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Application of the [5+2] Photocycloaddition to Alkaloid Synthesis and the Total Synthesis of (+)-Neostenine

Application of the [5+2] Photocycloaddition to Alkaloid Synthesis and the Total Synthesis of (±)-Neostenine

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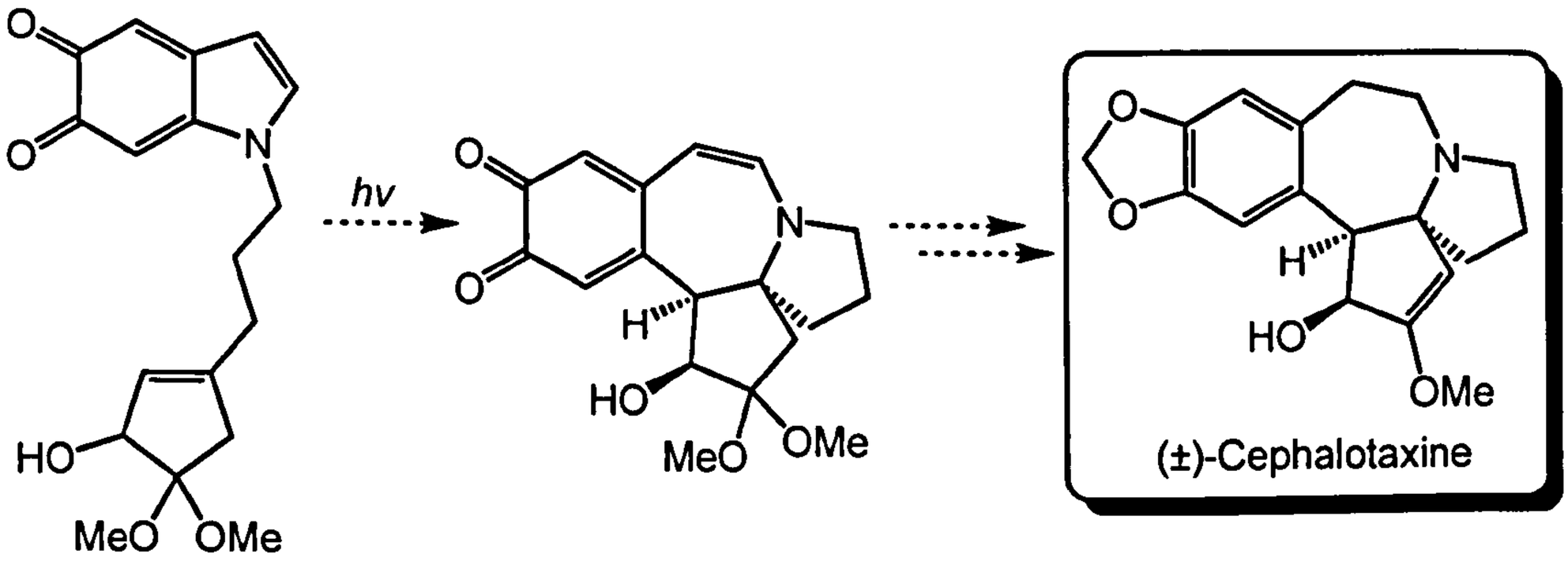
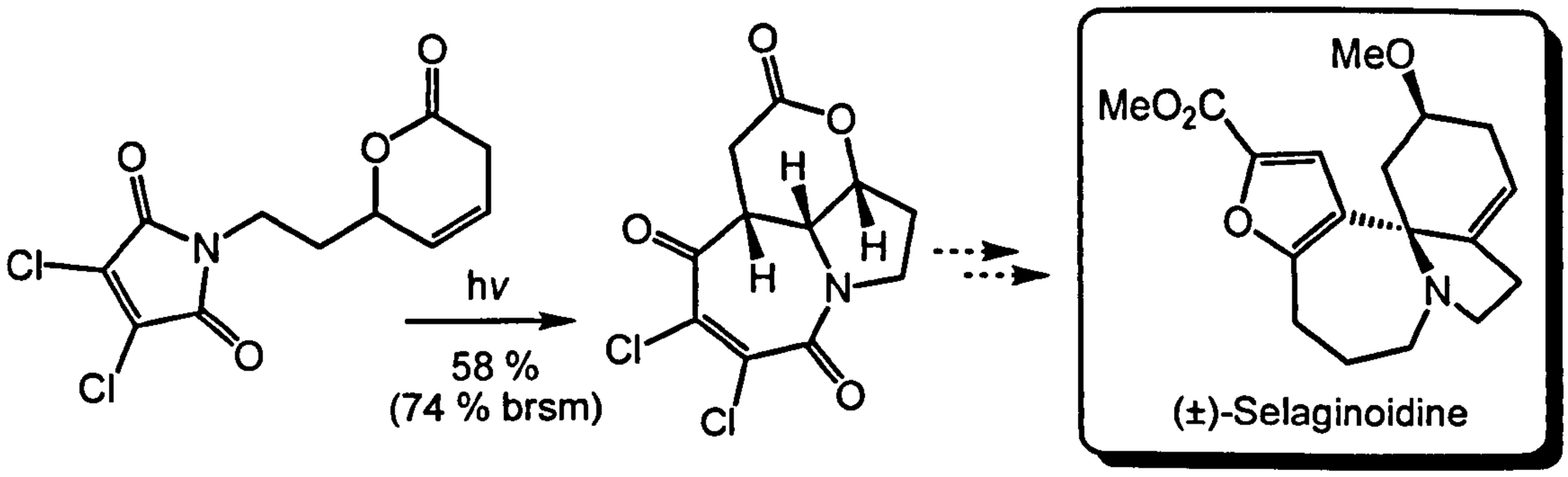
Abstract

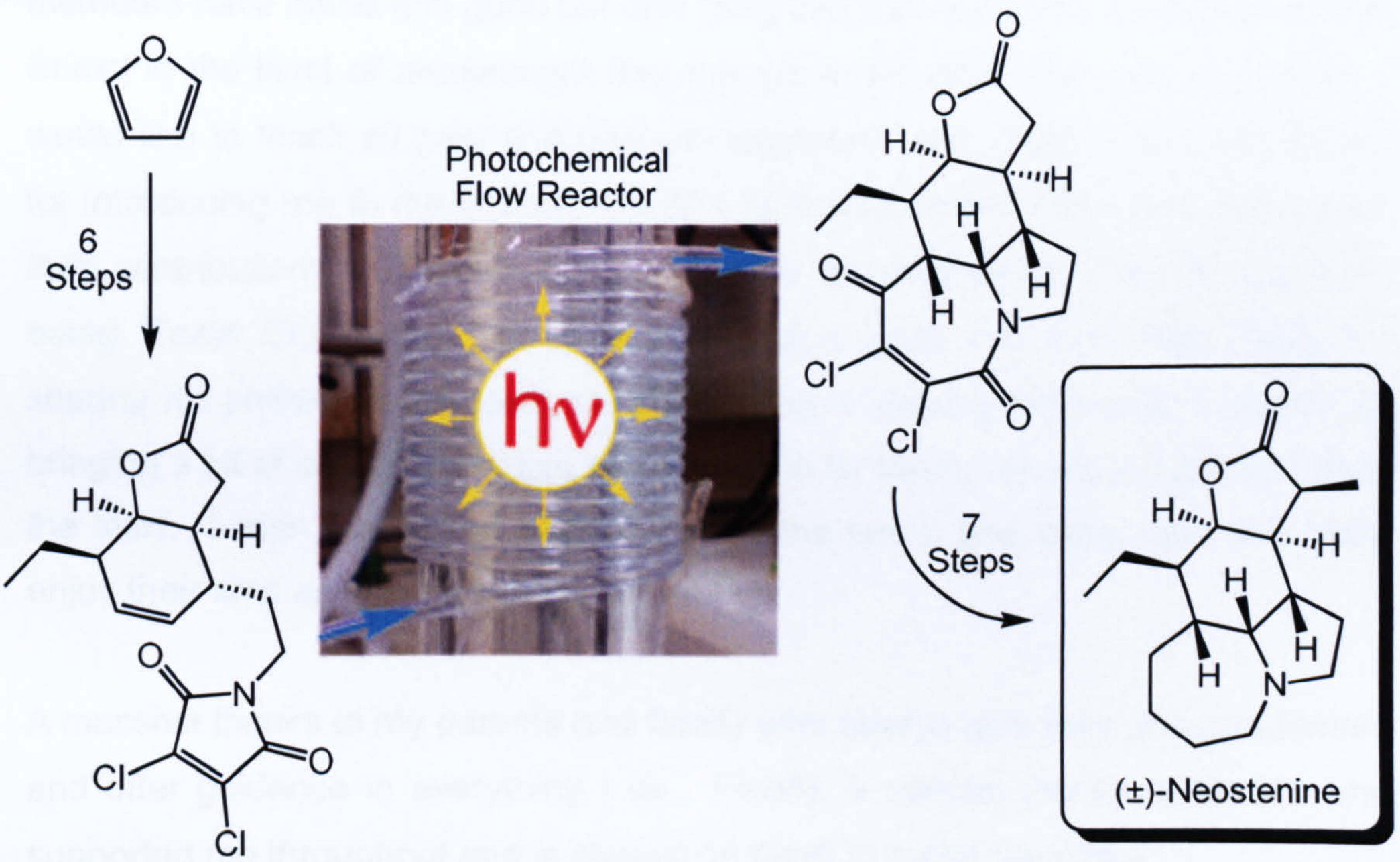
A study towards the total synthesis of cephalotaxine was attempted by testing the applicability of the maleimide [5+2] photocycloaddition to a substrate that was isoelectronic with maleimide. A model system was prepared using indole quinones. Although these compounds were shown to be photochemically active, no products were isolated.



After the study was undertaken, new insight into the mechanism of the maleimide [5+2] photocycloaddition demonstrated that the existing hypothesis that a concerted [2+2] cycloaddition process was not valid. The mechanism was actually found to involve an *a*-cleavage of the amide bond in maleimides. This indicated that [5+2] photocycloaddition with indole quinones may not be achievable.



Four different approaches were investigated towards the total synthesis of selaginoidine. The first two approaches would have led to advanced synthetic intermediates, had irradiation not demonstrated a preference for the [2+2] cycloaddition process. A third disconnection provided a [5+2] photocycloadduct in moderate yield. Unfortunately elaboration of the product was difficult, particularly with a-alkylation. With this in mind a fourth strategy was undertaken whereby a-alkylation would be avoided. This route has proven to be successful and rapidly affords an intermediate that may well be successful for the synthesis of (±)-selaginoidine.



The synthesis of (±)-neostenine has been achieved in 14 steps from furan in a 9.5 % overall yield. Anti selective S_N2' bislactone C_2-desymmetrisation provided the first key intermediate, which contained four of the seven requisite stereocentres of (±)-neostenine. Two more centres were established with complete control from a key [5+2] photocycloaddition. Methylation of the lactone completed the final of the seven stereocentres required for (±)-neostenine.

Acknowledgements

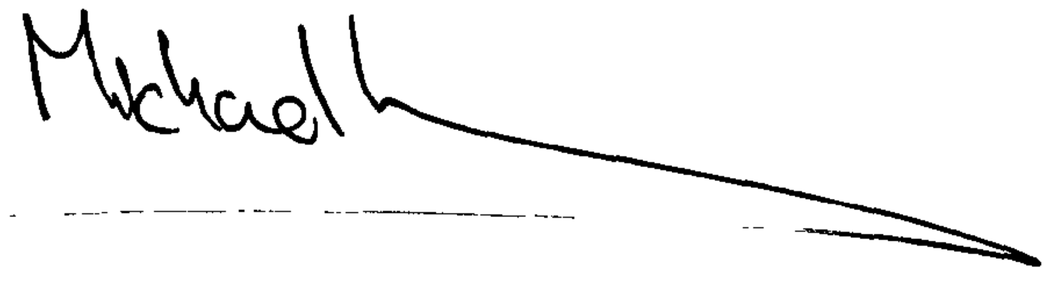
I would like to take this opportunity to thank all those who have contributed, both directly and indirectly, throughout my PhD. First and foremost, a huge thanks goes to Kev for giving me the opportunities and being a constant provider of support and enthusiasm. Thanks also to all of the technical staff in the Chemistry Department who were always on hand to make my research a little easier.

The Booker-Milburn lab has always been a real pleasure to work in – its members have come and gone but one thing that has remained during my time in Bristol is the level of amusement that the group provides. For this, and more, I would like to thank all past and present members: Ben, Scott, Dave and Wolfie for introducing me to the Scotchman and its football team; Piers and Marcus for their contributions to Neostenine and general lab tomfoolery; Chris' H and B for being 'Team Chris'; Clod for cooking the best pizza I've ever had; Pomy for sharing his philosophical views; Luke for being a walking Wikipedia; Caroline for bringing a bit of colour to the lab; and Paul(ine) for being my bouncing board from the start. I wish you all the best of luck in the future and hope Kara and Mark enjoy their time as much as I did.

A massive thanks to my parents and family who always give their encouragement and offer guidance in everything I do. Finally, a special thanks to Sarah, who supported me throughout and is always on hand to make me smile.

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the regulations of the University of Bristol. The work is original, except where indicated by special reference text, and no part of the dissertation has been submitted for any other academic award. Any views expressed in the dissertation are those of the author.

Signed: 

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Abbreviations

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
aq	aqueous
atm	pressure in atmospheres
BHT	butylated hydroxytoluene
Bn	benzyl
Bp	boiling point
br	broad
brsm	based on recovered starting material
Bu	butyl
CAN	ceric ammonium nitrate
cat.	catalytic
CI	chemical ionisation
CMPI	
Cp	cyclopentadienyl
d	doublet
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DHP	3,4-dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	*N,N*-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethyl sulfoxide

e.e.	enantiomeric excess
E^+	electrophile
EI	electron impact
eq	equivalents
Et	ethyl
FEP	fluorinated ethylene polypropylene
h	hours
HMDS	hexamethyldisilazane
HOMO	highest occupied molecular orbital
HRMS	High resolution mass spectrometry
Hv	electromagnetic radiation
i	iso
IC	internal conversion
IPA	isopropanol
IR	infrared
J	coupling constant
KSF	a type of montmorillonite clay
LDA	lithium diisopropylamide
Lit	literauture
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
m/z	mass to charge ratio
Me	methyl
min	minutes
mmol	millimolar
Mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MVK	methyl vinyl ketone
Naph	naphtyl

NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Nu	nucleophile
Ph	phenyl
PIFA	phenyliodonium *bis*(trifluoroacetate)
PPA	polyphosphoric acid
ppm	parts per million
*p*TSA	*para*toluene sulphonic acid
r.t.	room temperature
RCM	ring-closing metathesis
s	singlet
t	tert
t	triplet
TBAB	tetra-*N*-butylammonium bromide
TBAF	tetra-*N*-butylammonium flouride
TBDMS/TBS	tributylsilyl/*tert*-butyldimenthylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	toluenesulfonyl
UV	ultra-violet
VAA	vinyl acetic acid
wt %	weight %

Contents

Introduction

1. Alkaloids

1.1 Cephalotaxine

(–)-Cephalotaxine **1**, the major alkaloid component of the Chinese plum yew *Cephalotaxus fortunei* and of the Japanese plum yew *Cephalotaxus drupacea*, was first isolated in 1963 by Paudler *et al.*[1] Naturally occurring esters of cephalotaxine, such as homoharringtonine **2** have been found to be highly effective for the treatment of acute human leukaemia and are currently undergoing advanced clinical trials.[2] Homoharringtonine is also a potent agent against strains of chloroquinine-resistant *Plasmodium f.* malaria parasite in vitro.[3]

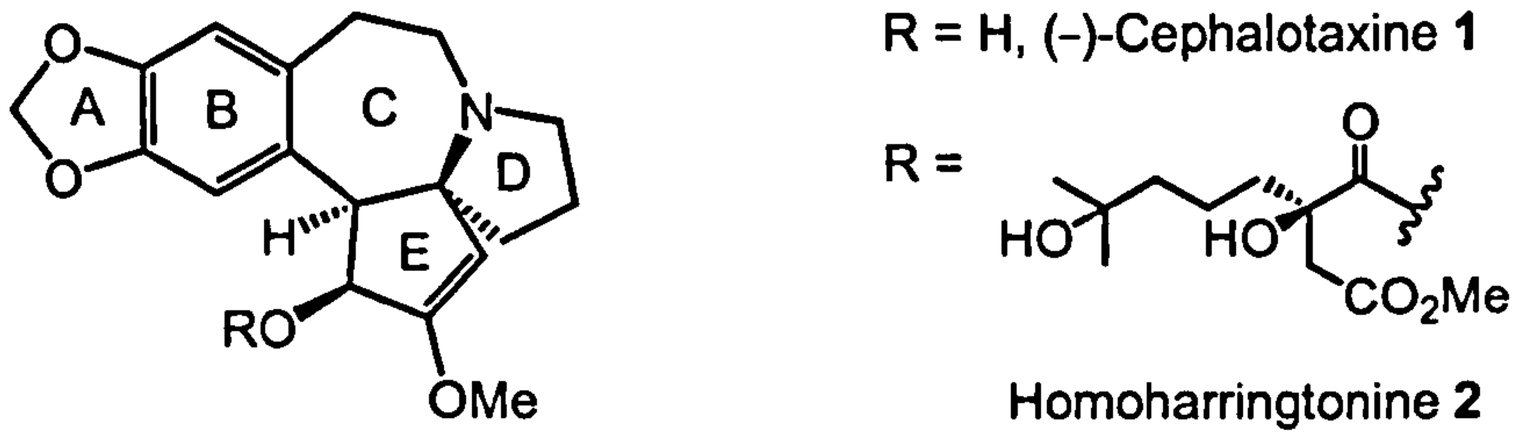
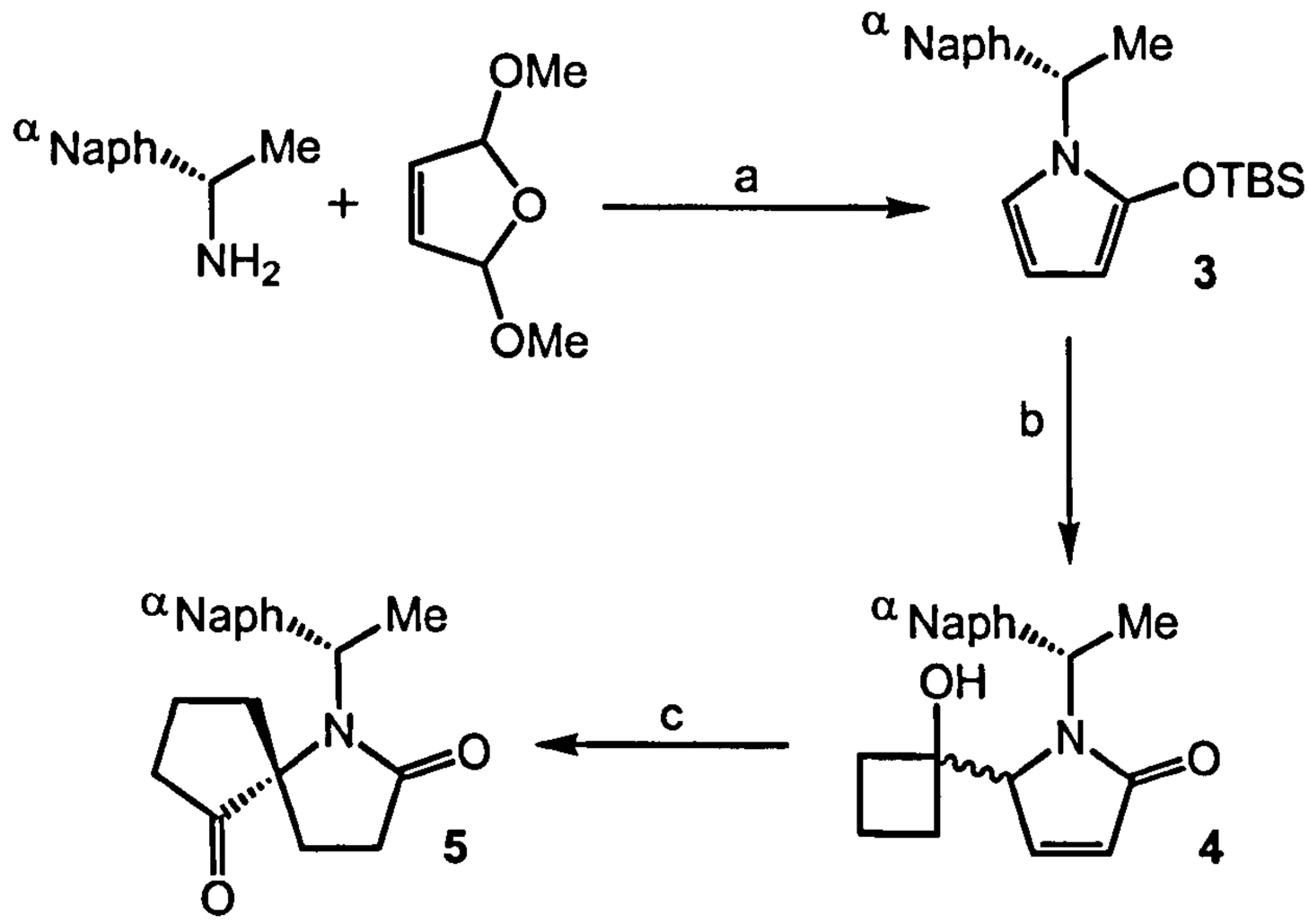


Figure 1

The structure of homoharringtonine **2** is unique in that it is comprised of two spiro-fused five-membered rings annular to a benzazepine system. This combined with the therapeutic potential of the group, has inspired synthetic research on cephalotaxine, which has led to several elegant total syntheses,[4] a recent example being carried out by Royer *et al*[5]. Royer's strategy was to use the chemistry of *a,ß*-unsaturated ?-lactams developed in their lab to construct the D and E ring moiety of cephalotaxine and then to follow the Kuehne synthesis to complete a stereoselective total synthesis of **1**. The synthesis commenced from (*S*)-1-(1-napthyl)ethylamine, which afforded the silyloxypyrrole **3** in a 54% yield **(Scheme 1)**.

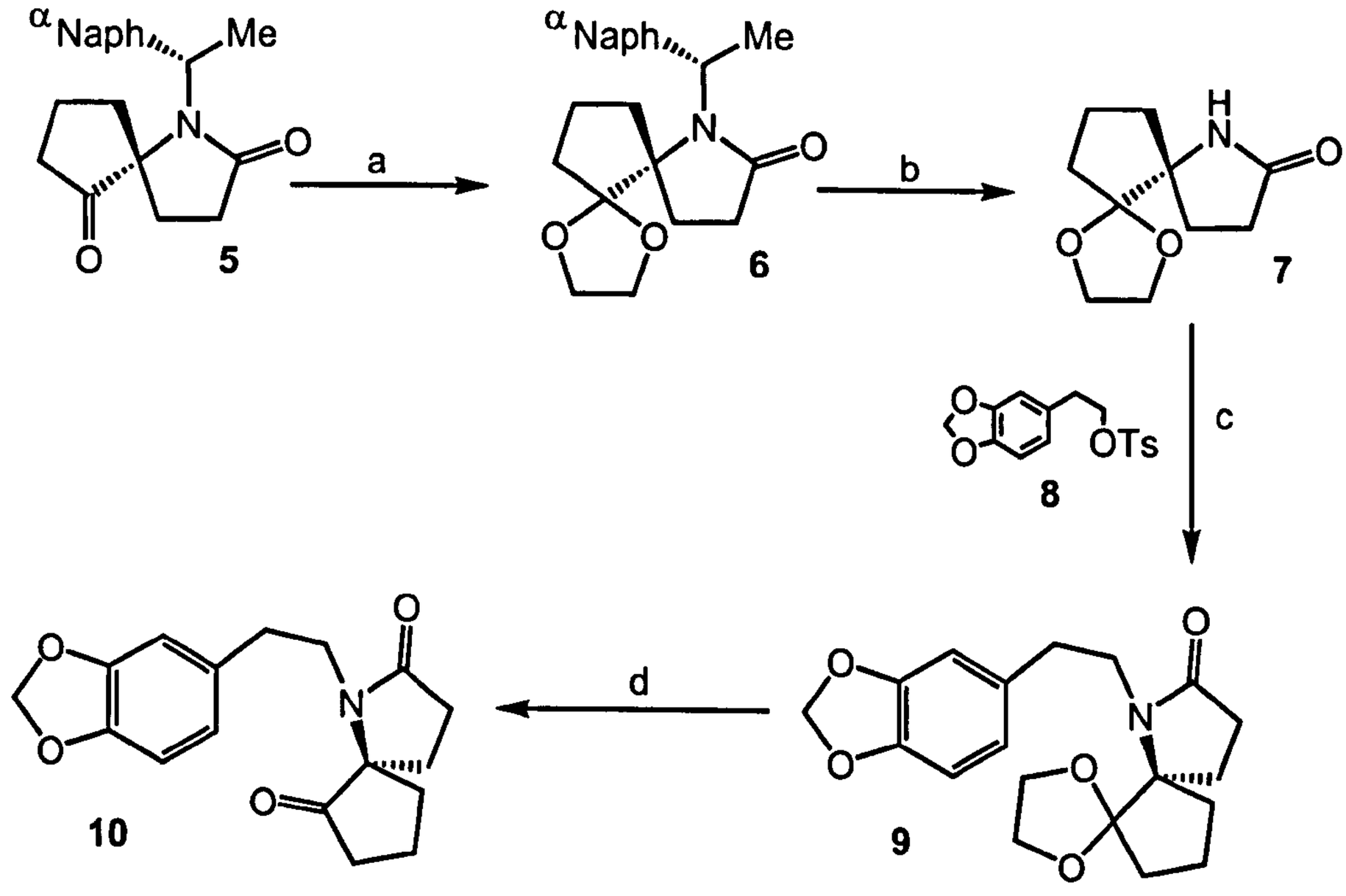


Reagents and Conditions: a) i) HCl aq, ii) TBSOTf, Et_3N, 54 %; b) cyclobutanone, $BF_3.Et_2O$, DCM, -78 °C, 78 %; c) HCl, DCM, 86 %.

Scheme 1

The vinylogous Mukaiyama aldol reaction of **3** with cyclobutanone affords the *a*,ß-unsaturated ?-lactam **4** with a 77 % yield. Acidic treatment of **4** furnished the desired spiro compound **5** in a quantitative yield with good selectivity (80 % d.e.). To perform the cleavage of the chiral attachment, the ketone function of **5** was protected as cyclic ketal **6**, using ethylene glycol under standard conditions **(Scheme 2)**.

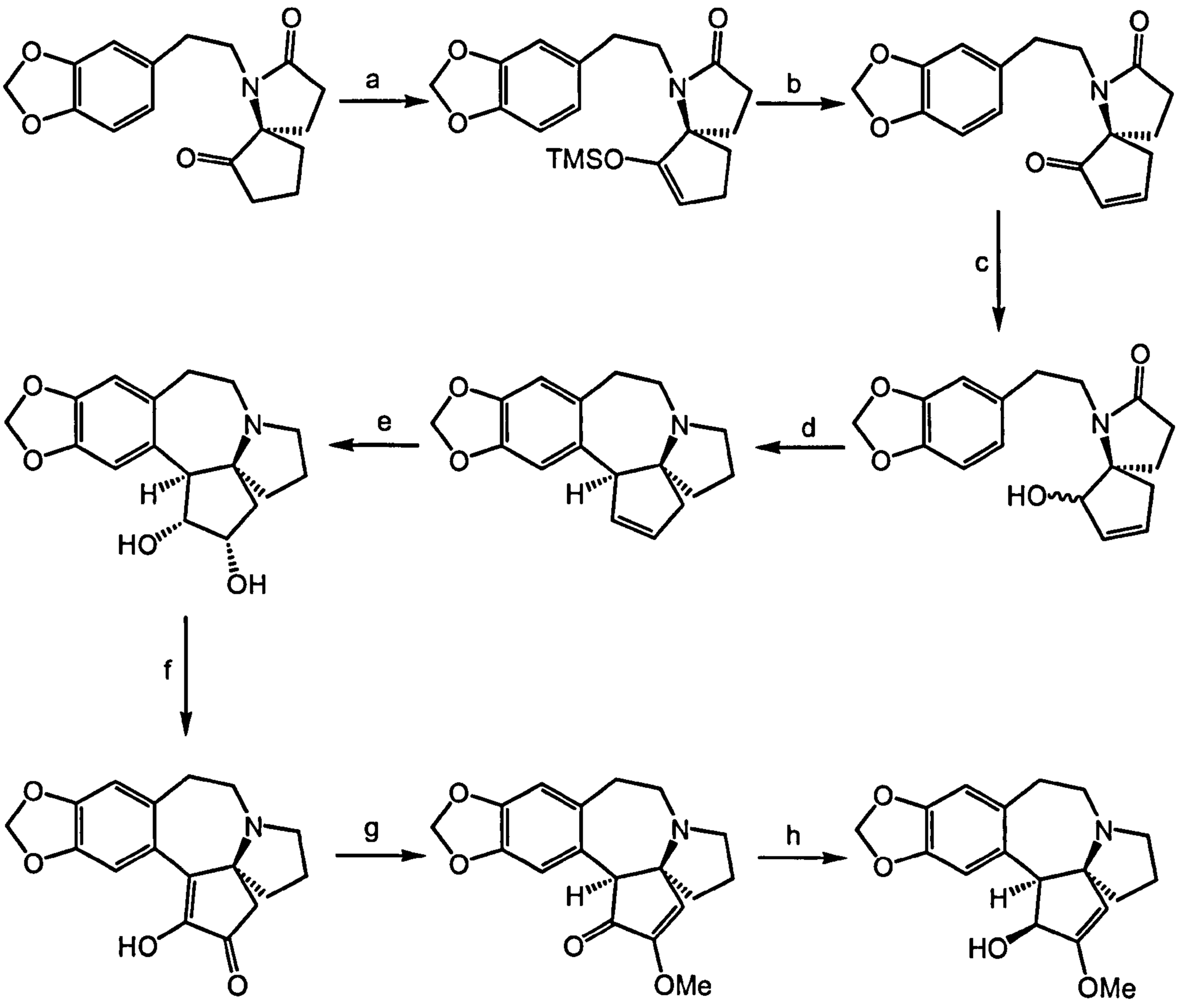
Reductive cleavage of the *N*-benzylic bond of **6** was then performed with lithium in liquid ammonia, and the bispiro lactam **7** was isolated in a quantitative yield over two steps. The material was used without purification for *N*-alkylation to give **9** in an 80 % yield. Deprotection of **9** in acidic medium finally provided **10** in a quantitative yield. Eventually, enantiopure **10** was transformed to (–)-cephalotaxine following the procedure used by Kuehne for his racemic synthesis of **1 (Scheme 3)**.



Reagents and Conditions: a) ethylene glycol, *p*TSA, toluene, 100 %; b) Li/NH_3, EtOH, -78 °C, 100 %; c) **8**, NaH, 80 %; d) AcOH, H_2O, 100 %.

Scheme 2

Royer's procedure led to the efficient synthesis of cephalotaxine in 98.7 % e.e. with an overall yield of 9.8 % over a 16-step sequence. A total synthesis of cephalotaxine with fewer steps is desirable given the potential pharmaceutical need.

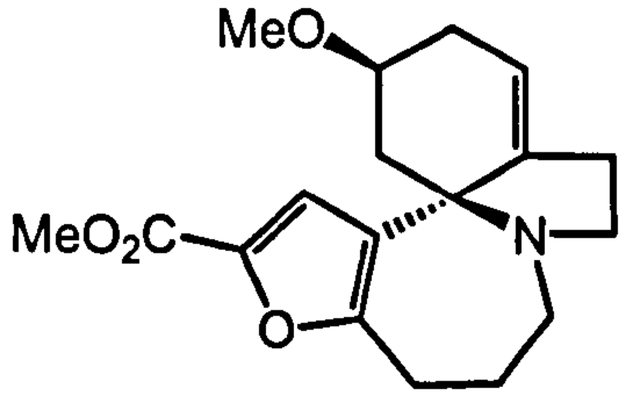


Reagents and Conditions: a) TMSI, $(TMS)_2NH$, DCM, 89 %; b) $Pd(OAc)_2$, DCM, 85 %; c) $Al(^iPrO)_3$, ^iPrOH, reflux; d) $SnCl_4$, CH_3NO_2, DCM, -78 °C, 80 % (for the two steps); e) OsO_4 cat., NMO, THF, $-H_2O$, 81 %; f) Me_2S, NCS, Et_3N, DCM; g) $MeOSiMe_3$, TfOH, DCM, 80 % (for the two steps); h) AlH_3, THF, 0 °C, 75 %.

Scheme 3

1.2. Selaginoidine

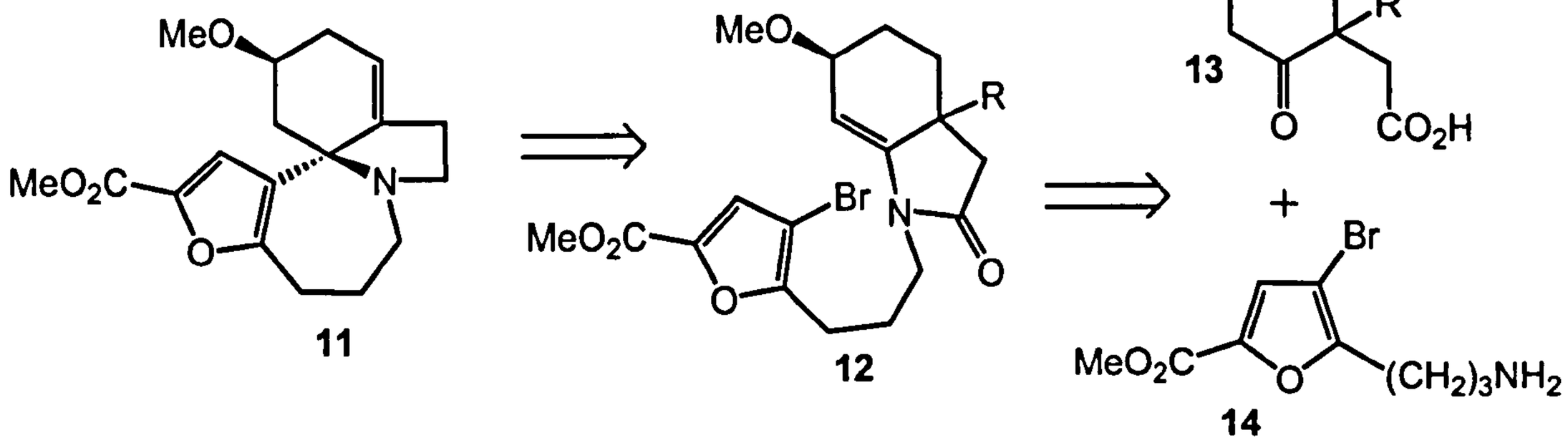
The taxodeaceous plant *Athrotaxis selaginoides*, known more commonly as the King Billy Pine, is native to the western mountains in Tasmania and is highly valued as a source of softwood timber.[6] It attains heights of up to 40 m and lives to be over 1000 years old. A number of homoerythrina alkaloids are present in all of its plant materials, including the bark and leaves.[6] The elucidation of the remaining base was assigned the structure of (±)-selaginoidine **11** by Bick *et al.*[7], corresponding to a unique nonbenzenoid member of the homoerythrina alkaloid family.



Selaginoidine **11**

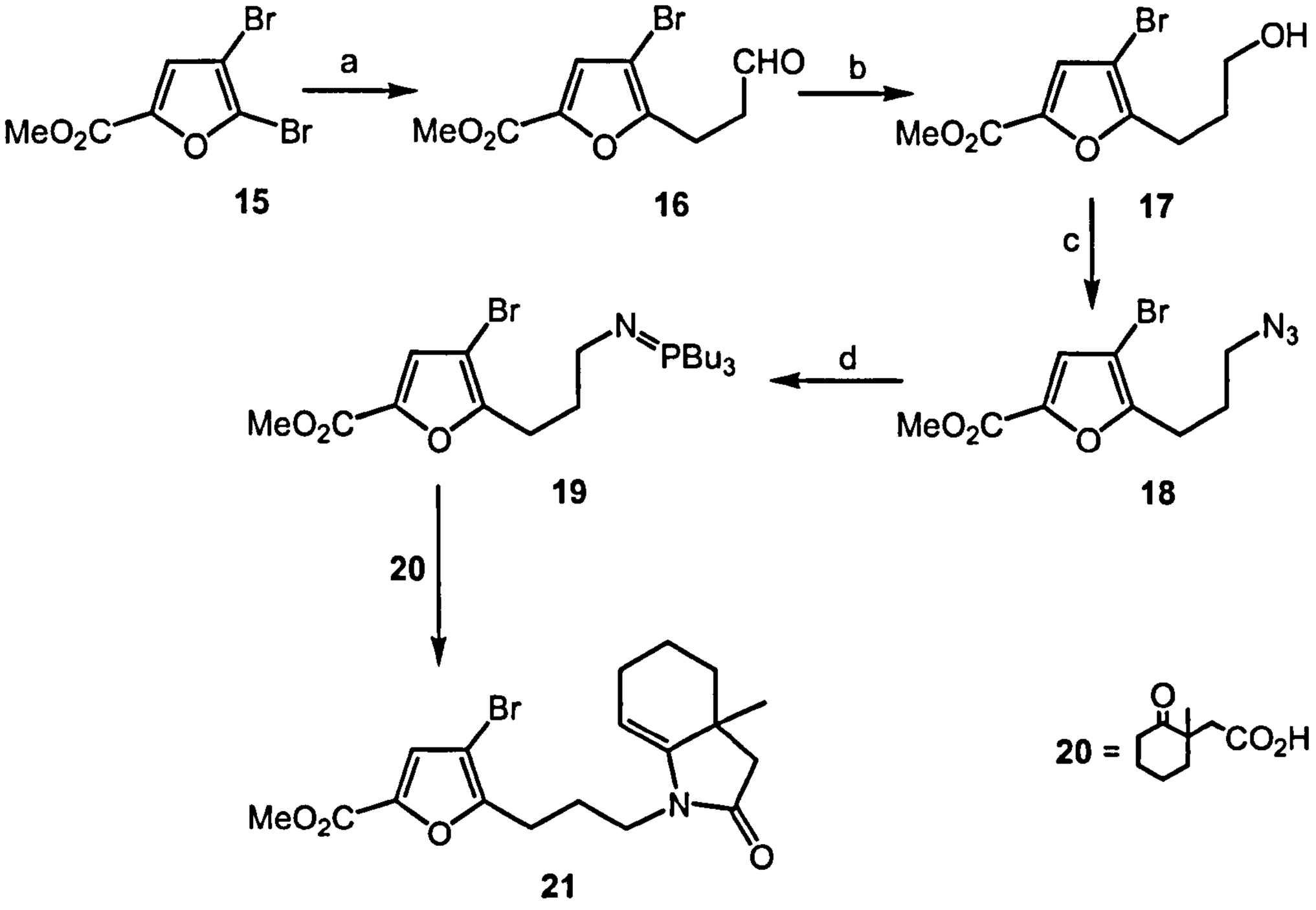
Figure 2

The total synthesis of selaginoidine **11** has not yet been achieved, although Padwa *et al.*[8] have developed an aza-wittig/*p*-furan cyclisation approach towards the alkaloid.



Scheme 4

Padwa envisaged that the skeleton of **11** could be accessed from either a Heck or radical-induced cyclisation of the bromo-furanyl hexahydroindolinone **12** **(Scheme 4)**. The construction of **12** would involve condensation of furanylamine **13** with a (1-substituted-2-oxo-cyclohexyl)acetic acid derivative **14** under Dean – Stark conditions.

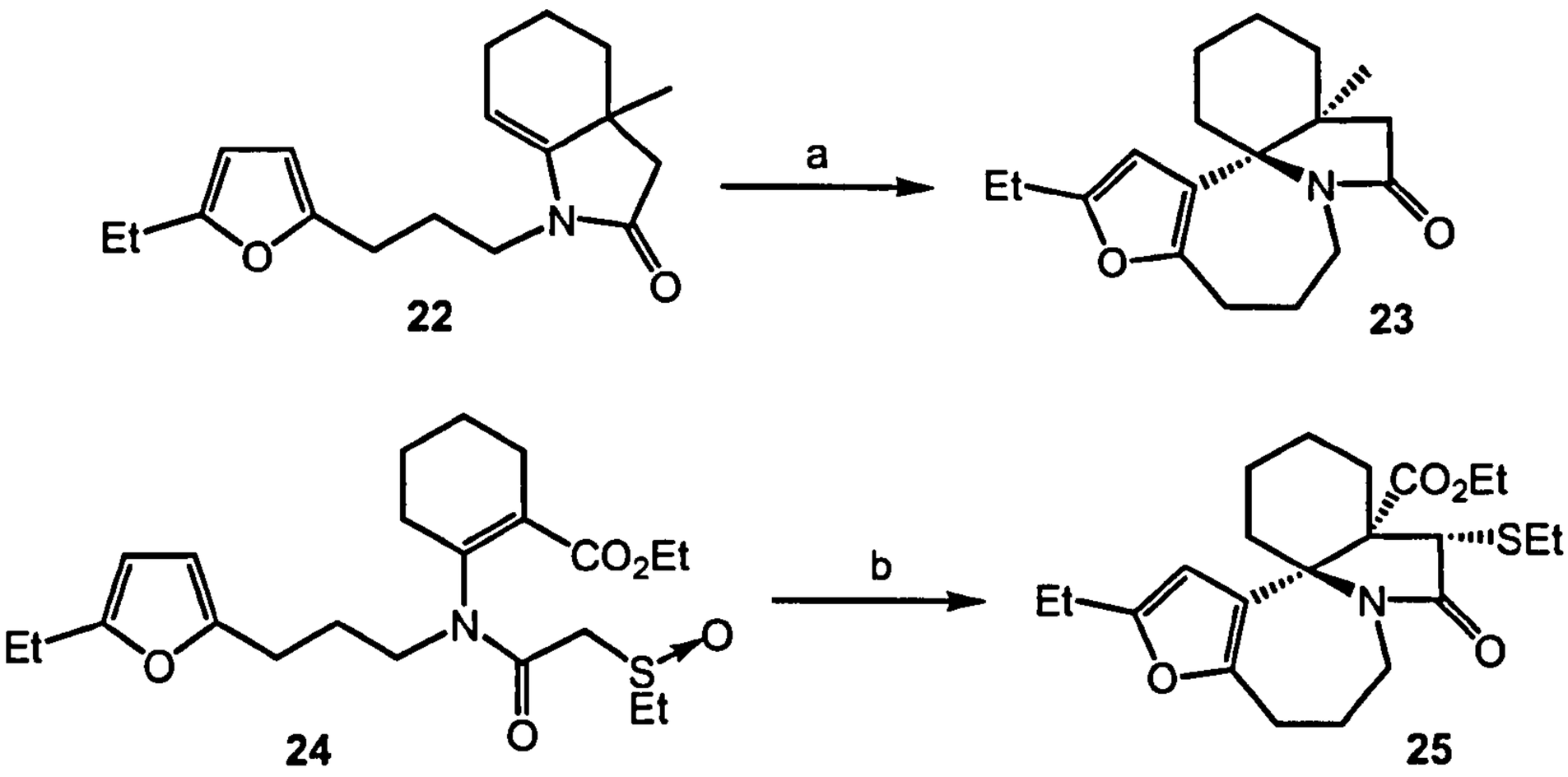


Reagents and Conditions: a) Pd(0), CH_2=$CHCH_2OH$, 70 %; b) $NaBH_4$; c) i) MsCl; ii) NaN_3, DMF, 93 % (for the three steps); d) i) Bu_3P ii) **20**, 150 °C microwave, 63 %.

Scheme 5

Accordingly, 2,3-dibromo-5-carbomethoxyfuran **15** was subjected to a Pd(0)-catalysed Heck coupling with allyl alcohol **(Scheme 5)**. This resulted in exclusive substitution at the 2-bromo position and gave aldehyde **16** in a 70 % yield. Subsequent reduction with sodium borohydride afforded the alcohol **17**, which in turn was converted into the corresponding mesylate. Treatment of the mesylate with NaN_3 in DMF furnished furanyl azide **18** in a 93 % yield. Padwa *et al.* had great difficulty in converting azide **18** to its corresponding amine. It was therefore

decided that **18** would be converted into **19**. An aza-Wittig reaction was performed under optimal microwave conditions producing hexahydroindolinone **21** in a 63% yield. The cyclisation of **21**, has not, as yet been carried out. It was found however that a similar hexahydroindolinone **22** could undergo a *p*-cyclisation with either triflouroacetic acid or trifluoromethane sulfonic acid giving lactam **23** in a >90 % yield. Padwa sought to demonstrate that this methodology could also be used for assembling the homoerythrina skeleton. The homologous enamido furanyl sulfoxide **24** was subjected to the acid catalysed conditions and underwent a Pummerer reaction followed by cyclisation **(Scheme 6)**. The major product isolated corresponded to the cyclised lactam **25**, but only in a 40 % yield. Further studies are being undertaken to maximise the yield to enable this methodology to apply to the synthesis of selaginoidine **11**.

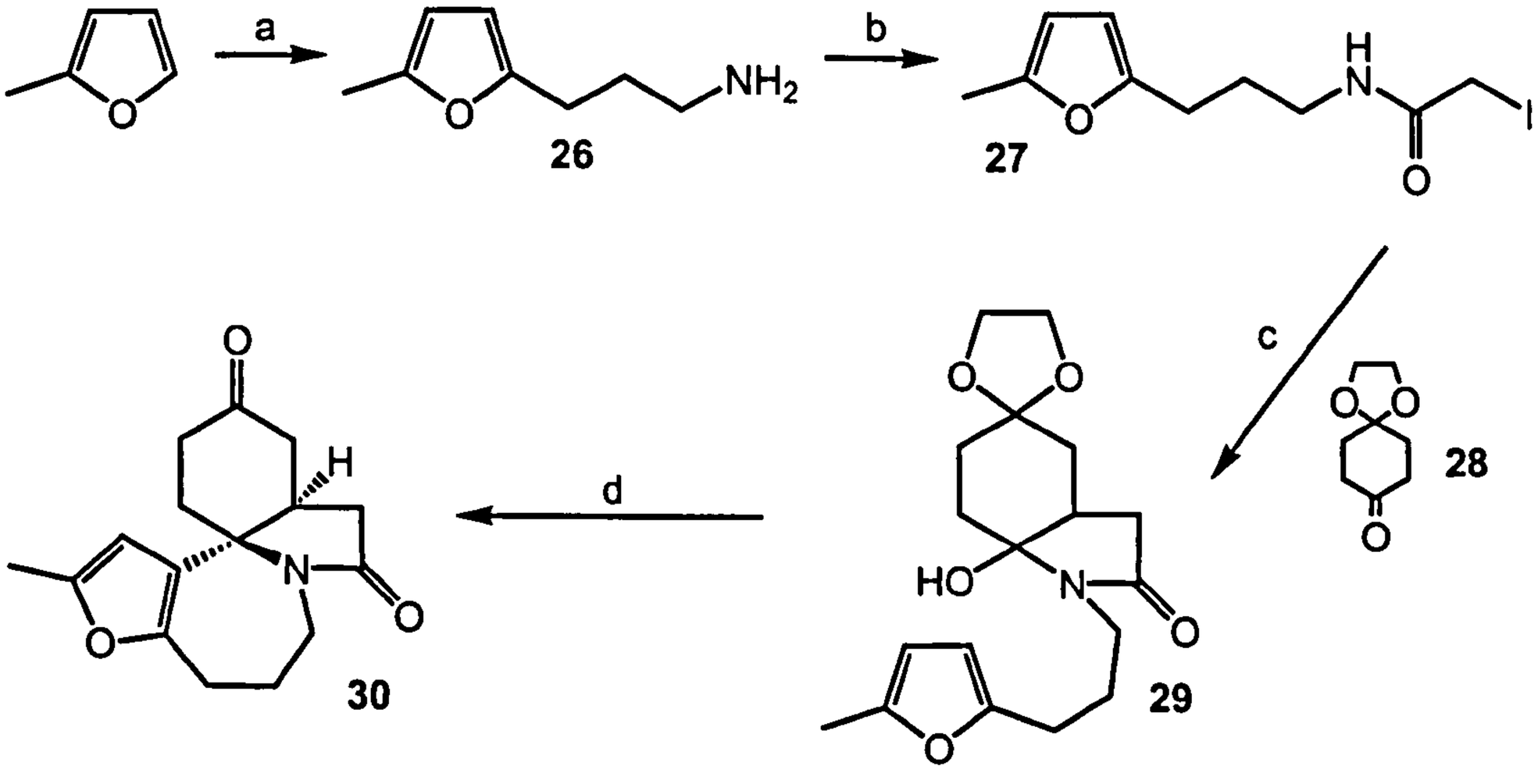


Reagents and Conditions: a) TFAA, TFA, >90 %; b) TFAA, TFA, 40 %.

Scheme 6

A more efficient approach has since been conducted by Tu *et al*. using a very similar strategy to Padwa **(Scheme 7)**.[9] Treatment of 2-methyl furan with ^{n}BuLi and 1-chloro-3-iodopropane was followed by the transformation into amine **26**

with NaN_3 and hydride reduction. Acylation and iodination of the corresponding amide gave **27** in a 96 % yield. Alkylation and intamolecular cyclisation gave the desired intermediate **29** in a good yield. Cyclisation to the selaginoidine core was conducted in acid to give **30** in good yield. Tu *et al.* intend to further their work towards the total synthesis of selaginoidine.



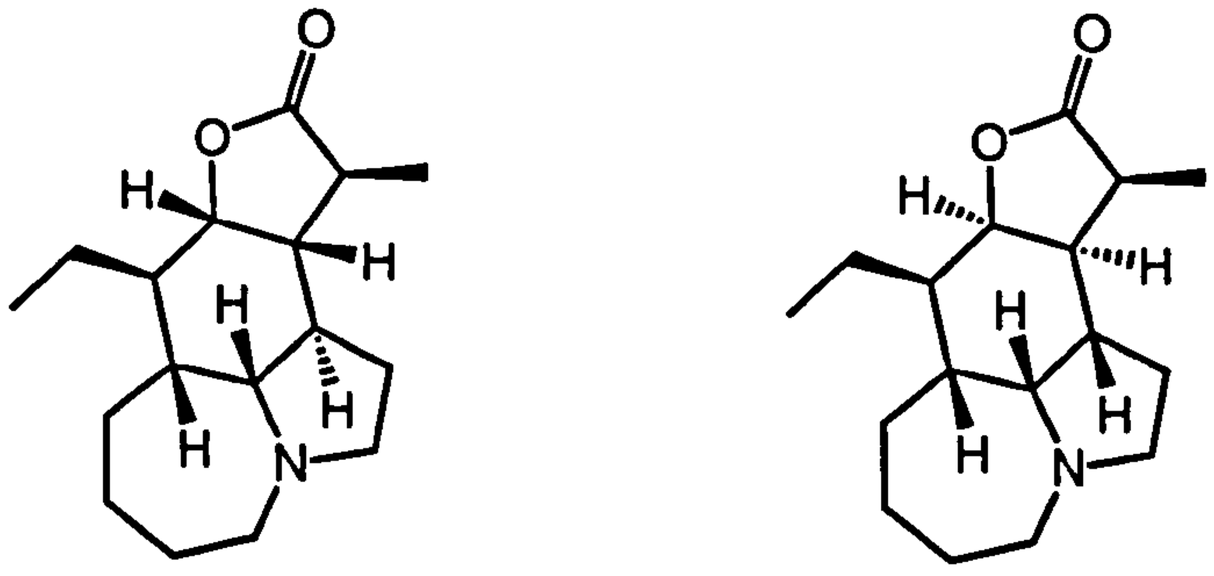
Reagents and Conditions: a) i) ^{n}BuLi, $I(CH_2)_3Cl$, THF, 93 %; ii) NaN_3, DMF, 80 °C, 97 %; iii) $LiAlH_4$, THF, 99 %; b) i) chloroacetyl chloride, *N*,*N*-Dimethylaniline, DCM, 0 °C, ii) NaI, 2-butanone, reflux, 96 %; c) **28**, LDA, THF, -78 °C, 86 %; d) TFA, DCM, 83 %.

Scheme 7

1.3. Neostenine

Extracts from the roots of the *Stemona Tuberosa* have been used for centuries in traditional Chinese and Japanese remedies for a variety of respiratory complaints.[10] The *Stemona* alkaloids are characterised by their perhydroazaazulene core and are divided into five different groups. One of these structural groups is the Stenine-type category, with Stenine **31** being the parent member **(Figure 3)**. Neostenine **32** belongs to this category and has been examined for antitussive activity in the guinea pig after cough induction by citric acid aerosol stimulation.[11] Neostenine showed a considerable increase in

antitussive activity compared to its family members. From structural activity relationships, it was shown that the primary key structure contributing to this increase in activity was the perhydroazaazulene nucleus containing the all-*cis* configuration at the three ring junction.[11]

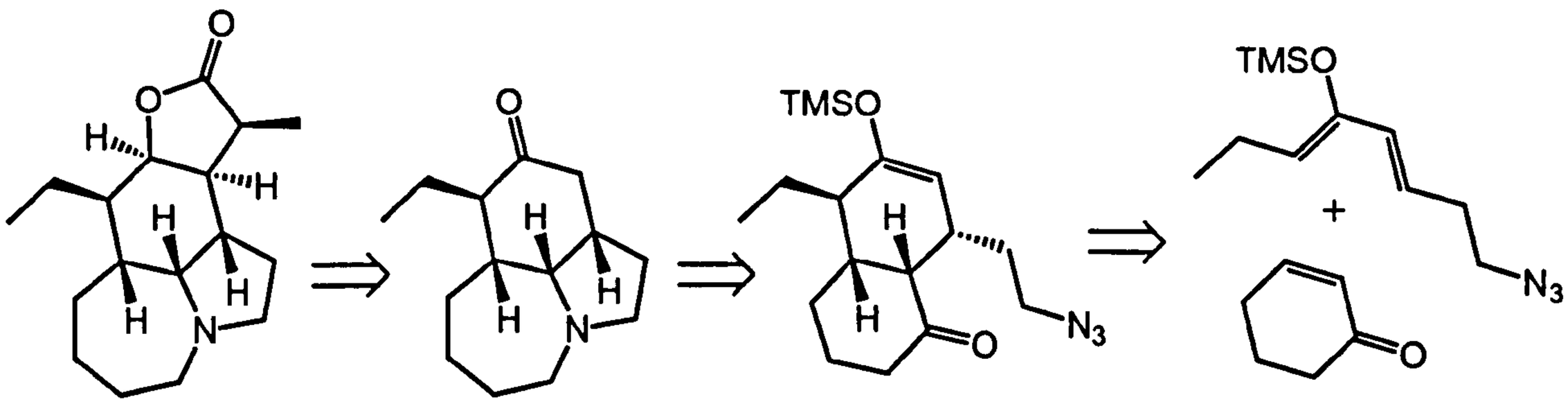


Stenine **31**

Neostenine **32**

Figure 3

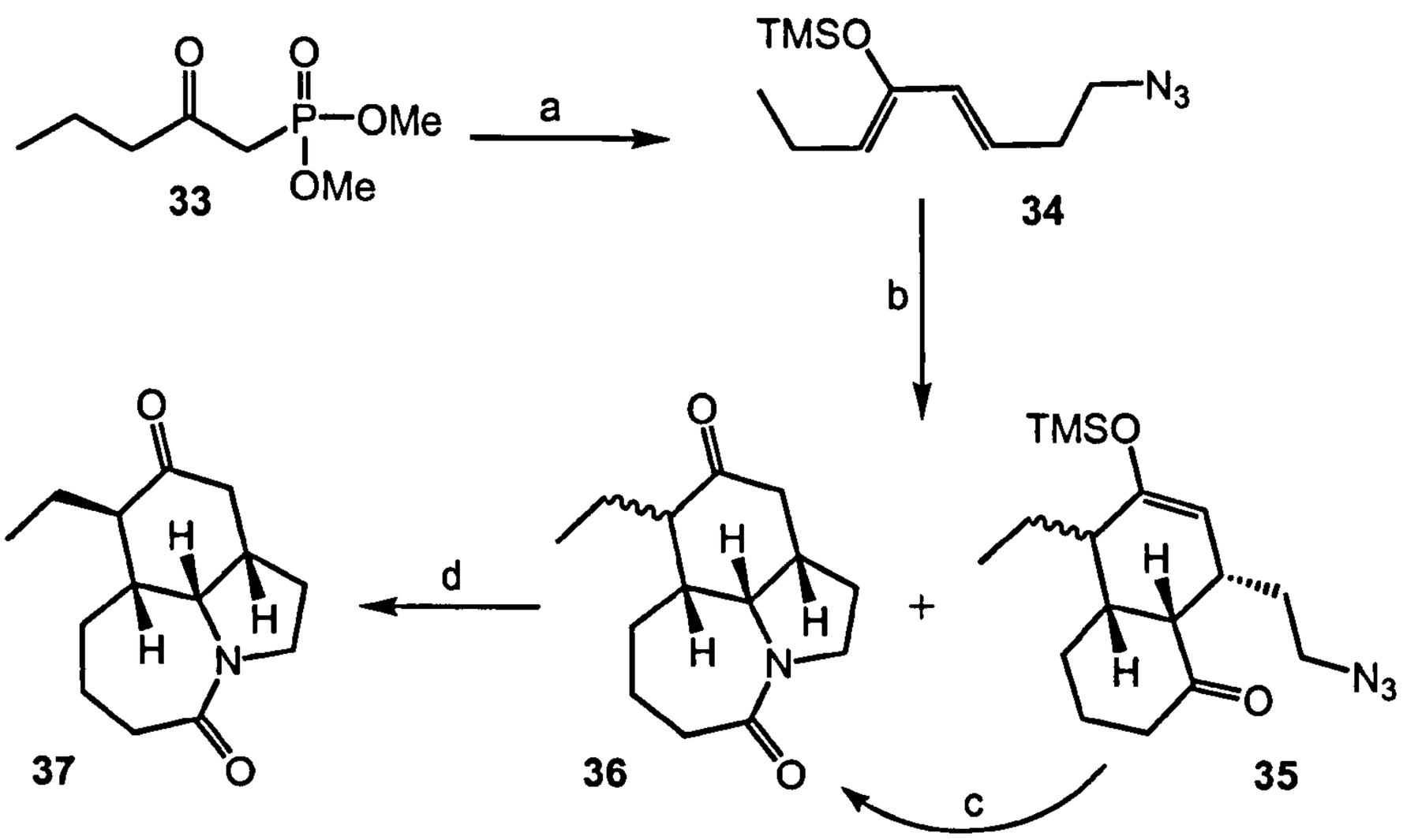
Neostenine did not yield to total synthesis until the conclusion of my project. Aube *et al*. sought to utilise a Diels-Alder/Azido-Schmidt reaction that had been exploited during their synthesis of stenine **(Scheme 8)**.[12]



Scheme 8

Aube's synthesis started from known Horner-Wadsworth-Emmons reagent **33** with olefination of a literature azide **(Scheme 9)**.[12] The resulting enone was readily converted to its silyl ether **34**, providing a diene for the key Diels-

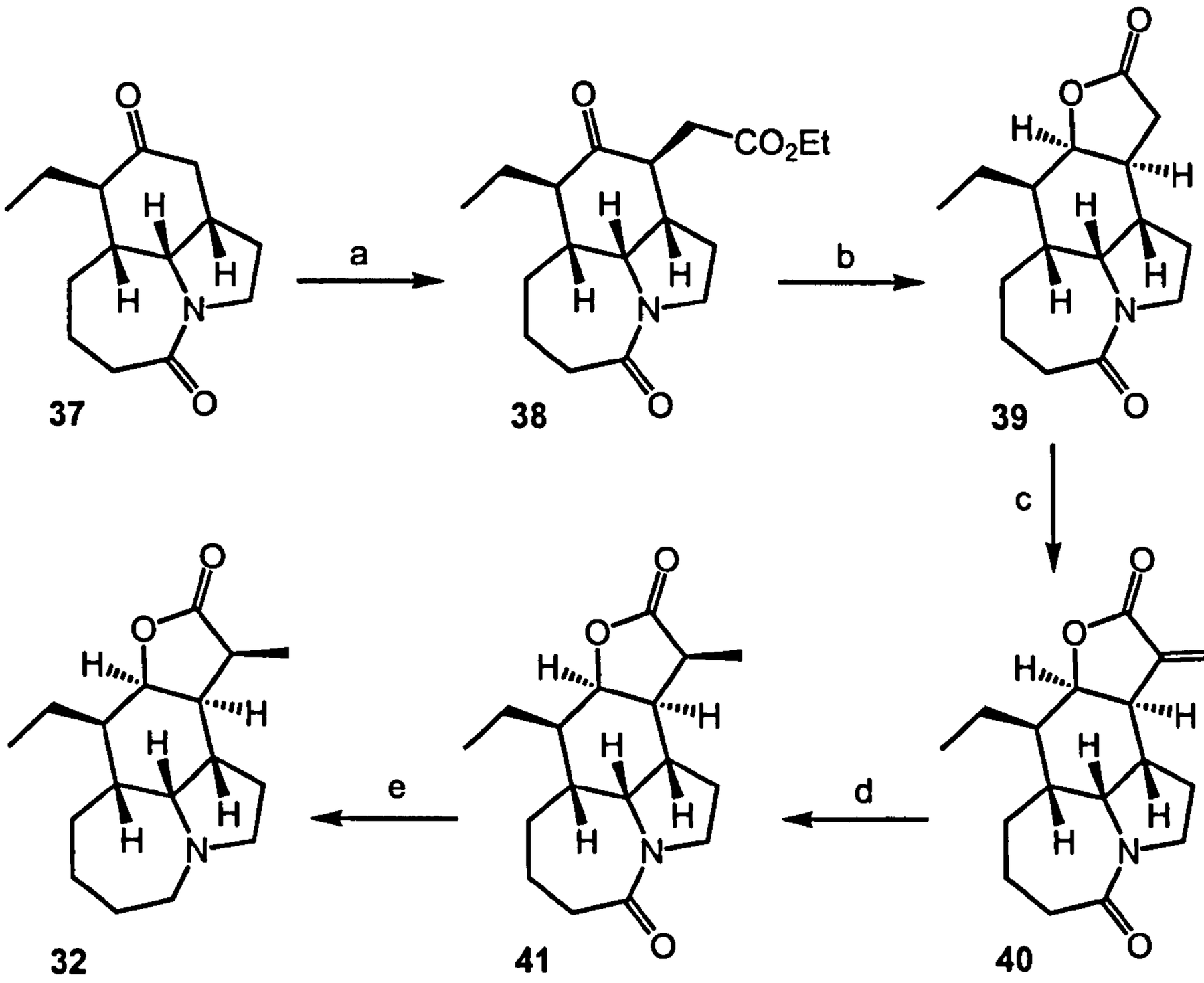
Alder/Schmidt reaction. Addition of **34** (1.5 equiv) to a mixture of cyclohex-2-en-1-one (1 eq) and $BF_3.Et_2O$ (1 eq) was carried out at -78 °C. A further addition of $BF_3.Et_2O$ (1.5 eq) was made at -30 °C providing tricyclic lactam **36** as a mixture of epimers in 43 % yield. Also isolated from the reaction mixture was azide **35** that was converted to **36** by treatment with $TiCl_4$. Keto-amide mixture **36** was converted to **37** under basic conditions.



Reagents and Conditions: a) i) NaH, $N_3CH_2CH_2CHO$, ii) TMSOTf, 87 % (for the two steps); b) $BF_3.Et_2O$, cyclohex-2-en-1-one, 43 % **36**; c) $TiCl_4$, 12 % **36** (from **35**); d) MeOH/NaOMe, 83 %.

Scheme 9

Alkylation was achieved from the less hindered face of **37** to give 1,4 dicarbonyl **38**. Reduction of **38** with $CeCl_3$ and L-Selectride gave a mixture of the corresponding lactol and lactone. The mixture was subjected to TPAP oxidation, affording lactone **39** in a 62 % yield. Methylenation was carried out in a two step procedure, with initial formation of an *a*-carboxylic acid followed by condensation with formaldehyde and subsequent decarboxylation to **40 (Scheme 10)**. Hydrogenation over Adams catalyst gave a single isomer methyl lactone **41** in a 45 % yield for the three steps. Finally, thioamide formation and reduction with Raney Nickel delivered neostenine **32**.



Reagents and Conditions: a) i) LiHMDS; ii) $BrCH_2CO_2Et$, 89 %; b) i) L-Selectride, $CeCl_3$, 77 %; ii) TPAP, NMO, 62 %; c) i) LiHMDS, CO_2 (g); ii) H_2CO, PhNHMe, AcOH, NaOAc, 49 % (for the two steps); d) H_2, PtO_2, 91 %; e) i) P_2S_{10}; ii) Raney Ni, 93 % (for the two steps).

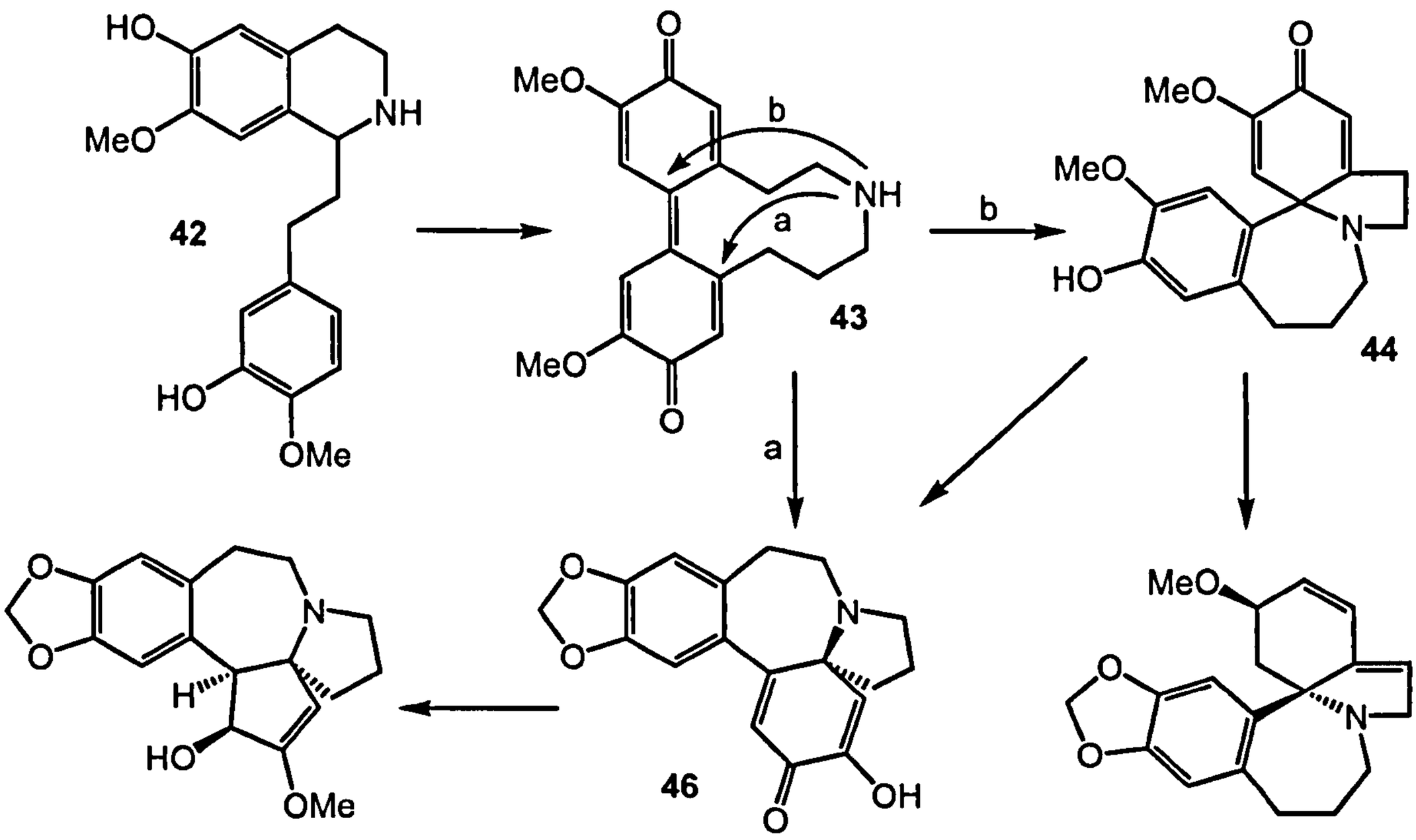
Scheme 10

Aube's synthesis is completed in an impressive 12 steps from literature compound **33**, with an overall 8.4 % yield. However, this short synthesis falters with its key step. Unfortunately 1.5 equivalents of compound **34** is required, thus the initial yield of **36** based upon **34** is actually just 29 %. With further conversion of azide **35** this brings the yield of the key step up to 37 % (55 % based on cyclohex-2-en-1-one). Nonetheless Aube has demonstrated that his Diels-Alder/Schmidt methodology is applicable not only to stenine, but also to that of neostenine.

1.4. Alkaloid biosynthesis

1.4.1. *Erythrina* and *Cephalotaxus* alkaloids

The presence of homoerythrinan alkaloids, such as schelhammeridine, in *Cephalotaxus* has led to the proposal that both cephalotaxine and the homoerythrinan bases may arise from a derivative such as **43 (Scheme 11).**[13]

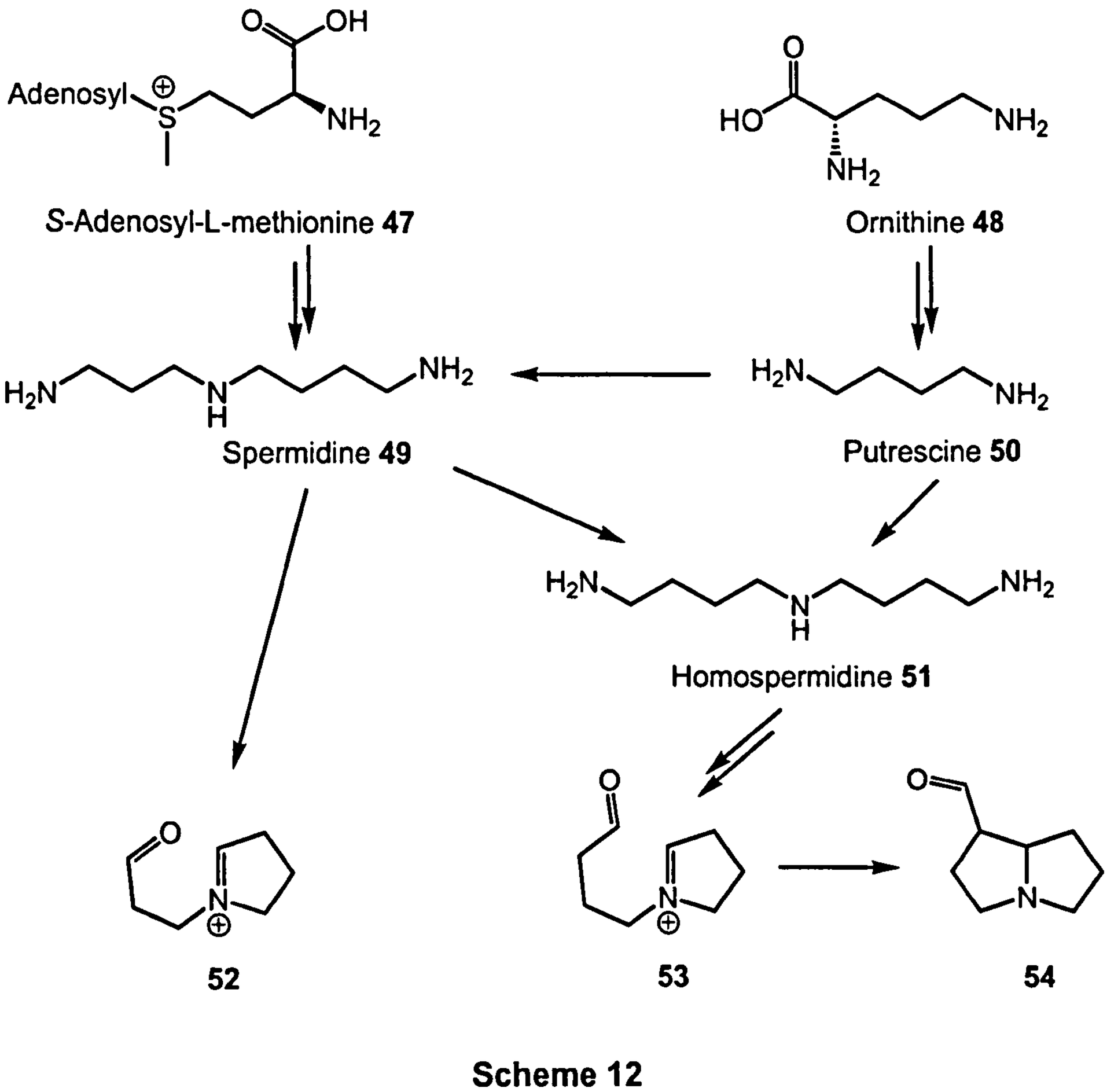


Scheme 11

Phenylethylisoquinoline **42**, derived from tryptophan or phenylalanine, undergoes oxidative phenol coupling to give **43**. Cyclisation of **43** can occur in two ways: *path a* leads to enone **46** that undergoes ring contraction to give the *Cephalotuxus* alkaloid **1**; ring closure *via path b* gives homoerythrinan alkaloid intermediate **44**, which can either convert to the *Cephalotaxus alkaloid* **1** or undergo functionalisation to give abnormal-type *Erythrinan* alkaloids, such as schelhammeridine **45**.

1.4.2. *Stemona* alkaloids

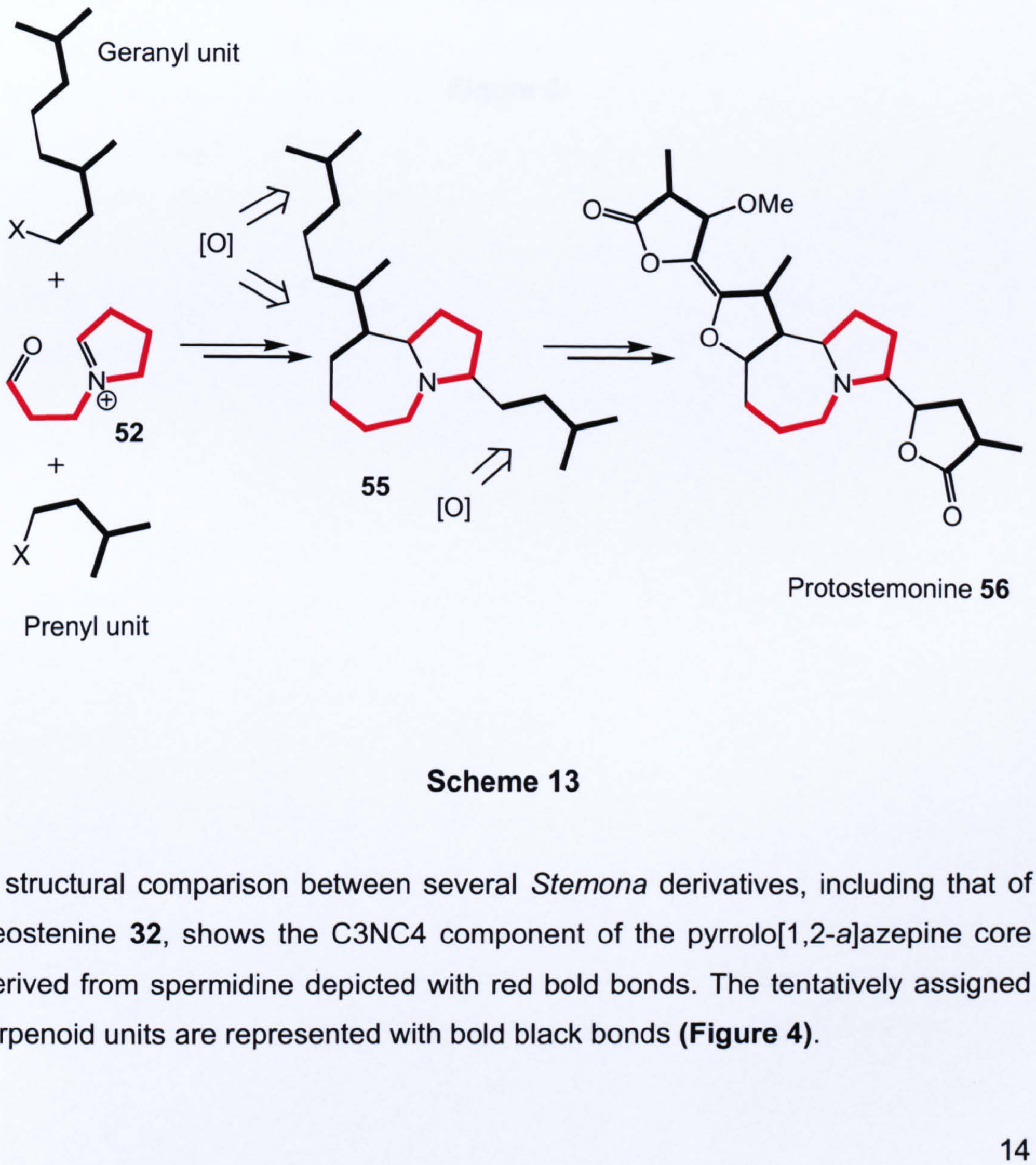
Although biosynthetic studies on *Stemona* alkaloids have not been reported, a proposed biosynthetic pathway has been made by Seger *et al.* leading to the pyrrolo[1,2-*a*]azepine *Stemona* alkaloids.[14] Seger postulates that the central azepine core could pursue a pathway related to the biosynthesis of pyrrolizidines **(Scheme 12)**.



Scheme 12

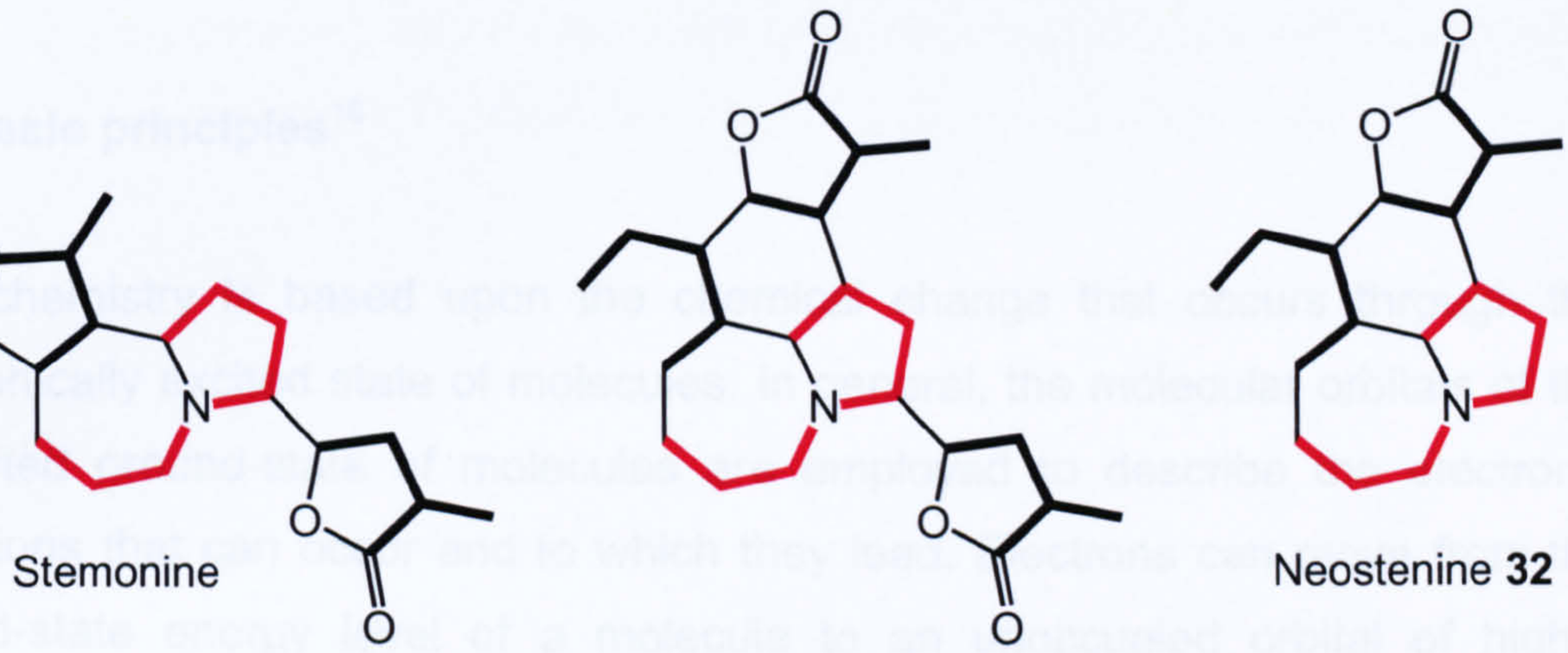
For this, a C4NC4 building block is required which is represented by homospermidine **51** and originates from spermidine **49** and putrescine **50** by homospermidine synthase (HSS). Spermidine **49** itself is biosynthesised *via* **50** (from ornithine **48**) and a C3 unit supplied by *S*-adenosyl-L-methionine **47** (SAM).

The two cyclisation steps from homospermidine to the pyrrolizidines system can take place *via* oxidative de-amination of the terminal amine to its corresponding aldehyde, with the first step forming the monocyclic imminium ion **53** and the second step affording hexahydropyrrolizidine-1-carbaldehyde **54**. Seger proposed that imminium **52** could be cyclised in a similar manner to the pyrrolizidines with an activated geranyl unit to give the pyrrolo[1,2-*a*]azepine core found in the *Stemona* alkaloids. Further incorporation of an activated prenyl unit would give **55** and, upon oxidation and functionalisation, would give protostemonine **56**.



Scheme 13

A structural comparison between several *Stemona* derivatives, including that of neostenine **32**, shows the C3NC4 component of the pyrrolo[1,2-*a*]azepine core derived from spermidine depicted with red bold bonds. The tentatively assigned terpenoid units are represented with bold black bonds **(Figure 4)**.



Stemonine

Neotuberstemonine **57**

Neostenine **32**

Figure 4

2. Photochemistry

2.1. Basic principles[15]

Photochemistry is based upon the chemical change that occurs through the electronically excited state of molecules. In general, the molecular orbitals of the unexcited ground-state of molecules are employed to describe the electronic transitions that can occur and to which they lead. Electrons can move from the ground-state energy level of a molecule to an unoccupied orbital of higher energy. For a molecule to reach an excited state it must absorb a photon that has the same energy as the difference between the ground and excited states **(Figure 5)**. Consequently, for most organic molecules there are four types of electronic excitation: *s*? *s** for alkanes that have no *n* or *p* electrons, *n*? *s** for alcohol, amine and ether excitation; *p*? *p** as a pathway predisposed for alkenes as well as carbonyls; and *n*? *p** as a further option for carbonyl compounds. The latter two are of greatest interest, as they fall in the most accessible region of the UV spectrum.

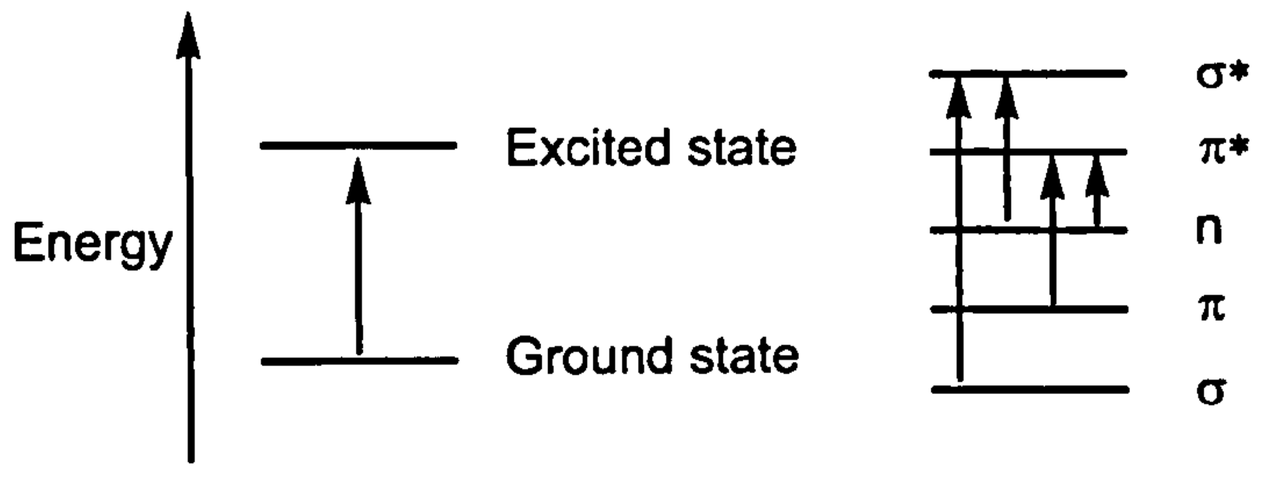


Figure 5

Any molecule has a series of states that can be obtained by electronic transitions. These are designated S_1, S_2, S_3... for singlet states in order of increasing energy, and T_1, T_2, T_3... for triplet states in order of increasing energy. It is uncommon for ground state (S_0) molecules, to adopt a triplet state. Photochemical reactions generally occur through S_1 or T_1. This is because most

excited states of a higher energy decay very rapidly to give the S_1 or T_1 state. For example the n? *p** transition found in carbonyl groups represents the HOMO-LUMO transition which affords the S_1 and T_1 state that is commonly established to be responsible for the reaction of carbonyl compounds **(Figure 6)**.

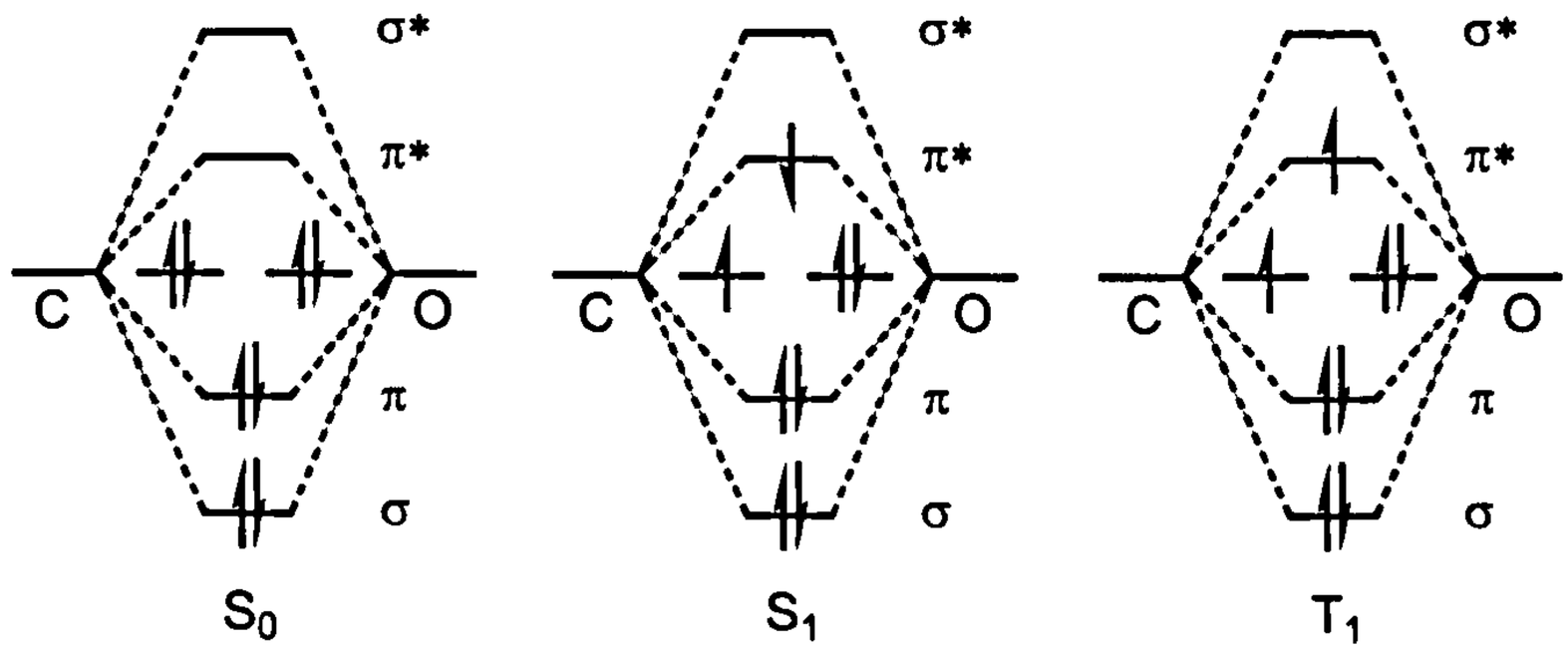
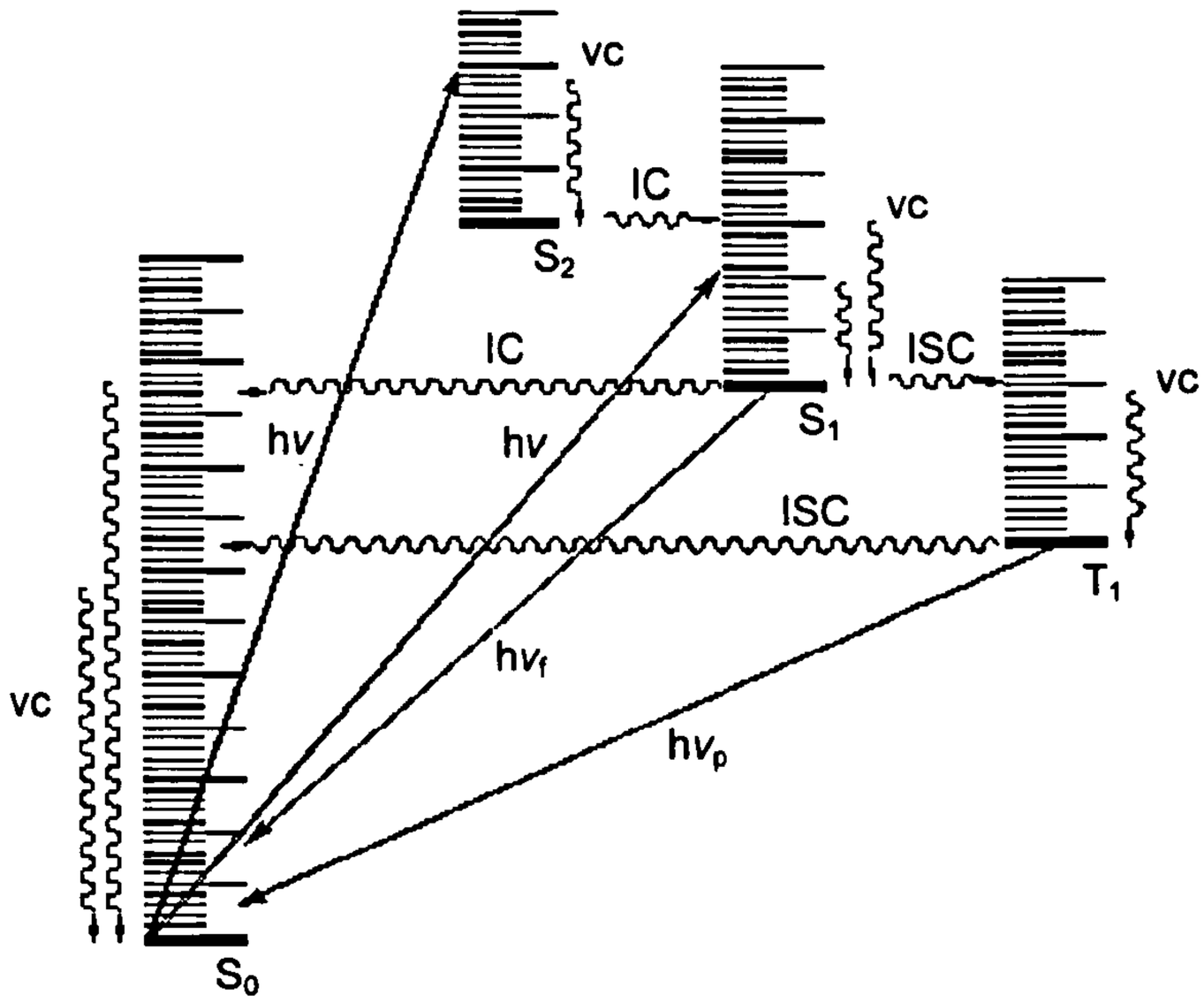


Figure 6

As the *n*-orbitals do not occupy the same space as the *p** orbitals this electronic excitation is symmetry forbidden. However, vibrational effects can allow this selection rule to be broken. The observed effect of this is that the n? *p** transition is considerably weaker than its allowed *p*? *p**. The physical processes of excitation and deactivation that occur for a particular substrate can be displayed on a Jablonski diagram **(Figure 7)**. A molecule can be photochemically excited to an excited state, mostly with promotion from the S_0 to S_1 state. Promotions to S_2 and higher states do take place, but usually drop very quickly to S_1. Excitations of S_0 to triplet states are forbidden. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0, which is known as internal conversion (IC). However IC is usually quite slow. This can also occur by a process called fluorescence, which gives off the energy in the form of light but this is also relatively slow. Most molecules in the S_1 state can undergo intersystem crossing (ISC) to the lowest triplet state by entering T_1 at a higher vibrational energy level and cascading down to its lowest vibrational level. This process is of course forbidden, but has taken place by compensations in the system. A molecule in the T_1 state may return to S_0 by giving up heat (ISC) or light (phosphorescence).

As these are still forbidden processes, they occur very slowly. This means that triplet states have longer lifetimes (10^{-5} to 30s) than singlet states (10^{-9} to 10^{-5}s).



Radiative processes are shown by straight lines, radiationless processes by wavy lines. IC = internal conversion; ISC = intersystem crossing; vc = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

Figure 7

This is why most photochemical reactions occur through the triplet state, as the singlet is too short lived. The feasibility of a photochemical process is different to that of thermal reactions. Photochemical reactions cannot undergo the reversibility that takes place in thermal reactions and therefore cannot lead to a thermodynamic equilibrium. Photochemical reactions as a result almost without exception operate under kinetic control.

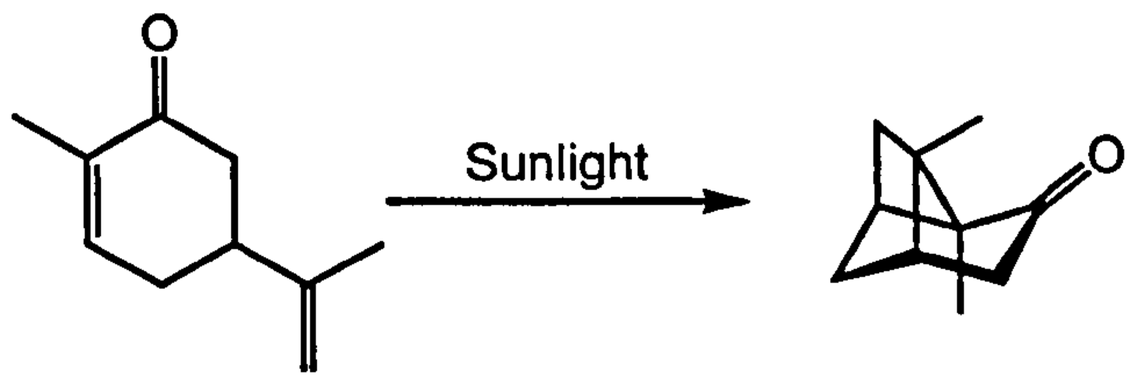
Scheme 14

A major reason for this is that the pathway **(Scheme 14)** of an excited state of the substrate R* to the observed product P does not go through an excited state of

the product. There is usually a large energy difference between R* and P, and product does not revert to the excited state of the substrate.

2.2. Carbonyls

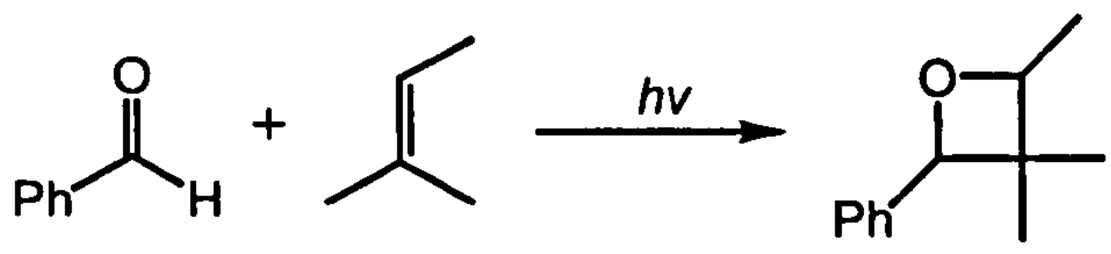
The first reported example of a [2+2] photocycloaddition was discovered by Camician *et al.*[16] in a sunny Mediterranean climate in 1908. They discovered that leaving carvone **58** in sunlight for a year yielded the unusual cycloadduct carvonecamphor **59 (Scheme 15)**. This intramolecular cycloaddition demonstrates how photochemistry can be used to efficiently build complex and highly strained molecules.



58 **59**

Scheme 15

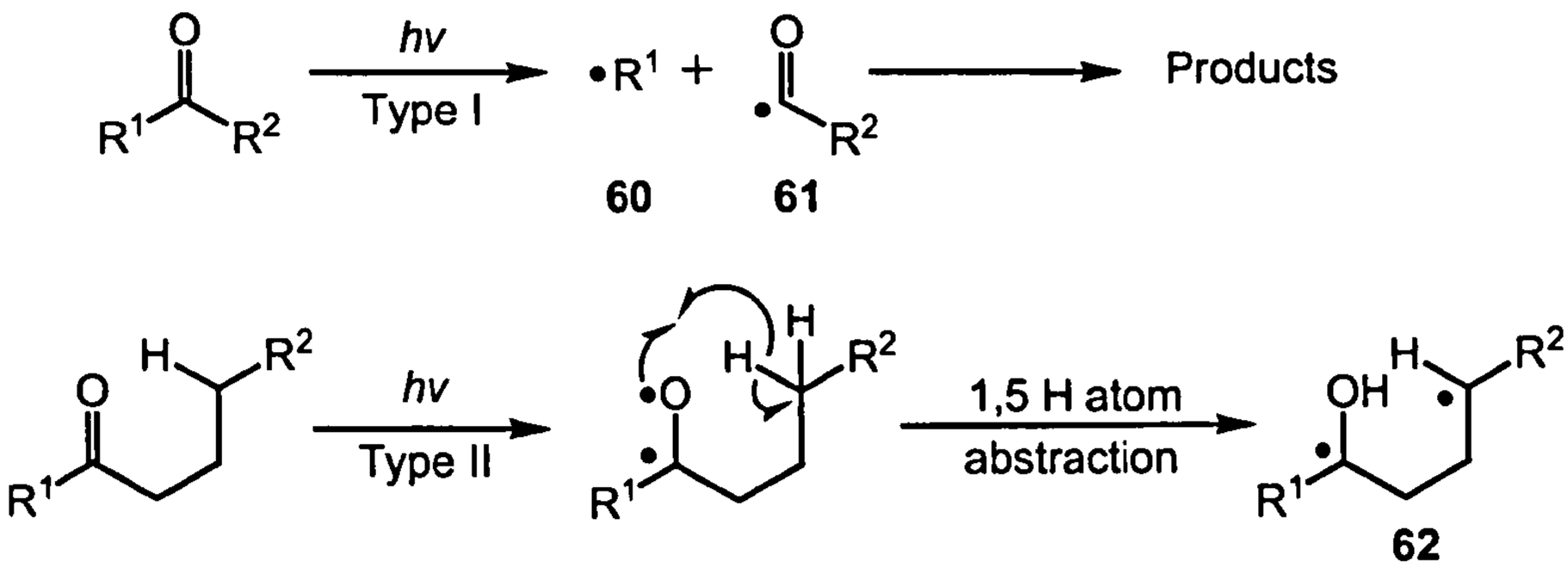
Following on from the discovery of the [2+2] photocycloaddition, this reaction has found increasingly frequent and effective use in complex molecule synthesis.[17] A reaction that has become a commonly used method of synthesising oxetanes was first discovered in 1909 by Paterno *et al.*[18] **(Scheme 16)**, however the reaction was not reinvestigated until the work of Buchi *et al.*[19] in 1954. Since then thousands of examples of these [2+2] photocycloadditions have been observed[17] and are now referred to as the Paterno-Buchi reaction.



Scheme 16

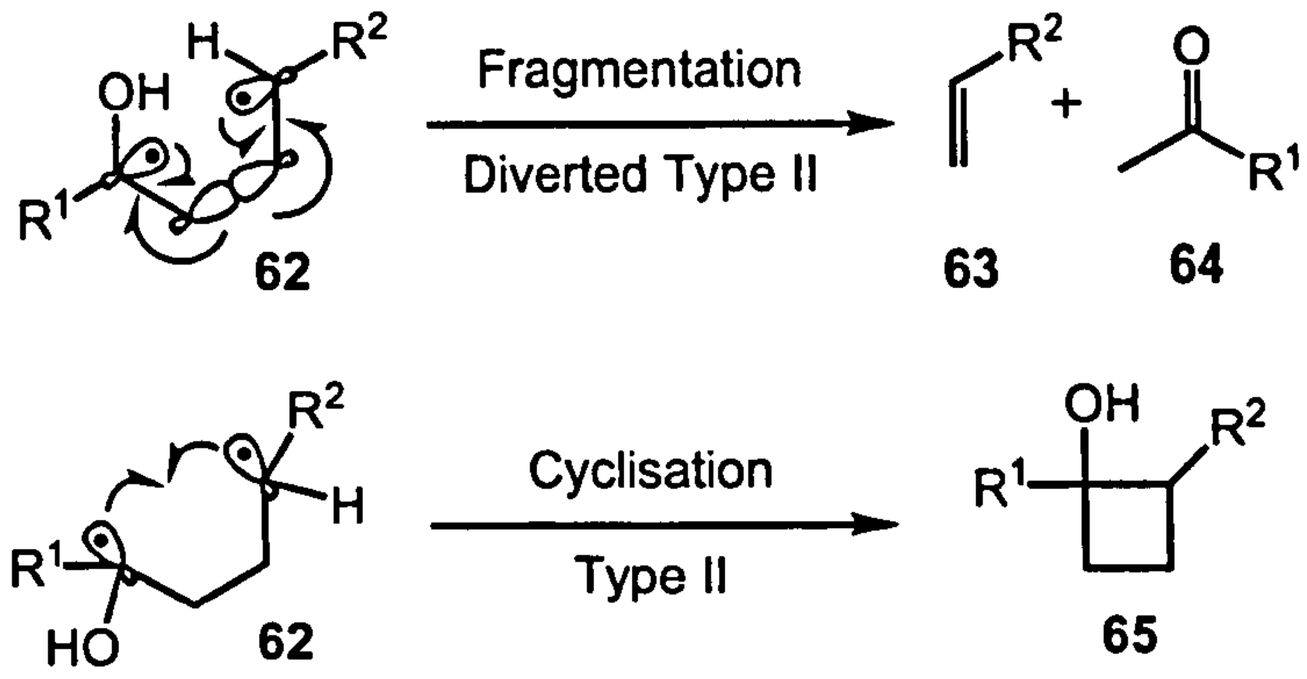
2.2.1. Norrish type I/II

The study of a broad range of ketones and aldehydes by Norrish *et al.*[20] in the mid 1930's led to the understanding of a number of intramolecular photochemical reactions. The two main processes that they observed became known as the Norrish Type I and II reactions. The Type I process involves an initial cleavage to give two radical species **60** and **61 (Scheme 17)**.



