RADICAL CYCLISATION STUDIES OF CHIRAL α-ACYLAMINO RADICALS: A MODEL STUDY TOWARDS TACAMAN INDOLE ALKALOID SYNTHESIS

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ABSTRACT

The radical cyclisation of chiral 4,5-substituted N-acyl-2-aza-6-heptenyl radicals, derived from D-ribose, has been undertaken as a model study towards Tacaman indole alkaloid synthesis. The radical cyclisations were conducted using tributyltin hydride/AIBN in refluxing benzene. The α-acylamino radicals added to double bonds which were activated by an ethoxycarbonyl substituent. No reduction of the radicals by the tributyltin hydride was observed. Those radicals incorporating an isopropylidene ketal at the 4 and 5 positions as chiral auxiliary showed excellent regio- and stereoselectivity. Out of a possible 4 diastereomers, only two were obtained in a 2:8 ratio. It was established that the isopropylidene ketal directed the cyclisation stereoselectively and that no stereoselectivity was observed in the absence of the chiral auxiliary.

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ABBREVIATIONS:

$[\alpha]_D$	optical rotation
Ac	acetate or acetyl
Ar	aryl
AIBN	2,2'-Azobisisobutyronitrile
Bn	benzyl
br.s	broad singlet
Bu	butyl
ca.	approximately
CAN	ceric ammonium nitrate
cat.	catalytic
d	doublet (NMR), day
DIBAH	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO-d_6	deuterated dimethyl sulfoxide
Et	ethyl
h	hour
IR	infra red spectroscopy
J	coupling constant
m/z	mass-to-charge-ratio
MCPBA	meta-chloroperbenzoic acid
Me	methyl
MHz	megahertz
min	minute
ml	milliliter
mmol	millimole
mpt.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
PDC	pyridinium dichromate

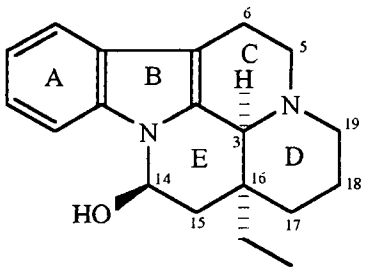
mmol	millimole
mpt.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance spectroscopy
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
pyr	pyridine
quart	quartet
R	alkyl radical
RT	room temperature
R	rectus
s	singlet
S	sinister
t	triplet
TBDMS	t-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
p-TsOH	para-toluenesulfonic acid

CHAPTER 1

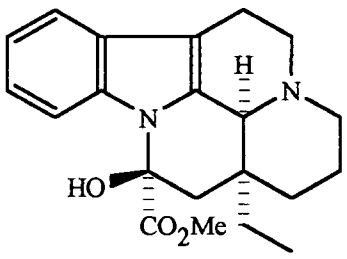
INTRODUCTION

Eburna alkaloids

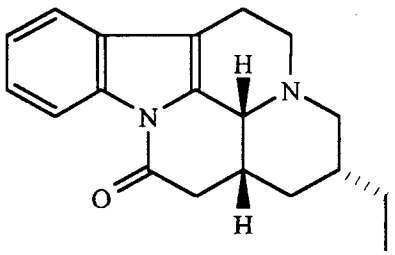
The Eburna alkaloids are a class of pentacyclic, biologically active indole alkaloids whose more common members are shown below. (Fig. 1)



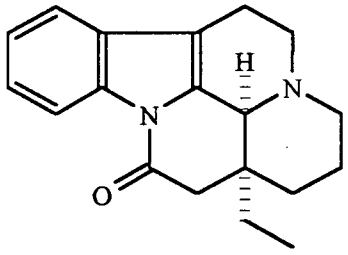
(+)-eburnamine



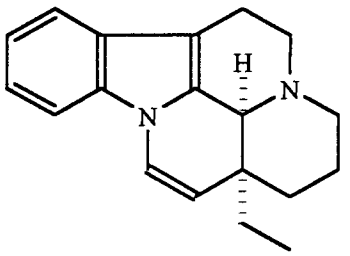
(+)-vincamine



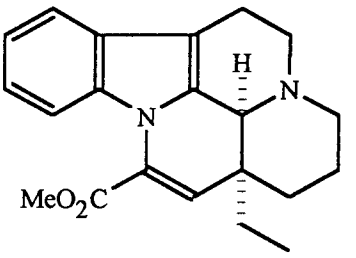
tacamine
(pseudovincamine)



(-)-vincamone



(-)-eburnamenine



(+)-apovincamine

Figure 1

Vincamine, eburnamine and their derivatives are the most important members. Alkaloids of the Tacaman subgroup have only recently been studied and their true potential is still largely unknown. Cuanzine and Schizozygine (not shown) are members of a subgroup that is less important and outside the scope of this thesis.

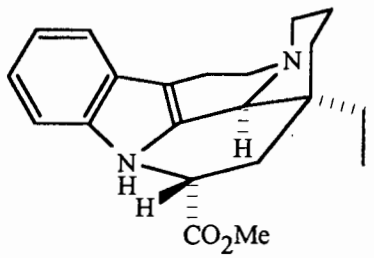
1.1. Vincamine, Eburnamine and their derivatives

Vincamine, the major alkaloid of *Vinca minor* L. (Apocyanaceae), was first isolated in 1953,[1] and is useful in the medical treatment of cerebral insufficiency in man. Similarly, the semi-synthetic (+)-ethylapovincaminate (Cavinton^{R}) is used in many countries for the treatment of cognitive and behavioural symptoms associated with vascular and degenerative disorders of the central nervous system. It also has beneficial effects in the treatment of cerebral eschemia[2].

1.1.1. Structure

In 1965, Wenkert and co-workers[3] established the absolute configuration of vincamine as having the D/E ring fusion cis with the ethyl group α. With an sp^3-like nitrogen at one of the bridgehead positions of the C/D ring system, the quinolizidine moiety could either adopt a cis- or trans-ring fusion. When the hydrogen of the bridgehead carbon is in a trans-diaxial configurational relationship with the lone pair of electrons of the nitrogen, the ring fusion is said to be trans.

Although trans-fused quinolizidine is more stable than the cis-fused conformer, the C/D ring system of eburna alkaloids is cis-fused. (Fig. 2)



Vincamine

Figure 2

The following two spectroscopic methods have been employed to distinguish the cis- and trans-ring systems.

a) Infra red spectroscopy

During an investigation of a large number of alkaloids containing the quinolizidine nucleus, Bohlmann[4] found characteristic bands in the 2700-2860 cm^{-1} region of compounds with the quinolizidine moiety trans-fused. These 'trans bands' were absent when the ring system was cis-fused. In a more rigorous study of various quinolizidines, Skolik *et.al.*[5] established that at least two trans-diaxial orientations between the lone pair of electrons of the nitrogen and a hydrogen are needed in order for 'Bohlmann bands' to be observed. Whereas there are three such orientations in trans-quinolizidine, only one is found in cis-quinolizidine which does not exhibit any Bohlmann bands (Fig. 3).

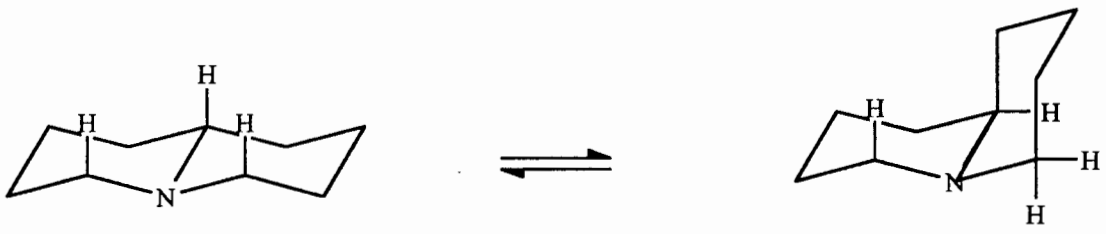


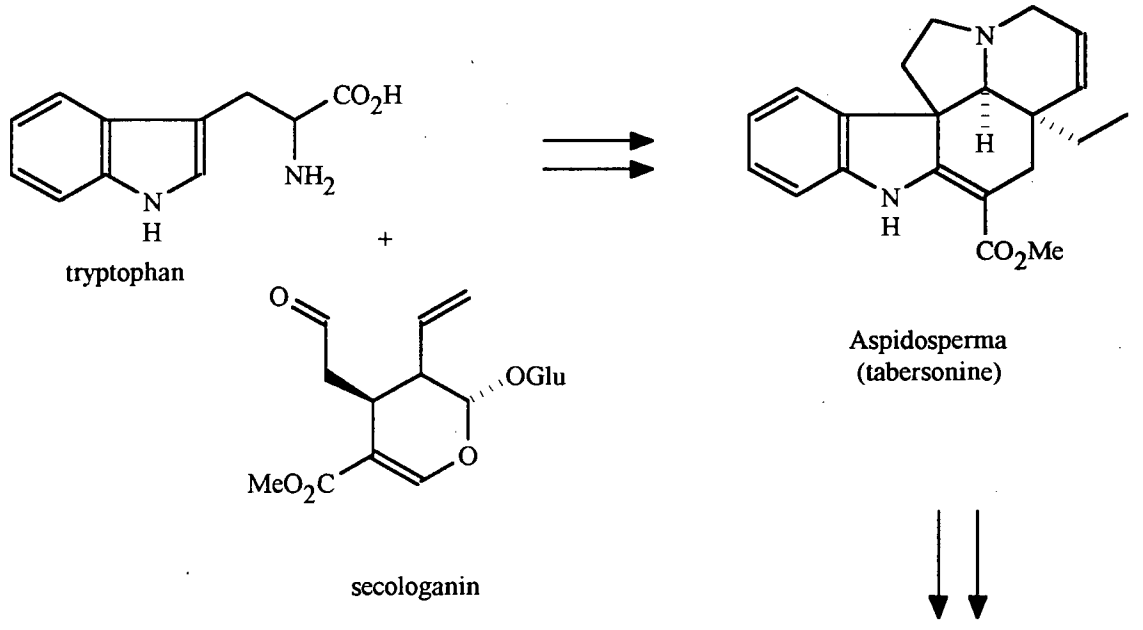
Figure 3

b) ^{1}H NMR spectroscopy

Hamlow *et.al.*[6] investigated the ^{1}H NMR spectrum of quinolizidine and found the chemical shifts of the equatorial protons of the two carbons adjacent to nitrogen to be near 2.7 ppm. The corresponding axial protons showed up as a broad shoulder near 2.0 ppm. The theory that the nitrogen lone pair of electrons is responsible for shielding the axial proton is supported by the decreased shielding of this proton in a protic solvent. Thus, comparing the chemical shifts of the proton of the bridgehead carbon of a cis-fused quinolizidine nucleus with that of a trans-fused system allows one to assign conformers.

1.1.2. Biosynthesis

The biosynthesis of Vinca and Aspidosperma alkaloids as well as other indole alkaloids involves the coupling of the amino acid tryptophan with secologanin, an acetogenin. In fact, the Eburna skeleton is formed via the rearrangement of the Aspidosperma skeleton. (Scheme 1)



Scheme 1

1.1.3. Total Synthesis

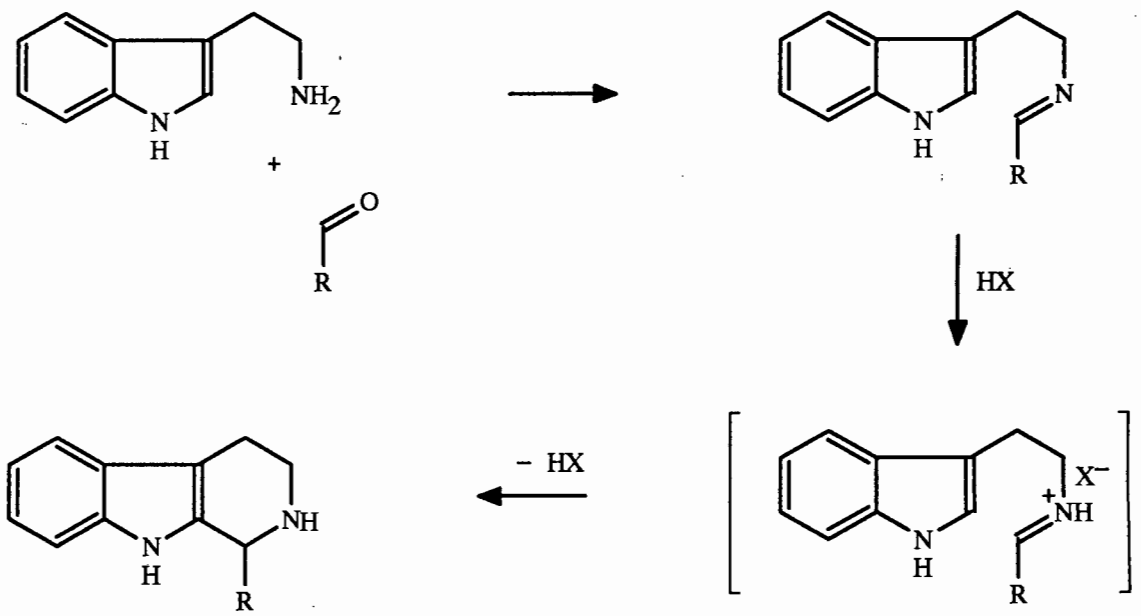
The first racemic synthesis of vincamine was reported as early as 1964 by Kuehne[7], although it was not until 1975 that Oppolzer *et.al.*[8] synthesised optically pure vincamine for the first time. Since 1965, numerous syntheses of Eburna alkaloids have been reported, with most of them producing racemic material even in the last five years.[9,10] Most of the syntheses which did yield the optically pure compound, involved optical resolution of a racemate (like Oppolzer's synthesis). Thus, only a handful of procedures have been truly asymmetric. With few exceptions[10,11], synthetic effort has been based on the biosynthetic pathway. Thus, tryptamine is used in place of tryptophan and a C_9 or C_{10} unit replaces secologanin. This route inevitably implies ring C closure about the C(2)-C(3) carbon-carbon bond, via either the Pictet-Spengler or Bischler-Napieralski cyclisation reactions.

Consequently, the majority of syntheses employing the above methodology have led to the formation of the C(3) epimer as an unwanted by-product (D-E ring junction trans). The stereochemical problem in any Eburna alkaloid synthesis thus centres around the assembly of the centres C(3) and C(16) with correct relative (cis) and absolute configuration (3S, 16S). While the stereochemistry of C(3) is difficult to control using the above methodology, C(16) is easily constructed stereoselectively by employing asymmetric synthesis of the C_9 or C_{10} non-tryptamine unit. The selected syntheses that follow illustrate the different approaches, with emphasis on the construction of the chiral non-tryptamine unit and the stereoselective introduction of C(3).

1.1.4. Selected Syntheses

1.1.4.1. The Pictet-Spengler Approach

The Pictet-Spengler cyclisation reaction can be regarded as a special example of the Mannich reaction and is illustrated by way of an example in Scheme 2.

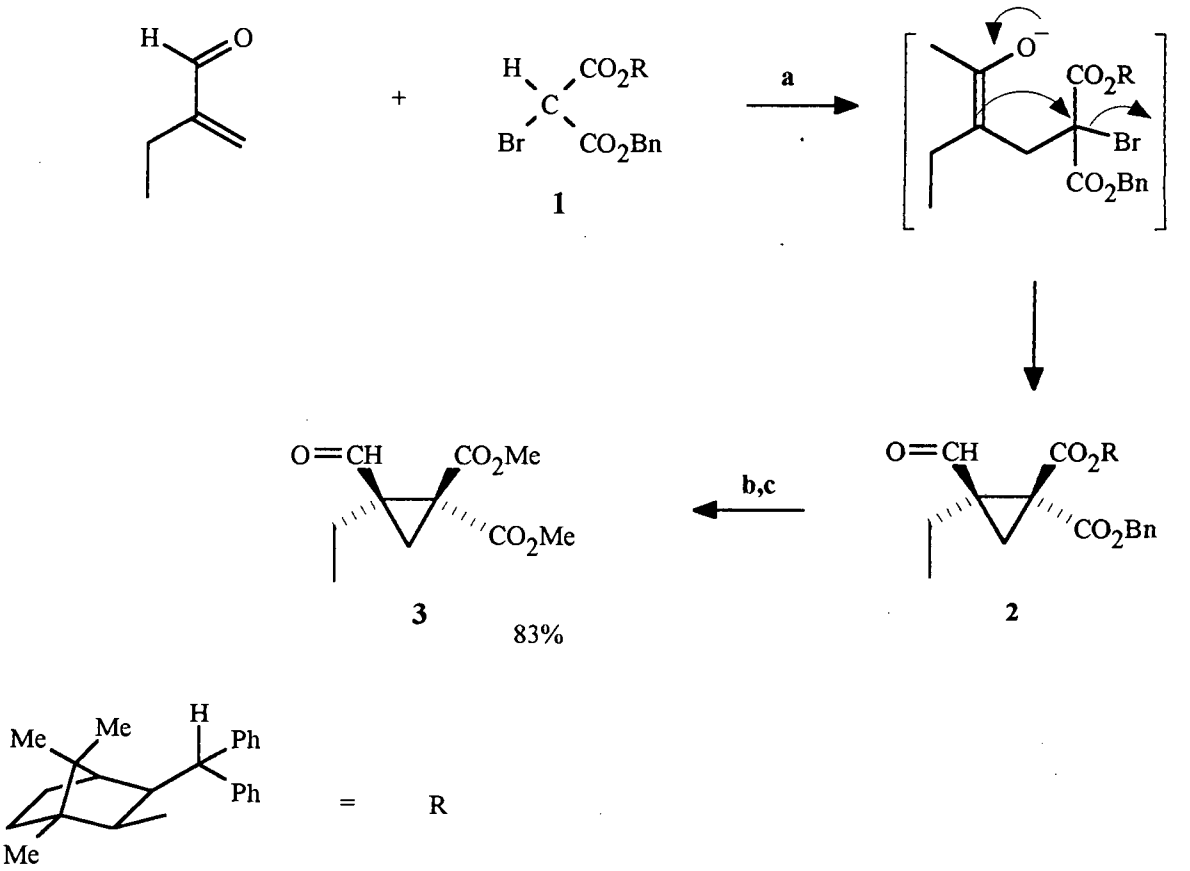


Scheme 2

The overall reaction is conducted in an acidic medium at elevated temperatures. The conditions required for the reaction suggest initial formation of an imine (or enamine in the case of a secondary amine), followed by protonation to give an iminium species. This positively charged species subsequently effects intramolecular electrophilic substitution to form a 1-substituted-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]indole species.

In a truly asymmetric synthesis, Winterfeldt *et.al.*[12] synthesised both (+)- and (-)-eburnamonine from a common intermediate using a highly stereoselective Pictet-Spengler cyclisation.

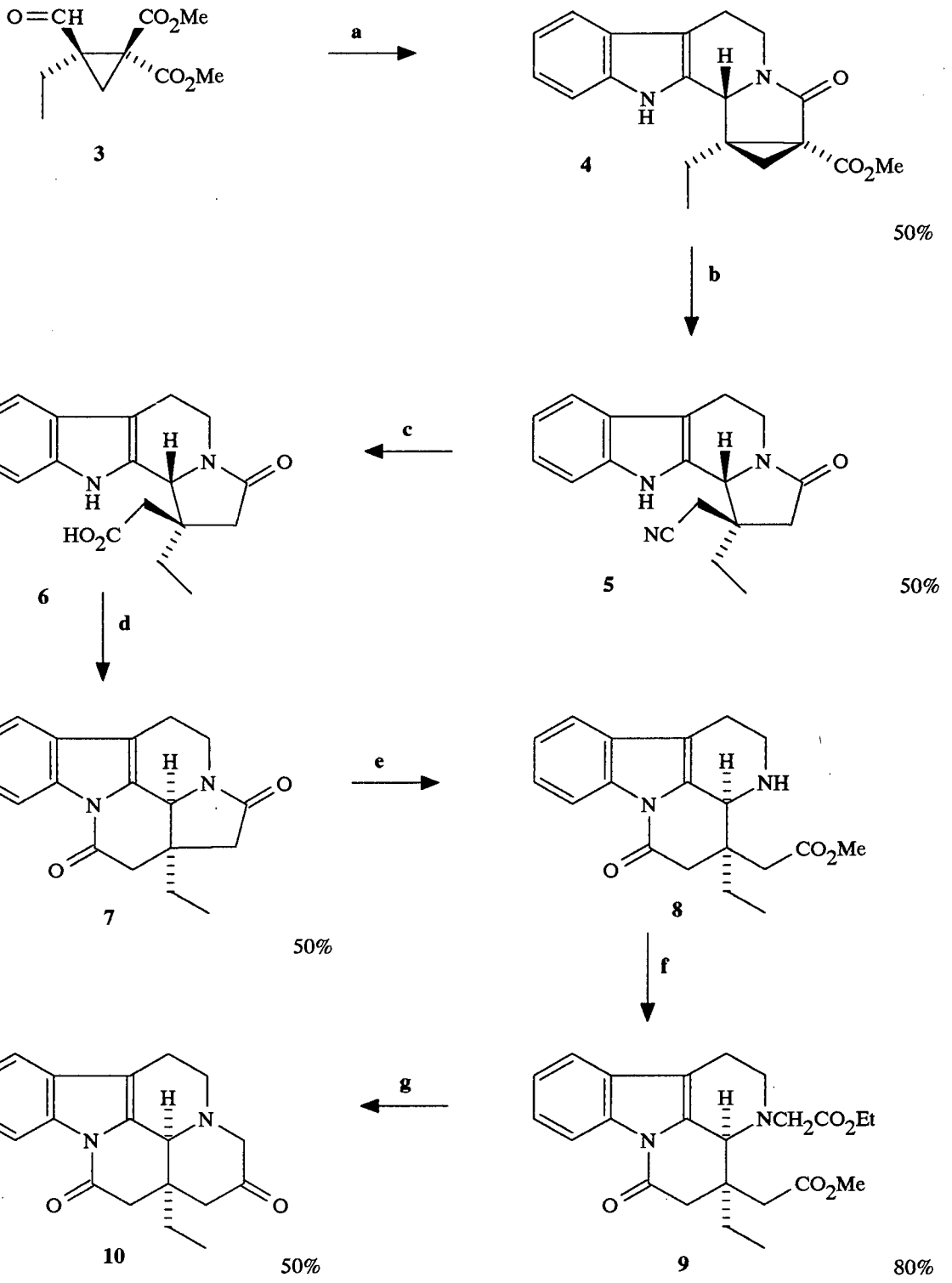
The chiral, non-tryptamine unit **3** was synthesised enantioselectively from α-ethyl acrolein and a chiral bromo-malonate **1** in a base-catalysed Michael-addition cyclisation sequence (Scheme 3).



Reagents: (a) NaH/cyclohexane, (b) i) KOH/MeOH/ 20°C, ii) H^+, (c) CH_2N_2

Scheme 3

The chiral auxiliary (isoborneol derivative) was recovered in the transesterification of **2**. The Pictet-Spengler cyclisation of the cyclopropane carboxaldehyde **3** with tryptamine provided the lactam **4** with high trans- preference (H and Et trans) in a 85:15 ratio (Scheme 4).

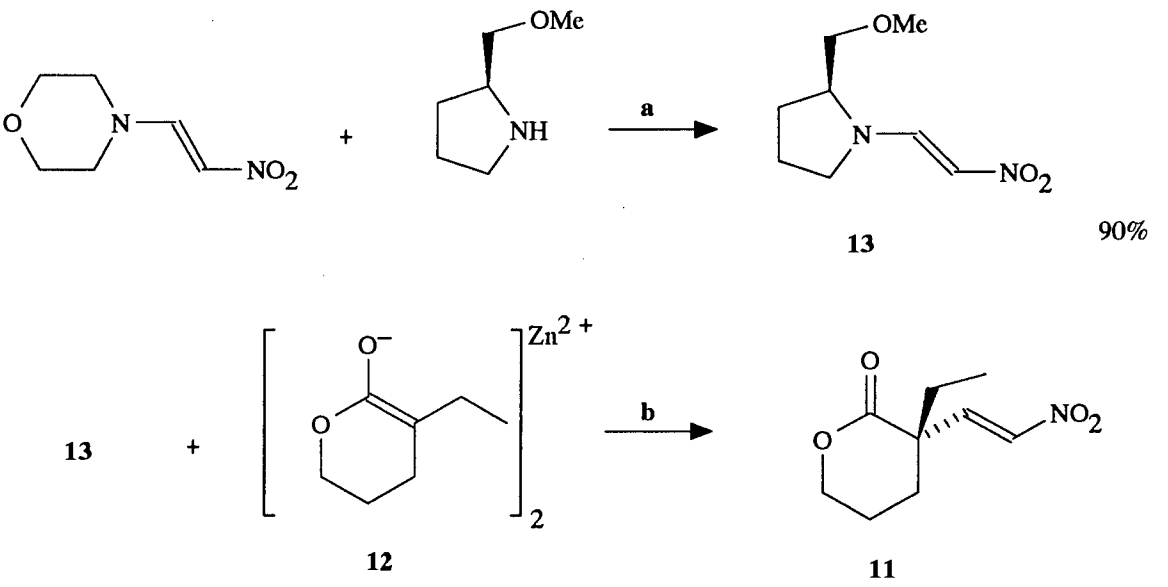


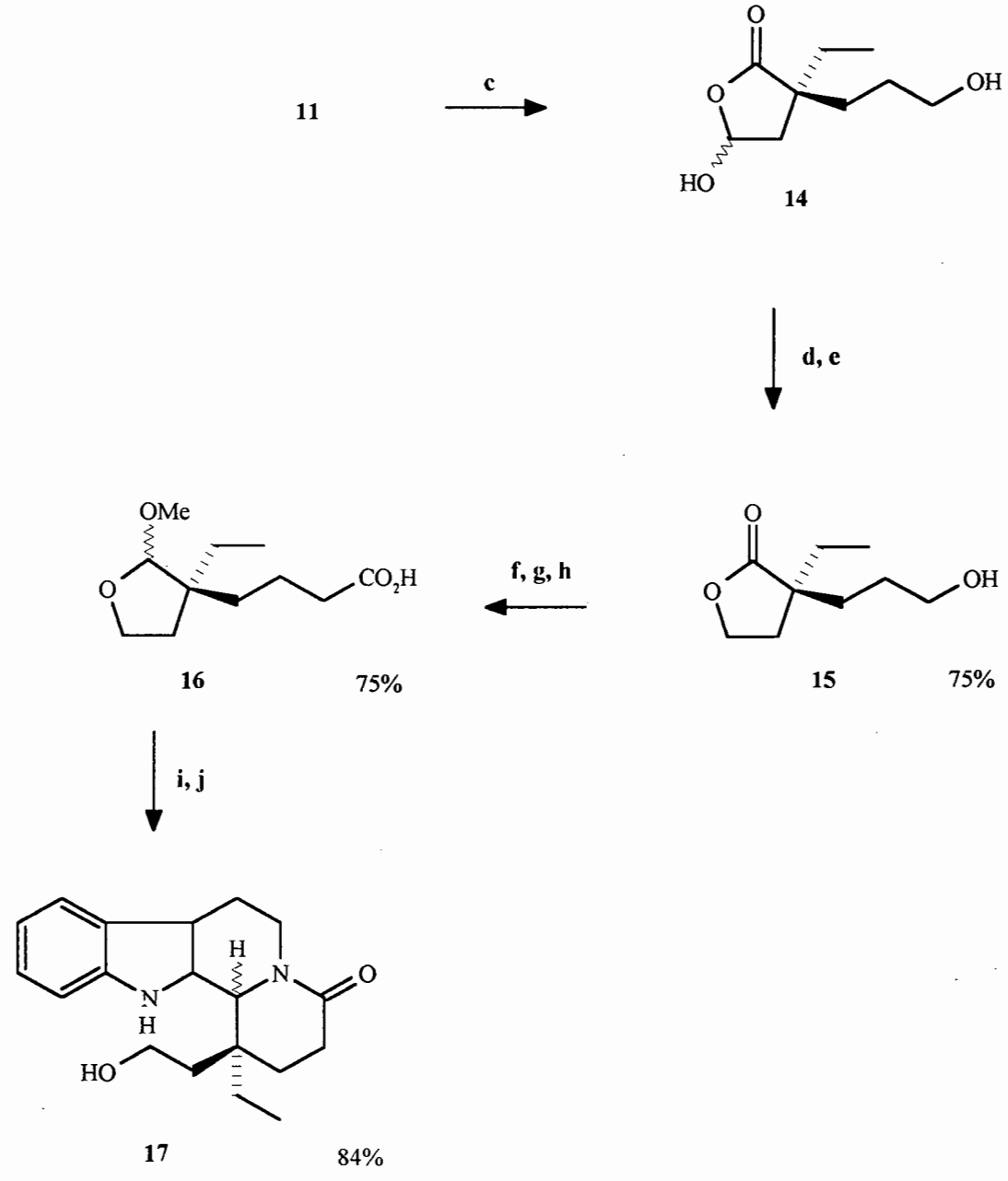
Reagents: (a) AcOH/tryptamine/6d (b) KCN/LiI/DMF (c) $KOH/H_2O_2/MeOH$ (d) TFA
(e) $Et_3OPF_6/MeOH/CH_2Cl_2$ (f) $BrCH_2CO_2Et/Et_2Ni^iPr$ (g) i) NaH/dioxane/EtOH ii) LiI/DMF

Scheme 4.

With (-)-eburnamonine as the target, the cyclopropane ring of **4** was subjected to nucleophilic ring-opening and subsequent decarboxymethylation, yielding lactam **5**. Hydrolysis of the nitrile formed the acid **6** which underwent acid-catalysed cyclisation accompanied by inversion at C(3). The hydrindane-like ring combination of **7** enforces the desired cis-ring junction. Treatment of **7** with Meerwein's reagent opened the lactam to form amino ester **8** after methanolysis. Alkylation with ethyl bromoacetate gave the diester **9** which smoothly underwent Dieckmann cyclisation accompanied by decarboxylation providing ketone **10**. Thioketal formation followed by Raney-Nickel desulfurisation yielded (-)-eburnamonine. In their synthesis, Winterfeldt *et.al.* controlled the stereochemistry at C(16) by asymmetric synthesis of the non-tryptamine unit. The good stereoselectivity of the Pictet-Spengler cyclisation was by no means accidental, but had been carefully planned and was controlled by the steric effect of the cyclopropane ring.

Fuji *et.al.*[13] synthesised their chiral non-tryptamine unit **11** in high enantiomeric excess and in excellent yield through a novel asymmetric addition-elimination sequence which is illustrated in Scheme 5.



