A STUDY OF ALKYLATION REACTIONS α- TO NITROGEN FOR APPLICATION IN ALKALOID SYNTHESIS

BY

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This thesis begins with a review (Chapter 1) of methodologies for carbon-carbon bond formation α to nitrogen of relevance to alkaloid synthesis, from which a specific structural motif for study in this thesis is identified. In the first phase of the research component (Chapter 2) relating to benzylic secondary aza stereogenic centres, a study has been undertaken of the stereoselective synthesis of tetrahydropyrido[2,1-*a*]isoindolones, via radical and carbanionic cyclisation of a N-tethered α-sulfanyl lactam incorporating an enoate ester as the acceptor and an allylic *tert*-butyldiphenylsilyloxy group (OTBDPS) as stereocontrol element. The product stereochemistries have successfully modelled the required *cis*-stereochemistry of the D/E ring fusion of the indole alkaloid tacamonine in which the pyrido and indolo rings of the natural product have been replaced by pyrrolo and phenyl respectively. The N-tether was constructed in a high-yielding sequence from (*S*)-malic acid.

The radical cyclisation occurred with good diastereoselectivity, to afford of the four possible diastereomers, a major product (~ 50%) with the hydrogens of the two new stereocentres in a *cis* relationship. Similarly the carbanionic cyclisation gave a major product in even higher diastereoselectivity (~80%), which could be desulfurised with retention of configuration to give the other *cis* diastereomer. These results complement the radical approach, providing the required stereochemistry for the Tacaman alkaloid D/E ring fusion. A transition-state model is presented for the radical cyclisation in which the acceptor substituent adopts a pseudoaxial configuration in the transition-state as a result of the imposing steric effect of the OTBDPS group. This is in stark contrast to other 6-exo-trig cyclisations in which the acceptor group is normally pseudoequatorial.

The second phase of this study (Chapter 3) addresses formation of tertiary aza allylic stereocentres as expressed in a successful synthetic sequence for the tricyclic core of the marine alkaloid lepadiformine, incorporating a *trans*-azadecalin ring system. The strategy was to initially construct an A/C ring azaspirocyclic ketone followed by annulation of the B-ring. The azaspirocycle was synthesised via a 5,5-spirotetramate using new methodology based on the silyl dienol ether of methyl tetramate. Subsequently, chain extension and Grubb's metathesis furnished the A/C ring skeleton, which was efficiently reduced by dissolving metal reduction to afford the saturated C-ring, and converted to the tricyclic core. The sequence lays the foundation for generation of other systems containing the tertiary aza motif as well as an enantioselective synthesis of lepadiformine.

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Finally the love of my life Karen for enduring the many challenges with me - thank you!

I declare that '***A Study of Alkylation Reactions α to Nitrogen for Application in Alkaloid Synthesis***' is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Signed by candidate

Philip Richards

CONTENTS

CHAPTER 1
INTRODUCTION

"Alkaloid" is a loosely defined term used to describe a large and varied class of naturally occurring amines derived from animal or plant sources, as well as synthetic analogues. A great number of alkaloids have significant medicinal importance. Some well-known examples (Figure 1.1) are morphine (an analgesic), quinine (the first antimalarial drug), and reserpine (an antihypertensive agent).

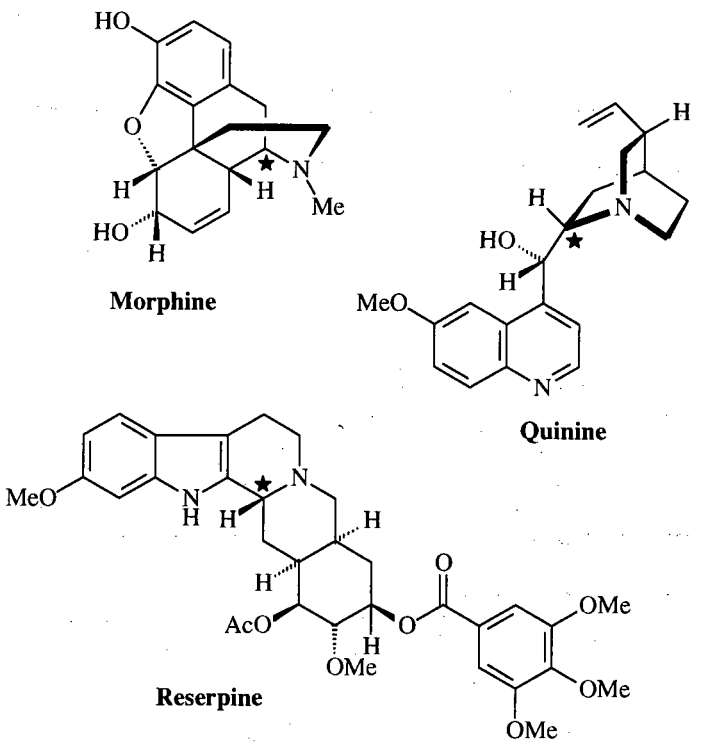


Figure 1.1 Well known alkaloids

Alkaloids continue to feature significantly in the search for new and better treatments for every kind of medical condition. Consequently, the methods that synthetic organic chemists use to construct these molecules are continually expanding in order to access any potential drug molecule. A new method may permit access to a target that was previously unattainable, or it may be easier or higher yielding than the current methods to produce a known drug molecule.

A common structural feature encountered in many alkaloids is a stereogenic centre adjacent to nitrogen (★in Figure 1). It may be secondary aza (a carbon bonded to a nitrogen, a hydrogen and two carbon atoms) or tertiary aza (a carbon bonded to a nitrogen and three carbon atoms), (Figure 1.2).

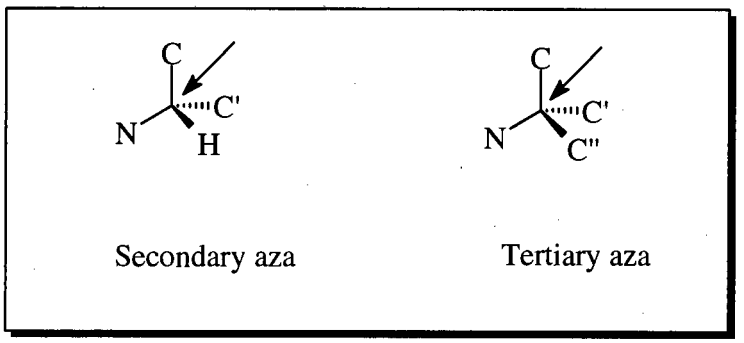


Figure 1.2 Stereogenic centres adjacent to nitrogen

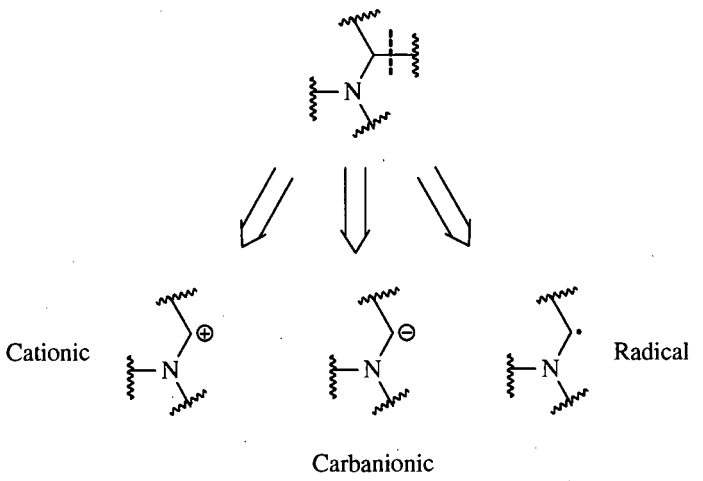
A key issue in the synthesis of these kinds of alkaloids is the stereocontrolled construction of this centre in relation to other stereogenic centres in the molecule. The motivation behind this research project was to develop improved methodologies for assembling these kinds of centres *via* alkylation alpha to nitrogen.

A review of the syntheses of alkaloids possessing such stereocentres revealed the methodologies that have been thoroughly explored and those that warrant further study.

1.1
Review of Secondary aza and Tertiary aza Construction in Alkaloid Synthesis

1.1.1 Secondary aza Construction

A huge number of methods exist for the construction of secondary aza centres in alkaloids, and of interest to this thesis are those that utilize alkylation alpha to nitrogen. This conversion can be divided into cationic, radical, and carbanion methodologies (Scheme 1.1).



Scheme 1.1 Alkylation alpha to nitrogen

1.1.1 (a) Cationic Methodology

Alkylation alpha to nitrogen using cationic methodology proceeds via iminium ions or *N*-acyliminium ion intermediates (Figure 1.3).

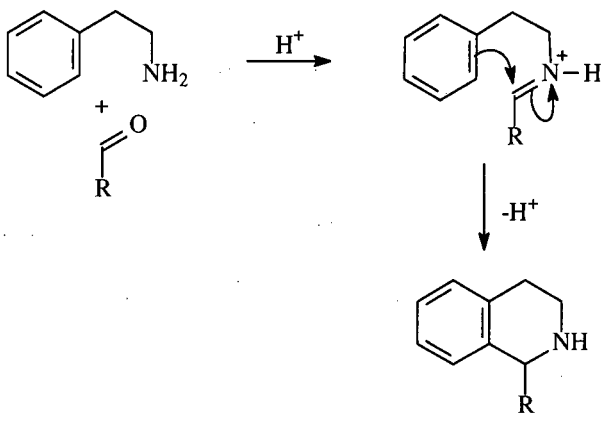
Figure 1.3 Cationic methodology for alkylation alpha to nitrogen

Iminium Ions

The use of iminium chemistry takes advantage of the inherent reactivity of amines, and construction of secondary aza centres biosynthetically involves the intermediacy of iminium ions produced *in vivo* by Mannich reactions. Not surprisingly, therefore, the synthetic chemist has adopted this approach as the method of choice. The two most important methods during the "classical era" of alkaloid synthesis for tetrahydroisoquinoline and tetrahydro-β-carboline ring construction are now known as the Bischler-Napieralski and the Pictet-Spengler[1] reactions.

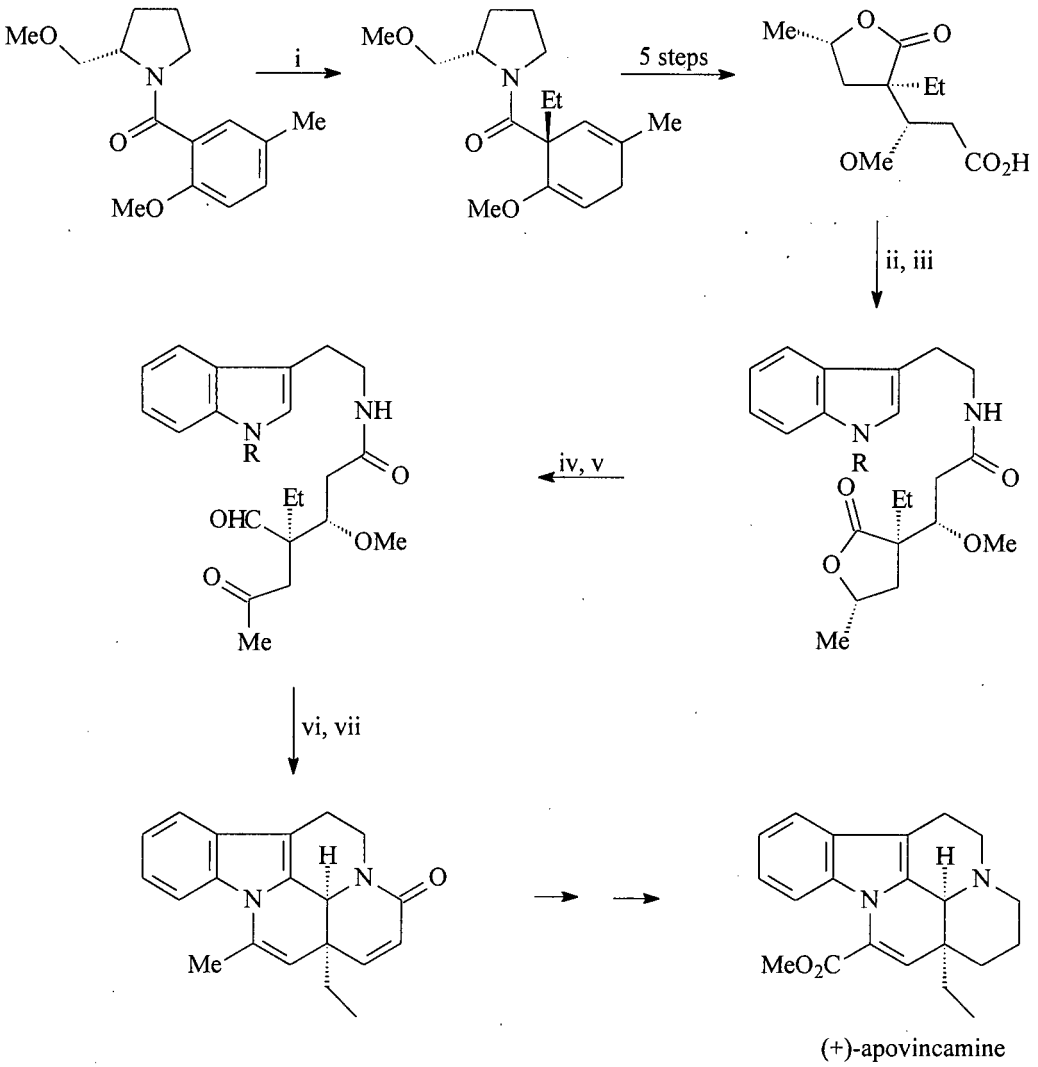
The Bischler-Napieralski reaction does not form a stereocentre by alkylation, rather involving a cyclodehydration reaction to an imine product, which can be subsequently reduced to give a chiral centre. Hence it does not fall within the scope of this review.

The acid-catalysed Pictet-Spengler reaction between 2-phenylethylamine and an aldehyde involves the aromatic electrophilic substitution of a protonated iminium ion. This generates a tetrahydroisoquinoline containing a benzylic secondary aza stereocentre (Scheme 1.2).



Scheme 1.2 Pictet-Spengler reaction of 2-phenylethylamine with an aldehyde

The early syntheses using this chemistry gave the products as racemates. More recently asymmetric syntheses have been achieved using these reactions. In some of the more elegant syntheses of tetrahydro-β-carboline ring construction an enantiopure non-tryptamine unit was synthesised. This chiral unit was synthesised either directly from the chiral pool or by using a chiral auxiliary. When reacted with tryptamine, the crucial benzylic centre was obtained in a highly stereoselective manner. A good example of this is the synthesis of apovincamine by Schultz *et al.*[2] (Scheme 1.3).



Scheme 1.3 *Reagents and conditions:* (i) K, NH_3, *tert*-BuOH, -78°C, piperylene; EtI, -78°C to 25°C (ii) tryptamine, $(PhO)_2P(O)N_3$, DMF, Et_3N, 0°C to 25°C (iii) $(Boc)_2O$, CH_2Cl_2 (iv) $LiBH_4$, THF (v) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, -78°C to 25°C (vi) CF_3CO_2H, CH_2Cl_2, 25°C (vii) *tert*-BuOK, *tert*-BuOH, reflux

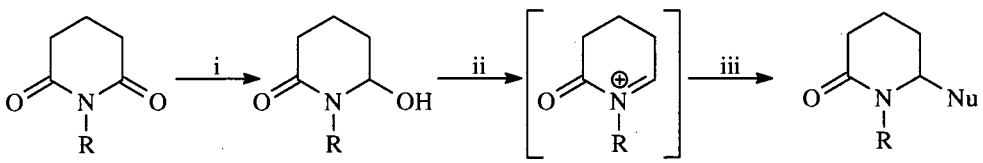
The starting material for this synthesis was a chiral benzamide, which undergoes diastereoselective alkylation (>100:1) following a Birch reduction. Subsequent cleavage and functional group elaboration generated a γ-lactone that was coupled with tryptamine, reduced and oxidized to the aldehyde. Diastereoselective Pictet-Spengler cyclisation with concomitant methanol elimination resulted in the pentacyclic alkaloid, which could be elaborated to (+)-apovincamine.

N-Acyliminium ions

The development of reactions that proceed via *N*-acyliminium intermediates is relatively recent in comparison to those involving iminium cations. The electrophilicity of an iminium ion or species is

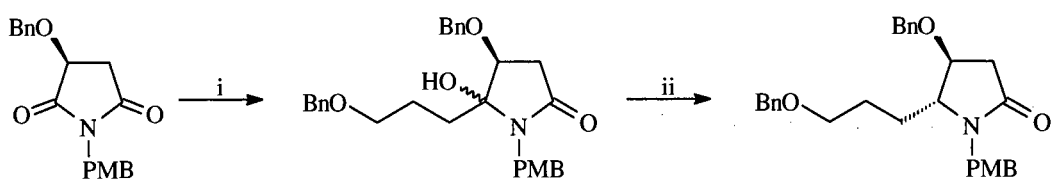
greatly enhanced when a carbonyl group is introduced next to the nitrogen atom enabling a broader range of nucleophiles to be used for C-C bond formation. This is due to the electron withdrawing effect of the carbonyl group making the imino carbon more electrophilic than in the normal iminium ion. These acyliminium ions are reactive with a large variety of nucleophiles, such as alkenes, alkynes, aromatic and heteroaromatic species.

Another illustration of the difference in reactivity is that iminium salts can be isolated, whereas the *N*-acyliminium equivalent has seldom been isolated. The acyliminium ion is usually formed *in situ* using protic or Lewis-acidic conditions, and then undergoes nucleophilic addition to give the product. The acyliminium may be formed by the heterolysis of an α-substituent, most often an oxygen functionality that departs on activation, such as in α-hydroxy or α-alkoxylactams (Scheme 1.4). Other substituents that may be utilised are α-chloroalkyl amides and α-thioalkyl amides.



Scheme 1.4 *Reagents and conditions:* (i) $NaBH_4$ (ii) Lewis acid (iii) Nucleophile

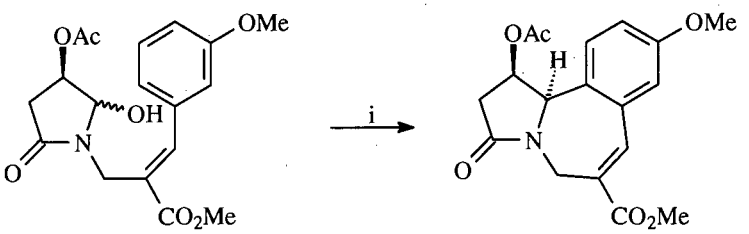
The most common method for synthesis of α-hydroxylactams is reduction of a cyclic imide in an alcohol. The tertiary hydroxylactams that are produced by reaction of cyclic imides with Grignard reagents are also excellent precursors to acyliminium intermediates[3] (Scheme 1.5). α-Alkoxylactams can be prepared by exchange of the hydroxy precursor *via* the acyliminium ion.



Scheme 1.5 *Reagents and conditions:* (i) $BnO(CH_2)_3MgBr$, THF, 0°C (ii) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, -78°C to rt

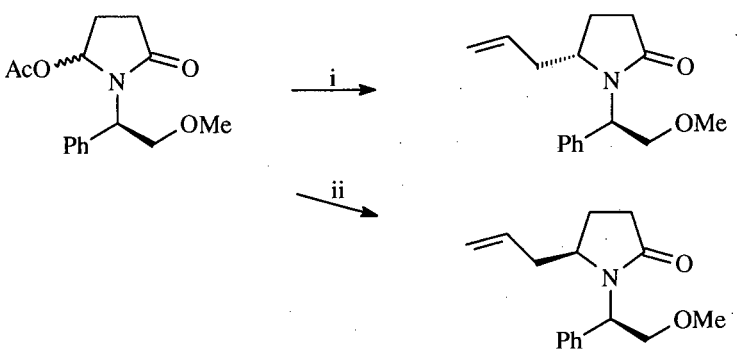
Other methods of generating α-oxygenated amides include the acid-catalysed addition of an amide to an aldehyde or ketone, and electrochemical oxidation of amides. Carbon-carbon bond formation in alkaloid synthesis has been achieved using mainly cyclic acyliminium intermediates in which bond formation can be divided into intramolecular C-C formation and intermolecular bond formation.

The intramolecular reaction can be divided into endocyclic and exocyclic variants. The nucleophile is invariably a nucleophilic alkene, alkyne or aromatic ring, and the most frequent transformation of this type is the formation of 5,6-bicycles *via* an endocyclic acyliminium derived from succinimide. Many of these include the presence of chiral elements mainly in the hydroxylactam (Scheme 1.6).[4]



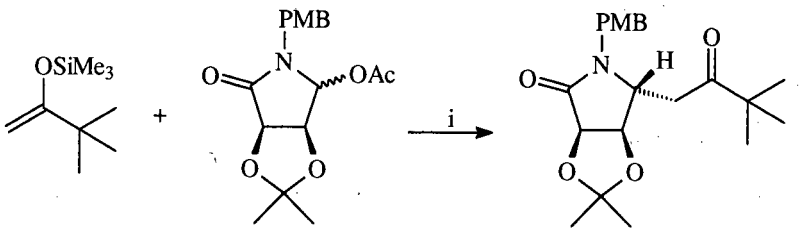
Scheme 1.6 *Reagents and conditions:* (i) 5% CF_3SO_3H, CH_2Cl_2

For intermolecular C-C bond formation the new stereocentre is created using either auxiliary control or inherent stereocontrol. Auxiliary control has generally utilized a chiral group attached at nitrogen, with allyltrimethylsilane the nucleophile of choice. The choice of Lewis acid can also have a marked effect. An example is Ukaji's allylation of a chiral α-acyloxylactam.[5] In this reaction, changing the Lewis acid from TMSOTf, $BF_3.Et_2O$, or $TiCl_4$ to $SnCl_4$ gave opposite stereochemical induction (Scheme 1.7).



Scheme 1.7 *Reagents and conditions:* (i) allylTMS, $BF_3.Et_2O$ (ii) allylTMS, $SnCl_4$

The majority of intermolecular applications use the inherent stereocontrol of a chiral precursor. In many of these studies the factors that determine the stereocontrol are optimized. Three types of nucleophile are used. These are alkenylsilanes and stannanes, organocuprates and enol derivatives.[6] The stereoselectivity in these syntheses may arise from using chelation control or simple steric factors (Scheme 1.8).



Scheme 1.8 *Reagents and conditions:* (i) $BF_3.Et_2O$, CH_2Cl_2, 0°C to rt, 88%

To illustrate the popularity and scope of this methodology, a few of the compounds successfully synthesised in the last 10 years using *N*-acyliminium precursors are shown in Figure 1.4.

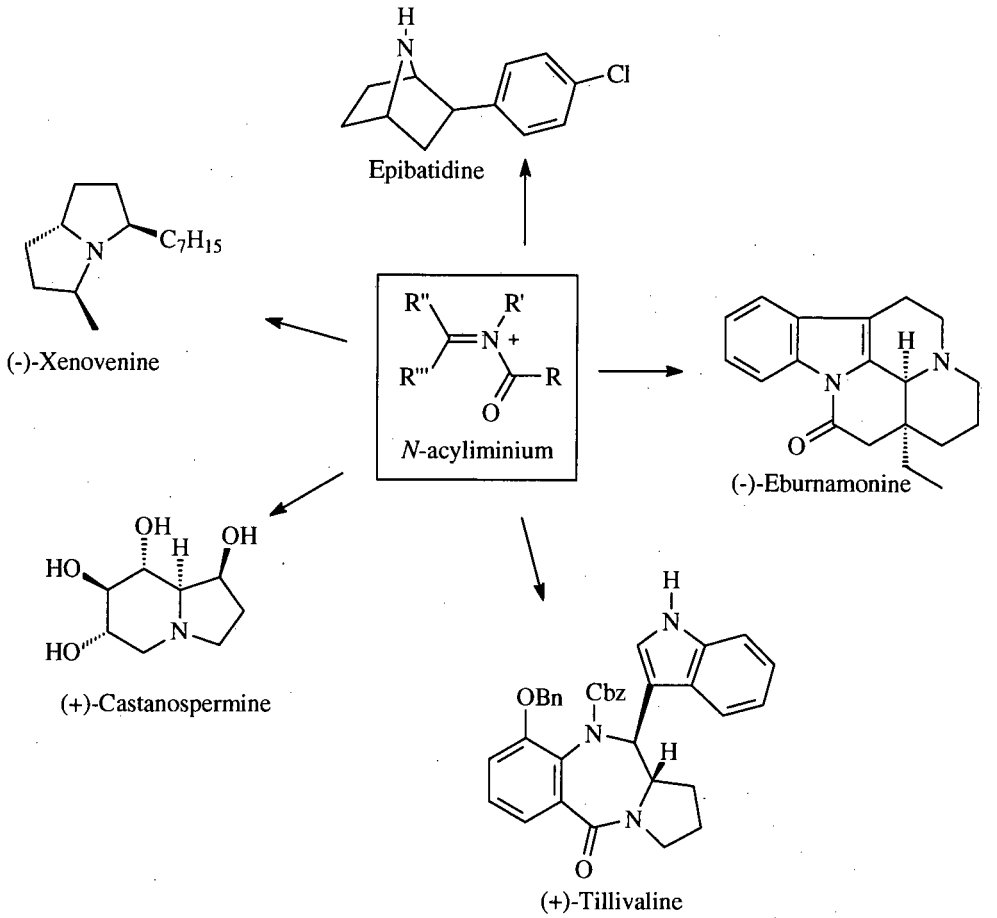
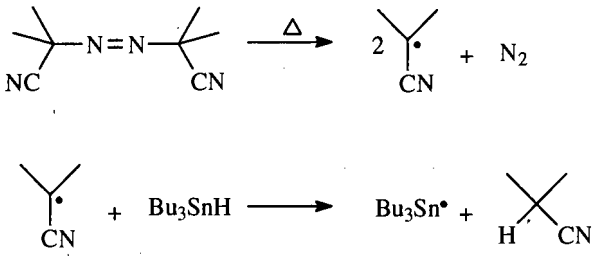


Figure 1.4 Alkaloids recently synthesised via *N*-acyliminium intermediates

1.1.1 (b) Radical Methodology

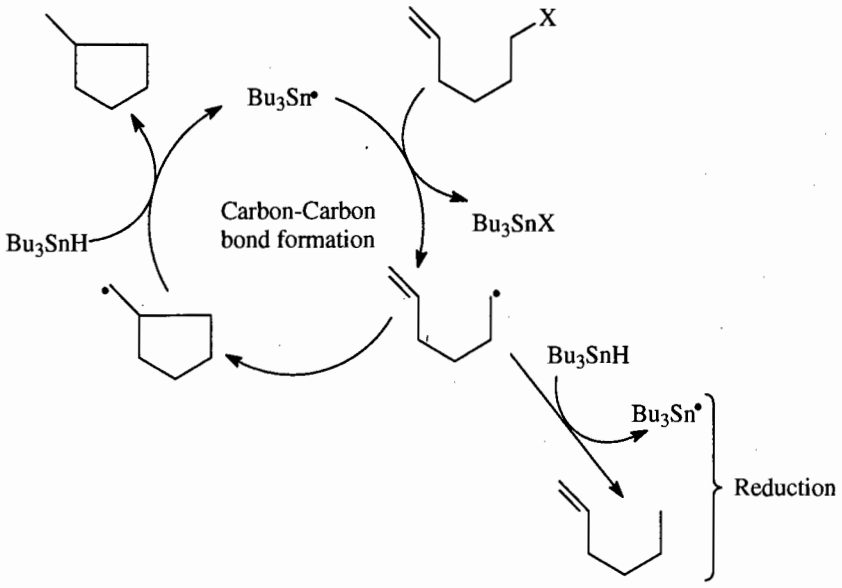
The use of radicals in organic synthesis is now widespread, since radical reactions have certain advantages over ionic reactions.[7] They generally have higher reaction rates and occur under milder, neutral conditions. They circumvent the need for functional group protection, and have early, reactant-like transition states that are generally less cluttered than ionic reactions (no counter-ion) and can thus accommodate crowded bond formation. Three distinct steps occur in radical reactions: initiation, propagation and termination. During the initiation step, the initiator *e.g.* azobisisobutyronitrile (AIBN), undergoes a thermally-induced homolytic cleavage to give a α-cyano radical that reacts with tributyltin hydride to generate a tributyltin radical (Scheme 1.9).



Scheme 1.9 Initiation

This tin radical abstracts X (where X is a halide, SPh, SePh, or OC(S)SMe) to give a carbon radical, in which the driving force is formation of the strong tin-X bond. For the propagation step, the radical then attacks a double bond to form a new carbon-carbon bond and the new radical thus generated then abstracts a hydrogen from a new tributyltin hydride molecule to regenerate the tin radical.

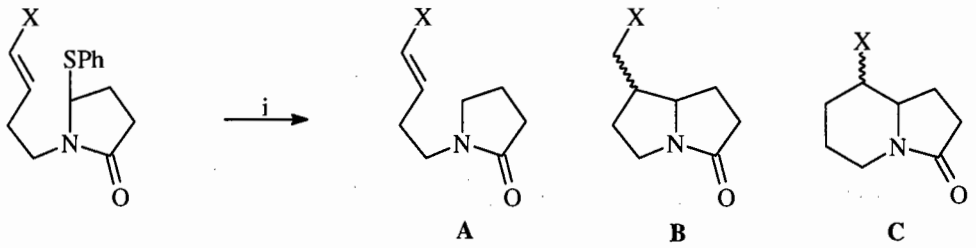
There is a competitive reaction involving the initial carbon radical and tributyltin hydride itself resulting in reduction of RX. The formation of a new carbon-carbon bond only occurs if the rate of addition to the double bond it greater than the rate of reduction. To minimize the risk of reduction the tributyltin hydride concentration is kept as low as possible by the slow dropwise addition of the reagent to the reaction mixture. The general mechanism for the formation of a carbon-carbon bond onto a double bond using tin radicals is illustrated (Scheme 1.10).



Scheme 1.10 Propagation

The construction of carbon-carbon bonds adjacent to nitrogen using radical methods had been largely overlooked until the early 1980's, when Hart demonstrated the versatility of intramolecular α-acylamino radical cyclisations for synthesis of indolizidines and pyrrolizidines.[8] Having established that α-chlorolactams were unmanageable as radical precursors, attention was directed at sulfides and it was found that α-phenylthiolactams were most suitable. This has allowed the preparation of reasonably complicated compounds using a synthetically easy method.[9]

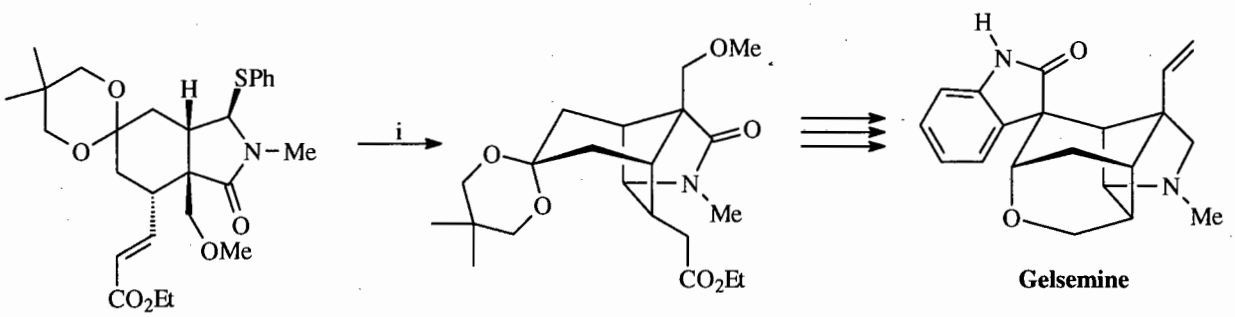
As expected, the cyclisations follow Baldwin's rules in which the 5-*exo* and 6-*exo* modes are faster than the corresponding *endo* modes. However, the proportion of *endo* product in the nitracycle is higher than in the corresponding carbocycle, especially when forming 5-membered rings. To combat this the cyclisation can be directed to the *exo* mode by the inclusion of an electron-withdrawing group at the alkene terminus (Scheme 1.11). According to FMO theory the singly occupied molecular orbital (SOMO) of the radical interacts with the lowest unoccupied molecular orbital (LUMO) of the alkene, with the rate of addition being affected by the substituents on the alkene. Electron withdrawing groups on the alkene lower the energy of the LUMO, increasing the addition rate by reducing the SOMO-LUMO energy difference.



Scheme 1.11 *Reagents and conditions:* (i) *n*-Bu_3SnH, AIBN (catalytic amount), PhH; X = CH_3, A = 13%, B = 47%, C = 23% yield;
X = CN, A = 0%, B = 85%, C = 0% yield

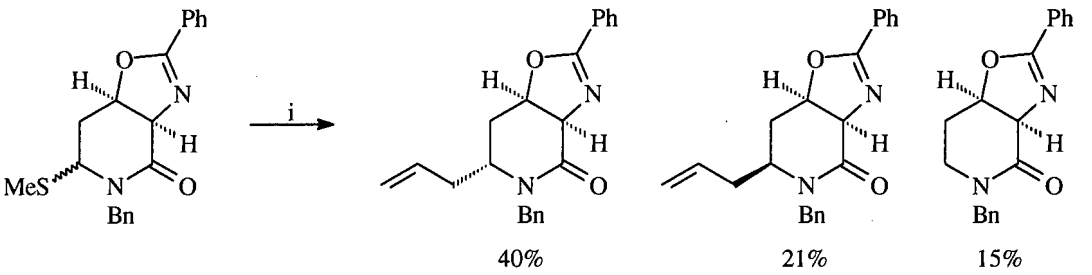
The acyl group plays an important role. When Padwa[10] attempted similar radical cyclisations with α-amino radicals, he only achieved reduction of the phenylsulfanyl group and no cyclisation occurred. From this result it was concluded that the rate of cyclisation is related to the stability of the radical formed. In α-acylamino radicals the electron-withdrawing effect of the acyl group retards the electronic assistance the amino group gives to the radical centre, resulting in a less stable radical. The electronic effect of the acyl is to raise the SOMO energy, increasing interaction with the LUMO acceptor. This enhances the reactivity of the radical towards "soft" cyclisation.

Not surprisingly, the intramolecular cyclisation of α-acylamino radicals has emerged as a powerful methodology for alkaloid synthesis. Synthetic targets using this methodology include complicated alkaloids such as gelsemine. In Hart's synthesis of this alkaloid,[11] the key transformation was an intramolecular acylamino radical cyclisation to prepare the tricyclic core (Scheme 1.12).



Scheme 1.12 *Reagents and conditions:* (i) *n*-Bu_3SnH, AIBN (cat), PhH

Intermolecular alkylation of α-acylamino radicals has been less successful. Naito achieved moderate yields in the radical reaction of a methylsulfanyl lactam with allyltributyltin under photochemical conditions[12] (Scheme 1.13).

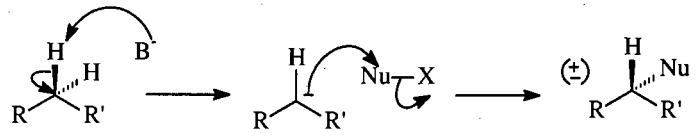


Scheme 1.13 *Reagents and conditions:* (i) CH_2=$CHCH_2SnBu_3$, *hv*, MeCN-toluene

Jones, however, obtained low yields and very poor diastereoselectivites in similar reactions of pyrrolidines and piperidines carrying a chiral auxiliary on nitrogen.[13] The poor diastereoselection was attributed to the nature of the transition state of the reaction. The transition state is early, when the radical and reactant are far apart, as a result of the high reactivity of the radical. Consequently steric effects have a weak influence over the stereochemical outcome.

1.1.1 (c) Carbanionic Methodology

Electrophilic substitution alpha to nitrogen is an inversion of the customary reactivity at this position (Umpolung). To achieve this, carbanionic methodology needs to be utilised. Carbanions are formed by a heterolytic cleavage via either a metal-hydrogen exchange or a metal-X (X = halogen, tin, sulfur) exchange, to give a weak ionic bond between the metal and the newly formed carbanion. Of these, the more common method is the metal-hydrogen exchange of an acidic proton using a base such as sodium hydride, butyllithium or lithium diisopropylamide. The less stabilized the carbanion is by adjacent functionality, the stronger the base needed to remove the proton. Carbanions are utilised in the formation of new bonds, with C-C bond formation of interest in this context. The carbanion attacks electophiles such as alkyl halides or electrophilic double bonds (Scheme 1.14).

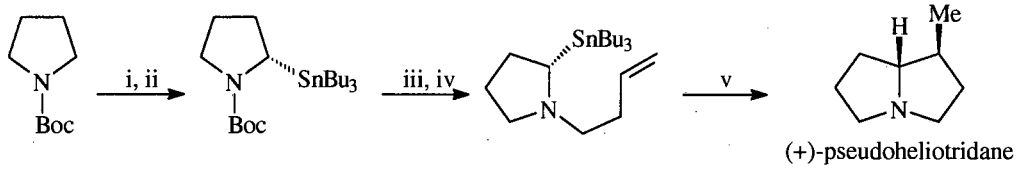


Scheme 1.14 Carbanionic formation and alkylation

α-Amino carbanions can be classified as stabilized or non-stabilized. Stabilized α-amino substituted carbanions are those with any stabilizing group on the anionic carbon or on the nitrogen (*e.g.* acyl). Non-stabilized α-amino carbanions contain solely alkyl or benzylic groups.

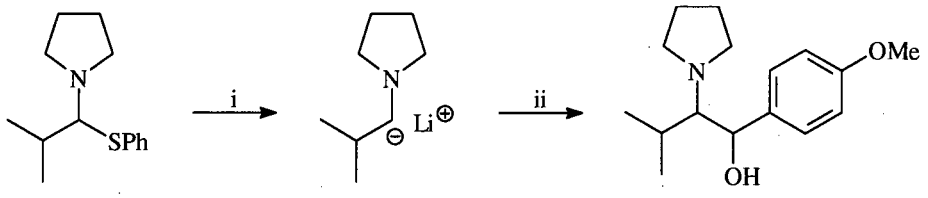
Non-stabilized α-amino carbanions

Problems arise with generation of non-stabilized α-amino carbanions, in that the direct deprotonation of tertiary amines is difficult. This led to the development of indirect methods.[14] Most widespread of these is the transmetallation of α-aminostannanes, introduced by Peterson.[15] In a number of syntheses the stannane is formed from a stabilized amino carbanion and the stabilizing group is subsequently removed. A notable application[16] of this methodology was in the synthesis of (+)-pseudoheliotridane in high yield (87%) with excellent stereoselectivity (94% ee) (Scheme 1.15).



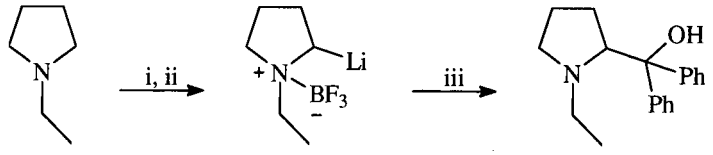
Scheme 1.15 *Reagents and conditions:* (i) ^{s}BuLi, (-)-sparteine, Et_2O, -78°C (ii) Bu_3SnCl, Et_2O (iii) *B*-bromocatechol borane, CH_2Cl_2; but-3-enoyl chloride (iv) AlH_3, Et_2O, 0°C (v) ^{n}BuLi, hexane-ether (10:1), -78°C to r.t., (ii) MeOH -78°C

Another method is by reductive lithiation of α-amino sulfides using lithium naphthalenide or lithium di-*tert*-butylbiphenylide (LiDBB) (Scheme 1.16).[17]



Scheme 1.16 *Reagents and conditions:* (i) LiDBB, THF, -95°C (ii) *p*-anisaldehyde

Lewis acids have also been used to promote α-deprotonation. The positive charge developed on coordination of the nitrogen lone pair to a Lewis acid, inductively facilitates the α-deprotonation of this preformed amine-Lewis acid complex (Scheme 1.17).[18]

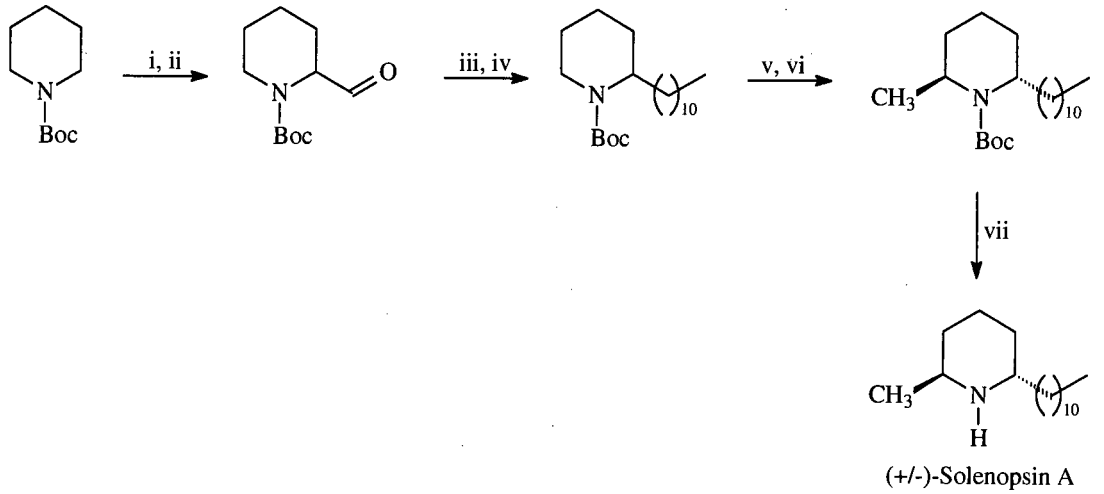


Scheme 1.17 *Reagents and conditions:* (i) $BF_3.Et_2O$ (ii) ^sBuLi / ^tBuOK (iii) Ph_2CO, 85%

Stabilized α-amino carbanions

Owing to the difficulty in generating unstabilized α-amino carbanions, the stabilized equivalent has seen far more synthetic activity. These usually contain a temporary activating group on nitrogen to facilitate deprotonation to give a dipole-stabilized carbanion that can then be intercepted by an electrophile, followed by removal of the auxiliary activator. The most widely utilized activating groups are amide, formamidine, oxazoline, and nitroso functionalities.

Early work using amides showed them to be effective activators but the conditions for the addition and removal of the group were harsh. More recently, Beak has demonstrated that the *tert*-butoxycarbonyl (Boc) group is an effective activator, with the advantage of easy addition and cleavage. Thus the Boc derivatives of cyclic secondary amines were α-lithiated using s-butyllithium and a variety of electrophiles were successfully introduced. Two such transformations were used in synthesis of the piperidine alkaloid Solenopsin A[19] (Scheme 1.18). The overall yield for the synthesis was 49% from *N*-Boc-piperidine.

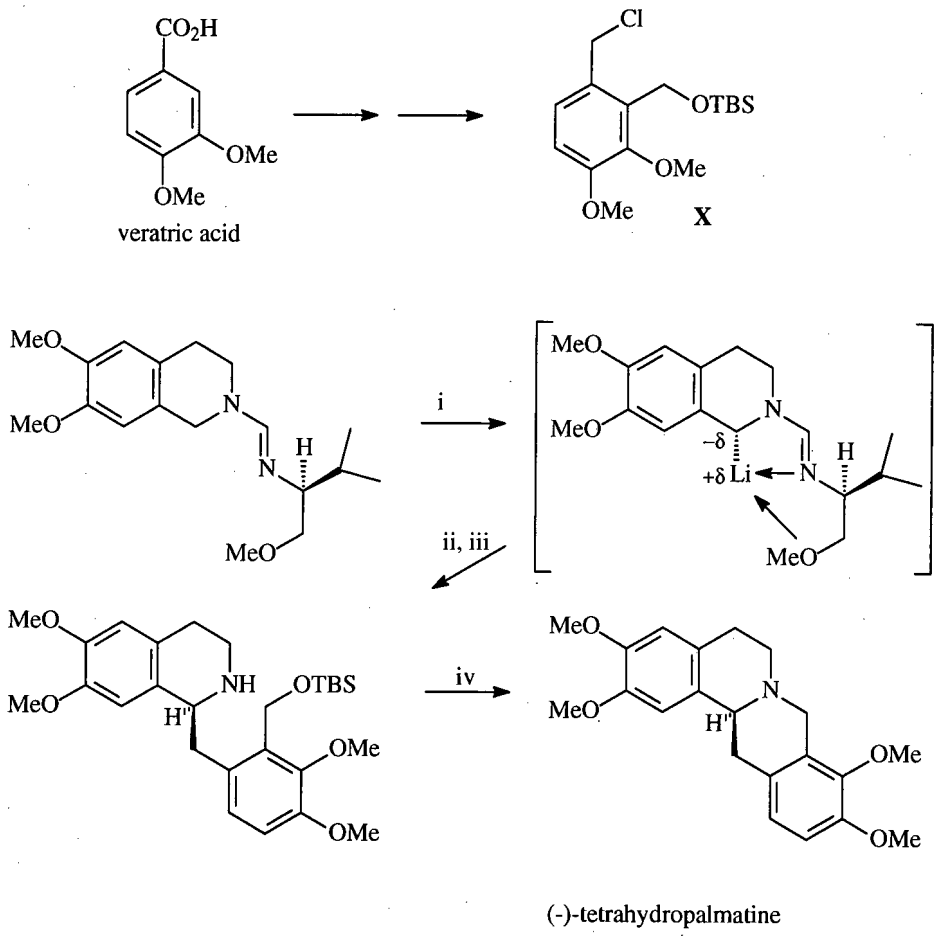


Scheme 1.18 *Reagents and conditions:* (i) ^{s}BuLi (ii) DMF (iii) $Ph_3P{=}CH(CH_2)_8CH_3$ (iv) H_2, Pd/C (v) ^{s}BuLi (vi) Me_2SO_4 (vii) TFA

Similarly, Meyers has developed formamidine methodology for the construction of a number of alkaloids using this group to promote formation of the carbanion, followed by selective removal of the group later in the synthesis.[20]

A good example of the latter is the total synthesis[21] of the protoberberine alkaloid, (–)-tetrahydropalmatine (Scheme 1.19), in which the stereogenic centre is constructed by utilising α-stabilized carbanions that are activated by chiral formamidines.

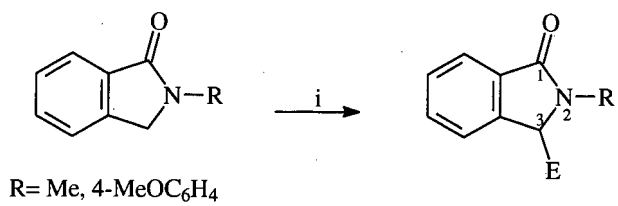
The benzyl chloride **X** was synthesised in three steps from veratric acid and reacted with the carbanion of a chiral formamidine to give the alkylated product. The chiral auxiliary directed lithium coordination to the α-face resulting in exclusive alkylation on the unobstructed β-face. It was subsequently removed, and the berberine bridge closed to give the desired product (88% ee).



Scheme 1.19 *Reagents and conditions:* (i) ^{t}BuLi, -78°C (ii) -105°C, **X** (iii) $N_2H_4.H_2O$ (iv) Ph_3P, Br_2

Chiral oxazolines have been used in a similar fashion to dialkylate isoindolines.[22]

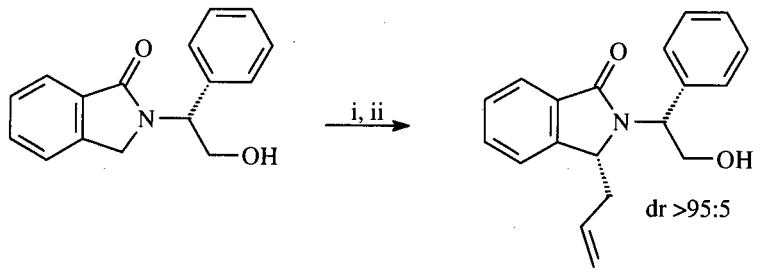
Benzylic alkylation on isoindolinones have been carried out by Couture.[23] Deprotonation with LDA followed by alkylation with a wide variety of electophiles (Scheme 1.20) and reduction allowed synthesis of a range of 3-substituted isoindolines.



R= Me, 4-MeOC$_6$H$_4$

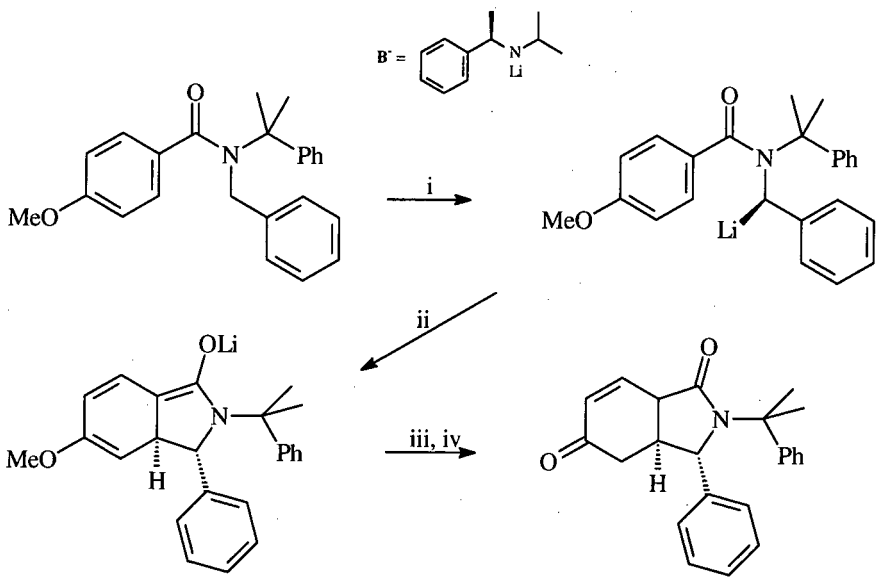
Scheme 1.20 *Reagents and conditions:* (i) LDA, THF, -78°C (ii) E^+, THF, -78°C to rt (iii) H_3O^+

In this case the activating group, the *N,N*-dialkylcarboxamide, is embedded in the skeleton of the molecule promoting the metallation without the need for a removable activating group on nitrogen. This work has since been extended to the synthesis of 3-alkyl-2,3-dihydro-1*H*-isoindol-1-ones by use of a protecting group on nitrogen[24] and the diastereoselective addition of metallated isoindol-1-ones to aldehydes.[25] Recently Royer developed an asymmetric synthesis of 3-alkyl-isoindolin-1-ones.[26] A chiral 2-hydroxy-1-phenylethyl appendage on nitrogen gave highly diastereoselective alkylation in modest yields (Scheme 1.21).



