

Complexity-Generating Reactions and the Synthesis of Alkaloids

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ASLIB Abstract

Complexity-Generating Reactions and the Synthesis of Alkaloids

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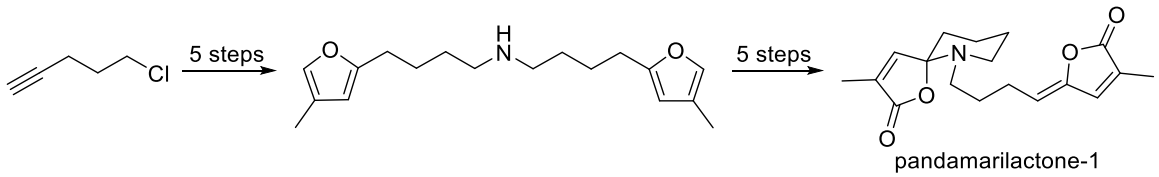
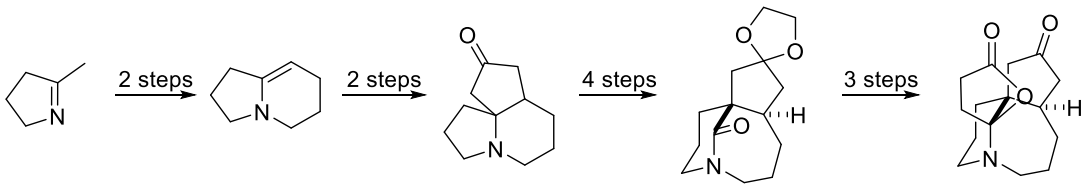
This thesis describes attempts to apply the furan oxidative *N*-spirocyclisation methodology to the synthesis of three alkaloids, namely pandamarilactone-1, lycopladine D and hederacine B.

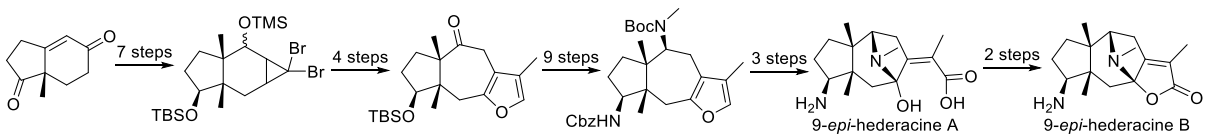
Starting from 5-chloro-1-pentyne, pandamarilactone-1 is synthesised in 10 steps and 9% overall yield. The structure of pandamarilactone-1 is confirmed by HMBC data and site-specific hydrogen-deuterium exchange in methanol-d_4. Furthermore, the reactivity of pandamarilactone-1 with aqueous ammonia shows that pandamarine is not an experimental artifact from the isolation process and is most likely a genuine natural product.



Along the synthetic route towards lycopladine D, the versatile chemistry of a bicyclic enamine is demonstrated by its ability to generate complex multicyclic molecules. A key tricyclic lactam, which is a common structural core found in several other fawcettimine-type *Lycopodium* alkaloids, is also furnished. The synthesis of the spiro-*N*,*O*-acetal and its stereochemistry is also discussed. Furthermore, isotopic labelling studies show that the ammonium ylids of a tricyclic aminoketone intermediate undergo intramolecular Hofmann elimination in preference to Stevens rearrangement. This provides an alternative pathway for tricyclic aminoketone ring expansion to afford bicyclic enones.



For the synthesis of hederacine B, a key spirocyclisation precursor is synthesised by dibromocyclopropane electrocyclic ring expansion step followed by intramolecular Heck cyclisation. The regioselectivity of the ring expansion and cycloheptenyl cation capture is controlled using two different approaches. Applying the furan oxidative *N*-cyclisation methodology, the formal synthesis of 9-*epi*-hederacine A and 9-*epi*-hederacine B is completed in 23 and 25 steps, respectively, from Hajos–Parrish ketone.



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Finally, the deepest gratitude goes to my family who have been giving me moral support my entire life and teaching me to have determination and perseverance in everything I do.

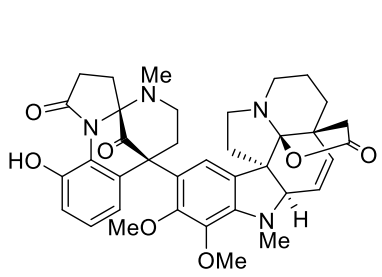
Abbreviations

Acac	Acetylacetonate
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
Aq.	Aqueous
Bn	Benzyl
Bz	Benzoyl
Boc	*tert*-butyloxycarbonyl
B.p.	Boiling point
CAN	Cerium(IV) ammonium nitrate
Cbz	Benzyloxycarbonyl
Conc.	Concentrated
CSA	Camphorsulfonic acid
d	Day(s)
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DMDO	Dimethyldioxirane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethylsulfoxide
EI	Electron ionisation (impact)
Eq.	Equivalent
ESI	Electrospray ionisation
Grubbs II	Grubbs catalyst, 2nd generation
h	Hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HMPT	Hexamethylphosphorous triamide
Hz	Hertz
i-Bu	Isobutyl
i-Pr	Isopropyl
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
M	Molar
Mc	Chloromethanesulfonyl
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Min	Minute(s)
Ms	Methanesulfonyl
m/z	Mass to charge ratio
N	Normal
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PCC	Pyridinium chlorochromate
PMB	4-Methoxybenzyl

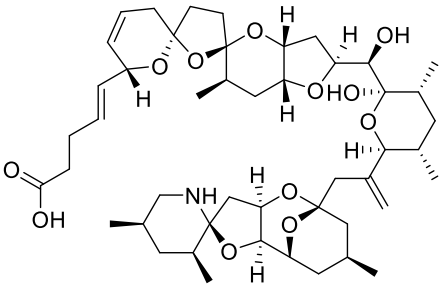
PPTS	Pyridinium *p*-toluenesulfonate
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
R_f	Retention factor
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TEBA	Benzyltriethylammonium chloride
Teoc	Trimethylsilylethoxycarbonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSE	2-Trimethylsilylethyl
Tris	2,4,6-Triisopropylbenzenesulfonyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	*p*-Toluenesulfonyl

Chapter 1: Introduction

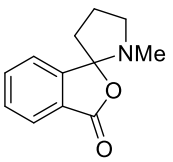
The spiro-*N*,*O*-acetal moiety is found in a number of natural products like haplophytine[1] **1**, azaspiracid[2] **2**, shihunine[3] **3**, pandamarilactone-1[4] **4**, lycopladine D[5] **5**, huperzine Q[6] **6** and hederacine B[7] **7** (Figure 1.1). Some of these alkaloids are biologically active and possess cytotoxic properties. The class of marine neurotoxins, azaspiracids and steroidal alkaloids like tomatidine[8] **8**, contains the 5,6-spiro-*N*,*O*-acetal moiety, whereas the novel immunosuppressant, sanglifehrin A[9] **9** contains the 6,6-spiro-*N*,*O*-acetal moiety.



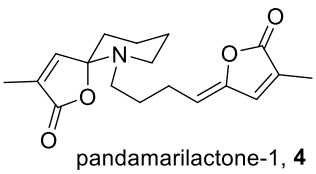
haplophytine, **1**



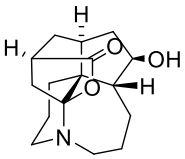
azaspiracid-1, **2**



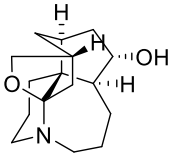
(±)-shihunine, **3**



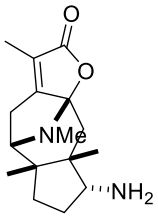
pandamarilactone-1, **4**



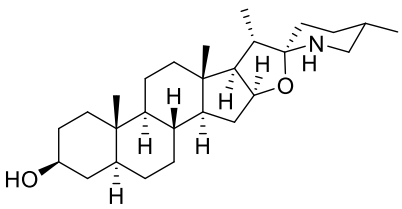
lycopladine D, **5**



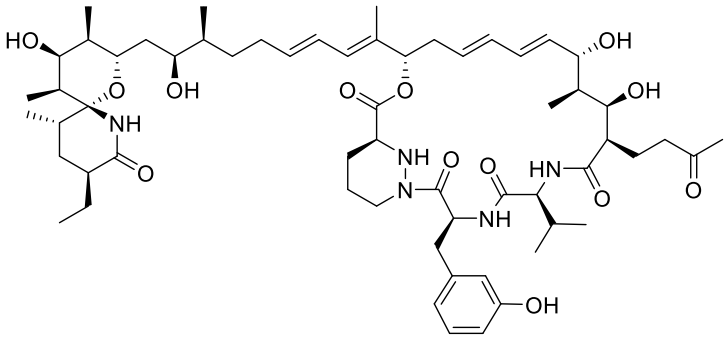
huperzine Q, **6**



hederacine B, **7**



tomatidine, **8**



sanglifehrin A, **9**

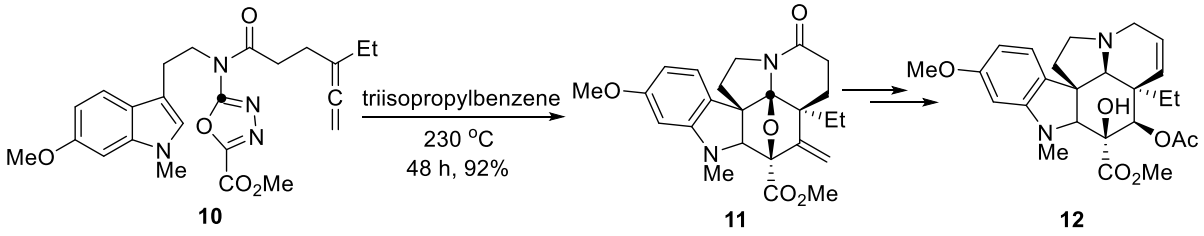
Figure 1.1: Alkaloids containing the spiro-*N*,*O*-acetal moiety.

1.1 Spiro-*N*,*O*-acetal synthesis

Over the years, different methodologies have been developed to construct the spiro-*N*,*O*-acetal functionality for application in the total synthesis of a few natural products. These synthetic approaches may be separated into three categories: (1) ring closure, (2) monocyclisation, and (3) bicyclisation.

1.1.1 Ring closure

The synthetic approach is defined as ring closure if the precursor contains both nitrogen and oxygen atoms attached to the carbon at the spirocentre. For example, in the synthesis of (–)-vindoline **12**, Boger and co-workers formed a spiro-*N*,*O*-acetal intermediate **11** from a 1,3,4-oxadiazole precursor **10** using a tandem intramolecular [4+2]/[3+2] cycloaddition cascade (Scheme 1.1).[10]

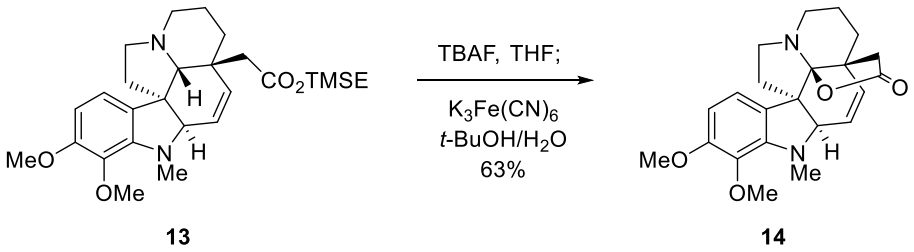


Scheme 1.1: Tandem intramolecular [4+2]/[3+2] cycloaddition cascade.

1.1.2 Monocyclisation

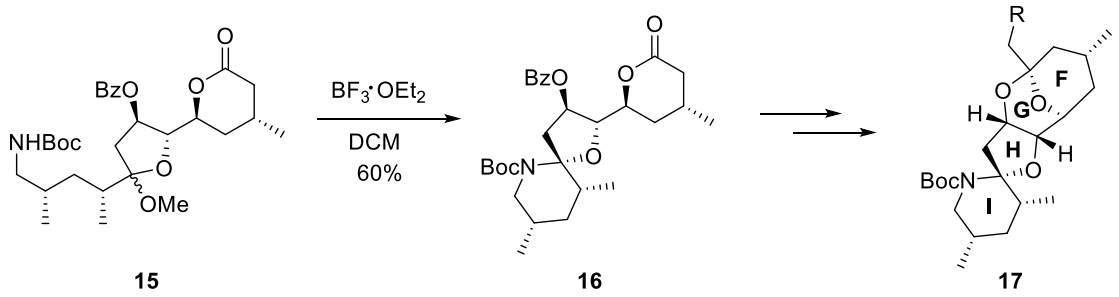
This synthetic strategy is much more commonly employed compared to ring closure as the spirocyclisation precursors are easier to synthesise. In monocyclisation, the precursor has only one heteroatom attached to the spirocentre.

Nicolaou and co-workers reported the use of a one-pot ester hydrolysis/oxidative lactonisation protocol to furnish aspidophytine **14** from spirocyclisation of precursor **13** (Scheme 1.2).[11]



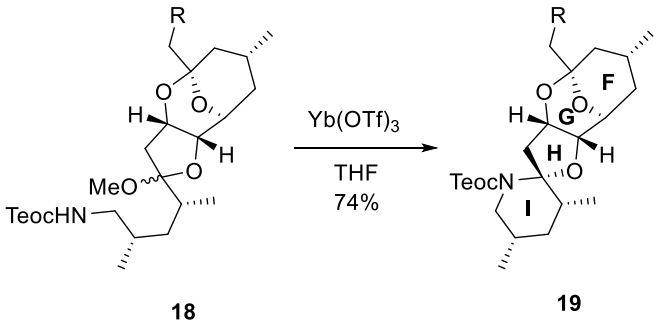
Scheme 1.2: Nicolaou's synthesis of aspidophytine.

Several groups worked on the synthesis of the southern FGHI ring system **17** of azaspiracid-1, employing a variety of Lewis acids for the *N*-spirocyclisation. Nicolaou's group used $BF_3{\cdot}OEt_2$ to effect spirocyclisation to form spiro-*N*,*O*-acetal **16** as the use of protic acids led mainly to decomposition of precursor **15** (Scheme 1.3).[12]



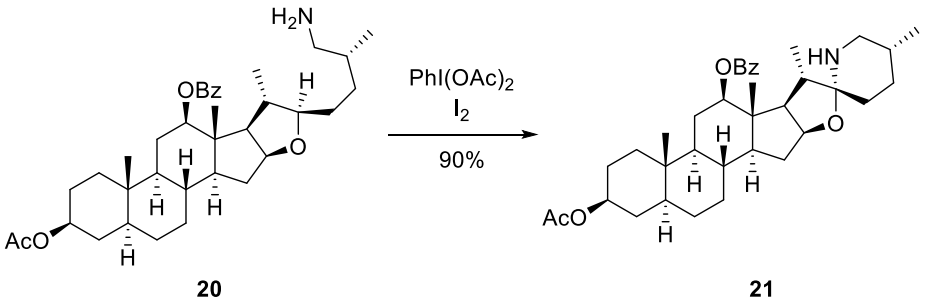
Scheme 1.3: Nicolaou's synthesis of the FGHI ring system of azaspiracid-1.

Carter and co-workers employed $Yb(OTf)_3$ in THF to effect spirocyclisation of a late-stage intermediate **18** to form spiroaminoacetal **19** with the desired stereochemistry at the spirocentre (Scheme 1.4).[13]



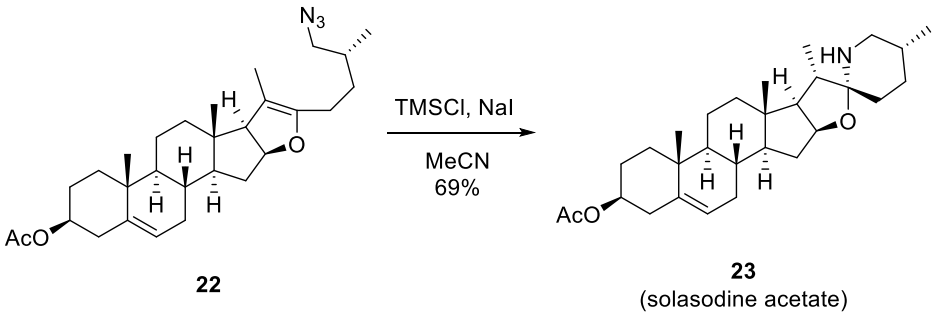
Scheme 1.4: Use of $Yb(OTf)_3$ for spirocyclisation.

In the synthesis of a cephalostatin analogue, Lee and co-workers formed the spiro-*N*,*O*-acetal **21** by subjecting the precursor **20** to Suarez hypoiodite oxidation conditions (Scheme 1.5).[14] The aminyl-radical cyclisation of the primary amine forms the oxazaspiroketal stereoselectively via a 1,6 H atom transfer, iodination of carbon radical and trapping of oxocarbenium ion by the amine.



Scheme 1.5: Oxazaspiroketal synthesis via aminyl-radical cyclisation of primary amine.

In the synthesis of a similar steroidal alkaloid, solasodine, the Tian group employed TMSI generated *in situ* to reduce the azide in precursor **22**; the so-formed amino end tether cyclised during work-up and purification to form spiroaminoacetal **23** (Scheme 1.6).[15]

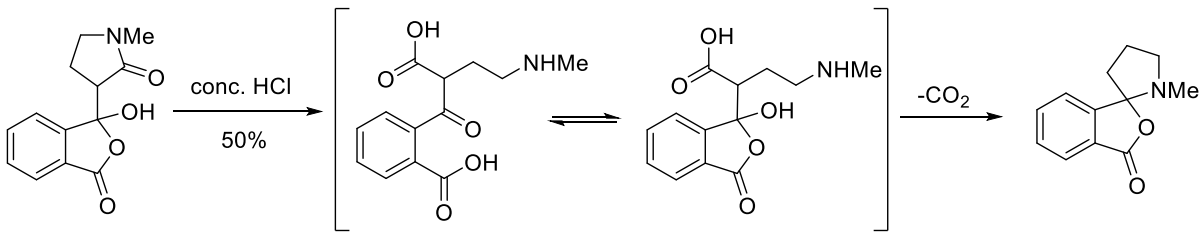


22 **23** (solasodine acetate)

Scheme 1.6: One-pot azide reduction and spirocyclisation.

1.1.3 Bicyclisation

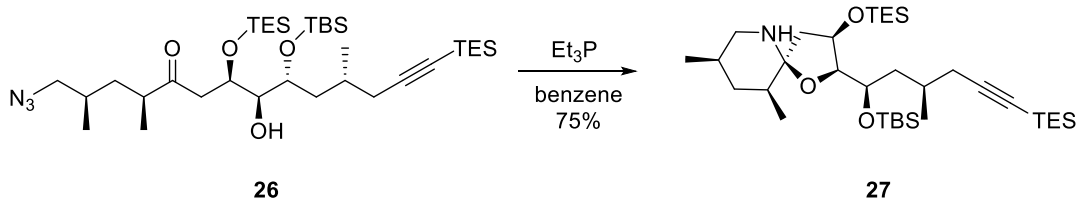
In this spirocyclisation approach, neither of the heteroatoms are attached to the spirocentre carbon in the linear precursor and a sequential double cyclisation of the hydroxyl and amino groups onto a central ketone forms the spiro-*N*,*O*-acetal. One of the earliest examples of this approach is in the synthesis of shihunine **25**, a spiro phthalide pyrrolidine alkaloid. Narasimhan and co-workers used conc. HCl to bring about hydrolysis, decarboxylation and spirocyclisation of precursor **24** to form the spiroaminoacetal (Scheme 1.7).[16]



24 **25**

Scheme 1.7: Narasimhan's synthesis of shihunine.

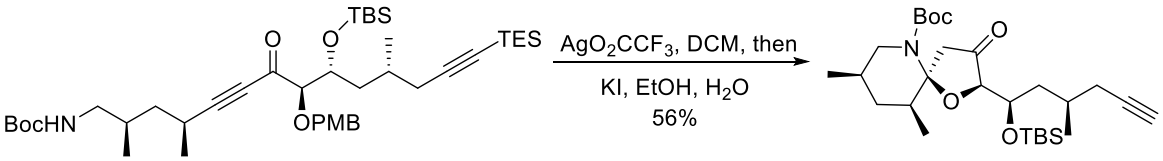
More recently, the Forsyth group developed two novel methods for the synthesis of the spiro-*N*,*O*-acetal in azaspiracid-1.[17] One method involved the use of triethylphosphine to convert linear precursor **26** into spiroaminoacetal **27** *via* the Staudinger reduction-aza-Wittig process (Scheme 1.8).



26 **27**

Scheme 1.8: Spiroaminal synthesis *via* Staudinger reduction-aza-Wittig process.

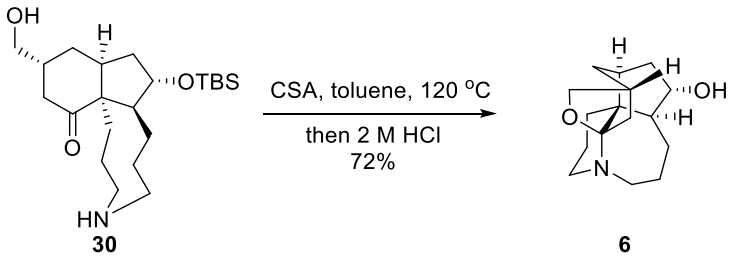
The second method involved a double intramolecular hetero-Michael addition when the linear alkyne precursor **28** was subjected to AgO_2CCF_3 followed by treatment with ethanolic KI (Scheme 1.9).[17] Under Ag(I) catalysis, the protected amine adds to the alkyne and the PMB group is deprotected to give the free alcohol which then adds stereoselectively into the enone under thermodynamic control to give the spiroaminoacetal **29**. This stereochemistry of the spiro-*N,O*-acetal is preferred due to stabilisation by anomeric effect.



28 **29**

Scheme 1.9: Spiroaminoacetal synthesis *via* double intramolecular hetero-Michael addition.

In the synthesis of huperzine Q **6**, Zhao and co-workers treated the spirocyclisation precursor **30** with CSA then dilute HCl to form the desired natural product (Scheme 1.10).[18]



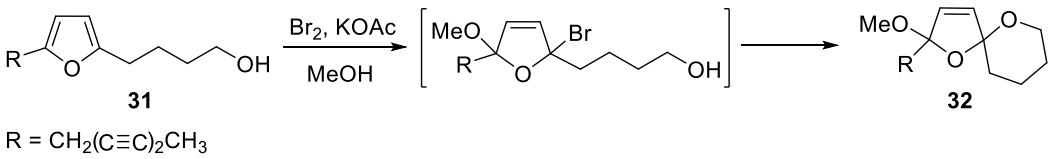
30 **6**

Scheme 1.10: Zhao's synthesis of huperzine Q.

1.2 Furan oxidative *N*-spirocyclisation

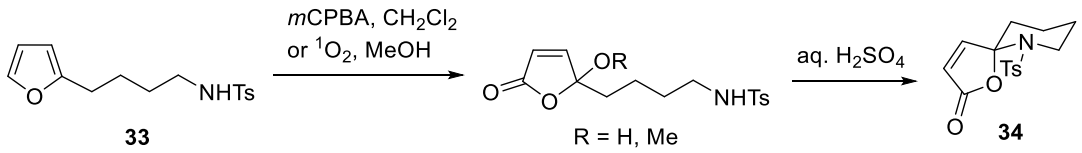
1.2.1 Aza-Bohlmann cyclisation

Previous work undertaken in the group established the aza-Bohlmann cyclisation methodology for the synthesis of spiro-*N*,*O*-acetals.[19] This method is analogous to the Bohlmann cyclisation as it involves furan oxidation and spirocyclisation to form a spiroacetal product. In Bohlmann's original work, δ-hydroxyfuran **31** was converted into spiroketal **32** (Scheme 1.11).[20]



Scheme 1.11: Bohlmann cyclisation.

However, the aza-Bohlmann cyclisation of aminoalkyl furan precursor **33** involves a two-stage process: oxidation of the furan (*m*CPBA or $^1O_2$) to hydroxy- or methoxybutenolides, then acid-catalysed spirocyclisation of the protected amine to form spiroaminoacetal **34** (Scheme 1.12).[21]

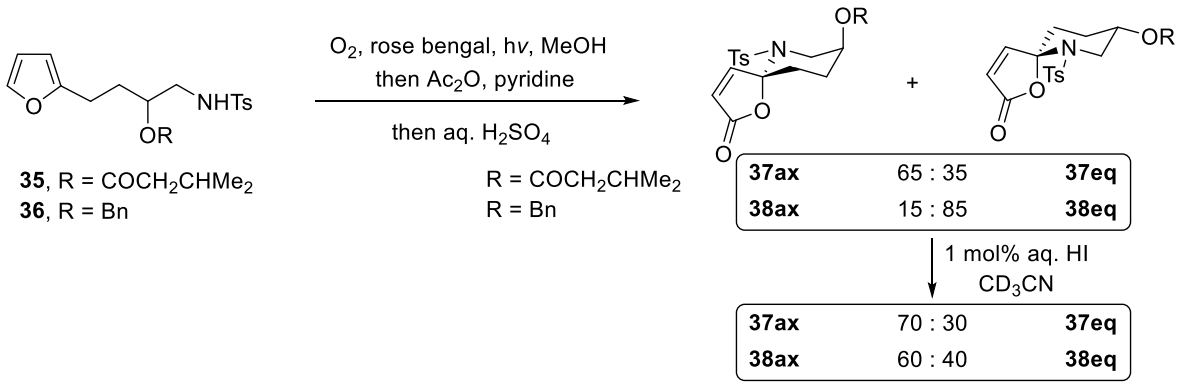


Scheme 1.12: Aza-Bohlmann cyclisation.

In order to expand the scope of this methodology, substrates bearing a variety of amine protecting groups were treated with the aza-Bohlmann cyclisation conditions. Only the sulfonamide protected substrates were able to form the desired spiro-*N*,*O*-acetals. Attempts to remove the sulfonyl protecting groups mainly resulted in decomposition.[21]

1.2.2 Conformational preferences of spiroaminoacetals

As the aza-Bohlmann cyclisation forms spiro-*N,O*-acetals as a racemic mixture, attempts were made to control the absolute configuration of the spirocentre. *O*-protected δ-amino-γ-hydroxyfurans bearing different protecting groups were synthesised to determine whether the axial/equatorial conformational preference of the protected hydroxyl group would relay to the stereochemistry at the spirocentre. The isovalerate substrate **35** and benzyl substrate **36** underwent photo-oxidation with singlet oxygen to form the methoxybutenolides and these were cyclised under acidic conditions to afford a mixture of axial–equatorial diastereomers (Scheme 1.13).[19] The isovalerate spiroaminoacetals **37** were obtained as a 65:35 mixture of axial–equatorial diastereomers, whereas the benzyl spiroaminoacetals **38** were obtained as a 15:85 mixture of axial–equatorial diastereomers. Equilibrations were conducted on the mixture of diastereomers by treating them with 1 mol% aq. HI in CD_3CN. The ratio of diastereomers changed drastically for the benzyl spiroaminoacetal **38** with the major diastereomer bearing the axial oxy-substituent. This axial preference may arise from stabilisation by the *gauche* effect in which two additional (C–H)σ-(C–O)σ* interactions are possible in the axial isomer.



Scheme 1.13: Equilibration studies.

1.3 *Pandanus* alkaloids

The genus *Pandanus* which belongs to the family Pandanaceae consists of more than 600 species found throughout tropical and subtropical regions. *Pandanus amaryllifolius* is one out of 52 *Pandanus* species found in the Philippines.[22] Commonly known as 'pandan-mabango' or fragrant screwpine, it is extensively used for flavouring rice in Southeast Asia, with 2-acetyl-1-pyrroline being the main fragrant component. Various parts of the plant are used as traditional medicine for treatment of minor ailments (fever, headaches, sore throat) and more serious conditions (leprosy, rheumatism, epilepsy). New alkaloids continue to be isolated from various parts of the plant collected in different countries (Thailand, Indonesia) at different times (Figure 1.2).[23,24,25,26]

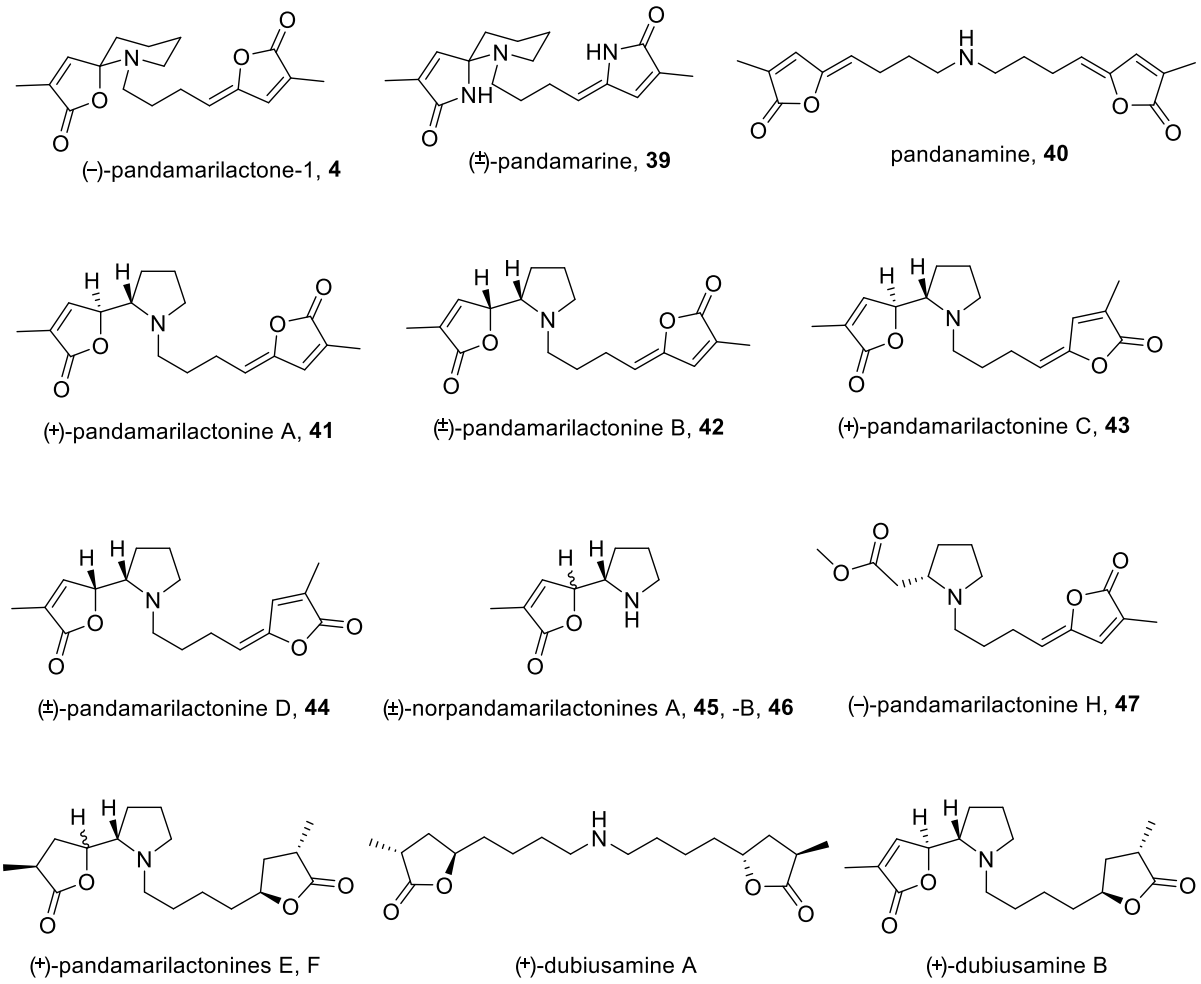
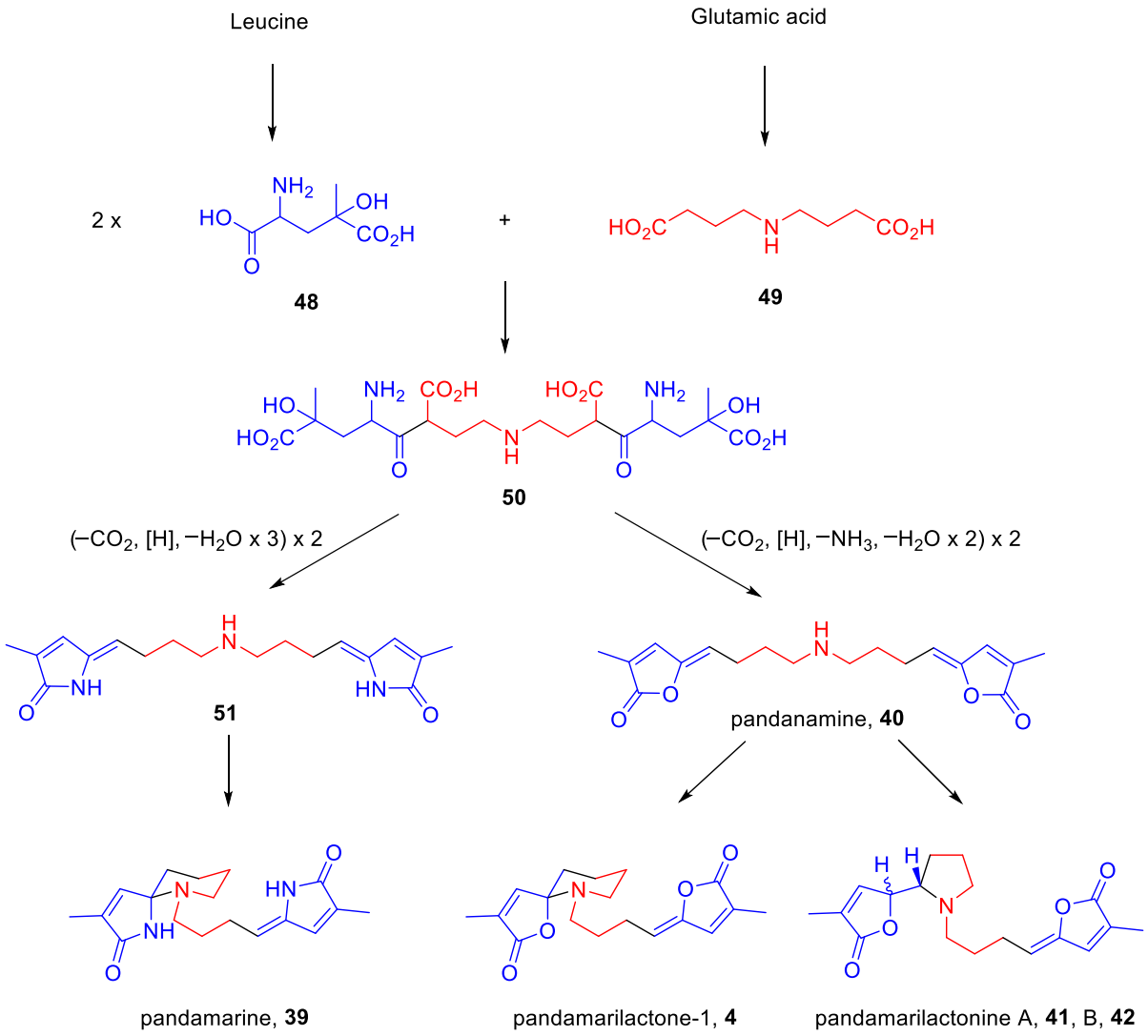


Figure 1.2: *Pandanus* alkaloids.

Pandamarilactone-1 **4** is a piperidine alkaloid first isolated and identified by Nonato and co-workers in 1993.[4] It was originally isolated from *P. amaryllifolius* leaves collected from Manila, Philippines and contains a spiro-*N*,*O*-acetal core. Intriguingly, one year before pandamarilactone-1 was reported, Byrne's group reported an analogous bislactam alkaloid, pandamarine **39** as the major base isolated from *P. amaryllifolius* leaves collected from Isabela province in the Philippines.[27] Even though the same plant species was harvested in both cases, pandamarine was not observed in the plant samples from which pandamarilactone-1 was isolated. Therefore, either two different subspecies were involved or environmentally-induced variability in transaminase activity results in the different phytochemical profiles.

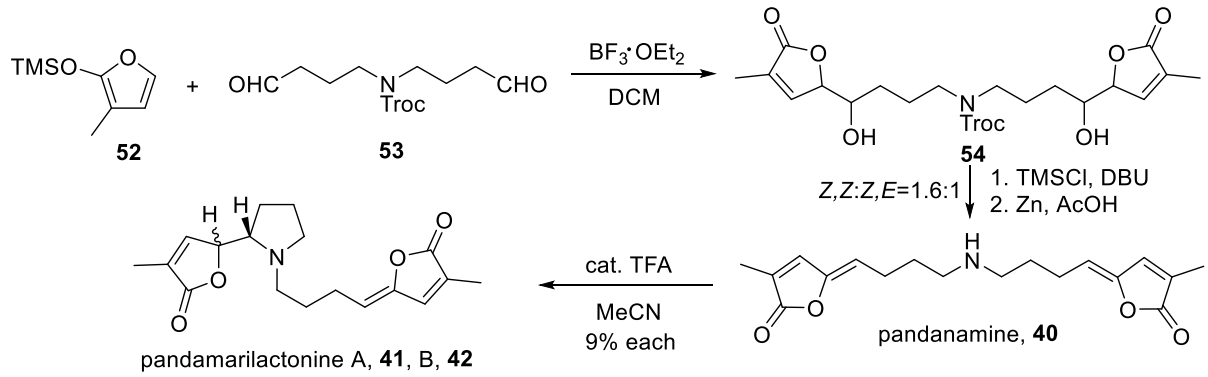
Subsequently, Takayama and co-workers isolated two new diastereomeric pyrrolidine alkaloids, pandamarilactonines A **41** and B **42** from *P. amaryllifolius* leaves.[28] The biosynthesis of these *Pandanus* alkaloids was proposed by Garson[29] and Takayama[30] and thought to involve an intermediate alkaloid, pandanamine **40** which was later isolated (Scheme 1.14). Condensation of two units of 4-hydroxy-4-methylglutamic acid **48**, derived from leucine, and a dicarboxylic acid **49**, derived from glutamic acid forms the carbon backbone **50**. Further decarboxylation, cyclisation, reduction and dehydration affords symmetrical lactam **51** and lactone, pandanamine **40**. Spirocyclisation of the precursors would form pandamarine **39** and pandamarilactone-1 **4**, whereas intramolecular 1,6-addition of the amine would form pandamarilactonines A and B.



Scheme 1.14: Proposed biosynthesis of *Pandanus* alkaloids.

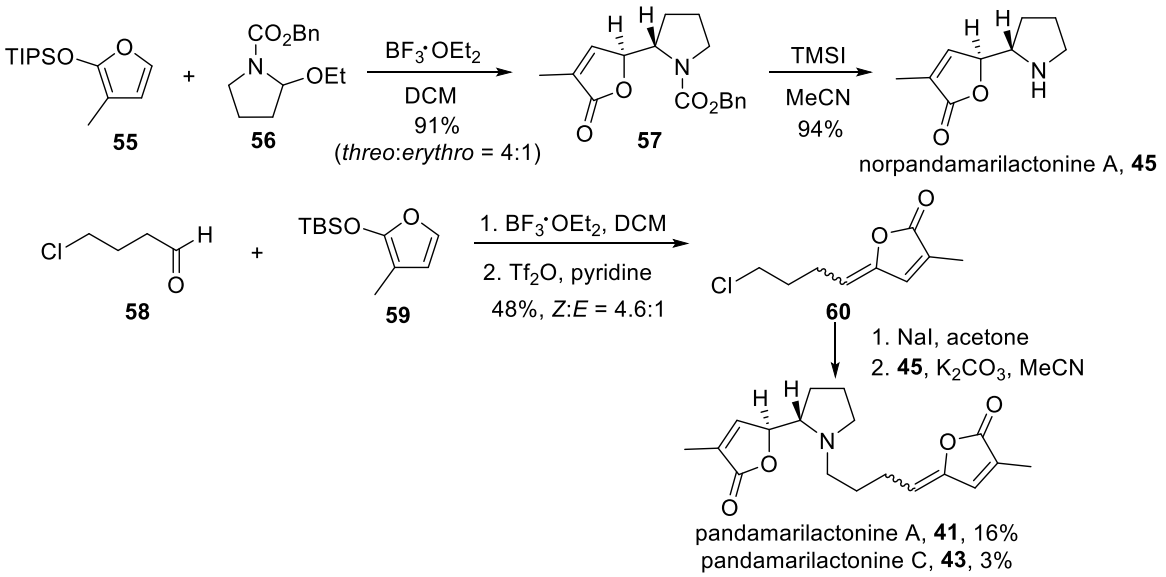
1.3.1 Previous syntheses of *Pandanus* alkaloids

The first total synthesis of the proposed biogenetic intermediate, pandanamine **40** and pandamarilactonines A and B was carried out by Takayama and co-workers (Scheme 1.15).[28] Lewis acid mediated addition of siloxy furan **52** to dialdehyde **53** afforded diol **54** which was then dehydrated and deprotected to form pandanamine **40**. The acid-labile pandanamine was treated with TFA to afford pandamarilactonines A **41** and B **42**, each in 9% yield.



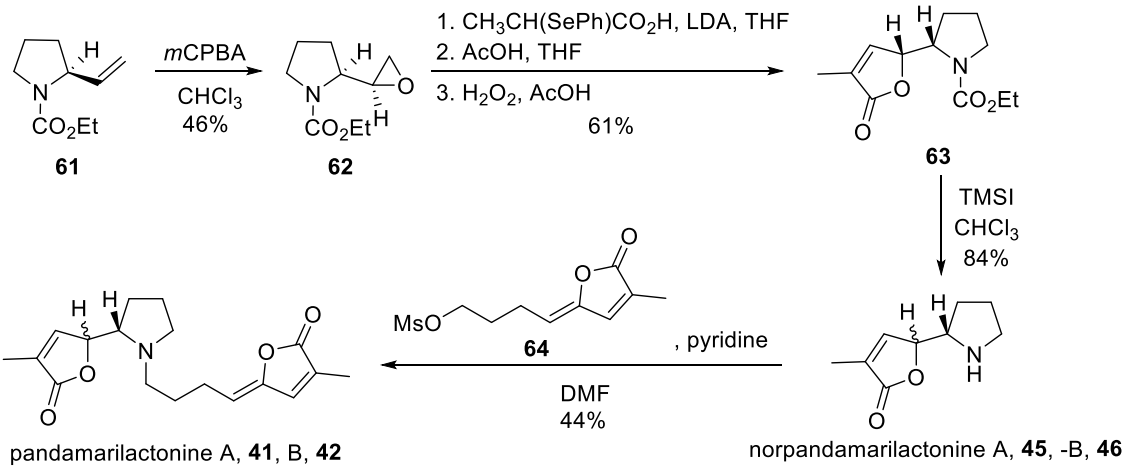
Scheme 1.15: First synthesis of pandamarilactonines A and B.

Takayama's group then isolated another two pyrrolidine alkaloids, pandamarilactonines C **43** and D **44** in which the γ-alkylidenebutenolide moiety is in the *E* configuration.[31] In order to confirm the stereochemistry, the group carried out the synthesis of pandamarilactonines A **41** and C **43** (Scheme 1.16). The stereoselective vinylogous Mannich coupling reaction of **55** and **56** formed bicyclic **57** which was deprotected to afford norpandamarilactonine A **45**. This stereoselectivity could be due to less steric interactions between the substituents in the transition state. Addition of siloxy furan **59** to aldehyde **58**, followed by triflate elimination afforded butenolide **60** which was then treated with amine **45** to form pandamarilactonines A and C.



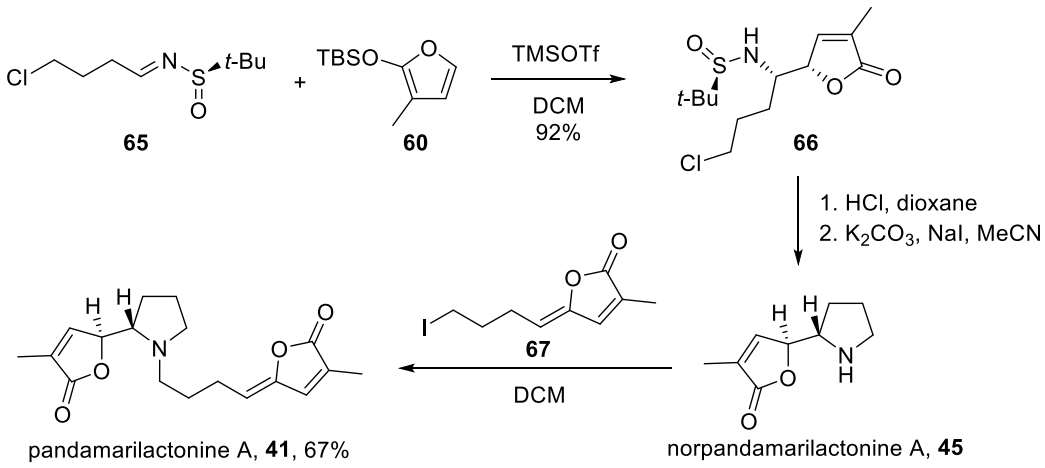
Scheme 1.16: Takayama's synthesis of pandamarilactonines A and C.

Shortly after, the Figueredo group synthesised pandamarilactonines A **41** and B **42** using a different approach (Scheme 1.17).[32] Carbamate **61** which was prepared from (*S*)-prolinol was oxidised stereoselectively on the less sterically hindered face to afford epoxide **62**. A three-step protocol, epoxide ring-opening by the dianion of 2-phenylselenopropionic acid, lactonisation and selenoxide elimination afforded bicyclic **63**. Removal of the carbamate group with TMSI resulted in epimerisation of the stereogenic centre on the butenolide to give a mixture of norpandamarilactonines A and B. Finally, the displacement of mesylate **64** by the pyrrolidine afforded pandamarilactonines A and B.



Scheme 1.17: Figueredo's synthesis of pandamarilactonines A and B.

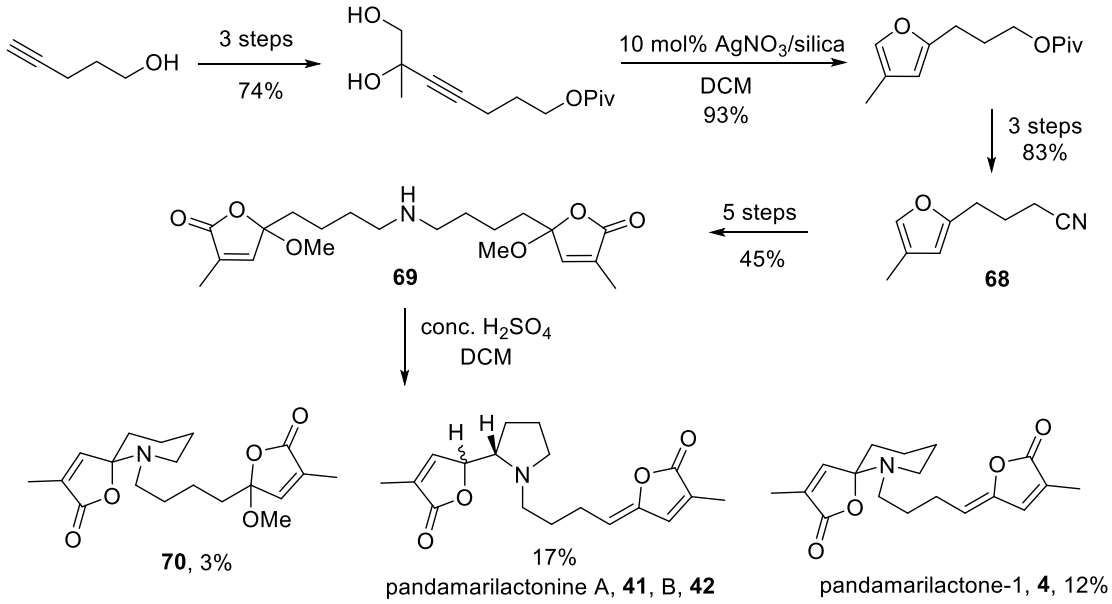
More recently, Huang and co-workers carried out an asymmetric synthesis of (–)-pandamarilactonine A **41** using the stereoselective vinylogous Mannich reaction of siloxy furan **60** and *N*-*tert*-butanesulfinimine **65** (Scheme 1.18).[33] This reaction afforded butenolide **66** which, upon *N*-sulfinyl group cleavage and chloride displacement, gave norpandamarilactonine A **45**. No epimerisation of stereocentres took place under these conditions and alkylation with butenolide **67** furnished (–)-pandamarilactonine A **41**.



Scheme 1.18: Huang's asymmetric synthesis of (–)-pandamarilactonine A.

1.3.2 Previous work in Robertson group

Work towards the total synthesis of pandamarilactone-1 **4** was undertaken by a previous DPhil student in the group based on the furan oxidative *N*-spirocyclisation methodology (Scheme 1.19).[21] Starting from 4-pentyn-1-ol, this alkaloid **4** was synthesised in 13 steps and 3% overall yield. Nitrile **68** was synthesised in 7 steps from 4-pentyn-1-ol using a key Ag-catalysed cyclisation step to form the 2,4-disubstituted furan.[34] A further 5 steps, including furan photo-oxidation, afforded the *N*-spirocyclisation precursor **69**. The crucial acid-catalysed *N*-spirocyclisation reaction yielded a mixture of four products, pandamarilactone-1 **4**, pandamarilactonines A **41** and B **42** and pandamarilactone-1 intermediate **70**.



Scheme 1.19: Pandamarilactone-1 synthesis *via* aza-Bohlmann cyclisation.

However, the structure of pandamarilactone-1 could only be partly confirmed by NMR spectroscopy. The ^{1}H NMR spectrum of synthetic pandamarilactone-1 matched the literature data, but the peaks for the piperidine ring protons C(11)–C(14) in the synthetic compound appeared broad (Figure 1.3). The ^{13}C NMR data also matched up within 0.1–0.2 ppm.

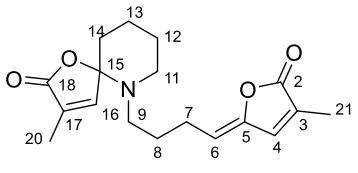
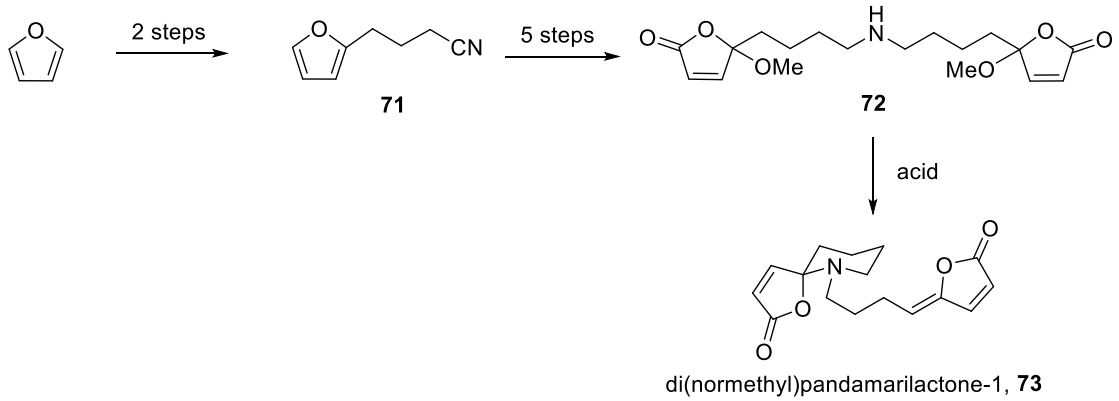


Figure 1.3: Pandamarilactone-1.

1.3.3 Project aims

As pandamarilactone-1 **4** was isolated in optically active form ($[\alpha]_D$ –33.0 (MeOH)), but pandamarine **39** was isolated as the racemate, it was speculated that pandamarine **39** could possibly be an artifact of the isolation process which uses concentrated ammonia solution to release the alkaloids from acidic solution. Furthermore, the structure of synthetic pandamarilactone-1 **4** had only been proposed on the basis of ^{1}H and ^{13}C NMR data.

Therefore, we decided to apply the furan oxidative *N*-spirocyclisation methodology to the synthesis of model compound, di(normethyl)pandamarilactone-1 **73** which lacks the methyl groups (Scheme 1.20). This was expected to simplify the chemistry so that the spirocyclisation reaction could be optimised and, with large quantities of spirocyclic products in hand, they could be rigorously characterised, including by X-ray, and the structure of pandamarilactone-1 confirmed by analogy.



Scheme 1.20: Route to a pandamarilactone-1 analogue for full structural elucidation.

Nitrile **71** was to be prepared from furan then, after another 5 steps, spirocyclisation precursor **72** could be furnished. Acid-catalysed *N*-spirocyclisation would, it was hoped, form pandamarilactone-1 analogue **73** for full structural elucidation.

Additionally, it was intended to shorten and optimise the total synthesis of pandamarilactone-1 so that more material could be obtained for biological testing, X-ray crystallographic analysis and to explore whether pandamarine is an experimental artifact from the isolation process.

1.4 Lycopladine D

Over the years, more than 200 alkaloids have been isolated from the club moss *Lycopodium complanatum* and classified into four different groups based on their structure (Figure 1.4).[35] Members of this family have cardiovascular and neuromuscular effects. The unique polycyclic ring systems in these alkaloids have attracted great interest from synthetic chemists. Gupta and co-workers proposed a biosynthesis of lycopodine where two molecules of isopelletierine undergo a series of enamine and aldol additions to form the skeletal core of lycopodine.[36] Radiolabelling studies showed that the biogenetic precursor, isopelletierine was derived from lysine and acetoacetic acid.

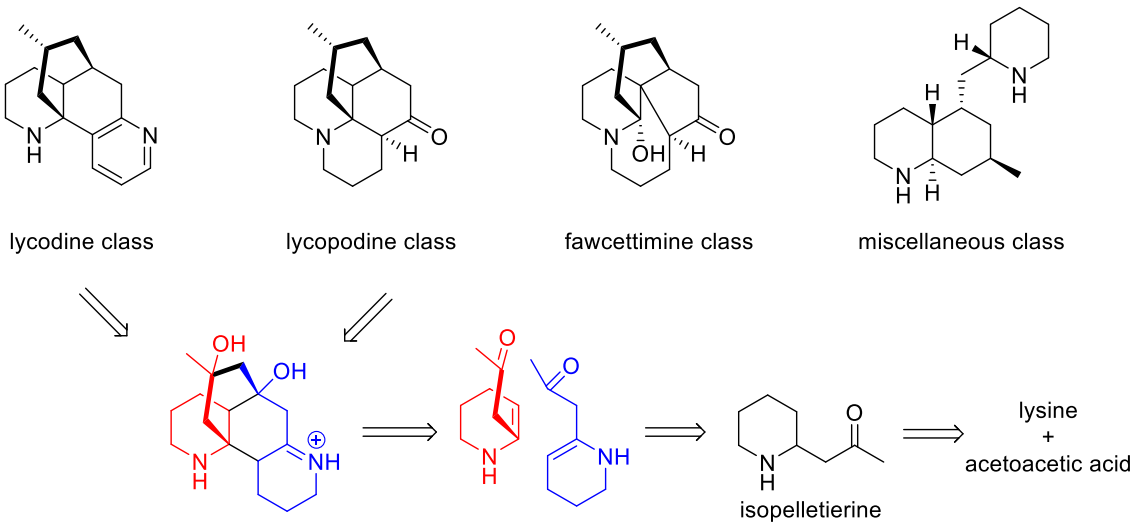


Figure 1.4: Four major classes of *Lycopodium* alkaloids and proposed biosynthesis.

Lycopladine D **5** was isolated from *Lycopodium complanatum* and its structure reported in 2006 by Kobayashi and co-workers.[5] It belongs to the fawcettimine class of *Lycopodium* alkaloids and contains the spiro-*N*,*O*-acetal moiety (Figure 1.5). Similarly, huperzine Q **6**, which is essentially the tetra-epimer of lycopladine D at a lower oxidation state, is also a spiroaminoacetal alkaloid, whereas fawcettimine **74** contains the hemiaminal functionality. Fawcettidine **76**, which has an enamine group, is the dehydrated form of fawcettimine **74**.

Lycopladine B **75** and lycoposerramine Q **77** also contain the enamine functionality but the ketone on the five-membered ring is reduced.

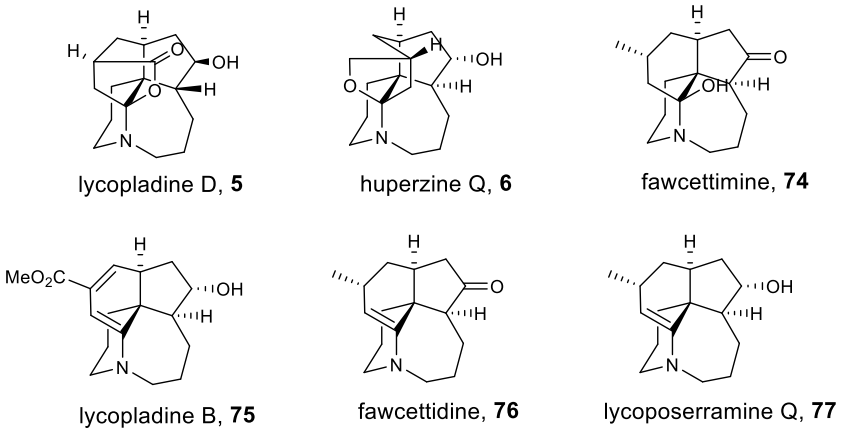
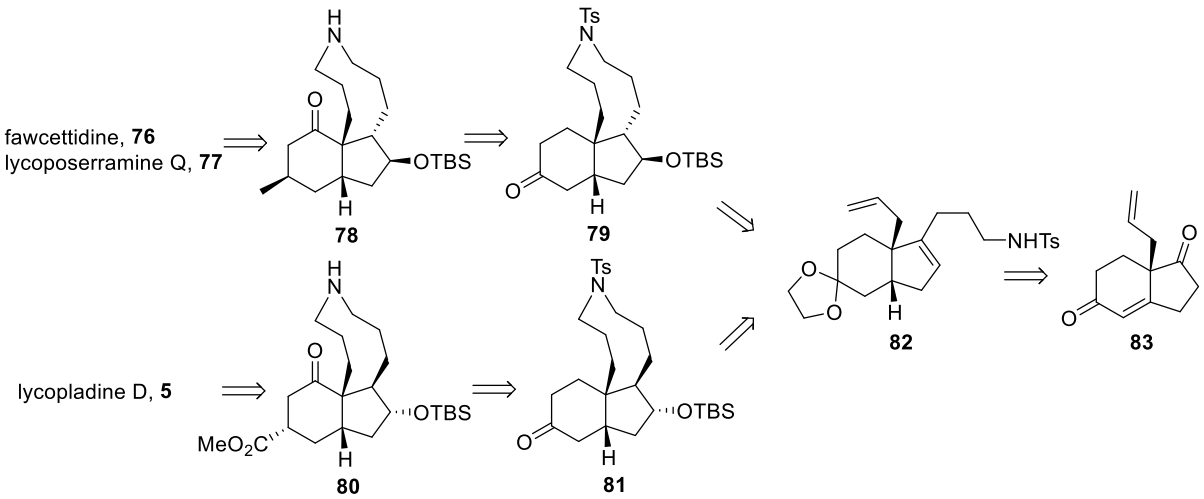


Figure 1.5: Selected fawcettimine-type *Lycopodium* alkaloids.

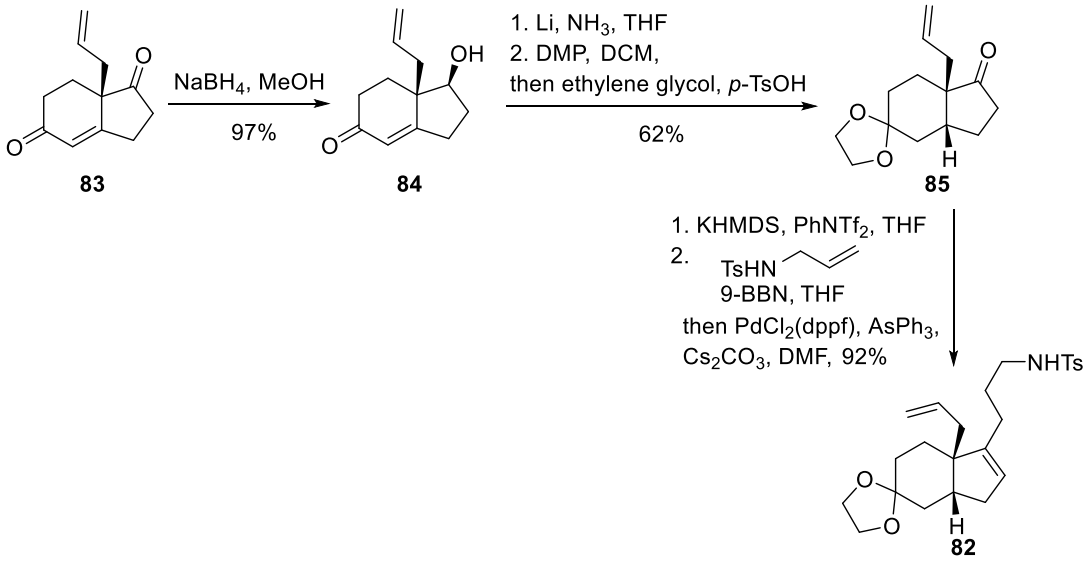
1.4.1 Previous synthesis of lycopladine D

In 2013, Zhao and co-workers completed the first total synthesis of (–)-lycopladine D **5** as well as the total synthesis of (+)-fawcettidine **76** and (+)-lycoposerramine Q **77** using divergent routes from a common intermediate **82** (Scheme 1.21).[37]



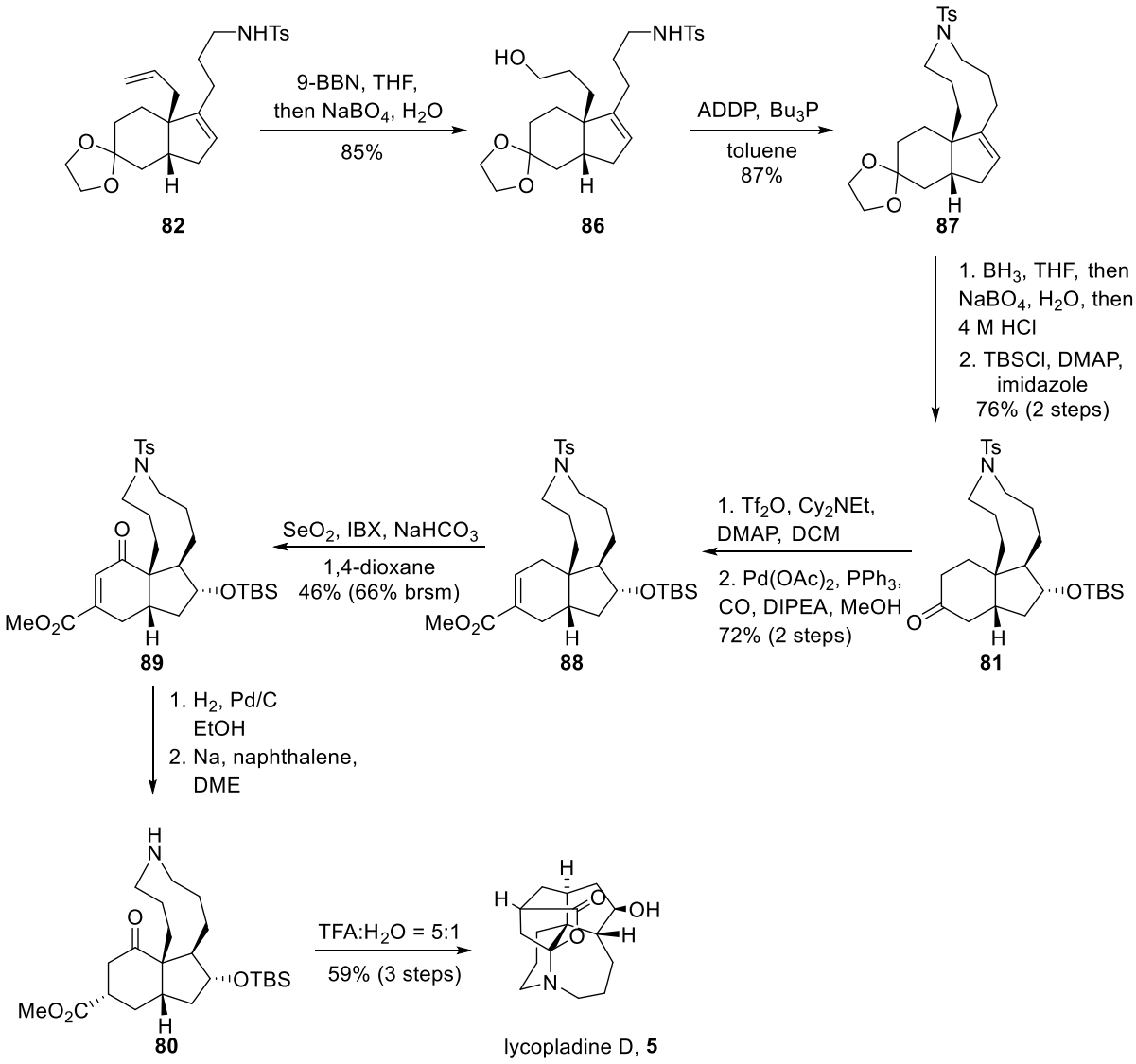
Scheme 1.21: Retrosynthetic analysis of Zhao's divergent total synthesis.

The authors envisaged that fawcettidine **76** and lycoposerramine Q **77** could be obtained by condensation of precursor **78** which could, in turn, be formed from the oxidative rearrangement of ketone **79**. On the other hand, lycopladine D **5** would be obtained *via* biomimetic aminoketalisation of precursor **80** which, in turn, could be constructed from ketone **81**. Both medium-ring amines **79** and **81** were to be assembled from common intermediate **82**, derived from Hajos–Parrish-like diketone **83**.



Scheme 1.22: Synthesis of common intermediate **82**.

Diketone **83**, prepared from 1,3-cyclopentadione, was reduced stereoselectively with $NaBH_4$ to afford alcohol **84** (Scheme 1.22). Reduction of the enone with Li in liquid NH_3 occurred with *cis*-stereoselectivity then oxidation and regioselective protection gave acetal **85**. The derived enol triflate underwent Suzuki coupling with the boron species generated in situ from *N*-allyl toluenesulfonamide to furnish common intermediate **82**.

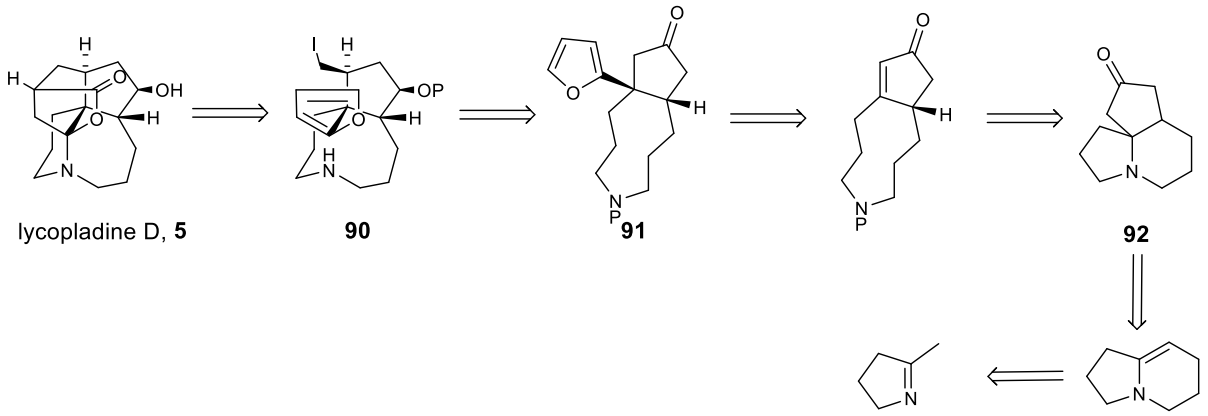


Scheme 1.23: Zhao's synthesis of lycopladine D.

Selective hydroboration and oxidation of intermediate **82** afforded alcohol **86** which, with a modified intramolecular Mitsunobu reaction, formed azonane ring **87** (Scheme 1.23). Subjecting compound **87** to stereoselective hydroboration/oxidation, ketal deprotection, then silylation furnished ketone **81**. Treatment with Tf_2O and Cy_2NEt as hindered base yielded an enol triflate which was converted into methyl ester **88** by a palladium-catalysed carbonylation reaction. After allylic oxidation with SeO_2 and IBX to form enone **89**, stereoselective hydrogenation and *N*-tosyl deprotection afforded spirocyclisation precursor **80**. Finally, with aqueous TFA, precursor **80** cyclised to give lycopladine D **5**.

1.4.2 Project aims

As lycopladine D contains the spiro-*N*,*O*-acetal moiety, we planned to apply the furan oxidative *N*-spirocyclisation methodology to the synthesis of this alkaloid as it would provide a stringent test of the method in a complex setting (Scheme 1.24). It was envisaged that lycopladine D **5** would be formed from precursor **90** followed by reduction and halide displacement. Precursor **90** should be available from cyclopentanone derivative **91** after a series of functional group transformations. From 2-methyl-1-pyrroline, two successive enamine alkylations would lead to tricyclic aminoketone **92** which could undergo ring opening to form a bicyclic enone. Subsequent conjugate addition of a furyl copper reagent to the enone would then furnish intermediate amine **91**.



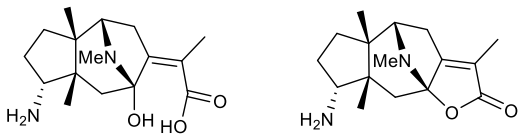
Scheme 1.24: Retrosynthetic approach to lycopladine D.

However, due to the higher complexity in structure of lycopladine D as compared to pandamarilactone-1, at the outset of the project we also envisaged assembling the alkaloid by *N*-cyclisation onto non-furan substrates with ring closure of the butyrolactone ring later in the synthesis. With either strategy, new methodology could be discovered in the process and further interesting non-natural alkaloid-like compounds could be synthesised.

1.5 *Glechoma hederacea* alkaloids

Glechoma hederacea Lamiaceae, commonly known as 'ground ivy', is a perennial hairy herb with creeping stem found in temperate Asia, Europe and the USA. This plant has been widely used in folk medicine for centuries. Aerial parts of the plant possess unique biological properties (cardiotonic, diuretic, stimulant) and have been used to treat a variety of ailments (arthritis, bronchitis, diabetes, jaundice). Extracts of this plant have been reported to exhibit anti-bacterial, anti-oxidant activity and brine shrimp toxicity.[38]

In 2003, Sarker and co-workers reported two novel tropane alkaloids, hederacine A **93** and hederacine B **7** from the aerial parts of *Glechoma hederaceae* (Figure 1.6).[39] These alkaloids were shown to exhibit brine shrimp toxicity and moderate cytotoxicity against the colon cancer cell line, Caco-2.[40] Both alkaloids feature a unique skeleton containing an 8-azabicyclo[3.2.1]octane ring system fused to a cyclopentane ring. In addition, hederacine B **7** possesses a spiro-*N*,*O*-acetal core, whereas hederacine A **93** has a hemiaminal core with a ring-opened butenolide.

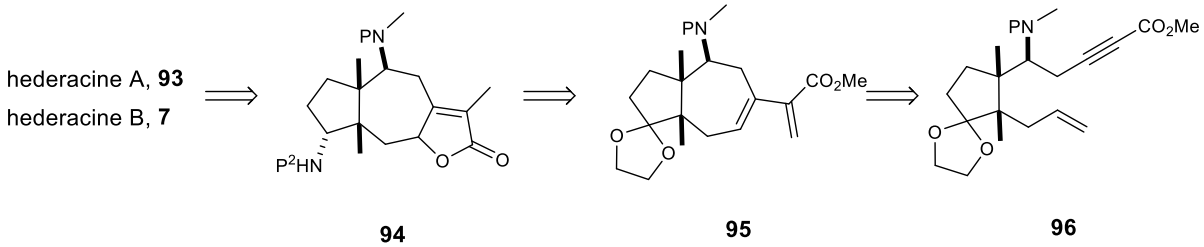


hederacine A, **93** hederacine B, **7**

Figure 1.6: Hederacine A and hederacine B.

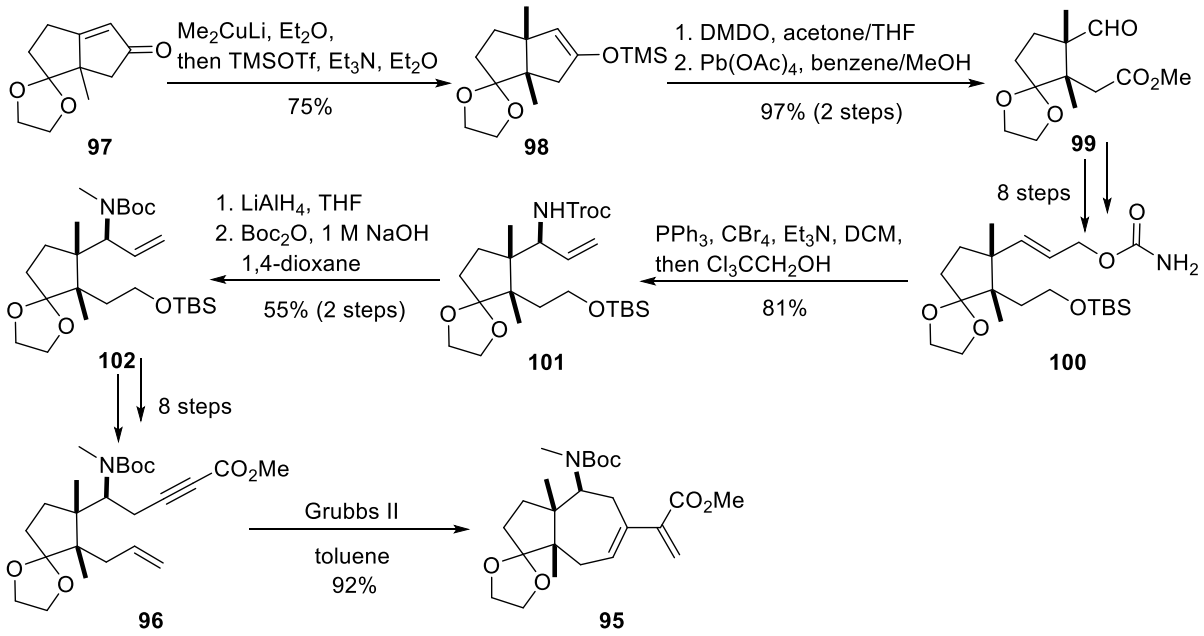
1.5.1 Previous synthesis of *Glechoma hederacea* alkaloids

In 2011, Aoyagi and co-workers completed the first racemic synthesis of 9-*epi*-hederacine A and 9-*epi*-hederacine B in 33 and 35 steps respectively. (Scheme 1.25).[41,42] The authors planned oxidation and acid-promoted transannular cyclisation of precursor **94** to furnish the alkaloids. Precursor **94** was planned to be constructed by lactonisation and reductive amination of the cyclopentanone in diene **95** which was formed from the enyne ring-closing metathesis of intermediate **96**.



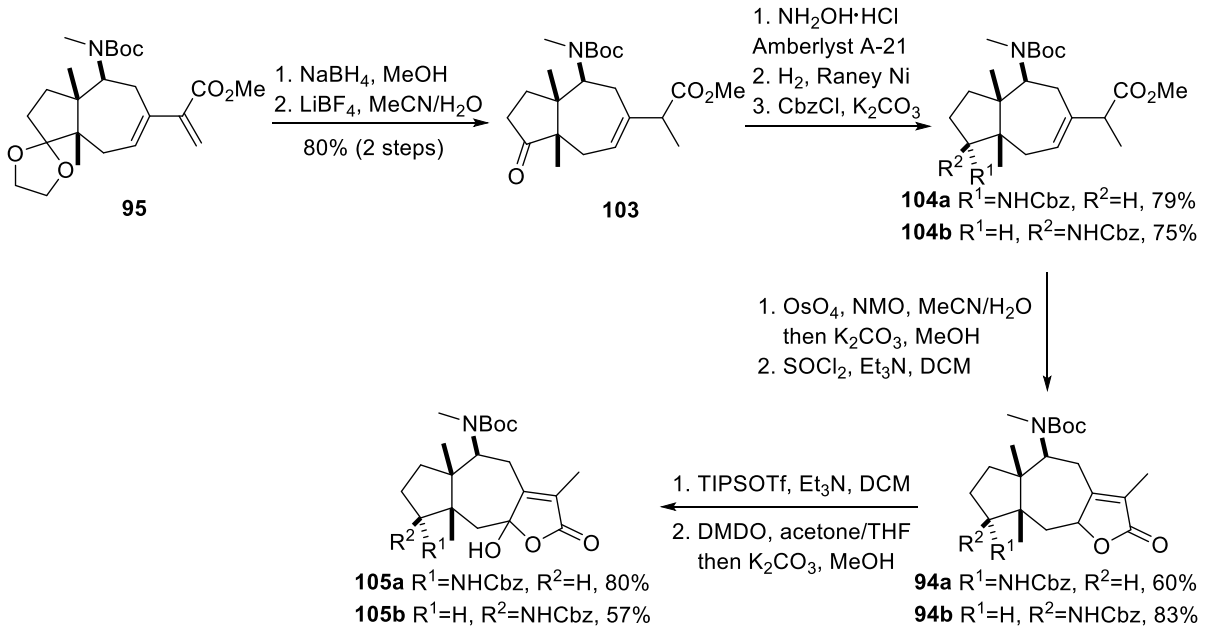
Scheme 1.25: Retrosynthetic approach to hederacines A and B.

Methyl cuprate addition to racemic pentalenone **97** and trapping of the enolate with TMSOTf afforded silyl enol ether **98** which was then cleaved to give aldehyde **99** (Scheme 1.26). After a series of transformations in 8 steps, so-formed carbamate **100** was converted into an allyl cyanate which rearranged by stereoselective [3,3]-shift to an allyl isocyanate that was trapped as Troc-carbamate **101**. Reduction of carbamate **101** and Boc-protection yielded carbamate **102** which was taken through a further 8 steps, including Corey–Fuchs homologation to furnish enyne **96**. Treatment of enyne **96** with Grubbs second-generation catalyst resulted in ring-closing enyne metathesis to form 1,3-dienecarboxylate **95**.



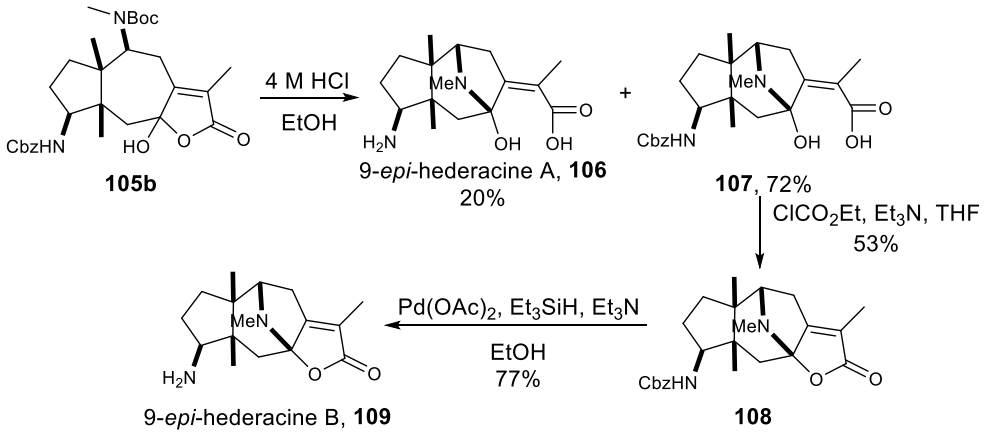
Scheme 1.26: Synthesis of diene **95** *via* ring-closing enyne metathesis.

Diene **95** underwent partial reduction and ketal deprotection to yield ketone **103** which was subjected to reductive amination and Cbz-protection to afford both carbamate diastereomers **104a** and **104b** (Scheme 1.27). Dihydroxylation of carbamate **104**, followed by lactonisation and dehydration furnished azuleno[5,6-*b*]furanone **94** which was converted into a silyloxyfuran and oxidised to hydroxybutenolide **105**.



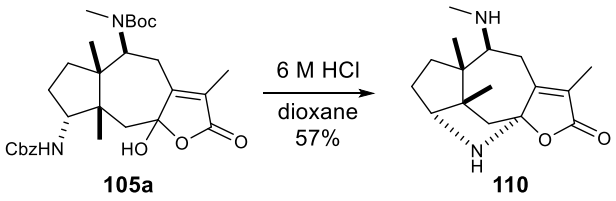
Scheme 1.27: Synthesis of spirocyclisation precursor **105**.

When hydroxybutenolide **105b** was treated with 4 M HCl, transannular hemiaminal formation occurred to afford 9-*epi*-hederacine A **106** and carbamate **107** which was then lactonised to form butenolide **108**. Subsequent Cbz-deprotection using Ohfune's procedure furnished 9-*epi*-hederacine B **109**.



Scheme 1.28: 9-*epi*-hederacines A and B synthesis by transannular cyclisation.

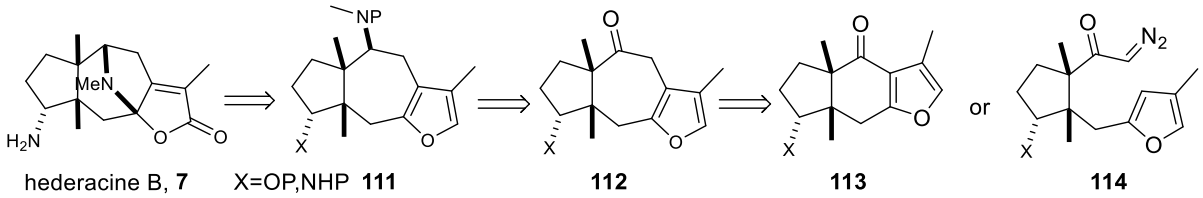
Attempts to synthesise hederacine A **93** and B **7** from hydroxybutenolide **105a** under acidic conditions led to the unexpected formation of tetracyclic spiroaminoacetal **110** by spirocyclisation of the free NH_2 instead of the *N*-methyl amine (Scheme 1.29).



Scheme 1.29: Unexpected formation of tetracyclic amine **110**.

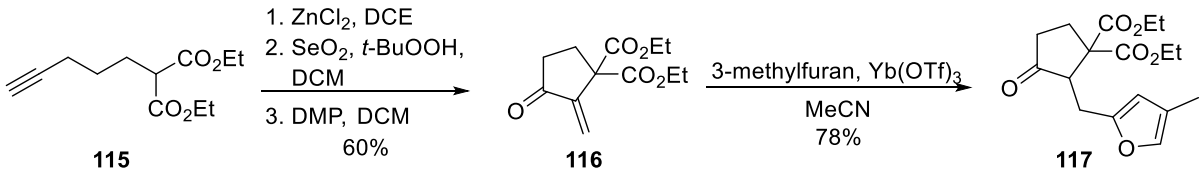
1.5.2 Previous work in Robertson group

As hederacine B **7** contains a similar piperidine/butenolide spiro-*N*,*O*-acetal core as pandamarilactone-1 **4**, we were interested in applying the furan oxidative *N*-spirocyclisation methodology to the synthesis of this natural product (Scheme 1.30). Strategically, the aza-Bohlmann cyclisation of furan amine precursor **111** requires access to tricyclic ketone **112**. Two synthetic approaches to tricyclic furan **112** were proposed initially, one involving the ring expansion of tricyclic ketone **113** and the other involving rhodium carbenoid cyclisation of diazo compound **114**.



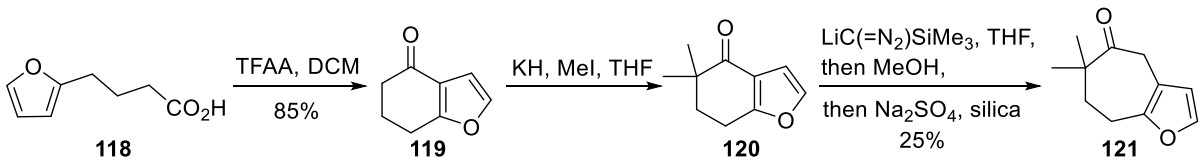
Scheme 1.30: Retrosynthetic approach to hederacine B.

A previous Part II student carried out experiments on simple model compounds to test the feasibility of the ring expansion method for the synthesis of tricyclic furan **112**.[43] Malonate derivative **115** was cyclised by Conia ene reaction then allylic oxidation afforded enone **116**; Lewis acid-promoted conjugate addition of 3-methylfuran then gave adduct **117** (Scheme 1.31).



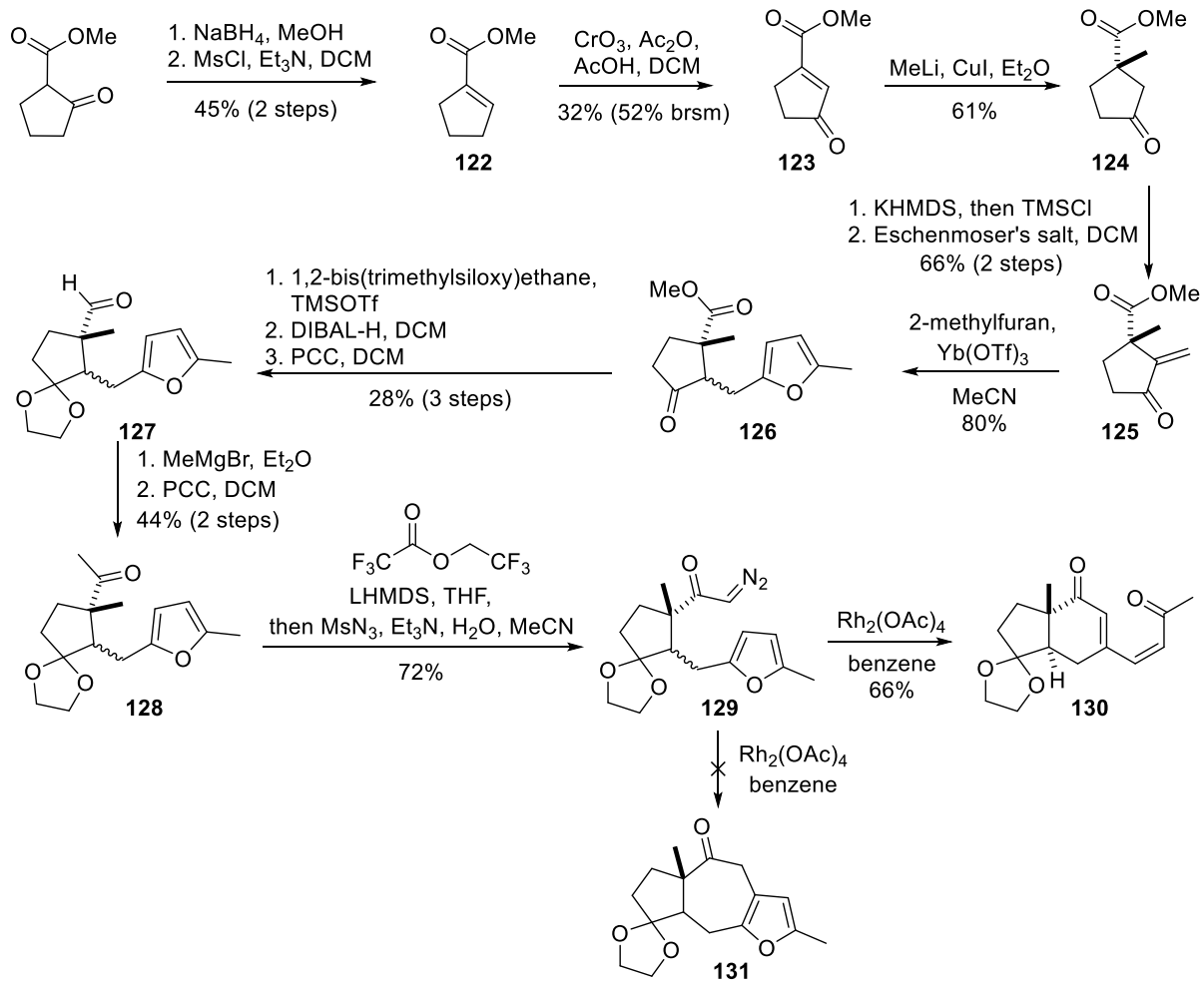
Scheme 1.31: Conjugate addition of 3-methylfuran to enone.

In a complementary study, treatment of carboxylic acid **118** with TFAA led to Friedel–Crafts reaction to yield ketone **119** which was dimethylated to ring expansion precursor **120** (Scheme 1.32). Treating precursor **120** with diazo(trimethylsilyl)methyllithium resulted in ring expansion with preferred migration of the furyl group to afford cycloheptanone **121**.



Scheme 1.32: Friedel–Crafts reaction and ring expansion.

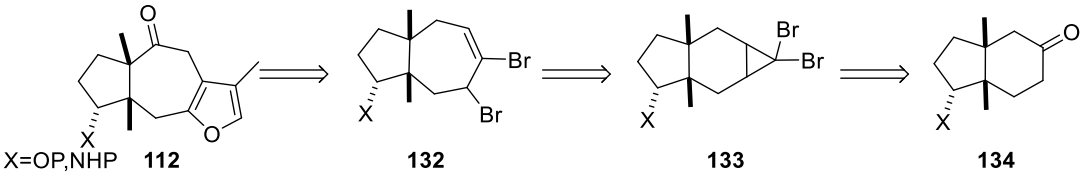
Subsequently, the second synthetic route towards tricyclic furan **112**, using the rhodium carbenoid cyclisation method, was explored by a postdoctoral fellow in our group (Scheme 1.33).[44] Ketone reduction and elimination of methyl 2-oxocyclopentanecarboxylate gave carboxylate **122** which was oxidised to give enone **123**. Methyl cuprate addition afforded ketone **124** which was enolised and trapped as the silyl enol ether before addition of Eschenmoser's salt to form enone **125**. Conjugate addition of 2-methylfuran to enone **125** gave ketone **126** which was protected and reduced to yield aldehyde **127**. Treatment of aldehyde **127** with methylmagnesium bromide then oxidation gave methylketone **128** which was converted into cyclisation precursor **129**. When α-diazoketone **129** was treated with rhodium(II) acetate dimer, dienone **130** was obtained, rather than tricyclic furan **131**.



Scheme 1.33: Progress towards tricyclic furan **112**.

1.5.3 Project aims

In this project a third approach for the synthesis of tricyclic furan **112** was proposed that involves the electrocyclic ring expansion of a dibromocyclopropane intermediate to form the *cis*-fused cycloheptyl ring system (Scheme 1.34). The furan and ketone in tricyclic furan **112** could be installed in various ways from cycloheptyl bromide **132** which could be formed from the electrocyclic ring expansion of dibromocyclopropane **133**. Ring expansion precursor **133** could be synthesised from the dibromocyclopropanation of an alkene derived from ketone **134** which could come from the Hajos–Parrish ketone.



Scheme 1.34: Electrocyclic ring expansion for tricyclic furan synthesis.

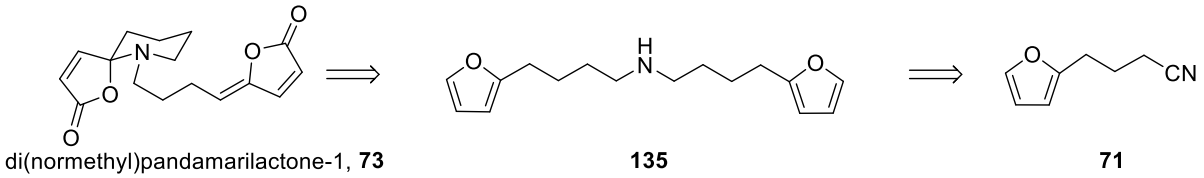
This synthetic route was to be explored in depth and the synthesis of tricyclic furan **112** would be attempted. Once tricyclic furan **112** was obtained, the furan amine precursor **111** could be furnished and the furan oxidative *N*-spirocyclisation methodology applied for the synthesis of hederacine A **93** and hederacine B **7** (Scheme 1.30).

Chapter 2: *Pandanus* Alkaloids Synthesis

2.1 Di(normethyl)pandamarilactone-1

2.1.1 Retrosynthetic approach

In order to simplify the chemistry so that spirocyclisation could be more easily optimised and provide further evidence to confirm the structure of pandamarilactone-1, the synthesis of model compound, di(normethyl)pandamarilactone-1 **73** was proposed (Scheme 2.1). It was envisaged that spiroaminoacetal **73** would be formed by oxidative *N*-spirocyclisation of precursor **135**, itself derived from readily accessible nitrile **71**.

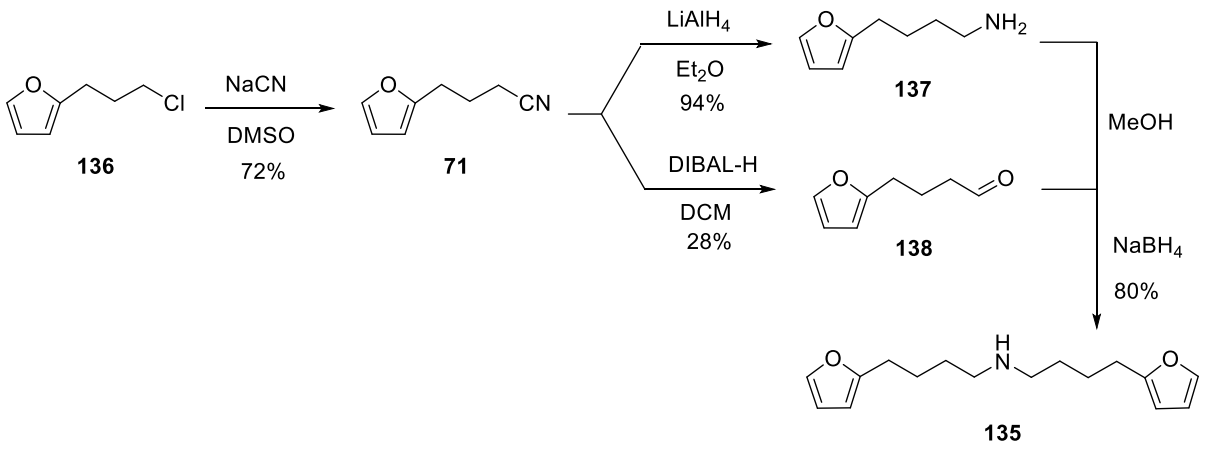


di(normethyl)pandamarilactone-1, **73** **135** **71**

Scheme 2.1: Retrosynthetic approach for synthesis of di(normethyl)pandamarilactone-1.

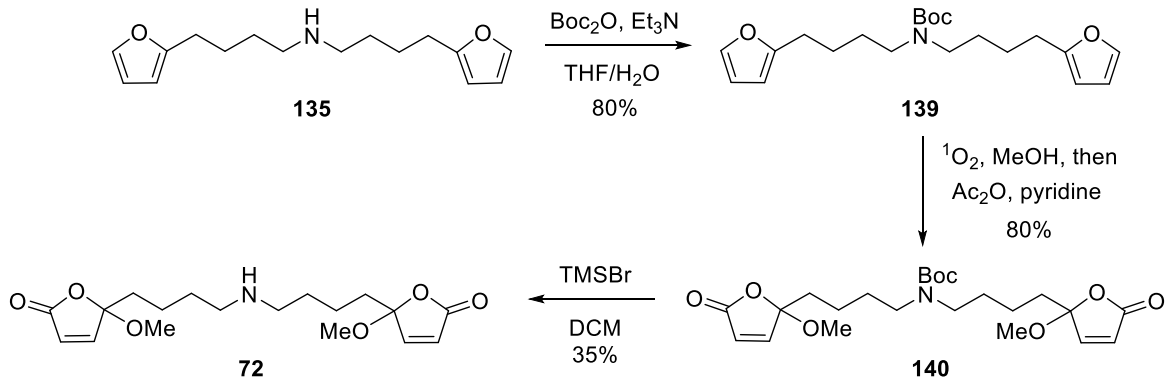
2.1.2 Initial attempt

Starting with chloropropylfuran **136**, displacement with NaCN afforded nitrile **71** which was separated into two portions (Scheme 2.2). Complete reduction of one portion of nitrile **71** yielded amine **137**, whereas partial reduction of another portion of nitrile **71** with DIBAL-H afforded aldehyde **138** in poor yield. The partial reduction was incomplete, most likely due to a lower concentration of DIBAL-H in the bottle. Reductive amination of aldehyde **138** with amine **137** and $NaBH_4$ furnished furan amine **135** in good yield.



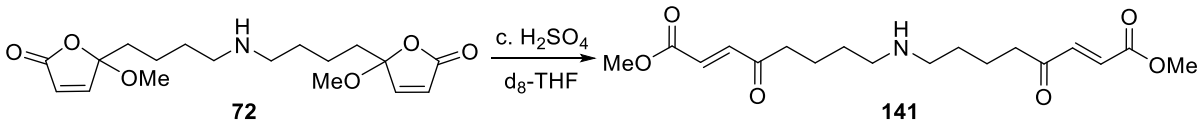
Scheme 2.2: Furan amine precursor **135** synthesis.

As previous studies showed that direct oxidation of amine **135** led to complex product mixtures and low yields,[21] the free amine was first Boc-protected to form carbamate **139** (Scheme 2.3). Furan photo-oxidation by bubbling oxygen through a methanolic solution of carbamate **139** in the presence of visible light (Exo-Terra PT-2056 200 W lamp) and Rose Bengal as the photosensitiser formed a hydroperoxy intermediate which, upon acetylation-elimination with acetic anhydride and pyridine, afforded methoxy butenolide **140**. Boc-deprotection of carbamate **140** with TMSBr as Lewis acid furnished spirocyclisation precursor **72** in low yield, possibly due to partial decomposition.



Scheme 2.3: Spirocyclisation precursor **72** synthesis.

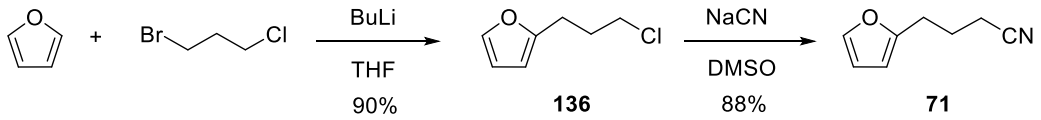
With a small amount of spirocyclisation precursor **72** in hand, the acid-catalysed spirocyclisation reaction was attempted as an NMR experiment. The addition of conc. H_2SO_4 to a solution of amine **72** in d_8-THF gave a homogeneous mixture which afforded a compound tentatively assigned as amine **141** after 5 days. The large coupling constant of 15 Hz for the *trans*-alkenic protons in **141** indicated that the butenolide rings in **72** opened to give an unsaturated ester, presumably representing the thermodynamic stability of this system.



Scheme 2.4: NMR experiment of acid-catalysed spirocyclisation.

2.1.3 Large scale synthesis

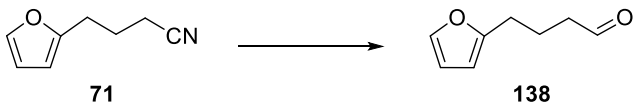
With insufficient amine **72** to attempt further spirocyclisation conditions, the synthetic route was scaled up starting with furan (Scheme 2.5). Lithiation and alkylation of furan gave chloropropylfuran **136** in good yield on multigram scale.



Scheme 2.5: Scale up synthesis of nitrile **71**.

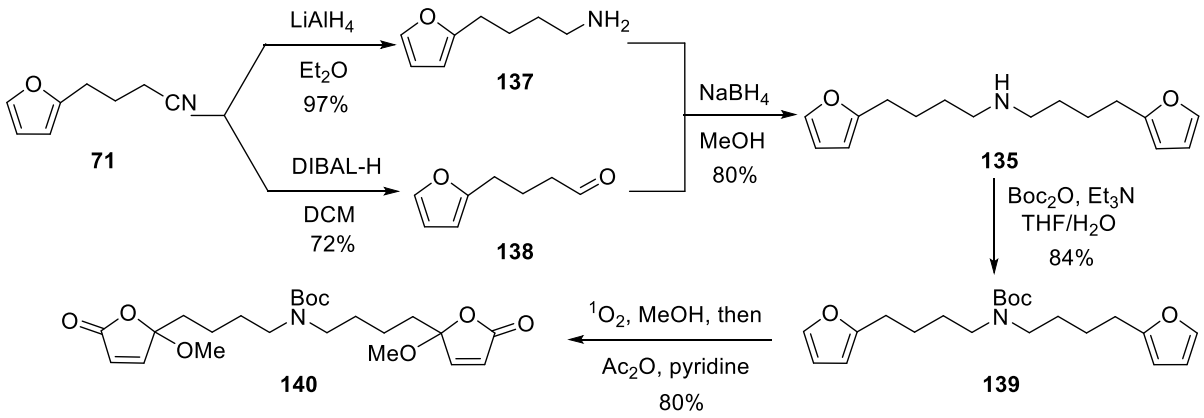
With more nitrile **71** in hand, the partial reduction with DIBAL-H was optimised to improve the yield of aldehyde **138**. Initial attempts with a new bottle of DIBAL-H gave yields of about 25% due to the oligomerisation of imine intermediates. Subsequently, other reducing agents and reaction conditions were attempted to minimise oligomerisation (Table 2.1). No reduction occurred when lithium ethoxyaluminohydride was used as reducing agent.[45,46] Diluting the reaction mixture and purifying aldehyde **138** with alumina instead of silica eventually resulted in a higher yield of 72% by minimising the formation of the oligomer.

Table 2.1: Optimisation of partial reduction of nitrile **71**.



Reducing agent	Solvent	[Nitrile]/ M	Yield/ %
$LiAlH(OEt)_3$	Et_2O	0.925	0
$LiAlH_2(OEt)_2$	Et_2O	0.925	0
$LiAlH_3(OEt)$	Et_2O	0.925	0
DIBAL-H	DCM	0.296	24
DIBAL-H	DCM	0.114	39
DIBAL-H	DCM	0.0617	72

Using these optimised reaction conditions for DIBAL-H reduction, larger quantities of aldehyde **138** were synthesised and the subsequent reductive amination, Boc-protection and furan photo-oxidation proceeded smoothly in excellent yields on multigram scale (Scheme 2.6).

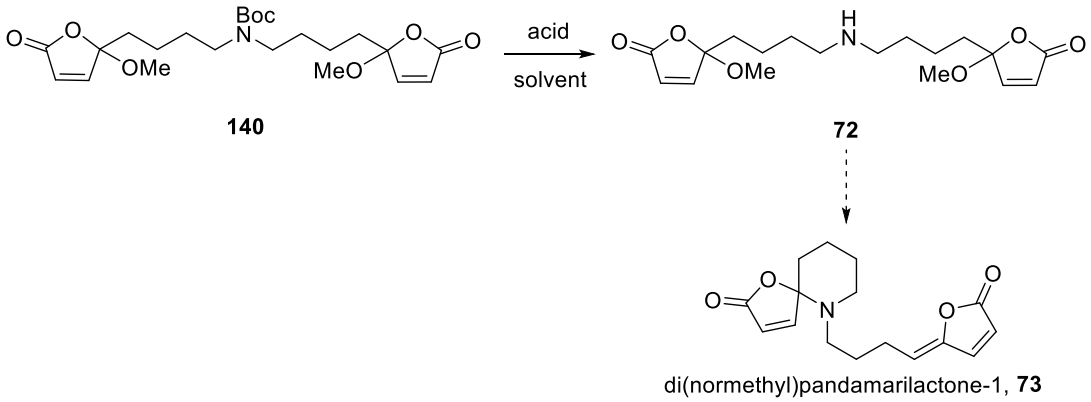


Scheme 2.6: Large scale synthesis of methoxybutenolide **139**.

Different Brønsted and Lewis acids[47] were then used to attempt the Boc-deprotection of methoxy butenolide **140** so as to optimise the yield of the deprotection and to determine the

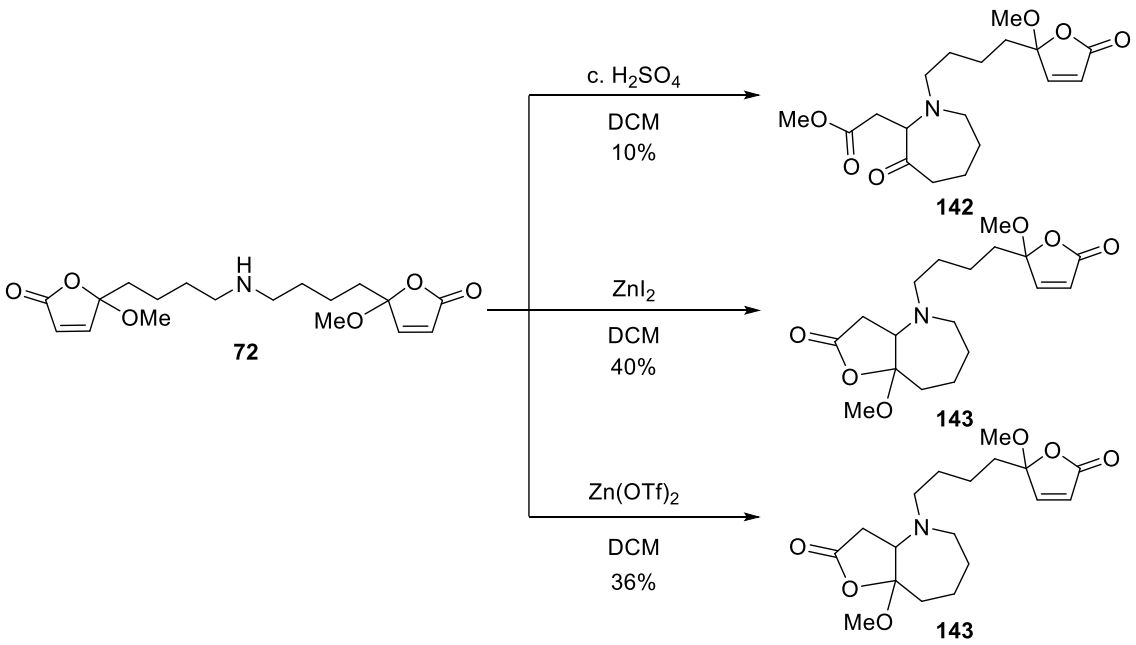
possibility of *N*-spirocyclisation occurring in one-pot (Table 2.2). However, the acids used only resulted in Boc-deprotection to afford amine **72** without further cyclisation. The use of 1% TFA gave the best yield of amine **72** and more spirocyclisation precursor was synthesised.

Table 2.2: Optimisation of acid-catalysed Boc-deprotection.



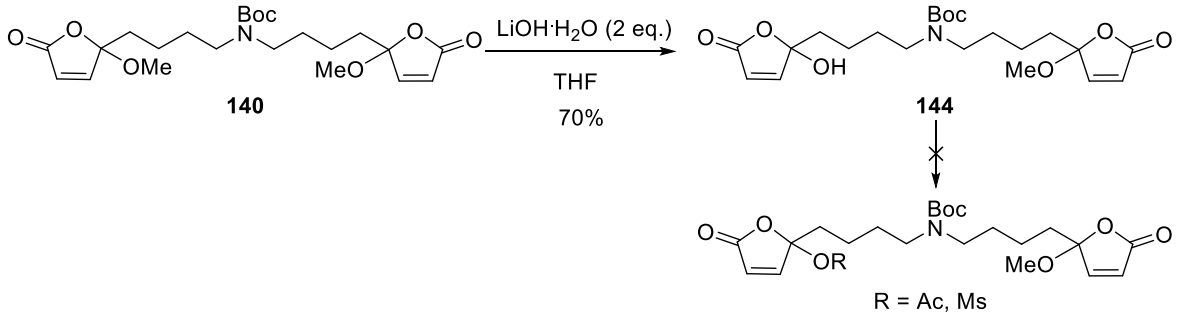
Acid	Solvent	Yield of amine 72/ %
TMSBr	DCM	44
TMSOTf	DCM	80
aq. HI	MeCN	Decomposition
1% TFA	DCM	90

Finally, different acids and conditions were employed to bring about *N*-spirocyclisation of precursor **72** (Scheme 2.7). When conc. H_2SO_4 was added to a solution of amine **72** in DCM, after 5 days the heterogeneous mixture afforded azepane **142** via intramolecular conjugate addition of the amine into the butenolide followed by butenolide methanolysis. Further *N*-spirocyclisation attempts using Lewis acids[48,49] like ZnI_2 and $Zn(OTf)_2$ yielded [3,2-*b*]-fused azepane **143**, the likely intermediate en route to **142**.



Scheme 2.7: Attempts to achieve the acid-catalysed *N*-spirocyclisation of amine **72**.

In order to determine if changing the methoxy group on the butenolide into a hydroxy group could promote *N*-spirocyclisation, partial hydrolysis of the methoxy butenolide **140** was attempted using LiOH·H_2O (Scheme 2.8).[50] Using 1 or 2 eq. of LiOH·H_2O afforded butenolide **144** with just one of the two acetal centres hydrolysed. Use of more than 2 eq. of LiOH·H_2O led to the formation of a gelatinous mixture which could not be extracted. Attempts to acetylate or mesylate the hydroxyl group of butenolide **144** were unsuccessful.[51]



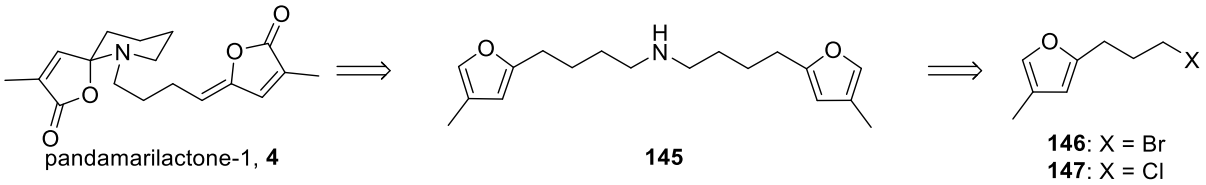
Scheme 2.8: Attempts at modifying the methoxy leaving group.

Unable to effect *N*-spirocyclisation to form di(normethyl)pandamarilactone-1 **73**, it is postulated that the methyl substituents on the butenolide in pandamarilactone-1 play an important role in sterically and electronically disfavouring intramolecular conjugate addition relative to *N*-spirocyclisation. Therefore, the focus shifted to the synthesis of pandamarilactone-1 **4**.

2.2 Pandamarilactone-1 synthesis

2.2.1 Retrosynthetic approach

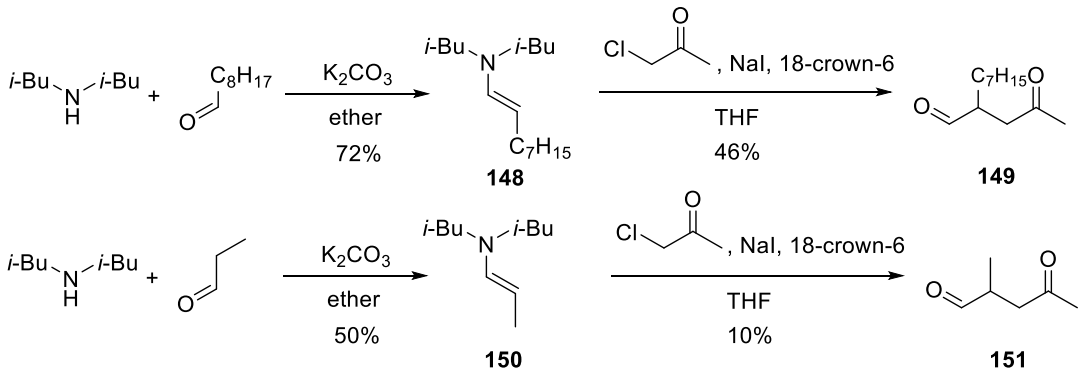
Building on the analogue synthesis, it was envisaged that pandamarilactone-1 **4** could be obtained from precursor **145**, derived from 2,4-disubstituted furan **146** or **147** (Scheme 2.9).



Scheme 2.9: Retrosynthetic approach for synthesis of pandamarilactone-1.

2.2.2 Paal–Knorr furan synthesis

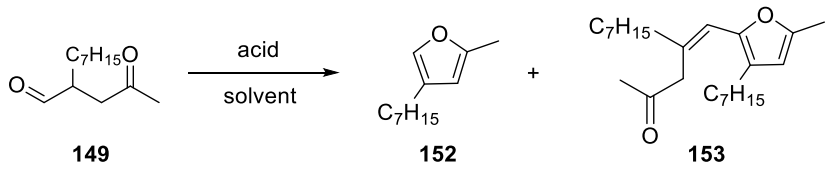
In order to synthesise the starting 2,4-disubstituted furan **146** or **147**, a Paal–Knorr approach was first attempted. Representative enamines **148** and **150** were synthesised from nonanal and propionaldehyde respectively in the presence of K_2CO_3 (Scheme 2.10). For model study purposes, the displacement reaction was carried out on chloroacetone using enamine **148** and **150** to afford 1,4-dicarbonyl **149** and **151** respectively.[52] The relatively poor yield of **151** was attributed to the instability of enamine **150**.



Scheme 2.10: Model studies for 1,4-dicarbonyl synthesis.

The acid-catalysed Paal–Knorr cyclisation was attempted with 1,4-dicarbonyl **149** using *p*-toluenesulfonic acid to yield furan **152** (Table 2.3).[53] However, side product **153** was formed as the major product from the Paal–Knorr reaction, resulting in a low yield of the desired furan. The side product was apparently formed by nucleophilic addition of the furan **152** into the aldehyde of 1,4-dicarbonyl **149**, then dehydration. Attempts to optimise the Paal–Knorr reaction by diluting the reaction mixture, adding the 1,4-dicarbonyl dropwise or using other acid catalysts like P_2O_5 and Amberlyst were unsuccessful and the side product was still obtained.[54,55]

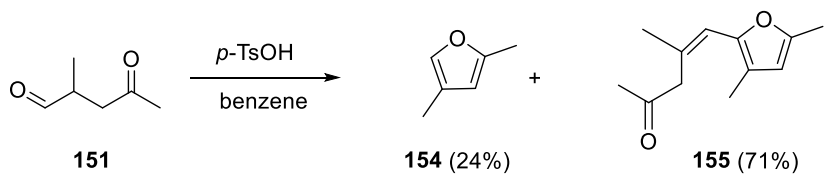
Table 2.3: Optimisation of Paal–Knorr cyclisation.



149 **152** **153**

Acid	Solvent	[1,4-dicarbonyl]/ M	Yield of 152/ %
p-TsOH (0.1 eq.)	benzene	0.066	44
p-TsOH (0.05 eq.)	benzene	0.033	33
p-TsOH (0.1 eq.)	benzene	0.066 (dropwise addition)	40
p-TsOH (1 eq.)	benzene	0.01 (dropwise addition)	40
P_2O_5 (12 eq.)	EtOH/ether	0.28	16
PPTS (0.05 eq.)	benzene	0.1	SM
$BF_3{\cdot}OEt_2$ (0.1 eq.)	ether	0.05	Decomposed
Amberlyst 15	benzene	0.05	25

Similarly, when 1,4-dicarbonyl **151** was subjected to the same Paal–Knorr cyclisation conditions, furan **154** and side product **155** were obtained (Scheme 2.11). Side product **155** could not be characterised fully by NMR spectroscopy due to its instability in $CDCl_3$, decomposing overnight.

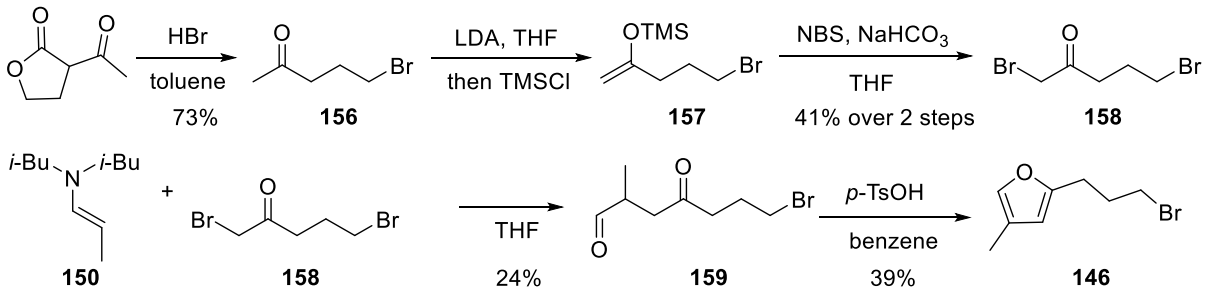


151 **154** (24%) **155** (71%)

Scheme 2.11: Paal–Knorr cyclisation of 1,4-dicarbonyl **151**.

In parallel, heating 2-acetylbutyrolactone with hydrobromic acid afforded bromoketone **156** which was enolised and trapped as silyl enol ether **157** (Scheme 2.12).[56] Bromination of

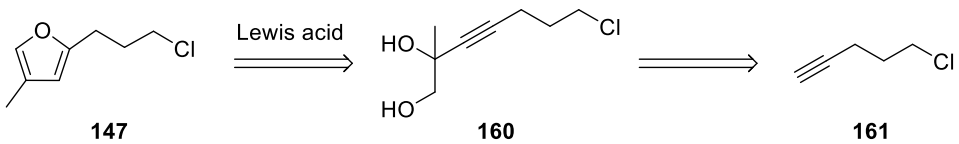
crude **157** with NBS yielded α-bromo ketone **158** which was alkylated with enamine **150** to afford 1,4-dicarbonyl **159**. Similar to previous model studies, Paal–Knorr cyclisation of **159** in the presence of *p*-TsOH gave furan **146** in 39% yield due to the formation of the side product analogous to **153**/**155**. Overall, the low yields of the enamine alkylation and Paal–Knorr steps made this approach unsuitable for scaling up to synthesise the starting furan **146**.



Scheme 2.12: Paal–Knorr approach to 2,4-disubstituted furan **146**.

2.2.3 Ag(I)-catalysed furan synthesis

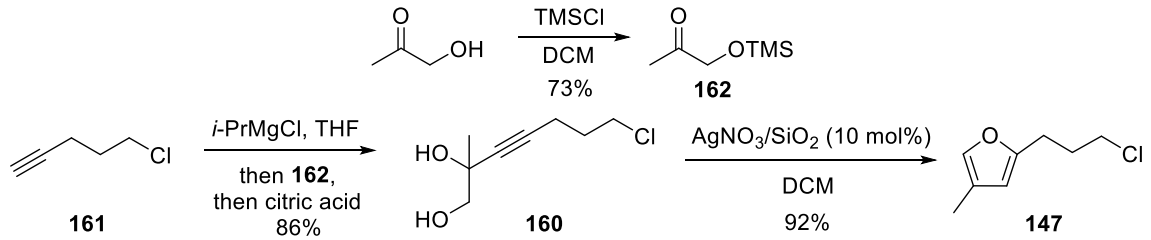
A convergent approach to 2,4-disubstituted furan **147** involves Lewis acid mediated cyclodehydration of alkynyl diol precursor **160** which may be formed from alkyne **161** (Scheme 2.13). Although this general approach was reported almost 60 years ago (with $HgCl_2$ as the catalyst),[57] versions with improved catalysts continue to be published.[58]



Scheme 2.13: Lewis acid catalysed synthesis of 2,4-disubstituted furan.

Based on previous studies,[21] the most efficient way to prepare alkynyl diol **160** was *via* organometallic addition of alkyne **161** to TMS-acetol **162** followed by acid workup.

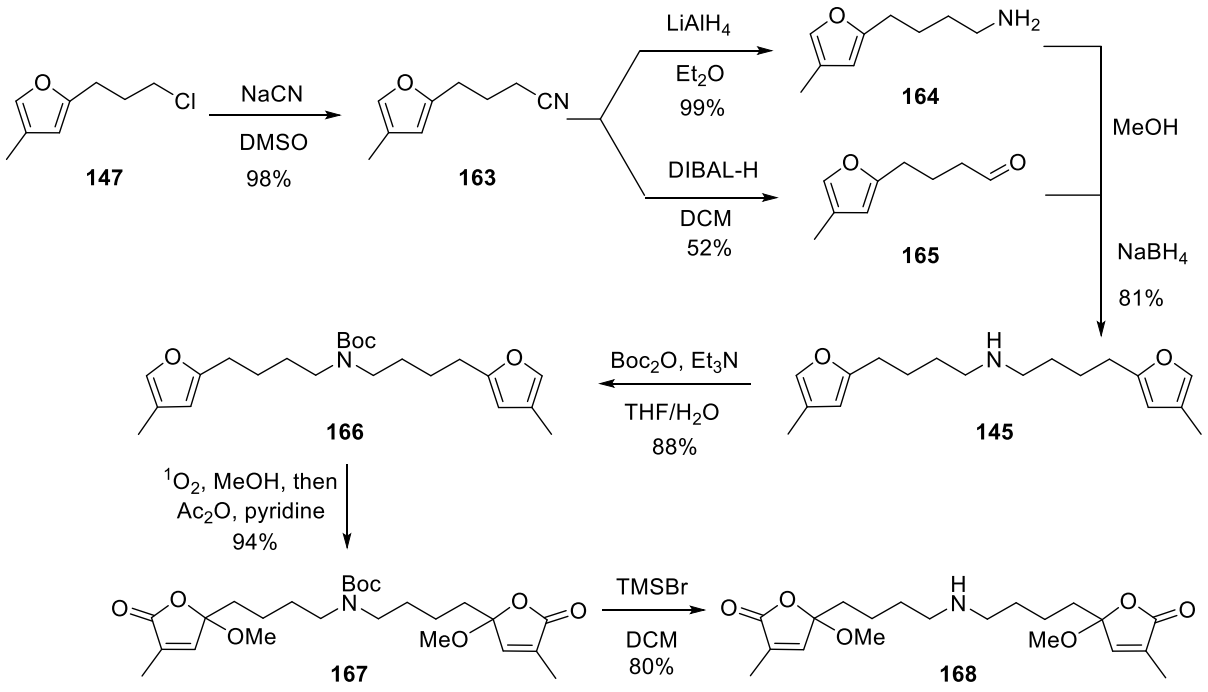
Silylation of hydroxyacetone afforded TMS-acetol **162** in moderate yield (Scheme 2.14).[59] Deprotonation of 5-chloro-1-pentyne **161** with *i*-PrMgCl and addition to TMS-acetol **162** then desilylation with methanolic citric acid yielded diol **160** in good yield. For the cyclodehydration, Knight's $AgNO_3$–SiO_2 variant was chosen as the catalyst is inexpensive, the procedure is operationally straightforward, and the products are obtained in high purity after filtration.[34] Pleasingly, this reaction proceeded cleanly and in high yield to afford the desired furan **147** on multigram scale.



Scheme 2.14: Ag(I)-catalysed synthesis of 2,4-disubstituted furan **147**.

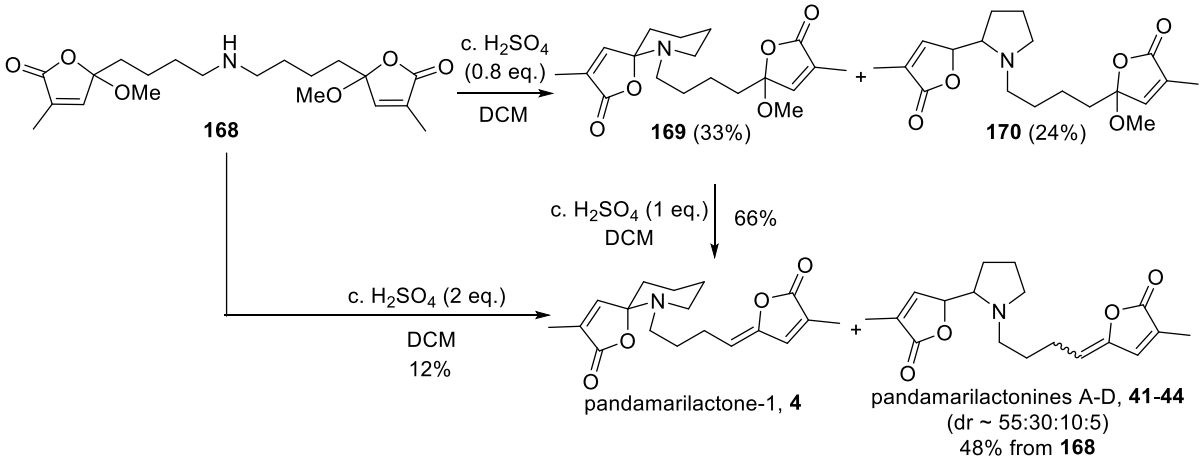
2.2.4 Progress towards pandamarilactone-1

From furan **147**, displacement with NaCN afforded nitrile **163** which was split into two portions for parallel reductions to the amine **164** and aldehyde **165** (Scheme 2.15) as before. The DIBAL-H reduction was somewhat capricious and even with relatively dilute reaction mixtures and dropwise addition of DIBAL-H, oligomerisation of imine intermediates resulted in a lowering of yields. Subsequent reductive amination afforded amine **145** which was Boc-protected to form carbamate **166**. Photo-oxidation with singlet oxygen gave methoxybutenolide **167** which was deprotected to furnish spirocyclisation precursor **168**.[60]



Scheme 2.15: Synthetic route towards pandamarilactone-1.

When 0.8 eq. of conc. H_2SO_4 was added to a solution of amine **168** in DCM, the vigorously stirred biphasic mixture gave pandamarilactone-1 and pandamarilactonine A/B variants **169** and **170**, respectively (Scheme 2.16). Resubmission of intermediate **169** to the reaction conditions (with 1.0 eq. of conc. H_2SO_4) brought about methanol elimination to yield pandamarilactone-1 **4**. When amine **168** was treated with 2.0 eq. of conc. H_2SO_4, *N*-spirocyclisation and methanol elimination took place in one-pot to afford pandamarilactone-1 **4** in 12% yield. An inseparable mixture of pandamarilactonines A–D **41–44** was also obtained as the major product from the one-pot reaction. Therefore, it is evident that the presence of methyl groups on the butenolide disfavour intramolecular conjugate addition relative to *N*-spirocyclisation. The methyl groups might assist oxocarbenium ion formation to bring about *N*-spirocyclisation.



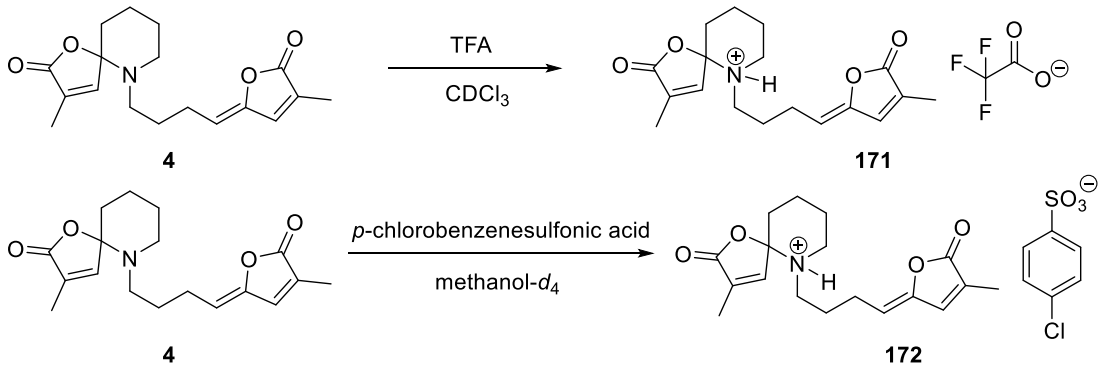
Scheme 2.16: Acid-catalysed *N*-spirocyclisation to pandamarilactone-1.

Despite several attempts to improve the yield and reproducibility of the *N*-spirocyclisation reaction, 12% was the optimum for the single-flask process. In summary, pandamarilactone-1 **4** was synthesised from 5-chloro-1-pentyne in 10 steps and 9% overall yield.

2.3 Structural Elucidation

2.3.1 Salt formation

Pandamarilactone-1 was reported to be an amorphous solid,[4] but the synthetic product was obtained as an oil. In an attempt to confirm the structure of synthetic pandamarilactone-1 **4** by X-ray crystallography, various salts of pandamarilactone-1 were prepared using different acids. No salt formation occurred when *p*-bromobenzoic acid was used. In the presence of TFA and *p*-chlorobenzenesulfonic acid, pandamarilactone-1 **4** formed the trifluoroacetate salt **171** and sulfonate salt **172** respectively (Scheme 2.17). Some resonances were shifted downfield in the ^{1}H NMR spectra of the salts, indicating that salt formation has occurred. This shift gave a good separation of peaks in the ^{1}H NMR spectra and HMBC data were suitable to confirm the spiro-*N*,*O*-acetal structure of pandamarilactone-1. However, attempts to purify the salts gave back the free base and efforts to crystallise them were fruitless.

