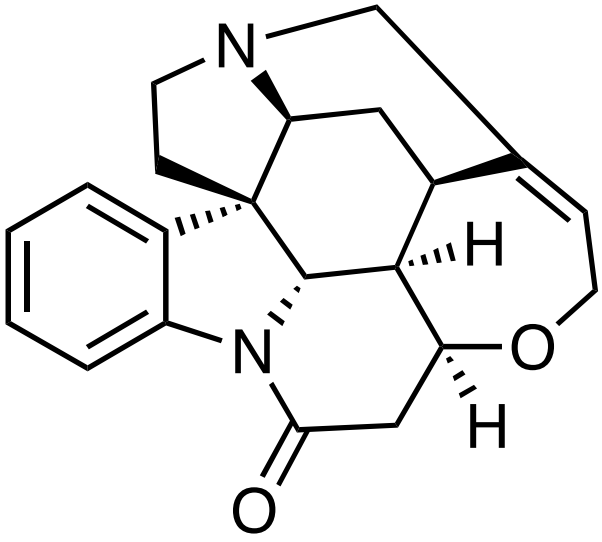
Towards a Total Synthesis of Strychnine



(-)-Strychnine *Strychnos nux vomica*

A thesis presented in partial fulfilment of the requirements for the Degree of Bachelor of Science (with Honours)

Rohan McGregor Mitchell

Under the supervision of **Prof. Martin Banwell**

The Research School of Chemistry

Australian National University

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by me, during the period from February 2010 to October 2010 and that it has not been previously presented for the examination of any other degree. This thesis is within 40 pages in length and within the required margins. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they were derived.

Rohan Mitchell
October 2010

Acknowledgements

Firstly I would like to thank Prof. Martin Banwell for his supervision and support during the year. His unwavering help and encouragement have made him a joy to work with.

I'd like to thank the members of the Banwell group for their support and friendship, which I deeply value. I'd especially like to acknowledge Tristan Reekie for his guidance and help in the lab, Andrew Lin for his assistance with the ozonolysis reaction and Brett Schwartz for proofreading and advice.

The RSC technical staff have provided an excellent service without which this project would not have been possible. I'd like to thank Dr. Xinghua Ma for technical assistance, the staff of the mass spectrometry unit, the NMR staff, Dr. Ian Cade for his assistance with X-ray crystal structures and finally the workshop, safety and administrative staff for creating a supportive environment within which to do this work.

The support of my friends this year has been wonderful. In particular, I'd like to thank my housemates Kishen, George and Jack, and also the other Honours students who have been welcoming from the start. A special mention goes out to the members of the Aiki-kai Aikido club.

Finally, I'd like to thank my parents and my brother and sister, for whose presence in my life I am indebted.

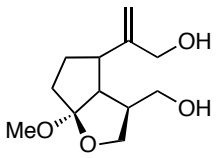
Abstract

A stereoselective synthesis of compound **104**, a potential precursor to the E-, F- and G-rings of strychnine, has been achieved over 9 steps and in 3.6% yield.

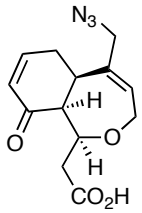
The pivotal Diels-Alder reaction was affected under high-pressure conditions, and utilising cyclopentenone as the dienophile.

Exploratory work has demonstrated the feasibility of the key ozonolysis reaction, including the associated elimination reaction to form the terminal alkene required for a projected final ring-closing metathesis (RCM) reaction.

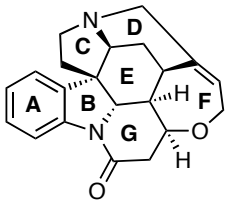
The present work should allow for the eventual preparation of cyclohexenone **35**, which it is expected could be annulated to the A-, B-, C- and D-rings of strychnine using protocols already established within the Banwell group.



104



35



1
[(-)-strychnine]

Glossary

Ac	acetyl
app.	apparent
Bn	benzyl
CSA	(+)-camphorsulfonic acid
ca.	*circa* (approximately)
δ	chemical shift (ppm)
Δ	delta (heating)
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
^{o}C	degrees Celsius
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNBC	3,5-dinitrobenzoyl chloride
EI	electron impact (mass spectrometry)
eq.	equivalents
Et	ethyl
et al.	*et alia* (and others)
eV	electron volts
FGI	functional group interconversion(s)
g	gram(s)
h	hour(s)
HMPA	hexamethyl phosphoramide
Hz	Hertz
i.v.	intravenous
J	coupling constant (Hz)
kbar	kilobar(s)
kg	kilogram(s)

LAH	lithium aluminium hydride
LD_{50}	median lethal dose
lit.	literature value
μL	microliter(s)
m	multiplet
$M^{+\bullet}$	molecular ion
Me	methyl
Mg	milligram
MHz	megahertz
min.	minute(s)
mL	millilitre(s)
mmol	millimol(s)
mol	mole(s)
m.p.	melting point (^{o}C)
Ms	mesyl
MS	mass spectrometry
m/z	mass-to-charge ratio
ν_{max}	infra-red absorption maxima (cm^{-1})
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PhH	benzene
PhMe	toluene
ppm	parts per million
q	quartet
RCM	ring-closing metathesis
R_f	retention factor
r.t.	room temperature (approx. 18 ^{o}C)
s	singlet
t	triplet
TEA	triethylamine
Tf	triflate
THF	tetrahydrofuran
TBS	*tert*-butyldimethylsilyl

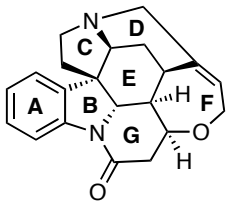
TMS	trimethylsilyl
Ts	tosyl
viz.	*videlicit* (that is, namely)
v/v	volume-to-volume ratio

Contents

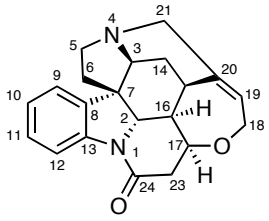
1 Introduction – The Biology and Chemistry of the Alkaloid Strychnine

1.1 Overview

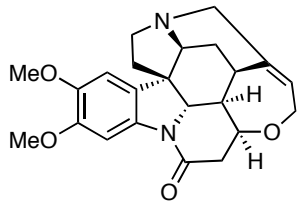
The natural product (-)-strychnine (**1**) has a rich history of medicinal use[1] and has been the target of numerous total synthesis studies since it was first prepared by Woodward in 1954.[2] It was isolated from the Asian-native evergreen tree *Strychnos nux vomica* in 1818, and its structure, including absolute stereochemistry, was shown to be as illustrated by single crystal X-ray analysis.[1] The compound contains a tryptamine core, and is related to the co-occurring alkaloid brucine (**2**), the 10,11-dimethoxy derivative, as well as to aspidospermidine (**3**), a structurally related, but somewhat simpler alkaloid.



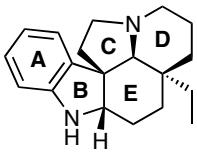
1
[(-)-strychnine]
(with ring labelling)



1
[(-)-strychnine]
(with atom numbering)



2
[(-)-brucine]



3
[(-)-aspidospermidine]

1.2 Biological Activity

Strychnine is highly toxic to almost all organisms, having an i.v. LD_{50} in rats of 0.96 mg/kg, with the lethal dose in adult humans beginning at *ca.* 1 mg/kg. Its toxicity stems from its potent stimulatory actions on the central nervous system, that lead to convulsions and, ultimately, death due to respiratory paralysis.

When given in low doses, strychnine's stimulant properties can convey an advantage in sports, and it has been used in this way as a doping agent. In medicine, it has been used as an analeptic (stimulating) agent and as an antidote for barbiturate and other centrally-paralysing sleeping agent poisons.[3]

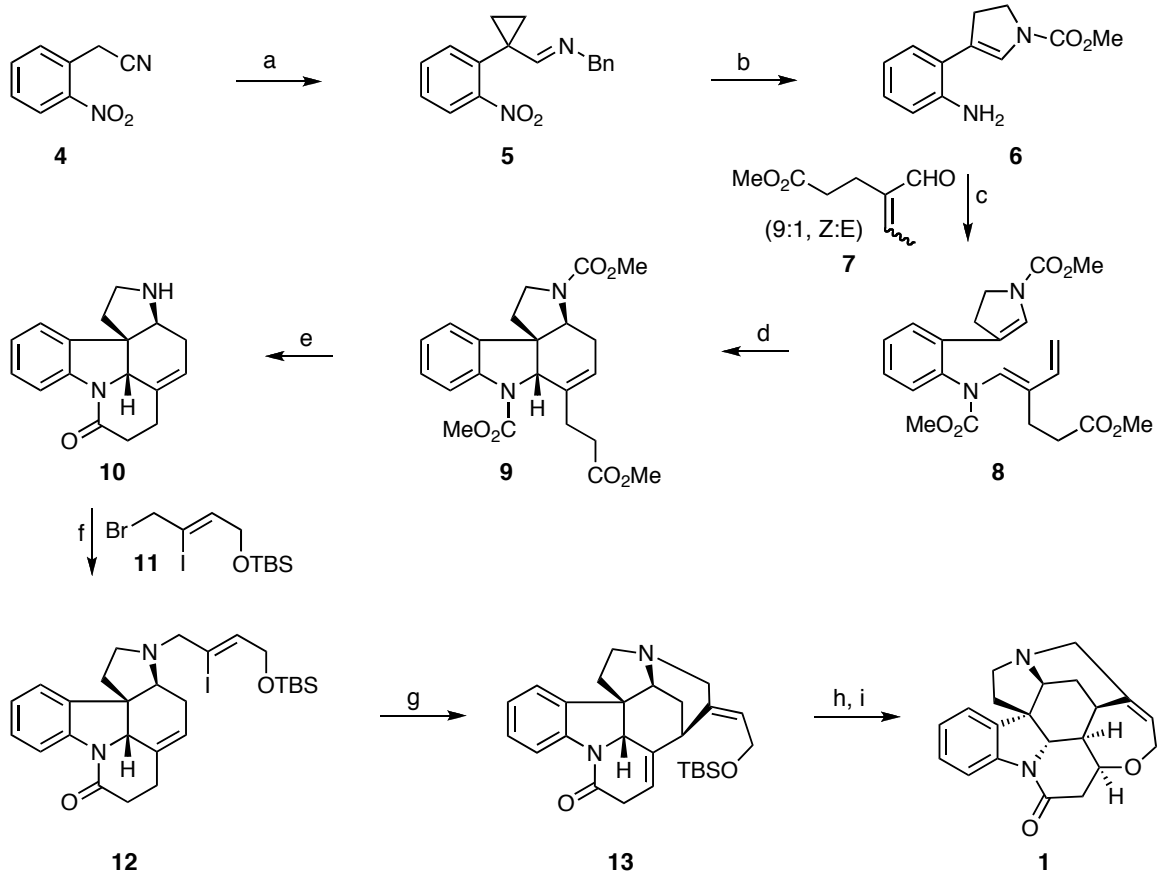
1.3 Noteworthy Previous Syntheses of Strychnine

Strychnine's polycyclic ring system and six stereocentres have made it a popular target for total synthesis, especially since it offers excellent opportunities to showcase novel synthetic methods. Since Woodward's first total synthesis in 1954,[2] many further total syntheses and formal total syntheses of strychnine have been reported.[4]

The following two sections will summarise the relatively recent syntheses reported by Rawal *et al.*[5] and Reissig *et al.*,[6] both of which are noteworthy for their elegance and brevity.

1.4 Rawal's Synthesis of (±)-Strychnine

Utilising a key intramolecular Diels-Alder (IMDA) reaction and an intramolecular Heck coupling as pivotal steps, Rawal and Iwasa achieved a total synthesis of (±)-strychnine in 10% yield over 15 steps.



Scheme 1. Total synthesis of Strychnine by Rawal and Iwasa.[5] *Reagents and conditions*: (a) 1. $BrCH_2CH_2Br$, NaOH, MeCN, $n$$Bu_4NBr$, rt.; 2. DIBAL-H, toluene, -78 °C; then H_3O^+ 3. $BnNH_2$, Et_2O, $MgSO_4$, 96%; (b) 1. Me_3SiCl (cat.), NaI (cat.), DMF, 60 °C; 2. $ClCO_2Me$, acetone, rt.; 3. 10% Pd/C, HCO_2NH_4, MeOH, 83%; (c) RCHO, neat, rt; then $ClCO_2Me$, $PhNEt_2$, 85%; (d) PhH, 185 °C, 4 h, 99%; (e) TMSI (10 eq.), $CHCl_3$, reflux, 5 h; MeOH quench, Δ, 6 h, 90%; (f) acetone-DMF (5:1), K_2CO_3, 83%; (g) $Pd(OAc)_2$ (0.3 eq.), Bu_4NCl, DMF, K_2CO_3, 70 °C, 3 h, 74%; (h) 2 N HCl, THF, 100%; (i) KOH, EtOH.