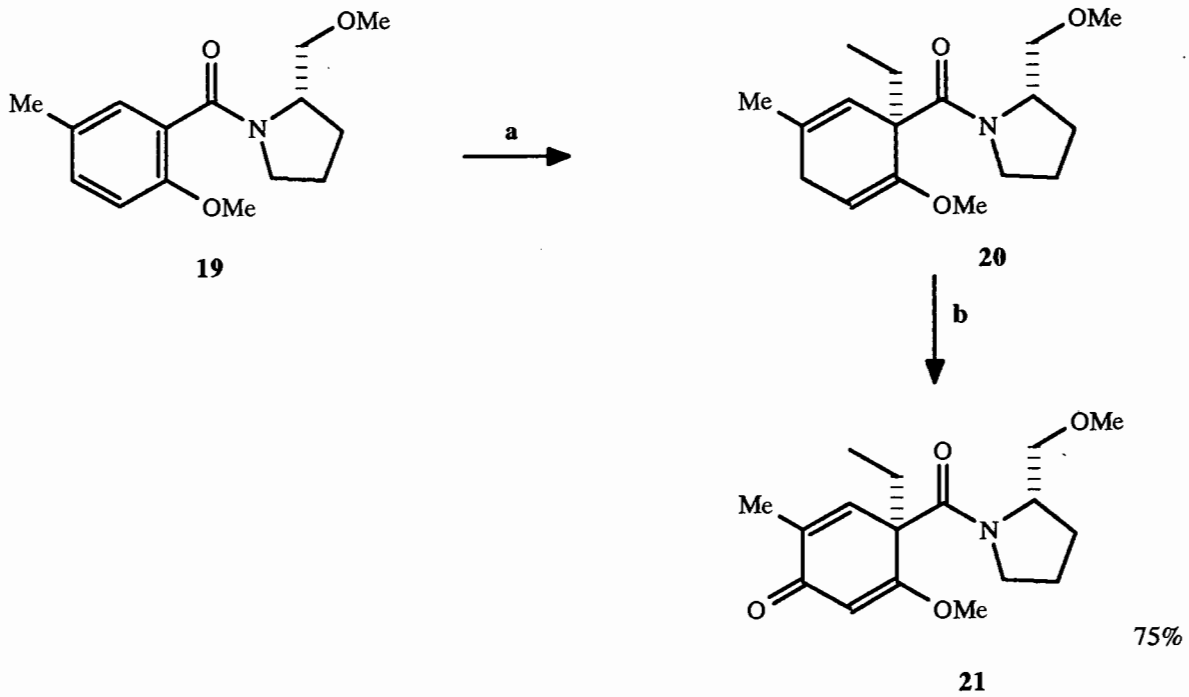


Reagents: (a) MeOH, (b) DME/Et_2O/-78°C, (c) $TiCl_3$/DME, (d) MeOH/$NaBH_4$,
(e) MeOH/dil.HCl/reflux, (f) Jones oxidation, (g) DIBAH/Et_2O,
(h) MeOH/p-TsOH, (i) tryptamine/AcOH/6d/reflux

Scheme 5

Nitroenamine **13** was prepared from 1-morpholinyl-2-nitroethene and (**S**)-2-(methoxymethyl)pyrrolidine in methanol in 90% yield. The nitroenamine **13** was then treated with three equivalents of the zinc enolate **12** in dimethoxyethane-ether at low temperature to afford the δ-lactone **11** in 99% yield and in 85% ee. Reductive denitration of **11** using the McMurry modification of the Nef reaction[14] gave **14** which was converted to the γ-lactone alcohol **15** in two steps in 75% overall yield from **11**. Oxidation of the alcohol to the carboxylic acid using Jones reagent followed by reduction of the lactone and subsequent acid treatment in methanol afforded the acetal **16** in 75% yield. The acetal was then condensed with tryptamine in acetic acid to yield, after basic work-up, a 1:1 mixture of diastereomers **17**. Enantiomeric enrichment by recrystallisation gave the desired intermediate. The unwanted isomer could be recycled because a 1:1 equilibrium was established with $BF_3{\cdot}OEt_2$ at ca. 40°C. Although their synthesis of the chiral non-tryptamine unit is somewhat more elaborate than that of Winterfeldt *et.al.*, Fuji *et.al.* were able to use **11** as a common intermediate for three other Aspidosperma alkaloids. However, as in their synthesis towards eburnamonine, the Pictet-Spengler cyclisation afforded a mixture of diastereomers in each case and elaborate chiral enrichment was necessary to effect optically pure intermediates.

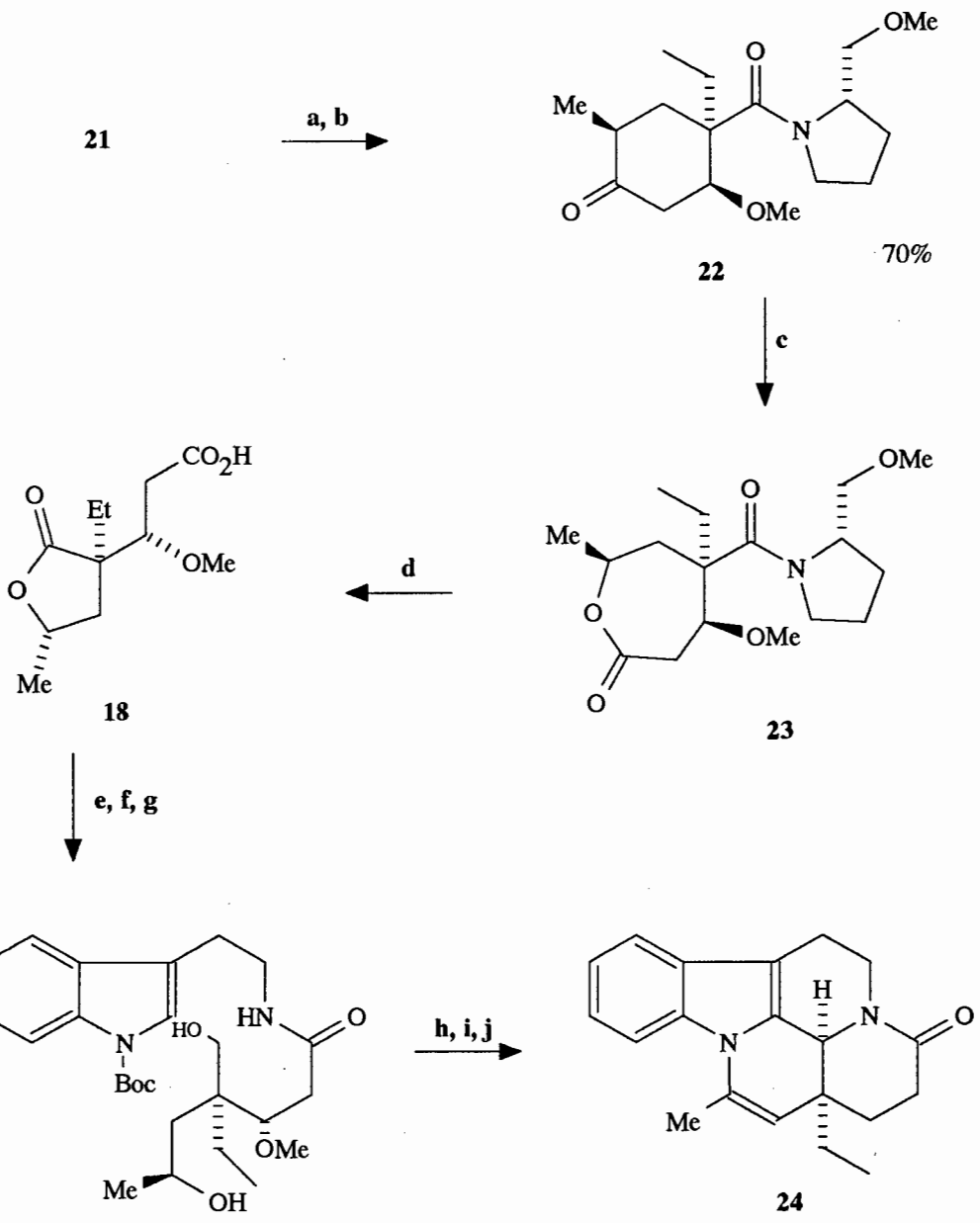
Recently, Schulz[15] has reported the asymmetric synthesis of the α, α, γ-trisubstituted-γ-butyrolactone **18** which served as the chiral non-tryptamine unit in his enantioselective synthesis of (+)-14,15-dehydroapovincamine (Scheme 7)



Reagents: (a) K/NH_3/t-BuOH/THF/EtI, (b) t-BuOOH/PDC/Celite/PhH

Scheme 6

Benzamide **19** was prepared by acylation of (S)-(+)-2-(methoxymethyl)pyrrolidine.[16] (Scheme 6). Birch reduction of the chiral benzamide **19** followed by stereoselective enolate alkylation with ethyliodide gave the 1,4-diene **20**. Allylic oxidation with pyridinium chlorochromate gave **21** in high yield which was efficiently converted to the single cyclohexanone **22** by amide-directed hydrogenation. Regioselective Baeyer-Villiger oxidation afforded the substituted caprolactam **23.** Acid-catalysed transesterification gave γ-butyrolactone **18** and released the chiral auxiliary for reutilisation. **18** was then coupled with tryptamine in a highly stereoselective Pictet-Spengler cyclisation to give the pivotal intermediate **24** from which many vincamine-type alkaloids could be derived (Scheme 7).



Reagents: (a) H_2/Pd/C, (b) Li/NH_3/t-BuOH, (c) MCPBA/CH_2Cl_2, (d) TsOH/H_2O/PhH/reflux, (e) tryptamine/DCC/4-Ppyr, (f) Boc_2O/DMAP/CH_2Cl_2, (g) $LiBH_4$/THF, (h) Swern ox., (i) AcOH/reflux, (j) t-BuOK/t-BuOH

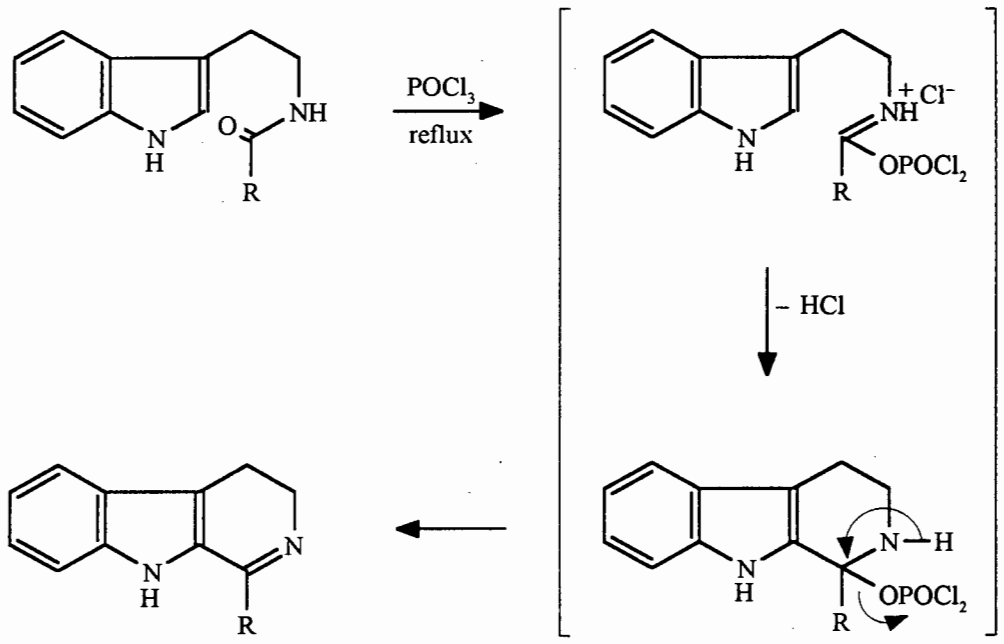
Scheme 7

As in the synthesis of Winterfeldt *et.al.*[12] and Fuji *et.al.*[13], Schulz used a chiral C_{10} unit to control the stereochemistry at C(16) of the eburna skeleton. The relatively short synthesis of the non-tryptamine unit proceeded with excellent stereocontrol to produce three stereogenic centres in seven steps.

The Pictet-Spengler cyclisation proceeded with excellent stereocontrol according to the author but it was not clear whether **24** was in fact the only isomer obtained since no yields were reported.

1.1.4.2. The Bischler-Napieralski Approach

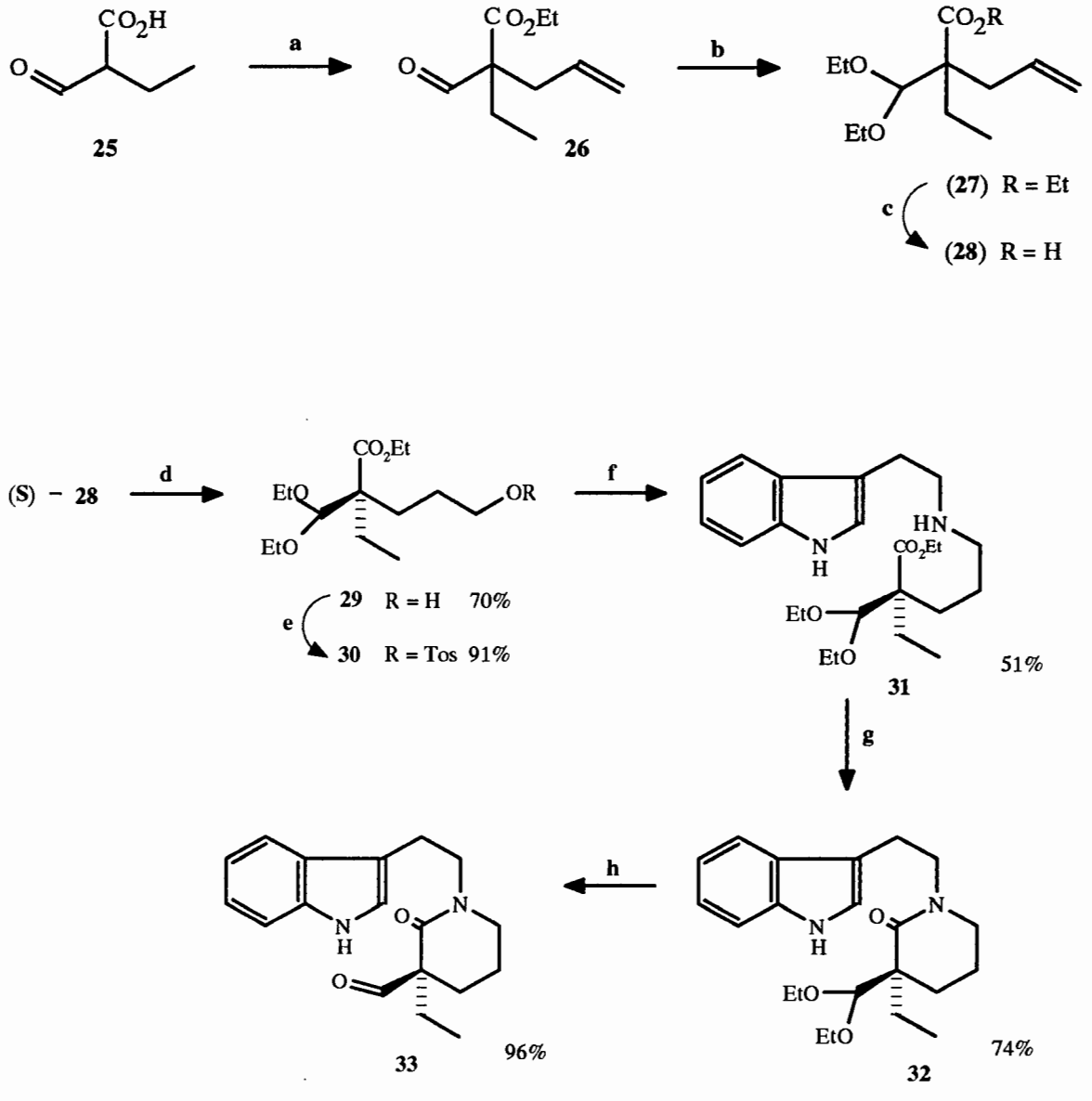
The Bischler-Napieralski cyclisation reaction is illustrated, by means of an example, in Scheme 8.



Scheme 8

This cyclodehydration process may be regarded as an intramolecular electrophilic substitution of the indole induced by initial attack of the dehydrating agent ($POCl_3$) at the oxygen atom of the amide group. This sequence is analogous to the Pictet-Spengler reaction but differs regarding the oxidation level in the product. In this case a 1-substituted-3.4-dihydro-9*H*-pyrido[3,4-b]indole is obtained.

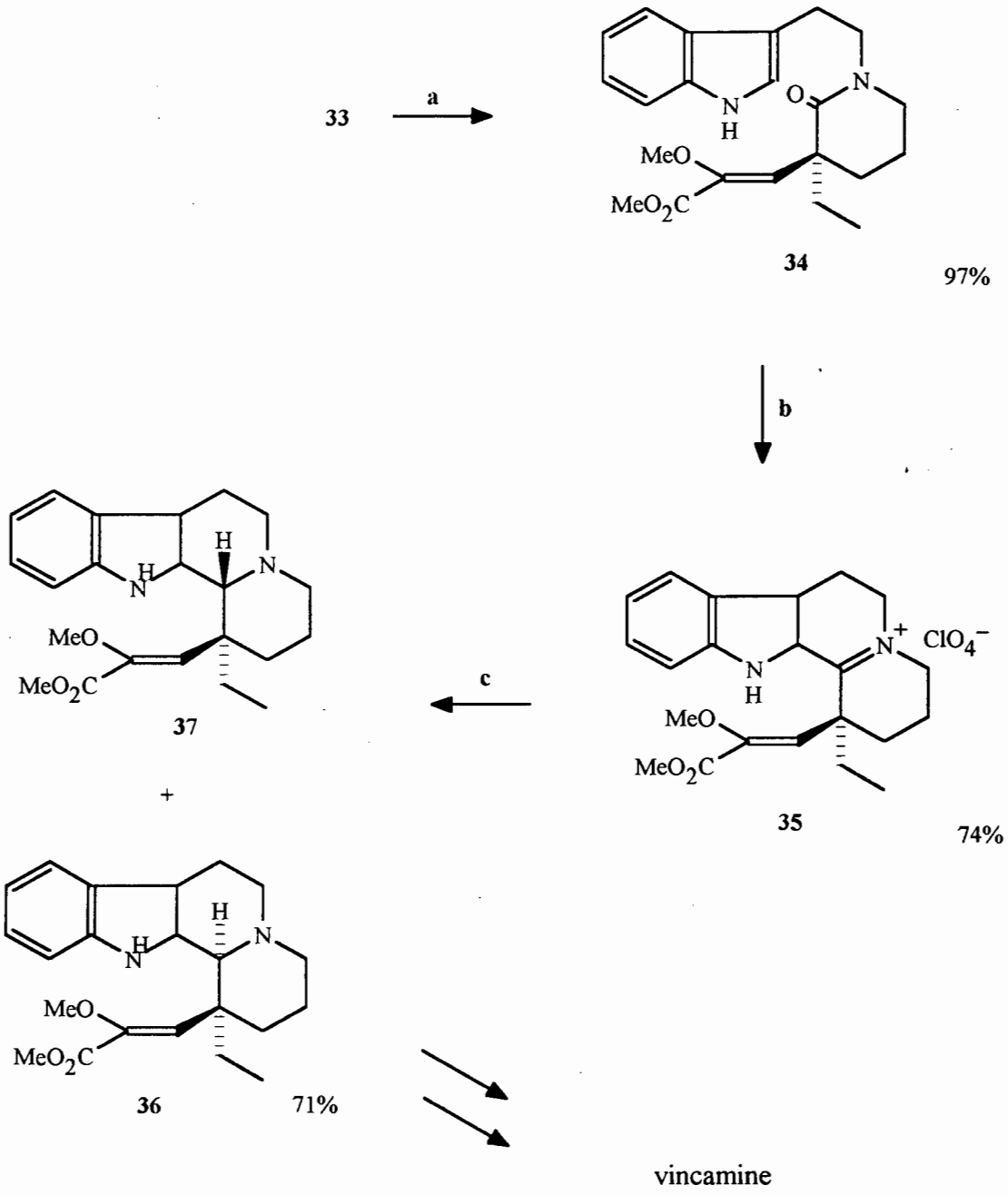
Oppolzer *et.al.*[8] were the first researchers to resolve a racemic mixture early in a synthetic sequence. They synthesised the non-tryptamine unit **28** as a racemate and resolved it using diastereomeric salt formation with L-(+)-pseudoephedrine (Scheme 9).



Reagents: (a) allylbromide/i·Pr_2EtN/PhMe/reflux, (b) $HC(OEt)_3$/TsOH/H_2O/EtOH/reflux,
(c) aqu. KOH/EtOH/reflux, (d) i) K_2CO_3/EtOH/Et_2SO_4, ii) BH_3·THF, iii) EtOH/KOH/H_2O_2,
(e) pyridine/TsCl, (f) tryptamine/DMSO/16h, (g) imidazole/130°C/20h,
(h) AcOH/H_2O/reflux

Scheme 9

Previous syntheses had all reported resolution of racemates which had the tryptamine and the non-tryptamine unit coupled together. Thus, alkylation of **25** with allylbromide provided a mixture of C- and O-alkylated product in a 7:3 ratio. Upon heating the mixture, the O-alkylated product underwent a Claisen rearrangement to provide pure **26**. The aldehyde **26** was converted to the diethylacetal **27** using triethylorthoformate in the presence of tosic acid. Ester hydrolysis yielded yielded the acid **28** which was then resolved. The optically pure acid **28** was re-esterified and subsequent hydroboration afforded alcohol **29**. Tosylation of the alcohol and subsequent coupling with tryptamine in DMSO afforded **31**. A mixture of **31** and imidazole were melted and stirred for 20h to provide the cyclised product **32**. Acetal hydrolysis then provided aldehyde **33**. **33** was then transformed into **34** using a Horner-Wittig reaction which underwent the Bischler-Napieralski cyclisation to afford iminium salt **35** (Scheme 10).

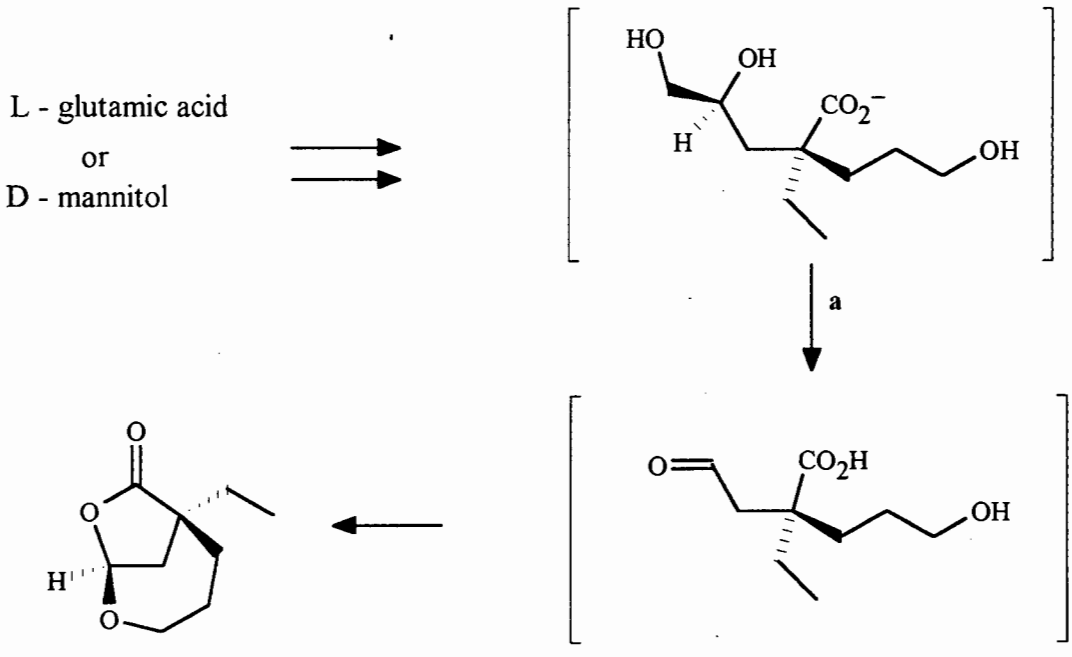


Reagents: (a) $(MeO)_2P(O)CH(OMe)CO_2Me/NaH/THF$, (b) i) $POCl_3$/reflux, ii) aqu. $NaClO_4$, (c) $H_2/Pd/C/EtOH/Et_3N$

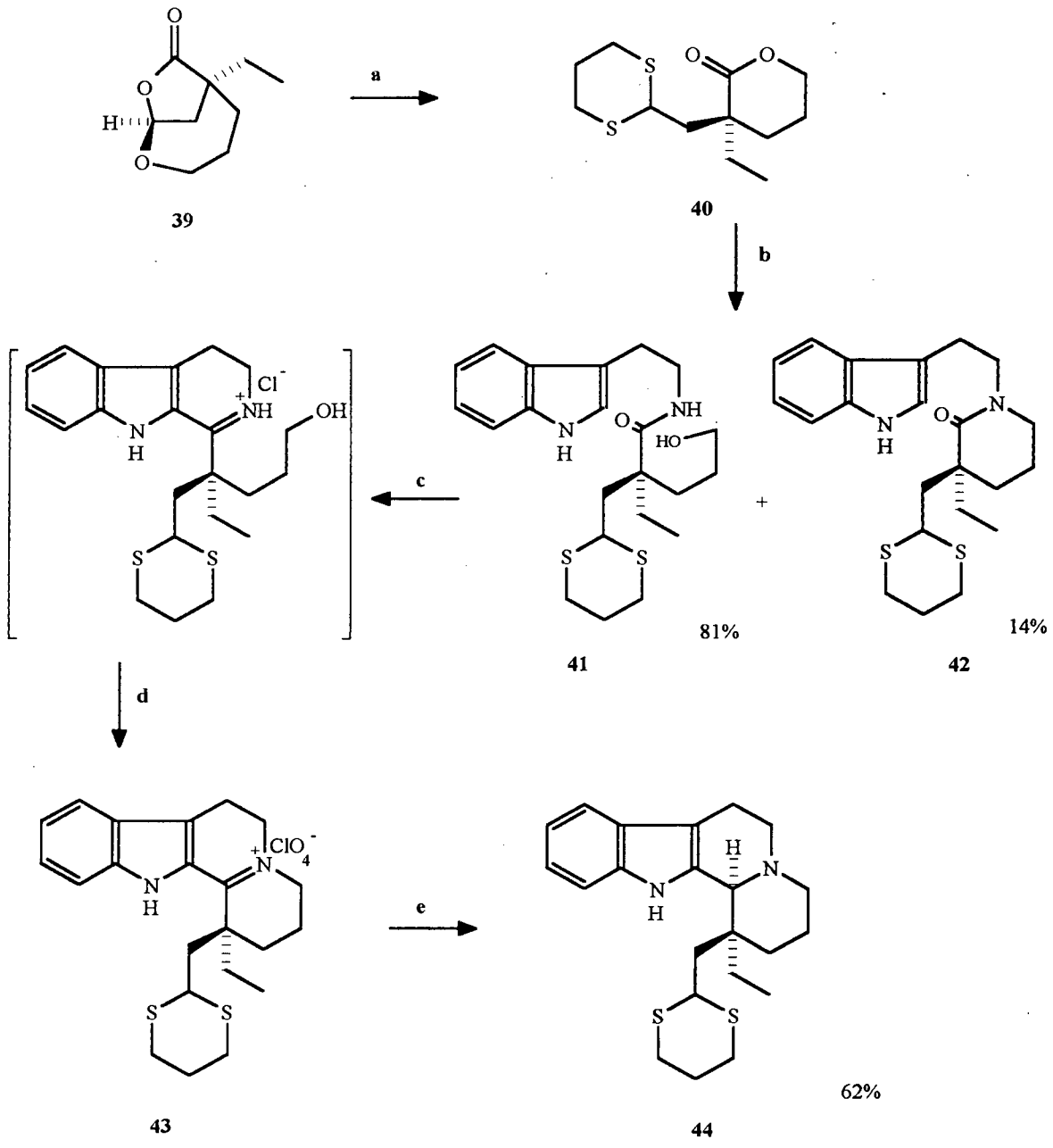
Scheme 10

Although reduction of **35** with sodium borohydride afforded only the unwanted trans-**37**, catalytic hydrogenation with palladium on charcoal afforded the cis-fused product **36** in 71% yield with **37** as a by-product. **36** was then transformed into vincamine. Although optical resolution of the chiral non-tryptamine unit was employed in the synthesis, it utilised simple and inexpensive reagents and proceeded in excellent yield. The catalytic hydrogenation of the Bischler-Napieralski cyclisation product was highly steroselective and a similar protocol was followed in the next synthesis.

Takano and co-workers[17] used L-glutamic acid as their starting material in the synthesis towards eburnamine (Scheme 11).



39 **38**



Reagents: (a) $HS(CH_2)_3SH/p^-TsOH/PhH/reflux$, (b) tryptamine/ 160°C, (c) $POCl_3$/reflux, (d) aqu.$LiClO_4$/ 0°C, (e) $LiAlH(Ot^-Bu)_3$/THF/ 0°C

Scheme 11

The acetal **39** was transformed into the dithianyl lactone **40** which was subsequently heated with tryptamine for 5h at 160°C to yield the secondary amide **41** and the lactam **42** in 81% and 14% respectively.

Refluxing the amide **41** in phosphoryl chloride and subsequent treatment with aqueous lithium perchlorate solution afforded the iminium perchlorate **43** which was reduced with lithium tri-t-butoxyaluminium hydride stereoselectively to afford **44** from which either (+)- or (-)-eburnamine could be obtained in one or two steps, respectively. Although the synthesis of **39** involved over ten synthetic steps, it could be shortened by using Fuji's procedure.[13] There was also no stereochemical problem in the Bischler-Napieralski cyclisation since an iminium salt was obtained which was elegantly reduced stereoselectively.

1.2. Tacamine and its Derivatives

These alkaloids are much more recently discovered natural products having only been isolated in the early 1980's by van Beek *et.al.*[18] from a small liana *Tabernaemontana eglandulosa* Stapf (Apocynaceae), widely distributed in Central Africa. In Zaire, the root is used against snake bites, but the developed countries still await any medicinal applications these alkaloids might have.

1.2.1. Structure and Biosynthesis

The absolute configuration of tacamine is shown in Figure 4 and shares the following similarities with vincamine:

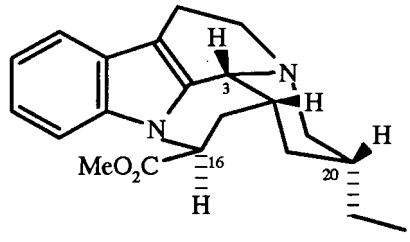
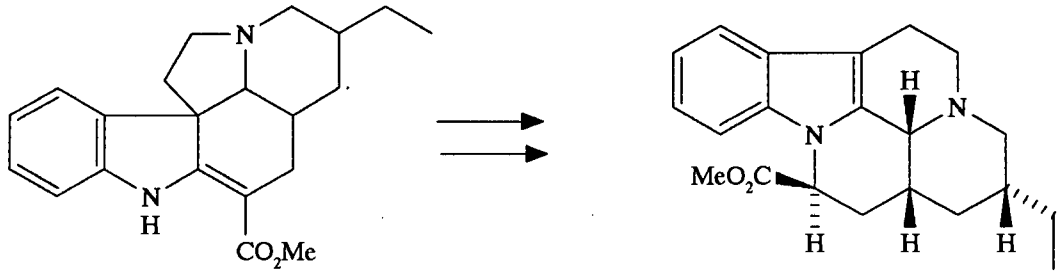


Figure 4

i) The configurations at C(3) and C(16) are the same as those of the enantiomer of (+)-vincamine.

ii) The C/D and D/E ring fusions are also both cis as evident from NMR and IR spectra.

The only difference lies in the position of the ethyl group. This suggests that biosynthetically, tacamine is probably derived from the pandoline type of alkaloids **45** (Scheme 12).