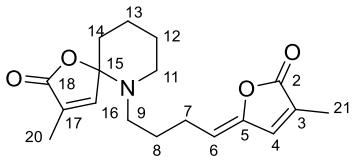


Scheme 2.17: Pandamarilactone-1 salt formation.

2.3.2 ^{13}C NMR data

In 2005, Nonato and co-workers isolated pandamarilactone-1 and other known alkaloids in a pH-neutral process from *Pandanus amaryllifolius* collected from Marikina, Philippines.[23] The ^{13}C NMR data of pandamarilactone-1 isolated in 2005 differed at C(9) from that in 1993 (Table 2.4). The ^{13}C NMR data of synthetic pandamarilactone-1 match the literature data in the more recent paper,[23] further confirming the structure of pandamarilactone-1 obtained.

Table 2.4: Comparison of ^{13}C NMR data with literature.



Carbon	Nonato 1993[4]	Nonato 2005[23]	Found
2	171.0	171.0	171.0
3	129.2	129.2	129.2
4	137.6	137.6	137.6
5	148.6	148.5	148.5
6	113.7	113.8	113.9
7	24.0	23.9	23.9
8	27.2	27.1	27.0
9	50.7	49.5	49.5
11	47.2	47.1	47.1
12	20.8	20.7	20.7
13	25.1	25.0	25.0
14	36.2	36.1	36.1
15	101.7	101.7	101.7
16	149.7	149.7	149.7
17	131.5	131.5	131.5
18	173.0	172.9	172.9
20	10.6	10.7	10.7
21	10.4	10.5	10.5

2.3.3 Site-specific hydrogen-deuterium exchange

In the ^{1}H NMR spectrum of synthetic pandamarilactone-1 in $CDCl_3$, the low-field resonances corresponded well to those reported but most of the methylene resonances in the 1.5–3.0 region were broadened, resulting in poor quality HMBC and HSQC data. However, in methanol-d_4, the spectrum sharpened sufficiently to enable convincing HMBC data to be obtained in support of the spiro-*N*,*O*-acetal core, all other aspects of the structure being unambiguous (Figure 2.1, Appendix A).

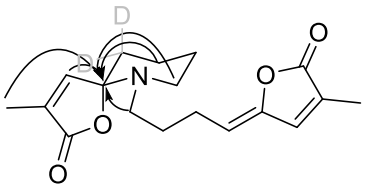
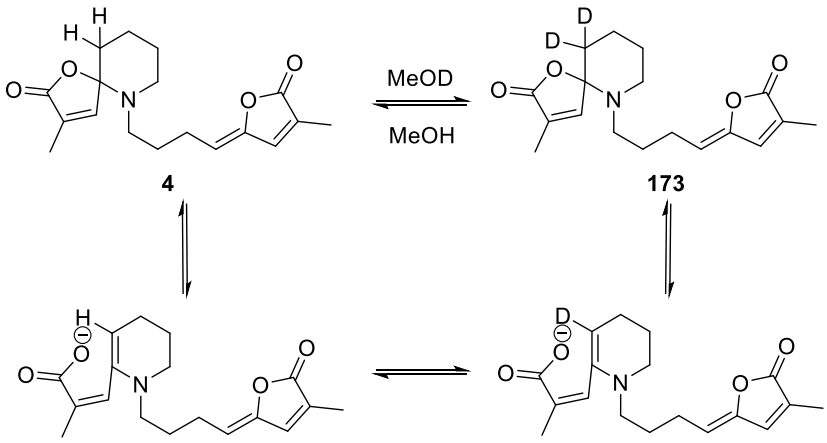


Figure 2.1: Key HMBC correlations supporting a spiro-*N*,*O*-acetal.

In the ^{13}C NMR spectrum of pandamarilactone-1 in methanol-d_4, the resonance at 36.2 ppm is a 1:2:3:2:1 'quintet' (J = 20 Hz) and the spiro-carbon at 107.7 ppm appears broadened and of low intensity. This is attributed to dideuteration of one of the methylenes next to the spirocentre, and reference back to the ^1H spectrum showed the integration of the methylenes to be reduced by two protons. Full proton integration was restored when the sample was allowed to stand in undeuterated methanol. These observations could be explained by the site-specific hydrogen-deuterium exchange in pandamarilactone-1 **4** dissolved in methanol-d_4 to form deuterated pandamarilactone-1 **173** which could revert back to **4** in methanol-d_0 (Scheme 2.18).



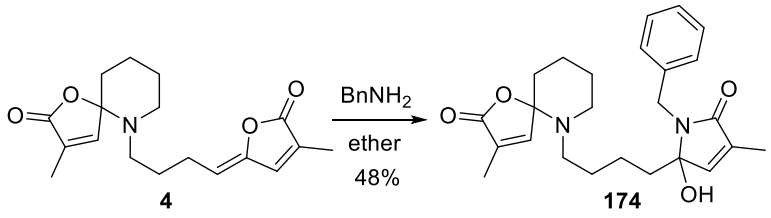
Scheme 2.18: Site-specific hydrogen-deuterium exchange in pandamarilactone-1.

This reversible chemical reactivity, combined with the HMBC data, provide strong corroboration of the assigned structure of pandamarilactone-1 **4**.

2.4 Reactivity of pandamarilactone-1

2.4.1 Reaction with benzylamine

In order to determine if the conversion of lactone to lactam functionality in pandamarilactone-1 is feasible, an ethereal solution of the natural product **4** was treated with benzylamine. After stirring at RT for 2 days, hydroxylactam **174** was obtained as the major product (Scheme 2.19). Extended treatment of this molecule with more benzylamine resulted in no further conversion and it appears that the spirocyclic butenolide is relatively unreactive towards amination processes, possibly due to equilibrium of the spirocycle with the ring opened carboxylate-iminium form.

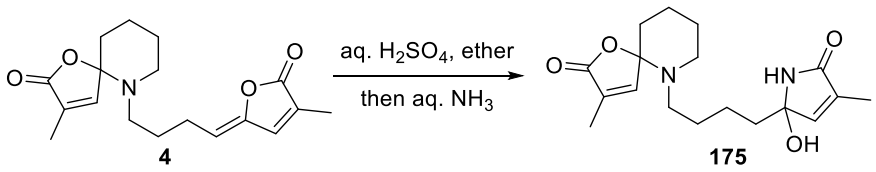


Scheme 2.19: Reactivity of pandamarilactone-1 with benzylamine.

2.4.2 Reaction with aqueous ammonia

Subsequently, we decided to test our speculation that pandamarine might be an experimental artifact formed during the basification step of its isolation. When a 4.4 mg sample of pandamarilactone-1 **4** in 0.5 mL of THF was treated with 5 eq. of conc. aq. NH_3 at RT for 14 h, no reaction occurred. On the other hand, a 2.1 mg sample of pandamarilactone-1 **4** in THF/aq. NH_3 (1:1, 0.4 mL) gave a complex mixture of lactam products after a similar reaction time. Next, in an attempt to more closely replicate the conditions described in the original isolation,[25] an ether solution of pandamarilactone-1 **4** was stirred with dilute H_2SO_4.

The aqueous layer was rendered basic with aq. NH_3, and the products were extracted into chloroform. This gave a mixture of pandamarilactone-1 and hydroxylactam **175** in roughly equal proportion (Scheme 2.20). Similarly, the spirocyclic butenolide is shown to be unreactive towards amination in this case. However, the use of hydroxylamine in Chapter 4 managed to convert a spirocyclic lactone into a lactam (*cf.* Scheme 4.56).



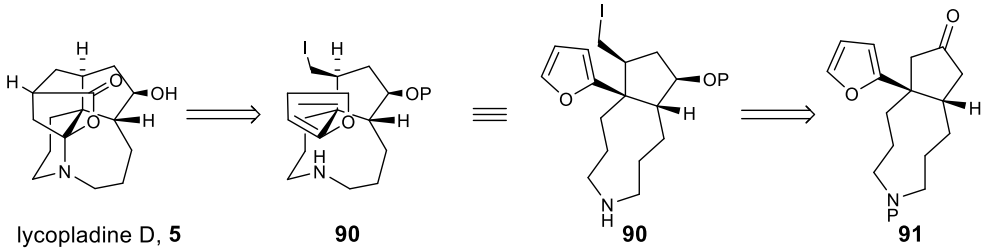
Scheme 2.20: Attempted conversion of pandamarilactone-1 to pandamarine.

As pandamarine was not observed in any of these experiments, we conclude that it is not an experimental artifact from the isolation process and is most likely a genuine natural product.

Chapter 3: Lycopladine D

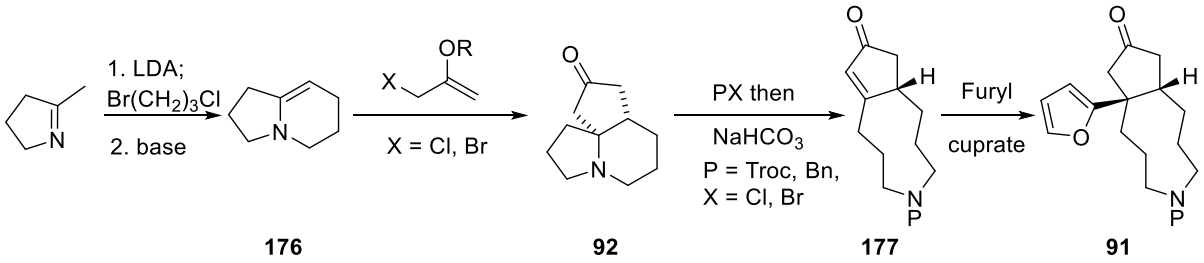
3.1 Retrosynthetic approach

It was envisaged that lycopladine D **5** would be formed from the cyclisation of precursor **90** followed by enolate alkylation. Precursor **90** would arise from ketone **91** after a series of functional group transformations (Scheme 3.1).



Scheme 3.1: Retrosynthetic approach to lycopladine D.

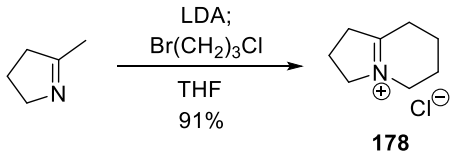
A general route to synthesise bicyclic amine **91** was proposed that began with alkylation of 2-methyl-1-pyrroline, to afford enamine **176**, then cyclopentannulation to form tricyclic amino ketone **92** (Scheme 3.2). *N*-Protection and elimination of the so-formed ammonium species would lead to ring expansion to give bicyclic amine **177**; furyl cuprate conjugate addition would then furnish bicyclic amine **91**.



Scheme 3.2: Proposed route to furan amine **91**.

3.2 Bicyclic enamine synthesis

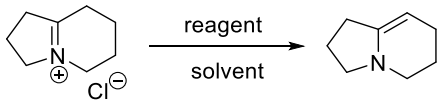
Following De Kimpe's procedure for the synthesis of indolizidines,[61] treatment of 2-methyl-1-pyrroline with LDA and dialkylation with 1-bromo-3-chloropropane afforded iminium salt **178** in excellent yield (Scheme 3.3).



Scheme 3.3: Synthesis of iminium salt **178**.

As there was no precedent for the synthesis of enamine **176** from iminium salt **178**, different bases and conditions were screened for the formation of enamine **176** (Table 3.1). The use of *t*-$BuNH_2$ as base led to a partial formation of enamine **176**, whereas the use of KOH or NaOH in MeOH gave back starting iminium salt.[62,63] Attempts to use Ag(I) salts to coordinate to the chloride anion to promote enamine formation were unsuccessful. Attempts to use KHMDS or LDA to effect deprotonation, followed by alkylation in situ, similarly gave back starting material. Finally, stirring iminium salt **178** in 2.0 M aq. NaOH solution for 2 h, then addition of pentane, stirring for 1 h and separating off the organic layer gave enamine **176** in 31% yield. Some starting iminium salt was still present after 2 h of reaction, resulting in the low yield. Increasing the reaction time to 12 h led to full consumption of starting material to give pure enamine **176** in 80% yield. Partial decomposition of enamine took place upon standing in C_6D_6 overnight, which suggested that the unstable nature of enamine **176** led to the merely moderate yield obtained.

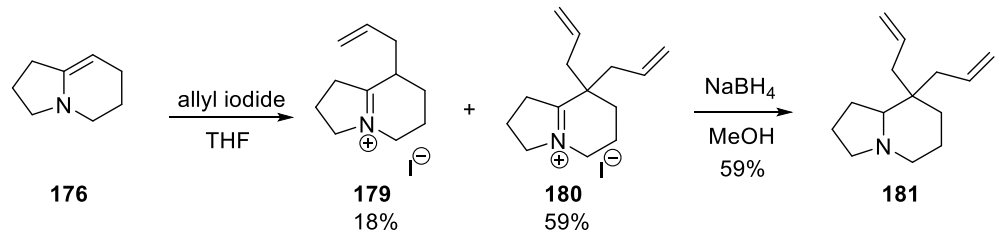
Table 3.1: Attempts to synthesise enamine **176**.



Reagent	Solvent	Duration/ h	Electrophile	Yield/ %
t-$BuNH_2$	benzene	12	-	~5
KOH (5.0 M)	MeOH	4	-	0
NaOH (5.0 M)	MeOH	4	-	0
Ag_2O	MeOH	2	-	0
Ag_2O	aq. NaOH (2.5 M)	4	-	0
$AgNO_3$	MeOH	4	-	0
KHMDS	THF	12	allyl iodide	0
KHMDS, *t*-$BuNH_2$	THF	12	allyl iodide	0
KHMDS, *t*-$BuNH_2$	THF	12	methyl iodide	0
LDA	THF	12	allyl iodide	0
NaOH (2.0 M)	H_2O	2	-	31
NaOH (2.0 M)	H_2O	12	-	80

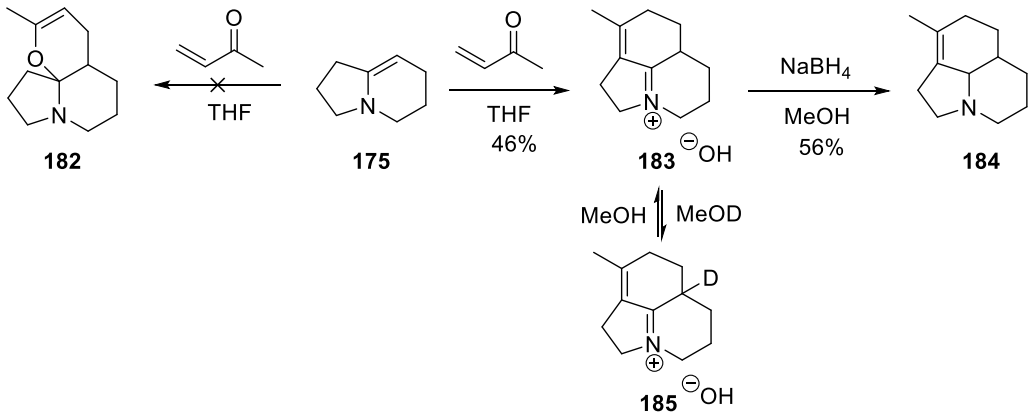
3.3 Versatile chemistry of bicyclic enamine

The somewhat unstable enamine **176** has to be used directly for alkylation to form stable iminium salts. When 1 eq. of allyl iodide was used as the electrophile, enamine **176** underwent alkylation readily within 2 h to afford dialkylated iminium salt **180** as the major product and monoalkylated iminium salt **179** as the minor product (Scheme 3.4). Monoalkylated iminium salt **179** proved to be unstable and could not be properly characterised. Reduction of dialkylated iminium salt **180** with $NaBH_4$ gave indolizidine **181**.



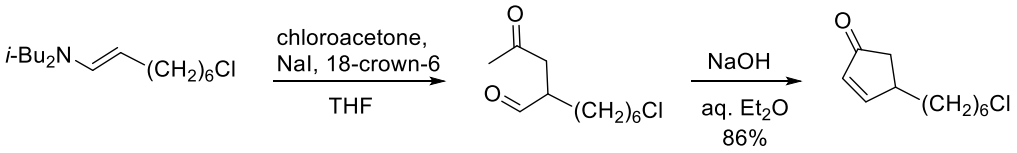
Scheme 3.4: Enamine alkylation with allyl iodide.

Subsequently, methyl vinyl ketone was used as the electrophile with the intention of trapping the first-formed iminium intermediate with the enolate generated from conjugate addition of enamine **176** to form spiroaminoacetal **182** (Scheme 3.5). However, this reaction gave tricyclic iminium salt **183** which, upon reduction with $NaBH_4$, gave tricyclic amine **184** arising from enamine formation in the pyrrolidine ring and condensation. The pyrrolidine enamine formation could be due to intramolecular proton transfer to the resulting enolate. The ^{13}C NMR spectrum of iminium salt **183** in methanol-d_4 showed a 1:1:1 'triplet' (J = 20 Hz) at 35.5 ppm, indicating deuteration of the proton next to the iminium functionality. This could be explained by the site-specific hydrogen-deuterium exchange in iminium salt **183** dissolved in methanol-d_4 to form deuterated iminium salt **185** which could revert back to **183** in methanol-d_0. Tricyclic amine **184** was obtained as a single isomer, indicating that the reduction was stereoselective. However, the stereochemistry of amine **184** could not be determined by NOE studies as the ^1H NMR resonances were broad and overlapping.



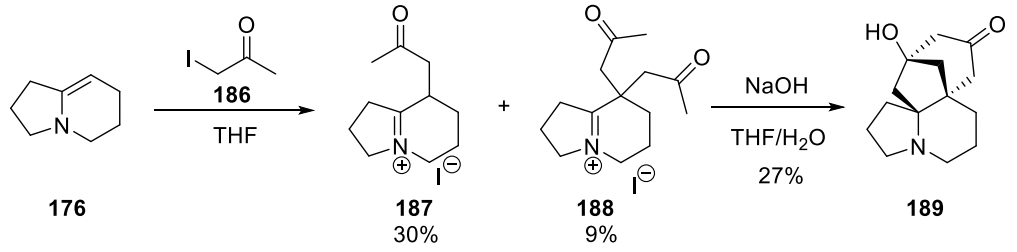
Scheme 3.5: Unexpected reactivity with methyl vinyl ketone.

The enamine cyclopentannulation reaction has been used in our group previously for the synthesis of roseophilin (Scheme 3.6) and extension to enamine **176** was envisaged (*cf.* Scheme 3.2).[64]



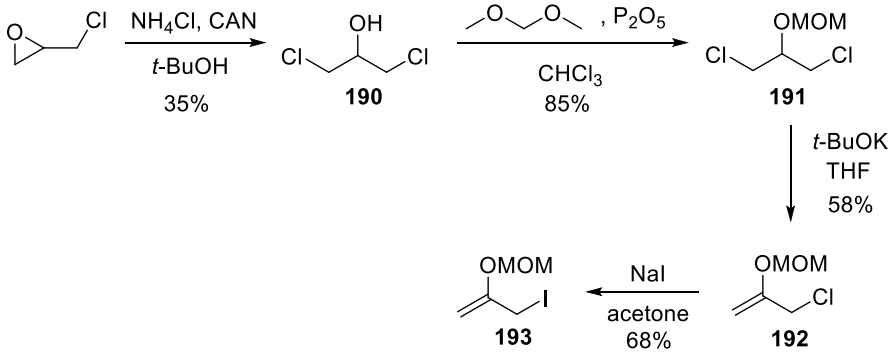
Scheme 3.6: Enamine cyclopentannulation in the synthesis of roseophilin.

However, with enamine **176** mainly starting material was recovered with only trace amounts of alkylated products. Alkylation with iodoacetone **186** gave monoalkylated iminium salt **187** as the major product along with a small amount of dialkylated iminium salt **188** (Scheme 3.7). The starting enamine was completely consumed in the reaction and the low yield of alkylated products was therefore attributed to the instability of enamine **176**. Monoalkylated iminium salt **187** could not be properly characterised as the NMR sample of this salt in methanol-d_4 showed multiple deuteration of the α-protons. Treating dialkylated iminium salt **188** with aq. NaOH resulted in cyclopentannulation and aldol cyclisation to form multicyclic amine **189**. As no other side products were obtained from this reaction, the low yield could be due to partial decomposition of the dialkylated iminium salt **188**.



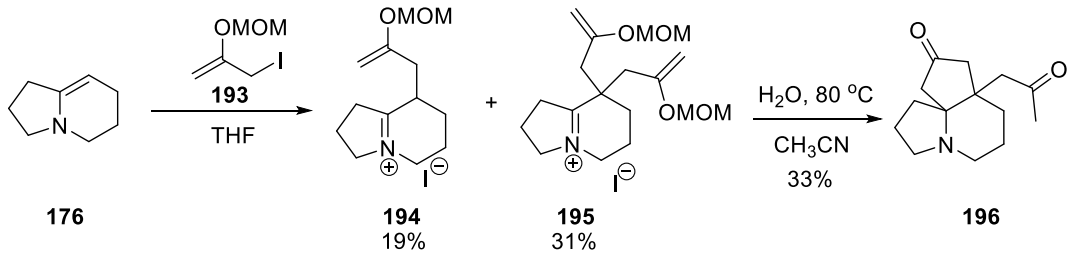
Scheme 3.7: Enamine reactivity with iodoacetone.

In parallel, an equivalent electrophile, enol ether **193**, was synthesised from epichlorohydrin over 4 steps (Scheme 3.8).[65,66,67]



Scheme 3.8: Synthesis of an enol ether equivalent of iodoacetone.

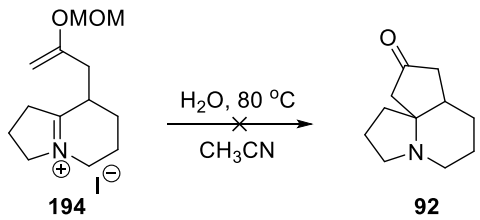
Treatment of enamine **176** with enol ether **193** afforded monoalkylated iminium salt **194**, and dialkylated iminium salt **195** as the major product (Scheme 3.9). Heating dialkylated iminium salt **195** at 80 ºC overnight resulted in cyclisation and hydrolysis to form aminoketone **196**.[68]



Scheme 3.9: Enamine reactivity with enol ether **193**.

3.4 Tricyclic aminoketone synthesis

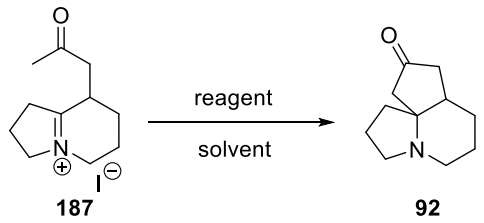
An attempt to form tricyclic aminoketone **92** by heating monoalkylated iminium salt **194** at 80 ºC overnight was unsuccessful, resulting mainly in decomposition (Scheme 3.10).



Scheme 3.10: Attempt to form tricyclic aminoketone.

When monoalkylated iminium salt **187** was treated with sodium ethoxide or L-proline, no cyclopentannulation took place (Table 3.2).[69] However, when a solution of this iminium in THF/H_2O (1:3) was treated with NaOH, cyclisation occurred to furnish tricyclic aminoketone **92** in excellent yield.

Table 3.2: Attempts at cyclopentannulation to form tricyclic aminoketone **92**.

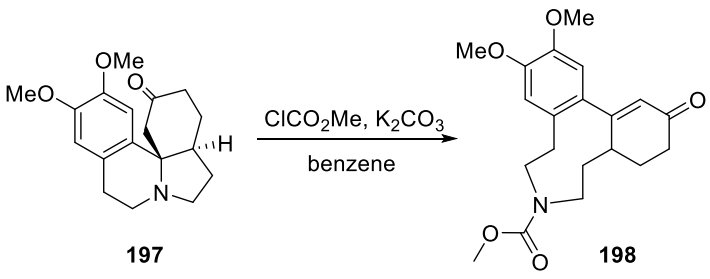


187 92

Reagent	Solvent	Duration/ h	Yield/ %
NaOEt	EtOH	24	0
L-proline	DMSO	24	0
NaOH	THF/H_2O (1:3)	24	99

3.5 Ring opening and enone synthesis

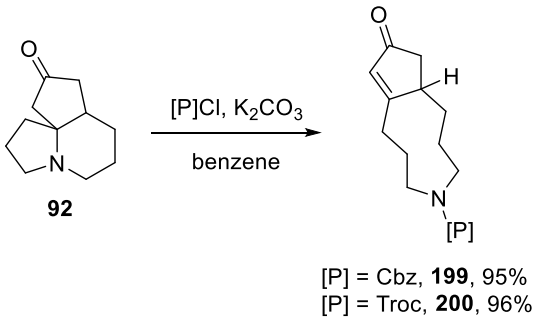
In the synthesis of laurifine, Bremner and co-worker employed a methyl chloroformate-induced ring expansion of erythrinan-3-one derivative **197** to form enone **198** (Scheme 3.11).[70]



197 198

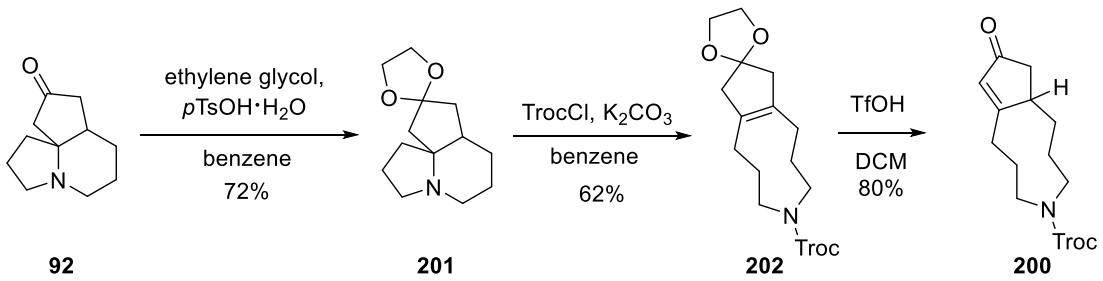
Scheme 3.11: Methyl chloroformate-induced ring expansion in the synthesis of laurifine.

Following the precedent, when aminoketone **92** was treated with benzyl chloroformate or 2,2,2-trichloroethyl chloroformate, *N*-acylation and β-elimination took place to afford bicyclic enones **199** and **200** respectively (Scheme 3.12). The NMR spectra of both enones showed doubling of resonances, indicating the presence of carbamate rotamers. Variable-temperature NMR experiments conducted at higher temperatures showed convergence of resonances at 100 ºC to give a single set of broad peaks.



Scheme 3.12: Ring expansion of tricyclic aminoketone **92**.

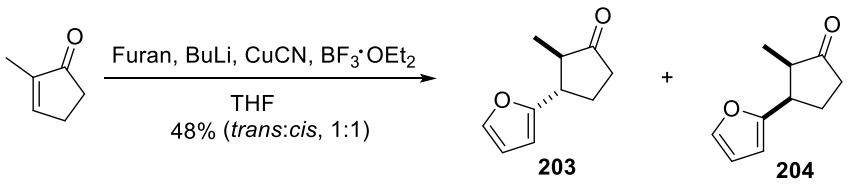
Protecting aminoketone **92** as the acetal **201** and applying the same acylation conditions resulted in the formation of carbamate **202** (Scheme 3.13) which, upon exposure to TfOH, hydrolysed and isomerised to form enone **200**. This could be due to the presence of water in TfOH used.



Scheme 3.13: Ring expansion of protected tricyclic aminoketone.

3.6 Furan conjugate addition

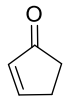
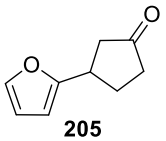
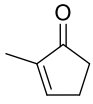
With bicyclic enone in hand, the most challenging furyl cuprate conjugate addition step was attempted. With 2-methylcyclopent-2-en-1-one as a simple model substrate, addition of furan-2-yl cyanocuprate gave both *trans* and *cis* diastereomers **203** and **204** in equal proportions (Scheme 3.14).[71,72] The stereochemistry of both diastereomers was determined based on comparison of NMR data with literature values.[71,72]



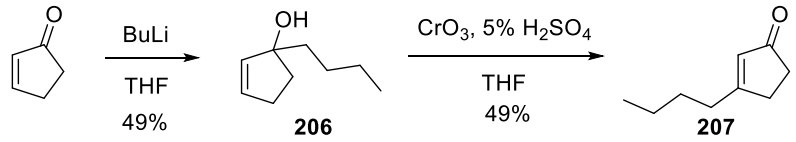
Scheme 3.14: Furyl cuprate addition to 2-methylcyclopent-2-en-1-one.

However, when the same reaction conditions were applied to bicyclic enone **200**, no addition took place and starting material was recovered. Other furan addition conditions were attempted on simple enones and the real system **200** but they were either unsuccessful or low yielding (Table 3.3).[73,74]

Table 3.3: Attempts at furan conjugate addition to enones.

Enone	Conditions	Product	Yield/ %
	Furan, $AuCl_3$, MeCN	 **205**	2
	Furan, TMSI, 2-methyl-2-butene, DCM		23
	–‖–	No reaction	-
200	–‖–	No reaction	-

Subsequently, a more realistic model enone **207** was synthesised from cyclopentenone via oxidative rearrangement of allylic alcohol **206** (Scheme 3.15).[75]



Scheme 3.15: Synthesis of model enone.

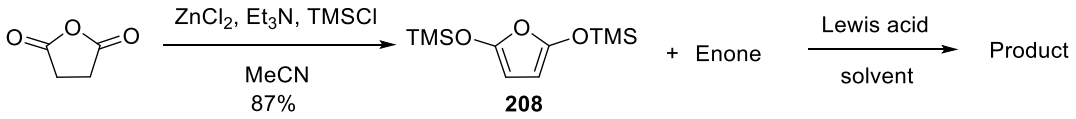
Furyl cuprate addition reactions using a variety of different copper salts and additives were attempted using model enone **207** (Table 3.4);[76,77] the starting enone was recovered unreacted in all cases.

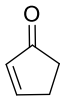
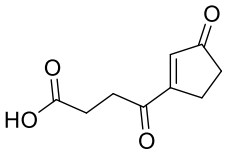
Table 3.4: Attempts at furyl cuprate addition to model enone **207**.

Copper salt	Additives	Yield/ %
CuCN (2 eq.)	$BF_3 \cdot OEt_2$ (2 eq.)	0
CuCN (10 eq.)	$BF_3 \cdot OEt_2$ (10 eq.)	0
CuCN (4 eq.)	LiCl (2 eq.)	0
CuCN (4 eq.)	TMSCl (2 eq.)	0
CuCN (4 eq.)	HMPT (2 eq.)	0
CuI (1.05 eq.)	Bu_3P (2.31 eq.)	0
CuI (1.25 eq.)	TMSI (5 eq.), Me_2S	0
$CuBr \cdot SMe_2$ (2 eq.)	Me_2S	0

A more nucleophilic furan, 2,5-bis(trimethylsiloxy)furan **208**, was synthesised from succinic anhydride and the Lewis acid-mediated conjugate addition to enones was attempted (Table 3.5).[78,79,80] In the presence of $TiCl_4$ in DCM, furan **208** added to cyclopentenone and then isomerised and ring-opened to form carboxylic acid **209**. No reaction occurred when enone **207** was used.

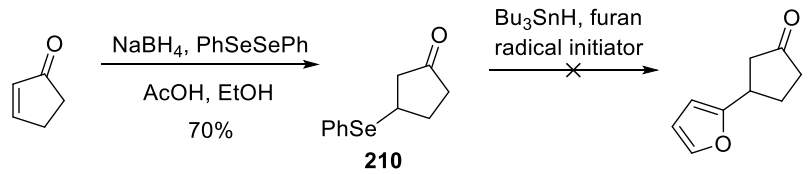
Table 3.5: Addition of 2,5-bis(trimethylsiloxy)furan to enones.



Enone	Lewis acid	Solvent	Product	Yield/ %
	$TMSNTf_2$	DCM	No reaction	-
	$TiCl_4$	DCM	 **209**	15
	$TiCl_4$	$MeNO_2$	No reaction	-
207	$TiCl_4$	DCM	No reaction	-

Subsequently, the addition of furan to cyclopentenone by radical means was attempted (Table 3.6). Selenide **210** was synthesised and different radical initiators were used to try to create and capture a 3-oxocyclopentyl radical but no desired product was obtained.[81,82]

Table 3.6: Attempts to add furan by radical means.



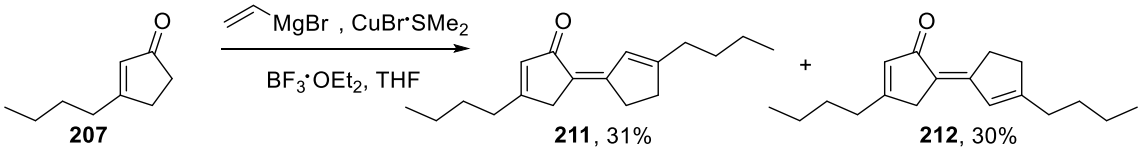
Radical initiator	Conditions	Outcome
Et_3B, O_2	RT	Decomposition
AIBN	40 ºC reflux	No reaction
AIBN	80 ºC in sealed tube	Cyclopentanone obtained

3.7 Conjugate addition of functional nucleophiles

After numerous unsuccessful attempts to add furan to the model enone **207**, it was concluded that the bulky alkyl substituent at the 3-position of the enone provides both steric and electronic impediments to conjugate addition with furan. Therefore, conjugate additions of other smaller functional nucleophiles were attempted to find a competent nucleophile for this deactivated enone.

Schwartz and co-workers reported the use of $Ni(acac)_2$ and DIBAL-H to catalyse alkynyl group transfer from dialkyl(alkynyl)aluminium compounds to a variety of enones.[83] When this reaction was attempted using cyclopentenone and 1-pentyne, a complex mixture of products was obtained. However, when model enone **207** was used, no reaction occurred.

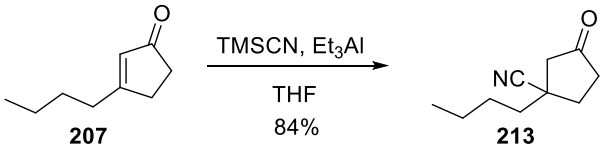
After that, attempts to add vinyl cuprates to model enone **207** resulted in aldol condensation to form dienones **211** and **212** (Scheme 3.16).[84]



207 **211**, 31% **212**, 30%

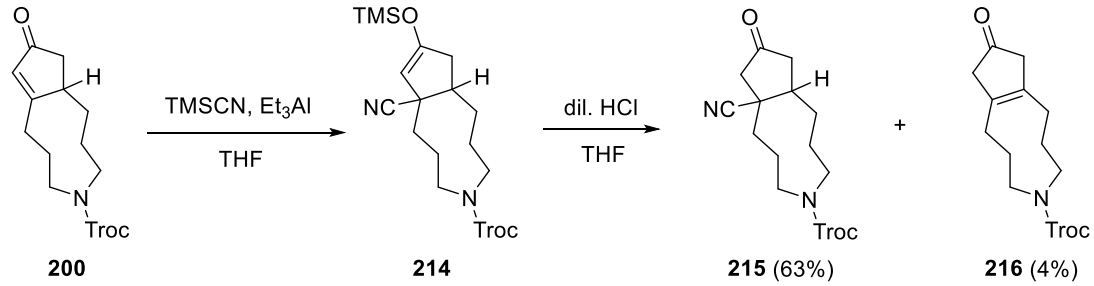
Scheme 3.16: Attempt to add vinyl cuprates to model enone.

In 1980, Nozaki and co-workers reported the conjugate addition of cyanotrimethylsilane to enones in the presence of triethylaluminium.[85] Application of this methodology to model enone **207** afforded nitrile **213** in 21% yield after 16 h of reflux (Scheme 3.17). Shortening the reflux duration to 5 h increased the yield to 84%.



Scheme 3.17: Conjugate addition of TMSCN to model enone.

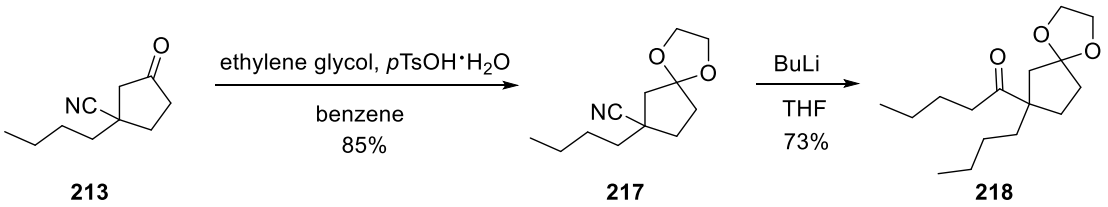
As the nitrile group is synthetically versatile, this conjugate addition was attempted on bicyclic enone **200** (Scheme 3.18). After 5 h of reflux, crude silyl enol ether **214** was obtained and, upon acid hydrolysis, nitrile **215** was furnished together with trace amounts of ketone **216**. The stereochemistry of the nitrile group could not be determined at this point as the ^{1}H NMR spectrum of **215** was complicated by the presence of carbamate rotamers.



Scheme 3.18: Conjugate addition of TMSCN to bicyclic enone **200**.

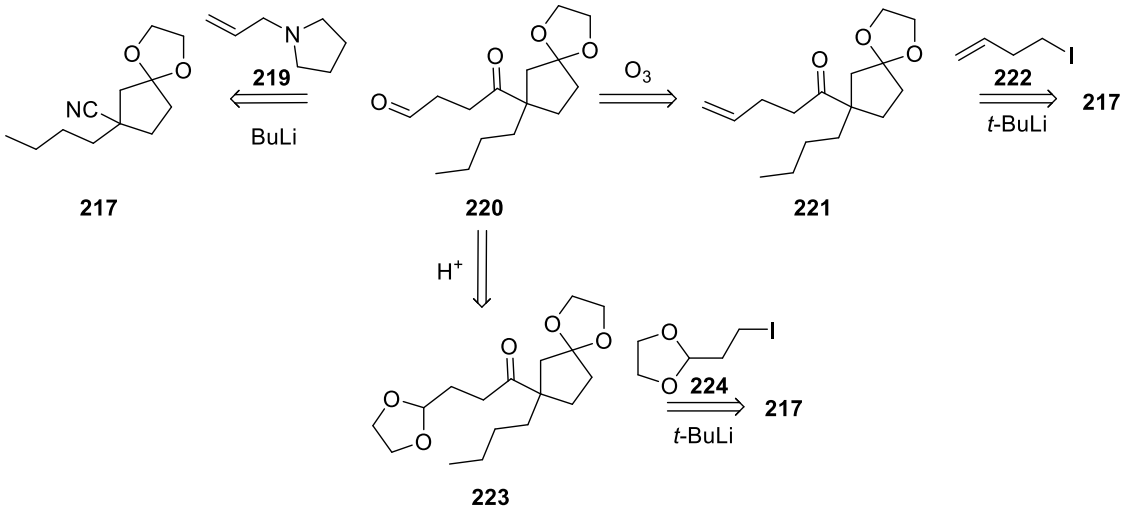
3.8 Addition of nucleophiles to nitrile 215

Subsequently, the susceptibility of the nitrile group to nucleophilic addition was tested with a variety of nucleophiles. Protection of ketone **213** afforded dioxolane **217** which gave ketone **218** upon treatment with BuLi (Scheme 3.19).



Scheme 3.19: Addition of BuLi to model nitrile **213**.

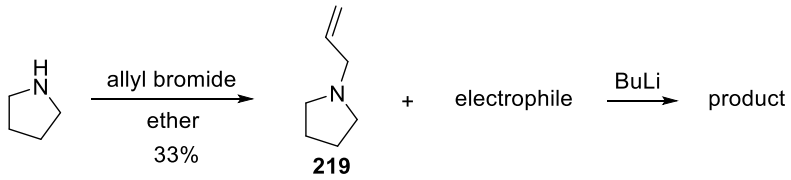
With the aim of synthesising 1,4-dicarbonyl **220**, synthetically equivalent to a 1,4-furan adduct, various nucleophiles and synthetic routes were proposed (Scheme 3.20). *N*-Allyl pyrrolidine **219** could be lithiated and added into nitrile **217** to form dicarbonyl **220** upon hydrolysis.[86] Addition of lithiated 4-iodo-1-butene **222** to nitrile **217** would form ketone **221** which upon ozonolysis would yield dicarbonyl **220**.[87] Furthermore, addition of lithiated dioxolane **224** to nitrile **217** could afford ketone **223** which upon acid hydrolysis would furnish dicarbonyl **220**.

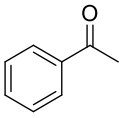
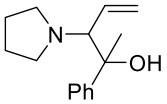
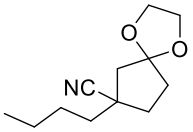
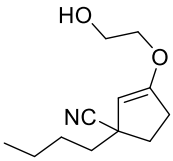


Scheme 3.20: Retrosynthetic approach to 1,4-dicarbonyl **220**.

Pyrrolidine was allylated to form *N*-allyl pyrrolidine **219** which was lithiated with *s*-BuLi or *t*-BuLi and added to different electrophiles (Table 3.7).[88] In order to test that the reaction works with literature substrates,[86] acetophenone was used as an electrophile. When *t*-BuLi was used, the desired pyrrolidine **225** was obtained. However, when nitrile **217** was used as electrophile, acetal ring opening occurred to afford enol ether **226**. Based on literature,[86] the regiochemical outcome of this reaction depends on the electrophile used as alkyl halides gave predominantly γ-adducts while carbonyls gave a mixture of α- and γ-adducts in roughly equal proportions.

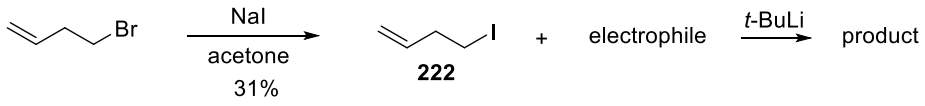
Table 3.7: Addition of lithiated *N*-allyl pyrrolidine to electrophiles.

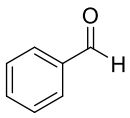
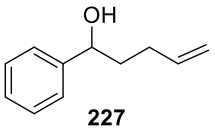
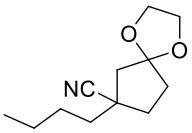
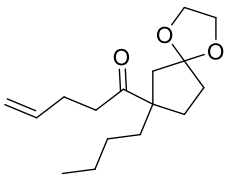


Electrophile	Lithiating agent	Product	Yield/ %
	*s*-BuLi	No reaction	-
	t-BuLi	 **225**	12
 **217**	*s*-BuLi	No reaction	-
	t-BuLi	 **226**	28

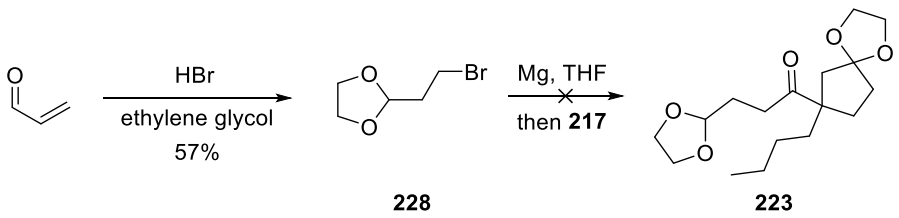
In parallel, 4-bromo-1-butene was converted into 4-iodo-1-butene **222** which was lithiated with *t*-BuLi (Table 3.8).[87] Addition of so-formed 3-butenyllithium to benzaldehyde as a test substrate afforded alcohol **227**, whereas addition to nitrile **217** afforded ketone **221**, both in low yields.

Table 3.8: Addition of lithiated 4-iodo-1-butene to electrophiles.



Electrophile	Product	Yield/ %
	 **227**	20
 **217**	 **221**	16

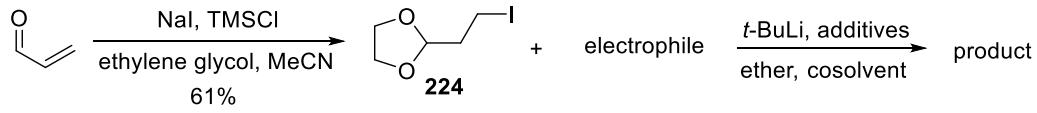
At the same time, dioxolane **228** was synthesised from acrolein and reacted with Mg to form the Grignard reagent (Scheme 3.21).[89] However, no addition to nitrile **217** occurred and starting material was recovered.

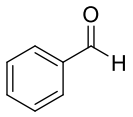
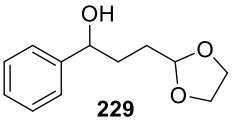
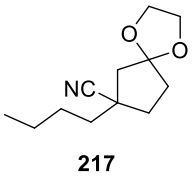


Scheme 3.21: Addition of Grignard reagent to nitrile **217**.

Similarly, dioxolane **224** was prepared and lithiated with *t*-BuLi for addition to electrophiles (Table 3.9).[90] Addition to benzaldehyde afforded alcohol **229** in good yield but addition to nitrile **217** led to recovery of starting material. With additives or cosolvents in the reaction were unsuccessful in bringing about addition to nitrile **217**.

Table 3.9: Addition of lithiated dioxolane **224** to electrophiles.

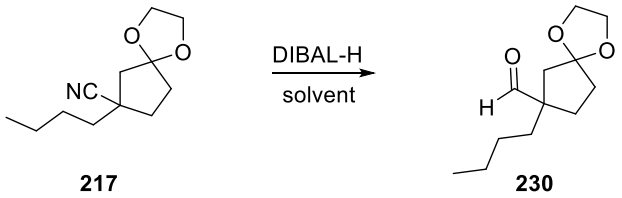


Electrophile	Additives/ Cosolvent	Product	Yield/ %
	-	 **229**	82
 **217**	-	No reaction	0
	LiCl (5 eq.)	No reaction	0
	DMPU (5 eq.)	No reaction	0
	THF-DMSO (3:1)	No reaction	0

3.9 Conversion to aldehyde

It was evident that the tertiary nitrile group in model compound **217** lacked reactivity towards nucleophilic attack most probably because of steric hindrance. Therefore, attempts were made to convert the nitrile functionality into a much more electrophilic aldehyde. Partial reduction of nitrile **217** with DIBAL-H in DCM afforded aldehyde **230** in low yield (Table 3.10) as a result of oligomerisation of imine intermediates. Changing the solvent to THF minimised oligomerisation and improved the yield to 25% but the reaction was incomplete.[91] A large excess of DIBAL-H in THF was necessary in order to achieve full conversion and a good yield of aldehyde **230**.

Table 3.10: Partial reduction of nitrile **217**.

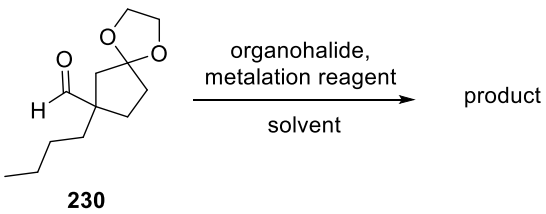


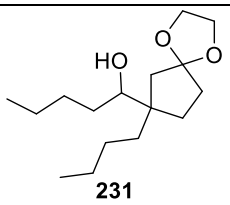
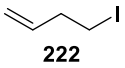
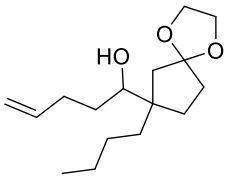
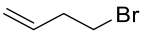
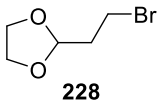
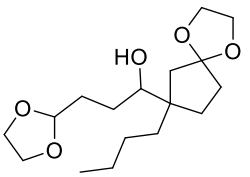
217 **230**

Eq. of DIBAL-H	Solvent	Yield/ %
1.2	DCM	15
1.5	THF	25 (49 brsm)
10	THF	77

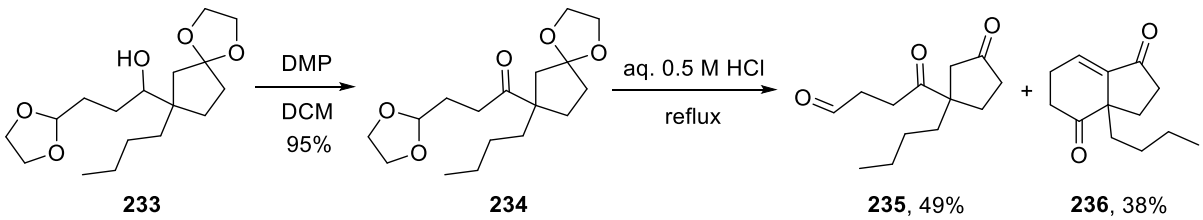
Subsequently, nucleophilic addition of various organolithium and Grignard reagents was attempted on aldehyde **230** (Table 3.11). BuLi added smoothly to afford alcohol **231** in good yield but the lithiated alkene derived from iodide **222** gave a poor yield of alcohol **232** due to formation of side products. Grignard reagents formed from 4-bromo-1-butene and dioxolane **228** furnished alcohols **232** and **233** respectively in good yields. The alcohol products were in all cases obtained as an inseparable mixture of diastereomers.

Table 3.11: Addition of organometallics to aldehyde **230**.



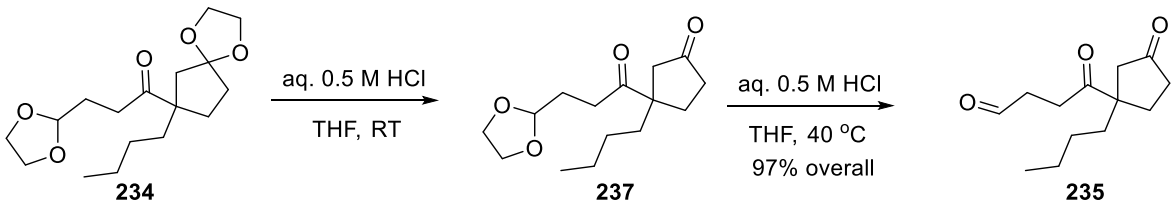
Organohalide	Metalation reagent	Solvent	Product	Yield/ %
-	BuLi	ether	 **231**	86
 **222**	*t*-BuLi	ether	 **232**	8
	Mg	THF		63
 **228**	Mg	THF	 **233**	93

Alcohol **233** was then oxidised with DMP to ketone **234** which was then stirred under reflux in aq. HCl to afford 1,4-dicarbonyl **235** and bicyclic enone **236** (Scheme 3.22), arising from intramolecular aldol condensation.



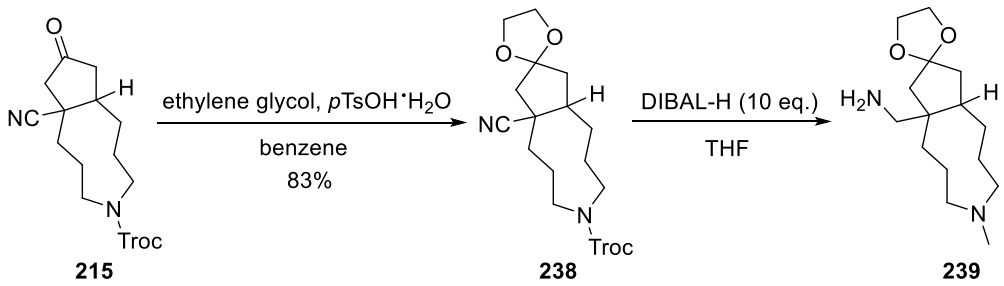
Scheme 3.22: Synthesis of 1,4-dicarbonyl **235**.

When a solution of ketone **234** in THF was stirred at RT with aq. HCl, the cyclopentyl acetal was selectively hydrolysed to afford ketone **237** which upon stirring at 40 ºC furnished 1,4-dicarbonyl **235** in excellent yield (Scheme 3.23). No aldol condensation product was formed under these reaction conditions.



Scheme 3.23: Selective acetal hydrolysis.

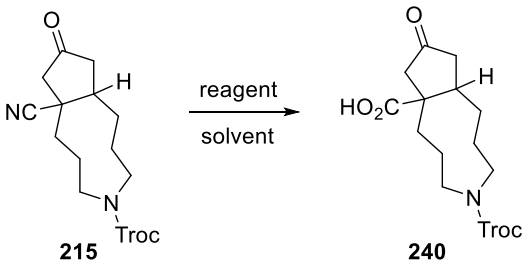
After 1,4-dicarbonyl **235** was obtained, the synthetic route was applied to nitrile **215**. Following protection of ketone **215** as acetal **238**, treatment with DIBAL-H under the previously optimised conditions led to reduction of both the Troc group and the nitrile group to afford diamine **239** (Scheme 3.24). This might be because the imine intermediate was unstable under these conditions and was further reduced to the amine.

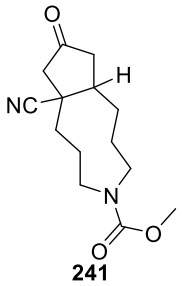


Scheme 3.24: Application of synthetic route to nitrile **215**.

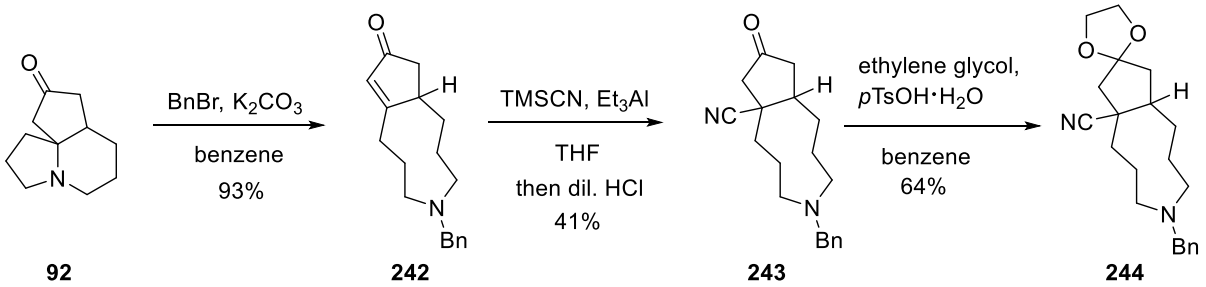
Subsequently, attempts were made to hydrolyse nitrile **215** into carboxylic acid **240** for eventual conversion into aldehyde (Table 3.12). The use of conc. aq. HCl with stirring under reflux afforded no product, whereas the use of 25% aq. NaOH in MeOH led to transesterification of the Troc carbamate to afford carbamate **241**. No desired carboxylic acid products were obtained.

Table 3.12: Attempts to hydrolyse the nitrile group in **215** to carboxylic acid **240**.



Reagent	Solvent	Product	Yield/ %
Conc. HCl	THF	No reaction	0
Conc. HCl	H_2O	No reaction	0
25% aq. NaOH	MeOH	 **241**	70
25% aq. NaOH	H_2O	Decomposition	0

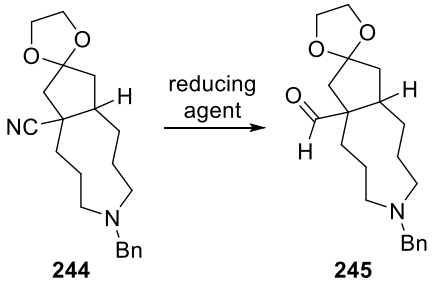
We decided to synthesise a nitrile with a more stable *N*-protecting group. Treating aminoketone **92** with BnBr afforded enone **242** which was then treated with TMSCN to furnish nitrile **243** (Scheme 3.25); protection of the ketone afforded dioxolane **244**.

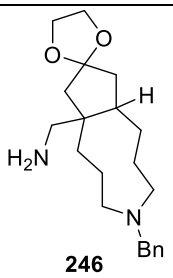


Scheme 3.25: Synthesis of *N*-benzyl protected nitrile.

Table 3.13 summarises attempts to reduce nitrile **244** with the aim of obtaining aldehyde **245**. The use of DIBAL-H in DCM afforded amine **246**. The use of other solvents or reducing agents did not bring about reduction of nitrile **244** and the study was halted.[46]

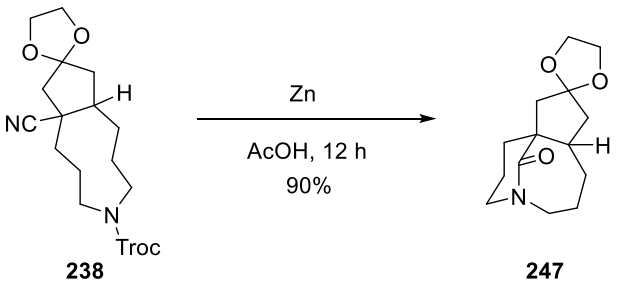
Table 3.13: Partial reduction of nitrile **244**.



Reducing agent	Solvent	Product	Yield/ %
DIBAL-H (1 eq.)	DCM	 246	30
DIBAL-H (2 eq.)	DCM		96
DIBAL-H (2 eq.)	THF	No reaction	0
$LiAl(OEt)_3H$	Ether	No reaction	0
$LiAl(OEt)_2H_2$	Ether	No reaction	0
Red-Al (1.5 eq.)	THF	No reaction	0

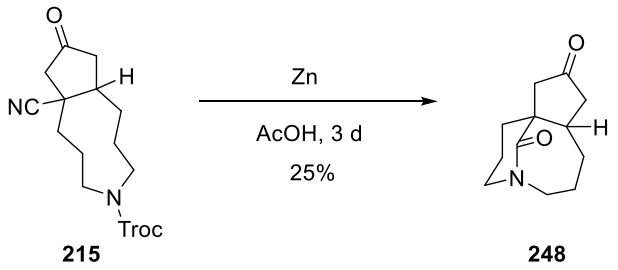
3.10 Tricyclic lactam synthesis

In order to prevent reduction of the Troc protecting group, we decided to remove the Troc group prior to reducing the nitrile. The attempt to cleave the Troc group using Zn and aq. KH_2PO_4 was very slow.[92] To our surprise, the use of zinc and glacial acetic acid on nitrile **238** furnished tricyclic lactam **247** by cyclisation of the deprotected amine onto the nitrile, presumably aided by $ZnCl_2$ formed during the deprotection (Scheme 3.26).[93]



Scheme 3.26: Troc-cleavage and tricyclic lactam synthesis.

When unprotected ketone **215** was treated with zinc and glacial acetic acid, the reaction was much slower, taking 3 days to afford tricyclic lactam **248** in poor yield (Scheme 3.27).



Scheme 3.27: Tricyclic lactam **248** synthesis.

In the absence of carbamate rotamers, the ^{1}H NMR spectrum of tricyclic lactam **247** could be analysed in detail to provide insights into the relative stereochemistry of H_a (Figure 3.1). The ^{1}H resonances of tricyclic lactam **247** in methanol-d_4 were dispersed and well resolved, allowing NOE studies to be carried out to determine the stereochemistry (Appendix B).

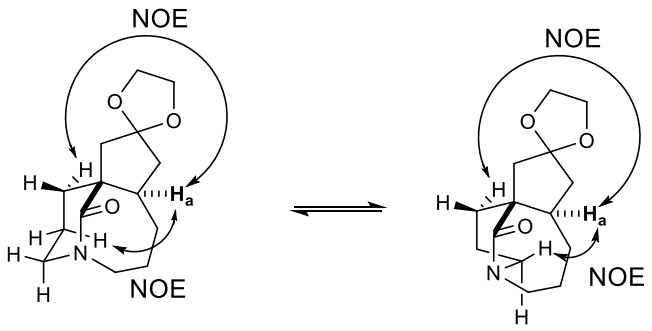
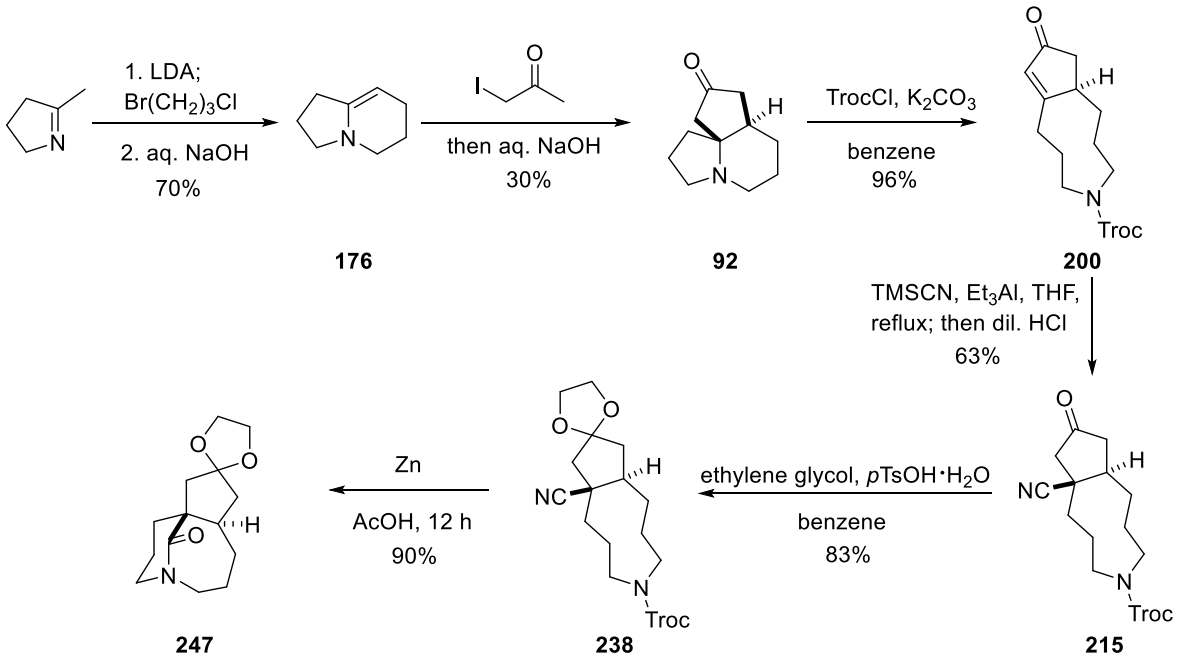


Figure 3.1: NOE correlations in tricyclic lactam **247**.

It is shown from NOE studies that H_a is *trans* to the lactam carbonyl, hence the stereochemistry is opposite to that in lycopladine D **5**. However, this same stereochemistry is found in several other fawcettimine-type *Lycopodium* alkaloids like lycopladine B **75**, huperzine Q **6** and fawcettimine **74**. Therefore, this brief synthetic route to tricyclic lactam **247** can be used to access this common structural core in the synthesis of fawcettimine-type *Lycopodium* alkaloids (Scheme 3.28).

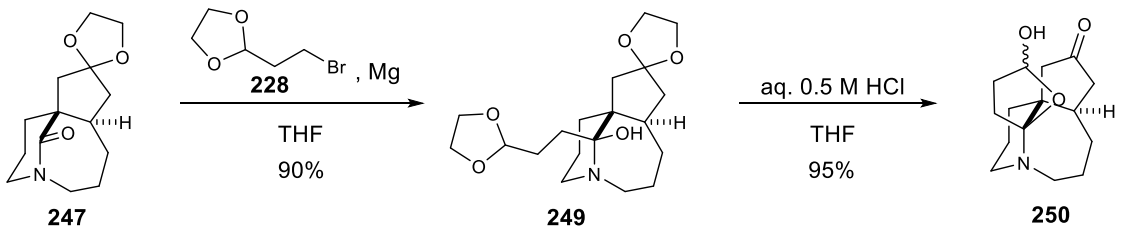


Scheme 3.28: Optimised synthetic route to tricyclic lactam **247**.

Based on the stereochemistry of tricyclic lactam **247**, the conjugate addition of TMSCN to bicyclic enone **200** was shown to give the *trans*-fused bicyclic nitrile **215**. Due to the presence of medium-sized azonane ring, this *trans*-fused configuration might minimise ring strain caused by transannular steric repulsion and be lower in energy relative to the *cis*-fused configuration.

3.11 Spiro-*N*,*O*-acetal synthesis

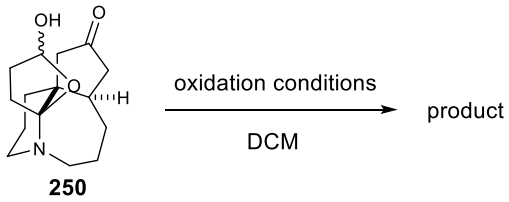
Subsequently, attempts were made to add the Grignard reagent generated from dioxolane **228** to tricyclic lactam **247** (Scheme 3.29). The addition occurred stereoselectively to afford hemiaminal **249** in excellent yield. The stereochemistry of hemiaminal **249** was proven by NOE studies which showed that the dioxolane substituent is axial and the hydroxyl group is equatorial with respect to the piperidine ring. Treating hemiaminal **249** with aq. HCl led to hydrolysis of both acetals and promoted cyclisation to form lactol **250** as a 2:1 mixture of diastereomers.



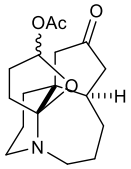
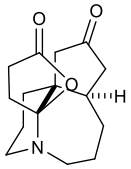
Scheme 3.29: Grignard addition and lactol formation.

With lactol **250** in hand, attempts were made to oxidise it to the lactone (Table 3.14). The use of I_2 and K_2CO_3 did not bring about oxidation,[94] DMP resulted in formation of acetate **251**; treatment with PCC in the presence of molecular sieves furnished lactone **252** in moderate yield, with decomposition products accounting for the mass balance.

Table 3.14: Oxidation of lactol **250**.

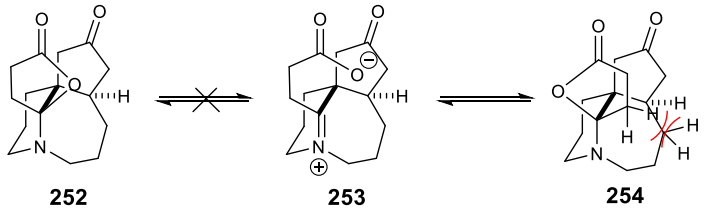


250

Oxidation conditions	Product	Yield/ %
I_2, K_2CO_3	No reaction	0
DMP	 **251**	43
PCC, 4 Å molecular sieves	 **252**	40

The stereochemistry of lactone **252** was confirmed by NOE studies and this showed that the spiro-*N*,*O*-acetal in this compound is not prone to epimerisation (Appendix C). This retention of configuration is perhaps due to the inability of the amine to strongly stabilise an opened butyrolactone as iminium **253** would be rather strained (Scheme 3.30). This stereochemistry about the spirocentre is the same as that in lycopladine D **5** and opposite of that in huperzine Q **6**. It was unusual for the C–O bond at the spirocentre to be equatorial with respect to the piperidine ring as stabilisation by anomeric effect brings about strong axial preference. However, as the lone pair of electrons on N is not aligned with the σ^* orbital of the axial C–O bond, it could not stabilise the bond by hyperconjugation and hence, loses the axial preference. Furthermore, this stereochemistry about the spirocentre might be preferred to

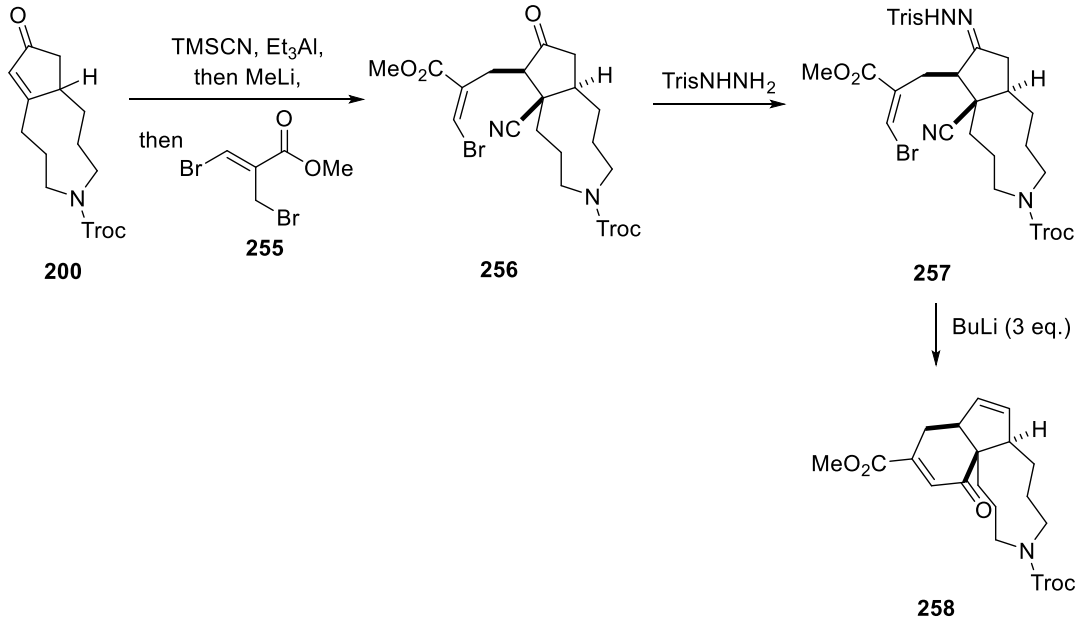
minimise steric repulsions between the butyrolactone methylenes and azepane methylenes in lactone **254**.



Scheme 3.30: Retention of spiro-*N*,*O*-acetal stereochemistry in lactone **252**.

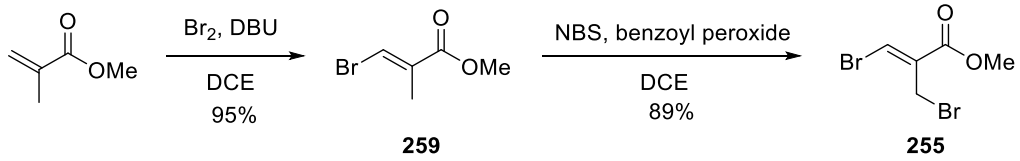
3.12 Addition of electrophiles to silyl enol ether

With these results, a general route was proposed for the synthesis of spirocyclisation precursor **258** from bicyclic enone **200** (Scheme 3.31) that involves conjugate addition of TMSCN to form a silyl enol ether which would then be trapped by electrophile **255** to form nitrile **256**.[95] Even though the rate of lithium-halogen exchange is much faster than nucleophilic addition, the so-formed vinyllithium would tend to add to the ketone instead of the nitrile. Therefore, the ketone has to be protected as hydrazone **257** prior to lithiation. Treating hydrazone **257** with 3 eq. of BuLi would bring about the Shapiro reaction and cyclisation to furnish spirocyclisation precursor **258**.



Scheme 3.31: General route for synthesis of spirocyclisation precursor.

Methyl methacrylate was brominated and dehydrobrominated to afford vinyl bromide **259**; subsequent allylic bromination with NBS furnished bromide **255** (Scheme 3.32).[96] The stereochemistry of vinyl bromide **259** was confirmed by comparison of NMR data with literature values. The dehydrobromination gave the *E*-isomer preferentially so as to minimise steric repulsion between the Br and ester group.

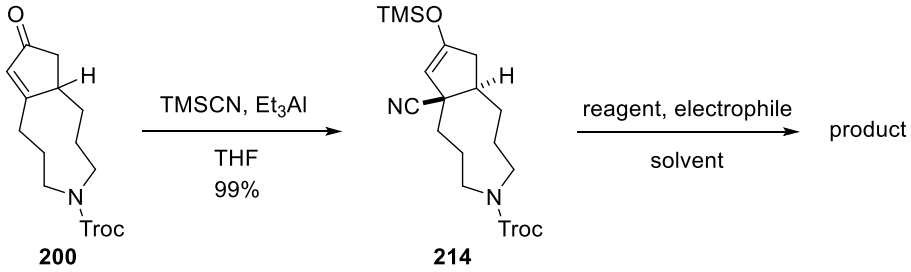


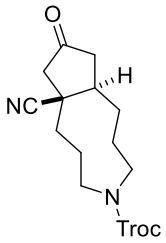
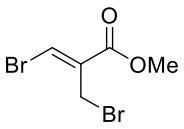
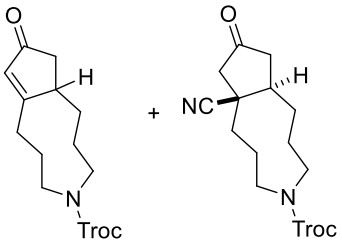
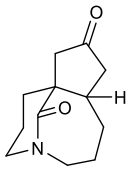
Scheme 3.32: Synthesis of electrophile **255**.

Subsequently, the addition of electrophiles to silyl enol ether **214** was attempted (Table 3.15). Attempting the Mukaiyama aldol addition with propionaldehyde led to formation of nitrile **215** with no addition occurring.[97] The use of electrophile **255** in the presence of $ZnBr_2$ only resulted in formation of starting enone **200** and nitrile **215**.[98] An attempt to form the enolate

using MeLi led to cleavage of the Troc group and cyclisation to form tricyclic lactam **248**. Therefore, silyl enol ether **214** seemed to be an unsuitable nucleophile for further elaboration.

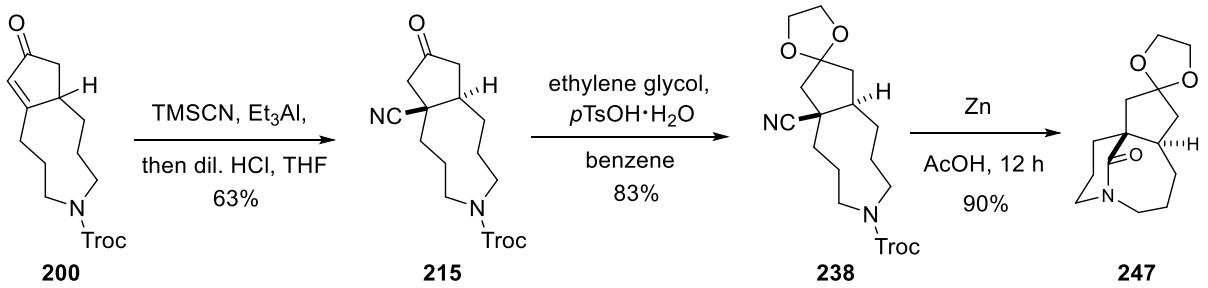
Table 3.15: Addition of electrophiles to silyl enol ether.



Electrophile	Reagent	Solvent	Product	Yield/%
Propionaldehyde	$TiCl_4$	DCM	 **215**	85
 **255**	$ZnBr_2$	DCM	 **200** + **215**	20 (**200**) 62 (**215**)
–‖–	MeLi	THF	 **248**	72

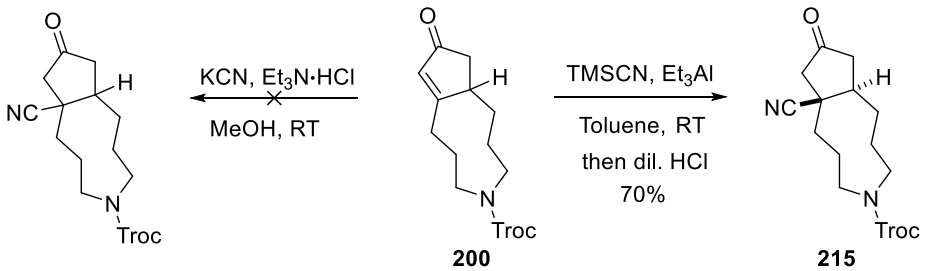
3.13 Stereochemical outcome of nitrile addition

The stereochemistry of tricyclic lactam **247** indicated that the conjugate addition of TMSCN to enone **200** occurred stereoselectively to afford *trans*-fused bicyclic nitrile **215** (Scheme 3.33).



Scheme 3.33: Stereochemical outcome of nitrile addition.

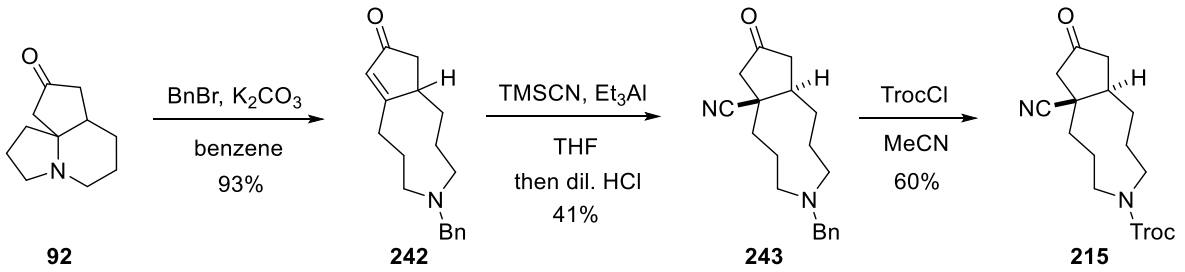
It is reported that the conjugate addition is thermodynamically controlled in THF at reflux and kinetically controlled in toluene;[85] therefore, attempts were made to see if the stereochemistry of the nitrile addition could be varied in order to obtain the *cis*-fused bicyclic product. Stirring the reaction mixture in toluene at RT afforded the same *trans*-fused bicyclic nitrile **215** (Scheme 3.34). Treating a methanolic solution of enone **200** with KCN and triethylammonium chloride at RT did not bring about nitrile addition.[99]



Scheme 3.34: Attempted nitrile addition under kinetic conditions.

Subsequently, we decided to test whether changing *N*-protecting groups would affect the stereochemistry of the nitrile addition. An attempt to nosylate tricyclic aminoketone **92** was unsuccessful, whereas the use of BnBr furnished enone **242** in excellent yield (Scheme 3.35).

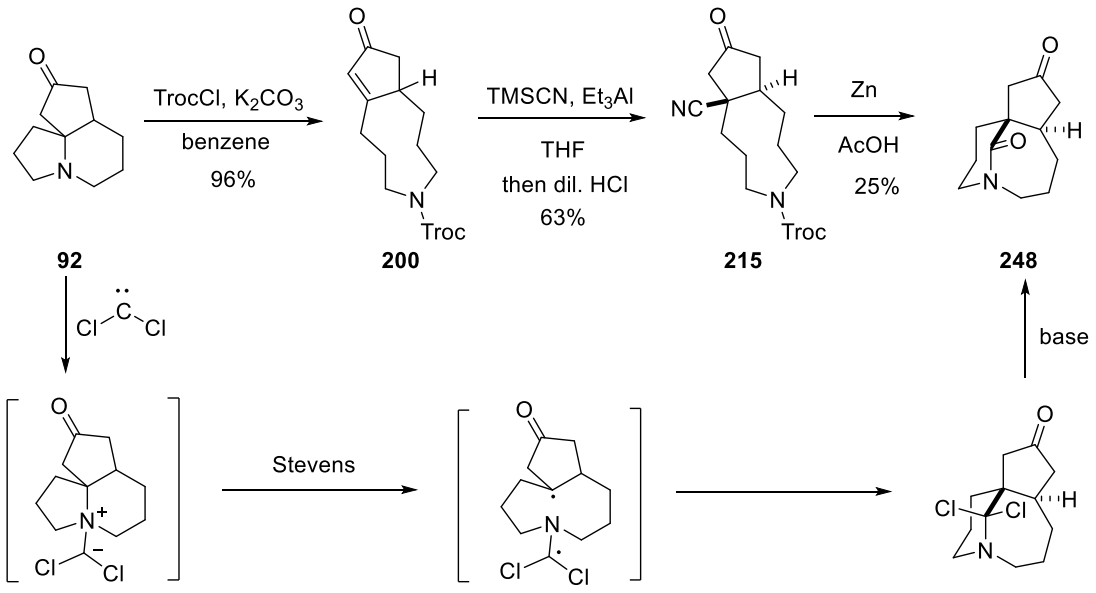
Conjugate addition of TMSCN afforded nitrile **243** which, upon debenzylation and protective group exchange, furnished carbamate **215** to confirm that changing the *N*-protecting group does not affect the stereochemistry of the nitrile addition.[100]



Scheme 3.35: Effect of *N*-protecting group on stereochemistry of nitrile addition.

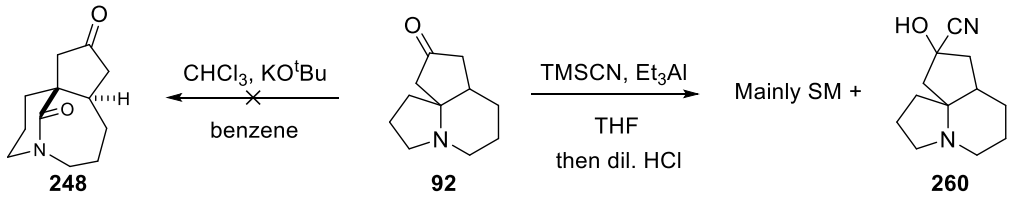
3.14 Carbene insertion

The synthesis of tricyclic lactam **248** from tricyclic aminoketone **92** took three steps but the transformation simply involves insertion of a carbonyl group between the amine and quaternary carbon (Scheme 3.36). Therefore, we decided to expose tricyclic aminoketone **92** to carbene or carbenoid to determine if this transformation is feasible.



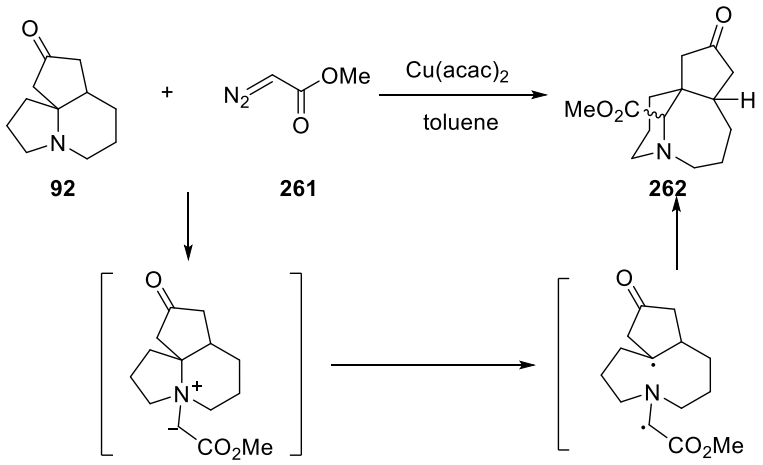
Scheme 3.36: Synthesis of tricyclic lactam from tricyclic aminoketone.

Firstly, we decided to treat aminoketone **92** with TMSCN conjugate addition conditions to determine whether Et_3Al could bring about ring opening so that upon nitrile conjugate addition, ring closure could furnish tricyclic lactam **248** in one-pot. However, treatment of tricyclic aminoketone **92** with TMSCN and Et_3Al afforded trace amounts of cyanohydrin **260** which is unstable to silica (Scheme 3.37). An attempt to add dichlorocarbene generated in situ to aminoketone **92** only led to recovery of starting material.[101]



Scheme 3.37: Attempts to add carbene and nitrile to tricyclic aminoketone.

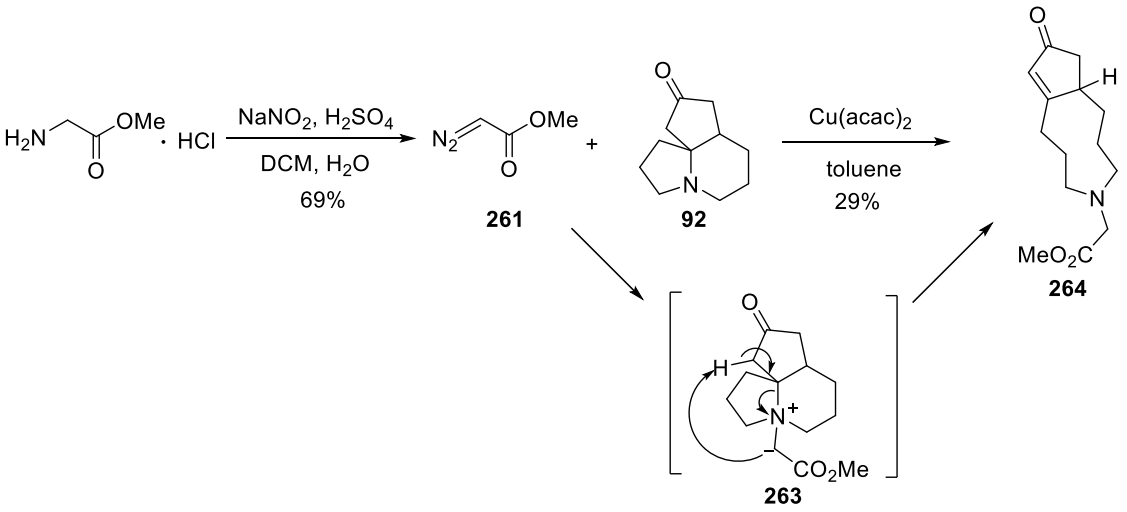
Subsequently, it was envisaged that addition of a carbenoid of diazoester **261** to aminoketone **92** would form an ammonium ylide which could undergo Stevens rearrangement to afford tricyclic ester **262** (Scheme 3.38).[102]



Scheme 3.38: Proposed carbenoid addition and Stevens rearrangement.

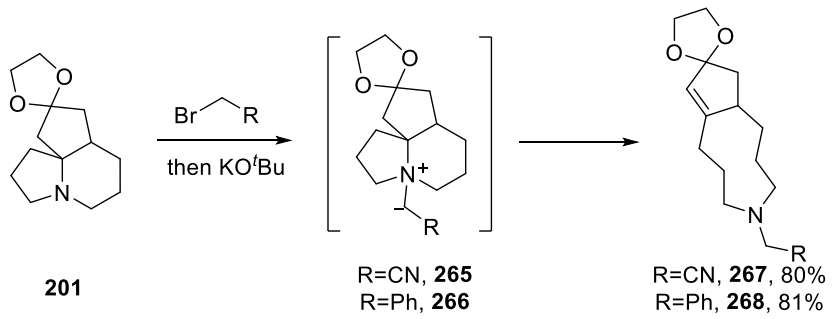
Glycine methyl ester was diazotised to afford diazoacetate **261** (Scheme 3.39).[103] Treating aminoketone **92** with this diazoester and $Cu(acac)_2$ formed ammonium ylide **263** which,

instead of Stevens rearrangement, underwent intramolecular Hofmann elimination to afford enone **264** in low yield, with starting material and decomposition products accounting for the mass balance. No reaction occurred when rhodium(II) acetate dimer was used to generate the carbenoid.



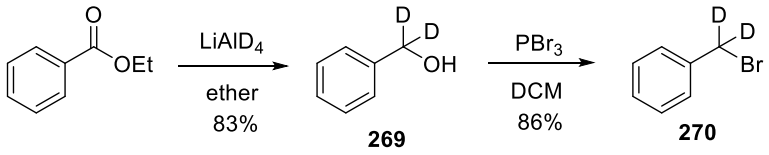
Scheme 3.39: Carbenoid addition and intramolecular Hofmann elimination.

Further ammonium ylids of amine **201** were prepared to determine if Stevens rearrangement was possible. The use of amine **201** with protected ketone was to prevent possible elimination and ring opening due to the acidity of α-protons. Treatment of amine **201** with bromoacetonitrile followed by KO^{t}Bu afforded amine **267** (Scheme 3.40); similarly, ammonium ylid **266** generated using BnBr also developed via Hofmann elimination to afford amine **268**.



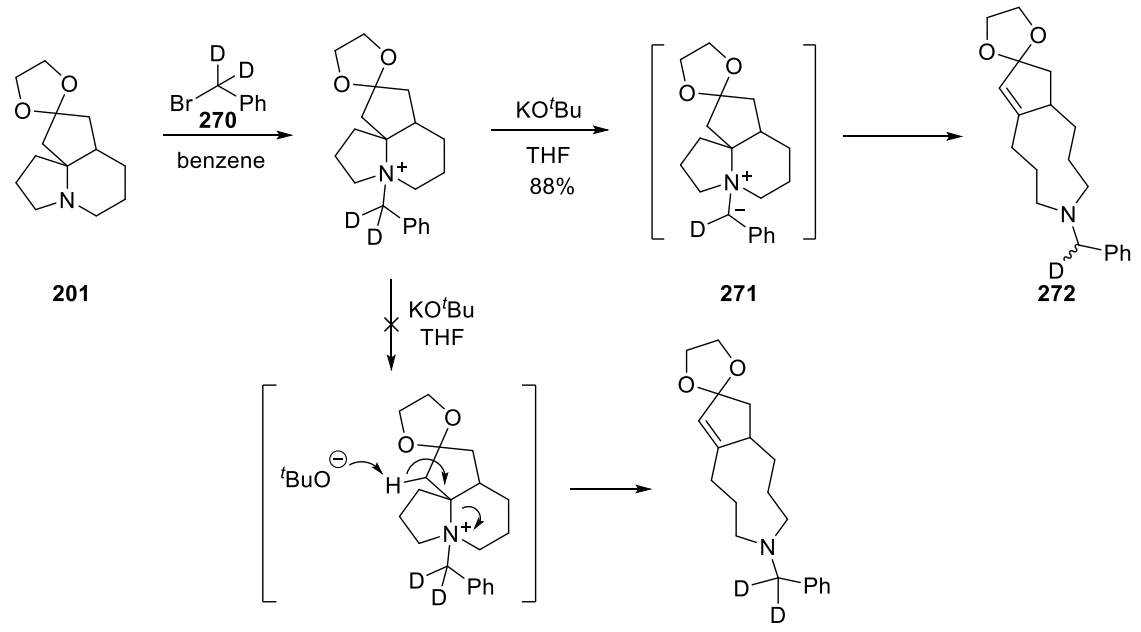
Scheme 3.40: Intramolecular Hofmann elimination of ammonium ylids.

Subsequently, isotopic labelling studies were reported to support the elimination pathway proposed in Scheme 3.39.[104] It might be possible that instead of forming the ammonium ylid, KO^{t}Bu deprotonated the α-proton of the acetal to bring about ring expansion. Therefore, in order to prove ammonium ylid formation, deuterated benzyl bromide was used as the alkylating reagent. Deuterated benzyl bromide was prepared from ethyl benzoate by reduction with $LiAlD_4$ and conversion of so-formed alcohol **269** into bromide **270** (Scheme 3.41).[105]



Scheme 3.41: Synthesis of deuterated benzyl bromide.

Amine **201** was alkylated with deuterated bromide **270** and treated with KO^{t}Bu to form monodeuterated amine **272** via ammonium ylid **271** (Scheme 3.42). This result proved that ammonium ylid **271** was formed upon treatment with KO^{t}Bu and the ring opening was not due to KO^{t}Bu deprotonation of the α-proton of the acetal.

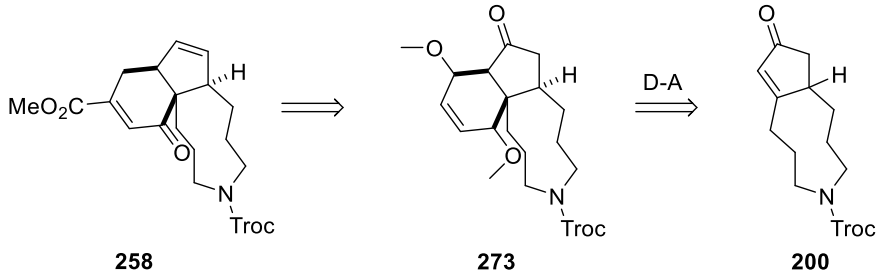


Scheme 3.42: Labelling study of intramolecular Hofmann elimination.

Therefore, it is shown that the ammonium ylids prefer, in this system, to undergo intramolecular Hofmann elimination instead of the Stevens rearrangement.

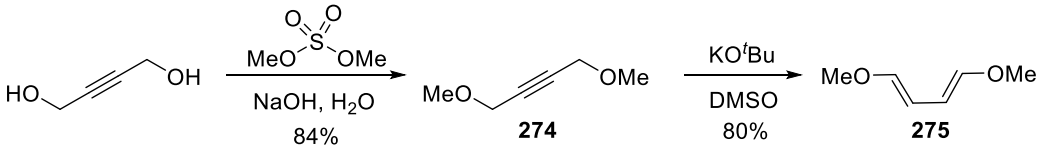
3.15 A Diels–Alder approach

As previous attempts to synthesise spirocyclisation precursor **258** from enone **200** were unsuccessful, we then opted to explore a construction of the tricyclic skeleton **273** using the Diels–Alder reaction (Scheme 3.43).



Scheme 3.43: Diels–Alder approach to tricyclic intermediate **258**.

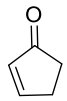
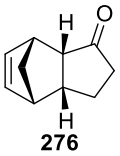
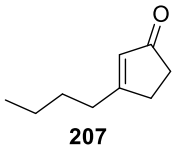
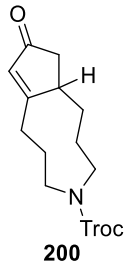
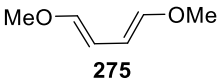
But-2-yne-1,4-diol was methylated to form alkyne **274** and isomerised to diene **275** (Scheme 3.44).[106]



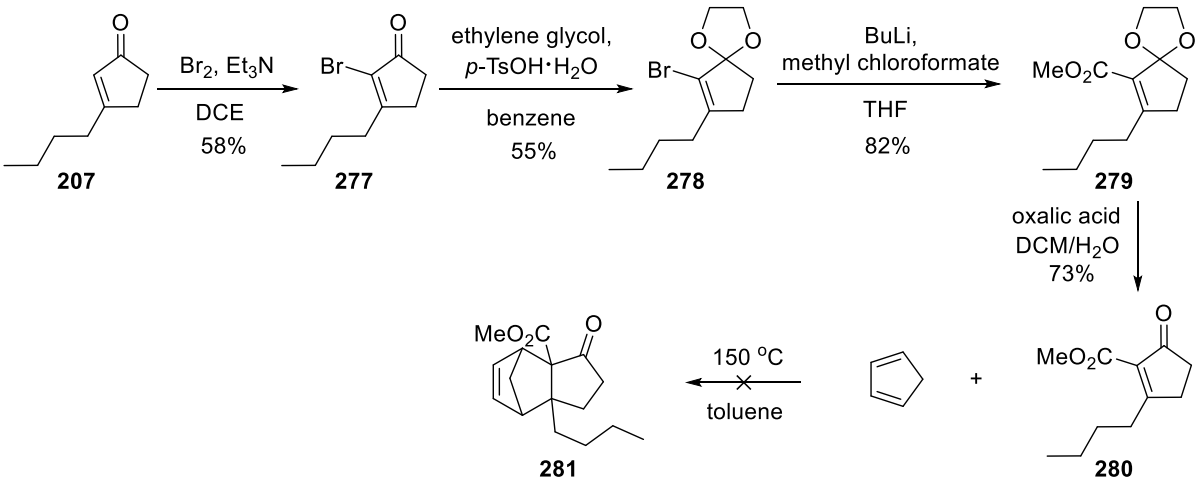
Scheme 3.44: Diene **275** synthesis.

Subsequently, the Diels–Alder reaction was investigated using various dienes and dienophiles in the presence of Lewis acids (Table 3.16). Cyclopentenone and cyclopentadiene reacted under thermal conditions to afford *endo*-cycloadduct **276**. However, no cycloaddition occurred when dienophile **207** or **200** were used under either thermal or Lewis acid-catalysed conditions. The substituent on the 3-position apparently renders the dienophile insufficiently electrophilic and too sterically hindered for cycloaddition to occur.

Table 3.16: Diels–Alder reaction of various dienes and dienophiles.

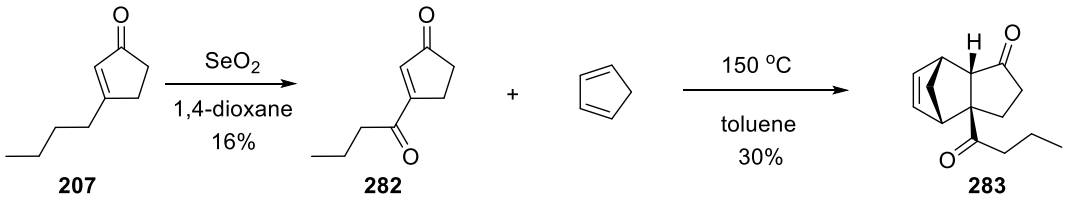
Dienophile	Diene	Lewis acid	Conditions	Product	Yield / %
		-	150 ºC in toluene for 16 h	 **276**	34
 **207**		-	150 ºC in toluene for 16 h	No reaction	0
		TfOH	RT in DCM for 16 h	No reaction	0
		$BF_3{\cdot}OEt_2$	RT in toluene for 16 h	No reaction	0
 **200**		$BF_3{\cdot}OEt_2$	150 ºC in toluene for 16 h	No reaction	0
	 **275**	-	150 ºC in toluene for 16 h	No reaction	0
		-	Neat at 150 ºC for 16 h	Decomposition	0

Accordingly, attempts were made to increase the electrophilicity of the dienophile. An attempt to add a carboxylic acid group to the α-position of enone **207** using magnesium methyl carbonate was unsuccessful.[107] As an alternative, enone **207** was brominated to give enone **277** which was protected as dioxolane **278** then lithiated and acylated to **279** and, finally, hydrolysed to α-ester enone **280** (Scheme 3.45).[108,109] However, even with this doubly-activated dienophile, cycloaddition attempts with cyclopentadiene under thermal conditions gave no evidence of adduct **281**.



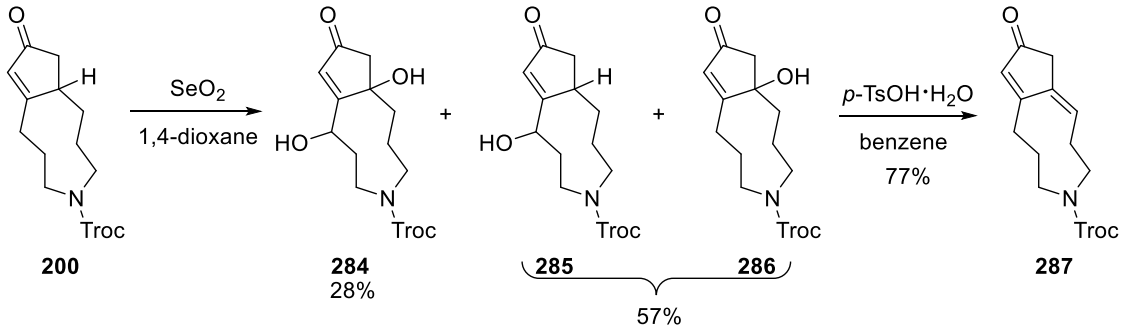
Scheme 3.45: Synthesis of α-ester enone for Diels–Alder.

Finally, dienophile **282**, derived from enone **207** by allylic oxidation, reacted successfully with cyclopentadiene under thermal conditions to afford *endo*-cycloadduct **283** (Scheme 3.46).[110]



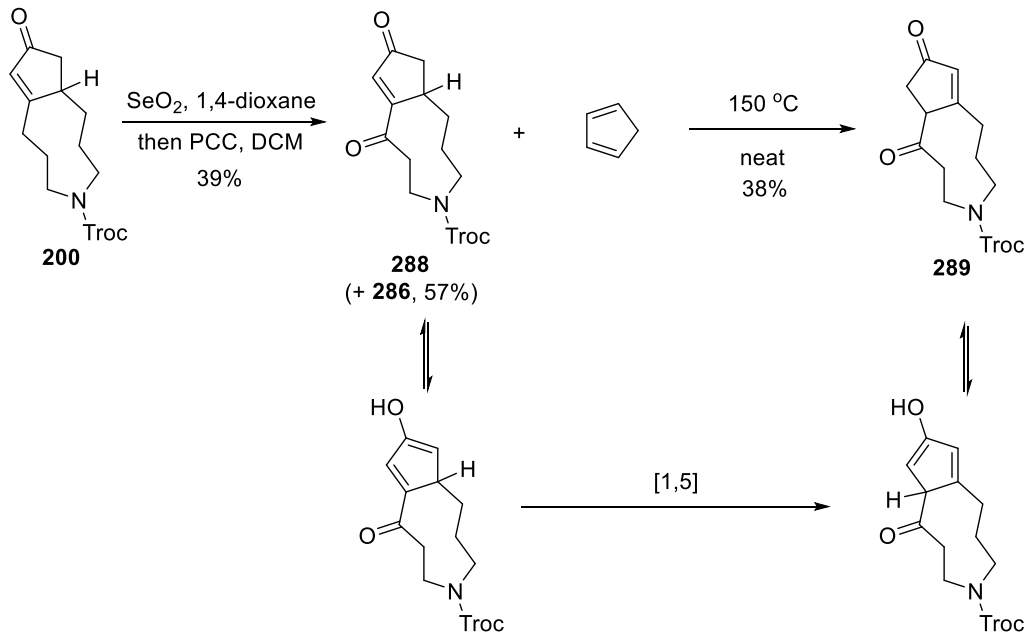
Scheme 3.46: Allylic oxidation of enone and Diels–Alder reaction.

Applying this sequence to enone **200** gave first a mixture of diol **284**, 2º alcohol **285** and 3º alcohol **286** (Scheme 3.47). No 1,4-dicarbonyl products were formed under these conditions. Treatment of 3º alcohol **286** with *p*-TsOH led to dehydration to afford dienone **287**.



Scheme 3.47: Allylic oxidation of bicyclic enone with SeO_2.

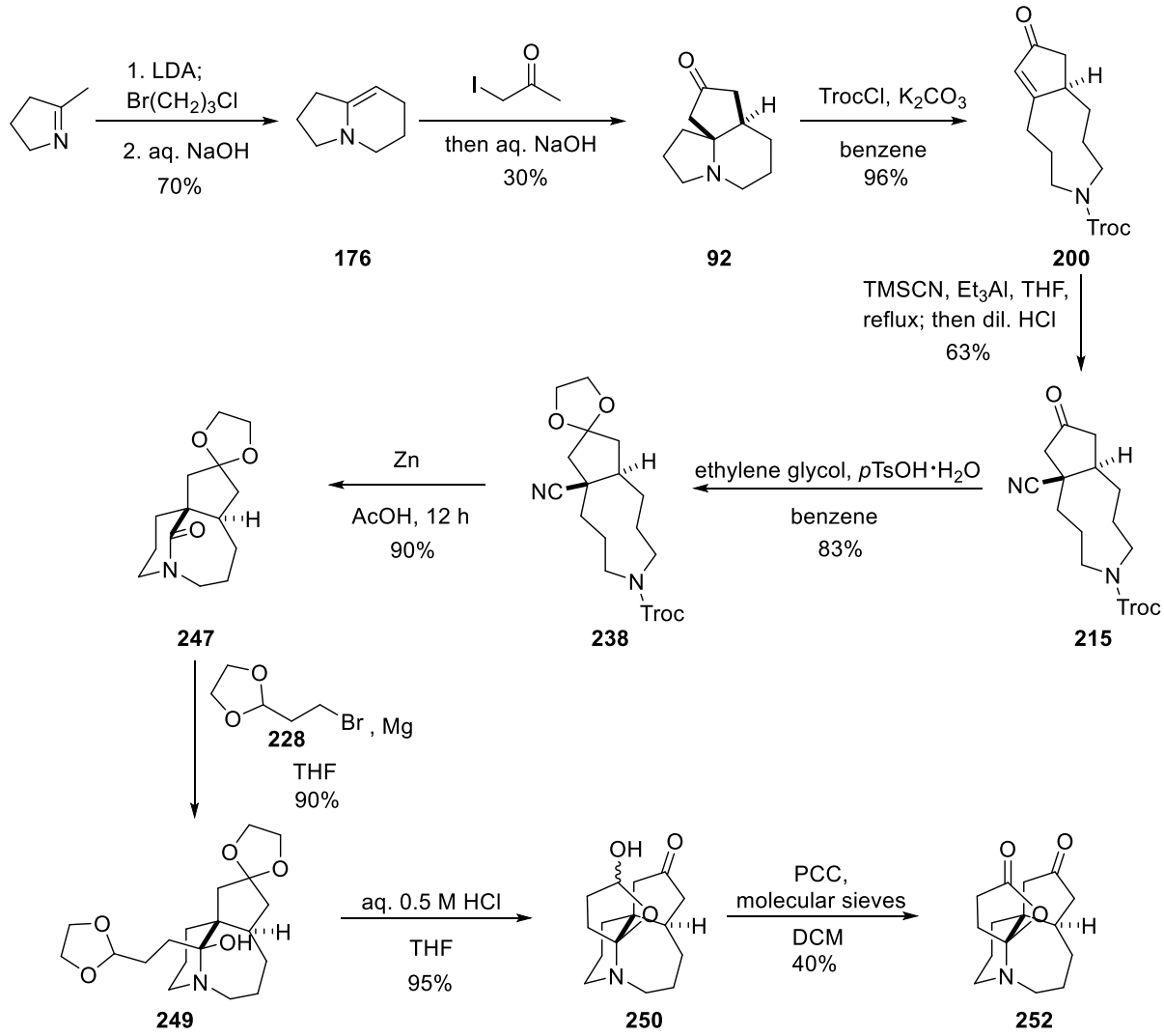
Allylic oxidation of enone **200** with SeO_2 then treatment with PCC afforded 1,4-dicarbonyl **288** in moderate yield (Scheme 3.48). However, heating dienophile **288** in cyclopentadiene led to isomerisation to enone **289** rather than cycloaddition because intramolecular hydrogen shift occurs faster than intermolecular Diels–Alder reaction. It was possible that under thermal conditions, dienophile **288** enolised and underwent a [1,5] hydride shift to form enone **289**.



Scheme 3.48: Allylic oxidation of bicyclic enone and Diels–Alder reaction.

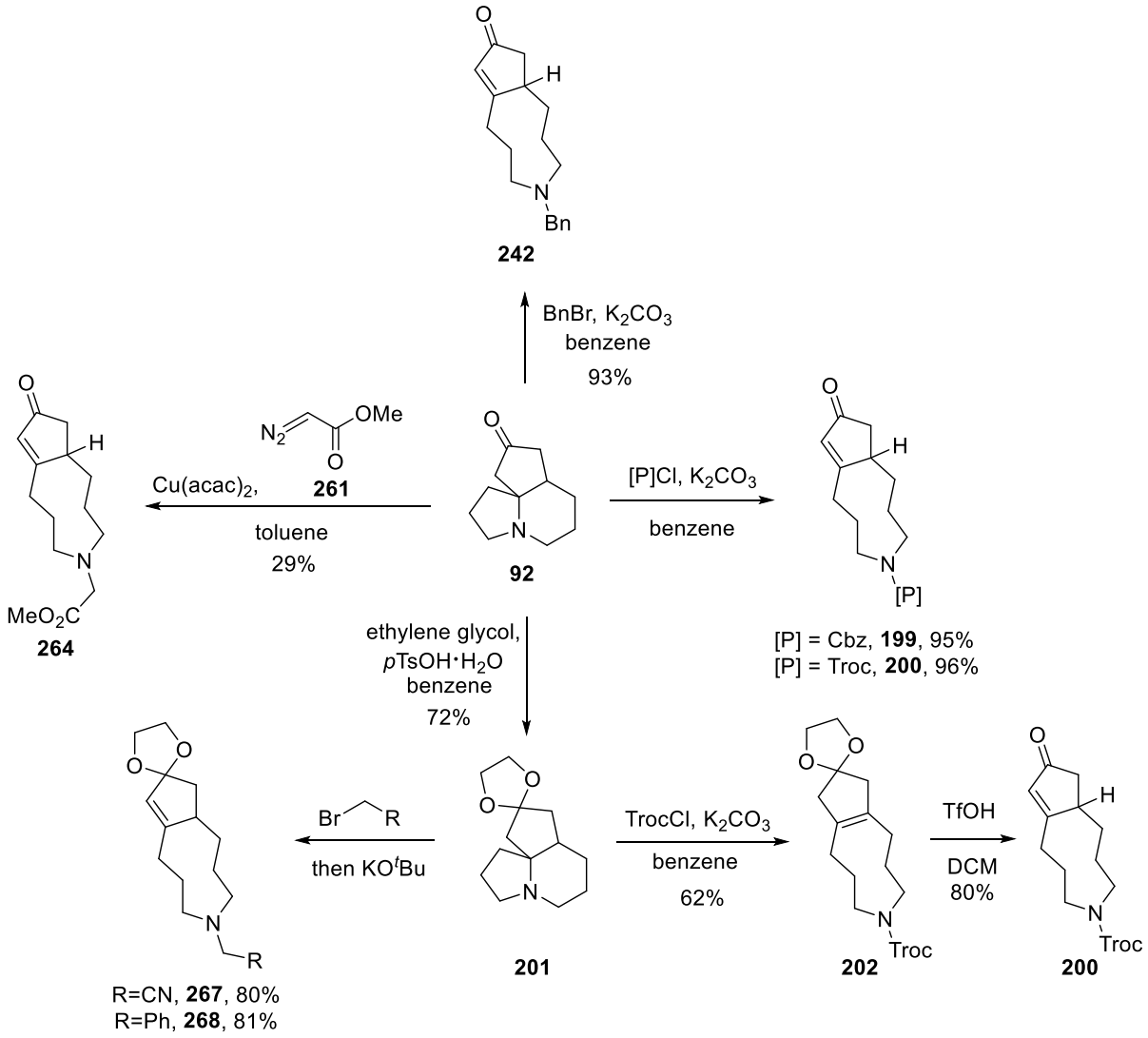
At this point, despite having a short access to enone **200**, it was concluded that there was little prospect of achieving an efficient cycloaddition and efforts turned to a more amenable natural product, hederacine B **7** which also contains the spiro-*N*,*O*-acetal moiety.

Overall, a brief synthetic route to tricyclic lactam **247** was developed to access this common structural core in the synthesis of fawcettimine-type *Lycopodium* alkaloids and further elaboration to lactone **252** was carried out (Scheme 3.49).



Scheme 3.49: Synthetic route to lactone **252**.

Besides, various fragmentation conditions for the synthesis of bicyclic enone from tricyclic aminoketone have been developed (Scheme 3.50).

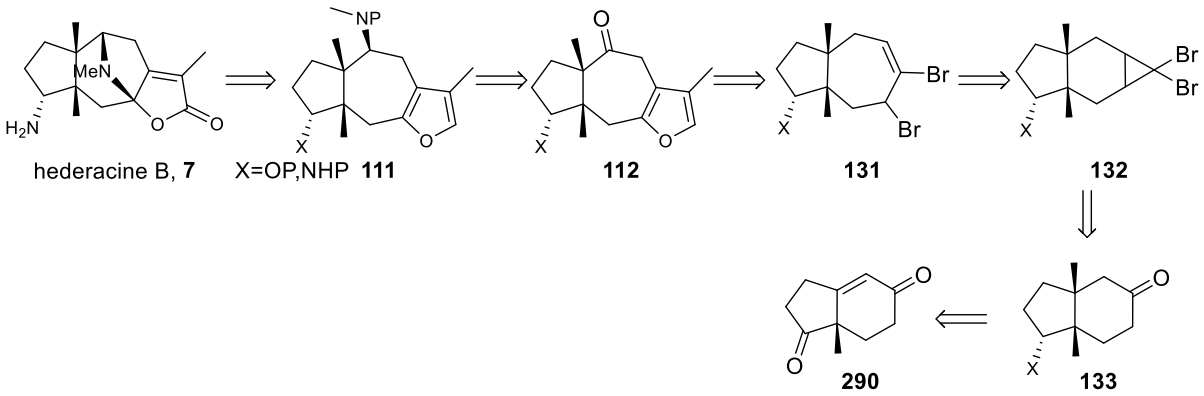


Scheme 3.50: Various fragmentation conditions for synthesis of bicyclic enone

Chapter 4: *Glechoma Hederacea* Alkaloids Synthesis

4.1 Retrosynthetic approach

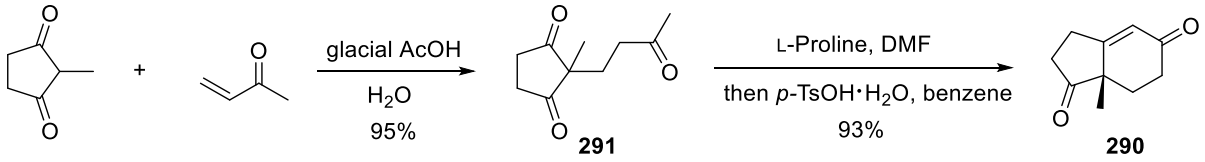
As hederacine B **7** contains a piperidine/butenolide spiro-*N*,*O*-acetal core, it was envisaged that this natural product could be synthesised from the furan oxidative *N*-spirocyclisation of furan amine precursor **111** (Scheme 4.1). In turn, precursor **111** could be constructed from reductive amination and methylation of tricyclic ketone **112**, formed from cycloheptyl bromide **131**. The seven-membered ring in **131** was expected to be available by electrocyclic ring expansion of dibromocyclopropane **132** derived from ketone **133**. *Cis*-fused bicyclic ketone **133** could be formed from Hajos–Parrish ketone **290**.



Scheme 4.1: Retrosynthetic approach to hederacine B.

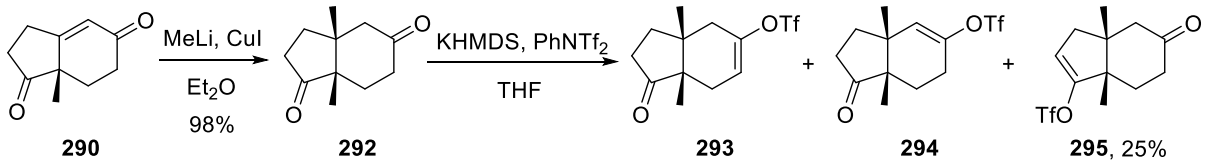
4.2 Initial synthesis of 5,7-bicyclic core

Following the literature procedure,[111] Michael addition of 2-methyl-1,3-cyclopentanedione to methyl vinyl ketone afforded ketone **291** which underwent organocatalytic aldol condensation to furnish Hajos–Parrish ketone **290** as a single enantiomer (Scheme 4.2). Davies and co-workers reported that the use of L-proline as organocatalyst gave ketone **290** in 93% e.e. based on chiral GC analysis.[112]



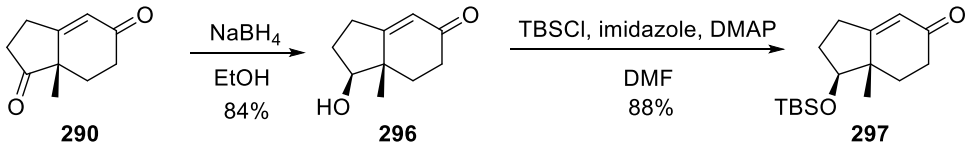
Scheme 4.2: Synthesis of Hajos–Parrish ketone.

The conjugate addition of lithium dimethylcuprate to Hajos–Parrish ketone **290** furnished *cis*-fused bicyclic ketone **292** in excellent yield (Scheme 4.3).[113] The NMR data of **292** matched literature data and based on literature, the stereochemistry of ketone **292** was proven by X-ray studies. Enolisation of ketone **292** with KHMDS and trapping the enolate afforded a mixture of enol triflate isomers **293**, **294** and **295**.[114] Both regioisomers **293** and **294** could not be separated from the excess $PhNTf_2$ used, so the yield could not be determined. Both regioisomers could be identified from the ^1H NMR spectrum of the mixture with the help of COSY data as the vinyl proton of **293** showed correlation with the adjacent methylene protons unlike the vinyl proton in **294**. Separated enol triflate **295** was also obtained.



Scheme 4.3: Lithium dimethylcuprate addition and enol triflate synthesis.

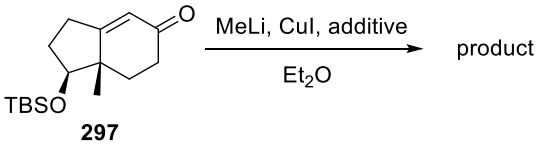
Therefore, in order to prevent the formation of enol triflate **295**, Hajos–Parrish ketone **290** was reduced stereoselectively with $NaBH_4$ to afford alcohol **296** which was protected with TBSCl to furnish enone **297** (Scheme 4.4).[115] The stereochemistry of alcohol **296** was proven by the lack of NOE between the methyl group and proton adjacent to the hydroxyl group.

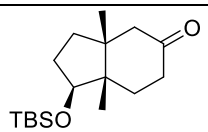
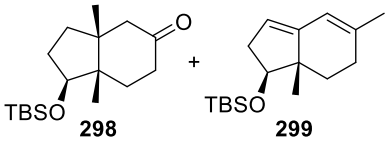
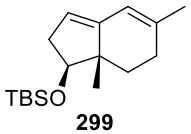


Scheme 4.4: Stereoselective reduction and TBSCl protection.

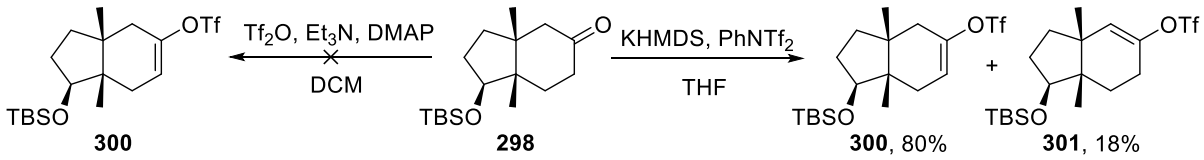
Subsequently, the conjugate addition of lithium dimethylcuprate to enone **297** was attempted with and without additives (Table 4.1). Without any additives used, ketone **298** was obtained in good yield. When TMSCl was used as additive, diene **299** was formed as the major product, most likely from the 1,2-addition of methyl cuprate followed by TMSOH elimination. When $BF_3{\cdot}OEt_2$ was used, diene **299** was formed as the only product in moderate yield. Therefore, it seems that in this case Lewis acids favour 1,2-addition of cuprates relative to 1,4-addition.

Table 4.1: Conjugate addition of lithium dimethylcuprate to enone **297**.



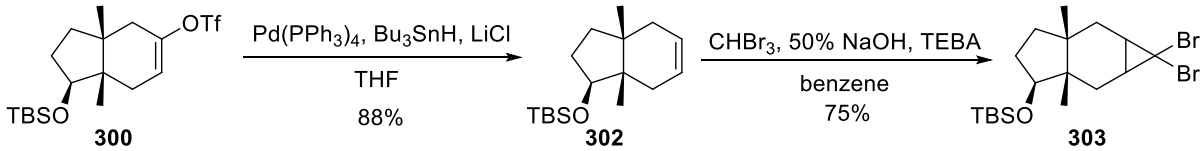
Additive	Product	Yield/ %
–	 **298**	75
TMSCl	 **298** + **299**	6 (**298**) 12 (**299**)
$BF_3{\cdot}OEt_2$	 **299**	42

An attempt to form enol triflate **300** with Tf_2O and triethylamine led to recovery of starting material (Scheme 4.5).[37] The use of KHMDS and *N*-phenyl-bis(trifluoromethanesulfonimide) led to regioselective enolisation and formation of enol triflate isomers **300** and **301** which were separated by column chromatography. Based on the ^{1}H NMR spectrum, enol triflate **300** was obtained as the major isomer and it was identified by strong correlation between the vinyl proton of **300** and the adjacent methylene protons in the COSY spectrum. This enolisation regioselectivity is due to the ease of abstracting the more accessible α-proton further away from the quaternary carbon.



Scheme 4.5: Enolisation and trapping as enol triflate.

When enol triflate **300** was subjected to Pd(0)-catalysed triflate cleavage in the presence of tributyltin hydride, alkene **302** was obtained in good yield (Scheme 4.6).[116] Dibromocyclopropanation of alkene **302** with dibromocarbene, generated in situ in a biphasic mixture with phase-transfer catalyst, afforded dibromocyclopropane **303** as a 1:1 mixture of diastereomers.[117] An attempt to effect dibromocyclopropanation using bromoform and potassium *tert*-butoxide in pentane gave only trace amounts of product.[118]

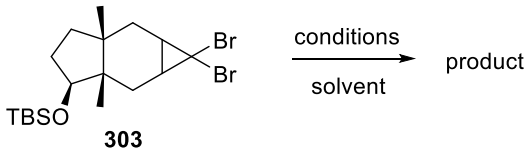


Scheme 4.6: Triflate cleavage and dibromocyclopropanation.

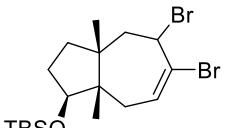
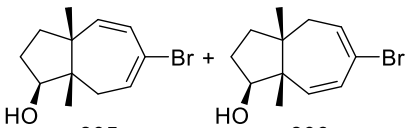
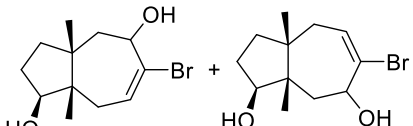
Subsequently, the electrocyclic ring expansion of dibromocyclopropane **303** was attempted under thermal and Ag(I)-promoted conditions (Table 4.2). Heating a solution of

dibromocyclopropane **303** in ACN at 100 ºC for 2 days afforded bromide **304** in poor yield due to incomplete reaction, whereas heating at 110 ºC for 3 days furnished diene isomers **305** and **306**.[119] Finally, the Ag(I)-promoted electrocyclic ring expansion of dibromocyclopropane **303** in semi-aqueous solution afforded diol isomers **307** and **308** in excellent yield.[120] Both diol isomers were obtained in roughly equal proportions and could be separated by column chromatography. The trapping of cation by water was stereoselective as both **307** and **308** were obtained as single diastereomers, but the stereochemistry was not determined as efforts turned to converting **308** into tricyclic furan.

Table 4.2: Electrocyclic ring expansion of dibromocyclopropane **303**.

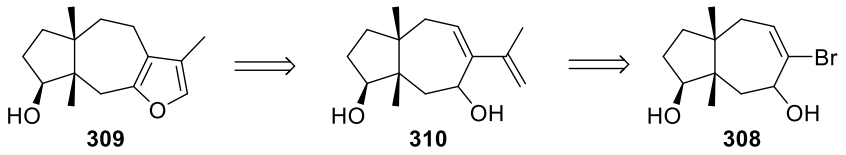


303

Conditions	Solvent	Product	Yield/ %
100 ºC, 2 days	ACN	 **304**	19
110 ºC, 3 days	ACN	 **305** **306**	14 (**305**) 18 (**306**)
$AgClO_4$ (1.7 eq.)	Acetone/H_2O (9:1)	 **307** **308**	50 (**307**) 47 (**308**)

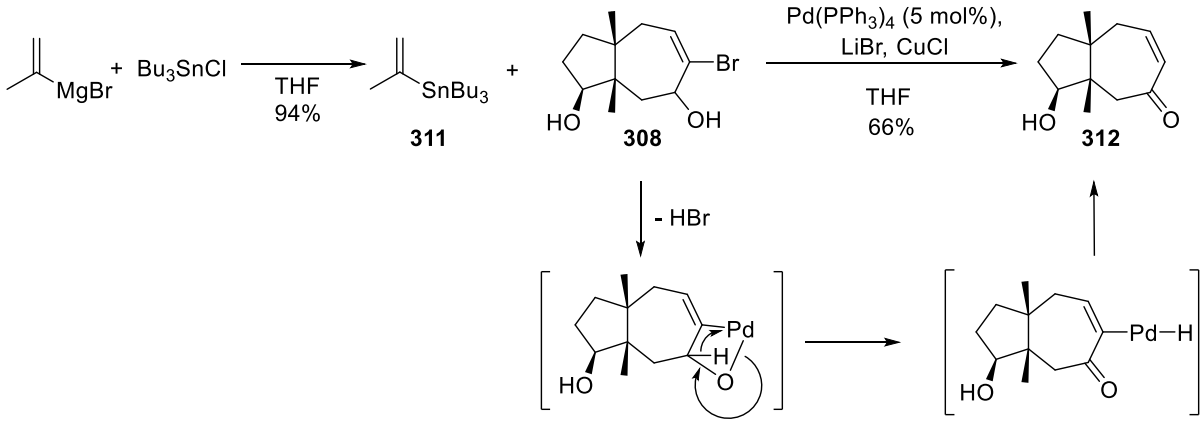
4.3 Initial attempts at tricyclic furan synthesis

With diol **308** in hand, it was postulated that tricyclic furan **309** would be formed from the oxidation and cyclisation of diene **310** which was expected to be accessible from the Stille coupling reaction of bromoalkene **308** (Scheme 4.7).



Scheme 4.7: Retrosynthetic approach to tricyclic furan.

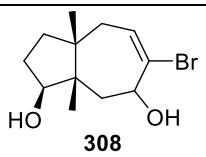
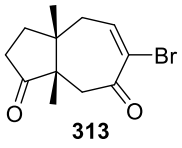
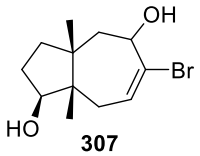
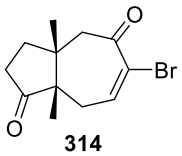
The addition of isopropenylmagnesium bromide to chlorotributylstannane afforded stannane **311** which was used for Stille coupling with bromoalkene **308** (Scheme 4.8).[121] However, enone **312** was formed under Stille coupling conditions and no desired diene **310** was obtained. Enone **312** was most likely formed when Pd(0) underwent oxidative addition to form a palladacycle followed by β-hydride elimination. The use of $Pd(OAc)_2$ and triphenylphosphine for the same reaction led to a complex mixture of products, including enone **312**.



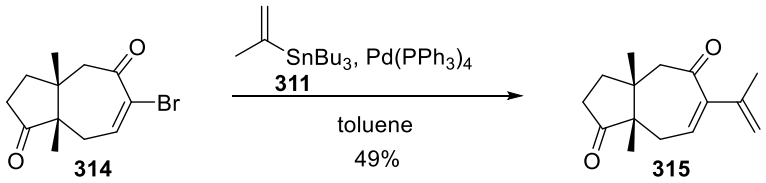
Scheme 4.8: Stannane synthesis and Stille coupling.

In order to prevent β-hydride elimination, diol **308** was first oxidised prior to Stille coupling (Table 4.3). The use of PCC afforded enone **313** in poor yield, whereas the use of DMP gave a high yield of the enone. Similarly, the oxidation of diol isomer **307** furnished enone **314** in excellent yield.

Table 4.3: Oxidation of diol.

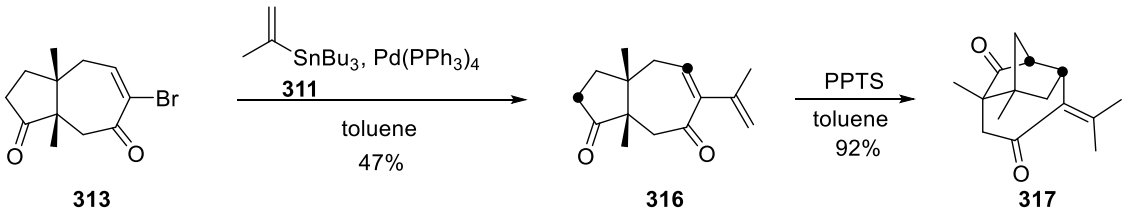
Diol	Oxidation condition	Product	Yield/ %
 **308**	PCC, 4Å molecular sieves, DCM	 **313**	33
	DMP, DCM		97
 **307**	DMP, DCM	 **314**	97

Using $Pd(PPh_3)_4$, the Stille reaction of enone **314** and stannane **311** proceeded smoothly to afford diene **315** in moderate yield, possibly due to partial decomposition of starting material (Scheme 4.9).



Scheme 4.9: Stille coupling of enone **314**.

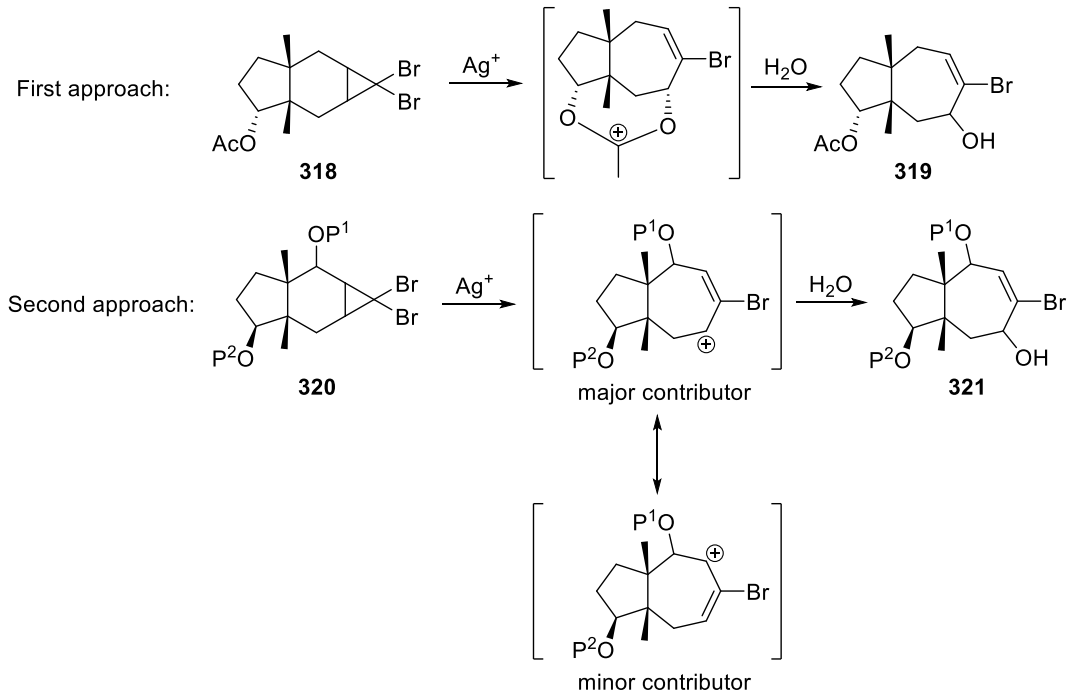
In parallel, the Stille reaction of enone **313** afforded diene **316** which, upon treatment with PPTS at 100 ºC, furnished tricyclic enone **317** via intramolecular Michael addition of enolised cyclopentanone into the enone, followed by alkene isomerisation (Scheme 4.10). No desired tricyclic furan products were formed from this acid-catalysed reaction.