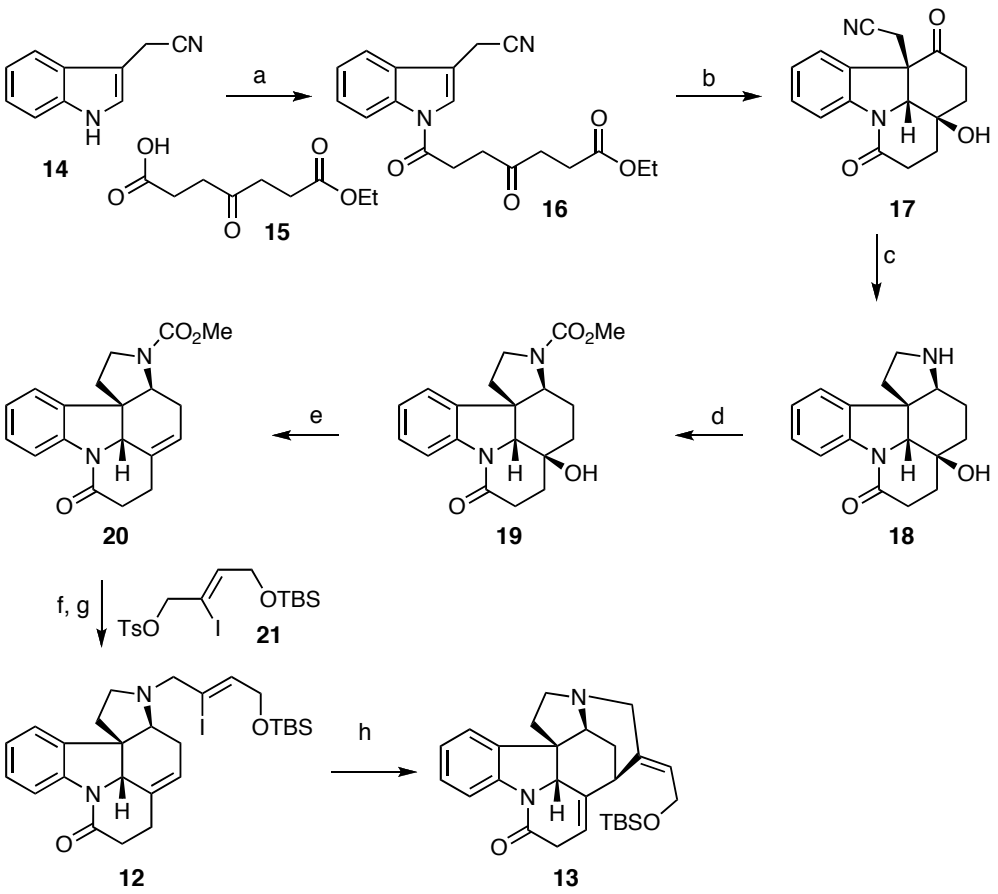
Thus, commercially available 2-nitrophenylacetonitrile (**4**) was treated with 1,2-dibromoethane and base under phase-transfer conditions to afford the cyclopropane. The nitrile group was selectively reduced to an aldehyde using DIBAL-H followed by work-up with aqueous acid. Condensation of the aldehyde with benzyl amine gave imine **5** that was treated with catalytic amounts of Me_3SiCl and NaI in DMF, so as to furnish the anticipated pyrroline derivative. This was converted into the aniline **6** by reaction with methyl chloroformate and chemoselective reduction under hydrogenation conditions.

In the presence of an excess of aldehyde **7**, pyrroline **6** was transformed into the expected imine and upon quenching, the desired diene-carbamate **8** was obtained. Diene **8** underwent a smooth intramolecular Diels-Alder cycloaddition reaction upon heating in benzene in a sealed tube, furnishing the tetracycle **9** which incorporates three of strychnine's stereocenters correctly set. The ester and two carbamate moieties within this adduct could then be demethylated by heating compound **9** with an excess of iodotrimethylsilane, and the pentacyclic lactam **10** was thus obtained in 90% yield.

In preparation for the formation of the bridging D-ring, secondary amine **10** was alkylated with the allylic bromide **11**. The resulting alkenyl iodide was subjected to the Jeffrey modification of the Heck reaction conditions,[7] furnishing the hexacyclic *strychnan* **13**. Removal of the silyl protecting group under acidic conditions gave *iso*-strychnine, which was subjected to base-mediated isomerisation to afford (±)-strychnine itself.

1.5 Reissig's Synthesis of (±)-Strychnine

Earlier this year, Beemelmanns and Reissig published an impressively concise formal total synthesis of strychnine,[6] the pivotal element of which was a samarium iodide-induced cascade reaction to form two rings of strychnine in a single step. This work sets a new benchmark for brevity in the total synthesis of strychnine, proceeding over seven steps and 22% yield to Rawal's precursor **12**, which could be converted, over a further three steps, into the racemic modification of the natural product. The details of this remarkable synthesis are presented in Scheme 2.



Scheme 2. Formal total synthesis of Strychnine by Beemelmanns and Reissig.[6] *Reagents and conditions*: (a) 1. $SOCl_2$ (1.5 eq.), **15**, DCM, 2 h, 2. **14** (1.5 eq.), DMAP (0.1 eq.), TEA (2.0 eq), DCM, 3 d, 82%; (b) 1. 2.4 eq. SmI_2, 10.0-12.0 eq. HMPA, THF, r.t., 5 min; 2. 1.25 eq. bromoacetonitrile, 12 h, 80%; (c) Raney Ni, H_2, 3 d, MeOH, 97%; (d) $ClCO_2Me$, DMAP, TEA, CH_2Cl_2, 4 h, 87%; (e) 1. MsCl, DMAP, TEA, 16 h, 2. DBU, 24 h, 88%; (f) 1. TMSI, $CHCl_3$, 60 °C 2 h, 2. MeOH, 60 °C, 1 h; (g) 1.2 eq. **21**, K_2CO_3, nBu_4NI, CH_3CN, 65% over 2 steps; (h) $Pd(OAc)_2$, K_2CO_3, nBu_4NCl, DMF, 70 °C, 3 h, 68%.

The synthesis starts with commercially available 3-indolylacetonitrile (**14**), which was *N*-acylated with 4-oxopimelic acid monoester (**15**). The resulting ester, **16**, was treated with samarium diiodide in the presence of HMPA, furnishing the diasteromerically pure tetracycle **17** as the major product, which includes appropriate functionality for installation of the C-ring and associated double bond.

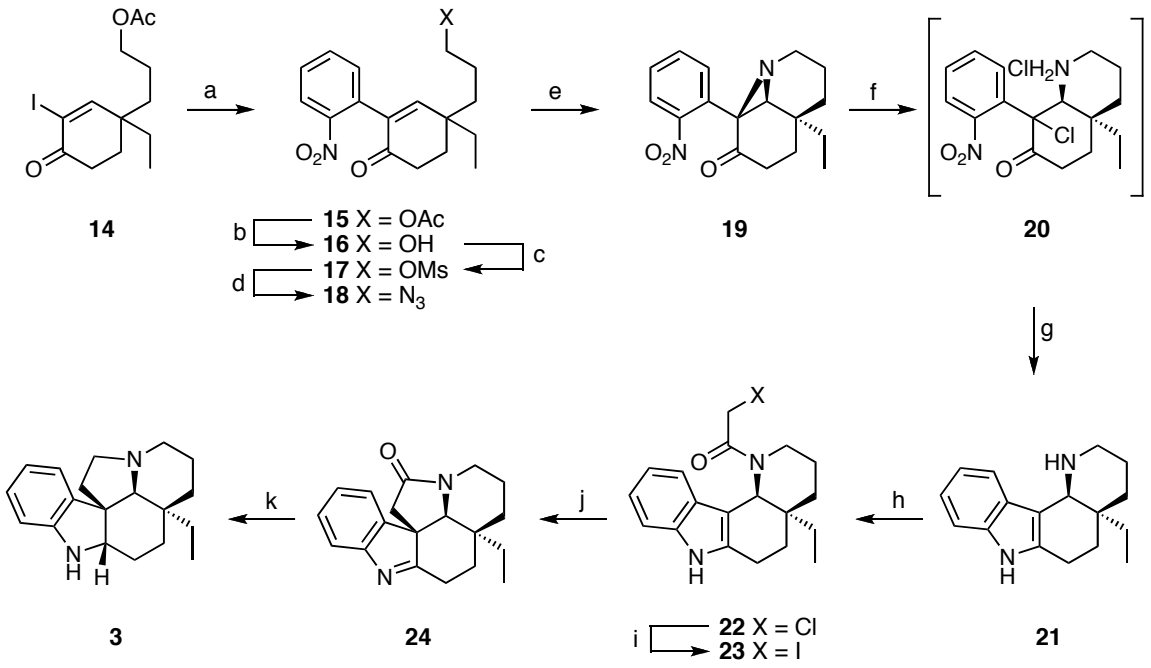
Reduction of the nitrile moiety to the corresponding amine within compound **17** using Raney nickel lead to cyclisation and formation of pentacyclic amine **18** which was obtained as a single diastereomer. The stage was almost set for the forthcoming elimination, but first the secondary amine residue within **18** needed to be protected. This was accomplished *via* acylation with methyl chloroformate, affording compound **19**. Elimination of the tertiary

alcohol contained within this compound could then be effected by treatment of alcohol **19** with mesyl chloride and DBU. By such means, alkene **20** was obtained in 88% yield.

In anticipation of implementing Rawal's end-game, namely using an intramolecular Heck reaction to form the D-ring, this compound was deprotected and subsequently alkylated to form the known strychnine precursor **12**. Finally, this compound was subjected to the Heck reaction itself, which afforded TBS-protected isostrychnine (**13**) in 68% yield, and thereby establishing a formal total synthesis of strychnine.

1.6 Relevant Past Work: The Lupton/Banwell Synthesis of the Structurally Related Alkaloid (±)-Aspidospermidine

As part of a program directed towards the total synthesis of the anti-cancer agent vinblastine, Banwell and co-workers published a report, in 2005,[8] on the total synthesis of the natural product (±)-aspidospermidine (**3**). The key aspects of the synthesis are shown in Scheme 3.



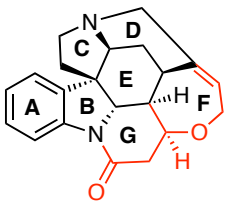
Scheme 3. Excerpt from the total synthesis of aspidospermidine by Banwell *et al.*[8] *Reagents and conditions*: (a) *o*-iodonitrobenzene, Cu, $Pd_2(dba)_3$ (cat.), DMSO, 70 °C, 5 h, 75%; (b) 1 M aq. K_2CO_3, MeOH, 18 °C, 16 h; (c) MsCl, TEA, Et_2O, 0 → 18 °C, 2 h; (d) NaN_3, DMF, 67 °C, 3 h, 87% from **15**; (e) C_6H_6, 75 °C, 72 h, 72%; (f) 1 M HCl in Et_2O, CH_2Cl_2, -15 °C, 1.5 h; (g) $TiCl_3$•3THF in 1/2/2 v/v/v H_2O/2.5 M aq. NH_4OAc/acetone, 18 °C, 0.33 h, 46% from **19**; (h) α-chloroacetyl chloride, TEA, CH_2Cl_2, 0 → 18 °C, 2 h, 69%; (i) NaI, acetone, 56 °C, 2 h; (j) AgOTf, THF, 18 °C, 0.5 h, 50% from **22**; (k) $LiAlH_4$, THF, 66 °C, 4 h, 77%.

The elements of this work that are relevant to the proposed synthesis of strychnine described in the following sections begins with the Ullman cross-coupling of compound **14** with *o*-iodonitrobenzene in the presence of copper powder and using $Pd_2(dba)_3$ as the catalyst. In this manner, the α-arylated enone **15** was obtained. Exposure of this product to K_2CO_3 afforded the corresponding alcohol **16**, which was converted under standard conditions into the mesylate **17**. The latter compound was, in turn, treated with NaN_3 to afford azide **18** in 87% yield from acetate **15**.

