Routes to chiral N-acyliminium ion precursors for the synthesis of optically active pure ring-fused pyrroloisoquinoline alkaloids.

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CONTENTS

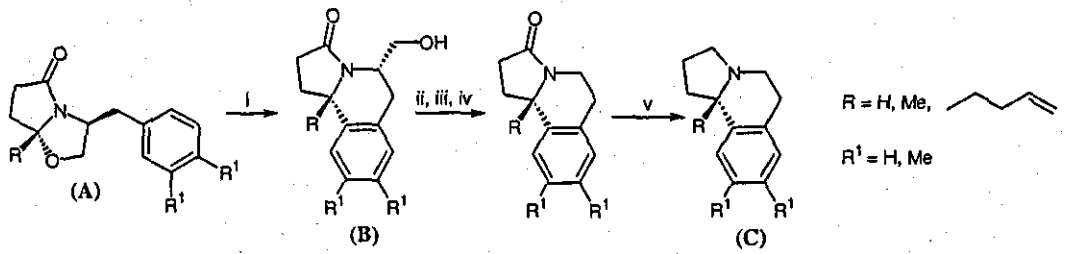
ABBREVIATIONS

AIBN	=	*Azo-bis-iso-butyronitrile*
Bn	=	Benzyl
Bt	=	Benzotriazole
CNS	=	Central nervous system
DBU	=	1,8-Diazabicyclo[5,4.0]undec-7-ene
DCM	=	Dichloromethane
DEAD	=	Diethyl azodicarboxylate
DMAP	=	*N,N*-dimethylaminopyridine
DMPU	=	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMS	=	Dimethyl sulfide
DMSO	=	Dimethyl sulfoxide
dppp	=	1,3-Bis(diphenylphosphino)propane
Et	=	Ethyl
g	=	Grams
h	=	Hours
HMPA	=	Hexamethylphosphoramide
KHMDS	=	Potassium bis(trimethylsilyl)amide
LA	=	Lewis acid
LDA	=	Lithium diisopropylamide
LHMDS	=	Lithium bis(trimethylsilyl)amide
*m*CPBA	=	*meta*-Chloroperbenzoic acid
Me	=	Methyl
mg	=	Milligrams
MHz	=	MegaHertz
ml	=	Millilitres
MP	=	Melting point
MS	=	Mass spectra
NOE	=	Nuclear Overhauser Effect
Nuc	=	Nucleophile
PDC	=	Pyridinium dichromate

PG	=	Protecting group
Ph	=	Phenyl
*i*Pr	=	*iso*-propyl
rt	=	Room temperature
SM	=	Starting material
TBDPS	=	*tert*-Butyl diphenylsilane
TBSCl	=	*tert*-Butyl dimethylsilyl chloride
TFA	=	Trifluoroacetic acid
TFAA	=	Trifluoroacetic anhydride
THF	=	Tetrahydrofuran
TIPS	=	Triisopropylsilane
TMEDA	=	*N,N,N',N'*-Tetramethylethylenediamine
TMS	=	Trimethylsilyl
TMSCN	=	Trimethylsilyl cyanide
TMSOTf	=	Trimethylsilyltriflate
*p*TSOH	=	*para*-toluenesulphonic acid
UV	=	Ultraviolet
wt	=	Weight

ABSTRACT

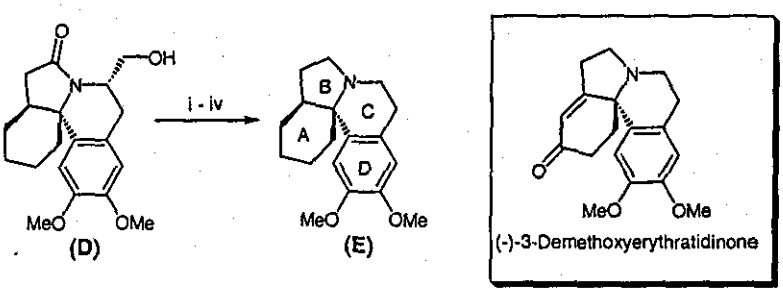
Pyrrolisoquinoline (**B**) is found as a major structural motif of the *erythrina* alkaloid group of natural products. We recognised that a suitably substituted bicyclic lactam (**A**) could act as a precursor in an intramolecular *N*-acyliminium mediated cyclisation reaction in a stereoselective approach to the core of the erythrinane target ring system.



i) $TiCl_4$, DCM, -78 °C, ii) Dess-Martin Periodinane, iii) $Rh(PPh_3)_2(CO)Cl$, dppp, Δ xylene, iv) Pd-C, EtOH, v) Red-Al, Toluene

In order to demonstrate the synthetic potential of this methodology we have established conditions for removal of the pendant hydroxymethyl substituent from a product of cyclisation. Further elaboration of the product structure by reduction of the lactam carbonyl group gives amine derivatives such as (**C**).

A cyclisation reaction has been utilised to furnish the indoloisoquinoline product (**D**) which has been manipulated further to yield the erythrinane skeleton (**E**) with a high degree of stereocontrol.



i) Dess-Martin Periodinane, ii) $Rh(PPh_3)_2(CO)Cl$, dppp, Δ xylene, iii) Pd-C, EtOH, iv) Red-Al, Toluene

We have utilised this methodology and herein describe the total formal asymmetric synthesis of the *erythrina* alkaloid, (-)-3-demethoxyerythratidinone.

S. M. Allin, S. L. James, M. R. J. Elsegood and W. P. Martin, *J. Org. Chem.*, 2002, **67**, 9464.

S. M. Allin, S. L. James, W. P. Martin, T. A. D. Smith and M. R. J. Elsegood, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3029

S. M. Allin, S. L. James, W.P. Martin and T. A. D. Smith, *Tetrahedron Lett.*, 2001, **42**, 3943

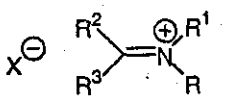
Chapter One

Introduction

1.1. *N*-acyliminium ions in synthesis

1.1.1. Introduction

The synthetic potential of *N*-acyliminium species (**1**) is well documented.[1] The reaction of such nitrogen-stabilised cations with various nucleophiles – also named amidoalkylation or Mannich-type condensations – has been used as the key carbon-carbon bond forming step in the synthesis of a variety of nitrogen heterocycles.



(1a) R = H, alkyl
(1b) R = acyl
(1c) R = COOR
(1d) R = $CONR_2$
(1e) R = Tos

Figure 1

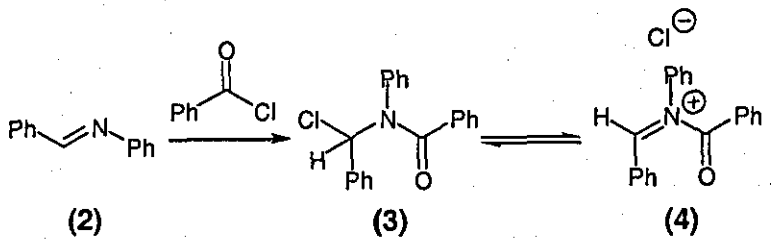
Substitution with electron-withdrawing groups (**1b – e**) at the nitrogen renders the Mannich-intermediate (**1a**) considerably more reactive by enhancing its cationic character and causing the imino carbon present in the molecule to be more electron deficient. Of the modified cations shown in Figure 1, *N*-acyl derivative (**1b**) has found an impressive number of synthetic applications.[1]

1.2. Formation of *N*-acyliminium ions

N-acyliminium ions are generated *in situ* as intermediates in irreversible processes to yield desired products. Numerous examples of acyliminium ion synthesis have been reported in the literature,[1] this section outlines the principle methods.

1.2.1. Acylation of imines

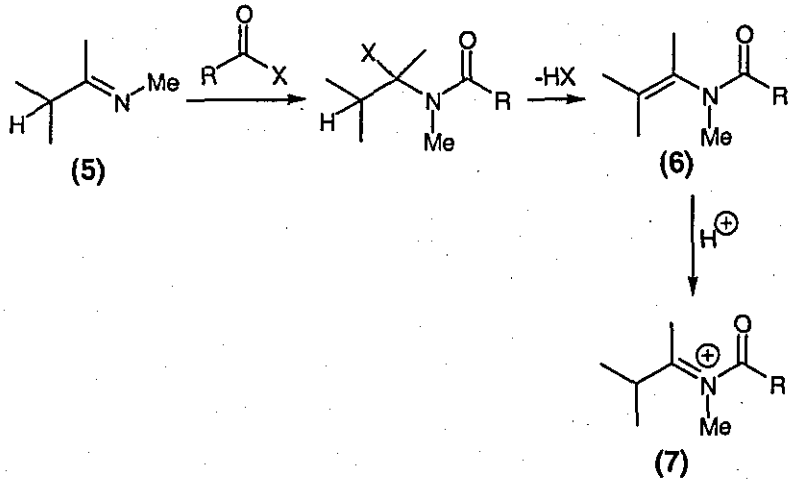
The acylation of imines with reactive carboxylic acid derivatives is an early example of a preparative route to *N*-acyliminium ion precursors. This was first reported by James and Judd,[2] with the reaction of (**2**) and benzoyl chloride (Scheme 1). The crystalline product (**3**) can then be activated to generate the *N*-acyliminium ion (**4**).



(2) (3) (4)

Scheme 1

The synthesis of *N*-acyliminium ions is possible *via* protonation of enamides.[3] Scheme 2 illustrates the formation of *N*-acyliminium (**7**) from enamide (**6**), which has in turn been synthesised by acylation of an imine (**5**) followed by elimination.



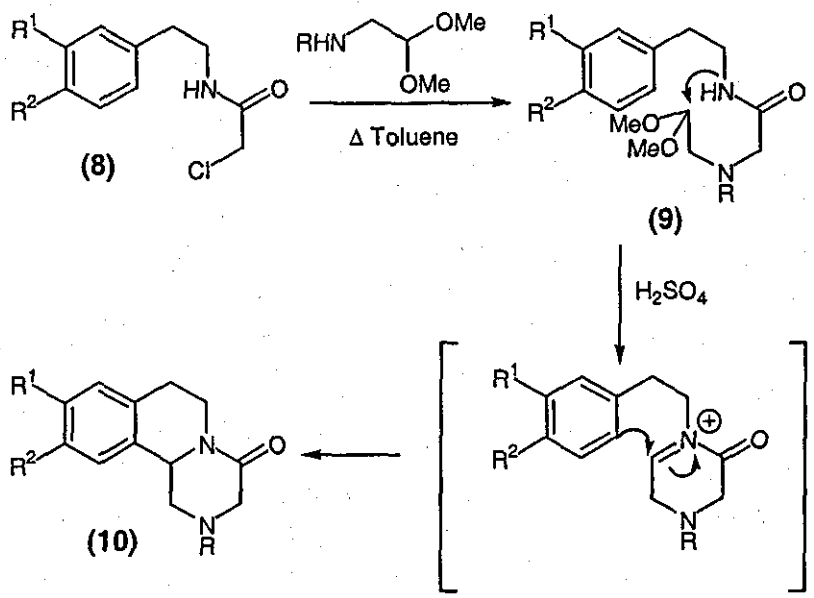
(5) (6) (7)

Scheme 2

1.2.2. Heterolysis of amides

N-acyliminium ions are generally formed by way of heterolysis of α-substituted amides. α-Substituted amides are mostly prepared by the intramolecular reaction of amides with aldehydes (or ketones),[4] or partial reduction of cyclic imides.[5]

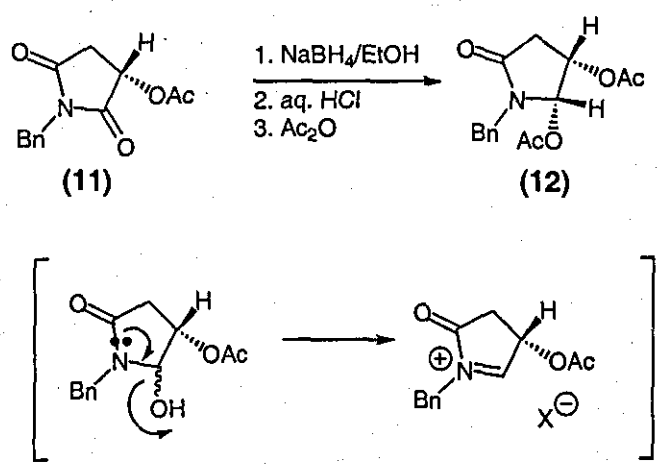
They can also be prepared by the intramolecular reaction of amides with acetals, for example Kim[6] *et al* synthesised the *N*-acyliminium ion precursor (**9**) by amidoalkylation reactions of (**8**). The group's interests were in the synthesis of isoquinoline targets (**10**) as shown in Scheme 3.



Scheme 3

1.2.3. Hydride addition to C=O of imides and lactams

The selective hydride reduction of one of the carbonyl groups in a cyclic imide or lactam species is another important route for the formation of *N*-acyliminium ion precursors.

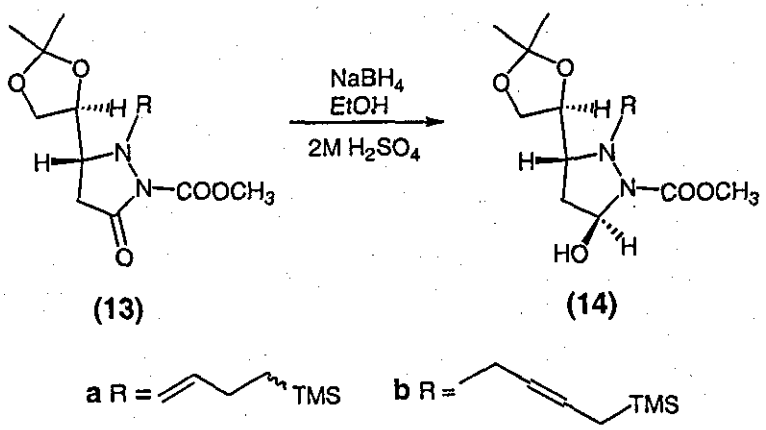


Scheme 4

Depending on the substrate, in some cases high stereoselectivity is observed. The almost exclusive formation of the *cis*-isomer **(12)** (Scheme 4) from sodium borohydride reduction of **(11)** depends strongly on the work-up. Neutralisation at

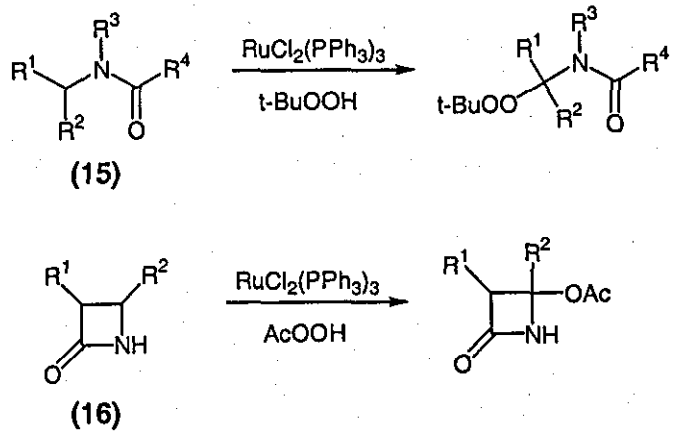
–23 °C with methanol-hydrochloric acid and acetylation affords the almost pure isomer (*cis/trans* 19:1).[7]

In another example, the pyrazolones **(13a)** and **(13b)** afforded the reduced oxylactam precursors **(14a)** and **(14b)** as single stereoisomers (Scheme 5).[8]



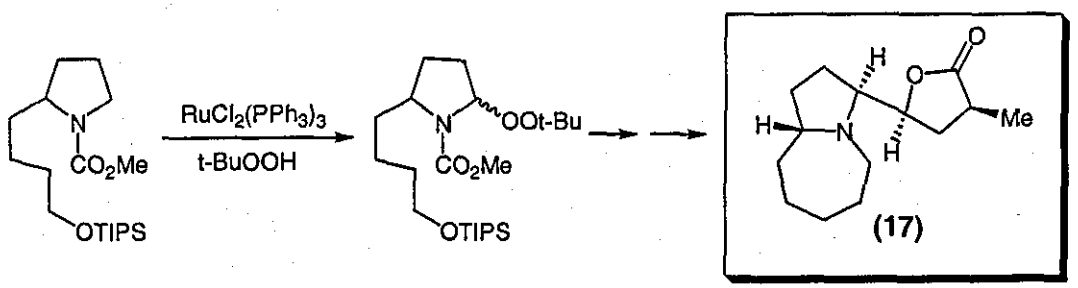
Scheme 5

1.2.4. Oxidation of amides and lactams



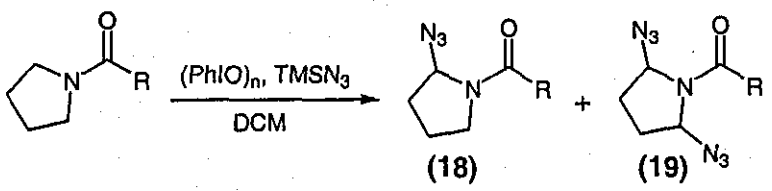
Scheme 6

Murahashi[9] has developed ruthenium catalysed selective oxidation of amides **(15)** and lactams **(16)** to generate precursors for the *N*-acyliminium species, shown in Scheme 6, and Morimoto[10] and co-workers have utilised this method towards the synthesis of the tricyclic ring system **(17)**, a common central structure present in most *stemona* alkaloids (Scheme 7).

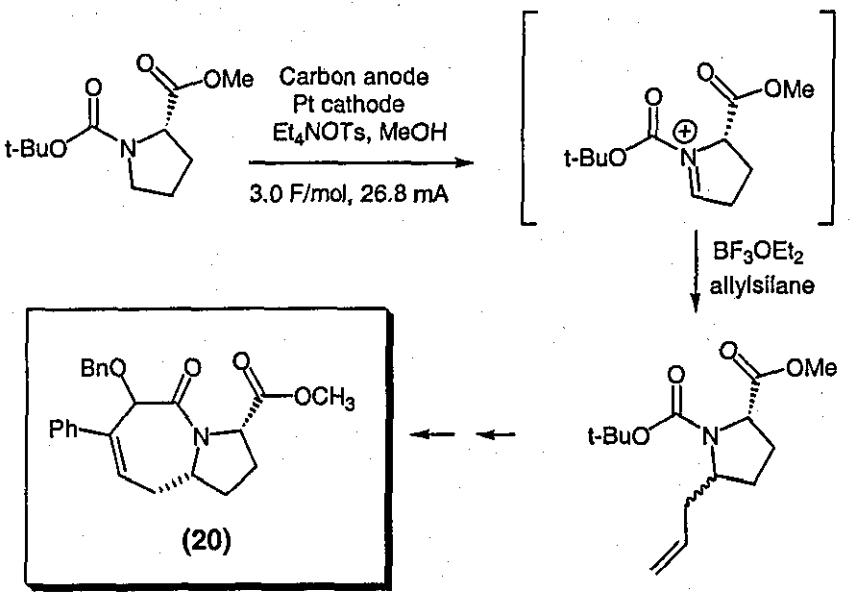


Scheme 7

Hypervalent iodine oxidations of amides, carbamates and ureas to give α-azidoamides such as **(18)** and **(19)**, shown in Scheme 8, have been studied by Magnus and Hulme,[11] These azidoamides are shown to act as *N*-acyliminium ion precursors.



Scheme 8



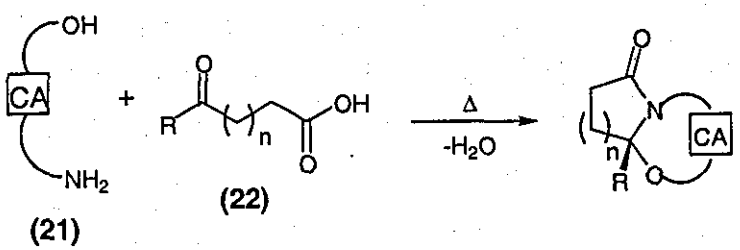
Scheme 9

The removal of a hydride from the α-carbon of an amide by an electrochemical method has been reported by a number of research groups. Since the pioneering

work of Shono,[12] who investigated the anodic oxidation of a variety of carbamates, this method has been applied frequently.

Beal and Moeller,[13] for example, have utilised electrochemical amide oxidation in a reaction sequence towards the synthesis of seven-membered ring lactams containing bicyclic peptidomimetics (**20**), (Scheme 9).

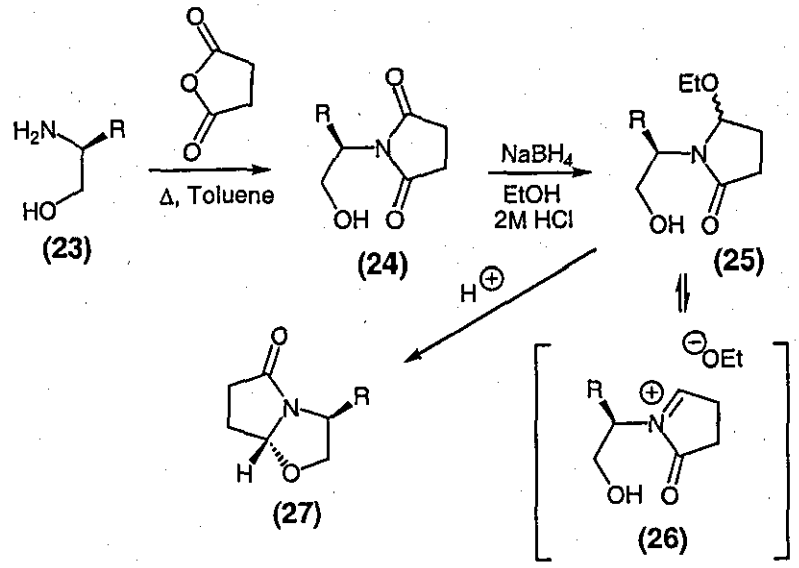
1.2.5. Synthesis of bicyclic and tricyclic lactams



CA = Chiral auxiliary

Scheme 10

Bicyclic lactams have been employed in various ways in asymmetric synthesis of tertiary and quaternary carbon centres. Two general methods have been developed for the construction of the bicyclic lactam system and involve condensation of an optically pure amino alcohol and a dicarbonyl compound.

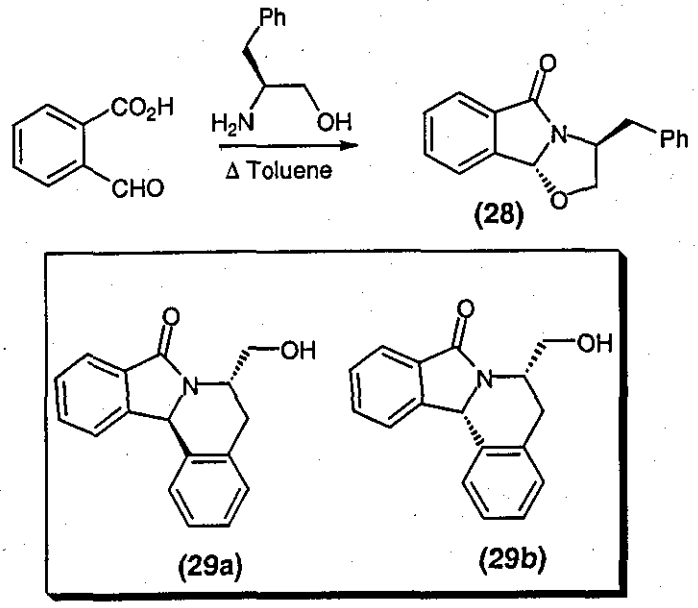


Scheme 11

In the first route a cyclodehydration process was utilised between an optically pure amino alcohol **(21)** and a γ-ketoacid **(22)**, (Scheme 10).[14] The second route developed to secure these bicyclic lactams is related to the extensive work of Speckamp[1, 15] involving *N*-acyliminium species, (Scheme 11).

Condensation of an optically pure amino alcohol **(23)** with a cyclic anhydride afforded the imide **(24)**, which, on addition of hydride, afforded the ethoxy lactam **(25)**. This intermediate was subjected to acidic conditions resulting in ring closure *via* the *N*-acyliminium ion species **(26)**, furnishing the lactam **(27)**.

Meyers has extensively studied the chemistry of such chiral lactams utilising and extending the scope of this methodology.[16-17] This group have also accessed these templates by condensation of β-amino alcohol derivatives with γ-carboxylic acids.[18] Applications of the Meyers bicyclic lactam substrates in synthesis are discussed in Section 1.4.



Scheme 12

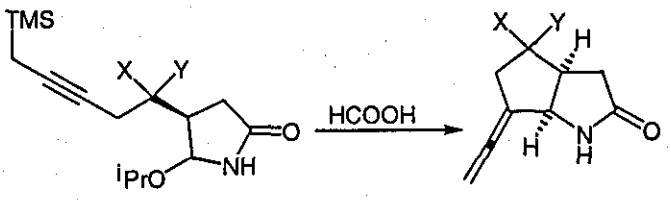
Tricyclic lactams as *N*-acyliminium ion precursors have been reported by Allin[19-22] *et al* for the synthesis of substituted isoindolinone derivatives. Diastereoisomerically pure *N*-acyliminium ion precursor **(28)** required for initial studies on isoindolinone

targets (**29**) was prepared directly from the corresponding enantiomerically pure amino alcohol substrate, (*S*)-phenylalaninol as outlined in Scheme 12.

1.3. Carbon-carbon bond formation using *N*-acyliminium intermediates

1.3.1. Intramolecular carbon-carbon bond formation

The reactions of *N*-acyliminium ions with tethered π-bonds are among the most important methods for preparing complex nitrogen containing heterocycles. Since the introduction of the *N*-acyliminium method as a versatile tool the γ-lactam derivatives have prominently figured in the field of intramolecular applications.



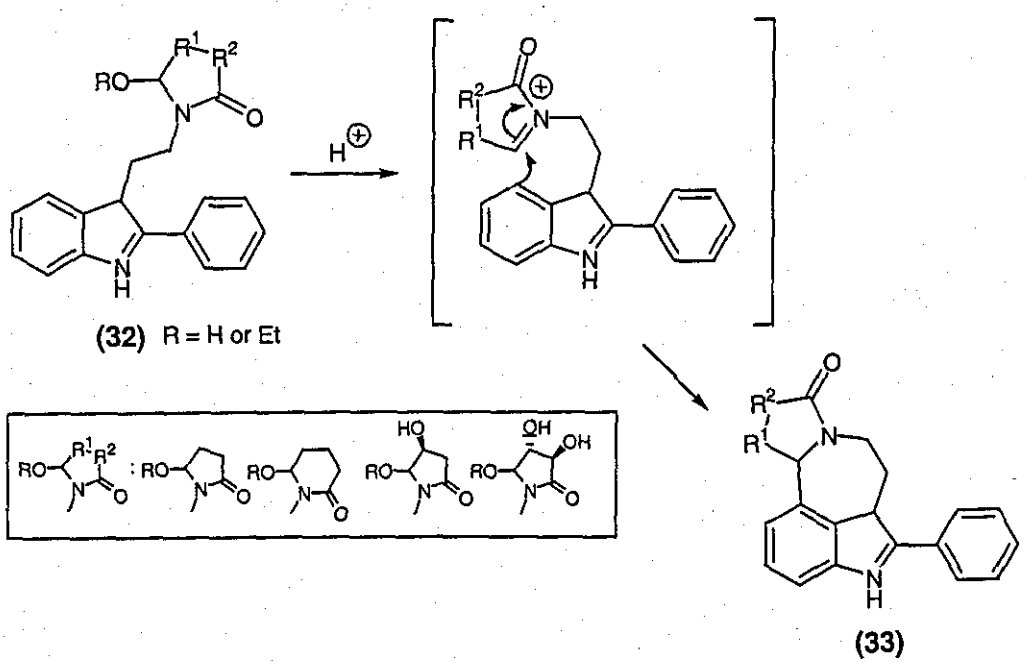
(30a) : X, Y = COOEt
(30b) : X = COOMe, Y = SO_2Ph

(31)

Scheme 13

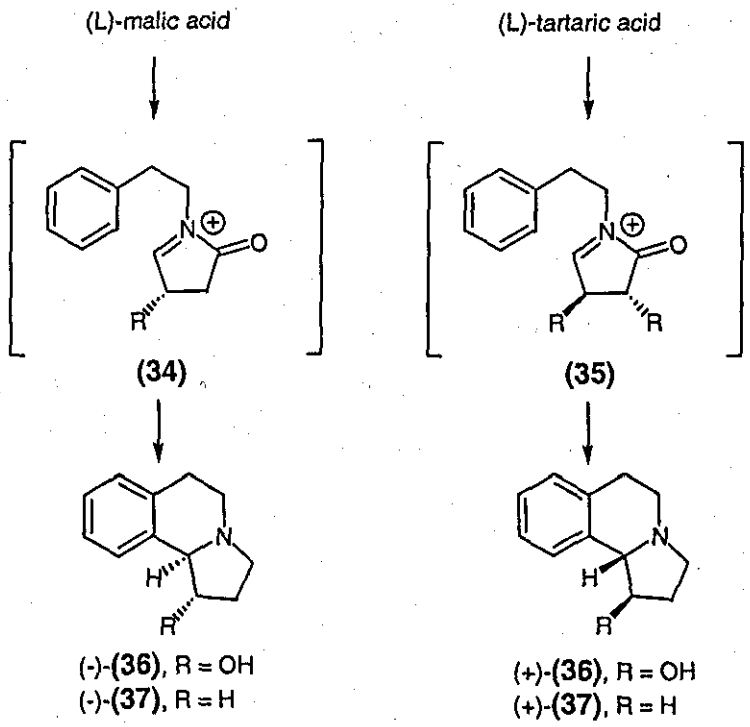
Many examples include the presence of chiral elements mostly in the starting alkoxylactam. Speckamp[23] *et al* examined cyclisation reactions between the tethered π nucleophile in **(30a – b)** and the iminium ion generated by acid-induced loss of the isopropoxy group resulting in **(31)**, (Scheme 13).

The synthesis of pyrrolidine and piperidine ring fused derivatives **(33)** has been accomplished through the *N*-acyliminium ion cyclisation of hydroxy and alkoxylactams **(32)**, (Scheme 14).[24]



Scheme 14

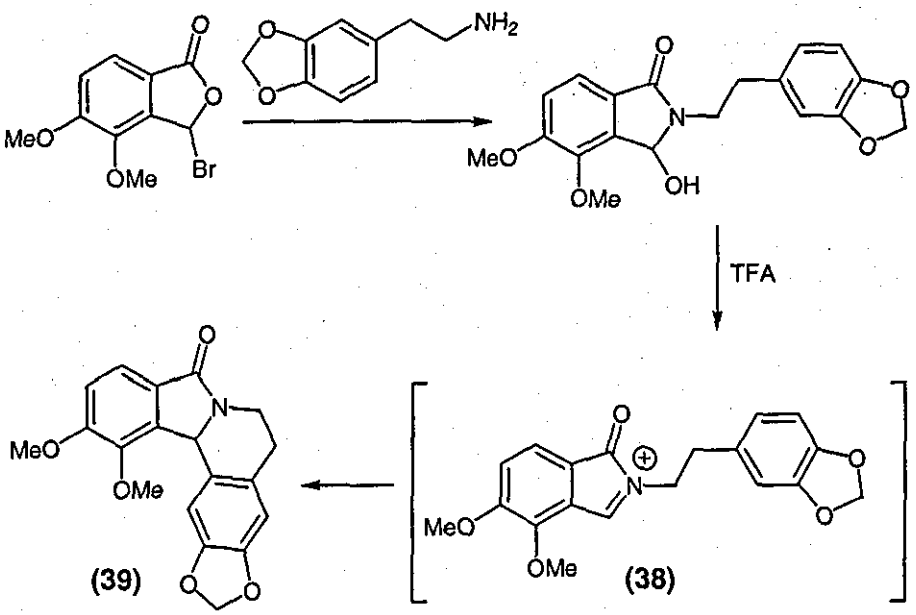
There has been much interest in the synthesis of isoindolinones[19-22, 25] and pyrroloisoquinolines[25-30] over recent years, with many approaches involving *N*-acyliminium ion cyclisation as a key ring forming step.



Scheme 15

Lee[29] *et al* targeted chiral acyliminium ions (**34**) and (**35**) as synthetic intermediates in the synthesis of pyrroloisoquinoline alkaloids (**36**) and (**37**). The free or protected hydroxy groups in the lactam control the stereochemical outcome of the cyclisation step and can be removed later in the synthesis (Scheme 15).

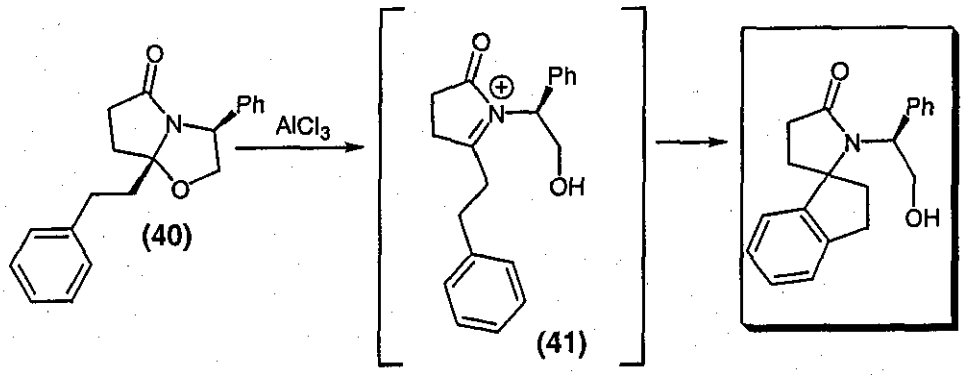
Benzenes or substituted benzenes are one of the most commonly used π nucleophiles in reactions of this type. Numerous polycyclic structures, including natural product systems can be accessed by the use of this particular reactive functional group, for example, neuvamine (**39**).



Scheme 16

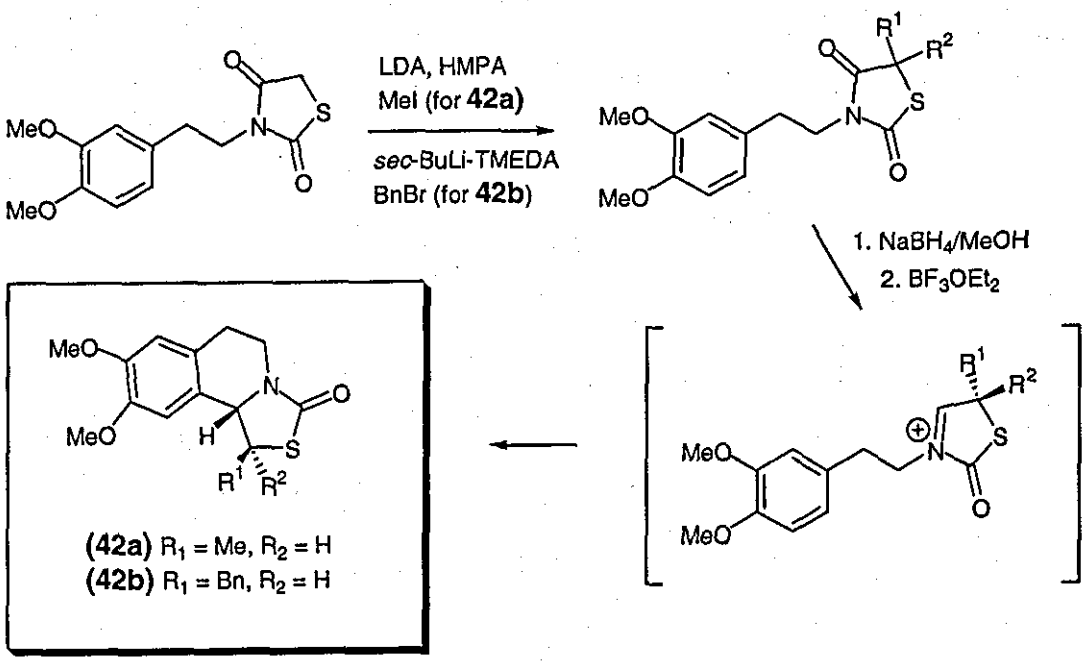
A racemic total synthesis of neuvamine has been reported by Alonso[31] (Scheme 16). The intramolecular cyclisation of an electron rich aromatic π nucleophile onto the generated *N*-acyliminium ion (**38**) is the key step in the synthetic route.

Vernon[32] and co-workers have investigated spiro cyclisations of fused oxazolidines such as (**40**) in which the bridgehead substituent -CH_2CH_2Ph provides the π nucleophile for intramolecular reactions with the *N*-acyliminium ion intermediate (**41**), (Scheme 17).



Scheme 17

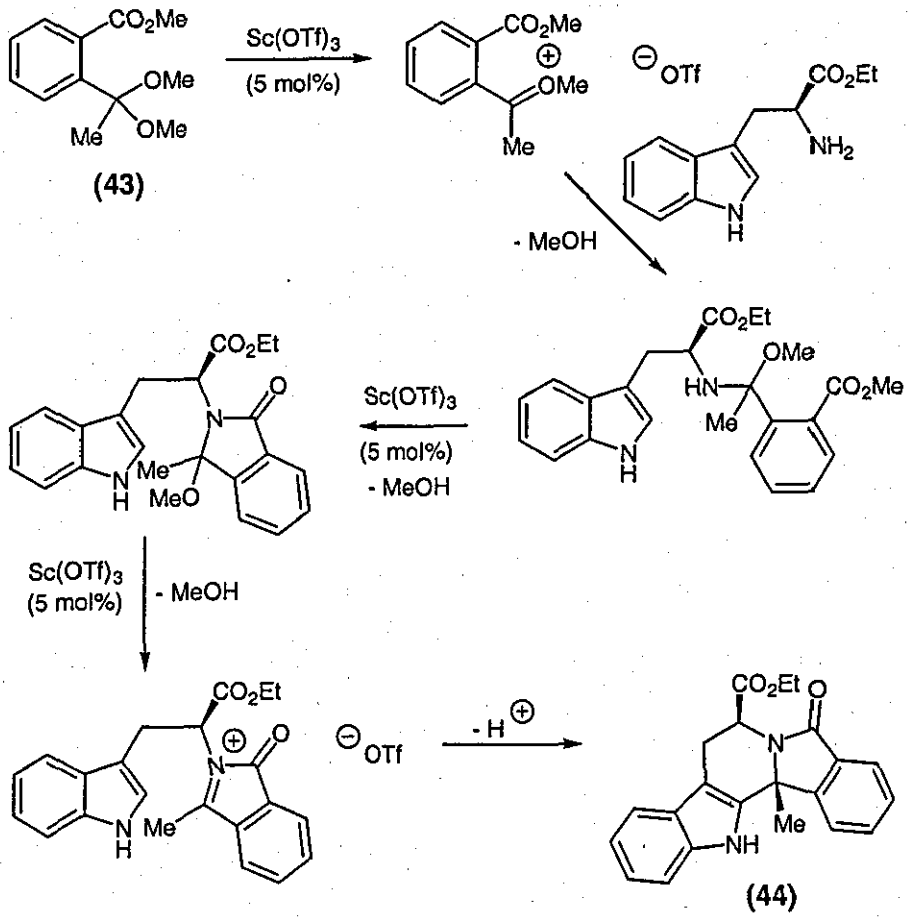
Lete[30] *et al* have shown that thiazolidine ions are effective intermediates for the synthesis of isoquinoline alkaloids. These ions can be regarded as masked iminium variants, since the sulfur atom can be removed in a stero-controlled fashion, thereby allowing formation of several heterocyclic systems.[33] The stereoselective synthesis of thiazoloisoquinolines (**42a – b**) have been investigated within the group employing intramolecular cyclisation of an aromatic π nucleophile to the cyclic *N*-acyliminium ion generated, (Scheme 18).



Scheme 18

In an asymmetric variation on the intramolecular amidoalkylation reaction, Heaney[34] *et al* have reported a cascade cyclisation reaction to the heterocyclic system (**44**)

shown in Scheme 19, utilising an indole substituent as an intramolecular nucleophile.



Scheme 19

Addition of 2-(1,1-dimethoxyethyl)benzoate **(43)** to the ethyl ester of tryptophan, with catalytic scandium (III) triflate leads to the cascade reaction affording the product **(44)** as a single diastereoisomer in 36% yield.

The Allin[35a-b] research group have more recently synthesised alkaloids of type **(45)** and **(46)** *via* Lewis acid mediated intramolecular *N*-acyliminium cyclisation of an indole substituent such as **(47)** (Figure 2).

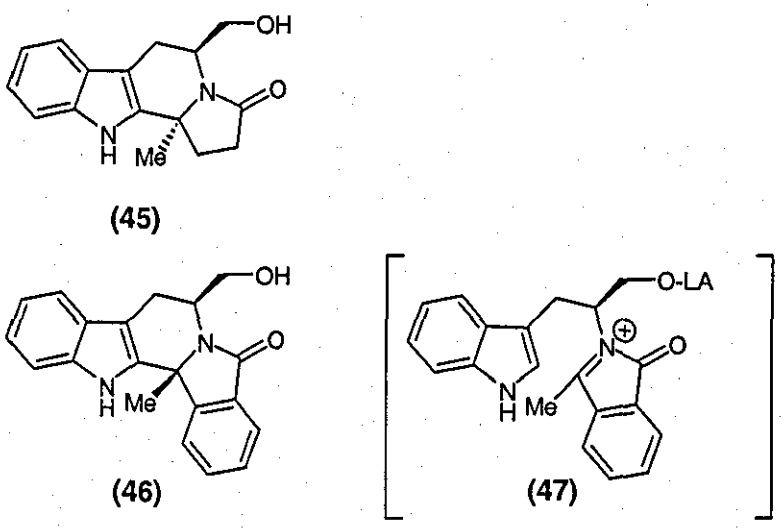
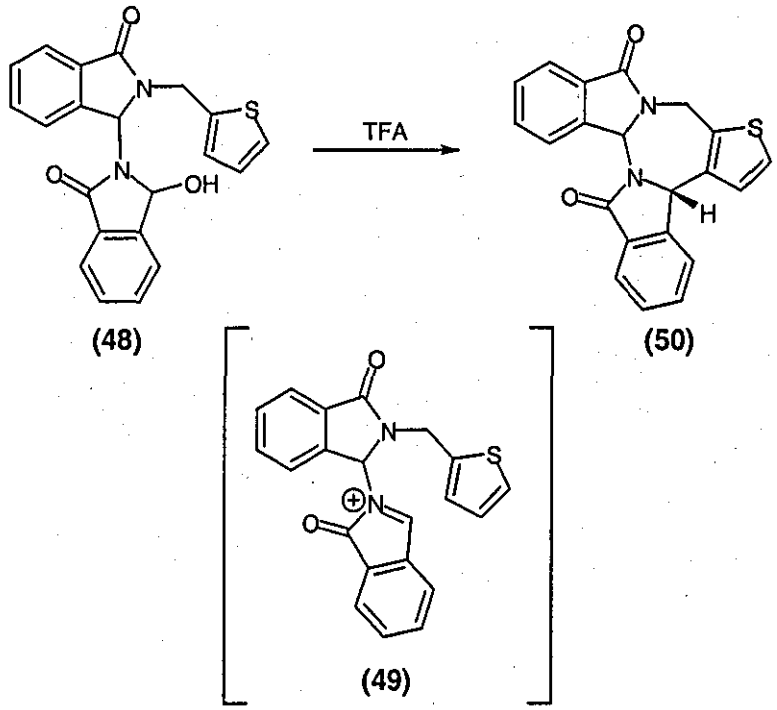


Figure 2

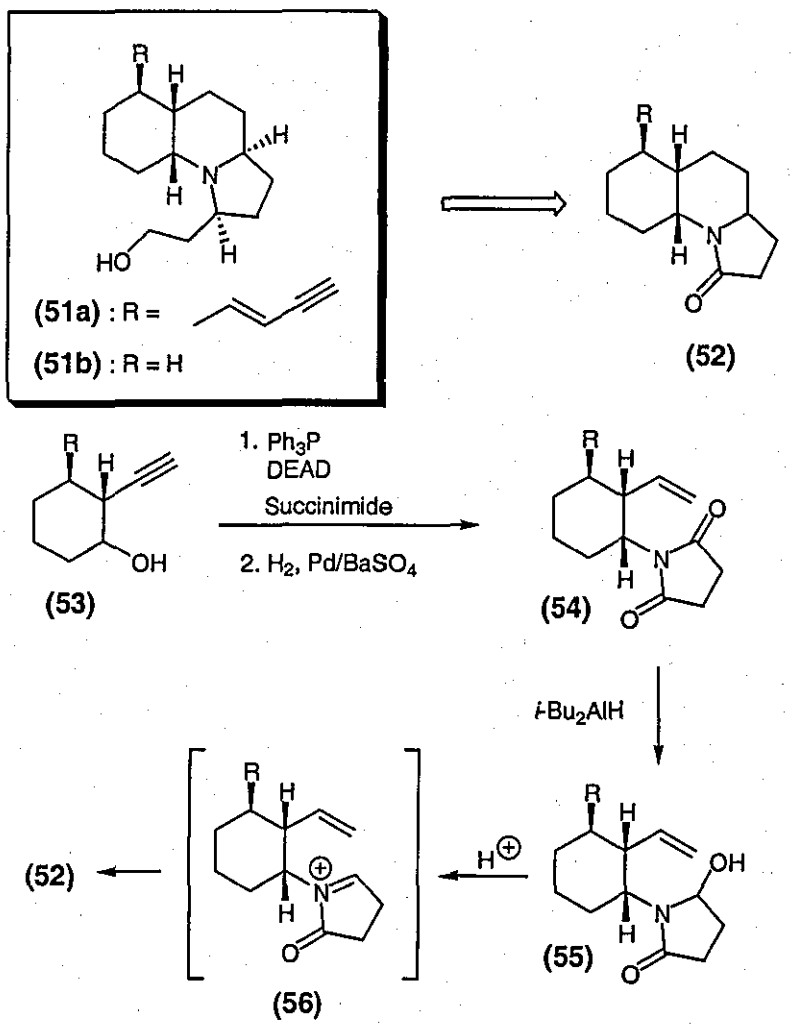
Decroix[36] investigated intramolecular addition reactions of thiophene to an *N*-acyliminium ion **(49)** formed from an isoindolinone derived hydroxylactam **(48)**. Diisoindolothienodiazepines such as **(50)** could be accessed readily by this method (Scheme 20).



Scheme 20

Other examples of tethered π nucleophiles that have been explored for carbon-carbon bond construction include vinyl and allyl groups. Hart[37a-b] *et al* reported the

total synthesis of Dentrobatid alkaloids such as gephyrotoxin **(51a)** and depentylperhydrogephyrotoxin **(51b)** from a tricyclic lactam of type **(52)**, *via* cyclisation of *N*-acyliminium or vinylogous *N*-acyliminium ions of type **(56)**, (Scheme 21).



Scheme 21

Treatment of a substituted 2-ethynylcyclohexanol **(53)** with succinimide under Mitsunobu conditions[38] followed by hydrogenation afforded imide **(54)**. Reduction of **(54)** with diisobutylaluminum hydride gave **(55)** which on treatment with formic acid gave the lactam precursor **(52)**.

Hart[39] has also extended this methodology to the preparation of vertaline **(57)** using *N*-acyliminium ion precursor **(58)** shown in Figure 3.

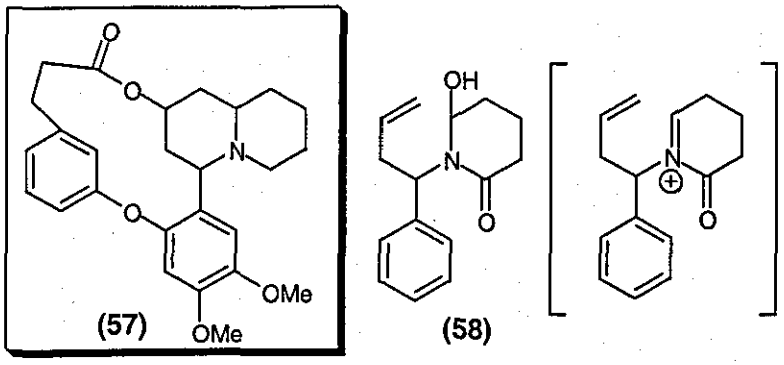
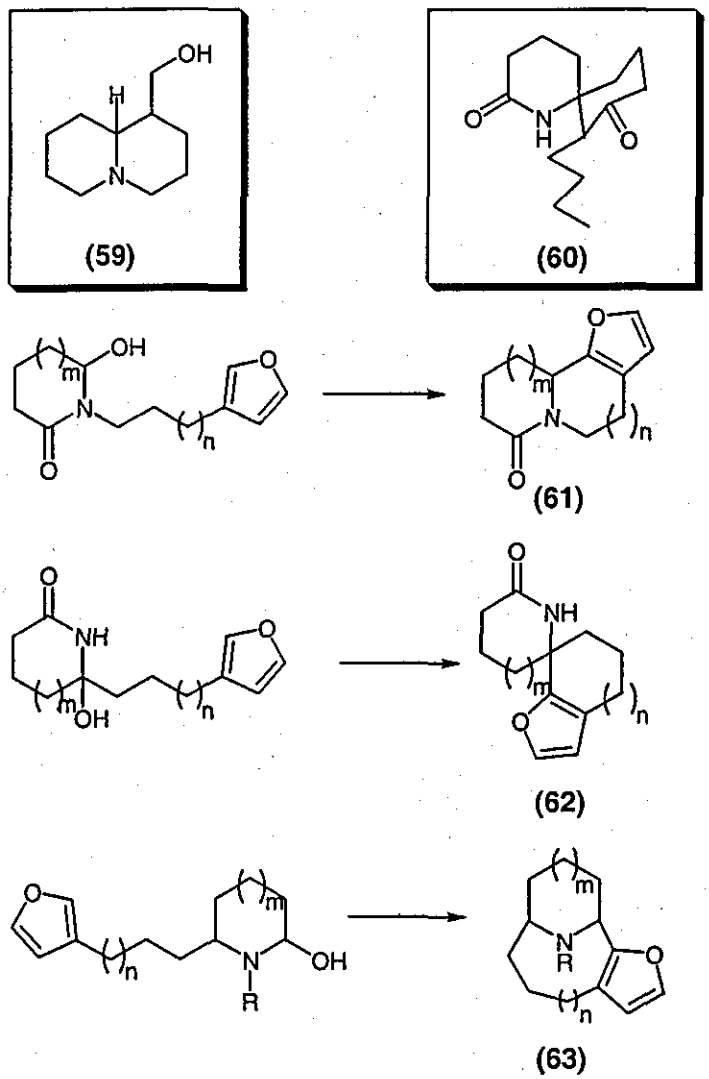


Figure 3

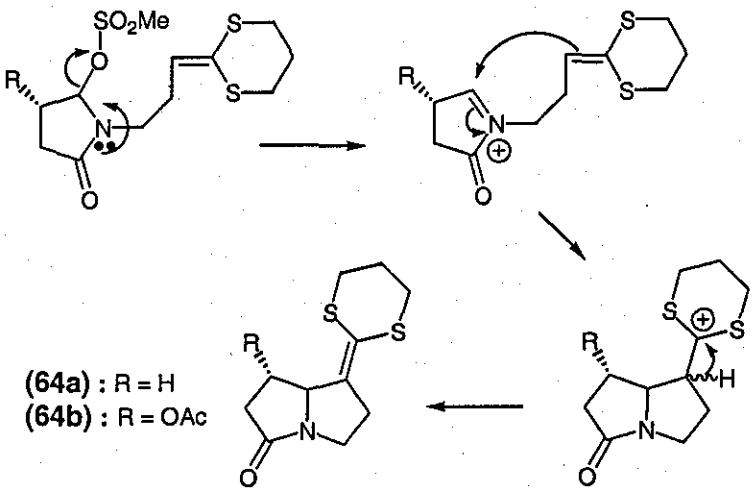
The furan moiety has been used in reactions of this type, to provide routes to a number of product systems such as (±)-epilupinine **(59)** and (±)-perhydrohistrionicotoxin **(60)**.



Scheme 22

In an extensive investigation of the intramolecular nucleophilic addition of terminal furan substituents onto *N*-acyliminium ions by Tanis,[40] routes towards alkaloid synthesis were devised. A variety of linearly-fused (**61**), spirocyclic (**62**), and bridged aza-cycles (**63**) could be synthesised by simply altering the placement of the furan tether on the *N*-acyliminium ion precursor as shown in Scheme 22.

During investigations into the synthesis of pyrrolizidine derivatives (**64**), Chamberlin and Chung[41] reported an efficient method of ring formation using a stereoselective acyliminium ion-ketene dithioacetal cyclisation (Scheme 23).



Scheme 23

Park[42] *et al* have studied imidazoles as internal nucleophiles for the synthesis of (±)-glochidine (**65**) and (±)-glochidicine (**66**) (Figure 4), and more recently, sulfur atoms as nucleophiles have been reported in the literature.[43]

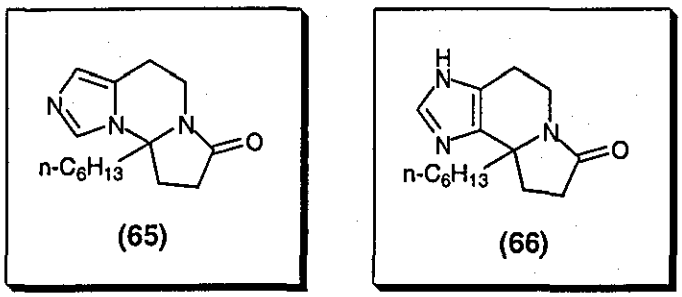
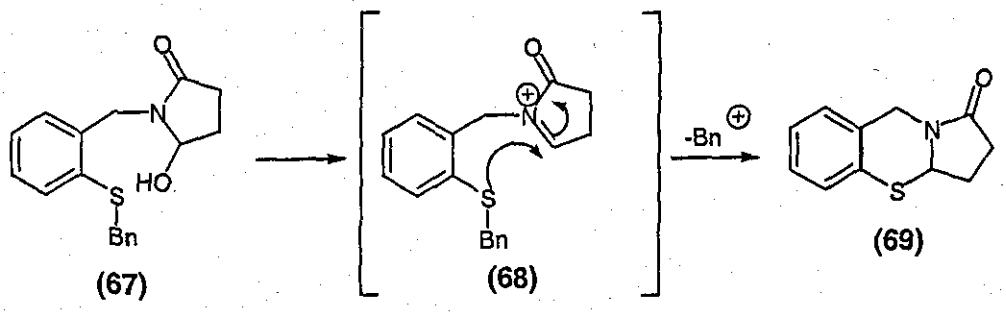


Figure 4

Decroix[43] *et al* showed that hydroxy lactam (**67**) could generate the *N*-acyliminium ion (**68**) in an acidic medium. The ring closure into (**69**) takes place through an intramolecular α-heteroamidoalkylation cyclisation, (Scheme 24).

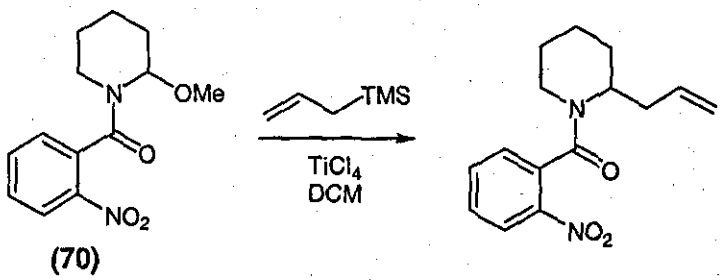


Scheme 24

1.3.2. Intermolecular carbon-carbon bond formation

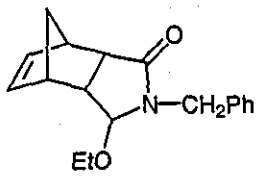
There has been recent interest in the synthetic utility and stereocontrol of the intermolecular *N*-acyliminium variant. A large number of new studies have been published,[1] both with respect to the type of precursors and activated nucleophiles, as well as the experimental conditions.

Allyl trimethylsilane in combination with titanium tetrachloride ($TiCl_4$) has been used frequently. For example Weinreb[44] *et al* commented on the efficiency of using titanium tetrachloride in the alkylation of α-alkoxyamides such as (**70**) with allyl trimethylsilane, (Scheme 25).



Scheme 25

Koizumi[45] *et al* examined the alkylation of the ethoxy compound (**71**) with allyl trimethylsilane in the presence of various Lewis acids and found titanium tetrachloride to be the most effective.

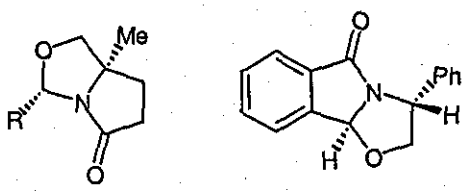


(71)

Figure 5

Meyers[46] and Allin[19] have prepared bicyclic lactam (72) and tricyclic lactam (73) respectively as single diastereoisomers and subjected them to aminal ring opening reactions using titanium tetrachloride and allyl trimethylsilane as the nucleophile.

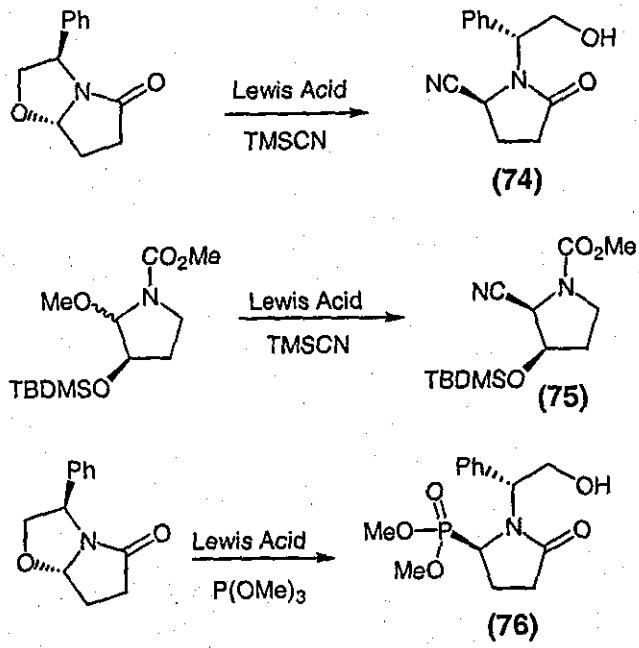
The latter group have also studied the effect on the stereochemical outcome of allyl trimethyl[19-20] and triethylsilane[21] intermolecular nucleophilic additions when varying the Lewis acid activator. It was shown that much higher levels of diastereoselectivity could be achieved using the triethylsilane protocol than with the Lewis acid/allyl trimethylsilane system, however titanium tetrachloride was still found to be the most effective activator.



(72) **(73)**

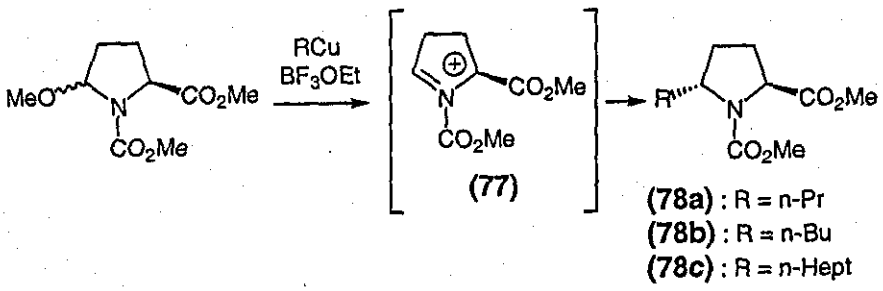
Figure 6

Examples of intermolecular additions of trimethylsilylcyanide **(74)**,[47] **(75)**[48] and trimethyl phosphite **(76)**[47] to *N*-acyliminium ion intermediates in the presence of titanium tetrachloride have been discussed in recent literature and are shown in Scheme 26.



Scheme 26

Highly diastereoselective additions of organocopper reagents to *N*-acyliminium ions have also been examined. Wistrand and Skrinjar[49] report addition of alkylcopper reagents to the optically active *N*-acyliminium ion (77) in the presence of boron trifluoride etherate (BF_3OEt_2) affording pyrrolidines (78a – c), (Scheme 27).



Scheme 27

1.3.3. Experimental conditions

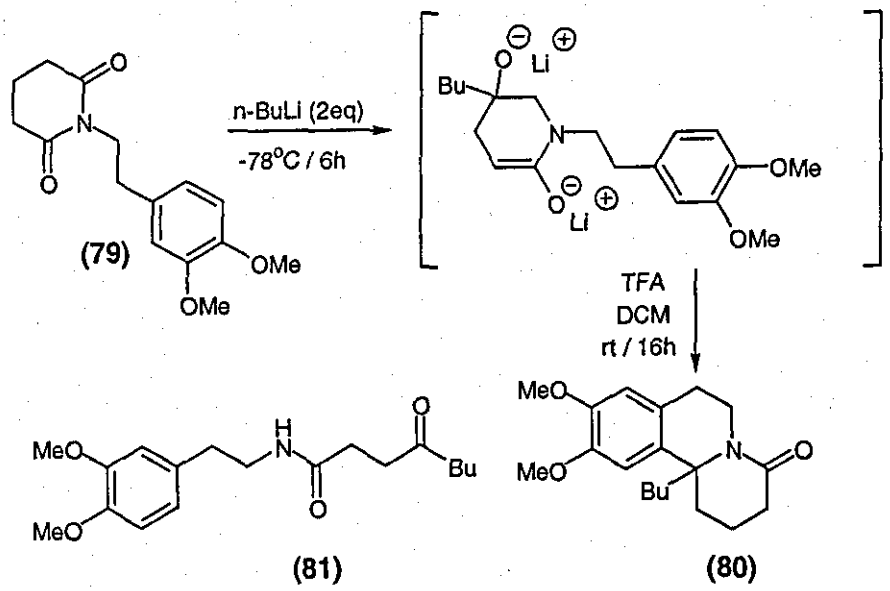
It has been discussed in Sections 1.3.1 and 1.3.2 that protic acids as well as Lewis acids have been used to effect carbon-carbon bond formation. In the Lewis acid mode a number of studies are concerned with the effects of different catalysts. From this data it is inferred that in the majority of reactions boron trifluoride etherate, tin

tetrachloride ($SnCl_4$) and titanium tetrachloride are superior in terms of convenience and results.

While the use of any particular combination of *Lewis acid* and *nucleophile* often dictates the *experimental conditions* some results have shown that the work-up technique determines the type of product formed.

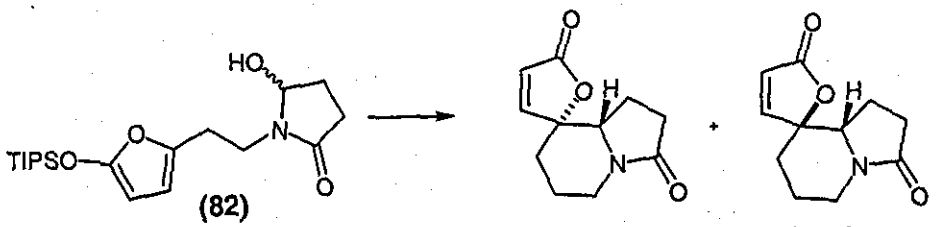
Lete[26] *et al* found that on simple aqueous work-up **(79)** yielded the oxo amide **(80)** in excellent yield (Scheme 28). Subsequent treatment with TFA resulted in the quantitative formation of the pyrroloisoquinoline derivative **(81)**.

When succinimide **(79)** was treated with *n*-butyl lithium at –78 °C and quenched directly with TFA, complete conversion to **(80)** was accomplished and no open-chain oxo amide **(81)** was detected.



Scheme 28

The adaptation of a particular combination of solvent and Lewis acid may also influence the outcome of the reaction. The cyclisation of substituted furan **(82)** was promoted with different Lewis acids, and the results of experiments in which the Lewis acid, temperature and solvent were varied are summarised in Table 1.[50] The diastereomeric ratio of **(83a)** : **(83b)** was moderately affected by the choice of Lewis acid, temperature and solvent.

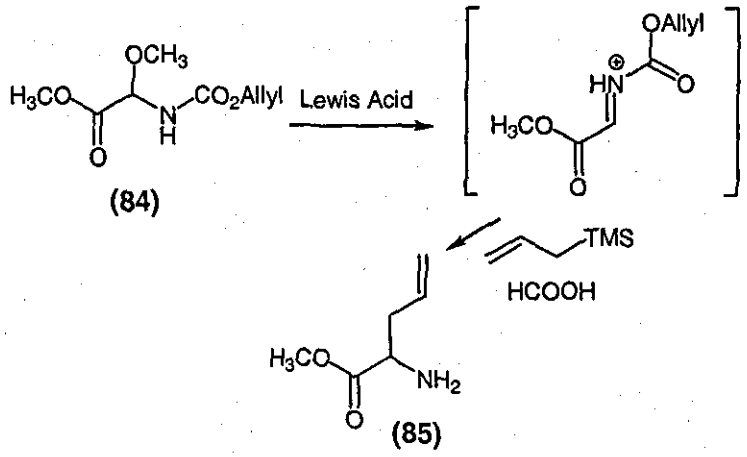


Substrate	Lewis acid	Solvent	Temp(°C)	(83a) : (83b)	Yield (%)
(82)	$ZnCl_2$	CH_2Cl_2	20	8.8 : 1	62
(82)	$ZnCl_2$	CH_3CN	20	4 : 1	51
(82)	$BF_3.OEt_2$	CH_3CN	20	6 : 1	64
(82)	Et_2AlCl	CH_3CN	20	6 : 1	83
(82)	Et_2AlCl	CH_2Cl_2	20	8.8 : 1	50
(82)	Et_2AlCl	THF	20	7 : 1	63
(82)	Et_2AlCl	CH_3CN	-20	8 : 1	72
(82)	Et_2AlCl	CH_3CN	40	5 : 1	77

Table 1: The effects of different Lewis acids, temperatures, and solvent

1.3.4. Stereocontrol

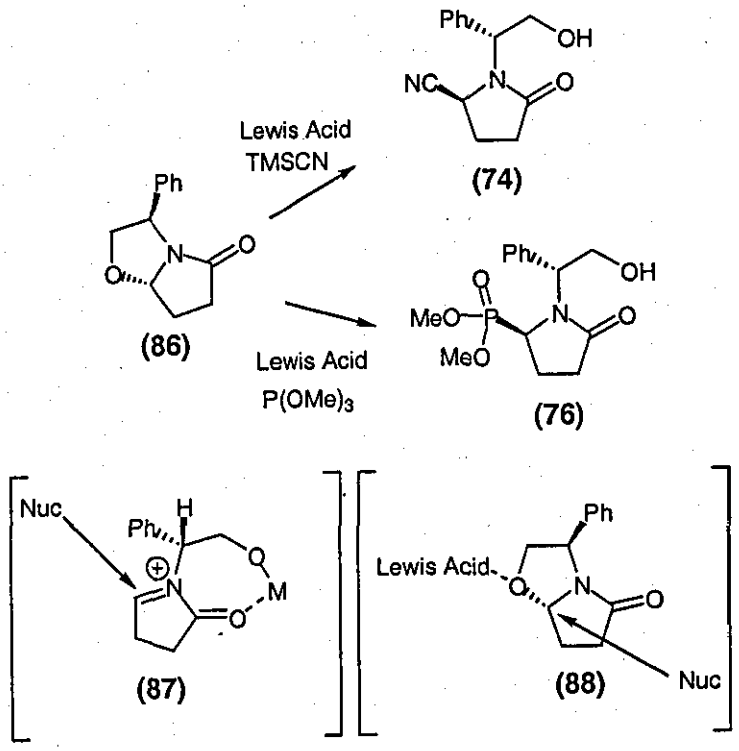
The mechanistic pathway for *N*-acyliminium reactions does not allow a direct control of the desired stereochemistry. An S_N1 type intermediate has been detected directly in NMR studies and is also chemically proven by experimental observations.[1]



Scheme 29

An example is found in the reaction of optically pure (+)-(**84**) with three types of nucleophiles. In all cases completely racemized products, for example (**85**), were obtained and the reactions proceeded *via* the mechanism shown in Scheme 29.[51]

Reactions of a similar type have been shown to proceed partly or completely *via* an S_N2 mechanism. Either by the formation of an intermediate complex between the starting material and the Lewis acid, allowing the attack of the nucleophile from only one side, or by using a very good leaving group, which enhances the reaction significantly and therefore allows a one-step substitution reaction.



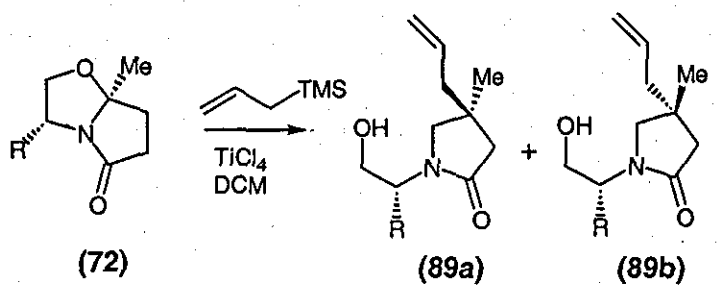
Scheme 30

Royer[47] *et al* have shown that nucleophilic additions to oxazolidine (**86**), (Scheme 30), gave pyrrolidinones (**74**) and (**76**), (discussed in Section 1.2.2) with good diastereoselectivity. They proposed that the mechanism of the reaction may involve an *N*-acyliminium intermediate (**87**), or an S_N2-like reaction through partial opening of the oxazolidine ring, (**88**).

It has been discussed in preceding sections that altering the nucleophile/Lewis acid combination can also dictate the stereochemical outcome of the reaction.

Another example of a stereocontrolled nucleophilic addition has been studied extensively by Meyers.[46] Stereochemistry can be influenced by the nature of the angular substituent incorporated into the fused bicyclic lactam (**72**), discussed in Section 1.2.2.

It was found that by changing the nature of the auxiliary group on (**72**) from small (methyl) to large (*tert*-butyl) the stereochemistry of the alkylation could be altered. This is shown in Scheme 31 and the results are represented in Table 2.



(72) **(89a)** **(89b)**

Scheme 31

R	Diastereomeric ratio (89a) : (89b)
methyl	8 : 1
phenyl	5 : 1
isopropyl	1 : 2
tert-butyl	1 : 11

Table 2: Stereochemical outcome of the alkylation reactions

Conformational models were proposed to explain the stereochemical rationale of the reactions (Figure 7), allylic 1,3-strain, and chelation effects are also thought to be an influencing factor in the stereocontrol.

Allin[21] *et al* have also proposed this rationale to explain observed product diastereoselectivities of isoindolinone targets.