Scheme 4.10: Stille coupling and unexpected Michael addition.

4.4 Controlling the regioselectivity of cycloheptenyl cation capture

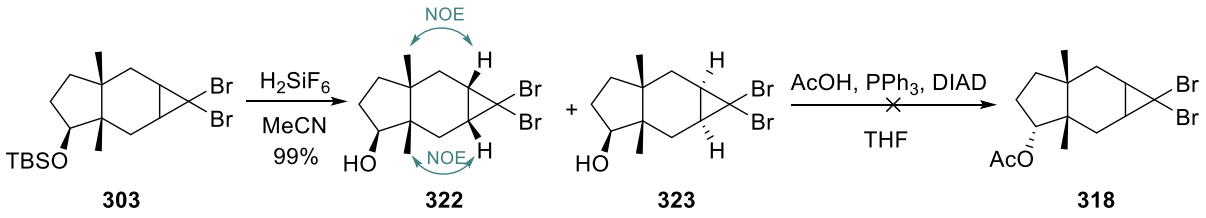
As the Ag(I)-promoted electrocyclic ring expansion of dibromocyclopropane **303** gave a 1:1 mixture of diol regioisomers **307** and **308**, we decided to control the regioselectivity of the ring expansion and cycloheptenyl cation capture in two plausible ways. One involved the use of a proximal acetyl or carbonate group in **318** to trap the carbocation resulting from the ring expansion regioselectively from which hydrolysis would afford alcohol **319** selectively (Scheme 4.11). Secondly, the presence of a protected hydroxyl group next to the dibromocyclopropane in **320** might favour the contributing structure with carbocation located further away from the electron-withdrawing hydroxyl group, allowing alcohol **321** to be selectively obtained.



Scheme 4.11: Approaches to control regioselectivity of cycloheptenyl cation capture.

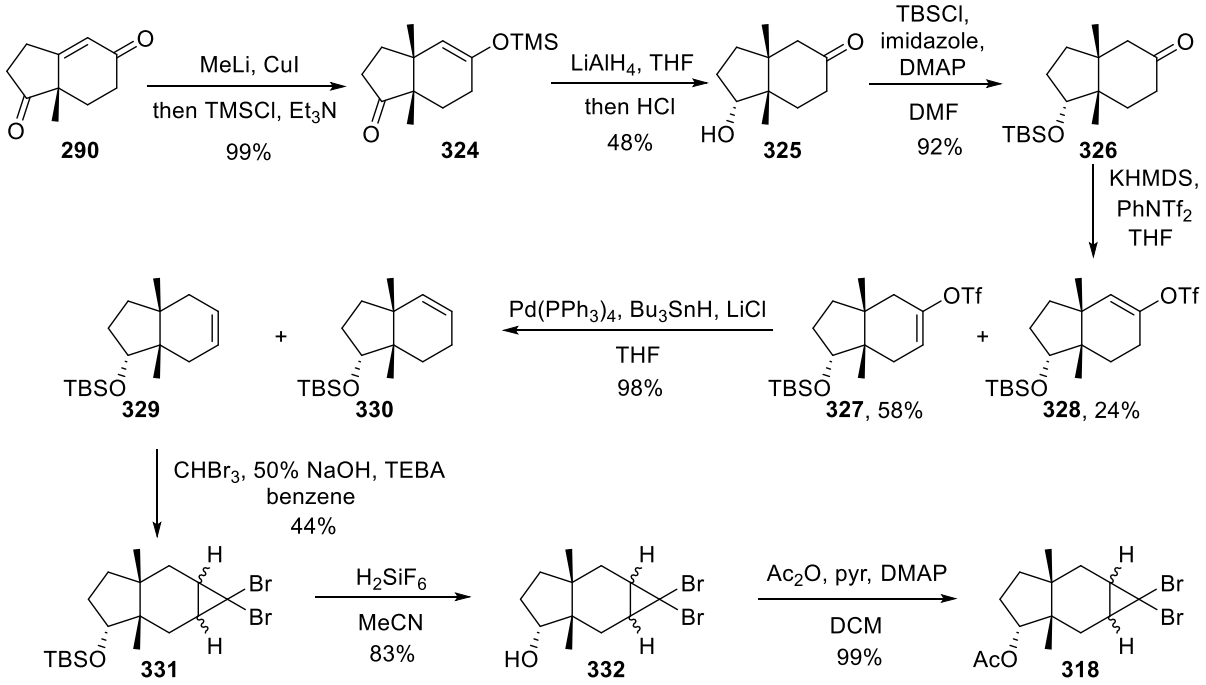
4.4.1 First approach

The TBS-deprotection of dibromocyclopropane **303** with TBAF or aq. HCl returned starting material but H_2SiF_6 in ACN cleaved the TBS group cleanly to afford alcohols **322** and **323** in excellent yield (Scheme 4.12).[122] The stereochemistry of the isomers **322** and **323** was confirmed by NOE studies where unlike **322**, there was no interaction between cyclopropane protons and the methyl groups in **323**. However, the attempt to obtain acetate epimer **318** under Mitsunobu conditions was unsuccessful, possibly due to steric constraints.[123]



Scheme 4.12: TBS-deprotection and Mitsunobu reaction.

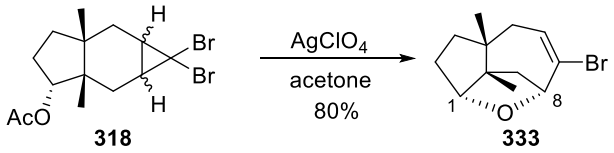
Therefore, an alternative synthetic route to epimer **318** was attempted (Scheme 4.13). Lithium dimethylcuprate addition to enone **290** followed by trapping with TMSCl afforded silyl enol ether **324** which was reduced stereoselectively from the less hindered face with $LiAlH_4$ and hydrolysed to give alcohol **325** as a single diastereomer.[124] Protection of alcohol **325** with TBSCl afforded ketone **326** which, upon enolisation and trapping with *N*-phenyl-bis(trifluoromethanesulfonimide), furnished enol triflate **328** as the minor isomer and **327** as the major isomer. The Pd(0)-catalysed triflate cleavage of the mixture of enol triflate isomers afforded alkene **329** and **330** which were separated by column chromatography. Dibromocyclopropanation of alkene **329** afforded dibromocyclopropane **331** which underwent TBS-deprotection to furnish alcohol **332**. Finally, acetylation of the alcohol provided acetate **318** in excellent yield.



Scheme 4.13: Alternative synthesis of acetate epimer.

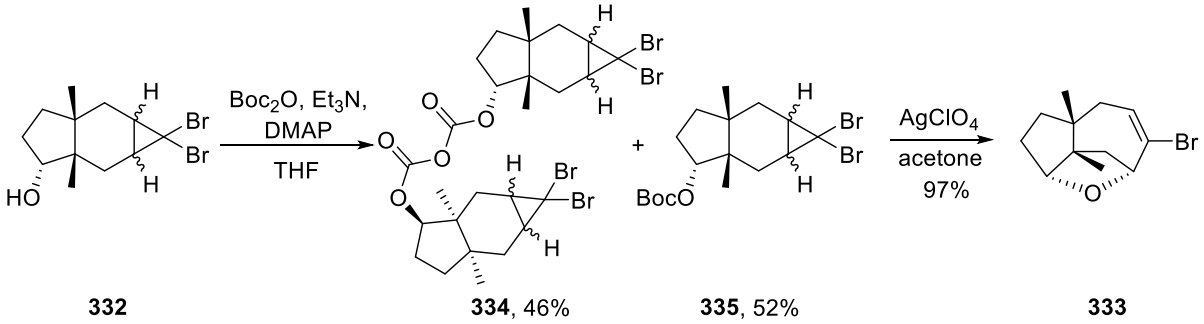
However, when acetate **318** was heated with $AgClO_4$ in acetone, the acetyl group was cleaved and the resulting hydroxyl trapped the carbocation to afford tricyclic hydrofuran **333**

(Scheme 4.14). The loss of C=O stretch in the IR spectrum indicates cleavage of acetyl group and the structure of **333** was confirmed by HMBC correlations between H(1) and C(8) and between H(8) and C(1) in the hydrofuran ring.



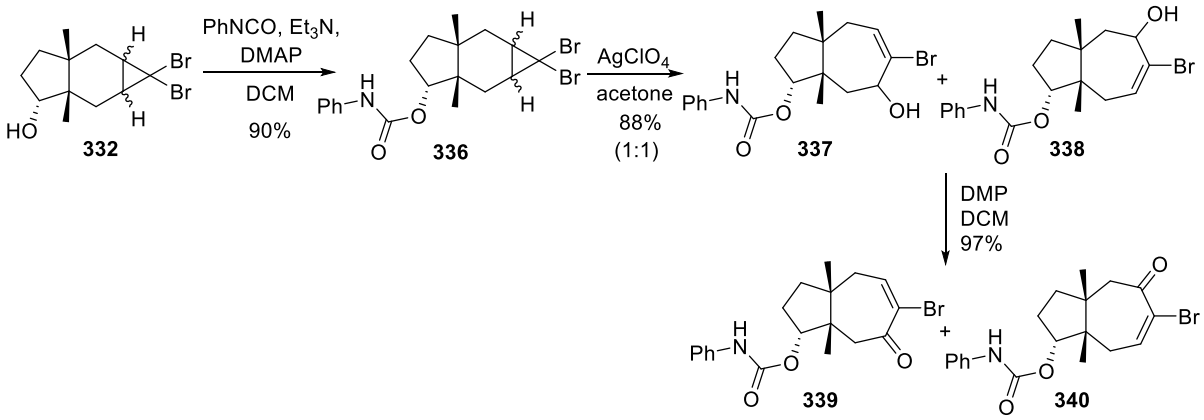
Scheme 4.14: Ag(I)-promoted electrocyclic ring expansion of acetate epimer.

In parallel, alcohol **332** was treated with Boc_2O to afford anhydride **334** and carbonate **335** in roughly equal proportions (Scheme 4.15). Treating carbonate **335** with $AgClO_4$ similarly resulted in Boc cleavage and hydroxyl trapping to furnish hydrofuran **333** in excellent yield.



Scheme 4.15: Carbonate synthesis and electrocyclic ring expansion.

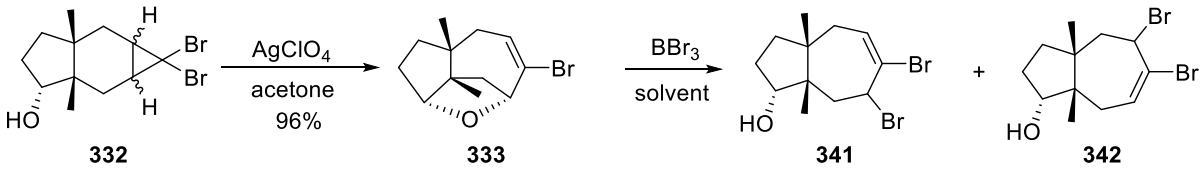
Due to the instability of acetyl and carbonate groups to Ag(I), carbamate **336** was synthesised from alcohol **332** using phenylisocyanate (Scheme 4.16).[125] The Ag(I)-promoted electrocyclic ring expansion of carbamate **336** afforded a 1:1 mixture of alcohol isomers **337** and **338**; these were oxidised with DMP to enones **339** and **340** respectively. This sequence showed that the carbamate group was stable to the ring expansion conditions but did not participate in controlling the regioselectivity of the ring expansion.



Scheme 4.16: Carbamate synthesis and electrocyclic ring expansion.

In the absence of protecting groups, alcohol **332** underwent ring expansion to afford hydrofuran **333** in excellent yield (Table 4.4). Subsequently, the opening of the hydrofuran ring with BBr_3 under different reaction conditions and solvents was attempted.[126] When the reaction mixture was heated at reflux in DCM for 4 h, dibromides **341** and **342** were obtained in a 3:2 ratio. Increasing the reaction time led to a decrease in overall yield and a change in isomer ratio to 1:1. When the reaction was conducted at RT, a poor overall yield was obtained due to incomplete reaction. Using ACN as the solvent resulted in a 1:4 ratio of **341**:**342**, but a poor overall yield precludes any meaningful mechanistic conclusions to be drawn.

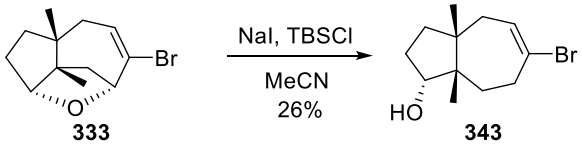
Table 4.4: Attempts to cleave hydrofuran ring with BBr_3.



332 333 341 342

Solvent	Conditions	Duration/ h	Overall yield/ %	Ratio (341:342)
DCM	Reflux	4	70	3:2
DCM	Reflux	6	45	1:1
DCM	Reflux	12	Decomposition	-
DCM	0 ºC → RT	12	35	3:2
ACN	RT	12	18	1:4
$MeNO_2$	RT	4	Decomposition	-

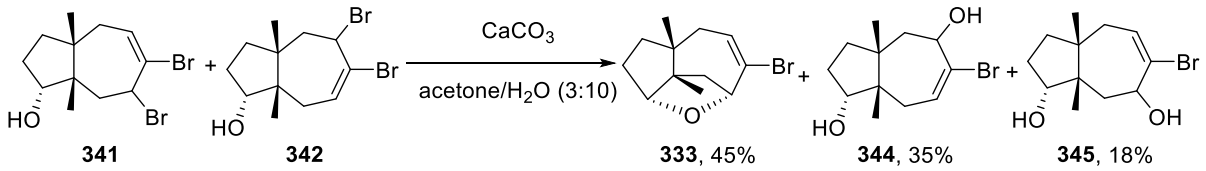
An attempt to open the hydrofuran ring with NaI and TBSCl afforded alcohol **343** which was most likely formed from reduction by NaI (Scheme 4.17).[127] Further attempt to open the hydrofuran ring with TMSBr and $BF_3{\cdot}OEt_2$ returned starting material.



333 343

Scheme 4.17: Hydrofuran ring opening with NaI.

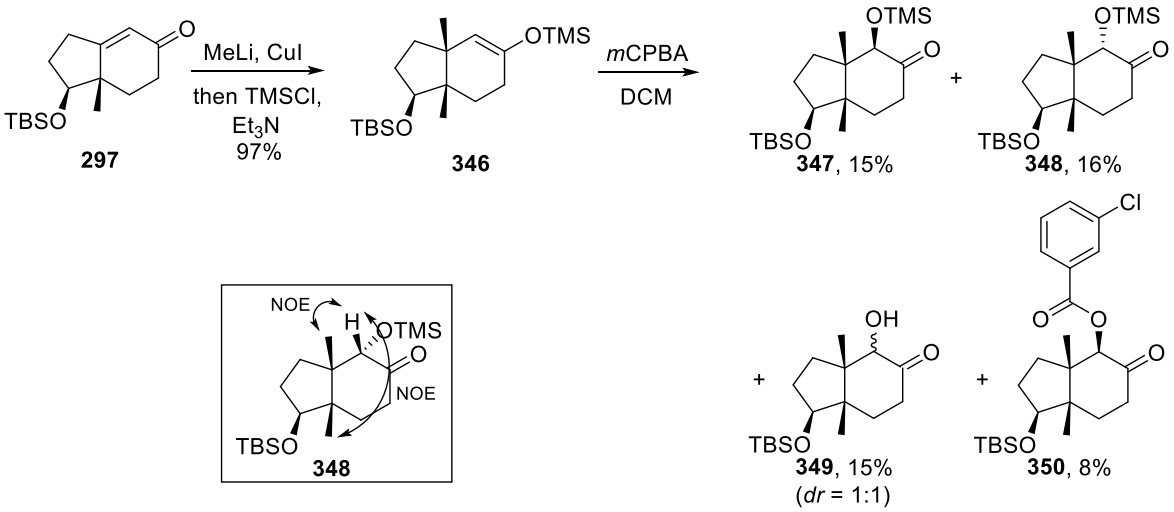
Hydrolysis of the 3:2 mixture of bromide isomers **341** and **342** afforded hydrofuran **333** and diol isomers **344** and **345** in roughly 2:1 ratio (Scheme 4.18).[128] Both **344** and **345** were obtained as single diastereomers but the stereochemistry was not determined.



Scheme 4.18: Hydrolysis of the mixture of bromide isomers.

4.4.2 Second approach

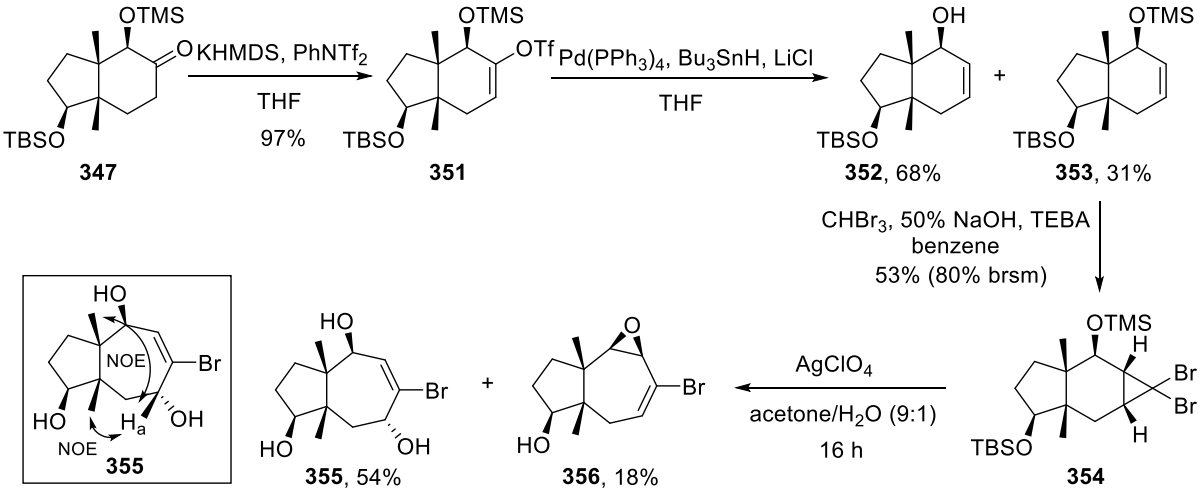
Lithium dimethylcuprate addition to enone **297** followed by enolate trapping with TMSCl afforded silyl enol ether **346** which underwent Rubottom oxidation with *m*CPBA to furnish TMS-ether diastereomers **347** and **348**, α-hydroxy ketone **349** and benzoate ester **350** (Scheme 4.19).[129] The stereochemistry of **347** and **348** was confirmed by NOE studies where unlike **347**, the α-proton adjacent to the TMS-ether in **348** showed correlation with the methyl groups. Similarly, the stereochemistry of benzoate ester **350** was proven by NOE data showing an absence of correlation between the α-proton adjacent to the ester group and the methyl groups.



Scheme 4.19: Silyl enol ether synthesis and Rubottom oxidation.

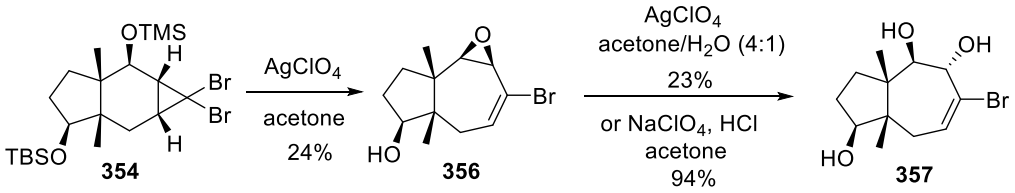
From ketone **347** the derived enol triflate **351** was reduced with Bu_3SnH and Pd(0)-catalysis to furnish allyl alcohol **352** and TMS-ether **353** (Scheme 4.20). The

dibromocyclopropanation of alkene **353** occurred stereoselectively to afford dibromocyclopropane **354** as a single diastereomer. The stereochemistry of **354** was confirmed by NOE data showing correlation between the cyclopropane protons and the methyl groups. The allylic silyl ether substituent presumably sterically hinders cyclopropanation from the *exo*-face. Finally, the Ag(I)-promoted electrocyclic ring expansion of dibromocyclopropane **354** afforded epoxide **356** as the minor product and triol **355** as the major product. This confirmed that the hydroxyl group adjacent to the dibromocyclopropane is able to influence the regioselectivity of allyl cation trapping as desired. Triol **355** was obtained as a single diastereomer and the stereochemistry was confirmed by NOE correlations between H_a and the methyl groups.



Scheme 4.20: Regioselective dibromocyclopropane ring expansion and trapping.

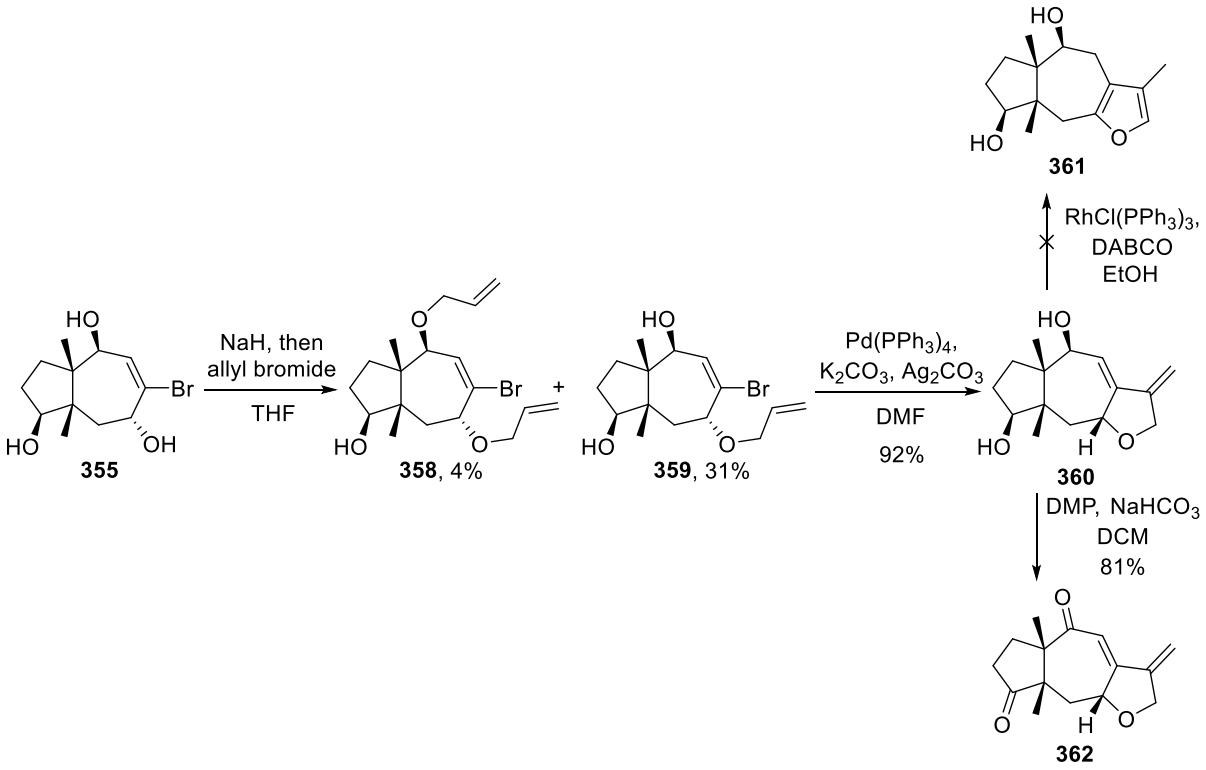
When the Ag(I)-promoted ring expansion was carried out in the absence of H_2O, only epoxide **356** was obtained, but in poor yield (Scheme 4.21). Opening the epoxide with $AgClO_4$ gave a poor yield of triol **357**, whereas the use of $NaClO_4$ and dil. HCl afforded triol **357** in excellent yield.[130] As no triol of above was obtained, the epoxide ring opening seems to proceed *via* an S_N2-like mechanism.



Scheme 4.21: Epoxide **356** synthesis and regioselective ring opening.

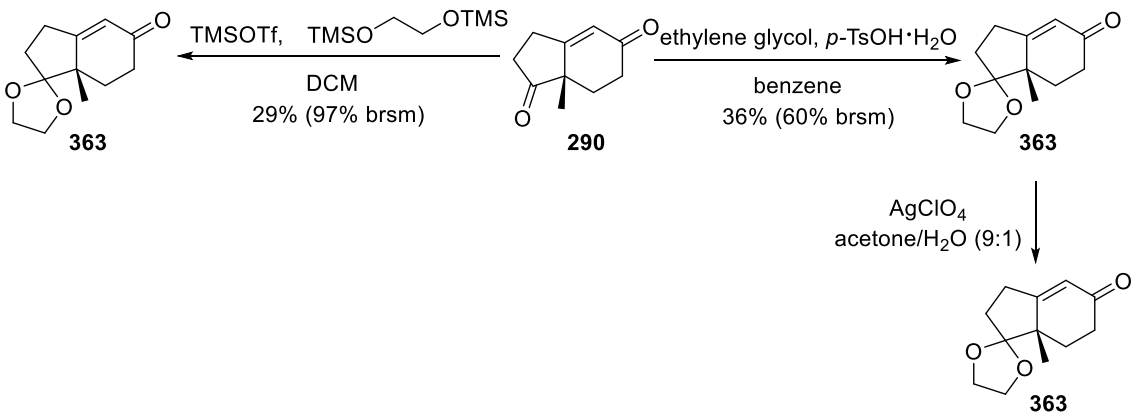
4.5 Tricyclic furan synthesis

As the previous cyclisation approach to tricyclic furan was unsuccessful (Scheme 4.10), another approach was considered which involves intramolecular Heck cyclisation and isomerisation. Starting with triol **355**, regioselective allylation of the less hindered hydroxyl group with allyl bromide afforded diol **359** as major product and a small amount of alcohol **358** (Scheme 4.22). The intramolecular Heck cyclisation of diol **359** proceeded smoothly and in excellent yield to furnish diene **360**.[131] An attempt to isomerise diene **360** with Wilkinson's catalyst was unsuccessful in forming tricyclic furan **361**, with starting material recovered.[132] Oxidation of diol **360** with DMP afforded dienone **362**.



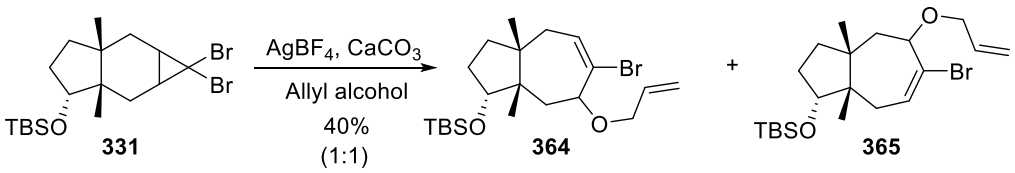
Scheme 4.22: Alternative approach to tricyclic furan.

It was envisaged that there might be difficulty distinguishing and functionalising the two hydroxyl groups in tricyclic furan **361**; therefore, attempts were made to maintain a protecting group on the hydroxyl on the 5-membered ring. The instability of TBS under the Ag(I)-promoted ring expansion conditions necessitated changing the protecting group. Acetalisation of Hajos–Parrish ketone **290** using standard conditions or Noyori's conditions afforded dioxolane **363** in poor yield (Scheme 4.23).[133] Subjecting dioxolane **363** to ring expansion conditions with $AgClO_4$ showed that the acetal is stable to these conditions. However, the low yield of the acetalisation made this overall approach unsuitable for scaling up.



Scheme 4.23: Acetalisation of Hajos–Parrish ketone.

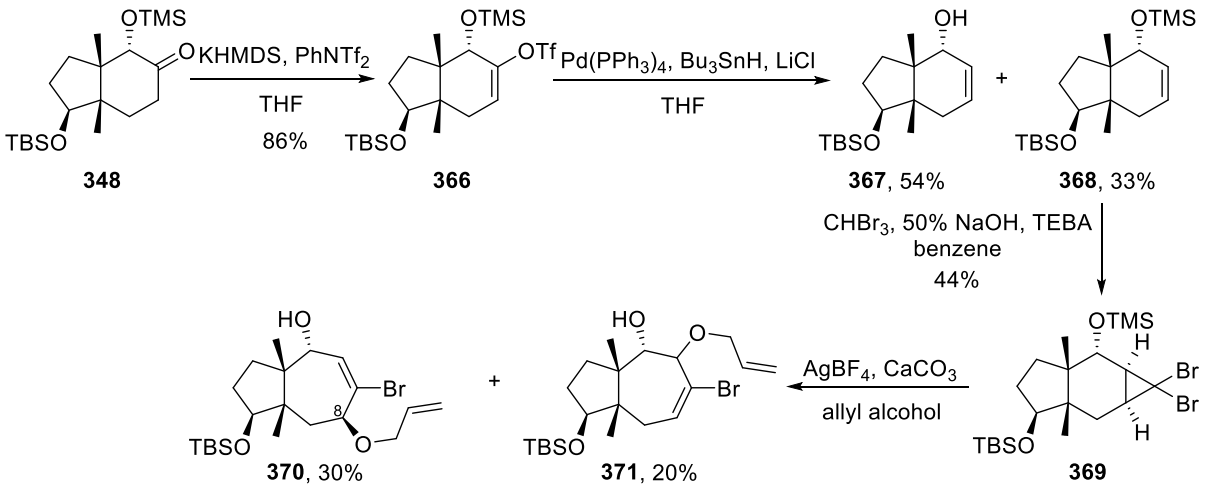
Wulff and co-workers have reported the use of $AgBF_4$ and $CaCO_3$ to promote dibromocyclopropane ring expansion and subsequent trapping of the carbocation with various alcohols as solvent.[134] Applying these conditions to dibromocyclopropane **331** using allyl alcohol as solvent afforded allyl ether **364** and **365** as a 1:1 mixture (Scheme 4.24). Pleasingly, the TBS-protecting group remained intact under these conditions. Both **364** and **365** were obtained as single diastereomers but the stereochemistry of the allyl ether group was not determined.



Scheme 4.24: Electrocyclic ring expansion and in situ trapping with allyl alcohol.

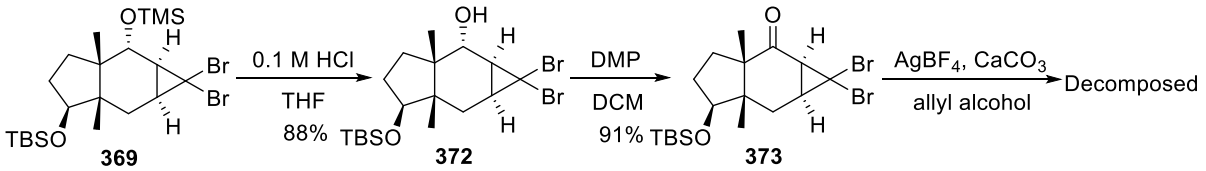
Subsequently, the regioselectivity of this modified ring expansion was tested. Ketone **348** was enolised and trapped as enol triflate **366** then reduced to afford allyl alcohol **367** and TMS-ether **368** (Scheme 4.25). Stereoselective dibromocyclopropanation of alkene **368** afforded dibromocyclopropane **369** and regioselective ring expansion with trapping in situ by allyl alcohol furnished allyl ether **370** and **371** in a 3:2 ratio. The desired allyl ether **370** was obtained as a single isomer and the stereochemistry was confirmed by the absence of NOE

correlation between H(8) and the methyl groups. This showed that the trapping of the carbocation by allyl alcohol was stereoselective and favoured attack from the *exo*-face of the bicyclic system, *anti*- to the existing hydroxyl group. Allyl ether **371** was also obtained as a single diastereomer but the stereochemistry was not determined.



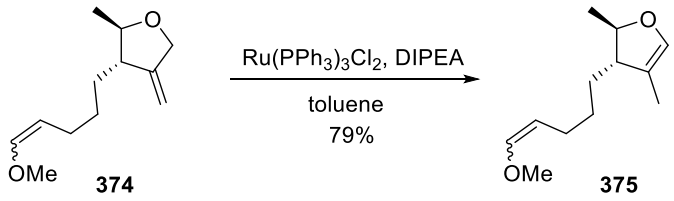
Scheme 4.25: Regioselectivity of ring expansion and trapping in situ with allyl alcohol.

In order to determine whether a carbonyl group adjacent to the dibromocyclopropane would affect the regioselectivity of the ring expansion, silyl ether **369** was hydrolysed to alcohol **372** and oxidised to ketone **373** (Scheme 4.26). Attempts to expand dibromocyclopropane **373** led mainly to decomposition.



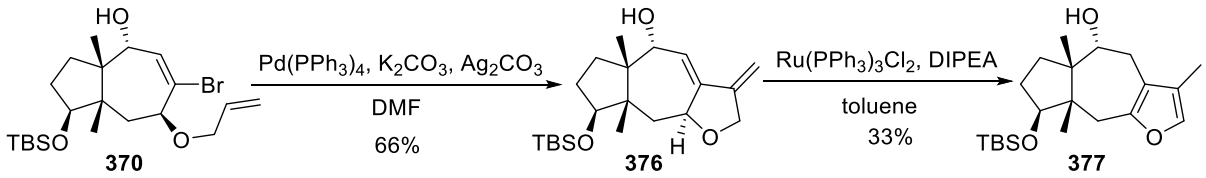
Scheme 4.26: Attempted ring expansion of ketone **373**.

Moeller and co-workers used a Ru(II) catalyst and *N*,*N*-diisopropylethylamine to isomerise the terminal alkene of methylenetetrahydrofuran **374** to afford dihydrofuran **375** (Scheme 4.27).[135]



Scheme 4.27: Isomerisation of terminal alkene in hydrofuran

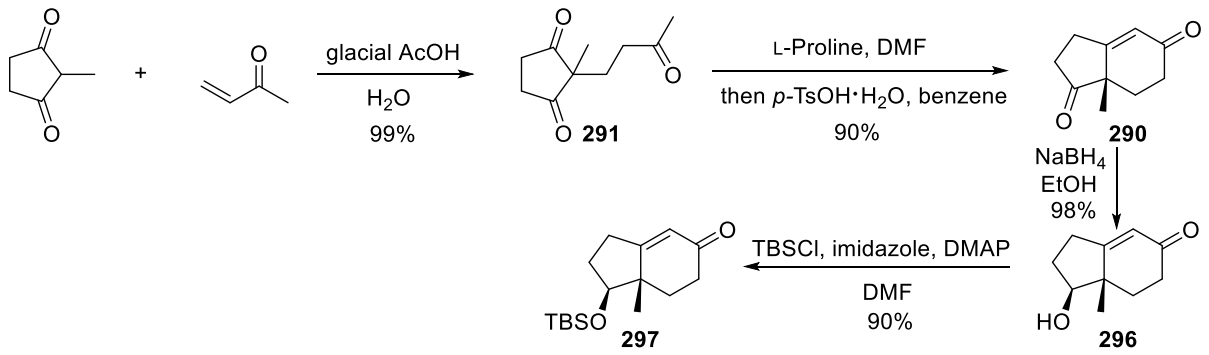
With allyl ether **370** in hand, the intramolecular Heck cyclisation afforded diene **376** which was treated with Ru(II)-catalyst to furnish tricyclic furan **377** (Scheme 4.28). The poor yield of furan **377** could be due to partial decomposition after prolonged heating.



Scheme 4.28: Intramolecular Heck cyclisation and isomerisation.

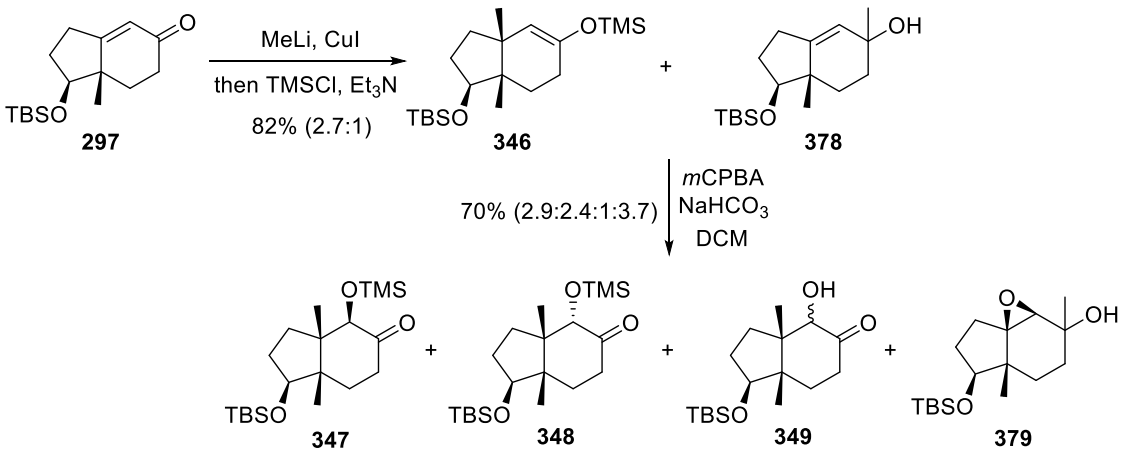
4.6 Scale up and optimisation

With the synthetic route to tricyclic furan **377** established, attention turned to scaling up the synthesis and optimising certain steps in the route. The Hajos–Parrish ketone **290** was synthesised in excellent yield on multigram scale (Scheme 4.29), and stereoselective reduction and TBS-protection proceeded smoothly to afford enone **297**.



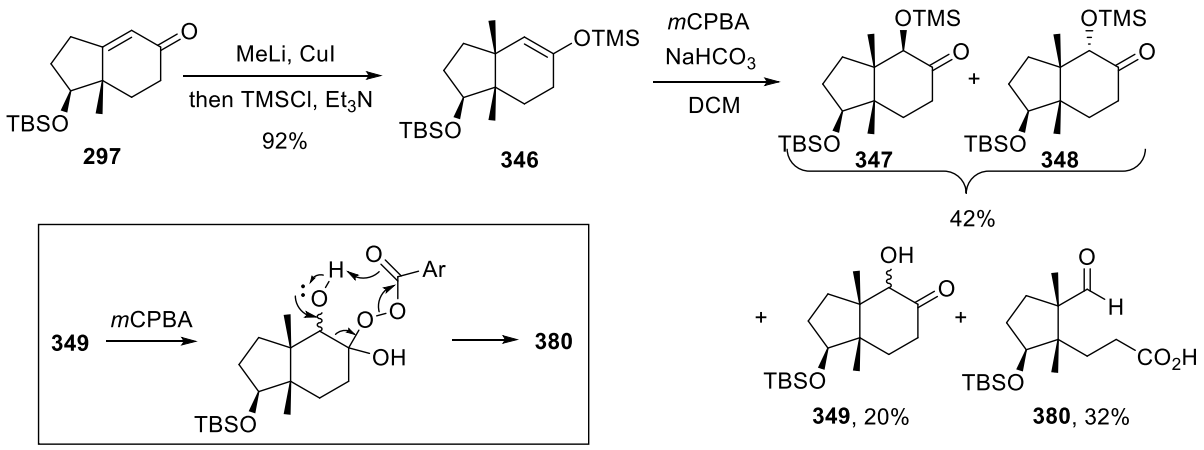
Scheme 4.29: Large scale synthesis of enone **297**.

Attempts were then made to optimise the Rubottom oxidation and minimise side product formation. Lithium dimethylcuprate addition and trapping with TMSCl afforded silyl enol ether **346** and allylic alcohol **378** in a 2.7:1 ratio, possibly due to impurities in the CuI used (Scheme 4.30). Rubottom oxidation of the crude mixture with *m*CPBA in the presence of $NaHCO_3$ as buffer afforded TMS-ether **347** and **348**, α-hydroxy ketone **349** and epoxide **379** arising from allylic alcohol **378**.[136] The use of basic buffer was successful in preventing the formation of benzoate ester **350** but the yield of the TMS-ethers was still low.



Scheme 4.30: Rubottom oxidation with *m*CPBA in the presence of buffer.

The CuI and *m*CPBA were purified before the reaction was repeated.[137] This time, silyl enol ether **346** was afforded in excellent yield, and Rubottom oxidation gave **347**, **348** and **349** in 62% yield (Scheme 4.31). This moderate yield of desired products was due to the formation of carboxylic acid **380** from the oxidative cleavage of α-hydroxy ketone **349**.



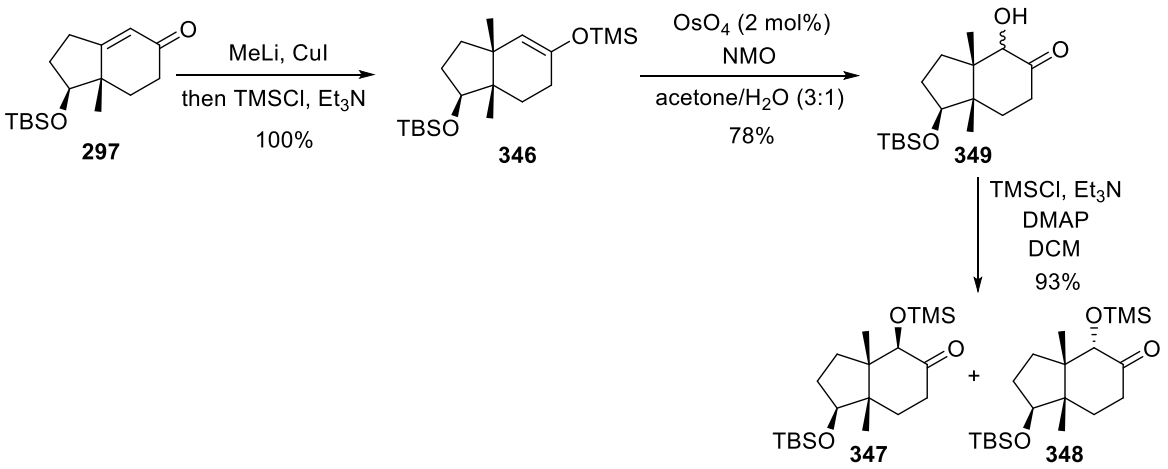
Scheme 4.31: Identifying side product of Rubottom oxidation.

Therefore, the oxidation of silyl enol ether **346** was attempted using other oxidants (Table 4.5). Upjohn dihydroxylation conditions afforded α-hydroxy ketone **349** in 72% yield,[138] whereas the Sharpless dihydroxylation of **346** afforded **349** in 31% yield and as a 1:1 ratio of diastereomers.[139] The use of DMDO afforded α-hydroxy ketone **349** in 74% yield but the synthesis of DMDO from acetone was low-yielding and cumbersome to scale up.[140] Following Kropp's procedure, oxidation with moist MMPP afforded TMS-ether **347** and **348** in 25% yield and ketone **349** in 43% yield.[141] Therefore, the Upjohn procedure was chosen for the scale up as the reaction was clean and the yield was acceptable.

Table 4.5: Oxidation of silyl enol ether **346**.

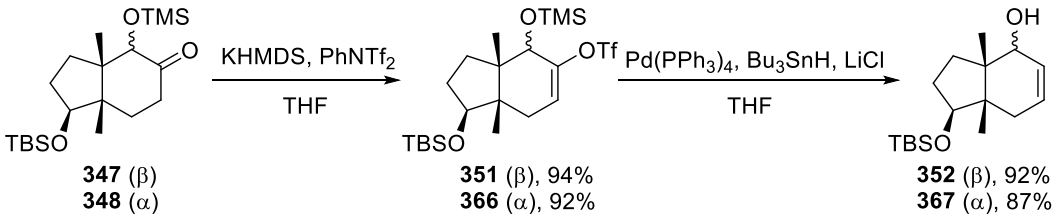
Oxidation conditions	Product	Yield/ %
OsO_4 (2 mol%), NMO, acetone/H_2O (3:1)	**349**	72
AD-mix-β, methanesulfonamide, *t*-BuOH/H_2O (1:1)	**349**	31
DMDO, acetone	**349**	74
Moist MMPP, DCM	**347**, **348**, **349**	25 (**347**+**348**), 43 (**349**)

Using Upjohn dihydroxylation with OsO_4, α-hydroxy ketone **349** was afforded in good yield and was protected with TMSCl to afford TMS-ether **347** and **348** on decagram scale (Scheme 4.32).



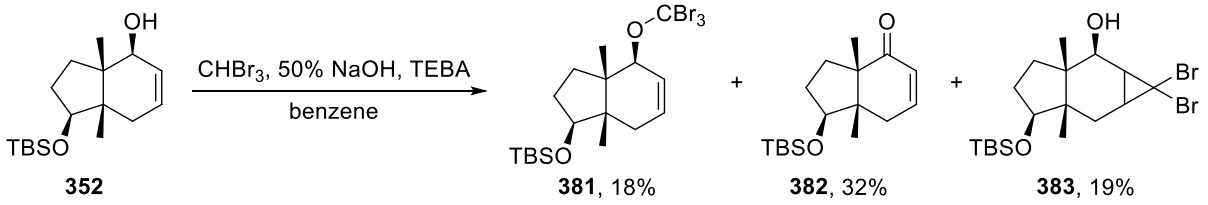
Scheme 4.32: Synthesis of TMS-ether on decagram scale.

The enolisation of ketones **347** and **348** was carried out in parallel to afford enol triflates **351** and **366** in excellent yield (Scheme 4.33). The Pd(0)-catalysed triflate cleavage proceeded smoothly on multigram scale to afford allylic alcohols **352** and **367**.



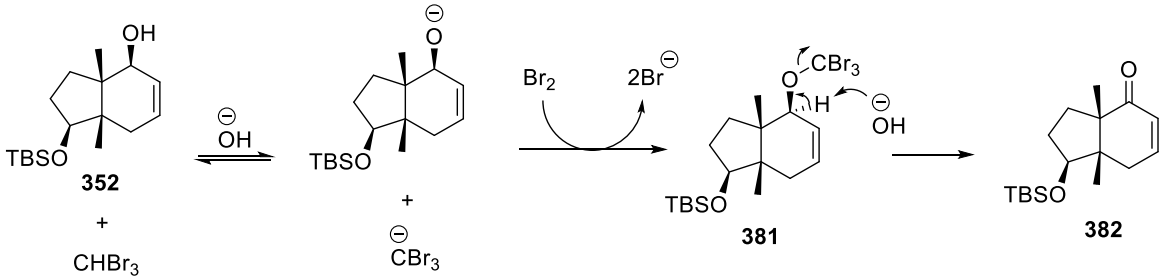
Scheme 4.33: Large scale synthesis of allylic alcohol.

The scale up and optimisation work was first carried out on hydroxyl epimer **352**. In order to determine whether the allylic hydroxyl in **352** had to be protected before dibromocyclopropanation, alcohol **352** was subjected to dibromocyclopropanation conditions (Scheme 4.34). A mixture of products was obtained, including bromide **381**, enone **382** and desired dibromocyclopropane **383**.



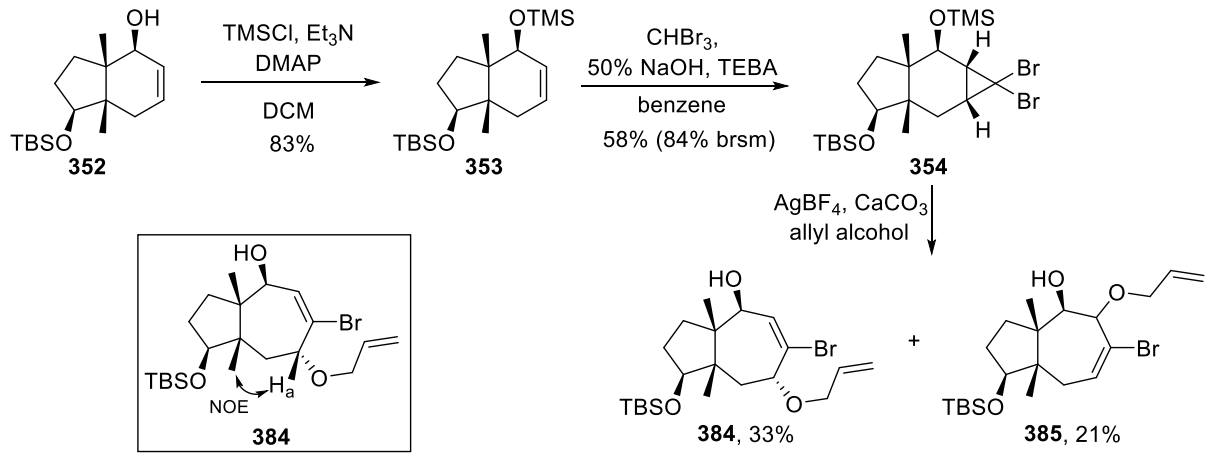
Scheme 4.34: Dibromocyclopropanation of allylic alcohol.

Surprisingly, the formation of side products **381** and **382** indicated that some kind of oxidation has taken place under these reaction conditions. A mechanism was proposed for the formation of these side products and was thought to involve Br_2 or Br^+ that might be present in bromoform (Scheme 4.35). Therefore, it was necessary to protect the alcohol before dibromocyclopropanation to prevent side reactions.



Scheme 4.35: Proposed mechanism for formation of side products.

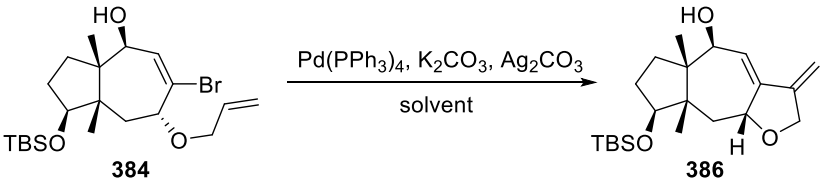
Allylic alcohol **352** was protected (→ **353**) and dibromocyclopropanated to furnish dibromocyclopropane **354** (Scheme 4.36). Treating this with $AgBF_4$ and $CaCO_3$ in allyl alcohol afforded allyl ether **384** as the major product and allyl ether **385** as minor product. Varying the amount of $AgBF_4$ and the duration of heating did not improve the yield of allyl ether **384**. The stereochemistry of **384** was confirmed by NOE correlation between H_a and the methyl groups. Allyl ether **385** was obtained as a single diastereomer but the stereochemistry was not determined.



Scheme 4.36: Large scale synthesis of allyl ether.

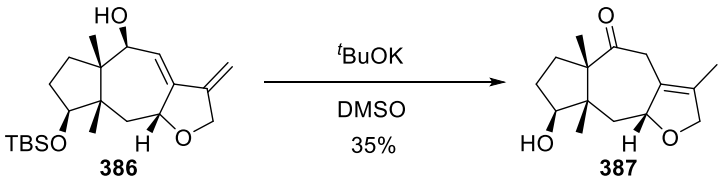
The intramolecular Heck cyclisation of allyl ether **384** was attempted using different solvents (Table 4.6) and it was found that the use of a less polar solvent, toluene, improved the yield of diene **386** to 85% and simplified the extraction process.

Table 4.6: Optimisation of intramolecular Heck cyclisation.



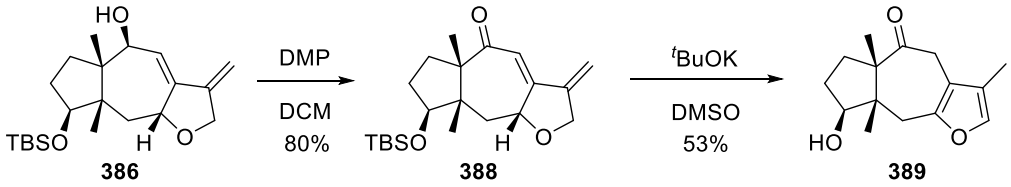
Solvent	Temperature/ ºC	Duration/ h	Yield/ %
DMF	100	1.25	70
ACN	80	1	75
toluene	85	1.5	85

The isomerisation of diene **386** was attempted using potassium *tert*-butoxide in DMSO, but ketone **387** was afforded and the TBS-protecting group was also cleaved (Scheme 4.37).[142]



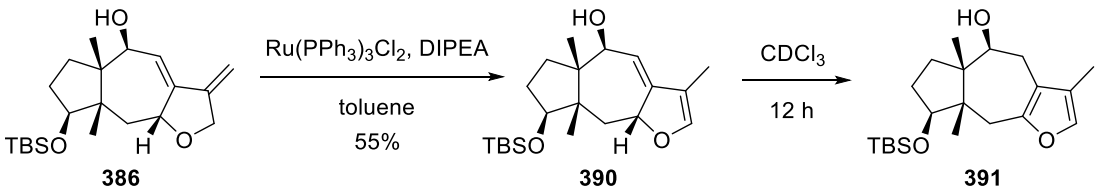
Scheme 4.37: Attempted isomerisation of diene **386**.

Therefore, alcohol **386** was first oxidised with DMP to dienone **388** before being treated with potassium *tert*-butoxide (Scheme 4.38). Tricyclic furan **389** was obtained in moderate yield but the TBS-protecting group was cleaved and multiple side products were formed. The use of TFA for the isomerisation of dienone **388** was unsuccessful in forming tricyclic furan, with starting material recovered.[143]



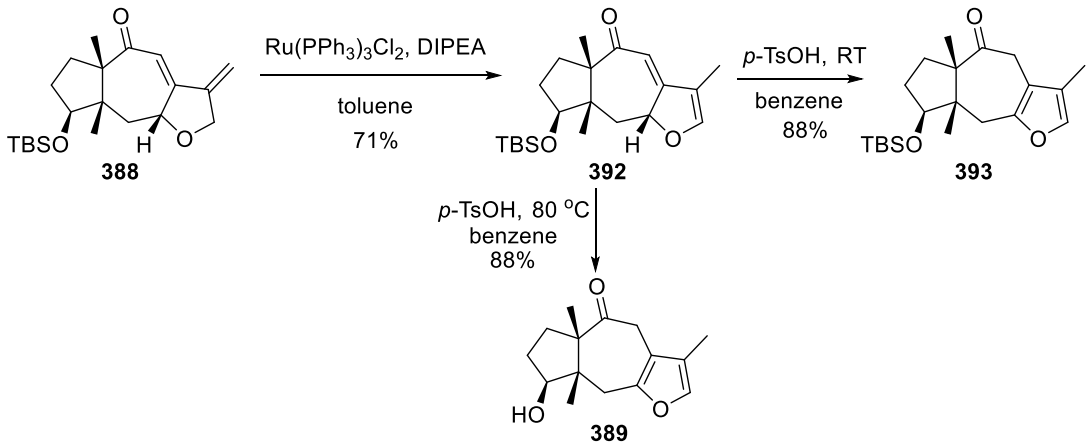
Scheme 4.38: Oxidation and isomerisation of diene **386**.

When $Ru(PPh_3)_3Cl_2$ and DIPEA were used to isomerise diene **386**, diene **390** was formed after 5 h at 80 ºC (Scheme 4.39). However, after standing in $CDCl_3$ overnight, further isomerisation took place to afford tricyclic furan **391**, possibly due to the presence of acidic impurities in the $CDCl_3$.



Scheme 4.39: Ru(II)-catalysed isomerisation of diene **386**.

In parallel, the Ru(II)-catalysed isomerisation of dienone **388** afforded dienone **392** after 2 h at 80 ºC (Scheme 4.40). Treating dienone **392** with *p*-TsOH in benzene at 80 ºC led to TBS-deprotection and isomerisation to afford tricyclic furan **389**. Pleasingly, the acid-catalysed isomerisation of dienone **392** took place at RT to afford tricyclic furan **393** in good yield. Therefore, the Ru(II)-catalysed isomerisation was chosen for tricyclic furan synthesis as the reaction was clean and the TBS group stayed intact.

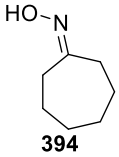
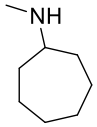
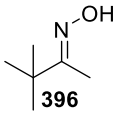
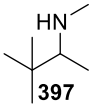


Scheme 4.40: Ru(II)-catalysed isomerisation of dienone **388**.

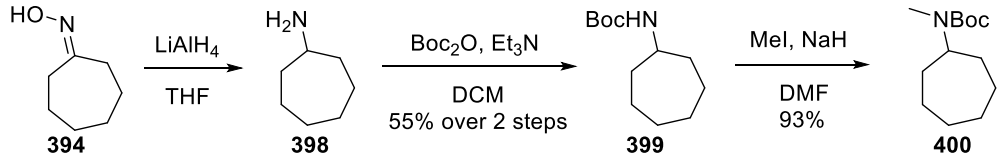
4.7 Furan amine precursor synthesis

In order to convert a ketone into an amine, we decided to attempt two different approaches: reductive amination, and oxime formation followed by reduction. These approaches were attempted on model compounds, cycloheptanone and pinacolone before attempting on tricyclic furan **393** (Table 4.7). Cycloheptanone and pinacolone underwent oxime formation to afford oximes **394** and **396** respectively in excellent yield.[42] Reductive amination also proceeded smoothly, to afford amines **395** and **397**, with the low yield of amine **397** attributed to its volatility.[144]

Table 4.7: Reductive amination and oxime formation in model compounds.

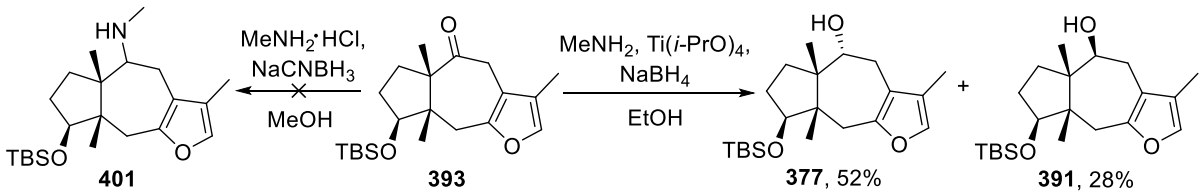
Ketone	Reaction conditions	Product	Yield/ %
cycloheptanone	$NH_2OH{\cdot}HCl$, pyridine, EtOH	 **394**	93
cycloheptanone	$MeNH_2{\cdot}HCl$, $NaCNBH_3$, MeOH	 **395**	63
pinacolone	$NH_2OH{\cdot}HCl$, pyridine, EtOH	 **396**	98
pinacolone	$MeNH_2{\cdot}HCl$, $NaCNBH_3$, MeOH	 **397**	13

Subsequently, oxime **394** was reduced with $LiAlH_4$ to afford amine **398** which was protected with Boc_2O to furnish carbamate **399** (Scheme 4.41).[145] Methylation of carbamate **399** with iodomethane and NaH afforded carbamate **400** in excellent yield.[146]



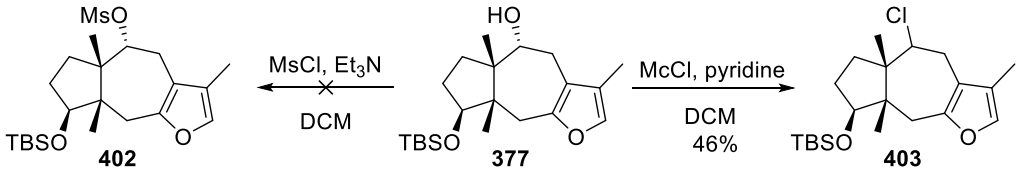
Scheme 4.41: Conversion of oxime **394** to a protected *N*-methylamine.

From tricyclic furan **393**, reductive amination was attempted to synthesise amine **401** (Scheme 4.42). The use of $MeNH_2{\cdot}HCl$ and $NaCNBH_3$ led to recovery of starting material, probably due to steric hindrance of the ketone adjacent to the quaternary centre. Following Bhattacharyya's reductive amination procedure using Ti(*i*-PrO)$_4$,[147] alcohol **377** was obtained as the major product and alcohol **391** as the minor product. In this ketone, reduction favoured attack from the more exposed convex face of the molecule.



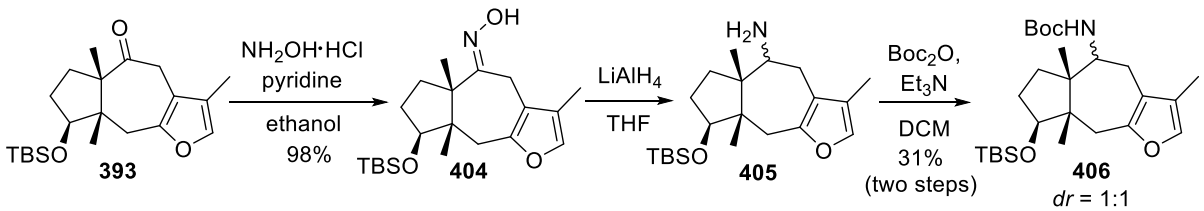
Scheme 4.42: Reductive amination of tricyclic furan.

Subsequently, an attempt was made to effect azide displacement of the mesylate of alcohol **377** then reduction to obtain the amine (Scheme 4.43). An attempt to form mesylate **402** led mainly to decomposition[148] and an attempt to form the chloromesylate formed chloride **403**, presumably by S_N2 displacement of chloromesylate by chloride anion.[149] However, the stereochemistry of **403** could not be determined as it decomposed rapidly over time.



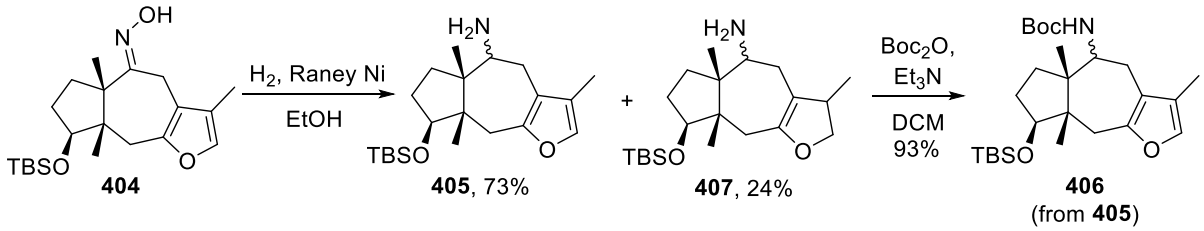
Scheme 4.43: Attempts at sulfonate synthesis.

After unsuccessful attempts to form an amine from **393** by reductive amination, the oxime approach was explored. Tricyclic furan **393** afforded oxime **404** in excellent yield (Scheme 4.44) and this was reduced with $LiAlH_4$ (→ **405**) and the amine Boc-protected to furnish carbamate **406** as an inseparable mixture of diastereomers in 1:1 ratio. However, the oxime reduction was not a clean reaction, resulting in the low overall yield of carbamate **406** from oxime **404**.



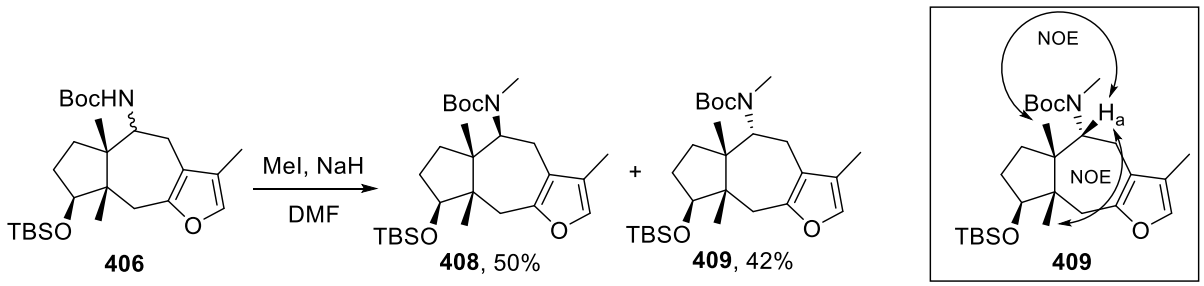
Scheme 4.44: Furan amine synthesis by oxime formation and reduction.

Reduction of oxime **404** with H_2 and Raney Ni afforded amine **405** in 73% yield and amine **407** in 24% yield (Scheme 4.45).[150] Amine **407** was formed from the partial reduction of furan but attempts to reduce the temperature and reaction time could not minimise its formation. Boc-protection of amine **405** afforded carbamate **406** in excellent yield. Therefore, this method of oxime reduction was preferred as it was cleaner and gave a better yield.



Scheme 4.45: Oxime reduction with H_2 and Raney Ni.

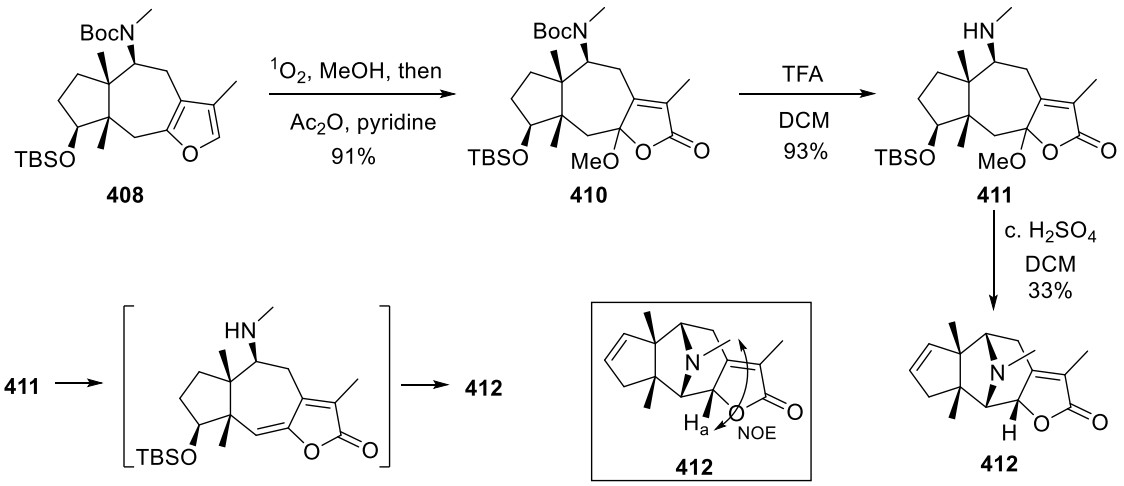
Finally, carbamate **406** was methylated with iodomethane and NaH to afford carbamate **408** and **409** in roughly equal proportions (Scheme 4.46). The diastereomers were separated by column chromatography but the NMR spectra showed the presence of carbamate rotamers. The stereochemistry of **408** and **409** were confirmed by NOE data where H_a showed a correlation with the methyl groups in **409** but this correlation was absent in **408**.



Scheme 4.46: Methylation of carbamate **406**.

4.8 Furan oxidative *N*-spirocyclisation

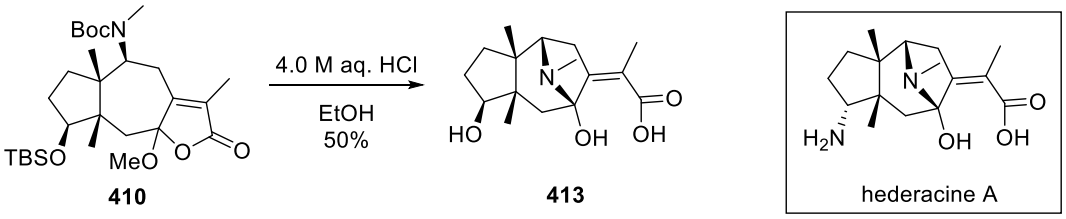
With furan amine **408** in hand, the oxidative *N*-spirocyclisation methodology could be attempted. Photo-oxidation of furan **408** with $^1O_2$ followed by acetylation and elimination in situ afforded methoxybutenolide **410** as a single diastereomer which was deprotected with TFA to furnish spirocyclisation precursor **411** (Scheme 4.47). Methoxybutenolides **410** and **411** were obtained as single diastereomers but the stereochemistry of the methoxy group was not determined. Interestingly, stirring a solution of methoxybutenolide **411** in DCM with c. H_2SO_4 at RT for 30 h afforded butenolide **412**. Similar to the synthesis of pandamarilactonines in Chapter 2, butenolide **412** was formed from MeOH elimination and intramolecular 1,6-addition of the free amine in precursor **411**. In addition, the TBS-group was deprotected and the resulting alcohol had dehydrated to an alkene which then isomerised. The stereochemistry of **412** was confirmed by NOE correlations between H_a and the methyl group as shown below (Appendix D). No desired spiro-*N*,*O*-acetal products were formed under these spirocyclisation conditions.



Scheme 4.47: Furan oxidative *N*-cyclisation of furan amine precursor.

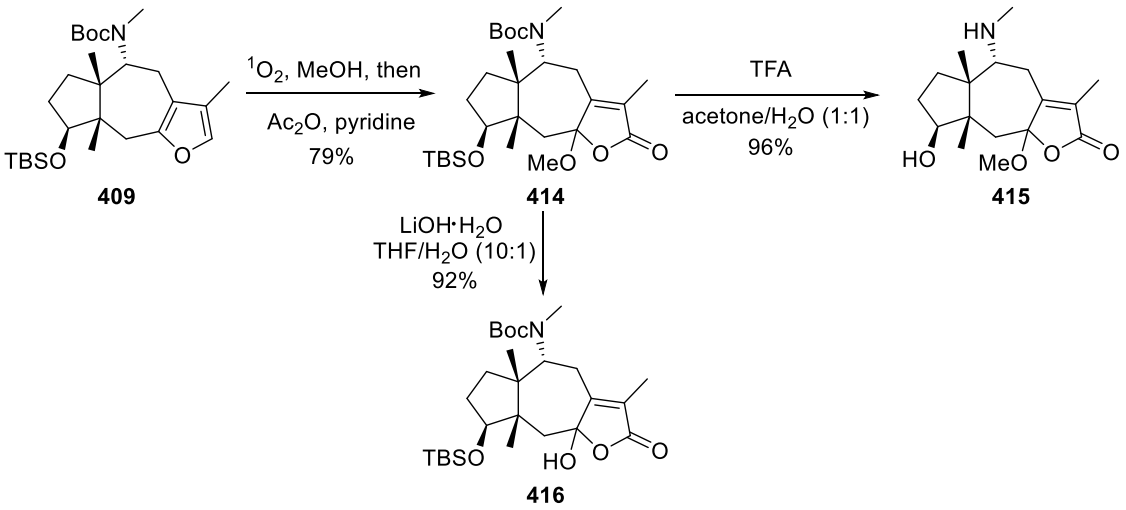
Pleasingly, treating an ethanolic solution of methoxybutenolide **410** with 4.0 M aq. HCl resulted in butenolide ring opening and *N*-cyclisation to afford carboxylic acid **413** in

moderate yield (Scheme 4.48).[42] Carboxylic acid **413** possesses the same core structure as hederacine A.



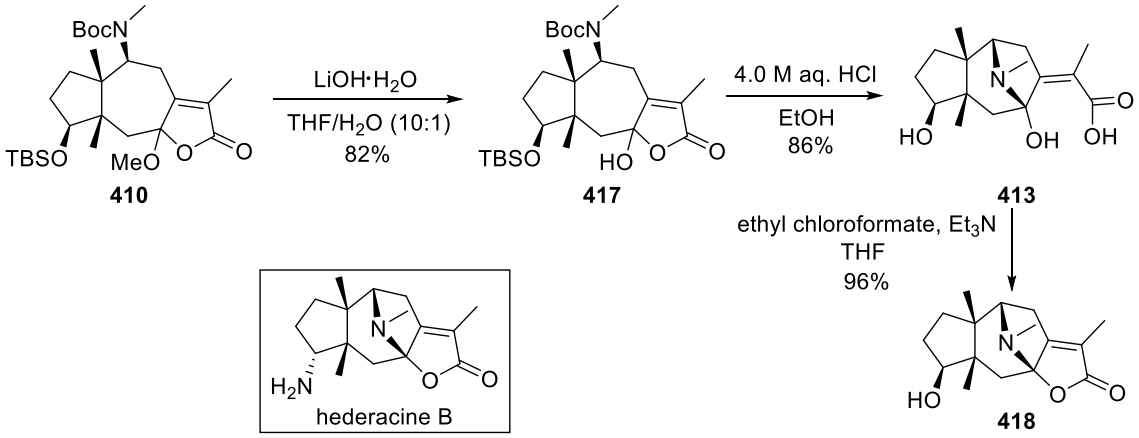
Scheme 4.48: Synthesis of hederacine A core.

Subsequently, we postulated that hydrolysing the methoxybutenolide in **410** or its epimer to the corresponding hydroxybutenolide would improve the yield of carboxylic acid **413**. The hydrolysis was first attempted on the undesired α-epimer **409** to minimise loss of the desired β-epimer product. Furan amine **409** was oxidised to methoxybutenolide **414** which, upon treatment with aq. TFA, afforded methoxybutenolide **415** (Scheme 4.49).[151] Both Boc and TBS-groups were deprotected but the methoxybutenolide was not hydrolysed under these conditions. Both methoxybutenolides **414** and **415** were obtained as single diastereomers but the stereochemistry of the methoxy group was not determined. When $LiOH{\cdot}H_2O$ was used, methoxybutenolide **414** underwent $B_{Ac}2$ hydrolysis and ring closure to afford hydroxybutenolide **416** in excellent yield.[50] Hydroxybutenolide **416** was obtained as a single diastereomer but the stereochemistry of the hydroxyl group was not known.



Scheme 4.49: Attempts to hydrolyse methoxybutenolide **414**.

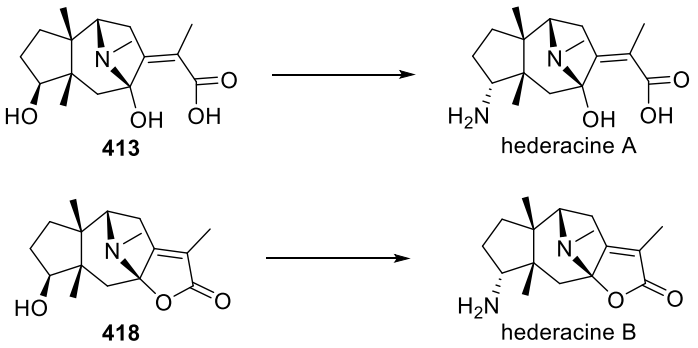
After successful hydrolysis of methoxybutenolide **414**, hydrolysing the β-amino epimer, methoxybutenolide **410**, with LiOH·H_2O afforded hydroxybutenolide **417** which underwent acid-promoted cyclisation to furnish carboxylic acid **413** in good yield (Scheme 4.50). Treatment of carboxylic acid **413** with ethyl chloroformate resulted in butenolide ring closure to furnish spiro-*N*,*O*-acetal **418** which has the core structure of hederacine B.[42]



Scheme 4.50: Methoxybutenolide hydrolysis and spiro-*N*,*O*-acetal synthesis.

4.9 Late-stage transformation of hydroxyl to amino group

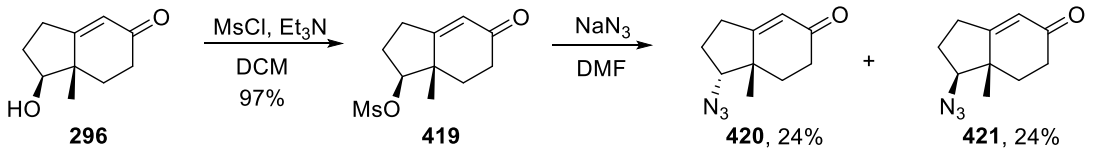
In order to synthesise hederacine A and B, the hydroxyl group on the 5-membered ring of carboxylic acid **413** and spiroaminoacetal **418** has to be converted to an amino group (Scheme 4.51).



Scheme 4.51: Late-stage transformation of hydroxyl to amino group.

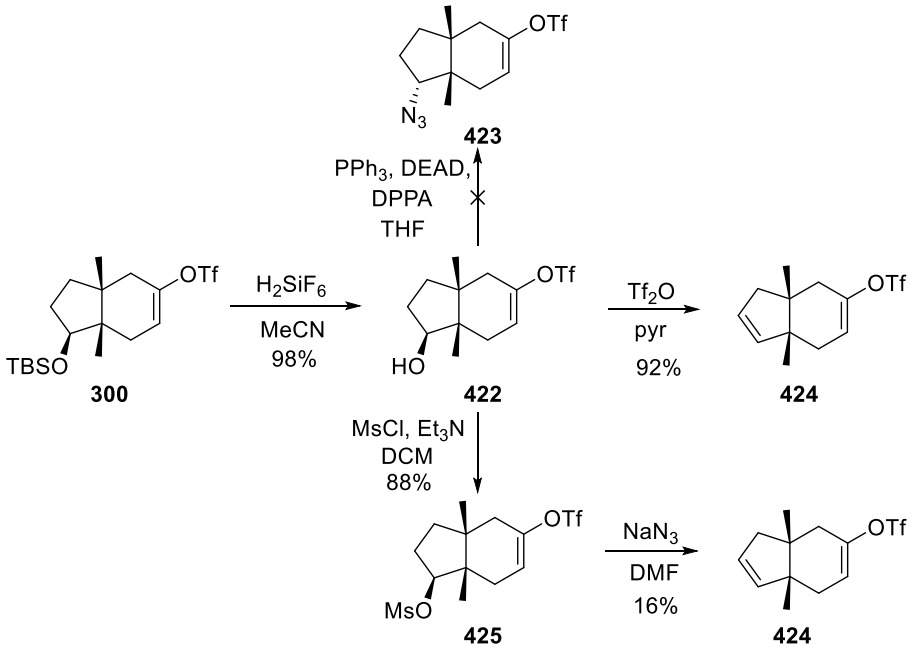
4.9.1 Azide displacement

The most direct approach was thought to be azide displacement followed by reduction. Before this approach was attempted on the real system of which only small quantities were available, model compounds were used to optimise the reaction conditions. Mesylation of alcohol **296** afforded mesylate **419** which was successfully displaced with NaN_3 to furnish azide diastereomers **420** and **421** in a 1:1 ratio (Scheme 4.52).[152] This implied that the azide displacement might occur *via* a double S_N2 inversion mechanism. Similarly, Caine and co-workers reported that the azide displacement of the tosylate of **296** gave a mixture of azide diastereomers and suggested possible S_N1-like mechanism by homoallylic stabilisation of carbocation but the mechanism was not proven. Therefore, a different model compound was chosen for azide displacement.



Scheme 4.52: Azide displacement of model mesylate.

Silyl ether **300** was deprotected with H_2SiF_6 to afford alcohol **422** (Scheme 4.53). Attempts to effect azide displacement of alcohol **422** under Mitsunobu conditions with DPPA were unsuccessful in forming azide **423**, possibly due to steric hindrance.[153,154] Treating alcohol **422** with Tf_2O led to triflate elimination to afford alkene **424** in excellent yield. Mesylation of alcohol **422** afforded mesylate **425** which when treated with NaN_3 formed alkene **424** in poor yield. No desired azide **423** was formed under these reaction conditions.

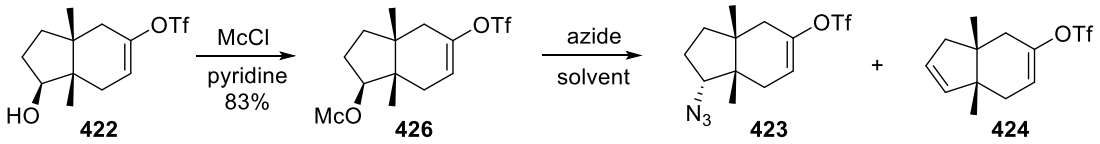


Scheme 4.53: Attempts to effect azide displacement of model compound **422**.

Subsequently, alcohol **422** was converted into chloromesylate **426** which underwent azide displacement under various conditions to afford azide **423** and alkene **424** in different ratios (Table 4.8).[149] With NaN_3 or LiN_3 in DMF or DMSO at 50 ºC, no reaction occurred. Increasing the temperature reduced the reaction time but did not change the product ratio,

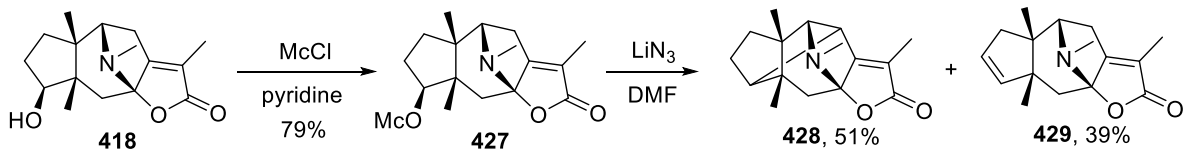
with alkene **424** being the major product. The use of LiN_3 in DMF or HMPA gave the highest yield of azide **423**. The use of other polar solvents like DMSO or acetone gave a lower yield of azide **423**. Therefore, LiN_3 in DMF at 70 ºC was chosen as the optimum reaction conditions due to the toxicity of HMPA.

Table 4.8: Optimisation of azide displacement of chloromesylate.



Azide	Solvent	T/ ºC	Duration/ h	Ratio (423:424)
NaN_3	DMF	50	48	No reaction
NaN_3	DMF	70	48	3:7
NaN_3	DMF	90	1	3:7
LiN_3	DMF	50	48	No reaction
LiN_3	DMF	70	16	4:6
LiN_3	DMSO	50	48	No reaction
LiN_3	DMSO	65	18	1:2
LiN_3	HMPA	50	24	4:6
LiN_3	acetone	65	72	1:3

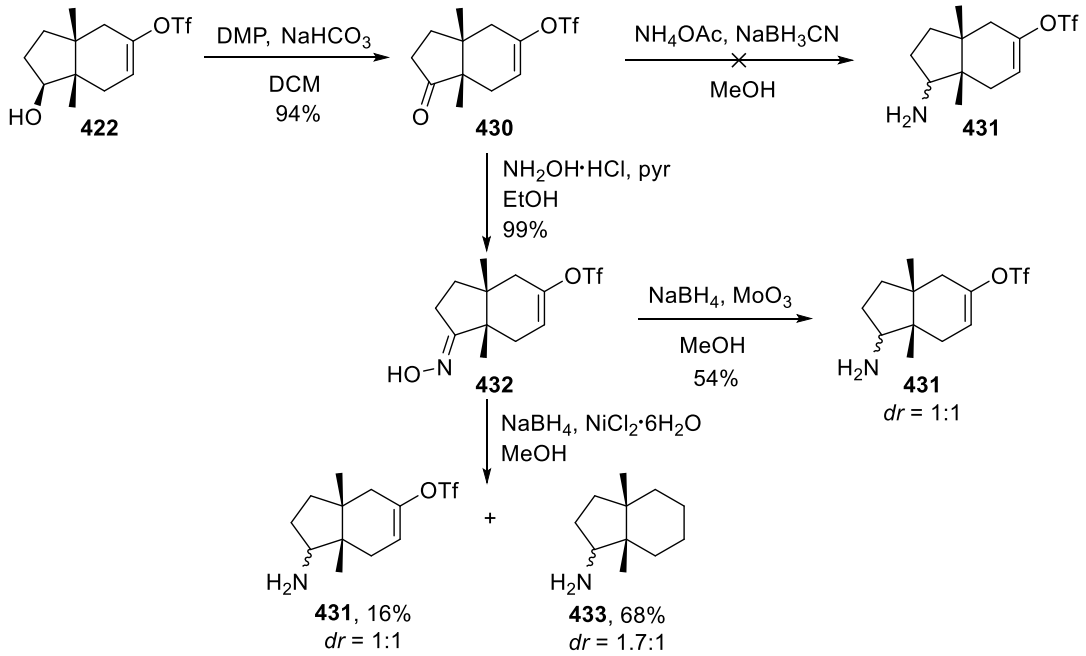
Treatment of spiroaminoacetal **418** with McCl afforded chloromesylate **427** but attempted azide displacement furnished alkene **429**, and spiroaminoacetal **428** (Scheme 4.54), formed from the intramolecular displacement of the chloromesylate by the butenolide dienolate. No desired azide product was formed in this reaction.



Scheme 4.54: Attempted azide displacement in spiroaminoacetal **418**.

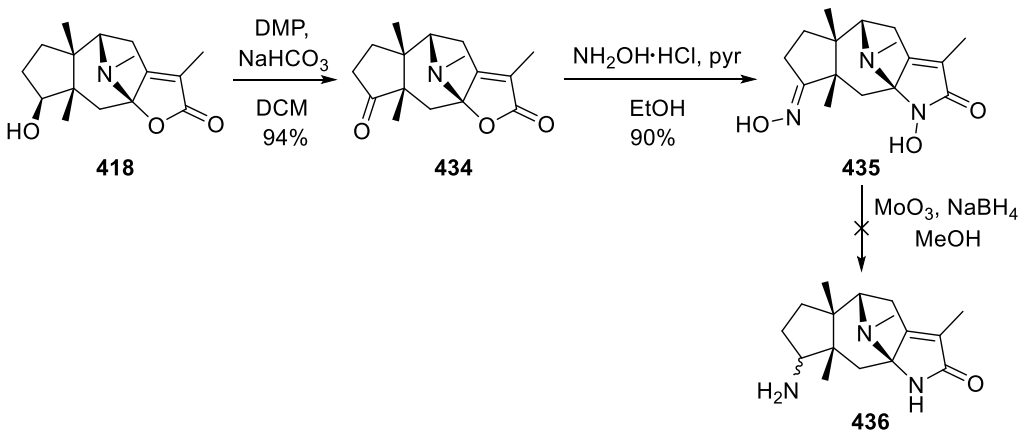
4.9.2 Reductive amination

As the azide displacement approach failed to give desired products, reductive amination was investigated, beginning with a model compound. Alcohol **422** was oxidised with DMP to ketone **430** which was subjected to standard reductive amination conditions with NH_4OAc and $NaBH_3CN$ (Scheme 4.55).[155] No desired amine **431** was formed under these conditions, possibly due to steric constraints. However, the derived oxime **432** was reduced with $NaBH_4$ and MoO_3 to afford amine **431** in moderate yield.[156] An attempt to reduce oxime **432** with $NaBH_4$ and $NiCl_2{\cdot}6H_2O$ furnished amine **431** only as the minor product with the majority being amine **433**.[157] The formation of over-reduced amine **433** showed that this reagent combination was too strong and not suitable for the real system bearing a butenolide group.



Scheme 4.55: Reductive amination of model compound.

Subsequently, spiroaminoacetal **418** was oxidised with DMP to ketone **434** which underwent oxime formation to afford oxime **435** (Scheme 4.56). Ironically, the butenolide in **434** was converted into the *N*-hydroxylactam **435** but previous attempt to achieve a similar conversion in accessing pandamarine in Chapter 2 was unsuccessful (*cf.* Scheme 2.20). An attempt to reduce oxime **435** with $NaBH_4$ and MoO_3 led to decomposition and amine **436** was not obtained.



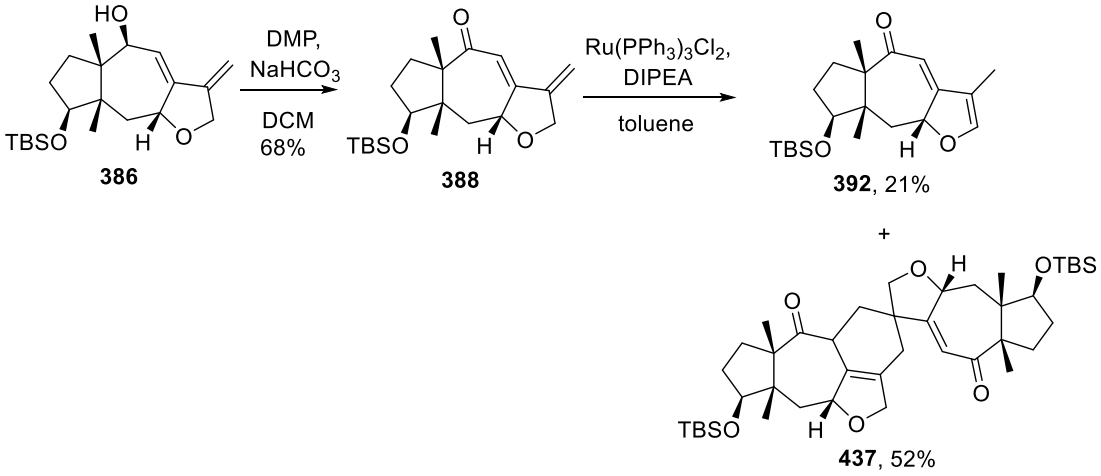
Scheme 4.56: Reductive amination of spiroaminoacetal.

The difficulty in late-stage conversion of the hydroxyl group to the amine meant that the amino group must be installed earlier in the synthetic route and before the oxidative *N*-spirocyclisation steps.

4.10 Optimisation of tricyclic furan synthesis

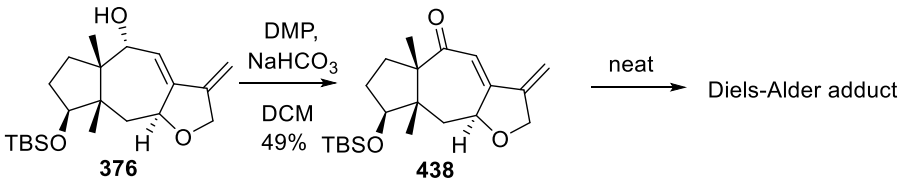
In order to attempt an alternative synthetic route that involves early-stage transformation of hydroxyl to amino group, more tricyclic furan had to be synthesised. However, in the large scale synthesis of tricyclic furan **393**, subjecting dienone **388** to Ru(II)-catalysed isomerisation conditions afforded dienone **392** only as the minor product with Diels–Alder adduct **437** making up the majority of the product (Scheme 4.57). Adduct **437** was obtained

as a single diastereomer but the stereochemistry was not determined. Attempts to bring about retro-Diels–Alder of adduct **437** under thermal conditions (>200 ºC) were unsuccessful, with starting material recovered.



Scheme 4.57: Unexpected intermolecular Diels–Alder of dienone **388**.

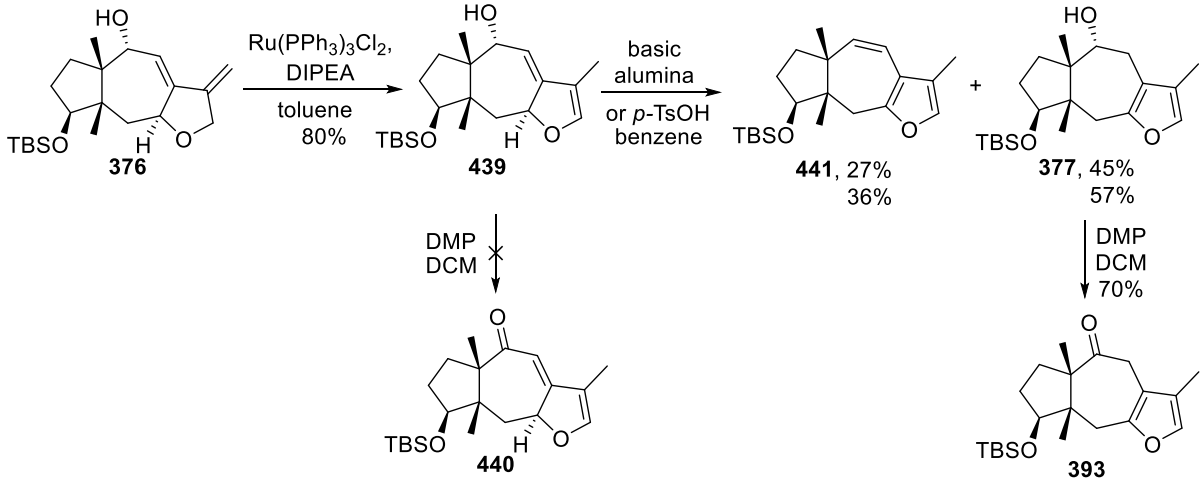
Furthermore, oxidation of diene **376**, the epimer of **386**, afforded dienone **438** in only moderate yield (Scheme 4.58). When dienone **438** was left standing neat overnight, it underwent intermolecular Diels–Alder to afford an adduct analogous to **437**.



Scheme 4.58: Instability of dienone **438**.

Due to the tendency of dienone **388** and **438** to undergo Diels–Alder reaction, an alternative synthetic route to tricyclic furan **393** which would avoid the formation of these dienones was attempted. Diene **376** underwent Ru(II)-catalysed isomerisation to afford diene **439** but this decomposed when oxidised with DMP (Scheme 4.59) and dienone **440** could not be obtained from this reaction. Purification of diene **439** with basic alumina resulted in dehydration to

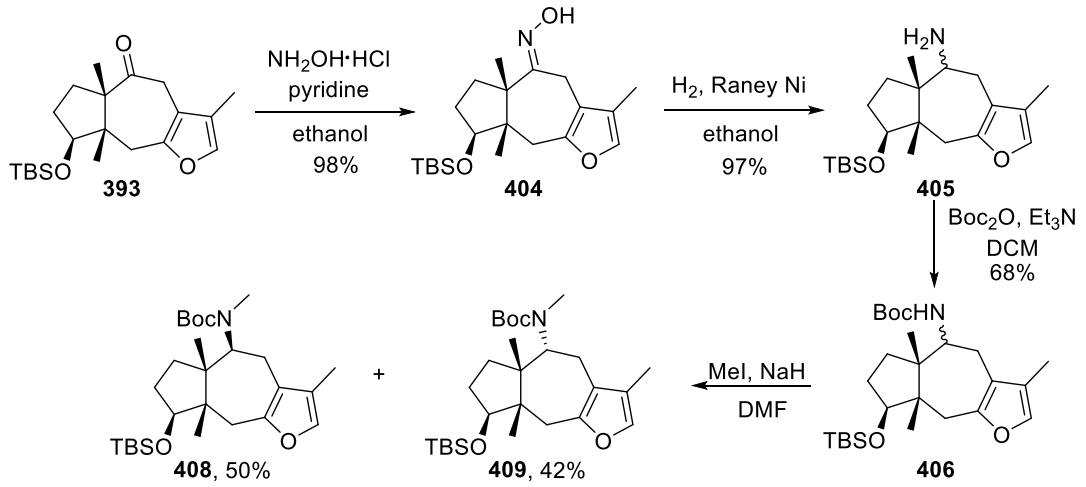
afford alkene **441** in addition to the desired isomerisation product **377**. Subjecting diene **439** to acid-catalysed isomerisation using *p*-TsOH or PPTS afforded a similar ratio of alkene **441** and furan **377**. Oxidation of alcohol **377** with DMP furnished tricyclic furan **393** in good yield. Therefore, this alternative synthetic route to tricyclic furan **393** prevented intermolecular Diels–Alder from taking place. Using this synthetic route and the remaining amount of dibromocyclopropane, 30 mg of tricyclic furan **393** was obtained.



Scheme 4.59: Alternative synthetic route to tricyclic furan **393**.

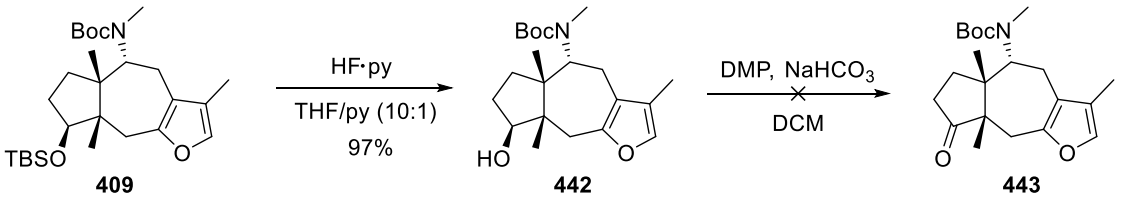
4.11 Formal synthesis of 9-*epi*-hederacine A and 9-*epi*-hederacine B

With tricyclic furan **393** in hand, amine epimers **408** and **409** were synthesised in good yield as before (Scheme 4.60). Instead of carrying out the furan oxidation, work proceeded on installing the amino group on the 5-membered ring.



Scheme 4.60: Furan amine synthesis.

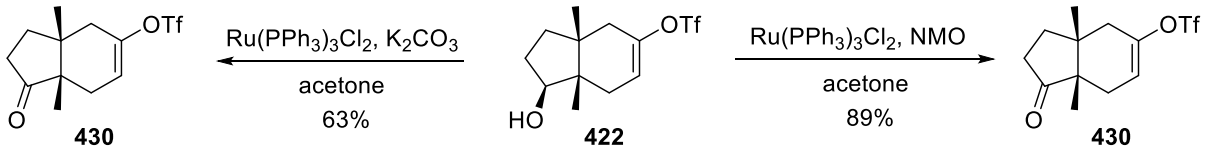
The TBS group on carbamate α-epimer **409** was deprotected with HF·py under basic conditions to afford alcohol **442** but this decomposed when treated with DMP and no desired ketone **443** was formed (Scheme 4.61).[158]



Scheme 4.61: TBS-deprotection and oxidation attempt.

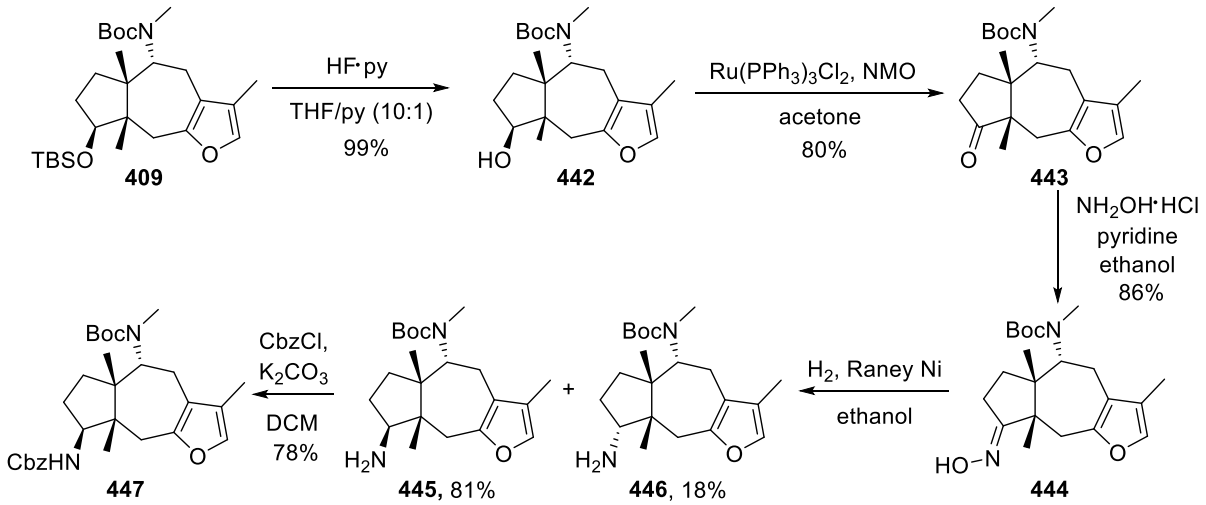
Bearing in mind the sensitivity of the trisubstituted furan, milder oxidation conditions were sought. Sharpless and co-workers have reported the use of ruthenium(II) catalysts for the oxidation of alcohols to aldehydes or ketones in the presence of a co-oxidant.[159] The ruthenium(II)-catalysed oxidation was first attempted on model alcohol **422** (Scheme 4.62). When this alcohol was treated with $Ru(PPh_3)_3Cl_2$ and K_2CO_3 in acetone as hydrogen acceptor, ketone **430** was afforded in moderate yield after 30 h of reflux.[160] The prolonged heating might have led to partial decomposition accounting for the reduced yield. When

NMO was used as the co-oxidant, the oxidation proceeded smoothly at RT to afford ketone **430** in excellent yield.



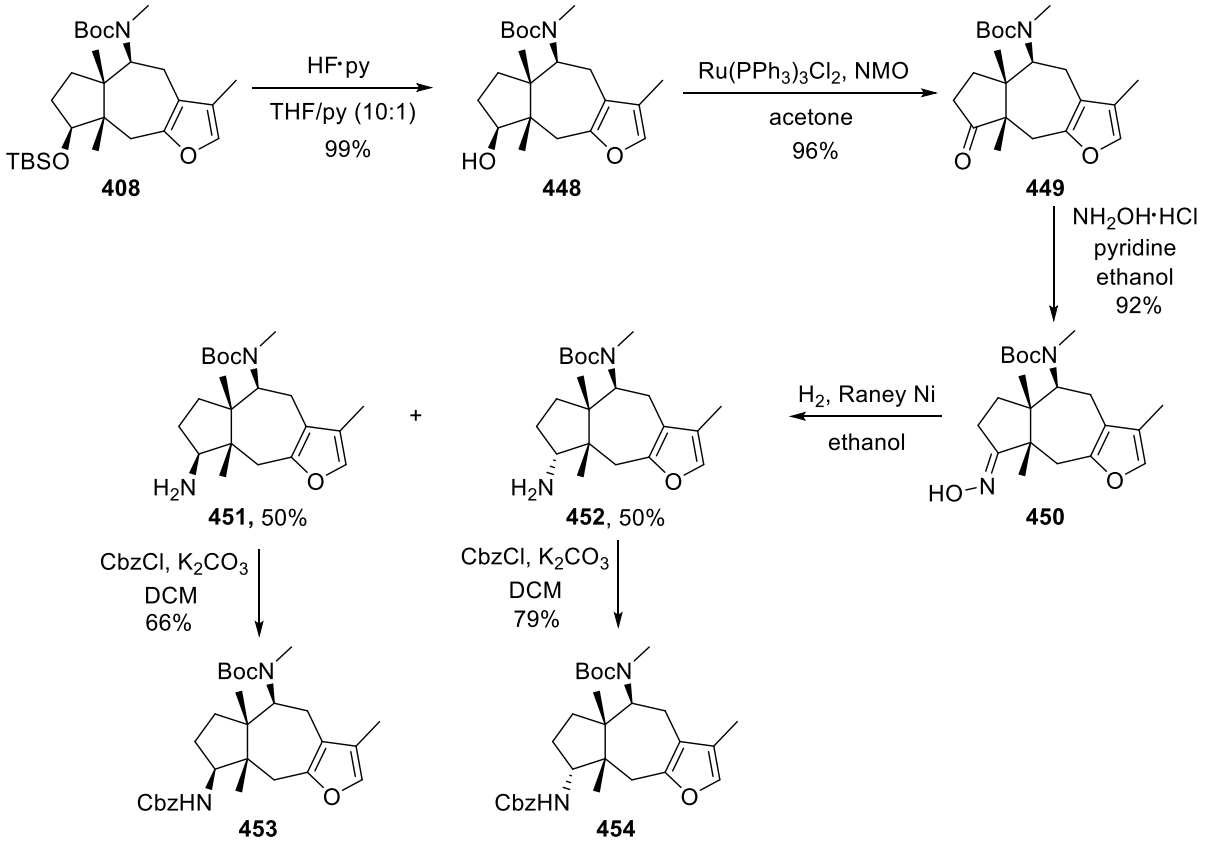
Scheme 4.62: Ruthenium(II)-catalysed oxidation of model alcohol **422**.

Subsequently, this ruthenium(II)-catalysed oxidation condition was applied to the real substrate **442** and the reaction proceeded smoothly to afford ketone **443** in good yield (Scheme 4.63). An NMR sample of ketone **443** in $CDCl_3$ decomposed when left overnight but the use of C_6D_6 as solvent allowed NMR data to be obtained. Treating ketone **443** with $NH_2OH{\cdot}HCl$ afforded oxime **444** which was hydrogenated with Raney Ni to furnish amine epimers **445** and **446**. This showed that the hydrogenation proceeded stereoselectively, with control presumably arising from the directing effect of the *N*-Boc group on the *endo* face of the molecule. Cbz-protection of amine **445** afforded carbamate **447** in good yield.



Scheme 4.63: Early-stage transformation of hydroxyl group to amino group.

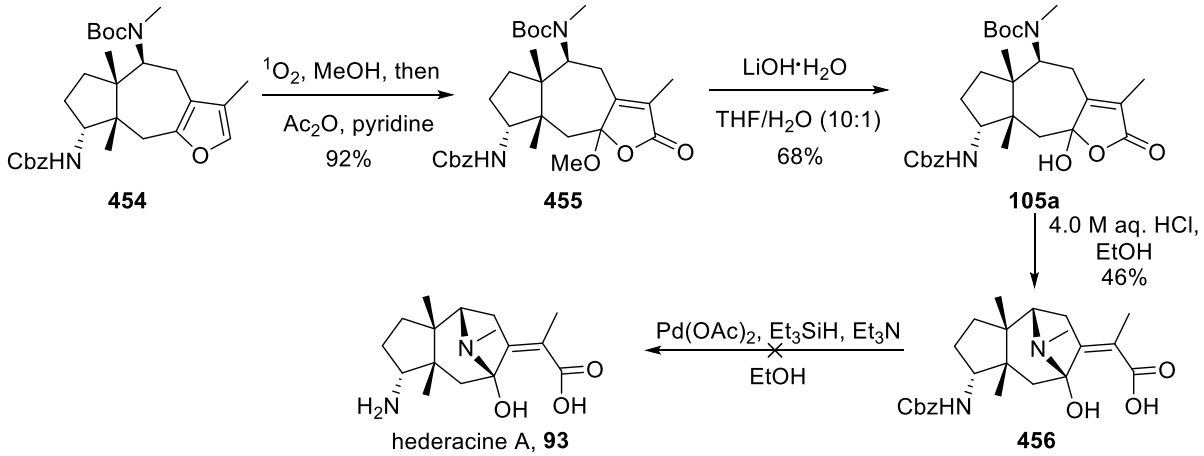
With success in transforming the hydroxyl group to an amino group, the synthetic route was applied to carbamate **408** bearing the desired β-*N*-Boc amino substituent (Scheme 4.64). TBS-deprotection with HF·py afforded alcohol **448** which underwent ruthenium(II)-catalysed oxidation to furnish ketone **449** in excellent yield. Reaction of ketone **449** with $NH_2OH{\cdot}HCl$ afforded oxime **450** which upon hydrogenation with Raney Ni furnished amine diastereomers **451** and **452** in equal proportions. Protection of amine **451** and **452** afforded carbamates **453** and **454** respectively in moderate yield.



Scheme 4.64: Progress towards the synthesis of hederacines A and B.

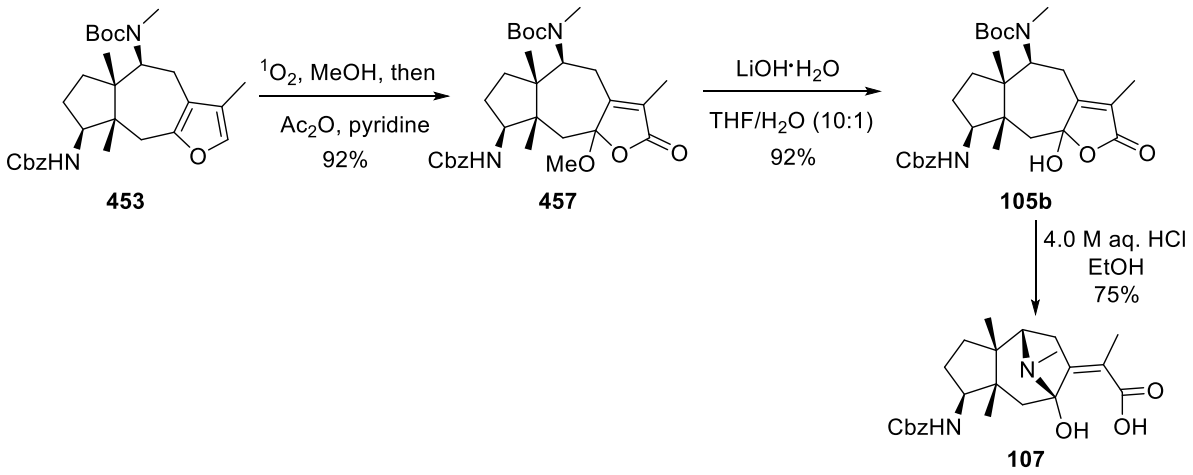
Photo-oxidation of furan **454** with $^1O_2$ afforded methoxybutenolide **455** which was hydrolysed with $LiOH{\cdot}H_2O$ to hydroxybutenolide **105a** in moderate yield (Scheme 4.65). Treating hydroxybutenolide **105a** with 4.0 M aq. HCl seemed to result in butenolide ring opening and cyclisation to form carboxylic acid **456**, based on ^1H NMR, IR and MS data. The

IR spectrum indicates the loss of butenolide C=O stretch at 1767 cm^{-1} and a new C=O stretch at 1700 cm^{-1} which corresponds to a carboxylic acid functionality. The MS spectrum shows an *m/z* value of 429 which corresponds to the MH^+ value of acid **456**. However, due to insufficient material (~0.3 mg), ^{13}C NMR and 2D-NMR data could not be obtained to confirm its structure. Therefore, *N*-Cbz hederacine A **456** was tentatively synthesised. Furthermore, an attempt to effect Cbz-deprotection using Ohfune's procedure led to decomposition, possibly due to complications caused by the free carboxylic acid group.[161]

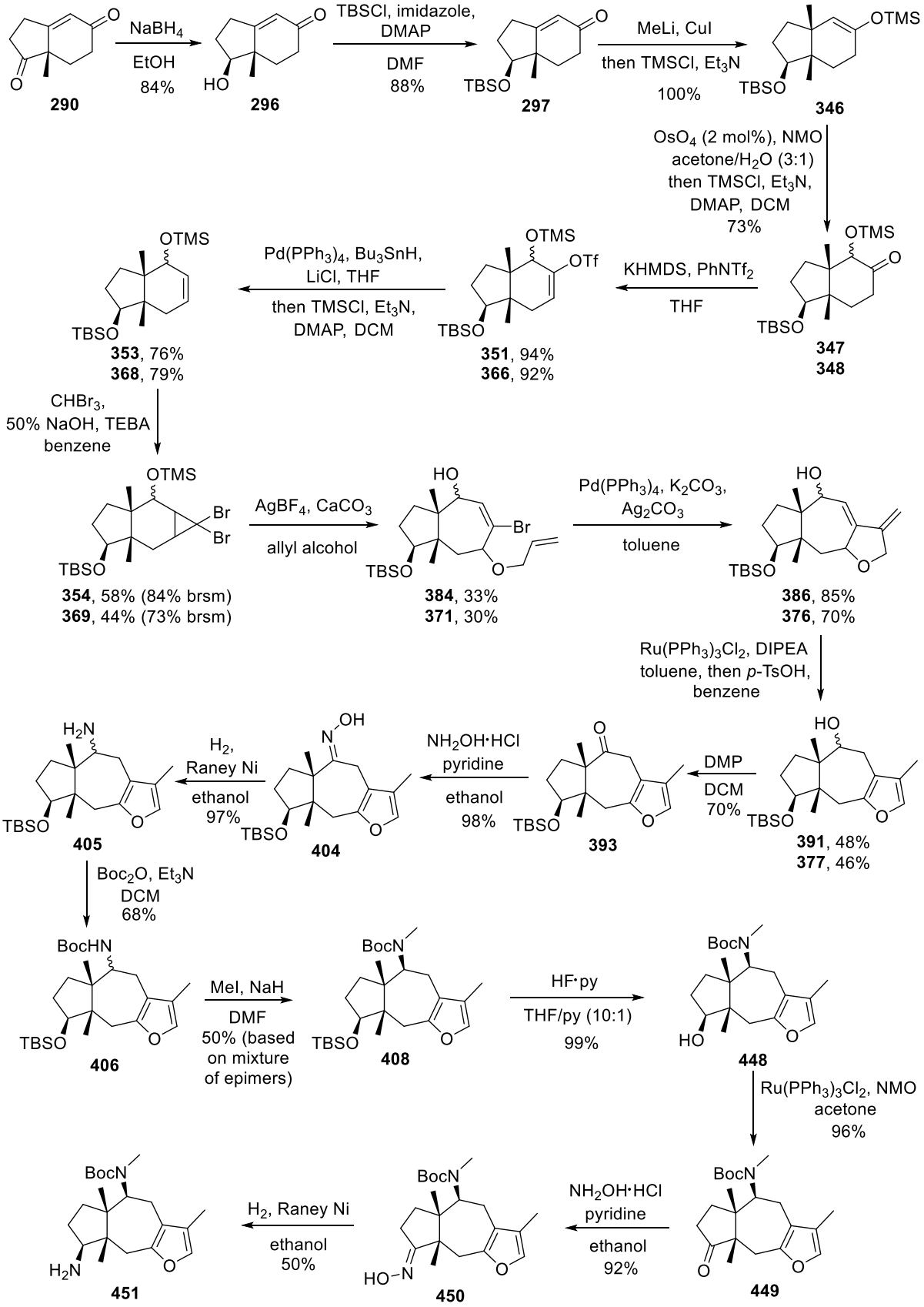


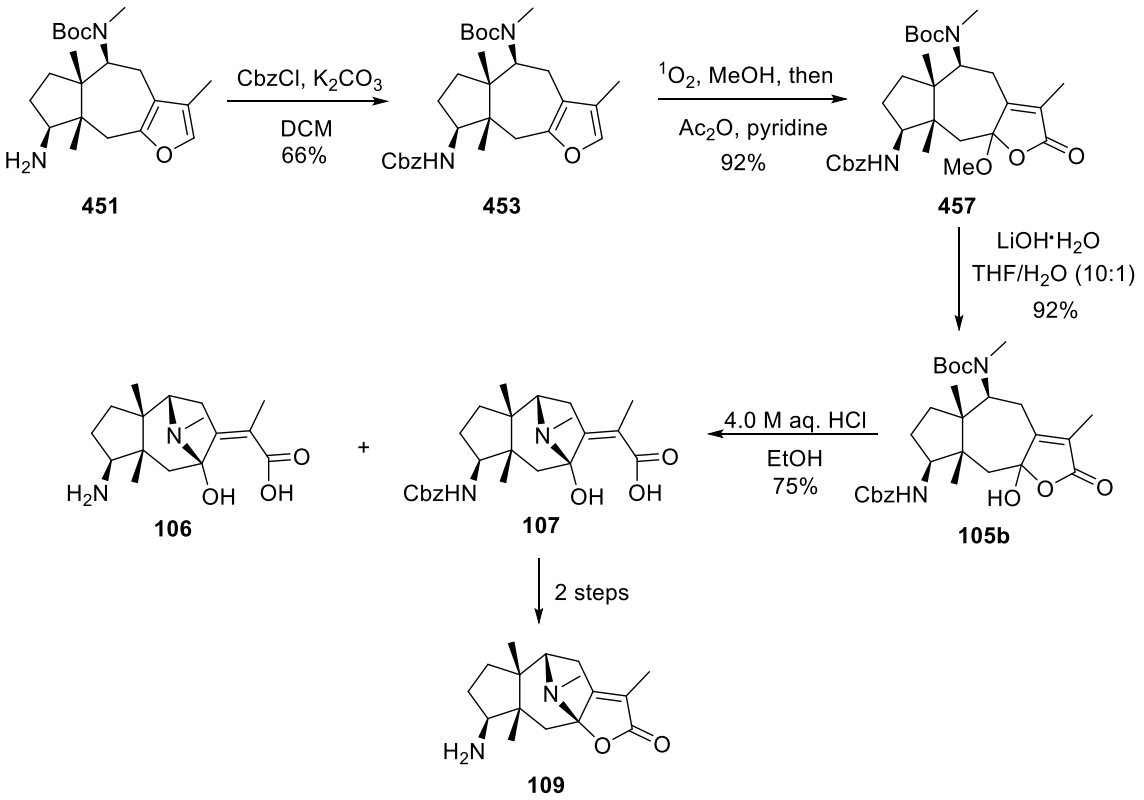
Scheme 4.65: Attempt to synthesise hederacine A.

Photo-oxidation of the 9-epimer **453** with $^1O_2$ afforded methoxybutenolide **457** which was hydrolysed with LiOH·H_2O to hydroxybutenolide **105b** in excellent yield (Scheme 4.66). Treating hydroxybutenolide **105b** with 4.0 M aq. HCl resulted in butenolide ring opening and *N*-cyclisation to afford Cbz-protected 9-*epi*-hederacine A **107**. Again, due to insufficient material (~0.6 mg), the butenolide ring closure could not be attempted. Both hydroxybutenolide **105b** and carboxylic acid **107** were late-stage intermediates and uncharacterised in Aoyagi's synthesis of 9-*epi*-hederacine A **106** and 9-*epi*-hederacine B **109**.[42] Therefore, as carboxylic acid **107** was fully characterised in this case, the formal synthesis of 9-*epi*-hederacine A **106** and 9-*epi*-hederacine B **109** was completed in 23 and 25 steps respectively, starting from Hajos–Parrish ketone **290** (Scheme 4.67).



Scheme 4.66: Synthesis of Cbz-protected 9-*epi*-hederacine A.


NaBH4
EtOH
84%
TBSCl, imidazole,
DMAP
DMF
88%
MeLi, CuI
then TMSCl, Et3N
100%
OsO4 (2 mol%), NMO
acetone/H2O (3:1)
then TMSCl, Et3N,
DMAP, DCM
73%
KHMDS, PhNTf2
THF
Pd(PPh3)4, Bu3SnH,
LiCl, THF
then TMSCl, Et3N,
DMAP, DCM
CHBr3,
50% NaOH, TEBA
benzene
AgBF4, CaCO3
allyl alcohol
Pd(PPh3)4, K2CO3,
Ag2CO3
toluene
Ru(PPh3)3Cl2, DIPEA
toluene, then p-TsOH,
benzene
DMP
DCM
70%
NH2OH·HCl
pyridine
ethanol
98%
H2,
Raney Ni
ethanol
97%
Boc2O, Et3N
DCM
68%
MeI, NaH
DMF
50% (based
on mixture
of epimers)
HF·py
THF/py (10:1)
99%
Ru(PPh3)3Cl2, NMO
acetone
96%
NH2OH·HCl
pyridine
ethanol
92%
H2, Raney Ni
ethanol
50%
290
296
297
346
347
348
351, 94%
366, 92%
353, 76%
368, 79%
354, 58% (84% brsm)
369, 44% (73% brsm)
384, 33%
371, 30%
386, 85%
376, 70%
391, 48%
377, 46%
393
404
405
406
408
448
449
450
451



Scheme 4.67: Formal synthesis of 9-*epi*-hederacine A and B.

Chapter 5: Conclusions and Future Work

5.1 Conclusions

In order to confirm the structure of pandamarilactone-1 by analogy, the synthesis of di(normethyl)pandamarilactone-1 was attempted. However, the application of furan oxidative *N*-spirocyclisation methodology to the analogue resulted in intramolecular conjugate addition to form azepanes. Believing that the methyl substituents on the butenolide in pandamarilactone-1 play an important role in sterically and electronically disfavouring intramolecular conjugate addition relative to *N*-spirocyclisation, the synthesis of pandamarilactone-1 was attempted. Pleasingly, the acid-promoted *N*-spirocyclisation proceeded smoothly to afford pandamarilactone-1 **4**, together with a mixture of pandamarilactonines A–D **41**–**44** (Figure 5.1). The structure of pandamarilactone-1 **4** was confirmed by HMBC data and site-specific hydrogen-deuterium exchange in methanol-d_4. Furthermore, the reactivity of pandamarilactone-1 **4** with aq. ammonia showed that pandamarine is not an experimental artifact from the isolation process and is most likely a genuine natural product. In summary, pandamarilactone-1 **4** was synthesised from 5-chloro-1-pentyne in 10 steps and 9% overall yield.

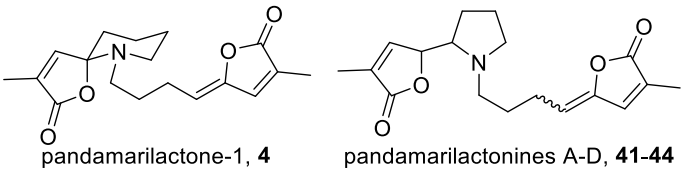
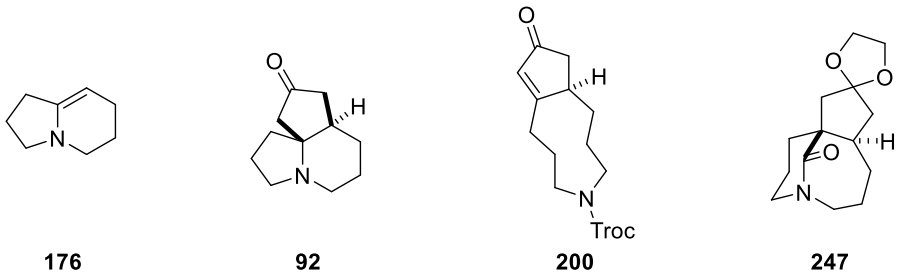


Figure 5.1: Pandamarilactone-1 and pandamarilactonines A–D.

Subsequently, the aza-Bohlmann cyclisation methodology was applied to the synthesis of lycopladine D. The ability of bicyclic enamine **176** to react with a range of different electrophiles to afford polycyclic molecules made it a good starting block for generating

complexity (Figure 5.2). Due to steric and electronic constraints, attempts to add furan to bicyclic enone **200** were unsuccessful. However, the conjugate addition of cyanide followed by carbamate deprotection furnished tricyclic lactam **247** which is a common structural core found in several other fawcettimine-type *Lycopodium* alkaloids. Isotopic labelling studies showed that the ammonium ylids of tricyclic aminoketone **92** prefer to undergo intramolecular Hofmann elimination instead of Stevens rearrangement. This provided an alternative pathway for tricyclic aminoketone ring expansion to afford bicyclic enones. With little prospect of achieving an efficient cycloaddition, efforts turned to a more amenable natural product, hederacine B.



176 **92** **200** **247**

Figure 5.2: Intermediates in lycopladine D project.

The furan oxidative *N*-spirocyclisation methodology was applied to the synthesis of hederacine B. The structural core of a spirocyclisation precursor was synthesised by the key dibromocyclopropane electrocyclic ring expansion step followed by intramolecular Heck cyclisation. The regioselectivity of the cycloheptenyl cation capture was controlled using two different approaches. Photo-oxidation of the furan amine precursor afforded the butenolide which underwent acid-promoted *N*-cyclisation to furnish the structural core of hederacine A. Butenolide ring closure then afforded the desired spiroaminoacetal. As the late-stage transformation of a hydroxyl group into an amino group was unsuccessful, the amino group was installed earlier in the synthesis before furan oxidation. Starting from Hajos–Parrish

ketone, the formal synthesis of 9-*epi*-hederacine A **106** and 9-*epi*-hederacine B **109** was completed in 23 and 25 steps respectively (Figure 5.3).

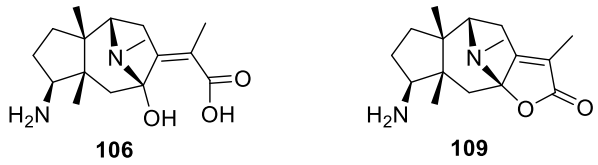


Figure 5.3: 9-*epi*-hederacine A and B.

5.2 Future Work

The versatile chemistry of bicyclic enamine **176** could be explored in depth and applied to the synthesis of multicyclic natural products. The Diels–Alder reaction of bicyclic enone **200** could be attempted under high pressure in the presence of Lewis acids in order to synthesise spirocyclisation precursors for *Lycopodium* alkaloids synthesis. Furthermore, the enolisation of lactone **252** and its reaction with formaldehyde could be attempted to obtain the skeletal core of lycopladine D.

For the hederacine B project, the synthetic route could be scaled up so that the possible structure of Cbz-protected hederacine A **456** could be confirmed and both hederacine A **93** and B **7** could be synthesised (Figure 5.4).

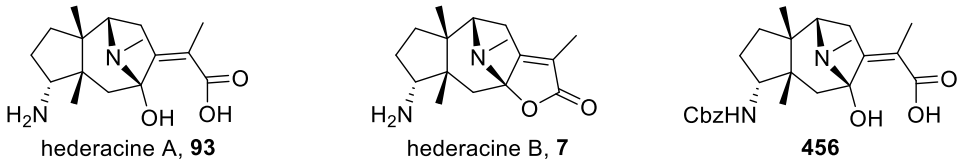


Figure 5.4: Hederacine B project compounds.

Chapter 6: Experimental

6.1 General experimental techniques

General directions. All reactions were carried out under a nitrogen atmosphere in dried glassware unless otherwise noted. Air and moisture sensitive liquid reagents were handled via a dry syringe. Heating was conducted using oil baths on stirrer hot plates.

Solvents and reagents. All solvents and reagents were obtained from the supplier unless otherwise noted. "Petrol" refers to the fraction of petroleum ether boiling in the range 30–40 °C. "Ether" refers to diethyl ether. Dry ether, dichloromethane and methanol were obtained from Grubbs canisters. Tetrahydrofuran was freshly distilled from sodium and benzophenone under an argon atmosphere.

Chromatography. Flash column chromatography was performed using silica gel (40-63 μm). Analytical and preparative thin-layer chromatography (TLC) were performed on aluminium plates pre-coated with silica gel (0.2 mm, Merck 60 F_{254}), which were developed using standard visualising agents: UV fluorescence (254 & 366 nm) and potassium permanganate or anisaldehyde.

Melting points. Melting points were determined using a Griffin MFB-700-010U melting point apparatus and are uncorrected.

Polarimetry. Specific rotations were determined using a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm and are quoted in 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g 100 mL^{-1}.

Infrared (IR) spectroscopy. These were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Selected absorbances (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br).

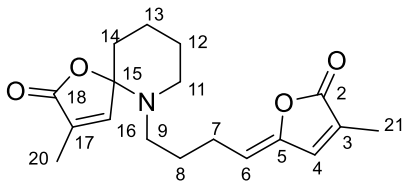
Nuclear magnetic resonance (NMR) spectroscopy. Proton (^{1}H) and carbon (^{13}C) spectra were recorded on Bruker AVC-500 (500/125 MHz), Bruker AVN-400 (400/100 MHz), or Bruker DPX-200 (200/50 MHz) spectrometers in deuterated solvents. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Assignments were made on the basis of chemical shifts, integrations and coupling constants using COSY, DEPT, HSQC, HMBC and NOE experiments where appropriate. Multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br (broad). Coupling constants (*J*) are reported to the nearest 0.5 Hz.

Mass spectrometry (MS). Low-resolution mass spectra were recorded on a Micromass LCT Premier spectrometer (ESI). High-resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory on a Bruker Daltonics MicroTOF spectrometer. Mass to charge ratios (*m/z*) are reported in Daltons.

Atom numbering. Atom numbering reflects NMR signal assignment and does not necessarily correspond to IUPAC nomenclature.

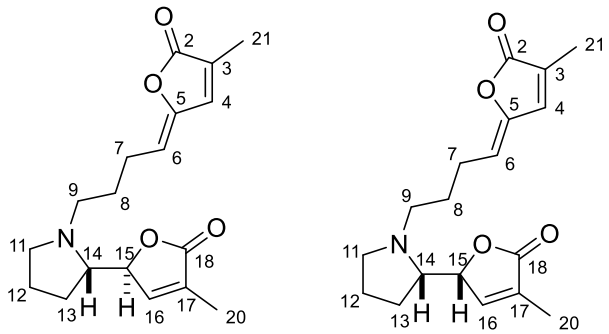
6.2 Compounds in Chapter 2

Pandamarilactone-1 (4)



Conc. H_2SO_4 (28.0 μL, 0.524 mmol) was added to a solution of methoxybutenolide **168** (100 mg, 0.262 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred at RT for 5 d. The mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless oil (10.0 mg, 12%). R_f 0.40 (ether); ν_{max} (thin film)/cm^{-1} 2941m, 1749s, 1444w, 1308w, 1159w, 1055m, 990m, 897w; δ_H (500 MHz, $CDCl_3$) 1.48−1.57 (2 H, m, C(8)H_2), 1.60−1.80 (6 H, m, C(12)H_2, C(13)H_2 and C(14)H_2), 1.90 (3 H, d, *J* 1.5, C(20)H_3), 2.00 (3 H, s, C(21)H_3), 2.30 (2 H, q, *J* 7.0, C(7)H_2), 2.37−2.53 (2 H, m, C(9)H_2), 2.72−2.84 (2 H, m, C(11)H_2), 5.07 (1 H, t, *J* 8.0, C(6)H), 6.71 (1 H, bs, C(16)H), 6.97 (1 H, d, *J* 1.5, C(4)H); δ_C (125 MHz, $CDCl_3$) 10.5 (C(21)), 10.7 (C(20)), 20.7 (C(12)), 23.9 (C(7)), 25.0 (C(13)), 27.0 (C(8)), 36.1 (C(14)), 47.1 (C(11)), 49.5 (C(9)), 101.7 (C(15)), 113.9 (C(6)), 129.2 (C(3)), 131.5 (C(17)), 137.6 (C(4)), 148.5 (C(5)), 149.7 (C(16)), 171.0 (C(2)), 172.9 (C(18)); *m/z* (ESI^+) 340 (MNa^+, 40%), 318 (MH^+, 100); HRMS (ESI^+): Found: 340.1530; $C_{18}H_{23}NNaO_4$ (MNa^+) requires: 340.1519.

(±)-Pandamarilactonine-A (41),(±)-Pandamarilactonine-B (42)



41 **42**

Conc. H_2SO_4 (28.0 μL, 0.524 mmol) was added to a solution of methoxybutenolide **168** (100 mg, 0.262 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred at RT for 5 d. The mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, EtOAc → 98:2 EtOAc:MeOH) afforded the *title compound* as an inseparable mixture of diastereomers (**41**/**42** *d.r.*, 55:30) as a colourless oil (39.9 mg, 48%). R_f 0.25 (98:2 EtOAc:MeOH); ν_{max} (thin film)/cm^{-1} 2950w, 1754s, 1051m, 991m, 758w; *m/z* (ESI^+) 318 (MH^+, 100%); HRMS (ESI^+): Found: 318.1692; $C_{18}H_{24}NO_4$ (MH^+) requires: 318.1700.

