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Synthetic approaches to tremorgenic indoles

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Synthetic Approaches To Tremorgenic Indoles

by

Carrie-Ann Harrison

A Doctoral Thesis

Submitted in partial fulfilment of the requirements

for the award of

Doctor of Philosophy

of the

Loughborough University of Technology

September 1994

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Abstract

The literature on the synthesis of tremorgenic indoles is reviewed in Chapter 1. These compounds are of great importance to agriculture, especially in New Zealand and the United States of America, as they affect the central nervous system of livestock grazing infected pastures.

The research centres on the synthesis of lolitrem B, a ten ring structure containing a central indole moiety. The central indole moiety is common for all of the tremorgenic indoles.

To this end, studies on the preparation of a *trans*-fused hydrindane system and its incorporation into the central indole moiety are discussed in Chapter 2.

Chapter 3 details investigations into the preparation of a pyrrole from a model used for the hydrindane system. Once obtained, the pyrrole is modified to give the pyranopyrrole, which, in turn, is reacted with dienophiles in Diels-Alder cycloadditions to give substituted indoles.

Utilising the model for the hydrindane, studies on the Fischer indole reaction were undertaken to give substituted indoles. Modification of these led to the synthesis of the left-hand side of paspalitrem B. This work is discussed in Chapter 4.

Preparation of the tetrahydrofuran portion of lolitrem B and incorporation onto the central indole moiety is detailed in Chapters 3 and 4.

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Aq.	Aqueous
BOMCl	Benzyl chloromethylether
b.p.	Boiling point
Bz	Benzoyl
Bu	Butyl
c	concentration
c.	concentrated
ca.	circa
<i>m</i> CPBA	<i>m</i> -Chloroperbenzoic acid
CPTS	Collidinium <i>p</i> -toluenesulfonate
CSA	Camphorsulfonic acid
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
Δ	Heat applied to system
DHP	Dihydropyran
DIBAH	Diisobutyl aluminium hydride
DIPT	Diisopropyl tartrate
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
DMAP	4-Dimethylaminopyridine
Et	Ethyl
eq.	Equivalents
FAM	Formic acid-acetic anhydride mixture
h	hour
HMPA	Hexamethylphosphoramide
<i>hν</i>	Photochemical excitation
IR	Infra red
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LDPB	Lithium 1,2-dimethylpropylborohydride
LHDSA	Lithium hexamethyldisilazide
Me	Methyl
min	minute

MOMCl	Chloromethyl methyl ether
m.p.	Melting point
MVK	Methyl vinyl ketone
NOE	Nuclear Overhauser effect
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
PNB	<i>p</i> -nitrobenzyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
<i>i</i> Pr	Isopropyl
psi	Pounds per square inch
Py.	Pyridine
RT	Room temperature
TBDMSCl	<i>tert</i> -Butyldimethylsilyl chloride
TBDMSOTf	<i>tert</i> -Butyldimethylsilyl trifluoromethanesulfonate
TBSCl	Tributylsilyl chloride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMSCl	Trimethylsilyl chloride
<i>p</i> TSA	<i>p</i> -Toluenesulfonic acid
UV	Ultra violet

CHAPTER 1

Tremorgenic Indoles

1.1 Introduction

The purpose of this research was to synthesise, at least in part, members of a group of natural products known as "tremorgenic mycotoxins", concentrating the efforts on a compound called lolitrem B. These compounds are secondary metabolites, i.e. non-essential metabolites, of microorganisms that cause tremors in livestock if they graze land affected by the toxin-producing organisms.

The most widely studied tremorgenic mycotoxins have been paxilline (*Penicillium paxilli*) first reported by Cole *et al.* in 1974 after isolation from insect-damaged pecans;^{1,2} paspaline, paspalicine, paspalinine and paspalitrems A and B isolated in 1966 by Arigoni *et al.* from the ergot fungus, *Claviceps paspali*;³⁻⁵ and penitrems A-F reported in 1968 by Wilson *et al.* after isolation from cultures of *Penicillium cyclopium*.⁶