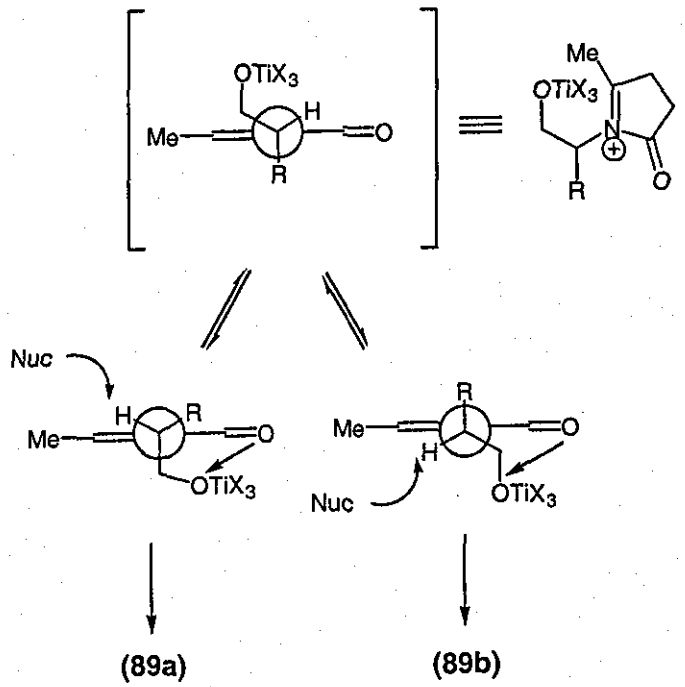


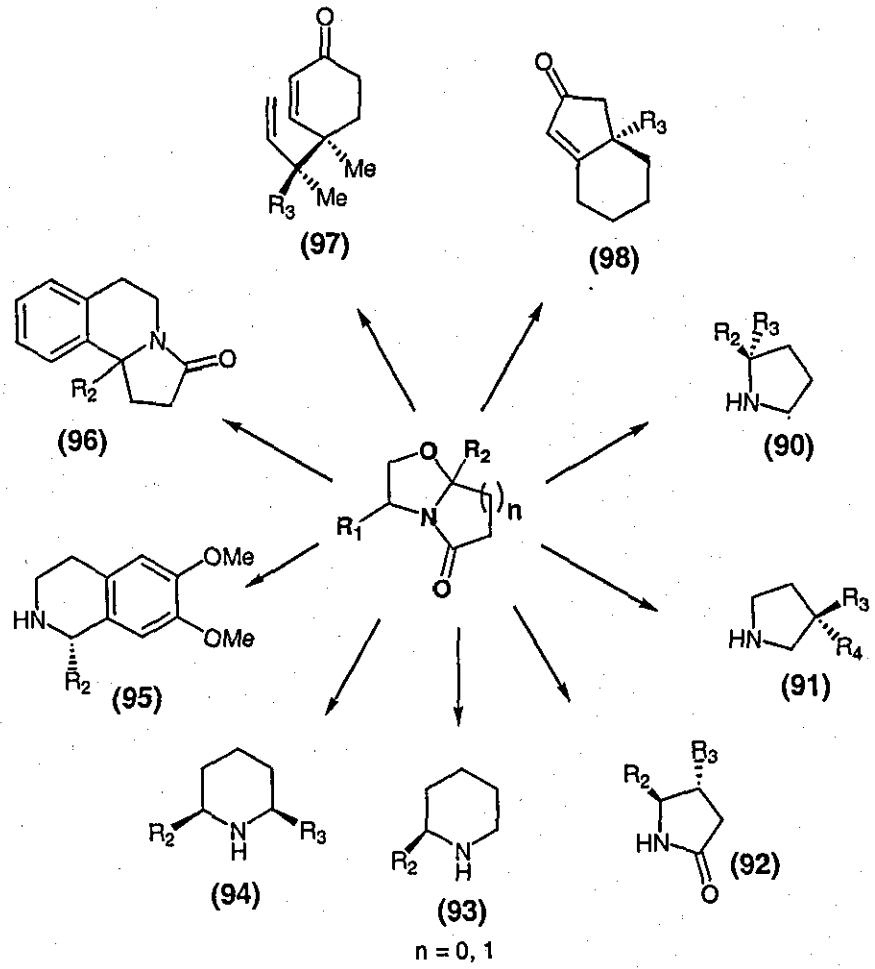
Figure 7

1.4. Applications of the Meyers bicyclic lactam substrates in synthesis

1.4.1. Introduction

Bicyclic lactams are an extremely versatile tool in the preparation of a plethora of optically active products, and provide access to a variety of natural and unnatural compounds such as pyrrolidines (**90**) and (**91**)[52-53] and pyrrolidinones (**92**)[53-54] shown in Scheme 32.[18]

Other examples of ring systems present in a number of naturally occurring carbocycles and heterocycles that can be synthesised from these chiral non racemic templates include piperidines (**93**) and (**94**),[55] tetrahydroisoquinolines (**95**),[56] pyrroloisoquinolines (**96**),[25] cyclohexenones (**97**)[57] and hexahydroindenones (**98**).[14]



Scheme 32

1.4.2. Synthesis of substituted pyrrolidines and pyrrolidinones

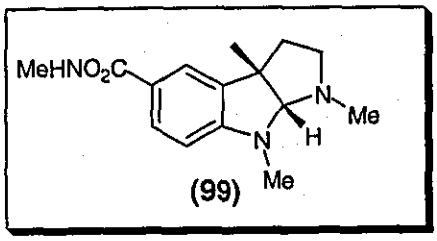
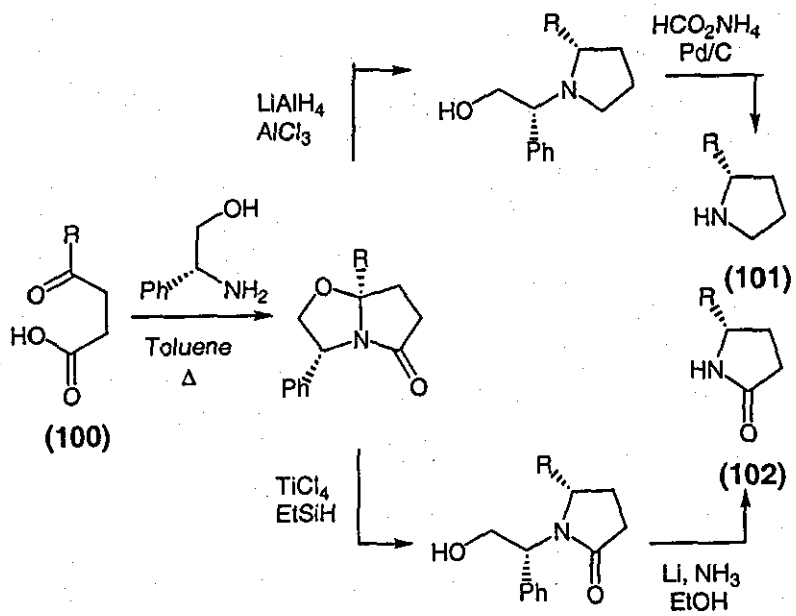


Figure 8

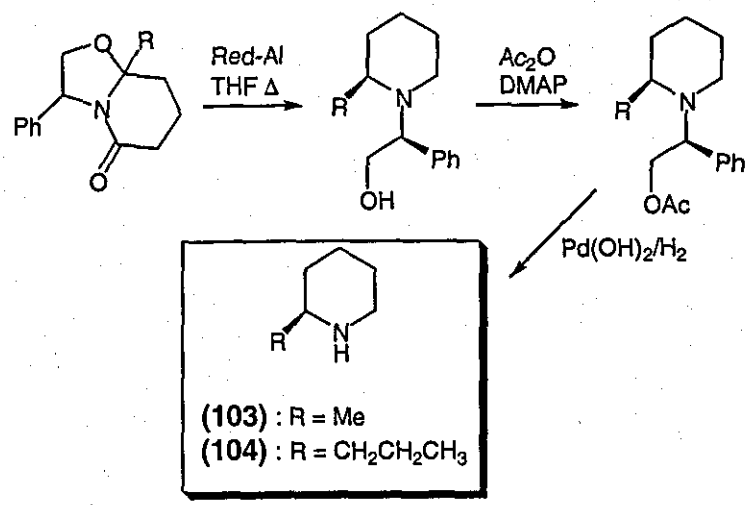
Highly functionalised pyrrolidines are compounds of considerable importance. They occur in a variety of natural products and pharmaceutically active compounds, either as isolated ring systems or embedded in more complex structures, which often possess wide ranging biological activity. For example, physostigmine[58] **(99)** is a representative of this class of compounds.

Meyers[53] describes an efficient asymmetric synthesis of substituted pyrrolidines (**101**) and pyrrolidinones (**102**) from keto acid (**100**) and phenylglycinol as shown in Scheme 33.



Scheme 33

1.4.3. Synthesis of piperidine

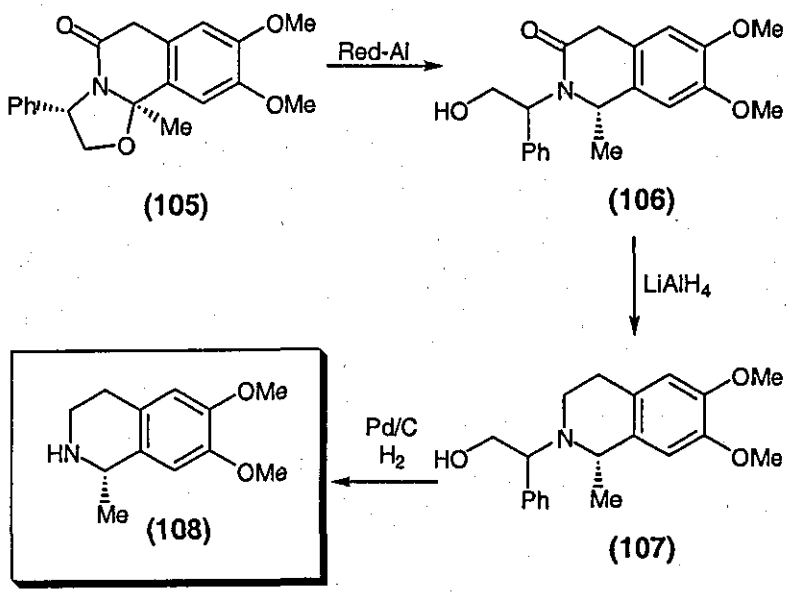


Scheme 34

The route to asymmetric pyrrolidines was extended to the piperidine series[55] (Scheme 34). This methodology was utilised in the synthesis of the natural products (-)-pipecoline **(103)** and (+)-coniine **(104)**.

1.4.4. Synthesis of tetrahydroisoquinolines

Routes to naturally occurring tetrahydroisoquinolines, such as salsolidine **(108)**, have been developed from chiral bicyclic lactams of type **(105)**[56] (Scheme 35). Treatment of **(105)** with sodium bis(methoxyethoxy)aluminium hydride (Red-Al) gave the ring-opened lactam **(106)** which upon additional reduction with lithium aluminium hydride gave the *N*-benzyl substituted isoquinoline **(107)**. Reductive removal of the *N*-benzyl group afforded the natural product **(108)**.

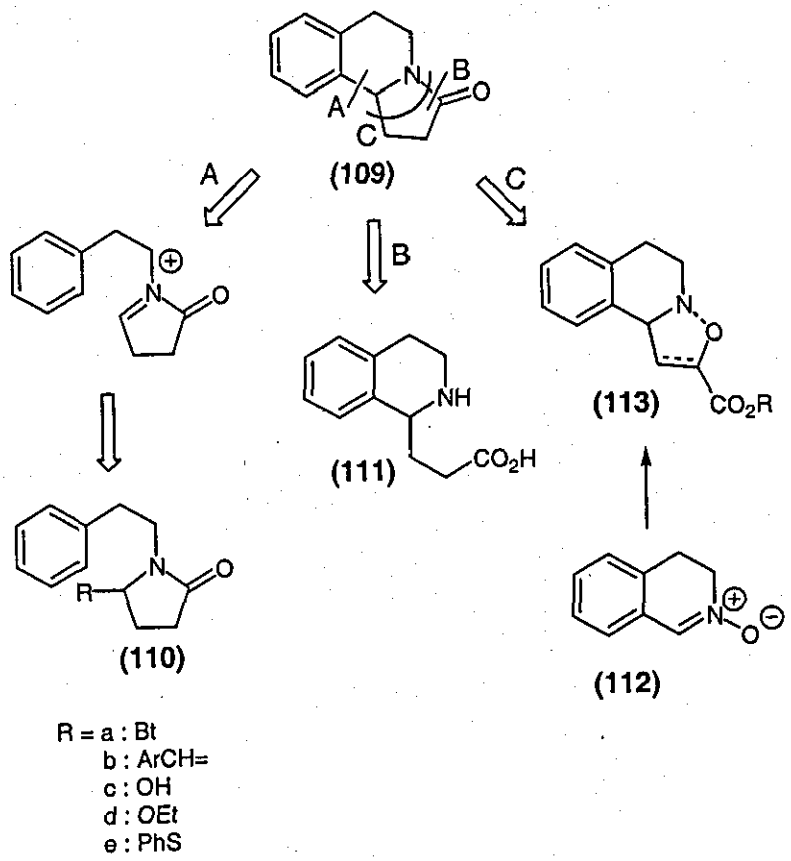


Scheme 35

1.4.5. Synthesis of substituted pyrroloisoquinolines

Katritzky[25] suggests that there are three main routes reported for the synthesis of pyrroloisoquinoline **(109)** as shown in Scheme 36. This research group have concentrated their efforts on route A, cyclisation of an *N*-acyliminium ion formed by loss of a benzotriazoyl anion **(110a)** in the presence of titanium tetrachloride.

Other groups have studied formation of *N*-acyliminium ion species generated by protonation of the carbon-carbon double bond of an enamide **(110b)**,[59] or by elimination of a hydroxy group **(110c)**,[26-29] ethoxy group **(110d)**,[60a-c] or alternatively a phenylthio group **(110e)**.[61]

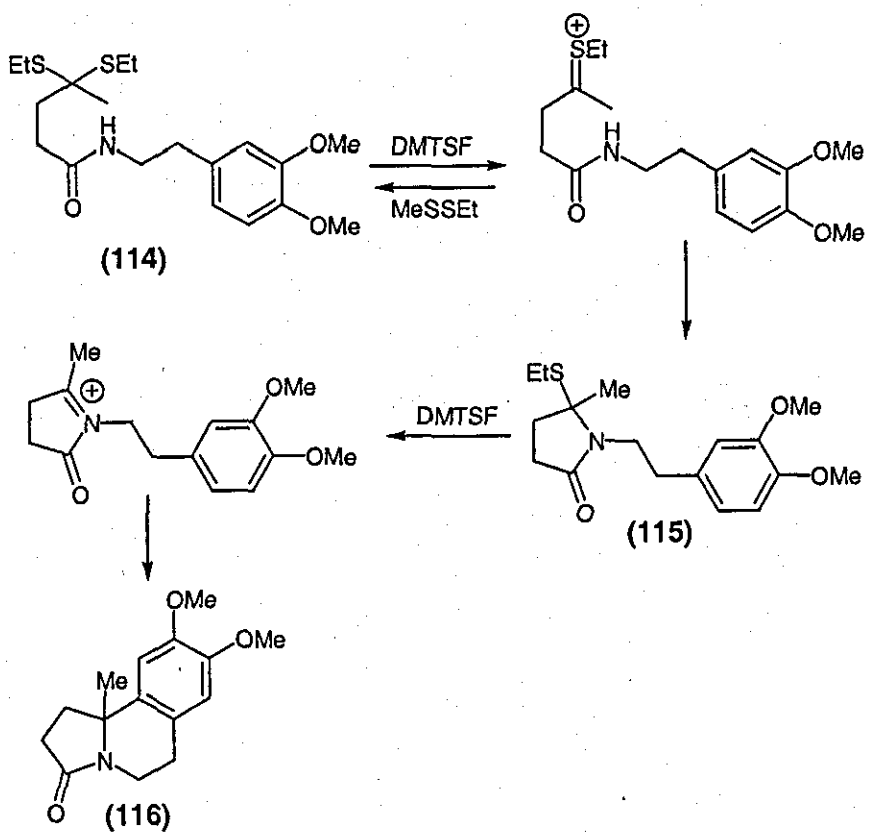


Scheme 36

Orito[62] *et al* reported the synthesis of **(109)** by intramolecular condensation of intermediate **(111)** with the elimination of water as outlined in route B. Other research groups have reported formation of **(109)** *via* route C, the reduction of intermediate **(113)**, obtained by 1,3-dipolar cycloadditions of nitrones **(112)** with ethylenes[63] or acetylenes.[64a-b]

Padwa[65] *et al* have recently described the preparation of pyrroloisoquinoline **(116)** by treatment of amido-substituted thioacetal **(114)** with *dimethyl*(methylthio)sulfonium tetrafluoroborate (DMTSF) giving five-membered thio-substituted lactams **(115)** (Scheme 37). Further reaction with DMTSF

generates an *N*-acyliminium ion which undergoes cyclisation with the tethered aromatic ring to produce the pyrroloisoquinoline **(116)**.

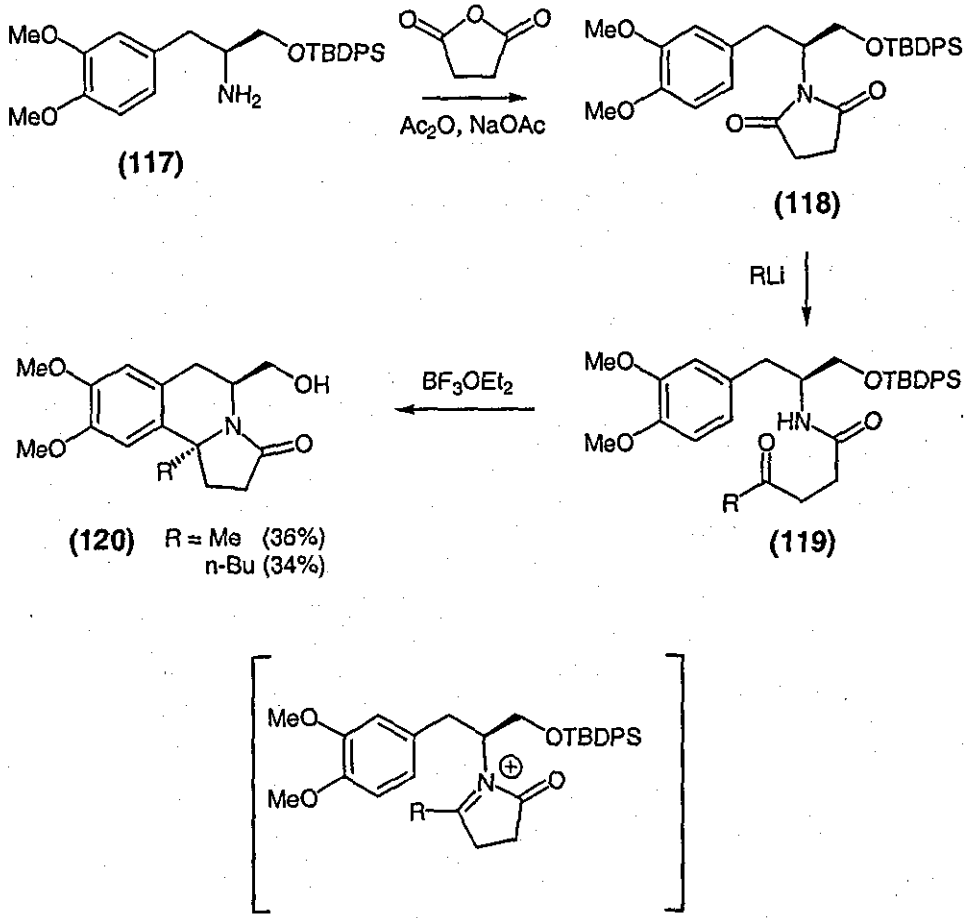


Scheme 37

Alternative methods include the stereocontrolled synthesis of **(120)** *via* tandem organolithium addition-*N*-acyliminium ion cyclisation, recently reported by Lete[66] *et al* (Scheme 38).

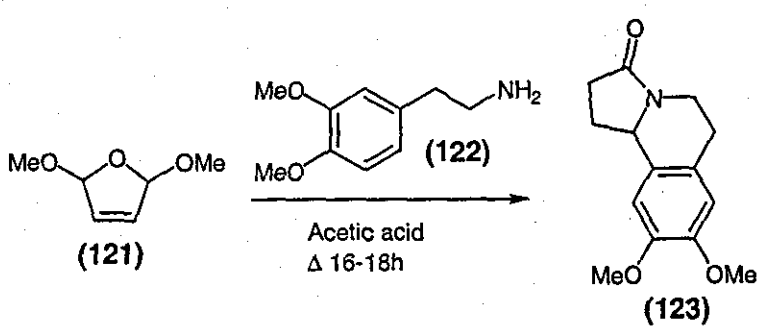
Sequential treatment of **(117)** with succinic anhydride followed by acetic anhydride and sodium acetate gave the succinimide **(118)**, which on treatment with organolithiums such as methyl- or butyl lithium yielded the corresponding oxoamides **(119)**. Stereoselective cyclisation of **(119)** with a Lewis acid afforded the desired pyrroloisoquinolines **(120)**.

Hydrolysis of the TBDPS group occurred at the same time.



Scheme 38

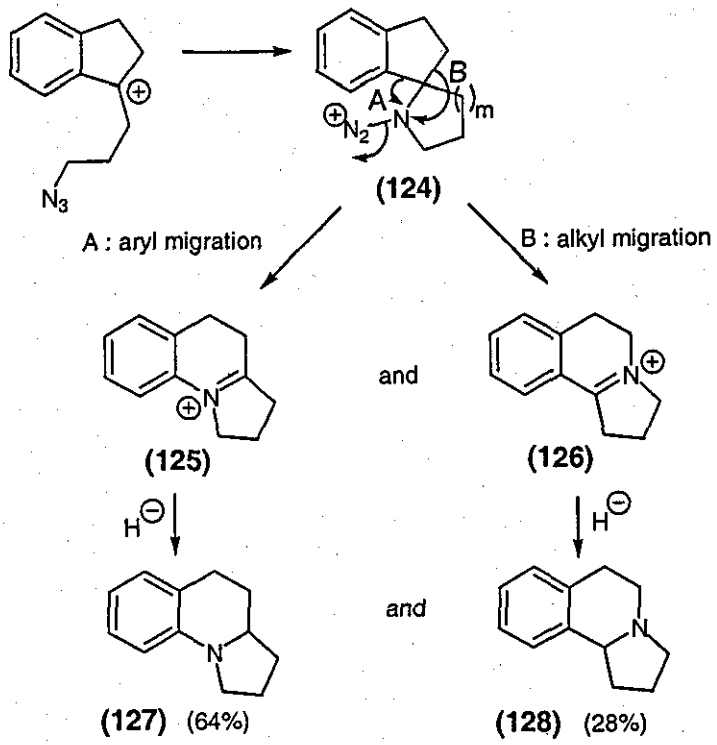
Royer[67] *et al* have described a straightforward one-step procedure to pyrroloisoquinoline (**123**) from 2,5-dimethoxy-2,5-dihydrofuran (**121**) and 3,4-dimethoxy phenylalanine (**122**) in a respectable 53% yield (Scheme 39).



Scheme 39

Pearson and Fang[68] found that isoquinoline alkaloids could be prepared by an intramolecular Schmidt reaction (Scheme 40). Aryl and alkyl migration in the intermediate aminodiazonium ion (**124**) led to iminium ions (**125**) and (**126**) which

undergo hydride reduction to produce products **(127)** and **(128)**. It was reported that in general aryl migration was preferred over alkyl migration, however **(127)** and **(128)** could be easily separated by flash column chromatography due to their diverse polarities.



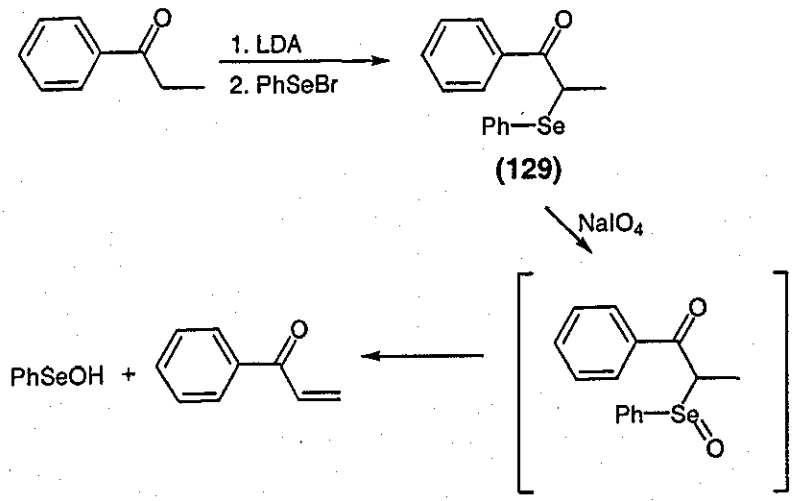
Scheme 40

1.5. Further functionalisation of bicyclic lactam substrates

The versatility of the bicyclic lactam as a template for the asymmetric synthesis of a variety of alkaloid ring systems is further demonstrated in the following section.

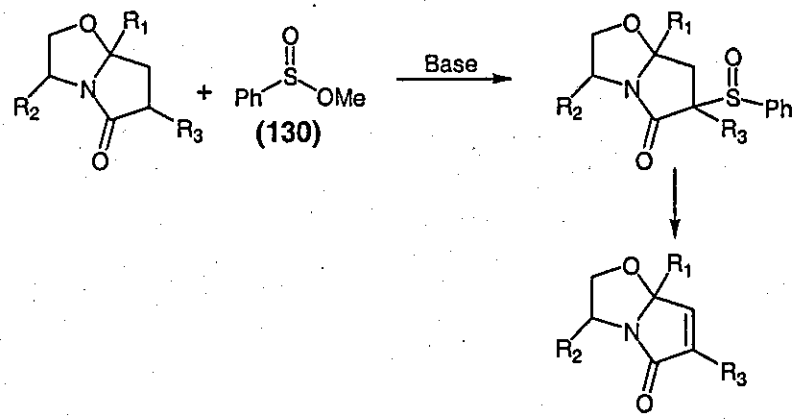
1.5.1. Unsaturated bicyclic lactams

The preparation of α,β-unsaturated carbonyl compounds is a useful and important transformation allowing further functionalisation of substrates. This process is most commonly carried out through the efficient eliminination of appropriate selenoxides developed by Reich,[69] who reported a method for the conversion of ketones and esters to their α,β-unsaturated derivatives.



Scheme 41

The reaction of lithium enolates with benzene selenyl bromide or chloride gives α-phenylselenocarbonyl compounds **(129)** that undergo elimination during an oxidation step (Scheme 41).

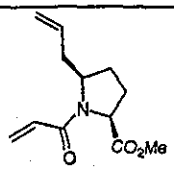
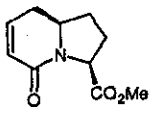
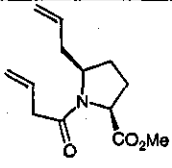
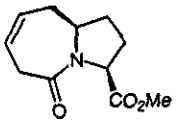
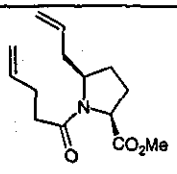
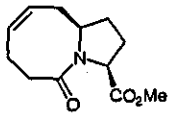


Scheme 42

Meyers[70] *et al* have proposed an alternative route avoiding the use of toxic selenium, using methyl phenylsulfinate **(130)** for the elimination (Scheme 42). This group prepared a variety of substituted α,β-unsaturated bicyclic lactams by this method, in good yields.

Wagner[71] *et al* have developed an efficient and versatile approach towards unsaturated fused bicyclic lactams *via* a ring-closing metathesis reaction. Table 3

shows examples of lactams possessing three different ring sizes, 6,5 **(131)**, 7,5 **(132)** and 8,5 **(133)**.

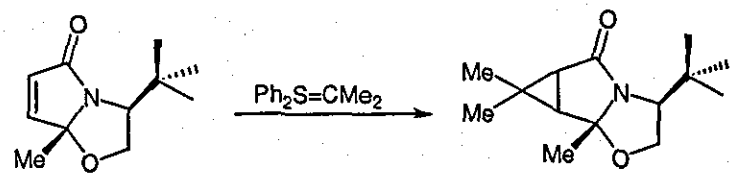
Substrate	Diene	Bicycle	Yield[a] (%)
(131)			94
(132)			81
(133)			35

[a]Conditions: $Cl_2(Pcy_3)Ru{=}CHPh$ (10-15%), DCM, reflux, 16h

Table 3: Results of the ring-closing metathesis

1.5.2. Cyclopropanations

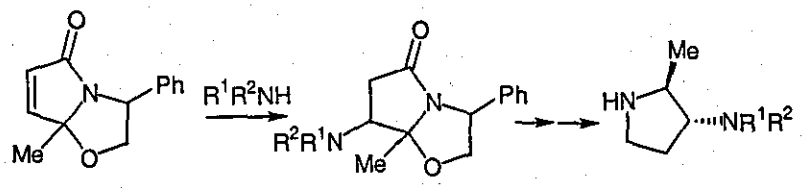
The first report on conjugate additions to bicyclic lactams includes cyclopropanations *via* the addition of sulfonium ylides[72a-b] as shown in Scheme 43.

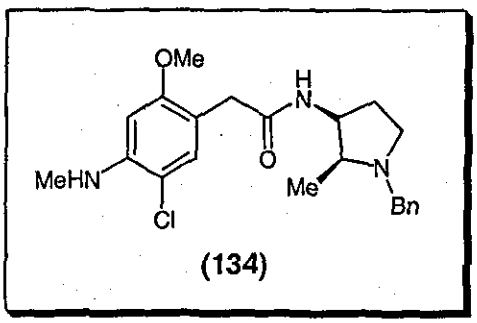


Scheme 43

1.5.3. Amine conjugate addition

Additions of amines to α,β-unsaturated bicyclic lactams (Scheme 44) have been applied to the synthesis of several benzamide derivatives such as **(134)**, neuroleptic drugs useful in the clinical treatment of schizophrenia.[18]



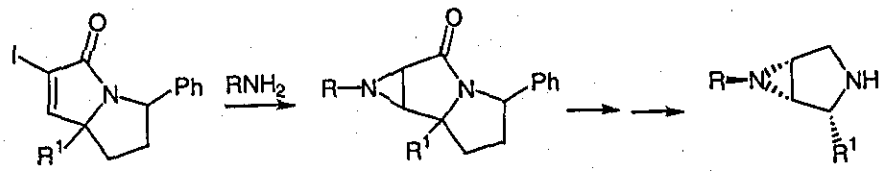


(134)

Scheme 44

1.5.4. Aziridination by conjugate addition

The amine conjugate addition was extended to construct the aziridine moiety with high efficiency (Scheme 45).[73]

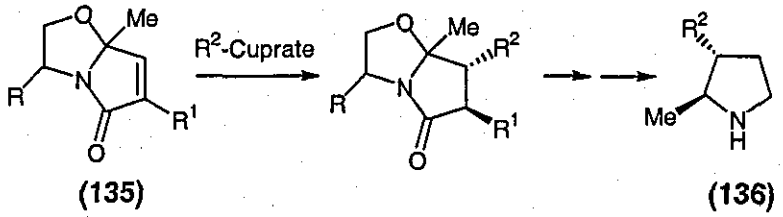


Scheme 45

1.5.5. Organocuprate conjugate additions

Conjugate addition reactions of cyanocuprates to lactams to give substituted pyrrolidines have been explored extensively in the literature.[74-75] For example, conjugate addition of various organocuprates to **(135)**, and subsequent cleavage of

the resultant β-substituted lactams to trans-2,3-disubstituted pyrolidines **(136)** (Scheme 46), have been studied by Meyers[74] and co-workers.



Scheme 46

Recently Amat[76] described the enantioselective preparation of diversely substituted piperidine alkaloids by conjugate addition of cyanocuprates to α,β-unsaturated lactams, and the application of this methodology to the synthesis of the antidepressive drug Femoxetine **(137)**.

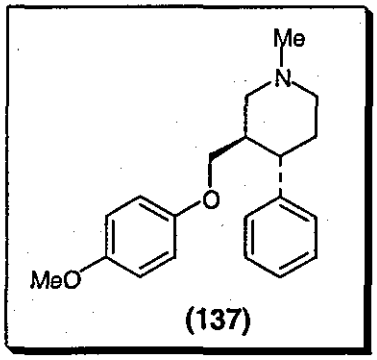
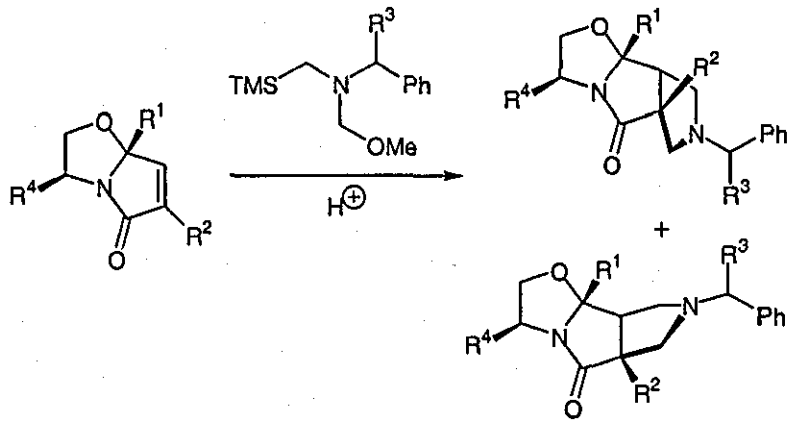


Figure 9

1.5.6. Azomethine ylide cycloadditions



Scheme 47

There are continuing efforts to construct substituted pyrrolidine derivatives using efficient and convergent procedures, and one such method involves the intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylides with olefins[77a-b] as shown in Scheme 47.

1.5.7. Diels-Alder additions

Moloney[78-79] *et al* have been interested in the development of methodology for the convenient synthesis of functionalised pyrrolidinones. This group, and others[80a-c] have demonstrated the utility of α,β-unsaturated lactams of type **(138)** by describing its Diels-Alder reactions with varying dienes and 1,3-dipoles. Examples are shown in Table 4.[79]

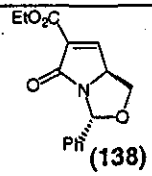
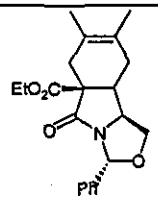
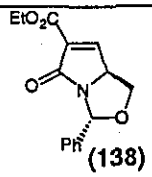
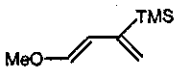
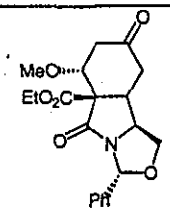
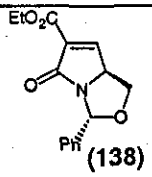
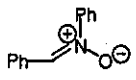
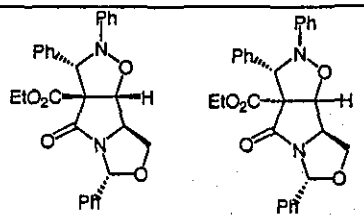
Lactam	Diene	Product
 **(138)**		
 **(138)**		
 **(138)**		

Table 4: Reactions of lactam (138) with dienes and 1,3-dipoles

1.6. Applications of *N*-acyliminium ion precursors in the synthesis of *erythrina* alkaloids

1.6.1. Introduction

The synthesis of optically pure compounds from chiral precursors is now a standard technique, and application of the bicyclic lactam chiral template as a precursor for the synthesis of a number of natural and unnatural products has been described in preceding sections.[81]

Functionalisation of unsaturated lactams has proven to be a convenient and efficient technique for synthesising a variety of alkaloid structures, and the *N*-acyliminium method has been used with great success in the synthesis of both simple and complex polycyclic ring systems.[1]

Several research groups have a current interest in the synthesis of a number of isoquinoline alkaloids.[25-30, 65-68] Such systems are common intermediates in the preparation of the *erythrina* alkaloids.[82]

1.6.2. *Erythrina* alkaloids

The genus *erythrina* is widely distributed in tropical and subtropical regions of the world and has been occasionally used as indigenous folk medicines.[83] In flowers, seeds and bark of the genus *erythrina*, there have been found erythrinane alkaloids, some of which have curare-like and hypnotic actions.

A variety of pharmacological effects, including sedative, hypotensive, neuromuscular blocking, and CNS depressant properties are also associated with the erythrinane skeleton.[84]

The vast majority of naturally occurring *erythrina* alkaloids possess the tetracyclic framework and substitution pattern shown in Figure 10.

Examples include (-)-3-demethoxyerythratidinone[85-86] **(139)**, an alkaloid isolated from *erythrina lithosperma* in 1973 by Barton[87] and colleagues; erysotramidine[84] **(140)**, 8-oxoerythraline[83] **(141)**, isolated from flowers of *erythrina* bidwillii; erythraline[88] **(142)**, found in *erythrina* crista-galli and erysotrine[89] **(143)**.

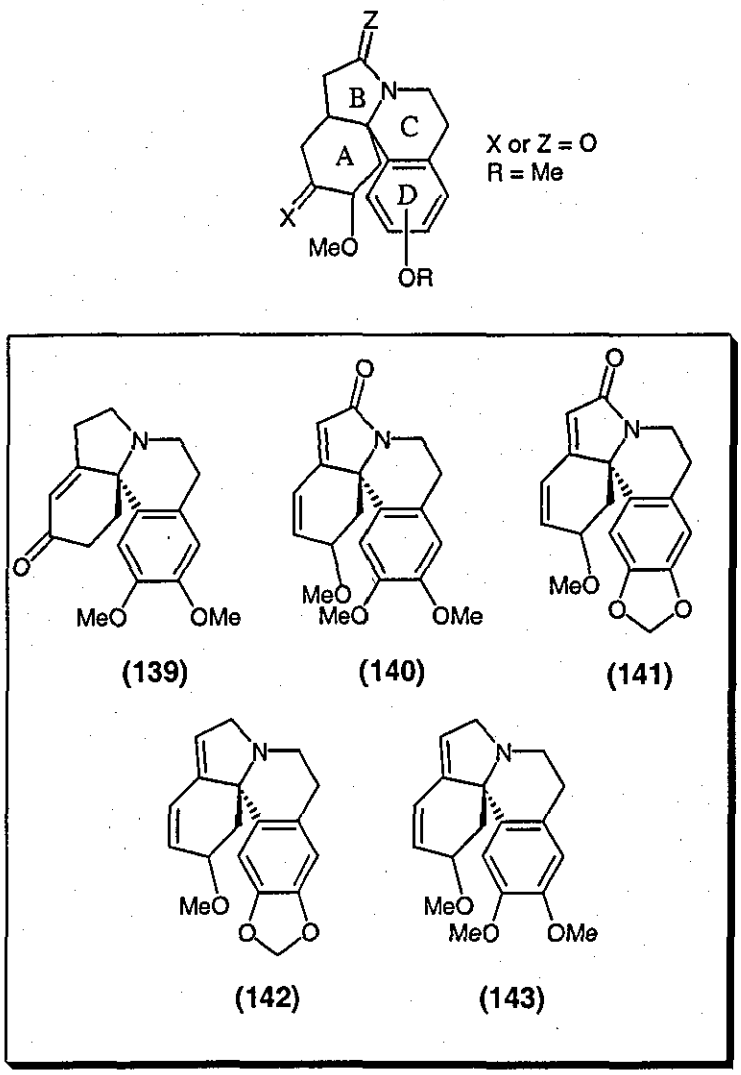


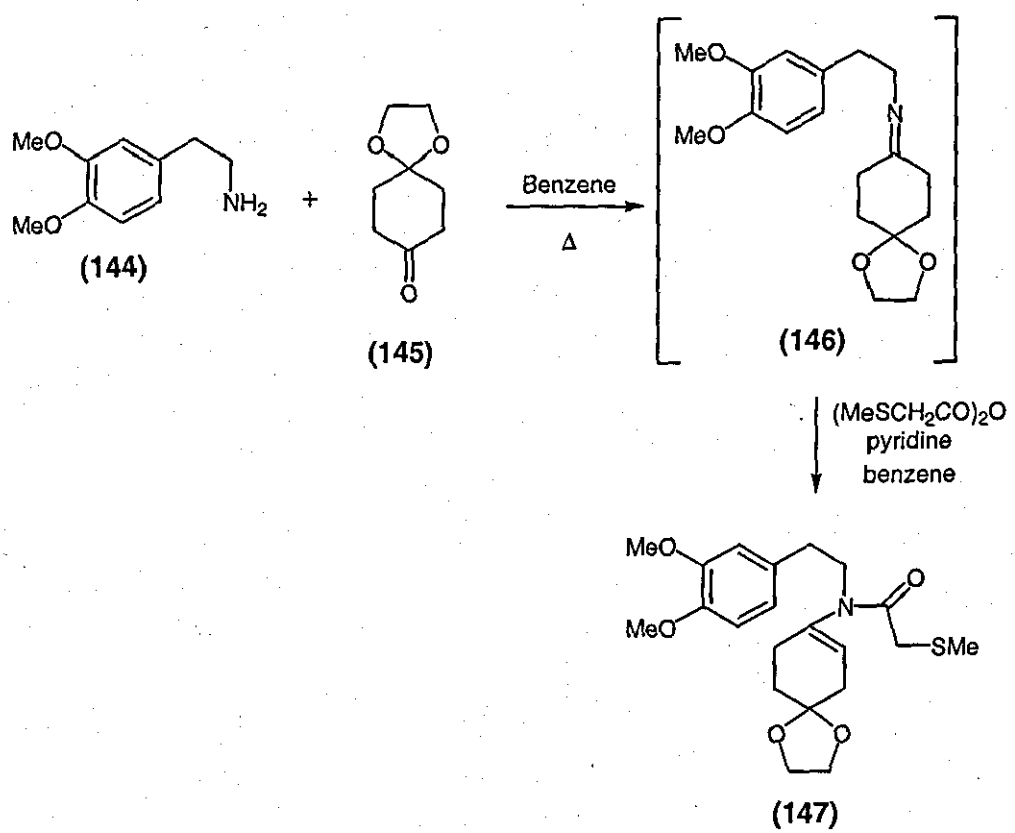
Figure 10

1.6.3. Synthesis of *erythrina* alkaloids

Over the last 40 years, numerous examples of synthetic approaches into the *erythrina* ring system have been developed,[84-86, 88-90, 91a-b] and a prominent theme has involved the generation of an *N*-acyliminium ion intermediate as a key step.

Ishibashi[85] succeeded in the synthesis of (±)-3-demethoxyerythratidinone **(139)** in nine steps and 37% overall yield from homoveratrylamine **(144)** and cyclohexane-1,4-dione monoethylene acetal **(145)** utilising *N*-acyliminium ion chemistry.

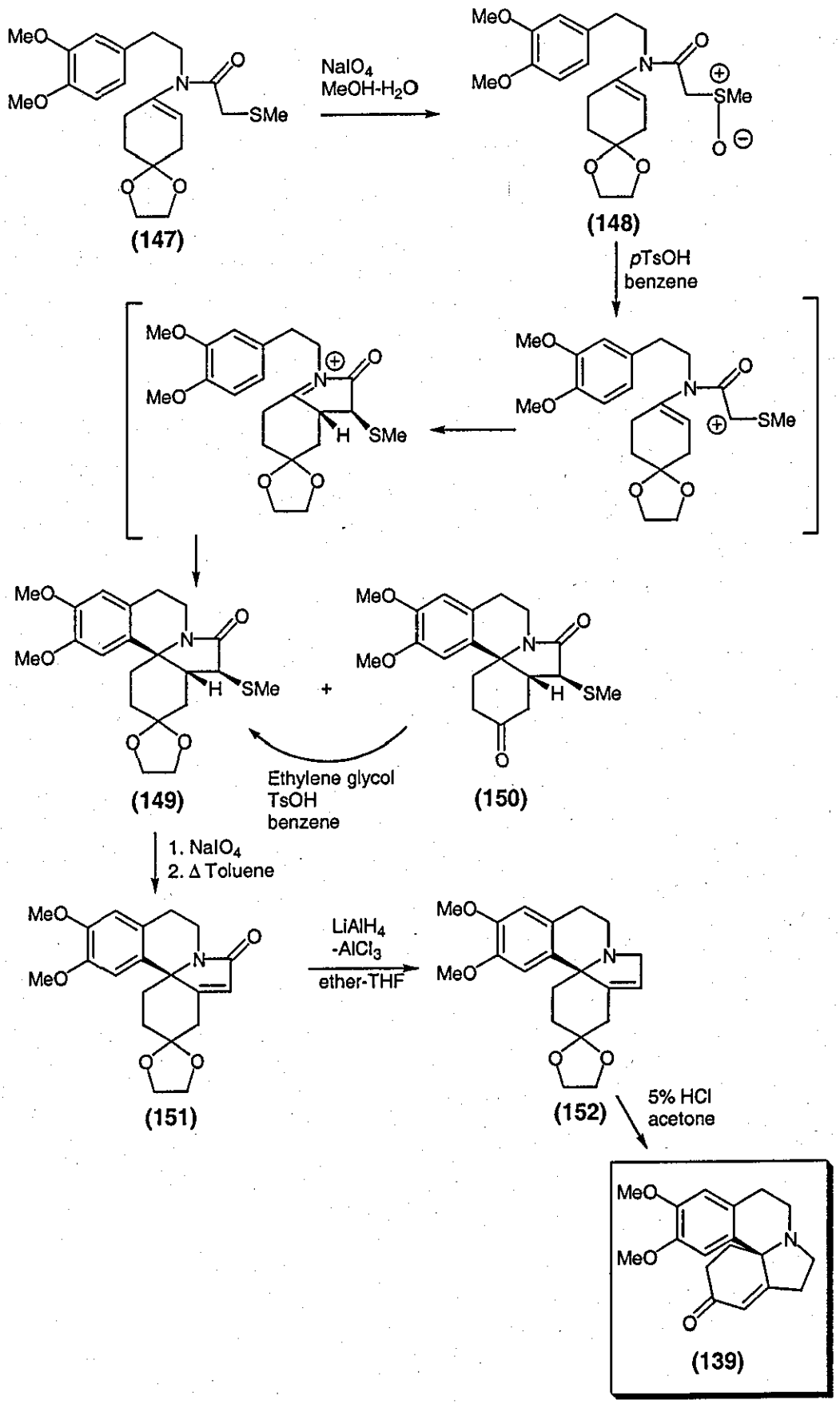
Heating (**144**) and (**145**) under Dean-Stark conditions followed by treatment of the resulting imine (**146**) with (methylthio)acetic anhydride and pyridine gave the acylenamide (**147**), (Scheme 48).



Scheme 48

Oxidation of (**147**) with sodium metaperiodate afforded the sulfoxide (**148**) which upon cyclisation with *p*-toluene sulfonic acid gave the erythrinane derivatives (**149**) and (**150**), the latter was re-protected with ethylene glycol under standard conditions yielding (**149**) in quantitative yield.

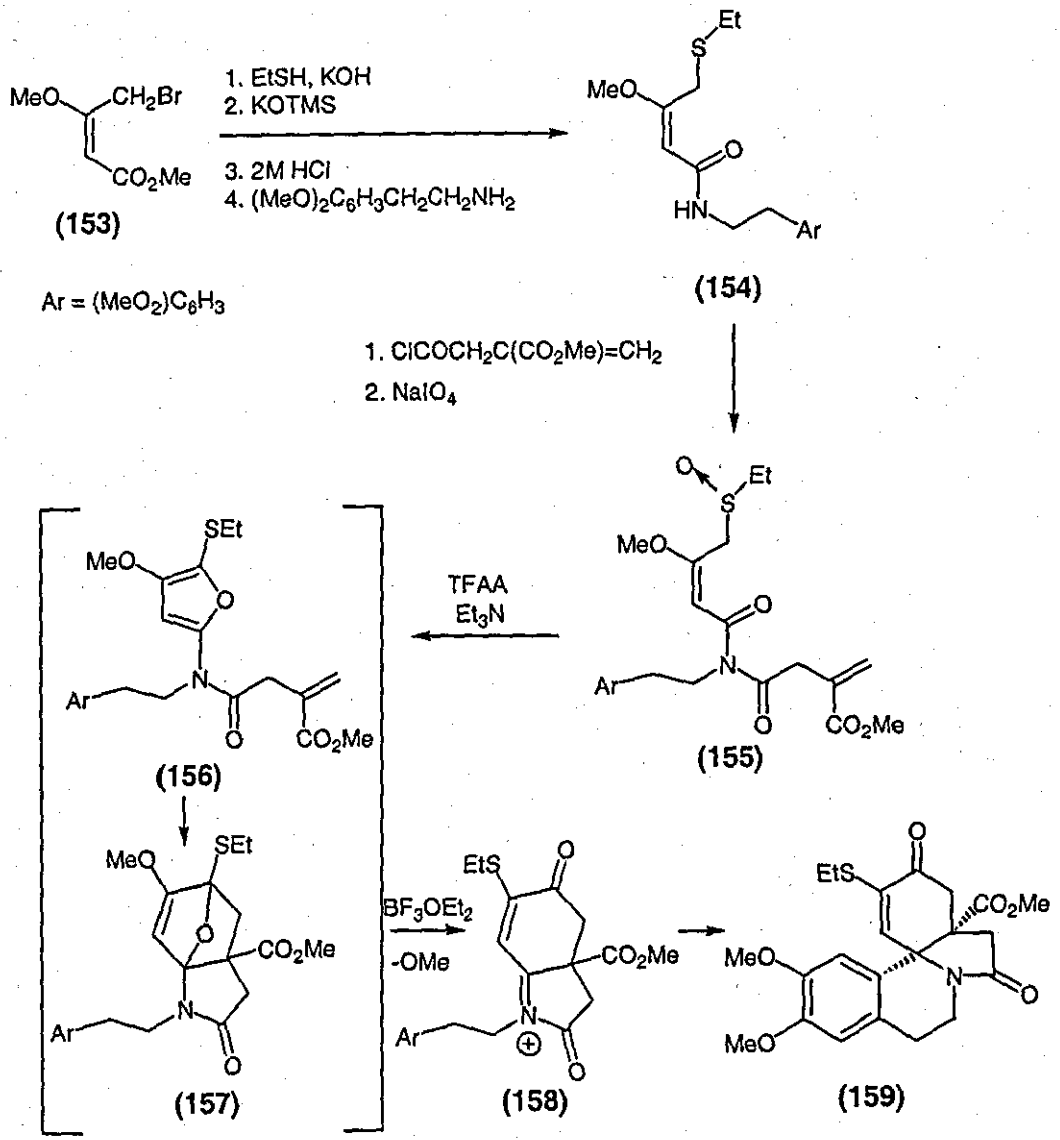
Sodium metaperiodate oxidation of compound (**149**) followed by refluxing the product in toluene gave the unsaturated lactam (**151**), which on reduction yielded the amine (**152**). This compound was then deprotected with 5% hydrochloric acid in acetone to furnish, with concomitant migration of the double bond, (±)-3-demethoxyerythratidinone (**139**), (Scheme 49).


MeO
MeO
N
O
SMe
(147)
NaIO4
MeOH-H2O
SMe
(148)
pTsOH
benzene
H
SMe
(149)
(150)
+
Ethylene glycol
TsOH
benzene
1. NaIO4
2. Δ Toluene
(151)
LiAlH4
-AlCl3
ether-THF
(152)
5% HCl
acetone
(139)

Scheme 49

Padwa[84] *et al* report a facile, stereocontrolled total synthesis of the *erythrina* alkaloid (±)-ersotramidine **(140)** involving a sequential combination of a Diels-Alder cycloaddition and *N*-acyliminium ion.

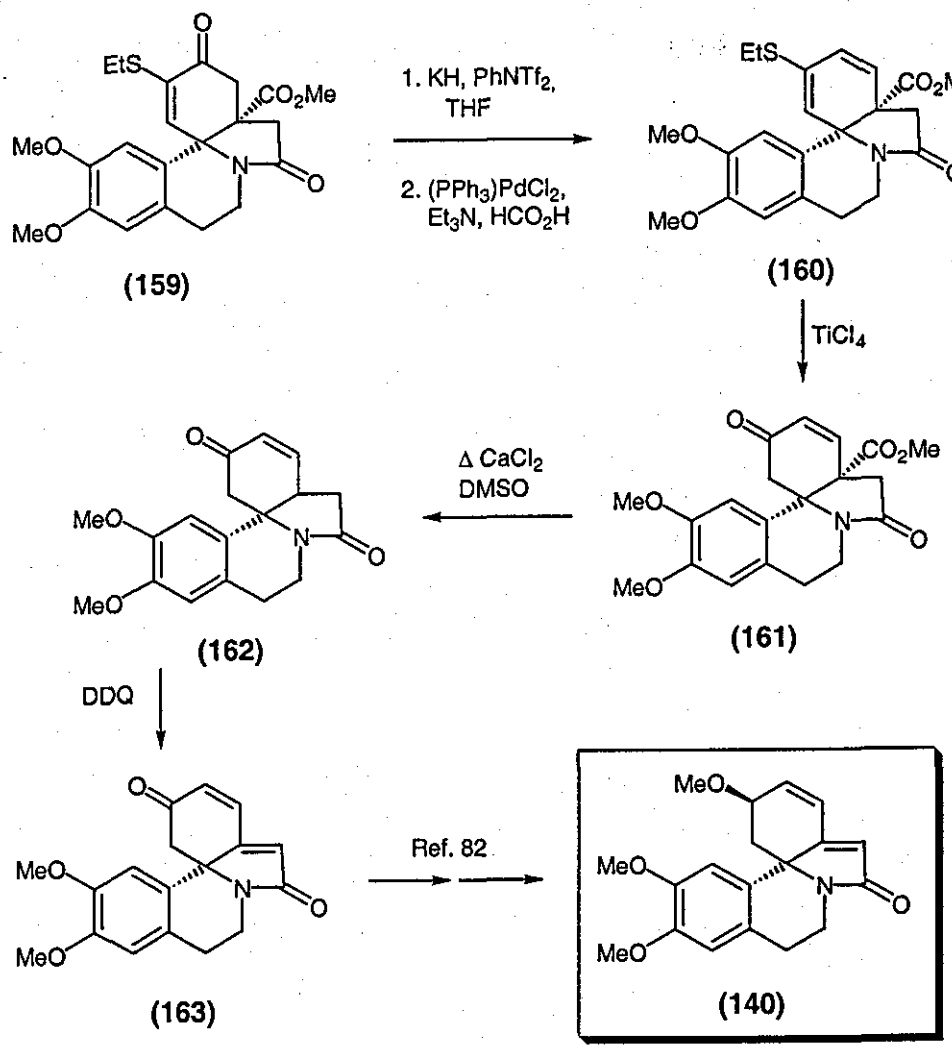
The starting imido sulfoxide **(155)**, possessing both a dienophilic and diactivated aromatic tether, was efficiently constructed from allylic bromide **(153)** *via* amide **(154)** in 82% yield. Cyclisation of **(155)** was initiated by adding trifluoroacetic anhydride and two equivalents of triethylamine affording the α-amido substituted furan intermediate **(156)**, (Scheme 50)



Scheme 50

Intermediate **(156)** underwent a subsequent intramolecular Diels-Alder cycloaddition across the tethered π-bond to give cycloaduct **(157)** that readily ring opens to generate the *N*-acyliminium ion **(158)**. Cyclisation of the aromatic π tether onto the *N*-acyliminium ion furnishes the tetracyclic amide **(159)**.

The thio-substituted diene **(160)** was synthesised by converting **(159)** into the corresponding vinyl triflate which, in turn, was subjected to a palladium catalysed reduction. Titanium mediated hydrolysis of **(160)** afforded ketone **(161)** in 54% yield, (Scheme 51).



Scheme 51

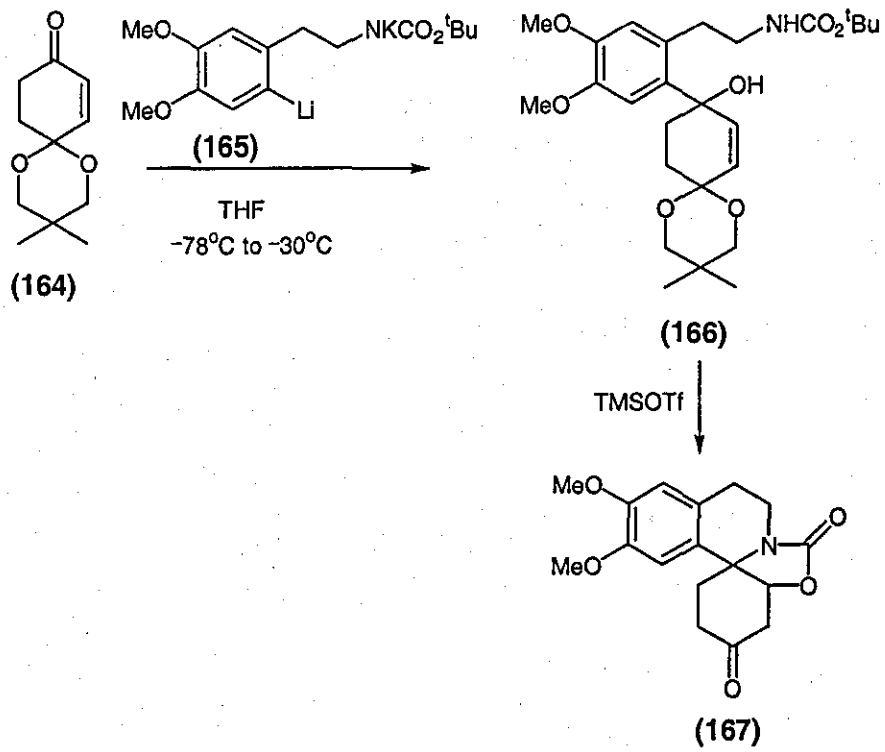
The total synthesis of (±)-ersotramidine **(140)** was completed by following the procedure used by Tsudo.[92] The methyl ester in **(161)** was smoothly

decarbomethoxylated on heating with calcium chloride in dimethylsulfoxide affording **(162)**, which upon oxidation gave the dienone **(163)**.

Stereoselective reduction of the enone, methylation and reductive removal of the lactam group gave the *erythrina* alkaloid **(140)**.

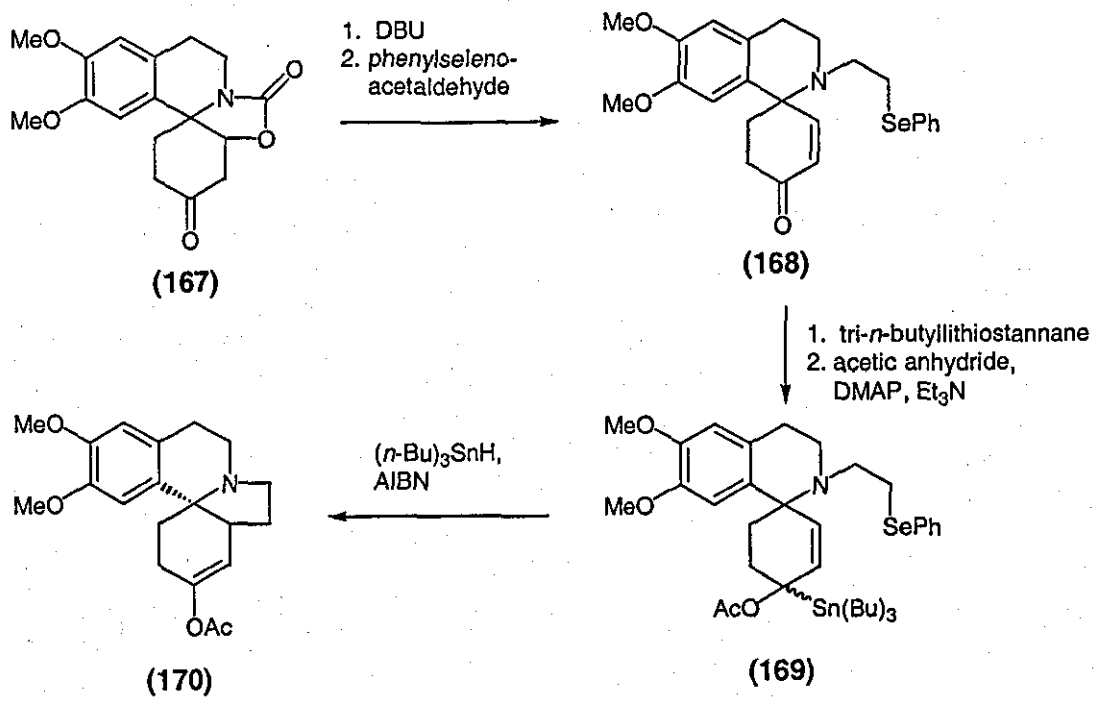
Danishefsky and Panek[86] propose an alternative synthesis of (±)-3-demethoxyerythratidinone **(139)** by demonstrating a radical cyclisation route.

The synthesis of starting materials **(164)** and **(165)** has been described by the group in the above referenced publication. Coupling of these materials afforded the tertiary alcohol **(166)** which undergoes transformation to **(167)** through the action of trimethylsilyltriflate in dichloromethane, (Scheme 52).



Scheme 52

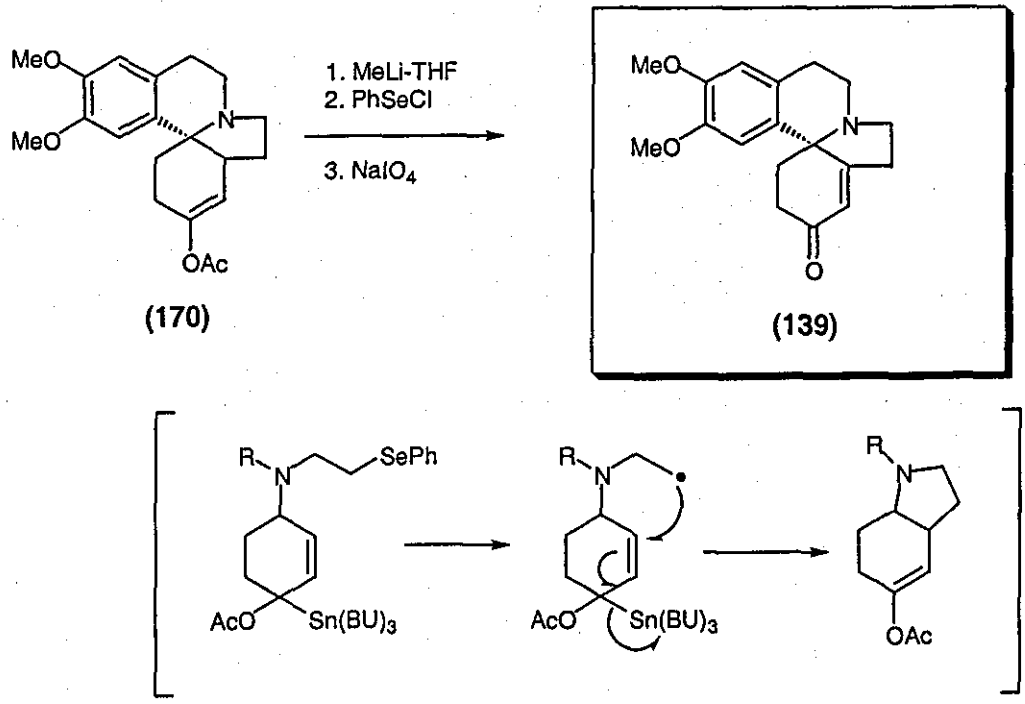
Treatment of **(167)** with DBU followed by reductive amination with phenylselenoacetaldehyde (using sodium cyanoborohydride) gave substrate **(168)**.



(167) (168) (169) (170)

Scheme 53

Treatment of **(168)** with tri-*n*-butyllithiostannane and immediate acetylation with acetic anhydride yielded **(169)** as a 1:1 mixture of stereoisomers. Further treatment of this with $(n\text{-Bu})_3SnH$ in the presence of catalytic AIBN afforded the precursor **(170)** in 65% yield as a single diastereoisomer, (Scheme 53).

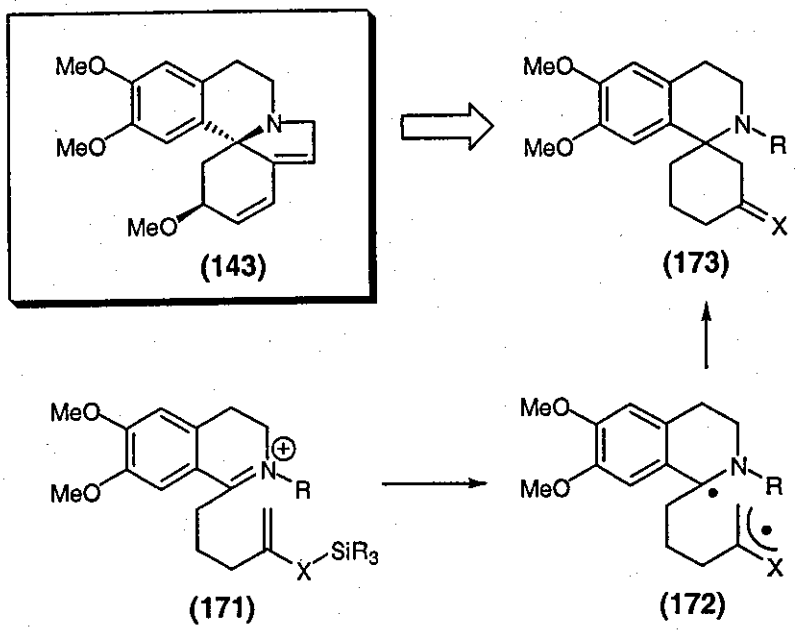


(170) (139)

Scheme 54

A final three-step sequence, as shown in Scheme 54, ultimately led to (±)-3-demethoxyerythratidinone (**139**) in 64% yield.

Ahmed-Schofield[90] has described a novel strategy for synthesis of the *erythrina* alkaloid family, featuring an electron-transfer-induced, photocyclisation process which is used to construct the spirocyclic tricyclic framework of these substances. Shown in Scheme 55 is a retrosynthetic analysis adopted by the group for the preparation of precursors of type (**173**) for the eventual synthesis of erysotrine (**143**).



Scheme 55

The synthesis of erysotrine (**143**) employs photocyclisation of appropriately substituted 1-(4-trimethylsilyl)methyl-4-pentenyl-3,4-dihydroisoquinolinium salts (**173**). Thus cyclisation of the diradical intermediate (**172**) generates the key spirocyclic substrate (**171**). Further functionality manipulation is required to complete the synthesis of the *erythrina* derivative.

Chapter Two

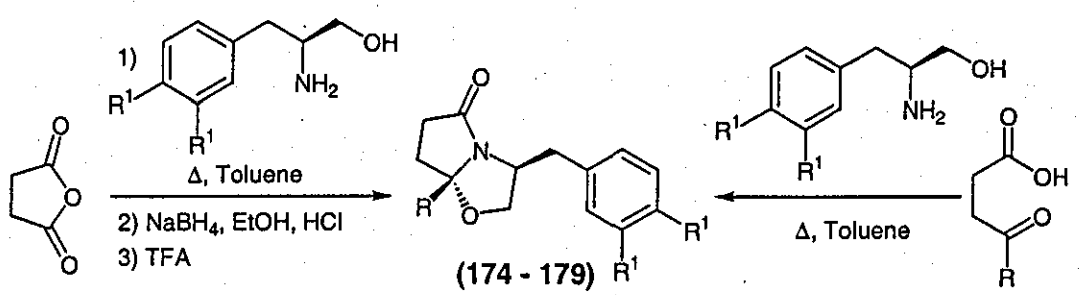
Results and Discussion

2.1. Stereoselective synthesis of chiral bicyclic lactams as *N*-acyliminium ion precursors

2.1.1. Introduction

The bicyclic lactams of Meyers have proven to be exceptional chiral templates for the construction of a wide variety of optically pure carbocycles and heterocycles. A vast number of papers have appeared addressing its application to the preparation of such systems, and notable advances continue to be made.

Over the past several years Meyers has demonstrated the synthetic utility of chiral, non-racemic, bicyclic lactams. Following the general methodology adopted by Meyers for the synthesis of such compounds, (Scheme 56), this section details the synthesis of novel chiral bicyclic lactams as *N*-acyliminium ion precursors for the asymmetric synthesis of nitrogen-containing heterocycles.



Scheme 56

2.1.2. Stereoselective synthesis of bicyclic lactams

It was proposed that lactams **(174 - 181)**, shown in Figure 11 and Table 5, could be prepared as described in the two general methods outlined above involving condensation of an optically pure amino alcohol and a dicarbonyl compound.

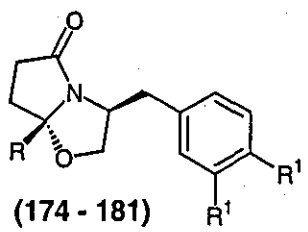


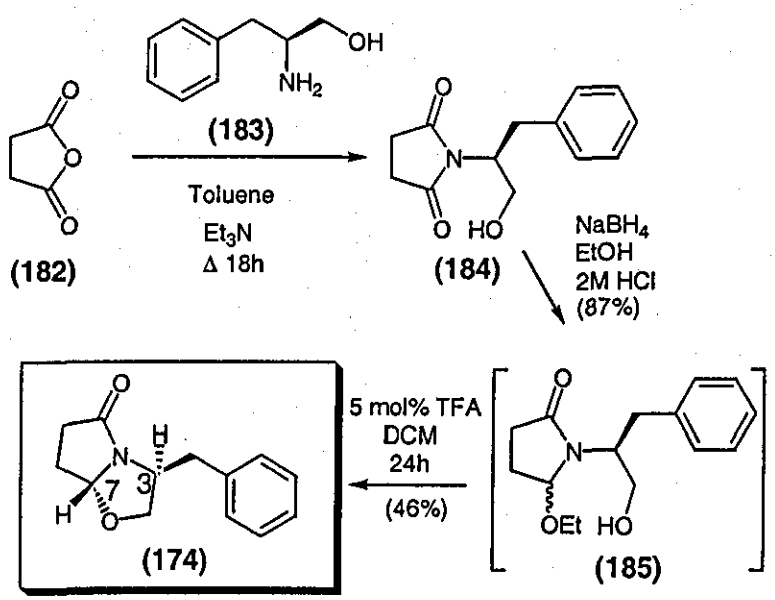
Figure 11

Lactam	R	R^1	Diastereoselectivity[a]	Yield (%)
(174)	H	H	exclusive	46
(175)	Me	H	exclusive	97
(176)	Ph	H	exclusive	88
(177)	Me	OMe	exclusive	81
(178)	Homoallyl	H	exclusive	85
(179)	Homoallyl	OMe	exclusive	77
(180)	Allyl	H	-	-
(181)	Vinyl	H	-	-

[a]Determined by crude 250 MHz ^{1}H NMR spectroscopy

Table 5: Synthesis of bicyclic lactams (174 – 181)

The method chosen for the synthesis of lactam **(174)** proceeded *via* a cyclic imide intermediate **(184)**.[15-16 ,53] This species was synthesised in good yield (87%) under relatively straightforward conditions. Equimolar amounts of commercially available succinic anhydride **(182)** and (*S*)-2-amino-3-phenyl-1-propanol **(183)** were heated at reflux in toluene for 18 hours (Scheme 57).



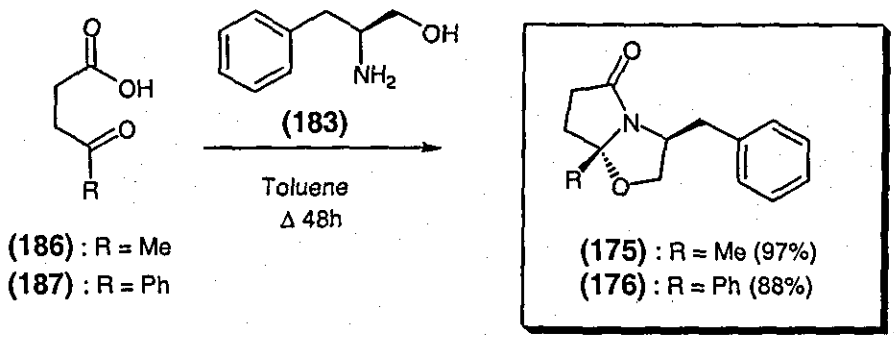
Scheme 57

Reduction of the cyclic imide **(184)** using sodium borohydride in ethanol afforded the ethoxy lactam intermediate **(185)** with sufficient purity to be used in

subsequent steps. Addition of trifluoroacetic acid in dichloromethane to this intermediate gave the target molecule.

The absence of an NOE between protons situated at positions 3 and 7 of product **(174)** is consistent with the expected structure,[53] suggesting the relative stereochemistry of the single product diastereoisomer was as indicated in product **(174)**.

Scheme 58 outlines the synthesis of bicyclic lactams **(175)** and **(176)**, obtained as single diastereoisomers in a one step condensation of (*S*)-2-amino-3-phenyl-1-propanol **(183)** with an equimolar amount of readily available levulinic acid **(186)** or 3-benzylpropionic acid **(187)** in toluene.

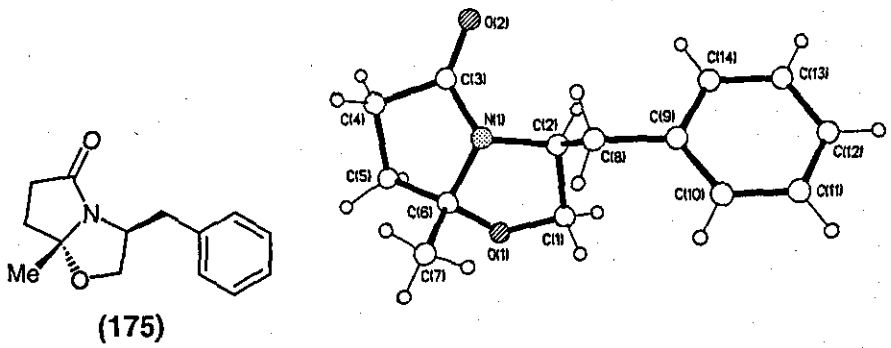


(186) : R = Me
(187) : R = Ph

(175) : R = Me (97%)
(176) : R = Ph (88%)

Scheme 58

An NOE study and single X-ray analysis was undertaken to confirm the relative stereochemistry of product **(175)** (Figure 12).