Scheme 1.21 *Reagents and conditions:* (i) LiHMDS, THF, -78°C (ii) Allyl bromide, 39%

The Clayden[27] group has constructed partially saturated isoindolones in a completely different fashion. The approach involves use of chiral lithium amide bases to give enantiomerically enriched benzylic organolithiums followed by a dearomatizing cyclisation of the pyrrole ring. The reaction occurs in good yield and enantiomeric excess. The *ee* could be improved to >99% by one recrystallisation.

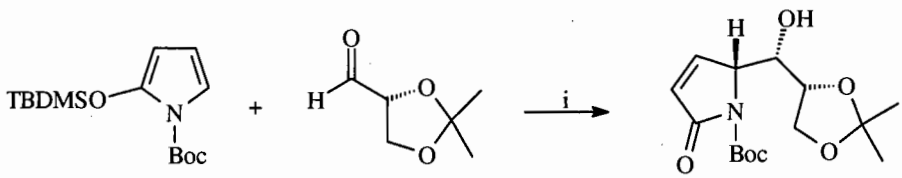


Scheme 1.22 *Reagents and conditions:* (i) B⁻, LiCl, THF (ii) –78°C to 0°C (iii) NH_4Cl, H_2O (iv) HCl, H_2O, 88% yield, 81% ee

In the reaction of isoindolone derivatives, alkylation can only occur at the 3-position directed by the rearomatisation of the 6-membered ring. However, when this methodology is extended to the pyrrolidine equivalent, alkylation can occur at the 3- or 5-position (Figure 1.5).

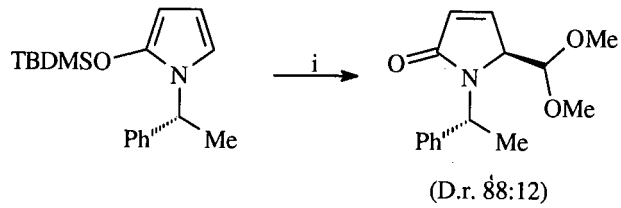
Figure 1.5 Alkylation of isoindolone *vs* pyrrolidinone

To ensure regioselective alkylation at only the 5-position of pyrrolidines, carbanionic α-alkylations have been extended to silyl enol ether chemistry. The dienol silyl ether is a soft nucleophile and reacts with the *ate* complex formed between a soft electrophile and a Lewis acid. The reaction is regioselective at the softer 5-position of the ambident nucleophile. Thus an approach that has become popular in the synthesis of 5-substituted pyrrolindinones is the Lewis acid-mediated Mukaiyama-type aldol reaction of 2-silyloxypyrroles, a 1,5-dihydro-2-pyrrolidinone 5-anion equivalent.[28] It was first reported by Ricci[29] in 1984 that N-methylsilyloxypyrroles could be regioselectively reacted with electrophiles at the C-5 position. The Casiraghi group extended this methodology using *N-t*-Boc-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP), prepared by reaction of *tert*-butyldimethysilyl trifluoromethanesulfonate with the *N-t*-Boc derivative of pyrrolinone in the presence of 2,6-lutidine. This was initially used for the synthesis of hydroxylated pyrrolidine derivatives[30] (Scheme 1.23).



Scheme 1.23 *Reagents and conditions:* (i) $SnCl_4$, Et_2O, -85°C, 80%

The Poli group were the first to study[31] the stereoselective aspects of reaction of a chiral 2-silyloxypyrrole with achiral and chiral formyl cation equivalents. The Lewis-acid-promoted reaction with trimethyl or triethyl orthoformate occurred with good diastereoselectivity (Scheme 1.24), whereas the use of a nor-ephedrine-derived electrophilic C-1 reagent gave a totally diastereoselective reaction.



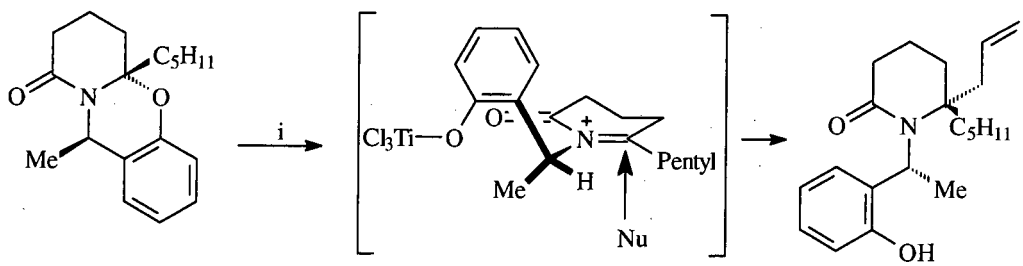
(D.r. 88:12)

Scheme 1.24 *Reagents and conditions:* (i) $BF_3.Et_2O$, $HC(OCH_3)_3$, CH_2Cl_2, -78°C, 66%

Similar studies have involved the reaction of a chiral 2-silyloxypyrrole with achiral aldehydes.[32]

1.1.2 Tertiary aza Construction

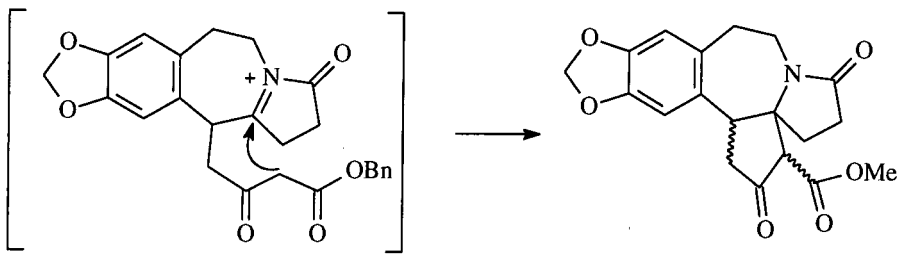
As with secondary aza centres, *N*-acyliminium intermediates have featured prominently in construction of tertiary aza centres in alkaloids. Intermolecular formation of this centre has been achieved with many substrates including pyrrolidinones[33] and isoindolones.[34] The stereoselectivity of the intermolecular reaction of allyltrimethylsilane with a pyrrolidinone-derived cyclic *N*-acyl-*N,O*-acetal incorporating various chiral auxiliaries has been studied.[35] A similar transformation was used in a synthesis of the piperidone alkaloid adalinine. In the synthesis[36] of the natural enantiomer, the chiral centre was formed by the Lewis acid-mediated allylation at high temperature of a cyclic *N*-acyl-*N,O*-acetal incorporating a chiral auxiliary (Scheme 1.25).



Scheme 1.25 *Reagents and conditions:* (i) AllylTMS, $TiCl_4$, CH_2Cl_2, 50°C

Two groups[37,38] have reported difficulty in the allyation of bicyclic lactams. Instead of a tertiary aza product, an enamide was produced. The cyclisation of tertiary hydroxylactams derived from the Grignard reaction of imides has successfully been used for the construction of azaspirocycles.[39] The cyclisation of a tertiary acyliminium ion onto a silyloxyfuran has also been achieved.[40]

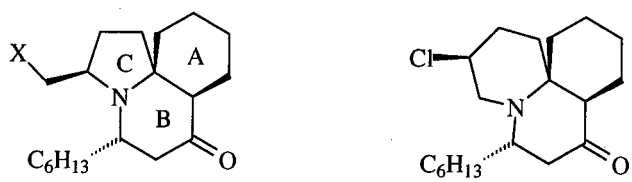
Intramolecular N-acyliminium cyclisations have also featured in tertiary aza formation for the synthesis of the biologically active *Cephalotaxus* alkaloids. The esters of cephalotaxine, such as harringtonine and homoharringtonine show antileukemic activity, and homoharringtonine has been examined for activity against chloroquine-resistant malaria. A recent synthesis[41] of racemic cephalotaxine utilized N-acyliminium intermediates in three transformations, the last of which was the construction of the cyclopentopyrrolobenzazepine ring system (Scheme 1.26).



Scheme 1.26 *N-acyliminium use in Cephalotaxine alkaloid synthesis*

A range of other methodologies has been employed for the tertiary aza formation in these alkaloids, such as palladium-catalyzed spirocyclisation,[42] Nazarov cyclisation,[38] or even simple alkylation of an enolate.[43]

A group of recently discovered alkaloids that has received a great deal of synthetic attention are the cylindricines. These tricyclic alkaloids were isolated from marine tunicates in the 1990s. The cylindricines (Figure 1.6) were isolated by Blackman *et al.* from the ascidian *Clavelina cylindrica* collected off the coast of Tasmania,[44] and by examination of the A/B-ring fusion, the cylindricines can be described as *cis*-azadecalin derivatives.



cylindricine A: X = Cl
C: X = OH
D: X = OMe
E: X = OAc

cylindricine B

Figure 1.6 The cylindricines

The related compound, fasicularin (Figure 1.7), was isolated from ascidian *Neptheis fasicularis* collected in Micronesia.[45] This compound has stirred interest because of its biological activity against a DNA repair-deficient strain of yeast. It has a *trans*-azadecalin A/B-ring fusion.

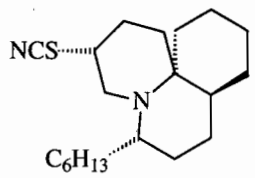
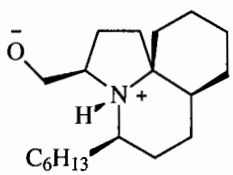
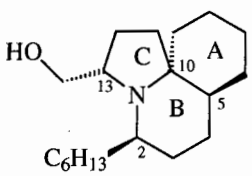


Figure 1.7 Fasicularin

In 1994 the compound lepadiformine (Figure 1.8) was isolated by the Biard group from the tunicate *Clavelina lepadiformis* collected in the Mediterranean near Tunisia. It has shown moderate *in vitro* cytotoxic activity against several tumor cell lines making it a good lead compound in drug discovery. Synthetic interest in this compound has thus been intense. The structure was originally assigned[46] as a cyclidricine *cis*-azadecalin skeleton in an unusual zwitterionic form (Figure 1.8). However Wienreb *et al.* demonstated by total synthesis of this proposed structure that the assignment was incorrect.[47] Pearson *et al.* synthesised the other 3 diastereomers at C-2 and C-13, none of which corresponded to the data for natural lepadiformine.[48] This suggested that lepadiformine belonged in the fasicularin *trans*-azadecalin stereochemical series. Kibayashi confirmed this view by synthesising a compound in a non-zwitterionic form that was identical to natural lepadiformine by spectral comparison.[49] Thus lepadiformine has demonstrated the value of total synthesis in natural product structure elucidation.[50]



Original Structure

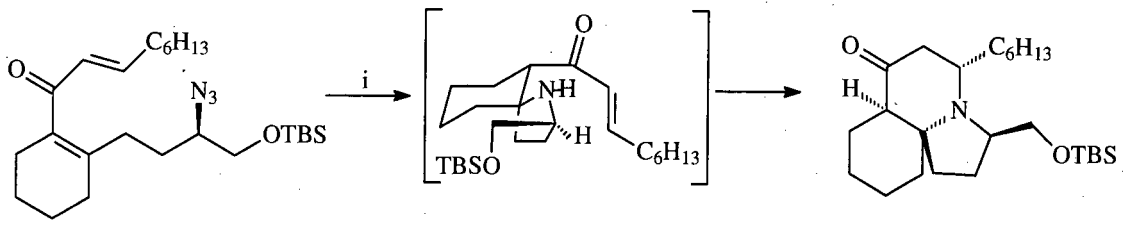


Revised Structure

Figure 1.8 Lepadiformine

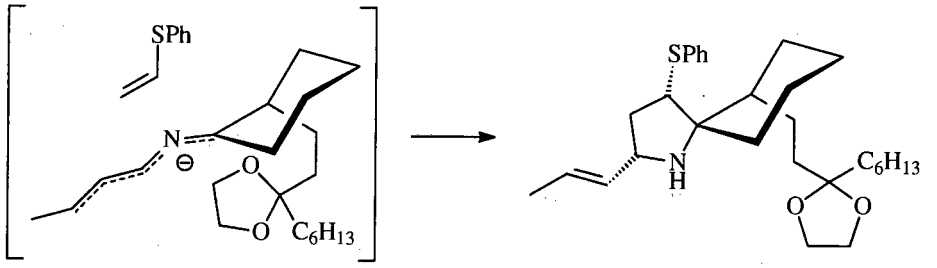
The biggest challenge in the synthesis of these alkaloids is the production of the requisite stereochemistry for the A/B-ring fusion, which includes the tertiary aza centre. Methodologies for the stereocontrolled formation of this portion have been confined to 3 types: Michael additions, cycloadditions and iminium intermediates.

Three groups have used double Michael additions for the synthesis of cylindricines. Snider[51] used the double Michael addition of ammonia to a diene in synthesising cylindricine A, D and E. A very similar approach[52] was taken by Heathcock to synthesise cylindricine A and B. In the total synthesis of (-)-cylindricine C by Molander, an azide is reduced to the corresponding amine which then undergoes a double Michael addition.[53] This reaction is the highlight of this synthesis, forming 3 new stereocentres with good selectivity (Scheme 1.27).



Scheme 1.27 *Reagents and conditions:* (i) $CrCl_2$, H_3O^+

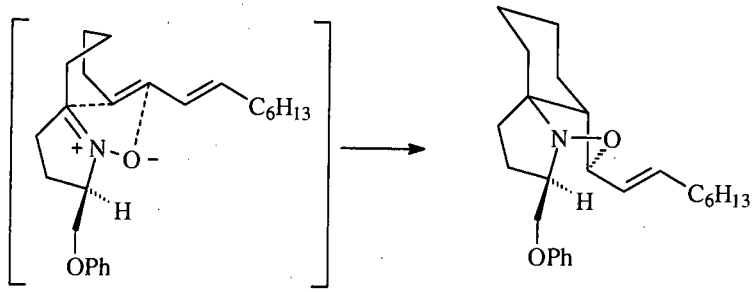
The first synthetic activity towards the constuction of lepadiformine was by Pearson *et al.* using a 2-azapentadienyl anion cycloaddition with phenyl vinyl sulfide.[54] The relative configurations of C-5 and C-10 resulted from cycloaddition from the face of the 2-azapentadienyl anion opposite to the side chain (Scheme 1.28), and the cycloadduct could be elaborated to 3 diastereomers of lepadiformine at C-2 and C-13.



Scheme 1.28 Pearson's azapentadienyl anion cycloaddition

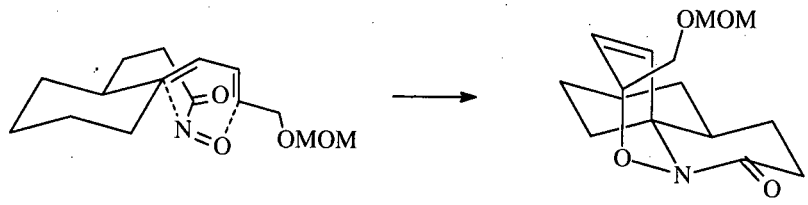
Weinreb *et al.* synthesised the putative stucture of lepadiformine using an intramolecular nitrone/diene dipolar cycloaddition as the key step.[47] A transition-state model that accounts for the observed stereoselectivity suggests a conformation as shown in which the bridging chain adopts a

boatlike conformation for stereoelectronic reasons, and the olefin approaches the face of the nitrone opposite to the phenoxymethyl group for steric reasons (Scheme 1.29).



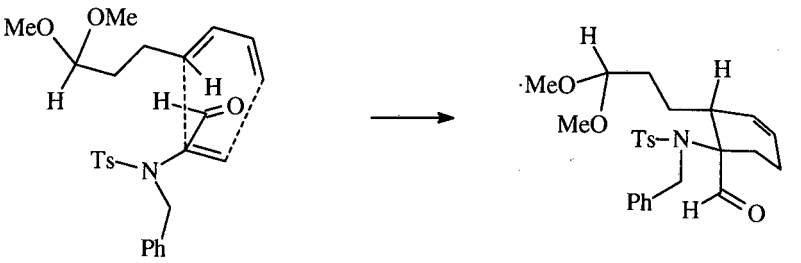
Scheme 1.29 Weinreb's nitrone/diene dipolar cycloaddition

Oppolzer *et al.* have also used an intramolecular nitrone/diene dipolar cycloaddition in their synthesis of the spirocyclic skeleton of the cylindricine group of alkaloids.[55] The first racemic synthesis of natural lepadiformine was achieved by the Kibayashi group using an intramolecular acylnitroso-Diels Alder reaction as the key step.[49] The cyclisation of the acylnitroso compound favoured formation of the *trans*-fused tricyclic lactam by adopting an *endo* transition-state that avoids unfavourable steric interactions, and in which the tethering side chain is positioned equatorially (Scheme 1.30).



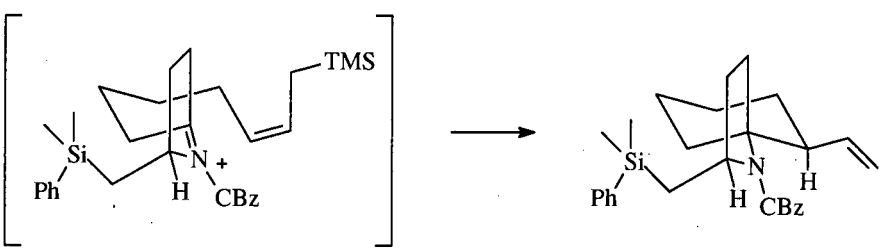
Scheme 1.30 Kibayashi's intramolecular acylnitroso-Diels Alder reaction

Another cycloaddition approach has been used by Funk and Greshock in their racemic synthesis of lepadiformine.[56] The key step involved the intramolecular cycloaddition of a 2-amidoacrolein with the dimethyl acetal of 4,6-heptadienal in a regio- and *endo*-selective manner to establish the eventual *trans*-perhydroquinoline stereochemistry (Scheme 1.31).



Scheme 1.31 Funk's intramolecular amidoacrolein cycloaddition

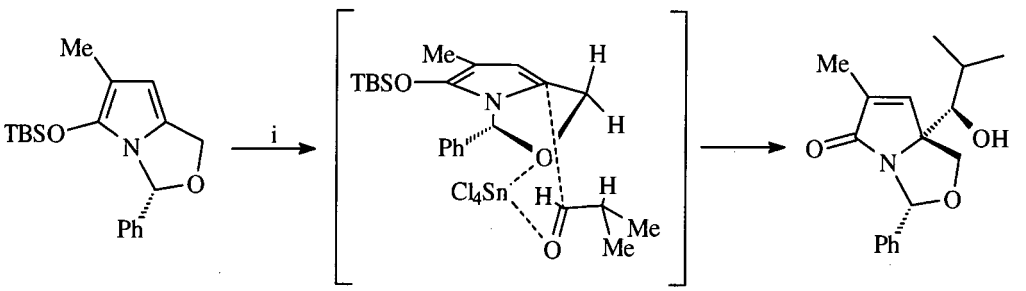
In a non-cycloaddition approach[57] to lepadiformine, Weinreb *et al.* recently achieved the first synthesis of its natural enantiomer starting from (*S*)-pyroglutamic acid. The crucial step involved the intramolecular attack of an allylsilane onto the sterically less hindered face of an acyliminium ion to give the A/C-ring sprirocycle (Scheme 1.32), again demonstrating the versatility of *N*-acyliminium ions in these transformations. The spirocycle was elaborated to the natural enantiomer of lepadiformine, shown in Figure 1.8.



Scheme 1.32 Weinreb's intramolecular acyliminium spirocyclisation

Subsequently, Kibayashi also synthesised the natural enantiomer *via* an *N*-acyliminium-ion-initiated azacyclisation.[58] This efficient synthesis gave lepadiformine in 31% overall yield. The cylindricine skeleton has been obtained by Speckamp using Kulinkovich conditions to obtain a *N,O*-acetal followed by intermolecular cyclisation of an acyliminium ion.[37]

Little attention has been given to tertiary aza formation involving bond formation *via* a nucleophilic α-carbon to nitrogen. A notable example in this regard is the key reaction in Baldwin's total synthesis of the neurotrophic factor (+)-lactacystin from (*R*)-glutamate, involving a stereoselective Mukaiyama-type aldol reaction of a silyloxypyrrole with an aldehyde (Scheme 1.33). The stereoselectivity of this reaction was achieved using chelation control with tin chloride and occurred with unexpected facial selectivity, adding to the same face as the phenyl substituent.[59]



Scheme 1.33 *Reagents and conditions:* (i) isobutyraldehyde, $SnCl_4$, Et_2O, -78°C

1.2 Overview of Thesis Objective

It is clear from the survey of secondary aza construction that more methodologies have centred on the use of iminium ions as key intermediates than on carbanionic and radical intermediates. Similarly, for tertiary aza construction, most methodologies have used iminium ion intermediates or cycloaddition reactions. Thus in identifying a specific research objective, it was considered that in the light of literature already reviewed, scope still existed for further research into carbanionic and radical methodologies for the stereocontolled formation of stereogentic centres alpha to nitrogen in alkaloid synthesis.

Consideration of relevant methodological factors resulted in identifying the following structural motif for exploration of both the radical and carbanionic approaches, which is shown below (Figure 1.9).

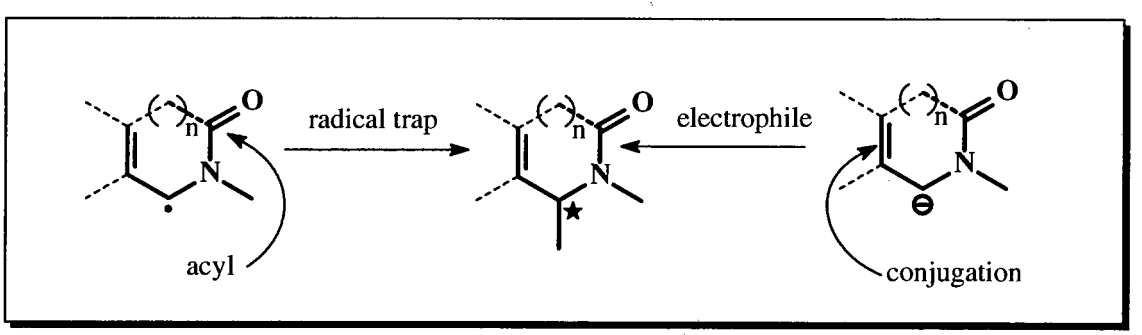


Figure 1.9 Motif to explore radical/carbanionic alkylations α to nitrogen

The factors involved the following. The acyl group has a destabilising effect on an α-acylamino carbon radical making it more reactive than its α-alkylamino equivalent, whereas it stabilizes a

carbanion allowing deprotonation to occur more easily. The conjugation is introduced to aid in stabilization of a carbanion and also provides the flexibility to access alkaloids possessing some aromaticity as well as to access aliphatic alkaloids (through reduction of the double bond). The acyl carbonyl may enhance this conjugation depending on n.

1.2.1 Formation of Secondary aza Centres

The scaffold just described lends itself to the construction of alkaloids in which the stereocentre is benzylic (Figure 1.10).

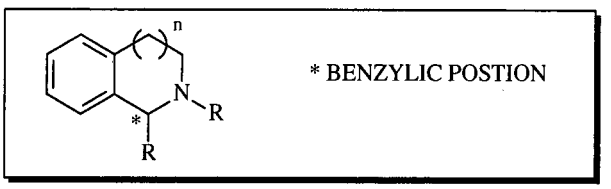


Figure 1.10 Chiral benzylic alkaloid framework

The Tacaman alkaloids and the isoindolone alkaloids are good examples of these, and these systems were initially chosen for developing the methodology of interest to us. The alkaloid Tacamonine (Figure 1.11) was isolated in 1982 by Van Beek[60] from the liane *Tabernaemontana eglandulosa*. The structure falls in the same class as a number of pharmacologically active alkaloids, such as vincamine, making it a synthetically interesting target.[61,62] Most syntheses of Tacamonine have utilized conventional Bischler-Napieralski and Pictet-Spengler methodology for formation of the C-2/C-3 bond, thus vindicating the choice of scaffold.

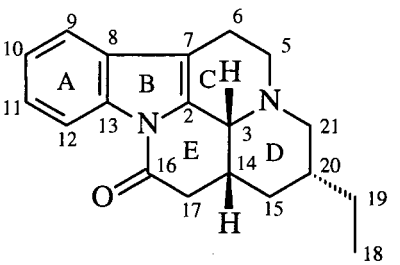
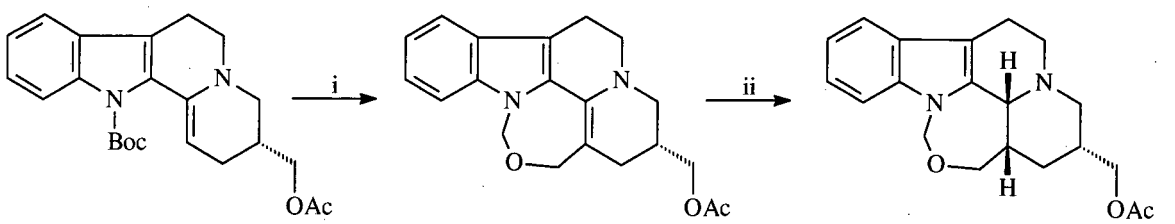


Figure 1.11 (+)-Tacamonine

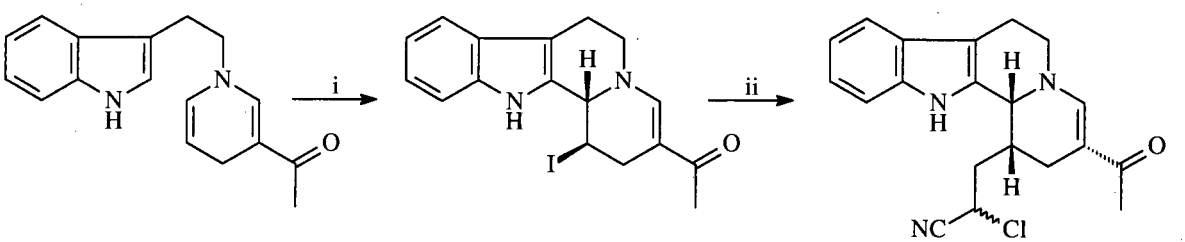
Syntheses that have utilized Bischler-Napieralski reactions require a stereoselective reduction of the iminium ion intermediate to obtain the required *cis*-stereochemical relationship at C-3 and C-14.

Fukomoto[63] experienced poor diastereoselectivity in this step in his asymmetric synthesis of Tacamonine. The recent synthesis by Ho[64] using Bischler-Napieralski methodology suffered from the same problem. Lesma's synthesis[65] has surmounted this problem (Scheme 1.34).



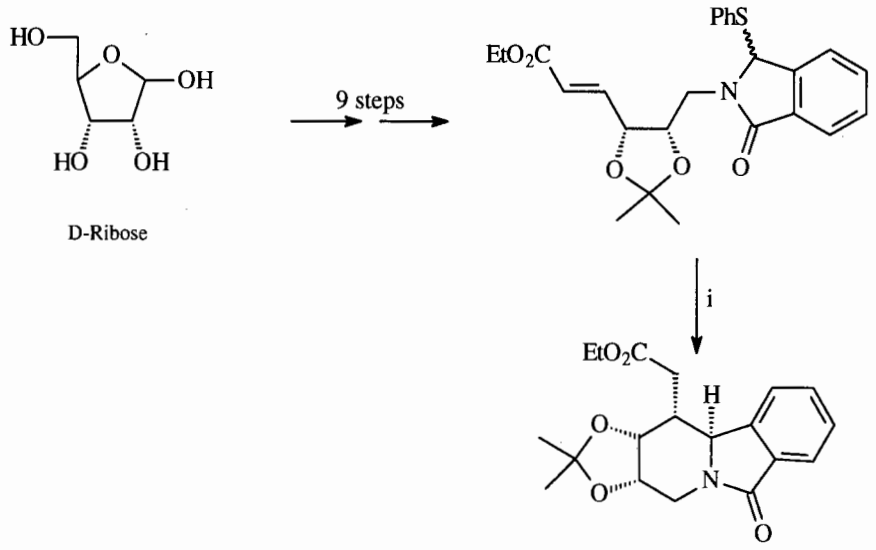
Scheme 1.34 *Reagents and conditions:* (i) $(CH_2O)_3$, THF, rt (ii) PtO_2, H_2, dioxane

In this synthesis the product of the Bischler-Napieralski reaction was converted to a pentacycle by heating with excess formaldehyde and catalytic formic acid. This could be stereoselectively hydrogenated due to the rigid framework holding the acetoxymethyl pseudo-axial, thus hindering approach from the bottom face. In a Pictet-Spengler approach, Ho reacted a chiral dinitrile with tryptamine, but the newly formed C-3 stereocentre translated to a trans D/E ring fusion.[66] A novel synthesis of Tacamonine was achieved by Lavilla[67] by performing a *non-biomimetic* oxidative halocyclisation followed by a Zn-mediated radical addition to α-chloroacrylonitrile with sonication to generate the *cis*-stereochemistry (Scheme 1.35).



Scheme 1.35 *Reagents and conditions:* (i) NIS, THF (ii) CH_2=C(CN)Cl, Zn, CuI, EtOH, H_2O,))))), rt

Interest in new approaches to Tacamonine gave birth to a model study from these laboratories prior to the study pertaining to this thesis involving the use of radical chemistry for construction of a suitably functionalised tetrahydropyrido[2,1-*a*]isoindolone.[68] The synthetic sequence to the radical precursor and cyclisation outcome is depicted (Scheme 1.36).



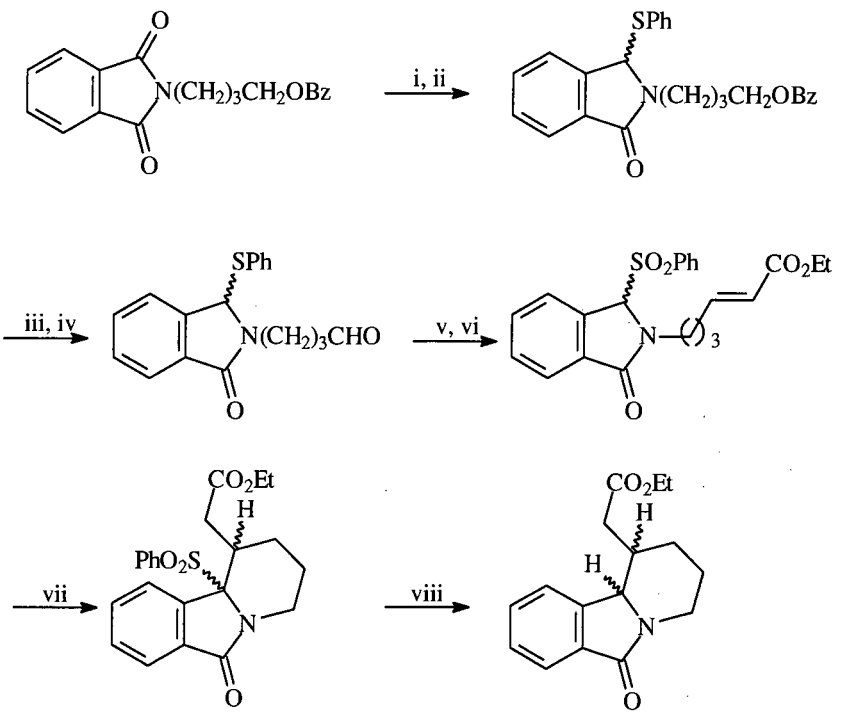
Scheme 1.36 *Reagents and conditions:* (i) Bu_3SnH, AIBN, Benzene, reflux

The study attempted to model the *cis* stereochemistry at the D/E Tacamonine ring junction, using a five-membered ring for the six-membered C-ring, and replacing indolo by phenyl. The ribose-derived side chain was prepared with an allylic/homoallylic ketal grouping present because this group had been reported[69] to show a strong directing influence in radical cyclisation of 6-membered rings. The α-phenylsulfanyl lactam was synthesised from D-ribose via the corresponding phthalimide over nine steps.

Although the radical cyclisation was highly stereoselective (8:2), the product displayed a *cis* relationship between the benzylic hydrogen and ethoxycarbonylmethylene group, translating to an undesirable *trans* D/E ring fusion in the Tacaman skeleton. All synthetic targets involving this kind of methodology that have been derived from an imide, have been derived from succinimide. In this synthesis the precursor was derived from phthalimide, as the first example involving a benzylic α-benzoylamino radical cyclisation in alkaloid synthesis. No reduction product was isolated in spite of the relative stability of the radical.

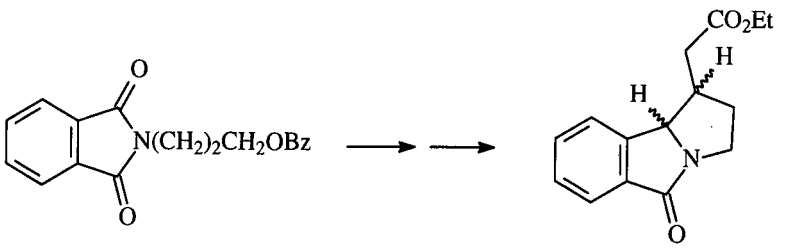
In a similar system cyclisation was achieved using carbanionic methods. Luzzio *et al.* synthesised isoindolones from a benzylic sulfone[70] using the acidity of the benzylic and α-sulfonyl proton and deprotonating with sodium hydride. The anion that was generated was successfully reacted intermolecularly with a variety of electrophiles and intramolecularly with an enoate ester to afford tricyclic tetrahydropyrido[2,1-*a*]isoindolone products.

The synthesis of Luzzio's cyclisation precursor is illustrated (Scheme 1.37). The phthalimide was reduced using an aluminium amalgam in a THF/water mixture to a hydroxylactam, which was then sulfenylated and saponified using lithium hydroxide in a water/methanol mixture to the corresponding alcohol. This alcohol was oxidised using PCC, and the resultant aldehyde reacted with ethoxycarbonylmethyltriphenylphosphorane generated *in situ* to give the α,β-unsaturated ester. The sulfide was then oxidised to the sulfone using MCPBA. Treatment of this sulfone with sodium hydride generated the sulfone-stabilized carbanion, which smoothly cyclised *via* a Michael addition to give a tricyclic product. This was then desulfurised using Raney® nickel to give a tetrahydropyrido[2,1-*a*]isoindolone as a 1:1 mixture of diastereomers (detected by NMR).



Scheme 1.37 *Reagents and conditions:* (i) Al(Hg), THF, H_2O, rt (ii) PhSH, *p*-TsOH, CH_2Cl_2, rt (iii) LiOH, H_2O, MeOH, rt (iv) PCC, silica gel, CH_2Cl_2, rt (v) $Ph_3P{=}CHCO_2EtBr$, NaOH, H_2O, CH_2Cl_2, rt (vi) MCPBA, CH_2Cl_2, rt (vii) NaH, DMSO, THF, rt (viii) Raney® nickel, ultrasound, EtOH

The pyrroloisoindolone analogue was synthesised using the same synthetic sequence as a 4:1 mixture of diastereomers (Scheme 1.38).



Scheme 1.38 Luzzio's synthesis of pyrroloisoindolones

In light of the earlier work by our group and work by Luzzio, it was apparent that the model study of Tacamonine could be extended by modification of the cyclisation precursor and the use of carbanionic and radical intermediates. Generation of the revised cyclisation precursor (Figure 1.12) would allow both cyclisation methodologies to be studied from one substrate in search of an enhanced diastereoselectivity modeling the *cis* D/E Tacamonine ring junction.

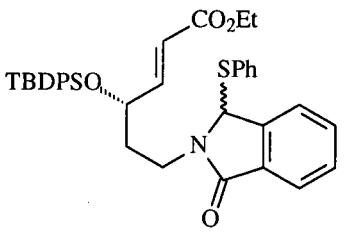


Figure 1.12 Cyclisation precursor

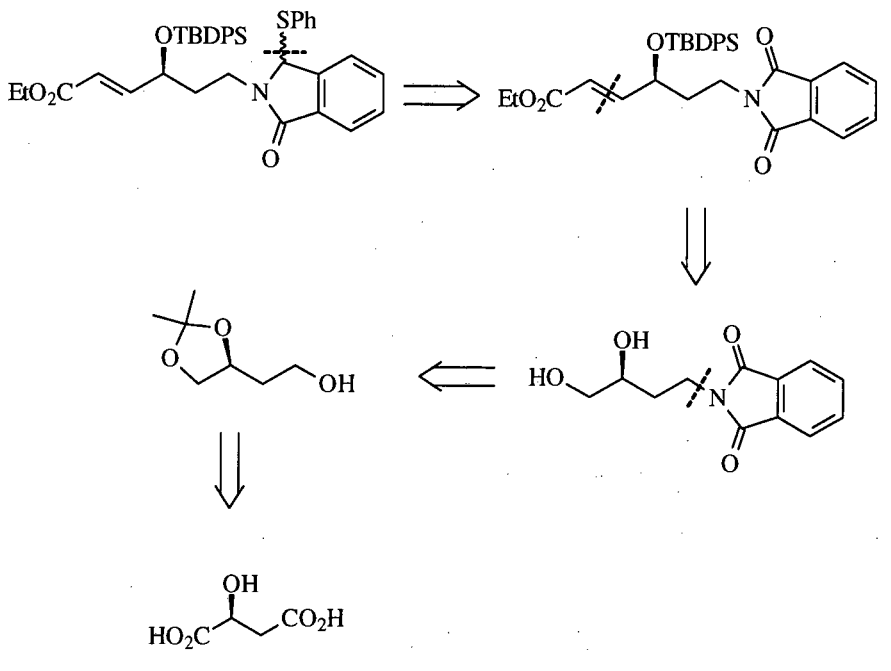
In the original model study the stereochemistry obtained in the cyclisation product translated to an undesired *trans* D/E ring junction in the Tacaman skeleton. The *cis*-fused ketal promoted two chair-like transition-states in which each C-O substituent was pseudoequatorial. Each transition-state could have lead to different stereochemical outcomes. Thus it was rationalised in this project that it would be better to have one chiral centre in the side chain promoting a single chair form in the transition state of the cyclisation. An allylic hydroxyl centre bearing a bulky protecting group was chosen as the stereodirecting centre such that it could be easily removed after the cyclisation. Secondary hydroxyl centres are commonly found in many chiral pool compounds, and the steric influence of this group would impart a facial bias on the cyclisation. Thus the *t*-butyldiphenylsilyl protecting group was chosen for several reasons:

- It would be stable in all reaction conditions during the synthesis.
- Its large bulk should optimize stereochemical preferences in the transition-state.

- The NMR spectral signals are simple and unlikely to interfere with other important signals.
- It is easily removed.

Use of a benzylic phenylsulfanyl group permits the formation of a carbon radical or carbanion at this position. The side chain could be synthesised from Malic acid, which is readily obtained in both enantiomeric forms.

The chosen synthetic route to the cyclisation precursor is shown (Scheme 1.39). Starting from malic acid, the termini of the acid could be chemodifferentiated, achievable using a known chemoselective reduction. Coupling to phthalimide, selective secondary hydroxyl protection and then extention of the tether would then form the enoate ester. The phenylsulfanyl lactam was then accessible through the known reduction/acyliminium substitution methodology used in the original study.

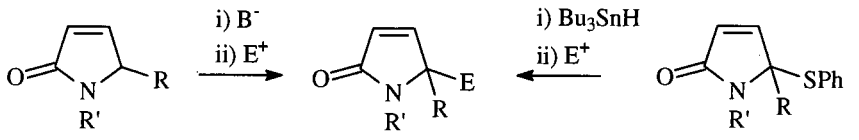


L-Malic acid

Scheme 1.39 Retrosynthesis

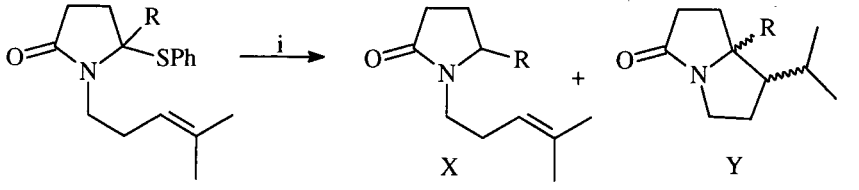
1.2.2 The Construction of Tertiary aza Centres

Given the intense interest in lepadiformine, its tricyclic core was selected as an appropriate target for testing out the methodology of the thesis. It was initially appealing to construct tertiary aza centres using carbanionic alkylation and radical reactions in keeping with our synthetic strategy (Scheme 1.40).



Scheme 1.40 Tertiary aza formation *via* carbanions or radicals

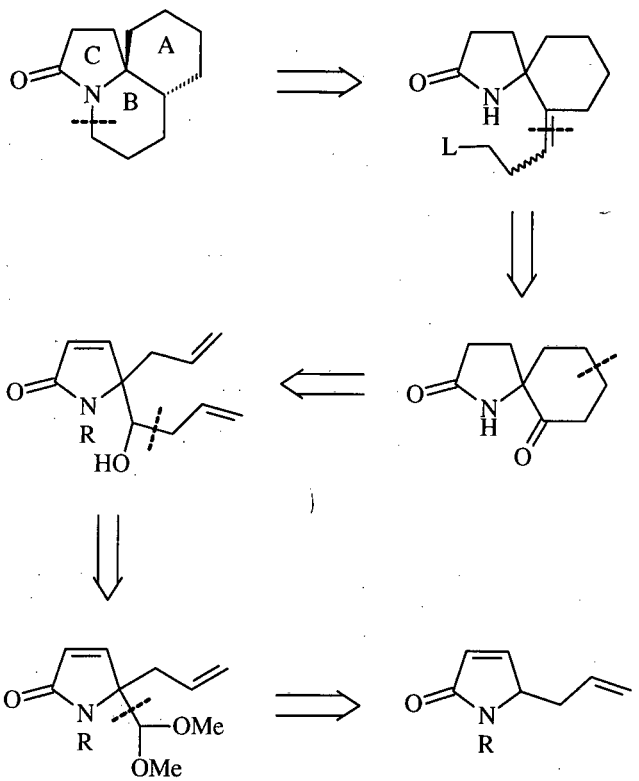
However Hart observed[71] that treatment of a tertiary phenylthiolactam under standard radical conditions gave only the reduced product (Scheme 1.41). The rate of the competing reduction reaction was far greater than the C-C bond formation due to steric constraints around the tertiary radical. Preliminary studies in our project yielded similar results.



Scheme 1.41 *Reagents and conditions:* (i) Bu_3SnH, AIBN; R=H X = 12% Y = 75%; R = CH_3 X = 91% Y = 0%

As a result it was decided to focus on carbanionic methodology, a more promising approach for tertiary aza construction.

The chosen synthetic route is depicted in the retrosynthesis (Scheme 1.42). The strategy was to achieve 5,5 dialkylation of a pyrrolidinone using alkylation of a 2-siloxypyrrole (Mukaiyama), a 1,5-dihydropyrrol-2-one-5-anion equivalent, for the key tertiary aza centre formation. This would be followed by chain extension to give appropriate vinyl residues for application of the popular ring-closing metathesis methodology to give an A/C-ring azaspirocycle. A number of avenues could then be envisaged for B-ring construction *via* alkylation of the A-ring with an appropriately functionalised tether for closure onto nitrogen.



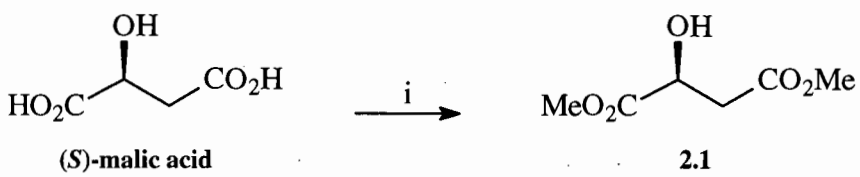
Scheme 1.42 Retrosynthesis

CHAPTER 2

SECONDARY AZA FORMATION: SYNTHESIS OF TETRAHYDROPYRIDO[2,1-*a*]ISOINDOLONES

2.1 Results and Discussion

2.1.1 Synthesis of Cyclisation Precursor

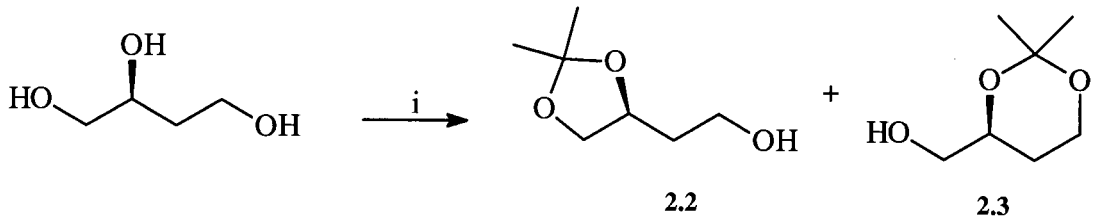


(*S*)-malic acid **2.1**

Scheme 2.1 *Reagents and conditions:* (i) H^+, MeOH, 93%

Malic acid is one of the most readily available reagents obtained from the chiral pool and consequently has found widespread use in synthesis. This feature, coupled with the fact that it provided an appropriate four-carbon tether with one stereogenic centre, made it an appropriate choice as the starting material for our synthetic sequence. The esterification of malic acid is also well documented in the literature,[72] and it was in our interest to select a convenient method for the large scale (50g) synthesis of dimethyl malate **2.1** (Scheme 2.1). In the chosen procedure dry HCl gas was bubbled through a solution of (*S*)-malic acid in methanol for a few minutes, which was then stirred for 24 hours. The solvent was then removed and the resulting oil was purified by vacuum distillation to give dimethyl malate **2.1** as a colourless oil. To ensure high yields the residue that remained was redissolved in methanol and the entire procedure was repeated to obtain a total yield in excess of 90%. The dimethyl malate was stored below 0°C because slow decomposition occurred at room temperature.

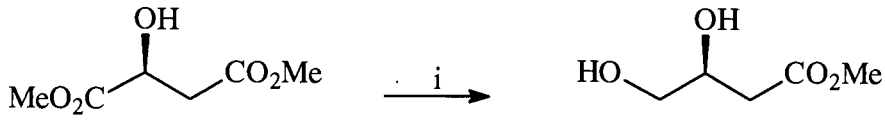
The next transformation was to differentiate the termini of **2.1**. From the literature, this has been achieved with some success by reduction to the triol followed by formation of the 1,2-acetonide. However, this protection is not completely selective and it has been shown[73] that as much as 10% of the product is the 1,4-acetonide **2.3** which is difficult to separate from **2.2** (Scheme 2.2).



2.2 **2.3**

Scheme 2.2 *Reagents and conditions:* (i) $(CH_3O)_2C(CH_3)_2$, *p*-TsOH, C_3H_6O

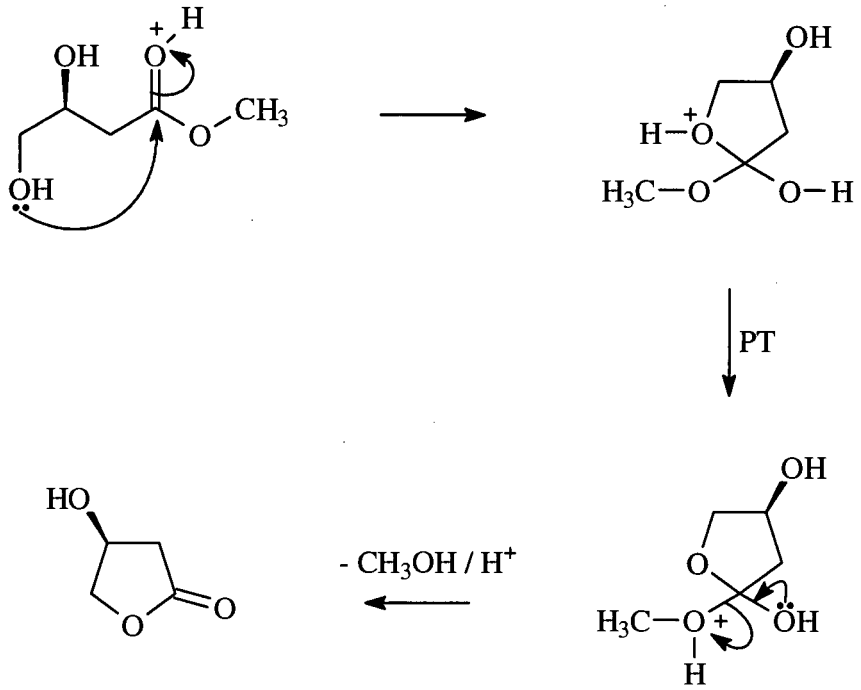
A better method for chemodifferentiation seemed to be *via* a chemoselective reduction using $BH_3.SMe_2$ and catalytic sodium borohydride, a method developed by Saito *et al.*[74] This is reported to give almost exclusive formation (99:1) of the 1,2-diol (Scheme 2.3).



2.1 **2.4**

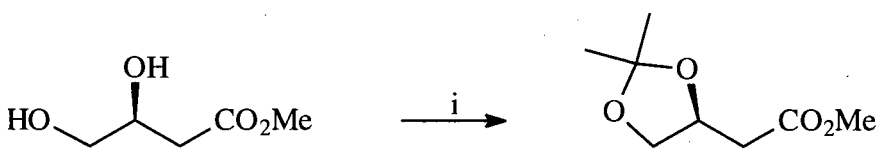
Scheme 2.3 *Reagents and conditions:* (i) $BH_3.SMe_2$, 5 mol % $NaBH_4$, THF, 79%

A mechanism for this reaction has been postulated. $BH_3.SMe_2$ exchanges initially with the exchangeable hydrogen of the hydroxyl group, with concomitant evolution of hydrogen gas. The borane then chelates to the nearest ester C=O group (C-1) and reduction occurs at that carbonyl leaving the other ester untouched, hence explaining the chemoselectivity. The reaction must be followed closely as over-reduction to the triol can occur if the reaction is not quenched immediately on consumption of starting material. The reaction was successfully carried out and the crude diol chromatographed to give pure **2.4** as a colourless oil in 79% yield. The identity of the product was confirmed using ^1H NMR. During non-aqueous work-up, 5 mol % *p*-toluenesulfonic acid (*p*-TsOH) and ethanol were added. The $B(OEt)_3$ was then removed by azeotroping with benzene. It was important that the work-up procedure be followed meticulously, since addition of too much *p*-TsOH resulted in lactonisation (Scheme 2.4).



Scheme 2.4 *Mechanism of lactonisation*

The next strategy pursued was to protect the primary hydroxyl of **2.4** with a temporary protecting group followed by protection of the secondary hydroxyl as the *tert*-butyldiphenylsilyloxy group needed in the cyclisation precursor. However before this diprotected product could be coupled to phthalimide the ester had to be reduced. When $LiAlH_4$ reductions were carried out on a similar compound, the silyl-protecting group migrated to the newly formed primary hydroxyl. Although the synthesis would be lengthened by a couple of steps, protection of the diol as an acetal was considered likely to avoid the possible transfer of a silyl-protecting group during the reduction. The silyl protection would then be carried out at a later stage.