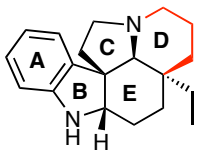
The stage was now set for the installation of the D-ring. To this end, the key 1,3-dipolar cycloaddition reaction was performed by heating a dilute solution of azide **18** in benzene at *ca.* 75 °C for three days and in this way the ring-fused aziridine **19** was obtained in 72% yield. Regioselective cleavage of the aziridine **19** was achieved by treating it with an ethereal solution of HCl. The resulting, highly unstable hydrochloride salt **20**, was obtained in quantitative yield and as a single diastereoisomer. This was then subjected to reduction with titanium trichloride in the presence of ammonium acetate, furnishing tetryhydrocarbazole **21** in 46% yield from aziridine **19**.

With the D-ring in place, all that remained was the installation of the C-ring, which was done by first converting carbazole **21** into the α-chloroamide **22** (69%) using α-chloroacetyl chloride. Compound **22** was, in turn, converted into the corresponding α-iodoamide **23** under Finkelstein conditions. Treatment of this last compound with silver(I) triflate then gave lactam **24** (50% from **22**) which was reduced with $LiAlH_4$ to give (±)-aspidospermidine (**3**, 77%).[8]

Strychnine has a similar structure to aspidospermidine, the key differences being the presence of the F- and G-rings on the south-eastern side of the former structure, and the 1,3-fusion of the D-ring, the equivalent ring in aspidospermidine having a 1,2-mode of ring-fusion.



1
[(-)-strychnine]

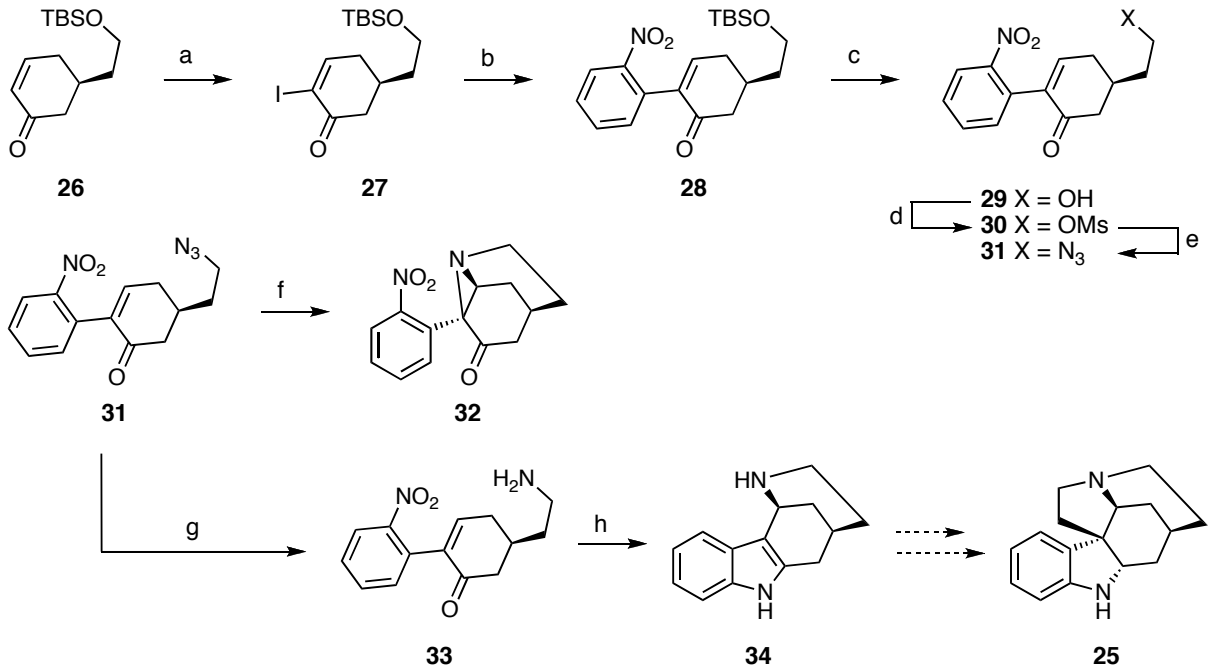


3
[(-)-aspidospermidine]

Noting the similarities in structure between aspidospermidine and strychnine, a total synthesis of strychnine was proposed that would exploit the chemistry developed during the course of the synthesis of aspidospermidine.

1.7 Relevant Past Work: A New Approach to the ABCDE-Ring System of Strychnine

Attention was turned to the structural differences between aspidospermidine and strychnine, in particular, the differing modes of attachment of the D-ring to the remainder of each of these structures. This difference could affect the applicability of the aspidospermidine synthesis protocols to the synthesis of strychnine. To test this, a model study is being conducted by Mr. Tristan Reekie, who is targeting compound **25** – an analogue of strychnine, lacking the F- and G-rings that are also absent in aspidospermidine. The progress Reekie has made to date is presented in Scheme 4.



Scheme 4. Progress of model study. *Reagents and conditions:* (a) I_2, CH_3Cl/pyridine, 89%; (b) *o*-iodonitrobenzene, Pd(0)/Cu(0), 92%; (c) HCl, 100%; (d) MsCl, TEA, 98%; (e) NaN_3, 76%; (f) mesitylene, reflux, 15%; (g) PPh_3, H_2O/THF; (h) Zn, HCl/MeOH, 85% over 2 steps.

Thus, the known cyclohexenone derivative **26**[9] was iodinated and then subjected to Ullman cross-coupling conditions along with *o*-iodonitrobenzene, which resulted in formation of the

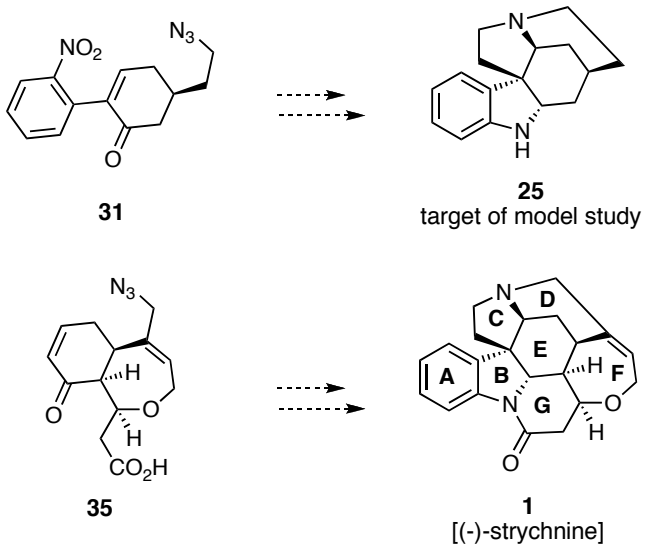
coupled product **28** in excellent yield. Compound **28** was then deprotected and the ensuing alcohol mesylated. The mesylate so-formed was then converted into the corresponding azide **31** in anticipation of carrying out the pivotal intramolecular 1,3-dipolar cycloaddition reaction.

When azide **31** was subjected to conditions known to affect the cycloaddition reaction, the desired aziridine product **32** was obtained and its structure confirmed by X-ray crystallography. However, the reaction proceeded in poor yield (15%), so another means was sought to achieve this transformation. To this end, azide **31** was reduced to the corresponding amine (**33**), which was then subjected to a zinc-promoted domino cyclisation reaction, furnishing tetracyclic indole **34** in 85% yield over the two steps involved.

Although a work in progress, this study has shown that the critical cyclisation reaction required to form the D-ring of strychnine can be achieved, providing support for the hypothesis that a total synthesis of strychnine could be achieved *via* this type of approach. Continuing work on this project will focus on completing the synthesis of target compound **25**.

1.8 Project Aim

The aim of the research described herein was to synthesise compound (±)-**35** in a manner that could be easily be adapted to the synthesis of either enantiomer in pure form or in high e.e. Future work will aim to establish a total synthesis of strychnine starting with this compound and following the protocol developed in the model study described above. In such a synthesis, target **35** would provide the functionality required to establish the F- and G-rings of strychnine, which are not present in the target compound (**25**) of Reekie's model study.



Such a synthesis would be valuable for two reasons. Firstly, it would showcase the Pd[0]-catalysed Ullman cross-coupling reaction, particularly in terms of its utility in synthesising indole derivatives.[10] Secondly, this synthesis would present an innovative approach to strychnine. Most existing syntheses construct the molecule beginning with the indole moiety or part thereof intact, whereas this synthesis would begin by constructing the E- and F-rings, on the opposite side of the molecule. This approach would provide access to strychnine analogues unlikely to be readily accessible by other means.

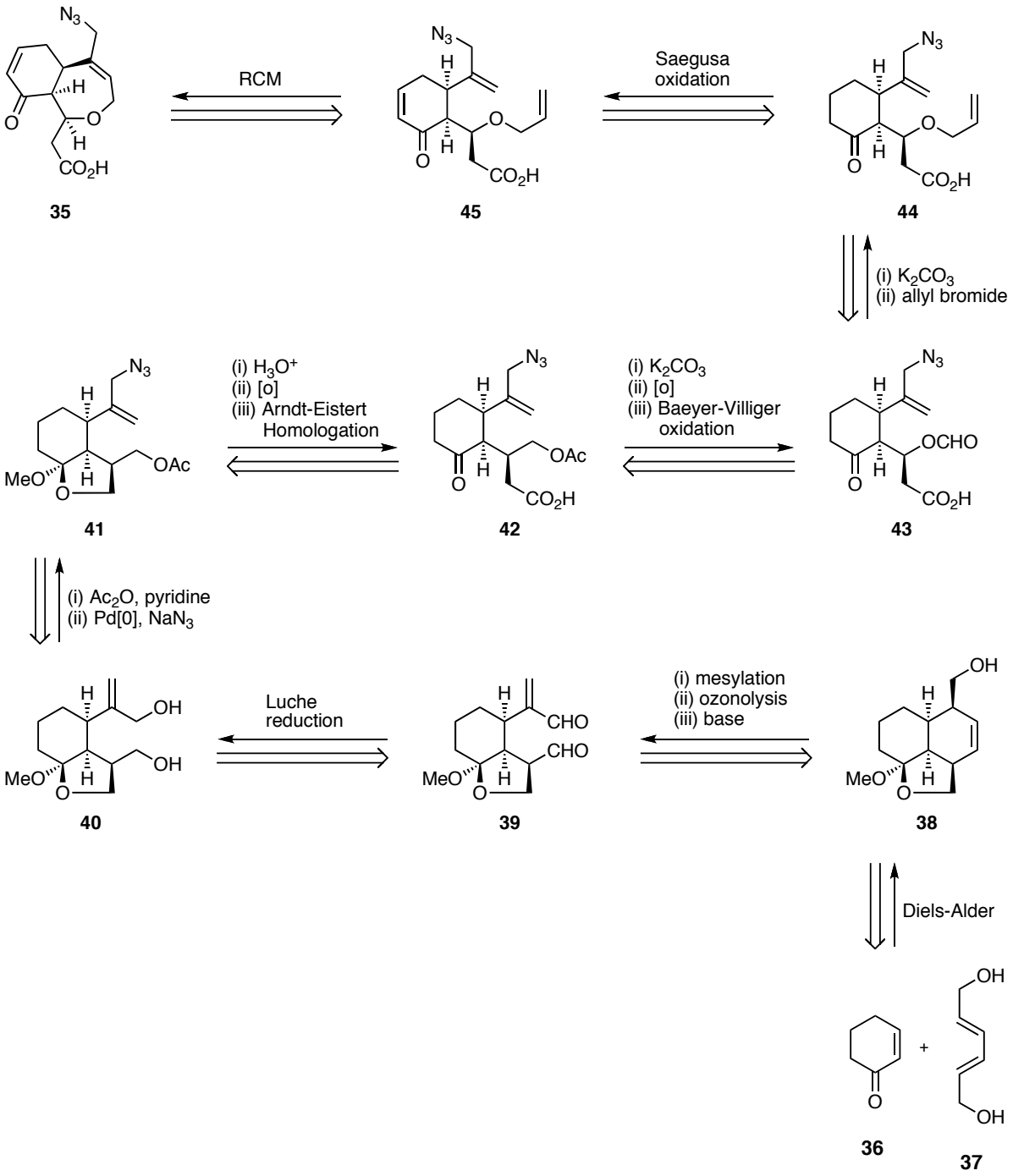
2 Retrosynthetic Analysis of Target Molecule and the Identification of Key Reactions and Intermediates

2.1 Retrosynthetic Analysis

The target molecule **35** presents a significant synthetic challenge given the presence of three contiguous stereocentres and a seven-membered heterocyclic ring. An approach that attempts to address these challenges in an economical manner is outlined in retrosynthetic form in Scheme 5.