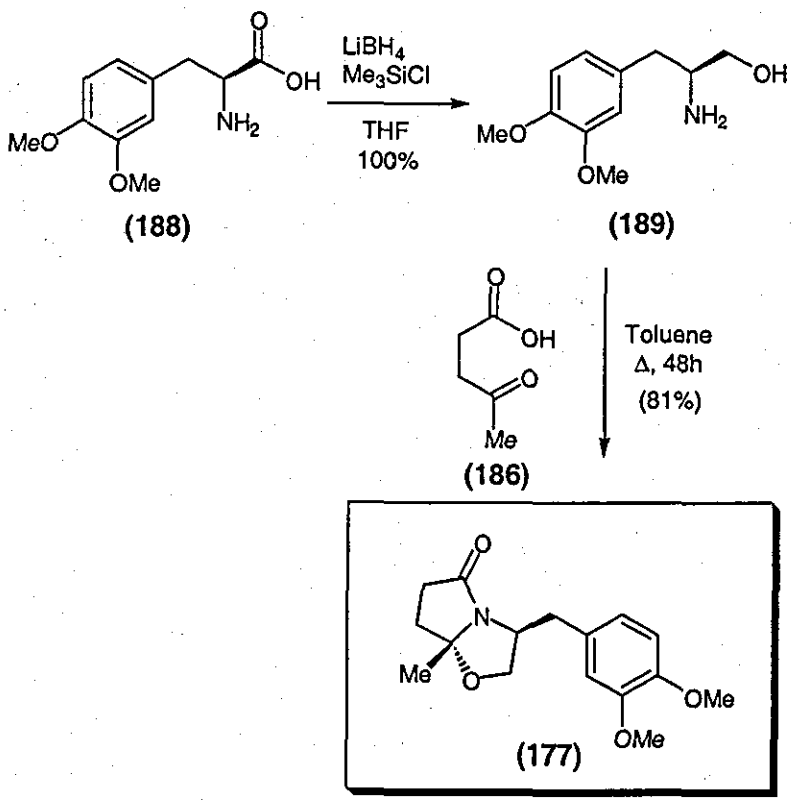
(175)

Figure 12

Optically pure β-amino alcohol and carboxylic acid precursors for the synthesis of lactams **(177 – 181)** are not commercially available; therefore, convenient literature procedures for their preparation were sought.

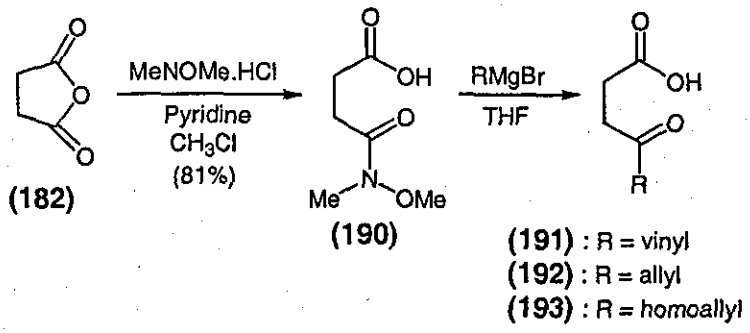
The β-amino alcohol **(189)** required for the preparation of **(177)** was synthesised in quantitative yield by reducing the commercially available amino acid, 3-(3,4-dimethoxyphenyl-*L*-alanine **(188)** with lithium borohydride in the presence of trimethylchlorosilane in tetrahydrofuran for 24 hours at room temperature.[93]

Condensation with levulinic acid **(186)** under Dean-Stark conditions in toluene for 48 hours gave 81% yield of the desired lactam **(177)** as a single diastereoisomer (Scheme 59).



Scheme 59

It has been reported[94a-c] that Grignard additions to Weinreb amides occurs readily and in very good yields, therefore our first approach towards the target carboxylic acids for the synthesis of **(178 – 181)** was based on this reaction (Scheme 60).



(182) (190)

(191) : R = vinyl
(192) : R = allyl
(193) : R = homoallyl

Scheme 60

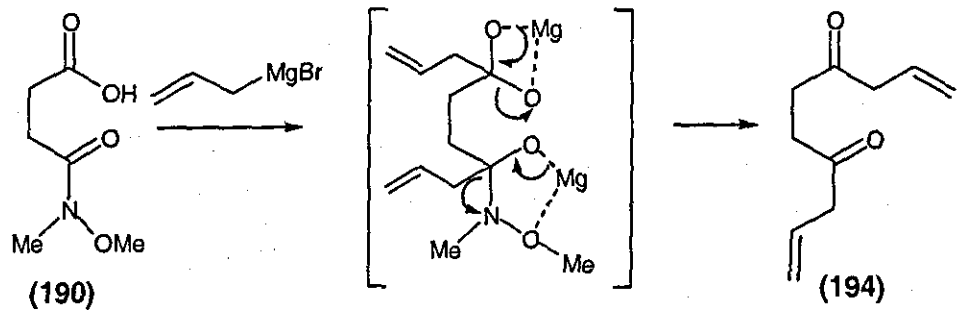
Synthesis of the Weinreb amide (**190**) from succinic anhydride (**182**) was carried out in good yield (81%). Using dichloromethane and triethylamine in place of chloroform and pyridine led to the desired product in poorer yields.

Carboxylic acid	Equiv. Grignard	Reaction time (h)	Yield (%)
(191)	3	24	38[a]
(192)	3	24	0
(192)	2	24	0
(192)	1	24	0
(193)	3	24	54[b]
(193)	3	2	55[b]

[a]Crude yield.
[b]Double addition occurs when homoallyl magnesiumbromide is used as the Grignard reagent in approx. 7% yield to form the diketone

Table 6: Synthesis of carboxylic acid precursors

With (**190**) in hand, attachment of the two, three and four carbon units was attempted. Table 6 shows the results obtained. Of the three Grignard reagents used, only addition of homoallyl magnesium bromide was successful. The more reactive/nucleophilic Grignard reagents gave very poor yields (vinyl magnesium bromide), or no desired product at all (allyl magnesium bromide). In the case of the latter reagent, formation of a diketone product, (**194**), occured and a possible mechanism is shown below (Scheme 61).

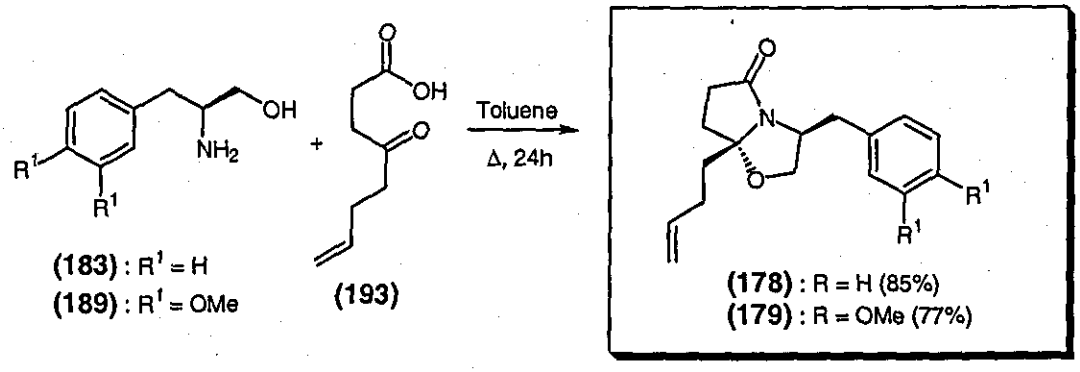


Scheme 61

Bicyclic lactams **(178)** and **(179)** were readily synthesised in good yields by a one-step condensation reaction of the respective (*S*)-amino alcohols with an equimolar amount of 4-oxo-oct-7-enoic acid **(193)** in toluene (Scheme 62).

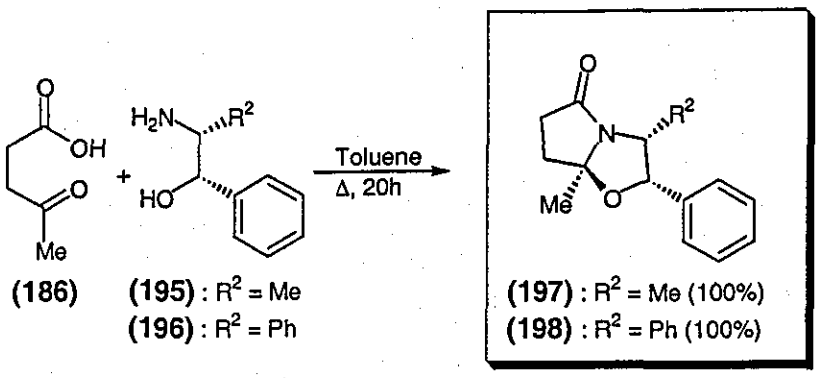
NOE analysis confirmed the relative stereochemistry of **(178)** and **(179)** as that shown.

Efforts to synthesise vinyl and allyl substituted carboxylic acid precursors were continued, and results are discussed in Section 2.1.4.



Scheme 62

A range of alternative substitution patterns were also available, as shown in Scheme 63. Synthesis of these chiral *N*-acyliminium ion precursors as single diastereoisomers was straightforward and followed the same reaction procedure for the preparation of bicyclic lactam **(175)**.

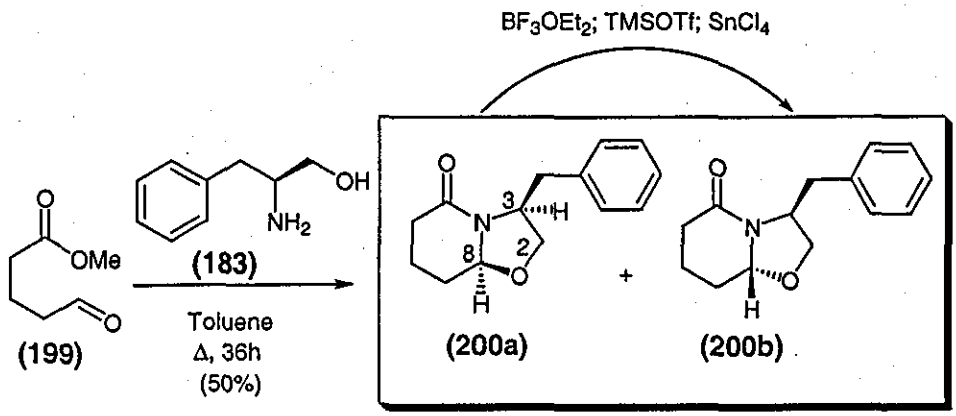


Scheme 63

Reacting levulinic acid **(186)** with either (1*S*,2*R*) norephedrine **(195)** or (1*S*,2*R*)-2-amino-1,2-diphenylethanol **(196)** under reflux in toluene afforded lactams **(197)** and **(198)** *respectively in quantitative yields.*

In addition to synthesising bicyclic lactams derived from β-amino alcohols *containing fused 5,5-ring systems, we have also prepared the corresponding* 5,6-system as a precursor in an *N*-acyliminium mediated cyclisation reaction leading to isoquinoline derivatives.

Synthesis of bicyclic lactam substrate **(200)** from (*S*)-2-amino-3-phenyl-1-propanol **(183)** followed the general method previously described by Amat.[76]



Scheme 64

Heating (*S*)-2-amino-3-phenyl-1-propanol **(183)** with methyl 5-oxopentanoate **(199)** in toluene at reflux under Dean-Stark conditions gave a 4 : 1 mixture of separable diastereoisomers **(200a)** and **(200b)**, respectively, in 50% overall yield (Scheme 64). The structure of the major diastereoisomer *cis* - **(200a)** was confirmed by NOE studies. Although no NOE was observed directly between protons H8 and H3, the stereoselectivity was determined to be *cis* since each gave a positive NOE to the same proton at C2 (3.5% for H8, 3.4% for H3).[95]

2.1.3. Stereoselective synthesis of unsaturated bicyclic lactams

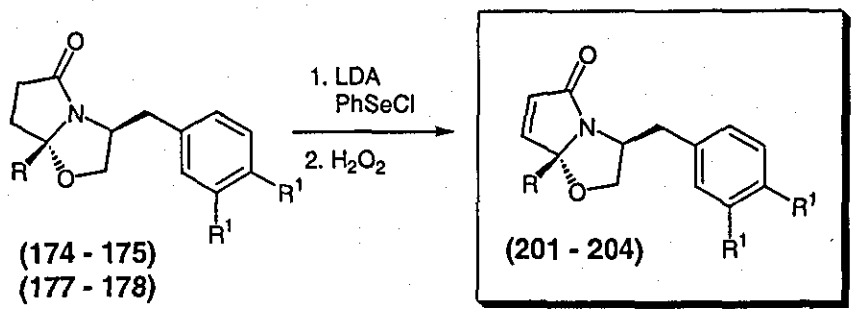
As has been discussed in section 1.5, the preparation of unsaturated carbonyl compounds from their corresponding saturated compound is a useful and important transformation in organic chemistry, and this process is most commonly carried out through *syn* elimination of appropriate selenoxides developed by Reich.[69] This method proved to be the most efficient way of synthesising the target unsaturated lactam systems (Table 7 and Scheme 65).

Lactam	R	R^1	Diastereoselectivity[a]	Yield (%)
(201)	H	H	exclusive	21[b]
(202)	Me	H	exclusive	51
(203)	Me	OMe	exclusive	36
(204)	homoallyl	H	exclusive	54

[a]Determined by crude 250 MHz ^{1}H NMR spectroscopy

[b]Recovered 11% saturated lactam and 6% of unknown by-product

Table 7: Synthesis of unsaturated bicyclic lactam precursors (201 - 204)

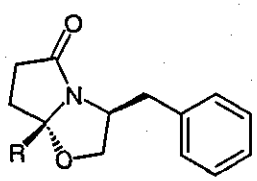


Scheme 65

Meyers'[70] route avoiding the use of toxic selenium was unsuccessful when applied to our lactams giving yields of <10%. Isolation of the selenyl intermediate in the method adopted by Amat and Bosch[96] caused loss in yields and was time consuming and unproductive.

Preparing *N*-acyliminium ion precursors (**201 - 204**) provided a handle for further derivatisation, either on these systems directly, as discussed previously in section 1.5, or on compounds synthesised from these systems. The latter is discussed in Section 2.2.3.

2.1.4. Further studies on the synthesis of bicyclic lactams

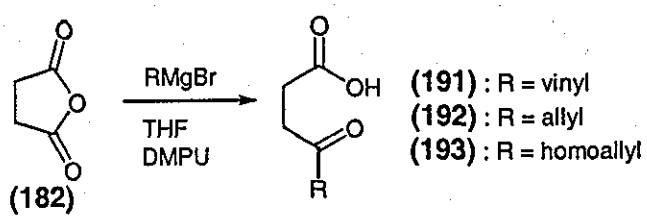


(180) : R = allyl
(181) : R = vinyl

Figure 13

The preparation of allyl and vinyl substituted carboxylic acid precursors for the synthesis of the desired bicyclic lactams **(180)** and **(181)** as shown in Figure 13, has proved problematic.

A number of different methods for the synthesis of the desired acid starting materials have been carried out, with little success.



(182)

(191) : R = vinyl
(192) : R = allyl
(193) : R = homoallyl

Scheme 66

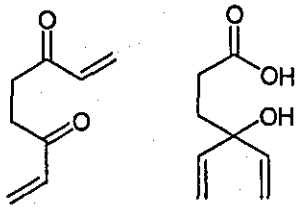
Martin Newcomb[97] and co-workers have shown that direct addition of homoallyl magnesium bromide to succinic anhydride **(182)** gives carboxylic acid **(193)** in 40% yield (Scheme 66).

We decided to follow this procedure using vinyl and allyl magnesium bromide as reagents in an attempt to synthesise the corresponding vinyl and allyl carboxylic acids, **(191)** and **(192)**.

Table 8 shows the results obtained. Purification of carboxylic acid **(191)** revealed the formation of **(205)** and **(206)** only (Figure 14). In the case of carboxylic acid **(192)**, the major product observed was the diketone **(194)** as shown in Scheme 61.

Carboxylic acid	Equiv. Grignard	Reaction time (h)	Yield (%)
(191)	1	6	0
(192)	1	6	11

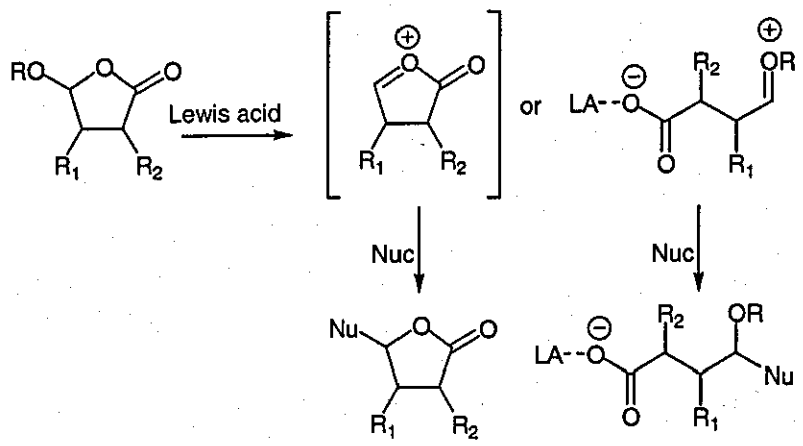
Table 8: Synthesis of carboxylic acid precursors



(205) **(206)**

Figure 14

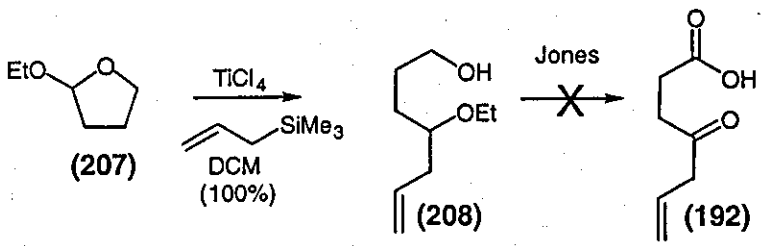
Feringa[98] *et al* have examined Lewis acid mediated nucleophilic additions to oxycarbenium ions derived from cyclic *O,O*-acetals (Scheme 67).



Scheme 67

As an alternative route towards the synthesis of our carboxylic acids we followed Feringa's methodology using ethoxytetrahydrofuran, **(207)**, titanium tetrachloride and allyltrimethylsilane (Scheme 68).

On obtaining **(208)** we hoped to oxidise both the alcohol and the ether to the corresponding acid and ketone. Chromium reagents have been used for such transformations with great success. Pinnick[99] *et al* have oxidised benzyl ethers to their corresponding ketones using Jones reagent in excess. Oxidation of **(208)** with Jones reagent was unsuccessful, unknown impurities can be seen in the crude ^{1}H NMR.



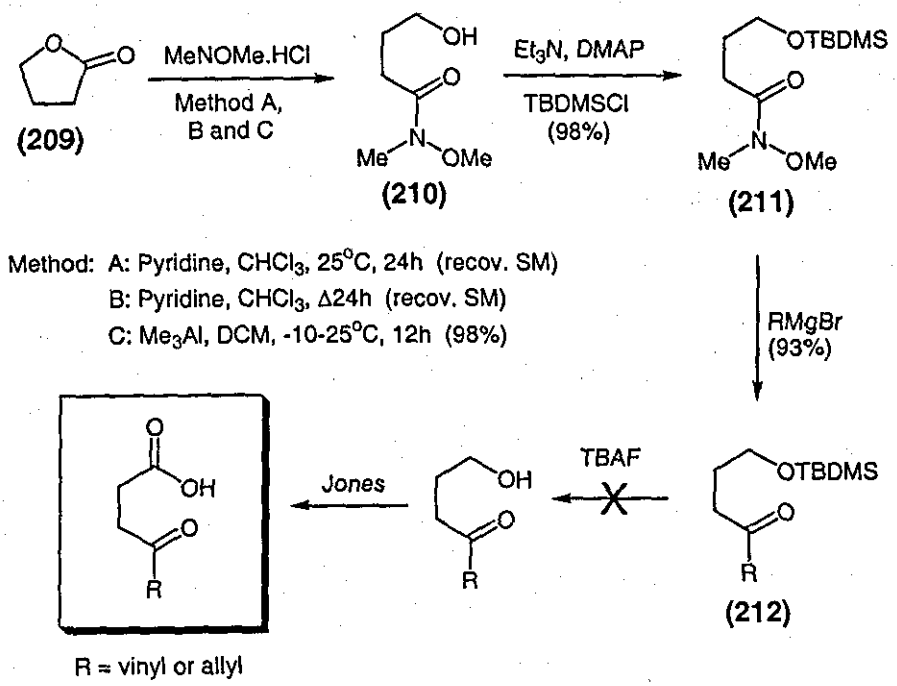
Scheme 68

The mechanism shown in Scheme 61 shows Grignard attack at both the acid, and amide groups within the Weinreb amide **(190)**. This is not entirely unexpected due to the very nucleophilic nature of the allyl magnesium bromide Grignard reagent. To overcome this problem the strategy outlined in Scheme 69 was proposed.

Treatment of the lactone **(209)** with the aluminum salt of methoxymethylamine afforded the Weinreb amide **(210)** in excellent yield. Protection of the primary

hydroxyl function of **(210)** with *tert*-butyldimethylchlorosilane (TBDMS-Cl) followed by Grignard reaction with allyl magnesium bromide afforded the respective ketone **(212)**. Addition of vinyl magnesium bromide proved unsuccessful.

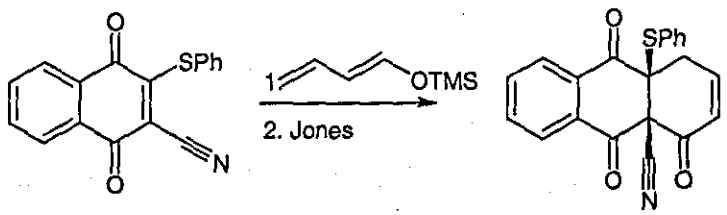
Decomposition of **(212)** occurred during purification by flash column chromatography, therefore removal of the TBDMS group was attempted on crude **(212)**.



Scheme 69

The usual method of choice for unmasking silyl ethers has employed tetra-*n*-butyl ammonium fluoride in tetrahydrofuran, however, base-induced desilylation caused decomposition of the product (sodium hydroxide was also tried as an alternative method of removal[100]). Acid mediated silyl ether cleavage[100-101] also resulted in the decomposition of the product.

Kraus and co-workers[102] have reported a successful -OTMS deprotection and subsequent oxidation using Jones' reagent (Scheme 70). Decomposition also occurred when following this methodology.

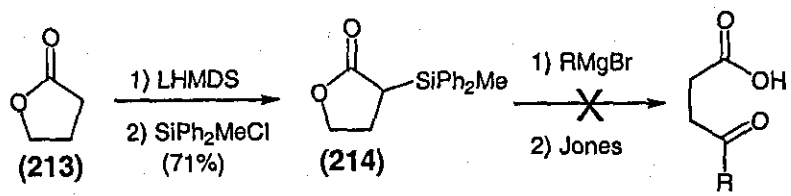


Scheme 70

Interestingly, when using potassium chlorochromate as the oxidising agent, traces of the aldehyde were seen in NMR studies implying that removal of the protecting group had occurred. This perhaps suggests that either Jones' reagent is "too strongly" acidic causing *decomposition* of **(212)**, or that the carboxylic acid **(192)** when formed is unstable.

Scheme 71 outlines a general method adopted by Larson[103a-c] *et al*, who have reported the synthesis of 4-oxo carboxylic acids from α-silyl lactones, **(214)**. These lactones are readily synthesised in good yields from γ-butyrolactone, **(213)**, and diphenylmethylchlorosilane in tetrahydrofuran.

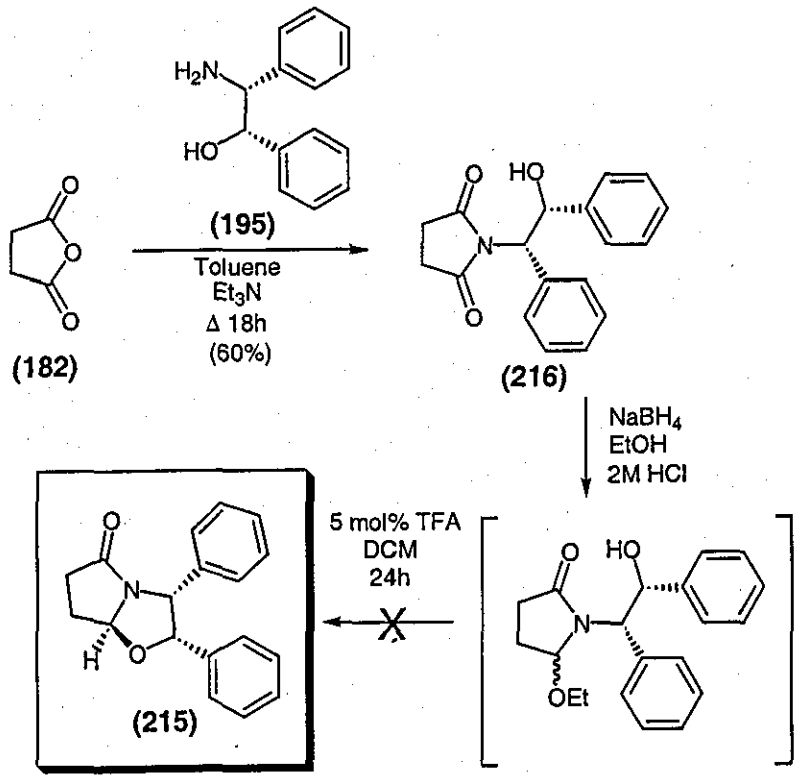
However, oxidation under Larsons conditions using Jones reagent was again unsuccessful.



Scheme 71

It was decided that future efforts would be directed towards the subsequent reactions of lactams **(174 – 179)** and, therefore, further studies on the synthesis of lactams **(180)** and **(181)** were not continued.

We attempted to synthesise lactam **(215)** *via* the method adopted previously to prepare bicyclic lactams **(174)** and **(201)** (Scheme 72).



Scheme 72

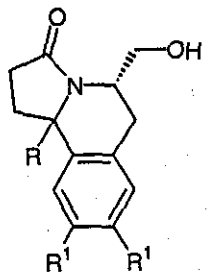
Cyclic imide (**216**) was prepared in 65% yield from succinic anhydride (**182**) and (1*S*,2*R*)-2-amino-1,2-diphenyl ethanol (**195**). Sodium borohydride reduction of (**216**) followed by treatment of the expected ethoxy intermediate with trifluoroacetic acid did not lead to the proposed lactam (**215**). There was no reaction observed and starting materials were reclaimed.

2.2. Asymmetric intramolecular reactions of chiral *N*-acyliminium ion precursors

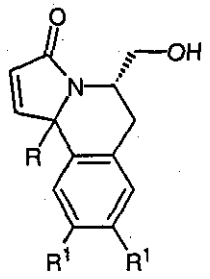
2.2.1. Introduction

Pyrroloisoquinoline ring systems (**217 - 222**) and the related unsaturated derivatives (**242 – 244**) are suitable intermediates for the synthesis of the *erythrina* alkaloid group of natural products, properties of which have been discussed in Section 1.6.2. There has been much interest in the synthesis of pyrroloisoquinolines over recent

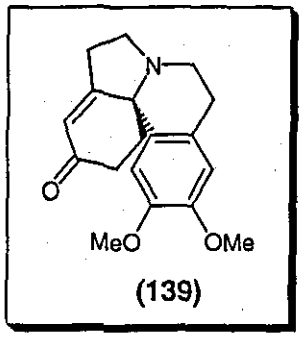
years, with many approaches involving *N*-acyliminium cyclisation as a key ring-forming step.[25-29, 66, 84]



(217 - 222)



(242 - 244)



(139)

Figure 15

Based on our groups novel stereoselective approach to the isoindoloisoquinoline ring system[22] we reasoned that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the target pyrroloisoquinolines.

This application, as a precursor in an intramolecular *N*-acyliminium mediated cyclisation reaction leading to the pyrroloisoquinoline targets, represents a novel application of the popular Meyers chiral lactam templates.

2.2.2. Stereoselective synthesis of pyrroloisoquinolines

Pyrroloisoquinoline	R	R^1	Diastereoselectivity[a]	Yield (%)[b]
(217)	H	H	exclusive	83
(218)	H	OMe	exclusive	91
(219)	Me	H	2 : 1	53
(220)	Me	OMe	2 : 1	69
(221)	homoallyl	H	5 : 1	42
(222)	homoallyl	OMe	5 : 1	54

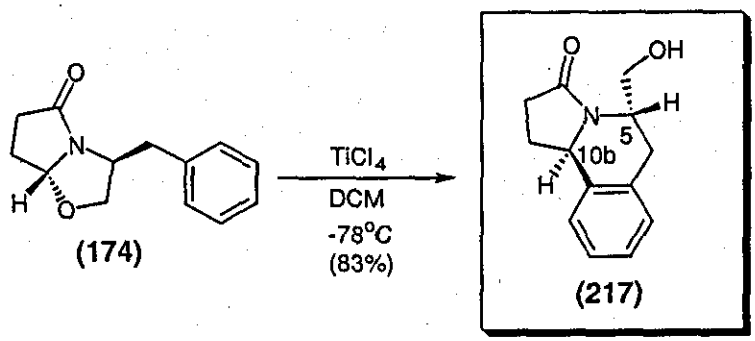
[a]Determined by crude 250MHz ^{1}H NMR spectroscopy

[b]Isolated yield of major isomer

Table 8: Synthesis of pyrroloisoquinolines (217 – 222)

With lactam (**174**) in hand, we turned to the proposed intramolecular *N*-acyliminuim cyclisation study (Scheme 73).

On treating (**174**) with titanium tetrachloride as a Lewis acid activator at –78 °C in dichloromethane for 20 hours, we were pleased to isolate the cyclised product, (**217**), in 53% yield. ^{1}H NMR analysis of the crude reaction mixture revealed the formation of only one product diastereoisomer.



Scheme 73

An NOE study was undertaken and the absence of an NOE between protons situated at positions 5 and 10b suggests that, as expected,[22] the relative stereochemistry of the single product diastereoisomer was as indicated in product (**217**), with inversion of stereochemistry at the newly created chiral centre.

Since the cyclisation of substrate (**174**) gave exclusively one diastereoisomer, a comparative NOE study on the minor isomer could not be carried out. This result is in agreement with recent results from Katritzky[25] (Figure 16).

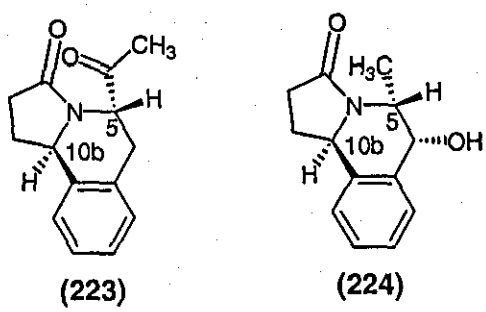
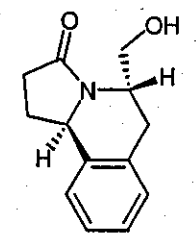


Figure 16

The absolute configuration at position 10b for **(223)** and **(224)** was further determined by NOE experiments. When the hydrogen at position 10b of **(223)** and **(224)** was irradiated, no significant NOE effect was observed for H5, suggesting that H10b and H5 are located in a *trans*-orientation.

Single crystal X-ray analysis was also undertaken to confirm the relative stereochemistry of product **(217)** (Figure 17).



(217)

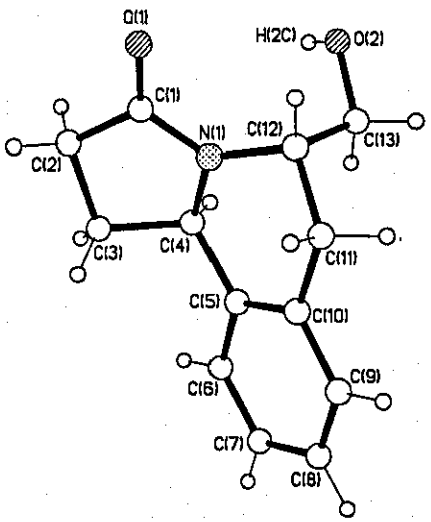
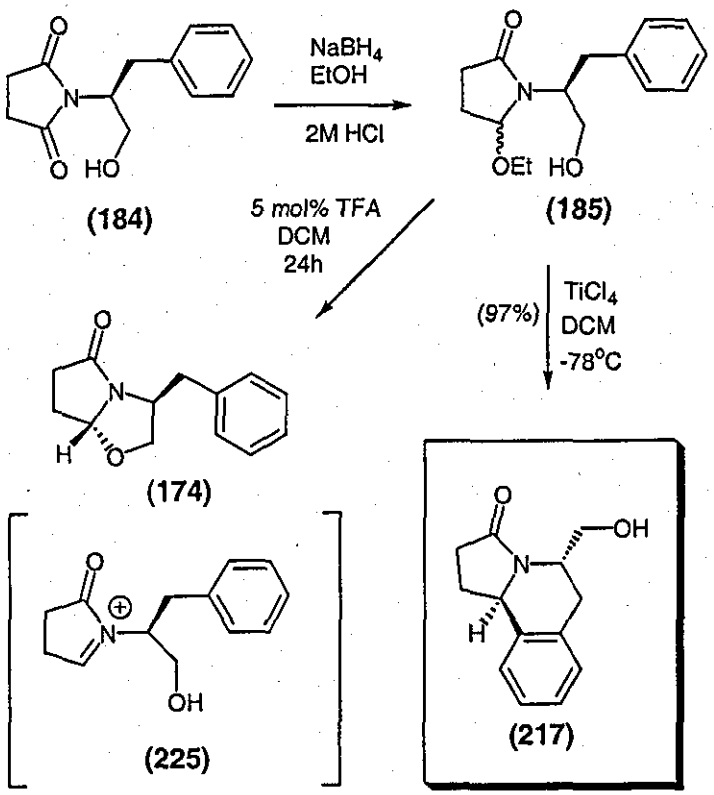


Figure 17

Other Lewis acids gave a similarly high level of diastereoselectivity in the cyclisation reaction (trimethylsilyltriflate, tin tetrachloride) with only boron trifluoride etherate giving no cyclisation product, and in this case the starting material was re-isolated.

We were interested to find that access to cyclised product (**217**) was available *via* a more direct route. The synthetic protocol followed to access the bicyclic lactam substrate (**217**) is highlighted in Scheme 74.

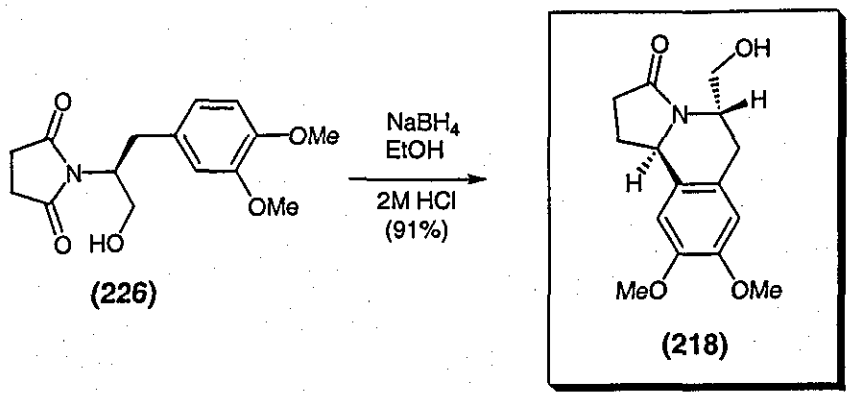


Scheme 74

Following reduction of the imide (**184**) with sodium borohydride in ethanol, the corresponding ethoxylactam (**185**) was cyclised under protic acid catalysis to generate the bicyclic lactam (**174**). Under these conditions no sign of cyclisation to product (**217**) was observed. However, when the ethoxy lactam intermediate was treated with titanium tetrachloride directly, clean conversion to yield only (**217**) was observed.

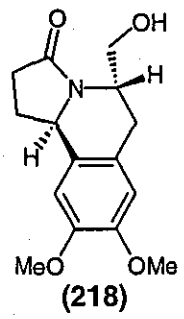
Presumably cyclisation to yield products (**174**) and (**217**) proceeded *via* the same *N*-acyliminium ion intermediate (**225**).

This methodology was applied to the synthesis of substituted pyrroloisoquinoline (**218**), synthesised from imide (**226**) as shown in Scheme 75.



Scheme 75

Subjecting imide **(226)** to a typical sodium borohydride reduction as described in Scheme 74, *en route* to the expected ethoxylactam precursor of the corresponding bicyclic lactam, resulted in direct and highly stereoselective cyclisation to **(218)** in excellent yield (91%).



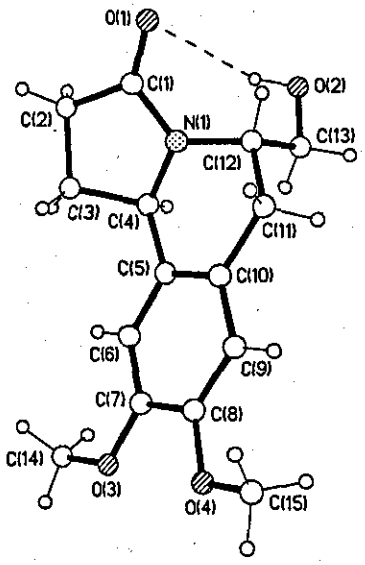


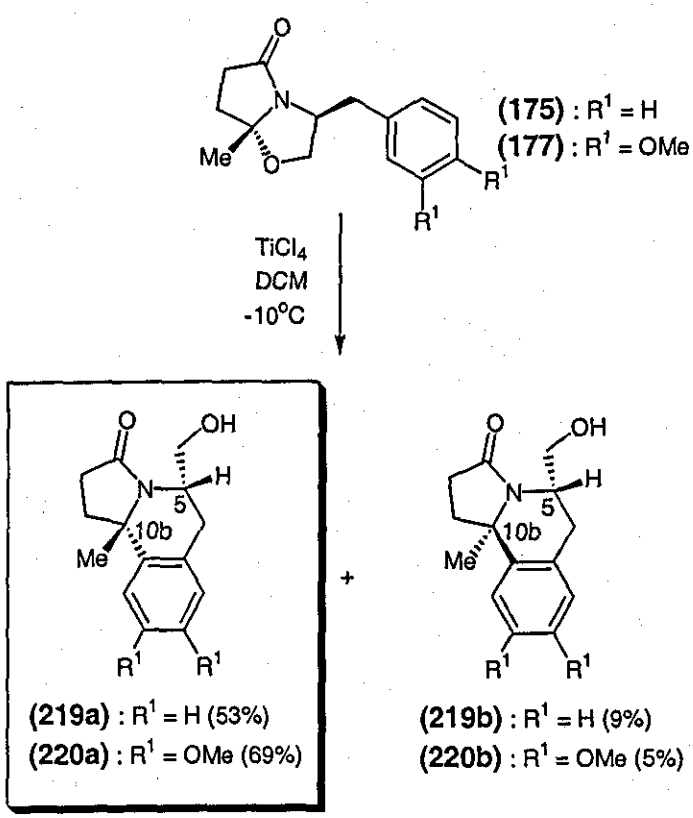
Figure 18

Presumably, under the acidic reaction conditions, the more nucleophilic methoxy-substituted aryl ring is able to cyclise onto the *N*-acyliminium intermediate that may be generated *in situ*. In this case, we were able to confirm the relative stereochemistry of this product by single crystal X-ray analysis (Figure 18).

Interestingly, the X-ray data revealed that **(218)** forms H-bonded chains *via* the hydroxy *OH* and carbonyl groups on neighbouring molecules [*OH*···O' = 1.87(2) Å, <O-H-O' = 164(2)°].

A lower level of diastereoselectivity was observed on cyclisation of the corresponding methyl-substituted substrates **(175)** and **(177)**.

In this case, treatment with titanium tetrachloride under our standard conditions led to a mixture of product diastereoisomers in 87% and 91% yield respectively, with a diastereoselectivity of 2 : 1, (Scheme 76).



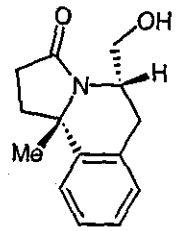
Scheme 76

Separation of the diastereoisomers was achieved by flash column chromatography, and the relative stereochemistry of the major isomer was investigated by NOE techniques and found to be as indicated in products **(219a)** and **(220a)** – these products having been formed with "retention" of stereochemistry, in contrast to the reaction of substrate **(174)**.

We were able to perform a set of comparative NOE studies on the separable diastereomeric products **(219a)** and **(219b)**. In the case of **(219a)** an NOE was observed between the methyl group at position 10b and the proton at position 5. In the case of the minor diastereoisomer **(219b)**, no NOE was observed.

Both results are in accord with predicted structures for the isolated diastereoisomers, and with the recent publication by Lete.[66]

The relative stereochemistry of **(219a)** was also determined by X-ray crystallography as illustrated in Figure 19.



(219a)

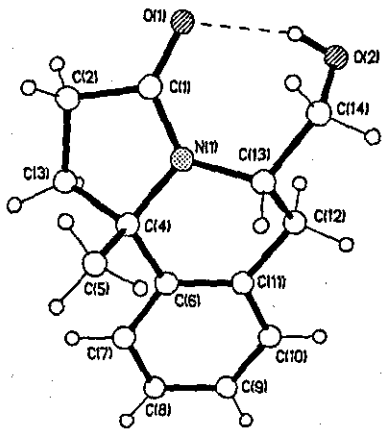


Figure 19

Lete[66] also has a keen interest in the synthesis of pyrroloisoquinolines of type **(219a)** and has undertaken NOE studies on the major diastereoisomer observing an NOE between the methyl group at position 10b and the proton at position 5 (Figure 20).

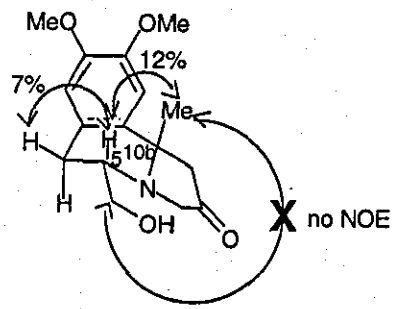
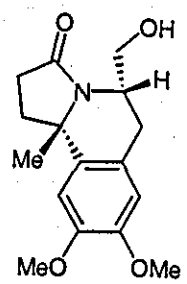


Figure 20

Lowering the reaction temperature to –78 °C did not lead to an increase in product diastereoselectivity.



(220a)

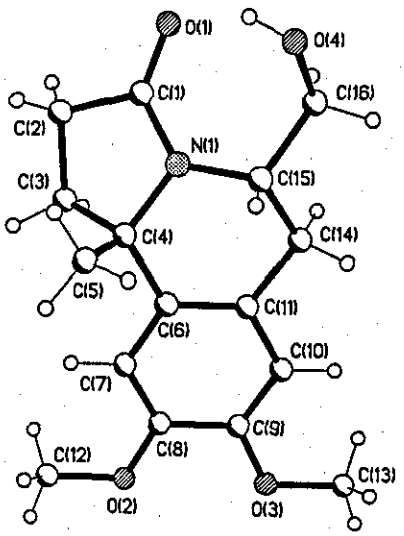
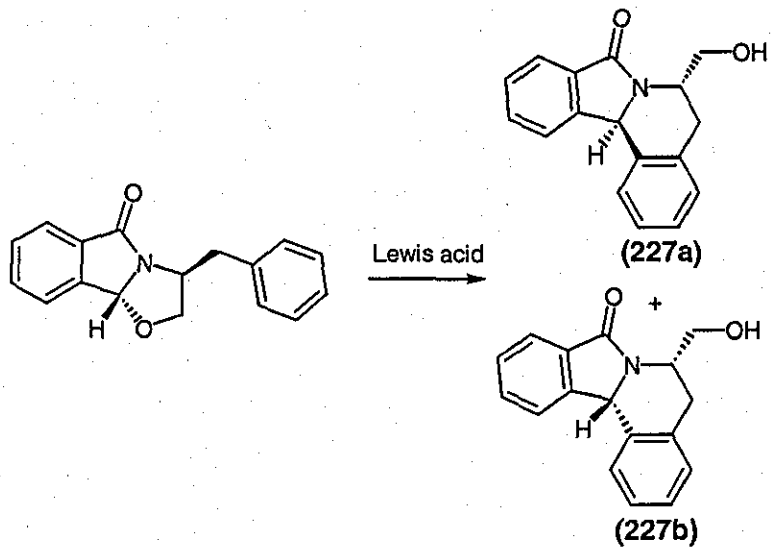


Figure 21

The relative stereochemistry of **(220a)** was determined by X-ray crystallography as illustrated in Figure 21. Compound **(220a)** forms an intramolecular hydrogen bond, similar to that in **(218)**, (O*H*...O' = 1.87(2) Å, <O-H-O' = 154(2)°).



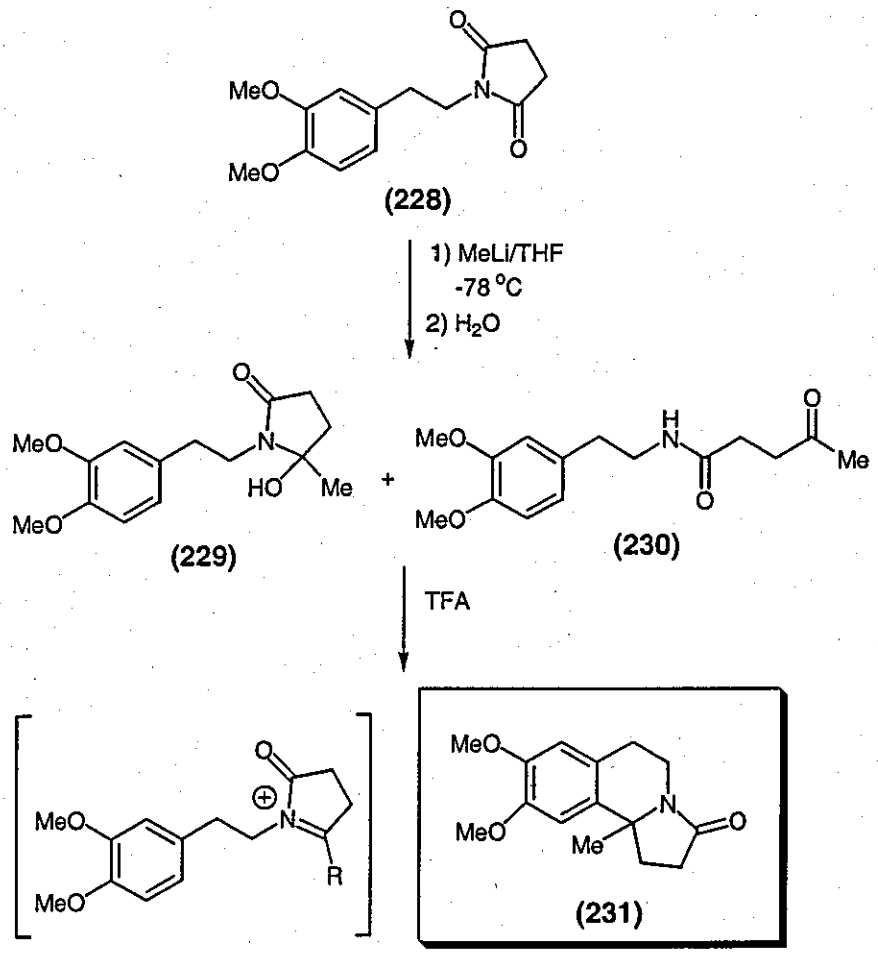
Scheme 77

In line with previous studies on the related isoindoloisoquinoline system,[22] we attempted the same cyclisation reaction as shown in Scheme 76 replacing titanium tetrachloride with trimethylsilyltriflate, expecting perhaps a similar increase in diastereoselectivity as noted for the isoindoloisoquinolines **(227a)** and **(227b)** (Scheme 77, Table 9).

Entry	Activator	Yield, (227) (%)	(227a) : (227b)
1	$SnCl_4$	98	2 : 1
2	$TiCl_4$	93	2 : 1
3	BF_3OEt_2	99	3 : 1
4	H_2SO_4	80	6 : 1
5	TMSOTf	97	≥ 49 : 1

Table 9: *N*-acyliminium cyclisation to products (227a) and (227b)

Unfortunately, cyclisation of lactams **(175)** and **(177)** using trimethylsilyltriflate as activator was unsuccessful. In this case, starting material was re-isolated.



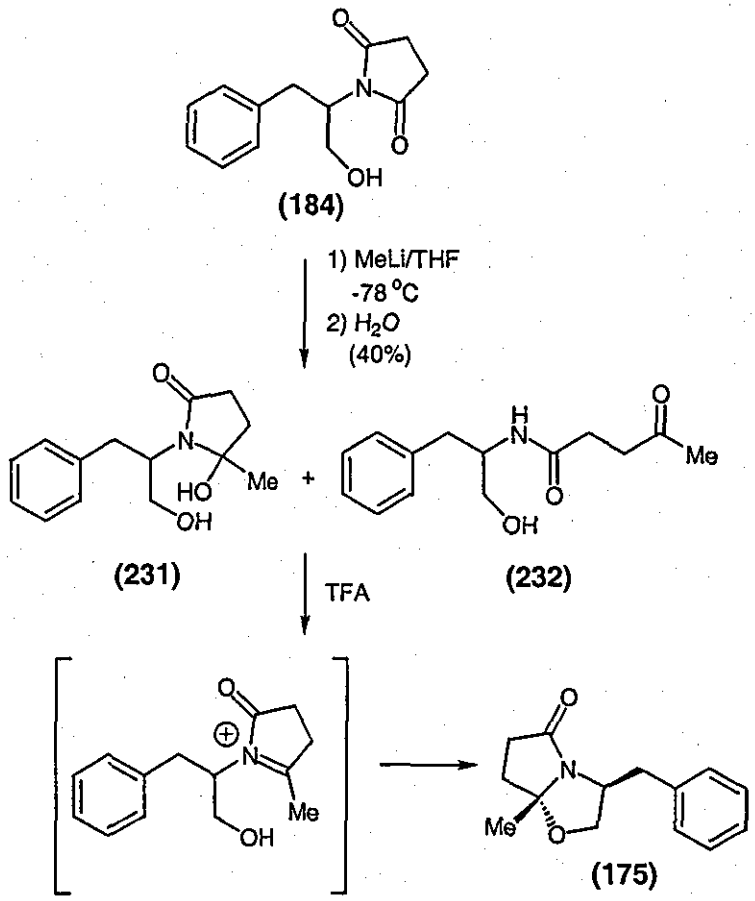
Scheme 78

We considered an alternative synthesis of pyrroloisoquinolines **(219)** and **(220)** utilising methodology adopted by Lete[26] *et al* (Scheme 78), in an attempt to increase the diastereomeric ratio of isomers, (2 : 1).

Lete treated succinimide **(228)** with methyl lithium at –78 °C over 6 hours, and then quenched the reaction with water. After work-up, equilibrium mixtures of hydroxy lactam **(229)** and the corresponding tautomeric oxo amide **(230)** were obtained.

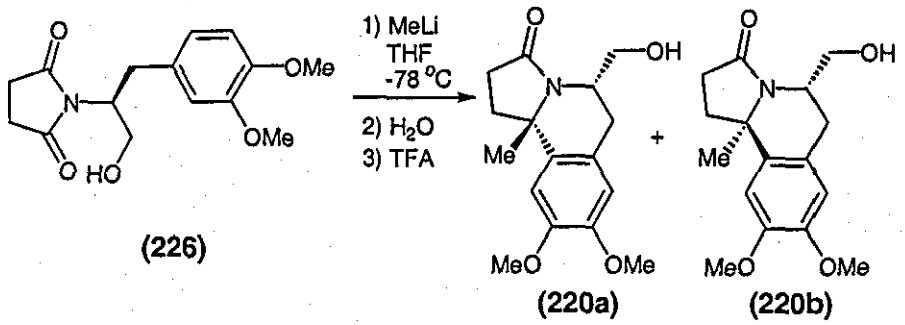
Cyclisation of the tautomeric mixture of **(229)** and **(230)** was accomplished with trifluoroacetic acid in dichloromethane to afford the desired pyrroloisoquinoline **(231)** in 87%.

Hydroxy lactam **(232)** and oxo amide **(233)** were synthesised by us following Lete's method, in a moderate 40% yield from imide **(184)** as shown in Scheme 79.



Scheme 79

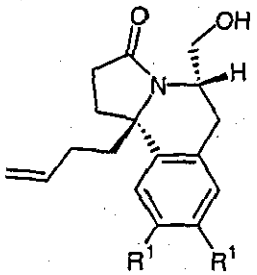
However, cyclisation of **(231)** and **(232)** initiated by trifluoroacetic acid resulted in sole formation of the bicyclic lactam **(175)**. Using titanium tetrachloride as the initiator gave mostly starting material and only traces of bicyclic lactam **(175)**.



Scheme 80

Treating imide **(226)** with the organolithium reagent, followed by addition of trifluoroacetic acid afforded our desired product diastereoisomers **(220a)** and **(220b)**, only this time with a decreased diastereoselectivity of 1 : 1 (Scheme 80).

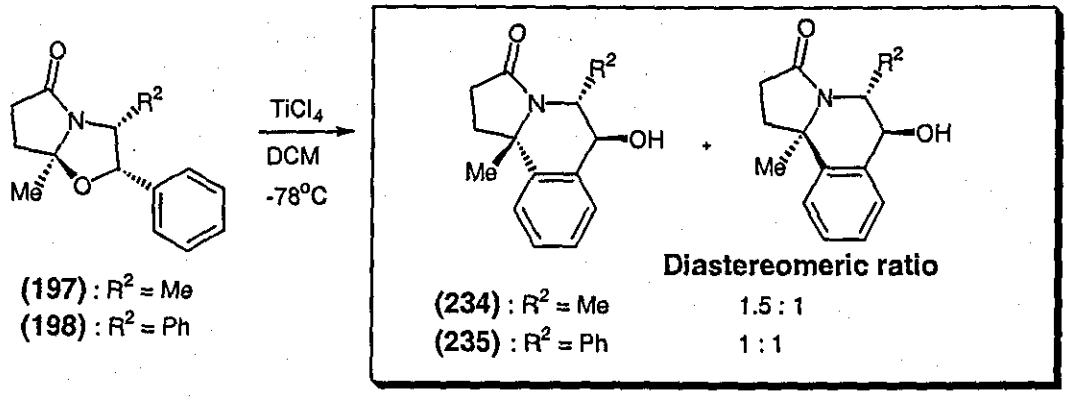
Interestingly, on synthesis of the homoallyl substituted pyrroloisoquinoline ring systems **(221)** and **(222)**, the diastereoselectivity was increased to 5 : 1 with the newly created chiral centre of the major diastereoisomer being formed with inversion of stereochemistry. Once again, NOE studies were undertaken to confirm the stereochemistry of the major diastereoisomer, and found to be as indicated in Figure 22.



(221) : R^1 = H (42%)
(222) : R^1 = OMe (54%)

Figure 22

Preparations of pyrroloisoquinolines **(234)** and **(235)** by inducing aromatic cyclisation from the corresponding lactams **(197)** and **(198)** were carried out following the same reaction procedure as used previously (Scheme 81). No improvements in diastereoselectivities were observed; yields were low (30% when R = Ph), and although reaction times were increased (60 hours when R = Me) starting material was still present after work-up and analysis.



(197) : R^2 = Me
(198) : R^2 = Ph

Scheme 81

We also recognised that a suitably substituted bicyclic lactam such as the fused 5,6-

ring system (**200**) could act as a precursor in a stereoselective approach towards a tricyclic tetrahydroisoquinoline ring, which can be seen as a sub-unit (BCD rings) of the protoberberine alkaloids exemplified by (-)-xylopinine (**236**) shown in Figure 23, and its derivatives.[104]

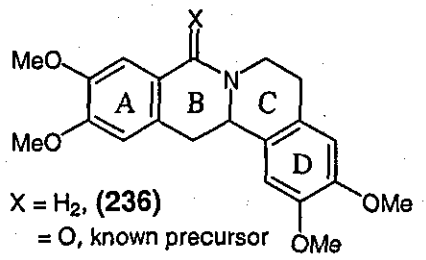


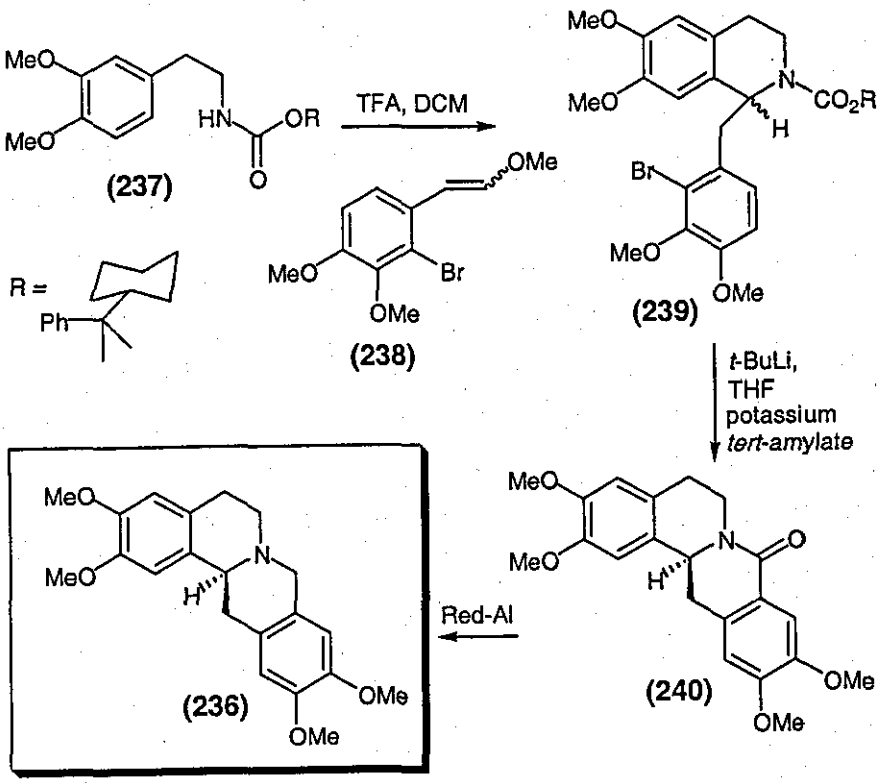
Figure 23

Comins[104] *et al* have investigated the synthesis of (-)-xylopinine using benzylisoquinoline (**239**) as an intermediate and utilising an asymmetric Pictet-Spengler reaction.

The Pictet-Spengler reaction is an important method for the construction of tetrahydroisoquinoline and β-carboline derivatives and, in general, involves the condensation of a β-arylethylamine with an aldehyde to give tetrahydroisoquinolines. The reaction proceeds *via* iminium or *N*-acyliminium ion formation and subsequent intramolecular aromatic electrophilic substitution.

The preparation of (**239**) involved the Pictet-Spengler reaction of carbamate (**237**) and vinyl ether (**238**) as shown in Scheme 82.

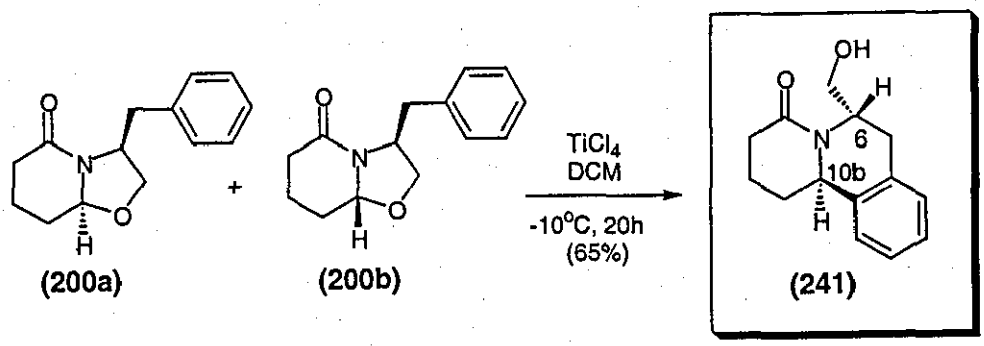
The 8-oxoberbine (**240**) was formed by attack of the aryl bromide in (**239**) on the *N*-acyl carbonyl carbon of the carbamate in an intramolecular fashion. This was followed by treatment of (**240**) with Red-Al in refluxing benzene to yield the desired (-)-xylopinine (**236**).



Scheme 82

On treating lactam diastereoisomers **(200a)** and **(200b)** with titanium tetrachloride as a Lewis acid activator at –10 °C in dichloromethane for 20 hours, we were pleased to isolate the cyclised product **(241)** as shown in Scheme 83.

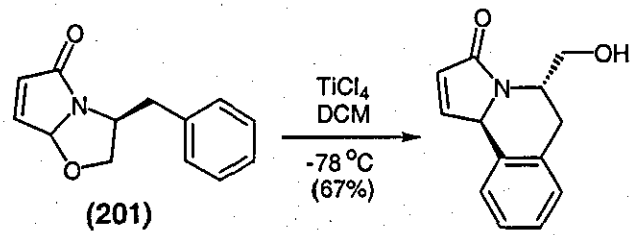
^{1}H NMR analysis of the crude reaction mixture revealed the formation of only one diastereoisomer, **(241)**. Interestingly both **(200a)** and **(200b)** led to the same diastereoisomer of cyclisation.



Scheme 83

An NOE study[95] indicated that the relative stereochemistry of the single product diastereoisomer **(241)** was as indicated in Scheme 83, with the protons at the 6 and 10b positions having a *trans*-relationship. This is consistent with the expected structure and with the previous pyrroloisoquinoline compounds **(217)** and **(218)**.

2.2.3. Stereoselective synthesis of unsaturated pyrroloisoquinoline ring systems

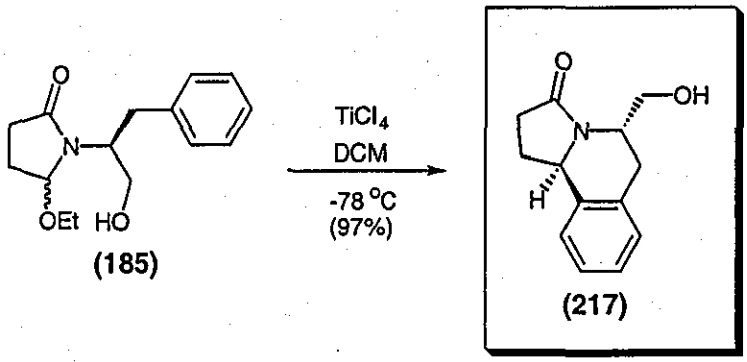


(201) **(242)**

Scheme 84

As expected, cyclisation of lactam **(201)** gave exclusively a single product diastereoisomer **(242)** as demonstrated in Scheme 84, in 67% yield

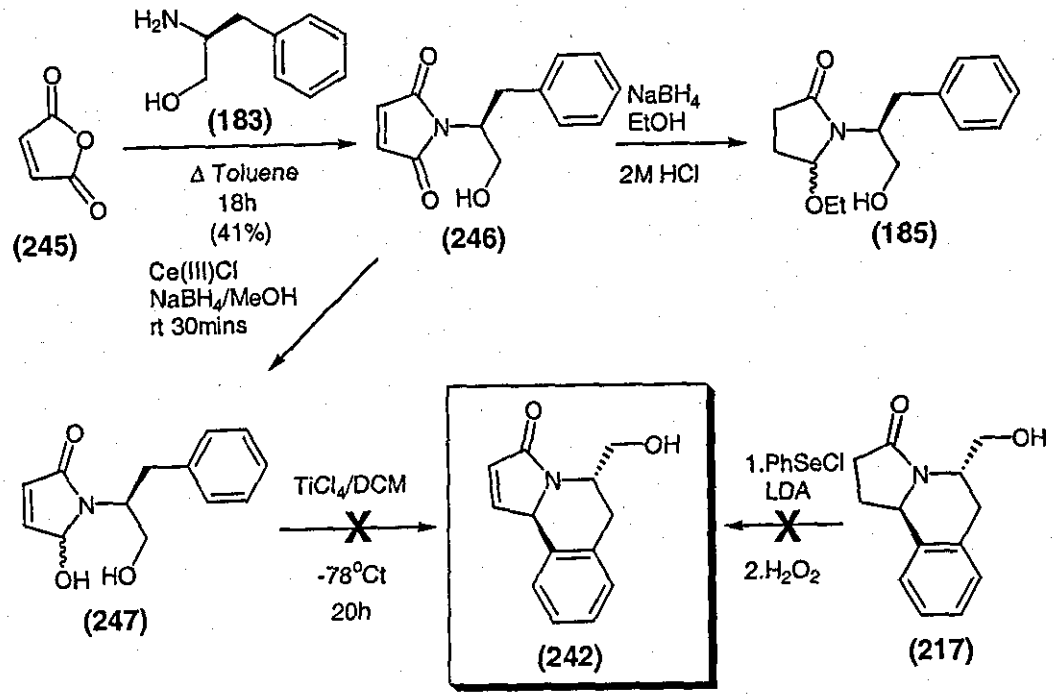
Alternative methods towards the synthesis of **(242)** were attempted. As demonstrated previously, the preparation of pyrroloisoquinoline **(217)** was successfully carried out from direct addition of titanium tetrachloride to the ethoxy lactam intermediate **(185)**, (Scheme 85).



(185) **(217)**

Scheme 85

We chose to follow this same method utilising imide (**246**), synthesised from commercially available malaeic anhydride (**245**) and (*S*)-2-amino-3-phenyl-1-propanol (**183**), (Scheme 86). However, the double bond was also reduced and ethoxy lactam intermediate (**185**) was obtained. Therefore, a new and efficient method was sought to carry out a reduction exclusively on the carbonyl group.

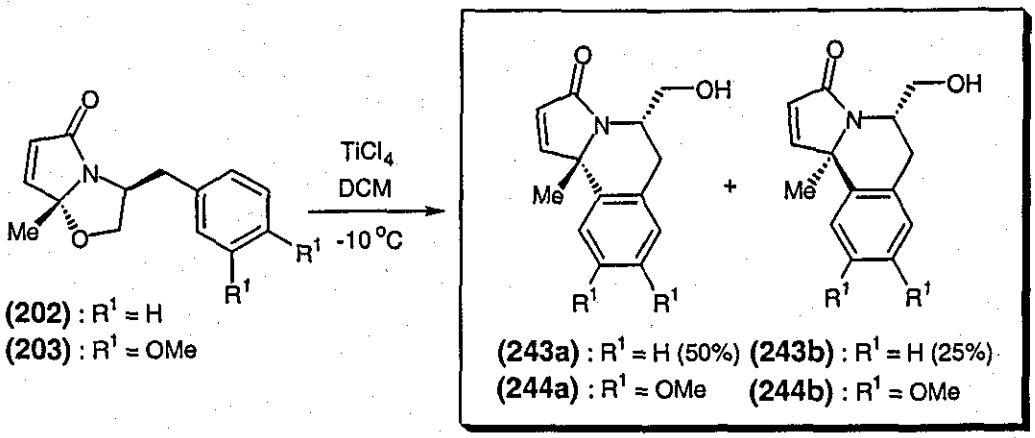


Scheme 86

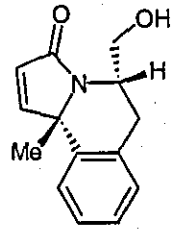
Luche[105] *et al* have adopted a procedure which enables the selective reduction of α-enones to allylic alcohols by sodium borohydride in methanol, in the presence of lanthanoid chlorides. Reduction of imide (**246**) afforded the "hydroxy" lactam intermediate (**247**) (determined by crude ^{1}H NMR), however, aromatic cyclisation using titanium chloride as initiator was not successful, (Scheme 86).

An alternatative method was to subject pyrroloisoquinoline (**217**) to our usual conditions for synthesising unsaturated compounds. This synthesis, however, was not viable, possibly due to interference from the free hydroxyl group. This is also illustrated in Scheme 86.

Interestingly, a slight increase in the level of diastereoselectivity was observed on cyclisation of the corresponding unsaturated alkyl-substituted lactams **(202)** and **(203)** when compared to the saturated analogues **(175)** and **(176)**, (Scheme 87).



Scheme 87



(243a)

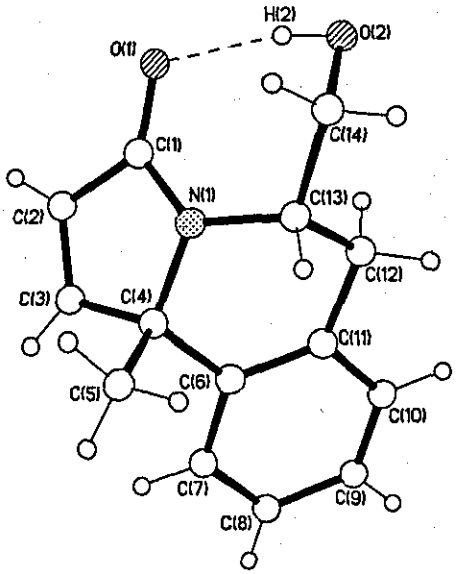
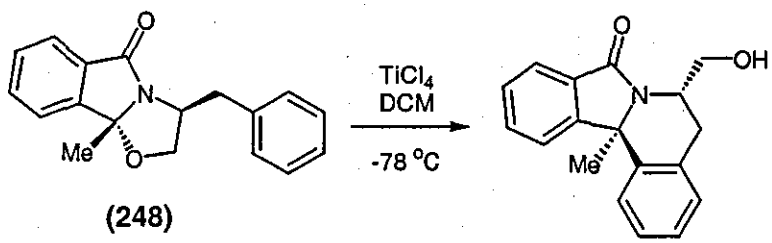


Figure 24

Whereas **(175)** and **(176)** produced the cyclised products **(219)** and **(220)** respectively as a 2 : 1 mixture of diastereoisomers (Scheme 76), cyclisation of the unsaturated substrates **(202)** and **(203)** proceeded with a modest increase in diastereoselectivity to 3 : 1 also in favour of the product of retention of stereochemistry **(243a)** and **(244a)** respectively.

Separation of the diastereoisomers was achieved by flash column chromatography, and the relative stereochemistry of the major isomer was investigated by X-ray crystallography, and found to be as indicated in **(243a)**, (Figure 24). The Minor isomer was investigated by NOE techniques and found to be as shown in **(243b)**.

Our group has shown in previous experiments[106] that lactam **(248)** shown in Scheme 88 gave the cyclised product **(249)** on Lewis acid addition as a single product diastereoisomer.



(248) **(249)**

Scheme 88

It was postulated that the diastereoselectivity observed above could be attributed to electronic effects associated with the fused benzene ring on **(248)**. This fused aromatic ring, making the aminal carbon benzylic in nature, provides increased activation of the resulting isoindolinone substrate towards formation of the reactive acyliminium species. In a similar way, electronic effects associated with the double bond in **(202)** and **(203)** could increase the activation of the acyliminium ion formed.

The rigidity of the 5 - membered ring in systems such as **(202)** and **(203)** perhaps could influence the diastereoisomers formed. On acyliminium formation, saturated lactam ring systems such as **(175)** and **(177)** have the ability to flip from one

conformation to another along the $-CH_2-CH_2-$ bond, whereas the unsaturated ring systems, **(202)** and **(203)** are rigid and flat.

Steric effects caused by the angular methyl substituent and the unsaturated ring hydrogens, or by the methyl substituent and axial hydrogens on the saturated analogue, could also contribute to the slight change in the diastereoselectivities observed for the target pyrroloisoquinolines **(243a)** and **(243b)**.

2.2.4. Rationalisation of the stereochemical outcome of the cyclisation reactions

In order to rationalise the stereochemical outcome of the cyclisation reactions we have invoked the conformational models highlighted in Figures 25 and 26 in which activation of the bicyclic lactam substrate by a Lewis acid leads to a formal *N*-acyliminium species as an intermediate.

