Novel Approaches to the Asymmetric Synthesis of Indole Alkaloids

by

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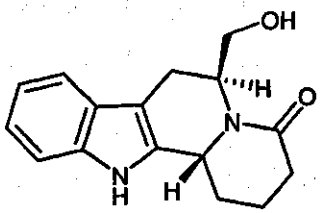
Abstract

The tetracyclic system **(219)** shares the same heterocyclic skeleton as a plethora of highly bioactive indole alkaloids, exemplified by ajmalicine **(161)** and deplancheine **(204)**.



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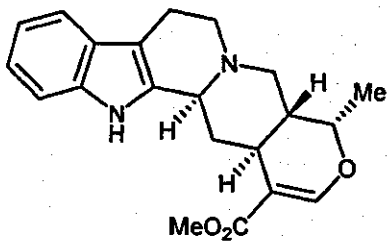

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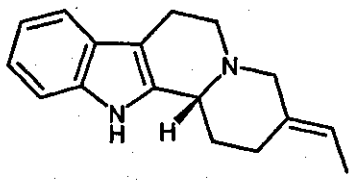
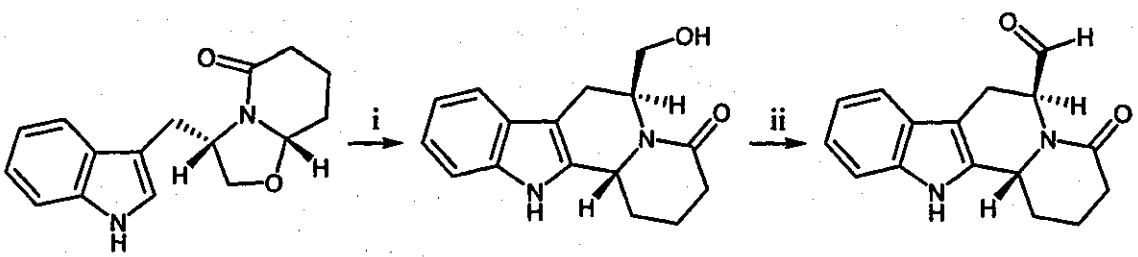
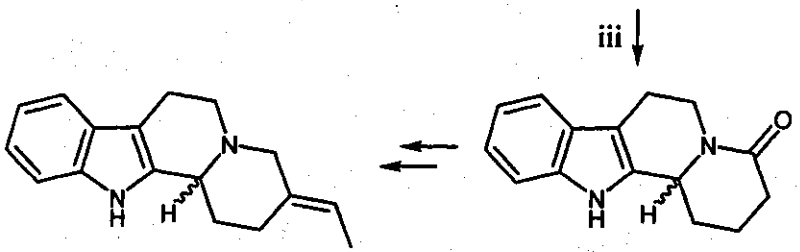


(204)

Building on earlier work from our research group we recognised that a suitably substituted bicyclic lactam **(266)** could act as a precursor in an intramolecular *N*-acyliminium mediated cyclisation leading to targets such as **(219)**.



(266) **(219)** **(311)**



(208) **(328)**

i) 2M HCl, EtOH, 20 h; ii) IBX, DMSO, 20 h; iii) $Rh(CO)(PPh_3)_2Cl$, mesitylene, Δ, 48 h

Methodology has been developed to remove the chiral auxiliary group. Manipulation of the template **(219)** has allowed us to achieve a novel total synthesis of deplancheine **(208)** and provided valuable insight for a future asymmetric synthesis of **(204)**.

Acknowledgements

I thank my supervisor Dr Steven Allin for the continual support, direction and enthusiasm which have been invaluable.

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Abbreviations

Ac	-	acetyl
AIBN	-	2,2'-azobisisobutyronitrile
atm	-	atmospheres
Bn	-	benzyl
Boc	-	*tert*-butoxycarbonyl
br	-	broad
Bu	-	butyl
CA	-	chiral auxiliary
Cbz	-	carbobenzyloxy
CCK	-	cholecystokinin
d	-	doublet
DBN	-	1,5-diazabicyclo[4.3.0]non-5-ene
DEAD	-	diethyl azodicarboxylate
DIBAL	-	diisobutylaluminium hydride
DMAP	-	4-dimethylaminopyridine
DME	-	1,2-dimethoxyethane
DMF	-	*N,N*-dimethylformamide
DMP	-	Dess-Martin periodinane
DMSO	-	dimethyl sulfoxide
dppe	-	1,2-bis(diphenylphosphino)ethane
dppp	-	1,3-bis(diphenylphosphino)propane
d.r.	-	diastereomeric ratio
E	-	electrophile
e.e.	-	enantiomeric excess
EI	-	electron impact
eq	-	equivalent(s)
Et	-	ethyl

FAB	-	fast atom bombardment
FT-IR	-	fourier transform infrared
h	-	hour(s)
HMPT	-	hexamethylphosphorous triamide
HPLC	-	high performance liquid chromatography
Hz	-	Hertz
IBX	-	2-iodoxybenzoic acid
J	-	coupling constant
LA	-	Lewis acid
LDA	-	lithium diisopropylamide
LHMDS	-	lithium hexamethyldisilazide
m	-	multiplet
m-CPBA	-	*meta*-chloroperoxybenzoic acid
Me	-	methyl
min	-	minute(s)
Mp	-	melting point
Ms	-	methanesulfonyl (mesyl)
NMO	-	*N*-methylmorpholine-*N*-oxide
NMR	-	nuclear magnetic resonance
NOE	-	nuclear Overhauser effect
Nu	-	nucleophile
PCC	-	pyridinium chlorochromate
Ph	-	phenyl
ppm	-	parts per million
R_f	-	retention factor
Ra-Ni	-	Raney nickel
Red-Al	-	sodium bis(2-methoxyethoxy)aluminium hydride
rt	-	room temperature
s	-	singlet
t	-	triplet
TBAF	-	tetra-*n*-butylammonium fluoride

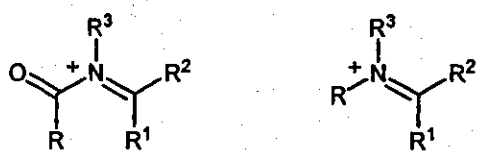
TBDMS	-	*tert*-butyldimethylsilyl
Tf	-	trifluoromethanesulfonyl (triflyl)
TFA	-	trifluoroacetic acid
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMB	-	3,4,5-trimethoxybenzoyl
TMS	-	trimethylsilyl, trimethylsilane, tetramethylsilane
TPAP	-	tetra-*n*-propylammonium perruthenate
Ts	-	*para*-toluenesulfonyl
q	-	quartet
UV	-	ultraviolet

Chapter 1

Introduction

1.1 *N*-Acyliminium Ions in Synthesis

The development of cyclisations that proceed *via* *N*-acyliminium species **(1)** are relatively recent, in contrast to those involving iminium cations **(2)** (**Figure 1**) such as the Mannich,[1-3] Bischler-Napieralski[4,5] and Pictet-Spengler[6-11] reactions.

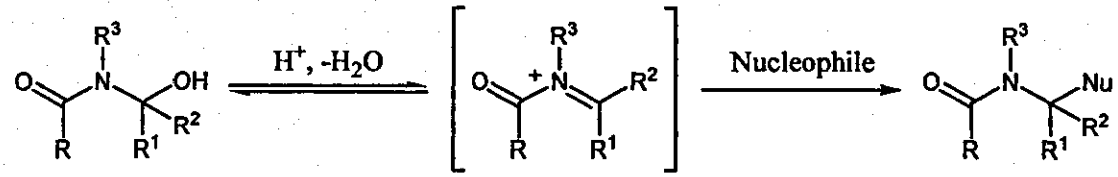


(1) **(2)**

Figure 1

The synthetic potential of *N*-acyliminium species **(1)** is well documented[12-14] and such intermediates are widely used, due to them exhibiting a broad versatility, with a range of synthetic applications.

The reaction between *N*-acyliminium ions and nucleophiles (also described as amidoalkylation or Mannich-type condensations)[13] has been extensively employed in the synthesis of alkaloidal and related systems. Through acid activation, the precursor **(3)** can be induced to form the corresponding *N*-acyliminium ion **(1)**. Subsequent amidoalkylation by nucleophilic addition yields the product **(4)** (**Scheme 1**).[12,14]

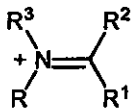


(3) **(1)** **(4)**

Scheme 1

1.2 Reactivity of *N*-Acyliminium Ions Relative to Iminium Ions

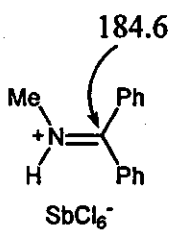
Substitution with electron-withdrawing groups at nitrogen renders the iminium cation **(2)** considerably more reactive by enhancing cationic character. The *N*-acyl derivative **(1)** and the carbamate **(5)** have been widely exploited. Alternative substituents such as the amide **(6)** and *N*-tosyl **(7)** cations have also been investigated (**Figure 2**).[13]



(2) R = H, Alkyl **(6)** R = $CONR_2$
(1) R = Acyl **(7)** R = Ts
(5) R = COOR

Figure 2

The ^{13}C NMR spectra of the iminium **(8)** and *N*-acyliminium **(9)** salts (**Figure 3**) demonstrate the increased electrophilicity of *N*-acyliminium ions.[15,16] The presence of an *N*-acetyl rather than *N*-methyl group shifts the corresponding imino carbon signal downfield by approximately 5 ppm.[12]



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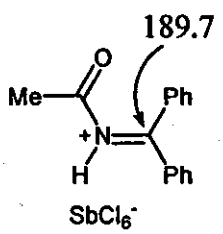
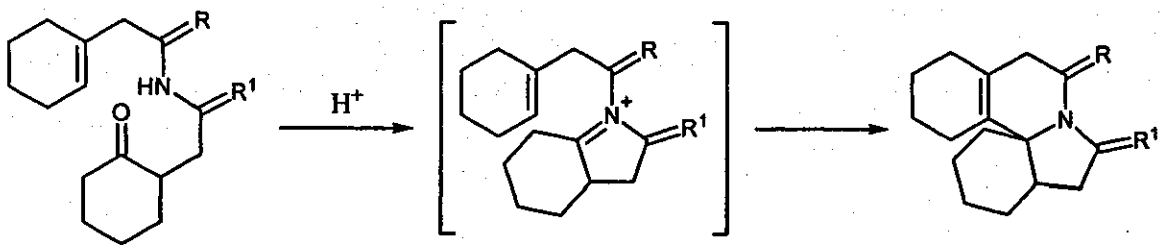


(9)

Figure 3

Boekelheide[17] illustrated the difference in reactivity between Mannich and *N*-acyliminium intermediates during olefin cyclisations. It was proposed that under acidic

conditions the keto amides **(10)** and **(11)** generated **(12)** and **(13)**. Subsequent intramolecular cyclisation produced **(14)** and **(15)** (**Scheme 2**).



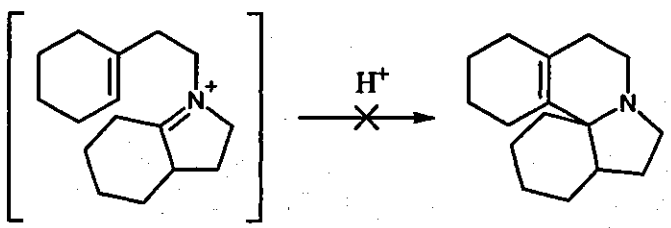
(10) R = O, $R^1 = H_2$
(11) $R = H_2$, R^1 = O

(12) R = O, $R^1 = H_2$
(13) $R = H_2$, R^1 = O

(14) R = O, $R^1 = H_2$
(15) $R = H_2$, R^1 = O

Scheme 2

In contrast, attempted ring closure of the species **(16)** to produce **(17)** was unsuccessful and resulted in unidentifiable products (**Scheme 3**).

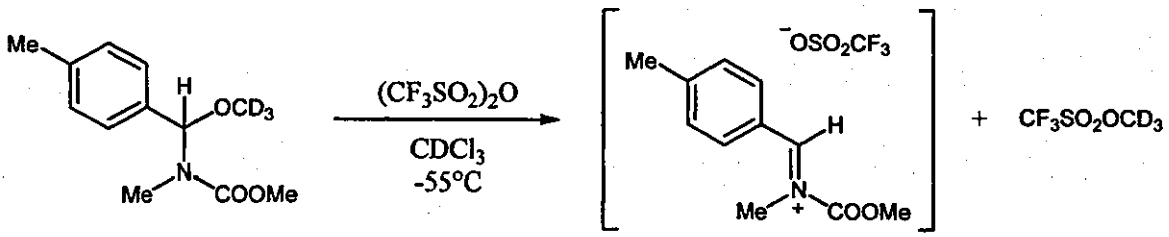


(16) **(17)**

Scheme 3

1.3 Experimental Evidence for *N*-Acyliminium Ions

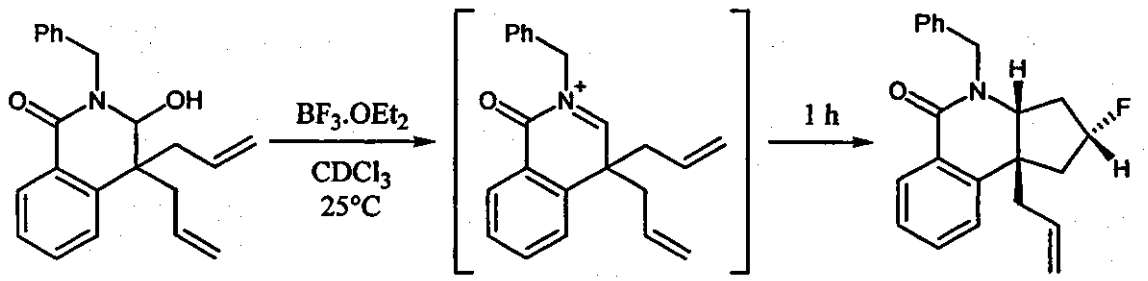
The observation of a transient *N*-acyliminium intermediate in dynamic NMR studies has only been reported twice.[13] Yamamoto[18] has shown that at -55°C in the presence of triflic anhydride the compound **(19)** was generated from the precursor **(18)** (**Scheme 4**). Presumably, cleavage of $CF_3SO_2OCD_3$ into $CF_3SO_2^+$ and $^-OCD_3$ under the reaction conditions would be difficult and the equilibrium is largely shifted to the right.



(18) (19)

Scheme 4

Heaney[19] has observed the ^{13}C NMR spectrum of the *N*-acyliminium ion **(21)** after treatment of **(20)** with $BF_3.OEt_2$ at ambient temperature **(Scheme 5)**. The intermediate **(21)** was gradually (1 h) converted to the fluoro compound **(22)**.



(20) (21) (22)

Scheme 5

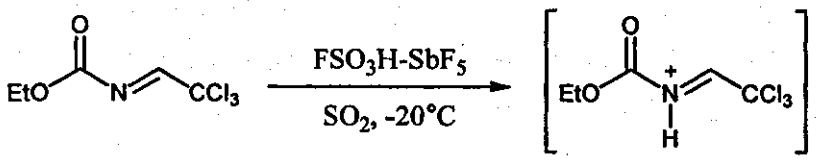
1.4 Generation of *N*-Acyliminium Ions

N-Acyliminium ions are almost always generated *in situ*, in view of their limited stability and high reactivity.[12] Five methods for the generation of *N*-acyliminium ions are listed below and are subsequently discussed.

- *N*-Protonation of *N*-acylimines
- Oxidation of amides
- *N*-Acylation of imines
- Heterolysis of amides
- Electrophilic addition to enamides

1.4.1 *N*-Protonation of *N*-Acylimines

The protonation of *N*-acylimines is a route to *N*-acyliminium species. However, it is not a common method due to the instability of *N*-acylimines, which readily tautomerise to the corresponding enamide (unless there are no α-hydrogen atoms present).[12] Treatment of the *N*-acylimine **(23)** with fluorosulfonic acid-antimony pentafluoride ("magic acid") generated the species **(24)** *via* *N*-protonation (**Scheme 6**).[20]

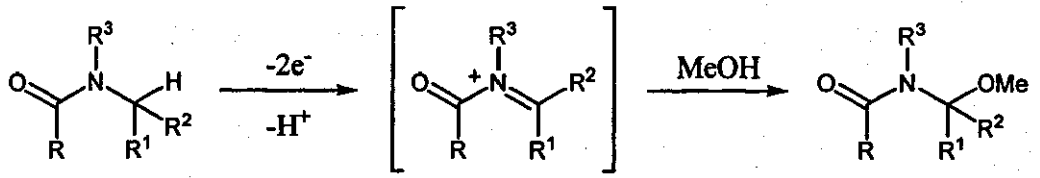


(23) **(24)**

Scheme 6

1.4.2 Oxidation of Amides

The removal of a hydride from the α-carbon of an amide results in an *N*-acyliminium ion.[12] This transformation can be effected using electrochemical techniques developed by Ross,[21] Shono[22] and Utley.[23] The mechanism involves the consecutive removal of an electron from the lone pair on nitrogen of **(25)**, followed by a proton and then a second electron. The intermediate **(1)** can be trapped with a nucleophile, typically methanol, to produce an α-methoxylated amide **(26)** (**Scheme 7**).

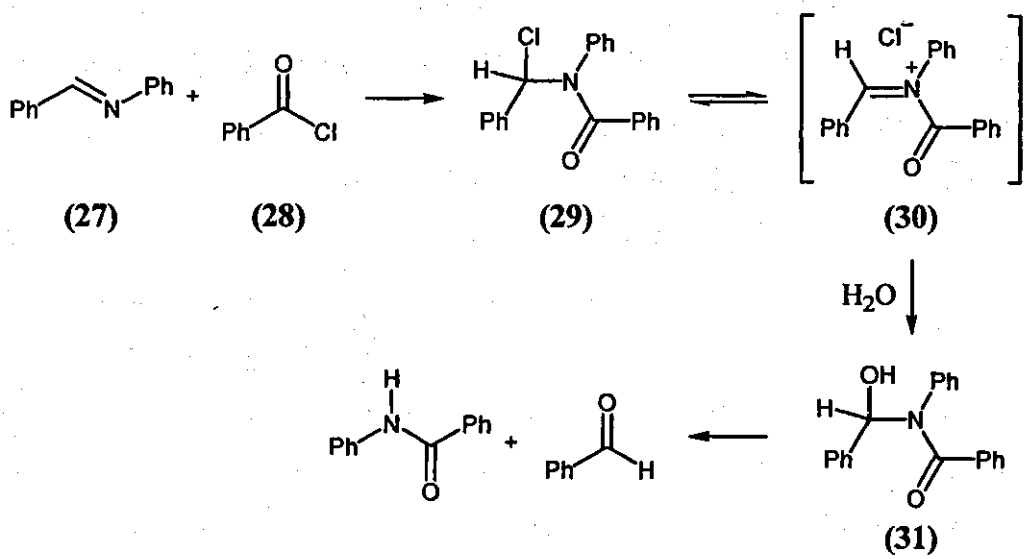


(25) **(1)** **(26)**

Scheme 7

1.4.3 *N*-Acylation of Imines

N-Acyliminium ions can be generated by the acylation of imines with reactive carboxylic derivatives. James and Judd[24] reacted the imine **(27)** with benzoyl chloride **(28)** and generated the crystalline product **(29)**. The latter compound was readily hydrolysed *via* the intermediacy of the *N*-acyliminium species **(30)** and compound **(31)** (**Scheme 8**).

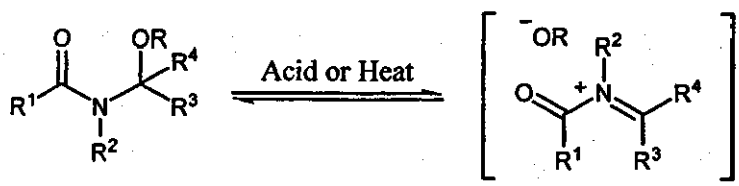


(27) **(28)** **(29)** **(30)** **(31)**

Scheme 8

1.4.4 Heterolysis of Amides

Brönsted or Lewis acids are generally used to generate the corresponding *N*-acyliminium ions **(33)** from amides such as **(32)** if R is an alkyl group or hydrogen. If R is an acetyl or methanesulfonyl group no acidic catalyst is required (**Scheme 9**).[12]

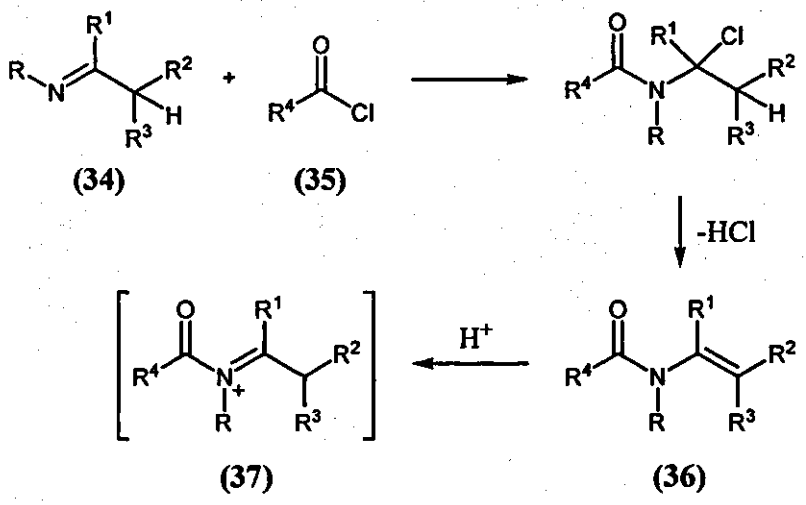


(32) **(33)**

Scheme 9

1.4.5 Electrophilic Addition to Enamides

Enamides such as **(36)** can be formed by the acylation of an imine **(34)** with an acid chloride **(35)** followed by elimination. Protonation of **(36)** results in the intermediate **(37)** (**Scheme 10**).[12]

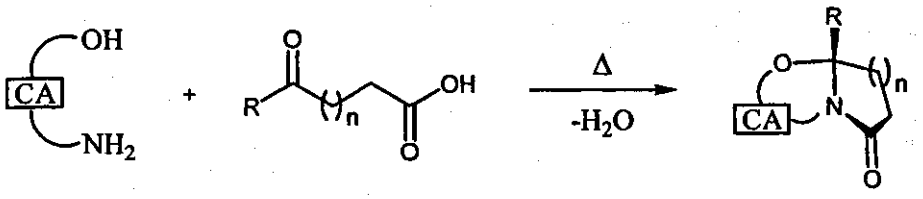


Scheme 10

1.5 Chiral Non-Racemic Lactams in Synthesis

Meyers has extensively employed chiral non-racemic bicyclic lactams for the synthesis of enantiopure carbocycles and nitrogen containing heterocycles.[25] Two general methods have been developed for the construction of bicyclic lactams.[26]

Cyclodehydration between an optically pure amino alcohol **(38)** and a keto acid **(39)** has been used to generate lactams such as **(40)** (**Scheme 11**).[26]

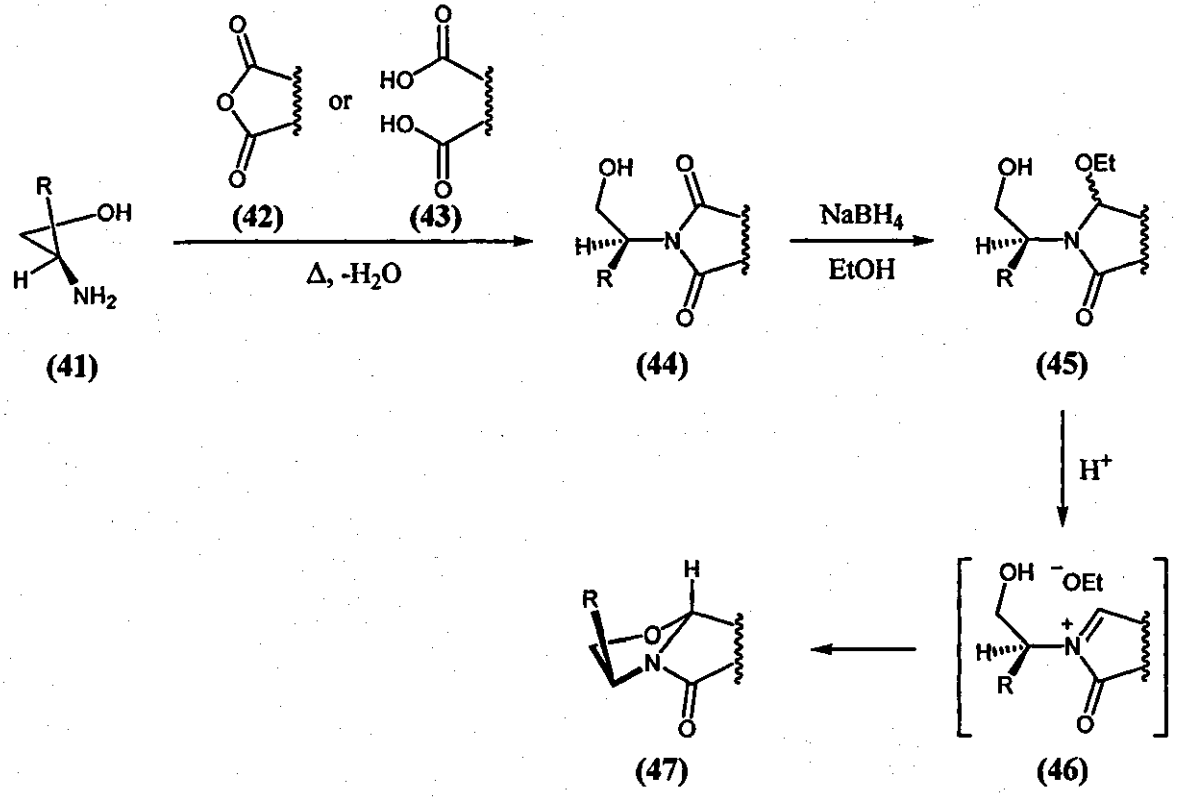


CA = Chiral Auxiliary n = 1, 2

(38) **(39)** **(40)**

Scheme 11

The second route is related to work by Speckamp[12,27] involving *N*-acyliminium species (**Scheme 12**). Condensation of an optically pure amino alcohol **(41)** with a cyclic anhydride **(42)** or dicarboxylic acid **(43)** afforded the imide **(44)**. Addition of a hydride source in ethanol generated the ethoxylactam **(45)**. Treatment of the latter with acid produced **(47)** *via* the intermediate **(46)**.[26,28]



Scheme 12

1.6 Applications of Chiral Bicyclic Lactams in Synthesis

Chiral 5,5- or 5,6-bicyclic lactams **(48)** are extremely versatile building blocks for the preparation of enantiopure heterocyclic compounds and have been used to synthesise pyrrolidines such as **(49)** and **(50)**, pyrrolidinones **(51)**, piperidines **(52)** and tetrahydroisoquinolines **(53)** (**Figure 4**).[26]

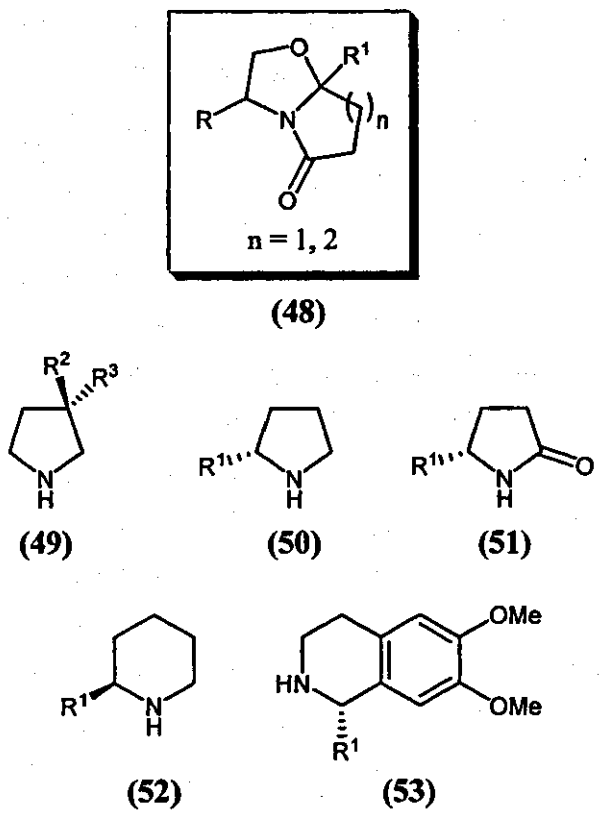
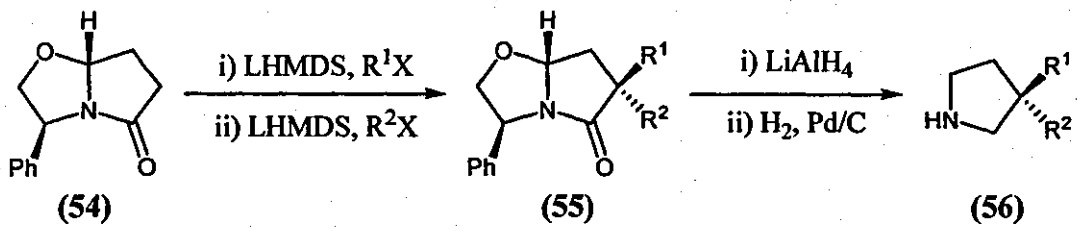


Figure 4

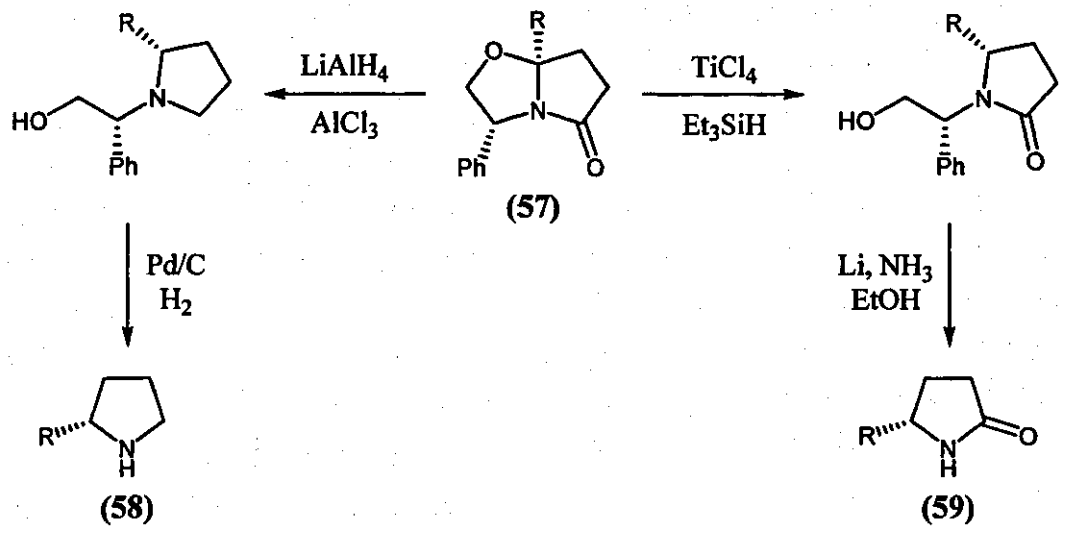
1.6.1 Synthesis of Pyrrolidines and Pyrrolidinones

A method to prepare 3- or 3,3-substituted pyrrolidines **(56)** involves the mono or dialkylation of lactams such as **(54)** followed by reduction and palladium-catalysed hydrogenolysis of **(55)** (**Scheme 13**).[30]



Scheme 13

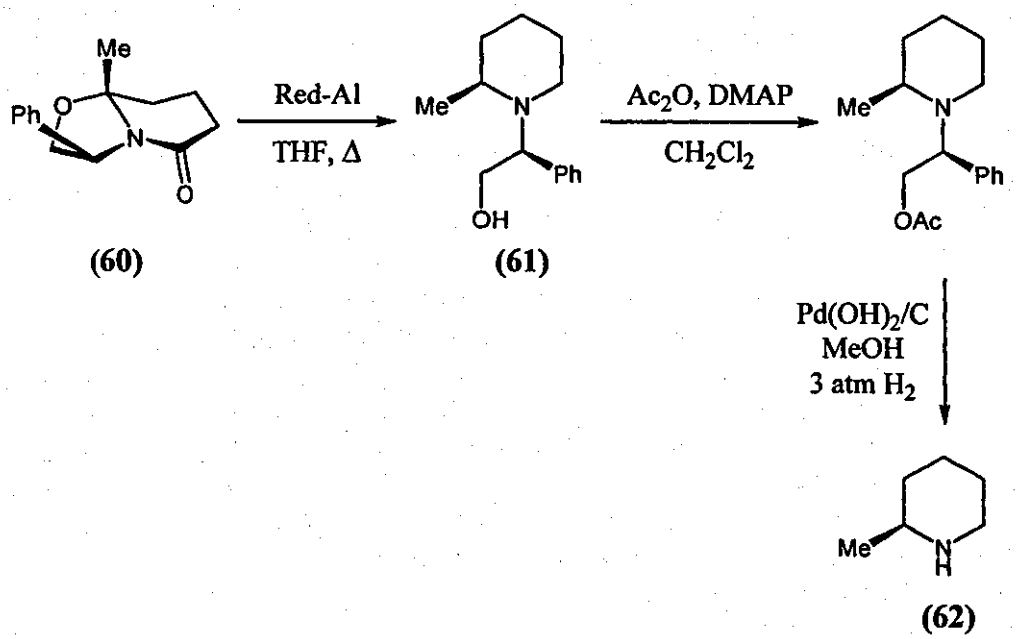
Meyers[31] has developed an efficient asymmetric synthesis of 2-substituted pyrrolidines **(58)** and 5-substituted pyrrolidinones **(59)** from the lactam **(57)** (**Scheme 14**).



Scheme 14

1.6.2 Synthesis of Piperidines

The lactam **(60)** can be readily transformed to enantiomerically pure 2-substituted piperidines, exemplified by the simple alkaloid, (-)-pipecoline **(62)** (**Scheme 15**).[31]



(60) (61) (62)

Scheme 15

It was postulated[31] that following carbonyl reduction of **(60)** with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al), the oxygen of the oxazolidine ring coordinates with $HAlR_2$ as shown in **(63)** (**Figure 5**). This process weakens the C-O bond and promotes iminium ion formation **(64)**. Subsequent hydride delivery from the oxygen-aluminium hydride face generated the compound **(61)**.

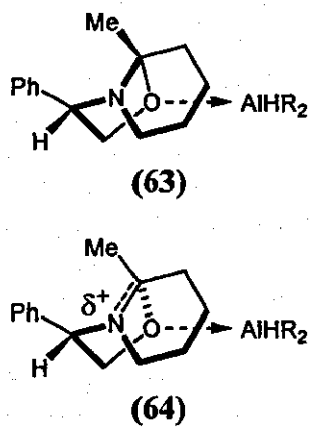
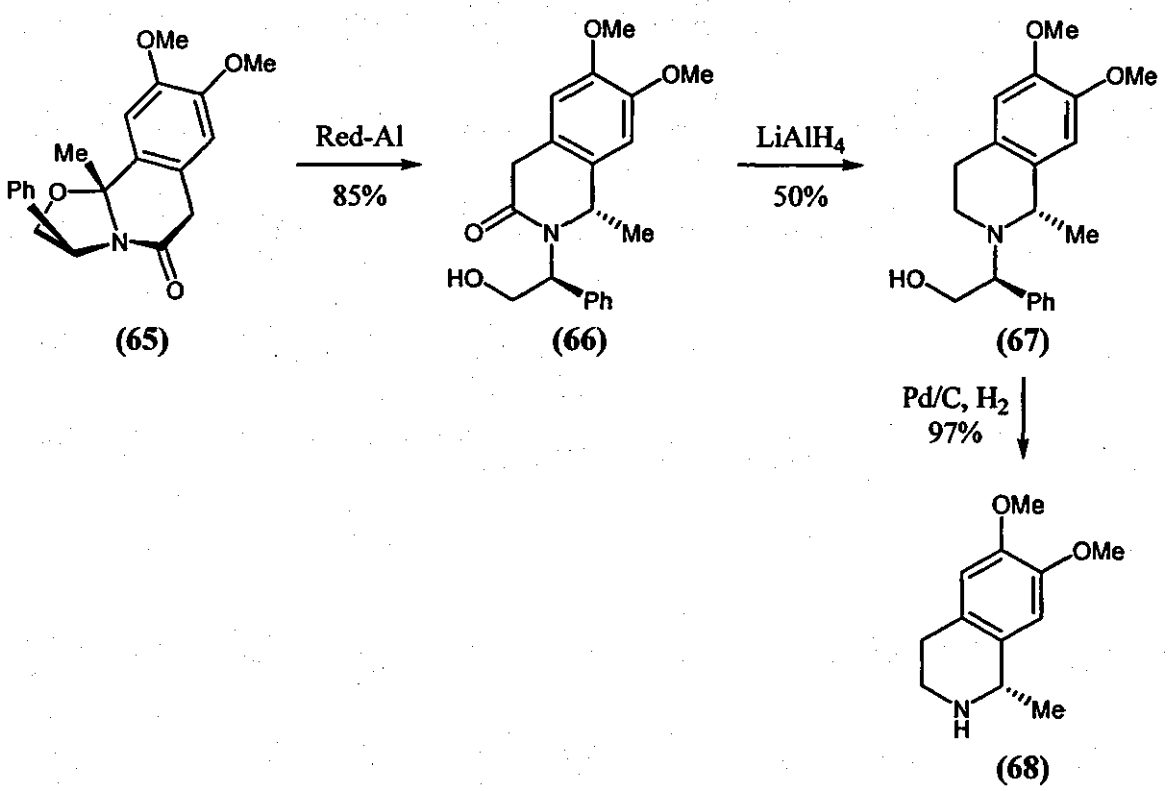


Figure 5

1.6.3 Synthesis of Tetrahydroisoquinolines

The tetrahydroisoquinoline, (-)-salsolidine **(68)**, has been synthesised from an appropriately functionalised 5,6-bicyclic lactam **(65)** (**Scheme 16**). The latter compound was subjected to a two step (Red-Al and $LiAlH_4$) reduction sequence. Reductive removal of the *N*-benzyl group from **(67)** gave compound **(68)**.[32]



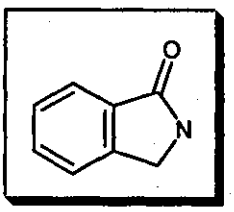
(65) **(66)** **(67)** **(68)**

Scheme 16

In contrast to similar work by Meyers[31] (**Scheme 15**) the lactam carbonyl of **(66)** was inert to Red-Al reduction although there was cleavage of the ring C-O bond. The reason for this discrepancy is not completely understood although it was suggested[32] that a conformational change could alter the steric and electronic behaviour of the amide moiety.

1.7 Applications of Chiral Tricyclic Lactams in Synthesis

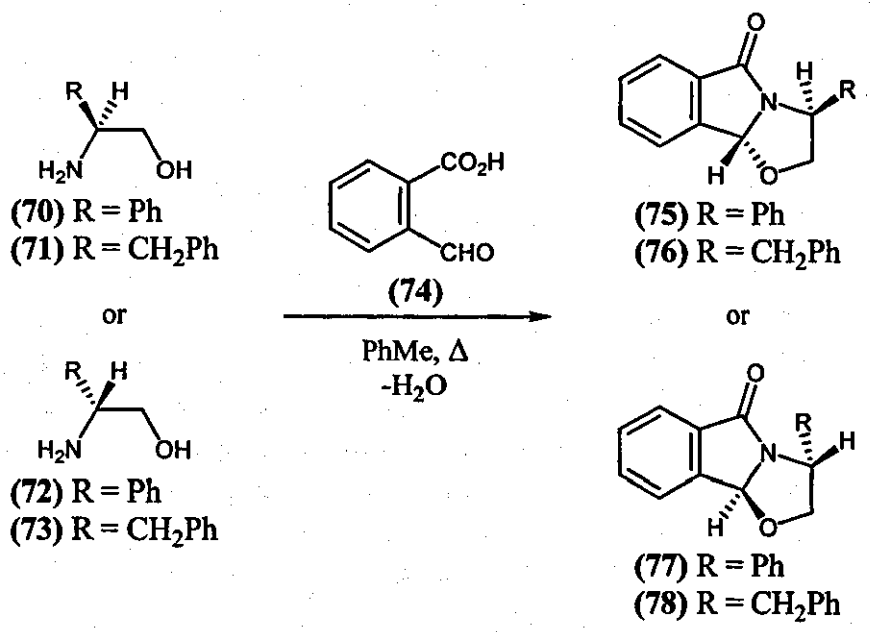
Chiral tricyclic (or appropriately functionalised 5,5-bicyclic) lactams based on the isoindolinone ring system **(69)** (**Figure 6**) have been reported by Allin.[33-36]



(69)

Figure 6

Condensation of the appropriate enantiomer of phenylglycinol **(70)** and **(72)** or phenylalaninol **(71)** and **(73)** with 2-carboxybenzaldehyde **(74)** produced the tricylic lactams **(75)** and **(77)** or **(76)** and **(78)** (**Scheme 17, Table 1**).[33]

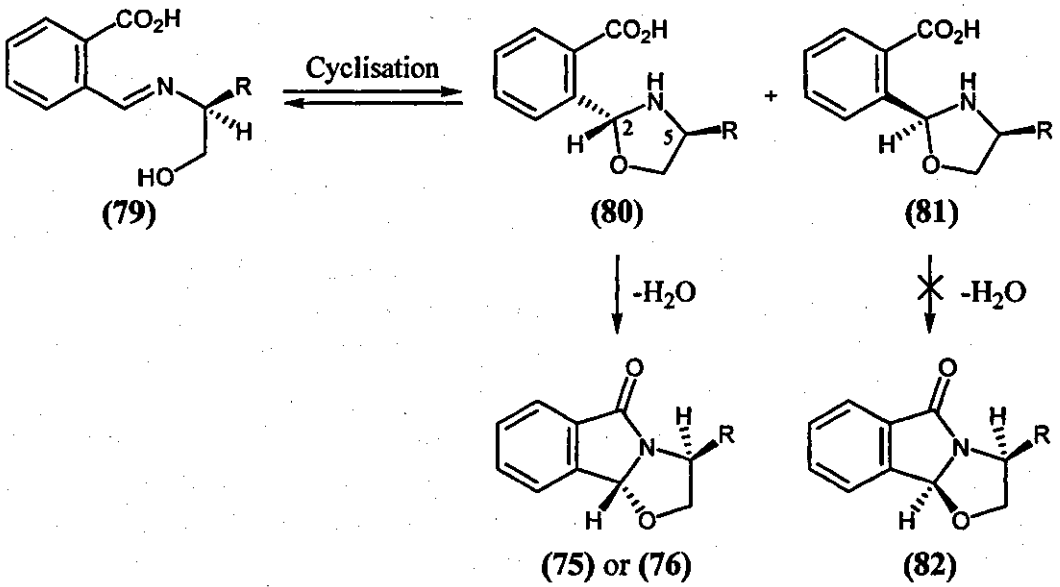


Scheme 17

Substrate	R	Yield (%)	Diastereoselectivity
(70)	Ph	70	(75), exclusive
(72)	Ph	70	(77), exclusive
(71)	CH_2Ph	72	(76), exclusive
(73)	CH_2Ph	71	(78), exclusive

Table 1

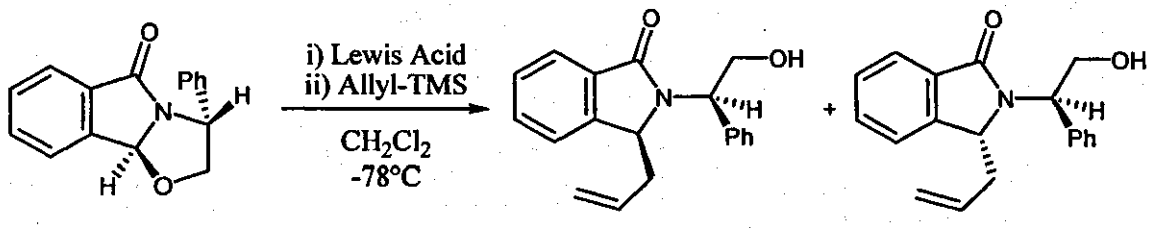
A mechanism to explain the stereochemical outcome of the reaction outlined in **Scheme 17** was proposed by Allin[33] (**Scheme 18**). Reversible cyclisation of the (*S*)-hydroxyimine **(79)** could produce either the *trans*-**(80)** or *cis*-**(81)** oxazolidine (referring to the stereochemistry at C-2 and C-5). Tricyclic lactams such as **(75)** and **(76)** would be generated by ring closure of **(80)**. It was suggested that cyclisation of **(81)** to generate **(82)** was highly disfavoured due to the remote orientation of the reactive functional groups.



Scheme 18

In an analogous manner, the *trans* tricyclic lactams **(77)** and **(78)** are the favoured products when the alternative (*R*)-hydroxyimine is considered.

Allin[34] investigated the synthetic potential of tricyclic lactams by subjecting **(83)** to an intermolecular amidoalkylation reaction (**Scheme 19**).

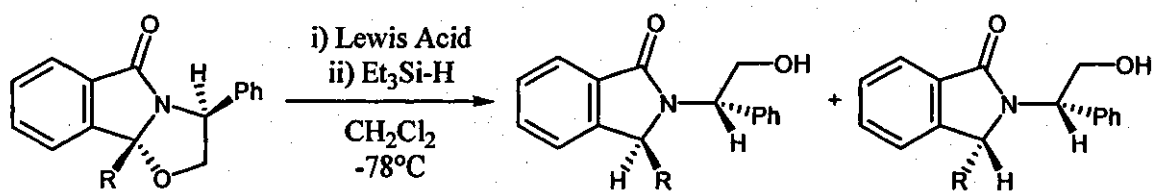


(83) **(84)** **(85)**

Scheme 19

The reaction proceeded in high yield (86%) although a 1:1 mixture of **(84)** and **(85)** was obtained when $TiCl_4$ was used in conjunction with allyl trimethylsilane. Alternative Lewis acids ($BF_3.OEt_2$, $SnCl_4$ and TMSOTf) or nucleophiles (TMS-CN, indole and furan) with $TiCl_4$ activation did not significantly improve the diastereoselectivity. Due to a poor level of product diastereoselectivity, an alternative approach to the synthesis of non-racemic 3-substituted isoindolin-1-one derivatives was investigated that involved the hydride ring-opening of alkyl-substituted lactams.[35]

The tricyclic lactams **(86)** or **(87)** were individually activated with $TiCl_4$ or TMSOTf followed by the addition of triethylsilane. The products from the reaction were the diastereoisomers **(88)** and **(89)** (**Scheme 20, Table 2**).



(86) R = Ph
(87) R = Me

(88) **(89)**

Scheme 20

Substrate	R	Lewis Acid	Yield (%)	Diastereoselectivity (88):(89)
(86)	Ph	$TiCl_4$	90	>98:2
(86)	Ph	TMSOTf	80	4:1
(87)	Me	$TiCl_4$	99	>98:2
(87)	Me	TMSOTf	89	1.5:1

Table 2

In order to rationalise the stereochemical outcome of the Lewis acid cyclisation of the bicyclic lactams **(86)** and **(87)**, the transition state models outlined in **Figure 7** were invoked by Allin.[35]

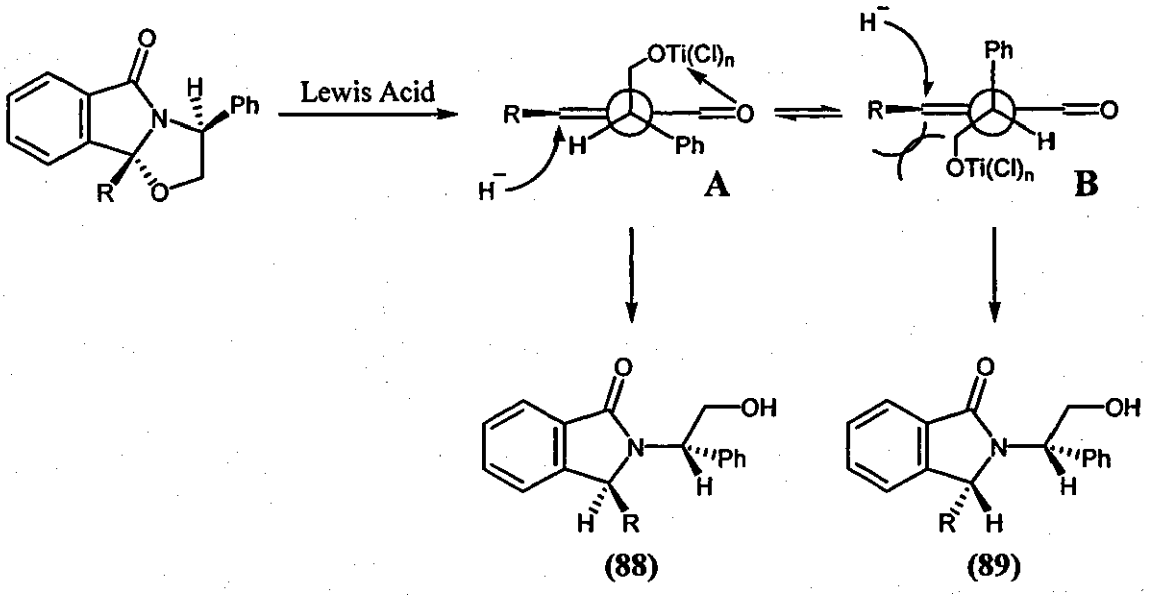
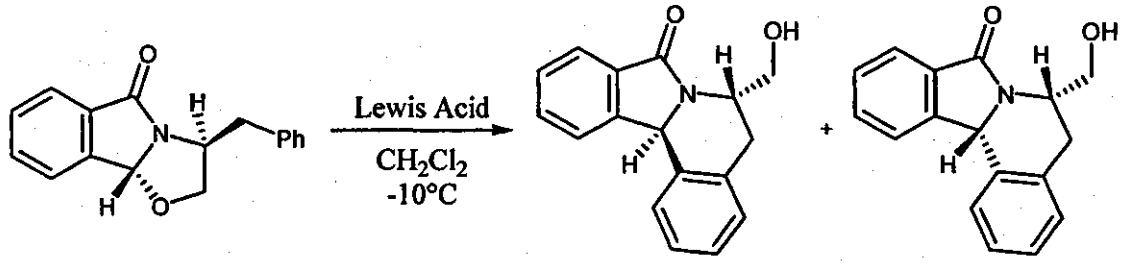


Figure 7

The size of the angular substituent appears to be a significant factor contributing to the observed levels of diastereoselectivity. When R = Ph **(86)**, the steric effect provided by this substituent is sufficient to favour transition state **A** and in turn produces **(88)**. It is

evident that conformation A places the Lewis acid-complexed oxymethyl substituent in a suitable orientation to allow chelation to occur with the amide oxygen atom. This chelation effect also appears to be significant as use of an activator incapable of multi-point coordination (TMSOTf), sees a significant decrease in diastereoselectivity (>98:2 to 4:1). These postulates were reinforced by the results obtained for the methyl-substituted substrate **(87)**. The angular methyl group produced a high diastereoselectivity (>98:2) with chelation control but only low stereoselection (1.5:1) was obtained when chelation could not be a contributing factor.

The potential of the tricyclic lactam **(90)** to act as a precursor for an intramolecular *N*-acyliminium ion cyclisation was investigated by Allin[36] during the synthesis of tetracyclic isoindolinone systems such as **(91)** and **(92)** (**Scheme 21**).



(90) **(91)** **(92)**

Scheme 21

A 2:1 mixture of the isoindolinone diastereoisomers **(91)** and **(92)** was obtained after activation of **(90)** with $TiCl_4$. Alternative activators were investigated (TMSOTf, $BF_3.OEt_2$ and $SnCl_4$) and the highest degree of diastereoselectivity was achieved with TMSOTf (**(91)**:**(92)** ≥49:1). Activation by $BF_3.OEt_2$ produced the next highest ratio (3:1) in favour of **(91)**. The stereochemical outcome of the reaction was rationalised by invoking the transition state models highlighted in **Figure 8**.

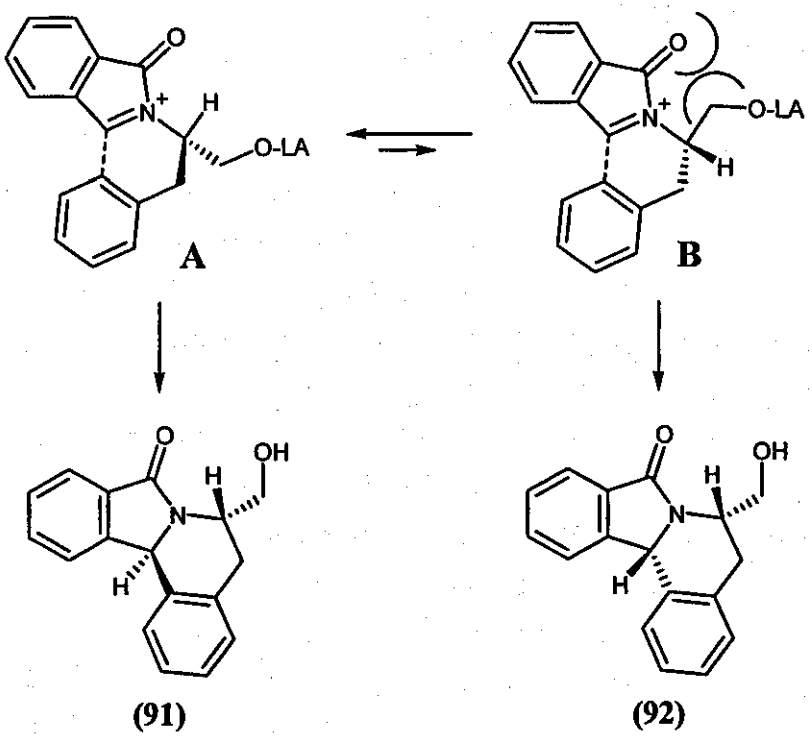


Figure 8

In transition state **A** (leading to the favoured diastereoisomer **(91)**), the carbonyl moiety would be eclipsed in a 1,3-fashion by the hydrogen atom at the chiral centre. In the alternative transition state **B** (leading to the disfavoured diastereoisomer **(92)**), an unfavourable 1,3-interaction exists between the carbonyl moiety and the more bulky Lewis acid-complexed oxymethyl group.

It may be expected that transition state **B** is more favourable as there is possibility of chelation between the amide oxygen atom and the alkoxy group with a metal counter-ion, to form a seven membered chelate. From consideration of the results, it is clear that if chelation is taking place it is resulting in a lower level of diastereoselection. The Lewis acids capable of multi-point coordination ($TiCl_4$, $BF_3.OEt_2$ and $SnCl_4$) lead to lower levels of product diastereoselectivity, probably due to an increased contribution of the chelated transition state similar in structure to **B**.

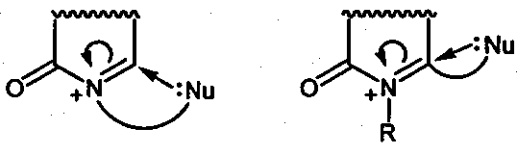
1.8 Amidoalkylations with Aromatic π-Nucleophiles

N-Acyliminium ions have historically[12-14] occupied an important position as versatile intermediates in organic synthesis. Of particular importance are the reactions of cyclic *N*-acyliminium ions with π-nucleophiles in carbon-carbon bond forming processes, with a great deal of attention given to cyclisations leading to alkaloids and other nitrogen-containing biologically active compounds.

Due to the vast quantity of literature being ascribed to the subject of intramolecular amidoalkylations with aromatic π-nucleophiles only a selected number of examples have been highlighted in this section.

1.8.1 Benzene and Substituted Benzene as a π-Nucleophile

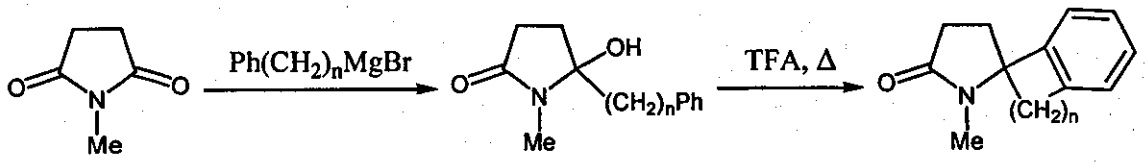
Intramolecular reactions of *N*-acyliminium ions typically follow the route illustrated by **(93)**. Less common are intramolecular reactions of the type **(94)** which result in the formation of spiro structures (**Figure 9**).[37,38]



(93) **(94)**

Figure 9

Vernon[38] has examined α,α-cyclisations **(94)** with an aromatic ring as the π-nucleophile. The hydroxylactam **(95)** afforded the 5,5-spiro lactam **(97)** by dehydration in refluxing trifluoroacetic acid (**Scheme 22**). In an identical manner, the 5,6-spiro lactam **(98)** was obtained from the homologous hydroxylactam **(96)**.

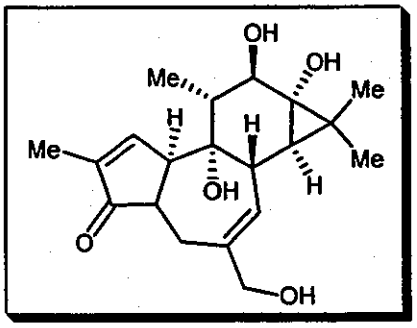


(95) n = 2
(96) n = 3

(97) n = 2
(98) n = 3

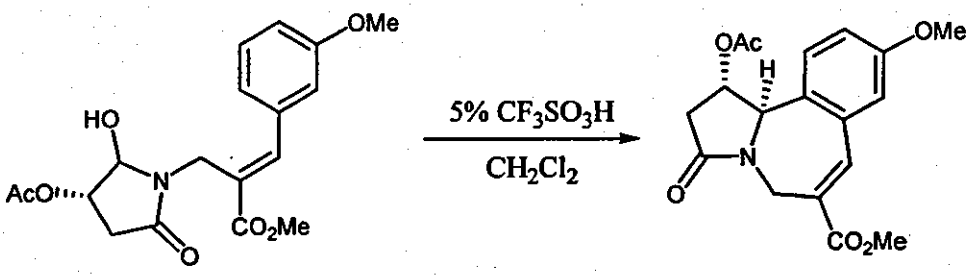
Scheme 22

A stereoselective approach to the synthesis of aromatic 5-7-6 fused systems related to the tumour-promoter phorbol **(99)** (**Figure 10**) was achieved by the cyclisation of **(100)** (**Scheme 23**).[39]



(99)

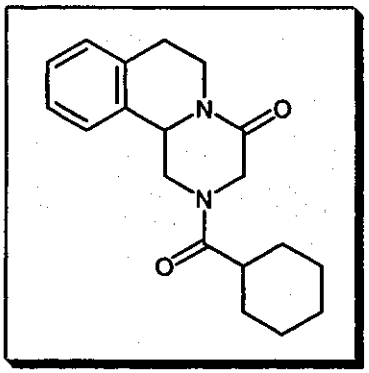
Figure 10



(100)

Scheme 23

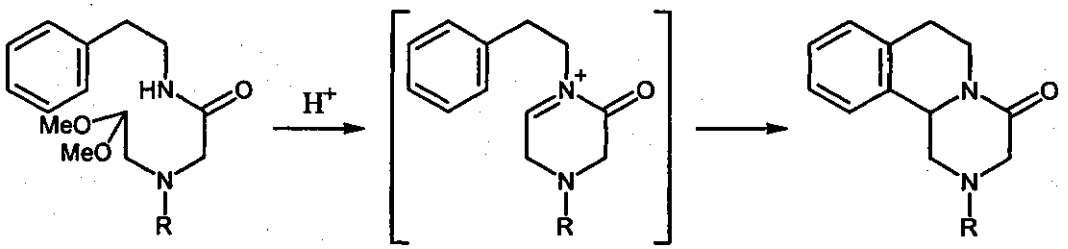
Kim[40] has developed an efficient synthesis to access pyrazinoisoquinolines such as Praziquantel **(101)** (**Figure 11**), a well known anthelmintic drug.



(101)

Figure 11

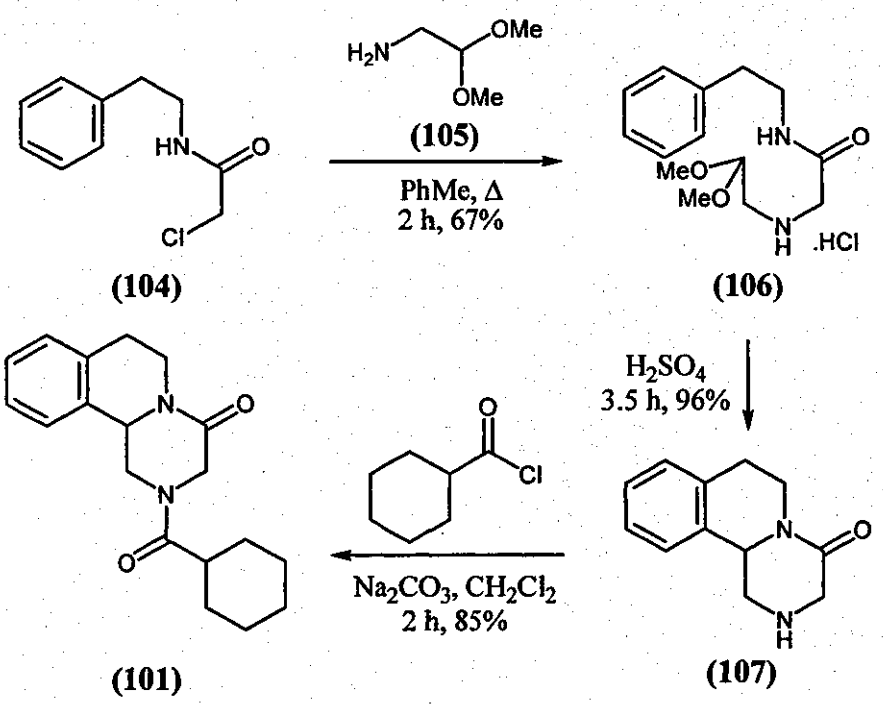
It was determined that structures such as Praziquantel **(101)** could be constructed by a one-pot procedure from an amido-acetal such as **(102)**. This involved the consecutive intramolecular amidoalkylation of an acetal with an amide, followed by cyclisation of the resultant *N*-acyliminium ion **(103)** with an aromatic π-nucleophile (**Scheme 24**).



(102) **(103)**

Scheme 24

The compound **(105)** was used as both reagent and base to trap hydrochloride, when compound **(104)** was converted to the amido-acetal **(106)** (**Scheme 25**). Praziquantel **(101)** was obtained after acid catalysed cyclisation of **(106)** and acylation of **(107)**.



Scheme 25

Lee[41] has efficiently synthesised the enantiomers **(108)** and **(109)** (**Figure 12**).

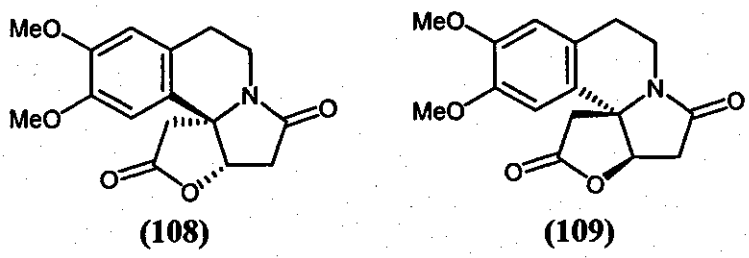
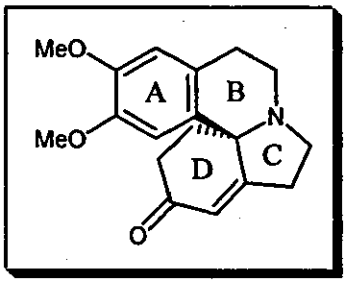


Figure 12

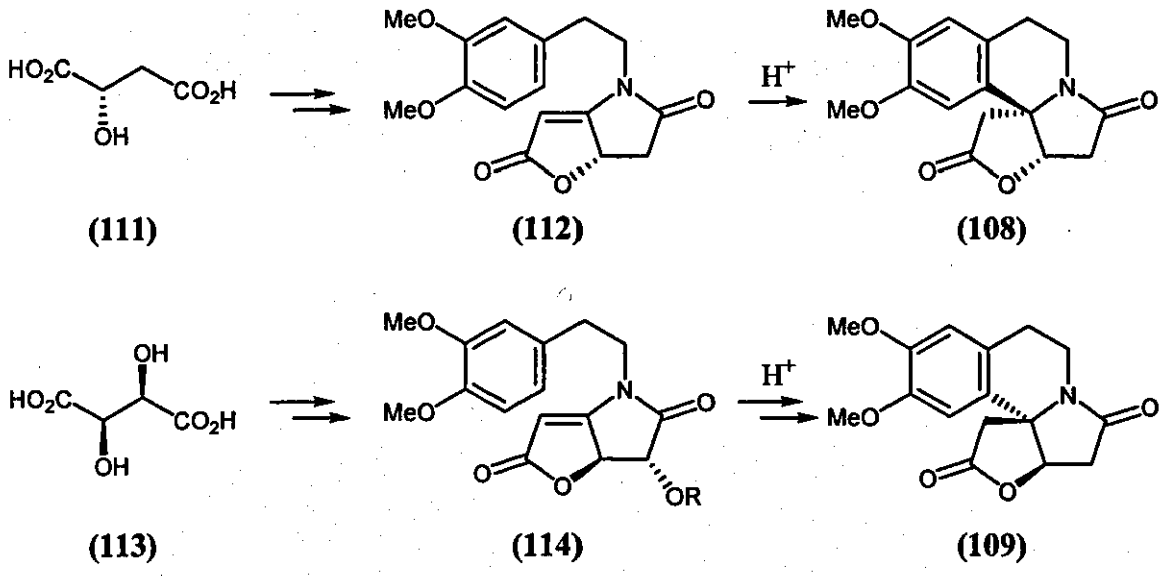
The tetracyclic compounds **(108)** and **(109)** are potential intermediates for the chiral synthesis of *Erythrina* alkaloids such as (-)-3-demethoxyerythratidinone **(110)** (**Figure 13**) since they already possess a requisite quaternary carbon centre and A/B/C ring system.