Scheme 17

These radicals can then undergo several other reactions. Carbonyl compounds containing ? C-H bonds can undergo upon excitation a 1,5-hyrogen abstraction to form a biradical **62**, that is characteristic of a Type II process. The biradical **62** can either undergo fragmentation to form an alkene **63** and carbonyl product **64 (Scheme 18)**.

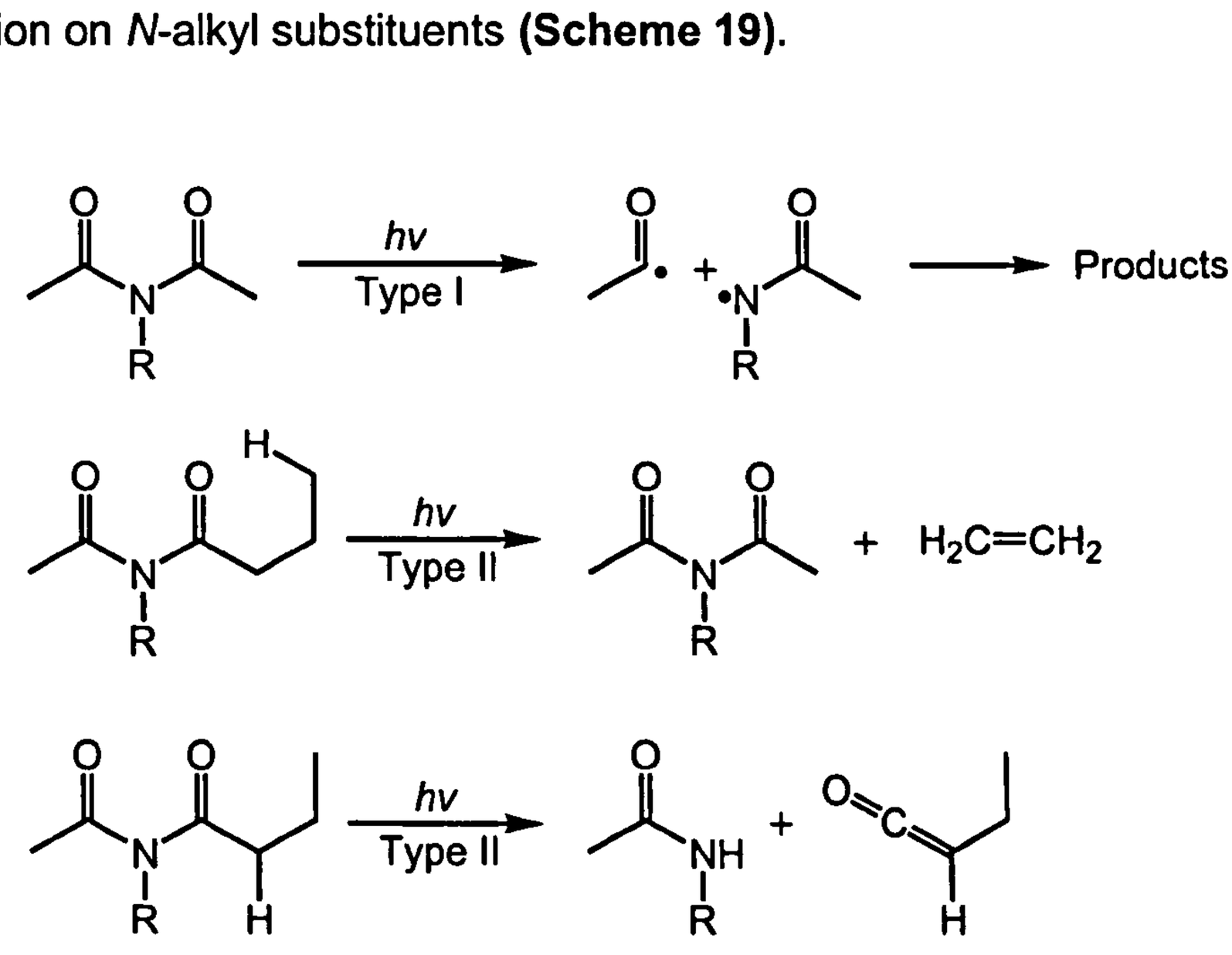


Scheme 18

Alternatively, and which most often accompanies fragmentation, is cyclobutanol formation **65**, which was reported by Yang *et al.*[21] in 1958. The competition between these two processes is well recognised[22] and is reliant upon the capability of the biradical to undergo each route. For cyclisation to occur the two radical centres must overlap, but for fragmentation the radicals must overlap with the bond that is being cleaved.

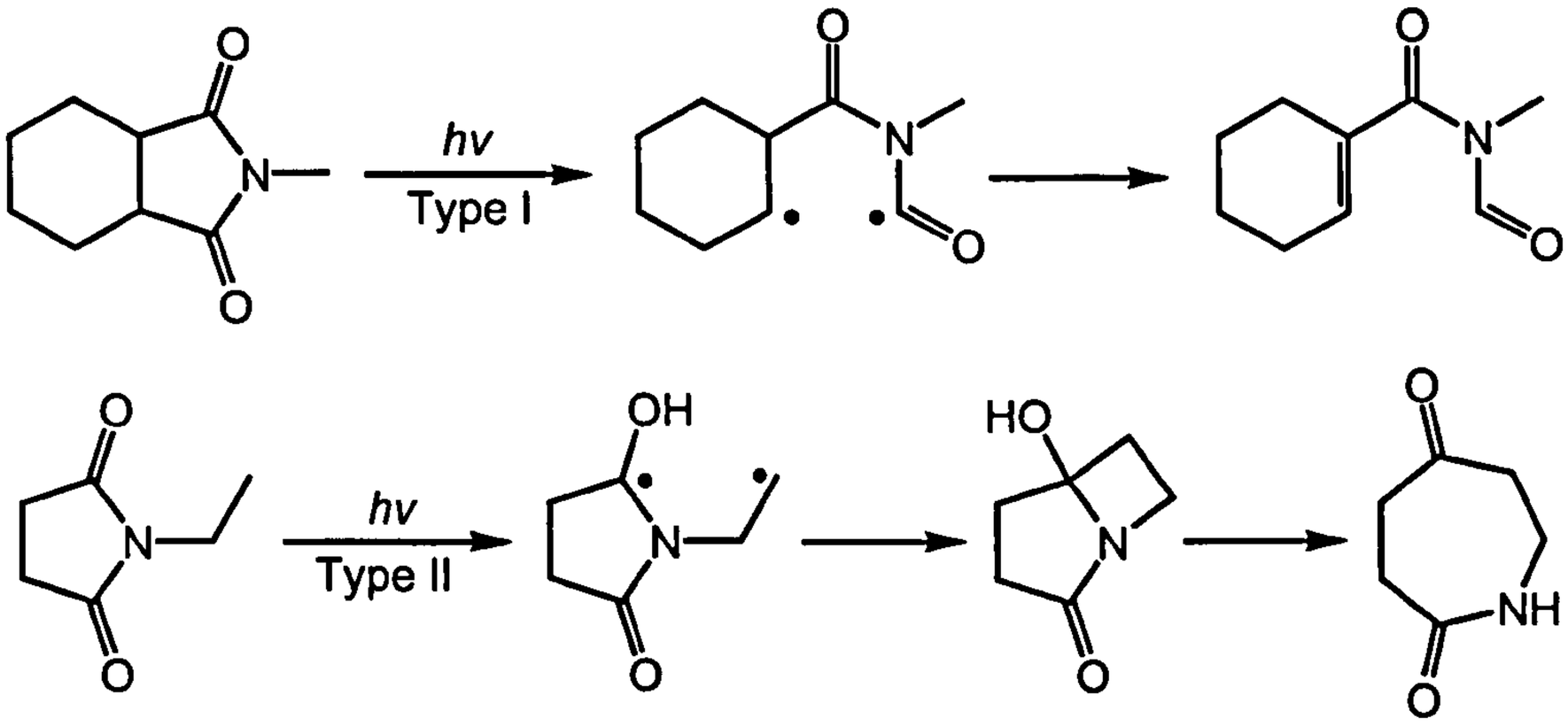
2.3. Imides

The photochemistry of imide carbonyl compounds has been extensively investigated and has generated considerable interest on the addition of alkenes to phthalimides.[15,17] It has become clear that there are dramatic differences between the photochemistry of the aliphatic, cycloaliphatic and aromatic imides.[23] Aliphatic imides can undergo Type I and Type II processes that were discussed in the previous section. The Type II abstraction occurs either on the C-alkyl group or across the imide moiety. They do not undergo Type II abstraction on *N*-alkyl substituents **(Scheme 19)**.



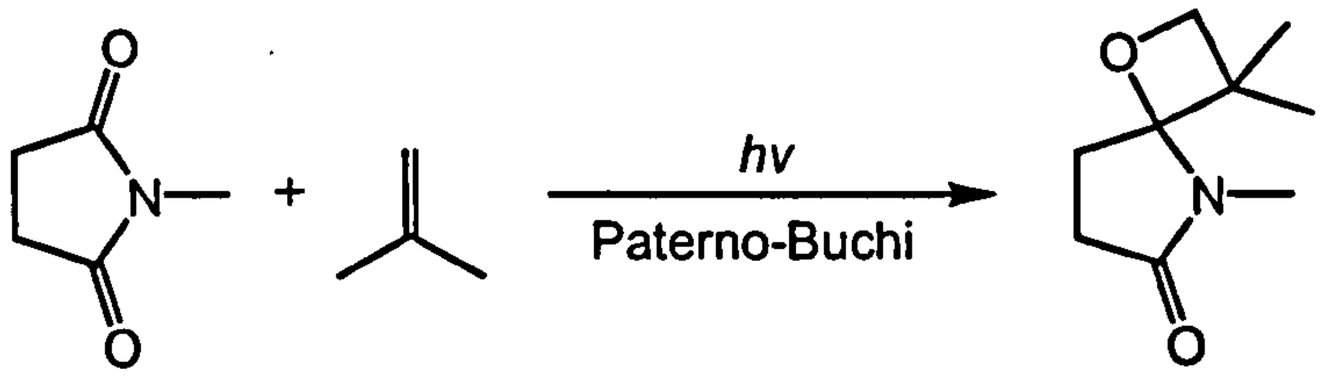
Scheme 19

Cycloaliphatic imides however, are not only more likely to undergo Type I C(O)-C than C(O)-N bond cleavage, but also participate in the Type II processes on the *N*-alkyl group **(Scheme 20)**. The photochemistry of the aromatic phthalimide systems are characterised by these Type II abstractions on the *N*-alkyl chain where there is a ?-H available.[24]



Scheme 20

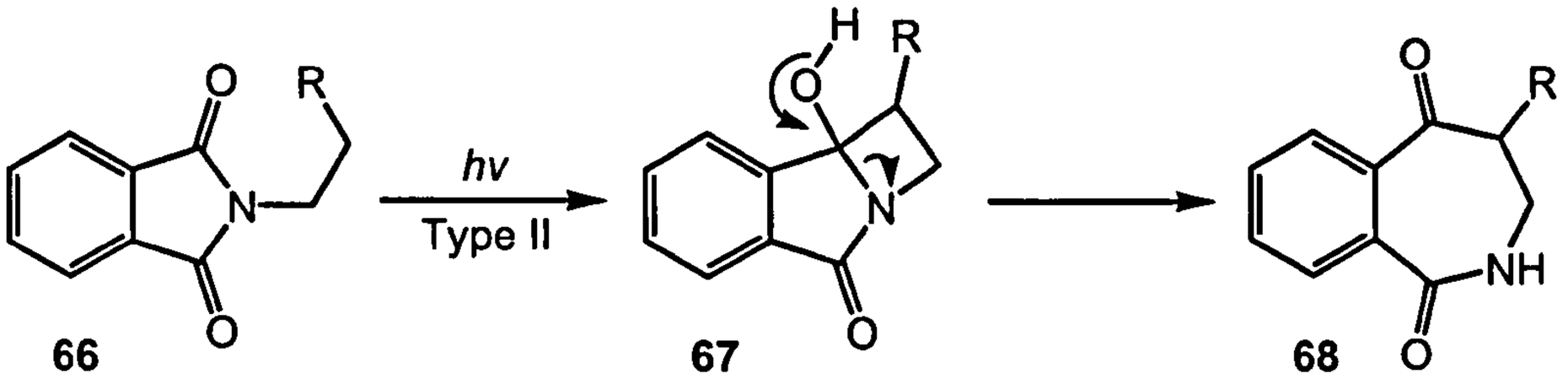
The photochemistry of these three classes of imides also differs in the presence of alkenes. Aliphatic imides are essentially unreactive[24a], whereas the cycloaliphatic imides undergo proficient inter- or intramolecular Paterno-Buchi reactions[23b,24] **(Scheme 21)**.



Scheme 21

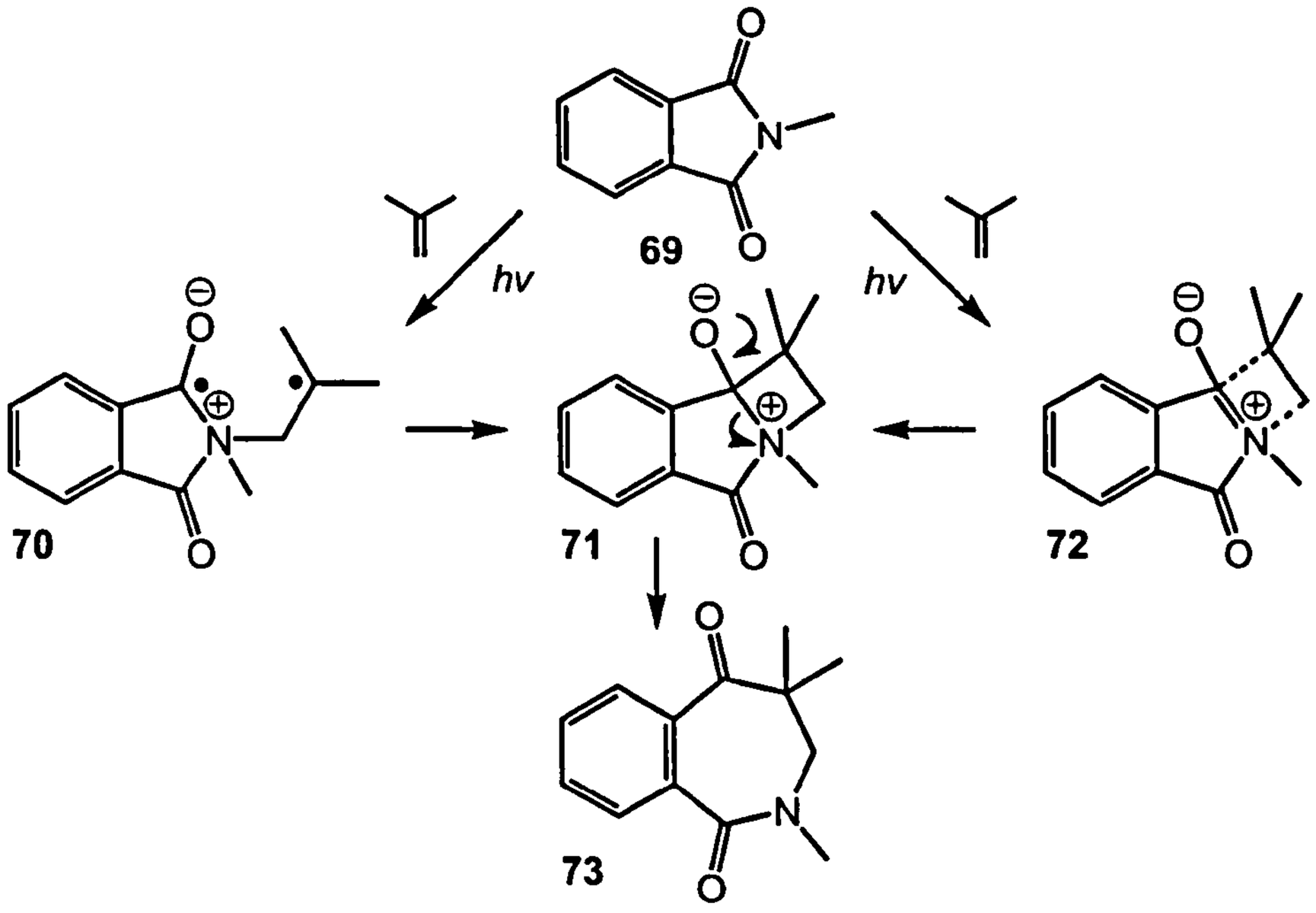
Phthalimides react inefficiently with alkenes in the Paterno-Buchi sense, but readily undergo electron-transfer chemistry and/or Type II addition to the C(O)-N bond to form benzazepinediones.[25] It is the reactivity of the *N*-alkylated phthalimides that is of greatest interest to this research project. In 1977

Mazzocchi *et al.*[25b] were investigating the photochemical rearrangement of *N*-alkylated phthalimides **66** to benzazepinediones **68**. The mechanistic proposal for this reaction was a Type II cyclisation of **66** giving **67**, followed by fragmentation to give the product **68 (Scheme 22)**.



Scheme 22

Mazzocchi decided that in order to study the mechanism, quenching studies were necessary.[26] Astonishingly, they found that the diene being used as the quencher was actually reacting smoothly with the phthalimide.

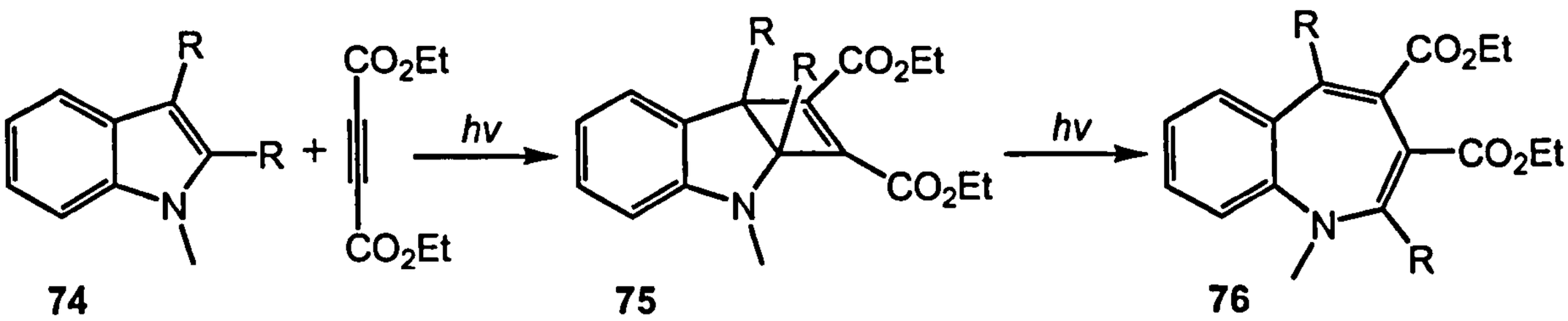


Scheme 23

It was realised that, to effectively study the mechanism, *N*-methylphthalimide **69** would be needed to avoid complications from the Type II processes. It was considered that the addition of alkenes to **69** to form benzazepinedione **73** could be rationalised by one of two possible mechanisms **(Scheme 23)**. The first is addition to afford biradical **70**, which would close to **71** and subsequently reopen to benzazepine **73**. The second possibility is that of a concerted addition, possibly through an oriented exciplex **72** to give intermediate **71** directly. Studies on the stereochemistry of the addition of alkenes to the phthalimide system were undertaken and they found the addition to be >95 % stereospecific. The mechanistic implication of this result is either that the photochemical addition is a concerted [2+2] addition or that any intermediate biradical closes faster than rotation around the C-C bond which would result in loss of stereochemistry.

2.4. Indoles

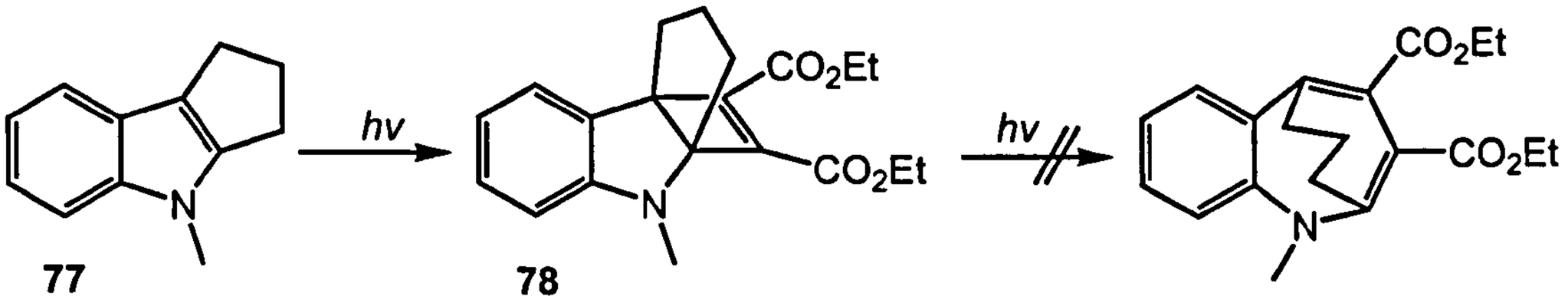
A large proportion of photochemical studies have been used on *N*-methyl or *N*-alkylated indoles, mostly because non-alkylated indoles undergo photochemical *N*-H bond scission and oxidise.[27] A great deal of work has been carried out by Neckers *et al.*[28] on activated 1-methylindoles. The acetophenone-sensitised photocycloaddition of butyne **74** produced [2+2] cycloadducts **75**. These cyclobutenes were then encouraged to undergo thermal or photochemical ring opening to benzazepines **76 (Scheme 24)**.



74 **75** **76**

Scheme 24

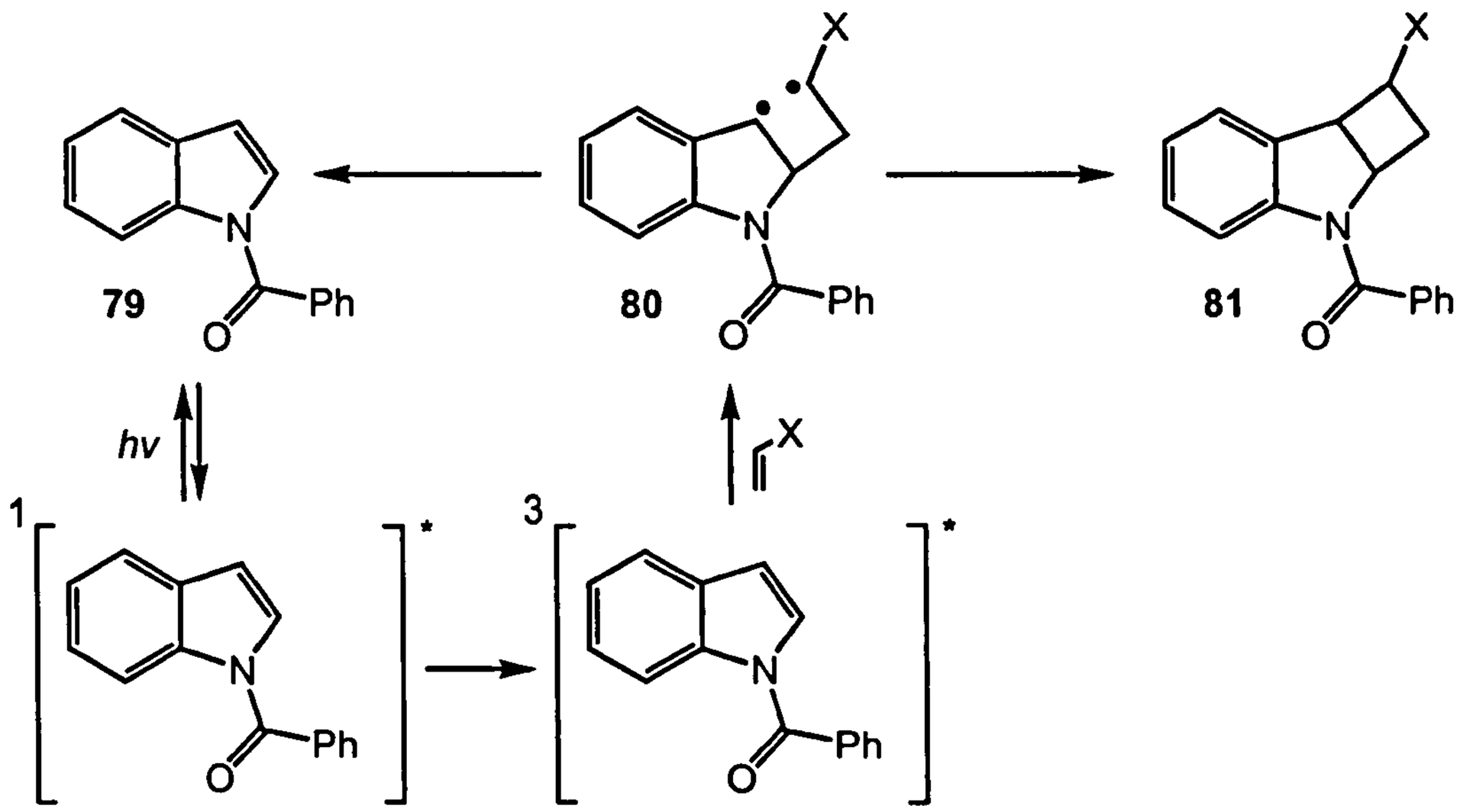
Yields were high in almost every case investigated. By bridging the C-2 and C-3 positions of the activated indole a compound **77** was built in which photochemical cyclobutene formation **78** could be guaranteed and benzazepine formation, either by thermal or photochemical means was suppressed **(Scheme 25)**.



77 78

Scheme 25

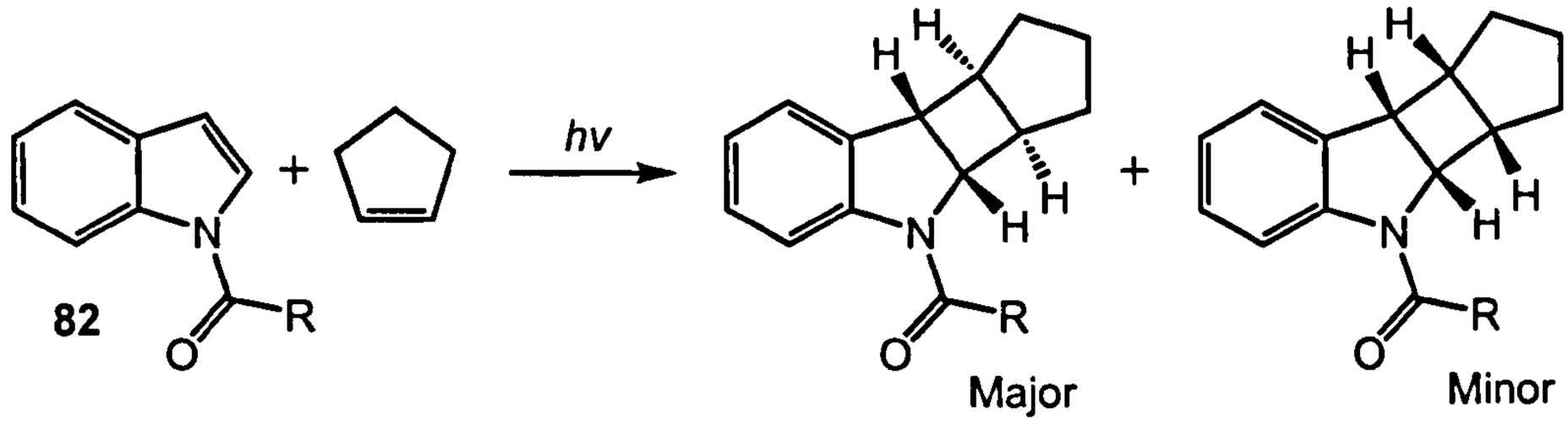
Weedon *et al.*[29] have investigated in depth the cycloaddition of alkenes to 1-acylindoles. They found that the lowest singlet excited state of the activated indoles **79** is a charge-transfer state[30] and that this is not involved in cycloaddition. If alkenes are present then they react *via* the triplet excited state[31] of the indole derivative to form biradicals **80**,[32] which either ring close to cycloadducts **81** or revert to the ground state of the starting materials[31,32] **(Scheme 26)**.



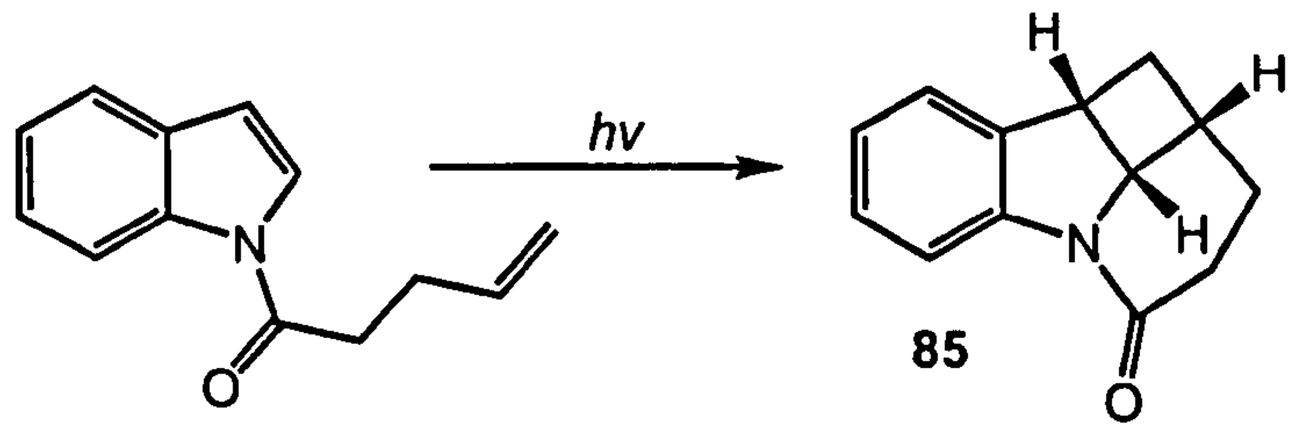
79 80 81

Scheme 26

It was found that a variety of acyl substituents activate the photochemical cycloaddition reaction of indoles **82** with cyclopentene **(Scheme 27)**. The yields were good if the reactions were sensitised so that a competing photo-Fries rearrangement could be avoided. The activating acyl groups could then be removed from the product under mild neutral, acidic or basic conditions.



R = OEt, $CH_2CH_2SiMe_3$, CH_2CH_2CN, O^{t}Bu, OPh and OCH_2Ph



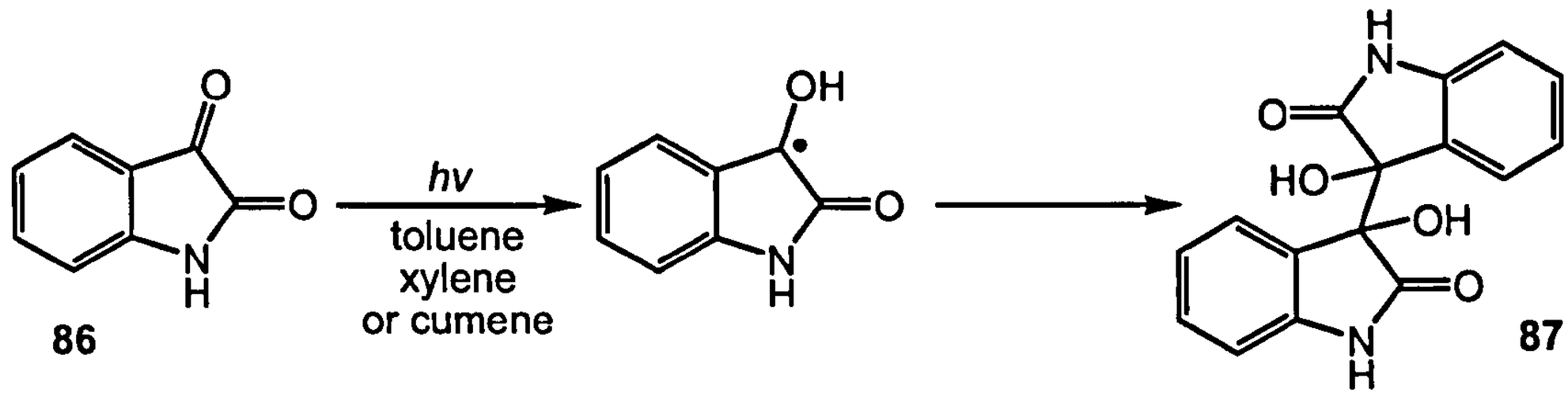
Scheme 27

Further investigations by Weedon *et al.*[29b] with mono-substituted alkenes lead to the regioselective cyclobutane formation of **83** over **84** by addition of the alkene to 1-acyl-indole **82**. The preferred regiochemistry of this reaction could be reversed if desired, by the attachment of the alkene to the indole nitrogen by

amide functionality. This would give an intramolecular cycloaddition affording cyclobutane **85**.

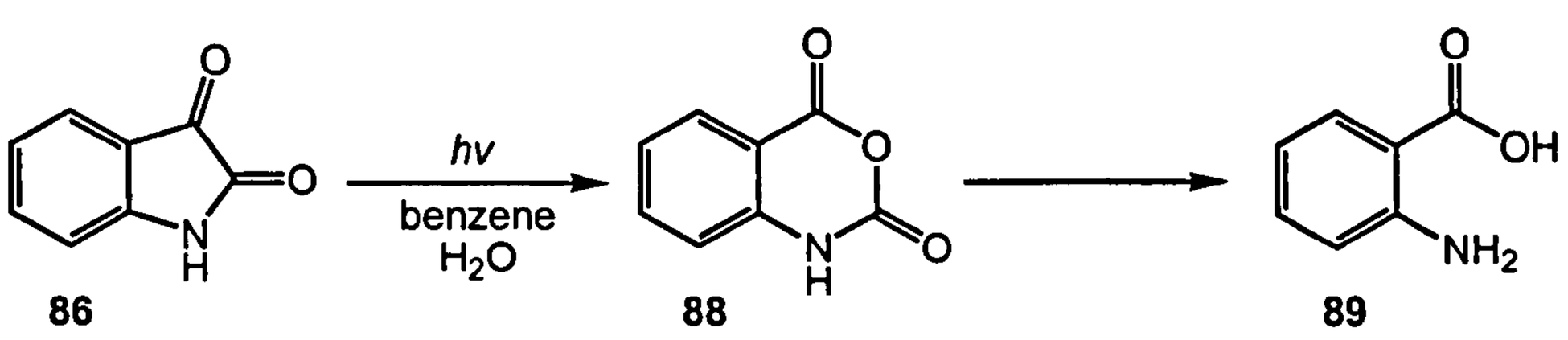
2.5. Isatins

Indoline-2,3-dione (isatin) derivatives exhibit various biological activities and have been widely used as precursors or building blocks for many natural and unnatural products.[33] However, their photochemical reactions have scarcely been investigated. The first photochemical studies of Isatin **86** by Haucke *et al.*[34] showed that fluorescence or phosphorescence did not occur in a variety of solvents. Upon excitation isatin undergoes very fast intersystem crossing to the triplet state. This triplet state is capable of hydrogen abstraction, from toluene, *p*-xylene and cumene, giving the formation of a pinacol isatide **87 (Scheme 28)**.



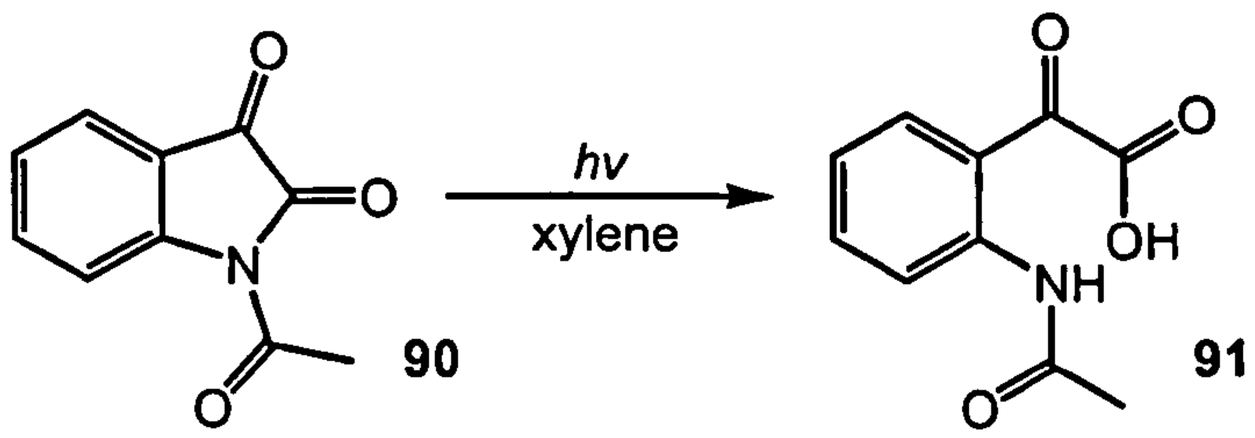
Scheme 28

Quite a different photochemical reaction was observed in benzene, since the solvent is a very poor hydrogen-atom donor. Nonetheless, photochemical decomposition of **86** occurred yielding an isatoic acid anhydride **88** and further reacts with water to give acid **89 (Scheme 29)**.



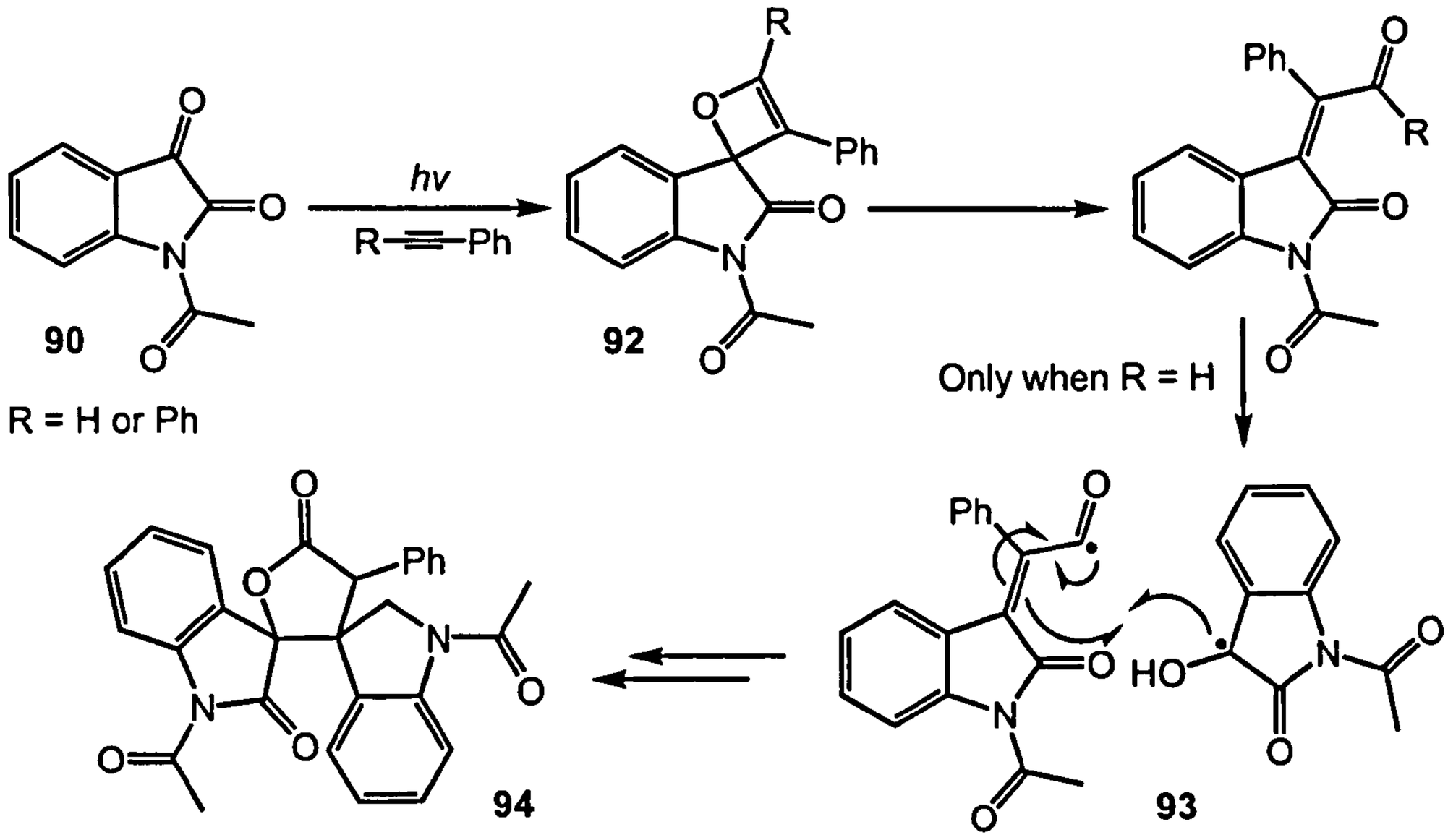
Scheme 29

The results obtained for the decomposition of 1-acetylisatin found that a quick decomposition to the isatic acid **91** occurred from photohydrolysis, indicating that water may play a crucial role **(Scheme 30)**. In addition, this result underlines the role of the nitrogen atom as an electon donor. The more this role is restricted the higher the photochemical reactivity of the carbonyl group. This is further supported by 1-methylisatin, which is photochemically inactive.



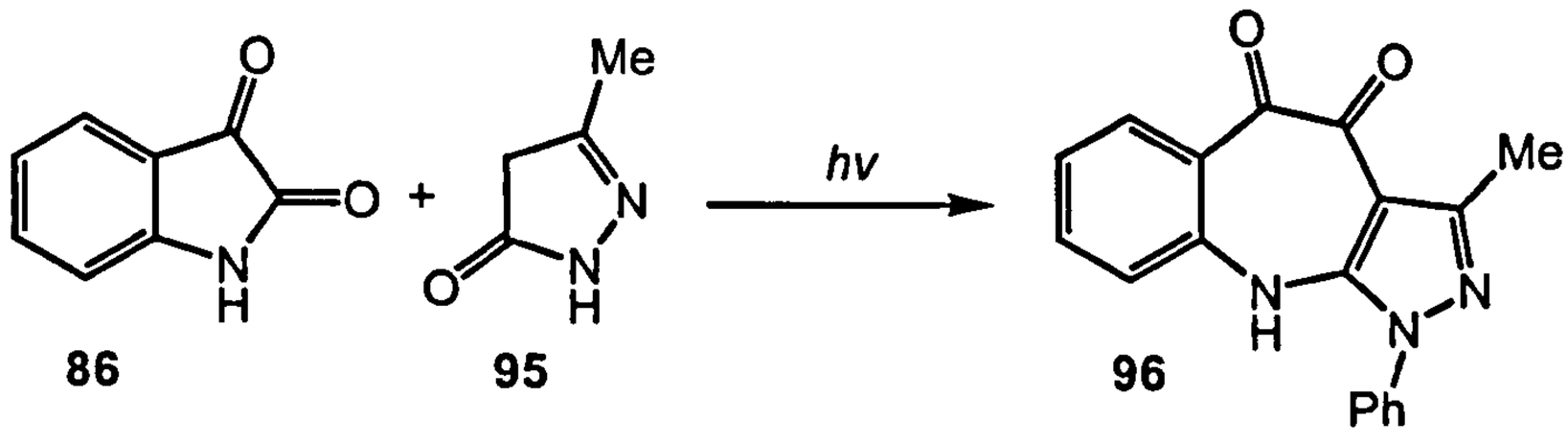
Scheme 30

The main studies of photoinduced reactions with isatin have been taken on by Xu *et al.*, with reactions of isatins with phenylacetylenes[33], enol ethers[35] and aldehydes[36].



Scheme 31

Photoinduced reactions with the diphenylacetylenes were found to undergo a [2+2] cycloaddition of the acetylene to the carbonyl C=O bond in the n ? p^* triplet state of **90**, followed by electrocyclic ring opening of the oxetene intermediate to **92 (Scheme 31)**. The phenylacetylenes however did not stop at this stage and hydrogen abstraction from another excited **90** molecule gave a triplet radical pair **93**. Intersystem crossing and radical combination followed by intamolecular nucleophilic attack of the hydroxyl group to the ketene functionality delivers the products **94**. Photolysis of enol ethers underwent similar [2+2] cycloadditions.[35] The photoinduced reactions with aldehydes gave only dimerisation products with the intended [2+2] cycloaddition not taking place. The only other type of photochemical reaction with isatin that has been observed was by Pardasani *et al.*[37], which involves the irradiation of isatin **86** with pyrrazalone **95** furnishing ring expanded compound **96** from the cleavage of the amide bond **(Scheme 32)**.



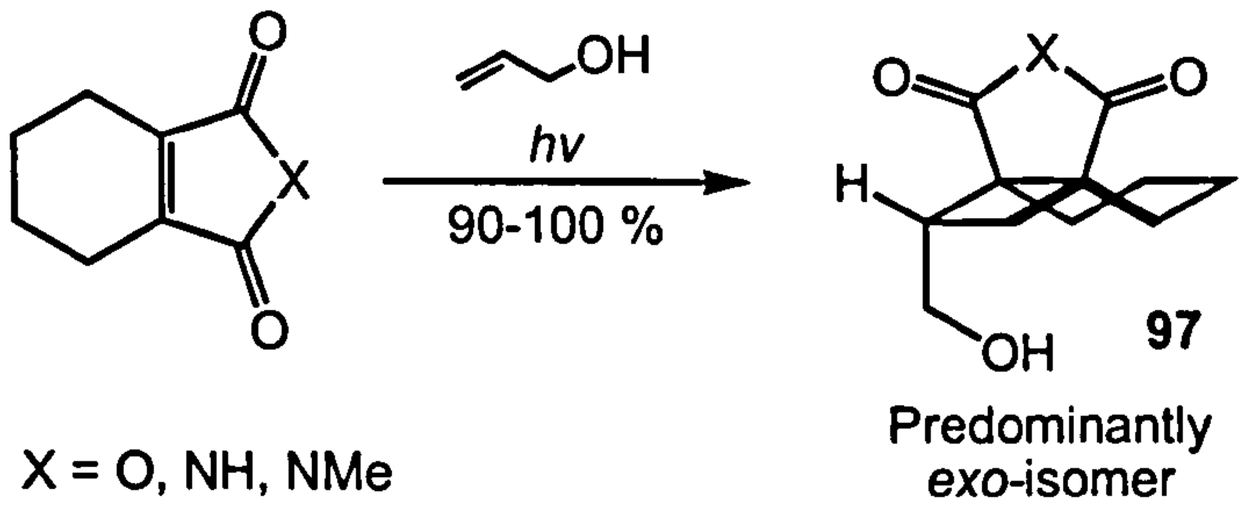
Scheme 32

Pardasani believes this to occur from the decomposition of isatin **86** to isatic acid, which then reacts with the enolic form of pyrazolone.

3. Maleimide [5+2] photocycloaddition

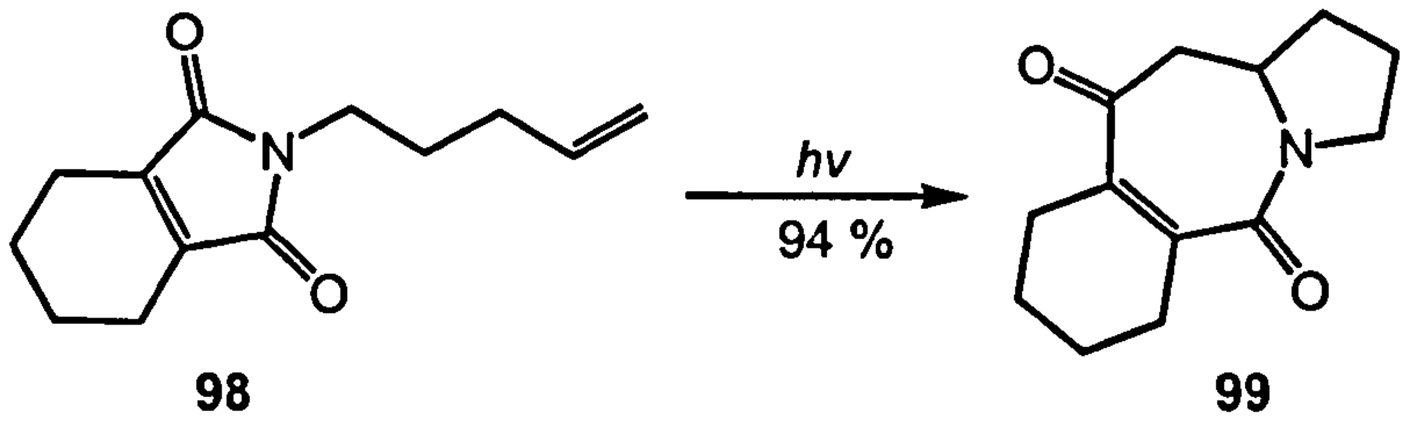
3.1. Discovery and mechanism

A few years prior to the discovery of the novel [5+2] photocycloaddition, the Booker-Milburn group had been studying the intermolecular [2+2] photocycloadditions of maleimides with alkenes.[38] They found that tricyclic structures, such as **97** could be formed efficiently and with high stereoselectivity **(Scheme 33)**.



Scheme 33

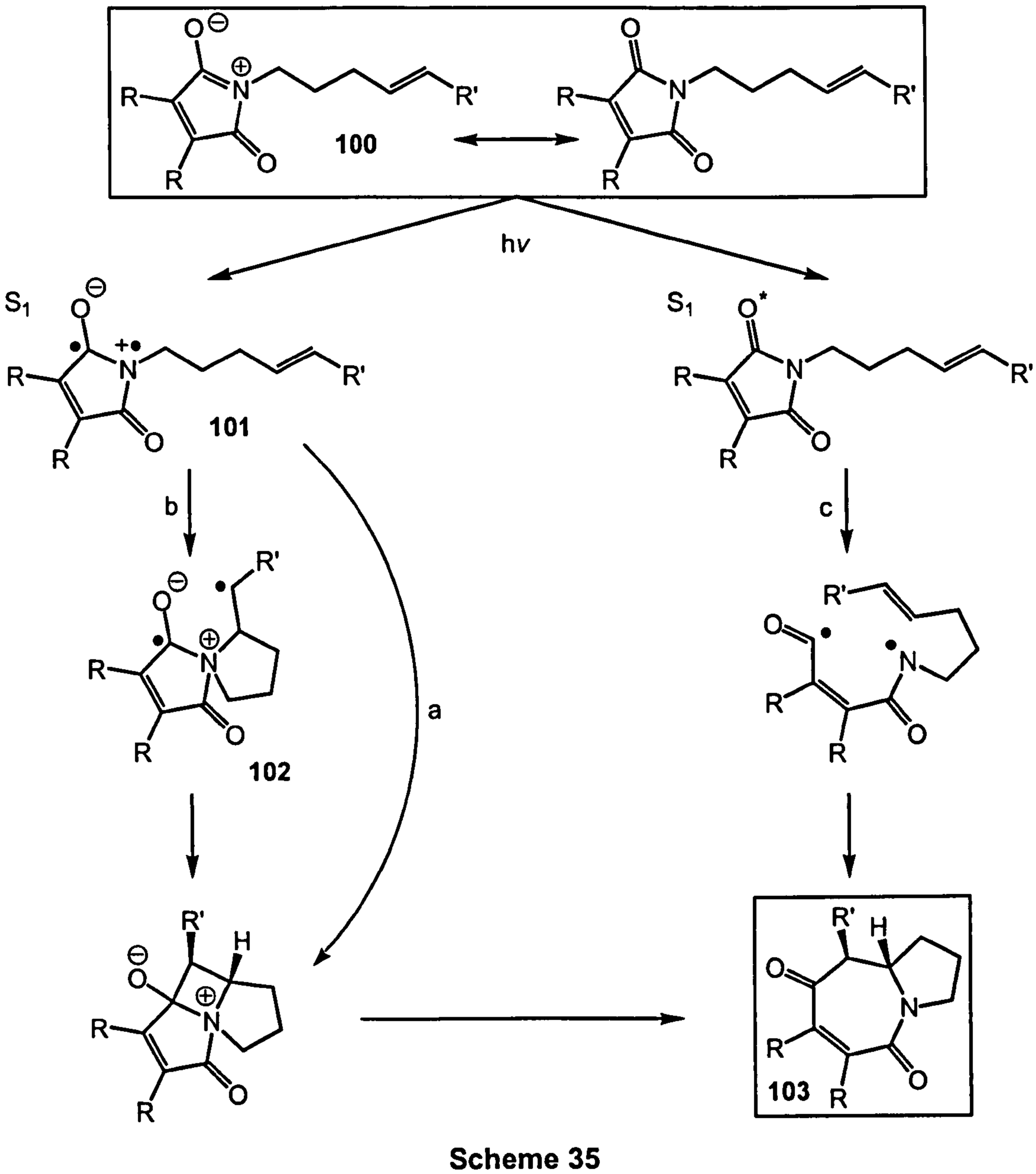
In 1998 Booker-Milburn *et al.*[39] attempted a similar, but intramolecular [2+2] photocyclisation of pentenyl substituted imide **98**. Surprisingly they discovered that instead, a tricyclic azepine **99** was formed in an excellent yield **(Scheme 34)**.



Scheme 34

This bears a great resemblance to the work Mazzocchi carried out with phthalimides[23-26], as discussed earlier (see section 2.3.). A plausible mechanism was proposed by Booker-Milburn based upon the mechanistic studies carried out by Mazzocchi **(Scheme 35)**. The reaction was thought to proceed *via* a

concerted [2+2] cycloaddition across the *p*-system described in the resonance form **100**, followed by fragmentation to azepine **103** (*path a*).



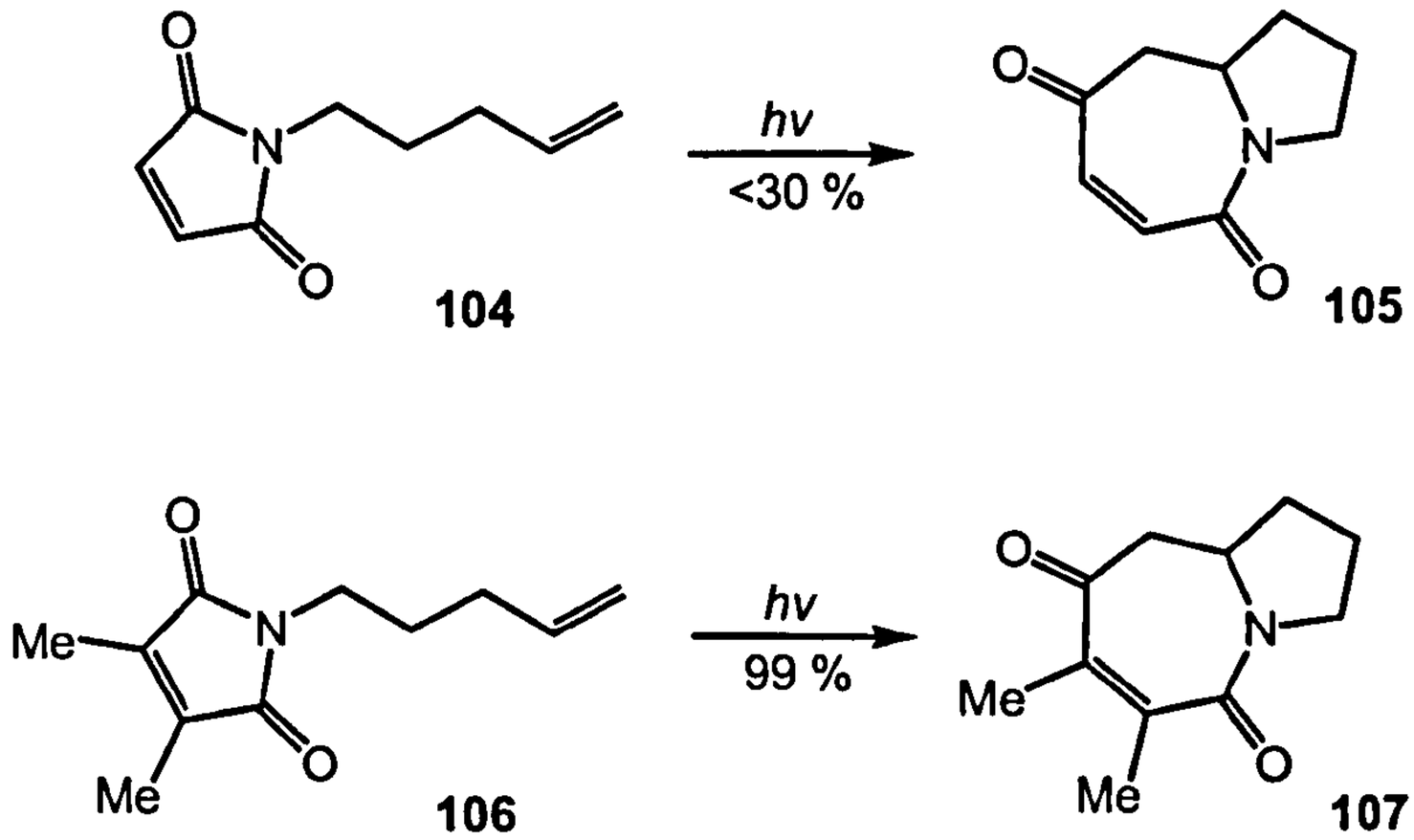
Scheme 35

A second plausible mechanism (*path b*) is a stepwise radical mechanism, in which the excited state **101** undergoes cyclisation to **102** followed by ring closure and cleavage to **103**, as before. These two mechanisms were adopted to clarify and support further investigations into the [5+2] photocycloaddition. Subsequent

in depth studies by Booker-Milburn *et al.* in 2006 used tuneable UV lasers and DFT calculations to conclude that the maleimide [5+2] mechanism should be rationalised as an *a*-cleavage process (*path c*).[40]

3.2. Application to synthesis

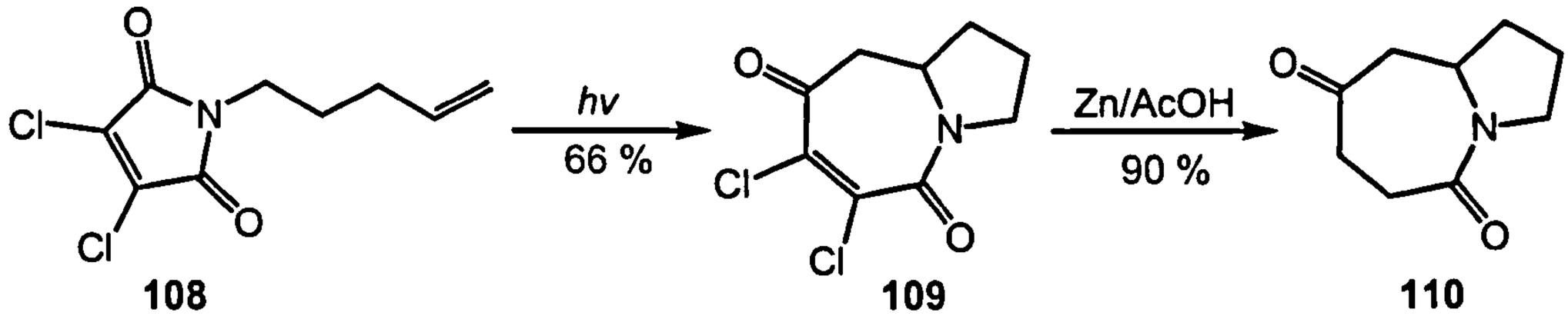
Further investigation into this novel reaction with irradiation of the parent maleimide **104** showed that all of the starting material had been used within two hours, with the apparent product being a [2+2] dimer between the starting material and the desired azepine **105**. Irradiation for shorter periods of time made it possible to isolate the desired product **105** from unreacted starting material, in reasonable yields. Dimerisation of the product was shown to be inhibited by using dimethyl imide **106** yielding azepine **107** quantitively **(Scheme 36)**.



Scheme 36

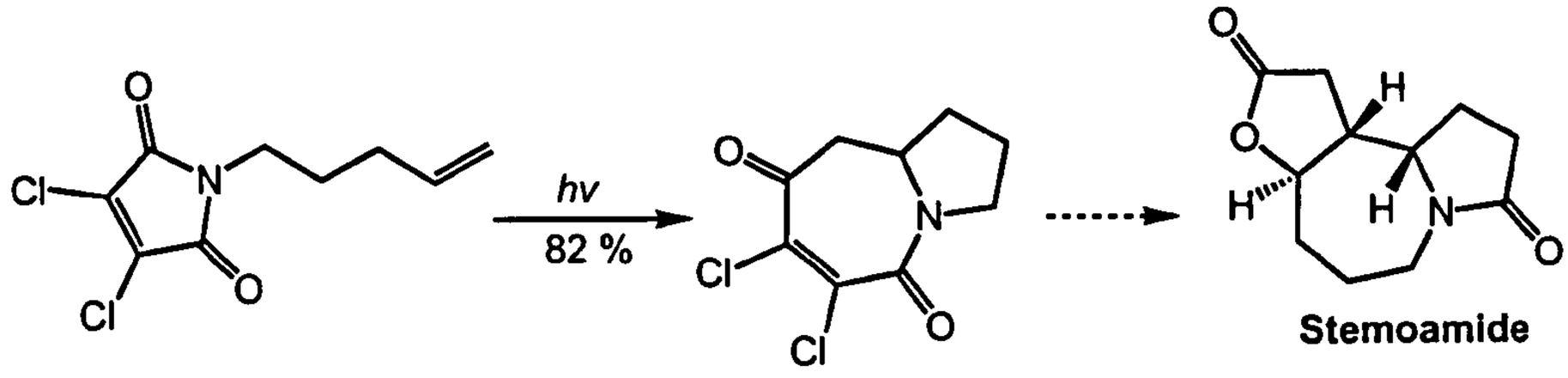
This result suggested that substitution of the imide alkene slows down competing dimerisation. However, dimethyl maleimide **106** imposes a severe constraint as the methyl groups present in the azepine product **107** cannot be removed. As a consequence, this does not lend itself to alkaloid synthesis.

This problem was overcome by the use of dichloro maleimide **108**, which itself undergoes photocyclisation, without any observable dimerisation to deliver azepine **109** in a 66 % yield.[41] Treatment of **109** with Zn/AcOH affords the reduced/dechlorinated product **110** in an excellent yield **(Scheme 37)**.



Scheme 37

Irradiation of a number of *N*-alkenylated maleimide derivatives has been investigated and has lead to the formation of complex perhydroazaazulenes in excellent yields.[41] The focus of the Booker-Milburn group has been to employ this methodology to the synthesis of a range of alkaloids that contain a pyrrolo[1,2-*a*]azepine unit **(Scheme 38)**.


hv
82 %
Stemoamide
hv
25 %
Selaginoidine
hv
73 %
Cephalotaxine
hv
60 %
Neostenine
hv
83 %
Bisdehydrrotuberostemonine

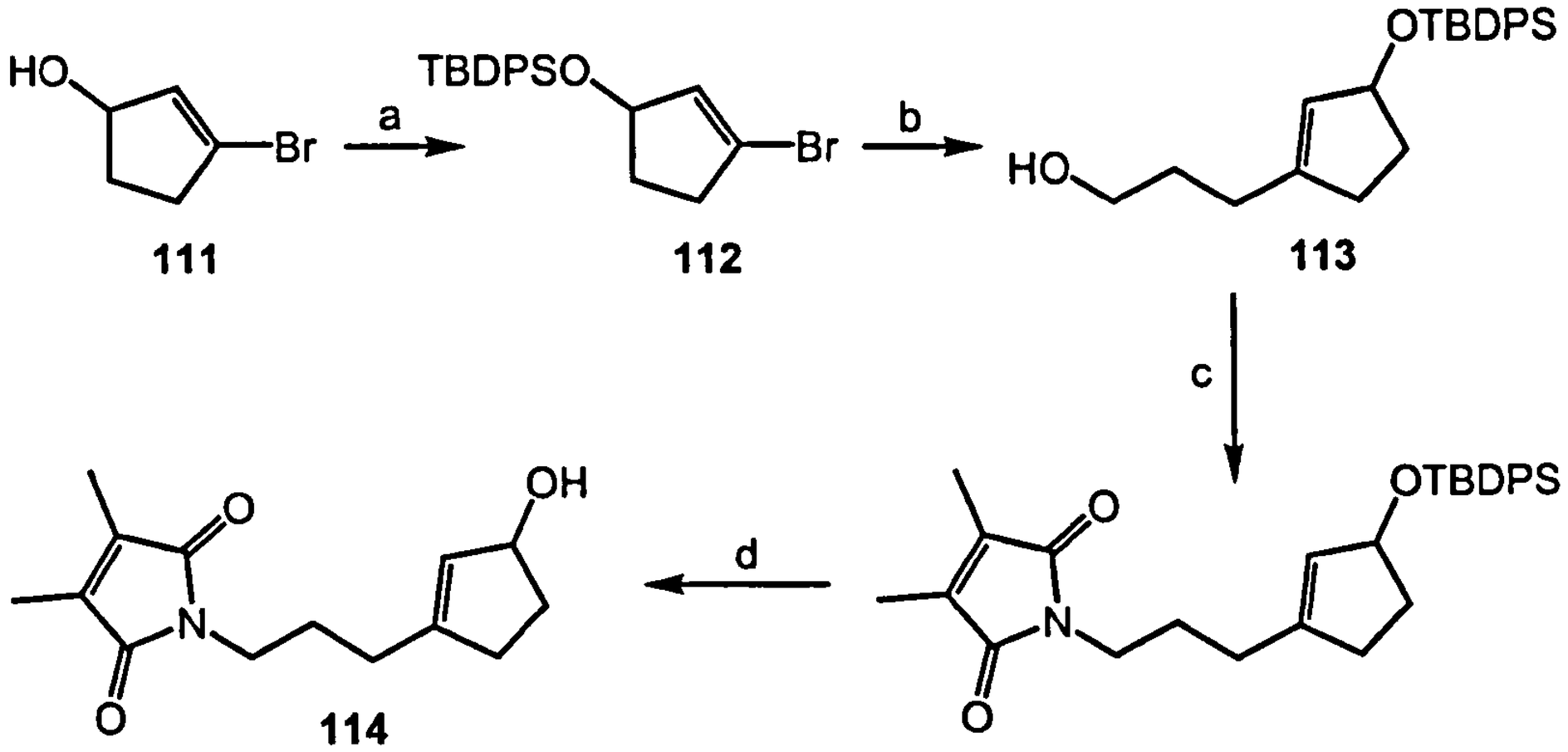
Scheme 38

Results and Discussion

4. Studies towards the synthesis of cephalotaxine

4.1. Synthesis of the C-D-E ring skeleton – Dudin[42]

The initial synthetic approach carried out by Dudin presented a rapid entry to the C-D-E ring core of cephalotaxine. The synthesis started from 3-bromo-2-cyclopentene-1-ol **111**, which was readily available in multigram quantities from cyclopentene-1,3-dione.[42] Protection of **111** gave silyl ether **112** in a 97 % yield. Formation of a vinyl lithium utilising ^{t}BuLi, followed by the opening of oxetane with $BF_3.Et_2O$ catalysis furnished alkenol **113** in good yield. Mitsunobu coupling, followed by desilylation gave photoprecursor **114** in a 58 % yield for the two steps **(Scheme 39)**.



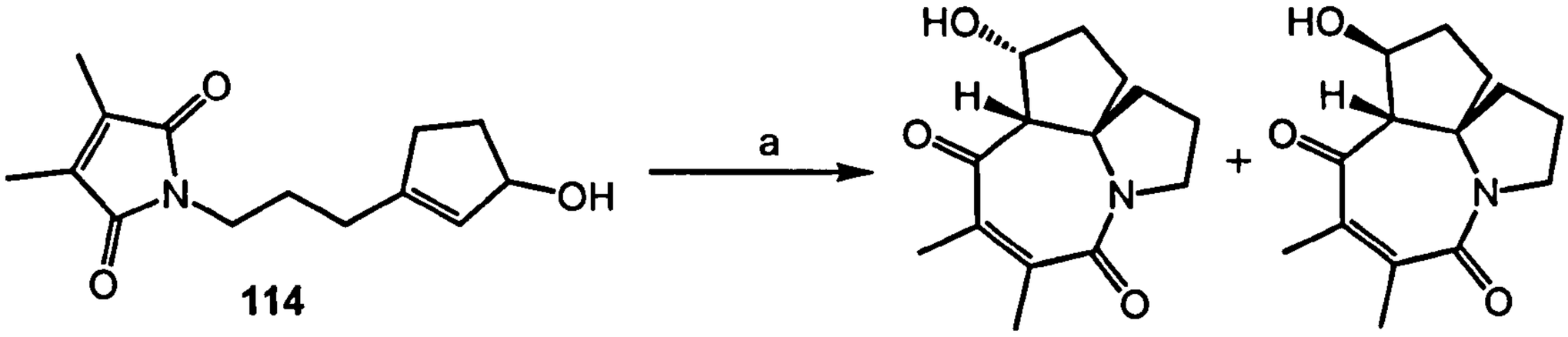
111 **112** **113** **114**

Reagents and Conditions: a)TBDPSCl, imidazole, DCM, 97 %; b) ^{t}BuLi, THF, -78 °C, then oxetane, $BF_3.Et_2O$, 74 %; c) dimethyl maleimide, DEAD, Ph_3P, THF, 79 %.

Scheme 39

Irradiation of **114** in MeCN gave the diastereomeric photocycloadducts **115** and **116** in a ratio of 2.5:1 **(Scheme 40, Table 1)**. It was proposed that the selectivity

of this reaction was attributed to a hydrogen-bonded excited state, controlled by the free hydroxy group. Changing to a less polar solvent increased the selectivity towards diastereomer **115**, which contains identical stereochemistry to that of the C-D-E ring core of cephalotaxine.



114 **115** **116**

Entry	Solvent	Yield / %	**115**:**116**
1	MeCN	65	2.5:1
2	Toluene	73	3.5:1
3	30 % Toluene/hexane	54	3.5:1

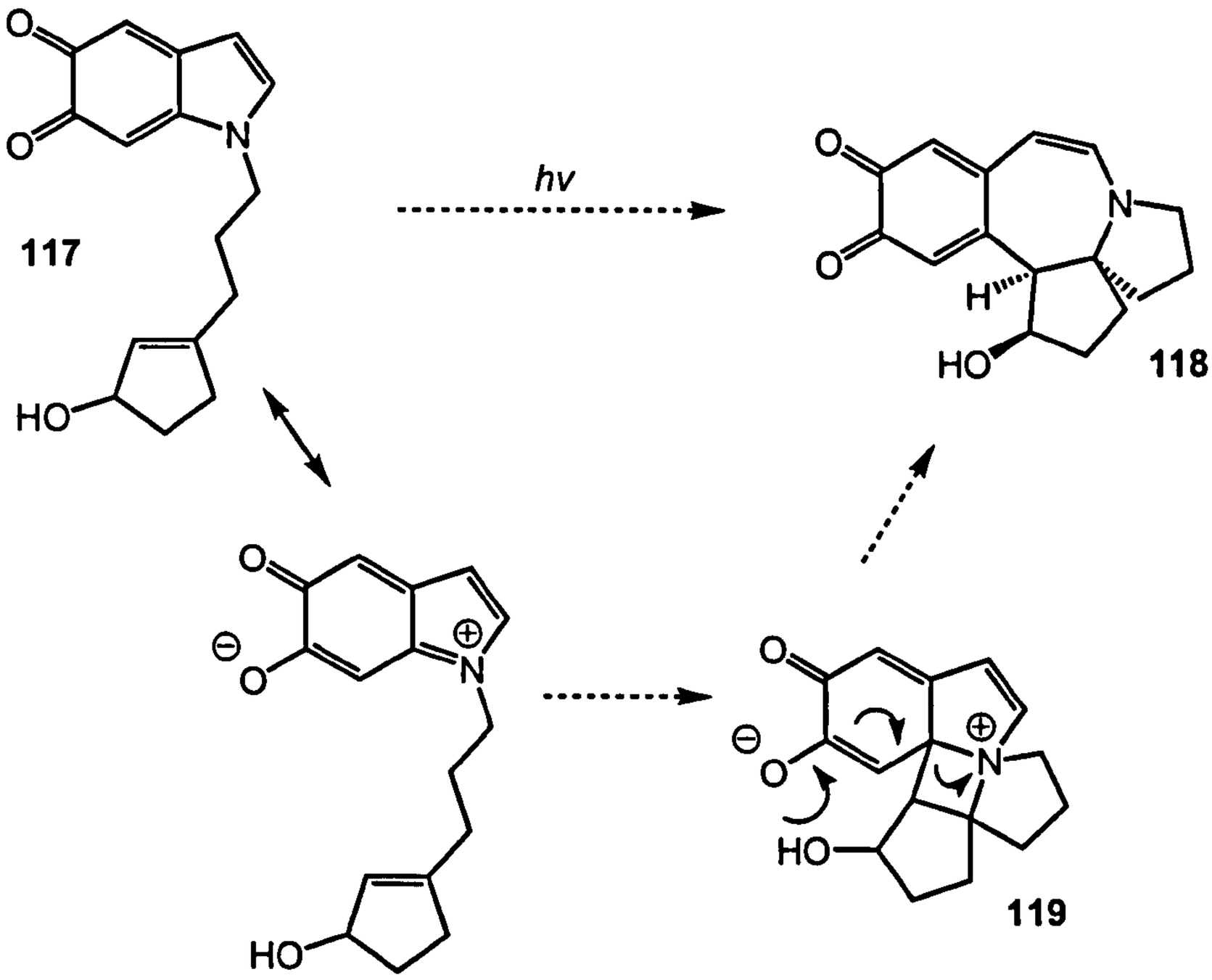
Reagents and Conditions: a) *hv*, solvent, Pyrex, 4 – 9 h.

Scheme 40 : Table 1

4.2. Retrosynthesis of cephalotaxine

As illustrated above, the maleimide [5+2] photocycloaddition has been shown to be highly efficient in building the cephalotaxine C-D-E ring skeleton. The difficulty in completing the synthesis of cephalotaxine using this methodology lies in the synthesis of the aryl ring. This is where the aim of the current project lies, namely to demonstrate the potential of this reaction using compounds that are isoelectronic with the maleimide system. Incorporation of the aryl ring before

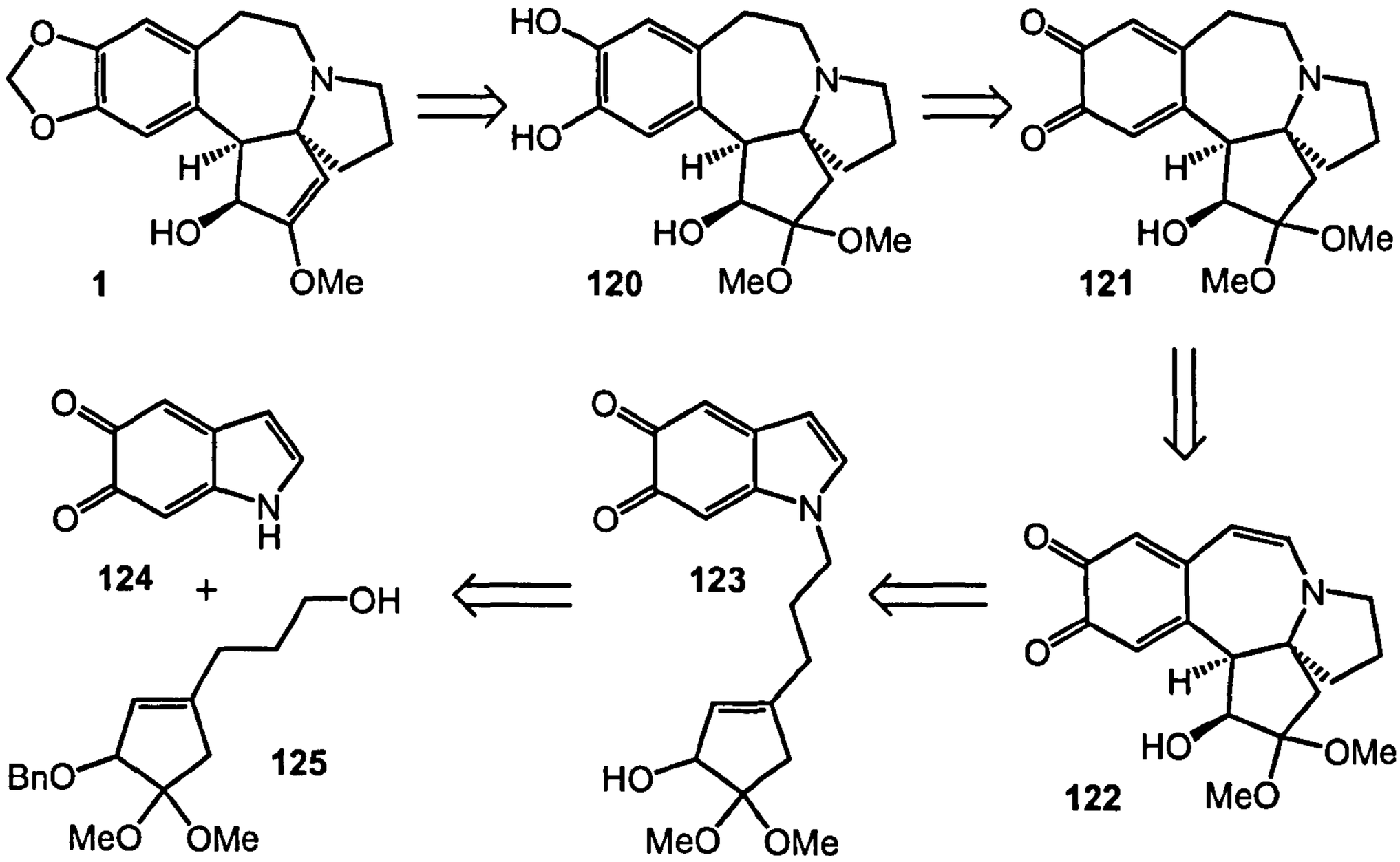
undertaking photocycloaddition would avoid the problems of building ring B at a later stage in the synthesis.



Scheme 41

It was considered that an *N*-alkenylated indole quinone **117** when undergoing photocycloaddition may perform a concerted [2+2] reaction to form zwitterionic species **119**. Subsequent fragmentation would lead to the desired product **118** **(Scheme 41)**. This product encompasses a great deal of the structural features and stereochemistry found in cephalotaxine **1**. The retrosynthetic analysis considered for **1** is shown below **(Scheme 42)**. Disconnection leads to azepine **120**, which can be accessed by a number of functional group interconversions. Oxidation leads back to **121** and reduction to **122** gives the product of the key [5+2] photocycloaddition reaction. *N*-Alkenyl indole quinone **123** should be readily available *via* Mitsunobu coupling of alkenol **125** with indole quinone **124**. To test the validity of the key [5+2] photocycloaddition, model substrates will be tested using simple pentenylated indole quinones. Alkenylated isatins will be

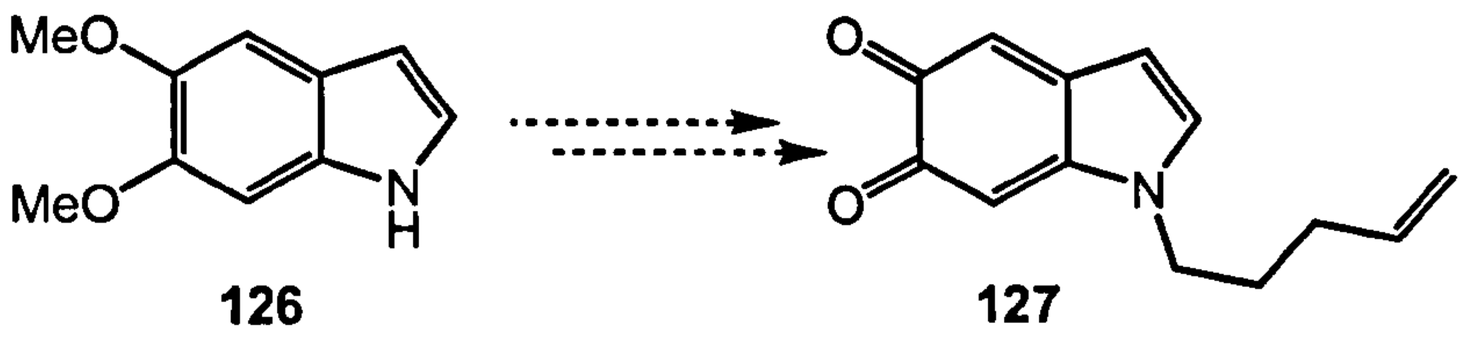
used to investigate whether the photocycloaddition can be carried out using compounds that are isoelectronic with maleimides.



Scheme 42

4.3. Indole quinone synthesis

It was anticipated that indole quinones **127** and **129** could be prepared from the corresponding dimethoxy indoles **126** and **128**, by oxidative demethylation and alkenylation **(Scheme 43)**.

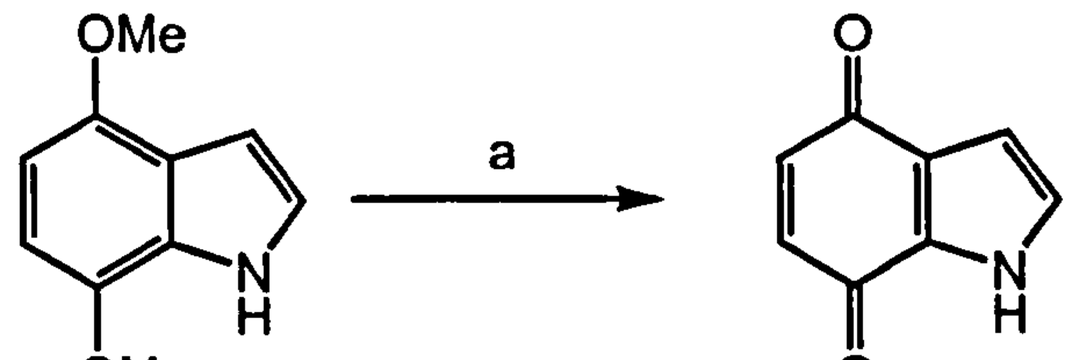


126 **127**

128 **129**

Scheme 43

Oxidation of **128** has been carried out by Cotelle *et al.*[43] using ceric ammonium nitrate (CAN) as the oxidizing agent to give **130 (Scheme 44)**. This may therefore also be carried out on **126**.



OMe O

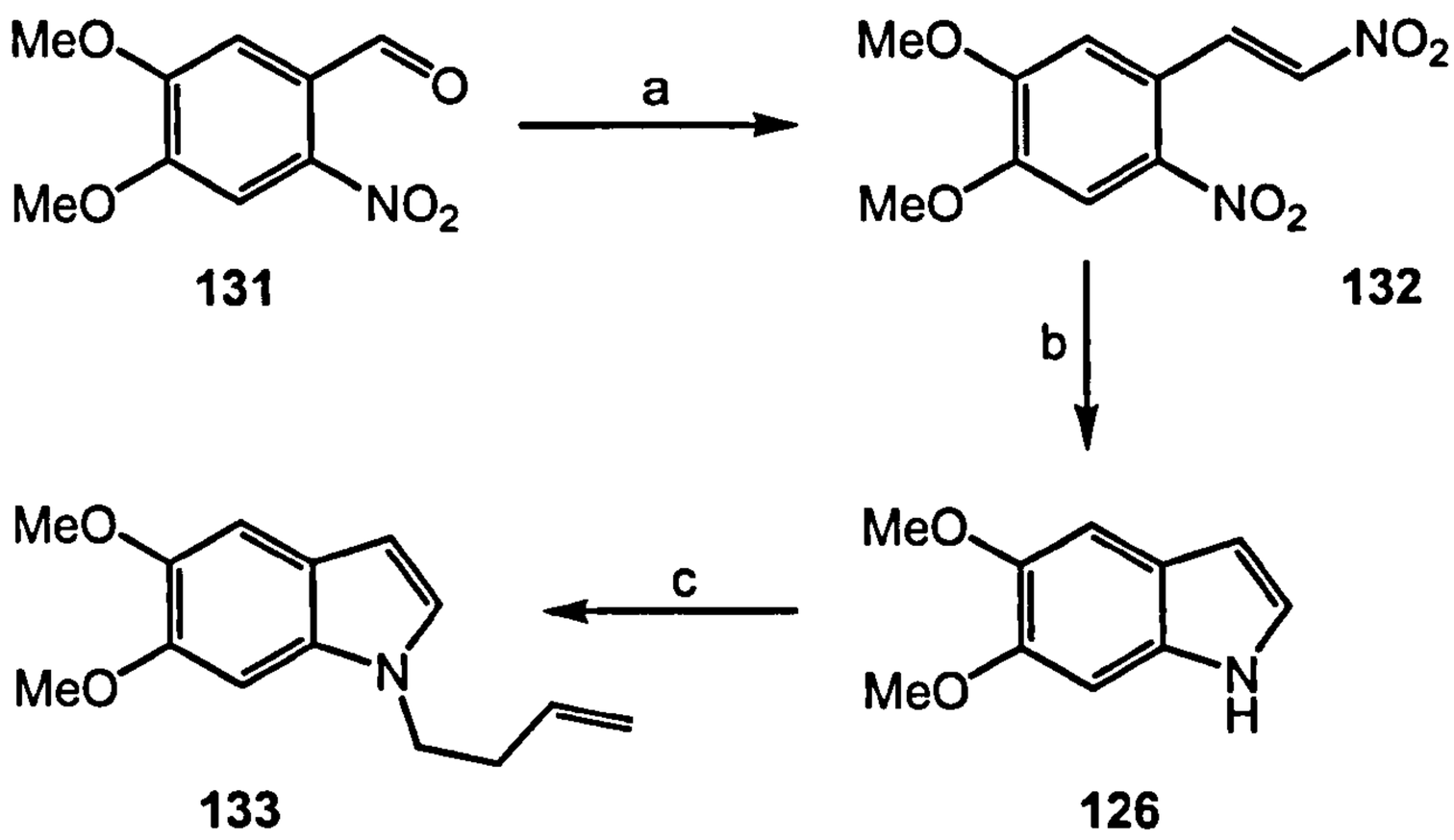
128 **130**

Reagents and Conditions: a) CAN, MeCN, 74 %.

Scheme 44

4.3.1. Attempted synthesis of 5,6-indole quinone 127

The research project began with the synthesis of indole **126**. There have been several previous syntheses of **126**,[44] with the Leimgruber-Batcho[44d] being the most successful. Firstly, nitrobenzaldehyde **131** underwent a Henry reaction to give **132**, then the nitrovinyl benzene was reduced with a metal/acid combination to give indole **126 (Scheme 45)**.[44d] For *N*-alkenylation of **126**, the competition between the 1 and 3 positions on the indole can be resolved using phase transfer conditions developed by Bocchi *et al.*[45], affording **133** exclusively.

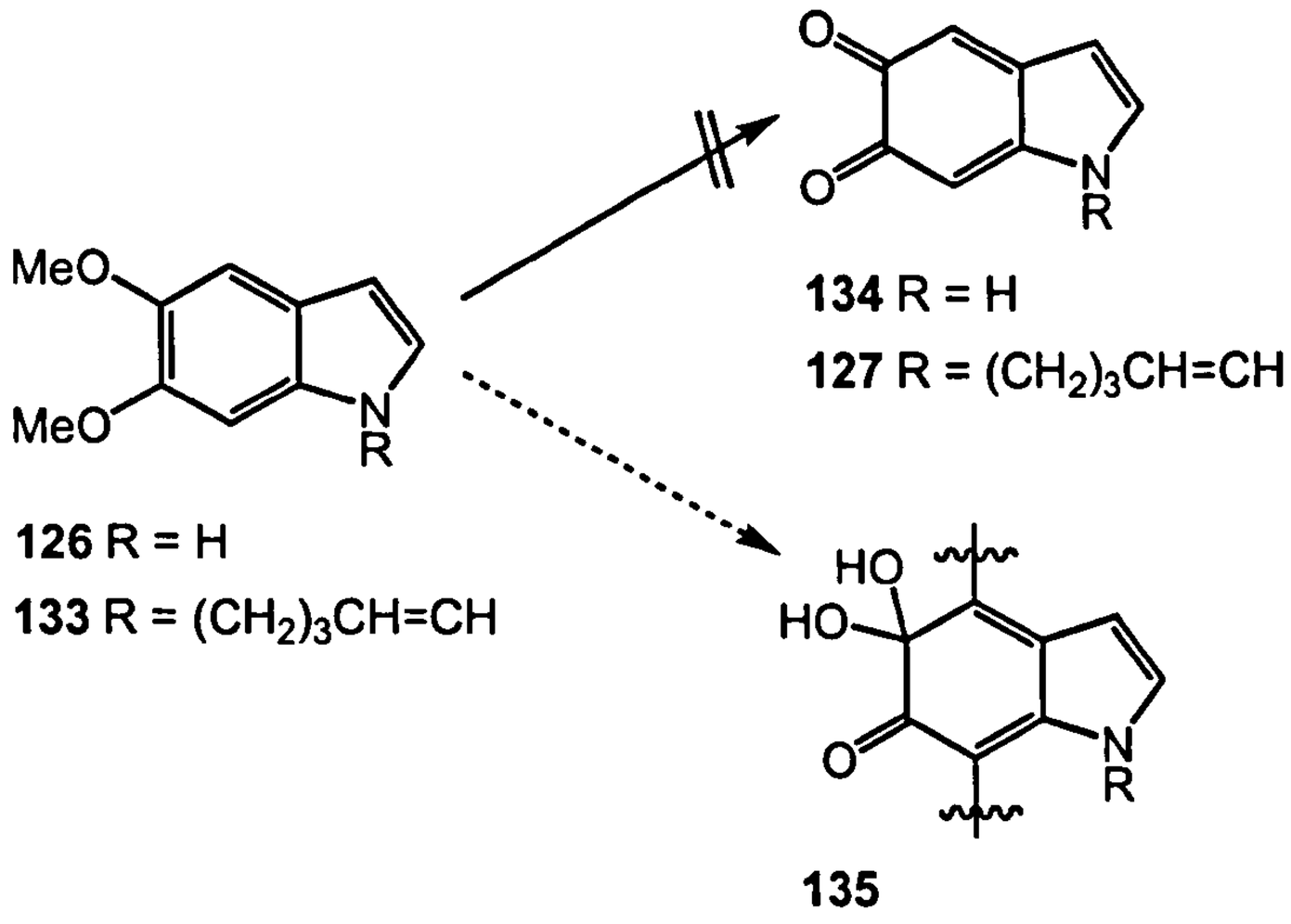


Reagents and Conditions: a) i) $MeNO_2$, MeOH, $NaOH/H_20$, 0 °C, 30 min, ii) Ac_2O NaOAc, 100 °C, 15 min, 78 %; b) Fe, AcOH, silica gel, 1:3 benzene/cyclohexane, reflux, 1 h, 90 %; c) $CH_2=CH(CH_2)_3Br$, TBAB, $NaOH/H_2O$, toluene, 24 h, 92 %.

Scheme 45

The oxidation of **126** and **133** was undertaken using CAN and both reacted immediately to give a dark red/brown polymer. Previous reports[46] on oxidations of 5,6-dihydroxy indoles gave evidence that **135** could have been formed *via* demethylation of **126** and **133**. It is also known that 5,6-dihydroxy indoles are the precursors of Melanin formation, and that they have reacted directly to form the red/brown polymers that are found in animal pigments **(Scheme 46)**.[46] As 5,6-

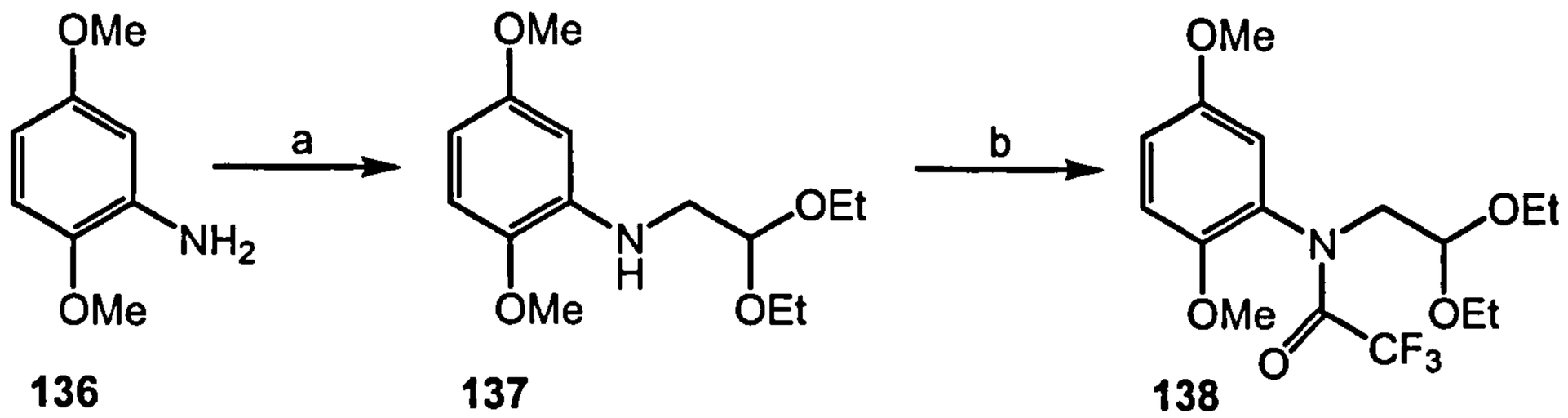
indole quinones **134** or **127** could not be isolated, a model system needed to be made with a 4,7-indole quinone.



Scheme 46

4.3.2. Synthesis of 4,7-indole quinone 129

Synthesis of 4,7-indole quinone **130** had been carried out by Cotelle *et al.*[43] Their strategy began with the preparation of indole **128** by an acid-catalysed cyclodehydration of acetal **137**. *N*-Alkylation of benzenamine **136** gave **137** and acetylation with triflouroacetic anhydride gave protected acetal **108 (Scheme 47)**. The protected acetal had been used in the synthesis of similar indoles by Nordlander *et al.*[47] The cyclisation of acetals **137** and **138** were attempted under several acidic conditions, however no cyclised product **128** or **139** were observed **(Scheme 48)**. The cyclisation of unprotected acetal **137** may have been unsuccessful due to the protonation of the amino group. This had been observed in previous attempts of acetal cyclisation with the use of Brønsted acids.[48] The success of Nordlander's method could be attributed to the effective reduction of the aniline nitrogen basicity through triflouroacetylation, which does not severely deactivate the aromatic or acetal functionality. Protection may also guard against further transformations that have been characteristic of free indoles in strong

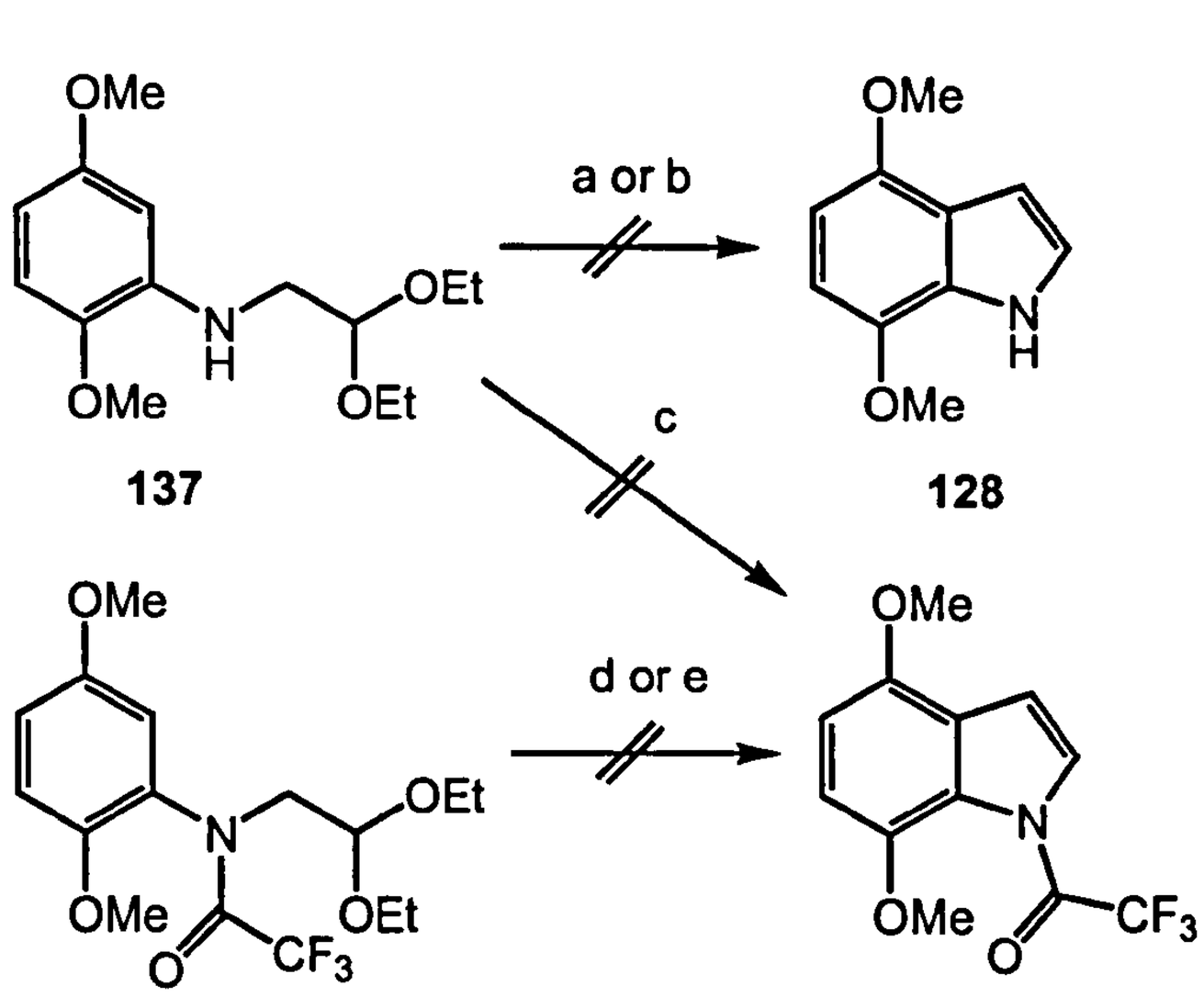


136 **137** **138**

Reagents and Conditions: $BrCH_2CH(OEt)_2$, $NaHCO_3$, DMF, reflux, 1 h, 71 %; b) $(CF_3CO)_2O$, Et_3N, hexane, 0 °C, 1 h, 78 %.

Scheme 47

acidic media.[48] Nordlander found that cyclisation reactions to produce 7-substituted indoles were difficult due to facile de-acylation when the triflouroacetyl group was forced out of coplanarity with the pyrrole ring.

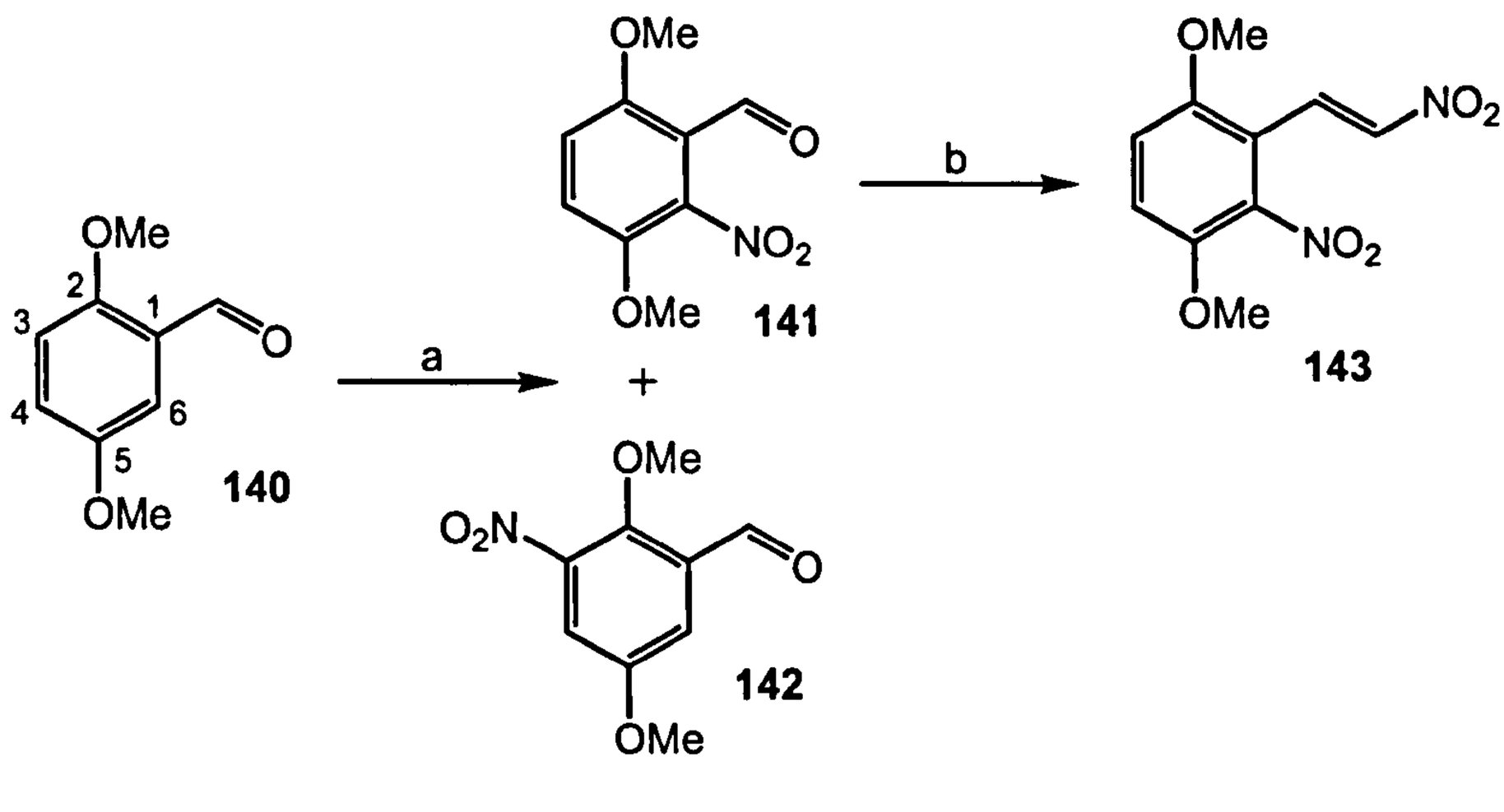


137 **128** **138** **139**

Reagents and Conditions: a) PPA, xylene, reflux; b) HCl/H_2O, THF; c) $(CF_3CO)_2O$, TFA, 0 °C to reflux; d) $(CF_3CO)_2O$, TFA, reflux; e) PPA, xylene, reflux.