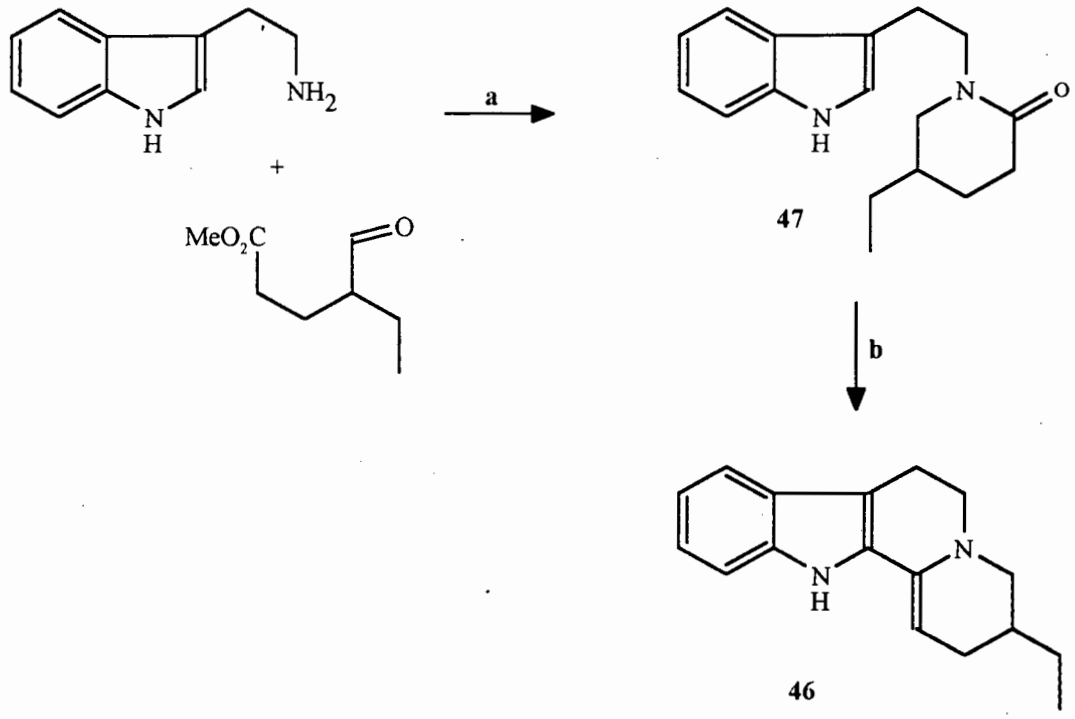


45

Scheme 12

1.2.2. Selected Syntheses

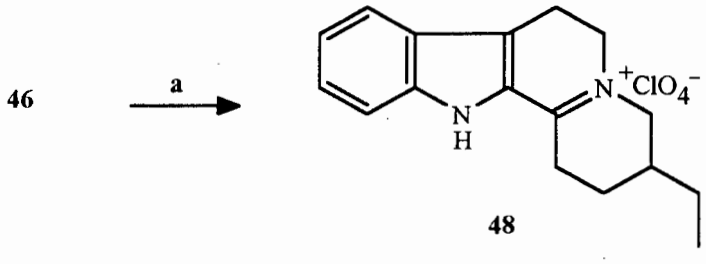
It was not until 1986 that the first total synthesis of (±)-tacamine and (±)-apotacamine was reported by Szántay and co-workers[19]. They used the enamine **46** as starting material for their synthesis. The enamine **46** had previously been prepared by Massiot *et.al.*[20] (Scheme 13)

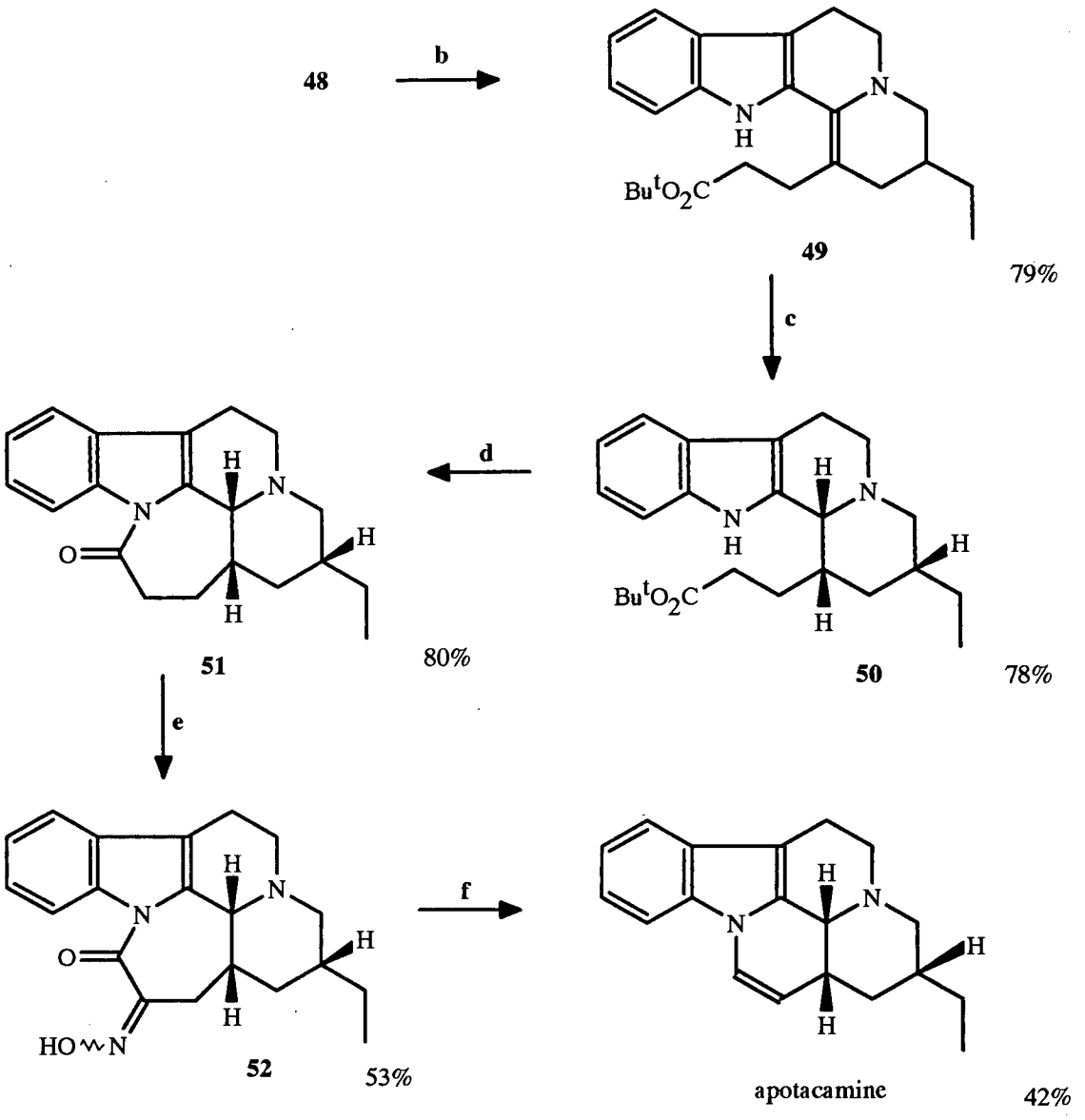


Reagents: (a) i) PhH/reflux, ii) $MeOH/NaBH_4$, (b) $PhMe/POCl_3$/reflux

Scheme 13

Thus, **47** was obtained from a reductive cyclisation between tryptamine and methyl-4-formyl hexanoate. Treatment of **47** with posphorous oxychloride in refluxing toluene (Bischler-Napieralski cyclisation) afforded enamine **46**. Scheme 14 illustrates the transformation of enamine **46** to (±)-apotacamine.



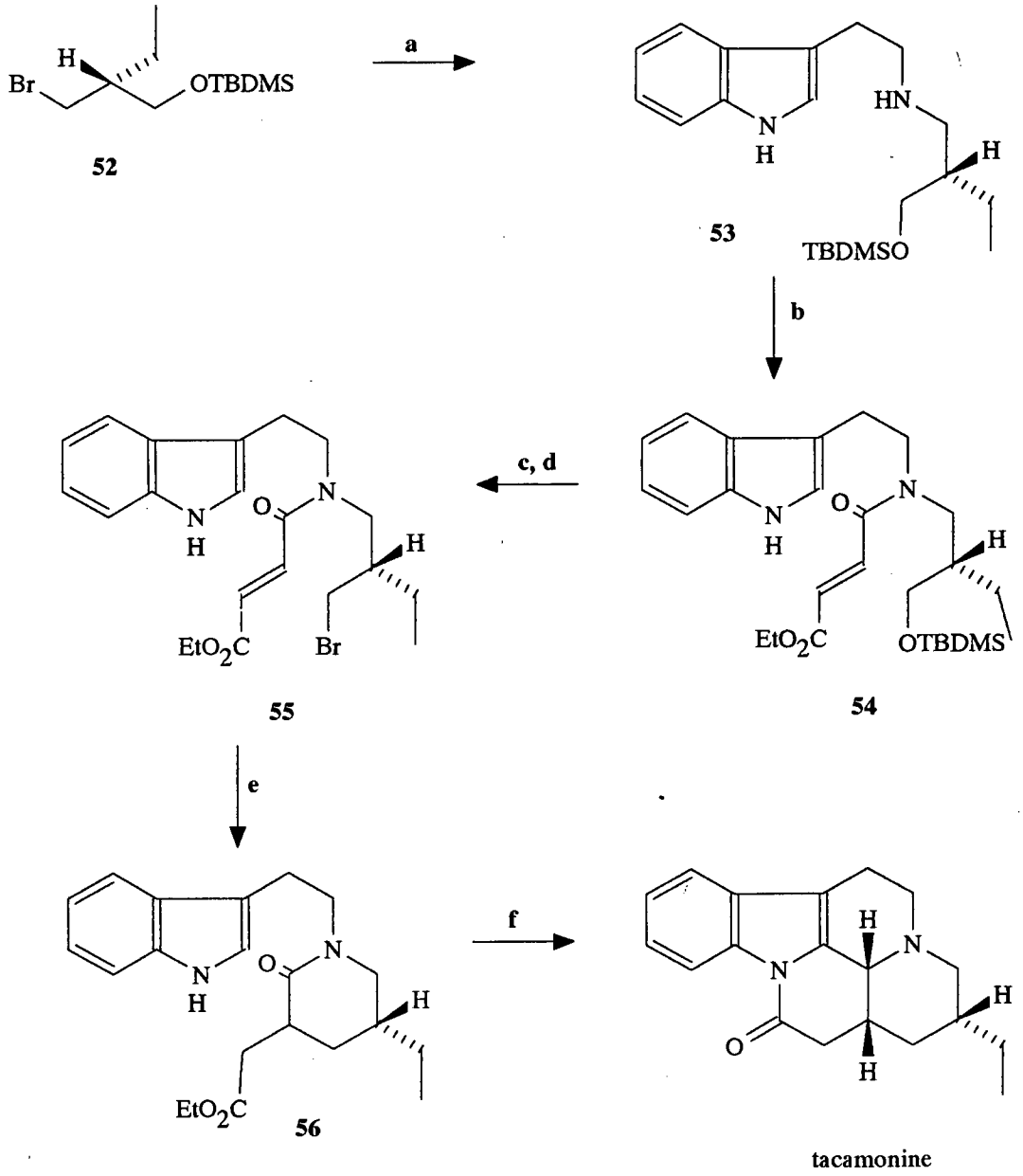


Reagents: (a) aqu. $LiClO_4$, (b) (i) t-butylacrylate/CH_2Cl_2/Et_3N, (ii) aqu. NaOH, (c) $NaBH_4$/MeOH, (d) $POCl_3$/$CHCl_3$/reflux, (e) t-$BuNO_2$/KOBu-t/PhMe, (f) H_2SO_4/MeOH/reflux

Scheme 14

The enamine **46** was converted to its perchlorate salt **48** which was subsequently reacted with t-butyl acrylate in dichloromethane in the presence of triethylamine. Base treatment afforded the ester **49** which upon reduction with sodium borohydride yielded three stereoisomers of which **50** comprised 30% of the yield. Treatment of **50** with $POCl_3$ in boiling chloroform gave lactam **51** which was transformed into the oxime **52**. Upon boiling **52** in acidified acetone, (±)-apotacamine was obtained in 42% yield.

The only example to date in the synthesis of Eburna alkaloids incorporating a radical cyclisation reaction was by Fukumoto and co-workers[21] who recently reported the first asymmetric total synthesis of tacamonine (Scheme 15).



Reagents: (a) tryptamine/DMF/80°C, (b) $EtO_2CCHCHCO_2H$/DMAP/DCC, (c) dil. AcOH/THF, (d) (i) MsCl/Et_3N/PhH (ii) LiBr/THF, (e) $(TMS)_3SiH$/AIBN/PhH/reflux, (f) (i) $POCl_3$/MeCN (ii) $NaBH_3CN$/MeOH (iii) NaOMe/MeOH/0°C

Scheme 15

The stereogenic centre at C(20) was derived from the chiral silyl ether **52** via N-alkylation of tryptamine in the first step to give **53**. N-acylation of **53** with fumaric acid monoethyl ester afforded **54** which was converted to the radical precursor **55** after deprotection of the silyl ether followed by bromination in 53% overall yield from **52**. The radical cyclisation was conducted in dry, refluxing benzene using tris(trimethylsilyl)silane and AIBN for 16h. **56** was isolated as a mixture of diastereomers in 72% yield and converted, via the Bischler-Napieralski cyclisation, to an unspecified mixture of isomers from which tacamonine **57** was isolated in a modest 9% yield. In their synthesis, Fukumoto *et.al.*[21] used chiral starting material in the construction of ring D in much the same way as all previous syntheses, except that the C(16)-C(17) bond is formed last. The radical cyclisation, however, was not stereoselective nor was the Bischler-Napieralski cyclisation to form ring C. It was thus not surprising that tacamonine was isolated in such low yield, suggesting the formation of its isomers in higher yield than the desired product itself.

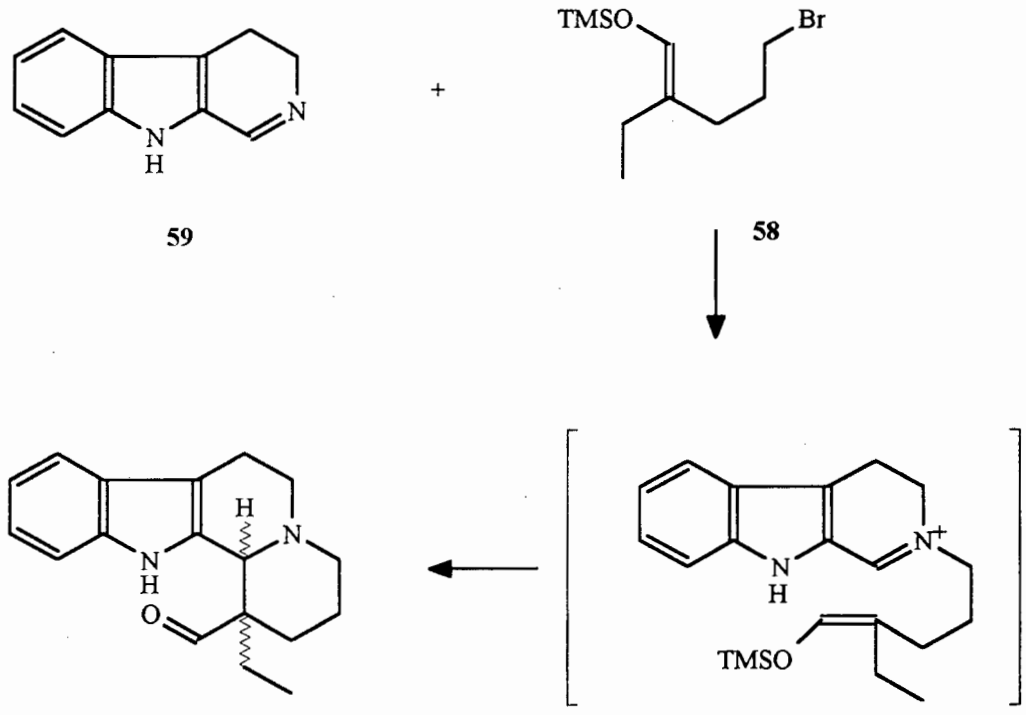
From the syntheses presented, it is quite clear that the asymmetric synthesis of Eburna alkaloids is by no means a trivial undertaking. More so than the Bischler-Napieralski cyclisation, the Pictet-Spengler cyclisation is especially problematic regarding stereoselectivity. In addition, the asymmetric synthesis of the chiral non-tryptamine unit is long and laborious.

CHAPTER 2

Model studies on the construction of the C/D ring system of the Tacaman group via radical cyclisation

2.1 Design of the model study

It is evident from the various synthetic routes presented concerning the construction of the Eburna alkaloid D ring, that the stereochemistry at the C-3 - C-16 ring junction is the most difficult aspect to control and, indeed, the focus of any synthesis. To our knowledge, only one attempt has been made to fuse the C/D rings via closure of the C-3 - C-16 bond. Oppolzer *et.al.*[22] reacted the silyl enol ether **58** with dihydro-β-carboline **59** to obtain, via an intramolecular Mannich reaction, a 1:1 mixture of the racemic trans-**60** and racemic cis isomers **61** (Scheme 16)



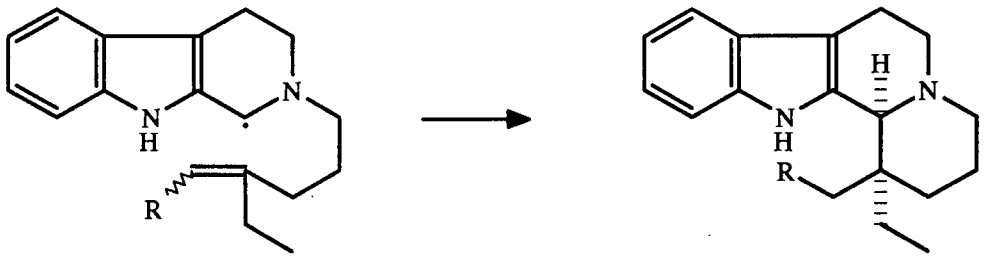
60 'trans'

61 'cis'

Scheme 16

60 and **61**, both as racemates, were then separated as their diastereomeric p-toluenesulfonate salts, with that of the trans-racemate **60** crystallising out selectively from dioxane. The desired **61**-α enantiomer was then separated from its enantiomer by selective crystallisation of the salt formed from (+)-malic acid. The Mannich reaction was thus completely non-stereoselective with each of the four stereoisomers forming in equal amounts.

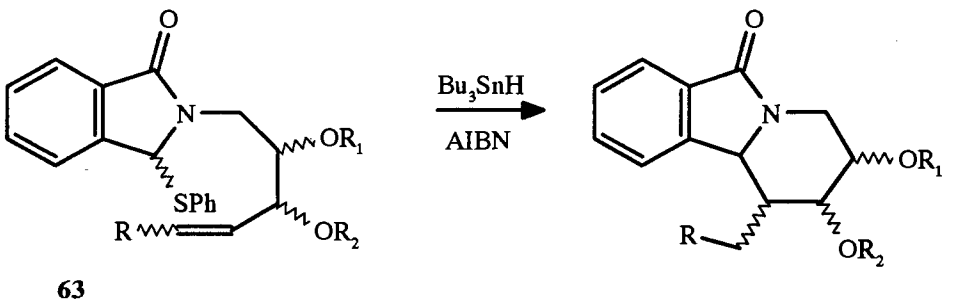
This thesis describes a study, utilising radical cyclisation methodology, to model the formation of the C/D rings of the Eburna skeleton. Of particular interest was the diastereoselectivity between the 2 new chiral centres modeling C-3 and C-16 in the natural product (Scheme 17).



62

Scheme 17

A simplified version of **62** was chosen in which the ethyl group at the quarternary carbon was replaced by hydrogen (Tacaman series) and the carboline unit by the phthalimide group. Scheme 18 shows the chosen radical precursor **63** as well as the expected radical cyclisation. The allylic and homoallylic substituents on the alkyl chain of **63** were chosen to serve as chiral auxiliaries for stereoselective radical coupling. They also allowed the alkyl chain to be synthesised from D-ribose.



63

Scheme 18

The choice of **63** introduced the following three aspects which deserve mentioning:

(a) α-acylamino radicals

(b) carbon-carbon double bonds as radical traps (i.e. α,β-unsaturated esters)

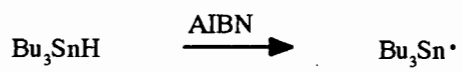
(c) the stereo- and regioselectivity of radical mediated 6-membered ring formation; the role of the allylic and homoallylic control elements.

What follows is a discussion of these aspects using examples from the recent literature, which is preceded by a short introduction of carbon radicals in general.

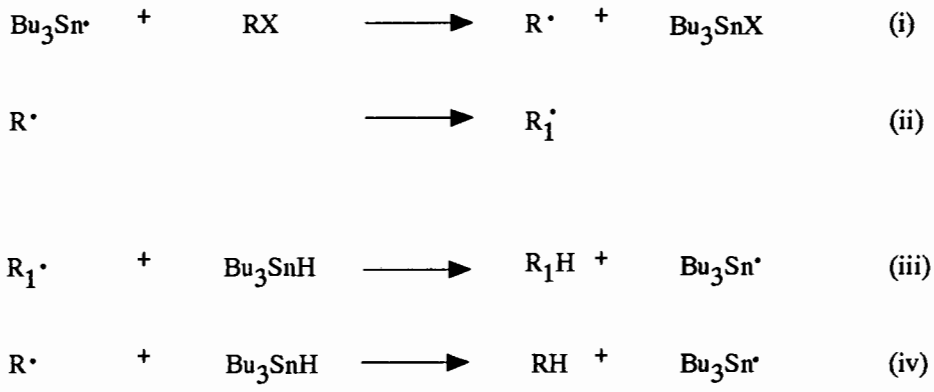
The use of radicals in organic synthesis is a relatively recent development, with the groundwork having been laid in the 1970's. It was not until the mid-1980's that the subject began to be used in natural product synthesis. Recent reviews by Curran[23] and the pioneers Giese[24] and Beckwith[25] have provided much insight into this fast developing field. Amongst the most important characteristics of radical reactions are the following:

Carbon radicals are highly reactive and reaction rates are generally much higher than those of ionic reactions. Radical reactions proceed under mild, neutral conditions and protection of hydroxyl, amino or carbonyl groups is unnecessary. This is of great advantage to the Carbohydrate Chemist. In view of their high reactivity, the lack of any counter-ions essential to ionic reactions and the fact that they involve early, reactant-like transition states, radicals are ideally suited for the synthesis of crowded bonds, e.g. quarternary centres. Radical additions to carbon-carbon double bonds are usually exothermic, irreversible and proceed under kinetic control. This often results in unique products that are unobtainable through conventional, ionic methods. In many cases, radical reactions outperform their ionic counterparts chemo-, regio- and stereo-selectively. Scheme 19 mechanistically illustrates reaction possibilities in the reaction of RX with tri-n-butyltin hydride as a reagent for radical production.

Initiation:



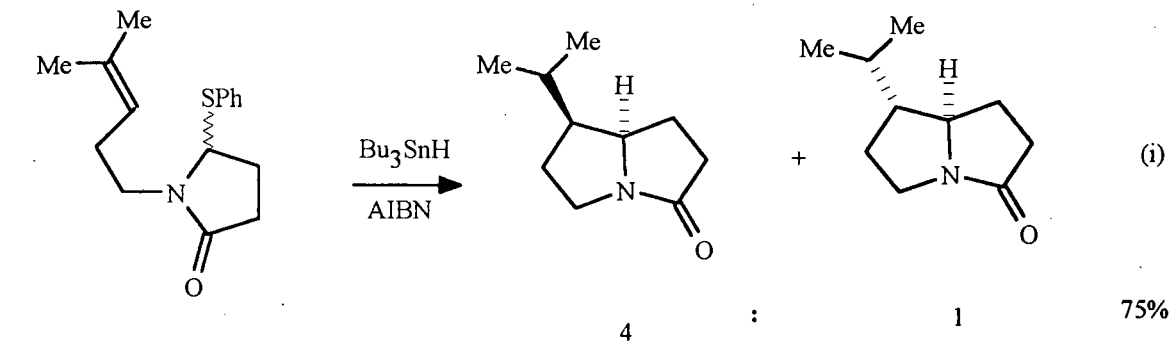
Propagation:



Scheme 19

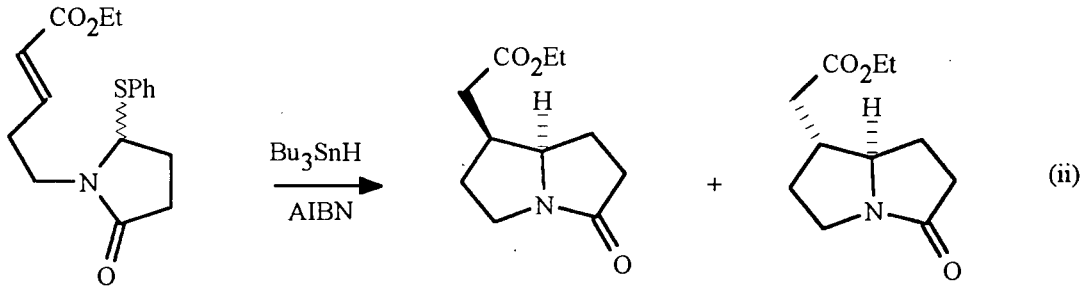
The tin radical abstracts X (I, Br, SePh, OC(S)SMe, Cl, SPh in order of reactivity) to form carbon radical R• in (i). Note the broad range of groups that may be utilised here stemming from the hydroxyl functionality. The newly formed radical R• may either be reduced by hydrogen addition (iv) or react with some other functional group, e.g. a double bond, in an alternative propagation step (ii). The two crucial reactions (ii) and (iv) are in direct competition with each other and the success of the carbon-carbon bond-forming process will only be feasible if the rate of that addition is greater than the quenching reaction of R• by Bu_3SnH (iv). In practice, this is achieved by adding the tin hydride slowly under high dilution conditions. Tin hydride is the most popular reagent because it is both mild and selective with no need to protect carbonyl, amine or hydroxyl groups. Tin containing by-products do, however, constitute a problem since they are difficult to get rid of. Tris(trimethylsilyl)silane, Chatgilialoglu's reagent[26], has recently emerged as an environmentally more friendly alternative to tin hydride.

All three important aspects just mentioned were investigated by Hart *et.al.*[27] in their synthetic application of α-acylamino radicals, an example of which is illustrated in Scheme 20.



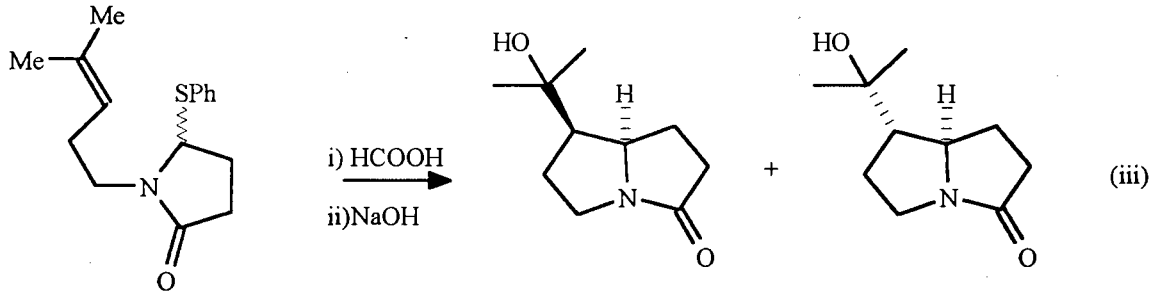
(i)

4 : 1 75%



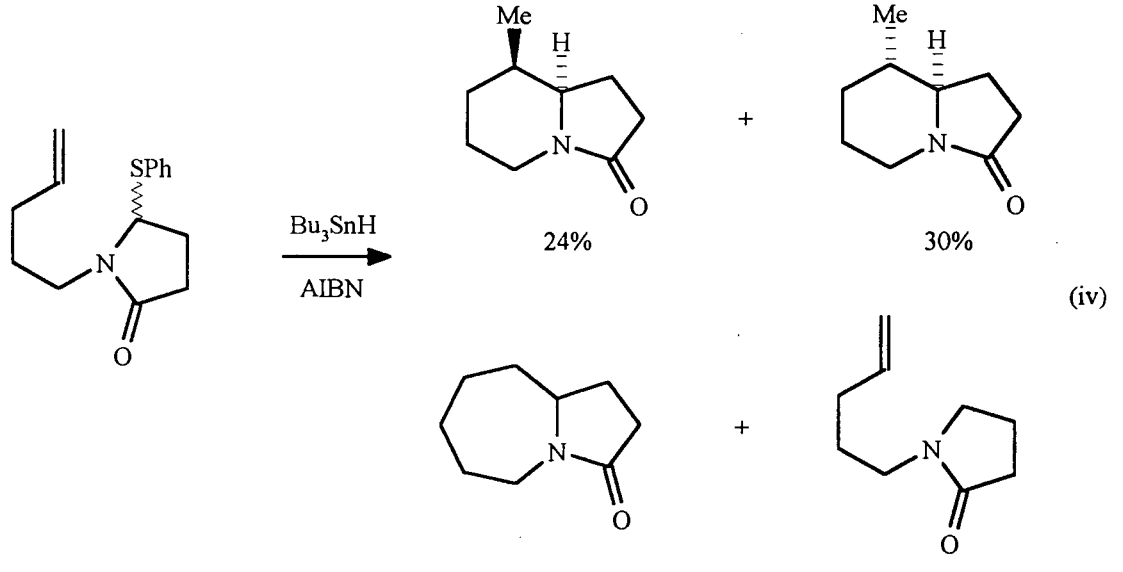
(ii)

9 : 1 81%



(iii)

1.4 : 1 82%

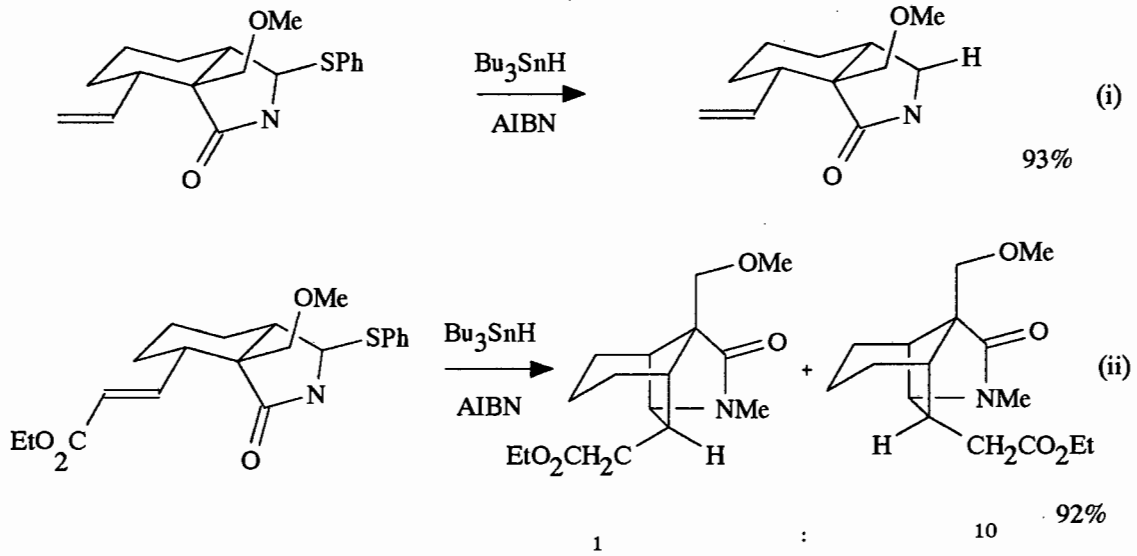


(iv)

Scheme 20

Despite the much reduced reactivity of α-acylamino radicals compared to ordinary carbon radicals, Hart *et.al.* have demonstrated that, under high dilution conditions, excellent stereo- and regio-selectivity can be obtained compared to conventional methodology (eqn. (iii) of Scheme 20). Having achieved excellent selectivity in the 5-membered ring formation with 5-exo cyclisation dominating over the 6-endo mode, less success was achieved in the synthesis of 6-membered rings. Equation (iv) illustrates that 7-endo cyclisation (*i.e.*, formation of the 7-membered ring) does indeed take place. Furthermore, it would appear as if there is no stereocontrol at all. A significant amount of reduced starting material was also observed. These results were not at all unexpected since it is well known that in the case of 6-heptenyl radicals the 6-exo cyclisation is only six times faster than 7-endo cyclisation whereas the 5-exo cyclisation of the 5-hexenyl radical is twenty times faster than 6-endo cyclisation[28]. The low reactivity and stereoselectivity of 6-exo cyclisations had also been observed in earlier literature.

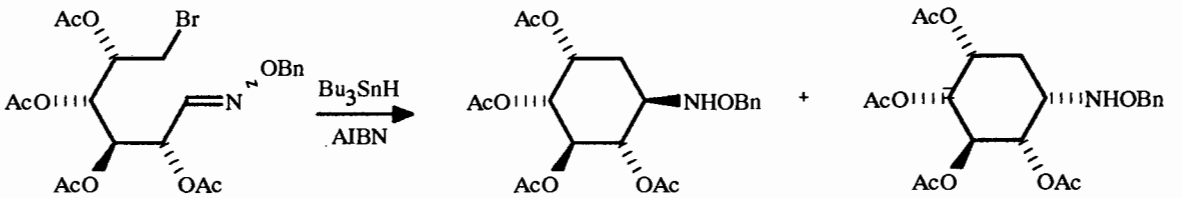
In their study towards the total synthesis of the alkaloid Gelsemine, Hart *et.al.*[29] have demonstrated that α-acylamino radicals can even be used to synthesise relatively strained compounds (Scheme 21).