(110)

Figure 13

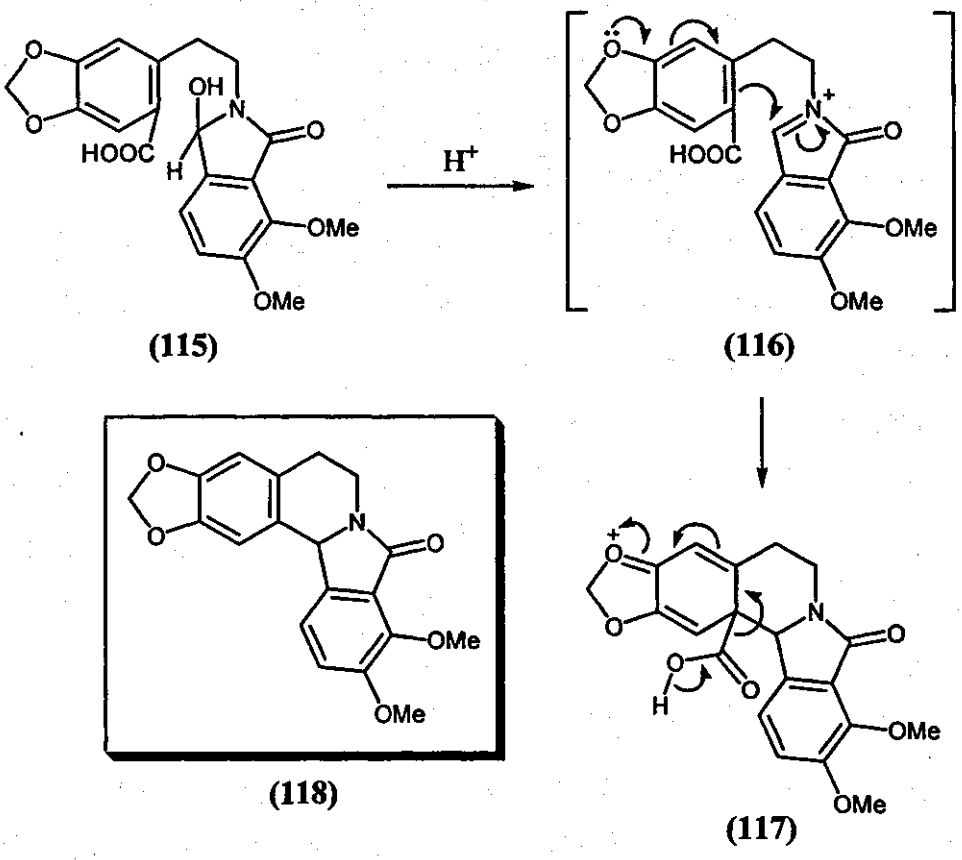
The synthetic approach focused on the diastereoselective *N*-acyliminium ion cyclisation of chiral enamides **(112)** and **(114)** derived from L-malic **(111)** and L-tartaric acid **(113)** **(Scheme 26).**



Scheme 26

It was proposed by Lee[41] that this approach allowed complete stereocontrol of the quaternary carbon centre in the cyclisation step by approach of the aromatic ring at the side opposite to the lactone substituent.

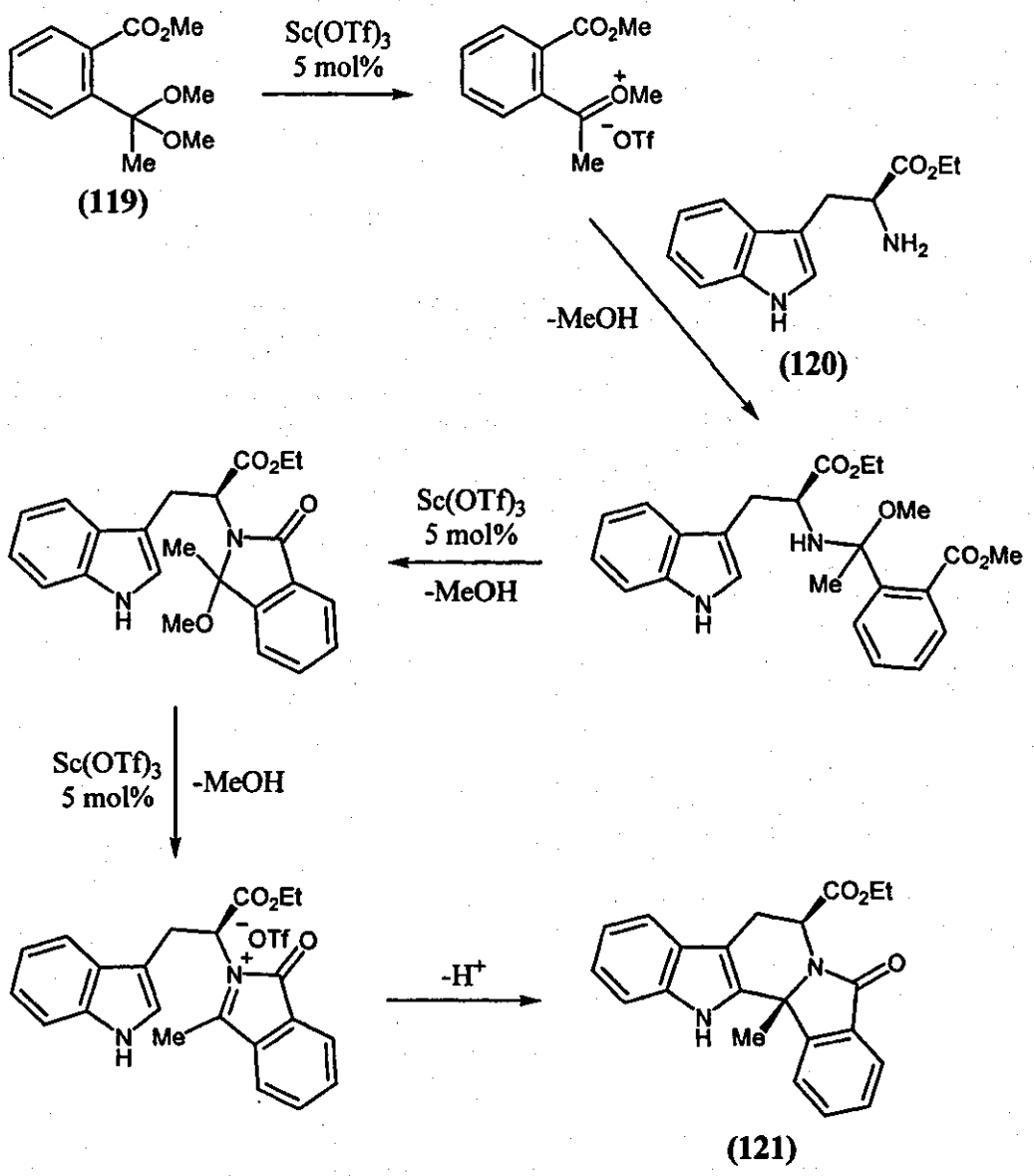
A route to (±)-neuvamine **(118)** was devised by Valencia[42] whereby compound **(115)** underwent acid catalysed cyclisation to **(117)** *via* the *N*-acyliminium intermediate **(116)**. The cation **(117)** suffered facile decarboxylation to yield the isoindoloisoquinoline **(118)** **(Scheme 27)**.



Scheme 27

1.8.2 Indole as a π-Nucleophile

In an asymmetric variation on the intramolecular amidoalkylation reaction, Heaney[43] has reported a route to the heterocyclic system **(121)** **(Scheme 28)** utilising indole as an intramolecular π-nucleophile.

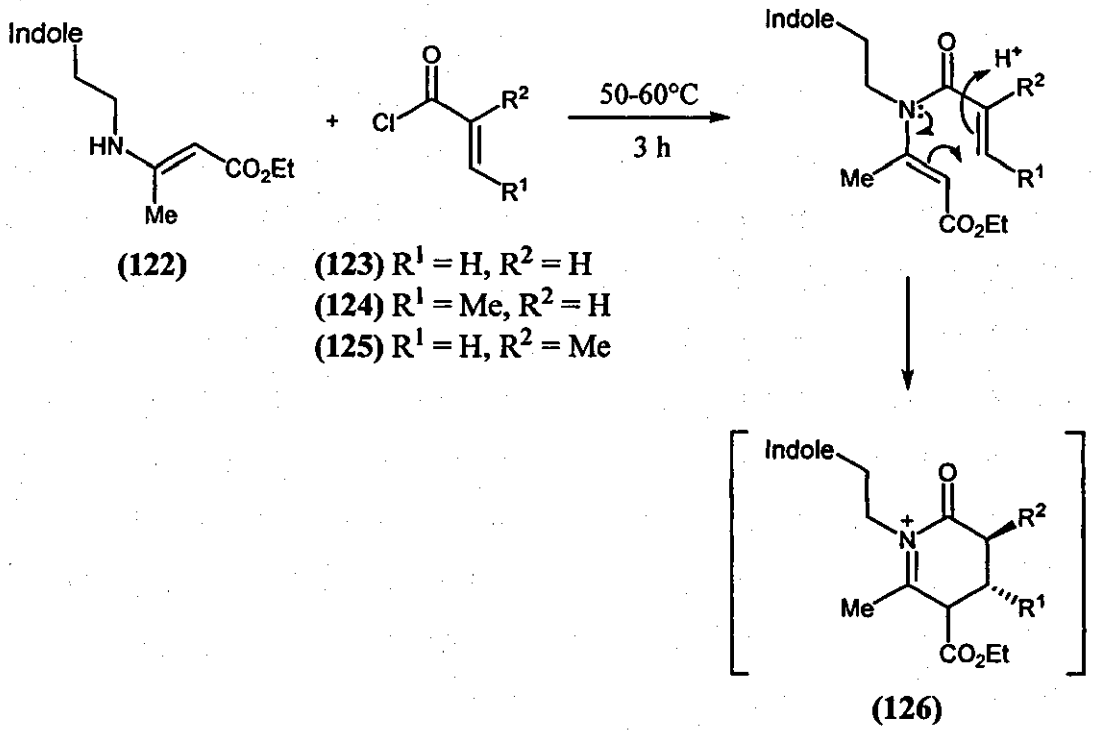


Scheme 28

Addition of 2-(1,1-dimethoxyethyl)benzoate **(119)** to the ethyl ester of tryptamine **(120)** with catalytic scandium triflate resulted in the cascade reaction. The product **(121)** was isolated as a single diastereoisomer in an overall yield of 36%.

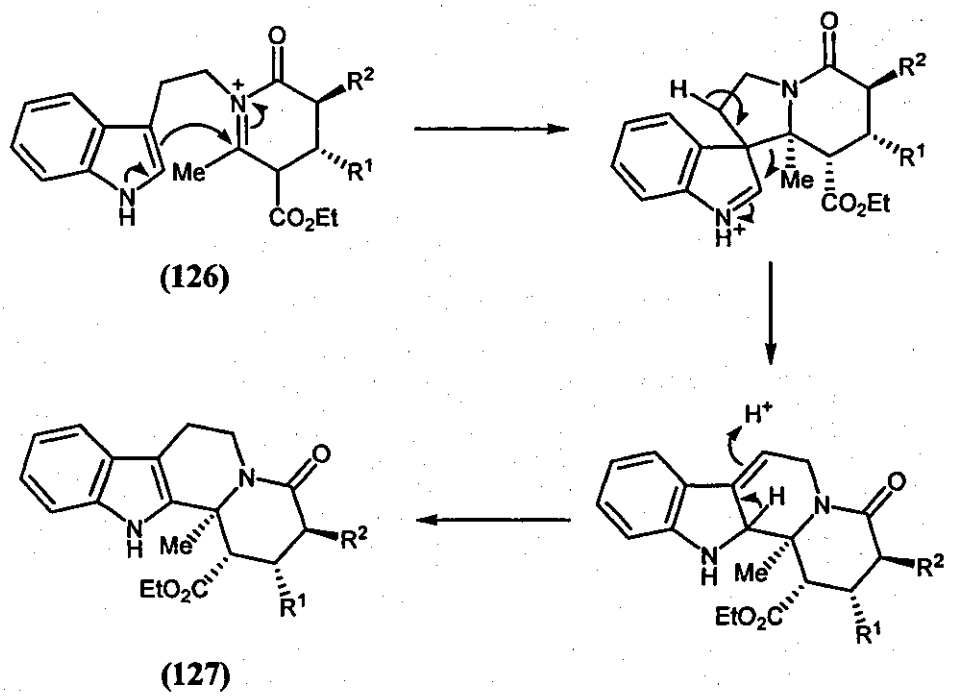
Abelman[44] has used *N*-acyliminium ions to access natural product-like heterocyclic systems. An aza-annulation[45-47] between the β-enamino ester of tryptamine **(122)** and

acryloyl **(123)**, crotonyl **(124)** or methallyl chloride **(125)** generated the intermediate **(126)** (**Scheme 29**).



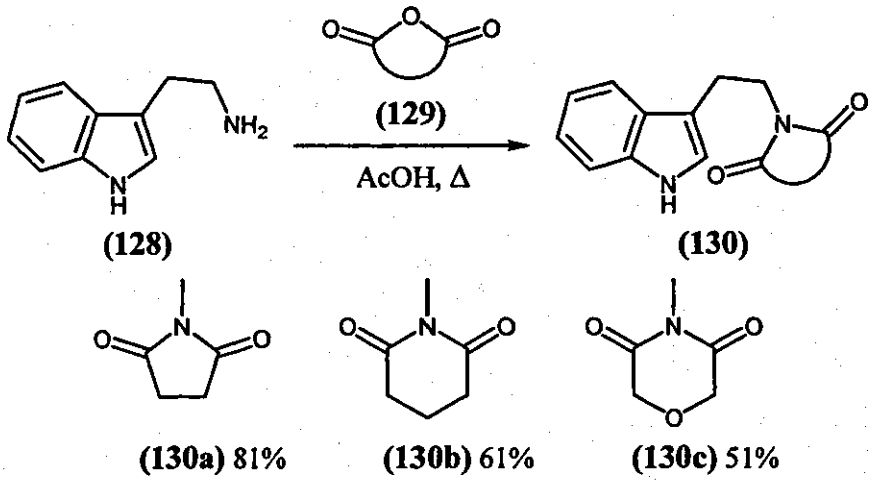
Scheme 29

The intermediate **(126)** proceeded to cyclise and the tetracyclic system **(127)** was obtained (**Scheme 30**).



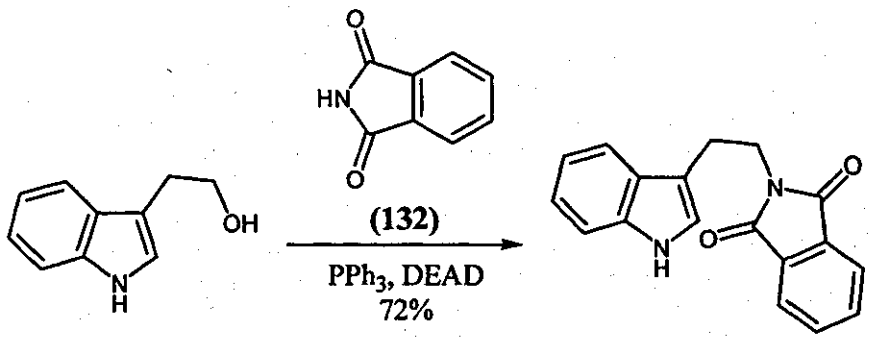
Scheme 30

N-[2-(3-Indolyl)ethyl]imides **(130)** have been employed by Lete[48] in *N*-acyliminium ion studies. Acylation of tryptamine **(128)** with a cyclic anhydride **(129)** produced the imides **(130a-c)** **(Scheme 31)**.



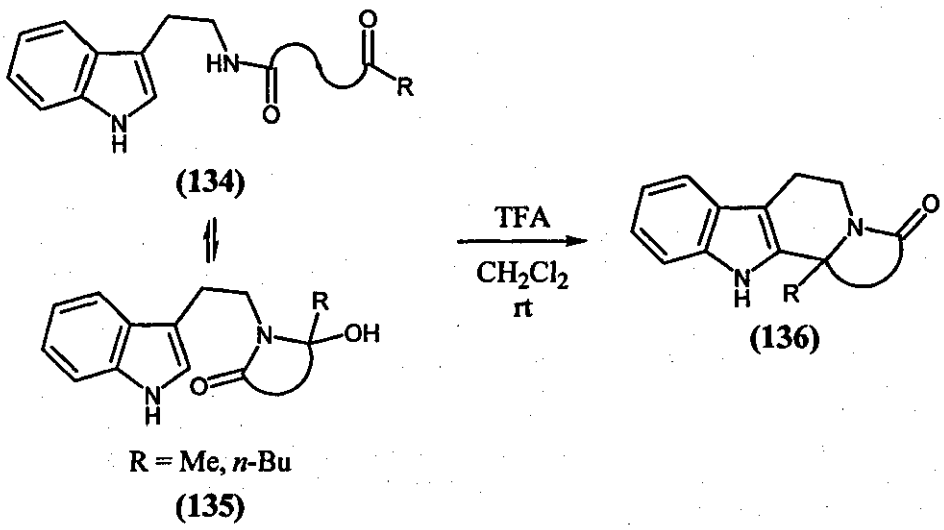
Scheme 31

The imide **(133)** was synthesised by a Mitsunobu reaction[49-51] of **(131)** with phthalimide **(132)** (**Scheme 32**).



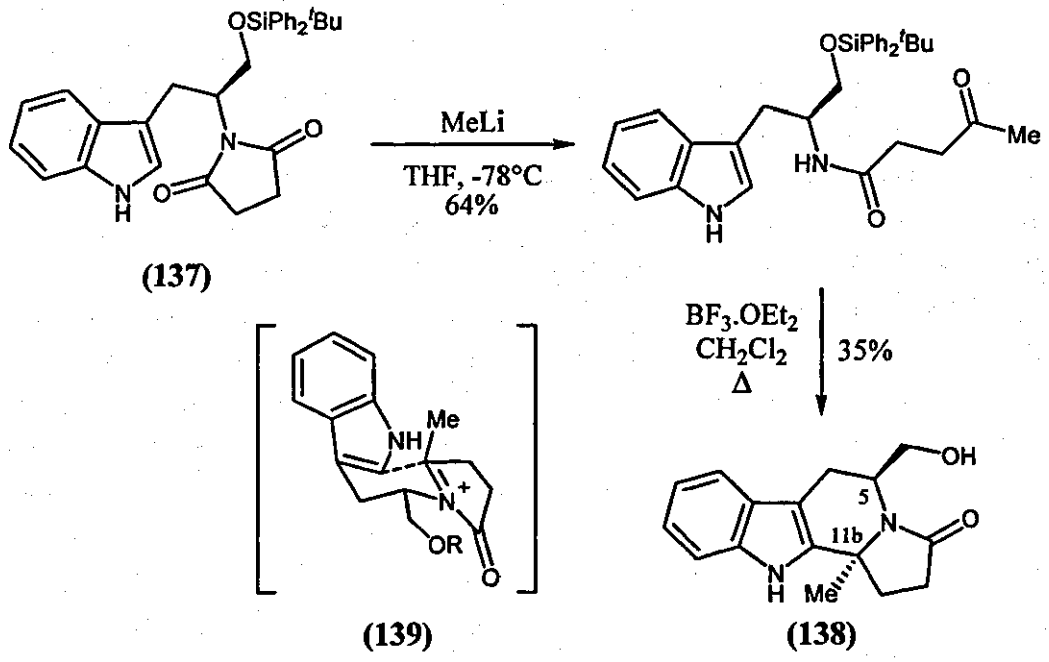
Scheme 32

Nucleophilic addition was observed when **(130a-c)** and **(133)** were subjected to MeLi or *n*-BuLi. The addition afforded the oxo-amide **(134)** or corresponding hydroxylactam **(135)**. The *N*-acyliminium ion precursors **(134)** and **(135)** were treated with trifluoroacetic acid which promoted cyclisation and produced **(136)** (**Scheme 33**).



Scheme 33

In order to achieve an asymmetric synthesis of a fused β-carboline such as **(138)**, the tandem organolithium addition-*N*-acyliminium ion cyclisation was applied to **(137)** (**Scheme 34**).

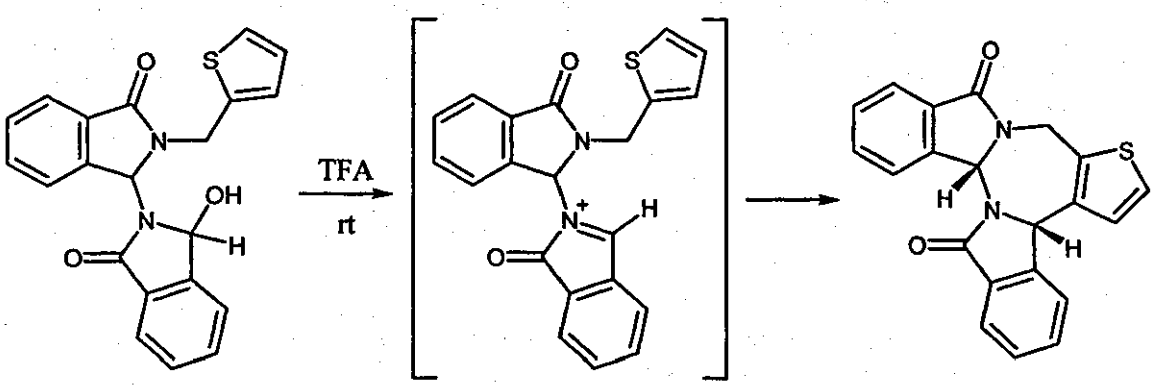


Scheme 34

The intramolecular α-amidoalkylation reaction was stereoselective and **(138)** was obtained as a single 5,11b-*trans* diastereoisomer; the corresponding *cis* diastereoisomer was not detected. The stereochemical outcome is consistent with a chair-like transition state **(139)**.[48]

1.8.3 Thiophene as a π-Nucleophile

A stereoselective approach to the diisoindolothieno[2,4]diazepine **(142)** from the hydroxylactam **(140)** has been reported by Decroix[52] (**Scheme 35**). Treatment of **(140)** with trifluoroacetic acid effected cyclisation *via* the *N*-acyliminium ion **(141)**.

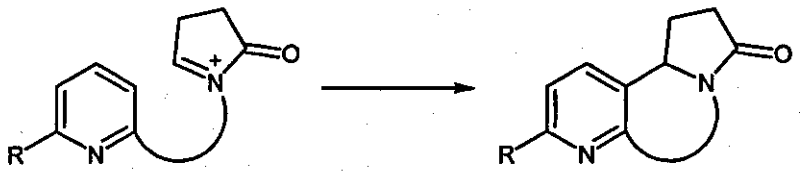


(140) (141) (142)

Scheme 35

1.8.4 Pyridine as a π-Nucleophile

Padwa[53] has reported the intramolecular cationic π-cyclisation of pyridines of type **(143)** with tethered *N*-acyliminium ions **(Figure 14)**.

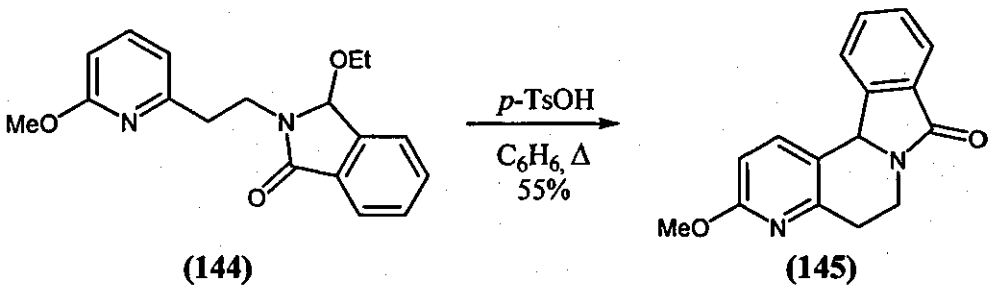


R = Donor Group

(143)

Figure 14

Attempts to cyclise the ethoxylactam **(144)** using a variety of Lewis acids such as $BF_3.OEt_2$, $TiCl_4$ and $SnCl_4$ resulted in the recovery of starting material or decomposition products **(Scheme 36)**. The synthesis of **(145)** was achieved by refluxing **(144)** in benzene with a catalytic amount of *p*-toluenesulfonic acid.

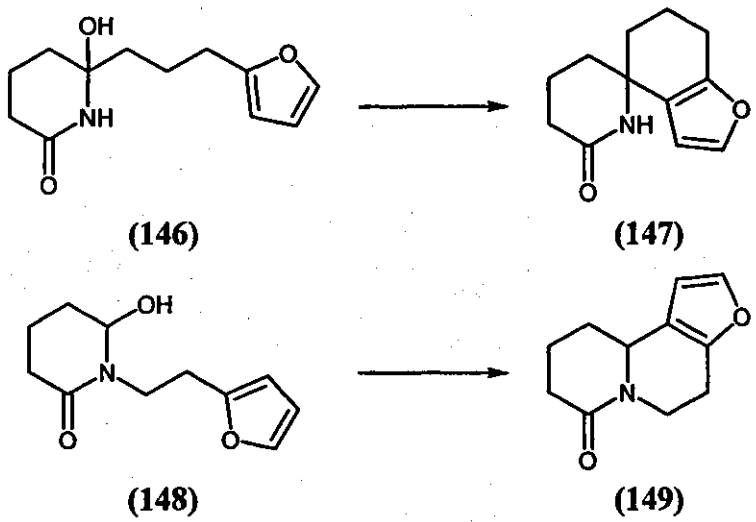


(144) (145)

Scheme 36

1.8.5 Furan as a π-Nucleophile

Furan-terminated *N*-acyliminium ion initiated cyclisations have been extensively investigated by Tanis.[54] Spirocyclic and linearly-fused compounds such as **(147)** and **(149)** were generated from the relevant *N*-acyliminium ion precursor **(146)** or **(148)** (**Figure 15**).

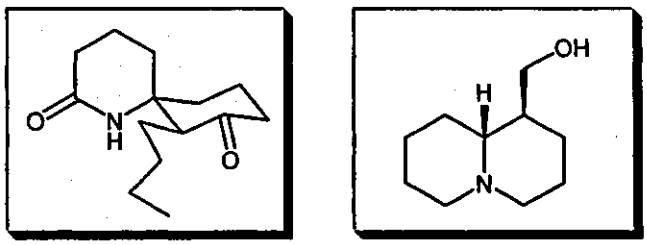


(146) (147)

(148) (149)

Figure 15

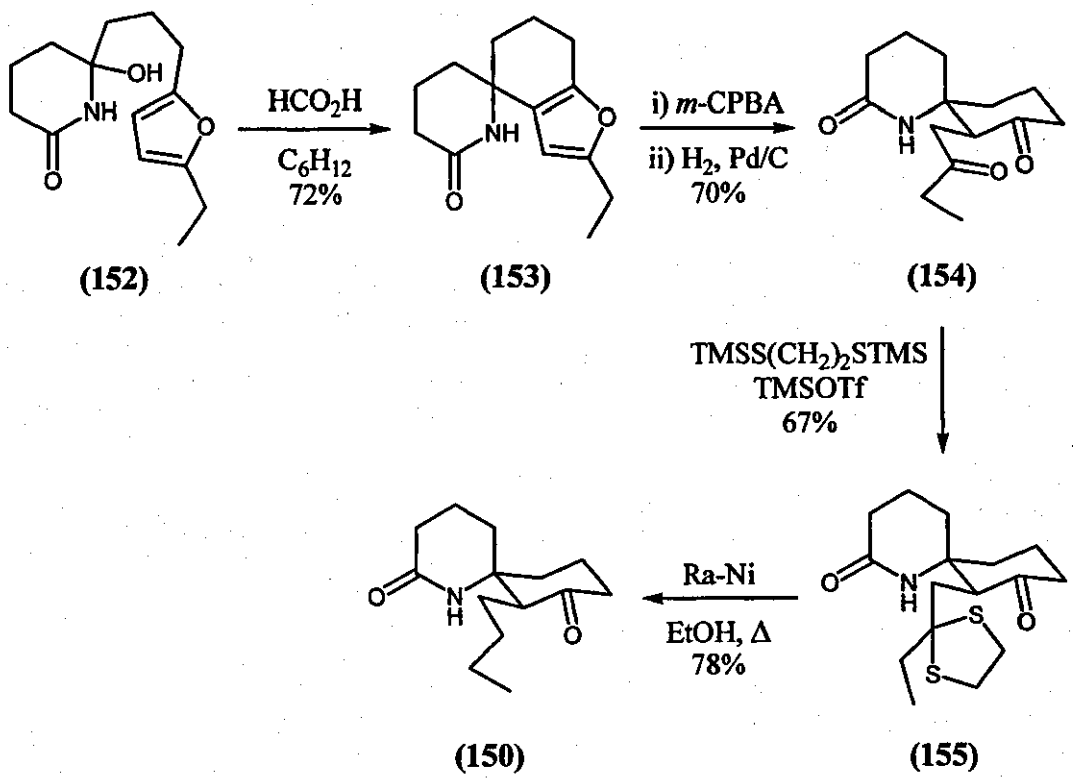
In order to show the validity of this chemistry, the natural products perhydrohistrionicotoxin **(150)** and epilupinine **(151)** were synthesised (**Figure 16**).



(150) (151)

Figure 16

The *N*-acyliminium ion precursor **(152)** used in the synthesis of perhydrohistrionicotoxin **(150)** was treated with formic acid, which facilitated cyclisation to yield the trisubstituted furan **(153)** (**Scheme 37**). Oxidative cleavage (*m*-CPBA) and catalytic hydrogenation afforded **(154)** which was subjected to selective thioketalisation. The target compound **(150)** was isolated after desulfurisation (Raney nickel) of **(155)**.

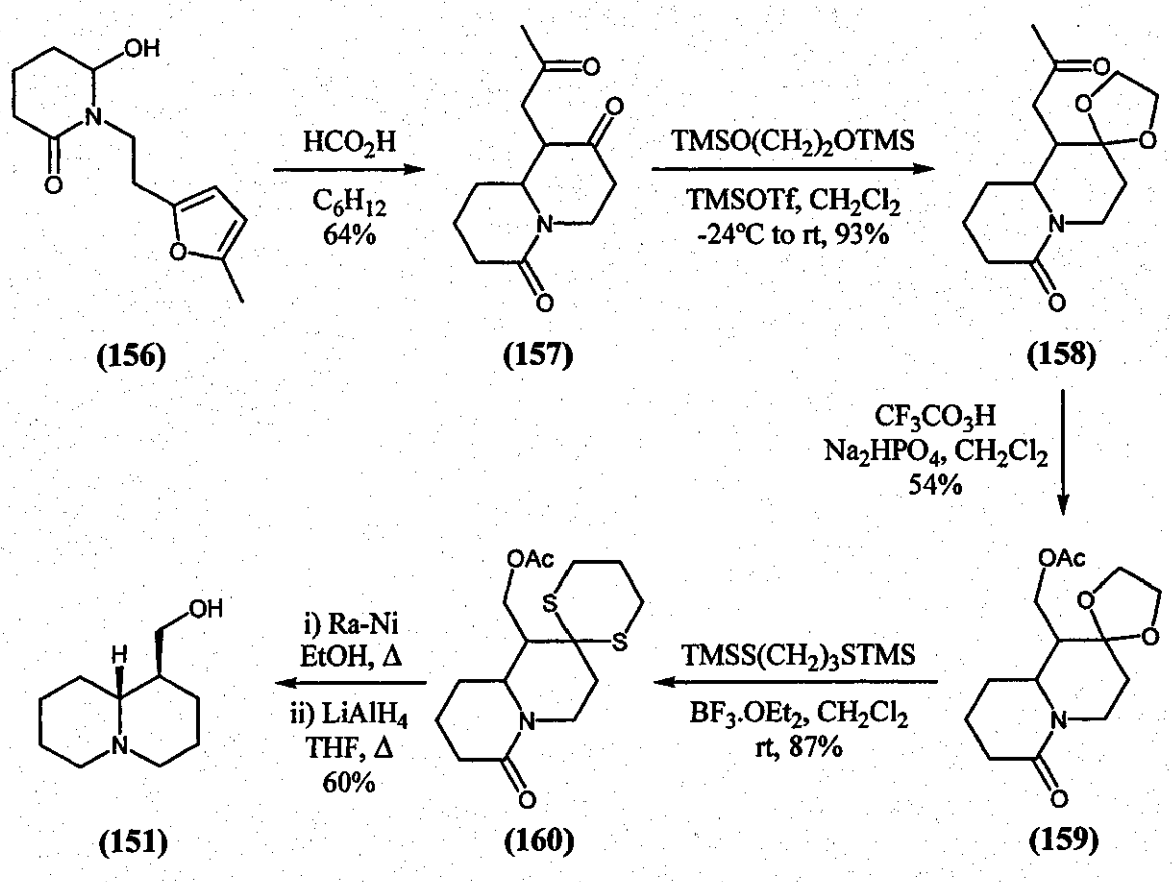


(152) (153) (154)

(150) (155)

Scheme 37

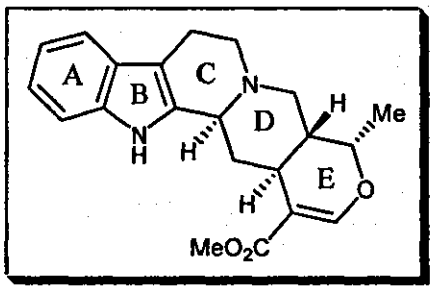
Epilupinine **(151)** was synthesised using the reaction sequence outlined in **Scheme 38.** Cyclisation of compound **(156)** yielded **(157)** and under kinetic ketalisation the ring ketal **(158)** was selectively formed. The latter compound was converted to the acetate **(159)** and subjected to a transketalisation. The target compound **(151)** was obtained from the thioketal **(160)** by a Raney nickel/$LiAlH_4$ reduction sequence.



Scheme 38

1.8.6 Miscellaneous π-Nucleophiles

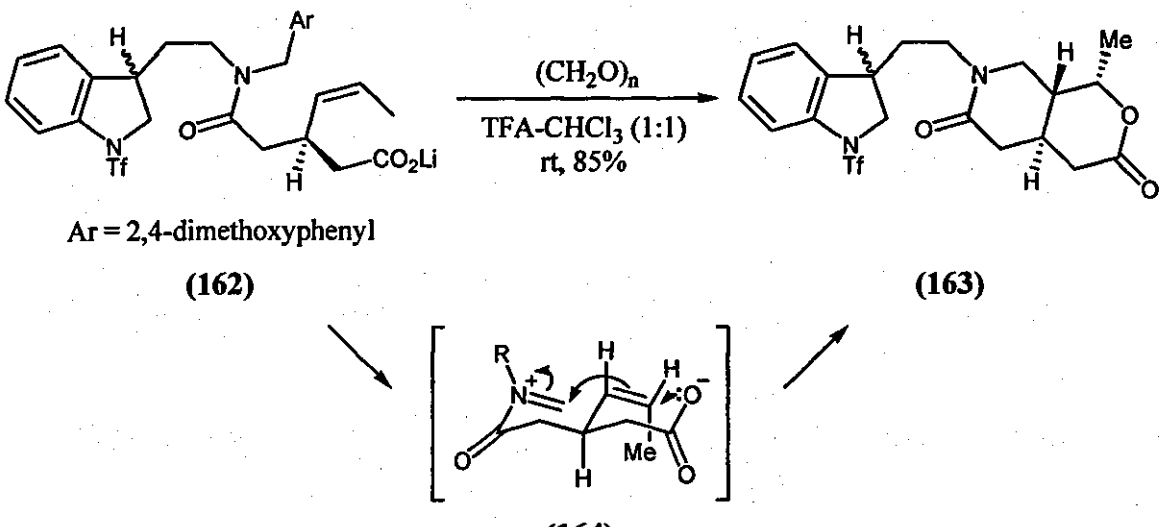
Ajmalicine **(161)**[55-59] **(Figure 17)** is a heteroyohimbine alkaloid isolated from the roots of *Catharanthus roseus*[55] and has a multitude of important pharmacological properties **(Section 1.11).**



(161)

Figure 17

The synthetic approach used by Overman[55] to synthesise ajmalicine **(161)** incorporated a carboxylate-terminated *N*-acyliminium bicyclisation, which assembled the D and E rings in a single step (**Scheme 39**). Treatment of the carboxylate **(162)** with paraformaldehyde in trifluoroacetic acid-chloroform cleaved the 2,4-dimethoxybenzyl protecting group and effected bicyclisation to yield **(163)** *via* the intermediate **(164)**.



Ar = 2,4-dimethoxyphenyl

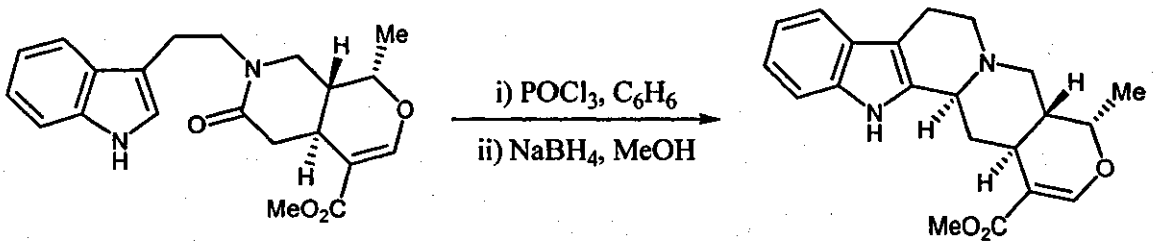
(162) **(163)**

(164)

Scheme 39

The final steps in the synthesis involved a Bischler-Napieralski[4,5] cyclisation of **(165)** followed by the direct reduction of the pentacyclic iminium ion product. This produced

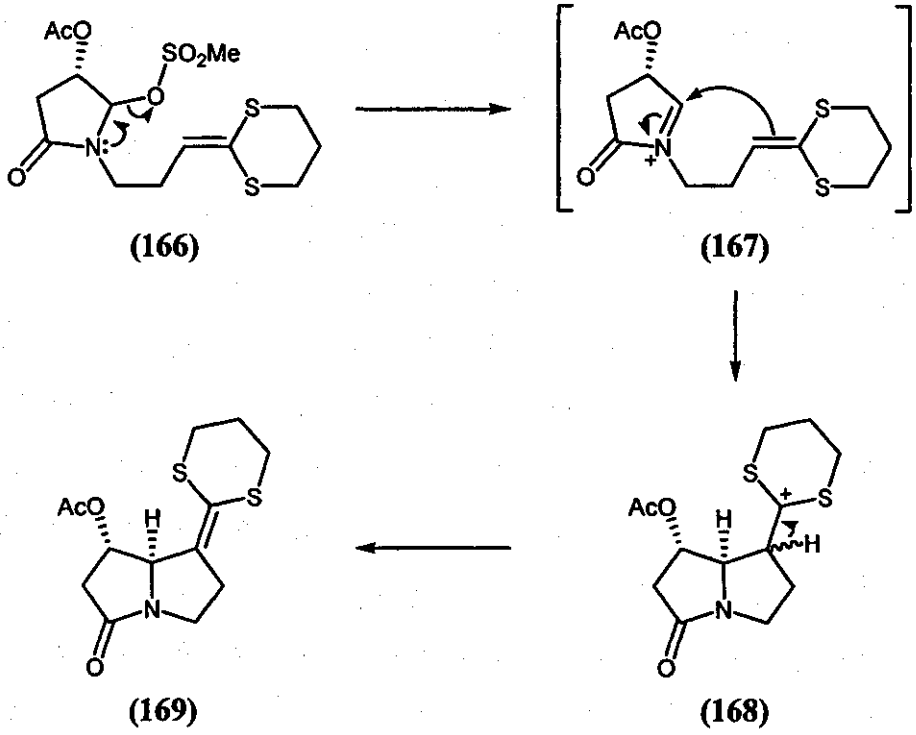
the target compound **(161)** in 11 steps (overall yield of 7%) (**Scheme 40**).



(165) **(161)**

Scheme 40

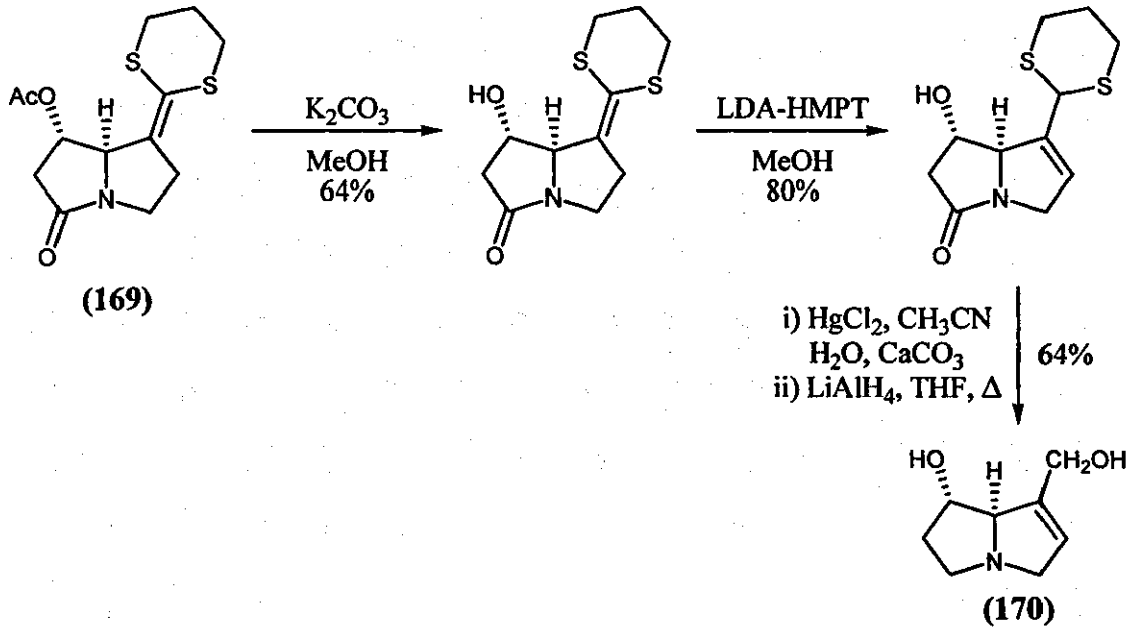
Pyrrolizidine derivatives such as **(169)** have been generated by Chamberlin[60] (**Scheme 41**). The mesylate **(166)** underwent elimination to the *N*-acyliminium ion **(167)** followed by cationic cyclisation and proton loss from **(168)**.



(166) **(167)** **(168)** **(169)**

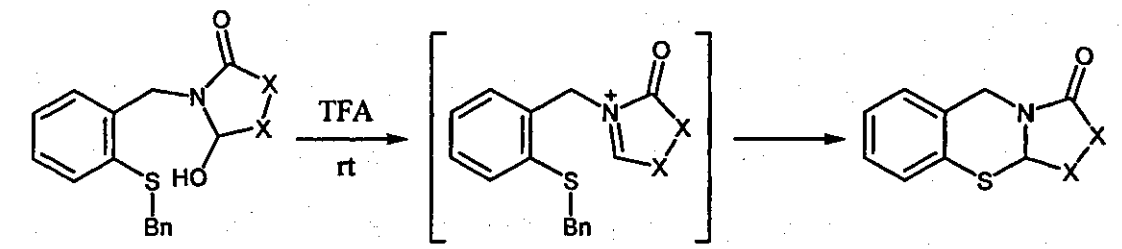
Scheme 41

The natural product, (+)-heliotridine **(170)** was synthesised after acetate cleavage of **(169)** **(Scheme 42)**.



Scheme 42

Daïch[61] has examined the use of sulfur as an intramolecular nucleophile to access pyrrolo[1,3]benzothiazines **(175)** and isoindolo[1,3]benzothiazines **(176)** **(Scheme 43)**.

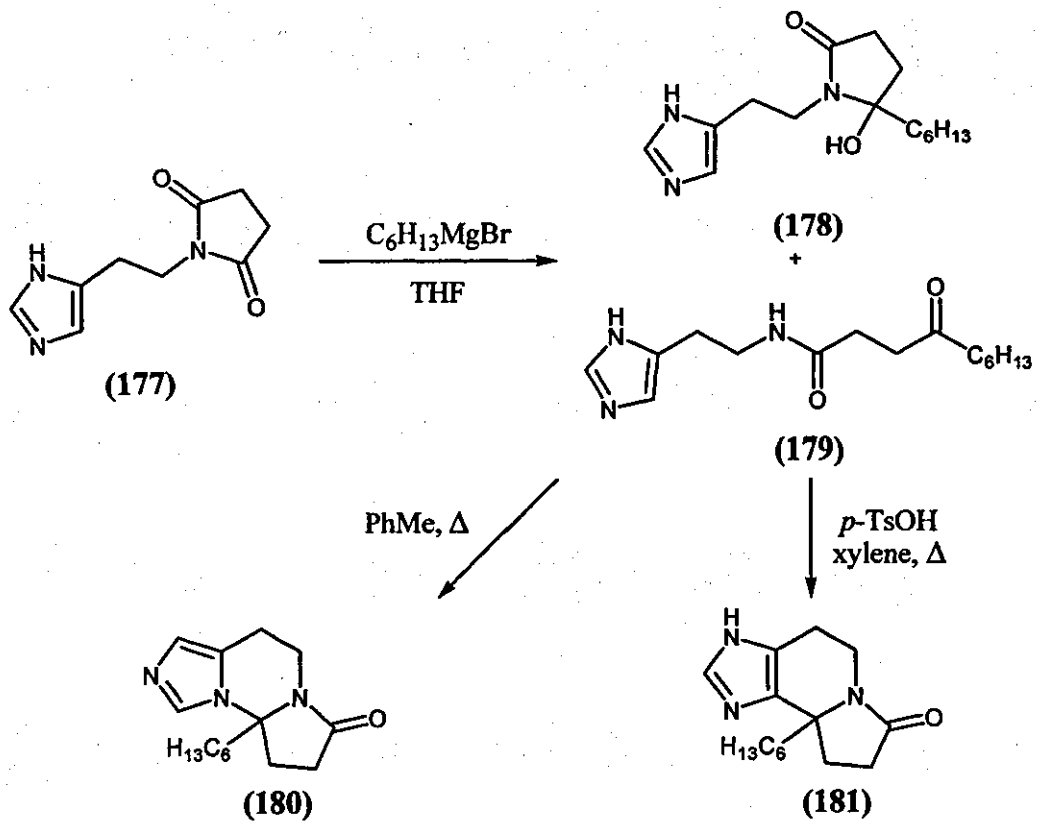


Scheme 43

The compounds **(171)** or **(172)** were subjected to an acidic medium which promoted cyclisation *via* **(173)** or **(174)**, followed by the loss of a stable benzylic carbocation from

the relevant sulfonium ion. The stability of the carbocation and the high nucleophilicity of the sulfur atom would favour the cyclisation process.

Park[62] has investigated the *N*-acyliminium ion cyclisation of imidazole containing compounds bearing both carbon and nitrogen nucleophiles. The imidazole alkaloids (±)-glochidine **(180)** and (±)-glochidicine **(181)** became target compounds for the research. It was determined that by heating with or without an acid catalyst, the cyclisation pathway of **(178)** and **(179)** could be controlled (**Scheme 44**).



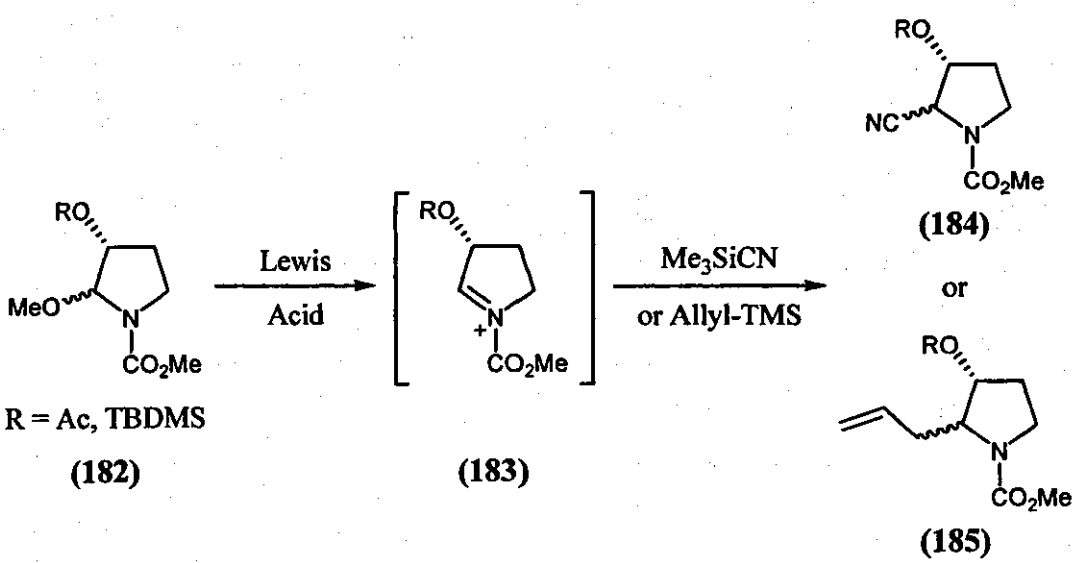
Scheme 44

Grignard addition of hexylmagnesium bromide to **(177)** generated a mixture of **(178)** and **(179)**. Since cyclisation of these compounds would yield the same product, additional purification was not required. The crude mixture was refluxed in toluene and afforded (±)-glochidine **(180)**. Alternatively, cyclisation of the same crude mixture with catalytic *p*-toluenesulfonic acid in refluxing xylene yielded (±)-glochidicine **(181)**.

1.9 Intermolecular Amidoalkylations

Intermolecular amidoalkylations are common in the literature and a few examples of this reaction type have been described in order to illustrate their existence.

The *N*-acyliminium ion **(183)** can be generated from the electrochemically prepared[21-23] α-methoxylated carbamate **(182)** (**Scheme 45**). It has been shown by Wistrand[63] that the product **(184)** can be obtained by reaction of **(183)** with Me_3SiCN. The stereoselectivity of **(184)** was controlled (*cis*:*trans* varying from 86:14 to 42:58) by altering the oxygen protecting group.



Scheme 45

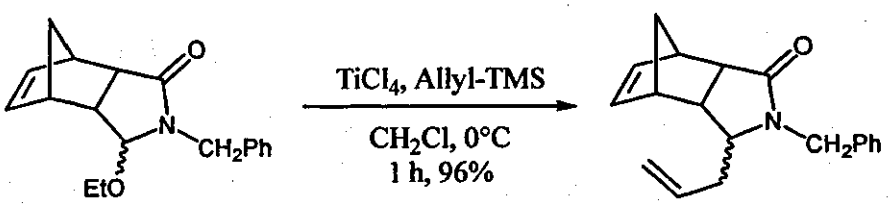
Related work by Wistrand[64] achieved the introduction of a carbon chain to **(183)** by using allyl trimethylsilane in place of Me_3SiCN and compounds such as **(185)** were generated (**Scheme 45**). Stereoselective control was again achieved by altering the oxygen protecting group (**Table 3**).

Protecting Group (R)	Lewis Acid	Temperature (°C)	Ratio (*cis:trans*)
Ac	$BF_3.OEt_2$	20	20:80
Ac	$BF_3.OEt_2$	-78	21:79
TBDMS	$TiCl_4$	20	22:78
TBDMS	$BF_3.OEt_2$	20	69:31
TBDMS	$BF_3.OEt_2$	-78	77:23

Table 3

Only small effects on the stereoselectivity were observed when the temperature and Lewis acid were altered.

Koizumi[65] has investigated the alkylation of the ethoxylactam **(186)** (**Scheme 46**). The (±)-allylated lactam **(187)** was obtained from treatment of **(186)** with $TiCl_4$ in conjunction with allyl trimethylsilane. It was found that alternative Lewis acids such as $BF_3.OEt_2$ and $SnCl_4$ were less effective.



(186) **(187)**

Scheme 46

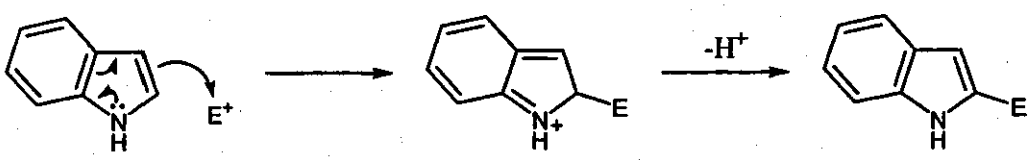
1.10 The Indole Moiety

A large proportion of the current work in the Allin research group incorporates the indole moiety in intramolecular π-nucleophile amidoalkylations. This section provides an insight into specific aspects of indole.

1.10.1 Electrophilic Substitution of Indole

As an electron-rich heterocycle, indole readily undergoes electrophilic substitution and reacts preferentially at the C-3 position with almost all reagents. Halogenation, nitration, sulfonation, Friedel-Crafts acylation and alkylation all occur cleanly at this position.[66,67]

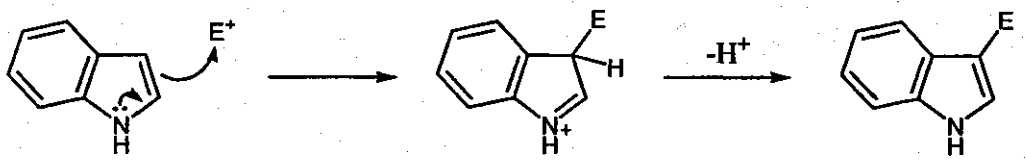
Electrophilic substitution at C-2 (**Figure 18**) results in disruption of the benzenoid ring as in **(188)**. This is therefore a high-energy intermediate and the pathway is slower because the first step is rate determining.



(188)

Figure 18

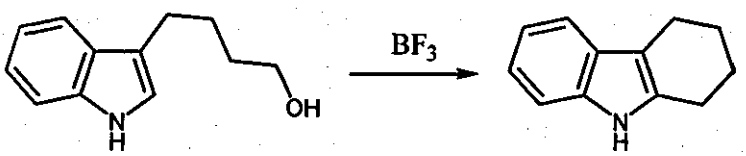
In contrast, the C-3 selectivity shown in **Figure 19** is in accordance with electrophilic substitution occurring at the site of highest electron density **(189)** and does not disturb the aromaticity of the benzene ring. In essence, indole tends to react like an enamine towards electrophiles with substitution occurring at the C-3 position, although substitution occurs at C-2 when C-3 is blocked.[66]



(189)

Figure 19

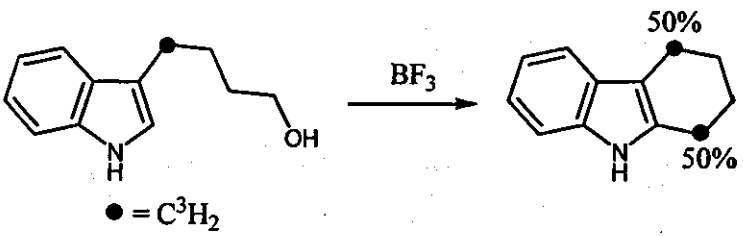
A mechanism for the formation of 2,3-disubstituted indoles such as **(191)** from **(190)** (**Scheme 47**) has been proposed whereby aromatic stability is not destroyed. A labelling study has added credibility to this hypothesis.[66]



(190) **(191)**

Scheme 47

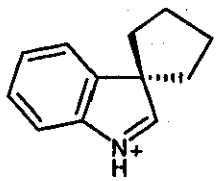
If compound **(190)** is labelled with tritium next to the ring generating **(192)**, the reaction shown in **Scheme 48** produces **(193)** with an equal distribution of the label.



(192) **(193)**

Scheme 48

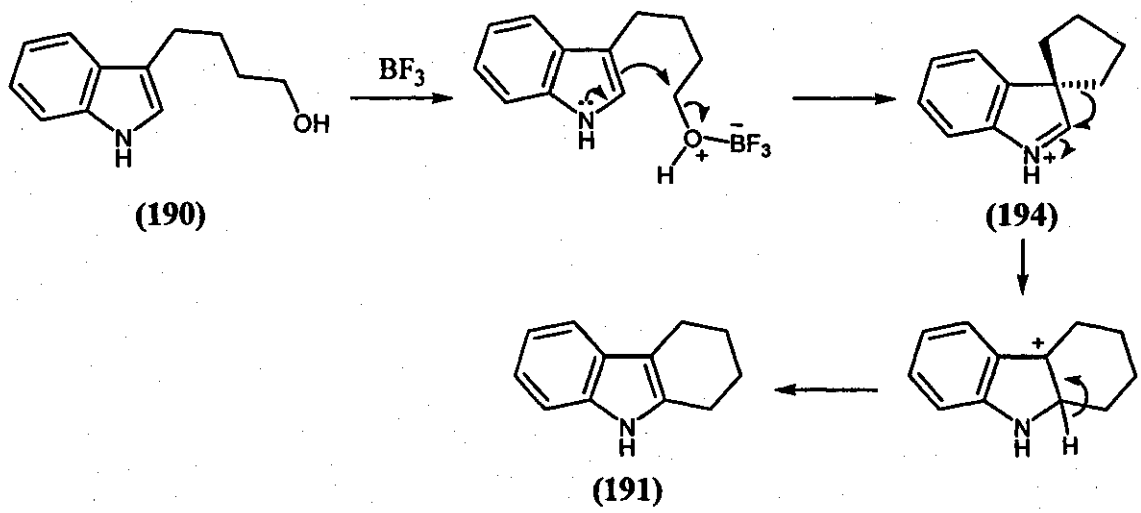
To give this result the reaction must have a symmetrical intermediate and the obvious candidate is **(194)** (**Figure 20**).



(194)

Figure 20

The intermediate **(194)** has the five membered ring at right angles to the indole with either CH_2 group having an equal opportunity to migrate. A feasible mechanism for the conversion of **(190)** to **(191)** is shown in **Scheme 49.**

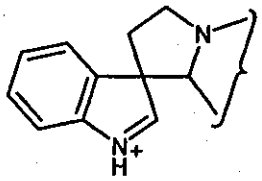


Scheme 49

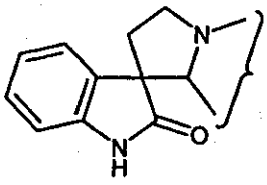
The migration is a pinacol-like rearrangement and it is now thought that most substitutions at C-2 go by this migration route although some go by direct attack with disruption of the benzene ring.[66]

1.10.2 Indole Alkaloid Systems from a Spiro Intermediate

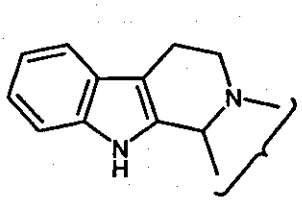
Three major classes of indole alkaloids could arise from the spiro intermediate **(195)**: **(196)** by hydration and oxidation, **(197)** by rearrangement and **(198)** by nucleophilic attack on C-2 of the indole system (**Figure 21**).[68]



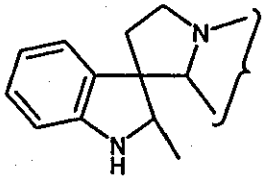
(195)



(196)



(197)

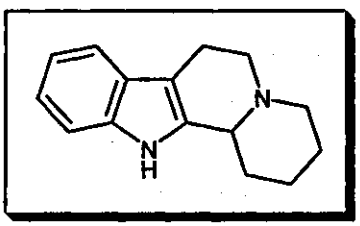


(198)

Figure 21

1.11 The Indolo[2,3-*a*]quinolizidine Ring System

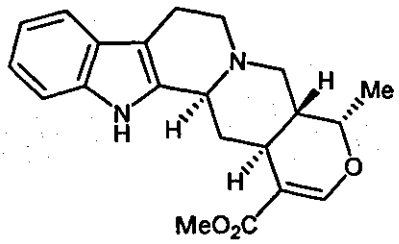
The indolo[2,3-*a*]quinolizidine ring system **(199)** (**Figure 22**) is found in the carbon skeleton of a plethora of indole alkaloids and such compounds have emerged as viable targets during the development of novel methodology in our research group.



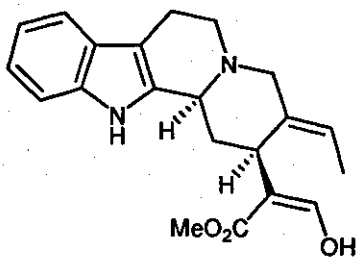
(199)

Figure 22

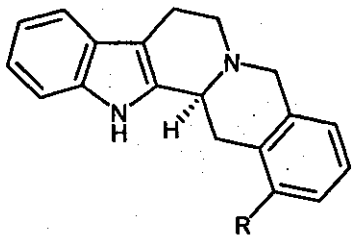
Indole alkaloids that possess the indolo[2,3-*a*]quinolizidine ring system **(199)** include ajmalicine **(161)**,[55-59] geissoschizine **(200)**,[3,69-77] dihydrogambirtannine **(201)**,[78-81] demethoxycarbonyldihydrogambirtannine **(202)**,[81] tangutorine **(203)**[82-86] and deplancheine **(204)**[87-95] (**Figure 23**).



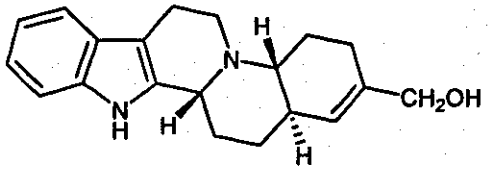
(161)



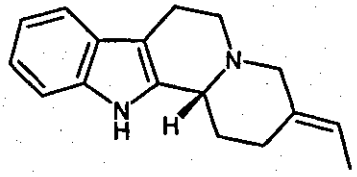
(200)



(201) R = CO_2Me
(202) R = H



(203)



(204)

Figure 23

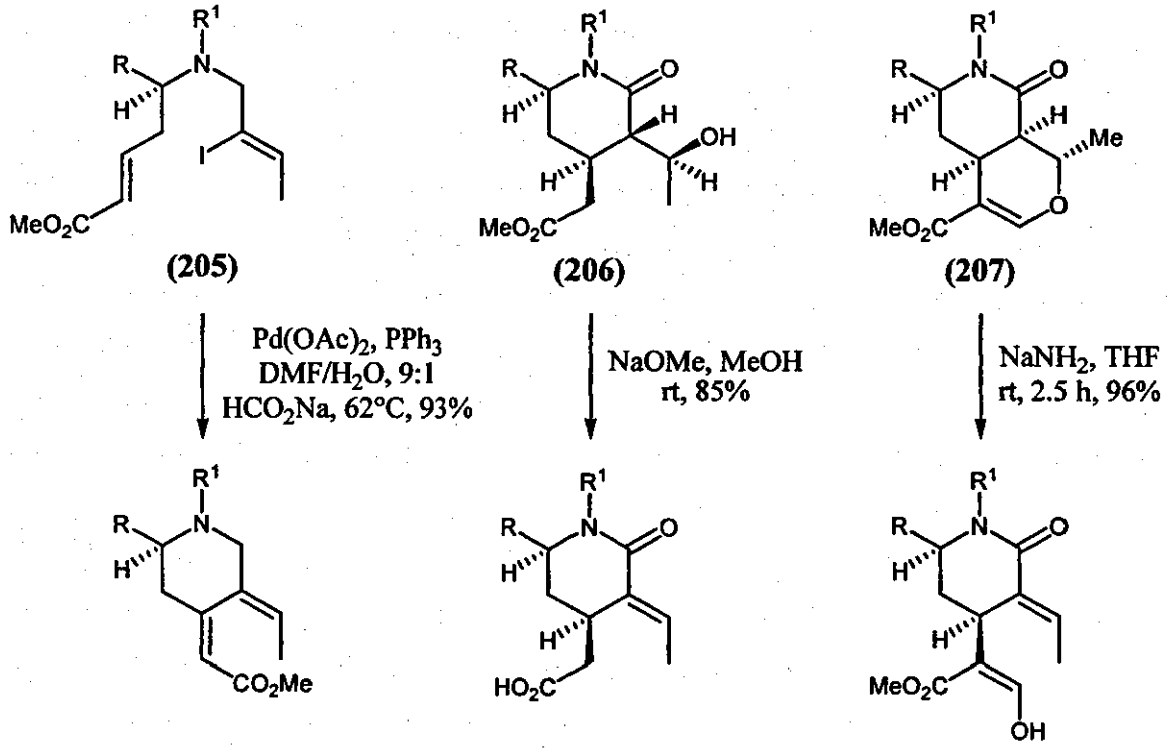
These natural products have been the subject of extensive chemical and synthetic investigations due to their important and interesting structural, physiological and biological properties.

Ajmalicine (also called raubasine or δ-yohimbine) **(161)** belongs to the heteroyohimbine family of indole alkaloids. It is a potent peripheral and central vasodilating agent, reduces platelet aggregation in patients at risk due to complications of atherosclerosis, can increase muscle calibre for short periods and has been prescribed for the treatment of Raynaud's disease.[55-58]

Due to the structural complexity and the scarce availability from natural sources of geissoschizine **(200)**, there have been numerous syntheses of this natural product. The first total synthesis of (±)-geissoschizine was by van Tamelen[69] and an enantioselective approach has been achieved by Overman,[70] Cook[71] and Martin.[72]

An important consideration in the total synthesis of geissoschizine **(200)** is the stereoselective introduction of the (*E*)-ethylidene unit.[73] This matter has been successfully

achieved by metal catalysed cyclisations of geometrically defined alkenyl iodides **(205)**[71] and the stereoselective base-induced β-elimination of β-hydroxy carbonyls **(206)**[72] or hydropyrans **(207)**[74] **(Scheme 50)**.



Scheme 50

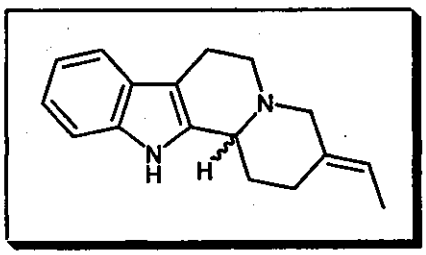
Dihydrogambirtannine **(201)** is an alkaloid initially extracted from the leaves and stems of Rubiacea *Uncaria gambier*, a tree growing in Southeast Asia.[78-81] The structurally related demethoxycarbonyldihydrogambirtannine **(202)** was isolated from the leaves of *Ochrosia lifuana* and *Ochrosia miana* and represents the major alkaloid of the fruits of *Strychnos usambarensis*, a plant found in Africa. Consumption of this fruit has been blamed for outbreaks of poisoning.[81]

The initial isolation of tangutorine **(203)** from the leaves of *Nitraria tangutorum* was reported by Che.[82] To date, this compound is the only known natural product containing the benz[*f*]indolo[2,3-*a*]quinolizidine unit.[84-86]

1.12 Synthetic Target: (*R*)-(+)-Deplancheine

The indole alkaloid, (*R*)-(+)-deplancheine **(204)** became the synthetic target during the course of the research.

(*R*)-(+)-Deplancheine **(204)** was isolated from the New Caledonian plant *Alstonia deplanchei*[87] and initially assigned the *S* configuration (based on an analogy with the majority of indole alkaloids).[88] After its structural elucidation a number of total syntheses were reported.[89-93] Its absolute configuration was never questioned as these synthetic approaches led to (±)-deplancheine **(208) (Figure 24)**.

