would expect for the *trans, anti, trans* stereochemistry. Using an analysis of the carbon spectra similar to the one employed by Pattenden and co-workers in the initial study of carbocyclic steroids we were able to predict the expected spectra for the *trans, anti, trans* stereochemistry.[117] This prediction was very similar to the actual spectra confirming our hypothesis that the compound we had isolated in 65 % yield was the *trans, anti, trans* tricycle **261**.



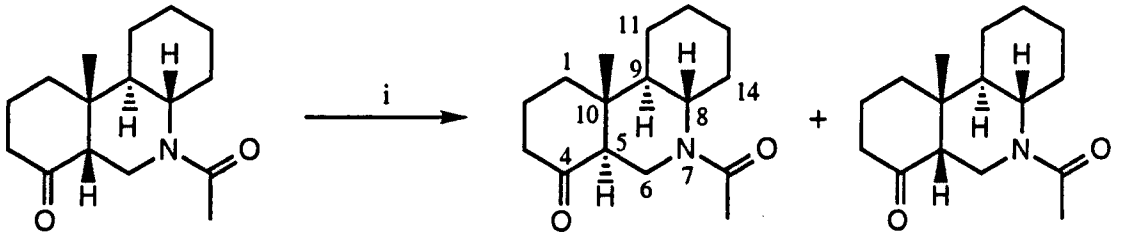
261; predicted carbon shifts



261; assigned carbon shifts
(numbers in brackets are tentative)

After one year following the completion of these studies we attempted to obtain a crystalline derivative of **261** as part of a model study into the stereochemistry of the tetracycle **296**. However, when we reinvestigated the molecule we found that it had undergone transformation into two compounds. Chromatographic separation of the mixture allowed us to isolate the initial tricyclic system **261** along with a related

rotameric crystalline material **291**.§ X-ray analysis confirmed its structure as the *cis, anti, trans* tricycle **291**. Upon submitting this compound to basic conditions (NaOMe, MeOH, reflux) we were able to regenerate an equilibrium system of the two tricyclic compounds **261** and **291** which were separated by chromatography (Scheme 77). As this compound **291** was rotameric we were unable to perform the interesting comparison between the n.m.r. spectra of the two isomers.



291 **261** **291**

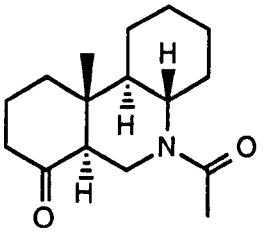
Reagents: i, MeONa, MeOH, reflux.

Scheme 77

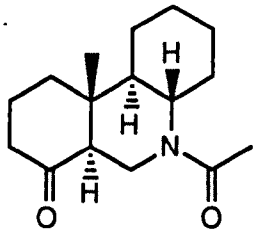
In an attempt to rationalise these findings we performed some molecular modelling (MM2 force field) on both systems and their two rotameric forms. The *trans, anti, trans* system, unsurprisingly, showed two chair, chair, chair conformations for the lowest energy forms of both rotamers **261** and **292**. However, the rotameric forms were vastly different in energy at 18.1 $kJmol^{-1}$ for the isolated material **261** and 34.7 $kJmol^{-1}$ for the unseen rotamer **292**. For the *cis, anti, trans* material the molecular modelling studies showed that the crystalline material **291** had the lowest energy conformation at 18.9 $kJmol^{-1}$. The structure of **291** from the molecular modelling was superimposable on the structure of **291** from the X-ray studies. The other rotameric form **293** had a very similar energy (21.4 $kJmol^{-1}$) and a twist boat, boat, chair conformation. These results explain the ability of the system (**261-291**) to

§ We were unable to obtain a melting point on this material due to the unsuitable nature of the semi-solid that was returned from the X-ray laboratory.

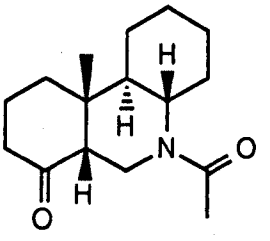
undergo epimerisation and the rotameric nature of the *cis, anti, trans* **291** system when compared to the *trans, anti, trans* system **261**.



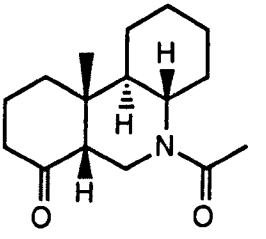
261



292

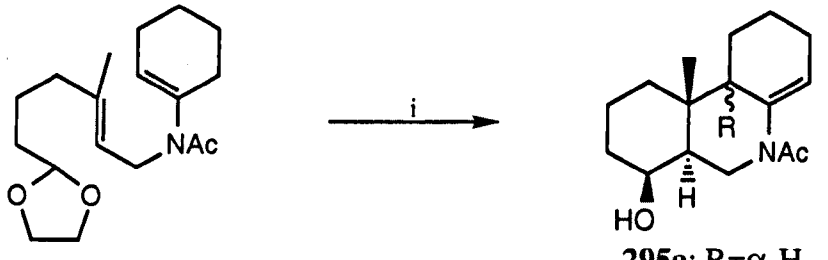


291



293

During the course of these initial studies contemporaneous work was published by Sen and co-workers using cationic cascades to synthesise a very similar system to the phenanthredine **261**.[123] Thus, the acetal protected *E*-aldehyde-enamide **294** cyclised when treated with iron (III) chloride in dichloromethane to yield the two tricycles **295a** and **295b** in 55 % and 10 % yield respectively (Scheme 78).



294

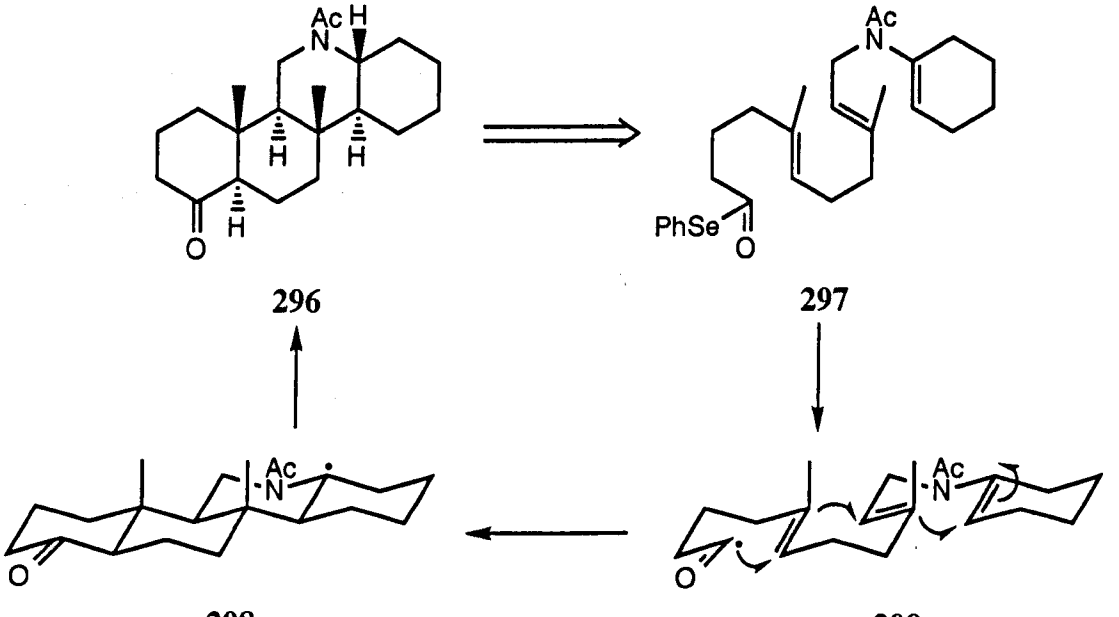
295a; R=α-H
295b; R=β-H

Reagents: i, $FeCl_3.6H_2O$, CH_2Cl_2, rt.

Scheme 78

2.6.3 Steroid Synthesis

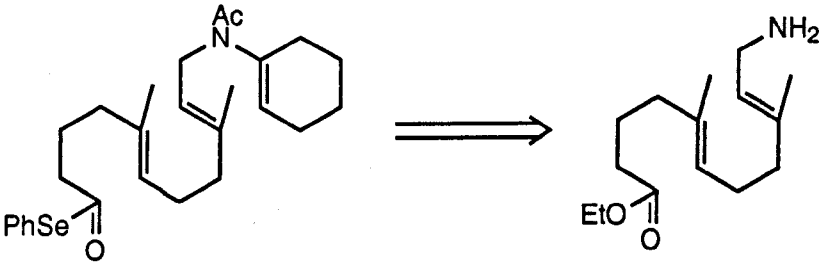
With the success of our initial studies towards the synthesis of the reduced phenanthridine **261** using a cyclohexenyl enamide as the terminating electrophore in a radical cascade, we undertook an investigation into the synthesis of a steroid system using similar methodology. Thus, disconnecting the 12-aza-D-homosteroid **296** identified a radical cascade reaction from the selenyl ester **297**. We thought that the acyl radical **299** could undergo three consecutive 6-*endo*-trig cyclisations to give the α-amidyl radical **298**. Quenching of the radical **298** would yield the steroid **296** (Scheme 79).



Scheme 79

Retrosynthetic analysis of the selenyl ester **297** showed that the allyl amine **300** or its protected equivalent would be a key component for this synthesis (Scheme 80). The synthetic route that we had used for the synthesis of the precursor **262** was rather long

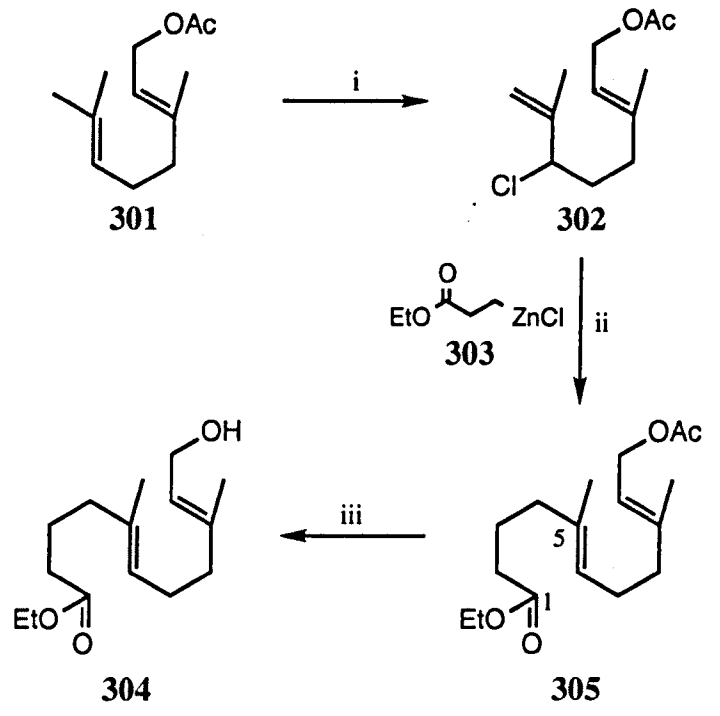
and we felt that a shorter route to these systems would be beneficial. We were aware of the work of Rollin and co-workers[124] utilising a Mitsunobu reaction for the synthesis of allyl azides from allyl alcohols and we decided to use this methodology in the synthesis of our amine portion **300**. Therefore, our initial target was the allylic alcohol **304** and this was achieved in three steps.



297 **300**

Scheme 80

Thus, using the methodology of Nakamara and co-workers,[125] we were able to synthesise the allylic chloride **302** from geranyl acetate **301**. Copper catalysed addition of the zinc homoenolate **303** yielded the allylic acetate **305** as a 2:1 mixture of *E:Z* isomers at the C-5 double bond. Again the geometry of the C-5 double bond was assigned by comparison with the spectra from known compounds along with the results from Nakamara and co-workers.[125] Potassium cyanide mediated transesterification in ethanol gave the key allylic alcohol **304** in 73 % overall yield (Scheme 81).



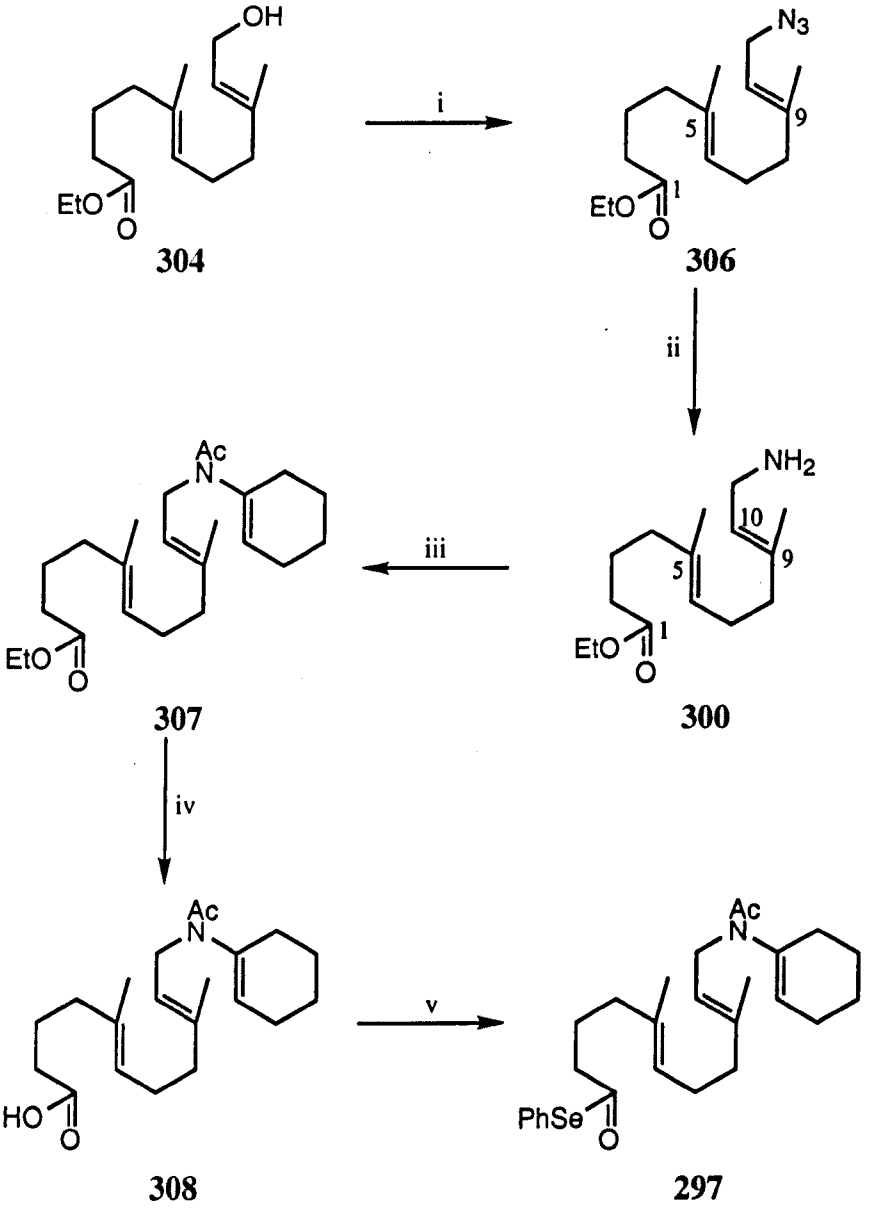
Reagents: i, *t*-BuOCl, silica, petrol, 0°C, 96%; ii, **303**, TMSCl, $CuBr_2.Me_2S$, Et_2O, DMF, rt, 89%; iii, KCN, EtOH, reflux, 83%.

Scheme 81

Formation of the precursor **297** followed the methodology that Rollin *et al.*[123] had developed in the synthesis of allylic azides. Thus, from the alcohol **304** we introduced the azide *via* a Mitsunobu reaction to yield **306**. This relied on the use of a zinc azide-dipyridine complex as a source of azide. The use of zinc azide was said to suppress S_N2' addition to allylic systems which is a major problem in the displacement of bromide with inorganic azides. Its use also removed the need to use highly toxic hydrazoic acid which has also been shown to undergo reactions with alcohols under Mitsunobu conditions.[126,127]

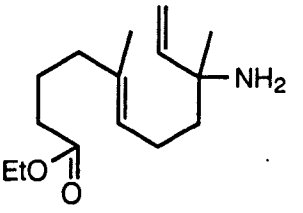
The ^1H n.m.r. spectra showed a terminal olefin in the molecule along with a broadened peak for the C-10 proton. This was consistent with a system that was in equilibrium with the S_N2' addition product and the *cis* isomer of the double bond. Therefore, the azide **306** was isolated as a mixture of compounds. However, upon Staudinger reduction of the azide **306** with triphenylphosphine and subsequent

hydrolysis of the intermediate iminophosphorane only the amine **300** was isolated. None of the S_N2' product **309** was seen. Analysis of the ^1H and ^{13}C spectra showed the amine **300** now existed as a 2:1 *E:Z* mixture at both C-5 and C-9 double bonds. The stereochemical scrambling that resulted from this reaction was most disappointing as it has been shown that the stereochemistry of the second double bond can affect the stereochemistry of the product from the radical reaction.[117-119]



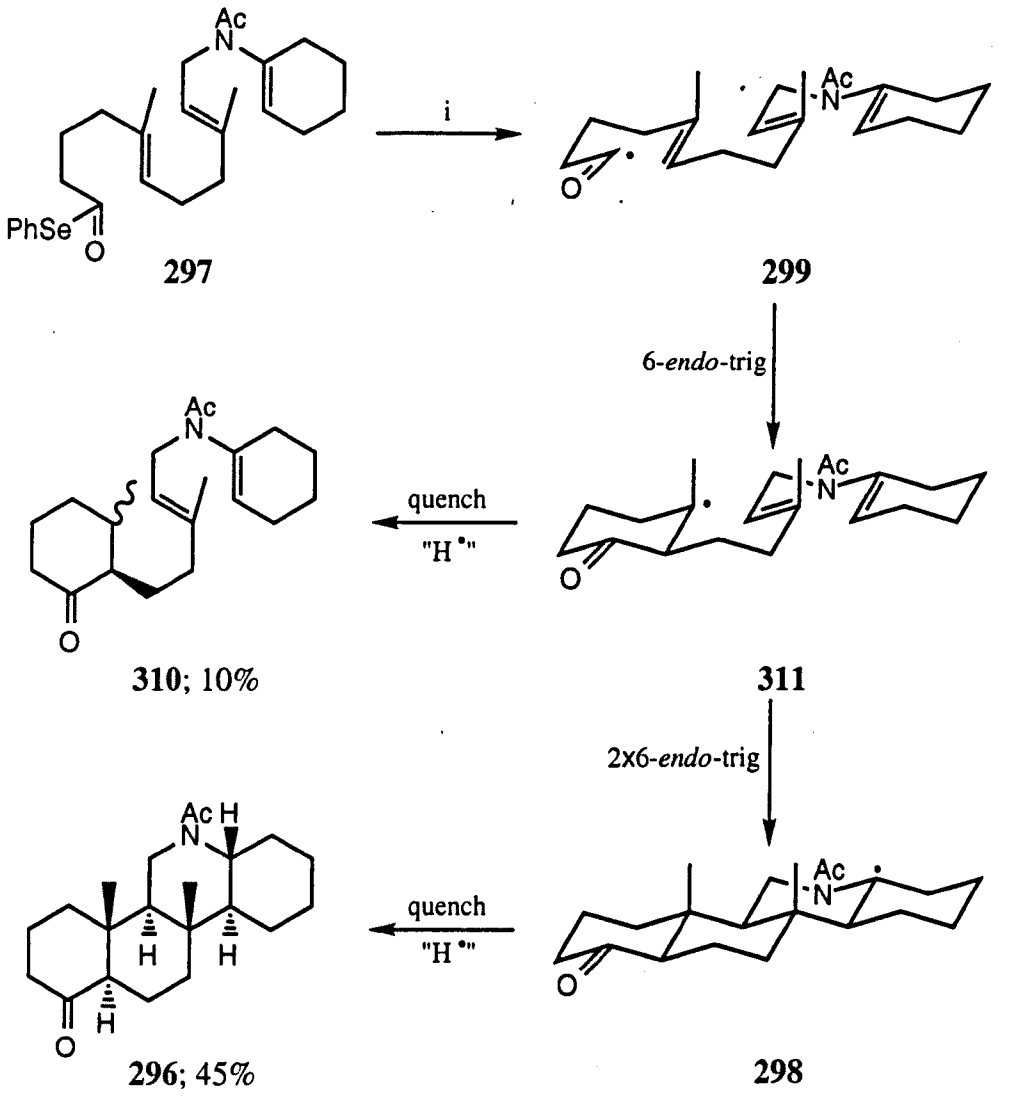
Reagents: i, $Zn(N_3)_2.2py$, DIAD, PPh_3, C_6H_5Me, rt, 62%; ii, PPh_3, THF; H_2O, THF, rt, 74%; iii, cyclohexanone, molecular sieves, C_6H_6; AcCl, lutidine, C_6H_6, rt, 43%; iv, LiOH, THF, H_2O, rt, 99%; v, *N*-PSP, Bu_3P, CH_2Cl_2, -30°C, 80%.

Scheme 82



309

The enamide formation proceeded smoothly to give the ester **307** which was subsequently hydrolysed to the acid **308**. Conversion of the acid in **308** into the selenyl ester produced the precursor **297** in 8 steps from geranyl acetate (Scheme 82). The selenyl ester **297** was subjected to a number of radical generating conditions in an attempt to optimise the cascade reaction. It was found that the highest yield (45 %) of the D-homo-12-azasteroid **296** resulted from syringe pump addition of a solution of tributyltin hydride (1.25 equivalents) and AIBN (catalytic) in degassed banzene over 8 hours to a refluxing 3 mM solution of **297** in degassed benzene followed by a further 4 hours reflux (Scheme 83). The tetracycle **296** was obtained as a 4:1 mixture of the *trans, anti, trans, anti, trans* diastereoisomer and another unidentified isomer. This product **296** resulted from three consecutive 6-*endo*-trig cyclisations from the acyl radical **299** terminating in the quenching of the α-amidyl radical **298** with tributyltin hydride. Also isolated from this reaction mixture was the monocyclised product **310** in 10 % yield resulting from just one 6-*endo*-trig cyclisation followed by quenching of the intermediate tertiary alkyl radical **311**.

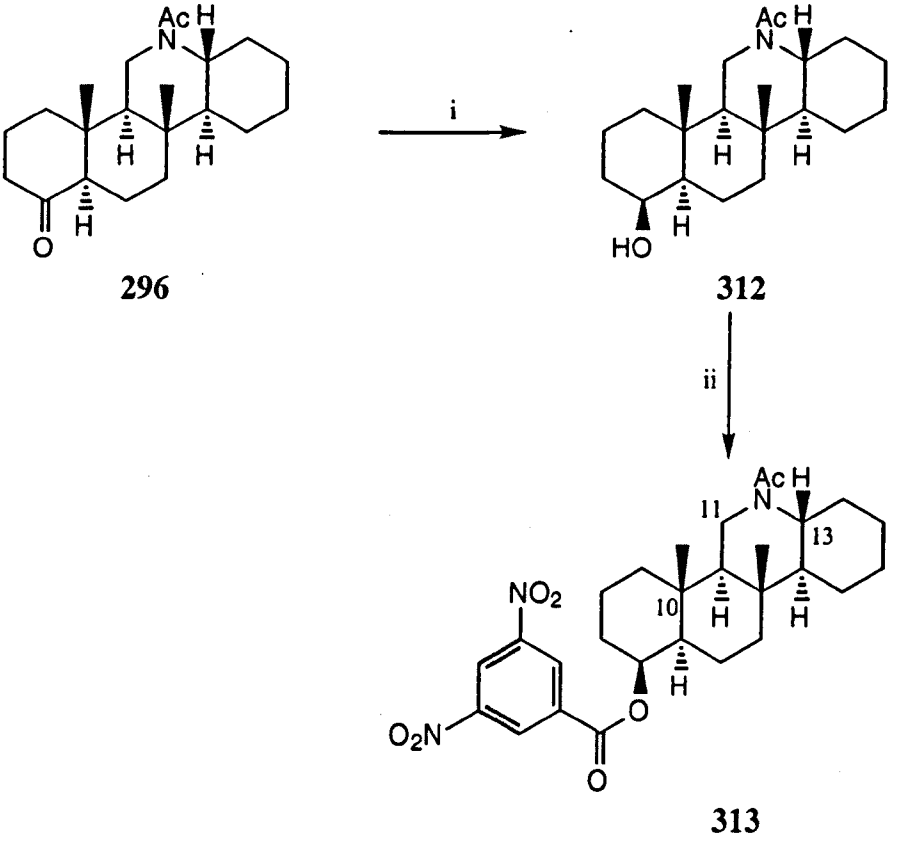


Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 83

The mixture of stereoisomers isolated from this reaction made the assignment of the structure quite complex. In order to confirm the proposed *trans, anti, trans, anti, trans* stereochemistry we attempted to synthesis a derivative of **296** suitable for X-ray analysis. Thus, a diastereoselective sodium borohydride reduction of the ketone in **296** resulted in the isolation of the alcohol **312**. Subsequent derivatisation with 3,5-dinitrobenzoyl chloride yielded the ester **313** (Scheme 84). The two isomers of this compound were separated by flash column chromatography. The major isomer was

isolated as a semi-solid but we were still unable to crystallise the material in order to obtain X-ray data.



Reagents: i, $NaBH_4$, MeOH, Et_2O, rt, 99%; ii, 3,5-dinitrobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, rt, 61%.

Scheme 84

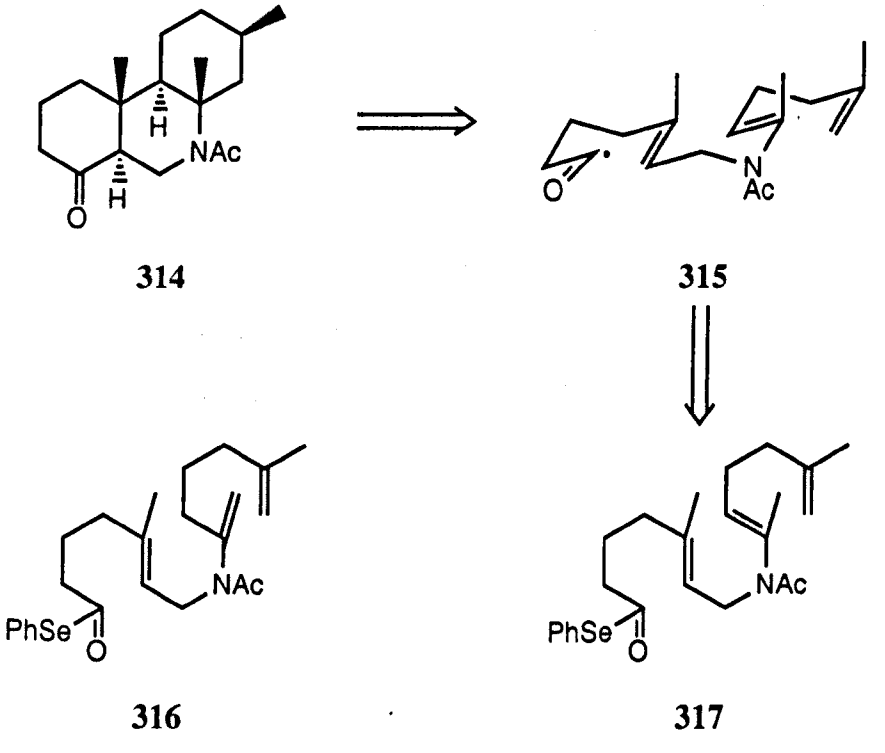
However, with a single isomer in hand we were able to perform a similar n.m.r. study to the one used in the identification of **261**. From all the data that we had obtained from the molecules **296, 312** and **313** we were able to see that the product we had isolated had undergone three cyclisation reactions as there were no olefinic protons present. Using data mainly from the single isomer **313** for which we had obtained variable temperature ^1H and ^{13}C n.m.r. spectra along with ^1H-^1H COSY and HMQC data we were able to identify the structure of the molecule. In the high temperature spectra of **313** the protons at C-11 and C-13 showed very similar coupling constants and chemical shifts as the protons at C-6 and C-8 respectively, in the molecule **261**. Using the HMQC spectra to assign carbons to the protons in this region of the spectra

we were able to show that the carbon signals were also similar to those in **261**. So the CH at C-13 was at δ 3.34 p.p.m. in the ^{1}H n.m.r. spectra and at δ 57.8 p.p.m. in the ^{13}C n.m.r. spectra (δ 3.37 p.p.m. in the ^{1}H n.m.r. spectra and δ 57.4 p.p.m. in the ^{13}C n.m.r. spectra of **261**). It appeared as an apparent triple doublet with vicinal coupling constants to H-14 and H-17a(α) of 10.7 Hz and to H-17a(β) of 2.8 Hz. The CH_2 at C-11 was at δ 3.54 and δ 3.40 p.p.m. in the ^{1}H n.m.r. spectra and at δ 40.7 p.p.m. in the ^{13}C n.m.r. spectra (δ 3.73 and δ 3.43 p.p.m. in the ^{1}H n.m.r. spectra and δ 40.1 p.p.m. in the ^{13}C n.m.r. spectra of **261**). It appeared as two double doublets with couplings of 13.3 Hz and 9.9 Hz at δ 3.54 p.p.m. and 13.3 Hz and 9.4 Hz at δ 3.40 p.p.m. These splitting patterns are very similar to the B, C ring junction in **261**. This information showed us that the molecule **313** contained at least three six membered rings with a *trans, anti, trans* stereochemistry.

When we looked at the ^{13}C and DEPT n.m.r. spectra for **313** we were able to see 6 C, 7 CH, 10 CH_2 and 3 CH_3. As we already knew that there were three six membered rings in the molecule and as this pattern of carbons could only correspond to either a 6, 6, 6, 6 molecule or a 5, 5, 6, 6 molecule we knew that the structure we had originally isolated was the steroid **296**. The chemical shift of the ketone signal from the ^{13}C n.m.r. spectra of **296** at δ 212.2 p.p.m. also pointed towards a 6 membered A ring. Chemically the 6, 6, 6, 6 structure was far more likely as the initial acyl radical has been shown to prefer a 6-*endo*-trig cyclisation pathway. We were able to assign the A, B ring junction as *trans* from the position of the methyl group in the ^{13}C n.m.r. spectra at δ 15.3 p.p.m. This chemical shift is indicative of a *trans* ring junction and very similar to previous studies in our work. From this collaborated evidence we were able to confidently assign the structure **296** as the *trans, anti, trans, anti, trans* 12-aza-D-homosteroid shown. We did not perform the same calculations to predict the carbon spectra of **296** as we had for **261** because we felt that the comparison of these two spectra gave us a better insight into the structure and stereochemistry of the molecule.

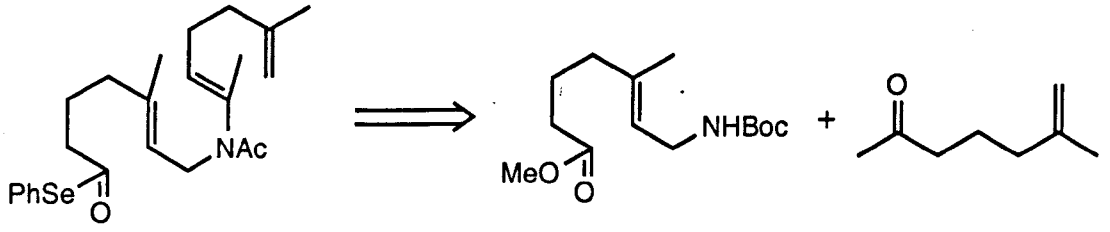
2.7 LINEAR ENAMIDES

Cyclohexenyl enamides have now been shown to be very useful electrophores in azasteroid synthesis by radical cascades. In an attempt to further investigate the behaviour of enamides in radical cascades we started looking at linear systems. Initial interest was in the synthesis of the tricyclic system **314** *via* three consecutive 6-*endo*-trig processes from the selenyl ester **317** with the acyl radical **315** as a reactive intermediate (Scheme 85). Disconnection of the precursor **317** led to the known ketone **318** and the amine **274b** which had been synthesised previously (Scheme 86). However, we had used an 11 step route in the synthesis of the amine **274b** and we felt that this could be improved by the use of the methodology employed in the synthesis of the amine **300**.