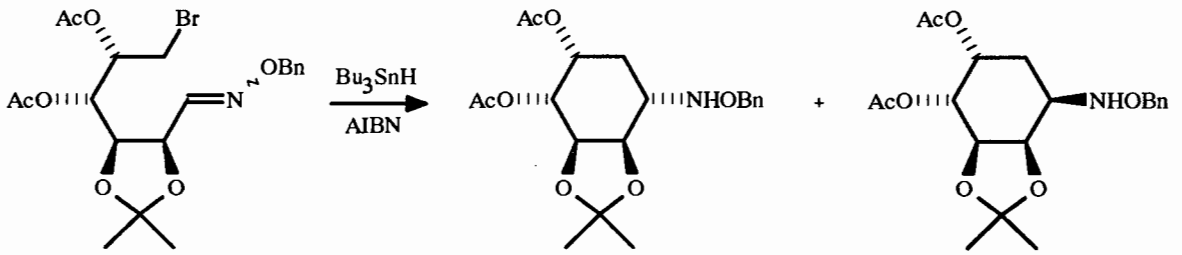
Scheme 21

Even under high dilution of the reagents, the radical precursor (eqn. (i)) would not cyclise but was trapped by the tin hydride instead. However, when an ester substituent was placed on the double bond, an excellent yield of cyclised products was obtained in high stereoselectivity. Unfortunately for Hart and co-workers it was the unwanted isomer that predominated. Newcomb *et.al.*[30] have explained the activating effect of electron-withdrawing groups using frontier molecular orbital theory. Reactions involving carbon radicals and double bonds are dominated by SOMO-LUMO interactions. The electron-withdrawing ester group lowers the LUMO energy of the olefin leading to increased SOMO-LUMO interaction and thereby accelerating the radical reaction. Thus, α,β-unsaturated esters present themselves as ideal radical traps where ordinary olefins have been unsuccessful.

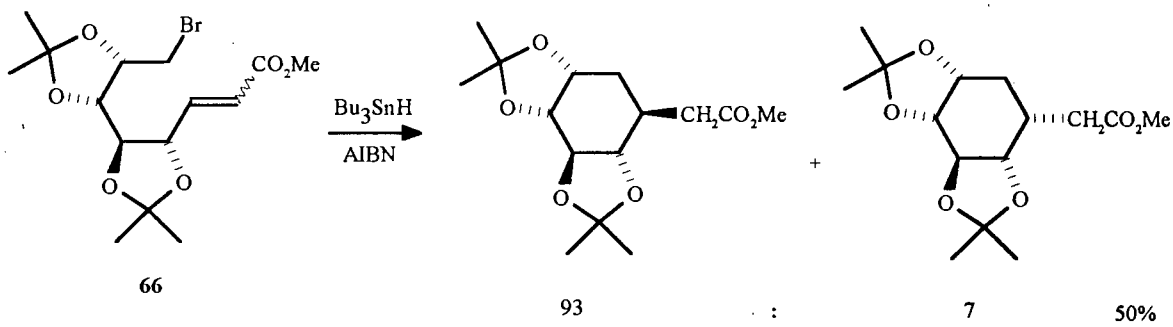
Recently, Marco-Contelles *et.al.*[31] have shown that the regio- and stereo-selective synthesis of 6-membered rings, using radical methodology, is indeed possible. Scheme 22 summarises their findings.



64 83 : 17 50%



65 97 : 3 50%

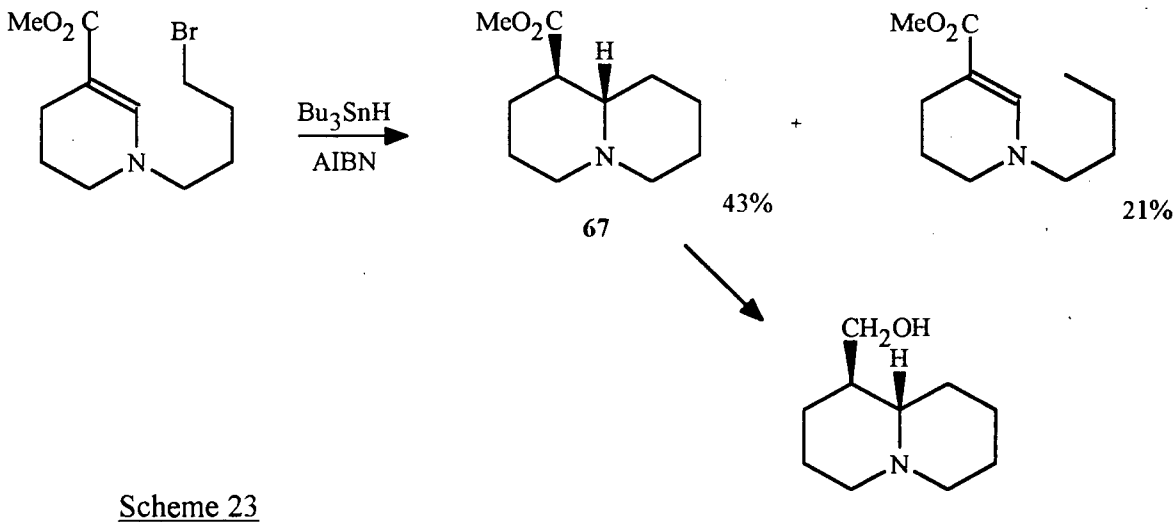


66 93 : 7 50%

Scheme 22

The authors have explained their results using chair-like transition states. Thus the radical derived from **64** cyclises via a chair-like transition state with the substituents occupying quasi-equatorial positions. In the radical derived from **65**, the gauche interactions between the isopropylidene ketal and the oxime group in the transition state direct the stereochemistry of the product. Similar stereoselectivities have been obtained from the cyclisation of **66** with an α,β-unsaturated ester serving as the radical trap. From the results it is evident that the allylic and homoallylic substituents determine the stereochemical outcome of the radical cyclisations with the substituents further removed from the double bonds having little or no effect.

Further evidence for successful stereoselective synthesis of 6-membered rings has been provided by a study conducted by Beckwith and Westwood[32] involving nitrogen heterocycles (Scheme 23).

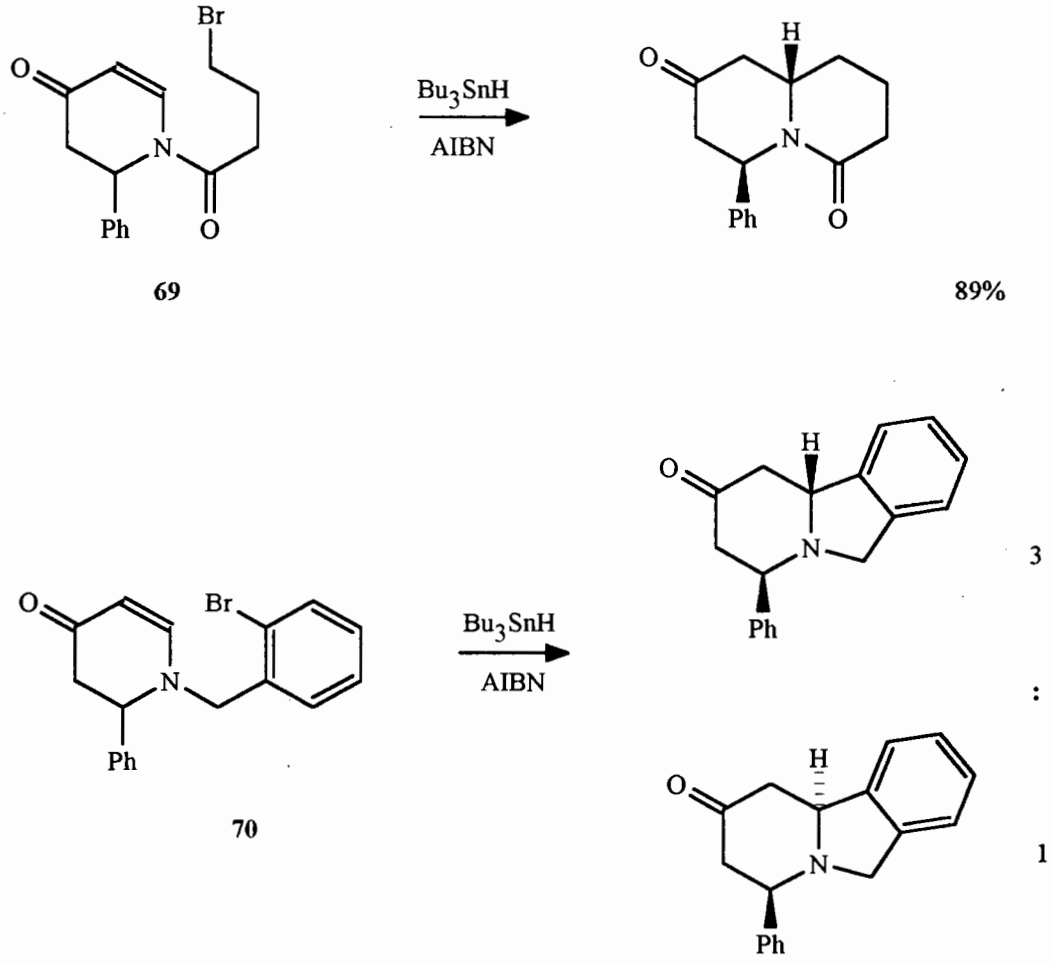


Scheme 23

67 68

Excellent stereocontrol was in fact achieved since **67** was the only isomer obtained from the cyclisation. Despite an α,β-unsaturated ester serving as the radical trap, a significant amount of reduced starting material was still obtained. The quinolizidine **67** was then reduced with LAH to afford the natural product (±)-epilupinine **68**.

In a more recent publication, Beckwith *et.al.*[33] investigated the use of directing groups to control the diastereoselectivity of 5-exo and 6-endo radical reactions. Once again, the study was based on nitrogen heterocycles (Scheme 24).



Scheme 24

The N-acyl-2-phenyl-dihydro-4-pyridinone **69** afforded a single isomer in excellent yield. The N-benzyl-2-phenyl-dihydro-4-pyridinone **70**, on the other hand, showed less stereoselectivity.

Using molecular mechanics, the authors proposed that non-bonded interactions between the pseudo-equatorial substituent at C-2 and the amide carbonyl in **69** directed radical attack anti to the phenyl substituent. Once again, this example demonstrates excellent stereoselectivity in a 6-exo cyclisation yielding a 6-membered ring.

2.2. Design of radical precursors and retrosynthetic analysis

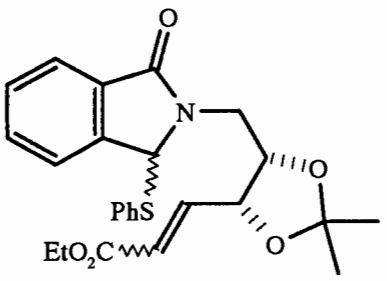
The following points, vital to the success of the model study, thus emerged from reviewing the literature:

1) Hart *et.al.*[27] have demonstrated the success of α-acylamino radicals derived from succinimide derivatives in radical reactions. The analogous phthalimide derivatives should thus, in principle, also give rise to α-acylamino radicals which would also be stabilised by virtue of their benzylic character. Furthermore, phthalimide derivatives carry the additional advantage of being crystalline in most cases. The α-phenylthiolactams, which were easily prepared[27], appeared to be appropriate radical precursors, although the α-phenylselenolactams were alternatives if needed.

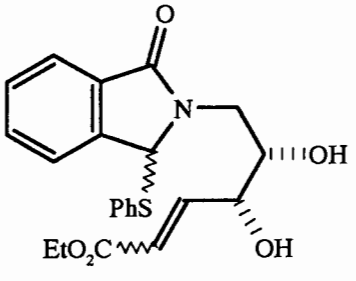
2) α,β-Unsaturated esters emerged as the the ideal radical trap in that they provide activated double bonds, primed for radical addition. The alkoxycarbonyl functionality can subsequently be functionalised according to a synthetic sequence. Marco-Contelles *et.al.*[31] carried out the radical addition on a mixture of E/Z isomers although in this thesis each isomer would be studied independently.

3) Beckwith *et.al.*[32,33], and especially Marco-Contelles *et.al.*[31], have shown that the stereoselective synthesis of 6-membered rings is readily achievable by using chiral auxiliaries or directing groups. The study by Marco-Contelles *et.al.* was especially enlightening in that the radical precursors were derived from chiral pool carbohydrates which are ideal starting materials for control of absolute stereochemistry. Marco-Contelles *et.al.* have also demonstrated that substituents in an allylic or homoallylic position to the double bond are most effective in directing the stereochemical outcome of radical cyclisations as illustrated in Scheme 22.

Following largely the examples set by Hart *et.al.*[27] and Marco-Contelles *et.al.*[31], it was decided to synthesise radical precursors **71** and its deprotected analogue **72** and study their radical cyclisation reactions.



71

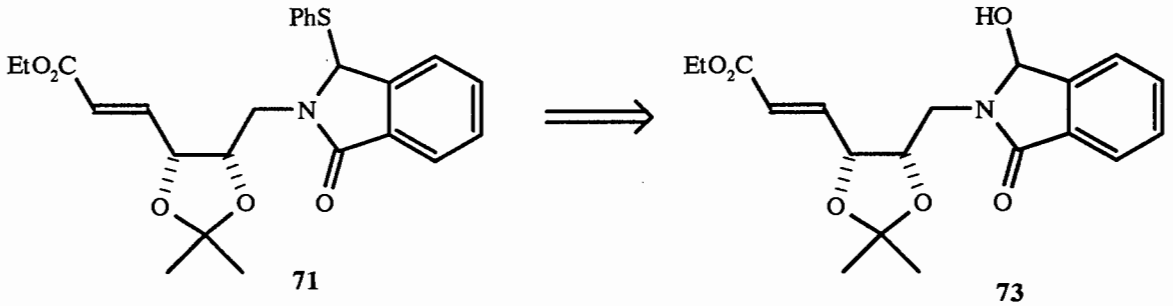


72

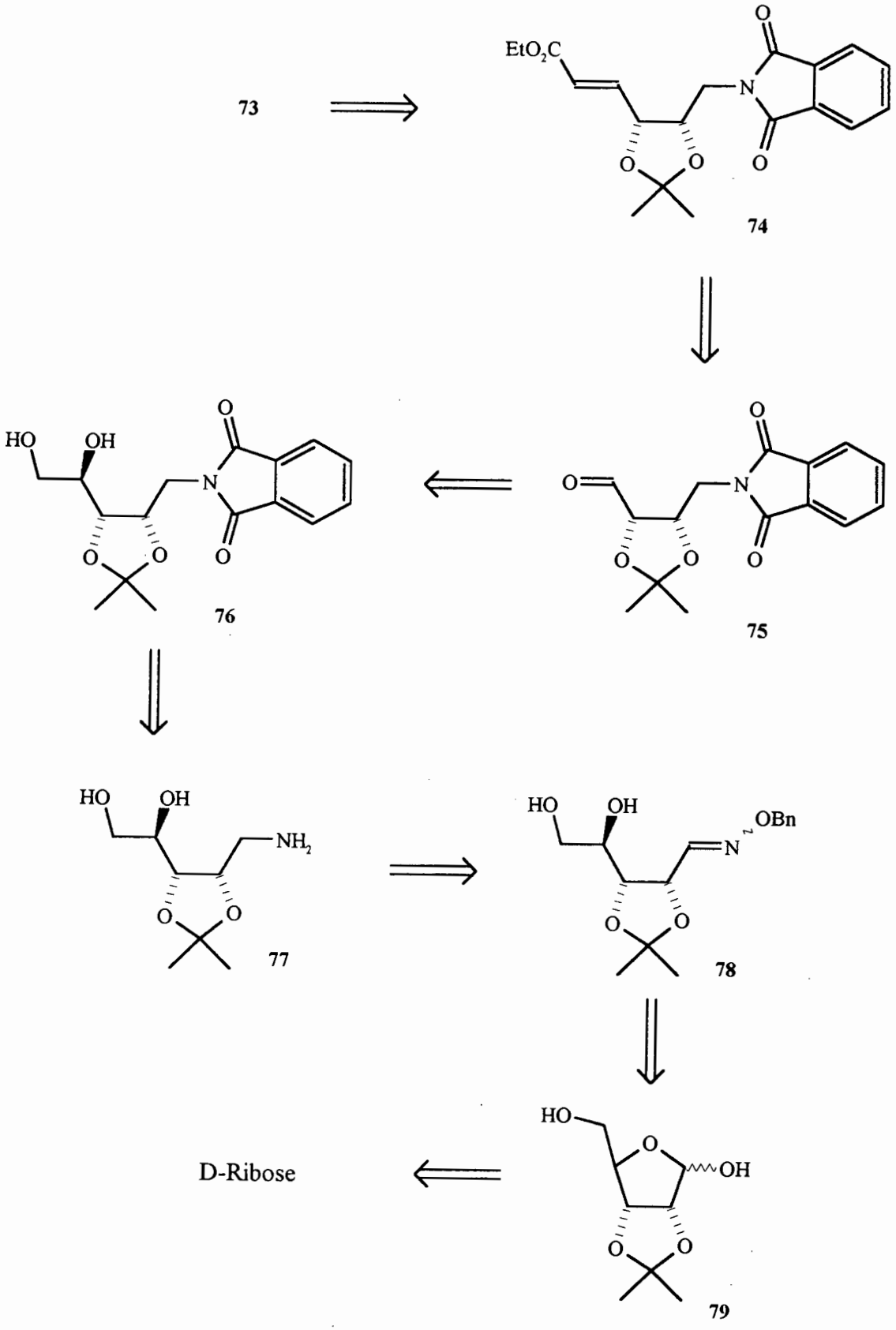
The choice of the stereochemistry at C-2 and C-3 was arbitrary as long as it was absolute and would hence be determined by the carbohydrate chosen. The reason for choosing the isopropylidene ketal as protecting group for **71** was two-fold:

the five-membered 1,3-dioxolane provided a certain amount of rigidity without being too bulky. Secondly, the ketal was stable to all reaction conditions used in the synthetic sequence.

If the E and Z isomers of **71** and **72** could be separated, their radical cyclisations would be studied individually. A retrosynthetic analysis of **71** is presented in Scheme 25 with D-ribose being the carbohydrate starting material.

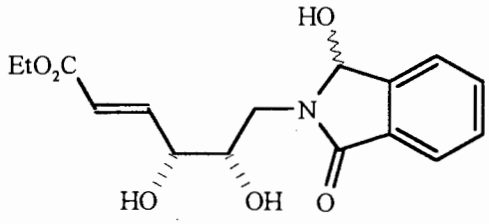


71 **73**

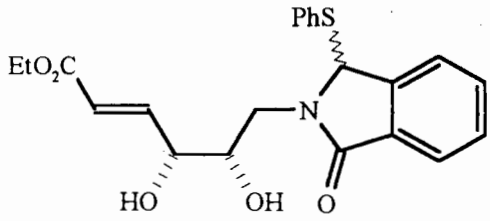

73
EtO2C
O
N
O
O
O
O
74
HO
OH
O
N
O
O
O
O
76
O
N
O
O
O
O
75
HO
OH
NH2
O
O
77
HO
OH
OBn
N
O
O
78
HO
O
OH
O
O
79
D-Ribose

Scheme 25

The deprotected derivatives **80** and **72** were obtained from the deprotection of **73.**



80



72

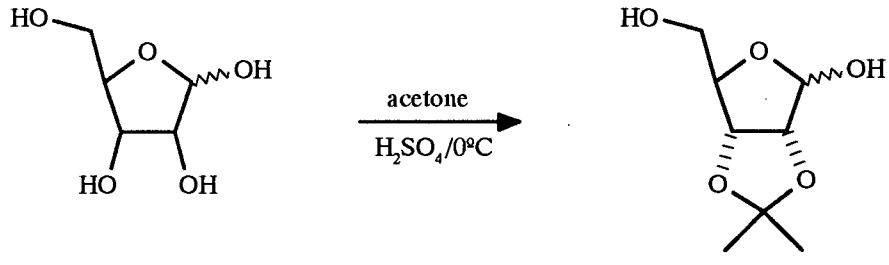
CHAPTER 3

RESULTS AND DISCUSSION

3.1. Synthesis of the Radical Precursor

3.1.1. Acetal synthesis

The acid-catalysed condensation of D-ribose with acetone to give 2,3-O-isopropylidene-D-ribofuranose **79** is well documented in the literature[34], with the isopropylidene group being widely used in carbohydrate chemistry for protecting 1,2-diols. The reaction is conducted in acetone to which an acid has been added that catalyses the reaction. Levene and Stiller[34a], who were the first to report the reaction in 1933, found it necessary to add two equivalents of anhydrous $CuSO_4$ as dehydrating agent in addition to a small amount of sulfuric acid. The authors conducted the reaction at 37°C for 20h and isolated the product in relatively low yield (ca. 50%). In this thesis, a slight excess of concentrated sulfuric acid was added with the reaction temperature being kept around 0°C (Scheme 26).

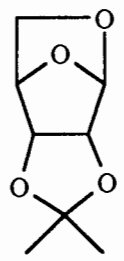


79

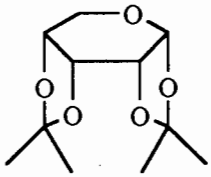
Scheme 26

The reaction was easily monitored since the product is soluble in acetone unlike the starting material . T.l.c. confirmed that the reaction was over in less than two hours. The reaction mixture was quenched with two equivalents of KOH in MeOH at 0°C.

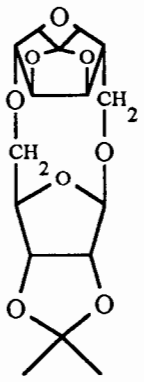
Two types of extraction were tried out: an aqueous extraction into ethyl acetate and a non-aqueous extraction where the insoluble potassium sulfate was filtered off and the acetone and methanol were removed *in vacuo*. In the aqueous extraction, it was observed that up to 40% of the product was lost by dissolution into water, hence the non-aqueous method was preferred. The addition of ca. three equivalents of potassium carbonate ensured that the precipitate was not too fine so as to clog the filter medium (Celite^{R}) as was observed when KOH alone was added to quench the reaction. The yield of crude syrupy product was 98%. Chromatography of a 500mg sample on silica gel (20g) using ethyl acetate in hexane as eluent afforded 410mg of pure product (80% yield). When C.A.N. was used as spray reagent, two other minor products were detected on the t.l.c. plate: one slightly more polar spot and a very non-polar spot on either side of the major spot. With anisaldehyde/ethanol/H_2SO_4 as spray reagent, up to six distinct spots were observed. In their work, Hughes and Speakmann[34b] isolated and characterised four distinct compounds in addition to **79**. In the non-polar fraction the authors identified 1,5-anhydro-2,3-O-isopropylidene-D-ribose **81** (9%); 1,2:3,4-di-O-isopropylidene-D-ribose **82** (3%) and di-(2,3-O-isopropylidene-β-D-ribose)-1,5':1',5-dianhydride **83** (5%).



81

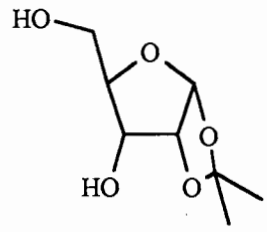


82



83

The polar fraction consisted of many components, from which 1,2-O-isopropylidene-D-ribose **84** was isolated (6%).



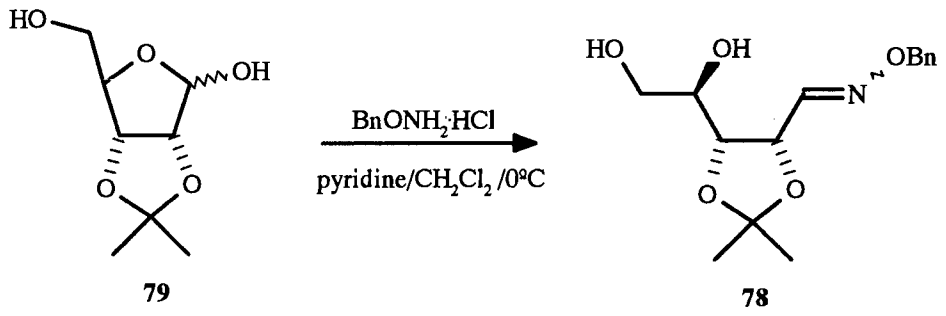
84

The authors also reported that the acetone used for the condensation reaction should be free of any methanol to avoid methyl glycoside formation. Although methanol was used in the work-up in this thesis, the possibility of methyl glycoside formation was excluded since no methyl singlet was observed at δ 3.4ppm in the NMR spectrum[34d] of **79** for a methoxy-signal. Furthermore, the NMR spectrum was identical to that from literature reports[35] with the two anomers being observed in the ^{13}C NMR.

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

3.1.2. Oxime formation

Oxime derivatives of carbohydrates from hydroxylamine were first reported in 1887[36] for characterising sugars. More recently, Bartlett *et.al.*[37] and Marco-Contelles and co-workers[38] have investigated the radical cyclisation reactions of oxime derivatives of carbohydrates in the synthesis of aminocyclitols. In this study, the O-benzyl oxime ether **78** was chosen to facilitate organic solubility of the diol derivative since the O-unprotected oxime synthesised was found to be water-soluble and non-crystalline. The oximation reaction of **79** (Scheme 27) was carried out in dichloromethane at 0°C.



79 **78**

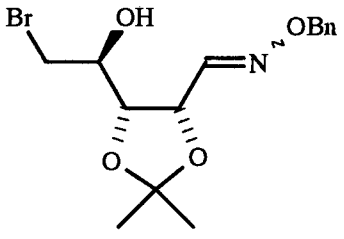
Scheme 27

Excess pyridine was added to liberate the O-benzylhydroxylamine from its hydrochloride. The reaction was stirred for 15h, after which time the reaction was worked up with dilute HCl at 0°C and the product extracted into ethyl acetate. After chromatography on silica gel, the oxime diol **78** was isolated in 85% yield.

In subsequent runs, a single recrystallisation of the crude reaction product from ethyl acetate/hexane afforded chromatographically pure **78** in 50% yield which was used in the next step. A second crop, amounting to ca. 20%, was isolated from a second recrystallisation of the mother liquors.

Buchanan *et.al.*[34e] and Finch and Merchant[39] observed weak bands due to the C=N stretch around 1660 cm^{-1} in the IR spectra of their O-unprotected carbohydrate oximes. This, unfortunately, is also the region where C=C stretching occurs, thus, making it impossible to differentiate the C=N band from the C=C bands of the aromatic ring in the IR of **78**.

^{1}H NMR clearly showed the presence of two geometrical isomers inseparable by t.l.c. NMR assignments were made with the help of 2D NMR and by comparison with NMR spectral data of **85**, reported by Marco-Contelles *et.al.*[38]



85

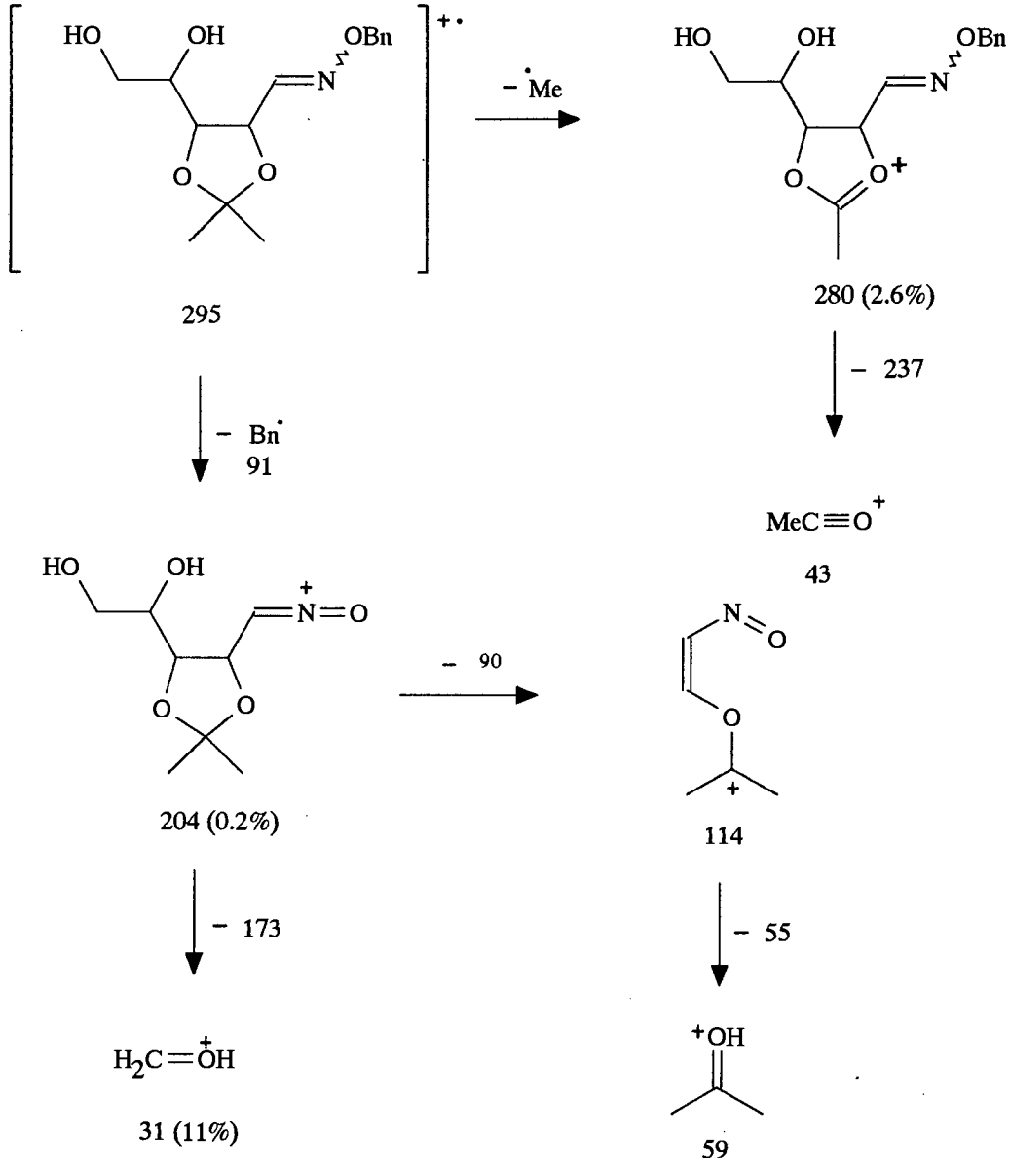
Table 1 compares the chemical shifts and coupling constants of the protons of **78** and **85**

Proton		**78**		**85**	
		δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
H-1	E	7.49	7.2	7.5	7.5
	Z	6.90	6.4	6.85	6.0
H-2	E	4.74	6.2; 7.2	4.8	6.0
	Z	5.27	6.4	5.3	6.0
H-3	E	4.12	6.2; 8.4	4.1	6.0; 7.5
	Z	4.23	6.4	4.25	6.0
BnCH	E	5.07		5.15	
	Z	5.11		5.15	
Ketal		1.49		1.45	
Me's		1.32		1.35	

Table 1

The presence of geometrical isomers also revealed itself in the ^{13}C NMR spectrum with the doubling-up of every peak. The methyl peaks of the ketal were upfield at around 25-28 ppm and the quaternary carbon at 110 ppm. The carbon of the C=N group resonates at ca. 150 ppm and the aromatic carbons resonated between 128 and 138 ppm. C-4 and C-5 could be distinguished from C-2 and C-3 by their different chemical shifts, since carbons bearing free hydroxyl groups are upfield from those bearing an alkylated oxygen[40]. Thus, C-4 and C-5 were upfield from C-2 and C-3 which bear the ketal moiety.

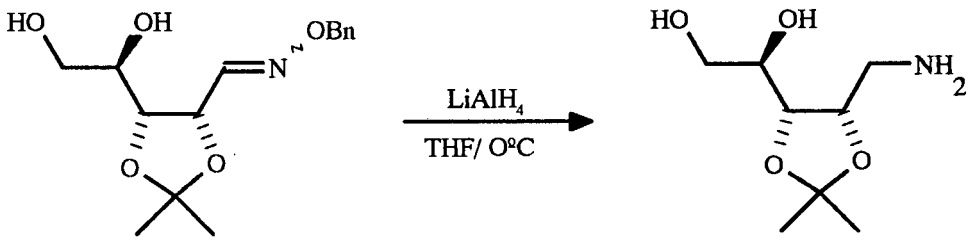
The dominant peaks in the mass spectrum were: m/z = 91 (100%), 59 (42%), 43 (39%), 114 (22%) and 173 (13%). The molecular ion was of very low abundance (0.8%). Scheme 28 shows a proposed fragmentation pattern. Both m/z = 43 and m/z = 59 are species characteristic of the isopropylidene ketal and have been reported in the literature[41].