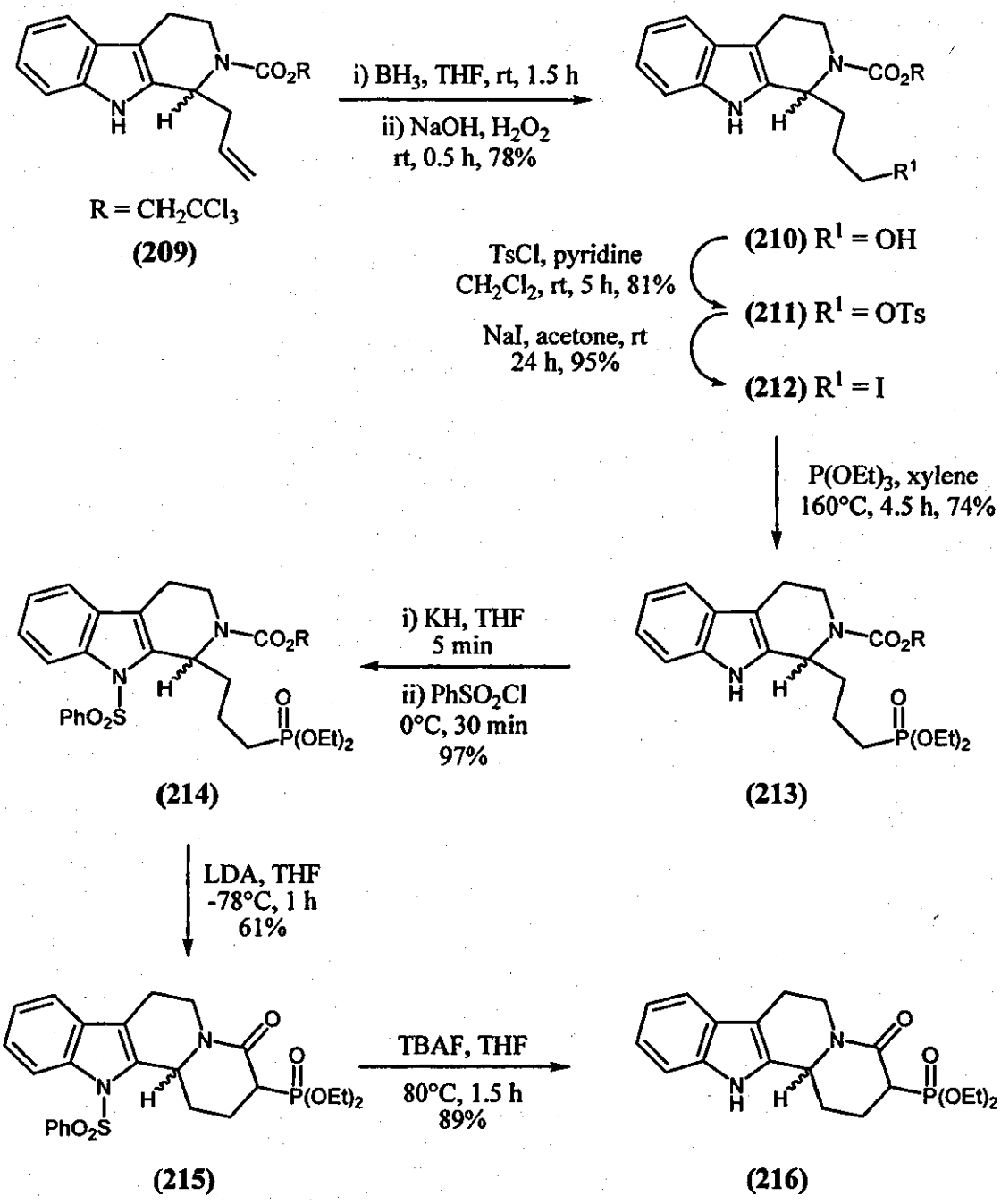


(208)

Figure 24

During the asymmetric synthesis of (*S*)-(-)-deplancheine by Meyers,[88] it was concluded that the original assignment was incorrect and that natural deplancheine possesses the *R* configuration.

The most recent synthesis of (±)-deplancheine **(208) (Figure 24)** (overall yield of 11%) was by Ohsawa.[95] The compound **(209)** was converted to **(210)** and the resultant terminal hydroxyl group was subjected to a sequence of transformations (passing through the tosyloxy **(211)** and iodo **(212)**) to produce the diethylphosphoryl compound **(213)**. Starting material was recovered after direct attempts to transform **(211)** to **(213)** **(Scheme 51)**.

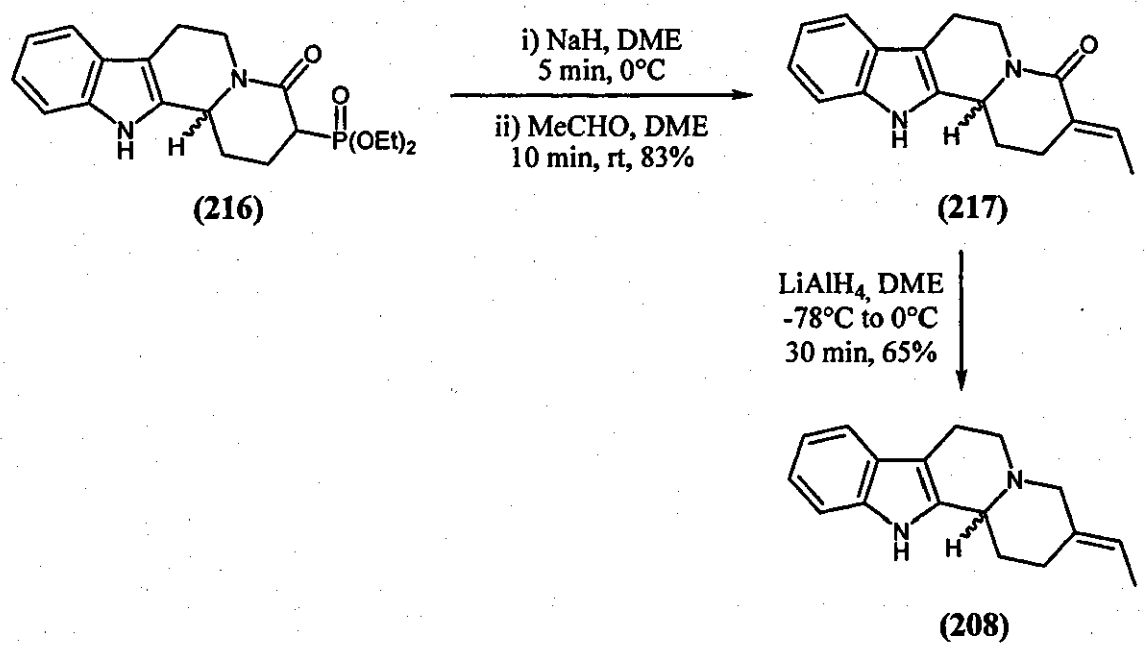


Scheme 51

Attempts to synthesise **(216)** by ring closure of **(213)** with lithium diisopropylamide (LDA) were unsuccessful and starting material was recovered. It was proposed that the inertness was due to the free indole NH. The intermediate **(213)** was converted to **(214)** using potassium hydride and phenylsulfonyl chloride. Treatment of the latter compound

with LDA produced **(215)** which was deprotected using a method developed by Yasuhara and Sakamoto.[96]

A two step literature procedure developed by Danieli[91] was used to complete the synthesis of (±)-deplancheine **(208)**. The compound **(216)** was converted to **(217)** and the final step was the selective reduction of the lactam carbonyl group (**Scheme 52**).



(216) **(217)** **(208)**

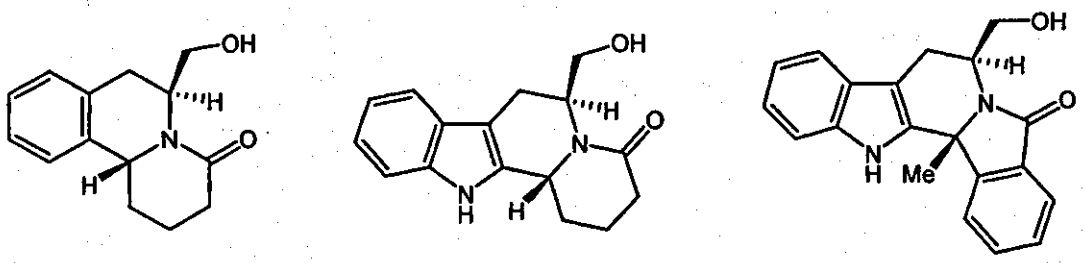
Scheme 52

Chapter 2

Results and Discussion

2.1 Preliminary Investigations Using *N*-Acyliminium Ions

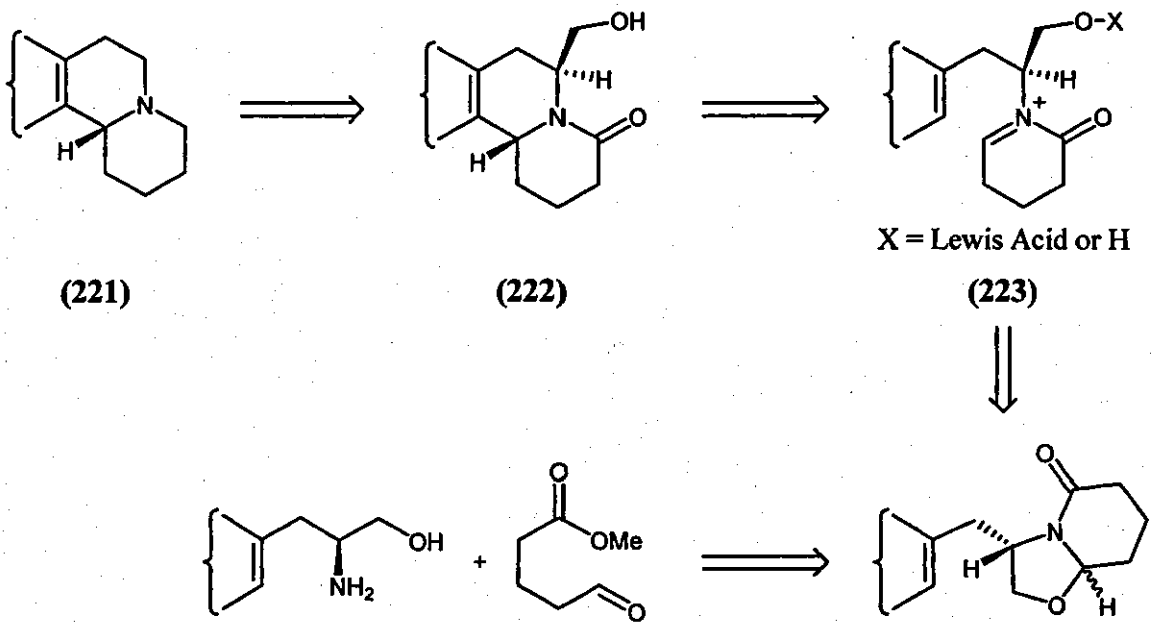
It was proposed by Allin that a suitably substituted bicyclic or tricyclic lactam could act as a precursor in an asymmetric approach towards isoquinoline and indole alkaloid systems such as **(218)**, **(219)** and **(220)** **(Figure 25)**.



(218) **(219)** **(220)**

Figure 25

2.1.1 Retrosynthetic Analysis



(221) **(222)** **(223)**

Scheme 53

Isoquinoline and indole alkaloids share the common feature of a substituted piperidine unit with a chiral centre. In both instances, one of the substituents at the chiral centre is an aromatic nucleus such as benzene or indole. An approach to access the model system **(221)** is outlined in **Scheme 53** and has become the prominent method used in this research. The key step is the asymmetric cyclisation of the aromatic nucleus *via* the *N*-acyliminium species **(223)**. Conversion of **(222)** to **(221)** could be achieved by an oxidation and decarbonylation sequence to remove the hydroxymethyl substituent (auxiliary) followed by lactam reduction.

An alternative method to that shown in **Scheme 53** has been used by Allin[97-99] to access similar systems to **(222)** using *N*-acyliminium species and relates to work by Speckamp[27] **(Section 1.5, Scheme 12)**. An example of this approach is shown **Section 2.1.3, Scheme 56.**

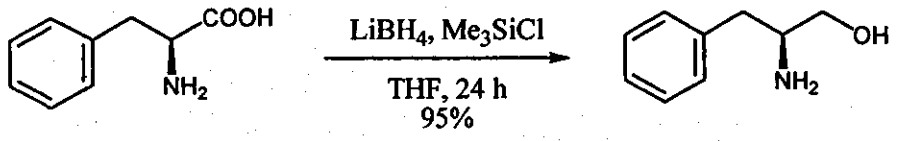
2.1.2 Generation of Amino Alcohols from Amino Acids

There are a number of methods available for the reduction of amino acids to amino alcohols. Reagents used to effect this transformation include $LiAlH_4$,[100-102] a mixture of $NaBH_4$ and H_2SO_4[103,104] or $NaBH_4$ and I_2.[105,106]

Giannis[107] has developed an effective reductive procedure for a range of amino acids using lithium borohydride and chlorotrimethylsilane in dry THF. Reduction of L-phenylalanine **(224)** using this approach generated (2*S*)-2-amino-3-phenylpropan-1-ol **(71) (Scheme 54)**. It was evident from the ^1H NMR spectrum of the crude reaction mixture that clean conversion of **(224)** to **(71)** had occurred.

The compound **(71)** was generated in near quantitative yield after purification by recrystallisation. Initial reactions were performed on 1 g of **(224)** and successfully scaled-up to 5 g without significant loss in yield. It was proposed[107] that a borane-THF complex

is produced *in situ* which acts as the reducing agent (**Scheme 54**). Care was necessary when conducting the reduction due to the rapid formation of the volatile silane, Me_3SiH.

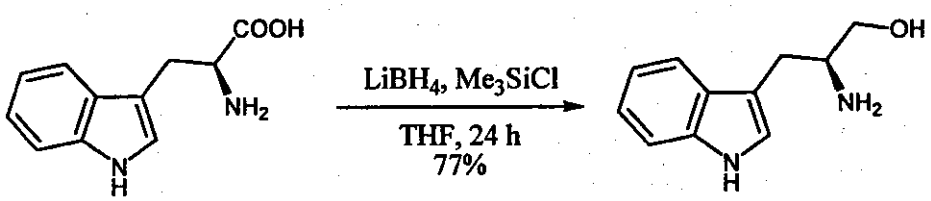


(224) **(71)**

$$LiBH_4 + Me_3SiCl \longrightarrow LiCl + Me_3SiH + BH_3.THF$$

Scheme 54

An analogous reaction was used to synthesise the amino alcohol **(226)** from L-tryptophan **(225)** (**Scheme 55**). The product (2*S*)-2-amino-3-(1*H*-indol-3-yl)propan-1-ol **(226)** was obtained in high yields following purification. Initial reactions were performed on 1 g of **(225)** and successfully scaled-up to 5 g without significant loss in yield. It was evident from the ^1H NMR spectrum of the crude reaction mixture that clean conversion of **(225)** to **(226)** had occurred. Care was required when the reduction was conducted due to the rapid formation of the volatile silane, Me_3SiH.



(225) **(226)**

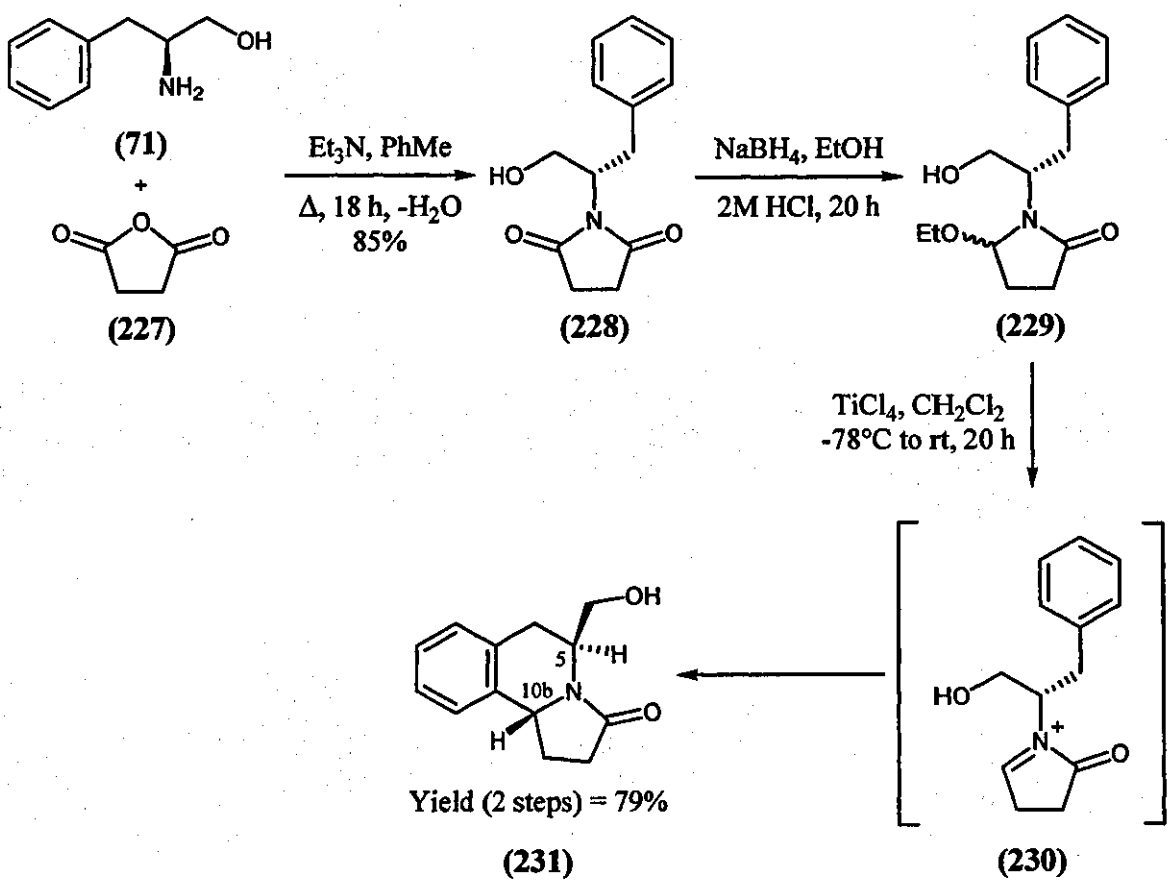
Scheme 55

In contrast to **(71)** the amino alcohol **(226)** was a foam which could not be induced to crystallise. Attempts to purify the latter by flash column chromatography on silica were successful when a polar solvent system was employed.

2.1.3 Intramolecular Cyclisation with Benzene as a π-Nucleophile

A short reaction sequence (**Scheme 56**) conducted in tandem with a colleague[98] was used to generate the cyclised product **(231)** and acted as an experimental introduction to the concept of *N*-acyliminium ion cyclisations.

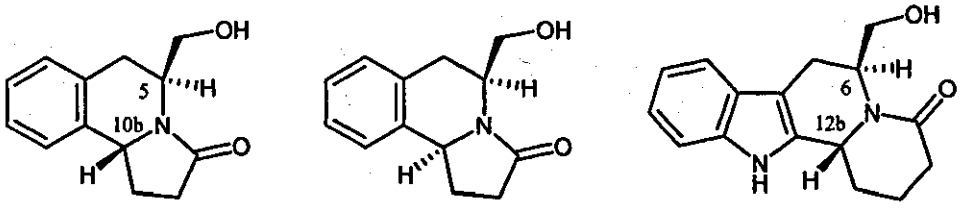
Condensation of the amino alcohol **(71)** and succinic anhydride **(227)** furnished **(228)** which on addition of a hydride source in ethanol produced the ethoxylactam **(229)**. Treatment of **(229)** with $TiCl_4$ generated the product **(231)** as a single diastereoisomer. Presumably, cyclisation to yield **(231)** proceeded *via* the *N*-acyliminium ion intermediate **(230)**.



Scheme 56

An NOE study was undertaken to determine the relative stereochemistry of the product **(231)**. The absence of an NOE between the protons positioned at C-5 and C-10b suggested that the relative stereochemistry is as shown in **Scheme 56**. The proposed stereochemistry can be criticised in respect that the absence of an NOE is inconclusive. A negative NOE is only valid if paired with a positive NOE in a comparative study. The first example of such a study is shown in **Section 2.2**.

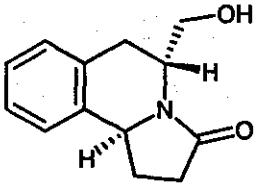
The stereochemical ambiguity could be overcome by epimerising the chiral centre of **(231)** at C-10b (**Figure 26**). The epimerised product **(232)** could then be used in a comparative NOE study. This proposal is feasible as analogous compounds such as **(219)** can be readily epimerised at C-12b with retention of stereochemistry at C-6 (**Section 2.7, Scheme 83**).



(231) **(232)** **(219)**

Figure 26

Based on work shown in **Section 2.7, Scheme 84**, the use of D-phenylalaninol **(73)** as a starting material would generate **(233)** (**Figure 27**). An absence of an NOE between the protons positioned at C-5 and C-10b would also be observed for **(233)** and not contribute to the stereochemical determination of **(231)**.

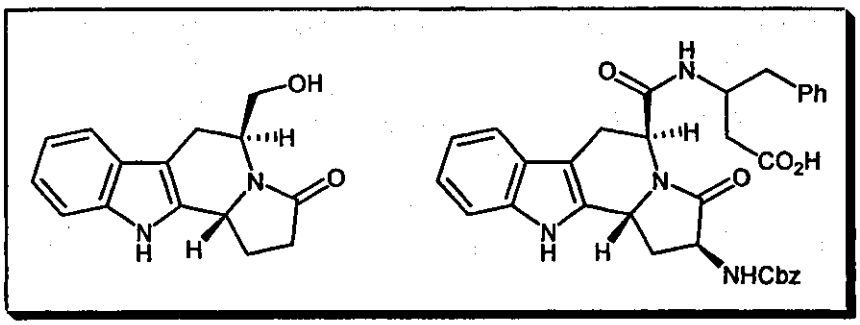


(233)

Figure 27

2.1.4 Intramolecular Cyclisation with Indole as a π-Nucleophile

Similar cyclisations to those outlined in **Scheme 56** have been successfully conducted by a colleague[99] where the intramolecular nucleophile is indole rather than benzene. This approach has enabled the synthesis of indolizino[8,7-*b*]indole derivatives such as **(234)** (**Figure 28**).



(234) **(235)**

Figure 28

Functionalised templates such as **(235)** display high binding affinity and selectivity for cholecystokinin - type 1 (CCK_1) receptors.[108,109]

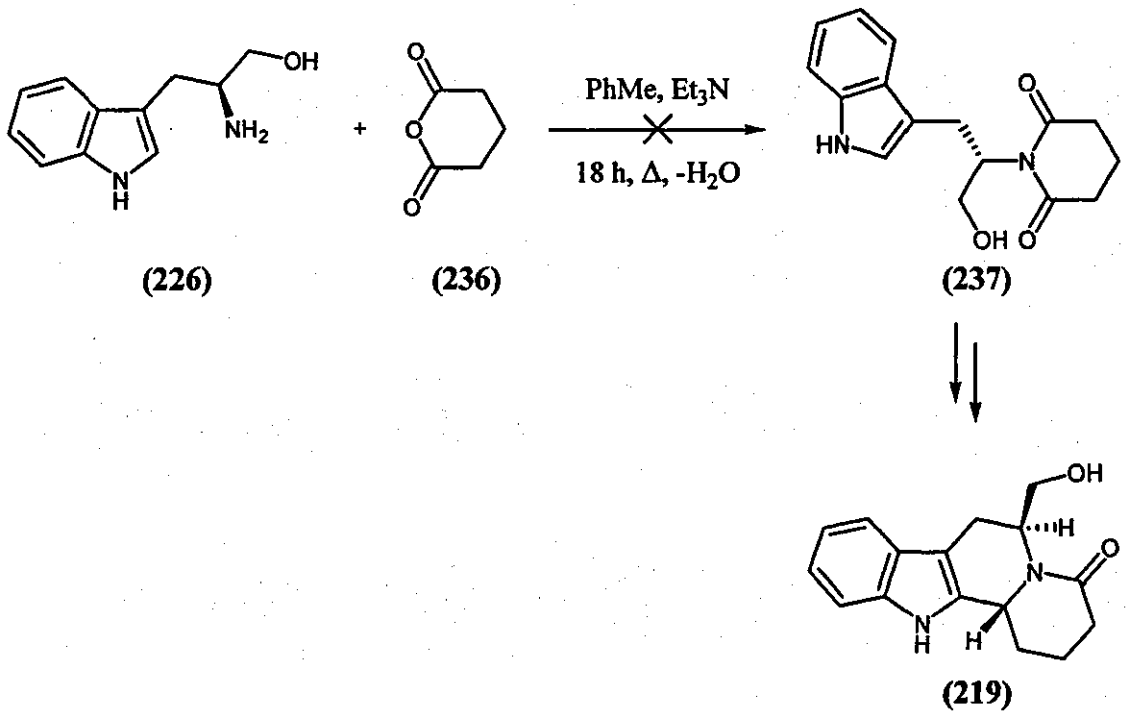
The CCK and gastrin families of peptides act as hormones and neuropeptides on central and peripheral CCK receptors to mediate secretion and motility in the gastrointestinal tract in the physiological response to a meal. CCK and its receptors are widely distributed in the central nervous system (CNS) and contribute to the regulation of satiety, anxiety, analgesia and dopamine-mediated behaviour. In humans, CCK occurs as COOH-terminal amidated 58- and 8-amino acid major forms processed from a 115-amino acid preprohormone.[108]

Although the wide distribution, myriad number of functions and reported pharmacological heterogeneity of CCK receptors would suggest a large number of

receptor sub-types, the application of modern molecular biological techniques has identified two CCK receptors, CCK_1 and CCK_2 that mediate the actions of CCK and gastrin; gastrin receptors have been found to be identical to CCK_2 receptors. CCK_1 receptors are predominantly found in the gastrointestinal system and select areas of the CNS whereas CCK_2 receptors are found predominantly in the CNS and select areas of the gastrointestinal system.[108-110]

It was envisaged that the chemistry used to synthesise the cyclised products **(231)** and **(234)** could also be applied to the synthesis of the indolo[2,3-*a*]quinolizidine derivative **(219)** (**Scheme 57**) prior to removal of the hydroxymethyl (auxiliary) and lactam reduction.

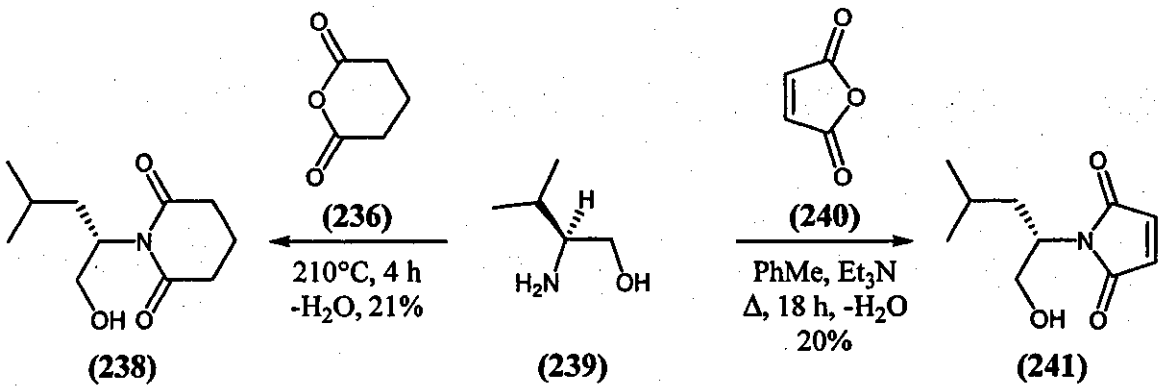
Condensation of (2*S*)-2-amino-3-(1*H*-indol-3-yl)propan-1-ol **(226)** with glutaric anhydride **(236)** produced an extremely complex ^{1}H NMR spectrum of the crude reaction mixture. There was no evidence of the expected product **(237)** or starting material.



(226) **(236)** **(237)** **(219)**

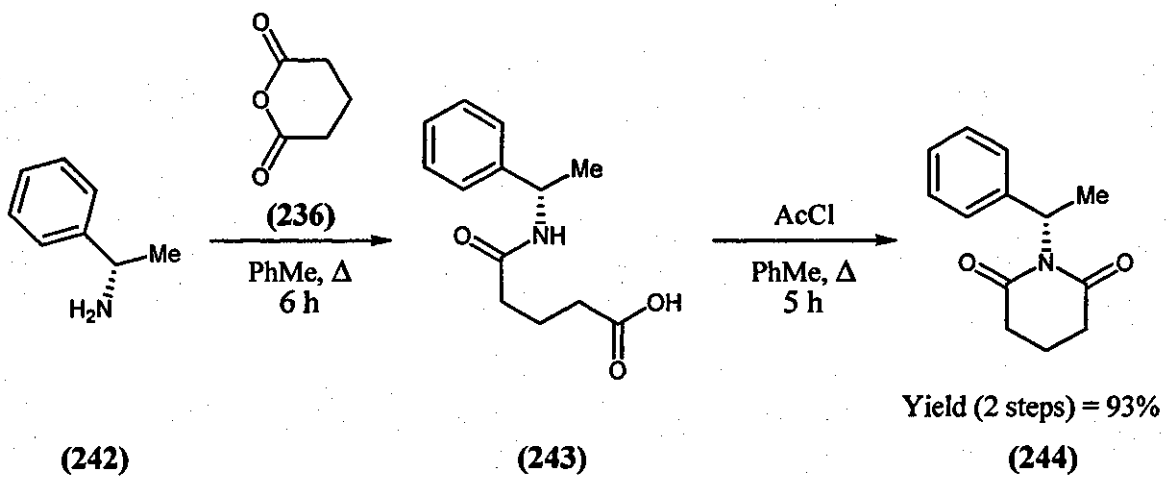
Scheme 57

Meyers[28] has reported similar findings for the condensation of (*S*)-valinol **(239)** with glutaric **(236)** or maleic anhydride **(240)** by two alternative methods (**Scheme 58**). The use of either anhydride gave a poor yield of the glutarimide **(238)** (21%) or maleimide **(241)** (20%) and it was reported that both reactions were accompanied with extensive polymerisation.



Scheme 58

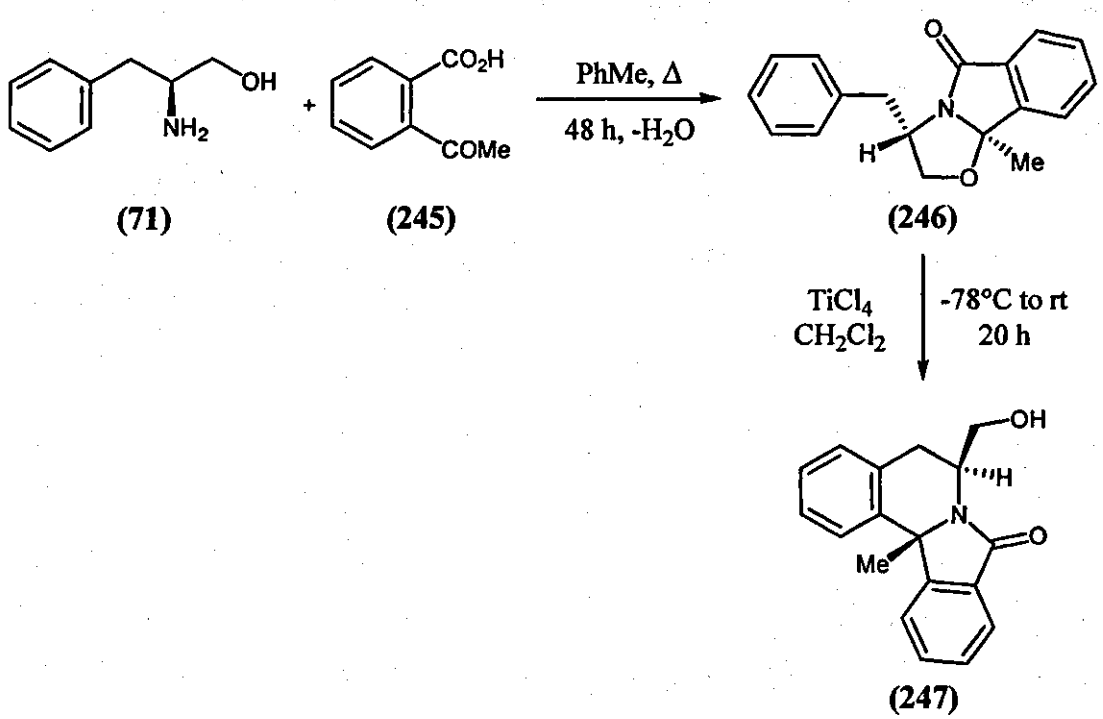
Interestingly, Naito[111] observed the formation of the carboxylic acid **(243)** when **(242)** was refluxed with **(236)**. The desired chiral imide **(244)** was generated by refluxing **(243)** with acetyl chloride (**Scheme 59**). This recently obtained literature could instigate further investigations for the synthetic approach outlined in **Scheme 57**.



Scheme 59

2.2 Synthesis and Cyclisation of Tricyclic Lactams

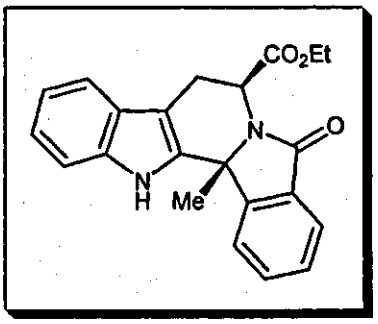
It has been shown[112] that the tricyclic lactam **(246)** can be readily synthesised from condensation of (2*S*)-2-amino-3-phenylpropan-1-ol **(71)** with 2-acetylbenzoic acid **(245)** (**Scheme 60**). Activation of the lactam **(246)** with $TiCl_4$ generated the cyclised product as a single diastereoisomer **(247)**.



(71) **(245)** **(246)** **(247)**

Scheme 60

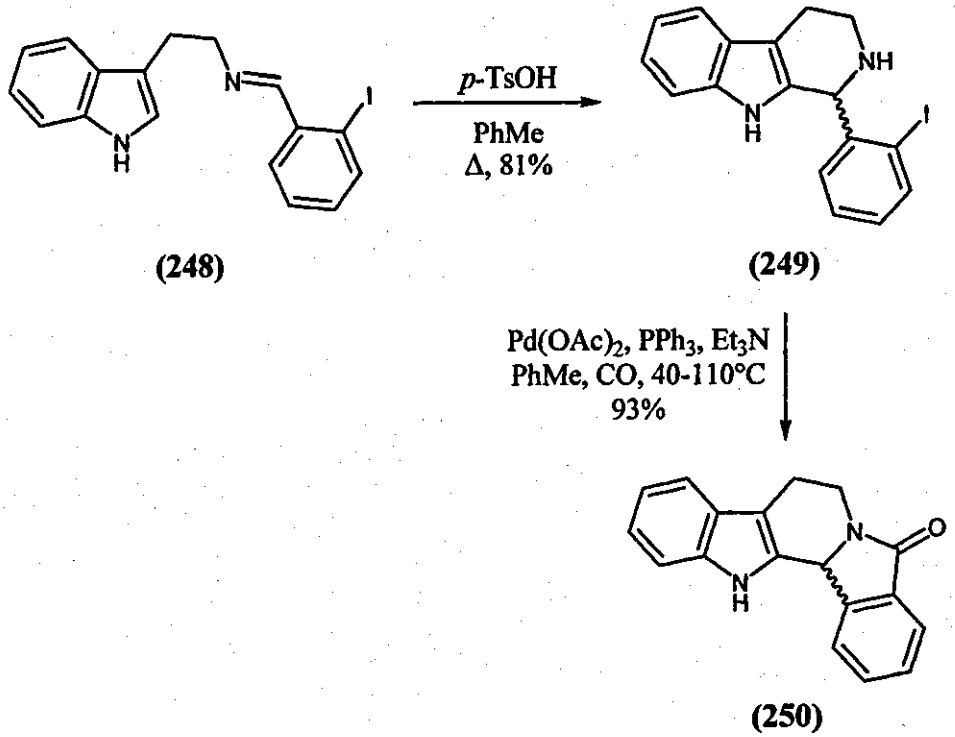
There are several methods in the literature[113-122] for the synthesis of β-carboline derivatives similar in structure to **(121)**[43] (**Figure 29**).



(121)

Figure 29

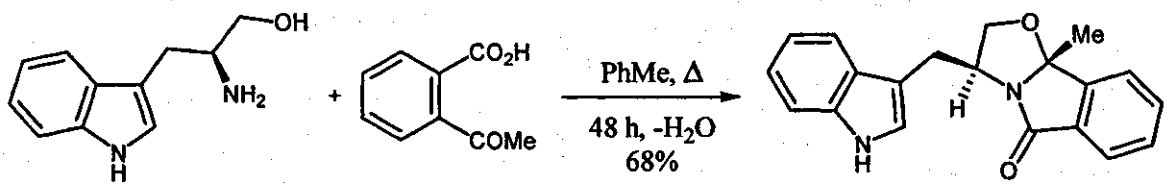
A recent approach has been developed by Grigg[113] which incorporated a sequential Pictet-Spengler[6-11]/palladium catalysed carbonylation sequence (**Scheme 61**). The cyclisation of imine **(248)** proceeded in a catalytic quantity of *p*-toluenesulfonic acid. The compound **(249)** was subjected to a palladium catalysed carbonylation and produced the β-carboline derivative **(250)**.



(248) **(249)** **(250)**

Scheme 61

In order to investigate the indole moiety as an intramolecular π-nucleophile, the tricyclic lactam **(251)** was prepared (**Scheme 62**). Equimolar quantities of the amino alcohol **(226)** and 2-acetylbenzoic acid **(245)** were heated at reflux for 48 h under Dean-Stark conditions. This generated the tricyclic lactam **(251)** as a single diastereoisomer in 68% yield. The reaction was routinely conducted on a 5 g scale after optimisation of the reaction.



(226) **(245)** **(251)**

Scheme 62

The relative stereochemistry of the diastereoisomer **(251)** was confirmed by single crystal X-ray analysis (**Figure 30**).

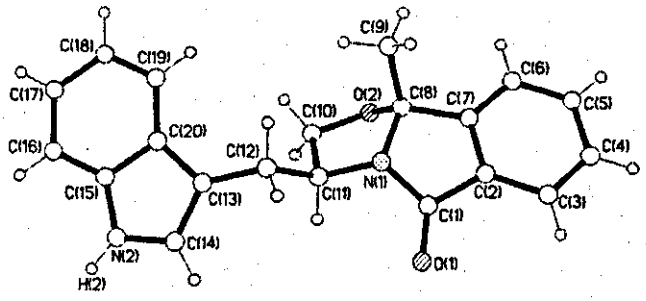
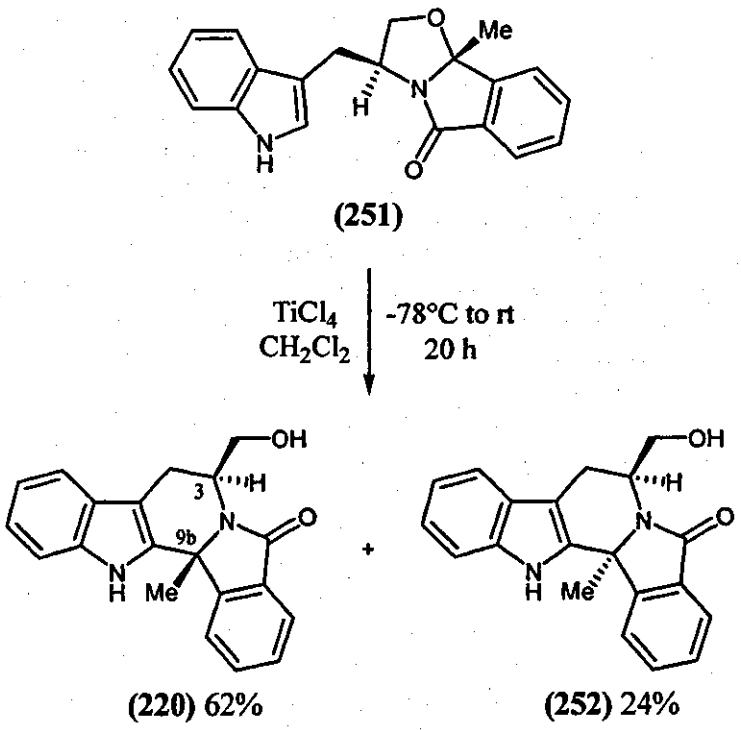


Figure 30

The Lewis acids $TiCl_4$, TMSOTf, $BF_3.OEt_2$ and $SnCl_4$ were individually used to promote the cyclisation of **(251)**. The diastereoisomers **(220)** and **(252)** were generated in a 5:2 ratio after treatment of the substrate **(251)** with $TiCl_4$ (**Scheme 63**). Following column chromatography on silica, the compounds **(220)** and **(252)** were isolated in yields of 62% and 24%. Separation of the diastereoisomers by flash column chromatography was

problematic as these compounds had extremely similar R_f values. This issue was overcome by use of a graduated elution.



Scheme 63

When TMSOTf, $BF_3.OEt_2$ and $SnCl_4$ were used it was evident from the ^1H and ^{13}C NMR spectra of the crude reaction mixture that only one diastereoisomer **(220)** had formed **(Table 4)**.

Lewis Acid Activator	**Diastereoselectivity[a] (220):(252)**
$TiCl_4$	5:2
TMSOTf	**(220)**, exclusive
$BF_3.OEt_2$	**(220)**, exclusive
$SnCl_4$	**(220)**, exclusive

[a]determined by 250 MHz ^1H NMR spectroscopy

Table 4

A comparative NOE study was undertaken to determine the relative stereochemistry of the major **(220)** and minor **(252)** diastereoisomers. In the case of the major diastereoisomer **(220)**, an NOE was not observed between the proton and methyl group at C-3 and C-9b. An NOE was observed between the proton and methyl group at C-3 and C-9b for the minor diastereoisomer **(252)**. These results support the proposed structures of **(220)** and **(252)** shown in **Scheme 63**.

The relative stereochemistry of the minor diastereoisomer **(252)** was confirmed by single crystal X-ray analysis (**Figure 31**).

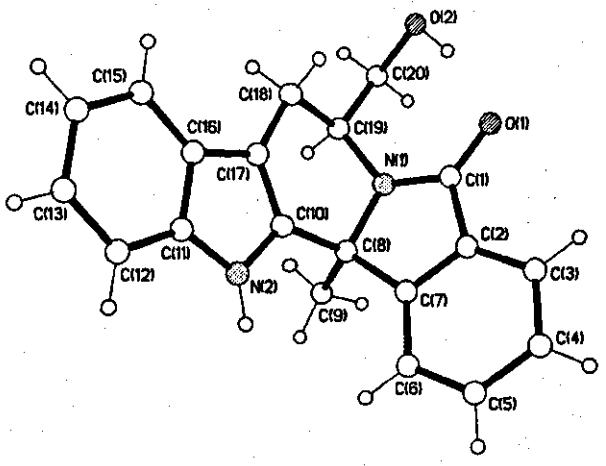
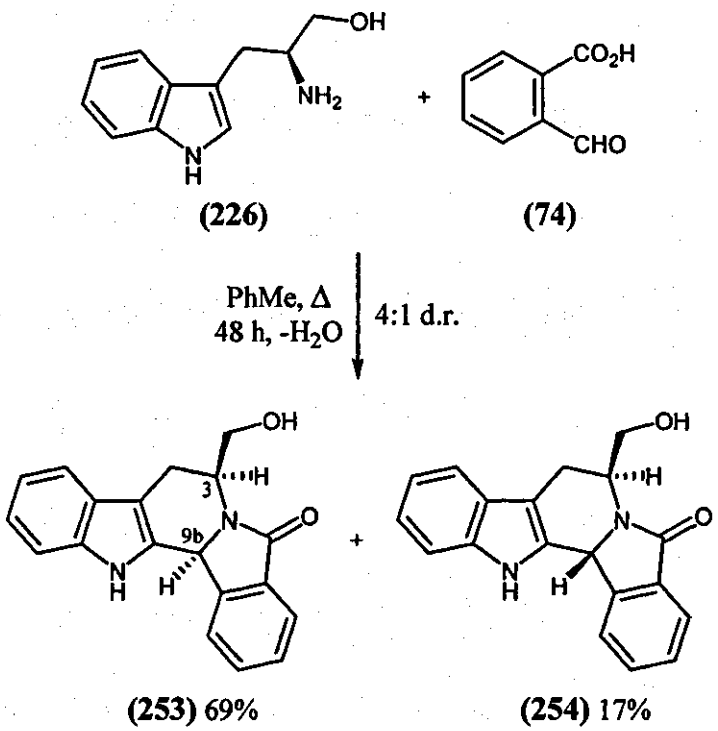


Figure 31

It was expected that on refluxing the amino alcohol **(226)** with 2-carboxybenzaldehyde **(74)** in toluene for 48 h under Dean-Stark conditions, a tricyclic lactam would be isolated in an analogous manner to the formation of **(251)** (**Scheme 62**). The experimental result was the direct cyclisation to the major **(253)** and minor **(254)** pentacyclic diastereoisomers (**Scheme 64**). The ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of the diastereoisomers **(253)** and **(254)** in a 4:1 ratio. Following column chromatography on silica, the compounds **(253)** and **(254)** were isolated in yields of 69% and 17%. Separation of the diastereoisomers by flash column chromatography was problematic as

these compounds had extremely similar R_f values. This issue was overcome by use of a graduated elution.



Scheme 64

A comparative NOE study was undertaken to determine the relative stereochemistry of the major **(253)** and minor **(254)** diastereoisomers. In the case of the major diastereoisomer **(253)**, an NOE was observed between the protons at C-3 and C-9b. An NOE was not observed between the protons at C-3 and C-9b for the minor diastereoisomer **(254)**. These results support the proposed structures of **(253)** and **(254)** shown in **Scheme 64**.

The relative stereochemistry of the major diastereoisomer **(253)** was confirmed by single crystal X-ray analysis (**Figure 32**).

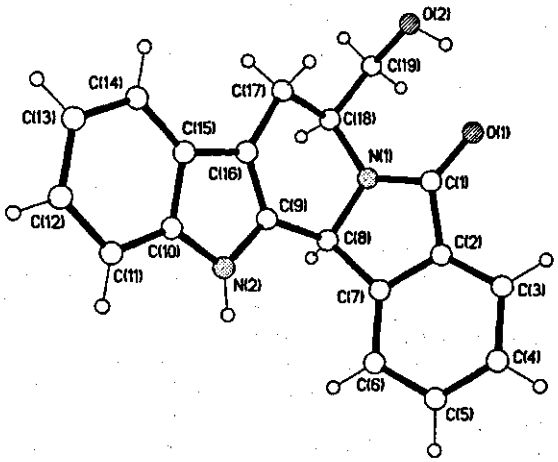
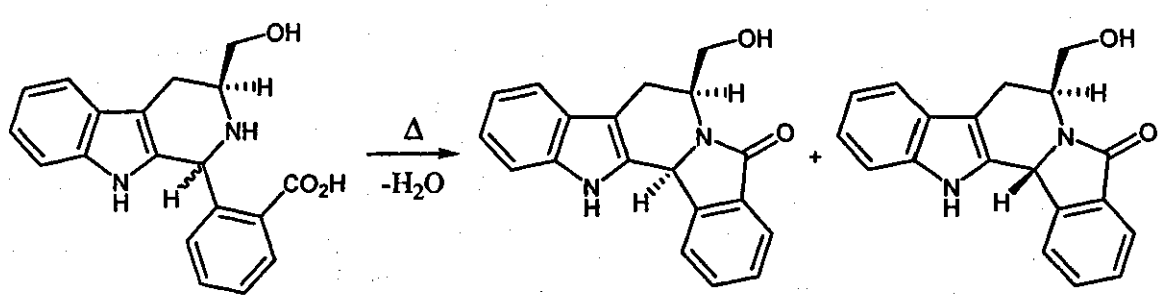


Figure 32

It should be noted that there is an alternative mechanism to explain the formation of the diastereoisomers **(253)** and **(254)** that avoids the intermediacy of a tricyclic lactam such as **(251)**. For example, condensation of the amino alcohol **(226)** with **(74)** as shown in **Scheme 64** could result in compound **(255)** (**Scheme 65**), which can then undergo lactam formation to yield the products **(253)** and **(254)**.[123]



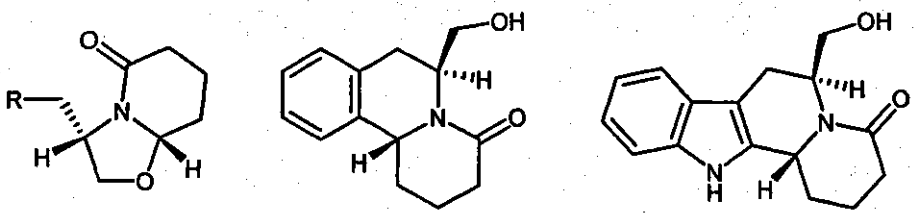
(255) **(253)** **(254)**

Scheme 65

However, to date, there have been no observed intermediates that would support this hypothesis.

2.3 Synthesis and Cyclisation of Bicyclic Lactams

Chiral 5,5- or 5,6-bicyclic lactams have been widely utilised in asymmetric synthesis (**Section 1.6**). The application of a fused 5,6-system such as **(256)** (**Figure 33**) in an *N*-acyliminium mediated cyclisation reaction to yield ring systems such as **(218)** and **(219)** is a novel application of these chiral templates.

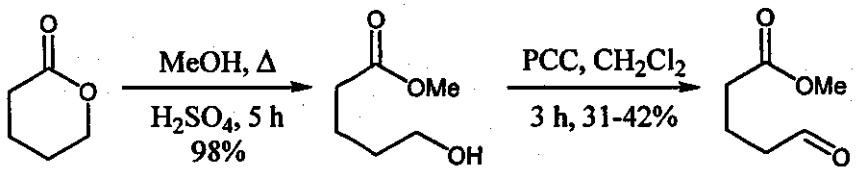


R = Ph, Indole

(256) **(218)** **(219)**

Figure 33

Methyl-5-oxopentanoate **(259)**, a precursor required for the synthesis of bicyclic lactams such as **(256)** was prepared from δ-valerolactone **(257)**. The initial step was an acid-catalysed transesterification in methanol (**Scheme 66**). It has been reported by Huckstep[124] that the product **(258)** is normally oxidised without purification in view of the ease with which it relactonises; distillation causes extensive relactonisation. The target compound **(259)** was isolated after a pyridinium chlorochromate oxidation of **(258)**.

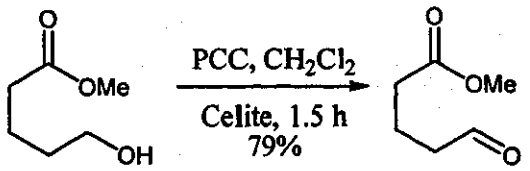


(257) **(258)** **(259)**

Scheme 66

The PCC oxidation was originally performed following a procedure by Huckstep[124] and this approach gave poor to adequate yields (31-42%) (**Scheme 66**). When the reaction was performed on a larger scale (>2 g of **(258)**) the yields were further decreased, ranging from (14-19%). The Cr(VI) reagent produced a tar which was extracted with difficulty and the removal of the toxic and carcinogenic chromium species required time-consuming filtration.

A literature search found a publication by Amat[125] that incorporated Celite during a pyridinium chlorochromate oxidation of **(258)** **(Scheme 67)**. The extraction was less problematic, time-consuming and more user-friendly as the chromium by-products were adsorbed onto the Celite. Extractions with diethyl ether were conducted on the Celite residue rather than a viscous tar. The reaction could be scaled-up and was routinely conducted on 10 g of **(258)** without a significant decrease in yield.



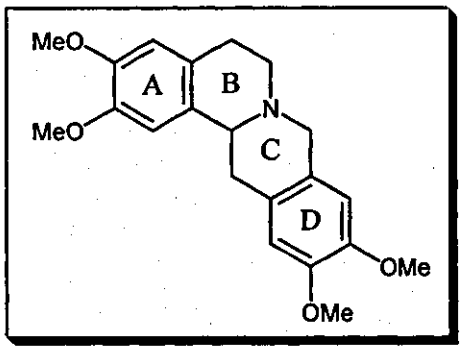
(258) **(259)**

Scheme 67

Conversion of **(258)** to **(259)** was also achieved by a Swern oxidation[126] (38%) and the use of TPAP/NMO[127] (44%).

2.4 The Tetrahydroisoquinoline Ring System

A suitably substituted 5,6-bicyclic lactam could act as a precursor in an asymmetric approach towards a tricyclic tetrahydroisoquinoline system that can be seen as a sub-unit (ABC rings) of the protoberbine alkaloids, exemplified by the naturally occurring xylopinine **(260)**[128,129] **(Figure 34)**.



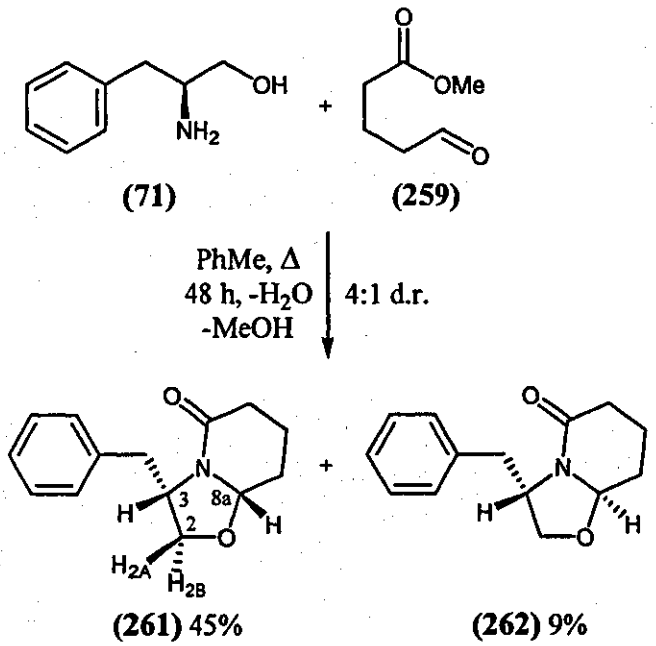
(260)

Figure 34

Considerable efforts have been expended in the study of these molecules for both their synthetic and biological significance. The biological properties attributed to this class of alkaloids include anti-microbial, anti-leukaemic, anti-tumour and anti-inflammatory.[130,131]

2.4.1 Synthesis of Phenyl Containing 5,6-Bicyclic Lactams

Equimolar quantities of the amino alcohol **(71)** and methyl-5-oxopentanoate **(259)** were heated at reflux for 48 h under Dean-Stark conditions (**Scheme 68**). The ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of the diastereoisomers **(261)** and **(262)** in a 4:1 ratio. Following column chromatography on silica, the compounds **(261)** and **(262)** were isolated in yields of 45% and 9%. Separation of the diastereoisomers by flash column chromatography was problematic as these compounds had extremely similar R_f values. This issue was overcome by use of a graduated elution.



Scheme 68

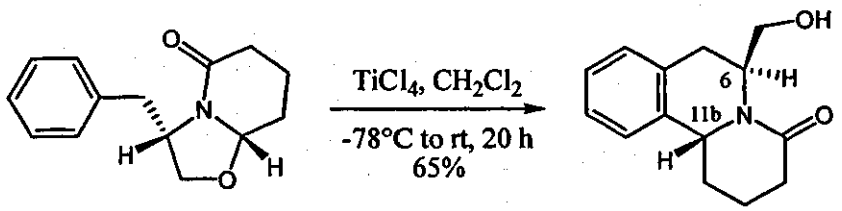
The relative stereochemistry of the major diastereoisomer **(261)** was confirmed by an NOE experiment. Although no NOE was observed between the protons at C-3 and C-8a, the proton at C-3 showed enhancement to H_{2A} but not to H_{2B}. It follows that the relationship between the proton at C-3 and H_{2A} must be *syn*. An NOE was observed between H_{2A} and the proton at C-8a. Thus the relationship between H_{2A} and the proton at C-8a must also be *syn*. Due to an observed NOE between the protons at C-3 and C-8a with H_{2A} and not H_{2B}, it can be inferred that the relative stereochemistry for **(261)** is as shown in **Scheme 68**.

An NOE experiment could not be performed on the minor diastereoisomer **(262)** due to coincidence of the signals corresponding to the protons at C-3 and C-8a in the ^1H NMR spectrum.

2.4.2 Synthesis of the Tetrahydroisoquinoline Ring System

Treatment of the lactam **(261)** with $TiCl_4$ **(Scheme 69)** generated the cyclised product

(218) in 65% yield. It was evident from the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture that only one diastereoisomer **(218)** had formed.

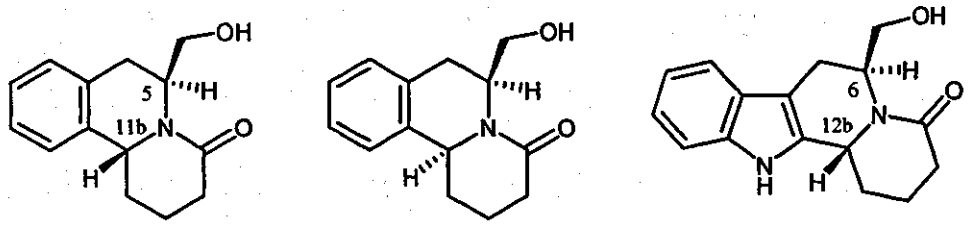


(261) **(218)**

Scheme 69

An NOE study was undertaken to determine the relative stereochemistry of the product **(218)**. The absence of an NOE between the protons at C-6 and C-11b suggested that the relative stereochemistry is as shown in **Scheme 69**. The proposed stereochemistry can be criticised in respect that a negative NOE is inconclusive. A negative NOE is only valid if paired with a positive NOE in a comparative study.

The stereochemical ambiguity could be overcome by epimerising the chiral centre of **(218)** at C-11b (**Figure 35**). The epimerised product **(263)** could then be used in a comparative NOE study. This proposal is feasible as analogous compounds such as **(219)** (**Section 2.7, Scheme 83**) can be readily epimerised at C-12b with retention of stereochemistry at C-6.



(218) **(263)** **(219)**

Figure 35

2.4.3 Rationale for the Stereochemical Outcome Following Lewis Acid Activation

In order to rationalise the stereochemical outcome of the Lewis acid cyclisation of the bicyclic lactam **(261)**, conformational (Felkin-Anh[66,132,133] like) models **(Figure 36)** have been invoked by Allin.[97,98]

In conformation **A** leading to the favoured product **(218)**, the carbonyl moiety is in close proximity with the small hydrogen atom at the β-amino alcohol chiral centre. The angular H-atom at the iminium carbon provides no significant steric bulk to interfere with the positioning of the benzyl or Lewis acid-complexed oxymethyl group. In this model, the Lewis acid-complexed oxymethyl group is viewed as the larger substituent.

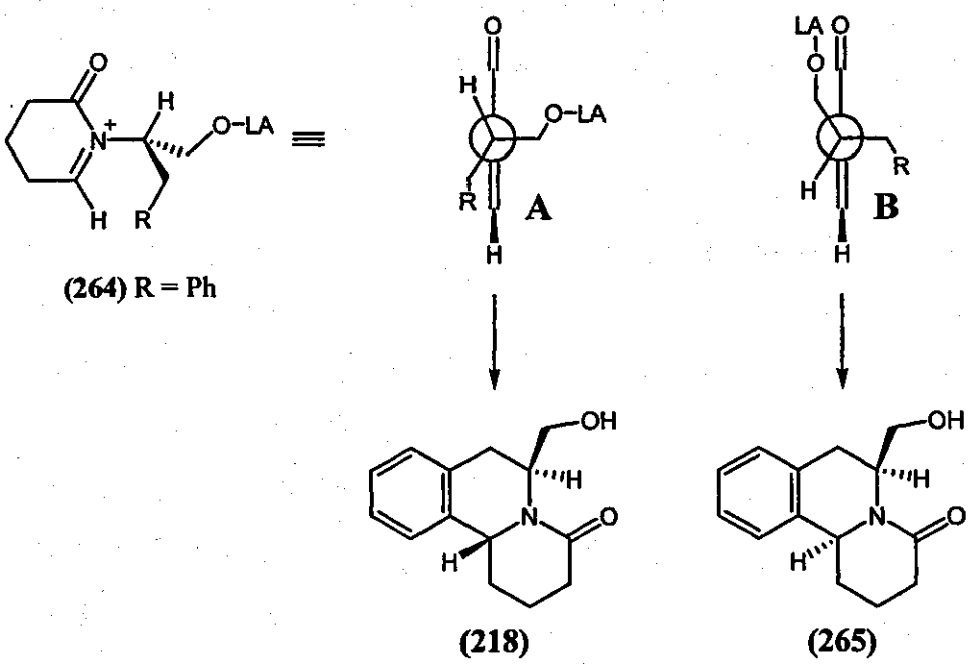


Figure 36

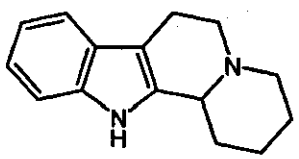
The alternative conformation **B** which would result in the minor (unobserved) diastereoisomer **(265)**, has the benzyl group positioned as the larger substituent. In this

scenario a more unfavourable 1,3-interaction appears to exist between the carbonyl group and the bulky Lewis acid-complexed oxymethyl group.

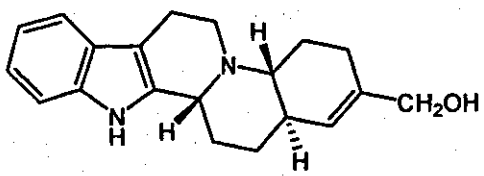
It was found by a colleague[134] that separate treatment of the diastereomeric bicyclic lactams **(261)** and **(262)** with $TiCl_4$ resulted in the same product diastereoisomer **(218)**. This result supports the proposed mechanism since both **(261)** and **(262)** would yield an identical *N*-acyliminium intermediate **(264)** on activation.

2.5 The Indolo[2,3-*a*]quinolizidine Ring System

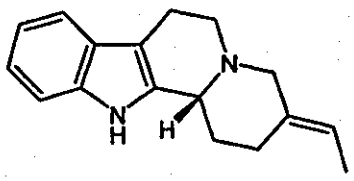
The indolo[2,3-*a*]quinolizidine ring system **(199)** is of great significance as it shares the same heterocyclic skeleton as a plethora of highly bioactive indole alkaloids, exemplified by tangutorine **(203)** and (*R*)-(+)-deplancheine **(204)** (**Figure 37**).



(199)



(203)



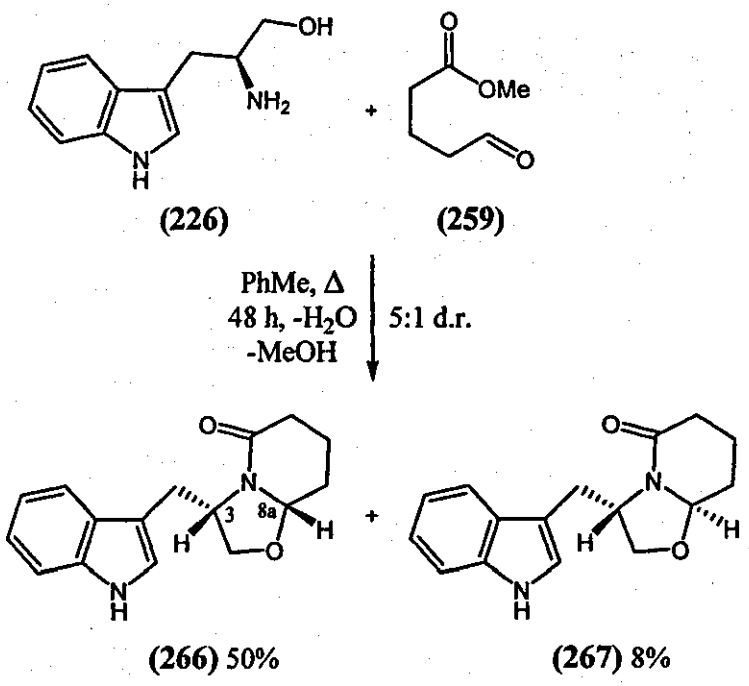
(204)

Figure 37

2.5.1 Synthesis of Indole Containing 5,6-Bicyclic Lactams

Equimolar quantities of the amino alcohol **(226)** and methyl-5-oxopentanoate **(259)** were heated at reflux for 48 h under Dean-Stark conditions (**Scheme 70**). The ^1H NMR

spectrum of the crude reaction mixture revealed the presence of the diastereoisomers **(266)** and **(267)** in a 5:1 ratio. Following column chromatography on silica, the compounds **(266)** and **(267)** were isolated in yields of 50% and 8%. Separation of the diastereoisomers by flash column chromatography was problematic as these compounds had extremely similar R_f values. This issue was overcome by use of a graduated elution.



Scheme 70

A comparative NOE study was undertaken to determine the relative stereochemistry of the major **(266)** and minor **(267)** diastereoisomers. In the case of the major diastereoisomer **(266)**, an NOE was observed between the protons at C-3 and C-8a. An NOE was not observed between the protons at C-3 and C-8a for the minor diastereoisomer **(267)**. These results support the proposed structures of **(266)** and **(267)** shown in **Scheme 70**.

The relative stereochemistry of the major diastereoisomer **(266)** was confirmed by single crystal X-ray analysis (**Figure 38**).

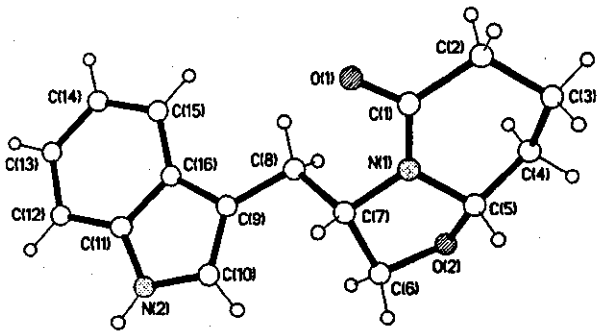
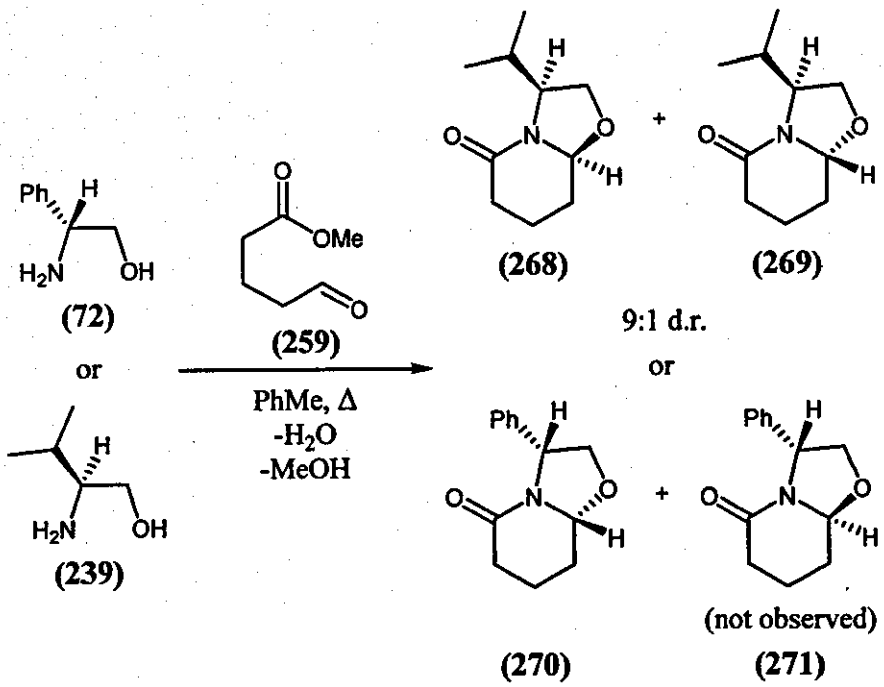


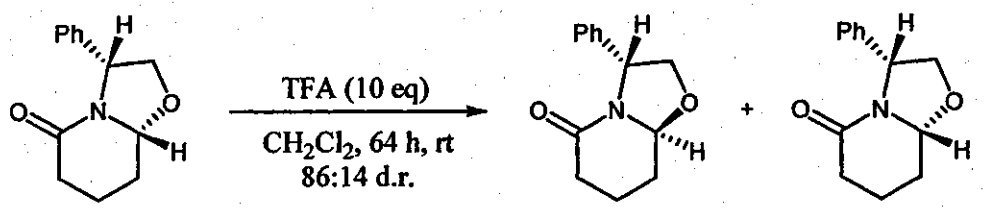
Figure 38

Amat[135] has conducted work which parallels the results obtained in **Scheme 68** and **Scheme 70**. (*R*)-Phenylglycinol **(72)** or (*S*)-valinol **(239)** and methyl-5-oxopentanoate **(259)** were refluxed in toluene with azeotropic removal of water. A 9:1 mixture of the lactams **(268)** and **(269)** were obtained, whereas **(270)** was formed as the sole product (**Scheme 71**).