Scheme 48

The Leimgruber-Batcho method was therefore preferred to access the 4,7 substituted indole **128**. Unfortunately nitrobenzaldehyde **141** was not commercially available, but could be made by nitration of 2,5-dimethoxybenzaldehyde **140**, affording a 4:1 (10:1 after recrystalisation) mix of the desired product **141** and **142 (Scheme 49)**. This result is surprising considering the electronic effects in **140** from the substituents. However, previous work by Rubenstein[49] is in agreement with this result.

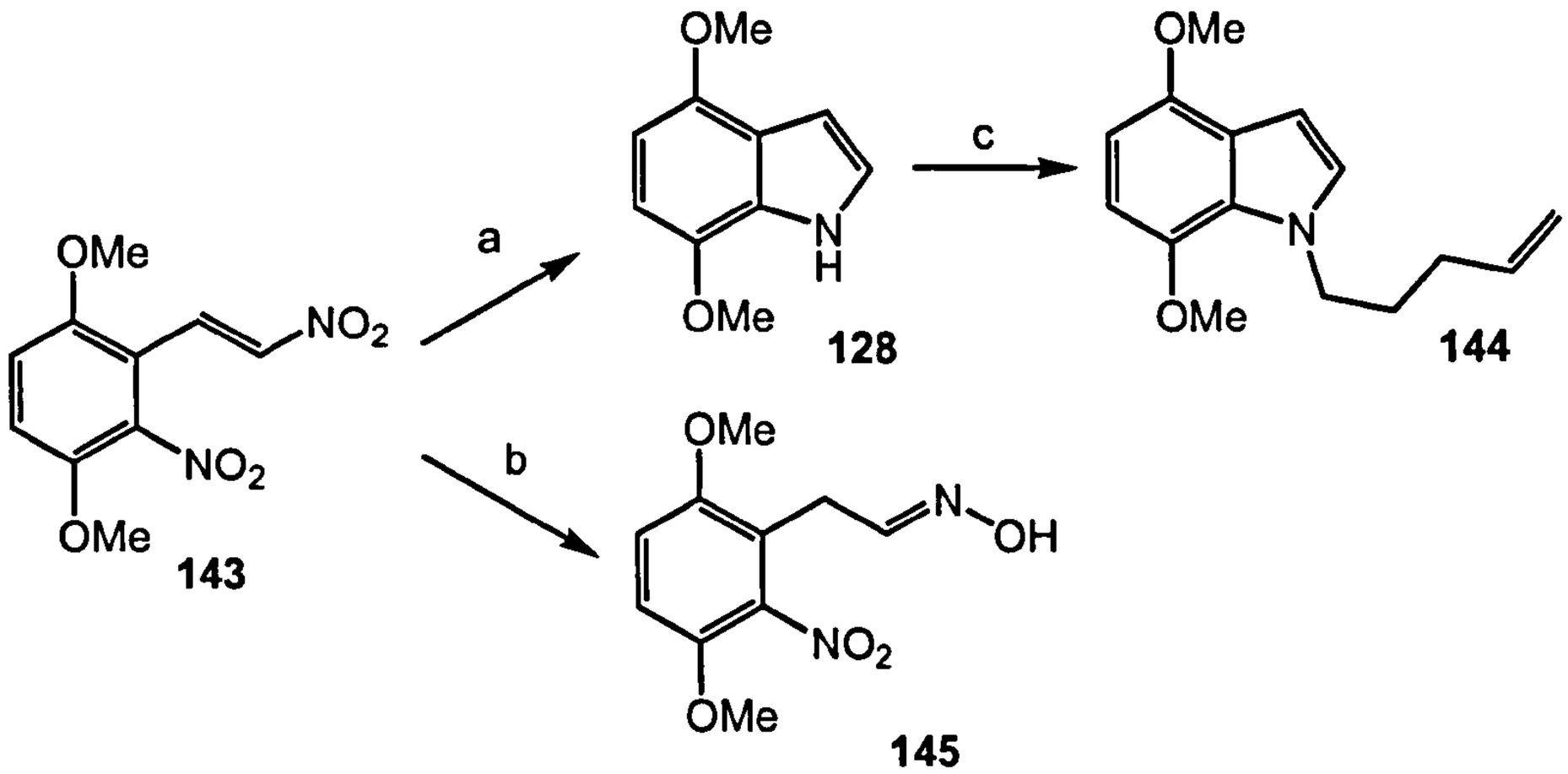


Reagents and Conditions: a) HNO_3, DCM, 0 °C, 1 h, 10:1 **141**:**142**, 87 %; b) $MeNO_2$, MeOH $NaOH/H_20$, 0 °C, 30 min, ii) Ac_2O NaOAc, 100 °C, 15 min 78 %.

Scheme 49

The Henry and reductive cyclisation procedures were carried out as before and gave indole **128** in a 60 % yield **(Scheme 50)**. Yields of the cyclisation were capricious, so an alternative system was tested by means of an improved method carried out by Cava *et al*.[50] This procedure has shown improved yields by using palladium-catalysed transfer hydrogenation. However, only partial reduction to oxime **145** was observed, with further reduction and cyclisation not taking place. Oximes are far less reactive than their free imines, as delocalisation of the imine bond decreases the *d*+ on the carbon atom and raises the energy of the LUMO, making them less susceptible to nucleophilic attack. This may explain

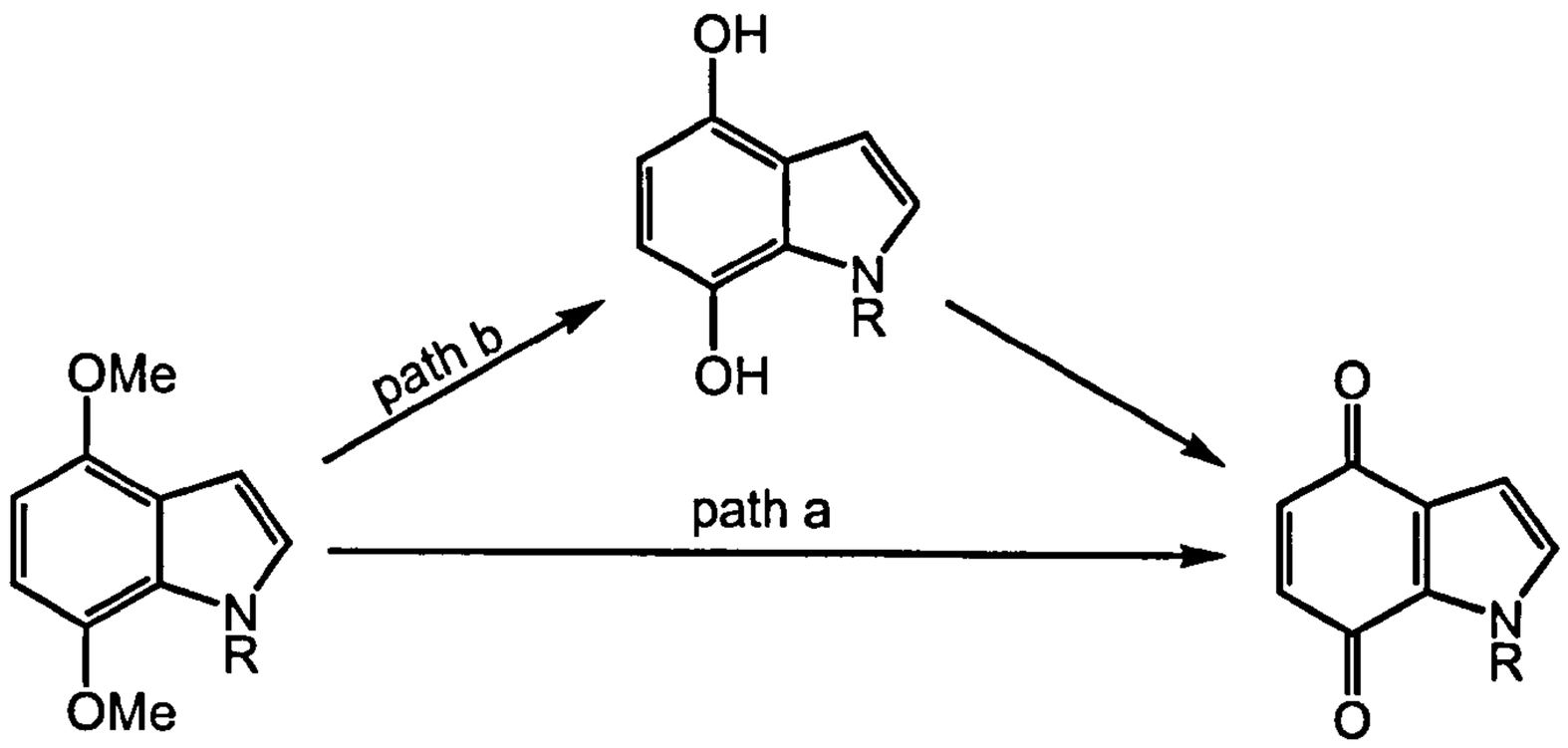
why after formation of **145** only baseline polymeric material was observed. *N*-Alkenylation of **128** with identical phase transfer conditions as before gave **144** quantitively.



Reagents and Conditions: a) Fe, AcOH, silica gel, 1:3 benzene/cyclohexane, reflux, 1 h, 36 – 60 %; b) Pd/C, HCO_2NH_4, $H_2C(O)$, EtOH, reflux, 1 h, 81 %; c) $CH_2CH(CH_2)_3Br$, TBAB, $NaOH/H_2O$, toluene, 24 h, 97 %.

Scheme 50

Indoles **128** and **144** could be oxidised to their corresponding benzoquinones **129** and **130** by either direct oxidation (*path a*) or demethylation – oxidation (*path b*) **(Scheme 51)**.[51] Although oxidation of 1,4-hydroquinones is much easier than that of 1,4-dimethoxybenzenes, the direct oxidation route (*path a*) is much more attractive over *path b* as a result of the difficulty of demethylation and the isolation of 1,4-hydroquinones. Several examples of similar methods to *path a* report that oxidative demethylations are carried out classically using ceric ammonium nitrate (CAN)[43,52] and silver(II) oxide[53]. More recent methods with NBS[54], cobalt(III) fluoride[55] and phenyl iodoso(III) bis(trifluoroacetate)[56] (PIFA) have been developed. These methods were applied to indoles **128** and **144** under various conditions **(Table 2)**. The procedures with CAN (*entries 1 – 7*) showed that **128** and **144** were extremely reactive with the reagent, though only gave baseline polymeric material.



128 R = H

144 R = $(CH_2)_3CH=CH$

130 R = H

129 R = $(CH_2)_3CH=CH$

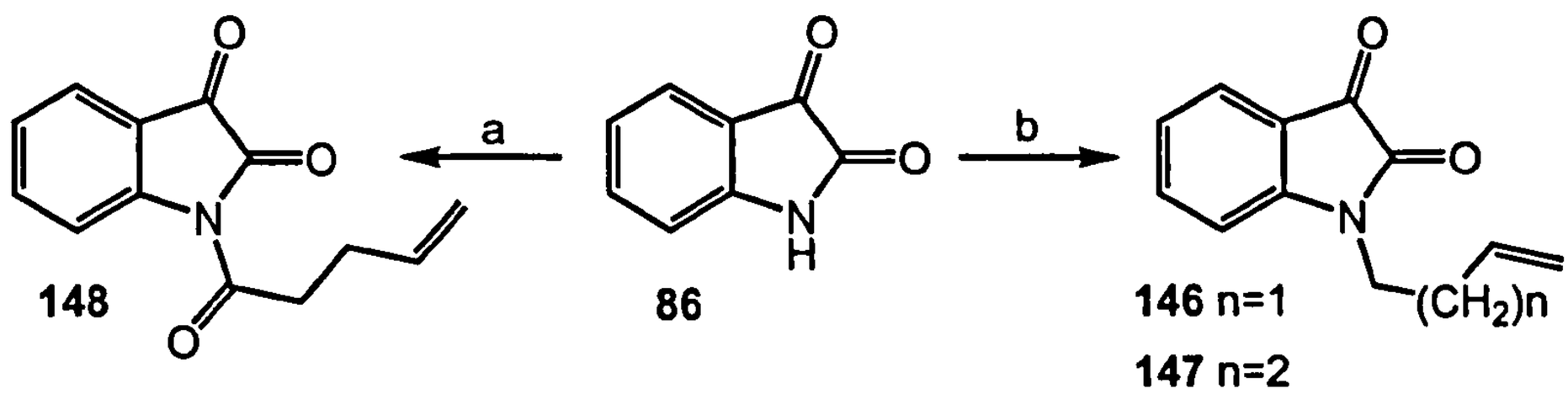
Entry	Reagent (eq)	Addition time / min	Reaction time / min	Temp. / °C	R	Yield / %
1	CAN (3)	10	60	25	H	0
2	//	//	//	//	$(CH_2)_3CH=CH_2$	0
3	//	//	//	0	H	0
4	//	//	//	//	$(CH_2)_3CH=CH_2$	0
5	//	//	//	-20	H	0
6	//	//	//	//	$(CH_2)_3CH=CH_2$	0
7	CAN (1)	60	60	0	H	0
8	NBS (1)	0	5	25	H	0
9	O_2	N/A	48 h	25	H	0
10	AgO (1)	0	10	0	H	0
11	AgO (1)	0	10	0	$(CH_2)_3CH=CH_2$	0
12	AgO (1)	0	1	0	$(CH_2)_3CH=CH_2$	34 – 63

Scheme 51 : Table 2

Milder conditions using an atmosphere of oxygen or NBS (*entries 7 – 8*) failed to show any oxidative demethylation, with full recovery of starting material with the former, and a large array of products with the latter. Oxidative demethylation with silver(II) oxide was extremely fast (*entries 10 – 12*) and required rapid purification by column chromatography. This system worked reasonably well on a small scale, but gave lower yields on scale-up. Nevertheless the synthesis of indole quinone **129** had been achieved, allowing the photochemistry of this compound to be studied.

4.4. Synthesis of *N*-Alkenylated isatins

Isatins are isoelectronic with indole quinones. They therefore provide an alternative method of testing the applicability of these groups of compounds towards a [5+2] photocycloaddition. For the preparation of *N*-alkylated isatins the phase transfer conditions applied to indole **146** and **148** cannot be used as sodium hydroxide will open up the isatin to its corresponding acid. One approach to *N*-alkylation of isatins can be carried out in the presence of an alkyl halide and potassium carbonate in DMF.[57] This procedure was used, affording *N*-alkenylated isatins **146** and **147** quantitively; however this approach did not yield acylated isatin **148**. For *N*-acylation the sodium salt of isatin **86** was prepared using NaH and acylated using the corresponding acyl halide to deliver **148** **(Scheme 52)**.

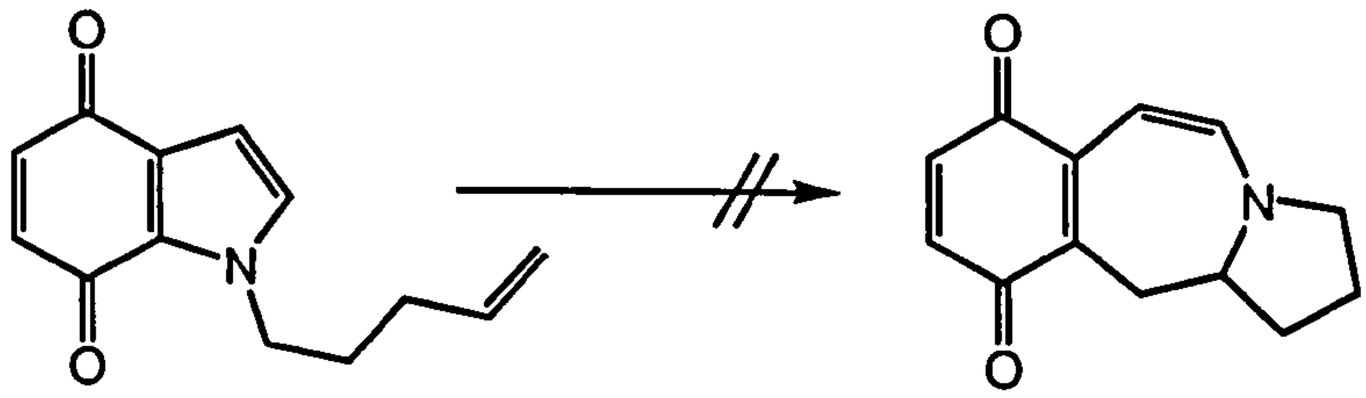


Reagents and Conditions: a) $BrCH_2(CH_2)_nCH=CH_2$, K_2CO_3, DMF, 24 h, 96 – 98 %; b) i) NaH, toluene, 0 °C, 10 min; ii) $ClC(O)(CH_2)_2CH=CH_2$, DMF, 3 min, 0 °C, 51 %.

Scheme 52

4.5. Photochemistry of Indoles and Isatins

Irradiation of Indole quinone **129** for 2 h resulted in the complete consumption of starting material, which delivered baseline polymeric material. At no point in the reaction was [5+2] photocycloaddition product **149** observed **(Scheme 53)**.

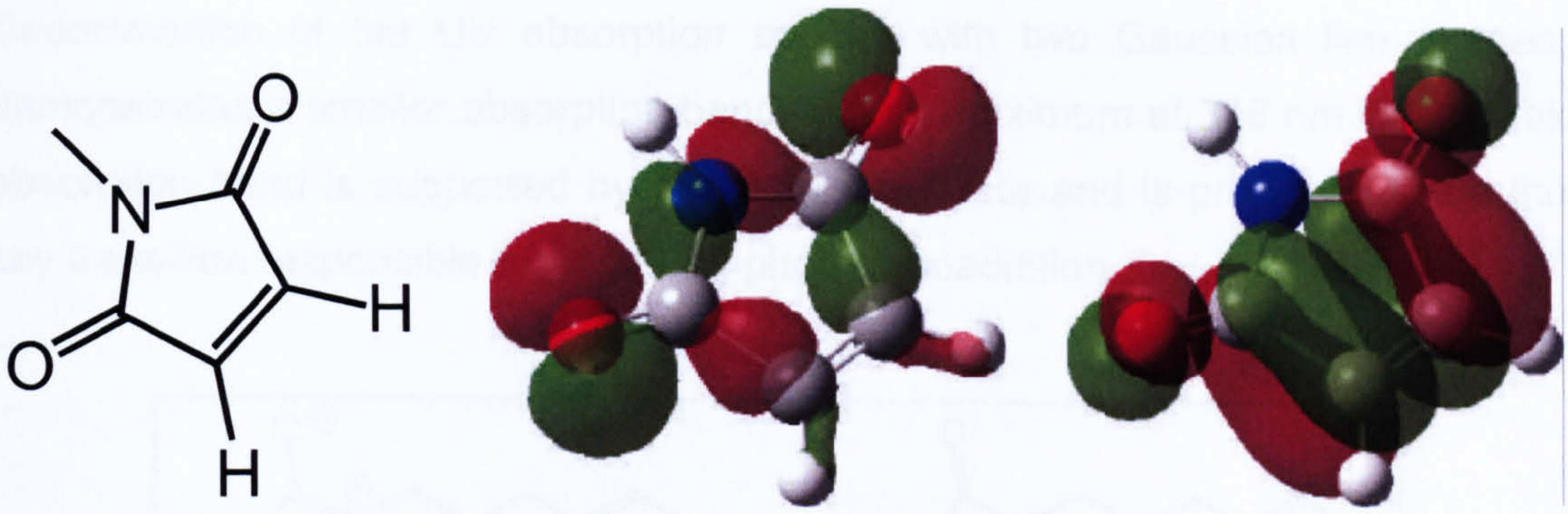


129 **149**

Reagents and Conditions: a) *hv*, Pyrex, MeCN, 2 h.

Scheme 53

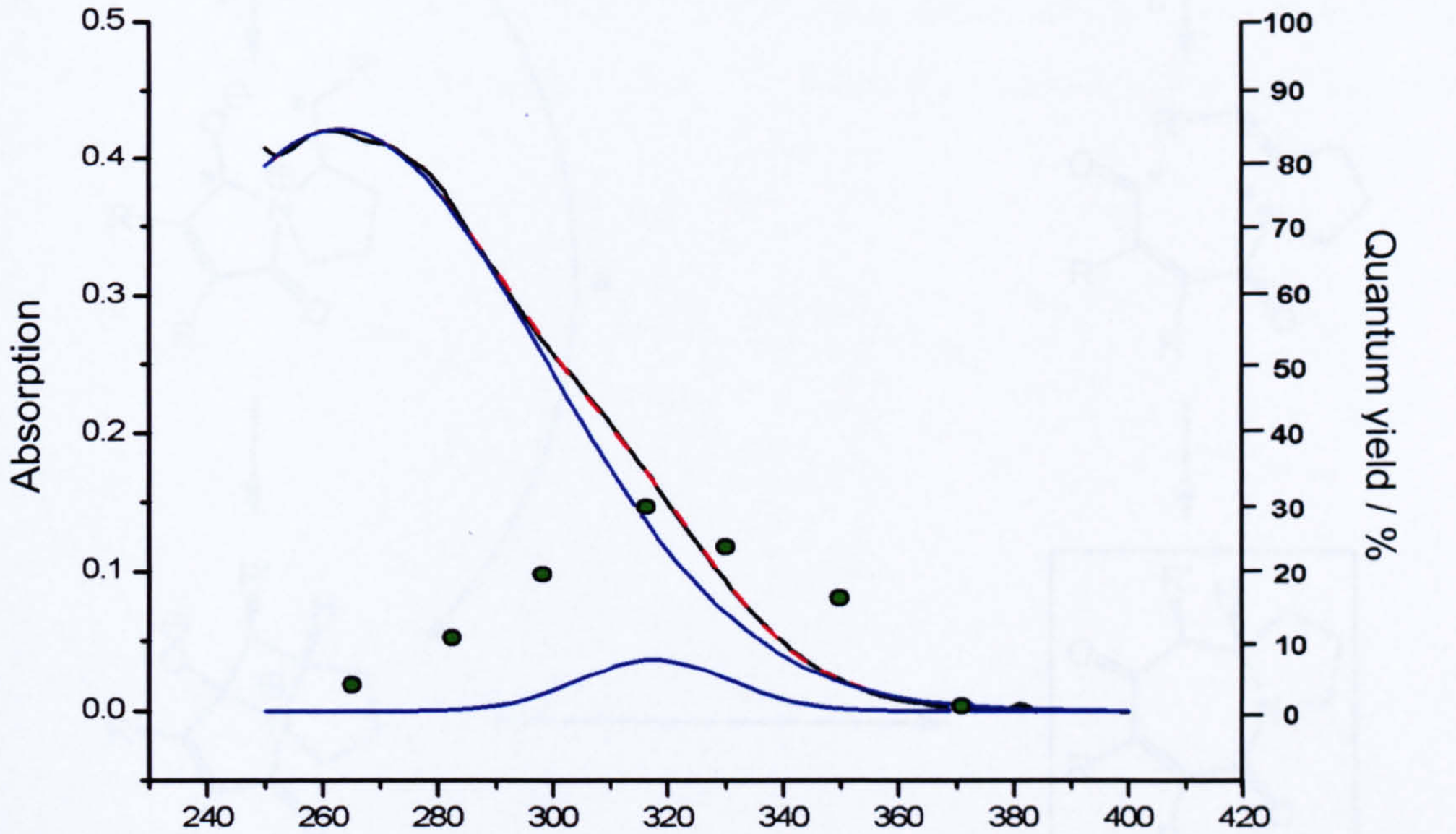
Unfortunately this shows that even though **129** is isoelectronic with maleimides, it does not posses the same excited state that leads to photocycloaddition. Recent time dependent DFT computational calculations have been carried out by Murray[40] on *N*-methyl maleimide **150**. These showed that the excited state of **150** does not necessarily agree with the concerted [2+2] mechanism that had been suggested for phthalimide substrates by Mazzocchi **(Figure 8)**. The assumption that the maleimides react in the same manner as phthalimide substrates could therefore be invalid. The excited state of *N*-methyl maleimide was expected to show high electron density between the C(O)-N bond that would allow for the concerted mechanism. Surprisingly the excited state, which is thought to be similar to **152** actually shows electron density to reside between the carbonyl and alkene bond. Importantly this means that there is no *p*-bond character at C-N, which is a requirement of the concerted mechanism. This could explain why indole quinone **129** cannot undergo the [5+2] photocycloaddition, as the resonance model is no longer applicable and a more electronically specific substrate is shown to be necessary.



150 **151** HOMO **152** LUMO

Figure 8

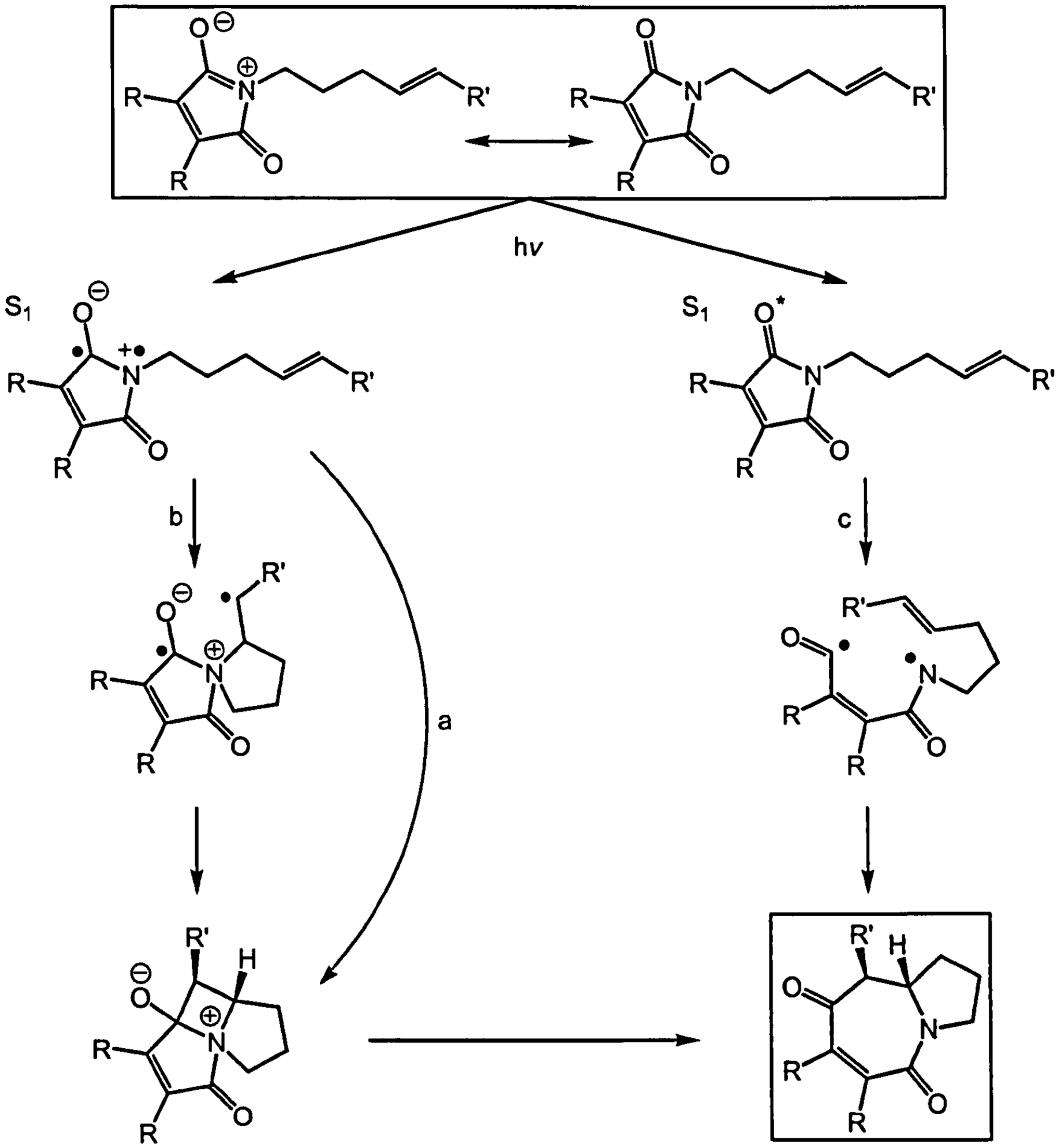
Further mechanistic investigations have since been made by Booker-Milburn *et al*. in 2006.[40] The use of tunable UV lasers demonstrated that the peak in quantum yield is actually 50 nm red-shifted from the observed maxima in the UV spectra **(Figure 9)**.



Key: — Recorded UV spectrum; — deconvoluted spectra; ? quantum yield.

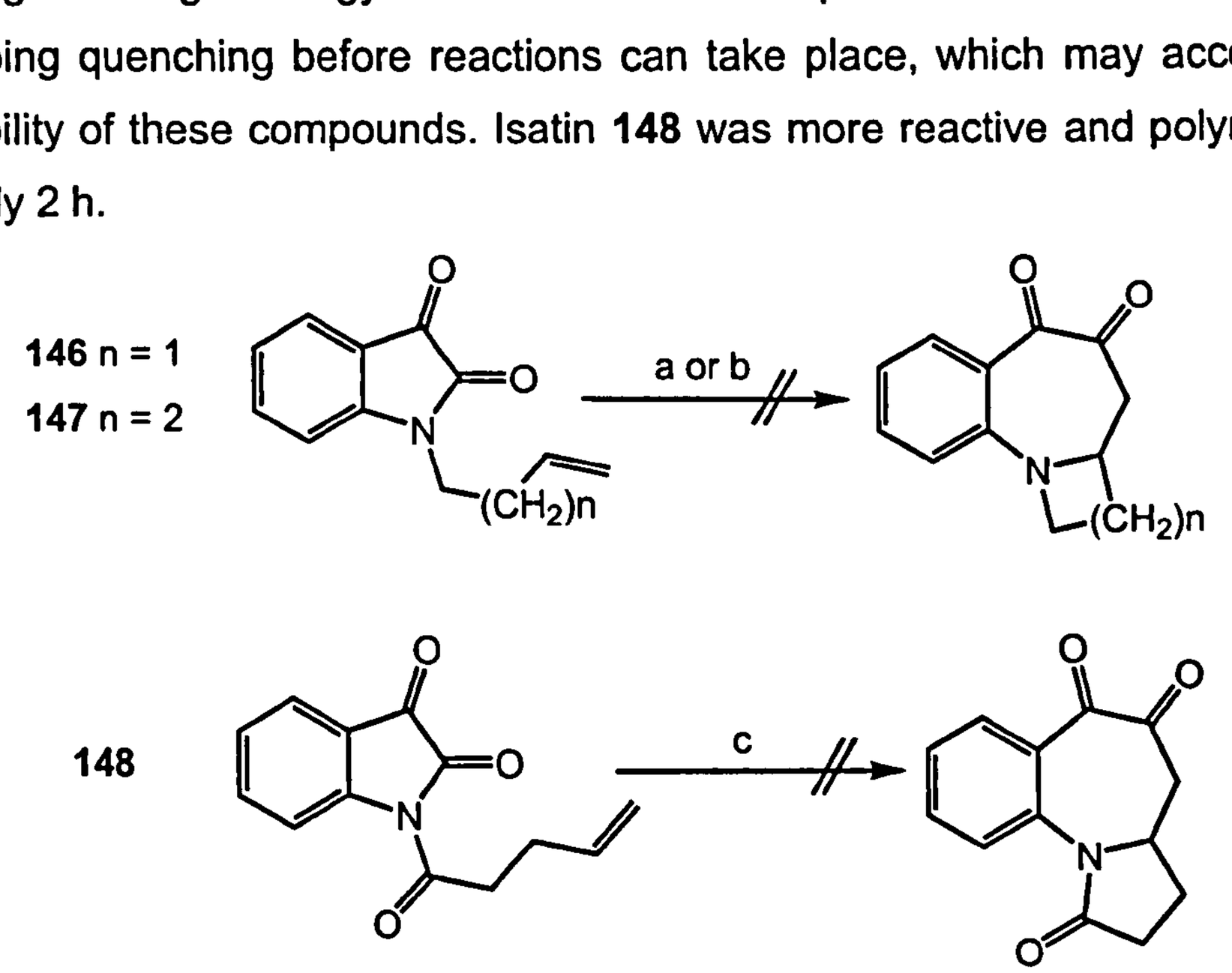
Figure 9

Deconvolution of the UV absorption spectra with two Gaussian line shapes, demonstrates a smaller absorption band with its maximum at 318 nm. This weak absorption band is supported by quantum yield data and is proposed to be the key transition responsible for the [5+2] photocycloaddition.



Scheme 54

These studies coupled with Murray's DFT calculations concluded that the key S_0? S_1 transition is n? p^* in nature. From this, fragmentation followed by cyclisation can be judiciously proposed to account for the mechanism **(Scheme 54)**. This new insight into the mechanism has ruled out substrates which are isoelectronic with maleimides and that do not contain an amide bond which undergoes a Norrish Type II process. Isatin substrates which are isoelectronic with maleimide have been shown to undergo a Type II process. The cleavage of the C-N bond in isatin was observed by Pardasani involving the ring expansion of isatin (see section 2.5.).[37] Isatins **146 – 148** were established to be very stable to UV light and were found to undergo no change even after being irradiated for up to 48 h **(Scheme 55)**. Shorter wavelength UV light was applied and isatins **146** and **147** were still found to be relatively photo-stable, however after 24 h degradation to baseline polymeric material was observed. When using a wavelength of 220 nm from a laser on **147**, a large quantum yield was observed indicating that high energy excited states were produced. These states are undergoing quenching before reactions can take place, which may account for the stability of these compounds. Isatin **148** was more reactive and polymerised after only 2 h.



Reagents and Conditions: a) *hv*, Pyrex, MeCN, 24 h; b) *hv*, Quartz, MeCN, 24 h; c) *hv*, Pyrex, MeCN, 2 h.

Scheme 55

4.6. Conclusion

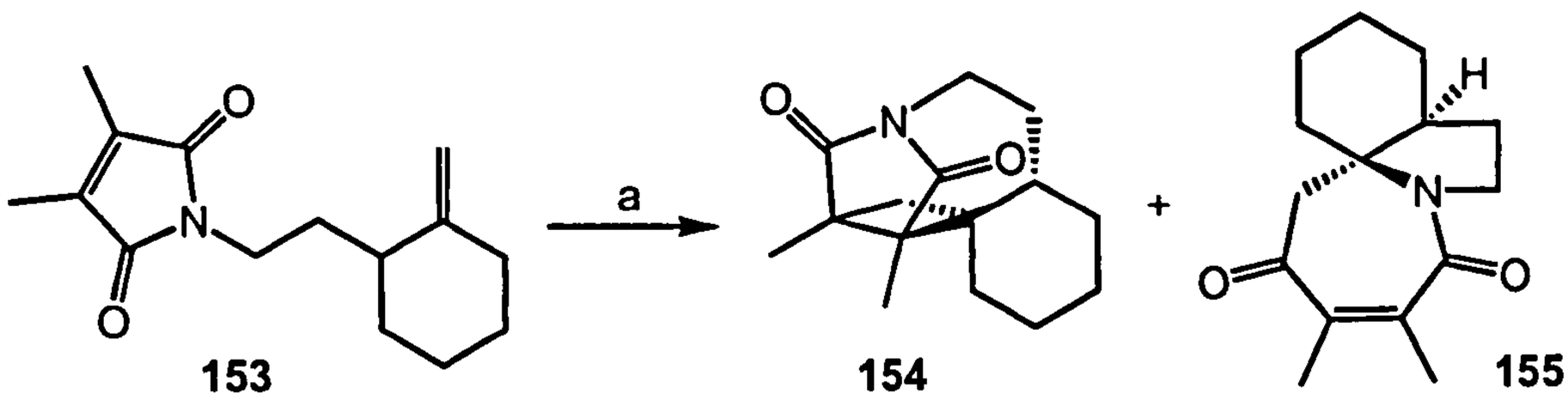
A model study for the synthesis of cephalotaxine was initially attempted with the synthesis of 5,6-indole quinone **127**. However it was found that oxidation of *N*-alkylated indole **126** may have led to a melanin type polymer. Instead, 4,7-indole quinone **129** was prepared and was shown to be photochemically active, although only to the formation of baseline polymeric material. Isatins **146 – 148** that are isoelectronic with **129** were established to be very stable to UV light and underwent no change even after being irradiated for up to 48 h. Shorter wavelengths led to decomposition, which was fastest with *N*-acyl isatin **148**. The increased reactivity of **148** is probably due to a more restricted nitrogen atom as an electron donor, resulting in a photochemically reactive increase of the carbonyl groups.

After the study was undertaken, new insight into the excited state of maleimides demonstrated that the resonance model for the [5+2] photocycloaddition mechanism was invalid; indicating that photocycloaddition of *N*-alkenyl indole quinones or isatins may not be achievable. With this in mind the aim of my project progressed to the total synthesis of selaginoidine, in which the use of the maleimide [5+2] photocycloaddition may be exploited.

5. Studies towards the synthesis of selaginoidine

5.1. A trial substrate for selaginoidine – Clissold[41]

A study by Booker–Milburn *et al*. tested the applicability of the [5+2] photocycloaddition for the rapid construction of azepine alkaloids.[41] Clissold irradiated maleimide **153** and discovered an unexpected result; although the formal [5+2] cycloadduct **155** was formed, the major product was the intramolecular [2+2] photocycloadduct **154 (Scheme 56)**.



153 **154** **155**

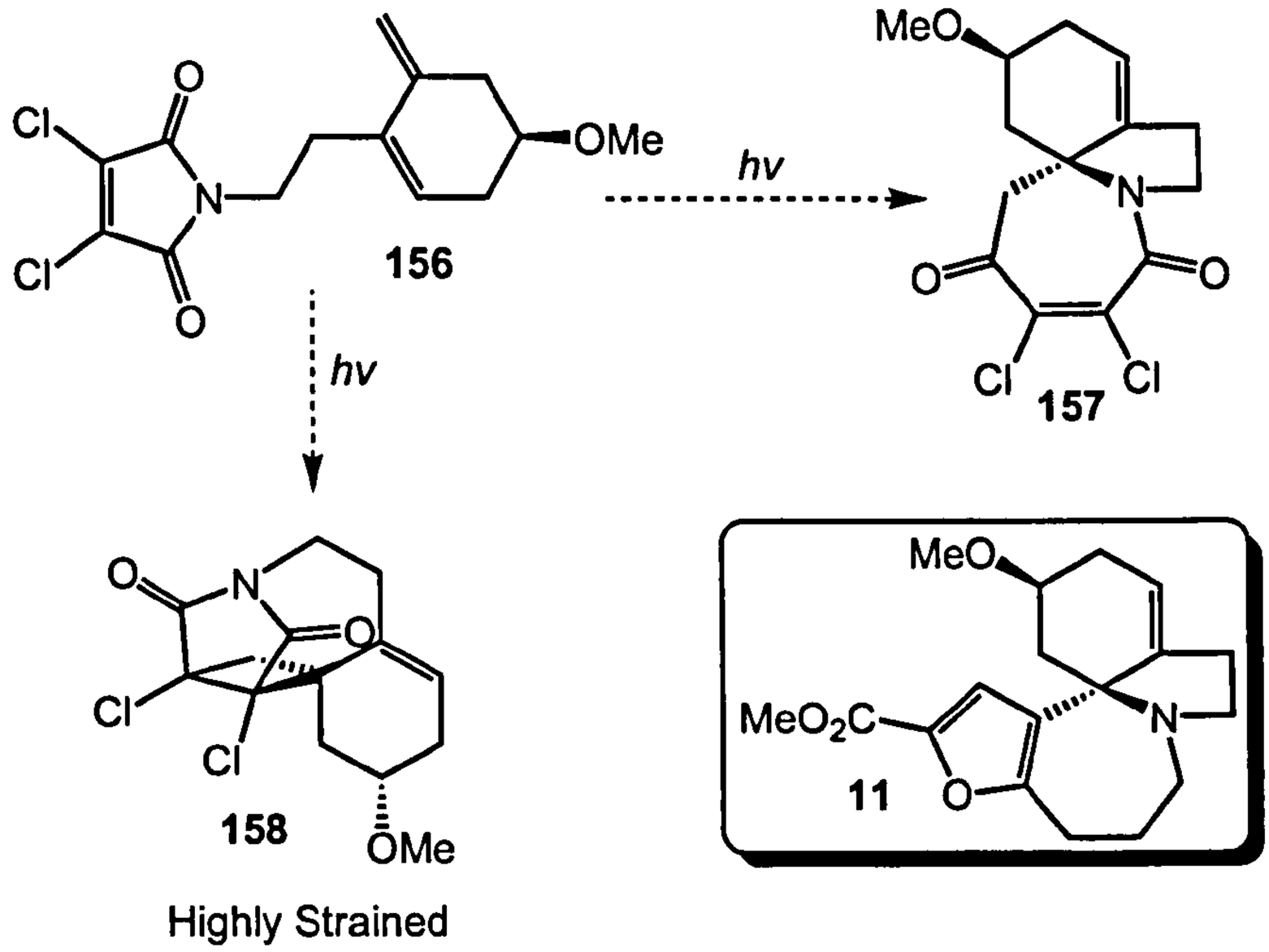
Reagents and Conditions: a) *hv*, Pyrex, MeCN, 7 h, **154** 75 %, **155** 20 %.

Scheme 56

It was suggested that due to the connectivity of maleimide **153** the transition state leading to [5+2] cycloaddition was less strained. A further study for increasing the selectivity to the [5+2] adduct **155** was required.

5.2. The 1st retrosynthesis of selaginoidine

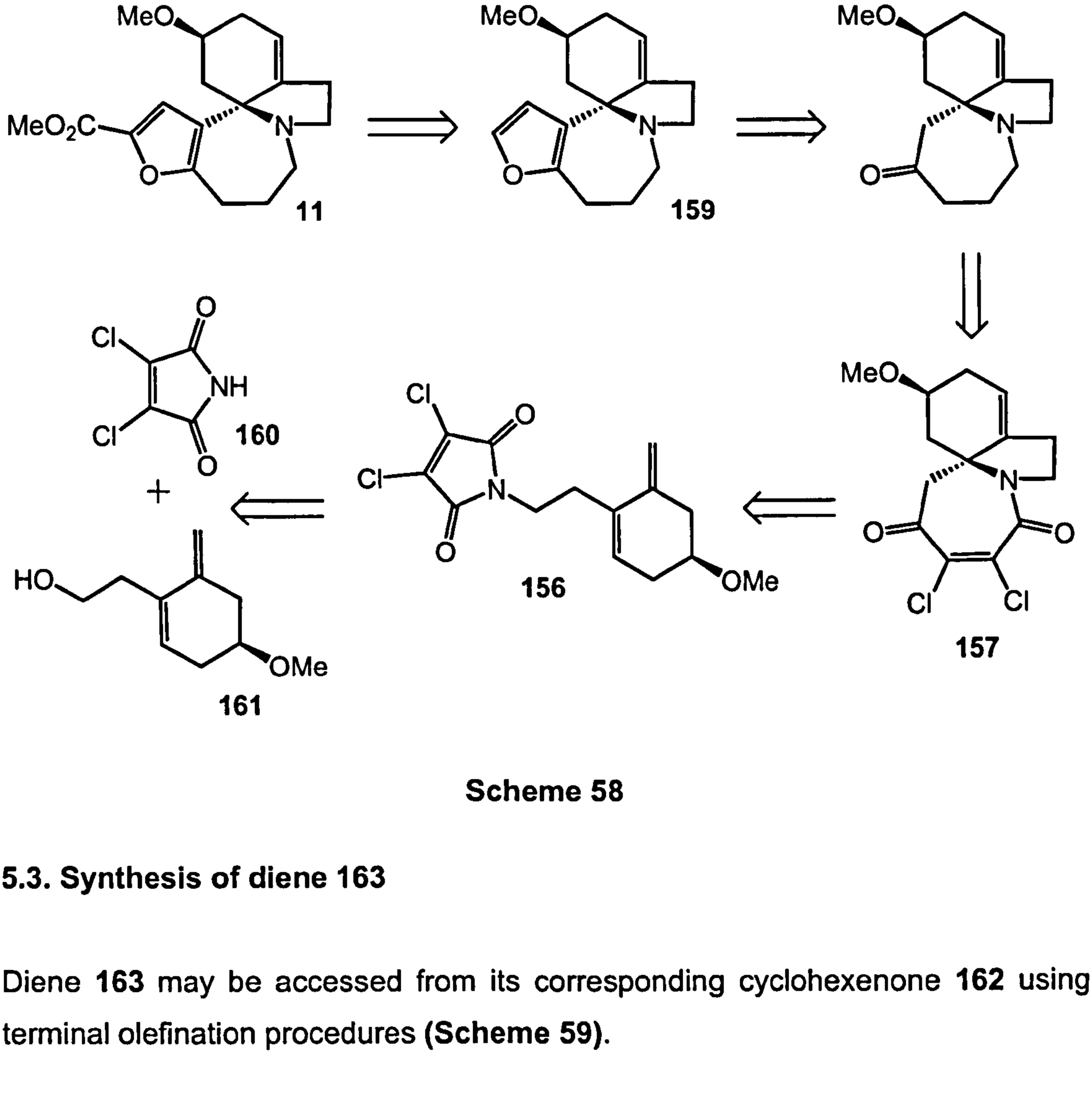
It was considered that an *N*-alkenylated maleimide **156**, on undergoing photocyclisation, would lead to the desired product **157 (Scheme 57)**. This product includes a large amount of the structural features and stereochemistry found in selaginoidine **11**. The key to this synthesis is whether a competing reaction that gives the [2+2] cycloadduct **158** could be controlled. Fortunately the double bond present in the cyclohexene ring may give a strained [2+2] product, thereby disallowing it on energetic grounds. Dreiding models are in good agreement with this.



Scheme 57

The retrosynthetic analysis considered for selaginoidine **11** is shown below **(Scheme 58)**. Selaginoidine **11** could be formed by the acylation of **159**, which might in turn be formed by a Feist–Benary furan synthesis. Two reductions lead back to **157**, which is the product of the key [5+2] photocycloaddition reaction of *N*-alkenyl maleimide **156**. In itself this should be readily available *via* Mitsunobu coupling of the alkenol **161** to maleimide **160**. To test the selectivity of the key

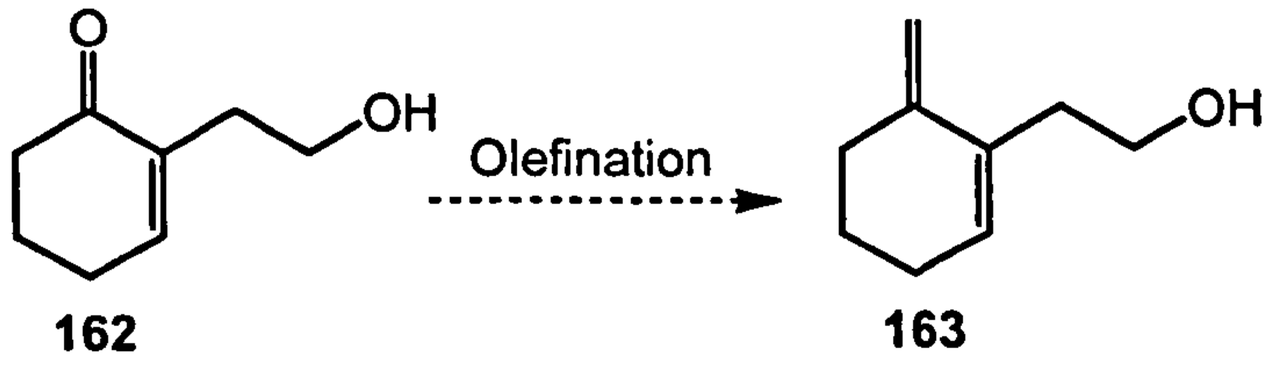
[5+2] photocycloaddition, a model substrate similar to **156** was used. This model is essentially identical, but does not contain the stereogenic methoxy group.



Scheme 58

5.3. Synthesis of diene 163

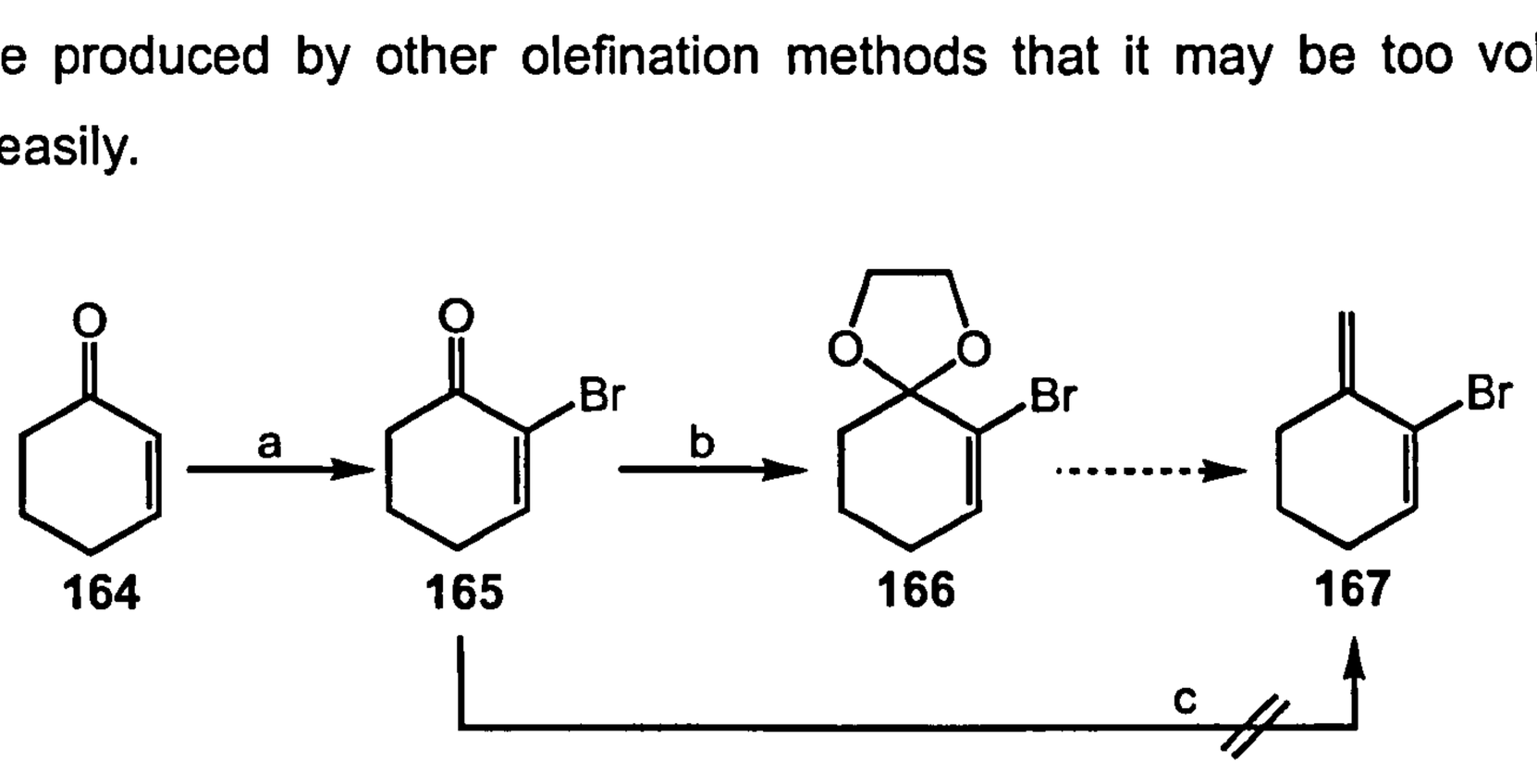
Diene **163** may be accessed from its corresponding cyclohexenone **162** using terminal olefination procedures **(Scheme 59)**.



Scheme 59

5.3.1. Cyclohexenone alkylation

The synthesis of diene **163** may be accessed by alkylation of the protected cyclohexenone **166** or alternatively, diene **167 (Scheme 60)**. Bromination of cyclohexenone **164** using bromine and Et_3N produced **165**, followed by protection with ethylene glycol gave **166** in a 68 % yield for the two steps.[58] Olefination would be preferable before alkylation takes place, thus avoiding a protection deprotection step. Traditional terminal olefinations can take place using Wittig[59], Peterson[60], Tebbe[61] or Petasis[62] procedures. The Peterson olefination has been shown in many cases to be more effective than the Wittig reaction.[63] Unfortunately even though Chan *et al.*[64] found the Peterson method useful for methylenation of several *a*,*ß*-unsaturated ketones, it was not so for cyclohex-2-enone as 1,4-addition and polymerisation predominated in these cases. For this reason a Wittig procedure was used for the olefination of **165**, however only baseline polymeric product was observed. It was decided that even if diene **167** could be produced by other olefination methods that it may be too volatile to handle easily.

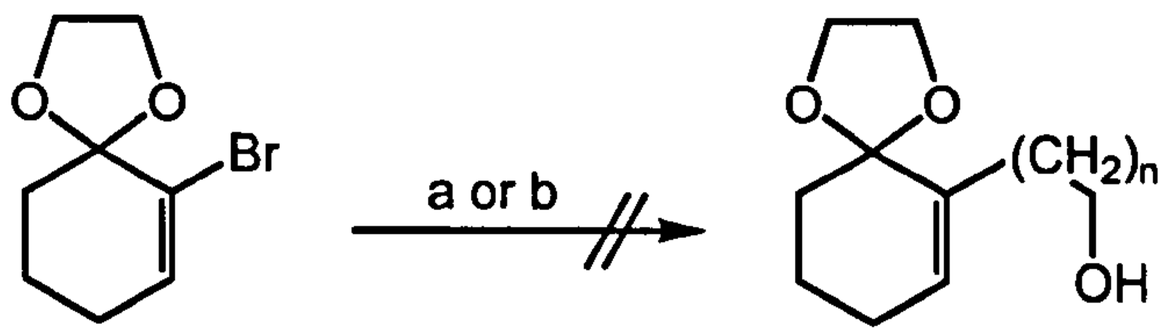


Reagents and Conditions: a) Br_2, Et_3N, DCM, 4 h, 72 %; b) $HO(CH_2)_2OH$, *p*TSA, toluene, reflux, 12 h, 94 %; c) Ph_3PCH_3Br, ^nBuLi, THF, -78 °C, 24 h.

Scheme 60

Similar alkylations of protected cyclohexenone **166** have been successfully carried out by Yadav *et al.*[65] and Overman *et al.*[66], with Spino *et al.*[67] effectively

alkylating a similar diene to that of **166**. Unfortunately alkylation of **166** with oxirane and oxetane was unsuccessful **(Scheme 61)**.



166

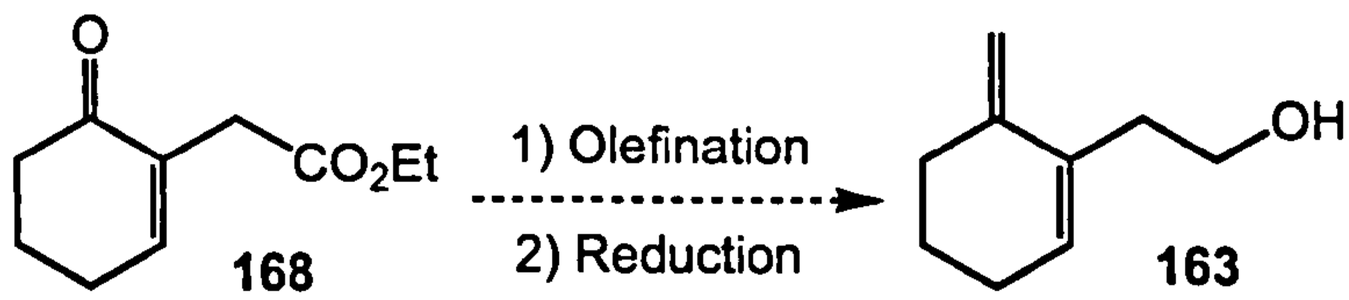
Reagents and Conditions: a) ^{n}BuLi, oxirane or oxetane, THF, -78 °C to 0 °C; b) ^{t}BuLi, oxirane or oxetane, $BF_3.Et_2O$, THF, -78 °C to 0 °C.

Scheme 61

It was found that two equivalents of ^{t}BuLi were needed for lithium halogen exchange, to prevent the exchange becoming reversible. The application of a Lewis acid to this procedure did not facilitate the opening of oxirane/oxetane.

5.3.2. Cyclohexanone alkylation

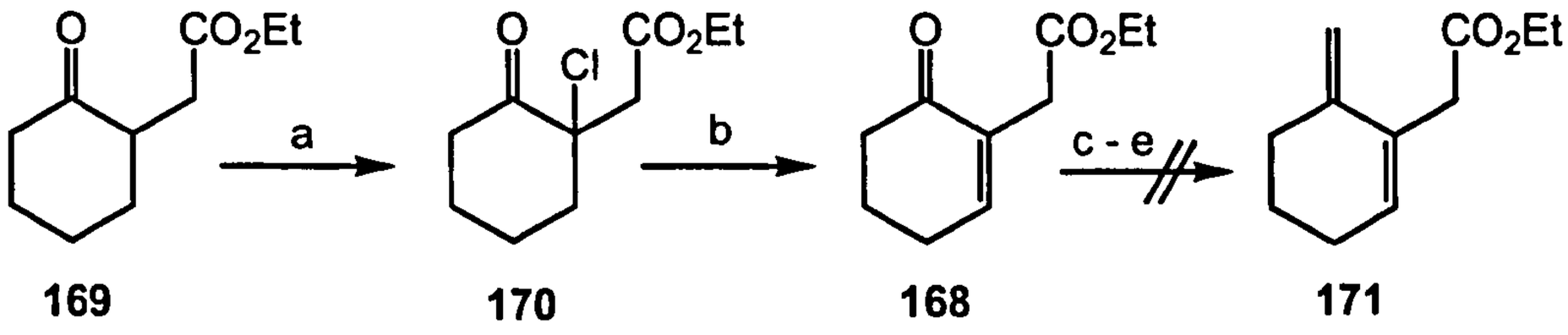
It was anticipated that diene **163** could be prepared from literature cyclohexenone **168 (Scheme 62)**.[68]



168 **163**

Scheme 62

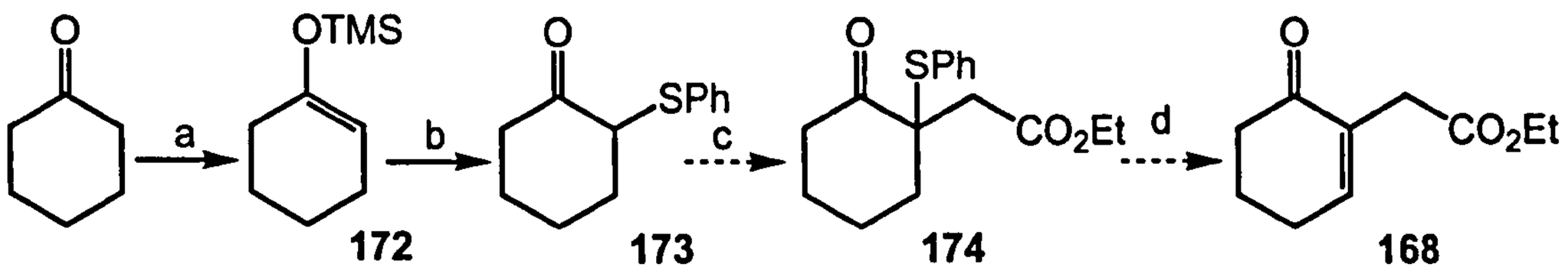
Cyclohexanone **170** was accessed by *a*-chlorination of cyclohexanone **169**, followed by elimination.[68] The elimination was troublesome giving poor yields requiring extensive purification **(Scheme 63)**.



Reagents and Conditions: a) SO_2Cl_2, DCM, 1 h, 70 %; b) Collidine, 145 °C, 40 min, 20 %; c) ^{t}BuOK, ^{t}BuOH, Et_2O, Ph_3PCH_3Br, 24 h; d) ^{n}BuLi, Ph_3PCH_3Br, THF, -78 °C to r.t. over 1 h, 24 h; e) i) ^{n}BuLi, Ph_3PCH_3Br, THF, -78 °C to r.t. over 1 h; ii) ^{t}BuLi, -78 °C to r.t. over 3 h, 24 h.

Scheme 63

A sufficient amount of **168** was obtained to carry out several Wittig olefination procedures. A range of methods using mild, standard and activated conditions[69] were employed, however no reaction took place. Other reagents could be applied, but their incompatibility with the ester functionality would require it to be reduced down to the alcohol prior to olefination. Larger quantities of **168** were required, so an alternative strategy was undertaken. Silyl enol ether **172** was produced from cyclohexenone in quantitative yields **(Scheme 64)**. Trapping with benzenesulfenyl chloride gave **173** in excellent yield, with difficult purification. Using the literature alkylation procedure to give **174**, elimination to **168** could have been achieved; nevertheless an easier route to diene **163** was accomplished by using a Birch reduction/alkylation procedure.

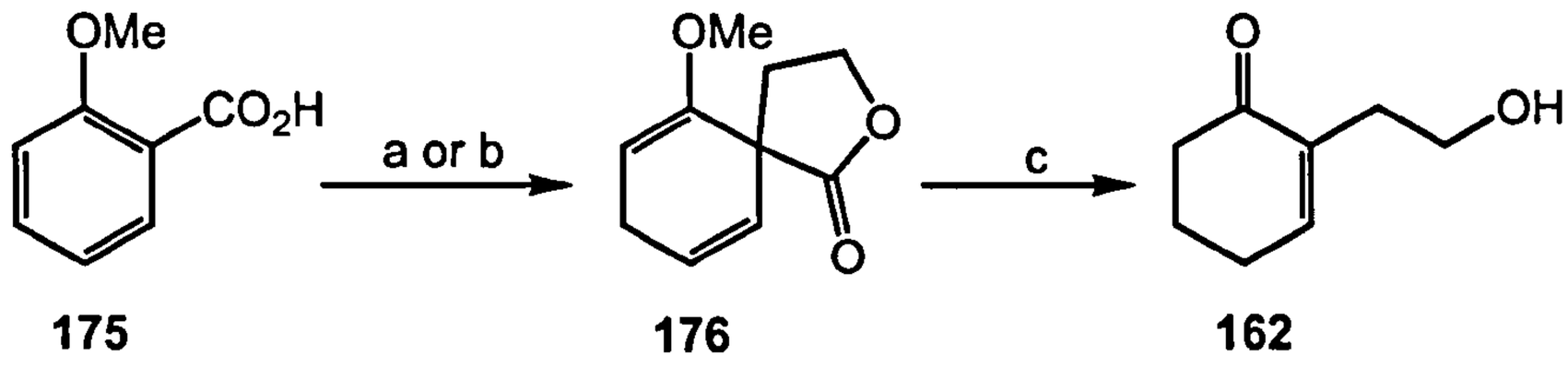


Reagents and Conditions: a) i) LDA, THF, -78 °C; ii) TMSCl, 99 %; b) PhSCl, DCM, 0 °C, 2 h 30 min, 70 %; c) i) NaH, THF, 0 °C to r.t. over 1 h; ii) $BrCH_2CO_2Et$, 8 h; d) H_2O_2, THF.

Scheme 64

5.3.3. Birch reduction/alkylation

A simple procedure to access 2-alkyl substituted cyclohexenones using the alkylation of the anion formed by a Birch reduction of *o*-anisic acid **175** was realised by Taber *et al.*[70] A modification of this method by Mariano *et al.*[71] gave spiro lactone **176** in variable yields, followed by acid hydrolysis to give alcohol **162 (Scheme 65).**



175 **176** **162**

Reagents and Conditions: a) i) Li/NH_3, THF, -78 °C; ii) $BrCH_2CH_2Cl$, 20 – 40 %; b) i) Li/NH_3, ^tBuOK, THF, -78 °C; ii) $BrCH_2CH_2Cl$, 71 %; c) HCl, $MeOH/H_2O$, reflux, 48 h, 86 %.

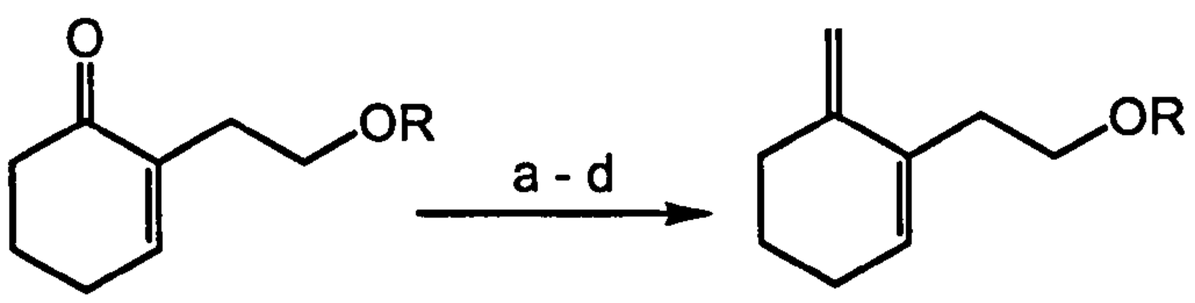
Scheme 65

Variation of Birch reduction conditions by addition of 1.0 equivalent of potassium ^{t}butoxide prior to addition of lithium metal, significantly improved the yield of this procedure. The role of the base was to ensure that the anion was not protonated before alkylation occurred.

5.3.4. Terminal olefination

Cyclohexenone **162** was protected as the silyl ether **177** and both compounds were subjected to a variety of olefination conditions **(Scheme 66, Table 3)**. Standard Wittig conditions (*entries 1 – 4*) only gave baseline polymeric material, whereas under milder conditions (*entries 5 – 6*) only starting material was recovered. Application of the Tebbe reagent (*entry 7*) gave a poor yield of diene **178**, partly due to the build up of Lewis acidic aluminium by-products that were difficult to separate from the product itself. The Petasis reagent (*entries 8 – 9*) on

the other hand was a more convenient alternative and is essentially air and water stable.[72]



Entry	Starting material	Reagent	Reaction time /h	Temp	Yield /%
1	**162**	Wittig A[a]	2 then 22	0 °C then r.t.	0
2	**177**	//	//	//	0
3	**162**	//	2 then 6	0 °C then reflux	0
4	**177**	//	//	//	0
5	**162**	Wittig B[b]	24	r.t.	0
6	**177**	//	//	//	0
7	**177**	Tebbe[c]	0.5 then 1.5	-40 °C then r.t.	19
8	**177**	Petasis[d]			50
9	**162**	//			56

Reagents and Conditions: a) ^{n}BuLi, Ph_3PCH_3Br, THF, -78 °C to r.t. over 1 h, 24 h; b) ^{t}BuOK, ^{t}BuOH, Et_2O, Ph_3PCH_3Br, 24 h; c) Tebbe reagent, pyridine, toluene:THF, -40 °C for 30 min, then r.t. 1 h 30 min; d) Petasis reagent, toluene/THF, 80 °C, 4 h.

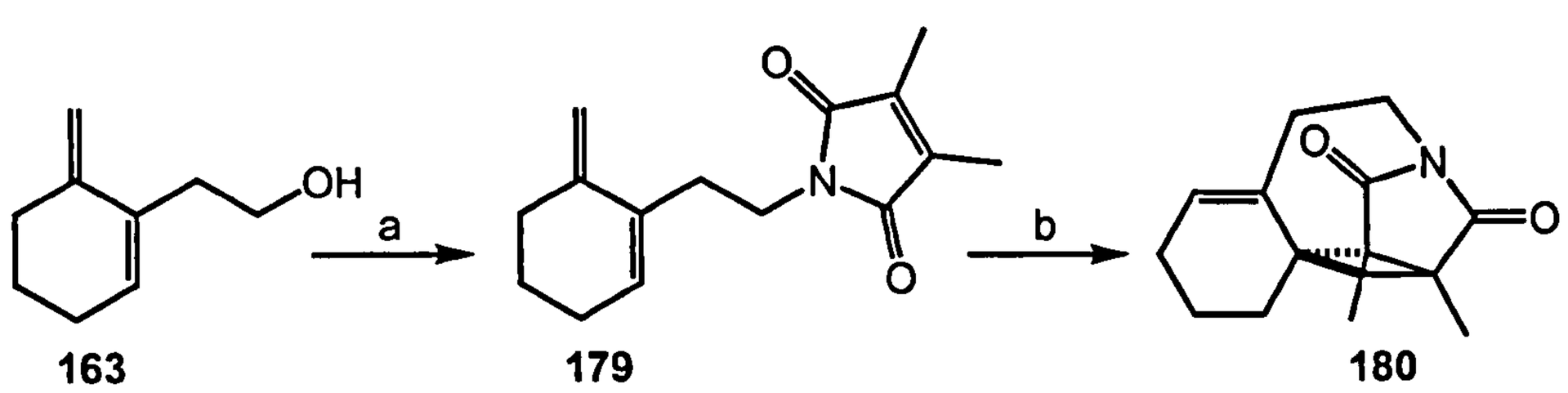
Scheme 66 : Table 3

On a small and large scale, a reasonable yield of **163** and **178** had been achieved. For olefination of protected cyclohexenone **177**, purification was difficult by flash column chromatography as the product was particularly non-polar and contained small amounts of titanium impurities. The purification and

yield of **163** was superior and also advantageous as a protection deprotection step was avoided.

5.4. Photochemistry of diene 179

Diene **163** was coupled under a modification of Mitsunobu conditions for maleimides established by Walker.[73] The Walker method forms a PPh_3/DEAD betaine first, followed by addition of alcohol then maleimide, with 5 min in-between additions. A modification of this method by Booker–Milburn *et al.* [73], by increasing the time between additions to 1 h has generally increased yields. This procedure furnished alkylated maleimide **179** in a good yield but with poor conversion **(Scheme 67)**. Nonetheless, the synthesis of diene **179** had been achieved, allowing the photochemistry of this molecule to be studied.



163 **179** **180**

Reagents and Conditions: a) PPh_3, DEAD, dimethylmaleimide, THF, -78 °C to r.t. over 24 h, 42 % or 64 % based on recovered starting material; b) *hv*, Pyrex, MeCN, 8 h, 56 %.

Scheme 67

Irradiation of diene **179** for 8 h resulted in complete conversion to a [2+2] photocycloaddition product **180** in a modest yield. Cycloadduct **180** was confirmed by X-ray crystallography **(Figure 10)**. However no [5+2] photocycloaddition was observed. The key to this synthesis was whether a competing reaction that gives the [2+2] cycloadduct could have been controlled. By adding the double bond to the cyclohexane ring, total selectivity was given to the [2+2] process, completely countering our original theory! This remarkable product contains a 4, 5, 6, 7 and 8 membered ring. The [5+2] cycloadduct is

believed to occur *via* a singlet excited state process. *N*-Alkenylated maleimide **179** is most likely to be excited to the singlet state and may have been converted to the triplet state of the enone *via* intersystem crossing, immediately followed by [2+2] cycloaddition.

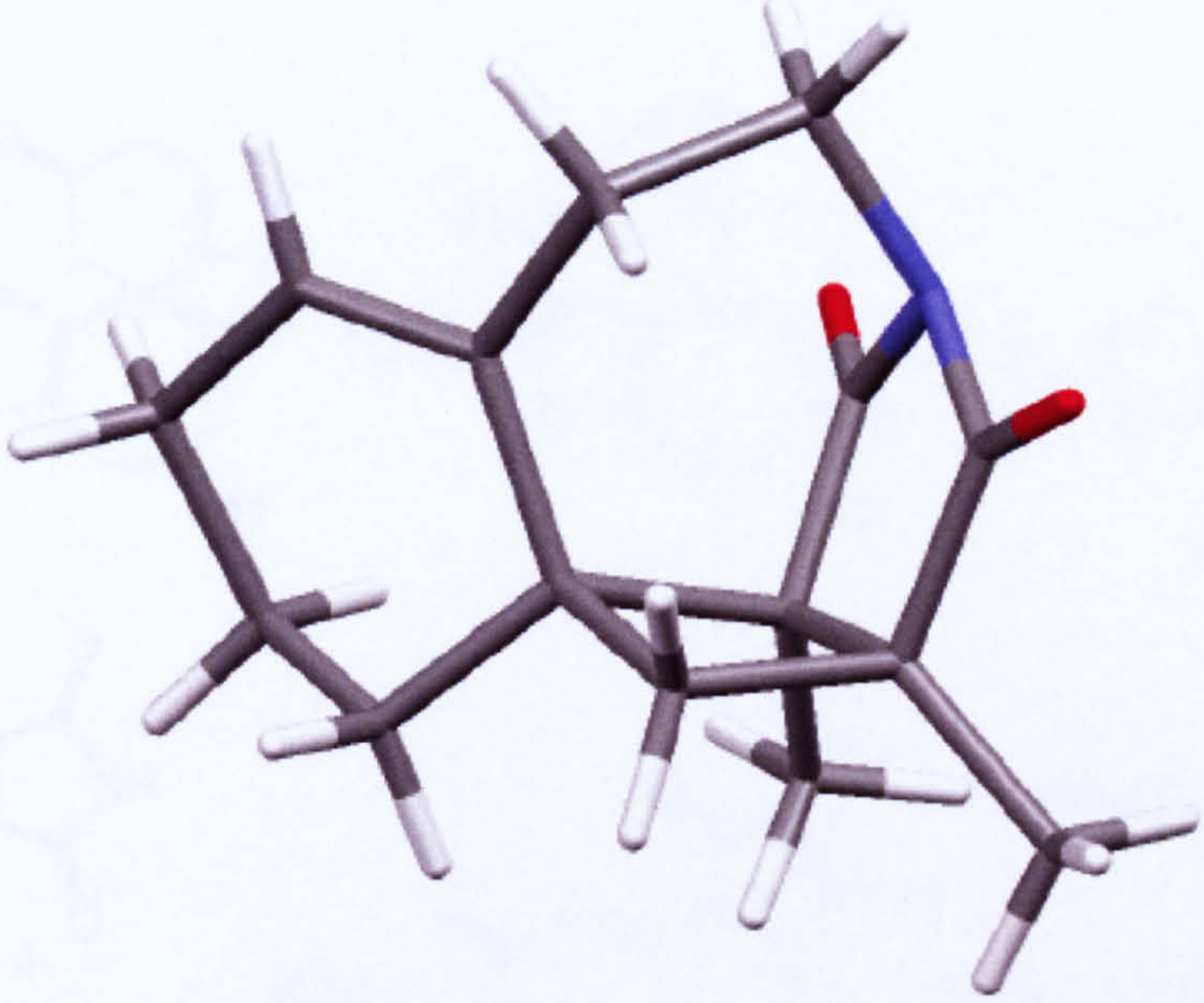


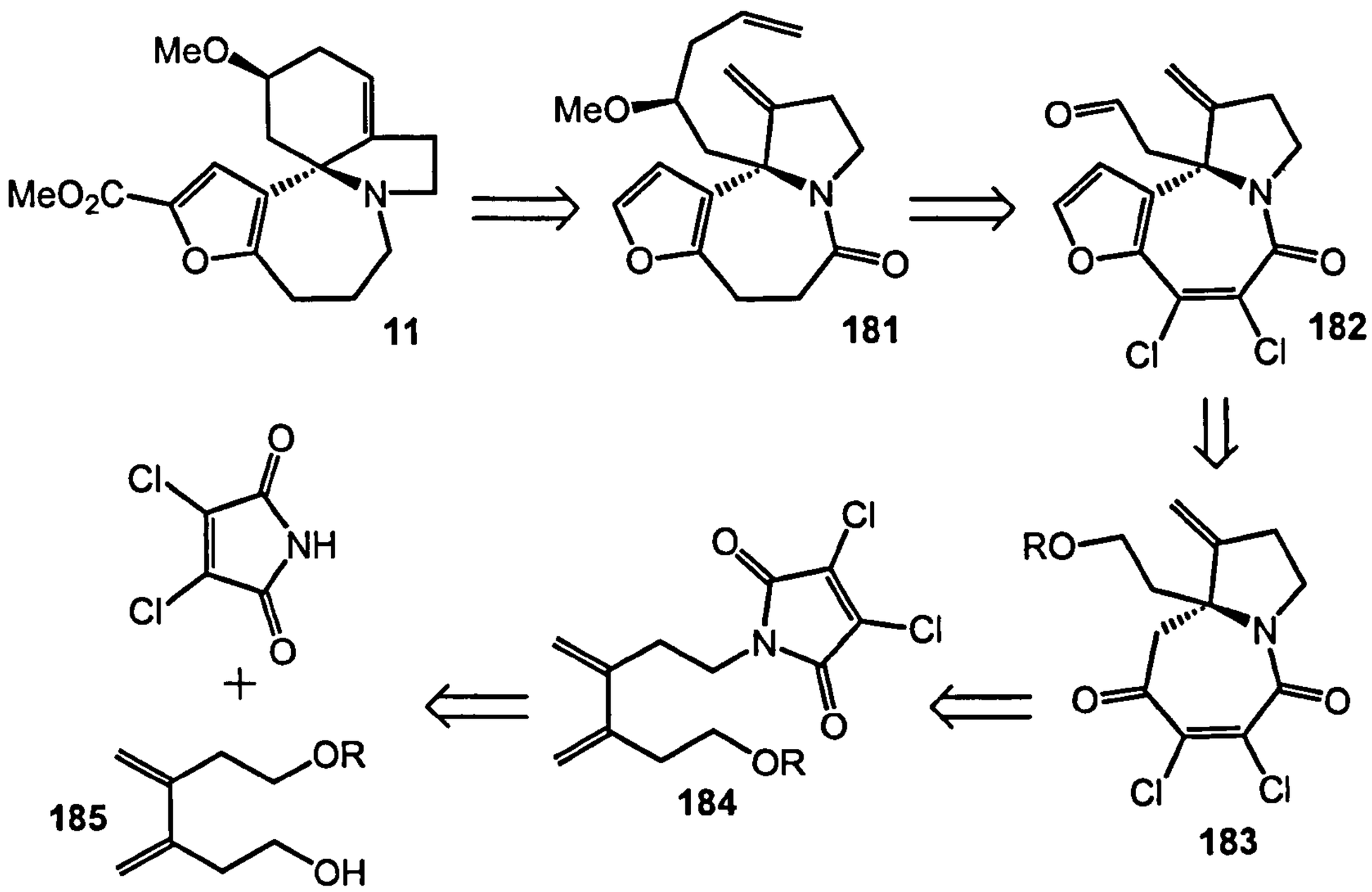
Figure 10 : X-ray structure of 180

The reason for the lack of reactivity of the singlet state could be attributed to quenching from the diene functionality, which would explain the long irradiation times required. Another likely explanation is that the *N*-alkenylated chain can not deliver the exocyclic double bond to the imide, where [5+2] photocycloaddition occurs. For this reason, it is important to retain the conformational flexibility of the *N*-alkenylated chain. Using this rationalisation a new strategy using a more flexible chain was employed.

5.5. The 2nd retrosynthesis of selaginoidine

Deliberation of the outcome of the previous strategy led us to conclude that the cyclohexene ring should be formed late on in the synthesis **(Scheme 68)**. Selaginoidine **11** could be readily available from Ring Closing Metathesis and

alkylation of **181**, which may in turn be formed by diastereoselective addition of allyl magnesium bromide to aldehyde **182**. An oxidation leads back to **183**, the product of the key [5+2] photocycloaddition of the *N*-alkenyl maleimide **184**, which itself should be readily available *via* Mitsunobu coupling of alkenol **185** with dichloromaleimide.

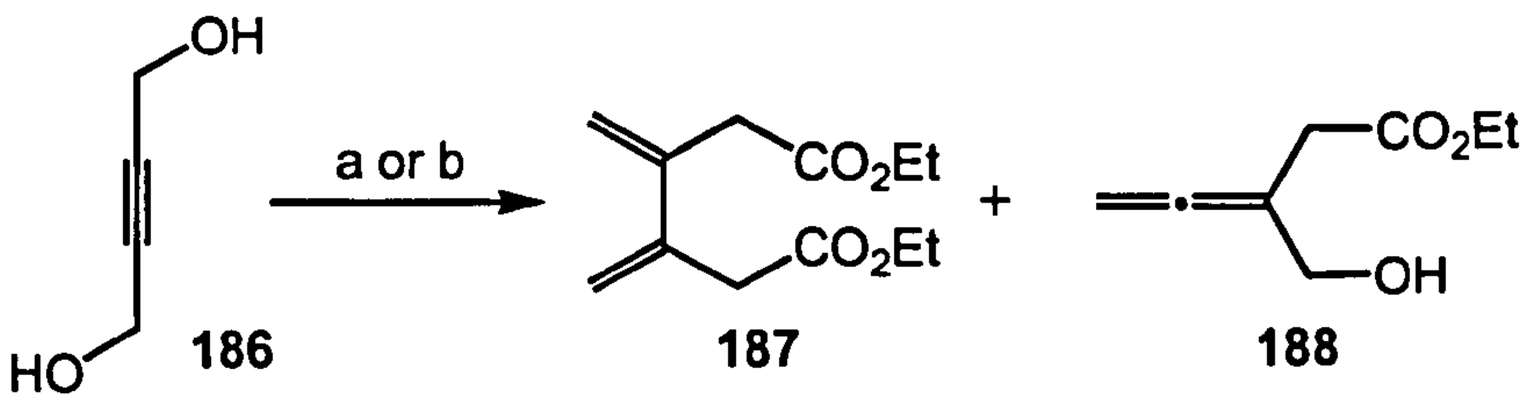


Scheme 68

5.6. Synthesis of dienes 190, 193 and 194

Alkenol **185** where R = H was prepared according to the literature procedures involving a double othoester Claisen rearrangement **(Scheme 69)**.[75] The best conditions from literature involved microwave assisted *ortho* Claisen rearrangement of 2-butyne-1,4-diol **186** with triethyl orthoacetate in the presence of a catalytic amount of acid, in only 15 min with a 92 % yield. Diene **187** was

given in varying yields under a range of reaction times, and catalyst loading **(Table 4)**.



186 **187** **188**

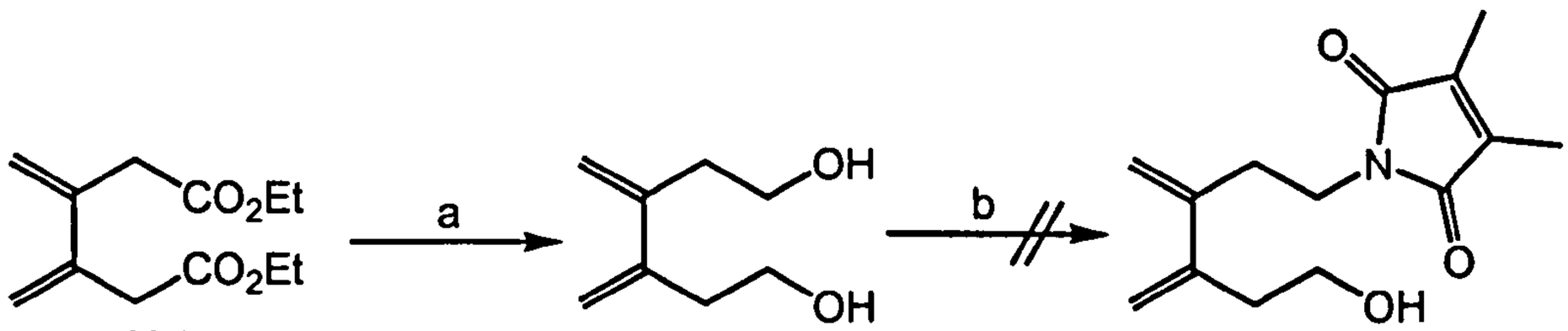
Entry	Catalyst	Loading / mmol	Reaction time at 140 °C / min	**187:188**	Yield / %
1	Monmorillonite KSF	25 mg	15	1:0	58
2	//	//	12.5	1:0	67
3	//	//	10	1:0	71
4	//	5 mg	10	1:1.4	100
5	propionic acid	3 µl	15	1:0.6	100
6	//	//	12.5	1:2	100

Reagents and Conditions: a) $CH_3CH(OEt)_3$, catalyst, DMF, *µv* 140 °C; b) $CH_3CH(OEt)_3$, propionic acid, 140 °C, 7 h, 84 %.

Scheme 69 : Table 4

These results showed that it was crucial for the reaction to be stopped once the entire mono *ortho* Claisen rearrangement product **188** had undergone further rearrangement; otherwise polymerisation of diene **187** occurs (*entries 1 – 3*). The manner in which yields of the reaction varied under slight changes in conditions (*entries 1 – 6*) meant that the microwave conditions were taking up too much time in optimisation. Thermally the rearrangement has been reported in yields of around 50 %.[75] However performing the reaction by heating diol **63** with an excess of ortho ester at 140 °C, 10 mol% propionic acid, distillative removal of EtOH and careful monitoring by TLC subsequently led to a 78 % yield of **64** and

6 % **188**. Reduction of compound **187** with $LiAlH_4$ in anhydrous THF gave the corresponding diol **189** in 94 % isolated yield **(Scheme 70)**.

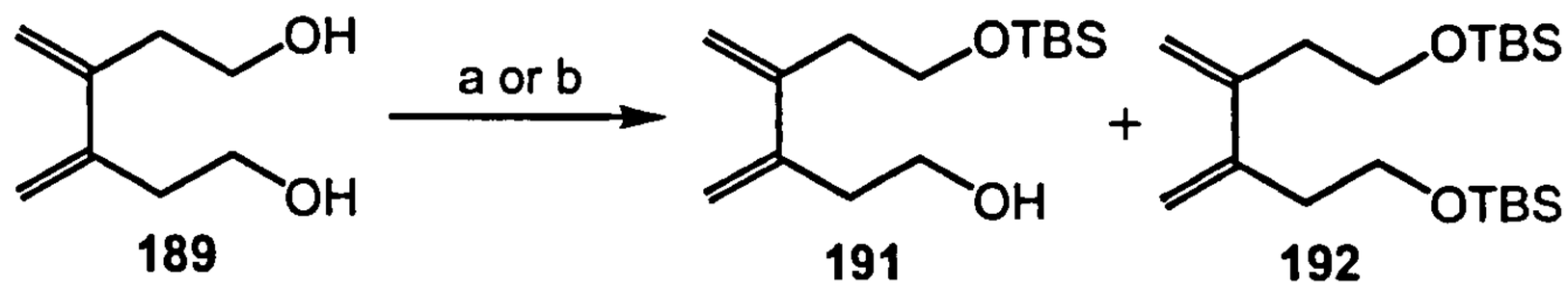


187 **189** **190**

Reagents and Conditions: a) $LiAlH_4$, THF, 12 h, 94 %; b) PPh_3, DEAD, dimethylmaleimide, THF -78 °C to r.t. over 24 h.

Scheme 70

A significant increase in yield from literature was attributed to quenching the reaction with NaOH aq, which helped to free up **189** from its aluminates. Mitsunobu coupling of diol **189** to dichloromaleimide did not take place; a possibility is that **189** has added twice to the betaine of PPh_3 and DEAD to give a species that is unreactive to the maleimide nucleophile. For this reason **189** was mono protected with the TBS silyl group **(Scheme 71)**.



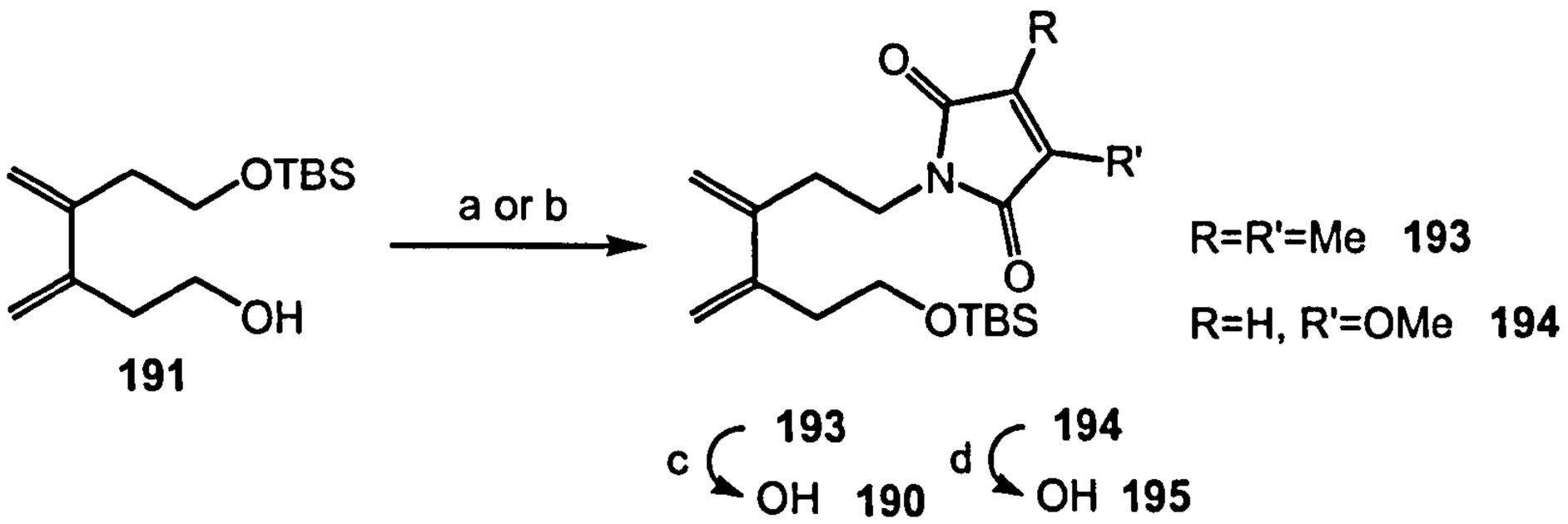
189 **191** **192**

Reagents and Conditions: a) **189** added to TBSCl, Et_3N, DMAP, DCM, 0 °C, 12 h, 59 % (1:1 **191**:**192**); b) TBSCl added to **189**, Et_3N, DMAP, DCM, 0 °C, 12 h, 71 % (2:1, **191**:**192**).

Scheme 71

Slowly adding diol **189** dropwise to a solution of TBSCl, Et_3N and DMAP in DCM gave a 74 % conversion to a 1:1 mixture of mono-protected **191** and di-protected **192**. By altering the reaction conditions so that TBSCl was added last in one portion, a similar conversion was given, but with a 2:1 mixture favouring **191**. The mono-protected alcohol **191** was then coupled to dichloromaleimide and 3-

methoxy-1*H*-pyrrole-2,5-dione **(Scheme 72)**. Dimethyl maleimide was initially coupled by the modified Walker method that was used to couple diene **163** earlier and afforded **193** in only a 9 % yield. By adding DEAD last to the reagents in solution at 0 °C gave a far superior yield. Surprisingly this method was not applicable to methoxy maleimide, with no conversion of starting material. The modified Walker procedure was used and gave the coupled diene **194** in a 78 % yield. Diene **194** was deprotected using TBAF in THF delivering a poor yield. It appeared that the maleimide was sensitive to the basic conditions; consequently the deprotection of diene **193** was carried out in acidic conditions with AcOH giving **190** in a quantitative yield.



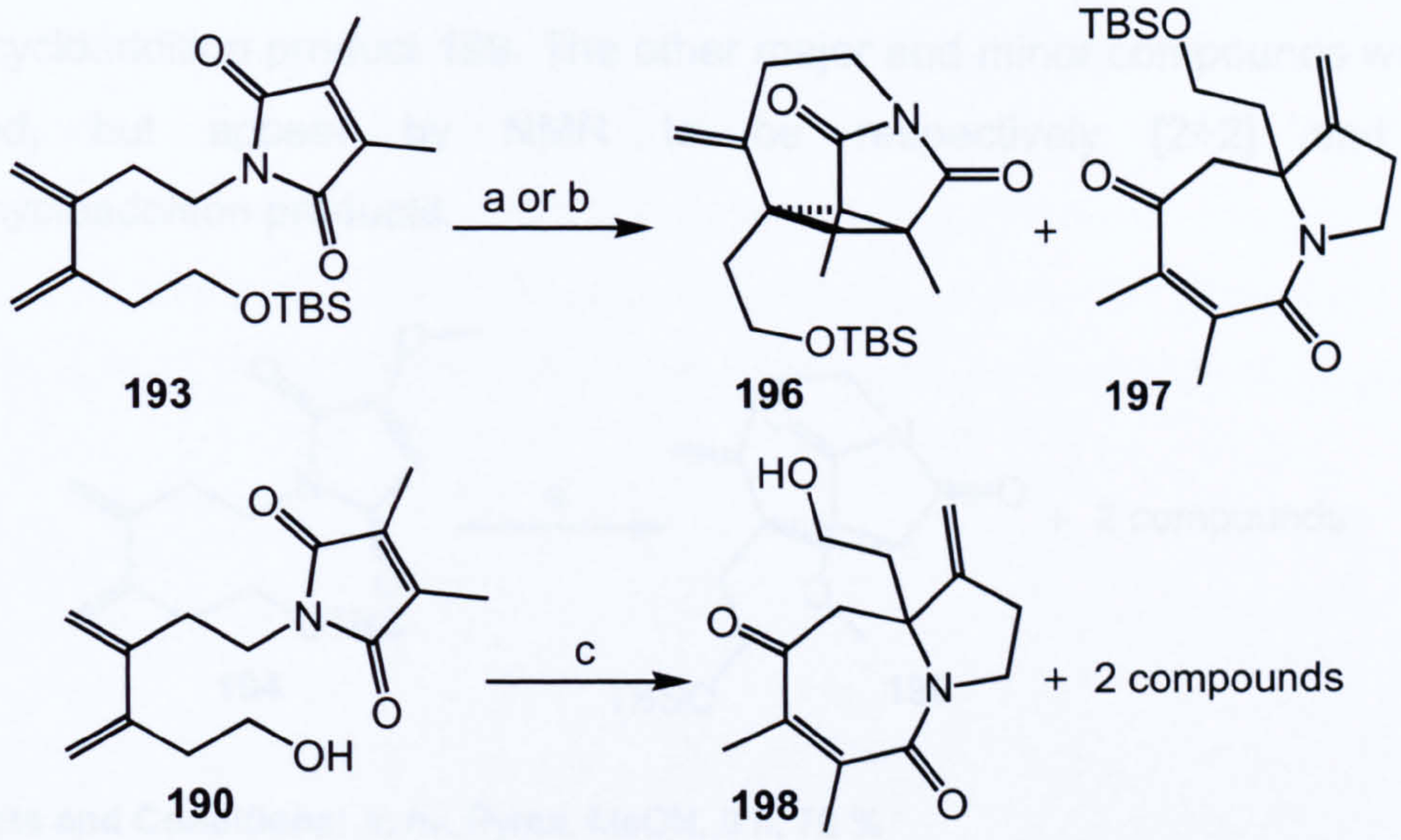
Reagents and Conditions: a) Walker Mitsunobu, 9 % **193** or 83 % **194**; b) Standard Mitsunobu, 80 % **193** or 0 % **194**; c) TBAF, THF, 24 h, 24 %; d) AcOH, TBAF, THF, 24 h, 99 %.

Scheme 72

5.7. Photochemistry of dienes 190, 193 and 194

Irradiation of diene **193** for 9 h in a Pyrex reaction well produced a 2:1 mixture of [2+2]:[5+2] (**196**:**197**) photocycloaddition adducts in a modest yield **(Scheme 73)**. The photochemistry was also undertaken using a Vycor well, allowing a wider range of wavelengths to be absorbed by **193**. As expected this dramatically increased the rate of consumption of starting material, however decreased the yield to 26 % and only small amounts of [5+2] cycloadduct **197** were observed. It appears that **197** is degraded more by UV light than **196**. Deprotected diene **190** was also subjected to irradiation and interestingly gave three compounds in a

66 % yield **(Scheme 73)**. Only the [5+2] cycloadduct **198** could be isolated in an 8 % yield, with the remaining material containing what appeared by ^{1}H NMR to be a [2+2], and an alternative [5+2] cycloaddition product.



Reagents and Conditions: a) *hv*, Pyrex, MeCN, 9 h, 62 %; b) *hv*, Vycor, MeCN, 1 h; c) *hv*, Pyrex, MeCN, 9 h, 66 %.

Scheme 73

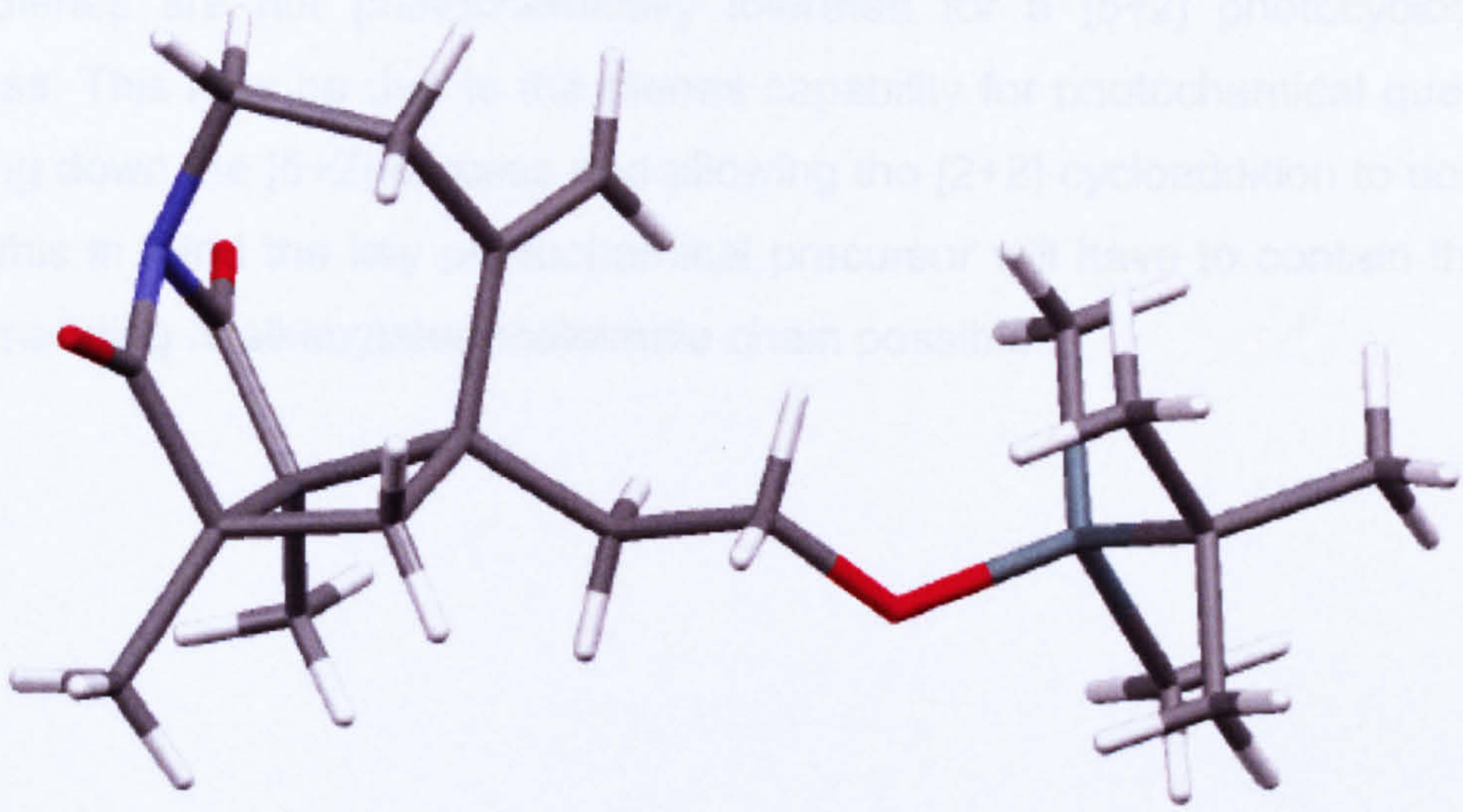
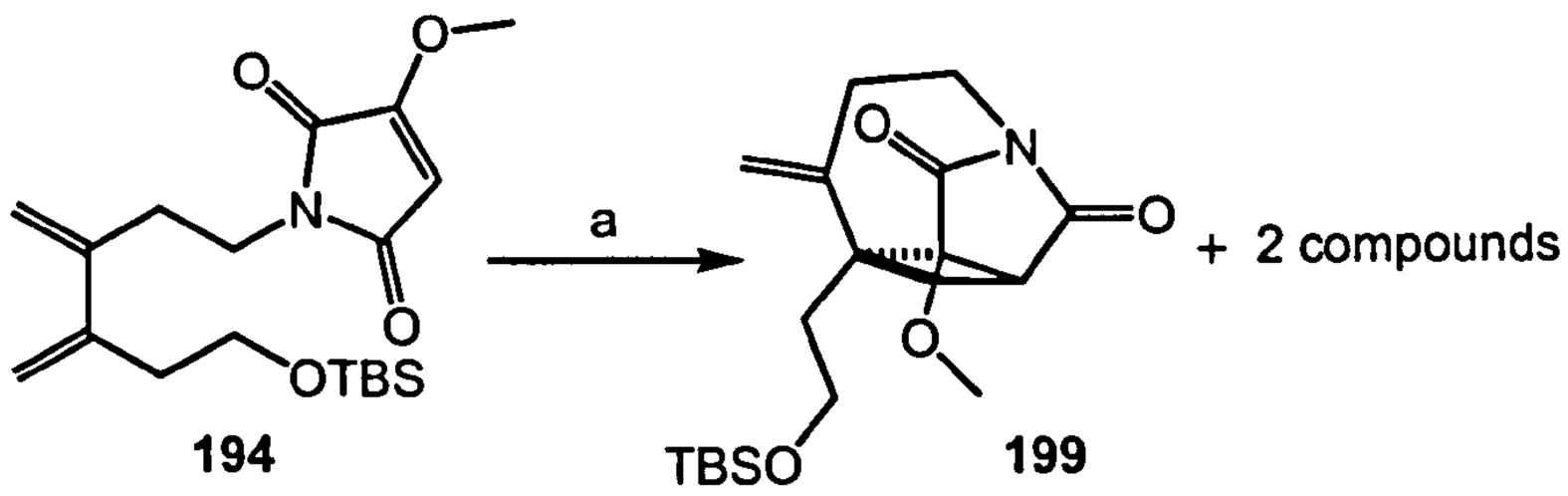


Figure 11 : X-ray structure of 196

Introduction of the electron rich maleimide **194** afforded 3 compounds in a 70 % yield **(Scheme 74)**. The compounds were separated and found to be in a 2:2:1 ratio. One of the major constituents could be identified as a [2+2] photocycloaddition product **199**. The other major and minor compounds were not isolated, but appear by NMR to be respectively [2+2] and [5+2] photocycloaddition products.