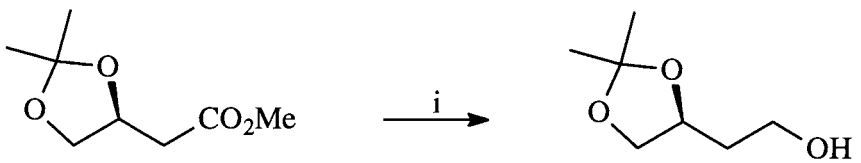


2.4 **2.5**

Scheme 2.5 *Reagents and conditions:* (i) $(CH_3O)_2C(CH_3)_2$, *p*-TsOH, C_3H_6O, 81%

To this end, diol **2.4** was converted to the ketal **2.5** using the published method[74] of *p*-toluenesulfonic acid (cat) with dimethoxypropane in acetone (Scheme 2.5). The reaction was rapid, within 20

minutes tlc showed no remaining starting material. The *p*-TsOH was neutralized by the addition of triethylamine and the mixture diluted with diethyl ether. The salt could then be removed by simple filtration through a silica-gel pad, which had to be rinsed thoroughly. To isolate the product, the filtrate was concentrated and the residue was purified by vacuum distillation. The ^{1}H NMR spectrum was identical to the published data.

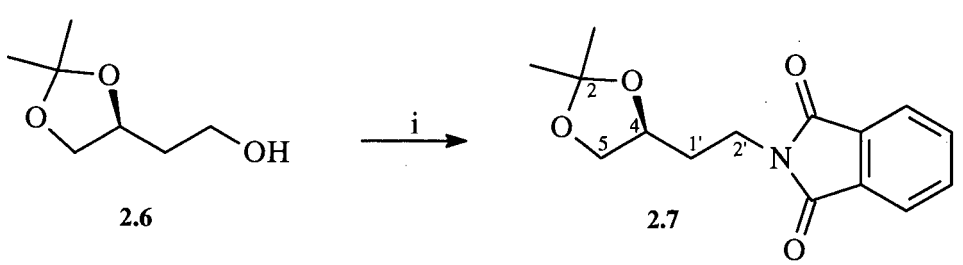


2.5 **2.6**

Scheme 2.6 *Reagents and conditions:* (i) $LiAlH_4$, THF, -40°C, 91%

A multitude of reagents can be used to reduce an ester to an alcohol, with the most widely used one being lithium aluminium hydride. This reagent (0.6 equivalents) reduced ester **2.5** at –40°C in THF (Scheme 2.6). As each molecule can deliver four hydrides, a stoichiometric amount of the reagent was unnecessary (two hydrides needed per ester), though in other substrates an excess may be required as the aluminium can complex to functionality that is not directly involved. The reaction was complete after 2 hours and was quenched by the slow addition of a 50:50 mixture of tetrahydrofuran and water until the aluminium salts were completely white. The mixture was filtered through Celite® to remove these salts and the filter cake was thoroughly washed with dichloromethane. The product was isolated by drying the filtrate with magnesium sulfate and evaporating to give an oil, which was purified using vacuum distillation to give the alcohol **2.6** as a colourless oil. The NMR spectrum of this product was identical to the reported data.

All compounds that follow are new compounds and were fully characterised.



2.6 **2.7**

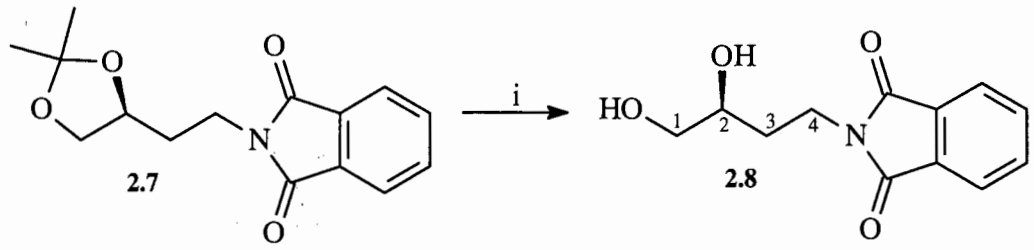
Scheme 2.7 Reagents *and conditions:* (i) DEAD, phthalimide, triphenylphosphine, THF, 94%

The Mitsunobu reaction[75] is a versatile, mild dehydration reaction, which can be used to form esters, ethers, C-N, C-S, and C-halide bonds. It is useful for inverting the configuration of stereocentres containing a hydroxyl group. The reaction of alcohols with phthalimide under Mitsunobu conditions is a widely used transformation,[76] and was considered to be a convenient means of forming the *N*-substituted phthalimide **2.7**. This reaction could be performed at room temperature and was easily monitored by tlc. It was carried out in tetrahydrofuran by the reaction of **2.6** with phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to give the imide **2.7** as a fairly stable low-melting solid (Scheme 2.7). For larger scale reactions (>5g), the solution was initially cooled before the DEAD was added. The reaction was worked up using the standard procedure.

The IR spectrum of imide **2.7** showed two absorbances in the 1700 cm^{-1} region. These bands at 1775 cm^{-1} (weak) and 1716 cm^{-1} (strong) correspond to the C=O stretches, one for the in-phase and one for the out-of-phase stretching of the two C=O groups.[77,78] The band at the lower wavenumber was more intense, which is typical of cylic imides. The ^{1}H NMR spectrum of **2.7** displayed the expected aromatic signals and the broad hydroxyl peak had disappeared. The spectrum also showed that the methylene protons on C-5 resonated as a doublet of doublets, one at 3.55 ppm ($J_{5,5}$ 7.8 Hz, $J_{5,4}$ 6.7 Hz) and the other at 4.05 ppm ($J_{5,5}$ 7.8 Hz, $J_{5,4}$ 5.9 Hz). The large difference in chemical shift between these diastereotopic hydrogens is due to large differences in their electronic environments because of their proximity to the chiral centre. Similarly the methylene protons on C-1' were split into two multiplets. However the more distant C-2' methylene protons resonated as a multiplet at 3.81 ppm. The C-4 hydrogen was present as a downfield multiplet at 4.14 ppm. The signals for the isopropylidene methyl groups were unchanged indicating that the ketal had not been affected during the reaction. The aromatic carbons in the ^{13}C NMR spectrum resonated as three singlets, while the two imide carbonyl groups resonated as one signal owing to the symmetrical nature of the phthalimide ring. The methylene carbon now bonded to nitrogen had shifted upfield to 35.1 ppm reflecting reduced deshielding of nitrogen versus oxygen.

The standard method for the cleavage of a ketal/acetal is by acid hydrolysis. This was successfully achieved for **2.7** by heating a solution of the acetal in a mixture of 1M HCl and THF (Scheme 2.8). As expected, tlc showed the product **2.8** as more polar than **2.7**, and after 30 minutes the reaction was neutralised with saturated sodium bicarbonate solution and subjected to standard work-up conditions.

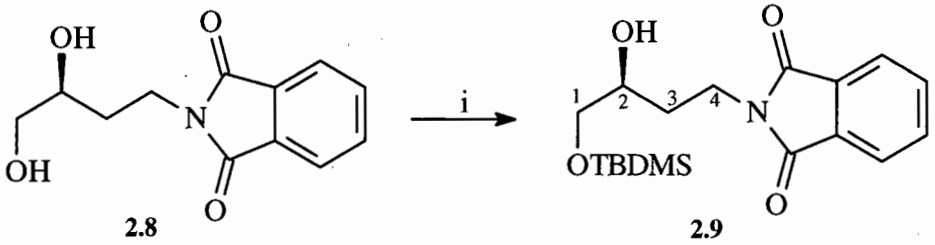
The final residue could be easily chromatographed to give the diol as a fluffy, white solid. This product displayed good stability, no decomposition being observed after storing for more than a year at room temperature.



Scheme 2.8 *Reagents and conditions:* (i) 1M HCl, THF, 60°C, 85%

The IR spectrum of this compound showed two broad absorbances at 3581 and 3508 cm^{-1} corresponding to the OH groups. Once again the carbonyl bands were present. Although it was immediately obvious that no isopropylidene methyl signals were present in the ^1H NMR spectrum and the broad hydroxyl peaks could clearly be seen, the spectrum was poorly resolved due to overlap of these OH resonances with the aliphatic protons. However, the aliphatic signals became clearly resolved after a D_2O wash. The resonance for the C-4 methylene hydrogens was virtually unaffected at 3.86 ppm but now resonated as a doublet of doublets ($J_{4,3}$ 5.6 Hz, $J_{4',3}$ 7.6 Hz). The H-1 and H-1' protons were again split into two doublets of doublets, one at 3.47 ppm ($J_{1,1'}$ 11.2 Hz, $J_{1,2}$ 7.2 Hz) and the other at 3.58 ppm ($J_{1',1}$ 11.2 Hz, $J_{1',2}$ 3.2 Hz) but the splitting was far smaller (0.1 ppm difference) and both had moved upfield (more shielded). The multiplet for H-2 and the H-3 methylene had also both shifted upfield. As expected, the 3 signals for the isopropylidene carbons had disappeared from the ^{13}C spectrum. The resonances for C-3 and C-4 were in a similar position to those in the ketal but both the C-2 and C-1 signals bonded to the free hydroxyls had shifted upfield to 66.1 and 69.1 ppm. The carbonyl and the three aromatic signals remained unchanged.

Chemodifferentiation of the vicinal diol was achieved using *tert*-butyldimethylsilyl chloride (TBDMSCl), which is well known in the literature for preferential primary alcohol protection.[79] Thereafter the secondary alcohol could be protected to a *tert*-butyldiphenylsilyl (TBDPS) ether as required for the radical cyclisation.



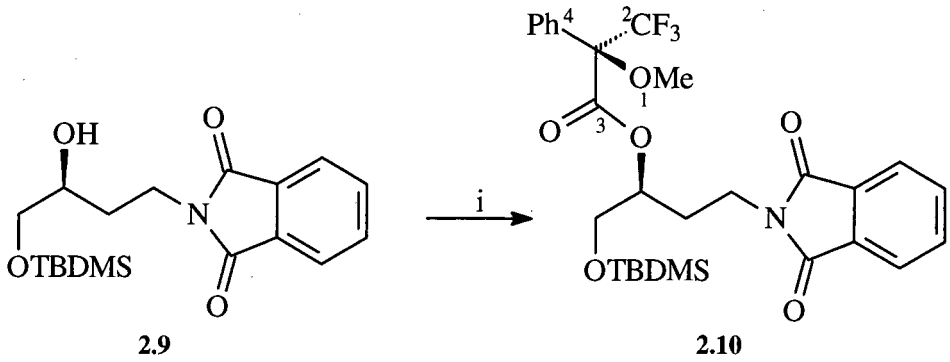
2.8 **2.9**

Scheme 2.9 *Reagents and conditions:* (i) TBDMSCl, imidazole, CH_2Cl_2, 0°C to rt, 97%

Thus the primary hydroxyl of **2.8** was protected by reacting the diol with *t*-butyldimethylsilyl chloride in dichloromethane using imidazole as a base and silylation transfer catalyst (Scheme 2.9). Once the reaction was complete, water was added and the product could be extracted. The residue was chromatographed to give the product **2.9** as an oil in high yield (97%). Care had to be taken with the number of equivalents of the silyl chloride to avoid protection of the secondary hydroxyl group. The IR spectrum of **2.9** now showed only one broad hydroxyl band at 3597 cm^{-1}. The ^1H NMR spectrum was used to confirm the structure of the product. Disilylation could be ruled out since only one set of signals for the *tert*-butyldimethylsilyl group could be seen. The singlet at 0.06 ppm had an integral of six protons, corresponding to the two highly shielded methyl groups bonded to the silicon. A large singlet was observed at 0.89 ppm corresponding to the nine *t*-butyl protons. The hydroxyl proton was seen as a broad singlet at 2.65 ppm. Interestingly the signals for the aliphatic protons were virtually unchanged including the H-1 methylene bonded to the silyloxy group. Four new resonances were observed in the ^{13}C NMR spectrum. The highly shielded diastereotopic methyl groups bonded to silicon resonated at –5.44 and –5.41 ppm, while a strong signal at 25.9 ppm corresponded to the three methyl carbons of the *t*-butyl group. The quaternary carbon of the *tert*-butyl group appeared as a very relaxed singlet at 18.3 ppm. The other signals were similar to the diol.

This secondary alcohol was a convenient compound for examination of the enantiomeric integrity of the compound thus far. The possibility existed that partial or total racemisation of the chiral centre had occurred during the synthesis when using harsh reagents or conditions, particularly prior to reduction, when the presence of the carbonyl group could promote enolisation. The most widespread method to find out if this had occurred was to form a diastereomer by reaction with another chiral compound of known purity. If racemisation had occurred the product would be a mixture of diastereomers instead of a single diastereomer. The purity of the alcohol could then be determined using NMR. This approach was used for the secondary alcohol **2.9** by formation of its Mosher's ester. Two samples of alcohol were synthesised, one from racemic and one from enantiopure malic

acid. Each alcohol was coupled to (*R*)-Mosher's acid using DCC and DMAP (catalytic) in dichloromethane in 84% yield (Scheme 2.10).



2.9 **2.10**

Scheme 2.10 ***Reagents and conditions:*** (i) (*R*)-Ph(F_3C)(MeO)CCO_2H, DCC, DMAP, CH_2Cl_2, rt, 84%

The ^{1}H NMR spectra of the enantio- and racemic-derived esters **2.10** were compared. Whereas the ester derived from racemic malic acid showed two clear sets of signals for the two diastereomers, the ester derived from enantiopure malic acid displayed only one set with no trace of the other diastereomer in the spectrum, indicating that no racemisation had occurred (*ee* 100% from NMR). Regions of the spectra have been expanded to illustrate this in Figure 2.1.

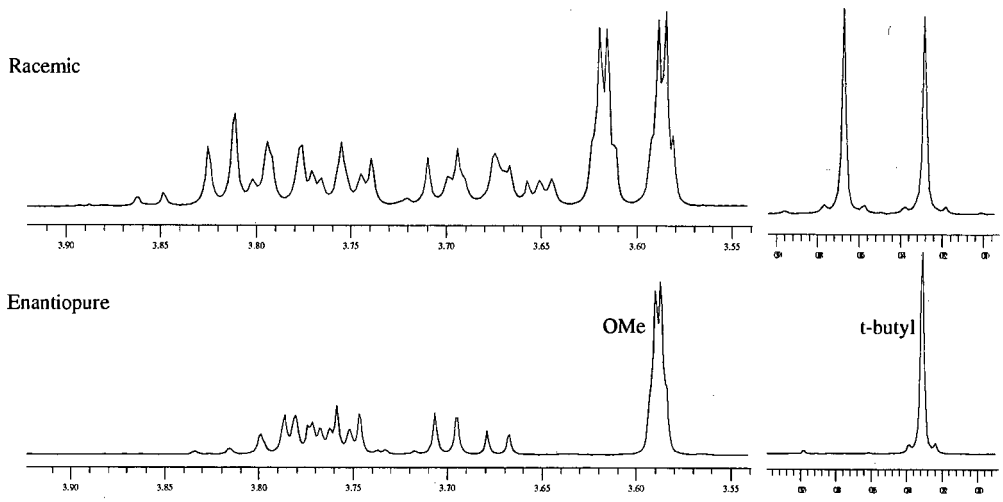
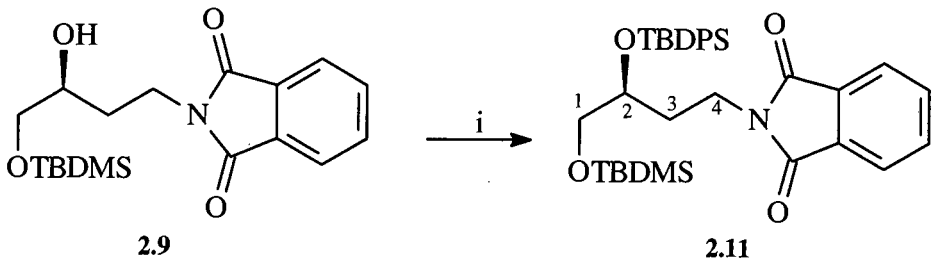


Figure 2.1 ^{1}H NMR Expansions of the Racemic and Enantiopure Mosher's esters **2.10**

The secondary hydroxyl **2.9** was protected as its TBDPS ether using *tert*-butyldiphenylsilyl chloride in the same manner as the previous silylation (Scheme 2.11). A small amount of dimethylformamide (DMF) was use as a co-solvent to aid solubility of the reagents and intermediates.

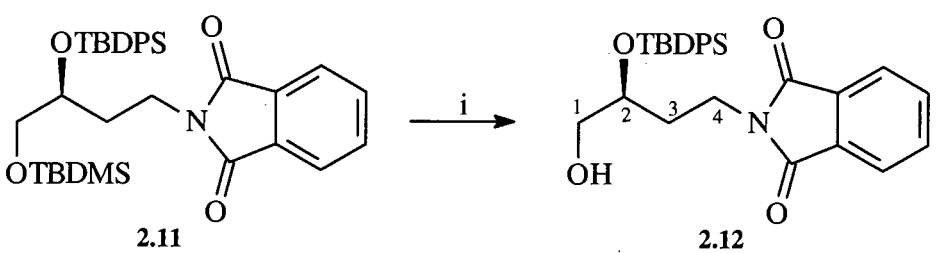


2.9 **2.11**

Scheme 2.11 *Reagents and conditions:* (i) TBDPSCl, imidazole, CH_2Cl_2, DMF, rt

A small amount of TBDPSOH was formed during this reaction, which coeluted with the nonpolar product **2.11** when the product was chromatographed. This contaminant was easily separated after the next deprotection step.

The presence of broad hydroxyl bands was noticeably absent from the 3500 cm^{-1} region of the IR spectrum. The key resonances in the ^1H NMR spectrum were the broadening of the aromatic region to integrate for 10 new protons, as well as the presence of a new singlet at 1.07 ppm for the TBDPS *tert*-butyl group. The signals for H-3 and H-3' were now split into two multiplets at 1.90 ppm and 2.03 ppm. The chemical shift for the H-1 signal remained the same, but resonated as a doublet at 3.53 (*J* 5.9 Hz). The resonances for H-4, H-4' and H-2 were poorly resolved and were present as a broad multiplet at 3.78 ppm. The protons of the TBDMS group remained unchanged. As expected, the ^{13}C NMR spectrum displayed new resonances characteristic of the TBDPS group, with signals at 19.3 ppm and 27.0 ppm for the central *t*-butyl carbon and the *t*-butyl methyl carbons respectively. The phenyl group of the TBDPS gave eight new resonances in the 130 ppm region consistent with aromatic carbons. The C-1 signal had shifted slightly upfield to 65.6 ppm and the C-2 signal downfield to 71.8 ppm. The remaining peaks were the same as in **2.9**.

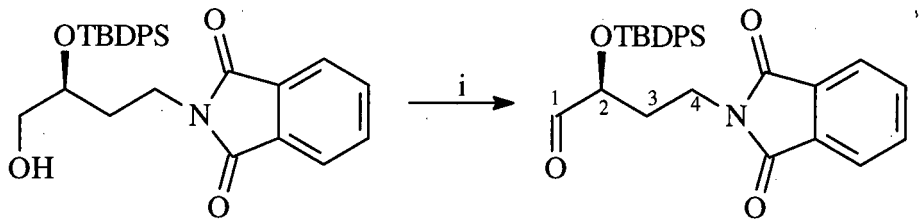


2.11 **2.12**

Scheme 2.12 *Reagents and conditions:* (i) HF, acetonitrile, rt, 89 % over 2 steps

The deprotection of a TBDMS group in the presence of a TBDPS group is a popular step in many syntheses. Many different methods have been described[79] and a mild method has recently been reported by our group.[80] For compound **2.11**, two methods were found to be effective for the formation of **2.12**. The first[81] was to dissolve it in a mixture of acetic acid, water, and THF (3:3:1) and heat overnight at 45°C. In the second method,[82] **2.11** was dissolved in a 10 % solution of HF in acetonitrile and stirred at room temperature (Scheme 2.12). This method became the preferred method since it was higher yielding, faster, and easier to work-up.

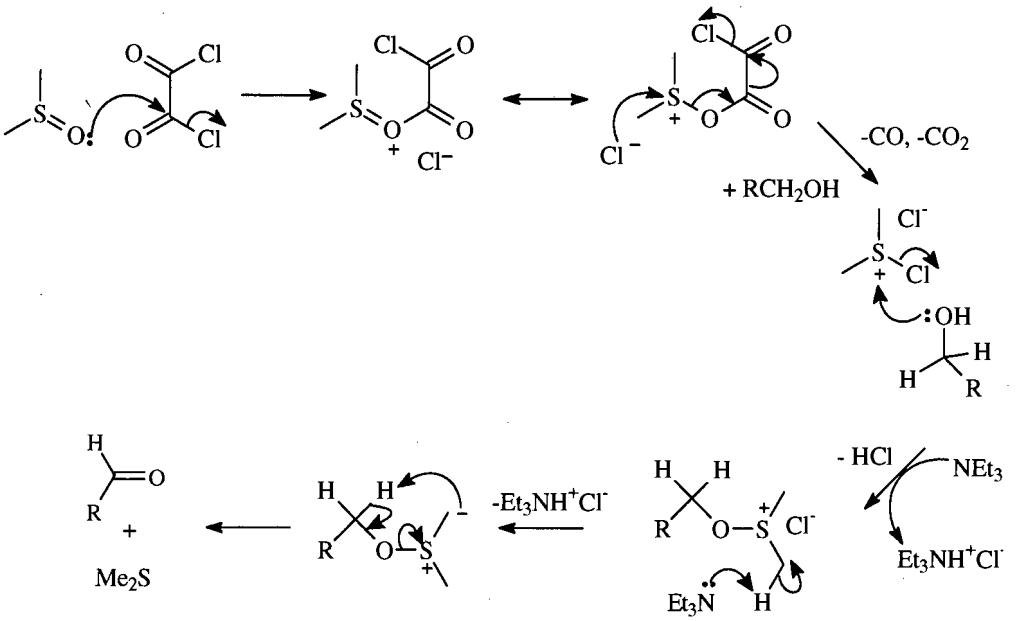
The IR spectrum of the product contained a broad absorbance at 3571 cm^{-1} due to the new hydroxyl group. The ^1H NMR spectrum was poorly resolved due to overlap of the aliphatic proton resonances. The two multiplets for H-3 and H-3' as well as the signals for the protons of the TBDPS group were unchanged. The methylene protons of H-1 and H-1' were not resolved and had shifted downfield to form part of a multiplet at 3.67 ppm. The resonances for H-4 and H-4'shifted slightly upfield to form part of the same multiplet. The H-2 multiplet now resonated at 3.82 ppm. Apart for the absence of the four TBDMS signals, the ^{13}C NMR spectrum was very similar to the previous spectrum. Similarly no signal shifted by more than 0.3 ppm other than the aromatic resonances.



2.12 **2.13**

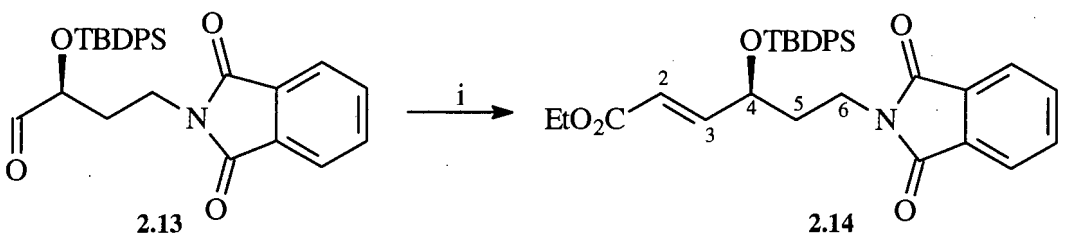
Scheme 2.13 *Reagents and conditions:* (i) DMSO, oxalyl chloride, NEt_3, CH_2Cl_2, -78°C to 0°C

A number of reagents are available to oxidize primary alcohols, and the Swern oxidation was found to be a suitable reaction for converting alcohol **2.12** to the aldehyde **2.13** (Scheme 2.13). Standard Swern conditions[83] were utilised and after work-up the crude aldehyde was sufficiently pure to continue with the next step although a dimethyl sulfide odour could be detected in the gummy product. In this reaction the Swern reagent is pre-formed, to which is added the alcohol to form an alkoxysulfonium intermediate followed by base. Scheme 2.14 summarises the reaction mechanism.



Scheme 2.14 Mechanism of the Swern oxidation

For characterisation purposes, the absence of a hydroxyl band was noticeable in the IR spectrum of **2.13**. The most conspicuous signal in the ^{1}H NMR spectrum was the resonance for the C-1 formyl proton which resonated as a doublet ($J_{1,2}$ 0.9 Hz), downfield of the aromatic region at 9.65 ppm due to the deshielding effect of the C-1 carbonyl oxygen. The signal for H-2 shifted downfield to 4.13 ppm and appeared as a triplet of doublets ($J_{2,3}$ 5.6 Hz, $J_{2,3'}$ 5.6 Hz, $J_{1,2}$ 0.9 Hz), while the multiplets for the C-4 and C-3 protons were not significantly shifted, nor were the signals for the aromatic and *t*-butyl protons. The most notable feature of the ^{13}C NMR spectum was the C-1 resonance at 203 ppm. Similarly, the C-2 carbon was shifted downfield to 76.2 ppm as a result of an inductive effect. The remaining signals resonated in the same position as those in the spectrum of compound **2.12**.



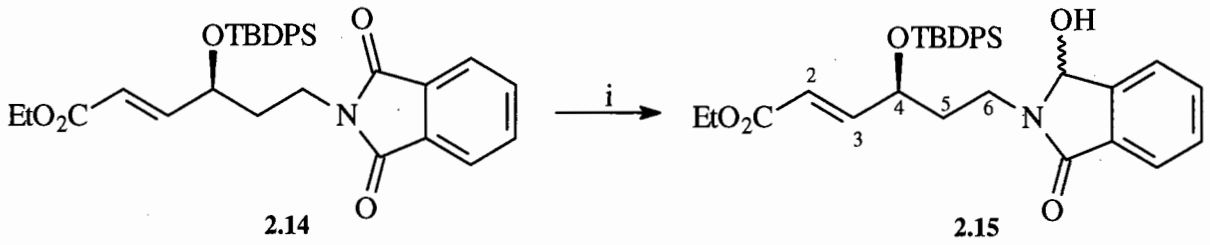
2.13 **2.14**

Scheme 2.15 *Reagents and conditions:* (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 96 % over 2 steps

The Wittig reaction was chosen to form the α,β-unsaturated ester from aldehyde **2.13** using ethoxycarbonylmethylenetriphenylphosphorane (Scheme 2.15). The latter is an isolable, stabilized ylide due to the presence of two stabilizing groups (ester and phosphorus) for the carbanion. For these stabilized ylides, changing the reaction solvent and reaction temperature can alter the stereoselectivity of the reaction with α-hydroxy aldehydes. When the reaction is carried out in non-polar solvents such as dichloromethane, *E*-alkenes are normally produced. However, if a polar solvent such as methanol is used, high *Z*-selectivity is reported to occur.[84]

By performing the reaction in dichloromethane at room temperature high *E*-selectivity was obtained and only traces of the *Z*-isomer were observed (<5%). The reaction was easily monitored by tlc. The α,β-unsaturated ester **2.14** appeared as a blue-green spot under anisaldehyde spray, while the aldehyde appeared as a brown streak. The yield was good (97%) over the two steps from the primary alcohol. Although *Z* to *E* isomerisation by tributyltin hydride is known to occur, the relative rates of isomerisation and cyclisation for the *Z*-isomer could not be predicted. However, from literature reports this feature was considered to have an important bearing on the stereoselectivity of the reaction if cyclisation were faster than isomerisation.[85] In our case, this was not an issue given the small quantities of *Z*-isomer present.

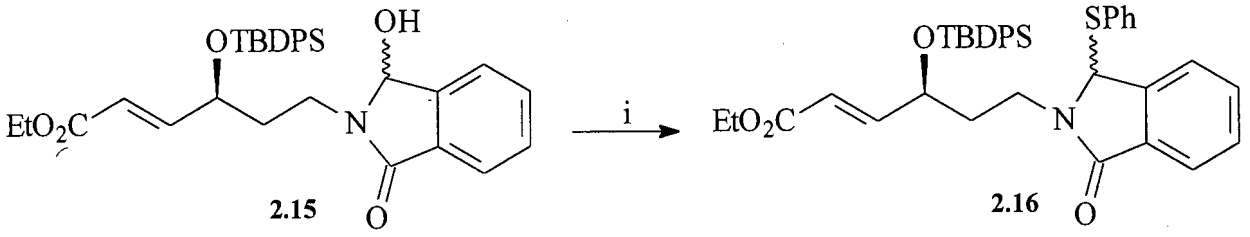
A notable absorbance in the IR spectrum was the weak band at 1663 cm^{-1} characteristic of the C=C stretch. Both olefinic protons, H-2 and H-3, resonated as doublet of doublets n the ^1H NMR spectrum with the H-3 signal (6.93 ppm) downfield to the H-2 signal (6.01 ppm) because it is β to the C=O group. The double bond was assigned as *E* on the basis of a large vicinal coupling constant between the vinyl protons ($J_{2,3}$ 15.6 Hz). Weak allylic coupling was observed between H-2 and H-4 ($J_{2,4}$ 1.5 Hz), and the deshielding effect of the double bond caused a downfield shift of the C-4 proton to 4.42 ppm. The remaining protons resonated at similar positions to those in the aldehyde **2.13**. New signals were observed at the expected chemical shifts for the methyl and methylene carbons of the ethoxy group, and for the C=O group of the ester in the ^{13}C NMR spectrum. The new olefinic C-2 and the C-3 signals were located at 121 and 148 ppm respectively. The C-4 resonance showed an upfield shift to 70.5 ppm from 76.1 ppm. The C-5 and C-6 signals revealed a downfield shift. The other signals were the same as in **2.13**.



Scheme 2.16 *Reagents and conditions:* (i) $NaBH_4$, MeOH, THF, -40°C to -20°C, 92%

Although the literature indicates that the double bond of an α,β-unsaturated ester is generally prone to reduction using sodium borohydride, reduction of a similar system[85] to afford the carbinol amide had been successfully achieved using sodium borohydride in a THF/methanol mixture at low temperature. Reduction of only one of the imide carbonyl groups occurred in view of diminished electrophilicity of the second carbonyl following the reduction. This method was successfully employed on **2.14** to give the desired product **2.15** as a foam in 92% yield (Scheme 2.16). The NMR spectra of this foam revealed it to be an approximately 50:50 mixture of epimers.

A broad band at 3056 cm^{-1} in the IR spectrum supported the presence of the hydroxyl group. Further confirmation was the disappearance of the imide C=O stretch in the 1770 cm^{-1} region and the appearance of a C=O resonance for the amide at 1680 cm^{-1}. As the two epimers of **2.15** were inseparable by chromatography and the NMR spectra of the mixture were poorly resolved due to peak overlap, the peaks of the major epimer were used to confirm the identity of the product. The key new signals in the ^1H NMR spectrum were the singlet at 5.20 ppm corresponding to the new benzylic proton, and a broad peak for the hydroxyl group. This spectrum again showed the characteristic signals for protons on the double bond ruling out reduction, with H-2 and H-3 both resonating as a doublet of doublets at 5.99 ppm and 6.86 ppm. The large vicinal coupling constant was observable between these protons ($J_{2,3}$ 15.8 Hz), and a small allylic coupling between H-2 and H-4 was apparent ($J_{2,4}$ 1.2 Hz). The ^{13}C NMR spectrum showed a new resonance at 82.4 ppm for the reduced benzylic position. As a result of the desymmetrisation, six individual aromatic signals were now apparent. The remaining signals were in similar positions to those in alkenoate ester **2.14**.



2.17 *Reagents and conditions:* (i) PhSH, $BF_3.Et_2O$, CH_2Cl_2, -78°C, 97%

Synthesis of the radical precursor was carried out by exchange of the hydroxyl group of **2.15** for a phenylsulfanyl group using thiophenol (benzenethiol) in the presence of a Lewis acid ($BF_3.Et_2O$) to give **2.16** (Scheme 2.17).[85] The reaction was carried out at -78°C in dichloromethane. This is an S_N1-type substitution in which the Lewis acid generates an acyliminium ion, which is attacked by the nucleophilic thiophenol (Figure 2.2). Hart *et al.* achieved the same transformation using *p*-toluenesulfonic acid in thiophenol at room temperature.[86] The drawback of their method was conjugate addition of the thiophenol to the enoate ester in several substrates.

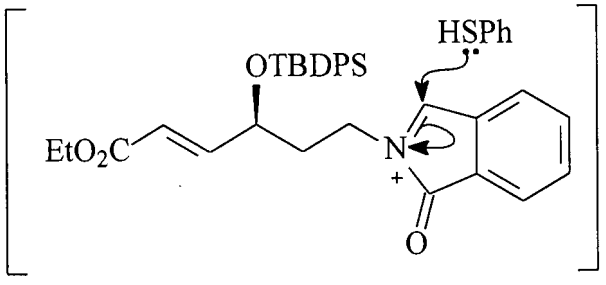


Figure 2.2 Nucleophilic attack by thiophenol on *N*-acyliminium intermedieate

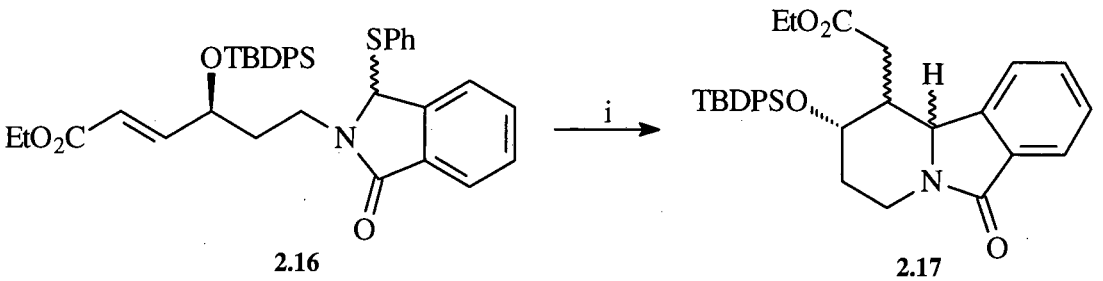
The reaction was high yielding (97%) and gave the product as a colourless gum that was fairly stable at low temperature (<0°C). However, if stored for several days at room temperature, a thiophenol odour could be detected and tlc showed the formation of several new compounds.

The absence of a hydroxyl band was a feature of the IR spectrum, and as expected the NMR spectra of the product showed a mixture of epimers making a complete assignment difficult. The peaks of the major epimer were used to identify the product, and once again the important resonance in the ^1H NMR spectrum was the benzylic singlet, which was located at 5.46 ppm. The aromatic region integrated for five new protons due to the new phenylsulfanyl group and the broad hydroxyl peak had vanished. The protons on the double bond were again apparent and resonated as in **2.15** showing that no conjugate addition by the thiophenol had occurred.

The phenylsulfanyl group had a shielding effect on the benzylic carbon in the ^{13}C NMR shifting the signal upfield to 66.7 ppm. New signals corresponding to the phenyl group were observed in the aromatic region. The chemical shifts of the remaining signals were similar to those of **2.15**.

2.1.2 Radical cyclisation

With the cyclisation precursor **2.16** in hand the stage was set for the radical cyclisation reaction.



2.16 **2.17**

Scheme 2.18 *Reagents and conditions:* (i) Bu_3SnH, AIBN, toluene, 90°C, 97%

Standard conditions were used for the radical cyclisation (Scheme 2.18). Dry, deoxygenated toluene was used as the solvent and a solution of tributyltin hydride and the initiator (AIBN) was added dropwise to a solution of the cyclisation precursor **2.16** at 90°C as the AIBN is only activated above 70°C. The concentration of tin hydride was kept low by slow addition to minimize reduction of the carbon radical by tributyltin hydride (mentioned earlier).

Within two hours thin layer chromatography of the reaction indicated the formation of one polar diffuse spot (30% ethyl acetate/petroleum ether), which appeared grey after spraying with anisaldehyde. After the starting material was consumed, the product was isolated by chromatography and ^1H NMR spectral analysis revealed it to be a mixture of all four possible diastereomers in a 4:2:1:1 ratio as determined from the integral values. The diastereomers were deduced from the presence of four doublets with δ = 5.12, *J* 3.7 Hz; 4.62, *J* 11.1 Hz; 4.44, *J* 11.1 Hz; 4.28, *J* 3.5 Hz., corresponding to the benzylic proton (H-10b) of each one. Of the four possible products of the cyclisation (Figure 2.3), two of the diastereomers, **A** and **B**, could be identified with H-1 and H-10b in a *cis* relationship, corresponding to a small coupling constant according to the Karplus equation (explained later). The other two diastereomers, **C** and **D**, had H-1 and H-10b in an *anti* relationship, corresponding to a large coupling constant. Since the major doublet had a coupling constant of 3.7 Hz it could be deduced that this product had a *cis* relationship between H-1 and H-10b, hence the

structure was either **A** or **B**. The doublet with half the integral value (the 2 of 4:2:1:1) had a coupling constant of 11.1 Hz, hence this product had an *anti* relationship between H-1 and H-10b as either **C** or **D**. The same reasoning could be used for the two smallest doublets with coupling constants of 11.1 and 3.5 Hz. Overlap of signals prevented assignment of the H-1/H-2 relationship, hence the structures of the products could not be fully established at this stage.

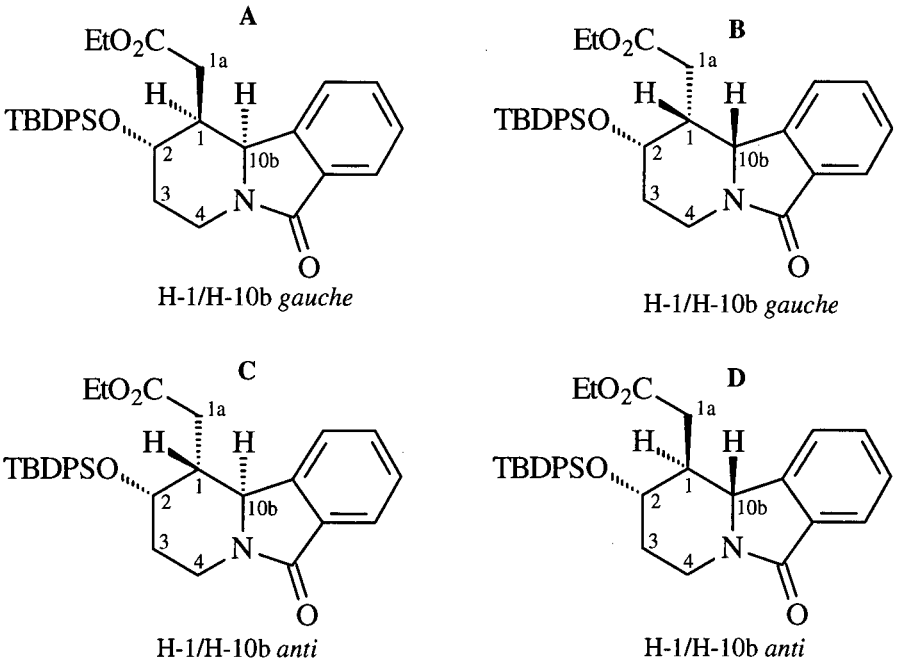
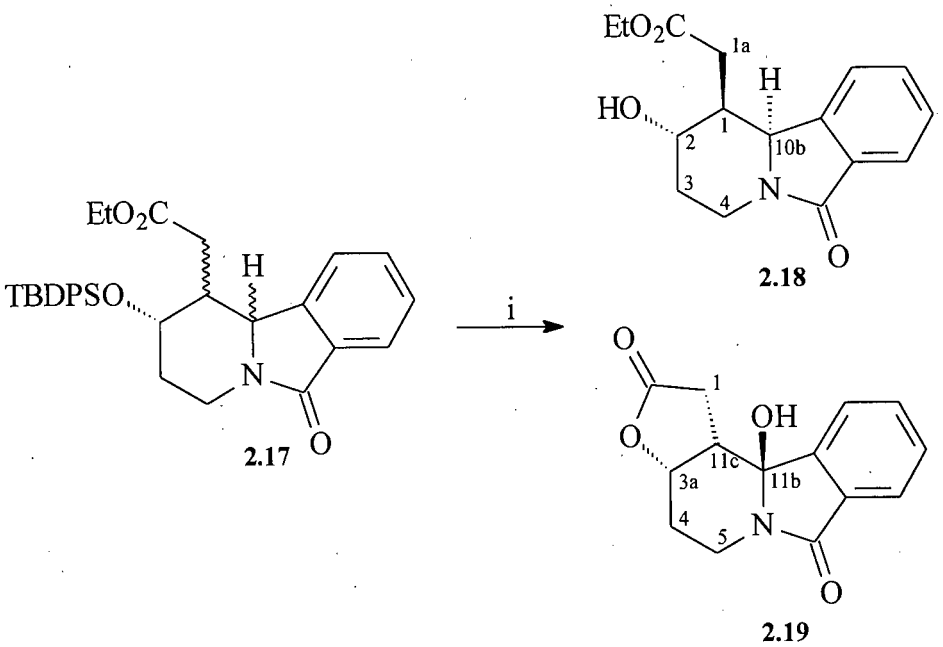


Figure 2.3 *The four diastereomers of the radical cyclisation*

Another notable feature in the ^{1}H NMR spectrum was that no double bond signals were observed, indicating the absence of any reduced starting material. This indicated that the rate of addition was much higher than the rate of reduction, and that the reactivity of the radical towards the double bond was very high. In order to separate these isomers the TBDPS group was removed using tetrabutylammonium fluoride (Scheme 2.19).



Scheme 2.19 *Reagents and conditions:* (i) TBAF, THF, rt

The crude deprotected residue revealed two products by tlc which were isolated by column chromatography.

Major Product 2.18

The more polar major product was isolated as a stable, crystalline solid in 53% yield and was identified as **2.18** based on coupling constants, 2D COSY, and decoupling experiments using NMR spectroscopy. This was consistent with the 4:2:1:1 approximated by ^{1}H NMR.

In the IR spectrum of **2.18** the C=C absorbance was no longer present. In the α-sulfanyl lactam **2.16** the strong bands for the C=O stretches of the ester (1710 cm^{-1}) and the amide (1697 cm^{-1}) overlapped at 1700 cm^{-1} to give a broad band. However in the reaction product the C=O stretch of the ester had shifted to 1730 cm^{-1} due to the loss of the double bond, while the lactam C=O stretch was at 1680 cm^{-1} resulting in two separate bands, giving evidence that cyclisation had occurred. Notably absent from the ^{1}H NMR spectrum were the signals for the phenylsulfanyl group and the double bond protons which was further evidence that cyclisation had occurred. As expected, the TBDPS protons were also absent. In terms of the model study, the crucial aspect was to determine the stereochemistry across the C-1/C-10b bond. The ^{1}H NMR coupling constants for the three

contiguous chiral centres were crucial in determining the stereochemistry of this major product. By applying the Karplus equation shown below, in which coupling constants can be used to calculate the dihedral angle (ϕ) between two vicinal protons, the configuration of these centres could be determined.

$$J = 8.5\cos^2\phi\text{-}0.28 \text{ for } 0°\leq\phi\leq 90°$$

$$J = 9.5\cos^2\phi\text{-}0.28 \text{ for } 90°\leq\phi\leq 180$$

The four possible diastereomers are illustrated (Figure 2.4). As the product was derived from (*S*)-malic acid the configuration at C-2 was fixed (2*S*). The signal for the H-10b proton was well resolved as a doublet with a coupling constant of 4 Hz. Assuming a chair-like conformation for the new heterocyclic ring meant that this proton was in an axial configuration with a *trans* ring junction. This is a consequence of four of the atoms of the five-membered ring being sp^2 resulting in a CO-N-CH-C_{Ar} dihedral angle of close to 0 degrees. This precludes a *cis*-fused ring junction and is supported by the X-ray structure of a similar compound prepared by Beckwith.[87] The coupling constant suggested a *gauche* relationship between this axial proton and H-1, resulting in H-1 being assigned as equatorial with the 2 protons in a *cis* relationship. Gratifyingly, this is the relationship needed for construction of the Tacamonine skeleton. In addition this was consistent with the *cis* relationship assigned to H-1/H-10b for the major diastereomer of the radical cyclisation (the 4 of 4:2:1:1), ruling out any epimerisation during the deprotection step. This assignment immediately ruled out compounds **A** and **B** (with H-1/H-10b *anti*) as possible structures. The resonance for H-2 revealed its stereochemical relationship to H-1 by its coupling pattern to the three vicinal protons. The distorted quartet, implying that the proton coupled to all three equally ($J_{1,2}$ $J_{2,3}$ $J_{2,3'}$ = 3 Hz), meant that H-2 was *gauche* to all three adjacent protons and thus in an equatorial configuration. This ruled out structure **C** with H-2 axial. This established the structure of **2.18** as **D** with absolute configurations at C-1 and C-10b as (1*S*, 10b*S*) respectively.

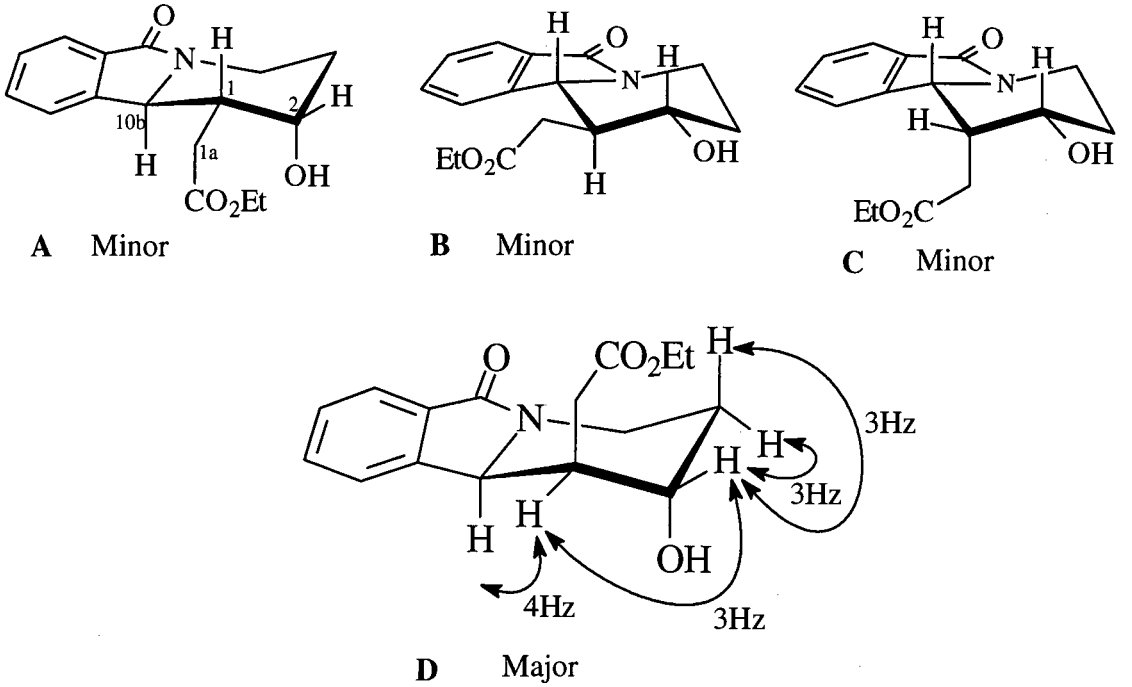


Figure 2.4 Assignment of the major product **2.18** using coupling constants

To confirm the sterochemistry, the multiplet for H-1 was spin decoupled by irradiating the methylene protons of the ethoxycarbonylmethylene substituent to give the H-1 resonance as a distorted triplet (*J* 3.5 Hz). This confirmed the *gauche* relationship that H-1 had with both H-10b and H-2.

A heteronuclear correlation (HETCOR) experiment was used to assign the ^{13}C NMR spectrum. The deshielding effect of the nitrogen atom α to the new stereogenic centre C-10b was apparent by the position of C-10b at 56.0 ppm. The other new stereogenic centre C-1 was at 40.2 ppm. The methylene carbon of the ethoxycarbonylmethylene substituent resonated at 30.7 ppm. The C-3 and C-4 carbons resonated at 67.8 and 27.0 ppm respectively. All of the six aromatic protons had different chemical shifts. The remaining carbons had similar shifts to the corresponding carbons in **2.16**.

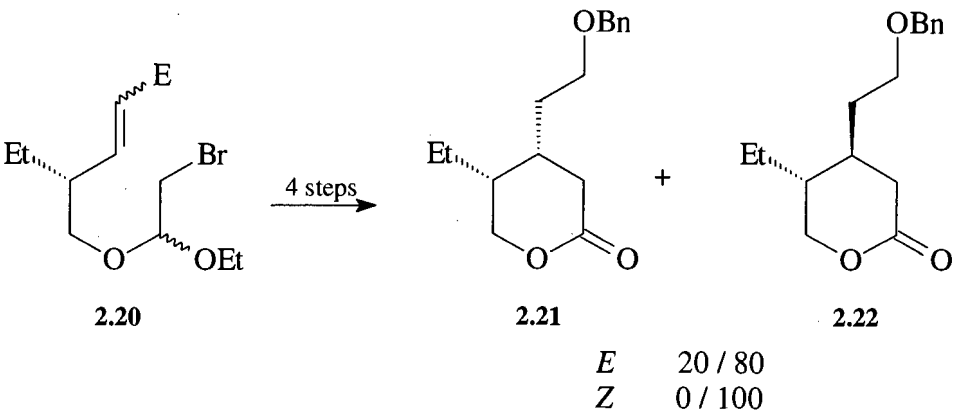
Transition-state Model for 2.18

Radical cyclisations are generally exothermic, kinetically controlled reactions with reactant-like transition states. Although the study of the stereoselective cyclisation of 6-*exo* radicals has received far less attention compared to that of 5-*exo* radicals, a model (Figure 2.5) has been proposed in which the transition states with the lowest energy are chair-like with one stretched bond.[88]

chair-E chair-A

Figure 2.5 *Chair-like models of 6-exo cyclisation*

The chair-E conformer has the radical acceptor in an equatorial position while the chair-A conformer has the radical acceptor in an axial position. These two transition structures are interconverted by rotation of the allylic bond. When a substituent is present on the chain (given that the substituent could be axial or equatorial), of the four possible transition states that are possible, the model predicts that the major product of the cyclisation would be where both substituent and acceptor are equatorial. This model predicts the correct major product for most simple carboxylic systems (usually having low stereoselectivities), as well at those systems with good selectivities. The systems most relevant to our model were those with an allylic stereocentre. In Fukumoto's[89] cyclisation of **2.20** (Scheme 2.20) the diasteromeric ratio was good (**2.21**:**2.22** 80:20). With the corresponding *Z*-alkene the selectivity was excellent (**2.21**:**2.22** 100:0).