Scheme 71

Amat[135] explained the stereochemical outcome by considering lactams **(269)** and **(271)** as thermodynamically more stable than the corresponding lactams **(268)** and **(270)**. This proposal was experimentally justified as treatment of pure **(270)** under acidic conditions resulted in a 86:14 mixture of **(271)** and **(270)** (**Scheme 72**). In a similar manner, **(269)** was obtained from **(268)** after acidic treatment.

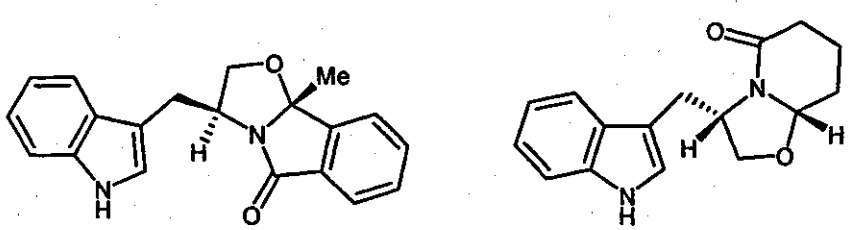


(270) **(271)** **(270)**

Scheme 72

2.5.2 Exception to Baldwin's Rules

During the synthesis of the tricyclic and bicyclic lactams such as **(251)** and **(266)** (**Figure 39**) an unfavourable *5-endo-trig* cyclisation must take place in accordance with Baldwin's rules.



(251) **(266)**

Figure 39

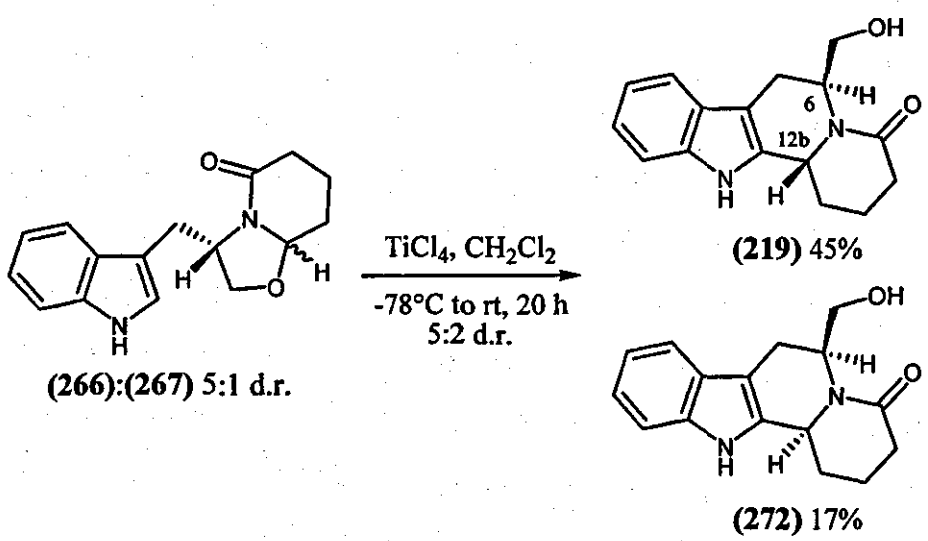
The formation of a cyclic acetal from ethylene glycol and a carbonyl compound (cations frequently disobey Baldwin's rules) also incorporates this process. These rules are only

guidelines and when there is no alternative pathway and when a reaction is thermodynamically favourable (Baldwin's rules describe the kinetic favourability of a reaction), 5-*endo-trig* reactions can occur.[66]

2.5.3 Synthesis of Indolo[2,3-*a*]quinolizidine Derivatives

Based on the previously described work on the isoquinoline ring system, the lactams **(266)** and **(267)**, following initial characterisation, were not separated before treatment with $TiCl_4$ to promote cyclisation (**Scheme 73**).

On treatment of the lactam mixture **(266)** and **(267)** with $TiCl_4$, the ^1H NMR spectrum of the crude reaction mixture revealed the presence of the diastereoisomers **(219)** and **(272)** in a 5:2 ratio. Following column chromatography on silica, the compounds **(219)** and **(272)** were isolated in yields of 45% and 17%. Separation of the diastereoisomers by flash column chromatography was problematic as these compounds had extremely similar R_f values. This issue was overcome by use of a graduated elution.



(266):**(267)** 5:1 d.r.

(219) 45%

(272) 17%

Scheme 73

A comparative NOE study was undertaken to determine the relative stereochemistry of the major **(219)** and minor **(272)** diastereoisomers. In the case of the major diastereoisomer **(219)**, an NOE was not observed between the protons at C-6 and C-12b. An NOE was observed between the protons at C-6 and C-12b for the minor diastereoisomer **(272)**. These results support the proposed structures of **(219)** and **(272)** shown in **Scheme 73**.

2.5.4 Rationale for the Stereochemical Outcome Following Lewis Acid Activation

The stereochemical outcome of the Lewis acid cyclisation of the bicyclic lactams **(266)** and **(267)** can be rationalised using the conformational (Felkin-Anh[66,132,133] like) models shown in **Figure 40**. These models are based on published material by Allin[97,98] (**Section 2.4.3**) where the π-intramolecular nucleophile was benzene.

In conformation **A** leading to the favoured product **(219)**, the carbonyl moiety is in close proximity with the small hydrogen atom at the β-amino alcohol chiral centre. The angular H-atom at the iminium carbon provides no significant steric bulk to interfere with the positioning of the indole or Lewis acid-complexed oxymethyl group. In this model, the Lewis acid-complexed oxymethyl group is viewed as the larger substituent.

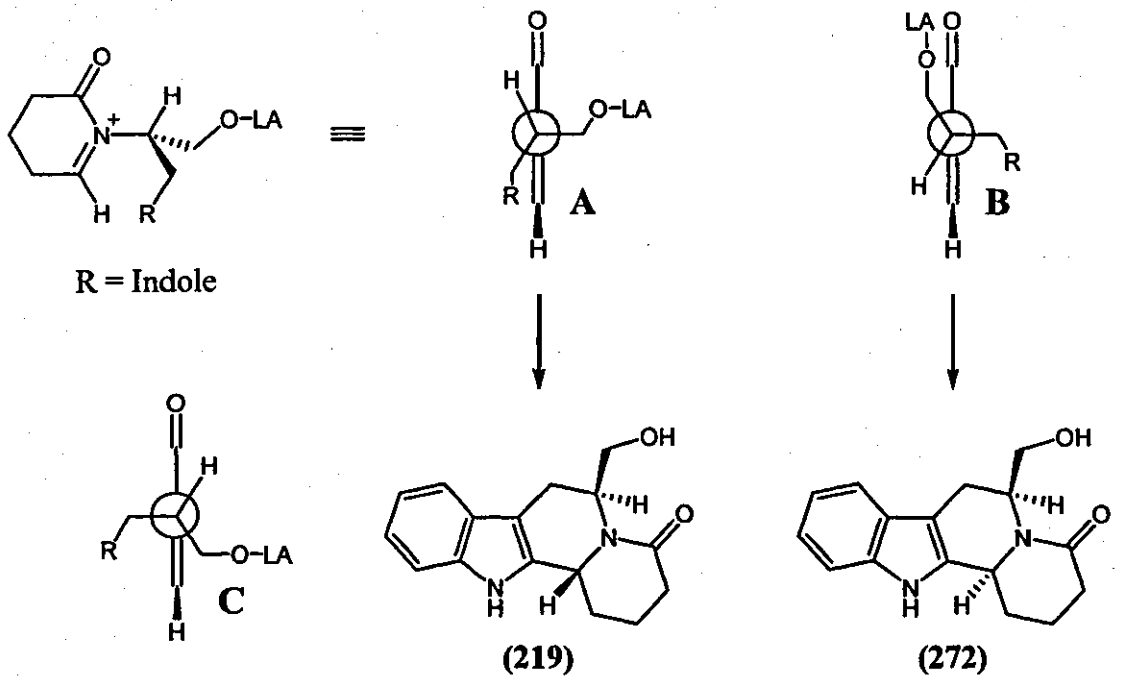


Figure 40

If the indole substituent is viewed to be larger than the Lewis acid-complexed oxymethyl group then conformation **C** appears to be the most favourable. This conformation orientates indole perpendicular to the carbonyl group and like **A** will favour diastereoisomer **(219)**. The difference between these two conformations is simply rotation about the C-N bond. Conformation **C** may need to assume conformation **A** in order to allow nucleophilic attack by the indole moiety at the iminium carbon.

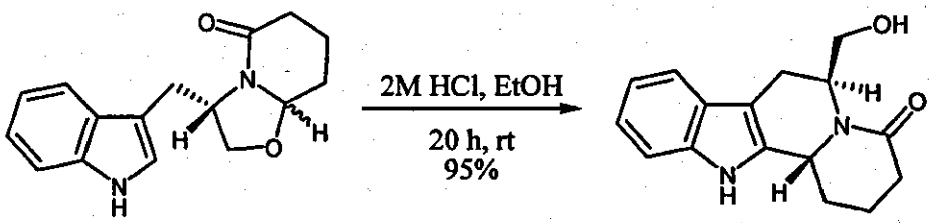
An alternative conformation **B** which would result in the minor diastereoisomer **(272)** also has the indole positioned as the larger substituent. In this scenario a more unfavourable 1,3-interaction appears to exist between the carbonyl group and the bulky Lewis acid-complexed oxymethyl group.

The most important feature of the conformations shown in **Figure 40** is that the favoured product **(219)** arises when the carbonyl moiety is in close proximity with the small

hydrogen atom at the β-amino alcohol centre rather than a large or medium sized substituent.

In transition state **B** there is a possibility of chelation between the amide oxygen atom and the alkoxy group with a metal counter-ion, to form a seven membered chelate. The Lewis acid $TiCl_4$ is capable of multi-point coordination and the level of product diastereoselectivity is probably due to an increased contribution of the chelated transition state similar in structure to **B**.

The product diastereoselectivity (5:2) in favour of the cyclised product **(219)** was poor and therefore an alternative method was examined. An ethanolic 2M HCl solution was investigated as a protic activation source. This ethanolic solution was readily available in the Allin group as it was used for procedures such as that shown in **Scheme 56**. By simply subjecting the mixture of bicyclic lactams **(266)** and **(267)** to 2M HCl in ethanol, it was evident from the ^1H and ^{13}C NMR spectra of the crude reaction mixture that only one diastereoisomer **(219)** had formed (**Scheme 74**).



(266):**(267)** 5:1 d.r. **(219)**

Scheme 74

It was the intention that Lewis acids such as TMSOTf, $BF_3.OEt_2$ and $SnCl_4$ would be used to activate the diastereomeric mixture of **(266)** and **(267)**. However, due to the consistently high yields, ease of reaction and preference for only one diastereoisomer, alternative approaches were not investigated.

The purified product **(219)** was isolated in 95% yield and the relative stereochemistry of the single diastereoisomer was determined by single crystal X-ray analysis (**Figure 41**).

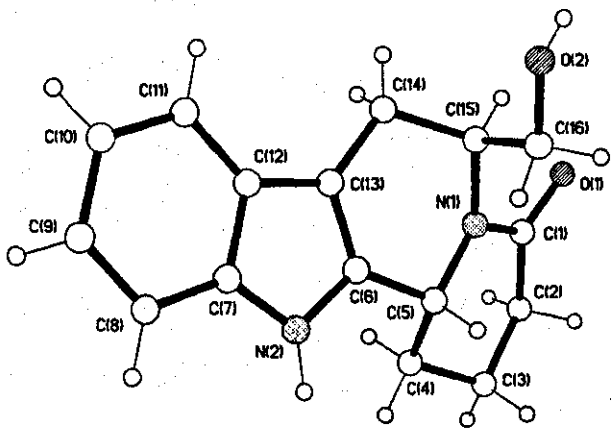


Figure 41

The single product diastereoisomer **(219)** was found to be identical to the major isomer favoured in the $TiCl_4$ mediated cyclisation (5:2 ratio of product diastereoisomers **(219)** and **(272)**).

2.5.5 Rationale for the Stereochemical Outcome Following Acid Activation

In order to rationalise the stereochemical outcome of the cyclisation of bicyclic lactams **(266)** and **(267)** with 2M HCl in ethanol, conformational (Felkin-Anh[66,132,133] like) models have been invoked (**Figure 42**). These models are based on published material by Allin[97,98] (**Section 2.4.3**) where the intramolecular π-nucleophile was benzene.

Conformation **A** appears to be the most favourable if indole is viewed to be larger than the hydroxymethyl group. This conformation orientates indole perpendicular to the carbonyl group and like **C** will favour diastereoisomer **(219)**. The difference between these two conformations is simply rotation about the C-N bond. Conformation **A** may

need to assume conformation **C** in order to allow nucleophilic attack by the indole moiety at the iminium carbon.

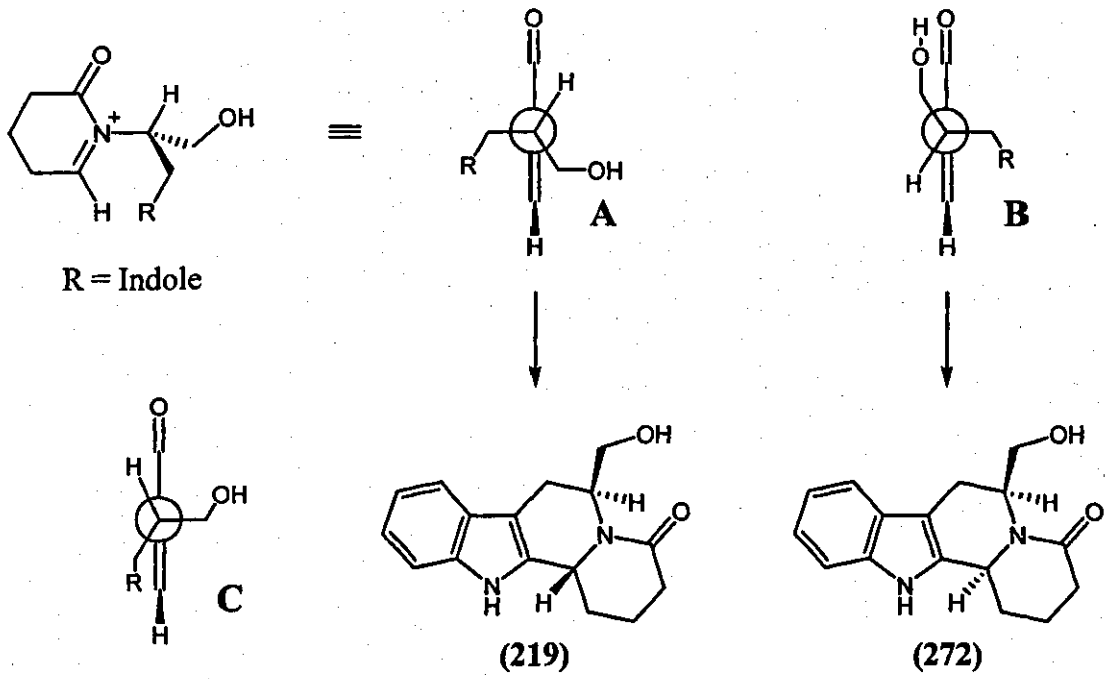


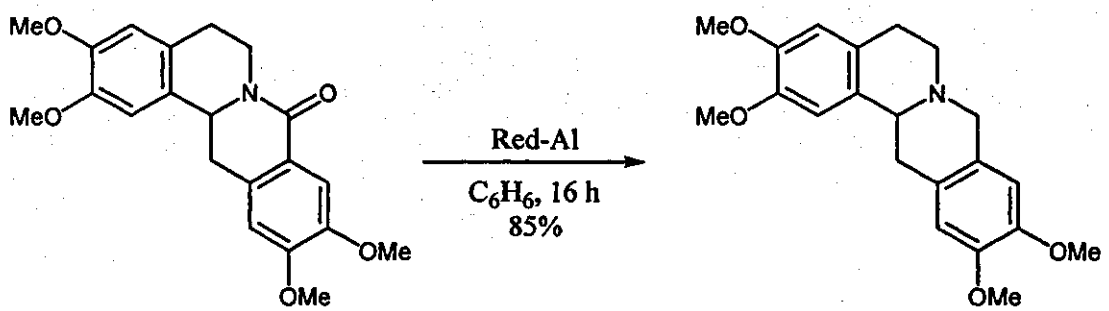
Figure 42

The absence of the minor diastereoisomer **(272)** reinforces the proposal of a chelation effect following activation of the bicyclic lactams **(266)** and **(267)** with the Lewis acid $TiCl_4$ **(Scheme 73)**.

In subsequent acid-catalysed epimerisation **(Section 2.7, Scheme 83)**, the cyclised product **(219)** was completely converted to **(272)**. This would indicate that **(219)** is the kinetic product and the (unobserved) diastereoisomer **(272)** is not initially formed and converted under the conditions shown in **Scheme 74**. Steric effects appear to be the predominant reason for the stereochemical outcome.

2.6 Amide Reduction of an Indolo[2,3-*a*]quinolizidine Derivative

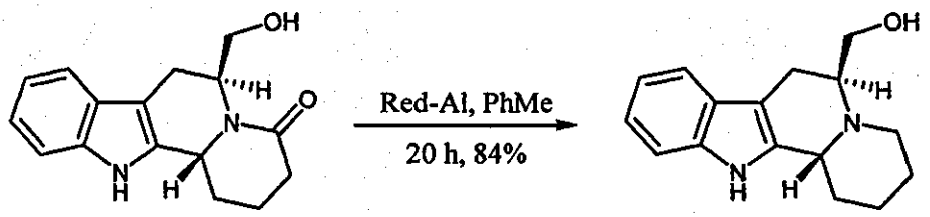
Lenz[129] has used two alternative methods to reduce **(273)**: reduction with $LiAlH_4$ in tetrahydrofuran or Red-Al in benzene. In general, amide reduction with Red-Al gave higher yields and cleaner products in comparison to $LiAlH_4$. Reduction of **(273)** gave the naturally occurring xylopinine **(260)** in 85% yield (**Scheme 75**).



(273) **(260)**

Scheme 75

The procedure developed by Lenz[129] was used to examine the reduction of the indolo[2,3-*a*]quinolizidine derivative **(219)**, with the exception that benzene was replaced by toluene. Following optimisation of the reaction the reduced product **(274)** was readily formed from **(219)** (**Scheme 76**) in 84% yield.

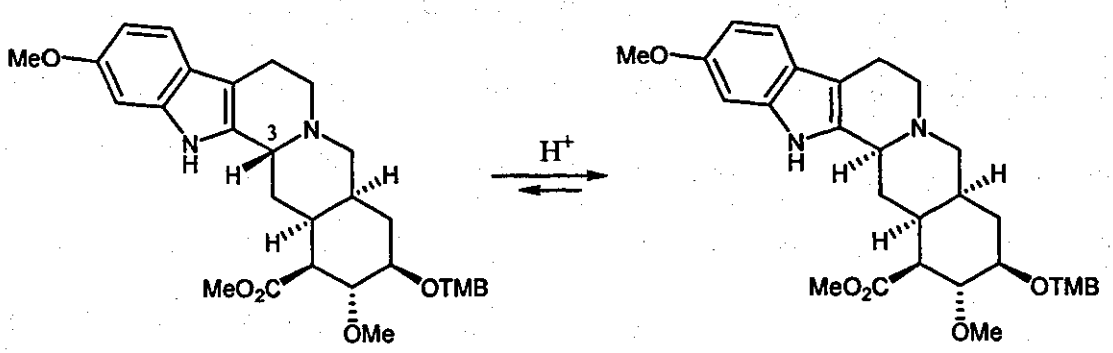


(219) **(274)**

Scheme 76

2.7 Epimerisation of Indolo[2,3-*a*]quinolizidine Derivatives

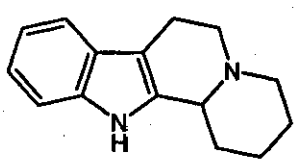
Lounasmaa[136] has produced an extensive review on the acid-catalysed epimerisation at C-3 of the indole alkaloid reserpine **(275)** to isoreserpine **(276)** (**Scheme 77**) and other closely related compounds containing the indolo[2,3-*a*]quinolizidine ring system **(199)** (**Figure 43**).



TMB = 3,4,5-trimethoxybenzoyl

(275) **(276)**

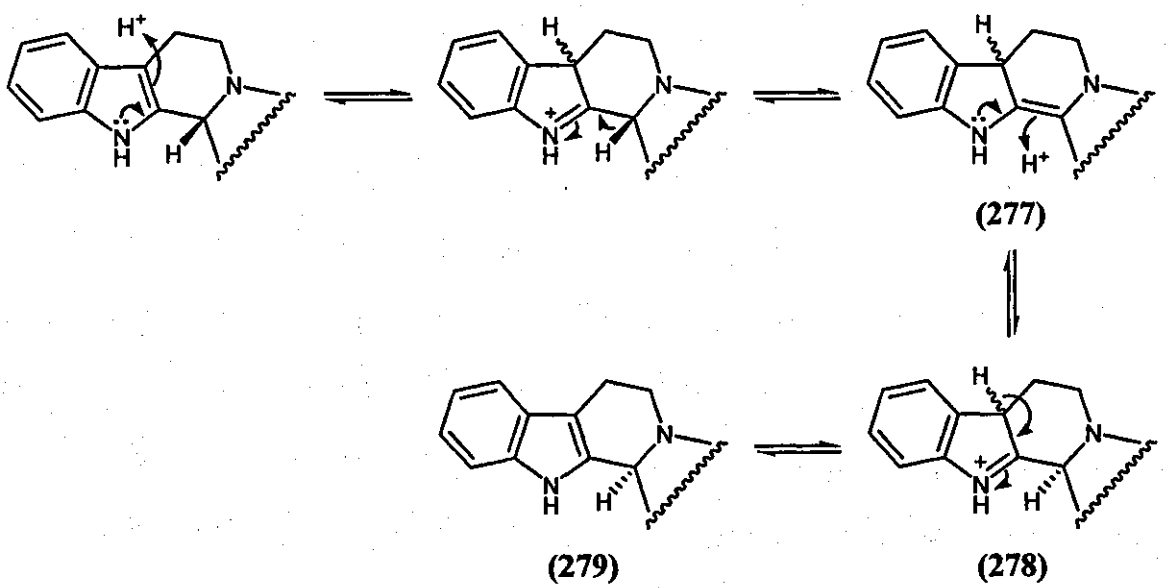
Scheme 77



(199)

Figure 43

Woodward[137] proposed the epimerisation mechanism outlined in **Scheme 78.** Protonation initially occurs at the β-position of indole followed by enamine formation to furnish **(277).** The configuration change to generate **(279)** is achieved by protonation of the enamine **(277)** and cleavage of a proton from **(278).**

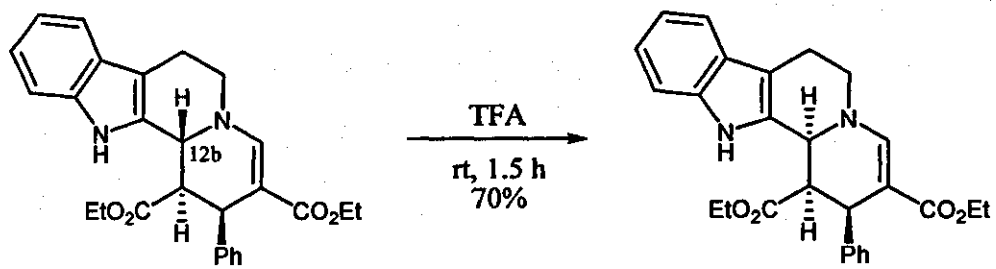


(277)

(279) (278)

Scheme 78

Experimental evidence for the mechanism outlined in **Scheme 78** has been reported by Rosentreter.[138] It was shown that the vinylogous urethane **(280)** was epimerised at room temperature with trifluoroacetic acid to yield **(281)** (**Scheme 79**). When the reaction was repeated with deuterated trifluoroacetic acid, deuterium was incorporated at C-12b.

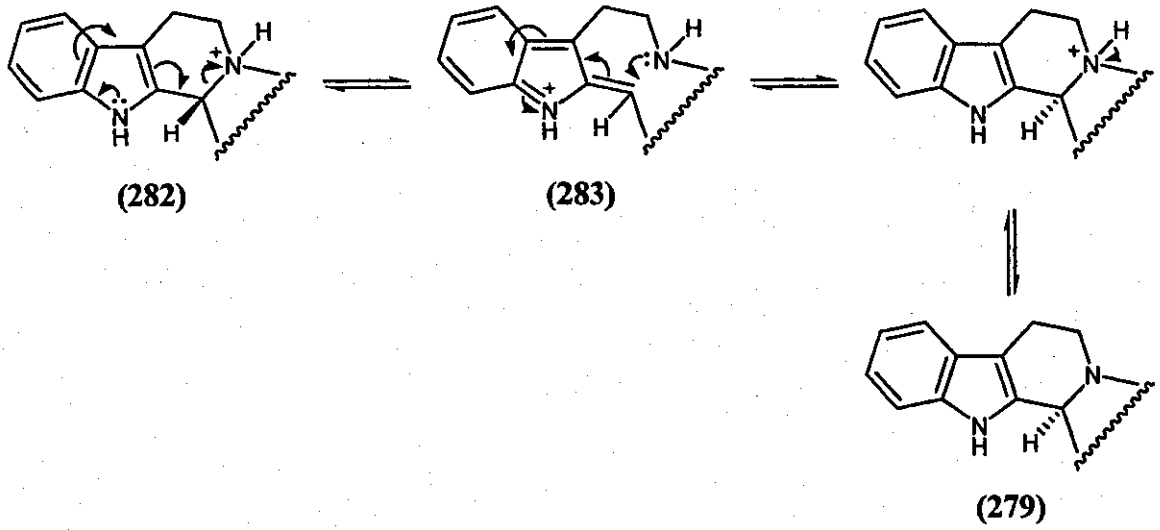


(280) (281)

Scheme 79

Wenkert[139] proposed an alternative mechanism (**Scheme 80**) which involves protonation of the non-indolic nitrogen (the most basic site) to produce **(282)**. The C-3 nitrogen bond of **(282)** is cleaved with participation of the indole lone pair giving rise to the intermediate

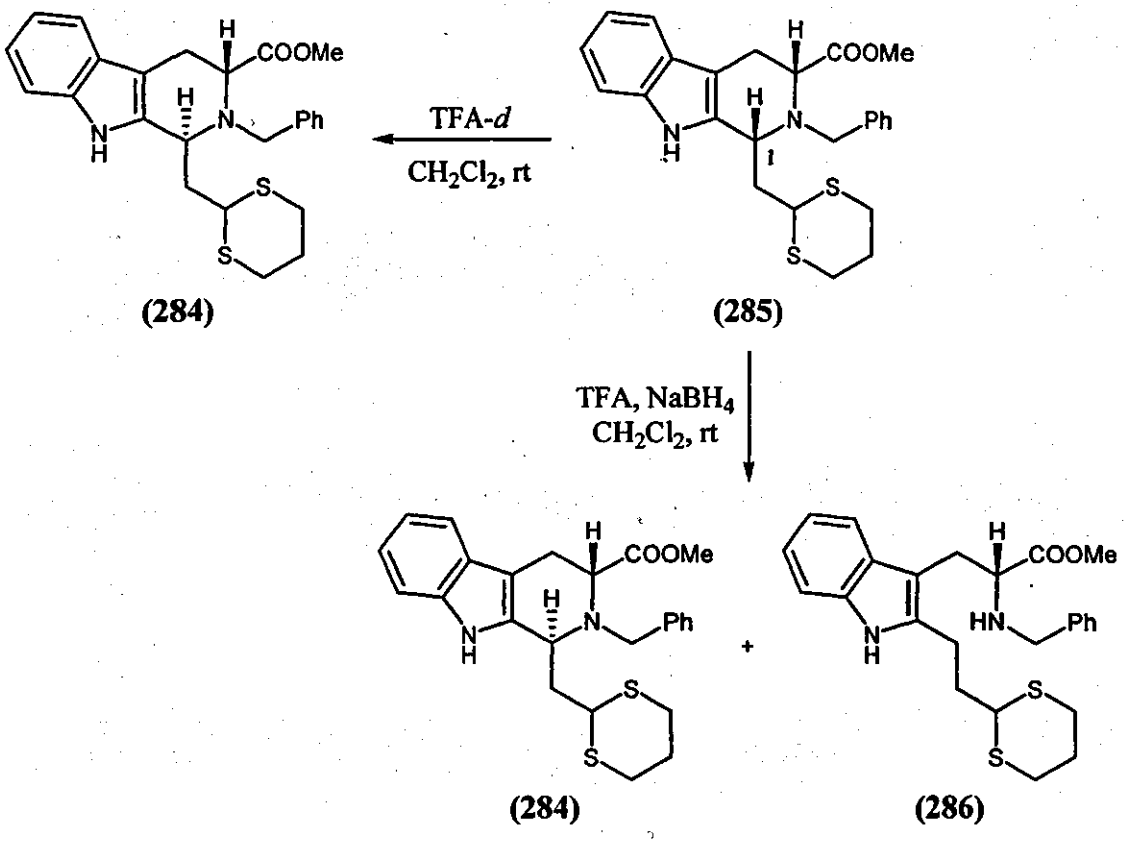
(283). Inversion at C-3 is effected by ring closure of **(283)** assisted by the nitrogen lone pair.



(282) **(283)** **(279)**

Scheme 80

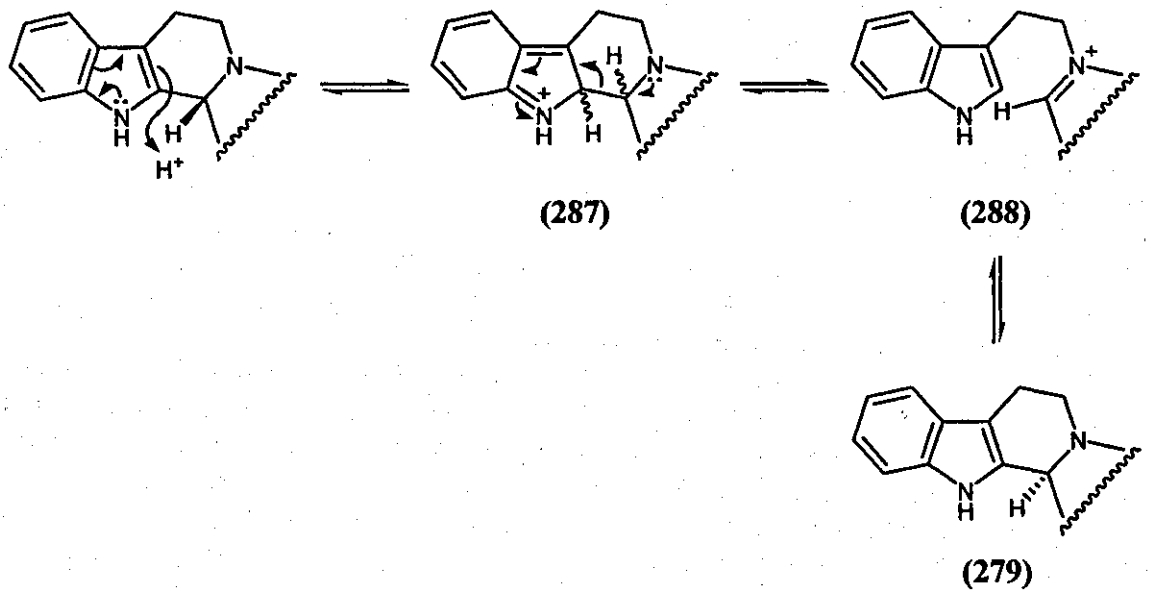
Cook[140] has observed that when compound **(285)** was epimerised with deuterated trifluoroacetic acid, the corresponding epimer **(284)** was furnished in high yield but there was no incorporation of deuterium at C-1 **(Scheme 81)**. When the reaction was repeated with TFA/$NaBH_4$ the products were **(284)** and the reduced ring-cleaved intermediate **(286)** in approximately equal quantities. There was no evidence of any starting material **(285)** and a reduction experiment (TFA/$NaBH_4$ in CH_2Cl_2) with **(284)** gave only starting material.



Scheme 81

The fact that there was no incorporation of deuterium dismisses the mechanism outlined in **Scheme 78.** The ring-cleaved intermediate **(286)** strongly supports the acid-catalysed epimerisation mechanism highlighted in **Scheme 80.**

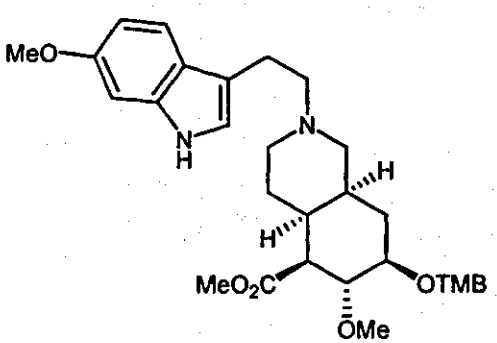
A final plausible mechanism involves formation of the intermediate **(287)** followed by cleavage of the C-2/C-3 bond to yield the iminium species **(288)** (**Scheme 82**). Acid-induced recyclisation of the iminium species **(288)** produces the epimerised product **(279).**[136]



(287) (288) (279)

Scheme 82

Gaskell and Joule[141] conducted an experiment to obtain possible mechanistic intermediates during the C-3 epimerisation of reserpine **(275)** (**Scheme 77**). Reserpine **(275)** was treated with zinc in acetic acid and besides reserpine **(275)** and isoreserpine **(276)**, the product 2,3-secoreserpine **(289)** (**Figure 44**) was isolated.

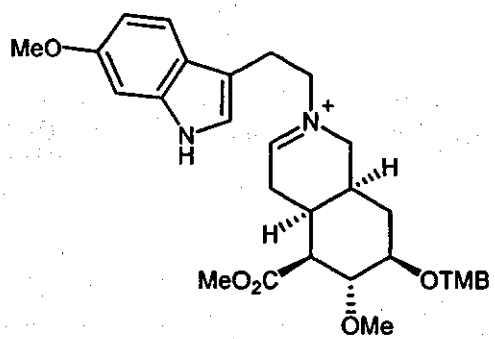


TMB = 3,4,5-trimethoxybenzoyl

(289)

Figure 44

It was concluded by Gaskell and Joule[141] that the epimerisation reaction occurred *via* the mechanism shown in **Scheme 82**, the iminium species **(290)** being the main intermediate (**Figure 45**).



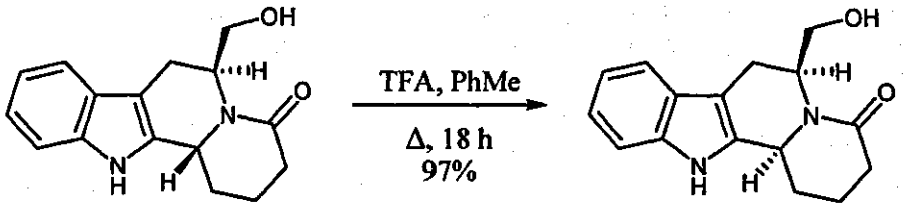
TMB = 3,4,5-trimethoxybenzoyl

(290)

Figure 45

From the review by Lounasmaa[136] it was concluded that the choice of epimerisation route appears to depend on the strength of the acid medium. The behaviour of reserpine **(275)** (**Scheme 77**) and indolo[2,3-*a*]quinolizidines **(199)** (**Figure 43**) in strong acids, such as trifluoroacetic acid, requires additional investigations. It was evident that different structural features of the epimerised compounds have an effect on the epimerisation reaction. Vinylogous urethanes such as **(280)** (**Scheme 79**) epimerise relatively fast at room temperature, whereas indolo[2,3-*a*]quinolizidines **(199)** typically require more vigorous conditions. A possible reason for these discrepancies is that the operating mechanisms are different. Many questions about the acid-catalysed C-3 epimerisation remain unresolved.

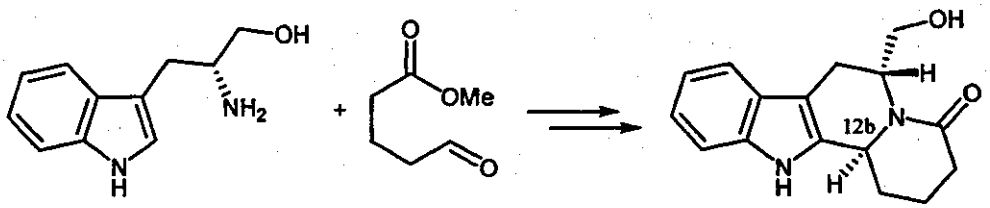
The tetracyclic system **(219)** was subjected to an acid-catalysed epimerisation and following optimisation, the product was isolated as a single diastereoisomer **(272)** in near quantitative yield (**Scheme 83**). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated clean conversion of **(219)** to the epimerised product **(272)**.



(219) (272)

Scheme 83

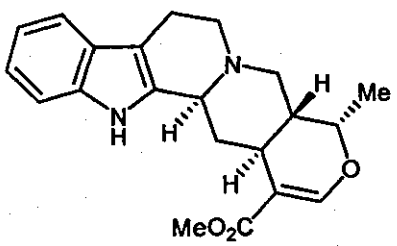
It has been shown by a colleague[142] that the cyclic product **(292)** can be accessed using the β-amino alcohol derivative of D-tryptophan **(291)** (**Scheme 84**).



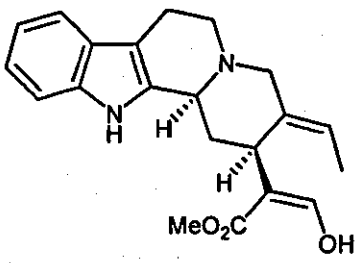
(291) **(259)** **(292)**

Scheme 84

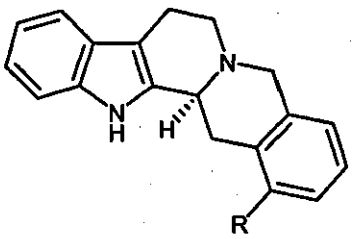
Either of the approaches shown in **Scheme 83** or **Scheme 84** improves the longevity and potential of the chemistry outlined in this thesis. The stereochemistry at C-12b can be controlled and used to synthesise the template of a plethora of natural products such as ajmalicine **(161)**, geissoschizine **(200)**, dihydrogambirtannine **(201)** and demethoxy-carbonyldihydrogambirtannine **(202)** (**Figure 46**).



(161)



(200)



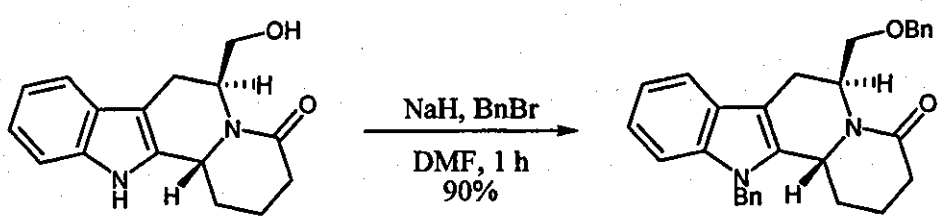
(201) R = CO_2Me
(202) R = H

Figure 46

2.8 Modification of an Indolo[2,3-*a*]quinolizidine Derivative

In these studies the hydroxyl and indole-nitrogen of **(219)** was protected with benzyl groups (**Scheme 85**) to prevent unwanted side reactions. It is common to find the free indole NH of compounds such as indolo[2,3-*a*]quinolizidines **(219)** to be protected during synthetic sequences.[95]

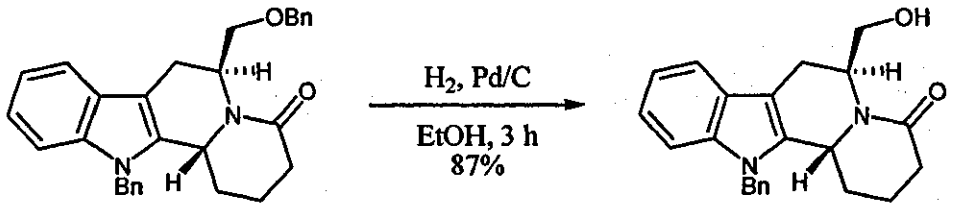
The tetracyclic system **(219)** was treated with NaH and BnBr to form the bis-protected compound **(293)** in 90% yield.



(219) (293)

Scheme 85

Mono-deprotection of the hydroxyl group was achieved by catalytic hydrogenation of **(293)** and the product **(294)** (**Scheme 86**) was generated in 87% yield.

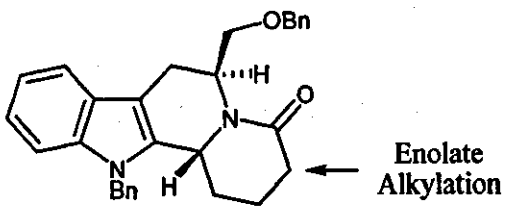


(293) (294)

Scheme 86

2.8.1 Functionalisation using Enolate Chemistry

An enolate alkylation of **(293)** (**Figure 47**) using methyl iodide as an electrophile was investigated to provide an insight into functionalisation at this position.



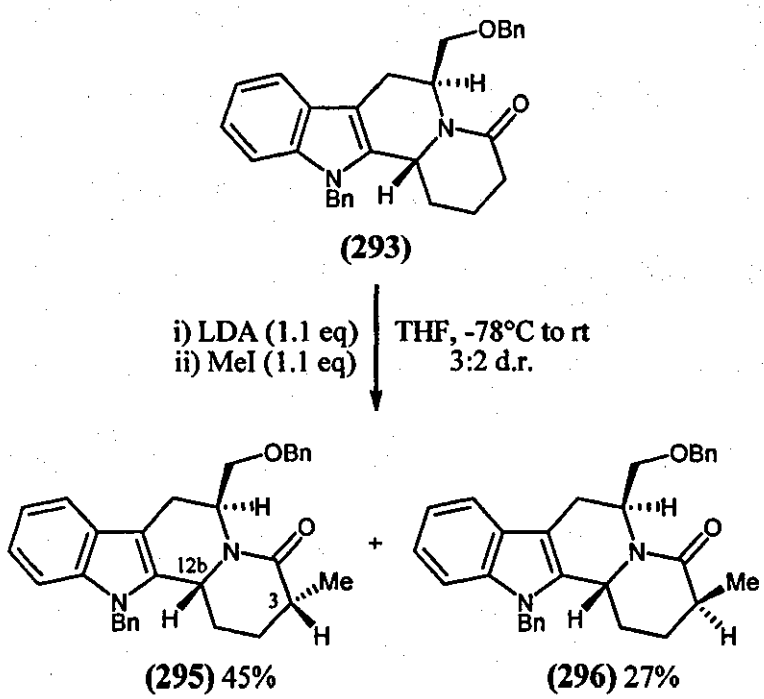
(293)

Figure 47

To demonstrate the formation of an enolate, the bis-protected compound **(293)** was treated with LDA followed by methyl iodide (**Scheme 87**). The *in situ* generation of LDA was problematic at the beginning of this investigation but was eventually overcome with experience. Formation of the enolate was confirmed by a distinct colour change (the yellow solution of **(293)** in THF changed to dark brown).

The ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of the diastereoisomers **(295)** and **(296)** in a 3:2 ratio. Following column chromatography on silica, the compounds **(295)** and **(296)** were isolated in yields of 45% and 27%. Separation

of the diastereoisomers by flash column chromatography was problematic as these compounds had extremely similar R_f values. This issue was overcome by use of a graduated elution.

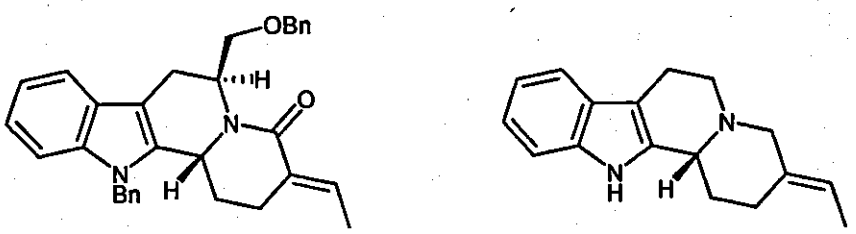


Scheme 87

A comparative NOE study was undertaken to determine the relative stereochemistry of the major **(295)** and minor **(296)** diastereoisomers. In the case of the major diastereoisomer **(295)**, an NOE was observed between the protons at C-3 and C-12b. An NOE was not observed between the protons at C-3 and C-12b for the minor diastereoisomer **(296)**. These results support the proposed structures of **(295)** and **(296)** shown in **Scheme 87**.

2.8.2 Introduction of an (*E*)-Ethylidene Unit

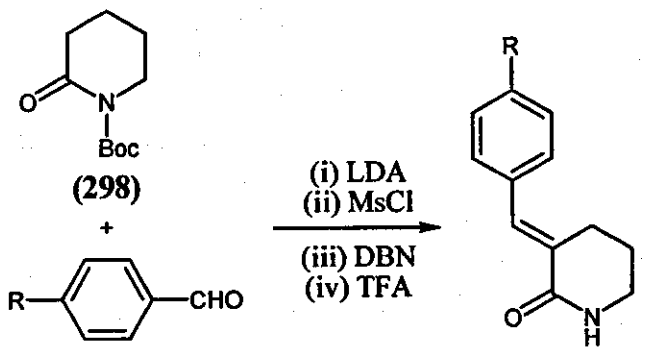
The compound **(297)** (**Figure 48**) which possesses an (*E*)-ethylidene unit as found in (*R*)-(+)-deplancheine **(204)** became a synthetic focus.



(297) (204)

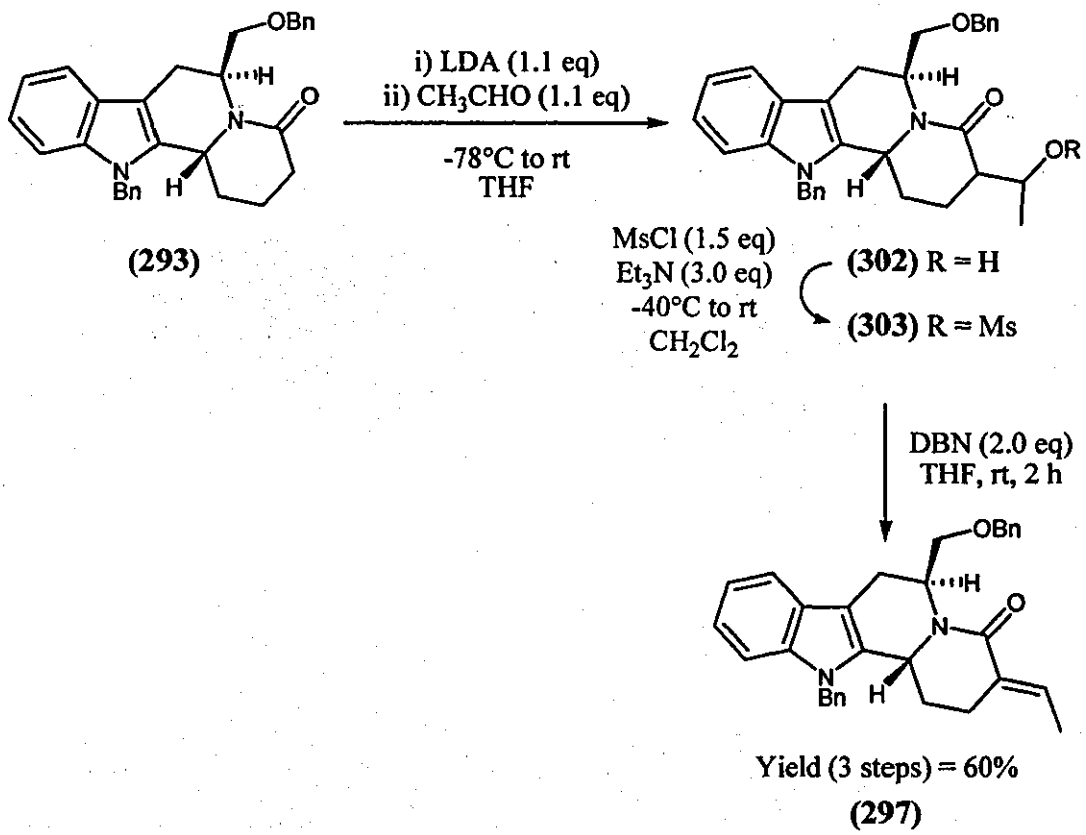
Figure 48

During work conducted by Campi,[143] piperidinone samples such as **(301)** were prepared from **(298)** and **(299)** or **(300)** by an aldol/dehydration sequence and *N*-Boc deprotection with trifluoroacetic acid **(Scheme 88).**



Scheme 88

As a result of the work shown in **Scheme 88**, the bis-protected compound **(293)** was subjected to the three step sequence shown in **Scheme 89**: lithium enolate generation and subsequent aldol reaction with acetaldehyde to form **(302)**, mesylation of the alcohol **(302)** to produce **(303)** and elimination to introduce α,β-unsaturation.



Scheme 89

The target compound **(297)** was isolated as a single diastereoisomer in an overall yield of 60% from **(293)**. The stereochemistry of the newly formed ethylidene unit was confirmed by single crystal X-ray analysis (**Figure 49**) and found to be as required for (*R*)-(+)-deplancheine **(204)**.

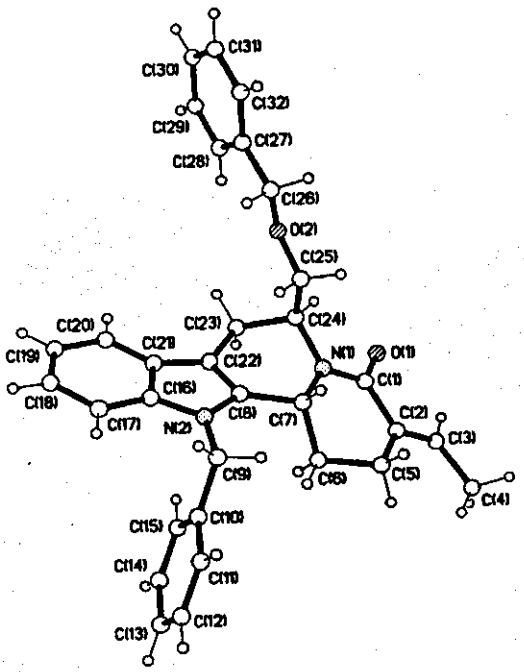
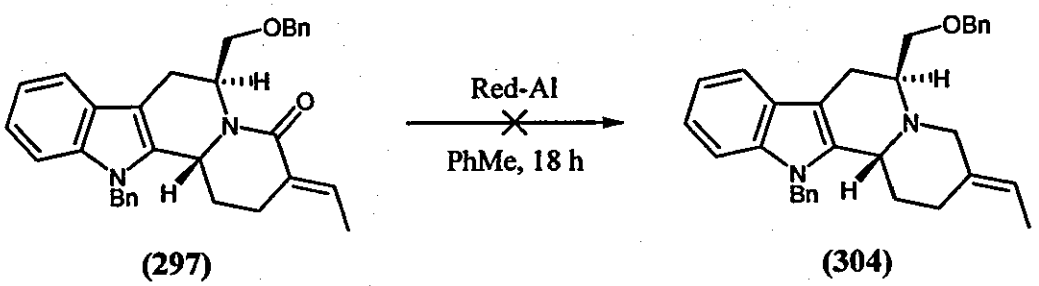


Figure 49

The modified procedure of Lenz[129] which had been used to reduce the indolo[2,3-*a*]quinolizidine derivative **(219)** (**Scheme 76**) was applied to **(297)** (**Scheme 90**). Unfortunately, the reduction was unsuccessful and an extremely complex ^{1}H NMR spectrum of the crude reaction mixture was obtained. There was no evidence of the desired product **(304)** or starting material. An alternative reductive procedure by Meyers[88] was therefore used in subsequent investigations (**Section 2.10**).

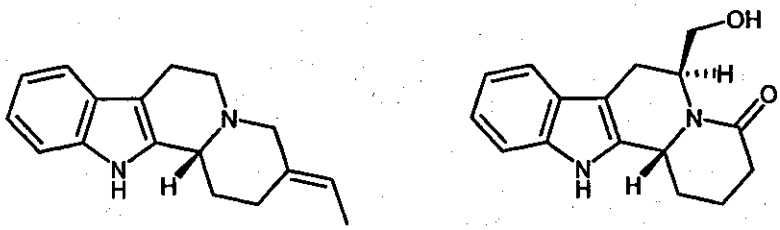


(297) **(304)**

Scheme 90

2.8.3 Removal of the Hydroxymethyl Substituent

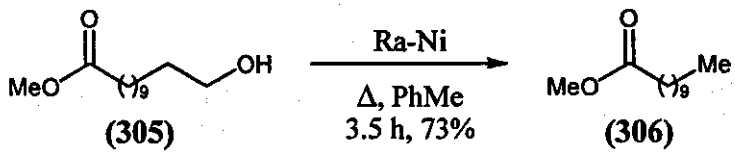
It is evident from the structure of (*R*)-(+)-deplancheine **(204)** that a procedure to remove the pendant hydroxymethyl substituent (auxiliary) from the cyclisation product **(219)** was required **(Figure 50)**.



(204) **(219)**

Figure 50

Krafft[144] has reported that in the presence of Raney nickel in refluxing toluene, primary alcohols generate deoxygenated compounds that contain one less carbon. For example, heating a toluene solution of **(305)** with Raney nickel gave rise to **(306)** in 73% yield **(Scheme 91)**.

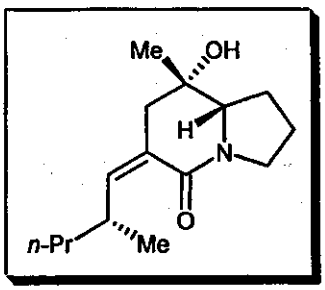


(305) **(306)**

Scheme 91

Krafft[144] proposed that the dehydroxymethylation procedure involves a reversible dehydrogenation (oxidation) of the alcohol to the aldehyde followed by an irreversible decarbonylation.

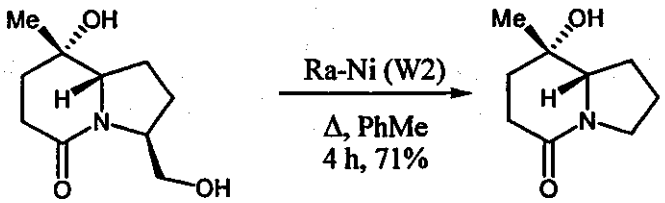
Martin[145] has used the methodology developed by Krafft[144] to remove a superfluous hydroxymethyl group during the formal asymmetric synthesis of pumiliotoxin 521D **(307)** **(Figure 51)**.



(307)

Figure 51

Heating a mixture of **(308)** with Raney nickel (W2)[146] in refluxing toluene produced **(309)** in 71% yield **(Scheme 92)**.

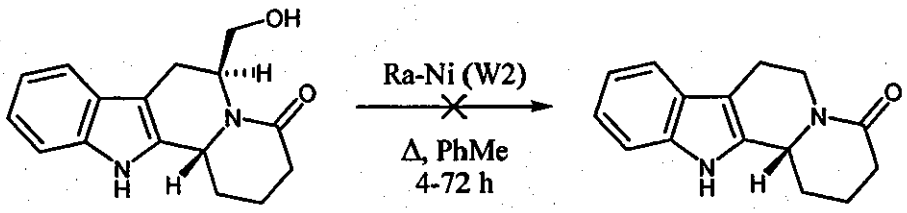


(308) **(309)**

Scheme 92

The quality of the Raney nickel was critical to the successful removal of the pendant hydroxymethyl group. The use of commercially available catalyst failed to promote the reaction to completion, even after prolonged heating. Alternatively, freshly prepared catalyst[146] effected the conversion in four hours.

On subjecting the indolo[2,3-*a*]quinolizidine derivative **(219)** to the reagents and reaction conditions described by Martin[145] only starting material was re-isolated (**Scheme 93**). Unfortunately, additional time and up to a two-fold excess of Raney nickel (W2) did not effect the desired transformation of **(219)** to **(310)**.



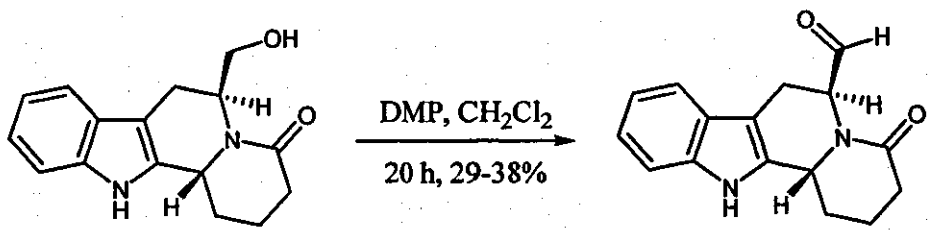
(219) **(310)**

Scheme 93

Due to the lack of success in removing the pendant hydroxymethyl substituent using Raney nickel (W2) an alternative approach was investigated. It was envisaged that **(219)** could be subjected to an oxidation and decarbonylation sequence to remove the hydroxymethyl substituent.

2.8.4 Oxidation Study

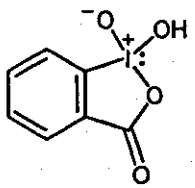
Initial attempts to oxidise the primary alcohol of **(219)** to the aldehyde **(311)** with commercially available Dess-Martin periodinane[147,148] were successful, although low yields were consistently obtained (29-38%) (**Scheme 94**).



(219) **(311)**

Scheme 94

A literature search found publications by Frigerio,[149,150] who has investigated 2-iodoxybenzoic acid (IBX) **(312)** (**Figure 52**) in DMSO as a mild oxidant.

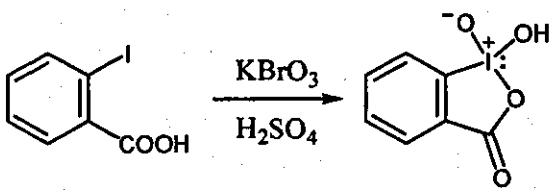


(312)

Figure 52

It was reported[149] that oxidisable heteroaromatic compounds such as furan, pyridine and indole were unaffected during such oxidations. Indoles, in particular those with an unsubstituted NH group, are known to be unstable in the presence of oxidising agents. Oxidation of indolyl alcohols with IBX does not require protection of the indole NH. The use of IBX in DMSO to oxidise the primary alcohol of **(219)** was therefore investigated.

IBX was readily prepared from the inexpensive, commercially available 2-iodobenzoic acid **(313)** and potassium bromate using a preparative procedure reported by Dess and Martin[147] (**Scheme 95**).

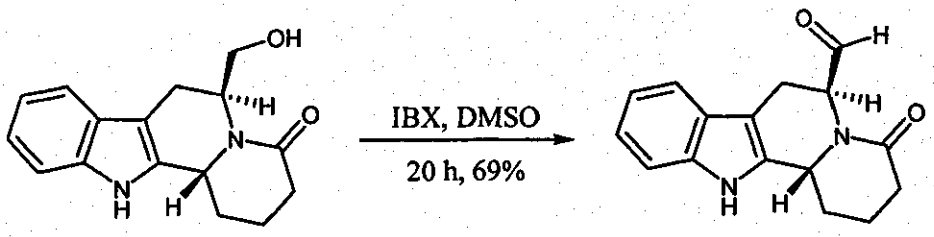


(313) **(312)**

Scheme 95

Oxidation of **(219)** using IBX generated the aldehyde **(311)** as a single diastereoisomer in

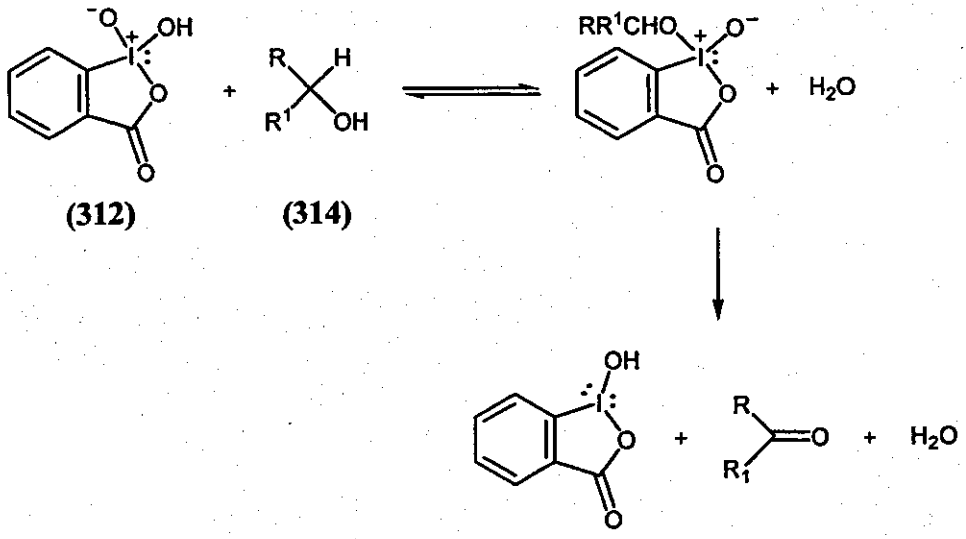
69% yield (**Scheme 96**). The oxidation was performed in an open flask without any particular precaution such as an inert atmosphere or dry solvent. The only significant problem with this chemistry was the large volume of water required to remove the DMSO during work-up. Ethyl acetate and dichloromethane were investigated as alternative solvents. However, the compound **(219)** had poor solubility in these solvents and starting material was recovered.



(219) **(311)**

Scheme 96

Frigerio[149] has proposed a mechanism for the oxidation of alcohols such as **(314)** by IBX **(312)** to produce the aldehyde **(315)** (**Scheme 97**).

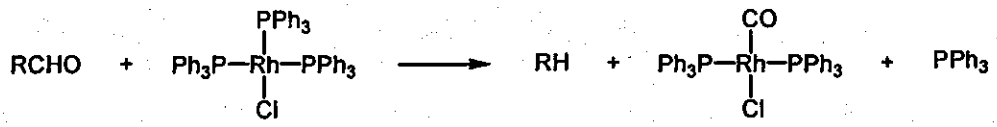


(312) **(314)** **(315)**

Scheme 97

2.8.5 Decarbonylation Study

Ohno and Tsuji[151,152] and Walborsky[153] have decarbonylated aldehydes such as **(316)** to produce **(318)** (**Scheme 98**) using tris(triphenylphoshine)rhodium(I) chloride (Wilkinson's catalyst)[154] **(317)**.

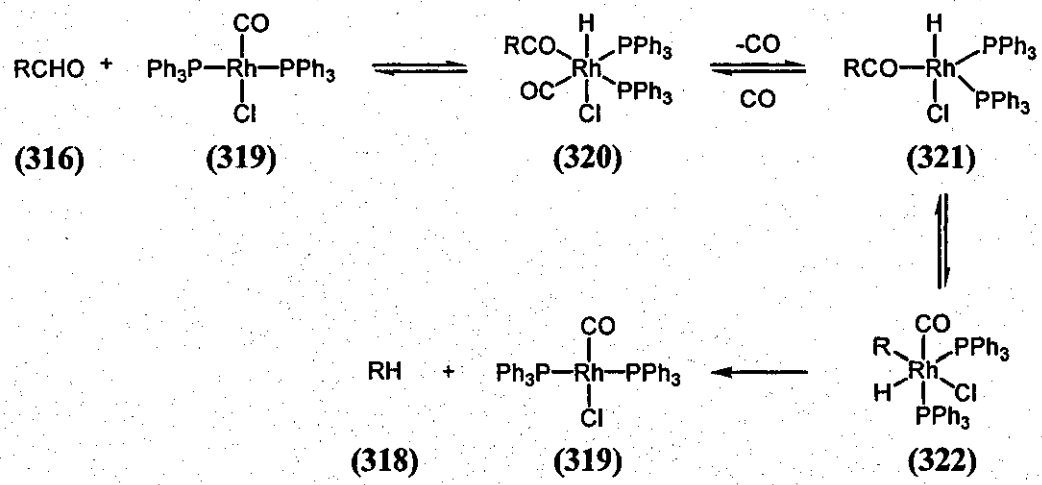


(316) **(317)** **(318)** **(319)**

Scheme 98

In addition to **(317)**, bis(triphenylphosphine)rhodium(I) carbonyl chloride **(319)** is also an extremely useful complex for the decarbonylation of aldehydes under mild conditions.[151] The compound **(319)** can be readily prepared in solution by reaction of Wilkinson's catalyst **(317)** with carbon monoxide at room temperature and atmospheric pressure.

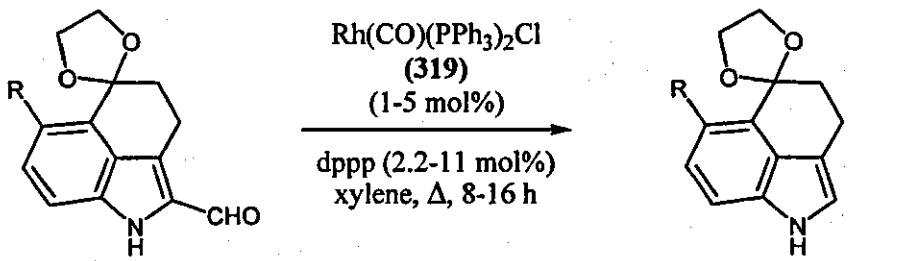
The proposed mechanism[152] for the decarbonylation of the aldehyde **(316)** with the rhodium complex **(319)** is shown in **Scheme 99**. The initial step is the oxidative addition of **(319)** to the aldehyde **(316)** to form **(320)**. When heated in the absence of carbon monoxide, one mole of carbon monoxide is lost to produce **(321)**. The complex **(322)** is generated from **(321)** and the final step is the regeneration of the catalyst **(319)** with formation of the decarbonylated product **(318)**.