A great deal of biosynthetic and biological work has been undertaken on the penitrems by de Jesus and Norris *et al.*⁷⁻¹¹ Tests have shown that penitrem A elicits sustained tremors, incoordination and convulsions in laboratory and farm animals. Pharmacological and biochemical studies indicate that this tremor-causing agent interferes with amino-acid neuro-transmitter-release mechanisms. De Jesus *et al.* have used carbon labelled reagents during the growth of *Penicillium crustosum* cultures to show which intermediates are present during the biosynthesis of the penitrems. This group deduced the absolute chirality of the penitrems by the partial resolution method of Horeau and it is based on their work that subsequent discoveries have been assigned either *R*- or *S*-configuration.¹² This and other relevant work is discussed in a detailed review by Steyn and Vleggaar and it is inappropriate to go into such detail here.¹³

As can be seen from the following structures, all the tremor-inducing agents contain an indole moiety linked to a diterpenoid unit with variations at the C4/C5 positions of the indole.

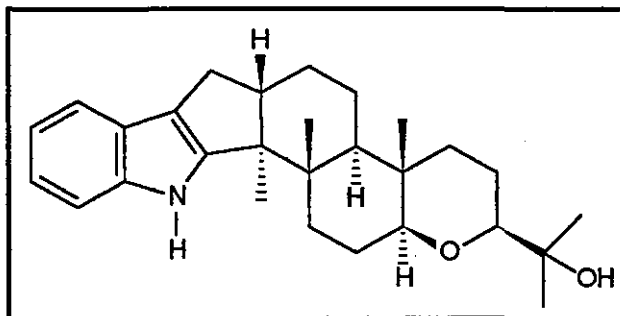


Figure 1: Paspaline - Isolated from *Claviceps paspali* on grass by Arigoni *et al.*, causes Dallis Grass Poisoning.^{3,4}

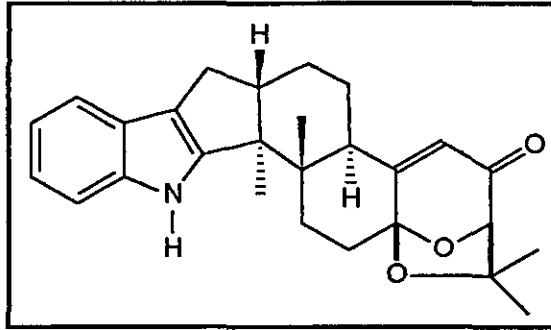


Figure 2: Paspalicine - Isolated from *Claviceps paspali* on grass by Arigoni *et al.*, causes Dallis Grass Poisoning.^{3,4}

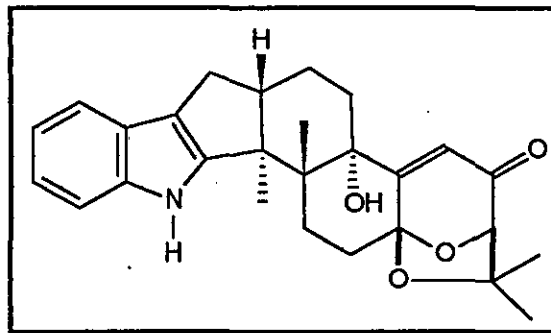


Figure 3: Paspalinine - Isolated from *Claviceps paspali* on grass by Arigoni *et al.*, causes Dallis Grass Poisoning.^{3,5}

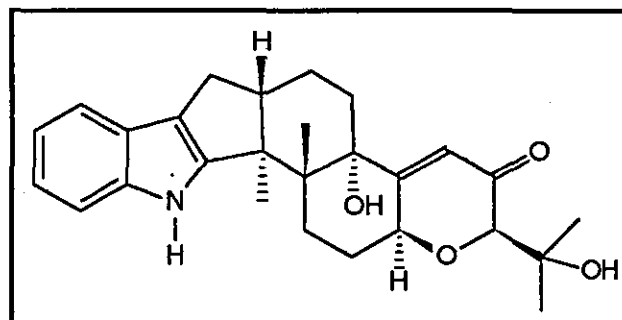


Figure 4: Paxilline - Isolated from *Penicillium paxilli* on insect-damaged pecans by Cole *et al.*, causes severe tremors.¹