Scheme 28

3.1.3. Oxime reduction/amine formation

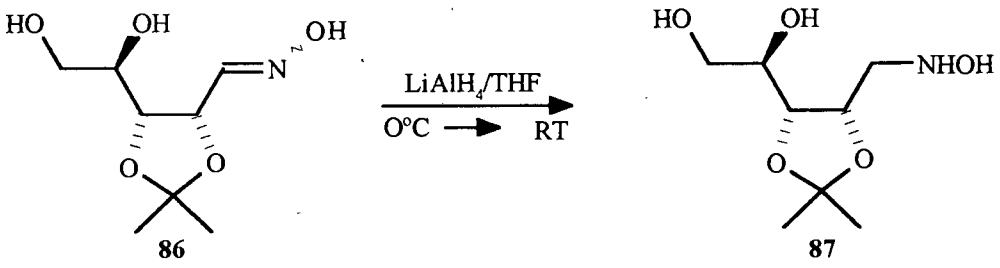
Quite a few reagents will reduce an oxime to an amine, the more common ones being: $LiAlH_4$, zinc in acetic acid, sodium in ethanol, boranes and other aluminium hydrides. Zinc in acetic acid was ruled out due to the acid sensitivity of the ketal. The reagent chosen to ensure complete reduction was $LiAlH_4$ in THF initially at 0°C, then warmed to room temperature overnight (Scheme 29).



78 **77**

Scheme 29

Work-up and subsequent isolation proved problematic due to the polar nature of the amine-diol. An aqueous work-up was thus ruled out. A few non-aqueous work-ups were tried and the most successful involved careful quenching of the excess $LiAlH_4$ with water at 0°C followed by addition of triethylamine and stirring until a white precipitate was obtained. Addition of the triethylamine was crucial in order to effect complete precipitation of the aluminium salts which otherwise passed through the filter together with the product. The suspension was filtered through Celite^R and washed with a MeOH:EtOAc:Et_3N (1:7:2) mixture to ensure that all the product was collected free of aluminium salts. Reduction of the unprotected oxime **86** was incomplete under the previously mentioned conditions and only yielded the hydroxylamine **87** (Scheme 30).

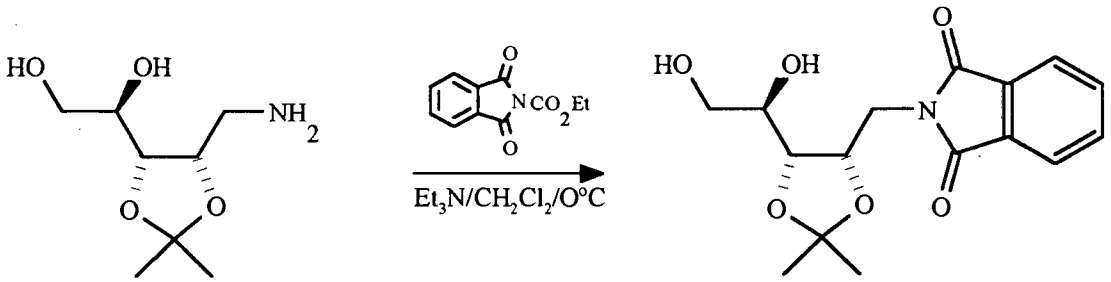


Scheme 30

To effect complete reduction, the reaction mixture had to be refluxed which resulted in the formation of by-products. This, together with the fact that **86** was very polar, supported our choice of the O-benzyl-protected oxime **78**. In addition to its high polarity, the amine **77** was rather unstable to chromatography and was hence characterised as the imide **76**, the next authentic intermediate in the synthetic sequence.

3.1.4. Imide formation

Phthalimides (sometimes abbreviated Phth or Pht) are synonymous with the Gabriel synthesis in which the sodium or potassium salt of phthalimide is alkylated by a primary alkyl halide. The resulting N-alkyl phthalimide is then hydrolysed to yield a primary amine. The use of phthalimides as a protecting group for amines increased with the discovery that hydrazinolysis offers a milder and more efficient method of deprotection.[42] The following reagents were screened for the conversion of the amine **77** to the imide **76**: refluxing the amine with phthalic anhydride in chloroform[43]; o-$(MeO_2C)C_6H_4COCl$ in the presence of base in THF[44]; phthaloylchloride in pyridine and N-carboethoxyphthalimide ($PhtCO_2Et$) in the presence of base[45]. The best results were obtained with the latter in the presence of triethylamine in dichloromethane at 0°C (Scheme 31).

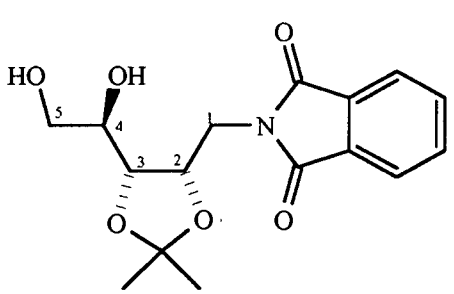


Scheme 31

The reaction conditions were especially mild and the reagent was conveniently prepared by refluxing a mixture of phthalimide, ethyl chloroformate and triethylamine in dichloromethane. The crude imide was chromatographed without prior work-up to afford a clean, crystalline material in up to 65% yield for the two steps which could be crystallised to analytical purity.

The IR of the imide diol **76** showed two bands corresponding to C=O stretching of the imide group: a weak one at 1773 cm^{-1}, and a very strong one at 1716 cm^{-1}. In addition, two broad bands at 3600 cm^{-1} and 3680 cm^{-1} indicated the presence of OH groups.

Although the carbohydrate chain is essentially the same as that of the oxime **78**, the signals in the ^1H NMR spectrum of the imide **76** were poorly resolved and very different to those of the oxime. The assignments of the protons was based entirely on coupling constants.

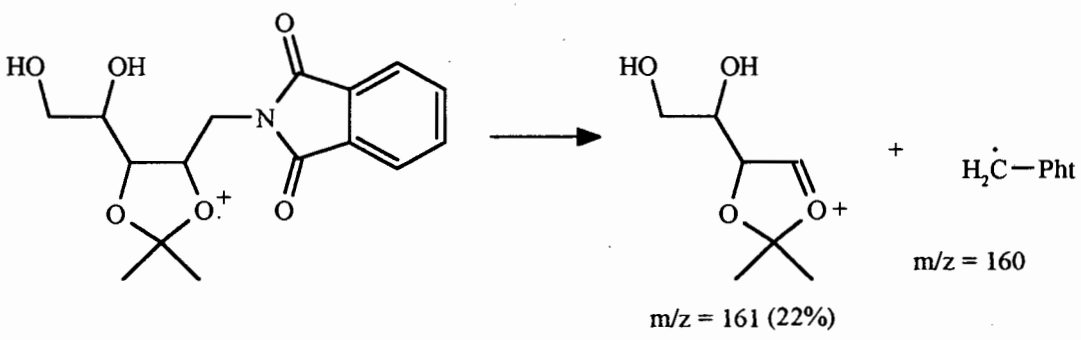


76

The geminal protons H-1 and H-1' constitute the AB part of an ABX system together with H-2: $J_{1,1'}$ = 13.9 Hz, $J_{1,2}$ = 9.8 Hz. H-1' was not resolved and formed part of the multiplet centered at 3.91 ppm. H-2 was significantly downfield from the rest (4.62 ppm) and resonated as a doublet of doublet of doublets: $J_{1,2}$ = 9.8 Hz, $J_{1',2}$ = 3.6 Hz and $J_{2,3}$ = 5.8 Hz. Proton 3, less downfield than 2, resonated as a doublet centered at 4.14 ppm; $J_{3,2}$ = 5.8 Hz and $J_{3,4}$ = 8.9 Hz. One of the methylene protons on C-5 was just upfield of the multiplet resonating as a doublet of doublets at 3.73 ppm ; J_{gem} = 11.9 Hz and J_{vic} = 6.3Hz. The other C-5 proton, together with H-1 and 4, formed the multiplet at 3.91 ppm. Two very broad singlets were observed for the OH protons and the ketal methyl groups and aromatic protons resonated at the expected chemical shifts.

Apart from functional group changes at C-1, the ^{13}C NMR spectrum was very similar to that of the oxime. The chemical shifts of the three ketal carbons were almost identical to those of the oxime, as were C-4 and C-5 which were assigned by analogy to those of the oxime. C-2 and C-3 could, however, not be distinguished. The carbonyl carbons of the imide group appeared far downfield at 168 ppm, and those of the aromatic ring at 134, 132 and 123 ppm. The signal for the quarternary carbons was less than one-third the size of the other two aromatic peaks. C-1 resonated close to the methyl carbons at 39 ppm.

The most diagnostic species in the mass spectrum were: m/z = 59 (100%), 43 (40%) and 306 (M^+-Me) with an abundance of 7%, all characteristic of the isopropylidene ketal. Fragments with m/z = 160 and 161 could be assigned to radical cleavage about the C-1 and C-2 bond as shown in Scheme 32.



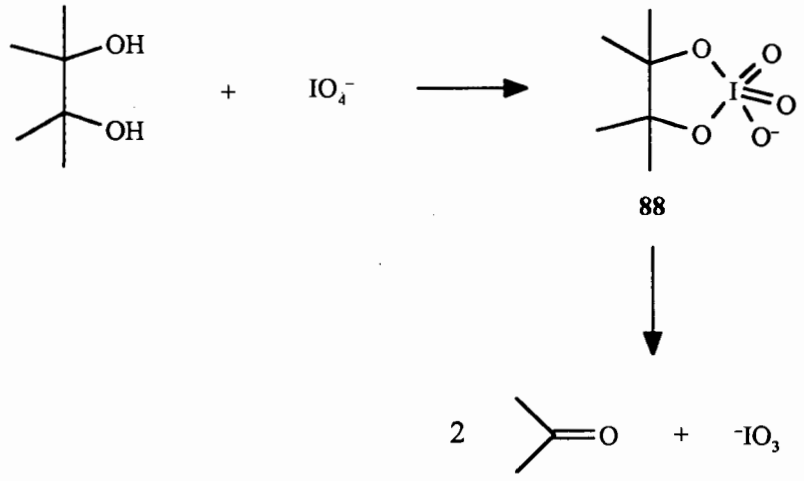
Scheme 32

Protonated formaldehyde (m/z = 31), with an abundance of 10%, was indicative of the 1,2 diol moiety. The parent molecular ion was not observed suggesting low stability and immediate fragmentation.

3.1.5. Diol cleavage/aldehyde synthesis

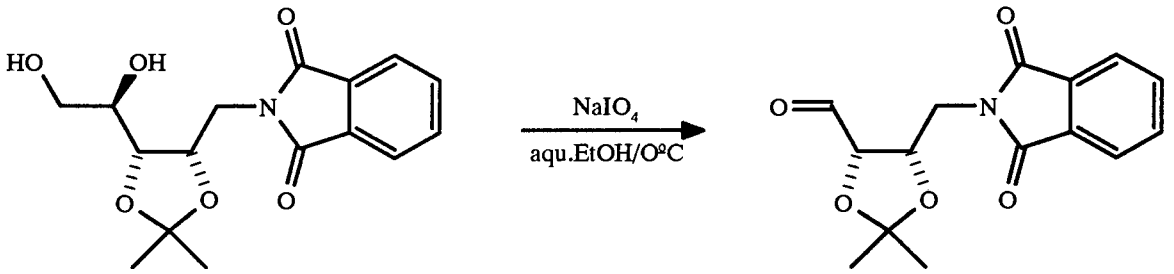
There are many reagents available that oxidatively cleave diols to afford aldehydes, e.g. activated MnO_2, thallium(III) salts, PCC and iodine triacetate, but the two most common ones are lead tetraacetate and the periodate ion.

For the latter case, experimental evidence supports the intermediacy of the cyclic intermediate **88** (Scheme 33).



Scheme 33

The reaction with sodium periodate (Scheme 34) proceeded slightly better than with lead tetraacetate.



76 75

Scheme 34

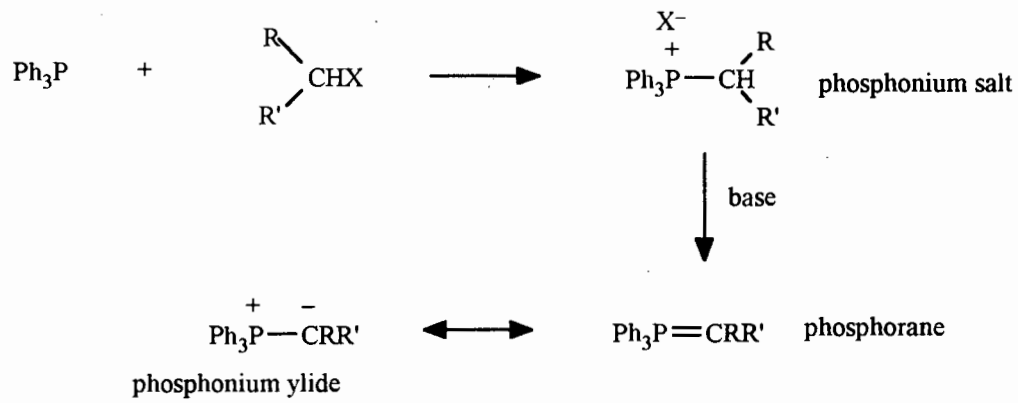
The reaction proceeded smoothly and in high yield (>95%) giving a syrup that slowly crystallised. The ^{1}H NMR (60 MHz) showed a signal integrating for one proton at ca. 10 ppm corresponding to the aldehyde hydrogen. Attempted recrystallisation of the solid proved unsuccessful as the aldehyde appeared to decompose on exposure to heat and air. Indeed, even further characterisation via further derivatisation, failed. For instance, chemoselective reduction of the aldehyde carbonyl group with $BH_3{\cdot}SMe_2$ in CH_2Cl_2 at 0°C gave the alcohol which also failed to be stable enough for characterisation. Even the 3,5-dinitrobenzoyl derivative of the alcohol could not be successfully characterised. Finally, when the phenylhydrazone derivative of **75** failed to crystallise, it was decided to characterise the aldehyde as the alkenoate ester, i.e. the next intermediate.

3.1.6. Alkenoate ester synthesis

3.1.6.1. Synthesis

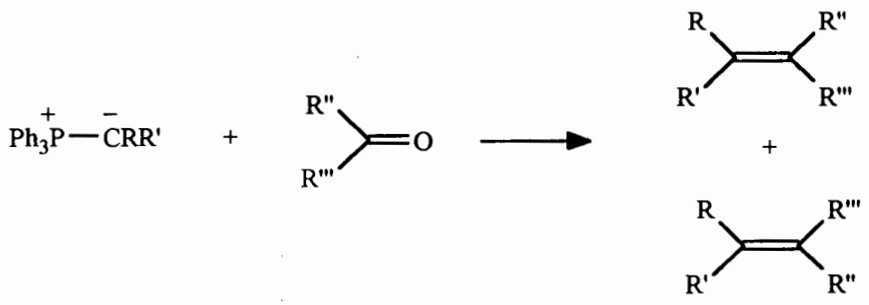
The Wittig reaction of carbohydrate derivatives is well documented in the literature[46]. α,β-Unsaturated esters are especially useful in radical methodology as they serve as excellent radical traps as exemplified by the pioneering work of Wilcox *et.al.*[46b,c] who used carbohydrate derivatives in radical cyclisation reactions to give substituted cyclopentanes. A number of variations of the reaction used include:

a) The classical Wittig reaction (Scheme 35).



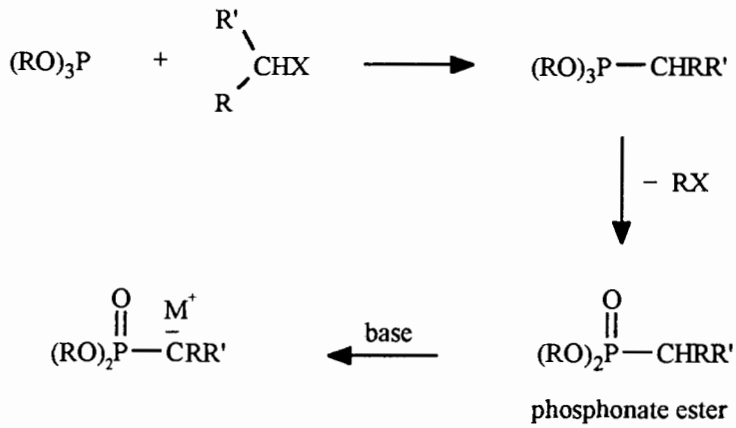
Scheme 35

The ylide then reacts with a carbonyl compound to form the olefin (Scheme 36).



Scheme 36

b) The Wadsworth-Emmons variation uses a phosphonate ester instead of a phosphonium salt and proceeds via a carbanion Scheme 37).



Scheme 37

The carbanion then reacts with a carbonyl compound as in Scheme 36. The carbanions prepared from phosphonates are generally more reactive than phosphorane ylides with equivalent organic groups, and the by-products of the former (a phosphate ester) are water-soluble whereas the by-product of the Wittig reaction (triphenylphosphine oxide) is not. The stereochemical outcome of the reaction, in general, is influenced by the following factors:

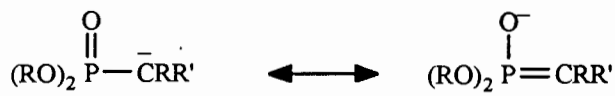
a) The stability of the ylide.

b) The substituents on phosphorus.

c) Solvent.

d) Temperature.

The carbanion derived from phosphonates is stabilised by electronic delocalisation into the P=O bond.



Generally, the Z-isomer predominates if the reaction conditions are under kinetic control while the E-isomer is favoured under thermodynamic control.

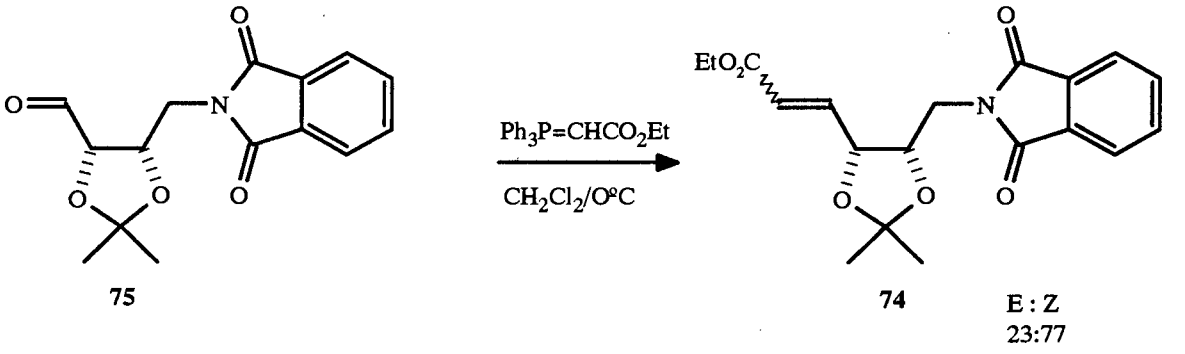
The latter may involve elevated temperatures in apolar, protic solvents; electron-rich substituents on phosphorus and if the betaine intermediates are sufficiently stabilised so that the intermediate favouring the E-isomer can accumulate. This, however, is just a general rule and in some cases it is impossible to manipulate the reaction conditions to favour only one isomer. In fact, in neither of the literature references[46] was the Wadsworth-Emmons variation stereoselective. Valverde *et.al.*[47] have studied the reaction of methoxy-carbonylmethylene triphenylphosphorane **89** with various carbohydrate derivatives in different solvents and at different temperatures.

$Ph_3P{=}CHCO_2Me$

89

Using methanol as solvent, high Z-selectivity was obtained which increased as the temperature was decreased. With dichloromethane as solvent, the E-isomer was favoured (1:2).

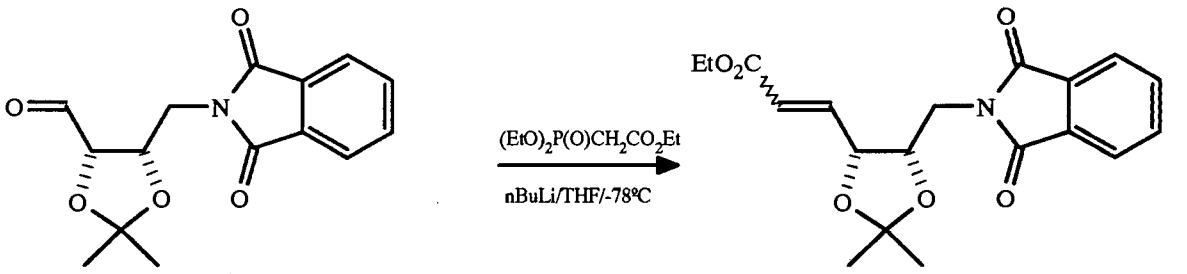
In this study, the aldehyde **75** was reacted with ethoxycarbonylmethylene triphenylphosphorane in dichloromethane at 0°C (Scheme 38).



75 **74**

Scheme 38

In the initial stages of the study, E-or Z-selectivity was not so much of an issue as the radical cyclisation itself. The radical cyclisation would first be tried out on the E/Z mixture of the radical precursor and if successful, individual isomers themselves would be separated and carried through. A t.l.c.-study of the radical cyclisation of the radical precursor (an E/Z mixture) indicated that the Z-isomer (as identified from ^{1}H NMR coupling constants) was consumed at a faster rate than the E-isomer. In subsequent radical cyclisation experiments of the purified Z-radical precursor, formation of the E-radical precursor was observed! Thus, Z to E isomerisation using tributyltin hydride/AIBN had occurred, the rate of which was faster than the radical cyclisation of either isomer. Thus, it became imperative to identify an efficient method for preparation of pure E-alkenoate ester in high yield. Following the guidelines discussed previously, a Wadsworth-Emmons variation was carried out by reacting the carbanion, derived from triethylphosphonoacetate and n-BuLi, with the aldehyde at -78°C in THF (Scheme 39).



75 74

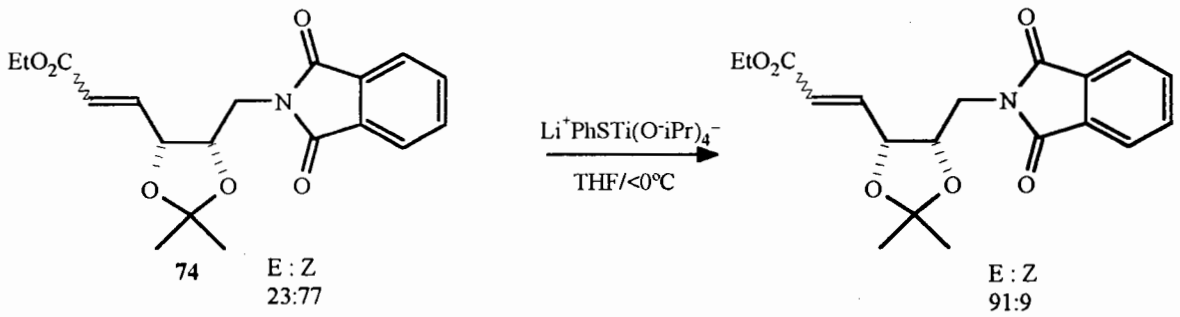
Scheme 39

Although the product showed that the E-isomer predominated, significant amounts of Z-isomer (ca. 30%) were still produced as determined from column chromatography. Furthermore, the yield was poor (<50%) and could not be increased. It was thus decided to isomerise the Z-isomer to the E-isomer.

3.1.6.2. Z to E isomerisation

The early literature on free radical chemistry revealed that iodine atoms[48] and thiyl radicals[49] add to double bonds reversibly, resulting in Z to E isomerisation.[50] The addition-elimination sequence of the phenylsulfanyl radical has also found wide applications.[51] The tributyltin radical is also known to isomerise double bonds but studies have been limited to very simple molecules. For example Kuivila and Sommer[52] studied 2-butene, while Chatgilialoglu *et. al.*[53] have recently studied 3-hexen-1-ol and methyl oleate. They have also introduced the tris(trimethylsilyl)silyl radical as a substitute for the phenylsulfanyl and tributyltin radicals in isomerisation reactions[53].

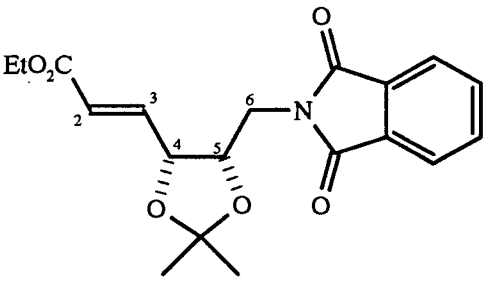
In separate work related to this study but not part of this thesis, it was discovered that yet another reagent, previously unreported, effected Z to E isomerisation of the alkenoate ester. In an attempted 1,4 addition reaction with $Li^{+}PhSe(OPr\text{-}i)_4Ti^{-}$, Z to E isomerisation was observed below 0°C. The lithium(phenylseleno)tetraisopropoxytitanate, first introduced by Leonard and Livinghouse[54], was prepared *in situ* via the reductive cleavage of diphenyldiselenide in THF with n-BuLi followed by the addition of one equivalent of titanium(IV)isopropoxide. Similar results were obtained when lithium(phenylthio)-tetraisopropoxytitanate was used. The latter was preferred to its selenium analogue in view of its ease of preparation from thiophenol, n-BuLi and $Ti(OPr)_4$ (Scheme 40).



Scheme 40

In both cases, the isomerisation did not proceed to completion but reached an equilibrium with an E to Z ratio of 10 to 1. The mechanism is believed to follow an addition-elimination sequence as observed for the other systems mentioned previously. However, the exact nature of the donor species, carbanionic or radical, remains an open question. The isomerisation of the ester **74** with lithium(phenylthio)tetraisopropoxytitanate was compared with the isomerisation using Bu_3SnH. A similar equilibrium mixture was obtained (E : Z; 10 : 1) but the yield obtained using tin hydride was much better (ca. 80% vs 50%). When using lithium(phenylthio)tetraisopropoxytitanate, careful temperature control is called for as 1,4 addition competes with the isomerisation at higher temperatures (> -30°C). The isomerisation with tributyltin hydride (1-2 equivalents) was conducted in deoxygenated, refluxing benzene using catalytic amounts of AIBN and equilibrium was obtained after 7-8 hours. The last trace of Z-olefin was removed by column chromatography.

The ^{1} H NMR spectrum of the E-isomer was assigned solely on the basis of coupling constants. The ketal protons appeared as two singlets (δ 1.55 and 1.31ppm) and the ethyl protons as a triplet (centered at δ 1.28ppm) and a quartet (centered at δ 4.19ppm). The aromatics appeared as two multiplets centered at δ 7.70 and 7.80ppm respectively.



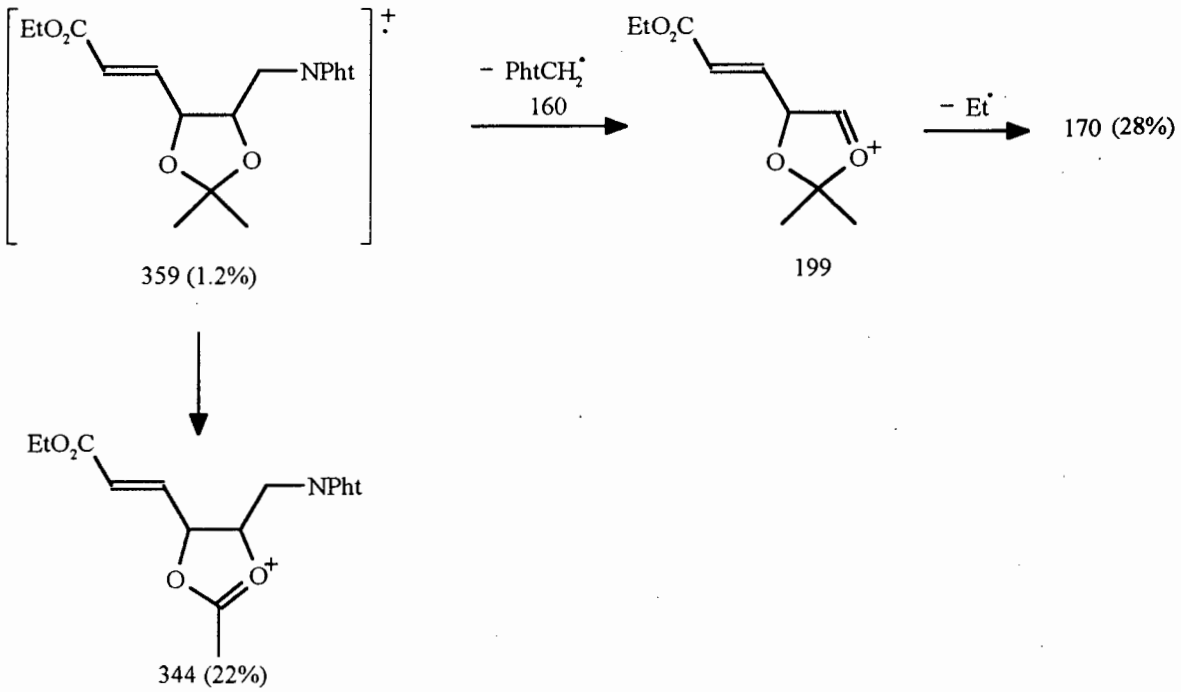
74

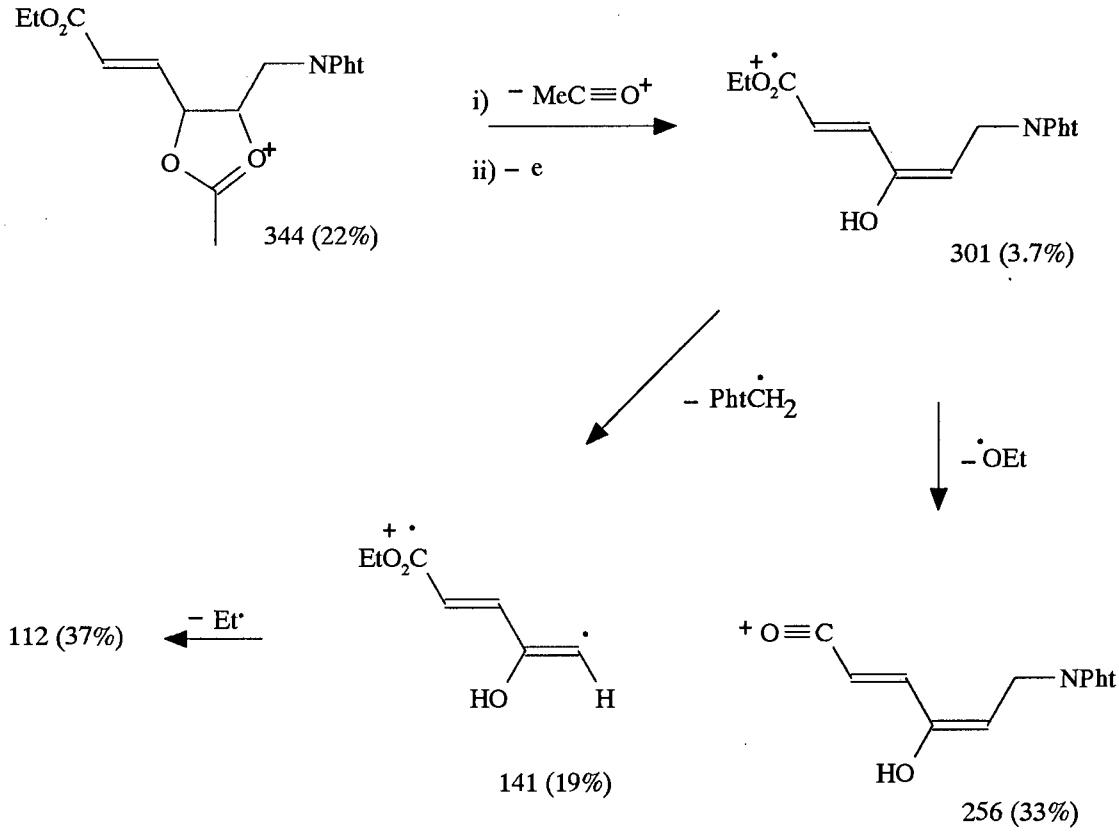
As in the case of imide diol **76**, the geminal protons H-6 and H-6' together with H-5 formed an ABX system: $J_{6,6'}$ = 13.8 Hz, $J_{6,5}$ = 10.4 Hz and $J_{6'5}$ = 3.45 Hz. H-4 appeared as a doublet of doublet of doublets, coupling with H-5, H-3 and H-2. The trans configuration at the double bond was reflected in the large vicinal coupling constant of the olefinic protons: $J_{2,3}$ = 15.6 Hz. The allylic coupling between H-2 and H-4 was very small as expected with $J_{2,4}$ = 1.6 Hz. H-3, because it is β- to the C=O group, resonated downfield from H-2.