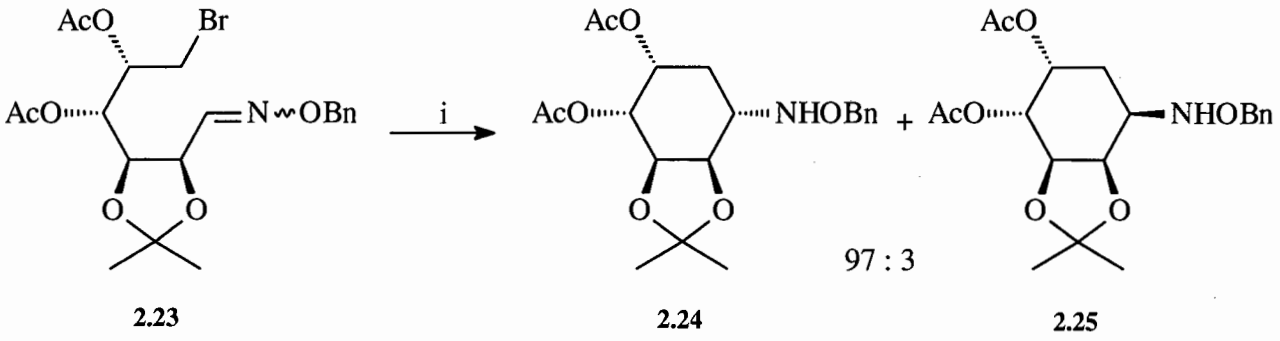


2.20 **2.21** **2.22**

E 20 / 80
Z 0 / 100

Scheme 2.20 Fukomoto's diastereoselective radical cyclisation

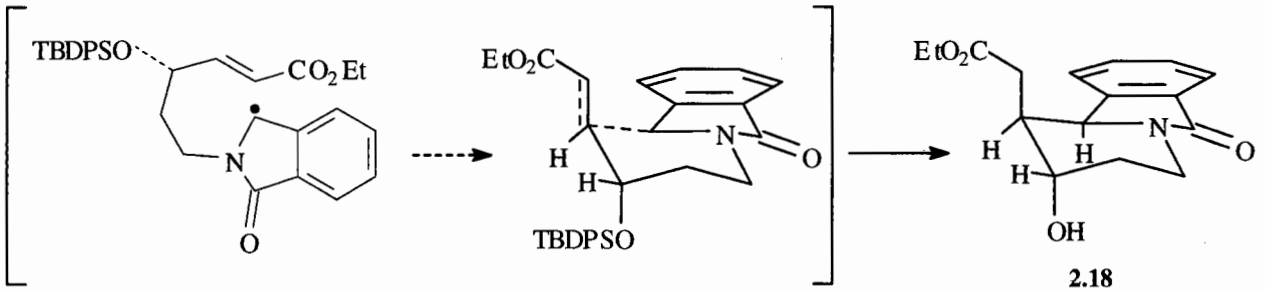
Substituents at this position tend to provide the best stereoselectivities and they dominate when there are multiple substitutions on the chain. As illustrated by Marco Contelles' cyclisation of **2.23** using an oxime ether as the radical acceptor (Scheme 2.21), the chair-like transition states of both products have two pseudoequatorial and two pseudoaxial substituents, but the major product **2.24** has the allylic substituent pseudoequatorial.[90]



2.23 **2.24** **2.25**

Scheme 2.21 *Reagents and conditions* (i) Bu_3SnH, AIBN, 50%

In the present study, involving a stabilized benzylic radical, the transition state was expected to be less reactant-like than normal. Since the major product **2.18** was derived from the highest energy cyclisation product (with TBDPS) having both C-1 and C-2 substituents axial, it may be concluded that **2.18** was produced under kinetic conditions. Thus the configuration of the product could be used to predict the nature of the kinetic transition state (Figure 2.6).



Radical from underneath face (*re*) of enoate ester

2.18

Figure 2.6 Transition-state model for the radical cyclisation

The striking feature of this transition state was that the radical acceptor (the enoate ester functionality) adopts a pseudoaxial orientation in the chair-like transition state, in sharp contrast to other known 6-*exo* cyclisations, including one of a similar compound carried out in a previous study in these laboratories.[85] In that case the substrate had contained a ribose-derived tether and the major product was formed via having the acceptor chain pseudoequatorial in the transition-state. To explain the stereoselectivity observed in our reaction the following transition-state model could be developed. The sterically unencumbered radical approaches from the face of the enoate ester on the same side as the chiral auxiliary so as to minimise steric strain between the ethoxycarbonylmethylene

and OTBDPS groups. The observed stereochemistry at C-1/C-10b shows that the enoate ester reacts with the radical in an *endo* sense, also to minimise its interaction with the bulky OTBDPS group. This results in the *trans* relationship observed between the C-1/C-2 substituents in the product. As the six-membered transition state takes shape the enoate ester functionality adopts a pseudoaxial orientation. These results in conjunction with those from the ribose-derived series indicate a powerful stereo-directing influence of the OTBDPS group overriding the normal preference for the acceptor chain to be pseudoequatorial.

Minor Product 2.19

The minor spot from the column was shown to be a mixture of at least two products by ^{1}H NMR. The major component was isolated by recrystallisation as a colourless solid (19%). The physical properties of this compound were quite different to that of **2.18**, and it decomposed above 140°C. This product was far less soluble than **2.18** and only sparingly soluble in $CDCl_3$. The IR spectrum gave two distinct bands for the carbonyl stretches, the C=O stretch of the ester shifting even further to 1780 cm^{-1} while the lactam C=O stretch remained at 1696 cm^{-1}. In the ^{1}H NMR spectrum the phenylsulfanyl and double bond resonances had disappeared offering evidence of cyclisation. The TBDPS signals had also vanished as expected. However the methylene and methyl signals for the ethyl ester were also missing, suggesting the free hydroxyl had attacked the ester to give a lactone. This implied that the groups on H-1 and H-2 were in a *cis* relationship, which was confirmed by their coupling constant as 7.5 Hz indicative of a *gauche* relationship. The H-2 multiplet had a bandwidth of 22 Hz implying that the coupling of the H-3 protons to H-2 consisted of one *gauche* and one *anti* relationship, only possible if the H-2 proton was axial. Notably absent from the spectrum was a signal corresponding to the benzylic hydrogen; instead a broad signal was present. This signal disappeared after a D_2O wash, suggesting an exchangeable proton such as found on a hydroxyl. All this evidence pointed to the structure **2.19**. This seemed unlikely but was confirmed by X-ray structure analysis (Figure 2.7).

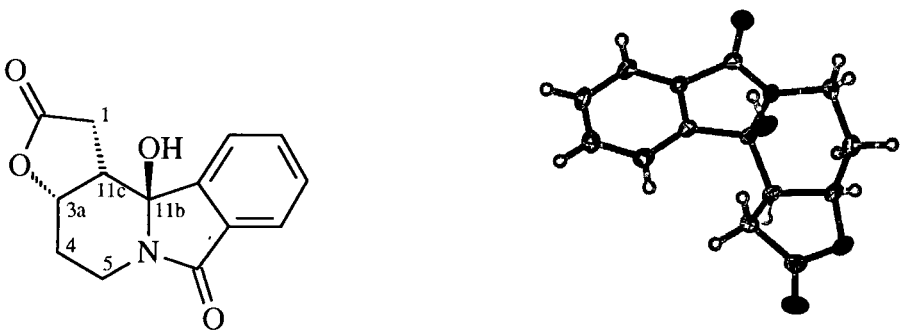
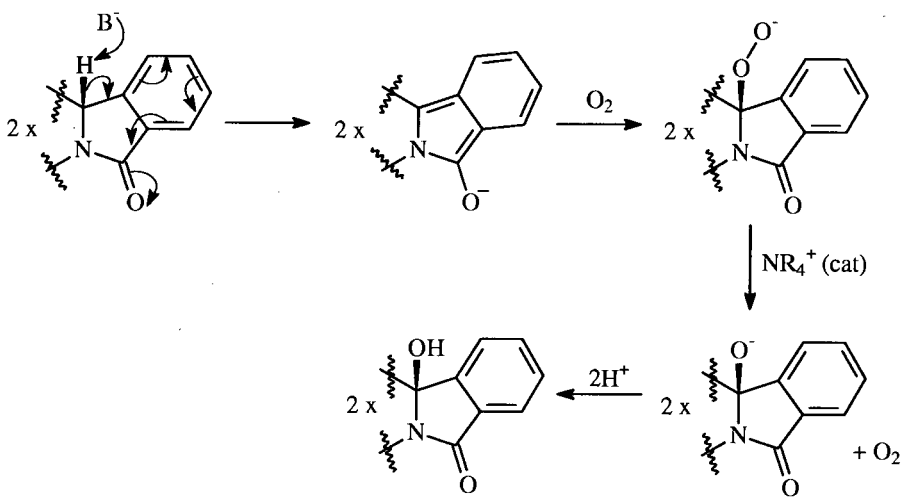


Figure 2.7 Assigned structure and X-ray crystal structure of **2.19**

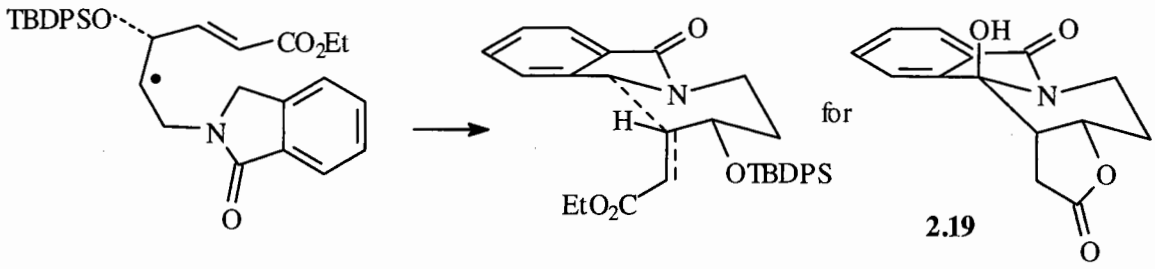
This product can be rationalised by oxidation during the TBAF deprotection. Oxidation of similar compounds by atmospheric oxygen in alkaline solutions has been reported.[91] The basic nature of TBAF may allow generation of a dienolate by abstraction of the benzylic proton (vindicated later). Precedence in the literature exists in which tetralkylammonium salts are known to promote allylic oxidation with oxygen via catalyzing the breakdown of the hydroperoxide intermediate.[92] A mechanism has been proposed in Scheme 2.22.



Scheme 2.22 *Proposed oxidation mechanism*

Compound **2.19** could have been formed from either one of the two diastereomers **A** or **C** (Scheme 2.3) of the original cyclised crude mixture having the ethoxycarbonyl substituent α. Figure 2.8 depicts the transition state for formation of the cyclised diastereomer **C** that is subsequently

desilylated with cyclisation to the lactone, and oxidised with retention of configuration at C-10b. As with formation of **2.18**, it also implies a pseudoaxial configuration for the acceptor side chain in the transition state. In this case, the steric implications of having the C-1/C-2 substituents *cis* is offset by the more favourable placing of the OTBDPS group as pseudoequatorial, as well as the radical approaching *anti* to the silyloxy group. However, the isolated yield of 19% suggests that formation of **2.19** may well have occurred from both of the diastereomers previously mentioned.



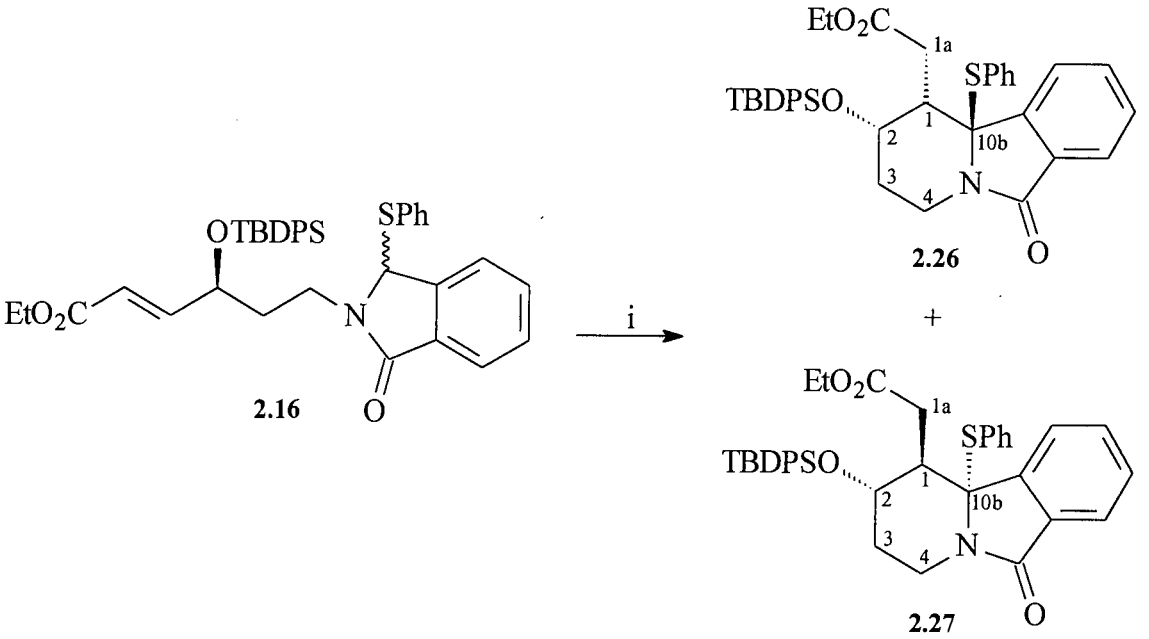
Radical from top face (*si*)
of enoate ester

Figure 2.8 Transition-state model for the diastereomer that undergoes oxidation

2.1.3 Carbanionic cyclisation

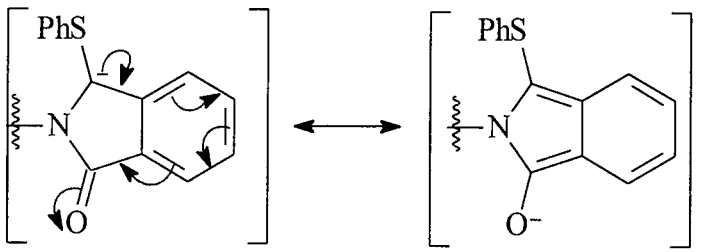
It was expected that the size and nature of the protecting group on the radical precursor would greatly influence the stereoselectivity of the reaction. With this in mind, the radical precursor was deprotected using TBAF so that the TBDPS group could be replaced with a different protecting group.

Interestingly, instead of the expected single product, two new close-running products (tlc) were formed within ten minutes. These products were only slightly more polar than the starting material, and each gave a brick red spot after spraying with anisaldehyde compared to the yellowish spot of the starting material. These new products were separated by careful chromatography eluting with 20 % ethyl acetate/petroleum ether.



Scheme 2.23 *Reagents and conditions:* (i) TBAF, THF, 0°C

Using ^{1}H NMR and COSY experiments, the compounds were identified as **2.26** (51% yield) and **2.27** (34% yield). Their formation could be explained by abstraction of the moderately acidic benzylic hydrogen (also α to PhS) by the basic TBAF to generate a carbanion as a resonance-stabilized dienolate followed by Michael addition to the double bond (Scheme 2.24).



Scheme 2.24 Delocalisation of the anion by the conjugated isoindolone framework

To increase the stereoselectivity, compound **2.16** was treated with lithium diisopropylamide at -78°C in THF. Once again the mixture of products was formed, and after chromatographic separation **2.26** was isolated in an improved 77% yield (**2.27** isolated in 18% yield), implying it to be the kinetic product. The increased proportion of **2.26** can be explained by comparison of the energy diagrams of the two products (Figure 2.9). When the reaction is carried out at low temperature, both reactions become irreversible. The molecules have enough energy to surmount the energy barrier from the

dienolate to **2.26** or **2.27** but not enough for the reverse reaction. Since **2.26** forms faster than **2.27** ($\Delta G_{2.27}° > \Delta G_{2.26}°$), the former is the major product.

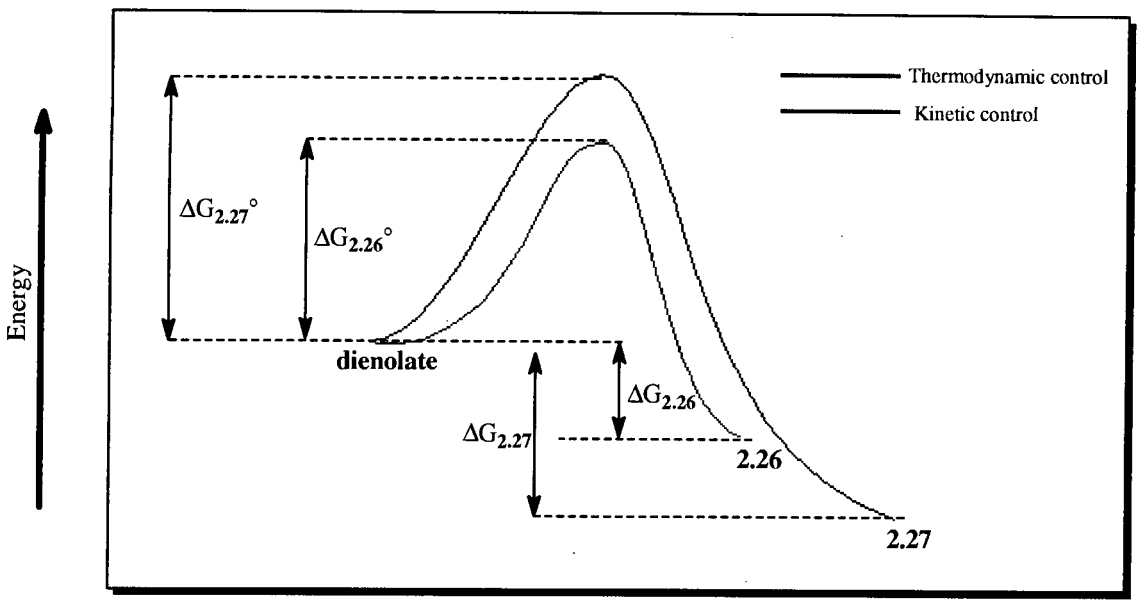
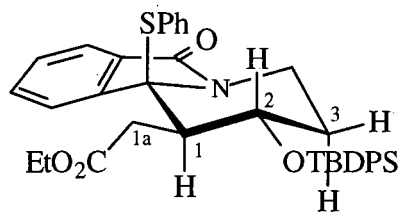


Figure 2.9 The energy diagrams for the formation of **2.26** and **2.27** from **2.16**

As in compound **2.18**, the IR spectrum of both **2.26** and **2.27** gave strong evidence that cyclisation had occurred. Once again the absorbances for the carbonyls were split into two separate bands at 1733 cm^{-1} and 1697 cm^{-1} and the absorbance for the C=C stretch was no longer present. In the ^{1}H and ^{13}C NMR spectra the TBDPS and phenylsulfanyl signals were present for both compounds but those for the double bond had gone.

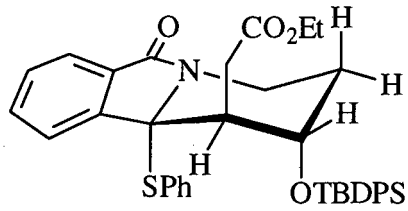
Major product 2.26

The stereochemistry of this compound was assigned purely on the dihedral angles derived from using the Karplus equation on coupling constants in the ^{1}H NMR spectrum. The four possible products are illustrated (Figure 2.10). The resonance for H-2 was a doublet of triplets, revealing H-2 to have one *anti* and two *gauche* interactions with the three vicinal hydrogens and thus to be in an axial configuration. This established **2.26** as structure **D** with the C-1/C-2 substituents *cis*. A small coupling constant for H-1/H-2 ($J_{2,1}$ 4.5 Hz) indicated H-1 to be equatorial. The phenylsulfanyl group is at a bridgehead and therefore is axial. Hence H-1, H-2, and the phenylsulfanyl group could all be assigned as *cis* with the two new chiral centres as (1S, 10bS).



A

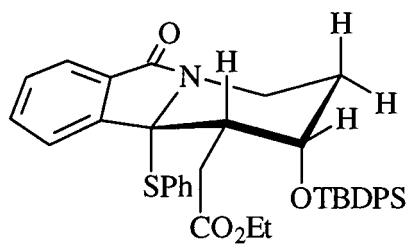
H-2 : H-1 *anti*
H-2 : H-3 *anti*
H-2 : H-3 *gauche*



B

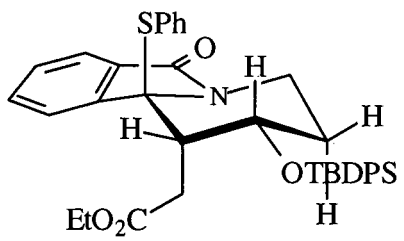
H-2 : H-1 *gauche*
H-2 : H-3 *gauche*
H-2 : H-3 *gauche*

2.27



C

H-2 : H-1 *gauche*
H-2 : H-3 *gauche*
H-2 : H-3 *gauche*



D

H-2 : H-1 *gauche*
H-2 : H-3 *anti*
H-2 : H-3 *gauche*

2.26

Figure 2.10 The four possible diastereomers from the carbanionic cyclisation

The methylene protons of the ethoxycarbonylmethylene substituent were separated by more than 1 ppm, as two doublets of doublets at 1.57 ppm ($J_{1a,1a'}$ 16.7 Hz, $J_{1a,1}$ 8.8 Hz) and 2.73 ppm ($J_{1a',1a}$ 16.7 Hz, $J_{1a',1}$ 2.1 Hz). The geminal protons of C-4 were also separated by more than 1 ppm, one resonating as a triplet of doublets at 3.21 ppm ($J_{4,4'}$ 13.2 Hz, $J_{4,3}$ 13.2 Hz, $J_{4,3'}$ 4.0 Hz), the other as a doublet of doublet of doublets at 4.24 ppm ($J_{4',4}$ 13.4 Hz, $J_{4',3'}$ 5.5 Hz, $J_{4',3}$ 1.3 Hz). The C-3 protons appeared as two multiplets (at 1.55 and 1.74 ppm) and the C-1 proton resonated as a multiplet at 3.38 ppm.

The ^{13}C NMR spectrum was assigned using a heteronuclear correlation experiment (HETCOR). The TBDPS, aromatic, carbonyl, and ethoxy signals resonated at the expected positions. The signal for C-10b resonated in a downfield position at 78.7 ppm due to the deshielding effect of the acylamino and phenylsulfanyl groups α to it. The signal for the other new stereogenic centre at C-1 was influenced by the sulfur bonded to C-10b and hence was shifted downfield compared to the same positon in compound **2.18**. The resonances for C-2, C-3, and C-4 were in very similar positions to those of

2.18. Another notable feature of this compound was the large optical rotation obtained ($[\alpha]_D$ = -190.1°).

Minor product 2.27

The stereochemistry of the minor product **2.27** was deduced by analysis of its ^{1}H NMR spectrum. The H-2 resonance was a quartet at 3.99 ppm ($J_{2,3}$ $J_{2,3'}$ $J_{2,1}$ 2.6 Hz), indicating this proton to be equally coupled to the H-3, H-3', and H-1 protons, and thus in an equatorial configuration (either **B** or **C** in Figure 2.10). As in **2.26**, the phenylsulfanyl group was in an axial position. The stereochemistry of H-1 could thus not be unambiguously assigned. On the basis that it is unlikely that the bulky TBDPS, ethoxycarbonyl methylene, and phenylsufanyl groups would all be *cis* owing to steric constraints in the transition state, **2.27** was assigned as structure **B**. In support of this assignment, no evidence of lactone formation was revealed by ^{1}H NMR or tlc when **2.27** was treated with TBAF.

The ^{13}C NMR spectrum of **2.27** was almost identical to that of **2.26**.

Transition-state Model for 2.26 and 2.27

As in the radical reaction, the stereoselectivity obtained for the major diastereomer **2.26** in the radical cyclisation could be rationalised using a transition-state model (Figure 2.11). As with the radical cyclisation the observed stereochemistry at C-1/C-10b shows that the enoate ester reacts with the carbanion in an *endo* sense in order to minimise its interaction with the bulky OTBDPS group. In contrast to the radical cyclisation, the carbanion is forced to approach from the face of the enoate ester on the opposite side to the chiral auxiliary so as to minimize steric conflict between the phenylsulfanyl and OTBDPS groups, indicating this interaction to be more dominant than the ethoxycarbonylmethylene/OTBDPS interaction in determining the facial attack. This results in the *cis* relationship seen between the C-1/C-2 substituents in the product. As the six-membered transition-state takes shape the enoate ester functionality adopts a pseudoaxial orientation.

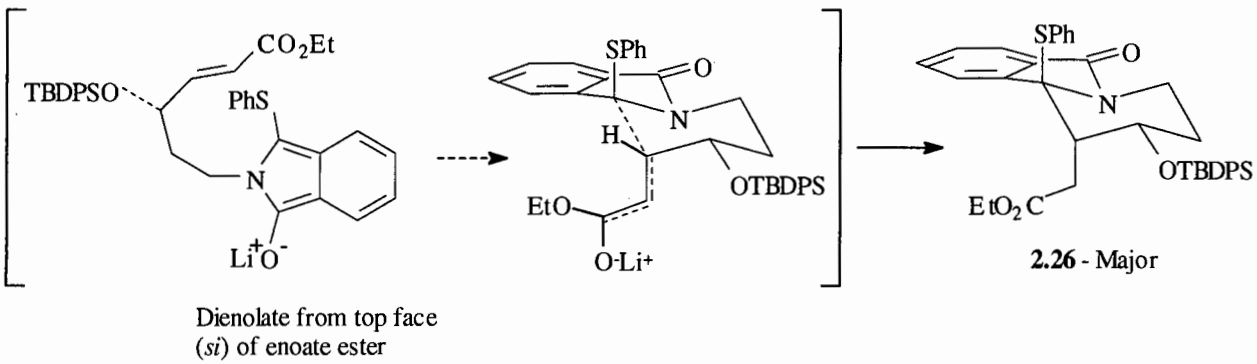
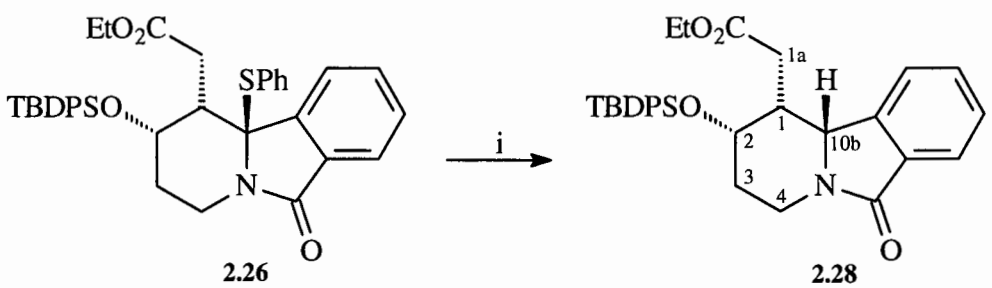


Figure 2.11 Transition-state model for the carbanionic cyclisation

A steric argument can be used to explain why **2.27** is the minor product. Approach of the dienolate is from the bottom face of the double bond promoting an unfavourable interaction between the phenylsulfanyl and the bulky silyl protecting group, although some compensation is obtained from the *trans* C-2/C-2 relationship developing in the product.

To convert **2.26** to an indolizidine (tetrahydropyrido[2,1-*a*]isoindolone), the phenylsulfanyl group had to be replaced with a hydrogen atom in a stereoselective manner. Unsurprisingly, owing to a sp^2-type radical intermediate and the high temperature involved, reduction using tributyltin hydride and AIBN gave a 1:1 mixture of epimers. The most common method for desulfurisation is to stir the sulfide in ethanol with Raney® nickel, and using this method compound **2.27** was successfully desulfurised to give only compound **2.28** in over 90% yield. This reaction required a very large excess of the expensive Raney® nickel, so a different method was sought. Nickel boride[93] was found to be a successful substitute (Scheme 2.25).

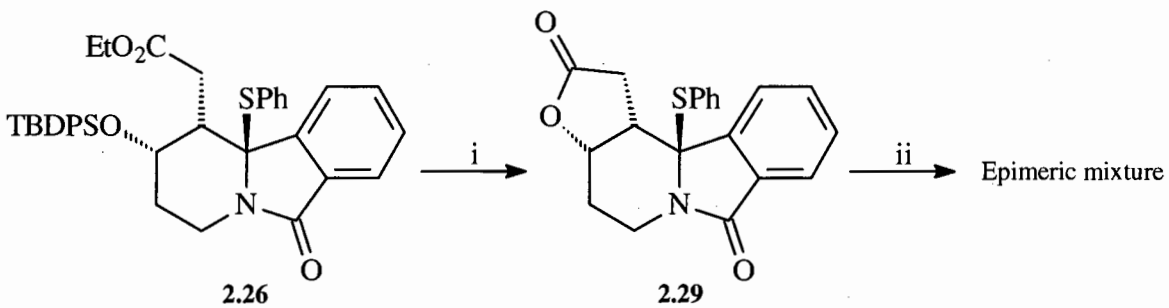


Scheme 2.25 *Reagents and conditions:* (i) $NiCl_2$, $NaBH_4$, EtOH, reflux, 92%

Nickel boride is formed when Nickel (II) salts are reduced with borohydride ion to give a black precipitate, the composition of which is close to Ni_2B. It is more easily prepared and handled than Raney® nickel and much cheaper to produce. It has been reported that the amount of desulfurisation

is increased by lowering the pH and using a high temperature.[94] In a solution of **2.26** in ethanol, nickel boride could be conveniently generated *in situ* by reacting nickel chloride hexahydrate with aqueous sodium borohydride. This mixture was heated under reflux and monitored by tlc. Upon completion, the black precipitate was removed by filtration through Celite®. Care had to be taken when the filtration was performed on a large scale because of the possibility of the precipitate exothermically oxidising after passing air through the dry filter cake following the filtration. NMR spectroscopy showed that the single product was identical to that produced when Raney® nickel was used.

If compound **2.26** was first deprotected with TBAF, to give the lactone, **2.29**, and then the desulfurisation performed using Raney® nickel or nickel boride, the outcome was not stereoselective and a mixture of the two epimers was formed (Scheme 2.26).



Scheme 2.26 *Reagents and conditions:* (i) TBAF, THF, rt (ii) $NiCl_2$, $NaBH_4$, EtOH, reflux

This suggested that the *cis* combination of the bulky TBDPS and ethoxycarbonyl methylene groups in **2.26** resulted in steric impedance on the α-face, resulting in exclusive formation of **2.28** from β-face attack when the TBDPS group was present. In addition, conformational flipping of **2.26** to the other chair would have resulted in an axial OTBDPS group. Desulfurisation of the minor cyclisation product **2.27** also gave a mixture of epimers further supporting structural assignment **B** in Figure 2.10. This epimerisation occurred to relieve 1.3-diaxial strain between the phenylsulfanyl and OTBDPS groups resulting in the OTBDPS group assuming an equatorial configuration.

The IR spectrum of **2.28** was very similar to that of **2.26**. In the ^{1}H NMR spectrum of **2.28**, the signals for the phenylsulfanyl group were no longer present and the signal for the new axial proton, H-10b, resonated as a doublet at 4.28 ppm ($J_{10b,1}$ 3.5 Hz), confirming H-1 to be in an equatorial configuration and that these protons are *cis* (Figure 2.12). Thus the stereochemistry at C-10b was conserved and the absolute configuration for the two new stereocentres was (1*R*, 10b*R*).

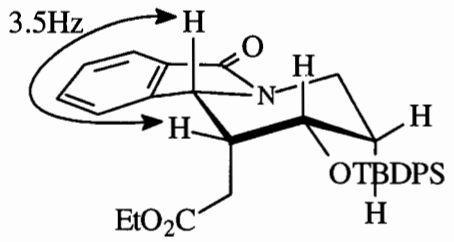
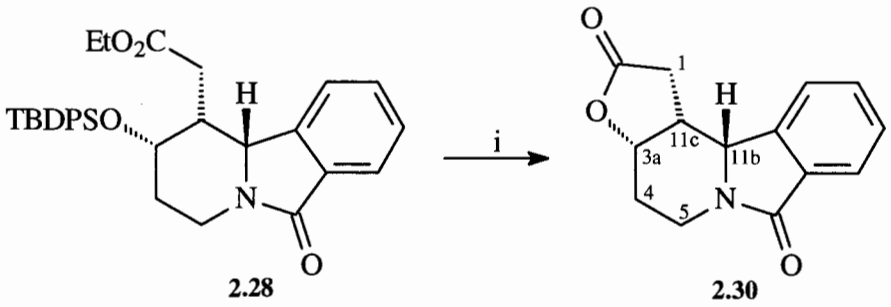


Figure 2.12 H-10b / H-1 coupling constant of **2.28**

The deshielding effect of the sulfur was now absent so the muliplet for H-1 had shifted upfield to 3.19 ppm. The H-2 multiplet had shifted upfield to 4.30 ppm. Both of the resonances for the methylene protons of the ethoxycarbonylmethylene substituent remained virtually unchanged. The protons H-3 and H-3' were now merged as one multiplet at 1.60 ppm. An even greater difference in chemical shift was observed between the geminal protons H-4 and H-4', which had both moved upfield to give a triplet of doublets at 2.73 ppm ($J_{4,4'}$ 13.4 Hz, $J_{4,3}$ 13.4 Hz, $J_{4,3'}$ 4.8 Hz) and a doublet of triplets at 4.12 ppm ($J_{4',4}$ 10.8 Hz, $J_{4',3}$ 4.8 Hz, $J_{4',3'}$ 4.8 Hz). The remaining resonances were similar to those of **2.26**. The aromatic resonances for the phenylsulfanyl group were absent from the ^{13}C NMR spectrum. The signals for the stereogenic centres of C-10b and C-1 were no longer deshielded by the sulfur, and had shifted upfield to 60.2 and 40.3 ppm respectively. A slight upfield shift of the C-2 and C-4 signals was observed, C-2 to 71.7 ppm and C-4 to 36.7 ppm. The C-3 carbon was now more shielded and resonated at 26.5 ppm. The remaining carbons resonated at positions similar to those in **2.26**.



2.28 **2.30**

Scheme 2.27 *Reagents and conditions:* (i) HF, acetonitrile, 45°C, 91%

As a final step, the TBDPS group was removed for further confirmation of the structural assignment of **2.28**. Initially TBAF was used to cleave this protecting group but the ^{1}H NMR spectrum of the product showed that a mixture of products had been formed. The basic nature of TBAF was thought to have promoted side reactions, most likely epimerisation via deprotonation at the benzylic position,

as well as benzylic oxidation. To overcome this problem, aqueous hydrogen fluoride in acetonitrile was used in place of TBAF (Scheme 2.27). Although a high concentration of the acid was needed and the reaction was slow, ^{1}H NMR showed that only one product, **2.30**, was formed in high yield. There was spectroscopic evidence of the formation of a lactone; the acidic conditions causing protonation of the ester carbonyl, which was subsequently attacked by the lone pair of the newly cleaved hydroxyl group to give the lactone. The mechanism is identical to that shown in Scheme 2.4.

The IR spectrum of **2.30** gave strong evidence that lactonisation had occurred. For compound **2.28** the C=O absorbance of the ester was at 1737 cm^{-1}, but in **2.30** the same C=O absorbance was at 1780 cm^{-1}, consistent with a 5-membered ring lactone. No hydroxyl band was observed. The TBDPS and ethoxy protons were absent from the ^{1}H NMR spectrum and no hydroxyl peak was present. There was a notable downfield shift for the H-3a resonance, as a triplet of doublets at 5.02 ppm ($J_{3a,4}$ 7.7 Hz, $J_{3a,11c}$ 7.7 Hz, $J_{3a,4'}$ 5.1 Hz) due to deshielding by the acyl substituent. The doublet for H-11b had shifted downfield to 4.75 ppm and the coupling constant increased to 4.8 Hz (Figure 2.13). This is consistent with a reduction in the H-11b/H-11c dihedral angle that would be caused by lactonisation.

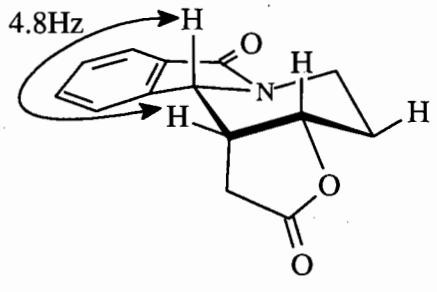


Figure 2.13 H-10b / H-1 coupling constant of **2.30**

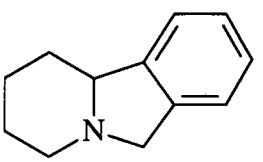
The H-1 multiplet also showed a downfield shift, to 3.42 ppm. The methylene protons of C-1 resonated as two doublets of doublets at 1.67 ppm ($J_{1,1'}$ 18.1 Hz, $J_{1,11c}$ 10.6 Hz) and 2.03 ppm ($J_{1',1}$ 18.1 Hz, $J_{1',11c}$ 9.2 Hz). The protons H-4 and H-4' were now split into two multiplets at 1.89 ppm and 2.28 ppm. A large difference in chemical shift was again observed between the geminal protons H-5 and H-5', and each resonated as two doublets of doublets of doublets at 3.30 ppm ($J_{5,5'}$ 13.2 Hz, $J_{5,4}$ 8.4 Hz, $J_{5,4'}$ 4.2 Hz) and 4.16 ppm ($J_{5',5}$ 13.7 Hz, $J_{5',4'}$ 7.0 Hz, $J_{5',4}$ 5.1 Hz). This large difference was attributed to the different electronic environments that these two hydrogens experience from the adjacent nitrogen lone pair. Typically the equatorial proton is deshielded whereas the axial proton,

which is *anti* to the nitrogen lone pair, is shielded. This effect has been evident in all the other cyclised compounds of this route.

As expected, ethoxy and TBDPS signals were absent from the ^{13}C NMR spectrum and the 2 carbonyl and 6 aromatic carbons were easily identified. The resonance for C-3a was now shifted further downfield to 75.6 ppm due to the electron withdrawing effects of the lactone carbonyl. The C-4 signal had moved slightly downfield to 27.3 ppm. The stereogenic centres of C-11c and C-11b were slightly more shielded and resonated at 37.3 and 55.7 ppm respectively. Both the C-1 and C-5 signals had moved slightly upfield, C-1 to 27.4 and C-5 to 34.9 ppm. Another notable feature of this lactone was a large optical rotation ($[\alpha]_D = +183.0°$).

2.1.4 Reduction of the lactam and aromatic ring

It was desirable to reduce the cyclised products **2.18** and **2.30** to the fully saturated derivatives (a benzo[b]indolizidine) as there was potential for pharmacological activity. The two methods that are well known for the reduction of lactams to cyclic amines are $LiAlH_4$ and $BH_3.SMe_2$. However, exposure of the lactam to these conditions resulted in an unstable product that couldn't be isolated and which turned orange on exposure to air. The instability of similar compounds is known; hexahydropyridoisoindole **2.31** (Figure 2.14) rapidly darkens on standing and is only stable as the hydrochloride salt.[95]



2.31

Figure 2.14 Hexahydropyridoisoindole

Similarly, when a Birch reduction of the aromatic ring was attempted on the lactone **2.30** no homogeneous product could be isolated.

2.1.5 Tertiary aza formation

With stereoselective formation of secondary aza centres via radical and carbanionic methodologies successfully achieved, it was appealing in light of both natural product synthesis and the possibility of modified pharmacological activity to attempt tertiary aza formation on the isoindolone framework. The tertiary α-phenylsulfanyl lactams **2.26** and **2.27** produced via the carbanionic cyclisation were attractive precursors for tertiary aza formation, since a number of avenues could be explored to achieve this transformation. Introduction of an allyl group was seen as an appropriate substituent, since its reactivity profile would allow further elaboration of the products.

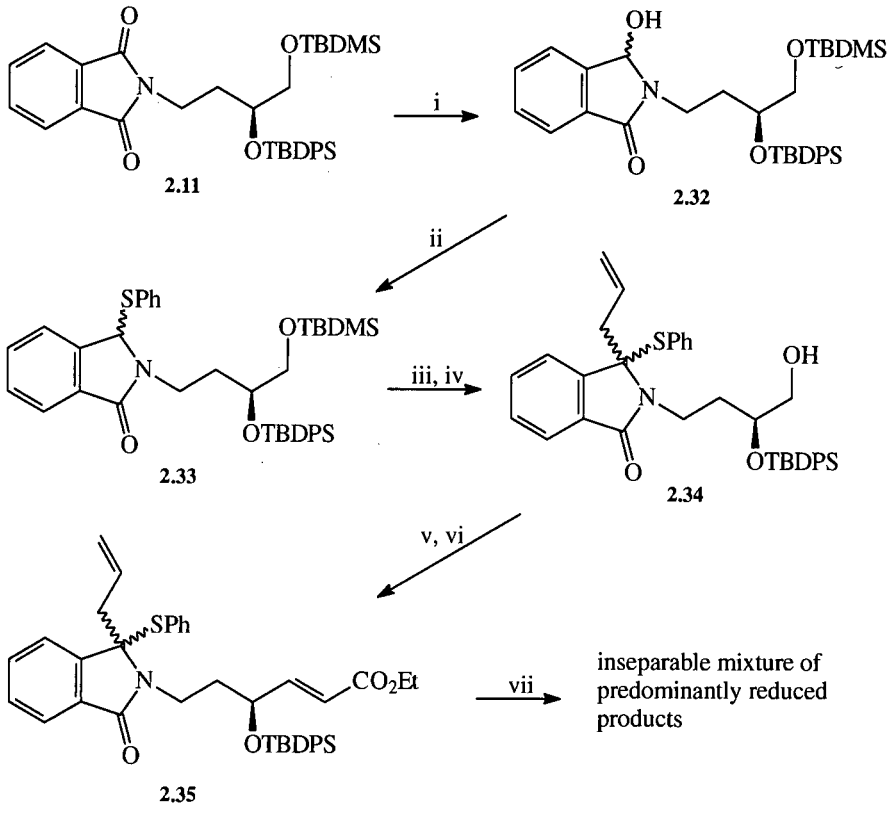
Intermolecular quaternisation was studied initially. The most obvious reaction to pursue was to alkylate using radical chemistry. Keck[96] has shown that substitution of a phenylsulfanyl group alpha to oxygen by allyl is possible using allyltributyltin under photochemical conditions in good yields. Although no literature precendent existed for such an allylation alpha to nitrogen to form a tertiary aza centre, allylation alpha to nitrogen to form a secondary aza centre has been successful in moderate yield.[12] A similar transformation was envisaged for the phenylsulfanyl group alpha to nitrogen in **2.26** and **2.27** so that the tertiary aza centre could be formed. However, all attempts to achieve this transformation (albeit under thermal conditions) upon our system failed.

Attention was thus directed towards developing a carbanionic approach. Direct metallation of the sulfur appeared to be an attractive possibility, followed by trapping the anion with allyl bromide. The most convenient methods of reductive lithiation are those using lithium naphthalenide or lithium di-*tert*-butylbiphenylide (LDBB).[97] LDBB was selected for use on our system since it is a more powerful reducing agent and the high steric environment of the *t*-butyls lead to electron transfer with little of the radical recombination seen using lithium naphthalenide.[98] It is also far easier to separate from the reaction products than lithium naphthalenide.[99] A solution of known LDBB concentration was easily prepared by the reaction of lithium metal with di-*tert*-butylbiphenyl in tetrahydrofuran at 0°C over 4 hours to give a dark blue-green solution. Attempts to form the carbanion using this LDBB solution followed by reaction with allyl bromide gave mainly unreacted starting material and an inseparable mixture of products. This may have been due to competing reaction at the ester functionality.

With the electrophilic methods exhausted, dissociative nucleophilic substitution *via* an acyliminium emerged as the final option. Although no literature precedent existed for this transformation with substitution of sulfur alpha to nitrogen specifically to form a quaternary centre, the equivalent

substitution of hydroxyl or alkoxy substituents is well established,[100,36,34,33] and the versatility of sulfur chemistry made similar transformations an attractive possibility. Although a number of Lewis acids ($BF_3.Et_2O$, $SnCl_4$, TMSOTf, $TiCl_4$) in conjunction with allyltrimethylsilane were used over a range of conditions, no product could be isolated. Two groups[37,38] have reported difficulty in the allyation of bicyclic lactams using acyliminium methodology, producing an enamide instead of a tertiary aza product. Another approach[101] was to convert the sulfide to a sulfone followed by substitution with an organozinc or organocopper reagent generated *in situ* using Grignard reagents and a zinc/copper species. The sulfone could also be used for conventional acyiminium substitution.[102] Attempts to synthesise the sulfone using *m*-CPBA proved unsuccessful, possibly because it was unstable owing to the enhanced reactivity of the benzylic position. Similarly the conversion of SPh to OH for dissociative nucleophilic substitution was unsuccessful.

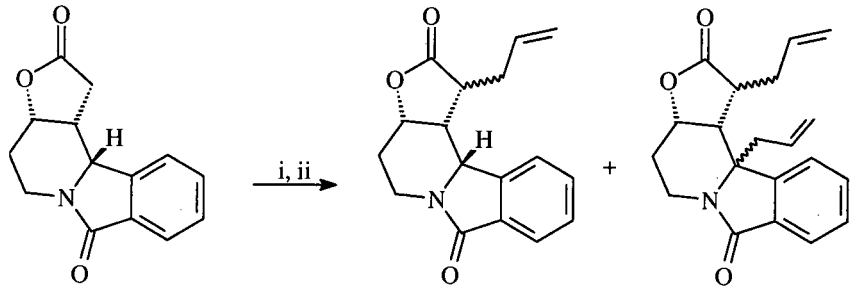
With intermolecular teritaryaza formation proving fruitless, an intramolecular process seemed more viable. To achieve this the allyl group was introduced before the cyclisation (Scheme 2.28). Thus the disilylated product **2.11** was reduced ($NaBH_4$) to give **2.32** and sulfenylated by exchange *via* an acyliminium intermediate in the same fashion as before ($BF_3.Et_2O$, PhSH), giving **2.33**. This sulfide was deprotonated and reacted with allyl bromide followed by chain extension to the enoate ester **2.35** (primary deprotection, Swern and Wittig) in high yield. When this tertiary α-phenylsulfanyl lactam **2.35** was subjected to radical conditions an inseparable mixture of products was formed. The presence of olefinic protons corresponding to the enoate ester in ^1H NMR spectra showed that predominantly reduction at the sulphur had occurred, although the benzylic triplet characteristic of the reduced product was not clearly resolved due to peak overlap. Work by Hart[71] showed similar results when attempting a radical cyclisation with a tertiary α-thioalkyl lactam (Scheme 1.40 in introduction).



Scheme 2.28 *Reagents and conditions:* (i) $NaBH_4$, MeOH, THF, 94% (ii) PhSH, $BF_3.Et_2O$, THF, 87% (iii) *n*-BuLi, allyl bromide, THF, -78°C to rt (iv) TBAF, 91% two steps (v) 'Swern' (vi) $PPh_3{=}CHCO_2Et$, 91% 2 steps (vii) Bu_3SnH, AIBN, PhH, 80°C

Having ruled out substitution of the sulfur by intermolecular and intramolecular methods, the most straightforward cyclisation approach to formation of the tertiary aza centre would be by deprotonation at the benzylic secondary aza centre after the desulfurisation of **2.26** or **2.27**.

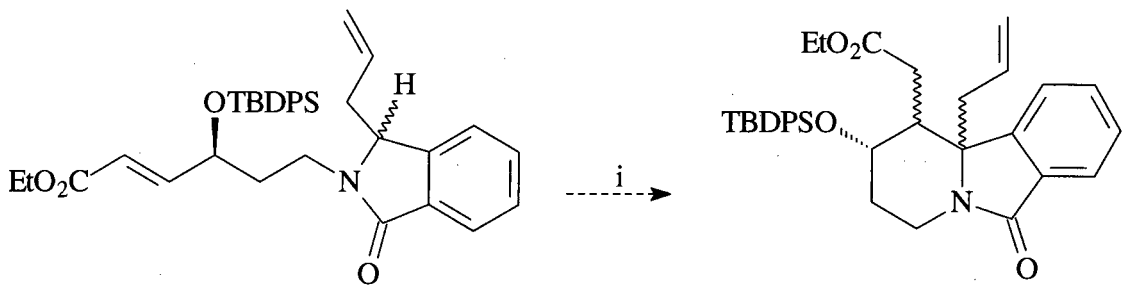
When the lactone **2.30** was treated with LDA (1 eq) followed by allyl bromide (excess), ^1H NMR revealed reaction occurred alpha to the lactone carbonyl to give **2.36** (Scheme 2.29). However there was evidence of some diallylated product **2.37** where allylation alpha to the lactone as well as allylation at the benzylic position had occurred, suggesting tertiary aza formation. The conversion and yield (12% yield for each product) were extremely low and the products could not be purified adequately for characterization purposes.



2.30 2.36 2.37

Scheme 2.29 *Reagents and conditions:* (i) LDA, THF, -78°C (ii) allyl bromide, -78°C to rt

Thus a viable option for further study would now be to induce carbanionic cyclisation of an isoindolone already containing an allyl group at the benzylic position (Scheme 2.30), thus eliminating the problems associated with direct allylation of the cyclised sulfides **2.26** and **2.27** and the chemoselectivity problem of allylation of the lactone **2.30**, as well as the competing reduction of the sulfur when attempting radical cyclisation of **2.35**. However, this route was not attempted.



Scheme 2.30 *Reagents and conditions:* (i) LDA, THF, -78°C

2.2 Conclusion

This study has shown that stereoselective synthesis of tetrahydropyrido[2,1-*a*]isoindolones is possible via radical and carbanionic cyclisation of *N*-tethered α-sulfanyl lactams containing a stereogenic centre allylic to the acceptor terminus. Using the bulky *tert*-butyldiphenylsilyloxy group at the chiral centre results in the acceptor group adopting a pseudoaxial configuration in the transition state. This contrasts with most reported 6-exo-trig radical cyclisations, which have the acceptor pseudoequatorial on steric grounds. This observation reflects a powerful steric effect imposed by the bulky silyl group.