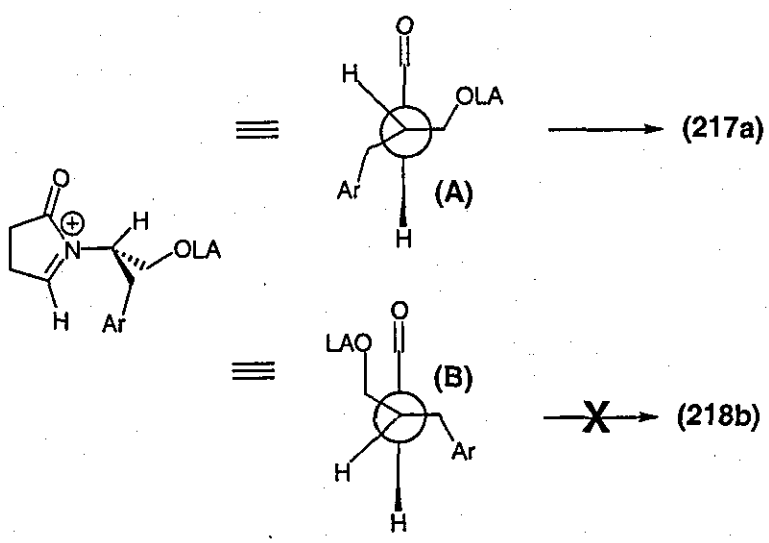


Figure 25

In conformation **(A)** where R = H, leading to the favoured product **(217a)** the carbonyl moiety is "eclipsed" in a 1,3-fashion by the small hydrogen atom at the β-amino alcohol chiral centre. The angular H-atom at the iminium carbon atom provides no significant steric bulk to interfere with the steric positioning of the benzyl or Lewis acid-complexed oxymethyl groups.

In this model, the Lewis acid-complexed oxymethyl group is viewed as the larger substituent.[107-108]

The alternative conformation, **(B)**, which would lead to the minor (unobserved) diastereoisomer, has the benzyl group positioned as the larger substituent. In this scenario an unfavourable 1,3-interaction appears between the carbonyl group and the more bulky Lewis acid-complexed oxymethyl group.

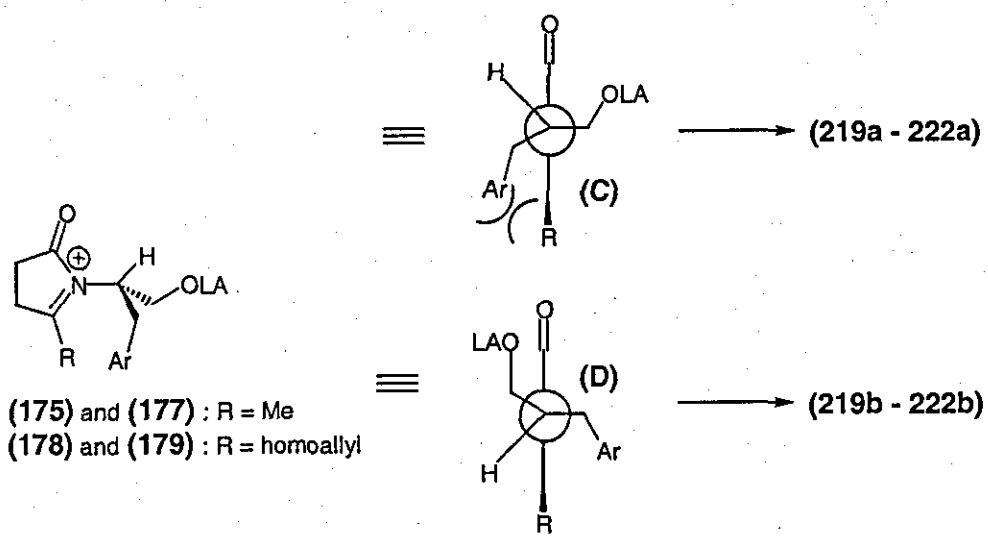


Figure 26

With substrates **(175)** and **(177 - 179)** (Figure 26), the steric influence provided by the angular methyl or homoallyl substituents (R = Me or homoallyl) at the iminium carbon atom overrides the conformational effect noted in Figure 25 and this leads to a major diastereoisomer of opposite relative stereochemistry. One can envisage interactions between this angular methyl or homoallyl group and the benzyl substituent (**C**, R = Me or homoallyl).

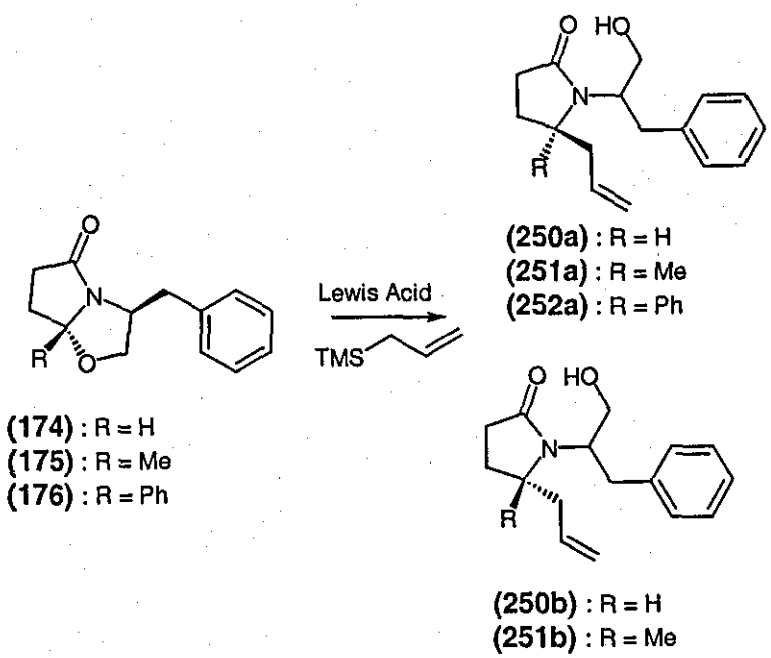
Bond rotation about the extra-annular C-N bond leads to an alternative conformation (**D**, R = Me and homoallyl) with minimised steric interference from the iminium carbon substituent which furnishes the observed major product diastereoisomers **(219a - 222a)** with retention of stereochemistry.

An increase in the diastereoselectivity to 5 : 1 was noted for compounds **(221)** and **(222)** where R is a bulkier homoallyl group compared to the smaller methyl

substituent found in (**219**) and (**220**) where the diastereomeric ratios were 2 : 1. A probable explanation of these results can be found by invoking the conformational models as illustrated in Figure 26. In this case, conformation (**D**) is clearly the more preferred, as a very unfavourable interaction between the angular homoallyl group and the benzyl substituent is present in transition state (**C**).

2.3. Asymmetric intermolecular reactions of chiral *N*-acyliminium ion precursors

We investigated bicyclic lactams (**174 – 176**) as potential *N*-acyliminium ion precursors for the asymmetric synthesis of a different class of compounds, 3-substitututed-pyrrol-2-ones (**250 - 252**).



Scheme 89

Substrates (**174 – 176**) were prepared as single diastereoisomers as previously described, and were subjected to an aminal ring opening reaction with allyl trimethylsilane as the nucleophile in the presence of a Lewis acid activator (Scheme 89).

As can be seen from Table 10, the use of titanium tetrachloride furnished the hydrogen (**250a/b**) and methyl (**251a/b**) 3-substututed-pyrrol-2-ones with only poor levels of diastereoselectivity. Altering experimental parameters such as temperature and time, and changing the Lewis acid had no effect on the diastereomeric ratio observed.

The ring opening of (**176**) did, however, afford the product with 'inversion' of stereochemistry (**252**) as a single diastereomer.

Compound	Lewis Acid	Reaction Temp.	Reaction Time (h)	Yield (%)	Diastereoselectivity[a]
(250)	$TiCl_4$	-78 °C - rt	20	81	1.5 : 1
(251)	$TiCl_4$	-10 °C - rt	20	78	1 : 1
(251)	$TiCl_4$	-78 °C - rt	20	86	1 : 1
(251)	$SnCl_4$	-10 °C - rt	20	70	1 : 1
(252)	$TiCl_4$	-10 °C - rt	48	100	1 : 0

[a]Determined by 250MHz ^{1}H NMR spectroscopy on crude reaction mixture

Table 10: Effect of Lewis acid on aminal ring opening of lactams (174 - 176)

In an attempt to rationalise the stereochemical outcome of the reaction, the conformational model shown in Figure 27 is proposed.

The *N*-acyliminium ion once generated, suffers from free rotation about the extra-annular C-N bond. From the model of Felkin-Anh,[107-108] the largest substituent of the stereocentre is positioned perpendicular to the carbonyl group, and the incoming nucleophile attacks from the opposite side. As the results suggest, where R = H or Me, the *N*-acyliminium species rotates about the C-N bond with little preference for the competing conformations during nucleophilic attack. That is, both the benzyl substituent and the Lewis acid-complexed oxymethyl group are relatively similar in size.

The size of the angular substituent (R) appears to be the significant factor contributing to the observed levels of diastereoselectivity. When R = Ph, the steric effect provided by this substituent is sufficient to favour one intermediate **(253a)**, that leading to retention of configuration at the new asymmetric centre.

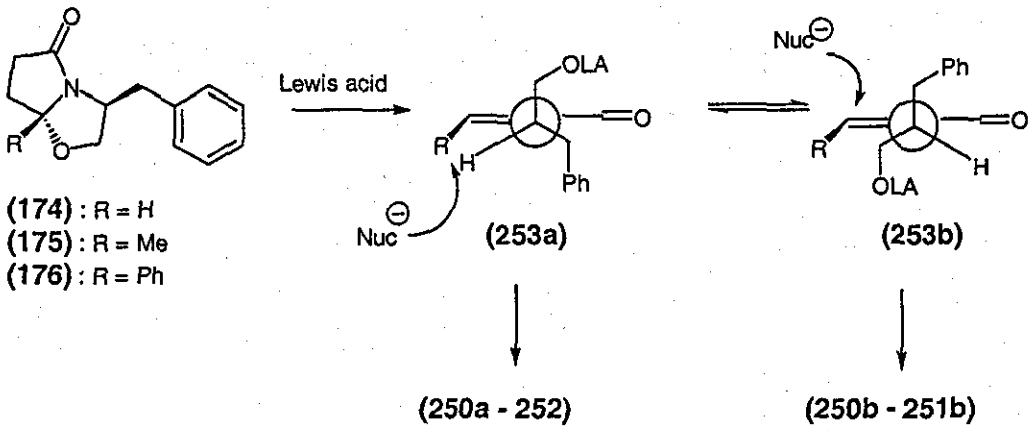


Figure 27

2.4. Further functionalisation of the pyrroloisoquinoline ring system

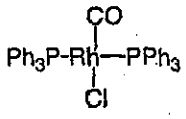
2.4.1. Introduction

In order to demonstrate the synthetic potential of the stereoselective cyclisation methodology we were required to establish conditions for removal of the pendant hydroxymethyl substituent (auxiliary) from our products of cyclisation, and perhaps reduce the amide carbonyl functional group to afford the amine. The following section outlines the methodology adopted in order to carry out both transformations.

2.4.2. Decarbonylation studies

In 1967 Tsuji and Ohno described a useful process for the decarbonylation of aldehydes and acyl halides using a versatile metallic palladium catalyst.[109] Decarbonylation reactions are useful in organic chemistry if they can be carried out smoothly under mild conditions.

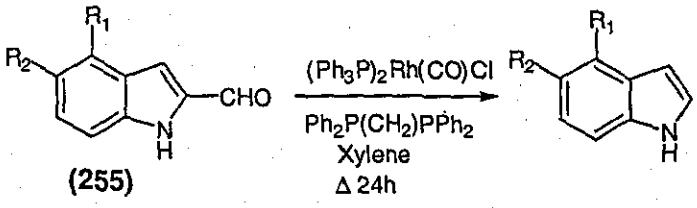
In the same year, Tsuji and Ohno described a 'better' method of carrying out the same decarbonylation reactions using rhodium complexes, in particular, [bis(triphenylphosphine]rhodium carbonyl chloride (**254**)[110] (Figure 28). These complexes are stable and easy to handle.



(254)

Figure 28

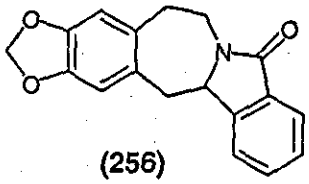
Meyers[111] *et al* have modified the published route of Tsuji and Ohno and extended the decarbonylation reaction to include indole-2-carboxaldehyde substrates (**255**) (Scheme 90).



(255)

Scheme 90

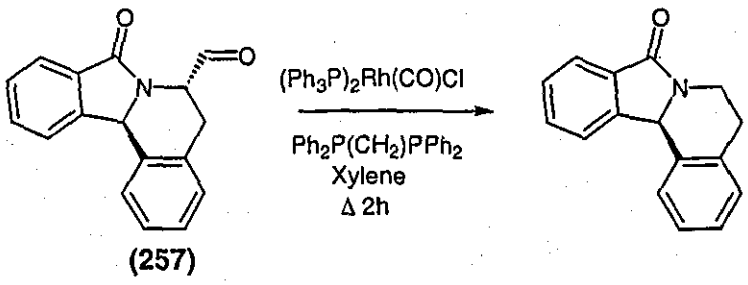
Moody and Warrellow[112a-b] utilised this method in their total synthesis of lennoxamine (**256**) (Figure 29).



(256)

Figure 29

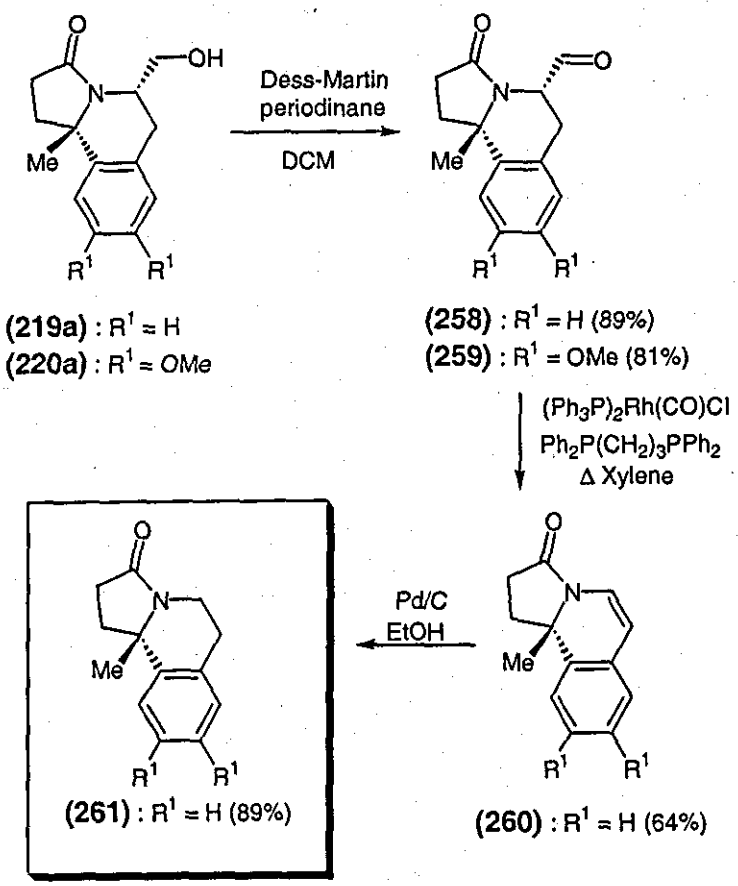
Our group[113] has previously investigated the removal of the pendant hydroxymethyl substituent from a product of cyclisation by conversion of the primary alcohol to an aldehyde (**257**), followed by decarbonylation using a rhodium complex as catalyst as shown in Scheme 91, using the method of Moody.[112a-b]



(257)

Scheme 91

Dess-Martin periodinane oxidation[114] of pyrroloisoquinolines **(219a)** and **(220a)** proceeded in excellent yields to provide aldehydes **(258)** and **(259)**, (Scheme 92).



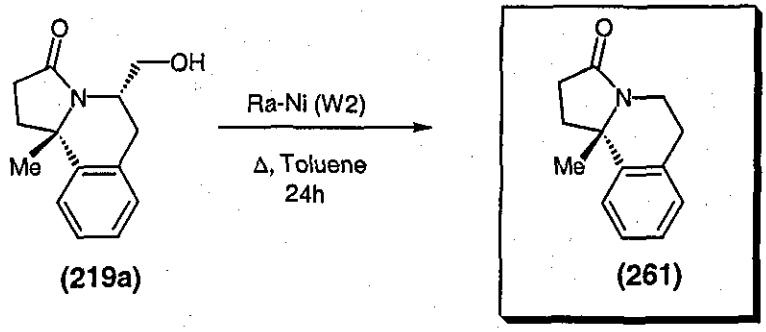
Scheme 92

Oxidation of **(220a)** proved problematic on first attempt. A TLC of the reaction mixture indicated that the reaction had gone to completion, however after the usual work-up procedure[114] only starting material was obtained. The desired compound proved to be soluble in the aqueous phase and only after continual extractions were we able to retrieve **(259)**. The synthesis was carried out again, and the aqueous

work-up was omitted. Direct filtration of the crude reaction mixture through silica gave the target compound in excellent yield (81%).

Following the method previously applied in our laboratory (Scheme 90) we attempted the rhodium-catalysed decarbonylation but found that the reaction proceeded to give only enamide **(260)**, with no sign of the desired compound **(261)**. Attempts were made to vary the reaction conditions in order to access **(261)** directly using the rhodium decarbonylation, but without success. Nevertheless, we were subsequently able to convert enamide **(260)** into the desired compound **(261)** by catalytic hydrogenation.

An alternative investigation into the removal of the hydroxymethyl substituent was considered, employing a raney-nickel catalysed reaction (Scheme 93).

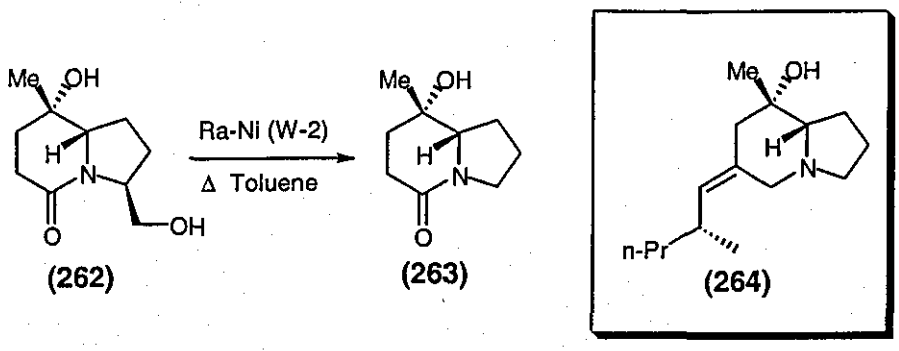


(219a) **(261)**

Scheme 93

Krafft[115] and co-workers reported a simple and efficient method for the oxidation of secondary alcohols to ketones and the deoxygenation of primary and tertiary alcohols using Raney-nickel. They showed that in the presence of Raney-nickel in refluxing toluene, primary alcohols were oxidised to aldehydes, and subsequently undergo decarbonylation under the reaction conditions.

Martin[116] *et al* used this method to successfully remove a hydroxymethyl group from bicyclic lactam **(262)** to yield **(263)**, a precursor in an approach to the asymmetric synthesis of pumiliotoxin A **(264)**, (Scheme 94).



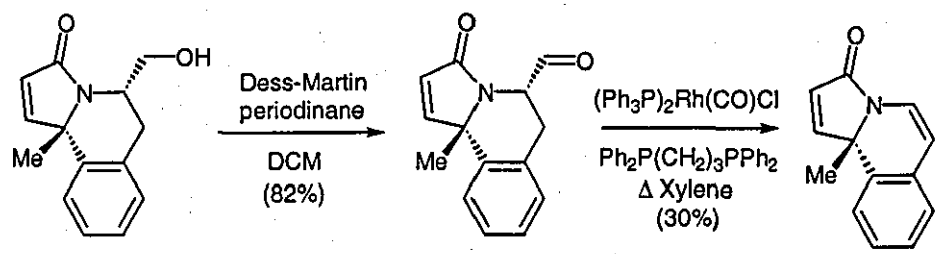
(262) (263) (264)

Scheme 94

When subjecting our pyrroloisoquinoline (**219a**) to Raney-nickel under the reaction conditions described by Martin, a high percentage of starting material was recovered. However, removal of the hydroxymethyl group had occurred resulting in the formation of enamide (**260**) in poor yield. This one-step removal of the auxiliary was therefore unsuccessful on our substrate.

We decided to carry out a rhodium-catalysed decarbonylation on unsaturated pyrroloisoquinoline (**265**), (Scheme 95).

It was thought that the double bond present in lactam (**243a**) would perhaps effect the way in which the rhodium complex reacted as it has already been noted that decarbonylation using a rhodium complex as catalyst proceeds smoothly with isoindolinone compound (**257**), (Scheme 91), where a second fused benzene ring was present.



(243a) (265) (266)

Scheme 95

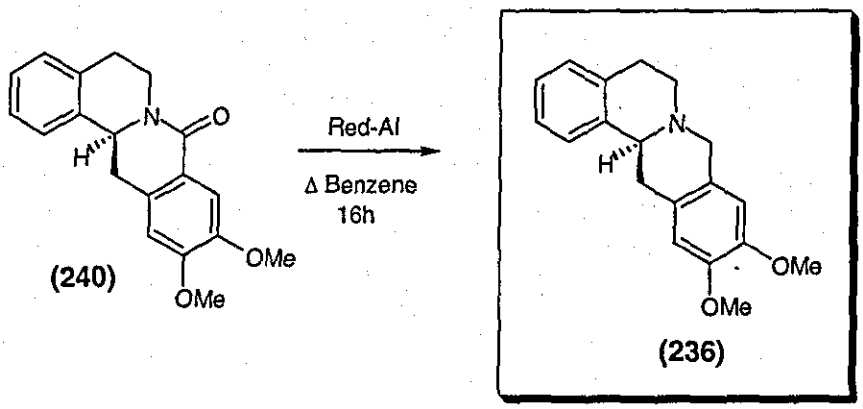
Synthesis of aldehyde (**265**) was relatively straightforward giving the product as one diastereoisomer in 82% yield. However, on refluxing in xylene in the presence of the

rhodium complex for 24 hours, loss of the aldehyde occurred giving the enamide (**266**). The aldehyde diastereoisomer was also isolated as a major product in 24% yield showing epimerisation of the aldehyde chiral centre.

2.4.3. Amide reduction

Catalytic hydrogenation of amides usually requires vigorous conditions (high pressures and elevated temperatures),[117a-b] therefore reduction using metal hydride complexes such as lithium aluminium hydride[118] or borane[119a-b] have been used in organic synthesis.

Lenz[118] used two methods to reduce racemic 8-oxoberbines: reduction with lithium aluminium hydride in tetrahydrofuran, and reduction with Red-Al in benzene. In general, he found that reductions using lithium aluminium hydride gave inferior yields and less clean products than reduction with the alternative hydride reagent.

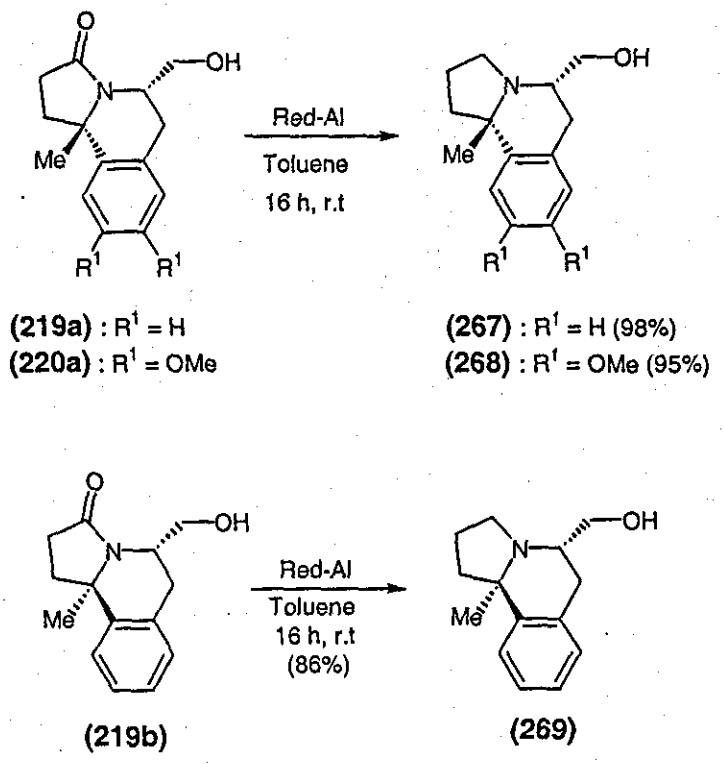


Scheme 96

Comins[104] *et al* have also used Red-Al for their reduction of chiral 8-oxoberbine (**240**) as shown in Scheme 96.

We initially followed the protocol of Lenz,[118] with the exception that toluene was used in place of benzene as solvent, and then optimised reaction conditions to suit our pyrroloisoquinoline ring systems.

It was found that reacting pyrroloisoquinolines **(219a)**, **(220a)** and the opposite diastereomer **(219b)** under the conditions outlined in Scheme 97 gave the desired products **(267)**, **(268)** and **(269)** respectively in high yields.



(219a) : R^1 = H
(220a) : R^1 = OMe

(267) : R^1 = H (98%)
(268) : R^1 = OMe (95%)

(219b)

(269)

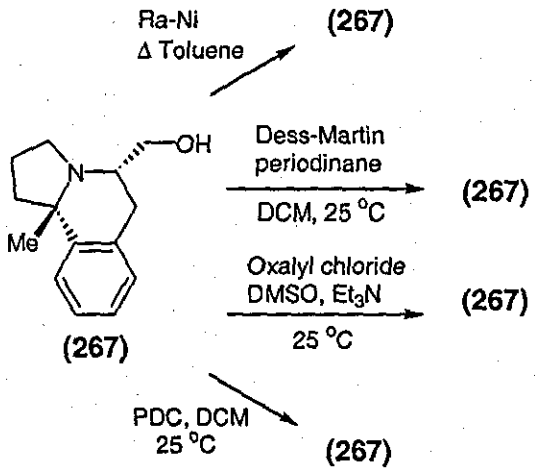
Scheme 97

With **(267)** in hand, our next objective was to carry out a decarbonylation reaction. We were interested to see whether the absence of the carbonyl functionality on the pyrroloisoquinoline would have an effect on the product outcome. Scheme 98 outlines our proposal and results.

The expected enamide was not obtained when **(267)** was subjected to the typical Raney-nickel reaction conditions, with only starting material recovered. Dess-Martin periodinane oxidation did not yield the expected aldehyde, therefore other known oxidation methods were attempted, Swern oxidation[120] and PDC oxidation.[121] Both were unsuccessful.

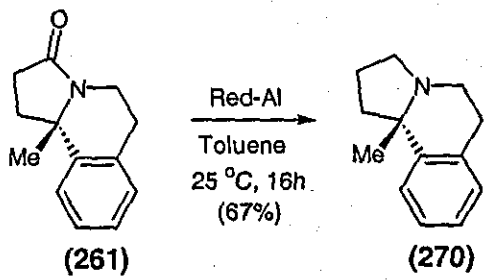
These findings indicate that the presence of the carbonyl functionality on the pyrroloisoquinoline seems to be required in order to allow removal of the pendant

hydroxymethyl substituent, although it is difficult to see why alcohol oxidation should prove problematic with substrate (**267**).



Scheme 98

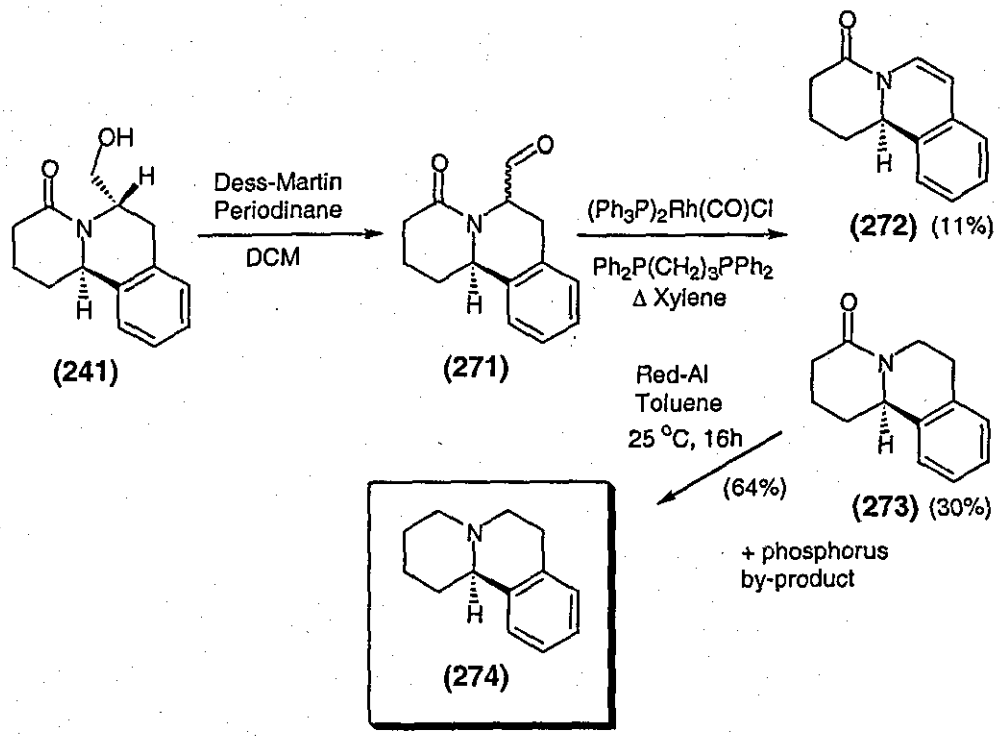
Removal of this auxiliary and Red-Al reduction of the amide carbonyl group has been successfully carried out on pyrroloisoquinoline (**261**) furnishing (**270**), (Scheme 99). This sequence of reactions is important and is discussed in forthcoming sections.



Scheme 99

In Section 2.2.2 we discussed the synthesis of ring system (**241**), an intermediate in the approach towards a tricyclic tetrahydroisoquinoline ring target. We also wished to demonstrate the removal of the hydroxymethyl substituent from this particular product employing the methodology described in Section 2.4.2.

Rhodium catalysed decarbonylation of aldehyde (**271**) gave a mixture of enamide (**272**), (11%) and decarbonylation product (**273**), which could not be separated from a phosphorus by-product by column chromatography, (Scheme 100).



Scheme 100

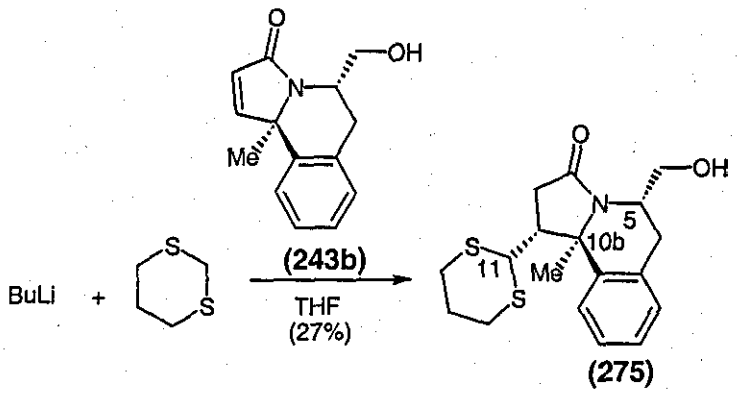
It was suggested that reduction of the amide by Red-Al using our usual reaction conditions would lead to the corresponding amine (**274**) which could then be separated from the phosphorous by-product. This was indeed the case, and only trace amounts of the impuritiy were still present after chromatography.

2.4.4. Conjugate addition reactions

Lete[122] *et al* have described diastereoselective conjugate additions of α-lithiodithioacetals to α,β-unsaturated bicyclic lactams. This is potentially useful chemistry for further functionalisation of systems such as (**243b**), prepared by us.

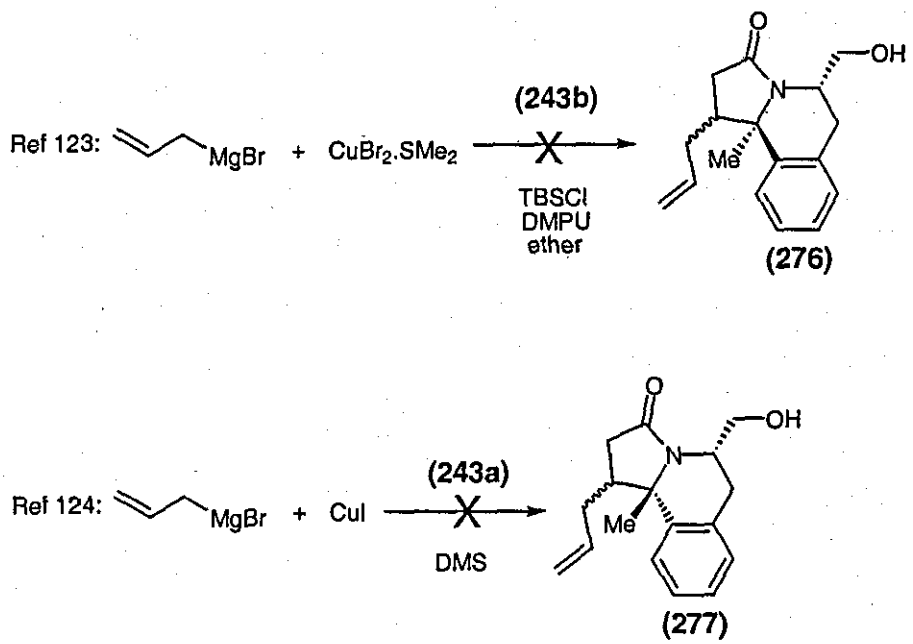
Following Lete's methodology, we have successfully introduced a nucleophilic dithiane moiety on to the pyrrolidine nucleus (**243b**) to generate the functionalised target (**275**). During the course of this project it was established that conjugate

addition of lithiated 1,3-dithiane was only successful on the "minor" pyrroloisoquinoline **(243b)** as shown in Scheme 101.



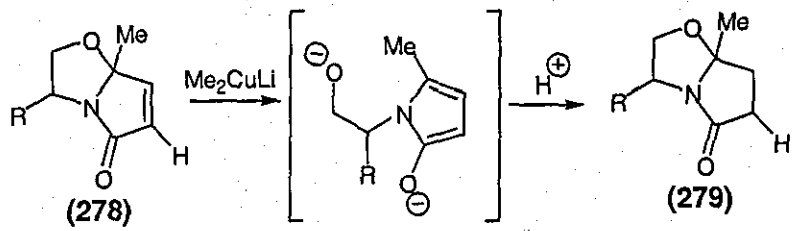
Scheme 101

An NOE study was undertaken to support the relative stereochemistry of product **(275)** as drawn in Scheme 100. The absence of an NOE between protons situated at positions 5 and 10b suggests that the relative stereochemistry of the single product diastereoisomer was as indicated in product **(275)**. When the hydrogen at position 11 of **(275)** was irradiated an NOE effect was observed for 10b, suggesting that the dithiane moiety and the methyl substituent are located in a *cis*-orientation.



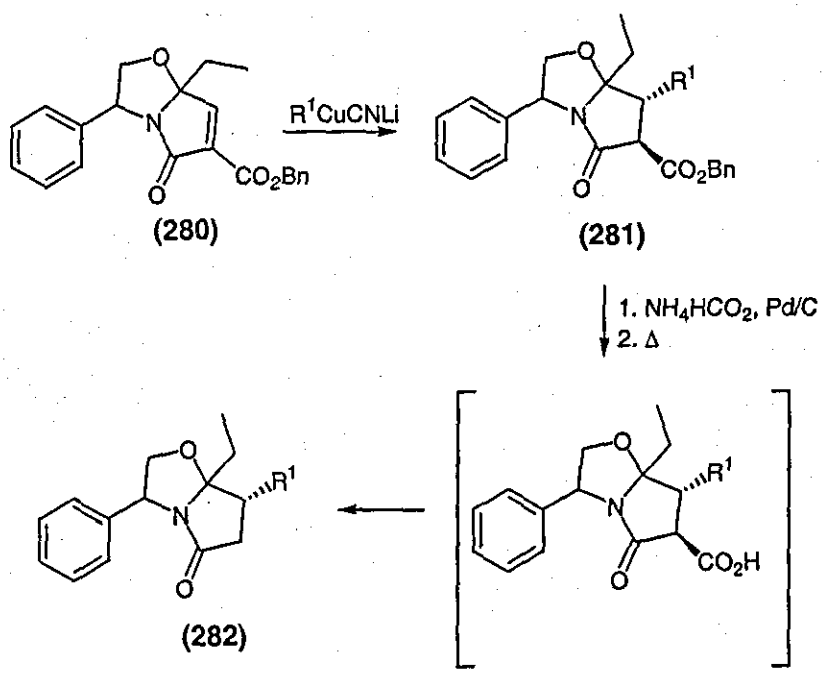
Scheme 102

Conjugate addition of allyl cuprates to pyrroloisoquinolines **(243a)** and **(243b)** were also examined following procedures outlined in the literature,[123-124] however products **(276)** and **(277)** were not successfully prepared, and in both cases only starting materials were recovered (Scheme 102).



Scheme 103

Meyers[14, 74-75] has described a study involving the conjugate addition of various organocuprates to unsaturated bicyclic lactams. Initially the group of Meyers found that attempts to add dialkyl organocuprates to lactam **(278)** were unsuccessful due to facile 1,4-reduction to the enone furnishing the saturated lactam **(279)**, (Scheme 103).[74]



Scheme 104

Previous studies carried out within the Meyer's research group showed that Diels-Alder cycloadditions to **(278)** were unsuccessful unless a "conjugate addition

activator" such as a carbomethoxy or carbobenzyloxy group was present at the α-position of the carbonyl.[74] Subsequently α-carboalkoxy lactams such as **(280)** were prepared and examined as electrophilic olefins for organocuprate addition reactions, (Scheme 104).

The carbobenzyloxy group in **(281)** was easily removed *via* hydrogenolysis[125] followed by decarboxylation in refluxing toluene affording target **(282)**.

Utilising this methodology, we sought to prepare lactam **(283)**, a potential intermediate in the synthesis of the *erythrina* alkaloid (-)-3-demethoxyerythratidinone **(139)** as shown in Figure 30.

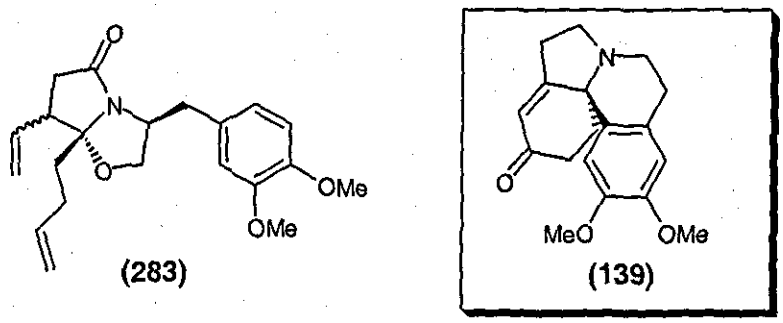


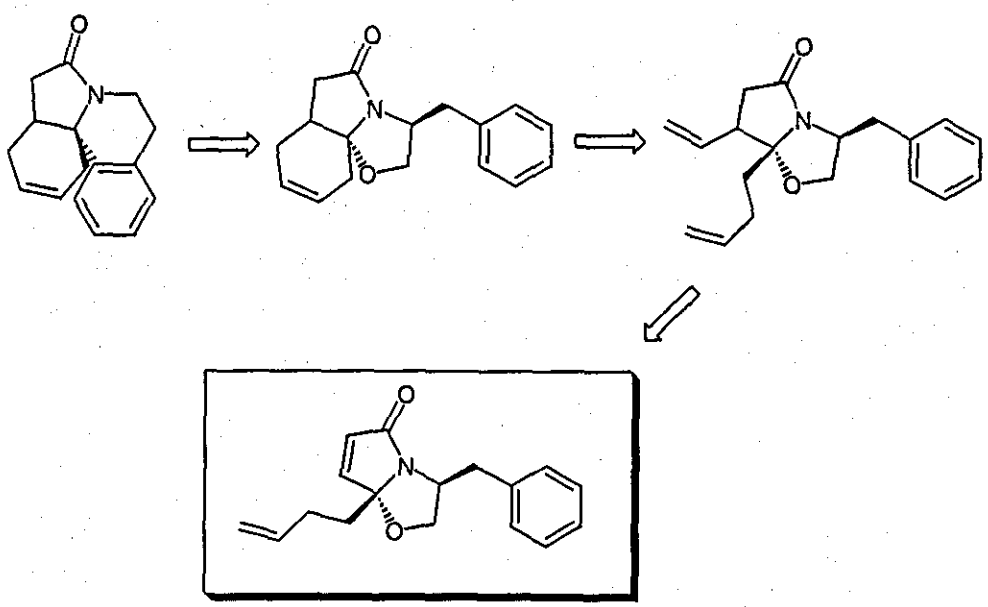
Figure 30

2.5. Applications of *N*-acyliminium ion precursors in the synthesis of *erythrina* alkaloids

Towards the end of this research project studies were initiated towards an asymmetric synthesis of the erythrinane alkaloid **(139)**, shown in Figure 30. The intention was to follow and expand on the methodology we had adopted throughout the course of the project. Based on our novel stereoselective approach to the pyrroloisoquinoline ring systems, we reasoned that a suitably substituted bicyclic lactam could act as a precursor in a facile and stereoselective approach to the tetracyclic core of the target erythrinane ring system.

2.5.1. A metathesis approach to the erythrinane skeleton

It was envisaged that a ring-closing metathesis approach followed by an *N*-acyliminium ion cyclisation reaction would allow access to the erythrinane skeleton as illustrated in Scheme 105.



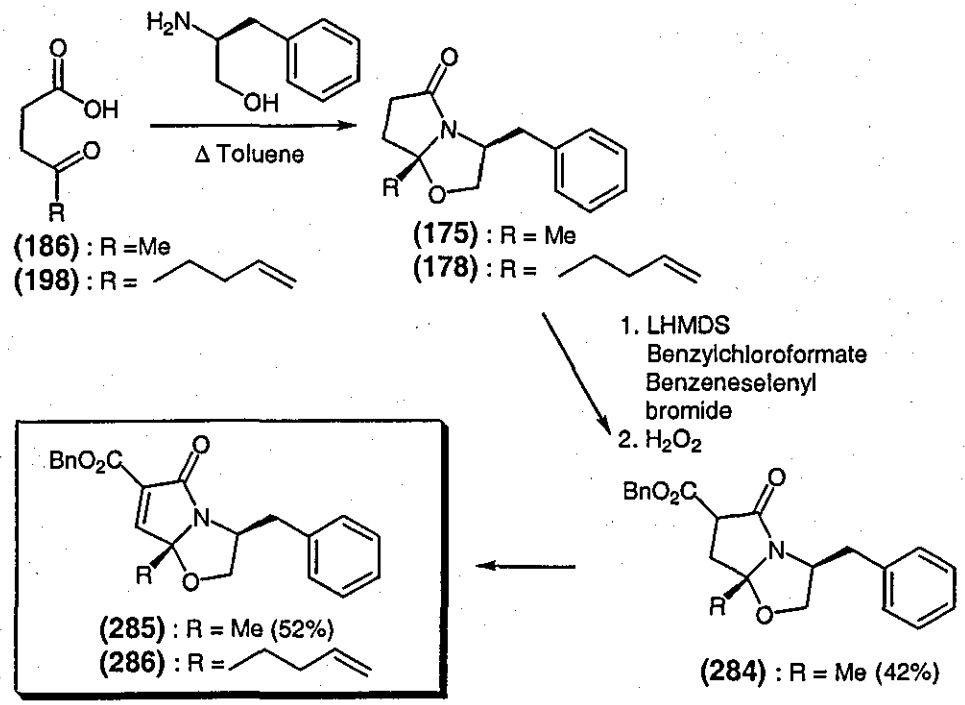
Scheme 105

As has been discussed in Section 2.4.4, Meyers[74] *et al* have studied conjugate addition reactions of organocuprates to bicyclic lactam substrates. Following this methodology, initial studies were carried out on lactam **(175)** as this substrate was relatively easy to synthesise in good yield from cheap and commercially available starting materials.

The unsaturated α-carbobenzyloxy lactam **(285)** was prepared in 52% from **(284)** as shown in Scheme 106. Unfortunately, unsaturated α-carbobenzyloxy lactam **(286)** was not synthesised from the corresponding starting lactam **(178)**, with only starting materials being recovered.

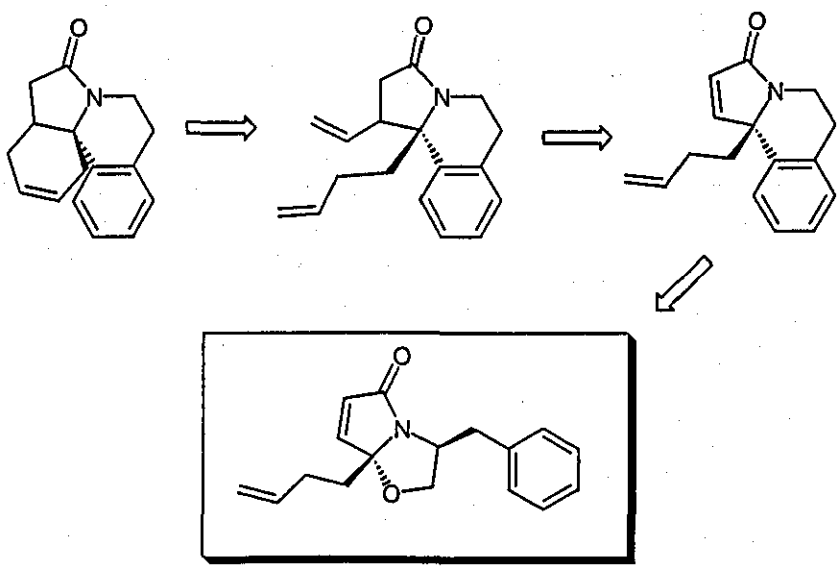
It was thought that the large homoallyl group (R) was sterically hindering either removal of a proton at the α-position of the carbonyl oxygen or the addition of benzylchloroformate. Possibly the base used in the reaction was too bulky to initially

remove the proton for benzylchloroformate addition, and/or, too bulky to remove the second proton for benzeneselenyl bromide addition.



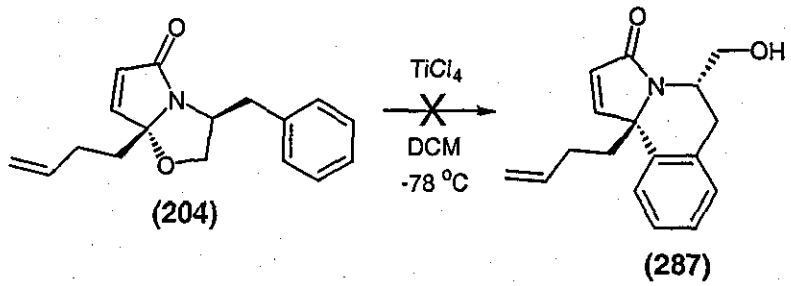
Scheme 106

An alternative procedure towards the erythrinane skeleton was attempted. The retrosynthetic pathway shown in Scheme 107 utilises an *N*-acyliminium ion cyclisation reaction, followed by a ring-closing metathesis.



Scheme 107

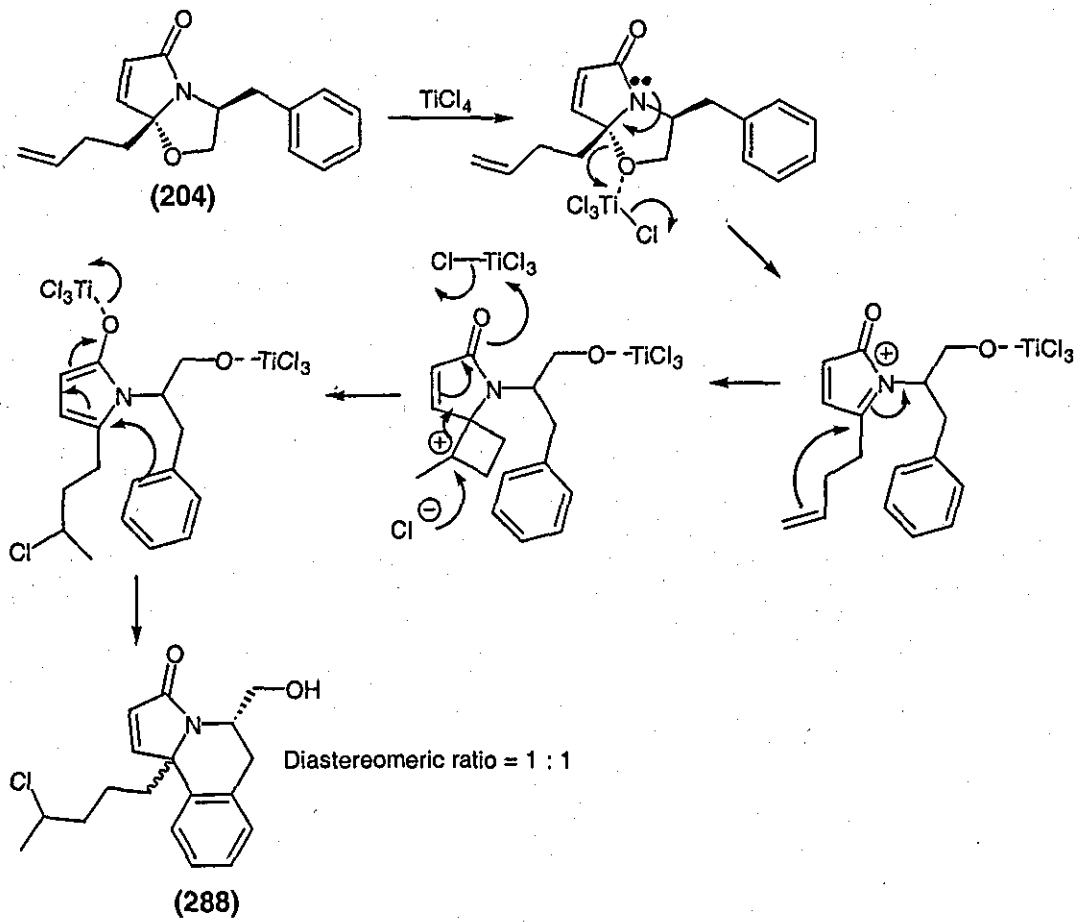
Lewis acid induced cyclisation of **(204)** on this occasion did not lead to the desired product **(287)**, (Scheme 108).



(204) **(287)**

Scheme 108

NMR studies suggest that HCl has added across the double bond during the titanium tetrachloride cyclisation affording **(288)**. A mechanism has been proposed and is shown below, (Scheme 109).



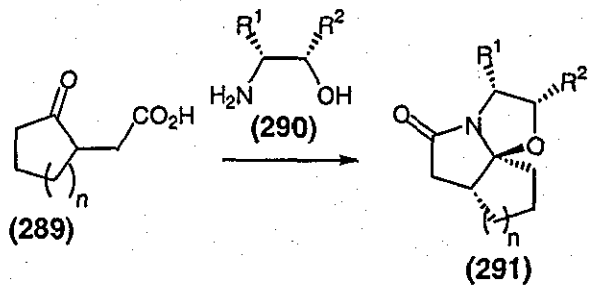
(204) **(288)**

Scheme 109

During these studies, a more viable route towards the synthesis of (-)-3-demethoxyerythratidinone **(139)** was realised. Due to time constraints further studies on the metathesis approach were dropped. However, the metathesis approach to this class of natural products has potential and can be considered for future work within this project.

2.5.2. Functionalised substrate approach to the erythrinane skeleton

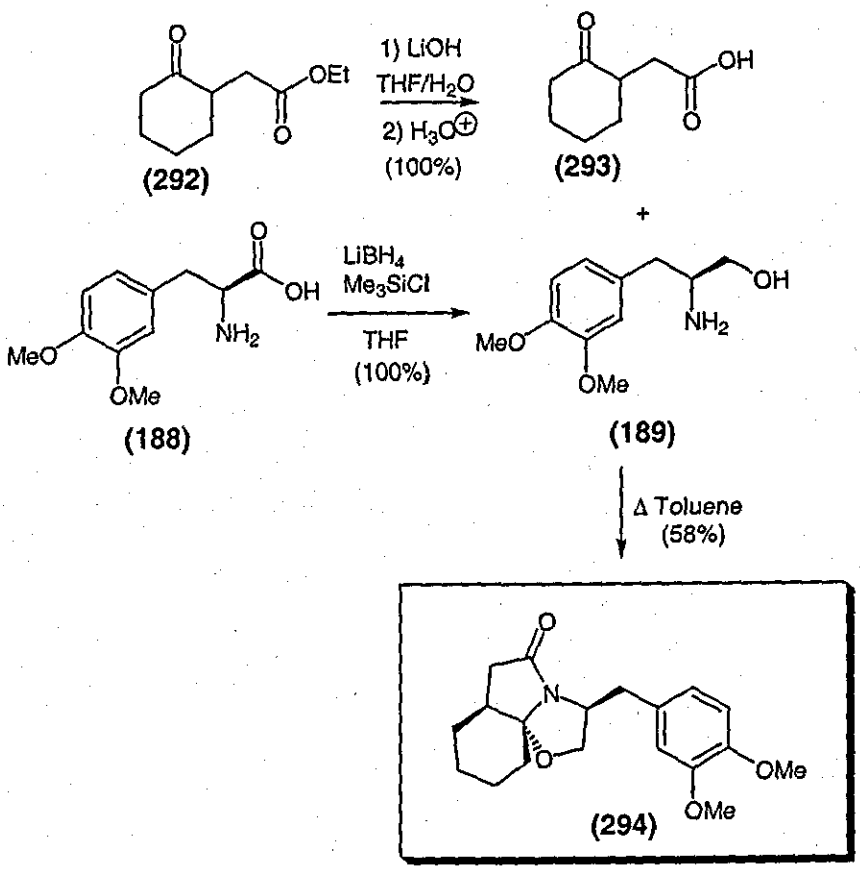
Ragan and Claffey[126] have reported alkylation reactions of chiral, non-racemic, tricyclic pyrrolidinones. Condensations of cyclic keto-acids **(289)** with chiral amino alcohols **(290)** provided tricyclic pyrrolidinones **(291)** with high levels of diastereoselectivity, (Scheme 110).



Scheme 110

Our synthesis of the required tricyclic lactam **(294)** followed a similar method from racemic keto-acid **(293)**, which was prepared from ethyl-2-cyclohexanoneacetate **(292)**, (Scheme 111).

The required β-amino alcohol **(189)** was synthesised in quantitative yield by reducing the commercially available amino acid 3-(3,4-dimethoxyphenyl)-*L*-alanine **(188)** with lithium borohydride in the presence of trimethylchlorosilane in tetrahydrofuran for 24 hours at room temperature.[93]



Scheme 111

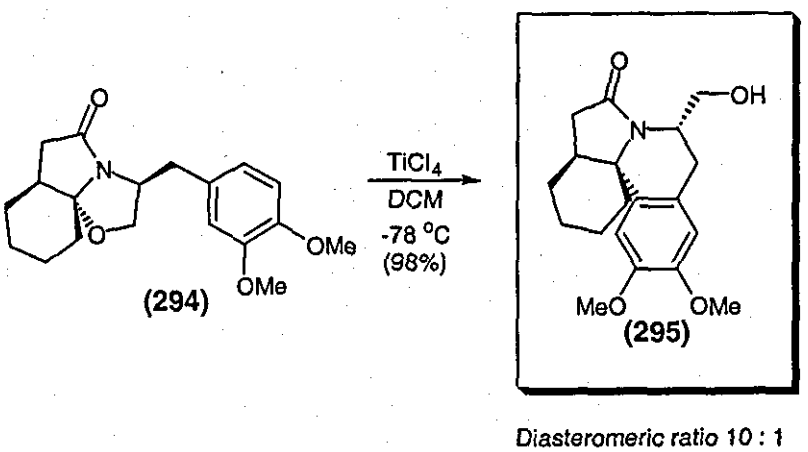
Condensation of substrates (**293**) and (**189**) under Dean-Stark conditions in toluene for 144 hours gave a 58% yield of the desired lactam (**294**) as a single diastereoisomer. The formation of a single product diastereoisomer of lactam (**294**) from a racemic keto-acid requires the epimerisation of the stereogenic centre adjacent to the ketone of (**293**) during the reaction. Others have noted this fact in the preparation of polycyclic lactams for use as *N*-acyliminium precursors.[127]

It was found that lactam (**294**) could be prepared directly from condensation of the ester (**292**) and (**189**), however this resulted in poorer yields of the product over the reaction time stated.

It was thought that addition of camphor sulphonic acid to the reaction mixture would activate the ethoxy substituent in (**292**) making it a better leaving group, however this approach did not increase yields or decrease reaction times. Molecular sieves were added to the reaction mixtures, but again, had no effect on yields or reaction times.

The condensation reaction was carried out in xylene to elevate the reaction temperature to see whether an increase in product yield over a shorter time period would occur. Unfortunately, NMR analysis showed only a mixture of unknown decomposition products.

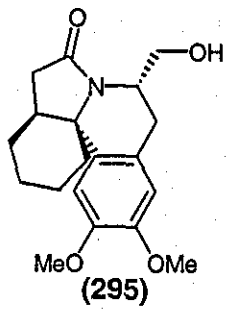
With **(294)** in hand, we turned to the proposed asymmetric *N*-acyliminium cyclisation study (Scheme 112).



Scheme 112

On treating lactam **(294)** with three equivalents of titanium tetrachloride as a Lewis acid activator at low temperature in dichloromethane over 20 hours we were pleased to isolate the desired tetracyclic erythrinane skeleton **(295)** in an excellent 98% yield.

^{1}H NMR Analysis of the crude product mixture revealed the formation of a 10 : 1 mixture of product diastereoisomers. The major diastereoisomer **(295)** was isolated by column chromatography, and the relative stereochemistry determined by X-ray crystallography (Figure 31).



(295)

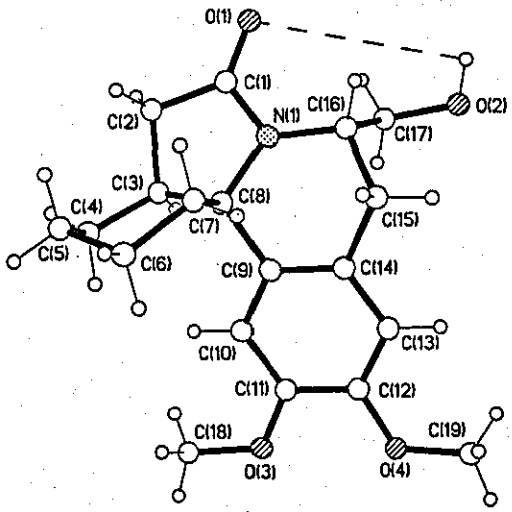


Figure 31

We were pleased to note that the stereochemical outcome of the cyclisation could be rationalised using the same conformational model previously proposed for related cyclisations. As highlighted in Figure 32, activation of the tricyclic lactam substrate by the Lewis acid leads to the formation of a formal *N*-acyliminium species.

In the proposed conformational model **A**, leading to the observed product diastereoisomer, the steric influence provided by the angular alkyl substituent, R, at the iminium carbon furnishes the observed major product diastereoisomer **(295)** with retention of stereochemistry.

One can envisage steric interactions between this angular alkyl group and the benzyl substituent that might disfavour the alternative conformation **B**. We have not ruled out the possible influence of chelation control with a Lewis acid such as titanium tetrachloride.

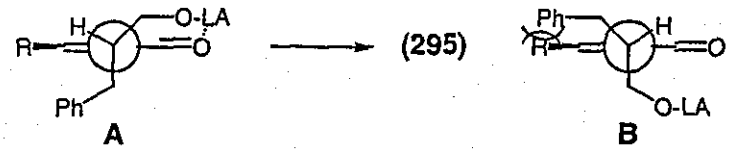
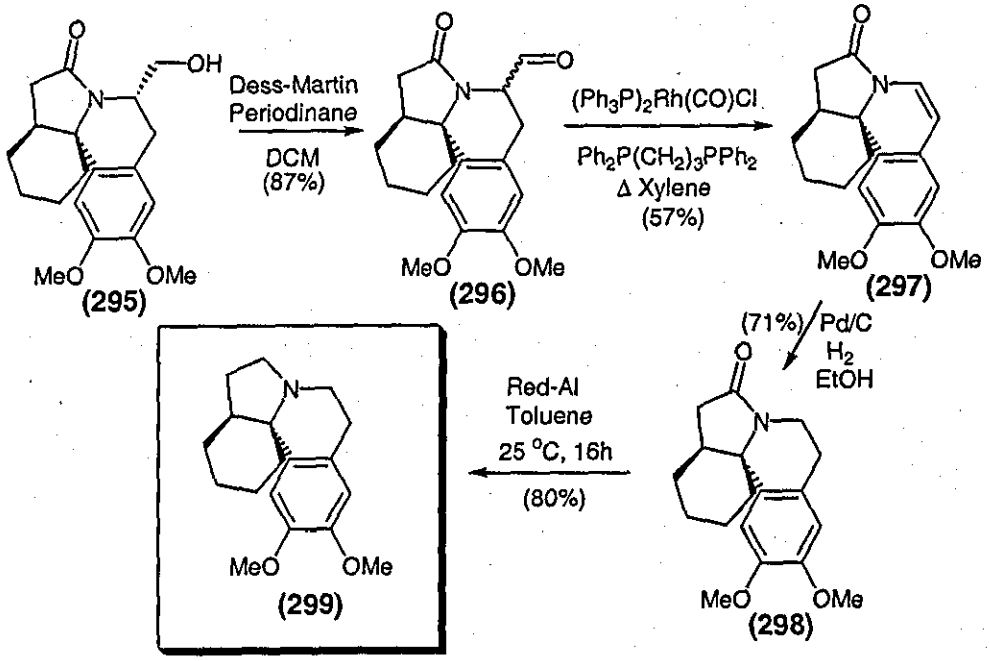


Figure 32

Removal of the pendant hydroxymethyl substituent (auxiliary) from the tetracyclic product (**295**) was achieved by application of a three-step procedure, (Scheme 113).

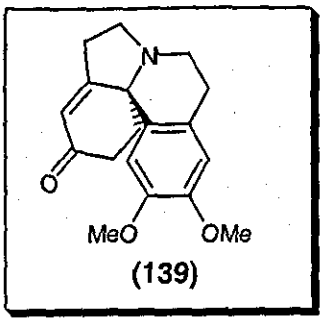
Dess-Martin periodinane oxidation of the primary alcohol proceeded in 87% yield to provide aldehyde (**296**). We then applied the rhodium-catalysed decarbonylation procedure which afforded enamide (**297**) in 57% yield. Catalytic hydrogenation of (**297**) furnished the desired compound (**298**) in 71% yield.

Further elaboration of the product by Red-Al reduction of the lactam carbonyl group gave the amine derivative (**299**) in 65% yield.



Scheme 113

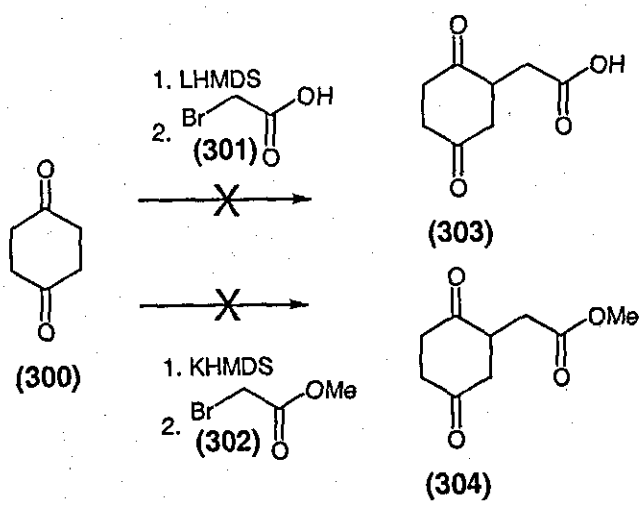
2.5.3. Total formal synthesis of (-)-3-demethoxyerythratidinone (139)



(139)

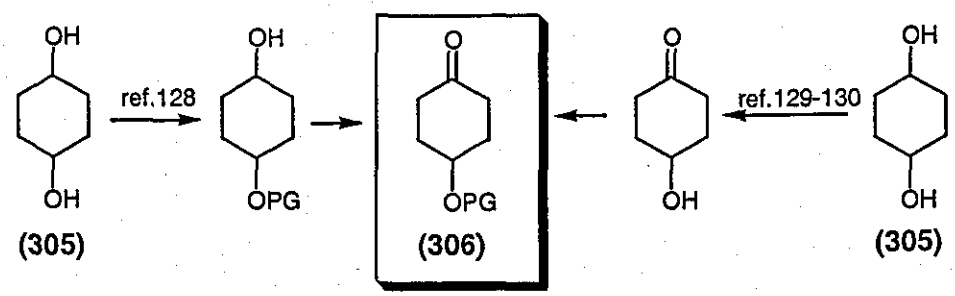
Figure 33

Our initial studies focused on functionalisation of the starting keto-acid (**293**). Alkylation of 1,4-cyclohexanone, (**300**) with bromoacetic acid, (**301**) or methyl bromoacetate, (**302**) should give the desired products (**303**) and (**304**) respectively, (Scheme 114). These reactions proved unsuccessful giving recovered starting materials and a mixture of unidentifiable products. It was postulated that a mono-protected cyclohexanone would give either (**303**) or (**304**).



Scheme 114

Monoprotected 4-cyclohexanone (**306**), (Scheme 115) has previously been obtained from 1,4-cyclohexanediol (**305**) by Jones and Sondheimer[128] by blocking one of the hydroxyl groups as the monobenzoate, followed by chromium oxidation of the second group.

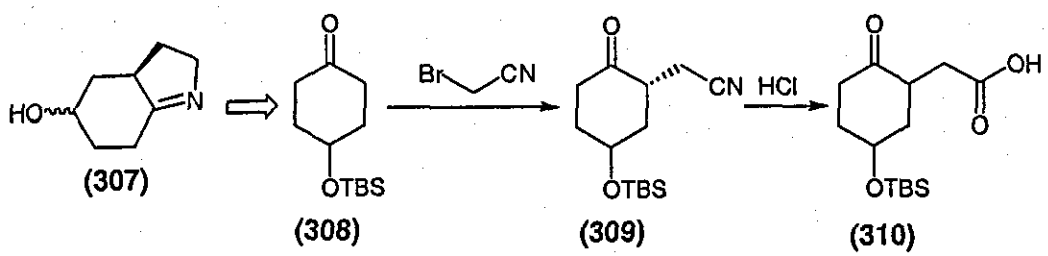


Scheme 115

We have found in previous experiments that benzyl protected alcohols do not withstand the Lewis acid cyclisation and so a different protecting group was sought. We tried using *tert*-butyldimethylchlorosilane as an alternative but this was unsuccessful as chromium oxidation led to the removal of the TBDMS group and gave the corresponding 1,4-diketone.

As an alternative, we followed combined methods of Kariv and Cohen[129] and Kitahara[130] *et al* which involved chromium oxidation of **(305)** with a single equivalent of chromium and then separating the products by silica gel chromatography.

Kitahara[130] synthesised imine **(307)** (Scheme 116) starting from mono-protected **(308)**[131] by oxidation of the corresponding 1,4-diol using Jones reagent. Alkylation of **(308)** with bromoacetonitrile gave the nitrile **(309)**. Preparation of **(309)** was interesting as it was envisioned that simple hydrolysis[132] of **(309)** would give the desired starting material **(310)**.

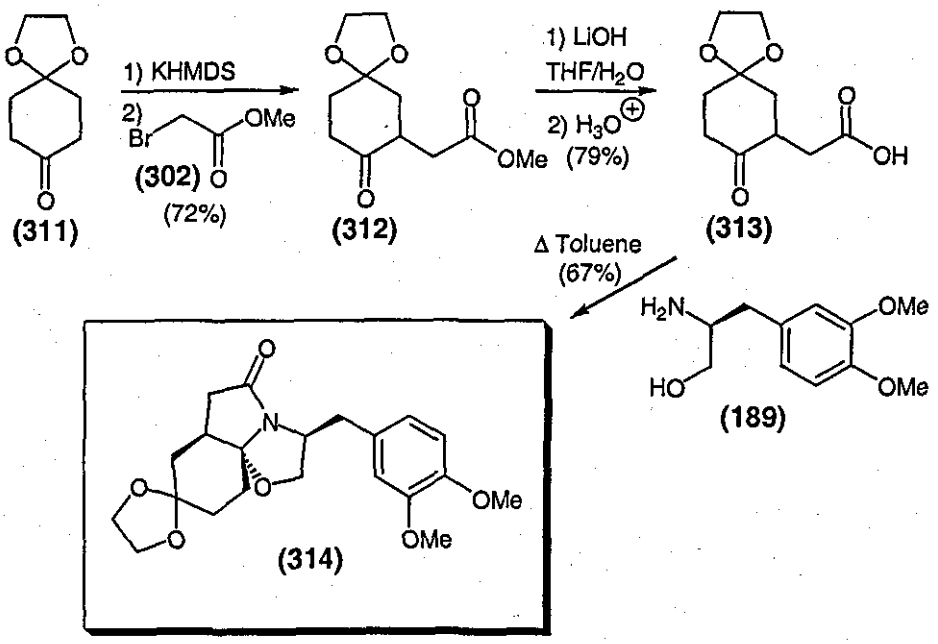


Scheme 116

The synthesis of **(308)** firstly by oxidation of the 1,4 - diol using Jones reagent was successful but in poor yield. The preparation of **(308)** was not further optimised. A more efficient way of synthesising the desired starting keto-acid was considered.

It was found by us that commercially available 1,4-cyclohexanedione monoethylene ketal **(311)** could be alkylated with methyl bromoacetate affording **(312)**, which was hydrolysed to the corresponding keto-acid **(313)** in good yield (80%), (Scheme 117).

Condensation of **(313)** with β-amino alcohol **(189)** in refluxing toluene for 168 hours under Dean-Stark conditions, gave the desired lactam **(314)** in 67% yield.



Scheme 117

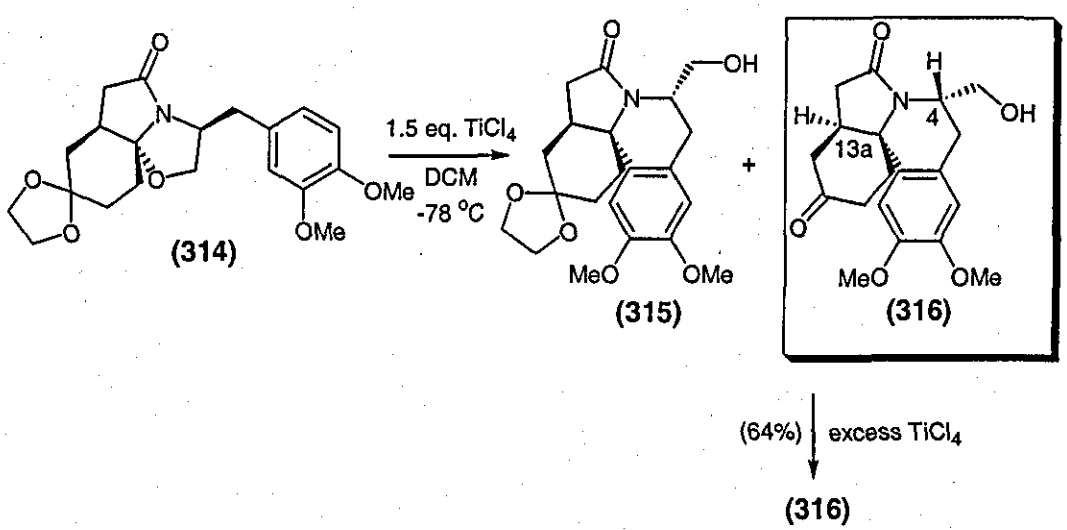
Yields of these "tetracyclic" lactam systems appear to be dependent only on reaction time.

Lewis acid induced cyclisation of **(314)**, employing our usual reaction conditions gave an inseparable mixture of protected and deprotected indoloisoquinoline systems, and traces of starting lactam, (Scheme 118). Stirring this mixture in excess titanium tetrachloride solution gave the deprotected indoloisoquinoline **(316)**. ^{1}H NMR Analysis of the crude product mixture revealed the formation of a 10 : 1 mixture of product diastereoisomers. The major diastereoisomer **(316)** was isolated

by column chromatography, and the stereochemistry determined by NOE studies. The absence of an NOE between protons situated at positions 4 and 13a suggests that the relative stereochemistry of the major product diastereoisomer was as indicated in product **(316)**.

Carrying out the cyclisation using 0.95 equivalents of the Lewis acid also gave access to a mixture of indoloisoquinoline products.