314 **315** **316** **317**

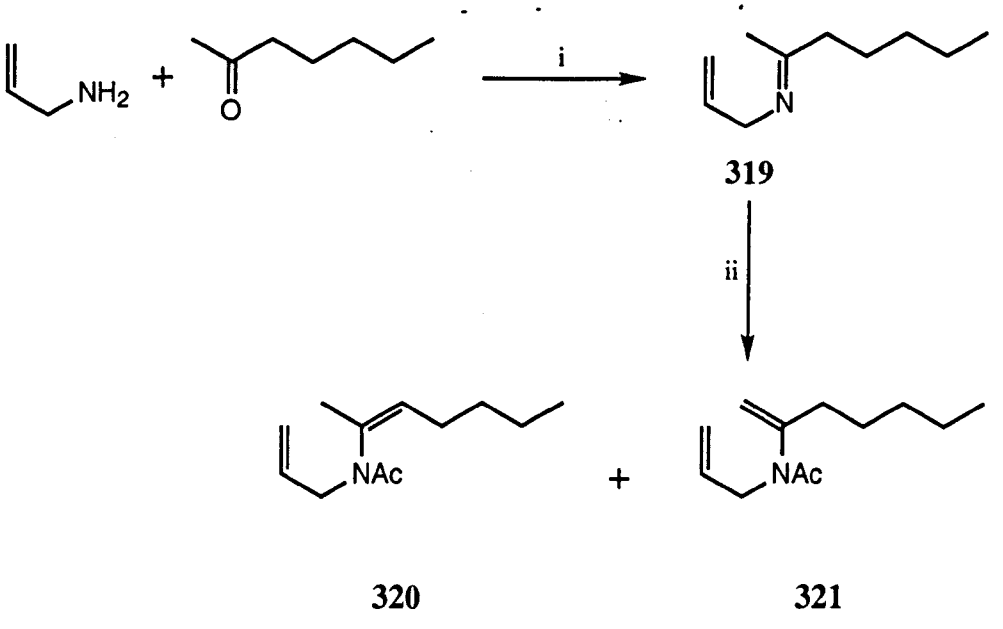
Scheme 85



317 274b 318

Scheme 86

Before attempts were made on the synthesis of this precursor **317** potential problems were identified with the regioselectivity of the formation of the enamide double bond. It was anticipated that the conditions used previously for this acylation step (i.e. acetyl chloride, Et_3N, DMAP, C_6H_6, rt) would generate mainly the undesired, kinetic product **316** and not the required thermodynamic product **317**. To test this hypothesis a model system was developed, using the condensation of 1-aminoprop-2-ene and heptan-2-one followed by the *in situ* acylation of the resulting imine **319** under standard conditions. It was hoped that if a problem was found it would be possible to optimise conditions in the model system and then apply these in the synthesis of the required enamide **317**. When this study was performed, acylation of the imine **319**, resulted in the isolation of the two regioisomers **320** and **321** in a ratio of 24:76 respectively, and an overall yield of 62 % (Scheme 87). Fortuitously, the regioisomers were readily separable by flash column chromatography and full characterisation and structural identification was possible by analysis of their ^1H and ^{13}C n.m.r. spectra.



320 **321**

Reagents: i, molecular sieves, C_6H_6, rt; ii, acetyl chloride, Et_3N, DMAP, C_6H_6, rt, 62%-2 steps.

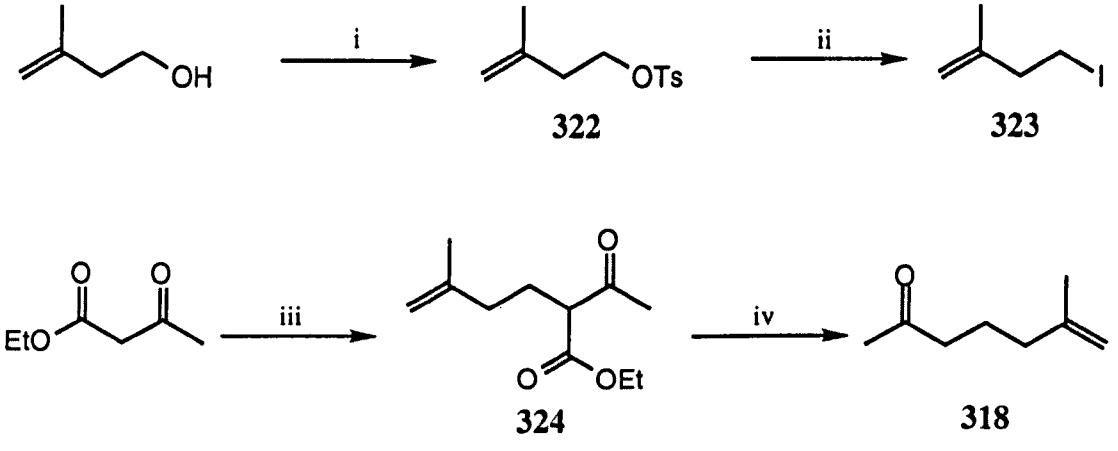
Scheme 87

The reaction was investigated at different temperatures to try and increase the yield of the required thermodynamic enamide **320** (Table 1). The ratios of **320** to **321** were calculated from the ^1H n.m.r. of the crude reaction mixture and the yields are the combined yields of the two products after purification by flash column chromatography. The most favourable ratio was obtained by performing the acylation in refluxing xylene. However, the reduced yield meant that the best conditions for the synthesis of **320** was the reaction carried out in refluxing toluene. The isolatable yield of the enamide **320** from this reaction was 39 %. With these optimised conditions in place we investigated the synthesis of the precursor **317**.

Temperature	Solvent	Ratio **320**:**321**	Overall yield	Yield of **320**
25°C	Benzene	1:3	62	15
42°C	Benzene	3:7	65	18
60°C	Benzene	1:2	64	20
110°C	Toluene	3:2	65	39
142°C	Xylene	2:1	52	35

Table 1

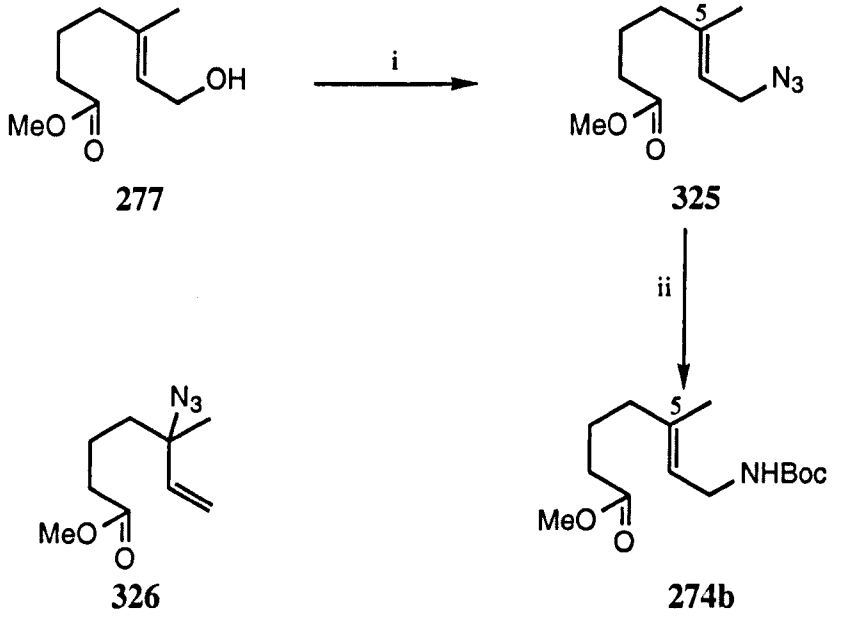
The ketone portion **318** for the selenyl ester **317** was synthesised *via* a modified literature procedure in an overall yield of 49 % (Scheme 88).[128] Thus, the known iodide **323**, was prepared in two steps from 3-methyl-3-buten-1-ol, *via* the tosylate **322**. Alkylation of the anion of ethyl acetoacetate gave the β-ketoester **324** which was decarboxylated, generating the required ketone **318**.



Reagents: i, TsCl, py, rt, 75%; ii, NaI, acetone, reflux, 77%;
iii, NaH, THF, rt; **323**, rt, 84%; iv, 50% NaOH, reflux, 100%.

Scheme 88

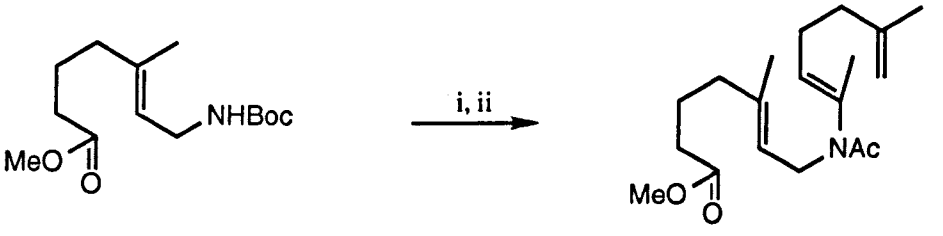
A modified version of the methodology employed in the synthesis of the amine **300** was utilised for our new approach towards the protected amine **274b**. Returning to the alcohol **277**, we used Rollin and co-workers zinc azide mediated Mitsunobu reaction to install the nitrogen functionality into our system.[124] The Mitsunobu reaction proceeded smoothly in 67 % yield, affording a 7:1 equilibrium mixture of the S_N2 product **325** and the S_N2' product **326**, respectively. Subsequent reduction of the azide mixture **325** and **326** with triphenylphosphine and hydrolysis of the resulting iminophosphorane, followed by *in situ* Boc protection of the amine gave the product **274b**, in 97 % yield. The high isolated yield of **274b** from this reaction suggests that the S_N2' product **326** does not react with triphenylphosphine and that the system is in equilibrium. The product was isolated as a 2:1 mixture of *E:Z* isomers after inversion of the C-5 the double bond (Scheme 89). The geometry of the double bond was assigned by comparison of the ^{13}C n.m.r. spectra obtained from similar systems. This high yielding five step route to the protected amine allowed us to access the large amounts of material required for our studies into the precursor **317** and its derivatives.



Reagents: i, $Zn(N_3)_2.2py$, DIAD, PPh_3, C_6H_5Me, rt, 67%;
ii, PPh_3, THF; H_2O, THF; Boc_2O, Et_3N, THF, rt, 97%.

Scheme 89

We then applied our optimised conditions for the synthesis of the enamide **327** to the protected amine **274b** and the ketone **318** (Scheme 90). The yields obtained for the synthesis of the model system **320** could not be reproduced and only 5 % of the desired product **327** was isolated. Attempting the reaction at room temperature also resulted in low yields.

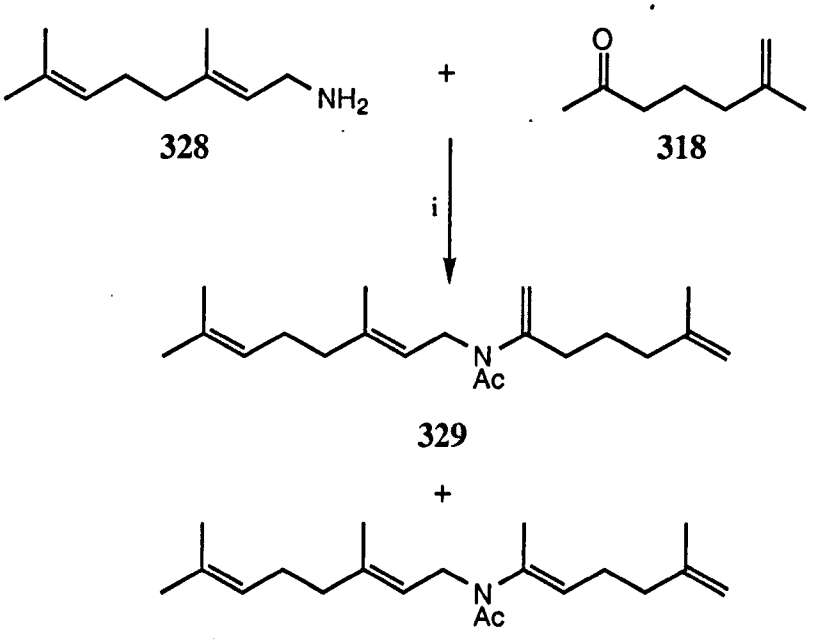


274b **327**

Reagents: i, TFA, rt; ii, **318**, molecular sieves, C_6H_5Me, rt; AcCl, Et_3N, C_6H_5Me, reflux, 5%-2steps.

Scheme 90

In order to investigate the problems associated with this synthetic route we attempted the synthesis of longer chain enamides as model systems. For example, condensation of geranyl amine **328** with the ketone **318** at room temperature resulted in the isolation of the enamides **329** and **330** in 31 % and 23 % yields, respectively (Scheme 91). However, we were still unable to repeat this reaction on our amine **274b**.



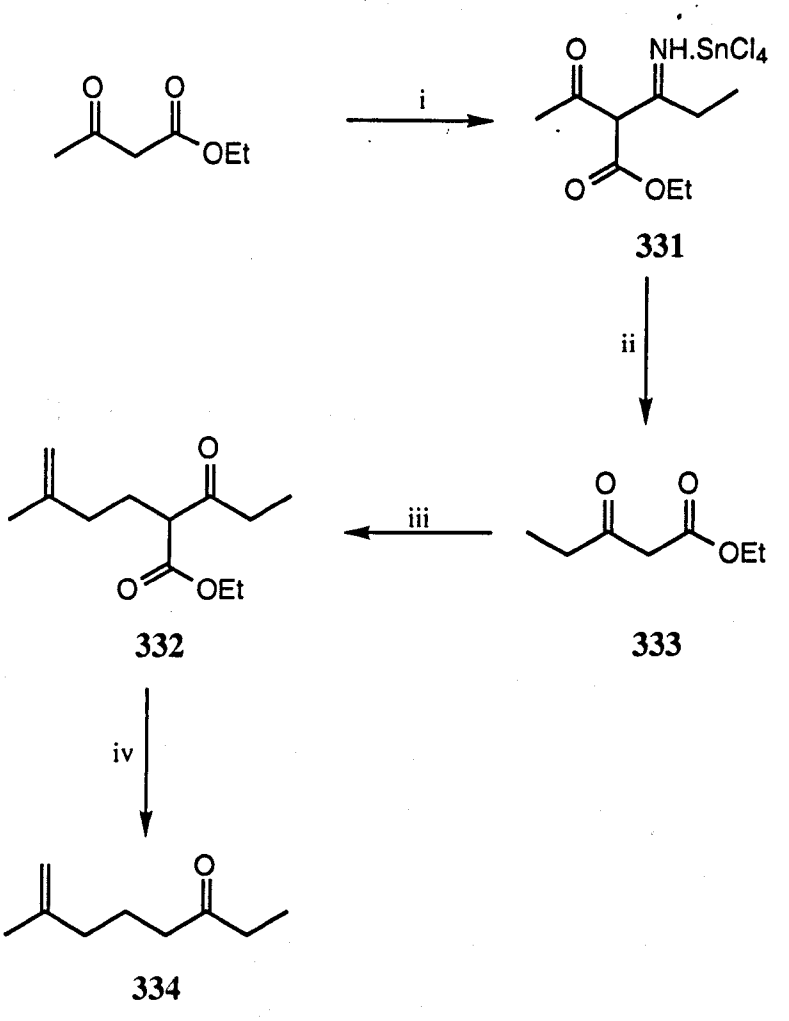
328 + 318

329 + 330

Reagents: i, molecular sieves, C_6H_6; AcCl, lutidine, C_6H_6, rt, 53%

Scheme 91

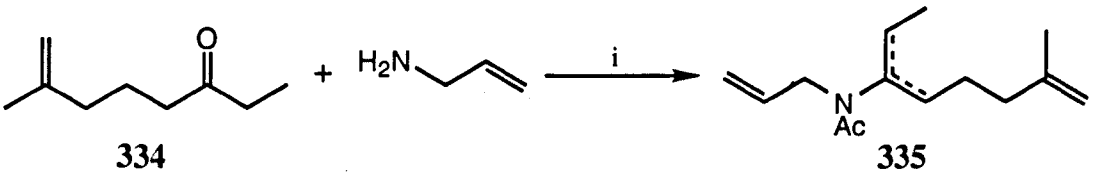
We also investigated the steric constraints of enamide formation by attempting the reaction with the ethyl ketone **334**. The synthesis of **334** followed the same strategy that we had used for the methyl ketone **318** (Scheme 88). Firstly, ethyl 3-oxopentanote **333** was prepared from ethyl acetoacetate *via* the tin chloride complex **331**.[129] Using the same iodide **323** as that employed in the synthesis of the ketone **318** we first alkylated ethyl 3-oxopentanote **333** to give the β-ketoester **332**. Decarboxylation, as before, then gave us the required ethyl ketone **334** (Scheme 92).



Reagents: i, $SnCl_4$, CH_3CH_2CN, C_6H_5Cl, 80°C, 86%; ii, 10% HCl (aq), $CHCl_3$, rt 83%; iii, NaH, THF; **323**, THF, 0°C, 87%; iv, 50% NaOH (w/v, aq), reflux, 85%.

Scheme 92

Using the ketone **334** in enamide forming reactions with 1-aminoprop-2-ene again gave low yield and an inseparable mixture of isomers in the product **335** (Scheme 93). We therefore changed our strategy to more stable intermediates in an attempt to obtain radical precursors in high yield.



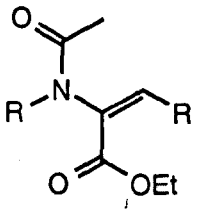
334 335

Reagents: i, molecular sieves, C_6H_6, rt; AcCl, lutidine, C_6H_6, rt, 52%.

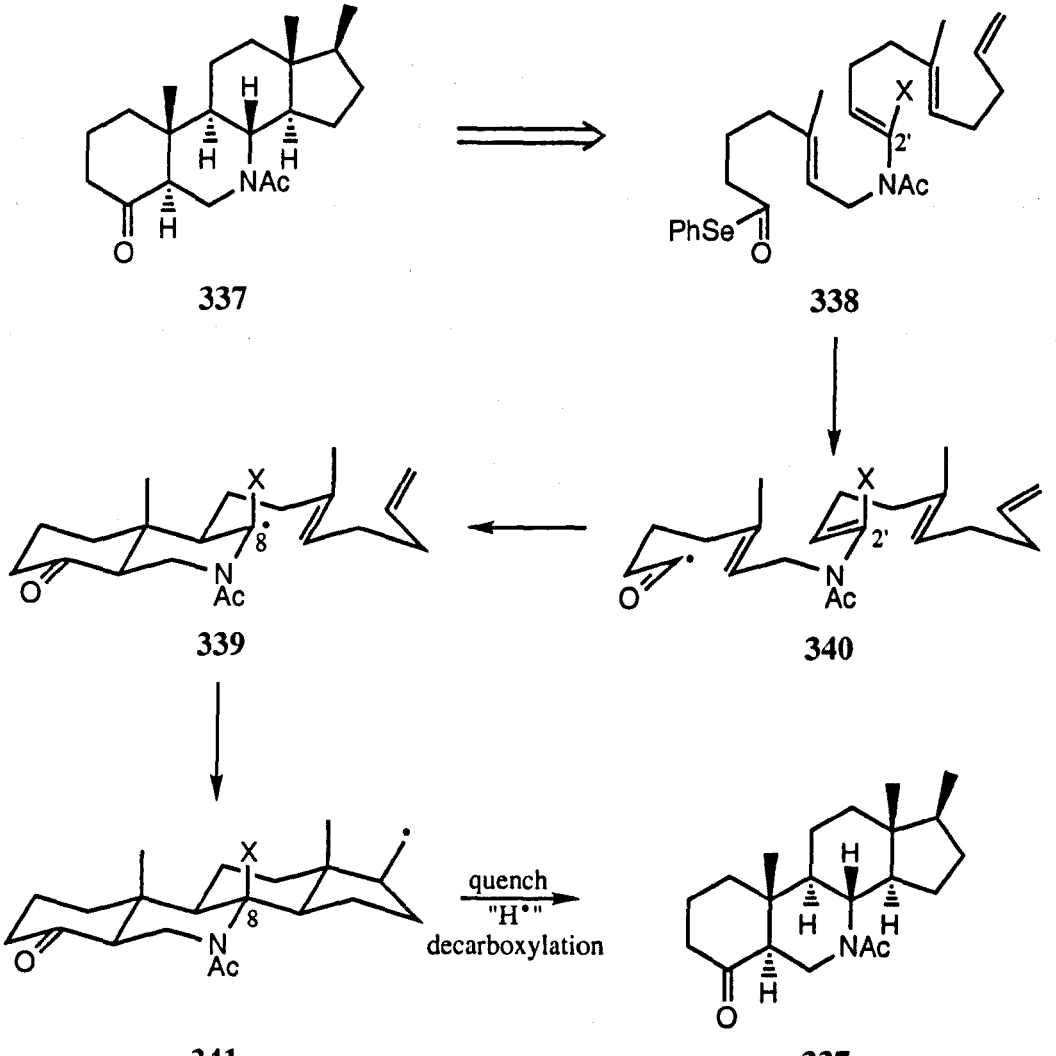
Scheme 93

2.8 STABILISED ENAMIDES

After previous attempts to synthesise fully linear precursors containing nitrogen had failed, we considered the use of stabilised enamines such as the functional group **336**. These groups overcome a number of problems that we had encountered in the synthetic attempts towards the precursor **317**. There were no regioselectivity issues arising as only one regiochemical product could be formed during the synthesis. The stability of the intermediate imines formed during the condensation reaction would be higher than the intermediates from the synthesis of **327**. Therefore, we felt that access to precursors for our radical reactions was possible. Looking at the 7-azaandrostane **337** as our initial synthetic target, we disconnected this molecule to the selenyl ester **338**. This step involved three 6-*endo*-trig cyclisations followed by a 5-*exo*-trig cyclisation from the acyl radical **340** to give the alkyl radical **341**. Quenching of the radical **341** would yield a steroid which could be converted into **337** after decarboxylation (Scheme 94). We recognised that during the course of this cascade one of the intermediate steps involved the cyclisation of the captodative α-amidyl, α-ester radical **339** in a 6-*endo*-trig manner. We felt that this step may be hindered due to the stability of this radical, but thought that if the cascade was halted at this stage we could regenerate a radical at the 8 position by a decarboxylation protocol.



336; R=alkyl



337 **338**

339 **340**

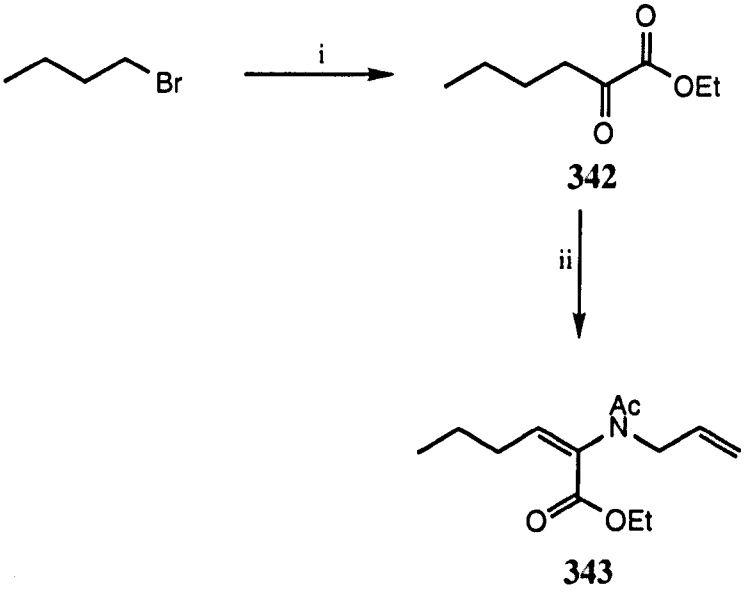
341 **337**

X=CO_2Et

Scheme 94

2.8.1 Model Studies

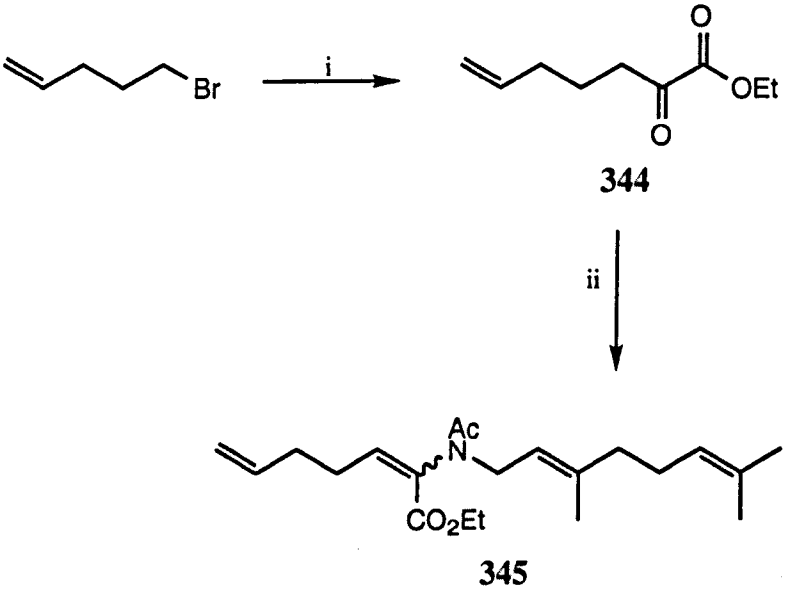
To test the stability of the functional group **336** in linear systems the model **343** was synthesised. Thus, 4-bromobutane was converted to the α-ketoester **342** using the modified Grignard conditions developed by Weinstock and co-workers.[130] The α-ketoester **342** was then successfully condensed with 1-aminoprop-2-ene and the intermediate imine was acylated using the methodology developed by Parsons *et al.*[94] This gave the enamide **343** in good overall yield as a 3:1 mixture of *E:Z* isomers about the newly formed double bond (Scheme 95). We were able to separate the major *E* isomer from this mixture and confirmed the stereochemistry using NOSEY studies. We tested the stability of the enamide **343** to hydrolysis and selenyl ester formation conditions using the technique applied to the synthesis of enamide **265** (Scheme 69). Even though there was an ester present in **343** it was stable enough to withstand these reaction conditions resulting in near quantitative reisolation of **343** at the end of the study.



Reagents: i, Mg, diethyl oxalate, THF, rt, 44%; ii, 1-amino-prop-2-ene, molecular sieves, C_6H_6, rt; AcBr, Et_2NPh, C_6H_6, rt, 77%.

Scheme 95

In order to confirm that long chain analogues of the ester-enamide systems such as **336** were also stable we synthesised the model **345**. Following exactly the same methodology that we had used in the synthesis of the model **343** we were able to make the α-ketoester **344** from 1-bromopent-4-ene, and successfully perform a condensation reaction with geranyl amine **328** to yield the enamide **345** in 73 %, as a 1:1 mixture of *E:Z* isomers (Scheme 96).



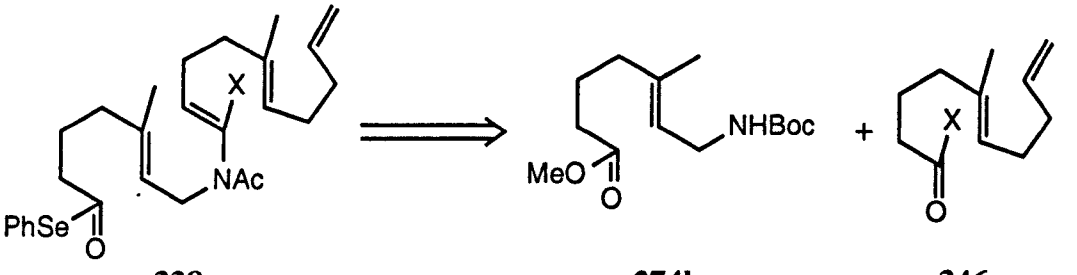
Reagents: i, Mg, diethyl oxalate, THF, rt, 37%; ii, **328**, molecular sieves, C_6H_6, rt; AcBr, Et_2NPh, C_6H_6, rt, 73%.

Scheme 96

2.8.2 Bicycle Synthesis

The methodology used in the synthesis of **345** was then applied to the selenyl ester **338**. Disconnection of this precursor gave the protected amine **274b** for the left hand portion of the molecule and the α-ketoester **346** for the right hand portion. The

convergent nature of the synthetic plan used for the synthesis of the initial precursor **262** was useful here due to the complex nature of both the left and right hand side in the selenyl ester **338** (Scheme 97).

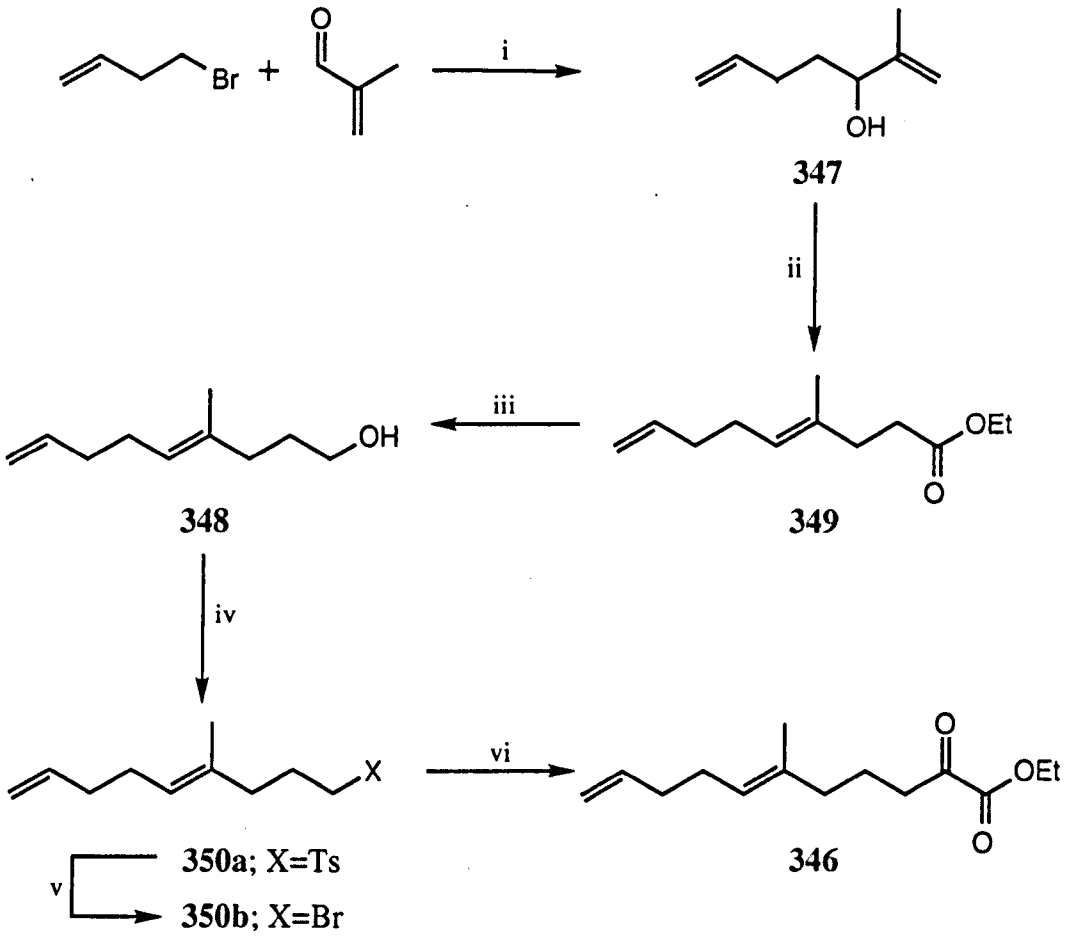


338 **274b** **346**

$X=CO_2Et$

Scheme 97

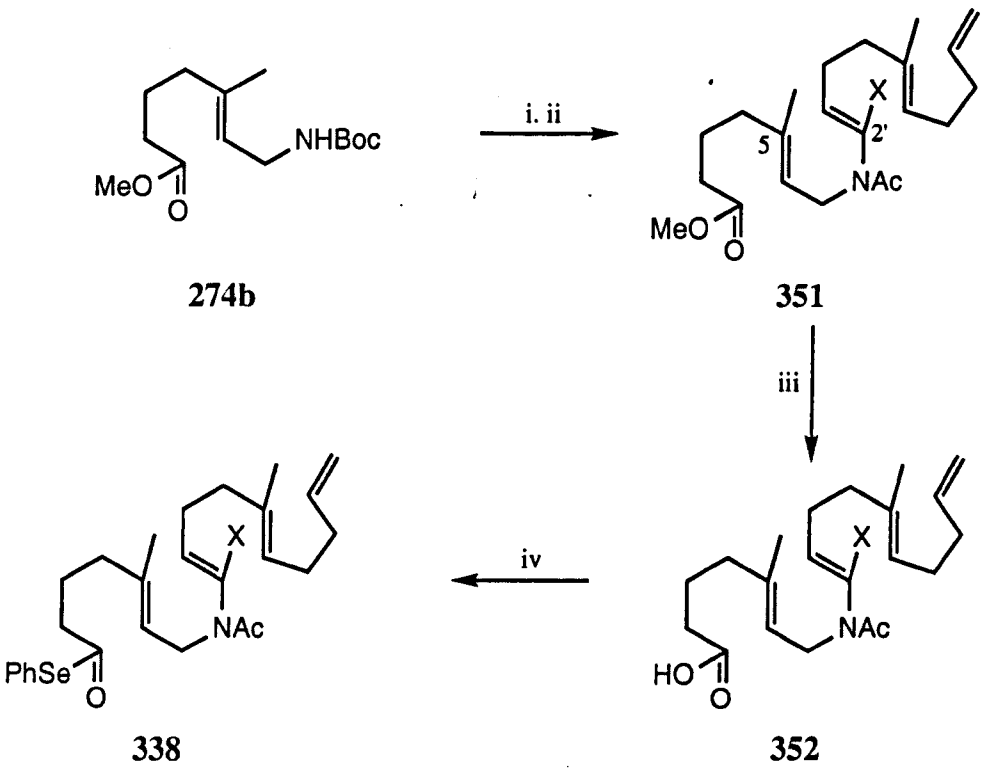
With a convenient high yielding route to the protected amine **274b** already established and the synthetic methodology for the synthesis of α-ketoesters explored we were confident that we would be able to access large quantities of both coupling components **274b** and **346**. For the synthesis of **346** we started from 1-bromobut-3-ene and followed a literature procedure for the synthesis of the intermediate alcohol **348**.[117] Thus, Grignard reaction of 1-bromobut-3-ene with methacrolein gave the allylic alcohol **347** which was converted to the diene ester **349** using a Claisen rearrangement. Subsequent reduction of the ester **349**, to the alcohol **348**, and then conversion to the tosylate **350a** followed by Finkelstein displacement gave the key bromide **350b**. This was reacted using the modified Grignard conditions to yield the α-ketoester **346** in just 6 steps (Scheme 98).