Scheme 99

An important component of catalytic decarbonylations is the expulsion of coordinated carbon monoxide and regeneration of the active catalyst. Doughty and Pignolet[155] have examined the decarbonylation of benzaldehyde and heptanal with cationic complexes of chelating diphosphine ligands. The complexes $[Rh(dppe)_2]Cl$ (dppe = 1,2-bis(diphenyl-phosphino)ethane) and $[Rh(dppp)_2]Cl$ (dppp = 1,3-bis(diphenylphosphino)propane) were prepared by reaction of **(319)** with excess diphosphine ligand in toluene. It was proposed that such complexes should bind carbon monoxide significantly less than **(319)** due to a decrease in Rh-CO π back-bonding. It became apparent that the catalytic activity was enhanced for the rhodium complexes with chelated diphosphine ligands, compared to those obtained for Wilkinson's catalyst **(317)**.

In an extension of the work by Doughty and Pignolet,[155] Meyer and Kruse[156] found that the active catalyst $[Rh(dppp)_2]Cl$ could be generated *in situ*. A near quantitative yield was obtained for the conversion of the aldehydes **(323)** and **(324)** to **(325)** and **(326)** (**Scheme 100**). Reactions of this type were typically complete in 8-16 h and 1-5 mol% of **(319)** was used.

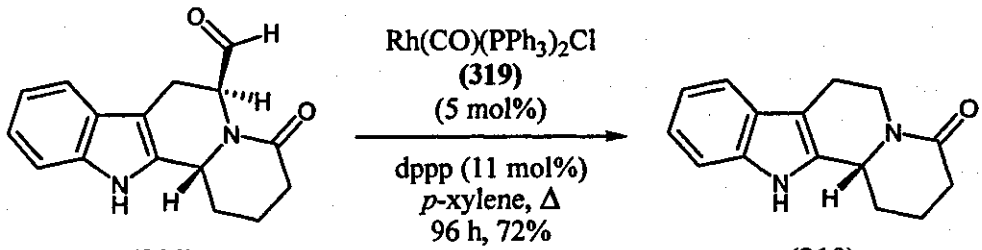


(323) R = H
(324) R = OMe

(325) R = H (97%)
(326) R = OMe (96%)

Scheme 100

Use of the catalyst **(319)** in conjunction with 1,3-bis(diphenylphosphino)propane appeared to be a sensible choice to effect the decarbonylation of **(311)**. Initial investigations were conducted using 5 mol% of **(319)** and 11 mol% of 1,3-bis(diphenylphosphino)propane in *p*-xylene (**Scheme 101**). The reaction was monitored by TLC and was complete after 96 hours. The ^{1}H NMR spectrum of the crude reaction mixture suggested complete conversion of **(311)** to the decarbonylated product **(310)**.



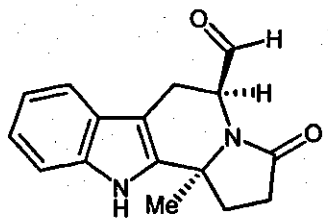
(311)

(310)
+ impurity

Scheme 101

Attempts were made to purify the product **(310)** by flash column chromatography and preparative TLC. However, the suspected product **(310)** consistently co-eluted with an impurity located between 7.10-7.68 ppm by ^{1}H NMR spectroscopy, presumably a phosphorous by-product. Varying combinations of mobile phase were investigated but all approaches were unsuccessful.

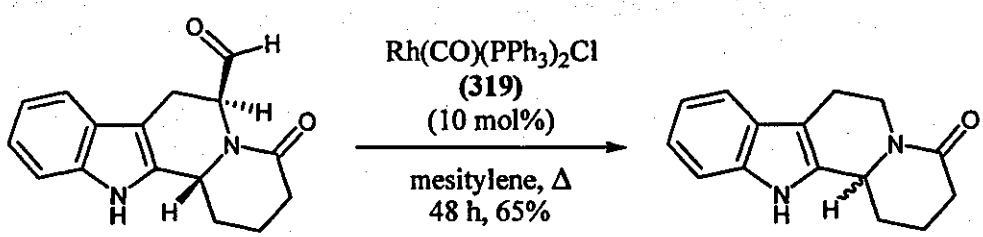
During the course of the previously described decarbonylation of **(311)**, a colleague[157] was simultaneously investigating and optimising the decarbonylation of the closely related indolizino[8,7-*b*]indole derivative **(327)** (**Figure 53**). Variables such as time, solvent, quantity of catalyst **(319)** and the relative proportion of diphosphine ligand were investigated.



(327)

Figure 53

As a result of the success attained decarbonylating **(327)**, an alternative procedure to that indicated in **Scheme 101** was investigated. The solvent *p*-xylene (137-138°C) was replaced with the higher boiling mesitylene (163-165°C) and 10 mol% of the catalyst **(319)** was used without 1,3-bis(diphenylphosphino)propane. The procedure was applied to **(311)** (**Scheme 102**) and after an unoptimised time of 48 h, the decarbonylated product **(328)** was isolated in 65% yield. Following purification there was no evidence of an impurity in the ^{1}H NMR spectrum. However, on overcoming the purification issue an additional problem was discovered.



(311) **(328)**

Scheme 102

A single crystal X-ray analysis (**Figure 54**) was obtained and suggested that during decarbonylation the remaining chiral centre had racemised.

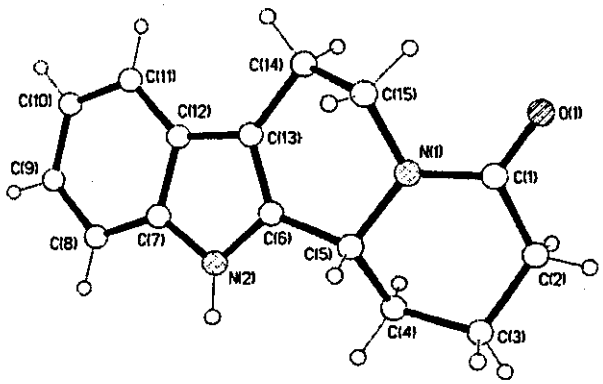
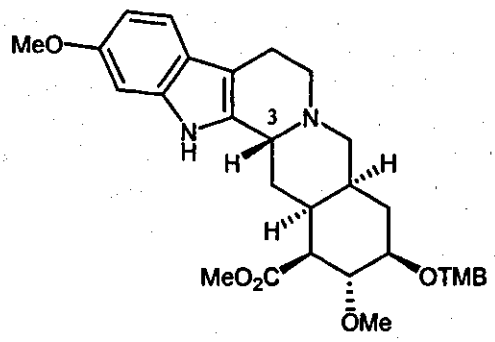


Figure 54

A racemic mixture will typically crystallise as a homogenous solid containing equimolecular amounts of both enantiomeric molecules. The crystal obtained from a racemic mixture usually has a centrosymmetric space group with the two enantiomers related by a symmetry centre. The symmetry of a unit cell is described by its space group which is represented by a cryptic symbol (like $P2_12_12_1$), in which a capital letter indicates the lattice type and the other symbols represent symmetry operations that can be carried out on the unit cell without changing its appearance. There are 230 possible space groups and these can be readily observed in crystallographic literature.[158] The single crystal X-ray analysis of **(328)** revealed that the space group was P*bca* which is centrosymmetric. This result provoked concern with regards to the stereochemistry of the decarbonylated product.

A single crystal X-ray analysis is not representative of bulk purity, therefore chiral HPLC (ChiralCel OD-H, 85:15 hexane/propan-2-ol, 0.4 mL min^{-1}) was performed on the sample used to prepare the crystal. The enantiomers were observed at 43.1 and 46.5 minutes.

Epimerisations of compounds such as reserpine **(275)** at C-3 **(Figure 55)** typically require an acidic source such as trifluoroacetic acid.[136] It would appear that refluxing in mesitylene is sufficient to effect inversion at the remaining chiral centre. An acidic source may be present which is either generated during the decarbonylation procedure or has been carried through from a previous process.

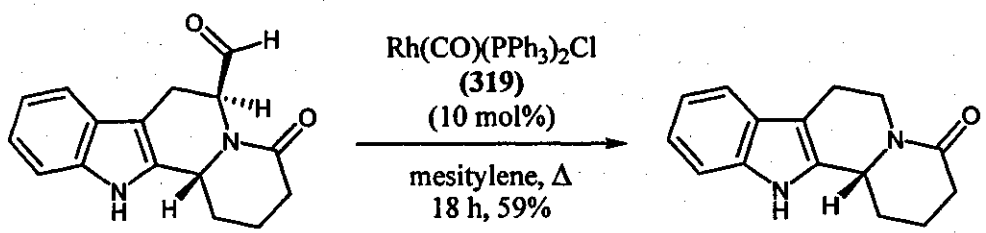


TMB = 3,4,5-trimethoxybenzoyl

(275)

Figure 55

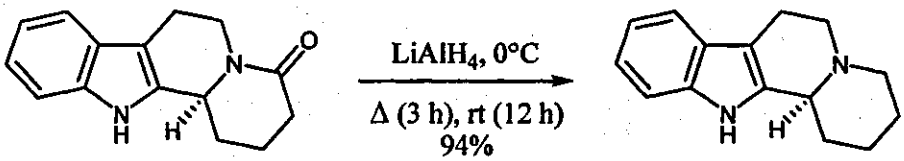
Monitoring of the reaction by ^{1}H NMR spectroscopy and TLC indicated clean decarbonylation of the aldehyde **(311)** after 18 h (previous unoptimised time for the racemised product **(328)** was 48 h). The major product **(310)** was proposed to be as shown in **Scheme 103** for reasons that are subsequently discussed.



(311) **(310)**

Scheme 103

The enantiomeric purity was determined by chiral HPLC (ChiralCel OD-H, 85:15 hexane/propan-2-ol, 0.4 mL min^{-1}). The enantiomers were obtained at 42.2 and 46.4 minutes which compared favourably with the racemic sample (43.1 and 46.5 minutes) and the *e.e.* was calculated to be 94%. During the course of the asymmetric synthesis of (*S*)-(-)-deplancheine by Meyers,[88] the indoloquinolizidine **(330)** was synthesised (**Scheme 104**). The precursor of **(330)** was the (*S*)-(-)-enantiomer **(329)** of **(310)**.



(329) **(330)**

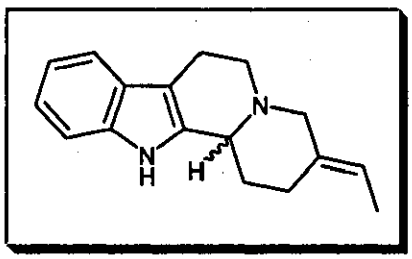
Scheme 104

The optical rotation of **(310)** $[\alpha]^{23}_{D}$ = +241.5 (*c* = 1.0, $CHCl_3$) was in accordance with that reported for its enantiomer **(330)** $[\alpha]^{20}_{D}$ = -232.0 (*c* = 1.0, $CHCl_3$).[88] This would suggest that the major decarbonylated product is the enantiomer **(310)** shown in **Scheme 103**.

A colleague[142] continued decarbonylation investigations of **(311)** and determined that the success of the procedure outlined in **Scheme 103** varied. The decarbonylation of **(311)** is always achieved within 18 hours but the *e.e.* values are inconsistent. This procedure is currently being subjected to additional investigation.

2.9 Modification of the Racemic Indolo[2,3-*a*]quinolizidine Template

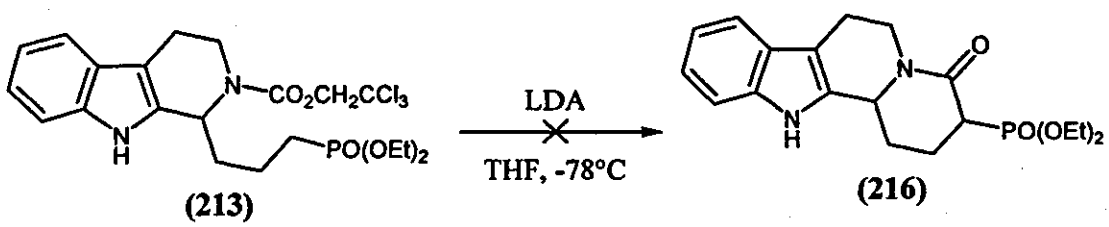
Due to development of the asymmetric decarbonylation of **(311)** and time restraints it was decided that a synthesis of (±)-deplancheine **(208)** (**Figure 56**) would be attempted. The synthesis of **(208)** would provide insight into the feasibility of applying the chemistry in a future asymmetric synthesis of (*R*)-(+)-deplancheine **(204)**.



(208)

Figure 56

During the formal synthesis of (±)-deplancheine **(208)** by Ohsawa[95] **(Scheme 51)** a ring closure of **(213)** to produce **(216)** was attempted **(Scheme 105)**.

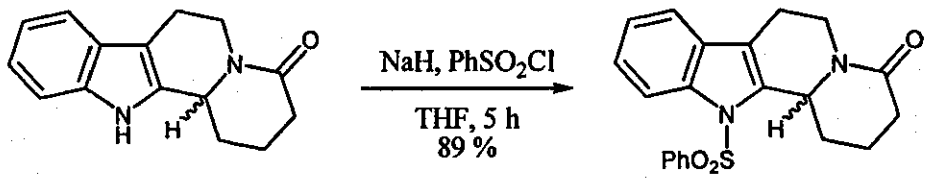


(213) **(216)**

Scheme 105

The reaction was unsuccessful and it was proposed that the inertness was due to the free indole NH. Successful cyclisation was achieved after protection of **(213)** using potassium hydride in conjunction with phenylsulfonyl chloride. Protection of the indole NH of **(328)** was therefore investigated to prevent any complications or unwanted side-reactions.

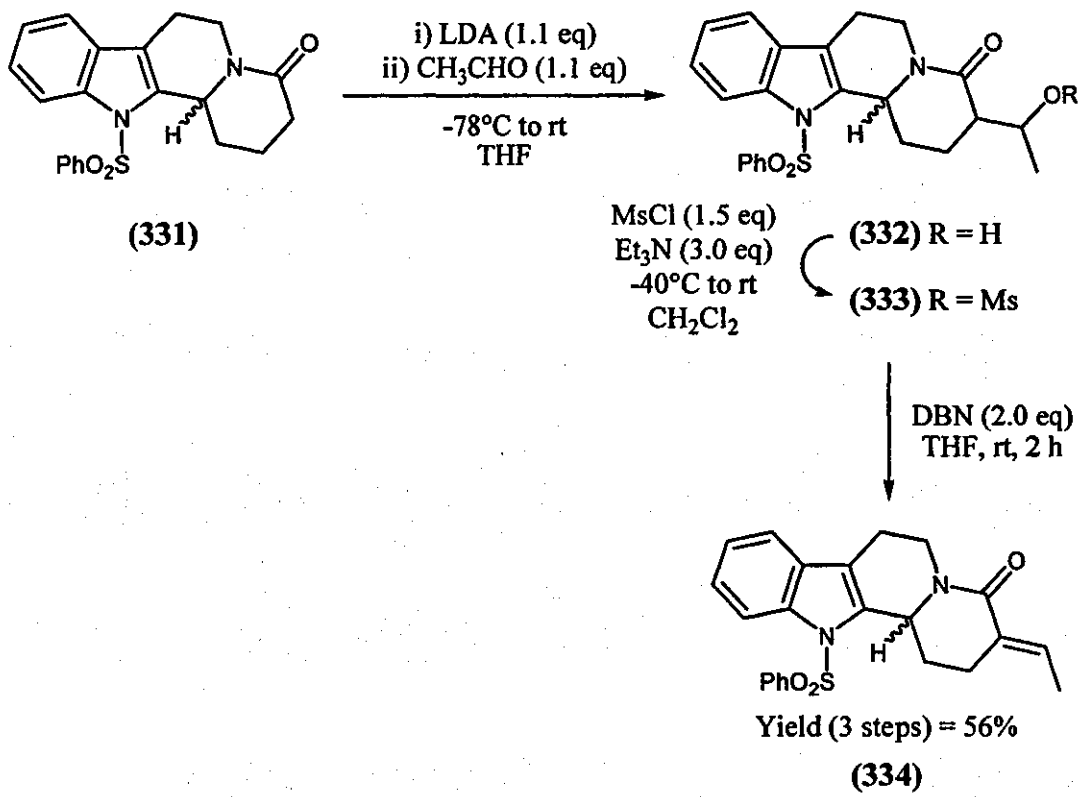
The indole of **(328)** was protected using sodium hydride and phenylsulfonyl chloride and the target compound **(331)** was obtained in 89% yield **(Scheme 106)**.



(328) (331)

Scheme 106

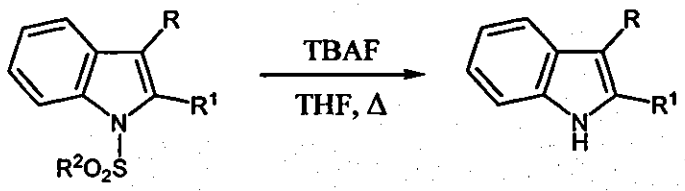
The protected compound **(331)** was subjected to the three step sequence shown in **Scheme 107**: lithium enolate generation and subsequent aldol reaction with acetaldehyde to form **(332)**, mesylation of the alcohol **(332)** to produce **(333)** and elimination to introduce the (*E*)-ethylidene unit. The target compound **(334)** was isolated in an overall yield of 56% from **(331)**.



(331) (334)

Scheme 107

Yashura and Sakamoto[96] have developed a mild and neutral method to deprotect *N*-phenylsulfonyl and *N*-methylsulfonyl protected indoles. A typical desulfonylation procedure involved refluxing the *N*-sulfonylindole **(335)** in tetra-*n*-butylammonium fluoride (TBAF) and THF to produce **(336)** (**Scheme 108**). Some representative examples are shown in **Table 5**.



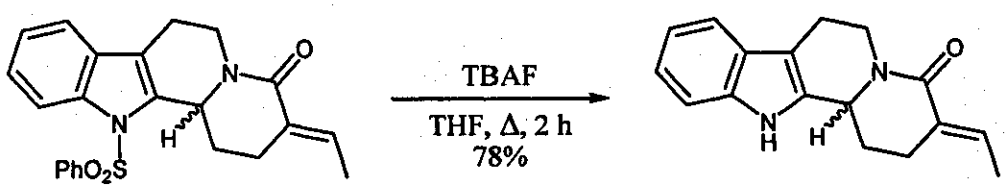
(335) **(336)**

Scheme 108

R	R^1	R^2	Time (h)	TBAF (eq)	Yield (%)
H	Ph	Ph	1.5	1	100
CHO	H	Me	1	1	100
COMe	H	Me	2	1	91
COOMe	Ph	Me	0.5	1	77

Table 5

The desulfonylation procedure was successfully applied to **(334)** and the desired product **(337)** was isolated in 78% yield (**Scheme 109**).

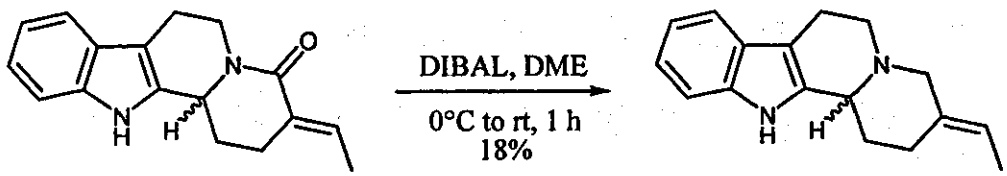


(334) **(337)**

Scheme 109

2.10 Selective Reduction and Generation of (±)-Deplancheine

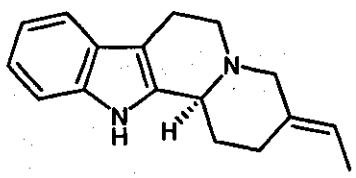
The selective reduction of **(337)** to **(208)** (**Scheme 110**) was achieved using methodology developed by Meyers.[88]



(337) **(208)**
+ impurity

Scheme 110

The compound **(208)** and an impurity after flash column chromatography were obtained in a combined yield of 18%. It appeared form TLC that the desired compound had been isolated as a single spot. However, it was evident from the ^{1}H NMR spectrum after purification that the impurity was significant and present in approximately 50%. It was also possible to observe peaks that compared favourably to those published in the literature[88] for (*E*)-(S)-(-)-deplancheine **(338)** (**Figure 57**).



(338)

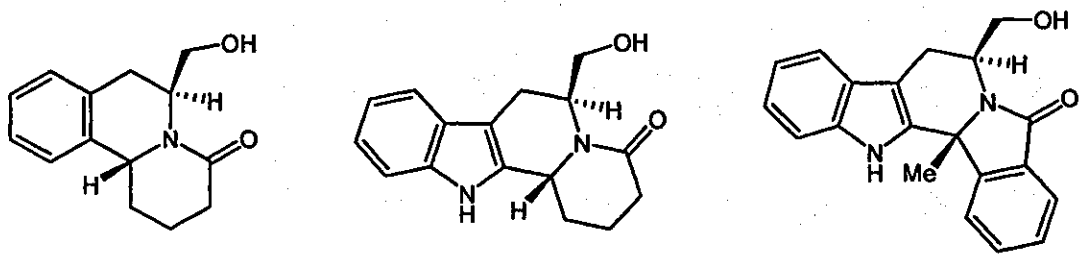
Figure 57

Additional purification of **(208)** by re-columning and preparative TLC were unsuccessful and inferior ^{1}H NMR spectra were progressively obtained. A possible reason for the impurity is that the work-up and purification attempts did not destroy all or any of the

DIBAL complexes associated with **(337)**. The impurity by ^{1}H NMR may be due to diisobutyl groups or components of DIBAL. Due to the quantity of material and time restraints we were unable to purify this material any further.

2.11 Conclusion

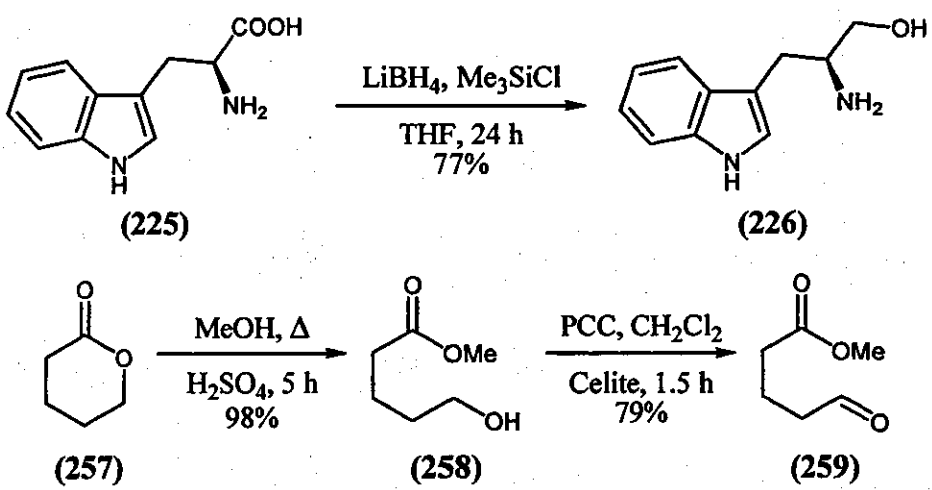
In conclusion we have developed methodology for the asymmetric synthesis of isoquinoline and indole alkaloid systems exemplified by **(218)**, **(219)** and **(220)** (**Figure 58**).



(218) **(219)** **(220)**

Figure 58

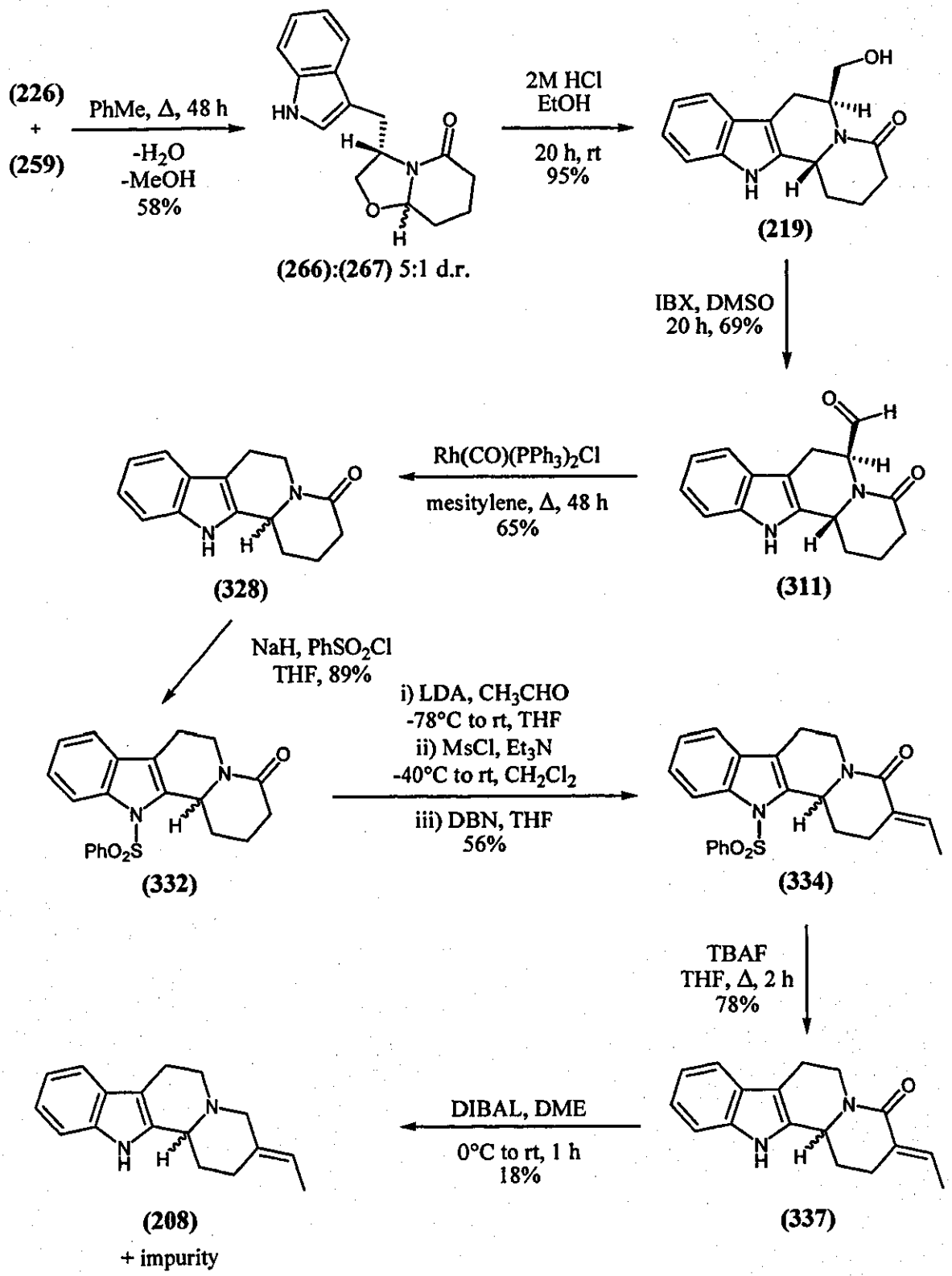
The most significant component of this thesis is the total synthesis of (±)-deplancheine **(208)** outlined in **Scheme 111** and **Scheme 112** (11 steps with an overall yield of 1.3% from **(257)**).



(225) **(226)**

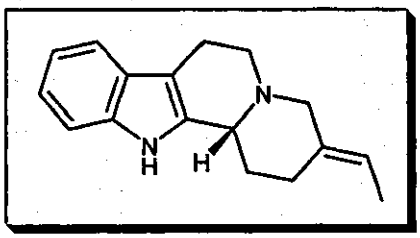
(257) **(258)** **(259)**

Scheme 111


(226)
+
(259)
PhMe, Δ, 48 h
-H2O
-MeOH
58%
(266):(267) 5:1 d.r.
2M HCl
EtOH
20 h, rt
95%
(219)
IBX, DMSO
20 h, 69%
(311)
Rh(CO)(PPh3)2Cl
mesitylene, Δ, 48 h
65%
(328)
NaH, PhSO2Cl
THF, 89%
(332)
i) LDA, CH3CHO
-78°C to rt, THF
ii) MsCl, Et3N
-40°C to rt, CH2Cl2
iii) DBN, THF
56%
(334)
TBAF
THF, Δ, 2 h
78%
(337)
DIBAL, DME
0°C to rt, 1 h
18%
(208)
+ impurity

Scheme 112

It is hoped that the preliminary research outlined in this thesis can be expanded on and provide an alternative, highly stereoselective route to (*R*)-(+)-deplancheine **(204)** (**Figure 59**) and a variety of indole alkaloids.



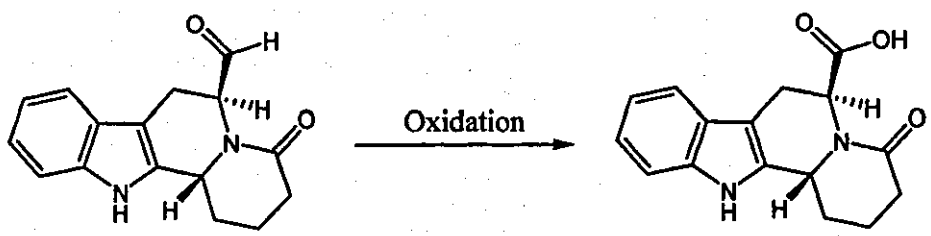
(204)

Figure 59

2.12 Future Work

2.12.1 Decarboxylation and Synthesis of (*R*)-(+)-Deplancheine

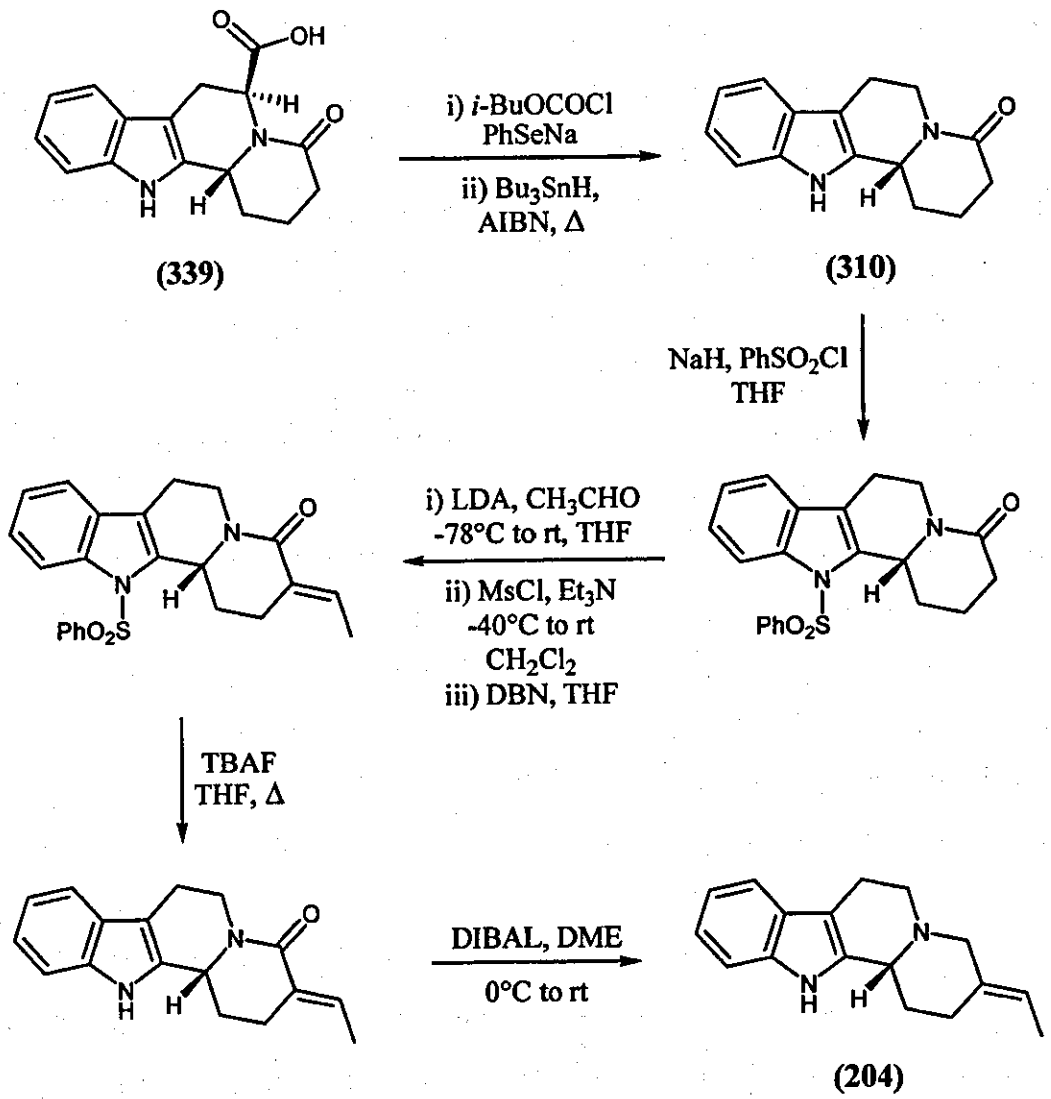
Alternative methods to remove the hydroxymethyl substituent (auxiliary) of **(219)** to that reported in **Section 2.8.3** and **Section 2.8.5** could be investigated. A different approach would be to oxidise the aldehyde **(311)** to the carboxylic acid **(339)** (**Scheme 113**) and decarboxylate the latter. The oxidative transformation could be possibly achieved by a Jones oxidation or potassium permanganate in acid or basic solution. An alternative method is silver(I) oxide which is a fairly specific oxidising agent for aldehydes.[66]



(311) **(339)**

Scheme 113

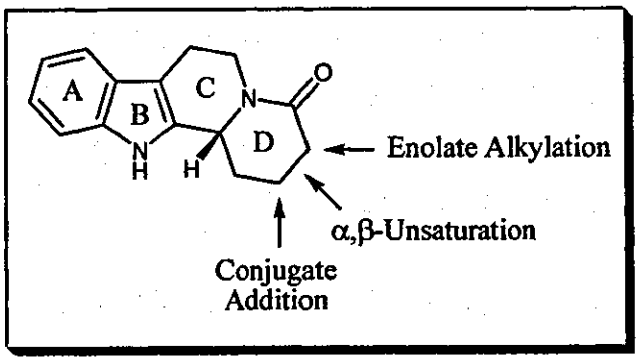
It is feasible that a radical pathway devised by Martin[72] could be used to decarboxylate **(339)**. The product **(310)** could then be used to synthesise (*R*)-(+)-deplancheine **(204)** (**Scheme 114**) utilising methodology reported in this thesis.



Scheme 114

2.12.2 Derivatisation of the Indolo[2,3-*a*]quinolizidine Ring System

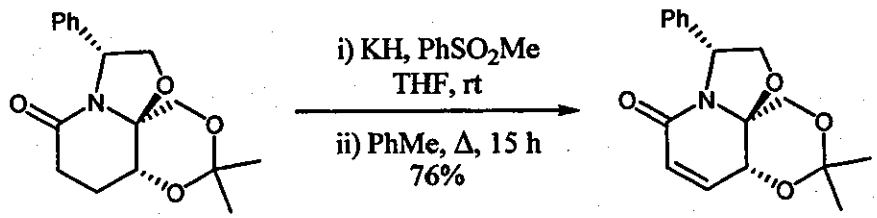
The presence of a carbonyl group on ring D of the decarbonylated product **(310)** (**Figure 60**) could allow future derivatisation through exploitation of the carbonyl group reactivity.



(310)

Figure 60

Amat[159] has developed a procedure that introduces α,β-unsaturation (**Scheme 115**) to systems such as **(340)**.

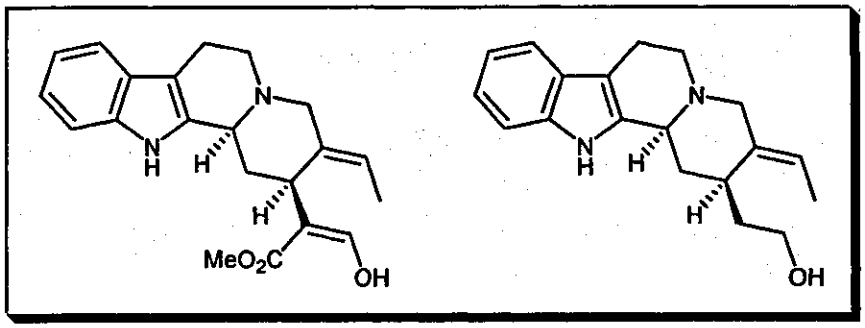


(340)

Scheme 115

The chemistry outlined in **Scheme 115** could be applied to the tetracyclic system **(310)** to produce α,β-unsaturation and enable conjugate addition. It has been demonstrated in this

thesis (**Scheme 89** and **Scheme 107**) that a three step sequence can be used to introduce an (*E*)-ethylidene unit. Both of these methods could be sequentially used during the synthesis of indole alkaloids such as geissoschizine **(200)** and geissoschizol **(341)**[71] **(Figure 61)**.



(200) **(341)**

Figure 61

Chapter 3

Experimental

3.1 General Procedures

3.1.1 Solvents and Reagents

Where necessary solvents were dried, distilled and used immediately or stored over 4Å molecular sieves prior to use.

Absolute Ethanol (>99.8%)	Used as purchased from Fisher Scientific, UK.
Acetonitrile (99.8%)	Used as purchased from Aldrich Chemical Co. Ltd.
Diethyl Ether (>99%)	Used as purchased from Fisher Scientific, UK.
Dichloromethane	Distilled from phosphorus pentoxide.
1,2-Dimethoxyethane (>99%)	Used as purchased from Lancaster Synthesis Ltd.
N,*N*-Dimethylformamide (>99.8%)	Used as purchased from Aldrich Chemical Co. Ltd.
Dimethylsulfoxide (>99.9%)	Used as purchased from Aldrich Chemical Co. Ltd.
Ethyl Acetate	Distilled from calcium chloride.
Hexane	Used as purchased from Fisher Scientific, UK.
Hexane (HPLC grade)	Used as purchased from Fisher Scientific, UK.
Isopropyl Alcohol (HPLC grade)	Used as purchased from Fisher Scientific, UK.
Light Petroleum Ether (40-60°C)	Distilled from calcium chloride.
Mesitylene (98%)	Used as purchased from Aldrich Chemical Co. Ltd.
Methanol	Used as purchased from Fisher Scientific, UK.
Tetrahydrofuran	Distilled from sodium and benzophenone.
Toluene	Distilled from sodium.
p-Xylene (>99%)	Used as purchased from Aldrich Chemical Co. Ltd.

Other chemicals used in this work were purchased from Acros (Fisher) Chemicals Ltd., Aldrich Chemical Co. Ltd., Lancaster Synthesis Ltd. and Merck Chemicals Ltd.

3.1.2 Chromatographic Procedures

Thin layer chromatography (TLC) was carried out using aluminium backed plates coated with silica gel (Merck Kiesegel 60 F_{254}). Plates were visualised under UV light (254 nm) or by staining with potassium permanganate, phosphomolybdic acid or 2,4-dinitrophenylhydrazine.

Flash column chromatography was conducted using silica gel (Merck Kiesegel 60 H). Pressure was applied to the column by hand bellows and samples were applied as saturated solutions in an appropriate solvent or adsorbed onto the minimum quantity of silica.

Chiral HPLC was performed using a Thermoseparations modular machine (V100 UV detector, P200 pump and TSP chromatographic integrator) with a ChiralCel OD-H column (250 x 4.6 mm) purchased from Merck Chemicals Ltd.

3.1.3 Infrared and Nuclear Magnetic Resonance Spectroscopy

Infrared spectra were recorded on a Paragon 1000 Perkin Elmer FT-IR Spectrophotometer (with internal calibration) in the range 4000-600 cm^{-1}. Samples were either dissolved in an appropriate solvent and run as a thin film on sodium chloride plates or as a potassium bromide disc.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were acquired using either a Bruker AC 250 or Bruker DPX 400 Spectrometer. All NMR samples were prepared in deuterated solvents with tetramethylsilane (TMS) as the internal standard. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). Coupling constants (*J* values) are reported in Hertz (Hz). Diastereomeric ratios were calculated from the integration of suitable peaks in the ^{1}H NMR spectrum.

3.1.4 Mass Spectrometry

Mass spectra were recorded on a Jeol SX102 mass spectrometer using electron impact (EI) or fast atom bombardment (FAB) ionisation techniques.

3.1.5 Melting Points, Elemental Analysis and Optical Rotations

Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected.

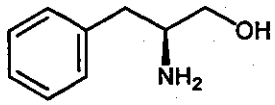
Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance.

Optical rotations were measured using an Optical Activity AA-2001 Automatic Polarimeter using a 0.25 dm cell.

3.1.6 X-Ray Crystallography

Data sets were collected on a Bruker SMART 1000 CCD diffractometer with graphite monochromated Mo-Kα radiation operating at low temperature (150K). The software used for data collection was SMART (Bruker, 2001) and cell refinement/data reduction was achieved using the program SAINT (Bruker, 2001). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the software SHELXTL (Sheldrick, G. M. (2001). Version 6.12, Bruker-AXS Inc., Madison, Wisconsin, USA).

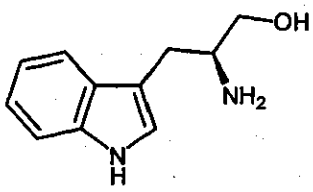
(2*S*)-2-Amino-3-phenylpropan-1-ol[107]



(71)

A solution of chlorotrimethylsilane (15.4 mL, 121.1 mmol) was added to $LiBH_4$ (1.32 g, 60.5 mmol) in dry THF (50 mL) under a nitrogen atmosphere. L-Phenylalanine **(224)** (5.0 g, 30.3 mmol) was added over a 5 min period and the mixture was stirred for 24 h at room temperature. MeOH (30 mL) was cautiously added to the reaction vessel and volatiles were removed under reduced pressure. A 20% KOH solution (25 mL) was added to the residue and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. The target compound **(71)** was isolated as a yellow solid which was recrystallised from CH_2Cl_2/hexane to yield colourless crystals (4.35 g, 95%). Mp 91-93°C (lit.[105] 90-92°C); ν_{max}/cm^{-1} (film) 3354, 3296, 2920, 2853, 1583, 1495, 1453, 1058, 743, 700; δ_H ($CDCl_3$, 400 MHz) 1.78 (1H, br, s, O*H*), 2.53 (1H, dd, *J* 13.5, 8.6, C*H*(H)CHNH$_2$), 2.80 (1H, dd, *J* 13.5, 5.2, C*H*(H)CHNH$_2$), 3.09-3.16 (1H, m, C*H*NH$_2$), 3.39 (1H, dd, *J* 10.6, 7.2, C*H*(H)OH), 3.64 (1H, dd, *J* 10.6, 3.9, C*H*(H)OH), 7.19-7.33 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 41.1 (CH_2), 54.2 (CH), 66.5 (CH_2), 126.4 (CH), 128.6 (2 x CH), 129.2 (2 x CH), 138.7 (C).

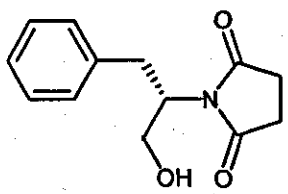
(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol[107]



(226)

A solution of chlorotrimethylsilane (12.4 mL, 97.9 mmol) was added to $LiBH_4$ (1.07 g, 49.0 mmol) in dry THF (60 mL) under a nitrogen atmosphere. L-Tryptophan **(225)** (5.0 g, 24.5 mmol) was added over a 5 min period and the mixture was stirred for 24 h at room temperature. MeOH (30 mL) was cautiously added to the reaction vessel and volatiles were removed under reduced pressure. A 20% KOH solution (25 mL) was added to the residue and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure to yield a viscous orange oil. The oil was adsorbed onto silica and purified by flash column chromatography (9:1 EtOAc:MeOH). The target compound **(226)** was isolated as a yellow foam (3.59 g, 77%) which could not be induced to crystallise. $[\alpha]^{23}_D$ = -21.5 (*c* = 1.0, MeOH) (lit.[160] $[\alpha]_D$ = -19.0 (*c* = 1.0, MeOH); ν_{max}/cm^{-1} (KBr) 3404, 2902, 1592, 1455, 1059, 958, 747, 493; δ_H (DMSO, 400 MHz) 2.57 (1H, dd, *J* 14.1, 7.2, C*H*(H)CHNH$_2$), 2.79 (1H, dd, *J* 14.1, 5.9, C*H*(H)CHNH$_2$), 2.95-3.01 (1H, m, C*H*NH$_2$), 3.23 (1H, dd, *J* 10.4, 6.7, C*H*(H)OH), 3.36 (1H, dd, *J* 10.3, 4.7, C*H*(H)OH), 6.94 (1H, t, *J* 7.4, Ar*H*), 7.05 (1H, t, *J* 6.8, Ar*H*), 7.14 (1H, s, NHC*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.54 (1H, d, *J* 8.0, Ar*H*), 10.85 (1H, br, s, N*H*), O*H* not visible; δ_C (DMSO, 100 MHz) 29.6 (CH_2), 53.5 (CH), 66.0 (CH_2), 111.2 (CH), 111.6 (C), 118.0 (CH), 118.4 (CH), 120.7 (CH), 123.2 (CH), 127.5 (C), 136.1 (C); *m/z* (EI) 190 (M^+, 3%), 130 (100%). Accurate mass: found 190.1102, $C_{11}H_{14}N_2O$ requires 190.1106.

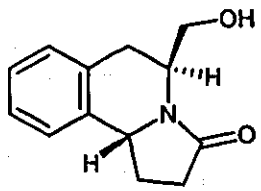
1-[(1*S*)-2-Hydroxy-1-(phenylmethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione



(228)

(2*S*)-2-Amino-3-phenylpropan-1-ol **(71)** (3.0 g, 19.8 mmol) and succinic anhydride **(227)** (1.99 g, 19.8 mmol) were dissolved in toluene (150 mL) with stirring. Triethylamine (5 mL) was added and the solution was refluxed for 18 h. The reaction vessel was allowed to cool to room temperature and solvent was removed under reduced pressure. The resultant yellow solid was adsorbed onto silica and purified by flash column chromatography (3:1 EtOAc:hexane). The target compound **(228)** was isolated as a white solid (3.93 g, 85%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield colourless needles. Mp 130-132°C; $[\alpha]^{22}_D$ = -92.8 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3417, 1689, 1402, 1375, 1168, 705; δ_H ($CDCl_3$, 400 MHz) 2.50-2.67 (4H, m, 2 x C*H*$_2$CO), 3.07-3.17 (2H, m, CC*H*$_2$CH), 3.84 (1H, dd, *J* 12.0, 3.2, C*H*(H)OH), 4.00 (1H, dd, *J* 12.0, 7.1, C*H*(H)OH), 4.48-4.55 (1H, m, NC*H*), 7.16-7.30 (5H, m, Ar*H*), O*H* not visible; δ_C ($CDCl_3$, 100 MHz) 28.0 (2 x CH_2), 33.8 (CH_2), 55.8 (CH), 62.4 (CH_2), 126.8 (CH), 128.5 (2 x CH), 129.1 (2 x CH), 137.2 (C), 178.1 (2 x C); *m/z* (EI) 233 (M^+, 14%), 134 (100%). Accurate mass: found 233.1054, $C_{13}H_{15}NO_3$ requires 233.1052.

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

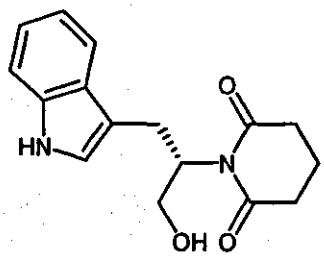


(231)

1-[(1*S*)-2-Hydroxy-1-(phenylmethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione **(228)** (3.0 g, 12.9 mmol) was dissolved in absolute EtOH (50 mL), cooled to 0°C and $NaBH_4$ (0.97 g, 25.7 mmol) was added with stirring. The solution was acidified to pH 1 by addition of 2M HCl in absolute EtOH and the resultant white suspension was stirred for an additional 20 h at room temperature. The mixture was quenched by careful addition of saturated aqueous sodium bicarbonate solution (40 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure to yield a colourless oil which was dissolved in dry CH_2Cl_2 (30 mL) under a nitrogen atmosphere. The mixture was cooled to -78°C and $TiCl_4$ (2.12 mL, 19.3 mmol) was added dropwise. After stirring for 10 min, the mixture was allowed to warm to room temperature and stirred for an additional 20 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL), extracted with CH_2Cl_2 (3 x 30 mL), dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield a green oil which was adsorbed onto silica and purified by flash column chromatography (100% EtOAc). The target compound **(231)** was isolated as a pale green solid (2.21 g, 79%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield colourless needles. Mp 110-111°C; $[\alpha]^{22}_D$ = +97.4 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3354, 1662, 1419, 1062, 732; ($CDCl_3$, 400 MHz) 1.93-2.03 (1H, m, C*H*(H)CH_2CO), 2.42-2.48 (1H, m, C*H*(H)CO), 2.62-2.70 (2H, m, C*H*(H)CO & C*H*(H)CH_2CO), 2.73 (1H, dd, *J* 16.5, 3.8, CC*H*(H)CH), 3.04 (1H, dd, *J* 16.3, 6.5, CC*H*(H)CH), 3.62 (1H, dd, *J* 11.4, 8.7, C*H*(H)OH), 3.71 (1H, dd, *J* 11.5,

5.2, C*H*(H)OH), 4.09 (1H, br, s, O*H*), 4.43-4.49 (1H, m, C*H*CH_2OH), 4.84 (1H, t, *J* 7.7, CC*H*), 7.11-7.27 (4H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 26.6 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 49.7 (CH), 54.5 (CH), 63.0 (CH_2), 124.3 (CH), 126.8 (CH), 127.2 (CH), 129.1 (CH), 132.4 (C), 136.8 (C), 175.2 (C); *m/z* (EI) 217 (M^+, 51%), 130 (100%). Accurate mass: found 217.1103, $C_{13}H_{15}NO_2$ requires 217.1103.

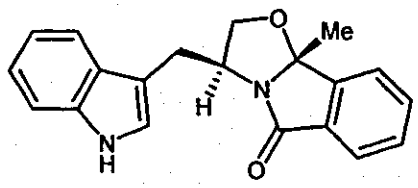
1-[(1*S*)-2-Hydroxy-1-(1*H*-indol-3-ylmethyl)ethyl]hexahydropyridine-2,6-dione



(237)

(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol **(226)** (2.65 g, 13.9 mmol), glutaric anhydride **(236)** (1.59 g, 13.9 mmol) and triethylamine (5 mL) were refluxed in toluene (150 mL) for 18 h with stirring. The solution was allowed to cool to room temperature before solvent was removed under reduced pressure to yield a viscous yellow oil. An extremely complex ^{1}H NMR spectrum of the crude reaction mixture was obtained and there was no evidence of the expected product **(237)**.

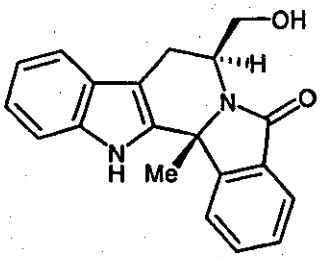
(3*S*,9b*R*)-3-(1*H*-Indol-3-ylmethyl)-9b-methyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one



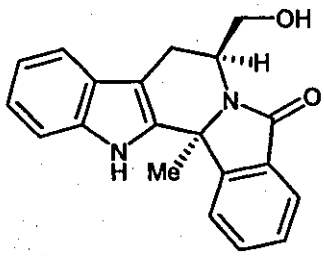
(251)

(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol **(226)** (4.55 g, 23.9 mmol) and 2-acetylbenzoic acid **(245)** (3.93 g, 23.9 mmol) were refluxed in toluene (150 mL) for 48 h under Dean-Stark conditions. The mixture was allowed to cool to room temperature before solvent was removed under reduced pressure. The resultant brown viscous oil was adsorbed onto silica and purified by flash column chromatography (3:2 EtOAc:hexane). The target compound **(251)** was isolated as a white solid (5.18 g, 68%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield colourless needles. Mp 184-185°C; $[\alpha]^{23}_D$ = -109.9 (*c* = 1.1, $CHCl_3$); ν_{max}/cm^{-1} (film) 3341, 1700, 1355, 1010, 909, 739; (Found: C, 75.31; H, 5.65; N, 8.64. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80%); δ_H ($CDCl_3$, 400 MHz) 1.70 (3H, s, C*H*$_3$), 3.17 (1H, dd, *J* 14.8, 8.6, CC*H*(H)CH), 3.42 (1H, dd, *J* 14.8, 5.7, CC*H*(H)CH), 4.18 (1H, dd, *J* 8.9, 6.4, C*H*(H)O), 4.31 (1H, dd, *J* 8.9, 7.4, C*H*(H)O), 4.56-4.63 (1H, m, NC*H*), 7.13-7.23 (2H, m, Ar*H*), 7.24-7.25 (1H, m, NHC*H*), 7.37 (1H, dt, *J* 8.0, 1.0, Ar*H*), 7.49-7.53 (2H, m, Ar*H*), 7.58-7.61 (1H, m, Ar*H*), 7.72-7.74 (1H, m, Ar*H*), 7.76-7.78 (1H, m, Ar*H*), 8.17 (1H, br, s, N*H*); δ_C ($CDCl_3$, 100 MHz) 23.1 (CH_3), 30.7 (CH_2), 56.1 (CH), 74.8 (CH_2), 99.0 (C), 111.2 (CH), 111.7 (C), 118.8 (CH), 119.5 (CH), 122.1 (2 x CH), 122.5 (CH), 124.3 (CH), 127.7 (C), 130.1 (CH), 131.7 (C), 133.2 (CH), 136.2 (C), 147.4 (C), 174.4 (C); *m/z* (EI) 318 (M^+, 43%), 130 (100%). Accurate mass: found 318.1368, $C_{20}H_{18}N_2O_2$ requires 318.1368.

(3*S*,9b*R*) and (3*S*,9b*S*)-3-(Hydroxymethyl)-9b-methyl-3,4,9,9b-tetrahydro-1*H*-isoindolo[1,2-*a*]β-carbolin-1-one



(220)



(252)

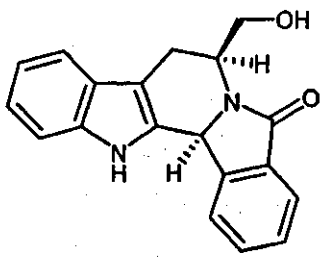
(3*S*,9b*R*)-3-(1*H*-Indol-3-ylmethyl)-9b-methyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]isoindol-5-one **(251)** (0.85 g, 2.67 mmol) was dissolved in dry CH_2Cl_2 (15 mL) under a nitrogen atmosphere, cooled to -78°C and $TiCl_4$ (0.44 mL, 4.01 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for an additional 20 h. The mixture was quenched with saturated aqueous NH_4Cl solution (15 mL), extracted with EtOAc (3 x 15 mL), dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield a brown oil which was shown to be a mixture of diastereoisomers (5:2) by ^1H NMR spectroscopy. The oil was adsorbed onto silica and purified by flash column chromatography (2:3 to 3:2 EtOAc/hexane).

Major isomer (220) (0.53 g, 62%). Isolated as colourless blocks. Mp 286-288°C (EtOAc/hexane); $[\alpha]^{22}_D$ = +172.2 (*c* = 1.0, DMSO); (Found: C, 75.26; H, 5.59; N, 8.80. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80%); ν_{max}/cm^{-1} (KBr) 3196, 1655, 1404, 1329, 1248, 1032, 741; δ_H (DMSO, 400 MHz) 1.86 (3H, s, C*H*$_3$), 2.73 (1H, dd, *J* 15.6, 6.8, CC*H*(H)CHN), 2.98 (1H, d, *J* 16.0, CC*H*(H)CHN), 3.62-3.72 (2H, m, C*H*$_2$OH), 4.95-5.01 (1H, m, NC*H*), 5.08 (1H, t, *J* 5.4, O*H*), 7.00 (1H, t, *J* 7.6, Ar*H*), 7.12 (1H, t, *J* 7.6, Ar*H*), 7.40-7.43 (2H, m, Ar*H*), 7.53 (1H, t, *J* 7.4, Ar*H*), 7.71-7.75 (2H, m, Ar*H*), 8.28 (1H, d, *J* 7.6, Ar*H*), 11.44 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 21.7 (CH_2), 28.2 (CH_3), 50.3 (CH), 61.4 (CH_2), 61.7 (C), 104.2 (C), 111.0 (CH), 118.1 (CH), 118.6 (CH), 121.4

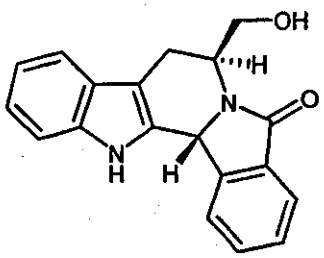
(CH), 122.3 (CH), 123.0 (CH), 126.3 (C), 128.3 (CH), 129.5 (C), 132.2 (CH), 133.5 (C), 136.4 (C), 149.7 (C), 168.4 (C); *m/z* (EI) 318 (M^+, 37%), 303 (100%). Accurate mass: found 318.1371, $C_{20}H_{18}N_2O_2$ requires 318.1368.

Minor isomer (252) (0.20 g, 24%). Isolated as colourless blocks. Mp 294-295°C (EtOAc/hexane); $[\alpha]^{23}_D$ = -178.2 (*c* = 1.1 , DMSO); (Found: C, 75.15; H, 5.63; N, 8.70. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80%); ν_{max}/cm^{-1} (KBr) 3273, 1653, 1457, 1419, 1092, 724; δ_H (DMSO, 400 MHz) 1.88 (3H, s, C*H*$_3$), 2.78 (1H, dd, *J* 15.3, 11.4, CC*H*(H)CHN), 2.94 (1H, dd, *J* 15.3, 3.6, CC*H*(H)CHN), 3.81-3.88 (1H, m, NC*H*), 4.27-4.38 (2H, m, C*H*$_2$OH), 5.17 (1H, t, *J* 6.2, O*H*), 6.98 (1H, t, *J* 7.1, Ar*H*), 7.09 (1H, t, *J* 7.6, Ar*H*), 7.36 (1H, d, *J* 8.0, Ar*H*), 7.41 (1H, d, *J* 7.8, Ar*H*), 7.53 (1H, t, *J* 7.4, Ar*H*), 7.67 (1H, d, *J* 7.2, Ar*H*), 7.73 (1H, td, *J* 7.5, 1.2, Ar*H*), 8.30 (1H, d, *J* 7.7, Ar*H*), 11.31 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 24.7 (CH_2), 24.8 (CH_3), 55.3 (CH), 61.7 (CH_2), 64.3 (C), 107.2 (C), 111.1 (CH), 118.2 (CH), 118.8 (CH), 121.5 (CH), 122.6 (CH), 123.0 (CH), 125.8 (C), 128.6 (CH), 130.5 (C), 132.3 (CH), 135.6 (C), 136.2 (C), 149.0 (C), 168.2 (C); *m/z* (EI) 318 (M^+, 35%), 303 (100%). Accurate mass: found 318.1371, $C_{20}H_{18}N_2O_2$ requires 318.1368.

(3*S*,9b*S*) and (3*S*,9b*R*)-3-(Hydroxymethyl)-3,4,9,9b-tetrahydro-1*H*-isoindolo[1,2-*a*]β-carbolin-1-one



(253)



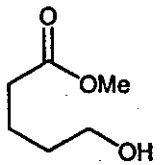
(254)

(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol **(226)** (3.0 g, 15.8 mmol) and 2-carboxybenzaldehyde **(74)** (2.37 g, 15.8 mmol) were refluxed in toluene (150 mL) for 48 h under Dean-Stark conditions. The mixture was allowed to cool to room temperature before solvent was removed under reduced pressure. This yielded a brown viscous oil which was shown to be a mixture of diastereoisomers (4:1) by ^{1}H NMR spectroscopy. The oil was adsorbed onto silica and purified by flash column chromatography (2:3 to 3:2 EtOAc:hexane).

Major isomer (253) (3.31 g, 69%). Isolated as colourless crystals. Mp 233-235°C (EtOH); $[\alpha]^{23}_D$ = -101.9 (*c* = 1.3, DMSO); (Found: C, 74.79; H, 5.52; N, 9.13. $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20%); ν_{max}/cm^{-1} (KBr) 3420, 1653, 1457, 1419, 1092, 724; δ_H (DMSO, 400 MHz) 2.80-2.85 (1H, m, CC*H*(H)CH), 2.95 (1H, dd, *J* 15.3, 3.6, CC*H*(H)CH), 3.85-3.89 (1H, m, C*H*CH$_2$OH), 4.29-4.32 (2H, m, C*H*$_2$OH), 5.18 (1H, t, *J* 5.7, O*H*), 6.12 (1H, s, NHCC*H*), 6.99 (1H, t, *J* 7.0, Ar*H*), 7.09 (1H, t, *J* 7.1, Ar*H*), 7.38 (1H, d, *J* 8.1, Ar*H*), 7.43 (1H, d, *J* 7.8, Ar*H*), 7.55 (1H, t, *J* 7.5, Ar*H*), 7.70-7.75 (2H, m, Ar*H*), 8.28 (1H, d, *J* 7.6, Ar*H*), 11.29 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 24.7 (CH$_2$), 58.3 (CH), 59.2 (CH), 61.3 (CH$_2$), 108.0 (C), 111.2 (CH), 118.0 (CH), 118.8 (CH), 121.4 (CH), 123.0 (CH), 123.5 (CH), 126.0 (C), 128.6 (CH), 131.3 (C), 131.9 (CH), 132.1 (C), 136.5 (C), 143.3 (C), 167.7 (C); *m/z* (EI) 304 (M^+, 63%), 273 (100%). Accurate mass: found 304.1217, $C_{19}H_{16}N_2O_2$ requires 304.1212.

Minor isomer (254) (0.81 g, 17%). Isolated as a pale yellow oil. $[\alpha]^{22}_{D}$ = +89.3 (*c* = 1.0, DMSO); ν_{max}/cm^{-1} (KBr) 3423, 1653, 1404, 1329, 1030, 741; δ_H (DMSO, 250 MHz) 2.74-2.82 (1H, m, CC*H*(H)CH), 2.90 (1H, d, *J* 16.0, CC*H*(H)CH), 3.56-3.61 (2H, m, CH_2OH), 4.80-4.89 (1H, m, C*H*CH$_2$OH), 4.96 (1H, t, *J* 5.7, O*H*), 5.96 (1H, s, NHCC*H*), 6.98 (1H, t, *J* 7.3, Ar*H*), 7.09 (1H, t, *J* 7.4, Ar*H*), 7.37-7.42 (2H, m, Ar*H*), 7.56 (1H, t, *J* 7.3, Ar*H*), 7.70-7.77 (2H, m, Ar*H*), 8.32 (1H, d, *J* 7.6, Ar*H*), 11.30 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 31.7 (CH_2), 48.7 (CH), 53.8 (CH), 60.9 (CH_2), 105.4 (C), 111.2 (CH), 118.0 (CH), 118.7 (CH), 121.4 (CH), 123.0 (CH), 123.7 (CH), 126.4 (C), 128.6 (CH), 129.6 (C), 131.7 (CH), 131.8 (C), 136.5 (C), 143.4 (C), 167.2 (C); *m/z* (EI) 304 (M^+, 72%), 273 (100%). Accurate mass: found 304.1209, $C_{19}H_{16}N_2O_2$ requires 304.1212.

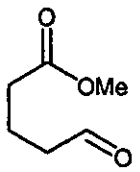
Methyl-5-hydroxypentanoate[124]



(258)

To a stirred solution of δ-valerolactone **(257)** (20.0 g, 200 mmol) in MeOH (200 mL) was added 20 drops of concentrated H_2SO_4. The mixture was refluxed for 5 h and then the reaction vessel was cooled in an ice/salt bath. $NaHCO_3$ (5 g) was added, the mixture stirred for 10 min, filtered and solvent was removed under reduced pressure. This yielded the target compound **(258)** as a colourless oil (25.9 g, 98%) which was used without additional purification. ν_{max}/cm^{-1} (film) 3418, 2950, 2872, 1738, 1438, 1202, 1169, 1060; δ_H ($CDCl_3$, 400 MHz) 1.56-1.63 (2H, m, CH_2CH_2OH), 1.69-1.79 (2H, m, $CH_2CH_2CH_2OH$), 2.37 (2H, t, *J* 7.2, CH_2COOCH_3), 3.47 (1H, br, s, O*H*), 3.64-3.65 (2H, m, CH_2OH), 3.68 (3H, s, CH_3); δ_C ($CDCl_3$, 100 MHz) 21.1 (CH_2), 32.0 (CH_2), 33.7 (CH_2), 51.6 (CH_3), 62.2 (CH_2), 174.4 (C).

Methyl-5-oxopentanoate



(259)

Pyridinium chlorochromate oxidation[125]

Methyl-5-hydroxypentanoate **(258)** (12.0 g, 90.8 mmol) was slowly added to a suspension of PCC (29.4 g, 136 mmol) and Celite (29.4 g) in dry CH_2Cl_2 (185 mL). The mixture was stirred for 2 h at room temperature, the solution decanted and the solids were washed with Et_2O (3 x 100 mL). The combined organic fractions were filtered through an alumina column and solvent was removed under reduced pressure. The resultant brown residue was adsorbed onto silica and purified by flash column chromatography (4:1 EtOAc:hexane). The target compound **(259)** was isolated as a colourless oil (9.34 g, 79%). ν_{max}/cm^{-1} (film) 2952, 1733, 1436, 1249, 1198, 1168; δ_H ($CDCl_3$, 400 MHz) 1.92-2.00 (2H, m, CH_2CH_2CHO), 2.39 (2H, t, *J* 7.4, CH_2COOCH_3), 2.54 (2H, td, *J* 7.2, 1.2, CH_2CHO), 3.68 (3H, s, CH_3), 9.78 (1H, t, *J* 1.2, *CH*O); δ_C ($CDCl_3$, 100 MHz) 17.4 (CH_2), 32.6 (CH_2), 42.9 (CH_2), 51.6 (CH_3), 173.4 (C), 201.4 (CH); *m/z* (EI) 130 (M^+, 6%), 115 (100%). Accurate mass: found 130.0628, $C_6H_{10}O_3$ requires 130.0630.

Swern oxidation

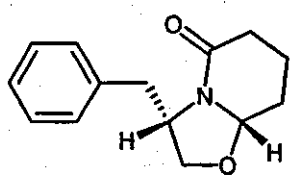
The Swern reagent was prepared from DMSO (1.18 mL, 16.7 mmol) and oxalyl chloride (0.73 mL, 8.32 mmol) in CH_2Cl_2 (30 mL) at -78°C. The mixture was stirred at -60°C for 2 min and then a solution of methyl-5-hydroxypentanoate **(258)** (1.0 g, 7.57 mmol) in CH_2Cl_2 (10 mL) was added. After 20 min triethylamine (5.27 mL, 37.8 mmol) was added and the reaction mixture stirred for 5 min at -60°C and then at room temperature for 30

min. Water (50 mL) was added to the mixture and the aqueous layer extracted with additional CH_2Cl_2 (50 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous $MgSO_4$. The combined organic fractions were filtered and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto silica and purified by flash column chromatography (4:1 EtOAc:hexane). The target compound **(259)** was isolated as a colourless oil (0.37 g, 38%). Spectroscopic data were identical with those previously reported for **(259)**.