The radical cyclisation route occurred diastereoselectively, giving a major product **2.18** with a *cis* relationship between the benzylic H-10b and the hydrogen at C-1. Similarly, the carbanionic

cyclisation and stereoselective reduction also produces the *cis*-relationship in the major product **2.28**, but as a different diastereomer with opposite absolute configuration to that obtained from the radical cyclisation. These results provide effective models for the D/E junction stereochemistry found in Tacamonine. This suggests that an equivalent study to prepare indolo[2,3a]quinolizidines would be a worthwhile project pursuing based on the expectation that expanding the five-membered ring to a six and changing phenyl to indolo would retain the stereoselectivity.

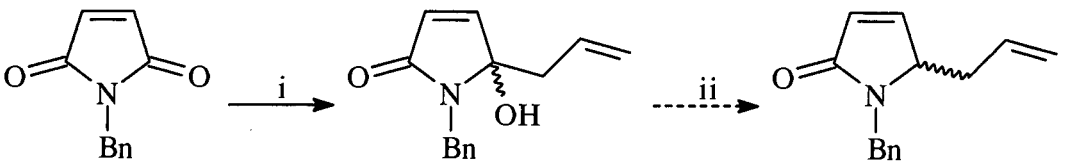
Benzylic quaternisation proved to be challenging, but exploring the reactivity of a carbanionic secondary aza centre, in which the carbanion can be delocalised into a highly conjugated enelactam remains an exciting prospect for further study in tertiary aza synthesis, including systems without the aromatic ring. This study is taken further in the next chapter.

CHAPTER 3

TERTIARY AZA FORMATION: SYNTHESIS OF THE TRICYCLIC LEPADIFORMINE CORE

3.1 Results and Discussion

An attractive route to access the 5-allylpyrrol-2-one **3.2** was *via* a two-step procedure using allyl Grignard reaction on commercially available *N*-benzylmaleimide followed by reduction of the tertiary alcohol thus formed (Scheme 3.1).

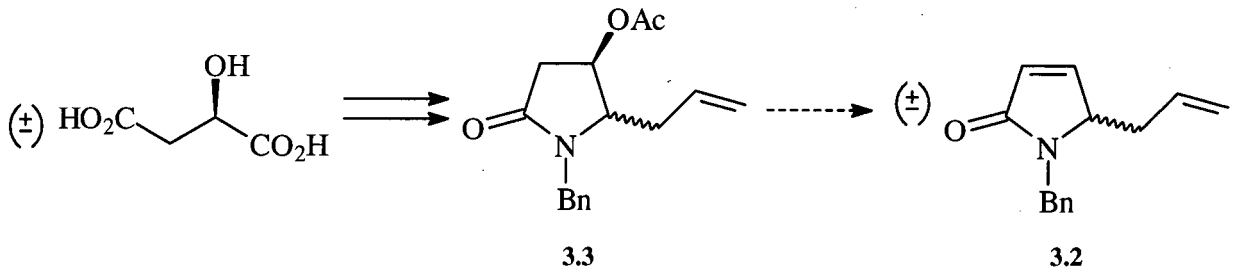


3.1 **3.2**

Scheme 3.1 *Reagents and conditions:* (i) allylMgCl, THF (ii) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2

Grignard reactions on imides are well known, and the electrophilicity of the second carbonyl is significantly reduced after the first alkylation, thus preventing dialkylation. The Grignard was attempted at several temperatures but all reactions gave a poor yield of product **3.1** (<10%), which could not be satisfactorily purified despite multiple chromatographic attempts. It is plausible that the complex reaction profile is due to competing Michael addition on the maleimide.

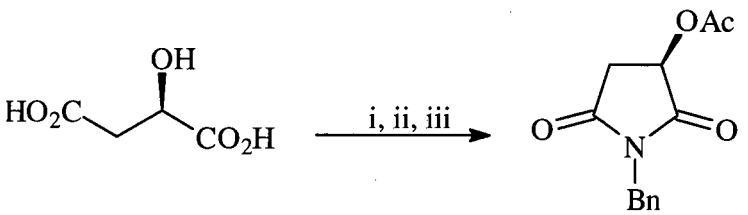
A potential solution to this problem was to introduce the conjugated double bond after allylation. A 5-step procedure was envisaged in which malic acid was first converted to the pyrrolidinone **3.3** via known procedures. The double bond would then be introduced by hydrolysis of the acetate, activation of the liberated hydroxyl to a mesylate and elimination (Scheme 3.2).



3.3 3.2

Scheme 3.2 Proposed route for conversion of malic acid to **3.2**

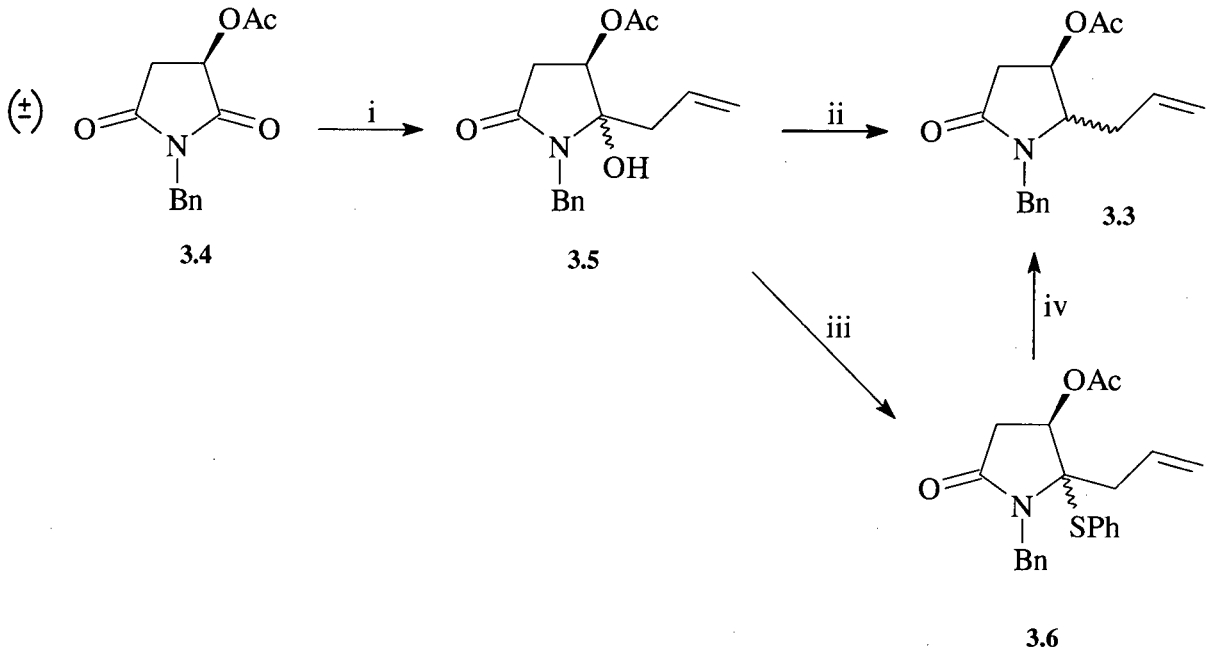
Thus malic acid was heated under reflux with acetyl chloride to form an acetylated anhydride, which was reacted with benzylamine to give an acid-amide which was cyclised with acetyl chloride to afford imide **3.4** in 68 % overall yield (Scheme 3.3).[103]



3.4

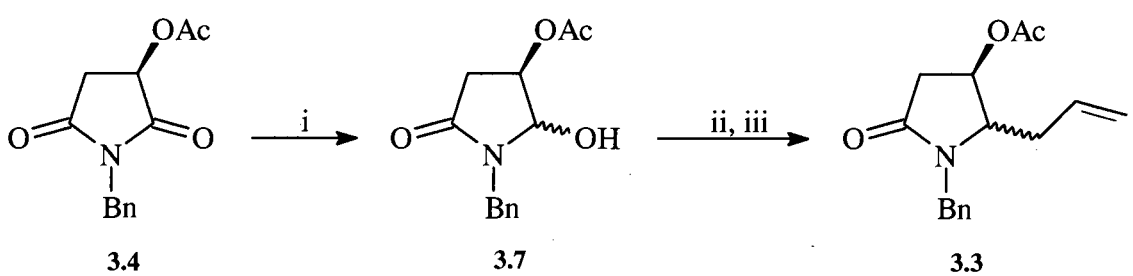
Scheme 3.3 *Reagents and conditions:* (i) AcCl, Δ (ii) $BnNH_2$, THF, rt (iii) AcCl, Δ, 68%

The allyl group could be introduced using two methods. In the first (Scheme 3.4), as before, the imide was subjected to a Grignard reaction using allylmagnesium chloride. Regioselective addition adjacent to the acetyl group was ensured by chelation of the magnesium to the acetyl carbonyl. The tertiary hydroxyl was reduced using triethylsilane *via* an acyliminium intermediate (40% over the two steps). A less efficient reduction could also be carried out in two steps by nucleophilic substitution of the amide with benzenethiol followed by desulfurisation with tributyltin hydride (32% over 3 steps).



Scheme 3.4 *Reagents and conditions:* (i) allylMgCl, THF, -78°C to 0°C (ii) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, -78°C, 40% over 2 steps (iii) PhSH, $BF_3.Et_2O$, CH_2Cl_2, -20°C (iv) Bu_3SnH, AIBN, PhH, 80°C, 32% over 3 steps

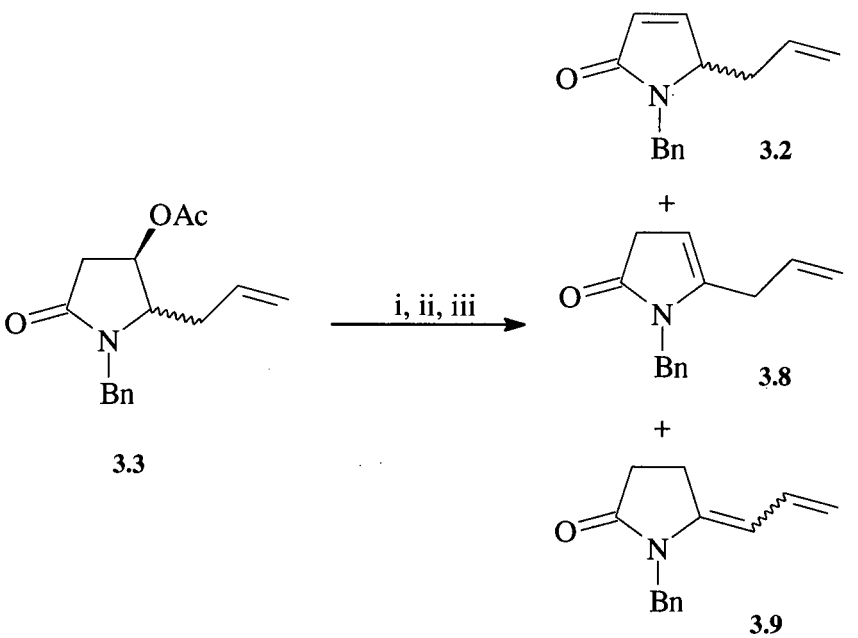
The second and preferred method[103] involved regioselective reduction of the imide **3.4** with sodium borohydride (70% yield). Once again, regioselectivity was achieved by chelation of the boron to the acetyl group. The hydroxyl was acetylated, and then substituted in good yield (2 steps 76% yield) using allyltrimethylsilane and a Lewis acid *via* an *N*-acyliminim intermediate (Scheme 3.5). Though this reaction is reported[104] as stereoselective (2.5:1 of *trans* : *cis*), the diasteroselectivity of the reaction was unimportant owing to loss of the chiral centre in the next step and thus separation of the diastereomeric products was thus unnecessary. Furthermore the subsequent formylation step occurred without stereoselectivity, so formation of a racemate was inevitable, even from enantiopure starting material.



Scheme 3.5 *Reagents and conditions:* (i) $NaBH_4$, EtOH, THF, -40°C, 70% (ii) AcCl, NEt_3, DMAP, CH_2Cl_2 (iii) AllylTMS, TMSOTf, CH_2Cl_2, -20°C, 76%

For double bond introduction, the acetate **3.3** was first hydrolysed using potassium carbonate in methanol, then mesylated at 0°C followed by elimination with triethylamine in refluxing dichloromethane.

The elimination failed to cleanly produce the desired conjugated lactam following chromatography. Instead, isomers **3.8** and **3.9** due to double bond migration were obtained, and the process occurred even on pure enelactam following chromatography (Scheme 3.6). Thus it was not possible to obtain pure enelactam **3.2** for the Mukaiyama reaction (or for characterisation), and the proportion of each product varied between different reactions.

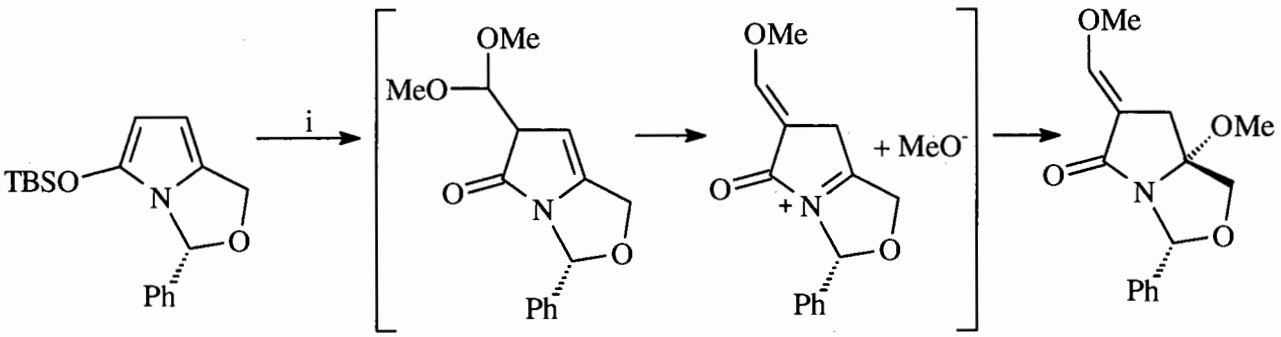


Scheme 3.6 *Reagents and conditions:* (i) K_2CO_3, 90% MeOH/H_2O, rt (ii) MsCl (1eq), NEt_3 (excess), CH_2Cl_2, 0°C (iii) Δ

With the 5-allylpyrrol-2-one **3.2** available (albeit impure), the aim was to introduce a formyl cation equivalent. Vinylogous Mukaiyama aldolization at the 5-position of 2-silyloxypyrroles has received considerable attention in recent years. A major drawback with these approaches popularised by Casiraghi,[105] is the use of the expensive *tert*-butyldimethysilyl trifluoromethanesulfonate for trapping to the silyl dienol ether which is subsequently isolated as a moisture-sensitive[28] product before the dissociative reaction is carried out. In spite of this, a procedure has recently been described for the multikilogram synthesis of the Casiraghi reagent, *N*-Boc-2-*tert*-butyldimethylsiloxy-pyrrole (TBSOP), in pursuit of a clinical candidate.[106]

Precedence for 5-formylation of pyrrol-2-ones using the Casiraghi methodology is well established in the literature,[28] and we were interested in developing a one-pot procedure using the much cheaper chlorotrimethylsilane. Generation of the dienolate was envisaged via deprotonation using *n*-butyllithium, which would be trapped with chlorotrimethylsilane to a trimethylsilyl dienol ether. This would then be used *in situ* in the dissociative formylation step.

However, when the reaction was attempted with the enelactam **3.2**, a very complicated product profile was seen on tlc and none of the desired product could be isolated. The proportion of products due to double bond migration in the crude product mixture appeared to have increased. Langlois[107] attempted the same kind of reaction at the 5-position in a similar molecule obtaining low yields of the desired product. Instead electrophilic addition occurred in a non-vinylogous manner at the 2-position (Scheme 3.7), suggesting analogous events for the complex reaction profile obtained with our enelactam.

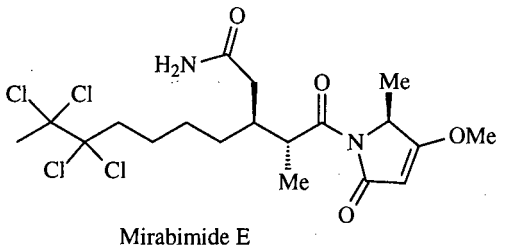


Scheme 3.7 *Reagents and conditions:* (i) $BF_3.Et_2O$, $HC(OCH_3)_3$, CH_2Cl_2, -78°C

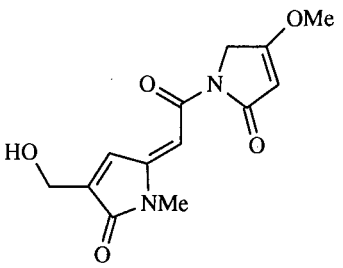
Although no equivalent studies have been carried out on the silyl dienol ether from an appropriately *N*-protected 4-methoxy-3-pyrrolin-2-one (methyl tetramate), it seemed an attractive substrate for the Mukaiyama aldol reaction. We rationalised that the increased steric factor caused by the 5-allyl substituent would be offset by the 4-methoxy group enhancing the 5-coefficient in the HOMO thus favouring regioselective reaction at the 5-position. Another favourable feature of this framework was that the allyl group could be introduced using direct alkylation of a dienolate, avoiding the acyliminium intermediates used so far. Reduction of the enol ether (after tertiary aza formation) was considered to be a challenging but not insurmountable transformation. An unrelated study in these laboratories had shown the 4-*O*-methyl tetramate framework to be readily synthesised, stable and easy to handle.

After taking these factors into account the focus was now switched to the 4-*O*-methyl tetramate framework to achieve tertiary aza formation.

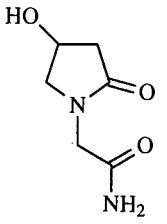
The 4-*O*-methyl tetramate unit is related to the pyrrolidine-2,4-dione (tetramic acid) unit found in many natural products, such as 3-acyltetramic acids,[108] which are biologically important molecules found in microorganisms. The antibiotic tirandamycin is an example, acting by inhibiting bacterial RNA polymerase.[109] The 4-*O*-methyl tetramate unit has proven to be a versatile building block and a number of syntheses have utilized this unit as an intermediate, such as in the synthesis of pukeleimide A,[110] oxiraetam[111] and mirabimide E[112] (Figure 3.1).



Mirabimide E



Pukeleimide

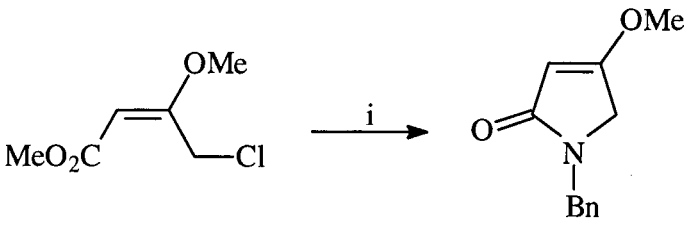


Oxiracetam

Figure 3.1 Natural products synthesised from the 4-*O*-methyl tetramate unit

The most convenient method to access the 4-*O*-methyl tetramate skeleton was by reaction of methyl (*E*)-4-chloro-3-methoxybutenoate with an appropriate amine. Methyl (*E*)-4-chloro-3-methoxy butenoate is available commercially or it can be easily made on a large scale from methyl 4-chloroacetoacetate.[113]

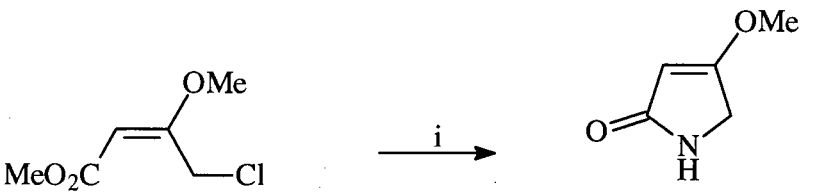
The *N*-benzylated product **3.10** was synthesised in moderate yield by stirring a solution of the butenoate in acetonitrile with benzylamine and Hűnig's base at elevated temperatures (Scheme 3.8).



3.10

Scheme 3.8 *Reagents and conditions:* (i) $BnNH_2$, diisopropylethylamine, MeCN, 50°C, 58%

A superior approach involved using ammonia (Scheme 3.9), which not only returned a high yield (82%) of **3.11** and one much higher than reported in the literature, but also allowed isolation by direct crystallisation to give long needles of colourless crystalline product without the need for tedious chromatography. Subsequent *N*-protection of **3.11** could then be effected with a range of protecting groups.



3.11

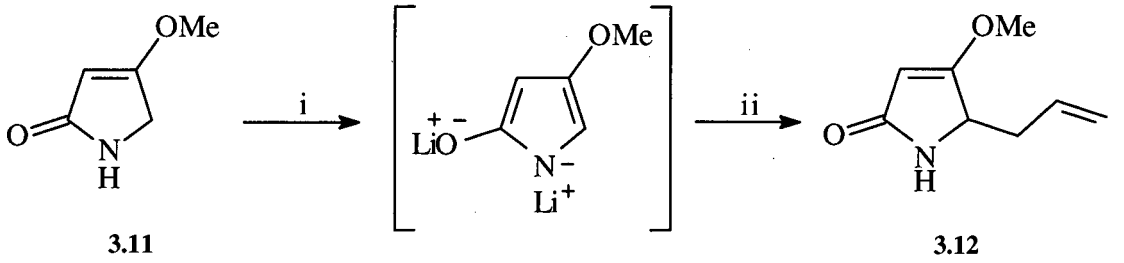
Scheme 3.9 *Reagents and conditions:* (i) 10% NH_3 (aq), 65°C, 82%

Attempts to obtain the 5-allylated product **3.13** by alkylation of the lithium dienolate of *N*-benzylated **3.10** were frustrated by a lack of regioselectivity, a mixture of the 3- and 5-alkylated and dialkylation products always being obtained.

To surmount this problem, other methods of 5-alkylation were scrutinized. The synthesis of 5-ethyl 4-methoxy-3-pyrrolin-2-ones has been reported[114] by treating the dianion of methyl acetoacetate with one equivalent of ethyl iodide followed by conversion to the corresponding bromoalkenoate and reaction with an appropriate amine. However, the yields of product were only moderate.

Jones[115] reported monobenzylation and monomethylation at the 5-position when 4-*O*-methyl tetramate **3.11** was treated with an excess of base to generate the dianion followed by *C*-alkylation using one equivalent of the appropriate alkyl halide. Though monoallylation was not attempted, it was likely that the analogous alkylation with an allyl halide would be successful. As expected, the dianion was successfully C-monoalkylated using one equivalent of allyl bromide (Scheme 3.10) to

afford chromatographically pure 5-allylated product **3.12** in 79% yield as well as a mixture of the 3-allylated product and recovered starting material (approx 15%).



3.11 **3.12**

Scheme 3.10 *Reagents and conditions:* (i) *n*-BuLi (2eq), THF, -78°C (ii) allyl bromide (1eq), 79%

Alkylation at the 5-position was confirmed using ^{1}H NMR (Figure 3.2). The H-3 signal was unchanged whereas the two proton H-5 singlet of the starting material now integrated as a one-proton doublet of doublets consistent with coupling to the allyl methylene protons. The broad NH proton was unaffected during the reaction, eliminating the possibility of *N*-alkylation.

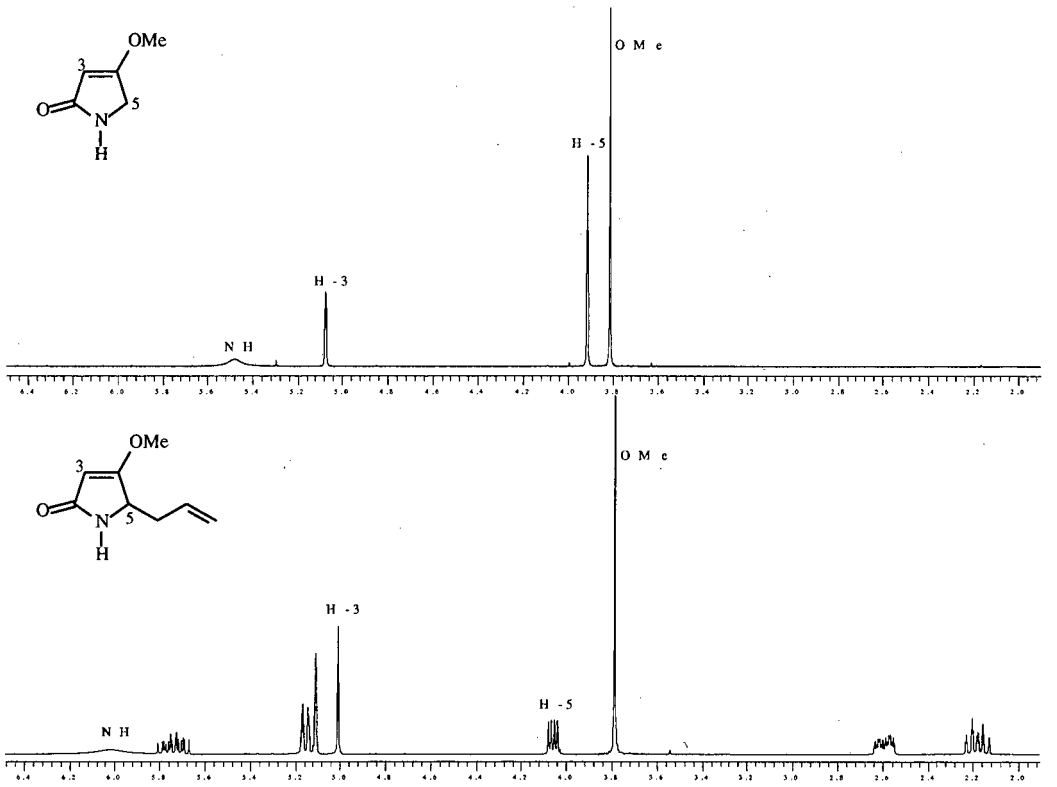
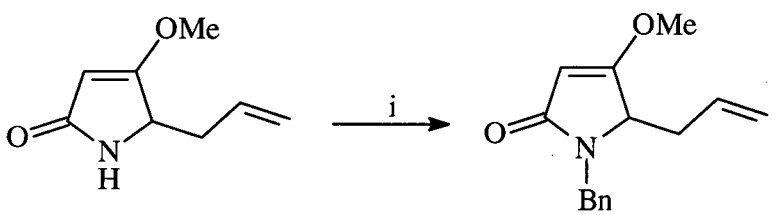


Figure 3.2 Comparison of **3.11** and **3.12** ^{1}H NMR spectra

The IR spectrum of **3.12** showed characteristic peaks at 3453cm^{-1} (NH), 1684 cm^{-1} (C=O) and 1627 cm^{-1} (C=C stretch of vinyl ether). Similarly, the ^{13}C NMR spectrum showed C-3 virtually unchanged whereas C-5 had moved downfield, consistant with substitution. The three new signals of the allyl group were also apparent.

Alkylation at nitrogen could then be achieved in two ways.[116] One method involved deprotonation with *n*-butyllithium and addition of benzyl bromide. The other more convenient method used phase-transfer conditions (benzyl bromide, powdered potassium hydroxide and tetrabutylammonium hydrogensulfate), the catalytic tetraalkylammonium cation acting as a counter-ion for the hydroxyl anion thus aiding its solubility in the organic solvent. Using the latter method, the *N*-benzylated product **3.13** was obtained in high yield (88%) as a stable crystalline solid after column chromatography (Scheme 3.11).



3.12 **3.13**

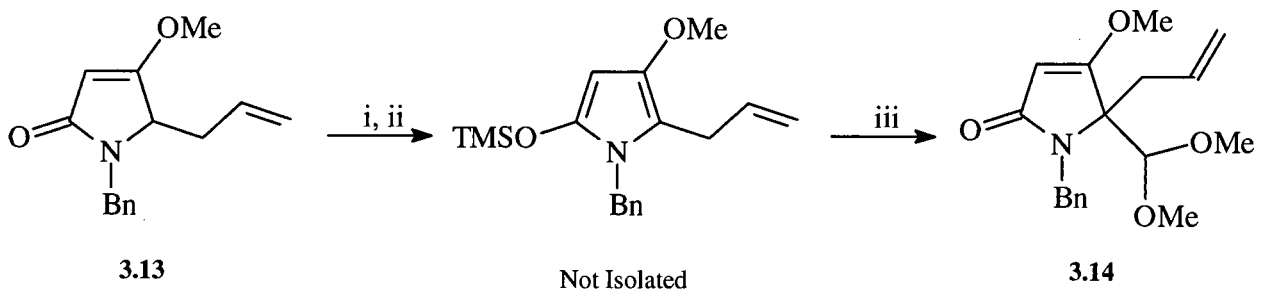
Scheme 3.11 *Reagents and conditions:* (i) BnBr, KOH, Bu_4NHSO_4, THF, rt, 88%

As expected, the exchangeable NH signal had vanished from the ^{1}H NMR spectrum of **3.13** and the new benzyl signals were now visible. The influence of the C-5 stereocentre in the spectrum was evident by the diastereotopic benzylic protons resonating as two doublets, compared to the singlet observed for the enantiotopic benzylic protons in **3.10**. The IR spectrum was similar to that of **3.12** apart from loss of the broad NH peak. Five new peaks were seen in the ^{13}C NMR spectrum, with the benzylic carbon resonating at 43.2 ppm.

With **3.13** in hand the stage was set for the pivotal tertiary aza centre construction. In light of the poor regioselectivity of the alkylation with the lithium dienolate, the Mukaiyama aldol presented itself as a more attractive prospect than by direct alkylation of the carbanion. γ-Alkylation was considered to be favoured for the much softer silyl dienol ether, and as mentioned earlier, we were interested in developing a one-pot procedure using chlorotrimethylsilane. Jones reported[116] preparing

the TMS silyl dienol ether of 4-methoxy-1-methyl-3-pyrrolin-2-one, but carried out no dissociative reactions on it.

Gratifyingly the 5,5-disubstituted product **3.14** was obtained as the only product in high yield (88%) by sequential treatment of **3.13** with *n*-butyllithium, chlorotrimethylsilane, trimethylorthoformate, and boron trifluoride etherate (Scheme 3.12). This constitutes the first one-pot reaction of its class, giving a higher yield than any analogous procedure in which the silyl ether has been isolated, and uses the far cheaper chlorotrimethylsilane (instead of *tert*-butyldimethysilyl trifluoromethanesulfonate) making it industrially attractive for Fine Chemicals production. It seems plausible that the methoxy group has enhanced the efficiency of this reaction.



3.13 Not Isolated **3.14**

Scheme 3.12 *Reagents and conditions:* (i) *n*-BuLi (1.2eq), THF, -78°C; (ii) TMSCl (1.5eq); (iii) $HC(OMe)_3$, $BF_3{\cdot}Et_2O$, 88%.

The ^1H NMR spectrum confirmed the regioselectivity of formylation, with the expected H-3 signal unchanged and the H-5 signal absent, thus confirming alkylation had occurred at the 5-position (Figure 3.3). Predictably, the two new methoxy groups of the acetal appeared as two non-equivalent diastereotopic singlets, being in close proximity to the new stereogenic centre, and the acetal proton also appeared as a singlet. Whereas the benzylic protons in the starting material **3.13** resonated as two doublets with a difference of more that 1 ppm (3.98 and 5.16 ppm), the same two benzylic protons in the product resonated as a singlet (4.61 ppm), revealing a much similar electronic environment on each face of the pyrrolin-2-one.

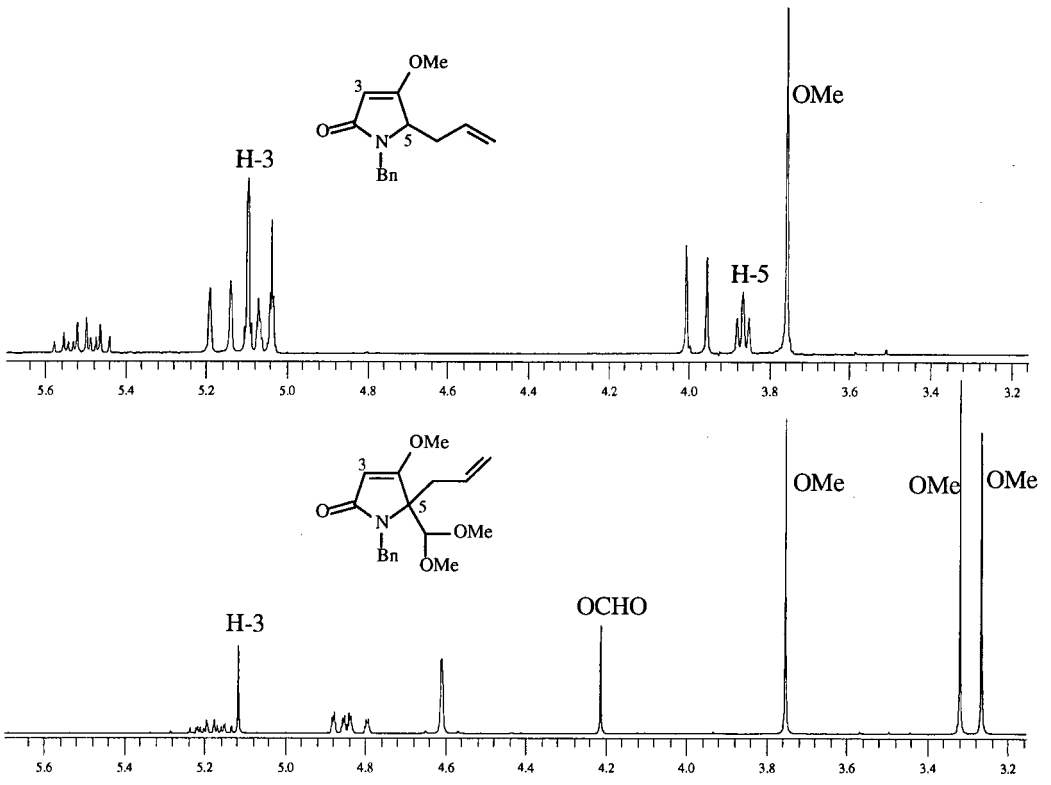
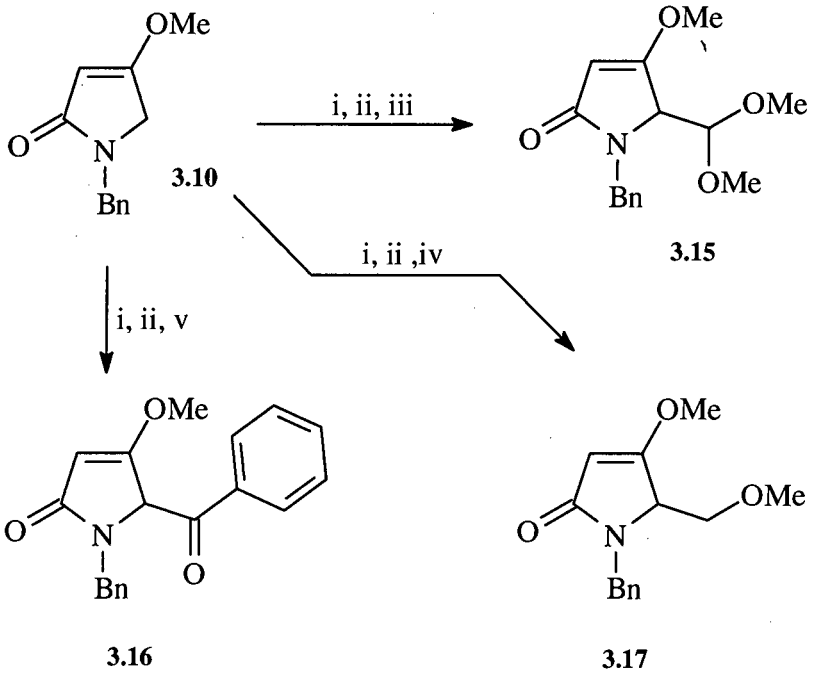


Figure 3.3 Expanded section of **3.13** and **3.14** ^{1}H NMR spectra

In the IR spectrum of **3.14** the peaks for the carbonyl and vinyl ether stretches were now closer at 1669 cm^{-1} and 1640 cm^{-1} respectively. The C-5 peak in the ^{13}C NMR spectrum was more deshielded (71.8 ppm) whereas C-3 was relatively unchanged. Two new methoxy carbon signals were observed and the deshielding effect of these methoxy groups could be seen on the new acetal carbon by its downfield resonance (107.6 ppm).

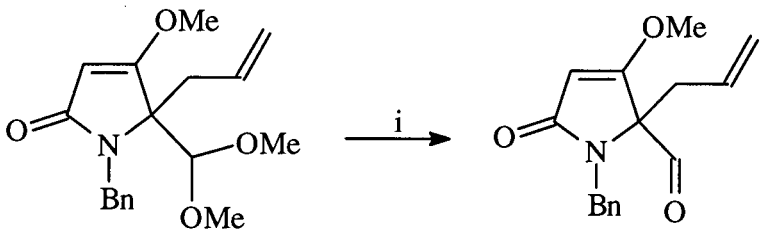
In order to test the scope of the new one-pot Mukaiyama aldol reaction, a range of electrophiles were tested using the *N*-benzyl 4-methoxy-3-pyrrolin-2-one **3.10** as substrate (Scheme 3.13). Though reaction was successful with all these electrophiles, complete consumption of the starting material was not achieved and the products and starting material could not be separated. Rather than devoting time to developing the scope of this methodology, effort was instead directed towards elaboration of **3.14** to the tricyclic lepadiformine framework.



Product	Yield (%)	Conversion (%)
3.15	>90	87
3.16	>90	55
3.17	69	47

Scheme 3.13 *Reagents and conditions:* (i) *n*-BuLi, THF, -78°C (ii) TMSCl (iii) $HC(OMe)_3$, $BF_3{\cdot}Et_2O$, >90% based on 13% unreacted **3.10** in ^1H NMR (iv) $H_2C(OMe)_2$, TMSOTf >90% based on 53% unreacted **3.10** in ^1H NMR (v) BzCl, $SnCl_4$, CH_2Cl_2, 69% based on 45% unreacted **3.10** in ^1H NMR

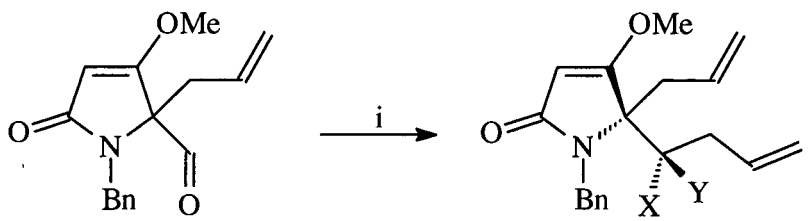
In order to perform the metathesis chemistry, the acetal **3.14** had to be deprotected to form an aldehyde, which could then be extended using a Grignard reaction. Hydrolysis of the usually labile dimethoxy acetal to the aldehyde was surprisingly stubborn, probably as a result of destabilization of the intermediate oxocarbenium ion by the adjacent electron-withdrawing acylamino group. It was stable in *p*-toluenesulfonic acid in acetone, HCl/THF and H_2SO_4/THF. It was eventually removed by stirring for a sustained period in trifluoroacetic acid (24h) at 35°C to give the aldehyde **3.18** in quantitative yield (Scheme 3.14). If the reaction was heated above 40°C decomposition products were observed. The crude ^1H NMR spectrum showed the characteristic downfield signal of an aldehyde (8.6 ppm), as well as loss of 2 methoxy signals. It also streaked on tlc, another characteristic aldehyde trait. Given that the aldehyde decomposed when exposed to air for several days, it was reacted immediately after isolation.



3.14 **3.18**

Scheme 3.14 *Reagents and conditions:* (i) CF_3CO_2H (1% H_2O), 35°C, 95%

Reaction of the aldehyde **3.18** with allylmagnesium chloride at 0°C gave a complex mixture of products, possibly due to competing Michael addition at the 4-position. However, when the Grignard reagent was added at -78°C, and the reaction was allowed to slowly warm to 0°C, only 2 products were observed by tlc after work-up (Scheme 3.15). From ^{1}H NMR of the crude residue, these were assigned as the two diastereomers of the homoallylic alcohol, present in a 3:1 ratio. Although the mixture of alcohols would be oxidized to give one product later in the synthesis, the diastereomers were separated to aid characterization of the intermediate reactions. Column chromatography of the crude product achieved partial separation. The major diastereomer **3.19** was a colourless, crystalline solid whereas the minor diastereomer **3.20** was a colourless oil. The major diastereomer could also be crystallized out of the crude residue using diethyl ether. The relative stereochemistry of each diastereomer could not be assigned at this point.



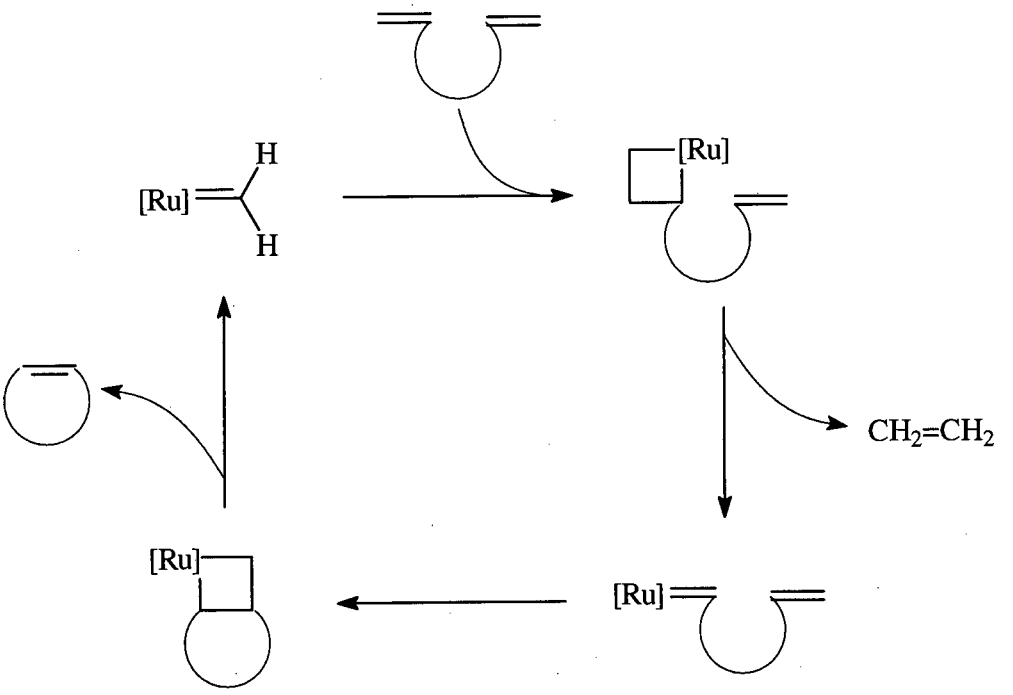
3.18

3.19 X = OH, Y = H
3.20 X = H, Y = OH

Scheme 3.15 *Reagents and conditions:* (i) allylMgCl, THF, -78°C to rt, 76% (**3.19** : **3.20** 3:1)

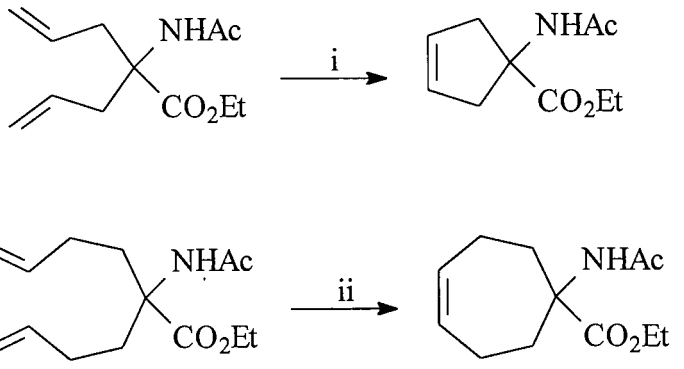
The only notable difference in the IR spectra of **3.19/3.20** from the spectrum of **3.18** was a new peak in the 3500 cm^{-1} region (OH). The ^{13}C NMR spectra of **3.19** and **3.20** were very similar, the new allyl signals resonating in the expected positions and the signal for the carbon α to OH appearing at 73.4 ppm for **3.19** and 72.8 ppm for **3.20**.

The stage was now set for the ring-closing metathesis, and commercially available Grubb's catalyst was chosen for this purpose. This is a ruthenium-based alkylidene complex that has been carefully tuned to enhance reactivity and stability. This catalyst has a high functional group tolerance, being stable toward many groups, such as alcohols, amides, aldehydes and carboxylic acids. It reacts preferentially with carbon-carbon double bonds, and operates under mild conditions generating ethylene as the side product with a loading of only 5 mol % usually being necessary for ring-closing metathesis. A simplified mechanistic cycle is illustrated (Scheme 3.16).



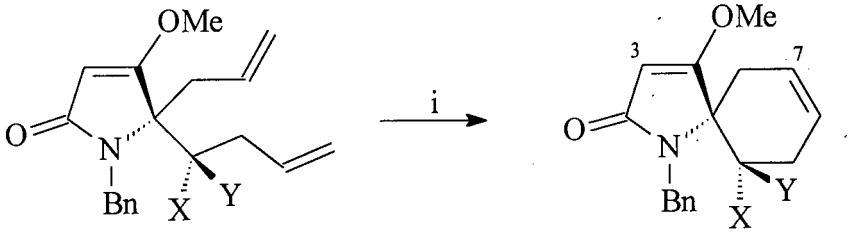
Scheme 3.16 Simplified mechanism of ring-closing metathesis

Ring-closing metathesis has been widely utilized in synthesis of nitrogen-containing compounds,[117] and it has mainly been used where the newly formed ring is heterocyclic. It has been applied to a few carbocyclic systems with nitrogen functional groups such as simple carbocyclic amino acids[118] (Scheme 3.17).



Scheme 3.17 *Reagents and condtions:* (i) $RuCl_2(PCy)_3$=CHPh (cat), PhMe, 110°C, 90% (ii) $RuCl_2(PCy)_3$=CHPh, PhMe, 110°C, 92%

In our system, both diastereomers **3.19** and **3.20** were easily and cleanly cyclised by refluxing with the catalyst in dichloromethane to give the spirocycles **3.21** and **3.22** respectively, both in high yield (Scheme 3.18). Provided the starting material was pure, the reaction was very efficient and a catalyst concentration of only 2 mol % was needed. During the reaction, the colour of the solution changed from purple to brown, and the change on tlc was notable. Using anisaldehyde spray the starting material appeared as a less polar bright purple spot whereas the product was a far more polar orange spot.



3.19 X = OH, Y = H
3.20 X = H, Y = OH

3.21 X = OH, Y = H
3.22 X = H, Y = OH

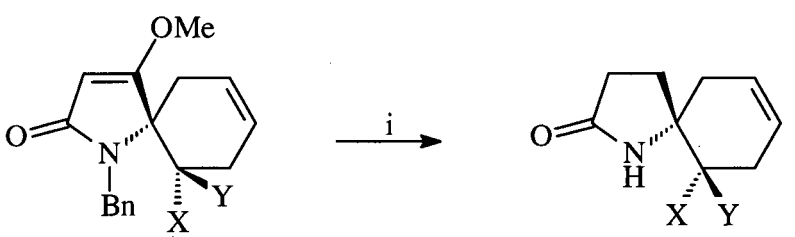
Scheme 3.18 *Reagents and conditions:* (i) $RuCl_2(PCy)_3$=CHPh, CH_2Cl_2, 40°C, 2h, 92%

A common problem with such metathesis reactions is separation of ruthenium byproducts from the reaction products. Methods to overcome this problem have been reported[119,120]. However, in this case it was found that pure products could be obtained by simple evaporation of the reaction solvent, followed by chromatography and recrystallisation. Both spirocycles **3.21** and **3.22** were colourless, crystalline solids, and the cyclisation was corroborated by ^{1}H NMR spectrometry. The spectra displayed a number of changes in the olefinic region with each new compound showing only one multiplet integrating for two alkene protons consistent with the expected stucture. The position of the

upfield vinyl ether singlet remained unchanged. As expected, the hydroxyl group had not been affected, as evidenced by an exchangeable signal in the spectra of both spirocycles. The IR spectra confirmed this by virtue of a peak at 3550 cm^{-1} (OH group). Each ^{13}C NMR spectrum had lost two signals corresponding to the loss of ethylene, and only two olefinic resonances were now observed.

In order to access the fully saturated lepadiformine core, the vinyl ether and the isolated double bond had to be reduced. Laffan has reported[111] on hydrogenolysis of the vinyl ether of a 4-*O*-methyltetramate using platinum catalysis. Dissolving metal reduction in a related system of an α,β-unsaturated lactam has also been achieved,[32] and this cheaper alternative was eventually chosen. However, the analogous reaction on a 4-*O*-methyl tetramate was unknown at the time of this study and complete reduction of a vinyl ether is a multistep transformation.

Initial attempts at reduction using lithium or sodium gave mixtures of partially reduced products. Gratifyingly, after some fine-tuning, the benzyl and vinyl ether functionality could both be completely reduced by refluxing the spirocycles **3.21** or **3.22** at -33°C for a sustained period with excess sodium metal in a mixture of liquid ammonia/THF to give spirocycles **3.23** or **3.24** respectively (Scheme 3.19) in high overall yield (85%). The liquid ammonia was pre-dried over a small amount of sodium to remove water and trace impurities. After work-up with solid ammonium chloride, the solid residue had to be thoroughly extracted with dichloromethane to recover the polar products. Ethyl acetate could not be used, as the products were only partially soluble in this solvent. Once again, both products were colourless, crystalline solids. The UV activity of **3.23** and **3.24** on tlc was substantially diminished compared to **3.21** and **3.22**, owing to the loss of conjugation and aromatic functionality.



3.21 X = OH, Y = H
3.22 X = H, Y = OH

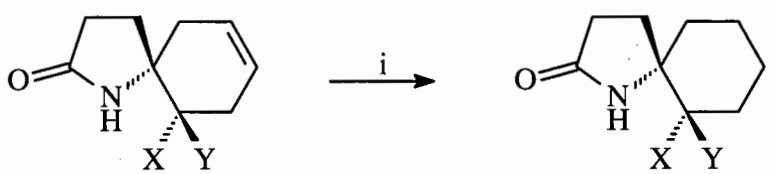
3.23 X = OH, Y = H
3.24 X = H, Y = OH

Scheme 3.19 *Reagents and conditions:* (i) Na, NH_3 (liq), THF, -33°C, 85%

The ^{1}H NMR spectra of the products **3.23** and **3.24** showed loss of the benzyl resonances and the appearance of a broad NH singlet in the downfield region typical of a lactam. The signals for the vinylic proton and methoxy group had vanished and integration of the aliphatic region showed that four new aliphatic protons were present. Dissolving metal reductions are known to only reduce conjugated double bonds, so unsurprisingly the isolated double bond was not affected during the reaction.