In realising a total synthesis of target **35**, there are three significant conversions that need to be achieved, namely the Diels-Alder cycloaddition reaction to form the tricyclic system **38**, the ring-opening of the mesylate-protected form of this product through ozonolytic cleavage of the double bond so as to form compound **39** upon elimination of the mesylate, and the ring-closing metathesis of diene **45** to generate the seven-membered heterocyclic ring.

Before detailing the implementation of this plan, a general commentary is provided on each of these pivotal steps of the proposed synthesis.



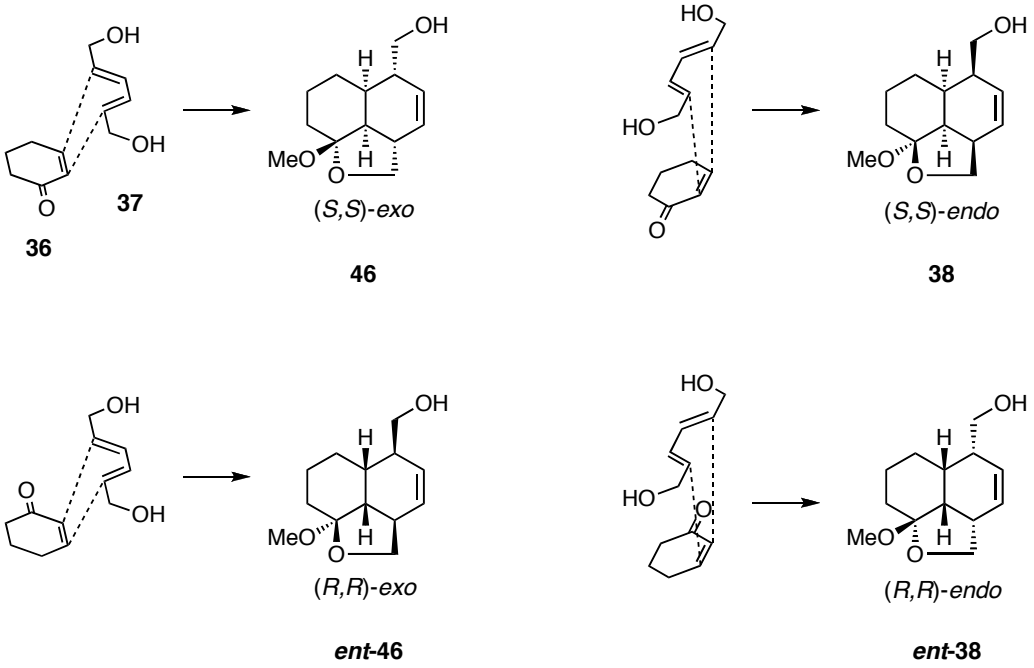
Scheme 5. Retrosynthetic analysis of target **35**.

2.2 The Diels-Alder Cycloaddition Reaction

The use of the Diels-Alder cycloaddition reaction at the beginning of the synthesis is a powerful step that not only establishes the three stereogenic centres associated with the target compound, but also provides protection of the "southern" alcohol group through a concomitant ketalisation reaction, thereby forming the tricyclic compound **38**. In principle, the use of this reaction provides the opportunity to establish an enantioselective synthesis through the use of a chiral Lewis acid to promote the cycloaddition process. In analysing the title reaction (a normal electron demand Diels-Alder reaction), the factors of stereoselectivity and reactivity will be addressed.

In a Diels-Alder cycloaddition reaction involving a symmetric diene such as that between dienophile **36** and diene **37**, *endo*-*exo*- and facial-stereoselectivity must be considered. Figure 1 shows all the possible transition states that could be involved and the products that would be expected to arise from these transition states.

Figure 1. The possible products of a Diels-Alder reaction between substrates **36** and **37**.

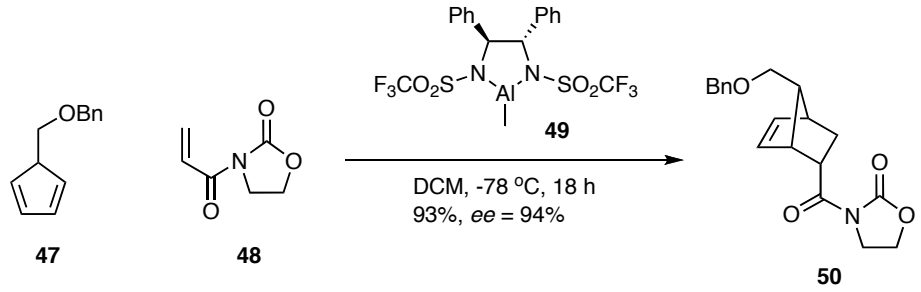


The relative stereochemical outcome of the Diels-Alder reaction is determined by the transition state, which may be *endo*-mode, with the bulkier sides of the diene and dienophile placed above one other, or *exo*-mode, in which these sides face away from one another.

Selectivity between the *endo*- and *exo*-modes of cycloaddition results from an interplay of two factors. The *exo*-mode transition state is thermodynamically more stable due to steric effects. However, the product formed *via* the *endo*-transition state usually predominates, and this is attributed to stabilising effects arising through secondary orbital interactions in the transition state.[11] A previous study of the *endo*-*exo* diastereoselectivity of the Diels-Alder reaction between cyclohexenone and various acyclic dienes[12] found almost complete selectivity for the product arising from involvement of the *endo*-transition state.

Facial selectivity, and thus control of absolute stereochemistry, is dependent on which face of the dienophile is approached by the diene. Given the achiral nature of the dienophile, a racemic mixture of products would be expected. In situations such as these, enantioselectivity might be achieved through the use of a chiral Lewis acid.[11]

For example, Corey and Sarshar have shown that when **47** and **48** were reacted in the presence of the chiral Lewis acid catalyst **49**, cycloadduct **50** was obtained in 93% yield and 94% enantiomeric excess.[13]



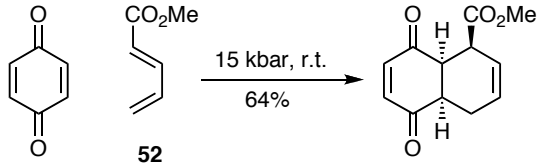
47 **48** **50**

The facility of a Diels-Alder reaction depends on the HOMO / LUMO energy separation of reacting components. A smaller separation results in a lower activation energy, while a larger separation results in a higher activation energy. In normal electron demand Diels-Alder reactions (as would be involved in the reaction of compounds **36** and **37**), the HOMO of the diene interacts with the LUMO of the dienophile. Therefore, the reactivity can be improved by increasing the electron density of the diene (increasing the energy of the HOMO) or by decreasing the electron density of the dienophile (decreasing the energy of the LUMO).[11]

A number of techniques are known for facilitating Diels-Alder reactions between otherwise unreactive compounds. These may involve forcing conditions (eg. the use of microwave

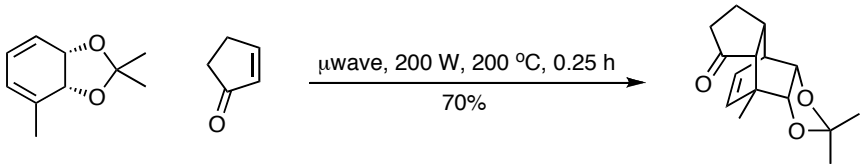
radiation or high pressure conditions) or exploitation of electronic effects (eg. Lewis acid catalysis and ionic Diels-Alder reactions).[14] The following are some typical examples of these methods.

As an example of the use of high-pressure conditions to affect a Diels-Alder reaction, Dauben and co-workers synthesised **53** from *p*-benzoquinone **51** and the electron-deficient diene **52** in 64% yield.[15] The use of high pressure replaced the need for higher temperatures, a feature that avoided loss of the product **53** due to aromatisation.



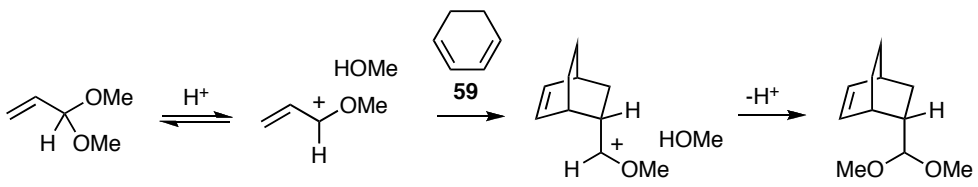
51 **52** **53**

The use of microwave reactors provides a cheap and convenient method to facilitate a range of processes, including Diels-Alder cycloaddition reactions. In a paper published by Reekie and co-workers,[16] the acetonide-protected dihydrocatechol derivative **54** together with cyclopentenone **55** was subjected to microwave irradiation for 15 minutes, affording the Diels-Alder adduct **56** in 70% yield.



54 **55** **56**

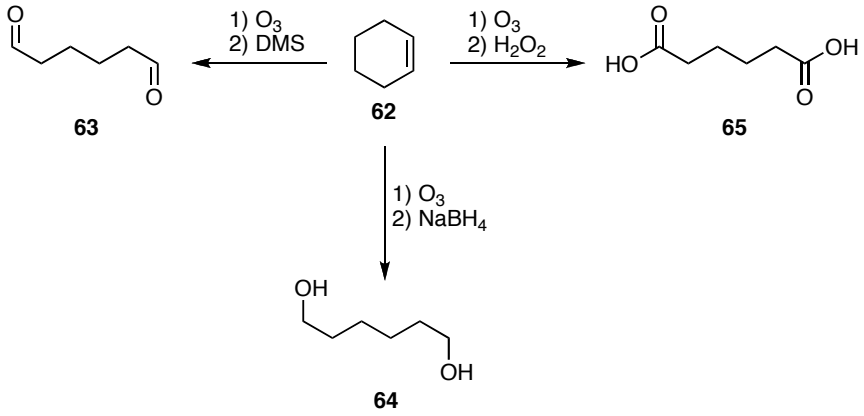
Ionic Diels-Alder reactions, proceeding through a highly activated allyl cation such as **58**, have been shown to afford moderate to excellent yields of the desired cycloadduct in situations otherwise requiring long reaction times at high temperature.[17] The following is a reaction reported by Gassman and co-workers which proceeded in 57% yield.



57 **58** **60** **61**

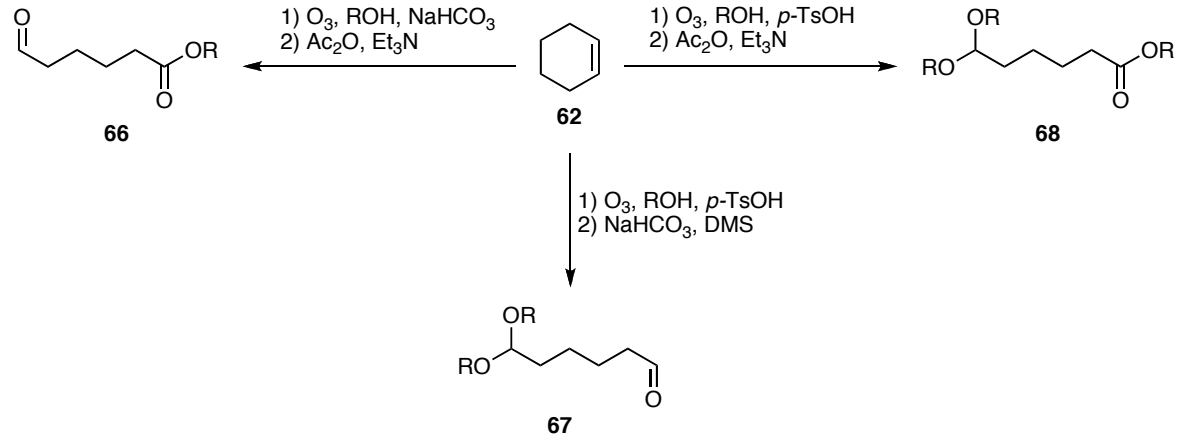
2.3 The Ozonolysis Reaction

The ozonolysis reaction provides a route to a range of products, the nature of which depends on the choice of the workup procedure applied to the unstable intermediate ozonide. Aldehydes, ketones, carboxylic acids and/or alcohols can all be produced, depending on the starting alkene and the conditions used (Scheme 6).[18]



Scheme 6. Possible products obtained through symmetrical ozonolysis.