194 **199**

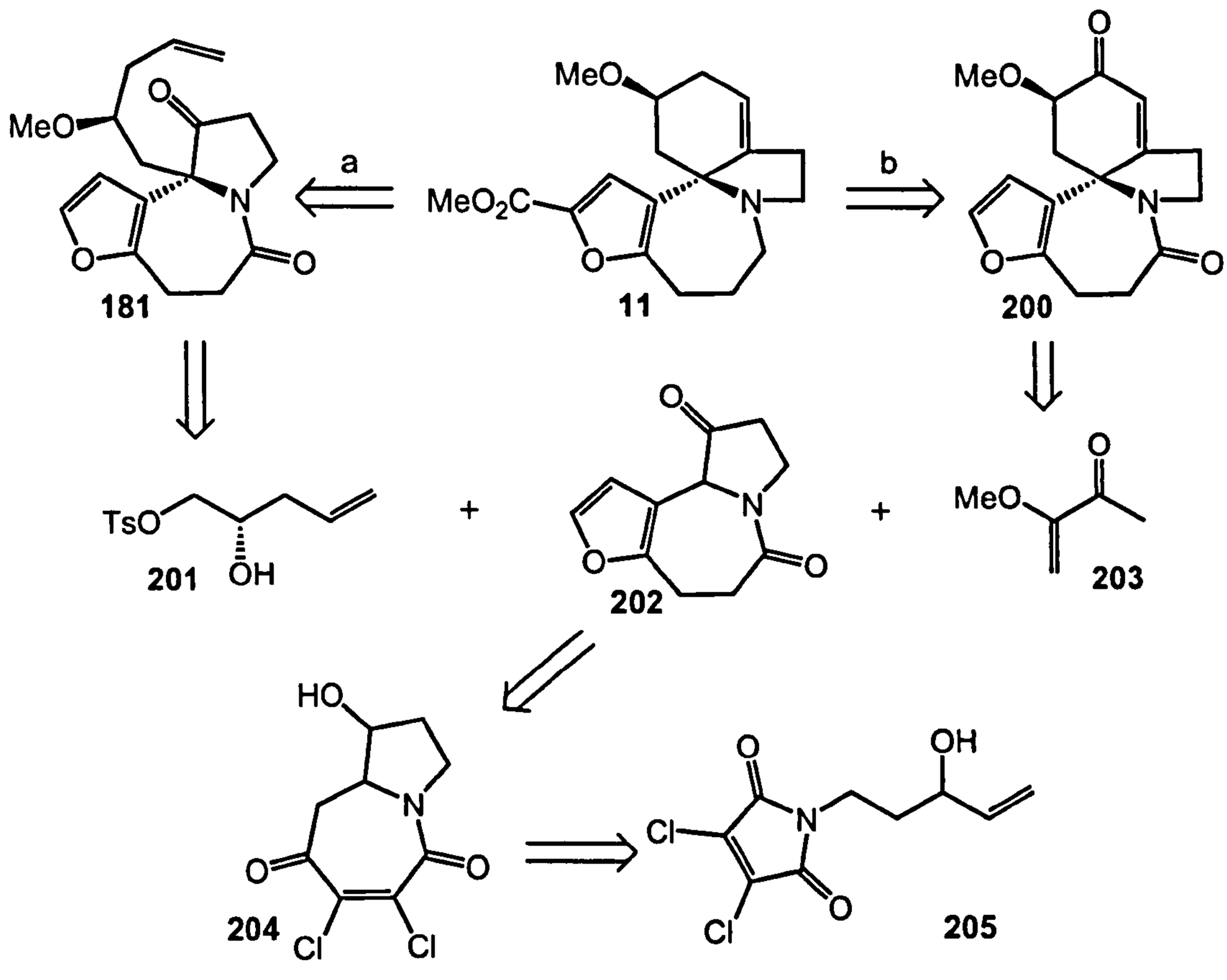
Reagents and Conditions: a) *hv*, Pyrex, MeCN, 9 h, 70 %

Scheme 74

By considering the photochemistry of dienes **179**, **190**, **193** and **194**, it was apparent that not only is *N*-alkenyl chain conformation flexibility important, but that dienes are not photochemically tolerated for a [5+2] photocycloaddition process. This may be due to the dienes capability for photochemical quenching; slowing down the [5+2] process and allowing the [2+2] cycloaddition to dominate. With this in mind the key photochemical precursor will have to contain the most undemanding *N*-alkenylated maleimide chain possible.

5.8. The 3rd retrosynthesis of selaginoidine

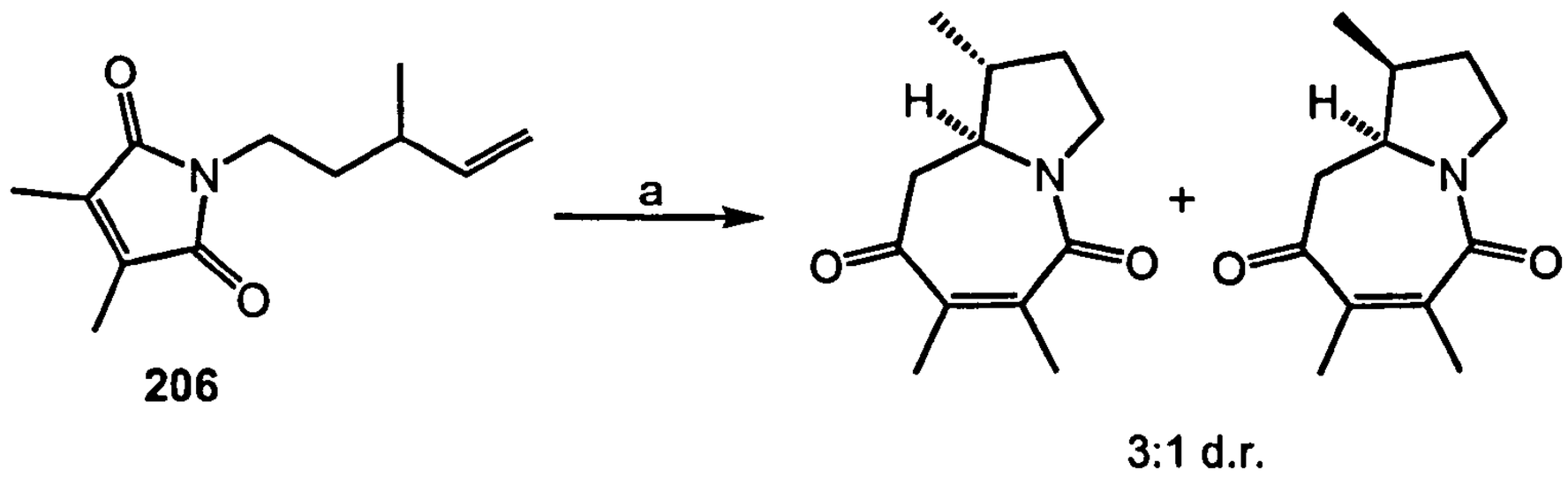
Following the previous strategy to selaginoidine with a RCM as the first disconnection (*arrow a*), followed by oxidation of the furan functionality leads back to **181 (Scheme 75)**. This in turn may well be accessed by the alkylation of the thermodynamic enolate of **202** with literature compound **201**[76]. An additional route (*arrow b*) leads back from **11** to **200** *via* oxidation of the furan and a reduction of the enone functionality. A Robinson annulation procedure may in turn afford **200** from **202** after epimerisation of the stereogenic methoxy group.



Scheme 75

Both *route a* and *route b* use common intermediate **202**, which may be accessed from **204** after furan synthesis, which in turn may be attained from the [5+2]

photocycloaddition of **205**. A similar photocycloaddition has been accomplished by Booker – Milburn *et al.*[41] using dimethylmaleimide containing an allylic methyl group **206** affording [5+2] photocycloadducts with a 3:1 d.r. **(Scheme 76)**. We can therefore anticipate that the hydroxyl group in **206** has a similar steric presence to the methyl group and can consequently predict similar results.



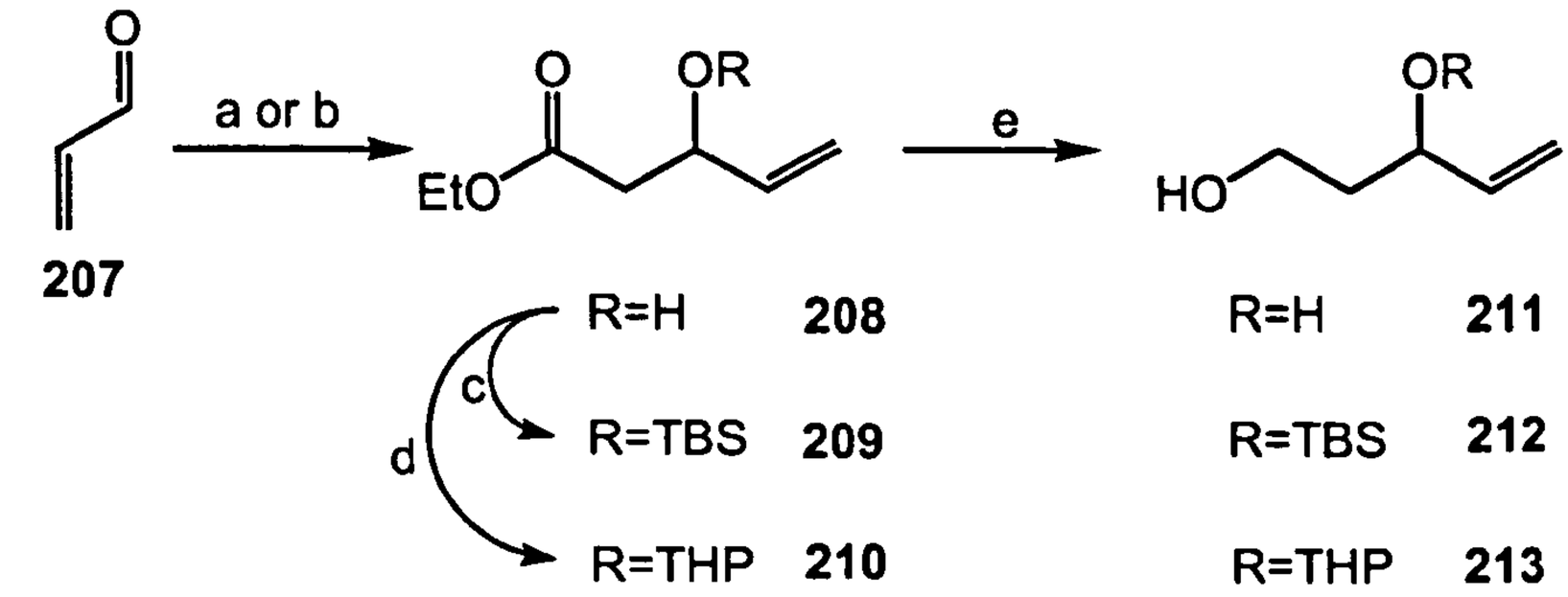
Reagents and Conditions: a) *hv*, Pyrex, MeCN, 4 h, 90 %.

Scheme 76

5.9. Synthesis of allylic alcohol 214

The synthesis of the *N*-alkenyl chain can be conducted by an aldol condensation followed by a $LiAlH_4$ reduction **(Scheme 77)**. The aldol reaction can be carried out by forming either a zinc[77] or lithium enolate[78]. Reformatsky additions to acrolein **207** have been carried out previously in moderate yields.[77] However these procedures used granular zinc to condense *a*-bromoesters to **207** using extended reaction times or elevated temperatures. Rathke *et al.*[79] found that a commercially available suspension of lithium in mineral oil reacts directly with $ZnCl_2$ in Et_2O at r.t. and produces a particularly active form of zinc. They showed significant improvement in the yields of a range of literature preparations. Unfortunately this method did not enhance the yield of **208**. On the other hand employing a lithium enolate produced quantitative yields for aldol condensation to **208**, without any further purification required. Protection of the allylic alcohol

could be achieved with either THP or TBS groups giving **209** and **210** respectively. For the silyl protecting group, long reaction times were necessary.



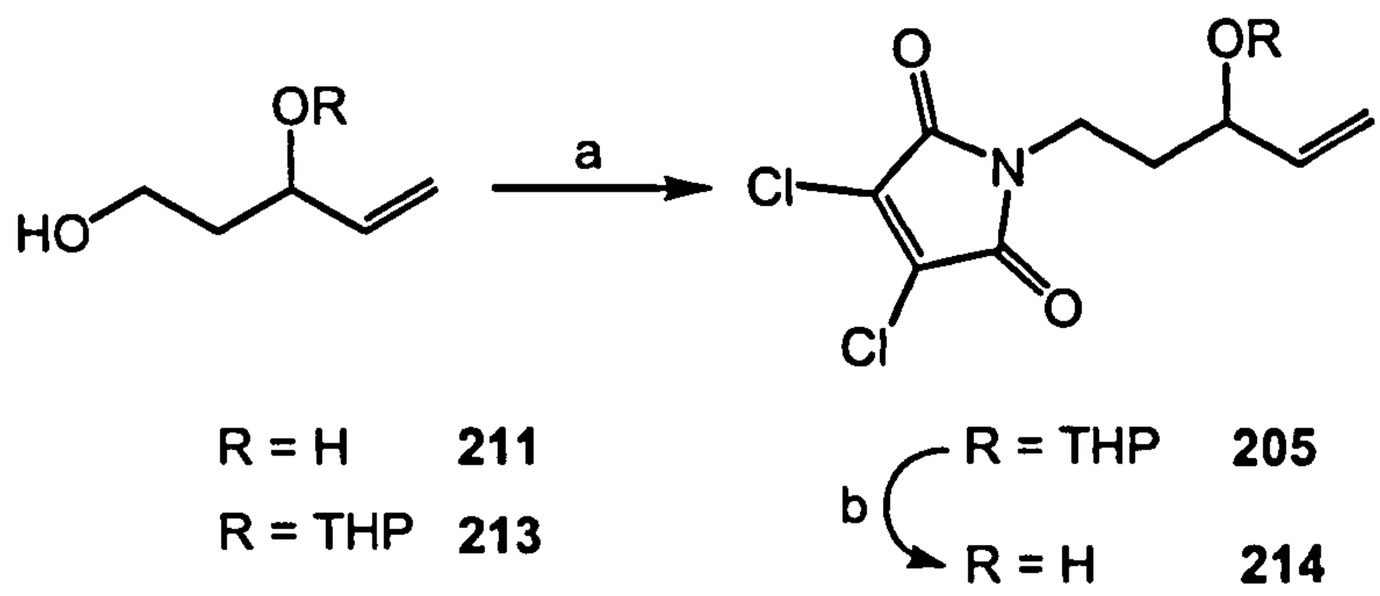
Reagents and Conditions: a) $ZnCl_2$, Li, $BrCH_2CO_2Et$, THF, 2 h, 50 %; b) LiHMDS, EtOAc, THF, -78 °C, 1 h 30 min, 99 %; c) TBSCl, Et_3N, DMAP, DCM, 5 days, 95 %; d) *p*TSA, DHP, DCM, 0 °C, 1 h, 99 %; e) see Table 5.

Entry	R =	Reducing Agent	Temperature / °C	Reaction time / h	Yield / % (deprotected / %)
1	OH	$LiAlH_4$	0	2	82 (N/A)
2	OTBS	//	0	2	10 (46)
3	OTBS	//	-40	2	10 (46)
4	OTHP	//	0	1	80 (17)
5	OTHP	//	-20	1	99
6	OTBS	$LiAlH(O^tBu)_3$	r.t.	24	0
7	OTBS	$LiAlH(OMe)_3$	r.t.	24	0

Scheme 77 : Table 5

Reduction of the ester functionality with $LiAlH_4$ was undertaken successfully for **208** and **210** (*entries 1 and 5*) **(Table 5)**. The reaction conditions for the THP protected alcohol **210** needed to be kept below 0 °C to prevent deprotection taking place (*entries 4 – 5*). Reduction in the presence of the silyl protecting

group proved to be far more difficult. Using $LiAlH_4$ at low temperatures (*entries 2 – 3*) reduced **209**, however a considerable amount of deprotection had taken place. It is known that addition of an alcohol to give a 3:1 complex of alcohol:$LiAlH_4$ reduces the reactivity exhibited by $LiAlH_4$.[80] In terms of reactivity[81] it is possible to rank hydride reagents as follows: $LiAlH_4$ > $LiAlH(OMe)_3$ > $LiAlH(O^tBu)_3$ > $NaBH_4$. However both $LiAlH(O^tBu)_3$ and $LiAlH(OMe)_3$ failed to react with **209**. Mitsunobu coupling using the modified Walker method of diol **211** resulted in a poor yield. Alcohol **213** on the other hand afforded **214** in an 84 % yield **(Scheme 78)**. Deprotection proved more troublesome giving poor yields of **214 (Table 6)**. Due to the poor yields encountered in deprotection, a new synthetic route was devised **(Scheme 79)**.

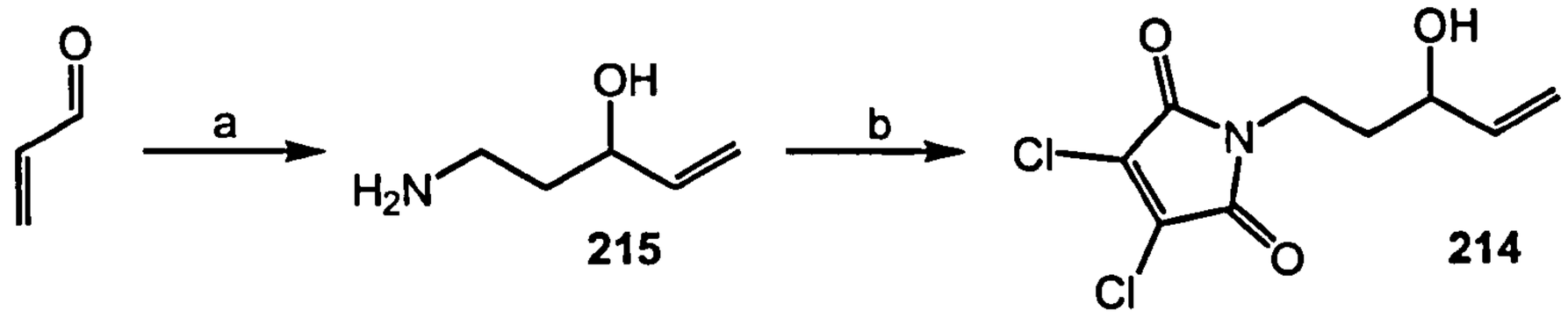


Reagents and Conditions: a) Modified Walker Mitsunobu procedure, 10 % **205** or 84 % **214**; b) see Table 4.

Entry	Conditions	Temperature / °C	Reaction time / h	Yield / %
1	AcOH/THF/H_2O	40	12	19
2	MeOH/*p*TSA	r.t.	12	31
3	$MgBr_2.Et_2O/Et_2O$	r.t.	24	0

Scheme 78 : Table 6

Amino-alcohol **215** had been prepared previously by Tamaru *et al.* in a two step procedure from acrolein.[82] Attack of **215** upon dichloromaleic anhydride under Dean–Stark conditions afforded **214** in a good yield, though a drop in yield was observed on scale-up. However allylic alcohol **214** was provided by a superior 3 stage procedure, with an overall yield of 62 % containing only one purification step.

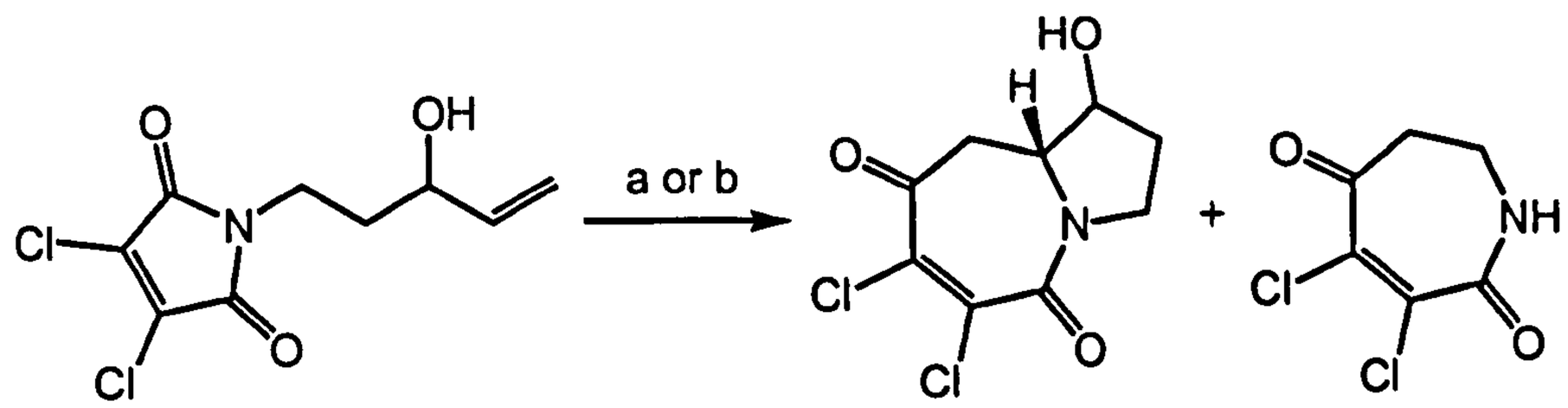


Reagents and Conditions: a) i) MeCN, ^{n}BuLi, THF, -78 °C, 35 min, 98 %; ii) $LiAlH_4$, THF, reflux, 2 h, 86 %; b) dichloromaleic anhydride, toluene, 140 °C Dean–Stark, 50 – 73 %.

Scheme 79

5.10. Photochemistry of allylic alcohol 214

Irradiation of maleimide **214** for 2 h 20 min resulted in a 3:2 d.r. of [5+2] cycloadduct **216** in a 30 % yield **(Scheme 80)**. The yield of this photochemical process was less than adequate, however it was difficult to determine by TLC or ^{1}H NMR the point of the reaction where most of the starting material had been consumed.

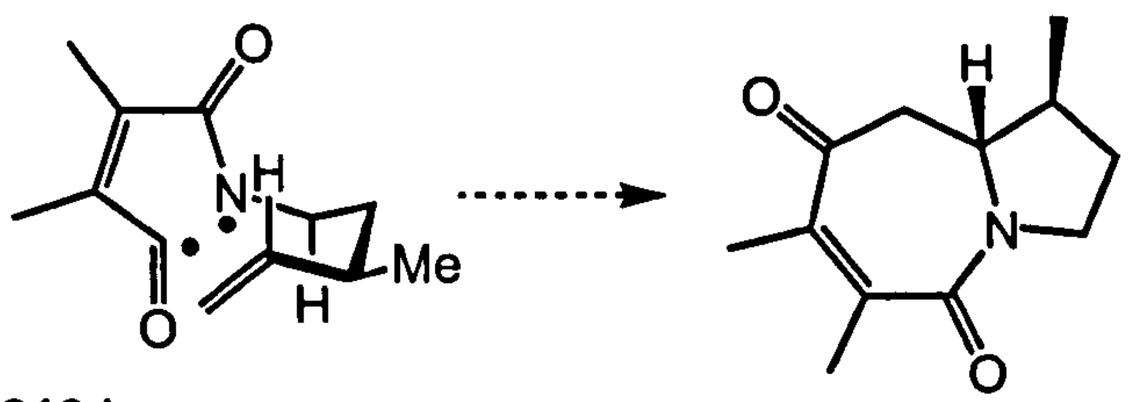


214 **216** 3:2 d.r. **217**

Reagents and Conditions: a) *hv*, Pyrex, MeCN, 2 h 20 min, 29 % **216**; b) *hv*, Pyrex, MeCN, 50 min, 30 % **216** (73 % brsm) and 5 % **217**.

Scheme 80

For this reason a test irradiation time of only 50 min was conducted. The results gave the same yield as before, but with 59 % recovery of starting material **214**. This confirmed that long irradiation times were causing the product to degrade. It is possible that the diastereomer containing two *anti* H's on the pyrrolidine ring is the major diastereoisomer, as this is the case for the photoproduct **219 (Scheme 81)**. It has been postulated by Booker-Milburn *et al.*[41]that the transition state **218** in which the alkenyl side chain adopts a conformation where the allylic group is equatorial, leading to the major isomer **219 (Scheme 81)**.



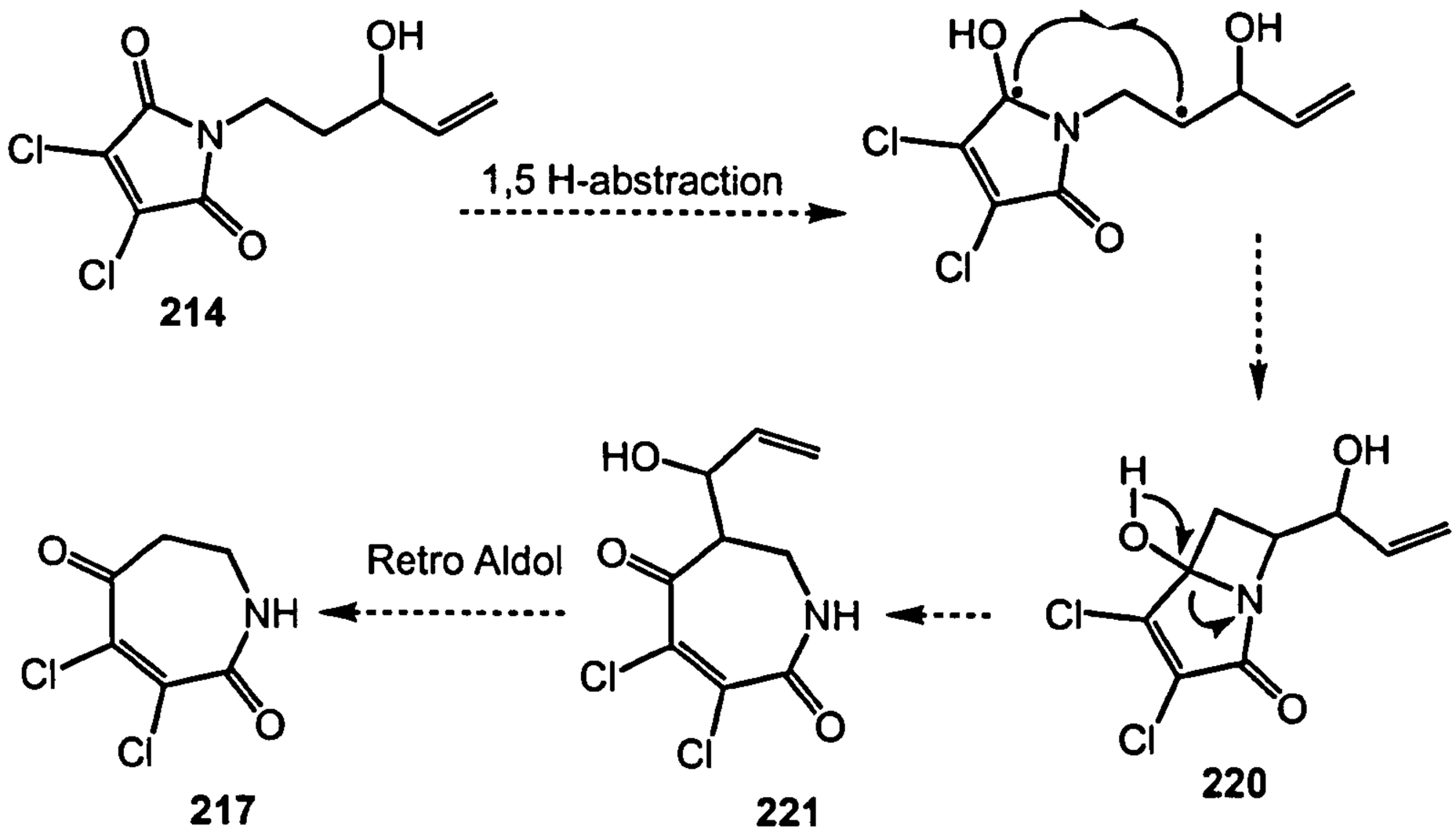
218 Lower energy transition state with allylic group equatorial

219 Observed major isomer

Scheme 81

The diastereomers were separable, and to prove the stereochemistry of **216a** and **216b** careful NOE studies were undertaken. However due to overlapping ^{1}H signals, results were inconclusive.

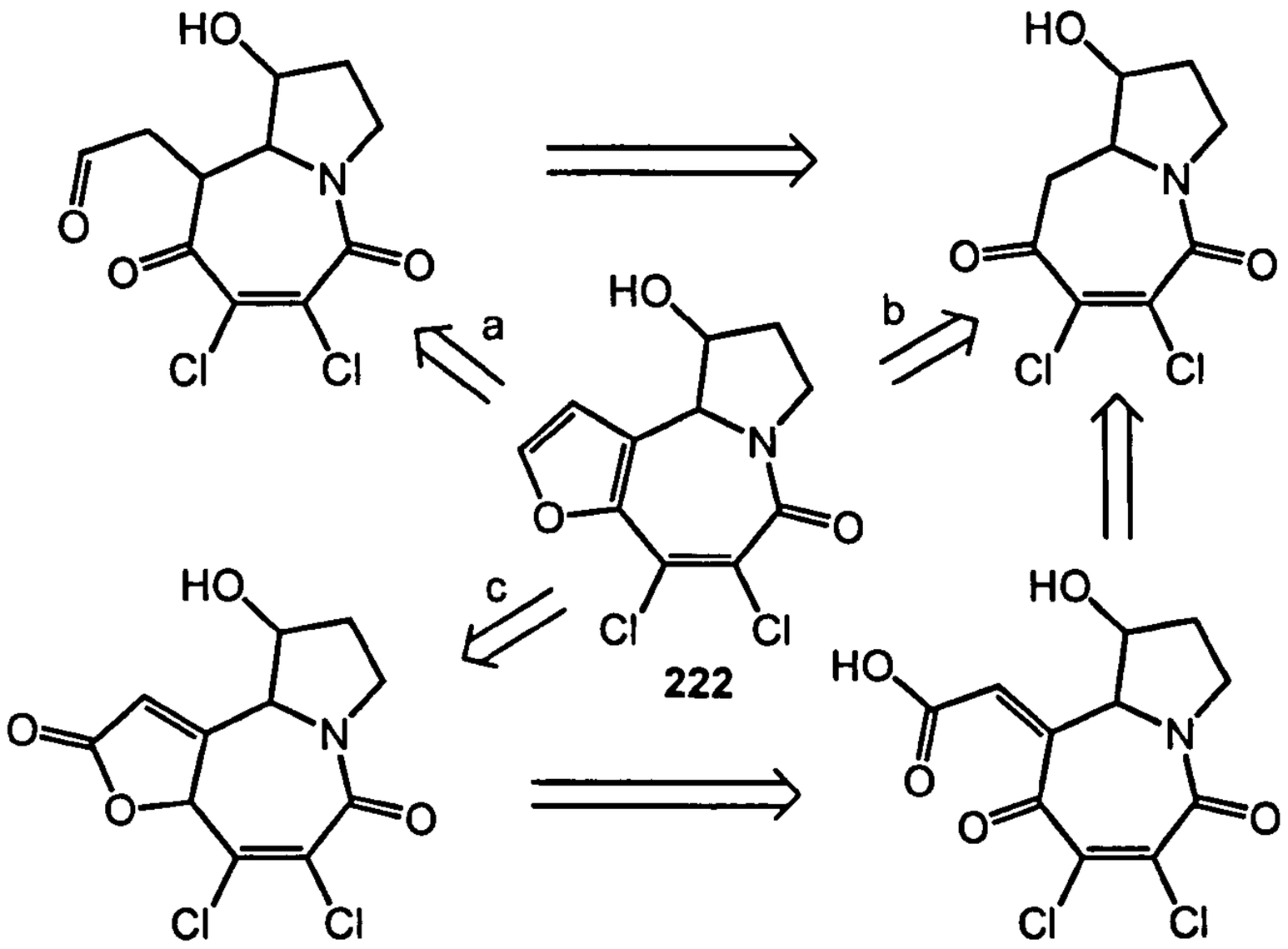
Also observed was azepine **217** albeit in just a 5 % yield. This product could be rationalised by a 1,5 proton abstraction of **214**, cyclisation to **220** followed by fragmentation to give azepine **221**. A retro-aldol process would release acrolein and provide observed adduct **217 (Scheme 82)**.



Scheme 82

5.11. Furan Synthesis

Appropriate disconnections of the furan functionality for **222** can be accomplished in several different ways **(Scheme 83)**. Many routes to furans have been achieved,[83] but the majority are variants on the Paal Knorr method of dehydrating ring closure of 1,4-dicarbonyl substrates (*arrow a*).[84] Classical Feist-Benary synthesis (*arrow b*) relies upon an initial aldol condensation at the carbonyl atom of an *a*-chloroaldehyde, followed by intramolecular ring closure achieved by displacement of halide by enolate oxygen.[85] A very different approach requiring more steps than the previous examples is butenolide reduction (*arrow c*).

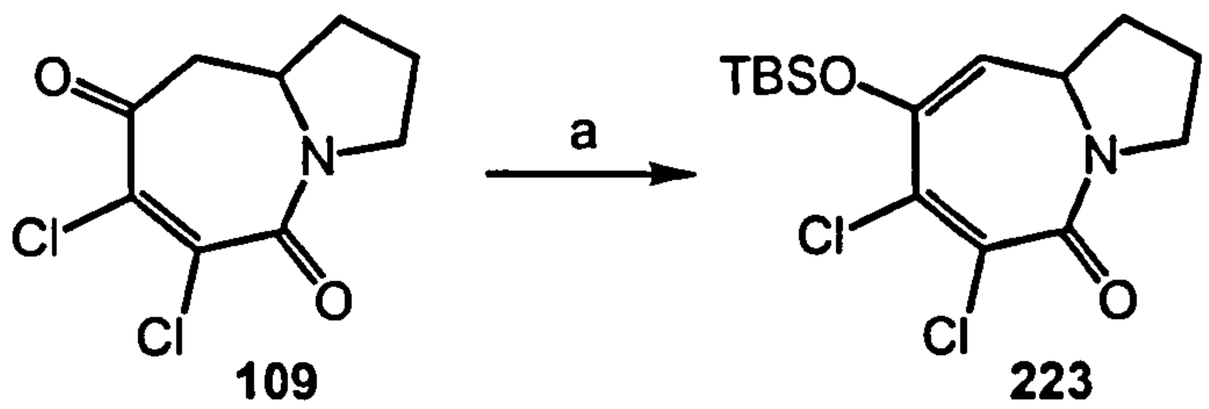


Conditions: a) Paal-Knorr; b) Feist-Benary; c) butenolide reduction.

Scheme 83

5.11.1. Alkylations on [5+2] adducts 109, 216 and 223

For test alkylations, the parent [5+2] cycloadduct **109** was used. Samples of this were donated by a fellow group member, Ben Hook and the preparation is discussed elsewhere.[86] The parent photoproduct was also converted into its subsequent enol ether **223 (Scheme 84)**.



109 **223**

Reagents and Conditions: a) TBSOTf, Et_3N, DCM, 30 min, 95 %.

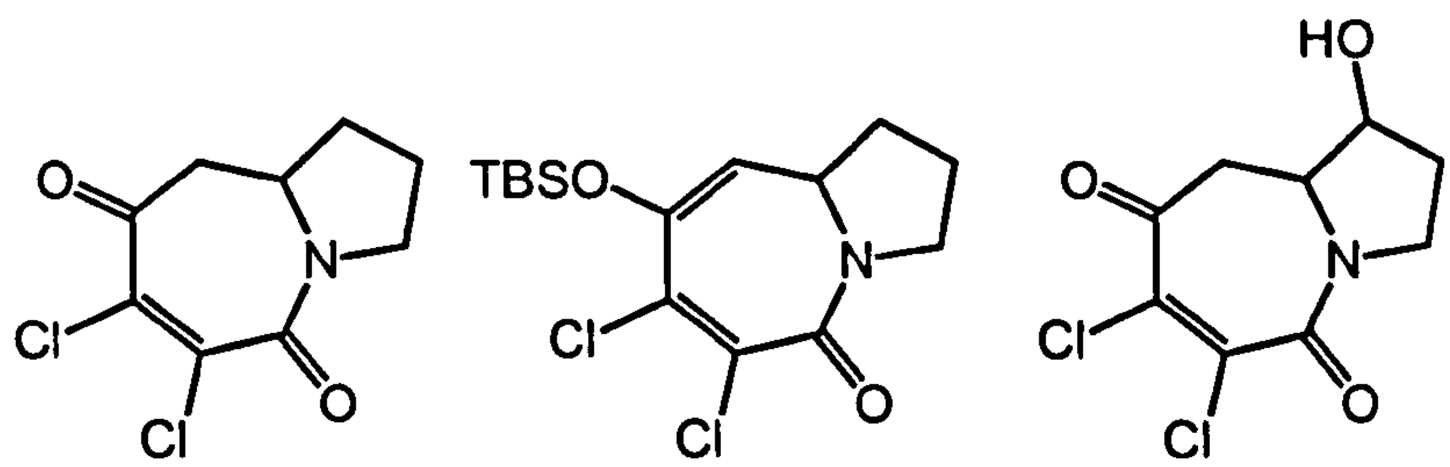
Scheme 84

Further to **109** and **223**, photoadduct **216** was also applied to a wide range of alkylation procedures **(Table 7)**.

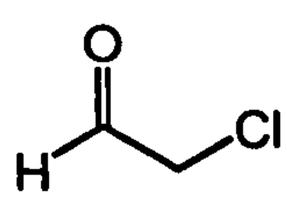
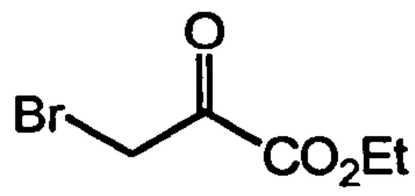
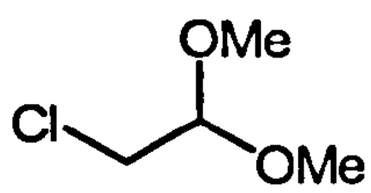
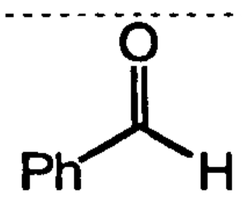
A Feist-Benary procedure by Kanematsu *et al.*[87] using $NaHCO_3$ and 2-chloroacetaldehyde (*entry 1*) did not indicate the formation of any reaction intermediates. Screening of other bases and conditions resulted in either polymeric baseline material or recovery of starting material. Comparable buffered conditions to the alkylation of **109** with glyoxylic acid (see scheme 90) were also used (*entry 4*), however only starting material remained. Under conditions used by Yamaguchi *et al.*[88] with ethyl bromo pyruvate, no reaction took place (*entry 6*). Yet again, altering the procedure (*entries 7 – 9*) was unsuccessful.

A different approach was to use a silyl enol ether in a Mukaiyama aldol condensation.[89] Mukaiyama *et al.* have applied their methodology to create an analogous furan synthesis to the Feist-Benary.[90] The majority of these condensations are undertaken with TMS silyl enol ethers; however their TBS equivalents have been used. Yamamoto *et al.* have utilised the bulkier silyl group to aid in diastereoselective aldol synthesis.[91] Under Mukaiyama's conditions (*entry 10*) enol ether **223** showed no reactivity towards the acetal.

Use of Noyori's catalytic TMSOTf conditions was also ineffective (*entry 11*).[92] The TMS enol ether was produced *in situ* and subjected to Noyori's procedure (*entry 12*), but only recovery of starting material was observed. Noyori has employed catalytic TBAF to a diverse group of silyl enol ethers, with a wide range of electrophiles.[93] Its application to **223** however was ineffective (*entry 13*).



109 **223** **216**

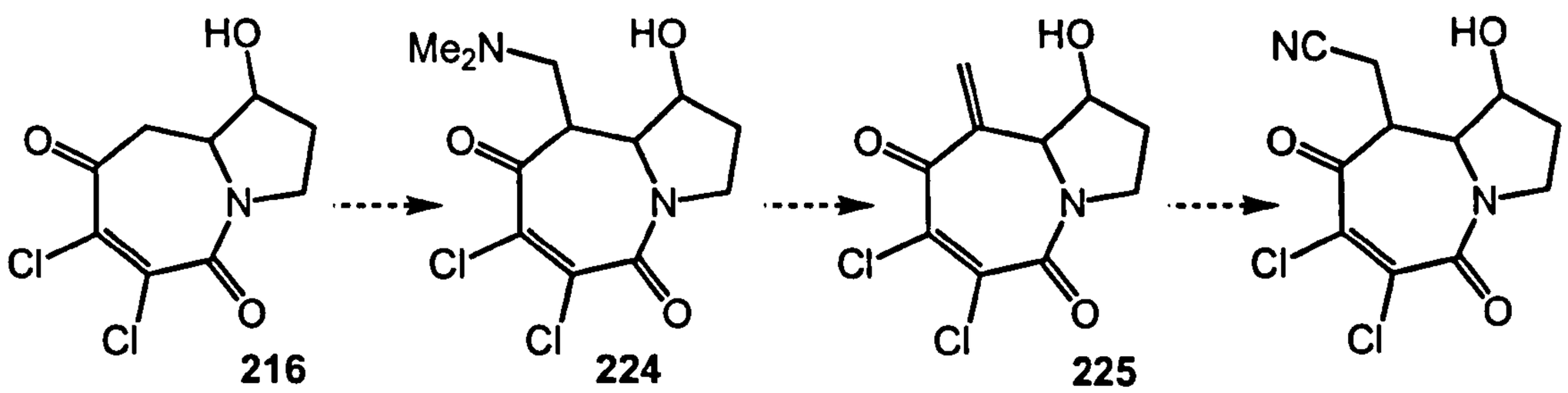
Entry	Nu	E^+	Conditions
1	**109**		$NaHCO_3$, H_2O/DMF, 40 °C
2	"		NaH, DMF, r.t. or -78 °C
3	"		LDA, THF -78 °C to r.t.
4	"		AcOH, cat. NaOH, 4 Å MS, 80 °C
5	**216**[a]		TBAF, Et_3N, THF
6	**109**		NaOMe, MeOH, 65 °C
7	"		NaH, DMF, r.t. or 80 °C
8	"		LDA, THF, -78 °C to r.t.
9	**216**[a]		TBAF, Et_3N, THF
10	**223**		$TiCl_4$, DCM, -78 °C to r.t.
11	"		cat. TMSOTf, Et_3N, DCM
12	**109**		TMSOTf, Et_3N, DCM, -78 °C to r.t.
13	**223**		cat. TBAF, THF -78 °C to r.t.

a) Major diastereomer used

Table 7

5.11.2. Successful 'alkylations'

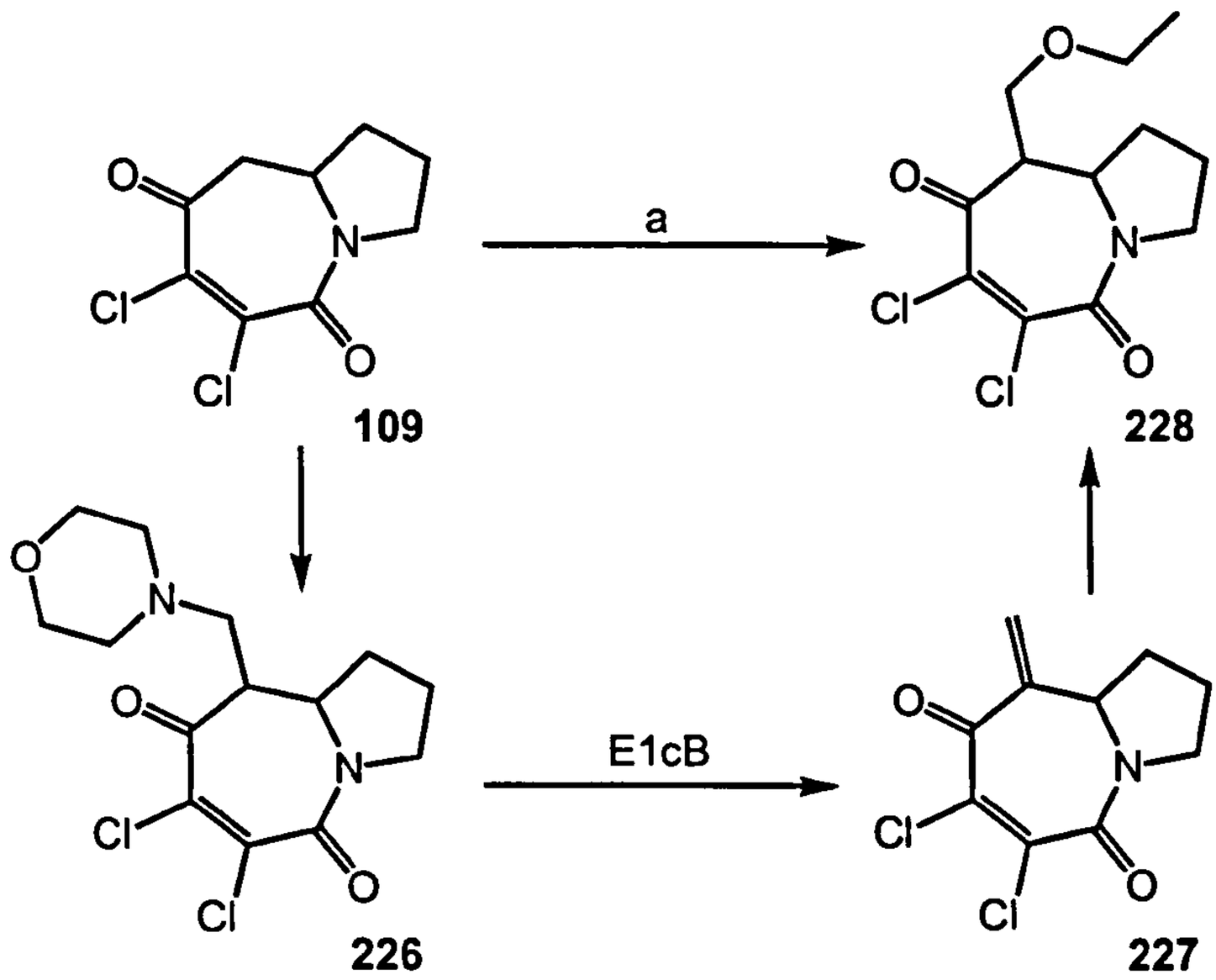
With little success being achieved, attention turned to an alternative strategy. Having discovered incompatibility problems with a variety of bases, it was considered that an acid catalysed Mannich reaction may prove to be more useful. It was proposed that reaction of azepine **216** with an imine salt would give Mannich base **224** and *N*-methylation followed by E1cB elimination to furnish the *exo*-methylene compound **225 (Scheme 85)**. Enone **225** could then be attacked by a suitable nucleophile to provide a substrate that could later be transformed into a 1,4-dicarbonyl.



Scheme 85

Parent photoadduct **109** was subjected to Mannich conditions with formation of the requisite imine salt by condensation of morpholine and paraformaldehyde **(Scheme 86)**. The reaction did not stop at the Mannich base **226**, but underwent E1cB elimination to give enone **227**. Acid catalysis then promoted conjugate addition of the alcohol upon **227**. Switching the solvent to DMF did not lead to any isolatable compounds, although ^{1}H NMR did suggest that *exo*-methylene **227** had been produced.

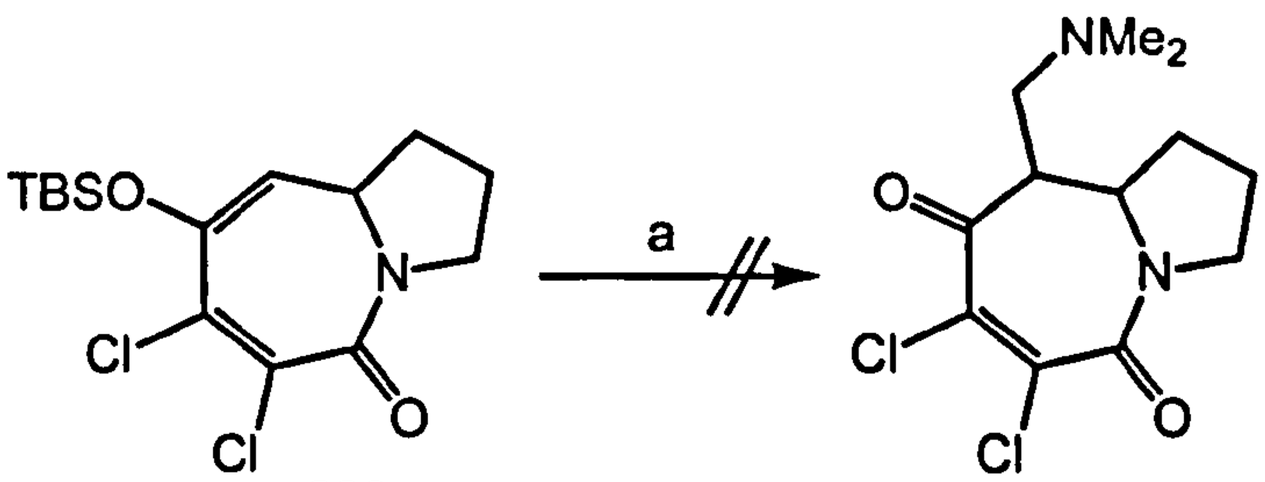
Alternative conditions using silyl enol ether **223** and Eschenmoser's salt with catalytic TBAF, showed no consumption of starting material by TLC. However once one equivalent of TBAF was added, full conversion of enol ether was observed **(Scheme 87)**.



Reagents and Conditions: a) morpholine, paraformaldehyde, HCl, EtOH, reflux, 2 h, 24 %.

Scheme 86

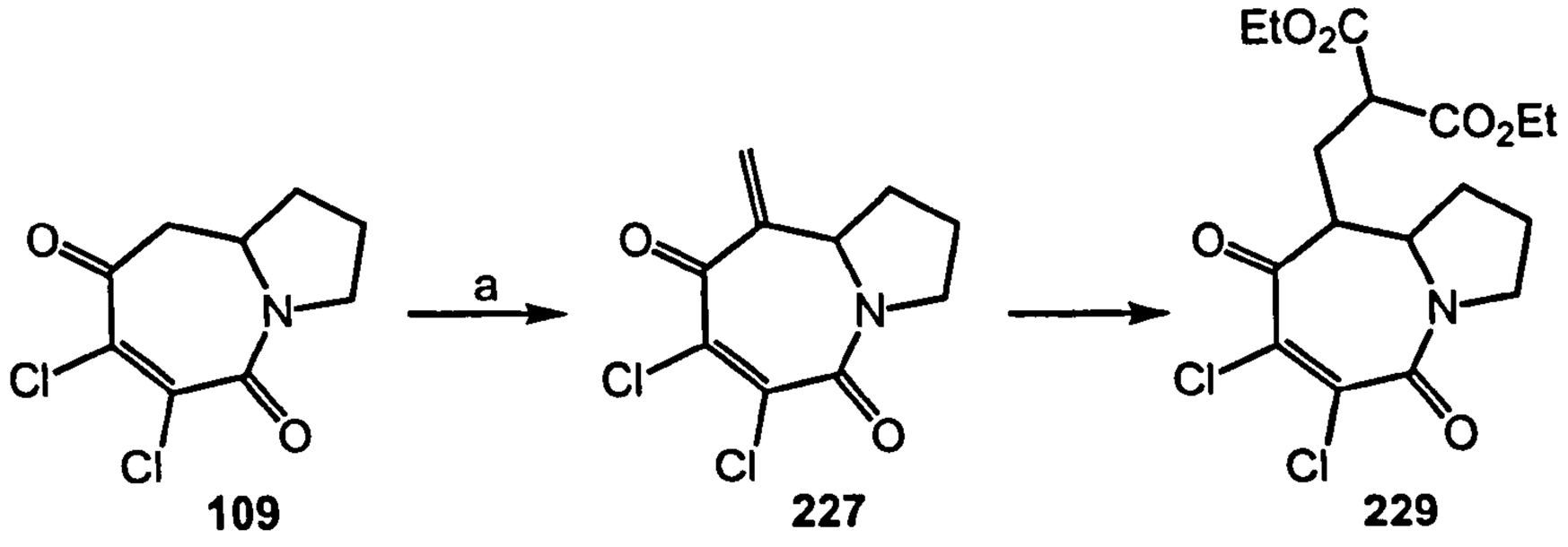
Again ^{1}H NMR suggested that *exo*-methylene **227** had been produced, though wasn't isolated. TBAF may have converted the enol ether into its corresponding ketone, and subsequently either the enol had reacted with the imine salt or TBAF was used as a base to promote this. A trial reaction with azepine **109** and Eschenmoser's salt concluded that the addition of TBAF was required for a reaction to take place.



Reagents and Conditions: a) cat. TBAF, $CH_2{=}NMe_2^{+}I^{-}$, DCM; b) TBAF (1 equiv), $CH_2{=}NMe_2^{+}I^{-}$, DCM.

Scheme 87

It was apparent that the Mannich products were very unstable, but could enone **227** undergo conjugate addition with a nucleophile other than ethanol? To investigate this, diethylmalonate was incorporated into the reaction mixture. This confirmed that the malonate did attack enone **227**, however reaction times were long and poor yields were observed **(Scheme 88)**.

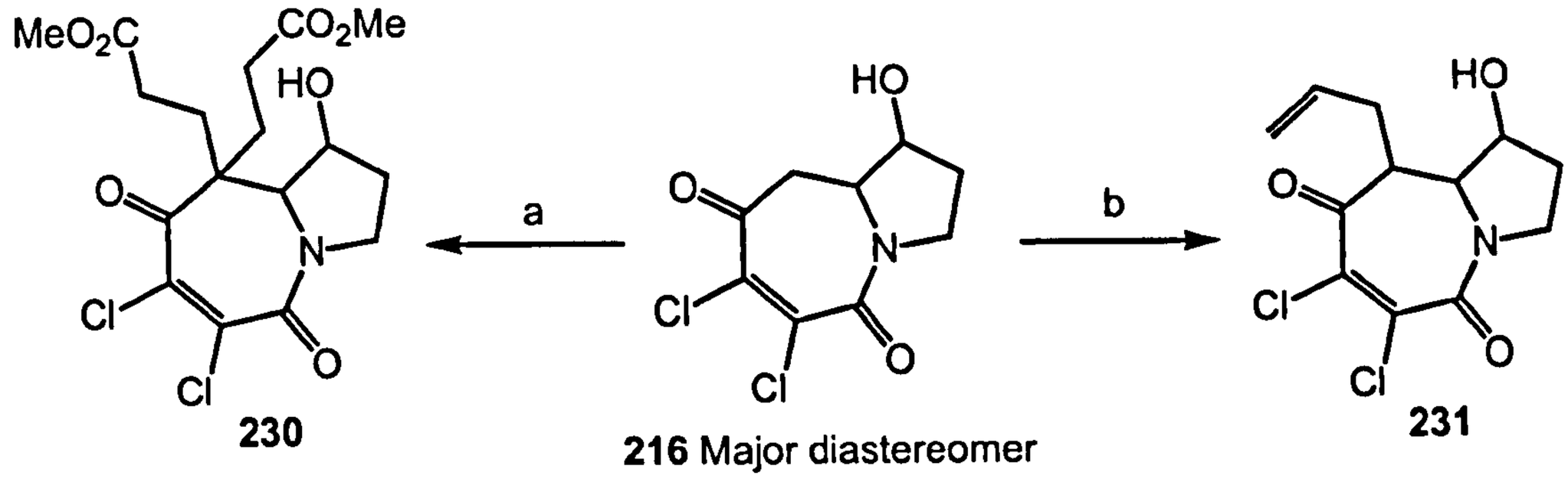


109 **227** **229**

Reagents and Conditions: a) diethyl malonate, $CH_2=NMe_2^+I^-$, TBAF, DCM, 96 h, 16 %.

Scheme 88

To consider whether other electrophiles could be used as an alternative to imine salts, Michael acceptors were investigated. Using catalytic TBAF and excess methyl acrylate provided double addition product **230** in a good yield **(Scheme 89)**.



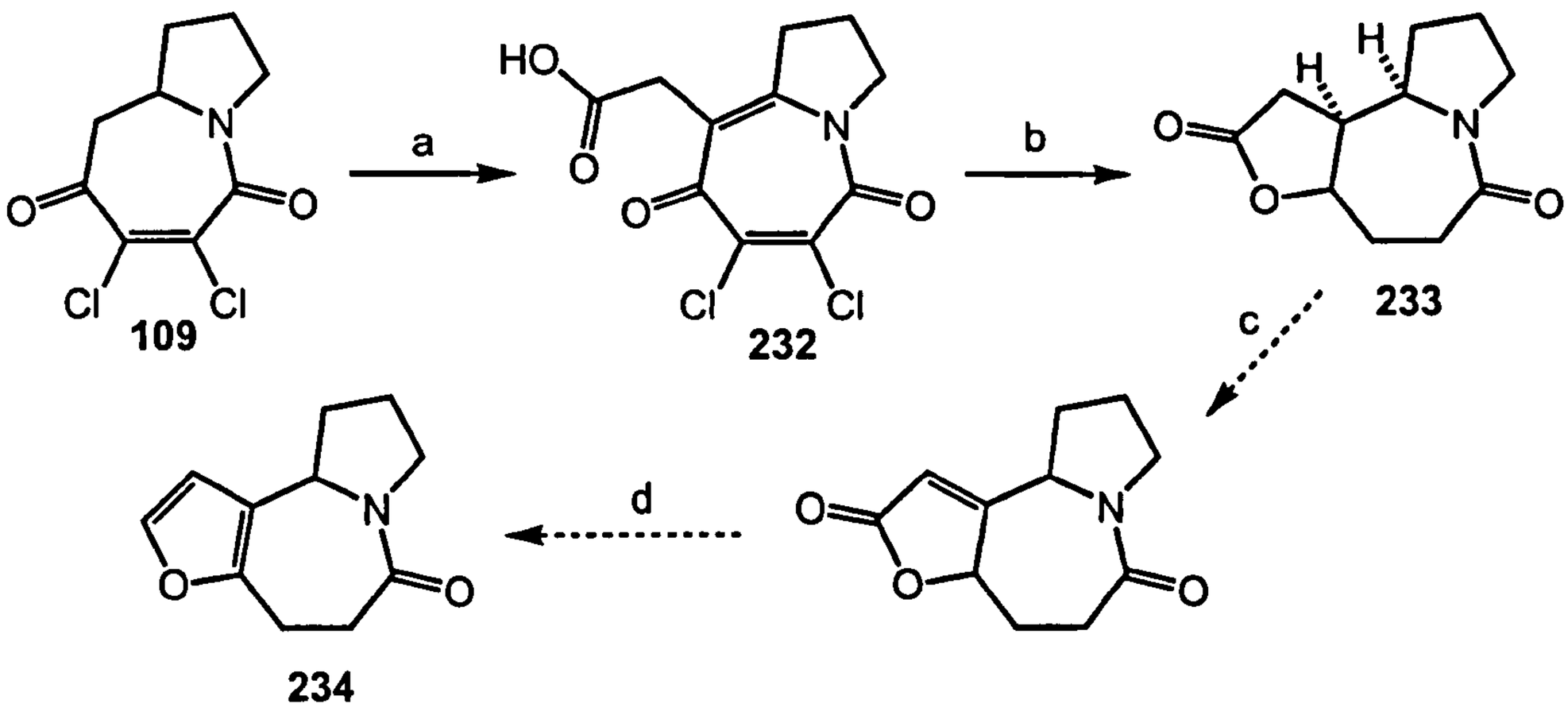
230 **216** Major diastereomer **231**

Reagents and Conditions: a) methyl acrylate, TBAF, THF, 48 h, 70 %; b) allyl bromide, pyridine, TBAF, THF, 24 h, <5 %.

Scheme 89

Unfortunately reducing to one equivalent of acrylate produced poor conversions and resulted in only the double addition product **230**. Mono alkylation was achieved using allyl bromide to give **231**. Unfortunately under various reaction conditions merely trace quantities were isolated. It was thought that perhaps oxidative cleavage of the terminal alkene may have provided the desired 1,4-dicarbonyl for Paal-Knorr furan synthesis.

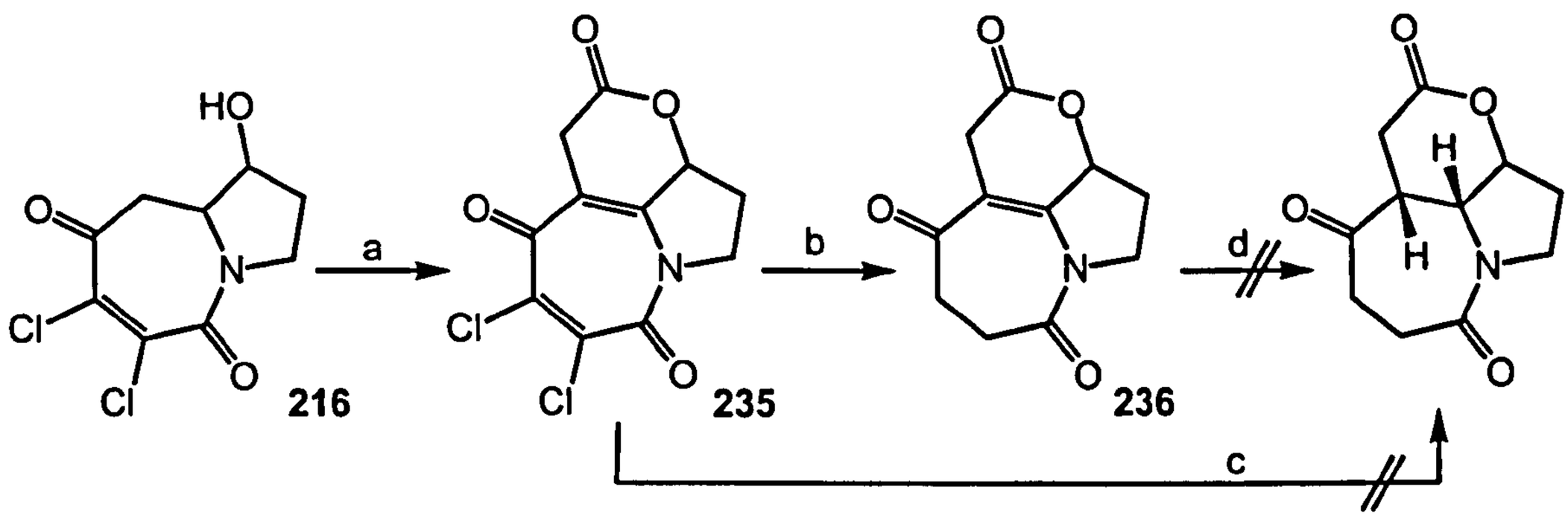
A route towards the synthesis of stemoamide by Hook[86] may possibly be applied for the synthesis of selaginoidine **(Scheme 90)**. Alkylation of photocycloaddition adduct **109** was performed under mild conditions using NaOH as the base, achieving aldol condensation with glyoxylic acid. Elimination and isomerisation followed giving the tetrasubstituted alkene **232** in a good yield. Global hydrogenation afforded lactone **233** in a 78 % yield. There is precedent in literature for the efficient *a*-seleneylation and elimination of a very similar compound to **233** by Sibi *et al.*[94] for the synthesis of stemoamide. Reduction of butenolides has been carried out successfully with DIBAL at -40 °C in excellent yields and may afford **234**.[95]



Reagents and Conditions: a) Glyoxylic acid, NaOH, DMF, 4 Å MS, 80 °C, 1 h 20 min, 67 %; b) i) H_2 (100 atm), Pd/C, MeOH, NaOAc, 45 h; ii) 2 M HCl, 16 h, 78 %; c) i) LiHMDS, PhSeBr; ii) H_2O_2; d) DIBAL.

Scheme 90

Application of the aldol conditions to azepine **216** worked reasonably well, with ring closing of the alcohol to form lactone **235** in a 46 % yield **(Scheme 91)**. Lactone **235** underwent simultaneous reduction and dehalogenation with zinc in acetic acid to afford keto-amide **236** in a 43 % yield. Hydrogenation of **235** and **236** was unsuccessful. Complete consumption of starting material was observed, but only polymeric material was isolated. Due to the low yield of the aldol product and the problems of hydrogenation a new approach was devised. A [5+2] photoproduct containing a substituent alpha to the ketone was desired, thus circumventing the difficulty of alkylation.

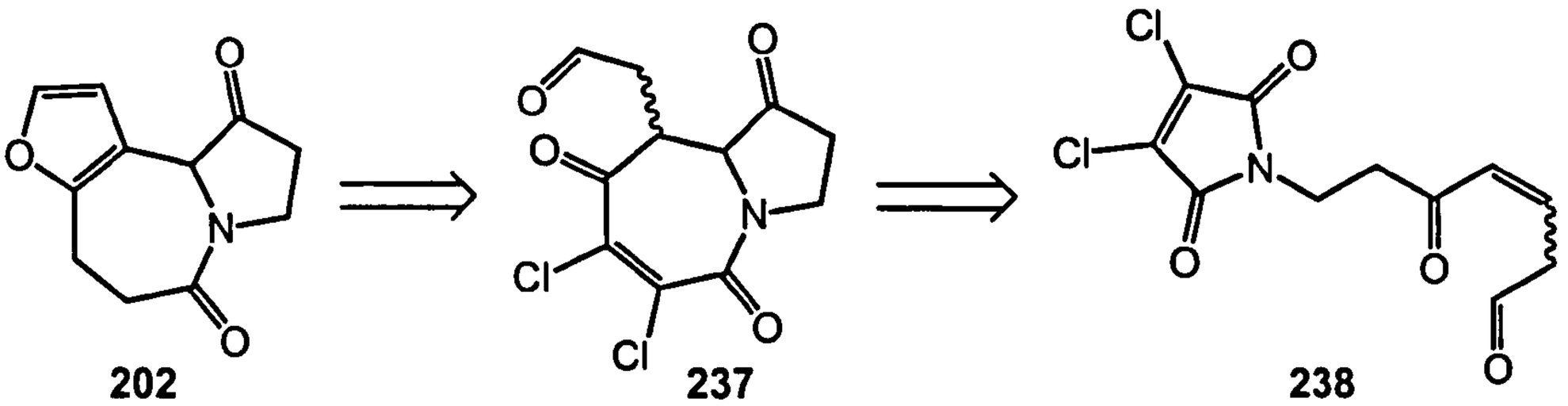


Reagents and Conditions: a) Glyoxylic acid, NaOH, DMF, 4 Å MS, 80 °C, 1 h 20 min, 46 %; b) Zn, AcOH, 10 min, 43 %; c) H_2, Pd/C, K_2CO_3, MeOH, 16 h; d) H_2, Pd/C, MeOH, 16 h;

Scheme 91

5.12. The 4th retrosynthesis of selaginoidine

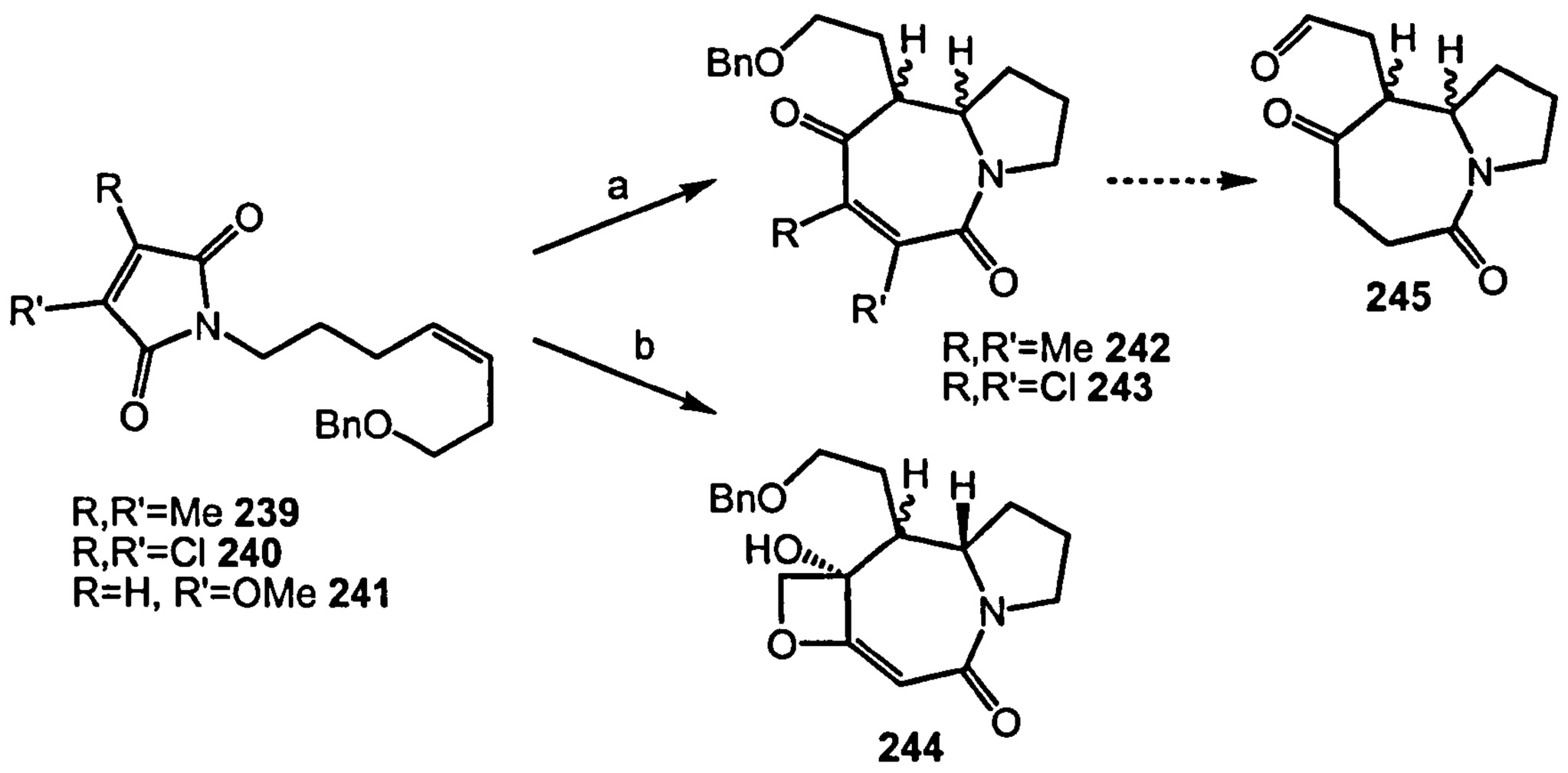
The 3rd retrosynthesis of selaginoidine (see scheme 75) had two disconnection paths leading back to furan **202**. Disconnection of **202** can be carried out in an alternative way. Previously, a Feist-Benary approach was taken for furan synthesis. However a Paal-Knorr disconnection leads to *a*-alkylated photoadduct **237 (Scheme 92)**. This in turn may be accessed from photoprecursor **238**.



Scheme 92

5.13. Methoxy approach

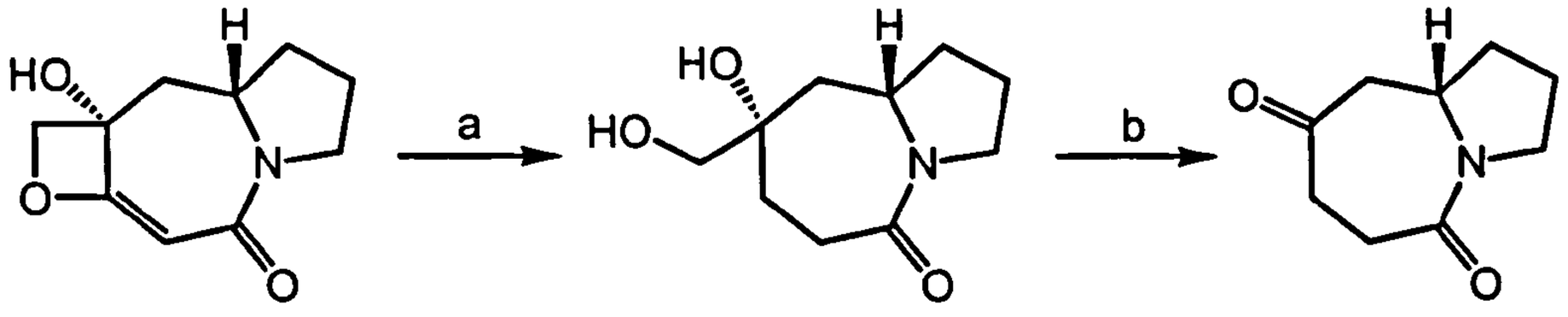
Britton and Baker have carried out photochemical studies on a relevant project towards the total synthesis of stemoamide.[96] Britton photolysed dimethyl **239** and dichloro **240** maleimides producing azepines **242** and **243** which contain alkyl substituents alpha to the ketone **(Scheme 93)**.[96a] Deprotection, followed by oxidation of **243** may lead to 1,4-dicarbonyl **245**, which may then be used towards the synthesis of selaginoidine.



Reagents and Conditions: a) h*v* , Pyrex, MeCN; **242** 64 % 7:1 cis:trans and **243**, 27 % 5:3 cis:trans; b) h*v* , Pyrex, MeCN, 30 min, 55 %.

Scheme 93

Due to poor stereoselectivity, **242** and **243** were however of no use to the synthesis of stemoamide. Baker improved on Britton's work utilising maleimide **241**.[96b] Although **241** was not as high yielding as its' dimethyl derivative, **239**, the removal of the oxetane functionality has been demonstrated in a two step process to give ketone **246** in an overall yield of 83 % **(Scheme 94)**.[96b] Reduction of the methyl groups in **242** is not achieved so easily. In light of Britton and Baker's work, it appeared that methoxy maleimide substrates were better suited than its' dichloro derivative for the synthesis of photoproducts containing *a*-substituents. Its application to selaginoidine was therefore undertaken.

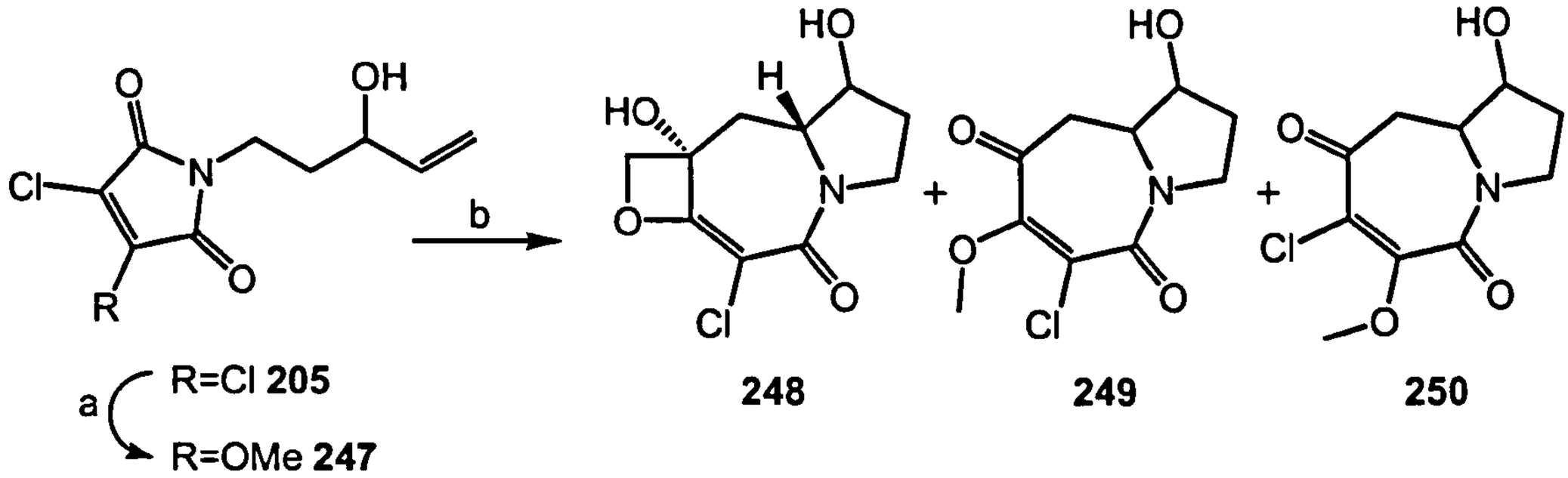


244 **246**

Reagents and Conditions: a) $Pt/C/H_2$, EtOH, 52 h, 83 %; b) $NaIO_4$, $EtOH/H_2$) (4:1), 2 h, 99 %.

Scheme 94

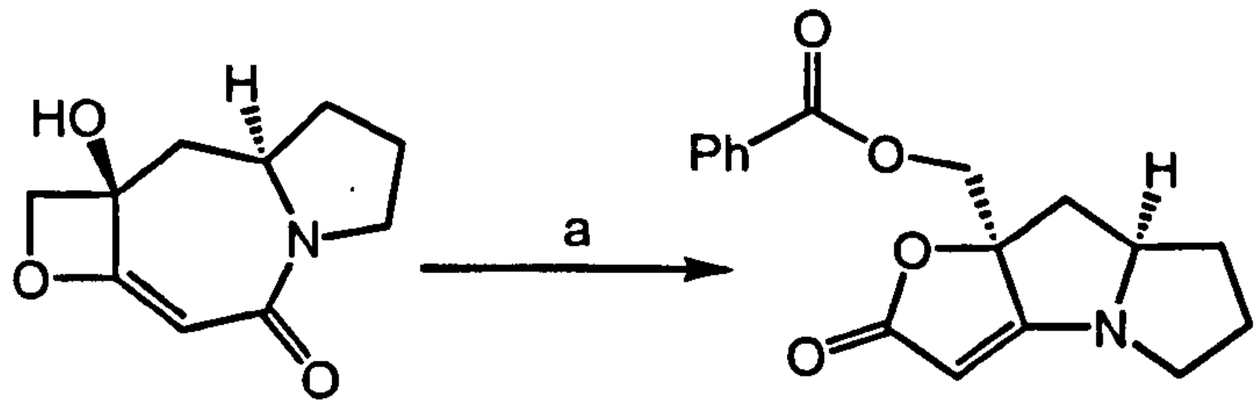
A simple modification to previously synthesised alcohol **205** provided methoxy maleimide **247**. This was then subjected to photolysis to asses whether an allylic hydroxy group would be tolerated **(Scheme 95)**. The first compounds isolated from irradiation of **247** were inseparable and appeared by ^{1}H and ^{13}C NMR to be a mixture of regioisomers **249** and **250** in a 28 % yield. The final compound was identified to be oxetane **248** as a single diastereomer and was recovered in a 40 % yield. Compound **248** was found to be very unstable in solution. This may be attributed to an alcohol-mediated rearrangement of the photoproduct. Baker and Hickford discovered the rearrangement of these photoadducts to tricyclic lactones, such as **251 (Scheme 96)**.[97] The rearrangements worked best under acidic conditions, however by refluxing **244** in ethanol, rearranged products were also observed.



Reagents and Conditions: a) NaOMe, MeOH, 10 min, 48 % (also 24 % dimethyl acetal); b) h*v*, MeCN, 30 min, 40 % **248** and 28 % mix of **249** and **250**.

Scheme 95

It is a possibility that the hydroxy group present on the pyrolidine ring of **248** is participating in such a process leading to dimer and polymer formation. With this in mind, further photochemical precursors of this type must not contain a free hydroxyl group.



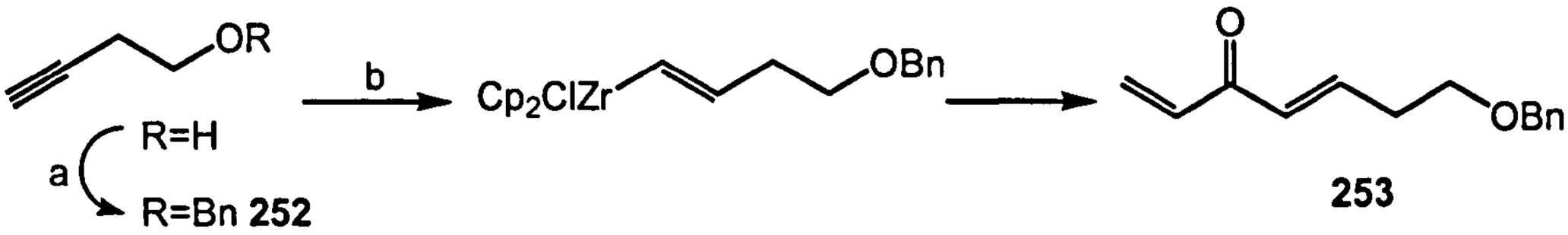
244 **251**

Reagents and Conditions: a) $PhCO_2H$, $MgSO_4$, toluene, reflux, 69 %.

Scheme 96

Because of the relative photochemical success of **247**, a more functionalised compound was synthesised. Firstly, 3-butyn-1-ol was benzylated to give **252**. The alkyne was then treated to a Negishi Type coupling procedure developed by Cox *et al.* and this gave di-enone **253** in good yield **(Scheme 97)**.[98] The beauty of this procedure is that the zirconium species directly transmetallates with the

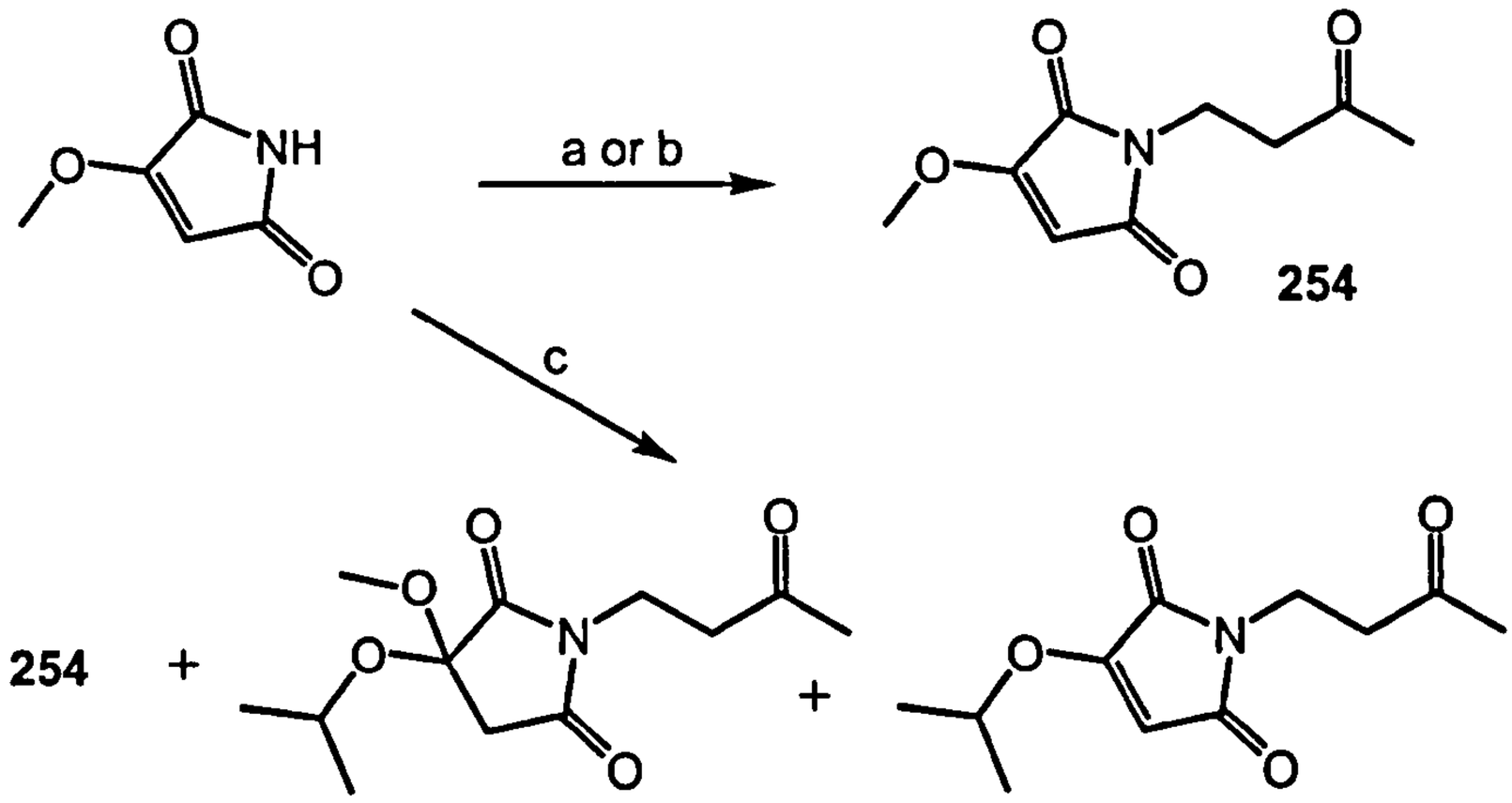
palladium catalyst. In the main, literature procedures require transmetallation of hydrozirconated products to form zincates before further transmetallation with a palladium species.[98]



Reagents and Conditions: a) BnBr, NaH, THF, 0 °C, 97 %; b) Schwartz reagent, toluene, 50 °C, 30 min, then $Pd(PPh_3)_2Cl_2$, acryloyl chloride, r.t., 1 h 30 min, 40 %.

Scheme 97

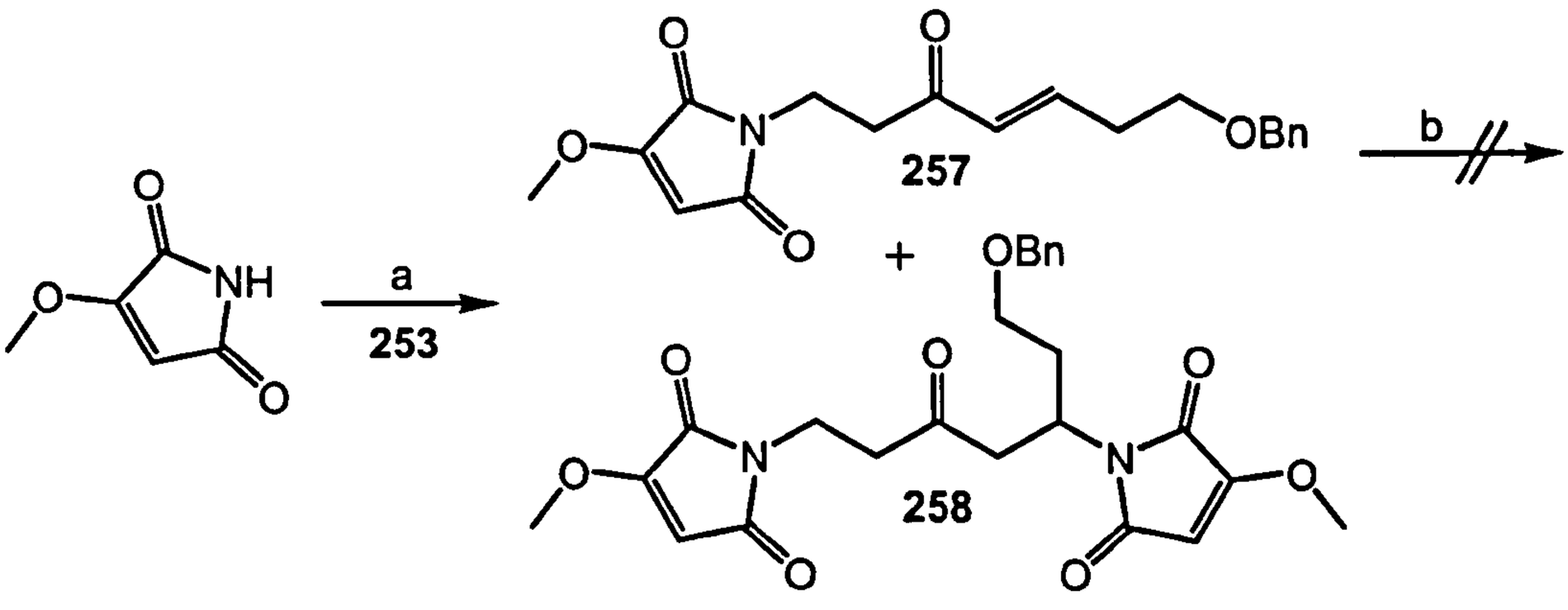
Before methoxy maleimide was used to perform conjugate addition on the di-enone **253** several conditions were tested using methyl vinyl ketone (MVK). There are no reported procedures for the use of maleimides as nucleophiles for conjugate addition. Several methods are reported using phthalimide or its corresponding potassium salt.[99]



Reagents and Conditions: a) MVK, $Bn(Me)_3N^+OH^-$ (40 wt% in MeOH), EtOAc, 80 °C, 15 min, 48 %; b) MVK, Et_3N, K_2CO_3, ^tBuOH, 80 °C, 3 h 30 min, 67 %; c) MVK, Et_3N, K_2CO_3, IPA, 80 °C, 2 h, 33 % **254**, 15 % **255** and 12 % **256**.

Scheme 98

Formation of the methoxy maleimide salt is not an option, as this would perform conjugate addition upon itself. Mild conditions are therefore required. The use of Triton B as a base has been used with phthalimides. With methoxy maleimide it was established that better results were achieved using catalytic amounts of Triton B **(Scheme 98)**. Following a procedure designed for 1,4-addition with succinimides[100], attack of the solvent IPA on the maleimide was observed. Prevention of this attack was achieved by using a more hindered alcohol as the solvent. This gave a 67 % yield on our model system. Application of these techniques on di-enone **253** gave contrasting results. The lower yielding method for MVK with Triton B afforded a similar result producing the photoprecursor **257** in a 40 % yield. Also isolated was 10 % of the double addition product **258 (Scheme 99)**. Surprisingly the conditions that were superior for MVK only afforded recovery of starting material. Nonetheless, enough compound was available for photolysis.

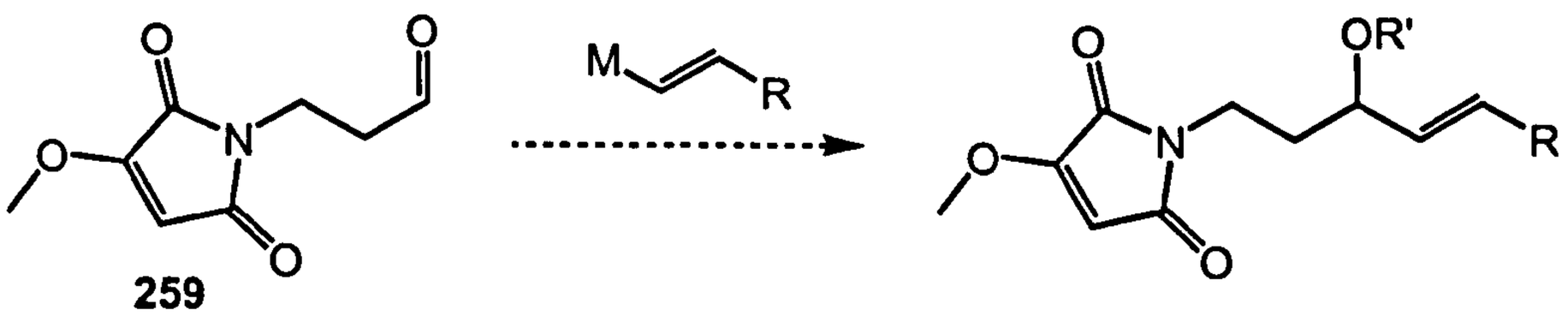


Reagents and Conditions: a) **253**, $Bn(Me)_3N^+OH^-$ (40 wt% in MeOH), EtOAc, 80 °C, 1 h 30 min min, 40 %; b) h*v*, Pyrex, MeCN, 40 min.

Scheme 99

Irradiation for 40 min consumed the majority of the starting material, without the observation of any isolatable products. An explanation as to why this was unsuccessful compared to Britton and Bakers results[96] could be due to the introduction of an sp^2 centre in the *N*-alkenyl chain. Reducing the chain flexibility

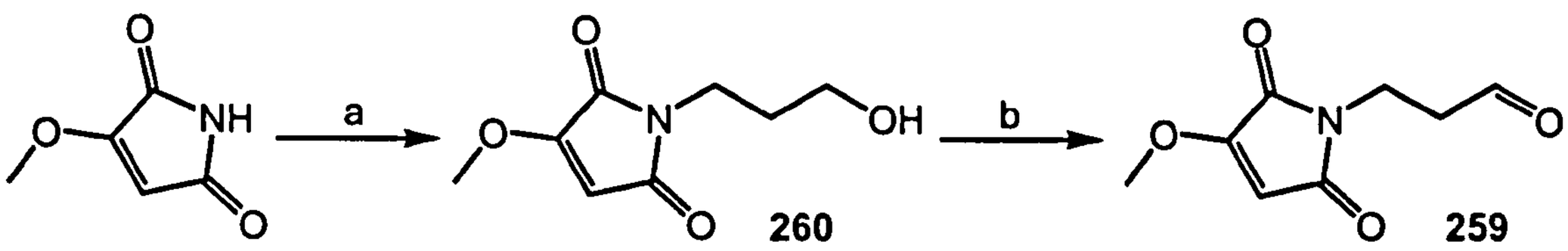
could prevent the exocyclic double bond being delivered to the amide, where [5+2] photocycloaddition occurs. The enone unit of the chain could also be effectively quenching the excited state of the maleimide by intersystem crossing, thus preventing turnover of the substrate. With this in mind, a synthesis was required of a methoxy maleimide compound with an *N*-alkenyl chain that did not contain hydroxyl groups, enone functionality or inflexibility. It was envisaged that such a compound could be accessed from attack of an organometallic reagent upon aldehyde **259**, followed by protection of the allylic alcohol **(Scheme 100)**.



259

Scheme 100

Aldehyde **259** was prepared from a two step procedure: Firstly by alkylation of methoxy maleimide under basic conditions with 3-bromo-1-propanol furnishing alcohol **260**; secondly, Dess-Martin oxidation to **259**. These two steps produced a 42 % yield of **259 (Scheme 101)**.

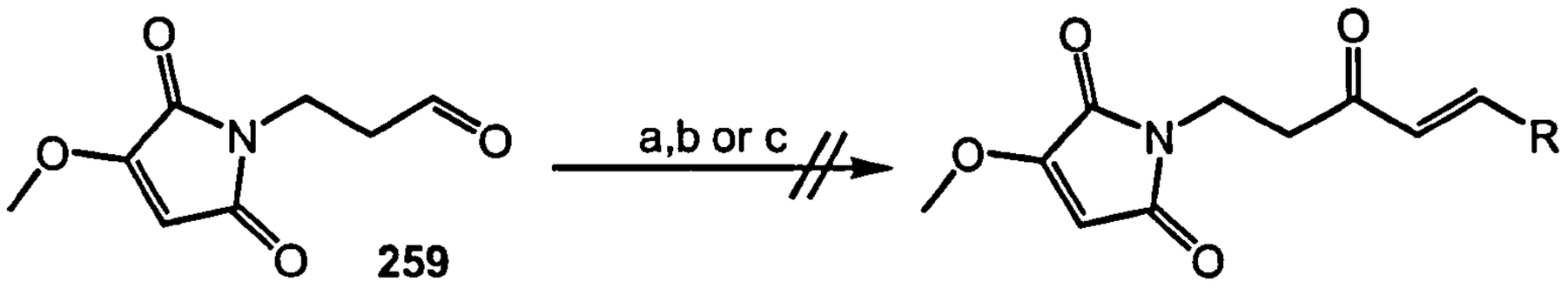


260 **259**

Reagents and Conditions: a) 3-bromo-1-propanol, K_2CO_3, MeCN, reflux, 3 h 15 min, 67 %; b) DMP, DCM, 2 h, 63 %.

Scheme 101

Unfortunately attempts to react aldehyde **259** with several organometallic reagents were ineffective, possibly due to the susceptibility of **259** to 1,4-addition **(Scheme 102)**. While further methods are still to be tried, some similar approaches using dichloro maleimides were attempted.

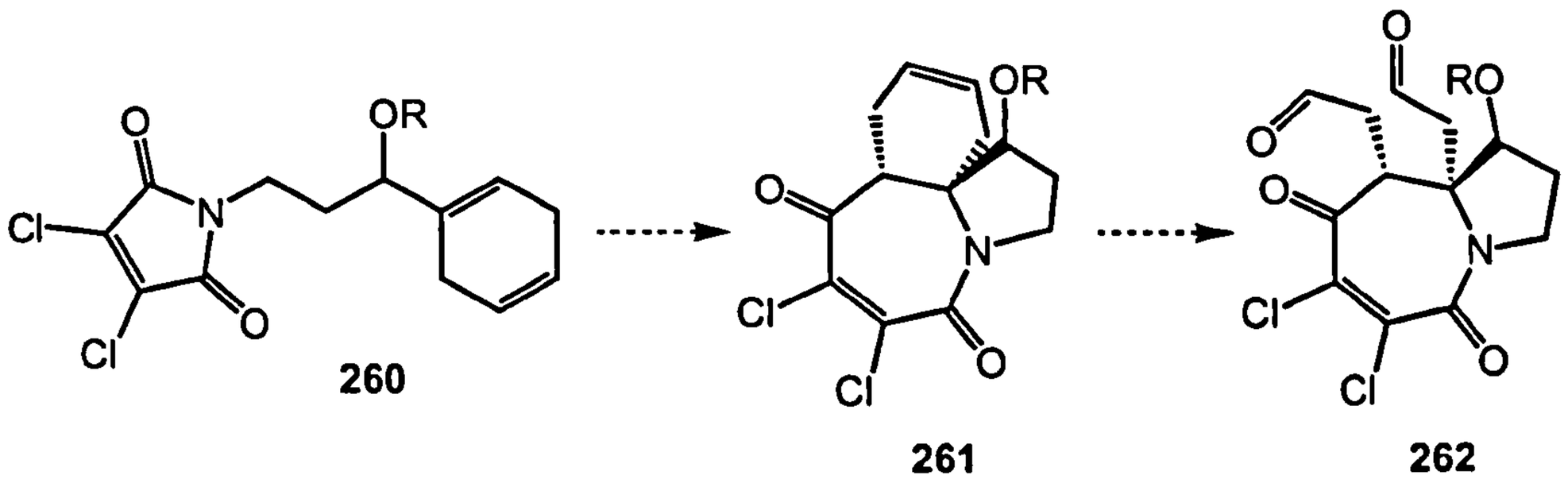


Reagents and Conditions: a) vinyl magnesiumbromide, -78 °C to r.t.; b) vinyl bromide, $CrCl_2$, $NiCl_2$, DMF, 0 °C to r.t.; c) **252**, Schwartz reagent, DCM, 30 min, then Me_2Zn, 0 °C 30 min, then **259**.

Scheme 102

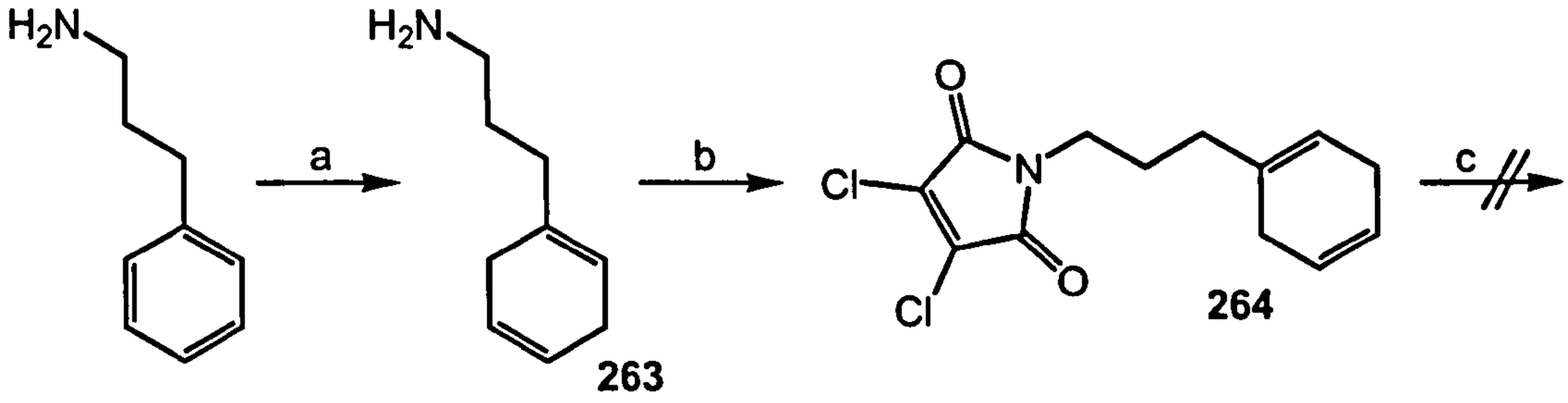
5.14. Dichloro approach

It was proposed that a maleimide such as **260** may undergo [5+2] photocycloaddition to afford compound **261 (Scheme 103)**. Following oxidative cleavage this may access **262**, which not only contains the desired 1,4-dicarbonyl, but also the quaternary centre present in selaginoidine.