NMR data of (±)-Pandamarilactonine-A (**41**):

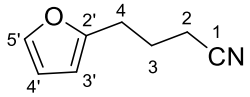
δ_H (500 MHz, $CDCl_3$) 1.42−1.56 (1 H, m, C(12)**H**H′), 1.58−1.72 (3 H, m, C(8)H_2 and C(13)**H**H′), 1.74−1.84 (2 H, m, C(12)H**H′** and C(13)H**H′**), 1.93 (3 H, d, *J* 2.0, C(20)H_3), 1.99 (3 H, s, C(21)H_3), 2.23−2.31 (1 H, m, C(11)**H**H′), 2.44 (2 H, q, *J* 7.5, C(7)H_2), 2.41−2.51 (1 H, m, C(9)**H**H′), 2.86 (1 H, dt, *J* 7.5, 5.5, C(14)H), 2.91−3.03 (1 H, m, C(9)H**H′**), 3.07−3.15 (1 H, m, C(11)H**H′**), 4.80−5.01 (1 H, m, C(15)H), 5.18 (1 H, t, *J* 8.0, C(6)H), 7.00 (1 H, d, *J* 1.5, C(4)H), 7.09 (1 H, quin, *J* 1.5, C(16)H); δ_C (125 MHz, $CDCl_3$)

10.5 (C(21)), 10.7 (C(20)), 23.7 (C(7)), 23.9 (C(13)), 25.8 (C(12)), 28.3 (C(8)), 54.1 (C(11)), 54.9 (C(9)), 65.7 (C(14)), 83.3 (C(15)), 113.9 (C(6)), 129.2 (C(3)), 131.4 (C(17)), 137.7 (C(4)), 146.7 (C(16)), 148.7 (C(5)), 171.1 (C(2)), 174.1 (C(18)).

NMR data of (±)-Pandamarilactonine-B (**42**):

δ_H (500 MHz, $CDCl_3$) 1.58−1.72 (2 H, m, C(8)H_2), 1.74−1.84 (4 H, m, C(12)H_2 and C(13)H_2), 1.93 (3 H, d, *J* 2.0, C(20)H_3), 1.99 (3 H, s, C(21)H_3), 2.23−2.31 (1 H, m, C(11)**H**H′), 2.33−2.39 (1 H, m, C(7)**H**H′), 2.41−2.51 (2 H, m, C(7)H**H′** and C(9)**H**H′), 2.68−2.78 (2 H, m, C(9)H**H′** and C(14)H), 3.17−3.26 (1 H, m, C(11)H**H′**), 4.71−4.77 (1 H, m, C(15)H), 5.16 (1 H, t, *J* 8.0, C(6)H), 7.00 (1 H, d, *J* 1.5, C(4)H), 7.06 (1 H, s, C(16)H); δ_C (125 MHz, $CDCl_3$) 10.5 (C(21)), 10.8 (C(20)), 23.7 (C(7)), 23.9 (C(13)), 27.0 (C(12)), 28.3 (C(8)), 54.2 (C(11)), 55.7 (C(9)), 66.3 (C(14)), 83.3 (C(15)), 113.9 (C(6)), 129.2 (C(3)), 130.9 (C(17)), 137.7 (C(4)), 147.4 (C(16)), 148.7 (C(5)), 171.1 (C(2)), 174.1 (C(18)).

4-Furan-2-ylbutyronitrile (71)[162]

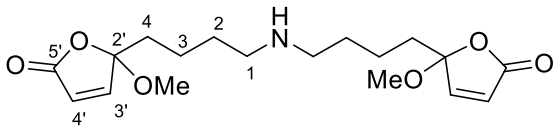


A solution of NaCN (7.46 g, 0.152 mol) in DMSO (100 mL) was heated to 80 °C, the heat removed whilst furan **136** (20.0 g, 0.138 mol) in DMSO (20 mL) was added dropwise with rapid stirring. The reaction mixture was stirred at 80 °C for 5 h. The solution was cooled to RT, poured into water (600 mL) and extracted with ether (3 × 600 mL). The ether layers were combined, washed with water (500 mL), brine (500 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless oil that was used in subsequent reactions

without further purification (16.5 g, 88%). R_f 0.27 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3107w, 2946m, 2248m, 1597m, 1508m, 1153m, 1007m, 737s; δ_H (400 MHz, $CDCl_3$) 2.01 (2 H, quin, *J* 7.0, C(3)H_2), 2.36 (2 H, t, *J* 7.0, C(2)H_2), 2.80 (2 H, t, *J* 7.0, C(4)H_2), 6.07 (1 H, dd, *J* 3.0, 1.0, C(3′)H), 6.30 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 7.32 (1 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (100 MHz, $CDCl_3$) 16.4 (C(2)), 24.1 (C(3)), 26.7 (C(4)), 106.3 (C(3′)), 110.3 (C(4′)), 119.3 (C(1)), 141.6 (C(5′)), 153.3 (C(2′)); *m/z* (ESI^+) 158 (MNa^+, 40%).

*Take note of toxicity of NaCN – Use bleach to oxidise washings and aqueous extracts.

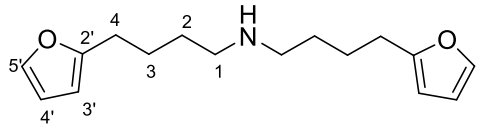
Bis[4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl]amine (72)



To a solution of methoxybutenolide **140** (100 mg, 0.220 mmol) in dichloromethane (2.5 mL) at 0 °C was added trifluoroacetic acid (25.5 μL, 0.331 mmol). The reaction mixture was stirred at RT for 12 h then diluted with sat. aq. $NaHCO_3$ (4 mL) and the aqueous layer extracted with dichloromethane (3 × 4 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* apparently as a single diastereomer as a yellow oil (68.0 mg, 87%). R_f 0.40 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2941m, 1770s, 1458w, 1166m, 915m, 827w, 686w; δ_H (400 MHz, $CDCl_3$) 1.49−1.57 (4 H, m, C(3)H_2), 1.84−1.99 (8 H, m, C(2)H_2 and C(4)H_2), 2.94 (4 H, t, *J* 8.0, C(1)H_2), 3.19 (6 H, s, OCH_3), 6.24 (2 H, d, *J* 6.0, C(3′)H), 7.21 (2 H, d, *J* 6.0, C(4′)H); δ_C (100 MHz, $CDCl_3$) 20.7 (C(3)), 25.5 (C(2)), 36.5 (C(4)), 47.4 (C(1)), 51.2 (OCH_3), 110.7

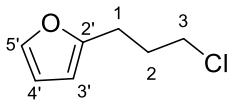
(C(2′)), 125.1 (C(3′)), 153.7 (C(4′)), 169.8 (C(5′)); *m/z* (ESI^+) 376 (MNa^+, 30%), 354 (MH^+, 100); HRMS (ESI^+): Found: 354.1904; $C_{18}H_{28}NO_6$ (MH^+) requires: 354.1911.

Bis(4-furan-2-ylbutyl)amine (135)



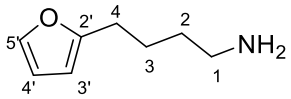
A solution of amine **137** (242 mg, 1.74 mmol) and aldehyde 1**38** (200 mg, 1.45 mmol) in methanol (4 mL) was stirred at RT for 4 h. $NaBH_4$ (88 mg, 2.32 mmol) was added and the reaction mixture was stirred for a further 40 min before diluting with 1 M NaOH (8 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with water (40 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 EtOAc:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (340 mg, 90%). R_f 0.50 (100:10:1 EtOAc:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2933m, 1596w, 1507m, 1459m, 1146m, 1006m, 798m, 727s; δ_H (400 MHz, $CDCl_3$) 1.49−1.56 (4 H, m, C(2)H_2), 1.63−1.71 (4 H, m, C(3)H_2), 2.61 (4 H, t, *J* 7.0, C(1)H_2), 2.63 (4 H, t, *J* 7.5, C(4)H_2), 5.98 (2 H, dd, *J* 3.0, 1.0, C(3′)H), 6.27 (2 H, dd, *J* 3.0, 2.0, C(4′)H), 7.29 (2 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (100 MHz, $CDCl_3$) 25.9 (C(3)), 27.9 (C(4)), 29.7 (C(2)), 49.8 (C(1)), 104.8 (C(3′)), 110.1 (C(4′)), 140.7 (C(5′)), 156.2 (C(2′)); *m/z* (ESI^+) 262 (MH^+, 100%); HRMS (ESI^+): Found: 262.1807; $C_{16}H_{24}NO_2$ (MH^+) requires: 262.1802.

2-(3-Chloropropyl)furan (136)[163]



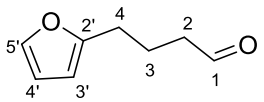
n-Butyllithium (140 mL, 0.350 mol, 2.5 M solution in hexanes) was added dropwise over 30 min to a stirred solution of furan (30.5 mL, 0.420 mol) in anhydrous THF (500 mL) at −78 °C. The solution was stirred for 1 h, then warmed to 0 °C and stirred for an additional 2 h. 1-Bromo-3-chloropropane (34.6 mL, 0.350 mol) was added dropwise to the yellow anion solution. The reaction mixture was allowed to warm to RT and stirred for 16 h. THF was removed *in vacuo*, then ether (250 mL) and sat. aq. NH_4Cl (250 mL) were added to the oily residue. The aqueous layer was extracted with ether (3 × 250 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by fractional vacuum distillation (60−80 °C/20 Torr) afforded the title compound as a colourless oil (45.6 g, 90%). R_f 0.90 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2961w, 2850w, 1508m, 1148m, 1008m, 921m, 803m, 730s; δ_H (400 MHz, $CDCl_3$) 2.11 (2 H, quin, *J* 7.0, C(2)H_2), 2.81 (2 H, t, *J* 7.0, C(1)H_2), 3.56 (2 H, t, *J* 7.0, C(3)H_2), 6.04 (1 H, dd, *J* 3.0, 1.0, C(3′)H), 6.29 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 7.31 (1 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (100 MHz, $CDCl_3$) 25.1 (C(1)), 30.9 (C(2)), 44.1 (C(3)), 105.6 (C(3′)), 110.2 (C(4′)), 141.2 (C(5′)), 154.4 (C(2′)); *m/z* (EI^+) 146 ($M(^{37}Cl)^+$, 33%), 144 ($M(^{35}Cl)^+$, 100).

4-Furan-2-ylbutylamine (137)[164]



To a stirred suspension of $LiAlH_4$ (1.68 g, 44.4 mmol) in ether (80 mL) at 0 °C was added nitrile **71** (4.00 g, 29.6 mmol) in ether (24 mL). The reaction was stirred at RT for 0.5 h then cooled to 0 °C and water (1.6 mL), 15% aq. NaOH (1.6 mL), and a further portion of water (5.6 mL) added sequentially. The mixture was stirred at RT for 10 min, filtered through a pad of celite then concentrated *in vacuo* to afford the title compound as a colourless oil (4.00 g, 97%). R_f 0 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2935s, 2863m, 1572s, 1507s, 1475s, 1313m, 1147m, 1007m, 730s; δ_H (400 MHz, $CDCl_3$) 1.25 (2 H, bs, NH_2), 1.49 (2 H, quin, *J* 7.5, C(2)H_2), 1.67 (2 H, quin, *J* 7.5, C(3)H_2), 2.64 (2 H, t, *J* 7.5, C(4)H_2), 2.71 (2 H, t, *J* 7.5, C(1)H_2), 5.98 (1 H, dd, *J* 3.0, 1.0, C(3′)H), 6.27 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 7.29 (1 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (100 MHz, $CDCl_3$) 25.4 (C(3)), 27.8 (C(4)), 33.4 (C(2)), 42.0 (C(1)), 104.8 (C(3′)), 110.1 (C(4′)), 140.8 (C(5′)), 156.2 (C(2′)); *m/z* (ESI^+) 140 (MH^+, 100%).

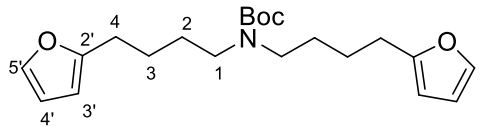
4-Furan-2-ylbutyraldehyde (138)[165]



To a stirred solution of nitrile **71** (200 mg, 1.48 mmol) in dichloromethane (24 mL) at −78 °C was added DIBAL-H (1.78 mL, 1.78 mmol, 1 M solution in hexanes). After stirring at −78 °C for 1 h, the reaction mixture was poured into sat. aq. potassium sodium tartrate (24 mL) and stirred at RT for 1 h. The separated aqueous layer was extracted with dichloromethane (2 × 60 mL), the combined organic layers dried over $MgSO_4$ and

concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5 petrol:ether) afforded the title compound as a colourless oil (147 mg, 72%). R_f 0.34 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2941m, 2821m, 1722s, 1596m, 1508m, 1146m, 1008m, 734s; δ_H (400 MHz, $CDCl_3$) 1.98 (2 H, quin, *J* 7.0, C(3)H_2), 2.48 (2 H, td, *J* 7.0, 1.5, C(2)H_2), 2.68 (2 H, t, *J* 7.0, C(4)H_2), 6.01 (1 H, dd, *J* 3.0, 1.0, C(3′)H), 6.28 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 7.31 (1 H, dd, *J* 2.0, 1.0, C(5′)H), 9.75 (1 H, t, *J* 1.5, C(1)H); δ_C (100 MHz, $CDCl_3$) 20.6 (C(3)), 27.1 (C(4)), 43.0 (C(2)), 105.5 (C(3′)), 110.2 (C(4′)), 141.2 (C(5′)), 154.9 (C(2′)), 202.0 (C(1)); *m/z* (EI^+) 138 (M^+, 100%).

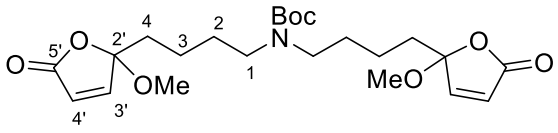
Bis(4-furan-2-ylbutyl)carbamic acid *tert*-butyl ester (139)



To a solution of amine **135** (300 mg, 1.15 mmol) in THF–H_2O (6 mL, 3:1) was added triethylamine (0.207 mL, 1.49 mmol) and di-*tert*-butyl dicarbonate (326 mg, 1.49 mmol). The reaction mixture was stirred at RT for 2 h then diluted with water (15 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with dichloromethane (3 × 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 12:1 petrol:ether) afforded the *title compound* as a colourless oil (344 mg, 83%). R_f 0.50 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2934m, 1688s, 1596w, 1416m, 1365m, 1162s, 1007m, 728s; δ_H (400 MHz, $CDCl_3$) 1.43 (9 H, s, C(CH_3)$_3$), 1.52−1.65 (8 H, m, C(2)H_2 and C(3)H_2), 2.64 (4 H, t, *J* 7.0, C(4)H_2), 3.16 (4 H, bs, C(1)H_2), 5.97 (2 H, dd, *J* 3.0, 1.0, C(3′)H), 6.27 (2 H, dd, *J* 3.0, 2.0, C(4′)H), 7.29 (2 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (100 MHz, $CDCl_3$) 25.3 (C(3)), 27.7 (C(4)), 27.8 (C(2)), 28.5 (C(**C**H_3)$_3$), 46.6 (C(1)), 79.1 (**C**(CH_3)$_3$), 104.8 (C(3′)),

110.1 (C(4′)), 140.8 (C(5′)), 155.6 (NC=O), 156.0 (C(2′)); *m/z* (ESI^+) 384 (MNa^+, 40%), 262 ($[M-Boc]H^+$, 100); HRMS (ESI^+): Found: 384.2136; $C_{21}H_{31}NNaO_4$ (MNa^+) requires: 384.2145.

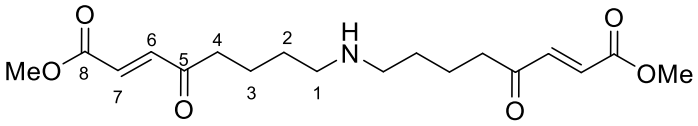
Bis[4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl]carbamic acid *tert*-butyl ester (140)



Oxygen was bubbled through a stirred solution of rose Bengal (2.43 mg, 2.5×10^{-3} mmol, 1×10^{-4} M) and carbamate **139** (300 mg, 0.830 mmol) in methanol (25 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 ^oC and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) for 45 min. The solvent was removed *in vacuo*, the resulting pink residue dissolved in pyridine (4.20 mL), acetic anhydride (78.3 μL, 0.830 mmol) added and the reaction mixture stirred at RT for 15 min. The mixture was diluted with ethyl acetate (42 mL), the organic layer washed with water (42 mL), sat. aq. $CuSO_4$ (2 × 42 mL), brine (42 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless viscous oil apparently as a single diastereomer (300 mg, 80%). R_f 0.50 (ether); ν_{max} (thin film)/cm^{-1} 2940w, 1771s, 1685m, 1418w, 1165m, 915m, 826w; δ_H (500 MHz, $CDCl_3$) 1.32−1.40 (4 H, m, C(3)H_2), 1.43 (9 H, s, C(CH_3)$_3$), 1.47−1.55 (4 H, m, C(2)H_2), 1.89−1.95 (4 H, m, C(4)H_2), 3.12 (4 H, bs, C(1)H_2), 3.21 (6 H, s, OCH_3), 6.21 (2 H, bs, C(3′)H), 7.12 (2 H, d, *J* 6.0, C(4′)H); δ_C (125 MHz, $CDCl_3$) 20.6 (C(3)), 27.9 (C(2)), 28.4 (C(**C**H_3)$_3$), 36.6 (C(4)), 46.7 (C(1)), 51.1 (OCH_3), 79.3 (**C**(CH_3)$_3$), 111.0 (C(2′)), 124.9 (C(3′)), 153.5 (C(4′)), 155.5

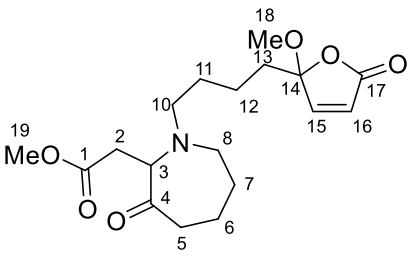
(NC=O), 169.9 (C(5′)); *m/z* (ESI$^+$) 476 (MNa$^+$, 100%); HRMS (ESI$^+$): Found: 476.2241; $C_{23}H_{35}NNaO_8$ (MNa$^+$) requires: 476.2255.

Dimethyl 8,8'-azanediyl(2*E*,2'*E*)-bis(4-oxooct-2-enoate) (141)



Conc. H_2SO_4 (3 μL, 0.045 mmol) was added to a solution of amine **72** (20 mg, 0.057 mmol) in d_8-THF in an NMR tube. The reaction was monitored by ^{1}H NMR and starting material was consumed after 2 weeks to afford the *title compound* as a yellow oil. R_f 0.60 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); δ_H (400 MHz, d_8-THF) 1.80−2.15 (8 H, m, C(2)H_2 and C(3)H_2), 2.75−2.90 (4 H, m, C(4)H_2), 3.05−3.21 (4 H, m, C(1)H_2), 3.30 (6 H, s, OCH_3), 6.70 (2 H, d, *J* 15.0, C(7)H), 7.00 (2 H, d, *J* 15.0, C(6)H); *m/z* (ESI$^+$) 376 (MNa$^+$, 30%), 354 (MH$^+$, 100); HRMS (ESI$^+$): Found: 354.1904; $C_{18}H_{28}NO_6$ (MH$^+$) requires: 354.1911.

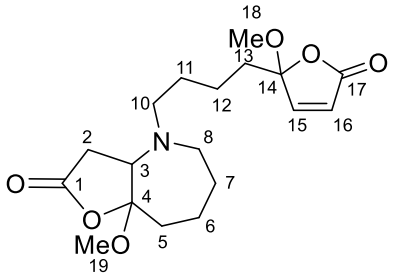
{1-[4-(2-Methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl]-3-oxoazepan-2-yl}acetic acid methyl ester (142)



Conc. H_2SO_4 (12.0 μL, 0.226 mmol) was added to a solution of methoxybutenolide **72** (100 mg, 0.283 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred at RT for 5

d. The mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless oil (10.0 mg, 10%). R_f 0.45 (ether); ν_{max} (thin film)/cm^{-1} 2918m, 2849w, 1771s, 1736m, 1700m, 1438w, 1166m, 915m; δ_H (500 MHz, $CDCl_3$) 1.36−1.45 (4 H, m, C(11)H_2 and C(12)H_2), 1.61−1.68 (3 H, m, C(6)H_2 and C(7)**H**H′), 1.79−1.92 (3 H, m, C(13)H_2 and C(7)H**H′**), 2.27−2.52 (4 H, m, C(10)H_2, C(8)**H**H′ and C(2)**H**H′), 2.74−2.91 (4 H, m, C(5)H_2, C(8)H**H′** and C(2)H**H′**), 3.21 (3 H, s, C(18)H_3), 3.68 (3 H, s, C(19)H_3), 4.00 (1 H, t, *J* 7.0, C(3)H), 6.23 (1 H, dd, *J* 6.0, 2.0, C(15)H), 7.13 (1 H, dd, *J* 6.0, 1.0, C(16)H); δ_C (125 MHz, $CDCl_3$) 20.6 (C(12)), 23.5 (C(6)), 26.3 (C(7)), 28.5 (C(11)), 33.3 (C(2)), 36.9 (C(13)), 42.3 (C(5)), 48.7 (C(10)), 51.1 (C(18)), 51.7 (C(19)), 51.8 (C(8)), 67.7 (C(3)), 111.1 (C(14)), 124.9 (C(15)), 153.5 (C(16)), 169.9 (C(17)), 172.8 (C(1)), 212.3 (C(4)); *m/z* (ESI^+) 376 (MNa^+, 30%), 354 (MH^+, 100); HRMS (ESI^+): Found: 376.1717; $C_{18}H_{27}NNaO_6$ (MNa^+) requires: 376.1731.

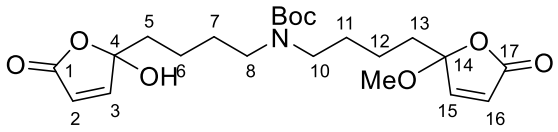
8a-Methoxy-4-[4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl]octahydrofuro[3,2-*b*]azepin-2-one (143)



Zinc iodide (22.6 mg, 0.0707 mmol) was added to a solution of methoxybutenolide **72** (25 mg, 0.0707 mmol) in dichloromethane (0.5 mL) and the reaction mixture was stirred at RT

for 3 d. The mixture was diluted with sat. aq. $NaHCO_3$ (1 mL) and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless oil (10.0 mg, 40%). R_f 0.45 (ether); ν_{max} (thin film)/cm^{-1} 2940m, 1770s, 1460w, 1165m, 1079m, 983m, 949m, 915m; δ_H (400 MHz, $CDCl_3$) 1.34−1.50 (5 H, m, C(11)H_2, C(6)**H**H′ and C(12)H_2), 1.53−1.71 (3 H, m, C(6)H***H′*** and C(7)H_2), 1.80−1.96 (3 H, m, C(13)H_2 and C(5)**H**H′), 2.22 (1 H, dd, *J* 15.0, 8.5, C(5)H***H′***), 2.36−2.43 (2 H, m, C(10)**H**H′ and C(2)**H**H′), 2.52−2.59 (2 H, m, C(8)**H**H′ and C(10)H***H′***), 2.86 (1 H, dd, *J* 15.0, 4.0, C(8)H***H′***), 2.93 (1 H, ddd, *J* 18.5, 8.5, 2.0, C(2)H***H′***), 3.21 (3 H, s, C(18)H_3), 3.31 (3 H, s, C(19)H_3), 3.45 (1 H, ddd, *J* 9.0, 4.0, 1.0, C(3)H), 6.23 (1 H, d, *J* 6.0, C(15)H), 7.12 (1 H, d, *J* 6.0, C(16)H); δ_C (100 MHz, $CDCl_3$) 20.8 (C(12)), 21.9 (C(6)), 28.0 (C(11)), 28.7 (C(7)), 30.5 (C(5)), 34.7 (C(2)), 37.0 (C(13)), 49.8 (C(19)), 50.3 (C(10)), 51.2 (C(18)), 51.4 (C(8)), 68.2 (C(3)), 111.0 (C(14)), 114.5 (C(4)), 124.9 (C(15)), 153.4 (C(16)), 169.8 (C(17)), 175.3 (C(1)); *m/z* (ESI^+) 376 (MNa^+, 20%), 354 (MH^+, 100); HRMS (ESI^+): Found: 376.1739; $C_{18}H_{27}NNaO_6$ (MNa^+) requires: 376.1731.

[4-(2-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)butyl]-[4-(2-methoxy-5-oxo-2,5-dihydrofuran-2-yl)butyl]carbamic acid *tert*-butyl ester (144)



Lithium hydroxide monohydrate (18.5 mg, 0.440 mmol) was added to a solution of methoxybutenolide **140** (100 mg, 0.220 mmol) in THF–H_2O (23.6 mL, 10:1) and the mixture

was stirred at RT for 2 h. Glacial acetic acid (0.2 mL) was added and the solvent was removed *in vacuo*. Water (20 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, EtOAc → 999:1 EtOAc:MeOH) afforded the *title compound* as an inseparable mixture of diastereomers as a colourless oil (68.0 mg, 70%). R_f 0.10 (EtOAc); ν_{max} (thin film)/cm^{-1} 3348br, 2927m, 1767s, 1661s, 1422m, 1164s, 918s, 732m; *m/z* (ESI^+) 462 (MNa^+, 100%); HRMS (ESI^+): Found: 462.2111; $C_{22}H_{33}NNaO_8$ (MNa^+) requires: 462.2098.

NMR data of major diastereomer:

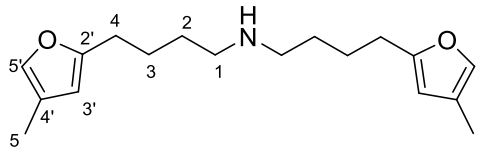
δ_H (500 MHz, $CDCl_3$) 1.30−1.40 (4 H, m, C(6)H_2 and C(12)H_2), 1.43 (9 H, s, C(CH_3)$_3$), 1.50−1.60 (4 H, m, C(7)H_2 and C(11)H_2), 1.85−2.04 (4 H, m, C(5)H_2 and C(13)H_2), 3.14 (4 H, bs, C(8)H_2 and C(10)H_2), 3.21 (3 H, s, OCH_3), 6.12 (1 H, bs, C(3)H), 6.21 (1 H, bs, C(15)H), 7.12 (1 H, d, *J* 6.0, C(16)H), 7.22 (1 H, d, *J* 6.0, C(2)H); δ_C (125 MHz, $CDCl_3$) 20.6 (C(6) and C(12)), 27.3 (C(7) and C(11)), 28.5 (C(**C**H_3)$_3$), 36.8 (C(5) and C(13)), 46.8 (C(8) and C(10)), 51.1 (OCH_3), 80.1 (**C**(CH_3)$_3$), 107.9 (C(14)), 110.9 (C(4)), 122.8 (C(3)), 125.0 (C(15)), 153.5 (C(16)), 154.3 (C(2)), 156.5 (NC=O), 169.9 (C(17)), 170.2 (C(1)).

NMR data of minor diastereomer:

δ_H (500 MHz, $CDCl_3$) 1.30−1.40 (4 H, m, C(6)H_2 and C(12)H_2), 1.43 (9 H, s, C(CH_3)$_3$), 1.50−1.60 (2 H, m, C(11)H_2), 1.60−1.67 (2 H, m, C(7)H_2), 1.85−2.04 (2 H, m, C(13)H_2), 2.05−2.15 (2 H, bs, C(5)H_2), 3.14 (2 H, bs, C(10)H_2), 3.21 (3 H, s, OCH_3), 3.31 (2 H, bs, C(8)H_2), 6.08 (2 H, bs, C(3)H and C(15)H), 7.23 (2 H, d, *J* 6.0, C(2)H and C(16)H); δ_C (125

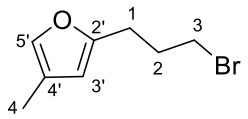
MHz, $CDCl_3$) 19.9 (C(12)), 20.6 (C(6)), 27.2 (C(11)), 27.3 (C(7)), 28.5 (C(**C**H_3)$_3$), 36.4 (C(13)), 36.8 (C(5)), 45.0 (C(10)), 46.8 (C(8)), 51.1 (OCH_3), 80.1 (**C**(CH_3)$_3$), 107.9 (C(14)), 110.9 (C(4)), 122.8 (C(3) and C(15)), 154.3 (C(16) and C(2)), 156.5 (NC=O), 170.5 (C(17) and C(1)).

Bis[4-(4-methylfuran-2-yl)butyl]amine (145)



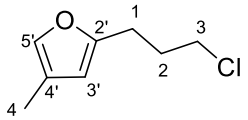
A solution of amine **164** (650 mg, 4.24 mmol) and aldehyde **165** (538 mg, 3.54 mmol) in methanol (10 mL) was stirred at RT for 4 h. $NaBH_4$ (214 mg, 5.66 mmol) was added and the reaction mixture was stirred for a further 40 min before diluting with 1 M NaOH (20 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 EtOAc:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow oil (823 mg, 81%). R_f 0.41 (100:10:1 EtOAc:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2929s, 2862m, 1618w, 1552m, 1458m, 1387w, 1120m, 946m; δ_H (400 MHz, $CDCl_3$) 1.49−1.56 (4 H, m, C(2)H_2), 1.60−1.68 (4 H, m, C(3)H_2), 1.97 (6 H, d, *J* 1.0, C(5)H_3), 2.58 (4 H, t, *J* 7.0, C(4)H_2), 2.60 (4 H, t, *J* 7.0, C(1)H_2), 5.85 (2 H, s, C(3′)H), 7.04 (2 H, s, C(5′)H); δ_C (100 MHz, $CDCl_3$) 9.8 (C(5)), 25.9 (C(3)), 28.0 (C(4)), 29.6 (C(2)), 49.7 (C(1)), 107.7 (C(3′)), 120.4 (C(4′)), 137.3 (C(5′)), 156.2 (C(2′)); *m/z* (ESI^+) 290 (MH^+, 100%); HRMS (ESI^+): Found: 290.2109; $C_{18}H_{28}NO_2$ (MH^+) requires: 290.2115.

2-(3-Bromopropyl)-4-methylfuran (146)[166]



1,4-Dicarbonyl **159** (9.00 mg, 40.7 μmol) was added to a solution of *p*-toluenesulfonic acid (0.701 mg, 4.07 μmol) in benzene (0.4 mL) and the mixture was stirred under reflux for 16 h. The mixture was diluted with sat. aq. $NaHCO_3$ (2 mL) and the aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the title compound as a colourless oil (3.2 mg, 39%). R_f 0.80 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2958s, 2923s, 1432m, 1249w, 1157m, 861w; δ_H (500 MHz, C_6D_6) 1.77 (2 H, quin, *J* 7.0, C(2)H_2), 1.78 (3 H, d, *J* 1.5, C(4)H_3), 2.45 (2 H, t, *J* 7.0, C(1)H_2), 2.90 (2 H, t, *J* 7.0, C(3)H_2), 5.67 (1 H, s, C(3′)H), 6.89 (1 H, s, C(5′)H); δ_C (125 MHz, C_6D_6) 9.8 (C(4)), 26.6 (C(1)), 31.2 (C(2)), 32.7 (C(3)), 108.8 (C(3′)), 120.6 (C(4′)), 138.1 (C(5′)), 154.5 (C(2′)); *m/z* (EI^+) 204 ($M(^{81}Br)^{+\cdot}$, 80%), 202 ($M(^{79}Br)^{+\cdot}$, 100).

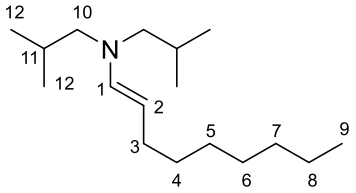
2-(3-Chloropropyl)-4-methylfuran (147)



To a solution of diol **160** (177 mg, 1.00 mmol) in dichloromethane (7.0 mL) at RT was added 5% w/w $AgNO_3$ on SiO_2 (340 mg, 0.100 mmol). The reaction mixture was stirred in the absence of light until TLC analysis showed complete consumption of starting material (typically 2 h) then filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil (145 mg, 91%). R_f 0.75 (95:5

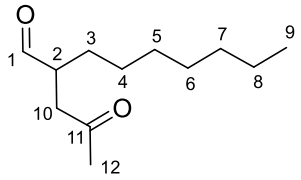
petrol:ether); ν_{max} (thin film)/cm^{-1} 2927w, 1619w, 1552w, 1443m, 1297w, 1112m, 928s, 805s, 744s, 648m; δ_H (400 MHz, C_6D_6) 1.70 (2 H, quin, *J* 7.0, C(2)H_2), 1.78 (3 H, d, *J* 1.0, C(4)H_3), 2.47 (2 H, t, *J* 7.0, C(1)H_2), 3.05 (2 H, t, *J* 7.0, C(3)H_2), 5.67 (1 H, s, C(3′)H), 6.90 (1 H, s, C(5′)H); δ_C (100 MHz, C_6D_6) 9.4 (C(4)), 25.0 (C(1)), 30.8 (C(2)), 43.6 (C(3)), 108.4 (C(3′)), 120.2 (C(4′)), 137.8 (C(5′)), 154.3 (C(2′)); *m/z* (FI$^+$) 160 (M(^{37}Cl)$^{+\cdot}$, 33%), 158 (M(^{35}Cl)$^{+\cdot}$, 100); HRMS (FI$^+$): Found: 158.0502; $C_8H_{11}ClO$ (M(^{35}Cl)$^{+\cdot}$) requires: 158.0493.

Diisobutylnon-1-enylamine (148)



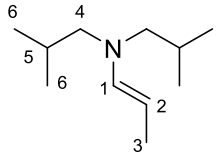
Nonanal (1.21 mL, 7.03 mmol) was added dropwise to a stirred solution of diisobutylamine (1.23 mL, 7.03 mmol) and potassium carbonate (0.972 g, 7.03 mmol) in ether (2 mL) at 0 ^oC. The mixture was stirred for 16 h at RT, then filtered and concentrated *in vacuo* to afford the *title compound* as a colourless oil (1.28 g, 72%). ν_{max} (thin film)/cm^{-1} 2955s, 2924s, 2855m, 1651m, 1467m, 1384m, 1112m; δ_H (400 MHz, C_6D_6) 0.82 (12 H, d, *J* 7.0, C(12)H_3), 0.89 (3 H, t, *J* 6.0, C(9)H_3), 1.22−1.35 (6 H, m, C(6)H_2, C(7)H_2 and C(8)H_2), 1.38−1.45 (2 H, m, C(5)H_2), 1.47−1.53 (2 H, m, C(4)H_2), 1.89 (2 H, non, *J* 7.0, C(11)H), 2.19 (2 H, q, *J* 7.0, C(3)H_2), 2.63 (4 H, d, *J* 7.0, C(10)H_2), 4.24 (1 H, dt, *J* 14.0, 7.0, C(2)H), 5.97 (1 H, d, *J* 14.0, C(1)H); δ_C (100 MHz, C_6D_6) 14.0 (C(9)), 20.2 (C(12)), 22.8 (C(8)), 27.0 (C(11)), 29.2 (C(5)), 29.4 (C(6)), 31.2 (C(3)), 32.0 (C(7)), 32.2 (C(4)), 60.6 (C(10)), 95.4 (C(2)), 138.6 (C(1)); *m/z* (ESI$^+$) 254 (MH$^+$, 100%).

2-(2-Oxopropyl)nonanal (149)



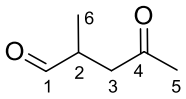
Chloroacetone (0.459 mL, 5.76 mmol), sodium iodide (0.349 g, 2.33 mmol) and 18-crown-6 (0.104 g, 0.395 mmol) were added to a stirred solution of enamine **148** (1.00 g, 3.95 mmol) in THF (8.5 mL) and the mixture was stirred at RT for 24 h. Water (10 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a yellow oil (250 mg, 46%). R_f 0.68 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2926s, 2857m, 1717s, 1365m, 1164m; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.0, C(9)H_3), 1.21−1.35 (10 H, m, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2 and C(8)H_2), 1.38−1.48 (1 H, m, C(3)**H**H′), 1.65−1.75 (1 H, m, C(3)H**H′**), 2.19 (3 H, s, C(12)H_3), 2.45 (1 H, dd, *J* 21.0, 7.5, C(10)**H**H′), 2.89 (1 H, dd, *J* 21.0, 8.5, C(10)H**H′**), 2.88−2.94 (1 H, m, C(2)H), 9.70 (1 H, s, C(1)H); δ_C (100 MHz, $CDCl_3$) 14.1 (C(9)), 22.6 (C(8)), 27.0 (C(4)), 28.6 (C(3)), 29.1 (C(6)), 29.6 (C(5)), 30.1 (C(12)), 31.7 (C(7)), 42.1 (C(10)), 46.8 (C(2)), 203.5 (C(1)), 206.7 (C(11)); *m/z* (ESI^+) 199 (MH^+, 100%); HRMS (ESI^+): Found: 221.1506; $C_{12}H_{22}NaO_2$ (MNa^+) requires: 221.1512.

Diisobutylpropenylamine (150)[167]



Propionaldehyde (1.25 mL, 17.2 mmol) was added dropwise to a stirred solution of diisobutylamine (3.01 mL, 17.2 mmol) and potassium carbonate (2.38 g, 17.2 mmol) in ether (5 mL) at 0 ^{o}C. The mixture was stirred for 16 h at RT, then filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (1.25 g, 43%). ν_{max} (thin film)/cm^{-1} 2959s, 2872m, 1657m, 1467m, 1384m, 1112m, 975m; δ_H (400 MHz, C_6D_6) 0.80 (12 H, d, *J* 7.0, C(6)H_3), 1.81 (3 H, dd, *J* 6.5, 1.0, C(3)H_3), 1.84 (2 H, non, *J* 7.0, C(5)H), 2.59 (4 H, d, *J* 7.0, C(4)H_2), 4.16 (1 H, dq, *J* 14.0, 6.5, C(2)H), 5.92 (1 H, dq, *J* 14.0, 1.0, C(1)H); δ_C (100 MHz, C_6D_6) 15.8 (C(3)), 20.2 (C(6)), 27.0 (C(5)), 60.7 (C(4)), 89.1 (C(2)), 139.1 (C(1)); *m/z* (ESI$^+$) 170 (MH^+, 100%).

2-Methyl-4-oxopentanal (151)[168]

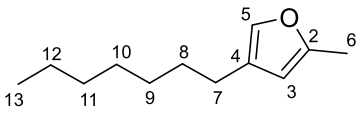


Chloroacetone (0.687 mL, 8.62 mmol), sodium iodide (0.522 g, 3.48 mmol) and 18-crown-6 (0.156 g, 0.591 mmol) were added to a stirred solution of enamine **150** (1.00 g, 5.91 mmol) in THF (12.5 mL) and the mixture was stirred at RT for 24 h. Water (10 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the title compound as a yellow oil (34.0

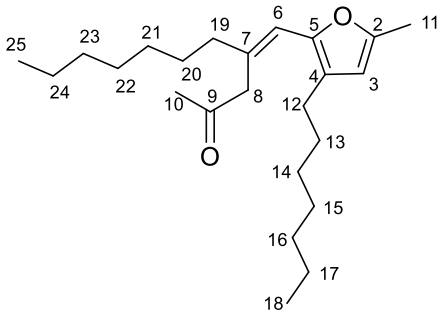
mg, 10%). R_f 0.30 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2963s, 2875m, 1715s, 1661s, 1466m, 1390m, 1113m; δ_H (400 MHz, $CDCl_3$) 1.15 (3 H, d, *J* 7.5, C(6)H_3), 2.19 (3 H, s, C(5)H_3), 2.45 (1 H, dd, *J* 20.5, 8.0, C(3)**H**H′), 2.88−2.94 (1 H, m, C(2)H), 2.92 (1 H, dd, *J* 20.5, 7.5, C(3)H**H′**), 9.68 (1 H, s, C(1)H); δ_C (100 MHz, $CDCl_3$) 13.5 (C(6)), 30.2 (C(5)), 41.6 (C(2)), 44.0 (C(3)), 203.3 (C(1)), 206.4 (C(4)); *m/z* (ESI$^+$) 115 (MH^+, 100%).

4-Heptyl-2-methylfuran (152) and

4-(3-Heptyl-5-methylfuran-2-ylmethylene)undecan-2-one (153)



152



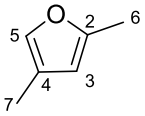
153

1,4-Dicarbonyl **149** (50.0 mg, 0.252 mmol) was added to a solution of *p*-toluenesulfonic acid (4.34 mg, 0.0252 mmol) in benzene (3.8 mL) and the mixture was stirred under reflux for 2 h. The mixture was diluted with sat. aq. $NaHCO_3$ (4 mL) and the aqueous layer extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded **152** as a colourless oil (18.2 mg, 40%). R_f 0.90 (93:7 petrol:ether); ν_{max} (thin film)/cm^{-1} 2924s, 2855m, 1464m, 1121w, 921w, 799w; δ_H (400 MHz, C_6D_6) 0.90 (3 H, t, *J* 6.5, C(13)H_3), 1.18−1.33 (8 H, m, C(9)H_2, C(10)H_2, C(11)H_2 and C(12)H_2), 1.45−1.53 (2 H,

m, C(8)H_2), 2.05 (3 H, d, *J* 0.5, C(6)H_3), 2.29 (2 H, t, *J* 7.5, C(7)H_2), 5.78 (1 H, s, C(3)H), 7.03 (1 H, s, C(5)H); δ_C (100 MHz, C_6D_6) 13.2 (C(6)), 14.0 (C(13)), 22.7 (C(12)), 25.0 (C(7)), 29.2 (C(10)), 29.3 (C(9)), 30.1 (C(8)), 31.9 (C(11)), 107.2 (C(3)), 126.1 (C(4)), 137.0 (C(5)), 151.9 (C(2)); *m/z* (EI^+) 180 ($M^{+\cdot}$, 100%).

Also obtained was **153** as a brown oil (27.3 mg, 60%). R_f 0.55 (93:7 petrol:ether); ν_{max} (thin film)/cm^{-1} 2925s, 2865m, 1716s, 1465m, 1364m, 1121m, 799w; δ_H (400 MHz, $CDCl_3$) 0.82−0.92 (6 H, m, C(18)H_3 and C(25)H_3), 1.17−1.35 (16 H, m, C(14)H_2, C(15)H_2, C(16)H_2, C(17)H_2, C(21)H_2, C(22)H_2, C(23)H_2 and C(24)H_2), 1.39−1.54 (4 H, m, C(13)H_2 and C(20)H_2), 2.12−2.17 (2 H, m, C(19)H_2), 2.18 (3 H, s, C(10)H_3), 2.24 (3 H, d, *J* 0.5, C(11)H_3), 2.34 (2 H, t, *J* 7.5, C(12)H_2), 3.59 (2 H, s, C(8)H_2), 5.85 (1 H, s, C(3)H), 6.09 (1 H, s, C(6)H); δ_C (100 MHz, $CDCl_3$) 13.8 (C(11)), 14.1 (C(18) and C(25)), 22.7 (C(17) and C(24)), 24.8 (C(12)), 28.1 (C(20)), 29.1 (C(14) and C(21)), 29.2 (C(15) and C(22)), 29.3 (C(10)), 30.4 (C(13)), 31.8 (C(16) and C(23)), 39.4 (C(19)), 47.6 (C(8)), 108.5 (C(3)), 114.2 (C(6)), 124.5 (C(4)), 131.1 (C(7)), 146.6 (C(5)), 150.3 (C(2)), 207.8 (C(9)); *m/z* (ESI^+) 383 (MNa^+, 30%), 361 (MH^+, 100%).

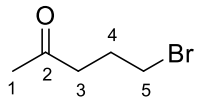
2,4-Dimethylfuran (154)[169]



1,4-Dicarbonyl **151** (25.0 mg, 0.219 mmol) was added to a solution of *p*-toluenesulfonic acid (4.0 mg, 0.0219 mmol) in benzene (3.5 mL) and the mixture was stirred under reflux for 16 h. The mixture was diluted with sat. aq. $NaHCO_3$ (4 mL) and the aqueous layer extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over

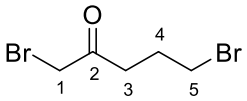
$MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the title compound as a colourless oil (5.0 mg, 24%). R_f 0.85 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2923s, 1609w, 1445m, 1259m, 1138w, 801s; δ_H (500 MHz, C_6D_6) 2.02 (3 H, d, *J* 0.5, C(6)H_3), 2.19 (3 H, s, C(7)H_3), 5.72 (1 H, s, C(3)H), 7.06 (1 H, s, C(5)H); δ_C (125 MHz, C_6D_6) 10.9 (C(7)), 13.5 (C(6)), 110.5 (C(3)), 117.7 (C(4)), 125.9 (C(5)), 150.7 (C(2)); *m/z* (EI^+) 96 ($M^{+\cdot}$, 20%).

5-Bromopentan-2-one (156)[56]



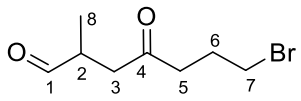
48% Hydrobromic acid (15.8 mL, 0.139 mol) was added to a solution of 2-acetylbutyrolactone (10.0 mL, 0.0929 mol) in toluene (60 mL). The reaction mixture was stirred at 80 ^oC for 16 h. Water (40 mL) was added and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with water (80 mL) and brine (80 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by Kugelrohr distillation under reduced pressure (80 ^oC/ 20 Torr) afforded the title compound as a colourless oil (11.0 g, 73%). R_f 0.30 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2963w, 1712s, 1434w, 1366m, 1247w, 1179m, 735w; δ_H (400 MHz, $CDCl_3$) 2.11 (2 H, quin, *J* 6.5, C(4)H_2), 2.16 (3 H, s, C(1)H_3), 2.64 (2 H, t, *J* 6.5, C(3)H_2), 3.44 (2 H, t, *J* 6.5, C(5)H_2); δ_C (100 MHz, $CDCl_3$) 26.4 (C(4)), 30.1 (C(1)), 33.4 (C(5)), 41.5 (C(3)), 207.4 (C(2)); *m/z* (EI^+) 166 ($M(^{81}Br)^{+\cdot}$, 97%), 164 ($M(^{79}Br)^{+\cdot}$, 100).

1,5-Dibromopentan-2-one (158)[56]



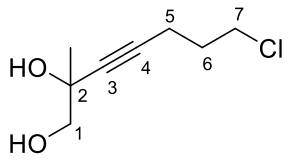
Ketone **156** (500 mg, 3.03 mmol) in THF (14 mL) was added dropwise over 14 min to a solution of lithium diisopropylamide (2.02 mL, 3.64 mmol, 1.8 M solution in THF) in THF (7 mL) at −78 °C and the mixture was stirred at −78 °C for 1 h. Chlorotrimethylsilane (0.769 mL, 6.06 mmol) was then added dropwise to the solution and the mixture was stirred −78 °C for 1 h. The mixture was poured into sat. aq. $NaHCO_3$ (40 mL) and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Crude silyl ether was dissolved in THF (20 mL), cooled to 0 °C and $NaHCO_3$ (0.382 g, 4.54 mmol) and *N*-bromosuccinimide (0.539 g, 3.03 mmol) were added. The mixture was stirred for 1 h and allowed to warm to RT. The mixture was poured into sat. aq. $NaHCO_3$ (30 mL) and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5 petrol:ether) afforded the title compound as a colourless oil (300 mg, 41%). R_f 0.35 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2963w, 1715s, 1402m, 1249w, 1190m, 1049w; δ_H (400 MHz, $CDCl_3$) 2.18 (2 H, quin, *J* 6.5, C(4)H_2), 2.88 (2 H, t, *J* 6.5, C(3)H_2), 3.46 (2 H, t, *J* 6.5, C(5)H_2), 3.91 (2 H, s, C(1)H_2); δ_C (100 MHz, $CDCl_3$) 26.5 (C(4)), 32.8 (C(5)), 34.1 (C(1)), 37.8 (C(3)), 201.0 (C(2)); *m/z* (EI^+) 246 (M($^{81}Br^{81}Br$)$^{+\cdot}$, 50%), 244 (M($^{81}Br^{79}Br$)$^{+\cdot}$, 100), 242 (M($^{79}Br^{79}Br$)$^{+\cdot}$, 50).

7-Bromo-2-methyl-4-oxoheptanal (159)



α-Bromoketone **158** (100 mg, 0.410 mmol) was added to a stirred solution of enamine **150** (69 mg, 0.410 mmol) in THF (0.6 mL) and the mixture was stirred at RT for 24 h. Water (5 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were washed with water (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (11.0 mg, 12%; 21% b.r.s.m). R_f 0.10 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2965m, 1714s, 1375m, 1249w; δ_H (400 MHz, $CDCl_3$) 1.17 (3 H, d, *J* 7.5, C(8)H_3), 2.14 (2 H, quin, *J* 6.5, C(6)H_2), 2.43 (1 H, dd, *J* 17.0, 5.0, C(3)**H**H′), 2.66 (2 H, t, *J* 7.0, C(5)H_2), 2.89 (1 H, dd, *J* 17.0, 7.5, C(3)H**H′**), 2.92−2.99 (1 H, m, C(2)H), 3.45 (2 H, t, *J* 6.5, C(7)H_2), 9.67 (1 H, s, C(1)H); δ_C (100 MHz, $CDCl_3$) 13.5 (C(8)), 26.3 (C(6)), 33.2 (C(7)), 40.8 (C(5)), 41.7 (C(2)), 43.2 (C(3)), 203.1 (C(1)), 207.4 (C(4)); *m/z* (EI^+) 222 ($M(^{81}Br)^{+\cdot}$, 100%), 220 ($M(^{79}Br)^{+\cdot}$, 60); HRMS (EI^+): Found: 220.0097; $C_8H_{13}O_2Br$ ($M(^{79}Br)^{+\cdot}$) requires: 220.0094.

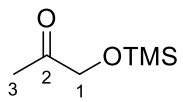
7-Chloro-2-methylhept-3-yne-1,2-diol (160)



i-Propylmagnesium chloride (0.975 mL, 1.95 mmol, 2.0 M solution in THF) was added to a solution of 5-chloro-1-pentyne **161** (0.207 mL, 1.95 mmol) in THF (3.3 mL) at 0 °C. The reaction mixture was stirred at RT for 1.5 h, then cooled to 0 °C and silyl ether **162** (0.285 g,

1.95 mmol) added. The reaction mixture was stirred at RT for 16 h then diluted with sat. aq. NH_4Cl (6.7 mL) and the THF removed *in vacuo*. The aqueous layer was diluted with water (27 mL), extracted with ether (3 × 33 mL), the combined organic layers washed with brine (33 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude silyl ether as a colourless oil (0.433 g, 89%). Citric acid (3.30 mg, 0.0174 mmol) was then added to a solution of crude silyl ether (0.433 g, 1.74 mmol) in methanol (2.5 mL) and the reaction mixture was stirred at RT for 4 h. The mixture was diluted with water (2.5 mL), the methanol removed *in vacuo* and the aqueous layer extracted with ethyl acetate (3 × 2.5 mL). The combined organic layers were washed with brine (2.5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless oil (0.290 g, 94%) that was used in subsequent reactions without purification. R_f 0.25 (95:5 CH_2Cl_2:MeOH); ν_{max} (thin film)/cm^{-1} 3375s, 2935m, 1442m, 1375m, 1291m, 1112m, 1057s, 1037s; δ_H (400 MHz, $CDCl_3$) 1.41 (3 H, s, CH_3), 1.94 (2 H, quin, *J* 7.0, C(6)H_2), 2.39 (2 H, t, *J* 7.0, C(5)H_2), 2.95 (2 H, bs, 2 × OH), 3.45 (1 H, d, *J* 11.0, C(1)**H**H′), 3.60 (1 H, d, *J* 11.0, C(1)H**H′**), 3.62 (2 H, t, *J* 7.0, C(7)H_2); δ_C (100 MHz, $CDCl_3$) 16.1 (C(5)), 25.6 (CH_3), 31.2 (C(6)), 43.7 (C(7)), 68.6 (C(2)), 70.7 (C(1)), 82.8 (C(4)), 83.0 (C(3)); *m/z* (ESI^+) 201 (M(^{37}Cl)Na^+, 33%), 199 (M(^{35}Cl)Na^+, 100); HRMS (ESI^+): Found: 199.0489; $C_8H_{13}ClNaO_2$ (MNa^+) requires: 199.0496.

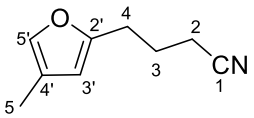
1-Trimethylsilanyloxypropan-2-one (162)[59]



To a stirred solution of hydroxyacetone (4.00 g, 54.0 mmol), triethylamine (8.97 mL, 64.8 mmol) and 4-dimethylaminopyridine (66.0 mg, 0.540 mmol) in dichloromethane (40 mL) at

−10 °C was added chlorotrimethylsilane (6.85 mL, 54.0 mmol). The reaction mixture was stirred at RT for 30 min then diluted with water (60 mL), the separated aqueous layer extracted with dichloromethane (2 × 60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting yellow liquid was filtered to remove $Et_3N{\cdot}HCl$ and then fractionally distilled under reduced pressure (60−63 °C/30 Torr) to afford the title compound as a colourless oil (5.80 g, 73%). R_f 0.30 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2959w, 1719m, 1355w, 1251m, 1114m, 970w, 838s, 750m; δ_H (400 MHz, $CDCl_3$) 0.15 (9 H, s, $Si(CH_3)_3$), 2.15 (3 H, s, C(3)H_3), 4.16 (2 H, s, C(1)H_2); δ_C (100 MHz, $CDCl_3$) –0.01 ($Si(CH_3)_3$), 26.4 (C(3)), 69.5 (C(1)), 208.9 (C(2)); *m/z* (ESI^+) 169 (MNa^+, 100%).

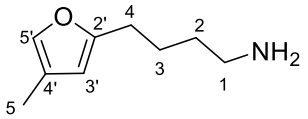
4-(4-Methylfuran-2-yl)butyronitrile (163)



A solution of NaCN (0.792 g, 16.2 mmol) in DMSO (10 mL) was heated to 80 °C, the heat removed whilst furan **147** (2.33 g, 14.7 mmol) in DMSO (2 mL) was added dropwise with rapid stirring. The reaction mixture was stirred at 80 °C for 8 h. The solution was cooled to RT, poured into water (60 mL) and extracted with ether (3 × 60 mL). The ether layers were combined, washed with water (100 mL), brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless oil that was used in subsequent reactions without further purification (2.17 g, 99%). R_f 0.20 (95:5 petrol:ether); ν_{max} (thin film)/cm^{-1} 2945m, 2247m, 1793s, 1761s, 1618m, 1553m, 1456m, 1388m, 1114s, 937s; δ_H (400 MHz, $CDCl_3$) 1.98 (2 H, quin, *J* 7.0, C(3)H_2), 1.99 (3 H, s, C(5)H_3), 2.35 (2 H, t, *J* 7.0, C(2)H_2), 2.74 (2 H, t, *J* 7.0, C(4)H_2), 5.93 (1 H, s, C(3′)H), 7.08 (1 H, s, C(5′)H); δ_C (100 MHz, $CDCl_3$) 9.7 (C(5)), 16.4 (C(2)), 24.0 (C(3)), 26.7 (C(4)), 109.1 (C(3′)), 119.3 (C(1)), 120.6

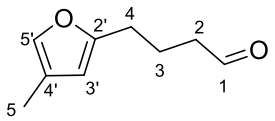
(C(4′)), 138.1 (C(5′)), 153.3 (C(2′)); *m/z* (EI^+) 149 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 149.0840; $C_9H_{11}NO$ ($M^{+\cdot}$) requires: 149.0836.

4-(4-Methylfuran-2-yl)butylamine (164)



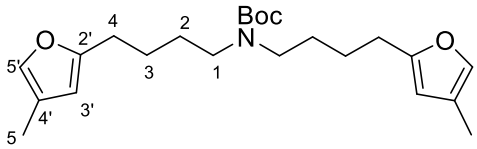
To a stirred suspension of $LiAlH_4$ (247 mg, 6.52 mmol) in ether (11.5 mL) at 0 °C was added nitrile **163** (648 mg, 4.34 mmol) in ether (3.5 mL). The reaction mixture was stirred at RT for 0.5 h then cooled to 0 °C and water (0.25 mL), 15% aq. NaOH (0.25 mL), and a further portion of water (0.80 mL) added sequentially. The mixture was stirred at RT for 10 min, filtered through a pad of celite then concentrated *in vacuo* to afford the *title compound* as a colourless oil (657 mg, 99%). R_f 0 (95:5 petrol:ether); ν_{max} (thin film)/cm^{-1} 2928s, 2865m, 1553s, 1475s, 1387m, 1312m, 1120m, 942w; δ_H (400 MHz, $CDCl_3$) 1.30 (2 H, bs, NH_2), 1.49 (2 H, quin, *J* 7.5, C(2)H_2), 1.65 (2 H, quin, *J* 7.5, C(3)H_2), 1.98 (3 H, d, *J* 1.0, C(5)H_3), 2.58 (2 H, t, *J* 7.5, C(4)H_2), 2.70 (2 H, t, *J* 7.5, C(1)H_2), 5.85 (1 H, s, C(3′)H), 7.05 (1 H, s, C(5′)H); δ_C (125 MHz, $CDCl_3$) 9.8 (C(5)), 25.3 (C(3)), 27.8 (C(4)), 33.0 (C(2)), 41.8 (C(1)), 107.7 (C(3′)), 120.4 (C(4′)), 137.3 (C(5′)), 156.1 (C(2′)); *m/z* (ESI^+) 154 (MH^+, 100%); HRMS (ESI^+): Found: 154.1229; $C_9H_{16}NO$ (MH^+) requires: 154.1226.

4-(4-Methylfuran-2-yl)butyraldehyde (165)



To a stirred solution of nitrile **163** (100 mg, 0.670 mmol) in dichloromethane (6 mL) at −78 °C was added DIBAL-H (0.804 mL, 0.804 mmol, 1 M solution in hexanes). After stirring at −78 °C for 1 h, the reaction mixture was poured into sat. aq. potassium sodium tartrate (6 mL) and stirred at RT for 1 h. The separated aqueous layer was extracted with dichloromethane (2 × 6 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5 petrol:ether) afforded the *title compound* as a colourless oil (53 mg, 52%). R_f 0.30 (95:5 petrol:ether); ν_{max} (thin film)/cm^{-1} 3436w, 2945m, 1754s, 1724s, 1453w, 1116m, 1055m, 956m; δ_H (400 MHz, $CDCl_3$) 1.96 (2 H, quin, *J* 7.0, C(3)H_2), 1.98 (3 H, s, C(5)H_3), 2.48 (2 H, td, *J* 7.0, 1.5, C(2)H_2), 2.62 (2 H, t, *J* 7.0, C(4)H_2), 5.88 (1 H, s, C(3′)H), 7.06 (1 H, s, C(5′)H), 9.75 (1 H, t, *J* 1.5, C(1)H); δ_C (100 MHz, $CDCl_3$) 9.8 (C(5)), 20.6 (C(3)), 27.2 (C(4)), 43.0 (C(2)), 108.4 (C(3′)), 120.5 (C(4′)), 137.7 (C(5′)), 154.9 (C(2′)), 202.1 (C(1)); *m/z* (EI^+) 152 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 152.0840; $C_9H_{12}O_2$ ($M^{+\cdot}$) requires: 152.0832.

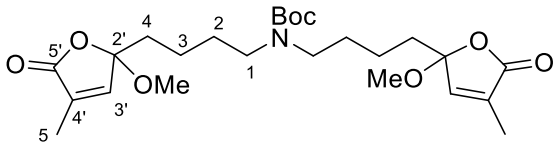
Bis[4-(4-methylfuran-2-yl)butyl]carbamic acid *tert*-butyl ester (166)



To a solution of amine **145** (810 mg, 2.80 mmol) in THF–H_2O (16 mL, 3:1) was added triethylamine (0.504 mL, 3.64 mmol) and di-*tert*-butyl dicarbonate (794 mg, 3.64 mmol). The

reaction mixture was stirred at RT for 2 h then diluted with water (40 mL) and the THF removed *in vacuo*. The aqueous layer was extracted with dichloromethane (3 × 60 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 94:6 petrol:ether) afforded the *title compound* as a colourless oil (954 mg, 88%). R_f 0.40 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2930m, 1693s, 1417m, 1366m, 1254w, 1164s, 799w; δ_H (400 MHz, $CDCl_3$) 1.43 (9 H, s, $C(CH_3)_3$), 1.53−1.61 (8 H, m, $C(2)H_2$ and $C(3)H_2$), 1.97 (6 H, d, *J* 1.0, $C(5)H_3$), 2.58 (4 H, t, *J* 7.0, $C(4)H_2$), 3.15 (4 H, bs, $C(1)H_2$), 5.84 (2 H, s, C(3′)H), 7.04 (2 H, s, C(5′)H); δ_C (100 MHz, $CDCl_3$) 9.8 (C(5)), 25.3 (C(3)), 27.8 (C(4)), 28.0 (C(2)), 28.5 ($C(\mathbf{C}H_3)_3$), 46.7 (C(1)), 79.1 ($\mathbf{C}(CH_3)_3$), 107.7 (C(3′)), 120.4 (C(4′)), 137.3 (C(5′)), 155.6 (NC=O), 156.0 (C(2′)); *m/z* (ESI^+) 412 (MNa^+, 100%); HRMS (ESI^+): Found: 412.2445; $C_{23}H_{35}NNaO_4$ (MNa^+) requires: 412.2458.

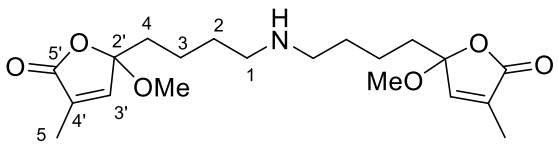
Bis[4-(2-methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl]carbamic acid *tert*-butyl ester (167)



Oxygen was bubbled through a stirred solution of rose Bengal (7.01 mg, 7.2×10^{-3} mmol, 1×10^{-4} M) and carbamate **166** (940 mg, 2.41 mmol) in methanol (72 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 ^oC and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) for 1.5 h. The solvent was removed *in vacuo*, the resulting pink residue dissolved in pyridine (12 mL), acetic anhydride (0.228 mL, 2.41 mmol) added and the reaction mixture was stirred at RT for 3 h. The mixture was diluted with ethyl acetate (120 mL), the organic layer washed with water (120 mL), sat. aq. $CuSO_4$ (2 × 120 mL), brine (120

mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless viscous oil apparently as a single diastereomer (1.10 g, 94%). R_f 0.20 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2938w, 1768s, 1687m, 1418w, 1366w, 1317w, 1154m, 959m; δ_H (400 MHz, $CDCl_3$) 1.31−1.38 (4 H, m, C(3)H_2), 1.43 (9 H, s, C(CH_3)$_3$), 1.46−1.53 (4 H, m, C(2)H_2), 1.87 (4 H, t, *J* 8.5, C(4)H_2), 1.96 (6 H, s, C(5)H_3), 3.12 (4 H, bs, C(1)H_2), 3.18 (6 H, s, OCH_3), 6.71 (2 H, q, *J* 1.5, C(3′)H); δ_C (125 MHz, $CDCl_3$) 10.5 (C(5)), 20.7 (C(3)), 28.0 (C(2)), 28.4 (C(**C**H_3)$_3$), 36.9 (C(4)), 46.4 (C(1)), 50.9 (OCH_3), 79.2 (**C**(CH_3)$_3$), 109.0 (C(2′)), 133.9 (C(4′)), 145.8 (C(3′)), 155.5 (NC=O), 171.3 (C(5′)); *m/z* (ESI^+) 504 (MNa^+, 100%); HRMS (ESI^+): Found: 504.2560; $C_{25}H_{39}NNaO_8$ (MNa^+) requires: 504.2568.

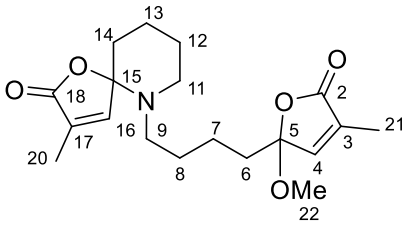
Bis[4-(2-methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl]amine (168)



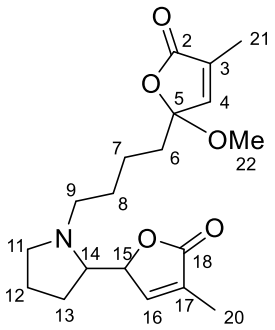
To a solution of methoxybutenolide **167** (100 mg, 0.208 mmol) in dichloromethane (1.4 mL) at 0 °C was added bromotrimethylsilane (0.260 mL, 1.97 mmol). The reaction mixture was stirred at RT for 5 h then diluted with sat. aq. $NaHCO_3$ (14 mL) and the aqueous layer extracted with ethyl acetate (3 × 14 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* apparently as a single diastereomer as a yellow oil (63.0 mg, 80%). R_f 0.41 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2941m, 1764s, 1457w, 1319m, 1152m, 960m, 761w; δ_H (400 MHz, $CDCl_3$) 1.44−1.52 (4 H, m, C(3)H_2), 1.78−1.92 (8 H, m, C(2)H_2 and C(4)H_2), 1.96 (6 H, d, *J*

1.5, C(5)H_3), 2.84 (4 H, t, *J* 8.5, C(1)H_2), 3.17 (6 H, s, OCH_3), 6.77 (2 H, q, *J* 1.5, C(3′)H); δ_C (100 MHz, $CDCl_3$) 10.6 (C(5)), 20.9 (C(3)), 26.6 (C(2)), 36.9 (C(4)), 47.9 (C(1)), 51.0 (OCH_3), 108.8 (C(2′)), 134.1 (C(4′)), 145.9 (C(3′)), 171.3 (C(5′)); *m/z* (ESI^+) 382 (MH^+, 100%); HRMS (ESI^+): Found: 382.2214; $C_{20}H_{32}NO_6$ (MH^+) requires: 382.2224.

6-[4-(2-Methoxy-4-methyl-5-oxo-2,5-dihydrofuran-2-yl)butyl]-3-methyl-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (169) and **5-Methoxy-3-methyl-5-{4-[2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-1-yl]butyl}-5*H*-furan-2-one (170)**



169



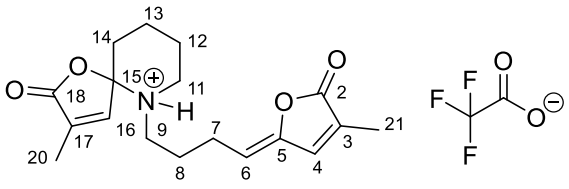
170

Conc. H_2SO_4 (11.0 μL, 0.210 mmol) was added to a solution of methoxybutenolide **168** (100 mg, 0.262 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred at RT for 5 d. The mixture was diluted with sat. aq. $NaHCO_3$ (20 mL) and the aqueous layer extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *spirocycle* **169** as a colourless oil (30.2 mg, 33%). R_f 0.40 (ether); ν_{max} (thin film)/cm^{-1} 2941m, 1763s, 1445w, 1311m, 1157m, 944m; δ_H (400 MHz, $CDCl_3$) 1.23−1.39 (4 H, m, C(7)H_2 and C(8)H_2), 1.60−1.75 (6 H, m, C(12)H_2, C(13)H_2 and C(14)H_2), 1.78−1.85 (2 H, m, C(6)H_2), 1.91 (3 H, d, *J* 1.5, C(20)H_3), 1.96 (3 H,

d, *J* 1.5, C(21)H_3), 2.30−2.47 (2 H, m, C(9)H_2), 2.75 (2 H, bs, C(11)H_2), 3.17 (3 H, s, C(22)H_3), 6.70 (1 H, q, *J* 1.5, C(4)H), 6.71 (1 H, q, *J* 1.5, C(16)H); δ_C (100 MHz, $CDCl_3$) 10.6 (C(21)), 10.7 (C(20)), 20.8 (C(12)), 21.0 (C(7)), 25.1 (C(13)), 27.6 (C(8)), 36.1 (C(14)), 37.2 (C(6)), 47.1 (C(11)), 49.8 (C(9)), 51.0 (C(22)), 101.8 (C(15)), 109.0 (C(5)), 131.5 (C(17)), 133.9 (C(3)), 145.9 (C(4)), 149.8 (C(16)), 171.4 (C(2)), 173.0 (C(18)); *m/z* (ESI^+) 372 (MNa^+, 25%), 350 (MH^+, 100); HRMS (ESI^+): Found: 372.1775; $C_{19}H_{27}NNaO_5$ (MNa^+) requires: 372.1781.

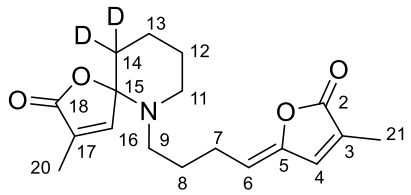
Further elution (silica, EtOAc → 98:2 EtOAc:MeOH) afforded the *pyrrolidine derivative* **170** as an inseparable mixture of diastereomers as a colourless oil (22.0 mg, 24%). R_f 0.23 (98:2 EtOAc:MeOH); ν_{max} (thin film)/cm^{-1} 2956w, 1761s, 1445w, 1048w, 620w; δ_H (500 MHz, $CDCl_3$) 1.32−1.41 (1 H, m, C(7)**H**H′), 1.42−1.55 (3 H, m, C(7)H**H′**, C(8)**H**H′ and C(12)**H**H′), 1.59−1.67 (2 H, m, C(8)H**H′** and C(13)**H**H′), 1.69−1.80 (2 H, m, C(12)H**H′** and C(13)H**H′**), 1.81−1.89 (2 H, m, C(6)H_2), 1.93 (3 H, d, *J* 2.0, C(20)H_3), 1.96 (3 H, d, *J* 1.5, C(21)H_3), 2.18−2.28 (1 H, m, C(11)**H**H′), 2.34−2.47 (1 H, m, C(9)**H**H′), 2.77−2.92 (2 H, m, C(9)H**H′** and C(14)H), 3.05−3.15 (1 H, m, C(11)H**H′**), 3.18 (3 H, s, C(22)H_3), 4.79−4.92 (1 H, m, C(15)H), 6.72 (1 H, q, *J* 1.5, C(4)H), 7.05 (1 H, quin, *J* 1.5, C(16)H); δ_C (125 MHz, $CDCl_3$) 10.5 (C(21)), 10.7 (C(20)), 21.1 (C(7)), 23.8 (C(13)), 25.8 (C(12)), 28.7 (C(8)), 37.2 (C(6)), 50.9 (C(22)), 54.2 (C(11)), 55.0 (C(9)), 65.4 (C(14)), 83.3 (C(15)), 109.1 (C(5)), 131.2 (C(17)), 133.9 (C(3)), 145.9 (C(4)), 146.9 (C(16)), 171.4 (C(2)), 174.3 (C(18)); *m/z* (ESI^+) 372 (MNa^+, 10%), 350 (MH^+, 100); HRMS (ESI^+): Found: 372.1770; $C_{19}H_{27}NNaO_5$ (MNa^+) requires: 372.1781.

Trifluoroacetate-3-methyl-6-[4-(4-methyl-5-oxo-5*H*-furan-2-ylidene)butyl]-2-oxo-1-oxa-6-azoniaspiro[4.5]dec-3-ene (171)



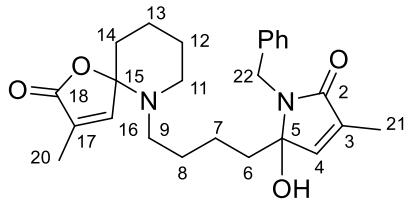
To a solution of Pandamarilactone-1 **4** (7.0 mg, 22.1 μmol) in $CDCl_3$ (0.5 mL) was added a solution of trifluoroacetic acid (1.7 μL, 22.1 μmol) in $CDCl_3$ (0.1 mL) and the mixture stirred. Mixture used for NMR analysis directly. ν_{max} (thin film)/cm^{-1} 2951w, 1764s, 1671w, 1187s, 1057w, 990w; δ_H (500 MHz, $CDCl_3$) 1.74−1.85 (4 H, m, C(8)H_2 and C(12)H_2), 1.91−1.95 (2 H, m, C(13)H_2), 1.97 (3 H, d, *J* 1.5, C(20)H_3), 1.99 (3 H, s, C(21)H_3), 1.97−2.00 (2 H, m, C(14)H_2), 2.32 (2 H, q, *J* 7.5, C(7)H_2), 2.69 (2 H, t, *J* 7.5, C(9)H_2), 3.19 (2 H, t, *J* 5.5, C(11)H_2), 5.04 (1 H, t, *J* 8.0, C(6)H), 6.97 (1 H, d, *J* 1.5, C(4)H), 7.33 (1 H, d, *J* 1.0, C(16)H); δ_C (125 MHz, $CDCl_3$) 10.5 (C(21)), 10.7 (C(20)), 19.0 (C(12)), 23.0 (C(13)), 23.5 (C(7)), 24.5 (C(8)), 34.0 (C(14)), 48.8 (C(11)), 49.5 (C(9)), 97.8 (C(15)), 111.2 (C(6)), 116.0 (q, *J* 292.0, CF_3), 129.8 (C(3)), 133.5 (C(17)), 137.5 (C(4)), 146.9 (C(16)), 149.2 (C(5)), 161.7 (q, *J* 36.0, CF_3**C**=O), 170.5 (C(2)), 170.6 (C(18)); *m/z* (ESI^+) 341 (MNa^+, 20%), 319 (MH^+, 80); *m/z* (ESI^-) 113 ($CF_3CO_2^-$, 100%).

Deuterated pandamarilactone-1 (173)



Pandamarilactone-1 **4** (10.0 mg, 0.0315 mmol) was dissolved in CD_3OD (0.5 mL) for characterisation. δ_H (500 MHz, CD_3OD) 1.59 (2 H, quin, *J* 7.0, C(8)H_2), 1.71−1.75 (4 H, m, C(12)H_2 and C(13)H_2), 1.86 (3 H, d, *J* 1.5, C(20)H_3), 1.95 (3 H, d, *J* 1.5, C(21)H_3), 2.32 (2 H, q, *J* 7.0, C(7)H_2), 2.51 (2 H, t, *J* 7.0, C(9)H_2), 2.83−2.86 (2 H, m, C(11)H_2), 5.27 (1 H, t, *J* 8.0, C(6)H), 6.91 (1 H, q, *J* 1.5, C(16)H), 7.25 (1 H, q, *J* 1.5, C(4)H); δ_C (125 MHz, CD_3OD) 10.3 (C(21)), 10.9 (C(20)), 21.7 (C(12)), 24.7 (C(7)), 25.9 (C(13)), 28.0 (C(8)), 36.2 (1:2:3:2:1 quin, *J* 20.0, C(14)), 48.5 (C(11)), 50.8 (C(9)), 107.7 (C(15)), 115.3 (C(6)), 130.1 (C(3)), 133.0 (C(17)), 139.7 (C(4)), 150.3 (C(5)), 151.0 (C(16)), 172.8 (C(2)), 174.8 (C(18)); *m/z* (ESI^+) 342 (MNa^+, 25%), 320 (MH^+, 100); HRMS (ESI^+): Found: 342.1645; $C_{18}H_{21}D_2NNaO_4$ (MNa^+) requires: 342.1645.

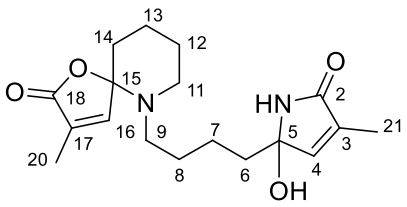
6-[4-(1-Benzyl-2-hydroxy-4-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)butyl]-3-methyl-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (174)



Benzylamine (7.5 μL, 0.0662 mmol) was added to a solution of Pandamarilactone-1 **4** (7.00 mg, 0.0221 mmol) in ether (0.2 mL) and the reaction mixture was stirred at RT for 2 d. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 99:1

EtOAc:MeOH) afforded the *title compound* as a colourless oil (4.5 mg, 48%). R_f 0.50 (99:1 EtOAc:MeOH); ν_{max} (thin film)/cm^{-1} 3332m, 2943m, 2863m, 1745s, 1691s, 1655m, 1496m, 1107m, 703s; δ_H (500 MHz, $CDCl_3$) 0.64−0.74 (1 H, m, C(7)**H**H′), 0.90−1.05 (2 H, m, C(7)H**H′** and C(8)**H**H′), 1.08−1.17 (1 H, m, C(8)H**H′**), 1.50−1.68 (5 H, m, C(6)**H**H′, $C(13)H_2$ and $C(14)H_2$), 1.69−1.77 (3 H, m, C(6)H**H′** and $C(12)H_2$), 1.92 (3 H, d, *J* 1.5, $C(20)H_3$), 1.93 (3 H, d, *J* 1.5, $C(21)H_3$), 2.10−2.23 (2 H, m, $C(9)H_2$), 2.61−2.72 (2 H, m, $C(11)H_2$), 4.44 (1 H, d, *J* 15.0, C(22)**H**H′), 4.56 (1 H, d, *J* 15.0, C(22)H**H′**), 6.46 (1 H, q, *J* 1.5, C(4)H), 6.63 (1 H, bs, C(16)H), 7.21−7.40 (5 H, m, Ph); δ_C (125 MHz, $CDCl_3$) 10.7 (C(21)), 10.8 (C(20)), 20.7 (C(12)), 21.4 (C(7)), 25.0 (C(13)), 27.5 (C(8)), 35.5 (C(6)), 36.1 (C(14)), 42.0 (C(22)), 47.0 (C(11)), 49.8 (C(9)), 90.9 (C(5)), 101.6 (C(15)), 127.3 (Ph), 128.4 (Ph), 128.5 (Ph), 131.4 (C(17)), 135.8 (C(3)), 141.4 (C(4)), 149.6 (C(16)), 170.3 (C(2)), 172.9 (C(18)); *m/z* (ESI^+) 447 (MNa^+, 25%), 425 (MH^+, 100); HRMS (ESI^+): Found: 447.2246; $C_{25}H_{32}N_2NaO_4$ (MNa^+) requires: 447.2254.

6-[4-(2-Hydroxy-4-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)butyl]-3-methyl-1-oxa-6-azaspiro[4.5]dec-3-en-2-one (175)

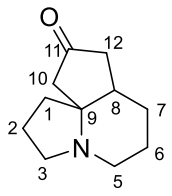


A sample of synthetic pandamarilactone-1 **4** (5.0 mg, 0.0158 mmol) was dissolved in ether (1.5 mL). 5% aq. H_2SO_4 (0.8 mL) was added and the mixture was stirred at RT for 10 mins. TLC showed the absence of pandamarilactone-1 in the ether layer. The ether layer was removed and the aqueous layer was basified with conc. aq. NH_3 (0.7 mL). The aqueous layer

was extracted with chloroform (3 × 2.4 mL) and the combined organic layers were concentrated *in vacuo*. Purification by flash chromatography (SiO_2, $CHCl_3$/MeOH/aq. NH_3 (18 M), 95:5:1) afforded the *title compound* as a colourless oil (1.0 mg, 19%). R_f 0.50 ($CHCl_3$/MeOH/aq. NH_3 (18 M), 100:10:1); ν_{max} (thin film)/cm^{-1} 3328m, 2937m, 1745s, 1699s, 1659m, 1312m, 1156m; δ_H (700 MHz, CD_3OD) 1.21−1.33 (2 H, m, C(7)H_2), 1.35−1.44 (2 H, m, C(8)H_2), 1.68−1.78 (6 H, m, C(6)H_2, C(12)H_2 and C(13)H_2), 1.81 (3 H, d, *J* 1.5 Hz, C(21)H_3), 1.88 (3 H, d, *J* 1.5 Hz, C(20)H_3), 2.46 (2 H, t, *J* 7.0 Hz, C(9)H_2), 2.79−2.86 (2 H, m, C(11)H_2), 6.57 (1 H, q, *J* 1.5 Hz, C(4)H), 6.93 (1 H, q, *J* 1.5 Hz, C(16)H); δ_C (175 MHz, CD_3OD) 10.5 (C(21)), 11.0 (C(20)), 21.8 (C(12)), 22.8 (C(7)), 26.1 (C(13)), 29.0 (C(8)), 36.4 (1:2:3:2:1 quin, $^2J_{CD}$ 19.0 Hz, C(14)), 38.9 (C(6)), 48.6 (C(11)), 51.4 (C(9)), 88.9 (C(5)), 107.5 (C(15)), 133.2 (C(17)), 135.2 (C(3)), 146.3 (C(4)), 151.2 (C(16)), 175.0 (C(18)), 175.1 (C(2)); *m/z* (ESI^+) 357 (MNa^+, 20%), 335 (MH^+, 100); HRMS (ESI^+) found 335.1957, $C_{18}H_{27}N_2O_4$ (MH^+) requires 335.1965.

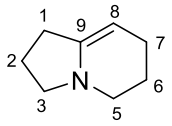
6.3: Compounds in Chapter 3

Octahydrocyclopenta[*h*]indolizin-9(1*H*)-one (92)



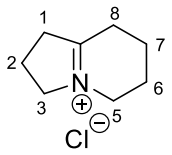
To a stirred solution of iminium salt **187** (3.77 g, 12.3 mmol) in THF–H_2O (270 mL, 1:3) was added powdered NaOH (4.92 g, 123 mmol) and the reaction mixture was stirred at RT for 24 h. Water (200 mL) was added and the mixture was extracted with ether (3 × 600 mL). The combined organic layers were dried over K_2CO_3, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow liquid (2.25 g, 98%). R_f 0.48 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2930m, 1740s, 1405w, 1150w; δ_H (500 MHz, $CDCl_3$) 1.13−1.24 (1 H, m, C(7)**H**H′), 1.57−1.71 (2 H, m, C(6)H_2), 1.73−1.83 (4 H, m, C(1)H_2, C(2)**H**H′ and C(7)H**H′**), 1.87 (1 H, d, *J* 18.5, C(10)**H**H′), 1.91−2.00 (1 H, m, C(2)H**H′**), 2.08 (1 H, d, *J* 18.5, C(12)**H**H′), 2.10−2.19 (1 H, m, C(8)H), 2.42 (1 H, dd, *J* 18.5, 7.0, C(12)H**H′**), 2.52−2.63 (2 H, m, C(5)**H**H′ and C(10)H**H′**), 2.63−2.73 (1 H, m, C(3)**H**H′), 2.86 (1 H, dt, *J* 12.5, 3.5, C(5)H**H′**), 3.03 (1 H, td, *J* 9.5, 3.5, C(3)H**H′**); δ_C (125 MHz, $CDCl_3$) 20.0 (C(2)), 22.2 (C(6)), 27.5 (C(7)), 36.8 (C(1)), 38.6 (C(8)), 39.7 (C(10)), 44.7 (C(12)), 45.0 (C(5)), 50.7 (C(3)), 66.5 (C(9)), 217.1 (C(11)); *m/z* (ESI^+) 180 (MH^+, 100%); HRMS (ESI^+): Found: 180.1386; $C_{11}H_{18}NO$ (MH^+) requires: 180.1383.

1,2,3,5,6,7-Hexahydroindolizine (176)[62]



To a stirred solution of iminium salt **178** (9.00 g, 56.4 mmol) in water (900 mL) was added powdered NaOH (56.4 g, 1.41 mol) and the reaction mixture was stirred at RT for 16 h. Pentane (900 mL) was added and the mixture was stirred at RT for 1 h. The organic layer was extracted, dried over K_2CO_3, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (5.15 g, 74%). ν_{max} (thin film)/cm^{-1} 2930s, 1683m, 1648w, 1445w, 1280m, 1185m; δ_H (400 MHz, C_6D_6) 1.47−1.56 (2 H, m, C(2)H_2), 1.81−1.88 (2 H, m, C(6)H_2), 2.12−2.18 (2 H, m, C(7)H_2), 2.24−2.31 (2 H, m, C(1)H_2), 2.66 (2 H, t, *J* 6.5, C(3)H_2), 2.80 (2 H, t, *J* 5.5, C(5)H_2), 4.43 (1 H, tt, *J* 3.5, 1.5, C(8)H); δ_C (100 MHz, C_6D_6) 21.6 (C(2)), 22.0 (C(7)), 23.2 (C(6)), 28.8 (C(1)), 46.7 (C(5)), 52.7 (C(3)), 87.8 (C(8)), 145.8 (C(9)); *m/z* (ESI$^+$) 124 (MH$^+$, 100%).

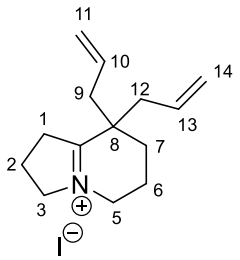
2,3,5,6,7,8-Hexahydro-1*H*-indolizin-4-ium chloride (178)[61]



n-Butyllithium (53.0 mL, 132 mmol, 2.5 M solution in hexanes) was added dropwise to a stirred solution of diisopropylamine (18.6 mL, 132 mmol) in THF (120 mL) at 0 °C. After 5 min, the solution was cooled to –78 °C and a solution of 2-methyl-1-pyrroline (11.4 mL, 120 mmol) in THF (120 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 2 h. A solution of 1-bromo-3-chloropropane (12.5 mL, 126 mmol) in THF (120 mL) was then

added dropwise and the mixture was stirred at RT for 16 h. The mixture was poured into 0.5 M NaOH solution (450 mL), extracted with ether (3 × 500 mL) and the combined organic layers were dried over K_2CO_3, filtered and concentrated *in vacuo* to afford the title compound as a yellow-orange salt (18.0 g, 94%). R_f 0.65 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3396w, 2950s, 2867m, 1644s, 1431m, 1303m, 1015w; δ_H (400 MHz, C_6D_6) 1.38−1.61 (6 H, m, C(2)H_2, C(6)H_2 and C(7)H_2), 1.89−2.00 (4 H, m, C(1)H_2 and C(8)H_2), 3.12 (2 H, t, *J* 6.5, C(5)H_2), 3.73 (2 H, ddquin, *J* 9.0, 5.5, 2.0, C(3)H_2); δ_C (100 MHz, C_6D_6) 22.5 (C(2)), 23.3 (C(7)), 32.1 (C(6)), 32.3 (C(8)), 36.9 (C(1)), 44.4 (C(5)), 60.9 (C(3)), 175.2 (C=N^+); *m/z* (ESI$^+$) 162 (M(^{37}Cl)H^+, 32%), 160 (M(^{35}Cl)H^+, 100), 124 ((M−Cl)$^+$, 35).

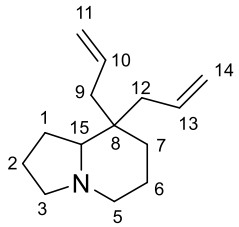
8,8-Diallyl-2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium iodide (180)



Allyl iodide (23.0 μL, 0.252 mmol) was added to a solution of enamine **176** (31.0 mg, 0.252 mmol) in THF (1 mL) and the reaction mixture was stirred at RT for 1 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 6:3:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a brown oil (49.1 mg, 59%). R_f 0.45 (6:3:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3427m, 2935m, 1669s, 1446m, 1314m, 1000m, 927s; δ_H (500 MHz, $CDCl_3$) 1.84−1.89 (2 H, m, C(7)H_2), 2.08−2.15 (2 H, m, C(6)H_2), 2.29 (2 H, quin, *J* 8.0, C(2)H_2), 2.49 (2 H, dd, *J* 14.0, 8.0, C(9)**H**H′ and C(12)**H**H′), 2.67 (2 H, dd, *J* 14.0, 7.0, C(9)H**H′** and C(12)H**H′**), 3.29−3.36 (2 H, m, C(1)H_2), 3.89 (2 H, t, *J* 6.0, C(5)H_2), 4.45 (2 H, t, *J* 8.0, C(3)H_2), 5.21−5.28 (4 H, m, C(11)H_2 and C(14)H_2),

5.72−5.84 (2 H, m, C(10)H and C(13)H); δ_C (125 MHz, $CDCl_3$) 17.6 (C(6)), 18.3 (C(2)), 26.7 (C(7)), 36.6 (C(1)), 41.3 (C(9) and C(12)), 43.0 (C(8)), 49.6 (C(5)), 62.1 (C(3)), 121.3 (C(11) and C(14)), 131.0 (C(10) and C(13)), 194.1 (C=N^+); *m/z* (ESI^+) 204 ($(M-I)^+$, 100%); *m/z* (ESI^-) 127 (I^-, 100%); HRMS (ESI^+): Found: 204.1749; $C_{14}H_{22}N$ ($(M-I)^+$) requires: 204.1747.

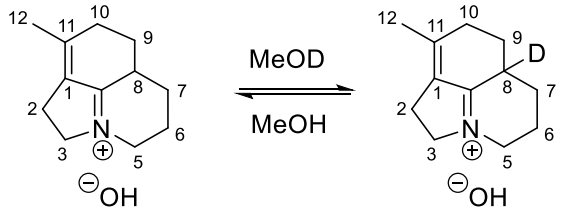
8,8-Diallyloctahydroindolizine (181)



Sodium borohydride (2.51 mg, 66.4 μmol) was added to a solution of iminium salt **180** (11.0 mg, 33.2 μmol) in methanol (1 mL) and the reaction mixture was stirred at RT for 1 h before diluting with 1 M NaOH (2 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with water (4 mL) and extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with brine (4 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow oil (4.04 mg, 59%). R_f 0.55 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3407w, 3073w, 2934s, 2780m, 1671m, 1638m, 1454m, 910s; δ_H (500 MHz, CD_3OD) 1.11−1.24 (1 H, m, C(7)**H**H′), 1.50−1.88 (8 H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H**H′** and C(15)H), 1.99−2.19 (5 H, m, C(5)**H**H′, C(9)H_2 and C(12)H_2), 2.45−2.54 (1 H, m, C(5)H**H′**), 3.01−3.16 (2 H, m, C(3)H_2), 5.01−5.12 (4 H, m, C(11)H_2 and C(14)H_2), 5.79−5.95 (2 H, m, C(10)H and C(13)H); δ_C (125 MHz, CD_3OD) 21.1 (C(6)), 22.2 (C(2)), 24.4 (C(1)), 32.4 (C(7)), 36.0 (C(5)), 39.1 (C(8)), 44.2 (C(9) and C(12)), 55.8 (C(3)),

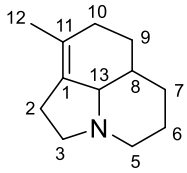
79.5 (C(15)), 118.0 (C(11) and C(14)), 135.8 (C(10) and C(13)); *m/z* (ESI^+) 206 (MH^+, 100%); HRMS (ESI^+): Found: 206.1907; $C_{14}H_{24}N$ (MH^+) requires: 206.1903.

9-Methyl-1,2,4,5,6,6a,7,8-octahydropyrrolo[3,2,1-*ij*]quinolin-3-ium hydroxide (183)



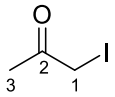
Methyl vinyl ketone (27.0 μL, 0.325 mmol) was added to a solution of enamine **175** (40.0 mg, 0.325 mmol) in THF (1.2 mL) and the reaction mixture was stirred at RT for 1 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 6:3:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow semi-solid (26.4 mg, 46%). R_f 0.20 (6:3:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3383s, 2942w, 1652s, 1430m, 1224w, 1088m; δ_H (500 MHz, CD_3OD) 1.39−1.48 (1 H, m, C(7)**H**H′), 1.55−1.65 (1 H, m, C(9)**H**H′), 2.03 (3 H, s, C(12)H_3), 2.00−2.10 (2 H, m, C(6)**H**H′ and C(7)H**H′**), 2.12−2.23 (2 H, m, C(6)H**H′** and C(9)H**H′**), 2.38−2.64 (2 H, m, C(10)H_2), 2.85−2.95 (2 H, m, C(2)H_2), 3.58−3.81 (2 H, m, C(5)H_2), 4.10 (2 H, t, *J* 7.0, C(3)H_2); δ_C (125 MHz, CD_3OD) 21.5 (C(12)), 22.1 (C(6)), 24.2 (C(2)), 24.3 (C(7)), 29.3 (C(9)), 32.9 (C(10)), 35.5 (1:1:1 t, *J* 20.5, C(8)), 48.3 (C(5)), 58.3 (C(3)), 132.0 (C(1)), 159.7 (C(11)), 180.6 (C=N^+); *m/z* (ESI^+) 176 ((M−OH)$^+$, 100%); HRMS (ESI^+): Found: 176.1436; $C_{12}H_{18}N$ ((M−OH)$^+$) requires: 176.1434.

9-Methyl-1,2,5,6,6a,7,8,9b-octahydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (184)



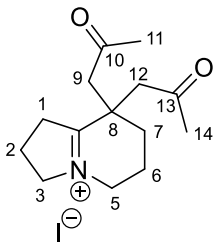
Sodium borohydride (12.9 mg, 0.341 mmol) was added to a solution of iminium salt **183** (26.4 mg, 0.137 mmol) in methanol (3 mL) and the reaction mixture was stirred at RT for 1 h before diluting with 1 M NaOH (6 mL). The methanol was removed *in vacuo*, the aqueous layer diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow oil (13.5 mg, 56%). R_f 0.48 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3372w, 2924s, 2852m, 1686w, 1436m, 1326m, 1263m; δ_H (500 MHz, CD_3OD) 1.02−1.12 (1 H, m, C(7)**H**H′), 1.25−1.34 (2 H, m, C(8)H and C(9)**H**H′), 1.58 (3 H, s, C(12)H_3), 1.66−1.82 (4 H, m, C(6)H_2, C(7)H**H′** and C(9)H**H′**), 1.92−2.00 (1 H, m, C(13)H), 2.03−2.10 (2 H, m, C(10)H_2), 2.14−2.27 (2 H, m, C(5)H_2), 2.35−2.44 (2 H, m, C(2)H_2), 3.10−3.17 (2 H, m, C(3)H_2); δ_C (125 MHz, CD_3OD) 18.4 (C(12)), 26.7 (C(6)), 27.4 (C(2)), 28.4 (C(9)), 31.1 (C(7)), 32.6 (C(10)), 38.9 (C(8)), 54.1 (C(3)), 54.2 (C(5)), 71.9 (C(13)), 125.7 (C(11)), 131.8 (C(1)); *m/z* (ESI^+) 178 (MH^+, 100%); HRMS (ESI^+): Found: 178.1596; $C_{12}H_{20}N$ (MH^+) requires: 178.1590.

1-Iodopropan-2-one (186)[170]



Sodium iodide (2.82 g, 18.8 mmol) was added to a solution of chloroacetone (1.00 mL, 12.6 mmol) in acetone (10 mL) and the reaction mixture was stirred at RT for 1 h. Water (20 mL) was added into the mixture and the solution was extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the title compound as a pale yellow oil (1.47 g, 64%). R_f 0.50 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2959w, 1703s, 1413w, 1358m, 1225m, 1133w, 963w; δ_H (400 MHz, $CDCl_3$) 2.41 (3 H, s, C(3)H_3), 3.81 (2 H, s, C(1)H_2); δ_C (100 MHz, $CDCl_3$) 6.7 (C(1)), 26.5 (C(3)), 200.8 (C(2)); *m/z* (EI^+) 184 (M^+, 100%).

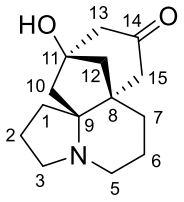
8,8-Bis(2-oxopropyl)-2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium iodide (188)



A solution of enamine **176** (10.3 g, 83.6 mmol) in THF (96 mL) was added dropwise to a stirred solution of iodide **186** (15.4 g, 83.6 mmol) in THF (144 mL) and the reaction mixture was stirred at RT for 1 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 18:2:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a brown oil (3.03 g, 10%). R_f 0.50 (40:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin

film)/cm^{-1} 3453m, 2953w, 1708s, 1674m, 1418w, 1361m, 1174m; δ_H (500 MHz, CD_3OD) 1.83−1.89 (2 H, m, C(7)H_2), 1.90−1.97 (2 H, m, C(6)H_2), 2.18 (6 H, s, C(11)H_3 and C(14)H_3), 2.20−2.26 (2 H, m, C(2)H_2), 3.00−3.10 (2 H, m, C(1)H_2), 3.17 (2 H, d, *J* 18.5, C(9)**H**H′ and C(12)**H**H′), 3.31 (2 H, d, *J* 18.5, C(9)H**H′** and C(12)H**H′**), 3.69−3.77 (2 H, m, C(5)H_2), 4.22 (2 H, t, *J* 8.0, C(3)H_2); δ_C (125 MHz, CD_3OD) 19.3 (C(6)), 19.6 (C(2)), 29.1 (C(7)), 30.8 (C(11) and C(14)), 36.6 (C(1)), 40.3 (C(8)), 49.2 (C(5)), 51.5 (C(9) and C(12)), 62.0 (C(3)), 194.6 (C=N$^+$), 208.5 (C(10) and C(13)); *m/z* (ESI$^+$) 236 ((M−I)$^+$, 100%); *m/z* (ESI$^-$) 127 (I$^-$, 100%); HRMS (ESI$^+$): Found: 236.1644; $C_{14}H_{22}NO_2$ ((M−I)$^+$) requires: 236.1645.

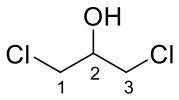
(7a*R*,11*S*,12a*S*)-11-hydroxyoctahydro-1*H*-7a,11-methanocyclohepta[*h*]indolizin-9(5*H*)-one (189)



To a stirred solution of iminium salt **188** (14.0 mg, 38.5 μmol) in THF–H_2O (1.3 mL, 1:3) was added powdered NaOH (46.3 mg, 1.16 mmol) and the reaction mixture was stirred at RT for 48 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over K_2CO_3, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow oil (2.5 mg, 27%). R_f 0.25 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3373br, 2944m, 1711s, 1441w, 1327m, 1122m; δ_H (500 MHz, $CDCl_3$) 1.32 (1 H, td, *J* 14.0, 4.5, C(7)**H**H′), 1.37−1.44 (1 H, m, C(1)**H**H′), 1.53−1.70

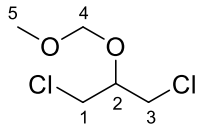
(5 H, m, C(2)**H**H′, C(6)**H**H′, C(7)H**H′**, C(10)**H**H′ and C(12)**H**H′), 1.79 (1 H, td, *J* 12.0, 8.0, C(1)H**H′**), 1.87−2.07 (4 H, m, C(2)H**H′**, C(6)H**H′**, C(12)H**H′** and OH), 2.16 (1 H, d, *J* 16.5, C(15)**H**H′), 2.23−2.33 (2 H, m, C(5)**H**H′ and C(15)H**H′**), 2.55−2.75 (4 H, m, C(3)**H**H′, C(5)H**H′** and C(13)H_2), 3.00−3.12 (2 H, m, C(3)H**H′** and C(10)H**H′**); δ_C (125 MHz, $CDCl_3$) 20.3 (C(2)), 21.3 (C(6)), 27.3 (C(1)), 29.6 (C(7)), 44.1 (C(8)), 47.5 (C(10)), 50.7 (C(5)), 51.8 (C(3)), 53.5 (C(15)), 54.4 (C(12)), 56.5 (C(13)), 73.7 (C(9)), 76.4 (C(11)), 209.2 (C(14)); *m/z* (ESI^+) 236 (MH^+, 100%); HRMS (ESI^+): Found: 236.1645; $C_{14}H_{22}NO_2$ (MH^+) requires: 236.1645.

1,3-Dichloropropan-2-ol (190)[65]



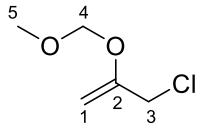
Ceric ammonium nitrate (5.61 g, 10.2 mmol) was added gradually to a mixture of epichlorohydrin (4.00 mL, 51.1 mmol) and ammonium chloride (8.21 g, 153 mmol) in *tert*-butanol (150 mL) and the reaction mixture was stirred at RT for 6 h. The solvent was removed *in vacuo*, water (150 mL) was added, and the mixture was extracted with ether (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by fractional vacuum distillation (85−90 °C/30 Torr) afforded the title compound as a colourless oil (2.31 g, 35%). R_f 0.30 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3389br, 2974w, 1281s, 1091w, 855m; δ_H (400 MHz, $CDCl_3$) 2.44 (1 H, bs, OH), 3.70 (4 H, d, *J* 5.0, C(1)H_2 and C(3)H_2), 4.07 (1 H, quin, *J* 5.0, C(2)H); δ_C (100 MHz, $CDCl_3$) 45.8 (C(1) and C(3)), 70.8 (C(2)); *m/z* (EI^+) 132 ($M(^{37}Cl^{37}Cl)^+$, 11%), 130 ($M(^{35}Cl^{37}Cl)^+$, 67), 128 ($M(^{35}Cl^{35}Cl)^+$, 100).

1,3-Dichloro-2-methoxymethoxypropane (191)[66]



Phosphorus pentoxide (2.57 g, 18.1 mmol) was added portionwise to a vigorously stirred solution of alcohol **190** (3.90 g, 30.2 mmol) and dimethoxymethane (6.15 mL, 69.5 mmol) in anhydrous chloroform (6.15 mL) at 45 °C. The reaction mixture was then stirred at RT for 18 h. The supernatant was decanted and washed with water (12 mL), 10% aq. $NaHCO_3$ (12 mL) and water (12 mL) sequentially. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil that was used in subsequent reactions without further purification (4.47 g, 85%). R_f 0.70 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2956w, 1442w, 1149m, 1105m, 1039s, 918m, 755m; δ_H (400 MHz, $CDCl_3$) 3.39 (3 H, s, C(5)H_3), 3.69 (4 H, d, *J* 5.0, C(1)H_2 and C(3)H_2), 3.95 (1 H, quin, *J* 5.0, C(2)H), 4.71 (2 H, s, C(4)H_2); δ_C (100 MHz, $CDCl_3$) 43.7 (C(1) and C(3)), 55.9 (C(5)), 76.6 (C(2)), 96.5 (C(4)).

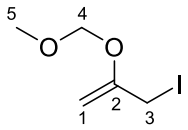
3-Chloro-2-methoxymethoxypropene (192)[66]



Potassium *tert*-butoxide (6.07 mL, 6.07 mmol, 1.0 M solution in THF) was added to a solution of ether **191** (1.00 g, 5.78 mmol) in anhydrous THF (10 mL) at –13 °C and the stirred solution was allowed to warm to RT over 12 h. Water (10 mL) was added and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over

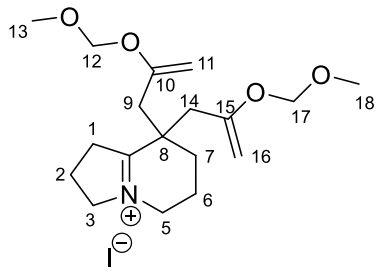
$MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil that was used in subsequent reactions without further purification (454 mg, 58%). R_f 0.50 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2927m, 1643m, 1289m, 1156s, 1035s; δ_H (400 MHz, C_6D_6) 3.09 (3 H, s, C(5)H_3), 3.60 (2 H, s, C(3)H_2), 4.09 (1 H, d, *J* 2.0, C(1)**H**H′), 4.29 (1 H, d, *J* 2.0, C(1)H**H′**), 4.63 (2 H, s, C(4)H_2); δ_C (100 MHz, C_6D_6) 44.7 (C(3)), 55.4 (C(5)), 88.9 (C(1)), 93.7 (C(4)), 156.1 (C(2)); *m/z* (EI^+) 138 ($M(^{37}Cl)^{+\cdot}$, 33%), 136 ($M(^{35}Cl)^{+\cdot}$, 100).

3-Iodo-2-methoxymethoxypropene (193)[67]



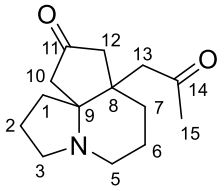
A solution of NaI (2.49 g, 16.6 mmol) in acetone (12.8 mL) was added to a solution of enol ether **192** (454 mg, 3.32 mmol) in acetone (3.2 mL) and the mixture was stirred at RT for 16 h. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5 petrol:ether) afforded the title compound as a colourless oil (515 mg, 68%). R_f 0.55 (9:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2936w, 1703s, 1414w, 1249m, 1150m, 1020s; δ_H (400 MHz, C_6D_6) 3.13 (3 H, s, C(5)H_3), 3.40 (2 H, s, C(3)H_2), 4.08 (1 H, d, *J* 2.0, C(1)**H**H′), 4.21 (1 H, d, *J* 2.0, C(1)H**H′**), 4.63 (2 H, s, C(4)H_2); δ_C (100 MHz, C_6D_6) 3.6 (C(3)), 55.7 (C(5)), 87.0 (C(1)), 93.5 (C(4)), 157.1 (C(2)); *m/z* (EI^+) 228 ($M^{+\cdot}$, 100%).

8,8-Bis[2-(methoxymethoxy)allyl]-2,3,5,6,7,8-hexahydro-1*H*-indolizin-4-ium iodide (195)



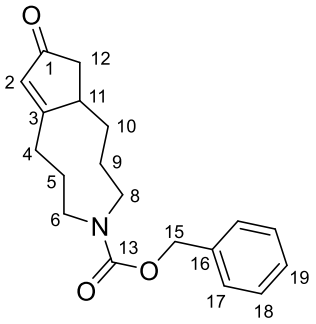
A solution of enamine **176** (40.0 mg, 0.325 mmol) in THF (0.7 mL) was added dropwise to a stirred solution of iodide **193** (74.0 mg, 0.325 mmol) in THF (0.3 mL) and the reaction mixture was stirred at RT for 6 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a brown oil (29.0 mg, 20%). R_f 0.25 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3445w, 2948w, 1639m, 1447w, 1153m, 1011s; δ_H (400 MHz, $CDCl_3$) 1.82−1.88 (2 H, m, C(7)H_2), 2.00−2.07 (2 H, m, C(6)H_2), 2.30 (2 H, quin, *J* 7.5, C(2)H_2), 2.44 (2 H, d, *J* 14.5, C(9)**H**H′ and C(14)**H**H′), 2.89 (2 H, d, *J* 14.5, C(9)H**H′** and C(14)H**H′**), 3.31−3.37 (2 H, m, C(1)H_2), 3.40 (6 H, s, C(13)H_3 and C(18)H_3), 3.75−3.83 (2 H, m, C(5)H_2), 4.19 (2 H, d, *J* 2.0, C(11)**H**H′ and C(16)**H**H′), 4.24 (2 H, d, *J* 2.0, C(11)H**H′** and C(16)H**H′**), 4.45 (2 H, t, *J* 7.5, C(3)H_2), 4.90 (2 H, d, *J* 12.0, C(12)**H**H′ and C(17)**H**H′), 4.92 (2 H, d, *J* 12.0, C(12)H**H′** and C(17)H**H′**); δ_C (100 MHz, $CDCl_3$) 18.3 (C(6)), 18.6 (C(2)), 25.6 (C(7)), 36.0 (C(1)), 41.2 (C(8)), 44.4 (C(9) and C(14)), 49.2 (C(5)), 57.1 (C(13) and C(18)), 62.0 (C(3)), 90.4 (C(11) and C(16)), 94.5 (C(12) and C(17)), 154.8 (C(10) and C(15)), 193.9 ($C=N^+$); *m/z* (ESI^+) 324 ($(M-I)^+$, 100%); *m/z* (ESI^-) 127 (I^-, 100%); HRMS (ESI^+): Found: 324.2164; $C_{18}H_{30}NO_4$ ($(M-I)^+$) requires: 324.2169.

7a-(2-Oxopropyl)octahydrocyclopenta[*h*]indolizin-9(1*H*)-one (196)



Water (1.5 μL, 64.3 μmol) was added to a solution of iminium salt **195** (29.0 mg, 64.3 μmol) in dry acetonitrile (0.5 mL) and the mixture was stirred under reflux at 80 °C for 16 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a pale yellow oil (5.00 mg, 33%). R_f 0.46 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2937m, 2797w, 1738s, 1713m, 1405m, 1360m, 1163m; δ_H (400 MHz, $CDCl_3$) 1.25 (1 H, td, *J* 14.0, 3.5, C(7)**H**H′), 1.40−1.50 (1 H, m, C(1)**H**H′), 1.52−1.60 (1 H, m, C(6)**H**H′), 1.61−1.95 (6 H, m, C(1)H**H′**, C(2)H_2, C(6)H**H′**, C(7)H**H′** and C(10)**H**H′), 2.16 (3 H, s, C(15)H_3), 2.25−2.41 (3 H, m, C(3)**H**H′, C(5)**H**H′ and C(12)**H**H′), 2.50 (1 H, d, *J* 16.5, C(13)**H**H′), 2.57 (1 H, d, *J* 18.0, C(10)H**H′**), 2.60 (1 H, d, *J* 18.5, C(12)H**H′**), 2.82 (1 H, d, *J* 11.0, C(5)H**H′**), 3.00 (1 H, t, *J* 8.0, C(3)H**H′**), 3.16 (1 H, d, *J* 16.5, C(13)H**H′**); δ_C (125 MHz, $CDCl_3$) 18.7 (C(2)), 21.8 (C(6)), 28.9 (C(7)), 31.3 (C(1)), 32.0 (C(15)), 36.6 (C(10)), 41.1 (C(8)), 44.7 (C(13)), 45.6 (C(5)), 50.9 (C(12)), 51.0 (C(3)), 69.4 (C(9)), 208.1 (C(14)), 216.6 (C(11)); *m/z* (ESI^+) 236 (MH^+, 100%); HRMS (ESI^+): Found: 236.1643; $C_{14}H_{22}NO_2$ (MH^+) requires: 236.1645.

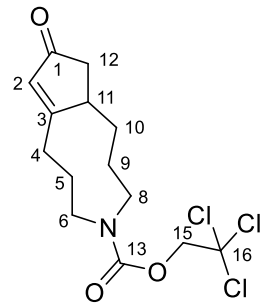
Benzyl-9-oxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (199)



Benzyl chloroformate (20.0 μL, 0.139 mmol) and K_2CO_3 (38.4 mg, 0.278 mmol) were added to a solution of amine **92** (5.00 mg, 0.0278 mmol) in benzene (0.3 mL) and the reaction mixture was stirred at RT for 5 h. Water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 99:1 $CHCl_3$:MeOH) afforded the *title compound* as a mixture of carbamate rotamers as a colourless viscous oil (8.30 mg, 95%). R_f 0.60 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2922w, 1684s, 1604w, 1418m, 1189m, 699m; δ_H (500 MHz, $CDCl_3$) 1.41−1.63 (4 H, m, 2 × C(10)H_2), 1.87−2.00 (5 H, m, C(5)**H**H′ and 2 × C(9)H_2), 2.01−2.12 (3 H, m, C(5)**H**H′ and 2 × C(12)**H**H′), 2.13−2.26 (2 H, m, 2 × C(5)H**H′**), 2.33−2.45 (2 H, m, 2 × C(4)**H**H′), 2.46−2.59 (3 H, m, C(4)H**H′** and 2 × C(12)H**H′**), 2.65−2.75 (1 H, m, C(4)H**H′**), 2.92−3.09 (4 H, m, C(6)**H**H′, C(8)**H**H′ and 2 × C(11)H), 3.19 (1 H, dt, *J* 14.0, 4.5, C(8)**H**H′), 3.24−3.39 (3 H, m, C(6)H_2 and C(8)H**H′**), 3.47 (1 H, dt, *J* 14.5, 3.5, C(6)H**H′**), 3.66 (1 H, ddd, *J* 13.5, 10.0, 4.0, C(8)H**H′**), 4.93 (1 H, d, *J* 12.0, C(15)**H**H′), 5.07 (1 H, d, *J* 12.0, C(15)**H**H′), 5.17 (1 H, d, *J* 12.0, C(15)H**H′**), 5.19 (1 H, d, *J* 12.0, C(15)H**H′**), 5.96 (1 H, s, C(2)H), 6.09 (1 H, s, C(2)H), 7.28−7.42 (10 H, m, 4 × C(17)H, 4 × C(18)H and 2 × C(19)H); δ_C (125 MHz, $CDCl_3$) 19.9/20.7 (C(10)), 26.0/26.8 (C(5)), 27.0 (C(9)), 27.7 (C(4)), 28.3 (C(9)), 29.6 (C(4)), 40.9/41.4 (C(12)), 43.0/43.1 (C(11)), 46.7/48.8 (C(8)), 50.3 (C(6)), 67.2/67.3 (C(15)), 128.0

(C(19)), 128.1 (C(17)), 128.5 (C(18)), 131.3/131.7 (C(2)), 136.6 (C(16)), 156.3/156.9 (C(13)), 184.2/184.6 (C(3)), 208.5 (C(1)); *m/z* (ESI^+) 336 (MNa^+, 100%), 314 (MH^+, 50); HRMS (ESI^+): Found: 336.1581; $C_{19}H_{23}NO_3Na$ (MNa^+) requires: 336.1570.

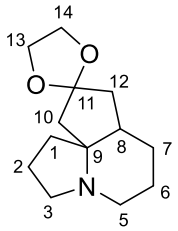
2,2,2-Trichloroethyl-9-oxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (200)



2,2,2-Trichloroethyl chloroformate (76.5 μL, 0.555 mmol) and K_2CO_3 (153 mg, 1.11 mmol) were added to a solution of amine **92** (20.0 mg, 0.111 mmol) in benzene (1.2 mL) and the reaction mixture was stirred at RT for 3 h. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless viscous oil (39.0 mg, 99%). R_f 0.30 (ether); ν_{max} (thin film)/cm^{-1} 2925w, 1710s, 1679s, 1605m, 1419m, 1189m, 715m; δ_H (500 MHz, toluene-d_8, 373 K) 1.14−1.25 (1 H, m, C(10)**H**H′), 1.26−1.41 (1 H, m, C(9)**H**H′), 1.49 (1 H, bs, C(10)H**H′**), 1.53−1.68 (2 H, m, C(5)**H**H′ and C(9)H**H′**), 1.79 (1 H, dd, *J* 18.5, 2.0, C(12)**H**H′), 1.87 (1 H, bs, C(5)H**H′**), 1.93−2.04 (1 H, m, C(4)**H**H′), 2.16 (1 H, dd, *J* 18.5, 7.0, C(12)H**H′**), 2.16−2.25 (1 H, m, C(4)H**H′**), 2.49 (1 H, bs, C(11)H), 2.77 (2 H, bs, C(6)**H**H′ and C(8)**H**H′), 3.06 (2 H, bs, C(6)H**H′** and C(8)H**H′**), 4.21−4.95 (2 H, m, C(15)H_2), 5.84 (1 H, s, C(2)H); δ_C (125 MHz, toluene-d_8, 373 K) 21.6 (C(10)), 26.7 (C(9)),

28.4 (C(4) and C(5)), 41.7 (C(12)), 43.4 (C(11)), 50.9 (C(6) and C(8)), 76.0 (C(15)), 96.8 (C(16)), 132.6 (C(2)), 154.9 (C(13)), 180.9 (C(3)), 205.2 (C(1)); *m/z* (EI^+) 359 ($M(^{37}Cl^{37}Cl^{37}Cl)^{+\cdot}$, 4%), 357 ($M(^{35}Cl^{37}Cl^{37}Cl)^{+\cdot}$, 33), 355 ($M(^{35}Cl^{35}Cl^{37}Cl)^{+\cdot}$, 100), 353 ($M(^{35}Cl^{35}Cl^{35}Cl)^{+\cdot}$, 100); HRMS ($EI^+$): Found: 353.0345; $C_{14}H_{18}NO_3Cl_3$ ($M(^{35}Cl^{35}Cl^{35}Cl)^{+\cdot}$) requires: 353.0347.

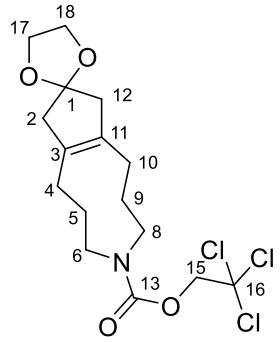
Octahydro-1*H*-spiro[cyclopenta[*h*]indolizine-9,2'-[1,3]dioxolane] (201)



p-TsOH·H_2O (34.9 mg, 0.183 mmol) was added to a solution of ketone **92** (30.0 mg, 0.167 mmol) and ethylene glycol (18.6 μL, 0.333 mmol) in benzene (2.7 mL) and the mixture was stirred under reflux for 16 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (23.0 mg, 62%). R_f 0.15 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2931s, 2788w, 1437w, 1343m, 1112s, 1066m; δ_H (500 MHz, CD_2Cl_2) 1.35−1.59 (5 H, m, C(6)H_2, C(7)H_2 and C(10)**H**H′), 1.60−1.87 (6 H, m, C(1)H_2, C(2)H_2, C(8)H and C(12)**H**H′), 2.02 (1 H, dd, *J* 14.0, 7.0, C(12)H**H′**), 2.17 (1 H, d, *J* 14.0, C(10)H**H′**), 2.51−2.62 (2 H, m, C(3)**H**H′ and C(5)**H**H′), 2.70 (1 H, dtd, *J* 12.5, 4.0, 1.0, C(5)H**H′**), 2.87 (1 H, td, *J* 9.0, 4.5, C(3)H**H′**), 3.74−3.88 (4 H, m, C(13)H_2 and C(14)H_2); δ_C (125 MHz, CD_2Cl_2) 20.3 (C(2)), 22.4 (C(6)), 27.0 (C(7)), 36.7 (C(1)), 38.4 (C(10)), 40.2 (C(8)), 41.9 (C(12)), 44.9 (C(5)), 50.6 (C(3)), 63.7 (C(13)),

63.9 (C(14)), 67.9 (C(9)), 115.9 (C(11)); *m/z* (ESI^+) 224 (MH^+, 100%); HRMS (ESI^+): Found: 224.1642; $C_{13}H_{22}NO_2$ (MH^+) requires: 224.1645.

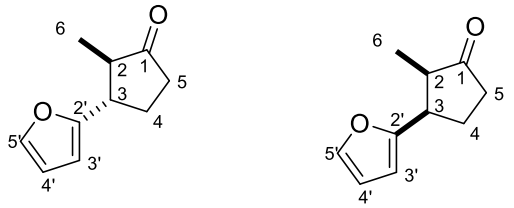
2,2,2-Trichloroethyl-2,3,6,7,8,10-hexahydro-1*H*-spiro[cyclopenta[*e*]azonine-9,2'-[1,3]dioxolane]-4(5*H*)-carboxylate (202)



2,2,2-Trichloroethyl chloroformate (27.7 μL, 0.202 mmol) and K_2CO_3 (27.9 mg, 0.202 mmol) were added to a solution of amine **201** (9.00 mg, 0.0403 mmol) in benzene (0.4 mL) and the reaction mixture was stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless viscous oil (10.0 mg, 62%). R_f 0.50 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2918w, 1715s, 1483m, 1312m, 1119s, 1018m; δ_H (500 MHz, CD_2Cl_2) 1.90 (2 H, quin, *J* 6.5, C(9)H_2), 1.95 (2 H, quin, *J* 6.5, C(5)H_2), 2.19 (2 H, t, *J* 6.5, C(10)H_2), 2.24 (2 H, t, *J* 6.5, C(4)H_2), 2.51 (2 H, s, C(12)H_2), 2.52 (2 H, s, C(2)H_2), 3.14 (2 H, t, *J* 6.5, C(8)H_2), 3.17 (2 H, t, *J* 6.5, C(6)H_2), 3.91 (4H, s, C(17)H_2 and C(18)H_2), 4.76 (2 H, s, C(15)H_2); δ_C (125 MHz, CD_2Cl_2) 23.1 (C(4)), 23.2 (C(10)), 23.6 (C(9)), 24.8 (C(5)), 45.2 (C(12)), 45.3 (C(2)), 52.0 (C(6)), 53.1 (C(8)), 64.1 (C(17) and C(18)), 74.7 (C(15)), 96.0 (C(16)), 115.7 (C(1)), 133.1 (C(11)), 133.2 (C(3)), 154.8 (C(13)); *m/z* (ESI^+) 426 (M($^{37}Cl^{37}Cl^{37}Cl$)Na^+, 4%), 424 (M($^{35}Cl^{37}Cl^{37}Cl$)Na^+, 33), 422

($M(^{35}Cl^{35}Cl^{37}Cl)Na^+$, 100), 420 ($M(^{35}Cl^{35}Cl^{35}Cl)Na^+$, 100); HRMS ($ESI^+$): Found: 420.0496; $C_{16}H_{22}NNaO_4Cl_3$ ($M(^{35}Cl^{35}Cl^{35}Cl)Na^+$) requires: 420.0507.

3-Furan-2-yl-2-methylcyclopentanone (*trans* 203, *cis* 204)[71,72]



trans **203** *cis* **204**

To a cooled solution of furan (1.51 mL, 20.8 mmol) in THF (21 mL) at –30 °C was added *n*-butyllithium (8.78 mL, 20.8 mmol, 2.37 M solution in hexanes) and the solution was stirred at 0 °C for 1 h. The mixture was then added to a suspension of CuCN (0.932 g, 10.4 mmol) in THF (2.6 mL) at –30 °C and the mixture was allowed to warm to 10 °C over 1 h. The solution was cooled to –78 °C and 2-methylcyclopent-2-en-1-one (0.511 mL, 5.20 mmol) and $BF_3{\cdot}OEt_2$ (1.28 mL, 10.4 mmol) were added. The mixture was allowed to warm to RT and stirred at 35 °C for 16 h before it was poured into a solution of sat. aq. NH_4Cl/c. aq. NH_3 (9:1, 65 mL) and ether (65 mL). The mixture was stirred at RT for 1 h and the ether layer was separated, washed with brine (65 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the title compound as a mixture of *trans* **203** and *cis* **204** isomers (*trans*:*cis*, 1:1) as a pale yellow oil (0.410 g, 48%).

Trans isomer **203**:

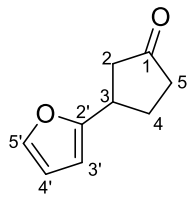
R_f 0.52 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2970w, 1739s, 1507w, 1456w, 1150m, 1011m, 736m; δ_H (500 MHz, C_6D_6) 1.05 (3 H, d, *J* 7.0, C(6)H_3), 1.44−1.55 (1 H, m, C(4)**H**H′), 1.60−1.78 (2 H, m, C(4)H**H′** and C(5)**H**H′), 1.89−2.02 (2 H, m, C(2)H and

C(5)H**H′**), 2.39 (1 H, td, *J* 11.5, 6.0, C(3)H), 5.78 (1 H, d, *J* 3.0, C(3′)H), 6.09 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 7.07 (1 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (125 MHz, C_6D_6) 12.7 (C(6)), 26.4 (C(4)), 36.5 (C(5)), 43.4 (C(3)), 48.8 (C(2)), 104.6 (C(3′)), 110.0 (C(4′)), 141.2 (C(5′)), 156.5 (C(2′)), 215.7 (C(1)); *m/z* (ESI^+) 187 (MNa^+, 100%), 165 (MH^+, 10).

Cis isomer **204**:

R_f 0.48 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2970w, 1739s, 1507w, 1456w, 1150m, 1011m, 736m; δ_H (500 MHz, C_6D_6) 0.83 (3 H, d, *J* 7.5, C(6)H_3), 1.50−1.60 (1 H, m, C(4)**H**H′), 1.68 (1 H, ddt, *J* 13.0, 9.0, 4.5, C(4)H**H′**), 1.88 (1 H, dddd, *J* 19.0, 9.5, 5.0, 1.0, C(5)**H**H′), 1.96−2.04 (1 H, m, C(2)H), 2.22 (1 H, dt, *J* 19.0, 9.0, C(5)H**H′**), 3.00 (1 H, td, *J* 7.5, 4.5, C(3)H), 5.71 (1 H, d, *J* 3.0, C(3′)H), 6.00 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 6.96 (1 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (125 MHz, C_6D_6) 10.4 (C(6)), 25.2 (C(4)), 35.4 (C(5)), 39.5 (C(3)), 47.2 (C(2)), 105.9 (C(3′)), 109.8 (C(4′)), 141.3 (C(5′)), 155.9 (C(2′)), 216.5 (C(1)); *m/z* (ESI^+) 187 (MNa^+, 100%), 165 (MH^+, 10).

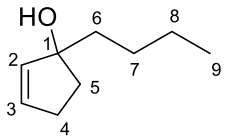
3-Furan-2-ylcyclopentanone (205)[73,74]



Iodotrimethylsilane (0.953 mL, 6.70 mmol) was added to a solution of 2-cyclopentenone (0.510 mL, 6.09 mmol) in dichloromethane (40 mL) at –78 °C and the solution was stirred for 1 h. Furan (0.443 mL, 6.09 mmol) was added, followed by 2-methyl-2-butene (1.29 mL, 12.2 mmol) and the reaction mixture was stirred at –78 °C for 5 h. Dilute HCl (40 mL) was added and the mixture was extracted with dichloromethane (3 × 40 mL). The combined

organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the title compound as a colourless oil (0.210 g, 23%). R_f 0.40 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2970w, 1741s, 1507w, 1406w, 1151m, 1012m, 735m; δ_H (500 MHz, C_6D_6) 1.50−1.58 (1 H, m, C(4)**H**H′), 1.60−1.73 (2 H, m, C(4)H**H′** and C(5)**H**H′), 1.86−1.95 (1 H, m, C(5)H**H′**), 2.03 (1 H, dd, *J* 18.0, 9.0, C(2)**H**H′), 2.12 (1 H, dd, *J* 18.0, 8.0, C(2)H**H′**), 2.78−2.89 (1 H, m, C(3)H), 5.70 (1 H, d, *J* 3.0, C(3′)H), 6.03 (1 H, dd, *J* 3.0, 2.0, C(4′)H), 7.03 (1 H, dd, *J* 2.0, 1.0, C(5′)H); δ_C (125 MHz, C_6D_6) 28.2 (C(4)), 35.1 (C(3)), 37.0 (C(5)), 42.8 (C(2)), 104.2 (C(3′)), 110.0 (C(4′)), 141.2 (C(5′)), 156.9 (C(2′)), 214.3 (C(1)); *m/z* (ESI^+) 173 (MNa^+, 20%).

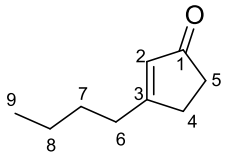
1-Butylcyclopent-2-enol (206)[75]



2-Cyclopentenone (2.50 mL, 29.8 mmol) was added dropwise to a solution of *n*-butyllithium (25.6 mL, 53.7 mmol, 2.1 M solution in hexanes) in THF (12.8 mL) at 0 °C and the mixture was stirred at RT for 5 h. The reaction mixture was poured into crushed ice (43.0 g) and extracted with ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless oil (2.05 g, 49%). R_f 0.40 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3349br, 2956s, 2930s, 1456m, 1174m, 1027s, 749s; δ_H (400 MHz, C_6D_6) 0.89 (3 H, t, *J* 7.0, C(9)H_3), 1.21−1.42 (4 H, m, C(7)H_2 and C(8)H_2), 1.50−1.62 (2 H, m, C(6)H_2), 1.67−1.76 (1 H, m, C(5)**H**H′), 1.79−1.88 (1 H, m, C(5)H**H′**), 1.98−2.09 (1 H, m, C(4)**H**H′), 2.18−2.29 (1 H, m, C(4)H**H′**), 5.57−5.65 (2 H, m, C(2)H and

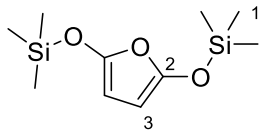
C(3)H); δ_C (100 MHz, C_6D_6) 14.0 (C(9)), 23.3 (C(8)), 26.6 (C(7)), 31.0 (C(4)), 37.7 (C(5)), 40.7 (C(6)), 85.3 (C(1)), 132.1 (C(2)), 137.2 (C(3)); *m/z* (ESI^+) 163 (MNa^+, 40%), 123 ($[M–OH]^+$, 100).

3-Butylcyclopent-2-enone (207)[75]



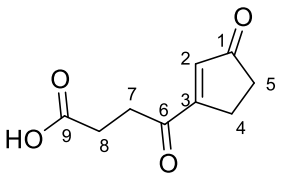
Alcohol **206** (1.50 g, 10.7 mmol) was dissolved in THF (30 mL) and cooled to –5 °C. A solution of CrO_3 (1.22 g, 12.2 mmol) in 5% w/v H_2SO_4 (12.2 mL) was added dropwise to the mixture over 1 h at 0 °C and stirred for 15 min. The reaction mixture was poured into water (15 mL) and extracted with ether (3 × 40 mL). The combined organic layers were washed with 5% $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless liquid (0.721 g, 49%). R_f 0.20 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2958w, 1707s, 1674m, 1615m, 1438w, 1180w, 841w; δ_H (500 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 7.5, C(9)H_3), 1.36 (2 H, sex, *J* 7.5, C(8)H_2), 1.56 (2 H, quin, *J* 7.5, C(7)H_2), 2.34−2.44 (4 H, m, C(5)H_2 and C(6)H_2), 2.54−2.59 (2 H, m, C(4)H_2), 5.93 (1 H, t, *J* 1.5, C(2)H); δ_C (125 MHz, $CDCl_3$) 13.8 (C(9)), 22.4 (C(8)), 29.2 (C(7)), 31.5 (C(4)), 33.2 (C(6)), 35.3 (C(5)), 129.4 (C(2)), 183.3 (C(3)), 210.3 (C(1)); *m/z* (ESI^+) 161 (MNa^+, 80%), 139 (MH^+, 80).