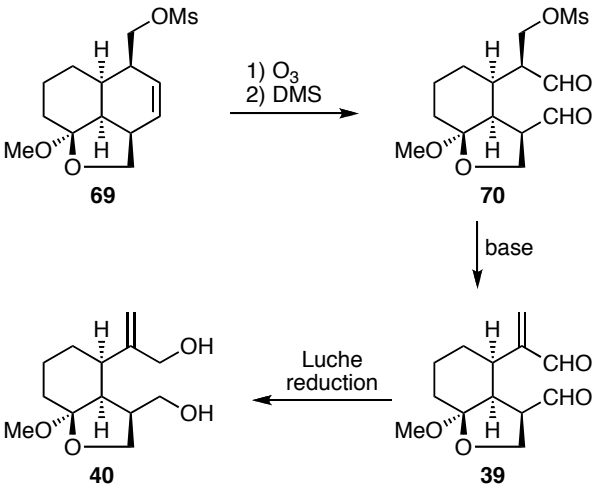
Furthermore, desymmetrising ozonolysis is known,[19] allowing for differentiation between the terminii of the cleaved double bond associated with the symmetrical starting olefin. Through the use of various reagents, an aldehyde-ester-, acetal-aldehyde- or acetal-ester- containing product may be obtained (Scheme 7).



Scheme 7. Possible products obtained through desymmetrising ozonolysis.

It is anticipated that the hydroxy groups of Luche reduction[20] product **40** will be differentiable because one is an allylic alcohol and the other is not. However, if this difference in reactivity proves insufficient to provide chemoselectivity, desymmetrising ozonolysis of **69** would provide an alternative approach to dealing with this matter.

The ordering of steps in this segment of the synthesis is critical. After treatment with ozone, the resulting ozonide is converted into an aldehyde rather than proceeding directly to a diol as the aldehyde is predicted to be more reactive in the subsequent elimination reaction due to the acidity of the proton alpha to the aldehyde.

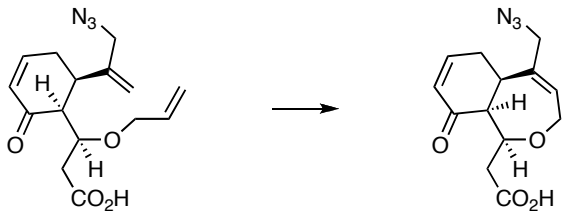


69 **70** **40** **39**

Following the elimination reaction, a Luche reduction is expected to reduce the resulting α,β-unsaturated aldehyde to the corresponding diol in a 1,2-fashion without affecting the double bond. The selectivity in the Luche reduction is attributed to the formation of various alkoxyborohydride species (*via* cerium trichloride catalysis) that are harder nucleophiles than the unmodified borohydride. This favours addition at the carbonyl carbon (a relatively hard electrophilic centre) and disfavours addition to the conjugated double bond (a relatively soft electrophilic centre).[21]

2.4 The Ring-Closing Metathesis Reaction

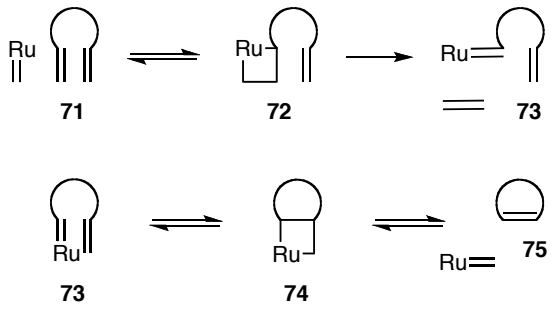
Ring-closing metathesis is a very valuable method for the formation of medium-sized and macrocyclic rings, with remarkable tolerance for different functional groups.[22] Considering that the starting compound **45** contains three olefin moieties, any of which might in principle participate in a metathesis reaction, the issue of regioselectivity is critical to the successful application of this reaction.



45 **35**

The loss of ethane is known to be the driving force of the RCM reaction.[23] As this can only occur *via* the reaction involving two terminal olefin moieties, it is anticipated that any reaction involving the internal double bond will be reversible and thus an undesired product arising from this reaction will not be observed.

Additionally, alkenes incorporating electron-withdrawing substituents have been shown to undergo RCM reactions more slowly than those that are more electron-rich.[24] Therefore, it is expected that the enone double bond of compound **45** would not participate in a metathesis reaction due to the electron-withdrawing carbonyl group, and that the desired product **35** would be formed through metathesis of the two terminal, and relatively electron-rich alkene groups.



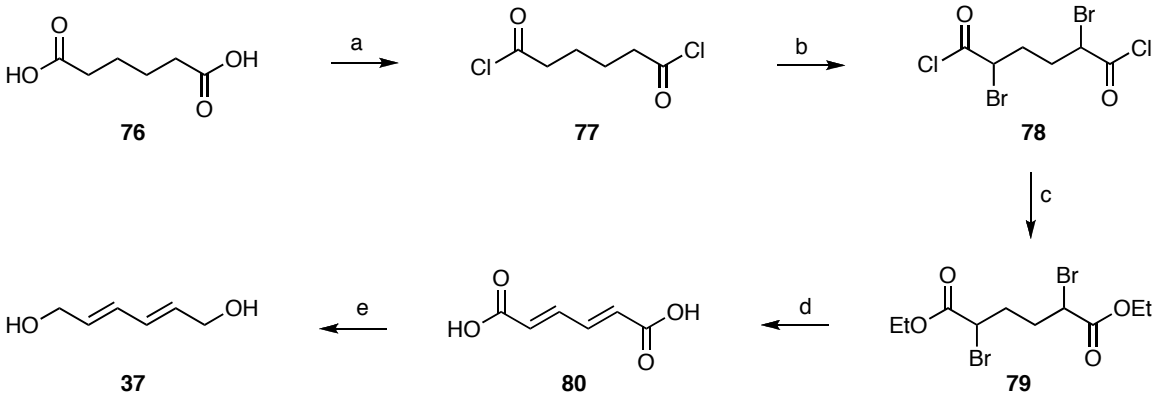
Scheme 8. Mechanism of the Ring-closing metathesis reaction.[25]

3 Results and Discussion

This section describes the implementation of the proposed reaction sequence detailed above.

3.1 The Diels-Alder Cycloaddition Reaction

Research into the title reaction began with the preparation of the relevant precursors. The dienophile, cyclohexenone **36**, was commercially available, but diene **37** was not, so it was synthesised following an established procedure,[26] using an application of the Hell-Volhard-Zelinsky reaction, as described in Scheme 9.



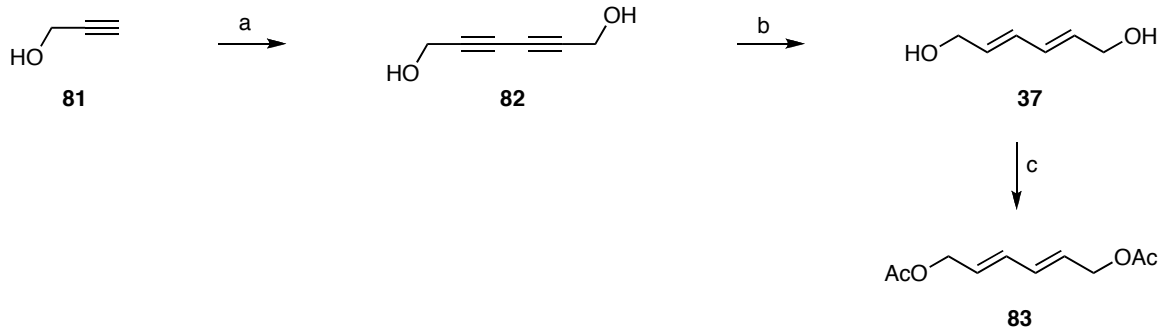
Scheme 9. *Reagents and conditions:* (a) $SOCl_2$, 75 °C, 2 h; (b) Br_2, 59 °C, 20 h; (c) EtOH, 0 °C → r.t., 7 h; (d) KOH, 65 °C, 16 h; (e) LAH, 66 °C, 16 h, 43% from **76**.

Thus, commercially available adipic acid **76** was treated with thionyl chloride. After removal of the excess reagent, the resulting di-acid chloride was brominated at the α-carbons and quenched with ethanol, thus affording the α-bromo-ester **79**. The subsequent elimination reaction was effected by heating this compound with potassium hydroxide for 16 hours, furnishing diene-acid **80**, which was reduced with LAH to afford the required diene-diol **37** in 43% yield over five steps from adipic acid.

Although diene **37** could be obtained by the pathway just described, purification of the final product proved difficult, so an alternate route was sought. To this end, commercially available propargyl alcohol **81** was subjected to a nickel-catalysed oxidative coupling protocol,[27] affording diyne **82** in excellent yield. Compound **82** was then reduced with LAH, following the protocol reported by Doyle *et al.*,[28] to produce the diene-diol **37** in 45% yield over two steps.

This diene later proved to have low solubility in several non-polar solvents that were considered appropriate media for the Diels-Alder reaction. Accordingly, the more soluble

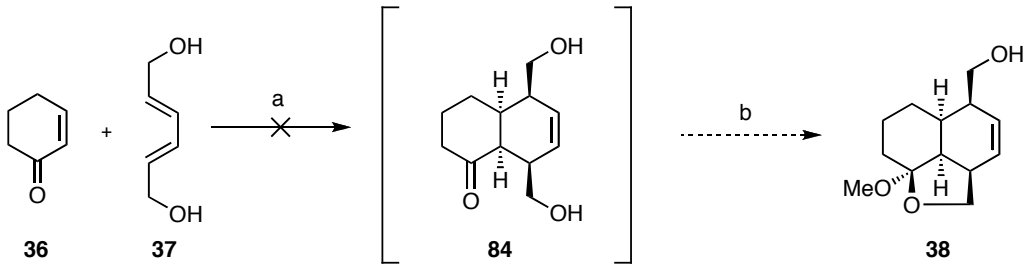
acetate derivative **83** was also synthesised by treating diene-diol **37** with acetic anhydride along with DMAP and triethylamine, producing acetate **83** in excellent yield (Scheme 10).



Scheme 10. *Reagents and conditions:* (a) $NiCl_2 \bullet 6H_2O$, TMEDA, CuI, THF, 16 h, 93%; (b) LAH, 66 ^oC, 20 h, 48%; (c) Ac_2O, DMAP, TEA, 0.5 h, 98%.

The spectral data gathered on acetate **83** support the assigned structure. The low resolution mass spectrum, as well as displaying the molecular ion, showed a prominent fragment at *m/z* 138, resulting from the loss of the elements of acetic acid from the molecular ion. The ^{13}C NMR spectrum of this material showed just five signals as would be expected for compound **83** which is a symmetrical species.

With dienes **37** and **83** as well as the dienophile **36** in hand, the Diels-Alder reaction could be attempted. To this end, mixtures of cyclohexenone **36** and diene-diol **37** were subjected, as shown in Scheme 11, to the various reaction conditions shown in Table 1.



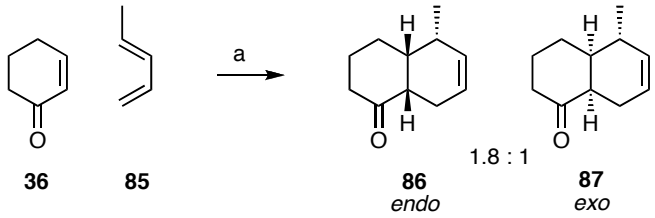
Scheme 11. *Reagents and conditions:* (a) see Table 1; (b) MeOH, H^+.

Table 1. Diels-Alder reaction conditions applied to compounds **36** and **37**.

Exp.	Temp (^{o}C)	Time (h)	Solvent	Notes	Outcome
1	110	24	PhMe		Dimerisation of **36**
2	120	1	MeOH	μwave, 300 W	Dimerisation of **36**
3	-78 → +66	12	THF	1.0 eq. BF_3•Et_2O	Decomposition

None of these conditions produced the desired product, and instead resulted in either the recovery of a suspected dimerisation product of cyclohexenone, or the decomposition of the starting materials.