Scheme 103

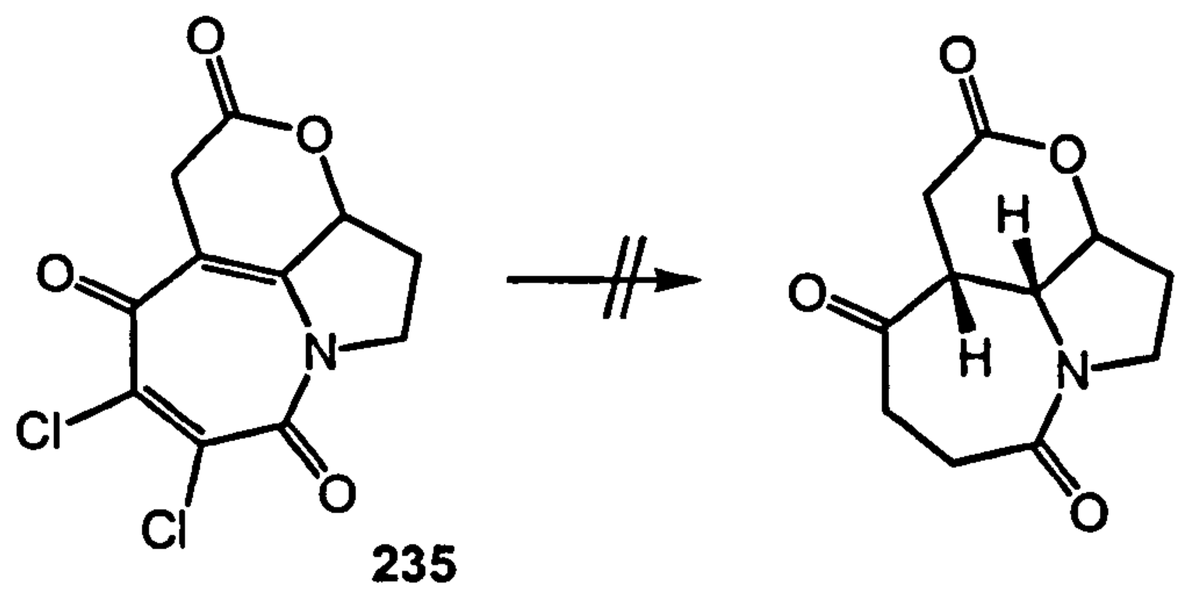
Literature compound **263** was synthesised from a Birch reduction of 3-phenylpropyl-1-amine **(Scheme 104)**.[101] Amine **263** was then coupled to dichloromaleic anhydride under Dean-Stark conditions in good yield. Irradiation of maleimide **264** did produce two distinct new compounds by TLC; however these were unidentifiable by NMR and appeared to be polymeric materials.



Reagents and Conditions: a) Li, NH_3, EtOH, -33 °C, 24 h, 99 %; b) dichloromaleic anhydride, toluene, 140 °C Dean–Stark, 3 h, 70 %; c) h*v*, Pyrex.

Scheme 104

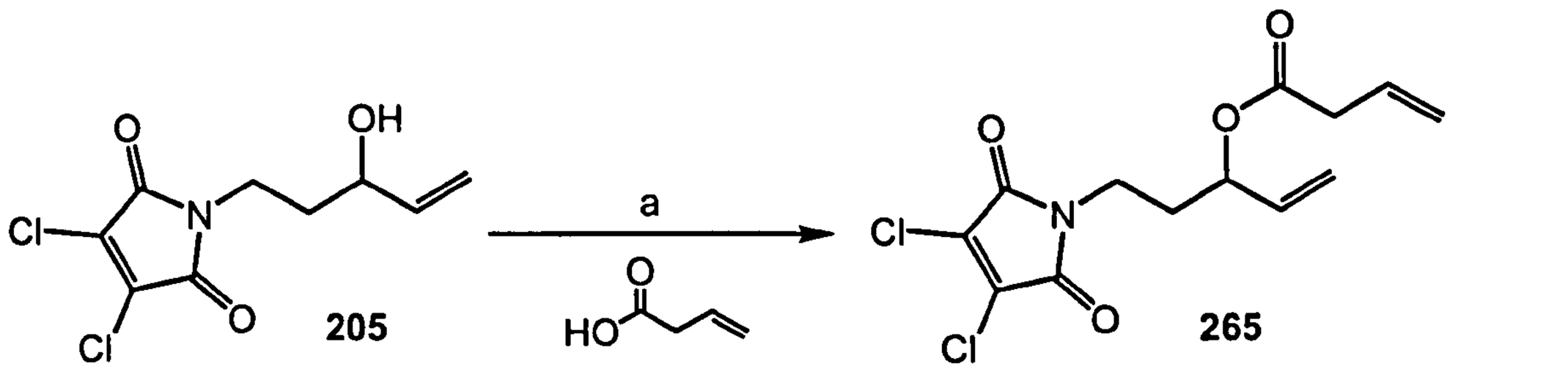
Earlier success was encountered with the construction of **235**; however reduction of the tetrasubstituted alkene present in the lactone ring proved to be problematic **(Scheme 105)** (also see scheme 91). Further elaboration towards selaginoidine can be achieved if a similar photoproduct can be prepared, without the inclusion of the troublesome alkene.



Scheme 105

Using previously synthesised alcohol **205**, the coupling of vinyl acetic acid (VAA) was attempted under several different procedures **(Scheme 106, Table 8)**. Disappointingly, literature procedures for coupling of VAA (*entries 1 and 2*) gave little success.[102] Both Mitsunobu and acyl chloride coupling (*entries 4 and 5*) gave a 39 % yield of ester **265**. Although these methods were not high yielding,

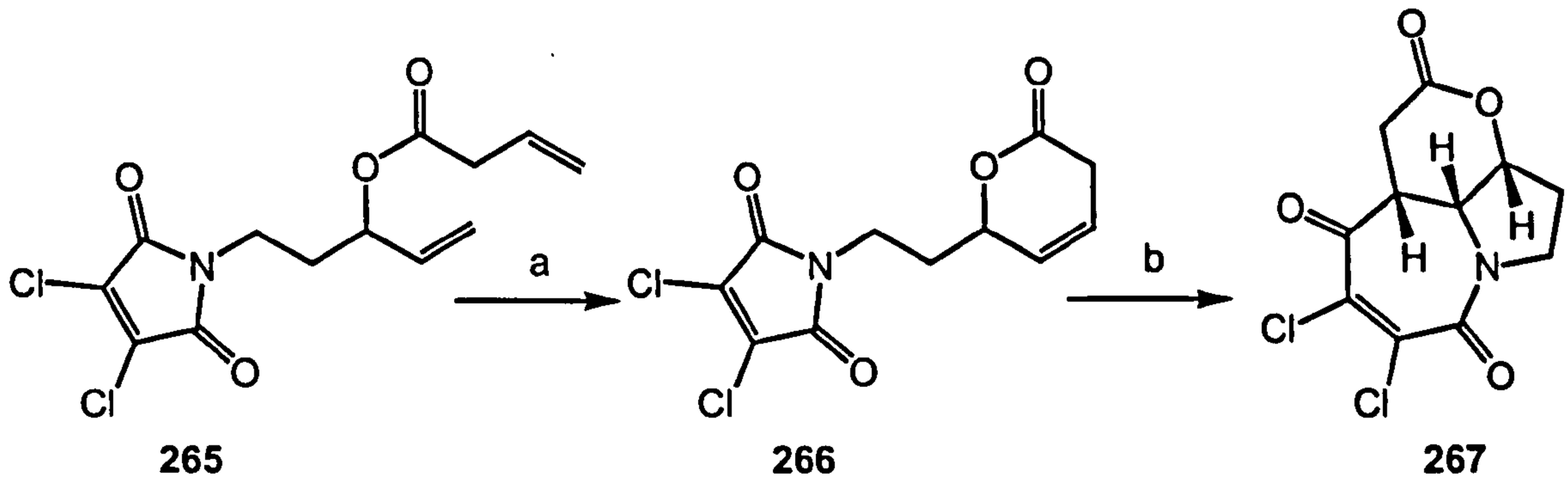
sufficient compound was brought through to trial the metathesis and photochemical steps.



Entry	Conditions	Yield / %
1	DCC, DMAP, DCM[102a]	13
2	*p*TSA, $CHCl_3$, Reverse Dean-Stark[102b]	0
3	CMPI, Et_3N, DCM, reflux	0
4	PPh_3, DIAD, THF, -78 °C to r.t.	39
5	DMF, oxalyl chloride, DCM	39

Scheme 106 : Table 8

The synthesis of *d*-lactones by Wang *et al*. has been achieved by RCM with Grubbs' first and second generation catalysts producing largely 90+ % yields.[102b] Since Wang observed higher yields with the second generation catalyst, this was employed for RCM of ester **265 (Scheme 107)**.



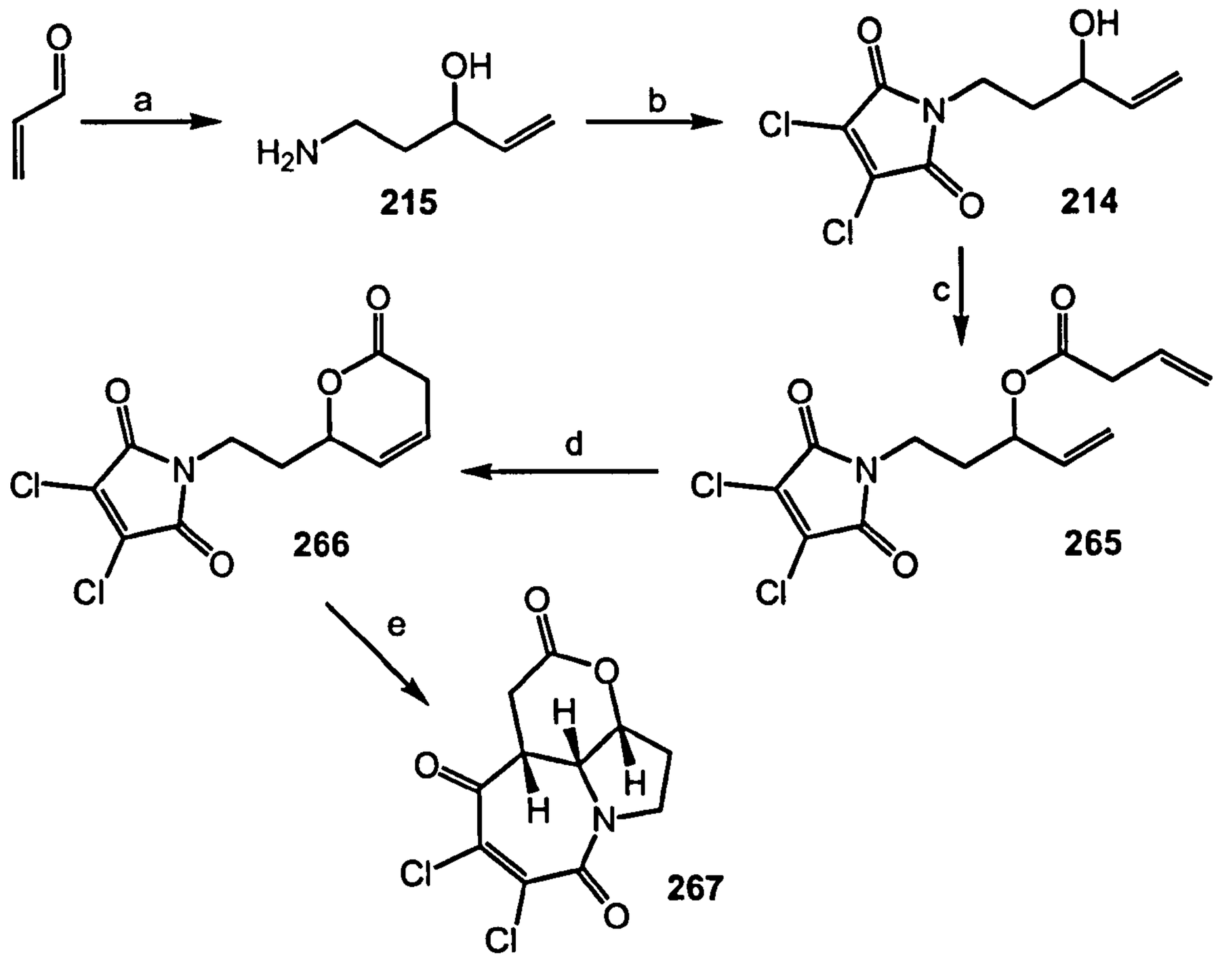
Reagents and Conditions: a) Grubbs II, DCM, 24 h, 67 % (74 % brsm); b) h*v*, Pyrex, MeCN, 58 % (74 % brsm).

Scheme 107

Ring Closing Metathesis was undertaken at room temperature with 1 mol% of Grubbs II catalyst at a concentration of 0.01 M, affording *d*-lactone **266** in a 67 % yield with a recovery of 10 % **265**. Gratifyingly, irradiation of **266** produced only the [5+2] cycloadduct as a single diastereomer in a 74 % yield based on recovered starting material. The photochemistry of **266** in a batch reactor provides a high mass recovery. This makes **266** an excellent candidate for scale-up, utilising a continuous-flow photochemical flow reactor developed by Booker-Milburn *et al.*[103] This will provide cycloadduct **267** in multigram quantities and should increase the yield of the photochemical process, by reducing dimerisation of the photoadduct.

5.15. Conclusion

Four different approaches were investigated towards the total synthesis of selaginoidine. The first two approaches would have led to advanced synthetic intermediates had irradiation of **179**, **190**, **193** and **194** not demonstrated a preference for the [2+2] cycloaddition process. The reason for this selectivity could have been due to quenching from the diene functionality. Another explanation was that the *N*-alkenylated chain could not deliver the exocyclic double bond to the amide, where [5+2] photocycloaddition occurs. For this reason, a third disconnection utilising an undemanding substrate that retained the conformational flexibility of the *N*-alkenylated chain was attempted. Unfortunately elaboration of the photochemical product was difficult, particularly with *a*-alkylation. With this in mind a fourth strategy was undertaken whereby *a*-alkylation was avoided. This route has proven to be highly successful and rapidly affords an intermediate that may well be successful for the synthesis of selaginoidine **(Scheme 108)**. The work on selaginoidine was carried out in parallel with that of neostenine (see section 6.). Unfortunately this meant no further time could be spent on completing the total synthesis of selaginoidine.



Reagents and Conditions: a) i) MeCN, ^{n}BuLi, THF, -78 °C, 35 min, 98 %; ii) $LiAlH_4$, THF, reflux, 2 h, 86 %; b) dichloromaleic anhydride, toluene, 140 °C Dean–Stark, 50 – 73 %; c) PPh_3, DIAD, THF, -78 °C to r.t., 39 %; d) Grubbs II, DCM, 24 h, 67 % (74 % brsm); e) hν, Pyrex, MeCN, 58 % (74 % brsm).

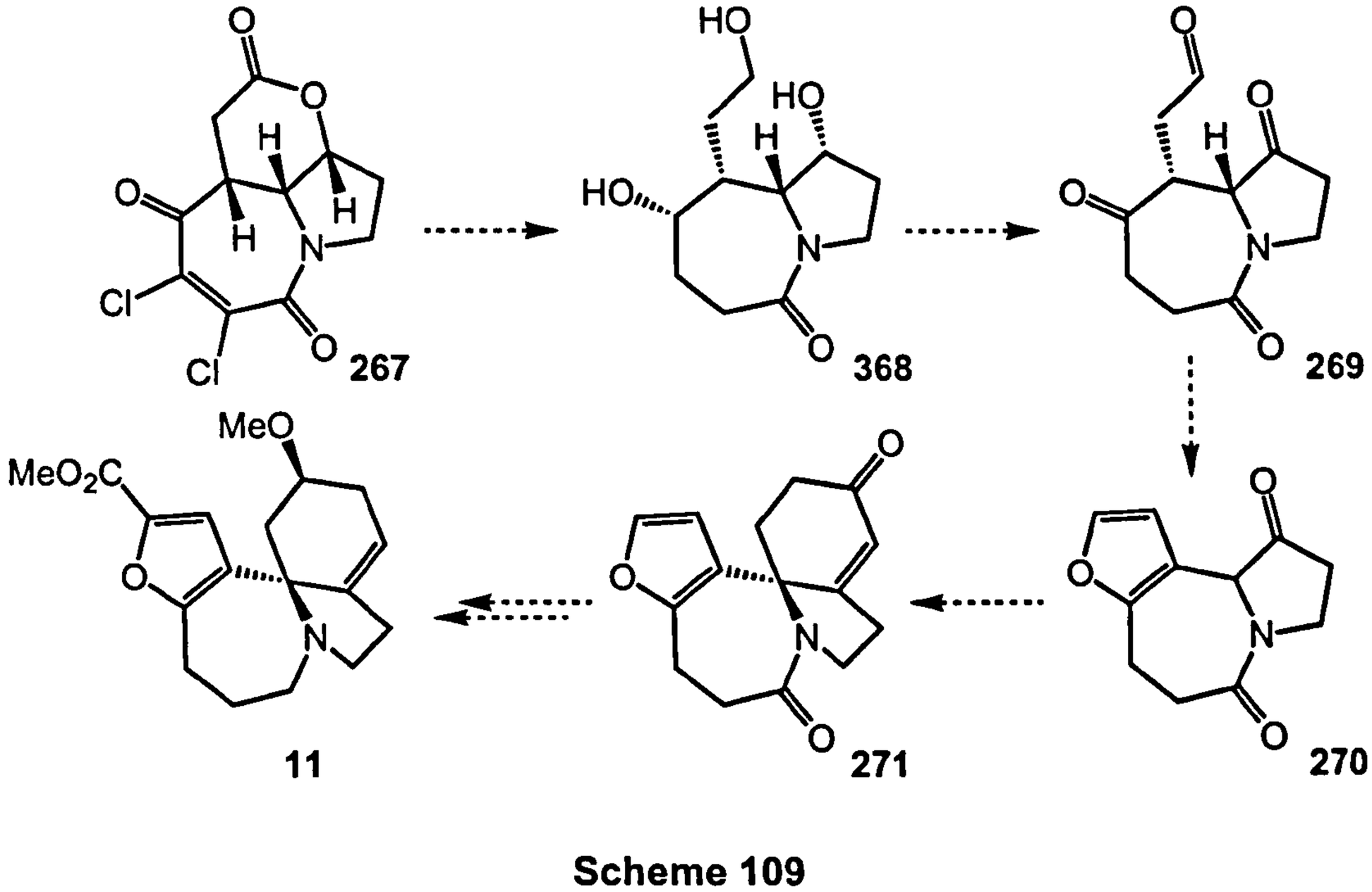
Scheme 108

5.16. Future work

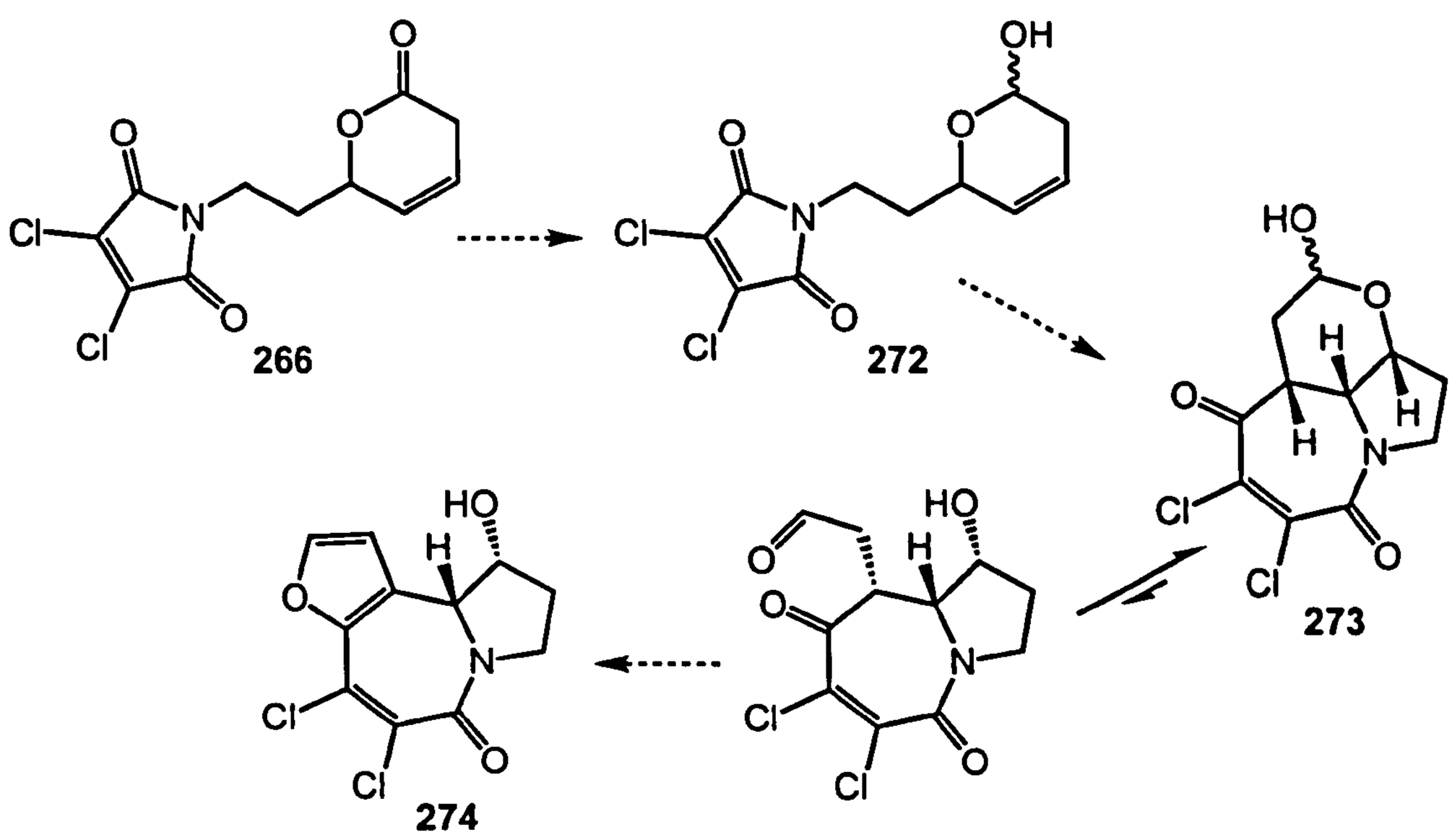
To synthesise the furan, compound **267** could undergo reduction to triol **268**. Upon oxidation of **268**, a desired 1,4-dicarbonyl **269** may be achieved. Dehydration under acidic conditions may furnish furan **270 (Scheme 109)**.

Construction of the cyclohexene ring may be achieved using a Robinson annulation strategy to give **271**, forming the tetracyclic structure of selaginoidine.

A slightly alternative approach would be to reduce the lactone to lactol **272** prior to [5+2] cyclisation **(Scheme 110)**. Irradiation could achieve photoadduct **273** that may, under dehydration, afford the desired furan **274**.



Scheme 109

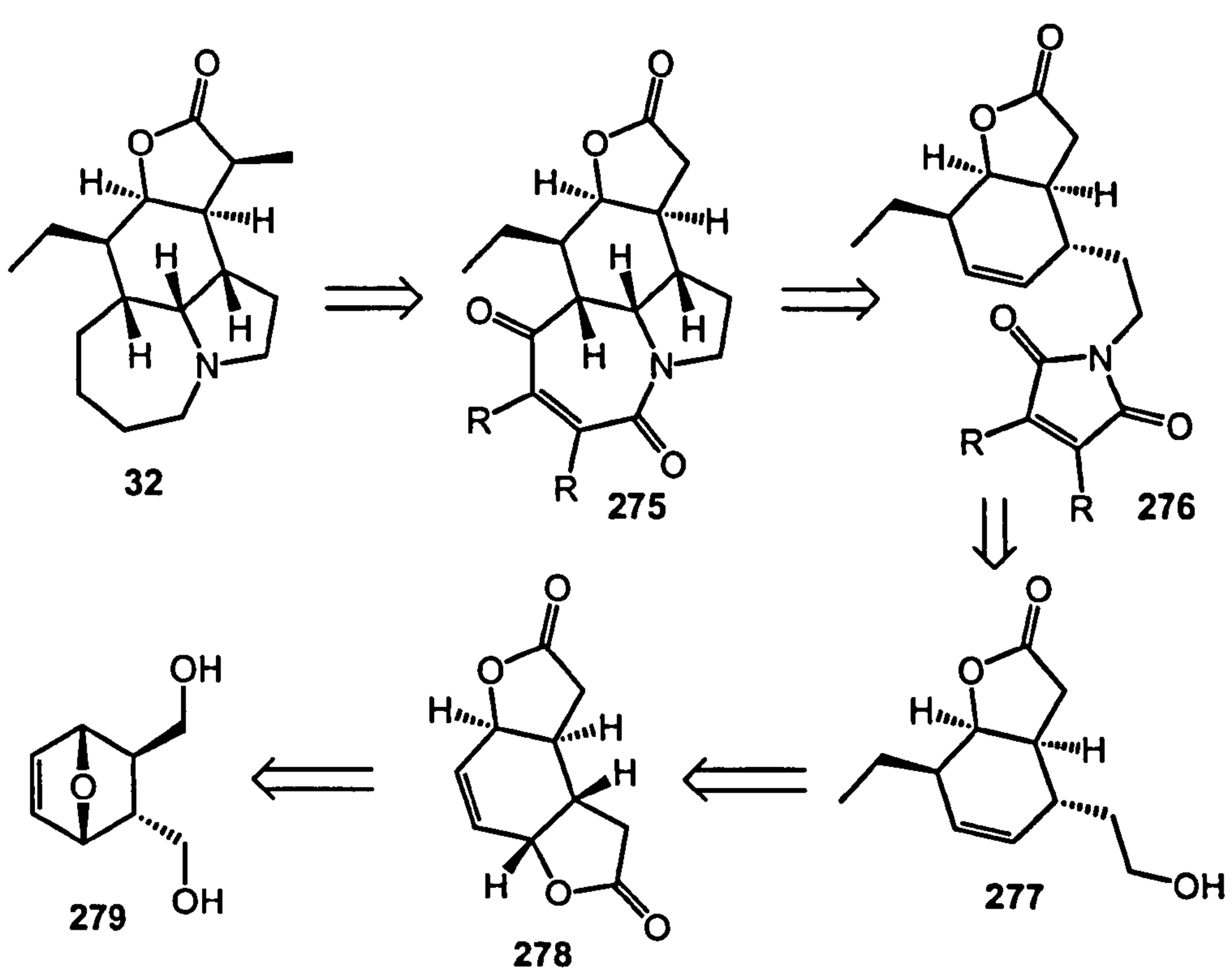


Scheme 110

6. The total synthesis of (±)-neostenine

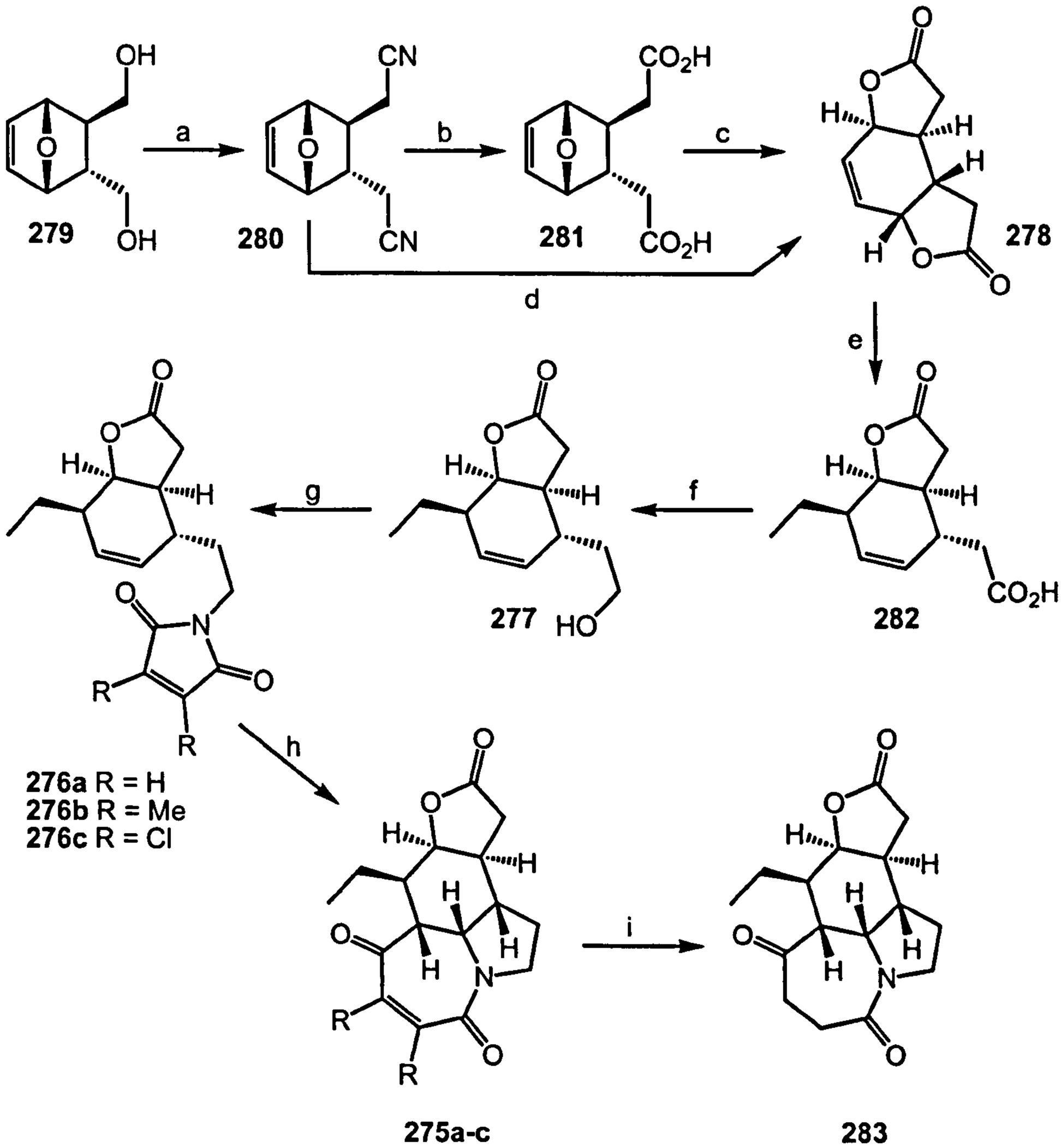
6.1. A retrosynthetic analysis of (±)-neostenine

It was considered that neostenine **32** could be accessed from an end game where the conjugated keto-amide functionality in the advanced tetracycle **275** would be reduced/deoxygenated **(Scheme 111)**. This, followed by methylation of the lactone from the *a*-face (front), would provide **32**. The construction of **275** would involve a [5+2] photocycloaddition of maleimide-cyclohexene **276**, which itself may be readily available *via* Mitsunobu coupling of alcohol **277** and its corresponding maleimide. Alcohol **277** may be prepared using a novel approach involving the anti-selective organocopper mediated S_N2' ring opening of C_2-symmetric bislactone **278**, with subsequent reduction of the acid functionality. A quick entry to **278** was planned to take place from an acid-catalysed bislactonisation of diacid **279**.



Scheme 111

6.2. Synthesis of the tetracyclic core – Hirst[104]



Reagents and Conditions: a) i) MsCl, Et_3N, Et_2O, 2 h; ii) KCN, DMSO, 100 °C, 5 h, 75 %; b) KOH, EtOH, H_2O, 85 %; c) *p*TSA, toluene, reflux, 93 %; d) H_2SO_4 (6M), reflux, 2 h, 45 %; e) EtMgBr (10 equiv), CuBr.Me_2S (10 equiv), THF/Me_2S (2:1), -20 °C, 89 % (8.5:1, anti:syn); f) EtOCOCl, Et_3N, then $NaBH_4$, 84 %; g) maleimide/dimethyl maleimide/dichloromaleimide, DIAD, PPh_3, THF, -78 °C to r.t., 24 h, **276a** 35 %, **276b** 31 % and **276c** 63 %; h) *hv*, Pyrex, MeCN, 30 – 120 min, **275a** 11 %, **275b** 75 % and **275c** 60 %; i) Zn, AcOH, 1.5 h, 95 %.

Scheme 112

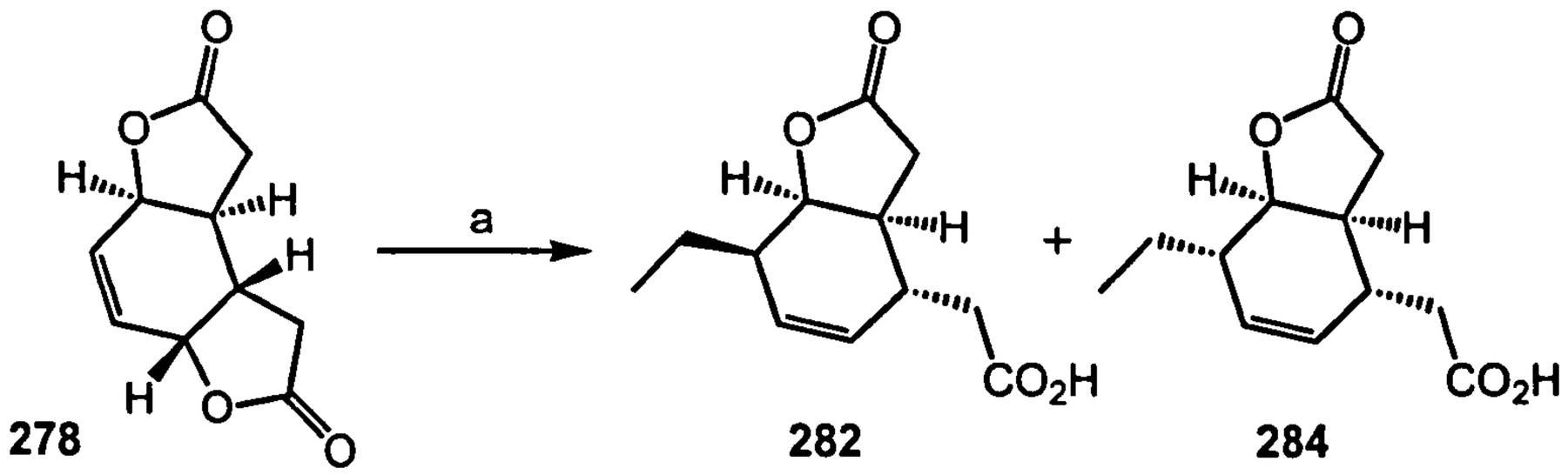
The initial synthetic approach carried out by Hirst afforded a rapid entry to the tetracyclic core of neostenine and neotuberostemonine.[104] The synthesis started from racemic diol **279** which could in turn be accessed from the Diels Alder/reduction of furan and fumaryl chloride.[105] Mesylation of **279** followed by displacement with KCN gave nitrile **280** in a 75 % overall yield. Hydrolysis under basic conditions gave diacid **281**, and acid-catalysed lactonisation afforded the C_2-symmetric bislactone in high yields. This same sequence was also possible in a single hydrolytic step from **280**, though dramatically affecting the yield. Due to the insolubility of bislactone **278** many literature conditions for S_N2' ring opening failed. Eventually it was discovered that increasing to 10 equivalents of the organocuprate, leads to the ring-opened lactone acid **282** in an 89 % yield as a separable mixture of isomers (*anti*/*syn* = 8.5:1). Selective reduction of acid **282** was achieved in good yield from a one pot procedure described by Zoutani *et al.*[106] Formation of a mixed anhydride is accomplished before reduction with $NaBH_4$ to give alcohol **277**. Mitsunobu coupling gave three photoprecursors **276a-c** in varying yields. Pleasingly, irradiation of the dimethyl and dichloro derivatives gave reasonable yields of **275b** and **275c** as single diastereomers. However, photoproduct **275a** was produced in just an 11 % yield due it's susceptibility to dimerisation. Cycloadduct **275c** was shown to be a desirable intermediate for the synthesis of neostenine, as **275c** undergoes simultaneous reduction and dehalogenation with zinc in acetic acid to afford keto-amide **283** in an 86 % yield.

Hirst devised a short synthesis, by utilising a complex photoprecursor and by excluding protecting groups. However some improvements to this route were needed, to allow for sufficient scale-up so that keto-amide **283** could be applied as an intermediate to the synthesis of (±)-neostenine **32**.

6.3. Optimisation and scale-up – Döhle and Taylor[107]

The first development was to minimise the unwanted *syn* adduct formed during the S_N2' ring opening. Dohle applied the same conditions as Hirst, but altered the

organocuprate equivalents from 10 to 3 and screened the effect of the additive on the *anti*/*syn* selectivity **(Scheme 113, Table 9)**.



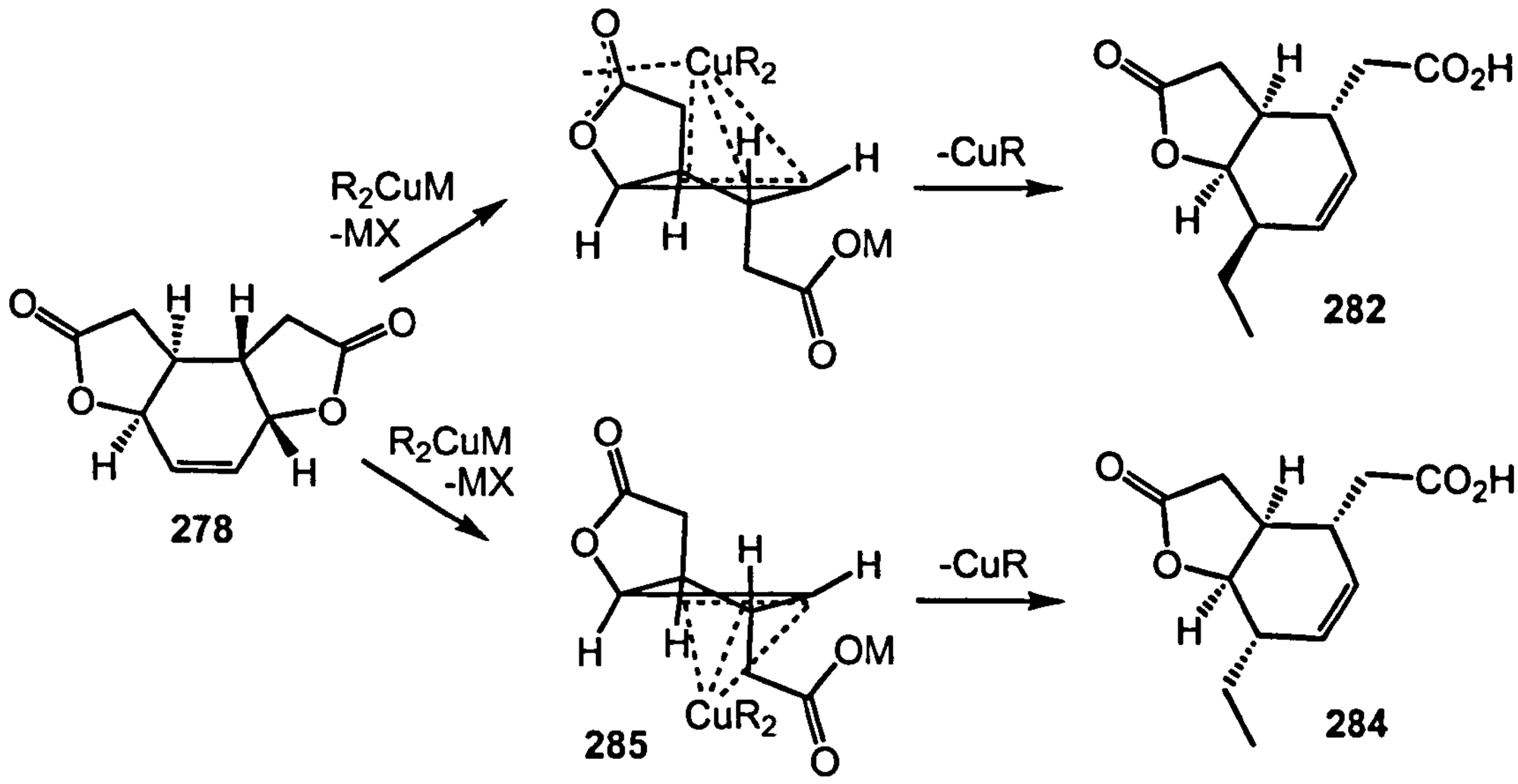
278 **282** **284**

Entry	Additive (equivalents)	*Anti*:*Syn* **282:284**	Yield / %
1	DMPU (4)	9.7:1	81
2	Me_2S (4)	12.2:1	85
3	Me_2S (2)	13.8:1	84
4	Me_2S (1)	14.2:1	86
5	None	15.6:1	94

Reagents and Conditions: a) EtMgBr (3 equiv), CuBr.Me_2S (3 equiv), THF, additive, - 20 °C.

Scheme 113, Table 9

Dohle established that use of an additive (*entries 1 – 4*) actually reduced the selectivity, with the best result (*entry 5*) employing no additive whatsoever. This result almost doubled the selectivity of Hirst to give 15.6:1 favouring the desired *anti* product. Co-ordination of the copper (I) species with lactone **278** may assist delivery of the cuprate anti to the leaving group. The reduction of selectivity by increasing the equivalents of Me_2S may be attributed to the additive disrupting lactone interactions, leading to an increase of *p*-allyl copper (III) system **285**, thereby enhancing *syn* adduct **284 (Scheme 114)**.



Scheme 114

The photochemical [5+2] reaction carried out by Hirst to give **275c** was performed on a 50 mg scale, in a 100 cm^3 immersion well batch photoreactor, using a 125 W medium-pressure Hg lamp. Attempted scale-up with batches greater than 100 mg led to yields dropping below 20 %, with total consumption of starting material. The use of a 400 cm^3 immersion well, with more dilute batches met equally poor results. Scale-up of **275c** using a batch reactor was therefore unsustainable as it would involve multiple batch reactions with substantial loss of photoprecursor **276c**. Recently, Booker-Milburn *et al.* developed a novel flow rector for continuous photochemical synthesis.[103] The reactor was comprised of a Pyrex immersion well wrapped in multiple loops of narrow bore fluorinated ethylene polymer (FEP) tubing contained a 125 – 400 W medium-pressure Hg lamp. The reactor was capable of producing >500 g maleimide/hex-1-yne photoadducts per day, and therefore could provide a solution to the scale-up of **275c**. After a great deal of experimentation, Taylor found that a custom reactor made up of 15 loops (10 cm^3 volume) of FEP, tubing using a 400 W Hg lamp, with a 0.001 M solution of **276c** in DCM, at a flow rate of 11 cm^3min^{-1} gave 63 % **275c** and 20 % recovery of photoprecursor **276c (Figure 12)**.

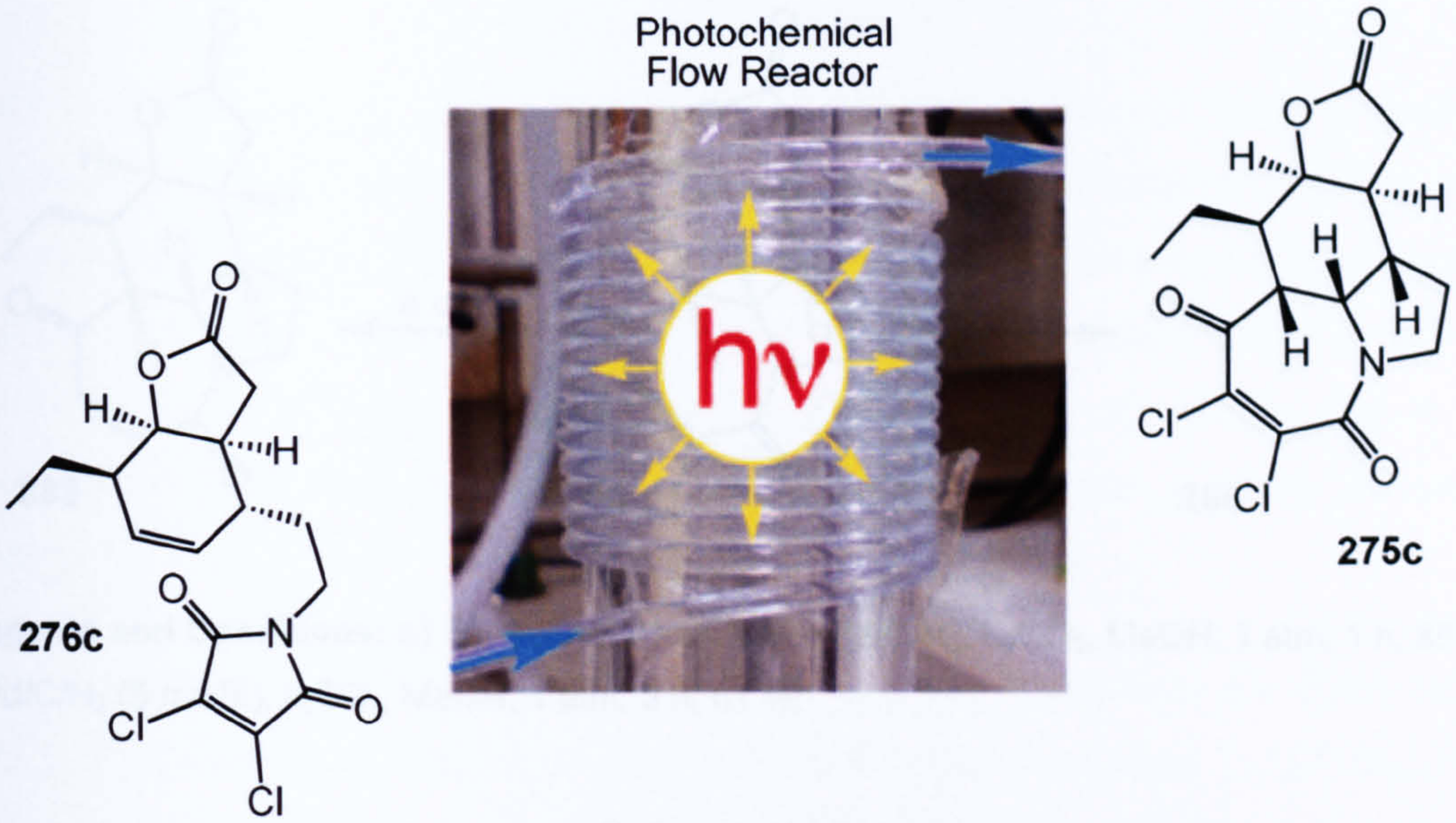
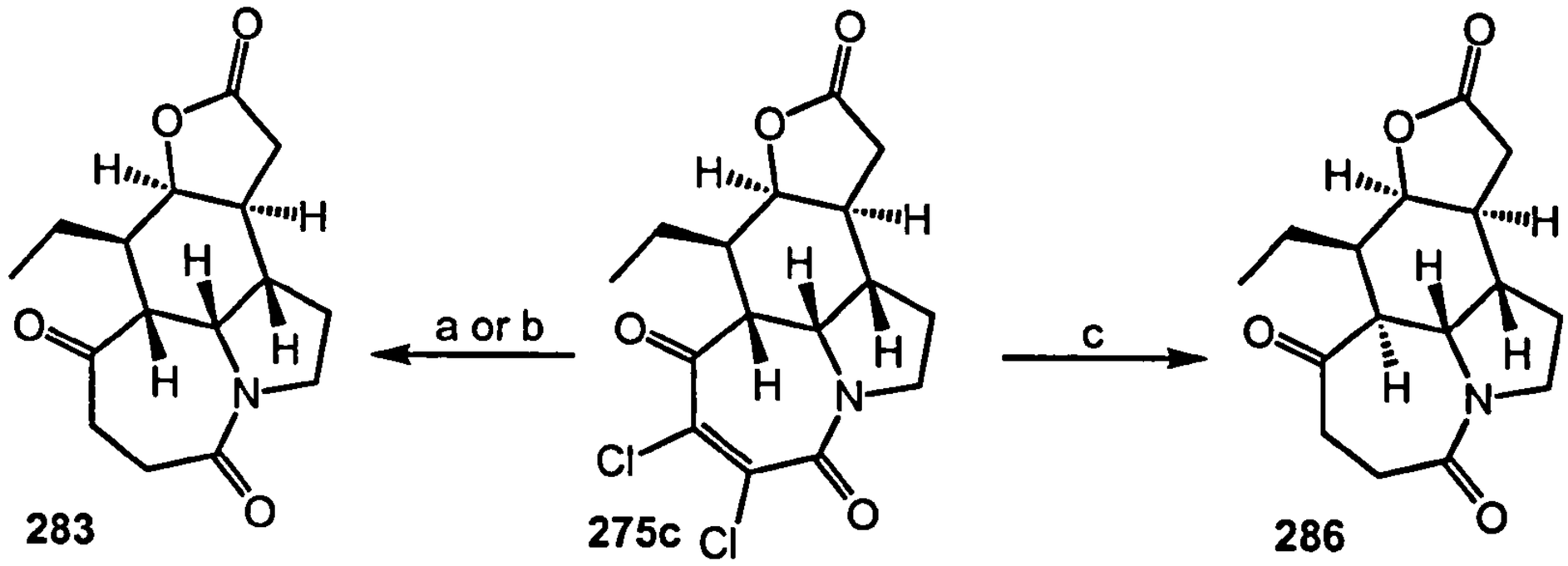


Figure 12

This allowed the synthesis of 1.3 g of **275c** in a single 9 h run. In a batch reactor, this would have required 42 consecutive irradiations, without the recovery of photoprecursor! The success of the flow reactor can be attributed to the fast flow rate of a dilute solution of **276c**, through a high power UV source (400 W). This allows for a short residence time, which therefore minimises the degradation of product as it forms.

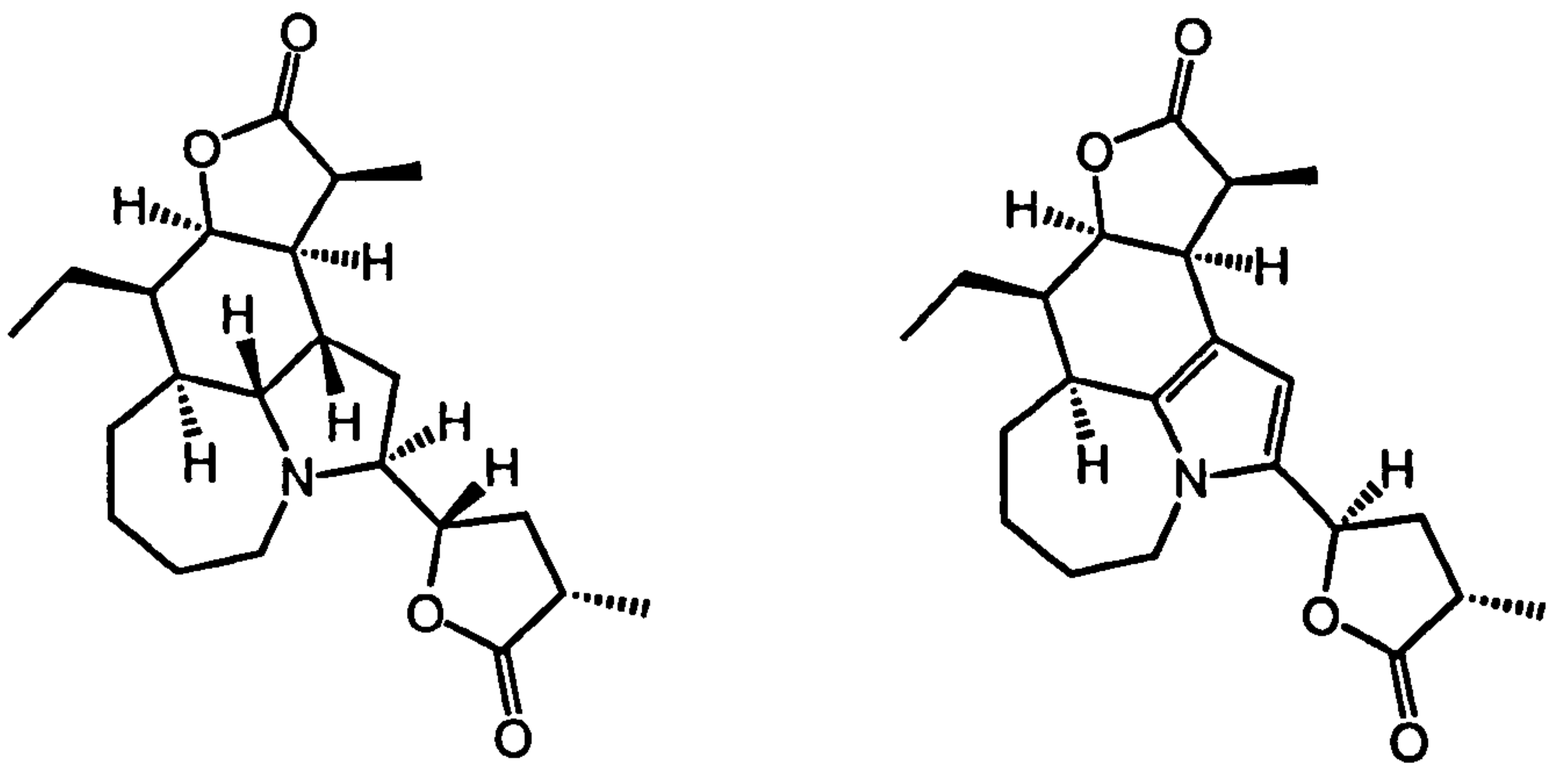
The simultaneous reduction and dehalogenation with zinc in acetic acid to afford keto-amide **283** was initially found at to be unreliable, affording wide-ranging yields. However by avoiding an aqueous work-up, consistently high yields were obtained. Hydrogenation conditions using excess palladium on carbon also provided a reliable method. However due to the large catalyst loading, this was scale-limited. Interestingly, repetition of the reduction with catalytic palladium gave an unusual result. The catalytic procedure required longer reaction times, under which epimerisation alpha to the ketone in **286** was observed **(Scheme 115)**.



Reagents and Conditions: a) Zn, AcOH, 1 h 95 %; b) $Pd/C/H_2$, K_2CO_3, MeOH, 1 atm, 1 h, 85 %; c) $Pd/C/H_2$ (5 mol%), k_2CO_3, MeOH, 1 atm, 3 h, 61 %;

Scheme 115

The epimerised product may provide a convenient way to access other alkaloids of the *Stemona* family. In fact, isolated alkaloids tuberostemonine H **287** and *epi*-bisdedehyroneotuberostemonine J **288** both contain the same stereochemistry of epimer **286 (Figure 13).**



Tuberostemonine H **287**

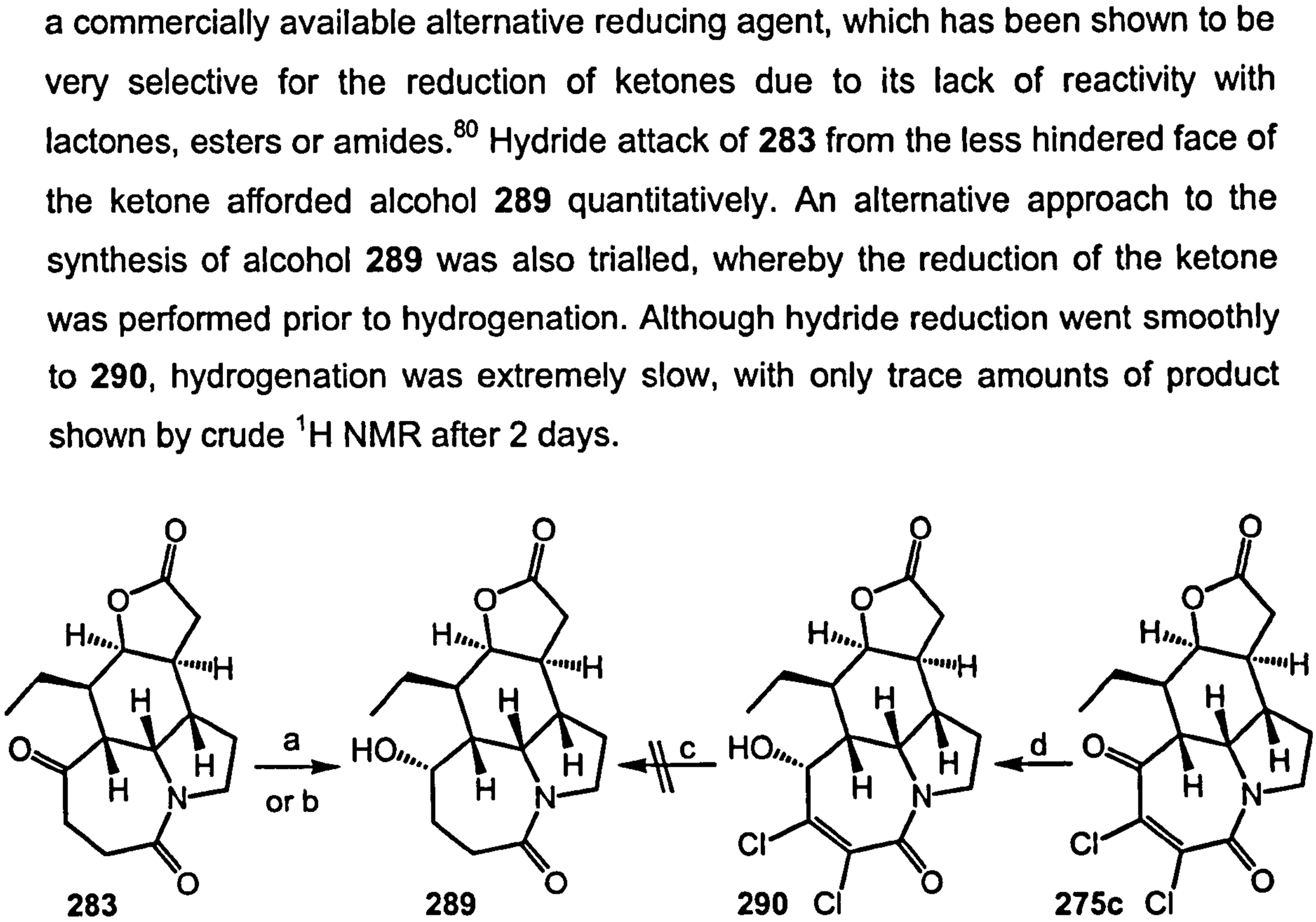
epi-Bisdehydroneotuberostemonine J **288**

Figure 13

6.4. Deoxygenation-Lainchbury

Taylor had explored methods for the deoxygenation of **283** including Clemmensen, modified Shapiro, thioacetal formation then RaNi or Bu_3SnH, and enol triflate/phosphate then hydrogenation, all of which were unsuccessful. Many problems occurred during derivitisation and it became apparent that the ketone was reasonably hindered. It was thought that reduction of ketone **283** to its corresponding alcohol, followed by deoxygenation would present a better strategy.

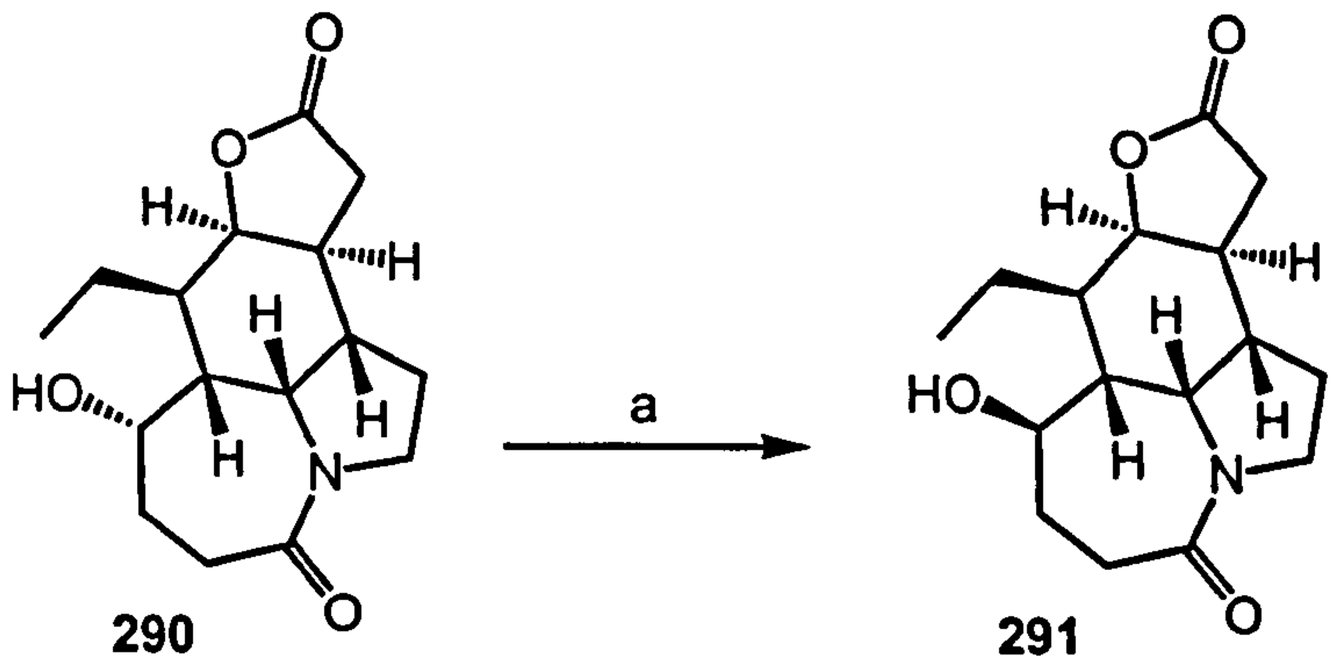
Reduction of keto-amide **283** had been carried out previously by Hirst using $NaBH_4$, however yield and conversion were poor **(Scheme 116)**. $LiAl(O^tBu)_3H$ is a commercially available alternative reducing agent, which has been shown to be very selective for the reduction of ketones due to its lack of reactivity with lactones, esters or amides.[80] Hydride attack of **283** from the less hindered face of the ketone afforded alcohol **289** quantitatively. An alternative approach to the synthesis of alcohol **289** was also trialled, whereby the reduction of the ketone was performed prior to hydrogenation. Although hydride reduction went smoothly to **290**, hydrogenation was extremely slow, with only trace amounts of product shown by crude ^1H NMR after 2 days.



Reagents and Conditions: a) $NaBH_4$, MeOH, 2 h, 11 – 40 %; b) $LiAl(O^tBu)_3H$, THF, 0 °C to r.t., 3 h, 99 %; c) $Pd/C/H_2$, K_2CO_3, MeOH, 1 atm, 2 days; d) $LiAl(O^tBu)_3H$, THF, 0 °C to r.t., 20 min, 99 %;

Scheme 116

Since a hydroxyl group is a poor leaving group, it is normally activated by mesylation or thiocarboxylation before treatment with a reducing agent.[108] However Baba *et al*. have demonstrated that direct reduction of secondary or tertiary alcohols can be achieved by using chlorodiphenyl silane as a hydride source in the presence of a catalytic amount of indium trichloride.[108] Application of these conditions to alcohol **290** unexpectedly gave a new compound that was more polar by TLC **(Scheme 117)**. Further investigation from IR, NMR and mass spectroscopy showed that the most likely outcome was inversion of the alcohol stereochemistry. The inverted alcohol **291** may be more polar due to lone pairs on the hydroxyl group being more accessible in this conformation, thereby hydrogen-bonding more strongly.



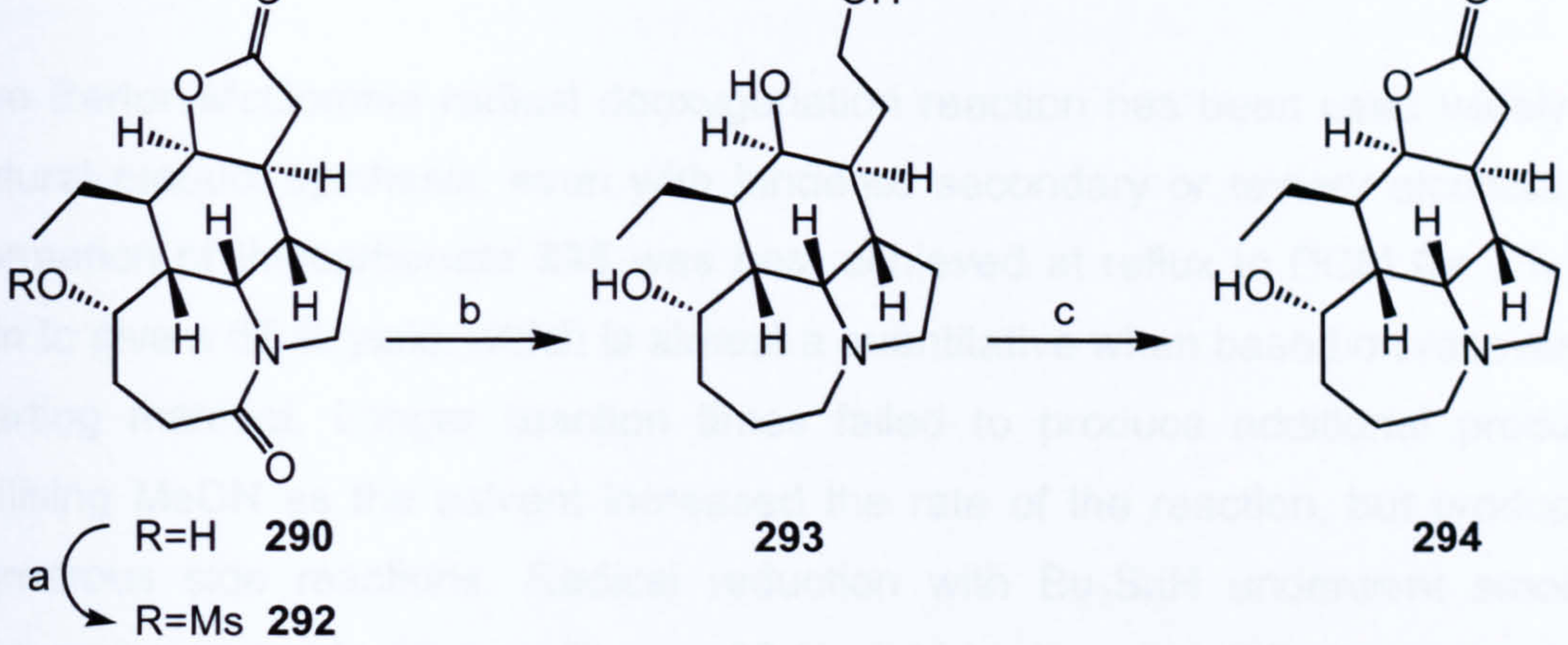
290 **291**

Reagents and Conditions: a) Ph_2SiHCl, $InCl_3$, DCM, reflux, 24 h.

Scheme 117

The subsequent approach was to activate the alcohol by mesylation, then to carry out reduction with a hydride source. Mesylation was quick, affording mesylate **292** in quantitative yield **(Scheme 118)**. An X-ray structure of **292** verifies the stereochemistry of the preceding ketone reduction **(Figure 14)**. The most successful reducing agents for mesylates are lithium amino borohydrides and $LiEt_3BH$, which can even reduce hindered alkyl sulfonates with nominal elimination. Unfortunately these reagents are extremely reactive and consequently open cyclic amides to their corresponding amino-alcohols.[80] $LiAlH_4$ has demonstrated its use for deoxygenation, but can be prone to furnish

elimination adducts.[80] Reduction of mesylate **292** with $LiAlH_4$ gave triol **293** in a 39 % yield. It is apparent that **292** is too hindered for displacement and so favours a sulfur-oxygen bond cleavage instead **(Scheme 118)**.



Reagents and Conditions: a) Et_3N, THF, 0°C, 5 min, 99 %; b) $LiAlH_4$ (8 equiv), THF, reflux, 39 %; c) $Ru(PPh_3)_2Cl_2$, benzene, 16 h, 57 %.

Scheme 118

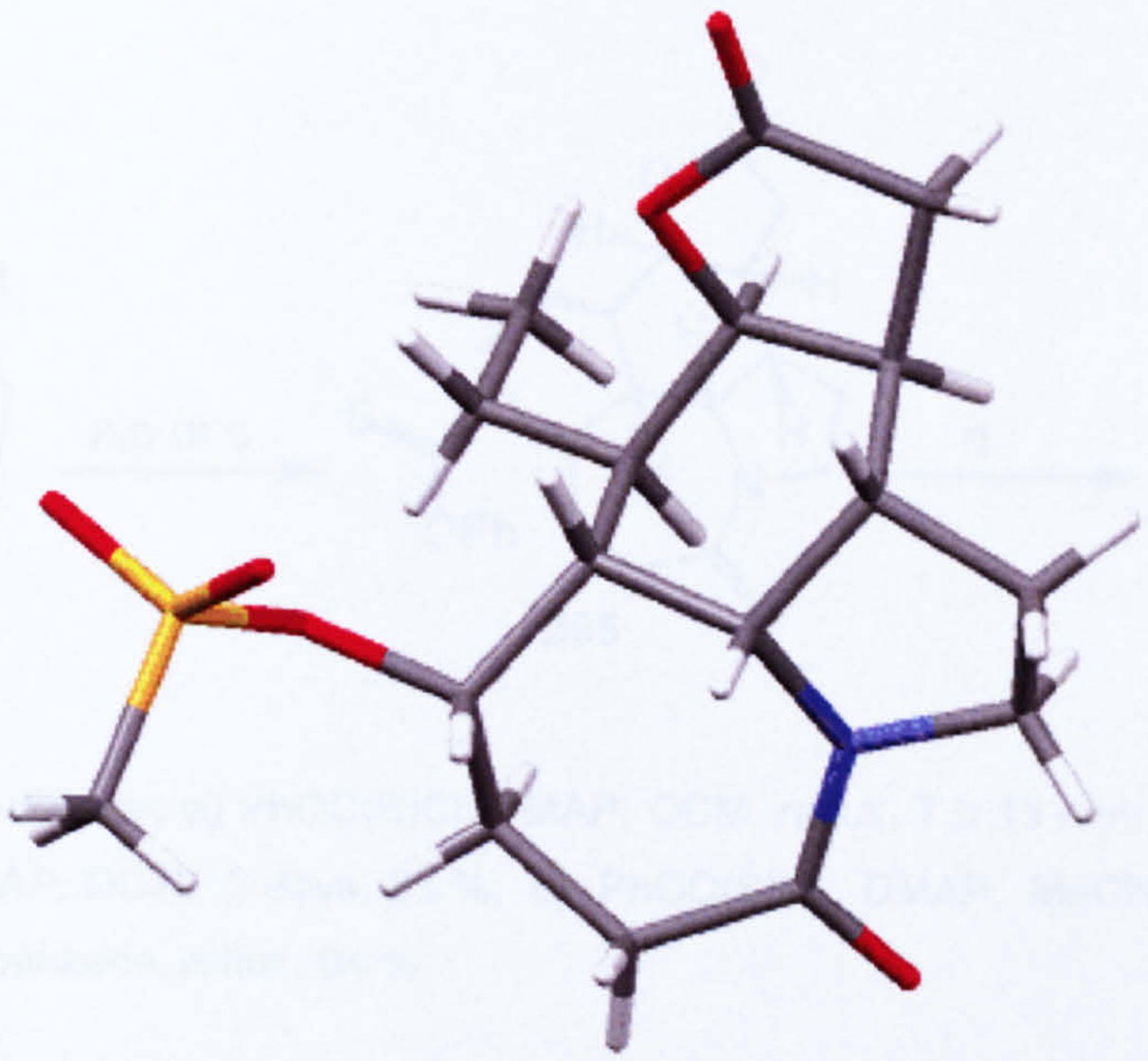
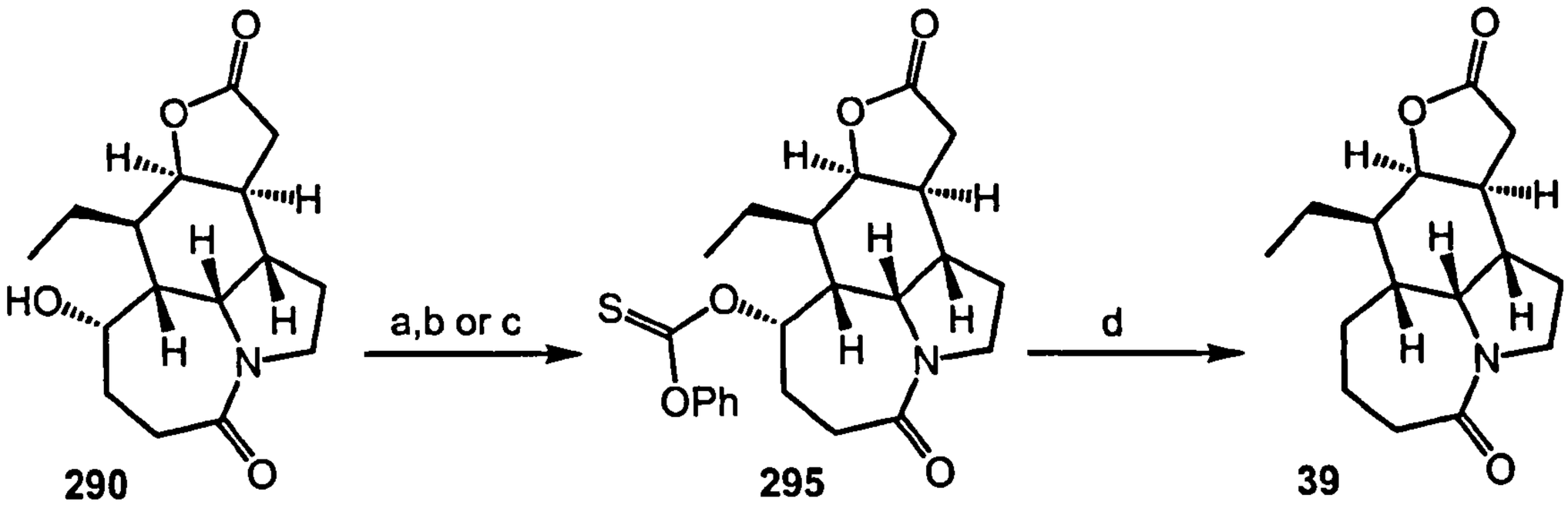


Figure 14 : X-ray structure of 292

In addition inseparable, mixtures of compounds in a 20 % yield were isolated, which appeared by ^{1}H NMR to contain elimination products. Initially there was some reservation to the identity of triol **293**, however oxidation to lactone **294** using $Ru(PPh_3)_2Cl_2$,[109] assisted in the assignment of **293** .

The Barton-McCombie radical deoxygenation reaction has been used widely in natural product synthesis, even with hindered secondary or tertiary alcohols.[110] Formation of thiocarbonate **295** was best achieved at reflux in DCM for 7 h 15 min to give a 67 % yield, which is almost a quantitative when based on recovered starting material. Longer reaction times failed to produce additional product. Utilising MeCN as the solvent increased the rate of the reaction, but produced numerous side reactions. Radical reduction with Bu_3SnH underwent smooth conversion to amide **39** providing an 88 % yield for the overall Barton procedure **(Scheme 119)**. Now that the hindered ketone had been deoxygenated, the final steps to afford (±)-neostenine required an amide reduction and lactone methylation.

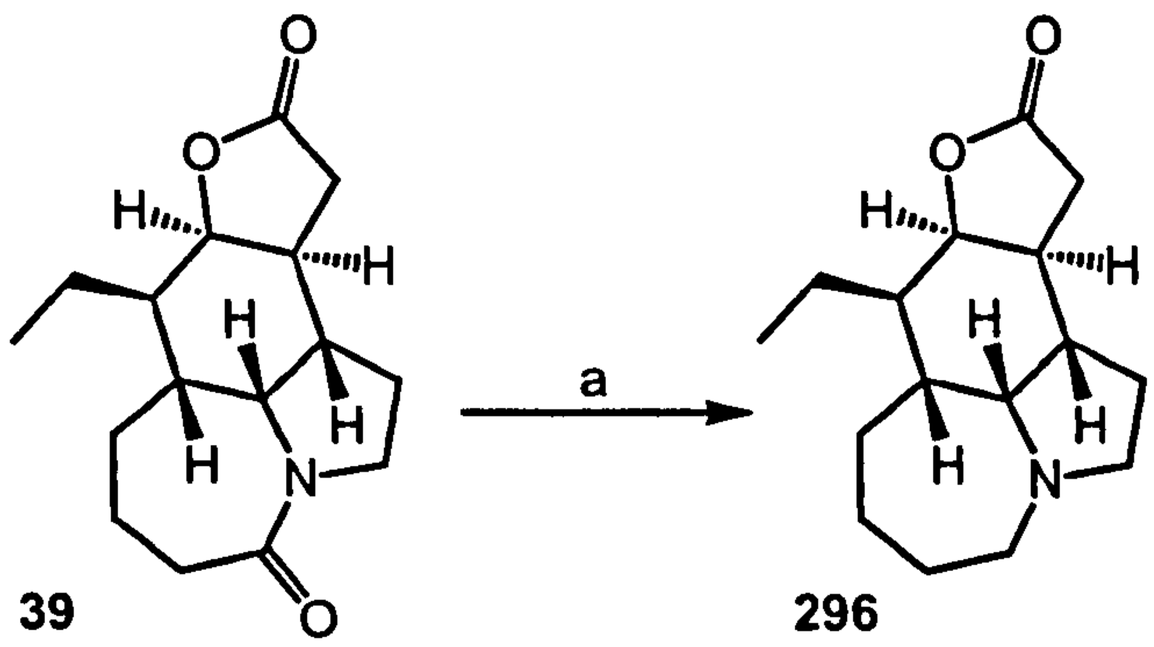


Reagents and Conditions: a) PhOC(S)Cl, DMAP, DCM, reflux, 7 h 15 min, 67 % (94 % brsm); b) PhOC(S)Cl, DMAP, DCM, 3 days, 38 %; c) PhOC(S)Cl, DMAP, MeCN, reflux , 2 h, 42 %; d) Bu_3SnH, AIBN, benzene, reflux, 94 %.

Scheme 119

6.5. Amide reduction and methylation

Aube, Hart and Wipf have used Lawesson's reagent, followed by Raney nickel to reduce an analogous amide present in their syntheses of enantiopure or racemic stenine.[12] The yields for this two step reduction vary from 73 – 83 % and may be applicable to our synthesis of (±)-neostenine. However in 1998 a method by Ito *et al.* achieved single step reductions of a wide variety of tertiary amides, using a reduction with diphenylsilane, catalysed by $RhH(CO)(PPH_3)_3$.[111] Gratifyingly, application of this methodology afforded amine **296** in a reasonable yield **(Scheme 120)**.



39 **296**

Reagents and Conditions: a) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$ (5 mol%), THF, 70 %.

Scheme 120

Nevertheless, due to the difficulty of purification and handling of **296** it was decided that amide reduction, together with further optimisation, should be left until the concluding stage of the synthesis. Methylation of amide **39** using LiHMDS and MeI gave a 7.8:1 mixture of diastereomers, favouring *epi*-oxoneostenine **297**, in an 82 % yield **(Scheme 121)**. Steric hindrance induced from the ethyl and methylene hydrogens present on the cyclohexane ring impedes attack from the *ß*-face of the enolate. The major isomer was identified from NOE experiments **(Figure 15)**.

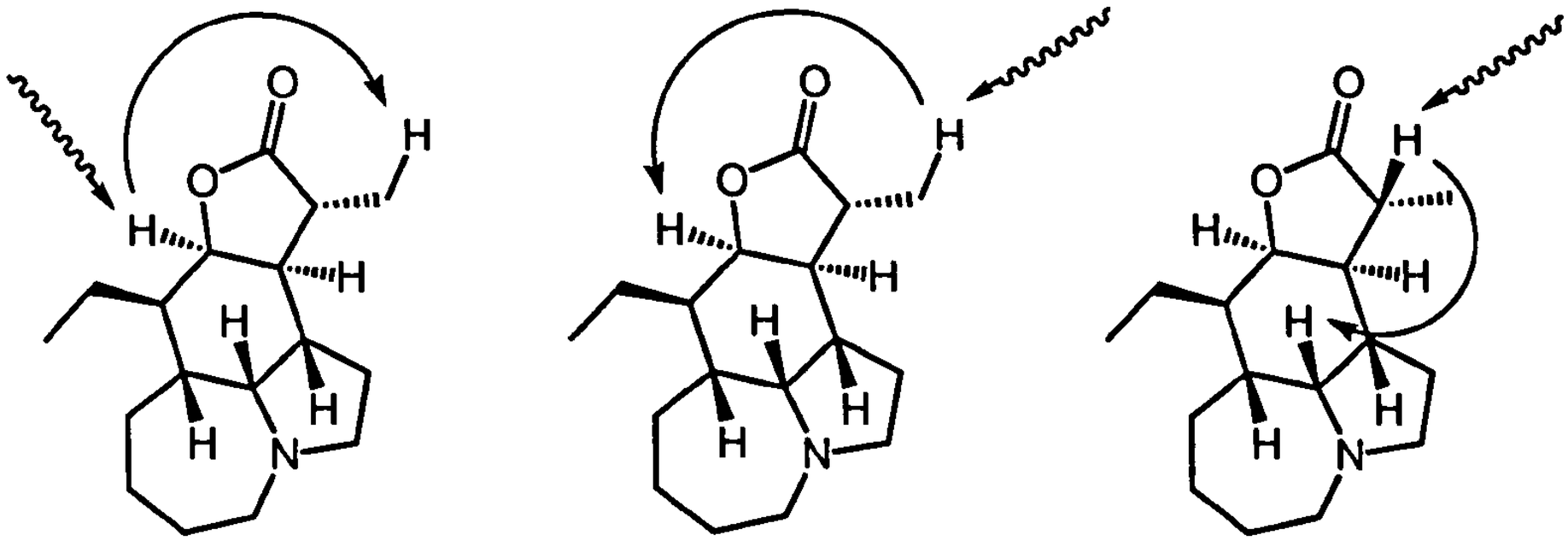
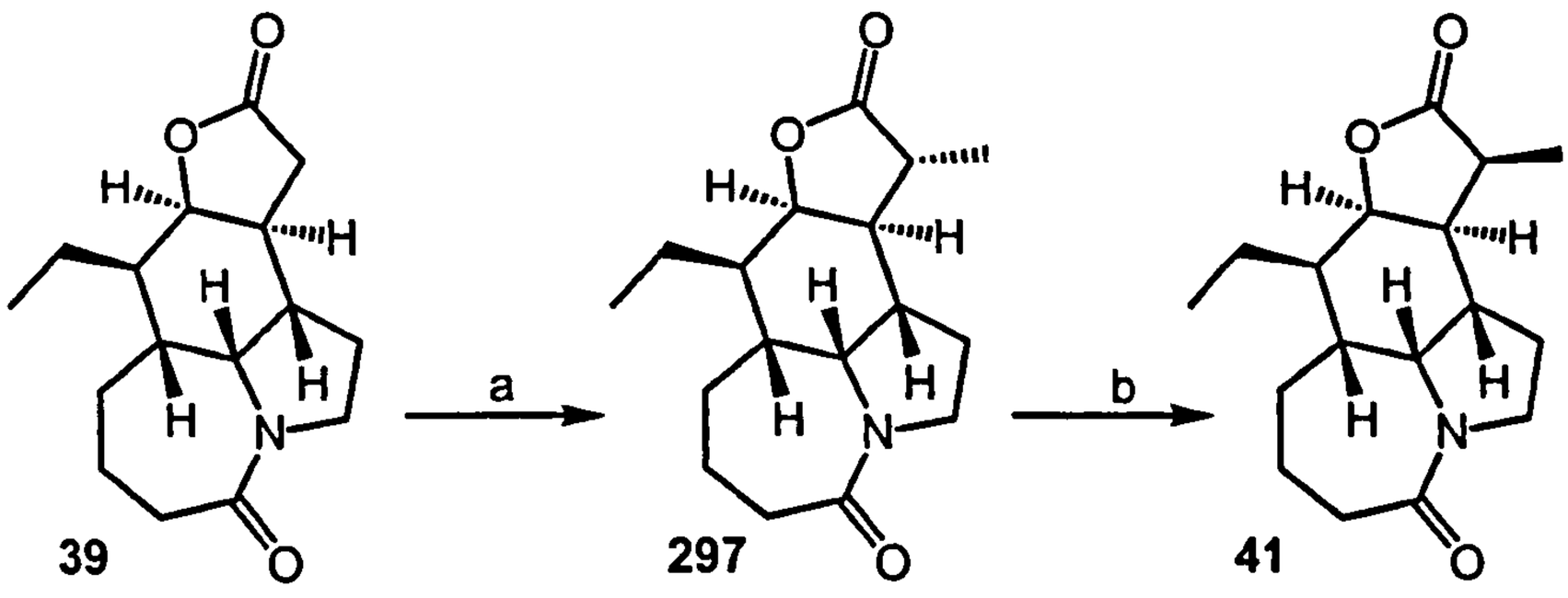


Figure 15

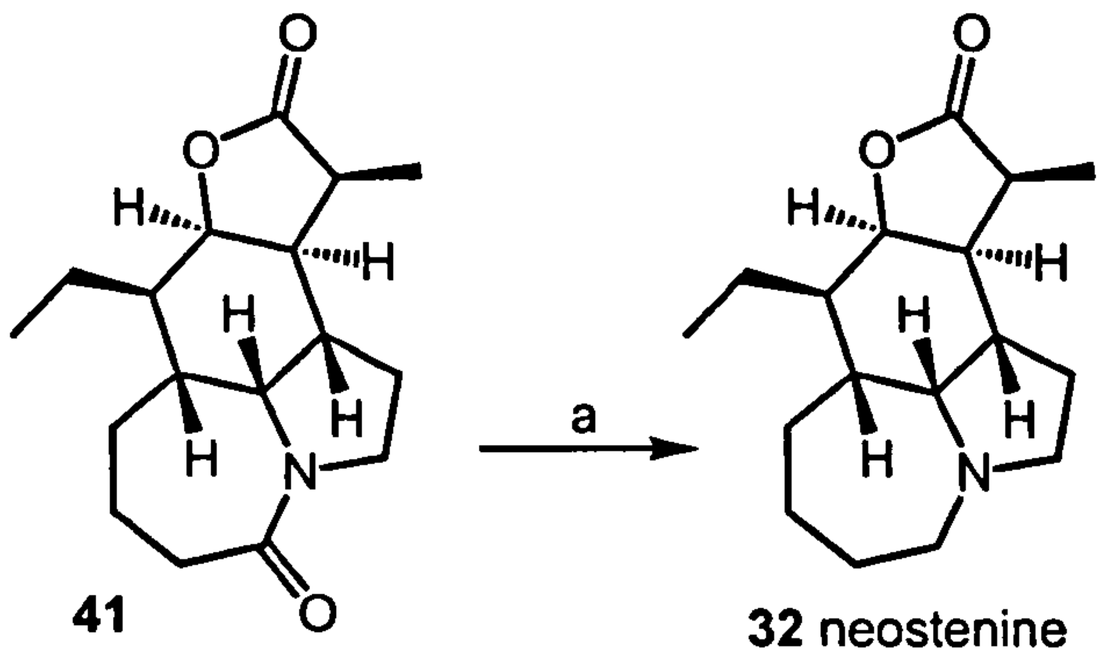
To transform the selectivity towards the desired oxoneostenine **41**, the mixture was re-enolised with LiHMDS and quenched, exploiting BHT as a "bulky" proton source. The reaction temperature must be brought to r.t. for complete deprotonation to take place. Protonation with BHT[112] followed at -78 °C, provided an 8.6:1 mix in favour of oxoneostenine **41** in a 93 % yield **(Scheme 121)**.



Reagents and Conditions: a) i) LiHMDS, THF, -78 °C, 1 h; ii) MeI, -78 °C, 2 h, 82 %; b) i) LiHMDS, THF, -78 °C to r.t., 30 min; ii) BHT, -78 °C, 15 min, 93 %.

Scheme 121

Recrystalisation in hexane:ethyl acetate gave pure **41**, which was then subjected to reduction with rhodium as before, affording (±)-neostenine **32** in a 70 % yield **(Scheme 122)**.



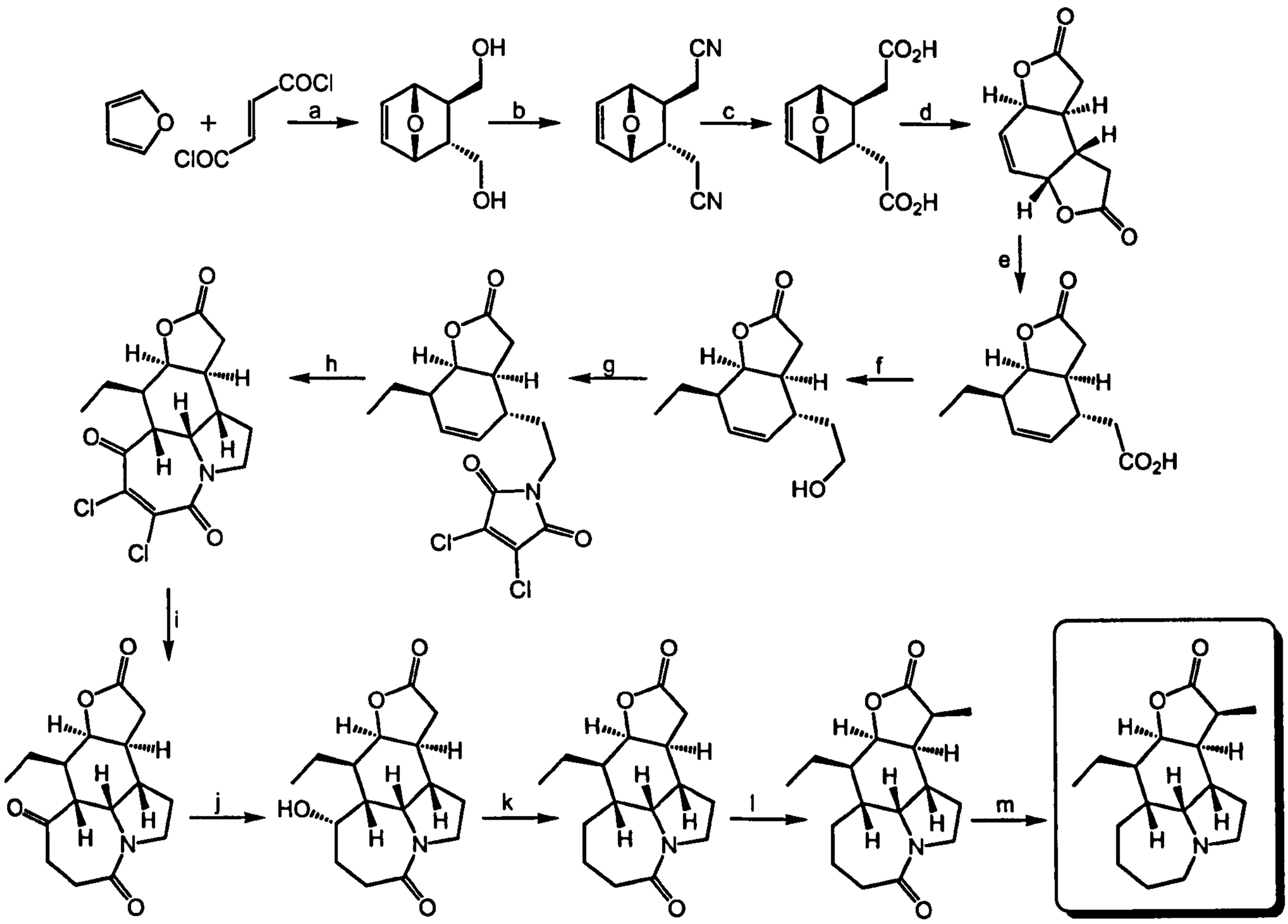
Reagents and Conditions: a) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$ (5 mol%), THF, 70 %.

Scheme 122

6.6. Conclusion

The synthesis of (±)-neostenine has been achieved in 14 steps from furan in a 9.5 % overall yield **(Scheme 123)**. Anti selective S_N2' ring opening of bislactone **278** provided the first key intermediate **282**, which contained four of the seven requisite stereocentres of neostenine. Two more centres were established with complete control from a key [5+2] photocycloaddition. Methylation of lactone **39** completed the final of the seven stereocentres required for (±)-neostenine **32**.

Overall synthesis of (±)-neostenine

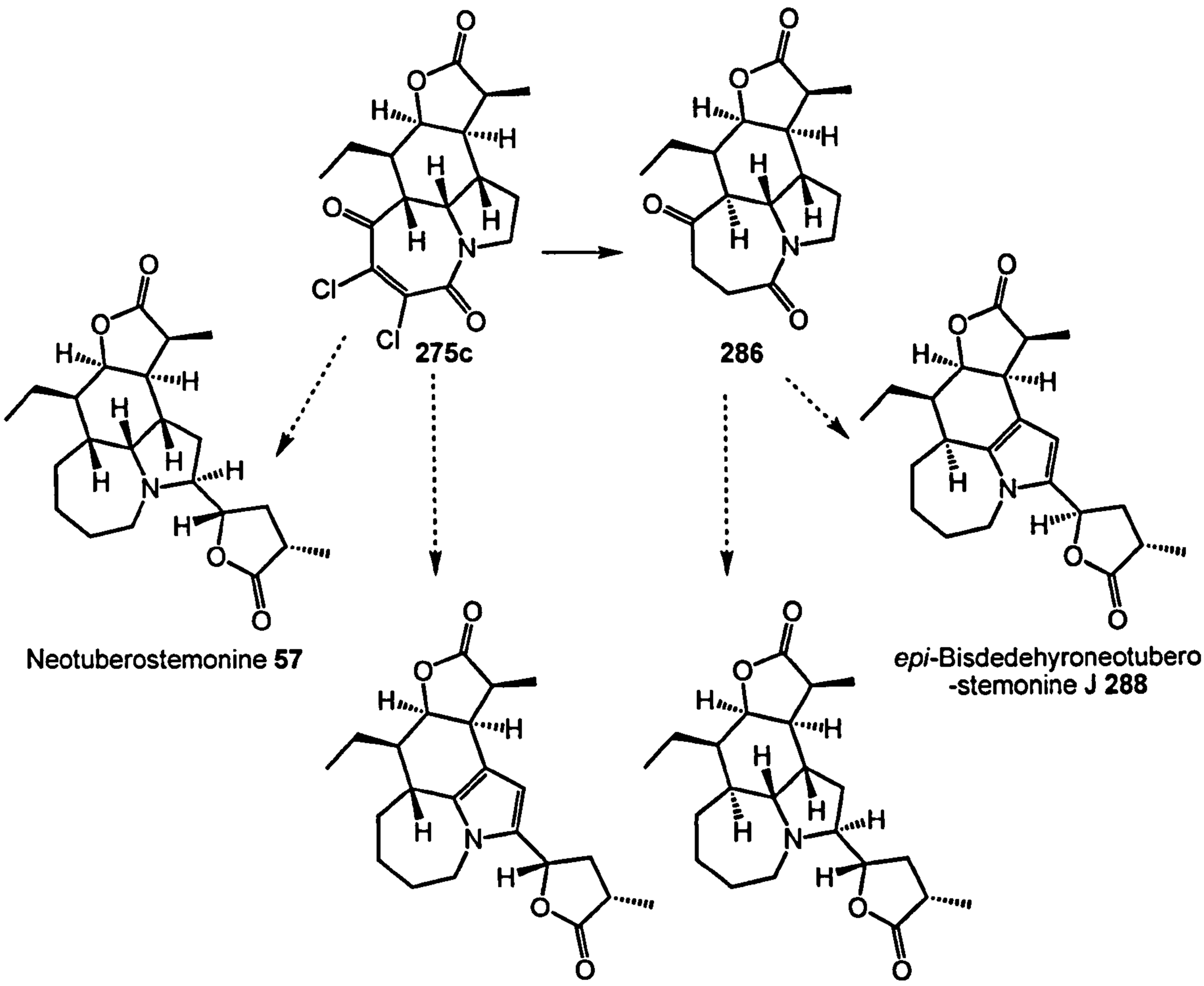


Reagents and Conditions: a) THF, 0 °C, 2 h then $LiAlH_4$, r.t. 48 h, 72 % b) i) MsCl, Et_3N, Et_2O, 2 h; ii) KCN, DMSO, 100 °C, 5 h, 75 %; c) KOH, EtOH, H_2O, 85 %; d) *p*TSA, toluene, reflux, 93 %; e) EtMgBr (3 equiv), CuBr.Me_2S (3 equiv), THF, -20 °C, 94 % (15.6:1, anti:syn); f) EtOCOCl, Et_3N, then $NaBH_4$, 84 % g) dichloromaleimide, DIAD, PPh_3, THF, -78 °C to r.t., 24 h, 71 %; h) *hv*, Pyrex 15-loop FEP flow reactor, MeCN, 63 % (80 % brsm); i) Zn, AcOH, 1.5 h 95 %; j) $LiAl(O^tBu)_3H$, THF, 0 °C to r.t., 3 h, 99 %; k) i) PhOC(S)Cl, DMAP, DCM, reflux, 7 h 15 min, 67% (94 % brsm); ii) Bu_3SnH, AIBN, benzene, reflux, 94 %; l) i) LiHMDS, THF, -78 °C, 1 h then MeI, -78 °C, 2 h, 82 %; ii) LiHMDS, THF, -78 °C to r.t., 30 min then BHT, -78 °C, 15 min, 93 %; m) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$ (5 mol%), THF, 70 %.

Scheme 123

6.7. Future work

The total synthesis of neostenine may be adapted to give concise routes to neotuberostemonine **57** and bisdehydroneotuberostemonine **298**. In fact, as found during the hydrogenation of photoadduct **275c**, the *a*-position to the ketone is easily epimerised (see scheme 115). The epimerised product may provide a convenient way to access two other alkaloids of the *Stemona* family, *epi*-bisdedehyroneotuberostemonine J **288** and tuberostemonine H **287**. Consequently an intermediate from the total synthesis of neostenine could give an entry to the four alkaloids **57**, **287**, **288** and **298 (Scheme 124)**.



Scheme 124

Experimental

7. Preparative methods and spectroscopic data

Anhydrous solvents were obtained from the University of Bristol dry solvent system, by passage through a column of activated alumina.

Unless preparations are supplied, all reagents were obtained from commercial sources, and used without further purification, with the exception of dichloromaleic anhydride, which was recrystalised in toluene.

^{1}H NMR and ^{13}C NMR spectra were measured, in the solvent stated, at 270 or 400 MHz, on JEOL JNM-GX270, JEOL JNM-GX400 or JEOL JNM-ECP400 spectrometers. Chemical shifts are quoted in parts per million (δ) from $SiMe_4$ and coupling constants (J) are given to the nearest 0.1 Hz. Multiplicities are abbreviated as follows: br (broad), s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

Mass spectrometry was carried out by the Bristol University mass spectrometry service, using electron impact, chemical ionisation or electrospray ionisation techniques.

Infrared spectra were measured on a Perkin Elmer Spectrum One FT-IR Spectrometer as solids or thin films, and were recorded in the range $4000cm^{-1}$ – $600cm^{-1}$. IR peaks are quoted in wavenumbers (cm^{-1}).

Column chromatography was performed using 60 silica of 230-400 mesh.

Microwave reactions were carried out in a CEM microwave reactor with Powermax cooling function enabled, using 7ml microwave reaction vessels containing stirrer bars.

All reactions were carried out at ambient temperature and under nitrogen unless otherwise stated. Reactions requiring anhydrous conditions were performed in flame dried glassware.

Photochemical reactions were carried out using a 125W medium pressure mercury lamp in a Pyrex, Vycor or Quartz immersion well. The solutions were degassed prior to irradiation by bubbling nitrogen through the system for 15 min.

Modified Walker Mitsunobu procedure

To a solution of PPh_3 (400 mg, 1.52 mmol) in anhydrous THF (15 cm^3) was added DEAD (0.23 cm^3, 1.45 mmol) dropwise at -78 °C. After 2 h a white ppt formed. Alcohol **X** (2.2 mmol) was added dropwise. Finally maleimide **X** (1.45 mmol) was added and the reaction mixture was allowed to warm to r.t. overnight. The solution was concentrated *in vacuo* and triphenylphosphine oxide was crystallised using Et_2O as the solvent. The mixture was filtered and the organic was concentrated *in vacuo* to give crude *N*-alkenylated maleimides.

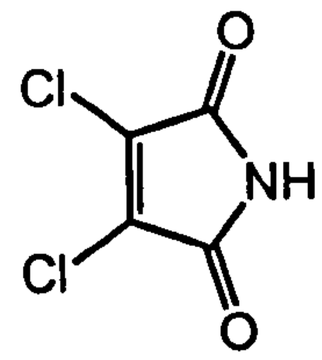
Standard Mitsunobu procedure

To a solution of alcohol **X** (1.0 mmol), maleimide **X** (1.0 mmol) and PPh_3 (400 mg, 1.5 mmol) in anhydrous THF (15 cm^3) was added DEAD (0.24 cm^3, 1.5 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to r.t. overnight. The solution was concentrated *in vacuo* and triphenylphosphine oxide was crystallised using Et_2O as the solvent. The mixture was filtered and the organic was concentrated *in vacuo* to give crude *N*-alkenylated maleimides.