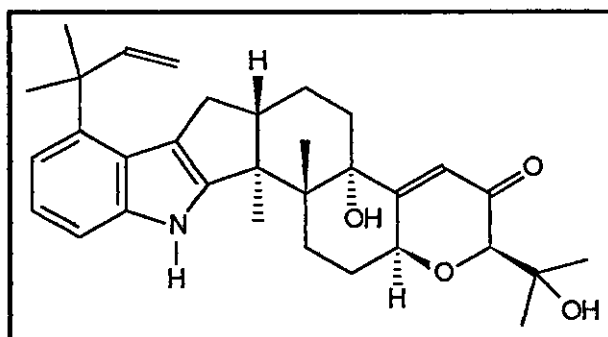
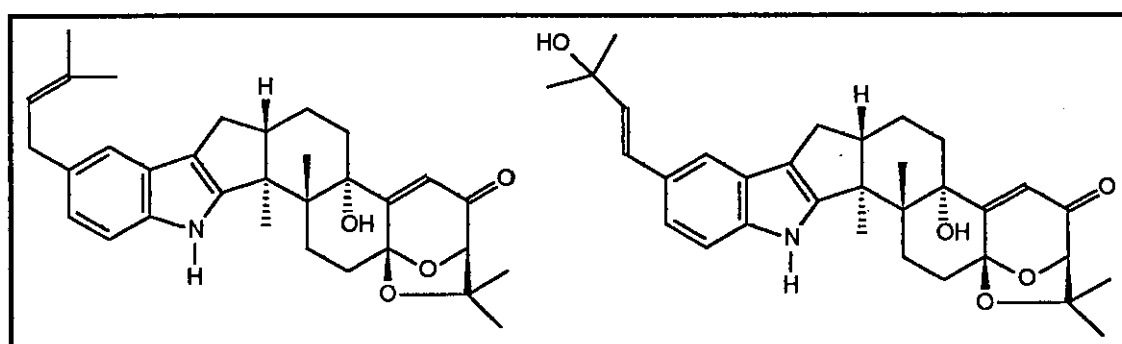


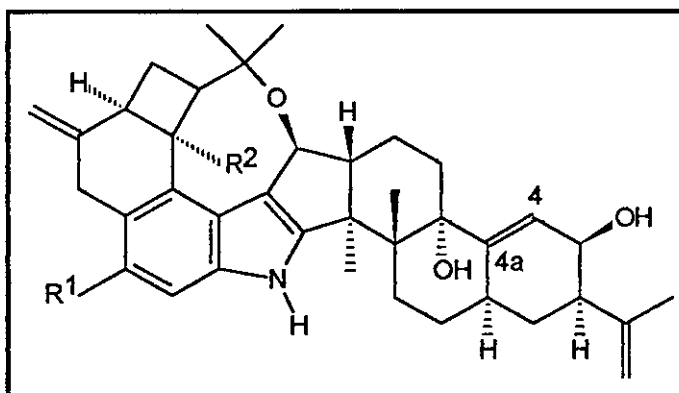
Figure 5: Aflatoxin B₁ - Isolated from *Aspergillus flavus* on potatoes, corn, millet and rice by Wilson *et al.*, causes tremors.^{14,15}



Paspalitrems A

Paspalitrems B

Figure 6: Paspalitrems A & B - Isolated from *Claviceps paspali* on grass by Cole *et al.*, causes Dallis Grass Poisoning.¹⁶



- A: $R^1 = \text{Cl}$, $R^2 = \text{OH}$; 4 α ,4a α -epoxide
 B: $R^1 = R^2 = \text{H}$; 4 α ,4a α -epoxide
 C: $R^1 = \text{Cl}$, $R^2 = \text{H}$
 D: $R^1 = R^2 = \text{H}$
 E: $R^1 = \text{H}$, $R^2 = \text{OH}$; 4 α ,4a α -epoxide
 F: $R^1 = \text{Cl}$, $R^2 = \text{H}$; 4 α ,4a α -epoxide

Figure 7: Penitrems A-F - Isolated from *Penicillium cyclopium* on silage and maize by Wilson *et al.*, causes tremors.⁶