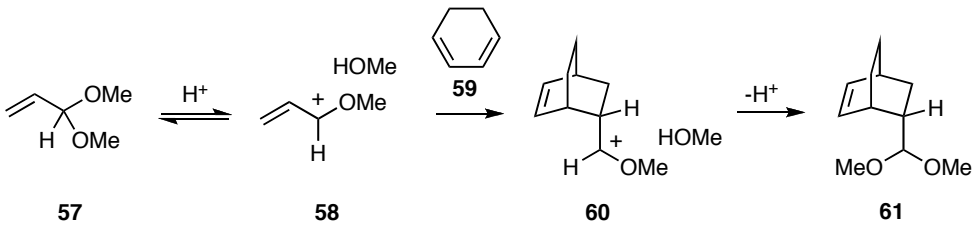
Fringuelli and co-workers have reported on the Diels-Alder reactions of cycloalkenones (including cyclohexenone), with various dienes and using $AlCl_3$ as a Lewis acid catalyst.[29] In a representative example, cyclohexenone and isoprene were reacted together in the presence of aluminium trichloride, thus furnishing a 1.8 : 1 mixture of the *endo*- and *exo*-forms of the expected product (Scheme 12).



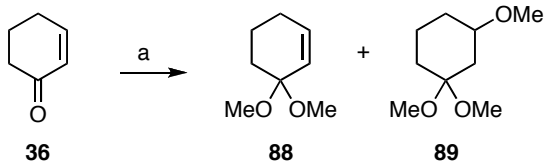
Scheme 12. *Reagents and conditions:* (a) $AlCl_3$ (0.25 eq.), 40 ^{o}C, 4 d, 81%.

The same protocol was used in an effort to effect reaction of cyclohexenone **36** with dienes **37** and **83**, but no useful outcomes were observed. It is expected that both the alcohol and acetate dienes **37** and **83** used would be less reactive than isoprene **85** as used by Fringuelli due to the inductive electron-withdrawing effect of the alcohol or acetate groups associated with these compounds. Additionally, the $AlCl_3$ would be expected to competitively coordinate with the alcohol or acetate groups on the diene, and thus reduce the availability of the catalyst to coordinate to the dienophile. Complexation of the $AlCl_3$ to the dienes would further deactivate these systems towards the desired Diels-Alder cycloaddition reaction. Furthermore, both of these dienes are more sterically hindered than isoprene, which would also decrease their reactivity.

Cyclohexenone is known to be a relatively unreactive dienophile.[29] With Lewis acid catalysis being unsuccessful, it was thought that an ionic Diels-Alder reaction, proceeding through a highly activated oxonium ion analogous to **58**, might be successful. Gassman and co-workers have reported on such reactions using acrolein acetals as allyl cation precursors,[17] a relevant example of which is presented in section 2.2, and is repeated below.



In order to investigate such a process, oxonium ion precursor **88** was required. Its synthesis was initially attempted *via* ketalisation of cyclohexenone with methanol. Thus, a solution of cyclohexenone in methanol was treated with *p*-toluenesulfonic acid and trimethylorthoformate, as described in Scheme 13. However, under these conditions compound **89** was the exclusive product of the reaction.



Scheme 13. *Reagents and conditions:* (a) MeOH, $(MeO)_3CH$, acid (cat.).

Several attempts were made to modify the outcome of this reaction by changing the acid catalyst, the reaction temperature and the concentration of substrate **36**. These attempts are summarised in Table 2.

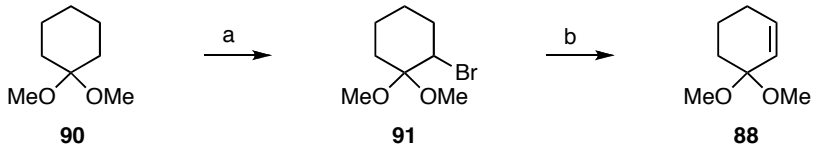
Table 2. Reaction conditions applied to substrate **36**.

Exp	Acid catalyst	Temperature	Concentration of 36	Ratio of products 88 : 89
1	Amberlyst-15	-78 °C	neat	0:1
2	*p*-TsOH	-78 °C	neat	1:15
3	(+)-CSA	-78 °C	neat	1:2
4	(+)-CSA	-78 °C	0.1 M in THF	1:0
5	(+)-CSA	-78 °C	1 M in THF	1:0
6	(+)-CSA	-78 °C	4 M in THF	Mixture[a]
7	(+)-CSA	-40 °C	1 M in THF	Mixture[a]

All reactions were performed with $(MeO)_3CH$. [a]Ratio was not determined.

Experiments 1, 2 and 3 show the results of the use of different acid catalysts, and demonstrate that the use of the weaker acids gave more favourable results. Experiments 4 and 5 show reactions carried out at 1 M concentrations at -78 °C allowed for completely selective formation of the desired product **88**. Experiments 6 and 7 demonstrate that the use of a more concentrated solution or of a higher temperature resulted in a loss of selectivity.

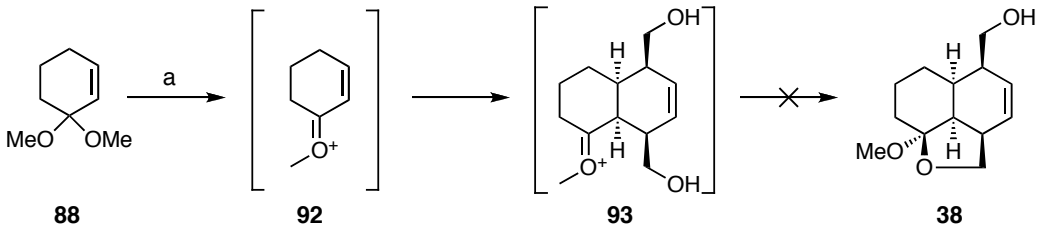
The optimised conditions shown in experiment 5 allowed for the synthesis of the target ketal **88**. However, the reaction proceeded very slowly under these conditions, so an alternate synthesis published by Garbisch was investigated.[30] Thus, as described in Scheme 14, cyclohexanone dimethyl ketal **90** was brominated and the resulting bromo-ketal **91** was treated with sodium hydroxide in methanol. The consequent elimination of the elements of hydrobromic acid proceeded slowly, and a small but usable yield of target **88** was obtained along with recovery of the starting material, **91**.



Scheme 14. *Reagents and conditions:* (a) Br_2, MeOH, 65 °C, 1 d, 80%; (b) NaOH, MeOH, 65 °C, 4 d, 4%.

With cyclohexenone dimethyl ketal **88** in hand, the Diels-Alder reaction between it and diene **37** was attempted following the protocol outlined by Gassman *et al.* (Scheme 15). However,

this reaction produced a complex mixture of products, with only a trace of a compound with the correct molecular weight being observed in the electron impact mass spectrum of the mixture.



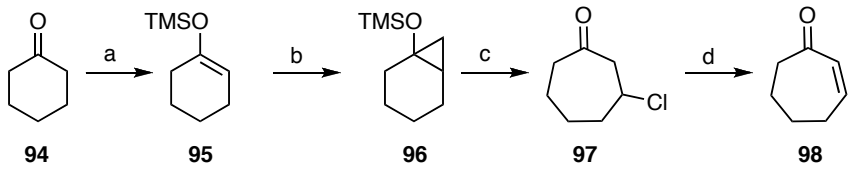
88 **92** **93** **38**

Scheme 15. *Reagents and conditions:* (a) TfOH, **37**, DCM, -78 °C → r.t.

The insolubility of the diene **37** in the reaction solvent (DCM) was thought to be the cause of some of the difficulties encountered in getting the desired reaction to take place in an efficient manner, and the use of low temperatures was thought to be exacerbating these difficulties. However, given the complex mixture of products obtained, the reaction was deemed to be synthetically non-viable, and attention was returned to using cyclohexenone iself rather than the corresponding oxonium ion **92**.

High pressure conditions are known to be very effective in promoting Diels-Alder reactions due to their large negative activation and reaction volumes.[14] Reactions under these conditions are commonly performed in "light" solvents such as DCM, that do not freeze at high pressure. In order to avoid solubility problems, which would have been exacerbated at high pressure, the less polar and more soluble diacetate diene **83** was used in investigating the high pressure reactions. However, when a solution of diene **83** and cyclohexenone **36** in DCM was subjected to 19 kbar of pressure for 25 h, no reaction was observed.

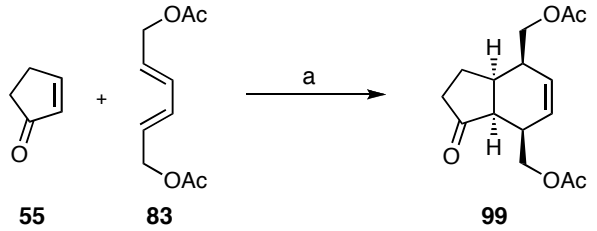
Cyclopentenone is known to be a more reactive dienophile then cyclohexenone,[29] so an alternative route was proposed in which the 5/6-membered fused ring system was formed, followed by a ring expansion later in the sequence. It was envisioned that this procedure might be used to simultaneously introduce the double bond required in the final compound, thus decreasing the number of additional steps required. A plausible procedure to achieve this, published by Ito and co-workers, was identified.[31] An application of this procedure to the synthesis of 2-cyclohepten-1-one (**98**) is presented in Scheme 16.



Scheme 16. *Reagents and conditions:* (a) TMSCl, TEA, 153 ^{o}C, 6 h, 81%; (b) CH_2I_2, Et_2Zn, 35 ^{o}C, 8 h, 80%; (c) $FeCl_3$, r.t., 2 h; (d) NaOAc, 65 ^{o}C, 3 h, 80% over 2 steps.

Thus, in Ito's procedure, a cycloalkanone is converted, under standard conditions, into the corresponding TMS enolate, which is then cyclopropanated with diiodomethane in the presence of diethyl zinc. This compound then undergoes ring opening and chlorination upon treatment with iron trichloride. Finally, elimination of the elements of HCl with sodium acetate furnishes the ring-expanded enone.

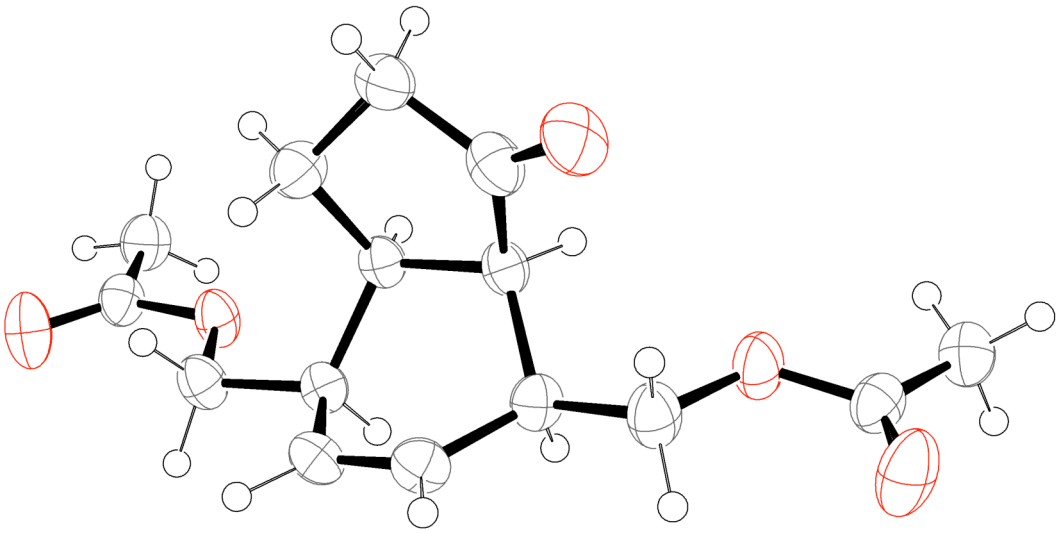
On the basis that a useful protocol exists for the conversion of a cyclopentanone into the corresponding cyclohexenone, the Diels-Alder reaction of the diacetate diene **83** and cyclopentenone **55** was attempted under high-pressure conditions (Scheme 17). Gratifyingly, a long sought after Diels-Alder adduct, **99**, was obtained in acceptable yield (39%).



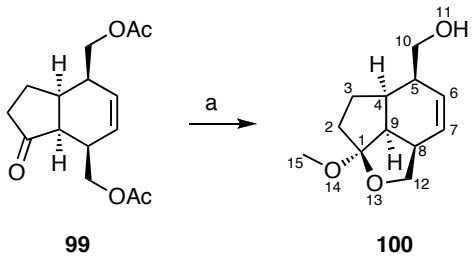
Scheme 17. *Reagents and conditions:* (a) DCM, 19 kbar, 39%.