Reagents: i, Mg, THF, reflux, 60%; ii, $(EtO)_3CCH_3$, propinoic acid, reflux, 90%; iii, $LiAlH_4$, Et_2O, rt, 85%; iv, TsCl, pyridine, 0°C, 80%; v, LiBr, acetone, reflux, 91%; vi, Mg, diethyl oxalate, THF, 0°C, 52%.

Scheme 98

With the α-ketoester **346** in hand we then condensed this with the protected amine **274b** to yield the tetraene **351** in 54 % yield. The product was isolated as an inseparable mixture of 2 and 5' double bond isomers. It was felt that this mixture of products would result in loss of the stereochemical integrity of the radical reaction. However, we continued the synthesis of the selenyl ester **338**. The methyl ester was selectively hydrolysed to give the acid **352** which was elaborated to the selenyl ester **338** using *N*-phenylselenophthalimide and tributylphosphine (Scheme 99).



274b 351 352 338

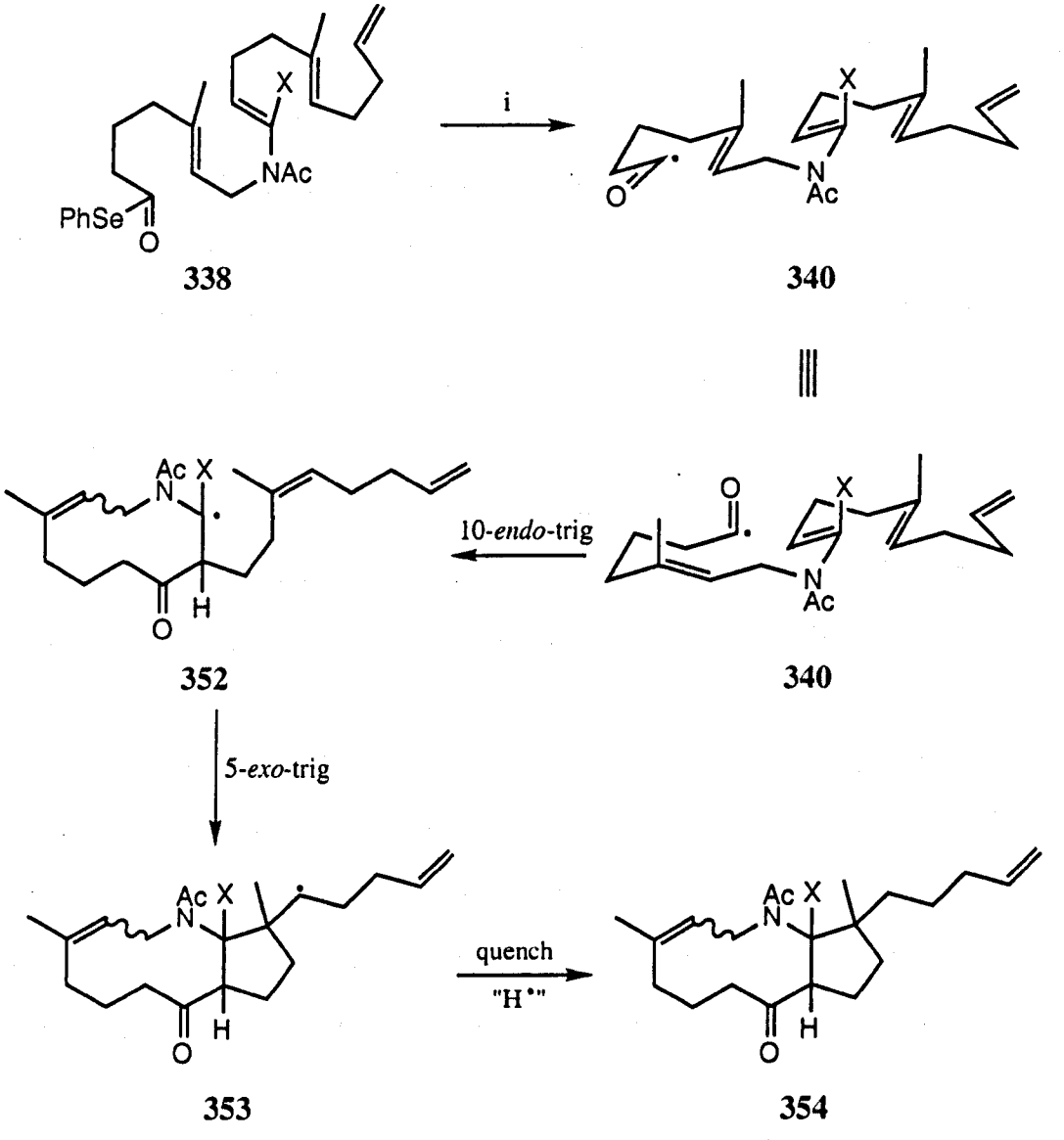
Reagents: i, TFA, rt; ii, Et_3N, C_6H_6, rt; **346**, molecular sieves, C_6H_6, rt; AcBr, Et_2NPh, C_6H_6, rt, 54%-2 steps; iii, LiOH, THF, H_2O, rt; iv, *N*-PSP, Bu_3P, CH_2Cl_2, -30°C, 63%-2steps.

X=CO_2Et

Scheme 99

After the successful synthesis of a fully linear precursor **338** we were excited at the prospect of attempting a radical cascade to give the azasteroid **337**. Upon treatment with tributyltin hydride and AIBN under standard radical generating conditions the selenyl ester **338** did not generate any steroidal material. However, after optimisation of the reaction conditions for the major product, using an eight hour syringe pump addition and four hours further reflux, we were able to isolate the unusual substituted bicyclo[8.3.0]tridecene **354** in 35 % yield (Scheme 100). This product resulted from an initial 10-*endo*-trig cyclisation of the acyl radical **340** to generate the captodative radical **352**. A 5-*exo*-trig cyclisation of the radical **352** gave the alkyl radical **353** which was quenched to yield the product **354**. The activation of the 10-*endo*-trig cyclisation by the ester group substituted on the double bond increased the rate of this

reaction so that it was faster than the 6-*endo*-trig cyclisation. Much to our surprise the intermediate captodative radical **352** underwent the second cyclisation in the formation of the bicycle **354**. The structure of the product **354** was confirmed by ^{1}H-^{1}H COSY and HMQC n.m.r. studies at 360 MHz, but we were unable to fully assign the stereochemistry of the of this molecule.



Reagents: i, Bu_3SnH, AIBN, C_6H_6, reflux, 35%.

X=CO_2Et

Scheme 100

Initial analysis of the ^{1}H n.m.r. spectra showed us that there were still two carbon-carbon double bonds present in the molecule that we had isolated though neither of them were the enamide double bond which could not be seen in either the ^{13}C or ^{1}H n.m.r spectra. One was a terminal monosubstituted olefin and the other was trisubstituted. We had therefore isolated a bicyclic molecule and our cascade reaction had not gone to completion. We obtained COSY and HMQC spectra along with a ^{13}C and DEPT study in order to fully characterise the molecule. It was possible to assign the sets of signals for the ester group, the amide and the terminal olefin from the HMQC and COSY spectra. However, this did not help in the identification of the core ring system. From the carbon and DEPT it was possible to see that there were three quaternary centres (one of which was in the remaining double bond), two CH (one of which was in the remaining double bond), nine CH_2 groups all in the aliphatic region and as expected, two remaining methyl groups. Therefore, in constructing our molecule we could see that the ring junctions and the position of the side chain involved one CH and two quaternary centres. This pattern of carbons can result from an even and an odd number of carbons in each ring so we returned to the ^{1}H n.m.r. spectra and 2D n.m.r.s to glean more information. Interestingly, the two sets of signals remaining above δ 2.4 p.p.m. in the ^{1}H n.m.r. spectra, a CH_2 at δ 3.85 and δ 3.70 p.p.m., and a CH at δ 2.91 p.p.m. were shown to be adjacent to each other by the COSY spectra and not on either side of the nitrogen as originally thought. The CH is almost certainly next to the ketone fragment. Therefore, the CH_2 at δ 40.0 p.p.m. in the carbon spectra is probably adjacent to the nitrogen with a quaternary centre on the other side of this key atom. From the HMQC it was possible to see that all but three of the CH_2s were diastereomeric and so only these three could possibly be outside the ring. This information showed us that the two carbon-carbon double bonds that had reacted were the enamide and the double bond at C-6 in the precursor. The remaining double bonds were the terminal olefin at C-10 and the internal double bond at C-5'.

Therefore, the only reaction pathway consistent with our n.m.r. data was an initial 10-*endo*-trig followed by a 5-*exo*-trig cyclisation to yield the aza-bicycle **354**. Comparison of the data we obtained to those obtained for a carbocyclic varient of this molecule synthesised in our laboratories confirmed our findings.[131]

3. EXPERIMENTAL

3.1 GENERAL DETAILS

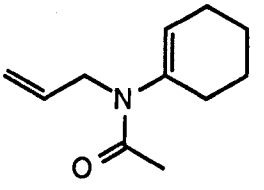
All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR or a Nicolet 20 SXB instrument as liquid films. The signals are designated by the following abbreviations: s, strong; m, medium; w, weak; br, broad. Proton (^{1}H) n.m.r. spectra were recorded on either a Bruker WM 250 (250 MHz), a Bruker DPX 360 (360 MHz), a Bruker AM 400 (400 MHz), a Bruker DRX 500 (500 MHz), a Joel JNM EX-270 (270 MHz) or a Varian VRX 400 (400 MHz) spectrometer as dilute solutions in deuteriochloroform and at 298 K unless otherwise stated. The chemical shifts are recorded relative to either added tetramethylsilane (0.0 p.p.m.) or residual chloroform (7.27 p.p.m.) as internal standards. The multiplicity of a signal is designated by one of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; br., broad; m, multiplet; app., apparent. All coupling constants *J*, are reported in Hertz (Hz). Carbon (^{13}C) n.m.r. were recorded on either a Brucker DPX 360 (90.6 MHz), a Bruker AM 400 (100.6 MHz), a Joel JNM EX-270 (at 67.8 MHz) or a Varian VRX 400 (100.6 MHz) instrument as dilute solutions in deuteriochloroform and at 298 K unless stated otherwise. Chemical shifts are reported relative to either added tetramethylsilane (0.0 p.p.m.) or to deuteriochloroform (77.0 p.p.m.) as internal standards on a broad band decoupled mode. The multiplicities were obtained using a DEPT sequence and are designated by the following symbols: q, primary methyl; t, secondary methylene; d, tertiary methine; s, quaternary; br, broad. Mass spectra were recorded on a VG Autospec or a MM-701CF spectrometer using electron ionisation (EI), fast atom bombardment (FAB) or chemical ionisation (CI) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography was performed on Merck silica gel 60 (230-400 mesh) as the stationary phase and the solvents employed were either of analytical grade or were distilled before use. All reactions were monitored by t.l.c. using Merck silica gel 60 F_{254} precoated aluminium backed plates which were visualised with ultraviolet light, iodine adsorbed on silica and then acidic alcoholic vanillin solution.

Organic solvents were dried by distillation from the following: tetrahydrofuran and benzene (potassium benzophenone ketyl), toluene and ether (sodium benzophenone ketyl), dichloromethane (calcium hydride), methanol (magnesium methoxide) and used directly or stored under nitrogen and/or over sodium wire. Other organic solvents and reagents were purified by the accepted literature procedures. Solvent was removed on a Buchi rotary evaporator under water pump pressure. All reactions were performed in a flame or oven dried apparatus under a nitrogen or argon atmosphere, unless stated otherwise. A Buchi GKR-50 Kugelrohr apparatus was used for bulb-to-bulb distillations.

3.2 CYCLOHEXENYL ENAMIDE STUDIES

1-Amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-prop-2-ene (**265**)[92a]

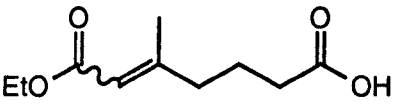


265

A stirred mixture of cyclohexanone (2.1 cm^3, 2.0 g, 20 mmol), 1-aminoprop-2-ene (7.5 cm^3, 5.7 g, 100 mmol) and toluene (10 cm^3) was heated in a sealed tube at 100°C for 2 h. The solution was reduced by distillation from the sealed tube, allowed to cool to room temperature and toluene (40 cm^3), followed by triethylamine (4.2 cm^3, 3.0 g, 30 mmol) and then 4-*N,N*-dimethylaminopyridine (240 mg, 2.0 mmol), were added sequentially in single portions. The mixture was cooled to 0°C and acetyl chloride (2.1 cm^3, 2.4 g, 30 mmol) was added dropwise over 5 min and the resulting suspension was stirred at 0°C for 1 h. The mixture was then allowed to warm to room temperature and saturated aqueous sodium hydrogen carbonate (20 cm^3) was then added. The separated organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave a brown residue, which was then purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:2) as eluant, to give the *enamide* (**265**) (1.9 g, 52 %) as a pale yellow oil. δ_H (500 MHz, $CDCl_3$) 5.80 (1H, m, $CH_2CH{=}CH_2$), 5.61 (1H, m, $NC{=}CHCH_2$), 5.11 (2H, m, $CH_2CH{=}CH_2$), 4.02 (2H, d, *J* 6.0 Hz, $CHCH_2N$), 2.11 (2H, m, $NC{=}CHCH_2$), 2.06 (2H, m, $CH_2C(N){=}CH$), 2.03 (3H, s, $NCOCH_3$), 1.71 (2H, m, $C{=}CHCH_2CH_2$), 1.59 (2H, m, $CH_2CH_2C(N){=}CH$); δ_C (90.6 MHz, $CDCl_3$) 169.0 (s), 138.6 (s), 133.4 (d), 127.0 (d), 116.5 (t), 48.2 (t), 27.6 (t), 24.2 (t), 22.2 (t), 21.1 (q), 21.0 (t); υ_{max} (liquid film)/cm^{-1} 2932 (m), 1650

(s), 1392 (s), 1279 (w), 1210 (w), 1142 (w), 1078 (w), 984 (w), 921 (w); m/z (EI) 180.1379 ($M+H^+$, $C_{11}H_{18}NO$ requires 180.1388).

3-Methylhept-2-endioic acid, 1-ethyl ester (**275**)

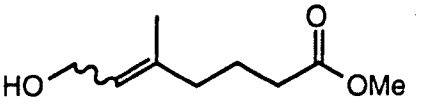


275

Triethyl phosphonoacetate (6.9 cm^3, 7.7 g, 34.6 mmol) was added dropwise over 20 min to a stirred mixture of sodium hydride (1.9 g, 46.1 mmol, 60 wt.% in oil) in tetrahydrofuran (90 cm^3) at 0°C. The mixture was allowed to warm to room temperature over 30 min, and was then cooled to 0°C. 5-Oxohexanoic acid (1.4 cm^3, 1.5 g, 11.5 mmol) was added dropwise over 10 min and the mixture was left to warm to room temperature overnight, acidified to pH 1 with hydrochloric acid (40 cm^3, 2 $moldm^{-3}$) and then evaporated *in vacuo*. The aqueous residue was extracted with ethyl acetate (3x120 cm^3), and the combined organic extracts were then washed with brine (40 cm^3), dried ($MgSO_4$) and reduced *in vacuo*. The yellow residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:3) as eluant to give the *half ester* (**275**) (2.2 g, 96 %) as an oily 2:1 mixture of *Z* and *E* isomers. Major *Z* isomer: δ_H (250 MHz, $CDCl_3$) 5.70 (1H, s, C=C*H*CO_2Et), 4.13 (2H, q, *J* 7.2 Hz, O$CH_2$$CH_3$), 2.69 (2H, t, *J* 7.5 Hz, CH_2C(Me)=CH), 2.42 (2H, t, *J* 7.5 Hz, CH_2CO_2H), 1.90 (3H, s, C(CH_3)=CH), 1.80 (2H, app. quin., *J* 7.5 Hz, $CH_2CH_2CH_2$), 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 179.0 (s), 165.9 (s), 158.7 (s), 116.6 (d), 59.2 (t), 33.2 (t), 32.0 (t), 24.5 (q), 22.6 (t), 13.8 (q); Minor *E* isomer: δ_H (250 MHz, $CDCl_3$) 5.69 (1H, s, C=C*H*CO_2Et), 4.13 (2H, q, *J* 7.2 Hz, O$CH_2$$CH_3$), 2.40 (2H, t, *J* 7.5 Hz, CH_2CO_2H), 2.20 (2H, t, *J* 7.5 Hz, CH_2C(Me)=CH), 2.18 (3H, s, C(CH_3)=CH), 1.80 (2H, app. quin., *J* 7.5 Hz,

$CH_2CH_2CH_2$), 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 178.6 (s), 166.3 (s), 158.2 (s), 115.9 (d), 59.2 (t), 39.5 (t), 32.8 (t), 21.9 (t), 18.1 (q), 13.8 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 2979 (m), 1711 (s), 1650 (s), 1445 (m), 1378 (m), 1225 (m), 1158 (m), 1096 (w), 1077 (w), 1035 (w); Found %: C, 59.4; H, 8.2 ($C_{10}H_{16}O_4$ requires C, 59.9; H, 8.1); m/z (EI) 200.1054 (M^+, $C_{10}H_{16}O_4$ requires 200.1049).

Methyl 7-hydroxy-5-methylhept-5-enoate **(277)**



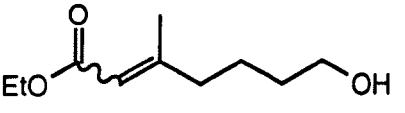
277

A solution of di-*iso*-butylaluminium hydride in toluene (19 cm^3, 1.5 $moldm^{-3}$, 29 mmol) was added dropwise, *via* syringe pump, over 20 min to a stirred solution of 3-methylhept-2-endioic acid, 1-ethyl ester (**275**) (2.3 g, 12 mmol) in dichloromethane (90 cm^3) at -78°C. The solution was then allowed to warm to room temperature over 30 min, then cooled to -78°C and methanol (10 cm^3) was added dropwise over 2 min. Hydrochloric acid (120 cm^3, 2 $moldm^{-3}$) was then added and the mixture was allowed to warm to room temperature over 10 min. The layers were separated and the acidic aqueous layer was extracted with ethyl acetate (3x100 cm^3), the combined organics were dried ($MgSO_4$) and reduced *in vacuo* to leave a colourless oil.

A solution of trimethylsilyl diazomethane in hexane (7 cm^3, 2 $moldm^{-3}$, 14 mmol) was added dropwise at room temperature, *via* syringe pump, over 20 min to a stirred solution of the colourless oil in benzene (100 cm^3) and methanol (30 cm^3). The solution was then left to stir for a further 5 min at room temperature and reduced *in vacuo* to leave a pale yellow oil. The oil was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:3) as eluant to give the *hydroxy ester*

(**277**) (1.6 g, 81 %) as an oily inseparable 2:1 mixture of *Z* and *E*-isomers. Major *Z* isomer: δ_H (400 MHz, $CDCl_3$) 5.42 (1H, t, *J* 6.7 Hz, C=C*H*CH_2), 4.04 (2H, d, *J* 6.7 Hz, CHC*H*$_2$OH), 3.62 (3H, s, CO_2CH_3), 2.25 (2H, t, *J* 7.3 Hz, C*H*$_2CO_2$Me), 2.07 (2H, t, *J* 7.0 Hz, C*H*$_2$C(Me)=CH), 1.71 (2H, m, $CH_2CH_2CH_2$), 1.68 (3H, s, CCH_3); δ_C (67.8 MHz, $CDCl_3$) 174.0 (s), 138.0 (s), 125.3 (d), 58.4 (t), 51.4 (q), 33.1 (t), 30.7 (t), 22.9 (q), 22.8 (t); Minor *E* isomer: δ_H (400 MHz, $CDCl_3$) 5.36 (1H, t, *J* 6.7 Hz, C=C*H*CH_2), 4.09 (2H, d, *J* 6.7 Hz, CHC*H*$_2$OH), 3.63 (3H, s, OCH_3), 2.25 (2H, t, *J* 7.3 Hz, C*H*$_2CO_2$Me), 2.00 (2H, t, *J* 7.0 Hz, C*H*$_2$C(Me)=CH), 1.71 (2H, m, $CH_2CH_2CH_2$), 1.62 (3H, s, CCH_3); δ_C (67.8 MHz, $CDCl_3$) 174.0 (s), 137.7 (s), 124.3 (d), 58.8 (t), 51.3 (q), 38.5 (t), 30.7 (t), 22.5 (t), 15.7 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3206 (b), 2953 (m), 2874 (m), 1874 (m), 1741 (s), 1439 (m), 1376 (m), 1252 (m), 1184 (m), 1011 (m); Found %: C, 62.5; H, 9.7 ($C_9H_{16}O_3$ requires C, 62.7; H, 9.4); m/z (EI) 155.1000 ($M\text{-}OH^+$, $C_9H_{15}O_2$ requires 155.1072).

Ethyl 7-hydroxy-3-methylhept-2-enoate **(280)**



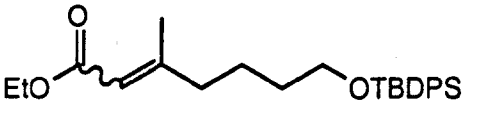
280

iso-Butyl chloroformate (1.1 cm^3, 1.1 g, 8.1 mmol) was added dropwise over 10 min at 0°C to a solution of 3-methylhept-2-endioic acid, 1-ethyl ester (**275**) (1.6 g, 8.1 mmol) and triethylamine (1.1 cm^3, 820 mg, 8.1 mmol) in dichloromethane (80 cm^3). The mixture was stirred for 1.5 h at 0°C and then reduced *in vacuo* to leave a white semi-solid. The residue was taken up in ether (50 cm^3), then filtered and the solvent removed *in vacuo* to leave a colourless oil.

Sodium borohydride (460 mg, 12.1 mmol) was added in one portion to a stirred solution of the oil in methanol (40 cm^3) at 0°C and then left to stir at 0°C for 5 min.

Water (30 cm^3) was then added and the solution was evaporated *in vacuo*. The resulting aqueous mixture was extracted with ethyl acetate (3x160 cm^3), the combined organic layers were then washed with brine (30 cm^3), dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave an oily residue. The residue was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (2:3) as eluant to leave the *alcohol* (**280**) (1.3 g, 84 %) as a colourless oily 2:1 mixture of *Z* and *E* isomers. Major *Z* isomer: δ_H (400 MHz, $CDCl_3$) 5.67 (1H, s, C=C*H*CO_2Et), 4.15 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 3.70 (2H, t, *J* 6.0 Hz, CH_2CH_2OH), 2.61 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.90 (3H, s, C(CH_3)=CH), 1.60 (4H, m, $CH_2CH_2CH_2CH_2$), 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 166.4 (s), 160.8 (s), 115.8 (d), 61.7 (t), 59.4 (t), 32.5 (t), 32.0 (t), 25.1 (q), 24.1 (t), 14.1 (q); Minor *E* isomer: δ_H (400 MHz, $CDCl_3$) 5.67 (1H, s, C=C*H*CO_2Et), 4.15 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 3.66 (2H, t, *J* 6.0 Hz, CH_2CH_2OH), 2.17 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 2.14 (3H, s, C(CH_3)=CH), 1.60 (4H, m, $CH_2CH_2CH_2CH_2$), 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 166.7 (s), 159.7 (s), 115.5 (d), 62.0 (t), 59.3 (t), 40.4 (t), 31.9 (t), 23.4 (t), 18.5 (q), 14.1 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3376 (s), 2979 (s), 2937 (s), 2866 (s), 1714 (s), 1646 (s), 1446 (s), 1378 (s), 1351 (m), 1324 (m), 1271 (m), 1226 (s), 1148 (s), 1039 (s), 984 (w), 859 (m), 725 (w); Found %: C, 64.0; H, 9.9 ($C_{10}H_{18}O_3$ requires C, 64.4; H, 9.7); m/z (EI) 186.1256 (M^+, $C_{10}H_{18}O_3$ requires 186.1256).

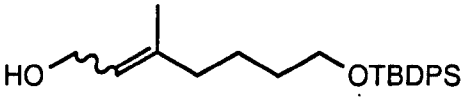
***Ethyl 7-(*tert*-butyldiphenylsilanyloxy)-3-methylhept-2-enoate* (279)**



279

Imidazole (500 mg, 7.4 mmol) was added in one portion to a stirred solution of ethyl 7-hydroxy-3-methylhept-2-enoate (**280**) (1.3 g, 6.8 mmol) and *tert*-butyldiphenylsilylchloride (1.9 cm^3, 2.0 g, 7.4 mmol) in dichloromethane (14 cm^3) at room temperature and the solution was stirred for 15 min. The solvent was removed *in vacuo* and the solid residue was then taken up in ether (25 cm^3), filtered and reduced *in vacuo* to leave the *protected alcohol* (**279**) (2.6 g, 100 %) as a colourless oil. Major *Z* isomer: δ_H (400 MHz, $CDCl_3$) 7.69-7.67 (4H, m, Ar-*H*), 7.44-7.37 (6H, m, Ar-*H*), 5.67 (1H, s, C=C*H*CO_2Et), 4.14 (2H, q, *J* 7.2 Hz, O$CH_2$$CH_3$), 3.69 (2H, t, *J* 6.0 Hz, CH_2CH_2OTBDPS), 2.64 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.88 (3H, s, C(CH_3)=CH), 1.56 (4H, m, $CH_2CH_2CH_2CH_2$), 1.29 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.06 (9H, s, Si$C(CH_3)_3$; δ_C (67.8 MHz, $CDCl_3$) 166.0 (s), 160.1 (s), 135.4 (d), 133.8 (s), 129.3 (d), 127.4 (d), 116.2 (d), 63.5 (t), 59.1 (t), 32.7 (t), 32.3 (t), 26.7 (q), 24.8 (q), 24.2 (t), 19.0 (s), 14.1 (q); Minor *E* isomer: δ_H (400 MHz, $CDCl_3$) 7.69-7.67 (4H, m, Ar-*H*), 7.44-7.37 (6H, m, Ar-*H*), 5.66 (1H, s, C=C*H*CO_2Et), 4.14 (2H, q, *J* 7.2 Hz, O$CH_2$$CH_3$), 3.69 (2H, t, *J* 6.0 Hz, C H_2CH_2OTBDPS), 2.15 (3H, s, C(CH_3)=CH), 2.14 (2H, t, *J* 7.4 Hz, CH_2 C(Me)=CH), 1.56 (4H, m, $CH_2CH_2CH_2CH_2$), 1.29 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.06 (9H, s, Si$C(CH_3)_3$); δ_C (67.8 MHz, $CDCl_3$) 166.5 (s), 159.6 (s), 135.4 (d), 133.8 (s), 129.3 (d), 127.4 (d), 115.5 (d), 63.3 (t), 59.2 (t), 40.3 (t), 31.8 (t), 26.7 (q), 23.4 (t), 19.0 (s), 18.4 (q), 14.1 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3071 (m), 3049 (m), 2932 (s), 2858 (s), 1959 (w), 1890 (w), 1824 (w), 1716 (s), 1647 (s), 1590 (w), 1472 (s), 1428 (s), 1389 (s), 1378 (s), 1273 (m), 1224 (s), 1145 (s), 1111 (s), 1040 (m), 1008 (w), 998 (w), 859 (m), 823 (s), 740 (s), 702 (s); Found %: C, 73.9; H, 8.7 ($C_{26}H_{36}O_3Si$ requires C, 73.5; H, 8.5); m/z (FAB) 367.1764 (M-^{t}Bu$^+$, $C_{22}H_{27}O_3Si$ requires 367.1729).

*7-(*tert*-Butyldiphenylsilanyloxy)-3-methylhept-2-en-1-ol* (281)

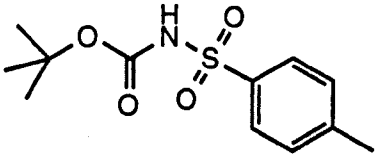


281

A solution of di-*iso*-butylaluminium hydride in toluene (11 cm^3, 1.5 $moldm^{-3}$, 17 mmol) was added dropwise over 5 min to a stirred solution of ethyl 7-(*tert*-butyldiphenylsilanyloxy)-3-methylhept-2-enoate (**279**) (2.6 g, 6.8 mmol) in dichloromethane (70 cm^3) at -78°C. The solution was stirred for 1 h at -78°C, then methanol (5 cm^3) was added and the mixture was allowed to warm to room temperature. A saturated aqueous solution of Rochelles salt (70 cm^3) was added and the mixture was left to stir vigorously for 2 h. The resulting clear layers were separated and the aqueous fraction was extracted with ethyl acetate (3x60 cm^3) and the combined organic layers were then washed with brine (30 cm^3), dried ($MgSO_4$) and reduced *in vacuo*. The yellow residue was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:2) as eluant to leave the *allylic alcohol* (**281**) (2.4 g, 92 %) as a colourless oil. Major *Z* isomer: δ_H (250 MHz, $CDCl_3$) 7.70-7.66 (4H, m, Ar-*H*), 7.48-7.36 (6H, m, Ar-*H*), 5.43 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 4.11 (2H, d, *J* 7.0 Hz, C=CHC*H*$_2$OH), 3.67 (2H, t, *J* 6.0 Hz, CH_2CH_2OTBDPS), 2.08 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.74 (3H, s, C(C*H*$_3$)=CH), 1.52 (4H, m, $CH_2CH_2CH_2CH_2$), 1.06 (9H, s, SiC(C*H*$_3$)$_3$; δ_C (67.8 MHz, $CDCl_3$) 140.1 (s), 135.5 (d), 134.0 (s), 129.5 (d), 127.6 (d), 124.2 (d), 63.6 (t), 59.0 (t), 32.2 (t), 31.5 (t), 26.8 (q), 24.4 (t), 23.3 (q), 19.2 (s); Minor *E* isomer: δ_H (250 MHz, $CDCl_3$) 7.70-7.66 (4H, m, Ar-*H*), 7.48-7.36 (6H, m, Ar-*H*), 5.40 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 4.15 (2H, d, *J* 7.0 Hz, CHC*H*$_2$OH), 3.67 (2H, t, *J* 6.0 Hz, CH_2CH_2OTBDPS), 2.02 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.66 (3H, s, C(C*H*$_3$)=CH), 1.52 (4H, m, $CH_2CH_2CH_2CH_2$), 1.06 (9H, s, SiC(C*H*$_3$)$_3$); δ_C (67.8

MHz, $CDCl_3$) 139.8 (s), 135.5 (d), 134.0 (s), 129.5 (d), 127.6 (d), 123.3 (d), 63.6 (t), 59.4 (t), 39.2 (t), 32.1 (t), 26.8 (q), 23.8 (t), 19.2 (s), 16.0 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3334 (b), 3070 (s), 3048 (s), 2997 (s), 3930 (s), 2856 (s), 2738 (m), 1958 (w), 1888 (w), 1823 (w), 1714 (w), 1667 (m), 1589 (m), 1567 (w), 1471 (s), 1462 (s), 1446 (s), 1427 (s), 1389 (s), 1360 (s), 1305 (w), 1262 (w), 1234 (w), 1188 (m), 1158 (m), 1111 (b), 998 (s), 940 (m), 858 (m), 823 (s), 764 (m), 740 (s), 701 (s), 688 (s), 614 (s); m/z (FAB) 381.2215 ($M-H^+$, $C_{25}H_{33}O_2Si$ requires 381.2250)

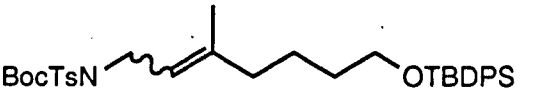
N-tert-*Butylcarboxy*, N-para-*toluenesulfonylamine* (282)[122]



282

para-Toluenesulfonyl isocyanate (7.6 cm^3, 10 g, 50 mmol) was added dropwise over 5 min to stirred *tert*-butanol (50 cm^3) at 25°C and the solution was left to stir for 48 h. The solvent was evaporated *in vacuo* and the residue dried under vacuum (0.5 mmHg) for 48 h to leave the *diprotected amine* (**282**) (14 g, 100%) as a white powder. m.p. 120-122°C (lit. m.p. 115-117°C); δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, *J* 8.3 Hz, Ar-*H*), 7.34 (2H, d, *J* 8.3 Hz, Ar-*H*), 2.46 (3H, s, Ar-C*H*$_3$), 1.39 (9H, s, OC(C*H*$_3$)$_3$); δ_C (67.8 MHz, $CDCl_3$) 149.3 (s), 144.6 (s), 135.9 (s), 129.4 (d), 128.1 (d), 84.0 (s), 27.8 (q), 21.6 (q); υ_{max} (liquid film)/cm^{-1} 3248 (b), 2981 (m), 2932 (w), 1745 (s), 1435 (m), 1396 (m), 1347 (s), 1237 (m), 1148 (s), 1089 (s), 912 (m), 830 (m), 733 (m).