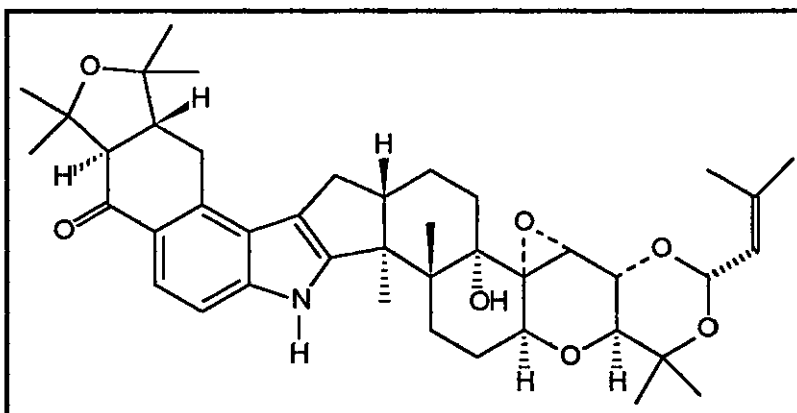


Figure 8: Lolitrem B - Isolated from *Acremonium lolli* on perennial ryegrass by Gallagher *et al.*, causes Ryegrass Staggers.¹⁷⁻¹⁹

Lolitrem B is produced by fungus which grows on perennial ryegrass (*Lolium perenne* L) and gives rise to a disorder known as "Perennial Ryegrass Staggers"²⁰ - a nervous disorder affecting grazing sheep, cattle, horses and deer, whose symptoms include severe incoordination and hypersensitivity to external stimuli. A remarkable feature of the disorder is the consistent lack of specific lesions in severely affected animals and the eventual complete recovery and return to normality of such intoxicated animals.¹⁸ It is of

considerable importance to the agriculture of Australia and New Zealand and occasional outbreaks have been reported in the UK - interestingly the dry weather experienced in the summer of 1991 in the UK was blamed for the increase in the number of cases of tremorgenic mycotoxicosis in both cattle and sheep.²¹

The structural elucidation of lolitrem B was reported by Gallagher *et al.* in 1984 and was based on its high-field ^1H and ^{13}C NMR spectra.¹⁸ The derived structure has twelve chiral centres in an array of ten fused rings (Figure 9).

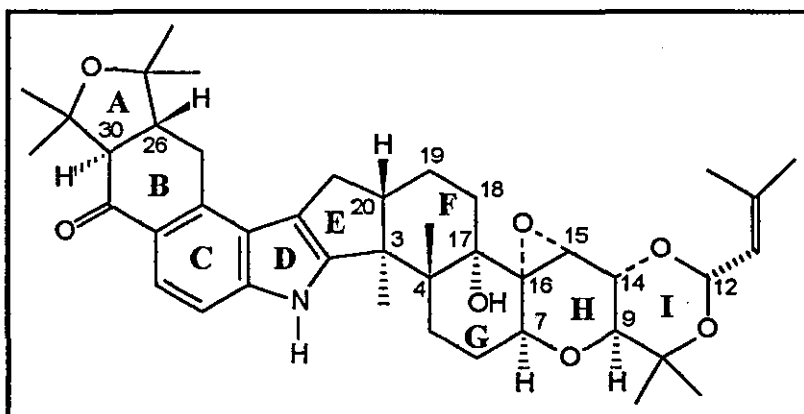


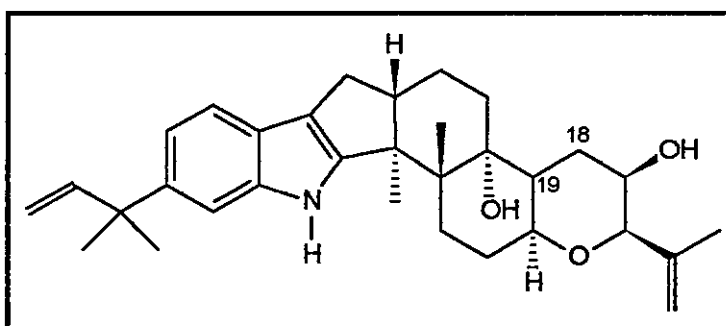
Figure 9: Lolitrem B showing important numbered centres and ring letters.