All of the spectral data obtained on this material were in complete accord with the assigned structure, but final confirmation of this followed from a single crystal X-ray analysis. The derived ORTEP is shown in Figure 2 and further details are presented in the experimental section.

Figure 2. ORTEP derived from compound **99**



The Diels-Alder adduct **99** was subjected to a deprotection/cyclisation reaction by treatment with acidic methanol at reflux (Scheme 18). This acted to simultaneously protect the ketone and "southern" alcohol group through formation of a five-membered heterocycle, whilst deprotecting the "northern" alcohol in preparation for the upcoming protection-ozonolysis-elimination sequence. The reaction proceeded in quantitative yield with no sign of epimerisation at C9.



99 **100**

Scheme 18. *Reagents and conditions:* (a) MeOH, H_2SO_4 (cat.), 1.5 h, 100%.

Having established synthesis of a Diels-Alder adduct using cyclopentenone as the dienophile and utilising high-pressure conditions, a number of alternative conditions were tested, in order to search for a faster, simpler, less expensive and/or safer protocol. The relevant experimental outcomes are detailed in Table 3, and as can be seen, none was found that produced the desired adduct **99**.

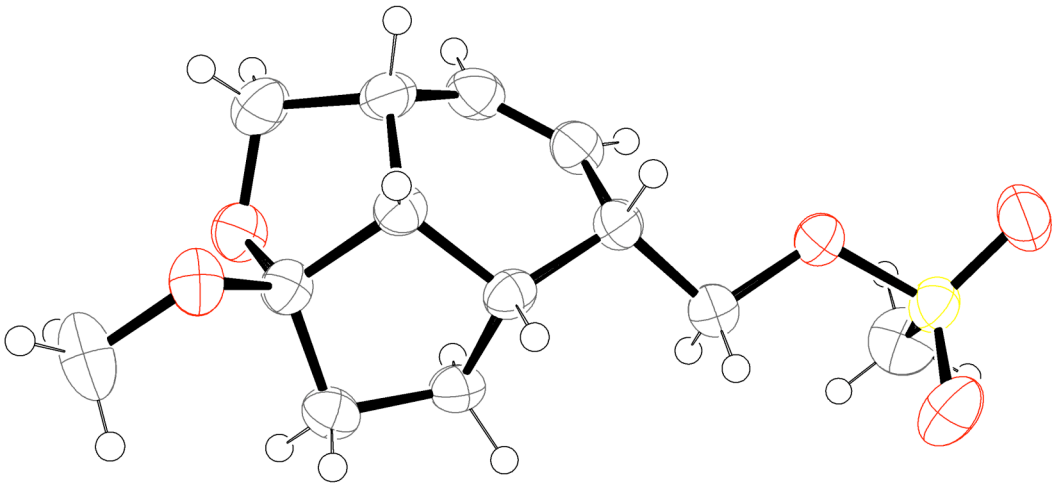
Table 3. Conditions used in attempts to effect a Diels-Alder reaction between cyclopentenone **55** and diene **83**.

Exp.	Catalyst	Solvent	Conditions	Outcome
1	–	PhMe	Reflux	No reaction
2	$AlCl_3$	PhMe	Reflux	Product not formed
3	$BF_3 \bullet Et_2O$	PhMe	-78 $^oC \rightarrow$ reflux	Decomposition
4	–	PhMe	μwave	Product not formed
5	–	DMF	μwave	Product not formed
6	$AlCl_3$	DMF	μwave	Product not formed

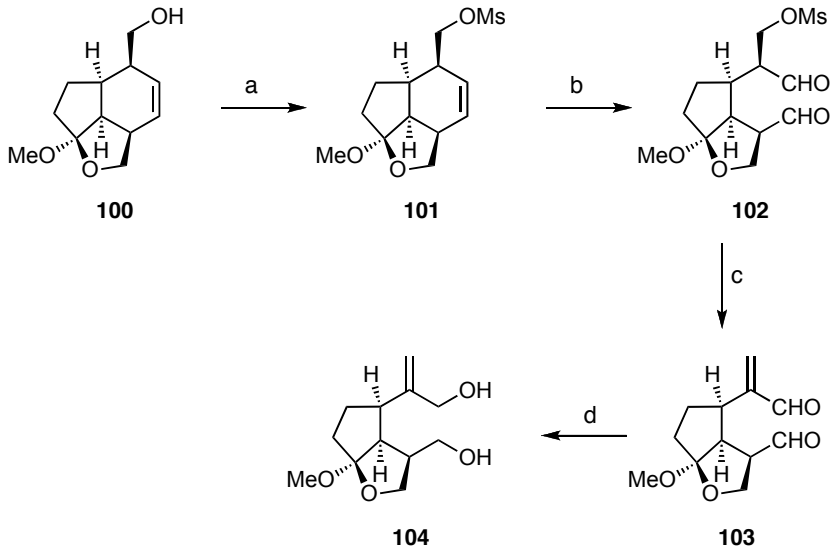
3.2 The Ozonolysis Reaction

In anticipation of carrying out the ozonolysis reaction, alcohol **100** was converted into the corresponding mesylate **101** in excellent yield, under conditions developed by Crossland and Servis (Scheme 19).[32] The spectral data derived from this compound were in complete accord with the illustrated structure. In particular, the ^1H NMR spectrum displayed a three-proton singlet at 3.04 ppm arising from the methyl group protons of the newly introduced mesyl group. Final confirmation of the structure came by single crystal X-ray analysis. The ORTEP derived from this compound is shown in Figure 3, and remaining details are presented in the experimental section.

Figure 3. ORTEP derived from mesylate **101**

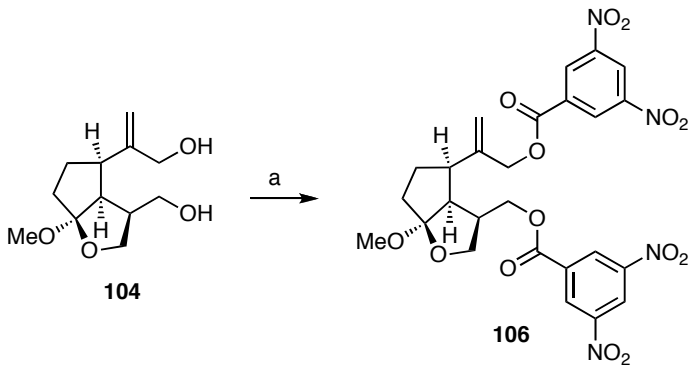


In initial efforts to effect the pivotal oxidative cleavage of the double bond within compound **101**, a small sample of this material was treated with ozone, and the crude material obtained was subjected to reductive workup with dimethylsulfide, affording dialdehyde **102**. This compound was treated with DBU so as to effect the elimination of the elements of methanesulfonic acid, furnishing the α,β-unsaturated aldehyde **103**. Finally, the latter compound was subjected to Luche reduction conditions.[20] In this manner, diol **104** was obtained as an oil in 23% overall yield from alkene **101**. The spectral data obtained from the diol **104** were consistent with the illustrated structure.



Scheme 19. *Reagents and conditions:* (a) MsCl, TEA, 0.5 h, 92%; (b) 1. O_3, -78 °C, 10 min., 2. DMS, 0 °C, 3 h; (c) DBU, -30 °C → r.t., 1 h; (d) $CeCl_3$, $NaBH_4$, MeOH, 0 °C → r.t., 16 h, 23% over 3 steps.

In an effort to generate a crystalline compound for X-ray analysis, diol **104** was converted into the corresponding bis-3,5-dinitrobenzoate by treatment with 3,5-dinitrobenzoyl chloride in the presence of DMAP and triethylamine (Scheme 20). The resulting crystalline diester **106** was obtained, albeit in only 20% yield (an outcome that may reflect the small quantities of diol **104** available). No evidence for the presence of a mono-protected product was seen.



Scheme 20. *Reagents and conditions:* (a) DNBC, TEA, DMAP, DCM, r.t., 0.5 h, 20%.

Unfortunately, all efforts to obtain a viable sample for crystallographic analysis have been unsuccessful thus far. Nevertheless, the ^{1}H NMR spectrum of compound **106** was in complete agreement with the assigned structure. In particular, signals characteristic of a terminal alkene function were visible at 5.38 and 5.25 ppm, each integrating to a single proton. A prominent singlet corresponding to the three protons attached to the methoxy group could be seen further upfield at 3.31 ppm. In the aromatic region, a pair of overlapping triplets assigned to the *para*-protons was observed at 9.24 ppm, and two doublets assigned to the *ortho*-protons were present at 9.18 and 9.11 ppm.

Additionally, an ESI mass spectrum was obtained, which displayed a prominent peak at the mass of the molecular ion plus an atom of sodium. An accurate mass measurement of this species established that it was of the expected composition, *viz*. $C_{26}H_{24}N_4O_{14}Na$. The ^{13}C NMR spectrum of this compound exhibited a low signal to noise ratio due to the small amounts of material available. Nevertheless, 20 of the 22 expected signals were distinguishable, with the 9 signals corresponding to the aliphatic carbon environments of the expected structure clearly present.

Given the time remaining and the dwindling supplies of material available for further experimentation, it was not possible to proceed beyond this point. Nevertheless, significant progress towards target **35** has been made, and compound **106** contains an allylic system that should be capable of engaging in a Pd[0]-catalysed substitution reaction that would introduce the required allylic azide unit. It is anticipated that work in this area will continue in the near future.

4 Conclusion

An effective means of promoting the Diels-Alder reaction between **55** and **83** has been found, and the feasibility of the ozonolysis sequence has been confirmed. Future work will focus on optimising the latter sequence of reactions, and then completing the synthesis of target **35**, with the aim of using this material to complete a total synthesis of strychnine. Additionally, the discovery of a means of promoting the Diels-Alder reaction mentioned above in an asymmetric fashion would allow for an enantioselective total synthesis of strychnine.

More broadly, the solution to the poor reactivity of cyclohexenone as a dienophile described herein, namely replacement of this compound with cyclopentenone followed by ring expansion, may be applicable to other syntheses, and may act as a route to more highly substituted octalones that would normally be unavailable *via* Diels-Alder reaction sequences.

5 Experimental Section

5.1 General Experimental Procedures

Melting points were measured on a Stanford Research Systems Optimelt – automated melting point system and are uncorrected. Unless otherwise specified, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian 400 spectrometer operating at 400 MHz for proton nuclei and 100 MHz for carbon nuclei. For ^{1}H NMR spectra recording in $CDCl_3$ the peak due to residual $CHCl_3$ (δ 7.26) was used as the reference and the central peak (δ 77.0) of the $CDCl_3$ "triplet" was used as the reference point for proton-decoupled ^{13}C NMR spectra. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer and samples were analysed as KBr disks (for solids) or as thin films on KBr plates (for oils). Low-resolution ESI mass spectra were recorded on a Micromass–Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution EI mass spectra were recorded on a VG Fisons AUTOSPEC three-sector double-focussing instrument. Flash chromatographic separations were carried out using the protocols defined by Still *et al.*[33] Acetonitrile, DCM, DMF, ethyl acetate, methanol, THF and toluene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al*.[34] Where necessary, reactions were performed under a nitrogen atmosphere.

5.2 Specific Transformations and Product Characterisation

Hexa-2,4-diyne-1,6-diol (82)

The title compound was prepared from commercially available propargyl alcohol (prop-2-yn-1-ol) using a protocol described by Yin *et al.*[27] The spectral data derived from compound **82**, which was obtained in 93% yield, matched those reported previously.[27]

(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol (37)

The title compound was prepared from **82** using a protocol described by Doyle *et al.*[28] The spectral data derived from compound **37**, which was obtained in 48% yield, matched those reported previously.[28]

2-Bromo-1,1-dimethoxycyclohexane (91)

The title compound was prepared from commercially available 1,1-dimethoxycyclohexane using a protocol described by Garbisch *et al.*[30] The spectral data derived from compound **91**, which was obtained in 80% yield, matched those reported previously.[30]

3,3-Dimethoxycyclohex-1-ene (88)

The title compound was prepared from **91** using a protocol described by Garbisch *et al.*[30] The spectral data derived from compound **88**, which was obtained in 4% yield with recovery of starting material, matched those reported earlier.[30]

(2*E*,4*E*)-Hexa-2,4-diene-1,6-diyl diacetate (83)

A magnetically stirred solution of diol **37** (1.58 g, 13.90 mmol) and DMAP (257 mg, 2.08 mmol) in triethylamine (30 mL) was cooled to 0 ^{o}C then treated with acetic anhydride (8.10 mL, 83.20 mmol). The resulting mixture was allowed to warm to 18 ^{o}C, stirred at this temperature for 0.5 h, then quenched with water and extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane) under reduced pressure afforded the *title diacetate* ***83*** (2.69 g, 98%) as a pale-yellow oil (Found: $M^{+\bullet}$, 198.0889. $C_{10}H_{14}O_4$ requires $M^{+\bullet}$, 198.0892). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.24 (m, 2H), 5.75 (m, 2H), 4.55 (d, J = 6.4 Hz, 4H), 2.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 132.7, 127.9, 64.2, 20.8; ν_{max} 3036, 3008, 2943, 2882, 1739, 1664, 1630, 1443, 1379, 1364, 1233, 1085, 1069, 1025, 993, 960 cm^{-1}; MS (EI, 70 eV) *m/z* 198 ($M^{+\bullet}$, 9%), 139 (23), 138 (60), 97 (36), 96 (72), 95 (49), 81 (25), 79 (51), 78 (31), 77 (33), 68 (56), 67 (100), 66 (27), 65 (21), 53 (21).