There was a notable change in the IR spectra of **3.23** and **3.24**. Instead of the two strong peaks in the 1630-1680 cm^{-1} region seen for **3.21/3.22**, only one peak could now be seen at 1695 cm^{-1} corresponding to the single lactam carbonyl signal as a result of the vinyl ether reduction. Two peaks were seen around 3500 cm^{-1} due to the hydroxyl and NH groups. As expected, the ^{13}C NMR spectra showed loss of the methoxy and five benzyl resonances. The signals for the two carbons of the vinyl ether double bond had shifted dramatically upfield into the aliphatic region, and the two isolated olefinic signals had not been affected.

The isolated double bond could be easily reduced with standard hydrogenation conditions using palladium on carbon-catalyst in ethanol under a hydrogen atmosphere to give the saturated spirocycles **3.25** and **3.26** respectively (Scheme 3.20). The reaction was difficult to follow by tlc as both starting material and product had the same Rf, and after visualizing the spots with anisaldehyde their colours were only subtly different. Fortunately, the reaction was rapid and went to completion within 60 minutes. The olefinic signals of the ^{1}H NMR spectra had vanished and integration of the aliphatic region showed that 4 new aliphatic protons were present.



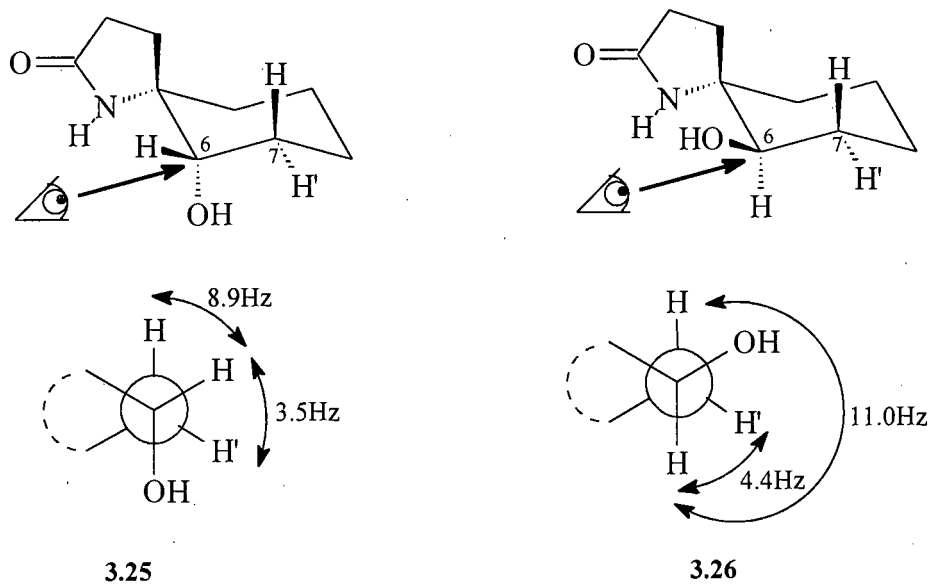
3.23 X = OH, Y = H
3.24 X = H, Y = OH

3.25 X = OH, Y = H
3.26 X = H, Y = OH

Scheme 3.20 *Reagents and conditions:* (i) H_2, Pd/C, EtOH, 92%

The IR spectra were similar to those of the starting materials. In the ^{13}C NMR spectra the signals for the now-reduced double bond carbons had shifted far upfield into the aliphatic region.

Conformational and stereochemical analysis of the products was now possible in view of the saturated six-membered carbocyclic ring now being able to adopt a chair conformation. Comparison of the coupling constants for H-6 in the D_2O washes of each diastereomer (to remove the OH coupling) followed by application of the Karplus equation allowed unambiguous assignment of relative stereochemistry. The favoured chair conformation was assumed using Weinreb's[57] configurational assignment of the A/C-ring spirocycle with nitrogen in an equatorial position (Figure 3.4). This is supported for **3.26** by hydrogen bonding between the nitrogen H and the hydroxyl O strongly favouring the *gauche* conformation shown, whereas the other conformer would have these two functionalities *anti*.



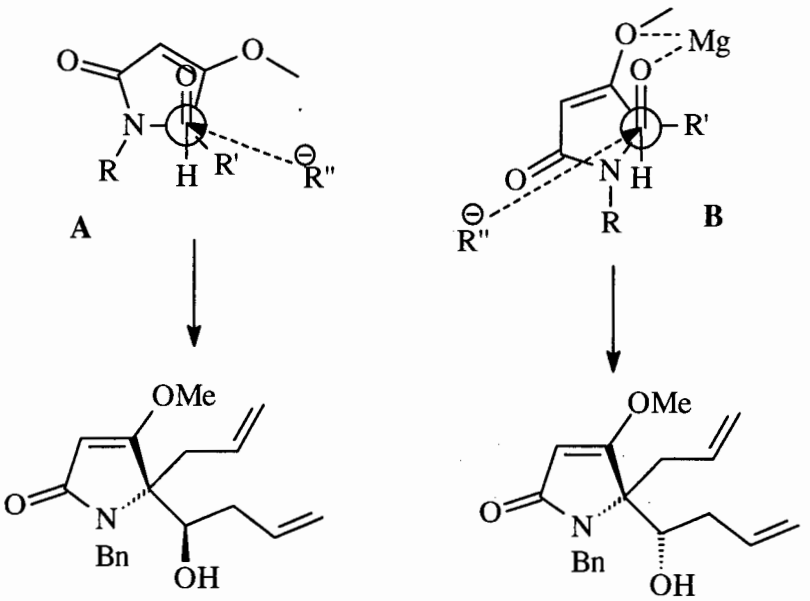
3.25 **3.26**

Figure 3.4 Newman projection along C6-C7

Predictably each H-6 signal of **3.25** and **3.26** was a doublet of doublets as a result of coupling to the two H-7 protons. For **3.25**, derived from the major Grignard product **3.19**, the coupling constants ($J_{6,7}$ 8.9 Hz, $J_{6,7'}$ 3.5 Hz) revealed a *gauche* relationship between H-6 and both H-7 protons establishing H-6 as equatorial, and thus *trans* to the lactam nitrogen. By comparison, **3.26**, derived from the minor Grignard product **3.20**, had coupling constants ($J_{6,7}$ 11.0, Hz $J_{6,7'}$ 4.4 Hz) corresponding to one *anti* and one *gauche* relationship thus establishing H-6 as axial, and thus *cis* to the lactam nitrogen.

Some interesting transtition-state model possibilities exist for rationalising the outcome of the Grignard reaction. By using the Felkin-Anh model[121] for the attack of a nucleophile at a carbonyl,

two possible scenarios may be envisaged. In the first, the nitrogen on the stereogenic centre adjacent to the carbonyl plays an important role. When the π^* of the C=O bond and σ^* of the C-N overlap a new, lower energy LUMO is formed, and this only occurs when the C-N is perpendicular to the C=O. The resultant conformation **A** (Scheme 3.21) is a more reactive one since HOMO/LUMO stabilization is greater in the transition state, and with the nucleophile attacking from the least hindered pathway results in formation of diastereomer **3.20**. The other possibility is a chelation model in which the magnesium ion chelates to the lone pairs of the carbonyl and methoxyl oxygens in a six-membered chelated transition state. Nucleophilic attack from the least hindered pathway on this conformation, **B** in Scheme 3.21, leads to the opposite diastereomer **3.19**. The assignment of major diasteromer **3.25** suggests that the chelation model is the favoured transition state, although the moderate stereoselectivity obtained shows that this model is not strongly preferred. Chelation of the lactam carbonyl is less likely since a weaker 7-membered chelated transtition state would result.



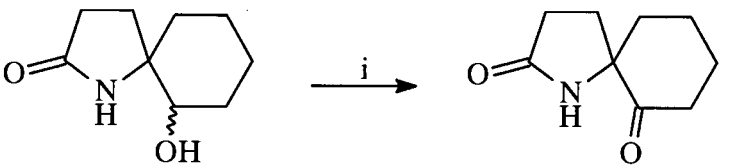
3.20 minor **3.19 major**

Scheme 3.21 Facial attack of the Grignard reagent

It seems likely that the selectivity of the addition could be improved by tuning the functionality to favour one of these transition states or by use of Lewis acids to enhance chelation effects.

The hydroxyl group could now be oxidized to obtain the spirocyclic ketone. Swern oxidation of the alcohols **3.25** and **3.26** gave an average yield of only 70% of the desired product **3.27**, but this yield could be improved using Ley's TPAP oxidation (Scheme 3.22).[122] This procedure involved stirring a

solution of **3.25** and **3.26** in acetonitrile with 4-methylmorpholine *N*-oxide, powdered molecular sieves and tetrapropylammonium perruthenate (5 mol %). After work-up and chromatography a yield of 85% was achieved. Apart from the broad NH peak, the ^{1}H NMR spectrum was a complex mixture of aliphatic signals. As expected though, the hydroxyl and H-6 peaks seen in **3.25/3.26** were not present in the spectrum of **3.27**.

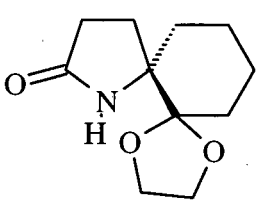


3.25/3.26 **3.27**

Scheme 3.22 *Reagents and conditions:* (i) TPAP (5mol%), NMO, powdered MS, MeCN, 85%

The ^{13}C NMR spectrum was more useful for assigning the structure. A new signal at 209 ppm confirmed formation of the ketone carbonyl, which had shifted downfield from 74 ppm for C-6 in **3.25/3.26**. Although two carbonyl peaks could not be seen in the IR spectrum, a strong and broad peak was seen at 1709 cm^{-1} suggesting overlap of the lactam carbonyl and ketone carbonyl peaks.

Although the ketone **3.27** is a new compound, a very similar molecule has been synthesised[123] as the acetal **3.28** (Figure 3.5). This acetal was synthesised in four steps *via* allylation of 2-nitrocyclohexanone. In this case attempts to carry out the sequence enantioselectively gave only very modest levels and in low overall chemical yield (11%). Although our synthesis was not enantioselective and had more steps, the overall yield was better (22% for 10 steps from commercially available methyl (*E*)-4-chloro-3-methoxy butenoate) and there is scope for an enantioselective synthesis, by targeting the chiral tetramate **3.14** *via* a number of strategies. These include using chiral Lewis acid catalysis or chiral protecting groups on nitrogen to influence the Mukaiyama aldol reaction.



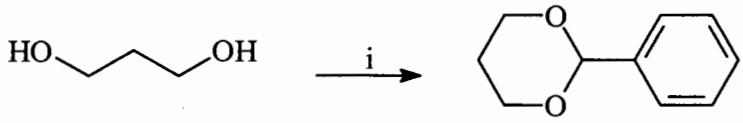
3.28

Figure 3.5 Known spirocyclic acetal

The strategy to complete the synthesis of the tricyclic lepadiformine core was to construct the B-ring by chain extension at the ketone carbonyl carbon to give a tether that could subsequently be cyclised onto the nitrogen. The two methods of chain extension that were considered were the Wittig reaction and the Grignard reaction. The Wittig reaction was the more attractive method on paper, as it would access the alkene directly, whereas the tertiary alcohol produced using the Grignard reaction would have to be dehydrated to obtain the alkene. The C-5 stereocentre of the target could then be introduced by reduction of this alkene.

Before these reactions could be studied, the appropriate tether had to be synthesised for reaction with the ketone. The obvious choice was an appropriately protected 3-bromo-1-propanol. This could be converted to the Grignard reagent using magnesium metal or the Wittig reagent using an appropriate phosphine. The protecting group could be subsequently removed for cyclisation onto nitrogen. A benzyl-protecting group was attractive because hydrogenation of the double bond and hydrogenolysis of the benzyl group could be achieved simultaneously. To this end 1-benzyloxy-3-bromopropane was conveniently prepared on a large scale in 4 steps from 1,3-propanediol using reported procedures.

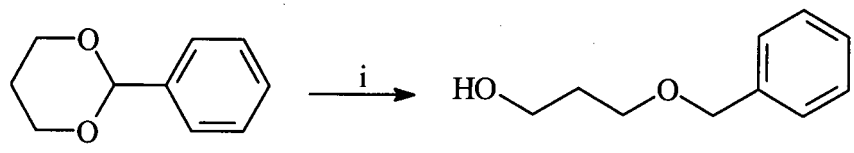
The first step was reaction of 1,3-propanediol with benzaldehyde under acidic conditions to generate 2-phenyl-1,3-dioxane **3.29** (Scheme 3.23). This material was conveniently purified by distillation to give the pure product as a low-melting solid in high yield.



3.29

Scheme 3.23 *Reagents and conditions:* (i) benzaldehyde, *p*-toluenesulfonic acid, benzene, reflux, 14h, 80%

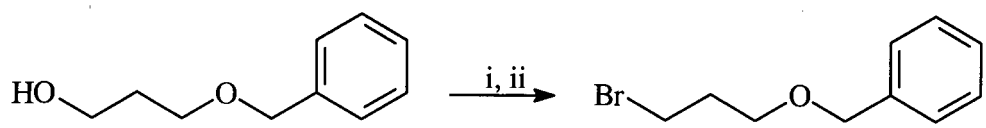
The acetal **3.29** could conveniently be reductively opened using a combination of aluminium trichloride and lithium aluminium hydride (Scheme 3.24), the Lewis acid opening the acetal to form an oxocarbenium ion, which then receives a hydride. This approach[124] to the monobenzylation of 1,3-propane diol **3.30** was much higher yielding than the conventional protection of the diol by deprotonation with a base, followed by alkylation with a benzyl halide.



3.29 **3.30**

Scheme 3.24 *Reagents and conditions:* (i) $AlCl_3$, $LiAlH_4$, diethyl ether, rt, 99%

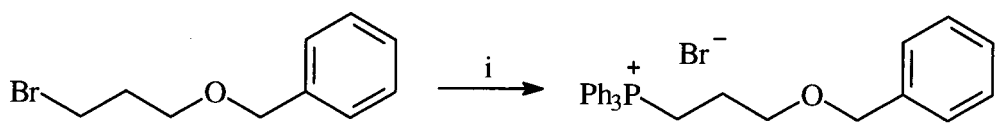
The hydroxyl was then converted to the mesylate using standard conditions (methanesulfonyl chloride and triethylamine in dichloromethane). After work-up the crude product was immediately reacted with lithium bromide in refluxing acetone, to effect an S_N2 displacement of mesylate by bromide. The product, 1-benzyloxy-3-bromopropane **3.31**, was purified by distillation to give a colourless oil in quantitative yield for the two steps (Scheme 3.25).



3.30 **3.31**

Scheme 3.25 *Reagents and conditions:* (i) MsCl, NEt_3, CH_2Cl_2, rt, 0.5hr; (ii) LiBr, acetone, reflux, 3h, 99%

Using the standard Wittig procedure,[125] the bromide could now be converted to the phosphonium salt **3.32** via refluxing a solution of the bromide and triphenylphosphine in toluene (Scheme 3.26). After cooling, the precipitate that formed was isolated and recrystallised from acetonitrile/ether to give salt **3.32** as a colourless, crystalline solid.



3.31 **3.32**

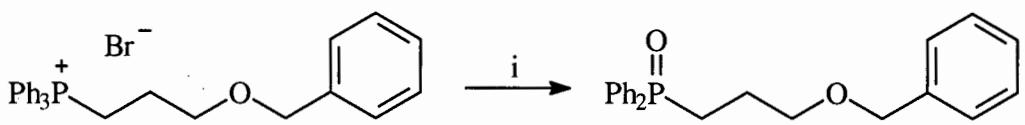
Scheme 3.26 *Reagents and conditions:* (i) PPh_3, toluene, reflux, 7h, 61%

The Wittig reaction could now be attempted by deprotonation of this salt using base to give a non-stabilized ylide, followed by reaction with the ketone **3.27**. This was initially attempted using *n*-

butyllithium in tetrahydrofuran. A bright red colour was produced, indicating successful generation of the ylide. The reaction between excess ylide and the spirocyclic ketone was investigated over a range of temperatures without success. A problem with non-stabilized ylides is their weak nucleophilicity and their instability at high temperatures. The successful reaction of these ylides with ketones is uncommon because of steric factors, and in this case steric congestion was increased by the proximity of the tertiary aza centre.

With this in mind, the more nucleophilic Horner variant of the Wittig seemed a more promising alternative. Horner[126] discovered that alkyldiphenylphosphine oxides could be readily deprotonated with strong base and reacted with carbonyl compounds to give alkenes. When a lithium base is used, β-hydroxyphosphine oxides are formed, unlike the Wittig reaction where alkenes are formed directly. The β-hydroxyphosphine oxides can be converted to the alkene by treatment with a non-lithium base, such as sodium hydride. The Horner reaction has the added bonus of forming a water-soluble phosphorus byproduct enabling easy separation from the products.[127]

The phosphonium salt **3.32** was converted to the phosphine oxide **3.33** by refluxing in aqueous sodium hydroxide (Scheme 3.27). The product was isolated as a colourless, crystalline solid, and its ^{1}H NMR data was identical to that published for the compound synthesised using a different method.[128]

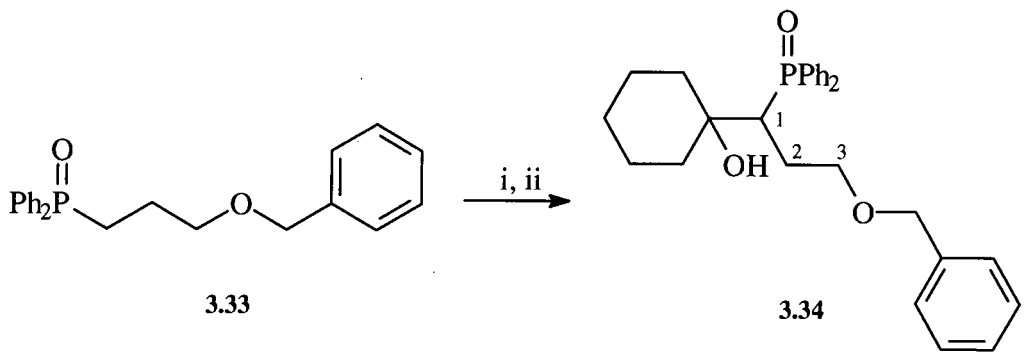


3.32 **3.33**

Scheme 3.27 *Reagents and conditions:* (i) NaOH (aq), reflux, 3h, 98%

To test out the viability of the Horner procedure with ketones, the phosphine oxide **3.33** was first reacted with cyclohexanone as a model substrate (Scheme 3.28). After generating a solution of the ylide in THF at 0°C with *n*-butyllithium (the solution turned orange), the solution was cooled to -78°C and the cyclohexanone added (solution turned yellow). The reaction was allowed to warm

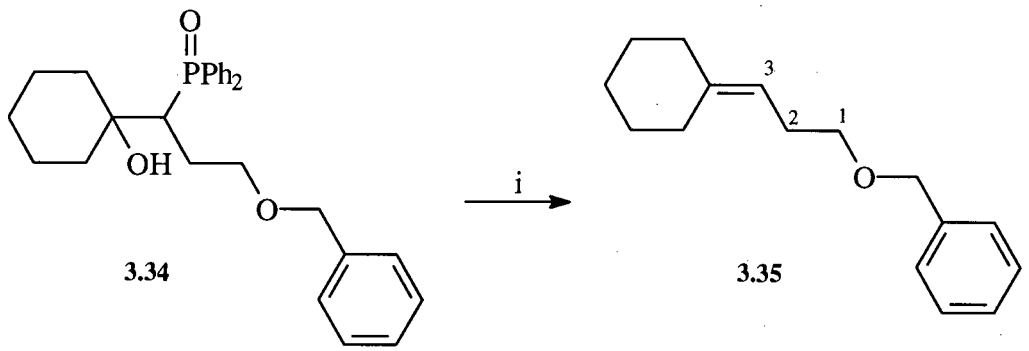
slowly to 0°C and then worked-up to give racemic β-hydroxyphosphine oxide **3.34** in quantitative yield as a colourless powder.



3.33 **3.34**

Scheme 3.28 *Reagents and conditions:* (i) *n*-BuLi, THF, 0°C (ii) cyclohexanone, -78°C to 0°C, 97%

^{1}H NMR spectrometry was used to confirm the structure of the product. An exchangeable broad signal corresponding to the hydroxyl was present (4.6 ppm). The resonance for H-1 was a multiplet (2.57 ppm), the several couplings due to coupling to the H-2 protons as well as phosphorus coupling. With a new stereocentre formed at C-1, the H-3 protons were now diastereotopic and split into two multiplets. Similarly the benzylic protons were split into 2 doublets (J = 11.9 Hz). Phosphorus-carbon coupling could be seen in the ^{13}C NMR spectrum, with the coupling constant for C-1 being very large (J = 67.1 Hz). The IR spectrum displayed a broad peak at 3380 cm^{-1} for the OH stretch.
To complete formation of the olefin the β-hydroxyphosphine oxide **3.34** was stirred with sodium hydride in DMF (Scheme 3.29). After work-up the crude residue was chromatographed to give 3-benzyloxypropylidenecyclohexane **3.35** as a highly non-polar, colourless oil in quantitative yield.



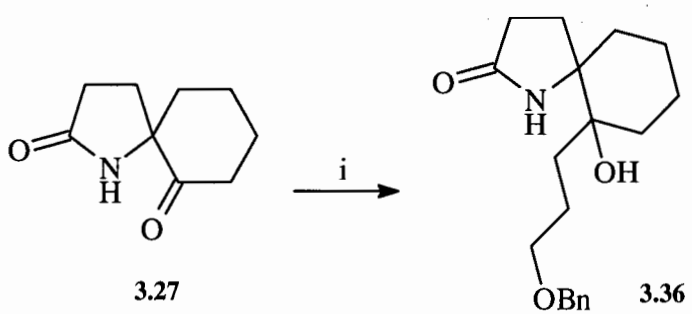
3.34 **3.35**

Scheme 3.29 *Reagents and conditions:* (i) NaH, DMF, rt, 100%

Olefin formation was confirmed by the presence of a vinylic resonance in the ^{1}H NMR spectrum (5.10 ppm). A number of differences between the spectra of **3.34** and **3.35** were observed, including loss of the hydroxyl signal seen in **3.34**. The chirality present in **3.34** had been lost in forming **3.35**, consequently the two H-1 protons were now enantiotopic and resonated together as a triplet (7.2 Hz). Similarly the signal of the benzylic protons was now a singlet. The signal for the two H-2 protons was well resolved, appearing as a quartet due to equal coupling (7.2Hz) to the two H-1 protons and the H-3 proton. The vinylic signal was a triplet of triplets (1.1 and 7.2 Hz), the small coupling constant due to allylic coupling to hydrogens in the cyclohexane ring. As expected, the ^{13}C NMR spectrum showed no signals due to phosphorus coupling. Two new olefinic signals were present (117 and 142 ppm). The only notable change in the IR spectrum was loss of the hydroxyl peak.

With the Horner procedure now successfully tested, a number of reactions were attempted between the phosphine oxide **3.33** and the spirocyclic ketone **3.27**. Only when a large excess (> 5 eq) of the anion was used was any product detected after work-up. To complicate matters the product co-eluted with the unreacted phosphine oxide. Only by treatment of the mixture with sodium hydride, could separation be effected. The overall yield was high (based on recovered starting material) but in very low conversion (<10%). It seems reasonable that the phosphine oxide carbanion could have been acting competitively as a base to enolise the ketone followed by regeneration of the starting material on work-up. This unacceptable result could not be improved upon by protection of the lactam NH with Boc before olefination.

With the Wittig approach ineffectual, attention was now focused on the Grignard approach (Scheme 3.30). To prepare the Grignard reagent, a concentrated solution of the bromide **3.31** in THF was slowly added to excess magnesium turnings. After the Grignard reagent was completely formed the solution was cooled and the spirocyclic ketone **3.27** was introduced as a solution in THF. The strong nucleophilicity of the Grignard reagent together with its lower steric demand ensured the reaction was rapid even at 0°C. The desired product **3.36** was isolated as an oil in good yield (89%) after work-up and chromatography. The diasteromeric ratio of this oil was estimated to be 4:3 from ^{1}H NMR based on integration of the hydroxyl proton of each diastereomer.



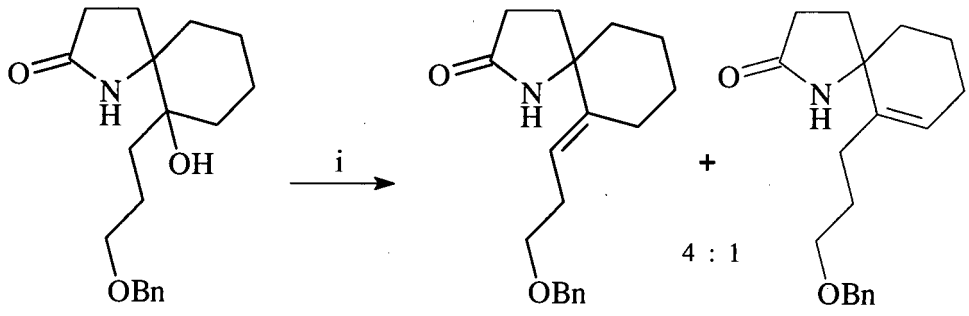
3.27 **3.36**

Scheme 3.30 *Reagents and conditions:* (i) $BnO(CH_2)_2MgBr$ (3eq), THF, 0°C, 89%

^1H NMR spectrometry confirmed the product structure by exhibiting the expected new benzylic and aliphatic signals of the side chain as well as the broad tertiary hydroxyl signal. Predictably, the resonance for the ketone carbonyl was no longer present in the ^{13}C NMR spectrum. Though this spectrum showed doubling of each peak, eight new signals could be picked out for each diastereomer, five for the benzyl group and three for the tether. The carbonyl peak in the IR spectrum was now less intense and shifted back to 1690 cm^{-1}.

The tertiary alcohol could now be transformed to an alkene by dehydration *via* an E1 process. However, a concern was that the strained spirocycle would undergo a carbocationic rearrangement. When the alcohol was subjected to the standard dehydration conditions of thionyl chloride in pyridine, the products were contaminated by an inseparable impurity possibly due to such a rearrangement. The reaction was much cleaner if phosphorus oxychloride was used as the dehydrating agent. In the event, the cleanest reaction and highest yields were obtained using a little known procedure using anhydrous copper sulfate[129] in refluxing *p*-xylene. The elimination proceeded smoothly to afford a 92% yield of exocyclic and endocyclic alkenes (Scheme 3.31). From ^1H NMR a ratio of 4:1 of exocyclic to endocyclic alkene isomers **3.37:3.38** was apparent.

The major product was assigned as an *exo* alkene, as the ^1H NMR data was identical to that of the Wittig reaction product. The stereochemistry of **3.37** was assigned on the basis that the bulky lactam would exclude the *Z* isomer.

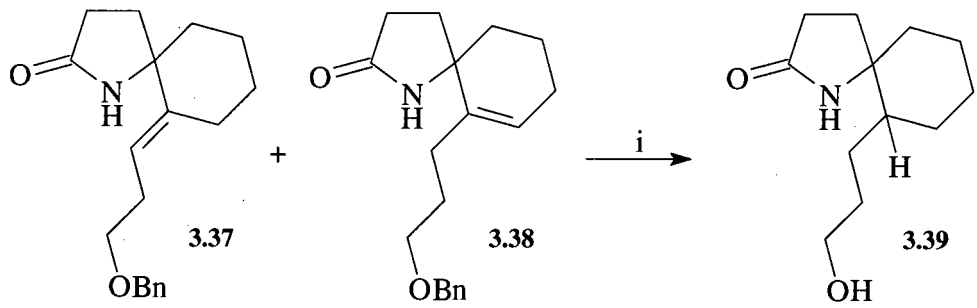


3.36 **3.37** **3.38**

Scheme 3.31 *Reagents and conditions:* (i) $CuSO_4$, *p*-xylene, 92%

For the major isomer **3.37** two new olefinic signals could be seen in the ^{13}C NMR spectrum at 116 and 143 ppm with concomitant loss of the signal for the carbon α to the hydroxyl and one of the aliphatic signals seen for **3.36**.

Hydrogenation of the double bond as well as hydrogenolysis of the benzyl protecting group in the next step was achieved using standard hydrogenation conditions with palladium on carbon as the catalyst (Scheme 3.32). The yield of the reaction fluctuated depending on the quality of catalyst used. In one instance a product corresponding to the cleavage of the ether bond of the tether instead of the benzyl ether bond was obtained. Notably, the hydrogenation of the double bond occurred with some stereoselectivity. Although the oily product **3.39** was an inseparable mixture of diastereomers, a 2:1 ratio could be observed using ^1H NMR. As in the assignment of **3.25** and **3.26**, the coupling constants of the H-6 signal was crucial for assigning the stereochemistry of each diastereomer. However, this proton was buried within a broad multiplet in the aliphatic region and no distinct peaks could be observed. Thus the stereochemistry of each diastereomer could only be confidently assigned following the subsequent cyclisation reaction.

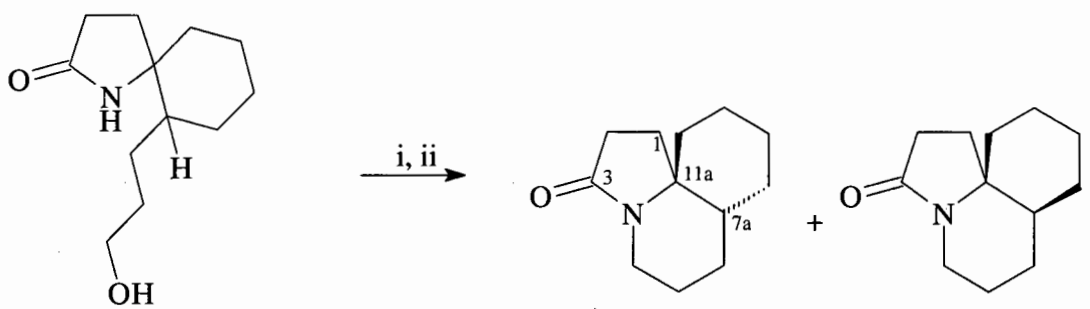


3.37 **3.38** **3.39**

Scheme 3.32 *Reagents and conditions:* (i) H_2, Pd/C, EtOH, 85%

The ^{13}C NMR spectrum of the mixture **3.39** revealed loss of the benzyl signals as well as a large upfield shift in the new aliphatic carbons compared to the analogous olefinic carbons in **3.37**. The IR spectrum was similar to **3.37** apart from a new peak at 3600cm^{-1} for the OH stretch.

Literature precedent[130] suggested that completion of the tricycle synthesis could be achieved via mesylation of the hydroxyl group followed by ring closure (Scheme 3.33). The mesylation proceeded uneventfully using standard conditions (methanesulfonyl chloride, triethylamine, dichloromethane). After work-up the crude mesylate was smoothly cyclised using sodium hydride in DMF. This furnished the tricyclic lactam as a mixture of diastereomers (2:1), that were separable using column chromatography.

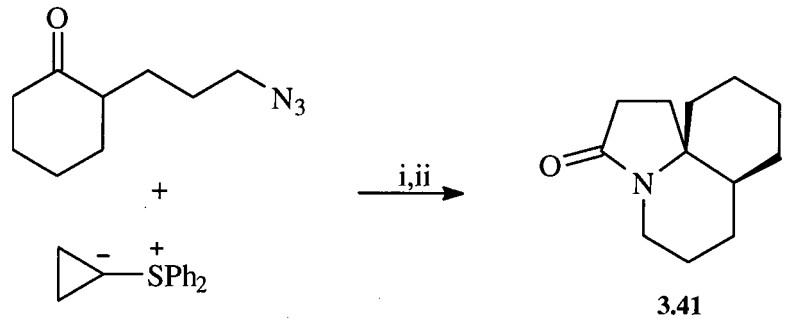


3.39 **3.40** **3.41**

Scheme 3.33 *Reagents and conditions:* (i) MsCl, NEt_3, CH_2Cl_2, 0°C (ii) NaH, DMF, rt, 24h, 88% **3.40**:**3.41** 2:1

Although many of the signals in their ^1H NMR spectra were grouped together in the aliphatic region, several peaks were resolved. Both C-5 protons could be seen in each diastereomer, and as in the cyclised compounds in the isoindolone series (such as **2.18** and **2.30**), the coupling constants revealed that the equatorial proton was downfield (**3.40** at 3.88 ppm, dd, *J* 8.4, 13.7 Hz; for **3.41** at 4.02 ppm, ddt, *J* 1.6, 4.8, 13.4 Hz) and the axial proton was more than 1 ppm further upfield (for **3.40** at 2.77 ppm, dddd, *J* 1.1, 7.0, 11.2, 13.7 Hz; for **3.41** at 2.66 ppm, t, *J* 13.4 Hz) offering evidence that cyclisation had occurred. Similarly in the ^{13}C NMR spectra of the two diastereomers, the signal for C-5 (the terminal carbon of the tether in **3.39**) had shifted upfield by 10 ppm due to the smaller deshielding effect by nitrogen compared to oxygen.

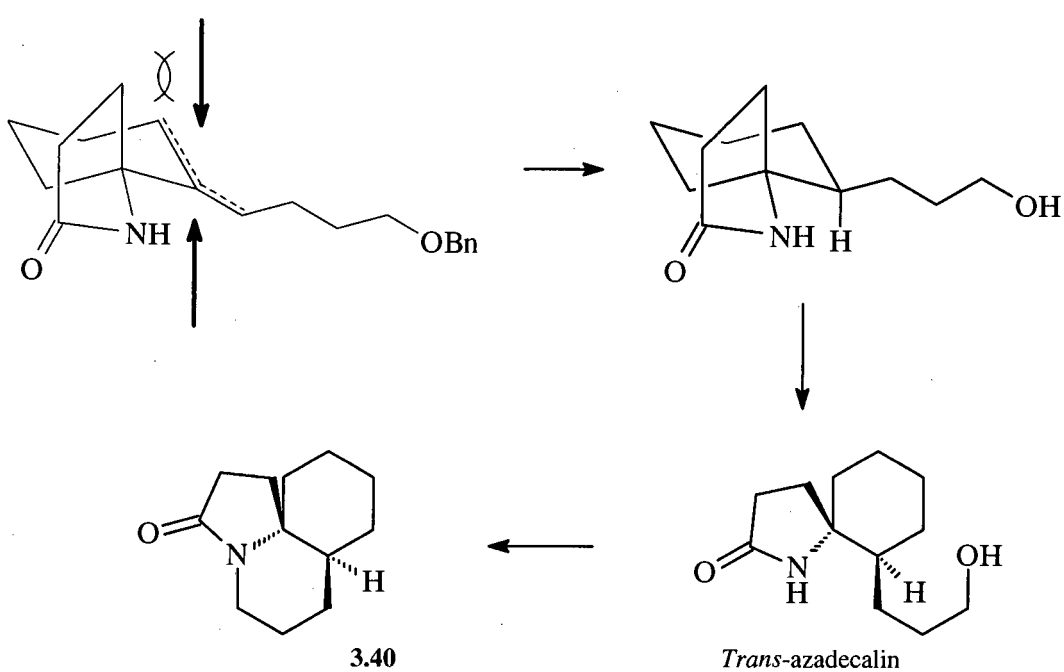
As the crucial H-7a was buried in the aliphatic region, the stereochemistry was determined using other means. The oily minor product **3.41** had identical spectroscopic data to the known *cis*-1-azadecalin synthesised by the Aubé group[131] *via* an intramolecular Schmidt reaction (Scheme 3.34).



3.41

Scheme 3.34 *Reagents and conditions:* (i) $LiBF_4$ (ii) $TiCl_4$, 81%

On this basis the major product, also isolated as an oil, was assigned as the desired *trans*-1-azadecalin ring system **3.40**, as a new addition to the chemical literature. The stereochemistry of the major product can be explained by a stereoselective hydrogenation of the least hindered face of the alkene/s (Scheme 3.35).



3.40 *Trans*-azadecalin

Scheme 3.35

3.2 Conclusion

In conclusion, new methodology for the synthesis of 5,5-spirotetramates has been developed and a sequence for the stereoselective formation of the lepadiformine core has been achieved. This is the first synthetic methodology involving a nucleophilic carbon alpha to nitrogen to be applied to this class of molecule. Several aspects of this route are worth emphasizing. The tetramate skeleton has been shown to be a useful synthetic building block, highlighted by construction of the tertiary aza centre using a one-pot Mukaiyama aldol that is more efficient and cost effective for industrial application than current procedures. In addition the tetramate skeleton was completely reduced to the fully saturated heterocycle using dissolving metal reduction in an efficient new procedure, widening the application of tetramate chemistry generally. Another notable feature was a stereoselective hydrogenation to give the *trans* aza-decalin as the major product, which could be elaborated to the lepadiformine core. This approach has laid the foundation for elaboration into an enantioselective synthesis of lepadiformine.

CHAPTER 4

EXPERIMENTAL

4.1 General Procedures

All solvents were freshly distilled. Diethyl ether and tetrahydrofuran was distilled under nitrogen and dried over sodium wire with benzophenone. Toluene and benzene was distilled over sodium under nitrogen. Dichloromethane was distilled over phosphorus pentoxide and the condensor was fitted with a drying tube. Other reagents were purified according to standard procedures.[132]

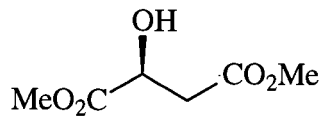
All chromatography was carried out using petroleum ether and ethyl acetate as eluents. Column chromatography was performed using silica gel 60 (Merck 7734). Thin layer chromatography (tlc) was carried out on aluminium backed Merck silica gel 60 F_{254} plates. Compounds were visualized on tlc by using a combination of UV lamp, iodine vapour, and either by spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v) or ceric ammonium sulfate solution and then heating at 150°C. For reactions that required extractive work-up the organic layers were dried by stirring with magnesium sulfate followed by filtration.

Nuclear Magnetic Resonance spectra were recorded on a Varian Unity 400 (100 MHz for ^{13}C) or Varian Mercury 300 MHz (75 MHz for ^{13}C) and were carried out in d-chloroform unless otherwise stated. Chemical shifts (δ) were recorded using residual chloroform (δ 7.24 in ^{1}H NMR and δ 77.00 in ^{13}C NMR) or tetramethylsilane as an internal standard. For D6-DMSO the residual DMSO peak (δ 39.52 in ^{13}C NMR) was used as an internal standard. All chemical shifts are reported in ppm. Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20°C. The concentration *c* refers to g/100ml.

Melting points were obtained using a Reichert Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHN elemental analyser. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in dichloromethane. These spectra were recorded from 4000 to 600 cm^{-1} on sodium chloride plates. High-resolution mass-spectrometry was performed at the mass-spectrometry unit of the Cape Technikon using a VG70-SEQ micromass spectrometer. All reagents were purchased from Aldrich or Merck. Low temperature reactions were carried out using dry ice in acetone.

4.2 Synthesis of tetrahydropyrido[2,1-*a*]isoindolones

Dimethyl (*S*)-malate (2.1)

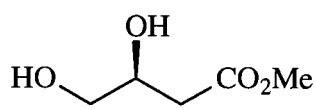


Hydrogen chloride gas was bubbled through a solution of *S*-malic acid (13.5g, 0.101mol) in methanol (60ml) for 5 minutes. The solution was stirred at room temperature for 24 hours. The solution was concentrated to a viscous oil. This was vacuum distilled to give the product as a colourless oil. The residue that remained was redissolved in methanol and the entire procedure was repeated. The distillates were combined to give dimethyl malate **2.1** (15.2g, 0.094 mol, 93% yield).

δ_H (200MHz, $CDCl_3$) 2.83 (2H, m, CH_2), 3.52 (1H, br s, OH), 3.61 (3H, s, CH_3), 3.70 (3H, s, CH_3), 4.44 (1H, m, CH).

This data corresponds to the published data for this compound.[74]

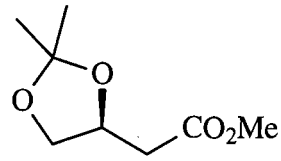
Methyl (*S*)-3,4-dihydroxybutanoate (2.4)



Borane dimethyl sulfide (3.14ml, 31.5mmol) was added to a solution of dimethyl malate **2.1** (5.00g, 30.5mmol) in tetrahydrofuran (60ml) under a nitrogen atmosphere at room temperature over 30 minutes. The solution was stirred for a futher 30 minutes and then cooled in ice-water (10°C). Solid sodium borohydride (0.058g, 5 mol %) was added at that temperature (exothermic) under vigourous stirring. When the exotherm subsided, the water bath was removed. The reaction was monitored by tlc. After the starting material had been consumed, ethanol (10ml) and *p*-toluenesulfonic acid (0.29g, 5 mol %) were added and the cloudy solution was stirred for 30 minutes at room temperature. The solution was concentrated to a colourless gum, which was redissolved in a mixture of benzene-ethanol (1:1) and concentrated again. This process was repeated. The residue was then repeatedly dissolved in benzene and concentrated, to remove as much $B(OEt)_3$ as possible. The residue was

chromatographed (ethyl acetate) to give the diol **2.4** as a colourless oil (3.24g, 24.2 mmol, 79%). Apon standing this compound readily lactonised therefore it was immediately converted to **2.5**.

Methyl (*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanoate (2.5)

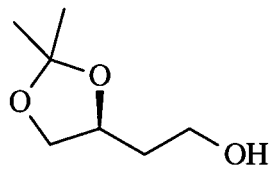


To a solution of the diol **2.4** (4.47g, 33.3 mmol) in acetone (20ml) was added 2,2-dimethoxypropane (4.6ml, 52.1 mmol) and *p*-toluenesulfonic acid (0.32g, 5 mol %). After stirring at room temperature for 20 minutes, triethylamine (0.5ml) was added and the solution was diluted with diethyl ether (50ml). The solution was passed through a pad of silica gel and the pad was rinsed with diethyl ether. The combined ether solutions were concentrated to give an oil. This was vacuum distilled to give pure acetal **2.5** (4.68g, 26.9 mmol, 81% yield) as a colourless oil.

δ_H (200MHz, $CDCl_3$) 1.36 (3H, s, CH_3), 2.50 (3H, s, CH_3), 2.52 (1H, dd, *J* 7.0, 15.5 Hz, H-2), 2.73 (1H, dd, *J* 6.4, 15.5 Hz, H-2), 3.65 (1H, dd, *J* 6.2, 8.3 Hz, H-4), 3.70 (3H, s, OCH_3), 4.14 (1H, dd, *J* 6.0, 8.3 Hz, H-4), 4.48 (1H, m, H-3).

This data corresponds to the published data for this compound.[74]

(*S*)-1,2-*O*-Isopropylidene-1,2,4-butantriol (2.6)



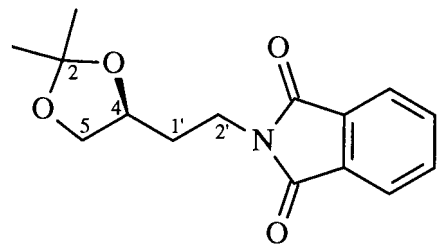
After cooling a solution of acetal **2.5** (7.88g, 45.3 mmol) in tetrahydrofuran (75ml) to -40°C, lithium aluminium hydride (1.03g, 27.2 mmol) was added in one portion. The solution was stirred for 3 hours at -40 to -30°C, and then dichloromethane (75ml) was introduced. The reaction was quenched by the dropwise addition of a mixture of tetrahydrofuran and water (1:1) until precipitation of the lithium salts had occurred. The solids were removed by filtration through a Celite® pad and the filter

cake was rinsed with dichloromethane. The filtrate was dried and concentrated to give an oily residue. The residue was vacuum distilled to give the alcohol as a colourless oil **2.6** (5.99g, 41.0 mmol, 91%).

δ_H (200MHz, $CDCl_3$) 1.35 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.81 (2H, m, H-3), 3.15 (1H, br s, OH), 3.60 (1H, dd, *J* 7.0, 7.9 Hz, H-1), 3.75 (2H, t, *J* 6.0 Hz, H-4), 4.10 (1H, dd, *J* 5.6 , 7.0 Hz, H-1), 4.28 (1H, m, H-2).

This data corresponds to the published data for this compound.[74]

(*S*)-2,2-Dimethyl-4 (2-phthalimido ethyl) 1,3-dioxolane (2.7)

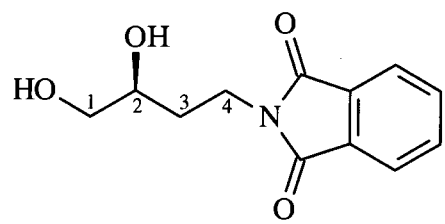


The alcohol **2.6** (0.43 g, 2.97 mmol) was dissolved in tetrahydrofuran (10 ml) with stirring under nitrogen. Phthalimide (0.57 g, 3.9 mmol) and triphenylphosphine (1.03 g, 3.9 mmol) were then added and the solution was cooled to 0°C. Diethyl azodicarboxylate (0.62 ml, 3.9 mmol) was added dropwise. The reaction was allowed to warm to room temperature and on completion (tlc), the solvent was evaporated and the residue dissolved in dichloromethane, then washed with potassium hydroxide (1M). The organic layer was then dried, the solvent evaporated and the residue chromatographed (20 % ethyl acetate/petroleum ether) to afford **2.7** as a colourless crystalline solid (0.77 g, 2.79 mmol, 94 % yield).

mp. 44-46°C (ethyl acetate/hexane); $[\alpha]_D$ = +10.6° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3057, 2986, 1775, 1716, 1398; δ_H (400MHz, $CDCl_3$) 1.28 (3H, d, isopropylidene-Me), 1.34 (3H, d, isopropylidene-Me), 1.90 (2H, m, H-1'), 3.56 (1H, dd, *J* 6.7, 7.8 Hz, H-5), 3.81 (2H, m, H-2'), 4.07 (1H, dd, *J* 5.9, 7.8 Hz, H-5), 4.14 (1H, m, H-4), 7.70 (2H, m, aromatic), 7.83 (2H, m, aromatic); δ_C (100MHz, $CDCl_3$) 25.5, 26.8 (2 x isopropylidene-Me), 32.3 (C-1'), 35.1 (C-2'), 69.1 (C-5), 73.9 (C-4), 109.0 (C-2), 123.1, 132.1, 133.8 (aromatic), 168.2 (C=O); Found: C, 65.57; H, 6.31; N, 5.28 %.

$C_{15}H_{17}NO_4$ requires: C, 65.44; H, 6.22; N, 5.09 %; Found: M^+, 260.9250. $C_{15}H_{17}NO_4$ requires 260.9228.

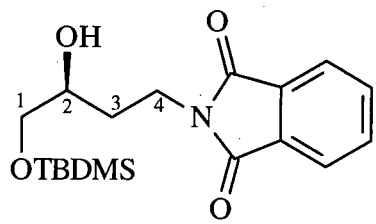
(*S*)-4-Phthalimido-1,2-butanediol (2.8)



The imide **2.7** (0.32 g, 1.16 mmol) was dissolved in a mixture of tetrahydrofuran (3 ml) and 1M hydrochloric acid (3ml) and heated at 60°C for 30 minutes. Aqueous sodium hydrogen carbonate was added and the tetrahydrofuran was removed on a rotary evaporator. The aqueous phase was extracted with 3 portions of ethyl acetate, and the organic layers were combined, dried, and evaporated to a residue. This was subjected to flash chromatography (80 % ethyl acetate/petroleum ether) to obtain **2.8** as a white crystalline solid (0.23 g, 0.98 mmol, 85 % yield).

mp 105-106°C (ethyl acetate/petroleum ether); $[\alpha]_D$ = -29.9° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2)/cm^{-1} 3581, 3061, 2963, 1775, 1707, 1396; δ_H (400MHz, $CDCl_3$) 1.75 (2H, m, H-3), 2.40 (1H, br s, OH), 3.46 (1H, dd, *J* 7.2, 11.2 Hz, H-1), 3.58 (1H, dd, *J* 3.2, 11.2 Hz, H-1), 3.58 (1H, br s, OH), 3.65 (1H, m, H-2), 3.86 (2H, dd, *J* 5.6, 7.6 Hz, H-4), 7.70-7.84 (4H, m, aromatic); δ_C (100MHz, $CDCl_3$) 32.0 (C-3), 34.4 (C-4), 66.4 (C-1), 69.1 (C-2), 123.4 & 132.0 & 134.1 (aromatic), 168.9 (C=O); Found: C, 61.45; H, 5.31; N, 5.86 %. $C_{12}H_{13}NO_4$ requires: C, 61.23; H, 5.57; N, 5.95 %; Found: M^+, 235.08197. $C_{12}H_{13}NO_4$ requires 235.08446.

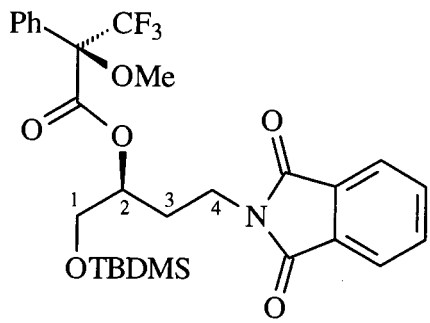
(*S*)-4-Phthalimido-1-(*tert*-butyldimethylsilyl)oxybutan-2-ol (2.9)



The diol **2.8** (3.14 g, 13.36 mmol) was dissolved in dichloromethane (60 ml) with stirring under nitrogen. Imidazole (1.00 g, 14.7 mmol) was added and the solution was cooled to 0°C. *Tert*-butyldimethylsilyl chloride (2.02 g, 13.4 mmol) was added and the solution was allowed to warm to room temperature overnight. Water was added and the mixture was extracted with three portions of dichloromethane. The organic layers were combined, dried, and evaporated to a residue. This was chromatographed (20 % ethyl acetate/petroleum ether) to give **2.9** as a colourless oil (4.52 g, 12.93 mmol, 97 % yield).