2,5-Bistrimethylsilanyloxyfuran (208)[78]



Triethylamine (4.42 mL, 31.7 mmol) and zinc chloride (100 mg, 0.734 mmol) were stirred vigorously under N_2 for 1 h. A solution of succinic anhydride (1.00 g, 9.99 mmol) in acetonitrile (8 mL) was then added to the mixture and stirred at RT for 5 min. Chlorotrimethylsilane (3.60 mL, 28.4 mmol) was then added to the mixture and stirred at RT for 16 h. Ether (40 mL) was added and the mixture was filtered and concentrated *in vacuo*. The residue was then diluted with hexane (60 mL), cooled to precipitate solids, filtered and concentrated *in vacuo* to afford the title compound as a yellow oil (2.12 g, 87%). ν_{max} (thin film)/cm^{-1} 2961w, 1781m, 1693m, 1419m, 1201m, 899s, 843s; δ_H (400 MHz, C_6D_6) 0.15 (18 H, s, C(1)H_3 × 6), 5.04 (2 H, s, C(3)H × 2); δ_C (100 MHz, C_6D_6) 0.0 (C(1)), 84.8 (C(3)), 148.4 (C(2)); *m/z* (ESI^+) 267 (MNa^+, 40%).

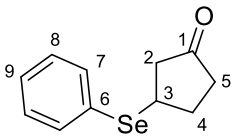
4-Oxo-4-(3-oxocyclopent-1-enyl)butyric acid (209)



Titanium(IV) chloride (66.8 μL, 0.609 mmol) was added to a solution of 2-cyclopentenone (50.0 mg, 0.609 mmol) and furan **208** (0.149 g, 0.609 mmol) in DCM (0.5 mL) at –78 °C and the mixture was stirred at –78 °C for 3 h before it was allowed to warm to RT overnight. Sat. aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound*

as a pale yellow oil (15.0 mg, 14%). R_f 0.25 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2929w, 1711s, 1684s, 1401w, 1149s, 826w; δ_H (400 MHz, $CDCl_3$) 2.46−2.59 (2 H, m, C(5)H_2), 2.76 (2 H, t, *J* 6.5, C(8)H_2), 2.80−2.85 (2 H, m, C(4)H_2), 3.11 (2 H, t, *J* 6.5, C(7)H_2), 6.70 (1 H, t, *J* 2.0, C(2)H); δ_C (100 MHz, $CDCl_3$) 26.5 (C(4)), 27.4 (C(8)), 34.6 (C(7)), 35.2 (C(5)), 136.6 (C(2)), 168.4 (C(3)), 177.3 (C(9)), 197.3 (C(6)), 210.1 (C(1)); *m/z* (ESI^+) 205 (MNa^+, 60%); HRMS (ESI^+): Found: 205.0474; $C_9H_{10}NaO_4$ (MNa^+) requires: 205.0471.

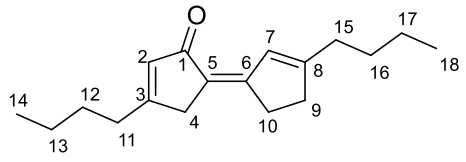
3-Phenylselanylcyclopentanone (210)[81]



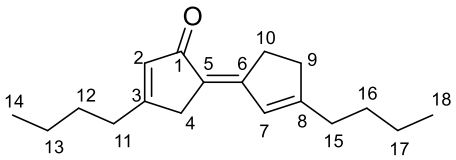
Sodium borohydride (59.9 mg, 1.58 mmol) was added portionwise to a mixture of diphenyldiselenide (0.247 g, 0.792 mmol) in ethanol (3 mL) at RT. The solution was cooled to 0 °C and glacial acetic acid (0.160 mL, 2.80 mmol) was added. A solution of 2-cyclopentenone (100 mg, 1.22 mmol) in ethanol (0.7 mL) was then added and the mixture was stirred at 0 °C for 2 h. The mixture was poured into water (24 mL) and extracted with ether (3 × 24 mL). The combined organic layers were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the title compound as a yellow liquid (0.203 g, 70%). R_f 0.35 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2952w, 1741s, 1477w, 1400w, 1153m, 738m; δ_H (500 MHz, $CDCl_3$) 2.01−2.10 (1 H, m, C(4)**H**H′), 2.16−2.25 (1 H, m, C(5)**H**H′), 2.29 (1 H, dd, *J* 19.0, 6.5, C(2)**H**H′), 2.34−2.41 (1 H, m, C(4)H**H′**), 2.41−2.50 (1 H, m, C(5)H**H′**), 2.64 (1 H, dd, *J* 19.0, 7.5, C(2)H**H′**), 3.87−3.94 (1 H, m, C(3)H),

7.28−7.35 (3 H, m, C(8)H × 2 and C(9)H), 7.53−7.58 (2 H, m, C(7)H × 2); δ_C (125 MHz, $CDCl_3$) 30.1 (C(4)), 37.3 (C(3)), 37.4 (C(5)), 45.7 (C(2)), 128.1 (C(9)), 128.3 (C(6)), 129.2 (C(8)), 135.0 (C(7)), 216.8 (C(1)); *m/z* (ESI^+) 263 (MNa^+, 50%).

4,3'-Dibutylbicyclopentylidene-3,2'-dien-2-one (211) and **4,3'-Dibutylbicyclopentylidene-3,2'-dien-2-one (212)**



211



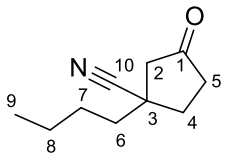
212

Vinylmagnesium bromide (0.724 mL, 0.724 mmol, 1 M in THF) was added dropwise to a solution of $CuBr{\cdot}SMe_2$ (74.4 mg, 0.362 mmol) in THF (1.1 mL) at –40 °C and stirred at –40 °C for 1.5 h. The mixture was then cooled to –78 °C and $BF_3{\cdot}OEt_2$ (44.5 μL, 0.362 mmol) was added dropwise. After 10 min, a solution of enone **207** (25.0 mg, 0.181 mmol) in THF (0.4 mL) was added dropwise and the mixture was stirred at –78 °C for 5 h before it was allowed to warm to RT. Sat. aq. NH_4Cl (2.5 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded dienone **211** as a yellow oil (7.20 mg, 31%). R_f 0.45 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2955m, 2926m, 1680s, 1620s, 1467w, 1201w; δ_H (500 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 7.5, C(18)H_3), 0.93 (3 H, t, *J* 7.5, C(14)H_3), 1.30−1.42 (4 H, m, C(13)H_2 and C(17)H_2), 1.50−1.61 (4 H, m, C(12)H_2 and C(16)H_2), 2.32 (2 H, t, *J* 7.5, C(15)H_2), 2.41 (2 H, t, *J* 7.5, C(11)H_2), 2.45−2.50 (2 H, m, C(9)H_2), 2.57−2.62 (2 H, m, C(10)H_2), 3.02 (2 H, s, C(4)H_2), 6.05 (1 H, t, *J* 1.5, C(2)H), 7.39 (1 H, t, *J* 1.5, C(7)H); δ_C (125 MHz, $CDCl_3$) 13.9 (C(14) and C(18)), 22.5 (C(17)), 22.6 (C(13)), 29.5 (C(16)), 29.9 (C(12)), 30.5 (C(10)), 32.2

(C(15)), 32.6 (C(11)), 33.6 (C(9)), 37.0 (C(4)), 121.7 (C(5)), 126.3 (C(7)), 132.3 (C(2)), 155.7 (C(8)), 165.7 (C(6)), 171.5 (C(3)), 196.3 (C(1)); *m/z* (ESI^+) 281 (MNa^+, 20%), 259 (MH^+, 100); HRMS (ESI^+): Found: 259.2067; $C_{18}H_{27}O$ (MH^+) requires: 259.2056.

Also obtained was dienone **212** as a yellow oil (7.00 mg, 30%). R_f 0.25 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2957m, 2929m, 1678s, 1628m, 1599s, 1280m, 1185w; δ_H (500 MHz, $CDCl_3$) 0.93 (6 H, t, *J* 7.5, C(14)H_3 and C(18)H_3), 1.31−1.42 (4 H, m, C(13)H_2 and C(17)H_2), 1.49−1.63 (4 H, m, C(12)H_2 and C(16)H_2), 2.32 (2 H, t, *J* 7.5, C(15)H_2), 2.41 (2 H, t, *J* 7.5, C(11)H_2), 2.52−2.61 (2 H, m, C(9)H_2), 3.09−3.13 (2 H, m, C(10)H_2), 3.13 (2 H, s, C(4)H_2), 6.03 (1 H, t, *J* 1.5, C(7)H), 6.08 (1 H, t, *J* 1.5, C(2)H); δ_C (125 MHz, $CDCl_3$) 13.9 (C(14) and C(18)), 22.5 (C(17)), 22.6 (C(13)), 29.5 (C(16)), 29.8 (C(10) and C(12)), 32.2 (C(15)), 32.5 (C(11)), 35.8 (C(9)), 36.6 (C(4)), 121.5 (C(5)), 126.8 (C(7)), 132.7 (C(2)), 156.0 (C(8)), 166.7 (C(6)), 171.6 (C(3)), 198.1 (C(1)); *m/z* (ESI^+) 281 (MNa^+, 20%), 259 (MH^+, 100); HRMS (ESI^+): Found: 259.2067; $C_{18}H_{27}O$ (MH^+) requires: 259.2056.

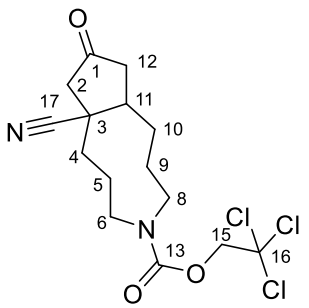
1-Butyl-3-oxocyclopentanecarbonitrile (213)



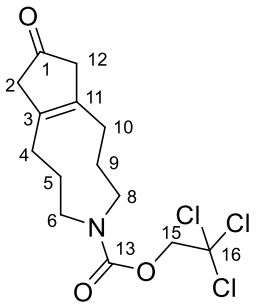
Trimethylsilyl cyanide (39.8 μL, 0.318 mmol) was added to a solution of triethylaluminium (0.289 mL, 0.289 mmol, 1 M in heptanes) in THF (0.4 mL). A solution of enone **207** (20.0 mg, 0.145 mmol) in THF (0.2 mL) was then added and the mixture was stirred under reflux for 5 h. Sat. aq. NH_4Cl (2.5 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title*

compound as a pale yellow oil (16.0 mg, 67%). R_f 0.50 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2935m, 2214w, 1749s, 1460w, 1406w, 1161m; δ_H (500 MHz, $CDCl_3$) 0.95 (3 H, t, *J* 7.5, C(9)H_3), 1.34−1.45 (2 H, m, C(8)H_2), 1.46−1.62 (2 H, m, C(7)H_2), 1.66−1.77 (2 H, m, C(6)H_2), 1.97−2.05 (1 H, m, C(4)**H**H′), 2.24 (1 H, d, *J* 18.5, C(2)**H**H′), 2.35−2.45 (1 H, m, C(5)**H**H′), 2.46−2.57 (2 H, m, C(4)H**H′** and C(5)H**H′**), 2.73 (1 H, d, *J* 18.5, C(2)H**H′**); δ_C (125 MHz, $CDCl_3$) 13.8 (C(9)), 22.6 (C(8)), 27.9 (C(7)), 33.8 (C(4)), 36.5 (C(5)), 38.1 (C(6)), 40.4 (C(3)), 48.7 (C(2)), 123.1 (C(10)), 213.1 (C(1)); *m/z* (ESI$^+$) 188 (MNa$^+$, 50%); HRMS (ESI$^+$): Found: 188.1041; $C_{10}H_{15}NNaO$ (MNa$^+$) requires: 188.1046.

2,2,2-Trichloroethyl-7a-cyano-9-oxodecahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (215) and **2,2,2-Trichloroethyl-9-oxo-2,3,5,6,7,8,9,10-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (216)**



215



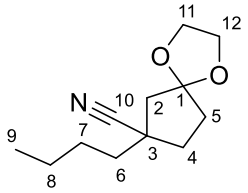
216

Trimethylsilyl cyanide (0.120 mL, 0.961 mmol) was added to a solution of triethylaluminium (0.874 mL, 0.874 mmol, 1 M in heptanes) in THF (2.4 mL). A solution of enone **200** (155 mg, 0.437 mmol) in THF (1.2 mL) was then added and the mixture was stirred under reflux for 5 h. Sat. aq. NH_4Cl (15 mL) was added and the mixture was extracted with ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude silyl enol ether was dissolved in THF (2 mL) and dil. HCl (1 mL) was

added. The mixture was stirred at RT for 10 mins and extracted with ether (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded *nitrile* **215** as a colourless viscous oil (105 mg, 63%). R_f 0.50 (ether); ν_{max} (thin film)/cm^{-1} 2950w, 2215w, 1751m, 1710s, 1422m, 1128m, 714m; δ_H (500 MHz, toluene-d_8, 363 K) 1.17−1.54 (5 H, m, C(5)H_2, C(9)H_2 and C(10)**H**H′), 1.56−1.87 (5 H, m, C(2)**H**H′, C(4)H_2, C(10)H**H′**, C(12)**H**H′), 1.90−2.18 (3 H, m, C(2)H**H′**, C(11)H and C(12)H**H′**), 2.22−2.58 (2 H, m, C(6)**H**H′ and C(8)**H**H′), 3.26−3.84 (2 H, m, C(6)H**H′** and C(8)H**H′**), 3.95−5.10 (2 H, m, C(15)H_2); δ_C (125 MHz, toluene-d_8, 363 K) 22.1 (C(9)), 25.3 (C(5)), 30.6 (C(10)), 34.8 (C(4)), 40.8 (C(11)), 44.4 (C(3)), 45.8 (C(12)), 49.6 (C(2), C(6) and C(8)), 74.8 (C(15)), 96.0 (C(16)), 121.0 (C(17)), 153.9 (C(13)), 207.5 (C(1)); *m/z* (ESI^+) 409 (M($^{37}Cl^{37}Cl^{37}Cl$)Na^+, 4%), 407 (M($^{35}Cl^{37}Cl^{37}Cl$)Na^+, 33), 405 (M($^{35}Cl^{35}Cl^{37}Cl$)Na^+, 100), 403 (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+, 100); HRMS (ESI^+): Found: 403.0366; $C_{15}H_{19}N_2NaO_3Cl_3$ (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+) requires: 403.0353.

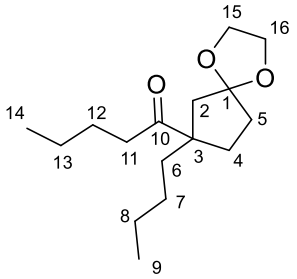
Also obtained was *ketone* **216** as a colourless viscous oil (6.0 mg, 4%). R_f 0.75 (ether); ν_{max} (thin film)/cm^{-1} 2920w, 1750m, 1715s, 1482w, 1313w, 1223m, 1116m; δ_H (500 MHz, C_6D_6) 1.63 (2 H, quin, *J* 6.5, C(9)H_2), 1.70 (2 H, quin, *J* 6.5, C(5)H_2), 1.94 (2 H, t, *J* 6.5, C(4)H_2), 2.00 (2 H, t, *J* 6.5, C(10)H_2), 2.43 (2 H, s, C(12)H_2), 2.45 (2 H, s, C(2)H_2), 2.63 (2 H, t, *J* 6.5, C(8)H_2), 2.69 (2 H, t, *J* 6.5, C(6)H_2), 4.60 (2 H, s, C(15)H_2); δ_C (125 MHz, C_6D_6) 23.2 (C(4), C(5) and C(10)), 24.4 (C(9)), 44.9 (C(12)), 45.0 (C(2)), 51.5 (C(8)), 53.0 (C(6)), 74.5 (C(15)), 96.2 (C(16)), 133.2 (C(11)), 133.5 (C(3)), 154.2 (C(13)), 212.8 (C(1)); *m/z* (ESI^+) 382 (M($^{37}Cl^{37}Cl^{37}Cl$)Na^+, 4%), 380 (M($^{35}Cl^{37}Cl^{37}Cl$)Na^+, 33), 378 (M($^{35}Cl^{35}Cl^{37}Cl$)Na^+, 100), 376 (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+, 100); HRMS (ESI^+): Found: 353.0345; $C_{14}H_{18}NO_3Cl_3$ (M($^{35}Cl^{35}Cl^{35}Cl$)$^+$) requires: 353.0352.

7-Butyl-1,4-dioxaspiro[4.4]nonane-7-carbonitrile (217)



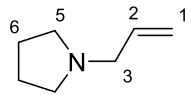
p-TsOH·H_2O (2.0 mg, 9.68 μmol) was added to a solution of nitrile **213** (16.0 mg, 0.0968 mmol) and ethylene glycol (6.0 μL, 0.107 mmol) in benzene (0.5 mL) and the mixture was stirred under reflux for 2 h. Sat. aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a pale yellow oil (15.0 mg, 85%). R_f 0.25 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2959m, 2875m, 2232w, 1459w, 1338m, 1109m, 1036m; δ_H (500 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 7.5, C(9)H_3), 1.35 (2 H, sex, *J* 7.5, C(8)H_2), 1.42−1.55 (2 H, m, C(7)H_2), 1.57−1.68 (2 H, m, C(6)H_2), 1.72−1.83 (1 H, m, C(5)**H**H′), 1.89 (1 H, d, *J* 14.5, C(2)**H**H′), 1.91−1.98 (1 H, m, C(4)**H**H′), 2.02−2.10 (1 H, m, C(4)H**H′**), 2.18−2.26 (1 H, m, C(5)H**H′**), 2.37 (1 H, d, *J* 14.5, C(2)H**H′**), 3.83−3.97 (4 H, m, C(11)H_2 and C(12)H_2); δ_C (125 MHz, $CDCl_3$) 13.9 (C(9)), 22.6 (C(8)), 28.0 (C(7)), 35.3 (C(4)), 35.6 (C(5)), 38.9 (C(6)), 40.6 (C(3)), 47.3 (C(2)), 64.5 (C(12)), 64.6 (C(11)), 116.2 (C(1)), 124.8 (C(10)); *m/z* (ESI^+) 232 (MNa^+, 100%), 210 (MH^+, 50); HRMS (ESI^+): Found: 232.1310; $C_{12}H_{19}NNaO_2$ (MNa^+) requires: 232.1308.

1-(7-Butyl-1,4-dioxaspiro[4.4]non-7-yl)pentan-1-one (218)



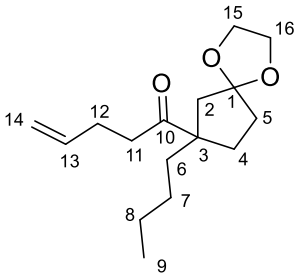
n-Butyllithium (11.5 μL, 0.0287 mmol, 2.5 M in hexanes) was added to a solution of nitrile **217** (5.00 mg, 0.0239 mmol) in THF (0.3 mL) at 0 °C and the mixture was stirred at RT for 4 h. Sat. aq. NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the *title compound* as a colourless oil (4.10 mg, 73%). R_f 0.45 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2957m, 2932m, 1703s, 1465m, 1336m, 1109m; δ_H (500 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7.5, C(9)H_3), 0.91 (3 H, t, *J* 7.5, C(14)H_3), 0.98−1.12 (2 H, m, C(7)H_2), 1.19−1.34 (4 H, m, C(8)H_2 and C(13)H_2), 1.52−1.60 (3 H, m, C(4)**H**H′ and C(12)H_2), 1.63−1.70 (2 H, m, C(6)H_2), 1.73 (1 H, d, *J* 14.5, C(2)**H**H′), 1.71−1.78 (1 H, m, C(5)**H**H′), 1.81−1.89 (1 H, m, C(5)H**H′**), 2.16−2.24 (1 H, m, C(4)H**H′**), 2.40 (1 H, d, *J* 14.5, C(2)H**H′**), 2.43 (2 H, t, *J* 7.5, C(11)H_2), 3.84−3.93 (4 H, m, C(15)H_2 and C(16)H_2); δ_C (125 MHz, $CDCl_3$) 13.9 (C(9) and C(14)), 22.5 (C(13)), 23.1 (C(8)), 26.2 (C(12)), 27.5 (C(7)), 31.8 (C(4)), 35.1 (C(5)), 36.9 (C(11)), 38.8 (C(6)), 43.5 (C(2)), 57.7 (C(3)), 64.2 (C(16)), 64.3 (C(15)), 117.0 (C(1)), 213.2 (C(10)); *m/z* (ESI^+) 291 (MNa^+, 80%), 269 (MH^+, 50); HRMS (ESI^+): Found: 291.1933; $C_{16}H_{28}NaO_3$ (MNa^+) requires: 291.1931.

1-Allyl-pyrrolidine (219)[88]



A solution of allyl bromide (6.00 mL, 69.3 mmol) in ether (20 mL) was added dropwise over 1 h to a solution of pyrrolidine (5.96 mL, 71.4 mmol) in ether (20 mL) at 0 °C and the solution was allowed to warm to RT overnight. The mixture was washed with 3 M KOH solution (3 × 25 mL) and extracted with DCM (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by fractional distillation (120 °C, atm) afforded the title compound as a colourless oil (2.54 g, 33%). ν_{max} (thin film)/cm^{-1} 2966m, 2773m, 1644w, 1419w, 1347m, 1145m, 915s; δ_H (400 MHz, $CDCl_3$) 1.70−1.86 (4 H, m, C(6)H_2 × 2), 2.38−2.57 (4 H, m, C(5)H_2 × 2), 3.09 (2 H, d, *J* 6.5, C(3)H_2), 5.08 (1 H, dt, *J* 10.0, 1.0, C(1)**H**H′), 5.18 (1 H, dt, *J* 17.0, 1.0, C(1)H**H′**), 5.92 (1 H, ddt, *J* 17.0, 10.0, 6.5, C(2)H); δ_C (100 MHz, $CDCl_3$) 23.5 (C(6)), 54.0 (C(5)), 59.3 (C(3)), 116.6 (C(1)), 136.3 (C(2)); *m/z* (ESI^+) 112 (MH^+, 100%).

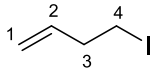
1-(7-Butyl-1,4-dioxaspiro[4.4]non-7-yl)pent-4-en-1-one (221)



t-Butyllithium (71.5 μL, 0.115 mmol, 1.6 M in pentanes) was added dropwise to a solution of iodide **222** (10.4 mg, 0.0573 mmol) in ether (0.57 mL) at –78 °C and the mixture was stirred at –78 °C for 1 h. A solution of nitrile **217** (10.0 mg, 0.0478 mmol) in ether (0.23 mL) was

then added dropwise and the mixture was stirred at –78 °C for 2 h before it was allowed to warm to RT. Sat. aq. NH_4Cl (2 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (2.00 mg, 16%). R_f 0.45 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2958m, 2932m, 1746m, 1704s, 1460w, 1337m, 1110m; δ_H (500 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7.5, C(9)H_3), 0.99−1.14 (2 H, m, C(7)H_2), 1.22−1.31 (2 H, m, C(8)H_2), 1.54−1.60 (1 H, m, C(4)**H**H′), 1.64−1.71 (2 H, m, C(6)H_2), 1.74 (1 H, d, *J* 14.0, C(2)**H**H′), 1.72−1.78 (1 H, m, C(5)**H**H′), 1.82−1.90 (1 H, m, C(5)H**H′**), 2.18−2.26 (1 H, m, C(4)H**H′**), 2.31−2.37 (2 H, m, C(12)H_2), 2.41 (1 H, d, *J* 14.0, C(2)H**H′**), 2.54 (2 H, t, *J* 7.0, C(11)H_2), 3.84−3.92 (4 H, m, C(15)H_2 and C(16)H_2), 4.97 (1 H, dq, *J* 10.0, 1.5, C(14)**H**H′), 5.05 (1 H, dq, *J* 17.0, 1.5, C(14)H**H′**), 5.81 (1 H, ddt, *J* 17.0, 10.0, 6.5, C(13)H); δ_C (125 MHz, $CDCl_3$) 13.9 (C(9)), 23.1 (C(8)), 27.5 (C(7)), 28.2 (C(12)), 31.8 (C(4)), 35.1 (C(5)), 36.6 (C(11)), 38.8 (C(6)), 43.5 (C(2)), 57.6 (C(3)), 64.2 (C(16)), 64.3 (C(15)), 115.2 (C(14)), 117.0 (C(1)), 137.6 (C(13)), 212.2 (C(10)); *m/z* (ESI^+) 289 (MNa^+, 100%), 267 (MH^+, 15); HRMS (ESI^+): Found: 289.1781; $C_{16}H_{26}NaO_3$ (MNa^+) requires: 289.1774.

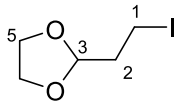
4-Iodobut-1-ene (222)[87]



4-Bromobut-1-ene (2.00 mL, 19.7 mmol) was added to a solution of sodium iodide (5.91 g, 39.4 mmol) in acetone (32 mL) and the mixture was stirred under reflux for 1 h. Water (20 mL) was added and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with sat. aq. Na_2SO_3 (50 mL) and brine (50 mL), dried over Na_2SO_4,

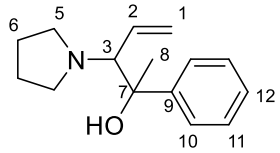
filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, pentane) afforded the title compound as a colourless liquid (1.10 g, 31%). R_f 0.50 (pentane); ν_{max} (thin film)/cm^{-1} 2956w, 1639w, 1425w, 1247m, 1169m, 991m, 917s; δ_H (400 MHz, C_6D_6) 2.13 (2 H, q, *J* 7.0, C(3)H_2), 2.60 (2 H, t, *J* 7.0, C(4)H_2), 4.82 (1 H, d, *J* 17.0, C(1)**H**H′), 4.90 (1 H, d, *J* 10.0, C(1)H**H′**), 5.40 (1 H, ddt, *J* 17.0, 10.0, 7.0, C(2)H); δ_C (100 MHz, C_6D_6) 4.0 (C(4)), 37.4 (C(3)), 116.4 (C(1)), 136.7 (C(2)); *m/z* (ESI$^+$) 183 (MH$^+$, 40%).

2-(2-Iodoethyl)-[1,3]dioxolane (224)[90]



Chlorotrimethylsilane (3.05 mL, 24.0 mmol) was rapidly added to a solution of sodium iodide (3.60 g, 24.0 mmol) and acrolein (1.34 mL, 20.0 mmol) in acetonitrile (50 mL) and the mixture was stirred at RT for 5 min. Ethylene glycol (1.34 mL, 24.0 mmol) was then rapidly added and the mixture was stirred for a further 5 min. The mixture was poured into 5% $NaHCO_3$ (20 mL) and pentane (60 mL) and the aqueous layer was removed. The combined organic layers were washed with 5% $Na_2S_2O_3$ (20 mL), brine (3 × 20 mL), dried over K_2CO_3, filtered and concentrated *in vacuo*. Purification by flash chromatography (alumina, hexane) afforded the title compound as a colourless liquid (2.76 g, 61%). R_f 0.10 (petrol); ν_{max} (thin film)/cm^{-1} 2882w, 1404w, 1125s, 1031m, 943m; δ_H (400 MHz, $CDCl_3$) 2.22 (2 H, td, *J* 7.5, 4.5, C(2)H_2), 3.21 (2 H, t, *J* 7.5, C(1)H_2), 3.81−4.03 (4 H, m, C(5)H_2 × 2), 4.93 (1 H, t, *J* 4.5, C(3)H); δ_C (100 MHz, $CDCl_3$) –2.1 (C(1)), 37.9 (C(2)), 65.0 (C(5)), 103.9 (C(3)); *m/z* (EI$^+$) 228 (M$^{+\cdot}$, 100%).

2-Phenyl-3-pyrrolidin-1-ylpent-4-en-2-ol (225)[86]



t-Butyllithium (0.312 mL, 0.499 mmol, 1.6 M in pentanes) was added dropwise to a solution of pyrrolidine **219** (55.5 mg, 0.499 mmol) in THF (0.8 mL) at –78 °C and the solution was allowed to warm to –10 °C and stirred for 2 h. The solution was then cooled to –78 °C and a solution of acetophenone (50.0 mg, 0.416 mmol) in THF (1 mL) was added. The mixture was stirred at –78 °C for 2 h and allowed to warm to RT overnight. Sat. aq. NH_4Cl (3 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the title compound as an inseparable mixture of diastereomers (*dr.* 1.2:1) as a pale yellow oil (11.4 mg, 12%). R_f 0.25 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 3370br, 2971m, 1601w, 1446m, 1367m, 1113m, 701s; *m/z* (ESI^+) 232 (MH^+, 50%).

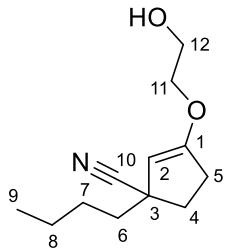
NMR data of major diastereomer:

δ_H (500 MHz, $CDCl_3$) 1.41 (3 H, s, C(8)H_3), 1.60−1.66 (4 H, m, C(6)H_2 × 2), 2.39−2.47 (4 H, m, C(5)H_2 × 2), 3.17 (1 H, d, *J* 10.0, C(3)H), 5.00 (1 H, dd, *J* 17.0, 2.0, C(1)**H**H′), 5.22 (1 H, dd, *J* 10.0, 2.0, C(1)H**H′**), 5.94 (1 H, dt, *J* 17.0, 10.0, C(2)H), 7.17−7.24 (1 H, m, C(12)H), 7.27−7.33 (2 H, m, C(11)H × 2), 7.45−7.50 (2 H, m, C(10)H × 2); δ_C (125 MHz, $CDCl_3$) 23.2 (C(6)), 27.3 (C(8)), 52.0 (C(5)), 73.7 (C(7)), 76.1 (C(3)), 119.6 (C(1)), 125.2 (C(10)), 126.3 (C(12)), 127.6 (C(11)), 133.8 (C(2)), 146.0 (C(9)).

NMR data of minor diastereomer:

δ_H (500 MHz, $CDCl_3$) 1.51 (3 H, s, C(8)H_3), 1.54−1.59 (4 H, m, C(6)H_2 × 2), 2.23−2.38 (4 H, m, C(5)H_2 × 2), 3.19 (1 H, d, *J* 10.0, C(3)H), 5.24 (1 H, dd, *J* 17.0, 2.0, C(1)**H**H′), 5.35 (1 H, dd, *J* 10.0, 2.0, C(1)H**H′**), 5.69 (1 H, dt, *J* 17.0, 10.0, C(2)H), 7.17−7.24 (1 H, m, C(12)H), 7.27−7.33 (2 H, m, C(11)H × 2), 7.40−7.45 (2 H, m, C(10)H × 2); δ_C (125 MHz, $CDCl_3$) 23.2 (C(6)), 28.2 (C(8)), 49.8 (C(5)), 73.4 (C(7)), 74.9 (C(3)), 120.9 (C(1)), 126.4 (C(12)), 126.6 (C(10)), 127.8 (C(11)), 131.8 (C(2)), 149.0 (C(9)).

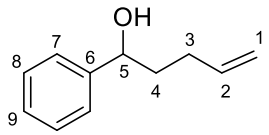
1-Butyl-3-(2-hydroxyethoxy)cyclopent-2-enecarbonitrile (226)



t-Butyllithium (36.0 μL, 0.0573 mmol, 1.6 M in pentanes) was added dropwise to a solution of pyrrolidine **219** (6.38 mg, 0.0573 mmol) in THF (0.2 mL) at –78 °C and the solution was allowed to warm to –10 °C and stirred for 2 h. The solution was then cooled to –78 °C and a solution of nitrile **217** (10.0 mg, 0.0478 mmol) in THF (0.3 mL) was added. The mixture was stirred at –78 °C for 2 h and allowed to warm to RT overnight. Sat. aq. NH_4Cl (2 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a pale yellow oil (2.80 mg, 28%). R_f 0.15 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3448br, 2934m, 2861m, 1643s, 1458m, 1348m, 1081m; δ_H (500 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7.5, C(9)H_3), 1.32−1.40

(2 H, m, C(8)H_2), 1.42−1.51 (2 H, m, C(7)H_2), 1.60−1.66 (2 H, m, C(6)H_2), 1.82 (1 H, bs, OH), 1.87−1.96 (1 H, m, C(5)**H**H′), 2.36−2.48 (2 H, m, C(4)**H**H′ and C(5)H**H′**), 2.56−2.66 (1 H, m, C(4)H**H′**), 3.81−3.94 (4 H, m, C(11)H_2 and C(12)H_2), 4.53 (1 H, t, *J* 1.5, C(2)H); δ_C (125 MHz, $CDCl_3$) 13.9 (C(9)), 22.7 (C(8)), 27.6 (C(7)), 30.7 (C(4)), 33.8 (C(5)), 40.1 (C(6)), 45.4 (C(3)), 61.1 (C(12)), 71.1 (C(11)), 96.8 (C(2)), 124.4 (C(10)), 162.5 (C(1)); *m/z* (ESI^+) 232 (MNa^+, 100%), 210 (MH^+, 20); HRMS (ESI^+): Found: 232.1310; $C_{12}H_{19}NNaO_2$ (MNa^+) requires: 232.1308.

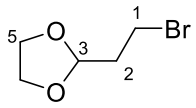
1-Phenylpent-4-en-1-ol (227)[171]



t-Butyllithium (0.141 mL, 0.226 mmol, 1.6 M in pentanes) was added dropwise to a solution of iodide **222** (20.6 mg, 0.113 mmol) in ether (1.1 mL) at –78 °C and the mixture was stirred at –78 °C for 1 h. A solution of benzaldehyde (10.0 mg, 0.0942 mmol) in ether (0.3 mL) was then added dropwise and the mixture was stirred at –78 °C for 2 h before it was allowed to warm to RT. Sat. aq. NH_4Cl (4 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless oil (3.00 mg, 20%). R_f 0.70 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3349br, 2936w, 1641w, 1453w, 1060w, 912m, 700s; δ_H (400 MHz, $CDCl_3$) 1.55 (1 H, bs, OH), 1.68−1.87 (2 H, m, C(4)H_2), 1.97−2.14 (2 H, m, C(3)H_2), 4.62 (1 H, dd, *J* 7.5, 5.5, C(5)H), 4.90 (1 H, ddt, *J* 10.0, 2.0, 1.0, C(1)**H**H′), 4.96 (1 H, dq, *J* 17.0, 2.0, C(1)H**H′**), 5.76 (1 H, ddt, *J* 17.0, 10.0, 6.5, C(2)H), 7.15−7.22 (2 H, m, C(7)H × 2), 7.25−7.28 (3 H, m,

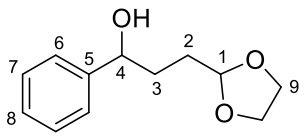
C(8)H × 2 and C(9)H); δ_C (100 MHz, $CDCl_3$) 30.1 (C(3)), 38.1 (C(4)), 74.1 (C(5)), 115.0 (C(1)), 125.9 (C(9)), 127.6 (C(7)), 128.5 (C(8)), 138.2 (C(2)), 144.6 (C(6)); *m/z* (ESI^+) 185 (MNa^+, 100%).

2-(2-Bromoethyl)-[1,3]dioxolane (228)[89]



Acrolein (5.00 mL, 74.8 mmol) was added to a solution of hydrogen bromide (9.08 g, 112 mmol) in ethylene glycol (13.6 mL, 243 mmol) at 5 °C and the mixture was stirred at RT for 1 h. The mixture was then extracted with pentane (3 × 30 mL). The combined organic layers were washed with 5% $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the title compound as a colourless oil (7.70 g, 57%). R_f 0.50 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2885m, 1410m, 1267m, 1130s, 1016m; δ_H (400 MHz, $CDCl_3$) 2.22 (2 H, td, *J* 7.0, 4.5, C(2)H_2), 3.47 (2 H, t, *J* 7.0, C(1)H_2), 3.80−4.04 (4 H, m, C(5)H_2 × 2), 5.01 (1 H, t, *J* 4.5, C(3)H); δ_C (100 MHz, $CDCl_3$) 27.2 (C(1)), 37.1 (C(2)), 65.0 (C(5)), 102.6 (C(3)); *m/z* (EI^+) 182 ($M(^{81}Br)^{+\cdot}$, 100%), 180 ($M(^{79}Br)^{+\cdot}$, 100).

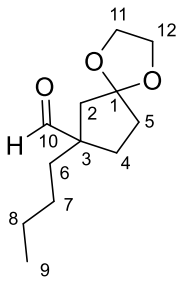
3-[1,3]Dioxolan-2-yl-1-phenylpropan-1-ol (229)[172]



t-Butyllithium (0.707 mL, 1.13 mmol, 1.6 M in pentanes) was added dropwise to a solution of iodide **224** (129 mg, 0.565 mmol) in ether (5.7 mL) at –78 °C and the mixture was stirred

at –78 °C for 1 h. A solution of benzaldehyde (50.0 mg, 0.471 mmol) in ether (1 mL) was then added dropwise and the mixture was stirred at –78 °C for 2 h before it was allowed to warm to RT. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the title compound as a pale yellow oil (80.0 mg, 82%). R_f 0.20 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3429br, 2882w, 1452w, 1138m, 1027m, 702s; δ_H (400 MHz, C_6D_6) 1.71−2.01 (5 H, m, C(2)H_2, C(3)H_2 and OH), 3.21−3.50 (4 H, m, C(9)H_2 × 2), 4.43−4.55 (1 H, m, C(4)H), 4.76 (1 H, t, *J* 4.0, C(1)H), 7.04−7.12 (1 H, m, C(8)H), 7.13−7.21 (2 H, m, C(7)H × 2), 7.22−7.31 (2 H, m, C(6)H × 2); δ_C (100 MHz, C_6D_6) 30.3 (C(2)), 33.6 (C(3)), 64.5 (C(9)), 73.7 (C(4)), 104.3 (C(1)), 125.8 (C(6)), 127.0 (C(8)), 128.2 (C(7)), 145.4 (C(5)); *m/z* (ESI^+) 231 (MNa^+, 100%).

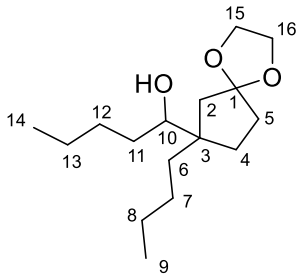
7-Butyl-1,4-dioxaspiro[4.4]nonane-7-carbaldehyde (230)



A solution of nitrile **217** (100 mg, 0.478 mmol) in THF (2 mL) was added dropwise to a solution of DIBAL (4.78 mL, 4.78 mmol, 1 M in hexanes) in THF (1 mL) at –78 °C and the mixture was stirred at –78 °C for 5 h. Sat. aq. potassium sodium tartrate (3 mL) was added and mixture was stirred at RT for 1 h. The mixture was then extracted with ether (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (77.6 mg, 77%). R_f 0.35 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2932m, 1725s, 1460w, 1338w, 1109m, 1036w; δ_H (500 MHz, C_6D_6) 0.76 (3 H, t, *J* 7.0, C(9)H_3), 0.96−1.14 (4 H, m, C(7)H_2 and C(8)H_2), 1.31−1.42 (3 H, m, C(4)**H**H′ and C(6)H_2), 1.64 (1 H, d, *J* 14.0, C(2)**H**H′), 1.71−1.80 (2 H, m, C(5)H_2), 1.92−2.02 (1 H, m, C(4)H**H′**), 2.36 (1 H, d, *J* 14.0, C(2)H**H′**), 3.34−3.48 (4 H, m, C(11)H_2 and C(12)H_2), 9.29 (1 H, s, C(10)H); δ_C (125 MHz, C_6D_6) 13.7 (C(9)), 23.1 (C(8)), 27.1 (C(7)), 29.6 (C(4)), 34.9 (C(5)), 35.9 (C(6)), 41.1 (C(2)), 55.1 (C(3)), 64.0 (C(11) and C(12)), 117.0 (C(1)), 202.5 (C(10)); *m/z* (ESI$^+$) 235 (MNa$^+$, 100%), 213 (MH$^+$, 5); HRMS (ESI$^+$): Found: 235.1307; $C_{12}H_{20}NaO_3$ (MNa$^+$) requires: 235.1305.

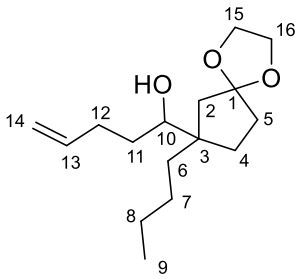
1-(7-Butyl-1,4-dioxaspiro[4.4]non-7-yl)pentan-1-ol (231)



n-Butyllithium (14.0 μL, 0.0353 mmol, 2.5 M in hexanes) was added to a solution of aldehyde **230** (5.00 mg, 0.0236 mmol) in ether (0.3 mL) at 0 °C and the mixture was stirred at RT for 4 h. Sat. aq. NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as an inseparable mixture of diastereomers (*dr.* 1.6:1) as a colourless oil (5.50 mg, 86%). R_f 0.35 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3491br, 2955s, 2932s, 1466w, 1340w,

1110m; δ_H (700 MHz, C_6D_6) 0.83−0.99 (6 H, m, C(9)H_3 and C(14)H_3), 1.15−1.61 (13 H, m, C(4)**H**H′, C(6)H_2, C(7)H_2, C(8)H_2, C(11)H_2, C(12)H_2 and C(13)H_2), 1.62−2.19 (5 H, m, C(2)H_2, C(4)H**H′** and C(5)H_2), 3.37−3.55 (5 H, m, C(10)H, C(15)H_2 and C(16)H_2); δ_C (175 MHz, C_6D_6) 14.0 (C(9)), 14.1 (C(14)), 22.8/22.9 (C(13)), 23.7 (C(8)), 26.5/26.6 (C(7)), 29.1/29.2 (C(12)), 30.1/31.5 (C(6)), 32.0 (C(4)), 35.6/35.8 (C(5)), 38.0/38.5 (C(11)), 42.5/44.5 (C(2)), 47.3/47.4 (C(3)), 63.6/63.8 (C(16)), 64.1/64.3 (C(15)), 75.9/76.3 (C(10)), 117.8/118.0 (C(1)); *m/z* (ESI^+) 293 (MNa^+, 100%), 271 (MH^+, 5); HRMS (ESI^+): Found: 293.2081; $C_{16}H_{30}NaO_3$ (MNa^+) requires: 293.2087.

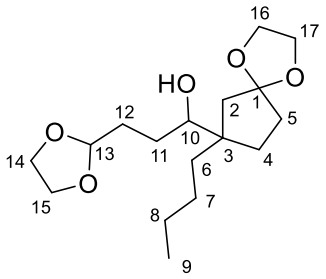
1-(7-Butyl-1,4-dioxaspiro[4.4]non-7-yl)pent-4-en-1-ol (232)



4-bromobutene (25.0 μL, 0.245 mmol) in THF (0.3 mL) was added dropwise to magnesium (5.7 mg, 0.236 mmol) at 30 °C and the mixture was stirred for 1 h. The mixture was then added to a solution of aldehyde **230** (5.00 mg, 0.0236 mmol) in THF (0.1 mL) at RT and stirred for 2 h. Sat. aq. NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as an inseparable mixture of diastereomers (*dr.* 1:1) as a colourless oil (4.00 mg, 63%). R_f 0.35 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3492br, 2932s, 1640w, 1448w, 1340m, 1108s; δ_H (700 MHz, C_6D_6) 0.83−0.90 (3 H, m, C(9)H_3), 1.13−1.56 (9 H, m, C(4)**H**H′,

C(6)H_2, C(7)H_2, C(8)H_2 and C(11)H_2), 1.64−2.16 (5 H, m, C(2)H_2, C(4)H**H′** and C(5)H_2), 2.08−2.49 (2 H, m, C(12)H_2), 3.37−3.54 (5 H, m, C(10)H, C(15)H_2 and C(16)H_2), 4.96−5.03 (1 H, m, C(14)**H**H′), 5.06−5.14 (1 H, m, C(14)H**H′**), 5.79−5.91 (1 H, m, C(13)H); δ_C (175 MHz, C_6D_6) 13.9/14.0 (C(9)), 23.7 (C(8)), 26.5/26.6 (C(7)), 30.0/31.1 (C(6)), 31.2 (C(12)), 31.7/31.9 (C(4)), 35.5/35.7 (C(5)), 38.0/38.6 (C(11)), 42.4/44.5 (C(2)), 47.2/47.3 (C(3)), 63.6/63.7 (C(16)), 64.2/64.3 (C(15)), 75.3/75.8 (C(10)), 114.4/114.5 (C(14)), 117.7/117.9 (C(1)), 138.9/139.1 (C(13)); *m/z* (ESI^+) 291 (MNa^+, 100%); HRMS (ESI^+): Found: 291.1920; $C_{16}H_{28}NaO_3$ (MNa^+) requires: 291.1931.

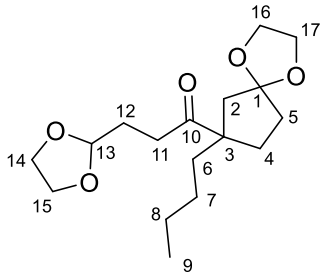
1-(7-Butyl-1,4-dioxaspiro[4.4]non-7-yl)-3-[1,3]dioxolan-2-ylpropan-1-ol (233)



Bromide **228** (0.248 g, 1.37 mmol) in THF (1.8 mL) was added dropwise to magnesium (32.0 mg, 1.32 mmol) at 30 °C and the mixture was stirred for 1 h. The mixture was then added to a solution of aldehyde **230** (56.0 mg, 0.264 mmol) in THF (1 mL) at RT and stirred for 2 h. Sat. aq. NH_4Cl (5 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as an inseparable mixture of diastereomers (*dr*. 1:1) as a colourless oil (77.5 mg, 93%). R_f 0.20 (1:3 petrol:ether); ν_{max} (thin film)/cm^{-1} 3492br, 2955m, 2873m, 1408w, 1341w, 1139s; δ_H (700 MHz, C_6D_6) 0.83−0.91 (3 H, m, C(9)H_3), 1.16−1.62 (8 H, m, C(6)H_2, C(7)H_2, C(8)H_2 and C(11)H_2), 1.67−2.26 (8 H, m, C(2)H_2, C(4)H_2, C(5)H_2 and C(12)H_2), 3.28−3.60 (9 H, m,

C(10)H, C(14)H_2, C(15)H_2, C(16)H_2 and C(17)H_2), 4.81−4.89 (1 H, m, C(13)H); δ_C (175 MHz, C_6D_6) 14.0 (C(9)), 23.7 (C(8)), 26.2/26.6 (C(7)), 30.1 (C(6)), 31.4 (C(12)), 32.1 (C(4)), 35.6/35.8 (C(5)), 38.0/38.4 (C(11)), 42.4/44.4 (C(2)), 47.4 (C(3)), 63.6/63.8 (C(17)), 64.1/64.2 (C(16)), 64.3/64.4 (C(15)), 64.5 (C(14)), 75.7/76.2 (C(10)), 104.6/104.7 (C(13)), 117.8/118.0 (C(1)); *m/z* (ESI^+) 337 (MNa^+, 100%); HRMS (ESI^+): Found: 337.1987; $C_{17}H_{30}NaO_5$ (MNa^+) requires: 337.1985.

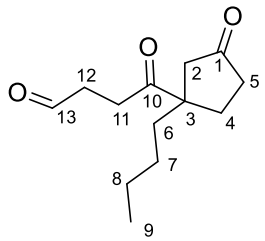
1-(7-Butyl-1,4-dioxaspiro[4.4]non-7-yl)-3-[1,3]dioxolan-2-ylpropan-1-one (234)



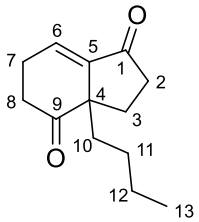
Dess–Martin periodinane (13.5 mg, 0.0318 mmol) was added to a solution of alcohol **233** (5.00 mg, 0.0159 mmol) in DCM (0.9 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (2 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) were added and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (5.40 mg, 95%). R_f 0.45 (1:3 petrol:ether); ν_{max} (thin film)/cm^{-1} 2933m, 1703s, 1438w, 1337m, 1139s, 1033s; δ_H (400 MHz, C_6D_6) 0.77 (3 H, t, *J* 7.0, C(9)H_3), 0.95−1.18 (4 H, m, C(7)H_2 and C(8)H_2), 1.36−1.66 (3 H, m, C(4)**H**H′ and C(6)H_2), 1.77 (1 H, d, *J* 14.0, C(2)**H**H′), 1.84 (2 H, t, *J* 7.5, C(5)H_2), 2.12−2.21 (2 H, m, C(12)H_2), 2.26−2.36 (1 H, m, C(4)H**H′**), 2.47−2.64 (3 H, m, C(2)H**H′** and C(11)H_2), 3.27−3.56 (8 H, m, C(14)H_2, C(15)H_2, C(16)H_2 and C(17)H_2), 4.85 (1 H, t, *J* 4.5, C(13)H);

δ_C (100 MHz, C_6D_6) 13.7 (C(9)), 23.1 (C(8)), 27.4 (C(7)), 28.4 (C(12)), 31.4 (C(11)), 31.7 (C(4)), 35.2 (C(5)), 38.7 (C(6)), 43.7 (C(2)), 57.5 (C(3)), 63.9 (C(17)), 64.0 (C(16)), 64.5 (C(14) and C(15)), 103.5 (C(13)), 117.0 (C(1)), 210.5 (C(10)); *m/z* (ESI^+) 335 (MNa^+, 100%); HRMS (ESI^+): Found: 335.1827; $C_{17}H_{28}NaO_5$ (MNa^+) requires: 335.1829.

4-(1-Butyl-3-oxocyclopentyl)-4-oxobutyraldehyde (235) and **3a-Butyl-3,3a,5,6-tetrahydro-2*H*-indene-1,4-dione (236)**



235



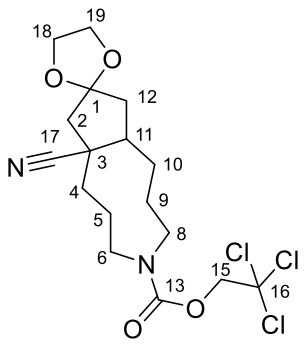
236

0.5 M aq. HCl (1.0 mL) was added to ketone **234** (10 mg, 0.0320 mmol) and the mixture was stirred under reflux for 1 h. The mixture was extracted with ether (3 × 10 mL). The combined organic layers were washed with 5% aq. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *1,4-dicarbonyl* **235** as a colourless oil (3.5 mg, 49%). R_f 0.25 (1:3 petrol:ether); ν_{max} (thin film)/cm^{-1} 2932m, 1742s, 1702s, 1406m; δ_H (500 MHz, C_6D_6) 0.77 (3 H, t, *J* 7.5, C(9)H_3), 0.81−0.89 (2 H, m, C(7)H_2), 1.02−1.09 (2 H, m, C(8)H_2), 1.10−1.16 (1 H, m, C(6)**H**H′), 1.22−1.28 (1 H, m, C(4)**H**H′), 1.30−1.37 (1 H, m, C(6)H**H′**), 1.69 (1 H, d, *J* 18.0, C(2)**H**H′), 1.82−1.95 (3 H, m, C(4)H**H′** and C(12)H_2), 1.96−2.03 (2 H, m, C(5)**H**H′ and C(11)**H**H′), 2.12−2.18 (1 H, m, C(5)H**H′**), 2.19−2.26 (1 H, m, C(11)H**H′**), 2.61 (1 H, d, *J* 18.0, C(2)H**H′**), 9.22 (1 H, s, C(13)H); δ_C (125 MHz, C_6D_6) 13.6 (C(9)), 23.0 (C(8)), 27.3 (C(7)), 28.9 (C(11)), 31.1 (C(4)), 35.9 (C(12)), 37.1 (C(5) and C(6)), 45.6 (C(2)), 56.0 (C(3)), 198.7

(C(13)), 209.4 (C(1)), 213.6 (C(10)); *m/z* (ESI$^+$) 247 (MNa$^+$, 100%); HRMS (ESI$^+$): Found: 247.1311; $C_{13}H_{20}NaO_3$ (MNa$^+$) requires: 247.1305.

Also obtained was *bicyclic enone* **236** as a colourless oil (2.50 mg, 38%). R_f 0.60 (1:3 petrol:ether); ν_{max} (thin film)/cm^{-1} 2958m, 1713s, 1652s, 1438w, 1202m; δ_H (500 MHz, C_6D_6) 0.72 (3 H, t, *J* 7.0, C(13)H_3), 0.92−1.07 (4 H, m, C(11)H_2 and C(12)H_2), 1.17−1.23 (1 H, m, C(10)**H**H′), 1.33−1.39 (1 H, m, C(10)H**H′**), 1.72−1.84 (4 H, m, C(3)H_2, C(7)**H**H′ and C(8)**H**H′), 1.91−1.98 (3 H, m, C(2)H_2 and C(7)H**H′**), 2.05−2.11 (1 H, m, C(8)H**H′**), 6.51 (1 H, dd, *J* 6.0, 3.0, C(6)H); δ_C (125 MHz, C_6D_6) 13.6 (C(13)), 22.9 (C(12)), 24.3 (C(7)), 26.3 (C(3)), 26.9 (C(11)), 33.6 (C(8)), 34.9 (C(2)), 37.0 (C(10)), 54.3 (C(4)), 130.4 (C(6)), 143.2 (C(5)), 202.6 (C(1)), 210.5 (C(9)); *m/z* (ESI$^+$) 229 (MNa$^+$, 95%), 207 (MH$^+$, 100); HRMS (ESI$^+$): Found: 206.1307; $C_{13}H_{18}O_2$ (M$^+$) requires: 206.1307.

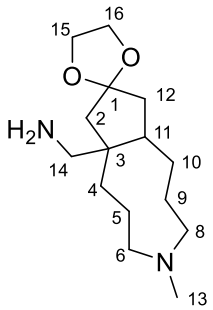
2,2,2-Trichloroethyl-7a-cyanooctahydro-1*H*-spiro[cyclopenta[*e*]azonine-9,2'-[1,3]dioxolane]-4(5*H*)-carboxylate (238)



p-TsOH·H_2O (1.0 mg, 3.41 μmol) was added to a solution of nitrile **215** (13.0 mg, 0.0341 mmol) and ethylene glycol (2.0 μL, 0.0375 mmol) in benzene (0.5 mL) and the mixture was stirred under reflux for 1 h. Sat. aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over Na_2SO_4,

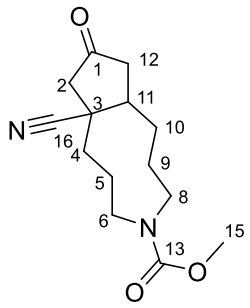
filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil as a mixture of carbamate rotamers (12.0 mg, 83%). R_f 0.60 (ether); ν_{max} (thin film)/cm^{-1} 2949w, 2210w, 1712s, 1421m, 1202m, 1127m; δ_H (400 MHz, toluene-d_8) 1.24−1.60 (9 H, m, C(5)H_2 × 2, C(9)H_2, C(9)**H**H′ and C(10)**H**H′ × 2), 1.61−1.86 (12 H, m, C(2)**H**H′ × 2, C(4)H_2 × 2, C(9)H**H′**, C(10)H**H′** × 2, C(12)H_2 and C(12)**H**H′), 1.90−1.99 (1 H, m, C(12)H**H′**), 2.02−2.12 (4 H, m, C(6)**H**H′, C(8)**H**H′ and C(11)H × 2), 2.15 (1 H, d, *J* 14.5, C(2)H**H′**), 2.20 (1 H, d, *J* 14.5, C(2)H**H′**), 2.30−2.42 (2 H, m, C(6)**H**H′ and C(8)**H**H′), 3.18−3.43 (8 H, m, C(18)H_2 × 2 and C(19)H_2 × 2), 3.49−3.57 (1 H, m, C(8)H**H′**), 3.62 (1 H, dd, *J* 14.0, 7.0, C(8)H**H′**), 3.70 (1 H, ddd, *J* 14.5, 8.0, 3.0, C(6)H**H′**), 3.85 (1 H, ddd, *J* 14.0, 11.0, 3.5, C(6)H**H′**), 4.08 (1 H, d, *J* 12.0, C(15)**H**H′), 4.16 (1 H, d, *J* 12.0, C(15)**H**H′), 5.00 (1 H, d, *J* 12.0, C(15)H**H′**), 5.03 (1 H, d, *J* 12.0, C(15)H**H′**); δ_C (100 MHz, toluene-d_8) 21.9/22.4 (C(9)), 24.9/25.5 (C(5)), 30.3/30.6 (C(10)), 35.7 (C(4)), 41.6/42.3 (C(11)), 44.9 (C(3)), 45.3/45.4 (C(12)), 49.1/49.2 (C(8)), 49.3 (C(2)), 49.7/50.4 (C(6)), 63.6 (C(19)), 64.2 (C(18)), 74.5/74.7 (C(15)), 95.8/96.0 (C(16)), 113.0/113.1 (C(1)), 122.3/122.5 (C(17)), 153.8/153.9 (C(13)); *m/z* (ESI^+) 453 (M($^{37}Cl^{37}Cl^{37}Cl$)Na^+, 4%), 451 (M($^{35}Cl^{37}Cl^{37}Cl$)Na^+, 33), 449 (M($^{35}Cl^{35}Cl^{37}Cl$)Na^+, 100), 447 (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+, 100); HRMS (ESI^+): Found: 447.0622; $C_{17}H_{23}N_2NaO_4Cl_3$ (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+) requires: 447.0616.

[4-Methyldecahydro-1*H*-spiro(cyclopenta[*e*]azonine-9,2'-[1,3]dioxolan)-7a-yl]methanamine (239)



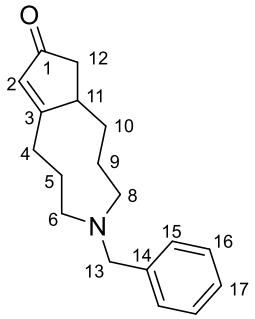
A solution of nitrile **238** (12.0 mg, 0.0282 mmol) in THF (0.2 mL) was added dropwise to a solution of DIBAL (0.282 mL, 0.282 mmol, 1 M in hexanes) in THF (0.1 mL) at –78 °C and the mixture was stirred at –78 °C for 5 h. Sat. aq. potassium sodium tartrate (1 mL) was added and mixture was stirred at RT for 1 h. The mixture was then extracted with DCM (3 × 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (5.20 mg, 69%). R_f 0.75 (16:4:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 3357br, 2923s, 2785m, 1451m, 1328m, 1107m; δ_H (500 MHz, $CDCl_3$) 1.27−1.39 (1 H, m, C(5)**H**H′), 1.43−1.84 (9 H, m, C(2)**H**H′, $C(4)H_2$, C(5)H**H′**, $C(9)H_2$, $C(10)H_2$ and C(12)**H**H′), 1.97 (1 H, d, *J* 14.0, C(2)H**H′**), 2.01−2.11 (1 H, m, C(12)H**H′**), 2.21−2.35 (5 H, m, C(6)**H**H′, C(8)**H**H′ and $C(13)H_3$), 2.41−2.57 (2 H, m, C(6)H**H′** and C(8)H**H′**), 2.68 (1 H, d, *J* 13.0, C(14)**H**H′), 2.78 (1 H, d, *J* 13.0, C(14)H**H′**), 2.80−2.87 (1 H, m, C(11)H), 3.79−3.96 (4 H, m, $C(15)H_2$ and $C(16)H_2$); δ_C (125 MHz, $CDCl_3$) 23.0 (C(9)), 26.2 (C(5)), 31.8 (C(4)), 34.0 (C(10)), 40.6 (C(11)), 44.4 (C(3)), 44.5 (C(14)), 44.9 (C(12)), 45.9 (C(2)), 57.3 (C(6)), 58.7 (C(8)), 63.8 (C(16)), 64.1 (C(15)), 115.2 (C(1)); *m/z* (ESI^+) 269 (MH^+, 100%); HRMS (ESI^+): Found: 269.2221; $C_{15}H_{29}N_2O_2$ (MH^+) requires: 269.2224.

Methyl-7a-cyano-9-oxodecahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (241)



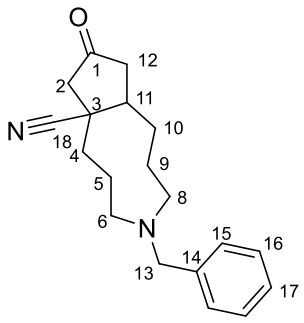
25% aq. NaOH (0.5 mL) was added to a solution of nitrile **215** (12.0 mg, 0.0282 mmol) in methanol (0.5 mL) and the mixture was stirred under reflux for 8 h. Dilute hydrochloric acid was added to the mixture until pH 7 and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil as a mixture of carbamate rotamers (5.21 mg, 70%). R_f 0.25 (ether); ν_{max} (thin film)/cm^{-1} 2924w, 1750s, 1693s, 1407m, 1214m, 774m; δ_H (500 MHz, $CDCl_3$) 1.68−2.04 (6 H, m, C(5)H_2, C(9)H_2 and C(10)H_2), 2.16 (1 H, ddd, *J* 18.0, 13.0, 1.0, C(12)**H**H′), 2.20−2.40 (4 H, m, C(2)**H**H′, C(4)H_2 and C(11)H), 2.45−2.60 (1 H, m, C(12)H**H′**), 2.64 (1 H, d, *J* 18.5, C(2)H**H′**), 2.71−2.89 (1 H, m, C(6)**H**H′), 2.94−3.05 (1 H, m, C(8)**H**H′), 3.72 (3 H, s, C(15)H_3), 3.79−4.15 (2 H, m, C(6)H**H′** and C(8)H**H′**); δ_C (125 MHz, $CDCl_3$) 21.6/22.5 (C(9)), 25.3/25.8 (C(5)), 30.3/31.2 (C(10)), 35.3 (C(4)), 40.7 (C(11)), 44.6 (C(3)), 46.4 (C(12)), 49.3/49.6 (C(8)), 49.8 (C(6)), 49.9 (C(2)), 50.7 (C(6)), 52.9/53.0 (C(15)), 121.9/125.5 (C(16)), 157.1/157.2 (C(13)), 211.2/211.4 (C(1)); *m/z* (ESI^+) 265 (MH^+, 100%); HRMS (ESI^+): Found: 265.1546; $C_{14}H_{21}N_2O_3$ (MH^+) requires: 265.1547.

4-Benzyl-2,3,4,5,6,7,7a,8-octahydrocyclopenta[*e*]azonin-9(1*H*)-one (242)



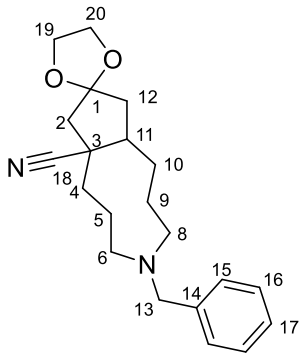
Benzyl bromide (33.0 μL, 0.278 mmol) and K_2CO_3 (76.7 mg, 0.555 mmol) were added to a solution of amine **92** (10.0 mg, 0.0555 mmol) in benzene (0.6 mL) and the reaction mixture was stirred at RT for 16 h. The mixture was filtered through a cotton plug, washed with dichloromethane (5 mL) and concentrated *in vacuo*. Purification by flash chromatography (silica, ether → 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a pale yellow oil (14.0 mg, 93%). R_f 0.30 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2922w, 1710s, 1683s, 1606m, 1451m, 726m; δ_H (500 MHz, $CDCl_3$) 0.99−1.13 (1 H, m, C(9)**H**H′), 1.27−1.40 (1 H, m, C(9)H**H′**), 1.54−1.73 (2 H, m, C(5)**H**H′ and C(10)**H**H′), 1.74−1.88 (1 H, m, C(5)H**H′**), 2.02 (1 H, dd, *J* 19.0, 2.0, C(12)**H**H′), 2.10−2.20 (1 H, m, C(10)H**H′**), 2.22−2.36 (3 H, m, C(6)**H**H′ and C(8)H_2), 2.39−2.59 (3 H, m, C(4)**H**H′, C(6)H**H′** and C(12)H**H′**), 2.84 (1 H, ddd, *J* 13.5, 12.5, 4.0, C(4)H**H′**), 2.99−3.10 (1 H, m, C(11)H), 3.41 (1 H, d, *J* 13.0, C(13)**H**H′), 3.68 (1 H, d, *J* 13.0, C(13)H**H′**), 6.09 (1 H, s, C(2)H), 7.23−7.27 (1 H, m, C(17)H), 7.28−7.35 (4 H, m, C(15)H × 2 and C(16)H × 2); δ_C (125 MHz, $CDCl_3$) 19.4 (C(9)), 24.4 (C(10)), 26.4 (C(4)), 27.0 (C(5)), 40.8 (C(12)), 44.3 (C(11)), 48.0 (C(6)), 52.3 (C(8)), 60.8 (C(13)), 126.9 (C(17)), 128.2 (C(16)), 129.2 (C(15)), 132.2 (C(2)), 139.9 (C(14)), 187.4 (C(3)), 209.4 (C(1)); *m/z* (ESI^+) 270 (MH^+, 100%); HRMS (ESI^+): Found: 270.1855; $C_{18}H_{24}NO$ (MH^+) requires: 270.1852.

4-Benzyl-9-oxododecahydrocyclopenta[*e*]azonine-7a-carbonitrile (243)



Trimethylsilyl cyanide (10.0 μL, 0.0817 mmol) was added to a solution of triethylaluminium (74.0 μL, 0.0742 mmol, 1 M in heptanes) in THF (0.3 mL). A solution of enone **242** (10.0 mg, 0.0371 mmol) in THF (0.2 mL) was then added and the mixture was stirred under reflux for 5 h. Sat. aq. NH_4Cl (15 mL) was added and the mixture was extracted with ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (4.5 mg, 41%). R_f 0.45 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2925m, 2215w, 1750s, 1452m, 1132w, 701m; δ_H (500 MHz, CD_2Cl_2) 1.43−1.61 (2 H, m, C(5)**H**H′ and C(9)**H**H′), 1.65−1.76 (2 H, m, C(4)**H**H′ and C(9)H**H′**), 1.77−1.86 (1 H, m, C(5)H**H′**), 1.87−2.00 (2 H, m, C(4)H**H′** and C(10)**H**H′), 2.07−2.22 (2 H, m, C(10)H**H′** and C(12)**H**H′), 2.32 (1 H, d, *J* 18.5, C(2)**H**H′), 2.37 (1 H, ddd, *J* 10.5, 7.0, 3.5, C(8)**H**H′), 2.48−2.59 (2 H, m, C(6)**H**H′ and C(12)H**H′**), 2.60−2.68 (2 H, m, C(2)H**H′** and C(8)H**H′**), 2.69−2.78 (1 H, m, C(6)H**H′**), 3.48−3.59 (1 H, m, C(11)H), 3.55 (1 H, d, *J* 13.0, C(13)**H**H′), 3.64 (1 H, d, *J* 13.0, C(13)H**H′**), 7.18−7.39 (5 H, m, C(15)H × 2, C(16)H × 2 and C(17)H); δ_C (125 MHz, CD_2Cl_2) 24.5 (C(9)), 26.0 (C(5)), 32.2 (C(4)), 35.9 (C(10)), 41.2 (C(11)), 45.5 (C(3)), 46.6 (C(12)), 51.2 (C(2)), 55.4 (C(8)), 56.8 (C(6)), 63.8 (C(13)), 122.4 (C(18)), 127.0 (C(17)), 128.2 (C(16)), 129.3 (C(15)), 139.8 (C(14)), 212.3 (C(1)); *m/z* (ESI^+) 297 (MH^+, 100%); HRMS (ESI^+): Found: 297.1962; $C_{19}H_{25}N_2O$ (MH^+) requires: 297.1961.

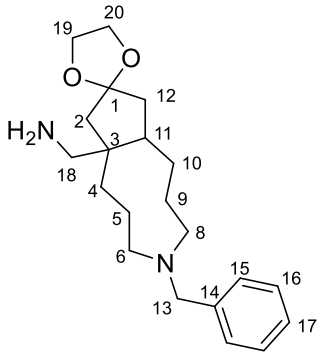
4-Benzyloctahydro-1*H*-spiro[cyclopenta[*e*]azonine-9,2'-[1,3]dioxolane]-7a(8*H*)-carbonitrile (244)



p-TsOH·H_2O (20.0 mg, 0.106 mmol) was added to a solution of ketone **243** (28.5 mg, 0.0962 mmol) and ethylene glycol (11.0 μL, 0.192 mmol) in benzene (1.6 mL) and the mixture was stirred under reflux for 4 h. Sat. aq. $NaHCO_3$ (3 mL) was added and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (21.0 mg, 64%). R_f 0.55 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2906br, 2228w, 1450m, 1327m, 1148s, 701s; δ_H (400 MHz, CD_2Cl_2) 1.40−1.65 (3 H, m, C(4)**H**H′, C(5)**H**H′ and C(9)**H**H′), 1.66−1.90 (5 H, m, C(4)H**H′**, C(5)H**H′**, C(9)H**H′**, C(10)**H**H′ and C(12)**H**H′), 1.91−2.10 (3 H, m, C(2)**H**H′, C(10)H**H′** and C(12)H**H′**), 2.25−2.34 (1 H, m, C(8)**H**H′), 2.41 (1 H, d, *J* 14.5, C(2)H**H′**), 2.48−2.60 (2 H, m, C(6)**H**H′ and C(8)H**H′**), 2.63−2.75 (1 H, m, C(6)H**H′**), 3.48 (1 H, d, *J* 13.0, C(13)**H**H′), 3.49−3.58 (1 H, m, C(11)H), 3.62 (1 H, d, *J* 13.0, C(13)H**H′**), 3.82−4.00 (4 H, m, C(19)H_2 and C(20)H_2), 7.20−7.39 (5 H, m, C(15)H × 2, C(16)H × 2 and C(17)H); δ_C (100 MHz, CD_2Cl_2) 25.2 (C(9)), 26.0 (C(5)), 31.9 (C(4)), 37.0 (C(10)), 42.5 (C(11)), 45.0 (C(3)), 45.4 (C(12)), 50.2 (C(2)), 55.6 (C(8)), 57.3 (C(6)), 64.0 (C(13)), 64.2 (C(19)), 64.7 (C(20)), 113.4 (C(1)), 123.9 (C(18)), 126.8 (C(17)), 128.1 (C(16)), 129.5 (C(15)), 140.1

(C(14)); *m/z* (ESI$^+$) 341 (MH$^+$, 100%); HRMS (ESI$^+$): Found: 341.2218; $C_{21}H_{29}N_2O_2$ (MH$^+$) requires: 341.2224.

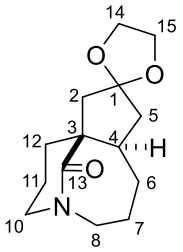
[4-Benzyloctahydro-1*H*-spiro(cyclopenta[*e*]azonine-9,2'-[1,3]dioxolan)-7a(8*H*)-yl]methanamine (246)



To a stirred solution of nitrile **244** (4.0 mg, 0.0117 mmol) in dichloromethane (0.25 mL) at −78 °C was added DIBAL-H (23.5 μL, 0.0235 mmol, 1 M solution in hexanes). After stirring at −78 °C for 1 h, the reaction mixture was poured into sat. aq. potassium sodium tartrate (0.25 mL) and stirred at RT for 1 h. The separated aqueous layer was extracted with dichloromethane (2 × 0.60 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 90:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (3.9 mg, 96%). R_f 0.20 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); ν_{max} (thin film)/cm^{-1} 2920br, 1451w, 1325w, 1024m, 732s, 699s; δ_H (500 MHz, CD_2Cl_2) 1.18−1.37 (2 H, m, C(4)**H**H′ and C(5)**H**H′), 1.39−1.88 (8 H, m, C(2)**H**H′, C(4)H***H′***, C(5)H***H′***, C(9)H_2, C(10)H_2 and C(12)**H**H′), 1.92−2.10 (2 H, m, C(2)H***H′*** and C(12)H***H′***), 2.23−2.36 (1 H, m, C(8)**H**H′), 2.42−2.50 (1 H, m, C(6)**H**H′), 2.51−2.75 (4 H, m, C(6)H***H′***, C(8)H***H′*** and C(18)H_2), 3.13−3.33 (1 H, m, C(11)H), 3.59 (2 H, s, C(13)H_2), 3.76−4.00 (4 H, m, C(19)H_2 and C(20)H_2), 7.19−7.42 (5 H, m, C(15)H × 2, C(16)H × 2 and C(17)H); δ_C (125 MHz, CD_2Cl_2)

23.5 (C(9)), 26.4 (C(5)), 28.2 (C(4)), 34.5 (C(10)), 40.4 (C(11)), 44.7 (C(12)), 45.0 (C(18)), 45.7 (C(2)), 46.3 (C(3)), 56.0 (C(8)), 56.5 (C(6)), 63.8 (C(13) and C(20)), 64.2 (C(19)), 115.3 (C(1)), 126.8 (C(17)), 128.1 (C(16)), 129.5 (C(15)), 140.8 (C(14)); *m/z* (ESI^+) 345 (MH^+, 100%); HRMS (ESI^+): Found: 345.2531; $C_{21}H_{33}N_2O_2$ (MH^+) requires: 345.2537.

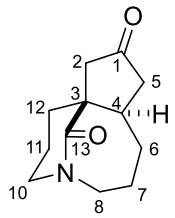
(4*S*,7a*R*,10a*R*)-Octahydro-1*H*-spiro[4,7a-methanocyclopenta[*e*]azonine-9,2'-[1,3]dioxolan]-11-one (247)



Zinc (37.0 mg, 0.564 mmol) was added to a solution of nitrile **238** (30.0 mg, 0.0705 mmol) in glacial acetic acid (0.9 mL) and the mixture was stirred at RT for 16 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (15.9 mg, 90%). R_f 0.45 (ether); ν_{max} (thin film)/cm^{-1} 2930m, 1678s, 1448m, 1321m, 1116m; δ_H (500 MHz, CD_3OD) 1.38−1.50 (2 H, m, C(5)**H**H′ and C(6)**H**H′), 1.50 (1 H, dd, *J* 13.5, 2.0, C(2)**H**H′), 1.51−1.57 (1 H, m, C(7)**H**H′), 1.58−1.67 (1 H, m, C(11)**H**H′), 1.75 (1 H, dt, *J* 15.0, 3.0, C(6)H**H′**), 1.86−1.94 (1 H, m, C(12)**H**H′), 1.94−2.03 (2 H, m, C(7)H**H′** and C(11)H**H′**), 2.12 (1 H, ddd, *J* 13.5, 8.0, 2.5, C(5)H**H′**), 2.19−2.26 (1 H, m, C(4)H), 2.31 (1 H, ddd, *J* 14.0, 8.0, 6.5, C(12)H**H′**), 2.82 (1 H, dd, *J* 13.5, 1.0, C(2)H**H′**), 2.95 (1 H, dd, *J* 14.0, 5.0, C(8)**H**H′), 3.18 (1 H, dddd, *J* 12.5, 7.5, 4.0, 1.0, C(10)**H**H′), 3.40 (1 H, dddd, *J* 12.5, 8.0, 3.5, 1.0, C(10)H**H′**), 3.79−3.94 (5 H, m, C(8)H**H′**, $C(15)H_2$ and $C(16)H_2$); δ_C (125

MHz, CD_3OD) 23.2 (C(11)), 28.4 (C(7)), 36.0 (C(6)), 38.6 (C(12)), 44.2 (C(2)), 44.5 (C(5)), 46.6 (C(4)), 48.9 (C(10)), 55.3 (C(8)), 56.1 (C(3)), 65.3 (C(15)), 65.6 (C(14)), 117.9 (C(1)), 187.8 (C(13)); *m/z* (ESI^+) 274 (MNa^+, 60%), 252 (MH^+, 100); HRMS (ESI^+): Found: 274.1414; $C_{14}H_{21}NNaO_3$ (MNa^+) requires: 274.1414.

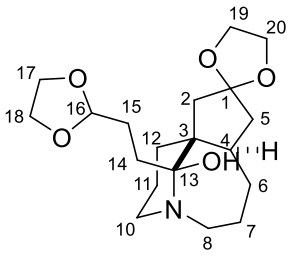
(4*R*,7a*S*,10a*R*)-Octahydro-4,7a-methanocyclopenta[*e*]azonine-9,11(1*H*)-dione (248)



Zinc (15.5 mg, 0.236 mmol) was added to a solution of nitrile **215** (9.00 mg, 0.0236 mmol) in glacial acetic acid (0.3 mL) and the mixture was stirred at RT for 48 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (1.20 mg, 25%). R_f 0.40 (ether); ν_{max} (thin film)/cm^{-1} 2933m, 1743s, 1665m, 1444w, 1321w, 1183m; δ_H (500 MHz, CD_2Cl_2) 1.64−1.71 (1 H, m, C(6)**H**H′), 1.72−1.81 (3 H, m, C(6)H**H′**, C(7)**H**H′ and C(11)**H**H′), 1.82−1.90 (1 H, m, C(7)H**H′**), 1.91−2.01 (3 H, m, C(2)**H**H′, C(11)H**H′** and C(12)**H**H′), 2.03−2.14 (2 H, m, C(5)**H**H′ and C(12)H**H′**), 2.40−2.50 (2 H, m, C(4)H and C(5)H**H′**), 2.83 (1 H, dt, *J* 13.5, 5.5, C(8)**H**H′), 3.16 (1 H, dd, *J* 18.5, 2.0, C(2)H**H′**), 3.31 (1 H, dtd, *J* 12.0, 4.5, 1.5, C(10)**H**H′), 3.46 (1 H, td, *J* 12.0, 3.0, C(10)H**H′**), 3.88 (1 H, ddd, *J* 13.5, 8.0, 5.5, C(8)H**H′**); δ_C (125 MHz, CD_2Cl_2) 21.6 (C(11)), 23.5 (C(7)), 30.6 (C(6)), 35.7 (C(12)), 42.7 (C(5)), 44.3 (C(4)), 47.8 (C(2)), 49.0 (C(10)), 51.0 (C(8)),

53.8 (C(3)), 183.6 (C(13)), 215.8 (C(1)); *m/z* (ESI^+) 230 (MNa^+, 100%), 208 (MH^+, 10); HRMS (ESI^+): Found: 208.1333; $C_{12}H_{18}NO_2$ (MH^+) requires: 208.1332.

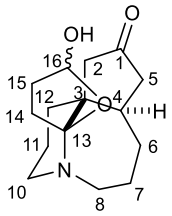
(4*S*,7a*R*,10a*R*,11*S*)-11-[2-(1,3-Dioxolan-2-yl)ethyl]octahydro-1*H*-spiro[4,7a-methanocyclopenta[*e*]azonine-9,2'-[1,3]dioxolan]-11-ol (249)



Bromide **228** (20.5 mg, 0.113 mmol) in THF (0.4 mL) was added dropwise to magnesium (2.6 mg, 0.108 mmol) at 30 °C and the mixture was stirred for 1 h. The mixture was then added to a solution of lactam **247** (22.7 mg, 0.0903 mmol) in THF (0.3 mL) at 0 °C and allowed to warm to RT over 4 h. Sat. aq. NH_4Cl (3 mL) was added and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil (23.0 mg, 72%). R_f 0.15 (ether); ν_{max} (thin film)/cm^{-1} 3471br, 2947m, 1706w, 1452w, 1120s, 1024s; δ_H (500 MHz, CD_2Cl_2) 1.23 (1 H, d, *J* 13.0, C(11)**H**H′), 1.31 (1 H, d, *J* 13.0, C(2)**H**H′), 1.34−1.40 (1 H, m, C(14)**H**H′), 1.54 (1 H, d, *J* 13.5, C(7)**H**H′), 1.60 (1 H, t, *J* 12.0, C(5)**H**H′), 1.64−1.70 (2 H, m, C(12)**H**H′ and C(15)**H**H′), 1.71−1.81 (3 H, m, C(6)**H**H′, C(7)H**H′** and C(11)H**H′**), 1.82−1.92 (3 H, m, C(5)H**H′**, C(12)H**H′** and C(15)H**H′**), 1.96−2.08 (2 H, m, C(4)H and C(6)H**H′**), 2.22 (1 H, dt, *J* 14.0, 7.0, C(14)H**H′**), 2.31 (1 H, d, *J* 13.0, C(2)H**H′**), 2.68 (1 H, d, *J* 14.5, C(8)**H**H′), 2.80 (1 H, dd, *J* 14.5, 4.5, C(10)**H**H′), 2.91 (1 H, td, *J* 14.5, 2.0, C(10)H**H′**), 3.37 (1 H, t, *J* 14.5, C(8)H**H′**), 3.58 (1 H, bs, OH), 3.75−3.99 (8 H, m, C(17)H_2, C(18)H_2, C(19)H_2 and C(20)H_2),

4.86 (1 H, t, *J* 3.5, C(16)H); δ_C (125 MHz, CD_2Cl_2) 22.7 (C(11)), 25.7 (C(15)), 26.8 (C(14)), 31.4 (C(7)), 34.0 (C(6)), 38.5 (C(12)), 45.5 (C(5)), 45.8 (C(2)), 47.6 (C(4)), 49.0 (C(10)), 51.8 (C(8)), 53.8 (C(3)), 64.0 (C(20)), 64.1 (C(19)), 64.9 (C(18)), 65.0 (C(17)), 88.7 (C(13)), 104.5 (C(16)), 115.2 (C(1)); *m/z* (ESI^+) 354 (MH^+, 100%); HRMS (ESI^+): Found: 354.2273; $C_{19}H_{32}NO_5$ (MH^+) requires: 354.2275.

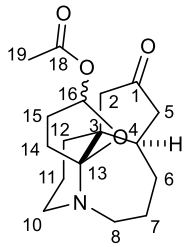
(2'*S*,4*S*,7a*R*,10a*R*)-5'-Hydroxydecahydro-3'*H*-spiro[4,7a-methanocyclopenta[*e*]azonine-11,2'-furan]-9(1*H*)-one (250)



0.5 M aq. HCl (0.5 mL) was added to a solution of hemiaminal **249** (6.00 mg, 0.0170 mmol) in THF (0.3 mL) and the mixture was stirred at RT for 1 h, then at 40 °C for 1.5 h. Sat. aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a colourless oil as an inseparable mixture of lactol diastereomers (4.50 mg, 100%, *dr*. 2:1). R_f 0.20 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 3413br, 2906m, 2855m, 1738s, 1452m, 1183m, 997s; δ_H (500 MHz, $CDCl_3$) 1.30−1.40 (1 H, m, C(11)**H**H′), 1.47−1.57 (1 H, m, C(11)**H**H′), 1.62−1.73 (6 H, m, C(7)**H**H′, C(12)H_2, C(12)**H**H′ and C(14)**H**H′ × 2), 1.74−1.91 (6 H, m, C(6)H_2, C(7)**H**H′, C(11)H**H′** × 2 and C(15)**H**H′), 1.93−2.02 (4 H, m, C(2)**H**H′, C(6)**H**H′, C(7)H**H′** and C(15)**H**H′), 2.04−2.17 (4 H, m, C(5)**H**H′, C(6)H**H′**, C(7)H**H′** and C(15)H**H′**), 2.17−2.31 (5 H, m, C(4)H × 2, C(5)**H**H′, C(12)H**H′** and C(14)H**H′**), 2.33−2.40

(1 H, m, C(15)H**H′**), 2.41−2.48 (1 H, m, C(5)H**H′**), 2.56 (1 H, dd, *J* 19.5, 2.5, C(2)H**H′**), 2.61−2.82 (5 H, m, C(2)**H**H′, C(5)H**H′**, C(8)**H**H′, C(10)**H**H′ and C(14)H**H′**), 2.90−3.04 (2 H, m, C(8)H**H′** and C(10)**H**H′), 3.14 (1 H, dd, *J* 17.5, 2.0, C(2)H**H′**), 3.19−3.36 (2 H, m, C(8)**H**H′ and C(10)H**H′**), 3.62−3.76 (2 H, m, C(8)H**H′** and C(10)H**H′**), 5.38 (1 H, dd, *J* 5.0, 1.5, C(16)H), 5.55−5.61 (1 H, m, C(16)H); δ_C (125 MHz, $CDCl_3$) 22.3/22.6 (C(11)), 28.2/29.9 (C(14)), 30.8/31.9 (C(7)), 33.7/34.2 (C(15)), 34.4/36.2 (C(6)), 39.2/40.4 (C(12)), 43.3/44.9 (C(4)), 47.7/47.9 (C(5)), 48.4/49.7 (C(10)), 50.1/50.5 (C(3)), 51.0/51.1 (C(2)), 52.0/52.3 (C(8)), 99.1/99.3 (C(16)), 101.8/102.3 (C(13)), 216.5/217.3 (C(1)); *m/z* (ESI^+) 266 (MH^+, 100%); HRMS (ESI^+): Found: 266.1749; $C_{15}H_{24}NO_3$ (MH^+) requires: 266.1751.

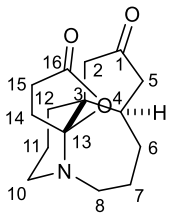
(2'*S*,4*R*,7a*S*,10a*R*)-9-Oxododecahydro-3'*H*-spiro[4,7a-methanocyclopenta[*e*]azonine-11,2'-furan]-5'-yl acetate (251)



Dess–Martin periodinane (32.0 mg, 0.0754 mmol) was added to a solution of lactol **250** (10.0 mg, 0.0377 mmol) in DCM (1.8 mL) at 0 °C and the mixture was stirred at RT for 6 h. Sat. aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a colourless oil as an inseparable mixture of acetoxy diastereomers (5.00 mg, 43%, *dr.* 2:1). R_f 0.50 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2916w, 1741s, 1668w, 1238m, 1184m, 994m; δ_H (500 MHz, $CDCl_3$) 1.30−1.40 (3 H, m, C(11)**H**H′ and C(11)H_2),

1.50−1.96 (15 H, m, C(2)**H**H′ × 2, C(6)**H**H′ × 2, C(7)**H**H′ × 2, C(11)H**H′**, C(12)H_2 × 2, C(14)**H**H′ × 2 and C(15)**H**H′ × 2), 2.02 (3 H, s, C(19)H_3), 2.09 (3 H, s, C(19)H_3), 2.06−2.46 (14 H, m, C(4)H × 2, C(5)H_2 × 2, C(6)H**H′** × 2, C(7)H**H′** × 2, C(14)H**H′** × 2 and C(15)H**H′** × 2), 2.67−2.84 (2 H, m, C(8)**H**H′ × 2), 2.92−3.12 (4 H, m, C(2)H**H′** × 2 and C(10)**H**H′ × 2), 3.16−3.36 (4 H, m, C(8)H**H′** × 2 and C(10)H**H′** × 2), 6.34 (1 H, d, *J* 5.0, C(16)H), 6.39−6.44 (1 H, m, C(16)H); δ_C (125 MHz, $CDCl_3$) 21.3/21.4 (C(19)), 22.1/22.2 (C(11)), 28.9/29.6 (C(14)), 30.5/30.8 (C(7)), 33.2/33.4 (C(15)), 34.1/34.2 (C(6)), 38.6/40.5 (C(12)), 44.7/44.8 (C(4)), 47.4/47.5 (C(5)), 50.1/50.2 (C(10)), 50.5/50.6 (C(3)), 50.7/50.8 (C(2)), 51.3/51.5 (C(8)), 99.0/100.3 (C(16)), 101.3/103.6 (C(13)), 216.2/217.0 (C(1)); *m/z* (ESI^+) 308 (MH^+, 100%); HRMS (ESI^+): Found: 308.1865; $C_{17}H_{26}NO_4$ (MH^+) requires: 308.1856.

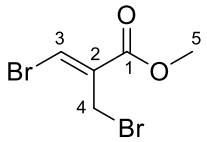
(2'*S*,4*S*,7a*R*,10a*R*)-Octahydro-3'*H*-spiro[4,7a-methanocyclopenta[*e*]azonine-11,2'-furan]-5',9(1*H*,4'*H*)-dione (252)



Powdered 4 Å molecular sieves (46.0 mg) was added to a solution of lactol **250** (11.3 mg, 0.0426 mmol) in DCM (0.9 mL) and the mixture was stirred at RT for 15 min. Pyridinium chlorochromate (46.0 mg, 0.213 mmol) was then added and the mixture was stirred at RT for 6 h. The mixture was filtered and washed with DCM. The filtrate was then washed with sat. aq. $NaHCO_3$ (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a colourless oil (4.50 mg, 40%). R_f 0.50 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2917m, 1782s, 1744s,

1456w, 1194m, 1054m, 916m; δ_H (500 MHz, CD_2Cl_2) 1.39 (1 H, dd, *J* 14.0, 3.5, C(11)**H**H′), 1.60−1.69 (2 H, m, C(12)H_2), 1.70−1.82 (2 H, m, C(7)**H**H′ and C(14)**H**H′), 1.85 (1 H, dd, *J* 17.0, 2.0, C(2)**H**H′), 1.82−1.94 (3 H, m, C(6)**H**H′, C(7)H**H′** and C(11)H**H′**), 2.04−2.17 (1 H, m, C(6)H**H′**), 2.24−2.37 (3 H, m, C(4)H, C(5)**H**H′ and C(15)**H**H′), 2.39−2.47 (1 H, m, C(5)H**H′**), 2.51−2.59 (1 H, m, C(14)H**H′**), 2.59−2.67 (1 H, m, C(15)H**H′**), 2.72 (1 H, dd, *J* 17.0, 1.5, C(2)H**H′**), 2.76−2.82 (1 H, m, C(8)**H**H′), 2.98 (1 H, dd, *J* 15.0, 5.5, C(10)**H**H′), 3.19 (1 H, td, *J* 15.0, 3.5, C(8)H**H′**), 3.32 (1 H, td, *J* 15.0, 4.5, C(10)H**H′**); δ_C (125 MHz, CD_2Cl_2) 21.7 (C(11)), 27.3 (C(15)), 28.8 (C(14)), 31.0 (C(7)), 33.9 (C(6)), 38.5 (C(12)), 44.4 (C(4)), 47.2 (C(3) and C(5)), 49.5 (C(10)), 50.1 (C(2)), 51.5 (C(8)), 101.3 (C(13)), 177.1 (C(16)), 214.2 (C(1)); *m/z* (ESI^+) 286 (MNa^+, 60%), 264 (MH^+, 100); HRMS (ESI^+): Found: 286.1416; $C_{15}H_{21}NNaO_3$ (MNa^+) requires: 286.1414.

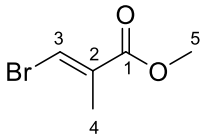
3-Bromo-2-bromomethylacrylic acid methyl ester (255)[96]



N-Bromosuccinimide (54.7 mg, 0.307 mmol) and benzoyl peroxide (3.5 mg, 0.0140 mmol) were added to a solution of ester **259** (50.0 mg, 0.279 mmol) in 1,2-dichloroethane (0.7 mL) and the mixture was stirred under reflux for 16 h. The solvent was removed under *vacuo*. Purification by flash chromatography (silica, 10:1 petrol:ether) afforded the title compound as a colourless oil (64.3 mg, 89%). R_f 0.5 (10:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2955w, 1721s, 1604m, 1436m, 1326m, 1244m, 1158m; δ_H (400 MHz, $CDCl_3$) 3.82 (3 H, s, C(5)H_3), 4.31 (2 H, s, C(4)H_2), 7.75 (1 H, s, C(3)H); δ_C (100 MHz, $CDCl_3$) 25.6 (C(4)), 52.8 (C(5)),

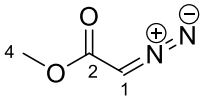
127.9 (C(3)), 134.9 (C(2)), 163.3 (C(1)); *m/z* (EI^+) 260 ($M(^{81}Br^{81}Br)^{+\cdot}$, 50%), 258 ($M(^{79}Br^{81}Br)^{+\cdot}$, 100), 256 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50).

3-Bromo-2-methylacrylic acid methyl ester (259)[96]



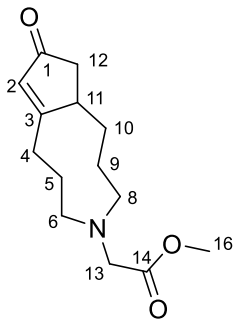
Bromine (0.479 mL, 9.35 mmol) in 1,2-dichloroethane (1 mL) was slowly added to a solution of methyl methacrylate (1.00 mL, 9.35 mmol) in 1,2-dichloroethane (2 mL) at 0 °C and the mixture was stirred at RT for 3 h. 1,8-Diazabicyclo[5.4.0]undec-7-ene (2.10 mL, 14.0 mmol) was added dropwise to the mixture at 0 °C and the mixture was stirred at 0 °C for 15 min, then at RT for 5 h. The mixture was then acidified to pH 1-2 with 5% HCl solution, organic layer separated and aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (1.59 g, 95%). R_f 0.65 (10:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2953w, 1721s, 1615m, 1436m, 1309m, 1232m, 1111m; δ_H (400 MHz, $CDCl_3$) 1.98 (3 H, d, *J* 1.5, C(4)H_3), 3.74 (3 H, s, C(5)H_3), 7.50 (1 H, q, *J* 1.5, C(3)H); δ_C (100 MHz, $CDCl_3$) 15.7 (C(4)), 52.3 (C(5)), 122.9 (C(3)), 133.9 (C(2)), 165.5 (C(1)); *m/z* (EI^+) 180 ($M(^{81}Br)^{+\cdot}$, 100%), 178 ($M(^{79}Br)^{+\cdot}$, 100).

Diazoacetic acid methyl ester (261)[103]



A solution of $NaNO_2$ (0.616 g, 8.92 mmol) in H_2O (2 mL) was added to a solution of glycine methyl ester hydrochloride (1.00 g, 7.96 mmol) in H_2O (2 mL) and DCM (4.4 mL) at –10 °C. 5% H_2SO_4 (0.722 mL) was then added dropwise to the solution and the mixture was stirred for 10 min. The organic layer was added to 5% Na_2CO_3 at 0 °C and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a yellow oil (0.550 g, 69%). ν_{max} (thin film)/cm^{-1} 3100w, 2106s, 1684s, 1437s, 1366s, 1197s, 741s; δ_H (500 MHz, C_6D_6) 3.30 (3 H, s, C(4)H_3), 3.92 (1 H, s, C(1)H); δ_C (125 MHz, C_6D_6) 45.1 (C(1)), 51.0 (C(4)), 166.0 (C(2)); *m/z* (EI^+) 100 ($M^{+\cdot}$, 100%).

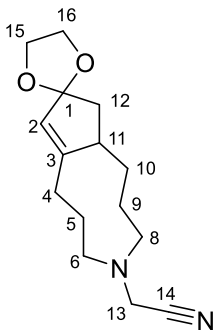
Methyl 2-[9-oxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonin-4(1*H*)-yl]acetate (264)



Copper (II) acetylacetonate (1.89 mg, 7.22 μmol) was added to a 0.025 M solution of amine **92** (13.0 mg, 0.0722 mmol) in toluene (2.9 mL) and the mixture was heated to reflux. A 0.1 M solution of diazo **261** (7.2 mg, 0.0722 mmol) in toluene (0.7 mL) was then added dropwise slowly to the mixture. The mixture was stirred under reflux for 16 h and cooled to RT before

washing with 0.5 M aq. K_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a brown oil (5.20 mg, 29%). R_f 0.45 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2927m, 2855m, 1739s, 1438m, 1198m; δ_H (500 MHz, CD_2Cl_2) 1.09−1.14 (1 H, m, C(9)**H**H′), 1.34−1.40 (1 H, m, C(9)H**H′**), 1.65−1.70 (1 H, m, C(5)**H**H′), 1.79−1.92 (2 H, m, C(5)H**H′** and C(10)**H**H′), 2.01−2.08 (1 H, m, C(12)**H**H′), 2.19−2.26 (1 H, m, C(10)H**H′**), 2.33−2.40 (1 H, m, C(8)**H**H′), 2.41−2.51 (2 H, m, C(4)**H**H′ and C(12)H**H′**), 2.52−2.63 (2 H, m, C(6)H_2), 2.65−2.70 (1 H, m, C(4)H**H′**), 2.80−2.86 (1 H, m, C(8)H**H′**), 3.06−3.11 (1 H, m, C(11)H), 3.16 (1 H, d, *J* 17.5, C(13)**H**H′), 3.26 (1 H, d, *J* 17.5, C(13)H**H′**), 5.07−5.15 (1 H, m, C(2)H); δ_C (125 MHz, CD_2Cl_2) 19.9 (C(9)), 25.3 (C(10)), 26.4 (C(4)), 26.9 (C(5)), 40.5 (C(12)), 44.1 (C(11)), 48.0 (C(6)), 51.1 (C(16)), 53.8 (C(8)), 54.9 (C(13)), 125.0 (C(2)), 172.2 (C(14)), 186.9 (C(3)), 208.4 (C(1)); *m/z* (ESI^+) 252 (MH^+, 100%); HRMS (ESI^+): Found: 252.1594; $C_{14}H_{22}NO_3$ (MH^+) requires: 252.1594.

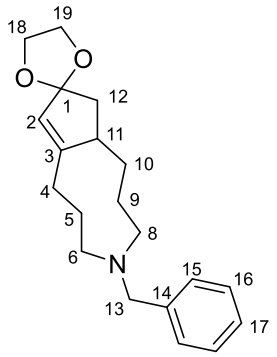
2-{2,3,6,7,7a,8-Hexahydro-1*H*-spiro[cyclopenta[*e*]azonine-9,2'-[1,3]dioxolan]-4(5*H*)-yl}acetonitrile (267)



Bromoacetonitrile (14.0 μL, 0.202 mmol) was added to a solution of amine **201** (9.00 mg, 0.0403 mmol) in benzene (0.5 mL) and the mixture was stirred at RT for 16 h. The solvent was removed in *vacuo* and the white solid was dissolved in THF (0.4 mL). Potassium *tert*-

butoxide (80.5 μL, 0.0806 mmol, 1 M in THF) was added to the mixture and stirred at 50 °C for 16 h. Water (1 mL) was added and the mixture was extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a colourless oil (8.50 mg, 80%). R_f 0.90 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 2933m, 1647w, 1307m, 1141m, 1087s, 997m; δ_H (500 MHz, CD_2Cl_2) 1.31−1.48 (2 H, m, C(9)H_2), 1.52−1.66 (2 H, m, C(5)**H**H′ and C(10)**H**H′), 1.67−1.77 (2 H, m, C(5)H**H′** and C(12)**H**H′), 1.85−1.93 (1 H, m, C(10)H**H′**), 2.13−2.25 (3 H, m, C(4)H_2 and C(12)H**H′**), 2.26−2.35 (2 H, m, C(6)**H**H′ and C(8)**H**H′), 2.63−2.72 (2 H, m, C(6)H**H′** and C(8)H**H′**), 2.77−2.84 (1 H, m, C(11)H), 3.42 (1 H, dd, *J* 17.0, 1.5, C(13)**H**H′), 3.56 (1 H, d, *J* 17.0, C(13)H**H′**), 3.83−3.90 (4 H, m, C(15)H_2 and C(16)H_2), 5.47 (1 H, t, *J* 1.5, C(2)H); δ_C (125 MHz, CD_2Cl_2) 19.7 (C(9)), 23.4 (C(4)), 25.3 (C(10)), 26.1 (C(5)), 40.5 (C(12)), 43.9 (C(13)), 45.1 (C(11)), 46.0 (C(6)), 53.5 (C(8)), 64.3 (C(16)), 64.4 (C(15)), 116.3 (C(14)), 119.1 (C(1)), 126.4 (C(2)), 153.7 (C(3)); *m/z* (ESI^+) 263 (MH^+, 100%); HRMS (ESI^+): Found: 263.1751; $C_{15}H_{23}N_2O_2$ (MH^+) requires: 263.1754.

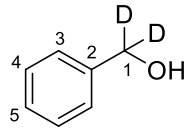
4-Benzyl-2,3,4,5,6,7,7a,8-octahydro-1*H*-spiro[cyclopenta[*e*]azonine-9,2'-[1,3]dioxolane] (268)



Benzylbromide (7.5 μL, 0.0605 mmol) was added to a solution of amine **201** (9.00 mg, 0.0403 mmol) in benzene (0.4 mL) and the mixture was stirred at RT for 16 h. The solvent was removed in *vacuo* and the white solid was dissolved in THF (0.4 mL). Potassium *tert*-butoxide (80.5 μL, 0.0806 mmol, 1 M in THF) was added to the mixture and stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the *title compound* as a colourless oil (10.2 mg, 81%). R_f 0.70 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2922m, 1452w, 1360w, 1087s, 1054m; δ_H (500 MHz, CD_2Cl_2) 1.25−1.37 (2 H, m, C(9)H_2), 1.43−1.53 (2 H, m, C(5)**H**H′ and C(10)**H**H′), 1.63−1.73 (2 H, m, C(5)H**H′** and C(12)**H**H′), 1.96 (1 H, dq, *J* 14.0, 4.0, C(10)H**H′**), 2.11−2.33 (5 H, m, C(4)**H**H′, C(6)**H**H′, C(8)H_2 and C(12)H**H′**), 2.52 (1 H, td, *J* 13.5, 4.5, C(4)H**H′**), 2.68 (1 H, td, *J* 13.0, 4.0, C(6)H**H′**), 2.78−2.87 (1 H, m, C(11)H), 3.37 (1 H, d, *J* 13.0, C(13)**H**H′), 3.70 (1 H, d, *J* 13.0, C(13)H**H′**), 3.80−3.93 (4 H, m, C(18)H_2 and C(19)H_2), 5.48 (1 H, t, *J* 2.0, C(2)H), 7.18−7.25 (1 H, m, C(17)H), 7.27−7.37 (4 H, m, C(15)H × 2 and C(16)H × 2); δ_C (125 MHz, CD_2Cl_2) 19.8 (C(9)), 23.5 (C(4)), 24.8 (C(10)), 27.2 (C(5)), 40.5 (C(12)), 45.3 (C(11)), 47.4 (C(6)), 52.4 (C(8)), 61.0 (C(13)), 64.3 (C(19)), 64.4 (C(18)), 119.4 (C(1)), 126.3 (C(2)),

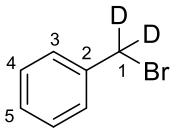
126.6 (C(17)), 128.0 (C(16)), 129.2 (C(15)), 140.7 (C(14)), 154.5 (C(3)); *m/z* (ESI^+) 314 (MH^+, 100%); HRMS (ESI^+): Found: 314.2108; $C_{20}H_{28}NO_2$ (MH^+) requires: 314.2115.

Benzyl alcohol-*α,α*-d_2 (269)[105]



A solution of ethyl benzoate (100 mg, 0.666 mmol) in ether (0.3 mL) was added to a suspension of lithium aluminium deuteride (42.0 mg, 0.999 mmol) in ether (0.3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and at RT for 2 h. Water (0.1 mL) was added and the mixture was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the title compound as a colourless oil (61.0 mg, 83%). R_f 0.45 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3315br, 2092w, 1449m, 1229m, 1059m, 715s; δ_H (500 MHz, $CDCl_3$) 1.69 (1 H, bs, OH), 7.28−7.33 (1 H, m, C(5)H), 7.35−7.39 (4 H, m, C(3)H × 2 and C(4)H × 2); δ_C (125 MHz, $CDCl_3$) 64.7 (1:2:3:2:1 quin, *J* 22.0, C(1)), 127.1 (C(3)), 127.7 (C(5)), 128.6 (C(4)), 140.8 (C(2)); *m/z* (EI^+) 110 ($M^{+\cdot}$, 100%).

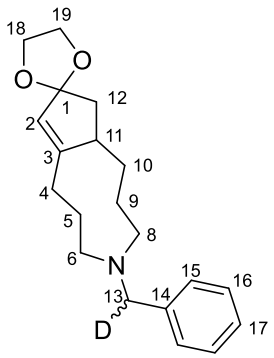
Benzyl bromide-*α,α*-d_2 (270)[105]



Phosphorus tribromide (21.5 μL, 0.227 mmol) was added to a solution of alcohol **269** (50.0 mg, 0.454 mmol) in DCM (0.5 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h and at

RT for 16 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the title compound as a colourless oil (67.9 mg, 86%). R_f 0.90 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3029w, 1495w, 1449m, 1229w, 942m, 745s; δ_H (500 MHz, $CDCl_3$) 7.28−7.32 (1 H, m, C(5)H), 7.33−7.37 (2 H, m, C(3)H × 2), 7.38−7.43 (2 H, m, C(4)H × 2); δ_C (125 MHz, $CDCl_3$) 33.2 (1:2:3:2:1 quin, *J* 24.0, C(1)), 128.5 (C(5)), 128.8 (C(3)), 129.0 (C(4)), 137.7 (C(2)); *m/z* (EI^+) 174 ($M(^{81}Br)^{+\cdot}$, 90%), 172 ($M(^{79}Br)^{+\cdot}$, 100).

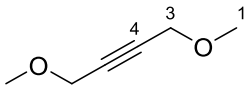
4-[Deutero(phenyl)methyl]-2,3,4,5,6,7,7a,8-octahydro-1*H*-spiro[cyclopenta[*e*]azonine-9,2'-[1,3]dioxolane] (272)



Bromide **270** (11.5 mg, 0.0675 mmol) was added to a solution of amine **201** (13.7 mg, 0.0613 mmol) in benzene (0.6 mL) and the mixture was stirred at RT for 16 h. The solvent was removed in *vacuo* and the white solid was dissolved in THF (0.6 mL). Potassium *tert*-butoxide (0.123 mL, 0.123 mmol, 1 M in THF) was added to the mixture and stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with DCM (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the *title compound* as a colourless oil (17.0 mg, 88%). R_f 0.70 (1:1 petrol:ether); ν_{max} (thin

film)/cm^{-1} 2936w, 1471w, 1362w, 1086s, 1003m, 715m; δ_H (500 MHz, CD_2Cl_2) 1.23−1.38 (2 H, m, C(9)H_2), 1.42−1.53 (2 H, m, C(5)**H**H′ and C(10)**H**H′), 1.62−1.74 (2 H, m, C(5)H**H′** and C(12)**H**H′), 1.96 (1 H, dq, *J* 14.0, 3.5, C(10)H**H′**), 2.10−2.33 (5 H, m, C(4)**H**H′, C(6)**H**H′, C(8)H_2 and C(12)H**H′**), 2.47−2.56 (1 H, m, C(4)H**H′**), 2.68 (1 H, tt, *J* 13.0, 3.5, C(6)H**H′**), 2.79−2.86 (1 H, m, C(11)H), 3.34 (1 H, s, C(13)HD), 3.67 (1 H, s, C(13)DH), 3.83−3.92 (4 H, m, C(18)H_2 and C(19)H_2), 5.49 (1 H, s, C(2)H), 7.19−7.25 (1 H, m, C(17)H), 7.27−7.36 (4 H, m, C(15)H × 2 and C(16)H × 2); δ_C (125 MHz, CD_2Cl_2) 19.8 (C(9)), 23.5 (C(4)), 24.8 (C(10)), 27.2 (C(5)), 40.5 (C(12)), 45.3 (C(11)), 47.3 (C(6)), 52.4 (C(8)), 60.6 (1:1:1 t, *J* 20.0, C(13)), 64.3 (C(19)), 64.4 (C(18)), 119.4 (C(1)), 126.3 (C(2)), 126.6 (C(17)), 128.0 (C(16)), 129.2 (C(15)), 140.6 (C(14)), 154.5 (C(3)); *m/z* (ESI$^+$) 315 (MH^+, 100%); HRMS (ESI$^+$): Found: 315.2165; $C_{20}H_{27}DNO_2$ (MH^+) requires: 315.2177.

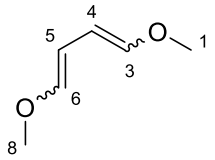
1,4-Dimethoxy-but-2-yne (274)[106]



Sodium hydroxide powder (5 × 2.10 g, 0.261 mmol) and dimethylsulfate (5 × 4.94 mL, 0.261 mmol) were added alternately to a solution of but-2-yne-1,4-diol (10.0 g, 0.116 mmol) in H_2O (18.6 mL), maintaining the temperature below 40 °C with an ice bath. The mixture was then stirred at 90 °C for 3 h. Ice water (17 mL) was added and mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless oil (11.2 g, 84%). R_f 0.50 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2823w, 1450w, 1353m, 1187m, 1086s, 904m; δ_H (400 MHz, $CDCl_3$) 3.39 (6 H, s,

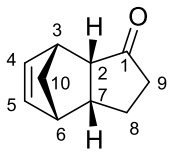
$C(1)H_3$ × 2), 4.15 (4 H, s, $C(3)H_2$ × 2); δ_C (100 MHz, $CDCl_3$) 57.6 (C(1)), 59.9 (C(3)), 82.3 (C(2)); *m/z* (ESI^+) 137 (MNa^+, 50%).

1,4-Dimethoxy-1,3-butadiene (275)[106]



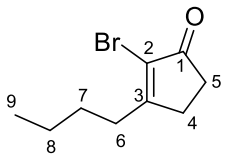
Potassium *tert*-butoxide (1.75 mL, 1.75 mmol, 1 M in THF) was added to a solution of alkyne **274** (2.00 g, 17.5 mmol) in DMSO (3.5 mL) and the mixture was stirred at 60 °C for 1.5 h. The mixture was then poured into water (10 mL) and extracted with ether (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 95:5 petrol:ether) afforded the title compound as a yellow oil as an inseparable mixture of isomers (*Z*,*Z*:*Z*,*E*:*E*,*E* = 5:3:1) (1.60 g, 80%). R_f 0.70 (85:15 petrol:ether); ν_{max} (thin film)/cm^{-1} 2936w, 1611m, 1453w, 1247m, 1092s, 938m; δ_H (400 MHz, C_6D_6) for *Z*,*Z* 3.15 (6 H, s, $C(1)H_3$ and $C(8)H_3$), 5.58 (2 H, dd, *J* 3.5, 1.5, C(3)H and C(6)H), 5.81 (2 H, dd, *J* 3.5, 1.5, C(4)H and C(5)H); for *Z*,*E* 3.11 (6 H, s, $C(1)H_3$ and $C(8)H_3$), 4.95 (1 H, dd, *J* 10.5, 6.0, C(4)H), 5.53 (1 H, d, *J* 6.0, C(3)H), 6.09 (1 H, ddd, *J* 12.5, 10.5, 1.0, C(5)H), 6.58 (1 H, d, *J* 12.5, C(6)H); for *E*,*E* 3.15 (6 H, s, $C(1)H_3$ and $C(8)H_3$), 5.36 (2 H, dd, *J* 9.0, 2.5, C(4)H and C(5)H), 6.38 (2 H, dd, *J* 9.0, 2.5, C(3)H and C(6)H); δ_C (100 MHz, $CDCl_3$) for *Z*,*Z* 55.1 (C(1) and C(8)), 100.4 (C(4) and C(5)), 145.0 (C(3) and C(6)); for *Z*,*E* 58.9 (C(1) and C(8)), 98.9 (C(5)), 103.3 (C(4)), 143.6 (C(3)), 148.6 (C(6)); for *E*,*E* 58.8 (C(1) and C(8)), 101.7 (C(4) and C(5)), 147.2 (C(3) and C(6)); *m/z* (EI^+) 114 ($M^{+\cdot}$, 100%).

(3a*R*,4*S*,7*R*,7a*S*)-2,3,3a,4,7,7a-Hexahydro-1*H*-4,7-methanoinden-1-one (276)[173]



Cyclopentadiene (0.316 g, 4.77 mmol) was added to a solution of 2-cyclopentenone (0.100 mL, 1.19 mmol) in toluene (1.6 mL) in a sealed tube and the mixture was stirred at 150 °C for 16 h. The solvent was removed in *vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a white solid (60.0 mg, 34%). R_f 0.45 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2962m, 1727s, 1342w, 1172m, 733m; δ_H (400 MHz, $CDCl_3$) 1.34−1.41 (1 H, m, C(10)**H**H′), 1.43−1.54 (2 H, m, C(8)**H**H′ and C(10)H**H′**), 1.86−2.03 (2 H, m, C(8)H**H′** and C(9)**H**H′), 2.04−2.17 (1 H, m, C(9)H**H′**), 2.77−2.85 (1 H, m, C(2)H), 2.89−3.01 (2 H, m, C(6)H and C(7)H), 3.16 (1 H, td, *J* 3.0, 1.5, C(3)H), 6.07 (1 H, dd, *J* 6.0, 3.0, C(4)H), 6.18 (1 H, dd, *J* 6.0, 3.0, C(5)H); δ_C (100 MHz, $CDCl_3$) 22.7 (C(8)), 40.6 (C(9)), 41.2 (C(7)), 47.0 (C(3)), 47.5 (C(6)), 52.3 (C(10)), 54.3 (C(2)), 134.8 (C(5)), 136.2 (C(4)), 222.3 (C(1)); *m/z* (ESI$^+$) 171 (MNa$^+$, 100%).

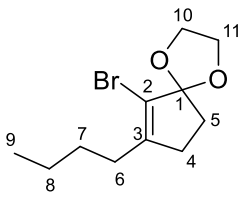
2-Bromo-3-butylcyclopent-2-enone (277)[108]



A solution of bromine (28.0 μL, 0.543 mmol) in DCE (0.2 mL) was added dropwise to a solution of enone **207** (50.0 mg, 0.362 mmol) in DCE (0.2 mL) at 0 °C and the mixture was stirred at 0 °C for 5 min. A solution of triethylamine (75.5 μL, 0.543 mmol) in DCE (0.2 mL) was added dropwise and the mixture was stirred at RT for 4 h. 5% HCl (1 mL) was added and

the organic layer was separated. The aqueous layer was extracted with ether (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless oil (45.3 mg, 58%). R_f 0.45 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2930w, 1715s, 1611m, 1435w, 1267w, 1155w; δ_H (400 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 7.5, C(9)H_3), 1.38 (2 H, sex, *J* 7.5, C(8)H_2), 1.55 (2 H, quin, *J* 7.5, C(7)H_2), 2.48−2.58 (4 H, m, C(5)H_2 and C(6)H_2), 2.61−2.69 (2 H, m, C(4)H_2); δ_C (100 MHz, $CDCl_3$) 13.8 (C(9)), 22.6 (C(8)), 28.7 (C(7)), 30.3 (C(4)), 32.5 (C(6)), 33.1 (C(5)), 122.9 (C(2)), 177.2 (C(3)), 201.7 (C(1)); *m/z* (ESI$^+$) 241 (M(^{81}Br)Na$^+$, 95%), 239 (M(^{79}Br)Na$^+$, 100), 219 (M(^{81}Br)H$^+$, 15), 217 (M(^{79}Br)H$^+$, 15).

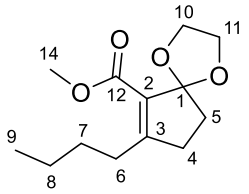
6-Bromo-7-butyl-1,4-dioxaspiro[4.4]non-6-ene (278)



p-TsOH·H_2O (4.0 mg, 20.9 μmol) was added to a solution of enone **277** (45.3 mg, 0.209 mmol) and ethylene glycol (35.0 μL, 0.626 mmol) in benzene (1.6 mL) and the mixture was stirred under reflux for 16 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a pale yellow oil (30.0 mg, 55%, 91% b.r.s.m.). R_f 0.80 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2931w, 1466w, 1319m, 1169m, 1031s, 949m; δ_H (400 MHz, CD_2Cl_2) 0.91 (3 H, t, *J* 7.5, C(9)H_3), 1.33 (2 H, sex, *J* 7.5, C(8)H_2), 1.42 (2 H, quin, *J* 7.5, C(7)H_2), 2.10−2.15 (2 H, m, C(5)H_2), 2.20 (2 H, t, *J* 7.5, C(6)H_2), 2.32−2.37 (2

H, m, C(4)H_2), 3.88−3.98 (2 H, m, C(10)H_2), 4.06−4.15 (2 H, m, C(11)H_2); δ_C (100 MHz, CD_2Cl_2) 13.6 (C(9)), 22.5 (C(8)), 28.7 (C(7)), 30.1 (C(6)), 30.6 (C(4)), 34.3 (C(5)), 65.7 (C(10) and C(11)), 118.2 (C(2)), 118.9 (C(1)), 148.1 (C(3)); *m/z* (EI^+) 262 ($M(^{81}Br)^{+\cdot}$, 100%), 260 ($M(^{79}Br)^{+\cdot}$, 100); HRMS (EI^+): Found: 260.0412; $C_{11}H_{17}O_2Br$ ($M(^{79}Br)^{+\cdot}$) requires: 260.0407.

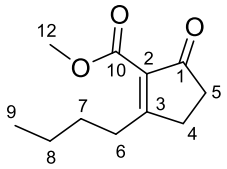
7-Butyl-1,4-dioxaspiro[4.4]non-6-ene-6-carboxylic acid methyl ester (279)



n-Butyllithium (56.0 μL, 0.139 mmol, 2.5 M in hexane) was added to a solution of bromide **278** (28.0 mg, 0.107 mmol) in THF (1.2 mL) at –78 °C and the mixture was stirred at –78 °C for 45 min. Methyl chloroformate (25.0 μL, 0.322 mmol) was then added and the mixture was stirred at –78 °C for 30 min and at RT for 15 min. 20% aq. Na_2HPO_4 (1 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a pale yellow oil (21.1 mg, 82%). R_f 0.45 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2955w, 1712s, 1641w, 1435w, 1304m, 1042s; δ_H (400 MHz, CD_2Cl_2) 0.91 (3 H, t, *J* 7.5, C(9)H_3), 1.33 (2 H, sex, *J* 7.5, C(8)H_2), 1.45 (2 H, quin, *J* 7.5, C(7)H_2), 1.98−2.03 (2 H, m, C(5)H_2), 2.39−2.44 (2 H, m, C(4)H_2), 2.54 (2 H, t, *J* 7.5, C(6)H_2), 3.70 (3 H, s, C(14)H_3), 3.84−3.92 (2 H, m, C(10)H_2), 4.01−4.10 (2 H, m, C(11)H_2); δ_C (100 MHz, CD_2Cl_2) 13.6 (C(9)), 22.7 (C(8)), 29.8 (C(7)), 30.7 (C(6)), 32.3 (C(4)), 36.2 (C(5)), 50.7 (C(14)), 65.5 (C(10) and C(11)), 119.9 (C(1)), 127.7 (C(2)), 165.0

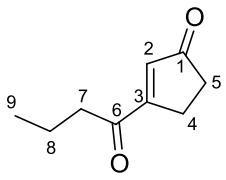
(C(12)), 165.5 (C(3)); *m/z* (ESI^+) 263 (MNa^+, 80%), 241 (MH^+, 30); HRMS (ESI^+): Found: 263.1250; $C_{13}H_{20}O_4Na$ (MNa^+) requires: 263.1254.

2-Butyl-5-oxocyclopent-1-enecarboxylic acid methyl ester (280)



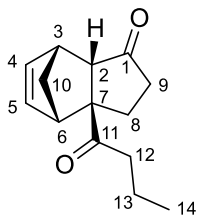
Oxalic acid (7.5 mg, 0.0816 mmol) was added to a solution of ester **279** (19.6 mg, 0.0816 mmol) in DCM/H_2O (1:1, 0.4 mL) and the mixture was stirred at RT for 24 h. Sat. aq. $NaHCO_3$ (1 mL) was added and the mixture was extracted with ether (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (11.6 mg, 73%). R_f 0.15 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2957w, 1745m, 1713s, 1622w, 1435w, 1024w; δ_H (500 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 7.5, C(9)H_3), 1.40 (2 H, sex, *J* 7.5, C(8)H_2), 1.57 (2 H, quin, *J* 7.5, C(7)H_2), 2.46−2.50 (2 H, m, C(5)H_2), 2.65−2.70 (2 H, m, C(4)H_2), 2.77 (2 H, t, *J* 7.5, C(6)H_2), 3.84 (3 H, s, C(12)H_3); δ_C (125 MHz, $CDCl_3$) 13.8 (C(9)), 22.8 (C(8)), 29.8 (C(7)), 30.4 (C(4)), 32.4 (C(6)), 35.0 (C(5)), 51.9 (C(12)), 132.3 (C(2)), 163.8 (C(10)), 189.0 (C(3)), 203.8 (C(1)); *m/z* (ESI^+) 219 (MNa^+, 80%), 197 (MH^+, 20); HRMS (ESI^+): Found: 219.0985; $C_{11}H_{16}O_3Na$ (MNa^+) requires: 219.0992.

3-Butyrylcyclopent-2-enone (282)



Selenium dioxide (22.5 mg, 0.203 mmol) was added to a solution of enone **207** (20.0 mg, 0.145 mmol) in 1,4-dioxane (1.4 mL) and the mixture was stirred under reflux for 16 h. The mixture was then filtered through Celite and the solvent was removed in *vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a pale yellow oil (3.50 g, 16%). R_f 0.40 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2962w, 1716s, 1679m, 1437w, 1153m; δ_H (500 MHz, $CDCl_3$) 0.97 (3 H, t, *J* 7.5, C(9)H_3), 1.71 (2 H, sex, *J* 7.5, C(8)H_2), 2.49−2.53 (2 H, m, C(5)H_2), 2.77 (2 H, t, *J* 7.5, C(7)H_2), 2.81 (2 H, dt, *J* 7.5, 2.0, C(4)H_2), 6.62 (1 H, t, *J* 2.0, C(2)H); δ_C (125 MHz, $CDCl_3$) 13.7 (C(9)), 17.3 (C(8)), 26.5 (C(4)), 35.3 (C(5)), 42.2 (C(7)), 136.1 (C(2)), 169.2 (C(3)), 199.8 (C(6)), 210.3 (C(1)); *m/z* (EI$^+$) 152 ($M^{+\cdot}$, 100%); HRMS (EI$^+$): Found: 152.0837; $C_9H_{12}O_2$ ($M^{+\cdot}$) requires: 152.0832.

(3a*S*,4*S*,7*R*,7a*S*)-3a-Butyryl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methanoinden-1-one (283)



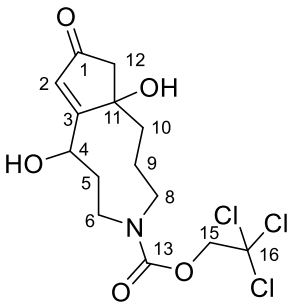
Cyclopentadiene (34.5 mg, 0.526 mmol) was added to enone **282** (8.00 mg, 0.0526 mmol) in a sealed tube and the mixture was stirred at 150 °C for 36 h. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (3.50 mg, 30%, 81% b.r.s.m.). R_f 0.25 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2962m, 1734s,

1702s, 1458w, 1174w; δ_H (500 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7.5, C(14)H_3), 1.41−1.47 (1 H, m, C(10)**H**H′), 1.53−1.59 (1 H, m, C(10)H**H′**), 1.60−1.74 (2 H, m, C(13)H_2), 1.83−1.93 (1 H, m, C(8)**H**H′), 2.12−2.20 (1 H, m, C(8)H**H′**), 2.29−2.38 (1 H, m, C(12)**H**H′), 2.44−2.66 (3 H, m, C(9)H_2 and C(12)H**H′**), 2.83−2.90 (1 H, m, C(2)H), 3.06−3.18 (1 H, m, C(6)H), 3.20−3.29 (1 H, m, C(3)H), 6.07 (1 H, dd, *J* 5.5, 3.0, C(5)H), 6.25 (1 H, dd, *J* 5.5, 3.0, C(4)H); δ_C (125 MHz, $CDCl_3$) 13.9 (C(14)), 17.1 (C(13)), 29.0 (C(8)), 40.3 (C(12)), 41.6 (C(9)), 46.3 (C(10)), 46.7 (C(3)), 51.7 (C(6)), 56.5 (C(2)), 66.4 (C(7)), 135.7 (C(5)), 139.3 (C(4)), 210.1 (C(11)), 217.5 (C(1)); *m/z* (EI^+) 218 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 218.1308; $C_{14}H_{18}O_2$ ($M^{+\cdot}$) requires: 218.1302.

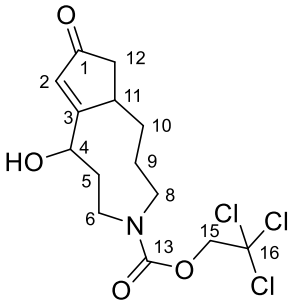
2,2,2-Trichloroethyl-1,7a-dihydroxy-9-oxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (284),

2,2,2-Trichloroethyl-1-hydroxy-9-oxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (285) and

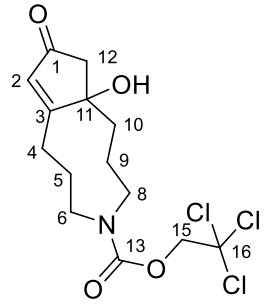
2,2,2-Trichloroethyl-7a-hydroxy-9-oxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (286)



284



285



286

Selenium dioxide (6.57 mg, 0.0592 mmol) was added to a solution of enone **200** (15.0 mg, 0.0423 mmol) in 1,4-dioxane (1.5 mL) and the mixture was stirred at 75 °C for 4 h. The mixture was then filtered through Celite and the solvent was removed in *vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded *diol* **284** as a yellow oil (4.00 mg, 24%). R_f 0.20 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 3402br, 2930w, 1692s, 1423m, 1129m, 717m; δ_H (500 MHz, $CDCl_3$) 1.40−1.53 (1 H, m, C(9)**H**H′), 1.66−1.76 (1 H, m, C(9)H**H′**), 2.00−2.12 (1 H, m, C(10)**H**H′), 2.15−2.27 (1 H, m, C(5)**H**H′), 2.32−2.41 (1 H, m, C(10)H**H′**), 2.43−2.76 (4 H, m, C(5)H**H′**, C(8)**H**H′ and C(12)H_2), 3.00 (1 H, ddd, *J* 15.0, 5.5, 1.5, C(6)**H**H′), 3.98 (1 H, dt, *J* 14.5, 3.0, C(8)H**H′**), 4.26 (1 H, td, *J* 14.0, 4.5, C(6)H**H′**), 4.37 (1 H, d, *J* 12.0, C(15)**H**H′), 4.83−4.92 (1 H, m, C(4)H), 4.92 (1 H, d, *J* 12.0, C(15)H**H′**), 6.21 (1 H, d, *J* 2.0, C(2)H); δ_C (125 MHz, $CDCl_3$) 21.5 (C(9)), 32.5 (C(5)), 39.1 (C(10)), 44.9 (C(6)), 51.9 (C(8)), 54.1 (C(12)), 67.0 (C(4)), 75.7 (C(15)), 79.9 (C(11)), 94.7 (C(16)), 129.5

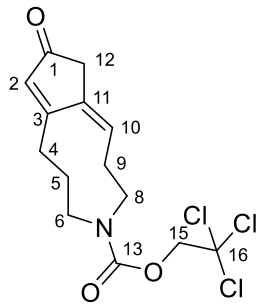
(C(2)), 155.7 (C(13)), 182.2 (C(3)), 202.3 (C(1)); *m/z* (EI^+) 391 (M($^{37}Cl^{37}Cl^{37}Cl$)$^{+\cdot}$, 4%), 389 (M($^{35}Cl^{37}Cl^{37}Cl$)$^{+\cdot}$, 33), 387 (M($^{35}Cl^{35}Cl^{37}Cl$)$^{+\cdot}$, 100), 385 (M($^{35}Cl^{35}Cl^{35}Cl$)$^{+\cdot}$, 100); HRMS (EI^+): Found: 385.0266; $C_{14}H_{18}NO_5Cl_3$ (M($^{35}Cl^{35}Cl^{35}Cl$)$^{+\cdot}$) requires: 385.0246.

Also obtained was *2º alcohol* **285** as a yellow oil (2.23 mg, 14%). R_f 0.40 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 3420br, 2928w, 1707s, 1420m, 1125m, 717m; δ_H (500 MHz, $CDCl_3$) 1.55−1.70 (2 H, m, C(9)H_2), 1.97−2.04 (1 H, m, C(10)**H**H′), 2.08−2.24 (3 H, m, C(5)**H**H′, C(10)H**H′** and C(12)**H**H′), 2.43−2.51 (1 H, m, C(5)H**H′**), 2.64−2.79 (2 H, m, C(8)**H**H′ and C(12)H**H′**), 2.96−3.03 (1 H, m, C(6)**H**H′), 3.12−3.18 (1 H, m, C(11)H), 3.98 (1 H, dt, *J* 14.5, 3.0, C(8)H**H′**), 4.27 (1 H, td, *J* 14.0, 4.5, C(6)H**H′**), 4.39 (1 H, d, *J* 12.0, C(15)**H**H′), 4.51−4.57 (1 H, m, C(4)H), 4.91 (1 H, d, *J* 12.0, C(15)H**H′**), 6.24 (1 H, t, *J* 1.5, C(2)H); δ_C (125 MHz, $CDCl_3$) 20.0 (C(9)), 31.2 (C(10)), 33.1 (C(5)), 39.4 (C(11)), 43.7 (C(12)), 44.6 (C(6)), 51.8 (C(8)), 70.5 (C(4)), 75.7 (C(15)), 94.8 (C(16)), 130.0 (C(2)), 155.7 (C(13)), 184.3 (C(3)), 207.1 (C(1)); *m/z* (EI^+) 375 (M($^{37}Cl^{37}Cl^{37}Cl$)$^{+\cdot}$, 4%), 373 (M($^{35}Cl^{37}Cl^{37}Cl$)$^{+\cdot}$, 33), 371 (M($^{35}Cl^{35}Cl^{37}Cl$)$^{+\cdot}$, 100), 369 (M($^{35}Cl^{35}Cl^{35}Cl$)$^{+\cdot}$, 100); HRMS (EI^+): Found: 369.0295; $C_{14}H_{18}NO_4Cl_3$ (M($^{35}Cl^{35}Cl^{35}Cl$)$^{+\cdot}$) requires: 369.0296.