***1-Amino-(N-tert-butylcarboxyl, N-para-toluenesulfonyl)-7-(tert-butyldiphenylsilanyloxy)-3-methylhept-2-ene* (283)**

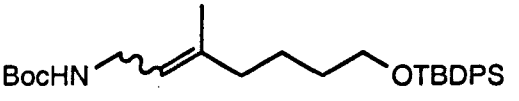


283

Diethyl azodicarboxylate (1.1 cm^3, 1.2 g, 6.9 mmol) was added dropwise over 10 min to a stirred solution of 7-(*tert*-butyldiphenylsilanyloxy)-3-methylhept-2-en-1-ol (**281**) (2.4 g, 6.3 mmol), triphenylphosphine (1.8 g, 6.9 mmol) and *N-tert*-butylcarboxy, *N-para*-toluenesulfonylamine (**282**) (1.9 g, 6.9 mmol) in tetrahydrofuran (90 cm^3) at room temperature. The solution was left to stir at room temperature for 2 h and then reduced *in vacuo* to leave a pale yellow semi-solid. The residue was adsorbed on silica and purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:9) as eluant, to leave the *protected amine* (**283**) (3.9 g, 99 %) as a pale yellow oil. Major *Z* isomer: δ_H (360 MHz, $CDCl_3$) 7.80-7.78 (2H, m, Ar-*H*), 7.71-7.68 (4H, m, Ar-*H*), 7.46-7.37 (6H, m, Ar-*H*), 7.31-7.26 (2H, m, Ar-*H*), 5.33 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.46 (2H, d, *J* 7.0 Hz, $CHCH_2N$), 3.70 (2H, t, *J* 6.0 Hz, CH_2CH_2O), 2.44 (3H, s, $C(CH_3)$=CH), 2.22 (2H, t, *J* 7.0 Hz, CH_2C(Me)=CH), 1.77 (3H, s, $ArCH_3$), 1.57 (4H, m, $CH_2CH_2CH_2CH_2$), 1.35 (9H, s, $OC(CH_3)_3$), 1.08 (9H, s, $SiC(CH_3)_3$; δ_C (90.6 MHz, $CDCl_3$) 150.9 (s), 143.8 (s), 140.1 (s), 137.5 (s), 135.5 (d), 134.0 (s), 129.5 (d), 129.1 (d), 127.9 (d), 127.6 (d), 120.7 (d), 83.9 (s), 63.7 (t), 44.6 (t), 32.3 (t), 31.6 (t), 27.9 (q), 26.8 (q), 24.2 (t), 23.3 (q), 21.5 (q), 19.1 (s); Minor *E* isomer: δ_H (360 MHz, $CDCl_3$) 7.80-7.78 (2H, m, Ar-*H*), 7.71-7.69 (4H, m, Ar-*H*), 7.46-7.37 (6H, m, Ar-*H*), 7.31-7.26 (2H, m, Ar-*H*), 5.35 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (2H, d, *J* 7.0 Hz, $CHCH_2N$), 3.70 (2H, t, *J* 6.0 Hz, CH_2CH_2O), 2.40 (3H, s, $C(CH_3)$=CH), 2.06 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.77 (3H, s, $ArCH_3$), 1.57 (4H, m, $CH_2CH_2CH_2CH_2$), 1.35 (9H, s, $OC(CH_3)_3$), 1.08 (9H, s,

$SiC(CH_3)_3$); δ_C (67.8 MHz, $CDCl_3$) 150.9 (s), 143.8 (s), 140.0 (s), 137.5 (s), 135.5 (d), 134.0 (s), 129.5 (d), 129.1 (d), 127.9 (d), 127.6 (d), 119.8 (d), 83.9 (s), 63.7 (t), 44.6 (t), 39.3 (t), 32.1 (t), 27.8 (q), 26.8 (q), 23.9 (t), 21.5 (q), 19.2 (s), 16.1 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 2932 (s), 2859 (s), 2360 (w), 1728 (s), 1598 (w), 1472 (m), 1457 (m), 1428 (s), 1358 (s), 1309 (m), 1276 (m), 1266 (m), 1154 (s), 1111 (s), 1080 (s), 998 (w), 929 (w), 848 (m), 822 (m), 768 (s), 703 (s), 675 (s); Found %: C, 67.9; H, 7.7; N, 2.2 ($C_{36}H_{49}NO_5SSi$ requires C, 68.0; H, 7.8; N, 2.2); m/z (FAB) 578.2391 (M-^{t}Bu$^+$, $C_{32}H_{40}NO_5SSi$ requires 578.2396)

***1-Amino-(N-tert-butylcarboxyl)-7-(tert-butyldiphenylsilanyloxy)-3-methylhept-2-ene* (285)**

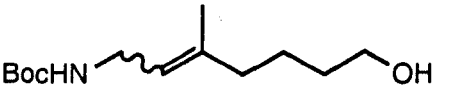


285

Sodium amalgam (35 g, 4.5 % w/w, 70 mmol) was added in one portion to a stirred mixture of 1-amino-(*N-tert*-butylcarboxyl, *N-para*-toluenesulfonyl)-7-(*tert*-butyldiphenylsilanyloxy)-3-methylhept-2-ene (**283**) (2.2g, 3.5 mmol) and disodium hydrogen phosphate (2.0 g, 14 mmol) in methanol (30 cm^3) at room temperature and the resulting mixture left to stir for 1 h. Water (30 cm^3) was added and the mixture was left to stir for 10 min, then filtered through a pad of celite and reduced *in vacuo*. The remaining aqueous portion was extracted with ethyl acetate (3x120 cm^3), the combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:7) as eluant to leave the *protected amine* (**285**) (1.4 g, 85 %) as a colourless oily 2:1 mixture of *Z:E* isomers. Major *Z* isomer: δ_H (270 MHz, $CDCl_3$) 7.73-7.69 (4H, m, Ar-*H*), 7.48-7.36 (6H, m, Ar-*H*), 5.22 (1H, t, *J* 7.0 Hz,

C=C*H*CH_2N), 4.47 (1H, br, CH_2N*H*Boc), 3.70 (4H, m, CH_2CH_2O and C=CHCH_2N), 2.07 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.72 (3H, s, C(CH_3)=CH), 1.53 (4H, m, $CH_2CH_2CH_2CH_2$), 1.46 (9H, s, OC(CH_3), 1.06 (9H, s, SiC(CH_3)$_3$; δ_C (67.8 MHz, $CDCl_3$) 155.7 (s), 139.4 (s), 135.5 (d), 133.9 (s), 129.4 (d), 127.5 (d), 121.4 (d), 79.0 (s), 63.6 (t), 38.1 (t), 32.2 (t), 31.4 (t), 28.4 (q), 26.8 (q), 24.2 (t), 23.2 (q), 19.1 (s); Minor *E* isomer: δ_H (270 MHz, $CDCl_3$) 7.73-7.69 (4H, m, Ar-*H*), 7.48-7.36 (6H, m, Ar-*H*), 5.18 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.47 (1H, br, CH_2N*H*Boc), 3.70 (4H, m, CH_2CH_2O and C=CHCH_2N), 2.00 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.65 (3H, s, C(CH_3)=CH), 1.53 (4H, m, $CH_2CH_2CH_2CH_2$), 1.46 (9H, s, OC(CH_3), 1.06 (9H, s, SiC(CH_3)$_3$; δ_C (67.8 MHz, $CDCl_3$) 155.7 (s), 139.1 (s), 135.5 (d), 133.9 (s), 129.4 (d), 127.5 (d), 120.6 (d), 79.0 (s), 63.6 (t), 39.O (t), 38.4 (t), 32.0 (t), 28.4 (q), 26.8 (q), 23.7 (t), 18.9 (s), 16.0 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3358 (m), 3071 (m), 2932 (s), 2858 (s), 1704 (s), 1589 (w), 1503 (s), 1472 (m), 1428 (m), 1390 (m), 1366 (m), 1247 (m), 1172 (s), 1111 (s), 936 (w), 866 (m), 823 (m), 758 (s), 703 (s), 688 (m), 666 (w), 613 (m); *m/z* (FAB) 482.3095 (M+H$^+$, $C_{29}H_{44}NO_3Si$ requires 482.3090).

***1-Amino-(N-tert-butylcarboxyl)-3-methylhept-2-en-7-ol* (284)**

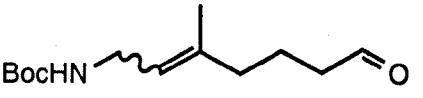


284

A solution of 1-amino-(*N-tert*-butylcarboxyl)-7-(*tert*-butyldiphenylsilanyloxy)-3-methylhept-2-ene (**285**) (1.2 g, 2.4 mmol) in tetrahydrofuran (25 cm^3) was added dropwise over 10 min to a stirred solution of *tert*-butylamonium floride (3.0 g, 9.5 mmol) and *para*-toluenesulfonic acid (0.9 g, 4.8 mmol) in tetrahydrofuran (50 cm^3) at room temperature and was left to stir for 3 days. The solvent was removed *in*

vacuo and the colourless oil was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:1) as eluant, to leave the *alcohol* (**284**) (580 mg, 100 %) as a colourless oil. Major *Z* isomer: δ_H (250 MHz, $CDCl_3$) 5.18 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (1H, br, CH_2N*H*Boc), 3.64 (4H, m, CH_2CH_2OH and CHCH_2N), 2.08 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.89 (1H, br, CH_2O*H*), 1.70 (3H, s, C(CH_3)=CH), 1.51 (4H, m, $CH_2CH_2CH_2CH_2$), 1.44 (9H, s, OC(CH_3); δ_C (67.8 MHz, $CDCl_3$) 155.8 (s), 139.1 (s), 121.3 (d), 79.0 (s), 62.1 (t), 38.0 (t), 32.1 (t), 31.3 (t), 28.3 (q), 24.0 (t), 23.1 (q); Minor *E* isomer: δ_H (250 MHz, $CDCl_3$) 5.18 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (1H, br, CH_2N*H*Boc), 3.65 (4H, m, CH_2CH_2OH and CHCH_2N), 2.01 (2H, t, *J* 7.4 Hz, CH_2C(Me)=CH), 1.89 (1H, br, CH_2O*H*), 1.64 (3H, s, C(CH_3)=CH), 1.53 (4H, m, $CH_2CH_2CH_2CH_2$), 1.46 (9H, s, OC(CH_3); δ_C (67.8 MHz, $CDCl_3$) 155.8 (s), 138.8 (s), 120.7 (d), 79.0 (s), 62.3 (t), 38.9 (t), 38.3 (t), 32.0 (t), 28.3 (q), 23.6 (t), 15.9 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3348 (br), 2934 (s), 1692 (s), 1524 (s), 1454 (s), 1391 (s), 1366 (s), 1275 (s), 1251 (s), 1173 (s), 1057 (m), 934 (w), 866 (w), 781 (w); *m/z* (EI) 187.1217 (M+H-^{t}Bu$^+$, $C_9H_{17}NO_3$ requires 187.1209).

7-Amino-(N-tert-butylcarboxyl)-5-methylhept-5-en-1-al **(286)**

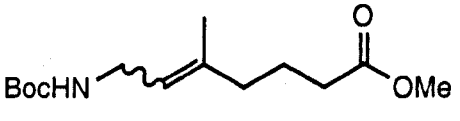


286

Dess Martin reagent (1.5 g, 3.6 mmol) was added in one portion to a stirred solution of 1-amino-(*N-tert*-butylcarboxyl)-3-methylhept-2-en-7-ol (**284**) (580 mg, 2.4 mmol) in dichloromethane (30 cm^3) and the mixture was left to stir at room temperature for 1 h. The mixture was diluted with ether (20 cm^3) and a solution of sodium hydrogen carbonate (1.2 g) and sodium thiosulfate pentahydrate (4.1 g) in water (60 cm^3) was

added in one portion and then left to stir for a further 30 min. The layers were separated and the aqueous was extracted with ether (2x120 cm^3) and the combined organics were washed with brine (30 cm^3), dried (Na_2SO_4) and reduced *in vacuo*. The resulting oil was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:4) as eluant, to leave the *aldehyde* (**286**) (410 mg, 70 %) as a colourless oil. Major *Z* isomer: δ_H (500 MHz, $CDCl_3$) 9.77 (1H, d, *J* 1.5 Hz, CH_2CHO), 5.24 (1H, t, *J* 7.0 Hz, C=$CHCH_2N$), 4.50 (1H, br, CH_2NHBoc), 3.70 (2H, br, $CHCH_2N$), 2.43 (2H, dt, *J* 1.5 Hz and 7.0 Hz, CH_2CH_2CHO), 2.10 (2H, t, *J* 7.0 Hz, CH_2C(Me)=CH), 1.75 (2H, m, $CH_2CH_2CH_2$), 1.71 (3H, s, C(CH_3)=CH), 1.44 (9H, s, OC(CH_3); δ_C (125.8 MHz, $CDCl_3$) 202.3 (d), 155.9 (s), 138.2 (s), 122.7 (d), 79.3 (s), 43.4 (t), 38.6 (t), 31.0 (t), 28.5 (q), 23.1 (q), 20.3 (t); Minor *E* isomer: δ_H (500 MHz, $CDCl_3$) 9.77 (1H, d, *J* 1.5 Hz, CH_2CHO), 5.19 (1H, t, *J* 7.0 Hz, C=$CHCH_2N$), 4.50 (1H, br, CH_2NHBoc), 3.70 (2H, br, $CHCH_2N$), 2.43 (2H, dt, *J* 1.5 Hz and 7.0 Hz, CH_2CH_2CHO), 2.03 (2H, t, *J* 7.0 Hz, CH_2C(Me)=CH), 1.75 (2H, m, $CH_2CH_2CH_2$), 1.65 (3H, s, C(CH_3)=CH), 1.44 (9H, s, OC(CH_3); δ_C (125.8 MHz, $CDCl_3$) 202.3 (d), 155.9 (s), 138.0 (s), 122.0 (d), 79.3 (s), 43.4 (t), 38.6 (t), 38.2 (t), 28.5 (q), 20.0 (t), 16.0 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3357 (br), 2976 (s), 2933 (s), 2723 (w), 2249 (w), 1699 (s), 1514 (s), 1454 (s), 1391 (s), 1366 (s), 1249 (s), 1172 (s), 1045 (m), 1023 (m), 934 (w), 866 (w), 757 (s), 666 (w); *m/z* (EI) 185.1068 (M+H-^{t}Bu$^+$, $C_9H_{15}NO_3$ requires 185.1052).

Methyl 7-amino-(N-tert-butylcarboxyl)-5-methylhept-5-enoate **(274b)**

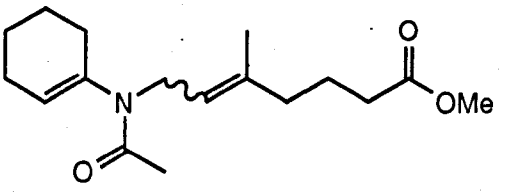


274b

A solution of sodium chlorite (1.2 g, 14 mmol) and potassium dihydrogen phosphate (1.5 g, 11 mmol) in water (20 cm^3) was added dropwise over 5 min to a solution of 1-amino-(*N-tert*-butylcarboxyl)-3-methylhept-2-en-7-al (**286**) (370 mg, 1.5 mmol) and 2-methylbut-2-ene (10 cm^3) in *tert*-butanol (40 cm^3) at room temperature and then stirred for 2 h. The solvent was reduced *in vacuo* and the resulting aqueous mixture was extracted with ether (3x75 cm^3) and the organics were dried (Na_2SO_4) and evaporated *in vacuo* to leave a colourless oil.

The oil was taken up in benzene (14 cm^3) and methanol (3.5 cm^3) and set stirring. A solution of trimethylsilyl diazomethane in hexanes (990 µl, 2.0 $moldm^{-3}$, 2.0 mmol) was added dropwise over 10 min to the stirred solution at room temperature and then stirred for 20 min. The solvent was removed *in vacuo* and to leave a pale yellow which oil was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:4) as eluant, to leave the *methyl ester* (**274b**) (380 mg, 92 %) as a colourless oily 2:1 mixture of *Z* and *E* isomers. Major *Z* isomer: δ_H (250 MHz, $CDCl_3$) 5.24 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (1H, br, CH_2N*H*Boc), 3.70 (2H, br, CHC*H*$_2$N), 3.67 (3H, s, CO_2C*H*$_3$), 2.29 (2H, t, *J* 7.5 Hz, C*H*$_2CO_2$Me), 2.10 (2H, t, *J* 7.0 Hz, C*H*$_2$C(Me)=CH), 1.73 (2H, m, CH_2C*H*$_2CH_2$), 1.70 (3H, s, CH_2C(C*H*$_3$)=CH), 1.45 (9H, s, OC(C*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 174.2 (s), 156.2 (s), 138.1 (s), 122.9 (d), 79.2 (s), 52.0 (q), 39.1 (t), 33.8 (t), 31.4 (t), 28.8 (q), 23.5 (q), 23.5 (t); Minor *E* isomer: δ_H (250 MHz, $CDCl_3$) 5.19 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (1H, br, CH_2N*H*Boc), 3.70 (2H, br, CHC*H*$_2$N), 3.67 (3H, s, CO_2C*H*$_3$), 2.28 (2H, t, *J* 7.5 Hz, C*H*$_2CO_2$Me), 2.02 (2H, t, *J* 7.0 Hz, C*H*$_2$C(Me)=CH), 1.73 (2H, m, CH_2C*H*$_2CH_2$), 1.65 (3H, s, CH_2C(C*H*$_3$)=CH), 1.45 (9H, s, OC(C*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 174.2 (s), 156.2 (s), 138.1 (s), 122.0 (d), 79.2 (s), 52.0 (t), 38.5 (t), 33.8 (t), 31.4 (t), 28.8 (q), 23.1 (t), 16.4 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3369 (br), 2975 (s), 1714 (s), 1516 (s), 1454 (m), 1437 (m), 1391 (m), 1366 (s), 1249 (s), 1172 (s), 1047 (m), 1018 (m), 934 (w), 865 (w); Found %: C, 61.9; H, 9.6; N, 4.9 ($C_{15}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2); m/z (EI) 214.1086 (M-^{t}Bu$^+$, $C_{10}H_{16}NO_4$ requires 214.1079).

Methyl 7-amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5-methylhept-5-enoate (288)



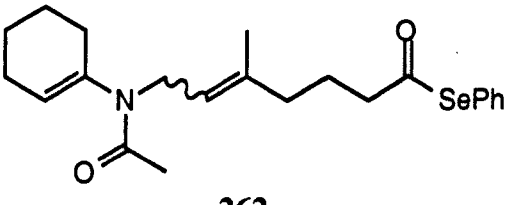
288

Triflouroacetic acid (1.0 cm^3, 1.6 g, 14 mmol) was added dropwise over 5 minutes to stirred methyl 7-amino-(*N-tert*-butylcarboxyl)-5-methylhept-5-enoate (**274b**) (380 mg, 1.4 mmol) at room temperature and the oil was left to stir for 5 min. Toluene (20 cm^3) was added and the solution was reduced *in vacuo* to leave a colourless oil.

The oil was taken up in benzene (40 cm^3), triethyl amine (200 µl, 140 mg, 1.4 mmol) was added in one portion and the resulting solution was stirred at room temperature for 5 min. Molecular sieves (4 Å, activated) were added to the solution followed by cyclohexanone (170 µl, 160 mg, 1.6 mmol) in one portion and the resulting mixture was left to stir at room temperature for 12 h. 4-*N,N*-Dimethylaminopyridine (17 mg, 0.14 mmol) and triethylamine (290 µl, 210 mg, 2.1 mmol) were added in two separate portions to the stirred mixture at room temperature followed by acetyl chloride (150 µl, 170 mg, 2.1 mmol) added dropwise over 5 min at room temperature and then left to stir for 2 h. The mixture was filtered through a pad of celite and washed with water (30 cm^3), brine (20 cm^3), dried (Na_2SO_4) and the solvent was removed *in vacuo* to leave a yellow oil. This oil was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:1) as eluant, to leave the *enamide* (**288**) (230 mg, 56 %) as a colourless oily 2:1 mixture of *Z:E* isomers. Major *Z* isomer: δ_H (250 MHz, $CDCl_3$) 5.58 (1H, m, C*H*=CN), 5.21 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 3.98 (2H, d, *J* 7.0 Hz, CHCH_2N), 3.66 (3H, s, CO_2CH_3), 2.28 (2H, t, *J* 7.5 Hz, CH_2CO_2), 2.11-2.04 (6H, m, CH_2C(Me)=CH and CH_2CH=C(N)CH_2), 1.99 (3H, s, NCOCH_3), 1.78-

1.52 (6H, m, $CH_2CH_2CH_2$ and $CH_2CH_2CH_2CH_2$), 1.69 (3H, s, $C(CH_3)$=CH); δ_C (67.8 MHz, $CDCl_3$) 174.0 (s), 168.6 (s), 139.3 (s), 137.7 (s), 127.5 (d), 121.9 (d), 51.6 (q), 43.4 (t), 38.9 (t), 33.6 (s), 31.1 (t), 28.4 (t), 24.9 (t), 23.3 (q), 22.9 (t), 21.7 (q), 21.7 (t); Minor *E* isomer: δ_H (250 MHz, $CDCl_3$) 5.58 (1H, m, C*H*=CN), 5.18 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.02 (2H, d, *J* 7.0 Hz, $CHCH_2$N), 3.66 (3H, s, CO_2CH_3), 2.25 (2H, t, *J* 7.5 Hz, $CH_2C\,O_2$), 2.11-2.04 (6H, m, CH_2C(Me)=CH and CH_2CH=C(N)CH_2), 1.99 (3H, s, $NCOCH_3$), 1.78-1.52 (6H, m, $CH_2CH_2CH_2$ and $CH_2CH_2CH_2CH_2$), 1.62 (3H, s, $C(CH_3)$=CH); δ_C (67.8 MHz, $CDCl_3$) 174.0 (s), 168.6 (s), 139.3 (s), 137.7 (s), 127.5 (d), 121.2 (d), 51.6 (q), 43.4 (t), 38.9 (t), 33.6 (s), 33.4 (t), 28.4 (t), 24.9 (t), 23.3 (t), 22.9 (t), 21.7 (q), 16.0 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 2932 (s), 1737 (s), 1650 (s), 1436 (s), 1396 (m), 1172 (m), 922 (w); m/z (EI) 293.1986 (M^+, $C_{17}H_{27}NO_3$ requires 293.1991).

***Phenyl 7-amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5-methylhept-5-enselenoate* (262)**

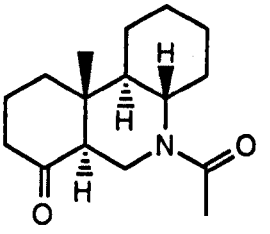


262

A solution of lithium hydroxide (50 mg, 1.2 mmol) in water (15 cm^3) was added in one portion to a stirred solution of methyl 7-amino-(*N*-acetyl, *N*-cyclohex-1'-en-1'-yl)-5-methylhept-5-enoate (**288**) (240 mg, 0.8 mmol) in tetrahydrofuran (15 cm^3) at room temperature and was left to stir for 2 h. The solution was reduced *in vacuo* and acidified to pH 1 with hydrochloric acid (2 $moldm^{-3}$). The aqueous was extracted with dichloromethane (3x20 cm^3), the combined organics were dried (Na_2SO_4) and reduced *in vacuo* to leave a colourless oily residue.

The residue was taken up in benzene (9 cm^3), diphenyl diselenide (510 mg, 1.6 mmol) was added and the solution was set stirring. Tri-*n*-butylphosphine (410 μl, 330 mg, 1.6 mmol) was added dropwise over 10 min to the stirred solution at room temperature and the mixture was left overnight. The solvent was removed *in vacuo* and to leave a yellow which oil was purified by chromatography on silica, using petroleum (b.p. 40-60°C) and then ether - petroleum (b.p. 40-60°C) (3:2) as eluant, to leave the *selenyl ester* (**262**) (210 mg, 62 %) as a very pale yellow oil. Major *Z* isomer: δ_H (400 MHz, $CDCl_3$) 7.50 (2H, m, Ar-*H*), 7.37 (3H, m, Ar-*H*), 5.58 (1H, s, C*H*=CN), 5.23 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 3.99 (2H, d, *J* 6.9 Hz, CHC*H*$_2$N), 2.69 (2H, t, *J* 7.2 Hz, C*H*$_2$COSe), 2.64-2.05 (6H, m, C*H*$_2$CH=C(N)C*H*$_2$ and C*H*$_2$C(Me)=CH), 2.00 (3H, s, NCOC*H*$_3$), 1.81-1.56 (6H, m, $CH_2CH_2CH_2CH_2$ and $CH_2CH_2CH_2$), 1.69 (3H, s, CC*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 199.5 (s), 169.0 (s), 138.8 (s), 136.8 (s), 135.3 (d), 128.9 (d), 128.4 (d), 127.0 (d), 126.1 (d), 121.7 (d), 46.5 (t), 42.9 (t), 30.3 (t), 27.8 (t), 24.4 (t), 23.1 (t), 22.7 (q), 22.4 (t), 21.2 (q), 21.2 (t); Minor *E* isomer: δ_H (400 MHz, $CDCl_3$) 7.50 (2H, m, Ar-*H*), 7.37 (3H, m, Ar-*H*), 5.58 (1H, s, C*H*=CN), 5.22 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.03 (2H, d, *J* 6.9 Hz, CHC*H*$_2$N), 2.67 (2H, t, *J* 7.2 Hz, C*H*$_2$COSe), 2.64-2.05 (6H, m, C*H*$_2$CH=C(N)C*H*$_2$ and C*H*$_2$C(Me)=CH), 2.00 (3H, s, NCOC*H*$_3$), 1.81-1.56 (6H, m, $CH_2CH_2CH_2CH_2$ and $CH_2CH_2CH_2$), 1.63 (3H, s, CC*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 199.5 (s), 169.0 (s), 138.8 (s), 136.8 (s), 135.3 (d), 128.9 (d), 128.4 (d), 127.0 (d), 126.1 (d), 121.1 (d), 46.3 (t), 38.0 (t), 30.3 (t), 27.8 (t), 24.4 (t), 23.1 (t), 22.7 (q), 22.4 (t), 21.2 (t), 15.5 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 3425 (b), 2931 (s), 2857 (m), 1722 (s), 1648 (s), 1578 (w), 1477 (w), 1438 (s), 1396 (s), 1365 (w), 1283 (w), 1260 (w), 1201 (w), 1139 (w), 1066 (w), 1021 (w), 999 (w), 979 (w), 922 (w), 840 (w), 740 (m), 690 (m), 671 (w); Found %: C, 63.0; H, 6.90; N, 3.4 ($C_{22}H_{29}NO_2Se$ requires C, 63.1; H, 7.0; N, 3.4); m/z (CI) 420.1437 ($M+H^+$, $C_{22}H_{30}NO_2{}^{80}Se$ requires 420.1442), 418.1425 ($M+H^+$, $C_{22}H_{30}NO_2{}^{78}Se$ requires 418.1450).

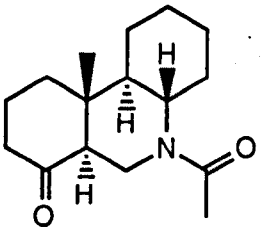
9-Aza-(N-acetyl)-4aβ-methyl-3, 4, 4bα, 5, 6, 7, .8, 8aβ, 10, 10aα-decahydrophenanthren-1(2H)-one (**261**)



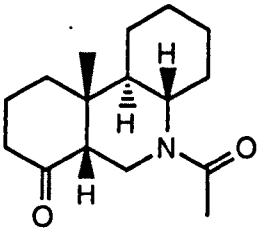
261

A solution of tributyltin hydride (60 μl, 60 mg, 0.21 mmol) and AIBN (7 mg) in degassed benzene (2 cm^3) was added dropwise over 2 h to a refluxing solution of phenyl 7-amino-(*N*-acetyl, *N*-cyclohex-1'-en-1'-yl)-5-methylhept-5-enselenoate (**262**) (70 mg, 0.17 mmol) and AIBN (8 mg) in degassed benzene (38 cm^3) under argon and the solution was left to reflux for a further 2 h. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:3) as eluant, to leave the *cyclised product* (**261**) (30 mg, 65 %) as a colourless oil. δ_H (500 MHz, $CDCl_3$) 3.73 (1H, dd, *J* 13.9 Hz and 8.3 Hz, C*H*HN), 3.43 (1H, dd, *J* 13.9 Hz and 7.1 Hz, CH*H*N), 3.37 (1H, app. td, *J* 10.7 Hz and 2.8 Hz, C*H*N), 2.51 (1H, app. t, *J* 7.7 Hz, COC*H*), 2.48-2.30 (3H, m, CH_2CO), 2.14 (3H, s, $NCOCH_3$), 2.10 (1H, m), 1.97 (1H, m), 1.91-1.73 (4H, m), 1.56-1.38 (4H, m), 1.32 (1H, m), 1.12 (1H, m), 0.71 (3H, s, CCH_3); δ_C (125.8 MHz, $CDCl_3$) 209.8 (s), 171.9 (s), 57.4 (d), 57.1 (d), 52.0 (d), 40.7 (s), 40.4 (t), 40.1 (t), 36.0 (t), 31.7 (t), 26.4 (t), 26.1 (t), 25.6 (t), 23.6 (q), 22.3 (t), 13.0 (q); υ_{max} (liquid film)/cm^{-1} 3395 (br), 2934 (s), 2359 (s), 1714 (s), 1634 (s), 1454 (s), 1200 (s), 1049 (m), 668 (s); m/z (EI) 263.1883 (M^+, $C_{16}H_{25}NO_2$ requires 263.1885).

Epimeristation reaction



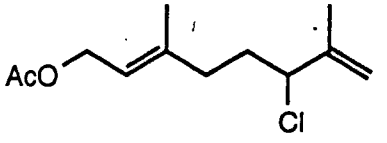
261



291

A mixture of the tricycle (**291**) (10 mg, 0.04 mmol) and sodium methoxide (5 mg) in methanol (1 cm^3) was heated at reflux for 60 h. The mixture was allowed to cool to room temperature and diluted with ethyl acetate (10 cm^3) and water (10 cm^3), the layers were separated and the aqueous fraction was extracted with ethyl acetate (2x10 cm^3). The combined organics were dried ($MgSO_4$) and reduced *in vacuo* to leave an oil which was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:3) as eluant, to give the *9-aza-(*N*-acetyl)-4aβ-methyl-3, 4, 4bα, 5, 6, 7, 8, 8aβ, 10, 10aα-decahydrophenanthren-1(2H)-one* (**261**) (4 mg, 40 %) eluted first, as a colourless oil, as before, and its *9-aza-(*N*-acetyl)-4aβ-methyl-3, 4, 4bα, 5, 6, 7, 8, 8aβ, 10, 10aβ-decahydrophenanthren-1(2H)-one* (**291**) (4 mg, 40%) eluted second, as a white crystaline solid. δ_H (500 MHz, $CDCl_3$, 328K) 4.00 (1H, br, C*H*N), 3.60 (1H, br, CH*H*N), 3.42 (1H, br, C*H*HN), 2.42 (2H, m), 2.27 (1H, m), 2.07 (3H, s, NCOCH_3), 2.02 (2H, m), 1.81 (4H, m), 1.57 (1H, m), 1.47 (1H, m), 1.35 (1H, m), 1.25 (1H, m), 1.15 (1H, m), 1.06 (3H, s, CCH_3); δ_C (125.8 MHz, $CDCl_3$, 328K) 213.0 (s), 169.2 (s), 56.1, 54.2, 47.2, 39.3, 37.7, 35.8, 30.7, 26.5, 26.0, 26.0, 25.3, 22.9, 21.6, 18.1; m/z (EI) 263.1883 (M^+, $C_{16}H_{25}NO_2$ requires 263.1885).

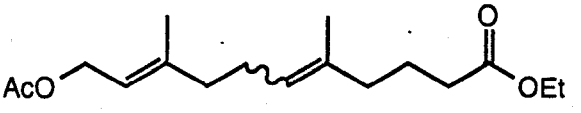
6-Chloro-3,7-dimethylocta-2,7-dienyl acetate (**302**)[125]



302

tert-Butylhypochlorite (2.2 cm^3, 2.1 g, 19 mmol) was added dropwise over 5 min to a stirred mixture of geranyl acetate (**301**) (3.8 cm^3, 3.4 g, 18 mmol) and silica (4.4 g) in petroleum (b.p. 40-60°C) (70 cm^3) at 0°C. The mixture was stirred for a further 40 min at 0°C and then allowed to warm to room temperature over 1.5 h. A saturated aqueous solution of sodium sulfite (70 cm^3) was added, the layers were separated and the aqueous layer was washed with pentane (2x60 cm^3). The combined organics were then washed with water (50 cm^3), dried (Na_2SO_4) and reduced *in vacuo* to leave a pale yellow oil. The oil was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:19) as eluant to leave the *allylic chloride* (**302**) (3.9 g, 96 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 5.34 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 4.98 (1H, s, C=C*H*H), 4.87 (1H, s, C=CH*H*), 4.55 (2H, d, *J* 7.0 Hz, CH$C\mathit{H}_2$OAc), 4.31 (1H, t, *J* 6.3 Hz, CCCl*H*CH_2), 2.18-1.84 (4H, m, CClHC$\mathit{H}_2C\mathit{H}_2$C), 2.02 (3H, s, $C\mathit{H}_3CO_2$), 1.78 (3H, s, CH_2=CCH_3), 1.68 (3H, s, C($C\mathit{H}_3$)=CH); δ_C (90.6 MHz, $CDCl_3$) 170.9 (s), 144.0 (s), 140.4 (s), 119.3 (d), 114.2 (t), 66.0 (d), 61.1 (t), 36.4 (t), 34.2 (t), 20.9 (q), 16.9 (q), 16.3 (q); υ_{max} (thin film) 2951 (m), 2360 (w), 2254 (w), 1739 (s), 1670 (w), 1646 (w), 1446 (m), 1366 (m), 1234 (s), 1024 (m), 956 (w), 911 (m), 790 (w), 734 (m).

Ethyl 11-acetoxy-5,9-dimethylundeca-5,9-dienoate (**305**)[125].