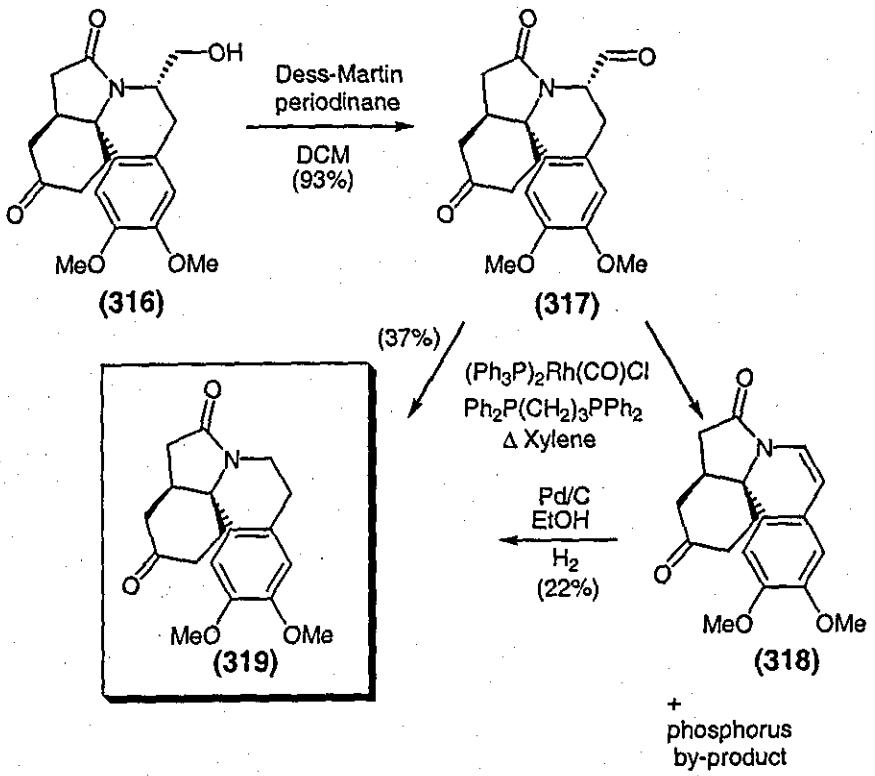
It would appear that cyclisation and deprotection of the acetal group are occurring simultaneously during the reaction. It was, therefore, impossible to synthesise and isolate **(315)**, however removal of the protecting group to give **(316)** at this stage in the reaction sequence was of no disadvantage to our future proposal. The protecting group could be incorporated at a later stage in the reaction sequence.



Scheme 118

Dess-Martin periodinane oxidation of indoloisoquinoline **(316)** proceeded in excellent yield to provide aldehyde **(317)** as a single diastereoisomer (Scheme 119).

Following the method previously applied in our laboratory we attempted a rhodium-catalysed decarbonylation and found that we were able to directly access the decarbonylated product **(319)** alongside the expected enamide **(318)**. Both compounds could be separated by flash column chromatography, however an inseparable phosphorus by-product co-eluted with enamide **(318)**.



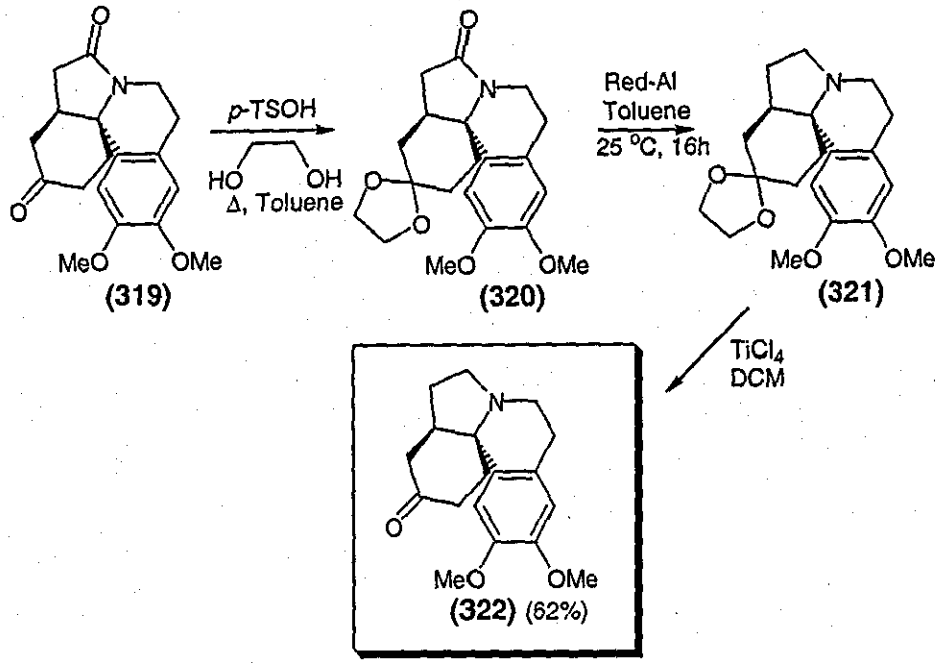
Scheme 119

Nevertheless, we were subsequently able to convert enamide (**318**) into the desired compound (**319**) by catalytic hydrogenation. At this stage column chromatography successfully separated the target product (**319**) from the phosphorus by-product.

Our next step was to further elaborate the product by Red-Al reduction of the lactam carbonyl group to afford the tertiary amine derivative (**322**). In order to carry out this reduction we first had to re-protect the ketone substituent on the ring to prevent reduction to the alcohol.

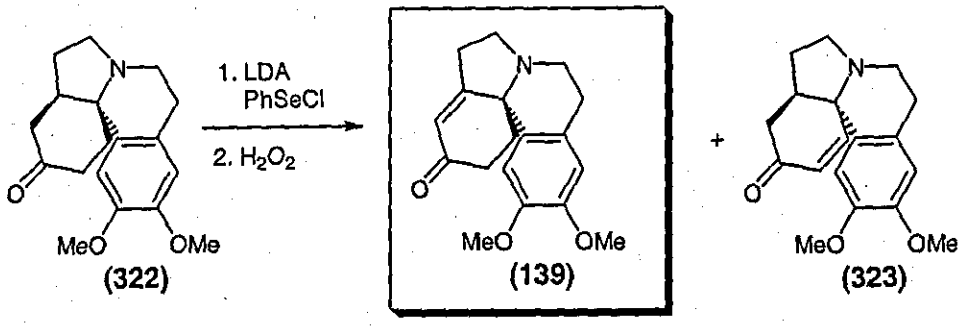
We used the acetal-protecting group as this was relatively straightforward to put on and we had already discovered a method for its easy removal. Scheme 120 outlines the synthetic route towards the desired compound (**322**).

It was found that purification of (**320**) and (**321**) was not necessary in order to obtain (**322**) in 62% overall yield from (**319**).



Scheme 120

With **(322)** in hand, it was envisioned that a double bond could be introduced to give the α,β-unsaturated carbonyl needed to furnish the natural product. We hoped to utilise the experimental procedure we had followed previously for the synthesis of unsaturated bicyclic lactam systems, using selenium chemistry, (Scheme 121).



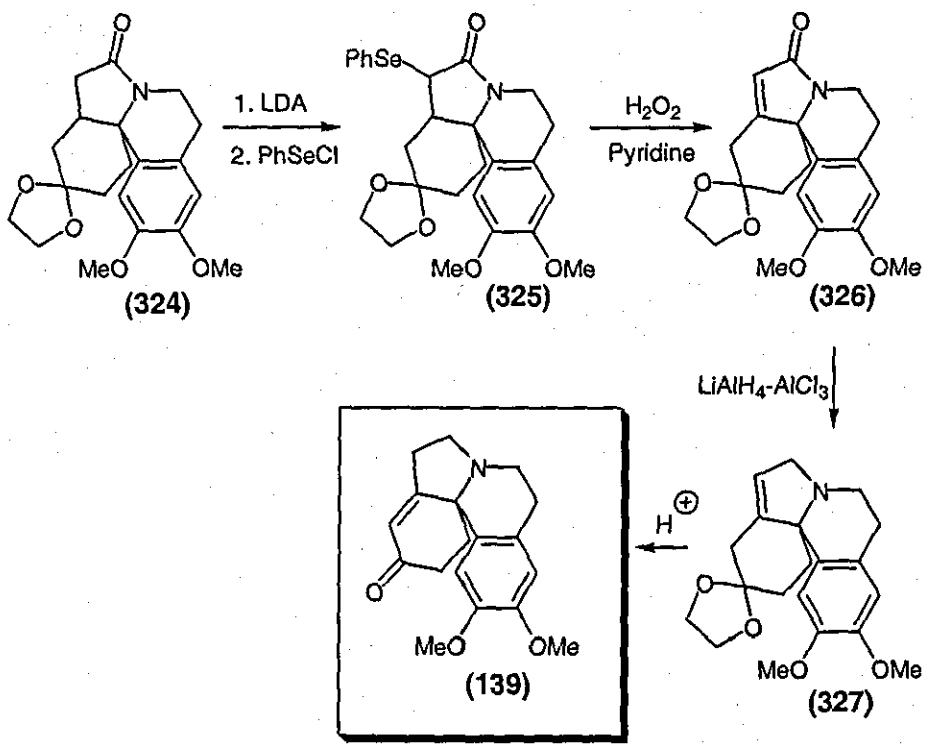
Scheme 121

Treatment of **(322)** with LDA in tetrahydrofuran, and benzeneselenenyl chloride followed by addition of hydrogen peroxide gave approximately 10-20 mg of a mixture of products according to TLC and crude ^{1}H NMR analysis. Due to the quantity obtained and time restraints we were unable to further purify this material using our usual purification techniques, however we were pleased to observe peaks within the crude ^{1}H NMR spectra corresponding to those published in the literature[85]

for (-)-3-demethoxyerythratidinone (**139**): δ_H(250 MHz, $CDCl_3$) 6.05, 1H, C=C*H*; 6.54, 1H, Ar*H*; 6.67 1H, Ar*H*; Lit: δ_H(60 MHz, $CDCl_3$) 6.09, 1H, C=C*H*; 6.57, 1H, Ar*H*; 6.66, 1H, Ar*H*.

On comparing our work with that of Tsuda's,[133] it is probable that the other major component in the reaction mixture is that of (**323**). This is not an unexpected proposal as LDA could abstract a proton from either side of the carbonyl as neither is particularly hindered (confirmed in the X-ray structure of compound (**295**), figure 31).

Tsuda[133] *et al* in 1984 described five different synthetic routes to (±)-3-demethoxyerythratidinone. Two of these routes, as illustrated in Scheme 122 and 123, have incorporated racemic alternatives of intermediates synthesised during this research project.

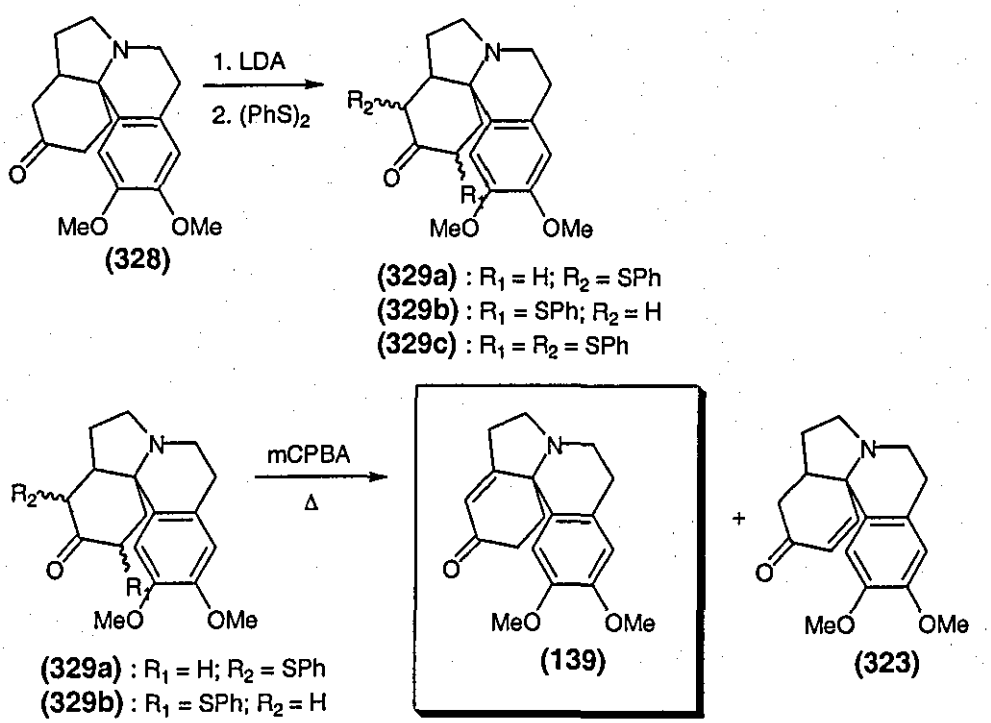


Scheme 122

Compound (**324**) was benzeneselenylated to (**325**) on treatment with LDA then with benzeneselenenyl chloride, (Scheme 122). Oxidative elimination of the benzeneselenenyl group from (**325**) resulted in (**326**). Reduction of (**326**) followed

by acid hydrolysis of the resulting amine (**327**) furnished, with concomitant migration of the double bond, alkaloid (**139**) in 77% yield.

Treatment of (**328**) with LDA followed by benzenesulfenylation resulted in a mixture of mono-(**329a**) and (**329b**) and di-(**329c**) benzenesulfides, (*Scheme* 123). The inseparable mixture of (**329a**) and (**329b**) was oxidised and the resulting sulfoxides were heated under reflux in carbon tetrachloride for 18 hours to afford (**139**) and (**323**), which were separated by silica gel chromatography.



Scheme 123

In conclusion, we have developed methodology for the synthesis of target pyrroloisoquinoline and indoloisoquinoline derivatives utilising *N*-acyliminium ion chemistry, and have applied this methodology towards the total formal asymmetric synthesis of the *erythrina* alkaloid (-)-3-demethoxyerythratidinone (**139**).

Chapter Three

Experimental

3.1. General information

3.1.1. Solvents

Where necessary solvents were dried, distilled and stored over 4Å molecular sieves prior to use:

Dichloromethane:	Distilled from phosphorus pentoxide.
Ethyl acetate:	Distilled from calcium chloride.
Light petroleum ether (40 - 60 °C):	Distilled from calcium chloride.
Hexane:	Used as bought from Fisher Scientific, UK.
Diethyl ether:	Used as bought from Fisher Scientific, UK.
Tetrahydrofuran:	Bought from Aldrich Chemical Company and distilled from sodium wire.
Toluene:	Distilled from sodium.
Absolute ethanol:	Used as bought from Fisher Scientific, UK.
Methanol:	Distilled from magnesium methoxide.

3.1.2. Reagents

Reagent chemicals were purchased from Lancaster Synthesis Ltd. and Aldrich Chemical Company Ltd.

3.1.3. Chromatographic procedures

Analytical thin layer chromatography (TLC) was carried out using aluminium - backed plates coated with 0.2 mm silica. Plates were visualised under UV light (254 nm) or by staining with potassium permanganate solution or iodine. Flash column chromatography was carried out using Merck silica gel (70-230 mesh ASTM).

3.1.4. Spectra

Infrared spectra (IR) were recorded in the range 4000-600 cm^{-1}, using a Perkin-Elmer Paragon 100 FT–IR spectrophotometer (with internal calibration), as Nujol mulls, thin films (DCM) or neat samples.

Nuclear Magnetic Resonance (NMR) spectra (^{1}H and ^{13}C) were recorded using either a Bruker Avance 400 MHz Spectrometer or a Bruker AC 250 MHz Spectrometer. All NMR samples were made up in deuterated chloroform with all values quoted in ppm relative to tetramethylsilane as internal reference. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublet of triplets (dt), double doublets (dd), doublet of double doublets (ddd), and multiplets (m). Coupling constants (*J* values) are reported in hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the ^{1}H NMR spectra.

Mass spectra were recorded using a Fisons VG Quattro II SQ instrument and Accurate-Mass mass spectra were recorded using a Kratos MS-80 instrument.

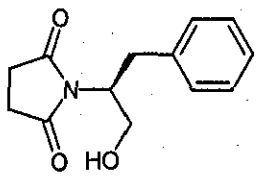
3.1.5. Other Data

Melting points were determined using an electrical 9100 Thermal Apparatus. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyser. Optical rotations were measured at 25 °C using an Optical Activity AA-10 Automatic Polarimeter and are reported in units of 10^{-1} deg cm^{2} g^{-1}. Yields (unless stated otherwise) are quoted for isolated pure products.

3.2. Stereoselective synthesis of chiral bicyclic lactams as *N*-acyliminium ion precursors

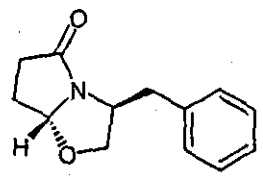
3.2.1. Stereoselective synthesis of bicyclic lactams

1-(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl-tetrahydro-1*H*-pyrrole-2,5-dione, **(184)**[135-136]



Succinic anhydride, **(182)**, (0.33 g, 3.3 mmol) and (*S*)-2-amino-3-phenyl-1-propanol, **(183)**, (0.50 g, 3.3 mmol) were dissolved in toluene (45 ml) under a nitrogen atmosphere. Triethylamine (1 ml) was added to the stirring mixture and the solution was heated at reflux for 18 hours. The solvent was removed by rotary evaporation and the resulting yellow oil was purified by flash column chromatography using 25% hexanes in ethyl acetate as eluent to yield a white solid (0.67 g, 87 %), a portion of which was recrystallised from dichloromethane and hexanes. Mp 130-131 °C; $[\alpha]_D$ = -89.8 (*c* = 0.48, DCM); (Found: C, 66.48; H, 6.38; N, 5.84. $C_{13}H_{15}NO_3$ requires C, 66.94; H, 6.48; N, 6.00%); ν_{max}(Nujol mull)/cm^{-1} 3411 (OH), 1764 and 1685 (imide); δ_H(250 MHz, $CDCl_3$) 2.45-2.70 (4H, m, 2 x C*H*$_2$CO), 2.80-2.91 (1H, br. s, O*H*), 3.04-3.20 (2H, m, C*H*$_2$Ar), 3.84 (1H, dd, *J* 12.0, 3.4, C*H*(H)OH), 4.00 (1H, dd, *J* 12.0, 7.1, C*H*(H)OH), 4.45-4.58 (1H, m, NC*H*), 7.16-7.30 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 28.0 (2 x *C*H$_2$CO), 33.8 (*C*H$_2$Ar), 55.8 (N*C*H), 62.4 (*C*H$_2$OH), 126.8 (Ar*C*H), 128.5 (2 x Ar*C*H), 129.1 (2 x Ar*C*H), 137.2 (Ar*C*), 178.0 (2 x *C*O); MS (EI) *m/z* 233 [M$^+$, 7.6%]; (Found: M$^+$, 233.1054. $C_{13}H_{15}NO_3$ requires 233.1052).

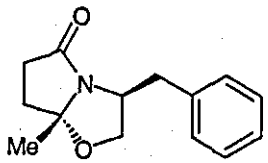
(3*S*,7a*R*)-3-(Phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(174)**[135-136]



1-(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl-tetrahydro-1*H*-pyrrole-2,5-dione, **(184)**, (2.00 g, 8.6 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (3.25 g, 85.5 mmol) was then added with stirring. HCl (2.0 M) in absolute ethanol (4.36 ml, 8.6 mmol) was added slowly *via* syringe over a 3 hour period. The solution was acidified to pH 1-3 by addition of HCl (2.0 M) in absolute ethanol over a 15 minute period, affording a white suspension which was stirred for an additional 20 hours at room temperature. The mixture was quenched by addition to a saturated aqueous sodium bicarbonate solution (100 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a colourless oil (1.43 g, 63%). The resulting oil, which was not purified, (0.45 g, 1.7 mmol) was stirred with a catalytic amount of TFA (5 mol%) in dichloromethane for 20 hours at room temperature. After the appropriate time the solvent was evaporated under reduced pressure to yield a colourless oil. This was purified further by flash column chromatography using a 1 : 1 mixture of hexanes and ethyl acetate as eluent yielding white crystals (0.17 g, 46%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 57-58 °C; $[\alpha]_D$ = +43.9 (*c* = 0.26, $CHCl_3$); (Found: C, 71.83; H, 6.98; N, 6.39. $C_{13}H_{15}NO_2$ requires C, 71.89; H, 6.91; N, 6.45 %); ν_{max}(Nujol mull)/cm^{-1} 1684 (lactam); δ_H(400 MHz, $CDCl_3$) 1.97-2.06 (1H, m, C*H*(H)CH_2CO), 2.29-2.38 (1H, m, C*H*(H)CH_2CO), 2.49 (1H, ddd, *J* 17.6, 10.4, 4.4, CH_2CH(H)CO), 2.64 (1H, ddd, *J* 17.6, 10.4, 7.2, CH_2CH(H)CO), 2.78 (1H, dd, *J* 13.9, 8.2, C*H*(H)Ar), 3.03 (1H, dd, *J* 13.9, 6.0, C*H*(H)Ar), 3.65 (1H, dd, *J* 8.8, 6.4, C*H*(H)O), 4.27 (1H, dd, *J* 8.8, 7.2, C*H*(H)O), 4.32-4.41 (1H, m, NC*H*CH_2O), 5.02 (1H, dd, *J* 6.0, 2.4, NC*H*O), 7.17-7.27 (3H, m, Ar*H*), 7.28-7.33 (2H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 24.5 (CH_2CH_2CO), 31.6 (CH_2CH_2CO), 39.3 (CH_2Ar), 55.3 (NCHCH$_2$O), 71.8 (CH_2O), 91.8 (NCHO), 126.8 (ArCH), 128.5 (ArCH), 128.6

(ArCH), 129.3 (2 x ArCH), 136.8 (ArC), 179.4 (CO); MS (EI) *m/z* 217 [M^+, 26.4 %]; (Found: M^+, 217.1107. $C_{13}H_{15}NO_2$ requires 217.1103).

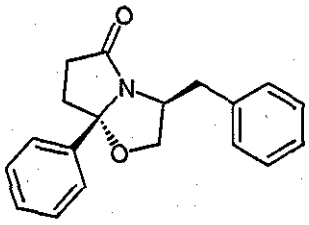
(3S,7a*R*)-7a-Methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(175)**[135-136]



(*S*)-2-Amino-3-phenyl-1-propanol, **(183)**, (1.00 g, 6.6 mmol) and levulinic acid, **(186)**, (0.68 ml, 6.6 mmol) were dissolved in toluene (150 ml) and refluxed under Dean-Stark conditions for 48 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation. The resulting purple oil was adsorbed onto silica and purified by column chromatography using a 1 : 1 mixture of diethyl ether and hexanes as eluent. Evaporation of the desired fraction afforded the target compound as pale yellow crystals (1.48 g, 97%), a portion of which was recrystallised from dichloromethane and hexanes to yield colourless needles. Mp 73-74 °C; $[\alpha]_D$ = +59.4 (*c* = 0.33, $CHCl_3$); (Found: C, 72.32; H, 7.37; N, 5.92. $C_{14}H_{17}NO_2$ requires C, 72.72; H, 7.36; N, 6.06%); ν_{max}(DCM)/cm^{-1} 1696 (lactam); δ_H(250 MHz, $CDCl_3$) 1.43 (3H, s, C*H*$_3$), 2.07-2.20 (2H, m, C*H*$_2$CH$_2$CO), 2.46 (1H, ddd, *J* 16.9, 8.0, 3.9, CH$_2$C*H*(H)CO), 2.67-2.84 (1H, m, CH$_2$C*H*(H)CO) 2.79 (1H, dd, *J* 13.6, 9.1, C*H*(H)Ar), 3.13 (1H, dd, *J* 13.6, 5.5, C*H*(H)Ar), 3.88 (1H, dd, *J* 8.9, 6.4, C*H*(H)O), 4.05 (1H, dd, *J* 8.9, 7.2, C*H*(H)O), 4.23-4.37 (1H, m, NC*H*CH$_2$O), 7.19-7.35 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 25.0 (*C*H$_3$), 33.3 (CH$_2$*C*H$_2$CO), 34.7 (*C*H$_2$CH$_2$CO), 40.3 (*C*H$_2$Ar), 55.8 (N*C*HCH$_2$O), 71.4 (*C*H$_2$O), 100.0 (*C*-CH$_3$), 126.7 (Ar*C*H), 128.6 (2 x Ar*C*H), 129.3 (2 x Ar*C*H), 137.1 (Ar*C*), 178.2 (*C*O); MS (EI) *m/z* 231 [M$^+$, 25.6%]; (Found: M$^+$, 231.1259. $C_{14}H_{17}NO_2$ requires 231.1259).

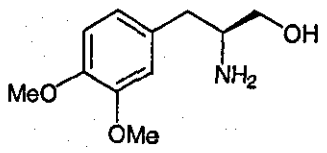
X-ray Crystal Data for (175): $C_{14}H_{17}NO_2$, *M*r = 231.29, orthorhombic, space group $P2_1P2_1P2_1$, *a* = 7.1177(3) Å, *b* = 10.5258(5) Å, *c* = 16.4294(8) Å, β = 90°, *V* = 1230.88(10) Å, *Z* = 4, D_{calcd} = 1.248 g cm^{-3}, *R* = 0.0145 for 2899 observed reflections, $F^2>2\sigma$ (2789) and 156 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

(3*S*,7a*R*)-7a-Phenyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*]oxazol-5-one, (**176**)



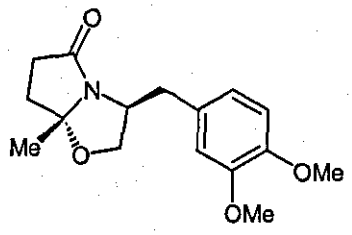
2-Amino-3-phenyl-1-propanol, (**183**), (1.00 g, 6.6 mmol) and 3-benzylpropionic acid, (**187**), (1.18 g, 6.6 mmol) were dissolved in toluene (150 ml) and refluxed under Dean-Stark conditions for 48 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation. The resulting dark orange oil was adsorbed on to silica and purified by column chromatography using a 1 : 1 mixture of diethyl ether and hexanes as eluent. Evaporation of the desired fraction afforded the target compound as yellow crystals (1.88 g, 88%), a portion of which was recrystallised from diethyl ether and hexanes to yield colourless needles. Mp 58-59 °C; $[\alpha]_D$ = +37.8 (*c* = 0.50, $CHCl_3$); (Found: C, 77.85; H, 6.50; N, 4.68. $C_{19}H_{19}NO_2$ requires C, 77.82; H, 6.48; N, 4.78%); ν_{max}(DCM)/cm^{-1} 1718 (lactam); δ_H(250 MHz, $CDCl_3$) 2.17-2.34 (1H, m, C*H*(H)CH_2CO), 3.30 (1H, dd, *J* 13.8, 9.4, C*H*(H)Ar), 2.43-2.63 (2H, m, C*H*(H)CH_2CO and CH_2C*H*(H)CO), 2.75-2.98 (1H, m, CH_2C*H*(H)CO), 2.95 (1H, dd, *J* 13.8, 6.1, C*H*(H)Ar), 3.58 (1H, dd, *J* 8.8, 6.9, C*H*(H)O), 4.13 (1H, dd, *J* 8.8, 7.4, C*H*(H)O), 4.36-4.49 (1H, m, NC*H*CH_2O), 7.04-7.30 (5H, m, Ar*H*), 7.33-7.54 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 33.1 (CH_2CH_2CO), 35.6 (*C*H_2CH_2CO), 40.5 (*C*H_2Ar), 57.1 (N*C*HCH_2O), 72.8 (*C*H_2O), 102.8 (*C*-Ar), 125.7 (2 x Ar*C*H), 127.2 (Ar*C*H), 128.8 (Ar*C*H), 129.1 (2 x Ar*C*H), 129.3 (2 x Ar*C*H), 129.5 (2 x Ar*C*H), 137.9 (Ar*C*), 143.3 (Ar*C*), 180.4 (*C*O); MS (EI) *m/z* 293 [M$^+$, 36.4%]; (Found: M$^+$, 293.1414. $C_{19}H_{19}NO_2$ requires 293.1416).

(2*S*)-2-Amino-3-(3,4-di(methyloxy)phenyl)propan-1-ol, **(189)**[137]



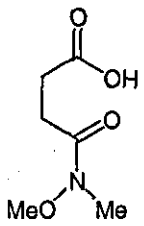
A solution of chlorotrimethylsilane (4.50 ml, 35.5 mmol) was added under nitrogen to a solution of lithium borohydride (8.88 ml of a 2.0 M solution in tetrahydrofuran, 17.7 mmol) in tetrahydrofuran (10 ml) over the course of 2 minutes. 3-(3,4-Dimethoxyphenyl)-*L*-alanine, **(188)**, (2.00 g, 8.9 mmol) was added portion wise to the mixture over 5 minutes, this was then left to stir at room temperature for 24 hours. Methanol (20 ml) was added slowly to the resulting blue solution and the solvents were removed by rotary evaporation. The residue was treated with 20% aqueous potassium hydroxide solution and extracted with dichloromethane (3 x 20 ml). The organic phases were combined, dried over anhydrous sodium sulfate, and the solvent evaporated to yield white crystals in quantitative yield (1.87 g, 100%) which required no further purification. Mp 82-83 °C, Lit: Mp 78-79 °C; $[\alpha]_D$ = -21.6 (c = 0.45, EtOH) Lit: $[\alpha]_D$ = $^{-}$21.5 (c = 8.0, EtOH); (Found: C, 62.29; H, 8.02; N, 6.53. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11; N, 6.63%); ν_{max}(DCM)/cm^{-1} 3356 (OH); δ_H(400 MHz, $CDCl_3$) 2.48 (1H, dd, J 13.6, 8.4, C*H*(H)CHNH$_2$), 2.69-2.76 (3H, br. s, O*H* and N*H*$_2$), 2.74 (1H, dd, J 13.6, 5.2, C*H*(H)CHNH$_2$), 3.08-3.13 (1H, m, NH$_2$C*H*), 3.42 (1H, dd, J 10.6, 6.9, C*H*(H)OH), 3.64 (1H, dd, J 10.6, 3.7, C*H*(H)OH), 3.85 (3H, s, C*H*$_3$O), 3.86 (3H, s, C*H*$_3$O), 6.71-6.74 (2H, m, Ar*H*), 6.78-6.80 (1H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 40.2 (*C*H$_2$CHNH$_2$), 54.3 (NH$_2$*C*H), 55.9 (2 x *C*H$_3$O), 66.1 (*C*H$_2$OH), 111.4 (Ar*C*H), 112.4 (Ar*C*H), 121.2 (Ar*C*H), 131.3 (Ar*C*), 147.7 (Ar*C*-OCH$_3$), 149.2 (Ar*C*-OCH$_3$); MS (EI) m/z 211 [M$^+$, 6.5%]; (Found: M$^+$, 211.1211. $C_{11}H_{17}NO_3$ requires 211.1208).

(3*S*,7a*R*)-3-(3,4-Di(methyloxy)phenylmethyl)-7a-methylperhydropyrrolo[2,1-*b*][1,3] oxazol-5-one, **(177)**[135]



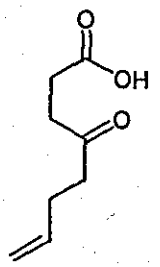
(2*S*)-2-Amino-3-(3,4-di(methyloxy)phenyl)propan-1-ol, **(189)**, (0.78 g, 3.7 mmol) and levulinic acid, **(186)**, (0.43 ml, 3.7 mmol) were dissolved in toluene (75 ml) and refluxed under Dean-Stark conditions for 48 hours. The solution was allowed to cool before the solvent was removed by rotary evaporation giving a red-brown oil. Purification by flash column chromatography using ethyl acetate and hexanes (2 : 1) as eluent yielded a pale yellow oil as the target compound (0.87 g, 81%). $[\alpha]_D$ = +36.5 (c = 0.37, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1706 (lactam); δ_H(250 MHz, $CDCl_3$) 1.45 (3H, s, C*H*$_3$), 2.11-2.22 (2H, m, C*H*$_2$CH$_2$CO), 2.47 (1H, ddd, *J* 16.9, 8.1, 3.9, CH$_2$CH(H)CO), 2.68-2.83 (1H, m, CH$_2$C*H*(H)CO) 2.73 (1H, dd, *J* 13.9, 9.4, C*H*(H)Ar), 3.09 (1H, dd, *J* 13.9, 5.6, C*H*(H)Ar), 3.83-3.93 (1H, m, C*H*(H)O), 3.83 (3H, s, C*H*$_3$O), 3.89 (3H, s, C*H*$_3$O), 4.05 (1H, dd, *J* 9.0, 7.2, C*H*(H)O), 4.29 (1H, ddd, *J* 15.4, 9.3, 6.0, NC*H*CH$_2$O), 6.72-6.83 (3H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 25.0 (*C*H$_3$), 33.3 (CH$_2$*C*H$_2$CO), 34.7 (*C*H$_2$CH$_2$CO), 39.8 (*C*H$_2$Ar), 55.7 (*C*H$_3$O), 55.9 (*C*H$_3$O), 56.0 (N*C*HCH$_2$O), 71.4 (*C*H$_2$O), 100.1 (*C*-CH$_3$), 111.3 (Ar*C*H), 112.4 (Ar*C*H), 121.3 (Ar*C*H), 129.7 (Ar*C*), 147.9 (Ar*C*-OCH$_3$), 149.0 (Ar*C*-OCH$_3$), 178.3 (*C*O); MS (EI) *m/z* 291 [M$^+$, 87.5%]; (Found: M$^+$, 291.1470. $C_{16}H_{21}NO_4$ requires 291.1471).

N-Methoxy-*N*-methyl-succinic acid, (**190**)



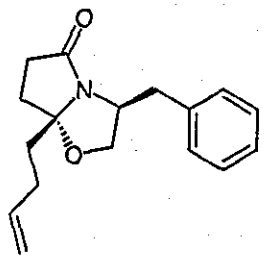
An ice cold suspension of succinic anhydride, (**182**), (1.00 g, 10.0 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.07 g, 11.0 mmol) in chloroform (10 ml) was treated in drop wise fashion with vigorous stirring, with pyridine (1.78 ml, 22.0 mmol) while maintaining a temperature between 0 - 5 °C. After addition was complete, the resulting colourless solution was stirred an additional 10 minutes at 0 - 5 °C, and then for 7 hours at room temperature. The solvents were evaporated off and extracted with a 1 : 1 mixture of dichloromethane and diethyl ether (10 ml) and brine (10 ml). The aqueous layer was extracted with dichloromethane (3 x 10 ml), washed with brine, dried using anhydrous sodium sulfate, and the solvents removed. Recrystallisation from ethyl acetate gave white crystals (1.19 g, 74%). Mp 89-90 °C; (Found: C, 44.60; H, 6.84; N, 8.57. $C_6H_{11}NO_4$ requires C, 44.72; H, 6.88; N, 8.69%); ν_{max}(DCM)/cm^{-1} 3008 (OH), 1725 (CO), 1616 (CO); δ_H(400 MHZ, $CDCl_3$) 2.67-2.72 (2H, m, CH_2COOH), 2.74-2.85 (2H, m, CH_2CON), 3.20 (3H, s, NCH_3), 3.72 (3H, s, OCH_3); δ_C(100 MHZ, $CDCl_3$) 27.2 (*C*H_2CON), 29.0 (*C*H_2COOH), 32.6 (N*C*H_3), 61.6 (O*C*H_3), 173.3 (*C*O), 178.0 (*C*O); MS (EI) *m/z* 161 [M$^+$, 1.1%]; (Found: M$^+$, 161.0685. $C_6H_{11}NO_4$ requires 161.0688).

4-Oxo-oct-7-enoic acid, **(193)**



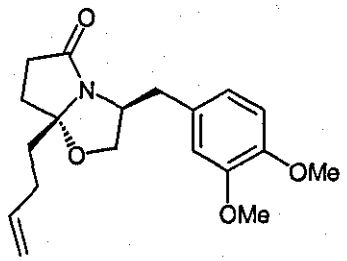
To a solution of *N*-methoxy-*N*-methyl-succinic acid, **(190)**, (0.50 g, 3.1 mmol) in tetrahydrofuran (20 ml) was added 3-butenylmagnesium bromide (18.60 ml of a 0.5 M solution in tetrahydrofuran, 9.3 mmol) at -78 °C under a nitrogen atmosphere. The resulting solution was stirred for 1 hour at -78 °C, warmed to room temperature and stirred for 2 hours. The resulting white solution was carefully quenched by the addition of HCl (2.0 M) and extracted with ethyl acetate (3 x 20 ml). The organic extracts were combined and washed with water and then brine and dried over anhydrous magnesium sulfate to give a yellow oil (0.38 g, 79%). Flash column chromatography using ethyl acetate and hexanes (1 : 5) as mobile phase gave the purified product as a pale yellow oil (0.26 g, 55 %). ν_{max}(Neat)/cm^{-1} 2923 (OH), 1705 (CO), 1642 (CO), 9.97 and 9.13 (CHR=CH_2); δ_H(400 MHz, $CDCl_3$) 2.31-2.37 (2H, m, CH_2), 2.54-2.58 (2H, m, CH_2), 2.61-2.64 (2H, m, CH_2), 2.71-2.74 (2H, m, CH_2), 4.96-5.06 (2H, m, CH_2=CH), 5.75-5.85 (1H, m, CH_2=CH), 9.80-10.60 (1H, br. s, OH); δ_C(100MHz, $CDCl_3$) 27.7 (CH_2), 27.8 (CH_2), 36.9 (CH_2), 41.7 (CH_2), 115.4 (CH_2=CH), 136.9 (CH_2=CH), 178.6 (CO), 208.2 (CO); MS (EI) *m/z* 157 [M^++1, 2.5%]; (Found: M^+, 156.0784. $C_8H_{12}O$ requires 156.0787).

(3*S*,7a*R*)-3-Benzyl-7a-but-3-enyl-tetrahydropyrrolo[2,1-*b*]oxazol-5-one, **(178)**



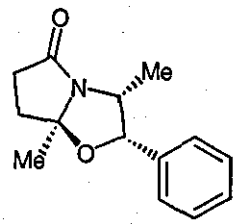
(*S*)-2-Amino-3-phenyl-1-propanol, **(183)**, (0.51 g, 3.4 mmol) and 4-oxo-oct-7-enoic acid, **(193)**, (0.53 g, 3.4 mmol) were dissolved in toluene (30 ml) and refluxed for 24 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation to give a yellow oil. Further purification by flash column chromatography using a 1 : 1 mixture of ethyl acetate and hexanes as eluent yielded the desired compound as a yellow oil (0.78 g, 85%). $[\alpha]_D$ = +34.4 (*c* 0.39 , $CHCl_3$); ν_{max}(neat)/cm^{-1} 1710 (CO), 997 and 912 CH_2=CH_2; δ_H(400 MHZ, $CDCl_3$) 1.68-1.83 (2H, m, C*H*$_2$CH$_2$CH=CH$_2$), 2.01-2.09 (1H, m, C*H*(H)CH$_2$CO), 2.11-2.22 (2H, m, CH$_2$C*H*$_2$CH=CH$_2$), 2.25-2.31 (1H, m, C*H*(H)CH$_2$CO), 2.47 (1H, ddd, *J* 17.3, 10.2, 2.0, CH$_2$C*H*(H)CO), 2.65-2.79 (1H, m, CH$_2$C*H*(H)CO), 2.76 (1H, dd, *J* 13.8, 9.5, C*H*(H)Ar), 3.15 (1H, dd, *J* 13.8, 5.6, C*H*(H)Ar), 3.86 (1H, dd, *J* 8.9, 6.9, CH$_2$C*H*(H)O), 4.06-4.15 (1H, m, C*H*(H)O), 4.28-4.36 (1H, m, NC*H*), 4.99-5.08 (2H, m, CH$_2$CH$_2$CH=C*H*$_2$), 5.78-5.86 (1H, m, CH$_2$CH$_2$C*H*=CH$_2$), 7.20-7.35 (5H, m, Ar*H*); δ_C(100 MHZ, $CDCl_3$) 28.4 (CH$_2$*C*H$_2$CH=CH$_2$), 31.4 (*C*H$_2$CH$_2$CO), 33.4 (CH$_2$CH$_2$CO), 36.4 (*C*H$_2$CH$_2$CH=CH$_2$), 40.6 (*C*H$_2$Ar), 55.9 (N*C*H), 71.4 (*C*H$_2$O), 102.0 (*C*-CH$_2$CH$_2$CH=CH$_2$), 115.0 (CH$_2$CH$_2$CH=*C*H$_2$), 126.8 (Ar*C*H), 128.6 (Ar*C*H), 129.0 (Ar*C*H), 129.2 (Ar*C*H), 129.5 (Ar*C*H), 137.0 (Ar*C*), 137.5 (CH$_2$CH$_2$*C*H=CH$_2$), 178.9 (*C*O); MS (EI) *m/z* 271 [M^+, 1.1%]; (Found: M^+, 271.1580. $C_{17}H_{21}NO_2$ requires 271.1572).

(3*S*,7a*R*)-7a-But-3-enyl-3-(3,4-dimethoxy-benzyl)-tetrahydropyrrolo[2,1-*b*]oxazol-5-one, **(179)**



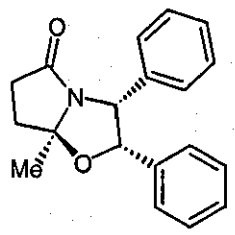
(2*S*)-2-Amino-3-(3,4-di(methyloxy)phenyl)propan-1-ol, **(189)**, (0.31 g, 1.5 mmol) and 4-oxo-oct-7-enoic acid, **(193)**, (0.23 g, 1.5 mmol) were dissolved in toluene (10 ml) and refluxed under Dean-Stark conditions for 24 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation to give a yellow oil. Further purification by flash column chromatography using a 1 : 1 mixture of ethyl acetate and hexanes as eluent yielded the desired compound as a yellow oil (0.37 g, 77%). $[\alpha]_D$ = +34.3 (*c* = 0.37 , $CHCl_3$); ν_{max}(Neat)/cm^{-1} 1703 (lactam); δ_H(400 MHz, $CDCl_3$) 1.70-1.85 (2H, m, C*H*$_2$CH$_2$CH=CH$_2$), 2.01-2.10 (1H, m, C*H*(H)CH$_2$CO), 2.11-2.22 (2H, m, CH$_2$C*H*$_2$CH=CH$_2$), 2.25-2.31 (1H, m, C*H*(H)CH$_2$CO), 2.47 (1H, ddd, *J* 17.3, 10.2, 2.3, CH$_2$C*H*(H)CO), 2.65-2.75 (2H, m, CH$_2$C*H*(H)CO and C*H*(H)Ar), 3.10 (1H, dd, *J* 13.8, 5.5, C*H*(H)Ar), 3.83-3.87 (1H, m, C*H*(H)O), 3.86 (3H, s, C*H*$_3$O), 3.88 (3H, s, C*H*$_3$O), 4.08 (1H, dd, *J* 8.9, 7.4, C*H*(H)O), 4.31 (1H, ddd, *J* 12.7, 9.2, 6.9, NC*H*CH$_2$O), 4.99-5.08 (2H, m, CH$_2$CH$_2$CH=C*H*$_2$), 5.78-5.86 (1H, m, CH$_2$CH$_2$C*H*=CH$_2$), 6.73-6.81 (3H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 28.3 (*C*H$_2$CH=CH$_2$), 31.3 (*C*H$_2$CH$_2$CO), 33.3 (CH$_2$*C*H$_2$CO), 36.4 (*C*H$_2$CH$_2$CH=CH$_2$), 40.1 (*C*H$_2$Ar), 55.75 (*C*H$_3$O), 55.8 (*C*H$_3$O), 55.9 (N*C*HCH$_2$O), 71.3 (*C*H$_2$O), 102.0 (*C*-CH$_2$CH$_2$CH=CH$_2$), 111.2 (Ar*C*H), 112.3 (Ar*C*H), 114.9 (CH$_2$CH$_2$CH=*C*H$_2$), 121.1 (Ar*C*H), 129.5 (Ar*C*), 137.4 (CH$_2$CH$_2$*C*H=CH$_2$), 147.8 (Ar*C*-OCH$_3$), 148.9 (Ar*C*-OCH$_3$), 178.8 (*C*O); MS (EI) *m/z* 331 [M^+, 67.4%]; (Found: M^+, 331.1782. $C_{19}H_{25}NO_4$ requires 331.1784).

(2S,3*R*,7aS)-3,7a-Dimethyl-2-phenylperhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, (**197**)



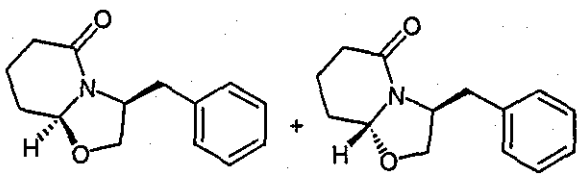
(1*S*,2*R*) Norephedrine, (**195**), (1.00 g, 6.6 mmol) and levulinic acid, (**186**), (0.68 ml, 6.6 mmol) were dissolved in toluene (150 ml) and refluxed under Dean-Stark conditions for 20 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation. The resulting yellow oil was adsorbed on to silica and purified by column chromatography using a 3 : 2 mixture of petroleum ether and ethyl acetate as eluent. Evaporation of the desired fraction afforded the target compound as a colourless oil in quantitative yield. $[\alpha]_D$ = +23.7 (*c* = 0.12, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1708 (lactam); δ_H(250 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.4 NCHC*H*$_3$), 1.68 (3H, s, C*H*$_3$), 2.07-2.34 (2H, m, C*H*(H)CH_2CO and CH_2C*H*(H)CO), 2.46 (1H, ddd, *J* 16.5, 8.8, 1.2, CH_2C*H*(H)CO), 2.63-2.81 (1H, m, C*H*(H)CH_2CO), 4.44 (1H, ddd, *J* 14.3, 7.2, 5.7, NC*H*CH_3), 5.00 (1H, d, *J* 5.6, OC*H*Ar), 7.25-7.41 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 15.3 (NCH*C*H$_3$), 27.6 (*C*H$_3$), 33.2 (CH_2*C*H_2CO), 37.2 (*C*H_2CH_2CO), 55.0 (N*C*HCH$_3$), 82.2 (O*C*HAr), 98.9 (*C*-CH$_3$), 126.1 (2 x Ar*C*H), 127.8 (Ar*C*H), 128.3 (2 x Ar*C*H), 136.5 (Ar*C*), 177.8 (*C*O); MS (EI) *m/z* 230 [M^+-1, 5.3%]; (Found: M^+, 231.1260. $C_{14}H_{17}NO_2$ requires 231.1259).

(2*S*,3*R*,7a*S*)-7a-Methyl-2,3-diphenylperhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(198)**



(1*S*, 2*R*)-2-Amino-1,2-diphenylethanol, **(196)**, (0.50 g, 2.3 mmol) and levulinic acid, **(186)**, (0.24 ml, 2.3 mmol) were dissolved in toluene (100 ml) and refluxed under Dean-Stark conditions for 20 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation. The resulting yellow oil was adsorbed on to silica and purified by column chromatography using a 2 : 1 mixture of petroleum ether and ethyl acetate as eluent. Evaporation of the desired fraction afforded the target compound in quantitative yield as white crystals, a portion of which was recrystallised from dichloromethane and hexanes to yield colourless crystals. Mp 127-130 °C; $[\alpha]_D$ = +59.4 (*c* = 0.35, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 1711 (lactam); δ_H(250 MHz, $CDCl_3$) 1.80 (3H, s, CH_3), 2.22-2.45 (2H, m, CH_2CH_2CO), 2.50-2.63 (1H, m, $CH_2CH(H)CO$), 2.77-2.94 (1H, m, $CH_2CH(H)CO$), 5.32 (1H, d, *J* 6.2, NC*H*Ar), 5.46 (1H, d, *J* 6.2, OC*H*Ar), 6.84-6.91 (2H, m, Ar*H*), 7.00-7.24 (8H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 26.7 (CH_3), 33.5 (CH_2CH_2CO), 37.7 (CH_2CH_2CO), 63.4 (NCHAr), 83.7 (OCHAr), 99.6 (*C*-CH_3), 127.0 (ArCH), 127.2 (2 x ArCH), 127.5 (2 x ArCH), 127.9 (ArCH), 128.0 (2 x ArCH), 128.1 (2 x ArCH), 135.7 (2 x Ar*C*), 178.8 (*C*O); MS (EI) *m/z* 292 [M^+-1, 4.2%]; (Found: M^+, 293.1409. $C_{19}H_{19}NO_2$ requires 293.1416).

(3*S*,8a*S*)-3-(Phenylmethyl)perhydropyrido[2-1,*b*][1,3]oxazol-5-one, **(200a)**[95, 134]
(3*S*,8a*R*)-3-(Phenylmethyl)perhydropyrido[2-1,*b*][1,3]oxazol-5-one, **(200b)**[95, 134]



(*S*)-2-Amino-3-phenyl-1-propanol, **(183)**, (2.67 g, 17.7 mmol) and methyl 5-oxopentanoate, **(199)**, (2.30 ml, 17.7 mmol) were dissolved in toluene (150 ml) and refluxed under Dean-Stark conditions for 48 hours. After this time the solution was allowed to cool and the solvent was removed by rotary evaporation. The resulting yellow oil was not purified and taken on to the next step.

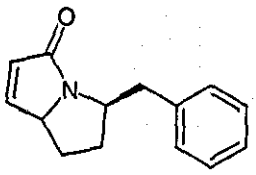
Major isomer (200a): ν_{max}(Neat)/cm^{-1} 1646 (lactam); δ_H(400 MHz, $CDCl_3$) 1.35-1.45 (1H, m, C*H*(H)CH_2CH_2CO), 1.65-1.75 (1H, m, CH_2CH(H)CH_2CO), 1.92-2.00 (1H, m, CH_2CH(H)CH_2CO), 2.16-2.24 (1H, m, C*H*(H)CH_2CH_2CO), 2.32-2.43 (2H, m, $CH_2CH_2CH_2CO$), 2.61 (1H, dd, *J* 13.3, 9.7, C*H*(H)Ar), 3.57 (1H, dd, *J* 13.3, 3.0, C*H*(H)Ar), 3.71 (1H, ddd, *J* 9.4, 6.3, 1.3, C*H*(H)O), 4.00 (1H, dd, *J* 9.3, 1.1, C*H*(H)O), 4.18-4.23 (1H, m, NC*H*CH_2O), 4.65 (1H, dd, *J* 10.0, 3.3, NC*H*), 7.19-7.32 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 17.9 ($CH_2CH_2CH_2CO$), 28.6 ($CH_2CH_2CH_2CO$), 31.4 ($CH_2CH_2CH_2CO$), 37.3 (CH_2Ar), 57.0 (NCHCH$_2$O), 69.6 (CH_2O), 89.3 (NCH), 126.8 (ArCH), 129.0 (2 x ArCH), 129.9 (2 x ArCH), 138.5 (ArC), 168.4 (CO); MS (EI) *m/z* 231 [M^+, 17%]; (Found: M^+, 231.1263. $C_{14}H_{17}NO_2$ requires 231.1259).

Minor isomer (200b): ν_{max} (Neat)/cm^{-1} 1640 (lactam); δ_H(400 MHz, $CDCl_3$) 1.33-1.48 (1H, m, C*H*(H)CH_2CH_2CO), 1.60-1.67 (1H, m, CH_2CH(H)CH_2CO), 1.82-1.97 (1H, m, CH_2CH(H)CH_2CO), 2.17-2.30 (1H, m, C*H*(H)CH_2CH_2CO), 2.35 (1H, ddd, *J* 18.1, 11.6, 6.6, CH_2CH_2CH(H)CO), 2.51 (1H, dd, *J* 18.1, 16.0, CH_2CH_2CH(H)CO), 2.82 (1H, dd, *J* 13.4, 9.1, C*H*(H)Ar), 3.30 (1H, dd, *J* 13.4, 3.7, C*H*(H)Ar), 3.64 (1H, dd, *J* 9.0, 7.6, C*H*(H)CO), 4.05 (1H, dd, *J* 9.0, 7.6, C*H*(H)CO), 4.45-4.54 (2H, m, NC*H* and NC*H*CH_2O), 7.15-7.37 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 17.5 ($CH_2CH_2CH_2CO$), 28.6 ($CH_2CH_2CH_2CO$), 31.7 ($CH_2CH_2CH_2CO$),

38.2 (CH_2Ar), 55.4 (N$CH$$CH_2O$), 69.6 ($CH_2O$), 89.7 (N$CH$), 127.1 (Ar$CH$), 128.9 (2 x Ar$CH$), 129.9 (2 x Ar$CH$), 137.3 (Ar$C$), 169.0 ($CO$).

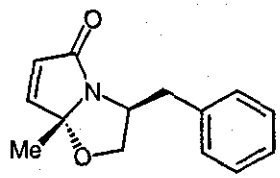
3.2.2. Stereoselective synthesis of unsaturated bicyclic lactams

(3*S*,7a*R*)-3-(phenylmethyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(201)**



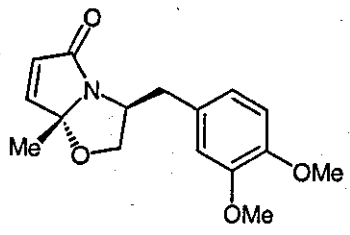
A solution of LDA (2.21 ml of a 2.0 M solution in heptane, 4.4 mmol) in anhydrous tetrahydrofuran (10 ml) was cooled to -78 °C and (3*S*,7a*R*)-3-(phenylmethyl) perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(174)**, (0.48 g, 2.2 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added drop wise and stirred for 10 minutes. Benzeneselenenyl chloride (0.64 g, 3.3 mmol) in tetrahydrofuran (5 ml) was added drop wise and the solution warmed to 0 °C. Water (1.5 ml), acetic acid (0.3 ml) and hydrogen peroxide (1.17 g of a 35% solution) were added and the reaction mixture was maintained below 25 °C for approximately 30 minutes. The solution was poured into saturated aqueous sodium bicarbonate solution (50 ml) and a 1 : 1 ether-hexane mixture (50 ml), and the organic layer was washed successively with water, HCl (0.1 M), water and saturated aqueous sodium chloride solution. Flash column chromatography using ethyl acetate and hexanes (1 : 2) as eluent gave reclaimed starting material (50 mg, 11%), an unknown by-product (6%) and the desired unsaturated lactam as a colourless oil (0.10g, 21%). ν_{max}(DCM)/cm^{-1} 1716 (lactam), 1654 and 1604 (C=C); δ_H(250 MHz, $CDCl_3$) 2.83 (1H, dd, *J* 13.9, 7.9, C*H*(H)Ar), 3.07 (1H, dd, *J* 13.9, 5.1 C*H*(H)Ar), 3.82-4.01 (1H, m, NC*H*CH_2O), 4.08-4.27 (2H, m, CH_2O), 5.41 (1H, s, NC*H*O), 6.13 (1H, d, *J* 5.8, CH=C*H*CO), 7.08 (1H, dd, *J* 5.8, 1.6, C*H*=CHCO), 7.17-7.37 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 40.0 (*C*H_2Ar), 53.8 (NCHCH$_2$O), 75.5 (*C*H_2O), 93.4 (NCHO), 127.2 (ArCH), 129.0 (2 x Ar*C*H), 129.8 (2 x ArCH), 131.5 (CH=*C*HCO), 137.7 (Ar*C*), 146.3 (*C*H=CHCO), 177.0 (*C*O); MS (EI) *m/z* 215 [M$^+$, 64.3%]; (Found: M$^+$, 215.0948. $C_{13}H_{13}NO_2$ requires 215.0946).

(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(202)**[135]



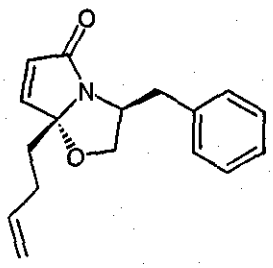
A solution of LDA (4.30 ml of a 2.0 M solution in heptane, 8.7 mmol) in anhydrous tetrahydrofuran (20 ml) was cooled to -78 °C and (3S,7a*R*)-7a-methyl-3-(phenyl methyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(175)**, (1.00 g, 4.3 mmol) in anhydrous tetrahydrofuran (10 ml) was slowly added drop wise and stirred for 3 hours. Benzeneselenenyl chloride (1.24 g, 6.5 mmol) in tetrahydrofuran (10 ml) was added drop wise and the solution warmed to 0 °C and stirred for an additional 1 hour. Water (3.0 ml), acetic acid (0.3 ml) and hydrogen peroxide (2.34 g of a 35% solution) was added and the reaction mixture was maintained below 25 °C for approximately 30 minutes and then stirred for an additional 12 hours at room temperature. The solution was poured into saturated aqueous sodium bicarbonate solution (100 ml) and a 1 : 1 ether-hexane mixture (100 ml), and the organic layer was washed successively with water, HCl (0.1 M), water and saturated aqueous sodium chloride solution. Flash column chromatography using ethyl acetate and hexanes (1 : 3) as eluent gave reclaimed starting material (0.39 g) and the target compound as colourless crystals (0.50 g, 51%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 72-73 °C; $[\alpha]_D$ = -7.0 (*c* = 0.14, $CHCl_3$); (Found: C, 73.14; H, 6.46; N, 6.11. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%); ν_{max}(DCM)/cm^{-1} 1712 (lactam), 1670 and 1654 (C=C); δ_H(400 MHz, $CDCl_3$) 1.51 (3H, s, CH_3), 2.91 (1H, dd, *J* 13.7, 9.0, C*H*(H)Ar), 3.14 (1H, dd, *J* 13.7, 5.6, C*H*(H)Ar), 4.00-4.11 (2H, m, CH_2O), 4.21-4.28 (1H, m, NC*H*CH_2O), 6.00 (1H, d, *J* 5.2, CH=C*H*CO), 7.00 (1H, d, *J* 5.6, C*H*=CHCO), 7.22-7.33 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 22.8 (CH_3), 40.1 (CH_2Ar), 57.1 (N*C*HCH_2O), 73.5 (CH_2O), 100.8 (*C*-CH_3), 126.7 (Ar*C*H), 127.8 (CH=*C*HCO), 128.5 (2 x Ar*C*H), 129.4 (2 x Ar*C*H), 137.3 (Ar*C*), 151.3 (*C*H=CHCO), 178.1 (*C*O); MS (EI) *m/z* 229 [M^+, 29.4%]; (Found: M^+, 229.1107. $C_{14}H_{15}NO_2$ requires 229.1103).

(3*S*,7a*R*)-3-(3,4-Di(methyloxy)phenylmethyl)-7a-methyl-2,3,5,7a-tetrahydro-pyrrolo [2,1-*b*][1,3]oxazol-5-one, (**203**)



A solution of LDA (0.86 ml of a 2.0 M solution in heptane, 1.7 mmol) in anhydrous tetrahydrofuran (5 ml) was cooled to –78 °C and (3*S*,7a*R*)-3-(3,4-di(methyloxy)phenylmethyl)-7a-methylperhydropyrrolo[2,1-b][1,3]oxazol-5-one, (**177**), (0.25 g, 0.9 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added drop wise and stirred for 10 minutes. Benzeneselenenyl chloride (0.25 g, 1.3 mmol) in tetrahydrofuran (5 ml) was added drop wise and the solution warmed to 0 °C. Water (1.5 ml), acetic acid (0.3 ml) and hydrogen peroxide (0.46 g of a 35% solution) was added and the reaction mixture was maintained below 25 °C for a further 30 minutes. The solution was poured into saturated aqueous sodium bicarbonate solution (50 ml) and a 1 : 1 ether-hexane mixture (50 ml), and the organic layer was washed successively with water, HCl (0.1 M), water and saturated aqueous sodium chloride solution. Flash column chromatography using ethyl acetate and hexanes (1 : 2) as eluent gave the target compound as a white solid (0.09 g, 36%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 123-124 °C; (Found: C, 65.52; H, 6.65; N, 4.54. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%) ν_{max}(DCM)/cm^{-1} 1714 (CO); δ_H(250 MHz, $CDCl_3$) 1.53 (3H, s, C*H*$_3$), 2.85 (1H, dd, *J* 14.1, 8.9, C*H*(H)Ar), 3.10 (1H, dd, *J* 14.1, 5.8, C*H*(H)Ar), 3.86 (3H, s, C*H*$_3$O), 3.89 (3H, s, C*H*$_3$O), 4.04 (1H, dd, *J* 8.9, 5.5, C*H*(H)O), 4.09 (1H, dd, *J* 8.9, 6.5, C*H*(H)O), 4.24 (1H, ddd, *J* 14.6, 8.8, 5.8, NC*H*), 6.01 (1H, d, *J* 5.6, CH=C*H*CO), 6.76-6.86 (3H, m, Ar*H*), 7.03 (1H, d, *J* 5.6, C*H*=CHCO); δ_C(100 MHz, $CDCl_3$) 23.0 (*C*H$_3$), 39.7 (*C*H$_2$Ar), 55.9 (*C*H$_3$O), 56.0 (*C*H$_3$O), 57.2 (N*C*H), 73.6 (*C*H$_2$O), 100.8 (*C*-CH$_3$), 111.3 (Ar*C*H), 112.5 (Ar*C*H), 121.3 (Ar*C*H), 127.82 (CH=*C*H), 129.9 (Ar*C*), 147.9 (Ar*C*-OCH$_3$), 149.1 (Ar*C*-OCH$_3$), 151.5 (*C*H=CH), 178.2 (*C*O); MS (EI) *m/z* 289 [M$^+$, 68.4%]; (Found: M$^+$, 289.1314. $C_{16}H_{19}NO_4$ requires 289.1314).

(3*S*,7a*R*)-7a-But-3-enyl-3-(phenylmethyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3] oxazol-5-one, (**204**)

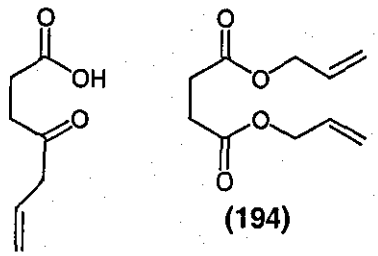


A solution of LDA (0.96 ml of a 2.0 M solution in heptane, 1.9 mmol) in anhydrous tetrahydrofuran (5 ml) was cooled to -78 °C and (3*S*,7a*R*)-3-benzyl-7a-but-3-enyl-tetrahydropyrrolo[2,1-*b*]oxazol-5-one, (**178**), (0.26 g, 1.0 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added drop wise and stirred for 1 hour. Benzeneselenenyl chloride (0.22 g, 1.2 mmol) in tetrahydrofuran (5 ml) was added rapidly drop wise and stirred at -78 °C for a further hour, warmed to 0 °C and stirred for 1 hour. Water (1.5 ml), acetic acid (0.3 ml) and hydrogen peroxide (0.24 ml of a 35% solution, 2.9 mmol) was added and the reaction mixture was maintained below 25 °C for a further 15 minutes, then stirred at room temperature for 12 hours. The solution was poured into saturated aqueous sodium bicarbonate solution (20 ml) and a 1 : 1 ether-hexane mixture (20 ml), and the organic layer was washed successively with water, HCl (0.1 M), water and saturated aqueous sodium chloride solution. Flash column chromatography using ethyl acetate and hexanes (1 : 3) as eluent gave starting material (0.05 g, 19 %) and the target compound as a yelow oil (0.14 g, 54%). $[\alpha]_D$ = +39.3 (*c* = 0.29, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1716 (lactam), 993 and 915 (C=C); δ_H(250 MHz, $CDCl_3$) 1.77-1.94 (1H, m, C*H*(H)CH_2CH=CH_2), 1.97-2.11 (3H, m, C*H*(H)CH_2CH=CH_2 and CH_2CH_2CH=CH_2), 2.88 (1H, dd, *J* 13.8, 8.7, C*H*(H)Ar), 3.12 (1H, dd, *J* 13.8, 5.9, C*H*(H)Ar), 3.98-4.06 (1H, m, C*H*(H)O), 4.08-4.16 (1H, m, C*H*(H)O), 4.19-4.30 (1H, m, N*CH*CH_2O), 4.96-5.04 (2H, m, CH_2CH_2CH=CH_2), 5.68-5.85 (1H, m, CH_2CH_2CH=CH_2), 6.02 (1H, d, *J* 5.8, CH=*CH*CO), 7.05 (1H, d, *J* 5.8, C*H*=CHCO), 7.20-7.40 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 28.4 (CH_2CH_2CH=CH_2), 34.8 (CH_2CH_2CH=CH_2), 40.3 (CH_2Ar), 57.1 (N*CH*CH_2O), 73.6 (CH_2O), 103.0 (*C*-CH_2CH_2CH=CH_2), 115.2 (CH_2CH_2CH=CH_2), 126.7 (Ar*CH*), 128.6 (Ar*CH*), 128.7 (Ar*CH*), 129.3 (2 x Ar*CH*), 137.3 (CH=*CH*CO,

$CH_2CH_2CH=CH_2$ and Ar*C*), 150.2 (*C*H=CHCO), 178.3 (*C*O); MS (EI) *m/z* 269 [M^+, 2.4%]; (Found: M^+, 269.1412. $C_{17}H_{19}NO_2$ requires 269.1416).

3.2.3. Further studies on the synthesis of bicyclic lactams

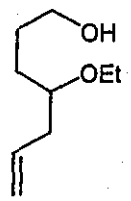
4-Oxo-hept-6-enoic acid, **(192)** and Succinic acid diallyl ester, **(194)**



(192) **(194)**

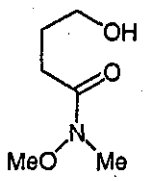
Succinic anhydride, **(182)**, (0.50 g, 5.0 mmol) was dissolved in tetrahydrofuran (20 ml) and DMPU (3 ml). The mixing solution was cooled to -78 °C and allyl magnesium bromide (5.50 ml, 5.5 mmol) was added carefully. The reaction mixture was stirred a further 6 hours at -78 °C and then cooled to room temperature. HCl (10 ml of a 2.0 M solution) was added and most of the tetrahydrofuran removed. Water (10 ml) was added and the mixture extracted with ethyl acetate (3 x 10 ml). The organic extracts were combined and washed with water (10 ml) and saturated aqueous ammonium chloride solution (25 ml). The solution was dried over anhydrous magnesium sulfate and the solvents evaporated to give a yellow oil. The crude ^{1}H NMR spectrum showed succinic acid diallyl ester as the major product. Flash column chromatography using ethyl acetate and hexanes (1 : 2) as eluent also gave the desired product as a yellow oil (74 mg, 11%). ν_{max}(Neat)/cm^{-1} 2935 (OH), 1710 (CO), 991 and 919 (C=C); δ_H(400 MHz, $CDCl_3$) 2.60-2.73 (4H, m, 2 x CH_2CO), 4.61 (2H, dt, *J* 5.8, 1.5, CH_2CH_2=CH), 5.24 (1H, ddd, *J* 10.4, 2.5, 1.3, CH(H)=CH), 5.33 (1H, ddd, *J* 17.0, 3.0, 1.5, CH(H)=CH), 5.86-5.91 (1H, m, CH=CH_2), 7.50-9.00 (1H, br. s, O*H*); δ_C(100 MHz, $CDCl_3$) 29.2 (CH_2CO), 29.3 (CH_2CO), 65.9 (CH_2CH=CH_2), 118.8 (CH_2=CH), 132.3 (CH_2=CH), 172.2 (*C*O), 178.3 (*C*O).

4-Ethoxy-hept-6-en-1-ol, **(208)**



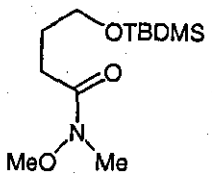
To a solution of 2-ethoxytetrahydrofuran, **(207)**, (0.45 g, 3.9 mmol) and allyltrimethylsilane (1.85 ml, 11.6 mmol) was added at -70°C a solution of titanium tetrachloride (0.64 ml, 5.8 mmol). The reaction mixture was stirred at this temperature for 1 hour and then poured into a mixture of water (30 ml) and ether (60 ml). The layers were separated and the water layer extracted with ether (30 ml). The combined organic extracts were washed with brine (30 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude product as a colourless oil in quantitative yield. Further purification on the crude material was not necessary. ν_{max}(Neat)/cm^{-1} 3379 (OH), 1062 (C-O-C), 994 and 911 (C=C), δ_H(400 MHz, $CDCl_3$) 1.13 (3H, s, *J* 7.0, OCH_2CH_3), 1.40-1.64 (4H, m, $CH_2CH_2CH_2OH$ and $CH_2CH_2CH_2OH$), 2.14-2.23 (3H, m, $CH_2CH{=}CH_2$ and O*H*), 3.25-3.31 (1H, m, C*H*OEt), 3.40 (1H, ddd, *J* 14.0, 9.1, 7.1, $OCH(H)CH_3$), 3.50-3.58 (3H, m, $OCH(H)CH_3$ and CH_2OH), 4.97-5.04 (2H, m, $CH_2CH{=}CH_2$), 5.68-5.78 (1H, m, $CH_2CH{=}CH_2$); δ_C(100 MHz, $CDCl_3$) 16.0 (OCH_2CH_3), 29.4 ($CH_2CH_2CH_2OH$), 31.2 ($CH_2CH_2CH_2OH$), 38.7 ($CH_2CH{=}CH_2$), 63.5 (CH_2OH), 64.9 (OCH_2CH_3), 79.4 (*C*HOEt), 117.5 ($CH_2CH{=}CH_2$), 135.3 ($CH_2CH{=}CH_2$).

4-Hydroxy-*N*-methoxy-*N*-methyl-butyramide, (**210**)



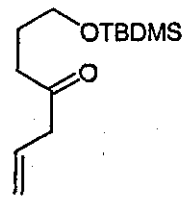
To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (3.93 g, 40.3 mmol) in dichloromethane (50 ml) at -10 °C was added drop wise trimethylaluminum (9.52 ml of a 2.0 M solution in hexane, 39.0 mmol) accompanied with evolution of gas. The resulting colourless solution was stirred at room temperature for 30 minutes and re-cooled to 0 °C. Gamma-butyrolactone, (**209**), (1.12 g, 13.0 mmol) was added and the mixture was stirred at room temperature for 12 hours. Aqueous potassium hydrogen sulfate (50 ml of a 2.0 M solution) was cautiously added to the resulting mixture and the mixture was extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried over anhydrous sodium sulfate, filtered and concentrated to give a yellow oil (1.87 g, 98%). ν_{max}(Neat)/cm^{-1} 3414 (OH), 1636 (CO); δ_H(400 MHz, $CDCl_3$) 1.86-1.93 (2H, m, CH_2CH_2OH), 2.60 (2H, t, *J* 6.7, CH_2CON), 2.90-3.05 (1H, s. br, O*H*), 3.20 (3H, s, NCH_3), 3.67-3.71 (2H, m, CH_2OH), 3.71 (3H, s, CH_3O); δ_C(100 MHz, $CDCl_3$) 27.3 (CH_2CON), 29.2 (CH_2CH_2OH), 32.3 (CH_3), 61.3 (CH_3O), 62.5 (CH_2OH), 174.9 (*C*O).

tert-Butyl-dimethyl-(5-methyl-4-methylene-heptyloxy)-silane, **(211)**



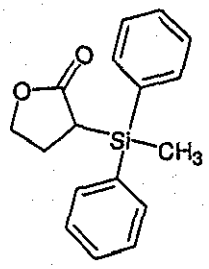
4-Hydroxy-*N*-methoxy-*N*-methyl-butyramide, **(210)**, (1.75 g, 11.9 mmol) was dissolved in dry dichloromethane (30 ml) and stirred under a nitrogen atmosphere. Triethylamine (1.99 ml, 14.3 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) were added, followed by the addition of *tert*-butyldimethylchlorosilane (1.97 g, 13.1 mmol). The colourless solution was left to stir at room temperature and after 5 minutes a white precipitate formed. The mixture was left to stir for an additional 18 hours at room temperature. The mixture was quenched with saturated aqueous ammonium chloride solution (30 ml) and the layers separated. The organic layer was washed with water and then dried over anhydrous sodium sulfate to yield a colourless oil (3.06 g, 98%). Purification by flash column chromatography gave a colourless oil (2.77 g, 89%). ν_{max}(Neat)/cm^{-1} 1667 (CO); δ_H(400 MHz, $CDCl_3$) 0.10 (6H, s, 2 x CH_3Si), 0.90 (9H, s, 3 x CH_3CSi), 1.81-1.88 (2H, m, CH_2CH_2OTBDMS), 2.51 (2H, t, *J* 7.5, CH_2CON), 3.18 (3H, s, NCH_3), 3.65-3.69 (2H, m, CH_2CH_2OTBDMS), 3.69 (3H, s, CH_3O); δ_C(100 MHz, $CDCl_3$) –5.4 (2 x CH_3Si), 18.2 (*C*-Si), 25.9 (3 x C-CH_3), 27.6 (CH_2CH_2OTBDMS), 28.2 (CH_2CON), 32.2 (NCH_3), 61.1 (CH_3O), 62.3 (CH_2CH_2OTBDMS), 174.5 (*C*O).