The ^{13}C NMR spectrum was assigned by analogy to that of the imide diol **76**. The methyl carbon of the ethyl group appeared at 14.2ppm and the methylene carbon at 60.7ppm. The aromatic protons, the quarternary carbon of the ketal, C-6 and the methyl carbons of the ketal were at almost identical chemical shifts as those of the imide diol. Thus, the carbonyl carbon of the ester was assigned a chemical shift of 165.6ppm. C-3 and C-2 resonated at 140.3ppm and 123.8ppm respectively, while C-4 was assigned at 75.9 and C-5 at 75ppm because C-4 is allylic.

In the IR-spectrum, the absence of peaks in the 3200-3600cm^{-1} region (OH stretch) was noted.

The following ions were the most abundant in the mass spectrum of **74**: m/z = 160 (100%); 199 (51%); 29 = Et$^{\cdot}$ (48%); 43 = MeCO^{+} from the ketal (41%); 112 (37%) and 256 (33%). The proposed fragmentation pattern is presented in Scheme 41.

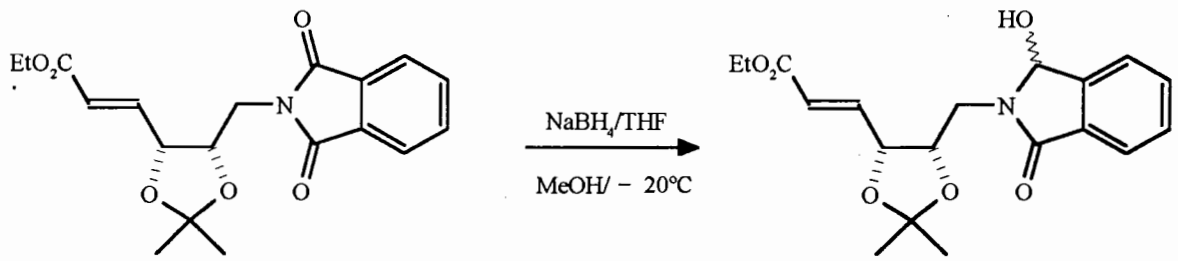




Scheme 41

3.1.7. Carbinol Amide Synthesis

For the chemoselective reduction of the imide functionality of **74** to its carbinol amide **73**, the procedure of Hart *et.al.*[27] was used. Unlike the procedure by Speckamp *et.al.*[55], who conducted the reaction in HCl-saturated ethanol, Hart *et.al.* used methanol as the solvent without any acid. In this thesis, a mixture of THF and methanol was used as the solvent. Hart *et.al.* conducted the reaction at 0°C, but owing to the anticipated lability of the ester under these conditions, the temperature in this work was kept below -20°C for the duration of the reaction (Scheme 42).



Scheme 42

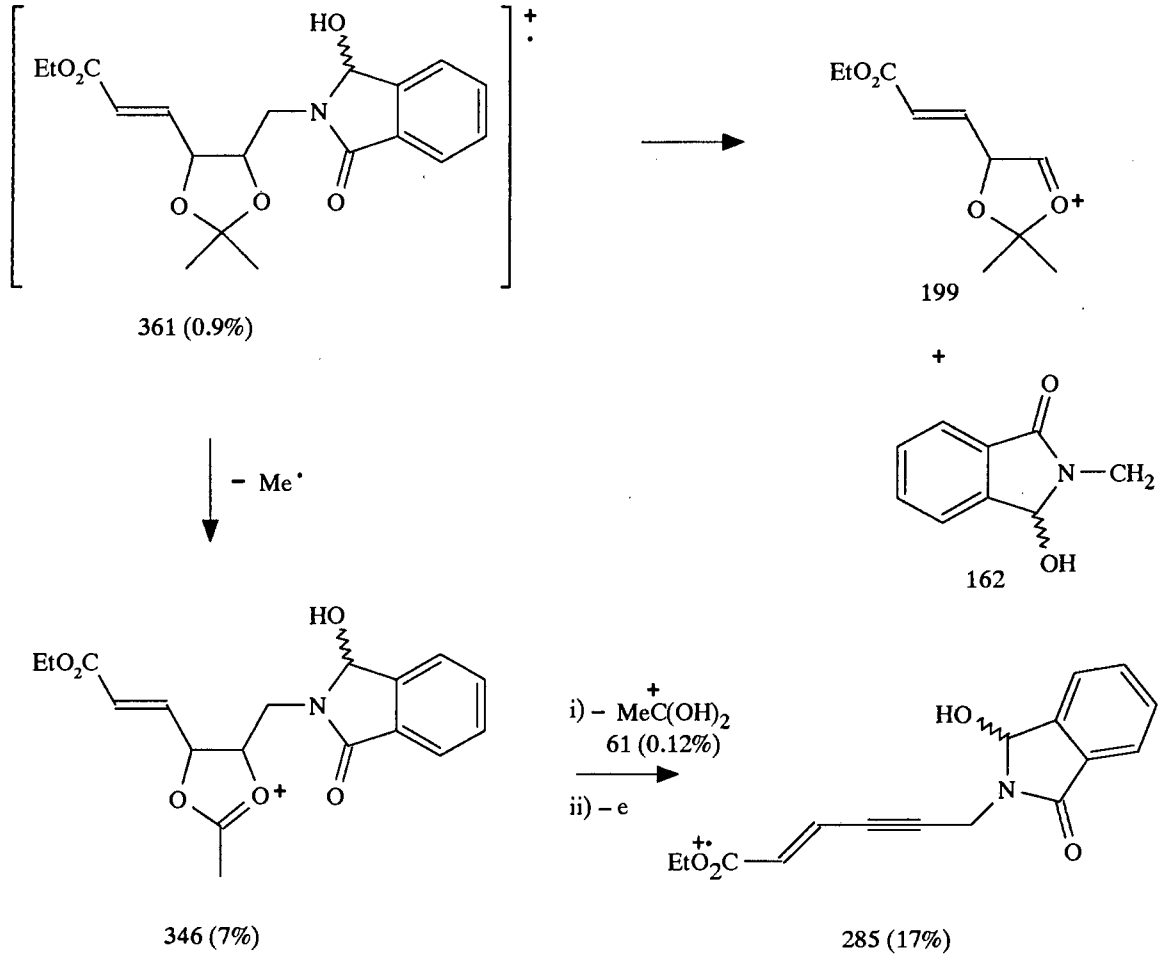
The reaction was then quenched with dilute HCl and the product extracted into ethyl acetate. Crystalline carbinol amide **73** was obtained in high yield (>95%) chemoselectively, leaving the ester functionality unchanged.

The weak imide band at 1770cm^{-1} in the IR spectrum of **73** had disappeared, leaving the amide band at 1680cm^{-1}, and two bands at 3370 and 3560cm^{-1} indicating the presence of a hydroxyl group.

NMR showed **73** to exist as one isomer with the benzylic proton appearing as a doublet centered at δ 6.05ppm. The rest of the ^{1}H NMR spectrum was essentially the same as that of the alkenoate ester **74**. The geminal protons H-6 and H-6', together with H-5 formed an ABX system as before. The vicinal olefinic protons appeared as two doublets of doublets (J_{vic} = 15.6 Hz). A small allylic coupling constant of 1.6 Hz was observed between H-2 and H-4.

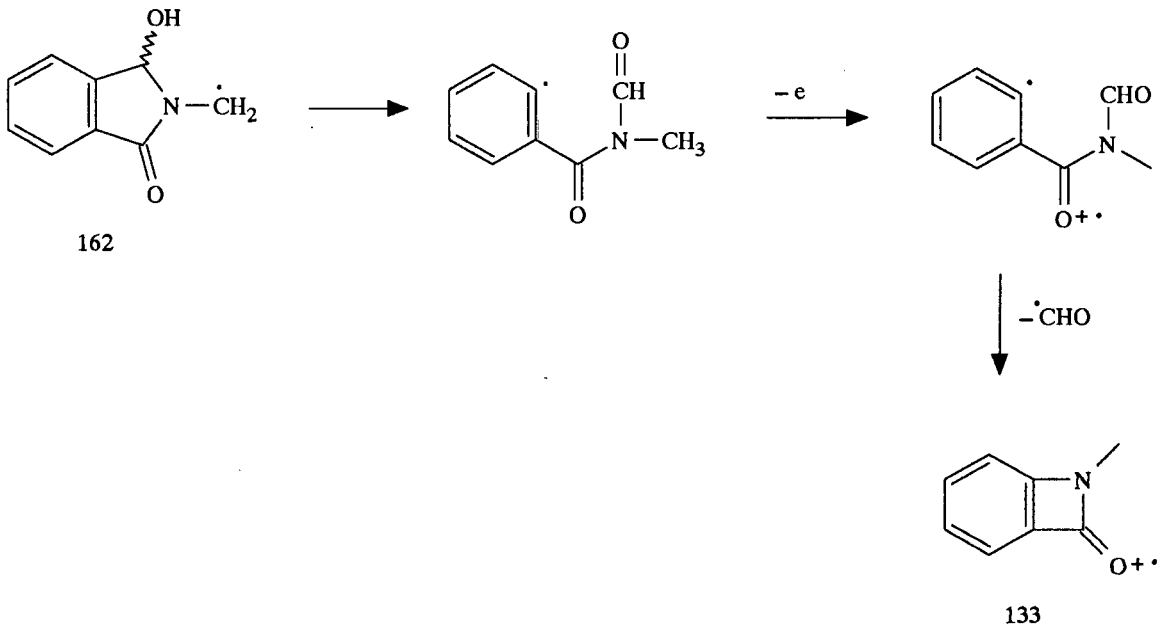
The loss of symmetry at the phthalimide group was evident from the aromatic region in the ^{13}C NMR spectrum. Two different quarternary carbons were observed with a 12.5ppm chemical shift difference between them. The two aromatic carbons adjacent to the quarternary ones also resonated at different chemical shifts (129.8 and 132.3ppm). The carbon bearing the hydroxyl group resonated at 82.7ppm. The rest of the spectrum was essentially the same as that of the alkenoate ester.

The following ionic species were most prominent in the mass spectrum: m/z = 133 (100%); 162 (56%); 163 (41%); 29 = Et· (39%); 43 = $MeCO^+$ (29%) and 199 (22%). A proposed fragmentation pattern is presented in Scheme 43.



Scheme 43

Once again, $MeCO^+$ appears, which is characteristic of the isopropylidene ketal. Protonated acetic acid, m/z = 61, has been reported in the literature[41a]. The origin of the species with m/z = 133 is proposed in Scheme 44.

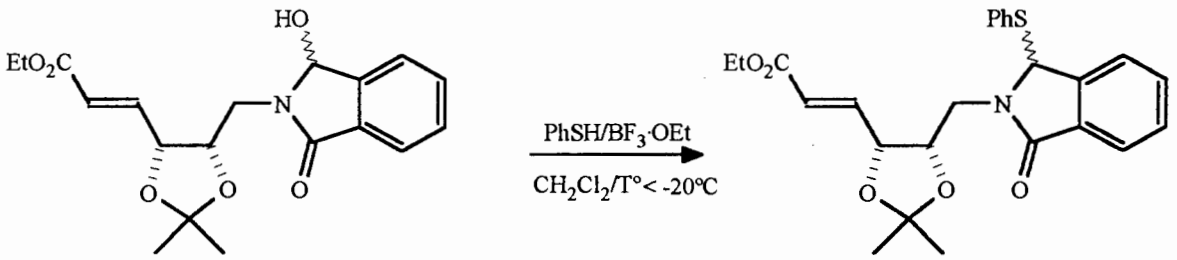


Scheme 44

3.1.8. Radical Precursor Synthesis

Fortunately there is quite a large selection of functional groups that can serve as radical precursors. In order of reactivity they are: I, Br, SePh, OC(S)SMe, Cl, SPh. What is more, they can all be derived from the hydroxyl functionality. Hart *et.al.*[27] found that the α-halolactams, derived from the carbinol amide, were unmanageable practically and thus turned to the phenyl sulfides which proved to be reactive enough. For the conversion to the sulfide, Hart *et.al.* treated the carbinol amide with catalytic p-toluenesulfonic acid in thiophenol at room temperature. However, with certain compounds containing double bonds, addition of thiophenol to the unsaturated component of the carbinol amide was observed. In this thesis, Hart *et.al.*'s procedure could not be applied due to the acid-sensitivity of the ketal protecting group.

The following conditions were thus developed. The carbinol amide was treated with thiophenol (3 equivalents) and $BF_3{\cdot}OEt_2$ (3 equivalents) in dichloromethane below -20°C in order to avoid addition to the double bond (Scheme 45).



73 71

Scheme 45

The reaction proceeded in good yield (ca. 75%) and the product was stable to brief chromatography. Unlike the carbinol amide **73**, the NMR spectra of the sulfide **71** indicated the presence of the two epimers with doubling-up of peaks being observed in the ^{13}C NMR. The identity of **71** was confirmed by high resolution mass spectrometry.

3.2. Radical Cyclisation Study

3.2.1. Radical Cyclisation of 71

With Z to E isomerisation occurring under tin hydride conditions, individual radical cyclisation studies of each isomer was thus not possible. The radical cyclisation was thus confined to the E-isomer only. The cyclisations were conducted in dry, deoxygenated benzene at reflux temperature. Water was kept out of the system to prevent hydrolysis of the sulfide. An inert atmosphere was necessary in order to prevent oxidation of the tin hydride. AIBN only becomes active as radical initiator at the reflux temperature of benzene. As discussed in chapter 2, the concentration of the tin hydride was kept as low as possible so as to prevent the reduction of the newly-formed carbon radical by tin hydride. This was realised practically by the slow addition of a Bu_3SnH/AIBN solution in benzene to a refluxing solution of **71** in benzene.

The results of the radical cyclisation study of **71** are summarised in Table 2

Reagents	Addition Time	Yield (main product fraction)
Bu_3SnH (1.5 equiv.) + AIBN (cat.)	10 min. addition + 4 h reflux	56 %
Bu_3SnH (1.5 equiv.) + AIBN (cat.)	3.5 h addition + 5 h reflux	57 %
Bu_3SnH (3.5 equiv.) + AIBN (cat.)	10 h addition + 48 h reflux	60 %

Table 2

The radical cyclisation was monitored by t.l.c. The main product fraction appeared as a diffuse UV-active spot on t.l.c. with polar by-products near the base-line of the plate. The yield of the main product fraction is shown in table 2. It is also evident from the results that the rate of addition of the tin hydride had no influence on the yield of the cyclisation product. This was also reflected in the absence of any reduced starting material being isolated, indicating that the radical is indeed highly reactive towards the double bond. The by-products were not identified. The main product fraction consisted of two compounds as evident from HPLC in a 8 : 2 ratio. A single recrystallisation from ethyl acetate/hexane of the main product fraction afforded the major component **89** (Figure 5) which was HPLC-pure and which was subsequently characterised.

3.2.2. Characterisation of the Major Component 89

From the ^{1}H and ^{13}C NMR spectra it was evident that the major component **89** was one isomer. The ^{1}H NMR spectrum also indicated the absence of the phenylsulfanyl protons and those of the double bond.

The assignment of the protons was made using 2D COSY and HETCOR experiments, decoupling experiments and coupling constants. Figure 5 shows the four possible isomers in their chair conformations.

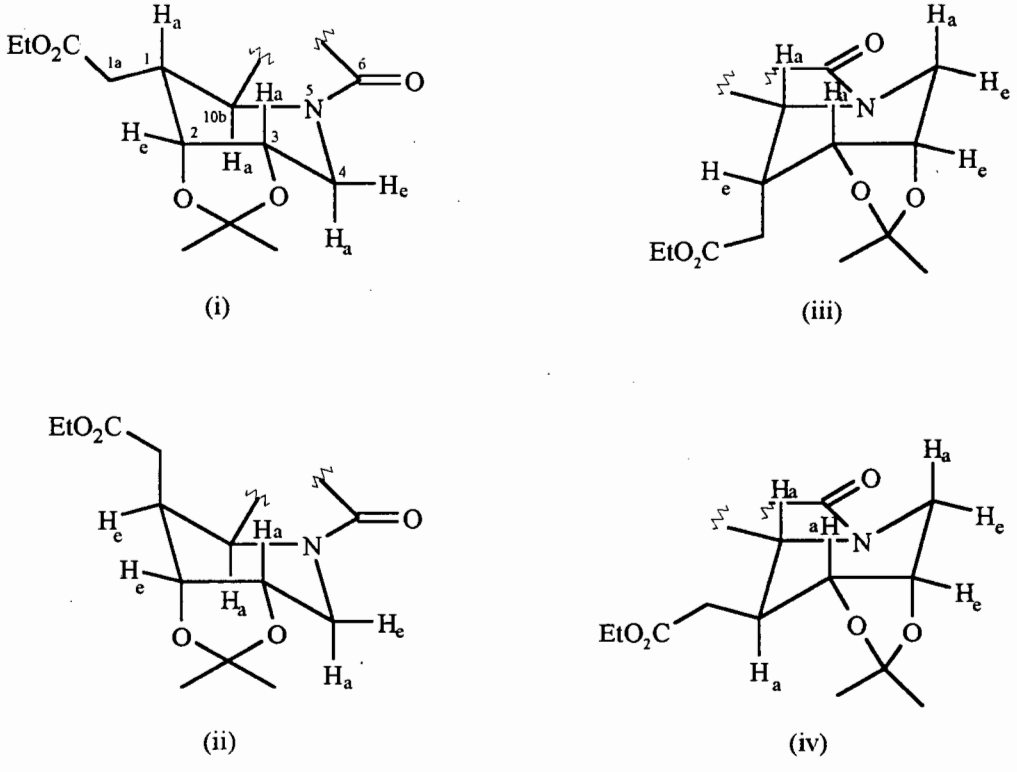


Figure 5

With the stereochemistry about the C-1/C-10b bond being the crux of the model study, the stereochemistry of the cyclisation product had to be determined unambiguously. In order to identify the correct isomer, the coupling constants $J_{1,2}$ and $J_{1,10b}$ needed to be known. The Karplus equation, which relates the three-bond coupling constant (J) to the dihedral angle (ϕ) between two vicinal protons is an indispensable tool in conformational analysis.

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

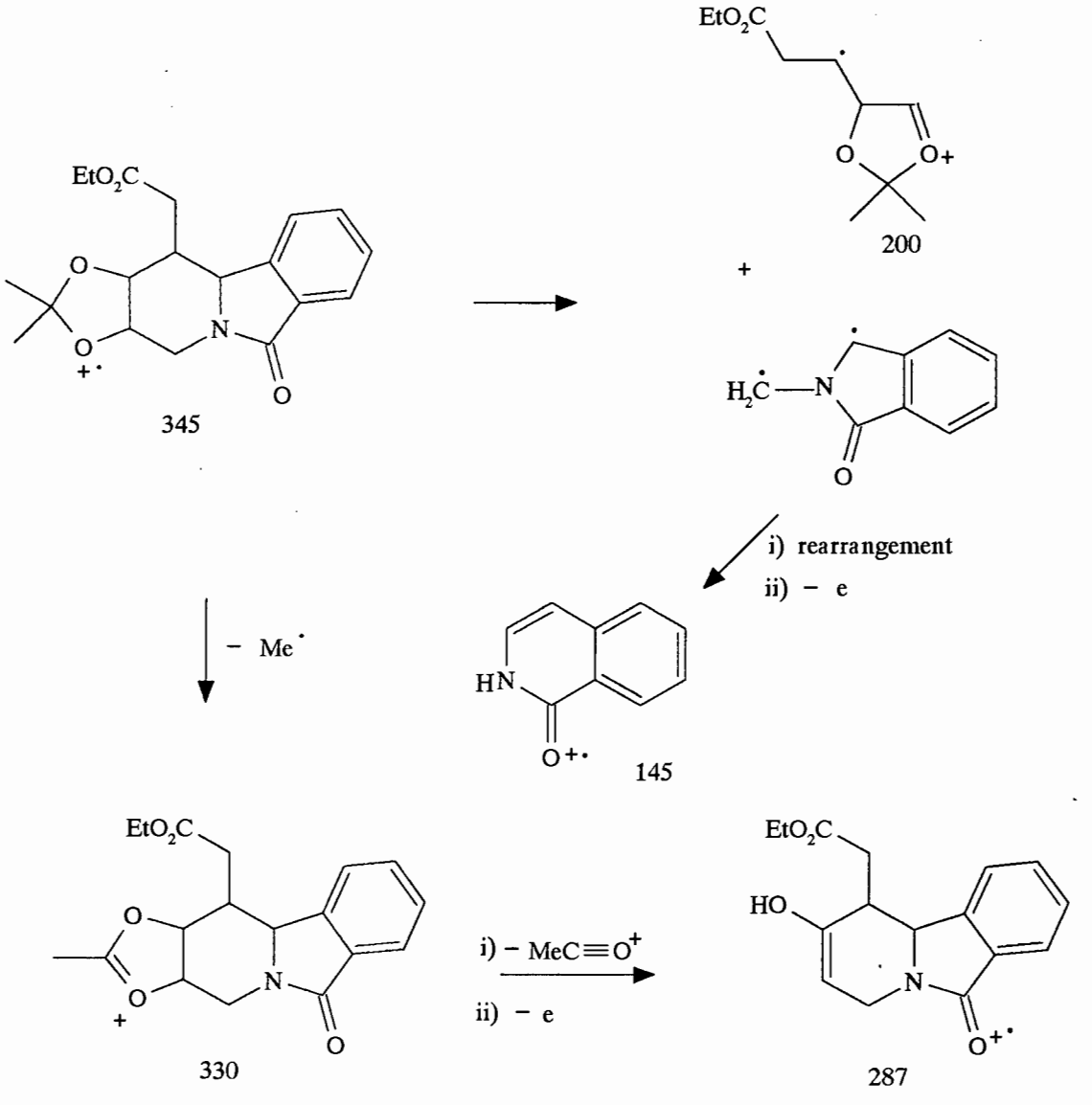
$$\text{and} \quad J = 9.5\cos^2\phi - 0.28 \quad \text{for} \quad 90° \leq \phi \leq 180°$$

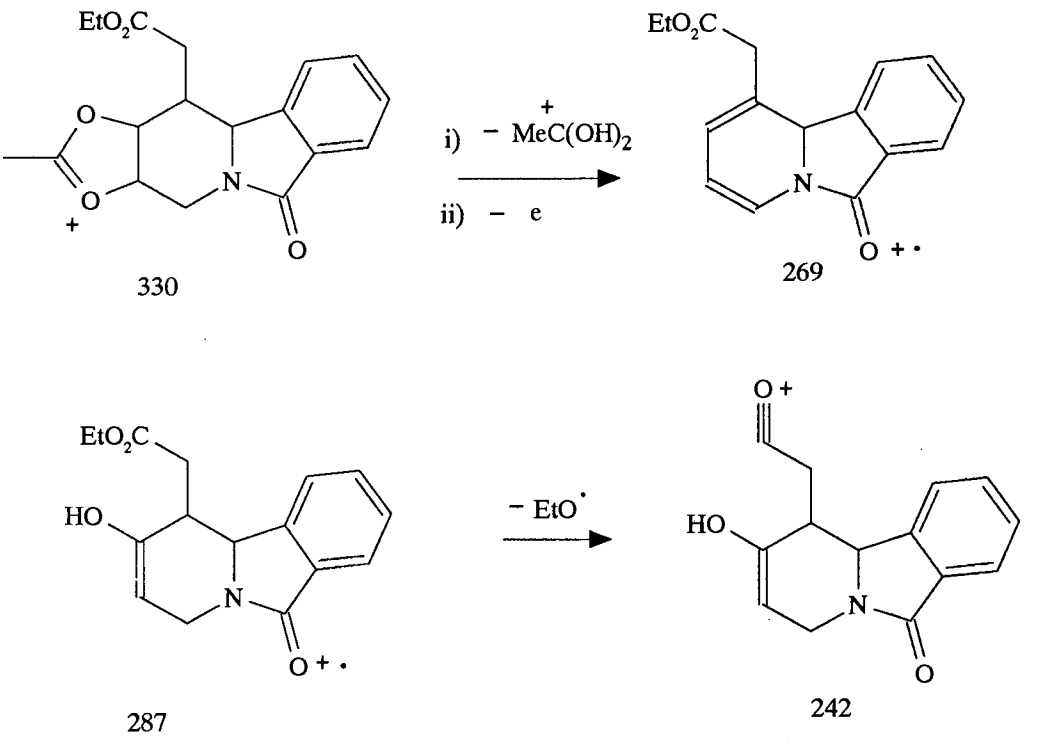
Thus, from the vicinal coupling constant between two protons one can determine the conformational orientation of the two protons. Unfortunately, the protons H-2 and H-10b of **89** were not resolved. However, this problem proved not to be insurmountable, because H-1 was well resolved. H-1 was subsequently spin-decoupled by irradiating the methylene protons of the carboethoxymethylene substituent at their radio frequency. This left H-1 resonating as a doublet of doublets with coupling constants of 3.2 and 11.2 Hz, thus, indicating a diaxial and an axial-equatorial orientation of protons, assuming a chair conformation of the isomer. This coupling pattern is only consistent with structure (i) in Figure 5 in which H-1 and H-10b are trans-diaxial. In a subsequent NOE experiment it was established that H-2 was in close proximity to H-1, thus ruling out a trans-diaxial orientation of these two protons.

The IR spectrum of **89** also proved to be diagnostic in the identification of the cyclisation product. The strong band at 1700cm^{-1} of the carbinol amide **73** containing both the C=O stretches of the α,β-unsaturated ester and of the amide appeared as two separated bands in the spectrum of **89**, since the loss of the double bond resulted in the shift of the ester C=O band to 1730cm^{-1} exposing that of the amide at 1690cm^{-1}.

The ^{13}C NMR spectrum of **89** was assigned with the help of a HETCOR experiment and by comparison with that of the carbinol amide. Each of the six aromatic carbons was found to resonate at a different chemical shift. The methylene carbon of the ethoxycarbonylmethyl substituent resonated at 33.1ppm. The new stereogenic centre C-10b appeared at 56.3ppm and was differentiated from C-2 (74.2ppm) by the fact that C-10b is α to a nitrogen while C-2 is α to an oxygen atom. As in the spectrum of the carbinol amide, C-4 resonated at 40.4ppm, C-3 resonated at 71.1ppm and the remaining carbons had almost identical chemical shifts to those of the carbinol amide.

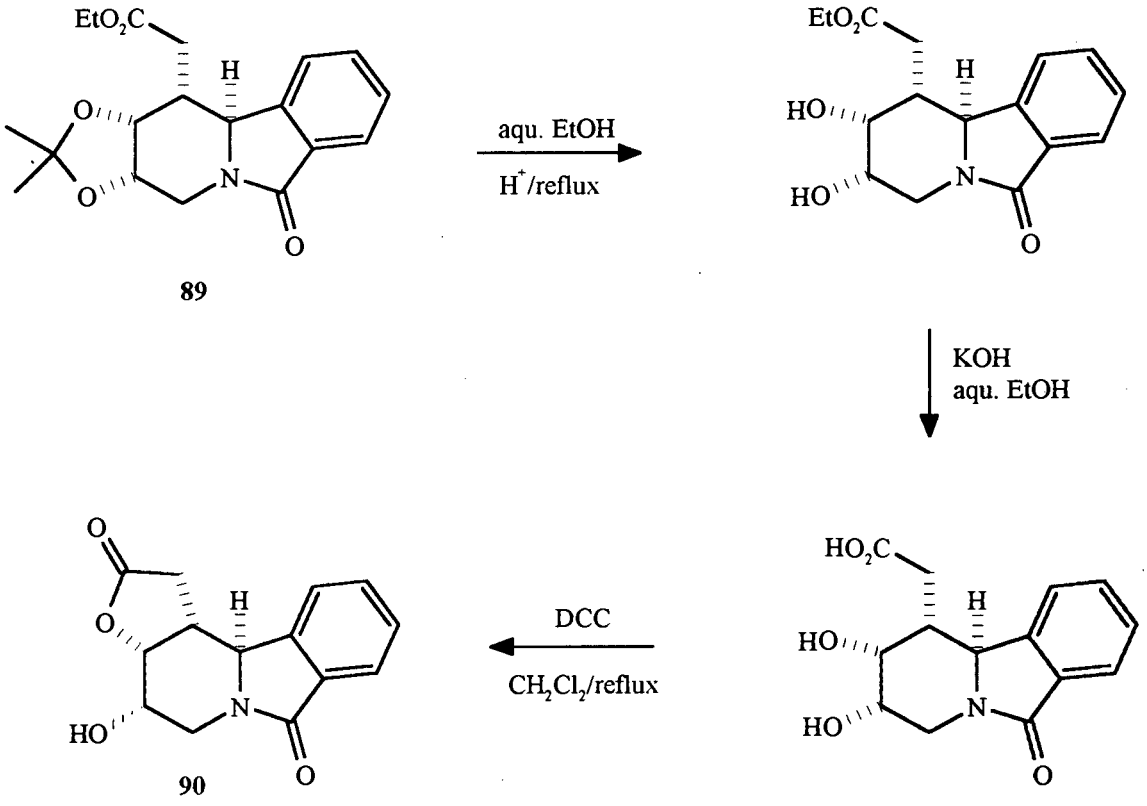
The following ionic species were observed in the mass spectrum: m/z = 200 (100%); 43 (99%); 345, the molecular ion (72.6%); 242 (59%); 287 (44.7%); 269 (44.7%); 145 (42.5%) and 29 (38.6%), with m/z = 43 being characteristic of the ketal group and m/z = 29 identifying with the ester functionality. A proposed fragmentation pattern is shown in Scheme 46.





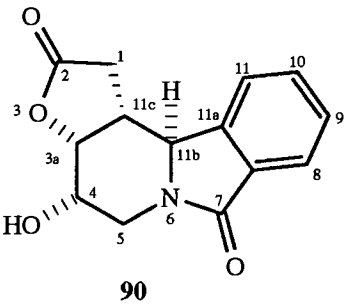
Scheme 46

In order to unambiguously verify the proposed cis- stereochemistry between the C-1/2 substituents of the cyclisation product, the latter was derivatised as its lactone **90** since a lactone was not expected to form if the substituents were trans (Scheme 47).



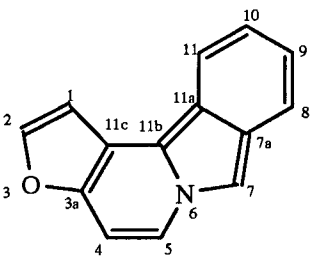
Scheme 47

Ketal and ester hydrolysis via separate treatment of acid and base proceeded uneventfully to the acid diol which was isolated but not characterised. Its lactonisation with $POCl_3$ as dehydrating agent in refluxing dichloromethane was unsuccessful. However, reaction using DCC in refluxing dichloromethane afforded a less polar product in complete conversion after ca. 8h to give **90** in 51% overall yield.



90

The tetracyclic ring system of **90** had thus far not been reported in the literature. The fully unsaturated parent **91** was named according to the Hantzsch-Widman notation as furo[3',2':3,4]pyrido[2,1-a]isoindole.



91

Thus, **90** was named (3a**R**,4**S**,11b**S**,11c**R**)-1,2,3a,4,5,11c-hexahydro-4-hydroxy-2(1*H*)-oxofuro[3',2':3,4]pyrido[2,1-a]isoindol-2(*H*),7(11b*H*)-dione.