Standard Maleimide procedure

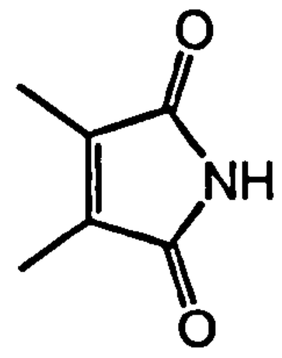
To a solution of 3,4-dichlorofuran-2,5-dione or 3,4-dimethylfuran-2,5-dione (6.0 mmol) and HMDS (2.5 cm^3, 12.0 mmol) in anhydrous MeCN (25 cm^3) was added MeOH (0.49 cm^3, 12.0 mmol) at r.t. and was then heated under reflux in an atmosphere of nitrogen for 30 min. The mixture was concentrated *in vacuo* to leave an orange oil, which was purified by column chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give 3,4-dichloro-1H-pyrrole-2,5-dione and 3,4-dimethyl-1H-pyrrole-2,5-dione as white crystalline solids;

3,4-Dichloro-1H-pyrrole-2,5-dione



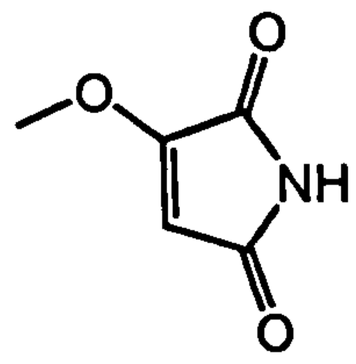
(0.87 g, 88 %); d_H (400 MHz; DMSO; Me_4Si) 11.75 (1H, bs, N*H*); d_C (400 MHz; DMSO; Me_4Si) 133.8 (2 x C) and 165.0 (2 x C); *m/z* (CI) 165.9469 (M^+ +H, requires 165.9463 $C_4H_2Cl_2NO_2$), (CI) 166 (M^+ +H 100 %), 148 (14), 122 (12) and 87 (15).

3,4-dimethyl-1H-pyrrole-2,5-dione



(0.74 g, 98 %); d_H (400 MHz; DMSO; Me_4Si) 1.87 (6H, s, 2 x CH_3) and 10.32 (1H, bs, N*H*); d_C (400 MHz; DMSO; Me_4Si) 10.8 (2 x CH_3), 134.2 (2 x C) and 173.4 (2 x C);

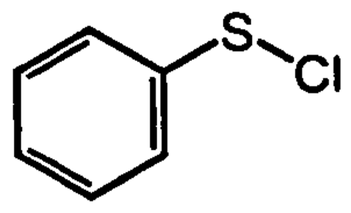
3-methoxy-1H-pyrrole-2,5-dione



To a solution of maleimide (0.52 g, 22.7 mmol) in MeOH (200 cm^3) was cautiously added bromine (4.0 cm^3, 77.3 mmol) dropwise at 0°C and left to stir at r.t. for 16 h. The reaction mixture was concentrated *in vacuo*, then redissolved in

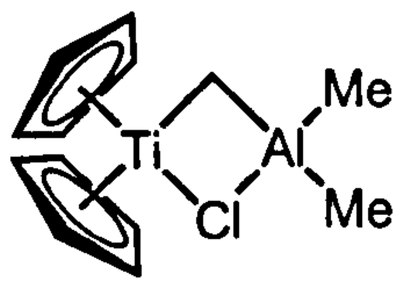
MeOH (75 cm^3) and added dropwise to a solution of sodium methoxide (11.1 g 0.21 mol) in MeOH (200 cm^3) and left to stir at r.t. for 20 h. The reaction mixture was neutralized with 7 M HCl. The product was extracted with EtOAc (2 x 200 cm^3), washed with brine (50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid. The solid (7.82 g, 49.2 mmol) and TsOH (0.75 g, 3.94 mmol) in toluene (200 cm^3) was heated to 110 °C with distillative removal of MeOH for 6 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography using 20 – 60 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give 3-methoxy-1H-pyrrole-2,5-dione (5.0 g , 77%) as a pale yellow solid: ν_{max}(film)/cm^{-1} 3213, 1714, 1635, 1291, 1237, 1113, 975 and 809; d_H (400 MHz; $CDCl_3$; Me_4Si) 3.95 (3H, s, OCH_3) and 5.44 (1H, s, C*H*=C); d_H (400 MHz; $CDCl_3$; Me_4Si) 59.1 (CH_3), 97.5 (CH), 161.1 (C), 165.2 (C) and 169.3 (C).

Stock solution of benzenesulfenyl chloride



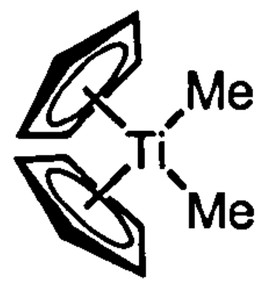
Benzenesulfenyl chloride was prepared immediately prior to its use in the following method: To a solution of diphenyl disulsulfide (2.57 g, 11.8 mmol) in DCM (32.1 cm^3) was added SO_2Cl_2 (0.95 cm^3, 11.8 mmol) at r.t. and left to stir for 5 min. The volume of the resulting yellow solution was completed to 53.5 cm^3 with DCM. The solution was used as such, assuming a concentration of 0.4 M benzenesulfenyl chloride.

Stock solution of Tebbe reagent[61]



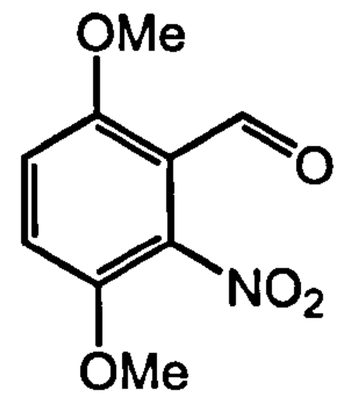
To a slurry of *bis*(cyclopentadienyl)titanium dichloride (4.88 g, 19.6 mmol) in toluene (10 cm^3) was added a 2 M $AlMe_3$ solution in toluene (19.6 cm^3, 39.2 mmol) to produce a dark red solution. The reaction mixture was allowed to stir for 48 h to give a 0.66 M solution of Tebbe reagent. The solution was stored at 0 °C under a nitrogen atmosphere.

Stock solution of Petasis reagent[72]

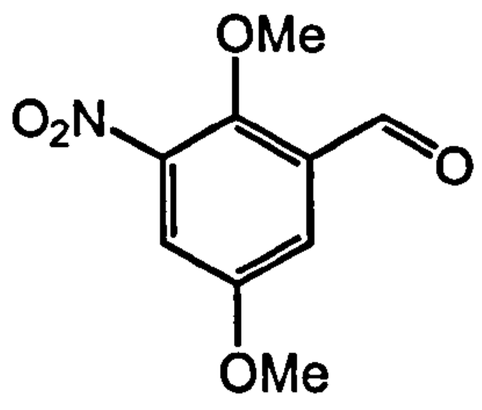


To a slurry of *bis*(cyclopentadienyl)titanium dichloride (4.2 g, 16.7 mmol) in anhydrous toluene (45 cm^3) was added a 3 M MeMgCl solution in THF (12.6 cm^3, 38 mmol) dropwise at -5 °C over 1 h. The resulting solution was mechanically stirred at 0 °C for 1 h, at which point the reaction was shown to be complete by ^1H NMR. The reaction mixture was quenched by dropwise addition of 6 % NH_4Cl (0.7 g, diluted to 11.7 cm^3) over a period of 30 min. The reaction mixture was diluted with toluene (5 cm^3) and the organic was washed with cold water (3 x 10 cm^3), brine (10 cm^3), dried over $MgSO_4$ and carefully concentrated *in vacuo* at a bath temperature of no more than 35 °C to a weight of 15 g. The solution was diluted with anhydrous THF (16 cm^3). The resulting orange solution was assayed by ^1H NMR to be a 0.46 M solution of Petasis reagent. The solution was stored at 0 °C under a nitrogen atmosphere.

3,6-Dimethoxy-2-nitrobenzaldehyde 141[49]

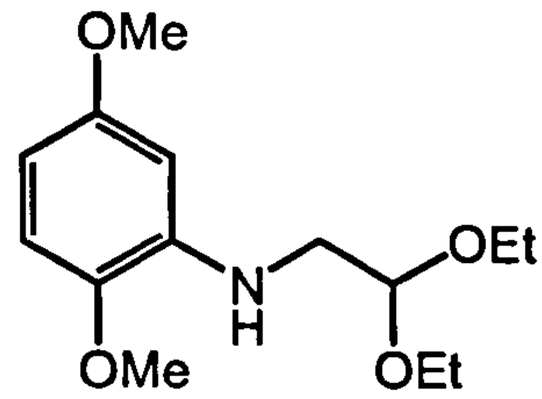


To a cooled solution of 2,5-dimethoxybenzaldehyde **140** (20 g, 0.12 mol) in anhydrous DCM (80 cm^3) was slowly added HNO_3 (80 cm^3) cautiously over 30 min at 0 °C. The mixture was kept at 0 °C for a further 30 min, after which ice-water (250 cm^3) was added and the product filtered after 1 h. After washing well with water and drying under reduced pressure, gave nitrobenzaldehyde **141** (17.8 g, 70 %) as a yellow solid; ν_{max}(film)/cm^{-1} 1692, 1536 and 1224; d_H (400 MHz; $CDCl_3$; Me_4Si) 3.86 (3 H, s, C*H*$_3$O), 3.94 (3 H, s, C*H*$_3$O), 7.10 (1H, d, *J* 9.3, Ar*H*) 7.28 (1H, d, *J* 9.3, Ar*H*) and 10.36 (1H, s, C*H*O); d_C (400 MHz; $CDCl_3$; Me_4Si) 55.8 (CH_3), 56.1 (CH_3), 110.4 (CH), 113.32 (C), 123.4 (C), 124.9 (CH), 153.6 (C), 156.7 (C) and 189.5 (C); *m/z* (EI) 211.0476 (M^+. requires 211.0481 $C_9H_9NO_5$), (EI) 211 (M^+ +H, 15 %), 195 (17), 179 (13), 163 (19), 151 (40), 135 (47), 123 (31), 107 (34), 92 (29), 75 (100) and 63 (32).



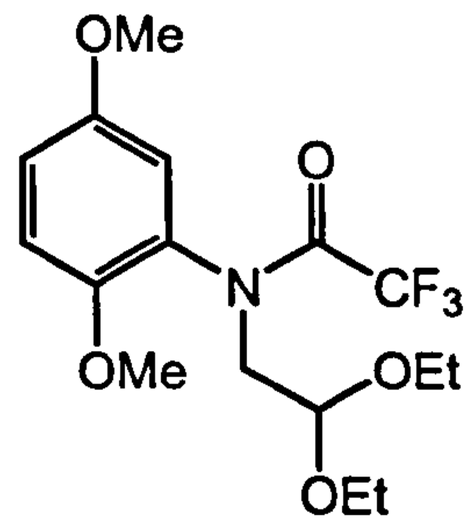
And nitrobenzaldehyde **142** (4.3 g, 17 %) as a yellow solid; d_H (400 MHz; $CDCl_3$; Me_4Si) 7.26 (6 H, s, 2 × C*H*$_3$O), 7.44 (1H, s, Ar*H*) 7.55 (1H, s, Ar*H*) and 10.47 (1H, s, C*H*O).

N-(2,2-Diethoxyethyl)-2,5-dimethoxybenzenamine 137[47]



A solution of 2,5-dimethoxybenzenamine (9.91 g, 60 mmol), $NaHCO_3$ (5.04 g, 60 mmol) and (2-bromo-1-ethoxyethoxy)ethane (9.03 cm^3, 60 mmol) in anhydrous DMF (75 cm^3) was heated under reflux in an atmosphere of nitrogen for 1 h. The mixture was concentrated *in vacuo* and then extracted with Et_2O (2 x 50 cm^3) and washed with H_2O (3 x 50 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a brown oil, which was purified by column chromatography on silica gel using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to leave a yellow oil. Further purification by distillation to give diethoxyethyl benzenamine **137** (11.5 g, 71 %) as a colourless oil; ν_{max}(film)/cm^{-1} 3427, 1738, 1520, 1215, 1048 and 1025; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.24 (6H,2 x t, *J* 6.8, 2 x OCH_2CH_3), 3.25 (2H, d, *J* 5.7, NCH_2CH), 2.53 – 3.61 (2H, m, OCH_2CH_3), 3.69 – 3.77 (2H, m, *J* 6.8, OCH_2CH_3), 3.74 (3H, s, CH_3O), 3.79 (3H, s, CH_3O), 4.38 (1H, bs, N*H*), 4.71 (1H, t, *J* 5.7, NCH_2CH), 6.16 (1H, dd, *J* 8.8 and 2.9, Ar*H*), 6.26 (1H, d, *J* 2.9, Ar*H*) and 6.66 (1H, d, *J* 8.8, Ar*H*); *m/z* (CI) 270.1700 (M^+ +H. requires 270.1705 $C_{14}H_{24}NO_4$), (CI) 270 (M^+ +H, 100 %), 224 (69), 178 (13), 166 (12), 103 (45) and 75 (12).

N-(Diethoxymethyl)-2,2,2-trifluoro-N-(2,5-dimethoxyphenyl)acetamide 138



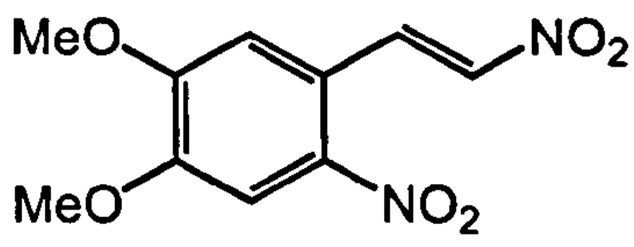
To a cooled solution of benzenamine **137** (1.0 g, 3.7 mmol) and Et_3N (0.6 cm^3, 4.3 mmol) in anhydrous hexane (10 cm^3) was slowly added triflouroacetic anhydride (0.6 cm^3, 4.1 mmol) over 5 min at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with H_2O (50 cm^3) and then extracted with Et_2O (2 x 50 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a brown oil, which was purified by distillation to give trifluoro acetamide **138** (1.1 g, 78 %) as a pale yellow oil; bp 95-100 °C (0.5 mm Hg); ν_{max}(film)/cm^{-1} 1738, 1698, 1120, 1067, 1044 and 899; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.18 (6H, sextet, *J* 3.9, 2 × OCH_2CH_3) 3.19 (1H, dd, *J* 13.7 and 6.9, NCH*H*CH), 3.47 – 3.74 (4H, m, 2 × OCH_2CH_3), 3.75 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.29 (1H, dd, *J* 13.7 and 4.9, NCH*H*CH), 4.80 (1H, dd, *J* 6.9 and 4.9, NCH_2CH) and 6.86 (3H, m, Ar*H)*.

General Procedure for Henry Reaction

To a cooled stirred suspension of nitrobenzaldehyde **131** or **141** (2.5 g, 12 mmol) in methanol (30 cm^3) was slowly added nitromethane (0.64 cm^3, 12 mmol) and NaOH solution (1 cm^3, 50 % w./v.) at 0 °C . The mixture was kept at 0 °C for a further 15 min, after which conc. HCl (7.5 cm^3) in H_2O (10 cm^3) was added. The yellow crystalline solid was filtered, washed well with water and finally with ethanol. Dehydration of the product was completed by heating on a steam bath with acetic anhydride (4 cm^3) and sodium acetate (1 g). The mixture was poured

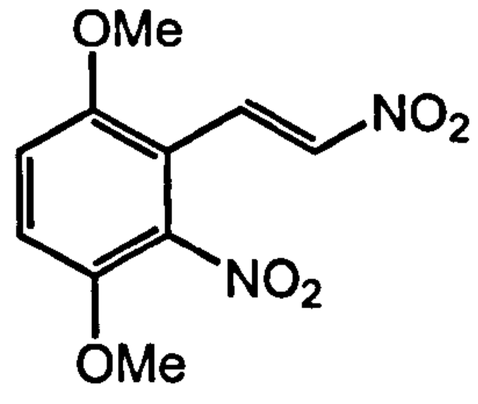
into ice-water (20 cm^3) and the product filtered after 1 h. After washing well with water and drying under reduced pressure gave the nitrovinylbenzene **132** and **143** as bright yellow solids;

1,4-Dimethoxy-2-nitro-3-((E)-2-nitrovinyl)benzene 132[44d]



(2.35 g, 78 %); ν_{max}(film)/cm^{-1} 1737, 1568, 1525, 1496, 1224 and 949; d_H (400 MHz; $CDCl_3$; Me_4Si) 4.01 (6 H, s, 2 x CH_3O), 6.90 (1H, s, Ar*H*), 7.42 (1H, d, *J* 13.4, Ar*CH*=$CHNO_2$), 7.74 (1H, s, Ar*H*) and 8.61 (1H, d, *J* 13.5, R*CH*=CHR); *m/z* (CI) 255.0611 (M^+ +H. requires 255.0617 $C_{10}H_{11}N_2O_6$), (CI) 255 (M^+ +H, 100 %), 239 (19), 208 (47), 192 (32), 180 (26), 152 (14), 79 (7) and 62 (9).

1,4-Dimethoxy-2-nitro-3-(2-nitrovinyl)-benzene 143

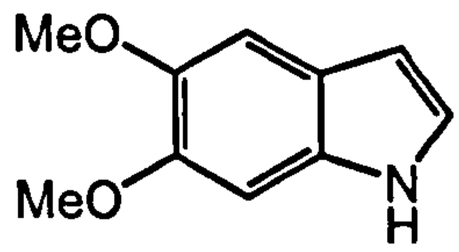


(2.29 g, 76 %); ν_{max}(film)/cm^{-1} 1526, 1508, 1495, 1219, 1191 and 851; d_H (400 MHz; $CDCl_3$; Me_4Si) 3.88 (3 H, s, CH_3O), 3.97 (3 H, s, CH_3O), 7.07 (1H, d, *J* 9.3, Ar*H*) 7.16 (1H, d, *J* 9.4, Ar*H*), 7.72 (1H, d, *J* 13.5, R*CH*=CHR) and 7.96 (1H, d, *J* 13.5, R*CH*=CHR); *m/z* (CI) 255.0618 (M^+ +H. requires 255.0617 $C_{10}H_{11}N_2O_6$), (CI) 255 (M^+ +H, 100 %), 212 (60), 208 (46), 191 (7), 178 (15), 165 (11), 150 (6), 120 (5), 107 (55) and 91 (9).

General Procedure for Reductive Cyclisation[44d]

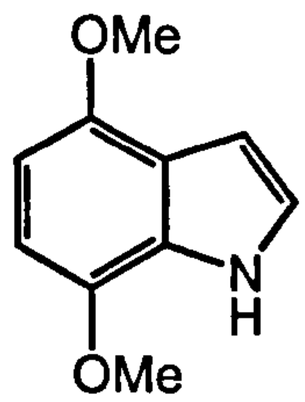
A mixture of nitrovinyl benzene **132** or **143** (2.0 g, 7.9 mmol), silica gel (8.0 g), reduced iron powder (8.0 g), glacial AcOH (24 cm^3) in benzene (20 cm^3) and cyclohexane (60 cm^3) was heated under reflux for 1 h with efficient mechanical stirring. A vigorous exothermic reaction was observed after 5 min, and the mixture turned dark. The dark colour disappeared on completion of the reaction. After which the reaction mixture was cooled, diluted with DCM (40 cm^3) and filtered. The filter cake was washed thoroughly with 10 % Et_2O in DCM (80 cm^3). The combined filtrates were washed with sodium metabisulfite solution (100 cm^3), $NaHCO_3$ solution (100 cm^3) and concentrated *in vacuo* to leave a brown solid, which was purified by column chromatography on silica gel using 30 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give indoles **126** and **128** as white crystalline solids;

5,6-dimethoxy-1H-indole 126



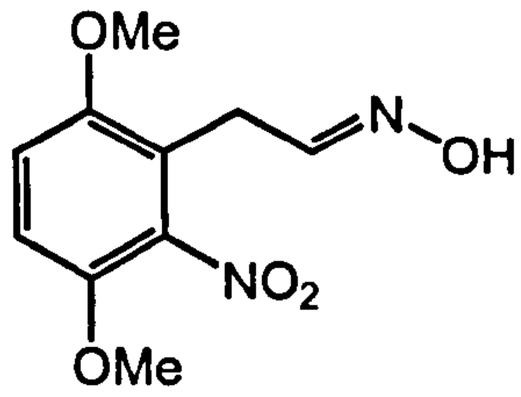
(1.25 g, 90 %); ν_{max}(film)/cm^{-1} 3367,1477, 1469, 1457, 1126, and 995; d_H (400 MHz; $CDCl_3$; Me_4Si) 3.90 (3H, s, CH_3O), 3.93 (3H, s, CH_3O), 6.46 (1H, t, *J* 2.4, RC*H*=CHR), 6.88 (1H, s, Ar*H*) 7.07-7.08 (1H, t, *J* 2.4, RC*H*=CHR), 7.10 (1H, s, Ar*H*) and 8.07 (1H, bs, N*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 56.1 (CH_3), 56.3 (CH_3), 94.5 (CH), 102.3 (CH), 102.4 (CH), 120.6 (C), 122.7 (CH), 130.1 (C), 145.1 (C) and 147.1 (C); *m/z* (CI) 178.0860 (M^+ +H. requires 178.0868 $C_{10}H_{12}NO_2$), (CI) 178 (M^+ +H, 100 %), 163 (38), 134 (10) and 79 (44).

4,7-dimethoxy-1H-indole 128



(0.5-0.8 g, 36-60 %); ν_{max}(film)/cm^{-1} 3364, 1737, 1524, 1500, 1258 and 974; d_H (400 MHz; $CDCl_3$; Me_4Si) 3.93 (3H, s, C*H*$_3$O), 3.93 (3H, s, C*H*$_3$O), 6.40 (1H, d, *J* 8.3, Ar*H*), 6.53 (1H, d, *J* 8.3, Ar*H*), 6.64 (1H, dd, *J* 2.9 and 2.3, RC*H*=CHR), 7.11 (1H, t, *J* 2.9, RC*H*=CHR) and 8.41 (1H, bs, N*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 55.6 (2 x CH_3), 98.7 (CH), 100.3 (CH), 101.4 (CH), 119.9 (C), 122.5 (CH), 127.6 (C), 141.1 (C) and 147.7 (C); *m/z* (CI) 178.0862 (M^+ +H. requires 178.0868 $C_{10}H_{12}NO_2$), (CI) 178 (M^+ +H, 84 %), 177 (100), 162 (29) and 134 (12).

(3,6-Dimethoxy-2-nitrophenyl)-acetaldehyde oxime 145



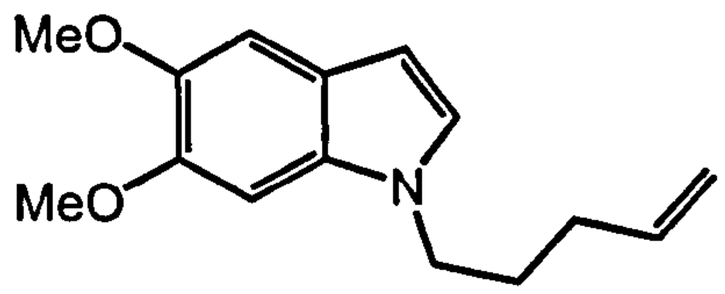
A mixture of 3,6-dimethoxy-2-nitrobenzaldehyde **143** (2.0 g, 8.2 mmol), ammonium formate (5.2 g, 82 mmol) and 10 % Pd/C (0.1g) in MeOH (80 cm^3) was heated under reflux for 1 h. The reaction mixture was cooled, filtered through celite, concentrated *in vacuo* to leave a brown solid, which was purified by column chromatography on silica gel using 30 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give oxime **145** (1.6 g, 81 %) as a pale green solid; ν_{max}(film)/cm^{-1} 3191, 1524, 1490 and 1261; d_H (400 MHz; DMSO; Me_4Si) 3.44 (2H, d, *J* 4.5, ArC*H*$_2$CH), 3.82 (6 H, s, 2 x C*H*$_3$O), 6.52 (1H, t, *J* 4.5, CH$_2$C*H*NR), 7.21 (1H, s, Ar*H*) and 7.21 (1H, s, Ar*H*); d_C (400 MHz; DMSO; Me_4Si) 22.1 (CH_2), 56.5 (CH_3), 56.7 (CH_3), 112.3 (CH), 113.7 (CH), 118.4 (C), 141.7 (C), 143.7 (C),

145.8 (CH) and 150.9 (C); *m/z* (CI) 241.0824 (M^+ +H. requires 241.0819 $C_{10}H_{13}N_2O_5$), (CI) 241 (M^+ +H, 50 %), 223 (25), 206 (46), 196 (100), 178 (31), 164 (14), 152 (6), 137 (5) and 120 (17).

General Procedure for Alkenylation of indoles[45]

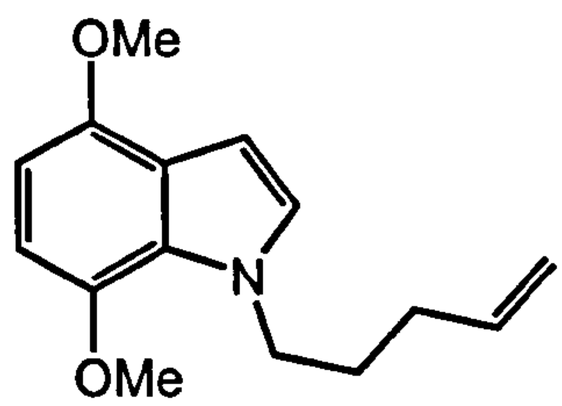
To a mixture of 5-bromopent-1-ene (0.04 cm^3, 0.42 mmol), 50 % NaOH (0.5 cm^3) and TBAB (20 mg, 20 mol %) in toluene (1 cm^3) was added indole **126** or **128** (50 mg, 0.28 mmol) at r.t. and was left to stir for 24 h. The mixture was diluted with H_2O (5 cm^3) and then extracted with EtOAc (4 x 10 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale green solid, which was purified by column chromatography on silica gel using 30 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give indole **133** as a pink solid and indole **144** as a colourless oil;

5,6-Dimethoxy-1-(pent-4-enyl)-1H-indole 133



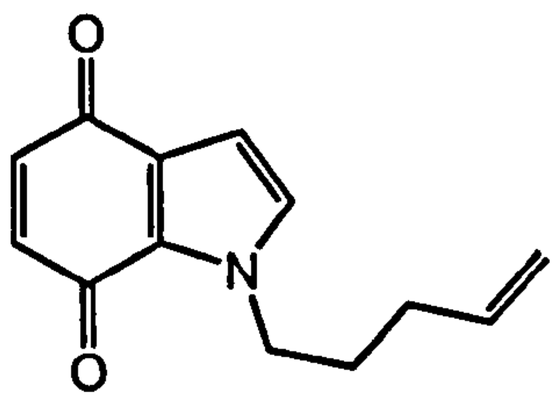
(64 mg, 92 %); (Found: C, 73.3; H, 8.1, N, 5.5. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8, N, 5.7%); ν_{max}(film)/cm^{-1} 1737, 1489, 1480, 1235, 1206, 992 and 917; d_H(400 MHz; $CDCl_3$; Me_4Si) 1.93 (2H, quintet, *J* 6.6, $CH_2CH_2CH_2$), 2.08 (2H, q, *J* 6.6, CH_2CH_2CH), 3.92 (3H, s, CH_3O), 3.95 (3H, s, CH_3O), 4.08 (2H, t, *J* 6.8 , NCH_2CH_2), 5.01 – 5.10 (2H, m, CH_2=CH), 5.74 – 5.89 (1H, m, CH_2CH=CH_2), 6.38 (1H, dd, *J* 3.0 and 0.6, RCH=CHR), 6.80 (1H, s, ArH), 6.98 (1H, d, *J* 3.0, RCH=CHR) and 7.08 (1H, s, ArH); d_C (400 MHz; $CDCl_3$; Me_4Si) 29.1 (CH_2), 30.7 (CH_2), 45.6 (CH_2), 56.3 (2 x CH_3), 93.0 (CH), 100.5 (CH), 102.6 (CH), 115.6 (CH_2), 121.1 (C), 126.2 (CH), 130.3 (C), 137.4 (CH), 144.9 (C) and 146.7 (C); *m/z* (CI) 246.1494 (M^+ +H. requires 246.1492 $C_{15}H_{20}NO_2$), (CI) 246 (M^+ +H, 100 %), 231 (18), 190 (11), 157 (17), 93 (5), 79 (51) and 65 (5).

4,7-Dimethoxy-1-(pent-4-enyl)-1H-indole 144



(68 mg , 97 %); ν_{max}(film)/cm^{-1} 1738, 1523, 1498, 1254, 1234, 980 and 911; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.95 (2H, quintet, *J* 6.6, $CH_2CH_2CH_2$), 2.08 (2H, q, *J* 6.6, CH_2CH_2CH), 3.92 (3H, s, CH_3O), 3.94 (3H, s, CH_3O), 4.39 (2H, t, *J* 6.8 , NCH_2CH_2), 5.01 – 5.10 (2H, m, CH_2=CH), 5.77 – 5.92 (1H, m, CH_2CH=CH_2), 6.38 (1H, d, *J* 8.2, Ar*H*), 5.54 (1H, d, *J* 8.3, Ar*H*), 6.56 (1H, d, *J* 2.6, R*CH*=CHR) and 6.95 (1H, d, *J* 2.7, R*CH*=CHR), d_C (400 MHz; $CDCl_3$; Me_4Si) 30.7 (CH_2), 31.2 (CH_2), 48.5 (CH_2), 55.5 (CH), 55.6 (CH), 98.1 (CH), 98.3 (CH), 101.8 (CH), 115.0 (CH_2), 121.6 (C), 126.6 (C), 127.9 (CH), 137.9 (CH), 142.4 (C) and 147.6 (C); *m/z* (CI) 246.1494 (M^+ +H. requires 246.1490 $C_{15}H_{20}NO_2$), (CI) 246 (M^+ +H, 75 %), 245 (100), 230 (10), 202 (20), 190 (14) and 176 (6).

1-(Pent-4-enyl)-1H-indole-4,7-dione 129



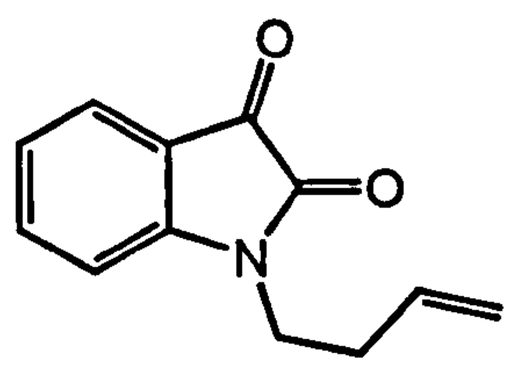
To a cooled solution of indole **144** (0.1 g, 0.41 mmol) in anhydrous THF (2.5 cm^3) was added silver(II) oxide (0.12 g) and conc. HCl (0.3 cm^3) at 0 °C. The mixture was immediately concentrated *in vacuo* to leave a black oil, which was quickly purified by column chromatography on silica gel using 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give dione **129** (55 mg, 63 %) as a yellow oil; ?$_{max}$(MeCN)/nm 339 and 412; ν_{max}(film)/cm^{-1} 1644, 1498, 984 and 912; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.91 (2H, quintet, *J* 6.6, $CH_2CH_2CH_2$), 2.09 (2H, q, *J* 6.6,

CH_2CH_2CH), 4.33 (2H, t, *J* 6.8, NCH_2CH_2), 5.00 – 5.09 (2H, m, CH_2=CH), 5.72 – 5.90 (1H, m, CH_2CH=CH_2), 6.52 (1H, d, *J* 15.3, CORCH=CHCOR), 6.57 (1H, d, *J* 15.2, CORCH=CHCOR), 6.59 (1H, d, *J* 2.7, RCH=CHR) and 6.88 (1H, d, *J* 2.7, RCH=CHR); d_C (400 MHz;$CDCl_3$; Me_4Si) 29.7 (CH_2), 30.4 (CH_2), 30.9 (CH_2), 48.4 (CH), 107.2 (CH), 115.8 (CH_2), 126.9 (CH), 128.6 (C), 129.6 (C), 136.9 (CH), 137.2 (CH), 177.8 (C) and 183.3 (C); *m/z* (CI) 216.1025 (M^+ +H. requires 216.1025 $C_{13}H_{14}NO_2$), (CI) 216 (M^+ +H, 90 %), 202 (6), 188 (100), 160 (12), 147 (6) and 133 (11).

General Procedure for Alkenylation of Isatins[57]

To a solution of indoline-2,3-dione **86** (2.0 g, 14 mmol) and K_2CO_3 (5.6 g, 41 mmol) in anhydrous DMF (100 cm^3) was added alkyl bromide (27 mmol) at r.t. and was left to stir for 24 h. The mixture was diluted with H_2O (100 cm^3) and then extracted with Et_2O (6 x 50 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the indolinediones, **146** as a bright red solid and **147** as a bright red oil;

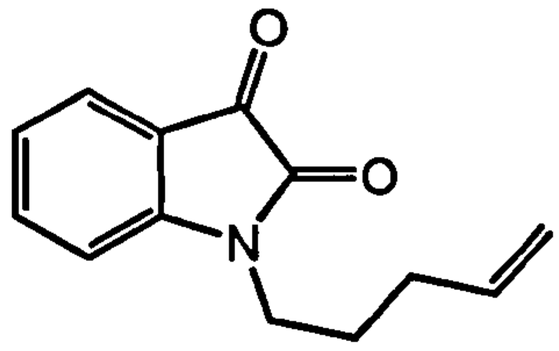
1-(But-3-enyl)indoline-2,3-dione 146



(2.7 g, 98 %); ?$_{max}$(MeCN)/nm 296 and 428; ν_{max}(film)/cm^{-1} 1728, 1599, 1470, 922 and 762; d_H (400 MHz; $CDCl_3$; Me_4Si) 2.47 (2H, q, *J* 6.8, CH_2CH_2CH), 3.80 (2H, t, *J* 6.8, NCH_2CH_2), 5.06 – 5.12 (2H, m, CH_2=CH), 5.75 – 5.85 (1H, m, CH_2CH=CH_2), 6.94 (1H, d, *J* 7.8, ArH), 7.11 (1H, t, *J* 7.8, ArH) and 7.57 – 7.60 (2H, m, 2 x ArH); d_C (400 MHz; $CDCl_3$; Me_4Si) 31.6 (CH_2), 39.6 (CH_2), 110.2 (CH), 117.5 (C), 118.2 (CH_2), 123.6 (CH), 125.4 (CH), 133.7 (CH), 138.3 (CH), 150.8 (C), 158.1 (C) and 183.4 (C); *m/z* (CI) 202.0868 (M^+ +H. requires 202.0868

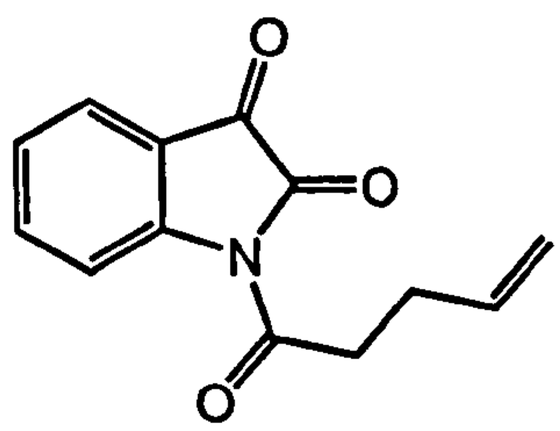
$C_{12}H_{12}NO_2$), (CI) 202 (M^+ +H, 100 %), 184 (12), 173 (15), 157 (24), 146 (7), 132 (69), 111 (6), 79 (29) and 65 (6).

1-(Pent-4-enyl)indoline-2,3-dione 147



(2.8 g, 96 %); ?$_{max}$(MeCN)/nm 296 and 428; ν_{max}(film)/cm^{-1} 1738, 1611, 1471, 1215 and 666; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.81 (2H, quintet, *J* 7.3, $CH_2CH_2CH_2$), 2.16 (2H, q, *J* 7.3, CH_2CH_2CH), 3.73 (2H, t, *J* 7.3, NCH_2CH_2), 5.01 – 5.10 (2H, m, CH_2=CH), 5.76 – 5.86 (1H, m, CH_2CH=CH_2), 6.89 (1H, d, *J* 7.8, Ar*H*), 7.11 (1H, t, *J* 8.3, Ar*H*) and 7.56 – 7.61 (2H, m, *J* 7.8, 2 × Ar*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 26.3 (CH_2), 30.8 (CH_2), 39.7 (CH_2), 110.1 (CH), 115.9 (CH_2), 117.6 (C), 123.6 (CH), 125.4 (CH), 136.8 (CH), 138.2 (CH), 151.0 (C), 158.1 (C) and 183.5 (C); *m/z* (CI) 216.1025 (M^+ +H. requires 216.1021 $C_{13}H_{14}NO_2$), (CI) 216 (M^+ +H, 100 %), 202 (12), 188 (85), 170 (35), 161 (34), 146 (22), 132 (43) and 105 (7).

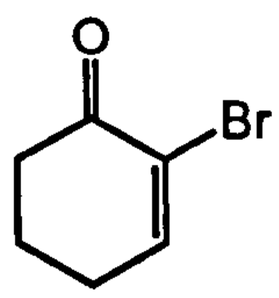
1-(pent-4-enoyl)indoline-2,3-dione 148



To a cooled solution of indoline-2,3-dione **61** (0.1 g, 0.68 mmol) in anhydrous THF (10 cm^3) was added NaH (0.02 g, 0.75 mmol) cautiously in portions over 5 min at 0 °C. After 10 min pent-4-enoyl chloride (0.075 cm^3, 0.68 mmol) was added dropwise. After 3 min the solution turned orange, indicating essential

completion of the reaction. The mixture was poured into ice-water (50 cm^3) and then extracted with Et_2O (4 x 50 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave an orange solid, which was purified by column chromatography on silica gel using 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give pentenoyl indolinedione **148** (79 mg, 51 %) as a yellow solid; ?$_{max}$(MeCN)/nm 281, 296 and 376; ν_{max}(film)/cm^{-1} 1780, 1749, 1702, 1591, 923 and 758; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.55 (2H, q, *J* 7.3, $COCH_2CH$), 3.23 (2H, t, *J* 7.3, $NCOCH_2$), 5.03 – 5.18 (2H, m, CH_2=CH), 5.84 – 5.99 (1H, m, CH_2CH=CH_2), 7.34 (1H, dt, *J* 7.6 and 0.66, Ar*H*), 7.69 – 7.80 (2H, m, 2 × Ar*H*) and 8.43 (1H, dd, *J* 8.3 and 0.66, Ar*H*); δ_C (400 MHz; $CDCl_3$; Me_4Si) 27.9 (CH_2), 37.6 (CH_2), 116.0 (CH_2), 118.3 (CH), 119.2 (C), 125.3 (CH), 126.1 (CH), 136.3 (CH), 138.9 (CH), 148.7 (C), 157.8 (C), 172.2 (C) and 180.2 (C); *m/z* (EI) 229 (M^+, 9 %), 202 (100), 184 (19), 179 (9), 174 (23), 146 (34), 120 (72), 92 (42), 83 (14), 77 (6), 65 (23) and 55 (61).

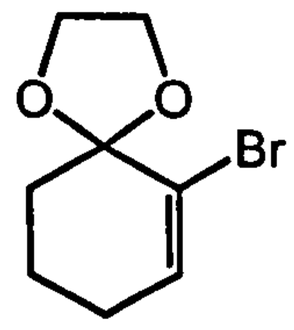
2-Bromocyclohex-2-enone 165[58]



A solution of bromine (2.55 cm^3, 50 mmol) in DCM (50 cm^3) was added dropwise over 30 min to a stirred solution of cyclohex-2-enone (4.86 cm^3, 50 mmol) in DCM (175 cm^3). The mixture stirred at r.t. for 1 h, after which Et_3N (7.08 cm^3, 50 mmol) was added. After a further 3 h the mixture was quenched with sodium thiosulfate (200 cm^3) and then extracted with DCM (2 x 100 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to leave a pale brown solid, which was purified by recrystalisation from EtOH and was washed with hexane to give bromocyclohexenone **165** (6.3 g, 72 %) as large colourless platelets: δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.02 (2H, quintet, *J* 6.1, $CH_2CH_2CH_2$), 2.41 (2H, q, *J* 6.0 and 4.5, CH_2CH_2CH), 2.57 (2H, t, *J* 6.6, $COCH_2CH_2$), 7.38 (1H, t, *J*

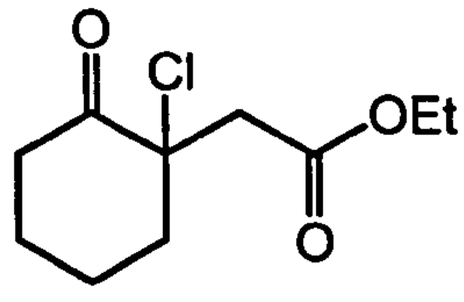
4.5, CH_2CHCBr); d_C (400 MHz;$CDCl_3$; Me_4Si) 22.5 (CH_2), 28.2 (CH_2), 38.2 (CH_2), 123.6(C), 151.1 (CH) and 191.0 (C); *m/z* (CI) 174.9753 (M^+ +H, requires 174.9758 $C_6H_8{}^{79}BrO$), (CI) 175 (M^+ +H, 100 %) 157 (65), 146 (26), 133 (18), 110 (21), 95 (23), 79 (28) and 67 (17).

1,4-Dioxa-6-bromospiro[4.5]dec-6-ene 166



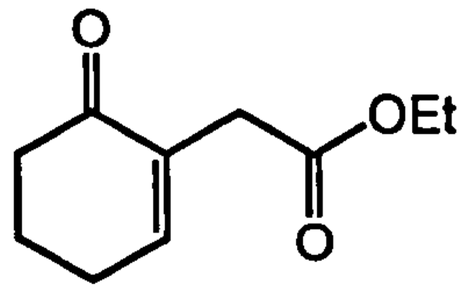
A mixture of 2-bromocyclohex-2-enone **165** (0.1 g, 0.58 mmol), ethane-1,2-diol (0.064 cm^3, 1.16 mmol) and p-TSA (5 mg, 5 mol %) in toluene (25 cm^3) was heated under reflux for 12 h under a Dean-Stark set up. The mixture was concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give acetal **166** (0.12g, 94 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1677, 1315 and 971; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.76 – 1.82 (2H, m, $CH_2CH_2CH_2$), 1.91 – 1.94 (2H, m, $CO_2CH_2CH_2$), 2.08 – 2.12 (2H, m, CH_2CH_2CH), 3.95 – 4.03 (2H, m, OCH_2CH_2), 4.16 – 4.23 (2H, m, OCH_2CH_2), 6.35 (1H, t, *J* 4.1, CH_2CHCBr); d_C (400 MHz;$CDCl_3$; Me_4Si) 20.4 (CH_2), 27.5 (CH_2), 35.7 (CH_2), 65.8 (2 x CH_2), 105.9 (C), 124.7 (C) and 136.0 (CH); *m/z* (CI) 220.9992 (M^+ +H. requires 221.0000 $C_8H_{12}{}^{81}BrO_2$), (CI) 219 (M^+ +H, 100 %), 190 (81 %), 177 (48), 139 (55), 99 (54) and 79 (14).

Ethyl 2-(1-chloro-2-oxocyclohexyl)acetate 170[68]



To a solution of ethyl 2-(2-oxocyclohexyl)acetate **169** (0.5 g, 2.7 mmol) in anhydrous DCM (5 cm^3) was added SO_2Cl_2 (0.24 ml, 3.0 mmol) in anhydrous DCM (0.24 cm^3) dropwise at r.t. and the solution was left to stir for 1 h. The reaction mixture was diluted with DCM (10 cm^3) and the organic was washed with water (2 x 50 cm^3), $NaHCO_3$ (50 cm^3), brine (50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The oil was purified by graduated column chromatography on silica gel using 5 – 20% EtOAc in petroleum ether 40 – 60 °C as the eluent to give ester **170** (0.41 g, 70 %) as a colourless oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 1.24 – 1.27 (3H, t, *J* 7.3, OCH_2CH_3), 1.65 – 1.78 (2H, m, $CH_2CH_2CH_2$), 1.98 – 2.09 (2H, m, $CH_2CH_2CH_2$), 2.34 – 2.48 (3H, m, $COCH_2CH_2$ and CH_2CHHC), 2.88 (1H, d, *J* 16.1, $CHHCO_2Et$), 2.96 (1H, ddd, *J*, 14.7, 13.2 and 5.4, CH_2CHHC), 3.13 (1H, d, *J* 16.1, $CHHCO_2Et$) and 4.13 (2H, q, OCH_2CH_3); d_C (400 MHz; $CDCl_3$; Me_4Si) 14.1 (CH_3), 21.3 (CH_2), 26.4 (CH_2), 37.1 (CH_2), 39.9 (CH_2), 43.4 (CH_2), 61.1 (CH_2), 69.7 (C), 169.9 (C) and 203.4 (C); *m/z* (EI) 219 (M^+, 9 %), 181 (40), 171 (93), 153 (76), 135 (40), 125 (44), 108 (39), 79 (100), 73 (97) and 61 (63).

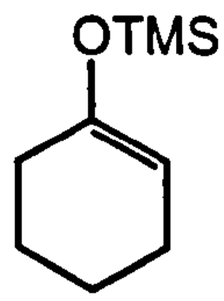
Ethyl 2-(6-oxocyclohex-1-enyl)acetate 168[68]



A mixture of ester **170** (0.41g, 1.9 mmol) and collidine (2 cm^3) was heated at 145 °C for 40 min. The reaction mixture was diluted with petroleum ether 40 – 60 °C (50 cm^3) and the collidine hydrochloride was removed by filtration. The organic

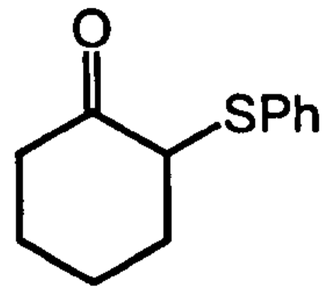
was washed with water (50 cm^3), $NaHCO_3$ (50 cm^3), brine (50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The oil was purified by column chromatography on silica gel using 10% EtOAc in petroleum ether 40 – 60 °C as the eluent to give ester **168** (69 mg, 20 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1171, 1695, 1181 and 1026; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.28 (3H, t, *J* 7.3, OCH_2CH_3), 1.75 – 1.81 (2H, m, CH_2CH_2), 1.86 – 1.94 (2H, m, CH_2CH_2), 2.52 (2H, t, *J* 6.8, CH_2CO_2Et), 3.39 (2H, dt, *J* 6.2 and 2.2, CH_2CH_2CO) 4.19 (2H, q, *J* 7.3, CH_2CH_3) and 6.46 (1H, t, *J* 2.6, C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 15.5 (CH_3), 23.8 (2 x CH_2), 29.1 (CH_2), 41.3 (CH_2), 60.8 (CH_2), 122.5 (CH), 151.6 (C), 166.4 (C) and 201.5 (C).

1-(trimethylsiloxy)cyclohex-1-ene 172



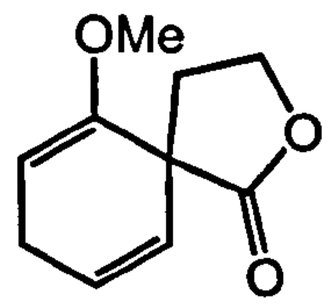
To a solution of diisopropylamine (16.4 cm^3, 0.12 mol) in anhydrous THF (100 cm^3) was added 2.5 M *n*-BuLi solution in hexanes (42.3 cm^3, 0.11 mol) dropwise at -78 °C. The solution was allowed to warm to r.t. and was then cooled back down to -78 °C. Cyclohexanone (10 cm^3, 96 mmol) was added dropwise over 15 min. The solution was left to stir for a further 30 min. The reaction mixture was quenched with TMSCl (24.4 cm^3, 0.19 mol) and the solution was allowed to warm to r.t. over 1 h. The solution was concentrated *in vacuo* to give a colourless oil. The oil was filtered through a plug of silica with 10% EtOAc in petroleum ether 40 – 60 °C as the eluent to give silyl enol ether **172** (16.3 g, 99 %) as a colourless oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 0.11 (9H, s, $Si(CH_3)_3$), 1.38 – 1.49 (2H, m, CH_2CH_2), 1.50 – 1.61 (2H, m, CH_2CH_2), 1.91 – 2.29 (4H, m, 2 x CH_2CH_2) and 4.71 (1H, s, C=C*H*); *m/z* (CI) 171 (M^+ +H, 16 %), 155 (15), 111 (9), 99 (38), 89 (31), 79 (100) and 61 (72).

2-(phenylthio)cyclohexenone 173



To a solution of silyl enol ether **172** (2.0 g, 11.8 mmol) in DCM (30 cm^3) was slowly added a 0.4 M benzenesulfenyl chloride solution in DCM (53.5 cm^3, 11.8 mmol) at 0 °C. After 2.5 h the reaction mixture was diluted with DCM (20 cm^3) and the organic washed with $NaHCO_3$ (100 cm^3), brine (100 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The oil was purified by column chromatography on silica gel using 10% EtOAc in petroleum ether 40 – 60 °C as the eluent and distilled *in vacuo* to give cyclohexenone **173** (1.5 g, 70 %) as a pale yellow oil: bp 145 – 147 °C (1.0 mbar); d_H (400 MHz; $CDCl_3$; Me_4Si) 1.66 – 2.33 (8H, m, 4 x CH_2CH_2), 2.87 – 2.94 (1H, m, $COCHR_2$) and 7.21 – 7.41 (5H, m, Ar*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 23.0 (CH_2), 27.7 (CH_2), 34.3 (CH_2), 39.4 (CH_2), 56.8 (CH), 127.7 (CH), 129.4 (2 x CH), 131.4 (2 x CH), 132.2 (C) and 207.9 (C).

6-Methoxy-2-oxa-spiro[4.5]deca-6,9-dien-1-one 176



Method A[71]

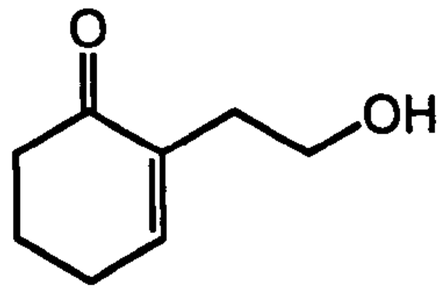
To a solution of 2-methoxybenzoic acid (2.5 g, 16.4 mmol) in anhydrous THF (30 cm^3) was distilled in ammonia (130 cm^3) at -33 °C. The resulting thick white suspension was stirred with efficient mechanical stirring. To which lithium (0.34 g), washed in hexane was added in small pieces, followed by 1-bromo-2-chloroethane (1.64 cm^3, 19.7 mmol). The ammonia was then allowed to

evaporate under a gentle stream of nitrogen. The mixture was concentrated *in vacuo* to give a pale orange oil. The oil was purified by column chromatography on silica gel using 25 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give spiro lactone **176** (0.59 – 1.18 g, 20 – 40 %) as a colourless oil that crystallised upon standing: d_H (400 MHz; $CDCl_3$; Me_4Si) 2.11-2.22 (1H, m, CC*H*HCH$_2$), 2.61 – 2.71(1H, m, CC*H*HCH$_2$), 2.75 – 3.01 (2H, m, *J* 22.7, 3.5 and 2.1 CHC*H*$_2$CH), 3.56 (3H, s, OC*H*$_3$), 4.29 – 4.45 (2H, m, OC*H*$_2$CH$_2$), 4.88 (1H, t, *J* 3.5 and 2.1,C*H*=C), 5.52 (1H, dt, *J* 9.8 and 2.1, C*H*=C), 5.96 (1H, ddt, *J* 9.8, 3.5 and 1.0,C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 26.2 (CH_2), 35.4 (CH_2), 48.1 (C), 54.4 (CH_3), 66.4 (CH_2), 93.4 (CH), 125.0 (CH), 127.0 (CH), 152.4 (C) and 177.7 (C); *m/z* (EI) 180.0780 (M^+, requires 180.0786 $C_{10}H_{12}O_3$), (EI) 180 (M^+, 83 %), 152 (82), 135 (100), 121 (92), 108 (94), 91 (45), 77 (61), 65 (36) and 53 (19).

Method B

Carried out as previous method, but with addition of 1.0 equivalent of potassium *t*-butoxide prior to lithium metal introduction. No purification was necessary affording **176** (2.10 g, 71 %).

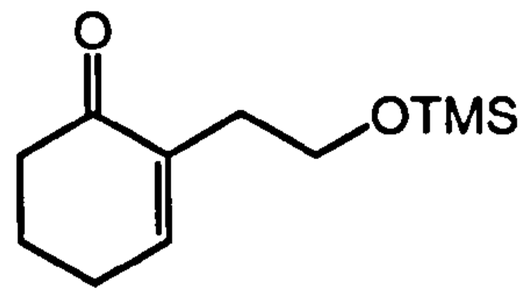
2-(2-hydroxyethyl)cyclohex-2-enone 162[71]



A mixture of spirolactone **176** (3.72, 20.7 mmol) in 2M HCl (200 cm^3) and MeOH (200 cm^3) was heated under reflux for 2 days. After cooling the mixture was diluted with H_2O (50 cm^3) and extracted with $CHCl_3$ (4 x 50 cm^3). The organic was washed with $NaHCO_3$ (50 cm^3), brine (50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil. The oil was purified by graduated column chromatography on silica gel using 25 – 75 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give alcohol **162** (2.50 g, 86 %) as a colourless oil:

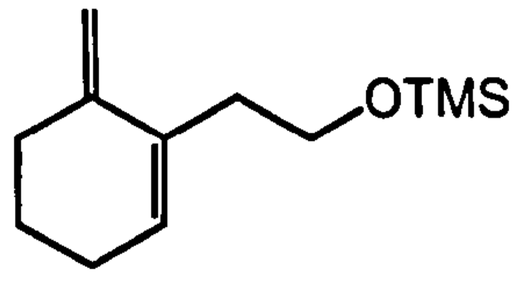
ν_{max}(film)/cm^{-1} 3400, 1651, 1423, 1377, 1100, 1042 and 884; d_H (400 MHz; $CDCl_3$; Me_4Si) 2.01 (2H, q, *J* 6.4, $CH_2CH_2CH_2$), 2.37 (2H, q, *J* 5.9 , CH_2CH_2OH), 2.42 – 2.46 (4H, m, CH_2CH_2), 3.16 (1H, bs, O*H*), 3.65 (2H, t, *J* 5.9, CH_2CH_2OH) and 6.83 (1H, t, *J* 4.0, C=C*H*); d_C (400 MHz;$CDCl_3$; Me_4Si) 22.9 (CH_2), 26.0 (CH_2), 33.9 (CH_2), 38.3 (CH_2), 62.1 (CH_2), 137.2 (C), 148.1 (CH) and 200.7 (C).

2-(2-trimethylsiloxyethyl)cyclohex-2-enone 177



To a solution of TMSCl (1.2 cm^3, 9.1 mmol), Et_3N (2.2 cm^3, 16 mmol) and DMAP (30 mg, 5 mol %) in DCM (30 cm^3) was added alcohol **162** (0.64 g, 4.6 mmol) dropwise at 0 °C and left to stir for 16 h. The reaction mixture was concentrated *in vacuo* onto silica gel and purified by column chromatography on silica gel using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give cyclohexenone **177** (0.75 g, 78 %) as a colourless oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 0.07 (9H, s, $Si(CH_3)_3$), 1.97 (2H, quintet, *J* 6.4, $CH_2CH_2CH_2$), 2.33 – 2.37 (2H, m, CH_2CH_2), 2.38 – 2.42 (4H, m, 2 x CH_2CH_2), 3.61 (2H, t, J 6.8, CH_2CH_2O) and 6.79 (1H, t, *J* 4.0, C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) -0.1 (CH_3), 23.4 (CH_2), 26.5 (CH_2), 33.5 (CH_2), 38.8 (CH_2), 61.8 (CH_2), 136.8 (C), 147.6 (CH) and 199.6 (C); *m/z* (EI) 139 (M^+ – TMS, 19 %) 123 (100), 111 (10) and 89 (9).

2-(6-methylenecyclohex-1-enyl) trimethylethoxysilane 178



Tebbe olefination procedure

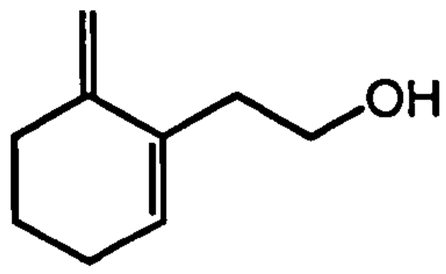
To a solution of cyclohexanone **177** (208 mg, 1 mmol) and pyridine (10 µl) in a 3:1 mix of anhydrous toluene:THF (1.26 cm^3, 0.5 cm^3) was added 0.66 M Tebbe reagent solution in toluene (1.6 cm^3, 1 mmol) dropwise at -40 °C and left to stir for 30 min. The reaction mixture was then allowed to warm to r.t. and stirred for a further 1 h 30 min. The reaction mixture was quenched at -10 °C with dropwise addition of 2 M NaOH (0.4 cm^3). The mixture was diluted with Et_20 (10 cm^3), dried over $MgSO_4$, filtered through Celite® and concentrated *in vacuo* to give a yellow oil. The oil was purified by column chromatography on silica gel using 5 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **178** (32 mg, 15 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1249, 1081, 845, 837 and 746; d_H (400 MHz; C_6D_6; Me_4Si) 0.20 (9H, s, $Si(CH_3)_3$), 1.60 – 1.67 (2H, m, CH_2CH_2) 2.02 – 2.06 (2H, m, CH_2CH_2) 2.34 – 2.38 (2H, m, CH_2CH_2), 2.69 (2H, t, *J* 7.3, CH_2CH_2OTMS), 3.86 (2H, t, *J* 7.3, CH_2CH_2O), 4.89 (1H, s, C=C*H*H), 5.13 (1H, s, C=C*H*H) and 5.73 (1H, t, *J* 4.0, C*H*=C); d_C (400 MHz; C_6D_6; Me_4Si) 0.2 (CH_3), 24.3 (CH_2), 27.3 (CH_2), 33.8 (CH_2), 37.9 (CH_2), 63.1 (CH_2), 108.5 (CH_2), 130.1 (CH), 134.7 (C) and 144.4 (C).

Petasis olefination procedure

A solution of cyclohexanone **177** (212 mg, 1.0 mmol) in 0.46 M Petasis reagent solution in toluene/THF (6.5 cm^3, 3.0 mmol) was aged in the dark for 4 h at 80 °C. After cooling to r.t. $NaHCO_3$ (0.12 g), MeOH (2 cm^3) and water (0.1 cm^3) were added, and the mixture was heated to 40 °C and left to stir overnight. The reaction mixture was cooled, filtered through Celite® and concentrated *in vacuo*

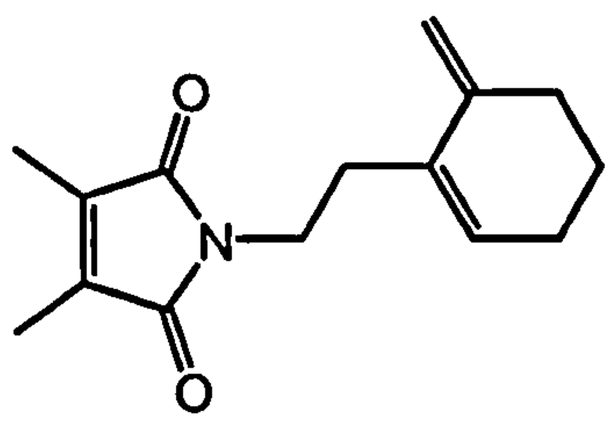
to give a yellow oil. The oil was purified by column chromatography on silica gel using 5 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **178** (32 mg, 50 %) as a colourless oil.

2-(6-methylenecyclohex-1-enyl)ethanol 163



Using the Petasis olefination procedure using **162** on a 7.1 mmol scale gave diene **163** (0.55 g, 56 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3363, 1014 and 734; d_H (400 MHz; C_6D_6; Me_4Si) 1.56 – 1.62 (3H, m and bs, CH_2CH$_2$ and O*H*), 1.97 – 2.01 (2H, m, CH_2CH$_2$), 2.30 – 2.33 (2H, m, CH_2CH$_2$), 2.46 (2H, t, *J* 6.6, CH_2CH$_2$O), 3.69 (2H, t, *J* 6.6, CH$_2$CH_2OH) 4.84 (1H, s, C=C*H*H), 5.02 (1H, s, C=C*H*H) and 5.72 (1H, t, *J* 4.0, C*H*=C); d_C (400 MHz; C_6D_6; Me_4Si) 24.2 (CH$_2$), 27.2 (CH$_2$), 33.7 (CH$_2$), 37.5 (CH$_2$), 62.3 (CH$_2$), 108.8 (CH$_2$), 130.2 (CH), 134.3 (C) and 144.1 (C); *m/z* (CI) 123 (M^+ +H – H_20, 70 %) 109 (63), 93 (44), 79 (35), 67 (20) and 61 (49).

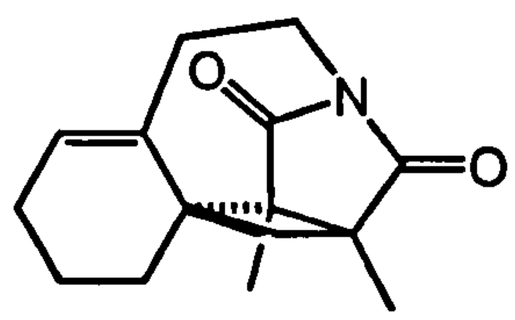
3,4-Dimethyl-1-(2-(6-methylenecyclohex-1-enyl)ethyl)-1H-pyrrole-2,5-dione 179



Alcohol **163** was coupled to 3,4-dimethyl-1H-pyrrole-2,5-dione, using the modified Walker Mitsunobu procedure. The oil was purified by graduated column chromatography on silica gel using 10 - 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give alcohol **163** (100 mg); as a colourless oil. Further elution with 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent gave diene **179**

(150 mg, 42 %) as a colourless oil: ?$_{max}$(MeCN)/nm 228 and 285sh; ν_{max}(film)/cm^{-1} 1697, 1405, 1360, 1220 and 733; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.62 (2H, quintet, *J* 6.4, $CH_2CH_2CH_2$), 1.92 (6H, s, 2 x CH_3), 2.04 – 2.09 (2H, m, CH_2CH_2), 2.28 – 2.31 (2H, m, CH_2CH_2), 2.39 (2H, t, *J* 7.3, CH_2CH_2N), 3.56 (2H, t, *J* 7.3, CH_2CH_2N), 4.79 (1H, s, C=C*H*H), 5.02 (1H, s, C=C*H*H) and 5.66 (1H, t, *J* 4.0, C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 8.9 (2 x CH_3), 23.4 (CH_2), 26.7 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 37.8 (CH_2), 108.3 (CH_2), 130.0 (CH), 133.9 (C), 137.3 (C), 143.0 (C) and 172.4 (2 x C); *m/z* (EI) 245.1416 (M^+. requires 245.1412 $C_{15}H_{19}NO_2$), (EI) 245 (M^+, 41 %), 138 (100), 126 (14), 120 (26), 105 (29), 91 (40), 79 (27) and 67 (16).

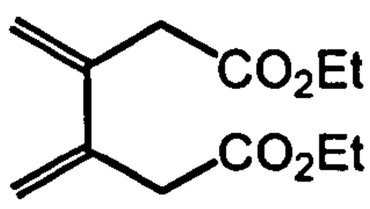
Cyclobutane 57



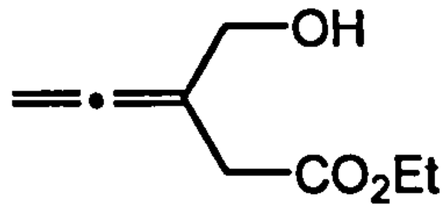
A solution of maleimide **179** (245 mg, 1 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 8 h. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 25 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give imide **180** (137 mg, 56 %) as a white crystalline solid: (Found: C, 73.3; H, 8.1; N, 5.8. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7 %); ν_{max}(film)/cm^{-1} 1768, 1700, 1010, 838 and 779; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.15 – 1.42 (2H, m, 2 x C*H*HCH_2), 1.20 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.54 – 1.59 (1H, m, C*H*HCH_2), 1.81 – 1.94 (2H, m, CH_2CH_2), 1.97 – 2.10 (2H, m, C*H*HCH_2 and C*H*HCH_2N), 2.07 (1H, d, *J* 12.7, CC*H*HC), 2.33 (1H, d, *J* 12.7, CC*H*HC), 2.71 – 2.80 (1H, m, C*H*HCH_2N), 3.59 (1H, dt, *J* 12.7 and 3.9, CH_2CHHN), 3.76 – 3.80 (1H, dd, *J* 12.7 and 5.9, CH_2CHHN) and 5.77 (1H, t, *J* 4.0, C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 8.2 (CH_3), 15.4 (CH_3), 19.6 (CH_2), 26.2 (CH_2), 35.1 (CH_2), 38.0 (CH_2), 42.7 (CH_2), 44.2 (C),

45.8 (C), 48.0 (CH_2), 58.4 (CH_2), 133.3 (CH), 136.2 (C), 184.6 (C) and 189.4 (C); *m/z* (ESI) 268.1306 (M^+ +Na. requires 268.1308 $C_{15}H_{19}NaNO_2$).

Diethyl 3,4-dimethylenehexanedioate 64 and ethyl 3-(hydroxymethyl)penta-3,4-dienoate 187[75]



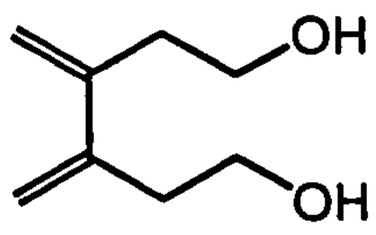
A mixture of but-2-yne-1,4-diol (3.0 g, 34.8 mmol), propionic acid (87 µl) and triethyl orthoacetate (59 cm^3, 0.32 mol) was heated to 140 °C with distillative removal of EtOH. After 7 h heating TLC showed only a small amount of single claisen rearrangement product. The reaction mixture was diluted with EtOAc (60 cm^3) and the organic washed with 2 M HCl (100 cm^3), $NaHCO_3$ (100 cm^3), brine (100 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil. The oil was purified by graduated column chromatography on silica gel using 5 – 15 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **187** (6.1 g, 78 %) as a colourless oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 1.24 (6H, t, *J* 7.3, 2 x OCH_2CH_3), 3.29 (4H, s, 2 x CH_2CO), 4.14 (4H, q, *J* 7.3, 2 x OCH_2CH_3), 5.16 (2H, s, 2 x *H*HC=C) and 5.28 (2H, s, 2 x *H*HC=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 14.4 (2 x CH_3), 40.8 (2 x CH_2), 61.1 (2 x CH_2), 117.5 (2 x CH_2), 139.8 (2 x C) and 171.7 (2 x C); *m/z* (EI) 226 (M^+, 62 %), 181 (49), 153 (100), 135 (52), 125 (60), 108 (47), 95 (31), 83 (27), 79 (91) and 67 (28).



Further elution with 15 – 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent gave ethyl 3-(hydroxymethyl)penta-3,4-dienoate **188** (325 mg, 6 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3424, 1962, 1729, 1025 and 733; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.24 (3H, t, *J* 7.3, OCH_2CH_3), 2.56 (1H, bs, O*H*), 3.08 (2H, t, *J* 2.4, CH_2CO), 4.13 (2H, q, *J* 7.3, OCH_2CH_3), 4.14 (2H, t, *J* 2.4, CH_2O) and 4.84 (2H,

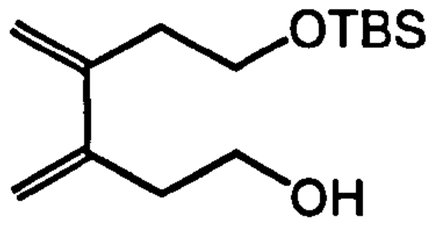
quintet, *J* 2.4, H_2C=C=C); d_C (400 MHz;$CDCl_3$; Me_4Si) 14.4 (CH_3), 36.0 (CH_2), 61.3 (CH_2), 63.5 (CH_2), 77.5 (CH_2), 97.6 (C), 172.1 (C) and 207.1 (C); *m/z* (CI) 139 (M^+ +H – H_20, 68 %), 127 (20), 111 (100), 101 (43), 89 (86), 83 (25) and 61 (100).

3,4-Dimethylenehexane-1,6-diol 189



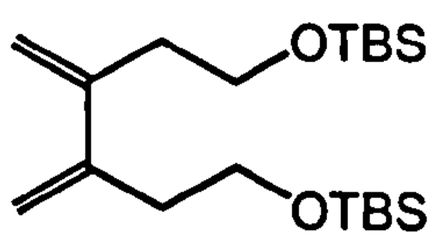
To a slurry of $LiAlH_4$ (2.0 g, 52.6 mmol) in anhydrous THF (200 cm^3) was added a solution of ester **187** (6.0 g, 26.5 mmol) in anhydrous THF (5 cm^3) dropwise at r.t. and left to stir for 16 h. The reaction mixture was quenched with water (2.0 cm^3), 15 % NaOH (2.0 cm^3) and additional water (6.0 cm^3). After 1 h the mixture was filtered through Celite® and the filter cake was washed with THF (5 x 100 cm^3), concentrated *in vacuo*, diluted with EtOAc (50cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale green oil. The oil was purified by distillation to give alcohol **189** (3.5 g, 94 %) as a colourless oil: bp 114 – 116 °C (0.1 mbar); d_H (400 MHz; $CDCl_3$; Me_4Si) 1.86 (2H, s, 2 x O*H*), 2.57 (4H, t, *J* 6.2, 2 x C$H_2$$CH_2$O), 3.75 (4H, t, *J* 6.2, 2 x CH_2CH_2O), 5.10 (2H, s, 2 x C=C*H*H) and 5.20 (2H, s, 2 x C=C*H*H); d_C (400 MHz; $CDCl_3$; Me_4Si) 38.0 (2 x CH_2), 61.5 (2 x CH_2), 115.1 (2 x CH_2) and 143.8 (2 x C); *m/z* (CI) 143 (M^+ +H, 21 %) 125 (28), 107 (48), 95 (63), 89 (62), 79 (32) and 61 (100).

6-*tert*-Butyldimethylsiloxy-3,4-dimethylenehexan-1-ol 191



Method A

To a solution of TBSCl (1.06 g, 7.0 mmol), Et_3N (6.9 cm^3, 49.3 mmol) and DMAP (86 mg, 5 mol %) in DCM (100 cm^3) was added alcohol **189** (2.0 g, 14.1 mmol) dropwise at 0 °C and left to stir overnight. The reaction mixture was concentrated *in vacuo* onto silica gel and purified by graduated column chromatography on silica gel using 33 – 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **192** (1.51 g, 29%) as a colourless oil:



ν_{max}(film)/cm^{-1} 1596, 1472, 1254, 1092, 832 and 772; d_H (400 MHz; C_6D_6; Me_4Si) 0.05 (12H, s, 2 x Si(CH_3)$_2$), 0.97 (18H, s, 2 x SiC(CH_3)$_3$), 2.53 (4H, t, *J* 7.3, 2 x CH_2CH_2O), 3.71 (4H, t, *J* 7.3, 2 x CH_2CH_2O), 4.97 (2H, s, 2 x C=CH*H*) and 5.16 (2H, s, 2 x C=CH*H*);

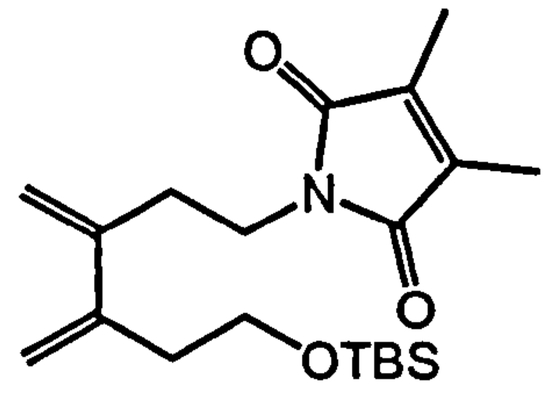
Further elution using 50 – 100 % Further elution with EtOAc gave title compound **191** (1.08 g, 30 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3353, 1595, 1472, 1254, 1094, 1044, 894 and 834; d_H (400 MHz; C_6D_6; Me_4Si) 0.02 (6H, s, Si(CH_3)$_2$), 0.95 (9H, s, SiC(CH_3)$_3$), 1.72 (1H, bs, O*H*), 2.39 (2H, dt, *J* 6.6 and 1.0, CH_2CH_2O), 2.45 (2H, dt, *J* 6.6 and 1.0, CH_2CH_2O), 3.57 (2H, t, *J* 6.6, CH_2CH_2O), 3.66 (2H, t, *J* 6.6, CH_2CH_2O), 4.92 (1H, s, C=C*H*H), 4.94 (1H, s, C=C*H*H), 5.07 (1H, d, *J* 1.3, C=C*H*H) and 5.09 (1H, d, *J* 1.3, C=C*H*H);

Further elution with EtOAc as the eluent gave starting material **189** (0.52 g, 26 %) as a colourless oil.

Method B

To a solution of alcohol **189** (2.0 g, 14.1 mmol), Et_3N (6.9 cm^3, 49.3 mmol) and DMAP (86 mg, 5 mol %) in DCM (100 cm^3) was added TBSCl (1.06 g, 7.0 mmol) in one portion at 0 °C and left to stir overnight. The reaction mixture was concentrated *in vacuo* onto silica gel and purified in the same way as Method A to give diene **192** (1.09 g, 21 %), diene **191** (1.80 g, 50 %) and starting material **189** (0.52 g, 26 %).

1-(6-*tert*-butyldimethylsiloxy-3,4-dimethylenehexyl)-3,4-dimethyl-1H-pyrrole-2,5-dione 193



Method A

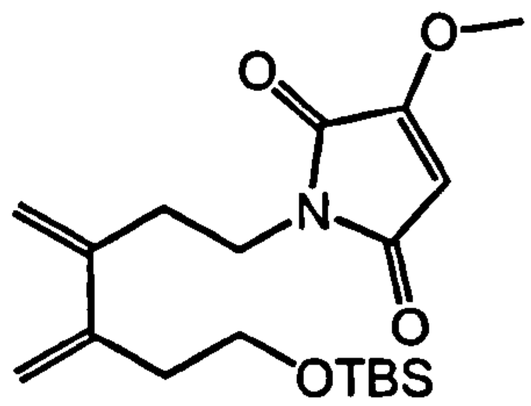
Alcohol **191** was coupled to dimethyl maleimide using the modified Walker Mitsunobu procedure. The oil was purified by graduated column chromatography on silica gel using 5 - 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **193** (48 mg, 9 %) as a colourless oil: $?_{max}$(MeCN)/nm 223 and 286sh; ν_{max}(film)/cm^{-1} 1702, 1405, 1090, 834, 775 and 732; d_H (400 MHz; C_6D_6; Me_4Si) 0.04 (12H, s, $Si(CH_3)_2$), 0.96 (18H, s, $SiC(CH_3)_3$), 1.55 (6H, s, CH_3), 2.52 (2H, t, *J* 7.3, CH_2CH_2X), 2.53 – 2.57 (2H, m, *J* 7.8, CH_2CH_2X), 3.57 – 3.61 (2H, m, *J* 7.8 and 1.5, CH_2CH_2X), 3.70 (2H, t, *J* 7.3, CH_2CH_2X), 4.90 (1H, s, C=C*H*H), 5.04 (1H, s, C=C*H*H), 5.09 (1H, s, C=C*H*H) and 5.37 (1H, s, C=C*H*H); d_C (400 MHz; C_6D_6; Me_4Si) -4.6 (2 x CH_3), 8.7 (2 x CH_3), 19.0 (C), 26.7 (3 x CH_3), 34.2 (CH_2),

38.3 (CH_2), 38.5 (CH_2), 63.5 (CH_2), 114.7 (CH_2), 115.1 (CH_2), 137.4 (2 x C), 144.0 (C), 144.8 (C) and 172.2 (2 x C); *m/z* (ESI) 386.2111 (M^+ +Na, requires 386.2122 $C_{20}H_{33}NaNO_3Si$), (EI) 363 (M^+, 7 %), 348 (56), 336 (23), 320 (56), 306 (100), 276 (24), 232 (14), 214 (44), 202 (27), 183 (100), 153 (21), 138 (100), 123 (25), 107 (36), 89 (33) and 75 (100).

Method B

Alcohol **191** was coupled to 3,4-dimethyl-1H-pyrrole-2,5-dione using the standard Mitsunobu procedure. The oil was purified by graduated column chromatography on silica gel using 5 - 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **193** (0.42 g, 80 %) as a colourless oil.

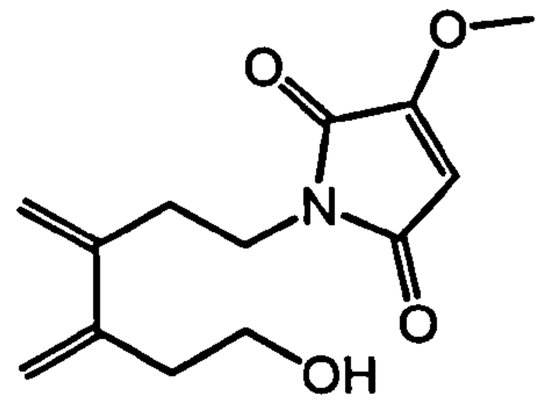
1-(6-*tert*-butyldimethylsiloxy-3,4-dimethylenehexyl)-3-methoxy-1H-pyrrole-2,5-dione 194



Alcohol **191** was coupled to methoxy maleimide using the standard Mitsunobu procedure. The oil was purified by graduated column chromatography on silica gel using 15 - 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **194** (0.44 g, 83 %) as a colourless oil: $?_{max}$(MeCN)/nm 239 and 404; ν_{max}(film)/cm^{-1} 1715, 1639, 1324, 1238, 1093, 836 and 777; d_H (400 MHz; C_6D_6; Me_4Si) 0.05 (6H, s, Si(CH_3)$_2$), 0.97 (9H, s, SiC(CH_3)$_3$), 2.49 – 2.56 (4H, m, *J* 7.3, CH_2CH_2X), 2.79 (3H, s, OCH_3), 3.56 (2H, t, *J* 7.3, CH_2CH_2X), 3.71 (2H, t, *J* 7.3, CH_2CH_2X), 4.65 (1H, s, C=C*H*R), 4.89 (1H, s, C=C*H*H), 5.04 (1H, s, C=C*H*H), 5.09 (1H, s, C=C*H*H) and 5.33 (1H, s, C=C*H*H); d_C (400 MHz; C_6D_6; Me_4Si) -0.5 (2 x CH_3), 19.0 (C), 26.7 (3 x CH_3), 34.0 (CH_2), 37.9 (CH_2), 38.5 (CH_2), 58.4 (CH_3), 63.5 (CH_2), 96.8 (CH), 114.8 (CH_2), 155.1 (CH_2), 144.0 (C), 144.7 (C),

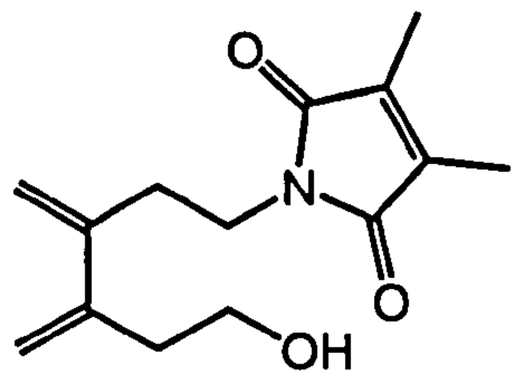
161.6 (C), 165.6 (C) and 170.2 (C); *m/z* (ESI) 388.1902 (M^+ +Na. requires 388.1915 $C_{19}H_{31}NaNO_4Si$), (EI) 365 (M^+, 11 %), 351 (29 %), 308 (100), 278 (39), 234 (44), 216 (64), 204 (33), 183 (84), 138 (61), 107 (67), 89 (35) and 75 (62).

1-(6-hydroxy-3,4-dimethylenehexyl)-3-methoxy-1H-pyrrole-2,5-dione 195



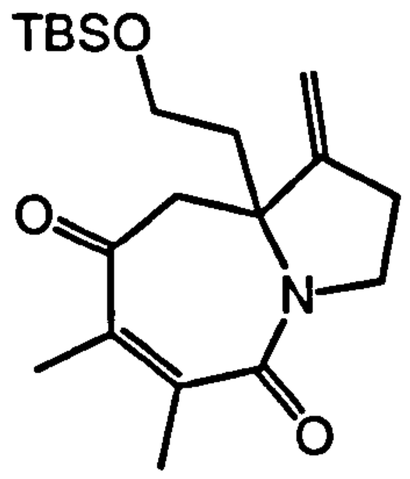
To a solution of Maleimide **194** (0.55 g, 1.5 mmol) in anhydrous THF (50 cm^3) was added 1M TBAF (3 cm^3, 3.0 mmol) dropwise at r.t. and left to stir for 24 h. The reaction mixture was quenched with water (25 cm^3) and diluted with EtOAc (50 cm^3). The organic was washed with brine (25 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The oil was purified by column chromatography on silica gel using 33 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **195** (92 mg, 24 %) as a colourless oil: $?_{max}$(MeCN)/nm 241 and 414; ν_{max}(film)/cm^{-1} 3405, 1708, 1638, 1323, 1044 and 779; d_H (400 MHz; $CDCl_3$; Me_4Si) 2.31 (1H, bs, O*H*), 2.48 (2H, t, *J* 6.4, CH_2CH_2X), 2.53 (2H, t, *J* 6.8, CH_2CH_2X), 3.58 – 3.65 (4H, m, *J* 6.8 and 6.4, CH_2CH_2X), 3.88 (3H, s, OCH_3), 4.92 (1H, s, C=C*H*H), 5.08 (1H, s, C=C*H*H), 5.11 (1H, s, C=C*H*H), 5.24 (1H, s, C=C*H*H) and 5.35 (1H, s, C=C*H*H); *m/z* (ESI) 252.1232 (M^+ +H, requires 252.1230 $C_{13}H_{18}NO_4$), (CI) 252 (M^+ +H, 44 %), 234 (24), 222 (55), 140 (47), 123 (72), 107 (100), and 95 (26).

1-(6-hydroxy-3,4-dimethylenehexyl)-3,4-dimethyl-1H-pyrrole-2,5-dione 190



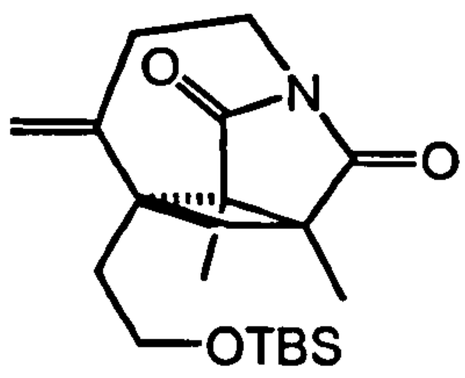
To a solution of maleimide **193** (364 mg, 1 mmol) and AcOH (0.29 cm^3, 5 mmol) in anhydrous THF (5 cm^3) was added 1M TBAF (5 cm^3, 5mmol) at r.t. and was left to stir for 24 h. The reaction mixture was quenched with water (25 cm^3) and diluted with EtOAc (25 cm^3). The organic was washed with $NaHCO_3$ (25 cm^3) and brine (25 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. The oil was purified by column chromatography on silica gel using 33 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give diene **190** (248 mg, 99 %) as a colourless oil: $?_{max}$(MeCN)/nm 231 and 295sh; ν_{max}(film)/cm^{-1} 3393, 1692, 1406, 1045 and 732; d_H (400 MHz; C_6D_6; Me_4Si) 1.41 (6H, s, 2 x C*H*$_3$), 1.76 (1H, bs, O*H*), 2.35 (2H, t, *J* 6.4, C*H*$_2$CH$_2$X), 2.50 (2H, t, *J* 6.8, C*H*$_2$CH$_2$X), 3.52 (2H, t, *J* 6.8, CH$_2$C*H*$_2$X), 3.55 (2H, t, *J* 6.4, C*H*$_2$CH$_2$X), 4.80 (1H, s, C=C*H*H), 4.93 (1H, s, C=C*H*H), 5.03 (1H, s, C=C*H*H) and 5.21 (1H, s, C=C*H*H); d_C (400 MHz; C_6D_6; Me_4Si) 8.7 (2 x CH_3), 34.2 (CH_2), 38.0 (CH_2), 38.5 (CH_2), 61.7 (CH_2), 115.3 (CH_2), 115.6 (CH_2), 137.5 (2 x C), 143.4 (C), 144.3 (C) and 172.5 (2 x C).

(Z)-2,3,9,9a-Tetrahydro-9a-(2-*tert*-butyldimethylsiloxyethyl)-6,7-dimethyl-1-methylene-1H-pyrrolo[1,2-a]azepine-5,8-dione 197 and Cyclobutane 196



Method A

A solution of maleimide **193** (363 mg, 1 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 9 h. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give cyclobutane **196** (152 mg, 42 %) as a crystalline solid:



ν_{max}(film)/cm^{-}1 1780, 1711, 1449, 1253, 1091, 1024, 834 and 775; d_H (400 MHz; $CDCl_3$; Me_4Si) 0.00 (6H, s, Si(CH_3)$_2$), 0.86 (9H, s, SiC(CH_3)$_3$), 1.22 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.77 – 1.89 (1H, m, C*H*HCH$_2$), 1.93 – 2.07 (1H, m, C*H*HCH$_2$), 2.33 – 2.62 (4H, m, 2 x CH_2CH_2), 3.38 – 3.44 (1H, m, OC*H*HCH$_2$), 3.47 – 3.57 (1H, m, OC*H*HCH$_2$), 3.67 – 3.77 (1H, m, ROC*H*HCH$_2$), 3.77 – 3.88 (1H, m, OC*H*HCH$_2$), 5.05 (1H, s, C=C*H*H) and 5.30 (1H, s, C=C*H*H); d_C (400 MHz; C_6D_6; Me_4Si) -4.7 (2 x CH_3), 8.9 (CH_3), 15.6 (CH_3), 19.0 (C), 26.7 (3 x CH_3), 35.6 (CH_2), 40.8 (CH_2), 46.3 (C), 48.7 (CH_2), 49.5 (C), 59.6 (C), 60.0 (CH_2), 60.6 (CH_2), 121.1 (CH_2), 170.6 (C), 184.6 (C) and 188.5 (C); *m/z* (ESI) 386.2106 (M^+ +Na. requires 386.2122 $C_{20}H_{33}NO_3SiNa$), (EI) 363 (M^+, 11 %), 348 (42), 306 (100),

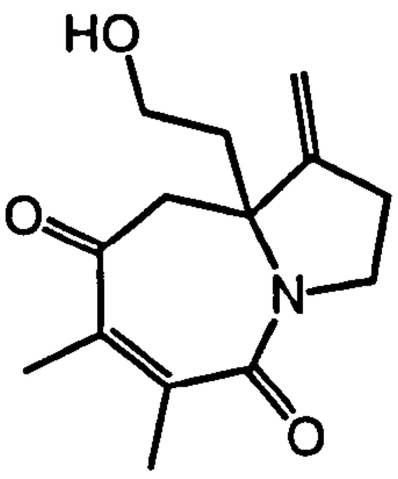
276 (35), 232 (17), 214 (46), 202 (30), 183 (91), 138 (88), 123 (21), 107 (29), 89 (27) 73 (70) and 59 (27).

Further elution with 33 % EtOAc gave azepine **197** (73 mg, 20 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1704, 1678, 1647, 1610, 1415, 1252, 1092, 834 and 776; d_H (400 MHz; C_6D_6; Me_4Si) -0.05 (6H, s, Si(C*H*$_3$)$_2$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 1.63 – 1.68 (1H, m, C*H*HCH$_2$N), 1.70 (3H, s, C*H*$_3$), 1.78 – 1.88 (1H, m, C*H*HCH$_2$N), 1.86 (3H, s, C*H*$_3$), 1.89 – 1.96 (1H, m, C*H*HCH$_2$O), 2.08 – 2.17 (1H, m, C*H*HCH$_2$O), 2.49 (1H, ddd, *J* 12.5, 9.0 and 5.0, CH$_2$C*H*HO), 2.69 (1H, d, *J* 14.4, COC*H*H), 3.39 (1H, dd, *J* 5.6 and 2.4, CH$_2$C*H*HN), 3.40 (1H, dd, *J* 5.9 and 1.7, CH$_2$C*H*HN), 4.25 (1H, dd, *J* 14.4 and 2.0, COC*H*H), 4.50 (1H, dddd, *J* 12.5, 6.6, 4.2 and 2.0, CH$_2$C*H*HO), 4.83 (1H, s, C=C*H*H) and 5.03 (1H, s, C=C*H*H); d_C (400 MHz; C_6D_6; Me_4Si) -4.8 (2 x CH$_3$), 16.7 (CH$_3$), 17.2 (CH$_3$), 18.9 (C), 26.6 (3 x CH$_3$), 34.5 (CH$_2$), 39.7 (CH$_2$), 46.5 (CH$_2$), 52.5 (CH$_2$), 60.3 (CH$_2$), 62.2 (C), 114.1 (CH$_2$), 137.1 (C), 138.6 (C), 145.7 (C), 170.4 (C) and 206.8 (C); *m/z* (CI) 364.2304 (M$^+$ +H. requires 364.2304 $C_{20}H_{34}NO_3Si$), (CI) 364 (M$^+$ +H, 83 %), 348 (20), 336 (41), 306 (64) and 232 (49).

Method B

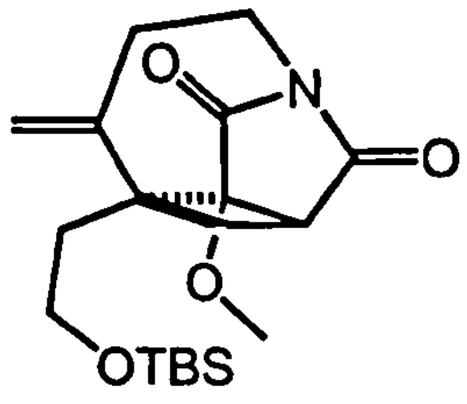
Carried out as Method A, but irradiation was performed in Vycor for 1 h to give cyclobutane **196** (87 mg, 24 %) and azepine **197** (11 mg, 3 %).

(Z)-2,3,9,9a-Tetrahydro-9a-(2-hydroxyethyl)-6,7-dimethyl-1-methylene-1H-pyrrolo[1,2-a]azepine-5,8-dione 198



A solution of maleimide **190** (249 mg, 1 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 9 h. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography on silica gel using 50 - 100 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **198** (20 mg, 8 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1670, 1639, 1608, 1409, and 775; d_H (400 MHz; C_6D_6; Me_4Si) 1.43 – 1.63 (1H, m, C*H*HCH$_2$N), 1.70 – 1.93 (1H, m, C*H*HCH$_2$N), 1.76 (3H, s, CH_3), 1.88 (3H, s, CH_3), 1.99 – 2.17 (1H, m, C*H*HCH$_2$O), 2.21 (1H, bs, O*H*), 2.52 (1H, ddd, *J* 12.5, 8.3 and 5.6, CH$_2$C*H*HO), 2.56 (1H, d, *J* 14.2, COC*H*H), 3.21 – 3.39 (2H, m, CH$_2$CH_2N), 4.13 (1H, dd, *J* 14.2 and 2.0, COC*H*H), 4.48 (1H, dddd, *J* 12.5, 6.9, 4.6 and 2.0, CH$_2$C*H*HO), 4.83 (1H, s, C=C*H*H) and 5.09 (1H, s, C=C*H*H); d_C (400 MHz; C_6D_6; Me_4Si) 17.3 (2 x CH$_3$), 34.2 (CH$_2$), 40.2 (CH$_2$), 46.4 (CH$_2$), 51.4 (CH$_2$), 58.9 (CH$_2$), 61.3 (C), 114.5 (CH$_2$), 137.3 (C), 138.1 (C), 145.5 (2 x C) and 171.0 (C).

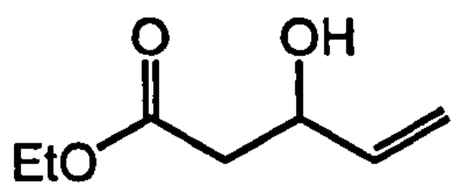
Cyclobutane 199



A solution of maleimide **194** (365 mg, 1 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 9 h. The reaction solution was concentrated *in vacuo*

onto silica gel and subjected to column chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give cyclobutane **199** (100 mg, 28 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1787, 1718, 1150, 1280, 1255, 1086, 992, 833 and 775; d_H (400 MHz; C_6D_6; Me_4Si) 0.00 (6H, s, Si(C*H*$_3$)$_2$), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 1.92 – 2.03 (2H, m, 2 x C*H*HCH$_2$X), 2.06 – 2.11 (1H, m, C*H*HCH$_2$X), 2.17 (1H, ddd, *J* 9.8, 8.8 and 4.9, C*H*HCH$_2$X), 2.24 (1H, d, *J* 11.7, CC*H*HCH), 2.57 (1H, d, *J* 8.8, CCH$_2$C*H*), 2.67 (1H, dd, *J* 11.7 and 8.8, CC*H*HCH), 2.93 (3H, s, OC*H*$_3$), 3.34 – 3.41 (1H, m, CH$_2$C*H*HX), 3.50 – 3.70 (3H, m, 3 x CH$_2$C*H*HX) and 4.81 (2H, s, C=C*H*$_2$); d_C (400 MHz; C_6D_6; Me_4Si) -4.6 (2 x CH_3), 19.0 (C), 26.7 (3 x CH_3), 34.2 (CH_2), 37.9 (CH), 39.9 (CH_2), 48.9 (CH_2), 55.3 (C), 48.9 (CH_2), 54.2 (CH_3), 60.2 (CH_2), 89.7 (C), 121.3 (CH_2), 148.6 (C), 181.0 (C) and 182.7 (C); *m/z* (EI) 366 (M^+ +H, 62 %) 350 (50), 308 (78), 278 (47), 264 (82), 249 (26), 234 (58), 216 (40) , 204 (29), 183 (100), 138 (76), 89 (75), 73 (100) and 59 (36).

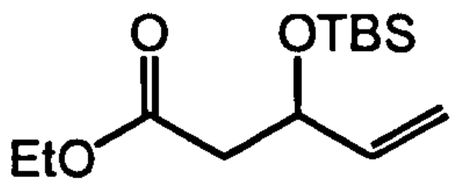
Ethyl 3-hydroxypent-4-enoate 208[78]



To a solution of HMDS (12.7 cm^3, 60 mmol) in anhydrous THF (50 cm^3) was added 2.5 M *n*-BuLi solution in hexanes (22 cm^3, 55 mmol) dropwise over 5 min at -78 °C. After the solution was stirred for 25 min, anhydrous ethyl acetate (4.9 cm^3, 50 mmol) in anhydrous THF (5 cm^3) was added dropwise over 30 min. This mixture was stirred for 20 min, subsequently acrolein (5.0 cm^3, 75 mmol) was added dropwise over 10 min. The resulting turquoise solution was stirred for 20 min and then quenched with sat. NH_4Cl (30 cm^3). The mixture was allowed to warm to r.t. and diluted with Et_20 (50 cm^3). The organic layer was washed with 0.1M HCl (5 x 100 cm^3), $NaHCO_3$ (100 cm^3), brine (100 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give ester **208** (8.6 g, 99 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3435, 1717, 1176, 1023 and 924; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.26 (3H, t, *J* 7.3, OCH$_2$C*H*$_3$) 2.48 – 2.60 (2H, m, COC*H*$_2$), 3.04 (1H, d, *J* 4.4,

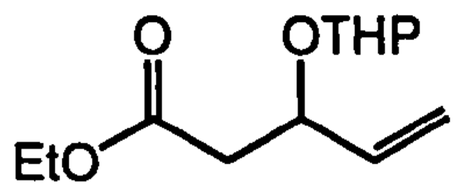
O*H*), 4.17 (2H, q, *J* 7.3, OC*H*$_2$CH$_3$), 4.56 – 4.50 (1H, m, C*H*OH), 4.90 (1H, ddd, *J* 10.3, 1.5 and 1.0, H*H*C=CH) 5.07 (1H, ddd, *J* 17.6, 1.5 and 1.0, H*H*C=CH) and 5.88 (1H, ddd, *J* 17.6, 10.3 and 5.4, H$_2$C=C*H*).

Ethyl 3-tert-butyldimethylsiloxypent-4-enoate 209



To a solution of hydroxy ester **208** (1.44 g, 10 mmol), Et$_3$N (4.9 cm^3, 35 mmol), DMAP (61 mg, 5 mol %) in DCM (50 cm^3) was slowly added TBSCl (1.81 g, 12 mmol) at r.t. and left to stir for 5 days. After which the mixture was concentrated *in vacuo* onto silica gel and purified by column chromatography on silica gel using 25 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give the ester **209** (2.5 g, 95 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1739, 1252, 1084, 830 and 776; d_H (400 MHz; CDCl$_3$; Me$_4$Si) 0.01 (6H, s, 2 x Si(C*H*$_3$)$_2$), 0.76 (9H, s, SiC(C*H*$_3$)$_3$), 1.15 (3H, t, *J* 7.3, OCH$_2$C*H*$_3$) 2.32 (1H, dd, *J* 14.7 and 5.4, COC*H*H), 2.41 (1H, dd, *J* 14.7 and 8.3, COC*H*H), 4.01 (2H, q, *J* 7.3, OC*H*$_2$CH$_3$), 4.44 – 4.92 (1H, m, C*H*OTBS), 4.96 (1H, ddd, *J* 10.7, 1.5 and 1.0, H*H*C=CH) 5.11 (1H, ddd, *J* 17.5, 1.5 and 1.0, H*H*C=CH) and 5.73 (1H, ddd, *J* 17.5, 10.7 and 6.4, H$_2$C=C*H*); d_C (400 MHz; CDCl$_3$; Me$_4$Si) -3.2 (2 x CH$_3$), 14.5 (CH$_3$), 18.4 (C), 26.0 (3 x CH$_3$), 44.2 (CH$_2$), 60.7 (CH$_2$), 71.3 (CH), 114.9 (CH$_2$), 140.8 (CH) and 171.4 (C).

Ethyl 3-(tetrahydro-2H-pyran-2-yloxy)pent-4-enoate 210



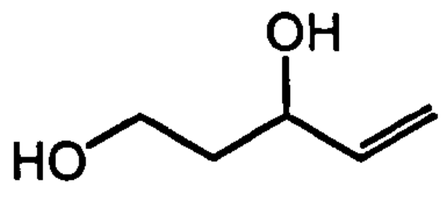
To a solution of hydroxy ester **208** (1.77 g, 6.9 mmol) and *p*TSA (64 mg, 5 mol %) in DCM (50 cm^3) was added DHP (0.66 cm^3, 7.2 mmol) dropwise at 0 °C. After 1 h the reaction mixture was quenched with NaHCO$_3$ (30 cm^3) and then

extracted with DCM (3 x 30 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil, which was purified by distillation to give the ester **210** (1.56 g, 99 %) as a colourless oil:

Major diastereomer: bp 100 – 102 °C (1.2 mbar); (Found: C, 63.2; H, 8.8; N, 0.0. $C_{12}H_{20}O_4$ requires C, 63.1; H, 8.8; N, 0.0 %); ν_{max}(film)/cm^{-1} 1736, 1117, 1019, and 981; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.20 (3H, t, *J* 7.3, OCH_2CH_3), 1.40 – 1.83 (6 H, m, 3 x CH_2CH_2), 2.43 (1H, dd, *J* 15.1 and 5.4, C*H*HCO), 2.59 (1H, dd, *J* 15.1 and 5.4, C*H*HCO), 3.37 – 3.48 (1H, m, CH_2CHHO), 3.74 – 3.83 (1H, m, CH_2CHHO), 4.02 – 4.14 (2H, m, *J* 7.3, OCH_2CH_3), 4.42 – 4.54 (1H, m, C*H*OR), 4.64 (1H, dd, *J* 4.4 and 2.2, C*H*OR), 5.14 – 5.28 (2H, m, H_2C=CH) and 5.61 (1H, ddd, *J* 17.1, 10.3 and 7.3, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 14.4 (CH_3), 19.2 (CH_2), 25.7 (CH_2), 30.7 (CH_2), 41.5 (CH_2), 60.6 (CH_2), 63.0 (CH_2), 73.0 (CH), 94.8 (CH), 118.5 (CH_2), 137.0 (CH) and 170.9 (C); *m/z* (ESI) 251.1257 (M^+ +Na, requires 251.1254 $C_{12}H_{20}NaO_4$).

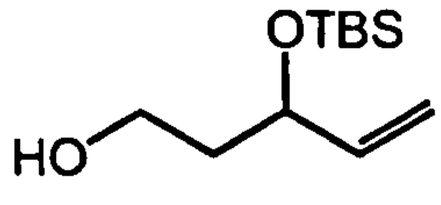
Minor diastereomer: bp 100 – 102 °C (1.2 mbar); (Found: C, 63.2; H, 8.8; N, 0.0. $C_{12}H_{20}O_4$ requires C, 63.1; H, 8.8; N, 0.0 %); ν_{max}(film)/cm^{-1} 1736, 1117, 1019, and 981; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.19 (3H, t, *J* 7.3, OCH_2CH_3), 1.40 – 1.83 (6 H, m, 3 x CH_2CH_2), 2.42 (1H, dd, *J* 15.1 and 5.4, C*H*HCO), 2.56 (1H, dd, *J* 15.1 and 5.4, C*H*HCO), 3.37 – 3.48 (1H, m, CH_2CHHO), 3.74 – 3.83 (1H, m, CH_2CHHO), 4.02 – 4.14 (2H, m, *J* 7.3, OCH_2CH_3), 4.42 – 4.54 (1H, m, C*H*OR), 4.68 (1H, dd, *J* 4.4 and 2.2, C*H*OR), 5.04 – 5.09 (2H, m, H_2C=CH) and 5.87 (1H, ddd, *J* 17.1, 10.7 and 7.3, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 14.4 (CH_3), 19.9 (CH_2), 25.7 (CH_2), 30.9 (CH_2), 40.8 (CH_2), 61.8 (CH_2), 62.8 (CH_2), 75.2 (CH) , 98.9 (CH), 115.7 (CH_2), 138.6 (CH) and 171.1 (C); *m/z* (ESI) 251.1257 (M^+ +Na, requires 251.1254 $C_{12}H_{20}NaO_4$).