Also obtained was *3º alcohol* **286** as a yellow oil as a mixture of diastereomers (6.67 mg, 43%, *dr*. 1.3:1). R_f 0.35 (10:1 $CHCl_3$:MeOH); ν_{max} (thin film)/cm^{-1} 3420br, 2928w, 1707s, 1420m, 1125m, 717m; δ_H (700 MHz, $CDCl_3$) 1.30−1.40 (1 H, m, C(9)**H**H′), 1.50−1.60 (1 H, m, C(9)**H**H′), 1.73−1.83 (2 H, m, C(9)H**H′** × 2), 1.87−1.93 (1 H, m, C(10)**H**H′), 2.00−2.13 (3 H, m, C(5)**H**H′ × 2 and C(10)**H**H′), 2.14−2.27 (3 H, m, C(5)H**H′** and C(10)H**H′** × 2), 2.33−2.43 (1 H, m, C(5)H**H′**), 2.44−2.69 (8 H, m, C(4)H_2 × 2 and C(12)H_2 × 2), 2.93−3.06 (2 H, m, C(6)**H**H′ and C(8)**H**H′), 3.19−3.25 (1 H, m, C(6)**H**H′), 3.26−3.34 (1 H, m, C(8)**H**H′), 3.35−3.45 (2 H, m, C(6)H**H′** and C(8)H**H′**), 3.62−3.71 (1 H, m, C(8)H**H′**), 3.74−3.83 (1 H, m, C(6)H**H′**), 4.41 (1 H, d, *J* 12.0, C(15)**H**H′), 4.60 (1 H, d, *J* 12.0,

C(15)**H**H′), 4.85 (1 H, d, *J* 12.0, C(15)H**H′**), 4.87 (1 H, d, *J* 12.0, C(15)H**H′**), 6.01 (1 H, s, C(2)H), 6.05 (1 H, s, C(2)H); δ_C (175 MHz, $CDCl_3$) 21.1/22.3 (C(9)), 24.0 (C(4)), 25.7 (C(5)), 25.8 (C(4)), 26.7 (C(5)), 35.0/36.8 (C(10)), 47.4 (C(6)), 49.7 (C(6) and C(12)), 50.6 (C(12)), 50.9 (C(8)), 75.2/75.5 (C(15)), 80.8/81.0 (C(11)), 95.4 (C(16)), 131.0/131.6 (C(2)), 154.3/155.1 (C(13)), 180.5/180.8 (C(3)), 204.0/204.3 (C(1)); *m/z* (EI^+) 375 ($M(^{37}Cl^{37}Cl^{37}Cl)^{+\cdot}$, 4%), 373 ($M(^{35}Cl^{37}Cl^{37}Cl)^{+\cdot}$, 33), 371 ($M(^{35}Cl^{35}Cl^{37}Cl)^{+\cdot}$, 100), 369 ($M(^{35}Cl^{35}Cl^{35}Cl)^{+\cdot}$, 100); HRMS ($EI^+$): Found: 369.0295; $C_{14}H_{18}NO_4Cl_3$ ($M(^{35}Cl^{35}Cl^{35}Cl)^{+\cdot}$) requires: 369.0296.

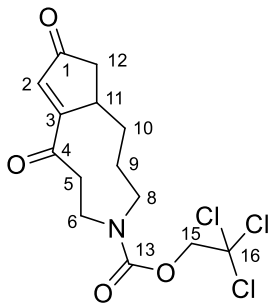
2,2,2-Trichloroethyl-(*Z*)-9-oxo-2,3,5,6,8,9-hexahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (287)



p-Toluenesulfonic acid (1.0 mg, 3.24 μmol) was added to a solution of alcohol **286** (6.00 mg, 0.0162 mmol) in benzene (1 mL) and the mixture was stirred under reflux for 2 h. The mixture was diluted with sat. aq. $NaHCO_3$ (1 mL) and the aqueous layer extracted with ether (3 × 2 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil as a mixture of carbamate rotamers (4.40 mg, 77%). R_f 0.40 (ether); ν_{max} (thin film)/cm^{-1} 2919w, 1710s, 1683s, 1420m, 1175m, 713m; δ_H (700 MHz, $CDCl_3$) 2.09−2.26 (4 H, m, C(5)H_2 × 2), 2.42−2.92 (8 H, m, C(4)H_2 × 2 and

C(9)H_2 × 2), 3.00 (4 H, d, *J* 17.5, C(12)H_2 × 2), 3.20−4.00 (8 H, m, C(6)H_2 × 2 and C(8)H_2 × 2), 4.57−4.73 (4 H, m, C(15)H_2 × 2), 5.75−5.84 (2 H, m, C(10)H × 2), 6.09 (1 H, s, C(2)H), 6.11 (1 H, s, C(2)H); δ_C (175 MHz, $CDCl_3$) 27.9/28.1 (C(9)), 29.1 (C(5)), 29.5/29.6 (C(4)), 30.4 (C(5)), 43.3 (C(12)), 48.3/48.7 (C(8)), 49.1/49.9 (C(6)), 75.1 (C(15)), 95.4 (C(16)), 124.6/124.8 (C(10)), 136.7/136.9 (C(2)), 138.8/138.9 (C(11)), 153.6/154.9 (C(13)), 173.9 (C(3)), 204.9/205.0 (C(1)); *m/z* (ESI^+) 380 (M($^{37}Cl^{37}Cl^{37}Cl$)Na^+, 4%), 378 (M($^{35}Cl^{37}Cl^{37}Cl$)Na^+, 33), 376 (M($^{35}Cl^{35}Cl^{37}Cl$)Na^+, 100), 374 (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+, 100); HRMS (ESI^+): Found: 374.0084; $C_{14}H_{16}NO_3Cl_3Na$ (M($^{35}Cl^{35}Cl^{35}Cl$)Na^+) requires: 374.0088.

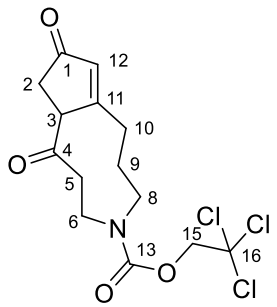
2,2,2-Trichloroethyl-1,9-dioxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (288)



Selenium dioxide (6.6 mg, 0.0592 mmol) was added to a solution of enone **200** (15.0 mg, 0.0423 mmol) in 1,4-dioxane (1.5 mL) and the mixture was stirred at 80 °C for 4 h. The mixture was then filtered through Celite and the solvent was removed in *vacuo*. Dichloromethane (1.5 mL) was added, followed by powdered 4 Å molecular sieves (45.0 mg) and the mixture was stirred at RT for 15 min. Pyridinium chlorochromate (45.6 mg, 0.211 mmol) was then added and the mixture was stirred at RT for 2 h. The mixture was filtered through Celite and the solvent was removed in *vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a yellow oil as a mixture of carbamate rotamers

(4.50 mg, 39%). R_f 0.55 (ether); ν_{max} (thin film)/cm^{-1} 2925w, 1712s, 1418m, 1223m, 1120m, 715m; δ_H (700 MHz, $CDCl_3$) 1.58−1.75 (6 H, m, C(9)H_2 × 2, C(10)**H**H′ × 2), 1.95−2.00 (2 H, m, C(10)H**H′** × 2), 2.12−2.20 (2 H, m, C(12)**H**H′ × 2), 2.63 (2 H, dd, *J* 19.0, 6.5, C(12)H**H′** × 2), 2.70−2.78 (1 H, m, C(5)**H**H′), 2.85−2.94 (1 H, m, C(5)**H**H′), 3.09 (1 H, ddd, *J* 14.5, 8.0, 3.0, C(8)**H**H′), 3.15−3.26 (1 H, m, C(8)**H**H′), 3.31 (1 H, ddd, *J* 13.5, 10.0, 3.5, C(6)**H**H′), 3.36−3.39 (1 H, m, C(5)H**H′**), 3.39−3.62 (5 H, m, C(5)H**H′**, C(6)**H**H′, C(8)H**H′** and C(11)H × 2), 3.62−3.73 (1 H, m, C(8)H**H′**), 3.73−3.89 (2 H, m, C(6)H**H′** × 2), 4.67 (1 H, d, *J* 12.0, C(15)**H**H′), 4.76 (1 H, d, *J* 12.0, C(15)H**H′**), 4.77−4.81 (2 H, m, C(15)H_2), 6.34 (1 H, s, C(2)H), 6.35 (1 H, s, C(2)H); δ_C (175 MHz, $CDCl_3$) 22.2/22.5 (C(9)), 31.0/31.1 (C(10)), 39.4/39.6 (C(11)), 40.9 (C(5)), 42.1 (C(12)), 42.4 (C(5)), 47.8/49.3 (C(6)), 51.8 (C(8)), 75.2/75.5 (C(15)), 95.1/95.3 (C(16)), 133.4 (C(2)), 154.1/154.8 (C(13)), 175.6/176.0 (C(3)), 205.2 (C(4)), 207.8/208.1 (C(1)); *m/z* (FI^+) 373 (M($^{37}Cl^{37}Cl^{37}Cl$)$^{+\cdot}$, 4%), 371 (M($^{35}Cl^{37}Cl^{37}Cl$)$^{+\cdot}$, 33), 369 (M($^{35}Cl^{35}Cl^{37}Cl$)$^{+\cdot}$, 100), 367 (M($^{35}Cl^{35}Cl^{35}Cl$)$^{+\cdot}$, 100); HRMS (FI^+): Found: 367.0157; $C_{14}H_{16}NO_4Cl_3$ (M($^{35}Cl^{35}Cl^{35}Cl$)$^{+\cdot}$) requires: 367.0140.

2,2,2-Trichloroethyl-7,9-dioxo-2,3,5,6,7,7a,8,9-octahydrocyclopenta[*e*]azonine-4(1*H*)-carboxylate (289)

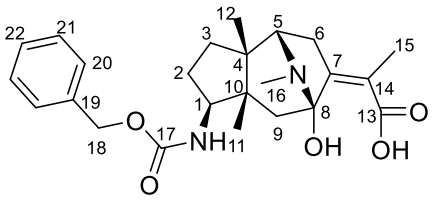


Cyclopentadiene (7.5 mg, 0.109 mmol) was added to enone **288** (4.00 mg, 0.0109 mmol) in a sealed tube and the mixture was stirred at 150 °C for 36 h. Purification by flash

chromatography (silica, ether) afforded the *title compound* as a colourless oil as a mixture of carbamate rotamers (1.50 mg, 38%). R_f 0.35 (ether); ν_{max} (thin film)/cm^{-1} 2927w, 1704s, 1608w, 1420m, 1122m, 716m; δ_H (700 MHz, $CDCl_3$) 1.80−2.07 (4 H, m, C(9)H_2 × 2), 2.09−2.25 (2 H, m, C(5)**H**H′ × 2), 2.37−2.55 (4 H, m, C(2)**H**H′ × 2 and C(10)**H**H′ × 2), 2.58−2.66 (2 H, m, C(2)H**H′** × 2), 2.83−2.91 (3 H, m, C(8)**H**H′ and C(10)H**H′** × 2), 2.95−3.25 (5 H, m, C(5)H**H′** × 2, C(6)**H**H′ × 2 and C(8)**H**H′), 3.70−3.78 (2 H, m, C(3)H × 2), 3.78−3.86 (1 H, m, C(8)H**H′**), 3.90 (1 H, ddd, *J* 14.0, 5.5, 2.5, C(6)H**H′**), 3.93−4.07 (2 H, m, C(6)H**H′** and C(8)H**H′**), 4.56 (1 H, d, *J* 12.0, C(15)**H**H′), 4.62 (1 H, d, *J* 12.0, C(15)**H**H′), 4.78 (1 H, d, *J* 12.0, C(15)H**H′**), 4.83 (1 H, d, *J* 12.0, C(15)H**H′**), 6.19 (1 H, s, C(12)H), 6.21 (1 H, s, C(12)H); δ_C (175 MHz, $CDCl_3$) 24.6/25.5 (C(9)), 31.2/31.9 (C(10)), 35.9/36.4 (C(5)), 38.3/38.7 (C(2)), 47.6/48.3 (C(6)), 49.0/49.5 (C(8)), 59.6/59.8 (C(3)), 75.5/75.8 (C(15)), 95.0 (C(16)), 133.3 (C(12)), 154.2 (C(13)), 177.1 (C(11)), 206.0 (C(1)), 211.4 (C(4)); *m/z* (FI^+) 373 ($M(^{37}Cl^{37}Cl^{37}Cl)^{+\cdot}$, 4%), 371 ($M(^{35}Cl^{37}Cl^{37}Cl)^{+\cdot}$, 33), 369 ($M(^{35}Cl^{35}Cl^{37}Cl)^{+\cdot}$, 100), 367 ($M(^{35}Cl^{35}Cl^{35}Cl)^{+\cdot}$, 100); HRMS ($FI^+$): Found: 367.0157; $C_{14}H_{16}NO_4Cl_3$ ($M(^{35}Cl^{35}Cl^{35}Cl)^{+\cdot}$) requires: 367.0140.

6.4: Compounds in Chapter 4

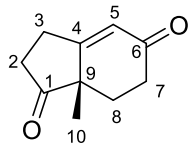
(*Z*)-2-{(1*S*,3a*S*,4*S*,7*R*,8a*S*)-1-{[(Benzyloxy)carbonyl]amino}-7-hydroxy-3a,8a,9-trimethyloctahydro-4,7-epiminoazulen-6(1*H*)-ylidene}propanoic acid (107)



Lithium hydroxide monohydrate (0.5 mg, 0.00369 mmol) was added to a solution of methoxybutenolide **457** (1.00 mg, 0.00184 mmol) in THF–H_2O (0.22 mL, 10:1) and the mixture was stirred at RT for 48 h. Glacial acetic acid (0.02 mL) was added and the solvent was removed *in vacuo*. Water (1 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded hydroxybutenolide **105b** as a mixture of carbamate rotamers as a colourless oil (0.90 mg, 92%). To a solution of hydroxybutenolide **105b** (0.90 mg, 0.00170 mmol) in EtOH (0.15 mL) was added 4.0 M HCl (0.05 mL). The reaction mixture was stirred at 70 ºC for 1 h then concentrated *in vacuo*. Purification by flash chromatography (silica, 25:9:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a white solid (0.55 mg, 75%). R_f 0.40 (25:9:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); m.p. 120–125 °C; $[\alpha]_D^{25}$ –16.0 (*c* 0.05, MeOH); ν_{max} (thin film)/cm^{-1} 3450br, 2955m, 1701s, 1564s, 1431m, 1348m; δ_H (500 MHz, CD_3OD) 0.83 (3 H, s, C(11)H_3), 1.29 (3 H, s, C(12)H_3), 1.56−1.77 (4 H, m, C(2)**H**H′, C(3)H_2 and C(9)**H**H′), 1.98 (3 H, s, C(15)H_3), 1.99−2.07 (1 H, m, C(2)H**H′**), 2.50 (1 H, d, *J* 14.5, C(9)H**H′**), 2.58−2.83 (4 H, m, C(6)**H**H′ and C(16)H_3), 3.03−3.15 (1 H, m, C(6)H**H′**), 3.36−3.51 (1 H, m, C(5)H), 4.19 (1 H, t, *J* 8.5, C(1)H), 5.00 (1 H, d, *J* 12.5, C(18)**H**H′), 5.05 (1 H, d, *J* 12.5, C(18)H**H′**), 7.23−7.41 (5 H, m, 2 × C(20)H, 2 × C(21)H and C(22)H); δ_C (125 MHz,

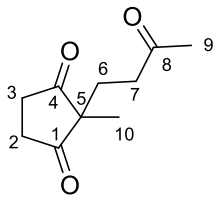
CD_3OD) 18.0 (C(15)), 19.7 (C(11)), 23.8 (C(12)), 28.1 (C(2)), 31.7 (C(6)), 32.5 (C(3)), 34.0 (C(16)), 45.4 (C(4)), 45.8 (C(10)), 45.9 (C(9)), 57.6 (C(1)), 65.9 (C(18)), 70.8 (C(5)), 95.4 (C(8)), 127.4 (C(20)), 127.6 (C(22)), 128.0 (C(21)), 135.9 (C(7)), 137.2 (C(19)), 138.5 (C(14)), 156.8 (C(17)), 172.4 (C(13)); *m/z* (ESI^+) 429 (MH^+, 100%); HRMS (ESI^+): Found: 429.2382; $C_{24}H_{33}O_5N_2$ (MH^+) requires: 429.2384.

(*S*)-7a-Methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione (290)[111]



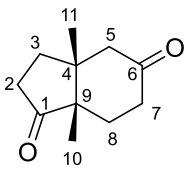
L-proline (95.0 mg, 0.823 mmol) was added to a solution of ketone **291** (5.00 g, 27.4 mmol) in DMF (28 mL) and the solution was stirred at RT for 20 h. The solvent was distilled off under *vacuo* to afford the crude alcohol which was dissolved in benzene (16 mL). *p*TsOH·H_2O (0.157 g, 0.823 mmol) was then added and the solution was stirred under reflux for 5 h. Sat. aq. $NaHCO_3$ (25 mL) was added and the mixture was extracted with ether (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the title compound as a white solid (4.21 g, 93%). R_f 0.45 (ether); m.p. 62–65 °C; $[\alpha]_D^{23}$ +333.4 (*c* 1.15, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2968w, 1745s, 1665s, 1410w, 1347w, 1147w; δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, s, C(10)H_3), 1.77−1.91 (1 H, m, C(8)**H**H′), 2.03−2.15 (1 H, m, C(8)H**H′**), 2.35−2.59 (3 H, m, C(2)**H**H′ and C(7)H_2), 2.68−2.86 (2 H, m, C(2)H**H′** and C(3)**H**H′), 2.88−3.02 (1 H, m, C(3)H**H′**), 5.96 (1 H, d, *J* 2.0, C(5)H); δ_C (100 MHz, $CDCl_3$) 20.6 (C(10)), 26.8 (C(3)), 29.2 (C(8)), 32.9 (C(7)), 35.9 (C(2)), 48.7 (C(9)), 123.9 (C(5)), 169.8 (C(4)), 198.2 (C(6)), 216.6 (C(1)); *m/z* (ESI^+) 187 (MNa^+, 100%), 165 (MH^+, 30).

2-Methyl-2-(3-oxobutyl)cyclopentane-1,3-dione (291)[111]



Glacial acetic acid (0.325 mL) and methyl vinyl ketone (12.5 mL, 0.154 mol) were added to a suspension of 2-methyl-1,3-cyclopentanedione (10.0 g, 0.0892 mol) in water (14.1 mL) and the mixture was stirred at 75 °C for 4 h. The mixture was then extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the title compound as a colourless oil (15.5 g, 95%). R_f 0.45 (ether); ν_{max} (thin film)/cm^{-1} 2929w, 1716s, 1417m, 1365m, 1168m, 1084w; δ_H (400 MHz, $CDCl_3$) 1.08 (3 H, s, C(10)H_3), 1.86 (2 H, t, *J* 7.0, C(6)H_2), 2.08 (3 H, s, C(9)H_3), 2.43 (2 H, t, *J* 7.0, C(7)H_2), 2.65−2.89 (4 H, m, C(2)H_2 and C(3)H_2); δ_C (100 MHz, $CDCl_3$) 19.1 (C(10)), 27.8 (C(6)), 30.0 (C(9)), 34.7 (C(2) and C(3)), 37.4 (C(7)), 55.1 (C(5)), 207.9 (C(8)), 215.8 (C(1) and C(4)); *m/z* (ESI^+) 205 (MNa^+, 100%), 183 (MH^+, 50).

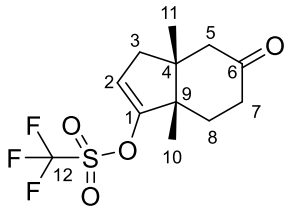
(3a*R*,7a*S*)-3a,7a-Dimethylhexahydro-1*H*-indene-1,5(4*H*)-dione (292)[113]



Methyllithium solution (0.990 mL, 1.58 mmol, 1.6 M in Et_2O) was added dropwise to a suspension of copper iodide (0.151 g, 0.792 mmol) in ether (2.1 mL) at –20 °C and the solution was stirred for 15 min. The solution was cooled to –78 °C and a solution of enone

290 (0.100 g, 0.609 mmol) in ether (1.6 mL) was added dropwise. The mixture was stirred at –15 °C for 1 h, and then allowed to warm to RT. Sat. aq. NH_4Cl (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the title compound as a white solid (0.107 g, 98%). R_f 0.65 (ether); m.p. 172–175 °C; $[\alpha]_D^{23}$ +48.0 (*c* 1.14, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2966w, 1731s, 1711s, 1459w, 1380w, 1039w; δ_H (400 MHz, $CDCl_3$) 1.01 (3 H, s, C(11)H_3), 1.02 (3 H, s, C(10)H_3), 1.51−1.62 (1 H, m, C(8)**H**H′), 1.70−1.85 (2 H, m, C(3)H_2), 2.11−2.28 (5 H, m, C(5)H_2, C(7)H_2 and C(8)H**H′**), 2.37−2.44 (2 H, m, C(2)H_2); δ_C (100 MHz, $CDCl_3$) 17.5 (C(10)), 22.5 (C(11)), 30.5 (C(8)), 31.7 (C(3)), 33.1 (C(2)), 37.8 (C(7)), 46.3 (C(4)), 50.0 (C(5)), 51.8 (C(9)), 210.4 (C(6)), 219.9 (C(1)); *m/z* (ESI^+) 203 (MNa^+, 100%), 181 (MH^+, 10).

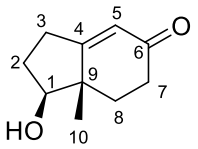
(3a*S*,7a*R*)-3a,7a-Dimethyl-6-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-inden-3-yl trifluoromethanesulfonate (295)



KHMDS (0.245 mL, 0.123 mmol, 0.5 M in toluene) was added dropwise to a solution of ketone **292** (17.0 mg, 0.0943 mmol) in THF (0.3 mL) at –78 °C and the solution was stirred at –78 °C for 30 min. *N*-Phenyl-bis(trifluoromethanesulfonimide) (37.0 mg, 0.104 mmol) was then added and the solution was stirred at –78 °C for 2 h. Sat. aq. NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography

(silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (7.50 mg, 25%). R_f 0.60 (1:1 petrol:ether); $[\alpha]_D^{23}$ +42.2 (*c* 0.77, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2973w, 1715m, 1419m, 1211s, 1141s, 1037w; δ_H (500 MHz, $CDCl_3$) 1.14 (3 H, s, C(11)H_3), 1.18 (3 H, s, C(10)H_3), 1.79 (1 H, ddd, *J* 14.5, 12.0, 5.0, C(8)**H**H′), 1.97 (1 H, dt, *J* 14.5, 5.0, C(8)H**H′**), 2.14−2.34 (4 H, m, C(3)H_2 and C(7)H_2), 2.37 (2 H, d, *J* 3.5, C(5)H_2), 5.67 (1 H, t, *J* 2.5, C(2)H); δ_C (125 MHz, $CDCl_3$) 20.1 (C(10)), 25.5 (C(11)), 31.0 (C(8)), 36.0 (C(7)), 42.3 (C(3)), 42.6 (C(4)), 47.9 (C(9)), 51.2 (C(5)), 113.0 (C(2)), 118.5 (q, *J* 317.5, C(12)), 151.0 (C(1)), 211.7 (C(6)); *m/z* (ESI^+) 335 (MNa^+, 100%), 313 (MH^+, 5); HRMS (ESI^+): Found: 335.0534; $C_{12}H_{15}O_4F_3NaS$ (MNa^+) requires: 335.0535.

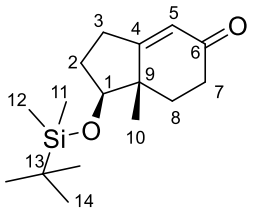
(1*S*,7a*S*)-1-Hydroxy-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (296)[115]



A solution of $NaBH_4$ (29.5 mg, 0.773 mmol) in EtOH (5 mL) at 0 °C was added dropwise to a solution enone **290** (0.500 g, 3.05 mmol) in EtOH (5 mL) at –15 °C and the mixture was stirred at –15 °C for 4 h. Water (10 mL) was added and the solvent was removed *in vacuo*. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the title compound as a white solid (0.426 g, 84%). R_f 0.25 (ether); m.p. 45–47 °C; $[\alpha]_D^{23}$ +67.2 (*c* 1.47, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3412br, 2969w, 1649s, 1347w, 1212w, 1079m; δ_H (400 MHz, $CDCl_3$) 1.14 (3 H, s, C(10)H_3), 1.70−1.90 (2 H, m, C(2)**H**H′ and C(8)**H**H′), 2.04−2.20 (2 H, m, C(2)H**H′** and C(8)H**H′**), 2.31−2.58 (3 H, m, C(3)**H**H′ and C(7)H_2), 2.70 (1 H, ddt, *J* 19.5, 11.5, 2.0, C(3)H**H′**), 3.78−3.91 (1 H, m,

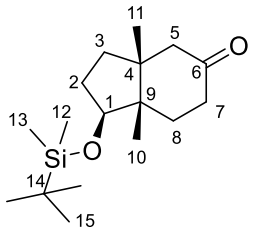
C(1)H), 5.78 (1 H, s, C(5)H); δ_C (100 MHz, $CDCl_3$) 15.1 (C(10)), 26.5 (C(3)), 29.1 (C(2)), 33.3 (C(7)), 34.1 (C(8)), 45.3 (C(9)), 80.6 (C(1)), 123.4 (C(5)), 175.5 (C(4)), 199.5 (C(6)); *m/z* (ESI^+) 189 (MNa^+, 80%), 167 (MH^+, 100).

(1*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (297)[115]



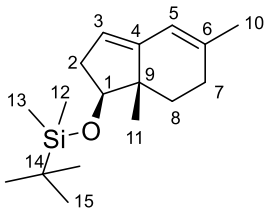
Imidazole (0.319 g, 4.69 mmol), TBSCl (0.530 g, 3.52 mmol) and DMAP (86.0 mg, 0.704 mmol) were added to a solution of alcohol **296** (0.390 g, 2.35 mmol) in DMF (16 mL) and the solution was stirred at RT for 16 h. Water (20 mL) was added and the mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless oil (0.577 g, 88%). R_f 0.85 (ether); $[\alpha]_D^{23}$ +28.0 (*c* 1.45, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1672s, 1471w, 1253w, 1110s, 837s; δ_H (400 MHz, $CDCl_3$) 0.05 (3 H, s, C(11)H_3), 0.06 (3 H, s, C(12)H_3), 0.90 (9 H, s, 3 × C(14)H_3), 1.10 (3 H, s, C(10)H_3), 1.64−1.86 (2 H, m, C(2)**H**H′ and C(8)**H**H′), 1.92−2.07 (2 H, m, C(2)H**H′** and C(8)H**H′**), 2.31−2.43 (2 H, m, C(3)**H**H′ and C(7)**H**H′), 2.45−2.58 (1 H, m, C(7)H**H′**), 2.62−2.75 (1 H, m, C(3)H**H′**), 3.75 (1 H, dd, *J* 10.0, 7.5, C(1)H), 5.77 (1 H, s, C(5)H); δ_C (100 MHz, $CDCl_3$) –4.9 (C(11)), –4.5 (C(12)), 15.3 (C(10)), 18.0 (C(13)), 25.8 (C(14)), 26.6 (C(3)), 29.6 (C(2)), 33.4 (C(7)), 34.4 (C(8)), 45.6 (C(9)), 80.8 (C(1)), 123.3 (C(5)), 175.2 (C(4)), 199.4 (C(6)); *m/z* (ESI^+) 303 (MNa^+, 100%), 281 (MH^+, 70).

(1*S*,3a*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyloctahydro-5*H*-inden-5-one (298)



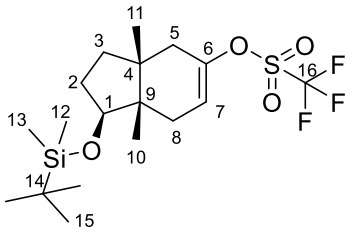
Methyllithium solution (2.09 mL, 3.35 mmol, 1.6 M in Et_2O) was added dropwise to a suspension of copper iodide (0.319 g, 1.67 mmol) in ether (4.3 mL) at –20 °C and the solution was stirred for 15 min. The solution was cooled to –78 °C and a solution of enone **297** (0.361 g, 1.29 mmol) in ether (3.6 mL) was added dropwise. The mixture was stirred at –15 °C for 1 h, and then allowed to warm to RT. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the *title compound* as a white solid (0.286 g, 75%). R_f 0.70 (3:1 petrol:ether); m.p. 67–70 °C; $[\alpha]_D^{23}$ +10.1 (*c* 1.00, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956m, 1713m, 1462w, 1252m, 1054s, 836s; δ_H (400 MHz, $CDCl_3$) 0.05 (6 H, s, C(12)H_3 and C(13)H_3), 0.90 (9 H, s, 3 × C(15)H_3), 0.96 (3 H, s, C(10)H_3), 0.99 (3 H, s, C(11)H_3), 1.40−1.47 (1 H, m, C(3)**H**H′), 1.50−1.67 (3 H, m, C(2)**H**H′, C(3)H**H′** and C(8)**H**H′), 1.71−1.81 (1 H, m, C(8)H**H′**), 2.04−2.17 (2 H, m, C(2)H**H′** and C(5)**H**H′), 2.24−2.36 (3 H, m, C(5)H**H′** and C(7)H_2), 4.13 (1 H, dd, *J* 8.0, 5.0, C(1)H); δ_C (100 MHz, $CDCl_3$) –5.0 (C(12)), –4.4 (C(13)), 16.3 (C(10)), 18.0 (C(14)), 24.1 (C(11)), 25.8 (C(15)), 31.1 (C(2)), 33.3 (C(8)), 36.5 (C(3)), 37.5 (C(7)), 46.4 (C(4)), 47.1 (C(9)), 50.9 (C(5)), 77.7 (C(1)), 212.3 (C(6)); *m/z* (ESI^+) 319 (MNa^+, 100%), 297 (MH^+, 30); HRMS (ESI^+): Found: 297.2242; $C_{17}H_{33}O_2Si$ (MH^+) requires: 297.2244.

tert-Butyl{[(1*S*,7a*S*)-5,7a-dimethyl-2,6,7,7a-tetrahydro-1*H*-inden-1-yl]oxy}dimethylsilane (299)



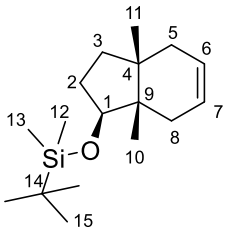
Methyllithium solution (0.842 mL, 1.35 mmol, 1.6 M in Et_2O) was added dropwise to a suspension of copper iodide (0.128 g, 0.674 mmol) in ether (1.5 mL) at –20 °C and the solution was stirred for 15 min. The solution was cooled to –78 °C, $BF_3.OEt_2$ (0.111 mL, 0.898 mmol) was added and the solution was stirred for 15 min. A solution of enone **297** (0.126 g, 0.449 mmol) in ether (1.3 mL) was added dropwise and the mixture was stirred at –15 °C for 1 h, and then allowed to warm to RT. Sat. aq. NH_4Cl (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the *title compound* as a colourless oil (53.0 mg, 42%). R_f 0.90 (3:1 petrol:ether); $[\alpha]_D^{23}$ +3.9 (*c* 1.15, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2957w, 1462w, 1249w, 1091m, 834s, 774s; δ_H (400 MHz, $CDCl_3$) 0.05 (6 H, s, C(12)H_3 and C(13)H_3), 0.90 (3 H, s, C(11)H_3), 0.91 (9 H, s, 3 × C(15)H_3), 1.25−1.37 (1 H, m, C(8)**H**H′), 1.77 (3 H, s, C(10)H_3), 1.78−1.83 (1 H, m, C(8)H**H′**), 1.98 (1 H, dd, *J* 18.5, 5.5, C(7)**H**H′), 2.19−2.32 (1 H, m, C(7)H**H′**), 2.33−2.41 (2 H, m, C(2)H_2), 3.92 (1 H, t, *J* 8.0, C(1)H), 5.15 (1 H, bs, C(3)H), 5.90 (1 H, s, C(5)H); δ_C (100 MHz, $CDCl_3$) –4.8 (C(12)), –4.5 (C(13)), 15.3 (C(11)), 18.1 (C(14)), 23.6 (C(10)), 25.9 (C(15)), 28.7 (C(7)), 34.3 (C(8)), 38.3 (C(2)), 45.0 (C(9)), 82.1 (C(1)), 116.0 (C(3)), 119.2 (C(5)), 138.0 (C(6)), 146.3 (C(4)); *m/z* (FI^+) 278 ($M^{+\cdot}$, 100%); HRMS (FI^+): Found: 278.2061; $C_{17}H_{30}OSi$ ($M^{+\cdot}$) requires: 278.2061.

(1*S*,3a*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (300)



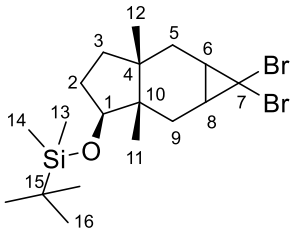
KHMDS (0.123 mL, 0.0614 mmol, 0.5 M in toluene) was added dropwise to a solution of ketone **298** (14.0 mg, 0.0472 mmol) in THF (0.15 mL) at –78 °C and the solution was stirred at –78 °C for 30 min. *N*-Phenyl-bis(trifluoromethanesulfonimide) (22.0 mg, 0.0614 mmol) was then added and the solution was stirred at –78 °C for 2 h. Sat. aq. NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 19:1 petrol:ether) afforded the *title compound* as a colourless oil (16.0 mg, 80%). R_f 0.90 (9:1 petrol:ether); $[\alpha]_D^{23}$ +18.6 (*c* 1.19, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956w, 1418m, 1208s, 1144s, 887m, 837m; δ_H (500 MHz, $CDCl_3$) 0.00 (3 H, s, C(12)H_3), 0.01 (3 H, s, C(13)H_3), 0.84 (3 H, s, C(10)H_3), 0.89 (9 H, s, 3 × C(15)H_3), 1.02 (3 H, s, C(11)H_3), 1.41−1.49 (1 H, m, C(3)**H**H′), 1.50−1.59 (1 H, m, C(2)**H**H′), 1.62−1.71 (1 H, m, C(3)H**H′**), 1.84−1.92 (1 H, m, C(8)**H**H′), 1.98−2.20 (3 H, m, C(2)H**H′**, C(5)**H**H′ and C(8)H**H′**), 2.24−2.34 (1 H, m, C(5)H**H′**), 3.95 (1 H, dd, *J* 8.5, 6.5, C(1)H), 5.63 (1 H, s, C(7)H); δ_C (125 MHz, $CDCl_3$) –5.2 (C(12)), –4.6 (C(13)), 16.2 (C(10)), 18.0 (C(14)), 22.6 (C(11)), 25.8 (C(15)), 29.7 (C(2)), 31.3 (C(8)), 35.6 (C(3)), 38.5 (C(5)), 42.2 (C(4)), 44.9 (C(9)), 76.3 (C(1)), 115.7 (C(7)), 118.5 (q, *J* 316.5, C(16)), 146.9 (C(6)); *m/z* (FI^+) 428 ($M^{+\cdot}$, 100%); HRMS (FI^+): Found: 428.1653; $C_{18}H_{31}O_4F_3SiS$ ($M^{+\cdot}$) requires: 428.1659.

***tert*-Butyl{[(1*S*,3a*R*,7a*S*)-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (302)**



A solution of triflate **300** (20.0 mg, 0.0467 mmol) in THF (0.5 mL) was added to LiCl (6.0 mg, 0.140 mmol) and $Pd(PPh_3)_4$ (1.0 mg, 0.933 μmol). Tributyltin hydride (15.5 μL, 0.0569 mmol) was added dropwise at RT and the mixture was stirred at 55 °C for 3 h. Ether (1 mL) was added and the mixture was washed with 10% aq. KF (1 mL) and brine (1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil (11.5 mg, 88%). R_f 0.85 (petrol); $[\alpha]_D^{23}$ +18.0 (*c* 0.98, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955m, 1471w, 1251m, 1113s, 1077s, 836s, 774s; δ_H (400 MHz, $CDCl_3$) 0.00 (6 H, s, C(12)H_3 and C(13)H_3), 0.81 (3 H, s, C(10)H_3), 0.89 (9 H, s, 3 × C(15)H_3), 0.94 (3 H, s, C(11)H_3), 1.27−1.41 (1 H, m, C(3)**H**H′), 1.44−1.54 (1 H, m, C(2)**H**H′), 1.58−1.79 (3 H, m, C(3)H**H′**, C(5)**H**H′ and C(8)**H**H′), 1.86−2.08 (3 H, m, C(2)H**H′**, C(5)H**H′** and C(8)H**H′**), 3.96 (1 H, dd, *J* 8.5, 6.0, C(1)H), 5.52 (2 H, s, C(6)H and C(7)H); δ_C (100 MHz, $CDCl_3$) –5.0 (C(12)), –4.5 (C(13)), 17.0 (C(10)), 18.1 (C(14)), 23.0 (C(11)), 25.9 (C(15)), 30.3 (C(2)), 32.3 (C(8)), 36.0 (C(3)), 36.8 (C(5)), 39.7 (C(4)), 44.9 (C(9)), 77.2 (C(1)), 124.5 (C(6) and C(7)); *m/z* (FI^+) 280 ($M^{+\cdot}$, 100%); HRMS (FI^+): Found: 280.2228; $C_{17}H_{32}OSi$ ($M^{+\cdot}$) requires: 280.2217.

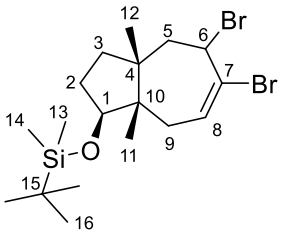
***tert*-Butyl{[(2a*S*,3*S*,5a*R*)-1,1-dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-yl]oxy}dimethylsilane (303)**



Benzyltriethylammonium chloride (1.0 mg, 2.03 μmol) and bromoform (53.0 μL, 0.610 mmol) were added to a solution of alkene **302** (57.0 mg, 0.203 mmol) in benzene (2.5 mL). 50% aq. NaOH (36.5 μL) was added dropwise and the mixture was stirred at 70 °C for 16 h. Water (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil as a mixture of diastereomers (68.6 mg, 75%, *dr*. 1:1). R_f 0.70 (petrol); $[\alpha]_D^{23}$ +15.1 (*c* 1.16, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2953m, 1471w, 1284m, 1111m, 1059m, 835s, 774s; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(13)H_3), 0.04 (3 H, s, C(13)H_3), 0.05 (3 H, s, C(14)H_3), 0.07 (3 H, s, C(14)H_3), 0.70−0.76 (3 H, m, C(5)**H**H′ and 2 × C(9)**H**H′), 0.77 (3 H, s, C(11)H_3), 0.80−0.85 (1 H, m, C(5)**H**H′), 0.89 (9 H, s, 3 × C(16)H_3), 0.91 (9 H, s, 3 × C(16)H_3), 0.93 (6 H, s, C(11)H_3 and C(12)H_3), 0.99 (3 H, s, C(12)H_3), 1.29−1.39 (2 H, m, 2 × C(3)**H**H′), 1.41−1.56 (4 H, m, C(2)**H**H′, C(2)H_2 and C(3)H**H′**), 1.59−1.87 (9 H, m, C(2)H**H′**, C(3)H**H′**, 2 × C(5)H**H′**, 2 × C(6)H, 2 × C(8)H and C(9)H**H′**), 1.94 (1 H, dd, *J* 15.0, 8.5, C(9)H**H′**), 3.58 (1 H, t, *J* 4.0, C(1)H), 3.78 (1 H, dd, *J* 8.5, 6.0, C(1)H); δ_C (125 MHz, $CDCl_3$) –4.9/–4.8 (C(13)), –4.5/–4.2 (C(14)), 18.1 (C(15)), 19.3/20.1 (C(11)), 25.8 (C(16)), 26.8/27.4 (C(12)), 27.6/27.7 (C(6)), 28.0/28.2 (C(8)), 30.7/31.4 (C(2)), 32.4/35.2 (C(9)), 35.6 (C(5)), 36.0 (C(3)), 36.8 (C(5)), 39.7 (C(3)), 40.1 (C(10)), 41.0 (C(4)), 42.8 (C(7)), 44.4 (C(10)), 46.4 (C(4)), 80.0/82.4 (C(1)); *m/z* (FI^+) 454 ($M(^{81}Br^{81}Br)^{+\cdot}$, 40%), 452 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 450

(M(^{79}Br^{79}Br)$^{+\cdot}$, 50); HRMS (FI^{+}): Found: 450.0585; $C_{18}H_{32}OBr_2Si$ (M(^{79}Br^{79}Br)$^{+\cdot}$) requires: 450.0584.

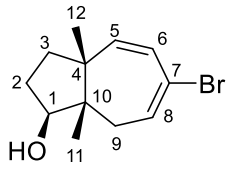
tert-Butyl{[(1*S*,3a*R*,8a*S*)-5,6-dibromo-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulen-1-yl]oxy}dimethylsilane (304)



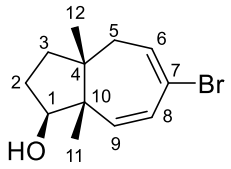
A solution of dibromocyclopropane **303** (11.0 mg, 0.0243 mmol) in ACN (0.1 mL) was stirred at 100 °C for 48 h. The solvent was then removed *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil as a mixture of diastereomers (2.10 mg, 19%, *dr*. 1:1). R_f 0.40 (petrol); $[\alpha]_D^{23}$ +2.2 (*c* 0.18, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954s, 1471w, 1255m, 1135m, 1070m, 836s, 775s; δ_H (500 MHz, $CDCl_3$) 0.04 (9 H, s, 2 × C(13)H_3 and C(14)H_3), 0.05 (3 H, s, C(14)H_3), 0.87 (3 H, s, C(11)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 0.92 (3 H, s, C(11)H_3), 1.01 (3 H, s, C(12)H_3), 1.03 (3 H, s, C(12)H_3), 1.35−1.43 (2 H, m, 2 × C(3)**H**H′), 1.46−1.52 (3 H, m, 2 × C(2)**H**H′ and C(3)H**H′**), 1.60−1.67 (2 H, m, C(2)H**H′** and C(3)H**H′**), 1.68−1.75 (1 H, m, C(2)H**H′**), 1.80 (1 H, dd, *J* 14.5, 10.0, C(9)**H**H′), 1.94 (1 H, dd, *J* 14.0, 10.0, C(9)**H**H′), 2.02−2.10 (2 H, m, 2 × C(5)**H**H′), 2.44 (1 H, dd, *J* 14.5, 6.0, C(9)H**H′**), 2.57−2.66 (2 H, m, C(5)H**H′** and C(9)H**H′**), 2.72 (1 H, dd, *J* 14.0, 12.0, C(5)H**H′**), 3.56−3.65 (2 H, m, 2 × C(1)H), 4.78−4.88 (2 H, m, 2 × C(6)H), 6.19−6.29 (2 H, m, 2 × C(8)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.4/–4.3 (C(14)), 17.0/17.1 (C(11)), 18.0 (C(15)), 24.8 (C(12)), 25.8 (C(16)), 26.4 (C(12)), 30.5/31.0 (C(2)), 37.7 (C(9)), 39.4 (C(3)), 40.5 (C(9)), 43.6/45.4 (C(4)), 47.5 (C(5)),

49.4/49.6 (C(10)), 50.1 (C(5)), 57.2/57.6 (C(6)), 81.3/84.2 (C(1)), 124.1/124.2 (C(7)), 134.7/135.1 (C(8)); *m/z* (FI^+) 454 ($M(^{81}Br^{81}Br)^{+\cdot}$, 40%), 452 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 450 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($FI^+$): Found: 450.0422; $C_{18}H_{32}OBr_2Si$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 450.0584.

(1*S*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,8,8a-hexahydroazulen-1-ol (305) and **(1*S*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,8a-hexahydroazulen-1-ol (306)**



305

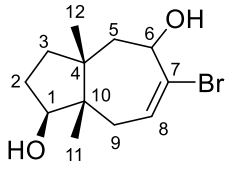


306

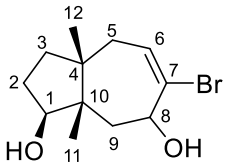
A solution of dibromocyclopropane **303** (7.00 mg, 0.0155 mmol) in ACN (0.1 mL) was stirred at 110 °C for 72 h. The solvent was then removed *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded *diene* **305** as a colourless oil (0.572 mg, 14%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +46.9 (*c* 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3350br, 2953s, 1629w, 1521w, 1044s; δ_H (500 MHz, $CDCl_3$) 0.91 (3 H, s, C(11)H_3), 1.09 (3 H, s, C(12)H_3), 1.39−1.44 (1 H, m, C(2)**H**H′), 1.47−1.51 (1 H, m, C(3)**H**H′), 1.67−1.79 (1 H, m, C(3)H**H′**), 1.97−2.07 (3 H, m, C(2)H**H′** and C(9)H_2), 4.02−4.09 (1 H, m, C(1)H), 5.54 (1 H, d, *J* 12.5, C(5)H), 5.77 (1 H, d, *J* 12.5, C(6)H), 6.20−6.29 (1 H, m, C(8)H); δ_C (125 MHz, $CDCl_3$) 17.4 (C(11)), 25.3 (C(12)), 29.1 (C(2)), 36.9 (C(9)), 38.0 (C(3)), 50.2 (C(10)), 51.9 (C(4)), 78.4 (C(1)), 118.5 (C(7)), 125.5 (C(6)), 131.3 (C(8)), 145.9 (C(5)); *m/z* (FI^+) 258 ($M(^{81}Br)^{+\cdot}$, 90%), 256 ($M(^{79}Br)^{+\cdot}$, 100); HRMS (FI^+): Found: 256.0467; $C_{12}H_{17}OBr$ ($M(^{79}Br)^{+\cdot}$) requires: 256.0458.

Also obtained was *diene* **306** as a colourless oil (0.728 mg, 18%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +46.9 (*c* 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3350br, 2953s, 1629w, 1521w, 1044s; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, s, C(11)H_3), 0.99 (3 H, s, C(12)H_3), 1.39−1.44 (1 H, m, C(2)**H**H′), 1.67−1.79 (2 H, m, C(3)H_2), 1.91 (1 H, dd, *J* 14.5, 9.0, C(5)**H**H′), 1.97−2.07 (1 H, m, C(2)H**H′**), 2.22 (1 H, dd, *J* 14.5, 5.5, C(5)H**H′**), 4.08−4.16 (1 H, m, C(1)H), 5.77 (1 H, d, *J* 12.5, C(9)H), 5.88 (1 H, d, *J* 12.5, C(8)H), 6.20−6.29 (1 H, m, C(6)H); δ_C (125 MHz, $CDCl_3$) 16.1 (C(11)), 24.7 (C(12)), 28.9 (C(2)), 37.2 (C(3)), 42.1 (C(5)), 48.4 (C(10)), 53.8 (C(4)), 82.0 (C(1)), 118.4 (C(7)), 126.4 (C(8)), 132.9 (C(6)), 143.5 (C(9)); *m/z* (FI^+) 258 ($M(^{81}Br)^{+\cdot}$, 90%), 256 ($M(^{79}Br)^{+\cdot}$, 100); HRMS (FI^+): Found: 256.0467; $C_{12}H_{17}OBr$ ($M(^{79}Br)^{+\cdot}$) requires: 256.0458.

(1*S*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulene-1,5-diol (307) and **(1*S*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulene-1,7-diol (308)**



307



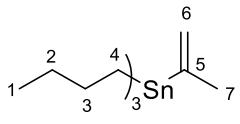
308

$AgClO_4$ (14.5 mg, 0.0695 mmol) was added to a solution of dibromocyclopropane **303** (18.5 mg, 0.0409 mmol) in acetone/H_2O (0.1 mL, 9:1) and the mixture was stirred under reflux for 1 h. The mixture was filtered and solvent removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded *diol* **307** as a white solid (5.65 mg, 50%). R_f 0.60 (ether); m.p. 125–130

°C; $[\alpha]_D^{23}$ +50.0 (*c* 0.18, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3346br, 2950m, 1644w, 1447w, 1023s; δ_H (500 MHz, $CDCl_3$) 0.89 (3 H, s, C(11)H_3), 1.07 (3 H, s, C(12)H_3), 1.41 (1 H, bs, OH), 1.51−1.62 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.64−1.72 (1 H, m, C(3)H**H′**), 1.81−1.89 (2 H, m, C(5)H_2), 1.91−2.00 (1 H, m, C(2)H**H′**), 2.01−2.15 (2 H, m, C(9)H_2), 2.27 (1 H, d, *J* 4.0, OH), 3.85−3.94 (1 H, m, C(1)H), 4.27−4.35 (1 H, m, C(6)H), 6.14 (1 H, dd, *J* 7.5, 6.5, C(8)H); δ_C (125 MHz, $CDCl_3$) 18.1 (C(11)), 28.1 (C(12)), 30.5 (C(2)), 34.9 (C(3)), 36.3 (C(9)), 42.9 (C(4)), 45.8 (C(5)), 48.6 (C(10)), 72.0 (C(6)), 78.8 (C(1)), 130.0 (C(7)), 130.1 (C(8)); *m/z* (FI^+) 276 ($M(^{81}Br)^{+\cdot}$, 100%), 274 ($M(^{79}Br)^{+\cdot}$, 80); HRMS (FI^+): Found: 274.0570; $C_{12}H_{19}O_2Br$ ($M(^{79}Br)^{+\cdot}$) requires: 274.0563.

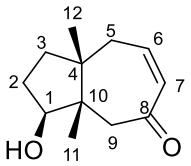
Also obtained was *diol* **308** as a white solid (5.31 mg, 47%). R_f 0.40 (ether); m.p. 145–149 °C; $[\alpha]_D^{23}$ +50.0 (*c* 0.18, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3346br, 2950m, 1644w, 1447w, 1023s; δ_H (500 MHz, $CDCl_3$) 0.96 (3 H, s, C(11)H_3), 1.01 (3 H, s, C(12)H_3), 1.32−1.41 (1 H, m, C(3)**H**H′), 1.51−1.65 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.78 (1 H, dd, *J* 15.5, 10.0, C(5)**H**H′), 1.83−1.92 (1 H, m, C(2)H**H′**), 1.94−2.06 (2 H, m, C(9)H_2), 2.39 (1 H, d, *J* 4.0, OH), 2.52 (1 H, d, *J* 14.5, C(5)H**H′**), 3.79−3.87 (1 H, m, C(1)H), 4.31−4.40 (1 H, m, C(8)H), 6.16 (1 H, dd, *J* 10.0, 4.5, C(6)H); δ_C (125 MHz, $CDCl_3$) 16.3 (C(11)), 26.2 (C(12)), 30.5 (C(2)), 38.0 (C(3)), 40.8 (C(5)), 43.6 (C(9)), 45.1 (C(4)), 45.4 (C(10)), 72.3 (C(8)), 82.6 (C(1)), 129.3 (C(7)), 131.8 (C(6)); *m/z* (FI^+) 276 ($M(^{81}Br)^{+\cdot}$, 100%), 274 ($M(^{79}Br)^{+\cdot}$, 80); HRMS (FI^+): Found: 274.0570; $C_{12}H_{19}O_2Br$ ($M(^{79}Br)^{+\cdot}$) requires: 274.0563.

Tributyl(prop-1-en-2-yl)stannane (311)



Isopropenylmagnesium bromide solution (7.37 mL, 3.69 mmol, 0.5 M in THF) was added dropwise to a solution of tributyltin chloride (1.00 mL, 3.69 mmol) in THF (12 mL) at –78 °C and the solution was stirred for 1 h. Sat.aq. NH_4Cl (20 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (alumina, petrol) afforded the title compound as a colourless oil (1.15 g, 94%). R_f 0.90 (petrol); ν_{max} (thin film)/cm^{-1} 2927s, 1463m, 1376w, 910s, 689m; δ_H (400 MHz, $CDCl_3$) 0.80−1.01 (15 H, m, 3 × C(1)H_3 and 3 × C(4)H_2), 1.25−1.39 (6 H, m, 3 × C(2)H_2), 1.42−1.53 (6 H, m, 3 × C(3)H_2), 1.97 (3 H, t, *J* 1.5, C(7)H_3), 5.09 (1 H, dd, *J* 3.0, 1.5, C(6)**H**H′), 5.70 (1 H, dd, *J* 3.0, 1.5, C(6)H**H′**); δ_C (100 MHz, $CDCl_3$) 9.2 (C(4)), 13.7 (C(1)), 27.3 (C(7)), 27.4 (C(2)), 29.2 (C(3)), 125.5 (C(6)), 150.4 (C(5)).

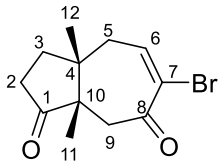
(3*S*,3a*S*,8a*R*)-3-Hydroxy-3a,8a-dimethyl-2,3,3a,4,8,8a-hexahydroazulen-5(1*H*)-one (312)



$Pd(PPh_3)_4$ (1.0 mg, 0.945 μmol), CuCl (2.8 mg, 0.0283 mmol) and LiBr (2.5 mg, 0.0283 mmol) were added to a solution of diol **308** (5.20 mg, 0.0189 mmol) and organotin **311** (9.4 mg, 0.0283 mmol) in THF (0.1 mL) and the mixture was stirred at 90 °C for 24 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether)

afforded the *title compound* as a colourless oil (2.40 mg, 66%). R_f 0.40 (ether); $[\alpha]_D^{23}$ +76.0 (*c* 0.25, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3412br, 2954m, 1656s, 1510s, 1377s, 1154m; δ_H (500 MHz, $CDCl_3$) 0.92 (3 H, s, C(11)H_3), 1.03 (3 H, s, C(12)H_3), 1.51−1.56 (1 H, m, C(3)**H**H′), 1.61−1.77 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.87−1.97 (1 H, m, C(2)H**H′**), 2.26 (1 H, dd, *J* 16.0, 9.0, C(5)**H**H′), 2.53 (1 H, dd, *J* 13.0, 2.0, C(9)**H**H′), 2.70 (1 H, d, *J* 16.0, C(5)H**H′**), 2.77 (1 H, d, *J* 13.0, C(9)H**H′**), 3.81−3.89 (1 H, m, C(1)H), 6.11 (1 H, dt, *J* 11.5, 2.0, C(7)H), 6.72 (1 H, ddd, *J* 11.5, 9.0, 4.5, C(6)H); δ_C (125 MHz, $CDCl_3$) 17.2 (C(11)), 26.5 (C(12)), 31.1 (C(2)), 38.9 (C(3)), 42.4 (C(5)), 46.8 (C(4)), 47.1 (C(10)), 55.4 (C(9)), 82.5 (C(1)), 134.1 (C(7)), 147.4 (C(6)), 201.4 (C(8)); *m/z* (ESI^+) 217 (MNa^+, 100%); HRMS (ESI^+): Found: 217.1198; $C_{12}H_{18}O_2Na$ (MNa^+) requires: 217.1199.

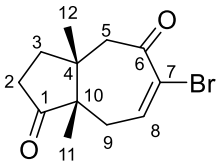
(3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-2,3,3a,4,8,8a-hexahydroazulene-1,7-dione (313)



Dess–Martin periodinane (40.0 mg, 0.0945 mmol) was added to a solution of diol **308** (6.5 mg, 0.0236 mmol) in DCM (1.3 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (2 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) were added and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless oil (6.00 mg, 94%). R_f 0.55 (ether); $[\alpha]_D^{23}$ +69.0 (*c* 0.30, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2971w, 1734s, 1683s, 1468w, 1340w, 1182w; δ_H (500 MHz, $CDCl_3$) 1.03 (3 H, s, C(11)H_3), 1.09 (3 H, s, C(12)H_3), 1.88−2.00 (2 H, m, C(3)H_2), 2.24−2.40 (2 H, m, C(2)**H**H′ and C(5)**H**H′), 2.43−2.56 (2 H, m, C(2)H**H′** and C(5)H**H′**),

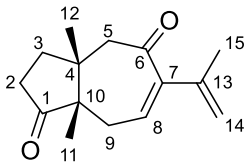
2.70 (1 H, d, *J* 15.0, C(9)**H**H′), 2.77 (1 H, d, *J* 15.0, C(9)H**H′**), 7.17 (1 H, dd, *J* 8.0, 6.5, C(6)H); δ_C (125 MHz, $CDCl_3$) 20.0 (C(11)), 23.9 (C(12)), 34.8 (C(3)), 35.6 (C(2)), 41.7 (C(5)), 46.0 (C(4)), 48.3 (C(9)), 52.1 (C(10)), 127.7 (C(7)), 143.6 (C(6)), 193.4 (C(8)), 220.8 (C(1)); *m/z* (ESI^+) 295 (M(^{81}Br)Na^+, 100%), 293 (M(^{79}Br)Na^+, 95); HRMS (ESI^+): Found: 293.0143; $C_{12}H_{15}O_2BrNa$ (M(^{79}Br)Na^+) requires: 293.0148.

(3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-2,3,3a,4,8,8a-hexahydroazulene-1,5-dione (314)



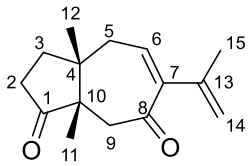
Dess–Martin periodinane (20.0 mg, 0.0465 mmol) was added to a solution of diol **307** (3.2 mg, 0.0116 mmol) in DCM (0.5 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (2 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) were added and the mixture was extracted with DCM (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless oil (3.00 mg, 95%). R_f 0.50 (ether); $[\alpha]_D^{23}$ +69.0 (*c* 0.30, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2971w, 1734s, 1683s, 1468w, 1340w, 1182w; δ_H (500 MHz, $CDCl_3$) 1.00 (3 H, s, C(11)H_3), 1.14 (3 H, s, C(12)H_3), 1.85−2.07 (2 H, m, C(3)H_2), 2.19−2.31 (1 H, m, C(2)**H**H′), 2.33−2.48 (2 H, m, C(2)H**H′** and C(9)**H**H′), 2.58 (1 H, dd, *J* 16.5, 6.5, C(9)H**H′**), 2.79 (1 H, d, *J* 13.0, C(5)**H**H′), 2.86 (1 H, d, *J* 13.0, C(5)H**H′**), 7.28 (1 H, t, *J* 7.0, C(8)H); δ_C (125 MHz, $CDCl_3$) 20.6 (C(11)), 24.1 (C(12)), 34.7 (C(3)), 36.1 (C(2)), 36.4 (C(9)), 44.1 (C(4)), 55.3 (C(10)), 55.6 (C(5)), 127.8 (C(7)), 145.8 (C(8)), 193.2 (C(6)), 221.5 (C(1)); *m/z* (ESI^+) 295 (M(^{81}Br)Na^+, 100%), 293 (M(^{79}Br)Na^+, 95); HRMS (ESI^+): Found: 293.0143; $C_{12}H_{15}O_2BrNa$ (M(^{79}Br)Na^+) requires: 293.0148.

(3a*R*,8a*S*)-3a,8a-Dimethyl-6-(prop-1-en-2-yl)-2,3,3a,4,8,8a-hexahydroazulene-1,5-dione (315)



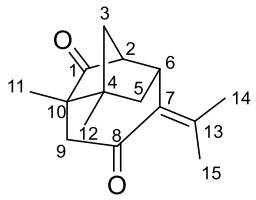
Organotin **311** (18.3 mg, 0.0553 mmol) and $Pd(PPh_3)_4$ (2.5 mg, 0.00221 mmol) were added to a solution of enone **314** (6.00 mg, 0.0221 mmol) in toluene (0.6 mL) and the mixture was stirred at 110 °C for 5 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (2.50 mg, 49%). R_f 0.80 (ether); $[\alpha]_D^{23}$ +64.4 (*c* 0.18, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2967w, 1737s, 1667m, 1453w, 1386w; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, s, C(11)H_3), 1.12 (3 H, s, C(12)H_3), 1.86 (3 H, s, C(15)H_3), 1.87−1.93 (1 H, m, C(3)**H**H′), 1.98−2.08 (1 H, m, C(3)H**H′**), 2.22−2.43 (3 H, m, C(2)H_2 and C(9)**H**H′), 2.57 (1 H, dd, *J* 16.5, 6.0, C(9)H**H′**), 2.67 (1 H, d, *J* 12.5, C(5)**H**H′), 2.74 (1 H, d, *J* 12.5, C(5)H**H′**), 4.98 (1 H, s, C(14)**H**H′), 5.00 (1 H, s, C(14)H**H′**), 6.47 (1 H, t, *J* 6.5, C(8)H); δ_C (125 MHz, $CDCl_3$) 19.7 (C(11)), 21.6 (C(15)), 24.2 (C(12)), 34.1 (C(3)), 34.6 (C(9)), 35.6 (C(2)), 44.4 (C(4)), 55.2 (C(10)), 56.3 (C(5)), 115.8 (C(14)), 136.2 (C(8)), 141.6 (C(7)), 147.2 (C(13)), 202.1 (C(6)), 222.4 (C(1)); *m/z* (ESI^+) 255 (MNa^+, 100%), 233 (MH^+, 30); HRMS (ESI^+): Found: 255.1351; $C_{15}H_{20}O_2Na$ (MNa^+) requires: 255.1356.

(3a*R*,8a*S*)-3a,8a-Dimethyl-6-(prop-1-en-2-yl)-2,3,3a,4,8,8a-hexahydroazulene-1,7-dione (316)



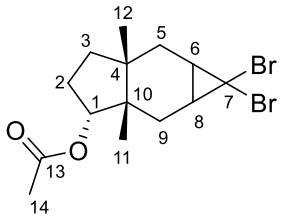
Organotin **311** (15.5 mg, 0.0461 mmol) and $Pd(PPh_3)_4$ (2.0 mg, 0.00184 mmol) were added to a solution of enone **313** (5.00 mg, 0.0184 mmol) in toluene (0.5 mL) and the mixture was stirred at 110 °C for 5 h. The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (2.00 mg, 47%). R_f 0.70 (ether); $[\alpha]_D^{23}$ +53.3 (*c* 0.12, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2969w, 1735s, 1672m, 1468w, 1384w; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, s, C(11)H_3), 1.09 (3 H, s, C(12)H_3), 1.80 (3 H, s, C(15)H_3), 1.90−2.03 (2 H, m, C(3)H_2), 2.18−2.45 (4 H, m, C(2)H_2 and C(5)H_2), 2.49 (1 H, d, *J* 17.5, C(9)**H**H′), 2.80 (1 H, d, *J* 17.5, C(9)H**H′**), 5.00 (1 H, s, C(14)**H**H′), 5.04 (1 H, s, C(14)H**H′**), 6.26 (1 H, t, *J* 7.5, C(6)H); δ_C (125 MHz, $CDCl_3$) 20.9 (C(11) and C(15)), 24.2 (C(12)), 33.9 (C(3)), 36.0 (C(2)), 40.1 (C(5)), 45.1 (C(4)), 48.1 (C(9)), 52.0 (C(10)), 116.5 (C(14)), 131.2 (C(6)), 139.4 (C(7)), 146.9 (C(13)), 204.1 (C(8)), 221.4 (C(1)); *m/z* (ESI^+) 255 (MNa^+, 100%), 233 (MH^+, 30); HRMS (ESI^+): Found: 255.1351; $C_{15}H_{20}O_2Na$ (MNa^+) requires: 255.1356.

3,9-Dimethyl-6-(propan-2-ylidene)tricyclo[5.3.0.0^{3,9}]decane-2,5-dione (317)



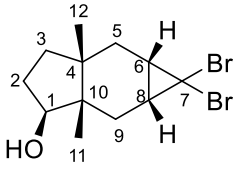
PPTS (1.5 mg, 0.00517 mmol) was added to a solution of enone **316** (1.20 mg, 0.00517 mmol) in toluene (0.2 mL) and the mixture was stirred at 100 °C for 24 h. The mixture was filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (1.10 mg, 92%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +34.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2964w, 1749s, 1681s, 1619w, 1464w; δ_H (500 MHz, $CDCl_3$) 1.00 (3 H, s, C(11)H_3), 1.15 (3 H, s, C(12)H_3), 1.51−1.60 (1 H, m, C(5)**H**H′), 1.70 (2 H, s, C(3)H_2), 1.80 (3 H, s, C(14)H_3), 1.83−1.89 (4 H, m, C(5)H**H′** and C(15)H_3), 2.33 (1 H, d, *J* 19.0, C(9)**H**H′), 2.45 (1 H, d, *J* 19.0, C(9)H**H′**), 2.89 (1 H, d, *J* 6.0, C(2)H), 3.35 (1 H, dd, *J* 10.0, 6.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 16.8 (C(12)), 18.1 (C(11)), 21.7 (C(14)), 22.6 (C(15)), 34.9 (C(6)), 40.8 (C(5)), 41.4 (C(3)), 47.5 (C(4)), 47.9 (C(10)), 50.7 (C(9)), 54.9 (C(2)), 137.8 (C(13)), 144.0 (C(7)), 204.2 (C(8)), 216.9 (C(1)); *m/z* (ESI$^+$) 255 (MNa$^+$, 100%), 233 (MH$^+$, 10); HRMS (ESI$^+$): Found: 255.1353; $C_{15}H_{20}O_2Na$ (MNa$^+$) requires: 255.1356.

(2a*S*,3*R*,5a*R*)-1,1-Dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-yl acetate (318)

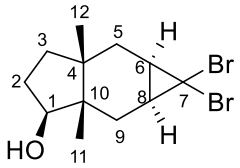


Acetic anhydride (4.00 µL, 0.0423 mmol), pyridine (4.5 µL, 0.0521 mmol) and DMAP (1.5 mg, 0.00976 mmol) were added to a solution of alcohol **332** (11.0 mg, 0.0325 mmol) in DCM (0.3 mL) and the mixture was stirred at RT for 4 h. Methanol (0.1 mL) was added and the mixture was stirred for 15 min. 0.1 M HCl (0.1 mL) was added and the organic layer was washed with sat. aq. $NaHCO_3$ (0.5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil as a mixture of diastereomers (12.3 mg, 99%, *dr.* 1:1). R_f 0.85 (1:1 petrol:ether); $[\alpha]_D^{23}$ +11.2 (*c* 1.25, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2957w, 1735s, 1375w, 1237s, 1028m, 750m; δ_H (500 MHz, $CDCl_3$) 0.70 (1 H, dd, *J* 15.0, 8.0, C(9)**H**H′), 0.85−0.90 (2 H, m, C(5)**H**H′ × 2), 0.92 (3 H, s, C(11)H_3), 0.95 (3 H, s, C(12)H_3), 1.01 (3 H, s, C(12)H_3), 1.02−1.07 (4 H, m, C(9)**H**H′ and C(11)H_3), 1.37−1.49 (3 H, m, C(2)**H**H′ and C(3)**H**H′ × 2), 1.50−1.62 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.64−1.75 (2 H, m, C(6)H × 2), 1.76−1.86 (5 H, m, C(3)H**H′**, C(5)H**H′**, C(8)H × 2 and C(9)H**H′**), 1.87−1.97 (3 H, m, C(2)H**H′** × 2 and C(5)H**H′**), 2.06 (3 H, s, C(14)H_3), 2.11 (3 H, s, C(14)H_3), 2.16−2.25 (1 H, m, C(9)H**H′**), 4.76−4.88 (2 H, m, C(1)H × 2); δ_C (125 MHz, $CDCl_3$) 21.2/21.4 (C(14)), 24.1/24.7 (C(11)), 26.6 (C(6)), 26.7/27.0 (C(12)), 27.1 (C(2)), 27.5 (C(6)), 28.2/28.5 (C(8)), 29.5 (C(2)), 29.8/30.7 (C(9)), 35.3/36.9 (C(5)), 37.0/38.5 (C(3)), 40.7/41.0 (C(4)), 42.1/43.0 (C(7)), 43.8/44.0 (C(10)), 83.5/83.8 (C(1)), 170.7/170.9 (C(13)); *m/z* (ESI^+) 405 (M($^{81}Br^{81}Br$)Na^+, 40%), 403 (M($^{81}Br^{79}Br$)Na^+, 100), 401 (M($^{79}Br^{79}Br$)Na^+, 80).

(1a*R*,2a*S*,3*S*,5a*R*,6a*S*)-1,1-Dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-ol (322) and **(1a*S*,2a*S*,3*S*,5a*R*,6a*R*)-1,1-Dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-ol (323)**



322



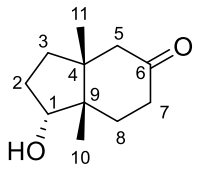
323

H_2SiF_6 (0.01 mL, 0.0166 mmol) was added to a solution of silyl ether **303** (25.0 mg, 0.0553 mmol) in ACN (0.5 mL) at 0 °C and stirred for 3 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded *alcohol* **322** as a colourless oil (9.30 mg, 50%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +7.3 (*c* 0.90, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3369br, 2951s, 1454m, 1029s, 748s; δ_H (500 MHz, $CDCl_3$) 0.74−0.82 (1 H, m, C(9)**H**H′), 0.84−0.90 (1 H, m, C(5)**H**H′), 1.00 (3 H, s, C(11)H_3), 1.03 (3 H, s, C(12)H_3), 1.36−1.46 (1 H, m, C(3)**H**H′), 1.52−1.59 (1 H, m, C(2)**H**H′), 1.63−1.70 (1 H, m, C(2)H**H′**), 1.73−1.78 (4 H, m, C(3)H**H′**, C(5)H**H′**, C(6)H and C(8)H), 1.85−1.90 (1 H, m, C(9)H**H′**), 3.64−3.70 (1 H, m, C(1)H); δ_C (125 MHz, $CDCl_3$) 19.2 (C(11)), 26.7 (C(12)), 27.7 (C(6)), 28.1 (C(8)), 30.3 (C(2)), 35.2 (C(9)), 36.6 (C(5)), 39.6 (C(3)), 41.4 (C(4)), 42.2 (C(7)), 45.9 (C(10)), 82.3 (C(1)); *m/z* (FI^+) 340 ($M(^{81}Br^{81}Br)^{+\cdot}$, 40%), 338 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 336 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($FI^+$): Found: 335.9662; $C_{12}H_{18}OBr_2$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 335.9719.

Also obtained was *alcohol* **323** as a colourless oil (9.20 mg, 49%). R_f 0.40 (1:1 petrol:ether); $[\alpha]_D^{23}$ +5.8 (*c* 0.90, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3369br, 2951s, 1454m, 1029s, 748s; δ_H (500 MHz, $CDCl_3$) 0.74−0.82 (1 H, m, C(9)**H**H′), 0.83 (3 H, s, C(11)H_3), 0.84−0.90 (1 H, m,

C(5)**H**H′), 0.95 (3 H, s, C(12)H_3), 1.36−1.46 (1 H, m, C(3)**H**H′), 1.48−1.59 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.73−1.78 (2 H, m, C(6)H and C(8)H), 1.79−1.84 (1 H, m, C(2)H**H′**), 1.85−1.90 (1 H, m, C(5)H**H′**), 1.99−2.07 (1 H, m, C(9)H**H′**), 3.84−3.92 (1 H, m, C(1)H); δ_C (125 MHz, $CDCl_3$) 18.5 (C(11)), 27.3 (C(12)), 27.5 (C(6) and C(8)), 31.4 (C(2)), 32.5 (C(9)), 35.6 (C(5)), 35.9 (C(3)), 40.7 (C(4)), 42.4 (C(7)), 43.7 (C(10)), 80.0 (C(1)); *m/z* (FI^+) 340 (M($^{81}Br^{81}Br$)$^{+\cdot}$, 40%), 338 (M($^{81}Br^{79}Br$)$^{+\cdot}$, 100), 336 (M($^{79}Br^{79}Br$)$^{+\cdot}$, 50); HRMS (FI^+): Found: 335.9662; $C_{12}H_{18}OBr_2$ (M($^{79}Br^{79}Br$)$^{+\cdot}$) requires: 335.9719.

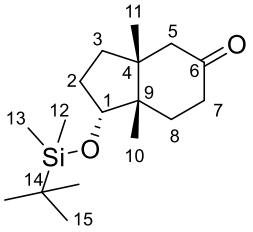
(1*R*,3a*R*,7a*S*)-1-Hydroxy-3a,7a-dimethyloctahydro-5*H*-inden-5-one (325)



Methyllithium solution (2.47 mL, 3.96 mmol, 1.6 M in Et_2O) was added dropwise to a suspension of copper iodide (0.377 g, 1.98 mmol) in ether (5.3 mL) at –20 °C and the solution was stirred for 15 min. The solution was cooled to –78 °C and a solution of enone **290** (0.250 g, 1.52 mmol) in ether (4 mL) was added dropwise. The mixture was stirred at –15 °C for 1 h, and then triethylamine (0.637 mL, 4.57 mmol) and TMSCl (0.386 mL, 3.05 mmol) were added. The mixture was stirred at 0 °C for 1 h and allowed to warm to RT. Sat. aq. $NaHCO_3$ (15 mL) was added and the mixture was extracted with ether (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. A solution of the crude enol ether in THF (8 mL) was added to a suspension of $LiAlH_4$ (85.7 mg, 2.26 mmol) in THF (4 mL) at –78 °C and the mixture was stirred at –78 °C for 2 h. 1 M HCl (8 mL) was added and the solution was stirred for 30 min. The mixture was then extracted with ether (3 × 15 mL). The combined organic layers were dried over Na_2SO_4,

filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a white solid (132 mg, 48%). R_f 0.45 (ether); m.p. 56–59 °C; $[\alpha]_D^{23}$ –8.5 (*c* 2.45, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3416br, 2957m, 1721s, 1454w, 1065w, 754m; δ_H (400 MHz, $CDCl_3$) 0.91 (3 H, s, C(11)H_3), 1.13 (3 H, s, C(10)H_3), 1.35 (1 H, ddd, *J* 13.0, 9.5, 4.5, C(3)**H**H′), 1.51−1.61 (1 H, m, C(2)**H**H′), 1.62−1.75 (2 H, m, C(3)H**H′** and C(8)**H**H′), 1.86 (1 H, td, *J* 13.5, 5.5, C(8)H**H′**), 2.02 (1 H, bs, OH), 2.09−2.19 (1 H, m, C(2)H**H′**), 2.22 (2 H, s, C(5)H_2), 2.29−2.40 (2 H, m, C(7)H_2), 4.16 (1 H, t, *J* 7.5, C(1)H); δ_C (100 MHz, $CDCl_3$) 18.6 (C(10)), 25.3 (C(11)), 29.3 (C(2)), 30.1 (C(8)), 34.5 (C(3)), 37.4 (C(7)), 44.6 (C(4)), 47.2 (C(9)), 50.1 (C(5)), 81.1 (C(1)), 213.0 (C(6)); *m/z* (ESI^+) 205 (MNa^+, 100%), 183 (MH^+, 20); HRMS (ESI^+): Found: 205.1201; $C_{11}H_{18}O_2Na$ (MNa^+) requires: 205.1199.

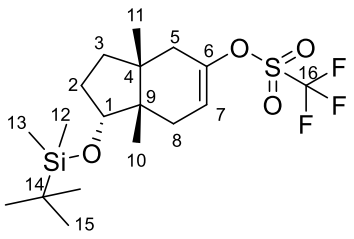
(1*R*,3a*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyloctahydro-5*H*-inden-5-one (326)



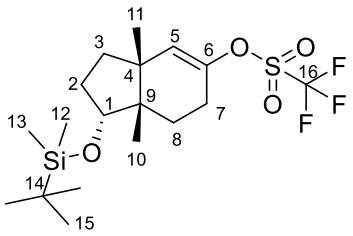
Imidazole (90.5 mg, 1.33 mmol), TBSCl (0.150 g, 0.996 mmol) and DMAP (24.3 mg, 0.199 mmol) were added to a solution of alcohol **325** (121 mg, 0.664 mmol) in DMF (4.0 mL) and the solution was stirred at RT for 16 h. Water (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the *title compound* as a white solid (0.181 g, 92%). R_f 0.70 (3:1

petrol:ether); m.p. 78–81 °C; $[\alpha]_D^{23}$ –24.8 (*c* 1.35, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956s, 1720s, 1462w, 1251m, 1081s, 836s; δ_H (400 MHz, $CDCl_3$) 0.03 (3 H, s, C(12)H_3), 0.05 (3 H, s, C(13)H_3), 0.88 (9 H, s, 3 × C(15)H_3), 0.92 (3 H, s, C(11)H_3), 1.07 (3 H, s, C(10)H_3), 1.31−1.40 (1 H, m, C(3)**H**H′), 1.50−1.61 (1 H, m, C(2)**H**H′), 1.63−1.75 (2 H, m, C(3)H**H′** and C(8)**H**H′), 1.83−1.95 (1 H, m, C(8)H**H′**), 1.97−2.08 (1 H, m, C(2)H**H′**), 2.19 (1 H, d, *J* 14.0, C(5)**H**H′), 2.26 (1 H, d, *J* 14.0, C(5)H**H′**), 2.33 (2 H, dd, *J* 9.5, 5.5, C(7)H_2), 4.07 (1 H, dd, *J* 8.5, 6.5, C(1)H); δ_C (100 MHz, $CDCl_3$) –5.0 (C(12)), –4.4 (C(13)), 18.0 (C(14)), 19.2 (C(10)), 25.3 (C(11)), 25.8 (C(15)), 30.0 (C(2)), 30.5 (C(8)), 35.0 (C(3)), 37.7 (C(7)), 45.1 (C(4)), 46.6 (C(9)), 50.4 (C(5)), 81.5 (C(1)), 213.2 (C(6)); *m/z* (ESI^+) 319 (MNa^+, 100%), 297 (MH^+, 20); HRMS (ESI^+): Found: 297.2241; $C_{17}H_{33}O_2Si$ (MH^+) requires: 297.2244.

(1*R*,3a*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (327) and **(1*R*,3a*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (328)**



327



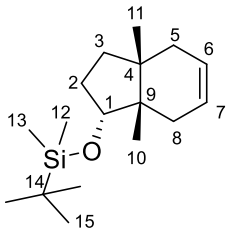
328

KHMDS (0.541 mL, 0.271 mmol, 0.5 M in toluene) was added dropwise to a solution of ketone **326** (61.7 mg, 0.208 mmol) in THF (0.66 mL) at –78 °C and the solution was stirred at –78 °C for 30 min. *N*-Phenyl-bis(trifluoromethanesulfonimide) (96.6 mg, 0.271 mmol) was then added and the solution was stirred at –78 °C for 2 h. Sat. aq. NH_4Cl (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried

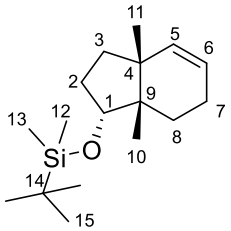
over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 19:1 petrol:ether) afforded *enol triflate* **327** as a colourless oil (52.0 mg, 58%). R_f 0.70 (9:1 petrol:ether); $[\alpha]_D^{23}$ –7.7 (*c* 1.11, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2958w, 1419m, 1207s, 1129m, 867m, 837m; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(12)H_3), 0.04 (3 H, s, C(13)H_3), 0.88 (12 H, s, C(10)H_3 and 3 × C(15)H_3), 0.90 (3 H, s, C(11)H_3), 1.32−1.41 (1 H, m, C(3)**H**H′), 1.50−1.61 (1 H, m, C(2)**H**H′), 1.75−1.90 (2 H, m, C(3)H**H′** and C(8)**H**H′), 2.02−2.12 (1 H, m, C(2)H**H′**), 2.15−2.24 (2 H, m, C(5)H_2), 2.29−2.42 (1 H, m, C(8)H**H′**), 4.03 (1 H, dd, *J* 9.0, 5.5, C(1)H), 5.69 (1H, s, C(7)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(12)), –4.4 (C(13)), 18.0 (C(14)), 19.3 (C(10)), 24.2 (C(11)), 25.8 (C(15)), 29.8 (C(2)), 30.4 (C(8)), 34.3 (C(3)), 36.8 (C(5)), 42.9 (C(4)), 44.1 (C(9)), 80.2 (C(1)), 116.3 (C(7)), 118.5 (q, *J* 319.5, C(16)), 146.5 (C(6)); *m/z* (ESI^+) 451 (MNa^+, 100%); HRMS (ESI^+): Found: 451.1552; $C_{18}H_{31}O_4F_3SiSNa$ (MNa^+) requires: 451.1557.

Also obtained was *enol triflate* **328** as a colourless oil (21.3 mg, 24%). R_f 0.70 (9:1 petrol:ether); $[\alpha]_D^{23}$ –7.7 (*c* 1.11, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2958w, 1419m, 1207s, 1129m, 867m, 837m; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(12)H_3), 0.04 (3 H, s, C(13)H_3), 0.88 (13 H, s, C(8)**H**H′, C(10)H_3 and 3 × C(15)H_3), 0.99 (3 H, s, C(11)H_3), 1.50−1.61 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.65−1.73 (2 H, m, C(7)H_2), 1.75−1.81 (1 H, m, C(3)H**H′**), 1.93−2.01 (1 H, m, C(2)H**H′**), 2.29−2.42 (1 H, m, C(8)H**H′**), 4.00 (1 H, t, *J* 8.5, C(1)H), 5.49 (1H, s, C(5)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(12)), –4.4 (C(13)), 18.0 (C(14)), 19.9 (C(10)), 24.5 (C(11)), 24.8 (C(8)), 25.8 (C(15)), 27.2 (C(7)), 30.7 (C(2)), 36.5 (C(3)), 42.9 (C(4)), 44.1 (C(9)), 80.7 (C(1)), 118.5 (q, *J* 319.5, C(16)), 126.9 (C(5)), 148.2 (C(6)); *m/z* (ESI^+) 451 (MNa^+, 100%); HRMS (ESI^+): Found: 451.1552; $C_{18}H_{31}O_4F_3SiSNa$ (MNa^+) requires: 451.1557.

***tert*-Butyl{[(1*R*,3a*R*,7a*S*)-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (329)** and ***tert*-Butyl{[(1*R*,3a*R*,7a*S*)-3a,7a-dimethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (330)**



329

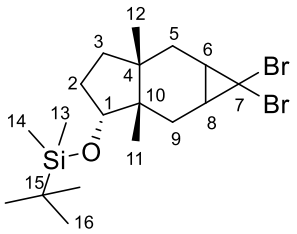


330

A solution of triflate isomers **327** and **328** (0.100 g, 0.233 mmol) in THF (2.5 mL) was added to LiCl (29.7 mg, 0.700 mmol) and $Pd(PPh_3)_4$ (5.39 mg, 4.67 μmol). Tributyltin hydride (76.6 μL, 0.285 mmol) was added dropwise at RT and the mixture was stirred at 55 °C for 3 h. Ether (5 mL) was added and the mixture was washed with 10% aq. KF (5 mL) and brine (5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded *alkene* **329** as a colourless oil (45.5 mg, 70%). R_f 0.85 (petrol); $[\alpha]_D^{23}$ –28.7 (*c* 1.24, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956m, 1461w, 1250m, 1093m, 836s, 774s; δ_H (400 MHz, $CDCl_3$) 0.02 (3 H, s, C(12)H_3), 0.03 (3 H, s, C(13)H_3), 0.86 (3 H, s, C(11)H_3), 0.87 (3 H, s, C(10)H_3), 0.89 (9 H, s, 3 × C(15)H_3), 1.14−1.26 (1 H, m, C(3)**H**H′), 1.48−1.67 (2 H, m, C(2)**H**H′ and C(8)**H**H′), 1.75−1.89 (3 H, m, C(3)H**H′** and C(5)H_2), 1.96−2.08 (1 H, m, C(2)H**H′**), 2.09−2.20 (1 H, m, C(8)H**H′**), 4.06 (1 H, dd, *J* 9.0, 6.0, C(1)H), 5.46−5.55 (1 H, m, C(6)H), 5.58−5.68 (1 H, m, C(7)H); δ_C (100 MHz, $CDCl_3$) –4.9 (C(12)), –4.4 (C(13)), 18.1 (C(14)), 19.4 (C(10)), 24.8 (C(11)), 25.9 (C(15)), 30.0 (C(2)), 30.4 (C(8)), 34.2 (C(3)), 35.1 (C(5)), 40.7 (C(4)), 43.8 (C(9)), 80.6 (C(1)), 123.6 (C(6)), 125.0 (C(7)); *m/z* (FI^+) 280 ($M^{+\cdot}$, 100%); HRMS (FI^+): Found: 280.2228; $C_{17}H_{32}OSi$ ($M^{+\cdot}$) requires: 280.2217.

Also obtained was *alkene* **330** as a colourless oil (18.6 mg, 28%). R_f 0.80 (petrol); $[\alpha]_D^{23}$ –1.9 (*c* 0.52, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956s, 1462w, 1251m, 1092s, 836s, 774s; δ_H (400 MHz, $CDCl_3$) 0.03 (3 H, s, C(12)H_3), 0.05 (3 H, s, C(13)H_3), 0.85 (3 H, s, C(10)H_3), 0.89 (3 H, s, C(11)H_3), 0.90 (9 H, s, 3 × C(15)H_3), 1.40−1.50 (3 H, m, C(3)**H**H′ and C(8)H_2), 1.55−1.64 (1 H, m, C(2)**H**H′), 1.68−1.78 (1 H, m, C(3)H**H′**), 1.88−2.05 (3 H, m, C(2)H**H′** and C(7)H_2), 4.01 (1 H, t, *J* 8.5, C(1)H), 5.41 (1 H, dt, *J* 10.0, 2.0, C(5)H), 5.56 (1 H, ddd, *J* 10.0, 4.5, 3.0, C(6)H); δ_C (100 MHz, $CDCl_3$) –4.9 (C(12)), –4.4 (C(13)), 18.1 (C(14)), 19.5 (C(10)), 21.9 (C(7)), 25.1 (C(11)), 25.5 (C(8)), 25.9 (C(15)), 30.5 (C(2)), 37.3 (C(3)), 42.8 (C(4)), 44.1 (C(9)), 81.3 (C(1)), 123.6 (C(6)), 136.9 (C(5)); *m/z* (FI^+) 280 ($M^{+\cdot}$, 100%); HRMS (FI^+): Found: 280.2228; $C_{17}H_{32}OSi$ ($M^{+\cdot}$) requires: 280.2217.

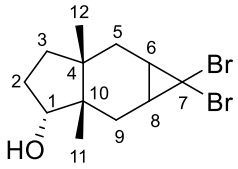
tert-Butyl{[(2a*S*,3*R*,5a*R*)-1,1-dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-yl]oxy}dimethylsilane (331)



Benzyltriethylammonium chloride (0.5 mg, 0.884 μmol) and bromoform (23.0 μL, 0.265 mmol) were added to a solution of alkene **329** (24.8 mg, 0.0884 mmol) in benzene (0.5 mL). 50% aq. NaOH (16.0 μL) was added dropwise and the mixture was stirred at 70 °C for 16 h. Water (2 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil as a mixture of diastereomers (17.7 mg, 44%, *dr*. 1:1). R_f 0.75 (petrol); $[\alpha]_D^{23}$ –6.3 (*c* 1.77,

$CHCl_3$); ν_{max} (thin film)/cm^{-1} 2953m, 1471w, 1251m, 1096m, 835s, 774s; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(13)H_3), 0.04 (3 H, s, C(13)H_3), 0.05 (3 H, s, C(14)H_3), 0.06 (3 H, s, C(14)H_3), 0.50 (1 H, dd, *J* 15.0, 8.0, C(9)**H**H′), 0.85 (3 H, s, C(11)H_3), 0.86−0.91 (14 H, m, C(3)**H**H′, C(5)**H**H′, C(12)H_3 and 3 × C(16)H_3), 0.93 (9 H, s, 3 × C(16)H_3), 0.96 (3 H, s, C(12)H_3), 0.98 (3 H, s, C(11)H_3), 0.99−1.05 (1 H, m, C(9)**H**H′), 1.26−1.41 (3 H, m, C(2)**H**H′, C(3)**H**H′ and C(5)**H**H′), 1.42−1.53 (2 H, m, C(2)**H**H′ and C(5)H**H′**), 1.61−1.87 (10 H, m, 2 × C(2)H**H′**, 2 × C(3)H**H′**, C(5)H**H′**, 2 × C(6)H, 2 × C(8)H and C(9)H**H′**), 2.35 (1 H, dd, *J* 15.0, 8.5, C(9)H**H′**), 3.63−3.72 (2 H, m, 2 × C(1)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.4 (C(14)), 18.1 (C(15)), 24.2/24.5 (C(11)), 25.9 (C(16)), 26.9 (C(12)), 27.2/27.5 (C(6)), 27.8 (C(12)), 28.4/28.9 (C(8)), 29.2/29.4 (C(9)), 30.4/32.9 (C(2)), 36.2/36.6 (C(3)), 37.1/38.4 (C(5)), 39.8/40.6 (C(4)), 42.8/44.2 (C(7)), 44.4/44.9 (C(10)), 82.3/82.9 (C(1)); *m/z* (FI^+) 454 ($M(^{81}Br^{81}Br)^{+\cdot}$, 40%), 452 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 450 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($FI^+$): Found: 450.0585; $C_{18}H_{32}OBr_2Si$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 450.0584.

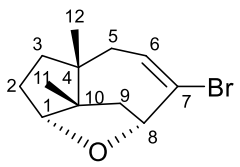
(2a*S*,3*R*,5a*R*)-1,1-Dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-ol (332)



H_2SiF_6 (0.01 mL, 0.0117 mmol) was added to a solution of silyl ether **331** (17.7 mg, 0.0391 mmol) in ACN (1 mL) at 0 °C and stirred for 3 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil as a mixture of diastereomers (11.0 mg, 83%, *dr.* 1:1). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ –4.4 (*c* 1.10, $CHCl_3$); ν_{max} (thin

film)/cm^{-1} 3349br, 2952s, 1450m, 1062s, 750s; δ_H (500 MHz, $CDCl_3$) 0.62 (1 H, dd, *J* 15.0, 8.0, C(9)**H**H′), 0.85−0.95 (9 H, m, C(5)**H**H′ × 2, C(9)**H**H′, C(11)H_3 and C(12)H_3), 0.99 (3 H, s, C(12)H_3), 1.04 (3 H, s, C(11)H_3), 1.31−1.57 (5 H, m, C(2)**H**H′ × 2, C(3)**H**H′ and C(3)H_2), 1.66−1.72 (2 H, m, C(6)H × 2), 1.73−1.90 (8 H, m, C(2)H**H′** × 2, C(3)H**H′**, C(5)H**H′** × 2, C(8)H × 2 and C(9)H**H′**), 2.32 (1 H, dd, *J* 15.0, 8.0, C(9)H**H′**), 3.72−3.85 (2 H, m, C(1)H × 2); δ_C (125 MHz, $CDCl_3$) 24.0/24.5 (C(11)), 26.7 (C(12)), 26.9/27.3 (C(6)), 27.5 (C(12)), 28.3/28.7 (C(8)), 28.9/29.0 (C(9)), 30.1/32.3 (C(2)), 35.6 (C(5)), 36.4 (C(3)), 37.0 (C(5)), 38.2 (C(3)), 40.6/41.2 (C(4)), 42.2/43.6 (C(7)), 44.2 (C(10)), 82.3/82.9 (C(1)); *m/z* (FI^+) 340 ($M(^{81}Br^{81}Br)^{+\cdot}$, 40%), 338 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 336 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($FI^+$): Found: 335.9662; $C_{12}H_{18}OBr_2$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 335.9719.

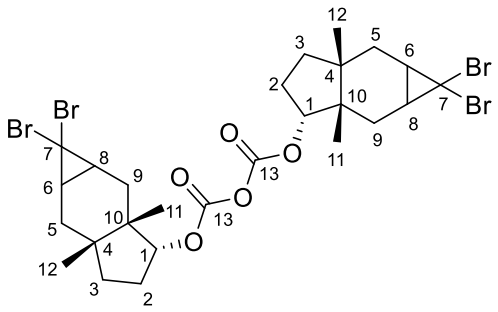
(1*R*,3a*R*,7*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydro-1,7-epoxyazulene (333)



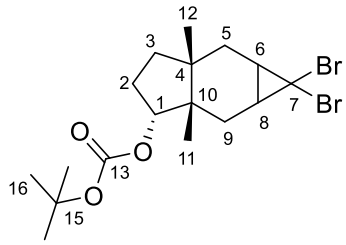
$AgClO_4$ (11.0 mg, 0.0537 mmol) was added to a solution of dibromocyclopropane **318** (12.0 mg, 0.0316 mmol) in acetone (0.2 mL) and the mixture was stirred under reflux for 1 h. The mixture was filtered and solvent removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (6.50 mg, 80%). R_f 0.80 (1:1 petrol:ether); $[\alpha]_D^{23}$ +42.2 (*c* 0.65, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955m, 1460w, 1242w, 1020s, 881s; δ_H (500 MHz, $CDCl_3$) 0.99 (3 H, s, C(12)H_3), 1.09 (3 H, s, C(11)H_3), 1.50 (1 H,

ddd, *J* 12.5, 8.0, 4.5, C(3)**H**H′), 1.71−1.86 (2 H, m, C(2)H_2), 1.87−2.05 (3 H, m, C(3)H**H′**, C(5)**H**H′ and C(9)**H**H′), 2.25 (1 H, dd, *J* 17.0, 2.5, C(5)H**H′**), 2.38 (1 H, d, *J* 13.0, C(9)H**H′**), 4.15 (1 H, dd, *J* 4.0, 2.5, C(1)H), 4.70 (1 H, dd, *J* 8.5, 1.5, C(8)H), 6.12 (1 H, ddd, *J* 10.0, 2.5, 2.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 23.0 (C(11)), 27.7 (C(12)), 29.5 (C(2)), 39.2 (C(3)), 41.6 (C(5)), 43.3 (C(9)), 47.7 (C(4)), 54.3 (C(10)), 85.4 (C(8)), 95.1 (C(1)), 125.7 (C(7)), 132.6 (C(6)); *m/z* (ESI^+) 259 ($M(^{81}Br)H^+$, 100%), 257 ($M(^{79}Br)H^+$, 100); HRMS (ESI^+): Found: 257.0537; $C_{12}H_{18}OBr$ ($M(^{79}Br)H^+$) requires: 257.0536.

Bis[(2a*S*,3*R*,5a*R*)-1,1-dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-yl] dicarbonate (334) and ***tert*-Butyl [(2a*S*,3*R*,5a*R*)-1,1-dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-yl] carbonate (335)**



334



335

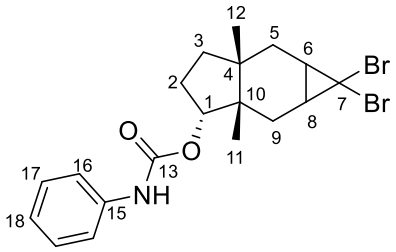
Boc anhydride (8.7 mg, 0.0400 mmol), triethylamine (7.0 µL, 0.0492 mmol) and DMAP (1.5 mg, 0.00923 mmol) were added to a solution of alcohol **332** (10.4 mg, 0.0308 mmol) in THF (0.4 mL) and the mixture was stirred at RT for 3 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded *anhydride* **334** as a colourless oil (5.00 mg, 46%). R_f 0.85 (1:1 petrol:ether); $[\alpha]_D^{23}$ +12.0 (*c* 0.50, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2958w, 1737m, 1258s, 996m,

749m; δ_H (500 MHz, $CDCl_3$) 0.66−0.78 (2 H, m, C(9)**H**H′ × 2), 0.86−0.94 (4 H, m, C(3)**H**H′ × 2 and C(5)**H**H′ × 2), 0.95 (6 H, s, C(12)H_3 × 2), 0.96 (6 H, s, C(11)H_3 × 2), 1.01 (3 H, s, C(12)H_3), 1.02 (3 H, s, C(12)H_3), 1.03−1.06 (2 H, m, C(9)**H**H′ × 2), 1.07 (3 H, s, C(11)H_3), 1.08 (3 H, s, C(11)H_3), 1.37−1.49 (4 H, m, C(3)**H**H′ × 2 and C(5)**H**H′ × 2), 1.51−1.61 (4 H, m, C(2)**H**H′ × 2 and C(3)H**H′** × 2), 1.64−1.74 (6 H, m, C(2)**H**H′ × 2 and C(6)H × 4), 1.76−2.03 (16 H, m, C(2)H**H′** × 4, C(3)H**H′** × 2, C(5)H**H′** × 4, C(8)H × 4 and C(9)H**H′** × 2), 2.16−2.25 (2 H, m, C(9)H**H′** × 2), 4.61−4.76 (4 H, m, C(1)H × 4); δ_C (125 MHz, $CDCl_3$) 24.1/24.2/24.8 (C(11)), 26.6 (C(12)), 26.7 (C(6) and C(12)), 26.8 (C(12)), 27.1/27.2 (C(2)), 27.5/27.6 (C(6)), 27.9/28.0/28.3/28.4 (C(8)), 29.4 (C(2)), 29.6/30.8/30.9 (C(9)), 35.0/35.1 (C(3)), 36.9/37.1/37.3 (C(5)), 38.3/38.4 (C(3)), 41.0/41.1/41.2 (C(4)), 41.9/43.0 (C(7)), 44.3/44.4/44.5 (C(10)), 87.2/87.3/87.9/88.1 (C(1)), 154.8/155.0/155.1/155.2 (C(13)); *m/z* (EI^+) 384 ([M($^{81}Br^{81}Br$)+H_2O]/$2^{+\cdot}$, 50%), 382 ([M($^{81}Br^{79}Br$)+H_2O]/$2^{+\cdot}$, 100), 380 ([M($^{79}Br^{79}Br$)+H_2O]/$2^{+\cdot}$, 50); HRMS (EI^+): Found: 379.9550; $C_{13}H_{18}O_3Br_2$ ([M($^{79}Br^{79}Br$)+H_2O]/$2^{+\cdot}$) requires: 379.9618.

Also obtained was *carbonate* **335** as a colourless oil as a mixture of diastereomers (7.00 mg, 52%, *dr*. 1:1). R_f 0.90 (1:1 petrol:ether); $[\alpha]_D^{23}$ +25.5 (*c* 0.60, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2961w, 1737s, 1368w, 1278s, 1162m; δ_H (500 MHz, $CDCl_3$) 0.70 (1 H, dd, *J* 15.5, 8.5, C(9)**H**H′), 0.87−0.94 (2 H, m, C(3)**H**H′ and C(5)**H**H′), 0.95 (3 H, s, C(12)H_3), 0.96 (3 H, s, C(11)H_3), 1.00 (3 H, s, C(12)H_3), 1.01−1.06 (1 H, m, C(9)**H**H′), 1.07 (3 H, s, C(11)H_3), 1.35−1.46 (2 H, m, C(3)**H**H′ and C(5)**H**H′), 1.49 (9 H, s, C(16)H_3 × 3), 1.51 (9 H, s, C(16)H_3 × 3), 1.53−1.58 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.62−1.74 (3 H, m, C(2)**H**H′ and C(6)H × 2), 1.76−1.96 (8 H, m, C(2)H**H′** × 2, C(3)H**H′**, C(5)H**H′** × 2, C(8)H × 2 and C(9)H**H′**), 2.22 (1 H, dd, *J* 15.5, 8.0, C(9)H**H′**), 4.63−4.72 (2 H, m, C(1)H × 2); δ_C (125 MHz, $CDCl_3$) 24.0/24.7 (C(11)), 26.7/26.8 (C(12)), 26.9 (C(6)), 27.0 (C(2)), 27.4 (C(6)), 27.8/27.9 (C(16)), 28.1/28.3 (C(8)), 29.4 (C(2)), 29.7/30.6 (C(9)), 35.1 (C(3)), 36.9/37.0 (C(5)), 38.3 (C(3)),

40.9/41.1 (C(4)), 41.9/43.2 (C(7)), 44.2 (C(10)), 81.9 (C(15)), 86.2/86.7 (C(1)), 153.7 (C(13)); *m/z* (FI^+) 384 ([M($^{81}Br^{81}Br$)–^{t}Bu]$^{+\cdot}$, 40%), 382 ([M($^{81}Br^{79}Br$)–^{t}Bu]$^{+\cdot}$, 100), 380 ([M($^{79}Br^{79}Br$)–^{t}Bu]$^{+\cdot}$, 60); HRMS (FI^+): Found: 379.9503; $C_{13}H_{18}O_3Br_2$ ([M($^{79}Br^{79}Br$)–^{t}Bu]$^{+\cdot}$) requires: 379.9618.

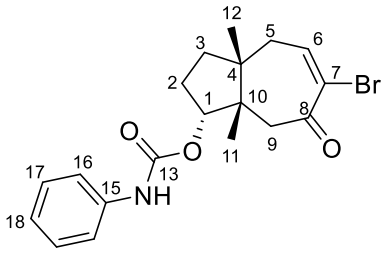
(2a*S*,3*R*,5a*R*)-1,1-Dibromo-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-3-yl phenylcarbamate (336)



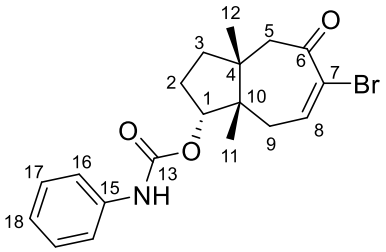
Phenyl isocyanate (10.0 µL, 0.0923 mmol), triethylamine (13.0 µL, 0.0923 mmol) and DMAP (11.3 mg, 0.0923 mmol) were added to a solution of alcohol **332** (10.4 mg, 0.0308 mmol) in DCM (0.4 mL) and the mixture was stirred at RT for 24 h. Water (0.5 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil as a mixture of diastereomers (12.7 mg, 90%, *dr.* 1:1). R_f 0.90 (1:1 petrol:ether); $[\alpha]_D^{23}$ +22.4 (*c* 1.27, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3321w, 2957w, 1702s, 1539s, 1443s, 1223s; δ_H (500 MHz, $CDCl_3$) 0.73 (1 H, dd, *J* 15.5, 8.5, C(9)**H**H′), 0.85−0.93 (2 H, m, C(3)**H**H′ and C(5)**H**H′), 0.98 (6 H, s, C(11)H_3 and C(12)H_3), 1.03 (3 H, s, C(12)H_3), 1.04−1.08 (1 H, m, C(9)**H**H′), 1.10 (3 H, s, C(11)H_3), 1.40−1.51 (4 H, m, C(2)**H**H′ × 2, C(3)**H**H′ and C(5)**H**H′), 1.61−2.06 (11 H, m, C(2)H**H′** × 2, C(3)H**H′** × 2, C(5)H**H′** × 2, C(6)H × 2, C(8)H × 2 and C(9)H**H′**), 2.26 (1 H, dd, *J* 15.5, 8.5, C(9)H**H′**), 4.81−4.92 (2 H, m, C(1)H × 2), 6.58 (2 H,

bs, NH × 2), 7.04−7.13 (2 H, m, C(18)H × 2), 7.29−7.52 (8 H, m, C(16)H × 4 and C(17)H × 4); δ_C (125 MHz, $CDCl_3$) 24.2/24.6 (C(11)), 26.6 (C(6)), 26.7/27.1 (C(12)), 27.3 (C(2)), 27.5 (C(6)), 28.2/28.5 (C(8)), 29.7 (C(2)), 29.9/30.5 (C(9)), 35.4 (C(3)), 36.9 (C(5)), 38.2 (C(3)), 40.7/41.1 (C(4)), 42.1/42.9 (C(7)), 43.8/44.0 (C(10)), 84.4/84.6 (C(1)), 118.6 (C(16)), 123.5 (C(18)), 129.1 (C(17)), 137.8 (C(15)), 153.3 (C(13)); *m/z* (ESI^+) 482 ($M(^{81}Br^{81}Br)Na^+$, 50%), 480 ($M(^{81}Br^{79}Br)Na^+$, 100), 478 ($M(^{79}Br^{79}Br)Na^+$, 50); HRMS (ESI^+): Found: 477.9990; $C_{19}H_{23}O_2NBr_2Na$ ($M(^{79}Br^{79}Br)Na^+$) requires: 477.9988.

(1*R*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-7-oxo-1,2,3,3a,4,7,8,8a-octahydroazulen-1-yl phenylcarbamate (339) and **(1*R*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-5-oxo-1,2,3,3a,4,5,8,8a-octahydroazulen-1-yl phenylcarbamate (340)**



339



340

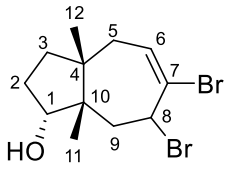
$AgClO_4$ (7.7 mg, 0.0372 mmol) was added to a solution of dibromocyclopropane **336** (10.0 mg, 0.0219 mmol) in acetone (0.3 mL) and the mixture was stirred under reflux for 1 h. The mixture was filtered and solvent removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the alcohol as a colourless oil (7.60 mg, 88%). Dess–Martin periodinane (13.6 mg, 0.0320 mmol) was added to a solution of alcohol (6.30 mg, 0.0160 mmol) in DCM (0.8 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (1

mL) and sat. aq. $Na_2S_2O_3$ (1 mL) were added and the mixture was extracted with DCM (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded *enone* **339** as a colourless oil (3.0 mg, 49%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ –29.2 (*c* 0.61, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3333w, 2963w, 1729s, 1674s, 1539s, 1224s; δ_H (500 MHz, $CDCl_3$) 1.04 (3 H, s, C(11)H_3), 1.06 (3 H, s, C(12)H_3), 1.62−1.68 (1 H, m, C(3)**H**H′), 1.71−1.78 (1 H, m, C(2)**H**H′), 1.80−1.89 (1 H, m, C(3)H**H′**), 2.03−2.13 (1 H, m, C(2)H**H′**), 2.32−2.44 (1 H, m, C(5)**H**H′), 2.70−2.81 (2 H, m, C(5)H**H′** and C(9)**H**H′), 2.99 (1 H, d, *J* 14.0, C(9)H**H′**), 4.86 (1 H, t, *J* 5.5, C(1)H), 6.69 (1 H, bs, NH), 7.05−7.14 (1 H, m, C(18)H), 7.29−7.44 (5 H, m, C(6)H, C(16)H × 2 and C(17)H × 2); δ_C (125 MHz, $CDCl_3$) 23.5 (C(11)), 26.1 (C(12)), 28.8 (C(2)), 39.2 (C(3)), 43.2 (C(5)), 46.7 (C(4)), 47.4 (C(10)), 49.2 (C(9)), 84.9 (C(1)), 118.6 (C(16)), 123.7 (C(18)), 128.0 (C(7)), 129.1 (C(17)), 137.6 (C(15)), 147.6 (C(6)), 152.6 (C(13)), 193.7 (C(8)); *m/z* (ESI^+) 416 (M(^{81}Br)Na^+, 95%), 414 (M(^{79}Br)Na^+, 100); HRMS (ESI^+): Found: 414.0674; $C_{19}H_{22}O_3NBrNa$ (M(^{79}Br)Na^+) requires: 414.0675.

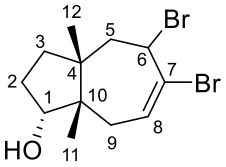
Also obtained was *enone* **340** as a colourless oil (3.0 mg, 49%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ –29.2 (*c* 0.61, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3333w, 2963w, 1729s, 1674s, 1539s, 1224s; δ_H (500 MHz, $CDCl_3$) 1.01 (3 H, s, C(12)H_3), 1.09 (3 H, s, C(11)H_3), 1.62−1.68 (1 H, m, C(3)**H**H′), 1.71−1.78 (1 H, m, C(2)**H**H′), 1.80−1.89 (1 H, m, C(3)H**H′**), 2.03−2.13 (1 H, m, C(2)H**H′**), 2.32−2.44 (1 H, m, C(9)**H**H′), 2.70−2.81 (2 H, m, C(5)**H**H′ and C(9)H**H′**), 2.99 (1 H, d, *J* 14.0, C(5)H**H′**), 4.95 (1 H, t, *J* 5.5, C(1)H), 6.65 (1 H, bs, NH), 7.05−7.14 (1 H, m, C(18)H), 7.29−7.44 (5 H, m, C(8)H, C(16)H × 2 and C(17)H × 2); δ_C (125 MHz, $CDCl_3$) 23.6 (C(11)), 25.5 (C(12)), 28.8 (C(2)), 35.6 (C(9)), 40.1 (C(3)), 43.3 (C(4)), 50.2 (C(10)), 56.1 (C(5)), 84.9 (C(1)), 118.6 (C(16)), 123.8 (C(18)), 128.0 (C(7)), 129.2 (C(17)), 137.6 (C(15)), 147.6 (C(8)), 152.9 (C(13)), 193.1 (C(6)); *m/z* (ESI^+) 416 (M(^{81}Br)Na^+, 95%),

414 (M(^{79}Br)Na^+, 100); HRMS (ESI$^+$): Found: 414.0674; $C_{19}H_{22}O_3NBrNa$ (M(^{79}Br)Na^+) requires: 414.0675.

(1*R*,3a*R*,8a*S*)-6,7-Dibromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulen-1-ol (341) and **(1*R*,3a*R*,8a*S*)-5,6-Dibromo-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulen-1-ol (342)**



341



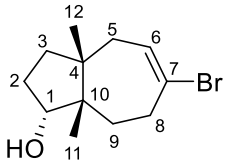
342

Boron tribromide (21.0 µL, 0.0210 mmol, 1 M in DCM) was added to a solution of hydrofuran **333** (5.40 mg, 0.0210 mmol) in DCM (0.1 mL) at 0 ºC and the mixture was stirred under reflux for 4 h. Water (1 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded *dibromide* **341** as a colourless oil (3.00 mg, 42%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +20.0 (*c* 0.45, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3383br, 2954s, 1466m, 1073m, 753s; δ_H (500 MHz, $CDCl_3$) 1.01 (3 H, s, C(12)H_3), 1.03 (3 H, s, C(11)H_3), 1.39−1.48 (1 H, m, C(3)**H**H′), 1.49−1.65 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.75−1.93 (2 H, m, C(2)H**H′** and C(5)**H**H′), 2.42 (1 H, dd, *J* 14.5, 7.5, C(9)**H**H′), 2.56 (1 H, dd, *J* 14.5, 12.0, C(9)H**H′**), 2.73 (1 H, dd, *J* 14.5, 6.0, C(5)H**H′**), 3.72 (1 H, dd, *J* 9.0, 6.0, C(1)H), 4.78−4.87 (1 H, m, C(8)H), 6.21 (1 H, dd, *J* 10.0, 6.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 20.8 (C(11)), 26.7 (C(12)), 30.1 (C(2)), 38.1 (C(3)), 39.4 (C(9)), 41.2 (C(5)), 44.7 (C(4)), 48.3 (C(10)), 58.0 (C(8)), 82.2 (C(1)), 124.7 (C(7)), 134.3 (C(6)); *m/z* (FI$^+$) 340 (M(^{81}Br^{81}Br)$^{+\cdot}$, 40%), 338 (M(^{81}Br^{79}Br)$^{+\cdot}$, 100), 336

(M(^{79}Br^{79}Br)$^{+\cdot}$, 60); HRMS (FI^{+}): Found: 335.9713; $C_{12}H_{18}OBr_2$ (M(^{79}Br^{79}Br)$^{+\cdot}$) requires: 335.9719.

Also obtained was *dibromide* **342** as a colourless oil (2.00 mg, 28%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +20.0 (*c* 0.45, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3383br, 2954s, 1466m, 1073m, 753s; δ_H (500 MHz, $CDCl_3$) 0.99 (3 H, s, C(11)H_3), 1.01 (3 H, s, C(12)H_3), 1.49−1.65 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.75−1.93 (3 H, m, C(2)H**H′**, C(3)H**H′** and C(9)**H**H′), 2.14 (1 H, dd, *J* 14.5, 7.0, C(5)**H**H′), 2.92−3.01 (2 H, m, C(5)H**H′** and C(9)H**H′**), 3.75−3.78 (1 H, m, C(1)H), 4.78−4.87 (1 H, m, C(6)H), 6.28 (1 H, dd, *J* 10.0, 6.0, C(8)H); δ_C (125 MHz, $CDCl_3$) 24.0 (C(11)), 24.2 (C(12)), 30.9 (C(2)), 32.7 (C(9)), 41.7 (C(3)), 45.0 (C(4)), 49.7 (C(10)), 50.0 (C(5)), 57.2 (C(6)), 83.7 (C(1)), 123.5 (C(7)), 134.9 (C(8)); *m/z* (FI^{+}) 340 (M(^{81}Br^{81}Br)$^{+\cdot}$, 40%), 338 (M(^{81}Br^{79}Br)$^{+\cdot}$, 100), 336 (M(^{79}Br^{79}Br)$^{+\cdot}$, 60); HRMS (FI^{+}): Found: 335.9713; $C_{12}H_{18}OBr_2$ (M(^{79}Br^{79}Br)$^{+\cdot}$) requires: 335.9719.

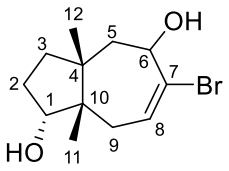
(1*R*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulen-1-ol (343)



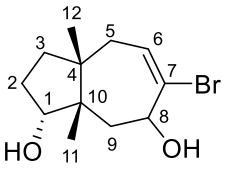
Sodium iodide (4.5 mg, 0.0292 mmol) and TBSCl (4.5 mg, 0.0292 mmol) were added to a solution of hydrofuran **333** (5.00 mg, 0.0194 mmol) in ACN (0.1 mL) and the mixture was stirred at 55 ºC for 16 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (1.30 mg, 26%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{23}$ +14.5 (*c* 0.13,

$CHCl_3$); ν_{max} (thin film)/cm^{-1} 3384br, 2955s, 1652w, 1457m, 1070m; δ_H (500 MHz, $CDCl_3$) 0.99 (3 H, s, C(11)H_3), 1.01 (3 H, s, C(12)H_3), 1.33−1.41 (1 H, m, C(9)**H**H′), 1.42−1.51 (1 H, m, C(3)**H**H′), 1.53−1.62 (1 H, m, C(2)**H**H′), 1.69−1.82 (2 H, m, C(3)H**H′** and C(5)**H**H′), 1.90−2.04 (1 H, m, C(2)H**H′**), 2.27 (1 H, ddd, *J* 15.0, 11.5, 3.5, C(9)H**H′**), 2.57−2.80 (3 H, m, C(5)H**H′** and C(8)H_2), 3.81 (1 H, t, *J* 6.0, C(1)H), 5.95 (1 H, dd, *J* 8.5, 5.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 21.9 (C(11)), 26.0 (C(12)), 30.2 (C(9)), 30.9 (C(2)), 36.8 (C(8)), 39.0 (C(3)), 40.5 (C(5)), 46.2 (C(4)), 47.7 (C(10)), 83.9 (C(1)), 125.0 (C(7)), 129.7 (C(6)).

(1*R*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulene-1,5-diol (344) and **(1*R*,3a*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulene-1,7-diol (345)**



344



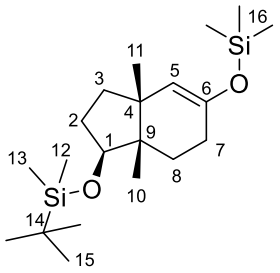
345

Calcium carbonate (1.5 mg, 0.0133 mmol) was added to a solution of bromide isomers **341** and **342** (3.00 mg, 0.00887 mmol) in acetone/H_2O (0.26 mL, 3:10) and the mixture was stirred under reflux for 16 h. The mixture was extracted with ether (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded *diol* **344** as a colourless oil (0.871 mg, 36%). R_f 0.45 (ether); $[\alpha]_D^{23}$ –30.8 (*c* 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3334br, 2956m, 1451w, 1073m, 1031s; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, s, C(11)H_3), 1.04 (3 H, s, C(12)H_3), 1.43−1.64 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.73−1.79 (1 H, m, C(3)H**H′**), 1.87−1.99 (3 H, m, C(2)H**H′**, C(5)**H**H′ and C(9)**H**H′), 2.14−2.28 (1 H, m, C(5)H**H′**), 2.55 (1

H, dt, *J* 15.5, 3.0, C(9)H**H′**), 3.82 (1 H, dd, *J* 7.5, 6.0, C(1)H), 4.30 (1 H, ddd, *J* 11.5, 4.0, 2.5, C(6)H), 6.22 (1 H, dd, *J* 10.5, 4.0, C(8)H); δ_C (125 MHz, $CDCl_3$) 22.7 (C(11)), 25.4 (C(12)), 30.4 (C(2)), 31.1 (C(9)), 40.2 (C(3)), 41.7 (C(4)), 47.4 (C(5)), 49.0 (C(10)), 72.6 (C(6)), 82.5 (C(1)), 128.8 (C(7)), 131.7 (C(8)); *m/z* (ESI^+) 299 ($M(^{81}Br)Na^+$, 100%), 297 ($M(^{79}Br)Na^+$, 100); HRMS (ESI^+): Found: 297.0461; $C_{12}H_{19}O_2BrNa$ ($M(^{79}Br)Na^+$) requires: 297.0461.

Also obtained was *diol* **345** as a colourless oil (0.429 mg, 17%). R_f 0.45 (ether); $[\alpha]_D^{23}$ –30.8 (*c* 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3334br, 2956m, 1451w, 1073m, 1031s; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, s, C(12)H_3), 1.03 (3 H, s, C(11)H_3), 1.43−1.64 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.67−1.72 (1 H, m, C(3)H**H′**), 1.81−1.86 (1 H, m, C(5)**H**H′), 1.87−1.99 (2 H, m, C(2)H**H′** and C(9)**H**H′), 2.14−2.28 (1 H, m, C(9)H**H′**), 2.65 (1 H, dd, *J* 15.0, 4.5, C(5)H**H′**), 3.78 (1 H, t, *J* 6.5, C(1)H), 4.38 (1 H, ddd, *J* 11.0, 5.0, 2.0, C(8)H), 6.16 (1 H, dd, *J* 9.5, 5.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 22.7 (C(11)), 26.3 (C(12)), 30.8 (C(2)), 37.3 (C(9)), 38.9 (C(3)), 40.7 (C(5)), 44.9 (C(4)), 46.1 (C(10)), 73.5 (C(8)), 83.7 (C(1)), 128.8 (C(7)), 131.8 (C(6)); *m/z* (ESI^+) 299 ($M(^{81}Br)Na^+$, 100%), 297 ($M(^{79}Br)Na^+$, 100); HRMS (ESI^+): Found: 297.0461; $C_{12}H_{19}O_2BrNa$ ($M(^{79}Br)Na^+$) requires: 297.0461.

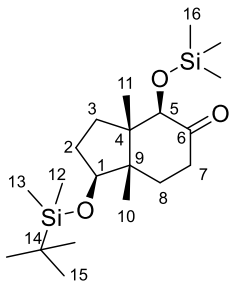
***tert*-Butyl{[(1*S*,3a*R*,7a*S*)-3a,7a-dimethyl-5-[(trimethylsilyl)oxy]-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (346)**



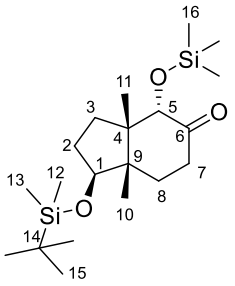
Methyllithium solution (2.83 mL, 4.52 mmol, 1.6 M in Et_2O) was added dropwise to a suspension of copper iodide (0.431 g, 2.26 mmol) in ether (6.4 mL) at –20 °C and the solution was stirred for 15 min. The solution was cooled to –78 °C and a solution of enone **297** (0.488 g, 1.74 mmol) in ether (4.8 mL) was added dropwise. The mixture was stirred at –15 °C for 1 h, and then triethylamine (0.728 mL, 5.22 mmol) and TMSCl (0.442 mL, 3.48 mmol) were added. The mixture was stirred at 0 °C for 1 h and allowed to warm to RT. Sat. aq. $NaHCO_3$ (15 mL) was added and the mixture was extracted with ether (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the *title compound* as a colourless oil (0.592 g, 92%). R_f 0.95 (3:1 petrol:ether); $[\alpha]_D^{25}$ +44.3 (*c* 0.40, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956m, 1668w, 1251m, 1188m, 837s; δ_H (500 MHz, C_6D_6) 0.04 (3 H, s, C(12)H_3), 0.06 (3 H, s, C(13)H_3), 0.19 (9 H, s, 3 × C(16)H_3), 0.91 (3 H, s, C(10)H_3), 0.99 (9 H, s, 3 × C(15)H_3), 1.00 (3 H, s, C(11)H_3), 1.34−1.41 (1 H, m, C(8)**H**H′), 1.42−1.49 (1 H, m, C(3)**H**H′), 1.50−1.61 (2 H, m, C(2)**H**H′ and C(8)H**H′**), 1.62−1.71 (1 H, m, C(3)H**H′**), 1.88−1.97 (1 H, m, C(2)H**H′**), 2.03 (1 H, dddd, *J* 17.5, 6.5, 3.0, 0.5, C(7)**H**H′), 2.16 (1 H, dddd, *J* 17.5, 10.0, 7.0, 2.0, C(7)H**H′**), 4.18 (1 H, dd, *J* 8.0, 7.5, C(1)H), 4.73 (1 H, s, C(5)H); δ_C (125 MHz, C_6D_6) –5.0 (C(12)), –4.3 (C(13)), 0.2 (C(16)), 16.7 (C(10)), 18.0 (C(14)), 25.2 (C(11)), 25.9 (C(15)), 26.9 (C(7)), 28.2 (C(8)), 30.8 (C(2)), 37.1 (C(3)), 43.0

(C(4)), 45.1 (C(9)), 75.7 (C(1)), 116.1 (C(5)), 147.7 (C(6)); *m/z* (FI^+) 368 ($M^{+\cdot}$, 100%); HRMS (FI^+): Found: 368.2581; $C_{20}H_{40}O_2Si_2$ ($M^{+\cdot}$) requires: 368.2562.

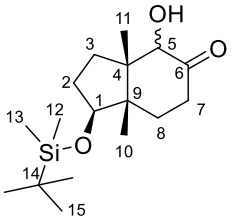
(1*S*,3a*S*,4*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-4-[(trimethylsilyl)oxy]octahydro-5*H*-inden-5-one (347), **(1*S*,3a*S*,4*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-4-[(trimethylsilyl)oxy]octahydro-5*H*-inden-5-one (348)**, **(1*S*,3a*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxy-3a,7a-dimethyloctahydro-5*H*-inden-5-one (349)** and **(1*S*,3a*S*,4*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-5-oxooctahydro-1*H*-inden-4-yl 3-chlorobenzoate (350)**



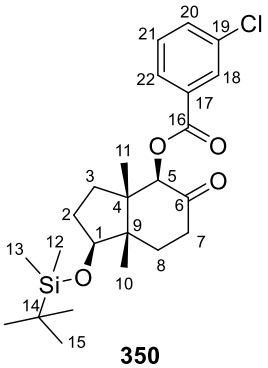
347



348



349



350

A solution of silyl enol ether **346** (0.508 g, 1.38 mmol) in DCM (7 mL) was added to a solution of *m*CPBA (0.309 g, 1.38 mmol) in DCM (16 mL) at –10 °C and stirred for 1 h. Sat. aq. $NaHCO_3$ (30 mL) was added and the mixture was extracted with DCM (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded *TMS-ether* **347** as a colourless oil (81.6 mg, 15%). R_f 0.95 (3:1 petrol:ether); $[\alpha]_D^{23}$ +7.4 (*c* 1.21, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1731w, 1250m, 1121m, 836s, 774m; δ_H (500 MHz, C_6D_6) –0.02 (3 H, s, C(12)H_3), 0.00 (3 H, s, C(13)H_3), 0.21 (9 H, s, 3 × C(16)H_3), 0.87 (3 H, s, C(10)H_3),

0.96 (9 H, s, 3 × C(15)H_3), 0.97 (3 H, s, C(11)H_3), 1.27−1.36 (1 H, m, C(8)**H**H′), 1.37−1.45 (1 H, m, C(3)**H**H′), 1.47−1.56 (1 H, m, C(2)**H**H′), 1.56−1.65 (1 H, m, C(8)H***H′***), 1.80−1.88 (1 H, m, C(3)H***H′***), 1.89−1.98 (1 H, m, C(2)H***H′***), 2.11−2.21 (1 H, m, C(7)**H**H′), 2.25−2.32 (1 H, m, C(7)H***H′***), 4.00 (1 H, s, C(5)H), 4.23 (1 H, dd, *J* 7.5, 7.0, C(1)H); δ_C (125 MHz, C_6D_6) –5.1 (C(12)), –4.5 (C(13)), 0.2 (C(16)), 16.6 (C(11)), 17.5 (C(10)), 18.0 (C(14)), 25.8 (C(15)), 30.6 (C(2)), 31.8 (C(8)), 33.2 (C(3)), 35.4 (C(7)), 47.9 (C(4)), 52.7 (C(9)), 77.2 (C(1)), 79.6 (C(5)), 207.9 (C(6)); *m/z* (ESI^+) 407 (MNa^+, 100%), 385 (MH^+, 90); HRMS (ESI^+): Found: 407.2399; $C_{20}H_{40}O_3Si_2Na$ (MNa^+) requires: 407.2408.

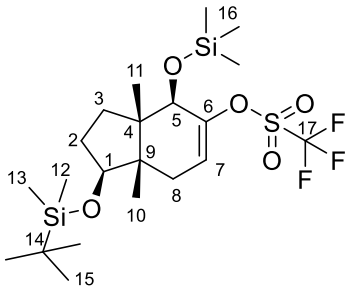
Also obtained was *TMS-ether* **348** as a colourless oil (84.7 mg, 16%). R_f 0.90 (3:1 petrol:ether); $[\alpha]_D^{23}$ +6.8 (*c* 0.85, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1731w, 1250m, 1121m, 836s, 774m; δ_H (500 MHz, C_6D_6) –0.01 (3 H, s, C(12)H_3), 0.00 (3 H, s, C(13)H_3), 0.23 (9 H, s, 3 × C(16)H_3), 0.96 (3 H, s, C(10)H_3), 0.97 (9 H, s, 3 × C(15)H_3), 0.99−1.07 (1 H, m, C(8)**H**H′), 1.20 (3 H, s, C(11)H_3), 1.23−1.34 (1 H, m, C(8)H***H′***), 1.43−1.55 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.57−1.65 (1 H, m, C(3)H***H′***), 1.80−1.89 (1 H, m, C(2)H***H′***), 2.02−2.12 (1 H, m, C(7)**H**H′), 2.18−2.27 (1 H, m, C(7)H***H′***), 3.65 (1 H, dd, *J* 7.5, 3.5, C(1)H), 3.85 (1 H, s, C(5)H); δ_C (125 MHz, C_6D_6) –5.2 (C(12)), –4.7 (C(13)), 0.2 (C(16)), 16.6 (C(10)), 18.0 (C(14)), 21.7 (C(11)), 25.9 (C(15)), 32.3 (C(2)), 32.4 (C(3)), 34.6 (C(8)), 35.5 (C(7)), 48.2 (C(4)), 53.1 (C(9)), 80.1 (C(1)), 82.0 (C(5)), 208.0 (C(6)); *m/z* (ESI^+) 407 (MNa^+, 100%), 385 (MH^+, 90); HRMS (ESI^+): Found: 407.2399; $C_{20}H_{40}O_3Si_2Na$ (MNa^+) requires: 407.2408.