7-(*tert*-Butyl-dimethyl-silanyloxy)-hept-1-en-4-one, **(212)**



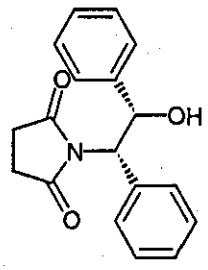
To a solution of *tert*-butyl-dimethyl-(5-methyl-4-methylene-heptyloxy)-silane, **(211)**, (0.61 g, 2.3 mmol) in tetrahydrofuran (25 ml) was added allylmagnesiumbromide (6.98 ml of a 1.0 M solution in diethyl ether, 7.0 mmol) at -78 °C under a nitrogen atmosphere. The resulting solution was stirred for 1 hour at -78 °C, warmed to room temperature and stirred overnight. The resulting white solution was carefully quenched by the addition of HCl (2.0 M) and extracted with ethyl acetate (3 x 20 ml). The organic extracts were combined and washed with water and then brine and dried over anhydrous magnesium sulfate to give a yellow oil (0.52 g, 93%). The compound was not purified further (due to decomposition). ν_{max}(Neat)/cm^{-1} 1716 (CO), 1095 (Si-O), 967 and 918 (C=C), 833 and 774 (Si-O); δ_H(400 MHz, $CDCl_3$) 0.04 (6H, s, 2 x CH_3Si), 0.89 (9H, s, 3 x CH_3CSi), 1.75-1.84 (2H, m, CH_2CH$_2$OTBDMS), 2.53 (2H, t, *J* 7.2, CH_2CO), 3.19 (2H, d, *J* 7.1, CH_2CH=CH$_2$), 3.61 (2H, t, *J* 6.0, CH$_2$CH_2OTBDMS), 5.11-5.19 (2H, m, CH$_2$CH=CH_2), 5.87-5.98 (1H, m, CH$_2$C*H*=CH$_2$); δ_C(100 MHz, $CDCl_3$) -5.0 (2 x *C*H$_3$Si), 18.7 (*C*-Si), 26.3 (3 x C-*C*H$_3$), 27.1 (*C*H$_2$CH$_2$OTBDMS), 39.0 (*C*H$_2$CO), 48.2 (*C*H$_2$CO), 62.5 (CH$_2$*C*H$_2$OTBDMS), 119.1 (CH$_2$CH=*C*H$_2$), 131.1 (CH$_2$*C*H=CH$_2$), 209.1 (*C*O).

5-(Methyl-diphenyl-silanyl)dihydro-furan-2-one, **(214)**[103a-c]



λ-Butyrolactone, **(213)**, (1.12 g, 13.0 mmol) in tetrahydrofuran (50 ml) was cooled to -78 °C whilst stirring under a nitrogen atmosphere. LHMDS (17.48 ml of a 1.0 M solution in tetrahydrofuran, 17.5 mmol) was added slowly and the mixture stirred for 30 minutes at -78 °C. After this time, diphenylmethylchlorosilane (3.06 ml, 14.6 mmol) was added drop wise. The reaction mixture was stirred at -78 °C for 1.5 hours, warmed to room temperature, stirred for a further 2 hours and then hydrolysed with HCl (20 ml of a 1.5 M solution). The organic layer was separated and evaporated off, and dried over anhydrous sodium sulfate. The colourless oil was further purified by flash column chromatography using a mixture of 1 : 5 ethyl acetate and hexanes as eluent to give the desired compound as a colourless oil (2.94 g, 71%). ν_{max}(Neat)/cm^{-1} 1751 (CO); δ_H(400 MHz, $CDCl_3$) 0.74 (3H, s, C*H*$_3$), 2.14-2.22 (1H, m, C*H*(H)CH_2O), 2.45-2.55 (1H, m, C*H*(H)CH_2O), 2.69 (1H, dd, *J* 10.3, 5.2, C*H*Si), 3.73 (1H, dd, *J* 16.8, 7.9, CH_2CH(H)O), 4.12-4.18 (1H, m, CH_2CH(H)O), 7.36-7.47 (6H, m, Ar*H*), 7.56-7.62 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) –4.5 (*C*H$_3$), 25.3 (*C*H$_2$CH$_2$O), 28.8 (*C*HSi), 67.4 (CH_2CH_2O), 128.2 (4 x Ar*C*H), 130.1 (Ar*C*H), 130.2 (Ar*C*H), 133.4 (Ar*C*), 133.6 (Ar*C*), 134.8 (2 x Ar*C*H), 134.9 (2 x Ar*C*H), 179.2 (*C*O).

1-(1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl-tetrahydro-1*H*-pyrrole-2,5-dione, **(216)**

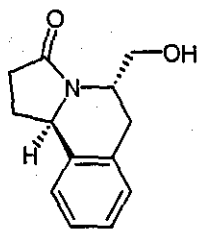


Succinic anhydride, **(182)**, (0.23 g, 2.3 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenyl ethanol, **(195)**, (0.50 g, 2.3 mmol) were dissolved in toluene (45 ml) under a nitrogen atmosphere. Triethylamine (1 ml) was added to the stirring mixture and the solution was heated at reflux for 40 hours. The solvent was removed by rotary evaporation and the resulting yellow oil was purified by flash column chromatography using a 1 : 1 mixture of hexanes and ethyl acetate as eluent to yield a white solid (0.41 g, 60%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 141-143 °C; $[\alpha]_D$ = +19.2 (*c* = 0.26, $CHCl_3$); (Found: C, 72.46; H, 5.75; N, 4.54. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%); ν_{max}(DCM)/cm^{-1} 3445 (OH), 1772 and 1698 (imide CO); δ_H(250 MHz, $CDCl_3$) 2.39 (4H, s, 2 x C*H*$_2$CO), 2.67 (1H, d, *J* 2.8, O*H*), 5.38 (1H, d, *J* 8.8, NC*H*Ar), 5.87 (1H, dd, *J* 8.8, 2.8, C*H*OH), 7.24-7.45 (8H, m, Ar*H*), 7.57-7.68 (2H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.8 (2 x *C*H$_2$CO), 61.5 (N*C*HAr), 72.2 (*C*HOH), 126.9 (Ar*C*H), 127.1 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.44 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 129.2 (Ar*C*H), 129.5 (Ar*C*H), 136.3 (Ar*C*), 140.4 (Ar*C*), 177.0 (2 x *C*O); MS (EI) *m/z* 295 [M$^+$, 3.0%]; (Found: M$^+$, 295.1211. $C_{18}H_{17}NO_3$ requires 295.1208).

3.3. Asymmetric intramolecular reactions of chiral *N*-acyliminium ion precursors

3.3.1. Stereoselective synthesis of pyrroloisoquinolines

(5*S*,10b*R*)-5-(Hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, (**217**)[135-136]



(3*S*,7a*R*)-3-(Phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, (**174**), (0.15 g, 0.7 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -10 °C and 1.5 equivalents of titanium tetrachloride (0.11 ml, 1.0 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The resulting yellow oil (0.12 g, 80%) was then further purified by column chromatography using 10 % methanol in dichloromethane as eluent. The solvent was removed by rotary evaporation to yield a pale green powder (0.08 g, 53%), a portion of which was recrystallised from dichloromethane and hexanes to give colourless, needle-like crystals. Mp 110-111 °C; $[\alpha]_D$ = +13.3 (*c* = 0.08, DCM); (Found: C, 71.82; H, 7.00; N, 6.31. $C_{13}H_{15}NO_2$ requires C, 71.89; H, 6.91; N, 6.45%); ν_{max}(DCM)/cm^{-1} 3262 (OH), 1648 (lactam); δ_H(250 MHz, $CDCl_3$) 1.94-2.12 (1H, m, C*H*(H)CH_2CO), 2.40-2.56 (1H, m, CH_2C*H*(H)CO), 2.57-2.71 (2H, m, C*H*(H)CH_2CO and CH_2C*H*(H)CO) 2.71 (1H, dd, *J* 16.2, 11.3, ArC*H*(H)CHN), 3.05 (1H, dd, *J* 16.2, 6.5, ArC*H*(H)CHN), 3.65 (1H, dd, *J* 11.5, 8.4, C*H*(H)OH), 3.74 (1H, dd, *J* 11.5, 5.0, C*H*(H)OH), 4.35-4.48 (1H, m,

NC*H*CH_2OH), 4.82 (1H, t, *J* 7.5, NC*H*Ar), 7.09-7.30 (4H, m, Ar*H*); O*H* not visible. δ_C(100 MHz, $CDCl_3$) 26.5 (*C*H_2CH_2CO), 29.7 (Ar*C*H_2CHN), 31.6 (CH_2*C*H_2CO), 49.8 (N*C*HAr), 54.6 (N*C*HCH_2OH), 63.3 (*C*H_2OH), 124.2 (Ar*C*H), 126.8 (Ar*C*H), 127.3 (Ar*C*H), 129.1 (Ar*C*H), 132.5 (Ar*C*), 136.8 (Ar*C*), 175.3 (*C*O); MS (EI) *m/z* 217 [M^+, 8.2%]; (Found: M^+, 217.1107. $C_{13}H_{15}NO_2$ requires 217.1103).

X-ray Crystal Data for (217): $C_{13}H_{17}NO_3$ (+ H_2O), *Mr* = 235.28, monoclinic, space group $P2_1$, a = 10.1671(8) Å, b = 7.9584(6) Å, c = 15.1474(11) Å, β = 91.810(2)°, V = 1225.02(16) Å, Z = 2, D_{calcd} = 1.276 g cm^{-3}, R = 0.0147 for 5400 observed reflections, $F^2>2\sigma$ (4972) and 325 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

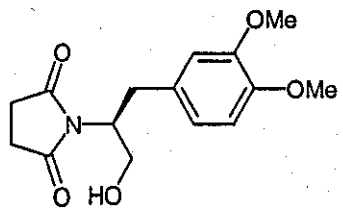
(5*S*,10b*R*)-5-(Hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(217)**, from direct cyclisation of ethoxy lactam intermediate

1-(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl-tetrahydro-1*H*-pyrrole-2,5-dione, **(174)**, (2.00 g, 8.6 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (3.25 g, 85.8 mmol) was then added with stirring. HCl (2.0 M) in absolute ethanol (4.36 ml, 8.6 mmol) was added slowly *via* syringe over a 3 hour period. The solution was then acidified to pH 1-3 by addition of HCl (2.0 M) in absolute ethanol over a 15 minute period, affording a white suspension which was stirred for an additional 20 hours at room temperature. The mixture was quenched by addition to saturated aqueous sodium bicarbonate solution (100 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield the ethoxy lactam intermediate as a colourless oil (1.38 g). This was not further purified, and was used directly in the Lewis acid mediated cyclisation to yield **(217)** as described below.

The intermediate ethoxy lactam (1.38 g, 5.3 mmol) was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.86 ml, 7.9 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture

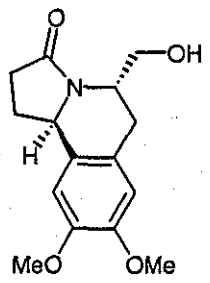
was then allowed to reach room temperature and left stirring for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (50 ml), extracted with dichloromethane (3 x 50 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The green oil (1.11 g, 97%) was purified by column chromatography using 10% methanol in dichloromethane as eluent. The solvent was removed by rotary evaporation to yield a pale green powder (0.95 g, 83%) which had identical spectral properties to the compound prepared by the alternative route.

1-[(1*S*)-2-(3,4-Di(methyloxy)phenyl)-1-(hydroxymethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione, **(226)**[135]



Succinic anhydride, **(182)**, (0.45 g, 4.5 mmol) and (2*S*)-2-amino-3-(3,4-di(methyloxy) phenyl)propan-1-ol, **(189)**, (0.94 g, 4.5 mmol) were dissolved in toluene (50 ml) under a nitrogen atmosphere. Triethylamine (1.2 ml) was added to the stirring mixture and the solution was heated at reflux for 18 hours. The solvent was removed by rotary evaporation to give a white solid (0.90 g, 69%), a portion of which was recrystallised from ethyl acetate and hexanes to give colourless crystals. Mp 124-125 °C; $[\alpha]_D = -72.9$ (c = 0.21, DCM); (Found: C, 61.18; H, 6.45; N, 4.61. $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78%); ν_{max}(DCM)/cm^{-1} 3449 (OH), 1771 and 1696 (imide); δ_H(250 MHz, $CDCl_3$) 2.53-2.60 (4H, m, 2 x CH_2CO), 2.98-3.14 (2H, m, CH_2Ar), 3.79-3.90 (1H, m, C*H*(H)OH), 3.84 (3H, s, CH_3O), 3.85 (3H, s, CH_3O), 4.01 (1H, dd, J 11.9, 7.3, C*H*(H)OH), 4.51 (1H, ddd, J 16.2, 7.6, 3.5, NC*H*CH$_2$OH), 6.65-6.79 (3H, m, Ar*H*), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 27.9 (2 x *C*H$_2$CO), 33.3 (*C*H$_2$Ar), 55.6 (NCHCH$_2$OH), 55.87 (*C*H$_3$O), 55.9 (*C*H$_3$O), 62.2 (*C*H$_2$OH), 111.2 (Ar*C*H), 112.1 (Ar*C*H), 121.1 (Ar*C*H), 129.6 (Ar*C*), 147.8 (Ar*C*-OCH$_3$), 148.9 (Ar*C*-OCH$_3$), 178.2 (2 x *C*O); MS (EI) m/z 293 [M$^+$, 19.6%]; (Found: M$^+$, 293.1261. $C_{15}H_{19}NO_5$ requires 293.1263).

(5*S*,10b*R*)-5-Hydroxy-8,9-di(methyloxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinoline-3-one, **(218)**[135]

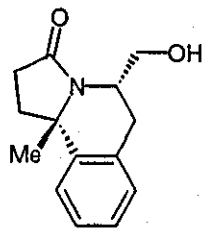


1-[(1*S*)-2-[3,4-Di(methyloxy)phenyl]-1-(hydroxymethyl)ethyl]tetrahydro-1*H*-pyrrole-2, 5-dione, **(226)**, (0.13 g, 0.4 mmol) was dissolved in absolute ethanol (10 ml) and cooled to 0 °C. Sodium borohydride (0.16 g, 4.3 mmol) was then added with stirring. HCl (2.0 M) in absolute ethanol (8.46 ml, 4.3 mmol) was added slowly *via* syringe over a 1 hour period. The solution was then acidified to pH 1-3 by addition of HCl (2.0 M) in absolute ethanol over a 15 minute period, affording a white suspension which was stirred for an additional 20 hours at room temperature. The mixture was quenched by addition to saturated aqueous sodium bicarbonate solution (10 ml) and extracted with dichloromethane (3 x 10 ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield the target compound as a white solid (0.11 g, 91%), a portion of which was recrystallised using dichloromethane and hexanes to give colourless crystals. The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy on the crude reaction mixture. Mp 177-179 °C; $[\alpha]_D$ = +110.8 (*c* = 0.25, $CHCl_3$); (Found: C, 64.64; H, 6.83; N, 4.96. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%); ν_{max}(DCM)/cm^{-1} 3263 (OH), 1664 (lactam); δ_H(400 MHz, $CDCl_3$) 1.86-1.98 (1H, m, C*H*(H)CH_2CO), 2.41-2.51 (1H, m, CH_2CH(H)CO), 2.56-2.69 (3H, m, C*H*(H)CH_2CO, CH_2CH(H)CO and ArC*H*(H)CHN), 2.99 (1H, dd, *J* 16.2, 6.6, ArC*H*(H)CHN), 3.56-3.70 (3H, m, CH_2OH and O*H*), 3.86 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 4.44-4.52 (1H, m, NC*H*CH_2OH), 4.77 (1H, t, *J* 7.7, NC*H*), 6.58 (1H, s, Ar*H*), 6.62 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.2 (CH_2CH_2CO), 29.0 (ArCH_2CHN), 31.8 (CH_2CH_2CO), 49.3 (NCH), 54.2 (NCHCH$_2$OH), 56.0 (CH_3O), 56.1 (CH_3O), 62.7 (CH_2OH), 107.5 (ArCH), 111.9 (ArCH), 124.2 (ArC), 128.5

(Ar*C*), 148.1 (Ar*C*-OCH_3), 148.2 (Ar*C*-OCH_3), 175.0 (*C*O); MS (EI) *m/z* 277 [M^+, 29.4%]; (Found: M^+, 277.1314. $C_{15}H_{19}NO_4$ requires 277.1314).

X-ray Crystal Data for (218): $C_{15}H_{19}NO_4$ (+ H_2O), *Mr* = 277.31, orthorhombic, space group $P2_12_12_1$, a = 5.3164(3) Å, b = 11.9673(7) Å, c = 20.8468(12) Å, β = 90°, V = 1326.34(13) Å, Z = 4, D_{calcd} = 1.389 g cm^{-3}, R = 0.0210 for 3150 observed reflections, $F^2>2\sigma$ (2853) and 186 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

(5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinolin-3-one, **(219a)**[135-136]



(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(175)**, (0.15 g, 0.7 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -10 °C and 1.5 equivalents of titanium tetrachloride (0.11 ml, 1.0 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow solid (0.13 g, 87%) was purified to yield the individual diastereoisomers by flash column chromatography using 100% ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield the target pyrroloisoquinoline diastereoisomers as colourless crystals.

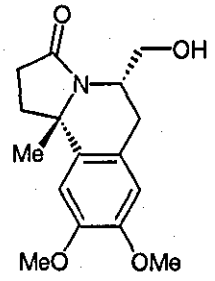
Major isomer (219a, 53%). Mp 103-105 °C (DCM/hexanes); $[\alpha]_D$ = -226.9 (*c* = 0.25, $CHCl_3$); (Found: C, 72.71; H, 7.32; N, 5.88. $C_{14}H_{17}NO_2$ requires C, 72.72; H, 7.36; N, 6.06 %); ν_{max}(DCM)/cm^{-1} 3386 (OH), 2927 (CH_3), 1654 (lactam); δ_H(250 MHz, $CDCl_3$) 1.58 (3H, s, C*H*$_3$), 2.17 (1H, dd, *J* 21.7, 11.4, C*H*(H)CH_2CO), 2.34-2.50 (2H, m, C*H*(H)CH_2CO and CH_2C*H*(H)CO), 2.61-2.73 (1H, m, CH_2C*H*(H)CO), 2.72 (1H, dd, *J* 16.3, 3.6, ArC*H*(H)CHN), 3.12 (1H, dd, *J* 16.3, 11.4, ArC*H*(H)CHN), 3.63-3.75 (1H, m, NC*H*CH_2OH), 3.94-4.12 (2H, m, C*H*$_2$OH), 4.75-5.00 (1H, br. s, O*H*), 7.07-7.29 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.9 (*C*H_3), 31.7 (CH_2*C*H_2CO), 31.9 (Ar*C*H_2CHN), 35.3 (*C*H_2CH_2CO), 54.2 (N*C*HCH_2OH), 62.9 (*C*H_2OH), 65.0 (*C*-CH_3), 125.0 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 129.5

(ArCH), 132.7 (ArC), 142.6 (ArC), 174.5 (CO); MS (EI) *m/z* 231 [M^+, 6.9%]; (Found: M^+, 231.1256. $C_{14}H_{17}NO_2$ requires 231.1259).

X-ray Crystal Data for (219a): $C_{14}H_{17}NO_2$, *Mr* = 231.29, monoclinic, space group $P2_1$, a = 7.7150(6) Å, b = 8.0282(6) Å, c = 10.0287(8) Å, β = 109.876(2)°, V = 584.15(8) Å, Z = 2, D_{calcd} = 1.315 g cm^{-3}, R = 0.0124 for 2514 observed reflections, $F^2>2\sigma$ (2421) and 159 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

Minor isomer (219b, 9%). Mp 107-109 °C (DCM/hexanes); $[\alpha]_D$ = +30.8 (c = 0.25, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3422 (OH), 1655 (lactam); δ_H(400 MHz, $CDCl_3$) 1.54 (3H, s, CH_3), 2.35-2.47 (3H, m, CH_2CH_2CO and $CH_2CH(H)CO$), 2.70-2.87 (1H, m, $CH_2CH(H)CO$), 2.84 (1H, dd, J 16.0, 9.2, ArCH(H)CHN), 3.03 (1H, dd, J 16.0, 6.8, ArCH(H)CHN), 3.69-3.88 (2H, m, CH_2OH), 4.18-4.30 (1H, m, $NCHCH_2OH$), 4.40-4.50 (1H, br. s, OH), 7.15-7.34 (4H, m, ArH); δ_C(100 MHz, $CDCl_3$) 29.1 (CH_3), 29.7 (CH_2CH_2CO), 30.3 ($ArCH_2CHN$), 35.0 (CH_2CH_2CO), 52.6 ($NCHCH_2OH$), 63.0 (C-CH_3), 67.8 (CH_2OH), 123.4 (ArCH), 126.9 (ArCH), 127.3 (ArCH), 128.4 (ArCH), 131.9 (ArC), 142.6 (ArC), 176.2 (CO).

(5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-8,9-di(methyloxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(220a)**[135]



(3*S*,7a*R*)-3-(3,4-Di(methyloxy)phenylmethyl)-7a-methylperhydropyrrolo[2,1-*b*][1,3] oxazol-5-one, **(177)**, (0.50 g, 1.7 mmol) was dissolved in dry dichloromethane (30 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.28 ml, 2.6 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated ammonium chloride solution (30 ml), extracted with dichloromethane (3 x 30 ml) and dried using anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow solid (0.46 g, 91%) was purified by flash column chromatography using 100% ethyl acetate as eluent, and recrystallised from ethyl acetate and hexanes to yield the target pyrroloisoquinoline diastereoisomers as colourless crystals.

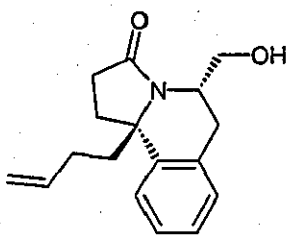
Major isomer (220a, 69%). Mp 138-139 °C (DCM/hexanes); $[\alpha]_D$ = -222.5 (*c* = 0.28, $CHCl_3$); (Found: C, 65.76; H, 7.21; N, 4.74. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.26; N, 4.81 %); ν_{max}(DCM)/cm^{-1} 3384 (OH), 1655 (lactam); δ_H(250 MHz, $CDCl_3$) 1.57 (3H, s, C*H*$_3$), 2.08-2.21 (1H, m, C*H*(H)CH$_2$CO), 2.34-2.49 (2H, m, C*H*(H)CH$_2$CO and CH$_2$C*H*(H)CO), 2.58-2.75 (1H, m, CH$_2$C*H*(H)CO), 2.62 (1H, dd, *J* 16.0, 4.1, ArC*H*(H)CHN), 3.05 (1H, dd, *J* 16.0, 11.3, ArC*H*(H)CHN), 3.61-3.70 (1H, m, NC*H*CH$_2$OH), 3.86 (3H, s, C*H*$_3$O), 3.87 (3H, s, C*H*$_3$O), 3.97-4.04 (2H, m, C*H*$_2$OH), 4.93 (1H, t, *J* 7.4, O*H*), 6.55 (1H, s, Ar*H*), 6.59 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.3 (*C*H$_3$), 31.1 (CH$_2$*C*H$_2$CO), 31.3 (ArCH$_2$CHN), 34.9 (*C*H$_2$CH$_2$CO), 54.0 (NCHCH$_2$OH), 55.9 (*C*H$_3$O), 56.2 (*C*H$_3$O), 62.5 (*C*H$_2$OH), 64.3

(*C*-CH_3), 107.6 (Ar*C*H), 111.4 (Ar*C*H), 124.5 (Ar*C*), 134.1 (Ar*C*), 148.0 (Ar*C*-OCH_3), 148.2 (Ar*C*-OCH_3), 174.1 (*C*O); MS (EI) *m/z* 291 [M^+, 14.1%]; (Found: M^+, 291.1474. $C_{16}H_{21}NO_4$ requires 291.1471).

X-ray Crystal Data for (220a): $C_{16}H_{21}NO_4$, *Mr* = 277.31, monoclinic, space group $P2_1$, a = 10.5447(10) Å, b = 9.5411(9) Å, c = 14.7057(13) Å, β = 94.006(2)°, V = 1475.9(2) Å, Z = 4, D_{calcd} = 1.311 g cm^{-3}, R = 0.0192 for 6544 observed reflections, $F^2>2\sigma$ (5287) and 388 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

Minor isomer (220b, 5%). Mp 152-154 °C (DCM/hexanes); $[\alpha]_D$ = +70.4 (c = 0.41, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3390 (OH), 1660 (lactam); δ_H(250 MHz, $CDCl_3$) 1.53 (3H, s, C*H*$_3$), 2.23-2.48 (3H, m, C*H*$_2$CH$_2$CO and CH$_2$C*H*(H)CO), 2.69-2.81 (1H, m, CH$_2$C*H*(H)CO), 2.79 (1H, dd, *J* 16.2, 8.3, ArC*H*(H)CHN), 2.97 (1H, dd, *J* 16.2, 7.1, ArC*H*(H)CHN), 3.71-3.81 (2H, m, C*H*$_2$OH), 3.87 (3H, s, C*H*$_3$O), 3.88 (3H, s, C*H*$_3$O), 4.24-4.35 (1H, m, NC*H*CH$_2$OH), 6.65 (1H, s, Ar*H*), 6.66 (1H, s, Ar*H*), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 29.0 (*C*H$_3$), 29.2 (CH$_2$*C*H$_2$CO), 30.5 (Ar*C*H$_2$CHN), 35.6 (*C*H$_2$CH$_2$CO), 51.4 (N*C*HCH$_2$OH), 56.0 (*C*H$_3$O), 56.2 (*C*H$_3$O), 62.5 (*C*-CH$_3$), 66.1 (*C*H$_2$OH), 107.2 (Ar*C*H), 111.7 (Ar*C*H), 123.7 (Ar*C*), 134.3 (Ar*C*), 148.11 (Ar*C*-OCH_3), 148.13 (Ar*C*-OCH_3), 175.5 (*C*O).

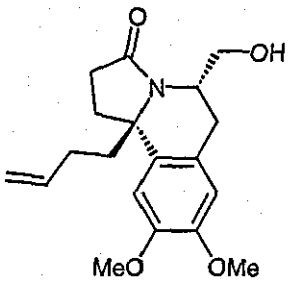
(5*S*,10b*S*)-10b-But-3-enyl-5-hydroxymethyl-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*] isoquinolin-3-one, **(221)**



(3*S*,7a*R*)-3-Benzyl-7a-but-3-enyl-tetrahydropyrrolo[2,1-*b*]oxazol-5-one, **(178)**, (0.26 g, 1.0 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to –78 °C and 1.5 equivalents of titanium tetrachloride (0.16 ml, 1.4 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude mixture. The white oil (0.26 g, 100%) was purified by flash column chromatography using a 1 : 1 ethyl acetate and hexanes as eluent. The solvent was removed by rotary evaporation to give recovered starting material (0.07 mg) and the target pyrroloisoquinoline as a pale yellow oil (0.08 mg, 42% based on recovered SM). $[\alpha]_D$ = -177.2 (*c* = 0.16, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3383 (OH), 1659 (CO); δ_H(400 MHZ, $CDCl_3$) 1.81-1.86 (1H, m, C*H*(H)$CH_2CH{=}CH_2$), 1.90-1.97 (1H, m, C*H*(H)$CH_2CH{=}CH_2$), 1.99-2.08 (2H, m, $CH_2CH_2CH{=}CH_2$), 2.22-2.34 (1H, m, *CH*(*H*)CH_2CO), 2.30-2.38 (1H, m, *CH*(*H*)CH_2CO) 2.41-2.48 (1H, m, CH_2CH(H)CO), 2.50-2.61 (1H, m, CH_2CH(H)CO), 2.67 (1H, dd, *J* 16.5, 4.3 ArC*H*(H)CHN), 3.11 (1H, dd, *J* 16.5, 11.1, ArC*H*(H)CHN), 3.59-3.65 (1H, m, NC*H*CH_2OH), 3.85-3.88 (2H, m, CH_2OH), 4.82 (1H, t, *J* 7.0, O*H*), 4.88-4.98 (2 H, m, $CH_2CH_2CH{=}CH_2$) 5.64-5.73 (1H, m, $CH_2CH_2CH{=}CH_2$), 7.00-7.18 (4H, m, Ar*H*); δ_C(100 MHZ, $CDCl_3$) 27.4 ($CH_2CH_2CH{=}CH_2$), 29.9 (ArCH_2CHN), 30.6 (CH_2CH_2CO and CH_2CH_2CO), 39.4 ($CH_2CH_2CH{=}CH_2$), 52.5 (NCHCH$_2$OH), 61.5 (CH_2OH), 66.1 (*C*-$CH_2CH_2CH{=}CH_2$), 114.3 ($CH_2CH_2CH{=}CH_2$), 123.8 (ArCH), 125.7 (ArCH), 125.9 (ArCH), 128.2 (ArCH), 131.4 (Ar*C*), 136.1

($CH_2CH_2CH=CH_2$), 141.4 (Ar*C*), 173.9 (*C*O); MS (EI) *m/z* 271 [M^+, 1.1%]; (Found: M^+, 271.1568. $C_{17}H_{21}NO_2$ requires 271.1572).

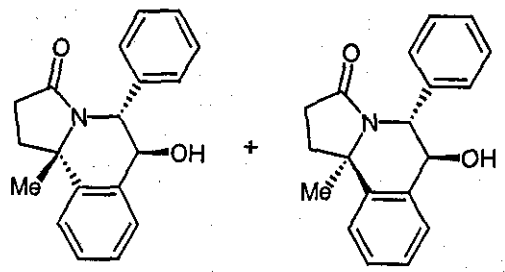
(5*S*,10b*S*)-10b-But-3-enyl-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, **(222)**



(3*S*,7a*R*)-7a-But-3-enyl-3-(3,4-dimethoxy-benzyl)-tetrahydropyrrolo[2,1-*b*]oxazol-5-one, **(178)**, (130 mg, 0.4 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.06 ml, 0.6 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The white oil (130 mg, 100%) was purified by flash column chromatography using 100% ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield the target pyrroloisoquinoline as white crystals (68 mg, 54%) a portion of which was recrystallised from dichloromethane and hexanes. Mp 119-121 °C; $[\alpha]_D$ = -206.5 (c = 0.12, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3256 (OH), 1655 (lactam); δ_H(400 MHz, $CDCl_3$) 1.85-1.94 (1H, m, C*H*(H)$CH_2CH{=}CH_2$), 1.96-2.05 (1H, m, C*H*(H)$CH_2CH{=}CH_2$), 2.06-2.17 (2H, m, $CH_2CH_2CH{=}CH_2$), 2.21-2.32 (1H, m, C*H*(H)CH_2CO), 2.39-2.53 (2H, m, C*H*(H)CH_2CO and CH_2CH(H)CO), 2.58-2.70 (2H, m, CH_2CH(H)CO and ArC*H*(H)CHN), 3.12 (1H, dd, J 16.3, 11.2, ArC*H*(H)CHN), 3.62-3.69 (1H, m, NC*H*CH_2OH), 3.86 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 3.99-4.05 (2H, m, CH_2OH), 4.92-5.07 (3H, m, $CH_2CH_2CH{=}CH_2$ and O*H*), 5.71-5.83 (1H, m, $CH_2CH_2CH{=}CH_2$), 6.54 (1H, s, Ar*H*), 6.58 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 28.4 ($CH_2CH_2CH{=}CH_2$), 30.5 ($ArCH_2CHN$), 31.6 (CH_2CH_2CO), 31.6 (CH_2CH_2CO), 40.5 ($CH_2CH_2CH{=}CH_2$), 53.7 (N*C*HCH_2OH), 55.9 (CH_3O), 56.1

(CH_3O), 62.4 (CH_2OH), 66.9 (C-$CH_2CH_2CH{=}CH_2$), 107.8 (Ar*C*H), 111.5 (Ar*C*H), 115.3 ($CH_2CH_2CH{=}CH_2$), 124.6 (Ar*C*), 134.4 (Ar*C*), 137.1 ($CH_2CH_2CH{=}CH_2$), 147.9 (Ar*C*-OCH_3), 148.0 (Ar*C*-OCH_3), 174.8 (*C*O); MS (EI) *m/z* 331 [M^+, 0.6%]; (Found: M^+, 331.1789. $C_{19}H_{25}NO_4$ requires 331.1784).

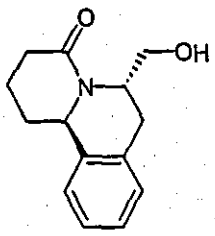
(5*S*,6*R*,10b*S*/*R*)-6-Hydroxy-10b-methyl-5-phenyl-1,2,3,5,6,10b-hexahydropyrrolo [2,1-*a*]isoquinolin-3-one, **(235)**



(2*S*,3*R*,7aS)-7a-Methyl-2,3-diphenylperhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(198)**, (0.10 g, 0.3 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to –78 °C and 1.5 equivalents of titanium tetrachloride (0.06 ml, 0.5 mmol) were added drop wise via syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (30 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation to give a 1 : 1 mixture of product diastereoisomers as colourless crystals (0.03 g, 30%). The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy on the crude reaction mixture. ν_{max}(DCM)/cm^{-1} 3449 (OH), 1691 (lactam); δ_H(250 MHz, $CDCl_3$) 0.94 (3H, s, C*H*$_3$), 1.48 (3H, s, C*H*$_3$), 2.07-2.84 (8H, m, 2 x C*H*$_2$CH$_2$CO and 2 x C*H*$_2$CO), 5.74 (1H, s, NC*H*Ar)*, 6.09 (1H, s, NC*H*Ar)*, 6.47 (1H, s, C*H*OH), 7.07-7.56 (19H, m, C*H*OH and 18 x Ar*H*), 2 x O*H* not visible; δ_C(100 MHz, $CDCl_3$) 27.0 (*C*H$_3$), 27.8 (*C*H$_3$), 30.2 (CH$_2$*C*H$_2$CO), 30.5 (CH$_2$*C*H$_2$CO), 32.2 (*C*H$_2$CH$_2$CO), 37.0 (*C*H$_2$CH$_2$CO), 55.7 (N*C*HAr), 57.4 (N*C*HAr), 60.9 (*C*-CH$_3$), 63.0 (*C*-CH$_3$), 115.6 (*C*HOH), 119.2 (*C*HOH), 122.6 (Ar*C*H), 122.6-129.9 (18 x Ar*C*H), 130.6 (Ar*C*), 131.7 (Ar*C*), 135.6 (Ar*C*), 138.2 (Ar*C*), 140.4 (Ar*C*), 141.4 (Ar*C*), 170.4 (*C*O), 171.4 (*C*O); MS (EI) *m/z* 293 [M$^+$, <1%]; (Found: M$^+$, 293.14100. $C_{19}H_{19}NO_2$ requires 293.1416).

* On heating to 45 °C these peaks became doublets with *J* values 1.6 and 0.8 respectively.

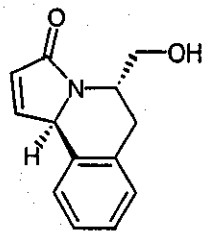
(6*S*,11b*R*)-6-(Hydroxymethyl)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*] isoquinoline-4-one, **(241)**[95, 134]



(3*S*,8a*S*/*R*)-3-(Phenylmethyl)perhydropyrido[2,1-*b*][1,3]oxazol-5-one, **(200a)** and **(200b)**, (4.08 g, 17.7 mmol) was dissolved in dry dichloromethane (50 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (2.91 ml, 26.5 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (50 ml), extracted with dichloromethane (3 x 20 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow oil was purified by flash column chromatography using ethyl acetate and hexanes (3 : 1) as eluent giving the target pyrroloisoquinoline as a yellow oil (2.65 g, 65 %). ν_{max}(Neat)/cm^{-1} 3390 (OH), 1613 (lactam); δ_H(250 MHz, $CDCl_3$) 1.90-1.99 (3H, m, $CH_2CH_2CH_2CO$ and $CH(H)CH_2CH_2CO$), 2.18-2.64 (3H, m, $CH(H)CH_2CH_2CO$ and $CH_2CH_2CH_2CO$), 2.71 (1H, dd, *J* 16.2, 4.4, $ArCH(H)CHN$), 3.06 (1H, dd, *J* 16.2, 6.2, $ArCH(H)CHN$), 3.54-3.72 (2H, m, CH_2OH), 4.59-4.70 (1H, m, NC*H*), 5.00-5.15 (1H, m, $NCHCH_2OH$), 7.05-7.35 (4H, m, Ar*H*), O*H* not visible; δ_C(67.5 MHz, $CDCl_3$) 19.2 ($CH_2CH_2CH_2CO$), 29.6 ($ArCH_2CHN$), 30.1 ($CH_2CH_2CH_2CO$), 32.7 ($CH_2CH_2CH_2CO$), 50.3 ($NCHCH_2OH$), 53.5 (NCH), 64.0 (CH_2OH), 124.7 (ArCH), 127.0 (ArCH), 127.5 (ArCH), 129.4 (ArCH), 132.4 (ArC), 137.9 (ArC), 172.2 (CO); MS (EI) *m/z* 231 [M^+, 20.0 %]; (Found: M^+, 231.1259. $C_{14}H_{17}NO_2$ requires 231.1259).

3.3.2. Stereoselective synthesis of unsaturated pyrroloisoquinoline ring systems

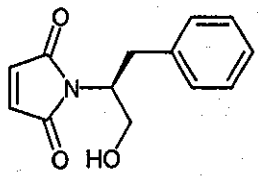
(5*S*,10b*S*)-5-(Hydroxymethyl)-3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **(242)***



(3*S*,7a*R*)-3-(Phenylmethyl)perhydropyrrolo[2,1-b][1,3]oxazol-5-one, **(201)**, (0.03 g, 0.1 mmol) was dissolved in dry dichloromethane (5 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.11 ml, 1.0 mmol) was added by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The resulting yellow oil was then further purified by column chromatography using 100% ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield a pale green oil (0.02 g, 67%). ν_{max}(neat)/cm^{-1} 3394 (OH), 1684 (lactam); δ_H(250 MHz, $CDCl_3$) 3.03 (1H, d, *J* 4.6, NC*H*), 3.25-3.35 (2H, m, ArCH_2CHN), 3.50-3.66 (2H, m, CH_2OH), 4.34-4.46 (1H, m, NC*H*CH$_2$OH), 5.64 (1H, t, *J* 2.78, CH=C*H*CO), 7.15-7.29 (4H, m, Ar*H*), 7.54-7.58 (1H, m, C*H*=CHCO), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 38.6 (Ar*C*H$_2$CHN), 50.9 (N*C*HCH$_2$OH), 62.9 (*C*H$_2$OH), 97.9 (N*C*H), 124.4-128.9 (4 x Ar*C*H and CH=*C*H), 132.1 (Ar*C*), 139.7 (Ar*C*), 146.3 (*C*H=CH), 178.3 (*C*O); MS (EI) *m/z* 215 [M$^+$, 24.3%]; (Found: M$^+$, 215.0943. $C_{13}H_{13}NO_2$ requires 215.0946).

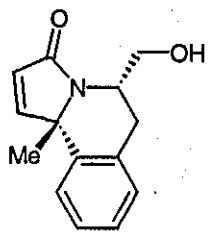
* Readily decomposes under acidic conditions

1-(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl-tetrahydro-1*H*-pyrrole-2,5-dione, **(246)**



Malaeic anhydride, **(245)**, (0.65 g, 6.6 mmol) and (*S*)-2-amino-3-phenyl-1-propanol (1.00 g, 6.6 mmol), **(183)**, were dissolved in toluene (100 ml) under a nitrogen atmosphere. Triethylamine (1.8 ml) was added to the stirring mixture and the solution was heated at reflux for 18 hours. The solvent was removed by rotary evaporation and the resulting yellow oil was purified by flash column chromatography using 50% hexanes in ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield a white solid (0.63 g, 41%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 89-90 °C; $[\alpha]_D$ = -79.7 (*c* 0.29 , $CHCl_3$); (Found: C, 67.64; H, 5.60; N, 5.99. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06%); ν_{max}(DCM)/cm^{-1} 3448 (OH), 1772 and 1706 (imide); δ_H(400 MHz, $CDCl_3$) 2.60-2.70 (1H, br. s, O*H*), 3.05-3.14 (2H, m, CH_2Ar), 3.84 (1H, dd, *J* 11.6, 4.0, C*H*(H)OH), 3.95-4.02 (1H, m, C*H*(H)OH), 4.41-4.46 (1H, m, NC*H*), 6.57 (2H, s, 2 x C*H*), 7.13-7.26 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 35.1 (*C*H_2Ar), 55.5 (N*C*H), 63.1 (*C*H_2OH), 127.1 (Ar*C*H), 127.3 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ar*C*H), 129.4 (Ar*C*H), 134.3 (2 x *C*H), 137.7 (Ar*C*), 171.7 (2 x *C*O); MS (EI) *m/z* 231 [M^+, 17.4%]; (Found: M^+, 231.0893. $C_{13}H_{13}NO_3$ requires 231.0895).

(5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-3,5,6,10b-tetrahydropyrrolo[2,1-*a*] isoquinolin-3-one, **(243a)**[135]



(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(202)**, (0.18 g, 0.8 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.13 ml, 1.2 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml), extracted with dichloromethane (3 x 20 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow oil (0.17 g, 91%) was purified by flash column chromatography using 100% ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield the target pyrroloisoquinoline diastereoisomers as colourless crystals.

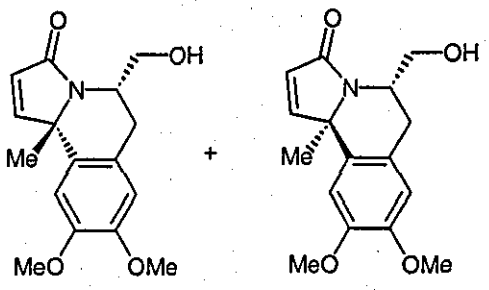
Major isomer (243a, 50%). Mp 101-103 °C; $[\alpha]_D$ = -292.0 (*c* = 0.27, $CHCl_3$); (Found: C, 72.77; H, 6.50; N, 5.72. $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11 %); ν_{max}(DCM)/cm^{-1} 3315 (OH), 1662 (lactam); δ_H(400 MHz, $CDCl_3$) 1.64 (3H, s, C*H*$_3$), 2.74 (1H, dd, *J* 16.7, 3.6, ArC*H*(H)CHN), 3.32 (1H, dd, *J* 16.7, 12.2, ArC*H*(H)CHN), 3.73-3.82 (1H, m, NC*H*CH$_2$OH), 4.06 (1H, ddd, *J* 12.8, 10.4, 5.2, C*H*(H)OH), 4.28 (1H, dd, *J* 12.8, 2.4, C*H*(H)OH), 5.30 (1H, dd, *J* 10.0, 4.4, O*H*), 6.08 (1H, d, *J* 5.6, CH=C*H*CO), 7.16-7.25 (4H, m, Ar*H*), 7.40 (1H, d, *J* 5.6, C*H*=CHCO); δ_C(100 MHz, $CDCl_3$) 26.9 (*C*H$_3$), 32.3 (ArCH$_2$CHN), 53.4 (NCHCH$_2$OH), 61.7 (*C*H$_2$OH), 68.8 (*C*-CH$_3$), 125.8 (CH=*C*HCO) 126.0 (Ar*C*H), 126.5 (Ar*C*H), 127.3 (Ar*C*H), 130.0 (Ar*C*H), 133.5 (Ar*C*), 136.8 (Ar*C*), 153.6

(*C*H=CHCO), 170.5(*C*O); MS (EI) *m/z* 229 [M^+, 4.5%]; (Found: M^+, 229.1102. $C_{14}H_{15}NO_2$ requires 229.1103).

X-ray Crystal Data for (243a): $C_{14}H_{15}NO_2$, *M*r = 229.27, orthorhombic, space group $P2_1P2_1P2_1$, a = 7.0090(6) Å, b = 8.3217(7) Å, c = 20.6004 (17) Å, β = 90 °, V = 1201.56(18) Å, Z = 4, D_{calcd} = 1.267 g cm^{-3}, R = 0.0134 for 2913 observed reflections, $F^2>2\sigma$ (2775) and 158 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

Minor isomer (243b, 25%). Mp 118-120 °C (DCM/hexanes); $[\alpha]_D$ = +26.0 (*c* = 0.10, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3388 (OH), 1669 (lactam); δ_H(400 MHz, $CDCl_3$) 1.60 (3H, s, C*H*$_3$), 2.99 (1H, dd, *J* 15.8, 11.0, ArC*H*(H)CHN), 3.08 (1H, dd, *J* 15.8, 6.8, ArC*H*(H)CHN), 3.74 (1H, dd, *J* 10.9, 3.3, C*H*(H)OH), 3.84 (1H, dd, *J* 10.9, 7.7, C*H*(H)OH), 3.90 (1H, br. s, O*H*), 4.11-4.18 (1H, m, NC*H*CH_2OH), 6.20 (1H, d, *J* 6.0, CH=C*H*CO), 7.15-7.27 (4H, m, Ar*H*), 7.57 (1H, d, *J* 6.0, C*H*=CHCO); δ_C(100 MHz, $CDCl_3$) 26.7 (*C*H_3), 29.8 (Ar*C*H_2CHN), 53.5 (NCHCH$_2$OH), 67.6 (*C*-CH_3), 68.2 (*C*H_2OH), 124.1 (Ar*C*H), 125.3 (CH=*C*HCO) 127.0 (Ar*C*H), 127.9 (Ar*C*H), 129.0 (Ar*C*H), 133.0 (Ar*C*), 138.3 (Ar*C*), 153.0 (C*H*=CHCO), 173.2 (*C*O).

(5*S*,10b*S/R*)-5-Hydroxy-10b-methyl-8,9-di(methyloxy)-3,5,6,10b-tetrahydro-pyrrolo [2,1-*a*]isoquinolin-3-one, **(244)**



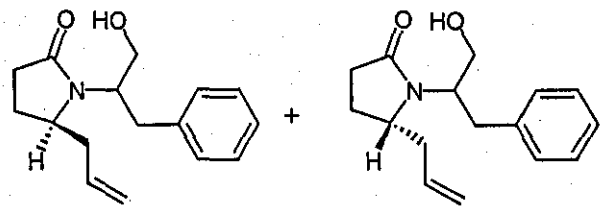
(3*S*,7a*R*)-3-(3,4-Dimethylphenyl)methyl-7a-methyl-2,3,5,7a-tetrahydropyrrolo [2,1-*b*] [1,3]oxazol-5-one, **(203)**, (90 mg, 0.3 mmol) was dissolved in dry dichloromethane (5 ml) under a nitrogen atmosphere. The mixture was cooled to –78 °C and 1.5 equivalents of titanium tetrachloride (0.05 ml, 0.5 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated ammonium chloride solution (5 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The resulting diastereoisomers could not be separated by flash column chromatography, therefore, analysis on the resulting pale yellow solid was carried out.

Major isomer (244a): ν_{max}(DCM)/cm^{-1} 3355 (OH), 1664 (lactam); δ_H(250 MHz, $CDCl_3$) 1.63 (3H, s, C*H*$_3$), 2.63 (1H, dd, *J* 16.3, 3.6, ArC*H*(H)CHN), 3.26 (1H, dd, *J* 16.3, 12.2, ArC*H*(H)CHN), 3.69-3.82 (1H, m, NC*H*CH$_2$OH), 3.84 (3H, s, C*H*$_3$O), 3.89 (3H, s, C*H*$_3$O), 3.95-4.13 (1H, m, C*H*(H)OH), 4.18-4.29 (1H, m, C*H*(H)OH), 6.08 (1H, d, *J* 5.8, CH=C*H*CO), 6.62 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 7.39 (1H, d, *J* 5.8, C*H*=CHCO); δ_C(100 MHz, $CDCl_3$) 27.0 (*C*H$_3$), 32.2 (ArCH$_2$CHN), 53.8 (NCHCH$_2$OH), 56.3 (*C*H$_3$O), 56.6 (*C*H$_3$O), 62.1 (*C*H$_2$OH), 67.7 (*C*-CH$_3$), 109.3 (Ar*C*H), 112.5 (Ar*C*H), 126.0 (CH=*C*HCO), 126.3 (Ar*C*), 129.1 (Ar*C*), 148.1 (Ar*C*-OCH$_3$), 148.8 (Ar*C*-OCH$_3$), 154.0 (*C*H=CHCO),170.9 (CO).

3.4. Asymmetric intermolecular reactions of chiral *N*-acyliminium ion precursors

3.4.1. Synthesis of 3-substututed-pyrrol-2-ones

(5*S*/*R*)-1-[2-Hydroxy-1-(phenylmethyl)ethyl]-5-prop-2-enyltetrahydro-1*H*-pyrrol-2-one, **(250)**

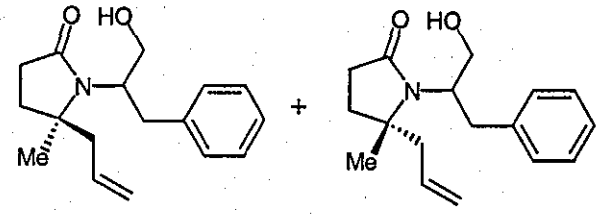


(250a) **(250b)**

(3*S*,7a*R*)-3-(Phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(174)**, (0.06 g, 0.3 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.07 ml, 0.4 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, allyltrimethylsilane (0.07 ml, 0.4 mmol) was added and then the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation to yield a mixture of isomers as a colourless oil (0.06 g, 81%). The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy on the crude reaction mixture. ν_{max}(Neat)/cm^{-1} 3390 (OH), 1660 (lactam); δ_H(250 MHz, $CDCl_3$) 1.58-1.85 (4H, m, 2 x C*H*$_2$CH$_2$CO), 1.98-2.47 (4H, m, 2 x CH$_2$C*H*$_2$CO), 2.53-2.59 (4H, m, 2 x C*H*$_2$=CHCH$_2$), 2.78-2.85 (1H, m, NC*H*CH$_2$OH), 3.11-3.33 (4H, m, 2 x C*H*$_2$Ar), 3.98-3.44 (1H, m, NC*H*CH$_2$OH), 3.57-3.71 (2H, m, 2 x NC*H*), 3.77-3.88 (4H, m, 2 x C*H*$_2$OH), 5.03-5.12 (4H, m, 2 x CH$_2$CH=C*H*$_2$), 5.53-5.65 (2H, m, 2 x CH$_2$C*H*=CH$_2$), 7.15-7.35 (10H, m, Ar*H*), 2 x O*H* not visible; δ_C(100 MHz, $CDCl_3$) 23.8 and 24.0 (*C*H$_2$CH$_2$CO), 30.5 and 30.6 (CH$_2$*C*H$_2$CO), 34.0 and 34.3 (*C*H$_2$Ar), 38.0 and 38.2 (*C*H$_2$CH=CH$_2$), 58.9 and 60.0 (N*C*H), 60.5 and 61.2 (N*C*HCH$_2$OH), 64.2 and 64.8 (*C*H$_2$OH), 118.6 and 118.9 (CH$_2$CH=*C*H$_2$), 126.6 (2 x

Ar*C*H), 128.5 (4 x Ar*C*H), 129.2 (4 x Ar*C*H), 132.6 and 133.2 ($CH_2CH{=}CH_2$), 138.5 and 138.9 (Ar*C*), 177.2 and 177.5 (*C*O).

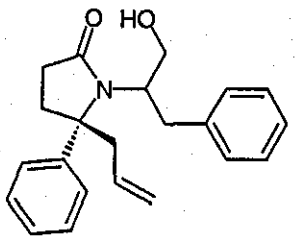
(5*S/R*)-1-(2-Hydroxy-1-(phenylmethyl)ethyl)-5-methyl-5-prop-2-enyltetrahydro-1*H*-pyrrol-2-one, **(251)**



(251a) **(251b)**

(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(175)**, (0.15 g, 0.7 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -10 °C and 1.5 equivalents of titanium tetrachloride (0.11 ml, 1.0 mmol) was added drop wise by syringe. After stirring at this temperature for 10 minutes, allyltrimethylsilane (0.15 ml, 1.0 mmol) was added and then the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation to yield a mixture of isomers as a colourless oil (0.14 g, 78%). The diastereoselectivity of the reaction was determined by ^{1}H NMR spectroscopy on the crude reaction mixture. ν_{max}(Neat)/cm^{-1} 3377 (OH), 1655 (lactam), 922 (C=C); δ_H(250 MHz, $CDCl_3$) 0.91 (3H, s, C*H*$_3$), 1.19 (3H, s, C*H*$_3$), 1.52-2.30 (8H, m, 2 x C*H*$_2$CH$_2$CO and 2 x CH$_2$C*H*$_2$CO), 2.34-2.46 (4H, m, 2 x C*H*$_2$CH=CH$_2$), 2.96-3.12 (2H, m, 2 x C*H*(H)Ar), 3.18-3.30 (2H, m, 2 x NC*H*CH$_2$OH), 3.37-3.62 (2H, m, 2 x C*H*(H)Ar), 3.71-3.84 (4H, m, 2 x C*H*$_2$OH), 5.02-5.19 (4H, m, 2 x CH$_2$CH=C*H*$_2$), 5.56-5.79 (2H, m, 2 x CH$_2$C*H*=CH$_2$), 7.17-7.36 (10H, m, Ar*H*), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 25.3 and 25.5 (*C*H$_3$), 29.7 (2 x *C*H$_2$CH$_2$CO), 30.9 and 31.1 (CH$_2$*C*H$_2$CO), 34.3 and 34.5 (*C*H$_2$Ar), 43.6 and 44.3 (*C*H$_2$CH=CH$_2$), 57.6 and 57.7 (N*C*HCH$_2$OH), 64.5 and 64.7 (*C*H$_2$OH), 100.0 (2 x *C*-CH$_3$), 119.4 and 119.6 (CH$_2$*C*H$_2$=CH), 126.5 and 126.7 (Ar*C*H), 128.5 (4 x Ar*C*H), 129.5 (2 x Ar*C*H), 129.6 (2 x Ar*C*H), 132.5 and 132.6 (CH$_2$*C*H=CH$_2$), 139.0 (2 x Ar*C*), 177.3 (2 x *C*O); MS (EI) *m/z* 273 [M$^+$, 2.6%]; (Found: M$^+$, 273.1725. $C_{17}H_{23}NO_2$ requires 273.1729).

(5*R*)-1-(2-hydroxy-1-(phenylmethyl)ethyl)-5-phenyl-5-prop-2-enyltetrahydro-1*H*-pyrrol-2-one, **(252a)**

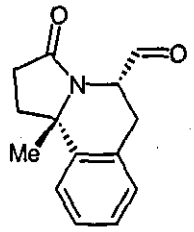


(3*S*,7a*R*)-7a-Phenyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, **(176)**, (0.15 g, 0.5 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to -10 °C and 1.5 equivalents of titanium tetrachloride (0.08 ml, 0.8 mmol) was added drop wise by syringe. After stirring at this temperature for 10 minutes, allyltrimethylsilane (0.15 ml, 0.8 mmol) was added and then the mixture was allowed to reach room temperature and left stirring for a further 60 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR on the crude reaction mixture. The purple oil was adsorbed onto silica and purified by column chromatography using a 1 : 1 mixture of ethyl acetate and hexanes as eluent. Evaporation of the desired fraction afforded the target compound as a purple oil (0.14 g, 79%). $[\alpha]_D$ = +28.5 (*c* = 0.13, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3355 (OH), 1654 (lactam), 923 (C=C); δ_H(250 MHz, $CDCl_3$) 1.99-2.09 (1H, m, $CH_2CH(H)CO$), 2.30-2.97 (7H, m, $CH_2CH=CH_2$, $NCHCH_2OH$, CH_2CH_2CO and CH_2Ar), 3.48-3.75 (3H, m, CH_2OH and $CH_2CH(H)CO$), 5.19-5.35 (2H, m, $CH_2CH=CH_2$), 5.77-5.94 (1H, m, $CH_2CH=CH_2$), 6.57-6.65 (1H, m, Ar*H*), 7.05-7.21 (4H, m, Ar*H*), 7.35-7.56 (5H, m, Ar*H*), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 30.5 (CH_2CH_2CO), 32.2 (CH_2Ar), 34.1 (CH_2CH_2CO), 41.1 ($CH_2CH=CH_2$), 58.6 ($NCHCH_2OH$), 63.0 (CH_2OH), 69.3 (*C*-Ar), 120.5 ($CH_2CH=CH_2$), 126.2 (Ar*C*H), 127.5 (2 x Ar*C*H), 128.1 (2 x Ar*C*H), 128.3 (Ar*C*H), 128.5 (2 x Ar*C*H), 129.5 (2 x Ar*C*H), 132.2 ($CH_2CH=CH_2$), 138.5 (Ar*C*), 143.0 (Ar*C*), 177.3 (*C*O); MS (EI) *m/z* 335 [M$^+$, 5.7%]; (Found: M$^+$, 335.1883. $C_{22}H_{25}NO_2$ requires 335.1885).

3.5. Further functionalisation of the pyrroloisoquinoline ring system

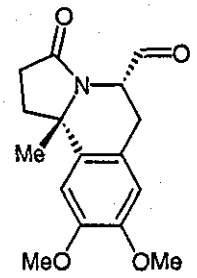
3.5.1. Decarbonylation studies

(5*S*,10b*S*)-10b-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-5-carbaldehyde, **(258)**[135]



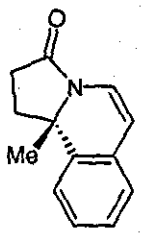
A solution of (5*S*,10b*S*)-5-(hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(218a)**, (0.15 g, 0.7 mmol) in dichloromethane (5 ml) was added to a solution of Dess-Martin periodinane (0.30 g, 0.7 mmol) in dichloromethane (10 ml) with stirring. After 20 hours, the mixture was diluted with ether (30 ml) and poured into saturated aqueous sodium bicarbonate solution (30 ml) containing a seven-fold excess of sodium thiosulfate (1.23 g, 5.0 mmol). The mixture was washed with saturated aqueous sodium bicarbonate solution and then with water. The ether was evaporated off to give the aldehyde in >95% d.e as a colourless oil (0.13 g, 89%) which required no further purification. ν_{max}(Neat)/cm^{-1} 1727 (CHO), 1683 (lactam); δ_H(250 MHz, $CDCl_3$) 1.57 (3H, s, CH_3), 2.37-2.52 (3H, m, CH_2CH_2CO and CH_2CH(H)CO), 2.61-2.80 (1H, m, CH_2CH(H)CO), 3.21 (2H, d, *J* 6.0, $ArCH_2CHN$), 4.32 (1H, t, *J* 6.1, NCHCHO), 7.10-7.31 (4H, m, Ar*H*), 9.63 (1H, s, C*H*O); δ_C(100 MHz, $CDCl_3$) 28.0 (CH_2CH_2CO), 28.6 (CH_3), 29.8 ($ArCH_2CHN$), 34.8 (CH_2CH_2CO), 57.5 (NCHCHO), 62.4 (*C*-CH_3), 123.8 (Ar*C*H), 127.4 (Ar*C*H), 127.4 (Ar*C*H), 128.9 (Ar*C*H), 130.9 (Ar*C*), 142.8 (Ar*C*), 175.1 (*C*O), 198.4 (*C*HO); MS (EI) *m/z* 229 [M^+, 2.7%]; (Found: M^+, 229.1106. $C_{14}H_{15}NO_2$ requires 229.1103).

(5*S*,10b*S*)-10b-Methyl-8,9-di(methyloxy)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo [2,1-*a*]isoquinolin-5-carbaldehyde, **(259)**



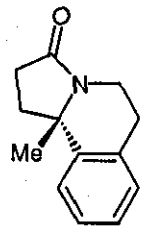
A solution of (5*S*,10b*S*)-5-(hydroxymethyl)-10b-methyl-8,9-di(methyloxy)-1,2,3,5,6, 10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(219a)**, (0.30 g, 1.0 mmol) in dichloromethane (20 ml) was added to a solution of Dess-Martin periodinane (3.23 ml of a 15% wt solution in dichloromethane, 1.1 mmol). After 20 hours, excess dichloromethane was removed and the yellow oil loaded directly on to silica. Purification by flash column chromatography using ethyl acetate and hexanes as mobile phase (9 : 1) yielded the target compound as a pale yellow solid (0.24 g, 81 %), a portion of which was recrystallised from dichloromethane and hexanes to give white crystals. Mp 179-181 °C; $[\alpha]_D$ = -172.8 (*c* = 0.38, $CHCl_3$); (Found: C, 65.83; H, 6.48; N, 4.64. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); ν_{max}(DCM)/cm^{-1} 1728 (CHO), 1684 (lactam); δ_H(250 MHz, $CDCl_3$) 1.56 (3H, s, CH_3), 2.36-2.50 (3H, m, CH_2CH_2CO and $CH_2CH(H)CO$), 2.61-2.75 (1H, m, $CH_2CH(H)CO$), 3.12 (2H, d, *J* 5.8, $ArCH_2CHN$), 3.85 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.23 (1H, t, *J* 6.4, $NCHCHO$), 6.63 (2H, s, Ar*H*), 9.68 (1H, s, C*H*O), δ_C(100 MHz, $CDCl_3$) 28.0 (CH_3), 29.0 (CH_2CH_2CO), 30.1 ($ArCH_2CHN$), 35.2 (CH_2CH_2CO), 56.3 (CH_3O), 56.5 (CH_3O), 57.9 (NCHCHO), 62.7 (*C*-CH_3), 107.6 (Ar*C*H), 112.1 (Ar*C*H), 123.6 (Ar*C*), 135.1 (Ar*C*), 148.5 (Ar*C*-OCH_3), 148.8 (Ar*C*-OCH_3), 175.6 (*C*O), 198.7 (*C*HO); MS (EI) *m/z* 289 [M^+, 21.5%]; (Found: M^+, 289.1310. $C_{16}H_{19}NO_4$ requires 289.1314).

(10b*S*)-10b-Methyl-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(260)**[135]



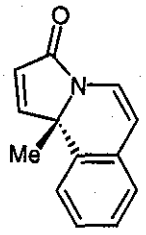
[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (20 mg, 0.03 mmol) was added to anhydrous xylene (10 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenylphosphino)propane (30 mg, 0.06 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (5*S*,10b*S*)-10b-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-carbaldehyde, **(258)**, (0.13 g, 0.6 mmol) in anhydrous xylene (10 ml) was added and the mixture was heated at reflux for 24 hours. The solvent was removed by rotary evaporation giving a thick green oil. Purification by flash column chromatography using ethyl acetate and hexanes (1 : 1) as mobile phase gave the product as colourless crystals (70 mg, 64%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 134-136 °C; $[\alpha]_D$ = -667.9 (*c* = 0.29, DCM); (Found: C, 77.51; H, 6.29; N, 6.76. $C_{13}H_{13}NO$ requires C, 78.36; H, 6.58; N, 7.03 %); ν_{max}(DCM)/cm^{-1} 1700 (lactam); δ_H(250 MHz, $CDCl_3$) 1.33 (3H, s, CH_3), 2.36-2.57 (3H, m, CH_2CH_2CO and $CH_2CH(H)CO$), 2.61-2.78 (1H, m, $CH_2CH(H)CO$), 6.03 (1H, d, *J* 7.6, ArC*H*=CHN), 6.90 (1H, d, *J* 7.4 ArCH=C*H*N), 7.05-7.12 (2H, m, Ar*H*), 7.17-7.28 (2H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 26.1 (CH_3), 30.0 (CH_2CH_2CO), 33.0 (CH_2CH_2CO), 61.9 (*C*-CH_3), 111.3 (Ar*C*H=CHN), 120.8 (ArCH=*C*HN), 123.0 (Ar*C*H), 125.3 (ArCH), 127.6 (Ar*C*H), 127.8 (Ar*C*H), 129.9 (Ar*C*), 138.6 (Ar*C*), 171.9 (*C*O); MS (EI) *m/z* 199 [M^+, 12.7%]; (Found: M^+, 199.0994. $C_{13}H_{13}NO$ requires 199.0997).

(10b*S*)-10b-Methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(261)**[135]



(10b*S*)-10b-Methyl-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(260)**, (90 mg, 0.5 mmol) was dissolved in absolute ethanol (10 ml) in a Schlenk tube. The reaction mixture was purged with nitrogen. A catalytic amount of 10% palladium/charcoal was added to the mixture, a balloon filled with hydrogen was fitted and the system purged with hydrogen, the mixture was then stirred for a further 20 hours. The mixture was filtered through Celite, the reaction vessel was washed with dichloromethane (3 x 10 ml) and poured onto the Celite. The organic extracts were collected, dried using anhydrous magnesium sulfate and evaporated off to give colourless needlelike crystals (80 mg, 89%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 125-127 °C; $[\alpha]_D$ = -261.2 (*c* = 0.30, $CHCl_3$); (Found: C, 77.52; H, 7.32; N, 6.83. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51; N, 6.91 %); ν_{max}(DCM)/cm^{-1} 1671 (lactam); δ_H(250 MHz, $CDCl_3$) 1.52 (3H, s, CH_3), 2.09 (1H, dd, *J* 21.5, 11.4, C*H*(H)CH_2CO), 2.35-2.47 (2H, m, C*H*(H)CH_2CO and CH_2CH(H)CO), 2.55-2.68 (1H, m, CH_2CH(H)CO), 2.71-2.80 (1H, m, ArC*H*(H)CH_2N), 2.86-3.01 (1H, m, ArC*H*(H)CH_2N), 3.03-3.16 (1H, m, $ArCH_2CH$(H)N), 4.29 (1H, ddd, *J* 13.0, 6.3, 2.1, $ArCH_2CH$(H)N), 7.07-7.26 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.5 (CH_3), 28.5 (ArCH_2CH_2N), 30.7 (CH_2CH_2CO), 34.0 ($ArCH_2CH_2N$), 34.7 (CH_2CH_2CO), 61.1 (*C*-CH_3), 125.0 (ArCH), 126.8 (ArCH), 126.9 (ArCH), 129.2 (ArCH), 132.3 (Ar*C*), 142.7 (Ar*C*), 172.3 (*C*O); MS (EI) *m/z* 201 [M^+, 3.3%]; (Found: M^+, 201.1149. $C_{13}H_{15}NO$ requires 201.1154).

(10b*S*)-10b-Methyl-3,10b-dihydropyrrolo[2,1-*a*]isoquinolin-3-one, **(266)**



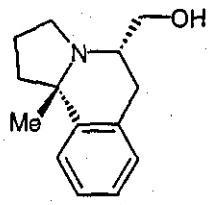
A solution of (5*S*,10b*S*)-5-(hydroxymethyl)-10b-methyl-3,5,6,10b-tetrahydropyrrolo [2,1-*a*]isoquinolin-3-one, **(242a)**, (0.11g, 0.5 mmol) in dichloromethane (5 ml) was added to a solution of Dess-Martin periodinane (0.22 g, 0.5 mmol) in dichloromethane (10 ml) with stirring. After 20 hours, the mixture was diluted with ether (30 ml) and poured into saturated aqueous sodium bicarbonate solution (30 ml) containing a seven- fold excess of sodium thiosulfate (0.83 g, 3.4 mmol). The mixture was washed with saturated aqueous sodium bicarbonate solution and then with water. The ether was evaporated off to give aldehyde **(265)** as a colourless oil (0.09 g, 82%) which required no further purification and was taken directly on to the next step.

[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (8 mg, 0.01 mmol) was added to anhydrous xylene (5 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenyl phosphino)propane (8 mg, 0.02 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (5*S*,10b*S*)-10b-methyl-3-oxo-3,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-5-carbaldehyde, **(265)**, (50 mg, 0.2 mmol) in anhydrous xylene (5 ml) was added and the mixture was heated at reflux for 24 hours. The solvent was removed by rotary evaporation giving a thick green oil. Purification by flash column chromatography using ethyl acetate and hexanes (1 : 2) as mobile phase gave racemized starting material (10 mg, 20%); the other aldehyde diastereoisomer (12 mg, 24%) and the product as a yellow oil (13 mg, 30%). $[\alpha]_D$ = -1110.0 (*c* = 0.04, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1699 (lactam); δ_H(400 MHz, $CDCl_3$) 1.46 (3H, s, C*H*$_3$), 6.11 (1H, d, *J* 7.2, ArC*H*=CHN), 6.25 (1H, d, *J* 6.0, CH=C*H*CO), 6.96 (1H, d, *J* 7.2, ArCH=C*H*N), 7.08-7.11 (1H, m, Ar*H*), 7.14-7.17 (1H, m, Ar*H*), 7.19-7.26 (2H, m, Ar*H*), 7.66 (1H, d, *J* 6.0, C*H*=CHCO). δ_C(100 MHz, $CDCl_3$) 27.9 (*C*H$_3$), 66.6 (*C*-CH$_3$), 112.4 (ArCH=CHN), 121.2

(ArCH=*C*HN), 123.1 (Ar*C*H), 126.3 (CH=*C*HCO) 127.1 (Ar*C*H), 127.75 (Ar*C*H), 127.8 (Ar*C*H), 130.4 (Ar*C*), 135.2 (Ar*C*), 150.2 (*C*H=CHCO), 168.5 (*C*O); MS (EI) *m/z* 197 [M^+, 11.7%]; (Found: M^+, 197.0841. $C_{13}H_{11}NO$ requires 197.0841).

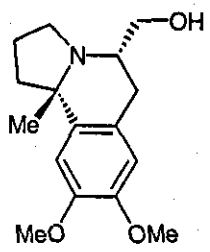
3.5.2. Amide reduction

(5*S*,10b*S*)-10b-Methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquin-5-yl-methanol, **(267)**



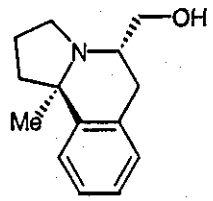
A solution of (5*S*,10b*S*)-5-(hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one, **(218a)**, (0.30 g, 1.3 mmol) in dry toluene (20 ml) was stirred at 25 °C, under nitrogen, with sodium bis(methoxyethoxy)aluminium hydride (70 wt % solution in toluene, 1.33 ml) for 16 hours. The reaction mixture was quenched by careful addition of saturated Rochelle salt (20 ml). The organic layer was separated and the salt solution extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent removed to yield a yellow oil. Purification by flash column chromatography using 10% methanol in dichloromethane gave the product as a yellow oil (0.20 g, 71%). $[\alpha]_D$ = -57.4 (*c* = 0.56, DCM); ν_{max}(neat)/cm^{-1} 3384 (OH); δ_H(400 MHz, $CDCl_3$) 1.45 (3H, s, C*H*$_3$), 1.49-1.61 (1H, m, $CH_2CH(H)CH_2N$), 1.73-1.83 (1H, m, $CH_2CH(H)CH_2N$), 2.07 (1H, ddd, *J* 12.4, 9.2, 6.8, $CH(H)CH_2CH_2N$), 2.20-2.27 (1H, ddd, *J* 12.4, 8.8, 5.2, $CH(H)CH_2CH_2N$), 2.42 (1H, dd, *J* 16.6, 4.4, ArC*H*(H)CHN), 2.65 (1H, dd, *J* 16.4, 12.0, $CH_2CH_2CH(H)N$), 2.78 (1H, dd, *J* 16.6, 12.0, ArC*H*(H)CHN), 2.86-2.92 (1H, m, $CH_2CH_2CH(H)N$), 3.00-3.40 (1H, s, br, O*H*), 3.42-3.49 (1H, m, NC*H*CH_2OH), 3.61 (1H, t, *J* 10.2, C*H*(H)OH), 3.70 (1H, dd, *J* 10.2, 4.8, C*H*(H)OH), 7.01-7.21 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 21.5 ($CH_2CH_2CH_2N$), 24.7 (ArCH_2CHN), 29.4 (CH_3), 40.2 ($CH_2CH_2CH_2N$), 43.0 ($CH_2CH_2CH_2N$), 52.3 (NCHCH$_2$OH), 63.6 (CH_2OH), 64.1 (*C*-CH$_3$), 125.7 (ArCH), 126.5 (ArCH), 126.8 (ArCH), 129.0 (ArCH), 133.1 (Ar*C*), 143.5 (Ar*C*), MS (EI) *m/z* 217 [M$^+$, 0.5%]; (Found: M$^+$, 217.1471. $C_{14}H_{19}NO$ requires 217.1467).