Pent-4-ene-1,3-diol 211



To a slurry of $LiAlH_4$ (0.8, 21 mmol) in anhydrous THF (25 cm^3) was added a solution of hydroxy ester **208** (1.03 g, 7.15 mmol) in anhydrous THF (5 cm^3) dropwise at r.t. and left to stir for 16 h. The reaction mixture was quenched with water (0.8 cm^3), 15 % NaOH (0.8 cm^3) and additional water (2.4 cm^3). After 1 h the mixture was filtered through Celite® and the filter cake was washed with THF (5 x 25 cm^3), concentrated *in vacuo*, diluted with EtOAc (50cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale green oil. The oil was purified by distillation to give diol **211** (0.46 g, 82 %): as a colourless oil; bp 80 – 85 °C (0.1 mbar); ν_{max}(film)/cm^{-1} 3313, 1050, 989 and 921; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.67 – 1.82 (2H, m, CH_2CH_2O), 3.31 (1H, bs, O*H*), 3.43 (1H, bs, O*H*), 3.73 – 3.87 (2H, m, CH_2CH_2O), 4.31 – 4.36 (1H, m, CH_2CHHO), 5.10 (1H, d, *J* 10.3, H*H*C=CH), 5.24 (1H, d, *J* 17.1, H*H*C=CH) and 5.87 (1H, ddd, *J* 17.3, 10.3 and 6.5, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 38.5 (CH_2), 53.1 (CH_2), 72.6 (CH_2), 114.8 (CH_2) and 140.9 (CH_2).

3-tert-Butyldimethylsiloxypent-4-en-1-ol 212

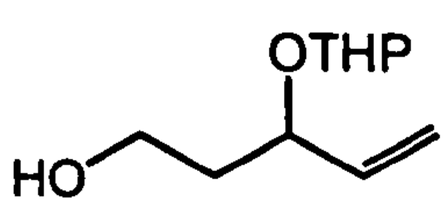


To a slurry of $LiAlH_4$ (228 mg, 6 mmol) in anhydrous THF (25 cm^3) was added a solution of hydroxy ester **209** (1.03 g, 7.15 mmol) in anhydrous THF (5 cm^3) dropwise at -40 °C and left to stir for 1 h. TLC showed incomplete reaction, so the mixture was left to stir at r.t. overnight. The reaction mixture was quenched with water (0.2 cm^3), 15 % NaOH (0.2 cm^3) and additional water (0.6 cm^3). After 1 h the mixture was filtered through Celite® and the filter cake was washed with THF (5 x 25 cm^3), concentrated *in vacuo*, diluted with EtOAc (50cm^3), dried over

$MgSO_4$ and concentrated *in vacuo* to give a pale green oil. The oil was purified by column chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give alcohol **212** (80 mg, 10 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3350, 1252, 1083, 834 and 774; d_H (400 MHz; $CDCl_3$; Me_4Si) 0.07 (6H, s, 2 x $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.79 – 1.87 (1H, m, $CHHCH_2O$), 1.66 – 1.73 (1H, m, $CHHCH_2O$), 2.61 (1H, bs, O*H*), 3.66 – 3.71 (1H, m, CH_2CHHO), 3.76 – 3.82 (1H, m, CH_2CHHO), 4.37 – 4.40 (1H, m, C*H*OTBS), 5.08 (1H, d, *J* 10.0, H*H*C=CH), 5.20 (1H, d, *J* 17.6, H*H*C=CH) and 5.84 (1H, ddd, *J* 17.6, 10.0 and 5.4, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) -4.7 (2 x CH_3), 18.4 (C), 26.0 (3 x CH_3), 39.5 (CH_2), 60.3 (CH_2), 73.4 (CH), 114.7 (CH_2) and 141.0 (CH);

Further elution with EtOAc gave **211** (183 mg, 46%) as a colourless oil.

3-(tetrahydro-2H-pyran-2-yloxy)pent-4-en-1-ol 213



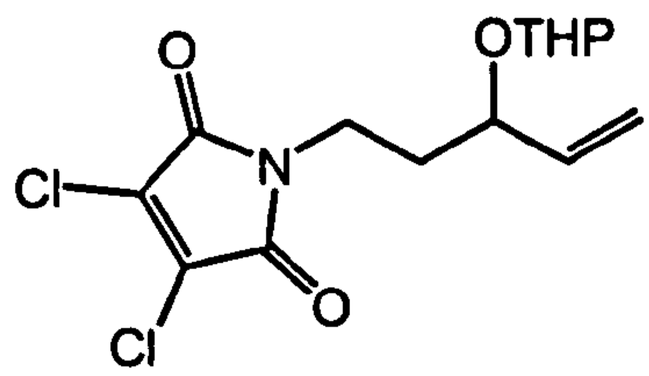
To a slurry of $LiAlH_4$ (228 mg, 6 mmol) in anhydrous THF (25 cm^3) was added a solution of hydroxy ester **210** (0.68 g, 2 mmol) in anhydrous THF (5 cm^3) dropwise at -10 °C and left to stir for 1 h. The reaction mixture was quenched with water (0.2 cm^3), 15 % NaOH (0.2 cm^3) and additional water (0.6 cm^3). After 1 h the mixture was filtered through celite and the filter cake was washed with THF (5 x 25 cm^3), concentrated *in vacuo*, diluted with EtOAc (50cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale green oil. The oil was purified by distillation to give alcohol **213** (0.37 g, 99 %) as a colourless oil:

Major diastereomer: bp 94 – 96 °C (1.0 mbar); (Found: C, 64.4; H, 9.95; N, 0.0. $C_{12}H_{20}O_4$ requires C, 64.5; H, 9.7; N, 0.0 %); ν_{max}(film)/cm^{-1} 3415, 1119, 1020 and 989; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 – 1.61 (4H, m, 2 x CH_2CH_2) 1.64 – 1.86 (4H, m, 2 x CH_2CH_2), 3.06 (1H, bs, O*H*), 3.41 – 3.50 (2H, m, CH_2OR), 3.64 –

3.73 (1H, m, R_2CHOR), 3.77 – 3.90 (2H, m, CH_2OR), 4.52 – 4.55 (1H, m, $ROCHR_2$), 5.05 – 5.25 (2H, m, H_2C=CH) and 5.68 (1H, ddd, *J* 17.1, 10.3 and 7.3, H_2C=CH); d_C (400 MHz; $CDCl_3$; Me_4Si) 20.3 (CH_2), 25.5 (CH_2), 31.0 (CH_2), 38.1 (CH_2), 59.6 (CH_2), 63.5 (CH_2), 75.2 (CH), 96.7 (CH), 116.8 (CH_2) and 138.3 (CH); *m/z* (ESI) 209.1151 (M^+ +Na, requires 209.1148 $C_{10}H_{18}NaO_3$), (EI) 101 (M^+ -THP, 34 %), 85 (100), 67 (24), 61 (16) and 55 (30).

Minor diastereomer: bp 94 – 96 °C (1.0 mbar); (Found: C, 64.4; H, 9.95; N, 0.0. $C_{12}H_{20}O_4$ requires C, 64.5; H, 9.7; N, 0.0 %); ν_{max}(film)/cm^{-1} 3415, 1119, 1020 and 989; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.45 – 1.61 (4H, m, 2 x CH_2CH_2), 1.64 – 1.86 (4H, m, 2 x CH_2CH_2), 2.57 (1H, bs, O*H*), 3.41 – 3.50 (2H, m, CH_2OR), 3.64 – 3.73 (1H, m, R_2CHOR), 3.77 – 3.90 (2H, m, CH_2OR), 4.69 – 4.71 (1H, m, $ROCHR_2$), 5.05 – 5.25 (2H, m, H_2C=CH) and 5.88 (1H, ddd, *J* 17.1, 10.7 and 7.3, H_2C=CH); d_C (400 MHz; $CDCl_3$; Me_4Si) 19.8 (CH_2), 25.6 (CH_2), 30.8 (CH_2), 37.5 (CH_2), 59.4 (CH_2), 62.8 (CH_2), 76.5 (CH), 98.3 (CH), 115.0 (CH_2) and 139.6 (CH); *m/z* (ESI) 209.1151 (M^+ +Na, requires 209.1148 $C_{10}H_{18}NaO_3$), (EI) 101 (M^+ -THP, 34 %), 85 (100), 67 (24), 61 (16) and 55 (30).

3,4-Dichloro-1-(3-(tetrahydro-2H-pyran-2-yloxy)pent-4-enyl)-1H-pyrrole-2,5-dione 205

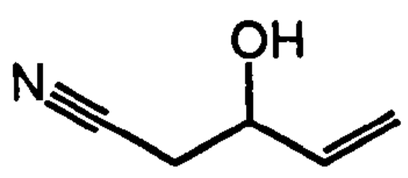


Alcohol **213** was coupled to dichloromaleimide using the modified Walker Mitsunobu procedure. The oil was purified by column chromatography on silica gel using 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **205** (0.41 g, 84 %); as a colourless oil:

Major diastereomer: ?$_{max}$(MeCN)/nm 287; ν_{max}(film)/cm^{-1} 1723, 1615, 1052 and 734; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.38 – 1.95 (8H, m, 4 x CH_2CH_2), 3.40 – 3.52 (2H, m, CH_2CH_2N), 3.76 – 3.88 (2H, m, CH_2OR), 4.14 – 4.19 (1H, m, R_2C*H*OR), 4.51 – 4.53 (1H, m, C*H*(OR)$_2$), 5.12 – 5.29 (2H, m, H_2C=CH) and 5.65 (1H, ddd, *J* 16.6, 10.3 and 7.3, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 20.1 (CH_2), 25.8 (CH_2), 30.9 (CH_2), 33.5 (CH_2), 36.5 (CH_2), 63.2 (CH_2), 74.4 (CH), 95.9 (CH), 118.5 (CH_2), 133.5 (2 x C), 137.3 (CH) and 163.3 (2 x C); *m/z* (ESI) 356.0435 (M^+ +Na, requires 356.0427 $C_{14}H_{17}{}^{35}Cl_2NaNO_3$) (CI) 335 ($M^+$ +H, 20 %), 232 (48), 178 (100), 85 (54), 67 (41) and 56 (40);

Minor diastereomer: ?$_{max}$(MeCN)/nm 287; ν_{max}(film)/cm^{-1} 1723, 1615, 1052 and 734; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.38 – 1.95 (8H, m, 4 x CH_2CH_2), 3.40 – 3.52 (2H, m, CH_2CH_2N), 3.76 – 3.88 (2H, m, CH_2OR), 4.05 – 4.10 (1H, m, R_2C*H*OR), 4.63 – 4.66 (1H, m, C*H*(OR)$_2$), 5.12 – 5.29 (2H, m, H_2C=CH) and 5.88 (1H, ddd, *J* 17.1, 10.3 and 6.8, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 20.2 (CH_2), 25.7 (CH_2), 31.0 (CH_2), 32.9 (CH_2), 36.0 (CH_2), 63.3 (CH_2), 76.2 (CH), 98.3 (CH), 116.1 (CH_2), 133.6 (2 x C), 138.8 (CH) and 163.3 (2 x C); *m/z* (ESI) 356.0435 (M^+ +Na, requires 356.0427 $C_{14}H_{17}{}^{35}Cl_2NaNO_3$) (CI) 335 ($M^+$ +H, 20 %), 232 (48), 178 (100), 85 (54), 67 (41) and 56 (40);

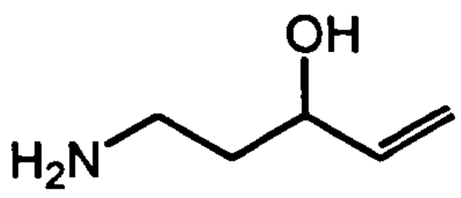
3-Hydroxypent-4-enenitrile[82]



To a solution of Acetonitrile (7.2 cm^3, 0.14 mol) in THF (150 cm^3) was added 2.5 M *n*-BuLi solution in hexanes (50 cm^3, 0.13 mol) dropwise over 30 min at -78 °C. After the solution was stirred for 2 h acrolein (11.1 cm^3, 0.15 mol) was added in one portion and the mixture was left to stir for 5 min. The reaction was quenched with 2M HCl (60 cm^3, 0.12 mol). The product was extracted with Et_20 (2 x 50 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give the nitrile (12.2 g, 98 %) as a pale red oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 2.57 (1H, dd, *J* = 6.4 and 16.6,

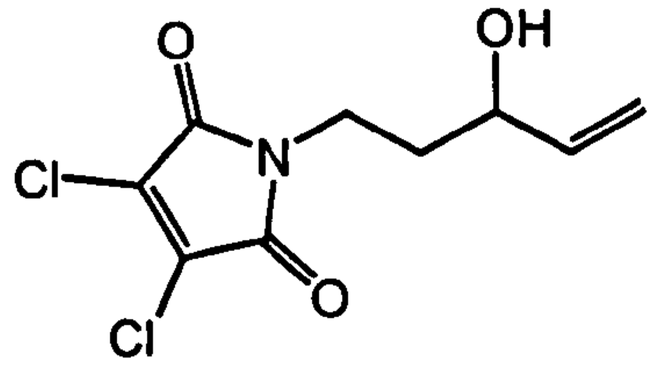
C*H*HCH(OH)), 2.63 (1H, dd, *J* = 5.6 and 16.6, C*H*HCH(OH)), 2.8 (1H, bs, CH(O*H*)), 4.42 – 4.48 (1H, m, C*H*(OH)), 5.29 (1H, ddd, *J* = 1.0 and 10.3, C*H*H=CH), 5.40 (1H, ddd, *J* = 1.2 and 17.1, C*H*H=CH) and 5.91 (1H, ddd, *J* = 5.9, 10.5 and 17.1, CH_2=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 26.3 (CH_2), 68.9 (CH), 117.2 (C), 117.9 (CH_2) and 137.4 (CH).

5-Aminopent-1-en-3-ol 215[82]



To a slurry of $LiAlH_4$ (1.2 g, 31 mmol) in anhydrous THF (50 cm^3) was added a solution of 3-Hydroxypent-4-enenitrile (2.0 g, 21 mmol) in anhydrous THF (10 cm^3) dropwise at r.t. and left to stir at reflux for 2 h. The reaction mixture was cooled and quenched with water (0.8 cm^3), 15 % NaOH (0.8 cm^3) and additional water (2.4 cm^3). After 1 h the mixture was filtered through Celite® and the filter cake was washed with THF (5 x 50 cm^3), concentrated *in vacuo*, diluted with EtOAc (50cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give **215** (1.82 g, 86 %) as a pale yellow oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 1.49 – 1.58 (1H, m, NCH_2C*H*H), 1.65 – 1.72 (1H, m, NCH_2C*H*H), 2.71 (3H, bs, NH_2 and O*H*), 2.87 (1H, ddd, *J* = 4.2, 8.5 and 12.5, NC*H*HCH_2), 3.05 (1H, ddd, *J* = 4.4, 6.4 and 12.5, NC*H*HCH_2), 4.29 – 4.34 (1H, m, CH_2C*H*(OH)), 5.06 (1H, ddd, *J* = 1.5 and 10.5, C*H*H=CH), 5.40 (1H, ddd, *J* = 1.7 and 17.1, C*H*H=CH) and 5.86 (1H, ddd, *J* = 5.4, 10.5 and 17.1, CH_2=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 30.8 (CH_2), 40.2 (CH_2), 73.4 (CH), 113.9 (CH_2) and 141.7 (CH).

3,4-Dichloro-1-(3-hydroxypent-4-enyl)-1H-pyrrole-2,5-dione 214



Method A

Alcohol **211** was coupled to dichloromaleimide using the modified Walker Mitsunobu procedure; with the exception that only 1 equivalent of **211** was used. The oil was purified by graduated column chromatography on silica gel using 10 - 33 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give starting material **211** (100 mg, 66 %). Further elution gave maleimide **214** (50 mg, 10 %); as a colourless oil, which upon standing produced a white solid: ?$_{max}$(MeCN)/nm 239 and 307; ν_{max}(film)/cm^{-1} 3408, 1717, 1620, 1396, 1370, 1197, 910, 879 and 729; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.70 – 1.85 (2H, m, NCH_2CH_2), 2.45 (1H, d, *J* 3.9, O*H*), 3.71 (2H, t, *J* 7.3, $R_2NCH_2CH_2$), 4.05 – 4.12 (1H, m, C*H*OH), 5.08 (1H, ddd, *J* 10.3, 1.5 and 1.0, H*H*C=CH), 5.21 (1H, ddd, *J* 17.1, 1.5 and 1.0, H*H*C=CH) and 5.80 (1H, ddd, *J* 17.1, 10.3 and 5.9, H_2C=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 35.2 (CH_2), 36.4 (CH_2), 70.5 (CH), 115.5 (CH_2), 133.5 (2 x C), 140.1 (CH) and 163.4 (2 x C); *m/z* (ESI) 271.9852 (M^+ +Na, requires 271.9852 $C_9H_9{}^{35}Cl_2NaNO_4$), (CI) 250 (M^+ +H, 55 %), 232 (100), 178 (16), 85 (41 67 (24) and 61 (13).

Method B

To a solution of acetic acid (12 cm^3), water (3 cm^3) and THF (6 cm^3) was added maleimide **205** (0.97 g, 2.9 mmol), the solution was then stirred for 3 h at 40 °C. The reaction mixture was diluted with EtOAc (40 cm^3) and the organic was washed with $NaHCO_3$ (40 cm^3), brine (40cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The oil was purified by column

chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **214** (140 mg, 19 %).

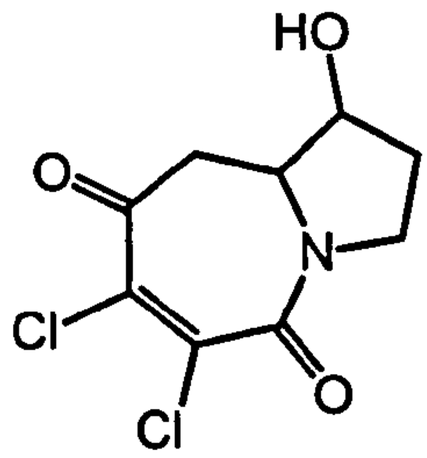
Method C

To a solution of maleimide **205** (0.45g, 1.3 mmol) in MeOH (10 cm^3) was added *p*TSA (12 mg, 5 mol %) and the solution was left to stir at r.t. for 3 h. The reaction mixture was concentrated *in vacuo* to give a yellow oil that was subjected to column chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **214** (111 mg, 33 %).

Method D

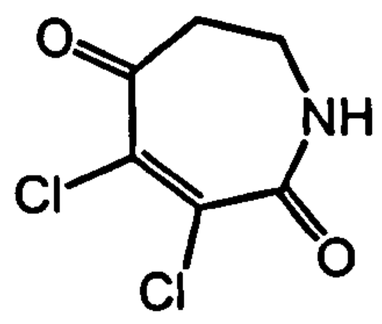
To a solution of dichloromaleic anhydride (0.37 g, 2.2 mmol) in toluene (100 cm^3) was added amine **215** (0.20 g, 2 mmol) dropwise then heated under reflux for under a Dean-Stark set up for 2 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography on silica gel using 5 – 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **214** (183 mg, 73 %).

(Z)-6,7-dichloro-2,3,9,9a-tetrahydro-1-hydroxy-1H-pyrrolo[1,2-a]azepine-5,8-dione 216 and (Z)-3,4-dichloro-6,7-dihydro-1H-azepine-2,5-dione 217



Method A

A solution of maleimide **214** (250 mg, 1 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 50 min. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give starting material **214** (148 mg, 59 %).



Further elution gave azepine **217** (10 mg, 5 %) as a white solid: d_H (400 MHz; $CDCl_3$; Me_4Si) 2.97 (2H, dd, *J* 5.4 and 6.4, NCH_2CH_2), 3.61 (2H, dd, *J* 6.4 and 11.6, NCH_2CH_2) and 7.96 (1H, bs, N*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 35.4 (CH2), 44.7 (CH2), 135.4 (C), 136.8 (C), 162.6 (C) and 190.9 (C).

Further elution gave minor diastereomer of azepine **216** (18 mg, 7 %) as a colourless crystalline solid: ν_{max}(film)/cm^{-1} 3381, 1692, 1637, 1111 and 737; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.85 – 1.94 (1H, m, NCH_2CHH), 2.02 – 2.10 (1H, m, NCH_2CHH), 2.87 (1H, dd, *J* 19.6 and 11.7, $COCHH$), 2.97 (1H, dd, *J* 19.6 and 2.9, $COCHH$), 3.42 (1H, bs, O*H*), 3.52 – 3.59 (1H, m, $NCHHCH_2$), 3.64 – 3.71 (1H, m, $NCHHCH_2$), 4.23 (1H, ddd, *J* 11.7, 6.6 and 2.9, R_3CH) and 4.46 (1H, app q, *J* 6.6, $CHOH$); d_C (400 MHz; $CDCl_3$; Me_4Si) 31.2 (CH_2), 44.7 (CH_2), 45.0 (CH_2),

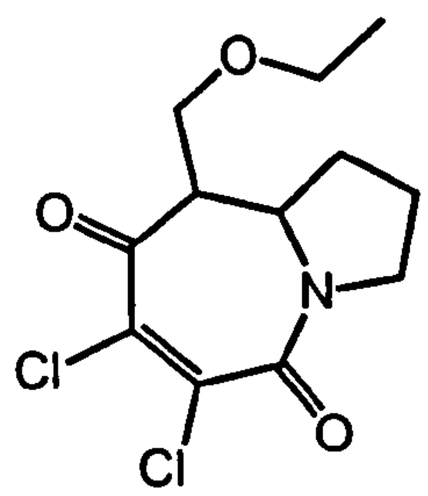
56.0 (CH), 70.8 (CH), 137.9 (C), 139.1 (C), 158.9 (C) and 131.4 (C); *m/z* (CI) 250.0037 *m/z* (CI) 250.0037 (M^+ +H, requires 250.0038 $C_9H_{10}{}^{35}Cl_2NO_3$) (CI) 250 (M^+ +H, 100 %), 234 (7), 222 (11), 214 (14) and 86 (57).

Further elution gave major diastereomer of azepine **216** (56 mg, 23 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 3419, 1697, 1631, 1106 and 728; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.91 – 1.94 (1H, m, NCH_2CHH), 2.63 – 2.04 (1H, m, NCH_2CHH), 2.67 (1H, dd, *J* 18.8 and 13.0, $COCHH$), 2.95 (1H, dd, *J* 19.1 and 2.2, $COCHH$), 3.63 (1H, bs, O*H*), 3.70 (2H, dd, *J* 9.3 and 5.1, NCH_2CH_2) and 4.10 (2H, m, R_3CH and $CHOH$); d_C (400 MHz; $CDCl_3$; Me_4Si) 31.1 (CH_2), 45.5 (CH_2), 48.6 (CH_2), 61.4 (CH), 74.7 (CH), 137.0 (C), 138.7 (C), 158.9 (C) and 190.8 (C); *m/z* (CI) 250.0037 (M^+ +H, requires 250.0038 $C_9H_{10}{}^{35}Cl_2NO_3$) (CI) 250 (M^+ +H, 100 %), 234 (7), 222 (11), 214 (14) and 86 (57).

Method B

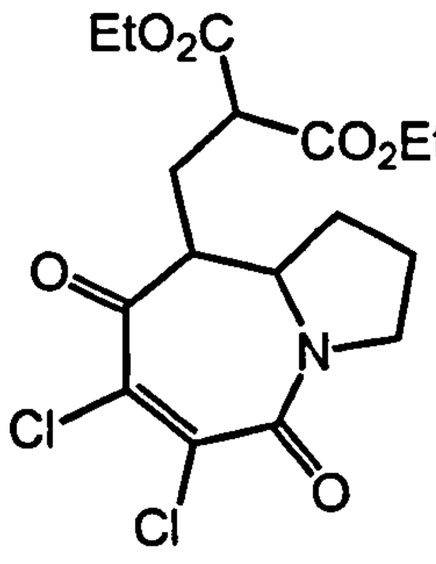
A solution of maleimide **214** (250 mg, 1 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 2 h 20 min. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **216** (73 mg, 29 %) as a 3:2 mixture of diastereomers.

(Z)-6,7-Dichloro-9-(ethoxymethyl)-2,3,9,9a-tetrahydro-1H-pyrrolo[1,2-a] azepine-5,8-dione 228



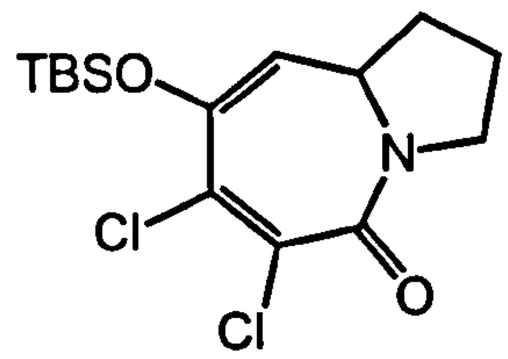
To a solution of morpholine (0.074 cm^3, 0.86 mmol), paraformaldehyde (40 mg, 0.13 mmol), and an aliquot of HCl in anhydrous EtOH (10 cm^3), was added azepine **109** (100 mg, 0.43 mmol), the solution was then heated at reflux for 2 h. The reaction mixture was cooled and quenched with sat. $NaHCO_3$ (30 cm^3). The product was extracted with Et_20 (2 x 30 cm^3), washed with brine (30 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil. The oil was purified by column chromatography on silica gel using 30 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **228** (30 mg, 24 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1702, 1651, 1572, 1416, 1208, 1107, 911, 777 and 727; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.13 (3H, t, J = 7.1, OCH_2CH_3), 1.88 – 1.99 (3H, m, 3 x $CHHCH_2$), 2.21 – 2.28 (1H, m, $CHHCH_2$), 2.74 (1H, ddd, J = 2.4, 3.4 and 11.5, $COCH$), 3.33 – 3.45 (2H, m, 2 x $XCHH$), 3.51 – 3.58 (1H, m, $XCHH$), 3.62 (1H, dd, J = 2.4 and 9.3, $OCHHCH$), 3.69 – 3.74 (1H, m, $XCHH$), 3.74 (1H, dd, J = 3.4 and 9.3, $OCHHCH$) and 4.57 (1H, ddd, J = 2.4, 7.6 and 11.5, NCH); d_C (400 MHz; $CDCl_3$; Me_4Si) 14.7 (CH_3), 22.9 (CH_2), 29.2 (CH_2), 46.9 (CH_2), 54.7 (CH), 61.6 (CH) 67.3 (CH_2), 71.1 (CH_2), 134.8 (C), 136.6 (C), 159.0 (C) and 196.7 (C); *m/z* (CI) 292.0505 (M^+ +H, requires 292.0507 $C_{12}H_{16}NO_3{}^{35}Cl_2$) (CI) 292 ($M^+$ +H. 100 %), 256 (17), 246 (23), 232 (20), 198 (29), 170 (22), 70 (42) and 59 (24).

Diethyl 2-(((Z)-6,7-dichloro-2,3,5,8,9,9a-hexahydro-5,8-dioxo-1H-pyrrolo[1,2-a]azepin-9-yl)methyl)malonate 229



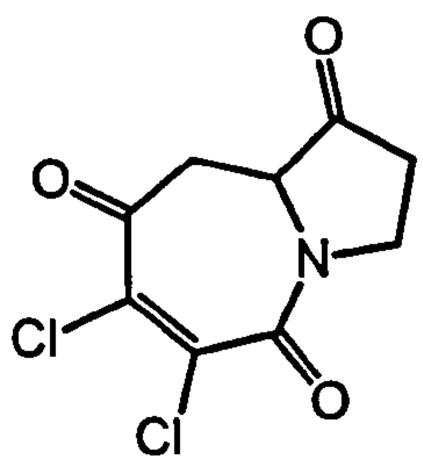
To a slurry of Eschenmoser's salt (59 mg, 0.58 mmol) in anhydrous DCM (5 cm^3) was added a solution of azepine **109** (100 mg, 0.29 mmol) in anhydrous DCM (5 cm^3) at r.t. and left to stir for 12 h. TLC showed no new products, so a solution of 1 M TBAF (0.58 cm^3, 0.58 mmol), *p*TSA (5 mg) and diethyl malonate (49 μcm^3, 0.32 mmol) was added and the resulting solution was left for 96 h. The reaction mixture was cooled and quenched with sat. $NaHCO_3$ (30 cm^3). The product was extracted with DCM (2 x 30 cm^3), washed with brine (30 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil. The oil was purified by graduated column chromatography on silica gel using 30 - 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **229** (20 mg, 16 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1702, 1652, 1573, 1417, 1208, 1108, 777 and 738; d_H (270 MHz; $CDCl_3$; Me_4Si) 1.26 (3H, t, *J* = 7.1, OCH_2CH_3), 1.31 (3H, t, *J* = 7.1, OCH_2CH_3), 1.81 – 2.31 (6H, m, 3 x CH_2), 2.75 (1H, dt, *J* = 11.4 and 3.0, C(O)C*H*), 3.42 - 3.72 (3H, m, C(O)C*H*C(O) and NCH_2) and 4.00 – 4.35 (5H, m, NC*H* and 2 x OCH_2CH_3); d_C (400 MHz; $CDCl_3$; Me_4Si) 14.0 (CH_3), 14.01 (CH_3), 22.8 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 47.1 (CH_2), 48.2 (CH), 57.8 (CH), 58.8 (CH), 61.9 (CH_2), 62.0 (CH_2), 134.0 (C), 134.8 (C), 159.2 (C), 168.4 (C), 168.5 (C) and 195.6 (C); *m/z* (CI) 406.0806 (M^+ +H. requires 406.0824 $C_{17}H_{22}NO_6{}^{35}Cl_2$), (CI) 406 ($M^+$ +H, 100 %), 370 (26), 360 (15), 342 (17), 324 (12) and 70 (26).

(6Z,8E)-6,7-Dichloro-2,3-dihydro-(8-tert-butyldimethylsiloxyethyl)-1H-pyrrolo[1,2-a]azepin-5(9aH)-one 223



To a solution of azepine **109** (0.5 g, 2.1 mmol) and Et_3N (0.45 cm^3, 3.2 mmol) in anhydrous DCM (50 cm^3) was added dropwise TBSOTf (0.74 cm^3, 3.2 mmol) at r.t. and left to stir for 30 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **223** (0.7 g, 95 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 1642, 1264, 1220 and 732; d_H (270 MHz; C_6D_6; Me_4Si) 0.04 (6H, s, 2 x SiCH_3), 0.82 – 1.40 (4H, m, 2 x CH_2CH_2), 0.92 (9H, s, Si$C(CH_3)_3$), 3.01 (1H, ddd, J = 4.9, 7.3 and 14.7, NC*H*H), 3.30 – 3.50 (2H m, NC*H*H and NC*H*) and 4.91 (1H, d, J = 5.9, C=C*H*); d_C (400 MHz; C_6D_6; Me_4Si) -5.0 (2 x CH_3), 18.4 (C), 24.2 (3 x CH_2), 25.7 (CH_3), 31.8 (CH_2), 46.4 (CH_2), 52.6 (CH), 117.7 (CH), 133.5 (C), 135.4 (C), 167.4 (C) and 178.4 (C); *m/z* (CI) 348.0948 (M^+ +H. requires 348.0953 $C_{15}H_{24}NO_2Si$) (CI) 348 (M^+ +H, 77 %), 314 (40), 32 (100), 290(53), 254(17), 226 (15), 198 (14), 93 (11) and 73 (29).

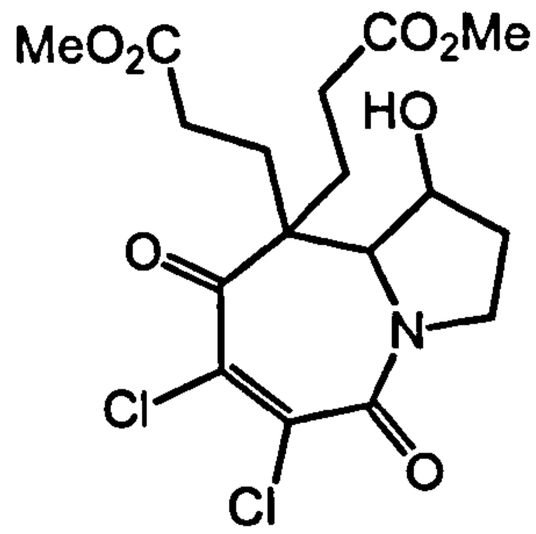
(Z)-6,7-dichloro-2,3,9,9a-tetrahydropyrrolo[1,2-a]azepine-1,5,8-trione



To a solution of azepine **216** (100 mg, 0.4 mmol) in anhydrous DCM (50 cm^3) was added dropwise 15 wt% solution of Dess-Martin periodinane in DCM (0.94 cm^3, 0.44 mmol) at r.t. and left to stir for 1 h 30 min. The reaction mixture was

concentrated *in vacuo* onto silica gel and subjected to column chromatography using 30 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give the azepine (62 mg, 63 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 1758, 1692, 1666, 1555,1439, 1187, 922, 731 and 713; d_H (270 MHz; CD_2Cl_2; Me_4Si) 2.60 – 2.83 (2H, m, NCH_2CH_2)), 2.90 (1H, dd, *J* = 12.5 and 19.1, C(O)C*H*H), 3.20 (1H, dd, *J* = 19.1 and 2.3, C(O)C*H*H), 3.78 (1H, dt, *J* = 12.9 and 8.9, NC*H*HCH_2), 4.21 (1H, dt, *J* = 12.9 and 4.8, NC*H*HCH_2) and 4.46 (1H dd, *J* = 12.5, 2.3, NC*H*); *m/z* (CI) 247.9873 (M^+ +H. requires 247.9881 $C_9H_8NO_3{}^{35}Cl_2$), (CI) 248 (M^+ +H, 100 %), 212 (18), 190 (14) and 84 (76).

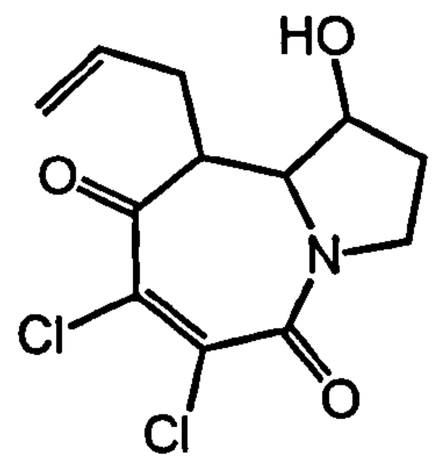
3-[6,7-Dichloro-1-hydroxy-9-(2-methoxycarbonyl-ethyl)-5,8-dioxo-2,3,5,8,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-9-yl]-propionic acid methyl ester 230



To a solution of azepine **216** (100 mg, 0.4 mmol) and methyl acrylate (4.4 mmol, 0.04 cm^3) in anhydrous THF (5 cm^3) was added 1.0 M TBAF solution in THF (0.04 mmol, 0.04 cm^3) at r.t. and left to stir for 48 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 60 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **230** (94 mg, 70 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3433, 1733, 1705, 1644, 1564, 1436, 1199, 1172 and 738; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.74 - 1.84 (1H, m, C*H*HCH_2)) 1.88 – 1.99 (2H, m, CH_2CH_2), 2.00 – 2.45 (7 H , m, 7 x C*H*H), 3.53 (1H, ddd, *J* = 13.13, 8.00 and 5.50, NC*H*H), 3.63 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.70 (1H, m, C*H*(OH)), 4.02 (1H, dt, *J* = 12.71 and 7.94, NC*H*H), 4.28 (1H, d, *J* = 2.20 , O*H*) and 4.55 – 4.63 (1H, m, NC*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 26.8 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 32.6 (CH_2), 32.9 (CH_2), 46.8 (CH_2),

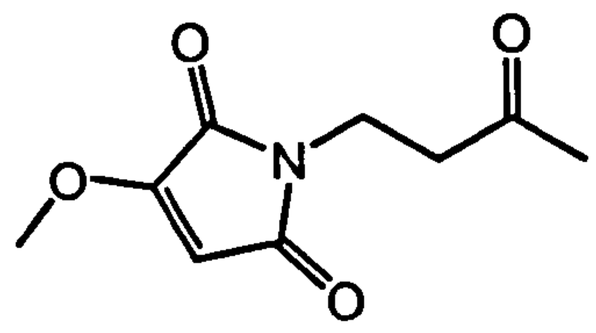
52.1 (CH_3), 52.4 (CH_3), 60.0 (C), 68.6 (CH), 73.0 (CH), 136.6 (C), 137.1 (C), 159.4 (C), 173.2 (C), 173.4 (C) and 196.5 (C); *m/z* (CI) 422.0768 (M^+ +H, requires 422.0773 $C_{17}H_{22}NO_7{}^{35}Cl_2$), (CI) 422 ($M^+$ +H. 70 %), 392 (17), 390 (34), 338 (33), 336 (50), 272 (14), 252 (27), 250 (42) and 86 (100).

(Z)-9-allyl-6,7-dichloro-2,3,9,9a-tetrahydro-1-hydroxy-1H-pyrrolo[1,2-a]azepine-5,8-dione 231



To a solution of azepine **216** (25 mg, 0.1 mmol), allyl bromide (0.12 mmol, 0.011 cm^3) and pyridine (0.24 mmol, 0.019 cm^3) in anhydrous THF (1 cm^3) was added 1.0 M TBAF solution in THF (0.1 mmol, 0.1 cm^3) at r.t. and left to stir for 24 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give azepine **231** (trace, <5 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3415, 1697, 1636, 1573, 1417, 1109 and 734; d_H (400 MHz; CD_2Cl_2; Me_4Si) 1.88 – 1.99 (2H, m, NCH_2CH_2), 2.11 (1H, bs, O*H*), 2.26 – 2.37 (1H, m, CH_2=CHC*H*H), 2.52 – 2.63 (1H, m, CH_2=CHC*H*H), 3.31 (1H, ddd, *J* = 11.6, 7.5 and 4.4, NC*H*H), 3.42 (1H, ddd, *J* = 12.0, 8.8 and 7.1, C(O)C*H*), 3.90 (1H, ddd, *J* = 11.8, 7.0 and 4.4, NC*H*H), 4.05 (1H, dd, *J* = 11.2 and 5.6, C*H*(OH)), 4.53 – 4.69 (1H, m, NC*H*), 5.02 – 5.10 (2H, m, CH_2=CH) and 5.54 – 5.75 (1H, m, C*H*=CH_2); d_C (400 MHz; CD_2Cl_2; Me_4Si) 33.8 (CH_2), 36.3 (CH_2), 45.1 (CH_2), 56.7 (CH), 60.5 (CH), 71.6 (CH), 119.4 (CH_2), 133.3 (CH and 2 x C), 168.7 (C), and 195.9 (C); *m/z* (CI) 290.0342 (M^+ +H. requires 290.0351 $C_{12}H_{14}NO_3{}^{35}Cl_2$), (CI) 290 ($M^+$ +H, 100 %), 254 (10), 220 (6), 205 (9) and 86 (38).

3-methoxy-1-(3-oxobutyl)-1H-pyrrole-2,5-dione 254

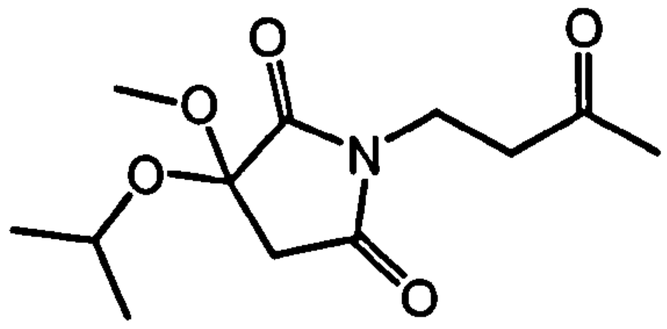


Method A

To a solution of methoxy maleimide(127 mg, 1.0 mmol) and methyl vinyl ketone (0.12 cm^3, 1.5 mmol) in EtOAc (10 cm^3) was added dropwise 40 wt% solution of benzyl trimethyl ammonium hydroxide in MeOH (0.12 mmol, 0.05 cm^3) at 80 °C and left to stir for 15 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography using 50 – 66 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **254** (100 mg , 48 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 1708, 1631, 1322, 1222 and 829; d_H (400 MHz; $CDCl_3$; Me_4Si) 2.10 (3H, s, C(O)CH_3), 2.72 (2H, t, J = 7.3, NCH_2CH_2), 3.69 (2H, t, J = 7.3, NCH_2CH_2) 3.88 (3H, s, OCH_3) and 5.37 (1H, s, C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 29.7 (CH_3), 32.4 (CH_2), 41.3 (CH_2), 58.8 (CH_3), 96.2 (CH), 160.8 (C), 165.2 (C), 169.7 (C) and 205.7 (C); *m/z* (EI) 197.0687 (M^+. requires 197.0688 $C_9H_{11}NO_4$), (CI) 197 (M^+, 56 %), 155 (53), 154 (65), 140 (83), 127 (14), 126 (14), 113 (34), 112 (32), 86 (15), 82 (14), 70 (17), 69 (100), 56 (16) and 55 (27).

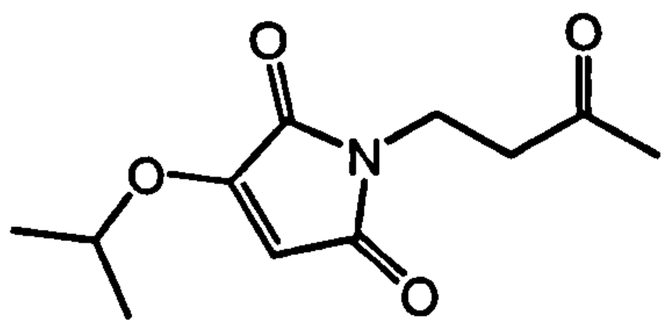
Method B

To a solution of methoxy maleimide (127 mg, 1.0 mmol) and methyl vinyl ketone (0.12 cm^3, 1.5 mmol) in IPA (5 cm^3) was added Et_3N (14 µl, 10 mol %) and K_2CO_3 (14 mg, 10 mol %) ad left to stir at 80°C for 2 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give acetal **255** (45 mg , 15 %) as a white crystalline solid:



ν_{max}(film)/cm^{-1} 1708, 1631, 1372, 1297, 1168, 1123, 1042 and 921; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.14 (3H, d, J = 6.4, OCHCH_3), 1.20 (3H, d, J = 6.4, OCHCH_3), 2.14 (3H, s, C(O)CH_3), 2.76 (2H, t, J = 7.6, NCH_2CH_2), 2.80 (2H, d, J = 4.4, $CH_2C(OR)_2$), 3.41 (3H, s, OCH_3), 3.77 (2H, t, J = 7.6, NCH_2CH_2) and 4.32 (1H, hept, J = 6.4, OCH(CH_3)$_2$); d_C (400 MHz; $CDCl_3$; Me_4Si) 23.3 (CH_3), 23.6 (CH_3), 29.8 (CH_3), 33.5 (CH_2), 40.4 (CH_2), 41.0 (CH_2), 51.4 (CH_3), 67.2 (CH), 98.5 (C), 171.8 (C), 172.2 (C) and 205.3 (C); *m/z* (CI) 258.1335 (M^+ +H, requires 258.1341 $C_{12}H_{20}NO_5$) (CI) 258 (M^+ +H, 8 %), 226 (58), 199 (16), 198 (100), 187 (25), 184 (56) and 144 (23).

Further elution gave maleimide **256** (28 mg, 12 %) as a white crystalline solid:



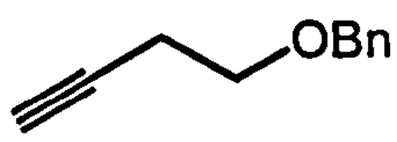
ν_{max}(film)/cm^{-1} 1705, 1626, 1305, 1101 and 814; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.41 (6H, d, J = 6.1, 2 x OCHCH_3), 2.15 (3H, s, C(O)CH_3), 2.77 (2H, t, J = 7.5, NCH_2CH_2), 3.75 (2H, t, J = 7.5, NCH_2CH_2), 4.43 (1H, hept, J = 6.1, OCH(CH_3)$_2$) and 5.30 (1H, s, CH=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 21.1 (2 x CH_3), 29.5 (CH_3), 32.6 (CH_2), 41.6 (CH_2), 59.0 (CH), 95.8 (CH), 159.0 (C), 165.9 (C), 170.4 (C) and 205.8 (C); *m/z* (EI) 225.0997 (M^+. requires 225.1001 $C_{11}H_{15}NO_4$) (CI) 225 (M^+, 19 %), 184 (18), 183 (76), 182 (11), 155 (12), 144 (18), 141 (43), 140 (31), 126 (32), 113 (13), 112 (73), 98 (14), 86 (34), 72 (11), 71 (53), 69 (100), 58 (16) and 55 (18).

Further elution gave title compound **254** (65 mg, 33 %) as a white crystalline solid.

Method C

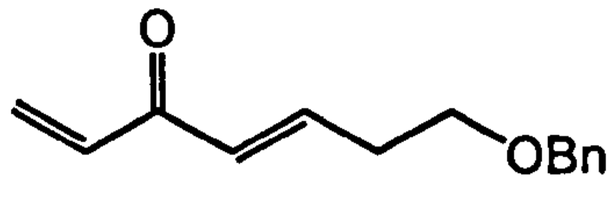
To a solution of methoxy maleimide (127 mg, 1.0 mmol) and methyl vinyl ketone (0.12 cm^3, 1.5 mmol) in ^tBuOH (5 cm^3) was added Et_3N (14 µl, 10 mol %) and K_2CO_3 (14 mg, 10 mol %) ad left to stir at 80°C for 3 h 30 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **254** (132 mg , 67 %) as a white crystalline solid.

1-((but-3-ynyloxy)methyl)benzene 252



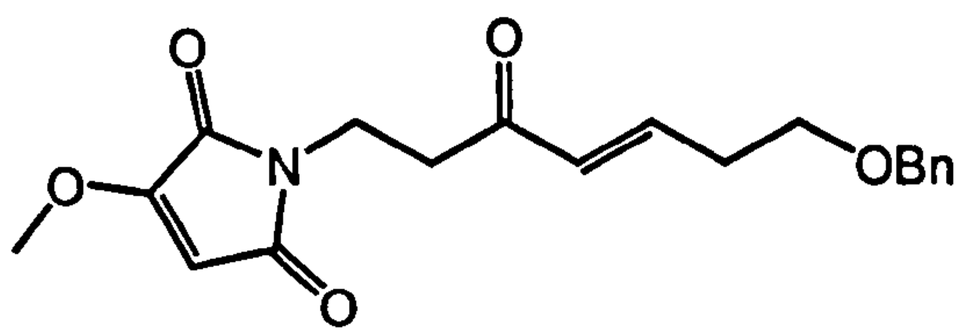
To a solution of NaH (1.0 g, 43 mmol) in anhydrous THF (60 cm^3) was added 3-butyn-1-ol (3.2 cm^3, 43 mmol) dropwise over 30 min at 0°C and left to stir at r.t. for 1 h. The solution was cooled to 0°C and benzyl bromide (4.6 cm^3, 39 mmol) was added dropwise over 30 min and left to stir at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 5 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give alkyne **252** (6.1 g, 97 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3293, 2864 and 1097; d_H (270 MHz; $CDCl_3$; Me_4Si) 2.01 (1H, t, J = 2.6, C*H*≡C), 2.52 (2H, dt, J = 6.9 and 2.6, OCH_2CH_2), 3.62 (2H, t, J = 6.9, OCH_2CH_2), 4.58 (2H, s, OCH_2Ar) and 7.28 – 7.42 (5H m, 5 x Ar*H*); *m/z* (CI) 160 (M^+ +H, 11 %), 159 (78), 129 (36), 123 (71), 107 (46), 105 (100), 91 (66), 79 (15) and 53 (15).

(E)-7-(benzyloxy)hepta-1,4-dien-3-one 253



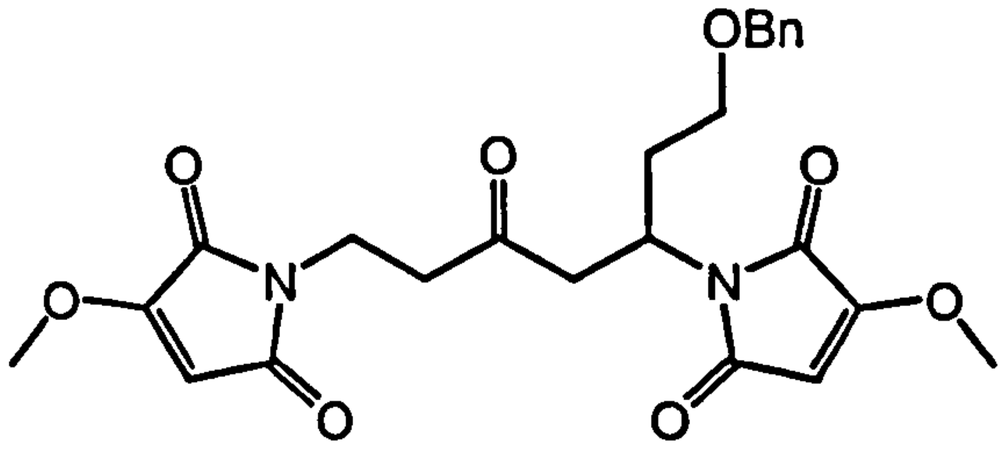
To a solution of alkyne **252** (176 mg, 1.1 mmol) in anhydrous toluene (5 cm^3) was added Schwartz reagent (289 mg, 1.12 mmol) in one portion and left to stir at 50^0C until a homogeneous solution had been formed (30 min). The solution was cooled to r.t. before $Pd(PPh_3)_2Cl_2$ (35 mg, 5 mol %) and acryloyl chloride (85 µl, 1 mmol) were added and left to stir at r.t. for 1 h 30 min. The reaction solution was loaded straight onto a column and subjected to column chromatography using 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give vinyl ketone **253** (136 mg, 63 %) as a colourless oil that polymerised rapidly upon standing: d_H (400 MHz; $CDCl_3$; Me_4Si) 2.58 (2H, m, J = 6.4, OCH_2CH_2), 3.63 (2H, dt, J = 6.4 and 0.7, OCH_2CH_2), 4.54 (2H, s, OCH_2Ar), 5.84 (1H, dt, J=10.7 and 1.0, C*H*H=CH), 6.3 (1H, dt, J = 17.6 and 1.1, C*H*H=CH), 6.45 (1H, ddd, J = 15.9, 2.4 and 1.0, C(O)C*H*=CH), 6.62 (1H, ddd, J = 17.3, 10.6 and 0.9, CH_2=C*H*), 6.97 (1H, ddt, J = 15.8, 6.9 and 0.7, C(O)CH=C*H*) and 7.28 - 7.42 (5H, m, 5 x Ar*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 33.1 (CH_2), 68.4 (CH_2), 73.1 (CH_2), 127.7 (CH), 128.2 (CH), 128.4 (CH), 129.7 (CH_2), 134.9 (CH), 138.1 (C), 138.2 (CH), 145.0 (CH) and 189.5 (C).

1-((E)-7-(benzyloxy)-3-oxohept-4-enyl)-3-methoxy-1H-pyrrole-2,5-dione 257



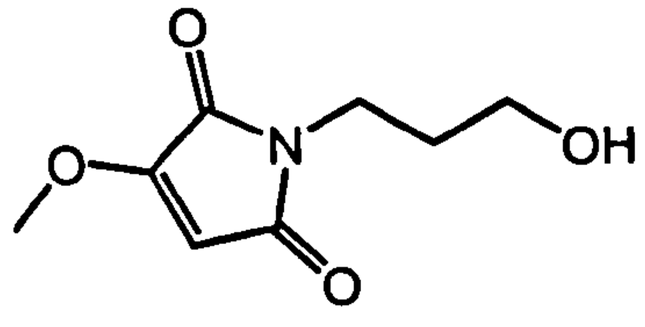
To a solution of methoxy maleimide (59 mg, 0.46 mmol) and vinyl ketone **253** (110mg, 0.51 mmol) in anhydrous EtOAc (5 cm^3) was added 40 wt% solution of Triton B in MeOH (51 µl, 5 mol %) and left to stir at 80°C for 1 h 30 min. The solution was allowed to cool and was then concentrated *in vacuo* onto silica gel

and subjected to column chromatography using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **257** (65 mg, 40 %) as a colourless oil: ?$_{max}$(MeCN)/nm 239 and 422; ν_{max}(film)/cm^{-1} 1708, 1671, 1360 and 1221; d_H (400 MHz; $CDCl_3$; Me_4Si) 2.53 (2H, dq, J = 6.4 and 1.7, OCH_2CH_2), 2.91 (2H, dd, J = 7.3 and 6.6, NCH_2CH_2), 3.59 (2H, t, J = 6.4, OCH_2CH_2), 3.82 (2H, dd, J = 7.3 and 6.6, NCH_2CH_2), 3.92 (3H, s, OCH_3), 4.52 (2H, s, OCH_2Ar), 5.41 (1H, s, C*H*=C), 6.13 (1H, dt, J = 15.9 and 1.6, C(O)C*H*=CH), 6.85 (1H, dt, J = 16.1 and 6.8, C(O)CH=C*H*) and 7.26 - 7.39 (5H, m, 5 x Ar*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 32.8 (CH_2), 32.9 (CH_2), 37.6 (CH_2), 58.8 (CH_3), 68.0 (CH_2), 73.0 (CH_2), 96.2 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 131.3 (CH), 137.9 (C), 144.7 (CH), 160.9 (C), 165.2 (C), 169.7 (C) and 197.1 (C); *m/z* (CI) 344.1494 (M^+ +H. requires 344.1498 $C_{19}H_{22}NO_5$) (CI) 344 (M^+ +H, 83 %), 326 (35), 252 (16), 237 (30), 236 (59), 235 (16), 183 (10), 182 (32), 181 (19), 140 (13), 131 (13), 119 (10), 105 (12), 91 (100) and 60 (57).



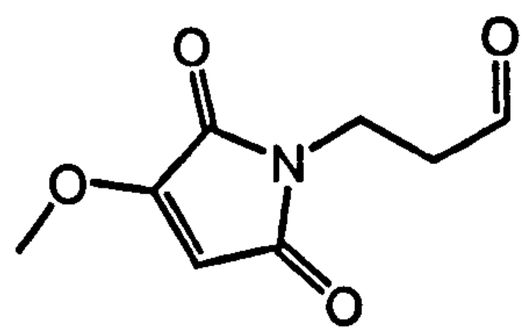
Further elution gave maleimide **258** (16 mg, 10 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1709, 1640 and 1321; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.74 – 1.89 (1H, m, OCH_2CHH) 2.09 – 2.27 (1H, m, OCH_2CHH), 2.63 – 2.75 (2H, m, NCH_2CH_2), 2.84 (1H, dd, J = 17.7, 5.8, NCHC*H*H), 3.15 (1H, dd, J = 17.8, 8.6, NCHC*H*H), 3.38 – 3.54 (2H, m, OCH_2CH_2), 3.70 (2H, t, J = 7.3, NCH_2CH_2), 3.73 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.31 (1H, d, J = 11.6, OC*H*HAr), 4.38 (1H, d, J=11.6, OC*H*HAr), 4.59 – 4.73 (1H, m, $NCHCH_2$), 5.17 (1H, s, C*H*=C), 5.36 (1H, s, C*H*=C) and 7.18 – 7.37 (5H, m, 5 x Ar*H*); *m/z* (CI) 471.1764 (M^+ +H. requires 471.1767 $C_{24}H_{27}N_2O_8$) (CI) 471 (M^+ +H, 13 %), 453 (11), 364 (42), 363 (58), 326 (11), 237 (15), 236 (100), 91 (12) and 59 (21).

1-(3-hydroxypropyl)-3-methoxy-1H-pyrrole-2,5-dione 260



To a solution of methoxy maleimide (0.38 g, 3 mol) and 3-bromo-1-propanol (0.27 cm^3, 9 mmol) in anhydrous MeCN (10 cm^3) was added finely ground K_2CO_3 (0.5 g, 3.6 mmol) and left to stir at reflux for 3 h 15 min. The solution was allowed to cool and was then concentrated *in vacuo* onto silica gel and subjected to column chromatography using 66 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give alcohol **260** (372 mg, 67 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 3326, 1710, 1640, 1291, 1237, 1113, 975 and 809; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.74 – 1.83 (2H, m, NCH_2CH_2), 2.38 (1H, bs, O*H*), 3.58 (2H, q, *J* = 5.2, CH_2OH) 3.67 (2H, dd, *J* = 6.4 and 5.6, NCH_2CH_2), 3.94 (3H, s, OCH_3) and 5.43 (1H, s, C*H*=C); d_C (400 MHz; $CDCl_3$; Me_4Si) 31.3 (CH_2), 33.9 (CH_2), 59.0 (CH_2), 59.0 (CH_3), 96.2 (CH), 161.0 (C), 166.0 (C) and 170.8 (C); *m/z* (EI) 185.0683 (M^+. requires 185.0688 $C_8H_{11}NO_4$), (EI) 185 (M^+, 19 %), 167 (16), 155 (15), 142 (16), 141 (17), 140 (64), 124 (15), 113 (48), 112 (13), 86 (64), 84 (100), 82 (11), 69 (56) and 56 (68).

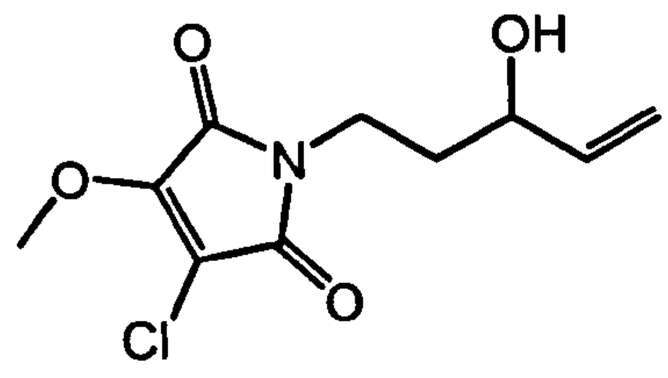
3-(3-methoxy-2,5-dioxo-2H-pyrrol-1(5H)-yl)propanal 259



To a solution of alcohol **260** (185 mg, 1 mmol) in anhydrous DCM (25 cm^3) was added 15 wt% solution of Dess-Martin periodinane in DCM (2.3 cm^3, 1.1 mmol) dropwise at r.t. and left to stir for 2 h. The reaction mixture was concentrated *in vacuo*, then redissolved in EtOAc (10 cm^3) and petroleum ether 40 – 60 °C (5 cm^3). The slurry was filtered through a pad of silica and concentrated *in vacuo* to

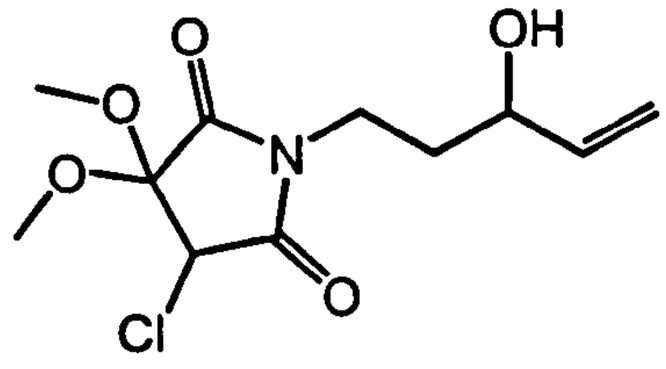
give aldehyde **259** (62 mg, 63 %) as a colourless oil that crystallised upon standing: ν_{max}(film)/cm^{-1} 1707, 1636, 1321, 910 and 728; d_H (270 MHz; $CDCl_3$; Me_4Si) 2.77 (2H, dt, *J* = 6.9 and 1.3, NCH_2CHH), 3.83 (2H, t, *J* = 6.9, $NCHHCH_2$), 3.92 (3H, s, OCH_3), 5.41 (1H, s, C*H*=C) and 9.75 (1H, s, C(O)*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 32.6 (CH_2), 41.4 (CH_2), 58.9 (CH_3), 96.3 (CH), 160.9 (C), 165.3 (C), 169.8 (C) and 205.7 (C); *m/z* (EI) 183.0527 (M^+, requires 183.0532 $C_8H_9NO_4$) (CI) 183 (M^+ +H, 8 %), 155 (32), 140 (40), 137 (13), 113 (25), 112 (21), 86 (65), 84 (100) and 69 (67).

3-chloro-1-(3-hydroxypent-4-enyl)-4-methoxy-1H-pyrrole-2,5-dione 247



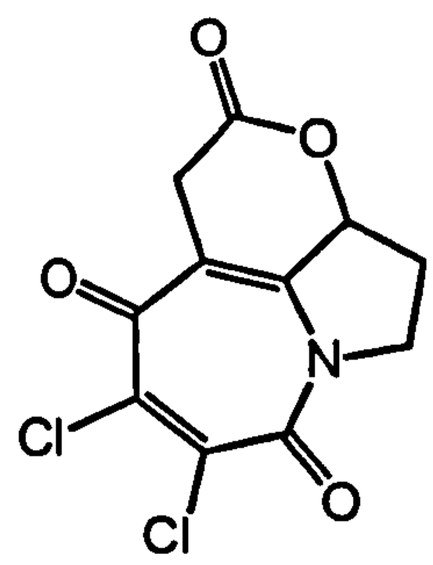
To a solution of maleimide **214** (1.0 g, 4 mmol) in anhydrous MeOH (25 cm^3) was added NaOMe (0.22 g, 4 mmol) portion-wise and left to stir for 30 min. The mixture was diluted with sat NH_4Cl (25 cm^3) and extracted with EtOAc (4 x 25 cm^3). The organic was washed with $NaHCO_3$ (25 cm^3), brine (25 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give an orange oil. The oil was purified by graduated column chromatography on silica gel using 10 – 33 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **247** (0.46 g, 48 %) as a colourless oil: ?$_{max}$(MeCN)/nm 330; ν_{max}(film)/cm^{-1} 3488, 1716, 1657, 1294, 907 and 727; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.68 – 1.87 (2H, m, NCH_2CH_2), 3.69 (2H, dd, *J* = 7.3 and 6.1, NCH_2CH_2), 4.05 – 4.13 (1H, m, C*H*OH), 4.33 (3H, s, OCH_3), 5.12 (1H, dt, *J* = 10.5 and 1.3, C*H*H=CH), 5.26 (1H, dt, *J* = 17.3 and 1.4, C*H*H=CH) and 5.85 (1H, ddd, *J* = 17.2, 10.4 and 5.6, CH_2=C*H*); d_C (400 MHz; $CDCl_3$; Me_4Si) 35.0 (CH_2), 35.3 (CH_2), 59.9 (CH_3), 69.9 (CH), 103.5 (C), 115.1 (CH_2), 139.8 (CH), 150.4 (C), 164.3 (C) and 165.9 (C); *m/z* (CI) 246.0531 (M^+ +H. requires 246.0533 $C_{10}H_{13}NO_4{}^{35}Cl$), (CI) 246 ($M^+$ +H, 21 %), 230 (49), 228 (100), 176 (19), 174 (53) and 59 (12).

Further elution gave the acetal (0.26 g, 24 %) as a colourless oil:



ν_{max}(film)/cm^{-1} 3505, 1716 and 1051; *m/z* (CI) 278.0785 (M^+ +H. requires 278.0795 $C_{11}H_{17}NO_5{}^{35}Cl$), (CI) 278 ($M^+$ +H, 4 %), 262 (44), 260 (100), 232 (21), 230 (30), 228 (41) 215 (14), 200 (13), 12 (10) and 115 (19).

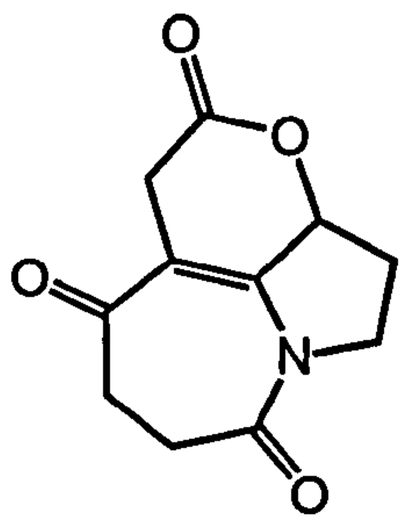
7,8-Dichloro-1,2,2a,5-tetrahydro-3-oxa-9a-aza-benzo[*cd*]azulene-4,6,9-trione 235



To a solution of azepine **216** (1.32 g, 5.3 mmol), glyoxylic acid (1.94 g, 21.1 mmol) and 3 Å molecular sieves (5.3 g, 1gmmol^{-1}) in anhydrous DMF (25 cm^3) was added NaOH (21 mg, 10 mol%) in one portion and left to stir at 80°C for 2 h. The reaction mixture was allowed to cool to r.t. then filtered, washed with DMF (3 x 5 cm^3) and concentrated *in vacuo* to give a brown oil. Remaining DMF was azeotroped with toluene (3 x 40 cm^3) to give a brown solid. The solid was purified by graduated column chromatography on silica gel using 1 – 4 % MeOH in DCM as the eluent to give azepine **235** (678 mg, 46 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 1742, 1656, 1608, 1432, 1254, 1117, 925 and 731; d_H (400 MHz; DMSO-d_6; Me_4Si) 2.01 – 2.27 (1H, m, NCH_2CHH), 2.65 – 2.76 (1H, m, NCH_2CHH), 3.40 (1H, dd, *J* = 18.6 and 2.2, C(O)C*H*H), 3.64 (1H, d, *J* = 18.6, C*H*HC(O)O), 3.91 (1H, dt, *J* = 11.9 and 6.6, NC*H*HCH_2), 4.29 (1H, dd, *J* = 12.1 and 9.7, NC*H*HCH_2) and 5.81 (1H, ddd, *J* = 10.3, 8.4 and 1.8, C*H*OR); d_C (400

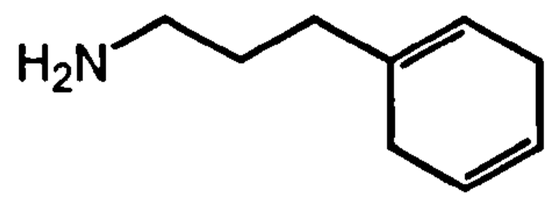
MHz; DMSO-d_6; Me_4Si) 26.2 (CH_2), 29.5 (CH_2), 50.5 (CH_2), 79.2 (CH), 106.7 (C), 140.10 (C), 144.5 (C), 147.4 (C), 156.1 (C), 169.4 (C) and 172.8 (C); *m/z* (EI) 286.9746 (M^+. requires 286.9752 $C_{11}H_7NO_4{}^{35}Cl_2$), (EI) 360 (M^+, 100 %) 217 (18), 215 (26), 208 (18), 203 (19), 89 (18), 87 (57), 80 (25), 78 (54) and 63 (63).

1,2,2a,5,7,8-Hexahydro-3-oxa-9a-aza-benzo[*cd*]azulene-4,6,9-trione 236



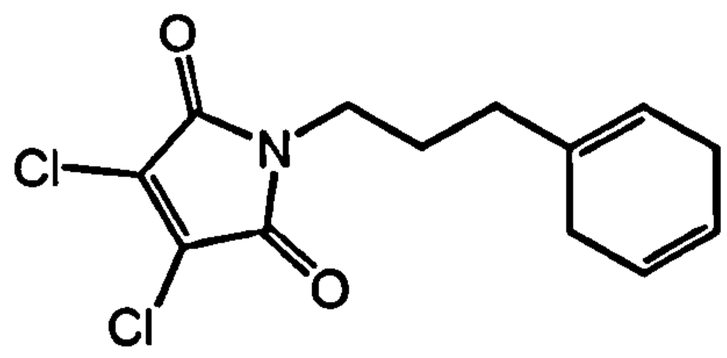
Zinc (158 mg, 2.4 mmol) was added to acetic acid (4 cm^3) and left to stir at r.t. for 30 min. A solution of azepine **235** (69 mg, 0.24 mmol) in acetic acid (1 cm^3) was added dropwise at r.t. over 10 min. The reaction mixture was filtered through Celite®, the filter cake was washed with acetic acid (3 x 5 cm^3), concentrated *in vacuo*, diluted with EtOAc (50cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The oil was purified by column chromatography on silica gel using 3 % MeOH in DCM as the eluent to give azepine **236** (23 mg, 43 %) as a white crystalline solid: d_H (400 MHz; DMSO-d_6; Me_4Si) 1.95 – 2.13 (1H, m, NCH_2CHH), 2.54 – 2.64 (2H, m, NCH_2CHH and $CHHC(O)N$), 2.69 – 2.86 (2H, m, $CHHC(O)N$ and $CHHC(O)R$), 3.09 (1H, dd, J = 18.3 and 2.5, $CHHC(O)O$), 3.14 – 3.31 (1H, m, $CHHC(O)R$), 3.50 (1H, d, J = 18.3, $CHHC(O)O$), 3.60 (1H, dt, J = 11.4 and 6.6, $NCHHCH_2$), 3.99 (1H, dd, J = 11.4 and 10.0, $NCHHCH_2$) and 5.60 (1H, ddd, J = 10.4, 8.4 and 2.4, $CHOR$); d_C (400 MHz; DMSO-d_6; Me_4Si) 26.6 (CH_2), 27.9 (CH_2), 30.4 (CH_2), 34.8 (CH_2), 46.5 (CH_2), 78.3 (CH), 105.3 (C), 147.4 (C), 170.0 (C), 171.7 (C) and 193.3 (C).

3-(cyclohexa-1,4-dienyl)propan-1-amine 263[101]



To a solution of amine 3-phenylpropyl-1-amine (5 g, 37 mmol) in anhydrous EtOH (17 cm^3) was distilled in ammonia (240 cm^3) at -33 °C. The solution was stirred and lithium washed in hexane was added in small pieces, until a deep blue colour persisted. Ammonium chloride (8 g) was added in one portion and the ammonia was then allowed to evaporate under a gentle stream of nitrogen overnight. The mixture was concentrated *in vacuo* to give amine **263** (5 g, 99 %) as a pale yellow oil: d_H (400 MHz; $CDCl_3$; Me_4Si) 1.12 (2H, bs, NH_2), 1.55 (2H, dt, J = 14.8 and 7.8, NCH_2CH_2), 1.98 (2H, t, J = 7.8, $NCH_2CH_2CH_2$), 2.50 – 2.76 (6H, m, NCH_2CH_2 and 2 x CH=CHCH_2), 5.39 – 5.44 (1H, m, CH=C) and 5.67 – 5.71 (2H, m, 2 x CH=CH); *m/z* (CI) 138 (M^+ +H, 83 %), 121 (100), 93 (53), 91 (42), 79 (58) and 67 (30).

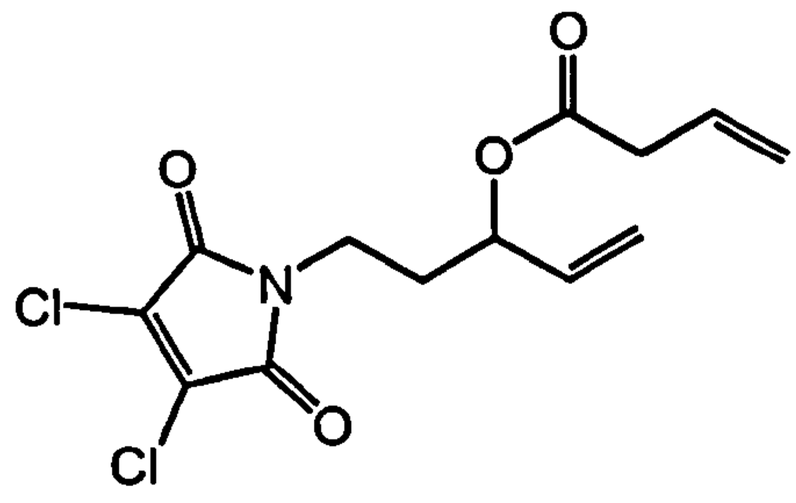
3,4-dichloro-1-(3-(cyclohexa-1,4-dienyl)propyl)-1H-pyrrole-2,5-dione 264



To a solution of dichloromaleic anhydride (2.44g, 15.6 mmol) in toluene (100 cm^3) was added amine **263** (2.0 g, 14.6 mmol) dropwise then heated under reflux for under a Dean-Stark set up for 3 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography on silica gel using 2.5 – 10 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **264** (2.9 g, 70 %) as a colourless oil: ?$_{max}$(MeCN)/nm 305; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.77 (2H, quin, J = 7.3, NCH_2CH_2), 2.00 (2H, t, J = 7.3, $NCH_2CH_2CH_2$), 2.52 – 2.59 (2H, m, CH=CHCH_2), 2.63 – 2.70 (2H, m,

CH=CHCH_2), 3.60 (2H, t, J = 7.3, NCH_2CH_2), 5.41 - 5.46 (1H, m, CH=C) and 5.67 - 5.71 (2H, m, 2 x CH=CH); d_C (400 MHz; $CDCl_3$; Me_4Si) 25.5 (CH_2), 26.7 (CH_2), 28.7 (CH_2), 34.4 (CH_2), 39.2 (CH_2), 119.4 (CH), 124.0 (CH), 124.2 (CH), 133.1 (C), 133.2 (C) and 163.0 (C); *m/z* (CI) 286.0400 (M^+ +H. requires 286.0402 $C_{13}H_{14}NO_2{}^{35}Cl_2$), (CI) 286 ($M^+$ +H, 100 %), 284 (48), 283 (27), 206 (15), 121 (54), 117 (49) and 91 (13).

5-(3,4-dichloro-2,5-dioxo-2H-pyrrol-1(5H)-yl)pent-1-en-3-yl but-3-enoate 265



Method A

To a solution of vinyl acetic acid (0.24 cm^3, 2.8 mmol) in anhydrous DCM (25 cm^3) was added DCC (0.62 g, 3 mmol) in one portion and left to stir at r.t. for 1 h. Maleimide **214** (0.5 g, 2 mmol) and DMAP (12 mg, 5 mol%) were added to the reaction mixture and left to stir for 30 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 20 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **265** (83 mg, 13 %) as a colourless oil: d_H (270 MHz; $CDCl_3$; Me_4Si) 1.89 – 2.10 (2H, m, NCH_2CH_2), 3.12 (2H, dt, J = 6.9 and 1.3, C(O)CH_2) 3.56 – 3.81 (2H, m, NCH_2CH_2), 5.14 – 5.33 (5H, m, 2 x CH_2=CH and CHOR), 5.68 – 5.86 (1H, m, CH_2=CH) and 5.87 – 6.03 (1H, m, CH_2=CH); d_C (400 MHz; $CDCl_3$; Me_4Si) 32.4 (CH_2), 35.6 (CH_2), 39.2 (CH_2), 71.9 (CH), 117.6 (CH_2), 118.7 (CH_2), 130.0 (CH), 133.4 (C), 135.1 (CH), 162.8 (C) and 167.6 (C); *m/z* (CI) 318.0298 (M^+ +H. requires 318.0300 $C_{13}H_{14}NO_4{}^{35}Cl_2$), (CI) 318 ($M^+$ +H, 31 %), 251 (18), 249 (27), 234 (80), 232 (100), 178 (9) and 69 (13).

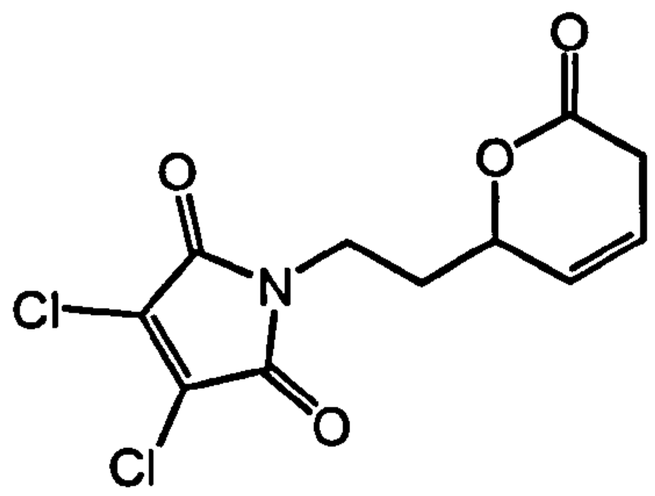
Method B

To a solution of vinyl acetic acid (5.6 cm^3, 60 mmol) and DMF (9 cm^3, 120 mmol) in anhydrous DCM (120 cm^3) was added 2.0 M oxalyl chloride solution in DCM (30 cm^3, 60 mmol) dropwise at r.t. and left to stir for 3 h. Maleimide **214** (1.5 g, 6 mmol) and diisopropyl ethylamine (11.4 cm^3, 60 mmol) were added to the reaction solution and left to stir for 16 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 5% EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **265** (735 mg, 39 %) as a colourless oil.

Method C

To a solution of PPh_3 (289 mg, 1.1 mmol) in anhydrous THF (25 cm^3) was added DIAD (0.19 cm^3, 1 mmol) dropwise at -78 °C. After 2 h a white ppt formed. Maleimide **214** (250 mg, 1 mmol) was added dropwise and left to stir at -78 °C for 1 h. Finally vinyl acetic acid (85 µl, 1 mmol) was added and the reaction mixture was allowed to warm to r.t. overnight. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 5% EtOAc in petroleum ether 40 – 60 °C as the eluent to give maleimide **265** (125 mg, 39 %) as a colourless oil.

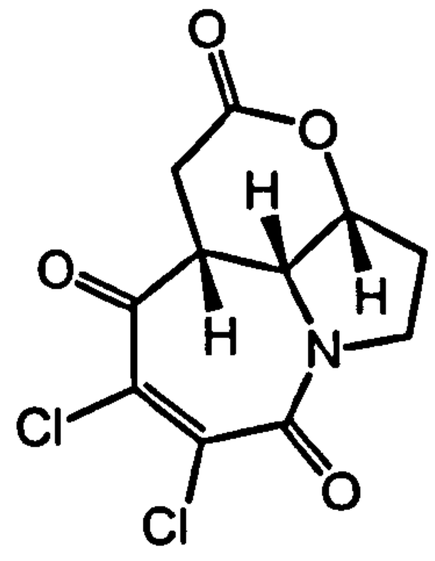
3,4-dichloro-1-(2-(5,6-dihydro-6-oxo-2H-pyran-2-yl)ethyl)-1H-pyrrole-2,5-dione 266



To a solution of maleimide **265** (0.68 g, 2.1 mmol) in anhydrous DCM (200 cm^3) was added Grubbs second generation catalyst (18 mg, 1 mol%) in one portion and left to stir for 24 h. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography on silica gel using 50 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give recovered **265** (68 mg, 10 %) as a colourless oil.

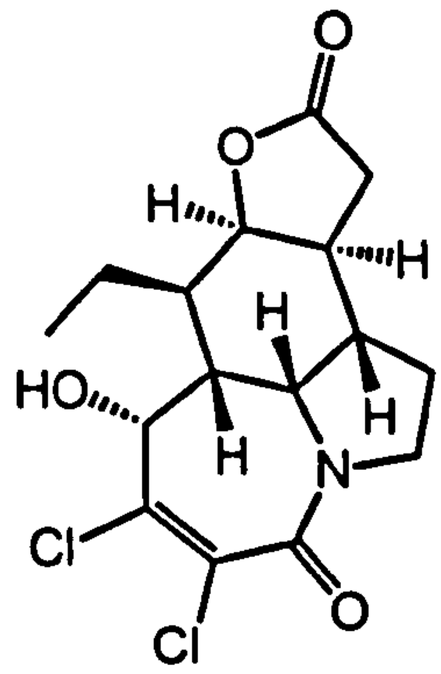
Further elution gave azepine **266** (0.42 g, 67 %) as a white crystalline solid: d_H (400 MHz; $CDCl_3$; Me_4Si) 1.97 – 2.14 (2H, m, NCH_2CH_2), 2.97 – 3.16 (2H, m, $C(O)CH_2$), 3.71 – 3.91 (2H, m, NCH_2CH_2), 5.00 – 5.09 (1H, m, CHOR), 5.80–5.83 (1H, m, CH=CH) and 5.87 – 5.93 (1H, m, CH=CH); d_C (400 MHz; $CDCl_3$; Me_4Si) 29.6 (CH_2), 33.7 (CH_2), 35.4 (CH_2), 77.3 (CH), 122.9 (CH), 125.2 (CH), 133.4 (C), 162.9 (C) and 167.7 (C); *m/z* (CI) 289.9975 (M^+ +H. requires 289.9987 $C_{11}H_{10}NO_4{}^{35}Cl_2$), (CI) 290 ($M^+$ +H, 42 %), 288 (13) and 107 (100).

(±)-(2aR,5aR,9bR)-7,8-Dichloro-1,2,2a,5,5a,9b-hexahydro-3-oxa-9a-aza-benzo[*cd*]azulene-4,6,9-trione 267



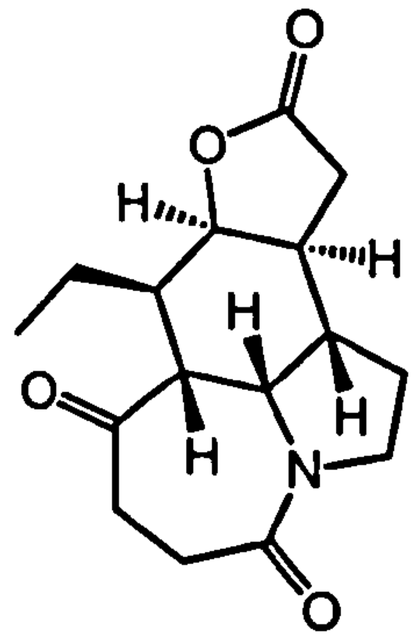
A solution of maleimide **266** (400 mg, 1.4 mmol) in degassed MeCN (100ml) was irradiated in a Pyrex well for 50 min. The reaction solution was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography on silica gel using 50 – 75 % EtOAc in petroleum ether 40 – 60 °C as the eluent to give recovered sm **267** (88 mg, 22 %). Further elution gave azepine **267** (233 mg, 58 %) as a white crystalline solid: *m/z* (CI) 289.9979 (M^+ +H, requires 289.9987 $C_{11}H_{10}NO_4{}^{35}Cl_2$), (CI) 290 ($M^+$ +H, 56 %), 272 (8), 256 (21), 254 (57), 244 (12), 226 (4), 220 (4), 79 (100) and 68 (28).

(±)-(31*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-5,6-Dichloro-8-ethyl-7-hydroxy 1,2,8,8a,11,11a-hexahydroazepino[3,2,1-*hi*]furo[3,2-e]indole-4,7,10(31*H*,11b*H*)-dione 290



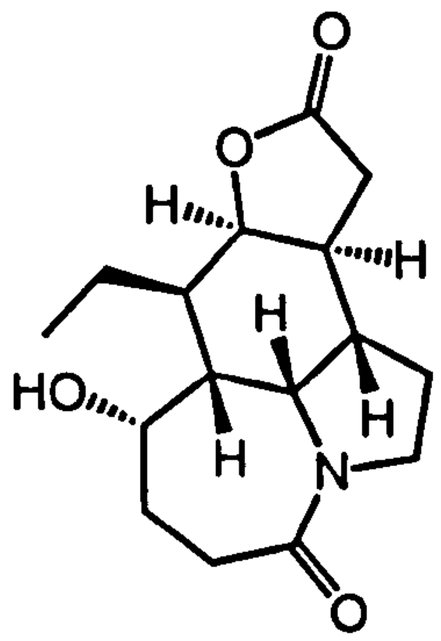
To a solution of azepine **275c** (99 mg, 0.28 mmol) in anhydrous THF (25 cm^3) was added 1.0 M $LiAl(O^tBu)_3H$ solution in THF (0.28 cm^3, 0.28 mmol) dropwise at 0°C and left to stir at r.t. for 20 min. The reaction mixture was quenched with dropwise addition of H_2O (0.35 cm^3) and left to stir for 30 min. The mixture was filtered through Celite® and the filter cake was washed with THF (5 x 15 cm^3). The solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 5 % MeOH in DCM as the eluent to give azepine **290** (99 mg, 99 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 3332, 1767, 1632, 1088 and 972; d_H (400 MHz; DMSO-d_6; Me_4Si) 0.94 (3H, t, *J* = 7.3,), 1.08 – 1.21 (1H, m,), 1.62 (1H, ddd, *J* = 12.6, 7.6, and 3.8,), 1.68 – 1.81 (1H, m,) 1.92 – 2.08 (3H, m,) 2.52 – 2.72 (3H, m,) 2.99 (1H, dd, *J* = 11.0 and 2.0,) 3.21 – 3.46 (2H, m,) 4.28 (1H, dd, *J* = 8.8 and 6.6,), 4.45 (1H, t, *J* = 3.9,), 4.99 (1H, dd, *J* = 9.5 and 3.7,) and 6.11 (1H, d, *J* = 3.7,); d_C (400 MHz; DMSO-d_6; Me_4Si) 20.2 (CH_3), 29.0 (CH_2), 31.7 (CH_2), 33.5 (CH), 34.1 (CH_2), 38.8 (CH), 43.0 (CH), 45.0 (CH_2), 54.4 (CH), 73.4 (CH), 76.9 (CH), 126.1 (C), 143.1 (C), 160.7 (C) and 176.4 (C); *m/z* (CI) 360.0764 (M^+ +H, requires 360.0769 $C_{16}H_{20}NO_4{}^{35}Cl_2$) (CI) 360 ($M^+$ +H, 68 %), 326 (35) and 324 (100).

(±)-(31*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyloctahydroazepino[3,2,1-*hi*]furo[3,2-e] indole-4,7,10-(31*H*,7a*H*,11b*H*)-trione 283



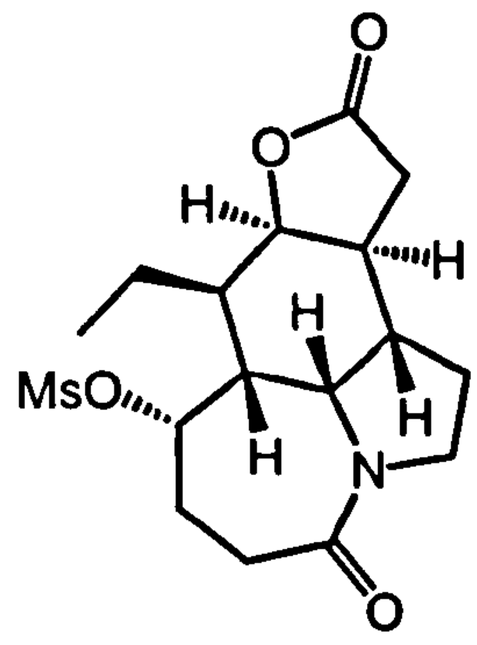
Zinc powder (2.9 g, 44.8 mmol) was activated by stirring with glacial acetic acid (40 cm^3) at r.t. for 20 min. A solution of **275c** (0.8 g, 2.2 mmol) in glacial acetic acid (28 cm^3) was added and left to stir at r.t. for 1 h. The reaction mixture was filtered through Celite, washed with EtOAc (3 × 50 cm^3), concentrated *in vacuo* onto silica gel and subjected to column chromatography using 10 % MeOH in DCM as the eluent to give azepine **283** (0.6 g, 95 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 1771, 1702, 1631, 1423, 1178 and 906; d_H (400 MHz; CD_2Cl_2; Me_4Si) 0.95 (3H, t, *J* = 7.4,), 1.14 – 1.26 (1H, m,), 1.38 – 1.52 (1H, m,), 1.61 – 1.67 (1H, m, *J* = 12.6, 6.5 and 1.2,) 1.86 – 2.01 (2H, m,), 2.01 – 2.08 (1H, m,), 2.23 (1H, ddd, *J* = 8.8, 7.2 and 4.8,) 2.32 (1H, d, *J* = 17.0,), 2.45 – 2.56 (2H, m,) 2.61 – 2.69 (2H, m,) 2.76 (1H, ddd, *J* = 12.3, 2.8 and 0.6,), 2.82 (1H, dd, *J*=17.1 and 7.2,), 3.44 (1H, dt, *J* = 11.7 and 6.4,), 3.87 (1H, dd, *J* = 12.2 and 8.3,), 3.92 (1H, dd, *J* = 5.0 and 3.1,) and 4.65 (1H, dd, *J* = 4.7 and 2.7,); d_C (400 MHz; CD_2Cl_2; Me_4Si) 11.2 (CH_3), 22.8 (CH_2), 29.0 (CH_2), 33.3 (CH_2), 35.1 (CH), 36.9 (CH_2), 37.0 (CH), 38.7 (CH_2), 43.0 (CH), 47.5 (CH_2), 52.2 (CH), 58.2 (CH), 78.8 (CH), 173.6 (C), 176.4 (C) and 210.3 (C); *m/z* (CI) 292.1548 (M^+ +H, requires 292.1549 $C_{16}H_{22}NO_4$), (CI) 292 (M^+ +H, 56 %)]+) 274 (9), 246 (7), 232 (31), 147 (8), 133 (7).

(±)-(31*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-7-hydroxydecahydroazepino [3,2,1-*hi*]furo[3,2-e]indole-4,10(31*H*,11b*H*)-dione 289



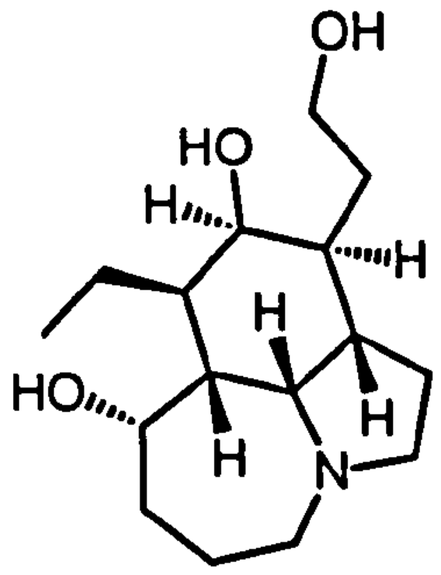
To a solution of azepine **283** (71 mg, 0.24 mmol) in anhydrous THF (25 cm^3) was added 1.0 M $LiAl(O^tBu)_3H$ solution in THF (0.24 cm^3, 0.24 mmol) dropwise at 0°C and left to stir at r.t. for 3 h. The reaction mixture was quenched with dropwise addition of H_2O (0.3 cm^3) and left to stir for 30 min. The mixture was filtered through Celite® and the filter cake was washed with THF (5 x 15 cm^3). The solution was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 10 % MeOH in DCM as the eluent to give azepine **289** (71 mg, 99 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 3378, 1759, 1627, and 906; d_H (400 MHz; CD_2Cl_2; Me_4Si) 0.93 (3H, t, *J* = 7.5,), 1.39 – 1.49 (1H, m,), 1.55 – 1.62 (1H, ddt, *J* = 12.5, 6.8 and 2.2,), 1.71 – 1.94 (4H, m,) 2.02 (1H, ddd, *J* = 14.2, 7.5 and 4.0,), 2.06 – 2.16 (2H, m,), 2.19 – 2.26 (1H, m,), 2.31 (1H, dd, *J* = 17.3 and 1.5,), 2.39 (1H, ddd, *J* = 15.6, 11.4 and 4.5,), 2.55 (1H, ddd, *J* = 15.5, 6.1 and 3.7,), 2.81 (1H, dd, *J* = 17.2 and 7.7,), 3.38 (1H, ddd, *J* = 12.1, 10.5 and 6.7,) 3.65 - 3.73 (1H, m,), 3.77 (1H, dd, *J* = 5.4 and 2.7,) 3.92 (1H, dt, *J* = 10.4 and 2.9,) and 4.75 (1H, dd, *J* = 5.4 and 2.6,); d_C (400 MHz; CD_2Cl_2; Me_4Si) 11.6 (CH_3), 21.8 (CH_2), 26.8 (CH_2), 29.1 (CH_2), 35.2 (CH), 35.6 (CH_2), 36.7 (CH), 38.6 (CH_2), 40.1 (CH), 43.7 (CH), 47.8 (CH_2), 60.1 (CH), 75.9 (CH), 80.8 (CH), 174.8 (C) and 177.5 (C); *m/z* (CI) 294.1704 (M^+ +H, requires 294.1705 $C_{16}H_{24}NO_4$), (CI) 294 (M^+ +H, 56 %)]+) 276 (30), 265 (4), 234 (4), 216 (4), 192 (3).

(±)-(31*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-4,10-ioxotetradecahydroazepino [3,2,1-*hi*]furo[3,2-e]indol-7-yl methanesulfonate 292



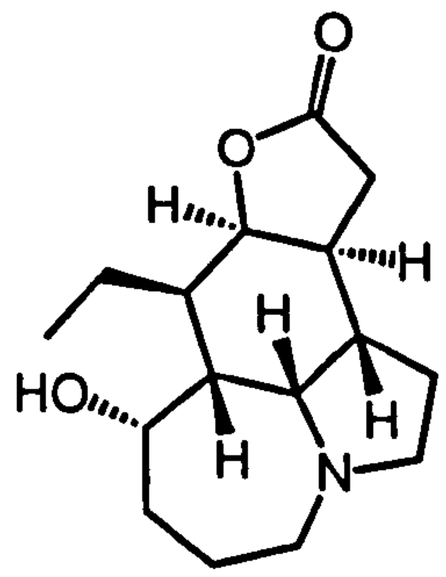
To a solution of azepine **290** (70 mg, 0.24 mmol) and triethylamine (166 µl, 1.2 mol) in anhydrous THF (20 cm^3) was added methanesulfonyl chloride (74 µl, 0.96 mmol) dropwise at 0°C and left to stir at r.t. for 5 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 5 % MeOH in DCM as the eluent to give azepine **292** (89 mg, 99 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 1773, 1628, 1461, 1350 and 1170; d_H (400 MHz; CD_2Cl_2; Me_4Si) 0.98 (3H, t, *J* = 7.3 Hz,), 1.15 – 1.29 (1H, m,), 1.46 – 1.65 (1H, m,), 1.77 – 1.93 (3H, m,), 2.00 – 2.09 (1H, m,), 2.09 – 2.24 (3H, m,), 2.32 (1H, d, *J* = 17.2,), 2.38 – 2.52 (2H, m,), 2.67 (1H, ddd, *J* = 15.5, 6.3 and 3.0,), 2.81 (1H, dd, *J* =17.2 and 7.6,), 3.03 (3H, s,), 3.40 (1H, ddd, *J* = 12.0, 11.1 and 6.6,), 3.76 (1H, dd, *J* = 8.9 and 7.6,) 3.79 (1H, dd, *J* = 4.5 and 2.5 Hz,), 4.71 (1H, dd, *J* = 4.3 and 2.0,) and 4.86 (1H, dt, *J* = 10.8 and 3.2,); d_C (400 MHz; DMSO-d_6; Me_4Si) 11.1 (CH_3), 21.2 (CH_2), 24.4 (CH_2), 28.1 (CH_2), 31.5 (CH), 33.2 (CH_2), 34.3 (CH), 35.5 (CH_2), 37.6 (CH), 37.9 (CH), 42.7 (CH_3), 46.9 (CH_2), 58.1 (CH), 79.0 (CH), 84.9 (CH), 171.7 (C) and 176.4 (C); *m/z* (ESI) 394.1308 (M^+ +Na. requires 394.1295 $C_{17}H_{25}NaNO_6S$), (CI) 371 (M^+ +H, 3 %), 323 (35), 322 (56), 292 (28), 290 (44), 276 (70) 178 (48), 102 (73), 97 (100), 86 (52) and 65 (52).

(±)-(31*S*,7*S*,7a*R*,8*R*,9*S*,10*S*,10a*S*)-8-Ethyl-10-(2-hydroxyethyl)-dodeca hydroazepino[3,2,1-*hi*]indole-7,9-diol 293



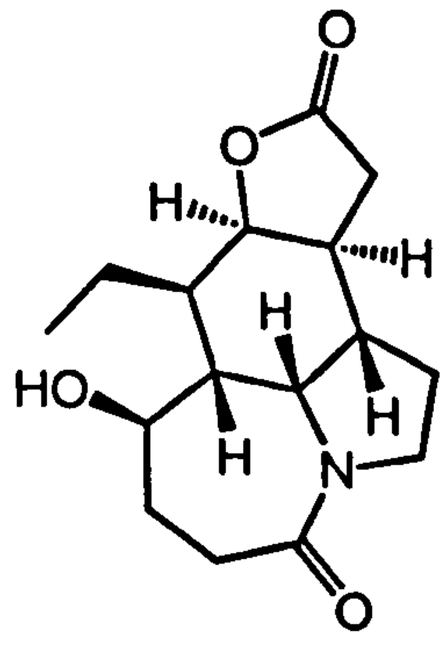
To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in anhydrous THF (10 cm^3) was added azepine **292** (125 mg, 0.34 mmol) portion-wise at 0 °C and then left to stir at reflux for 7 h 45 min. The reaction mixture was quenched with water (0.1 cm^3), 15 % NaOH (0.1 cm^3) and additional water (0.3 cm^3). After 1 h the mixture was filtered through Celite® and the filter cake was washed with THF (5 x 10 cm^3), concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography using 5 – 10 % 7 M NH_3 solution in MeOH with DCM as the eluent to give alcohol **293** (39 mg, 39 %) as a colourless oil: ν_{max}(film)/cm^{-1} 3364, 1119 and 972; d_H (400 MHz; MeOD; Me_4Si) 0.86 (3H, t, J = 7.3,), 1.24 – 1.35 (2H, m,), 1.40 – 1.74 (7H, m,), 1.75 – 1.97 (4H, m,), 2.0 - 2.1 (1H, m,), 2.30 – 2.47 (2H, m,), 2.58 – 2.73 (1H, m,), 2.82 (1H, dt, J = 12.2 and 4.3,), 3.03 (1H, dt, J = 10.5 and 7.2,), 3.44 – 3.66 (2H, m,), 3.85 (1H, t, J = 1.8,) and 4.01 (1H, dt, J = 8.6 and 3.1,); d_C (400 MHz; MeOD-d_4; Me_4Si) 10.7 (CH_3), 21.7 (CH_2), 22.9 (CH_2), 27.8 (CH_2), 30.3 (CH_2), 32.9 (CH2), 39.5 (CH), 41.0 (CH), 41.5 (CH), 42.7 (CH), 55.4 (CH_2), 59.2 (CH_2), 66.5 (CH), 68.8 (CH), 70.5 (CH); *m/z* (CI) 284.2216 (M^+ +H, requires 284.2226 $C_{16}H_{30}NO_3$), (CI) 284 (M^+ +H, 9 %), 266 (16), 115 (30) and 79 (100).

Azepine 294



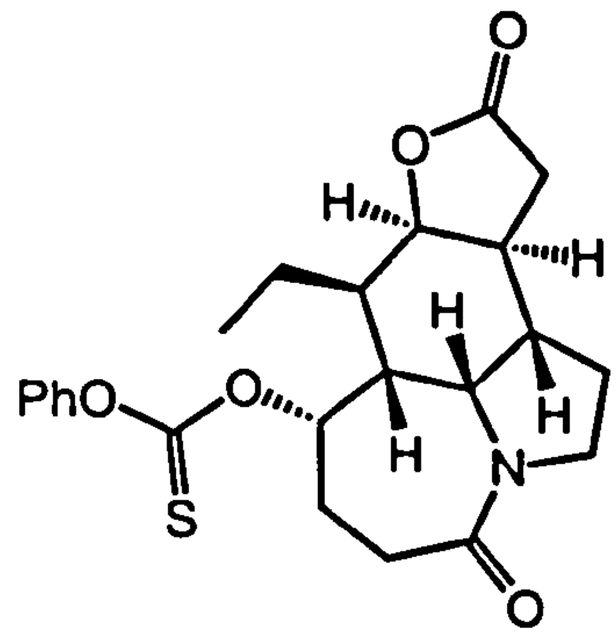
To a solution of alcohol **293** (23 mg, 0.09 mmol) in anhydrous benzene (5 cm^3) was added $Ru(PPh_3)_2Cl_2$ (100 mg, 0.10 mmol) in one portion and left to stir at r.t. for 16 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 10 % MeOH in DCM as the eluent to give lactone **294** (13 mg, 57 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 3350, 1768, 1175 and 950; d_H (400 MHz; $CDCl_3$; Me_4Si) 1.01 (3H, t, J = 7.3,), 1.33 – 1.46 (1H, m,), 1.46 – 1.71 (5H, m,), 1.77 – 2.18 (5H, m,), 2.20 – 2.46 (4H, m,), 2.70 – 2.85 (2H, m,), 2.93 – 3.11 (m, 3 H), 4.07 (1H, dd, J = 8.1 and 3.9,) and 5.01 (1H, dd, J = 8.3 and 4.2,); *m/z* (CI) 280.1907 (M^+ +H, requires 280.1913 $C_{16}H_{26}NO_3$), (CI) 280 (M^+ +H, 100 %), 262 (14) and 220 (3).

(±)-(31*S*,7*R*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-7-hydroxydecahydroazepino [3,2,1-*hi*]furo[3,2-e]indole-4,10(31*H*,11b*H*)-dione 291



To a solution of alcohol **290** (10 mg, 0.03 mmol) and chloro(diphenyl)silane (16 µl, 0.07 mmol) in anhydrous DCM (1 cm^3) was added $InCl_3$ (0.4 mg, 5 mol%) in one portion and left to stir at reflux for 16 h. The reaction mixture was allowed to cool to r.t. at which point a precipitate was observed. The reaction mixture was filtered; the solid washed with DCM (3 x 2 cm^3) and the filtrate was discarded. The solid was dissolved in acetone (2 cm^3), filtered and washed with acetone (3 x 2 cm^3). The filtrate was concentrated *in vacuo* to give alcohol **291** (10 mg, 99 %) as a white crystalline solid: ν_{max}(film)/cm^{-1} 3087, 1755, 1686, 1249, 1155 and 913; d_H (400 MHz; CD_3CO; Me_4Si) 1.04 (3H, t, *J* = 7.3,), 1.44 – 1.61 (1H, m,), 1.86 – 1.99 (1H, m,), 2.11 – 2.24 (2H, m,), 2.30 – 2.56 (7H, m,), 2.46 (1H, d, *J* = 16.9 Hz,), 2.66 – 2.77 (m, 1 H), 2.97 (1H, dd, *J* = 16.9 and 6.4,), 3.77 – 3.92 (2H, m,), 4.40 – 4.49 (1H, m,), 4.86 (1H, dd, *J* = 3.7 and 3.4,) and 5.06 (1H, ddd, *J* = 10.3, 6.1 and 2.9,); d_C (400 MHz; CD_3CO; Me_4Si) 11.5 (CH_3), 22.3 (CH_2), 26.7 (CH_2), 29.0 (CH_2), 29.9 (CH_2), 35.3 (CH), 36.4 (CH), 37.4 (CH), 38.3 (CH_2), 41.0 (CH), 46.4 (CH_2), 60.5 (CH), 78.9 (CH), 79.7 (CH), 175.9 (C) and 176.5 (C); *m/z* (CI) 294.1692 (M^+ +H, requires 294.1705 $C_{16}H_{24}NO_4$), (CI) 294 (M^+ +H, 100 %), 276 (48), 250 (6), 232 (9), 216 (8), 115 (75), 99 (5), 95 (13), 79 (46) and 59 (90).