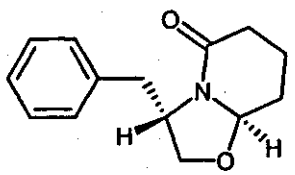
TPAP/NMO oxidation

Tetra-*n*-propylammonium perruthenate (0.13 g, 0.38 mmol) was added to methyl-5-hydroxypentanoate **(258)** (1.0 g, 7.57 mmol), *N*-methylmorpholine-*N*-oxide (1.33 g, 11.4 mmol) and powdered 4Å molecular sieves (4 g) in CH_2Cl_2 (20 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 20 h and then filtered through a short pad of silica, eluting with CH_2Cl_2. The filtrate was evaporated under reduced pressure and yielded a yellow oil which was adsorbed onto silica and purified by flash column chromatography (4:1 EtOAc:hexane). The target compound **(259)** was isolated as a colourless oil (0.43 g, 44%). Spectroscopic data were identical with those previously reported for **(259)**.

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



(261)



(262)

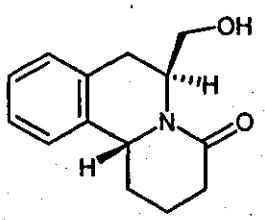
(2*S*)-2-Amino-3-phenylpropan-1-ol **(71)** (4.25 g, 28.1 mmol) and methyl-5-oxopentanoate **(259)** (3.66 g, 28.1 mmol) were refluxed in toluene (150 mL) for 48 h under Dean-Stark conditions. The mixture was allowed to cool to room temperature before solvent was removed under reduced pressure. This yielded a brown viscous oil which was shown to be a mixture of diastereoisomers (4:1) by ^{1}H NMR spectroscopy. The oil was adsorbed onto silica and purified by flash column chromatography (2:3 to 1:1 EtOAc:hexane).

Major isomer (261) (2.93 g, 45%). Isolated as colourless needles. Mp 91-92°C ($CHCl_3$/hexane); $[\alpha]^{24}_D$ = +52.3 (*c* = 1.1, $CHCl_3$); ν_{max}/cm^{-1} (film) 3484, 1602, 1476, 986, 705; δ_H ($CDCl_3$, 400 MHz) 1.36-1.45 (1H, m, C*H*(H)CHO), 1.63-1.73 (1H, m, C*H*(H)CH_2CO), 1.93-2.01 (1H, m, C*H*(H)CH_2CO), 2.18-2.24 (1H, m, C*H*(H)CHO), 2.33-2.46 (2H, m, CH_2CO), 2.60 (1H, dd, *J* 13.4, 9.8, C*H*(H)CC), 3.56 (1H, dd, *J* 13.4, 2.2, C*H*(H)CC), 3.67-3.73 (1H, m, C*H*(H)O), 4.00 (1H, d, *J* 9.6, C*H*(H)O), 4.19-4.24 (1H, m, NC*H*CH_2O), 4.66 (1H, dd, *J* 10.0, 3.2, NC*H*O), 7.20-7.32 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 17.5 (CH_2), 28.3 (CH_2), 31.1 (CH_2), 36.9 (CH_2), 56.7 (CH), 69.2 (CH_2), 89.0 (CH), 126.5 (CH), 128.5 (2 x CH), 129.6 (2 x CH), 138.1 (C), 168.1 (C); *m/z* (EI) 231 (M^+, 17%), 140 (100%). Accurate mass: found 231.1262, $C_{14}H_{17}NO_2$ requires 231.1259.

Minor isomer (262) (0.59 g, 9%). Isolated as a colourless oil. $[\alpha]^{23}_D$ = +34.5 (*c* =1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 1647, 1465, 1452, 999, 704; δ_H ($CDCl_3$, 400 MHz) 1.36-1.45 (1H, m, C*H*(H)CHO), 1.60-1.66 (1H, m, C*H*(H)CH_2CO), 1.87-1.93 (1H, m, C*H*(H)CH_2CO), 2.19-2.24 (1H, m, C*H*(H)CHO), 2.26-2.35 (1H, m, C*H*(H)CO), 2.51 (1H,

dd, *J* 18.0, 6.0, C*H*(H)CO), 2.80 (1H, dd, *J* 13.4, 9.2, C*H*(H)CC), 3.28 (1H, dd, *J* 13.4, 3.6, C*H*(H)CC), 3.62 (1H, dd, *J* 9.0, 7.6, C*H*(H)O), 4.02 (1H, dd, *J* 9.0, 7.6, C*H*(H)O), 4.45-4.54 (2H, m, NC*H*CH_2O & NC*H*O), 7.19-7.32 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 16.1 (CH_2), 27.2 (CH_2), 30.3 (CH_2), 36.7 (CH_2), 54.0 (CH), 68.2 (CH_2), 86.3 (CH), 125.7 (CH), 127.5 (2 x CH), 128.5 (2 x CH), 135.8 (C), 167.7 (C); *m/z* (EI) 231 (M^+, 25%), 140 (100%). Accurate mass: found 231.1257, $C_{14}H_{17}NO_2$ requires 231.1259.

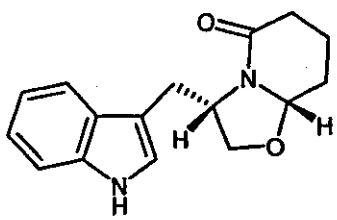
(6*S*,11b*R*)-6-(Hydroxymethyl)-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-4-one



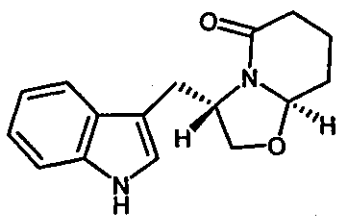
(218)

(3*S*,8a*S*)-3-(Phenylmethyl)perhydropyrido[2,1-*b*][1,3]oxazol-5-one **(261)** (3.2 g, 13.8 mmol) was dissolved in dry CH_2Cl_2 (30 mL) under a nitrogen atmosphere, cooled to -78°C and $TiCl_4$ (2.28 mL, 20.8 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for an additional 20 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted with CH_2Cl_2 (3 x 25 mL), dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield a brown oil which was adsorbed onto silica and purified by flash column chromatography (9:1 CH_2Cl_2:MeOH). The target compound **(218)** was isolated as a pale yellow solid (2.09 g, 65%), a portion of which was recrystallised from $CHCl_3$/hexane to yield colourless crystals. Mp 109-111°C; $[\alpha]^{23}_D$ = +87.2 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 3385, 2948, 2874, 1614, 1459, 1437, 1412, 1053, 728; δ_H ($CDCl_3$, 400 MHz) 1.87-1.96 (3H, m, CCHC*H*(H) & C*H*$_2$CH$_2$CO), 2.37-2.46 (2H, m, C*H*(H)CO & CCHC*H*(H)), 2.52-2.66 (1H, m, C*H*(H)CO), 2.73 (1H, dd, *J* 16.2, 4.2, CC*H*(H)CH), 3.05 (1H, dd, *J* 16.2, 6.2, CC*H*(H)CH), 3.55-3.68 (2H, m, C*H*$_2$OH), 4.61-4.64 (1H, m, CC*H*), 5.08-5.14 (1H, m, C*H*CH$_2$OH), 7.13-7.25 (4H, m, Ar*H*), O*H* not visible; δ_C ($CDCl_3$, 100 MHz) 18.9 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 32.3 (CH_2), 49.7 (CH), 53.2 (CH), 63.1 (CH_2), 124.4 (CH), 126.5 (CH), 127.1 (CH), 129.1 (CH), 133.0 (C), 136.4 (C), 171.8 (C); *m/z* (EI) 231 (M^+, 33%), 140 (100%). Accurate mass: found 231.1257, $C_{14}H_{17}NO_2$ requires 231.1259.

(3*S*,8a*S*) and (3*S*,8a*R*)-3-(1*H*-Indol-3-ylmethyl)perhydropyrido[2,1-*b*][1,3]oxazol-5-one



(266)



(267)

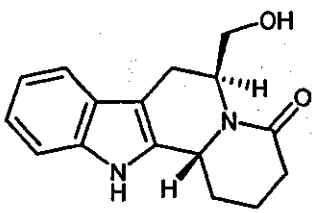
(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol **(226)** (4.55 g, 23.9 mmol) and methyl-5-oxopentanoate **(259)** (3.11 g, 23.9 mmol) were refluxed in toluene (150 mL) for 48 h under Dean-Stark conditions. The mixture was allowed to cool to room temperature before solvent was removed under reduced pressure. This yielded a brown viscous oil which was shown to be a mixture of diastereoisomers (5:1) by ^{1}H NMR spectroscopy. The oil was adsorbed onto silica and purified by flash column chromatography (3:7 to 3:2 EtOAc:hexane).

Major isomer (266) (3.23 g, 50%). Isolated as colourless needles. Mp 158-160°C (CH_2Cl_2/hexane); $[\alpha]^{23}_D$ = -59.2 (*c* = 1.0, $CHCl_3$); (Found: C, 70.85; H, 6.69; N, 10.48. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36%); ν_{max}/cm^{-1} (film) 3406, 3270, 2951, 2874, 1627, 1472, 1456, 745; δ_H ($CDCl_3$, 400 MHz) 1.44-1.54 (1H, m, C*H*(H)CHO), 1.64-1.76 (1H, m, C*H*(H)CH_2CO), 1.94-2.02 (1H, m, C*H*(H)CH_2CO), 2.22-2.28 (1H, m, C*H*(H)CHO), 2.41-2.45 (2H, m, C*H*(H)CO), 2.67 (1H, dd, *J* 14.0, 10.4, C*H*(H)CC), 3.67 (1H, ddd, *J* 9.2, 6.4, 1.6, C*H*(H)O), 3.72-3.76 (1H, m, C*H*(H)CC), 4.02 (1H, d, *J* 9.2, C*H*(H)O), 4.27-4.32 (1H, m, NC*H*CH_2O), 4.67 (1H, dd, *J* 10.0, 3.2, NC*H*O), 7.01 (1H, d, *J* 2.0, NHC*H*), 7.13 (1H, t, *J* 7.6, Ar*H*), 7.19 (1H, t, *J* 7.6, Ar*H*), 7.35 (1H, d, *J* 8.0, Ar*H*), 7.82 (1H, d, *J* 8.0, Ar*H*), 8.36 (1H, br, s, N*H*); δ_C ($CDCl_3$, 100 MHz) 17.5 (CH_2), 27.0 (CH_2), 28.4 (CH_2), 31.0 (CH_2), 56.1 (CH), 69.9 (CH_2), 89.0 (CH), 111.1 (CH), 112.5 (C), 119.3 (CH), 119.5 (CH), 122.1 (CH), 122.4 (CH), 127.7 (C), 136.2 (C), 168.1 (C); *m/z*

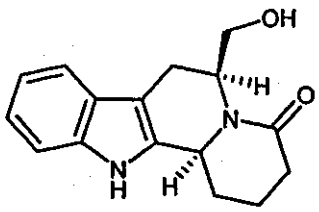
(EI) 270 (M^+, 33%), 130 (100%). Accurate mass: found 270.1369, $C_{16}H_{18}N_2O_2$ requires 270.1368.

Minor isomer (267) (0.52 g, 8%). Isolated as a yellow oil. $[\alpha]^{23}_D$ = -6.1 (*c* = 1.3, $CHCl_3$); (Found: C, 70.80; H, 6.70; N, 10.15. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36%); ν_{max}/cm^{-1} (film) 3406, 3280, 1731, 1626, 1470, 1458, 744; δ_H ($CDCl_3$, 400 MHz) 1.33-1.38 (1H, m, C*H*(H)CHO), 1.49-1.60 (1H, m, C*H*(H)CH_2CO), 1.83-1.87 (1H, m, C*H*(H)CH_2CO), 2.15-2.19 (1H, m, C*H*(H)CHO), 2.27-2.36 (1H, m, C*H*(H)CO), 2.53 (1H, dd, *J* 18.0, 6.0, C*H*(H)CO), 3.05 (1H, dd, *J* 14.4, 8.8, C*H*(H)CC), 3.32 (1H, ddd, *J* 14.2, 3.2, 0.8, C*H*(H)CC), 3.69 (1H, dd, *J* 8.8, 7.2, C*H*(H)O), 4.07 (1H, dd, *J* 9.0, 7.8, C*H*(H)O), 4.46 (1H, dd, *J* 9.2, 4.4, NC*H*O), 4.60-4.67 (1H, m, NC*H*CH_2O), 7.03 (1H, d, *J* 2.4, NHC*H*), 7.12 (1H, t, *J* 7.4, Ar*H*), 7.20 (1H, t, *J* 7.4, Ar*H*), 7.36 (1H, d, *J* 7.4, Ar*H*), 7.70 (1H, d, *J* 8.0, Ar*H*), 8.16 (1H, br, s, N*H*); δ_C ($CDCl_3$, 100 MHz) 17.1 (CH_2), 27.5 (CH_2), 28.2 (CH_2), 31.4 (CH_2), 54.4 (CH), 69.7 (CH_2), 87.3 (CH), 111.1 (CH), 111.3 (C), 119.2 (CH), 119.6 (CH), 122.2 (CH), 122.5 (CH), 128.3 (C), 136.2 (C), 168.8 (C); *m/z* (EI) 270 (M^+, 31%), 130 (100%). Accurate mass: found 270.1372, $C_{16}H_{18}N_2O_2$ requires 270.1368.

(6*S*,12b*R*) and (6*S*,12b*S*)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one



(219)



(272)

Using $TiCl_4$ as activator

A mixture of (3*S*,8a*S*) and (3*S*,8a*R*)-3-(1*H*-indol-3-ylmethyl)perhydropyrido[2,1-*b*][1,3]oxazol-5-one **(266)** and **(267)** (1.14 g, 4.22 mmol) were dissolved in dry CH_2Cl_2 (30 mL) under a nitrogen atmosphere, cooled to -78°C and $TiCl_4$ (0.69 mL, 6.33 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for an additional 20 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted with EtOAc (3 x 20 mL), dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield a brown oil which was shown to be a mixture of diastereoisomers (5:2) by ^1H NMR spectroscopy. The oil was adsorbed onto silica and purified by flash column chromatography (1:1 to 4:1 EtOAc:hexane).

Major isomer (219) (0.51 g, 45%). Isolated as colourless needles. Mp 273-275°C (EtOH); $[\alpha]^{22}_D$ = +139.4 (*c* = 1.0, DMSO); (Found: C, 70.81; H, 6.66; N, 10.28. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36%); ν_{max}/cm^{-1} (KBr) 3183, 2945, 1616, 1439, 1408, 1326, 1305, 1060, 742; δ_H (DMSO, 400 MHz) 1.53-1.63 (1H, m, CCHC*H*(H)), 1.73-1.83 (2H, m, C*H*$_2$CH$_2$CO), 2.26-2.42 (2H, m, C*H*$_2$CO), 2.59-2.62 (1H, m, CCHC*H*(H)), 2.67 (1H, ddd, *J* 15.6, 6.2, 2.2, CC*H*(H)CH), 2.80 (1H, d, *J* 15.6, CC*H*(H)CH), 3.33-3.42 (2H, m, C*H*$_2$OH), 4.64-4.66 (1H, m, NHCC*H*), 4.80 (1H, t, *J* 5.8, O*H*), 5.21-5.26 (1H, m, C*H*CH$_2$OH), 6.97 (1H, t, *J* 7.4, Ar*H*), 7.06 (1H, t, *J* 7.6, Ar*H*),

7.32 (1H, d, *J* 8.0, Ar*H*), 7.40 (1H, d, *J* 7.6, Ar*H*), 10.90 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 18.9 (CH_2), 20.6 (CH_2), 28.5 (CH_2), 32.2 (CH_2), 47.8 (CH), 50.1 (CH), 59.7 (CH_2), 104.6 (C), 111.0 (CH), 117.7 (CH), 118.4 (CH), 120.8 (CH), 126.7 (C), 133.2 (C), 136.2 (C), 168.4 (C); *m/z* (EI) 270 (M^+, 78%), 239 (100%). Accurate mass: found 270.1369, $C_{16}H_{18}N_2O_2$ requires 270.1368.

Minor isomer (272) (0.19 g, 17%). Isolated as colourless blocks. Mp 246-248°C (EtOH); $[\alpha]^{22}_D$ = -38.9 (*c* = 1.1, DMSO); (Found: C, 71.07; H, 6.75; N, 10.50. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36%); ν_{max}/cm^{-1} (KBr) 3168, 2954, 1623, 1419, 1324, 1076, 1053, 744; δ_H (DMSO, 400 MHz) 1.59-1.72 (2H, m, C*H*(H)CH_2CO & CCHC*H*(H)), 1.85-1.91 (1H, m, C*H*(H)CH_2CO), 2.17-2.23 (1H, m, C*H*(H)CO), 2.42-2.58 (2H, m, CCHC*H*(H) & C*H*(H)CO), 2.68 (1H, dd, *J* 15.4, 5.0, CC*H*(H)CH), 3.12 (1H, dd, *J* 15.4, 4.2, CC*H*(H)CH), 3.30-3.41 (2H, m, CH_2OH), 4.26-4.32 (1H, m, C*H*CH_2OH), 4.80-4.82 (1H, m, NHCC*H*), 4.92 (1H, t, *J* 5.8, O*H*), 6.98 (1H, t, *J* 7.4, Ar*H*), 7.06 (1H, t, *J* 8.0, Ar*H*), 7.33 (1H, d, *J* 8.0, Ar*H*), 7.43 (1H, d, *J* 7.6, Ar*H*), 10.97 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 17.4 (CH_2), 20.6 (CH_2), 27.3 (CH_2), 31.9 (CH_2), 52.2 (CH), 54.6 (CH), 61.2 (CH_2), 106.0 (C), 111.1 (CH), 117.7 (CH), 118.4 (CH), 120.8 (CH), 126.6 (C), 133.2 (C), 136.2 (C), 171.7 (C); *m/z* (EI) 270 (M^+, 75%), 239 (100%). Accurate mass: found 270.1363, $C_{16}H_{18}N_2O_2$ requires 270.1368.

Using HCl as activator

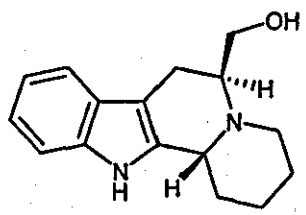
A mixture (3*S*,8a*S*) and (3*S*,8a*R*)-3-(1*H*-indol-3-ylmethyl)perhydropyrido[2,1-*b*][1,3]oxazol-5-one **(266)** and **(267)** (3.87 g, 14.3 mmol) were dissolved in absolute EtOH (60 mL) at room temperature. The solution was acidified to pH 1 by addition of 2M HCl in absolute EtOH. After stirring for 20 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (3 x 30 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield a brown solid which was adsorbed onto silica and purified by flash column chromatography (100% EtOAc). The target compound **(219)** was isolated as a

pale yellow solid (3.68 g, 95%), a portion of which was recrystallised from absolute EtOH to yield colourless blocks. Spectroscopic data were identical with those previously reported for **(219)**.

Epimerisation using TFA

Trifluoroacetic acid (7.32 mL, 95.1 mmol) was added to (6*S*,12b*R*)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(219)** (2.57 g, 9.51 mmol) in toluene (35 mL) and was heated at reflux for 18 h. The reaction was allowed to cool to room temperature, quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. This yielded a brown solid which was adsorbed onto silica and purified by flash column chromatography (100% EtOAc). The target compound **(272)** was isolated as a pale yellow solid (2.49 g, 97%), a portion of which was recrystallised from absolute EtOH to yield colourless blocks. Spectroscopic data were identical with those previously reported for **(272)**.

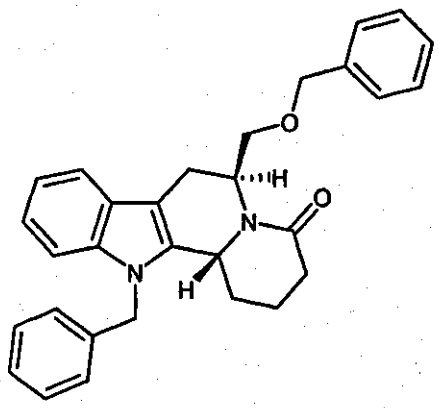
(6*S*,12b*R*)-1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-*a*]β-carbolin-6-ylmethanol



(274)

(6*S*,12b*R*)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(219)** (0.4 g, 1.48 mmol) in dry toluene (20 mL) was stirred at room temperature for 16 h under a nitrogen atmosphere with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (65+ wt% in toluene, 1.38 mL). The reaction mixture was quenched with saturated potassium sodium tartrate (Rochelle salt) solution (25 mL) and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto silica and purified by flash column chromatography (9:1 EtOAc:MeOH). The target compound **(274)** was isolated as a pale yellow oil (0.32 g, 84%). $[\alpha]^{23}_D$ = +68.8 (*c* = 1.1, EtOH); ν_{max}/cm^{-1} (KBr) 3280, 2923, 1453, 1044, 739; δ_H (DMSO, 400 MHz) 1.23-1.35 (1H, m, CCHC*H*(H)), 1.38-1.42 (1H, m, C*H*(H)CH_2CH_2N), 1.46-1.53 (1H, m, C*H*(H)CH_2N), 1.58-1.62 (1H, m, C*H*(H)CH_2N), 1.71-1.75 (1H, m, C*H*(H)CH_2CH_2N), 2.19-2.22 (1H, m, CCHC*H*(H)), 2.67-2.77 (2H, m, C*C*H_2CH), 2.81-2.90 (2H, m, N*C*H_2), 3.01-3.05 (1H, m, C*H*CH_2OH), 3.21-3.27 (1H, m, C*H*(H)OH), 3.56 (1H, d, *J* 8.6, NHCC*H*), 3.69-3.74 (1H, m, C*H*(H)OH), 4.45 (1H, t, *J* 5.1, O*H*), 6.92 (1H, t, *J* 7.0, Ar*H*), 7.00 (1H, t, *J* 7.5, Ar*H*), 7.26 (1H, d, *J* 8.0, Ar*H*), 7.36 (1H, d, *J* 4.8, Ar*H*), 10.65 (1H, s, N*H*); δ_C (DMSO, 100 MHz) 22.3 (CH_2), 23.9 (CH_2), 26.0 (CH_2), 30.7 (CH_2), 52.0 (CH_2), 53.3 (CH), 56.4 (CH_2), 60.5 (CH), 104.4 (C), 110.7 (CH), 117.3 (CH), 117.9 (CH), 120.1 (CH), 127.2 (C), 135.2 (C), 136.0 (C); *m/z* (EI) 256 (M^+, 7%), 225 (100%). Accurate mass: found 256.1573, $C_{16}H_{20}N_2O$ requires 256.1576.

(6*S*,12b*R*)-12-(Phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one

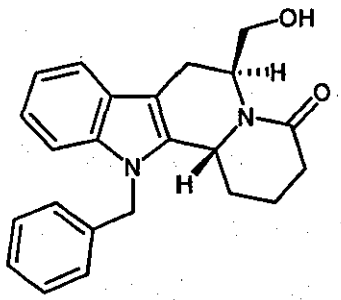


(293)

Sodium hydride (60% dispersion in mineral oil) (0.21 g, 5.18 mmol) was added to a dry round bottomed flask. Dry light petroleum ether (40-60°C) (10 mL) was added to the solid under a stream of nitrogen and the suspension was stirred for 1 min and then allowed to settle. The supernatant liquid was carefully removed *via* syringe and the washing procedure was repeated. The sodium hydride was re-suspended in dry DMF (10 mL) and the flask was cooled to 0°C in an ice bath. A solution of (6*S*,12b*R*)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(219)** (0.7 g, 2.59 mmol) in dry DMF (5 mL) was added and the mixture was stirred for 15 min at 0°C. Benzyl bromide (0.68 mL, 5.70 mmol) was added and the mixture was stirred for an additional 1 h at room temperature. The reaction was quenched with water (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto silica and purified by flash column chromatography (1:1 EtOAc:hexane). The target compound **(293)** was isolated as a yellow solid (1.05 g, 90%), a portion of which was recrystallised from $CHCl_3$/hexane to yield yellow blocks. Mp 121-122°C; $[\alpha]^{22}_D$ = +68.1 (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 2856, 1636, 1399, 1101, 736, 698; δ_H ($CDCl_3$, 400 MHz) 1.51-1.62 (1H, m, CCHC*H*(H)),

1.64-1.76 (1H, m, C*H*(H)CH_2CO), 1.79-1.87 (1H, m, C*H*(H)CH_2CO), 2.30-2.34 (1H, m, CCHC*H*(H)), 2.40-2.49 (1H, m, C*H*(H)CO), 2.53-2.60 (1H, m, C*H*(H)CO), 2.92 (1H, d, *J* 15.6, CC*H*(H)CH), 3.00 (1H, ddd, *J* 15.6, 5.6, 2.0, CC*H*(H)CH), 3.31-3.39 (2H, m, CHCH_2O), 4.35-4.53 (3H, m, NCC*H* & CCH_2O), 5.19 (1H, d, *J* 17.2, NC*H*(H)), 5.31 (1H, d, *J* 17.6, NC*H*(H)), 5.66-5.72 (1H, m, C*H*CH_2O), 6.87-6.89 (2H, m, Ar*H*), 7.12-7.25 (11H, m, Ar*H*), 7.55-7.58 (1H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 19.3 (CH_2), 22.0 (CH_2), 30.4 (CH_2), 32.0 (CH_2), 45.9 (CH), 47.7 (CH_2), 51.3 (CH), 68.3 (CH_2), 72.5 (CH_2), 107.8 (C), 109.7 (CH), 118.5 (CH), 119.8 (CH), 122.2 (CH), 125.7 (2 x CH), 127.0 (C), 127.4 (CH), 127.5 (2 x CH), 127.6 (CH), 128.3 (2 x CH), 128.9 (2 x CH), 133.4 (C), 137.2 (C), 138.2 (C), 138.3 (C), 170.4 (C); *m/z* (EI) 450 (M^+, 29%), 91 (100%). Accurate mass: found 450.2316, $C_{30}H_{30}N_2O_2$ requires 450.2307.

(6*S*,12b*R*)-6-(Hydroxymethyl)-12-(phenylmethyl)-1,2,3,4,6,7,12,12b-octahydro-pyrido[2,1-*a*]β-carbolin-4-one

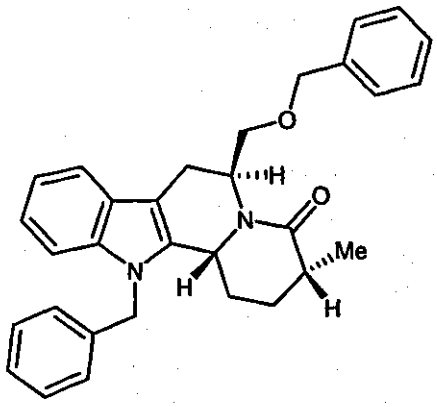


(294)

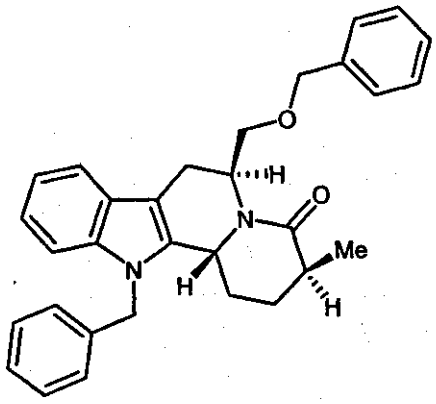
To a solution of (6*S*,12b*R*)-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(293)** (1.12 g, 2.49 mmol) in absolute EtOH was added a catalytic amount of palladium, 10 wt% on activated carbon. The reaction vessel was purged with nitrogen and then with hydrogen. A hydrogen filled balloon was fitted to the system and the mixture was stirred for 3 h. The contents of the reaction vessel were filtered through a Celite pad with additional CH_2Cl_2 (3 x 20 mL). The organic fractions were combined, dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto silica and purified by flash column chromatography (100% EtOAc). The target compound **(294)** was isolated as a pale yellow powder (0.78 g, 87%), a portion of which was recrystallised from $CHCl_3$/hexane to yield colourless blocks. Mp 232-233°C; $[\alpha]^{22}_D$ = +140.8 (*c* = 1.2, $CHCl_3$); ν_{max}/cm^{-1} (film) 3382, 1616, 1405, 1044, 735; δ_H ($CDCl_3$, 400 MHz) 1.60-1.70 (1H, m, CCHC*H*(H)), 1.83-1.90 (2H, m, C*H*$_2$CH$_2$CO), 2.36-2.40 (1H, m, CCHC*H*(H)), 2.50-2.55 (1H, m, C*H*(H)CO), 2.58-2.64 (1H, m, C*H*(H)CO), 2.89 (1H, d, *J* 15.6, CC*H*(H)CH), 3.05 (1H, ddd, *J* 16.0, 6.0, 2.0, CC*H*(H)CH), 3.48-3.53 (1H, m, CHC*H*(H)OH), 3.64 (1H, dd, *J* 11.0, 5.8, CHC*H*(H)OH), 4.62-4.65 (1H, m, NCC*H*), 5.29 (1H, d, *J* 17.2, NC*H*(H)), 5.40 (1H, d, *J* 17.2, NC*H*(H)), 5.49-5.54 (1H, m, C*H*CH$_2$OH), 6.97-7.00 (2H, m, Ar*H*), 7.14-7.21 (3H, m, Ar*H*), 7.26-7.34 (3H, m, Ar*H*), 7.56-7.58 (1H, m, Ar*H*), O*H* not visible; δ_C ($CDCl_3$, 100 MHz) 19.3 (CH_2), 21.8 (CH_2), 30.5 (CH_2), 31.9

(CH_2), 47.7 (CH_2), 49.0 (CH), 51.1 (CH), 63.1 (CH_2), 107.4 (C), 109.9 (CH), 118.4 (CH), 119.9 (CH), 122.3 (CH), 125.7 (2 x CH), 126.8 (C), 127.6 (CH), 129.0 (2 x CH), 133.0 (C), 137.1 (C), 138.2 (C), 172.3 (C); *m/z* (EI) 360 (M^+, 83%), 91 (100%). Accurate mass: found 360.1840, $C_{23}H_{24}N_2O_2$ requires 360.1838.

(3*R*,6*S*,12b*R*) and (3*S*,6*S*,12b*R*)-3-Methyl-12-(phenylmethyl)-6-{[(phenylmethyl)oxy] methyl}-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one



(295)



(296)

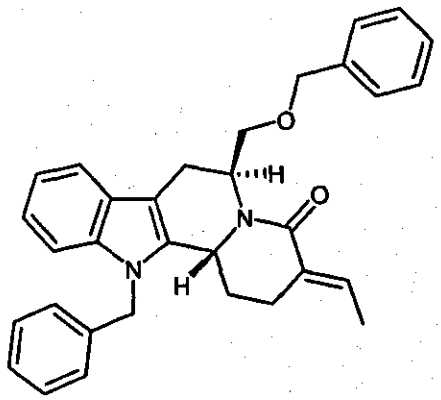
To a stirred solution of diisopropylamine (0.21 mL, 1.51 mmol) in dry THF (4 mL) was added *n*-BuLi in hexanes, 2.5M (0.61 mL, 1.51 mmol) dropwise at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min, cooled to -78°C whereupon addition of (6*S*,12b*R*)-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12, 12b-octahy-dropyrido[2,1-*a*]β-carbolin-4-one **(293)** (0.62 g, 1.38 mmol) in dry THF (4 mL) was achieved *via cannula*. The solution was stirred at -78°C for 30 min, MeI (0.09 mL, 1.51 mmol) was added and the reaction vessel was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure to yield a yellow oil which was shown to be a mixture of diastereoisomers (3:2) by ^1H NMR spectroscopy. The oil was adsorbed onto silica and purified by flash column chromatography (7:3 to 1:1 hexane:EtOAc).

Major isomer (295) (0.29 g, 45%). Isolated as a viscous yellow oil. $[\alpha]^{22}_D$ = +23.1 (*c* = 0.8, $CHCl_3$); ν_{max}/cm^{-1} (film) 2930, 1702, 1453, 1268, 738; δ_H ($CDCl_3$, 400 MHz) 1.22 (3H, d, *J* 7.2, C*H*$_3$), 1.45-1.53 (1H, m, C*H*(H)CHCH$_3$), 1.60-1.71 (1H, m, CCHC*H*(H)),

1.90-1.97 (1H, m, C*H*(H)CHCH$_3$), 2.15-2.21 (1H, m, CCHC*H*(H)), 2.48-2.54 (1H, m, C*H*CO), 2.96 (1H, ddd, *J* 15.6, 5.6, 1.6, CC*H*(H)CH), 3.07 (1H, d, *J* 14.4, CC*H*(H)CH), 3.26-3.35 (2H, m, CHCH_2O), 4.41-4.42 (1H, m, NCC*H*), 4.44 (2H, s, CCH_2O), 5.19 (1H, d, *J* 17.2, NC*H*(H)), 5.34 (1H, d, *J* 17.2, NC*H*(H)), 5.51-5.56 (1H, m, C*H*CH$_2$O), 6.83-6.86 (2H, m, Ar*H*), 7.13-7.23 (11H, m, Ar*H*), 7.58-7.60 (1H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 17.4 (CH_3), 21.6 (CH_2), 26.4 (CH_2), 28.8 (CH_2), 35.0 (CH), 46.5 (CH), 47.3 (CH_2), 49.8 (CH), 68.5 (CH_2), 72.5 (CH_2), 107.3 (C), 109.8 (CH), 118.5 (CH), 119.8 (CH), 122.1 (CH), 125.7 (2 x CH), 127.1 (C), 127.4 (3 x CH), 127.5 (CH), 128.2 (2 x CH), 128.9 (2 x CH), 133.6 (C), 137.3 (C), 138.1 (C), 138.3 (C), 174.6 (C); *m/z* (EI) 464 (M^+, 20%), 91 (100%). Accurate mass: found 464.2472, $C_{31}H_{32}N_2O_2$ requires 464.2464.

Minor isomer (296) (0.17 g, 27%). Isolated as a viscous yellow oil. $[\alpha]^{22}_D$ = +16.4 (*c* = 1.3, $CHCl_3$); ν_{max}/cm^{-1} (film) 2928, 1699, 1453, 1270, 739; δ_H ($CDCl_3$, 400 MHz) 1.27 (3H, d, *J* 7.2, CH_3), 1.41-1.48 (1H, m, C*H*(H)CHCH$_3$), 1.56-1.66 (1H, m, CCHC*H*(H)), 1.90-1.97 (1H, m, C*H*(H)CHCH$_3$), 2.30-2.35 (1H, m, CCHC*H*(H)), 2.40-2.47 (1H, m, C*H*CO), 2.86 (1H, d, *J* 16.0, CC*H*(H)CH), 3.01 (1H, ddd, *J* 15.8, 5.8, 2.2, CC*H*(H)CH), 3.34-3.42 (2H, m, CHCH_2O), 4.35-4.40 (2H, m, CCH_2O & NCC*H*), 4.50 (1H, d, *J* 12.0, CCH_2O), 5.20 (1H, d, *J* 17.6, NC*H*(H)), 5.30 (1H, d, *J* 17.2, NC*H*(H)), 5.73-5.78 (1H, m, C*H*CH$_2$O), 6.89-6.91 (2H, m, Ar*H*), 7.11-7.31 (11H, m, Ar*H*), 7.53-7.57 (1H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 18.6 (CH_3), 22.1 (CH_2), 28.7 (CH_2), 30.2 (CH_2), 37.3 (CH), 45.8 (CH), 47.8 (CH_2), 52.1 (CH), 68.4 (CH_2), 72.5 (CH_2), 108.0 (C), 109.8 (CH), 118.5 (CH), 119.8 (CH), 122.2 (CH), 125.8 (2 x CH), 127.0 (C), 127.4 (CH), 127.6 (3 x CH), 128.2 (2 x CH), 128.9 (2 x CH), 133.7 (C), 137.3 (C), 138.3 (C), 138.4 (C), 173.3 (C); *m/z* (EI) 464 (M^+, 23%), 105 (100%). Accurate mass: found 464.2461, $C_{31}H_{32}N_2O_2$ requires 464.2464.

(6*S*,12b*R*)-3-[(*E*)Ethylidene]-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2, 3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one

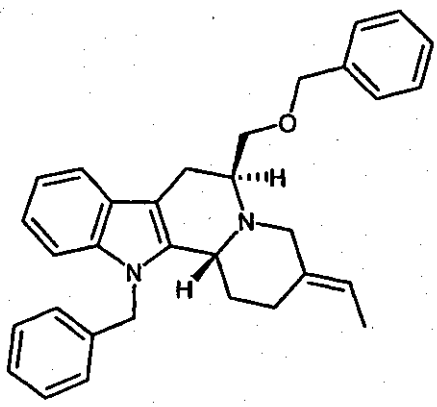


(297)

To a stirred solution of diisopropylamine (0.47 mL, 3.35 mmol) in dry THF (10 mL) was added *n*-BuLi in hexanes, 2.5M (1.34 mL, 3.35 mmol) dropwise at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min, cooled to -78°C whereupon addition of (6*S*,12b*R*)-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12, 12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(293)** (1.37 g, 3.04 mmol) in dry THF (10 mL) was achieved *via cannula*. The solution was stirred at -78°C for 30 min, acetaldehyde (0.19 mL, 3.35 mmol) was added and the reaction vessel was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. This yielded a yellow oil which was dissolved in dry CH_2Cl_2 (10 mL) containing triethylamine (1.27 mL, 9.12 mmol) and the mixture was cooled to -40°C. Methanesulfonyl chloride (0.35 mL, 4.56 mmol) was added dropwise and the mixture was stirred at -40°C for 20 min. The reaction vessel was allowed to warm to room temperature and stirred for an additional 3 h. A saturated aqueous NH_4Cl solution was added (10 mL) and the product was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced

pressure to yield a yellow oil. 1,5-Diazabicyclo[4.3.0]non-5-ene (0.75 mL, 6.08 mmol) was added to a solution of the mesylate in dry THF (10 mL) and the mixture was stirred for 2 h at room temperature. A saturated aqueous NH_4Cl solution was added (10 mL) and the product was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto silica and purified by flash column chromatography (4:1 hexane:EtOAc). The target compound **(297)** was isolated as a pale yellow solid (0.87 g, 60%), a portion of which was recrystallised from CH_2Cl_2/light petroleum ether (40-60°C) to yield yellow needles. Mp 182-184°C; $[\alpha]^{23}_D$ = +86.4 (*c* = 1.1, $CHCl_3$); ν_{max}/cm^{-1} (film) 1660, 1608, 1393, 1107, 737; δ_H ($CDCl_3$, 400 MHz) 1.58-1.70 (1H, m, CCHC*H*(H)), 1.74 (3H, d, *J* 7.0, C*H*$_3$), 2.24-2.34 (2H, m, C*H*(H)CCO & CCHC*H*(H)), 2.60-2.64 (1H, m, C*H*(H)CCO), 2.97-3.08 (2H, m, CC*H*$_2$CH), 3.29-3.36 (2H, m, CHC*H*$_2$O), 4.37 (1H, d, *J* 11.2, NCC*H*), 4.43 (2H, s, CC*H*$_2$O), 5.18 (1H, d, *J* 17.2, NC*H*(H)), 5.32 (1H, d, *J* 17.2, NC*H*(H)), 5.68-5.73 (1H, m, C*H*CH$_2$O), 6.84-6.87 (2H, m, Ar*H*), 7.02 (1H, q, *J* 7.2, C*H*CH$_3$), 7.12-7.25 (11H, m, Ar*H*), 7.58-7.60 (1H, m, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 13.8 (CH_3), 21.8 (CH_2), 23.6 (CH_2), 30.5 (CH_2), 46.5 (CH), 47.3 (CH_2), 50.9 (CH), 68.5 (CH_2), 72.5 (CH_2), 107.7 (C), 109.8 (CH), 118.6 (CH), 119.8 (CH), 122.1 (CH), 125.7 (2 x CH), 127.0 (C), 127.3 (CH), 127.5 (3 x CH), 128.2 (2 x CH), 128.9 (2 x CH), 129.0 (C), 133.1 (C), 135.1 (CH), 137.2 (C), 138.2 (C), 138.3 (C), 165.6 (C); *m/z* (EI) 476 (M^+, 100%). Accurate mass: found 476.2460, $C_{32}H_{32}N_2O_2$ requires 476.2464.

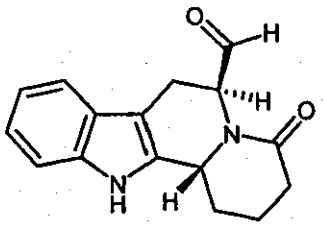
(6*S*,12b*R*)-3-[(*E*)Ethylidine]-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3, 4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carboline



(304)

(6*S*,12b*R*)-3-[(*E*)Ethylidene]-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4, 6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(297)** (0.15 g, 0.32 mmol) in dry toluene (10 mL) was stirred at room temperature for 16 h under a nitrogen atmosphere with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) (65+ wt% in toluene, 0.29 mL). The reaction mixture was quenched with saturated potassium sodium tartrate (Rochelle salt) solution (10 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. An extremely complex ^1H NMR spectrum of the crude reaction mixture was obtained and there was no evidence of the expected product **(304)**.

(6*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-6-carb-aldehyde



(311)

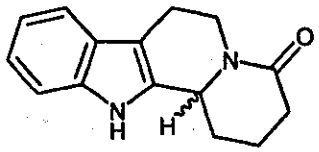
Dess-Martin periodinane oxidation

To a stirred solution of Dess-Martin periodinane (1.61 g, 3.78 mmol) in CH_2Cl_2 (15 mL) was added (6*S*,12b*R*)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(219)** (0.93 g, 3.44 mmol). After 20 h solvent was removed under reduced pressure and the resultant yellow oil was adsorbed directly onto silica. Purification by flash column chromatography (100% EtOAc) yielded the target compound **(311)** as a yellow foam (0.35 g, 38%). $[\alpha]^{23}_D$ = +197.8 (*c* = 1.3, CH_2Cl_2); ν_{max}/cm^{-1} (film) 3384, 3287, 1724, 1615, 1440, 1404, 1326, 739; δ_H ($CDCl_3$, 400 MHz) 1.68-1.79 (1H, m, CCHC*H*(H)), 1.97-2.05 (2H, m, C*H*$_2$CH$_2$CO), 2.41-2.55 (2H, m, CCHC*H*(H) & C*H*(H)CO), 2.70-2.76 (1H, m, C*H*(H)CO), 3.10 (1H, dd, *J* 15.6, 6.0, CC*H*(H)CH), 3.44 (1H, d, *J* 16.0, CC*H*(H)CH), 4.93 (1H, d, *J* 11.6, NHCC*H*), 5.99 (1H, d, *J* 6.4, C*H*CHO), 7.15 (1H, t, *J* 7.4, Ar*H*), 7.21 (1H, t, *J* 7.6, Ar*H*), 7.32 (1H, d, *J* 8.4, Ar*H*), 7.55 (1H, d, *J* 7.6, Ar*H*), 7.85 (1H, s, N*H*), 9.51 (1H, s, C*H*O); δ_C ($CDCl_3$, 100 MHz) 19.5 (CH_2), 20.0 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 52.1 (CH), 56.7 (CH), 106.5 (C), 111.0 (CH), 118.4 (CH), 120.1 (CH), 122.6 (CH), 126.5 (C), 132.6 (C), 136.4 (C), 170.2 (C), 199.3 (CH); *m/z* (EI) 268 (M^+, 91%), 239 (100%). Accurate mass: found 268.1212, $C_{16}H_{16}N_2O_2$ requires 268.1212.

IBX oxidation

(6*S*,12b*R*)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(219)** (2.45 g, 9.06 mmol) was dissolved in DMSO (15 mL) under a nitrogen atmosphere at room temperature. 2-Iodoxybenzoic acid (2.79 g, 9.97 mmol) was added and the mixture was stirred for 20 h. Solvent was removed under reduced pressure and EtOAc (30 mL) was added to the residue. The organic fraction was washed with H_2O (3 x 100 mL), dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. The resultant brown foam was adsorbed onto silica and purified by flash column chromatography (100% EtOAc). This yielded the target compound **(311)** as a pale yellow foam (1.68 g, 69%). Spectroscopic data were identical with those previously reported for **(311)**.

1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-*a*]β-carbolin-4-one

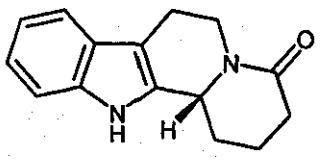


(328)

(6*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-6-carbaldehyde **(311)** (0.45 g, 1.68 mmol) was added to bis(triphenylphosphine)rhodium(I) carbonyl chloride **(319)** (0.12 g, 0.17 mmol) in mesitylene (20 mL) under a nitrogen atmosphere. After stirring for 48 h at reflux, the mixture was allowed to cool to room temperature before solvent was removed under reduced pressure. The resultant brown oil was adsorbed onto silica and purified by flash column chromatography (1:1 EtOAc:hexane). The target compound **(328)** was isolated as a pale yellow solid (0.26 g, 65%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield yellow blocks. Mp 248-249°C; ν_{max}/cm^{-1} (film) 3447, 1653, 1457, 724; δ_H ($CDCl_3$, 400 MHz) 1.73-1.89 (2H, m, NCHC*H*(H) & NCHCH$_2$C*H*(H)), 1.95-2.00 (1H, m, NCHCH$_2$C*H*(H)), 2.36-2.49 (2H, m, C*H*(H)CO & NCHC*H*(H)), 2.56-2.63 (1H, m, C*H*(H)CO), 2.71-2.92 (3H, m, NCH$_2$C*H*$_2$ & NC*H*(H)), 4.77-4.80 (1H, m, NC*H*), 5.14-5.22 (1H, m, NC*H*(H)), 7.10-7.14 (1H, m, Ar*H*), 7.16-7.20 (1H, m, Ar*H*), 7.34 (1H, d, *J* 7.9, Ar*H*), 7.51 (1H, d, *J* 7.7, Ar*H*), 8.07 (1H, br, s, N*H*); δ_H ($CDCl_3$, 100 MHz) 19.5 (CH_2), 21.0 (CH_2), 29.2 (CH_2), 32.5 (CH_2), 40.1 (CH_2), 54.4 (CH), 109.9 (C), 110.9 (CH), 118.5 (CH), 120.0 (CH), 122.3 (CH), 127.0 (C), 133.3 (C), 136.2 (C), 169.2 (C); *m/z* (EI) 240 (M^+, 100%). Accurate mass: found 240.0166, $C_{15}H_{16}N_2O$ requires 240.0167.

Chiral HPLC (ChiralCel OD-H, 85:15 hexane/propan-2-ol, 0.4 mL min^{-1}) on the purified sample indicated that the remaining chiral centre had racemised. The enantiomers were observed at 43.1 and 46.5 minutes.

(12b*R*)-1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-*a*]β-carbolin-4-one



(310)

Using Raney nickel (W2)

Raney nickel (W2) (1.02 g) was washed with H_2O (8 x 3 mL), *i*-PrOH (2 x 3 mL) and toluene (1 x 3 mL). To the Raney nickel was added (6*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carboline-6-carbaldehyde **(219)** (0.17 g, 0.63 mmol) and toluene (5 mL). The mixture was refluxed for 4 h, allowed to cool to room temperature and the solids were removed by filtration through Celite. The retained solids were washed with boiling MeOH (2 x 5 mL) and the combined filtrates were concentrated under reduced pressure. A ^{1}H NMR spectrum of the crude reaction mixture was obtained and there was no evidence of the expected product **(310)**, only starting material **(219)** was present. Additional time (72 h) and up to a two-fold excess of Raney nickel (W2) did not effect the desired transformation of **(219)** to **(310)**.

Using bis(triphenylphosphine)rhodium(I) carbonyl chloride and dppp

Bis(triphenylphosphine)rhodium(I) carbonyl chloride **(319)** (44 mg, 0.06 mmol) was added to *p*-xylene (8 mL) under a nitrogen atmosphere and the mixture was warmed to 80°C with stirring until the rhodium catalyst dissolved. 1,3-Bis(diphenyl-phosphino)propane (58 mg, 0.14 mmol) was added and the solution was stirred at 80°C (*ca.* 15 min) until a fine yellow precipitate formed. (6*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-6-carbaldehyde **(311)** (0.34 g, 1.27 mmol) was added, the mixture was heated at reflux for 96 h, allowed to cool to room temperature and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto

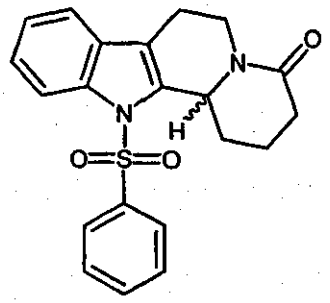
silica and purified by flash column chromatography (1:1 EtOAc:hexane). This yielded the target compound **(310)** and an inseparable impurity as a pale yellow solid (0.22 g, 72%). The purified ^{1}H NMR spectrum was identical with that previously reported for **(328)**, except for the impurity located between 7.10-7.68 ppm.

Using bis(triphenylphosphine)rhodium(I) carbonyl chloride

(6*S*,12b*R*)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-6-carbaldehyde **(311)** (0.57 g, 2.12 mmol) was added to bis(triphenylphosphine)rhodium(I) carbonyl chloride **(319)** (0.15 g, 0.21 mmol) in mesitylene (8 mL) under a nitrogen atmosphere. After stirring for 18 h at reflux, the mixture was allowed to cool to room temperature before solvent was removed under reduced pressure. The resultant brown oil was adsorbed onto silica and purified by flash column chromatography (1:1 EtOAc:hexane). This yielded the target compound **(310)** as a pale yellow solid (0.30 g, 59%), a portion of which was recrystallised from CH_2Cl_2/hexane to yield yellow blocks. Spectroscopic data were identical with those previously reported for **(328)**. Mp 248-249°C; $[\alpha]^{23}_D$ = +241.5 (c = 1.0, $CHCl_3$).

Chiral HPLC (ChiralCel OD-H, 85:15 hexane/propan-2-ol, 0.4 mL min^{-1}) on the purified sample indicated a 94% *e.e.* in favour of **(310)**. The enantiomers were observed at 42.2 and 46.4 minutes.

12-(Phenylsulfonyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one

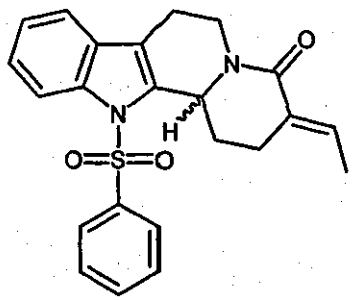


(331)

Sodium hydride (60% dispersion in mineral oil) (68 mg, 1.71 mmol) was added to a dry round bottomed flask. Dry light petroleum ether (40-60°C) (10 mL) was added to the solid under a stream of nitrogen and the suspension was stirred for 1 min and then allowed to settle. The supernatant liquid was carefully removed *via* syringe and the washing procedure was repeated. The sodium hydride was re-suspended in dry THF (10 mL) and the flask was cooled to 0°C in an ice bath. A solution of 1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(328)** (0.41 g, 1.71 mmol) in dry THF (5 mL) was added and the mixture was stirred for 15 min at 0°C. Benzenesulfonyl chloride (0.24 mL, 1.88 mmol) was added and the mixture was stirred for an additional 5 h at room temperature. The reaction was quenched with water (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. A brown solid was obtained which was adsorbed onto silica and purified by flash column chromatography (1:1 EtOAc:hexane). The target compound **(331)** was isolated as a yellow solid (0.58 g, 89%), a portion of which was recrystallised from EtOH to yield white crystals. Mp 263-265°C; ν_{max}/cm^{-1} (film) 1640, 1446, 1432, 1366, 1172, 981, 690; δ_H ($CDCl_3$, 400 MHz) 1.50-1.55 (1H, m, NCHC*H*(H)), 1.94-1.99 (2H, m, CH_2CH_2CO), 2.39-2.45 (1H, m, C*H*(H)CO), 2.52-2.56 (1H, m, NCH_2C*H*(H)), 2.60-2.67 (3H, m, C*H*(H)CO, NCH_2C*H*(H) & NC*H*(H)), 3.09-3.13 (1H, m, NCHC*H*(H)), 5.04-5.15 (2H, m, NC*H* & NC*H*(H)), 7.22-7.34 (5H, m, Ar*H*), 7.45 (1H, t, *J* 7.5, Ar*H*), 7.54-7.56 (2H, m,

Ar*H*), 8.10 (1H, d, *J* 8.2, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 19.7 (CH_2), 22.0 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 38.8 (CH_2), 56.5 (CH), 116.6 (CH), 118.7 (CH), 124.3 (C), 124.8 (CH), 125.4 (CH), 126.5 (2 x CH), 128.7 (2 x CH), 130.6 (C), 133.8 (CH), 135.9 (C), 136.2 (C), 138.5 (C), 169.8 (C); *m/z* (EI) 380 (M^+, 4%), 239 (100%). Accurate mass: found 380.1190, $C_{21}H_{20}N_2O_3S$ requires 380.1195.

3-[(*E*)Ethylidene]-12-(phenylsulfonyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one

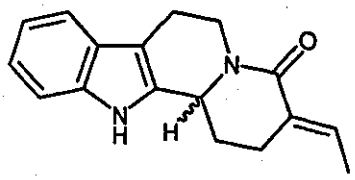


(334)

To a stirred solution of diisopropylamine (0.11 mL, 0.75 mmol) in dry THF (5 mL) was added *n*-BuLi in hexanes, 2.5M (0.3 mL, 0.75 mmol) dropwise at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min, cooled to -78°C whereupon addition of 12-(phenylsulfonyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(331)** (0.26 g, 0.68 mmol) in dry THF (5 mL) was achieved *via cannula*. The solution was stirred at -78°C for 30 min, acetaldehyde (0.04 mL, 0.75 mmol) was added and the reaction vessel was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. This yielded a yellow oil which was dissolved in dry CH_2Cl_2 (8 mL) containing triethylamine (0.29 mL, 2.05 mmol) and the mixture was cooled to -40°C. Methanesulfonyl chloride (0.08 mL, 1.03 mmol) was added dropwise and the mixture was stirred at -40°C for 20 min. The reaction vessel was allowed to warm to room temperature and stirred for an additional 3 h. A saturated aqueous NH_4Cl solution was added (5 mL) and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure to yield a yellow oil. 1,5-Diazabicyclo[4.3.0]non-5-ene (0.17 mL, 1.37 mmol) was added to a solution of the mesylate in dry THF (8 mL) and the mixture was stirred for 2 h at room temperature. A

saturated aqueous NH_4Cl solution was added (5 mL) and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and solvent was removed under reduced pressure. The resultant yellow oil was adsorbed onto silica and purified by flash column chromatography (1:1 EtOAc:hexane). The target compound **(334)** was isolated as white blocks (0.16 g, 56%), a portion of which was recrystallised from CH_2Cl_2/hexane to colourless blocks. Mp 246-247°C; ν_{max}/cm^{-1} (film) 2922, 1662, 1609, 1447, 1411, 1369, 1174, 725; δ_H ($CDCl_3$, 400 MHz) 1.51-1.62 (1H, m, CCHC*H*(H)), 1.80 (3H, d, *J* 7.2, C*H*$_3$), 2.50-2.78 (5H, m, C*H*$_2$CCO, NCH$_2$C*H*$_2$ & NC*H*(H), 3.04-3.09 (1H, m, CCHC*H*(H)), 5.08-5.11 (1H, m, NC*H*), 5.15-5.21 (1H, m, NC*H*(H)), 7.03 (1H, q, *J* 7.3, C*H*CH$_3$), 7.23-7.27 (1H, m, Ar*H*), 7.30-7.35 (4H, m, Ar*H*), 7.44-7.48 (1H, m, Ar*H*), 7.58-7.61 (2H, m, Ar*H*), 8.13 (1H, d, *J* 8.0, Ar*H*); δ_C ($CDCl_3$, 100 MHz) 13.8 (CH_3), 21.8 (CH_2), 23.5 (CH_2), 32.0 (CH_2), 38.9 (CH_2), 55.3 (CH), 116.3 (CH), 118.8 (CH), 123.8 (C), 124.7 (CH), 125.3 (CH), 126.4 (2 x CH), 128.8 (2 x CH), 129.3 (C), 130.3 (C), 133.9 (CH), 134.8 (CH), 135.6 (C), 136.2 (C), 138.2 (C), 165.1 (C); *m/z* (FAB) 407 ($(M+1)^+$, 41%), 154 (100%). Accurate mass: found 407.1463, $C_{23}H_{23}N_2O_3S$ requires 407.1460.

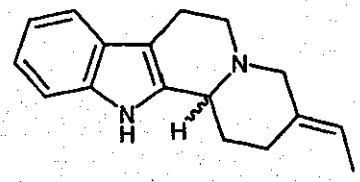
3-[(*E*)Ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one



(337)

Tetra-*n*-butylammonium fluoride (1.0M solution in tetrahydrofuran, 0.4 mL) was added to a stirred solution of 3-[(*E*)ethylidene]-12-(phenylsulfonyl)-1,2,3,4,6,7,12,12b-octahydro-pyrido[2,1-*a*]β-carbolin-4-one **(334)** (82 mg, 0.2 mmol) in THF (5 mL). The mixture was refluxed for 2 h, allowed to cool to room temperature, H_2O (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield a brown oil which was adsorbed onto silica and purified by flash column chromatography (3:2 hexane:EtOAc). The target compound **(337)** was isolated as a pale yellow oil (42 mg, 78%). ν_{max}/cm^{-1} (film) 3254, 1658, 1594, 1424, 724; δ_H ($CDCl_3$, 400 MHz) 1.78 (3H, d, *J* 7.2, 1.7, C*H*$_3$), 1.74-1.84 (1H, m, CCHC*H*(H)), 2.33-2.39 (1H, m, C*H*(H)CCO), 2.45-2.51 (1H, m, CCHC*H*(H)), 2.75-2.90 (3H, m, NCH$_2$C*H*$_2$ & C*H*(H)CCO), 2.94 (1H, dd, *J* 11.1, 4.2, NC*H*(H)), 4.81-4.85 (1H, m, NHCC*H*), 5.18-5.26 (1H, m, NC*H*(H)), 7.03 (1H, q, *J* 7.3, C*H*CH$_3$), 7.13 (1H, t, *J* 7.6, Ar*H*), 7.19 (1H, t, *J* 7.6, Ar*H*), 7.34 (1H, d, *J* 8.0, Ar*H*), 7.52 (1H, d, *J* 7.8, Ar*H*), 7.93 (1H, br, s, N*H*); δ_C ($CDCl_3$, 100 MHz) 13.7 (CH_3), 21.0 (CH_2), 22.7 (CH_2), 29.1 (CH_2), 40.5 (CH_2), 53.8 (CH), 109.9 (C), 110.9 (CH), 118.5 (CH), 119.8 (CH), 122.2 (CH), 126.9 (C), 129.1 (C), 133.2 (C), 134.0 (CH), 136.3 (C), 164.6 (C); *m/z* (EI) 266 (M^+, 100%). Accurate mass: found 266.1419, $C_{17}H_{18}N_2O$ requires 266.1419.

3-[(*E*)Ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carboline[88]



(208)

Diisobutylaluminium hydride (1.0M solution in toluene, 0.34 mL) was added dropwise at 0°C to 3-[(*E*)ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one **(337)** (30 mg, 0.11 mmol) in dry 1,2-dimethoxyethane (5 mL) under a nitrogen atmosphere. The solution was warmed to room temperature and stirred for 1 h. The reaction was quenched with MeOH (5 mL) and H_2O (1 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and filtered. Solvent was removed under reduced pressure to yield an orange oil which was adsorbed onto silica and purified by flash column chromatography (98:2 EtOAc:Et_3N). The target compound **(208)** (with traces of an inseparable impurity) was isolated as a yellow oil (5 mg, 18%).

Literature ^{1}H NMR signals[88] **for (338):**

δ_H ($CDCl_3$, 270 MHz) 7.75 (br, s, 1H), 7.48-7.08 (m, 4H), 5.42 (q, J = 6.8 Hz, 1H), 3.42-3.31 (m, 2H), 3.10-2.98 (m, 3H), 2.83-2.63 (m, 3H), 2.19-2.13 (m, 1H), 1.98 (br, t, 1H), 1.62 (d, J = 6.8 Hz, 3H), 1.65-1.53 (m, 1H).

Observed ^{1}H NMR signals for (208):

δ_H ($CDCl_3$, 400 MHz) 7.82 (br, s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16-7.06 (m, 2H), 5.43 (q, J = 6.9 Hz, 1H), 3.45 (d, J = 10.4 Hz, 1H), 3.35 (d, J = 11.9 Hz, 1H), 3.13-2.98 (m, 3H), 2.82-2.64 (m, 3H), 2.21-2.15 (m, 1H), 2.05-1.84 (signal masked by impurity), 1.63 (d, J = 6.7 Hz, 3H), 1.67-1.55 (m, 1H).

Chapter 4

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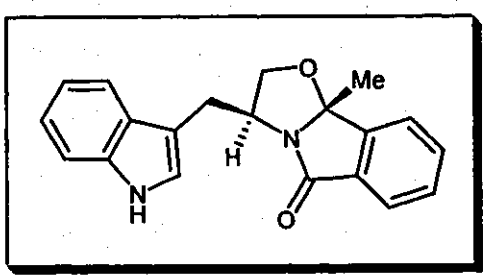
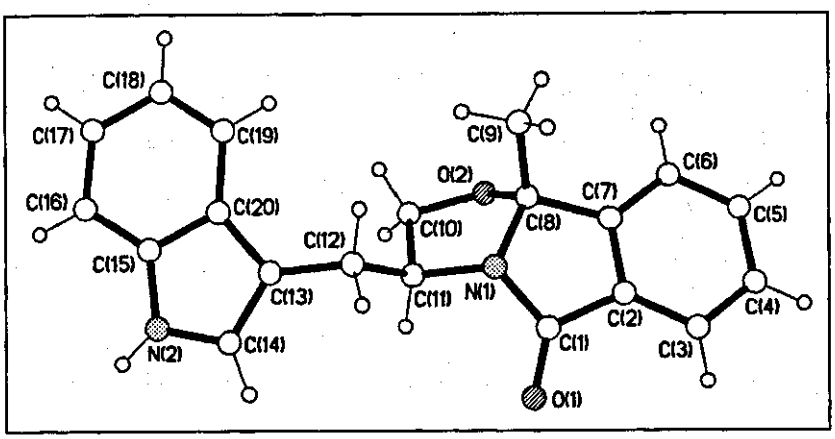
Appendix

Single Crystal X-Ray with Accompanying Data

(3*S*,9b*R*)-3-(1*H*-Indol-3-ylmethyl)-9b-methyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]isoindol-5-one



(251)



Crystal Data and Structure Refinement

Identification code	**(251)**	
Chemical formula	$C_{20}H_{18}N_2O_2$	
Formula weight	318.36	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 7.2249(7) Å	α = 90°
	b = 9.0792(8) Å	β = 90°
	c = 24.776(2) Å	γ = 90°
Cell volume	1625.2(3) $Å^3$	
Z	4	
Calculated density	1.301 g/cm^3	
Absorption coefficient μ	0.085 mm^{-1}	
F(000)	672	
Crystal colour and size	colourless, 0.71 × 0.50 × 0.04 mm^3	
Reflections for cell refinement	11068 (θ range 2.389 to 28.961°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.64 to 28.96°	
Index ranges	h –9 to 9, k –11 to 11, l –33 to 32	
Completeness to θ = 26.00°	99.9 %	
Intensity decay	0%	
Reflections collected	14364	
Independent reflections	3946 (R_{int} = 0.0144)	
Reflections with $F^2>2\sigma$	3753	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.942 and 0.997	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0542, 0.2220
Data / restraints / parameters	3946 / 0 / 219
Final R indices [$F^2>2\sigma$]	R1 = 0.0310, wR2 = 0.0836
R indices (all data)	R1 = 0.0330, wR2 = 0.0858
Goodness-of-fit on F^2	1.037
Absolute structure parameter	–0.1(9)
Extinction coefficient	0.0044(15)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.228 and –0.181 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$).