$[\alpha]_D$ = -3.9° (c = 1.0, $CDCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3597, 3048, 2955, 1775, 1713, 1398; δ_H (400MHz, $CDCl_3$) 0.06 (6H, s, CH_3), 0.89 (9H, s, t-butyl CH_3), 1.80 (2H, m, H-3), 2.65 (1H, br s, OH), 3.49 (1H, dd, *J* 6.7, 10.0 Hz, H-1), 3.63 (1H, dd, *J* 3.9, 10.0 Hz, H-1), 3.68 (1H, m, H-2), 3.88 (2H, m, H-4), 7.70-7.86 (4H, m, aromatic); δ_C (100MHz, $CDCl_3$) –5.4 (2 x CH_3), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 31.9 (C-3), 34.9 (C-4), 67.0 (C-1), 69.5 (C-2), 123.2 & 132.2 & 133.9 (aromatic), 168.5 (C=O); Found: $M^+(-CH_3)$, 334.14721. $C_{18}H_{27}NO_4Si$ requires 334.14746.

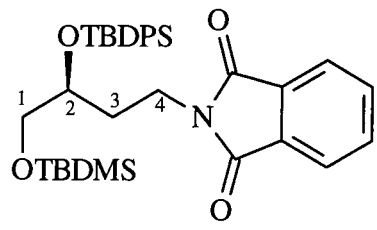
Mosher's ester 8a, (*S*)-1-(*tert*-butyldimethylsilyl)oxy-4-phthalimido-2-butyl 2-(*R*)-2-trifluoromethyl-2-methoxy-2-phenylethanoate (2.10)



For monitoring of enantiointegrity, the alcohol **2.9** (0.030g, 0.086mmol) and (R)-methoxy-trifluoromethylphenylacetic acid (0.030g, 0.13mmol) were stirred in dichloromethane (2ml) at 0°C. DMAP (5mg, cat.) and DCC (0.027g, 0.13mmol) were added and the reaction was warmed to room temperature and monitored by tlc. After 2 hours solvent was evaporated to leave a residue, which was diluted in ether, filtered and the residue washed with ether. The filtrate was concentrated and the residue chromatographed (20% ethyl acetate/petroleum ether) to give the product **2.10** as a colourless oil (0.041g, 0.073 mmol, 85% yield, 100% *ee* by 1H NMR relative to a sample from racemic **2.1**).

$[\alpha]_D$ = +9.1° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 2955, 2858, 1774, 1748, 1714, 1469, 1398; δ_H (400MHz, $CDCl_3$) 0.01 (6H, s, CH_3), 0.83 (9H, s, t-butyl CH_3), 2.07 (1H, m, H-3), 2.18 (1H, m, H-3), 3.59 (3H, s, OCH_3), 3.69 (1H, dd, *J* 4.6, 11.2 Hz, H-1), 3.77 (3H, m, 2 x H-4, H-1), 5.12 (1H, m, H-2), 7.40 (3H, m, aromatic) 7.59 (2H, m, aromatic), 7.71 (2H, aromatic), 7.84 (2H, m, aromatic); δ_C (100MHz, $CDCl_3$) –5.7 (2 x CH_3), 18.1 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 29.5 (C-3), 34.3 (C-4), 55.4 (OMe), 63.1 (C-1), 74.9 (C-2), 121.9 (*C*OMe), 123.3 (aromatic), 124.7 (CF_3), 127.6 & 128.4 & 129.5 & 132.1 & 132.2 & 134.0 (aromatic), 166. 2 & 168.1 (C=O); m/z 566 (M^++H, 3%), 508 (M^+-$C(CH_3)_3$, 45), 332.2 (100), 291 (26), 274 (25), 200 (24), 189 (32).

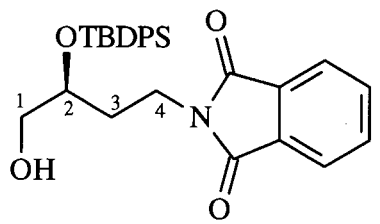
(*S*)-4-Phthalimido-2-(*tert*-butyldiphenylsilyl)oxy-1-(*tert*-butyldimethylsilyl) oxybutane (2.11)



To a solution of **2.9** (4.52 g, 12.93 mmol) in dichloromethane (50 ml) under a nitrogen atmosphere was added dimethylformamide (5 ml), imidazole (1.00 g, 14.7 mmol) and *tert*-butyldiphenylsilyl chloride (3.50 ml, 13.5 mmol). The mixture was stirred at room temperature until tlc indicated that the starting material had been consumed. Water was added and the mixture was extracted with 3 portions of dichloromethane. The organic layers were combined and dried, then evaporated to give a residue that was chromatographed (10 % ethyl acetate/petroleum ether) to remove dimethylformamide. The product fraction was evaporated to a residue (7.62g) contaminated with *tert*-butyldiphenylsilyl alcohol (TBDPSOH). The product **2.11** and this contaminant eluted at the same Rf. The contaminant could easily be separated from the product of the next step by chromatography so the mixture was not purified further. For characterisation purposes a portion of pure **2.12** was reprotected using the same procedure that was used to obtain **2.9** to give **2.11** free of TBDPSOH.

$[\alpha]_D$ = +19.0° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3057, 2933, 1771, 1715; δ_H (400MHz, $CDCl_3$) -0.12, and -0.07 (6H, s, TBDMS CH_3), 0.81 (9H, s, t-butyl CH_3), 1.07 (9H, s, t-butyl CH_3), 1.90 (1H, m, H-3), 2.03 (1H, m, H-3), 3.53 (2H, d, *J* 5.9 Hz, H-1), 3.78 (3H, m, H-2, 2 x H-4), 7.30-7.85 (14H, m, aromatic); δ_C (100MHz, $CDCl_3$) -5.6 (TBDMS 2 x CH_3), 18.2 & 19.3 ($C(CH_3)_3$), 25.8 & 27.0 ($C(CH_3)_3$), 32.6 (C-3), 34.4 (C-4), 65.6 (C-2), 71.8 (C-1), 123.0 & 127.5 & 127.6 & 129.5 & 129.6 & 132.4 & 133.7 & 133.8 & 134.3 & 135.8 & 135.9 (aromatic), 168.2 (C=O); m/z 572 (M^+-CH_3, 1%), 530 (M^+-$C(CH_3)_3$, 100), 452 (10), 271 (31), 209 (42), 135 (19).

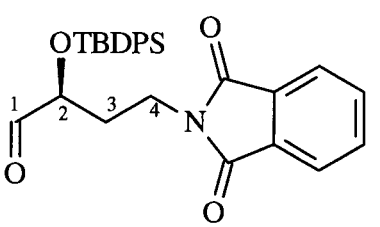
(*S*)-4-Phthalimido-2-(*tert*-butyldiphenylsilyl)oxy-1-butanol (2.12)



In a polypropylene container was placed a solution of the mixture of **2.11** and TBDPSOH in acetonitrile (12 ml) at room temperature. To this solution was added 40 % hydrofluoric acid (2.5 ml) and the reaction was monitored by tlc until the starting material had been consumed. The mixture was neutralized with aqueous sodium hydrogen carbonate and extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated to a residue. This was chromatographed (20 % ethyl acetate/petroleum ether) to give **2.12** (5.45 g, 11.52 mmol, 89 % yield over 2 steps).

$[\alpha]_D$ = +51.4° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3571, 3056, 2938, 1777, 1715, 1397; δ_H (400MHz, $CDCl_3$) 1.08 (9H, s, t-butyl CH_3), 1.85 (1H, br s, OH), 1.94 (2H, m, H-3), 3.67 (4H, m, H-1 and H-4), 3.82 (1H, m, H-2), 7.31-7.79 (14H, m, aromatic); δ_C (100MHz, $CDCl_3$) 19.2 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 32.6 (C-3), 34.4 (C-4), 65.4 (C-1), 71.7 (C-2), 123.1 & 127.6 & 127.7 & 129.7 & 129.8 & 132.1 & 133.2 & 133.7 & 133.8 & 135.6 & 135.8 (aromatic), 168.1 (C=O); Found: M^+(-CH_2OH), 442.18260. $C_{28}H_{31}NO_4Si$ requires 442.18385.

(*S*)-4-Phthalimido-2-(*tert*-butyldiphenylsilyl)oxy-butanal (2.13)

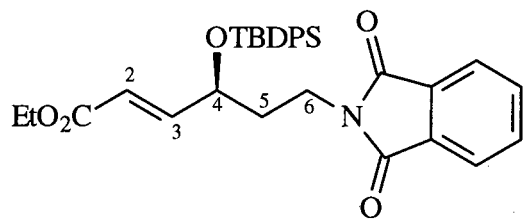


Dimethyl sulfoxide (1.73 ml, 24 mmol) was dissolved in dry dichloromethane and cooled to -78°C under nitrogen. Oxalyl chloride (1.45 ml, 16.6 mmol) was then added, and after 15 minutes the

alcohol **2.12** (5.25 g, 11.08mmol) was slowly added in a solution of dichloromethane. After a further 5 minutes, triethylamine (7.8 ml, 55 mmol) was added and the mixture was slowly allowed to warm to 0°C. The reaction was quenched by adding aqueous sodium carbonate and extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated to give crude **2.13,** which could be taken on to the next step. For characterisation purposes a small portion was chromatographed (20 % ethyl acetate/petroleum ether) and subjected to high vacuum for 24 hours to remove traces of dimethyl sulfide, to give **2.13** as a colourless gum.

$[\alpha]_D$ = +23.9° (c = 1.1, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3061, 2938, 1779, 1716, 1400; δ_H (400MHz, $CDCl_3$) 1.13 (9H, s, t-butyl CH_3), 2.05 (2H, m, H-3), 3.76 (2H, m, H-4), 4.13 (1H, td, *J* 0.9, 5.6, 5.6 Hz, H-2), 7.38 (6H, m, aromatic), 7.70 (6H, m, aromatic), 7.84 (2H, m, aromatic), 9.65 (1H, d, *J* 0.9 Hz, H-1); δ_C (100MHz, $CDCl_3$) 19.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 31.4 (C-3), 33.6 (C-4), 76.1 (C-2), 123.2 & 127.9 & 130.1 & 132.2 & 132.6 & 132.7 & 133.9 & 135.8 (aromatic), 168.0 (C=O), 202.6 (C-1); Found: $M^+(-C(CH_3)_3)$, 414.11722. $C_{24}H_{20}NO_4Si$ requires 414.11616.

Ethyl (2*E*,4*S*)-6-phthalimido-4-(*tert*-butyldiphenylsilyl)oxyhex-2-enoate (2.14)

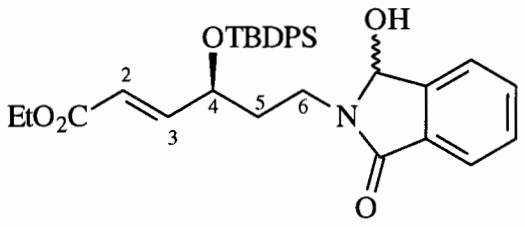


The crude aldehyde **2.13** was dissolved in dichloromethane and ethoxycarbonylmethylenetriphenylphosphorane (4.2 g, 12 mmol) was added. The mixture was stirred at room temperature and monitored by tlc. When the reaction was complete the solvent was evaporated and the residue chromatographed (20 % ethyl acetate/petroleum ether) to obtain **2.14** (5.78 g, 10.66 mmol, 96 % yield over 2 steps) as a colourless gum.

$[\alpha]_D$ = +34.0° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3058, 2989, 1777, 1714, 1663, 1398; δ_H (400MHz, $CDCl_3$) 1.11 (9H, s, t-butyl CH_3), 1.27 (3H, t, CH_2CH_3), 1.87 (2H, m, H-5), 3.67 (2H, m, H-6), 4.13 (2H, m, CH_2CH_3), 4.42 (1H, m, H-4), 6.01 (1H, dd, *J* 1.5, 15.6 Hz, H-2), 6.92 (1H, dd, *J* 5.3, 15.6 Hz, H-3), 7.30-7.83 (14H, m, aromatic); δ_C (100MHz, $CDCl_3$) 14.2 (CH_2CH_3), 19.3

($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 33.5 (C-5), 35.3 (C-6), 60.3 (CH_2CH_3), 70.5 (C-4), 121.3 (C-2), 123.1, 127.6, 127.7, 129.7, 129.8, 132.2, 133.1, 133.4, 133.8, 135.8, 135.8, 135.8 (aromatic), 148.3 (C-3), 166.2 &168.0 (C=O); Found: $M^+(-C(CH_3)_3)$, 484.15924. $C_{28}H_{26}NO_5Si$ requires 484.15803.

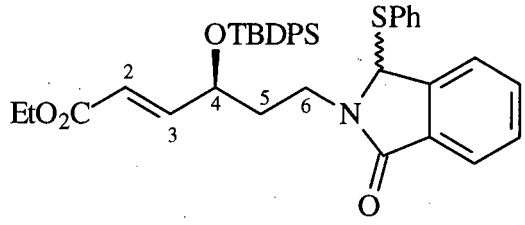
Ethyl (2*E*,4*S*)-6-(1,3-dihydro-3-hydroxy-1-oxoisoindol-2-yl)-4-(*tert*-butyldiphenylsilyl)oxy-hex-2-enoate (2.15)



To a solution of **2.14** (3.91 g, 7.22 mmol) in tetrahydrofuran (20 ml) and methanol (50 ml) at -40°C was added sodium borohydride (1.13 g, 30.0 mmol). The reaction was kept below -20°C and was monitored by tlc. When the starting material had been consumed the reaction was *carefully* quenched with aqueous ammonium chloride and the methanol was removed by evaporation. The aqueous phase was extracted with three portions of dichloromethane and the combined organic layers were dried, then evaporated to give a crude product. This was then chromatographed (40 % ethyl acetate/petroleum ether) to give **2.15** as a foam (3.61 g, 6.64 mmol, 2 epimers, 92.0 % yield).

IR ν_{max} (CH_2Cl_2) / cm^{-1} 3056, 2934, 1706, 1683, 1659, 1422; δ_H (400MHz, $CDCl_3$) 1.07 (9H, s, t-butyl CH_3), 1.25, 1.29 (3H, t, CH_2CH_3, 2 epimers), 1.70 (2H, m, H-5), 3.23 (2H, m, H-6), 4.12, 4.16 (2H, m, CH_2CH_3, 2 epimers), 4.33, 4.45 (1H, m, H-4, 2 epimers), 5.20, 5.51 (1H, s, benzylic H, 2 epimers), 5.99 (1H, dd, *J* 1.2, 15.8 Hz, H-2), 6.86 (1H, dd, *J* 5.1, 15.8 Hz, H-3), 7.23-7.68 (14H, m, aromatic); δ_C (100MHz, $CDCl_3$) 14.2 (CH_2CH_3), 19.3 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 34.7, 35.3, 35.5, 35.7 (C-5, C-6, 2 epimers), 60.4 (CH_2CH_3), 70.5, 70.7 (C-4, 2 epimers), 81.3, 82.4 (benzylic C, 2 epimers), 120.9, 121.1 (C-2, 2 epimers), 123-143 (aromatic), 148.7, 148.8 (C-3, 2 epimers), 166.4, 166.4 & 167.1, 167.1 (C=O, 2 epimers); Found: $M^+(-C(CH_3)_3)$, 486.17267. $C_{28}H_{28}NO_5Si$ requires 486.17368.

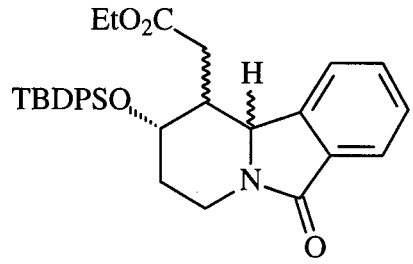
Ethyl (2*E*,4*S*)-6-(1,3-dihydro-3-phenylsulfanyl-1-oxoisoindol-2-yl)-4-(*tert*-butyl-diphenylsilyl)oxyhex-2-enoate (2.16)



The alcohol **2.15** (1.00 g, 1.84 mmol) was dissolved in dry dichloromethane and cooled to -78°C under nitrogen. $BF_3.Et_2O$ (0.47 ml, 3.7 mmol) and benzenethiol (0.38 ml, 3.7 mmol) were added and the solution was stirred at -78°C for 2 hours. The reaction was quenched with aqueous sodium carbonate and extracted with three portions of dichloromethane. The combined organic layers were washed with dilute potassium hydroxide and then dried and evaporated. The crude product was chromatographed (20 % ethyl acetate/petroleum ether) to give pure **2.16** as a gum (1.14 g, 1.78 mmol, 2 epimers, 97 % yield).

IR ν_{max} (CH_2Cl_2) / cm^{-1} 3054, 2988, 1710, 1697, 1659, 1426; δ_H (400MHz, $CDCl_3$) 1.10, 1.13 (9H, s, t-butyl CH_3, 2 epimers), 1.21, 1.30 (3H, t, CH_2CH_3, 2 epimers), 1.77 (2H, m, H-5), 3.52 (2H, m, H-6), 4.05, 4.20 (2H, m, CH_2CH_3, 2 epimers), 4.50, 4.41 (1H, m, H-4, 2 epimers), 4.98, 5.46 (1H, s, benzylic H, 2 epimers), 5.92 (1H, dd, *J* 1.5, 15.7 Hz, H-2), 6.82 (1H, dd, *J* 5.1, 15.7 Hz, H-3), 6.90-7.75 (19H, m, aromatic); δ_C (100MHz, $CDCl_3$) 14.2, 14.3 (CH_2CH_3, 2 epimers), 19.3, 19.3 ($C(CH_3)_3$, 2 epimers), 27.0 ($C(CH_3)_3$), 34.9 (C-5), 35.8 (C-6), 60.3, 60.4 (CH_2CH_3, 2 epimers), 65.7, 66.7 (benzylic C, 2 epimers), 70.3, 70.9 (C-4, 2 epimers), 120.7, 121.3 (C-2, 2 epimers), 123-143 (aromatic), 148.5, 148.7 (C-3, 2 epimers), 166.0 & 167.3 (C=O); Found: M^+(-$C(CH_3)_3$), 578.17981. $C_{34}H_{32}NO_4SSi$ requires 578.18213.

Radical Cyclisation

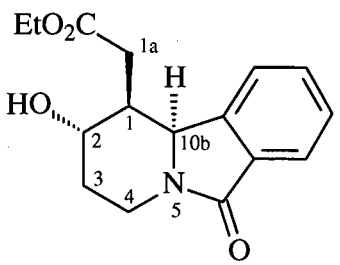


To a solution of the sulfide **2.16** (0.46 g, 0.71 mmol) in dry, deoxygenated toluene (30 ml) at 90°C was added a solution of tributyltin hydride (0.60 ml, 2.2 mmol) and AIBN (15 mg) in toluene (20 ml) dropwise over 30 minutes. The solution was stirred until tlc indicated that no starting material remained. Carbon tetrachloride (1ml) was then added and the solvent evaporated. The residue was chromatographed (30 % ethyl acetate/petroleum ether) to give **2.17** as a gum (0.36 g, 0.69 mmol, 97 % yield). ^{1}H NMR spectral analysis of this crude residue indicated that 4 diastereomers were present in a 4:2:1:1 ratio.

Deprotection of mixture of cyclisation products

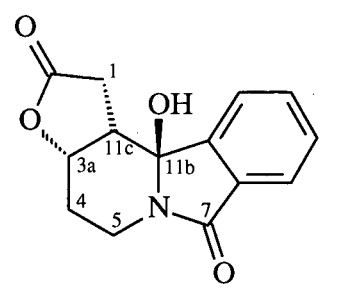
The mixture of isomers **2.17** (0.606 g, 1.15 mmol) were dissolved in tetrahydrofuran (10 ml) and 1M tetrabutylammonium fluoride in tetrahydrofuran (4 ml) was added. The mixture was stirred at room temperature and water was added when tlc indicated that no starting material remained. The tetrahydrofuran was evaporated and the aqueous phase was extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated and the residue chromatographed (80 % ethyl acetate / petroleum ether) to give the alcohol **2.18** (0.177g, 0.63 mmol, 53 % yield) as a colourless crystalline solid. A band of mixed products was also isolated. This mixture was purified by recrystallisation (ethyl acetate/petroleum ether) to give a minor product identified as **2.19** using x-ray crystallography as a colourless crystalline solid (0.057g, 0.22 mmol, 19 % yield).

Major product: **(1*S*,2*S*,10b*S*)-1,2,3,4,10b-Tetrahydro-1-ethoxycarbonylmethyl-2-hydroxypyrido[2,1-*a*]isoindol-6(4H)-one (2.18)**



mp 123-125°C (ethyl acetate/petroleum ether); $[\alpha]_D$ = -15.3° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3608, 3059, 2994, 1732, 1679, 1431; δ_H (400MHz, $CDCl_3$) 1.03 (3H, t, CH_2CH_3), 1.66 (1H, dd, *J* 6.7, 16.3 Hz, H-1a), 1.73 (1H, dd, *J* 7.0, 16.3 Hz, H-1a), 1.78 (2H, m, H-3), 2.66 (1H, br s, OH), 3.03 (1H, m , H-1), 3.39 (1H, ddd, *J* 5.8, 11.6, 13.0 Hz, H-4), 3.81 (2H, m, CH_2CH_3), 4.19 (1H, m, H-2), 4.27 (1H, ddd, *J* 2.2, 5.2, 13.0 Hz, H-4), 5.03 (1H, d, *J* 4.0 Hz, H-10b), 7.36 (1H, d, *J* 7.8 Hz, H-10), 7.47 (2H, m, aromatic), 7.88 (1H, d, *J* 7.6 Hz, H-7); δ_C (100MHz, $CDCl_3$) 13.9 (CH_2CH_3), 27.0 (C-3), 30.7 (C-1a), 33.9 (C-4), 40.2 (C-1), 55.9 (C-10b), 60.6 (CH_2CH_3), 67.8 (C-2), 122.8 & 123.9 & 128.2 & 131.0 & 133.4 & 143.2 (aromatic), 166.7 & 172.0 (C=O); Found: M^+, 289.13040. $C_{16}H_{19}NO_4$ requires 289.13141.

Minor product: **(3a*S*,11b*S*,11c*R*)-3a,4,5,11c-Tetrahydro-10b-hydroxy-furo-[3',2' :3,4] pyrido[2,1-*a*]isoindol-2(1*H*),7(11b*H*)-dione (2.19)**



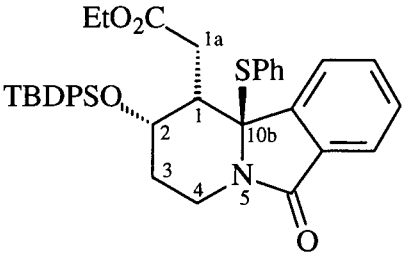
mp decomposes >140°C; $[\alpha]_D$ = -74.1° (c = 0.5, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3326, 1785, 1696; δ_H (400MHz, $CDCl_3$) 1.52 (1H, dd, *J* 12.2, 17.6 Hz, H-1), 1.59 (1H, m, H-4), 2.00 (1H, dd, *J* 9.0, 17.6 Hz, H-1), 2.37 (1H, m, H-4), 3.08 (1H, ddd, *J* 4.1, 10.3, 13.5 Hz, H-5), 3.42 (1H, ddd, *J* 7.5, 8.8,

12.2 Hz, H-11c), 3.78 (1H, dt, *J* 5.4, 13.7 Hz, H-5), 4.00 (1H, d, *J* 3.0 Hz, OH), 5.06 (1H, m, H-3a), 7.40-7.61 (4H, m, aromatic); δ_C (100MHz, D6-DMSO) 26.4 (C-4), 29.5 (C-1), 31.8 (C-5), 41.7 (C-11c), 75.3 (C-3a), 86.1 (C-11b), 122.2, 122.6, 129.5, 130.9, 132.2, 146.3 (aromatic), 164.6 (C=O), 174.6 (C=O); Found: M^+, 259.08325. $C_{14}H_{13}NO_4$ requires 259.08446.

Carbanionic cyclisation

Diisopropylamine (0.80 ml, 5.7 mmol) was added to dry tetrahydrofuran (10 ml) under nitrogen at 0°C. *n*-Butyllithium (2.15 ml of a 2.5M solution in hexanes, 5.4 mmol) was then added and the mixture was stirred for 15 minutes. The mixture was then cooled to -78°C and the sulfide **2.16** (1.14 g, 1.79 mmol) was slowly added as a solution in tetrahydrofuran (5 ml), turning the solution yellow. After 60 minutes the reaction was quenched by adding aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dried and evaporated to a residue consisting of 2 products by tlc. These were separated by chromatography (20 % ethyl acetate/petroleum ether) to give the less polar major product **2.26** (0.87 g, 1.37 mmol, 77 % yield) as a colourless, crystalline solid and the more polar minor product **2.27** (0.20 g, 0.32 mmol, 18 % yield), also as a colourless, crystalline solid.

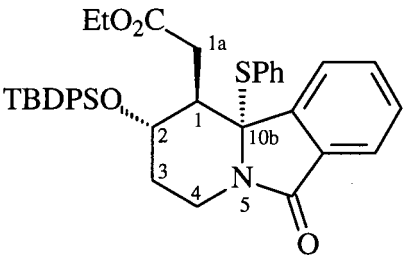
(1*S*,2*S*,10b*S*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-10b-phenylsulfanyl-2-(*tert*-butyldiphenylsilyl)oxypyrido[2,1-*a*]isoindol-6(4*H*)-one (2.26)



mp 126-128°C (ethyl acetate/petroleum ether); $[\alpha]_D$ = -190.1° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3055, 2988, 2306, 1733, 1697, 1432; δ_H (400MHz, $CDCl_3$) 0.99 (3H, t, CH_2CH_3), 1.11 (9H, s, t-butyl CH_3), 1.54 (1H, m, H-3), 1.57 (1H, dd, *J* 8.8, 16.7 Hz, H-1a), 1.74 (1H, m, H-3), 2.73 (1H, dd, *J* 2.1, 16.7 Hz, H-1a), 3.21 (1H, td, *J* 4.0, 13.2, 13.3 Hz , H-4), 3.38 (1H, m, H-1), 3.79 (2H, m, CH_2CH_3), 4.24 (1H, ddd, *J* 1.3, 5.5, 13.3 Hz, H-4), 4.79 (1H, dt, *J* 4.5, 4.5, 11.7 Hz, H-2), 6.65-7.83

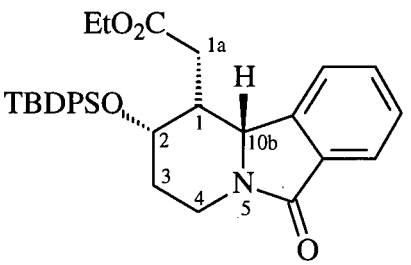
(19H, m, aromatic); δ_C (100MHz, $CDCl_3$) 13.9 (CH_2CH_3), 19.2 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 29.2 (C-3), 29.3 (C-1a), 34.2 (C-4), 43.8 (C-1), 60.3 (CH_2CH_3), 69.0 (C-2), 78.7 (C-10b), 122.8, 124.3, 127.7, 127.9, 128.2, 128.4, 128.5, 129.2, 129.9, 130.1, 130.9, 131.6, 133.0, 133.9, 135.8, 136.0, 136.0, 144.4 (aromatic), 165.9 & 172.5 (C=O); Found: C, 71.74; H, 6.69; N, 2.43; S, 4.87 % $C_{38}H_{41}NO_4SSi$ requires C, 71.78; H, 6.50; N 2.20; S 5.04 %; Found: $M^+(-SC_6H_5)$, 526.24096. $C_{32}H_{36}NO_4Si$ requires 526.24136.

(1*R*,2*S*,10b*R*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-10b-phenylsulfanyl-2-(*tert*-butyldiphenylsilyl)oxypyrido[2,1-*a*]isoindol-6(4H)-one (2.27)



mp 133-135°C (ethyl acetate/petroleum ether); $[\alpha]_D$ = +40.7° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3058, 2984, 2307, 1732, 1696, 1427; δ_H (400MHz, $CDCl_3$) 0.94 (3H, t, CH_2CH_3), 1.22 (9H, s, t-butyl CH_3), 1.45 (2H, m, H-3), 1.55 (1H, dd, *J* 7.9, 16.1 Hz, H-1a), 1.75 (1H, dd, *J* 6.2, 16.1 Hz, H-1a), 3.42 (1H, ddd, *J* 2.3, 6.2, 7.9 Hz, H-1), 3.77 (2H, m, CH_2CH_3), 3.90 (1H, m, H-4), 3.99 (1H, q, *J* 2.6 Hz, H-2), 4.20 (1H, m, H-4), 6.90 (4H, m, aromatic), 7.05 (1H, m, aromatic), 7.14 (1H, m, aromatic), 7.30 (1H, m, aromatic), 7.42 (7H, m, aromatic), 7.55 (1H, m, aromatic), 7.81 (4H, m, aromatic); δ_C (100MHz, $CDCl_3$) 13.9 (CH_2CH_3), 19.4 ($C(CH_3)_3$), 27.1 ($C(CH_3)_3$), 27.8 (C-3), 31.1 (C-1a), 34.9 (C-4), 44.5 (C-1), 60.6 (CH_2CH_3), 70.0 (C-2), 76.2 (C-10b), 122.9, 123.9, 127.7, 127.8, 128.0, 128.8, 129.9, 129.9, 130.7, 131.1, 131.4, 133.0, 134.0, 136.0, 136.1, 136.3, 145.5 (aromatic), 165.7 & 171.1 (C=O); Found: C, 71.87; H, 6.66; N, 2.42; S, 4.98 %
$C_{38}H_{41}NO_4SSi$ requires: C, 71.78; H, 6.50; N, 2.20; S, 5.04 %; Found: $M^+(-SC_6H_5)$, 526.24355. $C_{32}H_{36}NO_4Si$ requires 526.24136.

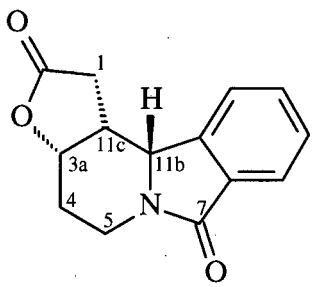
(1*R*,2*S*,10b*R*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-2-(*tert*-butyldiphenylsilyl)oxypyrido[2,1-*a*]isoindol-6(4H)-one (2.28)



A 2-necked flask was fitted with a condenser, a pressure-equilibrating dropping funnel and a stirrer bar. The system was purged with nitrogen and **2.26** (0.30 g, 0.47 mmol) was added as a solution in ethanol (150 ml). Nickel Chloride hexahydrate (2.85 g, 12 mmol) was then added. When the solution was homogeneous, the dropping funnel was filled with aqueous sodium borohydride (0.90 g, 24 mmol in $10cm^3$) and this was added dropwise to the green solution of nickel chloride. This solution immediately turned black. When the addition was complete, the reaction mixture was heated under reflux until tlc indicated that no starting material remained. This mixture was filtered through Celite® and the filter cake was washed thoroughly with dichloromethane. The filtrate was evaporated and the residue extracted with dichloromethane. The organic phase was then dried, and evaporated. The final product was purified with flash chromatography (30 % ethyl acetate/petroleum ether) to give **2.28** (0.23 g, 0.43 mmol, 92 % yield) as a colourless, crystalline solid.

mp 102-104°C (ethyl acetate / petroleum ether); $[\alpha]_D$ = -97.8° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3061, 2990, 2314, 1737, 1698, 1429; δ_H (400MHz, $CDCl_3$) 0.97 (3H, t, CH_2CH_3), 1.08 (9H, s, t-butyl CH_3), 1.56 (1H, dd, *J* 8.8, 16.5 Hz, H-1a), 1.60 (2H, m, H-3), 2.54 (1H, dd, *J* 2.4, 16.5 Hz, H-1a), 2.73 (1H, td, *J* 4.7, 13.4, 13.4 Hz, H-4), 3.19 (1H, m, H-1), 3.63-3.86 (2H, m, CH_2CH_3), 4.12 (1H, dt, *J* 4.8, 4.8, 10.8 Hz, H-2), 4.28 (1H, d, *J* 3.5 Hz, H-10b), 4.30 (1H, ddd, *J* 1.5, 5.7, 13.4 Hz, H-4), 7.30-7.80 (14H, m, aromatic); δ_C (100MHz, $CDCl_3$) 13.9 (CH_2CH_3), 19.1 ($C(CH_3)_3$), 26.5 (C-3), 26.9 ($C(CH_3)_3$), 29.0 (C-1a), 36.7 (C-4), 40.3 (C-1), 60.2 (C-10b), 60.4 (CH_2CH_3), 71.7 (C-2), 123.5 & 123.7 & 127.7 & 127.8 & 128.3 & 129.9 & 130.0 & 130.8 & 133.3 & 133.4 & 133.8 & 135.8 & 135.9 & 141.7 (aromatic), 166.7 & 172.9 (C=O); Found: C, 72.70; H, 7.22; N, 2.75 %; $C_{32}H_{37}NO_4Si$ requires: C, 72.83; H, 7.07; N, 2.65 %; Found: $M^+(-C(CH_3)_3)$, 470.17758. $C_{28}H_{28}NO_4Si$ requires 470.17876.

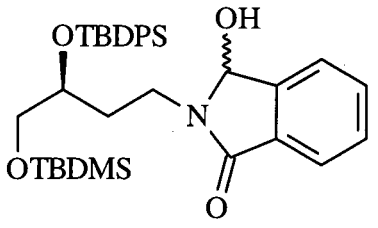
(3a*S*,11b*R*,11c*R*)-3a,4,5,11c-Tetrahydro-furo-[3',2' :3,4] pyrido[2,1-*a*]isoindol-2(1H),7(11bH)-dione (2.30)



A solution of **2.28** (1.58g, 2.99 mmol) in acetonitrile (6 ml) was made up in a polypropylene container. To this solution was added 40 % hydrofluoric acid in acetonitrile (4 ml) and the mixture was stirred for 5 days at 45°C. Solid sodium hydrogen carbonate was then added until the effervescence ceased. The mixture was diluted with water and extracted with dichloromethane. The organic layer was dried with magnesium sulfate and evaporated. The crude product was chromatographed (80 % ethyl acetate/petroleum ether) to obtain pure **2.30** (0.66 g, 2.71 mmol, 91 % yield) as a colourless, crystalline solid.

mp 223-226°C (ethyl acetate/petroleum ether); $[\alpha]_D$ = +183.0° (c = 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3058, 2987, 1780, 1694, 1424; δ_H (400MHz, $CDCl_3$) 1.67 (1H, dd, *J* 10.6, 18.1 Hz, H-1), 1.89 (1H, m, H-4), 2.03 (1H, dd, *J* 9.2, 18.1 Hz, H-1), 2.28 (1H, m, H-4), 3.30 (1H, ddd, *J* 4.2, 8.4, 13.5 Hz, H-5), 3.42 (1H, m, H-11c), 4.16 (1H, ddd, *J* 5.1, 7.0, 13.5 Hz, H-5), 4.75 (1H, d, *J* 4.8, H-11b), 5.02 (1H, td, *J* 5.1, 7.7, 7.7 Hz, H-3a), 7.37-7.87 (4H, m, aromatic); δ_C (100MHz, $CDCl_3$) 27.3 (C-4), 27.4 (C-1), 34.9 (C-5), 37.3 (C-11c), 55.7 (C-11b), 75.6 (C-3a), 121.8 & 124.2 & 129.0 & 131.9 & 132.8 & 142.6 (aromatic), 167.2 & 174.5 (C=O); Found: M^+, 243.08877. $C_{14}H_{13}NO_3$ requires 243.08954.

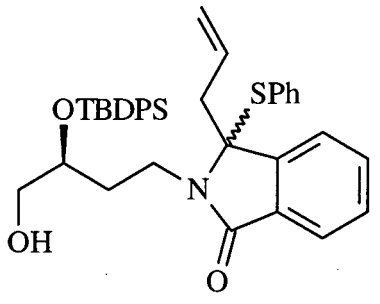
(*S*)-4-(1,3-dihydro-3-hydroxy-1-oxoisoindol-2-yl)-2-(*tert*-butyldiphenylsilyl)oxy-1-(*tert*-butyldimethylsilyl)oxybutane (2.32)



A solution of **2.11** (11.3 mmol) in methanol (60 ml) and tetrahydrofuran (30 ml) under a nitrogen atmosphere was cooled to -40°C followed by addition of sodium borohydride (1.76g, 46.5 mmol). The reaction was kept below -20°C and was monitored by tlc. When the starting material had been consumed the reaction was *carefully* quenched with aqueous ammonium chloride and the methanol was removed by evaporation. The aqueous phase was extracted with three portions of dichloromethane and the combined organic layers were dried, then evaporated to give a crude product. This was then chromatographed (20 % ethyl acetate/petroleum ether) to give **2.32** as an oil (6.28 g, 10.6 mmol, 2 epimers, 94.0 % yield).

IR ν_{max} (CH_2Cl_2) / cm^{-1} 3370, 3054, 2931, 1702; δ_H (400MHz, $CDCl_3$) –0.12, -0.09, -0.07, -0.05 (6H, s, TBDMS CH_3, 2 epimers), 0.79, 0.82 (9H, s, t-butyl CH_3, 2 epimers), 1.05 (9H, s, t-butyl CH_3), 1.90 (2H, m, H-3, 2 epimers), 2.66, 2.73 (1H, d, J 11.4 Hz, OH, 2 epimers), 3.55 (4H, m, H-1, H-4), 3.83 (1H, m, H-2), 5.41, 5.60 (1H, d, J 11.4 Hz, benzylic H, 2 epimers), 7.25-7.75 (14H, m, aromatic); δ_C (100MHz, $CDCl_3$) -5.5 (TBDMS 2 x CH_3), 18.2, 18.3 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 25.8 & 27.0 ($C(CH_3)_3$), 32.2, 32.3 (C-3, 2 epimers), 35.7, 35.9 (C-4, 2 epimers), 65.7, 65.9 (C-1, 2 epimers), 71.9, 72.0 (C-2, 2 epimers), 81.6, 82.1 (benzylic C, 2 epimers), 123 – 143 (aromatic), 166.9, 167.0 (C=O); Found: M^+(+3H), 592.32743. $C_{34}H_{50}Si_2NO_4$ requires 592.32784.

(*S*)-4-(3-allyl –2,3-dihydro-3-phenylsulfanyl-1-oxoisoindol-2-yl)-2-(*tert*-butyldiphenylsilyl)-oxy-1-butanol (2.34)

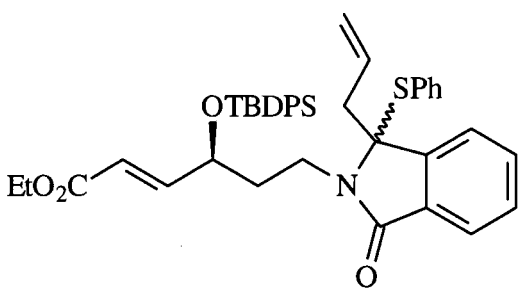


The alcohol **2.32** (6.12 g, 10.4 mmol) was dissolved in dry dichloromethane (80 ml) and cooled to -78°C under nitrogen. $BF_3.Et_2O$ (2.63 ml, 20.8 mmol) and benzenethiol (2.13 ml, 20.8 mmol) were added and the solution was warmed from -78°C to -35°C over 2 hours. The reaction was quenched with aqueous sodium carbonate and extracted with three portions of dichloromethane. The combined organic layers were washed with dilute potassium hydroxide and then dried and evaporated. The crude product was chromatographed (10 % ethyl acetate/petroleum ether) to give pure **2.33** as a gum (6.30 g, 9.24 mmol, 2 epimers, 87 % yield).

Diisopropylamine (0.65 ml, 4.98 mmol) was added to dry tetrahydrofuran (15 ml) under nitrogen at 0°C. *n*-Butyllithium (2.75 ml of a 1.6M solution in hexanes, 4.40 mmol) was then added and the mixture was stirred for 15 minutes. The mixture was then cooled to -78°C and the sulfide **2.33** (2.00 g, 2.93 mmol) was slowly added as a solution in tetrahydrofuran (10 ml) followed by allyl bromide (0.40ml, 4.62 mmol). The reaction was allowed to warm to rt and was then quenched with aqueous saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 x), and the combined organic layers were dried and evaporated to a residue. This was chromatographed (20 % ethyl acetate/petroleum ether) to give the oily product (2.05 g). This oily residue was dissolved in acetonitrile (4 ml) at room temperature and transferred to a polypropylene container at room temperature. To this solution was added 40 % hydrofluoric acid (2ml) and the reaction was monitored by tlc until the starting material had been consumed. The mixture was neutralized with solid sodium hydrogen carbonate and extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated to a residue. This was chromatographed (30 % ethyl acetate/petroleum ether) to give **2.34** (1.62g, 2.66 mmol, 91 % yield over 2 steps).

IR ν_{max} (CH_2Cl_2) / cm^{-1} 3370, 3054, 2933, 1694; δ_H (400MHz, $CDCl_3$) 1.14, 1.16 (9H, s, t-butyl CH_3, 2 epimers), 1.68 (1H, br s, OH), 1.89 (1H, m, H-3), 2.05 (2H, m, H-3), 2.68-3.05 (2H, allyl CH_2), 3.40-3.80 (4H, m, H-1, H-4), 4.01 (1H, m, H-2), 4.96 (2H, m, CH=CH_2), 5.25 (1H, m, CH=CH_2), 6.72-7.82 (19H, m, aromatic); δ_C (100MHz, $CDCl_3$) 19.4, 19.5 ($C(CH_3)_3$, 2 epimers), 27.1 & 27.2 (C(CH_3)$_3$, 2 epimers), 32.0, 32.8 (C-3, 2 epimers), 36.0, 37.4 (C-4, 2 epimers), 40.6 (allyl CH_2), 65.2, 66.4 (C-1, 2 epimers), 72.1, 72.7 (C-2, 2 epimers), 79.0, 80.2 (benzylic C, 2 epimers), 119.8, 119.9 (CH=CH_2, 2 epimers), 122 – 144 (aromatic, CH=CH_2), 167.9, 168.0 (C=O, 2 epimers); Found: M^+(+H) 608.26565. $C_{37}H_{42}SSiNO_3$ requires 608.26547.

Ethyl (2*E*, 4*S*)-6-(3-allyl –2,3-dihydro-3-phenylsulfanyl-1-oxoisoindol-2-yl)-4-(*tert*-butyldiphenylsilyl)oxyhex-2-enoate (2.35)

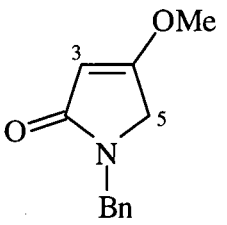


Dimethyl sulfoxide (0.38 ml, 5.35 mmol) was dissolved in dry dichloromethane and cooled to -78°C under nitrogen. Oxalyl chloride (0.32 ml, 3.67 mmol) was then added, and after 15 minutes the alcohol **2.34** (1.47 g, 2.42 mmol) was slowly added in a solution of dichloromethane. After a further 5 minutes, triethylamine (1.7 ml, 12.2 mmol) was added and the mixture was slowly allowed to warm to 0°C. The reaction was quenched by adding aqueous sodium carbonate and extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated to give crude aldehyde (1.611g), which could be taken on to the next step. This crude aldehyde was dissolved in dichloromethane (50ml) and ethoxycarbonylmethylenetriphenylphosphorane (0.9 g, 2.6 mmol) was added. The mixture was stirred at room temperature and monitored by tlc. When the reaction was complete the solvent was evaporated and the residue chromatographed (20 % ethyl acetate/petroleum ether) to obtain **2.35** (1.49 g, 2.21 mmol, 91% yield over 2 steps) as a colourless gum.

IR ν_{max} (CH_2Cl_2) / cm^{-1} 3054, 2933, 1703, 1697; δ_H (400MHz, $CDCl_3$) 1.17 (9H, s, t-butyl CH_3), 1.29, 1.32 (3H, t, CH_3, 2 epimers), 1.81 (1H, m, H-5), 2.19 (2H, m, H-5), 2.64-3.02 (2H, allyl CH_2), 3.57 (2H, m, H-6), 4.20 (2H, m, ethyl CH_2, 2 epimers), 4.54, 4.61 (1H, m, H-4, 2 epimers), 4.96 (2H, m, CH=C*H*$_2$), 5.25 (1H, m, C*H*=CH_2), 5.90, 6.04 (1H, dd, *J* 1.5 15Hz, H-2, 2 epimers), 6.70-7.80 (20H, m, aromatic & H-3); δ_C (100MHz, $CDCl_3$) 14.2 (CH_2*C*H_3), 19.4 (*C*(CH_3)$_3$), 27.1 (C(*C*H_3)$_3$), 35.0, 35.5 (C-5, 2 epimers), 36.0, 37.1 (C-6, 2 epimers), 40.5, 40.6 (allyl CH_2, 2 epimers), 60.4 (*C*H_2CH$_3$), 71.2, 71.4 (C-4, 2 epimers), 78.9 (benzylic C), 119.7, 119.9 (CH=*C*H_2, 2 epimers), 121.0, 121.2 (C-2, 2 epimers), 123-146 (aromatic), 148.8, 149.0 (C-3, 2 epimers), 166.2 & 166.3 (ester C=O, 2 epimers), 167.8 (lactam C=O); Found: M^+(+H) 676.29170. $C_{41}H_{46}SSiNO_4$ requires 676.29168.

4.3 Synthesis of tricyclic lepadiformine core

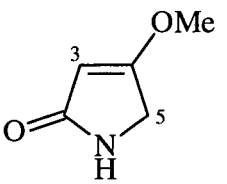
1-Benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (3.10)



Methyl (*E*)-4-chloro-3-butenoate (3.0ml, 22.1mmol) was dissolved in dry acetonitrile (25ml) under nitrogen. The solution was cooled to 0°C and diisopropylethylamine (3.42ml, 26.5mmol) was added, followed by the slow addition of benzylamine. The solution was then heated to 50°C and stirred at that temperature for 36h. The orange solution was then cooled and saturated sodium hydrogencarbonate solution was added. The mixture was extracted with three portions of ethyl acetate, and the combined organic layers were then dried and concentrated to an orange oily residue. The residue was purified by column chromatography (80% ethyl acetate/petroleum ether) to give the product **3.10** as an off-white solid (2.63g, 12.9mmol, 58% yield).

δ_H (200MHz, $CDCl_3$) 3.65 (2H, s, CH_2), 3.70 (3H, s, OCH_3), 4.52 (2H, s, benzylic CH_2), 5.04 (1H, s, C-3), 7.20 (5H, m, aromatic).

4-Methoxypyrrol-2(1*H*)-one (3.11)

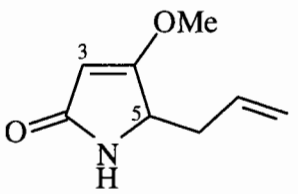


Methyl (*E*)-4-chloro-3-butenoate (5.0ml, 36.8mmol) was slowly added to 10% aqueous ammonia solution (23ml) over 1 hour at 65°C. The reaction was stirred for a further 1.5 hours and then the orange solution was cooled to room temperature. The solution was thoroughly extracted with dichloromethane. The organic layers were combined, dried and concentrated to give a yellow solid.

The solid was recrystallised from benzene to give off-white needles of the pyrrolone **3.11** (3.41g, 30.1mmol, 82% yield).

δ_H (200 MHz, $CDCl_3$): 3.78 (3H, s, OCH_3), 3.90 (2H, s, H-5), 5.04 (1H, s, H-3), 6.84 (1H, br s, N*H*).

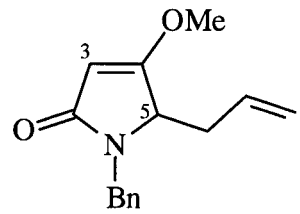
5-Allyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (3.12)



The substrate **3.11** (1.00g, 8.84mmol) was dissolved in dry tetrahydrofuran (40ml) under nitrogen with stirring. After cooling to -78°C the solution became cloudy. A solution of *n*-butyl lithium in hexanes (11.6ml of a 1.6M solution, 2.1eq) was added dropwise. When the addition was complete the solution became clear with a pale yellow colour. The solution was stirred for 30min at -78°C. Allyl bromide (0.80ml, 1.05eq) was added slowly and the solution was then stirred for 60min at -78°C. Saturated sodium hydrogen carbonate solution (50ml) was added and the tetrahydrofuran was then evaporated. The aqueous solution was extracted thoroughly with dichloromethane and the organic layers were combined, dried and evaporated to give a colourless residue that slowly crystallised. The residue was purified by column chromatography to give alkylated product **3.12** as a colourless crystalline solid (1.07g, 6.99mmol, 79% yield) as well as an inseparable mixture (0.217g) of recovered **3.11** and the 3-alkylated regioisomer of **3.12**.

mp (ethyl acetate) = 91-93°C; δ_H (300MHz, $CDCl_3$): 2.18 (1H, m, CH_2), 2.59 (1H, m, CH_2), 3.79 (3H, s, OCH_3), 4.06 (1H, dd, *J* 3.9, 8.1 Hz, H-5), 5.01 (1H, s, H-3), 5.14 (2H, m, $CH{=}CH_2$), 5.74 (1H, m, $CH{=}CH_2$), 6.02 (1H, br s, N*H*); δ_C (75 MHz, $CDCl_3$): 36.3 (CH_2), 56.8 (C-5), 58.3 (OCH_3), 93.8 (C-3), 118.8 ($CH{=}CH_2$), 132.5 ($CH{=}CH_2$), 177.6 (C=O, C-4); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3452, 3015, 1683, 1626; Found: M^+, 153.07875. $C_8H_{11}NO_2$ requires *M*, 153.07898.

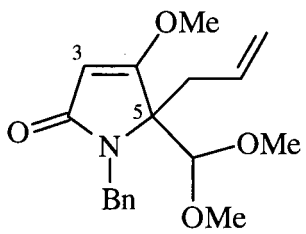
5-Allyl-1-benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (3.13)



The substrate **3.12** (0.610g, 3.92mmol) was dissolved in dry tetrahydrofuran (15ml) under nitrogen at room temperature. Benzyl bromide (1.40ml, 11.8mmol, 3eq) and powdered potassium hydroxide (0.550g, 9.8mmol, 2.5eq) were added. The mixture was stirred for a few minutes then tetrabutylammonium hydrogensulfate (0.133g, 0.39mmol, 0.1eq) was added. After 60 minutes tlc indicated that the starting material had been consumed. Saturated ammonium chloride solution was added and the mixture was extracted with 3 portions of dichloromethane. The organic layers were combined, dried with magnesium sulphate and evaporated to give an oily residue. This residue was purified by column chromatography (ethyl acetate : petroleum ether = 4 : 6), to afford the benzylated product **3.13** as a colourless crystalline solid (0.834g, 3.43mmol, 88% yield).

mp (ethyl acetate/petroleum ether) = 59-61°C; δ_H (300 MHz, $CDCl_3$): 2.47 (2H, m, CH_2), 3.76 (3H, s, OCH_3), 3.87 (1H, t, *J* 4.5 Hz, H-5), 3.98 (1H, d, *J* 15.4 Hz, $PhCH_2$), 5.07 (2H, m, $CH{=}CH_2$), 5.10 (1H, s, C-3), 5.16 (1H, d, *J* 15.4 Hz, $PhCH_2$), 5.51 (1H, m, $CH{=}CH_2$), 7.27 (5H, m, aromatic); δ_C (75 MHz, $CDCl_3$): 32.6 (CH_2), 43.2 ($PhCH_2$), 58.0 & 58.6 (C-5, OCH_3), 94.2 (C-3), 118.8 ($CH{=}CH_2$), 127.4 & 128.0 & 128.7 (aromatic), 131.0 ($CH{=}CH_2$), 137.6 (aromatic), 171.7 (C-4), 175.3 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3052, 2940, 1677, 1629, 1368; Found: M^+, 243.12629. $C_{15}H_{17}NO_2$ requires *M*, 243.12593; Found: C, 74.18; H, 7.06; N, 5.69. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%.