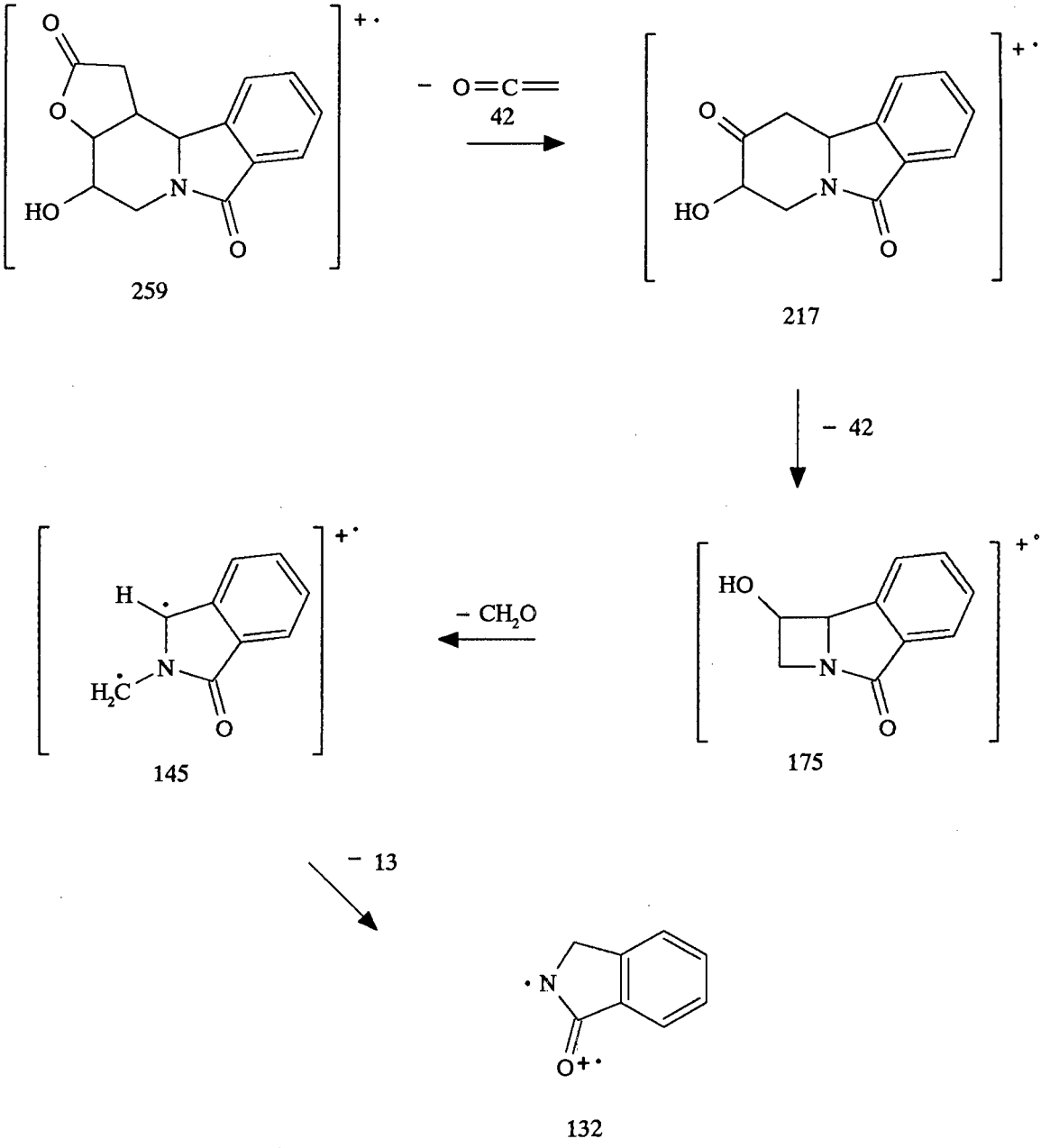
The IR spectrum of **90** showed two CO stretching bands: one at 1770 cm^{-1} indicative of a five-membered lactone ring, and another at 1700 cm^{-1} for the five-membered lactam ring.

In the ^{1}H NMR spectrum of **90**, the crucial proton H-11b was well resolved and appeared as a doublet with a large coupling constant of 10 Hz indicating a trans-diaxial orientation with H-11c.

This, thus, supports the proposed stereochemistry of the cyclisation product **89** in which H-1 and H-10b are also in a trans-diaxial orientation. Protons H-4 and H-11c of **90** appeared as unresolved multiplets but H-3a resonated as a doublet of doublets with vicinal coupling constants of 3 Hz and 7 Hz consistent with the cis-lactone grouping. Of interest was also the large difference in chemical shift of H-5 and H-5'.

As in the spectrum of **89**, the difference in chemical shift amounted to almost 0.9ppm. This is probably due to one of the geminal protons being shielded by the π electrons of the lactam C=O group.

The following ionic species were most prominent in the mass spectrum of **90**: m/z = 259, the molecular ion (100%); 132 (97%); 217 (68%); 145 (33%) and 175 (21%). A proposed fragmentation pattern is shown in Scheme 48.



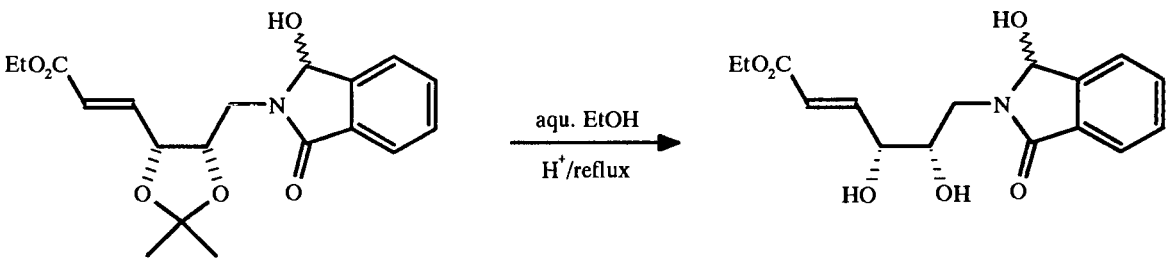
Scheme 48

3.3. Cyclisation Study of the Unprotected Radical Precursor

The stereochemical directing ability of the isopropylidene ketal was tested by studying the radical cyclisation of the unprotected diol **72** as discussed in chapter 2.

3.3.1. Synthesis of the Radical Precursor

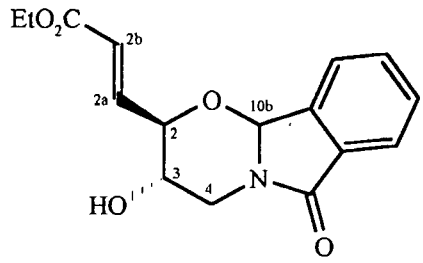
The 4,5-O-deprotected carbinol amide **80** was obtained from the acid hydrolysis of **73** (Scheme 49).



73 **80**

Scheme 49

Deprotection was chosen to follow sodium borohydride reduction because **80** was anticipated to be too polar to be extracted from an aqueous work-up. However, the product obtained after hydrolysis was found to be extractable into ethyl acetate after quenching with aqueous $NaHCO_3$. Subsequent characterisation of **80** soon explained its relatively non-polar nature. Elemental analysis confirmed that it had, in fact, cyclised to **80a** with loss of water. From the ^1H NMR spectrum it was not apparent whether **80** had cyclised to form a five-membered ring or the six-membered ring **80a**. Structure **80a** was proposed on the basis that a six-membered ring would form preferentially.



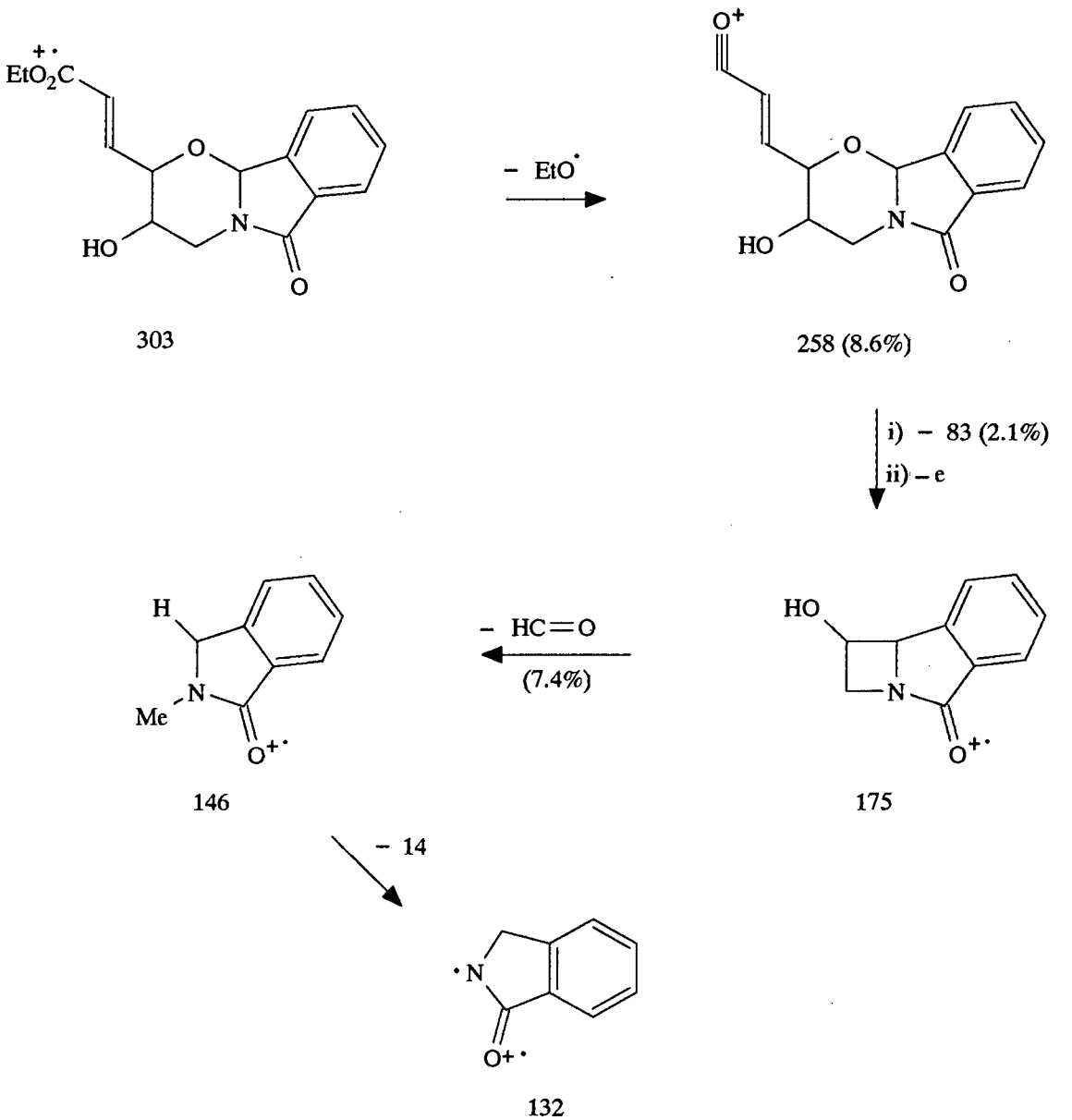
80a

^{1}H and ^{13}C NMR indicated that only one isomer of **80a** was present. All assignments in the ^{1}H NMR spectrum were made based on coupling constants. H-10b resonated as a singlet far downfield at 5.70ppm. The downfield shift is due to H-10b being both benzylic and α to both a nitrogen and oxygen atom as in the carbinol amide **73**. The olefinic protons H-2a and H-2b resonated both as a doublet of doublets at 7.15ppm and 6.15ppm respectively. H-3 was well resolved as a doublet of doublets centered at 3.51ppm.

As in the case of the cyclisation product **89** and the lactone **90**, the geminal protons H-4 resonated at two very different chemical shifts. In this case the difference was more than 1.5ppm. H-2 was well resolved and resonated as a doublet of doublet of doublets, centered at 4.30ppm.

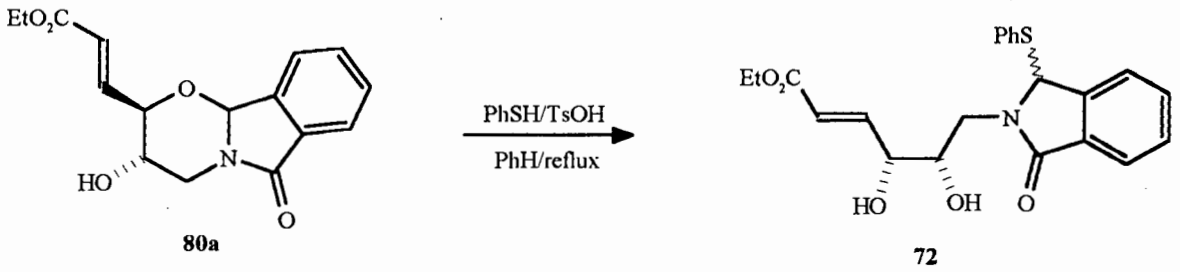
The ^{13}C NMR spectrum was assigned by comparison with that of the carbinol amide **73**, the cyclisation product **89** and the lactone **90**. The carbonyl carbons of the ester and amide appeared as one signal at 166.3ppm. The olefinic carbons C-2a and C-2b were found in the aromatic region with C-2a resonating at 142.9ppm. C-2b could not be distinguished from the aromatic carbons. C-10b resonated at 84.5ppm and C-4 at 44.3ppm. C-3 and C-2 could not be assigned with absolute certainty because the ring-size of **80a** could not be determined without further 2D NMR experiments. The ^{1}H NMR spectrum of **80a** was run in DMSO-d_6, but no coupling between the OH-proton and that of the attached carbon was observed.

The major ionic species in the mass spectrum were: m/z = 175 (100%); 132 (94.3%) and 146 (25.8%). A proposed fragmentation pattern is shown in Scheme 50.



Scheme 50

In the transformation of **80a** to the radical precursor **72**, the protocol of Hart *et.al.*[27] was followed (Scheme 51).



Scheme 51

72 was obtained in 50% yield, with an uncharacterised by-product making up the balance. Using $BF_3{\cdot}OEt_2$ as the Lewis acid at low temperature (ca. -40°C), the same by-product was also obtained. It was evident from NMR that the by-product was in fact a mixture of at least two isomers which made the characterisation very difficult. ^1H NMR did, however, indicate the presence of the double bond, thus excluding the addition of thiophenol to the olefinic bond.

Unlike the 4,5-O-protected radical precursor **71**, **72** was present as a single isomer as was evident from ^1H and ^{13}C NMR. Most signals in the ^1H NMR spectrum were not resolved and thus not assigned. In the ^{13}C NMR spectrum, the benzylic carbon bearing the phenylsulfanyl group had moved upfield noticeably to 73ppm (84.5ppm in **80a**). The structure of **72** was confirmed by high resolution mass spectrometry.

3.3.2. Radical Cyclisation of 72

The reaction conditions were the same as those used in the cyclisation of **71**. The tin hydride/AIBN in benzene was added over a 3h period and the reaction was refluxed overnight. T.l.c. showed absence of starting material. The reaction mixture was purified by column chromatography and the product fraction was isolated in 60% yield.

^{1}H and ^{13}C NMR spectroscopy of the cyclisation product showed the presence of at least two isomers. HPLC analysis showed the product to consist of three components in equal proportions. ^{1}H NMR confirmed that **72** had in fact cyclised as expected: The olefinic protons had disappeared together with the phenylsulfanyl group. H-10b of one isomer (δ 5.01ppm) stood out from the multiplet and resonated as a doublet with $J_{1,10b}$ = 4.0 Hz suggesting that H-1 and H-10b are in a cis orientation.

3.4. Conclusion

With a view to developing new methodology for constructing the C/D ring system of the Eburna alkaloids, the study of α-acylamino radicals by Hart *et.al.*[27] has been extended to more complex N-acyl-2-aza-6-heptenyl radicals. Although the desired cis-ring fusion about the newly-formed bond was not achieved, the radical cyclisation showed excellent regio- and stereoselectivity. Out of a possible four diastereomers, only two were obtained in an 8 : 2 ratio. Whereas Hart *et.al.* only studied simple N-acyl-2-aza-5-hexenyl and N-acyl-2-aza-6-heptenyl radicals which were alkyl-substituted at the olefinic bond, the N-acyl-2-aza-6-heptenyl radicals in this study have incorporated a radical auxiliary at the 4 and 5 position. Furthermore, the double bond has been activated by an ethoxycarbonyl group resulting in excellent regiocontrol of addition as well as inhibition of radical reduction by Bu_3SnH.

Once again, a sugar from the carbohydrate chiral pool, in this case D-ribose, proved to be an excellent starting material for the α-acylamino radical precursor incorporating a chiral auxiliary. This chiral auxiliary, the isopropylidene ketal, proved to be very effective in that the radical cyclisation was highly stereoselective.

In the absence of the isopropylidene ketal, the radical cyclisation was almost completely unselective with three out of four diastereomers being obtained in equal proportions. This demonstrates unambiguously the effectiveness of the ketal as a stereoselective directing group.

The directing ability of the ketal is thought to be a result of the rigidity of the five-membered dioxolane ring that controls the conformation of the transition-state. More research, in conjunction with molecular modeling, needs to be undertaken to gain more insight into the relationship between the chiral auxiliary and the diastereoselectivity of the radical cyclisation.

CHAPTER 4

Experimental Section

4.1.General

4.1.1.Characterisation of compounds

All melting points were determined on a Reichert Jung hot stage microscope and are uncorrected. Optical rotations were determined in the solvents indicated at 20°C using a Perkin Elmer 141 polarimeter. The concentration *c* refers to g/100ml with *l* = 10cm.

Infra-red spectra were recorded in chloroform or dichloromethane using a Perkin Elmer Paragon 1000 FT-IR spectrometer.

Routine proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM 360 (60MHz) spectrometer. High resolution ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-200 (200.057MHz and 50.31MHz respectively) or on a Varian Unity (399.951MHz and 100.579MHz respectively) in deuteriochloroform, unless otherwise stated. The chemical shifts (δ) are given in ppm relative to the signal of tetramethylsilane TMS (δ 0.00) or the residual chloroform (δ 7.24) in the deuteriochloroform.

Mass spectra were recorded on a VG micromass 16F mass-spectrometer at 70eV with an accelerating voltage of 4kV or at the mass-spectrometry unit of the Cape Technicon. Elemental analyses for C, H and N were carried out using a Heraeus CHN-rapid combustion analyser.

All reactions were monitored by t.l.c. using Merck t.l.c. aluminium sheets, silica gel 60 F_{254}, layer thickness 0.2mm. Detection was done by one of the following methods:

i) using an ultra-violet lamp (wavelength 254nm),

ii) by placing the plate in iodine vapours,

iii) by spraying the plate with a 1% solution of CAN in 9M H_2SO_4 followed by heating at ca. 100°C or

iv) by spraying the plate with a 2.5% solution of anisaldehyde in H_2SO_4/EtOH (1:10 v/v) followed by heating at ca. 100°C.

Column chromatography was carried out using silica gel (Merck, silica gel 60, particle size 0.063-0.200mm) on a gravity column, eluting with the solvents indicated.

4.1.2. Purification of solvents

THF: Dried over Na wire and then distilled from Na and benzophenone under a nitrogen atmosphere immediately before use.

Benzene/toluene: Distilled from Na wire under a nitrogen atmosphere immediately before use.

Dichloromethane: Distilled from phosphorus pentoxide under a dry atmosphere ($CaCl_2$ drying-tube) immediately before use.

Pyridene/triethylamine: Distilled from calcium hydride under a nitrogen atmosphere and stored over 4Å molecular sieves.

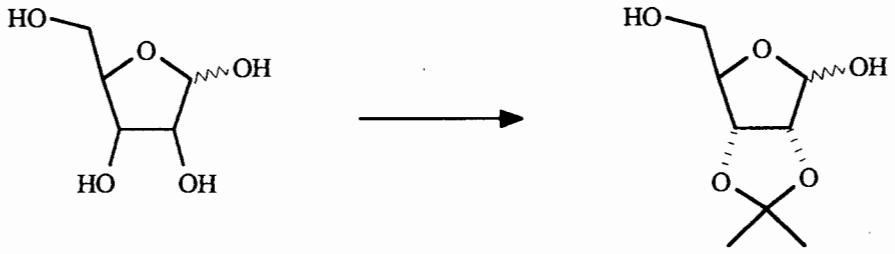
4.1.3. Experimental conditions

All non-aqueous reactions were done under a nitrogen atmosphere and the reagents were introduced into the reaction flask via syringe or addition funnel.

The standard work-up procedure refers to the addition of an aqueous solution of a salt, and extraction with a specified solvent (usually three times the equivalent volume of the aqueous phase).

4.2. Syntheses of Compounds

4.2.1. Synthesis of 2,3-O-isopropylidene-D-ribofuranose **79**



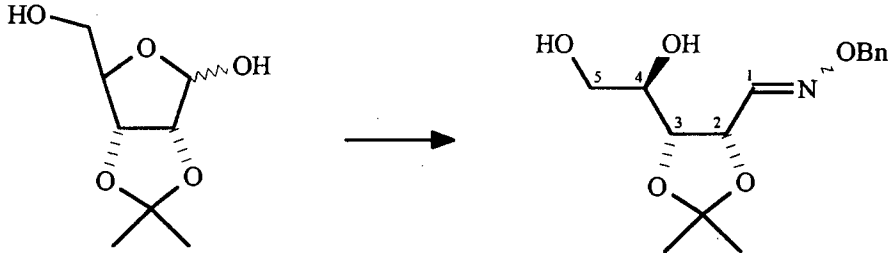
79

To a suspension of D-ribose (5.0g, 33.4mmol) in acetone (150ml) at 0°C was added conc. H_2SO_4 (2ml, 36mmol) dropwise. Once the solid had all dissolved, the reaction was stirred for a further 1.5h before being quenched with a solution of KOH (4.5g, 80.2mmol) in methanol (50ml) at 0°C. To the suspension was added K_2CO_3 (2.5g, 18.1mmol), and the mixture left stirring for 0.5h. After the solids had been filtered off and washed with acetone, the volume of solvent was reduced *in vacuo*, leaving a syrup of 2,3-O-isopropylidene-D-ribofuranose **79** (6.2g, 32.6mmol, 98% yield) which was used without further purification.

δ_H (200 MHz) 1.23 and 1.48 (6H, 2s, isopropylidene-Me's), 3.55 (2H, br.s, -OH), 3.68 (2H, d, J 3.3 Hz, H-5), 4.36 (1H, t, J 3.2 Hz, H-4), 4.50 (1H, d, J 6.0 Hz, H-3), 4.79 (1H, d, J 6.0 Hz, H-2), 5.48 (1H, s, H-1).

δ_C (50 MHz) 24.6, 26.0 and 26.2 (isopropylidene-Me, major and minor); 63.0 and 63.4 (C-5, major and minor); 81.0 and 81.5 (C-4, major and minor); 86.5 (C-3); 87.4 (C-2); 102.5 (C-1); 112.0 (-CMe_2)

4.2.2. Synthesis of 1-benzyloxyimino-2,3-O-isopropylidene-D-ribose **78**



79 **78**

To a solution of 2,3-O-isopropylidene-D-ribofuranose (4.61g, 24.3mmol) in dichloromethane (25ml) and pyridine (10ml) was added O-benzylhydroxylamine hydrochloride (3.95g, 24.7mmol) at 0°C. The mixture was stirred for 15h after which time an ice-cold solution of dil. HCl was added until the mixture became acidic. The product was extracted into ethyl acetate and the organic phases washed with sat. $NaHCO_3$ solution and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered and the volume of solvent reduced *in vacuo* to afford the crude 1-benzyloxyimino-2,3-O-isopropylidene-D-ribose **78** (7g, 98% yield). The crude product was recrystallised from ethyl acetate/hexane to afford white crystals mpt. 90-91°C.

$[\alpha]_D = 31.4°C$ (c = 0.5, $CHCl_3$)

IR ν_{max} 3586 cm^{-1} (OH), 3014, 1602

MS, m/z: 295 (M^+, 0.8); 280 (M^+-15, 2.6); 173 (13); 114 (22); 91 (100); 59 (42); 55 (7); 43 (39); 31 (11)

δ_H (200 MHz) E-isomer: 1.32 (3H, s, isopropylidene-Me), 1.43 (3H, s, isopropylidene-Me), 2.6-3.4 (2H, br.s, -OH), 3.5-3.8 (3H, m, H-4 and H-5), 4.12 (1H, dd, J 6.2, 8.4 Hz, H-3), 4.74 (1H, dd, J 6.2, 7.2 Hz, H-2), 5.07 (2H, s, $BnCH_2$-), 7.2-7.4 (5H, m, arom.), 7.50 (1H, d, J 7.2 Hz, H-1).

δ_H (200 MHz) Z-isomer: 1.32 (3H, s, isopropylidene-Me), 1.43 (3H, s, isopropylidene-Me), 2.6-3.4 (2H, br. s, -OH), 3.53-3.78 (3H, m, H-4 and H-5), 4.23 (1H, t, J 6.4 Hz, H-3), 5.12 (2H, dd, J_{gem} 12 Hz, $BnCH_2$-), 5.27 (1H, t, J 6.4 Hz, H-2), 6.90 (1H, d, J 6.4 Hz, H-1), 7.2-7.4 (5H, m, arom.).

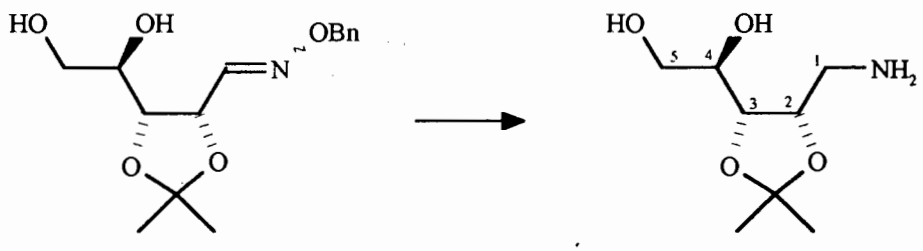
δ_C (50 MHz) E-isomer: 25.9 and 28.2 (isopropylidene-Me's); 64.6 (C-5); 70.2 (C-4); 75.6 (C-2); 76.7 ($BnCH_2$-); 78.3 (C-3); 110.7 (isopropylidene-C); 128.8, 128.9, 129.0 and 137.7 (arom.); 149.5 (C-1)

δ_C (50 MHz) Z-isomer: 25.6 and 27.9 (isopropylidene-Me's); 64.4 (C-5); 71.2 (C-4); 72.2 (C-2); 77.6 ($BnCH_2$-); 79.2 (C-3); 110.4 (isopropylidene-C); 128.6, 129.1, 129.3 and 136.9 (arom.); 151.5 (C-1)

Found: C, 61.4; H, 7.1; N, 4.6%

$C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.2; N, 4.7%

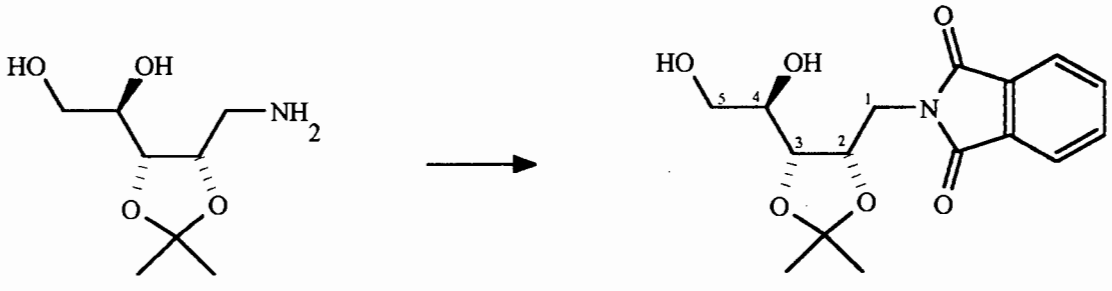
4.2.3. Synthesis of 1-amino-2,3-O-isopropylidene-D-ribose 77



78 77

To a solution of 1-benzyloxyimino-2,3-O-isopropylidene-D-ribose **78** (4.0g, 13.6mmol) in THF (120ml) was added lithium aluminium hydride (2.1g, 54.3mmol) in small portions at 0°C. The reaction was left to stir for 48h after which time water (8ml) was added slowly at 0°C followed by triethylamine (45ml). The white precipitate was filtered through Celite and washed with Et_3N/MeOH/EtOAc (2x 10:40:5ml). The volume of solvent was reduced *in vacuo* to afford a syrup of 1-amino-2,3-O-isopropylidene-D-ribose **77** (2.05g, 79% yield) which was used without any further purification.

4.2.4. Synthesis of 1-phthalimido-2,3-O-isopropylidene-D-ribose **76**



77 **76**

To a solution of 1-amino-2,3-O-isopropylidene-D-ribose **77** (2.05g, 10.72mmol) in triethylamine (12ml) and dichloromethane (45ml) was added N-ethoxycarbonylphthalimide (3.06g, 13.94mmol) at 0°C. After 12h the volume of solvent was reduced *in vacuo* and the crude product was chromatographed on silica gel (250g) eluting with ethyl acetate/hexane yielding crystalline 1-phthalimido-2,3-O-isopropylidene-D-ribose **76** (3.13g, 91% yield).

Mpt. 129-133°C (ethyl acetate/hexane)

$[\alpha]_D$ = -66.0° (c = 0.5, MeOH)

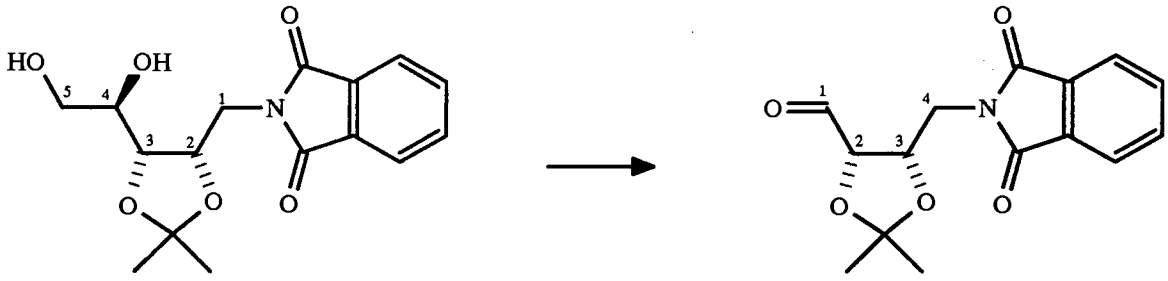
IR ν_{max} 3599 (OH); 3056, 2988, 2938; 1773 and 1716 (C=O, imide)

MS, m/z: 306 (M^+-Me, 7); 161 (22); 160 (33); 59 (100); 43 (40)

δ_H (400 MHz) 1.26 (3H, s, isopropylidene-Me), 1.46 (3H, s, isopropylidene-Me), 3.0 (1H, br.s, -OH), 3.6 (1H, br.s, -OH), 3.73 (1H, dd, J 6.3, 11.9 Hz, H-5), 3.86-3.95 (3H, m, H-4, H-5), 3.92 (1H, dd, J 3.6, 13.8 Hz, H-1), 3.99 (1H, dd, J 9.8, 13.8 Hz, H-1), 4.14 (1H, dd, J 5.8, 8.9 Hz, H-3), 4.62 (1H, ddd, J 3.6, 5.8, 9.8 Hz, H-2), 7.6-7.8 (4H, m, arom.).
δ_C (100 MHz) 25.8 and 27.8 (isopropylidene-Me's); 38.8 (C-1); 64.7 (C-5); 69.5 (C-4); 74.3 (C-2); 76.4 (C-3); 109.5 (isopropylidene-C); 123.3, 132.1 and 133.9 (arom.); 168.5 (imide CO).