Lolitrem B, $\text{C}_{42}\text{H}_{55}\text{NO}_7$, has a melting point of 303-304°C. A major mass spectral fragmentation arises through cleavage of the C3-C4 and C18-C19 bonds with hydrogen transfer to the indole containing fragment, leading to an abundant ion at m/z 348. The IR spectrum shows the presence of OH and NH groups and a carbonyl absorption at 1664 cm^{-1} . The UV absorptions at 267 (ϵ 26 800) and 290 nm (ϵ 6 700) indicate a 2,3-disubstituted indole nucleus with a carbonyl group in conjugation with the aromatic ring. Various proton NMR experiments established the (^1H , ^1H) connectivity pattern of lolitrem B.

The relative configuration of lolitrem B was determined from proton-proton coupling constants and proton-proton NOE's. The relative configurations at C3, C4, C7, C15, C16, C17 and C20 are the same as the penitrems - as determined by the partial resolution method of Horeau.¹² The nuclear Overhauser effect between 9H and 7H shows that 9H is *cis* to 7H and the *trans* configuration of 9H and 14H is based on the fact that no NOE is observed between these protons and the vicinal (H,H) coupling constant is 9.5 Hz. This indicates that rings H and I are *trans* fused and 14H being on β face of the molecule indicates that C14 must have the *R*-configuration. The relative configuration at C12 was established by the NOE observed between 14H and 12H. In comparison to the penitrems and subsequent

synthetic work it follows that C3 must have the *S*-configuration. The *trans*-fusion of rings A-B was deduced from the coupling (J 14.3 Hz) for 26H and 30H. The relative and absolute configuration of these two chiral centres has recently been verified as 26 β , 30 α .²²

New members of this family of mycotoxins are continually being isolated, for example; sulfinines A-B, secopenitrem B and 14-(*N,N*-dimethyl-L-valyloxy)paspalinine (Figures 10-12).²³⁻²⁵



Sulfinine A: 18-19 = α epoxide

Sulfinine B: 18-19 = olefin

Figure 10: Sulfinine A & B - Isolated from *Aspergillus sulfureus* on corn kernels by Gloer *et al.*, is an antiinsectant.^{23,24}

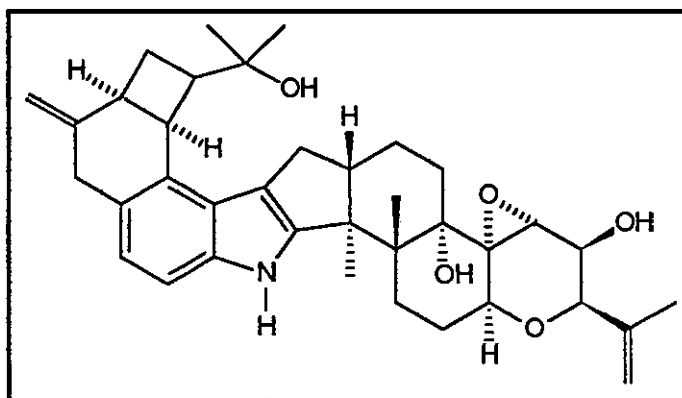


Figure 11: Secopenitrem B - Isolated from *Aspergillus sulfureus* on corn kernels by Gloer *et al.*, is an antiinsectant.^{23,24}

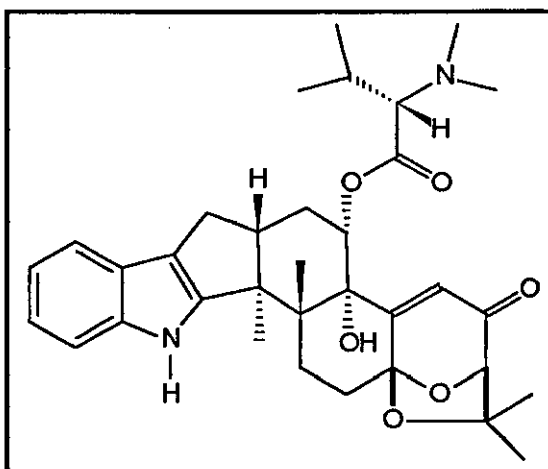


Figure 12: 14-(*N,N*-Dimethyl-*L*-valyloxy)paspalinine - isolated by Gloer *et al.*, is an antiinsectant.²⁵

The reason for synthesising tremorgenic indoles is that they have a marked effect on the agriculture of New Zealand and parts of the USA, as the main pasture of these areas is contaminated by toxin-producing endophytes. Problems that these toxins cause include weight loss of livestock, low fertility and tremors. With the upsurge of consumer concern about diseases of the central nervous system (i.e. tremors) it is essential to eradicate such disorders from livestock and this can be tackled in a variety of ways:

- 1) Immunise livestock,
- 2) Genetically engineer livestock that are immune to the toxins,
- 3) Genetically engineer pasture that does not support the mycotoxins,
- 4) Replace infected pasture.