U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
O(1)	0.34770(15)	0.80205(12)	0.84586(3)	0.0401(2)
N(1)	0.09480(13)	0.65835(10)	0.82304(4)	0.02298(19)
C(1)	0.26150(16)	0.72668(13)	0.81351(4)	0.0257(2)
O(2)	0.06921(13)	0.41289(9)	0.80688(3)	0.03013(19)
N(2)	–0.19184(15)	0.59250(12)	1.04601(4)	0.0316(2)
C(2)	0.31535(15)	0.68861(13)	0.75734(4)	0.0245(2)
C(3)	0.45910(17)	0.74379(15)	0.72598(5)	0.0317(3)
C(4)	0.48084(19)	0.68426(17)	0.67447(5)	0.0382(3)
C(5)	0.3629(2)	0.57505(17)	0.65551(5)	0.0399(3)
C(6)	0.2182(2)	0.52189(15)	0.68712(5)	0.0347(3)
C(7)	0.19774(15)	0.57996(13)	0.73857(4)	0.0250(2)
C(8)	0.04901(16)	0.55172(12)	0.78025(4)	0.0241(2)
C(9)	–0.14482(17)	0.57421(15)	0.75774(5)	0.0329(3)
C(10)	–0.00423(18)	0.43497(13)	0.86047(5)	0.0312(3)
C(11)	0.04227(16)	0.59702(12)	0.87586(4)	0.0248(2)
C(12)	–0.11919(17)	0.68149(12)	0.90162(4)	0.0259(2)
C(13)	–0.17691(15)	0.62289(12)	0.95575(4)	0.0243(2)
C(14)	–0.10169(18)	0.66269(14)	1.00446(5)	0.0312(2)
C(15)	–0.33058(16)	0.50722(12)	1.02489(4)	0.0244(2)
C(16)	–0.46356(18)	0.42093(13)	1.05111(5)	0.0305(2)
C(17)	–0.59172(19)	0.34816(15)	1.01945(6)	0.0378(3)

C(18)	–0.58858(18)	0.36164(16)	0.96282(6)	0.0383(3)
C(19)	–0.45862(16)	0.44794(14)	0.93690(5)	0.0292(2)
C(20)	–0.32555(15)	0.52248(12)	0.96787(4)	0.0225(2)

Bond Lengths [Å] and Angles [°]

O(1)–C(1)	1.2241(14)	N(1)–C(1)	1.3752(15)
N(1)–C(11)	1.4721(13)	N(1)–C(8)	1.4732(13)
C(1)–C(2)	1.4858(15)	O(2)–C(8)	1.4301(13)
O(2)–C(10)	1.4438(14)	N(2)–C(15)	1.3705(15)
N(2)–C(14)	1.3749(15)	C(2)–C(7)	1.3825(16)
C(2)–C(3)	1.3906(16)	C(3)–C(4)	1.3947(18)
C(4)–C(5)	1.389(2)	C(5)–C(6)	1.393(2)
C(6)–C(7)	1.3873(15)	C(7)–C(8)	1.5122(15)
C(8)–C(9)	1.5212(16)	C(10)–C(11)	1.5566(16)
C(11)–C(12)	1.5349(16)	C(12)–C(13)	1.5020(14)
C(13)–C(14)	1.3718(16)	C(13)–C(20)	1.4403(15)
C(15)–C(16)	1.3997(16)	C(15)–C(20)	1.4199(14)
C(16)–C(17)	1.3818(19)	C(17)–C(18)	1.4084(19)
C(18)–C(19)	1.3813(18)	C(19)–C(20)	1.4039(16)

C(1)–N(1)–C(11)	123.30(9)	C(1)–N(1)–C(8)	111.69(9)
C(11)–N(1)–C(8)	109.46(8)	O(1)–C(1)–N(1)	125.83(10)
O(1)–C(1)–C(2)	127.60(11)	N(1)–C(1)–C(2)	106.57(9)
C(8)–O(2)–C(10)	105.32(8)	C(15)–N(2)–C(14)	108.81(9)
C(7)–C(2)–C(3)	121.88(10)	C(7)–C(2)–C(1)	108.67(10)
C(3)–C(2)–C(1)	129.44(11)	C(2)–C(3)–C(4)	117.12(13)
C(5)–C(4)–C(3)	121.12(12)	C(4)–C(5)–C(6)	121.18(11)
C(7)–C(6)–C(5)	117.70(13)	C(2)–C(7)–C(6)	120.98(11)
C(2)–C(7)–C(8)	109.15(9)	C(6)–C(7)–C(8)	129.69(11)
O(2)–C(8)–N(1)	102.97(8)	O(2)–C(8)–C(7)	113.07(9)
N(1)–C(8)–C(7)	102.73(9)	O(2)–C(8)–C(9)	112.41(10)
N(1)–C(8)–C(9)	112.48(10)	C(7)–C(8)–C(9)	112.40(9)
O(2)–C(10)–C(11)	106.10(9)	N(1)–C(11)–C(12)	112.12(9)
N(1)–C(11)–C(10)	101.26(8)	C(12)–C(11)–C(10)	114.22(10)
C(13)–C(12)–C(11)	113.90(9)	C(14)–C(13)–C(20)	106.19(10)
C(14)–C(13)–C(12)	125.60(11)	C(20)–C(13)–C(12)	128.12(10)
C(13)–C(14)–N(2)	110.42(10)	N(2)–C(15)–C(16)	129.87(10)
N(2)–C(15)–C(20)	107.82(10)	C(16)–C(15)–C(20)	122.28(11)
C(17)–C(16)–C(15)	117.65(11)	C(16)–C(17)–C(18)	120.87(12)
C(19)–C(18)–C(17)	121.56(12)	C(18)–C(19)–C(20)	119.01(11)
C(19)–C(20)–C(15)	118.63(10)	C(19)–C(20)–C(13)	134.57(10)
C(15)–C(20)–C(13)	106.75(10)		

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0474(5)	0.0497(6)	0.0233(4)	–0.0069(4)	0.0037(4)	–0.0225(5)
N(1)	0.0268(4)	0.0228(4)	0.0194(4)	–0.0009(3)	0.0028(3)	–0.0010(4)
C(1)	0.0283(5)	0.0282(5)	0.0206(5)	0.0002(4)	0.0020(4)	–0.0032(4)
O(2)	0.0416(5)	0.0202(4)	0.0287(4)	0.0005(3)	0.0027(4)	0.0030(3)
N(2)	0.0387(5)	0.0352(5)	0.0208(4)	–0.0030(4)	0.0017(4)	–0.0072(4)
C(2)	0.0244(5)	0.0299(6)	0.0191(4)	0.0012(4)	0.0004(4)	0.0039(4)
C(3)	0.0249(5)	0.0434(7)	0.0267(5)	0.0074(5)	0.0023(4)	0.0028(5)
C(4)	0.0330(6)	0.0546(8)	0.0271(6)	0.0106(6)	0.0084(5)	0.0161(6)
C(5)	0.0503(8)	0.0494(8)	0.0201(5)	–0.0012(5)	0.0038(5)	0.0214(7)
C(6)	0.0460(7)	0.0339(6)	0.0241(5)	–0.0047(5)	–0.0032(5)	0.0086(5)
C(7)	0.0281(5)	0.0263(5)	0.0206(5)	0.0007(4)	–0.0010(4)	0.0061(4)
C(8)	0.0293(5)	0.0202(5)	0.0229(5)	–0.0017(4)	–0.0008(4)	0.0006(4)
C(9)	0.0301(5)	0.0326(6)	0.0361(6)	0.0027(5)	–0.0070(5)	–0.0053(5)
C(10)	0.0396(6)	0.0235(5)	0.0305(6)	0.0032(4)	0.0058(5)	0.0005(5)
C(11)	0.0288(5)	0.0255(5)	0.0201(5)	0.0024(4)	0.0040(4)	–0.0017(4)
C(12)	0.0302(5)	0.0233(5)	0.0241(5)	0.0016(4)	0.0068(4)	–0.0011(4)
C(13)	0.0274(5)	0.0217(5)	0.0237(5)	–0.0009(4)	0.0044(4)	–0.0024(4)
C(14)	0.0356(6)	0.0311(6)	0.0268(5)	–0.0046(4)	0.0042(5)	–0.0095(5)
C(15)	0.0284(5)	0.0216(5)	0.0233(5)	–0.0006(4)	0.0044(4)	0.0023(4)
C(16)	0.0372(6)	0.0262(5)	0.0281(5)	0.0049(5)	0.0111(5)	0.0024(5)
C(17)	0.0337(6)	0.0347(6)	0.0450(7)	0.0041(5)	0.0126(5)	–0.0073(5)
C(18)	0.0298(6)	0.0406(7)	0.0444(7)	–0.0029(6)	0.0011(5)	–0.0109(5)
C(19)	0.0277(5)	0.0316(6)	0.0285(5)	–0.0020(4)	–0.0005(4)	–0.0015(5)
C(20)	0.0246(5)	0.0193(5)	0.0235(5)	0.0001(4)	0.0042(4)	0.0018(4)

Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

	x	y	z	U
H(2)	–0.1649	0.6010	1.0805	0.038
H(3)	0.5390	0.8188	0.7391	0.038
H(4)	0.5779	0.7190	0.6520	0.046
H(5)	0.3813	0.5359	0.6204	0.048
H(6)	0.1363	0.4484	0.6739	0.042

H(9A)	–0.1682	0.5019	0.7292	0.049
H(9B)	–0.1553	0.6738	0.7428	0.049
H(9C)	–0.2358	0.5614	0.7867	0.049
H(10A)	0.0538	0.3657	0.8863	0.047
H(10B)	–0.1398	0.4189	0.8608	0.047
H(11)	0.1515	0.5988	0.9006	0.037
H(12A)	–0.0831	0.7861	0.9057	0.039
H(12B)	–0.2268	0.6776	0.8769	0.039
H(14)	–0.0015	0.7293	1.0088	0.037
H(16)	–0.4656	0.4127	1.0893	0.037
H(17)	–0.6832	0.2882	1.0361	0.045
H(18)	–0.6780	0.3102	0.9420	0.046
H(19)	–0.4593	0.4567	0.8987	0.035

Hydrogen Bonds [Å and °]

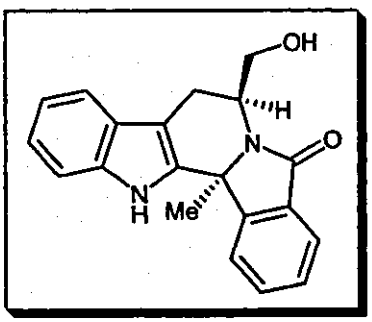
D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(2)–H(2)...O(1A)	0.88	2.03	2.8591(13)	157.2

Symmetry Operations for Equivalent Atoms

A x–1/2,–y+3/2,–z+2

Single Crystal X-Ray with Accompanying Data

(3*S*,9b*S*)-3-(Hydroxymethyl)-9b-methyl-3,4,9,9b-tetrahydro-1*H*-isoindolo[1,2-*a*]β-carbolin-1-one



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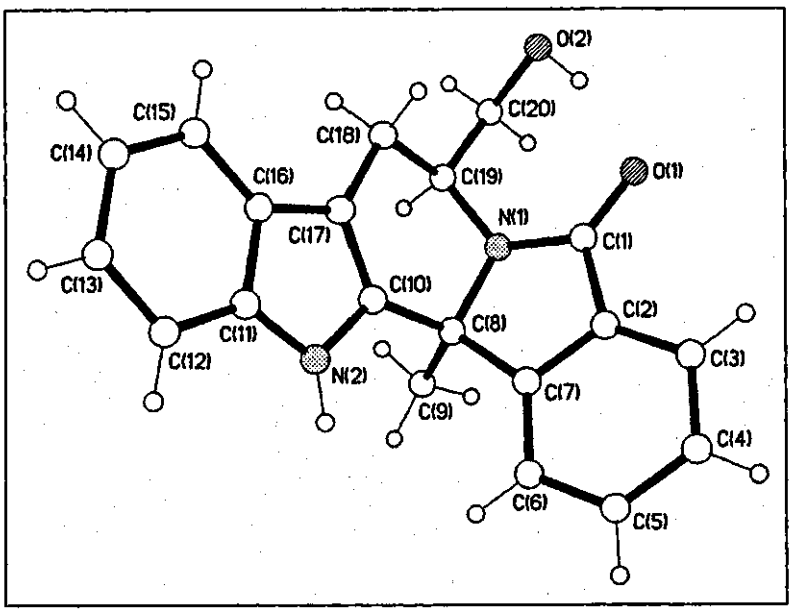


Crystal Data and Structure Refinement

Identification code	**(252)**	
Chemical formula	$C_{20}H_{18}N_2O_2$	
Formula weight	318.36	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 8.7222(7) Å	α = 90°
	b = 10.4742(8) Å	β = 90°
	c = 17.4454(14) Å	γ = 90°
Cell volume	1593.8(2) $Å^3$	
Z	4	
Calculated density	1.327 g/cm^3	
Absorption coefficient μ	0.087 mm^{-1}	
F(000)	672	
Crystal colour and size	colourless, 2.35 × 0.08 × 0.04 mm^3	
Reflections for cell refinement	5004 (θ range 2.27 to 28.37°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.27 to 28.97°	
Index ranges	h −11 to 11, k −13 to 14, l −22 to 22	
Completeness to θ = 26.00°	100.0 %	
Intensity decay	0%	
Reflections collected	14124	
Independent reflections	3847 (R_{int} = 0.0345)	
Reflections with $F^2>2\sigma$	3073	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.822 and 0.997	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0344, 0.3943
Data / restraints / parameters	3847 / 0 / 225
Final R indices [$F^2>2\sigma$]	R1 = 0.0373, wR2 = 0.0769
R indices (all data)	R1 = 0.0583, wR2 = 0.0873
Goodness-of-fit on F^2	1.020
Absolute structure parameter	–0.1(13)
Extinction coefficient	0.0022(8)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.233 and –0.197 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$).
U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
N(1)	0.69084(15)	–0.00543(13)	0.22688(7)	0.0216(3)
C(1)	0.6567(2)	0.09394(15)	0.17928(9)	0.0227(4)
O(1)	0.52987(14)	0.14407(11)	0.16933(7)	0.0302(3)
C(2)	0.8015(2)	0.13133(16)	0.14117(9)	0.0242(4)
C(3)	0.8255(2)	0.22207(17)	0.08457(10)	0.0293(4)
C(4)	0.9737(2)	0.23774(18)	0.05678(10)	0.0334(4)
C(5)	1.0923(2)	0.16313(19)	0.08515(10)	0.0336(4)
C(6)	1.0676(2)	0.07273(18)	0.14221(9)	0.0284(4)
C(7)	0.91977(19)	0.05928(16)	0.17074(9)	0.0222(3)
C(8)	0.85894(18)	–0.02945(15)	0.23183(9)	0.0215(3)
C(9)	0.8990(2)	–0.16910(16)	0.21432(10)	0.0278(4)
C(10)	0.90332(19)	0.00940(15)	0.31239(9)	0.0216(3)
N(2)	1.05240(16)	0.02644(14)	0.33680(8)	0.0236(3)
C(11)	1.04882(19)	0.06392(15)	0.41247(10)	0.0237(4)
C(12)	1.1685(2)	0.09669(17)	0.46169(10)	0.0299(4)
C(13)	1.1300(2)	0.13428(18)	0.53529(10)	0.0347(4)
C(14)	0.9773(2)	0.13847(18)	0.55967(11)	0.0336(4)
C(15)	0.8589(2)	0.10401(17)	0.51166(10)	0.0295(4)
C(16)	0.8939(2)	0.06710(15)	0.43623(9)	0.0238(4)
C(17)	0.80352(19)	0.03149(16)	0.37115(9)	0.0232(4)
C(18)	0.63291(19)	0.01645(18)	0.36404(9)	0.0265(4)
C(19)	0.59597(19)	–0.05669(16)	0.29021(9)	0.0244(4)

C(20)	0.42572(19)	–0.06441(18)	0.27338(11)	0.0297(4)
O(2)	0.34750(14)	0.05460(13)	0.27499(8)	0.0350(3)

Bond Lengths [Å] and Angles [°]

N(1)–C(1)	1.364(2)	N(1)–C(19)	1.481(2)
N(1)–C(8)	1.490(2)	C(1)–O(1)	1.237(2)
C(1)–C(2)	1.480(2)	C(2)–C(7)	1.378(2)
C(2)–C(3)	1.386(2)	C(3)–C(4)	1.390(3)
C(4)–C(5)	1.387(3)	C(5)–C(6)	1.391(2)
C(6)–C(7)	1.389(2)	C(7)–C(8)	1.510(2)
C(8)–C(10)	1.513(2)	C(8)–C(9)	1.535(2)
C(10)–C(17)	1.365(2)	C(10)–N(2)	1.380(2)
N(2)–C(11)	1.378(2)	C(11)–C(12)	1.395(2)
C(11)–C(16)	1.414(2)	C(12)–C(13)	1.384(3)
C(13)–C(14)	1.399(3)	C(14)–C(15)	1.378(3)
C(15)–C(16)	1.405(2)	C(16)–C(17)	1.432(2)
C(17)–C(18)	1.502(2)	C(18)–C(19)	1.533(2)
C(19)–C(20)	1.516(2)	C(20)–O(2)	1.421(2)

C(1)–N(1)–C(19)	127.49(14)	C(1)–N(1)–C(8)	112.26(13)
C(19)–N(1)–C(8)	116.44(12)	O(1)–C(1)–N(1)	127.19(15)
O(1)–C(1)–C(2)	126.01(15)	N(1)–C(1)–C(2)	106.80(14)
C(7)–C(2)–C(3)	121.92(16)	C(7)–C(2)–C(1)	109.00(14)
C(3)–C(2)–C(1)	129.07(16)	C(2)–C(3)–C(4)	118.03(17)
C(5)–C(4)–C(3)	120.13(17)	C(4)–C(5)–C(6)	121.58(18)
C(7)–C(6)–C(5)	117.98(17)	C(2)–C(7)–C(6)	120.33(16)
C(2)–C(7)–C(8)	109.76(14)	C(6)–C(7)–C(8)	129.89(16)
N(1)–C(8)–C(7)	101.59(12)	N(1)–C(8)–C(10)	105.07(12)
C(7)–C(8)–C(10)	113.57(13)	N(1)–C(8)–C(9)	111.94(13)
C(7)–C(8)–C(9)	111.47(13)	C(10)–C(8)–C(9)	112.51(13)
C(17)–C(10)–N(2)	110.33(14)	C(17)–C(10)–C(8)	125.45(15)
N(2)–C(10)–C(8)	124.22(14)	C(11)–N(2)–C(10)	108.13(14)
N(2)–C(11)–C(12)	130.03(16)	N(2)–C(11)–C(16)	108.03(14)
C(12)–C(11)–C(16)	121.94(16)	C(13)–C(12)–C(11)	117.35(17)
C(12)–C(13)–C(14)	121.46(17)	C(15)–C(14)–C(13)	121.37(17)
C(14)–C(15)–C(16)	118.59(17)	C(15)–C(16)–C(11)	119.27(16)
C(15)–C(16)–C(17)	133.99(16)	C(11)–C(16)–C(17)	106.72(14)
C(10)–C(17)–C(16)	106.77(14)	C(10)–C(17)–C(18)	123.52(15)
C(16)–C(17)–C(18)	129.70(15)	C(17)–C(18)–C(19)	109.28(14)
N(1)–C(19)–C(20)	114.97(14)	N(1)–C(19)–C(18)	109.15(13)
C(20)–C(19)–C(18)	113.29(14)	O(2)–C(20)–C(19)	114.81(14)

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0226(7)	0.0294(6)	0.0387(7)	0.0048(6)	–0.0006(5)	0.0059(5)
N(1)	0.0194(7)	0.0221(7)	0.0231(7)	0.0005(6)	0.0003(6)	–0.0007(6)
C(1)	0.0247(9)	0.0209(8)	0.0226(8)	–0.0031(6)	0.0003(7)	0.0003(7)
O(2)	0.0203(6)	0.0427(7)	0.0421(7)	0.0063(6)	0.0048(6)	0.0041(6)
N(2)	0.0190(8)	0.0278(8)	0.0239(7)	0.0019(6)	0.0010(6)	–0.0003(6)
C(2)	0.0261(9)	0.0234(8)	0.0232(8)	–0.0037(7)	0.0003(7)	–0.0022(7)
C(3)	0.0348(11)	0.0273(9)	0.0258(9)	0.0027(7)	0.0016(8)	0.0006(8)
C(4)	0.0438(12)	0.0313(10)	0.0250(9)	0.0029(8)	0.0067(8)	–0.0059(9)
C(5)	0.0307(10)	0.0433(11)	0.0268(9)	–0.0020(8)	0.0076(8)	–0.0082(9)
C(6)	0.0252(9)	0.0366(11)	0.0234(8)	–0.0025(8)	0.0010(7)	0.0004(8)
C(7)	0.0231(9)	0.0230(8)	0.0205(7)	–0.0033(7)	0.0009(6)	–0.0019(7)
C(8)	0.0185(8)	0.0235(8)	0.0224(8)	0.0011(6)	0.0016(6)	0.0022(7)
C(9)	0.0294(10)	0.0241(9)	0.0298(9)	–0.0016(7)	0.0016(8)	0.0039(7)
C(10)	0.0191(8)	0.0205(8)	0.0251(8)	0.0027(6)	–0.0015(7)	0.0013(7)
C(11)	0.0258(9)	0.0205(8)	0.0248(8)	0.0042(7)	–0.0003(7)	0.0000(7)
C(12)	0.0248(9)	0.0315(9)	0.0333(10)	0.0057(7)	–0.0053(8)	–0.0037(8)
C(13)	0.0373(11)	0.0364(10)	0.0304(10)	0.0038(8)	–0.0121(8)	–0.0071(9)
C(14)	0.0418(11)	0.0351(10)	0.0239(9)	0.0024(8)	–0.0010(8)	–0.0039(9)
C(15)	0.0316(10)	0.0314(9)	0.0255(9)	0.0039(7)	0.0029(7)	–0.0007(8)
C(16)	0.0241(9)	0.0230(8)	0.0243(8)	0.0035(7)	0.0003(7)	–0.0002(7)
C(17)	0.0228(9)	0.0241(9)	0.0229(8)	0.0012(7)	0.0003(7)	–0.0004(7)
C(18)	0.0198(9)	0.0345(9)	0.0252(8)	0.0012(7)	0.0014(7)	–0.0008(7)
C(19)	0.0214(8)	0.0230(8)	0.0289(9)	0.0024(7)	0.0028(7)	–0.0009(7)
C(20)	0.0216(9)	0.0339(10)	0.0334(9)	–0.0005(8)	0.0024(8)	–0.0043(8)

Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

	x	y	z	U
H(2)	0.398(3)	0.100(2)	0.2371(13)	0.053
H(2A)	1.140(2)	0.0291(17)	0.3083(10)	0.028
H(3)	0.7432	0.2721	0.0654	0.035
H(4)	0.9938	0.2996	0.0183	0.040
H(5)	1.1927	0.1741	0.0651	0.040

H(6)	1.1493	0.0217	0.1611	0.034
H(9A)	0.8504	–0.2247	0.2524	0.042
H(9B)	1.0105	–0.1803	0.2163	0.042
H(9C)	0.8618	–0.1914	0.1630	0.042
H(12)	1.2723	0.0934	0.4454	0.036
H(13)	1.2090	0.1578	0.5700	0.042
H(14)	0.9547	0.1656	0.6104	0.040
H(15)	0.7558	0.1052	0.5292	0.035
H(18A)	0.5835	0.1015	0.3627	0.032
H(18B)	0.5926	–0.0308	0.4089	0.032
H(19)	0.6312	–0.1464	0.2987	0.029
H(20A)	0.4116	–0.1032	0.2221	0.036
H(20B)	0.3776	–0.1221	0.3114	0.036

Hydrogen Bonds [Å and °]

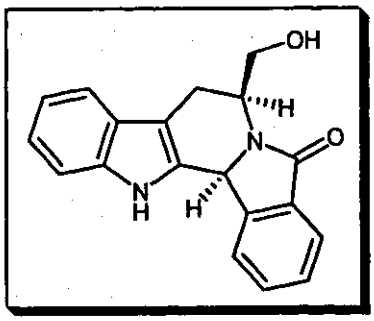
D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1)	0.93(2)	1.71(2)	2.6088(17)	162(2)

Symmetry operations for equivalent atoms

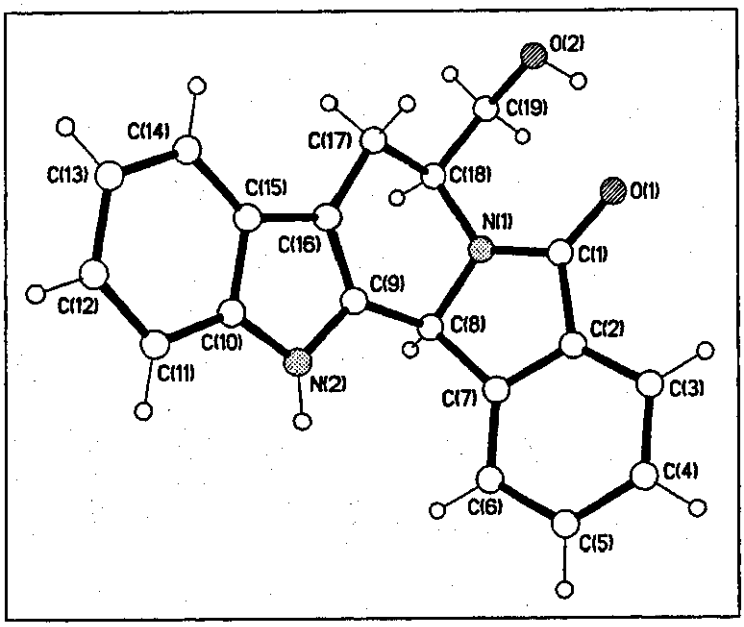
A x,y–1,z

Single Crystal X-Ray with Accompanying Data

(3*S*,9b*S*)-3-(Hydroxymethyl)-3,4,9,9b-tetrahydro-1*H*-isoindolo[1,2-*a*]β-carbolin-1-one



(253)



Crystal Data and Structure Refinement

Identification code	**(253)**	
Chemical formula	$C_{19}H_{16}N_2O_2$	
Formula weight	304.34	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 8.4483(15) Å	α = 90°
	b = 8.7128(15) Å	β = 90°
	c = 24.267(4) Å	γ = 90°
Cell volume	1786.3(5) $Å^3$	
Z	4	
Calculated density	1.447 g/cm^3	
Absorption coefficient μ	0.381 mm^{-1}	
F(000)	808	
Crystal colour and size	colourless, 0.40 × 0.13 × 0.10 mm^3	
Reflections for cell refinement	3446 (θ range 2.48 to 26.42°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.68 to 25.00°	
Index ranges	h −10 to 10, k −10 to 10, l −25 to 28	
Completeness to θ = 25.00°	99.6 %	
Intensity decay	0%	
Reflections collected	10192	
Independent reflections	3138 (R_{int} = 0.0523)	
Reflections with $F^2>2\sigma$	2652	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.863 and 0.963	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0954, 5.4989
Data / restraints / parameters	3138 / 0 / 241
Final R indices [$F^2>2\sigma$]	R1 = 0.0832, wR2 = 0.2200
R indices (all data)	R1 = 0.0969, wR2 = 0.2283
Goodness-of-fit on F^2	1.185
Absolute structure parameter	0.00
Extinction coefficient	0.014(3)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.417 and –0.487 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$).

U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
O(1)	0.3675(7)	0.5324(5)	1.0640(2)	0.0366(13)
N(1)	0.5060(7)	0.3694(6)	1.0066(2)	0.0247(13)
C(1)	0.4172(9)	0.4031(8)	1.0520(3)	0.0263(15)
O(2)	0.4126(7)	0.7106(5)	0.9799(2)	0.0363(13)
N(2)	0.3901(7)	0.0079(6)	0.9375(2)	0.0257(13)
C(2)	0.3974(8)	0.2588(8)	1.0842(3)	0.0255(16)
C(3)	0.3241(10)	0.2381(9)	1.1349(3)	0.0327(17)
C(4)	0.3214(10)	0.0909(10)	1.1550(3)	0.0391(19)
C(5)	0.3951(9)	–0.0289(9)	1.1276(3)	0.0340(18)
C(6)	0.4642(9)	–0.0064(8)	1.0758(3)	0.0276(16)
C(7)	0.4628(8)	0.1405(8)	1.0548(3)	0.0253(15)
C(8)	0.5274(8)	0.2027(7)	1.0000(3)	0.0221(14)
C(9)	0.4315(8)	0.1573(8)	0.9491(3)	0.0268(15)
C(10)	0.3005(9)	0.0119(7)	0.8896(3)	0.0261(15)
C(11)	0.2251(10)	–0.1073(9)	0.8617(3)	0.0365(19)
C(12)	0.1407(10)	–0.0691(9)	0.8150(3)	0.0399(19)
C(13)	0.1265(10)	0.0804(9)	0.7963(3)	0.0372(18)
C(14)	0.2025(8)	0.1984(8)	0.8239(3)	0.0291(16)
C(15)	0.2912(8)	0.1661(8)	0.8712(3)	0.0236(15)
C(16)	0.3788(9)	0.2550(7)	0.9112(3)	0.0272(16)
C(17)	0.4071(9)	0.4259(7)	0.9131(3)	0.0253(15)
C(18)	0.5362(8)	0.4611(7)	0.9566(3)	0.0255(15)

C(19)	0.5565(9)	0.6321(8)	0.9673(3)	0.0320(17)

Bond Lengths [Å] and Angles [°]

O(1)–C(1)	1.238(8)	N(1)–C(1)	1.365(9)
N(1)–C(8)	1.472(8)	N(1)–C(18)	1.475(9)
C(1)–C(2)	1.490(10)	O(2)–C(19)	1.428(9)
N(2)–C(9)	1.377(9)	N(2)–C(10)	1.388(10)
C(2)–C(7)	1.370(10)	C(2)–C(3)	1.389(10)
C(3)–C(4)	1.373(11)	C(4)–C(5)	1.385(12)
C(5)–C(6)	1.400(11)	C(6)–C(7)	1.378(10)
C(7)–C(8)	1.535(10)	C(8)–C(9)	1.529(10)
C(9)–C(16)	1.329(10)	C(10)–C(11)	1.394(10)
C(10)–C(15)	1.418(9)	C(11)–C(12)	1.378(12)
C(12)–C(13)	1.384(12)	C(13)–C(14)	1.386(11)
C(14)–C(15)	1.399(10)	C(15)–C(16)	1.446(10)
C(16)–C(17)	1.509(9)	C(17)–C(18)	1.547(10)
C(18)–C(19)	1.522(9)		

C(1)–N(1)–C(8)	111.5(5)	C(1)–N(1)–C(18)	130.0(6)
C(8)–N(1)–C(18)	115.1(5)	O(1)–C(1)–N(1)	125.0(6)
O(1)–C(1)–C(2)	127.3(7)	N(1)–C(1)–C(2)	107.7(6)
C(9)–N(2)–C(10)	106.7(6)	C(7)–C(2)–C(3)	122.9(7)
C(7)–C(2)–C(1)	108.4(6)	C(3)–C(2)–C(1)	128.6(7)
C(4)–C(3)–C(2)	116.4(7)	C(3)–C(4)–C(5)	121.7(7)
C(4)–C(5)–C(6)	120.9(7)	C(7)–C(6)–C(5)	117.4(7)
C(2)–C(7)–C(6)	120.6(7)	C(2)–C(7)–C(8)	109.2(6)
C(6)–C(7)–C(8)	130.2(6)	N(1)–C(8)–C(9)	106.1(5)
N(1)–C(8)–C(7)	102.2(5)	C(9)–C(8)–C(7)	114.8(6)
C(16)–C(9)–N(2)	112.2(7)	C(16)–C(9)–C(8)	124.8(7)
N(2)–C(9)–C(8)	123.0(6)	N(2)–C(10)–C(11)	129.7(7)
N(2)–C(10)–C(15)	108.5(6)	C(11)–C(10)–C(15)	121.8(7)
C(12)–C(11)–C(10)	117.1(7)	C(11)–C(12)–C(13)	122.8(7)
C(12)–C(13)–C(14)	119.9(7)	C(13)–C(14)–C(15)	119.7(7)
C(14)–C(15)–C(10)	118.6(6)	C(14)–C(15)–C(16)	135.8(6)
C(10)–C(15)–C(16)	105.5(6)	C(9)–C(16)–C(15)	107.1(6)
C(9)–C(16)–C(17)	123.9(7)	C(15)–C(16)–C(17)	129.0(6)
C(16)–C(17)–C(18)	109.1(6)	N(1)–C(18)–C(19)	114.1(6)
N(1)–C(18)–C(17)	109.4(5)	C(19)–C(18)–C(17)	113.0(6)
O(2)–C(19)–C(18)	114.2(6)		

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.050(3)	0.015(2)	0.045(3)	–0.005(2)	0.007(3)	0.004(2)
N(1)	0.031(3)	0.011(3)	0.032(3)	–0.001(2)	0.002(3)	–0.006(2)
C(1)	0.034(4)	0.016(3)	0.028(4)	–0.002(3)	–0.006(3)	0.000(3)
O(2)	0.045(3)	0.014(2)	0.049(3)	0.002(2)	0.001(3)	0.008(2)
N(2)	0.033(3)	0.014(3)	0.030(3)	0.001(2)	0.006(3)	0.002(2)
C(2)	0.026(4)	0.024(3)	0.027(4)	–0.001(3)	0.000(3)	–0.002(3)
C(3)	0.033(4)	0.033(4)	0.033(4)	–0.002(3)	–0.006(4)	–0.005(3)
C(4)	0.041(4)	0.050(5)	0.027(4)	0.010(3)	0.004(3)	–0.021(4)
C(5)	0.034(4)	0.026(4)	0.042(4)	0.013(3)	–0.002(3)	–0.009(3)
C(6)	0.033(4)	0.017(3)	0.033(4)	0.001(3)	–0.004(3)	–0.003(3)
C(7)	0.021(3)	0.024(3)	0.030(4)	–0.003(3)	–0.011(3)	0.000(3)
C(8)	0.021(4)	0.019(3)	0.026(3)	–0.005(3)	–0.003(3)	0.000(3)
C(9)	0.022(3)	0.023(3)	0.035(4)	–0.002(3)	0.001(3)	0.000(3)
C(10)	0.029(4)	0.018(3)	0.031(4)	0.002(3)	0.004(3)	0.000(3)
C(11)	0.048(5)	0.026(4)	0.035(4)	–0.010(3)	0.011(4)	–0.006(4)
C(12)	0.039(4)	0.032(4)	0.050(5)	–0.014(3)	–0.003(4)	–0.004(4)
C(13)	0.038(4)	0.037(4)	0.037(4)	–0.006(3)	–0.006(4)	0.011(4)
C(14)	0.027(4)	0.026(3)	0.034(4)	–0.001(3)	0.002(3)	–0.005(3)
C(15)	0.022(4)	0.018(3)	0.030(4)	–0.002(3)	0.007(3)	0.002(3)
C(16)	0.028(4)	0.015(3)	0.039(4)	–0.002(3)	0.009(3)	0.004(3)
C(17)	0.033(4)	0.013(3)	0.030(4)	0.000(3)	0.002(3)	–0.002(3)
C(18)	0.022(4)	0.017(3)	0.038(4)	–0.001(3)	0.009(3)	–0.004(3)
C(19)	0.037(4)	0.015(3)	0.044(4)	0.003(3)	0.004(3)	–0.003(3)

Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

	x	y	z	U
H(2)	0.3897	0.6966	1.0133	0.054
H(2A)	0.4156	–0.0741	0.9567	0.031
H(3)	0.2784	0.3213	1.1545	0.039
H(4)	0.2677	0.0707	1.1886	0.047
H(5)	0.3987	–0.1276	1.1442	0.041
H(6)	0.5103	–0.0891	1.0560	0.033

H(8)	0.6417	0.1760	0.9953	0.03(2)
H(11)	0.2317	–0.2104	0.8742	0.044
H(12)	0.0901	–0.1487	0.7949	0.048
H(13)	0.0647	0.1019	0.7645	0.045
H(14)	0.1944	0.3009	0.8108	0.035
H(17A)	0.3078	0.4797	0.9229	0.030
H(17B)	0.4418	0.4627	0.8764	0.030
H(18)	0.6386	0.4238	0.9409	0.007(14)
H(19A)	0.6311	0.6459	0.9984	0.038
H(19B)	0.6045	0.6801	0.9343	0.038

Hydrogen Bonds [Å and °]

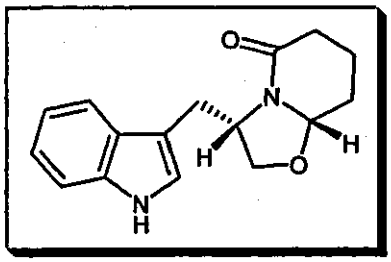
D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1)	0.84	1.90	2.592(7)	139.2
N(2)–H(2A)...O(2A)	0.88	1.96	2.794(7)	157.9

Symmetry operations for equivalent atoms

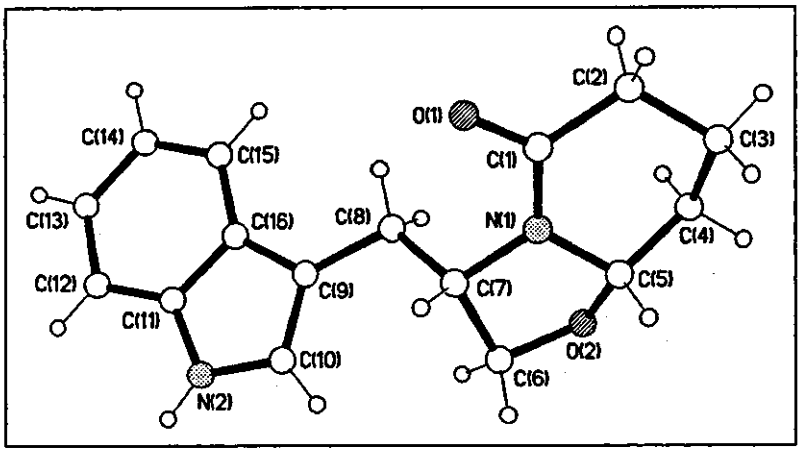
A x,y–1,z

Single Crystal X-Ray with Accompanying Data

(3*S*,8a*S*)-3-(1*H*-Indol-3-ylmethyl)perhydropyrido[2,1-*b*][1,3]oxazol-5-one



(266)



Crystal Data and Structure Refinement

Identification code	**(266)**	
Chemical formula	$C_{16}H_{18}N_2O_2$	
Formula weight	270.32	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, I2	
Unit cell parameters	a = 13.1781(14) Å	α = 90°
	b = 6.5138(7) Å	β = 98.163(2)°
	c = 16.3036(18) Å	γ = 90°
Cell volume	1385.3(3) $Å^3$	
Z	4	
Calculated density	1.296 g/cm^3	
Absorption coefficient μ	0.086 mm^{-1}	
F(000)	576	
Crystal colour and size	colourless, 2.40 × 0.26 × 0.18 mm^3	
Reflections for cell refinement	3141 (θ range 2.52 to 28.92°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.86 to 28.92°	
Index ranges	h –17 to 10, k –8 to 8, l –22 to 20	
Completeness to θ = 26.00°	99.9 %	
Intensity decay	0%	
Reflections collected	5817	
Independent reflections	3100 (R_{int} = 0.0389)	
Reflections with $F^2>2\sigma$	2937	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.819 and 0.985	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1396, 0.2705
Data / restraints / parameters	3100 / 1 / 184
Final R indices [$F^2>2\sigma$]	R1 = 0.0716, wR2 = 0.1874
R indices (all data)	R1 = 0.0733, wR2 = 0.1900
Goodness-of-fit on F^2	1.113
Absolute structure parameter	1.3(17)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.189 and –0.298 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$). U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
N(1)	0.22110(14)	0.7559(3)	0.98171(11)	0.0236(4)
O(1)	0.30542(15)	1.0538(3)	1.01505(10)	0.0344(4)
C(1)	0.26493(17)	0.9324(4)	0.96201(13)	0.0245(5)
C(2)	0.2551(2)	0.9872(4)	0.87043(13)	0.0303(5)
C(3)	0.22486(19)	0.8129(4)	0.80907(14)	0.0315(5)
C(4)	0.14412(18)	0.6734(5)	0.83945(14)	0.0316(5)
C(5)	0.18637(17)	0.5913(4)	0.92295(14)	0.0260(5)
O(2)	0.11207(14)	0.4881(3)	0.96168(11)	0.0322(4)
C(6)	0.1541(2)	0.4840(4)	1.04850(15)	0.0319(5)
C(7)	0.20352(16)	0.6978(3)	1.06568(13)	0.0240(5)
C(8)	0.13207(16)	0.8497(4)	1.10092(12)	0.0250(5)
C(9)	0.12596(15)	0.8133(4)	1.19159(13)	0.0229(4)
C(10)	0.16199(17)	0.6480(4)	1.23950(13)	0.0271(5)
N(2)	0.13997(16)	0.6728(4)	1.31930(12)	0.0291(4)
C(11)	0.08889(17)	0.8546(4)	1.32438(14)	0.0253(5)
C(12)	0.05164(17)	0.9445(4)	1.39198(14)	0.0301(5)
C(13)	0.00618(18)	1.1353(5)	1.37985(14)	0.0337(6)
C(14)	–0.00212(18)	1.2349(4)	1.30233(15)	0.0317(5)
C(15)	0.03310(17)	1.1434(4)	1.23485(14)	0.0273(5)
C(16)	0.07977(15)	0.9493(4)	1.24504(13)	0.0225(5)

Bond Lengths [Å] and Angles [°]

N(1)–C(1)	1.346(3)	N(1)–C(5)	1.467(3)
N(1)–C(7)	1.470(3)	O(1)–C(1)	1.236(3)
C(1)–C(2)	1.523(3)	C(2)–C(3)	1.528(3)
C(3)–C(4)	1.534(4)	C(4)–C(5)	1.494(3)
C(5)–O(2)	1.409(3)	O(2)–C(6)	1.445(3)
C(6)–C(7)	1.546(3)	C(7)–C(8)	1.532(3)
C(8)–C(9)	1.511(3)	C(9)–C(10)	1.375(3)
C(9)–C(16)	1.437(3)	C(10)–N(2)	1.382(3)
N(2)–C(11)	1.370(3)	C(11)–C(12)	1.397(3)
C(11)–C(16)	1.423(3)	C(12)–C(13)	1.382(4)
C(13)–C(14)	1.411(3)	C(14)–C(15)	1.388(3)
C(15)–C(16)	1.406(3)		

C(1)–N(1)–C(5)	124.96(18)	C(1)–N(1)–C(7)	124.88(18)
C(5)–N(1)–C(7)	110.14(18)	O(1)–C(1)–N(1)	122.5(2)
O(1)–C(1)–C(2)	120.3(2)	N(1)–C(1)–C(2)	117.04(19)
C(1)–C(2)–C(3)	116.5(2)	C(2)–C(3)–C(4)	110.92(19)
C(5)–C(4)–C(3)	108.67(19)	O(2)–C(5)–N(1)	103.20(17)
O(2)–C(5)–C(4)	112.71(18)	N(1)–C(5)–C(4)	112.0(2)
C(5)–O(2)–C(6)	104.68(18)	O(2)–C(6)–C(7)	104.71(19)
N(1)–C(7)–C(8)	111.69(18)	N(1)–C(7)–C(6)	100.43(17)
C(8)–C(7)–C(6)	112.58(19)	C(9)–C(8)–C(7)	112.75(18)
C(10)–C(9)–C(16)	106.28(19)	C(10)–C(9)–C(8)	128.1(2)
C(16)–C(9)–C(8)	125.6(2)	C(9)–C(10)–N(2)	109.9(2)
C(11)–N(2)–C(10)	109.2(2)	N(2)–C(11)–C(12)	129.8(2)
N(2)–C(11)–C(16)	107.4(2)	C(12)–C(11)–C(16)	122.8(2)
C(13)–C(12)–C(11)	117.2(2)	C(12)–C(13)–C(14)	121.2(2)
C(15)–C(14)–C(13)	121.4(2)	C(14)–C(15)–C(16)	118.9(2)
C(15)–C(16)–C(11)	118.5(2)	C(15)–C(16)–C(9)	134.3(2)
C(11)–C(16)–C(9)	107.2(2)		

Anisotropic Displacement Parameters (Å^2). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	0.0284(9)	0.0240(9)	0.0179(8)	–0.0023(7)	0.0020(7)	–0.0015(7)
O(1)	0.0477(10)	0.0334(10)	0.0230(8)	–0.0062(7)	0.0081(7)	–0.0126(8)
C(1)	0.0301(10)	0.0255(11)	0.0183(10)	–0.0034(8)	0.0051(8)	–0.0022(9)

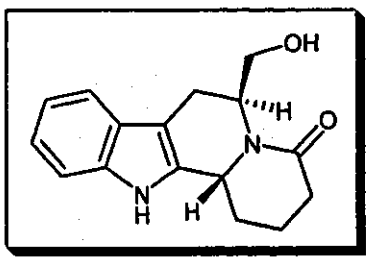
C(2)	0.0431(12)	0.0306(12)	0.0181(9)	–0.0028(9)	0.0074(9)	–0.0031(10)
C(3)	0.0374(11)	0.0385(14)	0.0187(9)	–0.0077(9)	0.0046(9)	–0.0034(10)
C(4)	0.0287(10)	0.0445(14)	0.0207(9)	–0.0052(10)	–0.0001(8)	–0.0048(10)
C(5)	0.0266(10)	0.0266(12)	0.0245(11)	–0.0061(9)	0.0020(8)	–0.0018(9)
O(2)	0.0346(8)	0.0338(9)	0.0275(8)	–0.0020(7)	0.0021(7)	–0.0109(7)
C(6)	0.0379(12)	0.0281(12)	0.0288(11)	0.0031(10)	0.0020(9)	–0.0051(10)
C(7)	0.0273(9)	0.0259(11)	0.0190(9)	0.0032(8)	0.0035(8)	0.0004(8)
C(8)	0.0284(10)	0.0285(11)	0.0184(9)	0.0020(8)	0.0039(8)	0.0023(8)
C(9)	0.0227(9)	0.0255(11)	0.0197(9)	0.0012(8)	0.0005(8)	–0.0028(8)
C(10)	0.0300(10)	0.0295(12)	0.0210(10)	0.0015(9)	0.0014(8)	0.0017(9)
N(2)	0.0367(10)	0.0310(10)	0.0190(8)	0.0065(8)	0.0018(7)	0.0028(8)
C(11)	0.0235(9)	0.0326(12)	0.0190(9)	0.0038(8)	0.0006(8)	–0.0026(9)
C(12)	0.0282(10)	0.0418(14)	0.0204(10)	0.0040(9)	0.0041(8)	0.0000(10)
C(13)	0.0293(11)	0.0481(15)	0.0243(11)	–0.0002(10)	0.0055(9)	0.0056(11)
C(14)	0.0289(10)	0.0365(13)	0.0296(11)	0.0013(10)	0.0036(9)	0.0070(9)
C(15)	0.0278(10)	0.0325(12)	0.0213(9)	0.0042(9)	0.0021(8)	0.0007(9)
C(16)	0.0204(9)	0.0287(11)	0.0179(9)	0.0030(8)	0.0006(7)	–0.0038(8)

Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

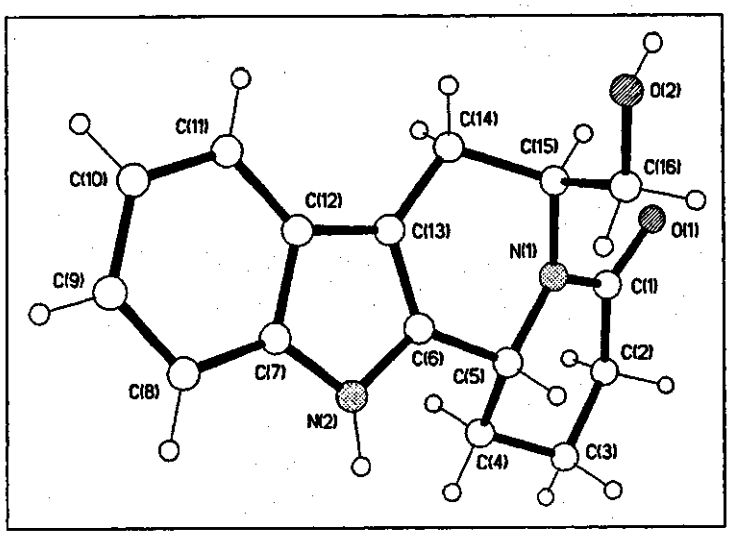
	x	y	z	U
H(2A)	0.3216	1.0436	0.8593	0.036
H(2B)	0.2035	1.0978	0.8592	0.036
H(3A)	0.2863	0.7309	0.8022	0.038
H(3B)	0.1971	0.8712	0.7544	0.038
H(4A)	0.0807	0.7523	0.8430	0.038
H(4B)	0.1271	0.5586	0.8001	0.038
H(5)	0.2447	0.4964	0.9177	0.031
H(6A)	0.2061	0.3741	1.0598	0.038
H(6B)	0.0994	0.4609	1.0833	0.038
H(7)	0.2701	0.6860	1.1034	0.029
H(8A)	0.1568	0.9912	1.0937	0.030
H(8B)	0.0625	0.8379	1.0691	0.030
H(10)	0.1969	0.5335	1.2205	0.032
H(2)	0.156(2)	0.602(6)	1.362(2)	0.035
H(12)	0.0573	0.8772	1.4441	0.036
H(13)	–0.0200	1.2007	1.4245	0.040
H(14)	–0.0325	1.3673	1.2962	0.038
H(15)	0.0258	1.2109	1.1827	0.033

Single Crystal X-Ray with Accompanying Data

(6*S*,12b*R*)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one



(219)



Crystal Data and Structure Refinement

Identification code	**(219)**	
Chemical formula	$C_{16}H_{18}N_2O_2$	
Formula weight	270.32	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 8.0611(7) Å	α = 90°
	b = 9.2410(7) Å	β = 110.012(2)°
	c = 9.9786(8) Å	γ = 90°
Cell volume	698.45(10) $Å^3$	
Z	2	
Calculated density	1.285 g/cm^3	
Absorption coefficient μ	0.086 mm^{-1}	
F(000)	288	
Crystal colour and size	colourless, 0.51 × 0.30 × 0.18 mm^3	
Reflections for cell refinement	4666 (θ range 2.20 to 28.74°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.17 to 28.92°	
Index ranges	h –10 to 10, k –12 to 12, l –13 to 13	
Completeness to θ = 26.00°	99.9 %	
Intensity decay	0%	
Reflections collected	6217	
Independent reflections	3182 (R_{int} = 0.0126)	
Reflections with $F^2>2\sigma$	3027	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.958 and 0.985	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0490, 0.0836
Data / restraints / parameters	3182 / 1 / 187
Final R indices [$F^2>2\sigma$]	R1 = 0.0311, wR2 = 0.0805
R indices (all data)	R1 = 0.0328, wR2 = 0.0821
Goodness-of-fit on F^2	1.049
Absolute structure parameter	0.2(8)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.193 and –0.177 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$).
U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
O(1)	0.10742(14)	0.91692(11)	0.03505(9)	0.0344(2)
N(1)	0.14219(13)	0.87195(11)	0.26536(11)	0.0224(2)
C(1)	0.13665(16)	0.96358(13)	0.15779(13)	0.0251(2)
O(2)	–0.12589(14)	0.53509(11)	0.20000(11)	0.0353(2)
N(2)	0.24514(15)	0.82373(11)	0.65713(11)	0.0267(2)
C(2)	0.17702(17)	1.12221(13)	0.18935(13)	0.0284(3)
C(3)	0.17330(19)	1.17743(14)	0.33152(15)	0.0327(3)
C(4)	0.24960(17)	1.06408(13)	0.44720(14)	0.0276(3)
C(5)	0.14437(16)	0.92399(13)	0.40683(12)	0.0236(2)
C(6)	0.21833(16)	0.80663(14)	0.51348(12)	0.0242(2)
C(7)	0.30700(16)	0.69448(14)	0.72459(13)	0.0263(3)
C(8)	0.34764(18)	0.65661(17)	0.86785(13)	0.0338(3)
C(9)	0.40839(19)	0.51725(18)	0.90768(15)	0.0383(3)
C(10)	0.42661(17)	0.41787(17)	0.80758(15)	0.0336(3)
C(11)	0.38318(16)	0.45416(14)	0.66519(14)	0.0277(3)
C(12)	0.32206(15)	0.59491(13)	0.62148(12)	0.0240(2)
C(13)	0.26497(15)	0.66996(13)	0.48744(12)	0.0241(2)
C(14)	0.24475(17)	0.62180(13)	0.33956(12)	0.0270(3)
C(15)	0.10726(17)	0.71621(12)	0.23062(13)	0.0231(2)
C(16)	–0.08343(17)	0.68404(13)	0.21987(13)	0.0268(3)

Bond Lengths [Å] and Angles [°]

O(1)–C(1)	1.2426(16)	N(1)–C(1)	1.3558(15)
N(1)–C(5)	1.4857(15)	N(1)–C(15)	1.4845(15)
C(1)–C(2)	1.5112(17)	O(2)–C(16)	1.4159(15)
N(2)–C(6)	1.3837(15)	N(2)–C(7)	1.3779(16)
C(2)–C(3)	1.5175(19)	C(3)–C(4)	1.5239(18)
C(4)–C(5)	1.5244(17)	C(5)–C(6)	1.4933(17)
C(6)–C(13)	1.3678(17)	C(7)–C(8)	1.3974(17)
C(7)–C(12)	1.4161(17)	C(8)–C(9)	1.387(2)
C(9)–C(10)	1.401(2)	C(10)–C(11)	1.3833(18)
C(11)–C(12)	1.4063(18)	C(12)–C(13)	1.4354(15)
C(13)–C(14)	1.4959(16)	C(14)–C(15)	1.5319(17)
C(15)–C(16)	1.5330(17)		

C(1)–N(1)–C(5)	122.45(10)	C(1)–N(1)–C(15)	117.93(10)
C(15)–N(1)–C(5)	118.38(9)	O(1)–C(1)–N(1)	120.49(11)
O(1)–C(1)–C(2)	119.78(11)	N(1)–C(1)–C(2)	119.63(11)
C(7)–N(2)–C(6)	108.02(10)	C(1)–C(2)–C(3)	116.70(11)
C(2)–C(3)–C(4)	110.18(10)	C(3)–C(4)–C(5)	109.86(10)
N(1)–C(5)–C(6)	108.30(10)	N(1)–C(5)–C(4)	110.52(10)
C(6)–C(5)–C(4)	112.21(10)	N(2)–C(6)–C(5)	122.55(11)
C(13)–C(6)–N(2)	110.28(11)	C(13)–C(6)–C(5)	127.15(11)
N(2)–C(7)–C(12)	108.36(10)	N(2)–C(7)–C(8)	129.48(12)
C(8)–C(7)–C(12)	122.15(12)	C(9)–C(8)–C(7)	117.51(13)
C(8)–C(9)–C(10)	121.15(13)	C(11)–C(10)–C(9)	121.46(13)
C(10)–C(11)–C(12)	118.78(13)	C(7)–C(12)–C(13)	106.45(10)
C(11)–C(12)–C(7)	118.93(11)	C(11)–C(12)–C(13)	134.62(11)
C(6)–C(13)–C(12)	106.89(10)	C(6)–C(13)–C(14)	121.19(11)
C(12)–C(13)–C(14)	131.87(11)	C(13)–C(14)–C(15)	109.80(10)
N(1)–C(15)–C(14)	110.68(10)	N(1)–C(15)–C(16)	108.05(9)
C(14)–C(15)–C(16)	113.82(10)	O(2)–C(16)–C(15)	112.76(10)

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0521(6)	0.0275(5)	0.0218(4)	0.0039(4)	0.0106(4)	–0.0045(4)
N(1)	0.0276(5)	0.0188(5)	0.0211(5)	–0.0013(4)	0.0087(4)	–0.0004(4)
C(1)	0.0256(5)	0.0222(5)	0.0261(6)	0.0029(5)	0.0069(4)	0.0005(5)
O(2)	0.0560(6)	0.0271(5)	0.0292(5)	–0.0074(4)	0.0231(5)	–0.0162(4)
N(2)	0.0327(5)	0.0264(6)	0.0217(5)	–0.0018(4)	0.0100(4)	0.0020(4)

C(2)	0.0327(6)	0.0207(5)	0.0289(6)	0.0049(5)	0.0067(5)	–0.0007(5)
C(3)	0.0412(7)	0.0187(6)	0.0376(7)	–0.0005(5)	0.0129(6)	0.0010(5)
C(4)	0.0336(6)	0.0220(6)	0.0277(6)	–0.0044(5)	0.0111(5)	–0.0022(5)
C(5)	0.0276(5)	0.0214(5)	0.0223(5)	–0.0014(4)	0.0091(4)	0.0011(5)
C(6)	0.0272(6)	0.0248(6)	0.0210(5)	–0.0024(5)	0.0088(4)	–0.0002(5)
C(7)	0.0257(5)	0.0294(6)	0.0229(6)	0.0000(5)	0.0073(4)	–0.0005(5)
C(8)	0.0359(6)	0.0436(8)	0.0209(6)	–0.0003(5)	0.0084(5)	–0.0016(6)
C(9)	0.0386(7)	0.0484(9)	0.0251(7)	0.0103(6)	0.0072(6)	–0.0029(6)
C(10)	0.0300(6)	0.0324(7)	0.0339(7)	0.0104(6)	0.0050(5)	–0.0003(6)
C(11)	0.0262(6)	0.0258(6)	0.0284(6)	0.0024(5)	0.0058(5)	–0.0013(5)
C(12)	0.0231(5)	0.0265(6)	0.0216(5)	0.0013(5)	0.0068(4)	–0.0004(5)
C(13)	0.0284(5)	0.0224(5)	0.0213(5)	0.0022(5)	0.0083(4)	0.0020(5)
C(14)	0.0378(6)	0.0223(6)	0.0215(5)	–0.0010(4)	0.0106(5)	0.0051(5)
C(15)	0.0328(6)	0.0165(5)	0.0210(5)	–0.0020(4)	0.0106(5)	–0.0009(4)
C(16)	0.0342(6)	0.0220(6)	0.0260(6)	–0.0038(5)	0.0126(5)	–0.0036(5)

Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

	x	y	z	U
H(2)	0.208(2)	0.8999(19)	0.6973(17)	0.032
H(2A)	0.0910	1.1792	0.1127	0.034
H(2B)	0.2956	1.1419	0.1846	0.034
H(2C)	–0.126(3)	0.508(2)	0.122(2)	0.053
H(3A)	0.0502	1.1996	0.3237	0.039
H(3B)	0.2431	1.2677	0.3574	0.039
H(4A)	0.2449	1.1002	0.5392	0.033
H(4B)	0.3747	1.0456	0.4587	0.033
H(5)	0.0201	0.9434	0.4012	0.028
H(8)	0.3342	0.7238	0.9354	0.041
H(9)	0.4382	0.4887	1.0045	0.046
H(10)	0.4697	0.3235	0.8382	0.040
H(11)	0.3944	0.3853	0.5982	0.033
H(14A)	0.2069	0.5193	0.3267	0.032
H(14B)	0.3595	0.6296	0.3244	0.032
H(15)	0.1174	0.6986	0.1348	0.028
H(16A)	–0.1015	0.7175	0.3081	0.032
H(16B)	–0.1648	0.7393	0.1390	0.032

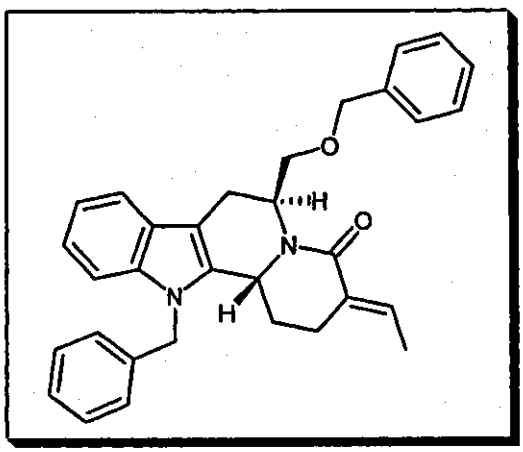
Hydrogen Bonds [Å and °]

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(2)–H(2)...O(2')	0.912(17)	1.872(17)	2.7765(14)	171.0(15)
O(2)–H(2C)...O(1")	0.82(2)	1.83(2)	2.6372(13)	169(2)

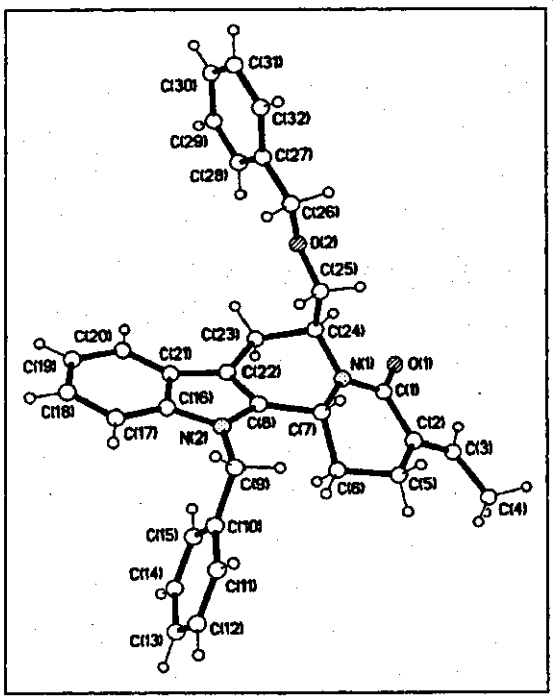
Symmetry operations for equivalent atoms
' –x,y+1/2,–z+1 " –x,y–1/2,–z

Single Crystal X-Ray with Accompanying Data

(6*S*,12b*R*)-3-[(*E*)Ethylidene]-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]β-carbolin-4-one



(297)



Crystal Data and Structure Refinement

Identification code	**(297)**	
Chemical formula	$C_{32}H_{32}N_2O_2$	
Formula weight	476.60	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 5.7452(3) Å	α = 90°
	b = 20.2369(12) Å	β = 90°
	c = 21.5207(13) Å	γ = 90°
Cell volume	2502.1(2) $Å^3$	
Z	4	
Calculated density	1.265 g/cm^3	
Absorption coefficient μ	0.079 mm^{-1}	
F(000)	1016	
Crystal colour and size	yellow, 1.43 × 0.20 × 0.18 mm^3	
Reflections for cell refinement	13619 (θ range 2.22 to 28.80°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.89 to 28.96°	
Index ranges	h –7 to 7, k –27 to 26, l –29 to 28	
Completeness to θ = 26.00°	100.0 %	
Intensity decay	0%	
Reflections collected	22222	
Independent reflections	6059 (R_{int} = 0.0236)	
Reflections with $F^2>2\sigma$	5616	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.896 and 0.986	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0514, 0.5100
Data / restraints / parameters	6059 / 0 / 326
Final R indices [$F^2>2\sigma$]	R1 = 0.0369, wR2 = 0.0945
R indices (all data)	R1 = 0.0412, wR2 = 0.0981
Goodness-of-fit on F^2	1.021
Absolute structure parameter	–0.6(10)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.213 and –0.166 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$).
U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
O(1)	–0.2106(2)	0.43893(6)	0.22658(5)	0.0450(3)
N(1)	0.1077(2)	0.49095(5)	0.18913(5)	0.0314(2)
C(1)	–0.0417(3)	0.47537(6)	0.23607(6)	0.0317(3)
O(2)	0.2018(2)	0.38483(6)	0.05339(5)	0.0417(3)
N(2)	0.5200(2)	0.61511(5)	0.12154(5)	0.0281(2)
C(2)	0.0029(3)	0.50313(7)	0.29963(7)	0.0349(3)
C(3)	–0.1475(3)	0.48698(8)	0.34470(8)	0.0449(4)
C(4)	–0.1383(4)	0.50807(9)	0.41118(8)	0.0554(5)
C(5)	0.2117(3)	0.54563(9)	0.30878(7)	0.0449(4)
C(6)	0.2639(3)	0.58414(7)	0.24961(6)	0.0362(3)
C(7)	0.3069(3)	0.53705(6)	0.19564(6)	0.0298(3)
C(8)	0.3368(2)	0.57259(6)	0.13448(6)	0.0258(2)
C(9)	0.6995(2)	0.63984(6)	0.16274(6)	0.0296(3)
C(10)	0.6594(2)	0.71059(6)	0.18480(6)	0.0259(2)
C(11)	0.8352(2)	0.74314(7)	0.21720(6)	0.0298(3)
C(12)	0.8072(3)	0.80837(7)	0.23619(6)	0.0314(3)
C(13)	0.6028(3)	0.84166(7)	0.22342(6)	0.0323(3)
C(14)	0.4272(2)	0.80965(7)	0.19124(6)	0.0329(3)
C(15)	0.4555(2)	0.74433(7)	0.17216(6)	0.0298(3)
C(16)	0.4983(3)	0.63548(6)	0.06012(6)	0.0301(3)
C(17)	0.6413(3)	0.67724(7)	0.02597(7)	0.0387(3)
C(18)	0.5816(3)	0.68796(8)	–0.03551(8)	0.0462(4)
C(19)	0.3836(4)	0.65885(8)	–0.06177(7)	0.0465(4)

C(20)	0.2414(3)	0.61763(7)	–0.02759(6)	0.0382(3)
C(21)	0.2997(2)	0.60485(6)	0.03477(6)	0.0294(3)
C(22)	0.2016(2)	0.56459(6)	0.08284(6)	0.0278(3)
C(23)	0.0133(3)	0.51372(7)	0.07961(6)	0.0317(3)
C(24)	0.0667(3)	0.46022(7)	0.12779(6)	0.0323(3)
C(25)	0.2718(3)	0.41705(7)	0.10908(6)	0.0353(3)
C(26)	0.3805(3)	0.34999(8)	0.02347(7)	0.0380(3)
C(27)	0.2894(3)	0.32235(7)	–0.03702(6)	0.0333(3)
C(28)	0.0785(3)	0.34192(8)	–0.06197(7)	0.0414(3)
C(29)	0.0004(3)	0.31602(9)	–0.11813(8)	0.0493(4)
C(30)	0.1331(4)	0.26986(9)	–0.14924(7)	0.0543(5)
C(31)	0.3393(5)	0.24932(10)	–0.12435(8)	0.0612(6)
C(32)	0.4188(3)	0.27560(9)	–0.06853(7)	0.0486(4)

Bond Lengths [Å] and Angles [°]

O(1)–C(1)	1.2358(18)	N(1)–C(1)	1.3628(18)
N(1)–C(24)	1.4781(16)	N(1)–C(7)	1.4830(17)
C(1)–C(2)	1.501(2)	O(2)–C(26)	1.4021(19)
O(2)–C(25)	1.4223(16)	N(2)–C(8)	1.3879(16)
N(2)–C(16)	1.3902(17)	N(2)–C(9)	1.4491(17)
C(2)–C(3)	1.339(2)	C(2)–C(5)	1.489(2)
C(3)–C(4)	1.494(2)	C(5)–C(6)	1.523(2)
C(6)–C(7)	1.5225(19)	C(7)–C(8)	1.5096(17)
C(8)–C(22)	1.3653(18)	C(9)–C(10)	1.5260(17)
C(10)–C(15)	1.3826(18)	C(10)–C(11)	1.3928(18)
C(11)–C(12)	1.3912(19)	C(12)–C(13)	1.382(2)
C(13)–C(14)	1.385(2)	C(14)–C(15)	1.3938(19)
C(16)–C(17)	1.389(2)	C(16)–C(21)	1.408(2)
C(17)–C(18)	1.384(2)	C(18)–C(19)	1.400(3)
C(19)–C(20)	1.380(2)	C(20)–C(21)	1.4072(19)
C(21)–C(22)	1.4321(19)	C(22)–C(23)	1.4950(19)
C(23)–C(24)	1.530(2)	C(24)–C(25)	1.521(2)
C(26)–C(27)	1.511(2)	C(27)–C(32)	1.381(2)
C(27)–C(28)	1.383(2)	C(28)–C(29)	1.392(2)
C(29)–C(30)	1.379(3)	C(30)–C(31)	1.365(3)
C(31)–C(32)	1.391(3)		

C(1)–N(1)–C(24)	117.65(11)	C(1)–N(1)–C(7)	124.17(11)
C(24)–N(1)–C(7)	118.17(11)	O(1)–C(1)–N(1)	120.69(13)
O(1)–C(1)–C(2)	120.53(13)	N(1)–C(1)–C(2)	118.78(12)
C(26)–O(2)–C(25)	114.24(12)	C(8)–N(2)–C(16)	107.83(11)
C(8)–N(2)–C(9)	129.14(11)	C(16)–N(2)–C(9)	122.91(11)
C(3)–C(2)–C(5)	124.40(14)	C(3)–C(2)–C(1)	117.29(15)