Found: C, 59.56; H, 5.92; N, 4.20%
$C_{16}H_{19}NO_6$ requires C, 59.81; H, 5.96; N, 4.36%

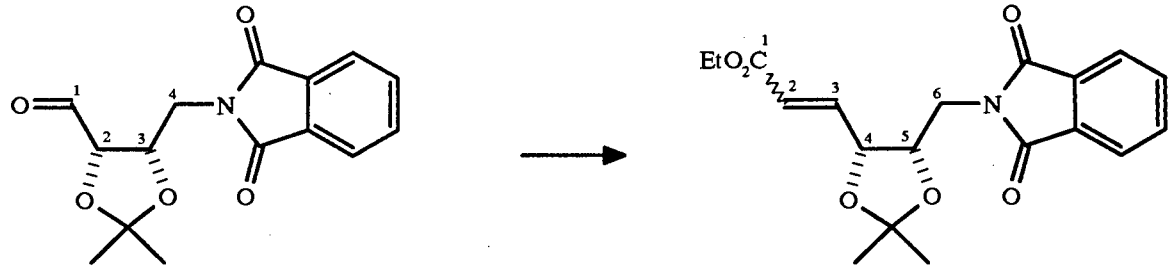
4.2.5. Synthesis of (2S,3S)-4-N-phthalimido-2,3-isopropylidenedioxybutanal **75**



76 **75**

To a solution of 1-phthalimido-2,3-O-isopropylidene-D-ribose **76** (2.0g, 6.23mmol) in ethanol (100ml) was added sodium periodate (2.0g, 9.32mmol) in water (38ml) at 0°C. The solution was stirred for 12h after which time the volume of solvent was reduced *in vacuo* and the crude product was partitioned between water and ethyl acetate. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The volume of solvent was subsequently reduced *in vacuo* to afford crude (2S,3S)-4-N-phthalimido-2,3-isopropylidenedioxybutanal (1.71g, 95% yield) which was used without any further purification.

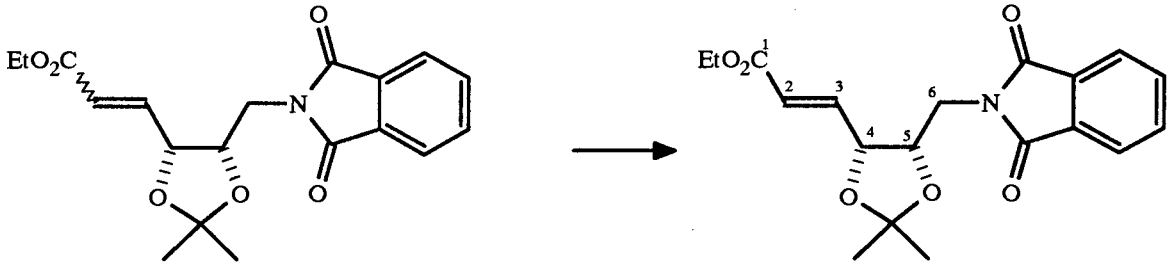
4.2.6. Synthesis of Ethyl-(4**R**,5**S**)-6-N-phthalimido-4,5-isopropylidenedioxyhex-2-enoate **74**



75 **74**

To a solution of (2**S**,3**S**)-4-N-phthalimido-2,3-isopropylidenedioxybutanal (1.71g, 5.9mmol) in dichloromethane (100ml) was added ethoxycarbonylmethylene-triphenylphosphorane (2.46g, 7.08mmol) at 0°C. The mixture was stirred for 3h after which time acetone (10ml) was added in order to quench any unreacted ylide. The volume of solvent was reduced *in vacuo* and the crude product mixture was chromatographed on silica gel (60g) eluting with ethyl acetate/hexane to afford ethyl-(4**R**,5**S**)-6-N-phthalimido-4,5-isopropylidendioxyhex-2-enoate (1.9g, 89% yield).

4.2.7. Isomerisation of ethyl-(4**R**,5**S**)-6-N-phthalimido-4,5-isopropylidenedioxyhex-2-enoate **74**



74

To a solution of ethyl-(4**R**,5**S**)-6-N-phthalimido-4,5-isopropylidendioxyhex-2-enoate (1.0g, 2.77mmol) in dry, deoxygenated benzene (25ml) was added tributyltin hydride (0.78ml, 2.77mmol) and AIBN (25mg, 0.15mmol).

The solution was refluxed for 6h after which time more tributyltin hydride (0.4ml, 1.39mmol) and AIBN (10mg, 0.06mmol) were added and refluxing was continued for another 12h. The volume of solvent was subsequently reduced *in vacuo* and the crude product was chromatographed on silica gel (70g) eluting with ethyl acetate/hexane to give pure ethyl-(*E*)-(4**R**,5**S**)-6-N-phthalimido-4,5-isopropylidenedioxyhex-2-enoate (700mg, 70% yield).

Mpt. 123-124°C (ethyl acetate/hexane)

$[\alpha]_D$ = -110.4° (c = 0.5, $CHCl_3$)

IR ν_{max} 3022; 1774 and 1717 (CO); 1662,1615

MS, m/z: 359 (M^+, 1.2); 344 (M^+-Me, 22); 301 (3.7); 256 (33); 199 (51); 170 (28); 160 (100); 141 (19); 112 (37); 43 (41); 29 (48)

δ_H (400 MHz) 1.28 (3H, t, Et), 1.31 (3H, s, isopropylidene-Me), 1.55 (3H, s, isopropylidene-Me), 3.40 (1H, dd, J 3.3, 13.8 Hz, H-6), 3.79 (1H, dd, J 10.4, 13.8 Hz, H-6), 4.19 (2H, quart., Et), 4.68 (1H, ddd, J 3.3, 6.6 and 10.4 Hz, H-5), 4.86 (1H, ddd, J 1.6, 5.1 and 6.6 Hz, H-4), 6.24 (1H, dd, J 1.6, 15.6 Hz, H-2), 6.93 (1H, dd, J 5.1, 15.6, H-3), 7.66-7.84 (4H, m, arom.).

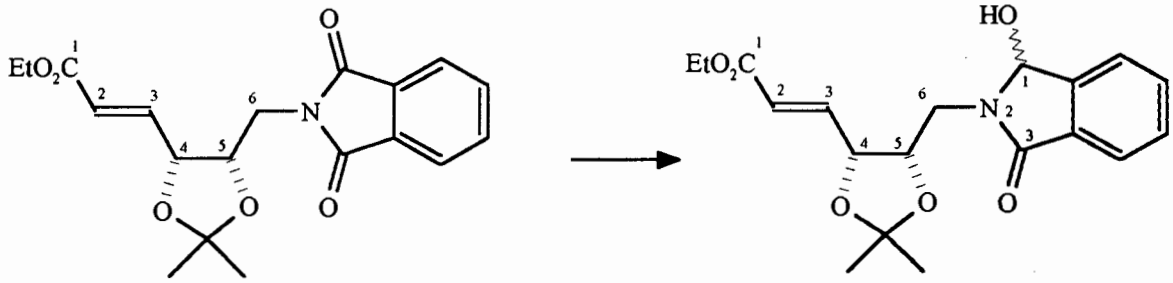
δ_C (100 MHz) 14.2 (Me of Et); 25.7 and 27.7 (isopropylidene-Me's); 39.6 (C-6); 60.7 (CH_2 of Et); 74.5 and 75.9 (C-4 and C-5); 110.0 (isopropylidene-C); 123.3 (arom.); 123.8 (C-2); 132.0 (arom.); 134.0 (arom.); 140.3 (C-3); 165.6 and 168.1 (C=O).

Found: C, 63.28; H, 5.86; N, 3.73%
$C_{19}H_{21}NO_6$ requires C, 63.50; H, 5.89; N, 3.90%

4.2.8. Isomerisation of **74** using $Li^{+}PhS(O\text{-}iPr)_4Ti^{-}$

To a solution of thiophenol (0.08ml, 0.81mmol) in THF (1.5ml) was added a 2.5M solution of n-BuLi in hexane (0.31ml, 0.77mmol) at 0°C. The solution was stirred at that temperature for 15min. after which time titanium (IV) isopropoxide (0.27ml, 0.923mmol) was added at 0°C followed by a solution of **74** (278mg, 0.77mmol) in THF (2ml) 10 min. later at -78°C. The temperature was increased to -30°C over 5h and the solution was kept below -20°C for a further 12h. The reaction was quenched by adding water at -30°C and the product was extracted into ethyl acetate. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and the volume of solvent was reduced *in vacuo*. The crude product mixture was subsequently chromatographed on silica gel (20g) eluting with ethyl acetate/hexane to afford pure E-**74** (136mg, 49% yield).

4.2.9. Synthesis of ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-hydroxy-1-oxoisoindolyl)-4,5-isopropylidenedioxyhex-2-enoate **73**



74 **73**

To a solution of ethyl-(*E*)-(4**R**,5**S**)-6-N-phthalimido-4,5-isopropylidenedioxyhex-2-enoate (780mg, 2.17mmol) in THF (12ml) and MeOH (30ml) was added sodium borohydride (1.07g, 28.2mmol) at -40°C. The reaction temperature was kept below -20°C for 1.5h after which time the reaction was quenched with sat. NH_4Cl solution and the product extracted into EtOAc. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The volume of solvent was reduced *in vacuo* to yield crystalline ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-hydroxy-1-oxoisoindolyl)-4,5-isopropylidenedioxyhex-2-enoate (740mg, 94% yield).

Mpt. 121-126°C (CCl_4/hexane)

$[\alpha]_D$ = -33.6° (c = 0.5, $CHCl_3$)

IR ν_{max} 3557 and 3368 (OH); 1703 (C=O)

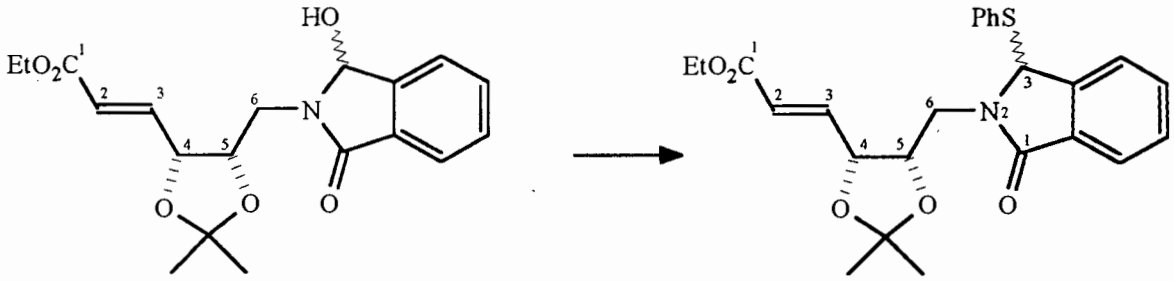
MS, m/z: 361 (M^+, 0.9); 346 (M^+-Me, 7); 285 (17); 199 (22); 163 (41); 162 (56); 133 (100); 43 (29); 29 (39)

δ_H (200 MHz) 1.27 (3H, t, Et), 1.34 (3H, s, isopropylidene-Me), 1.60 (3H, s, isopropylidene-Me), 3.31 (1H, dd, J 10.2, 14.3 Hz, H-6), 3.77 (1H, dd, J 2.5, 14.3 Hz, H-6), 4.16 (2H, quart., Et), 4.59 (1H, ddd, J 2.5, 7.1, 10.2 Hz, H-5), 4.82 (1H, ddd, J 1.6, 5.6, 7.1 Hz, H-4), 6.07 (1H, d, J 9.9 Hz, benzylic-H), 6.15 (1H, dd, J 1.6, 15.6 Hz, H-2), 6.90 (1H, dd, J 5.6, 15.6 Hz, H-3), 7.4-7.8 (4H, m, arom.).

δ_C (50 MHz) 14.2 (Me of Et); 25.4 and 27.8 (isopropylidene-Me); 40.3 (C-6); 60.7 (CH_2 of Et); 76.2 and 77.0 (C-4 and C-5); 82.7 (benzylic-C); 109.8 (isopropylidene-C); 123.4 (arom.); 123.6 (C-2); 129.8, 131.5 and 132.3 (arom.); 141.7 (C-3); 144.0 (arom.); 165.8 and 167.3 (C=O).

Found: C, 62.81; H, 6.42; N, 3.76%
$C_{19}H_{23}NO_6$ requires: C, 63.15; H, 6.42; N, 3.87%

4.2.10. Synthesis of Ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-isopropylidene-dioxyhex-2-enoate **71**



73 **71**

To a solution of ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-hydroxy-1-oxoisoindolyl)-4,5-isopropylidene-dioxyhex-2-enoate (553mg, 1.53mmol) in dichloromethane (12ml) was added thiophenol (0.47ml, 4.60mmol) followed by boron trifluoride etherate (0.56ml, 4.60mmol) which was added dropwise at -78°C. The reaction was stirred for 4h at a temperature below -20°C after which time it was quenched by adding a saturated solution of Na_2CO_3. The crude product was extracted into ethyl acetate, the organic phase washed with brine and dried over anhydrous $MgSO_4$. After the volume of solvent had been reduced *in vacuo*, the crude product was chromatographed on silica gel (40g) eluting with ethyl acetate/hexane yielding ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-isopropylidenedioxy-hex-2-enoate (490mg, 80% yield, based on 70mg recovered starting material) as an oil.

δ_H (400 MHz) major: 1.2-1.4 (6H, m, Me of Et and isopropylidene-Me), 1.50 (3H, s, isopropylidene-Me), 3.41 (1H, dd, J 4.0, 14.2 Hz, H-6), 3.52. (1H, dd, J 10.6, 14.2 Hz, H-6), 4.16 (2H, quart, CH_2 of Et), 4.51 (1H, m, H-5), 4.79 (1H, ddd, J 1.6, 5.2, 6.4 Hz, H-4), 5.82 (1H, s, benzylic-H), 6.18 (1H, dd, J 1.6, 15.6 Hz, H-2), 6.8-7.7 (10H, m, H-3 and arom.).

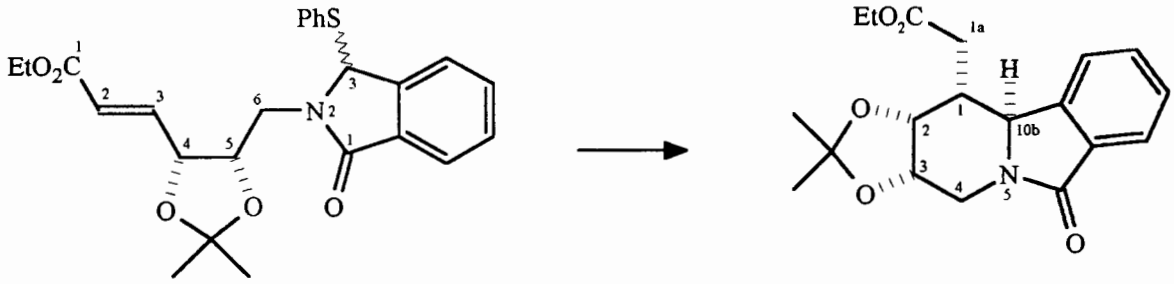
δ_H (400 MHz) minor: 1.2-1.4 (6H, m, Me of Et and isopropylidene-Me), 1.56 (3H, s, isopropylidene-Me), 3.98 (1H, dd, J 2.0, 13.9 Hz, H-6), 4.12-4.18 (1H, m, H-6), 4.25 (2H, quart, CH_2 of Et), 4.48-4.54 (1H, m, H-5), 4.83 (1H, ddd, J 1.6, 5.2 and 6.4 Hz, H-4), 6.04 (1H, s, benzylic-H), 6.23 (1H, dd, J 1.6 and 15.6 Hz, H-2), 6.8-7.7 (10H, m, H-3 and arom.).

δ_C (100 MHz) major: 14.2 (Me of Et); 25.6, and 27.8 (isopropylidene-Me's); 40.4 (C-6); 60.6 (CH_2 of Et); 66.6, 76.1 and 77.4 (benzylic-C, C-4 and C-5); 109.8 (isopropylidene-C); 123.1-135.3 (C-2 and arom.); 140.9 (C-3); 142.7 (arom.); 165.7 and 167.7 (C=O).

δ_C (100 MHz) minor: 14.3 (Me of Et); 25.4 and 27.8 (isopropylidene-Me's); 40.7 (C-6); 60.7 (CH_2 of Et); 68.3, 74.7 and 76.2 (benzylic-C, C-4 and C-5); 109.8 (isopropylidene-C); 123.1-135.3 (C-2 and arom.); 141.4 (C-3); 143.5 (arom.), 165.7 and 167.4 (C=O).

Found: M^+, 453.1591; $C_{25}H_{27}NO_5S$ requires 453.1610

4.2.11. Radical cyclisation of Ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-isopropylidenedioxyhex-2-enoate **71**



71 **89**

To a refluxing solution of ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-isopropylidenedioxyhex-2-enoate (490mg, 1.08mmol) in dry, deoxygenated benzene (30ml) was added a solution of tributyltin hydride (0.44ml, 1.62mmol) and AIBN (10mg, 0.06mmol) in dry, deoxygenated benzene (20ml) dropwise (see chapter 2, table 2). After the disappearance of starting material, the volume of solvent was reduced *in vacuo* and the crude product was chromatographed on silica gel (40g) eluting with ethyl acetate/hexane. The pure product fraction (225mg, 60% yield) was recrystallised from ethyl acetate/hexane yielding (1**R**,2**R**,3**S**,10b,**S**)-1,2,3,10b-tetrahydro-1-carbethoxymethyl-2,3-isopropylidene-dioxypyrido[2,1-a]isoindol-6(4*H*)-one **89** (130mg, 35% overall yield).

Mpt. 149-152°C (ethyl acetate/hexane)

$[\alpha]_D = 26.2°$ (c = 1.074, EtOH)

IR ν_{max} 3053, 2986, 2937; 1730 (ester C=O); 1690 (amide C=O); 1617

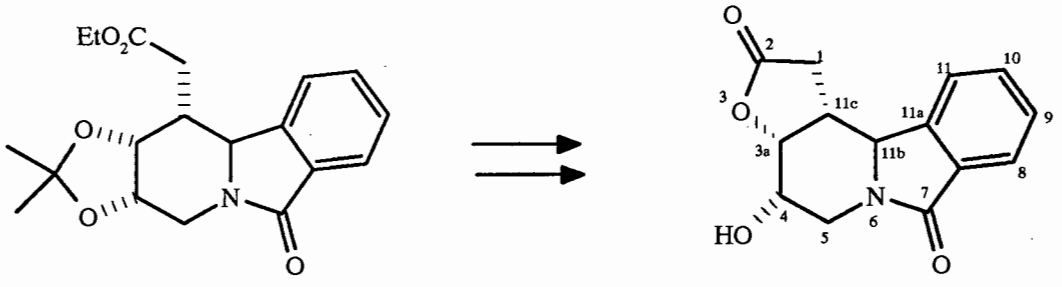
MS, m/z: 345 (M^+, 73) 330 (M^+-Me, 4.5); 287 (44.7); 269 (44.7); 242 (59); 200 (100); 145 (42.5); 132 (24); 43 (99); 29 (37)

δ_H (400 MHz) 1.23 (3H, t, Et), 1.37 (3H, s, isopropylidene-Me), 1.54 (3H, s, isopropylidene-Me), 2.02 (1H, m, J 3.2, 3.2, 6.8 and 11.2 Hz, H-1), 2.88 (1H, dd, J 3.2 and 15.9 Hz, H-1a), 2.93 (1H, dd, J 6.9 and 15.9 Hz, H-1a), 3.32 (1H, dd, J 6.6, 13.8 Hz, H-4), 4.12 (2H, quart., Et), 4.28 (1H, dd, J 6.4, 13.8 Hz, H-4), 4.38 (1H, quart., J 3 x 6.4 Hz, H-3), 4.45 (1H, d, J 11.2 Hz, H-10b), 4.47 (1H, t, J 3.2 and 5.7 Hz, H-2), 7.49 (3H, m, arom.); 7.85 (1H, m, arom.).

δ_C (100 MHz) 14.2 (Me of Et); 25.5 and 27.8 (isopropylidene-Me's); 33.1 (C-1a); 39.8 (C-1); 40.4 (C-4); 56.3 (C-10b); 60.8 (CH_2 of Et); 71.1 (C-3); 74.2 (C-2); 109.2 (isopropylidene-C); 123.3, 124.2, 128.6, 131.2, 132.6 and 144.1 (arom.); 166.9 and 171.2 (C=O)

Found: C, 65.98; H, 6.95; N, 4.02%
$C_{19}H_{23}NO_5$ requires: C, 66.07; H, 6.70; N, 4.05%

4.2.12. Derivatisation of (1**R**,2**R**,3**S**,10b**S**)-1,2,3,10b-tetrahydro-1-carbethoxymethyl-2,3-iso-propylidenedioxypyrido[2,1-a]isoindol-6(4*H*)-one; synthesis of **90**



89 **90**

To a solution of (1**R**,2**R**,3**S**,10b**S**)-1,2,3,10b-tetrahydro-1-carbethoxymethyl-2,3-isopropyl-idenedioxypyrido[2,1-a]isoindol-6(4*H*)-one (98mg, 0.28mmol) in ethanol (10ml) and water (1ml) was added conc. H_2SO_4 (0.04ml, 0.72mmol) and the solution was refluxed for 3h. Potassium hydroxide (121mg, 2.16mmol) was added and the solution was stirred for 12h at room temperature. The pH was adjusted to 8 with hydrochloric acid and the volume of solvent was reduced *in vacuo*. Acetone and acetic acid was added and the solids were filtered off and washed with more acetone and acetic acid. The volume of solvent was reduced *in vacuo* with the acetic acid being azeotroped off with toluene. A portion of the crude product (52mg, 19mmol) was dissolved in THF/CH_2Cl_2 (3:3 ml) and dicyclohexylcarbodiimide (415mg, 2.0mmol) was added. The solution was refluxed for 7h and stirred for a further 12h at room temperature. The solids were then filtered off and washed with hot ethyl acetate. The volume of solvent was subsequently reduced *in vacuo* to afford the crude product which was chromatographed on silica gel (15g) eluting with ethyl acetate/hexane. The yield of (3a**R**,4**S**,11b**S**,11c**R**)-1,2,3a,4,5,11c-hexahydro-4-hydroxy-2(1*H*)-oxofuro[3',2':3,4]pyrido[2,1-a]isoindol-2(1*H*),7(11b*H*)-dione **90** amounted to 25mg (34%).

Mpt. 223-230°C (ethyl acetate/acetone)

$[\alpha]_D$ = 37.1° (c = 0.641, EtOH)

IR ν_{max} 1770 cm^{-1} (CO of lactone); 1700 cm^{-1} (CO of lactam)

MS, m/z: 259 (M^+, 100); 217 (68); 175 (21); 145 (33); 132 (97); 42 (4.7)

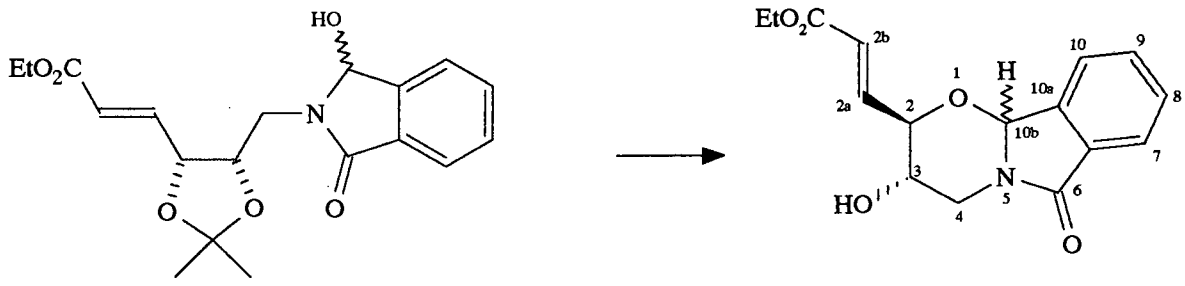
δ_H (400 MHz) acetone-d_6: 2.75 1H, m, J 5.1, 7.2, 8.8 and 9.6 Hz, H-11c); 2.93 (1H, dd, J 5.1, 17.4 Hz, H-1); 3.04 (1H, dd, J 8.8, 17.4 Hz, H-1); 3.42 (1H, dd, J 6.0, 13.3 Hz, H-5); 4.10 (1H, dd, J 4.4, 13.3 Hz, H-5'); 4.25 (1H, m, H-4); 4.69 (1H, d, J 9.6 Hz, H-11b); 4.73 (1H, dd, J 3.0, 7.2 Hz, H-3a); 4.98 (1H, d, J 5.4 Hz, OH); 7.50-7.74 (4H, m, arom.)

δ_C (100 MHz) acetone-d_6: 34.7 (C-1); 40.2 (C-5); 42.8 (C-11c); 59.3 (C-11b); 66.6 (C-4); 80.0 (C-3a); 123.1, 123.9, 129.2, 132.4, 133.0 and 146.7 (arom.); 167.1 and 176.3 (C=O)

Found: C, 64.89; H, 5.14; N, 5.42%

$C_{14}H_{13}NO_4$ requires: C, 64.86; H, 5.05; N, 5.40%

4.2.13. Synthesis of (2**R**,3**S**)-4*H*-2,3-dihydro-2-((*E*)-2-carbethoxyethenyl)-3-hydroxy-[1,3]oxazino[2,3-a]isoindol-6-(10b*H*)-one **80a**



73 **80a**

To a solution of ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-hydroxy-1-oxoisoindolyl)-4,5-isopropylidene-dioxyhex-2-enoate (606mg, 1.68mmol) in ethanol (7ml) was added water (1ml) and conc. H_2SO_4 (0.10ml, 1.8mmol). The solution was refluxed for 12h after which time the reaction was quenched by adding excess Na_2CO_3 solution. The volume of solvent was reduced *in vacuo*, water was added and the product extracted into ethyl acetate. The organic phase

was washed with brine, dried over anhydrous $MgSO_4$ and the volume of solvent was reduced *in vacuo*.

The crude product was chromatographed on silica gel (25g) eluting with ethyl acetate/hexane to yield crystalline (2**R**,3**S**)-4*H*-2,3-dihydro-2-((*E*)-2-carbethoxyethenyl)-3-hydroxy[1,3]oxazino[2,3-a]isoindol-6-(10b*H*)-one (335mg, 66% yield).

Mpt. 170-173°C (ethyl acetate/hexane)

$[\alpha]_D$ = -80° (c = 0.7, $CHCl_3$)

IR ν_{max} 3600, 3410 (OH); 3060, 2980; 1710 (CO); 1660, 1618

MS, m/z: 258 (8.6); 175 (100); 146 (26); 132 (94); 83 (2.1); 29 (7.4)

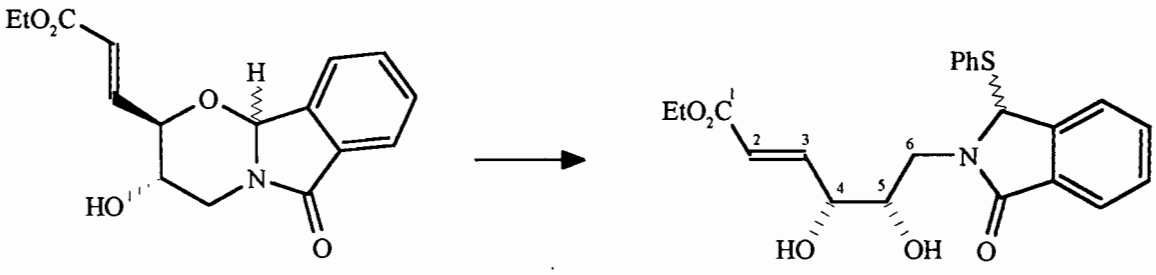
δ_H (400 MHz) DMSO-d_6: 1.20 (3H, t, Et), 3.09 (1H, dd, J 10.1, 12,5 Hz, H-4), 3.22 (1H, ddd, J 5.4, 9.4 and 10.1 Hz, H-3), 4.12 (2H, quart., Et), 4.32 (1H, dd, J 5.4 and 12.5 Hz, H-4), 4.38 (1H, ddd, J 1.7, 4.4 and 9.4 Hz, H-2), 5.79 (1H, d, J 5.6 Hz, OH), 5.94 (1H, s, H-10b), 6.00 (1H, dd, J 1.7, 15.8 Hz, H-2b), 7.01 (1H, dd, J 4.4, 15.8 Hz, H-2a), 7.58-7.74 (4H, m, arom.).

δ_C (50 MHz) 14.1 (Me of Et); 44.3 (C-4); 60.7 (CH_2 of Et); 66.0 (C-3); 79.5 (C-2); 84.5 (C-10b); 122.9, 123.6, 123.8, 130.3, 132.3, 140.3 and 142.9 (C-2a, C-2b and arom.); 166.3 (C=O)

Found: C, 63.46; H, 5.69; N, 4.62%

$C_{16}H_{17}NO_5$ requires: C, 63.34; H, 5.65; N, 4.62%

4.2.14. Synthesis of ethyl-(*E*)-(4**R**,5**S**)-6-(3-phenylthio-1-oxoisoindolyl)-4,5-dihydroxyhex-2-enoate **72**



80a **72**

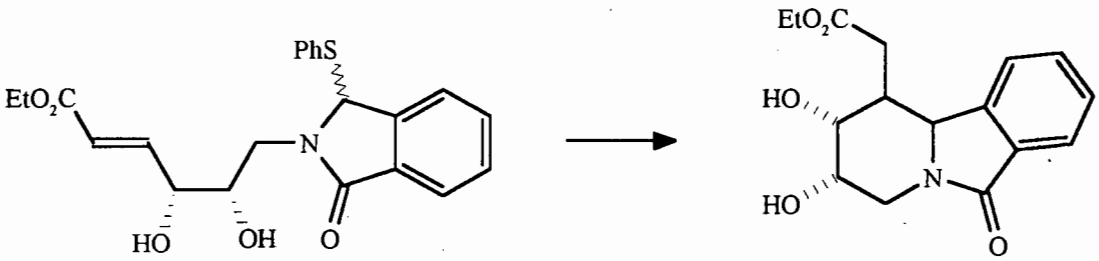
To a solution of (2**R**,3**S**)-4,10b-dihydro-2-((*E*)-2-carbethoxyethenyl)-3-hydroxy[1,3]oxazino[2,3-a]isoindol-6-(10b*H*)-one (214mg, 0.71mmol) in dichloromethane (6ml) was added thiophenol (0.37ml, 3.57mmol), p-toluenesulfonic acid (130mg, 0.75mmol) and excess anhydrous $MgSO_4$ at room temperature. The solution was stirred for 24h at room temperature after which time a saturated solution of Na_2CO_3 was added and the product was extracted into dichloromethane. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and the volume of solvent was reduced *in vacuo*. The crude product fraction was chromatographed on silica gel (20g) eluting with ethyl acetate/hexane to afford pure ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-dihydroxyhex-2-enoate as an oil (128mg, 44% yield) and a pure diastereomer. An uncharacterised oil (125mg) was obtained as a by-product.

δ_H (200 MHz) 1.25 (3H, t, Et); 3.53 (1H, br.s, OH); 3.97 (1H, dd, J 3.1, 14.8 Hz, H-6); 4.05 (1H, m, H-4 and H-5); 4.14 (2H, quart., Et); 4.27 (1H, dd, J 3.6, 14.8 Hz, H-6); 4.83 (1H, br.d, J 4.1 Hz, OH); 6.04 (1H, s, benzylic-H); 6.18 (1H, dd, J 1.8, 15.7 Hz, H-2); 6.95-7.67 (10H, m, H-3 and arom.)

δ_C (50 MHz) 14.2 (Me of Et); 42.0 (C-6); 60.5 (CH_2 of Et); 69.4 (benzylic-C); 71.6 and 74.3 (C-4 and C-5); 122.6, 123.9, 124.6, 128.3, 129.4, 130.0, 131.3, 132.9, 136.1, 144.5 and 147.4 (C-2, C-3 and arom.); 167.8 and 170.9 (C=O)

Found : M^+, 413.1290; $C_{22}H_{23}NSO_5$ requires: 413.1297

4.2.15. Radical Cyclisation of Ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-dihydroxyhex-2-enoate **72**



72

To a refluxing solution of ethyl-(*E*)-(4**R**,5**S**)-6-N-(3-phenylthio-1-oxoisoindolyl)-4,5-dihydroxyhex-2-enoate **72** (92mg, 0.22mmol) in dry, deoxygenated benzene (20ml) was added a solution of tributyltin hydride (0.10ml, 0.33mmol) and AIBN (10mg, 0.06mmol) in dry, deoxygenated benzene (10ml) over a period of 3 h. Refluxing was continued for a further 12 h. After t.l.c. indicated absence of starting material, the volume of solvent was reduced *in vacuo* and the crude product mixture was chromatographed on silica gel (15g). Elution with ethyl acetate/hexane afforded the pure product as an oil (40mg, 60% yield).

^{1}H NMR showed the product to consist of more than one isomer. HPLC analysis indicated a total of three isomers in equal proportions.

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