However, there is still discussion as to which part of the molecules cause toxicity, so a synthetic route which will allow selective modification at all stages will be invaluable in the search for the specific section of the molecule, and will allow the agricultural governing bodies to decide on the best mode of action to confront the problem.

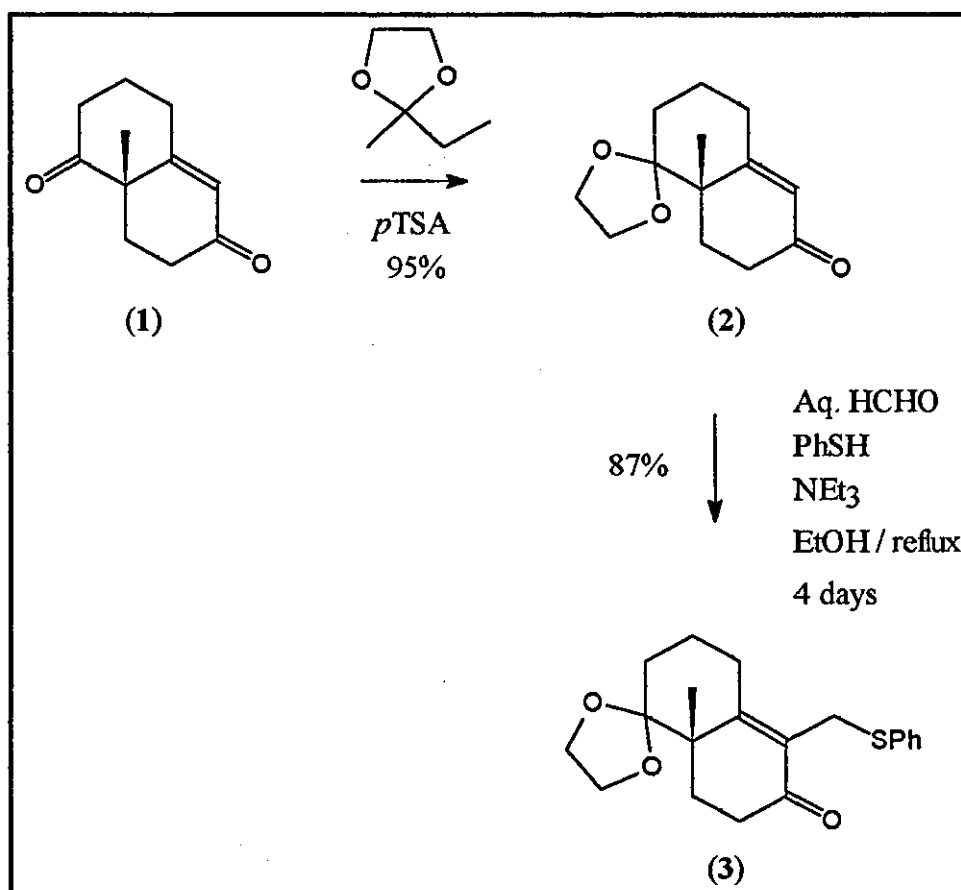
It was decided to concentrate our efforts on lolitrem B as no work has been published on the synthesis of the left-hand portion of this compound and, at the outset of the work the absolute configuration at C26 and C30 was unknown. As the absolute configuration at C3 was known, it was hoped that a synthesis of the left-hand portion of lolitrem B would allow determination of the absolute configuration at C26 and C30, however, in March 1994, a group in New Zealand deduced the absolute configuration at these centres.²²