C(5)–C(2)–C(1)	118.30(13)	C(2)–C(3)–C(4)	126.94(17)
C(2)–C(5)–C(6)	110.12(13)	C(7)–C(6)–C(5)	110.47(12)
N(1)–C(7)–C(8)	107.77(10)	N(1)–C(7)–C(6)	109.92(11)
C(8)–C(7)–C(6)	112.67(11)	C(22)–C(8)–N(2)	109.97(11)
C(22)–C(8)–C(7)	126.05(12)	N(2)–C(8)–C(7)	123.82(11)
N(2)–C(9)–C(10)	114.00(11)	C(15)–C(10)–C(11)	118.63(12)
C(15)–C(10)–C(9)	122.02(12)	C(11)–C(10)–C(9)	119.33(12)
C(12)–C(11)–C(10)	120.80(13)	C(13)–C(12)–C(11)	120.15(13)
C(12)–C(13)–C(14)	119.40(12)	C(13)–C(14)–C(15)	120.38(13)
C(10)–C(15)–C(14)	120.63(13)	C(17)–C(16)–N(2)	129.07(14)
C(17)–C(16)–C(21)	122.82(13)	N(2)–C(16)–C(21)	108.10(12)
C(18)–C(17)–C(16)	117.04(16)	C(17)–C(18)–C(19)	121.42(15)
C(20)–C(19)–C(18)	121.35(15)	C(19)–C(20)–C(21)	118.58(15)
C(20)–C(21)–C(16)	118.78(13)	C(20)–C(21)–C(22)	134.41(14)
C(16)–C(21)–C(22)	106.81(11)	C(8)–C(22)–C(21)	107.27(12)
C(8)–C(22)–C(23)	122.07(12)	C(21)–C(22)–C(23)	130.00(12)
C(22)–C(23)–C(24)	108.11(11)	N(1)–C(24)–C(25)	110.76(12)
N(1)–C(24)–C(23)	109.84(11)	C(25)–C(24)–C(23)	112.46(11)
O(2)–C(25)–C(24)	105.51(12)	O(2)–C(26)–C(27)	109.16(13)
C(32)–C(27)–C(28)	118.49(14)	C(32)–C(27)–C(26)	119.35(14)
C(28)–C(27)–C(26)	122.15(13)	C(27)–C(28)–C(29)	120.77(16)
C(30)–C(29)–C(28)	119.90(18)	C(31)–C(30)–C(29)	119.71(16)
C(30)–C(31)–C(32)	120.48(17)	C(27)–C(32)–C(31)	120.62(18)

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0456(6)	0.0431(6)	0.0463(6)	–0.0031(5)	0.0083(5)	–0.0141(5)
N(1)	0.0377(6)	0.0286(5)	0.0279(5)	–0.0031(4)	0.0010(5)	–0.0063(5)
C(1)	0.0349(7)	0.0251(6)	0.0351(7)	0.0022(5)	0.0022(6)	0.0010(5)
O(2)	0.0429(6)	0.0444(6)	0.0379(5)	–0.0165(4)	–0.0003(5)	–0.0024(5)
N(2)	0.0305(5)	0.0270(5)	0.0270(5)	–0.0011(4)	–0.0007(4)	–0.0026(4)
C(2)	0.0457(8)	0.0282(6)	0.0308(7)	0.0024(5)	0.0028(6)	0.0047(6)
C(3)	0.0568(10)	0.0348(7)	0.0430(8)	–0.0008(6)	0.0128(8)	0.0019(7)
C(4)	0.0809(14)	0.0459(9)	0.0393(8)	0.0008(7)	0.0195(9)	0.0080(9)
C(5)	0.0539(10)	0.0541(9)	0.0267(6)	–0.0006(6)	–0.0010(7)	–0.0107(8)
C(6)	0.0464(8)	0.0353(7)	0.0269(6)	–0.0041(5)	–0.0009(6)	–0.0096(6)
C(7)	0.0348(7)	0.0277(6)	0.0268(6)	0.0001(5)	–0.0028(5)	–0.0047(5)
C(8)	0.0281(6)	0.0224(5)	0.0268(6)	–0.0018(4)	–0.0007(5)	–0.0006(5)
C(9)	0.0270(6)	0.0268(6)	0.0350(6)	–0.0021(5)	–0.0033(5)	–0.0008(5)

C(10)	0.0278(6)	0.0261(6)	0.0239(5)	0.0019(4)	0.0016(5)	–0.0012(5)
C(11)	0.0282(6)	0.0303(6)	0.0310(6)	0.0011(5)	–0.0029(5)	0.0017(5)
C(12)	0.0344(7)	0.0312(6)	0.0287(6)	–0.0026(5)	–0.0021(5)	–0.0043(6)
C(13)	0.0409(8)	0.0270(6)	0.0289(6)	–0.0013(5)	0.0037(6)	0.0016(6)
C(14)	0.0313(7)	0.0334(7)	0.0341(7)	0.0020(6)	0.0013(6)	0.0048(5)
C(15)	0.0276(6)	0.0323(6)	0.0295(6)	–0.0010(5)	–0.0022(5)	–0.0014(5)
C(16)	0.0350(7)	0.0263(6)	0.0289(6)	–0.0005(5)	0.0030(5)	0.0041(5)
C(17)	0.0418(8)	0.0338(7)	0.0404(7)	0.0018(6)	0.0081(7)	–0.0019(6)
C(18)	0.0611(10)	0.0386(8)	0.0389(8)	0.0104(7)	0.0159(8)	0.0040(8)
C(19)	0.0669(11)	0.0441(8)	0.0286(7)	0.0055(6)	0.0022(7)	0.0119(8)
C(20)	0.0480(8)	0.0375(7)	0.0290(6)	–0.0006(5)	–0.0038(6)	0.0097(7)
C(21)	0.0343(7)	0.0262(6)	0.0276(6)	–0.0020(5)	–0.0010(5)	0.0066(5)
C(22)	0.0299(6)	0.0263(6)	0.0272(6)	–0.0022(5)	–0.0017(5)	0.0024(5)
C(23)	0.0314(7)	0.0323(7)	0.0316(6)	–0.0062(5)	–0.0051(5)	–0.0024(6)
C(24)	0.0383(7)	0.0291(6)	0.0297(6)	–0.0051(5)	–0.0006(6)	–0.0084(6)
C(25)	0.0492(9)	0.0272(6)	0.0294(6)	–0.0027(5)	–0.0039(6)	–0.0026(6)
C(26)	0.0451(8)	0.0365(7)	0.0325(7)	–0.0011(6)	–0.0036(6)	0.0064(6)
C(27)	0.0436(8)	0.0297(6)	0.0266(6)	0.0027(5)	0.0030(6)	0.0006(6)
C(28)	0.0464(9)	0.0442(8)	0.0337(7)	–0.0016(6)	–0.0012(7)	0.0056(7)
C(29)	0.0526(9)	0.0602(10)	0.0349(7)	0.0080(7)	–0.0073(7)	–0.0094(9)
C(30)	0.0867(14)	0.0498(9)	0.0264(7)	–0.0014(6)	0.0017(8)	–0.0202(10)
C(31)	0.0939(16)	0.0518(10)	0.0380(8)	–0.0096(8)	0.0167(10)	0.0129(11)
C(32)	0.0569(10)	0.0522(9)	0.0366(7)	0.0020(7)	0.0072(7)	0.0163(8)

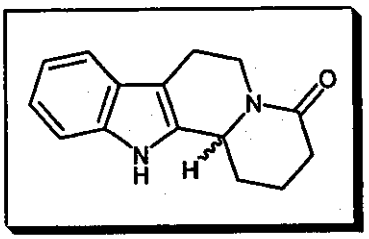
Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

	x	y	z	U
H(3)	–0.2734	0.4591	0.3332	0.054
H(4A)	–0.0080	0.5387	0.4172	0.083
H(4B)	–0.1166	0.4692	0.4377	0.083
H(4C)	–0.2843	0.5302	0.4223	0.083
H(5A)	0.3472	0.5178	0.3198	0.067
H(5B)	0.1835	0.5768	0.3434	0.067
H(6A)	0.1310	0.6134	0.2397	0.054
H(6B)	0.4031	0.6122	0.2561	0.054
H(7)	0.4508	0.5109	0.2044	0.045
H(9A)	0.8511	0.6377	0.1410	0.044
H(9B)	0.7091	0.6106	0.1995	0.044
H(11)	0.9759	0.7205	0.2264	0.036
H(12)	0.9290	0.8301	0.2580	0.038
H(13)	0.5828	0.8861	0.2366	0.039

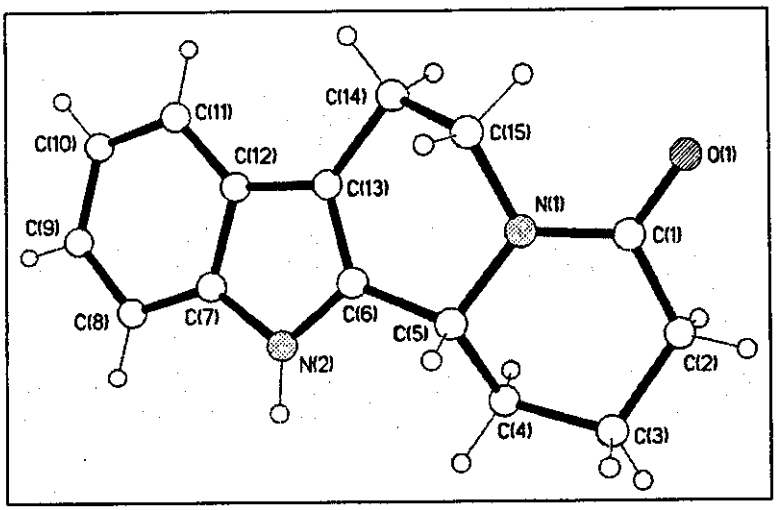
H(14)	0.2865	0.8323	0.1821	0.039
H(15)	0.3337	0.7228	0.1503	0.036
H(17)	0.7742	0.6975	0.0440	0.046
H(18)	0.6770	0.7157	–0.0604	0.055
H(19)	0.3464	0.6676	–0.1040	0.056
H(20)	0.1069	0.5983	–0.0458	0.046
H(23A)	0.0075	0.4941	0.0375	0.048
H(23B)	–0.1394	0.5343	0.0885	0.048
H(24)	–0.0735	0.4312	0.1314	0.048
H(25A)	0.4121	0.4444	0.1018	0.053
H(25B)	0.3067	0.3843	0.1420	0.053
H(26A)	0.4355	0.3135	0.0504	0.057
H(26B)	0.5134	0.3799	0.0153	0.057
H(28)	–0.0141	0.3734	–0.0405	0.050
H(29)	–0.1441	0.3301	–0.1350	0.059
H(30)	0.0812	0.2524	–0.1878	0.065
H(31)	0.4292	0.2168	–0.1453	0.073
H(32)	0.5634	0.2613	–0.0519	0.058

Single Crystal X-Ray with Accompanying Data

1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-*a*]β-carbolin-4-one



(328)



Crystal Data and Structure Refinement

Identification code	**(328)**	
Chemical formula	$C_{15}H_{16}N_2O$	
Formula weight	240.30	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, Pbca	
Unit cell parameters	a = 12.2720(9) Å	α = 90°
	b = 13.2782(10) Å	β = 90°
	c = 15.0736(11) Å	γ = 90°
Cell volume	2456.2(3) $Å^3$	
Z	8	
Calculated density	1.300 g/cm^3	
Absorption coefficient μ	0.083 mm^{-1}	
F(000)	1024	
Crystal colour and size	yellow, 0.65 × 0.30 × 0.16 mm^3	
Reflections for cell refinement	5622 (θ range 2.63 to 27.6°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.63 to 29.08°	
Index ranges	h −16 to 16, k −18 to 17, l −19 to 19	
Completeness to θ = 26.00°	100.0 %	
Intensity decay	0%	
Reflections collected	20279	
Independent reflections	3061 (R_{int} = 0.0334)	
Reflections with $F^2>2\sigma$	2196	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.948 and 0.987	
Structure solution	direct methods	

Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0545, 0.9661
Data / restraints / parameters	3061 / 0 / 166
Final R indices [$F^2>2\sigma$]	R1 = 0.0426, wR2 = 0.1049
R indices (all data)	R1 = 0.0703, wR2 = 0.1235
Goodness-of-fit on F^2	1.021
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.295 and –0.190 e $Å^{-3}$

Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($Å^2$).

U_{eq} is Defined as One Third of the Trace of the Orthogonalised U^{ij} Tensor

	x	y	z	U_{eq}
O(1)	0.36169(9)	0.10064(8)	0.67567(8)	0.0403(3)
N(1)	0.23541(10)	0.22393(9)	0.68233(8)	0.0291(3)
C(1)	0.33678(12)	0.19024(11)	0.66388(10)	0.0296(3)
N(2)	0.03119(10)	0.42282(9)	0.63249(8)	0.0289(3)
C(2)	0.41964(12)	0.26184(12)	0.62661(10)	0.0332(3)
C(3)	0.39381(12)	0.37268(12)	0.63563(11)	0.0334(3)
C(4)	0.27449(11)	0.39001(11)	0.61445(10)	0.0299(3)
C(5)	0.20320(11)	0.33132(10)	0.67770(10)	0.0282(3)
C(6)	0.08475(12)	0.33424(10)	0.65186(9)	0.0269(3)
C(7)	–0.07495(11)	0.39999(11)	0.61089(9)	0.0280(3)
C(8)	–0.16015(12)	0.46286(12)	0.58523(10)	0.0343(4)
C(9)	–0.25968(13)	0.41869(13)	0.56617(11)	0.0385(4)
C(10)	–0.27393(13)	0.31422(14)	0.57269(10)	0.0381(4)
C(11)	–0.18995(12)	0.25194(12)	0.59859(10)	0.0333(3)
C(12)	–0.08774(12)	0.29399(11)	0.61744(9)	0.0274(3)
C(13)	0.01624(12)	0.25431(10)	0.64325(9)	0.0277(3)
C(14)	0.05333(13)	0.14841(10)	0.66177(11)	0.0334(3)
C(15)	0.15463(12)	0.15429(11)	0.71999(11)	0.0334(4)

Bond Lengths [Å] and Angles [°]

O(1)–C(1)	1.2412(18)	N(1)–C(1)	1.3509(19)
N(1)–C(5)	1.4814(18)	N(1)–C(15)	1.4696(18)

C(1)–C(2)	1.501(2)	N(2)–C(6)	1.3786(18)
N(2)–C(7)	1.3764(18)	C(2)–C(3)	1.512(2)
C(3)–C(4)	1.516(2)	C(4)–C(5)	1.511(2)
C(5)–C(6)	1.505(2)	C(6)–C(13)	1.360(2)
C(7)–C(8)	1.393(2)	C(7)–C(12)	1.420(2)
C(8)–C(9)	1.385(2)	C(9)–C(10)	1.402(2)
C(10)–C(11)	1.378(2)	C(11)–C(12)	1.402(2)
C(12)–C(13)	1.434(2)	C(13)–C(14)	1.5040(19)
C(14)–C(15)	1.524(2)		

C(1)–N(1)–C(5)	123.70(12)	C(1)–N(1)–C(15)	119.49(12)
C(15)–N(1)–C(5)	116.35(11)	O(1)–C(1)–N(1)	120.99(14)
O(1)–C(1)–C(2)	119.59(13)	N(1)–C(1)–C(2)	119.41(13)
C(7)–N(2)–C(6)	108.26(12)	C(1)–C(2)–C(3)	116.16(12)
C(2)–C(3)–C(4)	109.35(12)	C(5)–C(4)–C(3)	110.37(12)
C(6)–C(5)–C(4)	112.50(12)	N(1)–C(5)–C(4)	111.82(12)
N(1)–C(5)–C(6)	107.13(11)	N(2)–C(6)–C(5)	122.49(12)
C(13)–C(6)–N(2)	110.54(13)	C(13)–C(6)–C(5)	126.97(13)
N(2)–C(7)–C(8)	130.10(14)	N(2)–C(7)–C(12)	107.85(13)
C(8)–C(7)–C(12)	122.05(13)	C(9)–C(8)–C(7)	117.76(14)
C(8)–C(9)–C(10)	120.97(15)	C(11)–C(10)–C(9)	121.36(14)
C(10)–C(11)–C(12)	119.18(15)	C(11)–C(12)–C(7)	118.66(14)
C(7)–C(12)–C(13)	106.55(12)	C(11)–C(12)–C(13)	134.79(14)
C(6)–C(13)–C(12)	106.80(12)	C(6)–C(13)–C(14)	121.65(13)
C(12)–C(13)–C(14)	131.53(13)	C(13)–C(14)–C(15)	107.81(12)
N(1)–C(15)–C(14)	111.11(12)		

Anisotropic Displacement Parameters ($Å^2$). The Anisotropic Displacement Factor Exponent Takes the Form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.0367(6)	0.0282(6)	0.0561(7)	–0.0048(5)	–0.0034(5)	0.0096(5)
N(1)	0.0299(6)	0.0243(6)	0.0332(6)	0.0017(5)	0.0031(5)	0.0035(5)
C(1)	0.0298(7)	0.0300(8)	0.0291(7)	–0.0049(6)	–0.0043(6)	0.0051(6)
N(2)	0.0269(6)	0.0225(6)	0.0373(7)	0.0001(5)	–0.0037(5)	–0.0005(5)
C(2)	0.0259(7)	0.0398(9)	0.0338(8)	–0.0005(6)	–0.0015(6)	0.0055(6)
C(3)	0.0278(7)	0.0353(8)	0.0372(8)	0.0011(6)	0.0005(6)	–0.0020(6)
C(4)	0.0281(7)	0.0273(7)	0.0343(8)	0.0006(6)	0.0009(6)	0.0010(6)
C(5)	0.0278(7)	0.0234(7)	0.0335(8)	0.0007(6)	0.0006(6)	0.0030(6)
C(6)	0.0300(7)	0.0226(7)	0.0282(7)	–0.0003(5)	0.0020(6)	0.0016(5)
C(7)	0.0280(7)	0.0296(7)	0.0263(7)	–0.0007(6)	–0.0008(6)	–0.0023(6)

C(8)	0.0322(8)	0.0340(8)	0.0368(8)	0.0050(6)	–0.0035(6)	0.0021(6)
C(9)	0.0286(8)	0.0511(10)	0.0357(8)	0.0065(7)	–0.0045(7)	0.0013(7)
C(10)	0.0285(8)	0.0551(10)	0.0306(8)	–0.0007(7)	–0.0008(6)	–0.0095(7)
C(11)	0.0352(8)	0.0354(8)	0.0292(8)	–0.0034(6)	0.0033(6)	–0.0090(7)
C(12)	0.0316(7)	0.0282(7)	0.0225(7)	–0.0032(5)	0.0027(6)	–0.0025(6)
C(13)	0.0300(7)	0.0251(7)	0.0279(7)	–0.0027(5)	0.0038(6)	–0.0005(6)
C(14)	0.0374(8)	0.0226(7)	0.0403(9)	–0.0025(6)	0.0081(7)	–0.0017(6)
C(15)	0.0362(8)	0.0237(7)	0.0404(9)	0.0051(6)	0.0072(7)	0.0039(6)

Hydrogen Coordinates and Isotropic Displacement Parameters ($Å^2$)

	x	y	z	U
H(2)	0.0575(13)	0.4859(13)	0.6387(11)	0.035
H(2A)	0.4292	0.2465	0.5628	0.050
H(2B)	0.4902	0.2488	0.6563	0.050
H(3A)	0.4399	0.4121	0.5944	0.050
H(3B)	0.4096	0.3953	0.6969	0.050
H(4A)	0.2576	0.4627	0.6193	0.045
H(4B)	0.2594	0.3685	0.5528	0.045
H(5)	0.2108	0.3614	0.7382	0.042
H(8)	–0.1503	0.5337	0.5809	0.041
H(9)	–0.3192	0.4598	0.5484	0.046
H(10)	–0.3429	0.2858	0.5590	0.046
H(11)	–0.2012	0.1814	0.6036	0.040
H(14A)	0.0705	0.1134	0.6055	0.050
H(14B)	–0.0049	0.1105	0.6926	0.050
H(15A)	0.1338	0.1774	0.7801	0.050
H(15B)	0.1873	0.0864	0.7255	0.050

Hydrogen Bonds [Å and °]

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(2)–H(2)...O(1A)	0.902(17)	1.901(17)	2.7797(16)	163.9(15)

Symmetry Operations for Equivalent Atoms

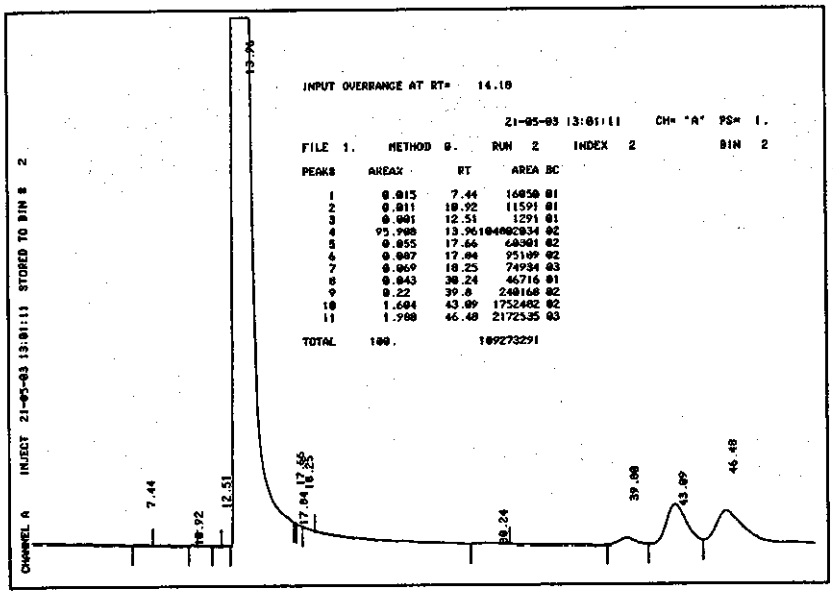
A x–1/2,–y+3/2,–z+2

Determination of Enantiomeric Excess

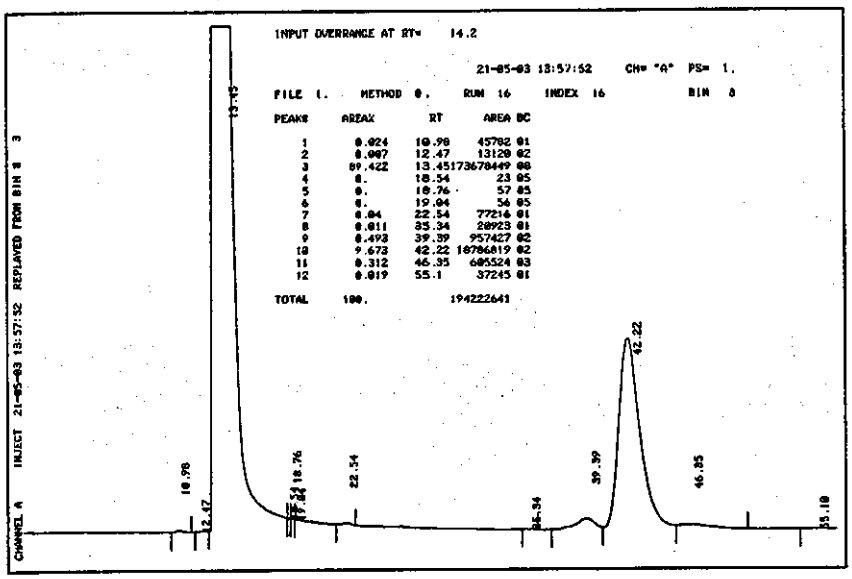
Column: ChiralCel OD-H

Conditions: 85:15 hexane/propan-2-ol, 0.4 mL min^{-1}

Racemic Sample **(328)**

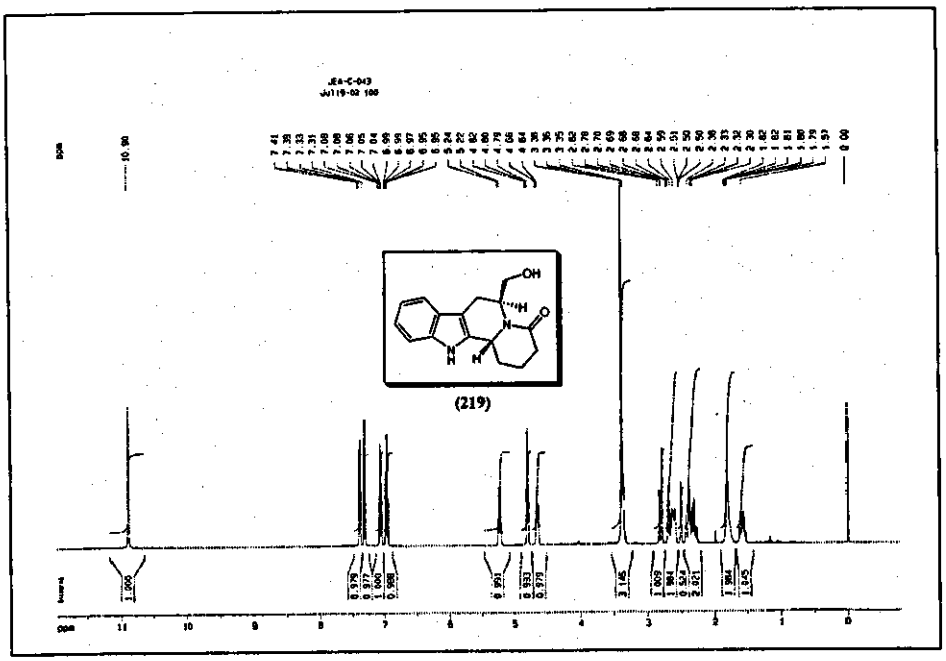


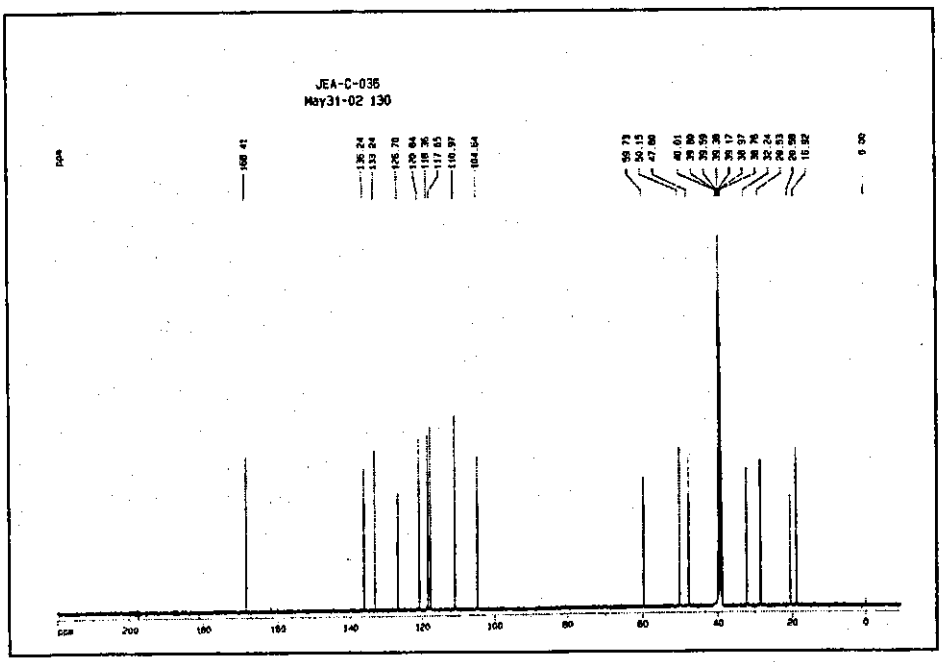
Enantiomerically Enriched Sample **(310)**



^{1}H and ^{13}C NMR Spectra

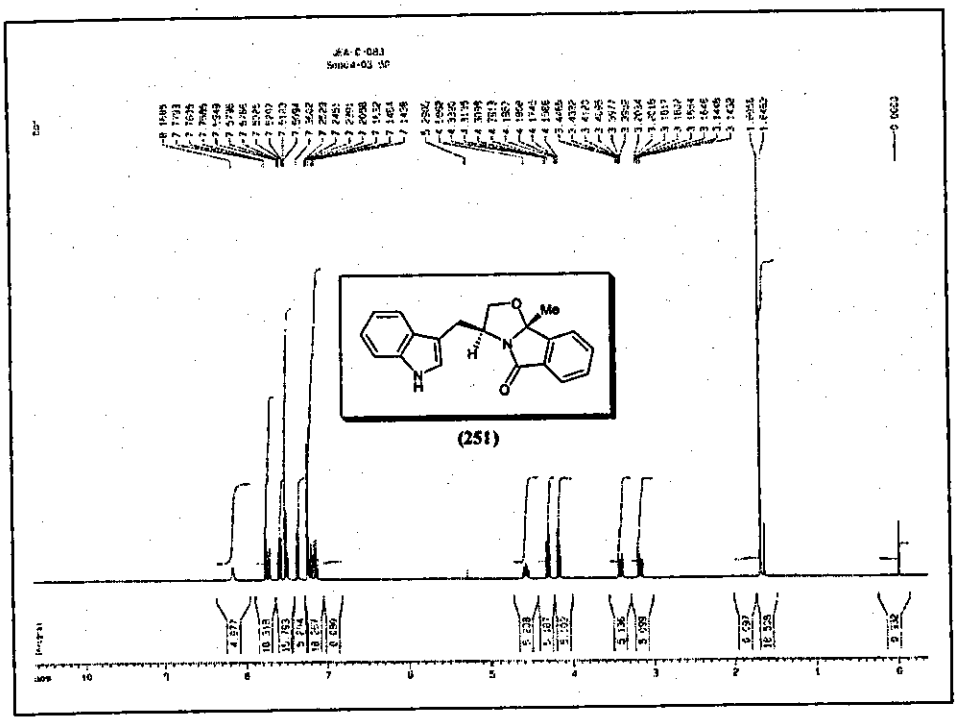
Compound: **(219)**



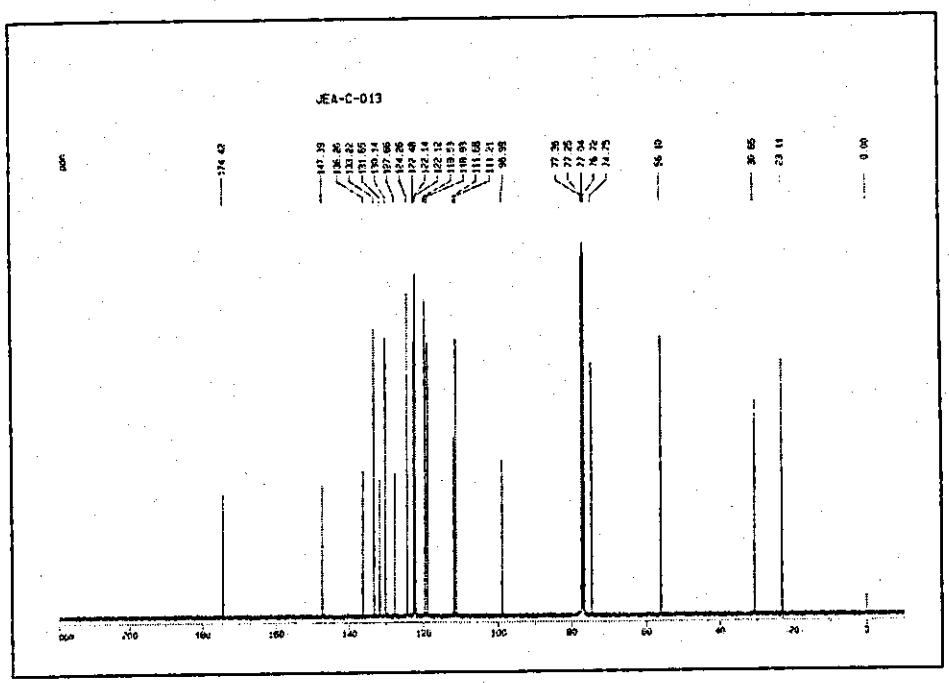


^{1}H and ^{13}C NMR Spectra

Compound: **(251)**

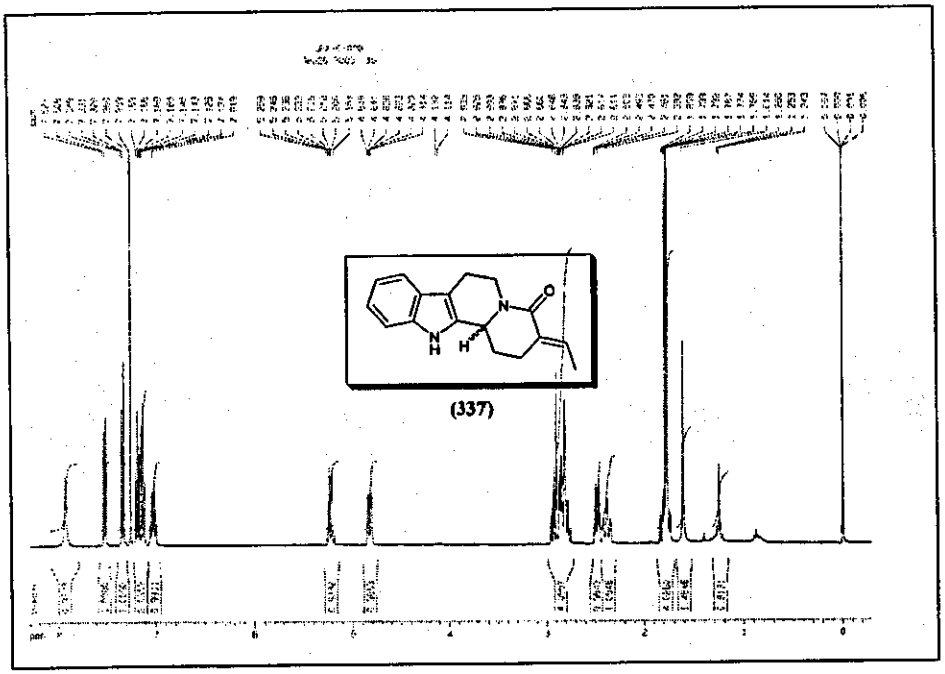


(251)

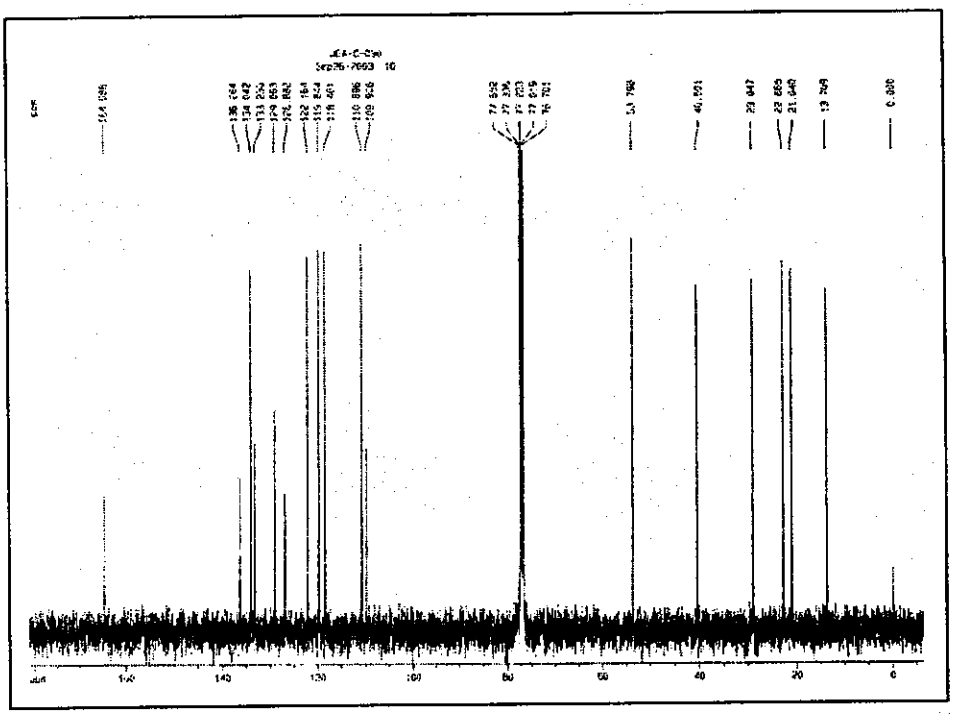


^{1}H and ^{13}C NMR Spectra

Compound: **(337)**

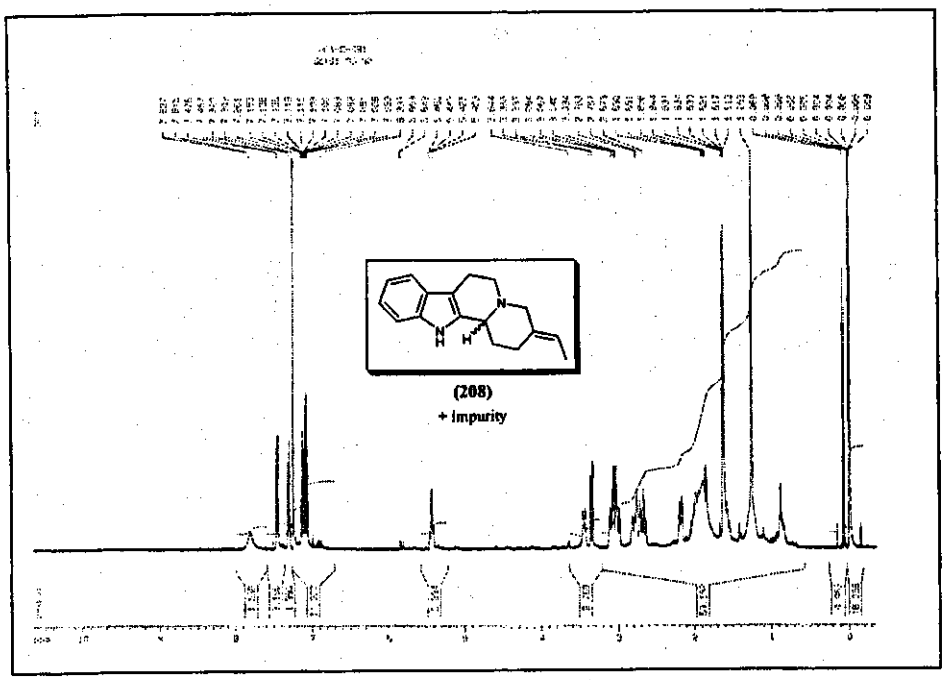


(337)



^{1}H NMR Spectrum

Compound: **(208)** + impurity



Pergamon

Tetrahedron Letters 43 (2002) 3661–3663

TETRAHEDRON LETTERS

Stereoselective synthesis of isoquinoline derivatives from bicyclic lactam templates

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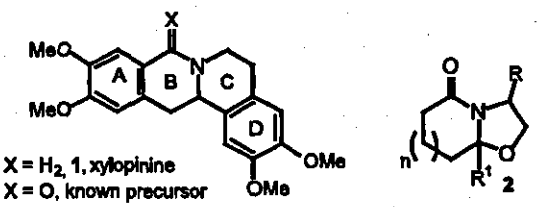
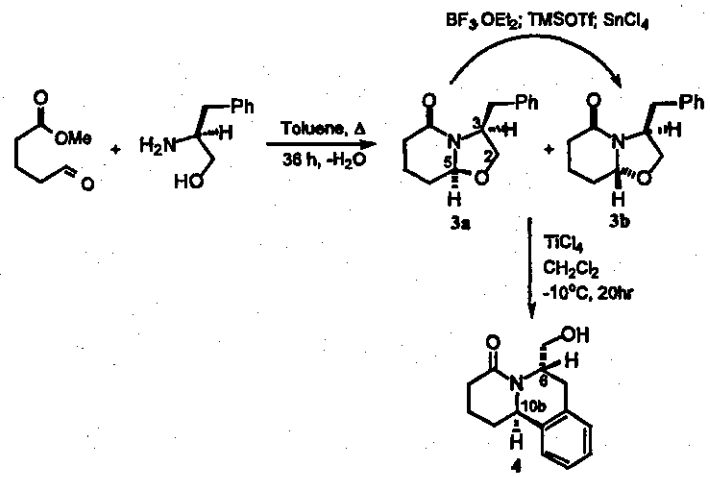
Abstract—We report a novel, facile and stereoselective approach to a tricyclic tetrahydroisoquinoline ring system from readily available, non-racemic, bicyclic lactam substrates.

Derivatives of the isoquinoline ring system are found as major structural motifs in a wide range of natural products and biologically active compounds and therefore new synthetic routes to these targets are of general interest.[1] Based on our novel stereoselective approach to the isoindoloisoquinoline[2] and pyrroloisoquinoline[3] ring systems, we recognized that a suitably substituted bicyclic lactam 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 1 and its derivatives.[4] Our approach allows the introduction of asymmetry during the key ring-forming step: the stereoselective cyclization of a bicyclic lactam substrate via an *N*-acyliminium intermediate.



Although bicyclic lactams derived from β-aminoalcohols containing fused 5,5- (2, $n=0$, Meyers)[5] and 5,6-



Scheme 1.

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PII: S0040-4039(02)00628-7

ring systems (**2**, $n=1$, Amat and Bosch)[6] have been widely utilized in asymmetric synthesis, to the best of our knowledge the present application of the corresponding fused 5,6-system ($n=1$) as a precursor in an *N*-acyliminium mediated cyclization reaction leading to tetrahydroisoquinoline targets represents a novel application of this chiral template.

Our synthesis of the required bicyclic lactam substrate **3** from commercially available (*S*)-phenylalaninol followed the general method previously described by Amat.[6] Heating (*S*)-phenylalaninol with methyl 5-oxopentanoate in toluene at reflux under Dean–Stark conditions gave a 4:1 mixture of separable diastereoisomers, **3a** and **3b**, respectively, in 50% overall yield (Scheme 1). The structure of the major diastereoisomer *cis*-**3a** was confirmed by NOE studies,[7] and is consistent with the results reported by Amat for the corresponding phenylglycinol-derived lactam diastereoisomers.[6]

With **3a** in hand we turned our attention to the proposed *N*-acyliminium cyclization reaction. On treating lactam **3a** with $TiCl_4$ as Lewis acid activator at −10°C in dichloromethane for 20 h, we were pleased to isolate the cyclized product in 65% yield (Scheme 1). ^1H NMR analysis of the crude product mixture revealed the formation of only one diastereoisomer, **4**. An NOE study indicated that the relative stereochemistry of the single product diastereoisomer **4** was as indicated in Scheme 1, with the protons at the 6 and 10b positions having a *trans*-relationship.[8]

All other Lewis acids that were employed as activators failed to induce cyclization ($BF_3{\cdot}OEt_2$, TMSOTf, $SnCl_4$), leading only to complete equilibration from *cis*-**3a** to *trans*-lactam **3b**. This result is in accordance with the report of Amat, in which TFA was used to effect the same equilibration reaction.[6]

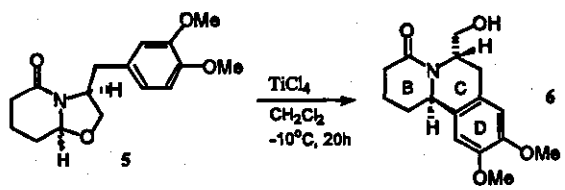
On treating *trans*-diastereoisomer **3b** with $TiCl_4$ as described above we were able to isolate 34% of the desired cyclization product **4**. Interestingly both **3a** and **3b** lead to the *same* diastereoisomer of the cyclization product **4**. This result supports the mechanism previously proposed by us for this type of cyclization,[3] since both **3a** and **3b** would yield the same *N*-acyliminium ion intermediate on activation.

Higher yields of both the corresponding bicyclic lactam precursor and the cyclization product were obtained with a methoxy-substituted substrate (Scheme 2). In this case the bicyclic lactam **5** was isolated in 94% yield as a 6:1 mixture of diastereoisomers. Based on the results described above for cyclization of separated diastereoisomers **3a** and **3b**, we chose not to separate the diastereoisomers of **5** prior to cyclization. Treating **5** with $TiCl_4$ under our usual conditions gave a 68% yield of the tetrahydroisoquinoline **6** as a single diastereoisomer.

The stereochemical outcome of these cyclizations are in accord with our previously proposed models.[3]

We were able to obtain further confirmation of the stereochemical outcome of these cyclizations by X-ray crystallography on compound **6**.[9] As shown in Fig. 1 this product, formed as a single diastereoisomer, has protons at positions **C5** and **C15** in a *trans* relationship, as had been indicated by the NOE on the simpler compound **4**.

In summary, we report a facile and highly stereoselective approach to the tricyclic tetrahydroisoquinoline ring system representing the BCD sub-unit of the protoberberine alkaloids, from readily available non-racemic bicyclic lactam substrates. Previous work from our group in the pyrroloisoquinoline series[3] has demonstrated the removal of the hydroxymethyl auxiliary group from similar products of cyclization through a three-step procedure. Current work is focused on extending this methodology to protoberberine targets, and our progress will be reported in due course.



Scheme 2.

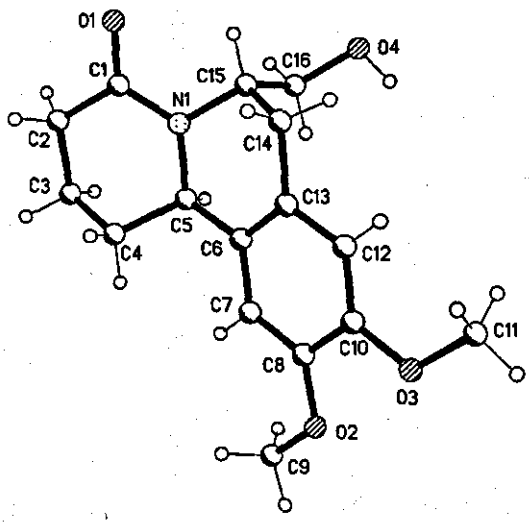


Figure 1.

Acknowledgements

Loughborough and Huddersfield Universities (joint studentship to D.G.V.), Loughborough University and GlaxoSmithKline (joint studentship to S.L.J.), EPSRC (Quota studentship to J.E.A.).

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7. *cis*-**3a**: Although no NOE was observed directly between protons H3 and H5, the stereochemistry was determined to be *cis* since each gave a positive NOE to the same proton at C2 (3.5% for H5, 3.4% for H3).
8. The absence of an NOE between protons situated at the 6 and 10b positions of product **4** is consistent with the expected structure and with previous reports from our group for related compounds.[3] Since the cyclization of substrate **3a** gave exclusively one product diastereoisomer, a comparative NOE could not be carried out on the minor diastereoisomer.
9. CCDC reference number 17860.

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TETRAHEDRON LETTERS

Stereoselective synthesis of the indolizinoindole ring system

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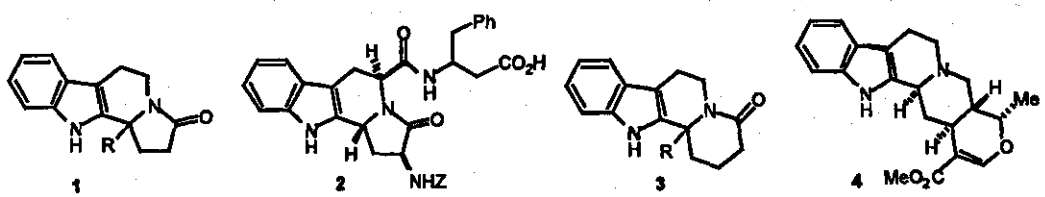
Abstract—We report a novel, facile and stereoselective approach to the indolizino[8,7-*b*]indole ring system from a readily available, non-racemic chiral template.

Indolizino[8,7-*b*]indoles of general structure **1** are of interest to the pharmaceutical industry having been used as intermediates in the preparation of diuretic compounds,[1] and are also known to exhibit analgesic and anti-inflammatory activity in their own right.[2] Other, more functionalised, templates such as **2** have been shown to act as β-turn mimics and display high binding affinity and selectivity for CCK_1 receptors.[3] The lactam homologue **3** is perhaps of greater significance in natural product chemistry, sharing the same heterocyclic skeleton with a plethora of highly bioactive indole alkaloids, including tacamine,[4] geissoschizine,[5] and ajmalicine **4**.[6]



1 **2** **3** **4**

Over recent years, we have reported a new approach to a range of non-racemic heterocycles involving stereoselective cyclisation onto *N*-acyliminium intermediates as the key ring-forming step. Based on our novel and stereoselective approach to both the isoindoloisoquinoline and pyrroloisoquinoline ring systems,[7] we recognised that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the indolizino[8,7-*b*]indole ring system.

Our approach to the synthesis of the required bicyclic lactam substrate **5** followed the general method previously used in our group.[7] The β-amino alcohol derivative of (*S*)-tryptophan was reacted under Dean–Stark conditions with the appropriate keto-acid for 48 h (Scheme 1). Under these reaction conditions we were able to isolate the expected bicyclic lactam **5** in only 3% yield. The major product of the reaction, isolated in 55% yield, was found to be the target indolizino[8,7-*b*]indole derivative **6**.[8]

Examination of the crude reaction mixture by 250 MHz ^{1}H NMR spectroscopy revealed the formation of **6** as a single diastereoisomer.

The relative stereochemistry of product **6** was determined by single crystal X-ray analysis (Fig. 1), and was found to be as expected based on our experience of cyclisation reactions involving similar *N*-acyliminium precursors. Effectively, retention of configuration at the methyl-bearing chiral centre is observed if one considers bicyclic lactam **5** to be an intermediate.[7b,c]

Interestingly, compound **6** was observed to form two crystallographically unique hydrogen bonds: one intramolecular O(2)–H(2A)···O(1) {O(1)···O(2)= 2.597(2) Å, O(2)–H(2A)···O(1)=154°} and one intermolecular N(2)–H(2)···O(2A) {N(2)···O(2A)=2.788(3) Å, N(2)–H(2)···O(2A)=168°} forming chains along the crystallographic *c*-direction.[9]

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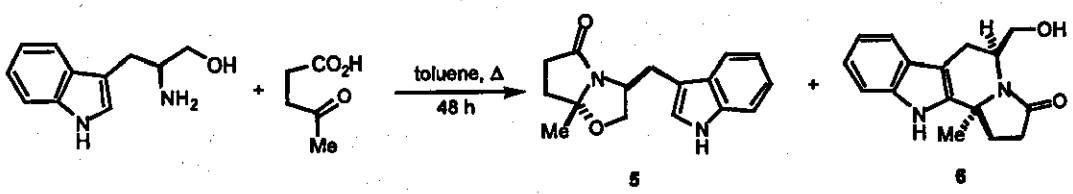


Scheme 1.

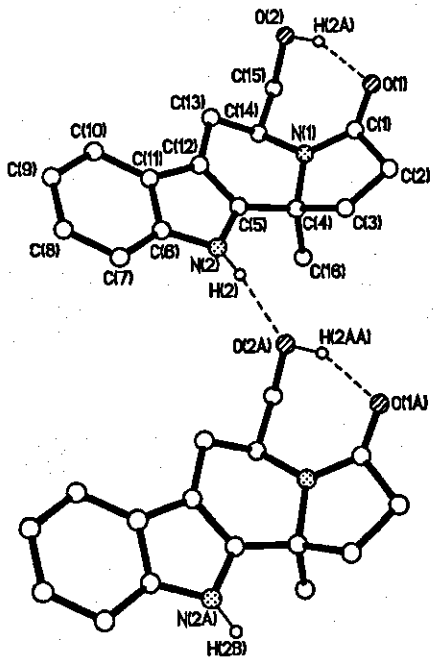


Figure 1. Crystal structure of **6**, omitting most H atoms and the solvent molecule of crystallisation. The intra- and intermolecular H-bonds are highlighted and the numbering scheme is defined.

Of course, one could envisage an alternative mechanism to explain the formation of **6** that avoids the intermediacy of bicyclic lactam **5**: a stereoselective Pictet–Spengler reaction in which condensation of the β-amino alcohol and keto-acid substrate results in formation of a tetrahydro-β-carboline derivative which then undergoes lactam formation to yield **6** in the final step.[10] To date, no intermediates have been observed by us that would support this hypothesis with our substrates.

An alternative approach to the indolizino[8,7-*b*]indole ring system was also investigated through formation and subsequent borohydride reduction of the imide intermediate **7**, accessed in 54% yield from the required β-amino alcohol and succinic anhydride.[7] In this approach, summarised in Scheme 2, the intermediate ethoxy-lactam derivative **8** was not isolated since, under the reaction conditions, direct cyclisation via an *N*-acyliminium intermediate was observed to yield the target heterocycle **9** in 45% yield and as a 9:1 mixture of diastereoisomers. The major diastereoisomer was isolated by crystallisation and the relative stereochemistry of this product was determined to be as shown in Scheme 2 by NOE studies.[11] Again, the relative stereochemistry observed on cyclisation of the attacking aromatic nucleus was as expected based on previous results from our group.[7c]

As noted above, access to the six-membered lactam homologue through application of this methodology would be highly attractive as it would allow access to a wide range of desirable indole targets. With this in mind we successfully prepared the bicyclic lactam substrate **10** as a 5:1 mixture of diastereoisomers in 58% overall yield. The relative stereochemistry of the major isomer, represented in Scheme 3, was determined by NOE studies.[12] Based on our previous work in a related area,[13] these substrate diastereoisomers were not separated, but were treated with $TiCl_4$ to promote the stereoselective cyclisation reaction (Scheme 3).

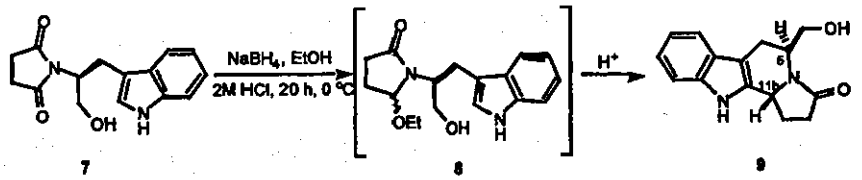
We were pleased to isolate the cyclised product, **11**, in 54% yield and ^{1}H NMR analysis of the crude reaction mixture revealed the formation of this product as a 5:2 mixture of diastereoisomers. A comparative NOE study was undertaken on the isolated diastereoisomers to confirm that the relative stereochemistry of the major diastereoisomer is as shown in Scheme 3.[14]

To demonstrate the potential synthetic utility of this new methodology we followed a method previously used by us to remove the hydroxymethyl auxiliary group (Scheme 4).[7b,c] Oxidation of **6** to the corresponding aldehyde was achieved in 90% yield using IBX (*o*-iodoxybenzoic acid) in DMSO;[15] subsequent decarbonylation gave a mixture of enamide **12** and target lactam **13**. This product mixture was subjected to catalytic hydrogenation to convert the unwanted enamide through to lactam **13**. Finally, lactam reduction generated the tertiary amine derivative **14** in 27% overall yield from the aldehyde.

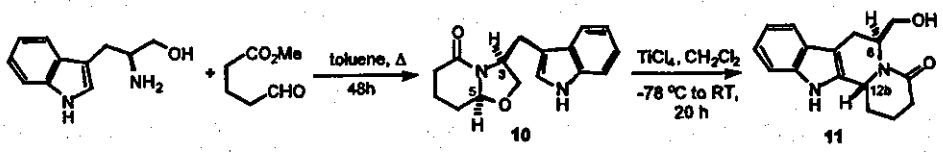
In summary, we report a facile and highly stereoselective approach to a range of indole-containing heterocycles from readily available non-racemic substrates. Current work is focused on extending this methodology to specific indole alkaloid targets, and our progress will be reported in due course.

Acknowledgements

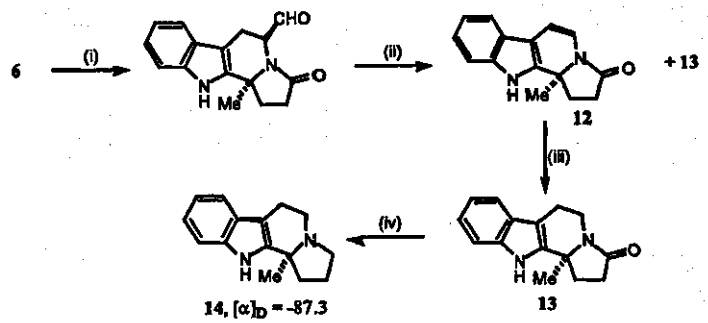
Loughborough University and OSI Pharmaceuticals (joint studentship to C.I.T.), EPSRC (Quota studentship to J.E.A.).



Scheme 2.



Scheme 3.



Scheme 4. *Reagents and conditions*: (i) IBX, DMSO, 24 h; (ii) $Rh(PPh_3)_2(CO)Cl$, xylene, Δ, 5 days; (iii) H_2/10% Pd–C, EtOH, 48 h; (iv) Red-Al, toluene, 20 h, rt.

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8. Compound **5** was observed to begin to convert to **6** on standing in an NMR tube in $CDCl_3$ solvent.
9. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 198533).
10. (a) Bocchi, V.; Casnati, G.; Gardini, G. P. *Tetrahedron Lett.* **1971**, *12*, 683–684; (b) De La Figuera, N.; Rozas, I.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. *J. Chem. Soc., Chem. Commun.* **1994**, 613–614.
11. The absence of an NOE between the protons situated at positions 5 and 11b of product **9** is consistent with the proposed structure. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative NOE study. This result is in agreement with related work from our group (Ref. 7b).
12. We were able to perform a set of comparative NOE studies on the separable diastereoisomers of product **10**. In the case of the major diastereoisomer, **10**, an NOE was observed between protons at positions 3 and 5. In the case of the minor diastereoisomer, no NOE was observed. Both results are in accord with previous results from our group detailing the preparation of 5,6-fused bicyclic lactams (Ref. 11).
13. Allin, S. M.; Vaidya, D. G.; James, S. L.; Allard, J. E.; Smith, T. A. D.; McKee, V.; Martin, W. P. *Tetrahedron Lett.* **2002**, *43*, 3661–3663.
14. We were able to perform a set of comparative NOE studies on the separable diastereoisomers of product **11**. In the case of the minor diastereoisomer an NOE was observed between protons at positions 6 and 12b. In the case of the major diastereoisomer, **11**, no NOE was observed.
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Tetrahedron Letters

Highly stereoselective synthesis of the indolo[2,3-*a*]quinolizine ring system and application to indole natural product synthesis

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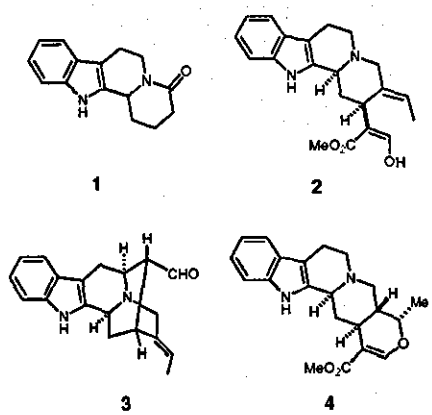
Abstract—We report a novel, facile and highly stereoselective approach to the indolo[2,3-*a*]quinolizine ring system from a readily available, non-racemic chiral template. We demonstrate the potential for application of this methodology to natural product synthesis through conversion of the template to a simple indole alkaloid with high enantiomeric purity.

The indolo[2,3-*a*]quinolizine ring system **1** is of great interest and significance since this heterocyclic template is found within a plethora of highly bioactive indole alkaloids, including geissoschizine **2**,[1] vellosimine **3**[2] and ajmalicine **4**.[3] The presence of the lactam carbonyl in templates such as **1** would allow for possible further functionalisation en route to the natural product targets. Recent approaches to the construction of this heterocyclic target system by other groups have included the diastereoselective vinylogous Mannich reaction,[4] Bischler–Napieralski reaction,[5] Fischer indole synthesis[6] and the asymmetric Pictet–Spengler reaction.[7]



1 **2** **3** **4**

We have recently developed a new and general approach for the stereoselective synthesis of a range of non-racemic heterocycles that involves the cyclisation of pendent aromatic substituents onto *N*-acyliminium intermediates as the key ring-forming step.[8] Based on our novel approach to the indolizino[8,7-*b*]indole ring system,[8a] we recognised that a suitably substituted bicyclic lactam could act as a precursor in a stereoselective approach to the indolo[2,3-*a*]quinolizine ring system.

Our approach to the synthesis of the required bicyclic lactam substrate **5** followed the general method previously used in our group.[8] The β-amino alcohol derivative of (*S*)-tryptophan was reacted under Dean–Stark conditions in toluene with an appropriate functionalised substrate for 48 h (Scheme 1). Under these reaction conditions, we were able to isolate the expected bicyclic lactam in 69% yield as a 5:1 mixture of separable diastereoisomers, **5a** and **5b**.

The relative stereochemistry of the major diastereoisomer **5a** was determined by single crystal X-ray analysis (Fig. 1).[9] This indole-containing bicyclic lactam is a novel example of the fused 5,6-ring system favoured by Amat et al.,[10] and the relative stereochemistry observed for the major isomer **5a** is consistent with results obtained both by these researchers and in our own previous work in other areas.[8b]

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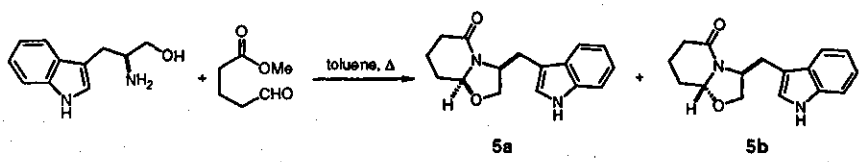


Scheme 1.

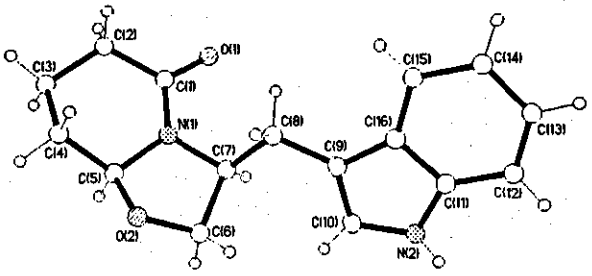
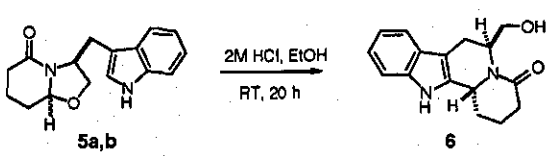


Figure 1. Crystal structure of 5a.

In a previous communication, we noted briefly that treatment of the initial mixture of diastereoisomers of substrate **5** with $TiCl_4$ gave the desired indolo[2,3-*a*]quinolizine target **6** in 54% yield, but with only a poor level of product diastereoselectivity (5:2).[8a] We have now discovered that simply treating the mixture of bicyclic lactam substrate diastereoisomers, **5a** and **5b**, with 2M HCl in ethanol at room temperature for 20 h gives an excellent yield of 95% for the cyclisation reaction, and leads to the formation of the desired indolo[2,3-*a*]quinolizine product as a *single* diastereoisomer (Scheme 2).

The relative stereochemistry of the single diastereoisomer **6** was determined by single crystal X-ray analysis (Fig. 2)[9] and was found to be as favoured in the $TiCl_4$ mediated cyclisation reaction that had previously given only a 5:2 ratio of product diastereoisomers.

To highlight the potential synthetic utility of our new methodology in the target synthesis of complex indole alkaloids and their synthetic analogues, we undertook the synthesis of a simple indole alkaloid, (*S*)-(−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine, **11**, the main constituent of *Dracontomelum mangiferum* B1.[11] In order to access the natural (*S*)-enantiomer of the target we were required to work with the opposite stereochemical series of the template. Hence compound **7** was prepared as a single diastereoisomer from (*R*)-tryptophan by analogous chemistry to that described above,



Scheme 2.

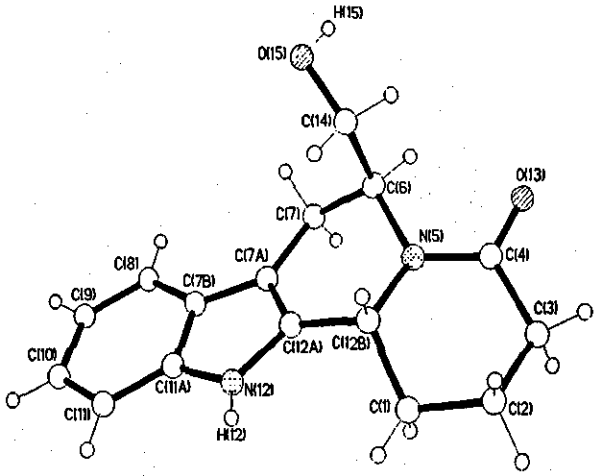
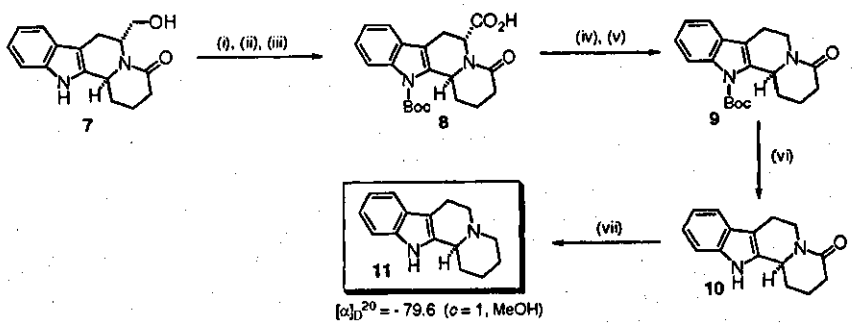


Figure 2. Crystal structure of 6.

an X-ray crystal structure of **7** was also obtained. Our synthetic route to the natural product **11** from **7** is highlighted in Scheme 3.

Our previous method to remove the hydroxymethyl 'auxiliary' group from templates such as **7** has involved a rhodium-induced decarbonylation sequence.[8a] Due to the rather long reaction times generally needed for our substrates in this protocol we have now applied an easier approach that relies upon a decarboxylation strategy. Compound **7** was oxidised to the carboxylic acid derivative **8** through the corresponding aldehyde; from **8** we generated the acyl selenide derivative and subsequently performed a tin-mediated deacylation to yield the indolo[2,3-*a*]quinolizine ring system **9**. Deprotection of the indole nitrogen gave known compound **10** in >95% ee by comparison of optical rotation data.[12a] Reductive removal of the lactam carbonyl group completed the synthesis of the natural product. Target (*S*)-(−)-**11** was found to have an ee of 95% and the same absolute configuration as the natural product by comparison of optical rotation data.[12b]

In summary, we report a facile and highly stereoselective approach to the important indolo[2,3-*a*]quinolizine template from readily available non-racemic substrates, and have demonstrated the structural modification of the template to deliver a simple indole alkaloid with high enantiomeric purity. Current work is focused on extending the methodology described in this paper to other, more complex indole alkaloid targets. Our progress will be reported in due course.



Scheme 3. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (65%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (54%); (iii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexane, CH_3CN, *t*-BuOH, H_2O, 0 °C to rt, 18 h (70%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (66%); (v) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 2 h (98%); (vi) TBAF, THF, Δ, 3 h then rt, 9 h (63%); (vii) $LiAlH_4$, THF, Δ, 9 h (96%).

Acknowledgements

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12. (a) Compound **10** gave $[\alpha]_D^{20}$ −286 (*c* 1, $CHCl_3$). The same compound is quoted as having $[\alpha]_D^{20}$ −232 (*c* 1.02, $CHCl_3$) at an ee of 96%[13]; (b) Compound **11**: $[\alpha]_D^{20}$ −79.6 (*c* 1, MeOH); lit.[13]: $[\alpha]_D^{20}$ −84 (*c* 1, MeOH).
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