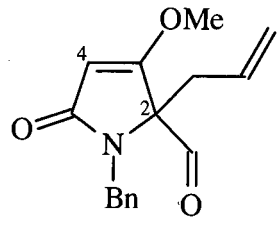
5-Allyl-1-benzyl-5-dimethoxymethyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (3.14)



The substrate **3.13** (0.73g, 3mmol) was dissolved in dry tetrahydrofuran (30ml) under N_2 and cooled to -78°C. A solution of *n*-butyl lithium in hexanes (2.25ml of a 1.6 M solution, 3.6mmol, 1.2eq) was added dropwise. After stirring for 30 minutes at -78°C chlorotrimethylsilane (0.57ml, 4.5mmol, 1.5eq) was added dropwise and the solution was stirred for a further 30 minutes at -78°C. Trimethyl orthoformate (1.00ml, 9.0mmol, 3eq) was then added, followed by $BF_3.Et_2O$ (0.57ml, 4.5mmol, 1.5eq). The reaction was allowed to slowly warm to -20°C over 2 hours. Saturated sodium hydrogen carbonate solution was then added and the tetrahydrofuran was removed by evaporation. The remaining aqueous layer was extracted with 3 portions of ethyl acetate. The organic layers were combined, dried and concentrated to give an oily residue. The product was isolated by column chromatography to give the acetal as an oil that slowly crystallised as a colourless, waxy solid **3.14** (0.699g, 2.20mmol) in 88% yield based on recovered starting material (0.125g, 0.51mmol).

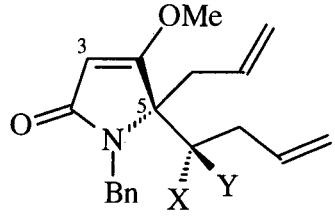
δ_H (400 MHz, $CDCl_3$): 2.37 (1H, ddt, *J* 1.1, 7.7, 14.7 Hz, CH_2), 2.54 (1H, dd, *J* 6.6, 14.7 Hz, CH_2), 3.27 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.21 (1H, s, OC*H*O), 4.61 (2H, s, PhCH_2), 4.84 (2H, m, CH=CH_2), 5.12 (1H, s, H-3), 5.18 (1H, m, C*H*=CH_2), 7.15-7.38 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$): 33.8 (*C*H_2), 43.6 (Ph*C*H_2), 57.8 & 57.9 & 58.0 (3 x O*C*H_3), 71.8 (C-5), 95.2 (C-3), 107.6 (O*C*HO), 118.6 (CH=*C*H_2), 126.6 & 128.0 & 128.5 (aromatic), 130.9 (*C*H=CH$_2$), 139.6 (aromatic), 172.2 (C-4), 174.5 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3019, 1669, 1640, 1346; Found: M^+(+H), 318.17144. $C_{18}H_{24}NO_4$ requires *M*, 318.17053.

2-Allyl-1-benzyl-3-methoxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carbaldehyde (3.18)



The acetal **3.14** (0.233g, 0.73mmol) was dissolved in trifluoroacetic acid (3ml) and water (0.07ml) and the solution was stirred at 35°C for 20 hours. The solution was poured into a saturated solution of sodium hydrogen carbonate, and the aqueous mixture extracted with 3 portions of dichloromethane. The organic layers were combined, dried and evaporated to give the aldehyde **3.18** as a pale yellow oil (0.189g, 0.69mmol, 95% yield). This aldehyde was somewhat unstable and was reacted immediately without further purification.

5-Allyl-1-benzyl-5-(1-hydroxybut-3-enyl)-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (PP6)



3.19 X = OH, Y = H
3.20 X = H, Y = OH

The aldehyde **3.18** (0.189g, 0.69mmol) was dissolved in dry tetrahydrofuran (7ml) under nitrogen and cooled to -78°C. A solution of allylmagnesium chloride (0.40ml of a 2.0M solution, 0.80mmol, 1.2eq) in tetrahydrofuran was slowly added. Once the addition was complete the reaction was allowed to slowly warm to 0°C. The reaction was then quenched by addition of saturated ammonium chloride solution and the tetrahydrofuran was evaporated. The aqueous layer was extracted with 3 portions of dichloromethane. The combined organic layers were dried and evaporated to give an oily, yellow residue. This residue contained a 3:1 ratio of diastereomers (from ^{1}H NMR). Column chromatography of the residue gave the more polar major diastereomer **3.19** as a colourless crystalline solid (0.060g, 0.19mmol), the less polar minor diastereomer **3.20** as an oil (0.018g,

0.06mmol) and a mixed fraction of both diastereomers (0.087g, 0.28mmol). The combined yield was 76%.

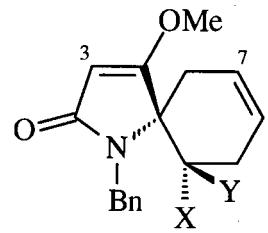
Major **3.19**

mp (ethyl acetate) = 122-124°C; δ_H (400 MHz, $CDCl_3$): 1.53 (1H, m, C*H*$_2$), 1.78 (1H, d, *J* 9.5 Hz, O*H*), 1.97 (1H, m, C*H*$_2$), 2.60 (1H, dd, *J* 7.0, 15.0 Hz, C*H*$_2$), 2.98 (1H, ddt, *J* 1.1, 7.0, 15.0 Hz, C*H*$_2$), 3.44 (1H, td, *J* 1.8, 9.9 Hz, C*H*OH), 3.79 (3H, s, OC*H*$_3$), 3.94 (1H, d, *J* 15.4 Hz, PhC*H*$_2$), 4.71 (1H, m, CH=C*H*$_2$), 4.86 (1H, m, CH=C*H*$_2$), 4.99 (1H, d, *J* 15.4 Hz, PhC*H*$_2$), 5.05 (2H, m, CH=C*H*$_2$), 5.17 (1H, s, H-3), 5.18 (1H, m, C*H*=CH_2), 5.35 (1H, m, C*H*=CH_2), 7.20-7.40 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$): 34.7 (*C*H_2), 36.1 (*C*H_2), 42.8 (Ph*C*H_2), 58.3 (O*C*H_3), 71.5 (C-5), 73.4 (*C*OH), 95.4 (C-3), 117.6 & 119.1 (CH=*C*H_2 x 2), 127.5 & 128.6 & 128.7 (aromatic), 130.9 & 134.2 (*C*H=CH_2 x 2), 138.5 (aromatic), 171.7 (C-4), 175.8 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3578, 3014, 1671, 1632, 1348; Found: M^+, 313.16705. $C_{19}H_{23}NO_3$ requires *M*, 313.16779; Found: C, 72.87; H, 7.11; N, 4.49. $C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40; N, 4.47%.

Minor **3.20**

δ_H (400 MHz, $CDCl_3$): 1.45 (1H, br s, O*H*), 1.80 (1H, m, C*H*$_2$), 1.99 (1H, m, C*H*$_2$), 2.45 (1H, ddt, *J* 1.1, 7.3, 14.7 Hz, C*H*$_2$), 2.94 (1H, dd, *J* 7.0, 14.7 Hz, C*H*$_2$), 3.67 (1H, dd, *J* 2.9, 10.6 Hz, C*H*OH), 3.75 (3H, s, OC*H*$_3$), 4.19 (1H, d, *J* 15.0 Hz, PhC*H*$_2$), 4.66 (1H, m, CH=C*H*$_2$), 4.94 (1H, d, *J* 15.0 Hz, PhC*H*$_2$), 4.93-5.02 (3H, m, CH=C*H*$_2$), 5.14 (1H, s, H-3), 5.31 (1H, m, C*H*=CH_2), 5.59 (1H, m, C*H*=CH_2), 7.20-7.47 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$): 35.4 & 35.6 (*C*H_2 x 2), 43.6 (Ph*C*H_2), 58.1 (O*C*H_3), 72.1 & 72.8 (C-5, COH), 95.0 (C-3), 118.5 & 118.9 (CH=*C*H_2 x 2), 127.3 & 128.5 & 129.0 (aromatic), 131.1 & 134.3 (*C*H=CH_2 x 2), 139.4 (aromatic), 172.5 (C-4), 175.4 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3559, 3051, 1678, 1635, 1343; Found: M^+(+H), 314.1747. $C_{19}H_{24}NO_3$ requires *M*, 314.1756.

1-Benzyl-10-hydroxy-4-methoxy-1-azaspiro[4.5]deca-3,7-dien-2-one



3.21 X = OH, Y = H
3.22 X = H, Y = OH

The diallyl compound **3.19** (0.614g, 1.96mmol) was dissolved in dry deoxygenated dichloromethane (15ml), Grubbs catalyst (0.050g, 3 mol%) added in one portion, and the solution heated under reflux for 2 hours. During this period the colour turned from purple to brown. The solvent was evaporated and the black residue was chromatographed to give the azospiro compound **3.21** as a colourless crystalline solid (0.514g, 1.80mmol, 92% yield).

Major: **3.21**

mp (ethyl acetate) = 160-164°C; δ_H (300 MHz, $CDCl_3$): 1.65 (1H, m, H-9), 1.77 (1H, d, *J* 3.8 Hz, O*H*), 2.08 (1H, m, H-6), 2.38 (1H, m, H-9), 2.74 (1H, m, H-6), 3.83 (3H, s, OCH_3), 4.01 (1H, td, *J* 6.8, 10.2 Hz, H-10), 4.46 (1H, d, *J* 16.1 Hz, $PhCH_2$), 4.78 (1H, d, *J* 16.1 Hz, $PhCH_2$), 5.20 (1H, s, H-3), 5.64 (2H, m, H-7 + H-8), 7.17-7.32 (5H, m, aromatic); δ_C (75 MHz, $CDCl_3$): 31.7 (C-9), 32.3 (C-6), 44.2 ($PhCH_2$), 58.4 (OCH_3), 67.6 (C-10), 68.1 (C-5), 93.7 (C-3), 124.5 & 124.9 (C-7 + C-8), 126.8 & 126.9 & 128.6 & 140.1 (aromatic), 173.7 (C-4), 177.6 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3564, 3054, 1681, 1639, 1339; Found: M^+, 285.13703. $C_{17}H_{19}NO_3$ requires *M*, 285.13649; Found: C, 71.39; H, 6.72; N, 4.88. $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91%.

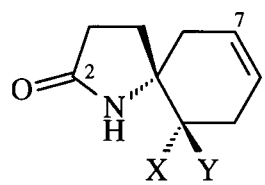
The experiment was repeated with **3.20** to give the azaspiro compound **3.22** as a colourless crystalline solid.

Minor: **3.22**

mp (ethyl acetate) = 156-158°C; δ_H (400 MHz, $CDCl_3$): 2.13 (1H, m, H-9), 2.16 (1H, d, *J* 3.7 Hz, O*H*), 2.40 (2H, m, H-6), 2.52 (1H, m, H-9), 3.76 (3H, s, OCH_3), 3.92 (1H, ddd, *J* 3.9, 7.2, 9.3 Hz, H-10), 4.40 (1H, d, *J* 16.1 Hz, $PhCH_2$), 4.72 (1H, d, *J* 16.1 Hz, $PhCH_2$), 5.15 (1H, s, H-3), 5.55 (2H, m,

H-7 + H-8), 7.22-7.39 (5H, m, aromatic); δ_C (100 MHz, $CDCl_3$): 31.0 (C-9), 31.6 (C-6), 41.6 ($PhCH_2$), 58.3 (OCH_3), 67.0 (C-10), 68.6 (C-5), 93.7 (C-3), 122.9 & 124.9 (C-7 + C-8), 127.5 & 127.6 & 129.0 & 139.1 (aromatic), 172.1 (C-4), 178.9 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3551, 3391, 3022, 1667, 1628, 1349; Found: M^+, 285.13735. $C_{17}H_{19}NO_3$ requires 285.13649.

10-Hydroxy-1-azaspiro[4.5]dec-7-en-2-one



3.23 X = OH, Y = H
3.24 X = H, Y = OH

The substrate **3.21** (0.500g, 1.75mmol) was added as a solution in tetrahydrofuran (12ml) to pre-dried liquid ammonia (30ml) at -78°C. Sodium (0.62g, mmol) was added in several pieces with vigorous stirring. Dissolution of the metal was observed and the solution turned a deep blue colour. The mixture was stirred at reflux (-33°C) for 90 minutes, before being quenched by addition of solid ammonium chloride until the blue colour disappeared. The mixture was allowed to warm to room temperature and the solvent evaporated. The solid was slurried in dichloromethane, filtered and washed thoroughly with dichloromethane to give a filtrate that was concentrated to obtain a solid residue. The residue was purified by column chromatography to afford the reduced product **3.23** as a colourless crystalline solid (0.248g, 1.48mmol, 85% yield).

Major: **3.23**

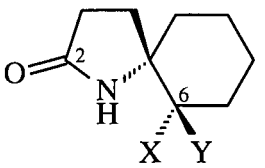
mp (methanol/ethyl acetate) = 172-174°C; δ_H (400 MHz, $CDCl_3$): 1.84 (1H, ddd, *J* 6.6, 9.5, 12.8 Hz, CH_2), 2.01-2.53 (7H, m, CH_2), 3.21 (1H, d, *J* 7.0 Hz, *OH*), 3.70 (1H, q, *J* 6.2 Hz, H-10), 5.59 (2H, m, H-7 + H-8), 6.62 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$): 30.1 (CH_2), 30.4 (CH_2), 31.9 (CH_2), 35.8 (C-3), 61.4 (C-5), 72.0 (C-10), 124.2 & 124.6 (C-7 + C-8), 178.1 (C=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3420, 3051, 1695; Found: M^+, 167.09455. $C_9H_{13}NO_2$ requires *M*, 167.09463.

The experiment was repeated with **3.22** to give the reduced product **3.24** as a colourless crystalline solid.

Minor: **3.24**

mp (ethyl acetate) = 133-139°C; δ_H (400 MHz, $CDCl_3$):1.66 (1H, ddd, *J* 7.0, 9.2, 12.8, C*H*$_2$), 2.06-2.53 (7H, m, C*H*$_2$), 3.82 (1H, m, C-10), 4.04 (1H, br s, O*H*), 5.55 (2H, m, H-7 + H-8), 7.08 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$): 25.7 (*C*H$_2$), 30.6 (*C*H$_2$), 31.7 (*C*H$_2$), 37.9 (C-3), 62.7 (C-5), 70.0 (C-10), 124.1 & 125.3 (C-7 + C-8), 179.0 (C=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3409, 3052, 2904, 1693, 1354; Found: M^+, 167.09449. $C_9H_{13}NO_2$ requires *M*, 167.09463.

6-Hydroxy-1-azaspiro[4.5]decan-2-one



3.25 X = OH, Y = H
3.26 X = H, Y = OH

The olefin **3.23** (0.187g, 1.12mmol) was dissolved in ethanol (8ml) and added to Pd/carbon (0.058g) under nitrogen at room temperature. A hydrogen atmosphere was introduced and the reaction was stirred vigorously for 60 minutes. The reaction mixture was then filtered through a plug of Celite® and the filter cake was washed with ethanol. The filtrate was concentrated to give a foamy residue. This residue was purified by column chromatography to give the hydrogenated product **3.25** as a colourless crystalline solid (0.175g, 1.03mmol, 92% yield).

Major: **3.25**

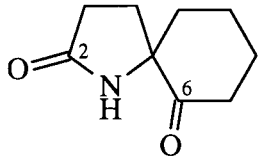
mp (ethyl acetate) = 154-155°C; δ_H (400 MHz, $CDCl_3$): 1.32 (1H, m, C*H*$_2$), 1.40-1.55 (4H, m, C*H*$_2$), 1.65-1.83 (4H, m, C*H*$_2$), 2.12 (1H, m, C*H*$_2$), 2.32 (1H, ddd, *J* 5.3, 10.3, 17.3 Hz, H-3), 2.45 (1H, ddd, *J* 7.1, 10.3, 17.3 Hz, H-3), 3.27 (1H, d, *J* 7.1 Hz, O*H*), 3.43 (1H, m, H-6), 7.37 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$): 22.2 (C*H*$_2$ x 2), 22.5 (C*H*$_2$), 30.6 (C*H*$_2$), 30.9 (C*H*$_2$), 36.3(C-3), 63.4 (C-5), 74.7 (C-6), 179.0 (C=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3426, 3053, 2938, 1688, 1401; Found: M^+, 169.11043. $C_9H_{15}NO_2$ requires *M*, 169.11028; Found: C, 64.04; H, 8.54; N, 8.20. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.93; N, 8.28%.

The experiment was repeated with **3.24** to give the hydrogenated product **3.26** as a colourless crystalline solid.

Minor: **3.26**

mp (methanol/ethyl acetate) = 172-174°C; δ_H (400 MHz, $CDCl_3$): 1.19-1.40 (3H, m, C*H*$_2$), 1.46 (1H, td, *J* 3.9, 12.6 Hz, C*H*$_2$), 1.57-1.73 (4H, m, C*H*$_2$), 1.87 (1H, m, C*H*$_2$), 2.30 (2H, m, H-3 + C*H*$_2$), 2.44 (1H, m, H-3), 3.46 (1H, m, H-6), 4.21 (1H, br s, O*H*), 7.22 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$): 22.4 (*C*H$_2$), 24.1 (*C*H$_2$), 24.9 (*C*H$_2$), 30.7 (*C*H$_2$), 31.2 (*C*H$_2$), 37.6 (C-3), 64.8 (C-5), 74.4 (C-6), 178.8 (C=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3412, 3024, 2937, 1681, 1450; Found: M^+, 169.10999. $C_9H_{15}NO_2$ requires *M*, 169.11028; Found: C, 64.11; H, 8.77; N, 8.16. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.93; N, 8.28%.

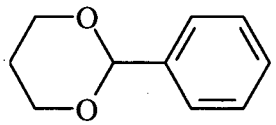
1-Azaspiro[4.5]decane-2,6-dione (3.27)



A mixture of the alcohols **3.25** and **3.26** (0.253g, 1.50mmol) was dissolved in dry acetonitrile (10ml) under nitrogen at room temperature. 4-Methylmorpholine *N*-oxide (0.90g), powdered molecular sieves(1.13g), and tetrapropylammonium perruthenate (0.026g) were added in several portions. The reaction was stirred for 18 hours at room temperature. The solvent was evaporated and the residue was filtered through a pad of silica gel, washing with dichloromethane and then 5% methanol in ethyl acetate. The filtrate was evaporated to give the ketone as a colourless crystalline solid **3.27** (0.213g, 1.27mmol, 85% yield).

mp (ethyl acetate/petroleum ether) = 123-125°C; δ_H (400 MHz, $CDCl_3$): 1.72-1.93 (4H, m, CH_2), 1.94-2.09 (3H, m, CH_2), 2.26-2.40 (3H, m, CH_2), 2.40-2.58 (2H, m, CH_2), 6.92 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$): 22.2 (*C*H$_2$), 27.0 (*C*H2), 29.5 (*C*H$_2$ x 2), 38.8 & 40.3 (C-3 + C-7), 68.1 (C-5), 177.1 (C-2), 208.8 (C-6); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3422, 3056, 2941, 1709, 1403; Found: M^+, 167.09465. $C_9H_{13}NO_2$ requires *M*, 167.09463; Found: C, 65.08; H, 7.57; N, 8.28. $C_9H_{13}NO_2$ requires C, 64.65; H, 7.84; N, 8.38%.

2-Phenyl-1,3-dioxane (3.29)

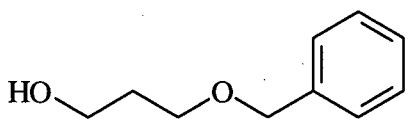


A mixture of 1,3-propanediol (7.61g, 0.10 mol), benzaldehyde (10.16ml, 0.10mol), and *p*-toluenesulfonic acid (0.95g, 5.0mmol) in benzene (100ml) was heated under reflux overnight in a flask fitted with a Dean-Stark trap. The flask was cooled to room temperature and ethyl acetate was added. The organic phase was washed with 2M sodium hydroxide, water and brine. It was then dried and concentrated to give an oil. The oil was distilled to give 2-phenyl-1,3-dioxane **3.29** (13.17g, 80.2 mmol, 80% yield) as a low-melting, colourless solid.

δ_H (200 MHz, $CDCl_3$): 1.44 (1H, m, CH_2), 2.24 (1H, m, CH_2), 4.01 (2H, m, CH_2O), 4.38 (2H, m, CH_2O), 5.52 (1H, s, OC*H*O), 7.32-7.55 (5H, m, aromatic).

This data corresponds to the published data for this compound.[124]

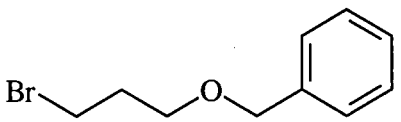
3-(Phenylmethoxy)-1-propanol (3.30)



Cold ether (500ml) was added to solid aluminium chloride (42g, 321mmol) at 0°C. After the solid had dissolved, lithium aluminium hydride (3.03g, 80.2mmol) was added in several portions. Gas evolution was observed during the initial additions. The mixture was stirred for 30 minutes at 0°C, then 2-phenyl-1,3-dioxane **3.29** (13.17g, 80.2mmol) dissolved in ether (80ml) was added dropwise. The reaction was warmed to room temperature and then stirred for 2 hours. The reaction was then cooled to 0°C and 2 N sulphuric acid (400ml) was very slowly added (*caution*). The heavy precipitate that formed needed some manual agitation. The solution was warmed to room temperature and the 2 layers were separated, and the aqueous layer was extracted with 2 further portions of ether. The organic layers were combined, dried and concentrated to give an oil. The oil was vacuum distilled to give the alcohol **3.30** (13.23g, 79.6mmol, 99%yield).

δ_H (200 MHz, $CDCl_3$): 1.87 (2H, quint, *J* 5.9 Hz, CH_2), 2.84 (1H, br s, O*H*), 3.66 (2H, t, *J* 5.9 Hz, CH_2O), 3.75 (2H, t, *J* 5.8 Hz, CH_2O), 4.52 (2H, s, $PhCH_2$), 7.34 (5H, m, aromatic).

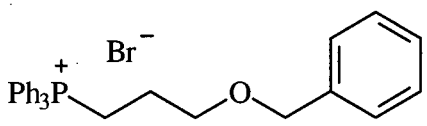
3-(Benzyloxy)propyl Bromide (3.31)



The alcohol **3.30** (12.86g, 77.4mmol) was dissolved in dichloromethane (100ml) and triethylamine (11.9ml, 85.4mmol, 1.1eq) was added. The solution was cooled to 0°C and methanesulfonyl chloride (6.3ml, 81.4mmol, 1.05eq) was added dropwise. After the addition was complete the reaction was stirred for 30 minutes at 0°C. Saturated sodium hydrogen carbonate was added and the mixture was extracted with dichloromethane (3 portions). The organic layers were combined, dried and concentrated to give an oil. The oil was dissolved in acetone (200ml) and anhydrous lithium bromide (50g, 0.58mol) was added. The reaction heated to reflux and monitored by tlc. After 3 hours the starting material had been consumed. The reaction was cooled to room temperature and water was added. The acetone was evaporated and the aqueous layer was extracted with ethyl acetate (3 portions). The combined organic layers were dried and evaporated to give an oily residue. This was distilled by vacuum distillation to give 3-(benzyloxy)propyl bromide **3.31** as a colourless oil (17.5g, 76.4mmol, 99% yield).

δ_H (200 MHz, $CDCl_3$): 2.15 (2H, m, CH_2), 3.56 (2H, t, *J* 6.5 Hz, CH_2), 3.62 (2H, t, *J* 5.7 Hz, CH_2), 4.53 (2H, s, $PhCH_2$), 7.35 (5H, m, aromatic).

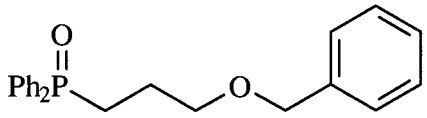
(3-(Benzyloxy)propyl)triphenylphosphonium Bromide (3.32)



The bromide **3.31** (3.0g, 13.1 mmol) was dissolved in toluene (15ml) at room temperature and triphenylphosphine (3.45g, 13.1 mmol) was added. The solution was heated at reflux for 7 hours. The solution was cooled and white precipitate formed. The supernatant was decanted and the sticky residue that remained was dried under vacuum. The residue was recrystallised from acetonitrile and ether to give the phosphonium salt **3.32** as a white solid (3.9g, 7.9mmol, 61% yield).

δ_H (200 MHz, $CDCl_3$): 1.98 (2H, m, CH_2), 3.82 (2H, t, *J* 5.0 Hz, CH_2), 3.91 (2H, m, CH_2), 4.47 (2H, s, PhCH_2), 7.29 (5H, m, aromatic), 7.60-7.93 (15H, m, aromatic).
This data corresponds to the published data for this compound.[125]

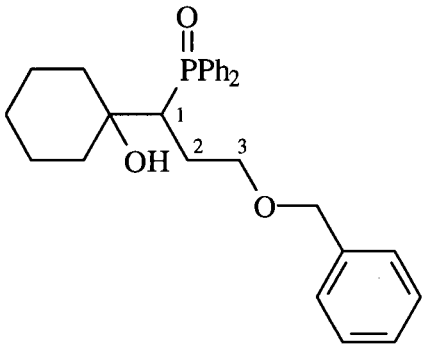
3-Diphenylphosphinoylpropyl benzyl ether (3.33)



A aqueous solution of sodium hydroxide (4.5g in 15 ml water) was added to the (3-(benzyloxy)propyl)triphenylphosphonium bromide **3.32** (1.724g, 3.51 mmol) and the solution was heated to reflux. After 3 hours the solution was cooled to room temperature, diluted with water (30ml) and extracted with ethyl acetate (3 portions). The organic layers were combined, dried and evaporated to give the phosphine oxide **3.33** as a colourless solid (1.204g, 3.44 mmol, 98% yield), pure by tlc.

δ_H (200 MHz, $CDCl_3$): 1.91 (2H, m, CH_2), 2.38 (2H, m, CH_2), 3.52 (2H, t, *J* 6.0 Hz; CH_2OBn), 4.44 (2H, s, PhCH_2), 7.20-7.83 (15H, m, aromatic).
This data corresponds to the published data for this compound.[128]

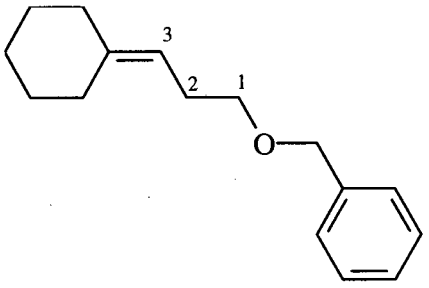
1-[3-Benzyloxy-1-(diphenyl-phosphinoyl)-propyl]-cyclohexanol (3.34)



The 3-diphenylphosphinoylpropyl benzyl ether **3.33** (0.50g, 1.43mmol) was dissolved in tetrahydrofuran (10ml) in a two-necked 25ml round-bottomed flask under nitrogen. After cooling the solution to 0°C, *n*-butyl lithium (0.83ml of a 1.6M solution in hexanes, 1.33mmol) was added dropwise. The solution turned an orange colour. The solution was stirred for 15 minutes at 0°C and then cooled to –78°C. Cyclohexanone (0.10ml, 0.97mmol) was added dropwise and the solution turned yellow. The solution was allowed to slowly warm to 0°C and the yellow colour faded. Saturated ammonium chloride solution was added and the tetrahydrofuran was removed by evaporation. The aqueous mixture was extracted with 3 portions of dichloromethane. The organic layers were combined, dried and evaporated to give a white solid. The solid was chromatographed to give the alcohol **3.34** as a white powder (0.419g, 0.934mmol, 97% yield).

mp (ethyl acetate/petroleum ether) = 153-155°C; δ_H (400 MHz, $CDCl_3$): 1.08 (1H, m, C*H*$_2$), 1.27 (3H, m, C*H*$_2$), 1.40-1.77 (5H, m, C*H*$_2$), 1.86 (2H, m, C*H*$_2$), 2.15 (1H, m, C*H*$_2$), 2.57 (1H, m, H-1), 3.19 (1H, m, H-3), 3.28 (1H, m, H-3), 4.25 (1H, d, *J* 11.9 Hz, PhC*H*$_2$), 4.35 (1H, d, *J* 11.9 Hz, PhC*H*$_2$), 4.60 (1H, br s, O*H*), 7.23-7.84 (15H, m, aromatic); δ_C (100 MHz, $CDCl_3$): 21.8, 22.0, 25.2, 25.6, 36.2, 36.3, 39.2, 39.3, 42.8 (d, *J* 67.1, C-1), 69.4 (d, *J* 6.2, C-3), 72.7 (Ph*C*H$_2$), 75.1 (d, *J* 4.0, *C*OH), 127-138 (aromatic); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3383, 2936, 2860, 1168, 1113; Found: M^+, 448.21716. $C_{28}H_{33}O_3P$ requires *M*, 448.21673.

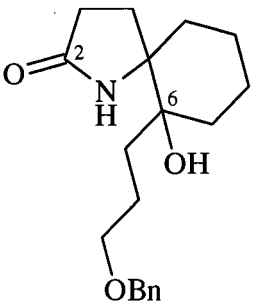
Benzyl 3-cyclohexylidenepropyl ether (3.35)



The alcohol **3.34** (0.30g, 0.67mmol) was dissolved in dry *N*,*N*-dimethylformamide (7ml) and stirred at room temperature under nitrogen. Sodium hydride (0.040g of a 60% dispersion in mineral oil, 1.0mmol) was added in one portion and the reaction was stirred for 2 hours. A white precipitate formed. Water was then added and the precipitate dissolved. The mixture was extracted with 3 portions of dichloromethane. The combined organic layers were dried and evaporated to give an oily residue. The residue was chromatographed (5% ethyl acetate/petroleum ether) to give the alkene **3.35** as a colourless oil (0.154g, 0.67mmol, 100%).

δ_H (300 MHz, $CDCl_3$): 1.52 (6H, m, CH_2), 2.12 (4H, m, CH_2), 2.33 (2H, quart, *J* 7.2 Hz, H-2), 3.45 (2H, t, *J* 7.2 Hz, H-1), 4.52 (2H, s, $PhCH_2$), 5.10 (1H, tt, *J* 1.1, 7.2 Hz, H-3), 7.25-7.35 (5H, m, aromatic); δ_C (75 MHz, $CDCl_3$): 26.9, 27.8, 27.8, 28.6, 28.8, 37.1, 70.5 (C-1), 72.8 ($PhCH_2$), 116.9, 127.4, 127.6, 128.3, 138.7, 141.8; IR ν_{max} (CH_2Cl_2) / cm^{-1} 2931, 2854, 1447, 1100; Found: M^+, 230.16737. $C_{16}H_{22}O$ requires *M*, 230.16707.

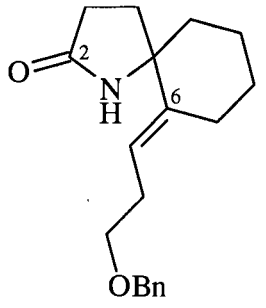
6-(3-Benzyloxypropyl)-6-hydroxy-1-azaspiro[4.5]decan-2-one (3.36)



Magnesium (0.25g, 10mmol, 6eq) was added to a two-necked round-bottomed flask under nitrogen. The bromide **3.31** (1.17g, 5.1mmol, 3eq) was then added slowly as a solution in tetrahydrofuran (3ml). The flask was cooled in ice-water as soon as an increase in the temperature of the solution was detected. The ice-water was removed 5 minutes after the addition was complete and the reaction was stirred for 60 minutes at room temperature. A further portion of tetrahydrofuran (2ml) was added to the flask and the mixture was cooled to 0°C. A solution of the ketone **3.27** (0.284g, 1.70mmol, 1eq) in tetrahydrofuran (5ml) was added dropwise. The reaction was stirred for 40 minutes, then quenched with saturated ammonium chloride solution. The tetrahydrofuran was removed by evaporation and the aqueous layer was extracted with 3 portions of ethyl acetate. The combined organic layers were dried and evaporated to give an oily residue. The residue was purified by column chromatography (5% methanol/ethyl acetate) to give the alcohol **3.36** as an inseparable mixture (4:3 from ^{1}H NMR) of diastereomers (0.479g, 1.51mmol, 89% yield).

δ_H (300 MHz, $CDCl_3$): 1.25-2.13 (13H, m, C*H*$_2$), 2.24-2.54 (3H, m, C*H*$_2$), 2.78 (1H, br s, major O*H*), 2.96 (1H, br s, minor O*H*), 3.48 (2H, m, C*H*$_2$OBn), 4.50 (2H, s, PhC*H*$_2$), 6.61 (1H, br s, N*H*), 7.26-7.37 (5H, m, aromatic); Major: δ_C (75 MHz, $CDCl_3$): 21.7 (*C*H$_2$), 22.1 (*C*H$_2$), 23.0 (*C*H$_2$), 28.3 (*C*H$_2$), 30.5 (*C*H$_2$), 30.7 (*C*H$_2$), 32.0 (*C*H$_2$), 36.6 (C-3), 66.1 (C-5), 70.7 (*C*H$_2$OBn), 73.1 (Ph*C*H$_2$), 74.8 (C-6), 127.6 & 127.7 & 128.4 & 138.0 (aromatic), 178.4 (C=O); Minor: δ_C (75 MHz, $CDCl_3$): 21.1 (*C*H$_2$), 22.0 (*C*H$_2$), 23.0 (*C*H$_2$), 27.6 (*C*H$_2$), 30.7 (*C*H$_2$), 31.2 (*C*H$_2$), 32.6 (*C*H$_2$), 35.7 (C-3), 65.9 (C-5), 70.8 (*C*H$_2$OBn), 73.0 (Ph*C*H$_2$), 74.3 (C-6), 127.6 & 127.7 & 128.4 & 138.1 (aromatic), 177.6 (C=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3422, 3054, 2940, 1690, 1402; Found: M$^+$, 317.19996. $C_{19}H_{27}NO_3$ requires *M*, 317.19909.

6-(3-Benzyloxy-1-propenyl)-1-azaspiro[4.5]decan -2-one (3.37)

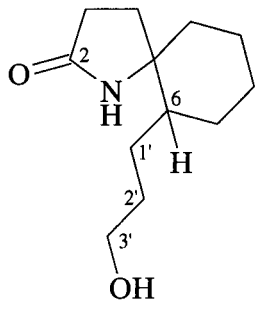


To a flask containing the tertiary alcohol **3.36** (0.256g, 0.807mmol) under nitrogen was added anhydrous copper sulphate (0.50g) and dry *p*-xylene (15ml). The mixture was heated to reflux for 24 hours and turned an orange colour. The flask was cooled to room temperature and the mixture was filtered, washing the collected solid with ethyl acetate. The filtrate was concentrated and the residue was chromatographed to give the colourless, oily alkenes **3.37:3.38** as an inseparable mixture (4:1 by ^{1}H NMR) of isomers (0.218g, 0.728mmol, 90% yield).

Major isomer (**3.37**)

δ_H (400 MHz, $CDCl_3$): 1.20 (1H, m, C*H*$_2$), 1.51 (1H, m, C*H*$_2$), 1.60-1.95 (4H, m, C*H*$_2$), 2.01 (3H, m, C*H*$_2$), 2.31 (4H, m, C*H*$_2$), 2.63 (1H, m, C*H*$_2$), 3.44 (2H, t, *J* 7.0 Hz, C*H*$_2$OBn), 4.49 (2H, s, PhC*H*$_2$), 5.33 (1H, td, *J* 1.3, 7.0 Hz, vinyl), 7.25-7.35 (5H, m, aromatic); δ_C ($CDCl_3$): 23.1 (CH_2), 26.2 (CH_2), 26.6 (CH_2), 27.8 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 40.8 (CH_2), 63.5 (C-5), 69.9 (*C*H$_2$OBn), 72.9 (PhC*H*$_2$), 116.1 (C=*C*H), 127.5 & 127.6 & 128.3 & 138.5 (aromatic), 142.7 (*C*=CH), 177.1 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3420, 2933, 1695, 1401; Found: M$^+$, 299.18771. $C_{19}H_{25}NO_2$ requires *M*, 229.18853.

6-(3-Hydroxypropyl)-1-azaspiro[4.5]decan-2-one (3.39)



The alkene **3.37/3.38** (0.174g, 0.58mmol) was dissolved in ethanol (10ml) under a nitrogen atmosphere. Palladium on carbon (10%, 0.062g) was added in one portion. A hydrogen atmosphere was introduced and the reaction was stirred at room temperature until no more starting material remained by tlc. The mixture was filtered through Celite® and the filter cake was thoroughly rinsed with ethanol. The filtrate was concentrated to give an oily residue, which was chromatographed to give the colourless, oily alcohol as an inseparable (2:1 from ^{1}H NMR) mixture of diastereomers **3.39** (0.104g, 0.49mmol, 85% yield).

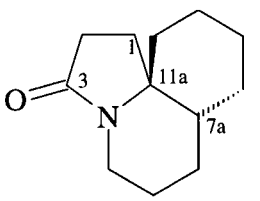
δ_H (300 MHz, $CDCl_3$): 0.97-1.48 (8H, m, C*H*$_2$), 1.54-2.16 (8H, m, C*H*$_2$ x 3, H-3, O*H*), 2.24-2.45 (2H, m, C*H*$_2$), 3.61 (2H, t, *J* 5.3 Hz, H-3), 6.54 (1H, br s, N*H* major), 6.87 (1H, br s, N*H* minor)
Major: δ_C (75 MHz, $CDCl_3$): 22.9 (*C*H$_2$), 23.1 (*C*H$_2$), 25.1 (*C*H$_2$), 25.2 (*C*H$_2$), 28.1 (*C*H$_2$), 30.5 (*C*H$_2$), 30.6 (*C*H$_2$), 39.9 (C-3), 45.5 (C-6), 62.2 (C-5), 62.8 (C-3'), 177.5 (*C*=O); Minor: δ_C (75 MHz, $CDCl_3$): 22.9 (*C*H$_2$), 24.1 (*C*H$_2$), 25.4 (*C*H$_2$), 25.5 (*C*H$_2$), 27.8 (*C*H$_2$), 30.3 (*C*H$_2$), 30.7 (*C*H$_2$), 39.3 (C-3), 45.2 (C-6), 62.2 (C-5), 62.4 (C-3'), 178.0 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 3417, 3055, 2931, 2860, 1683, 1449; Found: M$^+$, 211.15748. $C_{12}H_{21}NO_2$ requires *M*, 211.15723.

Formation of tricyclic lactam

The substrate **3.39** (0.101g, 0.478mmol) was dissolved in dry dichloromethane (10ml) under nitrogen. Triethylamine (0.20ml, 1.4mmol) was added and the solution was cooled to 0°C. Methanesulfonyl chloride (0.07ml, 0.9mmol) was added dropwise. The solution was stirred at 0°C for 30 minutes. Saturated sodium hydrogen carbonate solution was added and the mixture was extracted with 3 portions of dichloromethane. The organic layers were combined, dried, and evaporated to give an oily residue. The unpurified residue was used for the next reaction. The residue

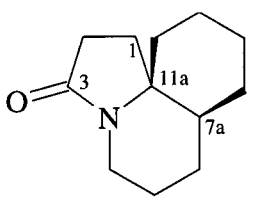
was dissolved in *N*,*N*-dimethylformamide under nitrogen at room temperature. Sodium hydride (0.055g of 60% dispersion in mineral oil, 1.4mmol) was added and the mixture was stirred at 30°C for 14 hours. Water was added and the mixture was extracted with 3 portions of dichloromethane. The combined organic layers were dried and evaporated to give an oily residue as a mixture of diastereomers. The residue was chromatographed (60% ethyl acetate/hexane) to give major diasteromer **3.40** (0.050g, 0.259mmol, 54% yield), minor diastereomer **3.41** (0.024g, 0.124mmol, 26%yield) and a mixed fraction (0.007g, 0.036mmol, 8% yield).

Major: **(7a*S***, 11a**S***)-Decahydro-3*H*-pyrrolo[2,1-*j*]quinolin-3-one (3.40)**



δ_H (400 MHz, $CDCl_3$): 1.11-1.39 (4H, m, C*H*$_2$), 1.41-1.87 (10H, m, C*H*$_2$), 1.93 (1H, dd, *J* 7.7, 12.3 Hz, CH_2), 2.20 (1H, dd, *J* 8.8, 16.5 Hz, H-2), 2.49 (1H, dddd, *J* 0.9, 7.9, 12.6, 16.5 Hz, H-2), 2.77 (1H, dddd, *J* 1.1, 7.0, 11.2, 13.7 Hz, H-5), 3.88 (1H, dd, *J* 8.4, 13.7 Hz, H-5); δ_C (75 MHz, $CDCl_3$): 21.4 (*C*H_2), 22.5 (*C*H_2), 23.5 (*C*H_2), 24.9 (*C*H_2), 26.0 (*C*H_2), 27.4 (*C*H_2), 30.6 (*C*H_2), 33.3 (C-5), 33.8 (C-2), 42.1 (C-7a), 64.1 (C-11a), 175.9 (*C*=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 2935, 2864, 1674, 1418; Found: M^+, 193.14725. $C_{12}H_{19}NO$ requires *M*, 193.14666.

Minor: **(7a*S***, 11a**R***)-decahydro-3*H*-pyrrolo[2,1-*j*]quinolin-3-one (3.41)**



δ_H (400 MHz, $CDCl_3$): 1.20-1.55 (7H, m, CH_2), 1.61-1.93 (7H, m, CH_2), 2.17 (1H, ddd, *J* 3.2, 9.5, 12.8 Hz, CH_2), 2.27-2.44 (2H, m, CH_2), 2.66 (1H, t, *J* 13.4 Hz, CH_2, H-5), 4.02 (1H, ddt, *J* 1.6, 4.8, 13.4 Hz, CH_2, H-5); δ_C (100 MHz, $CDCl_3$): 19.6 (*C*H_2), 23.2 (*C*H_2), 25.1 (*C*H_2), 25.5 (*C*H_2), 27.4

(CH_2), 28.3 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 36.4 (CH_2), 42.8 (C-7a), 62.2 (C-11a), 172.6 (C=O); IR ν_{max} (CH_2Cl_2) / cm^{-1} 2932, 2865, 1670, 1420.

This data corresponds to the published data for this compound.[131]

4.4 Crystal structure determination of 2.19

A single crystal of **2.19** was covered in a small amount of paratone oil and mounted on a glass fibre. X-ray intensity data were collected at 173 K on a Nonius Kappa CCD with 1.5 kW graphite monochromated Mo radiation. The diffraction patterns were indexed with a primitive monoclinic cell. The strategy for the data collection was evaluated using the *Collect* Software.[133] The detector to crystal distance was 40 mm. Data were collected by a phi scan and several omega scans. The data were scaled and reduced using *Denzo-SMN.*[134] Unit cell dimensions were refined on all data.

The space group P 2_1 was chosen on the basis of systematic absences and intensity statistics. The structure was solved and refined using *SHELX97.*[135] The molecular structure is chiral and the correct enantiomer was chosen by comparing Flack parameters for both enantiomers.

Hydrogen atoms were placed in calculated positions and included in the model during later stages of the refinement. Plots of the molecular structure were obtained with *ORTEP*[136] and *PLATON.*[137] The program *X-SEED*[138], an interface to shelx was used during the structure solution and refinements.

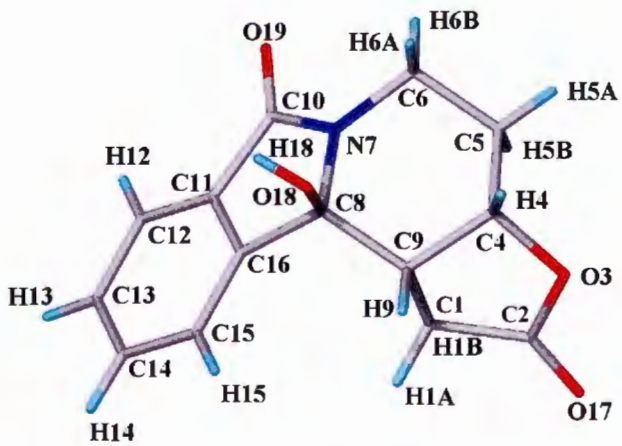


Figure 4.1 X-ray structure of **2.19**

Table 4.1 Crystal data and structure refinement for **2.19**.

Empirical formula	C14 H12 N1 O4	
Formula weight	259.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.375(1) Å	α= 90°.
	b = 7.653(1) Å	β= 100.634(1)°.
	c = 9.691(1) Å	δ = 90°.
Volume	610.47(13) $Å^3$	
Z	2	
Density (calculated)	1.410 Mg/m^3	
Absorption coefficient	0.104 mm^{-1}	
F(000)	272	
Crystal size	0.37 x 0.31 x 0.22 mm^3	
Theta range for data collection	2.14 to 27.39°.	
Index ranges	-10<=h<=10, -9<=k<=9, -12<=l<=10	
Reflections collected	5227	
Independent reflections	2511 [R(int) = 0.0144]	
Completeness to theta = 27.39°	99.7 %	
Max. and min. transmission	0.9774 and 0.9624	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2511 / 1 / 174	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0291, wR2 = 0.0675	
R indices (all data)	R1 = 0.0338, wR2 = 0.0701	
Absolute structure parameter	-0.5(8)	
Extinction coefficient	0.033(4)	
Largest diff. peak and hole	0.188 and -0.151 $e.Å^{-3}$	

Table 4.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.19**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(19)	3840(1)	7132(2)	9383(1)	34(1)
N(7)	5268(1)	6522(2)	11583(1)	24(1)
O(18)	6817(1)	4251(1)	12845(1)	31(1)
O(3)	6955(1)	8960(2)	15302(1)	36(1)
O(17)	8680(1)	11133(2)	15151(1)	45(1)
C(10)	5118(2)	6788(2)	10193(1)	24(1)
C(9)	7537(2)	7093(2)	13545(1)	25(1)
C(12)	7281(2)	6792(2)	8597(2)	31(1)
C(11)	6762(2)	6558(2)	9860(1)	24(1)
C(6)	3995(2)	6777(2)	12407(1)	29(1)
C(16)	7812(2)	6052(2)	11071(1)	25(1)
C(4)	6245(2)	7495(2)	14433(1)	29(1)
C(13)	8912(2)	6467(2)	8580(2)	38(1)
C(15)	9427(2)	5718(2)	11054(2)	34(1)
C(2)	8018(2)	9833(2)	14642(2)	33(1)
C(5)	4611(2)	8059(2)	13584(2)	31(1)
C(1)	8170(2)	8905(2)	13298(2)	30(1)
C(8)	6889(2)	5937(2)	12281(1)	23(1)
C(14)	9957(2)	5929(3)	9780(2)	41(1)

Table 4.3 Bond lengths (Å) for **2.19**

Bond	Length (Å)	Bond	Length (Å)
O(19)-C(10)	1.2336(17)	C(16)-C(8)	1.5214(19)
N(7)-C(10)	1.3455(16)	C(4)-C(5)	1.523(2)
N(7)-C(6)	1.4584(17)	C(13)-C(14)	1.383(3)
N(7)-C(8)	1.4702(17)	C(15)-C(14)	1.397(2)
O(18)-C(8)	1.4073(19)	C(2)-C(1)	1.509(2)
O(3)-C(2)	1.363(2)	C(9)-C(4)	1.533(2)
O(3)-C(4)	1.4611(18)	C(12)-C(11)	1.3842(19)
O(17)-C(2)	1.200(2)	C(12)-C(13)	1.391(2)
C(10)-C(11)	1.482(2)	C(11)-C(16)	1.3856(19)
C(9)-C(1)	1.519(2)	C(6)-C(5)	1.521(2)
C(9)-C(8)	1.5268(18)	C(16)-C(15)	1.379(2)

Table 4.4 Selected torsion angles for **2.19**

Bonds	Angle (°)	Bonds	Angle (°)
C(6)-N(7)-C(10)-O(19)	-7.1(3)	C(10)-C(11)-C(16)-C(8)	-0.38(17)
C(8)-N(7)-C(10)-O(19)	173.41(16)	C(2)-O(3)-C(4)-C(5)	-96.32(14)
C(6)-N(7)-C(10)-C(11)	173.72(14)	C(2)-O(3)-C(4)-C(9)	25.24(15)
C(8)-N(7)-C(10)-C(11)	-5.80(17)	C(1)-C(9)-C(4)-O(3)	-35.85(13)
C(13)-C(12)-C(11)-C(16)	1.2(2)	C(8)-C(9)-C(4)-O(3)	-164.56(11)
C(13)-C(12)-C(11)-C(10)	-179.50(16)	C(1)-C(9)-C(4)-C(5)	81.98(15)
N(7)-C(10)-C(11)-C(12)	175.70(15)	C(8)-C(9)-C(4)-C(5)	-46.73(18)
O(19)-C(10)-C(11)-C(16)	-175.50(16)	C(11)-C(12)-C(13)-C(14)	0.1(3)
N(7)-C(10)-C(11)-C(16)	3.68(17)	C(11)-C(16)-C(15)-C(14)	0.7(2)
C(10)-N(7)-C(6)-C(5)	-123.50(15)	C(8)-C(16)-C(15)-C(14)	179.88(15)
C(8)-N(7)-C(6)-C(5)	56.00(18)	C(4)-O(3)-C(2)-O(17)	176.53(15)
C(12)-C(11)-C(16)-C(15)	-1.6(2)	C(4)-O(3)-C(2)-C(1)	-3.87(17)
C(10)-C(11)-C(16)-C(15)	178.93(14)	N(7)-C(6)-C(5)-C(4)	-52.83(17)
C(12)-C(11)-C(16)-C(8)	179.05(13)	O(3)-C(4)-C(5)-C(6)	166.11(11)
O(19)-C(10)-C(11)-C(12)	-5.1(3)	C(9)-C(4)-C(5)-C(6)	51.75(18)

CHAPTER 5
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