(5*S*,10b*S*)-10b-Methyl-8,9-di(methyloxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinolin-5-yl-methanol, **(268)**



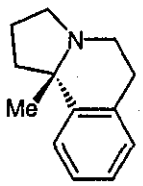
A solution of (5*S*,10b*R*)-5-(hydroxymethyl)-10b-methyl-8,9-di(methyloxy)-1,2,3,5,6, 10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(219a)**, (0.10 g, 0.3 mmol) in dry toluene (20 ml) was stirred at 25 °C, under nitrogen, with sodium bis(methoxyethoxy)aluminium hydride (70 wt % solution in toluene, 0.33 ml) for 16 hours. The reaction mixture was quenched by careful addition of saturated Rochelle salt (20 ml). The organic layer was separated and the salt solution extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent removed to yield a yellow oil (0.09 g, 96%). $[\alpha]_D$ = -44.4 (*c* = 0.44, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3408 (OH); δ_H(400 MHz, $CDCl_3$) 1.43 (3H, s, C*H*$_3$), 1.85-1.94 (1H, m, $CH_2CH(H)CH_2N$), 2.01-2.19 (2H, m, $CH_2CH(H)CH_2N$ and $CH(H)CH_2CH_2N$), 2.25-2.32 (1H, m, $CH(H)CH_2CH_2N$), 2.56-2.65 (1H, m, $CH_2CH_2CH(H)N$), 2.70 (1H, dd, *J* 15.2, 3.6, ArC*H*(H)CHN), 2.81-2.86 (1H, m, NC*H*CH$_2$OH), 2.94 (1H, dd, *J* 15.2, 10.0, ArC*H*(H)CHN), 3.48-3.55 (1H, m, $CH_2CH_2CH(H)N$), 3.53 (1H, dd, *J* 11.0, 3.8, C*H*(H)OH), 3.76 (1H, dd, *J* 11.0, 3.8, C*H*(H)OH), 3.86 (3H, s, C*H*$_3$O), 3.87 (3H, s, C*H*$_3$O), 4.20-4.35 (1H, s. br, O*H*), 6.65 (1H, m, Ar*H*), 6.68 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 23.8 ($CH_2CH_2CH_2N$), 30.0 (ArCH_2CHN), 33.4 (*C*H$_3$), 40.7 (*C*H$_2$CH$_2$CH$_2$N), 55.4 ($CH_2CH_2CH_2N$), 56.0 (*C*H$_3$O), 56.2 (*C*H$_3$O), 61.6 (NCHCH$_2$OH), 62.5 (*C*H$_2$OH), 64.3 (*C*-CH$_3$), 108.9 (Ar*C*H), 111.0 (Ar*C*H), 126.2 (Ar*C*), 135.3 (Ar*C*), 147.6 (Ar*C*-OCH$_3$), 148.0 (Ar*C*-OCH$_3$); MS (EI) *m/z* 277 [M$^+$, 0.9%]; (Found: M$^+$, 277.1675. $C_{16}H_{23}NO_3$ requires 277.1678).

(5*S*,10b*R*)-10b-Methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquin-5-yl-methanol, **(269)**



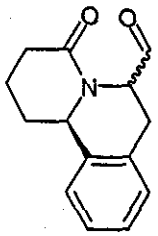
A solution of (5*S*,10b*R*)-5-(hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-3-one, **(218b)**, (0.15 g, 0.7 mmol) in dry toluene (20 ml) was stirred at 25 °C, under nitrogen, with sodium bis(methoxyethoxy)aluminium hydride (70 wt % solution in toluene, 0.60 ml) for 16 hours. The reaction mixture was quenched by careful addition of saturated Rochelle salt (20 ml). The organic layer was separated and the salt solution extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent removed to yield a yellow oil (0.12 g, 86%). $[\alpha]_D$ = +61.5 (*c* = 0.33, DCM); ν_{max}(neat)/cm^{-1} 3406 (OH); δ_H(250 MHz, $CDCl_3$) 1.32 (3H, s, C*H*$_3$), 1.80-1.91 (1H, m, $CH_2CH(H)CH_2N$), 1.93-2.14 (2H, m, $CH_2CH(H)CH_2N$ and $CH(H)CH_2CH_2N$), 2.20-2.31 (1H, m, $CH(H)CH_2CH_2N$), 2.45-2.56 (1H, m, $CH_2CH_2CH(H)N$), 2.66-2.77 (1H, m, $NCHCH_2OH$) 2.71 (1H, dd, *J* 16.1, 3.9, $ArCH(H)CHN$), 2.96 (1H, dd, *J* 16.1, 11.5, $ArCH(H)CHN$), 3.27-3.33 (1H, m, $CH_2CH_2CH(H)N$), 3.42 (1H, dd, *J* 10.4, 2.6, $CH(H)OH$), 3.69 (1H, dd, *J* 10.4, 3.9, $CH(H)OH$), 7.11-7.30 (4H, m, Ar*H*), *OH not visible*; δ_C(100 MHz, $CDCl_3$) 24.1 ($CH_2CH_2CH_2N$), 31.2 ($ArCH_2CHN$), 34.9 (CH_3), 40.8 ($CH_2CH_2CH_2N$), 54.7 ($CH_2CH_2CH_2N$), 60.6 ($NCHCH_2OH$), 62.5 (C-CH_3), 62.9 (CH_2OH), 125.2 (ArCH), 125.9 (ArCH), 126.8 (ArCH), 127.5 (ArCH), 134.6 (Ar*C*), 145.0 (Ar*C*), MS (EI) *m/z* 217 [M^+, 0.7%]; (Found: M^+, 217.1467. $C_{14}H_{19}NO$ requires 217.1467).

(10b*S*)-10b-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline, (**270**)



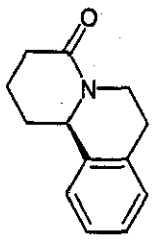
A solution of (10b*S*)-10b-Methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, (**261**), (49 mg, 0.2 mmol) in dry toluene (5 ml) was stirred at 25 °C, under nitrogen, with sodium bis(methoxyethoxy)aluminium hydride (70 wt % solution in toluene, 0.24 ml) for 16 hours. The reaction mixture was quenched by careful addition of saturated Rochelle salt (5 ml). The organic layer was separated and the salt solution extracted with dichloromethane (3 x 5 ml). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent removed to yield a yellow oil. Purification by flash column chromatography using 10% methanol in dichloromethane gave the product as a pale yellow oil (31 mg, 67%). $[\alpha]_D$ = -68.7 (*c* = 0.30, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2920 (CH_2); δ_H(400 MHz, $CDCl_3$) 1.46 (3H, s, CH_3), 1.68-1.72 (1H, m, $CH_2CH(H)CH_2N$), 1.85-1.92 (1H, m, $CH_2CH(H)CH_2N$), 2.11-2.18 (2H, $CH_2CH_2CH_2N$), 2.58-2.65 (1H, m, $ArCH(H)CH_2N$), 2.85-2.92 (1H, m, $CH_2CH_2CH(H)N$), 3.01-3.13 (3H, m, $ArCH(H)CH_2N$, $CH_2CH_2CH(H)N$ and $ArCH_2CH(H)N$), 3.22-3.27 (1H, m, $ArCH_2CH(H)N$), 7.04-7.19 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 22.3 ($CH_2CH_2CH_2N$), 24.3 ($ArCH_2CH_2N$), 29.9 (CH_3), 40.2 ($CH_2CH_2CH_2N$), 43.3 ($ArCH_2CH_2N$), 50.8 ($CH_2CH_2CH_2N$), 63.1 (*C*-CH_3), 125.7 (Ar*C*H), 126.4 (Ar*C*H), 126.7 (Ar*C*H), 128.6 (Ar*C*H), 133.5 (Ar*C*), 143.6 (Ar*C*); MS (EI) *m/z* 187 [M^+, 2.1%]; (Found: M^+, 187.1358. $C_{13}H_{17}N$ requires 187.1361).

(11b*R*)-4-oxo-1,3,4,6,7,11b-Hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-6-carbaldehyde, (**271**)



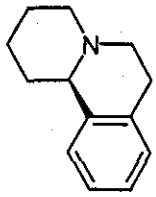
A solution of (6*S*,11b*R*)-6-(hydroxymethyl)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-a] isoquinolin-4-one, (**241**), (1.40 g, 6.1 mmol) in dichloromethane (50 ml) was added to a solution of Dess-Martin periodinane (18.86 ml of a 15% wt solution in dichloromethane, 6.7 mmol). After 20 hours, excess dichloromethane was removed and the yellow oil loaded directly on to silica. Purification by flash column chromatography using ethyl acetate and hexanes as mobile phase (3 : 1) yielded the target compound as a pale yellow oil[ref]. ν_{max}(Neat)/cm^{-1} 1718 (CHO), 1616 (lactam); δ_H(250 MHz, $CDCl_3$) 1.70-1.86 (1H, m, C*H*(H)CH_2CH_2CO), 1.93-2.07 (2H, m, C*H*(H)CH_2CH_2CO and CH_2CH(H)CH_2CO), 2.39-2.57 (2H, m, CH_2CH(H)CH_2CO and CH_2CH_2CH(H)CO), 2.68 (1H, dd, *J* 17.8, 4.0, CH_2CH_2CH(H)CO) 3.09 (1H, dd, *J* 15.9, 6.0, ArC*H*(H)CHN), 3.20 (1H, dd, *J* 16.0, 5.1 ArC*H*(H)CHN), 4.76 (1H, dd, *J* 10.7, 4.2, NC*H*Ar), 5.38 (1H, t, *J* 5.6, NC*H*CHO), 7.16-7.25 (4H, m, Ar*H*), 9.55 (1H, s, C*H*O); δ_C(67.5MHz, $CDCl_3$) 19.7 ($CH_2CH_2CH_2CO$), 28.2 (ArCH_2CHN), 30.6 ($CH_2CH_2CH_2CO$), 32.1 ($CH_2CH_2CH_2CO$), 55.4 (NCHAr), 57.9 (NCHCHO), 125.2 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 129.0 (ArCH), 132.2 (ArC), 136.4 (ArC), 171.4 (CO) 199.3 (CHO).

(11b*R*)-1,3,4,6,7,11b-Hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-4-one, **(273)**
(+ phosphorous by-product)



[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (0.12 g, 0.2 mmol) was added to anhydrous xylene (20 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenylphosphino)propane (0.18 g, 0.5 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (11b*R*)-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-6-carbaldehyde, **(271)**, (0.75 g, 3.3 mmol) in anhydrous xylene (20 ml) was added and the mixture was heated at reflux for 72 hours. The solvent was removed by rotary evaporation giving a thick green oil. Purification by flash column chromatography using ethyl acetate and hexanes (3 : 1) as eluent gave crude enamide as a yellow oil (0.07 g, 11%), racemised aldehyde (0.09 g, 12%) and the decarbonylated product (0.20 g, 30%) plus an inseparable phosphine by-product as a yellow oil. ν_{max}(Neat)/cm^{-1} 1638 (lactam); δ_H(400 MHz, $CDCl_3$) 1.65-1.77 (1H, m, C*H*(H)CH_2CH_2CO), 1.80-2.01 (2H, m, $CH_2CH_2CH_2CO$), 2.30-2.43 (1H, m, CH_2CH_2CH(H)CO), 2.49-2.63 (2H, m, C*H*(H)CH_2CH_2CO and CH_2CH_2CH(H)CO), 2.70-2.79 (1H, m, ArC*H*(H)CH_2N), 2.82-3.03 (2H, m, ArC*H*(H)CH_2N and $ArCH_2CH$(H)N), 4.67 (1H, dd, *J* 10.0, 6.0, $ArCH_2CH$(H)N), 4.79-4.84 (1H, m, NC*H*), 7.08-7.30 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 19.7 ($CH_2CH_2CH_2CO$), 28.9 ($ArCH_2CH_2N$), 30.6 ($CH_2CH_2CH_2CO$), 32.3 ($CH_2CH_2CH_2CO$), 39.7 ($ArCH_2CH_2N$), 56.9 (NCH), 124.9 (ArCH), 126.5 (ArCH), 126.7 (ArCH), 129.0 (ArCH), 135.1 (Ar*C*), 137.4 (Ar*C*), 169.4 (*C*O).

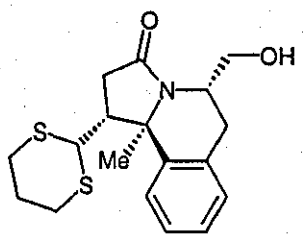
(11b*R*)-1,3,4,6,7,11b-Hexahydro-2*H*-pyrido[2,1-*a*]isoquinoline, **(274)**



A solution of (11b*R*)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-4-one, **(273)**, (+ phosphorous by-product) (0.40 g) in dry toluene (25 ml) was stirred at room temperature under nitrogen with sodium bis(methoxyethoxy)aluminium hydride (65 + wt % solution in toluene, 1.92 ml) for 16 hours. The reaction mixture was quenched with saturated aqueous Rochelle salt (25 ml). The organic layer was separated and the salt extracted with dichloromethane (3 x 25 ml). The combined organic extracts were removed to give a dark orange oil (0.32 g). This oil was acidified using HCl (2.0 M) and extracted into dichloromethane. The organic layer was dried using anhydrous sodium sulfate and the solvents removed to give the phosphorous by-product and other impurities (0.20 g). The aqueous layer was then basified using sodium hydroxide (2.0 M) and extracted into dichloromethane. The organic layer was dried using anhydrous sodium sulfate and the solvents removed to give a yellow oil which was purified using 5% methanol in dichloromethane yielding a colourless oil (0.12 g, 64%)[1]. ν_{max}(Neat)/cm^{-1} 2931 and 2852 (CH_2), 1429-1492 (CH_2); δ_H(250 MHz, $CDCl_3$) 1.34-1.56 (2H, m, C*H*(H)$CH_2CH_2CH_2N$ and CH_2CH(H)CH_2CH_2N), 1.60-1.80 (2H, m, $CH_2CH_2CH_2CH_2N$), 1.85-1.99 (1H, m, CH_2CH(H)CH_2CH_2N), 2.24-2.35 (2H, m, C*H*(H)$CH_2CH_2CH_2N$ and $CH_2CH_2CH_2CH$(H)N), 2.45-2.58 (1H, m, $ArCH_2CH$(H)N), 2.62-2.74 (1H, m, ArCH(H)CH_2N), 2.86-3.00 (2H, m, $CH_2CH_2CH_2CH$(H)N and $ArCH_2CH$(H)N), 3.08-3.31 (2H, m, ArCH(H)CH_2N and NC*H*), 7.03-7.25 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 25.1 ($CH_2CH_2CH_2CH_2N$), 25.5 ($CH_2CH_2CH_2CH_2N$), 29.6 ($ArCH_2CH_2N$), 31.3 ($CH_2CH_2CH_2CH_2N$), 52.7 ($ArCH_2CH_2N$), 57.0 ($CH_2CH_2CH_2CH_2N$), 63.6 (NCH), 124.7 (ArCH), 125.6 (ArCH), 125.8 (ArCH), 128.8 (ArCH), 134.5 (Ar*C*), 138.4 (Ar*C*); MS (EI) *m/z* 187 [M^+, 62.1%]; (Found: M^+, 187.1359. $C_{13}H_{17}N$ requires 187.1361). [1] and traces of an inseparable impurity

3.5.3. Conjugate addition reactions

(1*R*,5*S*,10b*R*)-1-(1,3-dithian-2-yl)-5-(hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(275)**

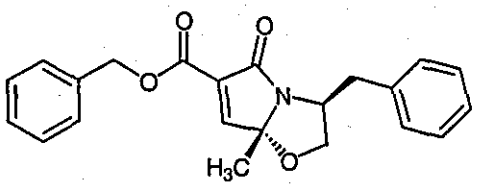


Butyl lithium (0.26 ml, of a 2.5 M solution in hexanes, 0.5 mmol) was added to a solution of 1,3-dithiane (0.06 g, 0.5 mmol) in tetrahydrofuran (10 ml) at -78 °C. The mixture was stirred for 30 minutes, warmed to room temperature and was immediately quenched by the addition of (5*S*,10b*S*)-5-(hydroxymethyl)-10b-methyl-3,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(243b)**, (0.10 g, 0.4 mmol) in tetrahydrofuran (10 ml). The resulting reaction mixture was stirred at room temperature for a further 1 hour, quenched with 5-10 drops of water and dried using anhydrous magnesium sulfate. The solvents were removed by rotary evaporation and the resulting yellow oil was further purified by flash column chromatography using a 1 : 1 mixture of ethyl acetate and hexanes as eluent yielding the target compound as a colourless oil (0.04 g, 27%). $[\alpha]_D = 0$ (c = 0.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3385 (OH), 1654 (lactam); δ_H(400 MHz, $CDCl_3$) 1.67 (3H, s, C*H*$_3$), 1.81-1.98 (1H, m, C*H*(H)CH$_2$S), 2.04-2.21 (1H, m, C*H*(H)CH$_2$S), 2.57 (1H, dd, *J* 21.4, 13.4, CHC*H*(H)CO), 2.80-3.05 (7H, m, CHC*H*(H)CO, CH$_2$C*H*$_2$S, ArC*H*$_2$CHN, C*H*CH$_2$CO and CH$_2$C*H*(H)S), 3.06-3.16 (1H, m, CH$_2$C*H*(H)S), 3.73-3.78 (2H, m, C*H*$_2$OH), 4.16-4.23 (1H, m, NC*H*CH$_2$OH), 4.63 (1H, d, *J* 2.8, C*H*S), 7.17-7.30 (3H, m, Ar*H*), 7.40 (1H, d, *J* 7.2, Ar*H*), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 24.2 (*C*H$_3$), 25.4 (*C*H$_2$CH$_2$S), 29.9 (ArCH$_2$CHN), 30.7 (*C*H$_2$S), 32.0 (*C*H$_2$S), 33.2 (CHCH$_2$CO), 48.3 (*C*HCH$_2$CO), 48.7 (*C*HS), 52.7 (NCHCH$_2$OH), 66.0 (*C*-CH$_3$), 67.6 (*C*H$_2$OH), 123.0 (Ar*C*H), 127.2 (Ar*C*H), 127.7 (Ar*C*H), 129.1 (Ar*C*H), 132.6 (Ar*C*), 142.5 (Ar*C*), 174.4 (*C*O); MS (EI) *m/z* 349 [M$^+$, 11.8%]; (Found: M$^+$, 349.1174. $C_{18}H_{23}NO_2S_2$ requires 349.1170).

3.6. Applications of *N*-acyliminium ion precursors in the synthesis of *erythrina* alkaloids

3.6.1. A metathesis approach to the erythrinane skeleton

Phenylmethyl(3*S*,7*aR*)-7a-methyl-5-oxo-3-(phenylmethyl)-2,3,5,7*a*-tetrahydro pyrrolo[2,1-*b*][1,3]oxazole-6-carboxylate, **(285)**



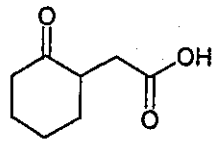
(3*S*,7*aR*)-3-Benzyl-7*a*-but-3-enyl-tetrahydropyrrolo[2,1-*b*]oxazol-5-one, **(175)**, (0.50 g, 2.2 mmol) in tetrahydrofuran (20 ml) at –78 °C under nitrogen was added LHMDS (2.38 ml of a 1.0 M solution in tetrahydrofuran, 2.4 mmol). After 1 hour benzylchloroformate (0.21 ml, 1.4 mmol) was added and the reaction was left to stir for 30 minutes. The reaction was quenched with 1.0 M HCl, and diluted with ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate and brine and dried over anhydrous magnesium sulfate. The solvents were evaporated off to give a yellow oil which was purified by flash column chromatography using diethyl ether and hexanes (1 : 1) as mobile phase to give unreacted starting material (0.19 g, 38%); unreacted benzylchloroformate (0.08 g) and **(284)** as a mixture of isomers (0.33 g, 42%).

To **(284)** in tetrahydrofuran (10 ml) at –78 °C was added LHMDS (0.91 ml of a 1.0 M solution in tetrahydrofuran, 0.9 mmol). The reaction was stirred for 1 hour and then benzeneselenyl bromide (0.32 g, 1.4 mmol) in tetrahydrofuran (10 ml) was added at –78 °C and stirred for 1 hour, warmed to 0 °C for 1 hour and then quenched with 1.0 M HCl. The mixture was diluted with ethyl acetate and the organic layer was washed with saturated sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and the solvent removed. The resulting yellow oil was dissolved in dichloromethane (20 ml), cooled to 0 °C and treated with hydrogen peroxide (0.23 ml of a 35% w/w aqueous solution, 2.7 mmol). After 15 minutes the

solution was warmed to room temperature and stirred for 1 hour at which time HCl (1.0 M) was added and the reaction mixture was extracted into ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate and brine and dried over anhydrous magnesium sulfate. The solvents were removed to yield a yellow oil which was purified by flash column chromatography using ether and hexanes (1 : 1) as mobile phase to give recovered starting material (0.05g, 15%) and the desired product as a colourless oil (0.17 g, 52%). $[\alpha]_D$ = -5.14 (*c* = 0.27, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1715 (CO), 1730 (CO); δ_H(250 MHz, $CDCl_3$) 1.47 (3H, s, C*H*$_3$), 2.92 (1H, dd, *J* 13.9, 8.6, C*H*(H)Ar), 3.12 (1H, dd, *J* 13.9, 6.0, C*H*(H)Ar), 3.99-4.14 (2H, m, C*H*$_2$O), 4.26-4.38 (1H, m, NC*H*), 5.28 (2H, s, ArC*H*$_2$O), 7.23-7.45 (10H, m, Ar*H*), 7.63 (1H, s, C*H*=CR); δ_C(100 MHz, $CDCl_3$) 22.6 (*C*H$_3$), 39.8 (*C*H$_2$Ar), 57.4 (N*C*H), 67.0 (Ar*C*H$_2$O), 73.5 (*C*H$_2$O), 97.7 (*C*-CH$_3$), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.6 (2 x Ar*C*H), 129.4 (2 x Ar*C*H), 130.7 (CH=*C*R), 135.2 (Ar*C*), 137.0 (Ar*C*), 156.7 (*C*H=CR), 160.7 (O*C*O), 172.3 (N*C*O); MS (EI) *m/z* 363 [M^+, 18.6%] (Found: M^+, 363.1473. $C_{17}H_{19}NO_2$ requires 363.1471).

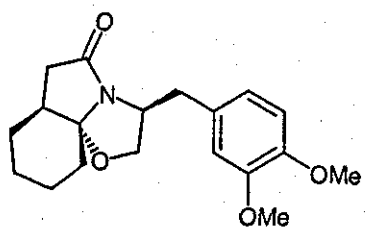
3.6.2. Functionalised substrate approach to the erythrinane skeleton

2-(2-Oxocyclohexyl)ethanoic acid, **(293)**[126]



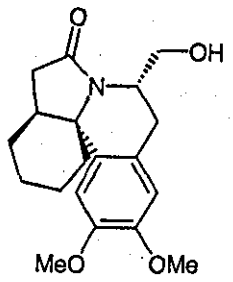
Ethyl-2-cyclohexanoneacetate, **(292)**, (0.50 g, 2.7 mmol) was dissolved in a mixture of tetrahydrofuran (18 ml) and water (8 ml). Lithium hydroxide (0.17 g, 4.1 mmol) was added and the mixture was stirred at room temperature for 20 hours. The reaction mixture was concentrated, re-suspended in water (30 ml) and acidified with HCl (1.0 M). The aqueous layer was then extracted into ethyl acetate, dried over anhydrous magnesium sulfate and evaporated to dryness giving a colourless oil (0.42 g, 100%). ν_{max}(Neat)/cm^{-1} 3200 (OH), 1702 (CO); δ_H(250 MHz, $CDCl_3$) 1.30-3.00 (11H, m, 5 x C*H*$_2$ and C*H*), 9.10-9.90 (1H, br. s, O*H*); δ_C(100 MHz, $CDCl_3$) 25.2 (*C*H$_2$), 27.8 (*C*H$_2$), 33.8 (*C*H$_2$), 34.3 (*C*H$_2$), 41.8 (*C*H$_2$), 46.9 (*C*H), 178.2 (*C*O), 211.4 (*C*OOH); MS (EI) *m/z* 156 [M$^+$, 37.3%]; (Found: M$^+$, 156.0787. $C_8H_{12}O_3$ requires 156.0787).

(3*S*,6a*S*,10a*R*)-3-(3,4-Di(methyloxy)phenyl)methyl-perhydro[1,3]oxazolo[2,3-i] indol-5-one, (**294**)[138]



(2*S*)-2-Amino-3-(3,4-di(methyloxy)phenyl)propan-1-ol, (**189**), (1.60 g, 7.6 mmol) and ethyl-2-cyclohexanoneacetate, (**293**), (1.18 g, 7.6 mmol) were dissolved in toluene (100 ml) and refluxed under Dean-Stark conditions for 144 hours. After this time the solution was allowed to cool and the solvent was removed by rotary evaporation. The resulting yellow oil was purified by flash column chromatography using a 1 : 1 mixture of ethyl acetate and hexanes as eluent. Evaporation of the desired fraction afforded the target compound as a yellow oil (1.45 g, 58%). $[\alpha]_D$ = +26.9 (*c* = 0.34, $CHCl_3$); ν_{max}(Neat)/cm^{-1} 1702 (lactam); δ_H(400 MHz, $CDCl_3$) 1.37-1.90 (8H, m, $NCCH_2CH_2$, $NCCH_2CH_2$, CH_2CH_2CH and CH_2CH_2CH), 2.30-2.41 (2H, m, $CHCH_2CO$ and $CHCH(H)CO$), 2.57-2.65 (1H, m, $CHCH(H)CO$), 2.69 (1H, dd, *J* 13.8, 9.2, $CH(H)Ar$), 3.04 (1H, dd, *J* 13.8, 5.2, $CH(H)Ar$), 3.85 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 3.93 (1H, dd, *J* 8.8, 5.6, $CH(H)O$), 4.02 (1H, dd, *J* 8.8, 6.8, $CH(H)O$), 4.23-4.27 (1H, m, $NCHCH_2O$), 6.72-6.81 (3H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 19.8 ($NCCH_2CH_2$), 20.9 (CH_2CH_2CH), 25.1 (CH_2CH_2CH), 32.8 ($NCCH_2CH_2$), 39.2 ($CHCH_2CO$), 39.6 (CH_2Ar) 40.8 ($CHCH_2CO$), 55.3 ($NCHCH_2O$), 55.9 (CH_3O), 56.0 (CH_3O) 71.7 (CH_2O), 99.6 ($NCCH_2CH_2$), 111.3 (Ar*C*H), 112.5 (Ar*C*H), 121.3 (Ar*C*H), 129.7 (Ar*C*), 147.9 (Ar*C*-OCH_3), 149.0 (Ar*C*-OCH_3), 176.2 (*C*O); MS (EI) *m/z* 331 [M^+, 41.2%]; (Found: M^+, 331.1786 $C_{19}H_{25}NO_4$ requires 331.1784).

(4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-2-one, (**295**)[138]

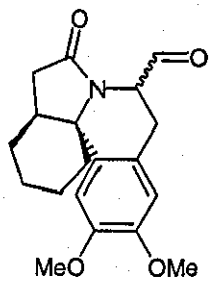


(3*S*,6a*S*,10a*R*)-3-(3,4-Di(methyloxy)phenyl)methyl-perhydro[1,3]oxazolo[2,3-1] indol-5-one, (**294**), (1.20 g, 3.6 mmol) was dissolved in dry dichloromethane (50 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 3 equivalents of titanium tetrachloride (1.19 ml, 10.9 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (50 ml), extracted with dichloromethane (3 x 50 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow oil was purified by flash column chromatography using 100% ethyl acetate as eluent yielding the target compound as a white solid (1.18 g, 98%), a portion of which was recrystallised from ethyl acetate to give colourless crystals. Mp 191-192 °C; $[\alpha]_D$ = -79.1 (*c* = 0.53, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3383 (OH), 1655 (lactam); δ_H(400 MHz, $CDCl_3$) 1.35-1.45 (1H, m, NCCH$_2$C*H*(H)), 1.46-1.55 (1H, m, NCCH$_2$C*H*(H)), 1.60-1.70 (2H, m, C*H*$_2$CH$_2$CH), 1.74-1.83 (1H, m, CH$_2$C*H*(H)CH), 1.85-1.95 (2H, m, NCC*H*$_2$CH$_2$), 2.00-2.09 (1H, m, CH$_2$C*H*(H)CH), 2.31-2.44 (2H, m, CHC*H*$_2$CO), 2.61-2.67 (1H, m, C*H*CH$_2$CO), 2.82 (1H, dd, *J* 16.0, 5.2, ArC*H*(H)CHN), 3.13 (1H, dd, *J* 16.0, 7.6, ArC*H*(H)CHN), 3.70-3.76 (1H, m, C*H*(H)OH), 3.80-3.85 (1H, m, C*H*(H)OH), 3.86 (3H, s, C*H*$_3$O), 3.89 (3H, s, C*H*$_3$O), 3.88-3.94 (1H, m, NC*H*CH$_2$OH), 4.63 (1H, dd, *J* 7.2, 6.0, O*H*), 6.65 (1H, s, Ar*H*), 6.88 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 20.8 (NCCH$_2$CH$_2$), 21.1 (*C*H$_2$CH$_2$CH), 27.5 (CH$_2$*C*H$_2$CH), 29.9 (Ar*C*H$_2$CHN), 36.2 (NC*C*H$_2$CH$_2$), 36.8 (CH*C*H$_2$CO), 38.1 (*C*HCH$_2$CO), 52.6 (N*C*HCH$_2$OH), 55.9 (*C*H$_3$O), 56.3 (*C*H$_3$O), 64.0 (NCCH$_2$CH$_2$),

65.2 (CH_2OH), 108.4 (Ar*C*H), 112.3 (Ar*C*H), 126.0 (Ar*C*), 134.0 (Ar*C*), 147.4 (Ar*C*-OCH_3), 148.0 (Ar*C*-OCH_3), 176.0 (*C*O); MS (EI) *m/z* 331 [M^+, 29.9%]; (Found: M^+, 331.1780. $C_{19}H_{25}NO_4$ requires 331.1784).

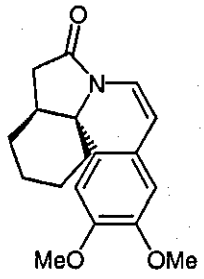
X-ray Crystal Data for (295): $C_{19}H_{25}NO_4$, *Mr* = 331.40, orthorhombic, space group $P2_12_12_1$, a = 9.4058(4) Å, b = 10.0200(4) Å, c = 17.9014(7) Å, β = 90°, V = 1687.14(12) Å, Z = 4, D_{calcd} = 1.305 g cm^{-3}, R = 0.0143 for 4095 observed reflections, $F^2>2\sigma$ (3902) and 220 parameters. All measurements were made on a Bruker AXS SMART 1000 CCD area detector with MO Kα radiation.

(9b*S*,13a*S*)-7,8-Di(methyloxy)-2-oxo-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo [7a,1-*a*]isoquinolin-4-carbaldehyde, **(296)**[138]



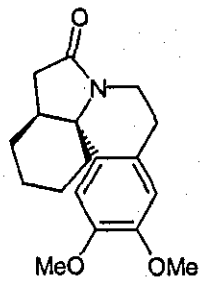
A solution of (4*S*,9b*S*,13a*S*)-4-(hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-2-one, **(295)**, (1.18 g, 3.6 mmol) in dichloromethane (25 ml) was added to a solution of Dess-Martin periodinane (11.1 ml of a 15% wt solution in dichloromethane, 3.9 mmol) in dichloromethane (25 ml) with stirring. After 20 hours, excess dichloromethane was removed and the yellow oil loaded directly on to silica. Purification by flash column chromatography using a 2 : 1 mixture of ethyl acetate and hexanes as eluent yielded a 1 : 1 mixture of aldehyde diastereoisomers as a colourless oil (1.02 g, 87%). ν_{max}(Neat)/cm^{-1} 1733 (CHO), 1683 (lactam); δ_H(250 MHz, $CDCl_3$) 1.21-3.16 (28H, m, 12 x C*H*$_2$ and 4 x C*H*), 3.80-3.85 (12H, m, 4 x C*H*$_3$O), 6.60 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 6.84 (1H, s, Ar*H*), 6.92 (1H, s, Ar*H*), 9.53 (1H, s, C*H*O), 9.66 (1H, s, C*H*O); δ_C(100 MHz, $CDCl_3$) 20.8 and 20.9 (NCCH$_2$*C*H$_2$), 21.2 and 21.6 (*C*H$_2$CH$_2$CH), 26.1 and 27.5 (CH$_2$*C*H$_2$CH), 27.7 and 28.1 (Ar*C*H$_2$CHN), 35.6 and 36.0 (NC*C*H$_2$CH$_2$), 36.8 and 37.2 (CH*C*H$_2$CO), 38.1 and 38.6 (*C*HCH$_2$CO), 55.9 and 56.0 (C*H*$_3$O), 56.3 and 56.4 (C*H*$_3$O), 57.1 and 57.2 (N*C*HCHO), 62.7 and 63.7 (N*C*CH$_2$CH$_2$), 108.2 and 108.4 (Ar*C*H), 112.08 and 112.13 (Ar*C*H), 124.0 and 124.4 (Ar*C*), 134.3 and 134.4 (Ar*C*), 147.7 and 147.8 (Ar*C*-OCH$_3$), 148.15 and 148.19 (Ar*C*-OCH$_3$), 174.4 and 176.0 (*C*O), 199.7 (2 x *C*HO); MS (EI) *m/z* 329 [M$^+$, 32.1%]; (Found: M$^+$, 329.1627. $C_{19}H_{23}NO_4$ requires 329.1627).

(9b*S*,13a*S*)-7,8-Di(methyloxy)-1,10,11,12,13,13a-hexahydro-2*H*-indolo[7a,1-*a*] isoquinolin-2-one, (**297**)[138]



[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (88 mg, 0.1 mmol) was added to anhydrous xylene (20 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenylphosphino)propane (0.12 g, 0.3 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (9b*S*,13a*S*)-7,8-Di(methyloxy)-2-oxo-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*] isoquinoline-4-carbaldehyde, (296), (0.81 g, 2.5 mmol) in anhydrous xylene (20 ml) was added and the mixture was heated at reflux for 192 hours. The solvent was removed by rotary evaporation giving a thick green oil. Purification by flash column chromatography using a mixture of 1 : 1 ethyl acetate and hexanes as eluent gave the product as white crystals (0.42 g, 57%), a portion of which was recrystallised from ethyl acetate to give colourless crystals. Mp 175-177 °C; $[\alpha]_D$ = -238.7 (*c* = 0.45, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 1696 (lactam), 730 (C=C); δ_H(250 MHz, $CDCl_3$) 1.14-1.61 (4H, m, C*H*(H)CH_2CH, NCC*H*(H)CH_2 and NCCH_2CH_2), 1.72-1.89 (1H, m, C*H*(H)CH_2CH), 1.96-2.24 (3H, m, CH_2CH_2CH and NCC*H*(H)CH_2), 2.48 (1H, dd, *J* 17.1, 9.3, CHC*H*(H)CO), 2.60 (1H, dd, *J* 17.1, 11.7, CHC*H*(H)CO), 2.80-2.97 (1H, m, C*H*CH_2CO), 3.89 (3H, s, CH_3O), 3.92 (3H, s, CH_3O), 5.94 (1H, d, *J* 7.4 ArC*H*=CHN), 6.67 (1H, s, Ar*H*), 6.85 (1H, d, *J* 7.6 ArCH=C*H*N), 6.97 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 20.0 (NCCH_2CH_2), 20.8 (CH_2CH_2CH), 27.0 (CH_2CH_2CH), 35.1 (NCCH_2CH_2), 35.3 (CHCH_2CO), 37.9 (CHCH_2CO), 56.0 (CH_3O), 56.4 (CH_3O), 61.9 (NCCH_2CH_2), 108.9 (ArCH), 109.2 (ArCH), 111.2 (ArCH=CHN), 119.5 (ArCH=CHN), 124.1 (Ar*C*), 130.2 (Ar*C*), 147.9 (Ar*C*-OCH_3), 148.2 (Ar*C*-OCH_3), 170.7 (*C*O); MS (EI) *m/z* 299 [M^+, 30.6%]; (Found: M^+, 299.1527. $C_{18}H_{21}NO_3$ requires 299.1521).

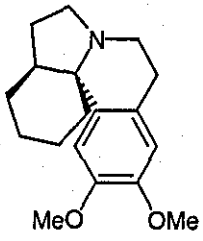
(9b*S*,13a*S*)-7,8-Di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*] isoquinolin-2-one, **(298)**[138]



(9b*S*,13a*S*)-7,8-Di(methyloxy)-1,10,11,12,13,13a-hexahydro-2*H*-indolo[7a,1-*a*] isoquinolin-2-one, **(297)**, (0.14 g, 0.5 mmol) was dissolved in absolute ethanol (15 ml) in a Schlenk tube. The reaction mixture was purged with nitrogen. A catalytic amount of 10% palladium-charcoal was added to the mixture, a balloon filled with hydrogen was fitted and the system purged with hydrogen, the mixture was then stirred for a further 20 hours. The mixture was filtered through Celite, the reaction vessel was washed with dichloromethane (3 x 10 ml) and poured onto the Celite. The organic extracts were collected, dried using anhydrous magnesium sulfate and evaporated off to give a yellow oil. Purification by flash column chromatography using a mixture of 4 : 1 ethyl acetate and hexanes as eluent gave the target compound as a colourless oil (0.10 g, 71%). $[\alpha]_D$ = -96.4 (*c* = 0.25, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1683 (lactam); δ_H(400 MHz, $CDCl_3$) 1.48-1.56 (2H, m, $NCCH_2CH_2$), 1.62-1.75 (3H, m, CH_2CH_2CH and $CH_2CH(H)CH$), 1.83 (1H, dd, *J* 14.3, 6.0, $NCCH(H)CH_2$), 1.90 (1H, dd, *J* 14.3, 6.2, $NCCH(H)CH_2$), 2.00-2.08 (1H, m, $CH_2CH(H)CH$), 2.32 (1H, dd, *J* 16.8, 7.6, $CHCH(H)CO$), 2.37 (1H, dd, *J* 16.8, 8.0, $CHCH(H)CO$), 2.54-2.60 (1H, m, $CHCH_2CO$), 2.68 (1H, ddd, *J* 16.2, 5.4, 3.0, $ArCH(H)CH_2N$), 2.94-3.02 (1H, m, $ArCH(H)CH_2N$), 3.22 (1H, ddd, *J* 13.2, 10.4, 5.6, $ArCH_2CH(H)N$), 3.85 (3H, s, CH_3O), 3.89 (3H, s, CH_3O), 4.11 (1H, ddd, *J* 13.2, 7.2, 2.8, $ArCH_2CH(H)N$), 6.59 (1H, s, Ar*H*), 6.88 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 20.4 ($NCCH_2CH_2$), 20.8 (CH_2CH_2CH), 27.18 (CH_2CH_2CH), 27.21 ($ArCH_2CH_2N$), 34.9 ($ArCH_2CH_2N$), 35.9 ($NCCH_2CH_2$), 36.6 ($CHCH_2CO$), 37.7 ($CHCH_2CO$), 55.9 (CH_3O), 56.2 (CH_3O), 62.3 ($NCCH_2CH_2$), 108.3 (Ar*C*H), 112.0 (Ar*C*H), 125.8 (Ar*C*), 134.9 (Ar*C*), 147.4 (Ar*C*-OCH_3), 147.9 (Ar*C*-OCH_3), 174.2

(*C*O); MS (EI) *m/z* 301 [M^+, 23.1%]; (Found: M^+, 301.1684. $C_{18}H_{23}NO_3$ requires 301.1678).

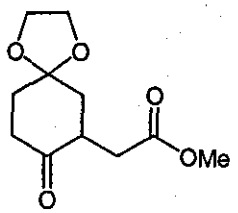
(9*bS*,13*aS*)-7,8-Di(methyloxy)-1,4,5,10,11,12,13,13*a*-octahydro-2*H*-indolo[7*a*,1-*a*] isoquinoline, **(299)**[138]



A solution of (9b*S*,13a*S*)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo [7a,1-*a*]isoquinolin-2-one, **(298)**, (0.10 g, 0.3 mmol) in dry toluene (10 ml) was stirred at 25 °C, under nitrogen, with sodium bis(methoxyethoxy)aluminium hydride (65^+ wt % solution in toluene, 0.33 ml) for 16 hours. The reaction mixture was quenched by careful addition of saturated Rochelle salt (10 ml). The organic layer was separated and the salt solution extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent removed to yield a yellow oil. Further purification by flash column chromatography using a 9 : 1 mixture of dichloromethane and methanol as eluent gave the product as a colourless oil (76 mg, 80%). $[\alpha]_D$ = -25.0 (*c* = 0.38, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2929 and 2848 (CH_2), 1123 and 1104 (C-O-C); δ_H(400 MHz, $CDCl_3$) 1.23-1.77 (9H, m, C*H*$_2$CH$_2$CHCH$_2$CH$_2$N, CH$_2$C*H*$_2$CHCH$_2$CH$_2$N, NCCH$_2$C*H*$_2$, NCC*H*(H)CH$_2$ and NCH$_2$C*H*$_2$), 1.89-2.00 (1H, m, NCC*H*(H)CH$_2$), 2.22-2.32 (2H, m, C*H*CH$_2$CH$_2$N and CHC*H*(H)CH$_2$N), 2.86 (1H, dt, *J* 10.4, 2.4, NC*H*(H)CH$_2$), 3.04-3.22 (4H, m, NC*H*(H)CH$_2$, CHC*H*(H)CH$_2$N and CHCH$_2$C*H*$_2$N), 3.83 (3H, s, C*H*$_3$O), 3.87 (3H, s, C*H*$_3$O), 6.50 (1H, s, Ar*H*), 6.70 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 21.3 (NCCH$_2$*C*H$_2$), 21.5 (CH*C*H$_2$CH$_2$N), 25.1 (*C*H$_2$CH$_2$CHCH$_2$CH$_2$N), 28.6 (NCH$_2$*C*H$_2$), 29.0 (CH$_2$*C*H$_2$CHCH$_2$CH$_2$N), 35.7 (NC*C*H$_2$CH$_2$), 40.4 (CHCH$_2$*C*H$_2$N), 43.6 (*C*HCH$_2$CH$_2$N), 46.2 (N*C*H$_2$CH$_2$), 55.7 (*C*H$_3$O), 56.0 (*C*H$_3$O), 64.5 (N*C*CH$_2$CH$_2$), 108.8 (Ar*C*H), 111.1 (Ar*C*H), 126.9 (Ar*C*), 136.0 (Ar*C*), 146.9 (Ar*C*-OCH$_3$), 147.2 (Ar*C*-OCH$_3$); MS (EI) *m/z* 287 [M^+, 24.3%]; (Found: M^+, 287.1885. $C_{18}H_{25}NO_2$ requires 287.1885).

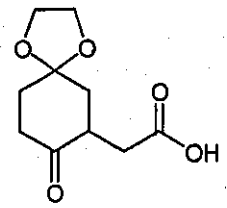
3.6.3. Total formal synthesis of (-)-3-demethoxyerythratidinone

Methyl-2-(-8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoate, **(312)**



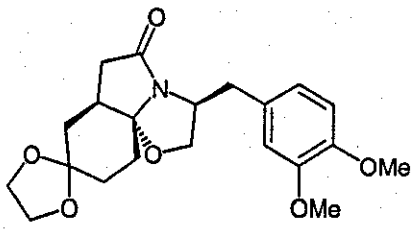
1,4-Cyclohexanedione monoethylene ketal, **(311)**, (2.00 g, 12.8 mmol) was dissolved in dry tetrahydrofuran (20 ml) and the solution cooled to -78 °C. KHMDS (28.16 ml of a 0.5 M solution in toluene, 14.1 mmol) was added and the mixture stirred at -78 °C for 1 hour. Methyl bromoacetate, **(302)**, (1.32 ml, 14.1 mmol) was added carefully to the mixture and left to stir for a further 1 hour. After this time, the mixture was allowed to cool to room temperature and stirred an additional 20 hours. The residue was quenched with HCl (2.0 M) and extracted into ether. The organic extracts were dried over anhydrous sodium sulfate and the resulting yellow oil was purified using a 2 : 1 mixture of ether and hexanes as eluent to give the product as a colourless oil (2.10 g, 72%). ν_{max}(Neat)/cm^{-1} 1734 (COOMe), 1718 (CO); δ_H(250 MHz, $CDCl_3$) 1.76 (1H, t, *J* 13.3, C*H*(H)C-acetal), 1.86-2.20 (4H, m, C*H*(H)C-acetal, CH_2C-acetal and CH_2CH(H)CO), 2.35 (1H, ddd, *J* 14.3, 4.9, 2.8, CH_2CH(H)CO), 2.59-2.75 (2H, m, CH_2COOMe), 3.08-3.22 (1H, m, CH_2CHCO), 3.62 (3H, s, CH_3O), 3.89-4.08 (4H, m, 2 x CH_2O); δ_C(100 MHz, $CDCl_3$) 33.7 (CH_2CH_2CO), 34.6 (*C*H_2COOMe), 37.8 (*C*H_2C-acetal), 40.3 (*C*H_2C-acetal), 43.1 (CH_2*C*HCO), 51.7 (*C*H_3O), 64.7 (*C*H_2O), 64.8 (*C*H_2O), 107.1 (*C*-acetal), 172.5 (*C*OOMe), 209.5 (*C*O); MS (EI) *m/z* 228 [M$^+$, 19.1%]; (Found: M$^+$, 228.0998. $C_{11}H_{16}O_5$ requires 228.0998).

2-(-8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoic acid, **(313)**



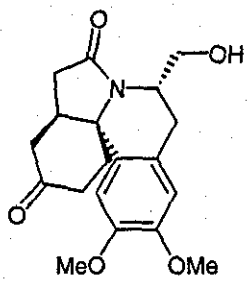
Methyl-2-(-8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoate, **(312)**, (2.10 g, 9.2 mmol) was dissolved in a mixture of tetrahydrofuran (70 ml) and water (30 ml). Lithium hydroxide (0.58 g, 9.2 mmol) was added and the mixture stirred at room temperature for 20 hours. The reaction mixture was concentrated, re-suspended in water (50 ml) and acidified to pH 3 using HCl (1.0 M). The aqueous layer was then extracted into ethyl acetate, dried over magnesium sulfate and evaporated to dryness to give a white solid (1.55 g, 79%). Further purification of the compound was not necessary. Mp 128-129 °C; (Found: C, 55.88; H, 6.62; O, 37.38. $C_{10}H_{14}O_5$ requires C, 55.07; H, 6.54; O, 37.21 %); ν_{max}(DCM)/cm^{-1} 3195 (OH), 1717 (CO) and 1700 (COOH); δ_H(250 MHz, $CDCl_3$) 1.83 (1H, t, *J* 13.3, C*H*(H)C-acetal), 1.90-2.29 (4H, m, C*H*(H)C-acetal, CH_2C-acetal and CH_2CH(H)CO), 2.35-2.45 (1H, m, CH_2CH(H)CO), 2.65-2.82 (2H, m, CH_2COOH), 3.12-3.22 (1H, m, CH_2CHCO), 3.97-4.09 (4H, m, 2 x CH_2O), 10.45 (1H, br. s, O*H*); δ_C(100 MHz, $CDCl_3$) 33.7 (CH_2CH_2CO), 34.5 (*C*H_2COOH), 37.8 (*C*H_2C-acetal), 40.2 (*C*H_2C-acetal), 42.9 (CH_2*C*HCO), 64.7 (*C*H_2O), 64.8 (*C*H_2O), 107.1 (*C*-acetal), 177.7 (*C*OOH), 209.5 (*C*O); MS (EI) *m/z* 214 [M^+, 4.3%]; (Found: M^+, 214.0837. $C_{10}H_{14}O_5$ requires 228.0998).

(3*S*,6*aS*,10*aR*)-3-(3,4-Di(methyloxy)phenyl-methyl)-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one, **(314)**



(2*S*)-2-Amino-3-(3,4-di(methyloxy)phenyl)propan-1-ol, **(189)**, (0.32 g, 1.5 mmol) and 2-(-8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoic acid **(313)**, (0.32 g, 1.5 mmol) were dissolved in toluene (25 ml) and refluxed under Dean-Stark conditions for 168 hours. After this time the solution was allowed to cool and the solvent was removed by rotary evaporation. The resulting yellow oil was purified by flash column chromatography using a 4 : 1 mixture of ethyl acetate and hexanes as eluent. Evaporation of the desired fraction afforded the target compound as a white solid (0.39 g, 67%), a portion of which was recrystallised from ethyl acetate and hexanes. Mp 98-99 °C; $[\alpha]_D$ = +56.3 (*c* = 0.42, $CHCl_3$); (Found: C, 64.78; H, 6.94; N, 3.59. $C_{21}H_{27}NO_6$ requires C, 64.70; H, 7.05; N, 3.35 %); ν_{max}(DCM)/cm^{-1} 1706 (lactam); δ_H(250 MHz, $CDCl_3$) 1.66-2.05 (6H, m, $NCCH_2CH_2$, $NCCH_2CH_2$ and $CHCH_2C$-acetal), 2.38-2.58 (2H, m, $CHCH_2CO$ and $CHCH(H)CO$), 2.71 (1H, dd, *J* 13.8, 9.1, $CH(H)Ar$), 2.89-3.06 (1H, m, $CH_2CHCH(H)CO$), 3.03 (1H, dd, *J* 13.8, 5.2, $CH(H)Ar$), 3.86 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 3.90-3.96 (5H, m, 2 x CH_2O and CH(H)O), 4.00-4.08 (1H, m, $CH(H)O$), 4.21-4.32 (1H, m, $NCHCH_2O$), 6.70-6.82 (3H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 30.5 ($NCCH_2CH_2$), 30.9 ($NCCH_2CH_2$), 33.8 ($CHCH_2CO$), 39.4 ($CHCH_2C$-acetal), 40.0 (CH_2Ar), 41.7 ($CHCH_2CO$), 55.3 ($NCHCH_2O$), 55.9 (CH_3O), 56.0 (CH_3O), 64.0 (CH_2O), 64.5 (CH_2O), 71.7 ($NCHCH_2O$), 99.6 ($NCCH_2CH_2$), 108.0 (*C*-acetal), 111.2 (Ar*C*H), 112.5 (Ar*C*H), 121.4 (Ar*C*H), 129.6 (Ar*C*), 147.9 (Ar*C*-OCH_3), 149.0 (Ar*C*-OCH_3), 176.4 (*C*O); MS (EI) *m/z* 389 [M^+, 63.5%]; (Found: M^+, 389.1842. $C_{21}H_{27}NO_6$ requires 389.1838).

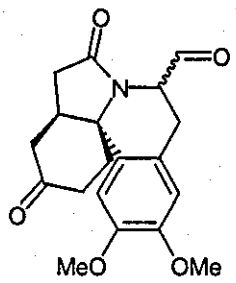
(4*S*,9*bS*,13*aS*)-4-(Hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13*a*-octahydro-2H-indolo[7*a*,1-*a*]isoquinolin-2,12-dione, **(316)**



(3*S*,6*aS*,10*aR*)-3-(3,4-Di(methyloxy)phenyl-methyl)-8-(1,3-dioxolane)perhydro[1,3] oxazolo[2,3-1]indol-5-one, **(314)**, (1.76 g, 4.5 mmol) was dissolved in dry dichloromethane (60 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 3 equivalents of titanium tetrachloride (1.49 ml, 13.6 mmol) were added drop wise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (60 ml), extracted with dichloromethane (3 x 60 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow oil (1.32 g, 75%) was purified by flash column chromatography using 5% methanol in dichloromethane as eluent yielding the target compound as a white solid (0.85 g, 64%), a portion of which was recrystallised from ethyl acetate. Mp 217-218 °C; $[\alpha]_D$ = -46.7 (c = 0.27, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3346 (OH), 1718 (CO) and 1664 (lactam); δ_H(400 MHz, $CDCl_3$) 2.21 (1H, dd, J 18.0, 6.8, CHC*H*(H)CO), 2.29-2.50 (4H, m, NCC*H*$_2$CH$_2$ and NCCH$_2$C*H*$_2$), 2.60 (1H, dd, J 16.3, 3.4, CHC*H*(H)CO), 2.62 (1H, dd, J 16.4, 4.0, ArC*H*(H)CHN), 2.73 (1H, dd, J 18.0, 10.8, CHC*H*(H)CO), 2.99 (1H, dd, J 16.3, 6.4, CHC*H*(H)CO), 3.05-3.15 (1H, m, C*H*CH$_2$CO), 3.27 (1H, dd, J 16.4, 12.0, ArC*H*(H)CHN), 3.55-3.70 (1H, m, NC*H*CH$_2$OH), 3.87 (3H, s, C*H*$_3$O), 3.88 (3H, s, C*H*$_3$O), 4.01-4.15 (2H, m, C*H*$_2$OH), 4.84 (1H, dd, J 9.6, 5.2, O*H*), 6.61 (1H, s, Ar*H*), 6.67 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 30.2 (ArCH$_2$CHN), 33.4 (NCCH$_2$CH$_2$), 35.2 (NCCH$_2$CH$_2$), 37.8 (CHCH$_2$CO), 38.2, (CHCH$_2$CO), 43.5 (CHCH$_2$CO), 53.9 (NCHCH$_2$OH), 56.0 (CH$_3$O), 56.4 (CH$_3$O), 62.1 (CH$_2$OH), 65.9 (NCCH$_2$CH$_2$), 107.2 (ArCH), 111.8

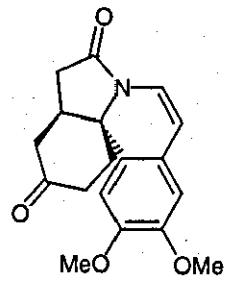
(ArCH), 126.0 (Ar*C*), 133.7 (Ar*C*), 148.3 (Ar*C*-OCH_3), 148.7 (Ar*C*-OCH_3), 173.9 (NCO), 209.6 (CO); MS (EI) *m/z* 345 [M^+, 13.9%]; (Found: M^+, 345.1576. $C_{19}H_{23}NO_5$ requires 345.1576).

(4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-4-carbaldehyde, **(317)**



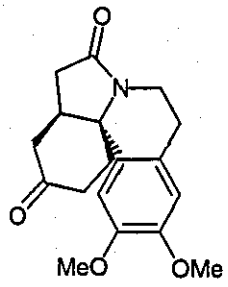
A solution of (4*S*,9b*S*,13a*S*)-4-(hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-2,12-dione, **(316)**, (0.60 g, 1.7 mmol) in dichloromethane (30 ml) was added to a solution of Dess-Martin periodinane (5.40 ml of a 15% wt solution in dichloromethane, 1.9 mmol) in dichloromethane (20 ml) with stirring. After 20 hours, excess dichloromethane was removed and the yellow oil loaded directly on to silica. Purification by flash column chromatography using 100% ethyl acetate as eluent yielded the aldehyde diastereoisomer as a pale yellow solid (0.56 g, 93%) a portion of which was recrystallised from dichloromethane and hexanes. Mp 169-170 °C; $[\alpha]_D$ = -7.7 (*c* = 0.26, $CHCl_3$); ν_{max}(Neat)/cm^{-1} 1734 (CHO), 1718 (CO) and 1685 (lactam); δ_H(400 MHz, $CDCl_3$) 2.21-2.50 (4H, m, NCC*H*$_2$CH$_2$ and NCCH$_2$C*H*$_2$), 2.27 (1H, dd, *J* 17.9, 7.4, CHC*H*(H)CO), 2.63 (1H, dd, *J* 16.0, 3.7, ArC*H*(H)CHN), 2.69 (1H, dd, *J* 17.9, 10.1, CHC*H*(H)CO), 2.97-3.27 (4H, m, ArC*H*(H)CHN, CHC*H*$_2$CO and C*H*CH$_2$CO), 3.87, (3H, s, C*H*$_3$O), 3.89 (3H, s, C*H*$_3$O), 4.00 (1H, m, NC*H*CHO), 6.65 (1H, s, Ar*H*), 6.70 (1H, s, Ar*H*), 9.83 (1H, s, C*H*O); δ_C(100 MHz, $CDCl_3$) 27.4 (ArCH$_2$CHN), 33.5 (NCCH$_2$CH$_2$), 35.4 (NCCH$_2$CH$_2$), 36.9 (CHCH$_2$CO), 38.9 (CHCH$_2$CO), 43.6 (CHCH$_2$CO), 56.0 (CH$_3$O), 56.4 (CH$_3$O), 57.8 (NCHCHO), 63.6 (NCCH$_2$CH$_2$), 107.3 (ArCH), 112.2 (ArCH), 124.3 (Ar*C*), 133.4 (Ar*C*), 148.5 (Ar*C*-OCH$_3$), 148.8 (Ar*C*-OCH$_3$), 174.7 (NCO), 196.4 (CHO), 209.4 (CO); MS (EI) *m/z* 343 [M^+, 15.5%]; (Found: M^+, 343.1424. $C_{19}H_{21}NO_5$ requires 343.1420).

(4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-2,12-dione, **(318)** (+ phosphorus by-product)



[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (50 mg, 0.1 mmol) was added to anhydrous xylene (15 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenylphosphino)propane (75 mg, 0.2 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-4-carbaldehyde, **(317)**, (0.50 g, 1.5 mmol) in anhydrous xylene (15 ml) was added and the mixture was heated at reflux for 240 hours. The solvent was removed by rotary evaporation giving a thick green oil. Purification by flash column chromatography using a 3 : 1 mixture of ethyl acetate and hexanes as eluent gave the product and co-eluting phosphorus by-product as a yellow oil (250 mg). ν_{max}(Neat)/cm^{-1} 1719 (CO), 1686 (lactam) and 722 (C=C); δ_H(250 MHz, $CDCl_3$) 1.82-1.97 (1H, m, NCC*H*(H)CH_2), 2.23-2.35 (4H, m, NCC*H*(H)CH_2, NCCH_2C*H*$_2$ and CHCH(H)CO), 2.75 (1H, dd, *J* 16.5, 3.6, CHC*H*(H)CO), 2.88 (1H, dd, *J* 18.1, 10.5, CHC*H*(H)CO), 3.00 (1H, dd, *J* 16.5, 6.0, CHC*H*(H)CO), 3.30-3.42 (1H, m, C*H*CH_2CO), 3.90 (3H, s, CH_3O), 3.89 (3H, s, CH_3O), 6.10 (1H, d, *J* 7.4, ArC*H*=CHN), 6.68 (1H, s, Ar*H*), 6.70 (1H, s, Ar*H*), 6.88 (1H, d, *J* 7.4, ArCH=C*H*N); δ_C(100 MHz, $CDCl_3$) 31.2 (NC*C*H$_2$CH$_2$), 34.6 (CH*C*H$_2$CO), 36.1 (*C*HCH$_2$CO), 37.1 (CH*C*H$_2$CO), 40.1 (NCCH$_2$*C*H$_2$) 56.1 (*C*H$_3$O), 56.4 (*C*H$_3$O), 62.3 (N*C*CH$_2$CH$_2$), 106.3 (Ar*C*H), 109.3 (Ar*C*H=CHN), 113.1 (Ar*C*H), 119.7 (ArCH=*C*HN), 123.5 (Ar*C*), 129.7 (Ar*C*), 148.7 (Ar*C*-OCH$_3$), 149.0 (Ar*C*-OCH$_3$), 170.8 (N*C*O), 209.9 (*C*O); MS (EI) *m/z* 313 [M$^+$, 13.3%]; (Found: M$^+$, 313.1309. $C_{18}H_{19}NO_4$ requires 313.1314).

(9b*S*,13a*S*)-7,8-Di(methyloxy)-1,4,5,10,11,12,13,13a,-octahydro-2*H*-indolo[7a,1-*a*] isoquinolin-2,12-dione, **(319)**[139]

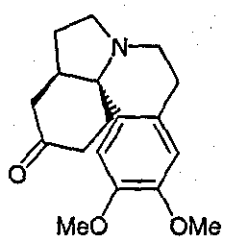


(4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-2,12-dione (+ phosphorous by-product), **(318)**, (0.26 g) was dissolved in absolute ethanol (20 ml) in a Schlenk tube. The reaction mixture was purged with nitrogen. A catalytic amount of 10% palladium-charcoal was added to the mixture, a balloon filled with hydrogen was fitted and the system purged with hydrogen, the mixture was then stirred for a further 20 hours. The mixture was filtered through Celite, the reaction vessel was washed with dichloromethane (3 x 20 ml) and poured onto the Celite. The organic extracts were collected, dried using anhydrous magnesium sulfate and evaporated off to give a yellow oil. Purification by flash column chromatography using 100% ethyl acetate as eluent gave the target compound as a yellow solid (0.22 g, 37% (from aldehyde, **(317)**). A portion of which was recrystallised from 100% ethyl acetate. Mp 160-161 °C, Lit: 163 °C; $[\alpha]_D$ = -33.2 (*c* = 0.31, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1716 (CO), 1684 (lactam); δ_H(250 MHz, $CDCl_3$) 2.14 (1H, dd, *J* 17.7, 7.1, CHC*H*(H)CO), 2.23-2.52 (4H, m, NCCH_2CH$_2$ and NCCH$_2$CH_2), 2.59-2.78 (2H, m, CHCH_2CO), 2.74 (1H, dd, *J* 17.7, 10.7, CHC*H*(H)CO), 2.92-3.16 (4H, m, ArCH_2CH$_2$N, ArCH$_2$C*H*(H)N and C*H*CH$_2$CO), 3.87 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.30-4.46 (1H, m, ArCH$_2$C*H*(H)N), 6.58 (1H, s, Ar*H*), 6.69 (1H, s, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.6 (Ar*C*H$_2$CH$_2$N), 33.5 (NC*C*H$_2$CH$_2$), 34.7 (CH*C*H$_2$CO), 35.2 (NCCH$_2$*C*H$_2$), 37.5 (*C*HCH$_2$CO), 37.8 (ArCH$_2$*C*H$_2$N), 43.3 (CH*C*H$_2$CO), 55.9 (*C*H$_3$O), 56.3 (*C*H$_3$O), 62.5 (N*C*H$_2$CH$_2$), 107.3 (Ar*C*H), 111.8 (Ar*C*H), 125.5 (Ar*C*), 134.4 (Ar*C*), 148.3 (Ar*C*-OCH$_3$), 148.4 (Ar*C*-OCH$_3$), 172.1 (N*C*O), 210.2 (*C*O); MS (EI) *m/z* 315 [M^+, 7.8%]; (Found: M^+, 315.1466. $C_{18}H_{21}NO_4$ requires 315.1471).

(9b*S*,13a*S*)-7,8-Di(methyloxy)-1,4,5,10,11,12,13,13a,-octahydro-2*H*-indolo[7a,1-*a*] isoquinolin-2,12-dione, **(319)**, prepared directly from **(317)**

[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (50 mg, 0.1 mmol) was added to anhydrous xylene (15 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenylphosphino)propane (75 mg, 0.2 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-4-carbaldehyde, **(317)**, (0.50 g, 1.5 mmol) in anhydrous xylene (15 ml) was added and the mixture was heated at reflux for 240 hours. The solvent was removed by rotary evaporation giving a thick green oil. Purification by flash column chromatography using a 3 : 1 mixture of ethyl acetate and hexanes as eluent gave the product and co-eluting phosphorous by-product as a yellow oil (130 mg, 22%) which had identical spectral properties to the compound prepared from **(318)**.

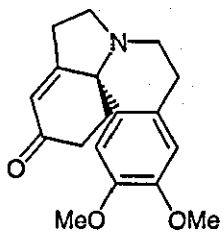
(9b*S*,13a*R*)-7,8-Di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*] isoquinolin-12-one, **(322)**[140]



(9b*S*,13a*S*)-7,8-Di(methyloxy)-1,4,5,10,11,12,13,13a,-octahydro-2*H*-indolo[7a,1-*a*]isoquin- -oline-2,12-dione, **(319)**, (0.22 g, 0.7 mmol) and *p*TsOH (5 mg) were dissolved in toluene (10 ml). Ethylene glycol (0.12 ml, 2.1 mmol) was added to the stirring mixture and the mixture was left at reflux for 20 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution (10 ml) and extracted in to ethyl acetate, dried over anhydrous magnesium sulfate and evaoporated to dryness giving the protected ketone as a yellow oil, **(320)**, (0.20 g, 80%), which was not purified. A solution of **(320)**, (0.20 g, 0.6 mmol) in dry toluene (10 ml) was stirred at 25 °C, under nitrogen, with sodium bis(methoxyethoxy)aluminium hydride (65^{+} wt % solution in toluene, 0.56 ml) for 16 hours. The reaction mixture was quenched by careful addition of saturated Rochelle salt (10 ml). The organic layer was separated and the salt solution extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent removed to yield a yellow oil **(321)**, which was taken up directly in to dichloromethane and cooled to –78 °C. Excess titanium tetrachloride was added to the stirring mixture and left to stir at –78 °C for 10 minutes. After this time, the mixture was allowed to warm to room temperature and stirred for a further 16 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted in to dichloromethane (3 x 10 ml) and dried over anhydrous magnesium sulfate to give a pale yellow oil (0.13 g, 62% (from **(319)**). $[\alpha]_D$ = +16.0 (*c* = 0.15, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1709 (CO), Lit: 1710 (C=O ketone); δ_H(400 MHz, $CDCl_3$) 1.35-1.45 (1H, m, CHC*H*(H)CH_2N), 1.85-1.91 (1H, m, CHC*H*(H)CH_2N), 2.02-2.14 (2H, m, NCC$H_2$$CH_2$), 2.24 (1H, dt, *J* 18.0, 3.4, NCCH2C*H*(H)), 2.31-2.38 (1H, m, ArC*H*(H)CH_2N), 2.51 (1H, dd, *J* 15.2, 2.8, CHC*H*(H)CO), 2.64-2.90 (5H, m, NCCH_2C*H*(H), C*H*$CH_2$$CH_2$N, CHC*H*(H)CO) and

$CHCH_2CH_2N$), 3.00-3.10 (1H, m, $ArCH(H)CH_2N$), 3.16-3.25 (2H, m, $ArCH_2CH_2N$), 3.86 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 6.54 (1H, s, ArH), 6.66 (1H, s, ArH); δ_C(100 MHz, $CDCl_3$) 21.6 ($ArCH_2CH_2N$), 31.0 ($CHCH_2CH_2N$), 33.8 ($NCCH_2CH_2$), 35.9 ($NCCH_2CH_2$), 41.4 ($ArCH_2CH_2N$), 43.9 ($CHCH_2CO$), 45.1 ($CHCH_2CH_2N$), 47.6 ($CHCH_2CH_2N$), 55.8 (CH_3O), 56.2 (CH_3O), 62.2 ($NCCH_2CH_2$), 109.1 (ArCH), 111.1 (ArCH), 125.7 (ArC), 128.3 (ArC), 147.4 (ArC-OCH_3), 147.9 (ArC-OCH_3), 213.6 (CO); MS (EI) *m/z* 301 [M^+, 4.8%]; (Found: M^+, 301.1684. $C_{18}H_{23}NO_3$ requires 301.1678).

(-)-3-Demethoxyerythratidinone, (**139**)[85]



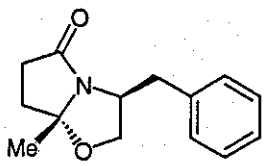
A solution of LDA (0.33 ml of a 2.0 M solution in heptane, 0.7 mmol) in anhydrous tetrahydrofuran (10 ml) was cooled to -78 °C and (9b*S*,13a*R*)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*] isoquinolin-12-one, (**322**) (0.20 g, 0.7 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added drop wise and stirred for 1 hour. Benzeneselenenyl chloride (0.19 g, 1.0 mmol) in tetrahydrofuran (2 ml) was added drop wise and the solution warmed to 0 °C and stirred for an additional 1 hour. Water (1.0 ml), acetic acid (0.1 ml) and hydrogen peroxide (0.36 g of a 35% solution) was added and the reaction mixture was maintained below 25 °C for approximately 30 minutes and then stirred for an additional 12 hours at room temperature. The solution was poured into saturated aqueous sodium bicarbonate solution (30 ml) and a 1 : 1 ether-hexane mixture (30 ml), and the organic layer was washed successively with water, HCl (0.1 M), water and saturated aqueous sodium chloride solution. Crude δ_H(250 MHz, $CDCl_3$) 6.05, 1H, C=C*H*; 6.54, 1H, Ar*H*; 6.67 1H, Ar*H*; Lit: δ_H(60 MHz, $CDCl_3$) 6.09, 1H, C=C*H*; 6.57, 1H, Ar*H*; 6.66, 1H, Ar*H*.

Chapter Four

Appendix

4.1. X-ray data

4.1.1. (3S,7a*R*)-7a-Methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, (175)



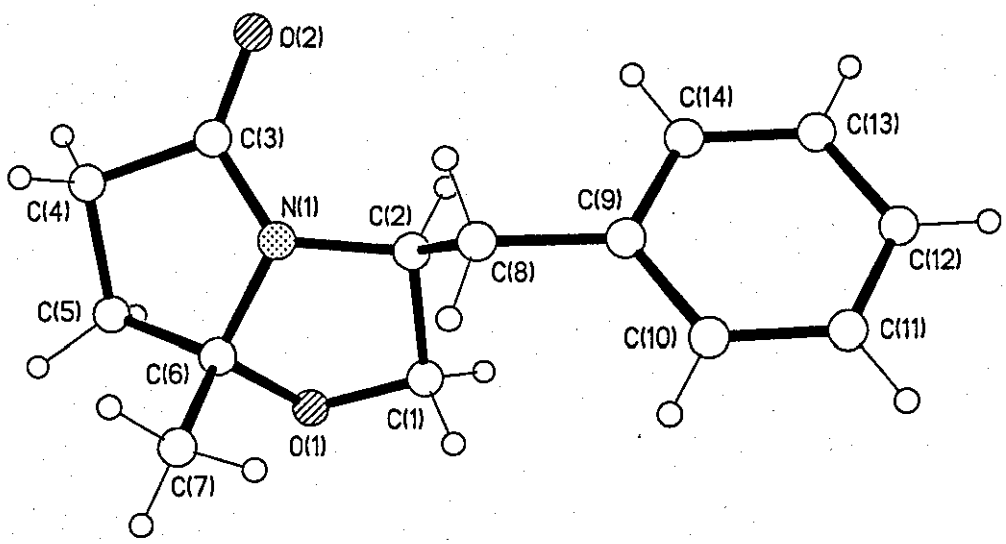


Table 1. Crystal data and structure refinement.