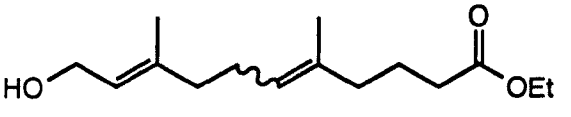


305

Zinc chloride (3.4 g, 25 mmol) was heated at 0.5 mmHg until it melted and then was left to cool to room temperature and ether (60 cm^3) was added. The mixture was heated at reflux for 1 h, left to cool to room temperature and ethoxy cyclopropyloxytrimethylsilane (10 cm^3, 8.8 g, 50 mmol) was added in one portion. The cloudy mixture was stirred at room temperature for 1 h and then refluxed for a further 30 min, cooled to room temperature and trimethylsilyl chloride (6.4 cm^3, 5.5 g, 50 mmol) was added in one portion. The resulting solution was transfered *via* cannula, dropwise over 5 min to a stirred solution of 6-chloro-3,7-dimethylocta-2,7-dienyl acetate (**303**) (3.9 g, 17 mmol) and copper bromide.dimethyl sulfide (210 mg, 1.0 mmol) in dimethyl formamide (80 cm^3) at room temperature. The pale yellow solution was left to stir overnight and then diluted with ether (600 cm^3) and water (600 cm^3). The layers were separated and the organic phase was washed with water (500 cm^3) and brine (200 cm^3), dried ($MgSO_4$) and reduced *in vacuo* to leave a colourless oil. The oil was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:9) as eluant to leave the *ester* (**305**) (4.5 g, 89 %) as an oily C-5 2:1 mixture of *E:Z* isomers. Major *E* isomer: δ_H (360 MHz, $CDCl_3$) 5.34 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 5.10 (1H, t, *J* 7.6 Hz, C=C*H*CH_2), 4.58 (2H, d, *J* 7.0 Hz, C=CHC*H*$_2O$), 4.12 (2H, q, *J* 7.2 Hz, OC*H*$_2CH_3$), 2.26 (2H, m, C*H*$_2CO_2Et$), 2.11-1.98 (6H, m, C*H*$_2$C=CHC*H*$_2$C*H*$_2$C), 2.06 (3H, s, C*H*$_3CO_2$), 1.72 (2H, m, $CH_2CH_2CH_2$), 1.70 (3H, s, C(C*H*$_3$)=CH), 1.59 (3H, s, C(C*H*$_3$)=CH), 1.26 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 173.4 (s), 170.7 (s), 141.7 (s), 134.2 (s),

124.4 (d), 118.2 (d), 61.0 (t), 59.9 (t), 39.2 (t), 38.7 (t), 33.6 (t), 25.9 (t), 22.8 (t), 20.7 (q), 16.2 (q), 15.5 (q), 14.0 (q); Minor *Z* isomer: δ_H (360 MHz, $CDCl_3$) 5.34 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 5.12 (1H, t, *J* 7.6 Hz, C=C*H*CH_2), 4.58 (2H, d, *J* 7.0 Hz, C=CHC*H*$_2$O), 4.12 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 2.26 (2H, m, C*H*$_2CO_2$Et), 2.11-1.98 (6H, m, C*H*$_2$C=CHC*H*$_2$C*H*$_2$C), 2.06 (3H, s, C*H*$_3CO_2$), 1.72 (2H, m, CH_2C*H*$_2CH_2$), 1.70 (3H, s, C(C*H*$_3$)=CH), 1.68 (3H, s, C(C*H*$_3$)=CH), 1.26 (3H, t, *J* 7.2 Hz, OCH_2C*H*$_3$); δ_C (90.6 MHz, $CDCl_3$) 173.4 (s), 170.7 (s), 141.7 (s), 134.2 (s), 125.0 (d), 118.2 (d), 61.0 (t), 59.9 (t), 39.5 (t), 33.6 (t), 30.8 (t), 25.8 (t), 22.9 (q), 22.9 (t), 20.7 (q), 15.5 (q), 14.0 (q); Both isomers: υ_{max} (thin film) 2934 (m), 1737 (s), 1446 (m), 1368 (m), 1233 (s), 1096 (w), 1026 (m), 955 (w), 858 (w); Found %: C, 68.7; H, 9.8 ($C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5); *m/z* (EI) 237.1831 (M-$OCOCH_3^+$, $C_{15}H_{25}O_2$ requires 237.1855).

***Ethyl 5,9-dimethyl-11-hydroxyundeca-5,9-dienoate* (304)**[125]



304

Potassium cyanide (920 mg, 14 mmol) was added in one portion to a stirred solution of ethyl 11-acetoxy-5,9-dimethylundeca-5,9-dienoate (**305**) (2.1 g, 7.1 mmol) in ethanol (50 cm^3) at room temperature and resulting mixture was heated at reflux for 15 h. The mixture was reduced *in vacuo* and taken up in ether (100 cm^3) and water (50 cm^3), the layers were then separated and the aqueous portion was washed with ether (50 cm^3), the combined organics were then washed with brine (25 cm^3), dried ($MgSO_4$) and reduced *in vacuo*. The oily residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:3) as eluant to leave the *alcohol* (**304**) (1.5 g, 83 %) as an oily 2:1 mixture of C-5 *E:Z* isomers. Major *E*

isomer: δ_H (400 MHz, $CDCl_3$) 5.41 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 5.12 (1H, t, *J* 7.6 Hz, C=C*H*CH_2), 4.14 (4H, m, C=CHC*H*$_2$O and OC*H*$_2$$CH_3$), 2.24 (2H, t, *J* 7.0 Hz, C*H*$_2$$CO_2$Et), 2.15-1.98 (6H, m, C*H*$_2$C=CHC*H*$_2$C*H*$_2$C), 1.61 (2H, m, CH_2C*H*$_2$$CH_2$), 1.57 (3H, s, C(C*H*$_3$)=CH), 1.50 (3H, s, C(C*H*$_3$)=CH), 1.26 (3H, t, *J* 7.2 Hz, OCH_2C*H*$_3$); δ_C (90.6 MHz, $CDCl_3$) 173.9 (s), 138.6 (s), 134.0 (s), 124.7 (d), 123.6 (d), 60.2 (t), 59.0 (t), 39.2 (t), 38.6 (t), 33.4 (t), 25.9 (t), 22.7 (t), 16.0 (q), 15.5 (q), 14.0 (q); Minor *Z* isomer: δ_H (400 MHz, $CDCl_3$) 5.41 (1H, t, *J* 7.0 Hz, C=C*H*CH_2O), 5.15 (1H, t, *J* 7.6 Hz, C=C*H*CH_2), 4.14 (4H, m, C=CHC*H*$_2$O and OC*H*$_2$$CH_3$), 2.24 (2H, t, *J* 7.0 Hz, C*H*$_2$$CO_2$Et), 2.15-1.98 (6H, m, C*H*$_2$C=CHC*H*$_2$C*H*$_2$C), 1.61 (2H, m, CH_2C*H*$_2$$CH_2$), 1.57 (6H, s, C(C*H*$_3$)=CH and C(C*H*$_3$)=CH), 1.26 (3H, t, *J* 7.2 Hz, OCH_2C*H*$_3$); δ_C (90.6 MHz, $CDCl_3$) 173.9 (s), 138.6 (s), 134.3 (s), 125.3 (d), 123.5 (d), 60.1 (t), 59.0 (t), 39.5 (t), 33.7 (t), 30.8 (t), 26.0 (t), 23.0 (q), 22.9 (t), 15.5 (q), 14.0 (q); Both isomers: υ_{max} (thin film) 3424 (br), 2933 (m), 1733 (s), 1446 (m), 1375 (m), 1304 (w), 1242 (m), 1197 (m), 1158 (m), 1096 (w), 1027 (m), 857 (w), 785 (w); Found %: C, 70.7; H, 10.3 ($C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3); *m/z* (EI) 236.1768 (M-H_2O^+, $C_{15}H_{24}O_2$ requires 236.1776).

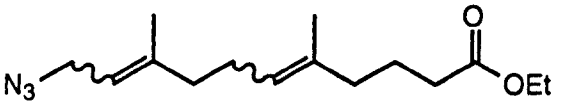
Zinc azide dipyridine complex[124]

$Zn(N_3)_2.2py$

A solution of sodium azide (3.0 g, 46 mmol) in water (23 cm^3) was added portionwise over 5 min to a stirred solution of zinc nitrate (6.9 g, 23 mmol) in water (12 cm^3) at room temperature. The solution was heated to 50°C for 2 h and then pyridine (7.5 cm^3, 7.3 g, 92 mmol) was added dropwise over 5 min resulting in the formation of a dense white precipitate. The suspension was allowed to cool to room temperature over 5 h, cooled in ice, filtered and washed with ice cold water. The collected white

solid was dried *in vacuo* (P_2O_5) for 4 h to leave the *azide* (5.7 g, 80 %) as a fine white crystalline solid.

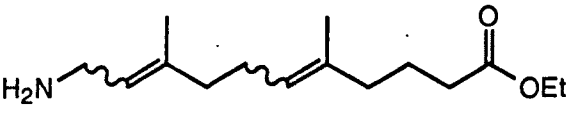
***Ethyl 11-azido-5,9-dimethylundeca-5,9-dienoate* (306)**



306

Di-*iso*-propyl azodicarboxylate (740 µl, 760 mg, 3.8 mmol) was added dropwise over 3 min at room temperature to a mixture of zinc azide (790 mg, 2.6 mmol), triphenylphosphine (990 mg, 3.8 mmol) and ethyl 5,9-dimethyl-11-hydroxyundeca-5,9-dienoate (**304**) (870 mg, 3.4 mmol) in toluene (36 cm^3). The solution was stirred for 10 min and then filtered through a pad of celite. The resulting clear pale yellow solution was reduced *in vacuo* and the residue was adsorbed on silica and then purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:9) as eluant to give the *azide* (**306**) (590 mg, 62 %) as an oily C-5 and C-9 *E:Z* mixture of isomers. Major C-5 *E* and C-9 *E* isomer: δ_H (360 MHz, $CDCl_3$) 5.30 (1H, t, *J* 7.3 Hz, C=C*H*CH_2N_3), 5.08 (1H, m, C=C*H*CH_2), 4.08 (2H, t, *J* 7.2 Hz, O$CH_2$$CH_3$), 3.73 (2H, d, *J* 7.3 Hz, C=CH$CH_2$$N_3$), 2.21 (2H, t, *J* 7.3 Hz, CH_2CO_2Et), 2.13-1.95 (6H, m, CH_2C=CH$CH_2$$CH_2$C), 1.72 (2H, m, $CH_2CH_2CH_2$), 1.67 (3H, s, C(CH_3)=CH), 1.57 (3H, s, C(CH_3)=CH), 1.22 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 173.6 (s), 142.8 (s), 134.4 (s), 124.3 (d), 117.0 (d), 60.0 (t), 47.8 (t), 39.3 (t), 38.7 (t), 33.5 (t), 26.1 (t), 22.9 (t), 16.0 (q), 15.6 (q), 14.1 (q); υ_{max} (thin film) 2925 (s), 2097 (s), 1736 (s), 1448 (m), 1375 (m), 1249 (m), 1032 (m), 879 (w); *m/z* (FAB) 252.1948 ($M+H-N_2^+$, $C_{15}H_{26}NO_2$ requires 252.1964).

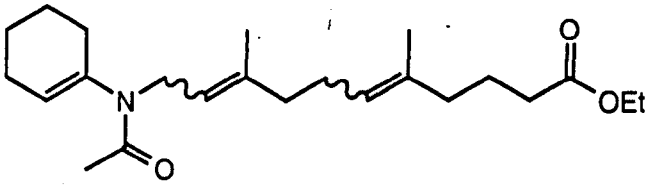
Ethyl 11-amino-5,9-dimethylundeca-5,9-dienoate (**300**)



300

Triphenylphosphine (520 mg, 2.0 mmol) was added in one portion to a stirred solution of ethyl 11-azido-5,9-dimethylundeca-5,9-dienoate (**306**) (370 mg, 1.3 mmol) in tetrahydrofuran (15 cm^3) at room temperature and left to stir overnight. Water (26 μl, 26 mg, 1.4 mmol) was then added at room temperature and the solution was left to stir overnight, diluted with water (20 cm^3) and ether (30 cm^3) and the layers were then separated. The aqueous layer was extracted with ether (2x30 cm^3) and the combined organics were then dried (Na_2SO_4) and reduced *in vacuo*. The resulting colourless residue was purified by chromatography on silica using dichloromethane - methanol - di-*iso*-propylamine (90:10:1) as eluant to give the *amine* (**300**) (240 mg, 74 %) as a colourless oily mixture of isomers. Major C-5 *E*, C-9 *E* isomer: δ_H (360 MHz, $CDCl_3$) 8.00 (2H, br, CH_2NH_2), 5.37 (1H, t, *J* 6.5 Hz, $C{=}CHCH_2NH_2$), 5.09 (1H, m, $C{=}CHCH_2$), 4.12 (2H, t, *J* 7.2 Hz, OCH_2CH_3), 3.59 (2H, br, $C{=}CHCH_2NH_2$), 2.25 (2H, t, *J* 7.6 Hz, CH_2CO_2Et), 2.10-1.97 (6H, m, $CH_2C{=}CHCH_2CH_2C$), 1.72 (5H, m, $CH_2CH_2CH_2$ and $C(CH_3){=}CH$), 1.48 (3H, s, $C(CH_3){=}CH$), 1.26 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 173.4 (s), 136.1 (s), 134.0 (s), 125.8 (d), 124.8 (d), 60.0 (t), 39.5 (t), 39.3 (t), 38.8 (t), 33.5 (t), 26.2 (t), 22.9 (t), 16.0 (q), 15.6 (q), 14.1 (q); υ_{max} (thin film) 3372 (br), 2931 (s), 2857 (m), 1734 (s), 1665 (w), 1589 (w), 1447 (m), 1374 (m), 1304 (w), 1246 (m), 1178 (m), 1157 (m), 1097 (w), 1031 (m), 856 (w); *m/z* (FAB) 254.2128 ($M+H^+$, $C_{15}H_{28}NO_2$ requires 254.2120).

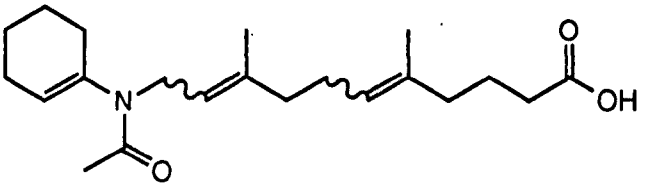
Ethyl 11-amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5,9-dimethylundeca-5,9-dienoate (**307**)



307

Cyclohexanone (200 μl, 190 mg, 1.9 mmol) was added in one portion at room temperature to a stirred mixture of ethyl 11-amino-5,9-dimethylundeca-5,9-dienoate (**300**) (240 mg, 0.96 mmol) and molecular sieves (4 Å, activated) in benzene (55 cm^3) and the mixture was left to stir for 24 h. Lutidine (170 μl, 150 mg, 1.4 mmol) was then added to the mixture in one portion at room temperature followed by acetyl chloride (100 μl, 105 mg, 1.3 mmol), in one portion also. The solution was then left to stir for 2 h, filtered through a pad of celite and reduced *in vacuo* to leave a yellow residue which was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:3) as eluant to give the *enamide* (**307**) (160 mg, 43 %) as a colourless oil. Major C-5 *E*, C-9 *E* isomer: δ_H (360 MHz, $CDCl_3$) 5.58 (1H, m, C*H*=CN), 5.21-5.07 (2H, m, 2xC=C*H*CH_2), 4.12 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.02 (2H, d, *J* 7.0 Hz, C=CHCH_2N), 2.27 (2H, m, CH_2CO_2Et), 2.11-1.97 (10H, m, CH_2C=CHCH_2CH_2C and CH_2C(N)=CHCH_2), 2.01 (3H, s, NCOCH_3), 1.76-1.56 (12H, m, CH_2CH_2C(CH_3)=CH, C(CH_3)=CH and $CH_2CH_2CH_2CH_2$), 1.26 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 173.8 (s), 169.5 (s), 139.2 (s), 138.6 (s), 134.2 (s), 127.3 (d), 124.9 (d), 120.1 (d), 60.2 (t), 43.4 (t). 39.5 (t), 33.9 (t), 33.7 (t), 29.7 (t), 28.2 (t), 24.8 (t), 23.4 (q), 23.1 (t), 22.8 (t), 21.6 (t), 21.6 (q), 15.7 (q), 14.2 (q); υ_{max} (thin film) 2929 (s), 2856 (m), 1733 (s), 1651 (s), 1446 (m), 1393 (m), 1259 (m), 1178 (m), 1031 (m); *m/z* (EI) 375.2770 (M^+, $C_{23}H_{37}NO_3$ requires 375.2773)

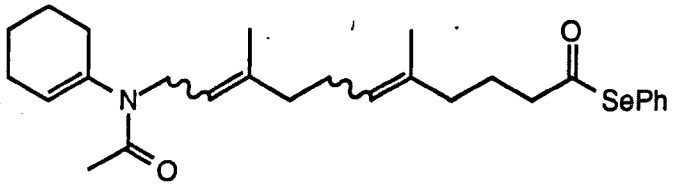
***11-amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5,9-dimethylundeca-5,9-dienoic acid* (308)**



308

A solution of lithium hydroxide (33 mg, 0.80 mmol) in water (8 cm^3) was added in one portion to a stirred solution of ethyl 11-amino-(*N*-acetyl, *N*-cyclohex-1'-en-1'-yl)-5,9-dimethylundeca-5,9-dienoate (**307**) (150 mg, 0.40 mmol) in tetrahydrofuran (8 cm^3) at room temperature. The solution was left to stir for 12 h and then acidified to pH 1 with hydrochloric acid (2 $moldm^{-3}$) and diluted with dichloromethane (30 cm^3) and water (20 cm^3). The layers were separated and the aqueous layer was extracted with dichloromethane (2x30 cm^3) and the combined organics were dried (Na_2SO_4) and reduced *in vacuo* to leave the *acid* (**308**) (140 mg, 99 %) as a colourless oily mixture of isomers. Major C-5 *E*, C-9 *E* isomer: δ_H (400 MHz, $CDCl_3$) 9.35 (1H, br, CO_2H), 5.60 (1H, m, C*H*=CN), 5.16 (2H, m, 2xC=C*H*CH_2), 4.02 (2H, d, *J* 7.0 Hz, C=CHCH_2N), 2.33 (2H, m, CH_2CO_2), 2.11-1.97 (10H, m, CH_2C=CHCH_2CH_2C and CH_2C(N)=CHCH_2), 2.03 (3H, s, NCOCH_3), 1.76-1.56 (12H, m, CH_2CH_2C(CH_3)=CH, C(CH_3)=CH and CH_2CH_2CH_2CH_2); δ_C (90.6 MHz, $CDCl_3$) 177.8 (s), 170.2 (s), 138.6 (s), 138.4 (s), 134.3 (s), 127.4 (d), 124.9 (d), 120.0 (d), 43.8 (t), 39.3 (t). 33.2 (t), 31.8 (t), 29.6 (t), 28.2 (t), 28.1 (t), 26.0 (t), 24.7 (t), 22.9 (t), 21.5 (q), 16.0 (q), 15.6 (q); υ_{max} (thin film) 3211 (br), 2930 (s), 2857 (m), 1731 (s), 1650 (s), 1678 (s), 1447 (m), 1409 (m), 1260 (m), 1031 (m); *m/z* (FAB) 348.2558 ($M+H^+$, $C_{21}H_{34}NO_3$ requires 348.2539).

***Phenyl 11-amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5,9-dimethylundeca-5,9-dienselenoate* (297)**

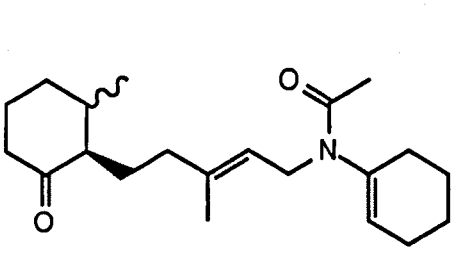


297

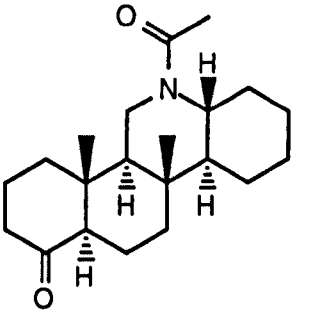
Tri-*n*-butylphosphine (150 µl, 120 mg, 0.59 mmol) was added dropwise over 2 min to a solution of 11-amino-(*N*-acetyl, *N*-cyclohex-1'-en-1'-yl)-5,9-dimethylundeca-5,9-dienoic acid (**308**) (140 mg, 0.40 mmol) in dichloromethane (3 cm^3) at -30°C and was left to stirr for 5 min. *N*-Phenylselenophthalamide (180 mg, 0.59 mmol) was added in one portion and then after 5 min at -30°C brine (4 cm^3) and water (4 cm^3) were added and the resulting mixture was allowed to warm to room temperature over 20 min. The mixture was diluted with dichloromethane (30 cm^3), the layers were separated and the aqueous layer was extracted with dichloromethane (2x30 cm^3), the combined organics were dried (Na_2SO_4) and reduced *in vacuo* to leave a pale yellow oil. The oil was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:3) to leave a pale yellow semi-solid which was further purified by titiration from pentane to give the *selenyl ester* (**297**) (160 mg, 80 %) as a colourless oily mixture of isomers. Major C-5 *E*, C-9 *E* isomer: δ_H (360 MHz, $CDCl_3$) 7.50 (2H, m, Ar-*H*), 7.39 (3H, m, Ar-*H*), 5.58 (1H, m, C*H*=CN), 5.20 (2H, m, 2xC=C*H*CH_2), 4.04 (2H, d, *J* 7.0 Hz, C=CHCH_2N), 2.66 (2H, m, CH_2COSe), 2.11-1.97 (10H, m, CH_2C=CHCH_2CH_2C and CH_2C(N)=CHCH_2), 2.01 (3H, s, NCOCH_3), 1.76-1.56 (12H, m, CH_2CH_2C(CH_3)=CH, C(CH_3)=CH and CH_2CH_2CH_2CH_2); δ_C (90.6 MHz, $CDCl_3$) 200.3 (s), 169.5 (s), 139.2 (s), 138.5 (s), 135.7 (d), 133.7 (s), 129.3 (d), 128.8 (d), 127.3 (d), 126.5 (s), 125.4 (d), 120.1 (d), 46.8 (t), 43.4 (t). 39.5 (t), 30.7 (t), 28.2 (t), 26.4 (t), 24.8 (t), 23.4 (t), 22.8 (t), 21.6 (q), 21.6 (t), 16.1 (q), 15.6 (q); υ_{max} (thin

film) 2930 (s), 2857 (m), 1725 (s), 1650 (s), 1438 (m), 1395 (m), 1281 (w), 1066 (w), 1022 (w), 922 (w); *m/z* (FAB) 488.2058 ($M+H^+$, $C_{27}H_{38}NO_2{}^{80}Se$ requires 488.2068), 486.2046 ($M+H^+$, $C_{27}H_{38}NO_2{}^{78}Se$ requires 486.2076).

1-Amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5-(3''-methylcyclohex-1''-on-2''-yl)-3-methylpent-2-ene **(310)** and ***tetracyclic compound*** **(296)**



310

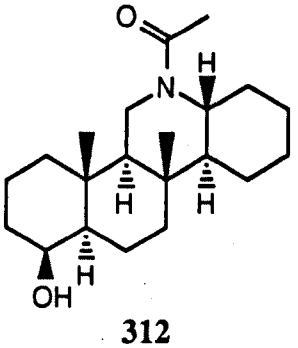


296

A solution of tri-*n*-butyltin hydride (70 μl, 75 mg, 0.26 mmol) and AIBN (5 mg) in degassed benzene (5 cm^3) was added dropwise over 8 h to a refluxing solution of phenyl 12-amino-(*N*-acetyl, *N*-cyclohex-1'-en-1'-yl)-5,9-dimethylundeca-5,9-dienselenoate (**297**) (100 mg, 0.21 mmol) and AIBN (5 mg) in degassed benzene (63 cm^3), under argon. The solution was left to reflux for a further 4 h and then allowed to cool to room temperature and reduced *in vacuo* to leave a colourless oil. The oil was then purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:3) to ethyl acetate - petroleum (b.p. 40-60°C) (7:3) as eluant to give *1-amino-(N-acetyl, N-cyclohex-1'-en-1'-yl)-5-(3''-methylcyclohex-1''-on-2''-yl)-3-methylpent-2-ene* (**310**) (10 mg, 10 %) as a colourless oily 4:1 mixture of isomers, eluted first. Major isomer: δ_H (500 MHz, $CDCl_3$) 5.58 (1H, m, NC=C*H*), 5.17 (1H, t, *J* 6.8 Hz, C=C*H*CH_2), 4.02 (2H, d, *J* 6.8 Hz, C=CHC*H*$_2$N), 2.45-2.25 (3H, m), 2.11-2.02 (4H, m), 2.00 (3H, s, NCOC*H*$_3$), 1.89 (2H, m), 1.69 (3H, s, CC*H*$_3$), 1.68-1.56

(6H, m), 1.29-1.23 (5H, m), 0.81 (3H, d, *J* 7.1 Hz, CHC*H*$_3$); δ_C (125.8 MHz, $CDCl_3$) 213.4 (s), 169.5 (s), 139.3 (s), 138.3 (s), 127.3 (d), 121.3 (d), 54.6 (d), 43.4 (t), 41.6 (t), 36.6 (t), 31.8 (t), 28.2 (t), 25.0 (t), 24.8 (t), 24.7 (t), 23.4 (t), 23.3 (q), 22.8 (t), 21.6 (q), 21.6 (t), 14.2 (q); *m/z* (EI) 331.2522 (M^+, $C_{21}H_{33}NO_2$ requires 331.2511) and the *tetracycle* (**296**) (42 mg, 45 %) as a colourless oily 4:1 mixture of isomers. Major *trans, anti, trans, anti, trans* isomer: δ_H (360 MHz, $CDCl_3$, 328 K) 3.55 (2H, m, CHC*H*$_2$N), 3.32 (1H, dd, *J* 10.6 Hz and 2.6 Hz, NC*H*CH$_2$), 2.32 (3H, m), 2.11 (3H, s, NCOC*H*$_3$), 2.15-0.97 (18H, m), 0.85 (3H, s, CC*H*$_3$), 0.83 (3H, s, CC*H*$_3$); δ_C (90.6 MHz, $CDCl_3$) 212.2 (s), 171.8 (s), 59.4 (d), 57.9 (d, br.), 55.8 (d), 55.0 (d), 43.0 (s), 41.7 (t, br.), 40.8 (t), 37.6 (t), 36.3 (t), 33.9 (s), 33.6 (t), 26.6 (t), 25.4 (t), 25.3 (t), 23.0 (q), 22.1 (t), 17.1 (t), 14.7 (q), 13.4 (q); *m/z* (EI) 331.2500 (M^+, $C_{21}H_{33}NO_2$ requires 331.2511).

Reduced tetracycle **(312)**

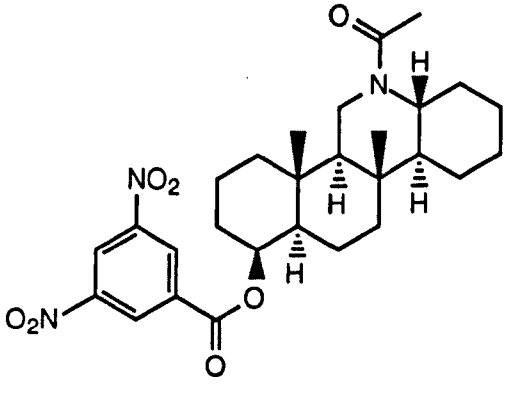


312

Sodium borohydride (1.5 mg, 39 μmol) was added in one portion at room temperature to a stirred solution of the ketone (**297**) (11 mg, 36 μmol) and methanol (5.0 μl, 4.8 mg, 120 μmol) in ether (2 cm^3) and left to stir for 4 hours. Methanol (5.0 μl, 4.8 mg, 120 μmol) was added in one portion followed by sodium borohydride (4.5 mg, 120 μmol) also in one portion and the mixture was left to stir at room temperature overnight. Water (10 cm^3) was added and the mixture was diluted with ether (5 cm^3),

the layers were separated and the aqueous fraction was washed with ether (2x5 cm^3). The combined organics were dried (Na_2SO_4) and reduced *in vacuo* to leave an oily residue. This residue was purified by chromatography on silica using methanol - dichloromethane (6:94) as eluant to leave the *reduced tetracycle* (**312**) (10 mg, 99%) as a colourless oily 4:1 mixture of isomers. Major *trans, anti, trans, anti, trans* isomer: δ_H (360 MHz, $CDCl_3$, 328K) 3.86 (1H, m, C*H*OH), 3.54 (1H, dd, *J* 13.3 Hz and 9.9 Hz, NC*H*HCH), 3.40 (1H, dd, *J* 13.3 Hz and 9.4 Hz, NC*H*HCH), 3.33 (1H, app. td, *J* 10.6 Hz and 2.6 Hz, NC*H*CH_2), 2.36 (1H, m, C*H*CHOH), 2.10 (3H, s, NCOC*H*$_3$), 1.89-1.01 (21H, m), 1.10 (3H, s, CC*H*$_3$), 0.87 (3H, s, CC*H*$_3$); δ_C (90.6 MHz, $CDCl_3$) 171.7 (s), 72.0 (d), 57.7 (d), 56.4 (d), 55.7 (d), 50.8 (d), 41.1 (t), 38.6 (t), 37.1 (s), 34.6 (s), 33.8 (t), 33.1 (t), 26.7 (t), 25.6 (t), 25.5 (t), 23.2 (t), 23.1 (q), 16.2 (t), 15.3 (q), 15.2 (q); *m/z* (EI) 333.2676 (M^+, $C_{21}H_{35}NO_2$ requires 333.2668)

Ester tetracycle **(313)**



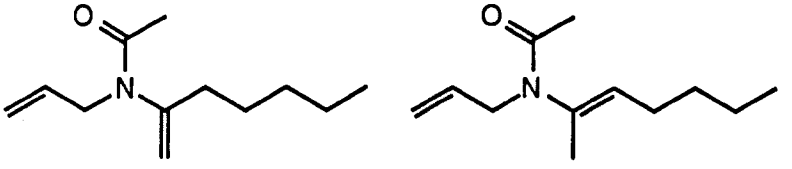
313

3,5-Dinitrobenzyl chloride (15 mg, 32 μmol) was added in one portion at room temperature to a stirred solution of the alcohol (**312**) (10 mg, 32 μmol), 4-*N,N*-dimethylaminopyridine (2 mg) and triethylamine (9.0 μl, 6.5 mg, 64 μmol) in dichloromethane (1.0 cm^3). The mixture was left to stir for 10 min at room temperature and then a saturated aqueous solution of sodium hydrogencarbonate (10

cm^3) and dichloromethane (10 cm^3) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (2x10 cm^3), then the combined organics were dried (Na_2SO_4) and reduced *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:5) as eluant to leave the *tetracycle* (**313**) *trans, anti, trans, anti, trans* isomer (10 mg, 61 %) as a white solid. δ_H (500 MHz, $CDCl_3$, 328K) 9.21 (1H, t, *J* 2.1 Hz, Ar-*H*), 9.15 (2H, d, *J* 2.1 Hz, Ar-*H*), 5.37 (1H, app. q, *J* 2.5 Hz, C*H*CO_2Ar), 3.68 (1H, dd, *J* 13.4 Hz and 9.8 Hz, NC*H*HCH), 3.44 (1H, dd, *J* 13.4 Hz and 8.4 Hz, NCH*H*CH), 3.34 (1H, app. td, *J* 10.7 Hz and 2.7 Hz, NC*H*CH_2), 2.37 (1H, m, C*H*H), 2.13 (3H, s, NCOC*H*$_3$), 2.04 (1H, m, C*H*HCHO), 1.85-1.73 (6H, m, C*H*H, C*H*H, CH_2, CH_2), 1.67 (3H, m, C*H*H, C*H*H, CH*H*CHO), 1.48 (1H, m, CH*H*), 1.45 (4H, m, CH*H*, CH*H*, NCH_2C*H*, C*H*CHO), 1.28-1.24 (2H, m, CH*H*, CH*H*), 1.26 (3H, s, CC*H*$_3$), 1.18-1.03 (3H, m, CH*H*, CH*H*, NCHC*H*), 0.89 (3H, s, CC*H*$_3$); δ_C (125.8 MHz, $CDCl_3$) 171.5 (s), 162.3 (s), 148.7 (s), 134.3 (s), 129.3 (d), 122.2 (d), 79.1 (d), 57.8 (d, br), 56.4 (d), 55.5 (d), 49.9 (d), 40.7 (t, br), 38.3 (t), 37.5 (t), 37.2 (s), 34.6 (s), 33.2 (t), 30.5 (t), 26.6 (t), 25.6 (t), 25.5 (t), 23.0 (q), 23.0 (t), 16.7 (t), 15.3 (q), 15.3 (q); *m/z* (EI) 527.2641 (M^+, $C_{28}H_{37}N_3O_7$ requires 527.2631).