[(3a*S*,4*S*,7*R*,7a*S*)-1-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-4,7-diyl]bis(methylene) diacetate (99)

A solution of diene **83** (1.02 g, 5.12 mmol) and 2-cyclopenten-1-one (2.19 mL, 25.60 mmol) in DCM (2 mL) was pressurised to 19 kbar in a PSIKA high-pressure reactor. After 72 h at *ca.* 18 ^{o}C the reaction mixture was removed from the reactor and concentrated under reduced pressure. The residual yellow oil was distilled under reduced pressure at 100 ^{o}C, affording two fractions, A and B.

Concentration of fraction A (boiling at < 100 ^{o}C) afforded unreacted cyclopentenone (0.43 g, 20% recovery) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B (boiling at > 100 ^{o}C) afforded a yellow oil that was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution), affording two fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane) afforded the starting diene **83** (57 mg, 6% recovery) as a pale-yellow oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.4 in 1:1 v/v ethyl acetate/hexane) afforded a light-yellow oil that formed crystals after standing for 16 h. These were triturated with chilled diethyl ether to afford the *title diacetate* ***99*** (553 mg, 39%) as white opaque crystals, mp = 71-73 ^{o}C, (Found: $M^{+\bullet}$, 280.1318. $C_{15}H_{20}O_5$ requires $M^{+\bullet}$, 280.1311). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (dt, *J* = 10.0 and 2.8 Hz, 1H), 5.72 (m, 1H), 4.41 (dd, *J* = 11.0 and 5.0 Hz, 1H), 4.23 (dd, *J* = 11.0 and 6.6 Hz, 1H), 4.18 (dd, *J* = 7.4 and 5.4 Hz, 2H), 2.80-2.60 (complex m, 4H), 2.16 (dd, *J* = 9.8 and 6.2 Hz, 2H), 2.09 (s, 3H), 2.02 (s, 3H), 1.92 (m, 1H), 1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 219.6, 171.0, 170.6, 130.0, 128.3, 65.0, 64.7, 47.1, 38.5, 36.8, 35.2, 34.2, 22.8, 20.9, 20.8; ν_{max} 2960, 2898, 1739, 1385, 1365, 1232, 1035 cm^{-1}; MS (EI, 70 eV) *m/z* 280 ($M^{+\bullet}$, <1%), 161 (20), 160 (94), 130 (21), 119 (27), 118 (94), 117 (39), 105 (55), 104 (100), 96 (23), 91 (60).

{(2a*R*,2a^1*S*,5*S*,5a*S*,7a*S*)-7a-Methoxy-2,2a,2a^1,5,5a,6,7,7a-octahydroindeno[1,7-*bc*]furan-5-yl}methanol (100)

A stirred solution of diacetate **99** (132 mg, 0.471 mmol) in methanol (50 mL) was treated with two drops of concentrated sulfuric acid and the resulting mixture heated under refluxing conditions for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the ensuing residue dissolved in dichloromethane (15 mL) and poured into sodium bicarbonate (15 mL of a saturated aqueous solution). This mixture was extracted with dichloromethane (3 × 15 mL), and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:1 v/v ethyl acetate/hexane elution) and the appropriate fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) were collected and concentrated under reduced pressure, resulting in a clear oil of the *title alcohol* ***100*** (100 mg, 100%) (Found: $M^{+\bullet}$, 210.1248, $C_{12}H_{18}O_3$ requires

$M^{+\bullet}$, 210.1256). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73 (d, *J* = 10.4 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 4.02 (dd, *J* = 8.0 and 6.4 Hz, 1H), 3.72 (d, *J* = 8.8 Hz, 1H), 3.60 (m, 2H), 3.28 (s, 3H), 2.74 (d, *J* = 5.6 Hz, 2H), 2.56-2.38 (complex m, 2H), 2.08 (app. q, *J* = 6.0 Hz, 1H), 1.56 (m, 2H), 1.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.5, 127.3, 120.4, 73.3, 65.1, 50.4, 50.0, 38.0, 37.6, 36.8, 33.7, 25.7; ν_{max} 3408, 2949, 2877, 2829, 1466, 1435, 1320, 1201, 1159, 1133, 1115, 1082, 1044, 1009, 950, 827, 787, 739, 696; MS (EI, 70 eV) *m/z* 210 ($M^{+\bullet}$, 12%), 180 (34), 149 (21), 119 (38), 118 (100), 117 (52), 105 (39), 93 (21), 92 (28), 91 (95), 79 (25), 77 (25).

{(2a*R*,2a^1*S*,5*S*,5a*S*,7a*S*)-7a-Methoxy-2,2a,2a^1,5,5a,6,7,7a-octahydroindeno[1,7-*bc*]furan-5-yl}methyl methanesulfonate (101)

A magnetically stirred solution of alcohol **100** (203 mg, 0.964 mmol) in diethyl ether (15 mL) with triethylamine (270 μL, 1.93 mmol) was treated dropwise with mesyl chloride (150 μL, 1.93 mmol) at 18 °C. After 0.5 h the solution was diluted with diethyl ether (15 mL), washed with H_2O (2 × 15 mL) and the combined aqueous phases extracted with diethyl ether (1 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica, 2:1 v/v ethyl acetate/hexane elution) and the appropriate fractions (R_f = 0.3 in 1:1 v/v ethyl acetate/hexane) concentrated under reduced pressure to afford the *title mesylate **101*** as a light-yellow oil (255 mg, 92%), which crystallised on standing overnight as light-yellow crystals, mp = 71-72 °C, (Found: $M^{+\bullet}$, 288.1030, $C_{13}H_{20}O_5S$ requires 288.1031). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.79 (d, *J* = 9.6 Hz, 1H), 5.56 (d, *J* = 9.6 Hz, 1H), 4.15 (t, *J* = 7.2 Hz, 2H), 4.03 (dd, *J* = 8.2 and 6.2 Hz, 1H), 3.73 (d, *J* = 8.8 Hz, 1H), 3.28 (s, 3H), 3.04 (s, 3H), 2.78-2.62 (complex m, 3H), 2.56-2.46 (complex m, 1H), 2.10 (dd, *J* = 11.2 and 6.0, 1H), 1.59 (m, 2H), 1.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 132.7, 125.0, 120.2, 73.1, 71.1, 50.5, 49.8, 37.9, 37.5, 36.5, 34.8, 33.6, 25.7; ν_{max} 3023, 2948, 2882, 2829, 1467, 1354, 1334, 1024, 1174, 1136, 1117, 1081, 1037, 953, 829, 788, 527; MS (EI, 70 eV) *m/z* 288 ($M^{+\bullet}$, 12%), 258 (67), 163 (84), 162 (52), 161 (21), 133 (29), 131 (36), 130 (86), 119 (31), 117 (38), 105 (64), 104 (39), 93 (23), 92 (23), 91 (100), 79 (28), 77 (23).

2-[3-(Hydroxymethyl)-6a-methoxyhexahydro-2H-cyclopenta[b]furan-4-yl]prop-2-en-1-ol (104)

A flask containing vigorously stirred mesylate **101** (21 mg, 0.07 mmol) in DCM (15 mL) was cooled to -78 ^{o}C. Ozone was bubbled through the reaction mixture until a blue colouration was observed (10 min). Power was removed from the ozone generator and oxygen was allowed to flow until the blue colour had dispersed. Dimethylsulfide (113 μL, 1.48 mmol) was added and the reaction mixture was warmed to 0 ^{o}C. After 3 h, the reaction mixture was cooled to -30 ^{o}C and DBU (23 μL, 0.15 mmol) was added. The reaction mixture was allowed to warm to -10 ^{o}C. After 1 h, $CeCl_3 \bullet 7H_2O$ (111 mg, 0.30 mmol) and MeOH (15 mL) were added, and the reaction mixture was warmed to 0 ^{o}C. The mixture was then treated in portions over a 0.5 h period with $NaBH_4$ (12 mg, 0.30 mmol). The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 16 h. After this time, NH_4Cl (15 mL of a saturated aqueous solution) was added slowly, and after gas evolution had ceased, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was extracted with DCM (3 × 15 mL) and the combined organic phases dried (Na_2SO_4). After concentrating under reduced pressure, the resulting residue was subjected to flash chromatography (silica, 1:19 v/v methanol/DCM elution) and the appropriate fractions (R_f = 0.3 in 1:9 v/v methanol/DCM) concentrated under reduced pressure to afford the *title alcohol **104*** (4 mg, 23%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.17 (s, 1H), 4.94 (s, 1H), 3.93 (s, 1H), 3.91 (t, *J* = 5.2 Hz, 1H), 3.85 (m, 1H), 3.48 (t, *J* = 9.8 Hz, 1H), 3.29 (s, 3H), 2.88 – 2.74 (m, 2H), 2.49 (m, 1H), 2.10 (m, 1H), 1.94 (m, 1H), 1.80 – 1.62 (m, 5H), 1.26 (s, 1H); MS (ESI) *m/z* 227 ($(M - H)^-$, <1%).

2-(3-((3,5-Dinitrobenzoyloxy)methyl)-6a-methoxyhexahydro-2*H*-cyclopenta[*b*]furan-4-yl)allyl 3,5-dinitrobenzoate (106)

A solution of diol **104** (4.0 mg, 0.02 mmol), triethylamine (17 μL, 0.12 mmol) and DMAP (15 mg, 0.12 mmol) in DCM (1 mL) maintained at 18 ^{o}C was treated with DNBC (22 mg, 0.09 mmol). The ensuing mixture was stirred at 18 ^{o}C for 0.5 h then $NaHCO_3$ (2 mL of a saturated aqueous solution) and DCM (5 mL) were added. The separated aqueous phase was extracted with DCM (2 × 5 mL) and the combined organic fractions were washed with brine (1 × 2 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the resulting residue to flash column chromatography (silica, 2:3 v/v ethyl

acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.7 in 1:1 v/v ethyl acetate/hexane) afforded the *title ester* ***106*** (2.2 mg, 20%) as a yellow oil. (Found: $(M + Na)^+$, 639.1187, $C_{26}H_{24}N_4O_{14}$ requires $(M + Na)^+$, 639.1187). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (app. q, *J* = 2.4 Hz, 2H), 9.18 (d, *J* = 2 Hz, 2H), 9.11 (d, *J* = 2 Hz, 2H), 5.38 (s, 1H), 5.25 (d, *J* = 2.4 Hz, 1H), 5.08 (s, 2H), 4.91 (m, 1H), 3.96 - 3.88 (m, 2H), 3.31 (s, 3H), 3.04 – 2.96 (m, 1H), 2.94 – 2.84 (m, 2H), 2.21 (t, *J* = 6.2 Hz, 1H), 2.16 – 2.02 (m, 2H), 1.90 – 1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 162.3, 148.7, 142.8, 133.6, 129.5, 129.4, 122.7, 122.5, 119.5, 114.9, 69.9, 68.5, 64.7, 53.1, 50.2, 43.7, 43.5, 33.6, 29.4; ν_{max} 3452, 3103, 2958, 2922, 2851, 1736, 1630, 1545, 1462, 1345, 1284, 1261, 1161, 1075, 1021, 921, 799, 721; MS (ESI) *m/z* 639 ($(M + Na)^+$, 9%), 373 (6), 193 (8), 161 (24), 141 (14), 133 (8), 117 (8), 105 (10), 85 (100).

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Citation convention: *Tetrahedron*.

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