Also obtained was *α-hydroxy ketone* **349** as a pale yellow oil as a mixture of diastereomers (65.0 mg, 15%, *dr*. 1:1). R_f 0.45 (3:1 petrol:ether); $[\alpha]_D^{23}$ –1.3 (*c* 1.08, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3494br, 2955m, 1720m, 1255m, 1056s, 837s; δ_H (400 MHz, $CDCl_3$) 0.01 (6 H, s, 2 × C(12)H_3), 0.05 (6 H, s, 2 × C(13)H_3), 0.75 (3 H, s, C(10)H_3), 0.84 (3 H, s, C(11)H_3), 0.89

(9 H, s, 3 × C(15)H_3), 0.90 (9 H, s, 3 × C(15)H_3), 1.18 (3 H, s, C(10)H_3), 1.23−1.28 (1 H, m, C(3)**H**H′), 1.29 (3 H, s, C(11)H_3), 1.50−1.70 (6 H, m, 2 × C(2)**H**H′, C(3)H_2 and 2 × C(8)**H**H′), 1.92−2.03 (3 H, m, C(3)H**H′** and 2 × C(8)H**H′**), 2.06−2.16 (2 H, m, 2 × C(2)H**H′**), 2.32−2.41 (2 H, m, 2 × C(7)**H**H′), 2.43−2.64 (2 H, m, 2 × C(7)H**H′**), 3.35 (1 H, d, *J* 5.0, OH), 3.42 (1 H, d, *J* 3.5, OH), 3.63−3.70 (1 H, m, C(1)H), 4.00 (1 H, dd, *J* 3.5, 1.0, C(5)H), 4.08 (1 H, d, *J* 4.0, C(5)H), 4.50 (1 H, t, *J* 7.5, C(1)H); δ_C (100 MHz, $CDCl_3$) –5.1/–5.0 (C(12)), –4.6/–4.3 (C(13)), 14.7/16.4 (C(10)), 17.3 (C(11)), 18.0 (C(14)), 22.0 (C(11)), 25.7/25.8 (C(15)), 29.9 (C(2)), 30.9/31.5 (C(3)), 32.3 (C(2)), 33.3 (C(8)), 35.0 (C(7)), 35.3 (C(8)), 35.4 (C(7)), 48.0/48.6 (C(4)), 53.0/53.8 (C(9)), 75.8 (C(1)), 77.6/80.0 (C(5)), 80.7 (C(1)), 211.8/211.9 (C(6)); *m/z* (ESI^+) 335 (MNa^+, 100%); HRMS (ESI^+): Found: 335.2006; $C_{17}H_{32}O_3SiNa$ (MNa^+) requires: 335.2013.

Also obtained was *benzoate ester* **350** as a pale yellow oil (48.3 mg, 8%). R_f 0.65 (3:1 petrol:ether); $[\alpha]_D^{23}$ +13.3 (*c* 1.21, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954w, 1722m, 1254s, 1151m, 836s, 775s; δ_H (400 MHz, $CDCl_3$) 0.09 (3 H, s, C(12)H_3), 0.10 (3 H, s, C(13)H_3), 0.91 (3 H, s, C(10)H_3), 0.92 (9 H, s, 3 × C(15)H_3), 1.06 (3 H, s, C(11)H_3), 1.52−1.82 (4 H, m, C(2)**H**H′, C(3)H_2 and C(8)**H**H′), 1.98−2.09 (1 H, m, C(8)H**H′**), 2.10−2.20 (1 H, m, C(2)H**H′**), 2.34−2.43 (1 H, m, C(7)**H**H′), 2.62 (1 H, td, *J* 13.5, 6.5, C(7)H**H′**), 4.62 (1 H, dd, *J* 8.0, 6.5, C(1)H), 5.29 (1 H, s, C(5)H), 7.41 (1 H, t, *J* 8.0, C(21)H), 7.53−7.59 (1 H, m, C(20)H), 7.96 (1 H, d, *J* 8.0, C(22)H), 8.03 (1 H, t, *J* 1.5, C(18)H); δ_C (100 MHz, $CDCl_3$) –4.9 (C(12)), –4.3 (C(13)), 16.3 (C(11)), 17.2 (C(10)), 18.0 (C(14)), 25.8 (C(15)), 29.8 (C(2)), 30.9 (C(8)), 33.3 (C(3)), 36.0 (C(7)), 48.7 (C(4)), 51.4 (C(9)), 75.4 (C(1)), 80.2 (C(5)), 128.0 (C(22)), 129.8 (C(21)), 129.9 (C(18)), 131.4 (C(17)), 133.3 (C(20)), 134.6 (C(19)), 165.0 (C(16)), 204.2 (C(6)); *m/z* (ESI^+) 475 (M(^{37}Cl)Na^+, 33%), 473 (M(^{35}Cl)Na^+, 100), 453 (M(^{37}Cl)H^+, 33), 451 (M(^{35}Cl)H^+, 100); HRMS (ESI^+): Found: 473.1876; $C_{24}H_{35}O_4ClSiNa$ (M(^{35}Cl)Na^+) requires: 473.1885.

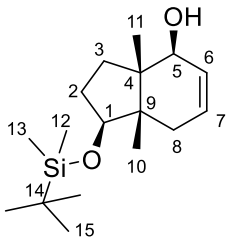
(1*S*,3a*S*,4*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-4-[(trimethylsilyl)oxy]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (351)



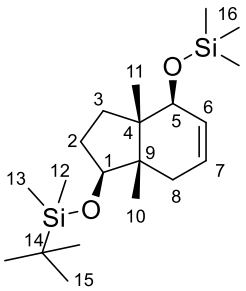
KHMDS (12.5 mL, 6.25 mmol, 0.5 M in toluene) was added dropwise to a solution of ketone **347** (1.85 g, 4.81 mmol) in THF (17 mL) at –78 °C and the solution was stirred at –78 °C for 30 min. *N*-Phenyl-bis(trifluoromethanesulfonimide) (1.89 g, 5.29 mmol) was then added and the solution was stirred at –78 °C for 2 h. Sat. aq. NH_4Cl (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 49:1 petrol:ether) afforded the *title compound* as a colourless oil (2.34 g, 94%). R_f 0.70 (19:1 petrol:ether); $[\alpha]_D^{23}$ +20.5 (*c* 1.33, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2957w, 1465m, 1209s, 1128m, 883s, 839s; δ_H (500 MHz, C_6D_6) –0.01 (3 H, s, C(12)H_3), 0.00 (3 H, s, C(13)H_3), 0.23 (9 H, s, 3 × C(16)H_3), 0.94 (3 H, s, C(10)H_3), 0.95 (9 H, s, 3 × C(15)H_3), 1.08 (3 H, s, C(11)H_3), 1.31−1.40 (1 H, m, C(3)**H**H′), 1.47−1.59 (3 H, m, C(2)**H**H′, C(3)H**H′** and C(8)**H**H′), 1.70 (1 H, ddd, *J* 19.0, 4.0, 1.5, C(8)H**H′**), 1.89−1.97 (1 H, m, C(2)H**H′**), 3.79 (1 H, dd, *J* 8.0, 4.5, C(1)H), 4.15 (1 H, s, C(5)H), 5.40 (1H, t, *J* 4.0, C(7)H); δ_C (125 MHz, C_6D_6) –5.3 (C(12)), –4.6 (C(13)), 0.2 (C(16)), 17.4 (C(11)), 17.8 (C(10)), 18.0 (C(14)), 25.9 (C(15)), 31.1 (C(2)), 32.5 (C(8)), 33.6 (C(3)), 46.5 (C(9)), 48.6 (C(4)), 72.7 (C(5)), 78.2 (C(1)), 117.6 (C(7)), 119.7 (q, *J* 325.0, C(17)), 148.2 (C(6)); *m/z* (ESI^+) 539 (MNa^+, 70%); HRMS (ESI^+): Found: 539.1890; $C_{21}H_{39}O_5F_3Si_2SNa$ (MNa^+) requires: 539.1901.

(1*S*,3a*S*,4*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-4-ol (352) and

***tert*-Butyl{[(1*S*,3a*S*,4*S*,7a*S*)-3a,7a-dimethyl-4-[(trimethylsilyl)oxy]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (353)**



352



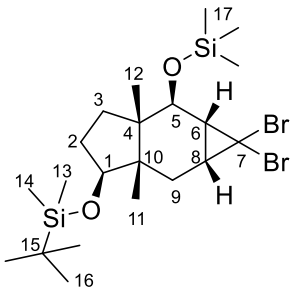
353

A solution of triflate **351** (4.84 g, 9.37 mmol) in THF (100 mL) was added to LiCl (1.19 g, 28.1 mmol) and $Pd(PPh_3)_4$ (0.216 g, 0.187 mmol). Tributyltin hydride (3.07 mL, 11.4 mmol) was added dropwise at RT and the mixture was stirred at 55 °C for 3 h. Ether (200 mL) was added and the mixture was washed with 10% aq. KF (200 mL) and brine (200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded *allyl alcohol* **352** as a colourless oil (1.89 g, 68%). R_f 0.20 (3:1 petrol:ether); $[\alpha]_D^{23}$ +47.9 (*c* 1.04, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3361br, 2955w, 1472w, 1251m, 1113s, 1028s; δ_H (400 MHz, C_6D_6) 0.01 (6 H, s, C(12)H_3 and C(13)H_3), 0.91 (6 H, s, C(10)H_3 and C(11)H_3), 0.97 (9 H, s, 3 × C(15)H_3), 1.20 (1 H, bs, OH), 1.40−1.57 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.58−1.75 (2 H, m, C(3)H**H′** and C(8)**H**H′), 1.83−1.94 (1 H, m, C(2)H**H′**), 2.00 (1 H, d, *J* 19.0, C(8)H**H′**), 3.82 (1 H, bs, C(5)H), 3.98 (1 H, dd, *J* 8.5, 7.0, C(1)H), 5.42−5.56 (2 H, m, C(6)H and C(7)H); δ_C (100 MHz, C_6D_6) –5.3 (C(12)), –4.6 (C(13)), 14.3 (C(10)), 17.4 (C(11)), 17.9 (C(14)), 25.8 (C(15)), 30.0 (C(2)), 32.0 (C(8)), 32.6 (C(3)), 45.3 (C(4)), 46.7 (C(9)), 70.9 (C(5)), 77.1

(C(1)), 126.0 (C(7)), 128.9 (C(6)); *m/z* (EI^+) 296 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 296.2171; $C_{17}H_{32}O_2Si$ ($M^{+\cdot}$) requires: 296.2167.

Also obtained was *TMS-ether* **353** as a colourless oil (1.07 g, 31%). R_f 0.20 (petrol); $[\alpha]_D^{23}$ +48.0 (*c* 0.59, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956m, 1473w, 1251m, 1063s, 837s, 774m; δ_H (500 MHz, C_6D_6) 0.03 (6 H, s, C(12)H_3 and C(13)H_3), 0.13 (9 H, s, 3 × C(16)H_3), 0.99 (9 H, s, 3 × C(15)H_3), 1.00 (3 H, s, C(10)H_3), 1.13 (3 H, s, C(11)H_3), 1.51−1.67 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.71 (1 H, dq, *J* 19.0, 3.0, C(8)**H**H′), 1.74−1.81 (1 H, m, C(3)H**H′**), 2.00−2.11 (2 H, m, C(2)H**H′** and C(8)H**H′**), 4.12−4.20 (2 H, m, C(1)H and C(5)H), 5.49−5.57 (1 H, m, C(6)H), 5.63 (1 H, dd, *J* 10.5, 2.0, C(7)H); δ_C (125 MHz, C_6D_6) –5.0 (C(12)), –4.4 (C(13)), 0.2 (C(16)), 15.5 (C(11)), 17.9 (C(10)), 18.2 (C(14)), 25.9 (C(15)), 30.6 (C(2)), 32.5 (C(8)), 33.0 (C(3)), 46.3 (C(4)), 47.0 (C(9)), 71.7 (C(5)), 77.9 (C(1)), 125.7 (C(6)), 129.8 (C(7)); *m/z* (EI^+) 368 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 368.2569; $C_{20}H_{40}O_2Si_2$ ($M^{+\cdot}$) requires: 368.2562.

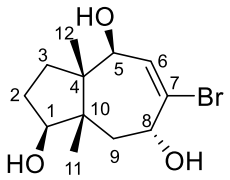
tert-Butyl{[(1a*R*,2a*S*,3*S*,5a*S*,6*S*,6a*R*)-1,1-dibromo-2a,5a-dimethyl-6-[(trimethylsilyl)oxy]decahydrocyclopropa[*f*]inden-3-yl]oxy}dimethylsilane (354)



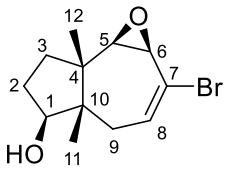
Benzyltriethylammonium chloride (3.0 mg, 0.0136 mmol) and bromoform (0.356 mL, 4.07 mmol) were added to a solution of alkene **353** (500 mg, 1.36 mmol) in benzene (10 mL). 50% aq. NaOH (0.244 mL) was added dropwise and the mixture was stirred at 70 °C for 16 h.

Water (40 mL) was added and the mixture was extracted with ether (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil (426 mg, 58%). R_f 0.70 (19:1 petrol:ether); $[\alpha]_D^{23}$ –1.9 (*c* 1.00, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1472w, 1251m, 1067m, 837s; δ_H (500 MHz, C_6D_6) 0.00 (3 H, s, C(13)H_3), 0.01 (3 H, s, C(14)H_3), 0.30 (9 H, s, 3 × C(17)H_3), 0.79 (1 H, dd, *J* 14.5, 9.0, C(9)**H**H′), 0.86 (3 H, s, C(11)H_3), 0.97 (9 H, s, 3 × C(16)H_3), 1.02 (3 H, s, C(12)H_3), 1.38−1.51 (3 H, m, C(2)H_2 and C(9)H**H′**), 1.53−1.63 (2 H, m, C(3)**H**H′ and C(8)H), 1.64−1.72 (2 H, m, C(3)H**H′** and C(6)H), 3.14 (1 H, d, *J* 7.5, C(5)H), 3.47 (1 H, t, *J* 5.0, C(1)H); δ_C (125 MHz, C_6D_6) –5.2 (C(13)), –4.8 (C(14)), 0.2 (C(17)), 17.9 (C(15)), 18.4 (C(12)), 19.9 (C(11)), 25.7 (C(16)), 28.8 (C(8)), 30.8 (C(2)), 34.0 (C(9)), 34.3 (C(6)), 35.6 (C(3)), 40.4 (C(7)), 46.7 (C(4)), 49.3 (C(10)), 75.5 (C(5)), 82.6 (C(1)); *m/z* (EI^+) 541 (M($^{81}Br^{81}Br$)$^{+\cdot}$, 50%), 539 (M($^{81}Br^{79}Br$)$^{+\cdot}$, 100), 537 (M($^{79}Br^{79}Br$)$^{+\cdot}$, 50); HRMS (EI^+): Found: 537.0851; $C_{21}H_{39}O_2Br_2Si_2$ (M($^{79}Br^{79}Br$)$^{+\cdot}$) requires: 537.0850.

(1*S*,3a*S*,4*S*,7*R*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulene-1,4,7-triol (355) and **(1a*R*,4a*S*,5*S*,7a*S*,7b*R*)-2-Bromo-4a,7a-dimethyl-1a,4,4a,5,6,7,7a,7b-octahydroazuleno[4,5-*b*]oxiren-5-ol (356)**



355



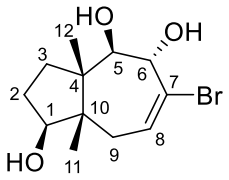
356

$AgClO_4$ (18.5 mg, 0.0881 mmol) was added to a solution of dibromocyclopropane **354** (28.0 mg, 0.0518 mmol) in acetone/H_2O (0.5 mL, 9:1) and the mixture was stirred under reflux for

16 h. The mixture was filtered and solvent removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ethyl acetate) afforded *triol* **355** as a white solid (8.00 mg, 53%). R_f 0.10 (ether); m.p. 187–189 °C; $[\alpha]_D^{23}$ +11.6 (*c* 0.80, MeOH); ν_{max} (thin film)/cm^{-1} 3350br, 2955w, 1447w, 1095s, 1031s; δ_H (600 MHz, CD_3OD) 0.90 (3 H, s, C(11)H_3), 0.93 (3 H, s, C(12)H_3), 1.39−1.49 (1 H, m, C(3)**H**H′), 1.51−1.63 (1 H, m, C(2)**H**H′), 1.64−1.72 (1 H, m, C(3)H**H′**), 1.73−1.81 (1 H, m, C(2)H**H′**), 1.85−2.00 (2 H, m, C(9)H_2), 3.61 (1 H, dd, *J* 9.5, 5.5, C(1)H), 4.16 (1 H, dd, *J* 11.0, 5.0, C(8)H), 4.51 (1 H, s, C(5)H), 6.05 (1 H, d, *J* 3.5, C(6)H); δ_C (150 MHz, CD_3OD) 15.9 (C(11)), 17.8 (C(12)), 29.4 (C(2)), 34.5 (C(3)), 43.4 (C(9)), 44.5 (C(10)), 49.3 (C(4)), 71.8 (C(8)), 73.7 (C(5)), 82.4 (C(1)), 124.6 (C(7)), 139.5 (C(6)); *m/z* (ESI$^+$) 315 (M(^{81}Br)Na$^+$, 100%), 313 (M(^{79}Br)Na$^+$, 100); HRMS (ESI$^+$): Found: 313.0410; $C_{12}H_{19}O_3BrNa$ (M(^{79}Br)Na$^+$) requires: 313.0410.

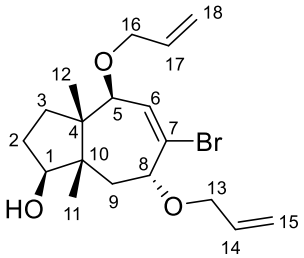
Also obtained was *epoxide* **356** as a colourless oil (2.70 mg, 19%). R_f 0.80 (ether); $[\alpha]_D^{23}$ –4.8 (*c* 0.27, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3433br, 2971w, 1380w, 1220m, 1040s; δ_H (500 MHz, $CDCl_3$) 0.94 (3 H, s, C(11)H_3), 1.12 (3 H, s, C(12)H_3), 1.40 (1 H, d, *J* 5.0, OH), 1.57−1.66 (1 H, m, C(2)**H**H′), 1.70−1.82 (1 H, m, C(3)**H**H′), 1.90−1.98 (1 H, m, C(3)H**H′**), 2.03 (1 H, dd, *J* 16.5, 8.0, C(9)**H**H′), 2.06−2.14 (1 H, m, C(2)H**H′**), 2.22 (1 H, ddd, *J* 16.5, 6.0, 2.5, C(9)H**H′**), 3.87 (1 H, d, *J* 9.5, C(5)H), 4.02 (1 H, dd, *J* 11.5, 5.5, C(1)H), 4.47 (1 H, dt, *J* 9.5, 2.0, C(6)H), 6.11 (1 H, ddd, *J* 8.0, 6.0, 2.0, C(8)H); δ_C (125 MHz, $CDCl_3$) 16.6 (C(12)), 17.5 (C(11)), 30.9 (C(2)), 36.3 (C(3) and C(9)), 45.4 (C(4)), 49.5 (C(10)), 76.2 (C(6)), 80.4 (C(1)), 82.0 (C(5)), 123.7 (C(7)), 129.6 (C(8)); *m/z* (EI$^+$) 274 (M(^{81}Br)$^{+\cdot}$, 100%), 272 (M(^{79}Br)$^{+\cdot}$, 100); HRMS (EI$^+$): Found: 272.0419; $C_{12}H_{17}O_2Br$ (M(^{79}Br)$^{+\cdot}$) requires: 272.0407.

(1*S*,3a*S*,4*R*,5*S*,8a*S*)-6-Bromo-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulene-1,4,5-triol (357)

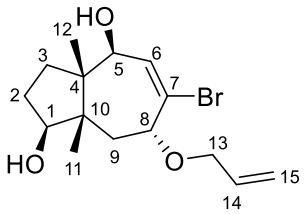


0.1 M $NaClO_4$ solution (0.2 mL) and 3 drops of 0.1 M HCl were added to a solution of epoxide **356** (1.50 mg, 0.00549 mmol) in acetone (0.02 mL) and the solution was stirred at 70 ºC for 16 h. Water (1 mL) was added and the mixture was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil (1.50 mg, 94%). R_f 0.15 (ether); $[\alpha]_D^{23}$ –29.3 (*c* 0.15, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3403br, 2966w, 1636w, 1102s, 1026m; δ_H (500 MHz, CD_3OD) 0.87 (3 H, s, C(11)H_3), 0.94 (3 H, s, C(12)H_3), 1.26−1.40 (1 H, m, C(3)**H**H′), 1.51−1.63 (1 H, m, C(2)**H**H′), 1.68−1.77 (1 H, m, C(2)H**H′**), 1.84−1.93 (1 H, m, C(3)H**H′**), 1.96 (1 H, dd, *J* 14.5, 10.0, C(9)**H**H′), 2.30 (1 H, dd, *J* 14.5, 5.5, C(9)H**H′**), 3.61 (1 H, dd, *J* 11.0, 6.0, C(1)H), 3.82 (1 H, d, *J* 9.0, C(5)H), 3.97 (1 H, dd, *J* 9.0, 1.0, C(6)H), 6.21 (1 H, dd, *J* 10.0, 5.5, C(8)H); δ_C (125 MHz, CD_3OD) 15.9 (C(11)), 18.1 (C(12)), 29.1 (C(2)), 34.9 (C(3)), 35.6 (C(9)), 45.8 (C(4)), 48.8 (C(10)), 77.6 (C(5)), 79.4 (C(6)), 80.5 (C(1)), 126.5 (C(7)), 131.6 (C(8)); *m/z* (ESI^+) 315 (M(^{81}Br)Na^+, 100%), 313 (M(^{79}Br)Na^+, 100); HRMS (ESI^+): Found: 313.0411; $C_{12}H_{19}O_3BrNa$ (M(^{79}Br)Na^+) requires: 313.0410.

(1*S*,3a*S*,4*S*,7*R*,8a*S*)-4,7-Bis(allyloxy)-6-bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulen-1-ol (358) and **(1*S*,3a*S*,4*S*,7*R*,8a*S*)-7-(Allyloxy)-6-bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulene-1,4-diol (359)**



358



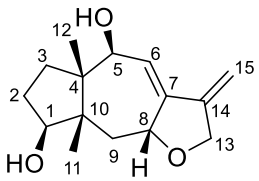
359

Sodium hydride (7.5 mg, 0.179 mmol) was added to a solution of alcohol **355** (40.0 mg, 0.137 mmol) in THF (1.2 mL) and the mixture was stirred at RT for 30 min. Allyl bromide (14.5 µL, 0.165 mmol) was added and the mixture was stirred at RT for 16 h. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded *alcohol* **358** as a colourless oil (2.00 mg, 4%). R_f 0.75 (ether); $[\alpha]_D^{25}$ +73.5 (*c* 0.20, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3450br, 2979w, 1646w, 1476w, 1077s, 923w; δ_H (500 MHz, $CDCl_3$) 0.93 (3 H, s, C(11)H_3), 0.98 (3 H, s, C(12)H_3), 1.50−1.59 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.66−1.69 (1 H, m, C(3)H**H′**), 1.80−1.86 (1 H, m, C(2)H**H′**), 1.89−1.94 (2 H, m, C(9)H_2), 3.75 (1 H, dd, *J* 8.5, 5.5, C(1)H), 3.84 (1 H, ddt, *J* 13.0, 6.0, 1.5, C(16)**H**H′), 4.03 (1 H, ddd, *J* 9.0, 7.5, 1.5, C(8)H), 4.08−4.16 (4 H, m, C(5)H, C(13)H_2 and C(16)H**H′**), 5.15−5.23 (2 H, m, C(15)**H**H′ and C(18)**H**H′), 5.25−5.36 (2 H, m, C(15)H**H′** and C(18)H**H′**), 5.83−5.93 (1 H, m, C(17)H), 5.94−6.02 (1 H, m, C(14)H), 6.15 (1 H, d, *J* 4.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 16.8 (C(11)), 19.5 (C(12)), 30.4 (C(2)), 35.0 (C(3)), 40.2 (C(9)), 45.2 (C(10)), 49.4 (C(4)), 70.9 (C(16)), 71.0 (C(13)), 79.7 (C(8)), 81.4 (C(5)), 82.9 (C(1)), 117.0 (C(18)), 117.7 (C(15)), 123.2 (C(7)), 134.4 (C(17)), 134.7 (C(14)),

139.5 (C(6)); *m/z* (ESI$^+$) 395 (M(^{81}Br)Na$^+$, 100%), 393 (M(^{79}Br)Na$^+$, 100); HRMS (ESI$^+$): Found: 393.1036; $C_{18}H_{27}O_3BrNa$ (M(^{79}Br)Na$^+$) requires: 393.1036.

Also obtained was *diol* **359** as a colourless oil (12.5 mg, 31%). R_f 0.45 (ether); $[\alpha]_D^{25}$ +37.0 (*c* 0.87, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3447br, 2954m, 1692w, 1471w, 1253m, 836s; δ_H (500 MHz, $CDCl_3$) 0.95 (3 H, s, C(11)H_3), 0.97 (3 H, s, C(12)H_3), 1.55−1.63 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.65−1.74 (1 H, m, C(3)H***H′***), 1.85−1.91 (1 H, m, C(2)H***H′***), 1.92−1.95 (2 H, m, C(9)H_2), 3.77 (1 H, dd, *J* 8.5, 5.5, C(1)H), 4.04 (1 H, ddd, *J* 10.5, 6.5, 1.5, C(8)H), 4.13 (2 H, dd, *J* 6.0, 1.5, C(13)H_2), 4.55−4.58 (1 H, m, C(5)H), 5.21 (1 H, dq, *J* 10.5, 1.5, C(15)**H**H′), 5.32 (1 H, dq, *J* 17.5, 1.5, C(15)H***H′***), 5.92−6.01 (1 H, m, C(14)H), 6.16 (1 H, d, *J* 3.5, C(6)H); δ_C (125 MHz, $CDCl_3$) 16.9 (C(11)), 18.6 (C(12)), 30.4 (C(2)), 34.7 (C(3)), 40.1 (C(9)), 45.3 (C(10)), 49.6 (C(4)), 70.8 (C(13)), 74.4 (C(5)), 79.3 (C(8)), 82.8 (C(1)), 117.6 (C(15)), 122.5 (C(7)), 134.7 (C(14)), 140.2 (C(6)); *m/z* (ESI$^+$) 355 (M(^{81}Br)Na$^+$, 100%), 353 (M(^{79}Br)Na$^+$, 100); HRMS (ESI$^+$): Found: 353.0723; $C_{15}H_{23}O_3BrNa$ (M(^{79}Br)Na$^+$) requires: 353.0723.

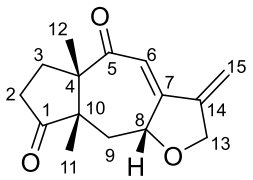
(5*S*,5a*S*,8*S*,8a*S*,9a*R*)-5a,8a-Dimethyl-3-methylene-2,3,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5,8-diol (360)



$Pd(PPh_3)_4$ (0.5 mg, 0.302 μmol), Ag_2CO_3 (2.0 mg, 0.00604 mmol) and K_2CO_3 (1.0 mg, 0.00664 mmol) were added into a solution of bromide **359** (1.00 mg, 0.00302 mmol) in DMF (0.2 mL) and the mixture was stirred at 110 ºC for 2 h. The mixture was filtered through

Celite and washed with ether (1 mL). The combined organic layers were washed with water (1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil (0.700 mg, 92%). R_f 0.20 (ether); $[\alpha]_D^{25}$ –3.5 (*c* 0.40, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3409br, 2921s, 1462w, 1261w, 1033s; δ_H (500 MHz, $CDCl_3$) 0.97 (3 H, s, C(12)H_3), 1.04 (3 H, s, C(11)H_3), 1.38−1.45 (1 H, m, C(3)**H**H′), 1.57−1.66 (1 H, m, C(2)**H**H′), 1.68−1.77 (1 H, m, C(9)**H**H′), 1.97−2.07 (2 H, m, C(2)H**H′** and C(9)H**H′**), 2.10−2.17 (1 H, m, C(3)H**H′**), 4.02 (1 H, t, *J* 8.5, C(1)H), 4.33−4.40 (2 H, m, C(5)H and C(13)**H**H′), 4.41−4.46 (1 H, m, C(8)H), 4.49 (1 H, dt, *J* 13.0, 2.0, C(13)H**H′**), 4.87 (1 H, s, C(15)**H**H′), 5.32 (1 H, t, *J* 2.0, C(15)H**H′**), 5.92 (1 H, t, *J* 2.0, C(6)H); δ_C (125 MHz, $CDCl_3$) 15.4 (C(11)), 18.9 (C(12)), 30.0 (C(2)), 32.2 (C(3)), 43.5 (C(9)), 45.6 (C(10)), 51.8 (C(4)), 71.0 (C(13)), 73.0 (C(5)), 76.8 (C(8)), 81.8 (C(1)), 101.3 (C(15)), 122.7 (C(6)), 141.1 (C(7)), 145.6 (C(14)); *m/z* (ESI^+) 273 (MNa^+, 100%); HRMS (ESI^+): Found: 273.1460; $C_{15}H_{22}O_3Na$ (MNa^+) requires: 273.1461.

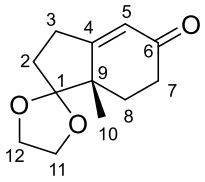
(5a*S*,8a*S*,9a*R*)-5a,8a-Dimethyl-3-methylene-2,3,5a,6,7,8a,9,9a-octahydroazuleno[5,6-*b*]furan-5,8-dione (362)



Dess–Martin periodinane (3.5 mg, 0.00805 mmol) and $NaHCO_3$ (1.5 mg, 0.0161 mmol) were added to a solution of alcohol **360** (1.00 mg, 0.00403 mmol) in DCM (0.2 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. $NaHCO_3$ (1 mL) and sat. aq. $Na_2S_2O_3$ (1 mL) were added and the mixture was extracted with DCM (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash

chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (0.800 mg, 81%). R_f 0.65 (ether); $[\alpha]_D^{25}$ +26.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2971w, 1738s, 1659m, 1546m, 1469w, 1282m; δ_H (500 MHz, $CDCl_3$) 1.26 (3 H, s, C(11)H_3), 1.28 (3 H, s, C(12)H_3), 1.57−1.61 (1 H, m, C(3)**H**H′), 1.69−1.77 (1 H, m, C(9)**H**H′), 2.26 (1 H, dd, *J* 14.5, 2.0, C(9)H**H′**), 2.32−2.45 (2 H, m, C(2)H_2), 2.59−2.67 (1 H, m, C(3)H**H′**), 4.46 (1 H, dt, *J* 13.0, 2.5, C(13)**H**H′), 4.60 (1 H, dt, *J* 13.0, 2.0, C(13)H**H′**), 4.64 (1 H, dt, *J* 11.0, 2.0, C(8)H), 5.23 (1 H, t, *J* 2.0, C(15)**H**H′), 5.64 (1 H, t, *J* 2.5, C(15)H**H′**), 6.28 (1 H, d, *J* 2.5, C(6)H); δ_C (125 MHz, $CDCl_3$) 19.9 (C(11)), 22.7 (C(12)), 30.1 (C(3)), 34.1 (C(2)), 42.3 (C(9)), 50.4 (C(4)), 60.0 (C(10)), 71.2 (C(13)), 77.9 (C(8)), 107.7 (C(15)), 118.7 (C(6)), 144.5 (C(14)), 154.8 (C(7)), 202.5 (C(5)), 220.5 (C(1)); *m/z* (EI^+) 246 ($M^{+\cdot}$, 30%); HRMS (EI^+): Found: 246.1257; $C_{15}H_{18}O_3$ ($M^{+\cdot}$) requires: 246.1251.

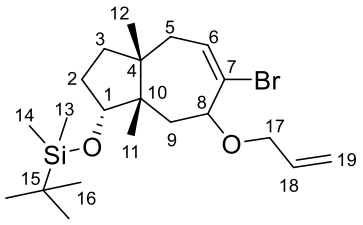
(*S*)-7a-Methyl-2,3,7,7a-tetrahydrospiro{indene-1,2'-[1,3]dioxolan}-5(6*H*)-one (363)[133]



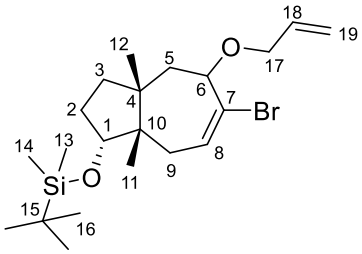
p-TsOH·H_2O (6.0 mg, 0.0305 mmol) was added to a solution of ketone **290** (50.0 mg, 0.305 mmol) and ethylene glycol (19.0 μL, 0.335 mmol) in benzene (2.3 mL) and the mixture was stirred under reflux for 3 h. Sat. aq. $NaHCO_3$ (3 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the title compound as a colourless oil (23.0 mg, 36%). R_f 0.50 (ether); $[\alpha]_D^{23}$ +7.5 (*c* 1.40, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954w, 1662s, 1157m, 1066m, 926m; δ_H (400 MHz, C_6D_6) 1.00 (3 H, s, C(10)H_3), 1.23 (1 H, ddd, *J* 12.5, 5.0, 2.5, C(8)**H**H′), 1.53−1.62 (1 H, m,

C(2)**H**H′), 1.80−1.90 (1 H, m, C(2)H**H′**), 2.07−2.21 (3 H, m, $C(3)H_2$ and C(8)H**H′**), 2.22−2.40 (2 H, m, $C(7)H_2$), 3.26−3.42 (4 H, m, $C(11)H_2$ and $C(12)H_2$), 5.83 (1 H, t, *J* 1.5, C(5)H); δ_C (100 MHz, C_6D_6) 19.6 (C(10)), 26.0 (C(3)), 26.8 (C(8)), 31.6 (C(2)), 33.0 (C(7)), 47.4 (C(9)), 64.3 (C(11)), 65.1 (C(12)), 117.3 (C(1)), 123.2 (C(5)), 172.0 (C(4)), 196.4 (C(6)); *m/z* (ESI^+) 231 (MNa^+, 50%), 209 (MH^+, 30).

{[(1*R*,3a*R*,8a*S*)-7-(Allyloxy)-6-bromo-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulen-1-yl]oxy}(*tert*-butyl)dimethylsilane (364) and {[**(1*R*,3a*R*,8a*S*)-5-(Allyloxy)-6-bromo-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulen-1-yl]oxy}(*tert*-butyl)dimethylsilane (365)**



364



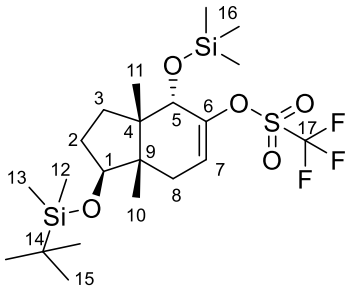
365

$AgBF_4$ (10.0 mg, 0.0521 mmol) and $CaCO_3$ (5.5 mg, 0.0521 mmol) were added to a solution of dibromocyclopropane **331** (15.7 mg, 0.0347 mmol) in allyl alcohol (0.2 mL) and the mixture was stirred at 80 ºC for 4 h. The mixture was filtered and solvent removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 49:1 petrol:ether) afforded *allyl ether* **364** as a colourless oil (3.00 mg, 20%). R_f 0.45 (19:1 petrol:ether); $[\alpha]_D^{23}$ –25.0 (*c* 0.60, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955m, 1471w, 1255m, 1061m, 835s; δ_H (500 MHz, $CDCl_3$) 0.02 (3 H, s, $C(13)H_3$), 0.04 (3 H, s, $C(14)H_3$), 0.89 (9 H, s, 3 × $C(16)H_3$), 0.96 (3 H, s, $C(11)H_3$), 0.99 (3 H, s, $C(12)H_3$),

1.36−1.63 (3 H, m, C(2)**H**H′ and C(3)H_2), 1.66−1.85 (2 H, m, C(2)H**H′** and C(5)**H**H′), 1.96−2.08 (2 H, m, C(9)H_2), 2.57−2.67 (1 H, m, C(5)H**H′**), 3.65 (1 H, dd, *J* 7.5, 5.5, C(1)H), 4.03−4.14 (3 H, m, C(8)H and C(17)H_2), 5.19 (1 H, d, *J* 10.0, C(19)**H**H′), 5.32 (1 H, dq, *J* 17.0, 1.5, C(19)H**H′**), 5.94−6.04 (1 H, m, C(18)H), 6.21 (1 H, dd, *J* 10.0, 5.0, C(6)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.5 (C(14)), 18.0 (C(15)), 21.9 (C(11)), 25.8 (C(16)), 26.6 (C(12)), 30.8 (C(2)), 34.6 (C(9)), 38.8 (C(3)), 41.0 (C(5)), 44.0 (C(4)), 46.1 (C(10)), 69.8 (C(17)), 80.5 (C(8)), 83.4 (C(1)), 117.3 (C(19)), 126.7 (C(7)), 133.1 (C(6)), 135.1 (C(18)); *m/z* (ESI^+) 453 (M(^{81}Br)Na^+, 80%), 451 (M(^{79}Br)Na^+, 80); HRMS (ESI^+): Found: 451.1639; $C_{21}H_{37}O_2BrSiNa$ (M(^{79}Br)Na^+) requires: 451.1638.

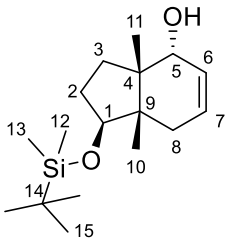
Also obtained was *allyl ether* **365** as a colourless oil (3.00 mg, 20%). R_f 0.45 (19:1 petrol:ether); $[\alpha]_D^{23}$ –25.0 (*c* 0.60, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955m, 1471w, 1255m, 1061m, 835s; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(13)H_3), 0.05 (3 H, s, C(14)H_3), 0.91 (9 H, s, 3 × C(16)H_3), 0.92 (3 H, s, C(11)H_3), 0.96 (3 H, s, C(12)H_3), 1.36−1.63 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.66−1.85 (4 H, m, C(2)H**H′**, C(3)H**H′**, C(5)**H**H′ and C(9)**H**H′), 2.23−2.31 (1 H, m, C(5)H**H′**), 2.57−2.67 (1 H, m, C(9)H**H′**), 3.69 (1 H, t, *J* 5.5, C(1)H), 4.03−4.14 (3 H, m, C(6)H and C(17)H_2), 5.19 (1 H, d, *J* 10.0, C(19)**H**H′), 5.32 (1 H, dq, *J* 17.0, 1.5, C(19)H**H′**), 5.94−6.04 (1 H, m, C(18)H), 6.29 (1 H, dd, *J* 10.5, 5.0, C(8)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.4 (C(14)), 18.1 (C(15)), 23.1 (C(11)), 25.3 (C(12)), 25.9 (C(16)), 30.7 (C(2)), 32.1 (C(9)), 40.8 (C(3)), 41.4 (C(4)), 44.7 (C(5)), 49.5 (C(10)), 70.1 (C(17)), 80.1 (C(6)), 83.0 (C(1)), 117.1 (C(19)), 125.3 (C(7)), 134.1 (C(8)), 135.2 (C(18)); *m/z* (ESI^+) 453 (M(^{81}Br)Na^+, 80%), 451 (M(^{79}Br)Na^+, 80); HRMS (ESI^+): Found: 451.1639; $C_{21}H_{37}O_2BrSiNa$ (M(^{79}Br)Na^+) requires: 451.1638.

(1*S*,3a*S*,4*S*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-4-[(trimethylsilyl)oxy]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (366)

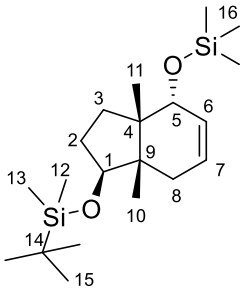


KHMDS (27.5 mL, 13.8 mmol, 0.5 M in toluene) was added dropwise to a solution of ketone **348** (4.07 g, 10.6 mmol) in THF (37 mL) at –78 °C and the solution was stirred at –78 °C for 30 min. *N*-Phenyl-bis(trifluoromethanesulfonimide) (4.16 g, 11.6 mmol) was then added and the solution was stirred at –78 °C for 2 h. Sat. aq. NH_4Cl (100 mL) was added and the mixture was extracted with ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 49:1 petrol:ether) afforded the *title compound* as a colourless oil (5.02 g, 92%). R_f 0.55 (19:1 petrol:ether); $[\alpha]_D^{23}$ –27.8 (*c* 0.95, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1420m, 1208m, 1076m, 835s; δ_H (500 MHz, C_6D_6) 0.03 (3 H, s, C(12)H_3), 0.05 (3 H, s, C(13)H_3), 0.20 (9 H, s, 3 × C(16)H_3), 0.80 (3 H, s, C(10)H_3), 0.86 (3 H, s, C(11)H_3), 0.98 (9 H, s, 3 × C(15)H_3), 1.37−1.50 (3 H, m, C(2)**H**H′, C(3)**H**H′ and C(8)**H**H′), 1.55−1.64 (1 H, m, C(3)H**H′**), 1.86−1.96 (1 H, m, C(2)H**H′**), 2.01 (1 H, dd, *J* 19.5, 4.0, C(8)H**H′**), 3.92 (1 H, s, C(5)H), 4.22 (1 H, dd, *J* 8.5, 6.0, C(1)H), 5.46 (1H, t, *J* 4.0, C(7)H); δ_C (125 MHz, C_6D_6) –4.9 (C(12)), –4.4 (C(13)), 0.2 (C(16)), 18.0 (C(10)), 18.2 (C(14)), 21.1 (C(11)), 26.0 (C(15)), 31.6 (C(2)), 31.8 (C(8)), 32.0 (C(3)), 45.4 (C(9)), 48.3 (C(4)), 75.5 (C(5)), 76.9 (C(1)), 118.6 (C(7)), 119.1 (q, *J* 321.5, C(17)), 148.9 (C(6)); *m/z* (ESI^+) 539 (MNa^+, 70%); HRMS (ESI^+): Found: 539.1890; $C_{21}H_{39}O_5F_3Si_2SNa$ (MNa^+) requires: 539.1901.

(1*S*,3a*S*,4*R*,7a*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-4-ol (367) and ***tert*-Butyl{[(1*S*,3a*S*,4*R*,7a*S*)-3a,7a-dimethyl-4-[(trimethylsilyl)oxy]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (368)**



367

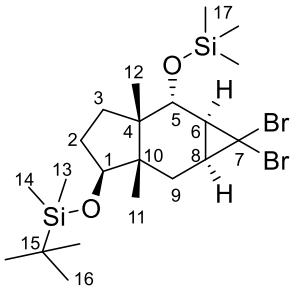


368

A solution of triflate **366** (7.48 g, 14.5 mmol) in THF (150 mL) was added to LiCl (1.84 g, 43.4 mmol) and $Pd(PPh_3)_4$ (0.335 g, 0.289 mmol). Tributyltin hydride (4.75 mL, 17.7 mmol) was added dropwise at RT and the mixture was stirred at 55 °C for 3 h. Ether (200 mL) was added and the mixture was washed with 10% aq. KF (200 mL) and brine (200 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded *allyl alcohol* **367** as a colourless oil (2.31 g, 54%). R_f 0.20 (3:1 petrol:ether); $[\alpha]_D^{25}$ –22.0 (*c* 1.34, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3359br, 2954w, 1463w, 1250m, 1060s, 833s; δ_H (400 MHz, $CDCl_3$) 0.01 (3 H, s, C(12)H_3), 0.02 (3 H, s, C(13)H_3), 0.89 (9 H, s, 3 × C(15)H_3), 0.91 (3 H, s, C(10)H_3), 1.17 (3 H, s, C(11)H_3), 1.41−1.53 (2 H, m, OH and C(3)**H**H′), 1.54−1.68 (3 H, m, C(2)**H**H′, C(3)H**H′** and C(8)**H**H′), 1.71−1.81 (1 H, m, C(8)H**H′**), 2.12−2.24 (1 H, m, C(2)H**H′**), 3.74 (1 H, dd, *J* 7.5, 3.0, C(1)H), 3.88−3.93 (1 H, m, C(5)H), 5.56−5.68 (2 H, m, C(6)H and C(7)H); δ_C (100 MHz, $CDCl_3$) –5.1 (C(12)), –4.6 (C(13)), 17.6 (C(10)), 18.0 (C(14)), 21.4 (C(11)), 25.8 (C(15)), 31.1 (C(3)), 32.4 (C(2)), 35.5 (C(8)), 46.9 (C(4)), 47.7 (C(9)), 74.2 (C(5)), 80.7 (C(1)), 126.6 (C(7)), 128.0 (C(6)); *m/z* (EI^+) 296 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 296.2171; $C_{17}H_{32}O_2Si$ ($M^{+\cdot}$) requires: 296.2167.

Also obtained was *TMS-ether* **368** as a colourless oil (1.77 g, 33%). R_f 0.50 (19:1 petrol:ether); $[\alpha]_D^{23}$ –45.7 (*c* 0.70, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1463w, 1251m, 1050m, 836s; δ_H (500 MHz, C_6D_6) 0.07 (6 H, s, C(12)H_3 and C(13)H_3), 0.14 (9 H, s, 3 × C(16)H_3), 1.01 (12 H, s, C(10)H_3 and 3 × C(15)H_3), 1.14 (3 H, s, C(11)H_3), 1.53 (1 H, ddt, *J* 18.5, 3.5, 2.0, C(8)**H**H′), 1.56−1.66 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.79−1.88 (2 H, m, C(3)H**H′** and C(8)H**H′**), 1.99−2.09 (1 H, m, C(2)H**H′**), 3.89 (1 H, dq, *J* 3.0, 1.5, C(5)H), 3.97 (1 H, dd, *J* 7.5, 4.5, C(1)H), 5.55 (1 H, dtd, *J* 10.0, 4.0, 1.5, C(7)H), 5.65 (1 H, ddt, *J* 10.0, 3.0, 2.0, C(6)H); δ_C (125 MHz, C_6D_6) –5.0 (C(12)), –4.6 (C(13)), 0.2 (C(16)), 18.1 (C(14)), 18.3 (C(10)), 21.8 (C(11)), 25.9 (C(15)), 32.0 (C(3)), 32.3 (C(2)), 34.4 (C(8)), 46.6 (C(4)), 46.7 (C(9)), 74.3 (C(5)), 79.6 (C(1)), 125.7 (C(7)), 129.0 (C(6)); *m/z* (EI^+) 368 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 368.2569; $C_{20}H_{40}O_2Si_2$ ($M^{+\cdot}$) requires: 368.2562.

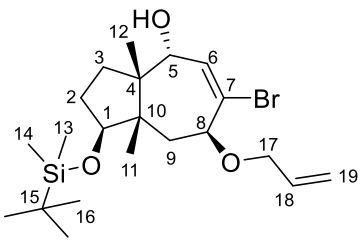
tert-Butyl{[(1a*S*,2a*S*,3*S*,5a*S*,6*R*,6a*S*)-1,1-dibromo-2a,5a-dimethyl-6-[(trimethylsilyl)oxy]decahydrocyclopropa[*f*]inden-3-yl]oxy}dimethylsilane (369)



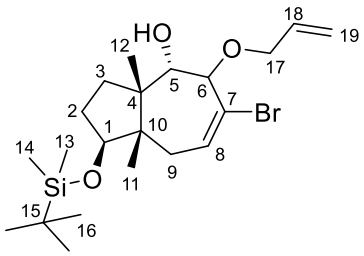
Benzyltriethylammonium chloride (11.0 mg, 48.0 μmol) and bromoform (1.26 mL, 14.4 mmol) were added to a solution of alkene **368** (1.77 g, 4.80 mmol) in benzene (35 mL). 50% aq. NaOH (0.864 mL) was added dropwise and the mixture was stirred at 70 °C for 16 h. Water (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil (1.08 g, 42%). R_f 0.65 (19:1 petrol:ether); $[\alpha]_D^{23}$ +30.3 (*c* 1.80, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1472w, 1251m, 1074s, 886s, 837s; δ_H (500 MHz, C_6D_6) –0.03 (3 H, s, C(13)H_3), 0.02 (3 H, s, C(14)H_3), 0.31 (9 H, s, 3 × C(17)H_3), 0.72−0.78 (1 H, m, C(9)**H**H′), 0.79 (3 H, s, C(11)H_3), 0.97 (9 H, s, 3 × C(16)H_3), 1.00 (3 H, s, C(12)H_3), 1.31−1.47 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.48−1.56 (1 H, m, C(2)H**H′**), 1.63−1.76 (4 H, m, C(3)H**H′**, C(6)H, C(8)H and C(9)H**H′**), 3.12 (1 H, d, *J* 6.0, C(5)H), 3.64 (1 H, dd, *J* 9.0, 5.5, C(1)H); δ_C (125 MHz, C_6D_6) –5.2 (C(13)), –4.5 (C(14)), 0.2 (C(17)), 17.9 (C(15)), 19.9 (C(11)), 23.0 (C(12)), 25.7 (C(16)), 28.3 (C(8)), 31.2 (C(3)), 31.3 (C(2)), 31.8 (C(9)), 34.1 (C(6)), 40.1 (C(7)), 45.8 (C(4)), 47.8 (C(10)), 76.1 (C(5)), 80.2 (C(1)); *m/z* (EI^+) 541 ($M(^{81}Br^{81}Br)^{+\cdot}$, 50%), 539 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 537 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($EI^+$): Found: 537.0851; $C_{21}H_{39}O_2Br_2Si_2$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 537.0850.

(1*S*,3a*S*,4*R*,7*S*,8a*S*)-7-(Allyloxy)-6-bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulen-4-ol (370) and **(1*S*,3a*S*,4*S*,8a*S*)-5-(Allyloxy)-6-bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulen-4-ol (371)**



370



371

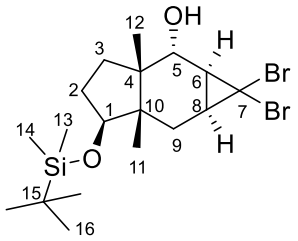
$AgBF_4$ (54.0 mg, 0.278 mmol) and $CaCO_3$ (27.8 mg, 0.278 mmol) were added to a solution of dibromocyclopropane **369** (100 mg, 0.185 mmol) in allyl alcohol (1.1 mL) and the mixture

was stirred at 90 ºC for 16 h. The mixture was filtered and solvent removed *in vacuo*. Water (10 mL) was added and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded *allyl ether* **370** as a colourless oil (24.6 mg, 30%). R_f 0.40 (3:1 petrol:ether); $[\alpha]_D^{23}$ –36.5 (*c* 0.40, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3447br, 2954m, 1471w, 1253m, 1057s, 836s; δ_H (500 MHz, $CDCl_3$) 0.06 (3 H, s, C(13)H_3), 0.09 (3 H, s, C(14)H_3), 0.91 (9 H, s, 3 × C(16)H_3), 0.96 (3 H, s, C(11)H_3), 1.04 (3 H, s, C(12)H_3), 1.36−1.43 (1 H, m, C(3)**H**H′), 1.49−1.67 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.71−1.82 (2 H, m, C(2)H**H′** and C(9)**H**H′), 1.86 (1 H, dd, *J* 15.0, 5.5, C(9)H**H′**), 4.04−4.16 (4 H, m, C(1)H, C(8)H and C(17)H_2), 4.19 (1 H, d, *J* 4.5, C(5)H), 5.20 (1 H, dq, *J* 10.5, 1.5, C(19)**H**H′), 5.32 (1 H, dq, *J* 17.0, 1.5, C(19)H**H′**), 5.92−6.02 (1 H, m, C(18)H), 6.20 (1 H, d, *J* 4.5, C(6)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –3.9 (C(14)), 18.0 (C(15)), 20.7 (C(11)), 23.5 (C(12)), 25.8 (C(16)), 30.6 (C(2)), 31.6 (C(3)), 37.4 (C(9)), 47.1 (C(10)), 48.4 (C(4)), 71.1 (C(17)), 76.4 (C(5)), 77.0 (C(1)), 80.2 (C(8)), 117.4 (C(19)), 125.9 (C(7)), 134.8 (C(18)), 138.5 (C(6)); *m/z* (ESI^+) 469 (M(^{81}Br)Na^+, 100%), 467 (M(^{79}Br)Na^+, 100); HRMS (ESI^+): Found: 467.1589; $C_{21}H_{37}O_3BrSiNa$ (M(^{79}Br)Na^+) requires: 467.1588.

Also obtained was *allyl ether* **371** as a colourless oil (16.4 mg, 20%). R_f 0.70 (3:1 petrol:ether); $[\alpha]_D^{23}$ +34.4 (*c* 0.32, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3553br, 2955m, 1471w, 1255m, 1064s, 837s; δ_H (500 MHz, $CDCl_3$) 0.03 (6 H, s, C(13)H_3 and C(14)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 0.90 (3 H, s, C(11)H_3), 1.22 (3 H, s, C(12)H_3), 1.50−1.64 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.83 (1 H, ddd, *J* 15.5, 6.5, 1.5, C(9)**H**H′), 1.86−2.00 (2 H, m, C(2)H**H′** and C(3)H**H′**), 2.07 (1 H, dd, *J* 15.5, 8.5, C(9)H**H′**), 3.02 (1 H, bs, OH), 3.46 (1 H, d, *J* 9.5, C(5)H), 3.74 (1 H, t, *J* 6.0, C(1)H), 3.99−4.07 (2 H, m, C(6)H and C(17)**H**H′), 4.34 (1 H, ddt, *J* 12.0, 5.5, 1.5, C(17)H**H′**), 5.24 (1 H, dd, *J* 10.5, 1.5, C(19)**H**H′), 5.36 (1 H, dq, *J* 17.0, 1.5, C(19)H**H′**), 5.93−6.04 (1 H, m, C(18)H), 6.23 (1 H, ddd, *J* 8.5, 6.5, 1.5, C(8)H); δ_C (125

MHz, $CDCl_3$) –5.0 (C(13)), –4.5 (C(14)), 18.0 (C(11)), 18.1 (C(15)), 23.6 (C(12)), 25.8 (C(16)), 29.8 (C(3)), 31.2 (C(2)), 36.5 (C(9)), 48.7 (C(4)), 50.5 (C(10)), 71.9 (C(17)), 74.7 (C(5)), 79.4 (C(6)), 80.1 (C(1)), 118.0 (C(19)), 126.1 (C(7)), 132.4 (C(8)), 133.7 (C(18)); *m/z* (ESI^+) 469 ($M(^{81}Br)Na^+$, 100%), 467 ($M(^{79}Br)Na^+$, 100); HRMS (ESI^+): Found: 467.1589; $C_{21}H_{37}O_3BrSiNa$ ($M(^{79}Br)Na^+$) requires: 467.1588.

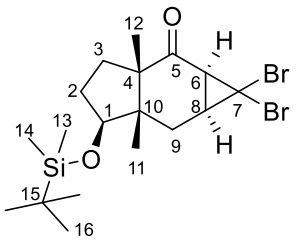
(1a*S*,2*R*,2a*S*,5*S*,5a*S*,6a*S*)-1,1-Dibromo-5-[(*tert*-butyldimethylsilyl)oxy]-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-2-ol (372)



0.1 M HCl (0.2 mL) was added to a solution of dibromocyclopropane **369** (10.0 mg, 0.0185 mmol) in THF (0.2 mL) and the mixture was stirred at RT for 6 h. The mixture was extracted with ether (3 × 1 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (7.60 mg, 88%). R_f 0.50 (3:1 petrol:ether); $[\alpha]_D^{23}$ +30.6 (*c* 0.77, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3396br, 2951m, 1463w, 1249m, 1034s, 837s; δ_H (500 MHz, $CDCl_3$) 0.06 (3 H, s, C(13)H_3), 0.07 (3 H, s, C(14)H_3), 0.76 (1 H, dd, *J* 15.0, 8.5, C(9)**H**H′), 0.81 (3 H, s, C(11)H_3), 0.91 (9 H, s, 3 × C(16)H_3), 1.06 (3 H, s, C(12)H_3), 1.32−1.39 (1 H, m, C(3)**H**H′), 1.49−1.59 (1 H, m, C(2)**H**H′), 1.66−1.85 (4 H, m, C(2)H**H′**, C(3)H**H′**, C(6)H and C(8)H), 1.89 (1 H, dd, *J* 15.0, 8.0, C(9)H**H′**), 3.13 (1 H, d, *J* 7.0, C(5)H), 3.81 (1 H, dd, *J* 9.5, 5.0, C(1)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.3 (C(14)), 18.0 (C(15)), 19.8 (C(11)), 22.9 (C(12)), 25.8 (C(16)), 28.7 (C(8)), 30.7 (C(3)), 31.4 (C(2)),

31.6 (C(9)), 33.5 (C(6)), 39.0 (C(7)), 45.4 (C(4)), 48.5 (C(10)), 76.3 (C(5)), 80.0 (C(1)); *m/z* (FI^+) 470 ($M(^{81}Br^{81}Br)^{+\cdot}$, 50%), 468 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 466 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($FI^+$): Found: 466.0367; $C_{18}H_{32}O_2Br_2Si$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 466.0533.

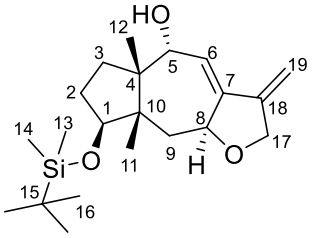
(1a*S*,2a*S*,5*S*,5a*S*,6a*S*)-1,1-Dibromo-5-[(*tert*-butyldimethylsilyl)oxy]-2a,5a-dimethyloctahydrocyclopropa[*f*]inden-2(1*H*)-one (373)



Dess–Martin periodinane (10.0 mg, 0.0235 mmol) was added to a solution of alcohol **372** (5.50 mg, 0.0117 mmol) in DCM (0.6 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (1 mL) and sat. aq. $Na_2S_2O_3$ (1 mL) were added and the mixture was extracted with DCM (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 19:1 petrol:ether) afforded the *title compound* as a colourless oil (5.00 mg, 91%). R_f 0.80 (3:1 petrol:ether); $[\alpha]_D^{23}$ +105.7 (*c* 0.53, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954s, 1697s, 1471m, 1252m, 1137s, 837s; δ_H (500 MHz, $CDCl_3$) 0.05 (3 H, s, C(13)H_3), 0.09 (3 H, s, C(14)H_3), 0.79 (3 H, s, C(11)H_3), 0.92 (9 H, s, 3 × C(16)H_3), 1.10 (3 H, s, C(12)H_3), 1.40−1.50 (2 H, m, C(2)**H**H′ and C(9)**H**H′), 1.62−1.70 (1 H, m, C(3)**H**H′), 1.71−1.80 (1 H, m, C(2)H**H′**), 1.95−2.04 (1 H, m, C(3)H**H′**), 2.13−2.19 (1 H, m, C(8)H), 2.24 (1 H, dd, *J* 15.0, 10.0, C(9)H**H′**), 2.47 (1 H, d, *J* 9.0, C(6)H), 4.07 (1 H, t, *J* 9.0, C(1)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.2 (C(14)), 16.5 (C(11)), 18.0 (C(15)), 21.1 (C(12)), 25.8 (C(16)), 26.5 (C(9)), 29.5 (C(2)), 30.3 (C(8)), 32.5 (C(7)), 34.8 (C(3)), 36.3 (C(6)), 48.5 (C(10)), 53.8 (C(4)), 76.4 (C(1)), 209.1

(C(5)); *m/z* (FI$^+$) 468 (M(^{81}Br^{81}Br)$^{+\cdot}$, 50%), 466 (M(^{81}Br^{79}Br)$^{+\cdot}$, 100), 464 (M(^{79}Br^{79}Br)$^{+\cdot}$, 50); HRMS (FI$^+$): Found: 464.0141; $C_{18}H_{30}O_2Br_2Si$ (M(^{79}Br^{79}Br)$^{+\cdot}$) requires: 464.0377.

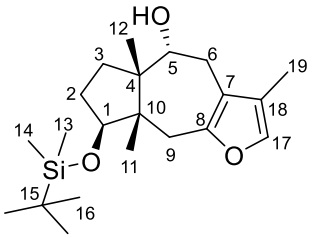
(5*R*,5a*S*,8*S*,8a*S*,9a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-5a,8a-dimethyl-3-methylene-2,3,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-ol (376)



$Pd(PPh_3)_4$ (1.0 mg, 0.831 μmol), Ag_2CO_3 (4.5 mg, 0.0166 mmol) and K_2CO_3 (2.5 mg, 0.0183 mmol) were added into a solution of bromide **370** (3.70 mg, 0.00831 mmol) in DMF (0.6 mL) and the mixture was stirred at 110 ºC for 2 h. The mixture was filtered through Celite and washed with ether (3 mL). The combined organic layers were washed with water (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (2.00 mg, 66%). R_f 0.40 (3:1 petrol:ether); $[\alpha]_D^{23}$ –38.7 (*c* 0.15, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3419br, 2954s, 1471w, 1255w, 1060s, 836s; δ_H (500 MHz, $CDCl_3$) 0.06 (3 H, s, C(13)H_3), 0.09 (3 H, s, C(14)H_3), 0.82 (3 H, s, C(11)H_3), 0.90 (3 H, s, C(12)H_3), 0.91 (9 H, s, 3 × C(16)H_3), 1.37−1.44 (1 H, m, C(9)**H**H′), 1.45−1.53 (1 H, m, C(2)**H**H′), 1.60−1.76 (2 H, m, C(3)H_2), 1.92 (1 H, dd, *J* 13.5, 3.0, C(9)H**H′**), 2.00−2.09 (1 H, m, C(2)H**H′**), 3.99 (1 H, d, *J* 6.5, C(5)H), 4.41 (1 H, dt, *J* 13.0, 2.5, C(17)**H**H′), 4.53 (1 H, dt, *J* 13.0, 2.0, C(17)H**H′**), 4.77 (1 H, t, *J* 8.0, C(1)H), 4.91 (1 H, t, *J* 2.0, C(19)**H**H′), 4.98 (1 H, dt, *J* 11.5, 2.5, C(8)H), 5.35 (1 H, t, *J* 2.5, C(19)H**H′**), 6.28 (1 H, dd, *J* 6.5, 2.5, C(6)H); δ_C (125 MHz, $CDCl_3$) –4.8 (C(13)), –4.3 (C(14)), 18.0 (C(15)), 21.0 (C(11)), 22.4 (C(12)), 25.9 (C(16)), 31.3 (C(2)), 35.3 (C(3)),

38.8 (C(9)), 47.2 (C(4)), 49.0 (C(10)), 71.4 (C(17)), 75.9 (C(1)), 77.8 (C(8)), 78.5 (C(5)), 102.1 (C(19)), 119.5 (C(6)), 145.1 (C(7)), 146.1 (C(18)); *m/z* (ESI^+) 387 (MNa^+, 100%); HRMS (ESI^+): Found: 363.2375; $C_{21}H_{35}O_3Si$ ($[M–H]^–$) requires: 363.2361.

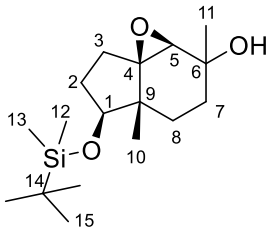
(5*R*,5a*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-ol (377)



$Ru(PPh_3)_3Cl_2$ (1.0 mg, 0.82 μmol) and *N*,*N*-diisopropylethylamine (1.0 μL, 0.00411 mmol) were added to a solution of diene **376** (1.50 mg, 0.00411 mmol) in toluene (0.1 mL) and the mixture was stirred at 80 ºC for 5 h. The mixture was filtered through Celite and washed with ether (1 mL). The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (0.5 mg, 33%). R_f 0.25 (3:1 petrol:ether); $[\alpha]_D^{25}$ +0.7 (*c* 0.28, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3431br, 2955s, 1472m, 1252m, 1097s, 836s; δ_H (500 MHz, $CDCl_3$) –0.13 (3 H, s, C(13)H_3), –0.06 (3 H, s, C(14)H_3), 0.87 (9 H, s, 3 × C(16)H_3), 0.89 (3 H, s, C(11)H_3), 1.06 (3 H, s, C(12)H_3), 1.37−1.46 (1 H, m, C(3)**H**H′), 1.51−1.61 (1 H, m, C(2)**H**H′), 1.65 (1 H, d, *J* 6.0, OH), 1.81−1.89 (1 H, m, C(2)H**H′**), 1.91 (3 H, d, *J* 1.5, C(19)H_3), 2.06 (1 H, dt, *J* 13.5, 8.5, C(3)H**H′**), 2.48−2.55 (2 H, m, C(6)**H**H′ and C(9)**H**H′), 2.67 (1 H, d, *J* 16.5, C(6)H**H′**), 2.85 (1 H, d, *J* 16.0, C(9)H**H′**), 3.66−3.72 (1 H, m, C(5)H), 3.85 (1 H, dd, *J* 8.0, 7.0, C(1)H), 7.02 (1 H, q, *J* 1.5, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.4 (C(13)), –4.6 (C(14)), 8.1 (C(19)), 18.0 (C(15)), 19.3 (C(11)), 22.4 (C(3)), 24.5 (C(12)), 25.8 (C(16)), 28.1 (C(6)), 31.0 (C(2)), 34.6 (C(9)), 49.0 (C(4)), 49.3

(C(10)), 77.7 (C(1) and C(5)), 114.8 (C(7)), 120.9 (C(18)), 136.5 (C(17)), 150.2 (C(8)); *m/z* (ESI^+) 387 (MNa^+, 70%), 365 (MH^+, 60); HRMS (ESI^+): Found: 365.2506; $C_{21}H_{37}O_3Si$ (MH^+) requires: 365.2507.

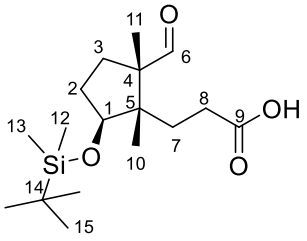
(1a*S*,4a*R*,5*S*,7a*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2,4a-dimethyloctahydroindeno[3a,4-*b*]oxiren-2-ol (379)



A solution of silyl enol ether **346** and allylic alcohol **378** (0.253 g, 0.686 mmol) in DCM (2.4 mL) was added to a mixture of $NaHCO_3$ (0.254 g, 3.02 mmol) and *m*CPBA (0.169 g, 0.755 mmol) in DCM (5.6 mL) at –20 °C and stirred at –10 ºC for 1 h. Sat. aq. $NaHCO_3$ (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (55.0 mg, 26%). R_f 0.20 (3:1 petrol:ether); $[\alpha]_D^{25}$ +22.0 (*c* 2.79, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3450br, 2930w, 1463w, 1251w, 1125m, 835s; δ_H (400 MHz, $CDCl_3$) 0.03 (6 H, s, C(12)H_3 and C(13)H_3), 0.88 (9 H, s, 3 × C(15)H_3), 0.94 (3 H, s, C(10)H_3), 1.09−1.17 (1 H, m, C(7)**H**H′), 1.29 (3 H, s, C(11)H_3), 1.35−1.54 (3 H, m, C(7)H**H′** and C(8)H_2), 1.68−1.91 (4 H, m, C(2)H_2 and C(3)H_2), 2.86 (1 H, s, C(5)H), 3.73 (1 H, dd, *J* 10.0, 7.0, C(1)H); δ_C (100 MHz, $CDCl_3$) –4.9 (C(12)), –4.4 (C(13)), 14.6 (C(10)), 18.0 (C(14)), 23.7 (C(11)), 25.7 (C(15)), 27.2 (C(3)), 29.9 (C(2)), 31.8 (C(8)), 33.3 (C(7)), 40.6 (C(9)), 67.2 (C(5)), 70.6

(C(4)), 71.8 (C(6)), 81.0 (C(1)); *m/z* (ESI^+) 335 (MNa^+, 100%), 313 (MH^+, 20); HRMS (ESI^+): Found: 335.2013; $C_{17}H_{32}O_3SiNa$ (MNa^+) requires: 335.2013.

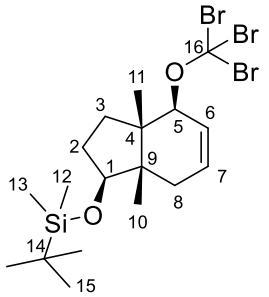
3-[(1*S*,2*S*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-formyl-1,2-dimethylcyclopentyl]propanoic acid (380)



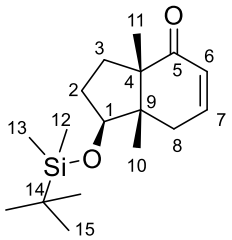
A solution of silyl enol ether **346** (96.0 mg, 0.260 mmol) in DCM (0.8 mL) was added to a mixture of $NaHCO_3$ (96.2 mg, 1.15 mmol) and *m*CPBA (52.5 mg, 0.286 mmol) in DCM (2.2 mL) at –20 °C and stirred at 0 ºC for 1 h. Sat. aq. $NaHCO_3$ (10 mL) was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a white solid (27.0 mg, 32%). R_f 0.20 (1:1 petrol:ether); m.p. 134–137 °C; $[\alpha]_D^{25}$ +27.2 (*c* 1.35, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954w, 1703s, 1415w, 1258m, 1083m, 836s; δ_H (500 MHz, $CDCl_3$) 0.05 (6 H, s, C(12)H_3 and C(13)H_3), 0.90 (9 H, s, 3 × C(15)H_3), 0.91 (3 H, s, C(10)H_3), 0.93 (3 H, s, C(11)H_3), 1.47−1.63 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.64−1.83 (2 H, m, C(7)H_2), 1.95−2.10 (2 H, m, C(2)H**H′** and C(3)H**H′**), 2.44 (1 H, ddd, *J* 16.0, 11.5, 5.5, C(8)**H**H′), 2.57 (1 H, ddd, *J* 16.0, 11.5, 5.0, C(8)H**H′**), 4.00 (1 H, t, *J* 8.0, C(1)H), 9.70 (1 H, s, C(6)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(12)), –4.0 (C(13)), 13.9 (C(10)), 17.4 (C(11)), 17.9 (C(14)), 25.8 (C(15)), 29.0 (C(3)), 29.5 (C(8)), 30.8 (C(2)), 30.9 (C(7)), 49.5 (C(5)), 57.1 (C(4)), 79.9 (C(1)), 180.2 (C(9)),

206.3 (C(6)); *m/z* (ESI^+) 351 (MNa^+, 100%); HRMS (ESI^+): Found: 351.1964; $C_{17}H_{32}O_4SiNa$ (MNa^+) requires: 351.1962.

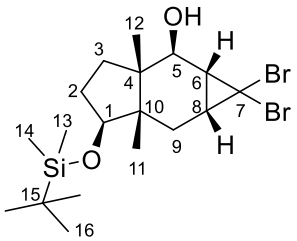
***tert*-Butyl{[(1*S*,3a*S*,4*S*,7a*S*)-3a,7a-dimethyl-4-(tribromomethoxy)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl]oxy}dimethylsilane (381)**, **(1*S*,3a*S*,7a*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-3a,7a-dimethyl-1,2,3,3a,7,7a-hexahydro-4*H*-inden-4-one (382)** and **(1a*R*,2*S*,2a*S*,5*S*,5a*S*,6a*R*)-1,1-Dibromo-5-[(*tert*-butyldimethylsilyl)oxy]-2a,5a-dimethyldecahydrocyclopropa[*f*]inden-2-ol (383)**



381



382



383

Benzyltriethylammonium chloride (0.5 mg, 0.843 μmol) and bromoform (22.0 μL, 0.253 mmol) were added to a solution of alkene **352** (25.0 mg, 0.0843 mmol) in benzene (0.65 mL). 50% aq. NaOH (15.0 μL) was added dropwise and the mixture was stirred at 70 °C for 16 h. Water (2 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded *bromide* **381** as a white solid (8.40 mg, 18%). R_f 0.95 (3:1 petrol:ether); m.p. 86–89 °C; $[\alpha]_D^{25}$ +2.6 (*c* 0.84, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1471w, 1252m, 1116s, 880s; δ_H (500 MHz, $CDCl_3$) 0.01 (3 H, s, C(12)H_3), 0.02 (3 H, s, C(13)H_3), 0.89 (12 H, s, C(10)H_3 and 3 × C(15)H_3), 1.10 (3 H, s, C(11)H_3), 1.37−1.47 (3 H, m, C(2)**H**H′ and C(3)H_2), 1.85 (1 H, d, *J* 19.5, C(8)**H**H′), 1.91−2.05 (1 H, m, C(2)H**H′**), 2.23 (1 H, dd, *J* 19.5, 2.0, C(8)H**H′**), 3.89 (1 H, s, C(5)H), 4.09 (1 H, dd, *J* 8.5,

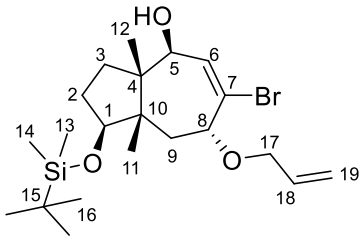
6.5, C(1)H), 6.15 (2 H, d, *J* 2.0, C(6)H and C(7)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(12)), –4.4 (C(13)), 18.0 (C(10) and C(14)), 19.9 (C(11)), 25.9 (C(15)), 28.3 (C(3)), 30.5 (C(2)), 30.8 (C(8)), 45.3 (C(4)), 45.9 (C(9)), 68.2 (C(16)), 73.7 (C(5)), 74.5 (C(1)), 118.4 (C(6)), 135.8 (C(7)).

Also obtained was *enone* **382** as a pale yellow oil (8.00 mg, 32%). R_f 0.75 (3:1 petrol:ether); $[\alpha]_D^{25}$ +17.2 (*c* 0.81, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1674s, 1471w, 1252m, 1119s, 836s; δ_H (500 MHz, $CDCl_3$) –0.03 (6 H, s, C(12)H_3 and C(13)H_3), 0.88 (9 H, s, 3 × C(15)H_3), 0.91 (3 H, s, C(10)H_3), 1.05 (3 H, s, C(11)H_3), 1.39−1.54 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.76−1.85 (1 H, m, C(2)H**H′**), 2.10−2.18 (1 H, m, C(8)**H**H′), 2.37 (1 H, ddd, *J* 20.5, 5.5, 1.0, C(8)H**H′**), 2.41−2.47 (1 H, m, C(3)H**H′**), 3.88 (1 H, dd, *J* 8.5, 8.0, C(1)H), 5.93 (1 H, ddd, *J* 10.0, 3.0, 1.5, C(6)H), 6.70 (1 H, ddd, *J* 10.0, 5.5, 2.5, C(7)H); δ_C (125 MHz, $CDCl_3$) –5.1 (C(12)), –4.4 (C(13)), 16.5 (C(10)), 18.0 (C(14)), 19.5 (C(11)), 25.8 (C(15)), 29.1 (C(2)), 29.2 (C(3)), 32.0 (C(8)), 47.4 (C(9)), 53.1 (C(4)), 74.7 (C(1)), 126.9 (C(6)), 146.0 (C(7)), 204.5 (C(5)); *m/z* (ESI^+) 317 (MNa^+, 100%); HRMS (ESI^+): Found: 317.1909; $C_{17}H_{30}O_2SiNa$ (MNa^+) requires: 317.1907.

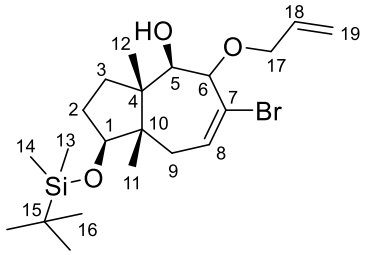
Also obtained was *dibromocyclopropane* **383** as a colourless oil (7.50 mg, 19%). R_f 0.65 (3:1 petrol:ether); $[\alpha]_D^{25}$ +1.2 (*c* 1.60, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3460br, 2954w, 1732w, 1462w, 1039s, 835s; δ_H (400 MHz, $CDCl_3$) 0.03 (6 H, s, C(13)H_3 and C(14)H_3), 0.83 (1 H, dd, *J* 14.0, 9.5, C(9)**H**H′), 0.89 (9 H, s, 3 × C(16)H_3), 0.98 (3 H, s, C(11)H_3), 1.00 (3 H, s, C(12)H_3), 1.46−1.64 (3 H, m, C(2)H_2 and C(3)**H**H′), 1.65−1.74 (2 H, m, C(3)H**H′** and C(6)H), 1.78 (1 H, dd, *J* 14.0, 8.0, C(9)H**H′**), 1.85−1.93 (1 H, m, C(8)H), 1.95 (1 H, d, *J* 4.0, OH), 3.13 (1 H, dd, *J* 8.0, 4.5, C(5)H), 3.58 (1 H, t, *J* 4.5, C(1)H); δ_C (100 MHz, $CDCl_3$) –4.9 (C(13)), –4.5 (C(14)), 18.1 (C(15)), 18.3 (C(12)), 19.9 (C(11)), 25.8 (C(16)), 29.4 (C(8)), 31.0 (C(2)), 33.6 (C(6)), 34.2 (C(9)), 35.8 (C(3)), 39.1 (C(7)), 46.0 (C(4)), 50.3 (C(10)), 75.8

(C(5)), 82.4 (C(1)); *m/z* (FI^+) 470 ($M(^{81}Br^{81}Br)^{+\cdot}$, 50%), 468 ($M(^{81}Br^{79}Br)^{+\cdot}$, 100), 466 ($M(^{79}Br^{79}Br)^{+\cdot}$, 50); HRMS ($FI^+$): Found: 466.0367; $C_{18}H_{32}O_2Br_2Si$ ($M(^{79}Br^{79}Br)^{+\cdot}$) requires: 466.0533.

(1*S*,3a*S*,4*S*,7*R*,8a*S*)-7-(Allyloxy)-6-bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3a,8a-dimethyl-1,2,3,3a,4,7,8,8a-octahydroazulen-4-ol (384) and **(1*S*,3a*S*,4*R*,8a*S*)-5-(Allyloxy)-6-bromo-1-[(*tert*-butyldimethylsilyl)oxy]-3a,8a-dimethyl-1,2,3,3a,4,5,8,8a-octahydroazulen-4-ol (385)**



384



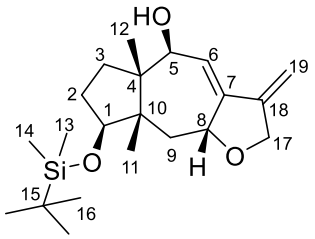
385

$AgBF_4$ (43.5 mg, 0.222 mmol) and $CaCO_3$ (22.5 mg, 0.222 mmol) were added to a solution of dibromocyclopropane **354** (80.0 mg, 0.148 mmol) in allyl alcohol (0.9 mL) and the mixture was stirred at 90 ºC for 16 h. The mixture was filtered and solvent removed *in vacuo*. Water (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded *allyl ether* **384** as a colourless oil (22.0 mg, 33%). R_f 0.20 (3:1 petrol:ether); $[\alpha]_D^{25}$ +28.2 (*c* 0.33, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3447br, 2955w, 1472w, 1252m, 1057s, 836s; δ_H (500 MHz, $CDCl_3$) 0.05 (3 H, s, C(13)H_3), 0.06 (3 H, s, C(14)H_3), 0.89 (3 H, s, C(11)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 0.95 (3 H, s, C(12)H_3), 1.47−1.60 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.62−1.76 (3 H, m, OH, C(2)H**H′** and C(3)H**H′**), 1.81−1.90 (2 H, m, C(9)H_2), 3.64 (1 H, dd, *J* 8.0, 5.5, C(1)H), 4.02 (1 H, ddd, *J*

10.5, 6.5, 2.0, C(8)H), 4.07−4.15 (2 H, m, C(17)H_2), 4.54 (1 H, ddd, *J* 5.5, 3.5, 2.0, C(5)H), 5.20 (1 H, dq, *J* 10.5, 1.5, C(19)**H**H′), 5.32 (1 H, dq, *J* 17.0, 1.5, C(19)H**H′**), 5.96 (1 H, ddt, *J* 17.0, 10.5, 6.0, C(18)H), 6.15 (1 H, d, *J* 3.5, C(6)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.3 (C(14)), 17.3 (C(11)), 18.0 (C(15)), 18.7 (C(12)), 25.8 (C(16)), 30.7 (C(2)), 35.1 (C(3)), 40.3 (C(9)), 46.0 (C(10)), 49.1 (C(4)), 70.8 (C(17)), 74.7 (C(5)), 79.3 (C(8)), 83.1 (C(1)), 117.6 (C(19)), 122.7 (C(7)), 134.8 (C(18)), 140.2 (C(6)); *m/z* (ESI^+) 469 (M(^{81}Br)Na^+, 100%), 467 (M(^{79}Br)Na^+, 100); HRMS (ESI^+): Found: 467.1589; $C_{21}H_{37}O_3BrSiNa$ (M(^{79}Br)Na^+) requires: 467.1588.

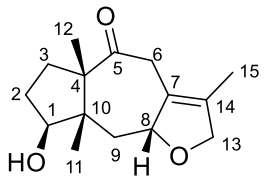
Also obtained was *allyl ether* **385** as a colourless oil (18.0 mg, 27%). R_f 0.45 (3:1 petrol:ether); $[\alpha]_D^{25}$ –42.2 (*c* 1.44, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3448br, 2954w, 1472w, 1251m, 1047s, 836s; δ_H (500 MHz, $CDCl_3$) 0.02 (3 H, s, C(13)H_3), 0.03 (3 H, s, C(14)H_3), 0.86 (3 H, s, C(11)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 0.98 (3 H, s, C(12)H_3), 1.41−1.58 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.67−1.75 (1 H, m, C(2)H**H′**), 1.88−1.99 (2 H, m, C(3)H**H′** and C(9)**H**H′), 2.17 (1 H, dd, *J* 15.0, 6.0, C(9)H**H′**), 3.65 (1 H, dd, *J* 9.5, 6.0, C(1)H), 3.95 (1 H, dd, *J* 9.0, 1.5, C(5)H), 4.03 (1 H, dd, *J* 9.0, 1.5, C(6)H), 4.13 (1 H, ddt, *J* 12.0, 6.0, 1.5, C(17)**H**H′), 4.33 (1 H, ddt, *J* 12.0, 6.0, 1.5, C(17)H**H′**), 5.22 (1 H, dq, *J* 10.5, 1.5, C(19)**H**H′), 5.35 (1 H, dq, *J* 17.0, 1.5, C(19)H**H′**), 6.00 (1 H, ddt, *J* 17.0, 10.5, 6.0, C(18)H), 6.32 (1 H, dd, *J* 9.5, 6.0, C(8)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.2 (C(14)), 17.4 (C(11)), 18.0 (C(15)), 18.4 (C(12)), 25.8 (C(16)), 30.4 (C(2)), 35.2 (C(3)), 36.3 (C(9)), 45.3 (C(4)), 49.9 (C(10)), 70.5 (C(17)), 75.0 (C(5)), 80.9 (C(1)), 85.4 (C(6)), 117.6 (C(19)), 124.0 (C(7)), 134.1 (C(8)), 134.5 (C(18)); *m/z* (ESI^+) 469 (M(^{81}Br)Na^+, 100%), 467 (M(^{79}Br)Na^+, 100); HRMS (ESI^+): Found: 467.1589; $C_{21}H_{37}O_3BrSiNa$ (M(^{79}Br)Na^+) requires: 467.1588.

(5*S*,5a*S*,8*S*,8a*S*,9a*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-5a,8a-dimethyl-3-methylene-2,3,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-ol (386)



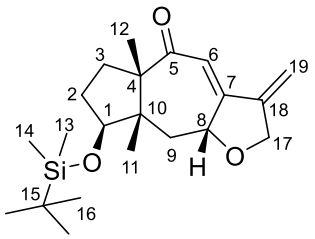
$Pd(PPh_3)_4$ (41.0 mg, 35.5 μmol), Ag_2CO_3 (0.196 g, 0.709 mmol) and K_2CO_3 (0.108 g, 0.780 mmol) were added into a solution of bromide **384** (0.158 g, 0.355 mmol) in toluene (25 mL) and the mixture was stirred at 100 ºC for 1.5 h. The mixture was filtered through Celite and washed with ether (50 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (0.106 g, 82%). R_f 0.15 (3:1 petrol:ether); $[\alpha]_D^{25}$ –1.0 (*c* 0.60, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3462br, 2954s, 1472w, 1253m, 1063s, 837s; δ_H (500 MHz, $CDCl_3$) 0.02 (6 H, s, C(13)H_3 and C(14)H_3), 0.88 (9 H, s, 3 × C(16)H_3), 0.94 (3 H, s, C(12)H_3), 1.00 (3 H, s, C(11)H_3), 1.39 (1 H, ddd, *J* 14.5, 11.5, 3.0, C(3)**H**H′), 1.54−1.66 (2 H, m, C(2)**H**H′ and C(9)**H**H′), 1.71 (1 H, bs, OH), 1.80−1.88 (1 H, m, C(2)H**H′**), 1.98 (1 H, dd, *J* 13.5, 1.5, C(9)H**H′**), 2.06−2.15 (1 H, m, C(3)H**H′**), 3.92 (1 H, dd, *J* 10.0, 7.5, C(1)H), 4.35 (1 H, dt, *J* 13.0, 2.5, C(17)**H**H′), 4.37−4.44 (2 H, m, C(5)H and C(8)H), 4.48 (1 H, dt, *J* 13.0, 2.0, C(17)H**H′**), 4.86 (1 H, t, *J* 2.0, C(19)**H**H′), 5.32 (1 H, t, *J* 2.5, C(19)H**H′**), 5.91 (1 H, s, C(6)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.2 (C(14)), 15.6 (C(11)), 18.0 (C(12)), 18.9 (C(15)), 25.8 (C(16)), 30.5 (C(2)), 32.5 (C(3)), 43.8 (C(9)), 46.1 (C(10)), 51.1 (C(4)), 71.0 (C(17)), 73.2 (C(5)), 77.0 (C(8)), 81.6 (C(1)), 101.1 (C(19)), 122.9 (C(6)), 141.0 (C(7)), 145.7 (C(18)); *m/z* (ESI^+) 387 (MNa^+, 100%); HRMS (ESI^+): Found: 363.2375; $C_{21}H_{35}O_3Si$ ($[M–H]^-$) requires: 363.2361.

(5a*S*,8*S*,8a*S*,9a*R*)-8-Hydroxy-3,5a,8a-trimethyl-2,5a,6,7,8,8a,9,9a-octahydroazuleno[5,6-*b*]furan-5(4*H*)-one (387)



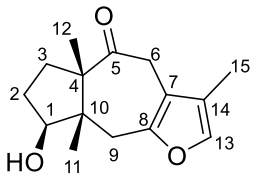
Potassium *tert*-butoxide (7.0 µL, 0.00686 mmol, 1 M in THF) was added to a solution of diene **386** (5.00 mg, 0.0137 mmol) in DMSO (0.2 mL) and the mixture was stirred at 80 ºC for 2 h. Water (0.2 mL) was added and the mixture was extracted with ether (3 × 0.5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil (1.20 mg, 35%). R_f 0.45 (ether); $[\alpha]_D^{25}$ +2.3 (*c* 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3460br, 2972m, 1700s, 1470w, 1043s; δ_H (500 MHz, $CDCl_3$) 1.19 (3 H, s, C(11)H_3), 1.26 (3 H, s, C(12)H_3), 1.42−1.55 (3 H, m, C(2)**H**H′, C(3)**H**H′ and C(9)**H**H′), 1.88 (1 H, dd, *J* 14.5, 3.5, C(9)H**H′**), 1.90−1.98 (1 H, m, C(2)H**H′**), 2.48−2.55 (1 H, m, C(3)H**H′**), 3.22 (1 H, d, *J* 12.0, C(6)**H**H′), 3.38−3.44 (1 H, m, C(6)H**H′**), 3.78 (1 H, t, *J* 6.5, C(1)H), 4.41−4.53 (2 H, m, C(13)H_2), 4.96−5.03 (1 H, m, C(8)H); δ_C (125 MHz, $CDCl_3$) 9.9 (C(15)), 16.8 (C(11)), 23.1 (C(12)), 29.3 (C(2)), 31.2 (C(3)), 37.6 (C(6)), 44.0 (C(9)), 47.4 (C(10)), 59.5 (C(4)), 77.9 (C(13)), 82.1 (C(1)), 84.5 (C(8)), 126.6 (C(14)), 130.9 (C(7)), 209.7 (C(5)); *m/z* (ESI^+) 273 (MNa^+, 100%); HRMS (ESI^+): Found: 273.1462; $C_{15}H_{22}O_3Na$ (MNa^+) requires: 273.1461.

(5a*S*,8*S*,8a*S*,9a*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-5a,8a-dimethyl-3-methylene-2,3,6,7,8,8a,9,9a-octahydroazuleno[5,6-*b*]furan-5(5a*H*)-one (388)



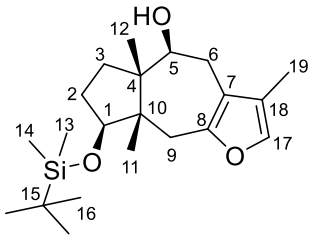
Dess–Martin periodinane (6.0 mg, 0.0137 mmol) was added to a solution of alcohol **386** (2.50 mg, 0.00686 mmol) in DCM (0.35 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (1 mL) and sat. aq. $Na_2S_2O_3$ (1 mL) were added and the mixture was extracted with DCM (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the *title compound* as a colourless oil (2.00 mg, 80%). R_f 0.65 (3:1 petrol:ether); $[\alpha]_D^{25}$ +17.6 (*c* 0.42, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1660s, 1470w, 1200m, 1068s, 833s; δ_H (500 MHz, $CDCl_3$) –0.03 (3 H, s, C(13)H_3), –0.01 (3 H, s, C(14)H_3), 0.86 (9 H, s, 3 × C(16)H_3), 1.09 (3 H, s, C(11)H_3), 1.18 (3 H, s, C(12)H_3), 1.27 (1 H, td, *J* 13.0, 4.0, C(3)**H**H′), 1.46−1.59 (2 H, m, C(2)**H**H′ and C(9)**H**H′), 1.87−1.96 (1 H, m, C(2)H**H′**), 2.16 (1 H, dd, *J* 13.5, 2.0, C(9)H**H′**), 2.62 (1 H, ddd, *J* 14.0, 10.0, 6.5, C(3)H**H′**), 3.54 (1 H, dd, *J* 9.5, 8.0, C(1)H), 4.44 (1 H, dt, *J* 13.0, 2.5, C(17)**H**H′), 4.57 (1 H, dt, *J* 13.0, 2.0, C(17)H**H′**), 4.66 (1 H, dt, *J* 11.0, 2.0, C(8)H), 5.19 (1 H, t, *J* 2.0, C(19)**H**H′), 5.61 (1 H, t, *J* 2.5, C(19)H**H′**), 6.25 (1 H, d, *J* 2.5, C(6)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.3 (C(14)), 15.2 (C(11)), 17.9 (C(15)), 24.1 (C(12)), 25.8 (C(16)), 29.7 (C(3)), 30.0 (C(2)), 46.0 (C(10)), 46.8 (C(9)), 59.7 (C(4)), 71.0 (C(17)), 78.5 (C(8)), 82.1 (C(1)), 106.9 (C(19)), 118.7 (C(6)), 144.8 (C(18)), 154.6 (C(7)), 204.4 (C(5)); *m/z* (ESI^+) 385 (MNa^+, 100%), 363 (MH^+, 60); HRMS (ESI^+): Found: 385.2169; $C_{21}H_{34}O_3SiNa$ (MNa^+) requires: 385.2169.

(5a*S*,8*S*,8a*S*)-8-Hydroxy-3,5a,8a-trimethyl-5a,6,7,8,8a,9-hexahydroazuleno[5,6-*b*]furan-5(4*H*)-one (389)



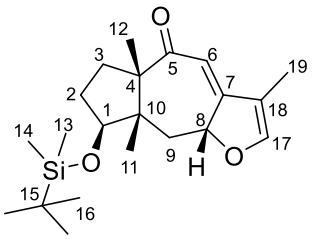
Potassium *tert*-butoxide (6.0 µL, 0.00607 mmol, 1 M in THF) was added to a solution of diene **388** (2.2 mg, 0.00607 mmol) in DMSO (0.2 mL) and the mixture was stirred at 80 ºC for 2 h. Water (0.2 mL) was added and the mixture was extracted with ether (3 × 0.5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (0.8 mg, 53%). R_f 0.40 (1:1 petrol:ether); $[\alpha]_D^{25}$ +4.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3433br, 2959m, 1744s, 1704m, 1457w, 1044m; δ_H (500 MHz, $CDCl_3$) 1.04 (3 H, s, C(11)H_3), 1.28 (3 H, s, C(12)H_3), 1.41−1.48 (1 H, m, C(3)**H**H′), 1.57−1.64 (1 H, m, C(2)**H**H′), 1.93 (3 H, d, *J* 1.5, C(15)H_3), 1.99−2.06 (1 H, m, C(2)H**H′**), 2.52 (1 H, dt, *J* 13.5, 8.5, C(3)H**H′**), 2.61−2.64 (2 H, m, C(9)H_2), 3.22 (1 H, d, *J* 15.0, C(6)**H**H′), 3.64 (1 H, d, *J* 15.0, C(6)H**H′**), 3.83 (1 H, td, *J* 6.5, 5.0, C(1)H), 7.03 (1 H, q, *J* 1.5, C(13)H); δ_C (125 MHz, $CDCl_3$) 8.1 (C(15)), 16.2 (C(11)), 22.5 (C(12)), 30.4 (C(2)), 31.6 (C(3)), 36.2 (C(6)), 36.4 (C(9)), 51.9 (C(10)), 59.3 (C(4)), 80.8 (C(1)), 113.2 (C(7)), 120.0 (C(14)), 137.1 (C(13)), 149.5 (C(8)), 211.7 (C(5)); *m/z* (EI^+) 248 ($M^{+\cdot}$, 30%); HRMS (EI^+): Found: 248.1412; $C_{15}H_{20}O_3$ ($M^{+\cdot}$) requires: 248.1408.

(5*S*,5a*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-ol (391)



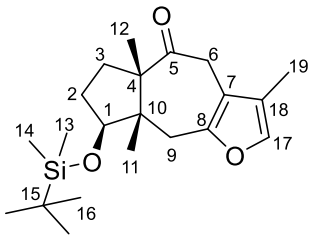
$Ru(PPh_3)_3Cl_2$ (1.0 mg, 0.00121 mmol) and *N*,*N*-diisopropylethylamine (1.0 µL, 0.00603 mmol) were added to a solution of diene **386** (2.20 mg, 0.00603 mmol) in toluene (0.2 mL) and the mixture was stirred at 80 ºC for 5 h. The mixture was filtered through Celite and washed with ether (1 mL). The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (1.20 mg, 55%). R_f 0.15 (3:1 petrol:ether); $[\alpha]_D^{25}$ +6.7 (*c* 0.12, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3421br, 2955w, 1472w, 963s, 726s; δ_H (500 MHz, $CDCl_3$) 0.00 (3 H, s, C(13)H_3), 0.02 (3 H, s, C(14)H_3), 0.82 (3 H, s, C(11)H_3), 0.89 (3 H, s, C(12)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 1.25−1.35 (2 H, m, C(3)H_2), 1.53−1.62 (1 H, m, C(2)**H**H′), 1.83−1.89 (1 H, m, C(2)H**H′**), 1.91 (3 H, s, C(19)H_3), 2.39−2.49 (1 H, m, C(9)**H**H′), 2.50−2.64 (2 H, m, C(6)H_2), 2.79 (1 H, d, *J* 15.5, C(9)H**H′**), 3.76 (1 H, t, *J* 6.5, C(1)H), 3.94−4.05 (1 H, m, C(5)H), 6.99 (1 H, s, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.1 (C(13)), –4.5 (C(14)), 8.1 (C(19)), 14.1 (C(12)), 18.0 (C(11)), 18.5 (C(15)), 22.4 (C(3)), 25.8 (C(16)), 28.2 (C(6)), 31.1 (C(2)), 36.2 (C(9)), 49.0 (C(4)), 49.9 (C(10)), 76.1 (C(1) and C(5)), 115.5 (C(7)), 120.6 (C(18)), 136.3 (C(17)), 149.8 (C(8)); *m/z* (ESI^+) 387 (MNa^+, 70%), 365 (MH^+, 60); HRMS (ESI^+): Found: 365.2506; $C_{21}H_{37}O_3Si$ (MH^+) requires: 365.2507.

(5a*S*,8*S*,8a*S*,9a*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-6,7,8,8a,9,9a-hexahydroazuleno[5,6-*b*]furan-5(5a*H*)-one (392)



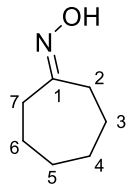
$Ru(PPh_3)_3Cl_2$ (2.5 mg, 0.00232 mmol) and *N*,*N*-diisopropylethylamine (2.0 µL, 0.0116 mmol) were added to a solution of diene **388** (4.20 mg, 0.0116 mmol) in toluene (0.4 mL) and the mixture was stirred at 80 ºC for 2 h. The mixture was filtered through Celite and washed with ether (1 mL). The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil (3.00 mg, 71%). R_f 0.20 (9:1 petrol:ether); $[\alpha]_D^{25}$ –9.3 (*c* 0.15, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1642m, 1598m, 1470w, 1111s, 835s; δ_H (500 MHz, $CDCl_3$) –0.04 (3 H, s, C(13)H_3), –0.02 (3 H, s, C(14)H_3), 0.87 (9 H, s, 3 × C(16)H_3), 1.14 (3 H, s, C(11)H_3), 1.17 (3 H, s, C(12)H_3), 1.29−1.35 (1 H, m, C(3)**H**H′), 1.40−1.47 (1 H, m, C(2)**H**H′), 1.54−1.60 (1 H, m, C(9)**H**H′), 1.75 (3 H, d, *J* 1.5, C(19)H_3), 1.85−1.94 (1 H, m, C(2)H**H′**), 2.28 (1 H, dd, *J* 13.0, 2.0, C(9)H**H′**), 2.72 (1 H, ddd, *J* 13.5, 10.0, 5.5, C(3)H**H′**), 3.52 (1 H, t, *J* 9.0, C(1)H), 5.29 (1 H, ddd, *J* 11.5, 3.0, 2.0, C(8)H), 5.70 (1 H, d, *J* 3.0, C(6)H), 6.91 (1 H, q, *J* 1.5, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.3 (C(14)), 7.3 (C(19)), 15.9 (C(11)), 17.9 (C(15)), 23.1 (C(12)), 25.8 (C(16)), 29.7 (C(2)), 30.0 (C(3)), 44.0 (C(10)), 46.9 (C(9)), 58.9 (C(4)), 82.5 (C(1)), 82.8 (C(8)), 112.6 (C(6)), 113.7 (C(18)), 155.4 (C(17)), 164.5 (C(7)), 201.9 (C(5)); *m/z* (ESI^+) 385 (MNa^+, 100%), 363 (MH^+, 60); HRMS (ESI^+): Found: 385.2169; $C_{21}H_{34}O_3SiNa$ (MNa^+) requires: 385.2169.

(5a*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-5a,6,7,8,8a,9-hexahydroazuleno[5,6-*b*]furan-5(4*H*)-one (393)



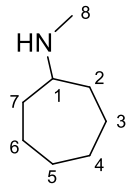
*p*TsOH·H_2O (0.5 mg, 0.00276 mmol) was added to a solution of enone **392** (1.00 mg, 0.00276 mmol) in benzene (0.2 mL) and the mixture was stirred at RT for 1 h. Sat. aq. $NaHCO_3$ (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil (0.800 mg, 80%). R_f 0.50 (9:1 petrol:ether); $[\alpha]_D^{25}$ –12.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1699m, 1471w, 1255m, 904s, 728s; δ_H (500 MHz, $CDCl_3$) 0.02 (3 H, s, C(13)H_3), 0.03 (3 H, s, C(14)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 0.98 (3 H, s, C(11)H_3), 1.26 (3 H, s, C(12)H_3), 1.40 (1 H, ddd, *J* 13.5, 9.5, 4.5, C(3)**H**H′), 1.50−1.57 (1 H, m, C(2)**H**H′), 1.84−1.91 (1 H, m, C(2)H**H′**), 1.92 (3 H, d, *J* 1.0, C(19)H_3), 2.50 (1 H, dt, *J* 13.5, 8.5, C(3)H**H′**), 2.54−2.58 (2 H, m, C(9)H_2), 3.21 (1 H, d, *J* 15.0, C(6)**H**H′), 3.63 (1 H, d, *J* 15.0, C(6)H**H′**), 3.73 (1 H, t, *J* 7.0, C(1)H), 7.02 (1 H, q, *J* 1.0, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.1 (C(13)), –4.4 (C(14)), 8.1 (C(19)), 16.8 (C(11)), 18.0 (C(15)), 22.7 (C(12)), 25.8 (C(16)), 30.8 (C(2)), 31.7 (C(3)), 36.3 (C(6)), 36.5 (C(9)), 52.5 (C(10)), 58.8 (C(4)), 80.9 (C(1)), 113.1 (C(7)), 120.0 (C(18)), 136.9 (C(17)), 149.7 (C(8)), 212.3 (C(5)); *m/z* (ESI^+) 385 (MNa^+, 100%), 363 (MH^+, 60); HRMS (ESI^+): Found: 385.2169; $C_{21}H_{34}O_3SiNa$ (MNa^+) requires: 385.2169.

Cycloheptanone oxime (394)[174]



$NH_2OH{\cdot}HCl$ (0.130 g, 1.87 mmol) and pyridine (0.103 mL, 1.27 mmol) were added to a solution of cycloheptanone (0.100 mL, 0.848 mmol) in EtOH (1.3 mL) and the mixture was stirred under reflux for 2 h. The solvent was removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a colourless oil (0.100 g, 93%). R_f 0.20 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3219br, 2923s, 1650w, 1454m, 969m; δ_H (400 MHz, $CDCl_3$) 1.50−1.74 (8 H, m, C(3)H_2, C(4)H_2, C(5)H_2 and C(6)H_2), 2.34−2.42 (2 H, m, C(7)H_2), 2.54−2.62 (2 H, m, C(2)H_2); δ_C (100 MHz, $CDCl_3$) 24.6 (C(3)), 27.6 (C(6)), 28.4 (C(2)), 30.4 (C(4)), 30.5 (C(5)), 33.8 (C(7)), 164.6 (C(1)); *m/z* (ESI^+) 128 (MH^+, 100%).

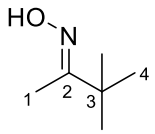
***N*-Methylcycloheptanamine (395)**[175]



$MeNH_2{\cdot}HCl$ (0.405 g, 6.00 mmol) and $NaBH_3CN$ (37.7 mg, 0.600 mmol) were added to a solution of cycloheptanone (0.118 mL, 1.00 mmol) in MeOH (2.5 mL) and the mixture was stirred at RT for 7 h. Sat. aq. $NaHCO_3$ (3 mL) was added and the solvent was removed *in vacuo*. The mixture was extracted with ethyl acetate (3 × 3 mL) and the combined organic

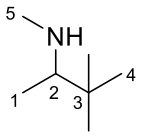
layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (80.0 mg, 63%). R_f 0 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3386br, 2928s, 2333m, 1463s, 1119s; δ_H (400 MHz, $CDCl_3$) 1.41−1.51 (2 H, m, C(6)H_2), 1.52−1.66 (6 H, m, C(4)H_2, C(5)H_2 and C(7)H_2), 1.69−1.79 (2 H, m, C(3)H_2), 1.97−2.04 (2 H, m, C(2)H_2), 2.56 (3 H, s, C(8)H_3), 2.88 (1 H, tt, *J* 9.0, 4.5, C(1)H); δ_C (100 MHz, $CDCl_3$) 24.0 (C(3) and C(6)), 27.9 (C(4) and C(5)), 31.9 (C(8)), 32.2 (C(2) and C(7)), 61.0 (C(1)); *m/z* (ESI^+) 128 (MH^+, 100%).

(*E*)-3,3-Dimethylbutan-2-one oxime (396)[176]



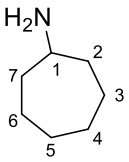
$NH_2OH{\cdot}HCl$ (0.122 g, 1.76 mmol) and pyridine (0.0970 mL, 1.20 mmol) were added to a solution of pinacolone (0.100 mL, 0.800 mmol) in EtOH (1.2 mL) and the mixture was stirred under reflux for 2 h. The solvent was removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the title compound as a white solid (90.0 mg, 98%). R_f 0.45 (3:1 petrol:ether); m.p. 74–75 °C; ν_{max} (thin film)/cm^{-1} 3250br, 2968m, 1463m, 1202m, 931s; δ_H (400 MHz, $CDCl_3$) 1.14 (9 H, s, 3 × C(4)H_3), 1.88 (3 H, s, C(1)H_3); δ_C (100 MHz, $CDCl_3$) 10.1 (C(1)), 27.4 (C(4)), 37.2 (C(3)), 164.4 (C(2)); *m/z* (ESI^+) 116 (MH^+, 100%).

_N_,3,3-Trimethylbutan-2-amine (397)[177]



$MeNH_2$·HCl (0.405 g, 6.00 mmol) and $NaBH_3CN$ (37.7 mg, 0.600 mmol) were added to a solution of pinacolone (0.125 mL, 1.00 mmol) in MeOH (2.5 mL) and the mixture was stirred at RT for 7 h. Sat. aq. $NaHCO_3$ (3 mL) was added and the solvent was removed *in vacuo*. The mixture was extracted with ethyl acetate (3 × 3 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound as a colourless oil (15.0 mg, 13%). R_f 0 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3500br, 2968s, 2342s, 1466s, 1120s; δ_H (500 MHz, $CDCl_3$) 1.06 (9 H, s, 3 × C(4)H_3), 1.29 (3 H, d, *J* 7.0, C(1)H_3), 2.71−2.83 (4 H, m, C(2)H and C(5)H_3); δ_C (125 MHz, $CDCl_3$) 11.4 (C(1)), 26.0 (C(4)), 32.8 (C(5)), 34.0 (C(3)), 66.3 (C(2)); *m/z* (ESI^+) 116 (MH^+, 100%).

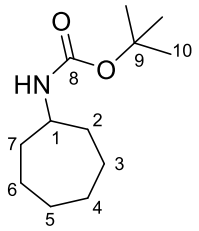
Cycloheptanamine (398)[178]



To a stirred suspension of $LiAlH_4$ (89.5 mg, 2.36 mmol) in THF (9 mL) at RT was added oxime **394** (0.100 g, 0.786 mmol) in THF (3 mL). The reaction was stirred under reflux for 2 h then cooled to 0 °C and water (0.2 mL), 15% aq. NaOH (0.2 mL), and a further portion of water (0.7 mL) added sequentially. The mixture was stirred at RT for 10 min, filtered through a pad of celite then concentrated *in vacuo* to afford the title compound as a colourless oil (89.0 mg, 100%). R_f 0 (1:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3250br, 2919s, 1572m, 1459m,

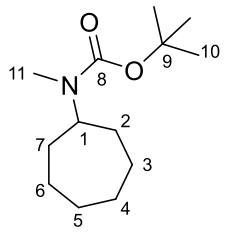
1345m; δ_H (400 MHz, $CDCl_3$) 1.24−1.72 (10 H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(6)H_2 and C(7)H_2), 1.76−1.87 (2 H, m, C(2)H_2), 2.92 (1 H, tt, *J* 8.5, 4.0, C(1)H); δ_C (100 MHz, $CDCl_3$) 24.1 (C(3) and C(6)), 28.1 (C(4) and C(5)), 38.5 (C(2) and C(7)), 52.8 (C(1)); *m/z* (ESI^+) 114 (MH^+, 100%).

***tert*-Butyl cycloheptylcarbamate (399)**[179]



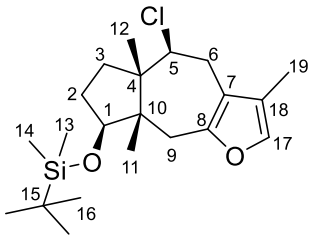
To a solution of amine **398** (89.0 mg, 0.786 mmol) in DCM (1.6 mL) was added triethylamine (0.142 mL, 1.02 mmol) and di-*tert*-butyl dicarbonate (0.223 g, 1.02 mmol). The reaction mixture was stirred at RT for 4 h then diluted with water (1.5 mL). The aqueous layer was extracted with DCM (3 × 1.5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the title compound as a colourless oil (92.0 mg, 55%). R_f 0.50 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 3330br, 2926m, 1684s, 1499m, 1167s; δ_H (400 MHz, $CDCl_3$) 1.26−1.68 (19 H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2 and 3 × C(10)H_3), 1.79−1.96 (2 H, m, C(2)H_2), 3.47−3.67 (1 H, m, C(1)H), 4.52 (1 H, bs, NH); δ_C (100 MHz, $CDCl_3$) 24.0 (C(3) and C(6)), 28.0 (C(4) and C(5)), 28.4 (C(10)), 35.4 (C(2) and C(7)), 51.7 (C(1)), 78.8 (C(9)), 155.1 (C(8)); *m/z* (ESI^+) 236 (MNa^+, 90%).

***tert*-Butyl cycloheptyl(methyl)carbamate (400)**



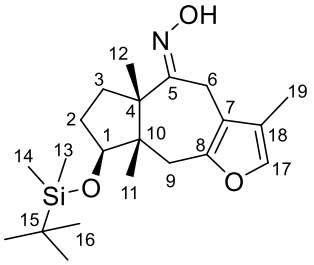
To a solution of carbamate **399** (92.0 mg, 0.431 mmol) in DMF (2 mL) at 0 ºC was added iodomethane (0.268 mL, 4.31 mmol). The reaction mixture was stirred at 0 ºC for 20 min then NaH (43.1 mg, 1.08 mmol) was added. The mixture was stirred at RT for 16 h then diluted with water (1.5 mL). The aqueous layer was extracted with ether (3 × 2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil (91.5 mg, 93%). R_f 0.55 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2925m, 1688s, 1479w, 1364m, 1139s; δ_H (400 MHz, $CDCl_3$) 1.29−1.80 (21 H, m, C(2)H_2, C(3)H_2, C(4)H_2, C(5)H_2, C(6)H_2, C(7)H_2 and 3 × C(10)H_3), 2.66 (3 H, s, C(11)H_3), 3.69−4.17 (1 H, m, C(1)H); δ_C (100 MHz, $CDCl_3$) 25.2 (C(3) and C(6)), 27.6 (C(4) and C(5)), 28.5 (C(10) and C(11)), 32.5 (C(2) and C(7)), 56.0 (C(1)), 78.9 (C(9)), 155.4 (C(8)); *m/z* (ESI^+) 250 (MNa^+, 50%); HRMS (ESI^+): Found: 250.1778; $C_{13}H_{25}O_2NNa$ (MNa^+) requires: 250.1778.

***tert*-Butyl{[(5*S*,5a*S*,8*S*,8a*S*)-5-chloro-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-8-yl]oxy}dimethylsilane (403)**



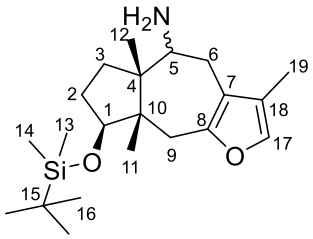
Chloromethanesulfonyl chloride (1.0 µL, 0.0103 mmol) and pyridine (1.5 µL, 0.0137 mmol) were added to a solution of alcohol **377** (2.50 mg, 0.00686 mmol) in DCM (0.2 mL) at 0 ºC and the mixture was stirred at 0 ºC for 1 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, petrol) afforded the *title compound* as a colourless oil (1.20 mg, 46%). R_f 0.95 (3:1 petrol:ether); $[\alpha]_D^{25}$ +8.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2929m, 1653w, 1463w, 1331m, 1127s; δ_H (500 MHz, C_6D_6) –0.17 (3 H, s, C(13)H_3), –0.10 (3 H, s, C(14)H_3), 0.88 (3 H, s, C(11)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 1.08 (3 H, s, C(12)H_3), 1.22−1.30 (2 H, m, C(3)H_2), 1.45−1.52 (1 H, m, C(2)**H**H′), 1.63 (3 H, d, *J* 1.5, C(19)H_3), 1.67−1.75 (1 H, m, C(2)H**H′**), 2.43 (1 H, d, *J* 16.5, C(9)**H**H′), 2.59 (1 H, ddd, *J* 17.0, 10.5, 2.0, C(6)**H**H′), 2.75−2.84 (2 H, m, C(6)H**H′** and C(9)H**H′**), 3.83 (1 H, dd, *J* 10.5, 2.5, C(5)H), 3.94 (1 H, dd, *J* 9.5, 7.0, C(1)H), 6.86 (1 H, q, *J* 1.5, C(17)H); δ_C (125 MHz, C_6D_6) –5.8 (C(13)), –4.9 (C(14)), 7.6 (C(19)), 17.8 (C(15)), 19.9 (C(11)), 22.4 (C(3)), 25.6 (C(12)), 25.7 (C(16)), 30.2 (C(2)), 31.2 (C(6)), 34.0 (C(9)), 49.9 (C(4)), 50.4 (C(10)), 71.6 (C(5)), 76.1 (C(1)), 119.9 (C(7)), 125.5 (C(18)), 136.5 (C(17)), 149.6 (C(8)); *m/z* (FI^+) 382 ($M^{+\cdot}$, 50%); HRMS (FI^+): Found: 382.2373; $C_{21}H_{35}ClO_2Si$ ($M^{+\cdot}$) requires: 382.2090.

(5a*S*,8*S*,8a*S*,*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-5a,6,7,8,8a,9-hexahydroazuleno[5,6-*b*]furan-5(4*H*)-one oxime (404)



$NH_2OH{\cdot}HCl$ (14.0 mg, 0.203 mmol) and pyridine (11.0 µL, 0.139 mmol) were added to a solution of ketone **393** (33.5 mg, 0.0924 mmol) in EtOH (2.3 mL) and the mixture was stirred under reflux for 2 h. The solvent was removed *in vacuo*. Water (10 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil (30.7 mg, 88%). R_f 0.25 (9:1 petrol:ether); $[\alpha]_D^{25}$ –22.4 (*c* 0.34, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3259br, 2955s, 1463m, 1253m, 1006m, 837s; δ_H (500 MHz, $CDCl_3$) 0.01 (3 H, s, C(13)H_3), 0.02 (3 H, s, C(14)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 0.96 (3 H, s, C(11)H_3), 1.23 (3 H, s, C(12)H_3), 1.52−1.61 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.90−1.96 (1 H, m, C(2)H***H′***), 1.98 (3 H, d, *J* 1.0, C(19)H_3), 2.38−2.48 (2 H, m, C(3)H***H′*** and C(9)**H**H′), 2.63 (1 H, d, *J* 15.5, C(9)H***H′***), 2.95 (1 H, dd, *J* 15.5, 1.0, C(6)**H**H′), 3.75 (1 H, t, *J* 6.5, C(1)H), 4.00 (1 H, d, *J* 15.5, C(6)H***H′***), 6.99 (1 H, q, *J* 1.0, C(17)H), 7.41 (1 H, bs, OH); δ_C (125 MHz, $CDCl_3$) –5.1 (C(13)), –4.5 (C(14)), 8.2 (C(19)), 17.5 (C(11)), 18.0 (C(15)), 18.3 (C(6)), 23.5 (C(12)), 25.8 (C(16)), 31.5 (C(2)), 32.9 (C(3)), 36.8 (C(9)), 51.5 (C(4)), 51.6 (C(10)), 81.2 (C(1)), 114.7 (C(7)), 120.0 (C(18)), 136.5 (C(17)), 150.1 (C(8)), 164.0 (C(5)); *m/z* (ESI^+) 378 (MH^+, 100%); HRMS (ESI^+): Found: 378.2460; $C_{21}H_{36}O_3NSi$ (MH^+) requires: 378.2459.

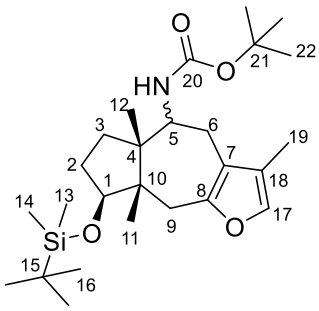
(5a*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-amine (405)



Raney Ni (8 mg) was added to a solution of oxime **404** (30.7 mg, 0.0813 mmol) in EtOH (1.6 mL) and the mixture was stirred under H_2 at RT for 48 h. The mixture was filtered through Celite, washed with EtOH and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a 1:1 mixture of diastereomers as a colourless oil (28.6 mg, 97%). R_f 0.45 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ –1.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1471w, 1252w, 1006m, 903s, 728s; δ_H (500 MHz, $CDCl_3$) –0.21 (3 H, s, C(13)H_3), –0.11 (3 H, s, C(13)H_3), 0.03 (3 H, s, C(14)H_3), 0.04 (3 H, s, C(14)H_3), 0.80 (3 H, s, C(11)H_3), 0.85 (9 H, s, 3 × C(16)H_3), 0.88 (3 H, s, C(11)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 1.00 (3 H, s, C(12)H_3), 1.09 (3 H, s, C(12)H_3), 1.55−1.74 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.76−1.94 (10 H, m, 2 × C(2)H**H′**, 2 × C(3)H**H′** and 2 × C(19)H_3), 2.27−2.40 (3 H, m, 2 × C(6)**H**H′ and C(9)**H**H′), 2.41−2.50 (2 H, m, 2 × C(6)H**H′**), 2.57 (1 H, d, *J* 16.5, C(9)**H**H′), 2.69 (1 H, d, *J* 16.5, C(9)H**H′**), 2.82−2.89 (2 H, m, C(5)H and C(9)H**H′**), 3.23 (1 H, d, *J* 10.5, C(5)H), 3.71 (1 H, t, *J* 6.5, C(1)H), 3.88 (1 H, dd, *J* 9.0, 7.0, C(1)H), 6.98 (1 H, q, *J* 1.0, C(17)H), 6.99 (1 H, q, *J* 1.0, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.6/–5.0 (C(13)), –4.7/–4.4 (C(14)), 8.1 (C(19)), 18.0 (C(15)), 18.1/19.9 (C(11)), 25.1 (C(12)), 25.8/25.9 (C(16)), 29.0/29.4 (C(6)), 30.8/31.4 (C(2)), 33.8/36.8 (C(9)), 37.6 (C(3)), 48.6 (C(4)), 49.7 (C(10)), 57.2/58.6 (C(5)), 77.3/83.4 (C(1)), 116.9/117.1 (C(7)), 120.5/120.6 (C(18)), 136.0/136.2 (C(17)), 149.8 (C(8)); *m/z*

(ESI$^+$) 364 (MH$^+$, 100%); HRMS (ESI$^+$): Found: 364.2667; $C_{21}H_{38}O_2NSi$ (MH$^+$) requires: 364.2666.

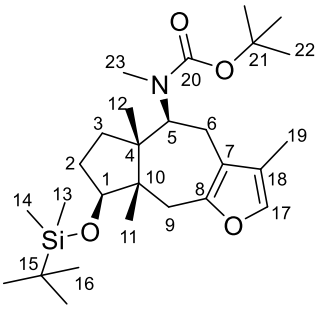
***tert*-Butyl{(5a*S*,8*S*,8a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}carbamate (406)**



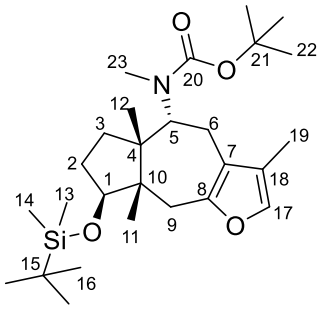
To a solution of amine **405** (13.0 mg, 0.0358 mmol) in DCM (0.9 mL) was added triethylamine (6.5 µL, 0.0465 mmol) and di-*tert*-butyl dicarbonate (10.0 mg, 0.0465 mmol). The reaction mixture was stirred at RT for 4 h then diluted with water (1.5 mL). The aqueous layer was extracted with DCM (3 × 1.5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil as a mixture of diastereomers (11.0 mg, 66%, *dr*. 1:1). R_f 0.75 (3:1 petrol:ether); $[\alpha]_D^{25}$ –4.0 (*c* 0.35, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3346br, 2955s, 1701s, 1499m, 1251s, 1172s; δ_H (500 MHz, $CDCl_3$) –0.11 (3 H, s, C(13)H_3), –0.06 (3 H, s, C(13)H_3), 0.02 (6 H, s, 2 × C(14)H_3), 0.79 (3 H, s, C(11)H_3), 0.86 (9 H, s, 3 × C(16)H_3), 0.89 (12 H, s, C(11)H_3 and 3 × C(16)H_3), 0.97 (3 H, s, C(12)H_3), 1.11 (3 H, s, C(12)H_3), 1.44 (9 H, s, 3 × C(22)H_3), 1.46 (9 H, s, 3 × C(22)H_3), 1.47−1.55 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.77−1.86 (4 H, m, 2 × C(2)H**H′** and 2 × C(3)H**H′**), 1.87 (3 H, s, C(19)H_3), 1.89 (3 H, d, *J* 1.0, C(19)H_3), 2.37−2.50 (3 H, m, 2 × C(6)**H**H′ and C(9)**H**H′), 2.57 (1 H, d, *J* 16.5, C(9)**H**H′), 2.62−2.71 (3 H, m, 2 × C(6)H**H′** and C(9)H**H′**), 2.94 (1 H, d, *J* 15.5, C(9)H**H′**), 3.73−3.82 (3 H, m, 2 ×

C(1)H and C(5)H), 4.08−4.20 (1 H, m, C(5)H), 4.69 (2 H, t, *J* 10.5, 2 × NH), 6.96 (1 H, s, C(17)H), 7.01 (1 H, q, *J* 1.0, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.4/–5.0 (C(13)), –4.6/–4.4 (C(14)), 8.2 (C(19)), 18.0 (C(11) and C(15)), 19.5 (C(11)), 25.1 (C(12)), 25.8 (C(16)), 26.3/27.4 (C(6)), 28.5 (C(22)), 30.8/31.5 (C(3)), 35.3 (C(9)), 36.3 (C(2) and C(9)), 48.1/49.3 (C(4)), 50.2/50.5 (C(10)), 55.3/57.1 (C(5)), 79.2 (C(1) and C(21)), 116.2 (C(7)), 120.4/120.9 (C(18)), 136.2/136.6 (C(17)), 149.5/149.8 (C(8)), 155.6/155.9 (C(20)); *m/z* (ESI^+) 486 (MNa^+, 100%); HRMS (ESI^+): Found: 486.3011; $C_{26}H_{45}O_4NNaSi$ (MNa^+) requires: 486.3010.

***tert*-Butyl{(5*S*,5a*S*,8*S*,8a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (408)** and ***tert*-Butyl{(5*R*,5a*S*,8*S*,8a*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (409)**



408



409

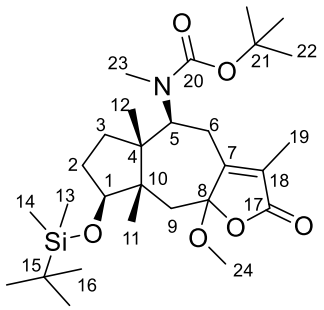
To a solution of carbamate **406** (24.4 mg, 0.0526 mmol) in DMF (1.3 mL) at 0 ºC was added iodomethane (33.0 µL, 0.526 mmol). The reaction mixture was stirred at 0 ºC for 20 min then NaH (5.5 mg, 0.132 mmol) was added. The mixture was stirred at RT for 16 h then diluted with water (1.5 mL). The aqueous layer was extracted with ether (3 × 1.5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1

petrol:ether) afforded *carbamate* **408** as a mixture of carbamate rotamers as a colourless oil (12.5 mg, 50%). R_f 0.40 (9:1 petrol:ether); $[\alpha]_D^{25}$ –46.2 (*c* 0.50, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956m, 1690s, 1473w, 1366m, 1147s, 837m; δ_H (500 MHz, $CDCl_3$) 0.04 (6 H, s, 2 × C(13)H_3), 0.05 (6 H, s, 2 × C(14)H_3), 0.78 (3 H, s, C(11)H_3), 0.79 (3 H, s, C(11)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 1.03 (3 H, s, C(12)H_3), 1.06 (3 H, s, C(12)H_3), 1.38−1.54 (22 H, m, 2 × C(2)**H**H′, 2 × C(3)**H**H′ and 6 × C(22)H_3), 1.80−2.03 (10 H, m, 2 × C(2)H**H′**, 2 × C(3)H**H′** and 2 × C(19)H_3), 2.23−2.46 (4 H, m, 2 × C(6)**H**H′ and 2 × C(9)**H**H′), 2.68−2.78 (2 H, m, 2 × C(6)H**H′**), 2.83 (3 H, s, C(23)H_3), 2.85 (3 H, s, C(23)H_3), 2.90 (1 H, d, *J* 16.0, C(9)H**H′**), 3.03 (1 H, d, *J* 16.0, C(9)H**H′**), 3.74−3.82 (2 H, m, 2 × C(1)H), 4.73 (1 H, dd, *J* 11.5, 2.5, C(5)H), 4.82 (1 H, dd, *J* 12.0, 1.5, C(5)H), 6.97 (1 H, s, C(17)H), 7.01 (1 H, s, C(17)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.4 (C(14)), 8.2 (C(19)), 17.6 (C(11)), 18.0/18.2 (C(15)), 19.7/20.3 (C(12)), 24.3/24.6 (C(6)), 25.9 (C(16)), 28.5 (C(22)), 31.0 (C(23)), 31.4/31.8 (C(2)), 32.0 (C(23)), 34.7/35.6 (C(3)), 37.4/37.5 (C(9)), 49.0 (C(10)), 50.3/51.3 (C(4)), 51.6 (C(10)), 57.9/58.3 (C(5)), 79.2/79.8 (C(21)), 82.6/83.3 (C(1)), 116.7/116.8 (C(7)), 120.2/120.5 (C(18)), 136.0/136.2 (C(17)), 149.6/149.9 (C(8)), 156.0/156.7 (C(20)); *m/z* (ESI^+) 500 (MNa^+, 100%), 478 (MH^+, 25); HRMS (ESI^+): Found: 500.3164; $C_{27}H_{47}O_4NNaSi$ (MNa^+) requires: 500.3167.

Also obtained was *carbamate* **409** as a mixture of carbamate rotamers as a colourless oil (10.2 mg, 41%). R_f 0.35 (9:1 petrol:ether); $[\alpha]_D^{25}$ +27.9 (*c* 0.48, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2956m, 1692s, 1472w, 1365m, 1145s, 904s; δ_H (500 MHz, $CDCl_3$) –0.09 (3 H, s, C(13)H_3), –0.06 (3 H, s, C(13)H_3), –0.05 (3 H, s, C(14)H_3), –0.04 (3 H, s, C(14)H_3), 0.86 (9 H, s, 3 × C(16)H_3), 0.88 (9 H, s, 3 × C(16)H_3), 0.93 (3 H, s, C(11)H_3), 0.95 (3 H, s, C(11)H_3), 0.98 (6 H, s, 2 × C(12)H_3), 1.24−1.34 (2 H, m, 2 × C(3)**H**H′), 1.45−1.49 (18 H, m, 6 × C(22)H_3), 1.51−1.64 (4 H, m, 2 × C(2)H_2), 1.76−1.88 (2 H, m, 2 × C(3)H**H′**), 1.89 (3 H, d, *J* 1.0, C(19)H_3), 1.92 (3 H, d, *J* 1.0, C(19)H_3), 2.33−2.44 (2 H, m, 2 × C(6)**H**H′), 2.48 (1 H, d, *J*

16.0, C(9)**H**H′), 2.50 (1 H, d, *J* 16.0, C(9)**H**H′), 2.70 (1 H, d, *J* 16.0, C(9)H**H′**), 2.73−2.86 (9 H, m, 2 × C(6)H**H′**, C(9)H**H′** and 2 × C(23)H_3), 3.58−3.65 (2 H, m, 2 × C(1)H), 4.64 (1 H, dd, *J* 12.0, 3.0, C(5)H), 4.77 (1 H, dd, *J* 12.0, 3.0, C(5)H), 6.96 (1 H, q, *J* 1.0, C(17)H), 6.99 (1 H, q, *J* 1.0, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.3 (C(13)), –4.6/–4.5 (C(14)), 8.2 (C(19)), 18.0 (C(15)), 20.2/20.3 (C(11)), 24.0/24.1 (C(12)), 25.3/25.6 (C(6)), 25.8 (C(16)), 28.5 (C(22)), 29.8/30.3 (C(23)), 31.4/31.6 (C(3)), 31.7/31.9 (C(2)), 36.1/36.8 (C(9)), 48.8 (C(4)), 52.2/52.4 (C(10)), 56.0/56.6 (C(5)), 78.0/78.4 (C(1)), 79.2/79.6 (C(21)), 116.2/116.3 (C(7)), 120.2/120.4 (C(18)), 136.3/136.5 (C(17)), 149.7/149.8 (C(8)), 155.8/156.2 (C(20)); *m/z* (ESI^+) 500 (MNa^+, 100%), 478 (MH^+, 25); HRMS (ESI^+): Found: 500.3164; $C_{27}H_{47}O_4NNaSi$ (MNa^+) requires: 500.3167.