3.3 LINEAR ENAMIDE STUDIES

2-Amino-(N-acetyl, N-prop-2'-en-1'-yl)-hept-1-ene **(321)** and ***2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-hept-2-ene*** **(320)**

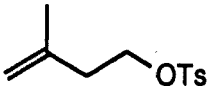


321 **320**

1-Aminoprop-2-ene (210 μl, 160 mg, 2.8 mmol), heptan-2-one (390 μl, 320 mg, 2.8 mmol) and molecular sieves (4 Å, activated) in benzene (80 cm^3) were set stirring at room temperature and left overnight. 4-*N,N*-dimethylaminopyridine (34 mg, 0.28 mmol) was added to the mixture in one portion at room temperature followed by triethylamine (590 μl, 430 mg, 4.2 mmol), also added in one portion, and then acetyl chloride (300 μl, 330 mg, 4.2 mmol) was added dropwise over 5 min at room temperature. The solution was allowed to stir at room temperature for 2 h and then filtered through a pad of celite and the solvent was removed *in vacuo*. The resulting oily residue was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:2) as eluant to give ***2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-hept-1-ene*** **(321)** (190 mg, 34%) eluted first, δ_H (250 MHz, $CDCl_3$) 5.81 (1H, m, $CH_2CH{=}CH_2$), 5.13 (2H, m, $CH_2CH{=}CH_2$), 5.06 (1H, s, C=C*H*H), 4.88 (1H, s, C=CH*H*), 4.04 (2H, d, *J* 6.2 Hz, $CHCH_2N$), 2.15 (2H, t, *J* 7.1 Hz, $CH_2{=}CCH_2$), 2.07 (3H, s, $COCH_3$), 1.46 (2H, m, $CH_2CH_2CH_2$), 1.32 (4H, m, $CH_2CH_2CH_2CH_3$), 0.90 (3H, m, CH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 169.1 (s), 148.3 (s), 133.3 (d), 116.8 (t), 113.1 (t), 48.1 (t), 34.0 (t), 31.1 (t), 26.1 (t), 22.1 (t), 21.4 (q), 13.6 (q); υ_{max} (liquid

film)/cm^{-1} 2928 (s), 2858 (s), 1654 (s), 1431 (m), 1388 (s), 1278 (m), 1240 (m), 1148 (w), 1106 (w), 1036 (w), 982 (m); *m/z* (EI) 195.1621 (M^+, $C_{12}H_{21}NO$ requires 195.1623), and *2-amino-(*N*-acetyl,* N*-prop-2'-en-1'-yl)-hept-2-ene* (**320**) (140 mg, 25%) eluted second, δ_H (250 MHz, $CDCl_3$) 5.80 (1H, m, $CH_2CH{=}CH_2$), 5.32 (1H, t, *J* 7.6 Hz, $CH_2CH{=}C$), 5.11 (2H, m, $CH_2CH{=}CH_2$), 4.01 (2H, d, *J* 6.1 Hz, $CHCH_2N$), 2.01 (5H, m, $CH_2CH{=}C$ and $COCH_3$), 1.77 (3H, s, $CH{=}C(N)CH_3$), 1.33 (4H, m, $CH_2CH_2CH_2CH_3$), 0.90 (3H, t, *J* 7.0 Hz, CH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 169.6 (s), 135.6 (s), 133.8 (d), 131.3 (d), 117.2 (t), 48.6 (t), 31.1 (t), 27.4 (t), 22.2 (t), 21.7 (q), 16.0 (q), 13.6 (q); υ_{max} (liquid film)/cm^{-1} 2928 (m), 2858 (m), 1655 (s), 1390 (s), 1277 (w), 1223 (s), 1036 (w), 982 (w).

***2-Methyl-4-*para*-toluenesulfonyloxybut-1-ene* (322)**[128]

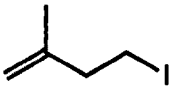


322

para-Toluenesulfonyl chloride (4.9 g, 26 mmol) was added in one portion to a stirred solution of 2-methylbut-1-en-4-ol (3.1 cm^3, 3.6 g, 23 mmol) in pyridine (25 cm^3) at 0°C and the resulting solution was allowed to warm to room temperature over 2 h. The mixture was diluted with ether (200 cm^3) and washed with water (200 cm^3), a saturated aqueous solution of copper (II) sulfate (300 cm^3), water (100 cm^3) and brine (100 cm^3). The organics were dried (Na_2SO_4), reduced *in vacuo* and the residue was then purified by chromatography on silica, using ether - petroleum (b.p. 40-60°C) (1:19) as eluant, to leave the *tosylate* (**322**) (7.6 g, 75 %) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.0 Hz, Ar-*H*), 7.35 (2H, d, *J* 8.0 Hz, Ar-*H*), 4.80 (1H, s, C=C*H*H), 4.69 (1H, s, C=CH*H*), 4.14 (2H, t, *J* 7.0 Hz, CH_2OTs), 2.46 (3H, s, Ar-CH_3), 2.36 (2H, t, *J* 7.0 Hz, $CH_2CMe{=}CH_2$), 1.67 (3H, s, $CH_2{=}CCH_3$); δ_C (67.8

MHz, $CDCl_3$) 144.6 (s), 139.9 (s), 132.8 (s), 129.6 (d), 127.6 (d), 112.8 (t), 68.3 (t), 36.4 (t), 22.0 (q), 21.3 (q); υ_{max} (liquid film)/cm^{-1} 3077 (m), 2970 (s), 1923 (w), 1810 (w), 1652 (s), 1560 (s), 1359 (s), 1176 (s), 1120 (m), 1097 (s), 1020 (m), 964 (s), 894 (s), 816 (s), 779 (s), 705 (w).

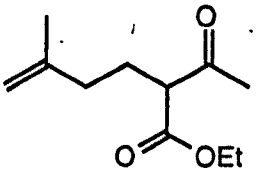
4-Iodo-2-methylbut-1-ene **(323)**[128]



323

Sodium iodoide (9.4 g, 63 mmol) was added in one portion to a stirred solution of 2-methyl-4-*para*-toluenesulfonyloxybut-1-ene (**322**) (7.5 g, 31 mmol) in acetone (90 cm^3) at room temperature and the mixture was then heated at reflux overnight. The solution was then allowed to cool to room temperature and diluted with petrol (200 cm^3) and the resulting suspension was filtered through a pad of celite. The filtrate was reduced *in vacuo* and then taken up in ether (400 cm^3) and the solution was then washed with 10 % w/v aqueous sodium thiosulfate solution (200 cm^3), water (200 cm^3) and then brine (100 cm^3), dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave the *iodide* (**323**) (4.7 g, 77 %) as a pale pink mobile liquid. δ_H (250 MHz, $CDCl_3$) 4.87 (1H, s, C=C*H*H), 4.76 (1H, s, C=CH*H*), 3.27 (2H, t, *J* 7.5 Hz, CH_2I), 2.59 (2H, t, *J* 7.5 Hz, $CH_2CMe{=}CH_2$), 1.75 (3H, s, $CH_2{=}CCH_3$); δ_C (67.8 MHz, $CDCl_3$) 143.7 (s), 112.2 (t), 41.8 (t), 21.6 (q), 3.4 (d); υ_{max} (liquid film)/cm^{-1} 3076 (m), 2968 (s), 2934 (s), 2866 (m), 1650 (s), 1445 (s), 1374 (m), 1339 (w), 1234 (s), 1170 (s), 1118 (w), 894 (s).

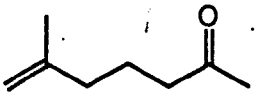
5-(Ethyl carboxy)-2-methylhept-1-en-6-one (**324**)



324

Ethyl acetoacetate (4.5 cm^3, 4.6 g, 35 mmol) was added dropwise over 10 min to a stirred slurry of sodium hydride (1.33 g, 33 mmol, 60 wt.% in oil) in tetrahydrofuran (34 cm^3) as 0°C and left to stir at 0°C for 30 min. The resulting clear solution was transfered *via* cannula, dropwise over 5 min, to a stirred solution of 4-iodo-2-methylbut-1-ene (**323**) (3.4 g, 18 mmol) in tetrahydrofuran (34 cm^3) at 0°C. The resulting solution was heated at reflux for 4 hours, cooled to room temperature and water (70 cm^3) was added. The mixture was reduced *in vacuo* and the resulting aqueous layer was extracted with ether (3x70 cm^3) and the combined organics were washed with brine (50 cm^3), dried ($MgSO_4$) and the solvent was removed *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:9) as eluant to give the *ketoester* (**324**) (3.0 g, 84 %) as a colourless mobile oil. δ_H (400 MHz, $CDCl_3$) 4.76 (1H, s, C=C*H*H), 4.69 (1H, s, C=CH*H*), 4.20 (2H, t, *J* 7.1 Hz, O$CH_2$$CH_3$), 3.43 (1H, m, $CH_2CH(CO_2Et)CO$), 2.24 (3H, s, COCH_3), 2.01 (4H, m, CH_2CH_2), 1.72 (3H, s, CH_2=CCH_3), 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (67.8 MHz, $CDCl_3$) 202.8 (s), 169.5 (s), 144.0 (s), 111.0 (t). 61.1 (t), 58.7 (d), 35.0 (t), 28.8 (q), 25.6 (t), 21.9 (q), 13.9 (q); υ_{max} (liquid film)/cm^{-1} 3074 (m), 2978 (s), 2937 (s), 1741 (s), 1717 (s), 1648 (m), 1447 (s), 1359 (s), 1243 (s), 1148 (s), 1096 (m), 1026 (m), 890 (m), 859 (w); *m/z* (EI) 180.1152 (M-H_2O+, $C_{11}H_{16}O_2$ requires 180.1150).

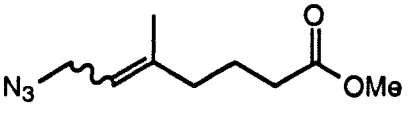
2-Methylhept-1-en-5-one (318)[128]



318

A stirred mixture of 5-(ethyl carboxy)-2-methylhept-1-en-6-one (**324**) (3.0 g, 15 mmol) and 50% aqueous w/v sodium hydroxide (16 cm^3) were heated at reflux for 4 h and then cooled to room temperature and acidified to pH 1 with hydrochloric acid (2 $moldm^{-3}$). The aqueous mixture was extracted with ether (3x60 cm^3) and the combined organics were dried ($MgSO_4$) and reduced *in vacuo* to leave the *ketone* (**318**) (1.9 g, 99 %) as a mobile colourless oil. δ_H (250 MHz, $CDCl_3$) 4.73 (1H, s, C=C*H*H), 4.68 (1H, s, C=CH*H*), 2.43 (2H, t, *J* 7.2 Hz, CH_2CO), 2.14 (3H, s, $COCH_3$), 2.02 (2H, t, *J* 7.0 Hz, $CH_2CMe{=}CH_2$), 1.71 (5H, m, $CH_2{=}CCH_3$ and $CH_2CH_2CH_2$); δ_C (67.8 MHz, $CDCl_3$) 208.5 (s), 144.9 (s), 110.5 (t), 42.9 (t), 36.9 (t), 29.9 (q), 22.1 (q), 21.3 (t); υ_{max} (liquid film)/cm^{-1} 2938 (s), 1717 (s), 1648 (m), 1446 (m), 1367 (m), 1224 (w), 1183 (w), 1158 (m), 889 (m), 757 (m).

Methyl 7-azido-5-methyl hept-5-enoate (325)

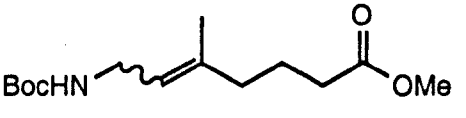


325

Di-*iso*-propyl azodicarboxylate (2.0 cm^3, 2.0 g, 10 mmol) was added dropwise over 3 min at room temperature to a mixture of zinc azide dipyridine complex (2.1 g, 6.8 mmol), triphenylphosphine (2.6 g, 10 mmol) and methyl 7-hydroxy-5-methylhept-5-enoate (**277**) (1.6 g, 9.1 mmol) in toluene (75 cm^3). The solution was stirred for 10

min and then filtered through a pad of celite. The resulting clear pale yellow solution was reduced *in vacuo* and the residue was absorbed on silica and purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:9) as eluant to give the *azide* (**325**) (1.2 g, 67 %) as an oily 2:1 mixture of *E* and *Z*-isomers. Major *E* isomer: δ_H (400 MHz, $CDCl_3$) 5.37 (1H, t, *J* 6.7 Hz, C=C*H*CH_2), 3.78 (2H, d, *J* 6.7 Hz, CHC*H*$_2N_3$), 3.68 (3H, s, OC*H*$_3$), 2.31 (2H, t, *J* 7.3 Hz, C*H*$_2CO_2$Me), 2.14 (2H, t, *J* 7.0 Hz, C*H*$_2$C(Me)=CH), 1.79 (2H, m, CH_2C*H*$_2CH_2$), 1.80 (3H, s, CC*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 173.7 (s), 142.0 (s), 117.8 (d), 51.4 (q), 47.8 (t), 38.6 (t), 33.1 (t), 23.1 (q), 22.7 (t); Minor *Z* isomer: δ_H (400 MHz, $CDCl_3$) 5.35 (1H, t, *J* 6.7 Hz, C=C*H*CH_2), 3.76 (2H, d, *J* 6.7 Hz, CHC*H*$_2N_3$), 3.69 (3H, s, OC*H*$_3$), 2.31 (2H, t, *J* 7.3 Hz, C*H*$_2CO_2$Me), 2.11 (2H, t, *J* 7.0 Hz, C*H*$_2$C(Me)=CH), 1.79 (2H, m, CH_2C*H*$_2CH_2$), 1.71 (3H, s, CC*H*$_3$); δ_C (67.8 MHz, $CDCl_3$) 173.6 (s), 142.0 (s), 118.6 (d), 51.4 (q), 47.7 (t), 38.6 (t), 31.0 (t), 23.0 (t), 16.1 (q); Both isomers: υ_{max} (liquid film)/cm^{-1} 2951 (s),2099 (s), 1737 (s), 1436 (m), 1364 (m), 1252 (s), 1174 (s), 1097 (w), 993 (w), 882 (m); m/z (EI) 169.1112 ($M-N_2^+$, $C_9H_{15}NO_2$ requires 169.1103).

Methyl 7-amino-(N-tert-butylcarboxylate)-5-methylhept-5-enoate **(274b)**

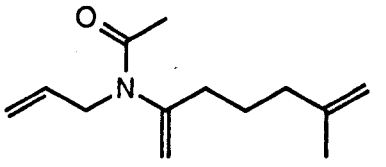


274b

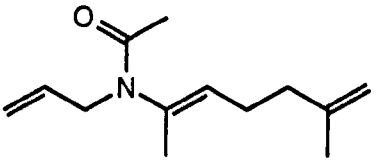
Triphenylphosphine (1.6 g, 6.1 mmol) was added in one portion to a stirred solution of methyl 7-azido-5-methylhept-5-enoate (**325**) (800 mg, 4.0 mmol) in tetrahydrofuran (40 cm^3) at room temperature. The solution was left to stir at room temperature for 24 h, then water (150 µl, 150 mg, 8.1 mmol) was added and the mixture was then left to stir for 24 h. *tert*-Butyl dicarboxylate (1.8 g, 8.1 mmol) then

triethylamine (620 μl, 450 mg, 4.4 mmol) were added in two separate portions and the mixture was then left to stir at room temperature for 24 h. The mixture was reduced *in vacuo* and partitioned between water (100 cm^3) and ether (100 cm^3). The layers were separated and the aqueous was extracted with ether (2x100 cm^3), the combined organics were then washed with saturated aqueous sodium bicarbonate (60 cm^3), brine (40 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60 °C) (1:4) as eluant, to leave the *protected amine* (**274b**) (1.1 g, 97 %) as a colourless oily 2:1 mixture of *E* and *Z* isomers. Major *E* isomer: δ_H (250 MHz, $CDCl_3$) 5.19 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (1H, br, CH_2N*H*Boc), 3.70 (2H, br, C=CH_2NHBoc), 3.67 (3H, s, CO_2CH_3), 2.28 (2H, t, *J* 7.5 Hz, CH_2CO_2Me), 2.02 (2H, t, *J* 7.0 Hz, CH_2C(Me)=CH), 1.73 (2H, m, $CH_2CH_2CH_2$), 1.65 (3H, s, CH_2C(CH_3)=CH), 1.45 (9H, s, OC(CH_3); δ_C (67.8 MHz, $CDCl_3$) 174.2 (s), 156.2 (s), 138.1 (s), 122.0 (d), 79.2 (s), 52.0 (t), 38.5 (t), 33.8 (t), 31.4 (t), 28.8 (q), 23.1 (t), 16.4 (q); Minor *Z* isomer: δ_H (250 MHz, $CDCl_3$) 5.24 (1H, t, *J* 7.0 Hz, C=C*H*CH_2N), 4.50 (1H, br, CH_2N*H*Boc), 3.70 (2H, br, CHCH_2N), 3.67 (3H, s, CO_2CH_3), 2.29 (2H, t, *J* 7.5 Hz, CH_2CO_2Me), 2.10 (2H, t, *J* 7.0 Hz, CH_2C(Me)=CH), 1.73 (2H, m, $CH_2CH_2CH_2$), 1.70 (3H, s, CH_2C(CH_3)=CH), 1.45 (9H, s, OC(CH_3); δ_C (67.8 MHz, $CDCl_3$) 174.2 (s), 156.2 (s), 138.1 (s), 122.9 (d), 79.2 (s), 52.0 (q), 39.1 (t), 33.8 (t), 31.4 (t), 28.8 (q), 23.5 (q), 23.5 (t); Both isomers: υ_{max} (liquid film)/cm^{-1} 3368 (m), 2975 (s), 1714 (s), 1516 (s), 1454 (m), 1437 (m), 1391 (m), 1366 (s), 1249 (s), 1172 (s), 1047 (m), 1018 (m), 934 (w), 865 (w), 137 (m); Found %: C, 61.9; H, 9.6; N, 4.9 ($C_{15}H_{25}NO_4$ requires C, 62.0; H, 9.3; N, 5.2); *m/z* (EI) 214.1086 (M-^{t}Bu$^+$, $C_{10}H_{16}NO_4$ requires 214.1079).

2-Amino-(N-acetyl, N-prop-2'-en-1'-yl)-6-methylhept-1,6-diene (**355**) and *2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-6-methylhept-2,6-diene* (**356**)



355

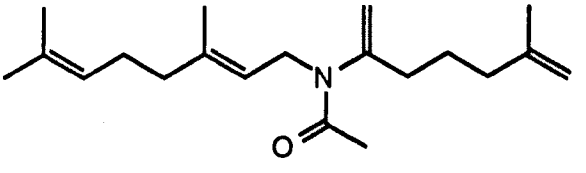


356

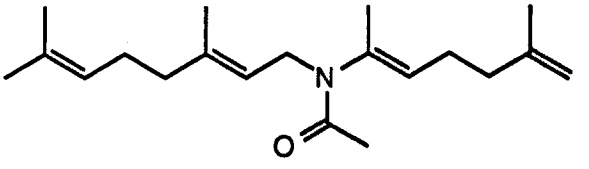
A mixture of 5-methylhept-5-en-2-one (**318**) (150 mg, 1.2 mmol) and 1-aminoprop-2-ene (90 μl, 68 mg, 1.2 mmol) in benzene (20 cm^3) with molecular sieves (4 Å, activated) was stirred for 12 h at room temperature. Lutidine (210 μl, 190 mg, 1.8 mmol) was added in one portion and then acetyl chloride (90 μl, 100 mg, 1.3 mmol) was added dropwise over 5 min at room temperature. The mixture was allowed to stir for 2 h, filtered through a pad of celite and the solvent evaporated *in vacuo* to give a yellow residue. The residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:3) as eluant to give *2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-6-methylhept-1,6-diene* (**355**) (75 mg, 30 %) as a colourless oil, δ_H (360 MHz, $CDCl_3$) 5.82 (1H, m, $CH_2CH{=}CH_2$), 5.10 (3H, m, $CH_2CH{=}CH_2$ and $C{=}CHH$), 4.87 (1H, s, $C{=}CHH$), 4.71 (1H, s, $C{=}CHH$), 4.65 (1H, s, $C{=}CHH$), 4.01 (2H, d, *J* 6.3 Hz, $CHCH_2N$), 2.12 (2H, t, *J* 7.6 Hz, $CH_2C{=}CH_2$), 2.04 (3H, s, $COCH_3$), 2.03 (4H, m, $CH_2CH_2C{=}CH_2$), 1.67 (3H, s, CCH_3); δ_C (67.8 MHz, $CDCl_3$) 169.5 (s), 148.4 (s), 144.7 (s), 133.5 (d), 117.2 (t), 113.6 (t), 110.4 (t), 48.4 (t), 37.1 (t), 33.7 (t), 24.6 (t), 22.1 (q), 21.7 (q); υ_{max} (liquid film)/cm^{-1} 2936 (m), 1645 (s), 1433 (m), 1386 (s), 1278 (m), 1238 (m), 983 (w), 920 (m), 890 (m); *m/z* (EI) 207.1628 (M^+, $C_{13}H_{21}NO$ requires 207.1623), and *2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-6-methylhept-2,6-diene* (**356**) (31 mg, 13 %) as a colourless oil, δ_H (360 MHz, $CDCl_3$) 5.78 (1H, m, $CH_2CH{=}CH_2$), 5.32 (1H, t, *J* 7.3, $C{=}CHCH_2$), 5.11 (2H, m, $CH_2CH{=}CH_2$), 4.74 (1H,

s, C=C*H*H), 4.68 (1H, s, C=CH*H*), 4.00 (2H, d, *J* 6.3 Hz, CHCH_2N), 2.20 (2H, apparent q, *J* 7.3 Hz, C=CHCH_2CH$_2$), 2.09 (2H, t, *J* 7.3 Hz, CH$_2$CH_2C), 2.01 (3H, s, COCH_3), 1.79 (3H, s, CCH_3), 1.72 (3H, s, CCH_3); δ_C (67.8 MHz, $CDCl_3$) 169.6 (s), 144.6 (s), 136.0 (s), 133.7 (d), 130.6 (d), 117.3 (t), 110.7 (t), 48.7 (t), 36.8 (t), 35.7 (t), 22.2 (q), 21.7 (q), 16.1 (q); υ_{max} (liquid film)/cm^{-1} 2922 (m), 1652 (s), 1393 (m), 1280 (w), 1039 (w), 887 (w); *m/z* (EI) 207.1625 (M^+, $C_{13}H_{21}NO$ requires 207.1623)

1-Amino-(N-acetyl, N-6'-methylhept-1',6'-dien-2'-yl)-3,7-dimethyloct-2,6-diene (**329**) and ***1-amino-(N-acetyl, N-6'-methylhept-2',6'-dien-2'-yl)-3,7-dimethyloct-2,6-diene*** (**330**)



329

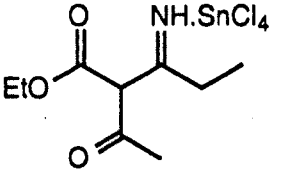


330

A mixture of 5-methylhept-5-en-2-one (**318**) (150 mg, 1.2 mmol) and geranyl amine (**328**) (220 µl, 108 mg, 1.2 mmol) in benzene (20 cm^3) with molecular sieves (4 Å, activated) was stirred for 12 h at room temperature. Lutidine (210 µl, 190 mg, 1.8 mmol) was added in one portion and then acetyl chloride (90 µl, 100 mg, 1.3 mmol) was added dropwise over 5 min at room temperature. The mixture was allowed to stir for 2 h, filtered through a pad of celite and the solvent evaporated *in vacuo* to give a yellow residue. The residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:3) as eluant to give *1-amino-(N-acetyl, N-6'-methylhept-1',6'-dien-2'-yl)-3,7-dimethyloct-2,6-diene* (**329**) (110 mg, 31 %) as a

colourless oil, eluted first, δ_H (360 MHz, $CDCl_3$) 5.17 (1H, app. td, *J* 6.9 Hz and 1.1 Hz, C=C*H*CH_2N), 5.03 (2H, m, C=C*H*CH_2 and C=C*H*H), 4.87 (1H, s, C=CH*H*), 4.72 (1H, s, C=C*H*H), 4.67 (1H, s, C=C*H*H), 4.04 (2H, d, *J* 6.9 Hz, CHCH_2N), 2.15-1.96 (8H, m, CHCH_2CH_2C and CH_2CH_2CH_2), 2.04 (3H, s, COCH_3), 1.70 (3H, s, CCH_3), 1.65 (3H, d, *J* 1.1 Hz, CH=CCH_3), 1.62 (3H, s, CCH_3), 1.60 (2H, m, CH_2C$H_2$$CH_2$), 1.57 (3H, s, CC$H_3$); δ_C (67.8 MHz, $CDCl_3$) 169.4 (s), 148.6 (s), 144.8 (s), 138.5 (s), 131.4 (s), 123.9 (d), 119.9 (d), 113.3 (t), 110.5 (t), 43.3 (t), 39.5 (t), 37.2 (t), 33.9 (t), 26.3 (t), 25.6 (q), 4.7 (t), 22.2 (q), 21.8 (q) 17.6 (q), 16.1 (q); υ_{max} (liquid film)/cm^{-1} 2966 (m), 2931 (m), 1655 (s), 1438 (m), 1588 (s), 1276 (w), 1107 (w), 977 (w), 888 (m); *m/z* (EI) 303.2552 (M^+, $C_{20}H_{33}NO$ requires 303.2562), and *1-amino-(*N*-acetyl,* N*-6'-methylhept-2',6'-dien-2'-yl)-3,7-dimethyloct-2,6-diene* (**330**) (82 mg, 23 %) as a colourless oil, eluted second, δ_H (360 MHz, $CDCl_3$) 5.32 (1H, t, *J* 7.2 Hz, C=C*H*CH_2), 5.19 (1H, t, *J* 7.0 Hz, C=C*H*CH_2), 5.08 (1H, t, *J* 5.3 Hz, C=C*H*CH_2), 4.72 (2H, m, C=CH_2), 4.04 (2H, d, *J* 7.0 Hz, C=CHCH_2N), 2.19 (2H, m, CH=CCH_2), 2.11-1.99 (6H, m, CHCH_2CH_2C, CHCH_2CH_2C), 2.00 (3H, s, COCH_3), 1.80 (3H, s, CCH_3), 1.73 (3H, s, CCH_3), 1.68 (3H, s, CCH_3), 1.63 (3H, s, CCH_3), 1.60 (3H, s, CCH_3); δ_C (67.8 MHz, $CDCl_3$) 169.7 (s), 144.6 (s), 138.7 (s), 136.1 (s), 131.5(s), 130.3 (d), 124.0 (d), 119.9 (d), 110.6 (t), 43.5 (t), 39.6 (t), 36.8 (t), 26.4 (t), 25.8 (t), 25.7 (q), 22.5 (q), 22.2 (q), 21.7 (q), 17.7 (q), 16.1 (q); υ_{max} (liquid film)/cm^{-1} 2966 (s), 1650 (s), 1445 (s), 1398 (s), 1283 (m), 1228 (m), 887 (m); *m/z* (EI) 303.2547 (M^+, $C_{20}H_{33}NO$ requires 303.2562)

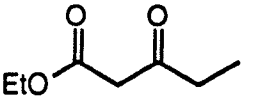
3-(Ethyl carboxy)-4-iminohex-2-one.tin tetrachloride complex (**331**)[129]



331

Tin tetrachloride (13 cm^3, 29 g, 110 mmol) was added dropwise over 20 min at room temperature to a solution of ethyl acetoacetate (26 cm^3, 26 g, 200 mmol) and propanonitrile (14 cm^3, 11 g, 200 mmol) in chlorobenzene (200 cm^3) and left to stir at room temperature for a further 30 min. The solution was warmed to 80°C for 4 h and then allowed to cool to room temperature over 30 min. Hexane (200 cm^3) was added and the precipitated solid was filtered under nitrogen, washed with hexane (50 cm^3) and dried under vacuum (P_2O_5) to leave the *tin complex* (**331**) (43 g, 86 %) as a pale yellow solid. δ_H (400 MHz, DMSO) 8.27 (1H, br, N*H*), 4.12 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 2.38 (2H, q, *J* 7.5 Hz, $C(=NH)CH_2CH_3$), 2.11 (3H, s, $COCH_3$), 1.23 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.11 (3H, t, *J* 7.5 Hz, $C(=NH)CH_2CH_3$); δ_C (100.6 MHz, DMSO) 172.3 (s), 172.3 (s), 169.7 (s), 60.0 (t), 28.2 (t), 14.5 (q), 14.4 (q), 13.8 (q).

Ethyl 3-oxopentanoate (**333**)[129]

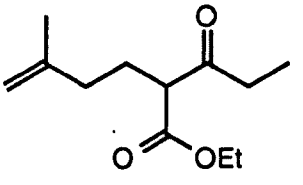


333

A solution of 3-(ethyl carboxy)-4-iminohex-2-one.tin tetrachloride complex (**331**) (45 g, 100 mmol) in chloroform (80 cm^3) was added in one portion at room temperature to 10 % aqueous hydrochloric acid (90 cm^3) and the mixture was stirred vigerously for 2 h at room temperature. Water (80 cm^3) was added and the layers were separated, the acidic aqueous layer was extracted with chloroform (2x100 cm^3) and the organics were combined, dried ($MgSO_4$) and reduced *in vacuo*. The resulting residue was purified by distillation (10 mmHg) to leave the *ketoester* (**333**) (12 g, 83 %) as a colourless oil. b.p. 84°C/10 mmHg; δ_H (400 MHz, $CDCl_3$) 4.20 (2H, q, *J* 7.0

Hz, OCH_2CH_3), 3.45 (2H, s, $COCH_2CO_2$), 2.58 (2H, q, *J* 7.5 Hz, $COCH_2CH_3$), 1.28 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.09 (3H, t, *J* 7.5 Hz, $COCH_2CH_3$); δ_C (100.6 MHz, $CDCl_3$) 203.4 (s), 167.3 (s), 61.3 (t), 49.0 (t), 36.3 (t), 14.1 (q), 7.6 (q); υ_{max} (liquid film)/cm^{-1} 2980 (m), 1743 (s), 1719 (s), 1413 (m), 1314 (m), 1251 (m), 1160 (m), 1026 (m).

5-(Ethyl carboxy)-2-methyloct-1-en-6-one **(332)**

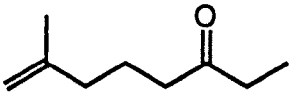


332

Ethyl 3-oxopentanoate (**333**) (7.3 g, 50 mmol) was added dropwise over 10 min to a stirred slurry of sodium hydride (1.9 g, 48 mmol, 60 wt.% in oil) in tetrahydrofuran (50 cm^3) as 0°C and left to stir at 0°C for 30 min. The resulting clear solution was transfered *via* cannula, dropwise over 5 min, to a stirred solution of 1-iodo-3-methylbut-3-ene (4.9 g, 25 mmol) in tetrahydrofuran (50 cm^3) at 0°C. The resulting solution was heated at reflux for 4 hours, cooled to room temperature and water (100 cm^3) was added. The mixture was reduced *in vacuo* and the resulting aqueous layer was extracted with ether (3x100 cm^3) and the combined organics were washed with brine (50 cm^3), dried ($MgSO_4$) and the solvent was removed *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (1:9) as eluant to leave the *ketoester* (**332**) (3.4 g, 87 %) as a colourless mobile oil. δ_H (400 MHz, $CDCl_3$) 4.74 (1H, s, C=C*H*H), 4.68 (1H, s, C=CH*H*), 4.18 (2H, t, *J* 7.1 Hz, OCH_2CH_3), 3.45 (1H, m, $CH_2CH(CO_2Et)CO$), 2.61 (1H, dq, *J* 18.4 Hz and 7.0 Hz, $COCHHCH_3$), 2.49 (1H, dq, *J* 18.4 Hz and 7.0 Hz, $COCHHCH_3$), 2.01 (4H, m, CH_2CH_2), 1.72 (3H, s, $CH_2=C(CH_2)CH_3$), 1.27 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.07

(3H, t, *J* 7.0 Hz, $COCH_2CH_3$); δ_C (100.6 MHz, $CDCl_3$) 205.8 (s), 169.9 (s), 144.3 (s), 111.2 (t). 61.3 (t), 58.0 (d), 35.4 (t), 35.4 (t), 26.0 (t), 22.1 (q), 14.1 (q), 7.7 (q); υ_{max} (liquid film)/cm^{-1} 2977 (m). 2931 (m), 1741 (s), 1718 (s), 1445 (m), 1359 (m), 1255 (m), 1214 (m), 1118 (m), 1032 (m), 891 (w); Found %: C, 67.7; H, 9.7 ($C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5); *m/z* (EI) 194.1305 ($M-H_2O^+$, $C_{12}H_{18}O_2$ requires 194.1307).

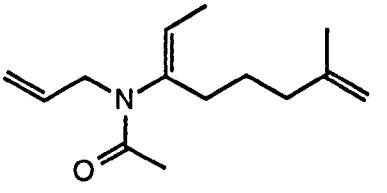
7-Methyloct-7-en-3-one **(334)**



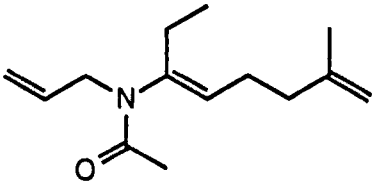
334

A stirred mixture of 5-(ethyl carboxy)-2-methyloct-1-en-6-one (**332**) (1.3 g, 5.9 mmol) and 50% aqueous w/v sodium hydroxide (6 cm^3) were heated at reflux for 4 h and then cooled to room temperature and acidified to pH 1 with hydrochloric acid (2 $moldm^{-3}$). The aqueous mixture was extracted with ether (3x20 cm^3) and the combined organics were dried ($MgSO_4$) and reduced *in vacuo* to leave the *ketone* (**334**) (700 mg, 85 %) as a mobile colourless oil. δ_H (400 MHz, $CDCl_3$) 4.73 (1H, s, C=C*H*H), 4.67 (1H, s, C=CH*H*), 2.42 (4H, m, CH_2COCH_2), 2.01 (2H, t, *J* 7.0 Hz, $CH_2CMe=CH_2$), 1.71 (5H, m, $CH_2=CCH_3$ and $CH_2CH_2CH_2$), 1.05 (3H, t, *J* 7.0 Hz, $COCH_2CH_3$); δ_C (67.8 MHz, $CDCl_3$) 211.7 (s), 145.1 (s), 110.5 (t), 41.6 (t), 37.1 (q), 36.0 (t), 22.2 (q), 21.5 (t), 7.9 (q); υ_{max} (liquid film)/cm^{-1} 2971 (m), 2931 (m), 1718 (s), 1459 (m), 1405 (w), 1373 (m), 1123 (m), 877 (m); *m/z* (EI) 140.1207 (M^+, $C_9H_{16}O$ requires 140.1201).