Identification code	**(175)**	
Chemical formula	$C_{14}H_{17}NO_2$	
Formula weight	231.29	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 7.1177(3) Å	α = 90°

	b = 10.5258(5) Å β = 90°
	c = 16.4294(8) Å γ = 90°
Cell volume	1230.88(10) $Å^3$
Z	4
Calculated density	1.248 g/cm^3
Absorption coefficient μ	0.083 mm^{-1}
F(000)	496
Crystal colour and size	colourless, 0.47 × 0.28 × 0.13 mm^3
Reflections for cell refinement	8005 (θ range 2.30 to 28.82°)
Data collection method	Bruker SMART 1000 CCD diffractometer
	ω-rotation with narrow frames
θ range for data collection	2.30 to 28.82°
Index ranges	h −9 to 9, k −13 to 13, l −21 to 21
Completeness to θ = 26.00°	100.0 %
Intensity decay	0%
Reflections collected	10642
Independent reflections	2899 (R_{int} = 0.0145)
Reflections with $F^2>2\sigma$	2789
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.962 and 0.989
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0471, 0.1729
Data / restraints / parameters	2899 / 0 / 156
Final R indices [$F^2>2\sigma$]	R1 = 0.0302, wR2 = 0.0789
R indices (all data)	R1 = 0.0314, wR2 = 0.0799
Goodness-of-fit on F^2	1.042
Absolute structure parameter	−0.3(8)
Extinction coefficient	0.012(2)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.207 and −0.183 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

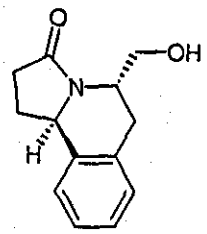
	x	y	z	U_{eq}
O(1)	0.06368(11)	0.72634(8)	0.06875(5)	0.02877(19)
C(1)	0.20437(17)	0.62838(11)	0.06787(7)	0.0304(2)
C(2)	0.38111(15)	0.68503(9)	0.10942(6)	0.0231(2)
N(1)	0.30200(12)	0.79944(8)	0.14655(5)	0.02269(19)
C(3)	0.38267(16)	0.91625(10)	0.14524(7)	0.0244(2)
O(2)	0.55044(11)	0.93704(8)	0.13716(6)	0.03091(19)
C(4)	0.22526(16)	1.01263(11)	0.15667(7)	0.0299(2)
C(5)	0.05059(16)	0.94244(11)	0.12510(7)	0.0293(2)
C(6)	0.09740(14)	0.80219(11)	0.13962(6)	0.0253(2)
C(7)	0.00097(18)	0.74609(14)	0.21399(8)	0.0376(3)
C(8)	0.47208(16)	0.59684(10)	0.17187(7)	0.0259(2)
C(9)	0.57357(15)	0.48502(10)	0.13383(6)	0.0243(2)
C(10)	0.51878(17)	0.36015(10)	0.14951(7)	0.0297(2)
C(11)	0.61649(19)	0.25802(11)	0.11610(7)	0.0337(3)
C(12)	0.76910(18)	0.27921(11)	0.06576(7)	0.0329(3)
C(13)	0.82536(17)	0.40320(12)	0.04943(7)	0.0320(3)
C(14)	0.72866(16)	0.50480(11)	0.08347(7)	0.0284(2)

Table 3. Bond lengths [Å] and angles [°].

O(1)–C(6)	1.4319(13)	O(1)–C(1)	1.4374(14)
C(1)–C(2)	1.5506(15)	C(2)–N(1)	1.4627(13)
C(2)–C(8)	1.5276(14)	N(1)–C(3)	1.3571(14)
N(1)–C(6)	1.4610(13)	C(3)–O(2)	1.2212(14)
C(3)–C(4)	1.5231(15)	C(4)–C(5)	1.5364(15)
C(5)–C(6)	1.5321(16)	C(6)–C(7)	1.5208(16)
C(8)–C(9)	1.5159(15)	C(9)–C(10)	1.3950(15)
C(9)–C(14)	1.3952(16)	C(10)–C(11)	1.3930(17)
C(11)–C(12)	1.3834(19)	C(12)–C(13)	1.3913(17)
C(13)–C(14)	1.3894(17)		

C(6)–O(1)–C(1)	106.94(8)	O(1)–C(1)–C(2)	106.55(9)
N(1)–C(2)–C(8)	112.54(9)	N(1)–C(2)–C(1)	100.83(9)
C(8)–C(2)–C(1)	113.95(9)	C(3)–N(1)–C(6)	113.74(9)
C(3)–N(1)–C(2)	125.19(9)	C(6)–N(1)–C(2)	111.56(9)
O(2)–C(3)–N(1)	125.30(10)	O(2)–C(3)–C(4)	127.83(10)
N(1)–C(3)–C(4)	106.87(9)	C(3)–C(4)–C(5)	103.49(9)
C(6)–C(5)–C(4)	103.58(9)	O(1)–C(6)–N(1)	102.68(9)
O(1)–C(6)–C(7)	111.17(9)	N(1)–C(6)–C(7)	112.31(9)
O(1)–C(6)–C(5)	111.97(9)	N(1)–C(6)–C(5)	104.36(8)
C(7)–C(6)–C(5)	113.64(10)	C(9)–C(8)–C(2)	113.38(9)
C(10)–C(9)–C(14)	118.12(10)	C(10)–C(9)–C(8)	121.48(10)
C(14)–C(9)–C(8)	120.38(10)	C(11)–C(10)–C(9)	120.99(11)
C(12)–C(11)–C(10)	120.21(11)	C(11)–C(12)–C(13)	119.51(11)
C(14)–C(13)–C(12)	120.12(11)	C(13)–C(14)–C(9)	121.05(10)

4.1.2. (5*S*,10bR)-5-(Hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinolin-3-one, **(217)**



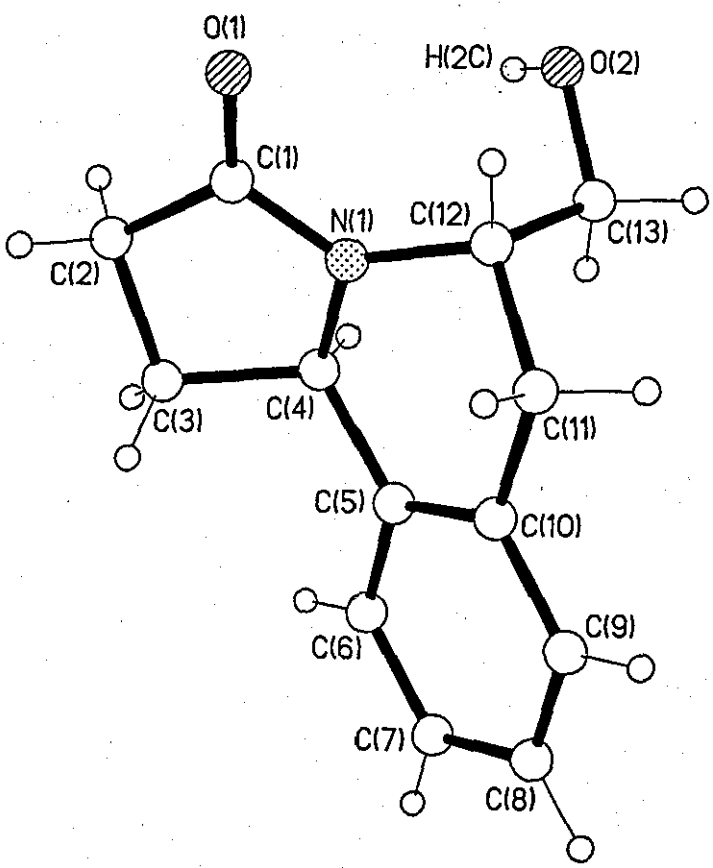


Table 1. Crystal data and structure refinement

Identification code	**(217)**
Chemical formula	$C_{13}H_{17}NO_3$
Formula weight	235.28
Temperature	150(2) K

Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 10.1671(8) Å	α = 90°
	b = 7.9584(6) Å	β = 91.810(2)°
	c = 15.1474(11) Å	γ = 90°
Cell volume	1225.02(16) $Å^3$	
Z	4	
Calculated density	1.276 g/cm^3	
Absorption coefficient μ	0.091 mm^{-1}	
F(000)	504	
Crystal colour and size	colourless, 0.77 × 0.26 × 0.18 mm^3	
Reflections for cell refinement	5653 (θ range 2.45 to 28.36°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.34 to 28.74°	
Index ranges	h −13 to 13, k −9 to 10, l −20 to 20	
Completeness to θ = 26.00°	99.8 %	
Intensity decay	0%	
Reflections collected	9196	
Independent reflections	5400 (R_{int} = 0.0147)	
Reflections with $F^2>2\sigma$	4972	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.934 and 0.984	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0529, 0.1597	
Data / restraints / parameters	5400 / 1 / 325	
Final R indices [$F^2>2\sigma$]	R1 = 0.0353, wR2 = 0.0897	
R indices (all data)	R1 = 0.0397, wR2 = 0.0931	
Goodness-of-fit on F^2	1.043	
Absolute structure parameter	0.1(7)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.232 and −0.191 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.20305(12)	0.72539(16)	0.55372(8)	0.0229(3)
C(1)	0.14596(14)	0.6432(2)	0.48513(10)	0.0242(3)
O(1)	0.14069(11)	0.48885(15)	0.47766(7)	0.0301(3)
C(2)	0.08967(16)	0.7723(2)	0.42098(10)	0.0308(4)
C(3)	0.16104(16)	0.9344(2)	0.44750(10)	0.0303(3)
C(4)	0.19824(15)	0.9092(2)	0.54649(10)	0.0238(3)
C(5)	0.32694(15)	0.9886(2)	0.57662(9)	0.0240(3)
C(6)	0.34408(17)	1.1624(2)	0.56564(11)	0.0305(3)
C(7)	0.46108(18)	1.2384(2)	0.59241(12)	0.0354(4)
C(8)	0.56270(18)	1.1439(2)	0.63064(12)	0.0350(4)
C(9)	0.54673(16)	0.9723(2)	0.64123(11)	0.0311(3)
C(10)	0.42886(15)	0.8933(2)	0.61562(10)	0.0250(3)
C(11)	0.41619(15)	0.7051(2)	0.62837(11)	0.0273(3)
C(12)	0.27323(15)	0.6456(2)	0.62796(9)	0.0237(3)
C(13)	0.20700(16)	0.6806(2)	0.71499(10)	0.0285(3)
O(2)	0.08041(12)	0.60636(16)	0.71681(8)	0.0335(3)
N(2)	0.19775(12)	1.19014(17)	0.94797(8)	0.0226(3)
C(14)	0.14898(14)	1.2755(2)	1.01615(10)	0.0248(3)
O(3)	0.14659(11)	1.43001(14)	1.02293(7)	0.0302(3)
C(15)	0.09705(17)	1.1489(2)	1.08157(10)	0.0311(4)
C(16)	0.16063(16)	0.9833(2)	1.05510(10)	0.0290(3)
C(17)	0.18927(15)	1.0066(2)	0.95609(10)	0.0237(3)
C(18)	0.31383(15)	0.9226(2)	0.92651(9)	0.0240(3)
C(19)	0.33248(17)	0.7515(2)	0.94405(11)	0.0297(3)
C(20)	0.44663(18)	0.6714(2)	0.91876(12)	0.0360(4)
C(21)	0.54282(17)	0.7609(2)	0.87593(12)	0.0361(4)
C(22)	0.52524(16)	0.9303(2)	0.85890(11)	0.0321(4)
C(23)	0.41007(15)	1.0129(2)	0.88289(10)	0.0252(3)
C(24)	0.39779(15)	1.1995(2)	0.86496(11)	0.0283(3)
C(25)	0.25667(14)	1.2659(2)	0.87074(9)	0.0240(3)

C(26)	0.17271(16)	1.2307(2)	0.78745(10)	0.0280(3)
O(4)	0.04555(11)	1.30236(16)	0.79295(8)	0.0302(3)
O(5)	−0.15495(13)	1.07022(18)	0.80893(9)	0.0379(3)
O(6)	−0.10407(14)	0.83307(19)	0.68382(9)	0.0434(3)

Table 3. Bond lengths [Å] and angles [°].

N(1)–C(1)	1.344(2)	N(1)–C(12)	1.4582(19)
N(1)–C(4)	1.468(2)	C(1)–O(1)	1.235(2)
C(1)–C(2)	1.514(2)	C(2)–C(3)	1.528(3)
C(3)–C(4)	1.548(2)	C(4)–C(5)	1.511(2)
C(5)–C(10)	1.400(2)	C(5)–C(6)	1.404(2)
C(6)–C(7)	1.384(3)	C(7)–C(8)	1.389(3)
C(8)–C(9)	1.385(3)	C(9)–C(10)	1.397(2)
C(10)–C(11)	1.516(2)	C(11)–C(12)	1.529(2)
C(12)–C(13)	1.525(2)	C(13)–O(2)	1.417(2)
N(2)–C(14)	1.344(2)	N(2)–C(25)	1.4613(19)
N(2)–C(17)	1.468(2)	C(14)–O(3)	1.234(2)
C(14)–C(15)	1.520(2)	C(15)–C(16)	1.527(3)
C(16)–C(17)	1.548(2)	C(17)–C(18)	1.513(2)
C(18)–C(23)	1.397(2)	C(18)–C(19)	1.399(2)
C(19)–C(20)	1.388(3)	C(20)–C(21)	1.387(3)
C(21)–C(22)	1.383(3)	C(22)–C(23)	1.401(2)
C(23)–C(24)	1.514(2)	C(24)–C(25)	1.534(2)
C(25)–C(26)	1.527(2)	C(26)–O(4)	1.418(2)

C(1)–N(1)–C(12)	124.97(13)	C(1)–N(1)–C(4)	114.50(12)
C(12)–N(1)–C(4)	120.40(12)	O(1)–C(1)–N(1)	124.85(14)
O(1)–C(1)–C(2)	127.00(15)	N(1)–C(1)–C(2)	108.15(14)
C(1)–C(2)–C(3)	103.74(12)	C(2)–C(3)–C(4)	104.16(13)
N(1)–C(4)–C(5)	111.59(13)	N(1)–C(4)–C(3)	102.01(13)
C(5)–C(4)–C(3)	114.92(12)	C(10)–C(5)–C(6)	119.39(15)
C(10)–C(5)–C(4)	121.54(14)	C(6)–C(5)–C(4)	119.06(14)

C(7)–C(6)–C(5)	120.29(16)	C(6)–C(7)–C(8)	120.46(16)
C(9)–C(8)–C(7)	119.56(16)	C(8)–C(9)–C(10)	120.94(16)
C(9)–C(10)–C(5)	119.35(15)	C(9)–C(10)–C(11)	118.99(14)
C(5)–C(10)–C(11)	121.63(14)	C(10)–C(11)–C(12)	112.97(13)
N(1)–C(12)–C(13)	111.61(13)	N(1)–C(12)–C(11)	108.07(12)
C(13)–C(12)–C(11)	112.69(13)	O(2)–C(13)–C(12)	111.52(13)
C(14)–N(2)–C(25)	125.26(13)	C(14)–N(2)–C(17)	114.47(12)
C(25)–N(2)–C(17)	120.27(12)	O(3)–C(14)–N(2)	125.18(14)
O(3)–C(14)–C(15)	126.74(14)	N(2)–C(14)–C(15)	108.07(14)
C(14)–C(15)–C(16)	104.02(13)	C(15)–C(16)–C(17)	104.19(13)
N(2)–C(17)–C(18)	111.30(12)	N(2)–C(17)–C(16)	102.34(12)
C(18)–C(17)–C(16)	114.76(13)	C(23)–C(18)–C(19)	119.84(15)
C(23)–C(18)–C(17)	121.21(14)	C(19)–C(18)–C(17)	118.95(14)
C(20)–C(19)–C(18)	120.25(16)	C(21)–C(20)–C(19)	120.09(17)
C(22)–C(21)–C(20)	119.91(16)	C(21)–C(22)–C(23)	120.86(17)
C(18)–C(23)–C(22)	119.04(15)	C(18)–C(23)–C(24)	122.30(14)
C(22)–C(23)–C(24)	118.58(15)	C(23)–C(24)–C(25)	113.55(13)
N(2)–C(25)–C(26)	110.68(12)	N(2)–C(25)–C(24)	108.14(12)
C(26)–C(25)–C(24)	112.90(13)	O(4)–C(26)–C(25)	111.38(13)

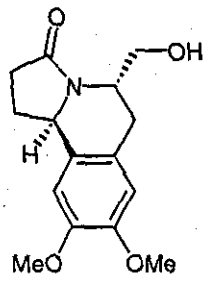
Table 4. Hydrogen bonds for [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2C)...O(6)	0.84(3)	1.81(3)	2.6389(18)	169(2)
O(4)–H(4A)...O(2')	0.82(2)	1.90(2)	2.7083(17)	172(2)
O(5)–H(5A)...O(3")	0.85(3)	1.94(3)	2.7795(17)	172(2)
O(5)–H(5B)...O(4)	0.86(3)	1.91(3)	2.7673(18)	169(2)
O(6)–H(6A)...O(1*)	0.90(3)	1.86(3)	2.7570(18)	173(2)
O(6)–H(6B)...O(5)	0.88(3)	1.87(3)	2.735(2)	171(3)

Symmetry operations for equivalent atoms

' x,y+1,z " –x,y–1/2,–z+2 * –x,y+1/2,–z+1

4.1.3. (5*S*,10b*R*)-5-Hydroxy-8,9-di(methyloxy)-1,2,3,5,6,10b-hexahydropyrrolo [2,1-*a*] isoquinoline-3-one, (**218**)



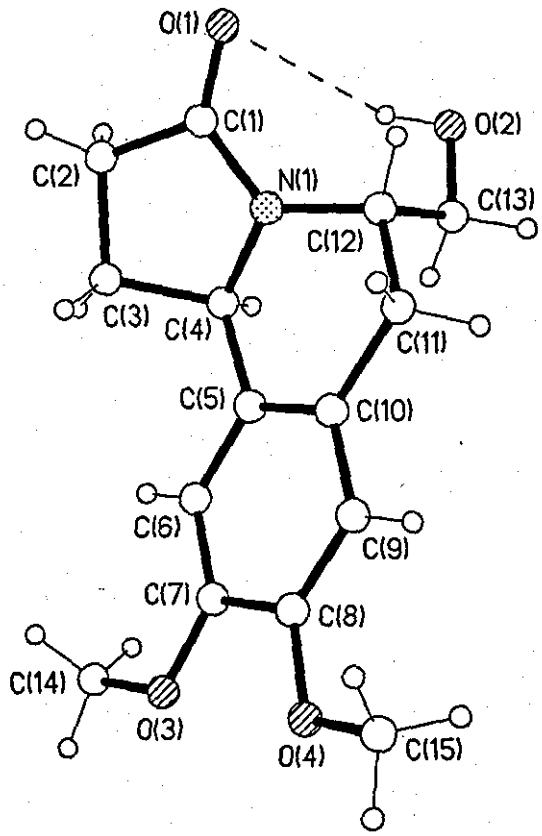


Table 1. Crystal data and structure refinement.

Identification code	**(218)**
Chemical formula	$C_{15}H_{19}NO_4$
Formula weight	277.31
Temperature	150(2) K

Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 5.3164(3) Å	α = 90°
	b = 11.9673(7) Å	β = 90°
	c = 20.8468(12) Å	γ = 90°
Cell volume	1326.34(13) $Å^3$	
Z	4	
Calculated density	1.389 g/cm^3	
Absorption coefficient μ	0.101 mm^{-1}	
F(000)	592	
Crystal colour and size	colourless, 0.38 × 0.09 × 0.06 mm^3	
Reflections for cell refinement	5324 (θ range 2.59 to 28.05°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω–rotation with narrow frames	
θ range for data collection	1.95 to 28.81°	
Index ranges	h –7 to 6, k –15 to 15, l –27 to 27	
Completeness to θ = 26.00°	100.0 %	
Intensity decay	0%	
Reflections collected	11448	
Independent reflections	3150 (R_{int} = 0.0210)	
Reflections with $F^2>2\sigma$	2853	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.963 and 0.994	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0467, 0.2395	
Data / restraints / parameters	3150 / 0 / 186	
Final R indices [$F^2>2\sigma$]	R1 = 0.0333, wR2 = 0.0798	
R indices (all data)	R1 = 0.0394, wR2 = 0.0835	
Goodness-of-fit on F^2	1.029	
Absolute structure parameter	–0.2(9)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.242 and –0.212 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.3312(2)	0.42863(9)	0.05317(5)	0.0178(2)
C(1)	0.2294(3)	0.32631(11)	0.06310(6)	0.0192(3)
O(1)	0.0402(2)	0.28999(8)	0.03584(5)	0.0235(2)
C(2)	0.3870(3)	0.26633(12)	0.11295(7)	0.0227(3)
C(3)	0.5483(3)	0.35929(11)	0.14234(7)	0.0262(3)
C(4)	0.5638(3)	0.44731(11)	0.08896(7)	0.0184(3)
C(5)	0.5782(3)	0.56652(11)	0.11248(6)	0.0176(3)
C(6)	0.7561(3)	0.59288(11)	0.16006(6)	0.0194(3)
C(7)	0.7725(3)	0.69944(12)	0.18525(6)	0.0195(3)
C(8)	0.6040(3)	0.78250(11)	0.16310(6)	0.0197(3)
C(9)	0.4345(3)	0.75675(11)	0.11496(6)	0.0193(3)
C(10)	0.4193(3)	0.64842(11)	0.08872(6)	0.0178(3)
C(11)	0.2220(3)	0.62489(11)	0.03801(6)	0.0194(3)
C(12)	0.2502(3)	0.51027(11)	0.00541(6)	0.0185(3)
C(13)	0.4335(3)	0.51352(11)	−0.05097(6)	0.0218(3)
O(2)	0.4292(3)	0.41521(9)	−0.08822(5)	0.0308(3)
O(3)	0.9384(2)	0.73175(8)	0.23174(5)	0.0249(2)
C(14)	1.1145(3)	0.64875(13)	0.25266(7)	0.0255(3)
O(4)	0.6237(2)	0.88443(8)	0.19230(5)	0.0248(2)
C(15)	0.4302(3)	0.96346(12)	0.17765(8)	0.0284(3)

Table 3. Bond lengths [Å] and angles [°].

N(1)–C(1)	1.3547(17)	N(1)–C(12)	1.4599(17)
N(1)–C(4)	1.4616(18)	C(1)–O(1)	1.2342(18)
C(1)–C(2)	1.516(2)	C(2)–C(3)	1.532(2)
C(3)–C(4)	1.5344(19)	C(4)–C(5)	1.5104(18)
C(5)–C(10)	1.3854(19)	C(5)–C(6)	1.4065(19)
C(6)–C(7)	1.3819(18)	C(7)–O(3)	1.3662(17)

C(7)–C(8)	1.416(2)	C(8)–O(4)	1.3673(16)
C(8)–C(9)	1.384(2)	C(9)–C(10)	1.4094(18)
C(10)–C(11)	1.5157(19)	C(11)–C(12)	1.5382(18)
C(12)–C(13)	1.527(2)	C(13)–O(2)	1.4099(17)
O(3)–C(14)	1.4327(18)	O(4)–C(15)	1.4305(18)

C(1)–N(1)–C(12)	126.25(12)	C(1)–N(1)–C(4)	113.47(11)
C(12)–N(1)–C(4)	119.69(11)	O(1)–C(1)–N(1)	124.99(13)
O(1)–C(1)–C(2)	126.83(12)	N(1)–C(1)–C(2)	108.19(12)
C(1)–C(2)–C(3)	103.86(11)	C(2)–C(3)–C(4)	103.80(11)
N(1)–C(4)–C(5)	110.67(11)	N(1)–C(4)–C(3)	102.69(11)
C(5)–C(4)–C(3)	114.57(11)	C(10)–C(5)–C(6)	120.23(12)
C(10)–C(5)–C(4)	121.42(12)	C(6)–C(5)–C(4)	118.34(12)
C(7)–C(6)–C(5)	121.16(12)	O(3)–C(7)–C(6)	124.85(13)
O(3)–C(7)–C(8)	116.19(12)	C(6)–C(7)–C(8)	118.95(13)
O(4)–C(8)–C(9)	124.86(13)	O(4)–C(8)–C(7)	115.64(12)
C(9)–C(8)–C(7)	119.50(12)	C(8)–C(9)–C(10)	121.57(13)
C(5)–C(10)–C(9)	118.50(13)	C(5)–C(10)–C(11)	122.68(11)
C(9)–C(10)–C(11)	118.76(12)	C(10)–C(11)–C(12)	113.97(11)
N(1)–C(12)–C(13)	110.72(11)	N(1)–C(12)–C(11)	108.92(10)
C(13)–C(12)–C(11)	112.31(11)	O(2)–C(13)–C(12)	113.11(12)
C(7)–O(3)–C(14)	116.20(11)	C(8)–O(4)–C(15)	116.08(11)

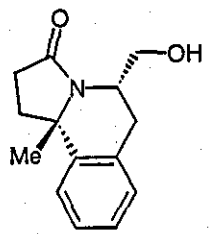
Table 4. Hydrogen bonds [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1')	0.91(2)	1.87(2)	2.7516(15)	163.7(19)

Symmetry operations for equivalent atoms

' x+1/2,–y+1/2,–z

4.1.4. (5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexahydropyrrolo [2,1-*a*] isoquinolin-3-one, **(219a)**



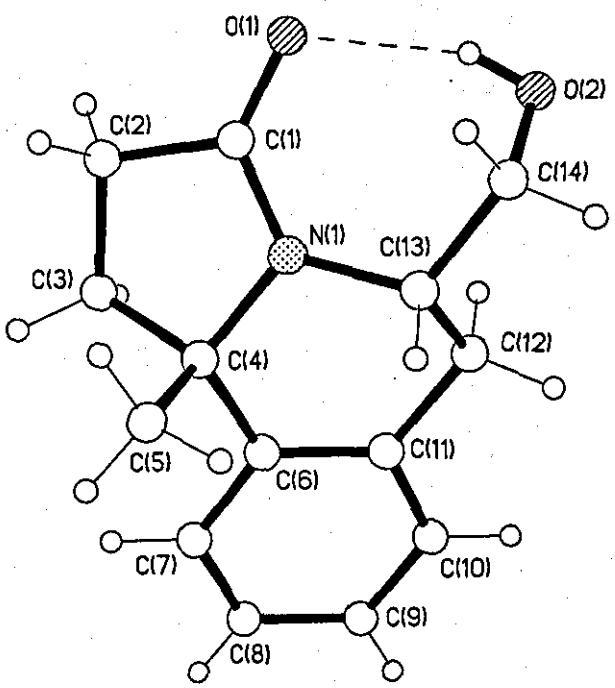


Table 1. Crystal data and structure refinement.

Identification code	**(219a)**
Chemical formula	$C_{14}H_{17}NO_2$
Formula weight	231.29
Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å

Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 7.7150(6) Å	$\alpha = 90°$
	b = 8.0282(6) Å	$\beta = 109.876(2)°$
	c = 10.0287(8) Å	$\gamma = 90°$
Cell volume	584.15(8) $Å^3$	
Z	2	
Calculated density	1.315 g/cm^3	
Absorption coefficient μ	0.088 mm^{-1}	
F(000)	248	
Crystal colour and size	colourless, $0.47 \times 0.35 \times 0.25$ mm^3	
Reflections for cell refinement	3799 (θ range 2.54 to 28.66°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.16 to 28.68°	
Index ranges	h −10 to 10, k −10 to 10, l −12 to 12	
Completeness to $\theta = 26.00°$	99.3 %	
Intensity decay	0%	
Reflections collected	5096	
Independent reflections	2514 ($R_{int} = 0.0124$)	
Reflections with $F^2>2\sigma$	2421	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.960 and 0.978	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0453, 0.0876	
Data / restraints / parameters	2514 / 1 / 159	
Final R indices [$F^2>2\sigma$]	R1 = 0.0298, wR2 = 0.0799	
R indices (all data)	R1 = 0.0310, wR2 = 0.0807	
Goodness-of-fit on F^2	1.059	
Absolute structure parameter	0.0(10)	
Extinction coefficient	0.002(4)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.264 and –0.173 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.24956(13)	0.70624(13)	0.27653(10)	0.0212(2)
C(1)	0.32797(17)	0.59837(18)	0.38252(13)	0.0262(3)
O(1)	0.27310(13)	0.56125(15)	0.48069(10)	0.0356(3)
C(2)	0.50022(18)	0.5279(2)	0.36292(15)	0.0324(3)
C(3)	0.47837(18)	0.57073(18)	0.20967(14)	0.0279(3)
C(4)	0.35341(16)	0.72670(17)	0.17765(12)	0.0217(2)
C(5)	0.4686(2)	0.88690(19)	0.21378(15)	0.0298(3)
C(6)	0.22147(16)	0.73251(17)	0.02563(12)	0.0215(2)
C(7)	0.29466(18)	0.72629(18)	–0.08430(14)	0.0271(3)
C(8)	0.1821(2)	0.7354(2)	–0.22495(14)	0.0315(3)
C(9)	–0.0064(2)	0.75352(18)	–0.25845(13)	0.0310(3)
C(10)	–0.08013(19)	0.75816(17)	–0.15049(13)	0.0270(3)
C(11)	0.03093(17)	0.74712(16)	–0.00781(13)	0.0222(2)
C(12)	–0.05501(17)	0.74967(19)	0.10718(13)	0.0253(3)
C(13)	0.08274(17)	0.80795(16)	0.24838(13)	0.0221(3)
C(14)	0.00148(19)	0.81283(18)	0.36711(14)	0.0257(3)
O(2)	–0.07879(14)	0.66110(14)	0.38893(11)	0.0300(2)

Table 3. Bond lengths [Å] and angles [°].

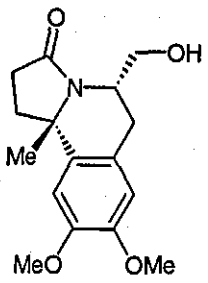
N(1)–C(1)	1.3448(16)	N(1)–C(13)	1.4683(16)
N(1)–C(4)	1.4807(14)	C(1)–O(1)	1.2332(16)
C(1)–C(2)	1.5173(19)	C(2)–C(3)	1.5273(19)
C(3)–C(4)	1.5460(19)	C(4)–C(6)	1.5190(16)
C(4)–C(5)	1.5351(18)	C(6)–C(11)	1.3971(17)
C(6)–C(7)	1.4000(16)	C(7)–C(8)	1.3843(19)
C(8)–C(9)	1.385(2)	C(9)–C(10)	1.3842(18)
C(10)–C(11)	1.3985(18)	C(11)–C(12)	1.5132(15)
C(12)–C(13)	1.5265(18)	C(13)–C(14)	1.5232(16)

C(14)–O(2)	1.4168(17)		
C(1)–N(1)–C(13)	129.75(10)	C(1)–N(1)–C(4)	113.60(10)
C(13)–N(1)–C(4)	116.62(9)	O(1)–C(1)–N(1)	127.04(12)
O(1)–C(1)–C(2)	124.53(12)	N(1)–C(1)–C(2)	108.43(11)
C(1)–C(2)–C(3)	104.16(11)	C(2)–C(3)–C(4)	103.83(10)
N(1)–C(4)–C(6)	110.18(9)	N(1)–C(4)–C(5)	109.67(10)
C(6)–C(4)–C(5)	110.36(11)	N(1)–C(4)–C(3)	102.25(10)
C(6)–C(4)–C(3)	113.02(10)	C(5)–C(4)–C(3)	111.06(10)
C(11)–C(6)–C(7)	119.16(11)	C(11)–C(6)–C(4)	122.33(10)
C(7)–C(6)–C(4)	118.50(10)	C(8)–C(7)–C(6)	121.29(12)
C(7)–C(8)–C(9)	119.74(12)	C(10)–C(9)–C(8)	119.35(12)
C(9)–C(10)–C(11)	121.80(12)	C(6)–C(11)–C(10)	118.65(11)
C(6)–C(11)–C(12)	121.07(10)	C(10)–C(11)–C(12)	120.27(11)
C(11)–C(12)–C(13)	111.34(10)	N(1)–C(13)–C(14)	115.52(10)
N(1)–C(13)–C(12)	107.23(10)	C(14)–C(13)–C(12)	113.04(10)
O(2)–C(14)–C(13)	114.60(11)		

Table 4. Hydrogen bonds [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1)	0.81(2)	1.95(2)	2.6759(14)	149(2)

4.1.5. (5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-8,9-di(methyloxy)-1,2,3,5,6,10b -hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, **(220a)**



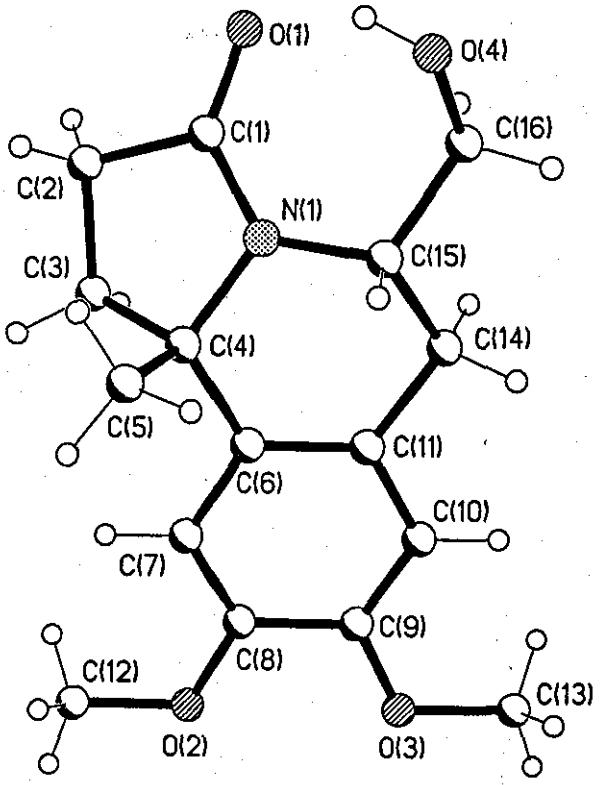


Table 1. Crystal data and structure refinement.

Identification code	**(220a)**
Chemical formula	$C_{16}H_{21}NO_4$
Formula weight	291.34
Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å

Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 10.5447(10) Å	$\alpha = 90°$
	b = 9.5411(9) Å	$\beta = 94.006(2)°$
	c = 14.7057(13) Å	$\gamma = 90°$
Cell volume	1475.9(2) $Å^3$	
Z	4	
Calculated density	1.311 g/cm^3	
Absorption coefficient μ	0.094 mm^{-1}	
F(000)	624	
Crystal colour and size	colourless, 0.43 × 0.18 × 0.04 mm^3	
Reflections for cell refinement	5288 (θ range 2.30 to 27.86°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω-scans with narrow frames	
θ range for data collection	1.94 to 28.80°	
Index ranges	h −13 to 14, k −12 to 12, l −19 to 19	
Completeness to θ = 26.00°	99.8 %	
Intensity decay	0%	
Reflections collected	12656	
Independent reflections	6544 (R_{int} = 0.0192)	
Reflections with $F^2>2\sigma$	5287	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.960 and 0.996	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0423, 0.0000	
Data / restraints / parameters	6544 / 1 / 388	
Final R indices [$F^2>2\sigma$]	R1 = 0.0351, wR2 = 0.0743	
R indices (all data)	R1 = 0.0497, wR2 = 0.0794	
Goodness-of-fit on F^2	0.974	
Absolute structure parameter	1.1(6)	
Extinction coefficient	0.0011(9)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.208 and −0.165 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	1.10357(12)	0.81380(14)	–0.19231(8)	0.0237(3)
C(1)	1.23214(15)	0.81087(19)	–0.18401(11)	0.0296(4)
O(1)	1.30374(11)	0.76863(14)	–0.24073(8)	0.0399(3)
C(2)	1.27620(17)	0.8708(2)	–0.09188(12)	0.0354(4)
C(3)	1.15636(16)	0.8736(2)	–0.04024(12)	0.0327(4)
C(4)	1.04873(16)	0.88934(17)	–0.11546(11)	0.0253(4)
C(5)	1.02603(18)	1.04400(18)	–0.14229(13)	0.0364(4)
C(6)	0.92626(14)	0.82136(17)	–0.09120(10)	0.0227(3)
C(7)	0.87632(16)	0.85670(17)	–0.00815(11)	0.0259(4)
C(8)	0.76451(15)	0.79781(17)	0.01728(10)	0.0256(4)
C(9)	0.69839(14)	0.70296(17)	–0.04226(11)	0.0255(3)
C(10)	0.74797(15)	0.66739(17)	–0.12340(11)	0.0261(4)
C(11)	0.86202(14)	0.72621(17)	–0.14866(10)	0.0241(3)
O(2)	0.71085(10)	0.82161(13)	0.09866(8)	0.0320(3)
C(12)	0.77801(19)	0.9125(2)	0.16186(13)	0.0417(5)
O(3)	0.58718(10)	0.65034(12)	–0.01263(8)	0.0315(3)
C(13)	0.52103(17)	0.5502(2)	–0.07139(13)	0.0399(5)
C(14)	0.91295(15)	0.68045(18)	–0.23733(11)	0.0291(4)
C(15)	1.01617(15)	0.77464(18)	–0.27083(10)	0.0264(4)
C(16)	1.07830(16)	0.70049(19)	–0.34774(11)	0.0328(4)
O(4)	1.15701(13)	0.78672(15)	–0.39726(8)	0.0452(4)
N(1A)	0.68567(12)	1.17030(14)	0.71573(9)	0.0257(3)
C(1A)	0.70321(16)	1.22292(19)	0.80066(11)	0.0313(4)
O(1A)	0.76696(13)	1.32653(14)	0.82468(9)	0.0451(3)
C(2A)	0.63186(18)	1.1335(2)	0.86392(12)	0.0367(4)
C(3A)	0.60380(17)	1.00000(19)	0.80996(11)	0.0310(4)
C(4A)	0.59698(15)	1.04877(17)	0.71008(11)	0.0252(4)
C(5A)	0.46281(16)	1.1001(2)	0.67883(13)	0.0371(4)

C(6A)	0.64236(15)	0.93845(17)	0.64513(11)	0.0241(4)
C(7A)	0.58117(15)	0.80713(18)	0.64050(11)	0.0273(4)
C(8A)	0.62016(15)	0.70322(18)	0.58387(11)	0.0271(4)
C(9A)	0.72323(15)	0.72736(19)	0.53043(11)	0.0268(4)
C(10A)	0.78253(15)	0.85649(18)	0.53434(11)	0.0268(4)
C(11A)	0.74289(15)	0.96265(18)	0.59135(11)	0.0246(4)
O(2A)	0.56652(11)	0.57209(13)	0.57407(9)	0.0364(3)
C(12A)	0.45984(18)	0.5435(2)	0.62413(14)	0.0460(5)
O(3A)	0.75835(11)	0.61761(13)	0.47796(8)	0.0335(3)
C(13A)	0.84889(18)	0.6466(2)	0.41351(14)	0.0455(5)
C(14A)	0.81219(16)	1.10091(18)	0.59310(11)	0.0275(4)
C(15A)	0.73637(15)	1.21979(19)	0.63030(11)	0.0277(4)
C(16A)	0.81478(17)	1.35409(19)	0.63819(13)	0.0362(4)
O(4A)	0.93020(11)	1.33751(15)	0.69388(10)	0.0434(3)

Table 3. Bond lengths [Å] and angles [°].

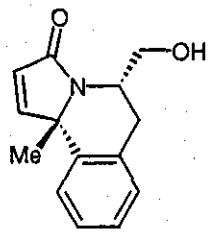
N(1)–C(1)	1.353(2)	N(1)–C(15)	1.4744(19)
N(1)–C(4)	1.491(2)	C(1)–O(1)	1.2313(19)
C(1)–C(2)	1.514(2)	C(2)–C(3)	1.519(2)
C(3)–C(4)	1.536(2)	C(4)–C(6)	1.510(2)
C(4)–C(5)	1.542(2)	C(6)–C(11)	1.385(2)
C(6)–C(7)	1.404(2)	C(7)–C(8)	1.381(2)
C(8)–O(2)	1.3779(19)	C(8)–C(9)	1.409(2)
C(9)–O(3)	1.3742(18)	C(9)–C(10)	1.378(2)
C(10)–C(11)	1.401(2)	C(11)–C(14)	1.509(2)
O(2)–C(12)	1.423(2)	O(3)–C(13)	1.436(2)
C(14)–C(15)	1.520(2)	C(15)–C(16)	1.521(2)
C(16)–O(4)	1.407(2)	N(1A)–C(1A)	1.347(2)
N(1A)–C(15A)	1.477(2)	N(1A)–C(4A)	1.488(2)
C(1A)–O(1A)	1.233(2)	C(1A)–C(2A)	1.503(3)
C(2A)–C(3A)	1.518(3)	C(3A)–C(4A)	1.538(2)
C(4A)–C(6A)	1.521(2)	C(4A)–C(5A)	1.537(2)
C(6A)–C(11A)	1.386(2)	C(6A)–C(7A)	1.409(2)

C(7A)–C(8A)	1.376(2)	C(8A)–O(2A)	1.376(2)
C(8A)–C(9A)	1.404(2)	C(9A)–O(3A)	1.3671(19)
C(9A)–C(10A)	1.381(2)	C(10A)–C(11A)	1.397(2)
C(11A)–C(14A)	1.507(2)	O(2A)–C(12A)	1.413(2)
O(3A)–C(13A)	1.419(2)	C(14A)–C(15A)	1.512(2)
C(15A)–C(16A)	1.525(2)	C(16A)–O(4A)	1.428(2)

C(1)–N(1)–C(15)	129.27(13)	C(1)–N(1)–C(4)	112.40(13)
C(15)–N(1)–C(4)	117.51(12)	O(1)–C(1)–N(1)	127.14(15)
O(1)–C(1)–C(2)	124.45(15)	N(1)–C(1)–C(2)	108.41(14)
C(1)–C(2)–C(3)	103.88(13)	C(2)–C(3)–C(4)	103.90(13)
N(1)–C(4)–C(6)	110.79(13)	N(1)–C(4)–C(3)	101.10(13)
C(6)–C(4)–C(3)	112.89(13)	N(1)–C(4)–C(5)	109.28(13)
C(6)–C(4)–C(5)	110.58(14)	C(3)–C(4)–C(5)	111.81(15)
C(11)–C(6)–C(7)	119.41(14)	C(11)–C(6)–C(4)	121.83(14)
C(7)–C(6)–C(4)	118.76(14)	C(8)–C(7)–C(6)	121.13(15)
O(2)–C(8)–C(7)	125.33(15)	O(2)–C(8)–C(9)	115.47(14)
C(7)–C(8)–C(9)	119.18(14)	O(3)–C(9)–C(10)	124.63(15)
O(3)–C(9)–C(8)	115.70(14)	C(10)–C(9)–C(8)	119.66(15)
C(9)–C(10)–C(11)	121.04(15)	C(6)–C(11)–C(10)	119.56(14)
C(6)–C(11)–C(14)	121.91(14)	C(10)–C(11)–C(14)	118.51(14)
C(8)–O(2)–C(12)	116.86(13)	C(9)–O(3)–C(13)	116.21(13)
C(11)–C(14)–C(15)	114.53(13)	N(1)–C(15)–C(14)	108.57(12)
N(1)–C(15)–C(16)	114.97(13)	C(14)–C(15)–C(16)	108.76(13)
O(4)–C(16)–C(15)	114.41(15)	C(1A)–N(1A)–C(15A)	129.44(14)
C(1A)–N(1A)–C(4A)	112.79(13)	C(15A)–N(1A)–C(4A)	117.71(13)
O(1A)–C(1A)–N(1A)	126.96(17)	O(1A)–C(1A)–C(2A)	124.37(16)
N(1A)–C(1A)–C(2A)	108.66(15)	C(1A)–C(2A)–C(3A)	103.92(14)
C(2A)–C(3A)–C(4A)	103.88(14)	N(1A)–C(4A)–C(6A)	110.50(13)
N(1A)–C(4A)–C(5A)	109.29(13)	C(6A)–C(4A)–C(5A)	110.86(14)
N(1A)–C(4A)–C(3A)	101.25(12)	C(6A)–C(4A)–C(3A)	113.25(13)
C(5A)–C(4A)–C(3A)	111.26(14)	C(11A)–C(6A)–C(7A)	119.13(15)
C(11A)–C(6A)–C(4A)	122.00(14)	C(7A)–C(6A)–C(4A)	118.87(14)
C(8A)–C(7A)–C(6A)	120.99(15)	C(7A)–C(8A)–O(2A)	125.47(15)

C(7A)–C(8A)–C(9A)	119.75(15)	O(2A)–C(8A)–C(9A)	114.77(14)
O(3A)–C(9A)–C(10A)	124.55(14)	O(3A)–C(9A)–C(8A)	116.17(15)
C(10A)–C(9A)–C(8A)	119.28(15)	C(9A)–C(10A)–C(11A)	121.20(15)
C(6A)–C(11A)–C(10A)	119.64(15)	C(6A)–C(11A)–C(14A)	121.70(15)
C(10A)–C(11A)–C(14A)	118.66(14)	C(8A)–O(2A)–C(12A)	117.18(14)
C(9A)–O(3A)–C(13A)	116.68(14)	C(11A)–C(14A)–C(15A)	113.25(13)
N(1A)–C(15A)–C(14A)	107.46(14)	N(1A)–C(15A)–C(16A)	115.50(14)
C(14A)–C(15A)–C(16A)	111.12(14)	O(4A)–C(16A)–C(15A)	112.74(15)

4.1.6. (5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-3,5,6,10b-tetrahydropyrrolo [2,1-*a*]isoquinolin-3-one, (**243a**)



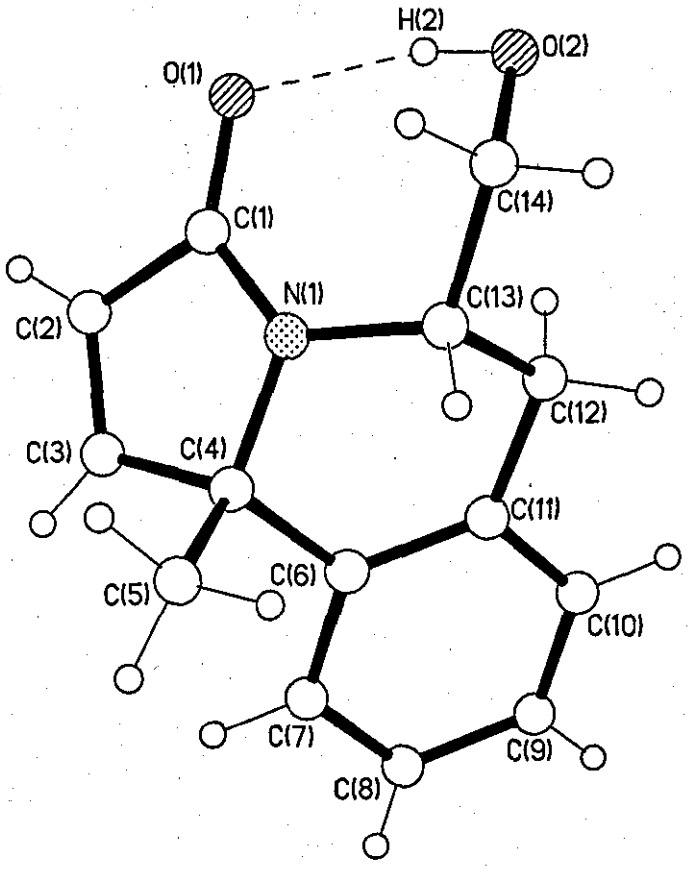


Table 1. Crystal data and structure refinement.

Identification code	**(243a)**
Chemical formula	$C_{14}H_{15}NO_2$
Formula weight	229.27
Temperature	150(2) K

Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 7.0090(6) Å	α = 90°
	b = 8.3217(7) Å	β = 90°
	c = 20.6004(17) Å	γ = 90°
Cell volume	1201.56(18) $Å^3$	
Z	4	
Calculated density	1.267 g/cm^3	
Absorption coefficient μ	0.085 mm^{-1}	
F(000)	488	
Crystal colour and size	colourless, 1.03 × 0.88 × 0.54 mm^3	
Reflections for cell refinement	7897 (θ range 2.64 to 28.80°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.98 to 28.84°	
Index ranges	h −9 to 9, k −11 to 10, l −26 to 27	
Completeness to θ = 26.00°	99.9 %	
Intensity decay	0%	
Reflections collected	10589	
Independent reflections	2913 (R_{int} = 0.0134)	
Reflections with $F^2>2\sigma$	2775	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.918 and 0.956	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0501, 0.1381	
Data / restraints / parameters	2913 / 0 / 158	
Final R indices [$F^2>2\sigma$]	R1 = 0.0297, wR2 = 0.0796	
R indices (all data)	R1 = 0.0317, wR2 = 0.0817	
Goodness-of-fit on F^2	1.052	
Absolute structure parameter	0.4(9)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.202 and −0.164 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.39092(12)	0.61267(10)	0.91799(4)	0.02242(18)
C(1)	0.20103(14)	0.63433(13)	0.90679(5)	0.0241(2)
O(1)	0.11226(11)	0.76265(10)	0.90852(4)	0.03199(19)
C(2)	0.12061(16)	0.47366(13)	0.89266(5)	0.0273(2)
C(3)	0.26045(15)	0.36646(13)	0.89154(5)	0.0272(2)
C(4)	0.44884(14)	0.44498(12)	0.90688(5)	0.0239(2)
C(5)	0.53625(17)	0.37144(13)	0.96875(6)	0.0309(2)
C(6)	0.58636(14)	0.43689(13)	0.84915(5)	0.0255(2)
C(7)	0.63319(16)	0.28555(15)	0.82380(6)	0.0331(2)
C(8)	0.75689(17)	0.27320(18)	0.77134(7)	0.0394(3)
C(9)	0.83209(17)	0.41096(18)	0.74351(6)	0.0396(3)
C(10)	0.78556(17)	0.56040(16)	0.76834(6)	0.0339(3)
C(11)	0.66413(14)	0.57601(14)	0.82206(5)	0.0266(2)
C(12)	0.62592(17)	0.74156(13)	0.84948(5)	0.0286(2)
C(13)	0.54511(15)	0.73222(12)	0.91809(5)	0.0252(2)
C(14)	0.49115(17)	0.89547(13)	0.94621(6)	0.0310(2)
O(2)	0.37569(13)	0.99157(10)	0.90557(4)	0.0359(2)

Table 3. Bond lengths [Å] and angles [°].

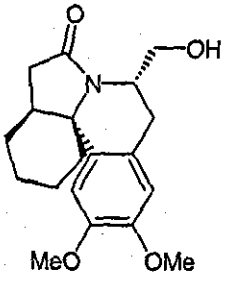
N(1)–C(1)	1.3628(13)	N(1)–C(13)	1.4689(13)
N(1)–C(4)	1.4712(12)	C(1)–O(1)	1.2364(14)
C(1)–C(2)	1.4799(15)	C(2)–C(3)	1.3255(15)
C(3)–C(4)	1.5068(14)	C(4)–C(6)	1.5324(14)
C(4)–C(5)	1.5408(14)	C(6)–C(11)	1.3960(15)
C(6)–C(7)	1.4024(15)	C(7)–C(8)	1.3892(18)
C(8)–C(9)	1.386(2)	C(9)–C(10)	1.3837(18)
C(10)–C(11)	1.4020(16)	C(11)–C(12)	1.5129(16)
C(12)–C(13)	1.5246(15)	C(13)–C(14)	1.5244(15)
C(14)–O(2)	1.4126(15)		

C(1)–N(1)–C(13)	128.99(9)	C(1)–N(1)–C(4)	111.63(9)
C(13)–N(1)–C(4)	116.08(8)	O(1)–C(1)–N(1)	126.93(10)
O(1)–C(1)–C(2)	126.46(10)	N(1)–C(1)–C(2)	106.61(9)
C(3)–C(2)–C(1)	109.26(9)	C(2)–C(3)–C(4)	110.64(10)
N(1)–C(4)–C(3)	101.66(8)	N(1)–C(4)–C(6)	109.63(8)
C(3)–C(4)–C(6)	111.67(9)	N(1)–C(4)–C(5)	110.96(9)
C(3)–C(4)–C(5)	110.47(9)	C(6)–C(4)–C(5)	111.99(9)
C(11)–C(6)–C(7)	120.30(10)	C(11)–C(6)–C(4)	121.29(9)
C(7)–C(6)–C(4)	118.41(10)	C(8)–C(7)–C(6)	120.14(12)
C(9)–C(8)–C(7)	119.86(12)	C(10)–C(9)–C(8)	120.06(11)
C(9)–C(10)–C(11)	121.20(12)	C(6)–C(11)–C(10)	118.41(11)
C(6)–C(11)–C(12)	122.47(9)	C(10)–C(11)–C(12)	119.11(10)
C(11)–C(12)–C(13)	111.44(9)	N(1)–C(13)–C(14)	114.93(9)
N(1)–C(13)–C(12)	107.85(8)	C(14)–C(13)–C(12)	113.51(9)
O(2)–C(14)–C(13)	114.93(9)		

Table 4. Hydrogen bonds [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1)	0.88(2)	1.81(2)	2.6536(13)	159.9(17)

4.1.7. (4*S*,9b*S*,13a*S*)-4-(Hydroxymethyl)-7,8-di(methyloxy)-1,4,5,10,11,12,13,13a-octahydro-2*H*-indolo[7a,1-*a*]isoquinolin-2-one, **(295)**



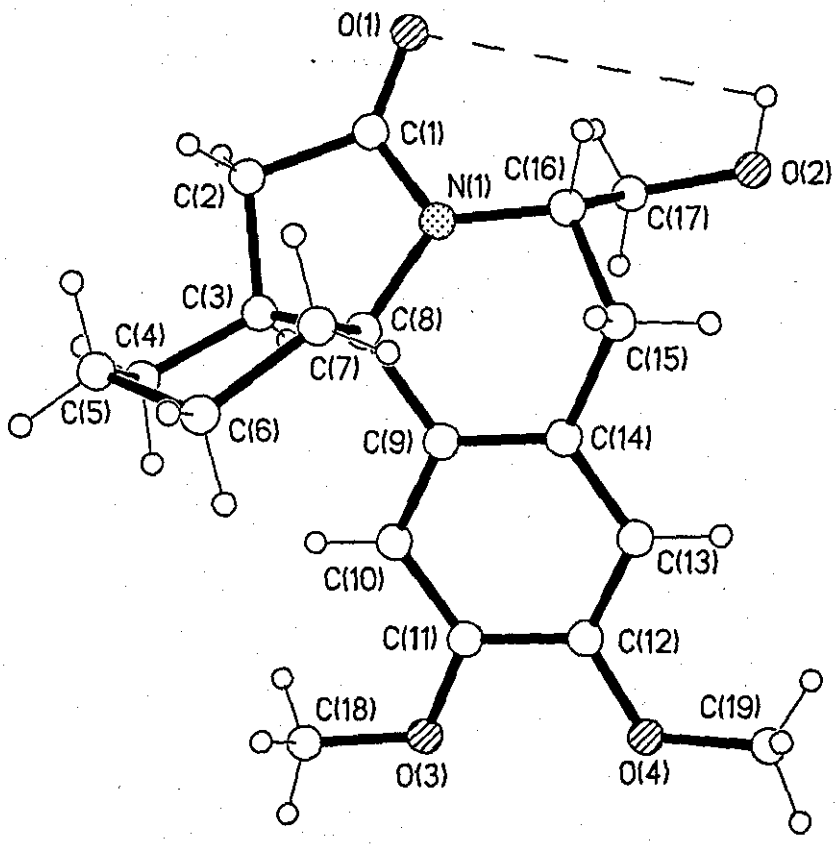


Table 1. Crystal data and structure refinement.

Identification code	**(295)**
Chemical formula	$C_{19}H_{25}NO_4$
Formula weight	331.40
Temperature	150(2) K

Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 9.4058(4) Å	α = 90°
	b = 10.0200(4) Å	β = 90°
	c = 17.9014(7) Å	γ = 90°
Cell volume	1687.14(12) $Å^3$	
Z	4	
Calculated density	1.305 g/cm^3	
Absorption coefficient μ	0.091 mm^{-1}	
F(000)	712	
Crystal colour and size	Colourless, 0.54 × 0.26 × 0.08 mm^3	
Reflections for cell refinement	11206 (θ range 2.28 to 29.06°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.28 to 29.06°	
Index ranges	h −12 to 12, k −13 to 13, l −23 to 24	
Completeness to θ = 26.00°	99.9 %	
Intensity decay	0%	
Reflections collected	15062	
Independent reflections	4095 (R_{int} = 0.0143)	
Reflections with $F^2>2\sigma$	3902	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.953 and 0.993	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0567, 0.2203	
Data / restraints / parameters	4095 / 0 / 220	
Final R indices [$F^2>2\sigma$]	R1 = 0.0310, wR2 = 0.0845	
R indices (all data)	R1 = 0.0332, wR2 = 0.0869	
Goodness-of-fit on F^2	1.039	
Absolute structure parameter	−0.4(7)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.266 and −0.154 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$). U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.11817(10)	0.89531(10)	0.87675(5)	0.02132(19)
C(1)	0.19178(13)	0.84131(12)	0.93384(6)	0.0238(2)
O(1)	0.13692(10)	0.79420(10)	0.99068(5)	0.0312(2)
C(2)	0.34856(12)	0.85095(12)	0.91636(6)	0.0250(2)
O(2)	–0.24927(9)	0.76373(10)	0.87438(5)	0.0305(2)
O(3)	0.22443(10)	0.88413(10)	0.54453(5)	0.0322(2)
C(3)	0.35198(12)	0.88079(11)	0.83199(6)	0.0220(2)
C(4)	0.48830(12)	0.95029(13)	0.80584(7)	0.0256(2)
O(4)	–0.05039(10)	0.90961(11)	0.53510(5)	0.0342(2)
C(5)	0.49557(13)	1.09673(13)	0.82829(7)	0.0285(2)
C(6)	0.36208(13)	1.17011(12)	0.80233(7)	0.0260(2)
C(7)	0.23157(12)	1.10880(12)	0.83974(6)	0.0223(2)
C(8)	0.21140(11)	0.95918(11)	0.81986(6)	0.0191(2)
C(9)	0.14162(12)	0.94263(11)	0.74398(6)	0.0205(2)
C(10)	0.21979(12)	0.91589(12)	0.67948(6)	0.0228(2)
C(11)	0.15361(13)	0.90628(11)	0.61037(6)	0.0251(2)
C(12)	0.00541(14)	0.92065(12)	0.60554(6)	0.0259(2)
C(13)	–0.07239(12)	0.94569(12)	0.67002(7)	0.0249(2)
C(14)	–0.00514(12)	0.95842(11)	0.73958(6)	0.0223(2)
C(15)	–0.08763(12)	0.98920(12)	0.80996(6)	0.0245(2)
C(16)	–0.03756(11)	0.90172(12)	0.87554(6)	0.0217(2)
C(17)	–0.09887(12)	0.76057(12)	0.86921(6)	0.0244(2)
C(18)	0.37656(14)	0.88808(15)	0.54798(7)	0.0330(3)
C(19)	–0.19814(15)	0.93764(16)	0.52653(8)	0.0385(3)

Table 3. Bond lengths [Å] and angles [°].

N(1)–C(1)	1.3478(14)	N(1)–C(16)	1.4663(13)
N(1)–C(8)	1.4885(14)	C(1)–O(1)	1.2346(15)

C(1)–C(2)	1.5105(16)	C(2)–C(3)	1.5399(15)
O(2)–C(17)	1.4180(14)	O(3)–C(11)	1.3719(14)
O(3)–C(18)	1.4328(16)	C(3)–C(4)	1.5324(16)
C(3)–C(8)	1.5532(14)	C(4)–C(5)	1.5229(18)
O(4)–C(12)	1.3704(14)	O(4)–C(19)	1.4261(16)
C(5)–C(6)	1.5274(17)	C(6)–C(7)	1.5273(16)
C(7)–C(8)	1.5524(16)	C(8)–C(9)	1.5178(14)
C(9)–C(14)	1.3917(16)	C(9)–C(10)	1.3948(15)
C(10)–C(11)	1.3883(15)	C(11)–C(12)	1.4040(17)
C(12)–C(13)	1.3895(17)	C(13)–C(14)	1.4026(16)
C(14)–C(15)	1.5114(16)	C(15)–C(16)	1.5390(15)
C(16)–C(17)	1.5316(16)		

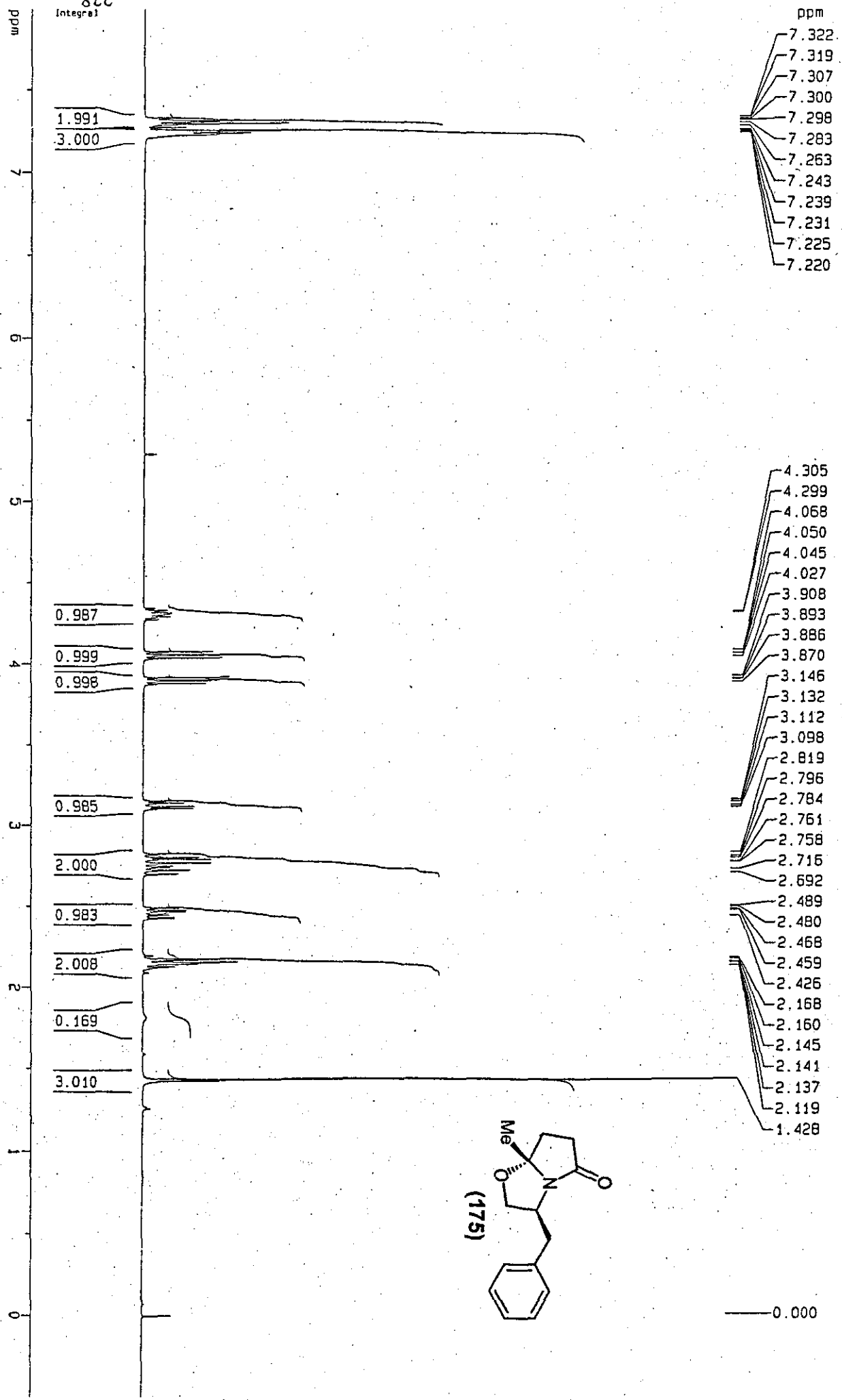
C(1)–N(1)–C(16)	122.81(9)	C(1)–N(1)–C(8)	112.88(9)
C(16)–N(1)–C(8)	124.03(8)	O(1)–C(1)–N(1)	124.31(11)
O(1)–C(1)–C(2)	127.10(10)	N(1)–C(1)–C(2)	108.58(10)
C(1)–C(2)–C(3)	103.65(9)	C(11)–O(3)–C(18)	116.32(9)
C(4)–C(3)–C(2)	113.92(9)	C(4)–C(3)–C(8)	116.09(9)
C(2)–C(3)–C(8)	102.56(9)	C(5)–C(4)–C(3)	113.25(10)
C(12)–O(4)–C(19)	117.15(11)	C(4)–C(5)–C(6)	110.28(10)
C(7)–C(6)–C(5)	109.49(10)	C(6)–C(7)–C(8)	112.72(9)
N(1)–C(8)–C(9)	108.09(9)	N(1)–C(8)–C(7)	109.29(9)
C(9)–C(8)–C(7)	111.32(9)	N(1)–C(8)–C(3)	100.86(8)
C(9)–C(8)–C(3)	115.98(9)	C(7)–C(8)–C(3)	110.63(9)
C(14)–C(9)–C(10)	119.86(10)	C(14)–C(9)–C(8)	117.85(10)
C(10)–C(9)–C(8)	122.27(10)	C(11)–C(10)–C(9)	120.97(10)
O(3)–C(11)–C(10)	124.00(11)	O(3)–C(11)–C(12)	116.48(10)
C(10)–C(11)–C(12)	119.53(10)	O(4)–C(12)–C(13)	125.26(11)
O(4)–C(12)–C(11)	115.38(11)	C(13)–C(12)–C(11)	119.36(10)
C(12)–C(13)–C(14)	121.09(11)	C(9)–C(14)–C(13)	119.16(11)
C(9)–C(14)–C(15)	119.03(10)	C(13)–C(14)–C(15)	121.81(10)
C(14)–C(15)–C(16)	111.26(9)	N(1)–C(16)–C(17)	109.68(9)
N(1)–C(16)–C(15)	109.99(9)	C(17)–C(16)–C(15)	110.75(9)
O(2)–C(17)–C(16)	110.50(10)		

Table 4. Hydrogen bonds [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1')	0.84	1.87	2.7052(12)	169.6

Symmetry operations for equivalent atoms

' x–1/2,–y+3/2,–z+2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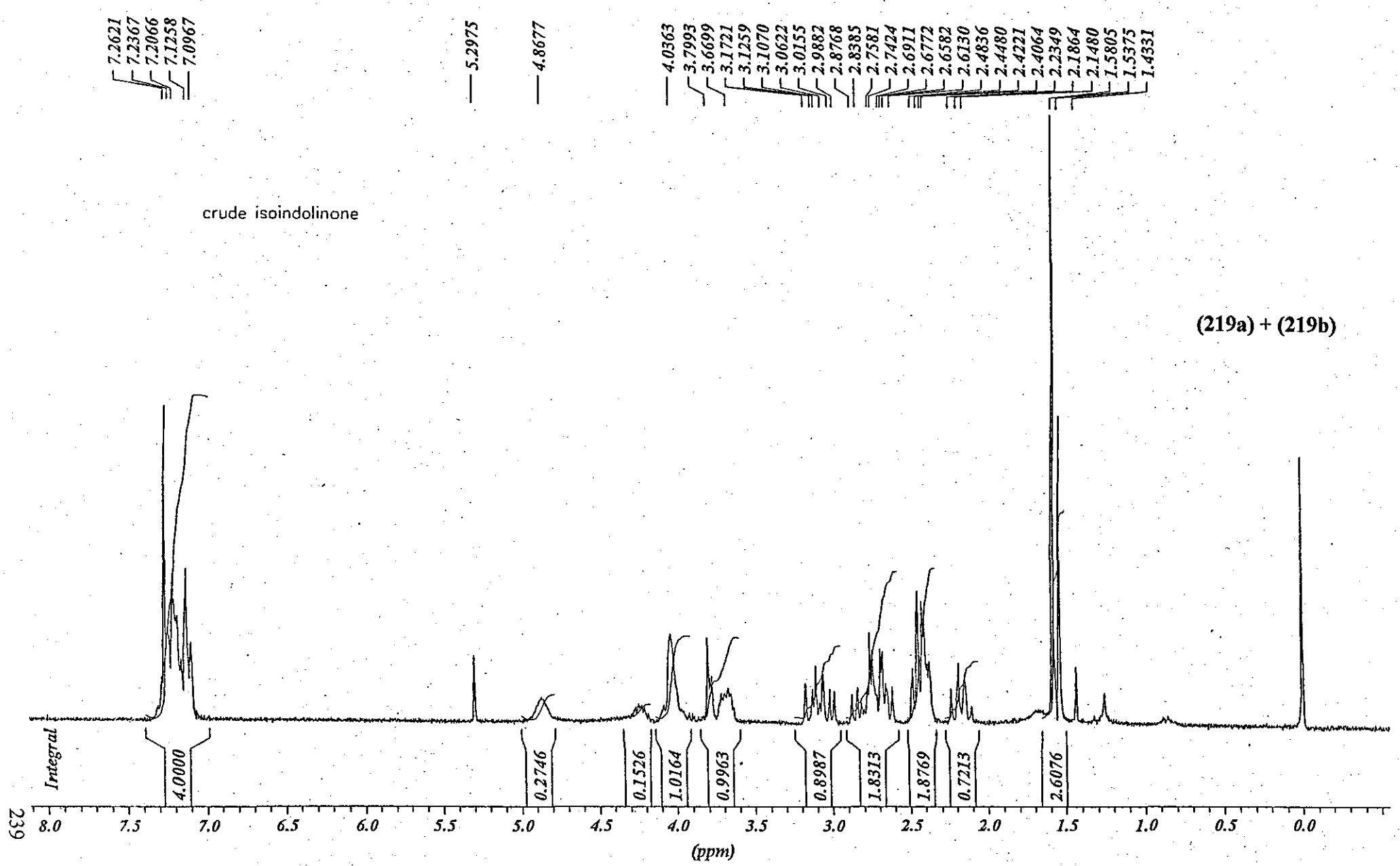
(17S)

Slj21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5.5
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3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

ppm
Integral
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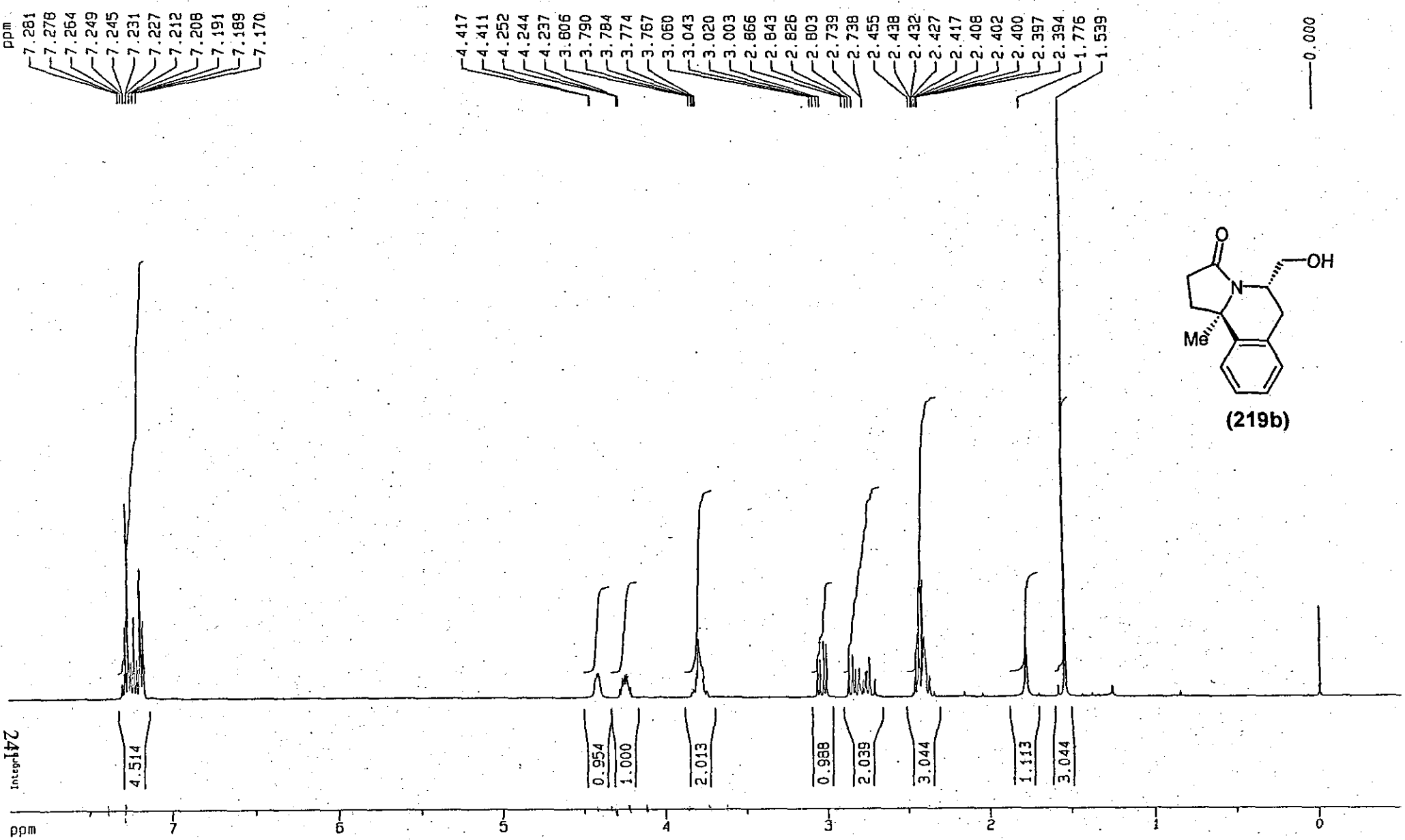
slj001-15-30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References

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