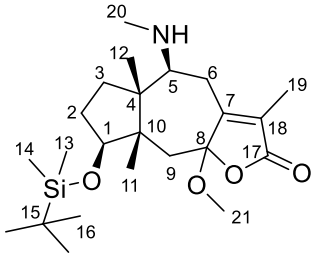
tert-Butyl{(5*S*,5a*S*,8*S*,8a*S*)-8-[(_tert_-butyldimethylsilyl)oxy]-9a-methoxy-3,5a,8a-trimethyl-2-oxo-2,4,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (410)



Oxygen was bubbled through a stirred solution of rose Bengal (0.5 mg, 0.15 μmol, 1×10^{-4} M) and carbamate **408** (12.5 mg, 0.0262 mmol) in methanol (1.5 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 ^oC and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) for 15 min. The solvent was removed *in vacuo*, the resulting pink residue dissolved in pyridine (0.75 mL), acetic anhydride (2.5 μL, 0.0262 mmol) added

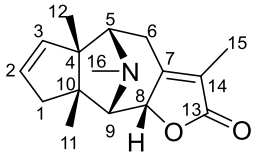
and the reaction mixture stirred at RT for 15 min. The mixture was diluted with ethyl acetate (4 mL), the organic layer washed with water (4 mL), sat. aq. $CuSO_4$ (2 × 4 mL), brine (4 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (12.5 mg, 91%). R_f 0.20 (1:1 petrol:ether); $[\alpha]_D^{25}$ +51.8 (*c* 0.40, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2929m, 1767s, 1692s, 1472w, 1140m, 838m; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(13)H_3), 0.05 (3 H, s, C(13)H_3), 0.08 (6 H, s, 2 × C(14)H_3), 0.69 (3 H, s, C(11)H_3), 0.77 (3 H, s, C(11)H_3), 0.88 (9 H, s, 3 × C(16)H_3), 0.90 (12 H, s, C(12)H_3 and 3 × C(16)H_3), 0.97 (3 H, s, C(12)H_3), 1.26−1.36 (2 H, m, 2 × C(2)**H**H′), 1.43−1.47 (2 H, m, 2 × C(9)**H**H′), 1.48 (9 H, s, 3 × C(22)H_3), 1.53 (9 H, s, 3 × C(22)H_3), 1.56−1.65 (4 H, m, 2 × C(3)H_2), 1.72−1.96 (8 H, m, 2 × C(2)H**H′** and 2 × C(19)H_3), 2.27−2.36 (2 H, m, 2 × C(6)**H**H′), 2.38−2.47 (2 H, m, 2 × C(9)H**H′**), 2.82 (3 H, s, C(23)H_3), 2.85 (3 H, s, C(23)H_3), 2.94−3.16 (2 H, m, 2 × C(6)H**H′**), 3.18 (6 H, s, 2 × C(24)H_3), 4.20 (1 H, t, *J* 8.0, C(1)H), 4.54 (1 H, t, *J* 7.5, C(1)H), 4.96 (1 H, dd, *J* 12.5, 4.0, C(5)H), 5.12 (1 H, dd, *J* 13.0, 4.5, C(5)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.3/–4.0 (C(14)), 8.5 (C(19)), 18.0 (C(15)), 18.5 (C(12)), 18.7 (C(11)), 19.3 (C(12)), 19.8 (C(11)), 25.8 (C(16)), 27.0/27.7 (C(6)), 28.4/28.7 (C(22)), 29.6 (C(23)), 29.7/30.0 (C(2)), 30.6 (C(23)), 32.9/33.4 (C(3)), 42.8/43.6 (C(9)), 48.2/48.3 (C(4)), 48.7 (C(10)), 50.2/50.4 (C(24)), 50.5 (C(10)), 51.9/52.1 (C(5)), 76.1/79.1 (C(1)), 79.6/80.2 (C(21)), 109.7/109.9 (C(8)), 125.5/126.9 (C(18)), 155.6/155.9 (C(7)), 156.0/156.2 (C(20)), 171.0/171.5 (C(17)); *m/z* (ESI^+) 546 (MNa^+, 100%); HRMS (ESI^+): Found: 546.3218; $C_{28}H_{49}O_6NNaSi$ (MNa^+) requires: 546.3221.

(5*S*,5a*S*,8*S*,8a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-9a-methoxy-3,5a,8a-trimethyl-5-(methylamino)-5,5a,6,7,8,8a,9,9a-octahydroazuleno[5,6-*b*]furan-2(4*H*)-one (411)



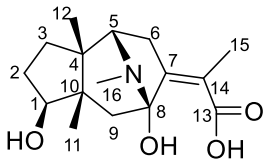
To a solution of methoxybutenolide **410** (4.10 mg, 0.00783 mmol) in dichloromethane (0.12 mL) at 0 °C was added trifluoroacetic acid (1.5 μL, 0.0157 mmol). The reaction mixture was stirred at RT for 6 h then diluted with sat. aq. $NaHCO_3$ (0.5 mL) and the aqueous layer extracted with dichloromethane (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (3.10 mg, 93%). R_f 0.40 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ +95.0 (*c* 0.30, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955m, 1766s, 1472w, 1255m, 1115m, 837m; δ_H (500 MHz, $CDCl_3$) 0.03 (3 H, s, C(13)H_3), 0.05 (3 H, s, C(14)H_3), 0.65 (3 H, s, C(11)H_3), 0.78 (3 H, s, C(12)H_3), 0.88 (9 H, s, 3 × C(16)H_3), 1.38−1.55 (3 H, m, C(2)**H**H′ and C(3)H_2), 1.61−1.68 (1 H, m, C(2)H**H′**), 1.88 (3 H, d, *J* 2.0, C(19)H_3), 2.11 (1 H, d, *J* 15.5, C(9)**H**H′), 2.26 (1 H, d, *J* 15.5, C(9)H**H′**), 2.37 (1 H, dd, *J* 16.0, 10.5, C(6)**H**H′), 2.51 (3 H, s, C(20)H_3), 2.69−2.77 (1 H, m, C(6)H**H′**), 2.89 (1 H, dd, *J* 10.5, 6.0, C(5)H), 3.13 (3 H, s, C(21)H_3), 3.53 (1 H, dd, *J* 9.5, 5.5, C(1)H); δ_C (125 MHz, $CDCl_3$) –4.9 (C(13)), –4.2 (C(14)), 8.4 (C(19)), 17.3 (C(11)), 18.0 (C(15)), 18.1 (C(12)), 25.8 (C(16)), 29.5 (C(2)), 29.9 (C(6)), 35.6 (C(20)), 36.1 (C(3)), 44.3 (C(9)), 46.0 (C(10)), 47.8 (C(4)), 49.4 (C(21)), 62.7 (C(5)), 83.2 (C(1)), 108.4 (C(8)), 127.2 (C(18)), 156.8 (C(7)), 171.9 (C(17)); *m/z* (ESI^+) 424 (MH^+, 100%); HRMS (ESI^+): Found: 424.2876; $C_{23}H_{42}O_4NSi$ (MH^+) requires: 424.2878.

(5*S*,5a*S*,8a*R*,9*S*,9a*S*)-3,5a,8a,10-Tetramethyl-5,5a,8,8a,9,9a-hexahydro-5,9-epiminoazuleno[5,6-*b*]furan-2(4*H*)-one (412)



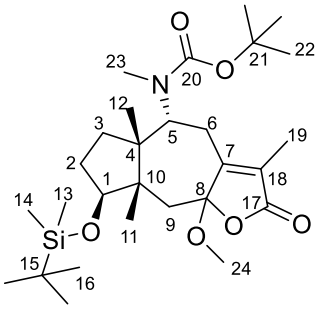
Conc. H_2SO_4 (0.5 μL, 0.00732 mmol) was added to a solution of methoxybutenolide **411** (3.10 mg, 0.00732 mmol) in dichloromethane (0.2 mL) and the reaction mixture was stirred at RT for 30 h. The mixture was diluted with sat. aq. $NaHCO_3$ (0.5 mL) and the aqueous layer extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, EtOAc → 98:2 EtOAc:MeOH) afforded the *title compound* as a white solid (0.60 mg, 32%). R_f 0.75 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); m.p. 85–90 °C; $[\alpha]_D^{25}$ –46.7 (*c* 0.06, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2918m, 1744s, 1680s, 1434w, 1277w, 1116w; δ_H (500 MHz, $CDCl_3$) 1.07 (3 H, s, C(12)H_3), 1.16 (3 H, s, C(11)H_3), 1.66 (3 H, s, C(15)H_3), 1.76 (1 H, dt, *J* 19.0, 2.0, C(1)**H**H′), 2.45 (1 H, d, *J* 16.0, C(6)**H**H′), 2.54 (1 H, dt, *J* 19.0, 2.0, C(1)H**H′**), 2.67 (3 H, s, C(16)H_3), 2.69−2.75 (1 H, m, C(6)H**H′**), 3.00 (1 H, d, *J* 5.0, C(5)H), 3.34 (1 H, d, *J* 5.0, C(9)H), 5.07−5.11 (1 H, m, C(8)H), 5.29 (1 H, dt, *J* 6.0, 2.0, C(3)H), 5.43 (1 H, dt, *J* 6.0, 2.0, C(2)H); δ_C (125 MHz, $CDCl_3$) 8.5 (C(15)), 24.3 (C(12)), 26.0 (C(6)), 27.7 (C(11)), 34.5 (C(16)), 39.6 (C(1)), 52.7 (C(4)), 62.3 (C(10)), 67.7 (C(5)), 71.0 (C(9)), 78.6 (C(8)), 121.4 (C(14)), 131.1 (C(2)), 132.1 (C(3)), 158.9 (C(7)), 175.4 (C(13)); *m/z* (ESI^+) 260 (MH^+, 100%); HRMS (ESI^+): Found: 260.1647; $C_{16}H_{22}O_2N$ (MH^+) requires: 260.1645.

(*Z*)-2-[(1*S*,3a*S*,4*S*,7*R*,8a*S*)-1,7-Dihydroxy-3a,8a,9-trimethyloctahydro-4,7-epiminoazulen-6(1*H*)-ylidene]propanoic acid (413)



To a solution of methoxybutenolide **410** (2.50 mg, 0.00477 mmol) in EtOH (0.3 mL) was added 4.0 M HCl (0.1 mL). The reaction mixture was stirred at 100 ºC for 7 h then concentrated *in vacuo*. Purification by flash chromatography (silica, 25:9:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (0.70 mg, 50%). R_f 0.10 (25:9:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ –12.9 (*c* 0.07, MeOH); ν_{max} (thin film)/cm^{-1} 3354br, 2958m, 1744s, 1463m, 1105m, 951m; δ_H (500 MHz, CD_3OD) 0.86 (3 H, s, C(11)H_3), 1.30 (3 H, s, C(12)H_3), 1.60−1.73 (3 H, m, C(2)**H**H′ and C(3)H_2), 1.80 (1 H, d, *J* 15.0, C(9)**H**H′), 1.90 (3 H, s, C(15)H_3), 1.95−2.03 (1 H, m, C(2)H**H′**), 2.41 (1 H, d, *J* 15.0, C(9)H**H′**), 2.55 (1 H, d, *J* 19.0, C(6)**H**H′), 2.74 (3 H, s, C(16)H_3), 3.04 (1 H, ddd, *J* 19.0, 8.0, 1.5, C(6)H**H′**), 3.47 (1 H, d, *J* 8.0, C(5)H), 4.05 (1 H, t, *J* 9.0, C(1)H); δ_C (125 MHz, CD_3OD) 17.5 (C(15)), 18.4 (C(11)), 23.7 (C(12)), 29.6 (C(2)), 30.3 (C(6)), 31.8 (C(3)), 33.7 (C(16)), 45.4 (C(9)), 45.6 (C(4)), 46.4 (C(10)), 70.8 (C(5)), 75.6 (C(1)), 96.1 (C(8)), 134.4 (C(7)), 135.4 (C(14)), 174.0 (C(13)); *m/z* (ESI^+) 296 (MH^+, 100%); HRMS (ESI^+): Found: 296.1859; $C_{16}H_{26}O_4N$ (MH^+) requires: 296.1856.

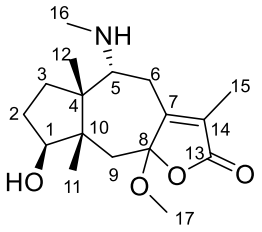
tert-Butyl{(5*R*,5a*S*,8*S*,8a*S*)-8-[(_tert_-butyldimethylsilyl)oxy]-9a-methoxy-3,5a,8a-trimethyl-2-oxo-2,4,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (414)



Oxygen was bubbled through a stirred solution of rose Bengal (0.5 mg, 0.17 μmol, 1×10^{-4} M) and carbamate **409** (13.9 mg, 0.0291 mmol) in methanol (1.7 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 ^{o}C and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) for 15 min. The solvent was removed *in vacuo*, the resulting pink residue dissolved in pyridine (0.83 mL), acetic anhydride (3.0 μL, 0.0291 mmol) added and the reaction mixture stirred at RT for 15 min. The mixture was diluted with ethyl acetate (4 mL), the organic layer washed with water (4 mL), sat. aq. $CuSO_4$ (2 × 4 mL), brine (4 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (12.0 mg, 79%). R_f 0.15 (1:1 petrol:ether); $[\alpha]_D^{25}$ –14.6 (*c* 1.00, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2929m, 1767s, 1692s, 1472w, 1140m, 838m; δ_H (500 MHz, $CDCl_3$) 0.00 (3 H, s, C(13)H_3), 0.01 (6 H, s, C(13)H_3 and C(14)H_3), 0.02 (3 H, s, C(14)H_3), 0.87 (9 H, s, 3 × C(16)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 1.00 (6 H, s, 2 × C(12)H_3), 1.20 (6 H, s, 2 × C(11)H_3), 1.21−1.27 (2 H, m, 2 × C(9)**H**H′), 1.47 (9 H, s, 3 × C(22)H_3), 1.51 (9 H, s, 3 × C(22)H_3), 1.52−1.70 (6 H, m, 2 × C(2)**H**H′ and 2 × C(3)H_2), 1.84 (6 H, d, *J* 0.5, 2 × C(19)H_3), 2.05−2.13 (2 H, m, 2 × C(9)H**H′**), 2.19−2.29 (2 H, m, 2 × C(2)H**H′**), 2.38−2.48 (2 H, m, 2 × C(6)**H**H′), 2.74 (3 H, s, C(23)H_3), 2.76 (3 H, s, C(23)H_3), 2.96−3.08 (2 H, m, 2 × C(6)H**H′**),

3.20 (3 H, s, C(24)H_3), 3.23 (3 H, s, C(24)H_3), 3.41−3.47 (2 H, m, 2 × C(1)H), 5.03 (1 H, dd, *J* 13.0, 3.5, C(5)H), 5.11 (1 H, dd, *J* 13.0, 4.0, C(5)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.8 (C(14)), 8.4/8.5 (C(19)), 17.8 (C(11)), 18.0 (C(11) and C(15)), 20.2/20.3 (C(12)), 25.8 (C(16)), 27.9/28.2 (C(6)), 28.5/28.6 (C(22)), 29.9/30.5 (C(23)), 32.0 (C(3)), 33.3/33.4 (C(2)), 47.8/47.9 (C(9)), 50.5/50.6 (C(10)), 50.8/50.9 (C(24)), 51.0 (C(4)), 51.7 (C(5)), 79.4 (C(1)), 80.0 (C(1) and C(21)), 109.7/109.8 (C(8)), 125.9/126.1 (C(18)), 155.5/155.9 (C(20)), 156.5/156.9 (C(7)), 170.8/171.0 (C(17)); *m/z* (ESI^+) 546 (MNa^+, 100%); HRMS (ESI^+): Found: 546.3218; $C_{28}H_{49}O_6NNaSi$ (MNa^+) requires: 546.3221.

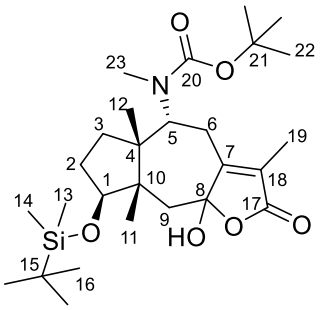
(5*R*,5a*S*,8*S*,8a*S*)-8-Hydroxy-9a-methoxy-3,5a,8a-trimethyl-5-(methylamino)-5,5a,6,7,8,8a,9,9a-octahydroazuleno[5,6-*b*]furan-2(4*H*)-one (415)



To a solution of methoxybutenolide **414** (3.00 mg, 0.00573 mmol) in acetone/H_2O (0.2 mL, 1:1) was added trifluoroacetic acid (0.1 mL). The reaction mixture was stirred at 35 ºC for 20 h then diluted with sat. aq. $NaHCO_3$ (0.5 mL) and the aqueous layer extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as a colourless oil (1.70 mg, 96%). R_f 0.40 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ –37.6 (*c* 0.17, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3448br, 2955m, 1756s, 1436w, 1116m, 939m; δ_H (500 MHz, $CDCl_3$) 1.09 (3 H, s, C(11)H_3), 1.19 (3 H, s, C(12)H_3), 1.44−1.65 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.78−1.87 (2 H, m, C(3)H**H′**

and C(9)**H**H′), 1.88 (3 H, d, *J* 1.5, C(15)H_3), 1.89−1.96 (1 H, m, C(2)H**H′**), 2.40 (3 H, s, C(16)H_3), 2.41−2.53 (3 H, m, C(5)H, C(6)**H**H′ and C(9)H**H′**), 2.91 (1 H, dd, *J* 15.0, 5.5, C(6)H**H′**), 3.15 (3 H, s, C(17)H_3), 4.00 (1 H, dd, *J* 11.0, 7.0, C(1)H); δ_C (125 MHz, $CDCl_3$) 8.5 (C(15)), 19.0 (C(11)), 24.5 (C(6)), 27.5 (C(12)), 30.0 (C(2)), 35.8 (C(3)), 36.3 (C(16)), 46.2 (C(10)), 46.5 (C(9)), 48.8 (C(4)), 49.9 (C(17)), 69.4 (C(5)), 83.6 (C(1)), 110.2 (C(8)), 127.7 (C(14)), 158.0 (C(7)), 171.5 (C(13)); *m/z* (ESI^+) 332 (MNa^+, 20%), 310 (MH^+, 100); HRMS (ESI^+): Found: 310.2014; $C_{17}H_{28}O_4N$ (MH^+) requires: 310.2013.

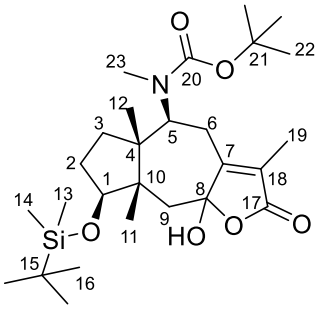
tert-Butyl{(5*R*,5a*S*,8*S*,8a*S*)-8-[(_tert_-butyldimethylsilyl)oxy]-9a-hydroxy-3,5a,8a-trimethyl-2-oxo-2,4,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (416)



Lithium hydroxide monohydrate (0.5 mg, 0.00764 mmol) was added to a solution of methoxybutenolide **414** (2.00 mg, 0.00382 mmol) in THF–H_2O (0.44 mL, 10:1) and the mixture was stirred at RT for 36 h. Glacial acetic acid (0.02 mL) was added and the solvent was removed *in vacuo*. Water (1 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.80 mg, 92%). R_f 0.40 (1:3 petrol:ether); $[\alpha]_D^{25}$ –4.7 (*c* 0.15, $CHCl_3$); ν_{max} (thin

film)/cm^{-1} 3336br, 2930m, 1758s, 1663s, 1443m, 1155s; δ_H (500 MHz, $CDCl_3$) 0.01 (3 H, s, C(13)H_3), 0.02 (6 H, s, C(13)H_3 and C(14)H_3), 0.03 (3 H, s, C(14)H_3), 0.88 (9 H, s, 3 × C(16)H_3), 0.90 (9 H, s, 3 × C(16)H_3), 1.02 (3 H, s, C(12)H_3), 1.03 (3 H, s, C(12)H_3), 1.25 (3 H, s, C(11)H_3), 1.29 (3 H, s, C(11)H_3), 1.30−1.38 (2 H, m, 2 × C(9)**H**H′), 1.46 (9 H, s, 3 × C(22)H_3), 1.49 (9 H, s, 3 × C(22)H_3), 1.50−1.60 (4 H, m, 2 × C(3)H_2), 1.61−1.73 (2 H, m, 2 × C(2)**H**H′), 1.78 (3 H, s, C(19)H_3), 1.80 (3 H, s, C(19)H_3), 2.04 (1 H, d, *J* 15.0, C(9)H**H′**), 2.08 (1 H, d, *J* 15.0, C(9)H**H′**), 2.19−2.29 (2 H, m, 2 × C(2)H**H′**), 2.51−2.60 (2 H, m, 2 × C(6)**H**H′), 2.74 (3 H, s, C(23)H_3), 2.76 (3 H, s, C(23)H_3), 2.88−3.03 (2 H, m, 2 × C(6)H**H′**), 3.43−3.49 (2 H, m, 2 × C(1)H), 5.17 (1 H, dd, *J* 13.0, 3.5, C(5)H), 5.24 (1 H, dd, *J* 13.0, 4.0, C(5)H); δ_C (125 MHz, $CDCl_3$) –5.0 (C(13)), –4.8/–4.7 (C(14)), 8.4 (C(19)), 17.7/17.9 (C(11)), 18.0 (C(15)), 20.2/20.3 (C(12)), 25.8 (C(16)), 27.5/27.8 (C(6)), 28.5/28.6 (C(22)), 29.8/30.5 (C(23)), 31.9 (C(3)), 33.3/33.4 (C(2)), 48.0/48.1 (C(9)), 50.6/50.7 (C(10)), 51.2 (C(5)), 51.6 (C(4)), 51.8 (C(5)), 79.7 (C(21)), 79.9/80.0 (C(1)), 106.2/106.3 (C(8)), 124.1/124.3 (C(18)), 155.6/156.2 (C(20)), 158.0/158.3 (C(7)), 170.8/171.0 (C(17)); *m/z* (ESI$^+$) 532 (MNa^+, 100%); HRMS (ESI$^+$): Found: 532.3064; $C_{27}H_{47}O_6NNaSi$ (MNa^+) requires: 532.3065.

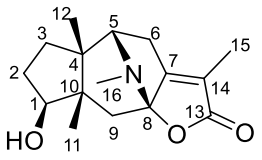
tert-Butyl{(5*S*,5a*S*,8*S*,8a*S*)-8-[(_tert_-butyldimethylsilyl)oxy]-9a-hydroxy-3,5a,8a-trimethyl-2-oxo-2,4,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (417)



Lithium hydroxide monohydrate (0.5 mg, 0.0111 mmol) was added to a solution of methoxybutenolide **410** (2.90 mg, 0.00554 mmol) in THF–H_2O (0.66 mL, 10:1) and the mixture was stirred at RT for 36 h. Glacial acetic acid (0.02 mL) was added and the solvent was removed *in vacuo*. Water (1 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (2.10 mg, 74%). R_f 0.10 (1:1 petrol:ether); $[\alpha]_D^{25}$ +30.5 (*c* 0.21, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3302br, 2955m, 1754s, 1685s, 1456s, 1151s; δ_H (500 MHz, $CDCl_3$) 0.04 (3 H, s, C(13)H_3), 0.06 (3 H, s, C(13)H_3), 0.09 (6 H, s, 2 × C(14)H_3), 0.70 (3 H, s, C(11)H_3), 0.76 (3 H, s, C(11)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 0.91 (9 H, s, 3 × C(16)H_3), 0.92 (3 H, s, C(12)H_3), 0.97 (3 H, s, C(12)H_3), 1.25−1.43 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.48 (9 H, s, 3 × C(22)H_3), 1.50 (9 H, s, 3 × C(22)H_3), 1.55−1.65 (2 H, m, 2 × C(3)H**H′**), 1.69 (1 H, d, *J* 15.5, C(9)**H**H′), 1.75−1.89 (8 H, m, 2 × C(2)H**H′** and 2 × C(19)H_3), 1.92 (1 H, d, *J* 15.0, C(9)**H**H′), 2.33−2.51 (4 H, m, 2 × C(6)**H**H′ and 2 × C(9)H**H′**), 2.83 (3 H, s, C(23)H_3), 2.86 (3 H, s, C(23)H_3), 2.94 (1 H, bs, OH), 2.95−3.10 (2 H, m, 2 × C(6)H**H′**), 3.30 (1 H, bs, OH), 4.19 (1 H, t, *J* 7.5, C(1)H), 4.39 (1 H, t, *J* 7.5, C(1)H), 5.10 (1 H, dd, *J* 12.5, 4.0, C(5)H), 5.21

(1 H, dd, *J* 13.0, 5.0, C(5)H); δ_C (125 MHz, $CDCl_3$) –4.8 (C(13)), –4.2/–4.0 (C(14)), 8.5 (C(19)), 18.0 (C(15)), 18.4 (C(11)), 18.8 (C(12)), 19.2 (C(11)), 19.3 (C(12)), 25.8 (C(16)), 26.6/27.1 (C(6)), 28.4/28.5 (C(22)), 29.7 (C(23)), 29.8/30.0 (C(2)), 30.7 (C(23)), 33.1/33.4 (C(3)), 43.6/44.4 (C(9)), 48.0/48.2 (C(4)), 48.8/50.0 (C(10)), 52.3 (C(5)), 77.4/79.2 (C(1)), 79.9/80.2 (C(21)), 106.3/106.5 (C(8)), 125.1/125.4 (C(18)), 155.7/156.5 (C(20)), 157.5/157.8 (C(7)), 171.0/171.4 (C(17)); *m/z* (ESI^+) 532 (MNa^+, 100%); HRMS (ESI^+): Found: 532.3064; $C_{27}H_{47}O_6NNaSi$ (MNa^+) requires: 532.3065.

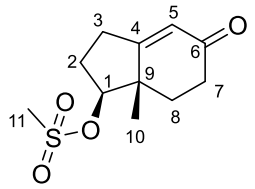
(5*S*,5a*S*,8*S*,8a*S*,9a*R*)-8-Hydroxy-3,5a,8a,10-tetramethyl-4,5,5a,6,7,8,8a,9-octahydro-2*H*-5,9a-epiminoazuleno[5,6-*b*]furan-2-one (418)



Ethyl chloroformate (1.0 µL, 0.00846 mmol) and triethylamine (1.5 µL, 0.00846 mmol) were added to a solution of carboxylic acid **413** (1.00 mg, 0.00339 mmol) in THF (0.3 mL) and the mixture was stirred at RT for 16 h. Water (1 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a white solid (0.90 mg, 96%). R_f 0.45 (ether); m.p. 81–84 °C; $[\alpha]_D^{25}$ +103.3 (*c* 0.09, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3419br, 2955m, 1765s, 1443w, 1239m, 1030m; δ_H (500 MHz, $CDCl_3$) 0.87 (3 H, s, C(11)H_3), 1.26 (3 H, s, C(12)H_3), 1.39−1.45 (1 H, m, C(3)**H**H′), 1.59−1.68 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.78 (1 H, d, *J* 13.5, C(9)**H**H′), 1.89 (3 H, t, *J* 1.5, C(15)H_3), 1.93 (3 H, s, C(16)H_3), 2.03 (1 H, d, *J* 13.5, C(9)H**H′**), 2.05−2.12 (1 H, m, C(2)H**H′**), 2.40 (1 H, d, *J* 19.0, C(6)**H**H′), 2.52 (1 H, ddd, *J*

19.0, 7.5, 1.0, C(6)H**H′**), 2.88 (1 H, d, *J* 7.5, C(5)H), 3.90−3.96 (1 H, m, C(1)H); δ_C (125 MHz, $CDCl_3$) 9.4 (C(15)), 19.0 (C(11)), 24.2 (C(6)), 26.5 (C(12)), 31.3 (C(2)), 32.2 (C(3)), 34.2 (C(16)), 43.7 (C(9)), 46.8 (C(10)), 46.9 (C(4)), 76.5 (C(5)), 79.3 (C(1)), 100.7 (C(8)), 123.9 (C(14)), 165.1 (C(7)), 173.9 (C(13)); *m/z* (ESI^+) 278 (MH^+, 100%); HRMS (ESI^+): Found: 278.1751; $C_{16}H_{24}O_3N$ (MH^+) requires: 278.1751.

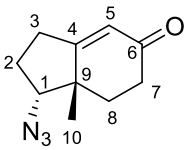
(1*S*,7a*S*)-7a-Methyl-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl methanesulfonate (419)



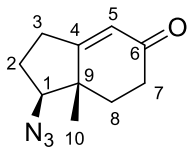
Triethylamine (14.0 μL, 0.102 mmol) was added to a solution of alcohol **296** (11.3 mg, 0.0680 mmol) in DCM (0.2 mL). Methanesulfonyl chloride (5.8 μL, 0.0748 mmol) was then added dropwise to the mixture at 0 ºC and stirred at 0 ºC for 45 min. Water (0.5 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a colourless oil (16.1 mg, 97%). R_f 0.30 (ether); $[\alpha]_D^{25}$ +22.5 (*c* 1.61, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2938w, 1667s, 1350s, 1173s, 957s; δ_H (400 MHz, $CDCl_3$) 1.23 (3 H, s, C(10)H_3), 1.90 (1 H, td, *J* 13.5, 5.5, C(8)**H**H′), 2.09−2.17 (1 H, m, C(2)**H**H′), 2.21 (1 H, ddd, *J* 13.5, 5.5, 2.0, C(8)H**H′**), 2.30−2.41 (1 H, m, C(2)H**H′**), 2.42−2.57 (3 H, m, C(3)**H**H′ and C(7)H_2), 2.82 (1 H, ddt, *J* 19.5, 12.0, 2.5, C(3)H**H′**), 3.07 (3 H, s, C(11)H_3), 4.66 (1 H, dd, *J* 10.0, 8.0, C(1)H), 5.83 (1 H, t, *J* 1.5, C(5)H); δ_C (100 MHz, $CDCl_3$) 16.4 (C(10)), 26.2 (C(3)), 27.0 (C(2)), 32.9 (C(7)), 33.8 (C(8)), 38.4 (C(11)), 44.8 (C(9)), 86.8 (C(1)), 124.3 (C(5)), 170.4 (C(4)), 198.2 (C(6));

m/z (ESI$^+$) 267 (MNa$^+$, 100%), 245 (MH$^+$, 40); HRMS (ESI$^+$): Found: 245.0843; $C_{11}H_{17}O_4S$ (MH$^+$) requires: 245.0842.

(1*R*,7a*S*)-1-Azido-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (420) and **(1*S*,7a*S*)-1-Azido-7a-methyl-1,2,3,6,7,7a-hexahydro-5*H*-inden-5-one (421)**[152]



420



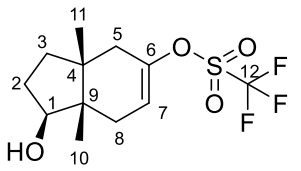
421

Sodium azide (12.8 mg, 0.196 mmol) was added to a solution of methanesulfonate **419** (16.0 mg, 0.0655 mmol) in DMF (0.2 mL) and the mixture was stirred at 90 ºC for 24 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded azide **420** as a pale yellow oil (3.00 mg, 24%). R_f 0.65 (ether); $[\alpha]_D^{25}$ –143.2 (*c* 0.22, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2957w, 2097s, 1660s, 1450w, 1274m; δ_H (500 MHz, $CDCl_3$) 1.22 (3 H, s, C(10)H_3), 1.80 (1 H, ddd, *J* 13.0, 5.5, 2.0, C(8)**H**H′), 2.07 (1 H, dddd, *J* 14.5, 8.5, 3.5, 1.0, C(2)**H**H′), 2.28−2.41 (2 H, m, C(2)H**H′** and C(8)H**H′**), 2.45 (1 H, dddd, *J* 18.0, 5.0, 2.0, 0.5, C(7)**H**H′), 2.54 (1 H, ddd, *J* 18.0, 14.5, 5.5, C(7)H**H′**), 2.64−2.78 (2 H, m, C(3)H_2), 3.79 (1 H, d, *J* 5.0, C(1)H), 5.88 (1 H, t, *J* 1.5, C(5)H); δ_C (125 MHz, $CDCl_3$) 22.3 (C(10)), 27.9 (C(2)), 28.3 (C(3)), 29.3 (C(8)), 33.0 (C(7)), 47.5 (C(9)), 71.2 (C(1)), 123.4 (C(5)), 173.7 (C(4)), 198.5 (C(6)); *m/z* (ESI$^+$) 214 (MNa$^+$, 100%), 192 (MH$^+$, 20).

Also obtained was azide **421** as a pale yellow oil (3.00 mg, 24%). R_f 0.75 (ether); $[\alpha]_D^{25}$ +24.6 (*c* 0.26, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2934w, 2097s, 1670s, 1467w, 1264m; δ_H (500 MHz,

$CDCl_3$) 1.17 (3 H, s, C(10)H_3), 1.85 (1 H, td, *J* 13.0, 5.0, C(8)**H**H′), 1.94 (1 H, dtd, *J* 13.0, 11.0, 9.0, C(2)**H**H′), 2.16 (1 H, ddd, *J* 13.0, 5.5, 2.0, C(8)H**H′**), 2.19−2.25 (1 H, m, C(2)H**H′**), 2.38−2.58 (3 H, m, C(3)**H**H′ and C(7)H_2), 2.77 (1 H, ddt, *J* 19.5, 11.5, 2.0, C(3)H**H′**), 3.56 (1 H, dd, *J* 11.0, 8.0, C(1)H), 5.81 (1 H, t, *J* 1.5, C(5)H); δ_C (125 MHz, $CDCl_3$) 16.4 (C(10)), 26.3 (C(2)), 27.0 (C(3)), 33.1 (C(7)), 34.6 (C(8)), 46.0 (C(9)), 70.3 (C(1)), 123.5 (C(5)), 173.0 (C(4)), 198.4 (C(6)); *m/z* (ESI^+) 214 (MNa^+, 100%), 192 (MH^+, 20).

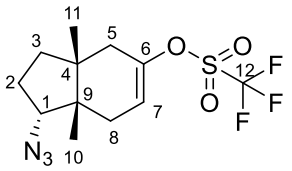
(1*S*,3a*R*,7a*S*)-1-Hydroxy-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (422)



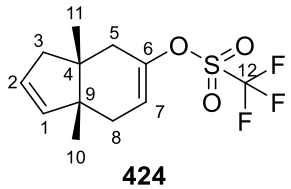
H_2SiF_6 (0.0728 mL, 0.154 mmol) was added to a solution of silyl ether **300** (0.220 g, 0.513 mmol) in ACN (4 mL) at 0 °C and stirred for 3 h. Sat. aq. $NaHCO_3$ (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (0.158 g, 98%). R_f 0.20 (3:1 petrol:ether); $[\alpha]_D^{25}$ +21.1 (*c* 3.68, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3420br, 2958w, 1414m, 1203s, 1140s, 871s; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, s, C(10)H_3), 1.04 (3 H, s, C(11)H_3), 1.42−1.80 (3 H, m, C(2)**H**H′ and C(3)H_2), 1.89−1.98 (1 H, m, C(8)**H**H′), 2.03 (1 H, d, *J* 18.0, C(5)**H**H′), 2.18−2.34 (3 H, m, C(2)H**H′**, C(5)H**H′** and C(8)H**H′**), 4.02 (1 H, dd, *J* 8.5, 6.5, C(1)H), 5.60−5.66 (1 H, m, C(7)H); δ_C (100 MHz, $CDCl_3$) 15.7 (C(10)), 22.5 (C(11)), 29.4 (C(2)), 31.3 (C(8)), 35.3 (C(3)), 38.2 (C(5)), 42.7 (C(4)), 44.3 (C(9)), 76.6 (C(1)), 115.6

(C(7)), 118.5 (q, *J* 320.5, C(12)), 146.7 (C(6)); *m/z* (CI^+) 332 ($[M+NH_4]^+$, 100%); HRMS (CI^+): Found: 332.1140; $C_{12}H_{21}O_4F_3NS$ ($[M+NH_4]^+$) requires: 332.1143.

(1*R*,3a*R*,7a*S*)-1-Azido-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (423) and **(3a*R*,7a*R*)-3a,7a-Dimethyl-3a,4,7,7a-tetrahydro-1*H*-inden-6-yl trifluoromethanesulfonate (424)**



423

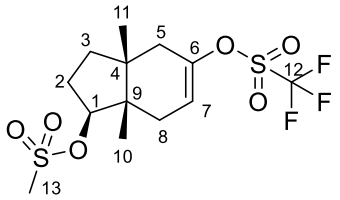


424

Sodium azide (8.7 mg, 0.134 mmol) was added to a solution of chloromethanesulfonate **426** (19.0 mg, 0.0445 mmol) in DMF (0.2 mL) and the mixture was stirred at 90 ºC for 20 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded *azide* **423** as a colourless oil (2.00 mg, 13%). R_f 0.75 (3:1 petrol:ether); $[\alpha]_D^{25}$ –19.5 (*c* 0.20, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2966w, 2096s, 1417s, 1205s, 1143s; δ_H (500 MHz, $CDCl_3$) 1.00 (3 H, s, C(11)H_3), 1.02 (3 H, s, C(10)H_3), 1.42−1.50 (1 H, m, C(3)**H**H′), 1.70−1.86 (2 H, m, C(2)**H**H′ and C(3)H**H′**), 1.91−1.99 (1 H, m, C(8)**H**H′), 2.17−2.27 (4 H, m, C(2)H**H′**, C(5)H_2 and C(8)H**H′**), 3.87 (1 H, dd, *J* 9.5, 6.0, C(1)H), 5.70 (1 H, d, *J* 5.0, C(7)H); δ_C (125 MHz, $CDCl_3$) 19.3 (C(10)), 24.1 (C(11)), 25.8 (C(2)), 30.7 (C(8)), 34.0 (C(3)), 36.1 (C(5)), 43.7 (C(4)), 44.3 (C(9)), 70.1 (C(1)), 115.4 (C(7)), 118.5 (q, *J* 320.5, C(12)), 146.1 (C(6)); *m/z* (CI^+) 357 ($[M+NH_4]^+$, 100%); HRMS (CI^+): Found: 357.1205; $C_{12}H_{20}O_3F_3N_4S$ ($[M+NH_4]^+$) requires: 357.1208.

Also obtained was *alkene* **424** as a colourless oil (8.50 mg, 64%). R_f 0.80 (3:1 petrol:ether); $[\alpha]_D^{25}$ +24.7 (*c* 0.85, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2975w, 1416m, 1202s, 1142s, 867m; δ_H (500 MHz, $CDCl_3$) 0.98 (3 H, s, C(10)H_3), 1.14 (3 H, s, C(11)H_3), 2.06 (1 H, d, *J* 17.5, C(5)**H**H′), 2.09−2.15 (1 H, m, C(8)**H**H′), 2.16 (1 H, dd, *J* 16.0, 1.0, C(3)**H**H′), 2.32 (1 H, d, *J* 16.0, C(3)H**H′**), 2.34−2.40 (1 H, m, C(8)H**H′**), 2.43 (1 H, dq, *J* 17.5, 2.5, C(5)H**H′**), 5.62 (2 H, s, C(1)H and C(2)H), 5.71 (1 H, t, *J* 5.0, C(7)H); δ_C (125 MHz, $CDCl_3$) 21.9 (C(11)), 23.2 (C(10)), 34.2 (C(8)), 39.3 (C(5)), 45.4 (C(4)), 46.5 (C(3)), 47.1 (C(9)), 116.4 (C(7)), 118.5 (q, *J* 321.5, C(12)), 128.1 (C(2)), 143.1 (C(1)), 148.5 (C(6)); *m/z* (CI^+) 314 ($[M+NH_4]^+$, 100%); HRMS (CI^+): Found: 314.1025; $C_{12}H_{19}O_3F_3NS$ ($[M+NH_4]^+$) requires: 314.1038.

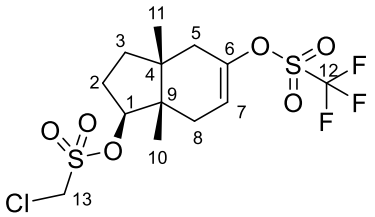
(1*S*,3a*R*,7a*S*)-3a,7a-Dimethyl-1-[(methylsulfonyl)oxy]-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (425)



Triethylamine (15.0 µL, 0.107 mmol) was added to a solution of alcohol **422** (22.5 mg, 0.0716 mmol) in DCM (0.2 mL). Methanesulfonyl chloride (6.0 µL, 0.0787 mmol) was then added dropwise to the mixture at 0 ºC and stirred at 0 ºC for 45 min. Water (0.5 mL) was added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (24.7 mg, 88%). R_f 0.40 (1:1 petrol:ether); $[\alpha]_D^{25}$ +3.2 (*c* 1.85, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1413m, 1205s, 1140s, 871s; δ_H (400 MHz, $CDCl_3$) 0.99 (3 H, s, C(10)H_3), 1.07 (3 H, s,

C(11)H_3), 1.55−1.64 (1 H, m, C(3)**H**H′), 1.72−1.82 (1 H, m, C(3)H**H′**), 1.89−1.99 (1 H, m, C(2)**H**H′), 2.00−2.07 (1 H, m, C(8)**H**H′), 2.14 (1 H, d, *J* 18.5, C(5)**H**H′), 2.24−2.34 (2 H, m, C(5)H**H′** and C(8)H**H′**), 2.35−2.46 (1 H, m, C(2)H**H′**), 3.01 (3 H, s, C(13)H_3), 4.78 (1 H, dd, *J* 9.0, 5.5, C(1)H), 5.68 (1 H, t, *J* 4.0, C(7)H); δ_C (100 MHz, $CDCl_3$) 16.5 (C(10)), 22.5 (C(11)), 27.3 (C(2)), 31.3 (C(8)), 35.2 (C(3)), 37.6 (C(5)), 38.1 (C(13)), 42.5 (C(4)), 44.6 (C(9)), 85.6 (C(1)), 115.2 (C(7)), 118.5 (q, *J* 321.0, C(12)), 146.3 (C(6)); *m/z* (CI^+) 410 ($[M+NH_4]^+$, 100%); HRMS (CI^+): Found: 410.0916; $C_{13}H_{23}O_6F_3NS_2$ ($[M+NH_4]^+$) requires: 410.0919.

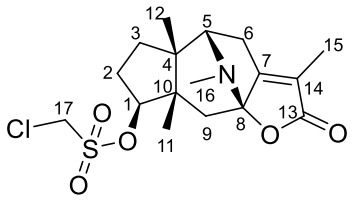
(1*S*,3a*R*,7a*S*)-1-{[(Chloromethyl)sulfonyl]oxy}-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (426)



Chloromethanesulfonyl chloride (10.5 µL, 0.117 mmol) was added dropwise to a solution of alcohol **422** (24.5 mg, 0.0779 mmol) in pyridine (0.2 mL) at 0 ºC and stirred at 0 ºC for 1 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (2 × 3 mL), brine (3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (27.6 mg, 83%). R_f 0.40 (3:1 petrol:ether); $[\alpha]_D^{25}$ –0.3 (*c* 1.90, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2960w, 1415m, 1204s, 1140s, 873s; δ_H (400 MHz, $CDCl_3$) 1.03 (3 H, s, C(10)H_3), 1.08 (3 H, s, C(11)H_3), 1.56−1.66 (1 H, m, C(3)**H**H′), 1.78 (1 H, ddd, *J* 13.0, 11.0, 5.0, C(3)H**H′**), 1.97−2.09 (2 H, m, C(2)**H**H′ and

C(8)**H**H′), 2.11−2.20 (1 H, m, C(5)**H**H′), 2.24−2.34 (2 H, m, C(5)H**H′** and C(8)H**H′**), 2.39−2.50 (1 H, m, C(2)H**H′**), 4.59 (2 H, s, C(13)H_2), 4.91 (1 H, dd, *J* 9.0, 5.5, C(1)H), 5.65−5.71 (1 H, m, C(7)H); δ_C (100 MHz, $CDCl_3$) 16.5 (C(10)), 22.6 (C(11)), 27.5 (C(2)), 31.4 (C(8)), 35.1 (C(3)), 37.4 (C(5)), 42.7 (C(4)), 44.9 (C(9)), 53.8 (C(13)), 89.7 (C(1)), 115.1 (C(7)), 118.5 (q, *J* 320.5, C(12)), 146.3 (C(6)); *m/z* (CI^+) 446 ($[M(^{37}Cl)+NH_4]^+$, 33%), 444 ($[M(^{35}Cl)+NH_4]^+$, 100); HRMS (CI^+): Found: 444.0524; $C_{13}H_{22}ClO_6F_3NS_2$ ($[M(^{35}Cl)+NH_4]^+$) requires: 444.0529.

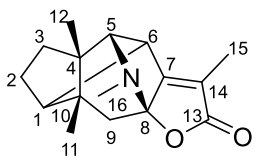
(5*S*,5a*S*,8*S*,8a*S*,9a*R*)-3,5a,8a,10-Tetramethyl-2-oxo-4,5,5a,6,7,8,8a,9-octahydro-2*H*-5,9a-epiminoazuleno[5,6-*b*]furan-8-yl chloromethanesulfonate (427)



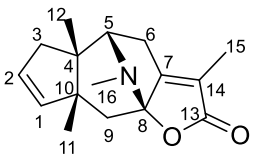
Chloromethanesulfonyl chloride (0.5 μL, 0.00487 mmol) was added to a solution of alcohol **418** (0.90 mg, 0.00324 mmol) in pyridine (0.2 mL) at 0 ºC and stirred at 0 ºC for 1 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:3 petrol:ether) afforded the *title compound* as a colourless oil (1.00 mg, 79%). R_f 0.65 (ether); $[\alpha]_D^{25}$ +81.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955w, 1764s, 1445w, 1368m, 1178m, 1039m; δ_H (500 MHz, $CDCl_3$) 0.97 (3 H, s, C(11)H_3), 1.30 (3 H, s, C(12)H_3), 1.49 (1 H, ddd, *J* 14.0, 10.0, 8.0, C(3)**H**H′), 1.78 (1 H, td, *J* 14.0, 3.5, C(3)H**H′**), 1.91 (1 H, d, *J* 14.0, C(9)**H**H′), 1.92 (3 H, t, *J* 1.5, C(15)H_3), 1.94 (3 H, s, C(16)H_3), 1.98−2.07 (1 H, m, C(2)**H**H′), 2.08 (1 H, d, *J* 14.0,

C(9)H**H′**), 2.27−2.35 (1 H, m, C(2)H**H′**), 2.37 (1 H, d, *J* 19.0, C(6)**H**H′), 2.60 (1 H, ddd, *J* 19.0, 7.5, 1.5, C(6)H**H′**), 2.91 (1 H, d, *J* 7.5, C(5)H), 4.52 (1 H, d, *J* 13.0, C(17)**H**H′), 4.57 (1 H, d, *J* 13.0, C(17)H**H′**), 4.90 (1 H, t, *J* 9.0, C(1)H); δ_C (125 MHz, $CDCl_3$) 9.4 (C(15)), 20.1 (C(11)), 24.1 (C(6)), 26.1 (C(12)), 28.7 (C(2)), 31.9 (C(3)), 34.1 (C(16)), 42.9 (C(9)), 46.3 (C(4)), 47.0 (C(10)), 54.0 (C(17)), 76.0 (C(5)), 89.9 (C(1)), 100.2 (C(8)), 124.9 (C(14)), 163.4 (C(7)), 173.5 (C(13)); *m/z* (ESI^+) 392 ($M(^{37}Cl)H^+$, 33%), 390 ($M(^{35}Cl)H^+$, 100); HRMS (ESI^+): Found: 390.1137; $C_{17}H_{25}O_5NClS$ ($M(^{35}Cl)H^+$) requires: 390.1137.

(7*S*,7a*R*,8a*R*,10*S*)-3,7,7a,9-Tetramethyl-4a,5,6,7,7a,8-hexahydro-8a,4,7-(epiminomethanetriyl)indeno[5,6-*b*]furan-2(4*H*)-one (428) and **(5*S*,5a*S*,8a*R*,9a*R*)-3,5a,8a,10-Tetramethyl-4,5,5a,6,8a,9-hexahydro-2*H*-5,9a-epiminoazuleno[5,6-*b*]furan-2-one (429)**



428



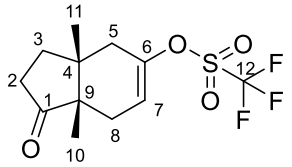
429

Lithium azide (0.5 mg, 0.00769 mmol) was added to a solution of chloromethanesulfonate **427** (1.00 mg, 0.00256 mmol) in DMF (0.2 mL) and the mixture was stirred at 70 ºC for 48 h. Water (0.5 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded *spiroaminoacetal* **428** as a colourless oil (0.34 mg, 51%). R_f 0.85 (ether); $[\alpha]_D^{25}$ +30.0 (*c* 0.06, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2952m, 1771s, 1447w, 1212w, 1028m; δ_H (500 MHz, $CDCl_3$) 0.83 (3 H, s, C(11)H_3), 1.23−1.28 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.44 (3 H, s, C(12)H_3), 1.48−1.64 (2

H, m, C(3)H**H′** and C(9)**H**H′), 1.72−1.80 (1 H, m, C(2)H**H′**), 1.82−1.86 (1 H, m, C(1)H), 1.89 (3 H, s, C(15)H_3), 1.91 (3 H, s, C(16)H_3), 2.18−2.24 (1 H, m, C(9)H**H′**), 2.71 (1 H, d, *J* 5.0, C(6)H), 2.83−2.88 (1 H, m, C(5)H); δ_C (125 MHz, $CDCl_3$) 8.4 (C(15)), 15.9 (C(11)), 25.9 (C(2)), 30.3 (C(12)), 31.6 (C(3)), 35.2 (C(16)), 41.0 (C(6)), 41.6 (C(9)), 46.5 (C(4)), 49.1 (C(10)), 52.2 (C(1)), 80.7 (C(5)), 97.6 (C(8)), 125.5 (C(14)), 168.1 (C(7)), 176.7 (C(13)); *m/z* (ESI^+) 260 (MH^+, 100%); HRMS (ESI^+): Found: 260.1646; $C_{16}H_{22}O_2N$ (MH^+) requires: 260.1645.

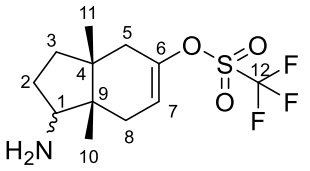
Also obtained was *alkene* **429** as a colourless oil (0.26 mg, 39%). R_f 0.85 (ether); $[\alpha]_D^{25}$ +30.0 (*c* 0.06, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2952m, 1771s, 1447w, 1212w, 1028m; δ_H (500 MHz, $CDCl_3$) 0.95 (3 H, s, C(12)H_3), 1.11 (3 H, s, C(11)H_3), 1.73−1.81 (1 H, m, C(9)**H**H′), 1.84 (3 H, s, C(15)H_3), 1.96 (3 H, s, C(16)H_3), 2.06 (1 H, d, *J* 19.0, C(3)**H**H′), 2.15 (1 H, d, *J* 13.0, C(9)H**H′**), 2.30−2.37 (1 H, m, C(6)**H**H′), 2.39 (1 H, d, *J* 19.0, C(3)H**H′**), 2.75−2.82 (1 H, m, C(6)H**H′**), 2.93−3.00 (1 H, m, C(5)H), 5.42−5.47 (1 H, m, C(1)H), 5.53−5.57 (1 H, m, C(2)H); δ_C (125 MHz, $CDCl_3$) 9.2 (C(15)), 14.7 (C(11)), 23.3 (C(6)), 29.7 (C(12)), 34.1 (C(16)), 44.0 (C(3)), 44.7 (C(9)), 46.5 (C(4)), 49.1 (C(10)), 76.5 (C(5)), 100.7 (C(8)), 125.5 (C(14)), 128.2 (C(2)), 143.4 (C(1)), 166.8 (C(7)), 175.4 (C(13)); *m/z* (ESI^+) 260 (MH^+, 100%); HRMS (ESI^+): Found: 260.1646; $C_{16}H_{22}O_2N$ (MH^+) requires: 260.1645.

(3a*R*,7a*S*)-3a,7a-Dimethyl-1-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (430)



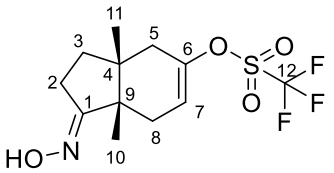
Dess–Martin periodinane (0.158 g, 0.374 mmol) and $NaHCO_3$ (62.8 mg, 0.747 mmol) were added to a solution of alcohol **422** (58.7 mg, 0.187 mmol) in DCM (8.7 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. $NaHCO_3$ (5 mL) and sat. aq. $Na_2S_2O_3$ (5 mL) were added and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a colourless oil (54.8 mg, 94%). R_f 0.40 (3:1 petrol:ether); $[\alpha]_D^{25}$ +39.3 (*c* 2.05, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2967w, 1743s, 1414s, 1204s, 1140s, 868s; δ_H (400 MHz, $CDCl_3$) 0.99 (3 H, s, C(10)H_3), 1.06 (3 H, s, C(11)H_3), 1.79 (1 H, ddd, *J* 13.0, 9.0, 5.5, C(3)**H**H′), 1.85−1.97 (2 H, m, C(3)H**H′** and C(8)**H**H′), 2.22−2.28 (2 H, m, C(5)H_2), 2.29−2.52 (3 H, m, C(2)H_2 and C(8)H**H′**), 5.68 (1 H, ddt, *J* 4.5, 3.5, 1.5, C(7)H); δ_C (100 MHz, $CDCl_3$) 16.9 (C(10)), 22.8 (C(11)), 29.9 (C(8)), 31.1 (C(3)), 32.6 (C(2)), 36.4 (C(5)), 41.6 (C(4)), 49.9 (C(9)), 115.1 (C(7)), 118.5 (q, *J* 320.5, C(12)), 146.3 (C(6)), 218.2 (C(1)); *m/z* (ESI^+) 335 (MNa^+, 100%); HRMS (ESI^+): Found: 335.0536; $C_{12}H_{15}O_4F_3NaS$ (MNa^+) requires: 335.0535.

(3a*R*,7a*S*)-1-Amino-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (431)



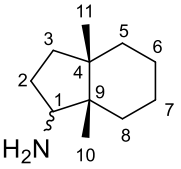
MoO_3 (9.8 mg, 0.0672 mmol) was added to a solution of oxime **432** (10.0 mg, 0.0306 mmol) in MeOH (0.4 mL) at 0 ºC and $NaBH_4$ (2.5 mg, 0.0672 mmol) was then added to the mixture at 0 ºC. The mixture was stirred at RT for 16 h. 1 M aq. KOH (0.1 mL) was added and the mixture was stirred at RT for 12 h. The mixture was filtered through Celite, concentrated *in vacuo* and extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as an inseparable mixture of diastereomers as a colourless oil (5.20 mg, 54%, *dr*. 1:1). R_f 0.30 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ +3.3 (*c* 0.52, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2957w, 1415m, 1207s, 1142s, 874m; δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, s, C(10)H_3), 0.93 (3 H, s, C(10)H_3), 0.97 (3 H, s, C(11)H_3), 1.02 (3 H, s, C(11)H_3), 1.29−1.49 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.58−1.66 (1 H, m, C(3)H**H′**), 1.70−1.78 (1 H, m, C(3)H**H′**), 1.83 (1 H, dd, *J* 18.0, 6.0, C(8)**H**H′), 1.89−1.95 (1 H, m, C(8)**H**H′), 1.98 (1 H, d, *J* 19.0, C(5)**H**H′), 2.11−2.30 (6 H, m, 2 × C(2)H**H′**, C(5)H_2 and 2 × C(8)H**H′**), 2.32−2.40 (1 H, m, C(5)H**H′**), 3.12 (1 H, t, *J* 9.0, C(1)H), 3.25 (1 H, dd, *J* 9.5, 7.5, C(1)H), 5.62 (1 H, dt, *J* 5.0, 2.5, C(7)H), 5.72 (1 H, d, *J* 5.5, C(7)H); δ_C (125 MHz, $CDCl_3$) 15.8/18.5 (C(10)), 22.1/24.4 (C(11)), 29.5 (C(2)), 29.7 (C(8)), 30.4 (C(2)), 30.5 (C(8)), 33.8/35.4 (C(3)), 36.5/38.6 (C(5)), 42.9 (C(9)), 43.4 (C(4)), 43.8 (C(9)), 44.0 (C(4)), 56.2/59.5 (C(1)), 115.5/115.6 (C(7)), 118.5 (q, *J* 317.5, C(12)), 146.7 (C(6)); *m/z* (ESI^+) 314 (MH^+, 100%); HRMS (ESI^+): Found: 314.1033; $C_{12}H_{19}O_3F_3NS$ (MH^+) requires: 314.1032.

(3a*R*,7a*S*,*E*)-1-(Hydroxyimino)-3a,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (432)



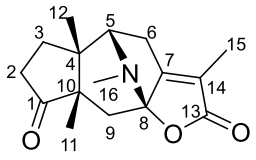
$NH_2OH{\cdot}HCl$ (20.0 mg, 0.289 mmol) and pyridine (16.0 μL, 0.197 mmol) were added to a solution of ketone **430** (41.0 mg, 0.131 mmol) in EtOH (1 mL) and the mixture was stirred under reflux for 5 h. The solvent was removed *in vacuo*. Water (5 mL) was added and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a colourless oil (42.5 mg, 99%). R_f 0.45 (1:1 petrol:ether); $[\alpha]_D^{25}$ +17.2 (*c* 1.85, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3250br, 2966w, 1414s, 1203s, 1140s, 870s; δ_H (400 MHz, $CDCl_3$) 1.00 (3 H, s, C(11)H_3), 1.08 (3 H, s, C(10)H_3), 1.64 (1 H, ddd, *J* 13.0, 8.5, 5.0, C(3)**H**H′), 1.74−1.84 (1 H, m, C(3)H**H′**), 2.04 (1 H, ddt, *J* 18.5, 4.5, 2.0, C(8)**H**H′), 2.16−2.33 (2 H, m, C(5)H_2), 2.47 (1 H, dq, *J* 18.5, 3.0, C(8)H**H′**), 2.53−2.67 (2 H, m, C(2)H_2), 5.68 (1 H, td, *J* 3.0, 1.5, C(7)H); δ_C (100 MHz, $CDCl_3$) 18.6 (C(10)), 22.7 (C(2) and C(11)), 32.8 (C(8)), 32.9 (C(3)), 35.8 (C(5)), 43.6 (C(4)), 45.2 (C(9)), 115.1 (C(7)), 118.5 (q, *J* 320.5, C(12)), 146.4 (C(6)), 168.6 (C(1)); *m/z* (ESI^+) 328 (MH^+, 100%); HRMS (ESI^+): Found: 328.0824; $C_{12}H_{17}O_4F_3NS$ (MH^+) requires: 328.0825.

(3a*S*,7a*S*)-3a,7a-Dimethyloctahydro-1*H*-inden-1-amine (433)



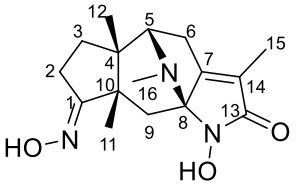
$NiCl_2.6H_2O$ (14.5 mg, 0.0611 mmol) was added to a solution of oxime **432** (10.0 mg, 0.0306 mmol) in MeOH (0.5 mL) and $NaBH_4$ (11.5 mg, 0.306 mmol) was then added to the mixture at RT. The mixture was stirred at RT for 16 h, filtered through Celite and concentrated *in vacuo*. Sat. aq. $NaHCO_3$ (1 mL) was added and extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded the *title compound* as an inseparable mixture of diastereomers as a colourless oil (3.50 mg, 68%, *dr*. 1.7:1). R_f 0.15 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ +8.0 (*c* 0.35, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2927s, 1727w, 1587m, 1461m, 1237s, 1157s; δ_H (500 MHz, $CDCl_3$) 0.70 (3 H, s, C(10)H_3), 0.81 (3 H, s, C(11)H_3), 0.92 (3 H, s, C(10)H_3), 0.95 (3 H, s, C(11)H_3), 1.07−1.22 (5 H, m, 2 × C(3)**H**H′, C(8)**H**H′ and C(8)H_2), 1.25−1.52 (15 H, m, 2 × C(2)**H**H′, 2 × C(5)H_2, 2 × C(6)H_2, 2 × C(7)H_2 and C(8)H**H′**), 1.53−1.62 (1 H, m, C(3)H**H′**), 1.94−2.03 (1 H, m, C(3)H**H′**), 2.07−2.32 (6 H, m, 2 × C(2)H**H′** and 2 × NH_2), 3.23 (1 H, t, *J* 9.0, C(1)H), 3.58 (1 H, t, *J* 9.0, C(1)H); δ_C (125 MHz, $CDCl_3$) 17.5/18.1 (C(10)), 21.5/21.7 (C(6)), 22.0 (C(11)), 22.6 (C(7)), 26.6 (C(11)), 28.5 (C(8)), 29.0/29.6 (C(2)), 30.5 (C(8)), 31.4 (C(3)), 33.8 (C(5)), 36.5 (C(3) and C(5)), 42.4/43.0 (C(4)), 43.7/44.6 (C(9)), 54.9/61.6 (C(1)); *m/z* (ESI^+) 168 (MH^+, 100%); HRMS (ESI^+): Found: 168.1747; $C_{11}H_{22}N$ (MH^+) requires: 168.1747.

(5*S*,5a*S*,8a*S*,9a*R*)-3,5a,8a,10-Tetramethyl-5,5a,6,7,8a,9-hexahydro-2*H*-5,9a-epiminoazuleno[5,6-*b*]furan-2,8(4*H*)-dione (434)



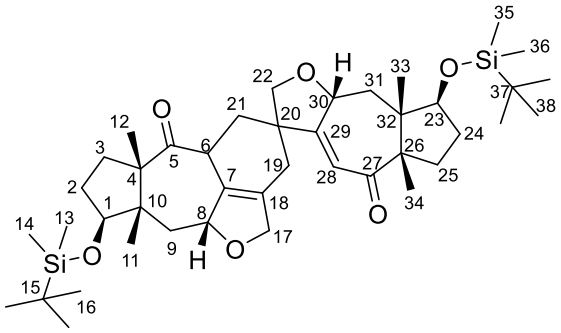
Dess–Martin periodinane (3.8 mg, 0.00865 mmol) and $NaHCO_3$ (1.5 mg, 0.0173 mmol) were added to a solution of alcohol **418** (1.20 mg, 0.00433 mmol) in DCM (0.2 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. $NaHCO_3$ (0.5 mL) and sat. aq. $Na_2S_2O_3$ (0.5 mL) were added and the mixture was extracted with DCM (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a white solid (1.10 mg, 92%). R_f 0.50 (ether); m.p. 125–128 °C; $[\alpha]_D^{25}$ +116.4 (*c* 0.11, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2980s, 1768s, 1737m, 1462w, 1382m, 1152m; δ_H (500 MHz, $CDCl_3$) 0.95 (3 H, s, C(11)H_3), 1.36 (3 H, s, C(12)H_3), 1.73 (1 H, ddd, *J* 14.5, 10.5, 4.5, C(3)**H**H′), 1.82 (3 H, t, *J* 1.5, C(15)H_3), 1.90 (3 H, s, C(16)H_3), 1.95 (1 H, ddd, *J* 14.5, 13.0, 6.5, C(3)H**H′**), 1.99−2.04 (2 H, m, C(6)**H**H′ and C(9)**H**H′), 2.25 (1 H, d, *J* 13.0, C(9)H**H′**), 2.35 (1 H, ddd, *J* 20.0, 10.5, 6.5, C(2)**H**H′), 2.51 (1 H, ddd, *J* 19.5, 7.5, 1.5, C(6)H**H′**), 2.63 (1 H, ddd, *J* 20.0, 13.0, 4.5, C(2)H**H′**), 2.97 (1 H, d, *J* 7.5, C(5)H); δ_C (125 MHz, $CDCl_3$) 9.2 (C(15)), 22.0 (C(6)), 23.1 (C(11)), 24.3 (C(12)), 28.3 (C(3)), 33.9 (C(16)), 34.8 (C(2)), 39.6 (C(9)), 45.3 (C(4)), 51.2 (C(10)), 76.1 (C(5)), 99.8 (C(8)), 122.9 (C(14)), 163.8 (C(7)), 173.9 (C(13)), 220.1 (C(1)); *m/z* (ESI^+) 276 (MH^+, 100%); HRMS (ESI^+): Found: 276.1594; $C_{16}H_{22}O_3N$ (MH^+) requires: 276.1594.

(5*S*,5a*S*,8a*S*,9a*R*,*E*)-1-Hydroxy-8-(hydroxyimino)-3,5a,8a,10-tetramethyl-4,5,5a,6,7,8,8a,9-octahydro-5,9a-epiminoazuleno[5,6-*b*]pyrrol-2(1*H*)-one (435)



$NH_2OH.HCl$ (0.5 mg, 0.00799 mmol) and pyridine (0.5 µL, 0.00545 mmol) were added to a solution of ketone **434** (1.00 mg, 0.00363 mmol) in EtOH (0.2 mL) and the mixture was stirred under reflux for 3 h. The solvent was removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 10:1 $CHCl_3$:MeOH) afforded the *title compound* as a colourless oil (1.00 mg, 90%). R_f 0.30 (10:1 $CHCl_3$:MeOH); $[\alpha]_D^{25}$ –25.0 (*c* 0.08, MeOH); ν_{max} (thin film)/cm^{-1} 3351br, 2921w, 1715s, 1449w, 940w; δ_H (500 MHz, CD_3OD) 1.00 (3 H, s, C(12)H_3), 1.10 (3 H, s, C(11)H_3), 1.42−1.49 (1 H, m, C(3)**H**H′), 2.20 (3 H, s, C(15)H_3), 2.26 (1 H, d, *J* 14.0, C(6)**H**H′), 2.34 (3 H, s, C(16)H_3), 2.38−2.45 (1 H, m, C(3)H**H′**), 2.50−2.68 (2 H, m, C(2)H_2), 2.75 (1 H, d, *J* 6.5, C(5)H), 3.09 (1 H, d, *J* 15.0, C(9)**H**H′), 3.14−3.21 (2 H, m, C(6)H**H′** and C(9)H**H′**); δ_C (125 MHz, CD_3OD) 11.3 (C(15)), 17.5 (C(11)), 21.1 (C(12)), 21.9 (C(2)), 26.6 (C(9)), 32.1 (C(3)), 35.7 (C(16)), 40.3 (C(6)), 48.9 (C(10)), 49.9 (C(4)), 66.0 (C(5)), 76.5 (C(8)), 131.5 (C(14)), 141.0 (C(7)), 165.9 (C(13)), 169.9 (C(1)); *m/z* (ESI^+) 306 (MH^+, 100%); HRMS (ESI^+): Found: 306.1813; $C_{16}H_{24}O_3N_3$ (MH^+) requires: 306.1812.

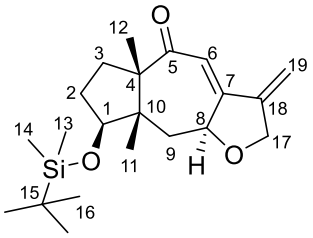
(5a'*S*,6a*S*,8'*S*,8a'*S*,9*S*,9a*S*,9a'*R*,10a*R*)-8',9-Bis[(*tert*-butyldimethylsilyl)oxy]-5a',6a,8a',9a-tetramethyl-3,5,5a,6a,6',7,7',8,8',8a',9,9a,9',9a',10,10a-hexadecahydro-2*H*,2'*H*,6*H*-spiro{azuleno[5,6,7-*cd*]isobenzofuran-4,3'-azuleno[5,6-*b*]furan}-5',6(5a'*H*)-dione (437)



$Ru(PPh_3)_3Cl_2$ (63.5 mg, 0.0662 mmol) and *N*,*N*-diisopropylethylamine (57.5 μL, 0.331 mmol) were added to a solution of diene **388** (0.120 g, 0.331 mmol) in toluene (11 mL) and the mixture was stirred at 80 ºC for 2 h. The mixture was filtered through Celite and washed with ether (10 mL). The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 3:1 petrol:ether) afforded the *title compound* as a yellow oil (62.0 mg, 52%). R_f 0.20 (3:1 petrol:ether); ν_{max} (thin film)/cm^{-1} 2930w, 1702w, 1656w, 1471w, 1251w, 834s; δ_H (400 MHz, $CDCl_3$) –0.03 (3 H, s, C(13)H_3), –0.02 (3 H, s, C(35)H_3), 0.00 (3 H, s, C(14)H_3), 0.01 (3 H, s, C(36)H_3), 0.85 (9 H, s, 3 × C(16)H_3), 0.87 (9 H, s, 3 × C(38)H_3), 1.09 (3 H, s, C(11)H_3), 1.10 (3 H, s, C(33)H_3), 1.14 (3 H, s, C(34)H_3), 1.15−1.22 (1 H, m, C(9)**H**H′), 1.23−1.37 (5 H, m, C(3)**H**H′, C(12)H_3 and C(25)**H**H′), 1.39−1.54 (3 H, m, C(2)**H**H′, C(24)**H**H′ and C(31)**H**H′), 1.64−1.74 (1 H, m, C(19)**H**H′), 1.79−1.94 (3 H, m, C(2)H**H′**, C(9)H**H′** and C(24)H**H′**), 2.09−2.33 (5 H, m, C(3)H**H′**, C(19)H**H′**, C(21)H_2 and C(31)H**H′**), 2.55 (1 H, ddd, *J* 13.5, 10.0, 6.0, C(25)H**H′**), 3.50 (1 H, t, *J* 9.0, C(23)H), 3.61 (1 H, t, *J* 7.0, C(1)H), 3.69−3.74 (1 H, m, C(6)H), 3.77 (1 H, d, *J* 9.0, C(22)**H**H′), 3.87 (1 H, d, *J* 9.0, C(22)H**H′**), 4.41−4.59 (2 H, m, C(17)H_2), 4.90 (1 H, d, *J* 11.0, C(30)H), 5.03−5.13 (1 H, m, C(8)H), 5.63 (1 H, d, *J* 2.5, C(28)H); δ_C (100 MHz, $CDCl_3$) –5.0 (C(13) and C(35)), –4.3

(C(14) and C(36)), 15.3 (C(33)), 16.5 (C(11)), 17.9 (C(15) and C(37)), 19.9 (C(21)), 23.4 (C(34)), 24.3 (C(12)), 25.8 (C(16) and C(38)), 29.9 (C(25)), 30.0 (C(24)), 30.3 (C(2)), 32.0 (C(19)), 32.1 (C(3)), 45.8 (C(9)), 46.0 (C(32)), 46.9 (C(31)), 47.7 (C(10)), 48.7 (C(20)), 51.3 (C(6)), 59.2 (C(4)), 59.8 (C(26)), 74.0 (C(22)), 75.9 (C(17)), 79.2 (C(30)), 82.2 (C(23)), 82.5 (C(8)), 83.2 (C(1)), 119.7 (C(28)), 130.9 (C(18)), 134.0 (C(7)), 169.2 (C(29)), 204.8 (C(27)), 211.2 (C(5)); *m/z* (LD^+) 724 (M^+, 70%).

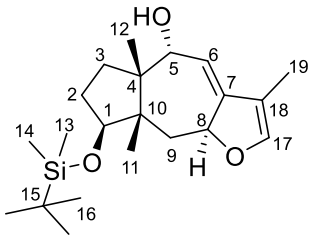
(5a*S*,8*S*,8a*S*,9a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-5a,8a-dimethyl-3-methylene-2,3,6,7,8,8a,9,9a-octahydroazuleno[5,6-*b*]furan-5(5a*H*)-one (438)



Dess–Martin periodinane (95.5 mg, 0.225 mmol) and $NaHCO_3$ (38.0 mg, 0.450 mmol) were added to a solution of alcohol **376** (41.0 mg, 0.112 mmol) in DCM (5.4 mL) at 0 °C and the mixture was stirred at RT for 2 h. Sat. aq. NH_4Cl (3 mL) and sat. aq. $Na_2S_2O_3$ (3 mL) were added and the mixture was extracted with DCM (3 × 6 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 4:1 petrol:ether) afforded the *title compound* as a colourless oil (20.0 mg, 49%). R_f 0.60 (3:1 petrol:ether); $[\alpha]_D^{25}$ +11.9 (*c* 2.00, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2954m, 1655m, 1463m, 1253m, 1066s, 835s; δ_H (400 MHz, $CDCl_3$) 0.03 (6 H, s, C(13)H_3 and C(14)H_3), 0.89 (9 H, s, 3 × C(16)H_3), 0.95 (3 H, s, C(11)H_3), 1.15 (3 H, s, C(12)H_3), 1.43−1.55 (2 H, m, C(2)**H**H′ and C(3)**H**H′), 1.84 (1 H, dd, *J* 14.0, 11.5, C(9)**H**H′), 1.95−2.05 (1 H, m, C(2)H**H′**), 2.10 (1 H, dd, *J* 14.0, 3.0, C(9)H**H′**), 2.43−2.51 (1 H, m, C(3)H**H′**), 3.90

(1 H, dd, *J* 8.5, 6.5, C(1)H), 4.40 (1 H, dt, *J* 13.0, 2.5, C(17)**H**H′), 4.49 (1 H, dt, *J* 11.0, 2.5, C(8)H), 4.58 (1 H, dt, *J* 13.0, 2.0, C(17)H**H′**), 5.16 (1 H, t, *J* 2.0, C(19)**H**H′), 5.56 (1 H, t, *J* 2.5, C(19)H**H′**), 6.25 (1 H, d, *J* 2.0, C(6)H); δ_C (100 MHz, $CDCl_3$) –5.0 (C(13)), –4.2 (C(14)), 17.9 (C(15)), 19.7 (C(11)), 20.5 (C(12)), 25.8 (C(16)), 30.2 (C(2)), 31.3 (C(3)), 40.3 (C(9)), 49.3 (C(10)), 59.5 (C(4)), 71.2 (C(17)), 76.4 (C(1)), 78.4 (C(8)), 106.5 (C(19)), 118.3 (C(6)), 144.6 (C(18)), 149.1 (C(7)), 206.5 (C(5)); *m/z* (ESI^+) 385 (MNa^+, 100%), 363 (MH^+, 60); HRMS (ESI^+): Found: 385.2169; $C_{21}H_{34}O_3SiNa$ (MNa^+) requires: 385.2169.

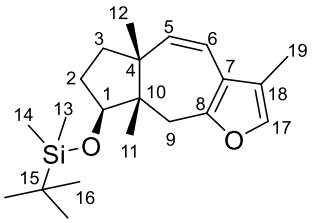
(5*R*,5a*S*,8*S*,8a*S*,9a*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5a,8a-trimethyl-5,5a,6,7,8,8a,9,9a-octahydroazuleno[5,6-*b*]furan-5-ol (439)



$Ru(PPh_3)_3Cl_2$ (2.6 mg, 0.00274 mmol) and *N*,*N*-diisopropylethylamine (2.5 μL, 0.0137 mmol) were added to a solution of diene **376** (5.00 mg, 0.0137 mmol) in toluene (0.5 mL) and the mixture was stirred at 80 ºC for 5 h. The mixture was filtered through Celite and washed with ether (1 mL). The solvent was removed *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil (4.00 mg, 80%). R_f 0.55 (3:1 petrol:ether); $[\alpha]_D^{25}$ –113.5 (*c* 0.86, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3507br, 2953m, 1471w, 1251m, 1094s, 835s; δ_H (500 MHz, C_6D_6) 0.17 (3 H, s, C(13)H_3), 0.23 (3 H, s, C(14)H_3), 0.81 (3 H, s, C(12)H_3), 0.90 (3 H, s, C(11)H_3), 1.04 (9 H, s, 3 × C(16)H_3), 1.46 (3 H, d, *J* 1.5, C(19)H_3), 1.48−1.60 (2 H, m, C(2)**H**H′ and C(9)**H**H′), 1.61−1.66 (2 H, m, C(3)H_2), 2.15−2.26 (2 H, m, C(2)H**H′** and C(9)H**H′**), 3.52 (1 H, dd, *J*

7.0, 2.0, C(5)H), 5.08−5.14 (2 H, m, C(1)H and C(6)H), 5.67 (1 H, dt, *J* 12.5, 3.0, C(8)H), 6.38 (1 H, q, *J* 1.5, C(17)H); δ_C (125 MHz, C_6D_6) –4.9 (C(13)), –4.4 (C(14)), 7.1 (C(19)), 18.0 (C(15)), 21.1 (C(11)), 21.9 (C(12)), 25.9 (C(16)), 31.0 (C(2)), 35.7 (C(3)), 36.2 (C(9)), 47.4 (C(4)), 50.0 (C(10)), 75.1 (C(1)), 79.5 (C(5)), 81.0 (C(8)), 109.6 (C(6)), 111.4 (C(18)), 150.7 (C(17)), 153.5 (C(7)); *m/z* (ESI^+) 387 (MNa^+, 70%), 365 (MH^+, 60); HRMS (ESI^+): Found: 365.2506; $C_{21}H_{37}O_3Si$ (MH^+) requires: 365.2507.

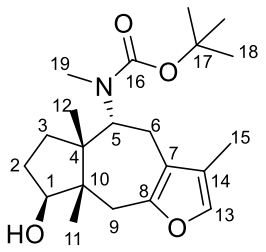
tert-Butyldimethyl{[(5a*R*,8*S*,8a*S*)-3,5a,8a-trimethyl-5a,6,7,8,8a,9-hexahydroazuleno[5,6-*b*]furan-8-yl]oxy}silane (441)



*p*TsOH·H_2O (1.0 mg, 0.00480 mmol) was added to a solution of alcohol **439** (3.50 mg, 0.00960 mmol) in benzene (0.7 mL) and the mixture was stirred at RT for 15 min. Sat. aq. $NaHCO_3$ (1 mL) was added and the mixture was extracted with ether (3 × 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 9:1 petrol:ether) afforded the *title compound* as a colourless oil (1.20 mg, 36%). R_f 0.90 (3:1 petrol:ether); $[\alpha]_D^{25}$ +38.5 (*c* 0.13, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2955s, 1471w, 1255m, 1107m, 776s; δ_H (500 MHz, $CDCl_3$) –0.27 (3 H, s, C(13)H_3), –0.15 (3 H, s, C(14)H_3), 0.85 (9 H, s, 3 × C(16)H_3), 0.92 (3 H, s, C(11)H_3), 1.07 (3 H, s, C(12)H_3), 1.35−1.43 (1 H, m, C(2)**H**H′), 1.57−1.65 (1 H, m, C(3)**H**H′), 1.78−1.86 (1 H, m, C(3)H**H′**), 1.87−1.95 (1 H, m, C(2)H**H′**), 1.96 (3 H, d, *J* 1.5, C(19)H_3), 2.63 (1 H, d, *J* 17.0, C(9)**H**H′), 2.72 (1 H, d, *J* 17.0, C(9)H**H′**), 3.93 (1 H, dd, *J* 9.0, 7.5, C(1)H), 5.29 (1 H,

d, *J* 12.5, C(5)H), 5.83 (1 H, d, *J* 12.5, C(6)H), 6.99 (1 H, q, *J* 1.5, C(17)H); δ_C (125 MHz, $CDCl_3$) –5.9 (C(13)), –4.8 (C(14)), 7.9 (C(19)), 17.9 (C(15)), 18.6 (C(11)), 24.2 (C(12)), 25.8 (C(16)), 29.0 (C(2)), 33.0 (C(9)), 37.4 (C(3)), 46.7 (C(10)), 48.8 (C(4)), 75.0 (C(1)), 113.1 (C(6)), 116.7 (C(7)), 119.4 (C(18)), 136.4 (C(17)), 138.1 (C(5)), 151.6 (C(8)); *m/z* (EI^+) 346 ($M^{+\cdot}$, 100%); HRMS (EI^+): Found: 346.2319; $C_{21}H_{34}O_2Si$ ($M^{+\cdot}$) requires: 346.2323.

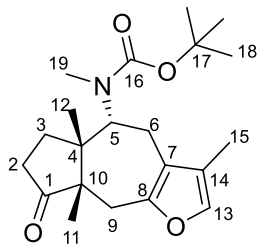
tert-Butyl[(5*R*,5a*S*,8*S*,8a*S*)-8-hydroxy-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl](methyl)carbamate (442)



To a solution of carbamate **409** (3.30 mg, 0.00692 mmol) in THF–pyridine (0.22 mL, 10:1) was added HF–pyridine (2.0 µL, 0.0692 mmol) and the reaction mixture was stirred at RT for 48 h. Sat. aq. $NaHCO_3$ (5 mL) was added slowly and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (2.50 mg, 99%). R_f 0.25 (1:1 petrol:ether); $[\alpha]_D^{25}$ +9.5 (*c* 0.20, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3430br, 2973m, 1742m, 1671s, 1444w, 1148s; δ_H (500 MHz, $CDCl_3$) 0.99 (9 H, s, C(11)H_3 and 2 × C(12)H_3), 1.01 (3 H, s, C(11)H_3), 1.29−1.35 (2 H, m, 2 × C(3)**H**H′), 1.47 (9 H, s, 3 × C(18)H_3), 1.48 (9 H, s, 3 × C(18)H_3), 1.58−1.64 (2 H, m, 2 × C(2)**H**H′), 1.71−1.88 (4 H, m, 2 × C(2)H**H′** and 2 × C(3)H**H′**), 1.89 (3 H, d, *J* 1.0, C(15)H_3), 1.92 (3 H, d, *J* 1.0, C(15)H_3), 2.36−2.47 (2 H, m, 2 × C(6)**H**H′), 2.49−2.59 (2 H, m, 2 × C(9)**H**H′),

2.71−2.81 (9 H, m, 2 × C(6)H**H′**, C(9)H**H′** and 2 × C(19)H_3), 2.91 (1 H, d, *J* 16.0, C(9)H**H′**), 3.66−3.73 (2 H, m, 2 × C(1)H), 4.68 (1 H, dd, *J* 12.0, 3.0, C(5)H), 4.81 (1 H, dd, *J* 12.0, 3.0, C(5)H), 6.96 (1 H, q, *J* 1.0, C(13)H), 7.00 (1 H, q, *J* 1.0, C(13)H); δ_C (125 MHz, $CDCl_3$) 8.2 (C(15)), 19.6 (C(11)), 24.0/24.2 (C(12)), 25.3/25.6 (C(6)), 28.5/28.6 (C(18)), 29.8/30.3 (C(19)), 31.1/31.4 (C(2)), 31.5/31.6 (C(3)), 36.3/37.0 (C(9)), 49.1 (C(10)), 51.7/51.8 (C(4)), 55.7/56.3 (C(5)), 78.1/78.4 (C(1)), 79.3/79.7 (C(17)), 116.3/116.4 (C(7)), 120.3/120.4 (C(14)), 136.6/136.7 (C(13)), 149.4/149.5 (C(8)), 155.8/156.2 (C(16)); *m/z* (ESI^+) 386 (MNa^+, 100%); HRMS (ESI^+): Found: 386.2302; $C_{21}H_{33}O_4NNa$ (MNa^+) requires: 386.2302.

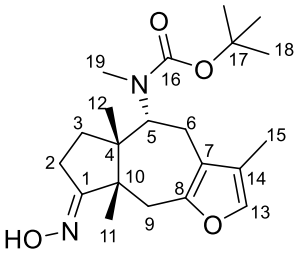
tert-Butylmethyl[(5*R*,5a*S*,8a*S*)-3,5a,8a-trimethyl-8-oxo-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl]carbamate (443)



To a solution of alcohol **442** (2.50 mg, 0.00688 mmol) in acetone (0.3 mL) was added $Ru(PPh_3)_3Cl_2$ (3.5 mg, 0.00344 mmol) and NMO (1.5 mg, 0.0138 mmol) and the reaction mixture was stirred at RT for 2 h. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (2.00 mg, 80%). R_f 0.25 (1:1 petrol:ether); $[\alpha]_D^{25}$ +47.5 (*c* 0.20, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2971m, 1741s, 1688s, 1331m, 1151s, 812m; δ_H (500 MHz, C_6D_6) 0.70 (3 H, s, C(12)H_3), 0.80 (3 H, s, C(12)H_3), 1.02−1.09 (8 H, m, 2 × C(3)**H**H′ and 2 × C(11)H_3), 1.36 (9 H, s, 3 × C(18)H_3), 1.46 (9 H, s, 3 × C(18)H_3), 1.61 (3 H, s, C(15)H_3), 1.68 (3 H, s, C(15)H_3), 1.76−2.00 (6 H, m, 2 × C(2)H_2

and 2 × C(3)H**H′**), 2.14−2.22 (2 H, m, 2 × C(6)**H**H′), 2.27−2.37 (2 H, m, 2 × C(9)**H**H′), 2.56 (3 H, s, C(19)H_3), 2.57−2.65 (4 H, m, 2 × C(6)H**H′** and 2 × C(9)H**H′**), 2.66 (3 H, s, C(19)H_3), 4.34 (1 H, dd, *J* 12.0, 2.0, C(5)H), 4.78 (1 H, dd, *J* 12.0, 2.0, C(5)H), 6.79 (1 H, s, C(13)H), 6.80 (1 H, s, C(13)H); δ_C (125 MHz, C_6D_6) 7.6/7.7 (C(15)), 15.5/15.7 (C(11)), 23.3 (C(12)), 23.6/23.8 (C(6)), 26.7/26.9 (C(3)), 28.1/28.2 (C(18)), 30.1/30.8 (C(19)), 32.4 (C(2)), 33.0/33.1 (C(9)), 49.4/49.7 (C(10)), 55.0 (C(5)), 55.6/55.8 (C(4)), 56.1 (C(5)), 78.8/79.0 (C(17)), 117.3/117.6 (C(7)), 119.8/120.0 (C(14)), 137.0/137.1 (C(13)), 148.9/149.0 (C(8)), 155.0/155.6 (C(16)), 216.5/216.7 (C(1)); *m/z* (ESI^+) 384 (MNa^+, 100%); HRMS (ESI^+): Found: 384.2145; $C_{21}H_{31}O_4NNa$ (MNa^+) requires: 384.2145.

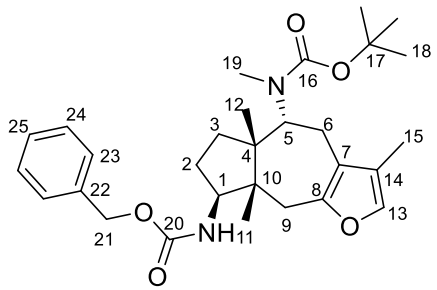
tert-Butyl[(5*R*,5a*S*,8a*S*,*E*)-8-(hydroxyimino)-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl](methyl)carbamate (444)



$NH_2OH{\cdot}HCl$ (0.5 mg, 0.00791 mmol) and pyridine (0.5 µL, 0.00539 mmol) were added to a solution of ketone **443** (1.30 mg, 0.00360 mmol) in EtOH (0.28 mL) and the mixture was stirred under reflux for 7 h. The solvent was removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.17 mg, 87%). R_f 0.30 (1:1 petrol:ether); $[\alpha]_D^{25}$ +23.5 (*c* 0.20, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3357br, 2972w, 1688s, 1330s, 1143m, 812s; δ_H (500 MHz, C_6D_6) 0.77 (3 H,

s, C(12)H_3), 0.88 (3 H, s, C(12)H_3), 1.02−1.09 (2 H, m, 2 × C(3)**H**H′), 1.27 (3 H, s, C(11)H_3), 1.30 (3 H, s, C(11)H_3), 1.37 (9 H, s, 3 × C(18)H_3), 1.45 (9 H, s, 3 × C(18)H_3), 1.64 (3 H, s, C(15)H_3), 1.70 (3 H, s, C(15)H_3), 1.71−1.86 (2 H, m, 2 × C(3)H**H′**), 2.11−2.21 (2 H, m, 2 × C(6)**H**H′), 2.31−2.45 (2 H, m, 2 × C(2)**H**H′), 2.46−2.61 (9 H, m, 2 × C(2)H**H′**, 2 × C(6)H**H′**, 2 × C(9)**H**H′ and C(19)H_3), 2.64 (3 H, s, C(19)H_3), 2.76 (1 H, d, *J* 16.0, C(9)H**H′**), 2.79 (1 H, d, *J* 16.0, C(9)H**H′**), 4.37 (1 H, dd, *J* 12.0, 2.0, C(5)H), 4.81 (1 H, dd, *J* 12.0, 2.0, C(5)H), 6.62 (1 H, s, OH), 6.67 (1 H, s, OH), 6.81 (1 H, s, C(13)H), 6.83 (1 H, s, C(13)H); δ_C (125 MHz, C_6D_6) 7.6/7.7 (C(15)), 17.1/17.4 (C(11)), 22.4/22.7 (C(2)), 22.8/22.9 (C(12)), 23.5/23.7 (C(6)), 28.1 (C(3) and C(18)), 28.2 (C(18)), 28.3 (C(3)), 30.4/30.7 (C(19)), 36.8 (C(9)), 51.5/51.6 (C(10)), 51.8/52.0 (C(4)), 54.9/56.0 (C(5)), 78.6/78.8 (C(17)), 117.4/117.7 (C(7)), 119.7/119.9 (C(14)), 136.7/136.8 (C(13)), 150.0/150.1 (C(8)), 155.0/155.6 (C(16)), 168.5/168.6 (C(1)); *m/z* (ESI$^+$) 399 (MNa$^+$, 100%); HRMS (ESI$^+$): Found: 399.2255; $C_{21}H_{32}O_4N_2Na$ (MNa$^+$) requires: 399.2254.

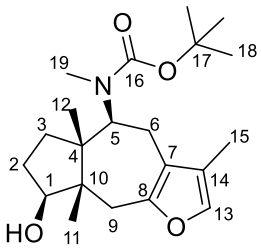
tert-Butyl{(5*R*,5a*S*,8*S*,8a*S*)-8-{[(benzyloxy)carbonyl]amino}-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (447)



Raney Ni (1 mg) was added to a solution of oxime **444** (1.80 mg, 0.00478 mmol) in EtOH (0.15 mL) and the mixture was stirred under H_2 at RT for 20 h. The mixture was filtered through Celite, washed with EtOH and concentrated *in vacuo*. Purification by flash

chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded amine **445** as the major diastereomer (1.40 mg, 81%). K_2CO_3 (1.0 mg, 0.00772 mmol) and benzyl chloroformate (1.0 μL, 0.00579 mmol) were added to a solution of amine **445** (1.40 mg, 0.00386 mmol) in DCM (0.15 mL) and the mixture was stirred at RT for 4 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.50 mg, 78%). R_f 0.60 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ +14.7 (*c* 0.15, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3339br, 2960m, 1689s, 1454m, 1255m, 1145s; δ_H (500 MHz, $CDCl_3$) 0.90 (6 H, s, 2 × C(12)H_3), 0.92 (3 H, s, C(11)H_3), 0.94 (3 H, s, C(11)H_3), 1.26−1.31 (2 H, m, 2 × C(3)**H**H′), 1.35−1.43 (2 H, m, 2 × C(2)**H**H′), 1.48 (9 H, s, 3 × C(18)H_3), 1.49 (9 H, s, 3 × C(18)H_3), 1.71−1.83 (2 H, m, 2 × C(3)H**H′**), 1.84−1.90 (2 H, m, 2 × C(2)H**H′**), 1.91 (3 H, s, C(15)H_3), 1.93 (3 H, s, C(15)H_3), 2.42−2.54 (2 H, m, 2 × C(6)**H**H′), 2.69 (1 H, d, *J* 16.0, C(9)**H**H′), 2.73−2.86 (10 H, m, 2 × C(6)H**H′**, C(9)H_2 and 2 × C(19)H_3), 2.95 (1 H, d, *J* 16.0, C(9)H**H′**), 3.71−3.82 (2 H, m, 2 × C(1)H), 4.55−4.63 (2 H, m, 2 × NH), 4.79 (1 H, dd, *J* 12.0, 2.0, C(5)H), 4.93 (1 H, dd, *J* 12.0, 2.0, C(5)H), 5.04−5.18 (4 H, m, 2 × C(21)H_2), 7.05 (1 H, s, C(13)H), 7.09 (1 H, s, C(13)H), 7.30−7.41 (10 H, m, 4 × C(23)H, 4 × C(24)H and 2 × C(25)H); δ_C (125 MHz, $CDCl_3$) 8.2 (C(15)), 21.3 (C(11)), 23.6/23.7 (C(12)), 25.6/25.9 (C(6)), 28.5/28.6 (C(18)), 29.7 (C(19)), 30.0/30.2 (C(2)), 30.3 (C(19)), 32.6/32.7 (C(3)), 37.3/37.9 (C(9)), 49.1/49.2 (C(10)), 50.7/50.9 (C(4)), 54.9/55.5 (C(5)), 57.5/57.7 (C(1)), 66.7/66.8 (C(21)), 79.3/79.8 (C(17)), 116.0/116.2 (C(7)), 119.9/120.1 (C(14)), 128.1 (C(23)), 128.2 (C(25)), 128.6 (C(24)), 135.8/136.6 (C(22)), 137.1/137.3 (C(13)), 149.1/149.2 (C(8)), 155.7 (C(16)), 156.0 (C(20)), 156.2 (C(16)); *m/z* (ESI^+) 519 (MNa^+, 100%); HRMS (ESI^+): Found: 519.2828; $C_{29}H_{40}O_5N_2Na$ (MNa^+) requires: 519.2829.

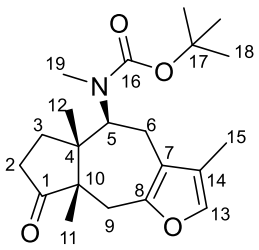
***tert*-Butyl{(5*S*,5a*S*,8*S*,8a*S*)-8-hydroxy-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (448)**



To a solution of carbamate **408** (3.30 mg, 0.00692 mmol) in THF–pyridine (0.22 mL, 10:1) was added HF–pyridine (2.0 μL, 0.0692 mmol) and the reaction mixture was stirred at RT for 48 h. Sat. aq. $NaHCO_3$ (5 mL) was added slowly and the mixture was extracted with ether (3 × 5 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (2.50 mg, 99%). R_f 0.25 (1:1 petrol:ether); $[\alpha]_D^{25}$ –39.5 (*c* 0.20, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3430br, 2974m, 1669s, 1441w, 1366s, 1149s; δ_H (500 MHz, $CDCl_3$) 0.84 (3 H, s, C(11)H_3), 0.86 (3 H, s, C(11)H_3), 1.05 (3 H, s, C(12)H_3), 1.07 (3 H, s, C(12)H_3), 1.41−1.46 (2 H, m, 2 × C(3)**H**H′), 1.47 (18 H, s, 6 × C(18)H_3), 1.50−1.56 (2 H, m, 2 × C(2)**H**H′), 1.87−1.94 (7 H, m, C(3)H**H′** and 2 × C(15)H_3), 1.95−2.09 (3 H, m, 2 × C(2)H**H′** and C(3)H**H′**), 2.26−2.38 (2 H, m, 2 × C(6)**H**H′), 2.42 (1 H, d, *J* 16.0, C(9)**H**H′), 2.49 (1 H, d, *J* 16.0, C(9)**H**H′), 2.68−2.78 (2 H, m, 2 × C(6)H**H′**), 2.83 (3 H, s, C(19)H_3), 2.86 (3 H, s, C(19)H_3), 2.96 (1 H, d, *J* 16.0, C(9)H**H′**), 3.08 (1 H, d, *J* 16.0, C(9)H**H′**), 3.86 (1 H, t, *J* 7.0, C(1)H), 3.91 (1 H, t, *J* 7.0, C(1)H), 4.72 (1 H, dd, *J* 12.0, 2.0, C(5)H), 4.84 (1 H, dd, *J* 12.0, 2.0, C(5)H), 6.98 (1 H, s, C(13)H), 7.02 (1 H, s, C(13)H); δ_C (125 MHz, $CDCl_3$) 8.2 (C(15)), 17.1/17.3 (C(11)), 19.7/20.0 (C(12)), 24.3/24.6 (C(6)), 28.5 (C(18)), 31.1 (C(2)), 31.2/31.9 (C(19)), 34.7/35.2 (C(3)), 37.4 (C(9)), 49.8/50.6 (C(10)), 50.7/50.9 (C(4)), 58.0/58.1 (C(5)),

79.4/79.9 (C(17)), 82.8/83.1 (C(1)), 116.9 (C(7)), 120.2/120.4 (C(14)), 136.2/136.4 (C(13)), 149.3/149.5 (C(8)), 156.0/156.7 (C(16)); *m/z* (ESI^+) 386 (MNa^+, 100%); HRMS (ESI^+): Found: 386.2302; $C_{21}H_{33}O_4NNa$ (MNa^+) requires: 386.2302.

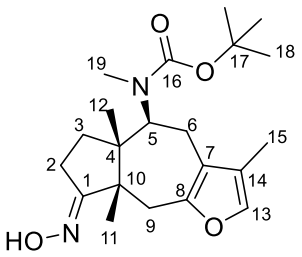
tert-Butylmethyl{(5*S*,5a*S*,8a*S*)-3,5a,8a-trimethyl-8-oxo-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}carbamate (449)



To a solution of alcohol **448** (2.50 mg, 0.00688 mmol) in acetone (0.3 mL) was added $Ru(PPh_3)_3Cl_2$ (3.5 mg, 0.00344 mmol) and NMO (2.0 mg, 0.0138 mmol) and the reaction mixture was stirred at RT for 2 h. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (2.40 mg, 96%). R_f 0.50 (1:1 petrol:ether); $[\alpha]_D^{25}$ –79.6 (*c* 0.24, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2973m, 1737s, 1688s, 1347m, 1151s, 752s; δ_H (500 MHz, C_6D_6) 0.56 (3 H, s, C(12)H_3), 0.58 (3 H, s, C(12)H_3), 0.88 (3 H, s, C(11)H_3), 0.90 (3 H, s, C(11)H_3), 1.35 (9 H, s, 3 × C(18)H_3), 1.47 (9 H, s, 3 × C(18)H_3), 1.53−1.57 (2 H, m, 2 × C(3)**H**H′), 1.58 (6 H, s, 2 × C(15)H_3), 1.85−1.96 (2 H, m, 2 × C(2)**H**H′), 1.99−2.22 (4 H, m, 2 × C(2)H**H′** and 2 × C(6)**H**H′), 2.26−2.44 (4 H, m, 2 × C(3)H**H′** and 2 × C(6)H**H′**), 2.52 (1 H, d, *J* 16.0, C(9)**H**H′), 2.58 (3 H, s, C(19)H_3), 2.65 (1 H, d, *J* 16.0, C(9)**H**H′), 2.72 (3 H, s, C(19)H_3), 2.88−3.00 (2 H, m, 2 × C(9)H**H′**), 4.66 (1 H, d, *J* 11.5, C(5)H), 5.02 (1 H, d, *J* 11.5, C(5)H), 6.83 (1 H, s, C(13)H), 6.87 (1 H, s, C(13)H); δ_C (125 MHz, C_6D_6) 7.6 (C(15)), 17.3/17.4 (C(12)), 18.4 (C(11)), 23.9/24.2 (C(6)), 28.0/28.2

(C(18)), 31.9 (C(19)), 32.2 (C(9)), 33.0 (C(3)), 34.0/34.1 (C(2)), 50.5/50.8 (C(4)), 54.8 (C(10)), 60.8/61.5 (C(5)), 78.8/79.3 (C(17)), 118.0/118.3 (C(7)), 119.7/119.8 (C(14)), 137.0/137.2 (C(13)), 147.6/148.1 (C(8)), 155.2/156.0 (C(16)), 220.0/220.2 (C(1)); *m/z* (ESI^+) 384 (MNa^+, 100%); HRMS (ESI^+): Found: 384.2145; $C_{21}H_{31}O_4NNa$ (MNa^+) requires: 384.2145.

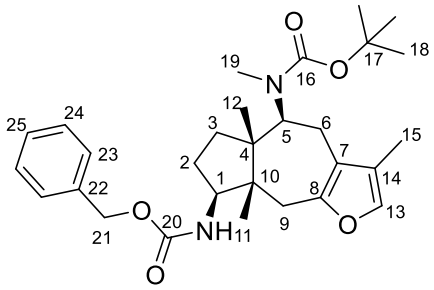
tert-Butyl{(5*S*,5a*S*,8a*S*,*E*)-8-(hydroxyimino)-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (450)



$NH_2OH{\cdot}HCl$ (1.0 mg, 0.0146 mmol) and pyridine (1.0 µL, 0.00996 mmol) were added to a solution of ketone **449** (2.40 mg, 0.00664 mmol) in EtOH (0.45 mL) and the mixture was stirred under reflux for 6 h. The solvent was removed *in vacuo*. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (2.30 mg, 92%). R_f 0.50 (1:1 petrol:ether); $[\alpha]_D^{25}$ –87.0 (*c* 0.23, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3337br, 2973m, 1687s, 1348m, 1157s, 946m; δ_H (500 MHz, C_6D_6) 0.62 (3 H, s, C(12)H_3), 0.65 (3 H, s, C(12)H_3), 1.12 (3 H, s, C(11)H_3), 1.16 (3 H, s, C(11)H_3), 1.35 (9 H, s, 3 × C(18)H_3), 1.46 (9 H, s, 3 × C(18)H_3), 1.50−1.62 (8 H, m, 2 × C(3)**H**H′ and 2 × C(15)H_3), 1.98−2.09 (1 H, m, C(3)H**H′**), 2.10−2.23 (2 H, m, 2 × C(6)**H**H′), 2.29−2.46 (5 H, m, 2 × C(2)**H**H′, C(3)H**H′** and 2 × C(6)H**H′**), 2.59 (3 H, s, C(19)H_3), 2.60−2.79 (6 H, m, 2 ×

C(2)H**H′**, C(9)**H**H′ and C(19)H_3), 2.88 (1 H, d, *J* 16.5, C(9)**H**H′), 3.14−3.25 (2 H, m, 2 × C(9)H**H′**), 4.67 (1 H, d, *J* 11.0, C(5)H), 5.03 (1 H, d, *J* 11.5, C(5)H), 6.77−6.92 (4 H, m, 2 × C(13)H and 2 × OH); δ_C (125 MHz, C_6D_6) 7.7 (C(15)), 17.0/17.1 (C(12)), 21.1/21.4 (C(11)), 23.7/23.8 (C(2)), 24.0/24.3 (C(6)), 28.0/28.2 (C(18)), 31.8/31.9 (C(19)), 35.4/35.6 (C(3)), 36.2/36.3 (C(9)), 50.6/50.7 (C(10)), 52.6/52.9 (C(4)), 60.8/61.2 (C(5)), 78.7/79.2 (C(17)), 117.9/118.2 (C(7)), 119.6/119.8 (C(14)), 136.6/136.8 (C(13)), 148.9/149.4 (C(8)), 155.2/155.8 (C(16)), 171.4/171.5 (C(1)); *m/z* (ESI^+) 399 (MNa^+, 100%); HRMS (ESI^+): Found: 399.2255; $C_{21}H_{32}O_4N_2Na$ (MNa^+) requires: 399.2254.

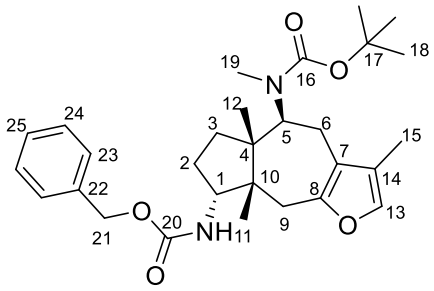
tert-Butyl{(5*S*,5a*S*,8*S*,8a*S*)-8-{[(benzyloxy)carbonyl]amino}-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (453)



Raney Ni (1 mg) was added to a solution of oxime **450** (2.30 mg, 0.00611 mmol) in EtOH (0.2 mL) and the mixture was stirred under H_2 at RT for 20 h. The mixture was filtered through Celite, washed with EtOH and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded amine **451** (1.10 mg, 50%). K_2CO_3 (1.0 mg, 0.00607 mmol) and benzyl chloroformate (1.0 µL, 0.00455 mmol) were added to a solution of amine **451** (1.10 mg, 0.00303 mmol) in DCM (0.15 mL) and the mixture was stirred at RT for 16 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4,

filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.00 mg, 66%). R_f 0.75 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ –51.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3332br, 2967m, 1691s, 1455m, 1260m, 1148s; δ_H (500 MHz, $CDCl_3$) 0.73 (3 H, s, C(11)H_3), 0.75 (3 H, s, C(11)H_3), 0.97 (6 H, s, 2 × C(12)H_3), 1.33−1.42 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.47 (9 H, s, 3 × C(18)H_3), 1.51 (9 H, s, 3 × C(18)H_3), 1.89 (3 H, s, C(15)H_3), 1.92 (3 H, s, C(15)H_3), 1.94−2.08 (4 H, m, 2 × C(2)H**H′** and 2 × C(3)H**H′**), 2.26−2.41 (2 H, m, 2 × C(6)**H**H′), 2.60−2.81 (4 H, m, 2 × C(6)H**H′** and 2 × C(9)**H**H′), 2.82 (3 H, s, C(19)H_3), 2.86 (3 H, s, C(19)H_3), 3.10 (1 H, d, *J* 16.0, C(9)H**H′**), 3.22 (1 H, d, *J* 16.0, C(9)H**H′**), 3.90−4.01 (2 H, m, 2 × C(1)H), 4.60−4.70 (2 H, m, 2 × NH), 4.85−4.94 (2 H, m, 2 × C(5)H), 5.04−5.19 (4 H, m, 2 × C(21)H_2), 6.96 (1 H, s, C(13)H), 7.00 (1 H, s, C(13)H), 7.30−7.43 (10 H, m, 4 × C(23)H, 4 × C(24)H and 2 × C(25)H); δ_C (125 MHz, $CDCl_3$) 8.2 (C(15)), 18.2/18.6 (C(11)), 19.0/20.0 (C(12)), 24.1/24.6 (C(6)), 28.5/28.6 (C(18)), 29.5/30.1 (C(2)), 30.8/32.0 (C(19)), 35.1/35.9 (C(3)), 37.7/38.2 (C(9)), 49.7/49.9 (C(10)), 50.1/51.3 (C(4)), 57.3/58.0 (C(5)), 61.9/62.4 (C(1)), 66.8 (C(21)), 79.4/80.2 (C(17)), 116.4/116.6 (C(7)), 120.0/120.3 (C(14)), 127.6 (C(23)), 128.2 (C(25)), 128.6 (C(24)), 136.3 (C(22)), 136.5 (C(13)), 149.3/149.8 (C(8)), 156.0 (C(16) and C(20)), 156.6 (C(16)); *m/z* (ESI^+) 519 (MNa^+, 100%); HRMS (ESI^+): Found: 519.2828; $C_{29}H_{40}O_5N_2Na$ (MNa^+) requires: 519.2829.

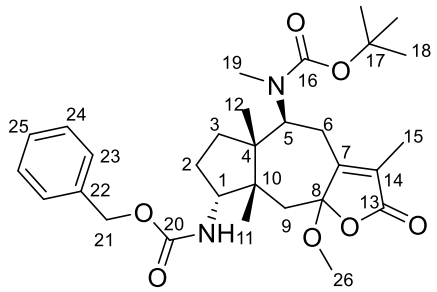
***tert*-Butyl{(5*S*,5a*S*,8*R*,8a*S*)-8-{[(benzyloxy)carbonyl]amino}-3,5a,8a-trimethyl-4,5,5a,6,7,8,8a,9-octahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (454)**



Raney Ni (1 mg) was added to a solution of oxime **450** (2.30 mg, 0.00611 mmol) in EtOH (0.2 mL) and the mixture was stirred under H_2 at RT for 20 h. The mixture was filtered through Celite, washed with EtOH and concentrated *in vacuo*. Purification by flash chromatography (silica, 100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)) afforded amine **452** (1.10 mg, 50%). K_2CO_3 (1.0 mg, 0.00607 mmol) and benzyl chloroformate (1.0 µL, 0.00455 mmol) were added to a solution of amine **452** (1.10 mg, 0.00303 mmol) in DCM (0.15 mL) and the mixture was stirred at RT for 3 h. Water (1 mL) was added and the mixture was extracted with ether (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (silica, 1:1 petrol:ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.20 mg, 79%). R_f 0.80 (100:10:1 $CHCl_3$:MeOH:aq. NH_3 (18 M)); $[\alpha]_D^{25}$ –58.3 (*c* 0.12, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3340br, 2970m, 1691s, 1454m, 1251m, 1149s; δ_H (500 MHz, $CDCl_3$) 0.89 (6 H, s, 2 × C(11)H_3), 1.07 (6 H, s, 2 × C(12)H_3), 1.36−1.44 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.45 (9 H, s, 3 × C(18)H_3), 1.47 (9 H, s, 3 × C(18)H_3), 1.89 (3 H, s, C(15)H_3), 1.92 (3 H, s, C(15)H_3), 1.95−2.08 (2 H, m, 2 × C(2)H**H′**), 2.23−2.33 (4 H, m, 2 × C(3)H**H′** and 2 × C(6)**H**H′), 2.39 (2 H, d, *J* 15.5, 2 × C(9)**H**H′), 2.59−2.69 (2 H, m, 2 × C(6)H**H′**), 2.83 (3 H, s, C(19)H_3), 2.85 (3 H, s, C(19)H_3), 2.95 (2 H, d, *J* 15.5, 2 × C(9)H**H′**), 4.08−4.17 (2 H, m, 2 × C(1)H), 4.75 (2 H, d, *J* 11.0, 2 × C(5)H), 5.01−5.19 (6 H, m, 2 ×

C(21)H_2 and 2 × NH), 6.98 (1 H, s, C(13)H), 7.03 (1 H, s, C(13)H), 7.29−7.42 (10 H, m, 4 × C(23)H, 4 × C(24)H and 2 × C(25)H); δ_C (125 MHz, $CDCl_3$) 8.2 (C(15)), 20.6 (C(12)), 21.6 (C(11)), 24.2 (C(6)), 28.2 (C(2)), 28.5 (C(18)), 30.1 (C(9)), 32.3 (C(19)), 35.3 (C(3)), 50.0 (C(10)), 50.7 (C(4)), 60.0 (C(5)), 60.9 (C(1)), 66.7 (C(21)), 79.6 (C(17)), 117.6 (C(7)), 120.0 (C(14)), 127.0 (C(23)), 128.0 (C(25)), 128.5 (C(24)), 136.5 (C(13)), 136.6 (C(22)), 149.3 (C(8)), 156.4 (C(20)), 157.1 (C(16)); *m/z* (ESI^+) 519 (MNa^+, 100%); HRMS (ESI^+): Found: 519.2828; $C_{29}H_{40}O_5N_2Na$ (MNa^+) requires: 519.2829.

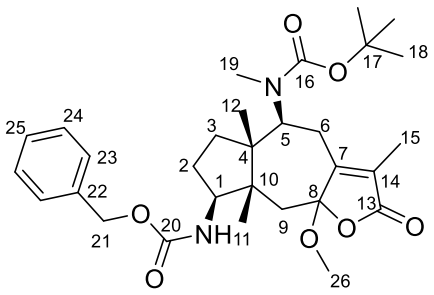
tert-Butyl{(5*S*,5a*S*,8*R*,8a*S*)-8-{[(benzyloxy)carbonyl]amino}-9a-methoxy-3,5a,8a-trimethyl-2-oxo-2,4,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (455)



Oxygen was bubbled through a stirred solution of rose Bengal (0.5 mg, 0.02 μmol, 1×10^{-4} M) and carbamate **454** (1.20 mg, 0.00242 mmol) in methanol (0.2 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 ^oC and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) for 15 min. The solvent was removed *in vacuo*, the resulting pink residue dissolved in pyridine (0.1 mL), acetic anhydride (0.5 μL, 0.00242 mmol) added and the reaction mixture stirred at RT for 15 min. The mixture was diluted with ethyl acetate (1 mL), the organic layer washed with water (1 mL), sat. aq. $CuSO_4$ (2 × 1 mL), brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash

chromatography (silica, ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.20 mg, 92%). R_f 0.50 (ether); $[\alpha]_D^{25}$ +16.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3339br, 2955m, 1767s, 1691s, 1367m, 1149m; δ_H (500 MHz, $CDCl_3$) 0.86 (6 H, s, 2 × C(11)H_3), 0.93 (3 H, s, C(12)H_3), 0.98 (3 H, s, C(12)H_3), 1.28−1.37 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.48 (18 H, s, 6 × C(18)H_3), 1.82−2.00 (10 H, m, 2 × C(2)H**H′**, 2 × C(3)H**H′** and 2 × C(15)H_3), 2.17 (2 H, d, *J* 16.0, 2 × C(9)**H**H′), 2.22−2.35 (3 H, m, 2 × C(6)**H**H′ and C(9)H**H′**), 2.48 (1 H, d, *J* 16.0, C(9)H**H′**), 2.85 (6 H, s, 2 × C(19)H_3), 2.90−3.07 (2 H, m, 2 × C(6)H**H′**), 3.11 (3 H, s, C(26)H_3), 3.12 (3 H, s, C(26)H_3), 3.82−3.96 (2 H, m, 2 × C(1)H), 4.78−4.88 (1 H, m, NH), 4.96 (1 H, d, *J* 11.5, C(5)H), 5.01−5.18 (5 H, m, C(5)H and 2 × C(21)H_2), 5.22−5.30 (1 H, m, NH), 7.29−7.42 (10 H, m, 4 × C(23)H, 4 × C(24)H and 2 × C(25)H); δ_C (125 MHz, $CDCl_3$) 8.6 (C(15)), 20.3/20.6 (C(12)), 23.1/23.4 (C(11)), 26.8/27.2 (C(6)), 28.2 (C(2)), 28.4/28.5 (C(18)), 30.9/31.1 (C(19)), 35.6/36.2 (C(3)), 41.0/41.6 (C(9)), 47.6/47.8 (C(10)), 49.5/49.7 (C(4)), 49.8/49.9 (C(26)), 53.4/54.9 (C(5)), 63.0/63.9 (C(1)), 66.7/67.0 (C(21)), 80.2/80.5 (C(17)), 108.7/109.0 (C(8)), 127.6 (C(14)), 128.0 (C(23)), 128.3 (C(25)), 128.5 (C(24)), 135.8 (C(22)), 154.9 (C(20)), 155.9 (C(7)), 156.0/156.3 (C(16)), 170.9/171.3 (C(13)); *m/z* (ESI^+) 565 (MNa^+, 100%); HRMS (ESI^+): Found: 565.2883; $C_{30}H_{42}O_7N_2Na$ (MNa^+) requires: 565.2884.

tert-Butyl{(5*S*,5a*S*,8*S*,8a*S*)-8-{[(benzyloxy)carbonyl]amino}-9a-methoxy-3,5a,8a-trimethyl-2-oxo-2,4,5,5a,6,7,8,8a,9,9a-decahydroazuleno[5,6-*b*]furan-5-yl}(methyl)carbamate (457)



Oxygen was bubbled through a stirred solution of rose Bengal (0.5 mg, 0.02 μmol, 1×10^{-4} M) and carbamate **453** (1.00 mg, 0.00201 mmol) in methanol (0.2 mL) for 2 min. Maintaining the stream of oxygen, the solution was cooled to 0 ^{o}C and irradiated with UV light (Exo-Terra PT-2056 200 W lamp) for 15 min. The solvent was removed *in vacuo,* the resulting pink residue dissolved in pyridine (0.1 mL), acetic anhydride (0.5 μL, 0.00201 mmol) added and the reaction mixture stirred at RT for 15 min. The mixture was diluted with ethyl acetate (1 mL), the organic layer washed with water (1 mL), sat. aq. $CuSO_4$ (2 × 1 mL), brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (silica, ether) afforded the *title compound* as a mixture of carbamate rotamers as a colourless oil (1.00 mg, 92%). R_f 0.40 (ether); $[\alpha]_D^{25}$ +69.0 (*c* 0.10, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3340br, 2959m, 1767s, 1689s, 1366m, 751s; δ_H (500 MHz, $CDCl_3$) 0.64 (3 H, s, C(11)H_3), 0.72 (3 H, s, C(11)H_3), 0.91 (3 H, s, C(12)H_3), 0.97 (3 H, s, C(12)H_3), 1.29−1.42 (4 H, m, 2 × C(2)**H**H′ and 2 × C(3)**H**H′), 1.48 (9 H, s, 3 × C(18)H_3), 1.55 (9 H, s, 3 × C(18)H_3), 1.63−1.77 (4 H, m, 2 × C(3)H**H′** and 2 × C(9)**H**H′), 1.89 (3 H, s, C(15)H_3), 1.91 (3 H, s, C(15)H_3), 2.04−2.14 (2 H, m, 2 × C(2)H**H′**), 2.31−2.39 (2 H, m, 2 × C(6)**H**H′), 2.42 (1 H, d, *J* 16.0, C(9)H**H′**), 2.50 (1 H, d, *J* 16.0, C(9)H**H′**), 2.85 (3 H, s, C(19)H_3), 2.87 (3 H, s, C(19)H_3), 2.91−3.01 (3 H, m, C(26)H_3), 3.05−3.15 (2 H, m, 2 × C(6)H**H′**), 3.23 (3

H, s, C(26)H_3), 4.01−4.15 (1 H, m, C(1)H), 4.39−4.53 (1 H, m, C(1)H), 4.55−4.66 (2 H, m, 2 × NH), 5.00−5.28 (6 H, m, 2 × C(5)H and 2 × C(21)H_2), 7.30−7.42 (10 H, m, 4 × C(23)H, 4 × C(24)H and 2 × C(25)H); δ_C (125 MHz, $CDCl_3$) 8.5 (C(15)), 18.5/18.9 (C(12)), 19.5/19.8 (C(11)), 27.4 (C(6)), 28.5 (C(2) and C(18)), 28.6 (C(18)), 29.6/30.9 (C(19)), 33.5/33.6 (C(3)), 43.1 (C(9)), 48.9 (C(4)), 49.1 (C(10)), 50.6 (C(26)), 52.2 (C(5)), 57.7 (C(1)), 66.9 (C(21)), 80.9 (C(17)), 109.2 (C(8)), 127.1 (C(14)), 128.2 (C(23) and C(25)), 128.6 (C(24)), 135.8 (C(22)), 155.6 (C(7)), 155.7 (C(20)), 155.9 (C(16)), 173.9 (C(13)); *m/z* (ESI^+) 565 (MNa^+, 100%); HRMS (ESI^+): Found: 565.2883; $C_{30}H_{42}O_7N_2Na$ (MNa^+) requires: 565.2884.

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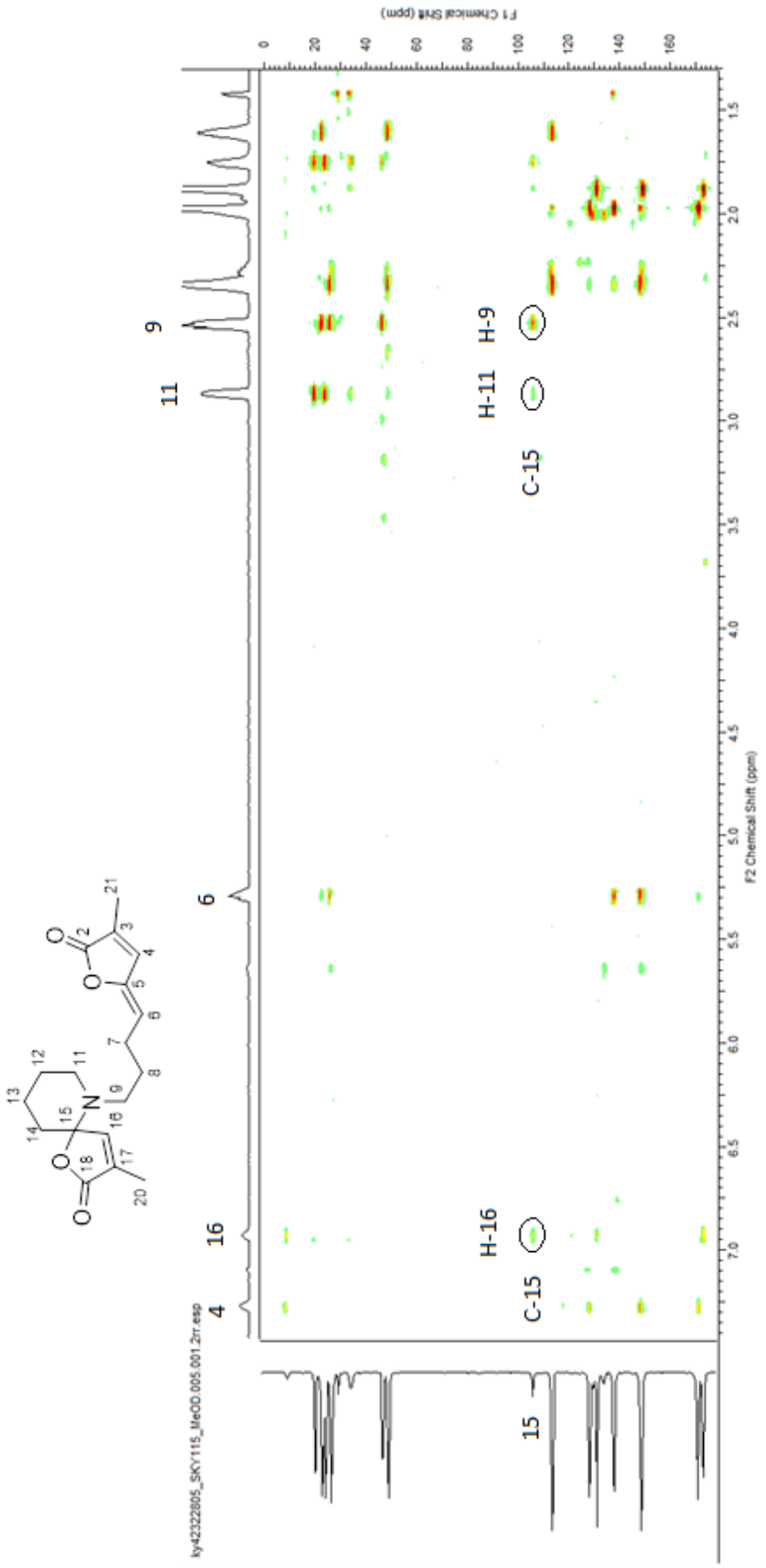
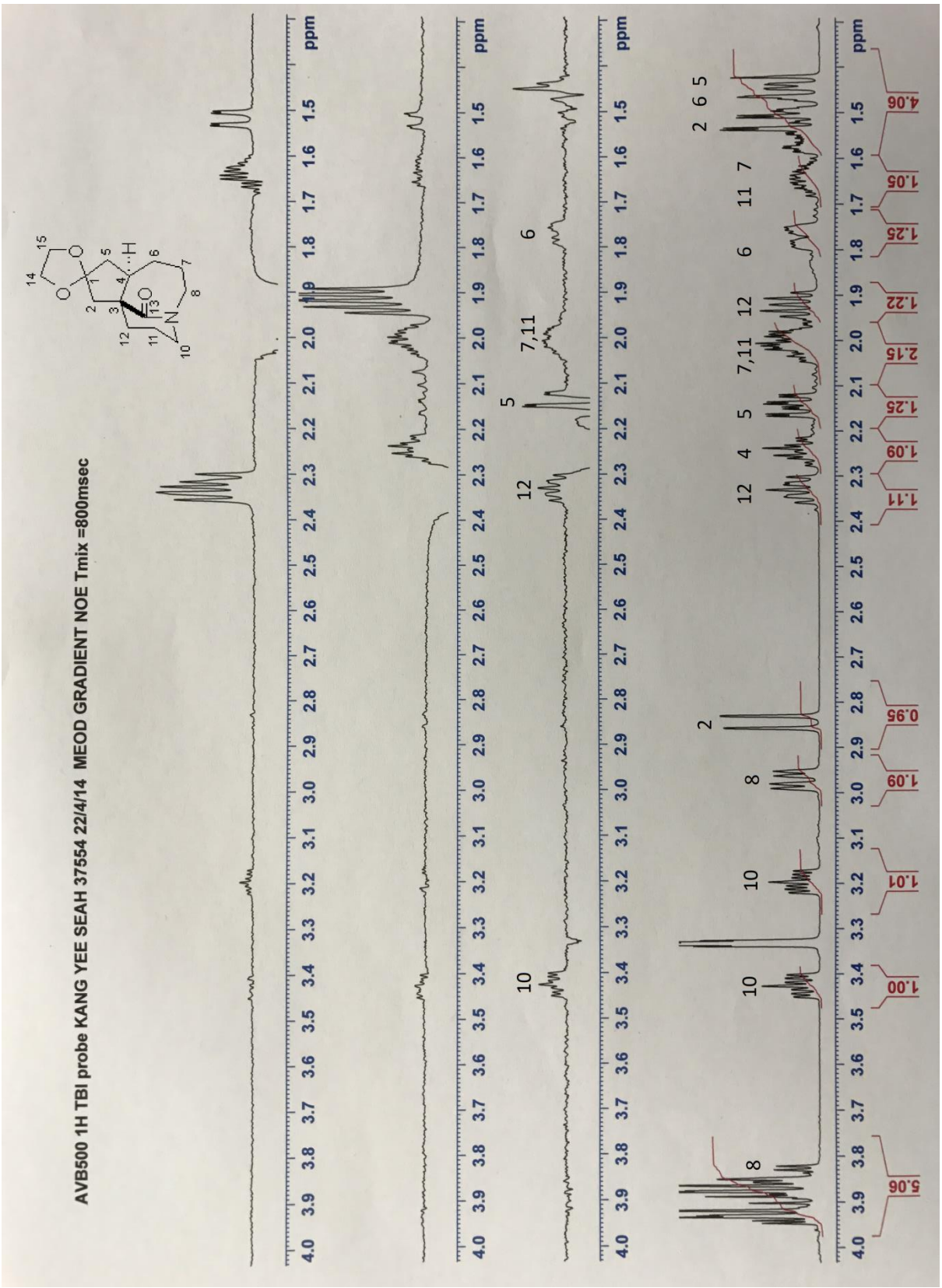
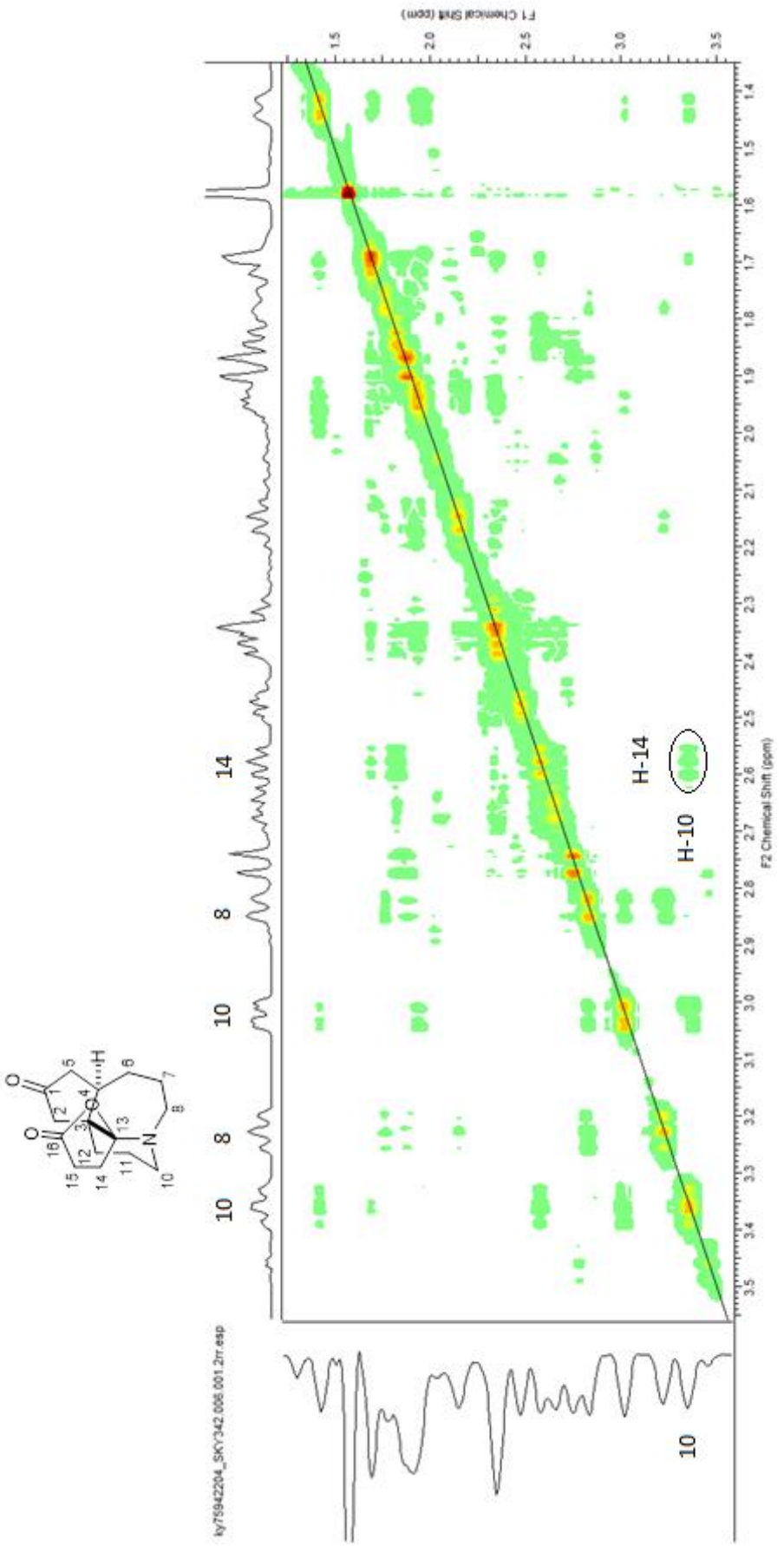
Appendix A: HMBC spectrum of pandamarilactone-1



Appendix B: NOE spectrum of compound 247



Appendix C: NOESY spectrum of compound 252



Appendix D: NOE spectrum of compound 412