3-Amino-(N-acetyl, N-prop-2'-en-1'-yl)-7-methyloct-2-ene (335a) and *3-amino-(N-acetyl, N-prop-2'-en-1'-yl)-7-methyloct-3-ene* (335b)



335a



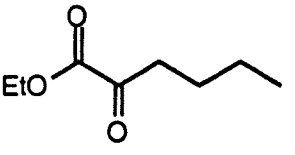
335b

A mixture of 7-methyl-7-en-3-one (**334**) (170 mg, 1.2 mmol) and 1-aminoprop-2-ene (90 μl, 68 mg, 1.2 mmol) in benzene (20 cm^3) with molecular sieves (4Å, activated) was stirred at room temperature for 12 h. Lutidine (120 μl, 190 mg, 1.8 mmol) was added in one portion followed by acetyl chloride (93 μl, 100 mg, 1.3 mmol), added dropwise over 5 min at room temperature. The mixture was left to stir for 2 h, filtered through a pad of celite and the solvent evaporated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:5) as eluant to leave the *enamides* (**335**) (140 mg, 52 %) as an inseperable (3:2) mixture of C-2 and C-3 double bond isomers. Both isomers: δ_H (360 MHz, $CDCl_3$) 5.76 (1H, m, $CH_2CH{=}CH_2$), 5.30 (0.6H, q, *J* 7.1 Hz, $NC{=}CHCH_3$), 5.20 (0.4H, t, *J* 7.4 Hz, $NC{=}CHCH_2$), 5.04 (2H, m, $CH_2CH{=}CH_2$), 4.69 (1H, app. s, C=CHH), 4.63 (1H, app. s, C=CHH), 3.95 (2H, br., NCH_2CH), 2.18 (0.8H, q, *J* 7.4 Hz, $NCCH_2CH_3$), 2.14-2.02 (2.4H, m), 1.98 (3H, s, $NCOCH_3$), 1.66 (3H, s, CCH_3), 1.67-1.62 (1.8H, m), 1.49 (2H, m), 1.20 (0.8H, m), 0.96 (1.2H, m); δ_C (90.6 MHz, $CDCl_3$) 170.1 (s), 170.0 (s), 144.7 (s), 144.4 (s), 140.7 (s), 140.2 (s), 133.6 (d), 133.5 (d), 129.6 (d), 124.9 (d), 117.0 (t), 116.9 (t), 110.6 (t), 110.4 (t), 48.7 (t), 48.5 (t), 37.6 (t), 37.0 (t), 28.7 (t), 25.2 (t), 24.8 (t), 22.3 (t), 22.1 (q), 22.0 (q), 21.9 (q), 21.8 (q), 12.8 (q), 11.7 (q); υ_{max} (liquid film)/cm^{-1} 2934 (m), 1652 (s), 1437

(w), 1388 (s), 1276 (w), 1219 (w), 1071 (w), 982 (w), 920 (w); *m/z* (EI) 221.1781 (M^+, $C_{14}H_{23}NO$ requires 221.1780).

3.4 STABILISED ENAMIDE STUDIES

Ethyl 2-oxohexanoate (**342**)[130]

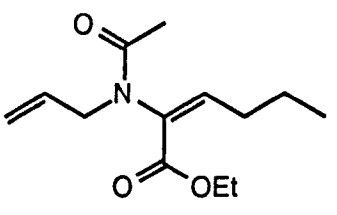


342

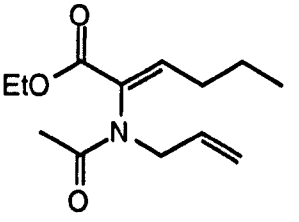
A solution of 1-bromobutane (660 µl, 840 mg, 6.2 mmol) in tetrahydrofuran (4 cm^3) was added dropwise over 15 min to a stirred mixture of magnesium (160 mg, 6.7 mmol) and iodine (1 crystal) in tetrahydrofuran (4 cm^3) maitaining a temperature of 50°C. The solution was then allowed to cool to room temperature over 30 min and transfered *via* cannula, over 20 min, to a stirred solution of diethyl oxalate (1.6 cm^3, 1.8 g, 12.2 mmol) at -78°C. The solution was allowed to come to room temperature over 2 h and then acidified to pH 1 with hydrochloric acid (2 $moldm^{-3}$) and diluted with dichloromethane (10 cm^3) and water (10 cm^3). The layers were separated and the aqueous layer was extracted with dichloromethane (2x10 cm^3), dried ($MgSO_4$) and reduced *in vacuo* to leave a colourless residue which was then purified by chromatography on silica using ether - petroleum (b.p. 40-60°C) (1:9) as eluant to leave the *α-keto ester* (**342**) (420 mg, 44 %) as a colourless mobile oil. δ_H (360 MHz, $CDCl_3$) 4.32 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 2.84 (2H, t, *J* 7.3 Hz, $COCH_2CH_2$), 1.62 (2H, app. quin., *J* 7.5, $CH_2CH_2CH_2$), 1.37 (5H, m, $CH_2CH_2CH_3$), 0.93 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 194.8 (s), 161.3 (s), 62.3 (t), 39.0 (t), 25.0 (t),

22.1 (t), 14.0 (q), 13.7 (q); υ_{max} (liquid film)/cm^{-1} 2961 (s), 2874 (s), 1728 (s), 1466 (m), 1402 (m), 1369 (m), 1275 (s), 1246 (s), 1145 (m), 1121 (s), 1055 (s), 1017 (m), 857 (w), 756 (w), 731 (w), 677 (w).

Ethyl 2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-hex-2(E)-enoate **(343a)** and ***ethyl 2-amino-(N-acetyl, N-prop-2'-en-1'-yl)-hex-2(Z)-enoate*** **(343b)**



343a

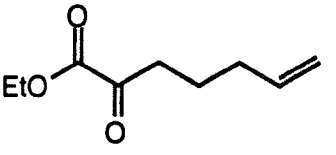


343b

A mixture of ethyl 2-oxohexanoate (**342**) (250 mg, 1.6 mmol), 1-aminoprop-2-ene (120 μl, 90 mg, 1.6 mmol) and molecular sieves (4 Å) in benzene (45 cm^3) was stirred at room temperature overnight and then *N,N*-diethylaniline (350 μl, 350 mg, 2.4 mmol) was added in one portion, followed by acetyl bromide (140 μl, 230 mg, 1.9 mmol) also in one portion. The mixture was stirred at room temperature for a further 2 h and then filtered through celite, reduced *in vacuo* to leave a brown oil which was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (3:7) as eluant to leave the *enamides* (**342**) (300 mg, 77 %) as a colourless mobile oily (3:1) mixture of *E* and *Z* isomers. The mixture was seperated by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (2:8) as eluant to leave a (1:1) mixture of the *E* and *Z* isomers (230 mg, 58 %) eluted first and the E *enamide* (**342a**) (64 mg, 17 %) eluted second. δ_H (360 MHz, $CDCl_3$) 6.17 (1H, t, *J* 7.6 Hz, C=C*H*CH$_2$), 5.77 (1H, m, CH$_2$=C*H*CH$_2$), 5.12 (2H, m, C*H*$_2$=CHCH$_2$), 4.23 (2H, q, *J* 7.2 Hz, CO$_2$C*H*$_2$CH$_3$), 4.05 (2H, d, *J* 6.6 Hz, CH$_2$=CHC*H*$_2$N), 2.61 (2H, app. q, *J* 7.6 Hz, C=CHC*H*$_2$CH$_2$), 1.96 (3H, s, NCOC*H*$_3$), 1.50 (2H, app. hexet, *J* 7.4 Hz,

$CH_2CH_2CH_3$), 1.30 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 0.96 (3H, t, *J* 7.4 Hz, $CH_2CH_2CH_3$); δ_C (90.6 MHz, $CDCl_3$) 170.5 (s), 164.2 (s), 148.9 (d), 133.1 (d), 131.5 (s), 188.2 (t), 61.1 (t), 50.5 (t), 30.4 (t), 22.1 (t), 22.0 (q), 14.1 (q), 13.8 (q); υ_{max} (liquid film)/cm^{-1} 2962 (s), 1722 (s), 1667 (s), 1392 (s), 1192 (s), 1140 (m), 1030 (m), 922 (w); m/z (EI) 239.1522 (M^+, $C_{13}H_{21}NO_3$ requires 239.1521).

Ethyl 2-oxohept-6-enoate **(344)**

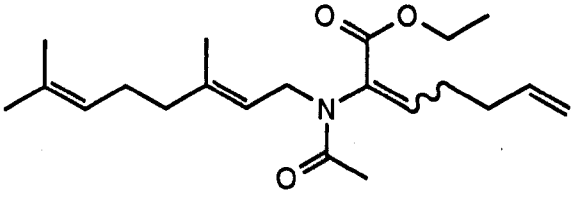


344

A solution of 1-bromopent-4-ene (460 μl, 580 mg, 4.0 mmol) in tetrahydrofuran (4 cm^3) was added over 10 min to a stirred mixture of magnesium (110 mg, 4.4 mmol) and iodine (1 crystal) in tetrahydrofuran (4 cm^3) maintaining a temperature of 50°C. After 10 min the resulting brown solution was transfered *via* cannula to a solution of diethyloxalate (1.1 cm^3, 1.2 g, 8.0 mmol) in tetrahydrofuran (4 cm^3) at -10°C and the resulting solution was allowed to warm to room temperature overnight. The solution was acidified to pH 1 with hydrochloric acid (2 $moldm^{-3}$) and diluted with dichloromethane (10 cm^3) and water (10 cm^3). The layers were separated and the aqueous layer was extracted with dichloromethane (2x10 cm^3), dried ($MgSO_4$) and reduced *in vacuo* to leave a colourless residue which was then purified by chromatography on silica using ether - petroleum (b.p. 40-60°C) (1:9) as eluant to leave a mixture of the α-keto ester and diethyloxalate as a colourless mobile oil. The mixture was separated by bulb to bulb distilation (1.0 mmHg) to give the ***α-keto ester*** **(344)** (250 mg, 37 %) as a colourless mobile oil. δ_H (360 MHz, $CDCl_3$) 5.78 (1H, m, $CH_2CH=CH_2$), 5.01 (2H, m, $CH_2CH=CH_2$), 4.32 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 2.85

(2H, t, *J* 7.2 Hz, O_2CCOCH_2), 2.11 (2H, app. q, *J* 7.4 Hz, CH_2=$CHCH_2$), 1.75 (2H, app. quin., *J* 7.3 Hz, $CH_2CH_2CH_2$), 1.37 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 194.4 (s), 161.1 (s), 137.4 (d), 115.5 (t), 62.3 (t), 38.3 (t), 32.7 (t), 22.0 (t), 13.9 (q); υ_{max} (liquid film)/cm^{-1} 2980 (m), 2938 (m), 1728 (s), 1446 (w), 1401 (w), 1369 (w), 1268 (s), 1185 (s), 1072 (s), 1043 (s), 915 (s), 861 (w); *m/z* (EI) 170.0939 (M^+, $C_9H_{14}O_3$ requires 170.0943).

1-amino-(N-acetyl, N-ethyl hept-2',6'-dienoat-2'-yl)-3,7-dimethyloct-2,6-diene **(345)**

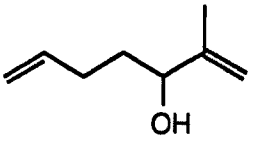


345

A mixture of ethyl 2-oxohept-6-enoate (**344**) (110 mg, 0.65 mmol), geranylamine (**328**) (60 µl, 50 mg, 0.32 mmol) and molecular sieves (4 Å) in benzene (12 cm^3) was stirred at room temperature for 38 h and then diethylanaline (76 µl, 72 mg, 0.48 mmol) was added in one portion, followed by acetyl bromide (26 µl, 43 mg, 0.35 mmol) also in one portion. The mixture was stirred at room temperature for a further 3 h and then filtered through celite, reduced *in vacuo* to leave a brown oil which was purified by chromatography on silica using ethyl acetate - petroleum (b.p. 40-60°C) (3:7) as eluant to leave the *enamide* (**345**) (81 mg, 73 %) as a colourless mobile oily (1:1) mixture of C-2' *E* and *Z* isomers. δ_H (360 MHz, $CDCl_3$) 6.94 (0.5H, t, *J* 7.4, O_2CC=$CHCH_2$), 6.12 (0.5H, t, *J* 7.4, O_2CC=$CHCH_2$), 5.77 (1H, m, CH_2CH=CH_2), 5.03 (4H, m, C=C*H*, C=C*H*, CH_2CH=CH_2), 4.22 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.07 (2H, d, *J* 7.3 Hz, $CHCH_2N$), 2.71 (1H, q, *J* 7.4 Hz, CH_2CH=CCO_2), 2.03 (7H, m, $CHCH_2CH_2CH$=CCO_2, $CHCH_2CH_2C$), 1.92 (1.5H, s, $COCH_3$), 1.1.87 (1.5H, s, $COCH_3$), 1.66 (3H, s, CCH_3), 1.57 (6H, s, $C(CH_3)_2$), 1.28 (3H, t, *J* 7.2 Hz,

OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 170.4 (s), 164.2 (s), 164.1 (s), 147.5 (d), 143.7 (d), 139.9 (s), 137.0 (d), 136.5 (d), 132.6 (s), 131.6 (s), 123.8 (d), 123.7 (d), 118.8 (d), 118.6 (d), 116.1 (t), 115.7 (t), 61.3 (t), 61.0 (t), 44.6 (t), 44.4 (t), 39.6 (t), 39.5 (t), 32.6 (t), 32.8 (t), 27.6 (t), 27.5 (t), 26.4 (t), 26.3 (t), 25.6 (q), 22.1 (q), 21.5 (q), 17.6 (q), 16.1 (q), 14.2 (q), 14.1 (q); υ_{max} (liquid film)/cm^{-1} 2977 (m), 2925 (s), 2855 (w), 1720 (s), 1668 (s), 1444 (m), 1386 (s), 1265 (s), 1202 (s), 1094 (w), 1042 (w), 993 (w), 914 (w); m/z (EI) 347.2455 (M^+, $C_{21}H_{33}NO_3$ requires 347.2460).

2-Methylhepta-1,6-dien-3-ol **(347)**[117]

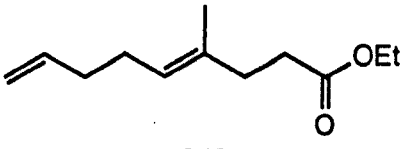


347

A solution of 1-bromobut-3-ene (4.5 cm^3, 6.0 g, 44 mmol) in ether (30 cm^3) was added dropwise over 20 min, whilst maintaining a steady reflux, to a mixture of magnesium turnings (1.3 g, 53 mmol) and iodine (1 crystal) in ether (10 cm^3). The resulting solution was left to cool to room temperature and then a solution of 2-methylprop-2-enal (3.9 cm^3, 3.3 g, 47 mmol) in ether (40 cm^3) was added dropwise over 45 min, whilst maintaining a steady reflux. The mixture was then refluxed for a further 2 h, cooled to room temperature and hydrochloric acid (80 cm^3, 2 $moldm^{-3}$) was added. The layers were separated and the aqueous was extracted with ether (2x80 cm^3), the organics were combined and washed with saturated sodium hydrogen carbonate (60 cm^3) and brine (40 cm^3), dried ($NaSO_4$) and reduced *in vacuo* to leave an oily residue. The residue was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:12) as eluant, to leave the *allylic alcohol* (**347**) (3.2 g, 60 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 5.84 (1H, m, $CH_2CH{=}CH_2$), 5.07-4.85 (4H, m, $C{=}CH_2$ and $CH{=}CH_2$), 4.09 (1H, t, *J* 6.5 Hz, $CCH(OH)CH_2$), 2.12

(2H, m, CH_2CH_2CH), 1.73 (3H, s, CCH_3), 1.65 (2H, m, $CH(OH)CH_2CH_2$); δ_C (90.6 MHz, $CDCl_3$) 147.4 (s), 138.3 (d), 114.8 (t), 111.1 (t), 75.3 (d), 34.0 (t), 29.8 (t), 17.5 (q); υ_{max} (liquid film)/cm^{-1} 3382 (s), 3076 (s), 2976 (s), 2940 (s), 1642 (m), 1447 (m), 1374 (m), 1304 (w), 1119 (w), 1062 (m), 905 (s).

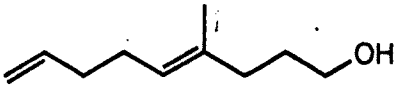
Ethyl 4-methylnona-4,8-dienoate **(349)**[117]



349

A stirred solution of 2-methylhepta-1,6-dien-3-ol (**347**) (3.2 g, 25 mmol) and propanoic acid (4 drops) in triethyl orthoacetate (46 cm^3) was heated to 140°C for 4 h. The solution was reduced *in vacuo* at 60°C to leave an oil which was purified by distillation (0.25 mmHg) to leave the E *diene* (**349**) (4.4 g, 90%) as a colourless oil. b.p. 54-55°C/0.25 mmHg; δ_H (360 MHz, $CDCl_3$) 5.82 (1H, m, $CH_2CH=CH_2$), 5.17 (1H, m, $C=CHCH_2$), 4.97 (2H, m, $CH=CH_2$), 4.12 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 2.39 (4H, m, $O_2CCH_2CH_2C$), 2.08 (4H, m, $CHCH_2CH_2CH$), 1.62 (3H, s, CCH_3), 1.26 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 173.2 (s), 138.3 (d), 133.6 (s), 124.4 (d), 114.4 (t), 60.0 (t), 34.5 (t), 33.7 (t), 33.1 (t), 27.2 (t), 15.8 (q), 14.1 (q); υ_{max} (liquid film)/cm^{-1} 3076 (w), 2978 (s), 2922 (m), 1737 (s), 1640 (w), 1445 (w), 1371 (w), 1343 (w), 1293 (w), 1251 (m), 1157 (s), 1096 (w), 1042 (m), 911 (m), 857 (w).

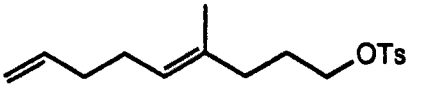
4-Methylnona-4,8-dien-1-ol (348)[117]



348

A solution of ethyl 4-methylnona-4,8-dienoate (**349**) (4.3 g, 22 mmol) in tetrahydrofuran (140 cm^3) was transferred *via* cannula to a stirred slurry of lithium aluminium hydride (2.1 g, 55 mmol) in tetrahydrofuran (45 cm^3) at room temperature. The resulting mixture was left to stir at room temperature for 12 h, then water (2.5 cm^3), a 10% w/v solution of sodium hydroxide (5.1 cm^3) and then water (7.7 cm^3) were added. The resulting thick suspension was filtered and the solid was washed with ether (100 cm^3). The washings were combined and reduced *in vacuo* to leave an oil which was then purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:4) as eluant, to give the E-*hydroxydiene* (**348**) (2.9 g, 85 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 5.82 (1H, m, CH_2CH=CH_2), 5.17 (1H, m, C=$CHCH_2$), 4.96 (2H, m, CH=CH_2), 3.62 (2H, t, *J* 6.6 Hz, CH_2CH_2OH), 2.07 (6H, m, $CH_2C(Me)$=$CHCH_2CH_2CH$), 1.66 (2H, app. quin., *J* 6.6 Hz, $CH_2CH_2CH_2$), 1.61 (3H, s, CCH_3); δ_C (90.6 MHz, $CDCl_3$) 138.6 (d), 135.0 (s), 124.2 (d), 114.4 (t), 62.6 (t), 35.8 (t), 33.9 (t), 30.5 (t), 27.3 (t), 15.8 (q); υ_{max} (liquid film)/cm^{-1} 3343 (b), 3076 (m), 2936 (s), 1712 (m), 1640 (m), 1441 (m), 1383 (m), 1269 (m), 1166 (w), 1059 (m), 1013 (m), 910 (s).

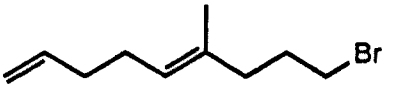
*4-Methyl-1-*para*-toluenesulfonyloxynona-4,8-diene* (**350a**)



350a

para-Toluenesulfonyl chloride (2.5 g, 13 mmol) was added in one portion to a stirred solution of 4-methylnona-4,8-dien-1-ol (**348**) (1.8 g, 12 mmol) in pyridine (20 cm^3) at 0°C and the resulting solution was then allowed to warm to room temperature over 2 h. The mixture was diluted with ether (30 cm^3) and then washed with water (20 cm^3), saturated aqueous copper (II) sulfate (50 cm^3), water (20 cm^3) andbrine (10 cm^3). The organic layer was dried (Na_2SO_4), reduced *in vacuo* and the residue was then purified by chromatography on silica, using ether - petroleum (b.p. 40-60°C) (1:9) as eluant, to give the E-*tosylated diene* (**350a**) (2.9 g, 80 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 7.81 (2H, Ar-*H*), 7.35 (2H, Ar-*H*), 5.79 (1H, m, CH_2CH=CH_2), 5.02 (3H, m, C=C*H*CH_2 and CH=CH_2), 4.00 (2H, t, *J* 6.6 Hz, TsOCH_2CH_2), 2.46 (3H, s, Ar-CH_3), 2.04 (6H, m, CH_2C(Me)=CHCH_2CH_2CH), 1.74 (2H, app. quin., *J* 6.6 Hz, $CH_2CH_2CH_2$), 1.54 (3H, s, CCH_3); δ_C (90.6 MHz, $CDCl_3$) 144.6 (Ar-s), 138.4 (d), 133.3 (s), 133.2 (Ar-s), 129.8 (Ar-d), 127.8 (Ar-d), 125.1 (d), 114.5 (t), 70.1 (t), 35.0 (t), 33.7 (t), 27.3 (t), 26.9 (t), 21.6 (q), 15.7 (q); υ_{max} (liquid film)/cm^{-1} 3072 (w), 2921 (s), 2852 (m), 1921 (w), 1732 (w), 1639 (m), 1598 (m), 1494 (w), 1447 (m), 1362 (s), 1306 (w), 1291 (w), 1210 (w), 1188 (s), 1098 (s), 1019 (m), 967 (s), 925 (s), 832 (s), 815 (s), 792 (w), 734 (s), 644 (s); Found %: C, 66.0; H, 7.8 ($C_{17}H_{24}O_3S$ requires C, 66.2; H, 7.8); m/z (FAB) 309.1506 ($M+H^+$, $C_{17}H_{25}O_3S$ requires 309.1524).

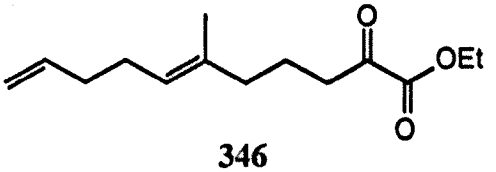
9-Bromo-6-methylnona-1,5-diene **(350b)**



350b

Lithium bromide (2.8 g, 33 mmol) was added in one portion to a stirred solution of 4-methyl-1-*para*-toluenesulfonyloxynona-4,8-diene (**350a**) (2.9 g, 9.3 mmol) in acetone (25 cm^3) at room temperature. The mixture was then heated at reflux for 4 h then cooled to room temperature and partitioned between ether (250 cm^3) and water (150 cm^3). The layers were then separated and the aqueous layer was washed with ether (250 cm^3), the combined organics were dried (Na_2SO_4) and reduced *in vacuo* to leave an oily residue. The residue was then purified by chromatography on silica, using pentane as eluant, to give the E-*bromo diene* (**350b**) (1.8 g, 91 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 5.82 (1H, m, $CH_2CH{=}CH_2$), 5.20 (1H, m, $C{=}CHCH_2$), 4.98 (2H, m, $CH{=}CH_2$), 3.38 (2H, t, *J* 7.1 Hz, $BrCH_2CH_3$), 2.11 (6H, m, $CH_2C(Me){=}CHCH_2CH_2CH$), 1.95 (2H, app. quin., *J* 7.1 Hz, $CH_2CH_2CH_2$), 1.61 (3H, s, CCH_3); δ_C (90.6 MHz, $CDCl_3$) 138.4 (d), 133.3 (s), 125.2 (d), 114.5 (t), 37.7 (t), 33.8 (t), 33.2 (t), 30.8 (t), 27.3 (t), 15.8 (q); υ_{max} (liquid film)/cm^{-1} 3073 (m), 2924 (s), 2359 (s), 2340 (m), 1638 (m), 1437 (m), 1382 (w), 1245 (m), 993 (m), 912 (s); Found %: C, 55.5; H, 8.1; Br, 36.9 ($C_{10}H_{17}Br$ requires C, 55.3; H, 7.9; Br, 36.8); m/z (EI) 216.0513 (M^+, $C_{10}H_{17}Br$ requires 216.0514).

Ethyl 6-methyl-2-oxoundeca-6,10-dienoate **(346)**

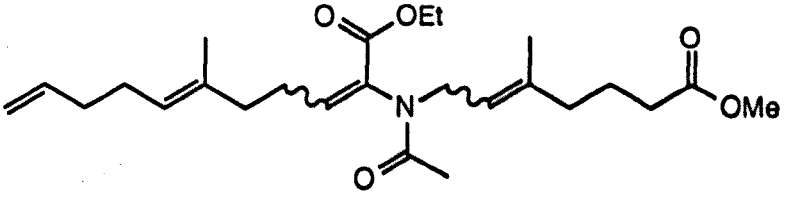


346

A solution of 1-bromo-4-methylnona-4,8-diene (**350**) (600 mg, 2.8 mmol) in tetrahydrofuran (2 cm^3) was added dropwise over 10 min, maintaining a temperature of 40°C, to a stirred mixture of magnesium (74 mg) and iodine (1 crystal) in tetrahydrofuran (2 cm^3). The mixture was left to cool to room temperature over 10 min and then transfered *via* cannula over 10 min to a stirred solution of diethyl

oxalate (750 µl, 810 mg, 5.5 mmol) in tetrahydrofuran (2 cm^3) at 0°C. The mixture was left to warm to room temperature over 4 h, acidified to pH 1 with hydrochloric acid (2 cm^3, 2 $moldm^{-3}$) and diluted with water (5 cm^3). The mixture was extracted with dichloromethane (3x10 cm^3) and the combined organics dried ($MgSO_4$) and reduced *in vacuo* to leave a colourless oil. The residue was then purified by chromatography on silica, using ethyl acetate-petroleum (b.p. 40-60°C) (1:19) as eluant, to leave the *α-ketoester* (**346**) (330 mg, 52 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$) 5.81 (1H, m, $CH_2CH{=}CH_2$), 5.14 (1H, m, $C{=}CHCH_2$), 4.98 (2H, m, $CH{=}CH_2$), 4.31 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 2.79 (2H, t, *J* 7.1 Hz, CH_2COCO_2), 2.09 (4H, m, $CHCH_2CH_2CH$), 2.03 (2H, t, *J* 7.1 Hz, $CH_2C(Me)$), 1.78 (2H, app. quin., *J* 7.1 Hz, $CH_2CH_2CH_2$), 1.59 (3H, s, CCH_3), 1.37 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 194.4 (s), 161.0 (s), 138.3 (d), 134.0 (s), 125.0 (d), 114.3 (t), 62.1 (t), 38.5 (t), 38.2 (t), 33.7 (t), 27.2 (t), 20.8 (t), 15.5 (q), 13.8 (q); υ_{max} (liquid film)/cm^{-1} 3076 (w), 2933 (s), 1730 (s), 1640 (w), 1446 (m), 1370 (w), 1267 (m), 1076 (m), 1044 (m), 912 (m); m/z (EI) 220.1451 ($M\text{-}H_2O^+$, $C_{14}H_{20}O_2$ requires 220.1463).

Ethyl 2-amino-(N-acetyl, N-methyl 5'-methylhept-5'-en-7'yloate)-6-methylundeca-2,6,10-trienoate (**351**)



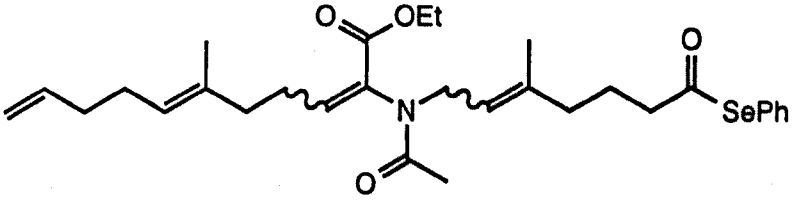
351

Triflouroacetic acid (430 µl, 630 mg, 5.5 mmol) was added in one portion to stirred methyl 7-amino-(*N-tert*-butylcarboxylate)-5-methylhept-5-enoate (**274b**) (150 mg,

0.55 mmol) at room temperature and the oil was left to stir for 5 min. Toluene (10 cm^3) was added and the solution was reduced *in vacuo* to leave a colourless oil. Triethylamine (77 μl, 56 mg, 0.55 mmol) was added in one portion to a stirred solution of the oil in benzene (15 cm^3) and stirred at room temperature for 5 min. Molecular sieves (4 Å, activated) were added to the solution, followed by ethyl 6-methyl-2-oxoundeca-6,10-dienoate (**346**) (140 mg, 0.61 mmol) and left to stir at room temperature for 12 h. *N,N*-Diethylaniline (130 μl, 120 mg, 0.83 mmol) was added in one portion to the stirred mixture at room temperature and then acetyl bromide (49 μl, 83 mg, 0.66 mmol) was added in one portion and the mixture was left to stir at room temperature for 2 h. The mixture was filtered through a pad of celite, washed with ethyl acetate (50 cm^3) and the solvent removed *in vacuo* to leave a yellow oil. The oil was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:2) as eluant, to give the *enamide* (**351**) (130 mg, 54 %) as a colourless oily mixture of 2 and 5' *E:Z* isomers. All isomers: δ_H (360 MHz, $CDCl_3$) 6.95 (0.5H, t, *J* 7.5 Hz, $C(CO_2Et)=CHCH_2$), 6.13 (0.5H, t, *J* 7.5 Hz, $C(CO_2Et)=CHCH_2$), 5.81 (1H, m, $CH_2CH=CH_2$), 5.17 (2H, m, $C(Me)=CHCH_2$ and $C(Me)=CHCH_2$), 4.99 (2H, m, $CH_2CH=CH_2$), 4.24 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.07 (2H, d, *J* 7.4 Hz, $C=CHCH_2N$), 3.67 (3H, s, CO_2CH_3), 2.74 (1H, apparent q, *J* 7.6 Hz, $C(CO_2Et)=CHCH_2$), 2.27 (3H, m, $C(CO_2Et)=CHCH_2CH_2$ and MeO_2CCH_2), 2.19-1.95 (8H, m, $CH_2C(Me)=CH$ and $CH_2C(Me)=CHCH_2CH_2CH$), 2.09 (3H, s, $NCOCH_3$), 1.70 (2H, m, $CH_2CH_2CH_2$), 1.62 (6H, m, $C(CH_3)=CH$ and $C(CH_3)=CH$), 1.31 (3H, T, *J* 7.1 HZ, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 173.8 (s), 170.5 (s), 164.2 (s), 148.1 (d), 144.3 (d), 138.8 (s), 138.4 (d), 133.9 (s), 133.4 (s), 131.4 (s), 125.4 (d), 125.1 (d), 120.6 (d), 119.8 (d), 114.6 (t), 61.4 (t), 61.1 (t), 51.5 (q), 44.7 (t), 44.5 (t), 44.2 (t), 38.9 (t), 38.4 (t), 37.6 (t), 33.8 (t), 33.5 (t), 30.9 (t), 29.7 (t), 27.3 (t), 27.0 (t), 26.7 (t), 23.3 (t), 23.2 (t), 23.1 (t), 22.8 (t), 22.0 (q), 21.5 (q), 15.9 (q), 15.8 (q), 14.2 (q); υ_{max} (liquid film)/cm^{-1} 2931 (s), 1721 (s), 1666 (s), 1435 (s), 1392 (s), 1251 (s),

1197 (s), 1096 (m), 1032 (m), 912 (w), 864 (w), 781 (w); m/z (EI) 433.2820 (M^+, $C_{25}H_{39}NO_5$ requires 433.2828).