(±)-*O*-(31*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-4,10-dioxotetradecahydro azepino[3,2,1-*hi*]furo[3,2-e]indol-7-yl *O*-phenyl carbonothioate 295



Method A

To a solution of alcohol **290** (25 mg, 0.09 mmol) and DMAP (16 mg, 0.13 mmol) in anhydrous DCM (3 cm^3) was added *O*-phenyl chlorothionoformate (14 µl, 0.10 mmol) dropwise and left to stir for 3 days. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 2 % MeOH in DCM as the eluent to give thiocarbonate **295** (14 mg, 38 %) as a white crystalline solid: mp 209 – 210 °C; ν_{max}(film)/cm^{-1} 1776, 1623, 1576, 1403, 1294 and 1194; d_H (400 MHz; $CDCl_3$; Me_4Si) 0.97 (3H, t, *J* = 7.3 Hz,), 1.39 – 1.56 (1H, m,), 1.62 (1H, dd, *J* = 12.5, and 6.4,), 1.72 – 1.97 (3H, m,), 2.04 – 2.23 (4H, m,), 2.37 (1H, d, *J* = 17.1,), 2.45 – 2.55 (1H, m,), 2.57 – 2.65 (1H, m,), 2.73 – 2.90 (2H, m,), 3.48 (1H, dt, *J* = 11.9 and 6.4,), 3.80 – 3.92 (2H, m,), 4.72 (1H, dd, *J* = 3.9 and 2.2,), 5.47 (1H, dt, *J* = 7.0 and 3.2,), 7.10 (2H, dd, *J* = 8.4 and 1.1,), 7.27 – 7.32 (1H, m,) and 7.39 – 7.46 (2H, m,); d_C (400 MHz; $CDCl_3$; Me_4Si) 11.4 (CH_3), 21.3 (CH_2) 23.3 (CH_2) 28.5 (CH_2) 34.1 (CH_2) 35.5 (CH) 36.7 (CH) 37.6 (CH) 38.4 (CH_2) 43.7 (CH) 47.7 (CH_2) 59.7 (CH) 79.6 (CH) 87.8 (CH) 122.0 (CH) 126.8 (CH) 129.7 (CH) 153.3 (C) 172.9 (C) 176.0 (C) 193.8 (C); *m/z* (ESI) 452.1495 (M^+ +H, requires 452.1502 $C_{23}H_{27}NaNO_5S$).

Further elution gave recovered sm **290** (6 mg, 24 %).

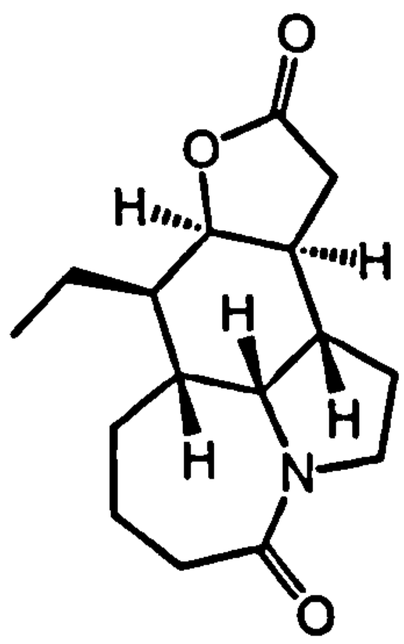
Method B

To a solution of alcohol **290** (25 mg, 0.09 mmol) and DMAP (16 mg, 0.13 mmol) in anhydrous MeCN (3 cm^3) was added *O*-phenyl chlorothionoformate (14 µl, 0.10 mmol) dropwise and left to stir at reflux for 2 h. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography using 1 – 2 % MeOH in DCM as the eluent to give thiocarbonate **295** (15 mg, 42 %).

Method C

To a solution of alcohol **290** (175 mg, 0.6 mmol) and DMAP (112 mg, 0.9 mmol) in anhydrous DCM (20 cm^3) was added *O*-phenyl chlorothionoformate (98 µl, 0.7 mmol) dropwise and left to stir at reflux for 7 h 15 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 2 % MeOH in DCM as the eluent to give thiocarbonate **295** (172 mg, 67 %). Further elution gave recovered sm **290** (51 mg, 29 %).

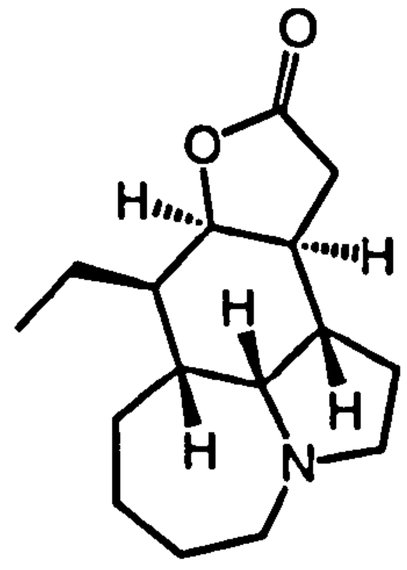
(±)-(31*R*,7a*R*,8*R*,8a*R*,11a*S*,11b*S*)-8-Ethyldecahydroazepino[3,2,1-*hi*]furo [3,2-e]indole-4,10(31*H*,11b*H*)-dione 39



To a solution of thiocarbonate **295** (143 mg, 0.33 mmol) and AIBN (16 mg, 0.11 mmol) in anhydrous benzene (12 cm^3) was added tributyltin hydride (181 µl, 0.66 mmol) dropwise and left to stir at reflux for 30 min. The reaction mixture was

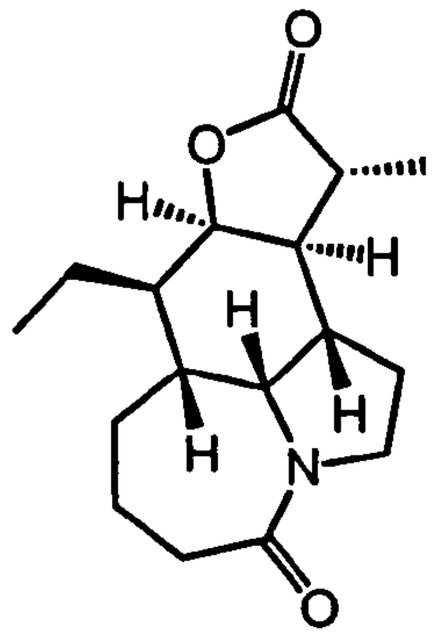
concentrated *in vacuo* onto silica gel and subjected to column chromatography using 1 % MeOH in DCM as the eluent to give azepine **39** (87 mg, 94 %) as a white crystalline solid: mp 172 – 173 °C; ν_{max}(film)/cm^{-1} 1765, 1617, 1430, 1263 and 1008; d_H (300 MHz; $CDCl_3$; Me_4Si) 0.97 (3H, t, *J* = 7.3,), 1.27 – 1.43 (1H, m,) 1.44 – 1.73 (6H, m,) 1.76 – 1.91 (1H, m,), 2.02 – 2.20 (4H, m,) 2.33 (1H, d, *J* =16.9,) 2.26 – 2.39 (1H, m,), 2.64 – 2.74 (1H, m,), 2.81 (1H, dd, *J* = 16.9 and 6.9,), 3.40 (1H, dt, *J* = 11.9 and 6.2,), 3.77 (1H, dd, *J* = 4.8 and 2.0,), 3.90 (1H, dd, *J* = 12.3 and 8.4,) and 4.65 (1H, dd, *J* = 4.5 and 2.4,); d_C (400 MHz; CD_3CO; Me_4Si) 11.4 (CH_3), 18.6 (CH_2), 21.9 (CH_2), 29.0 (CH_2), 31.7 (CH_2), 34.3 (CH), 34.5 (CH), 37.7 (CH), 38.9 (CH_2), 40.2 (CH_2), 44.4 (CH), 47.9 (CH_2), 62.1 (CH), 80.5 (CH), 174.5 (C) and 176.7 (C); *m/z* (CI) 278.1753 (M^+ +H. requires 278.1756 $C_{16}H_{24}NO_3$), (CI) 294 (M^+ +H, 100 %), 233 (4) and 218 (3).

(±)-Des-methyl neostenine 296



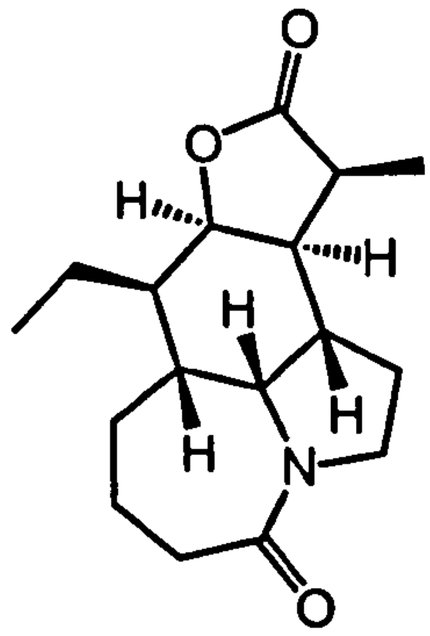
To a solution of amide **39** (28 mg, 0.1 mmol) and diphenylsilane (40 µl, 0.21 mmol) in anhydrous THF (3 cm^3) was added $Rh(CO)(PPh_3)_3H$ (5 mg, 5 mol%) in one portion and left to stir for 30 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to column chromatography using 1 % Et_3N and 1 % MeOH in DCM as the eluent to give azepine **296** (19 mg, 70 %) as a colourless oil: ν_{max}(film)/cm^{-1} 1775, 1260, 1017 and 798; d_C (300 MHz; $CDCl_3$; Me_4Si) 11.3 (CH_3), 20.6 (CH_2), 22.1 (CH_2), 29.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 34.5 (CH), 36.8 (CH), 37.3 (CH_2), 38.3 (CH), 41.0 (CH), 55.6 (CH_2), 56.7 (CH_2), 68.2 (CH), 80.4 (CH) and 177.2 (C); *m/z* (CI) 264.1956 (M^+ +H, requires 264.1964 $C_{16}H_{26}NO_2$), (CI) 264 (M^+ +H, 100 %), 262 (11), 248 (4) and 219 (3).

(±)-(31*R*,7a*R*,8*R*,8a*R*,11*R*,11a*R*,11b*S*)-8-Ethyl-11-methyldecahydroazepino [3,2,1-*hi*]furo[3,2-e]indole-4,10(31*H*,11b*H*)-dione 297



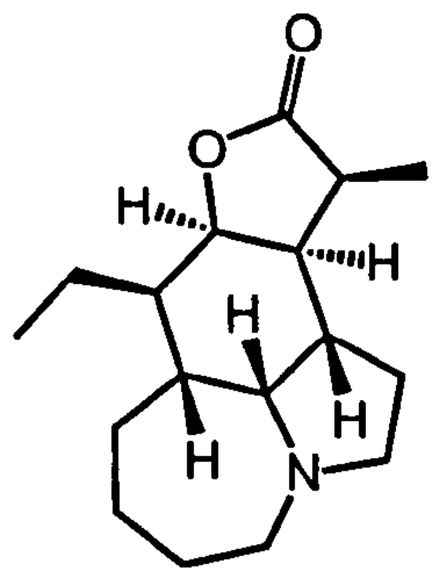
To a solution of azepine **39** (78 mg, 0.28 mmol) in anhydrous THF (14 cm^3) at -78 °C was added 1.0 M LiHMDS solution in THF (0.42 cm^3, 0.42 mmol) dropwise and left to stir at -78 °C for 1 h. Iodomethane (88 µl, 1.4 mmol) was added dropwise at -78 °C and left to stir for 2 h. The reaction mixture was quenched with IPA (2 cm^3) and left to warm to r.t. over 30 min. The reaction mixture was concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography using 1 – 2 % MeOH in DCM as the eluent to give oxo-neostenine **297** (67 mg, 82 %), a white crystalline solid as a 10:1 mixture of epimers: d_H (400 MHz; $CDCl_3$; Me_4Si) 0.95 (3H, t, *J* = 7.2,), 1.28 – 1.38 (1H, m,), 1.32 (3H, d, *J* = 7.6,), 1.46 – 1.62 (6H, m,), 1.78 – 1.89 (2H, m,), 1.92 – 2.04 (2H, m,), 2.08 – 2.16 (1H, m,), 2.33 (ddd, *J* = 15.0, 10.9 and 3.9, 1 H), 2.43 (1H, dq, *J* = 7.6 and 2.0,), 2.59 – 2.67 (1H, m,), 3.37 (1H, ddd, *J* = 12.2, 10.4 and 6.7,), 3.75 – 3.85 (2H, m,) and 4.76 (1H, dd, *J* = 5.5 and 2.6,); d_C (400 MHz; $CDCl_3$; Me_4Si) 11.0 (CH_3), 15.3 (CH_3), 17.6 (CH_2), 20.6 (CH_2), 28.5 (CH_2), 30.2 (CH_2), 33.4 (CH), 33.9 (CH), 38.8 (CH_2), 42.9 (CH), 43.6 (CH), 44.6 (CH), 46.9 (CH_2), 60.8 (CH), 77.3 (CH), 174.5 (C) and 179.2 (C).

(±)-(31*R*,7a*R*,8*R*,8a*R*,11*S*,11a*R*,11b*S*)-8-Ethyl-11-methyldecahydroazepino [3,2,1-*hi*]furo[3,2-e]indole-4,10(31*H*,11b*H*)-dione 41



To a solution of azepine **297** (112 mg, 0.38 mmol) in anhydrous THF (30 cm^3) at -78 °C was added 1.0 M LiHMDS solution in THF (0.42 cm^3, 0.42 mmol) dropwise and left to stir for 10 min. The reaction mixture was allowed to warm to r.t. for 15 min and then cooled back down to -78 °C. A 1.0 M solution of BHT in THF (3.8 cm^3, 3.8 mmol) was added dropwise at -78 °C and the mixture allowed to stir for 2 h. The reaction mixture was warmed to r.t. then concentrated *in vacuo* onto silica gel and subjected to graduated column chromatography using 1 – 2 % MeOH in DCM as the eluent to give **41** (78 mg, 70%) as a 5:1 mixture of epimers: mp 172 – 173 °C; ν_{max}(film)/cm^{-1} 1769, 1630, 1423, 1168 and 978; d_H (400 MHz; $CDCl_3$; Me_4Si) 0.98 (3H, t, *J* = 7.3,), 1.27 (3H, d, *J* = 7.3,), 1.33 – 1.74 (7H, m,), 1.80 – 1.93 (1H, m,), 2.03 – 2.22 (4H, m,), 2.27 – 2.38 (1H, m,), 2.67 – 2.76 (1H, m,), 2.94 (1H, quin, *J* = 6.6,), 3.40 (1H, dt, *J* = 12.2 and 6.1,), 3.78 (1H, dd, *J* = 4.4 and 1.95,), 3.93 (1H, dd, *J* = 12.3 and 8.4,) and 4.56 (1H, t, *J* = 3.1,); d_C (400 MHz; $CDCl_3$; Me_4Si) 9.5 (CH_3), 11.1 (CH_3), 17.6 (CH_2), 20.6 (CH_2), 29.2 (CH_2), 31.0 (CH_2), 33.2 (CH), 33.3 (CH), 38.3 (CH), 39.7 (CH_2), 40.6 (CH), 42.0 (CH), 47.2 (CH_2), 61.9 (CH), 78.2 (CH), 175.1 (C) and 178.7 (C); *m/z* (CI) 292.1909 (M^+ +H, requires 292.1913 $C_{17}H_{26}NO_3$), (CI) 292 (M^+ +H, 100 %), 278 (2), 247 (4), 218 (9).

(±)-Neostenine 32



To a solution of azepine **41** (35 mg, 0.1 mmol) and diphenylsilane (44 μL, 0.23 mmol) in anhydrous THF (4 cm^3) was added in a single portion $RhH(CO)(PPh_3)_3$ (6 mg, 5 mol %) and the mixture allowed to stir for 30 min. The reaction mixture was loaded directly onto an IST CBA cartridge (1 g, 0.7 mmol) and washed with MeCN (2 × 5 cm^3). The cartridge was then eluted with a Et_3N:MeCN solution (1:3 v/v, 2 × 5 cm^3). The eluent was concentrated *in vacuo* to give (±)-neostenine **32** (23 mg, 70%) as a white crystalline solid which was recrystalised from EtOAc: mp 122 – 123°C (lit.[11] mp 90 – 92 °C; lit.[12] 126 – 128 °C); ν_{max}(film)/cm^{-1} 1765, 1171, 953; d_H (400 MHz; $CDCl_3$; Me_4Si) 0.99 (3H, t, *J* = 7.5,), 1.21 (3H, d, *J* = 7.1,), 1.34 – 1.50 (2H, m,), 1.53 – 1.93 (10H, m,), 1.94 – 2.09 (1H, m,), 2.21 – 2.52 (4H, m,), 2.77 – 2.97 (1H, m,), 2.86 (1H, quin, *J* = 6.6,), 3.14 – 3.27 (1H, m,) and 4.51 (1H, dd, *J* = 4.0 and 2.3,); d_C (400 MHz; $CDCl_3$; Me_4Si) 10.1 (CH3), 11.3 (CH3), 21.1 (CH2), 21.2 (CH2), 28.1 (CH2), 28.4 (CH2), 30.2 (CH2), 34.3 (CH), 37.3 (CH), 37.4 (CH), 42.5 (CH), 42.9 (CH), 55.6 (CH2), 55.9 (CH2), 70.9 (CH), 79.3 (CH), 179.6 (C); *m/z* (CI) 278.2116 (M^+ +H, requires 278.2120 $C_{17}H_{28}NO_2$), (CI) 278 (M^+ +H, 100 %), 233 (8), 204 (10), 191 (7).

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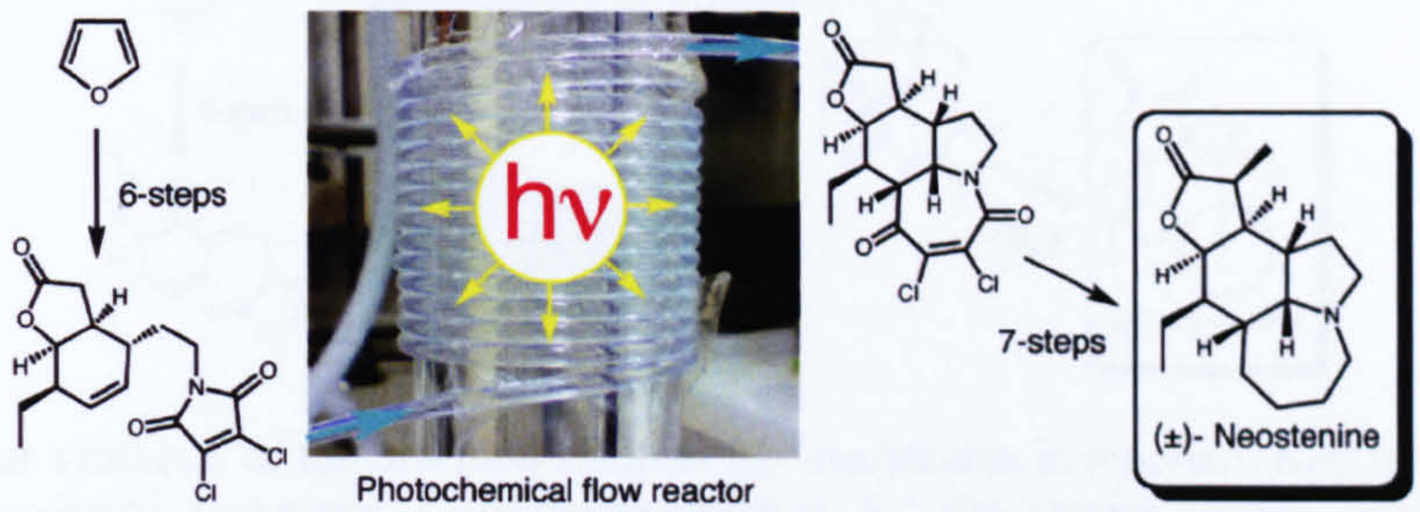

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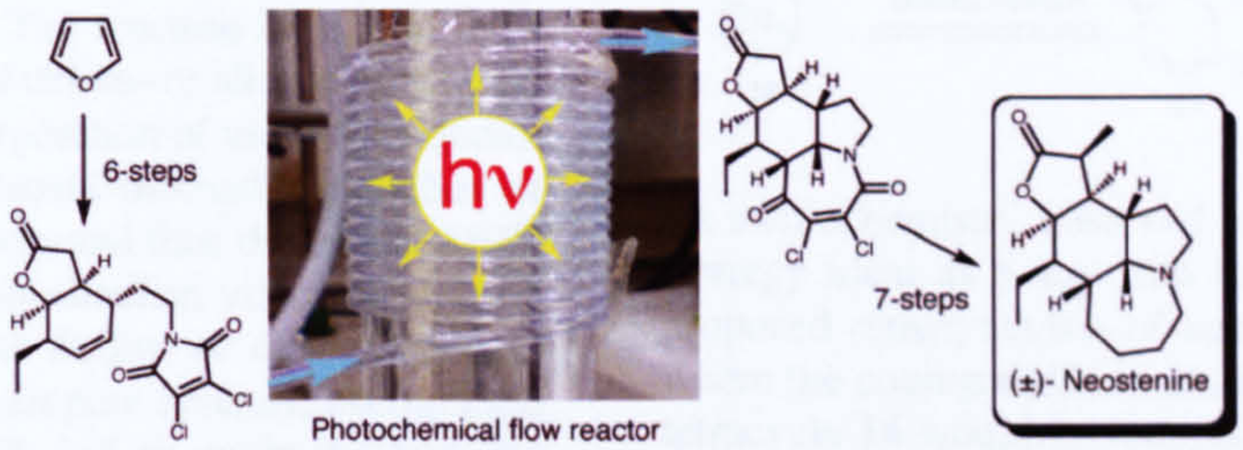

A concise, linear synthesis of the *Stemona* alkaloid (±)-neostenine is reported. Key features include an organocopper-mediated bislactone C_2-desymmetrization for the stereoselective construction of the cyclohexane−lactone C,D-rings. The assembly of the fused pyrrolo[1,2-*a*]azepine core was achieved by application of a [5 + 2] maleimide photocycloaddition. A custom FEP flow reactor was used to successfully overcome the scale limitations imposed by a classical immersion well batch reactor. The synthesis was completed in 14 steps from furan, in 9.5% overall yield, without the use of any protecting groups.

Introduction

The *Stemona* alkaloids are a diverse family of natural products isolated from Stemonaceae plant species. Nearly all members of this family contain the pyrrolo[1,2-*a*]azepine or perhydroazaazulene core. Unelaborated examples include stemoamide **1** and stemonine **2**; the latter contain a laterally fused butyrolactone ring that is prevalent throughout the *Stemona* alkaloids. The stenine group contains more intricate examples encompassing stenine **3** and pentacyclic member tuberostemonine **4**.[1] In 2003, neostenine **5** was isolated[2] from *Stemona tuberosa* and shown to be of the same stereogenicity as the previously characterized neotuberostemonine **6** and bisdehydroneotuberostemonine **7** (Figure 1).

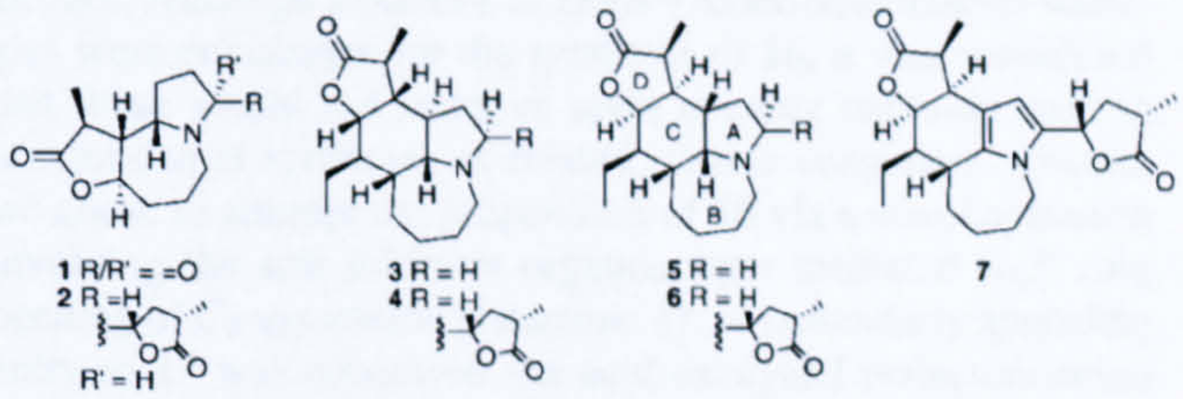

FIGURE 1. Representative examples of the *Stemona* alkaloids.

For centuries, extracts of a variety of Stemonaceae plant species have been utilized in Chinese and Japanese traditional medicine as cough treatments for human diseases such as tuberculosis and bronchitis. The plants have also been used as antihelminthic agents in the treatment of parasitic infestation in humans and livestock. Subsequent pharmacological studies have demonstrated that **4** had an effect on the motility of three different species of helminthic worms.[3] Further studies on neuromuscular transmission in crayfish showed that **4** depressed glutamate-induced responses at levels similar to established inhibitors.[4] Significantly, Lin[2] reported that **5** and **6** possessed antitussive activity when tested against guinea pig models, thus identifying these as the likely active agents in Stemonaceae preparations used as cough suppressants. The stenine class of alkaloids has captured the attention of synthetic chemists over the last two decades, due in no small part to the intriguing and challenging array of seven contiguous stereocenters within a fused tetracyclic system. In 1990, Hart and Chen[5] published

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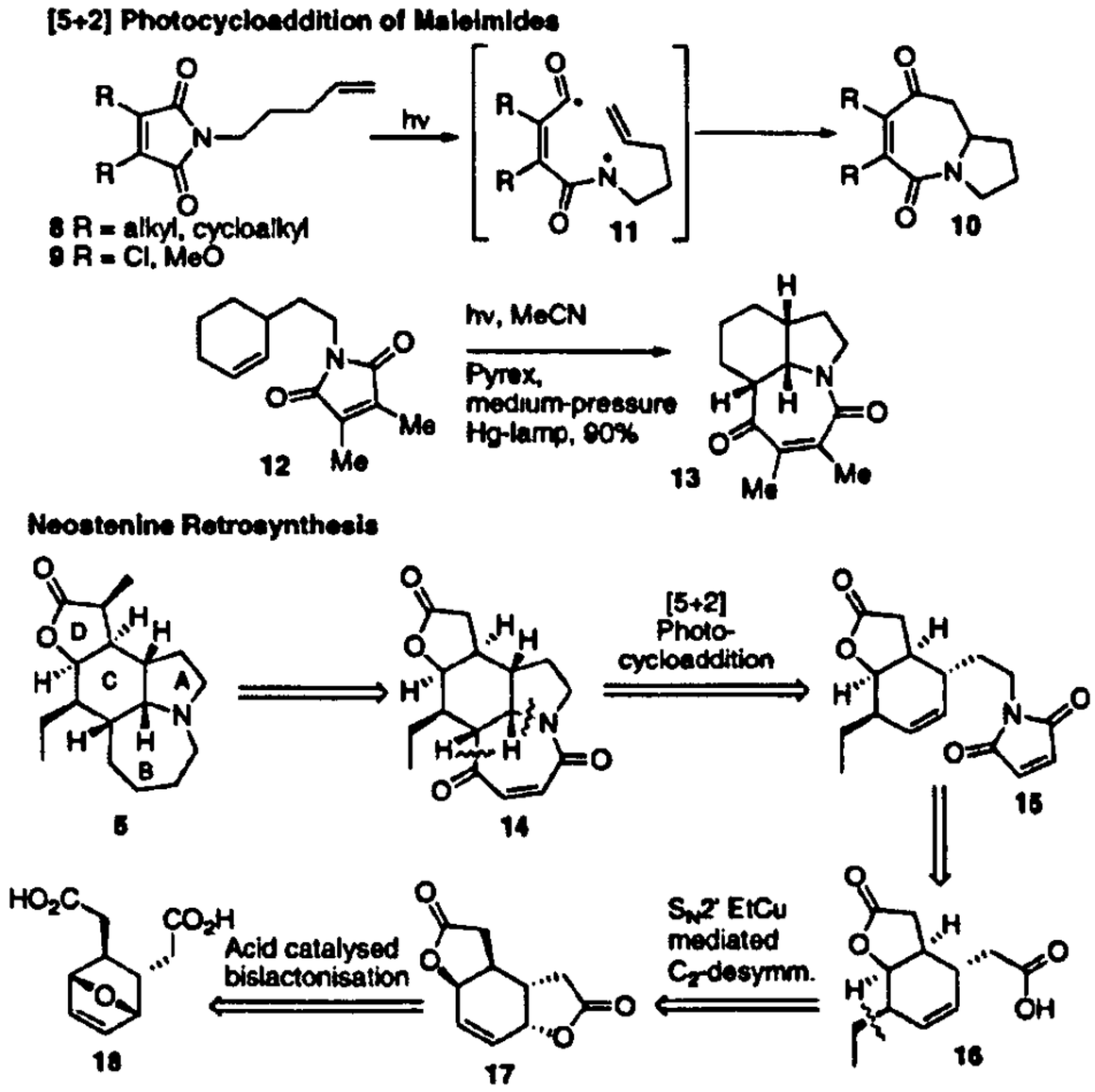
the first total synthesis of (±)-stenine which was followed by successful syntheses from Morimoto,[6] Padwa,[7] and Wipf.[8] In 2002, Wipf reported the total synthesis of (−)-tuberostemonine **4**, thus detailing the first successful approach to a pentacyclic member of the stenine family.[9] In 2005, Aubé reported an outstanding nine-step synthesis of (±)-stenine involving an elegant Diels−Alder/intramolecular Schmidt domino reaction strategy.[10] This group has very recently been able to modify their approach to deliver the first total synthesis of (±)-neostenine **5**.[11] In 2001, we embarked on a program to deliver neotuberostemonine **6** by a strategy that was to proceed via the use of an oxo derivative of neostenine **5** as an advanced intermediate.[12] At the time, **5** had not been identified, but following its isolation in 2003 it was evident that it would be within reach of our ongoing route to **6**.

For some time, we have had an interest in the application of organic photochemistry to the synthesis of natural products. While investigating a [2 + 2] photocycloaddition reaction of maleic anhydride derivatives,[13] we uncovered a powerful intramolecular [5 + 2] photocycloaddition of alkyl maleimides **8** which led directly to the pyrrolo[1,2-*a*]azepine **10** rather than the expected [2 + 2] adduct.[14,15] The reaction is general for a wide range of substrates, and use of chloro- or alkoxy-substituted maleimides **9** leads to further incorporation of useful functionality into the resulting azepines. Recent mechanistic studies of this process, using tunable UV lasers and time dependent-DFT, have led us to propose a singlet mechanism via cycloaddition of the diradical species **11**.[16] The ability of this reaction to deliver complex polycyclic fused azepine systems, exemplified in the cycloaddition of **12** to **13**, led us to investigate the application of it in alkaloid synthesis.[17] In particular, the all-

SCHEME 1. Retrosynthetic Analysis of (±)-Neostenine 5



cis stereochemistry observed for **13** made this photochemical strategy ideal as a key step in an approach to **5** and **6**. Our proposed retrosynthesis of neostenine involved an end game where the conjugated keto-amide functionality in the advanced tetracycle **14** would be reduced/deoxygenated and the lactone ring methylated to deliver **5**. Previously, we have described synthetic routes toward 7-desmethylasteriscanolide, pogostol, and kessane[18] which were devoid of standard protection/deprotection protocols, and so we were particularly keen that our stenine studies adhered to the same principles.[19]

We proposed that construction of **14** would involve photocycloaddition of the maleimide−cyclohexene−lactone **15**, which in turn would be readily available from reduction of the acid **16** and Mitsunobu coupling of maleimide with its corresponding alcohol. Although a number of Diels−Alder/lactonization strategies were envisioned for the synthesis of **16**, it was considered that these would not improve upon existing methods used in previous total syntheses of related stenine congeners. Instead, we chose to attempt the preparation of **16** via a novel approach involving the anti-selective organocopper mediated S$_N$2′ ring opening of C_2-symmetric bislactone **17**. A particularly appealing entry to **17** was conceived via acid-catalyzed bislactonization of the diacid **18** (Scheme 1).

Results and Discussion

Multigram quantities (>50 g) of diol (±)-**19** were readily available following Paquette's[20] sequential procedure for the Diels−Alder cycloaddition between furan and fumaryl chloride followed by reduction with $LiAlH_4$. Reaction of **19** with 2 equiv of MsCl followed by displacement with KCN gave dinitrile **20**

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(15) For related phthalimide photochemistry, see: (a) Mazzocchi, P. H.; Bowen, M. J.; Narain, N. K. *J. Am. Chem. Soc.* **1977**, *99*, 7063. (b) Mazzocchi, P. H.; Minamikawa, S.; Bowen, M. J. *J. Org. Chem.* **1978**, *43*, 3079. (c) Mazzocchi, P. H.; Minamikawa, S.; Wilson, P. *J. Org. Chem.* **1979**, *44*, 1186. (d) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikawa, S. *J. Org. Chem.* **1983**, *48*, 2981.

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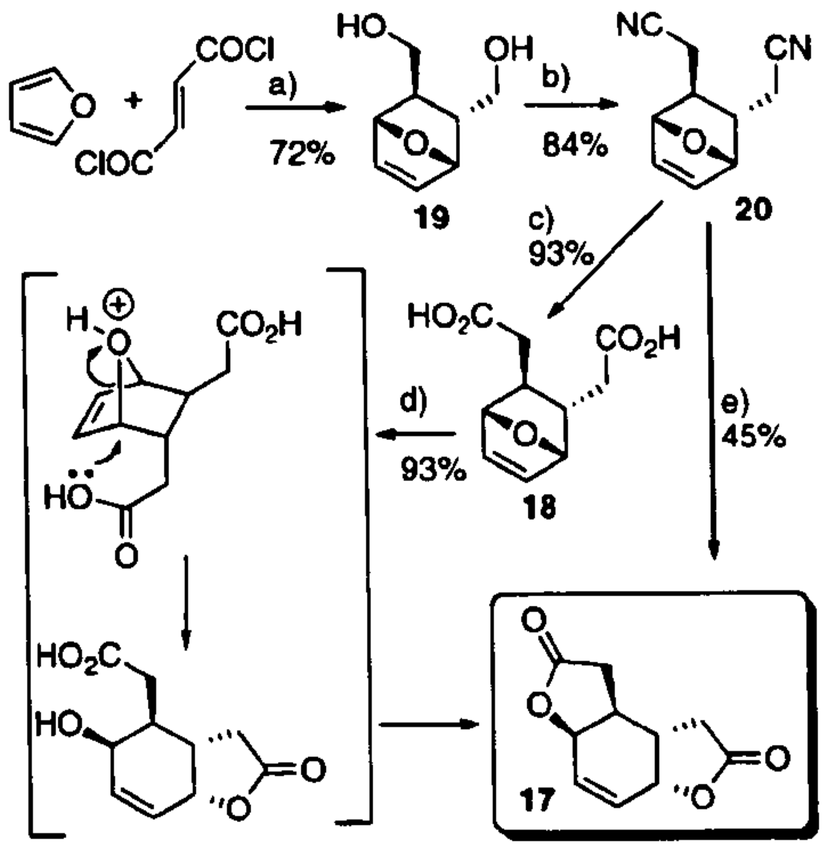
(19) For a recent example of the benefits of protecting group free strategies in complex alkaloid synthesis, see: Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404.

(20) Paquette, L. A.; Kravetz, T. M.; Charumilind, P. *Tetrahedron* **1986**, *42*, 1779.

SCHEME 2. Synthesis of the C_2-Symmetric Bislactone 17[a]



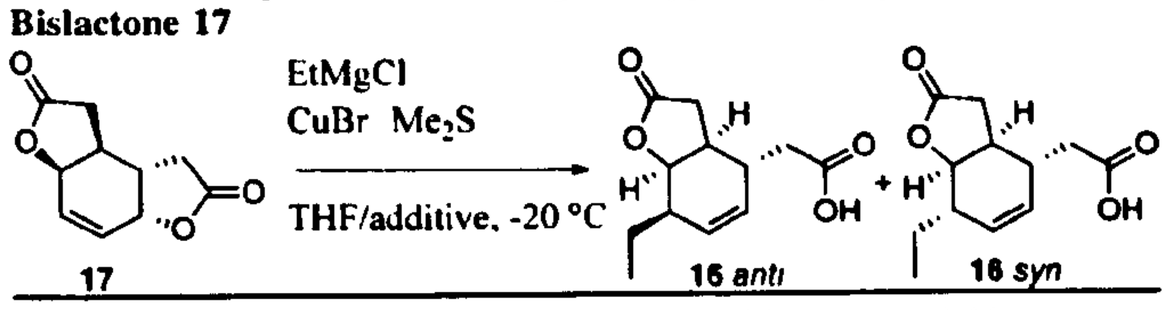
[a] Reagents and conditions: (a) THF, 0 °C, 2 h then $LiAlH_4$, 0 °C to rt, 48 h, 72% (ref 20); (b) (1) MsCl, Et_3N, THF, 25 °C, then KCN, DMSO, 100 °C, 84% overall; (c) KOH, H_2O, 100 °C, 93%; (d) *p*-TSA, PhMe, reflux, 93%; (e) H_2SO_4 (6 M), 100 °C, 2 h, 45%.

in 84% overall yield. Basic hydrolysis of **20** furnished key diacid **18** in good yield. We were then at the stage to examine the key acid-catalyzed bislactonization and were pleasantly surprised to see the clean formation of **17** on our first attempt with catalytic *p*-TSA on reflux in toluene. After optimization, the resulting highly crystalline bislactone could be consistently isolated in yields greater than 90%. The mechanism likely proceeds via protonation of the dihydrofuran oxygen followed by selective S_Ni cyclization of the *anti*-carboxylate and further lactonization of the resulting *syn*-hydroxy acid. It was also found that this could be achieved in one step from **20** by strong acid-promoted nitrile hydrolysis and concomitant cyclization of **18** in situ. Unfortunately, this attractive one-step procedure was not economic on scale-up (>3 mmol) as significant amounts of unidentified resinous material were formed from acid-catalyzed side reactions.

The subsequent step involved the attempted anti-selective organocopper-mediated S_N2' ring opening of **17** using conditions reported by Grieco,[21] Curran,[22] and Helmchen,[23] which typically employ 2−3 equiv of EtMgCl/CuBr·DMS and an unusual 2:1 solvent mixture of THF/DMS. The high crystallinity of **17** was a cause for concern, and even after it was ground into a fine powder it appeared to be completely insoluble in a range of solvents at room temperature. After a short optimization study, however, it was found that when a slurry of **17** was reacted with 10 equiv of EtMgCl/CuBr·DMS (1:1), the ring-opened and desymmetrized lactone−acid **16** was obtained as an 8.5:1 mixture of anti/syn isomers (Table 1, entry 1). Although these conditions were reproducible on a 2 mmol scale, we had great difficulty extending these to a larger scale, and >10 mmol resulted in incomplete reactions. DMPU (4 equiv) proved to be a useful substitute for DMS and gave good yields (81%) and a slightly improved anti/syn ratio (9.7:1; entry 6). Unfortunately, this variation also proved capricious on scale up, and complete removal of DMPU from product proved difficult. By reducing the amount of DMS cosolvent and equivalents of EtMgCl/CuBr·DMS an interesting trend was observed and a

(21) Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 2591.
(22) Curran, D. P.; Chen, M. H.; Leszcweski, D.; Elliot, R. L.; Rakiewiecz, D. M. *J. Org. Chem.* **1986**, *51*, 1612.
(23) Bergner, E. J.; Helmchen, G. *Eur. J. Org. Chem.* **2000**, *6*, 419.

TABLE 1. Optimization of Organocopper Ring-Opening of Bislactone 17



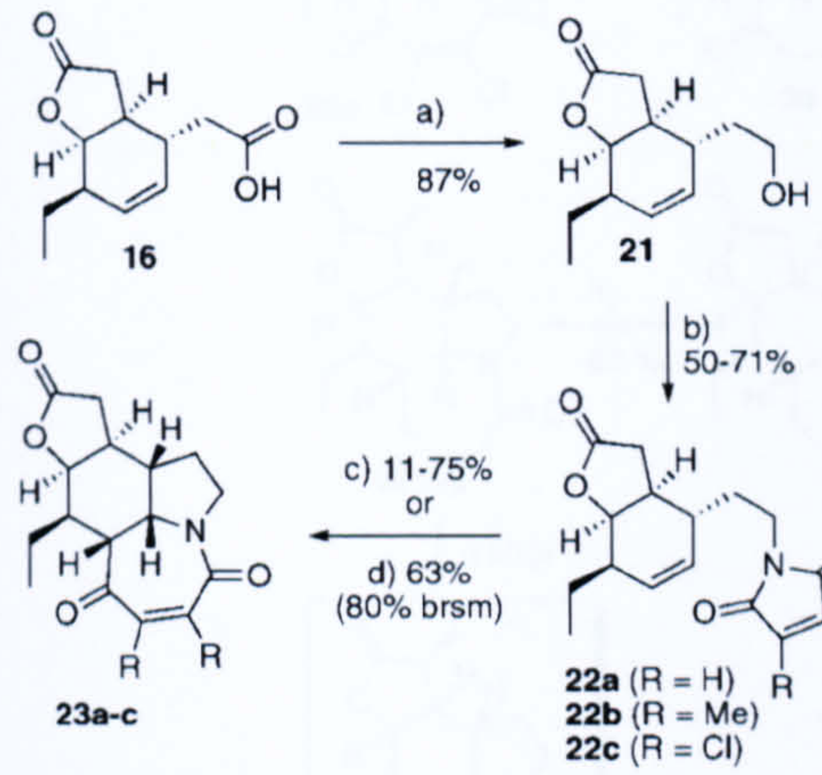
entry	EtMgCl (molar equiv)	CuBr·Me_2S (molar equi)	additive (molar equiv)	yield (%)	anti/syn
1	10	10	Me_2S (cosolvent)	89	8.5/1
2	3	3	Me_2S (4)	85	12.2/1
3	3	3	Me_2S (2)	84	13.8/1
4	3	3	Me_2S (1)	86	14.2/1
5	**3**	**3**	**none**	**94**	**15.6/1**
6	3	3	DMPU	81	9.7/1

solution to scale up was achieved. Use of only 4 equiv of DMS gave a superior ratio of 12.2:1, which improved further to 14.2:1 when only 1 equiv was used (entries 2 and 4). Portionwise addition of solid **17** to a stirred solution of EtMgCl/CuBr·DMS (3 equiv) at −20 °C in the *absence* of DMS gave an isolated yield of **16** of 94% with an anti/syn ratio of 15.6:1 (entry 5). These latter conditions could be reliably applied to the reaction of **17** on scales of 30 mmol. This was a most surprising result in view of the apparent nonexistent solubility of **17** in pure THF at even room temperatures. On addition of solid **17** to the organocopper solution at −20 °C, the initially formed suspension is digested rapidly by reaction. Our experience with this reaction clearly demonstrates that the selectivity of the organocopper species resulting from EtMgCl/CuBr·DMS is significantly increased when the Me_2S cosolvent is omitted. It is possible that excess DMS (or DMPU) competes with the lactone rings in **17** for coordination to the Cu center, thus disrupting the anti mode of S_N2' ring opening.

Selective reduction of the carboxylic acid moiety of **16** in the presence of the lactone could be achieved by conversion to the mixed anhydride with ethyl chloroformate followed by reduction with $NaBH_4$.[24] In general, this sequence worked in consistently high yields, although prolonged reaction times with $NaBH_4$ led to decreased yields of **21** due to lactone ring opening. In preparation for the key [5 + 2] photocycloaddition, hydroxy lactone **21** was coupled to three different maleimides using Mitsunobu conditions (Scheme 3). This gave the three photosubstrates **22a−c** in moderate to good yield. Dimethyl substrate **22b** was chosen simply as a model, delivering a photoproduct that ought to be resistant to further photoreactions. The parent **22a** and the dichloro derivatives were the key subtrates for incorporation into the rest of the synthesis. Irradiation in a Pyrex immersion well photoreactor (125 W medium-pressure Hg lamp) with constant monitoring (TLC) of all three substrates led to the desired tetracyclic [5 + 2] photocycloaddition products **23a−c** in varying yields. Dimethyl adduct **23b** was formed in 75% yield as a single diastereomer, and X-ray crystallography confirmed that the relative stereochemistry was the same as that found in neostenine. The parent system **23a** was formed but in a meager yield (11%) with no recovery of starting material. This was not unexpected, as our previous experience with unsubstituted maleimides has shown that the [5 + 2] products are susceptible to further reactions including [2 + 2] dimerization and photodegradation. This unfortunately severely limits the use of the parent maleimides in synthesis and led us to investigate dichloromaleimides as alternatives. In our prior experience, the

(24) N'Zoutani, M. A.; Pancrazi, A.; Ardisson, J. *Synlett* **2001**, 769.

SCHEME 3. Synthesis of Cycloaddition Precursors 22a−c and Optimization of Key Photocycloaddition by a Custom FEP Flow Reactor[a]



[a] Reagents and conditions: (a) EtOCOCl, Et_3N, then $NaBH_4$; (b) maleimide/dimethylmaleimide/dichloromaleimide/Ph_3P, DEAD, THF, −78 °C to rt; (c) **22a−c**, *hν*, 125 W Hg lamp, Pyrex, CH_3CN; (d) **22c**, *hν*, 400 W Hg lamp, Pyrex 15-loop FEP flow reactor, CH_2Cl_2.

dichloro [5 + 2] adducts generally undergo slower photodegradation than their parent derivatives.

Initially, we were pleased to find that irradiation of **22c** gave 40−60% yields of the key cycloadduct **23c**, although all starting material had been consumed. These initial key test reactions were performed on a 50 mg scale in a 100 mL immersion well batch photoreactor using a 125 W medium-pressure Hg lamp. When scaled up to >100 mg batches, the yields of **23c** plummeted to below 20%, with total consumption of starting material. Attempts to carry out the reactions with larger but more dilute batches were met with equally disappointing results. This left us with the practical dilemma of proceeding with the synthesis of neostenine with a key reaction constrained to a 50 mg scale. This was clearly an untenable strategy as it would have involved multiple batch reactions and the loss of 40% of the photoprecursor **22c**.

During the evolution of this synthesis, we developed a novel flow reactor for continuous photochemical synthesis.[25] This reactor consisted of multiple loops of narrow bore fluorinated ethylene polymer (FEP) tubing wrapped tightly around a Pyrex water cooled immersion well containing a 125−400 W medium-pressure Hg lamp. This reactor proved capable of synthesizing maleimide/hex-1-yne [2 + 2] photoadducts on scales of >500 g per day using photolysates of up to 0.4 M. With this flow, reactor residence time (i.e., time of irradiation in reactor) could be controlled by flow rate and by reactor volume (length of FEP tubing in contact with UV lamp). We speculated that a custom flow reactor could be constructed which would allow the photolysis of **22c** to key intermediate **23c** on preparatively desirable scales. More specifically, it was felt that if a dilute solution of **22c** were to enter a low volume reactor at a high flow rate then the residence time would be kept very low, thus minimizing the degradation of product as it forms. If this were coupled with a high power UV source (400 W), then an acceptable balance of conversion vs degradation would be achieved that would be amenable to the scales required for a linear total synthesis.

(25) Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558.

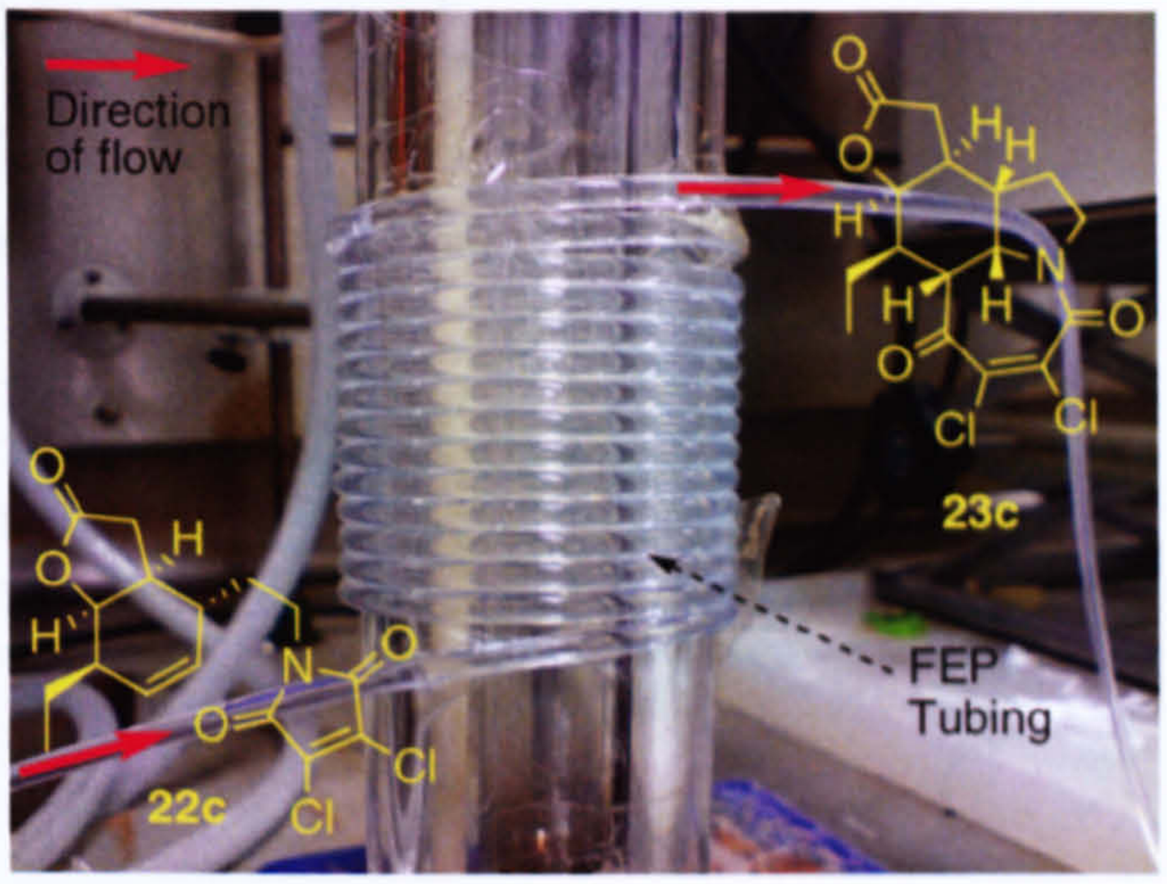
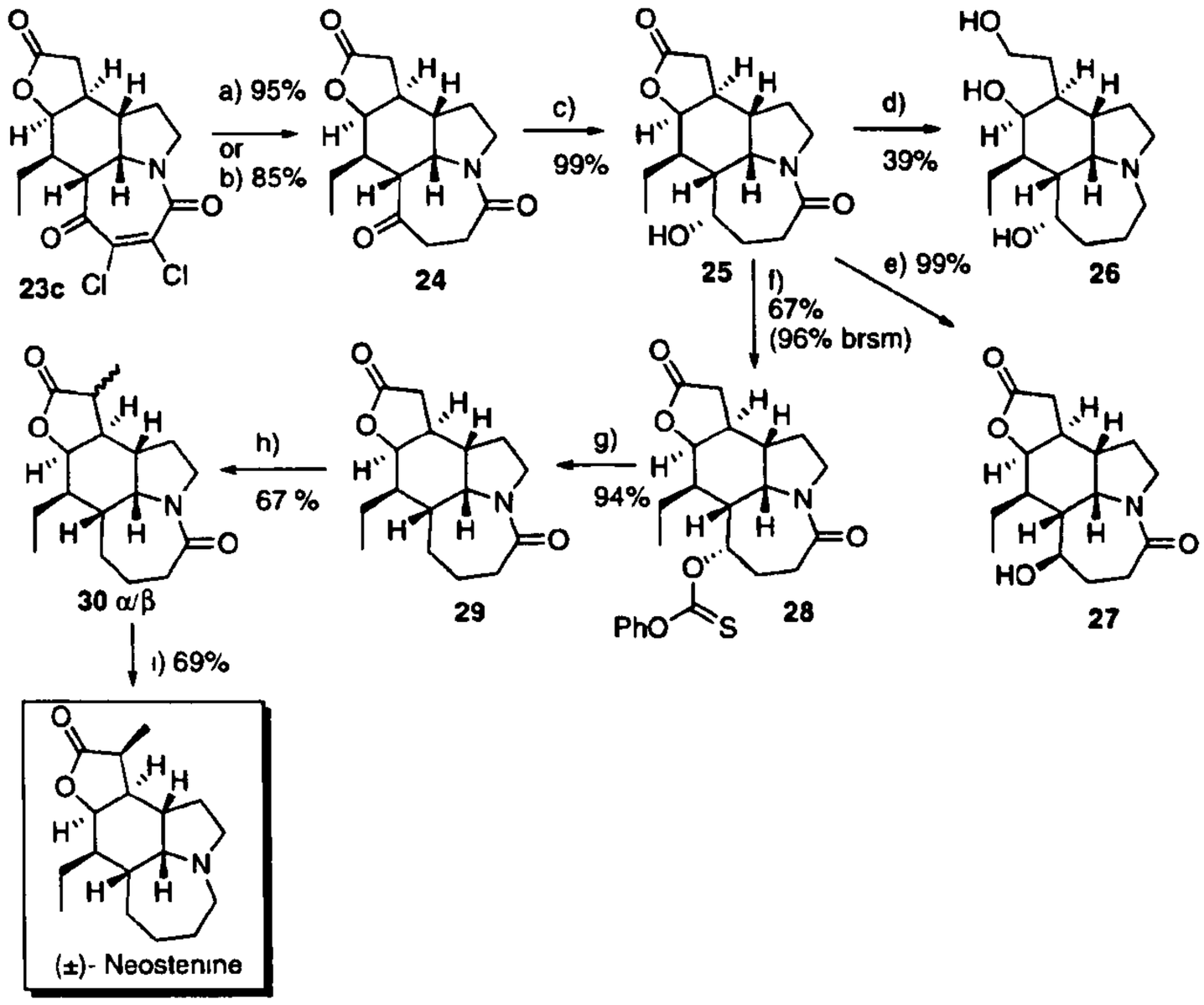


FIGURE 2. Custom high flow-rate/low volume continuous photochemical FEP reactor for the [5 + 2] photocycloaddition of maleimide **22c**.

After a great deal of experimentation, we found that construction of a reactor consisting of between 10 and 20 loops of FEP tubing wrapped around a custom water-cooled Pyrex immersion well gave promising results (Figure 2). After a number of optimization runs, we found that irradiation (400 W Hg lamp) of a 0.001 M solution of **22c** (2.1 g) in CH_2Cl_2 flowed through a 15-loop reactor (2 m FEP; 10 mL volume) at a flow rate of 11 mL min^{-1} allowed the isolation of 63% of **23c** and the recovery of 20% unreacted **22c**. This was a real breakthrough and enabled the synthesis of 1.3 g of the key [5 + 2] photoadduct in a single 9 h run. The importance of this cannot be overstated: to process 2.1 g of **22c** in batch at anywhere near this conversion would have required *42 successive* conventional immersion well irradiations, each on a maximum scale of 50 mg and with no recovery of starting material. We believe that high flow rate/low volume reactors configured in this way will prove generally useful for the scale up of sensitive photochemical reactions.

With a reliable, scale-tolerant route to **23c** now secured, we proceeded to the completion of neostenine, which involved selective reduction/deoxygenation of the B-ring functionality and stereoselective introduction of the methyl group in the lactone D-ring. Reduction of **23c** with either Pd/C/H_2 or Zn/AcOH[14] led to the reduced/dechlorinated product **24** in excellent yields. Hydrogenation was rather scale limited, as it required an excess of Pd/C to effect complete reduction. It was interesting to note that hydrogenation of **23c** with 10% Pd/C was slow and led to significant epimerization at the keto-stereocenter in **24**. More reproducible results were obtained with a Zn/AcOH reduction on various scales (0.5−0.8 g). The key to success with this latter reduction was to keep reaction times ≤1 h as prolonged reactions led to lower yields with the formation of unidentified high molecular weight compounds—perhaps through further acid-catalyzed aldol-type dimerization reactions of **24**. Considerable time was then spent investigating a variety of methods to reduce the ketone in **24** to the corresponding methylene, initially opting for a reduction/Barton−McCombie strategy. Preliminary attempts to selectively reduce the ketone in **24** with a variety of well-known metal hydride reagents were met with low yields and competing lactone reduction. Eventually, it was found that quantitative reduction to alcohol **25** could be achieved using $LiAl(O^tBu)_3H$.[26] Attempts were then made

SCHEME 4. Completion of the Total Synthesis of (±)-Neostenine 5[a]



[a] Reagents and conditions: (a) Zn, AcOH, 1 h; (b) Pd/C/H_2, K_2CO_3, MeOH, 1 atm; (c) $LiAl(O^tBu)_3H$, THF, 0 °C, 3 h; (d) (1) MsCl, Et_3N, THF; (2) $LiAlH_4$, THF, reflux; (e) 5% $InCl_3$, $ClPh_2SiH$, CH_2Cl_2, reflux, 16 h; (f) PhOCSCl, DMAP (1.5 equiv), CH_2Cl_2, reflux, 7 h; (g) Bu_3SnH, AIBN, C_6H_6, reflux, 30 min; (h) (1) LHMDS, MeI, THF, −78 °C (95%; α/β = 1/7); (2) LHMDS, BHT, THF, −78 °C to rt (70%; α/β = 5/1); (i) 5% $RhH(CO)(PPh_3)_3$, Ph_2SiH_2, THF, 30 min.

to convert **25** to suitable thiocarbonyl derivatives for Bu_3SnH-mediated deoxygenation using various reported reagent combinations and conditions. Unfortunately, all of these were met with failure, and only starting alcohol was recovered. It was clear that the hydroxyl group in **25** was very hindered, and a different reduction strategy was sought. Eventually, conditions were found where **25** could be converted to the corresponding mesylate; however, reduction with excess $LiAlH_4$ gave only triol amine **26** where the key alkoxy bond had remained intact. This was very likely a result of S−O cleavage due to shielding of the C−OMs bond by the concave environment of the ABC ring skeleton. It had been reported by Baba[27] that secondary alcohols could be reduced to alkanes by a $Ph_2SiHCl/InCl_3$ reductive protocol. To our surprise, the sole product isolated from this attempted reduction was inverted alcohol epimer **27** in quantitative yield. Clearly, reductive C−O cleavage had not taken place, and further investigations are ongoing to elucidate the mechanism and generality of this interesting inversion process. Investigations using a number of other techniques for the deoxygenation of **24** including Clemmensen, modified Shapiro, thioacetal formation then RaNi or Bu_3SnH, and enol triflate/phosphate then hydrogenation were unsuccessful, with many problems occurring during derivitization.

At this point, it was decided to return to the Barton−McCombie deoxygenation strategy and investigate more reactive conditions for thiocarbonate formation. Eventually, it was found that reaction of **25** with PhOCSCl with 1.5 equiv of DMAP[28] in refluxing CH_2Cl_2 led to the formation of the hindered thiocarbonate **28**. Unfortunately, **28** proved to be unstable to prolonged heating under the reaction conditions, and it was found that it was best to isolate this after 7 h (67%) and recover the unreacted starting material (29%) to recycle. Treatment of **28** under standard Bu_3SnH/AIBN conditions gave the long sought after deoxygenated lactone−amide **29** in excellent yield. Methylation of **29** with LHMDS/MeI gave methyl lactones **30** as a 7:1 mixture of epimers in favor of the unnatural β-epimer (95%). This was not unexpected, as simple molecular models of the enolate of **30** suggested that alkylation may proceed from the more accessible β-face (rear). We then investigated epimerization via an enolization/protonation sequence from the β-face. Pleasingly, treatment of the enolate of **30** with 10 equiv of 2,6-di-*tert*-butyl-4-methylphenol[29] (BHT) gave oxoneostenine **30** as a 5:1 mixture of α/β-epimers. Finally, reduction of purified (crystallization) **30α** to (±)-neostenine **5** was conveniently achieved, in one step, using a selective amide reduction with $RhH(CO)(PPh_3)_3/Ph_2SiH_2$ under conditions described by Ito.[30] These very selective conditions were particularly attractive as all previous Stenine alkaloid syntheses have adopted a two-step thionation/Ra−Ni reduction endgame to reduce the 7-membered amide. As such, this result highlights the usefulness of this catalyst/reagent combination for the reduction of amides in the presence of other metal hydride sensitive functionality (Scheme 4).

Conclusion

A unique total synthesis of (±)-neostenine **5** has been achieved in 14 linear steps from furan, in a strategy devoid of standard protection/deprotection protocols. Key findings include a novel approach to C_2-symmetric bislactones via the acid-

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catalyzed bislactonization of bridged bicyclic dihydrofuran acids. The C_2-symmetric bislactones have been shown to be useful substrates for the anti-selective EtMgCl/CuBr·DMS-mediated S_N2' ring opening to the neostenine C,D-ring system. Contrary to literature conditions, this organocopper ring opening gave the best selectivities in the absence of any additives such as DMS or DMPU. The key to this synthesis was the application of our [5 + 2] photocycloaddition maleimide reaction. This allowed the construction of the perhydroazaazulene A,B-rings and furnished the tetracyclic neostenine ring system in a single step. Crucial to the success of this, however, has been the novel application of our continuous FEP photochemical flow reactor technology. Adopting a high flow rate/low volume reactor topology coupled with a high power UV source has allowed the scale up of a key photochemical reaction that was severely limited in batch and thus unsustainable in our original route. We believe that our findings may stimulate others to adopt flow reactors for similarly sensitive or scale-compromised photoreactions. Present studies are concerned with adaptation of our current chemistry to provide concise routes to neotuberostemonine **5** and bisdehydroneotuberostemonine **6**.

Experimental Section

(±)-(1*R*,2*S*,3*S*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol (19).[20] Fumaryl chloride (95%, 80.48 g, 500 mmol) was added dropwise to furan (34.03 g, 500 mmol) over a period of 30 min at 0 °C. The mixture was stirred for a further 1 h, at which point the reaction mixture had solidified. THF (500 mL) was added, and the resulting solution was added dropwise to a solution of $LiAlH_4$ (438 mL, 2.4 M in THF, 1050 mmol) in THF (750 mL) at 0 °C, allowed to warm to rt, and stirred for 48 h. The reaction mixture was carefully quenched by addition of NaOH (2 M, 200 mL) at 0 °C, stirred for 4 h, allowed to warm to rt, filtered through Celite, and washed with THF (8 × 600 mL) and then THF/MeOH (4:1, 4 × 400 mL). The combined organic extracts were concentrated in vacuo and subjected to column chromatography (10% MeOH in EtOAc) to yield **19** (56.2 g, 72%) as a yellow oil: IR (film) 3338, 2926, 1318, 1083, 1029, 981 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 1.43−1.47 (1H, m), 2.09−2.14 (1H, m), 2.51 (2H, s), 3.26 (1H, dd, J = 9.5 and 9.0 Hz), 3.52 (1H, dd, J = 10.0 and 6.5 Hz), 3.64 (1H, dd, J = 10.0 and 8.0 Hz), 3.79 (1H, dd, J = 10.0 and 6.5 Hz), 4.74 (1H, s), 4.95 (1H, d, J = 4.0 Hz), 6.31 (1H, dd, J = 6.0 and 1.0 Hz), 6.47 (1H, dd, J = 6.0 and 2.0 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 45.4 (CH_2), 46.4 (CH_2), 64.4 (CH), 65.0 (CH), 79.7 (CH), 80.6 (CH), 133.3 (CH), 136.8 (CH); *m/z* (E.I.) 155 (5, M^+) 138 (20), 120 (26), 84 (65), 68 (100).

(±)-2,2′-((1*R*,2*R*,3*R*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-diyl)diacetonitrile (20). To a solution of **19** (19.2 g, 123 mmol) and Et_3N (51.4 mL, 369 mmol) in THF (500 mL) at 0 °C was added methanesulfonyl chloride (20.2 mL 27 mmol) dropwise over 20 min, and then the mixture was allowed to warm to rt and stirred for a further 2.5 h. Solvent was removed in vacuo and the residue partitioned between CH_2Cl_2 (500 mL) and water (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL), and the organic layers were combined, washed with brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo to yield the bis-mesylate (38.1 g, 99%) as a labile, pale yellow oil which was used immediately in the proceeding step: IR (film) 1330, 1166, 954, 812 cm^{-1}; ^1H (270 MHz; $CDCl_3$) δ 1.63−1.70 (2H, m), 3.01 (3H, s), 3.03 (3H, s), 3.88 (1H, dd, J = 9.9 and 9.6 Hz), 4.11 (1H, dd, J = 10.2 and 6.9 Hz), 4.20−4.33 (2 H, m), 4.81 (1H, s), 5.01 (1H, d, J = 4.0), 6.40 (1H, dd, J = 5.9 and 1.7 Hz), 6.50 (1H, dd, J = 5.9 and 1.7 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 37.6 (2 × CH_3), 42.7 (CH), 43.0 (CH), 70.2 (CH_2), 71.2 (CH_2), 79.5 (CH), 79.9 (CH), 133.8 (CH), 136.8 (CH); *m/z* (C.I.) 313 (22, $[M + H]^+$) 217 (27), 149 (65), 121 (100), 93 (46); HRMS found $[M + H]^+$, 313.0419, $C_{10}H_{17}O_7S_2$ requires 313.0416.

Potassium cyanide (3.1 g, 48.0 mmol) was added in one portion to a solution of the freshly prepared bis-mesylate (5.0 g, 16.0 mmol) in DMSO (128 mL) and heated to 100 °C for 4 h. After being cooled to rt, the reaction mixture was extracted with Et_2O/THF (1:1), (3 × 100 mL), the organic layers were combined concentrated in vacuo and partitioned between Et_2O (150 mL) and water (150 mL), and the aqueous layer was extracted with further Et_2O (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (10% MeCN in CH_2Cl_2) to yield **20** (2.3 g, 84%) as a pale yellow oil: IR (film) 2248, 1424, 1353, 1326, 1173, 1002, 885 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 1.58 (1H, dt, J = 7.6 and 3.5 Hz), 2.06−2.12 (1H, m), 2.18 (1H, dd, J = 16.6 and 8.3 Hz), 2.34 (1H, dd, J = 16.6 and 7.3 Hz), 2.53 (1H, dd, J = 16.6 and 8.3 Hz), 2.60 (1H, dd, J = 16.6 and 7.3 Hz), 4.73 (1H, s), 5.01 (1H, d, J = 4.4 Hz), 6.40 (1H, dd, J = 6.0 and 1.6 Hz), 6.56 (1H, dd, J = 5.9 and 1.7 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 19.9 (CH_2), 21.7 (CH_2), 41.8 (CH), 42.0 (CH), 80.6 (CH), 82.5 (CH), 118.0 (CH), 118.6 (CH), 133.3 (CH), 137.6 (CH); *m/z* (C.I.) 175 (31, $[M + H]^+$) 148 (97), 134 (48), 121 (20), 107 (100), 80 (94); HRMS found $[M + H]^+$, 175.0865, $C_{10}H_{11}N_2O$ requires 175.0871.

(±)-2,2′-((1*R*,2*R*,3*R*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-diyl)diacetic Acid (18). The dinitrile **20** (9.7 g, 55.7 mmol) was heated to reflux for 4 h in aqueous potassium hydroxide solution (1.27 M). After completion, the reaction was allowed to cool, acidified to pH 1 with HCl (2 M), and extracted with EtOAc (3 × 300 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo to yield **18** (11.0 g, 93%) as a colorless powder: mp 124−126 °C; IR (film) 3012, 1707, 1409 and 891 cm^{-1}; ^1H (270 MHz; CD_3OD) δ 1.49−1.56 (1H, m), 1.98−2.16 (2H, m), 2.31−2.49 (2H, m), 2.63 (1H, dd, J = 16.5 and 6.6 Hz), 4.60 (1H, s), 4.94 (1H, d, J = 4.0 Hz), 6.34 (1H, dd, J = 5.9 and 1.3 Hz), 6.50 (1H, dd, J = 5.9 and 1.7 Hz); ^{13}C (101 MHz; CD_3OD) δ 39.0 (CH_2), 40.3 (CH_2), 43.1 (CH), 43.7 (CH), 83.2 (CH), 85.1 (CH), 135.5 (CH), 138.7 (CH), 177.1 (CH), 177.5 (CH); *m/z* (C.I.) 213 (43, $[M + H]^+$) 195 (47), 149 (60), 121 (36), 99 (92), 81 (44); HRMS found $[M + H]^+$, 213.0765, $C_{10}H_{13}O_5$ requires 213.0763. Anal. Calcd for $C_{10}H_{13}O_5$: C, 56.76; H, 5.75. Found: C, 56.60; H, 5.70.

(±)-(3a*R*,5a*R*,8a*S*,8b*S*)-1,8,8a,8b-Tetrahydrobenzofuro[5,4-*b*]furan-2,7-(3a*H*,5a*H*)-dione (17). (a) A solution of **18** (11.0 g, 51.8 mmol) and *p*-TSA (2.5 g, 13.0 mmol) in toluene (300 mL) was heated to reflux for 3 h. After the solution was allowed to cool, it concentrated in vacuo and triturated using CH_2Cl_2 (150 mL) to yield **17** (9.4 g, 93%) as a colorless solid: 210 °C dec; IR (film) 1755, 1421, 1317, 1187, 1175, 1003, 984 cm^{-1}; ^1H (270 MHz; CD_3OD) δ 2.44 (2H, dd, J = 17.5 and 8.6 Hz), 2.69 (2H, dd, J = 17.5 and 8.3 Hz), 2.87−2.98 (2H, m), 5.08 (2H, dd, J = 5.9 and 1.3 Hz), 6.10 (2H, d, J = 1.7 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 32.8 (CH_2), 34.6 (CH), 72.6 (CH), 127.5 (CH), 177.5 (CH); *m/z* (C.I.) 195 (70, $[M + H]^+$) 177 (17), 149 (100), 135 (57), 121 (43); HRMS found $[M + H]^+$, 195.0667, $C_{10}H_{11}O_4$ requires 195.0657. Anal. Calcd for $C_{10}H_{11}O_4$: C, 61.85; H, 5.19. Found: C, 62.10; H, 5.38.

(b) Compound **20** (420 mg, 2.4 mmol) was heated at reflux in 6 M sulfuric acid (7 mL) for 30 min. Water (20 mL) was added to the cooled reaction mixture extracted with CH_2Cl_2 (4 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (EtOAc/CH_2Cl_2 1:2) to yield 17 (210 mg, 45%) as a colorless solid. The material was found to be identical in all aspects to that prepared in (a).

(±)-2-((3a*S*,4*R*,7*R*,7a*R*)-7-Ethyl-2-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran-4-yl)acetic Acid (16). Copper bromide−dimethyl sulfide complex (18.51 g, 90 mmol) was placed in a 250 mL RBF equipped with a large magnetic stirring bar and covered with anhydrous THF (60 mL). Ethylmagnesium chloride (45 mL, 2 M in THF, 90 mmol) was added dropwise via syringe at −20 °C. After 30 min of stirring, **17** (5.82 g, 30 mmol) was added portionwise as a solid (best done out of a vial) over 5 min and stirring continued for a further 1 h

while the reaction mixture was allowed to warm to 0 °C. HCl (2M, 50 mL) was then carefully added dropwise (gas formation). The organic solvent was then removed in vacuo and the residue diluted with HCl (2 M, 50 mL) and water (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and dry-loaded onto SiO_2 (20 g). Purification by flash column chromatography (SiO_2 100 g, hexane/EtOAc 1:1 and 1% AcOH) yielded a small amount of *syn*-**16** as a colorless solid (0.4 g, 6%). Further elution gave *anti*-**16** as a colorless solid (5.9 g, 88%): mp 106−109 °C; IR (film) 3109, 1770, 1731, 1705, 1416, 1158, 988, 726 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.44−1.66 (2H, m), 2.20−2.26 (1H, m), 2.31−2.35 (1H, m), 2.36−2.45 (4H, m), 2.75 (1H, dd, J = 17.2 and 7.2 Hz), 4.66 (1H, t, J = 4.4 Hz), 5.58 (1H, d, J = 10.3 Hz), 5.7s3 (1H, dt, J = 10.3 and 2.7 Hz), 11.54 (1H, s); ^{13}C (101 MHz; $CDCl_3$) δ 11.8 (CH_3), 24.5 (CH_2), 34.4 (CH_2), 37.8 (CH), 38.4 (CH_2), 38.5 (CH), 38.9 (CH), 80.7 (CH), 127.9 (CH), 128.9 (CH), 177.3 (CH), 177.5 (CH); *m/z* (C.I.) 225 (56, $[M + H]^+$), 207 (78), 179 (66), 165 (66), 133 (76), 119 (100); HRMS found $[M + H]^+$, 225.1126, $C_{12}H_{17}O_4$ requires 225.1127. Anal. Calcd for $C_{12}H_{17}O_4$: C, 64.27; H, 7.19. Found: C, 64.49; H, 7.41.

(±)-(3a*S*,4*R*,7*R*,7a*R*)-7-Ethyl-4-(2-hydroxyethyl)-3a,4,7,7a-tetrahydrobenzofuran-2(3*H*)-one (21). Ethyl chloroformate (3.0 mL, 31.7 mmol) was added dropwise to a solution of **16** (4.7 g, 21.1 mmol) and Et_3N (8.9 mL, 63.4 mmol) in THF (200 mL) at −20 °C and stirred for 30 min. A solution of sodium borohydride (8.0 g, 211.3 mmol) in water (105 mL) was cautiously added at −20 °C and the mixture allowed to warm to rt over 20 min with stirring. The reaction mixture was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography (EtOAc/hexane 1:1) to yield **21** (3.9 g, 87%) as a pale yellow oil: IR (film) 3420, 1760, 1156, 1056, 907, 705 cm^{-1}; ^1H (270 MHz; $CDCl_3$) δ 1.02 (3H, t, J = 7.4 Hz), 1.41−1.73 (5H, m), 2.03−2.13 (1 H, m), 2.20−2.43 (3 H, m), 2.74 (1H, dd, J = 17.2 and 7.3 Hz), 3.72 (2H, t, J = 6.4 Hz), 4.66 (1H, t, J = 4.5 Hz), 5.58 (1H, d, J = 10.2), 5.70 (1H, dt, J = 10.2 and 3.0 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 11.9 (CH_3), 24.6 (CH_2), 34.5 (CH), 37.4 (CH_2), 38.1 (CH), 38.7 (CH_2), 38.9 (CH), 60.4 (CH_2), 80.8 (CH), 128.1 (CH), 129.0 (CH), 177.2 (C); *m/z* (C.I.) 211 (44, $[M + H]^+$), 193 (88), 181 (40), 165 (46), 151 (68), 147 (76), 133 (100), 119 (42); HRMS found $[M + H]^+$, 211.1325, $C_{12}H_{19}O_3$ requires 211.1334.

(±)-3,4-Dichloro-1-(2-((3a*S*,4*R*,7*R*,7a*R*)-7-ethyl-2-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran-4-yl)ethyl)-1*H*-pyrrole-2,5-dione (22c). Diisopropyl azodicarboxylate (2.6 mL, 13.0 mmol) was added to a cooled solution of triphenylphosphine (3.6 g, 13.6 mmol) in THF (120 mL) at −78 °C and stirred for 2 h, after which a pale yellow precipitate formed. A solution of **21** (3.0 g, 14.2 mmol) in THF (3 mL) was added dropwise and stirred for 15 min after which dichloromaleimide (1.6 g, 13.0 mmol) was added in one portion. The resulting yellow solution was stirred for 10 min and allowed to warm to rt over 16 h. The reaction mixture was concentrated in vacuo and subjected to column chromatography (Et_2O/hexane 4:1) to yield **22c** (3.3 g, 71%) as pale yellow oil: IR (film) 1768, 1720, 1397, 1156, 877, 728 cm^{-1}; UV−vis (ν_{max}) 285 nm; ^1H (400 MHz; $CDCl_3$) δ 1.01 (3H, t, 7.3 Hz), 1.48−1.69 (3H, m), 1.79−1.86 (1H, m), 1.90−1.97 (1H, m), 2.19−2.26 (1H, m), 2.30 (1H, d, 17.2 Hz), 2.35−2.40 (1H, m), 2.76 (1H, dd, 16.8 and 7.3 Hz), 3.57−3.69 (2H, m), 4.67 (1H, t, 4.8 Hz), 5.61 (1H, d, 10.3 Hz), 5.70 (1H, dt, 10.3 and 2.9 Hz); ^{13}C (75 MHz; $CDCl_3$) δ 11.7 (CH_3), 24.4 (CH_2), 32.3 (CH_2), 35.3 (CH), 36.7 (CH_2), 37.9 (CH), 38.0 (CH), 38.4 (CH_2), 80.4 (CH), 127.5 (CH), 129.2 (CH), 133.4 (C), 162.9 (C), 176.5 (C); *m/z* CI 358 (8, $[M + H]^+$), 342 (58), 340 (73), 314 (25) 312 (36), 300 (33), 298 (48), 193 (27), 175 (16), 147 (93), 133 (100), 119 (16), 108 (38), 95 (15), 79 (12); HRMS found $[M + H]^+$, 358.0608, $C_{16}H_{18}NO_4Cl_2$ requires 358.0613.

Continuous Flow Photochemical Reactor. Flow reactors were constructed according to the literature method using between 15 and 20 loops of FEP tubing (2.7 mm inner diameter) wrapped around a water-cooled Pyrex immersion well.[24] The system was flushed with clean solvent before use. The substrate was dissolved in the stated solvent, and nitrogen was bubbled through the mixture for 5 min to remove dissolved oxygen. A 400 W medium-pressure mercury lamp was inserted into the well and switched on 5 min before commencing flow of the substrate solutions. Using a Masterflex peristaltic pump, the solution was pumped at the specified flow rate through the reactor system. After complete uptake of the substrate solution, a volume of clean solvent 2× the internal volume of the reactor was passed through the system and collected with the product solution before the lamp was turned off. The resulting mixtures were concentrated in vacuo and typically purified by column chromatography and/or recrystallization. Alternatively, the outflow tubing of the reactor can be connected to a rotary evaporator and the photosylate continuously evaporated as it exits the reactor.

(±)-(3^1*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-5,6-Dichloro-8-ethyl-1,2,8,8a,11,11a-hexahydroazepino[3,2,1-*hi*]furo[3,2-e]indole-4,7,10(3^1*H*,7a*H*,11b*H*)-trione (23c). A solution of **22c** (2.1 g, 5.8 mmol) was dissolved in CH_2Cl_2 (5.8 L) and passed through a 15-loop FEP flow reactor (2 m of FEP tubing; 10 mL reactor volume) at 11 mL min^{-1} (8 h 50 min) after which a further portion of CH_2Cl_2 (50 mL) was passed through the reactor. The combined photosylates were concentrated in vacuo and subjected to column chromatography (20% EtOAc in hexane) to yield recovered **22c** as a pale yellow oil (0.4 g, 20%). Further elution gave **23c** (1.3 g, 63%) as a colorless solid: 198 °C dec; IR (film) 1776, 1635, 1418, 1195, 1157, 906, 733 cm^{-1}; ^1H (400 MHz; CD_3Cl) δ 0.99 (3H, t, J = 7.3 Hz), 1.27−1.39 (1H, m), 1.55−1.67 (1H, m), 1.79−1.84 (1H, m), 1.96−2.12 (2H, m), 2.20−2.25 (1H, m), 2.27−2.32 (1H, m), 2.43 (1H, d, J = 17.3 Hz), 2.89 (1H, dd, J = 17.1 and 7.3 Hz), 3.27 (1H, dd, J = 12.5 and 3.2 Hz), 3.76−3.92 (2H, m), 4.11 (1H, dd, J = 4.6 and 3.4 Hz), 4.68 (1H, dd, J = 4.9 and 2.9 Hz); ^{13}C (101 MHz; CD_3Cl) δ 11.0 (CH_3), 22.6 (CH_2), 28.0 (CH_2), 34.4 (CH), 36.3 (CH), 37.9 (CH_2), 42.5 (CH), 48.9 (CH_2), 49.7 (CH), 55.6 (CH), 78.0 (CH), 138.7 (C), 140.4 (C), 157.9 (C), 175.0 (C), 189.7 (C); *m/z* (C.I.) 358 (100, $[M + H]^+$) 322 (70), 288 (30), 262 (12), 147 (18), 133 (24); HRMS found $[M + H]^+$, 358.0616, $C_{16}H_{18}NO_4Cl_2$ requires 358.0613.

(±)-(3^1*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyloctahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,7,10-(3^1*H*,7a*H*,11b*H*)-trione (24). Zinc powder (2.9 g, 44.8 mmol) was activated by stirring with glacial acetic acid (40 mL) for 20 min at rt. A solution of **23c** (0.8 g, 2.2 mmol) in glacial acetic acid (28 mL) was added and stirred at rt for 1 h. The reaction mixture was then filtered through Celite, washed with EtOAc (3 × 50 mL), concentrated in vacuo, and subjected to column chromatography (10% MeOH in EtOAc) to yield **24** (0.6 g, 95%) as a colorless solid: IR (film) 1771, 1702, 1631, 1423, 1178, 906 cm^{-1}; ^1H (400 MHz; CD_2Cl_2) δ 1.03 (3H, t, J = 7.2 Hz), 1.15−1.32 (3H, m), 1.63 (1H, dd, J = 12.8 and 6.0 Hz), 1.90−2.00 (1H, m), 2.25 (1H, d, J = 16.5 Hz), 2.46−2.55 (3H, m), 2.58−2.68 (2H, m), 2.78−2.88 (2H, m), 2.94−3.04 (1H, m), 3.17 (1H, dt, J = 11.9 and 6.0 Hz), 3.99 (1H, dd, J = 11.8 and 7.1 Hz), 4.07 (1H, d, J = 8.2 Hz), 4.94 (1H, dd, J = 8.4 and 6.8 Hz); ^{13}C (101 MHz; CD_2Cl_2) δ 15.7 (CH_3), 20.7 (CH_2), 28.6 (CH_2), 32.7 (CH_2), 35.0 (CH_2), 35.6 (CH), 35.7 (CH_2), 41.5 (CH), 42.9 (CH), 45.3 (CH_2), 58.3 (CH), 79.5 (CH), 80.3 (CH), 172.0 (C), 178.0 (C), 207.3 (C); *m/z* (C.I.) 292 (100, $[M + H]^+$) 274 (9), 246 (7), 232 (31), 147 (8), 133 (7); HRMS found $[M + H]^+$, 292.1548, $C_{16}H_{22}NO_4$ requires 292.1549.

(±)-(3^1*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-7-hydroxydecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (25). To a solution of **24** (71 mg, 0.24 mmol) in THF (25 mL) was added 1.0 M $LiAl(O^tBu)_3H$ solution in THF (0.24 mL, 0.24 mmol) dropwise at 0 °C and the mixture allowed to stir at rt for 3 h. The reaction mixture was quenched by the dropwise addition of H_2O (0.3 mL) and allowed to stir for 30 min. The mixture was filtered through Celite, and the filter cake was washed with THF (5 × 15 mL). The solution was concentrated in vacuo onto silica gel and

subjected to column chromatography (10% MeOH in CH_2Cl_2) to yield **25** (71 mg, 99%) as a colorless crystalline solid: IR (film) 3378, 1759, 1627, 906 cm^{-1}; ^1H (400 MHz; CD_2Cl_2) δ 0.94 (3H, t, J = 7.5 Hz), 1.43−1.54 (1H, m), 1.60 (1H, ddt, J = 12.5, 6.8 and 2.2 Hz), 1.73−1.94 (4H, m), 2.02 (1H, ddd, J = 14.2, 7.5 and 4.0 Hz), 2.06−2.17 (2H, m), 2.19−2.26 (1H, m), 2.31 (1H, dd, J = 17.3 and 1.5 Hz), 2.39 (1H, ddd, J = 15.6, 11.4 and 4.5 Hz), 2.63 (1H, ddd, J = 15.5, 6.1 and 3.7 Hz), 2.83 (1H, dd, J = 17.2 and 7.7 Hz), 3.36−3.46 (1H, m), 3.72−3.76 (1H, m), 3.79 (1H, dd, J = 5.4 and 2.7 Hz), 3.93 (1H, dt, J = 10.4 and 2.9 Hz), 4.75 (1H, dd, J = 5.4 and 2.4 Hz); ^{13}C (101 MHz; CD_2Cl_2) δ 11.5 (CH_3), 21.5 (CH_2), 26.6 (CH_2), 28.8 (CH_2), 34.7 (CH), 35.6 (CH_2), 36.5 (CH), 38.4 (CH_2), 40.1 (CH), 43.5 (CH), 47.4 (CH_2), 59.7 (CH), 76.6 (CH), 80.0 (CH), 173.7 (C), 176.3 (C); *m/z* (C.I.) 294 (100, $[M + H]^+$) 276 (30), 265 (4), 234 (4), 216 (4), 192 (3); HRMS found $[M + H]^+$, 294.1704, $C_{16}H_{24}NO_4$ requires 294.1705.

(±)-(3^1*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-4,10-dioxotetradecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indol-7-yl Methanesulfonate. To a solution of **25** (70 mg, 0.24 mmol) and Et_3N (166 μL, 1.2 mol) in THF (20 mL) was added methanesulfonyl chloride (74 μL, 0.96 mmol) dropwise at 0 °C and the mixture allowed to stir at rt for 5 min. The reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography (5% MeOH in CH_2Cl_2) to give the mesylate **25a** (89 mg, 99%) as a colorless crystalline solid: IR (film) 1773, 1628, 1461, 1350, 1170 cm^{-1}; ^1H (400 MHz; DMSO-d_6) δ 0.96 (3H, t, J = 7.3 Hz), 1.31−1.41 (1H, m), 1.54−1.58 (1H, m), 1.73−1.85 (3H, m), 1.93−2.06 (1H, m), 2.11−2.16 (3H, m), 2.33 (1H, d, J = 17.2 Hz), 2.44−2.54 (2H, m), 2.64 (1H, ddd, J = 15.5, 6.3 and 3.0 Hz), 2.91 (1H, dd, J = 17.2 and 7.6 Hz), 3.03 (3H, s), 3.40 (1H, m), 3.64 (1H, dd, J = 8.9 and 7.6 Hz), 3.92 (1H, dd, J = 4.5 and 2.5 Hz), 4.78 (1H, dd, J = 4.3 and 2.0 Hz), 4.88 (1H, dt, J = 10.8 and 3.2 Hz); ^{13}C (101 MHz; DMSO-d_6) δ 11.6 (CH_3), 21.8 (CH_2), 24.9 (CH_2), 28.7 (CH_2), 32.1 (CH_2), 33.7 (CH), 34.9 (CH_2), 36.1 (CH), 38.2 (CH_2), 38.4 (CH), 43.3 (CH_3), 47.5 (CH_2), 58.7 (CH), 79.5 (CH), 85.5 (CH), 172.3 (C), 176.9 (C); *m/z* (C.I.) 371 (3, $[M + H]^+$) 323 (35), 322 (56), 292 (28), 290 (44), 276 (70) 178 (48), 102 (73), 97 (100), 86 (52), 65 (52); HRMS found $[M + Na]^+$, 394.1308, $C_{17}H_{25}NaNO_6S$ requires 394.1295.

(±)-(3^1*S*,7*S*,7a*R*,8*R*,9*S*,10*S*,10a*S*)-8-Ethyl-10-(2-hydroxyethyl)-dodecahydroazepino[3,2,1-*hi*]indole-7,9-diol (26). To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (10 mL) was added **25a** (125 mg, 0.34 mmol) at 0 °C and then heated at reflux for 1 h. The reaction mixture was quenched with water (0.1 mL), 15% NaOH (0.1 mL), and additional water (0.3 mL). After 1 h, the mixture was filtered through Celite, and the filter cake was washed with THF (5 × 10 mL), concentrated in vacuo onto silica gel, and subjected to column chromatography (CH_2Cl_2/MeOH/NH_3 200:8:1) to give **26** (39 mg, 39%) as a colorless oil: IR (film) 3364, 1119 and 972 cm^{-1}; ^1H (400 MHz; D_3OD) δ 0.94 (3H, t, J = 7.3 Hz), 1.33−1.43 (2H, m), 1.52−1.80 (7H, m), 1.84−2.00 (4H, m), 2.10−2.17 (1H, m), 2.43−2.50 (2H, m), 2.70−2.75 (1H, m), 2.89 (1H, dt, J = 12.2 and 4.3 Hz), 3.10 (1H, dt, J = 10.5 and 7.2 Hz), 3.56−3.73 (2H, m), 3.93 (1H, t, J = 1.8 Hz), 4.09 (1H, dt, J = 8.6 and 3.1 Hz); ^{13}C (101 MHz; D_3OD) δ 10.7 (CH_3), 21.7 (CH_2), 22.9 (CH_2), 27.8 (CH_2), 30.3 (CH_2), 32.9 (CH_2), 39.5 (CH), 41.0 (CH), 41.5 (CH), 42.7 (CH), 55.4 (CH_2), 59.2 (CH_2), 66.5 (CH), 68.8 (CH), 70.5 (CH); *m/z* (C.I.) 284 (9, $[M + H]^+$) 266 (16), 115 (30), 79 (100); HRMS found $[M + H]^+$, 284.2216, $C_{16}H_{30}NO_3$ requires 284.2226.

(±)-(3^1*S*,7*R*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-7-hydroxydecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (27). To a solution of **25** (10 mg, 0.03 mmol) and chloro(diphenyl)silane (16 μL, 0.07 mmol) in CH_2Cl_2 (1 mL) was added $InCl_3$ (0.4 mg, 5 mol%) stirred at reflux for 16 h. The reaction mixture was allowed to cool to rt at which point a precipitate was observed. The reaction mixture was filtered and the solid washed with CH_2Cl_2 (3 × 2 mL). The solid was dissolved in acetone (15 mL) and filtered, and the filtrate was then concentrated in vacuo to give **27** (10 mg, 99%) as a colorless crystalline solid: IR (film) 3087, 1755, 1686, 1249, 1155, 913 cm^{-1}; ^1H (400 MHz; $CD_3C(O)$) δ 1.05 (3H, t, J = 7.3 Hz), 1.49−1.59 (1H, m), 1.91−1.99 (1H, m), 2.15−2.24 (2H, m), 2.34−2.54 (7H, m), 2.46 (1H, d, J = 16.9 Hz), 2.68−2.78 (1H, m), 2.98 (1H, dd, J = 16.9 and 6.4 Hz), 3.77−3.92 (2H, m), 4.43−4.49 (1H, m), 4.86 (1H, dd, J = 3.7 and 3.4 Hz), 5.06 (1H, ddd, J = 10.3, 6.1, and 2.9 Hz); ^{13}C (101 MHz; $CD_3C(O)$) δ 10.6 (CH_3), 21.5 (CH_2), 25.8 (CH_2), 28.1 (CH_2), 29.9 (CH_2), 34.4 (CH), 35.5 (CH), 36.5 (CH), 37.4 (CH_2), 40.2 (CH), 45.5 (CH_2), 59.6 (CH), 78.0 (CH), 78.8 (CH), 175.0 (C), 175.6 (C); *m/z* (C.I.) 294 (100, $[M + H]^+$) 276 (48), 250 (6), 232 (9), 216 (8), 115 (75), 99 (5), 95 (13), 79 (46), 59 (90); HRMS found $[M + H]^+$, 294.1692, $C_{16}H_{24}NO_4$ requires 294.1705.

(±)-*O*-(3^1*S*,7*S*,7a*R*,8*R*,8a*S*,11a*S*,11b*S*)-8-Ethyl-4,10-dioxotetradecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indol-7-yl *O*-Phenyl Carbonothioate (28). To a solution of **25** (175 mg, 0.6 mmol) and DMAP (112 mg, 0.9 mmol) in CH_2Cl_2 (20 mL) was added *o*-phenyl chlorothionoformate (98 μL, 0.7 mmol) dropwise and the mixture allowed to stir at reflux for 7 h 15 min. The reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography (2% MeOH in CH_2Cl_2) to yield **28** (172 mg, 67%) as a colorless crystalline solid (mp 209−210 °C) and recovered **25** (51 mg, 29%): IR (film) 1776, 1623, 1576, 1403, 1294, 1194 cm^{-1}; ^1H (400 MHz; $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz), 1.46−1.56 (1H, m), 1.63 (1H, dd, J = 12.5, and 6.4 Hz), 1.78−1.97 (3H, m), 2.07−2.21 (4H, m), 2.38 (1H, d, J = 17.1 Hz), 2.48−2.56 (1H, m), 2.57−2.65 (1H, m), 2.79−2.90 (2H, m), 3.49 (1H, dt, J = 11.9 and 6.4 Hz), 3.86−3.91 (2H, m), 4.73 (1H, dd, J = 3.9 and 2.2), 5.49 (1H, dt, J = 7.0 and 3.2 Hz), 7.11 (2H, dd, J = 8.4 and 1.1 Hz), 7.27−7.33 (1H, m), 7.39−7.46 (2H, m); ^{13}C (101 MHz; $CDCl_3$) δ 11.4 (CH_3), 21.3 (CH_2), 23.3 (CH_2), 28.5 (CH_2), 34.1 (CH_2), 35.5 (CH), 36.7 (CH), 37.6 (CH), 38.4 (CH_2), 43.7 (CH), 47.7 (CH_2), 59.7 (CH), 79.6 (CH), 87.8 (CH), 122.0 (CH), 126.8 (CH), 129.7 (CH), 153.3 (C), 172.9 (C), 176.0 (C), 193.8 (C); HRMS found $[M + Na]^+$ 452.1495, $C_{23}H_{28}NaNO_4S$ requires 452.1502.

(±)-(3^1*R*,7a*R*,8*R*,8a*R*,11a*S*,11b*S*)-8-Ethyldecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (29). A solution of **28** (143 mg, 0.33 mmol), AIBN (16 mg, 0.11 mmol), and tributyltin hydride (181 μL, 0.66 mmol) in benzene (12 mL) was heated at reflux for 30 min. The cooled reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography (1% MeOH in CH_2Cl_2) to give **29** (87 mg, 94%) as a colorless crystalline solid after recrystallization from EtOAc (mp 172−173 °C): IR (film) 1765, 1617, 1430, 1263, 1008 cm^{-1}; ^1H (300 MHz; $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.27−1.43 (1H, m) 1.44−1.73 (6H, m), 1.76−1.91 (1H, m), 2.02−2.20 (4H, m), 2.33 (1H, d, J = 16.9 Hz), 2.26−2.39 (1H, m), 2.64−2.74 (1H, m), 2.81 (1H, dd, J = 16.9 and 6.9 Hz), 3.40 (1H, dt, J = 11.9 and 6.2 Hz), 3.77 (1H, dd, J = 4.8 and 2.0 Hz), 3.90 (1H, dd, J = 12.3 and 8.4 Hz), 4.65 (1H, dd, J = 4.5 and 2.4 Hz); ^{13}C (101 MHz; CD_3CO) δ 11.2 (CH_3), 17.8 (CH_2), 20.9 (CH_2), 28.4 (CH_2), 31.0 (CH_2), 33.4 (CH), 33.7 (CH), 37.1 (CH), 38.7 (CH_2), 39.7 (CH_2), 43.5 (CH), 47.5 (CH_2), 61.8 (CH), 80.1 (CH), 175.2 (C), 176.4 (C); *m/z* (C.I.) 278 (100, $[M + H]^+$), 233 (4), and 218 (3); HRMS found $[M + H]^+$, 278.1753, $C_{16}H_{24}NO_3$ requires 278.1756.

(±)-(3^1*R*,7a*R*,8*R*,8a*R*,11*R*,11a*R*,11b*S*)-8-Ethyl-11-methyldecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (30/*f*). To a solution of **29** (112 mg, 0.41 mmol) in THF (20 mL) at −78 °C was added LiHMDS (0.43 mL, 0.43 mmol) dropwise and the mixture allowed to stir at −78 °C for 1 h. Iodomethane (76 μL, 1.2 mmol) was added dropwise at −78 °C and the mixture allowed to stir for 2 h. The reaction mixture was quenched with IPA (2 mL) and allowed to warm to rt over 30 min. The reaction mixture was concentrated in vacuo onto silica gel and subjected to column chromatography using (1% MeOH in CH_2Cl_2) to give **30** (112 mg, 95%) as a colorless crystalline solid as a 1:7 mixture of α/β-epimers. Major isomer: ^1H (400 MHz; $CDCl_3$) δ 0.95 (3H, t, J = 7.2 Hz), 1.28−1.38 (1H, m), 1.32 (3H, d, J = 7.6 Hz), 1.46−1.62 (6H, m),

1.78−1.89 (2H, m), 1.92−2.04 (2H, m), 2.08−2.16 (1H, m), 2.33 (1 H, ddd, J = 15.0, 10.9 and 3.9 Hz), 2.43 (1H, dq, J = 7.6 and 2.0 Hz), 2.59−2.67 (1H, m), 3.37 (1H, ddd, J = 12.2, 10.4 and 6.7 Hz), 3.75−3.85 (2H, m), 4.76 (1H, dd, J = 5.5 and 2.6 Hz); ^{13}C (101 MHz; $CDCl_3$) δ 11.0 (CH_3), 15.3 (CH_3), 17.6 (CH_2), 20.6 (CH_2), 28.5 (CH_2), 30.2 (CH_2), 33.4 (CH), 33.9 (CH), 38.8 (CH_2), 42.9 (CH), 43.6 (CH), 44.6 (CH), 46.9 (CH_2), 60.8 (CH), 77.3 (CH), 174.5 (C), 179.2 (C).

(±)-(3^1*R*,7a*R*,8*R*,8a*R*,11*S*,11a*R*,11b*S*)-8-Ethyl-11-methyldecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-4,10(3^1*H*,11b*H*)-dione (30α). LiHMDS (0.42 mL, 0.42 mmol) was added dropwise to a stirred solution of **30α/β** (1:7) (112 mg, 0.38 mmol) in THF (30 mL) at −78 °C. After 10 min, the reaction mixture was allowed to warm to rt for 15 min and then cooled back down to −78 °C. A 1 M solution of BHT (3.8 mL, 3.8 mmol) was added dropwise at −78 °C and the mixture allowed to stir for 2 h. The reaction mixture was warmed to rt, then concentrated in vacuo onto silica gel, and subjected to column chromatography (1% MeOH in CH_2Cl_2) to give a mixture of **30α/β** (5:1) (78 mg, 70%) (mp 167−169 °C). This was then recrystallized from EtOAc to give pure **30α** as a colorless crystalline solid: IR (film) 1769, 1630, 1423, 1168, 978 cm^{-1}; ^{1}H (400 MHz; $CDCl_3$) δ 0.99 (3H, t, J = 7.3 Hz), 1.29 (3H, d, J = 7.3 Hz), 1.31−1.74 (7H, m), 1.80−1.93 (1H, m), 2.06−2.22 (4H, m), 2.30−2.38 (1H, m), 2.73 (1H, dd, J = 16.4 and 6.8 Hz), 2.95 (1H, quin, J = 6.6 Hz), 3.41 (1H, dt, J = 12.2 and 6.1 Hz), 3.79 (1H, dd, J = 4.4 and 1.95 Hz), 3.94 (1H, dd, J = 12.3 and 8.4 Hz), 4.58 (1H, t, J = 3.1 Hz); ^{13}C (101 MHz; $CDCl_3$) 9.6 (CH_3), 11.2 (CH_3), 17.8 (CH_2), 20.7 (CH_2), 29.3 (CH_2), 31.2 (CH_2), 33.4 (CH), 33.5 (CH), 38.5 (CH), 39.9 (CH_2), 40.7 (CH), 42.2 (CH), 47.4 (CH_2), 62.1 (CH), 78.4 (CH), 175.3 (C), 178.8 (C); *m/z* (C.I.) 292 (100, $[M + H]^+$), 278 (2), 247 (4), 218 (9); HRMS found $[M + H]^+$, 292.1909, $C_{17}H_{26}NO_3$ requires 292.1913.

(±)-Neostenine (5). $RhH(CO)(PPh_3)_3$ (6 mg, 5 mol %) was added in a single portion to a solution of **30α** (35 mg, 0.1 mmol) and diphenylsilane (44 μL, 0.23 mmol) in THF (4 mL) and the mixture allowed to stir for 30 min. The reaction mixture was loaded directly onto an IST CBA cartridge (1 g, 0.7 mmol) and washed with MeCN (2 × 5 mL). Then cartridge was then eluted with 2 × 5 mL volumes of a Et_3N/MeCN solution (1/3 v/v). The eluent was concentrated in vacuo to give (±)-neostenine **5** (23 mg, 70%) as a colorless crystalline solid which was recrystallized from EtOAc: mp 122−123 °C (lit.[2] mp 90−92 °C; lit.[11] 126−128 °C); IR (film) 1765, 1171, 953 cm^{-1}; ^{1}H (400 MHz; CD_3Cl) δ 0.99 (3H, t, J = 7.5 Hz), 1.21 (3H, d, J = 7.5 Hz), 1.36−1.48 (2H, m), 1.57−1.91 (10H, m), 1.92−2.04 (1H, m), 2.23−2.48 (4H, m), 2.81−2.90 (2H, m), 3.17−3.25 (1H, m), 4.51 (1H, dd, J = 4.0 and 2.5 Hz); ^{13}C (101 MHz; CD_3Cl) δ 10.1 (CH_3), 11.3 (CH_3), 21.1 (CH_2), 21.2 (CH_2), 28.1 (CH_2), 28.4 (CH_2), 30.2 (CH_2), 34.3 (CH), 37.3 (CH), 37.4 (CH), 42.5 (CH), 42.9 (CH), 55.6 (CH_2), 55.9 (CH_2), 70.9 (CH), 79.3 (CH), 179.6 (C); *m/z* (C.I.) 278 (100, $[M + H]^+$), 233 (8), 204 (10), 191 (7); HRMS found $[M + H]^+$, 278.2116, $C_{17}H_{28}NO_2$ requires 278.2120.

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Supporting Information Available: Copies of ^{1}H/^{13}C spectra of all new compounds and the X-ray crystallographic files (CIF) for **23b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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