Ethyl 2-amino-(N-acetyl, N-phenyl 5'-methylhept-5'-en-7'-ylselenoate)-6-methylundeca-2,6,10-trienoate **(338)**



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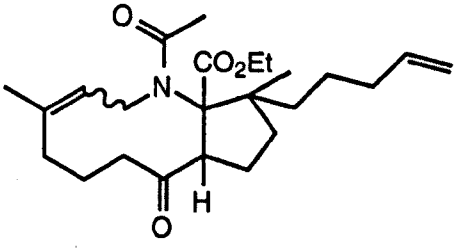
A solution of lithium hydroxide (18 mg, 0.44 mmol) in water (4 cm^3) was added in one portion to a stirred solution of ethyl 2-amino-(*N*-acetyl, *N*-methyl 5'-methylhept-5'-en-7'-yloate)-6-methylundeca-2,6,10-trienoate (**351**) (130 mg, 0.29 mmol) in tetrahydrofuran (4 cm^3) at room temperature. The resulting mixture was stirred at room temperature for 2 h, the solution was acidified to pH 1 with hydrochloric acid (10 drops, 2.0 $moldm^{-3}$) and then extracted with dichloromethane (3x30 cm^3). The combined organic extracts were dried (Na_2SO_4) and then the solvent was removed *in vacuo* to leave a colourless oil.

Tributylphosphine (110 μl, 89 mg, 0.44 mmol) was added in one portion to a stirred solution of the oil in dichloromethane (2 cm^3) and the solution was left stirring at -30°C for 5 min. *N*-Phenylselenophthalimide (130 mg, 0.44 mmol) was then added in one portion to the mixture solution at -30°C and left to stir for 5 min. Water (2 cm^3) and brine (2 cm^3) were added in one portion and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with dichloromethane (3x30 cm^3) and the combined organics were dried (Na_2SO_4) and reduced *in vacuo*. The resulting pale yellow semi solid was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (1:2) as

eluant, to leave a yellow oil which was titurated with pentane to give the *selenyl ester* (**338**) (100 mg, 63 %) as a pale yellow oily mixture of 2 and 5' *E*:*Z* isomers. All isomers: δ_H (360 MHz, $CDCl_3$) 7.51 (2H, m, Ar-*H*), 7.38 (3H, m, Ar-*H*), 6.95 (0.5H, t, *J* 7.5 Hz, $C(CO_2Et)=CHCH_2$), 6.13 (0.5H, t, *J* 7.5 Hz, $C(CO_2Et)=CHCH_2$), 5.80 (1H, m, $CH_2CH=CH_2$), 5.17 (2H, m, $C(Me)=CHCH_2$ and $C(Me)=CHCH_2$), 4.97 (2H, m, $CH_2CH=CH_2$), 4.23 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.07 (2H, d, *J* 7.4 Hz, $C=CHCH_2N$), 2.74 (1H, apparent q, *J* 7.6 Hz, $C(CO_2Et)=CHCH_2$), 2.66 (2H, m, $CH_2COSePh$), 2.27 (1H, m, $C(CO_2Et)=CHCH_2$), 2.19-1.95 (9H, m, $NCOCH_3$ and $CH_2C(Me)=CHCH_2CH_2CH$), 1.94 (2H, m, $CH_2C(Me)=CH$), 1.78 (2H, m, $CH_2CH_2CH_2$), 1.61 (6H, m, $C(CH_3)=CH$ and $C(CH_3)=CH$), 1.30 (3H, t, *J* 7.1 HZ, OCH_2CH_3); δ_C (90.6 MHz, $CDCl_3$) 200.0 (s), 170.5 (s), 164.2 (s), 148.0 (d), 144.3 (d), 138.4 (d), 135.7 (d), 134.1 (d), 133.9 (s), 133.4 (s), 131.4 (s), 129.3 (d), 128.8 (d), 126.3 (s), 125.4 (d), 123.4 (d), 121.0 (d), 120.1 (d), 114.6 (t), 61.4 (t), 61.0 (t), 46.9 (d), 44.7 (t), 44.6 (t), 44.2 (t), 38.5 (t), 38.3 (t), 37.6 (t), 33.7 (t), 30.6 (t), 29.6 (t), 27.3 (t), 26.9 (t), 26.8 (t), 26.7 (t), 23.4 (t), 23.2 (t), 23.1 (t), 23.1 (q), 22.0 (q), 21.5 (q), 15.9 (q), 15.8 (q), 15.7 (q), 14.2 (q); υ_{max} (liquid film)/cm^{-1} 2926 (m), 1722 (s), 1667 (s), 1439 (s), 1398 (s), 1266 (m), 1195 (s), 1096 (w), 1022 (w), 914 (w); *m/z* (FAB) 560.2274 ($M+H^+$, $C_{30}H_{42}NO_4{}^{80}Se$ requires 560.2279), 558.2271 ($M+H^+$, $C_{30}H_{42}NO_4{}^{78}Se$ requires 558.2287).

Ethyl 4-acetyl-3,7-dimethyl-11-oxo-3-pent-4-enyl-1,2,3,4,5,8,9,10,11,11a-decahydro-4-aza-cyclopentacyclodecene-3a-carboanoate **(354)**



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A solution of tributyltin hydride (76 μl, 82 mg, 0.28 mmol) and AIBN (5 mg) in degassed benzene (5 cm^3) was added dropwise over 8 h to a refluxing solution of the selenyl ester (**338**) (126 mg, 0.23 mmol) and AIBN (5 mg) in benzene (67 cm^3). The solution was refluxed for a further 4 h, allowed to cool to room temperature and reduced *in vacuo* to leave an oily residue. The residue was purified by chromatography on silica, using ethyl acetate - petroleum (b.p. 40-60°C) (3:7) to ethyl acetate - petroleum (b.p. 40-60°C) (7:3) as eluant, to the *bicyclic compound* (**354**) (34 mg, 35 %) as a colourless oil. δ_H (360 MHz, $CDCl_3$, 328 K) 5.83 (1H, m, $CH_2CH{=}CH_2$), 5.14 (1H, m, $C{=}CHCH_2$), 4.98 (2H, m, $CH_2CH{=}CH_2$), 4.20 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 3.85 (1H, app. t, *J* 10.1 Hz, $COCHCHH$), 3.70 (1H, app. t, *J* 10.1 Hz, $COCHCHH$), 2.91 (1H, t, *J* 10.1 Hz, $COCH$), 2.48 (2H, m, $COCHH$, CHH), 2.34 (1H, m, $COCHH$), 2.08 (3H, s, $NCOCH_3$), 2.09-1.87 (10H, m, CH_2N, CH_2, CH_2, CHH, CHH, CH_2), 1.58 (3H, s, CH_3), 1.44-1.30 (2H, m, CHH, CHH), 1.28 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.20 (3H, s, CH_3), 1.10 (1H, m, CHH); δ_C (90.6 MHz, $CDCl_3$) 209.6 (s), 170.0 (s), 168.9 (s), 138.7 (d), 134.7 (s), 124.4 (d), 114.4 (t), 76.3 (s), 61.0 (t), 58.1 (d), 51.3 (s), 49.8 (t), 40.0 (t), 37.2 (t), 33.9 (t), 31.5 (q), 29.9 (t), 27.4 (t), 24.3 (t), 23.4 (q), 22.3 (t), 18.7 (q), 15.9 (q), 14.2 (q); *m/z* (EI) 403.2735 ($M+H^+$, $C_{24}H_{37}NO_4$ requires 403.2723).

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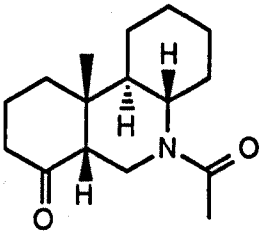
5. APPENDIX

5.1 CRYSTAL DATA

The following eight pages contain the crystallographic data from the X-ray study on the tricyclic compound **291.**

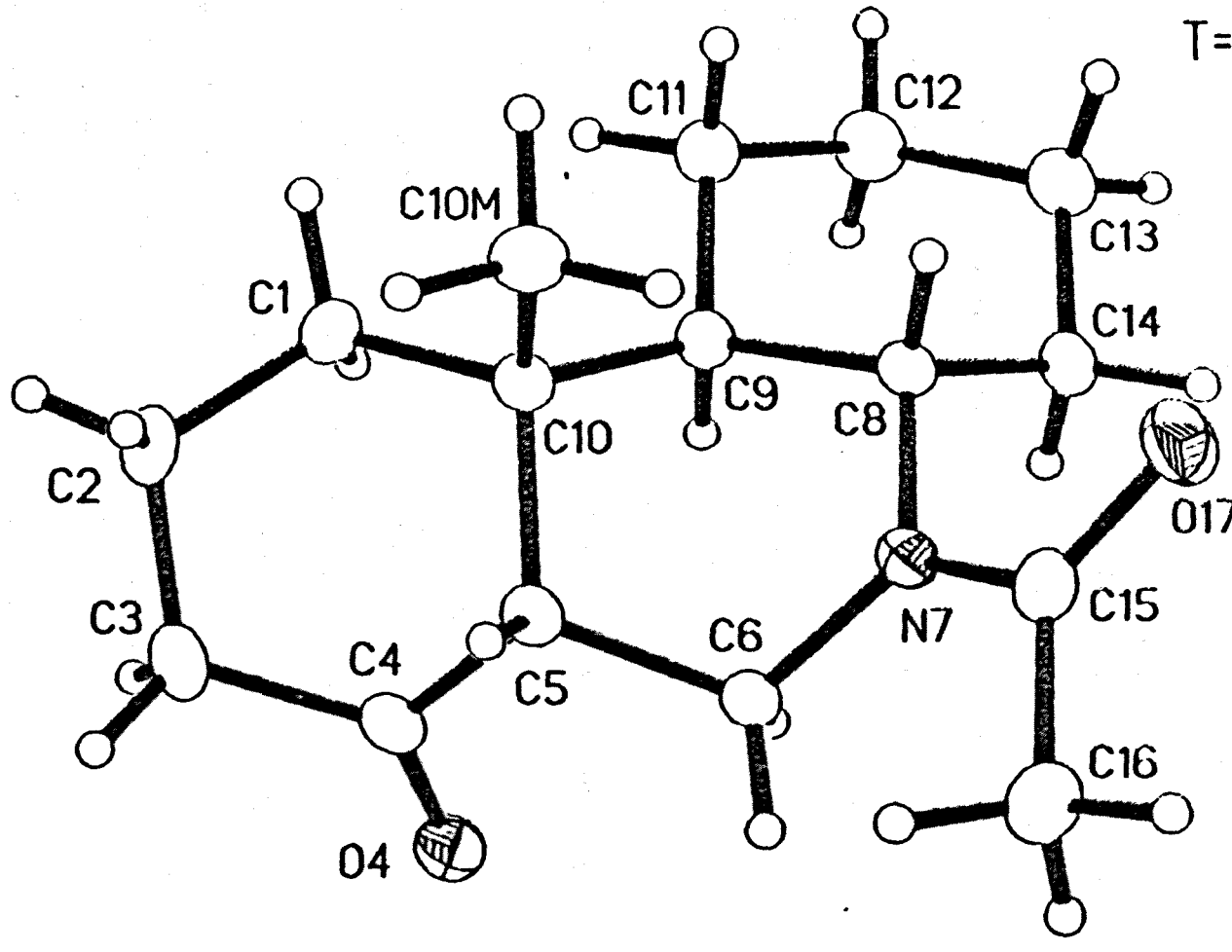


291

TRINCO #458

for PJD/GP

T=150K, 50%



File: trinco.pl1

Table 1. Crystal data and structure refinement for TRINCO at 150.0(2)K.

Empirical formula	C16 H25 N O2
Formula weight	263.37
Crystal description	colourless block
Crystal size	0.60 x 0.50 x 0.40 mm
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 5.884(2) A alpha = 77.23(3) deg. b = 9.265(3) A beta = 83.17(4) deg. c = 13.687(6) A gamma = 76.63(3) deg.
Volume	706.2(5) A^3
Reflections for cell refinement	40
Range in theta	14 to 16 deg.
Z	2
Density (calculated)	1.239 Mg/m^3
Absorption coefficient	0.080 mm^-1
F(000)	288
Diffractometer type	Stoe Stadi-4 four-circle
Wavelength	0.71073 A
Scan type	omega/theta
Reflections collected	2464
Theta range for data collection	2.50 to 24.98 deg.
Index ranges	-6<=h<=6, -10<=k<=10, 0<=l<=16
Independent reflections	2464
Observed reflections	2071 [I>2sigma(I)]
Decay correction	variation +/-2.3%
Structure solution by	direct methods
Hydrogen atom location	in calculated positions
Hydrogen atom treatment	riding model
Data / restraints / parameters	2464/0/174 (least-squares on F^2)
Final R indices [I>2sigma(I)]	R1 = 0.0438, wR2 = 0.0951
Final R indices (all data)	R1 = 0.0563, wR2 = 0.1062
Goodness-of-fit on F^2	1.153

Extinction coefficient	0.024(4)
Final maximum delta/sigma	0.001

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.035P)^2^+0.446P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole	0.28 and -0.21 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for TRINCO. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C1	-3687(3)	11361(2)	1710(1)	23(1)
C2	-4270(4)	12651(2)	2288(2)	28(1)
C3	-5783(3)	12215(2)	3244(2)	27(1)
C4	-5199(3)	10545(2)	3678(1)	20(1)
O4	-6642(2)	9904(1)	4192(1)	26(1)
C5	-2722(3)	9721(2)	3439(1)	19(1)
C6	-2376(3)	8042(2)	3944(1)	20(1)
N7	-309(2)	7149(2)	3489(1)	19(1)
C8	-412(3)	7134(2)	2425(1)	19(1)
C9	-2234(3)	8497(2)	1946(1)	18(1)
C10	-2033(3)	9957(2)	2271(1)	18(1)
C10M	473(3)	10206(2)	2069(1)	24(1)
C11	-2047(3)	8554(2)	814(1)	24(1)
C12	-2476(4)	7090(2)	604(2)	29(1)
C13	-812(4)	5698(2)	1141(1)	29(1)
C14	-914(3)	5666(2)	2262(1)	24(1)
C15	1688(3)	6471(2)	3946(1)	20(1)
C16	1760(3)	6528(2)	5035(1)	26(1)
O17	3402(2)	5804(2)	3490(1)	29(1)

Table 3. Bond lengths [A], angles and torsions [deg] for TRINCO.

C1-C2	1.528(3)
C1-C10	1.543(2)
C2-C3	1.524(3)
C3-C4	1.504(3)
C4-O4	1.215(2)
C4-C5	1.515(2)
C5-C6	1.533(2)
C5-C10	1.581(2)
C6-N7	1.461(2)
N7-C15	1.352(2)
N7-C8	1.468(2)
C8-C14	1.524(2)
C8-C9	1.533(2)
C9-C11	1.530(2)
C9-C10	1.547(2)
C10-C10M	1.529(2)
C11-C12	1.528(3)
C12-C13	1.526(3)
C13-C14	1.523(3)
C15-O17	1.233(2)
C15-C16	1.508(3)
C2-C1-C10	111.73(15)
C3-C2-C1	109.63(15)
C4-C3-C2	112.37(15)
O4-C4-C3	121.44(17)
O4-C4-C5	122.35(16)
C3-C4-C5	116.21(16)
C4-C5-C6	110.30(15)
C4-C5-C10	112.32(14)
C6-C5-C10	112.30(14)
N7-C6-C5	110.96(14)
C15-N7-C6	125.04(15)
C15-N7-C8	119.49(14)
C6-N7-C8	115.23(14)
N7-C8-C14	113.00(14)
N7-C8-C9	110.11(14)
C14-C8-C9	110.48(15)
C11-C9-C8	108.19(14)
C11-C9-C10	116.14(14)
C8-C9-C10	111.02(14)
C10M-C10-C1	108.56(15)
C10M-C10-C9	110.95(14)
C1-C10-C9	111.37(14)
C10M-C10-C5	109.30(14)
C1-C10-C5	110.18(14)
C9-C10-C5	106.46(14)
C12-C11-C9	110.30(15)
C13-C12-C11	111.80(16)
C14-C13-C12	111.42(16)
C13-C14-C8	109.53(15)
O17-C15-N7	120.93(16)
O17-C15-C16	120.69(16)
N7-C15-C16	118.37(16)
C10-C1-C2-C3	-68.4(2)
C1-C2-C3-C4	33.0(2)
C2-C3-C4-O4	-153.68(18)
C2-C3-C4-C5	26.5(2)

O4-C4-C5-C6	-0.8(2)
C3-C4-C5-C6	179.04(15)
O4-C4-C5-C10	125.34(18)
C3-C4-C5-C10	-54.9(2)
C4-C5-C6-N7	162.53(14)
C10-C5-C6-N7	36.4(2)
C5-C6-N7-C15	111.18(18)
C5-C6-N7-C8	-63.09(19)
C15-N7-C8-C14	82.1(2)
C6-N7-C8-C14	-103.29(17)
C15-N7-C8-C9	-153.84(15)
C6-N7-C8-C9	20.8(2)
N7-C8-C9-C11	172.44(14)
C14-C8-C9-C11	-62.06(18)
N7-C8-C9-C10	43.89(19)
C14-C8-C9-C10	169.40(14)
C2-C1-C10-C10M	-80.68(18)
C2-C1-C10-C9	156.88(15)
C2-C1-C10-C5	39.0(2)
C11-C9-C10-C10M	-70.99(19)
C8-C9-C10-C10M	53.15(19)
C11-C9-C10-C1	50.1(2)
C8-C9-C10-C1	174.20(14)
C11-C9-C10-C5	170.19(14)
C8-C9-C10-C5	-65.67(17)
C4-C5-C10-C10M	138.49(15)
C6-C5-C10-C10M	-96.49(17)
C4-C5-C10-C1	19.29(19)
C6-C5-C10-C1	144.30(15)
C4-C5-C10-C9	-101.61(16)
C6-C5-C10-C9	23.41(18)
C8-C9-C11-C12	59.06(19)
C10-C9-C11-C12	-175.35(15)
C9-C11-C12-C13	-55.9(2)
C11-C12-C13-C14	54.0(2)
C12-C13-C14-C8	-55.5(2)
N7-C8-C14-C13	-175.84(15)
C9-C8-C14-C13	60.30(19)
C6-N7-C15-O17	-176.05(16)
C8-N7-C15-O17	-2.0(2)
C6-N7-C15-C16	4.9(3)
C8-N7-C15-C16	178.91(15)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for TRINCO. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

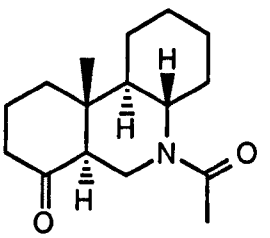
	U11	U22	U33	U23	U13	U12
C1	26(1)	18(1)	22(1)	-1(1)	-1(1)	-4(1)
C2	35(1)	15(1)	31(1)	-3(1)	-1(1)	-4(1)
C3	30(1)	18(1)	31(1)	-9(1)	-1(1)	-1(1)
C4	25(1)	20(1)	18(1)	-8(1)	-1(1)	-4(1)
O4	24(1)	26(1)	26(1)	-6(1)	4(1)	-4(1)
C5	20(1)	19(1)	18(1)	-5(1)	-2(1)	-3(1)
C6	21(1)	18(1)	16(1)	-3(1)	2(1)	1(1)
N7	20(1)	20(1)	16(1)	-4(1)	0(1)	1(1)
C8	19(1)	19(1)	16(1)	-4(1)	1(1)	0(1)
C9	19(1)	17(1)	18(1)	-4(1)	-1(1)	-2(1)
C10	20(1)	18(1)	17(1)	-4(1)	1(1)	-4(1)
C10M	24(1)	26(1)	23(1)	-5(1)	1(1)	-8(1)
C11	29(1)	23(1)	18(1)	-4(1)	-4(1)	-1(1)
C12	38(1)	29(1)	23(1)	-10(1)	-6(1)	-5(1)
C13	42(1)	23(1)	25(1)	-11(1)	1(1)	-5(1)
C14	32(1)	16(1)	23(1)	-5(1)	1(1)	0(1)
C15	22(1)	15(1)	22(1)	-2(1)	-2(1)	-3(1)
C16	29(1)	23(1)	24(1)	-2(1)	-7(1)	-3(1)
O17	22(1)	30(1)	30(1)	-8(1)	-3(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for TRINCO.

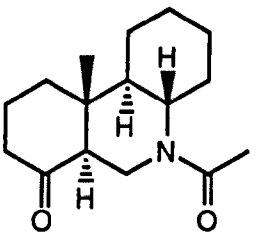
	x	y	z	U(eq)
H1A	-2936	11712	1040	27
H1B	-5154	11080	1610	27
H2A	-2806	12857	2461	33
H2B	-5118	13582	1863	33
H3A	-5561	12778	3749	32
H3B	-7451	12516	3093	32
H5	-1646	10167	3740	22
H6A	-2195	7928	4669	24
H6B	-3777	7661	3876	24
H8	1152	7238	2077	23
H9	-3812	8293	2212	22
H10A	905	10353	1345	36
H10B	1545	9320	2419	36
H10C	575	11106	2312	36
H11A	-3215	9426	488	28
H11B	-469	8695	526	28
H12A	-4113	7009	829	35
H12B	-2264	7123	-128	35
H13A	-1236	4772	1036	35
H13B	808	5704	847	35
H14A	258	4793	2583	29
H14B	-2485	5549	2573	29
H16A	3261	5932	5280	38
H16D	478	6109	5432	38
H16B	1588	7581	5099	38

5.2 MOLECULAR MODELS

The following four pages contain conformations for the global energy minimum of the four tricyclic structures **261**, **292**, **291** and **293** respectively.



261



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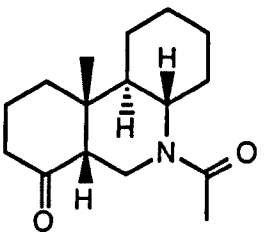

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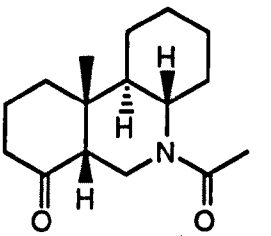

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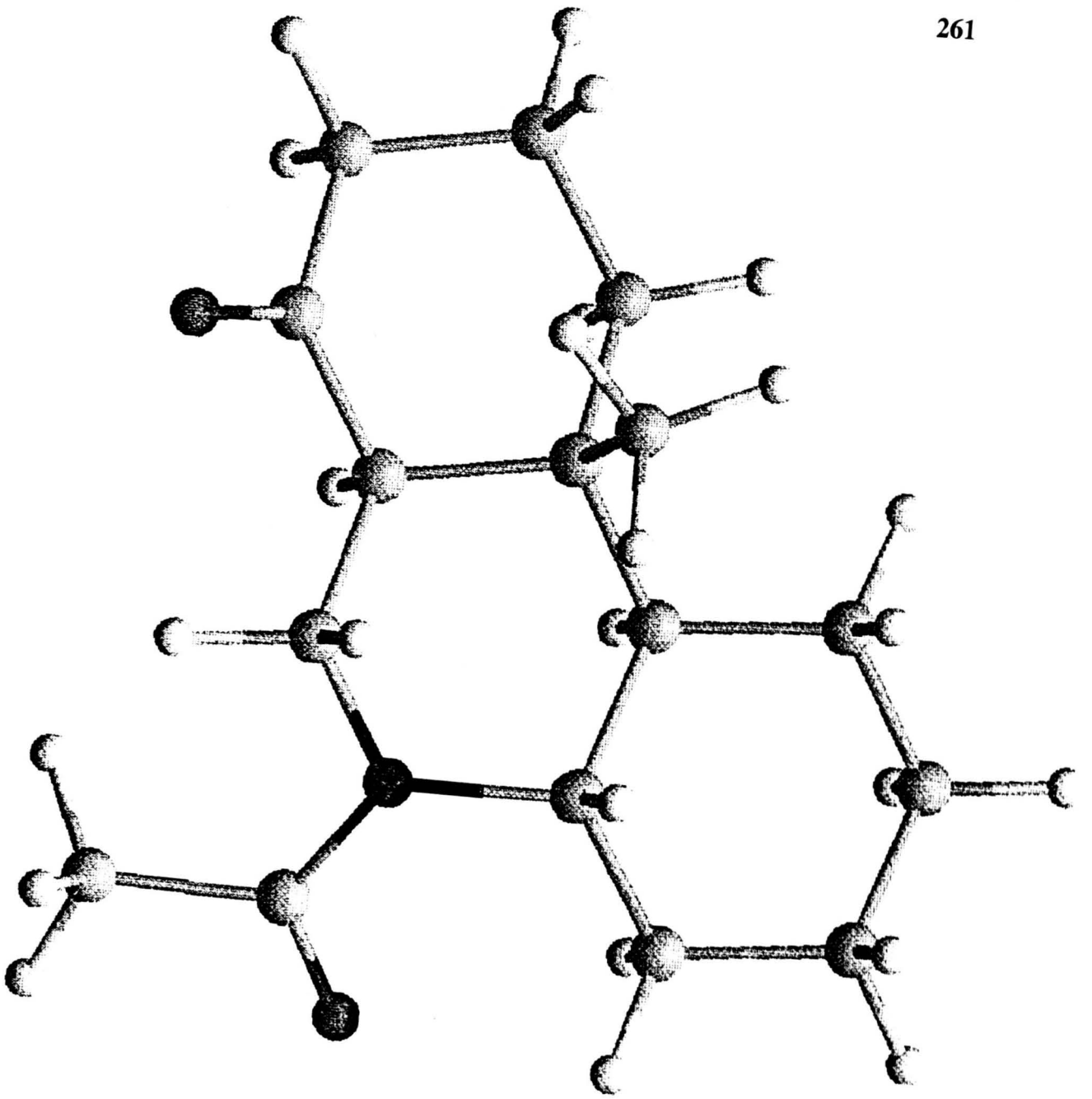

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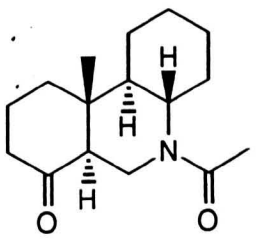

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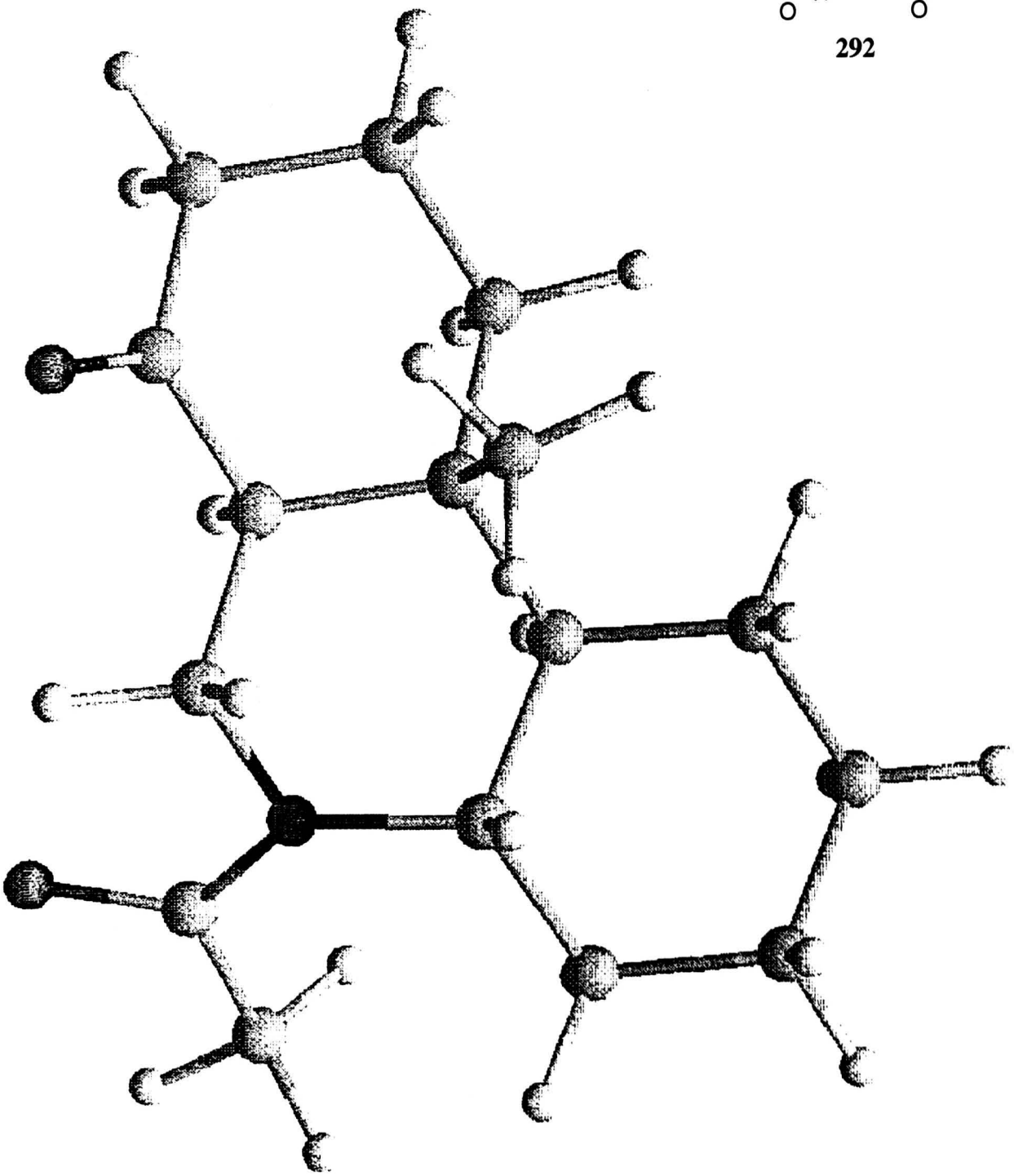

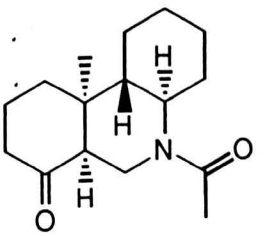

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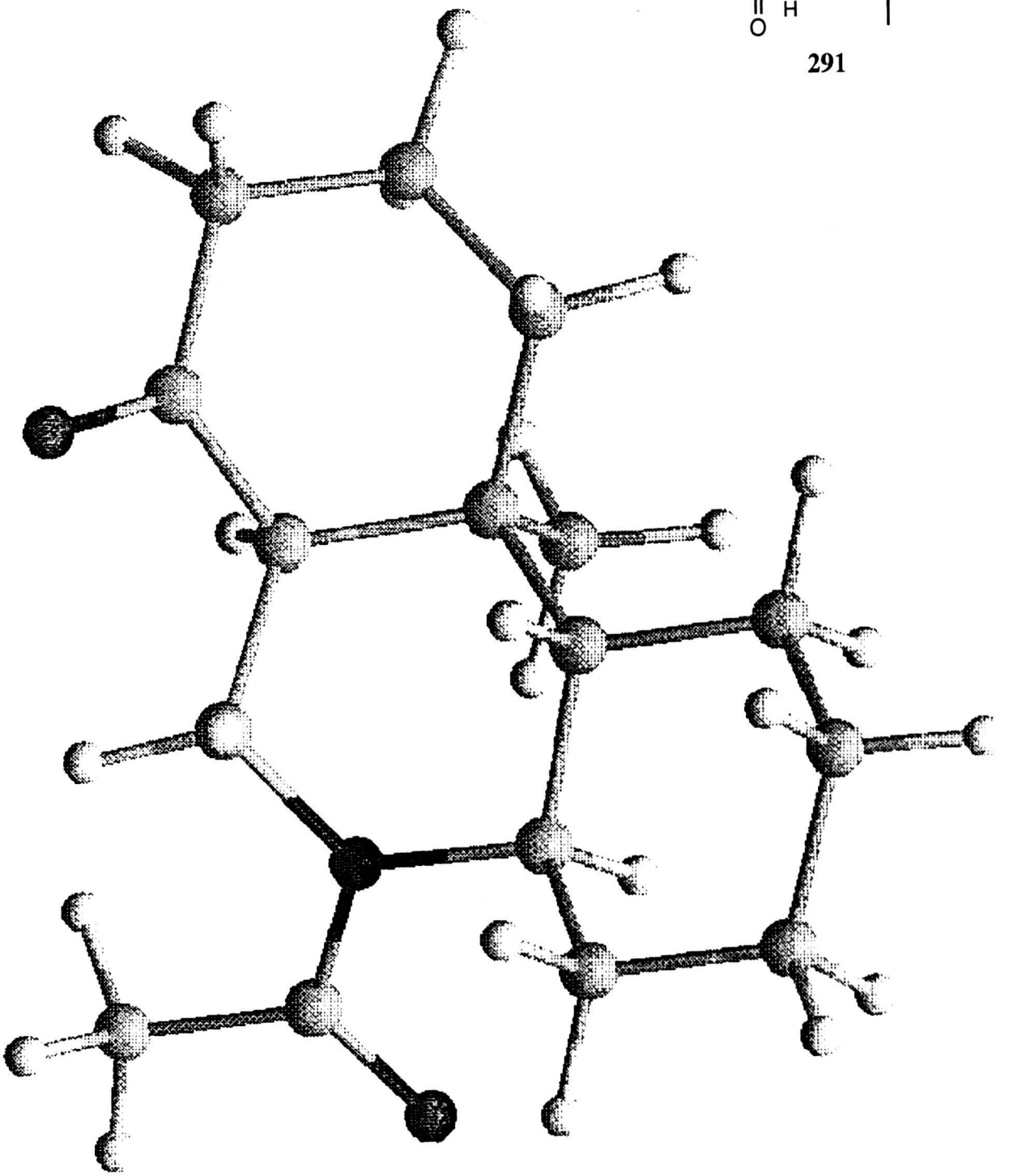

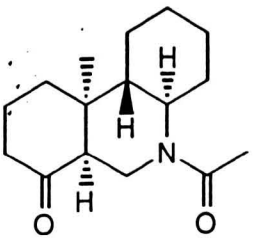

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