1.2 Synthetic Approaches

1.2.1 The total synthesis of (-)-paspaline

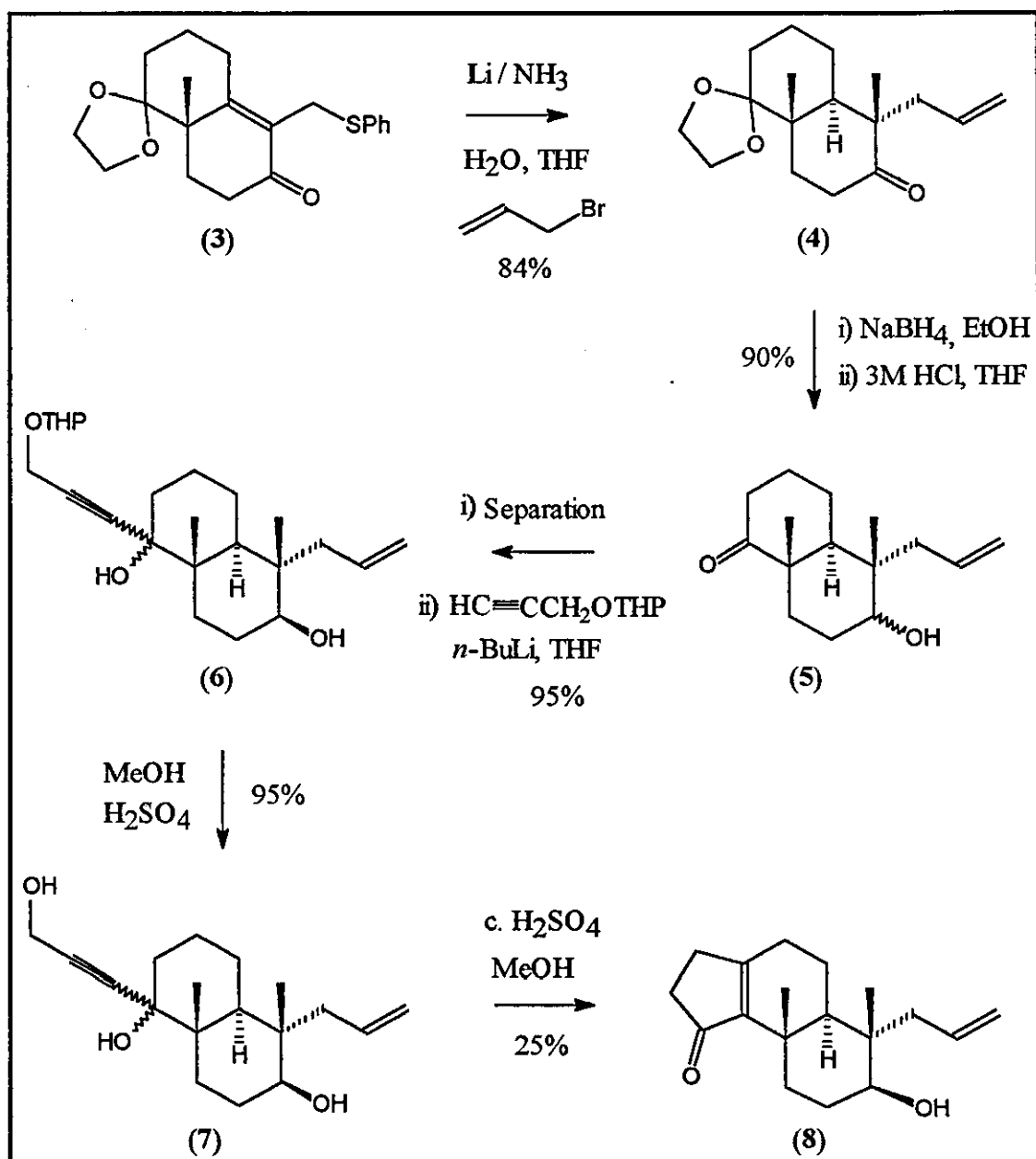
The first reported total synthesis of a tremorgenic mycotoxin was that of (-)-paspaline by Smith *et al.*^{26,27} in 1985 and involved 23 steps from the Wieland-Miescher ketone.^{28a-b} The synthesis is discussed below:-

(+)-Wieland-Miescher ketone (1) was prepared via the Hajos-Eder protocol and chemoselective transketalization of this species led to enone (2).^{28a-b,29} Treatment of the enone (2) with aqueous formaldehyde, thiophenol and triethylamine in ethanol gave the alkylated product (3) (Scheme 1).



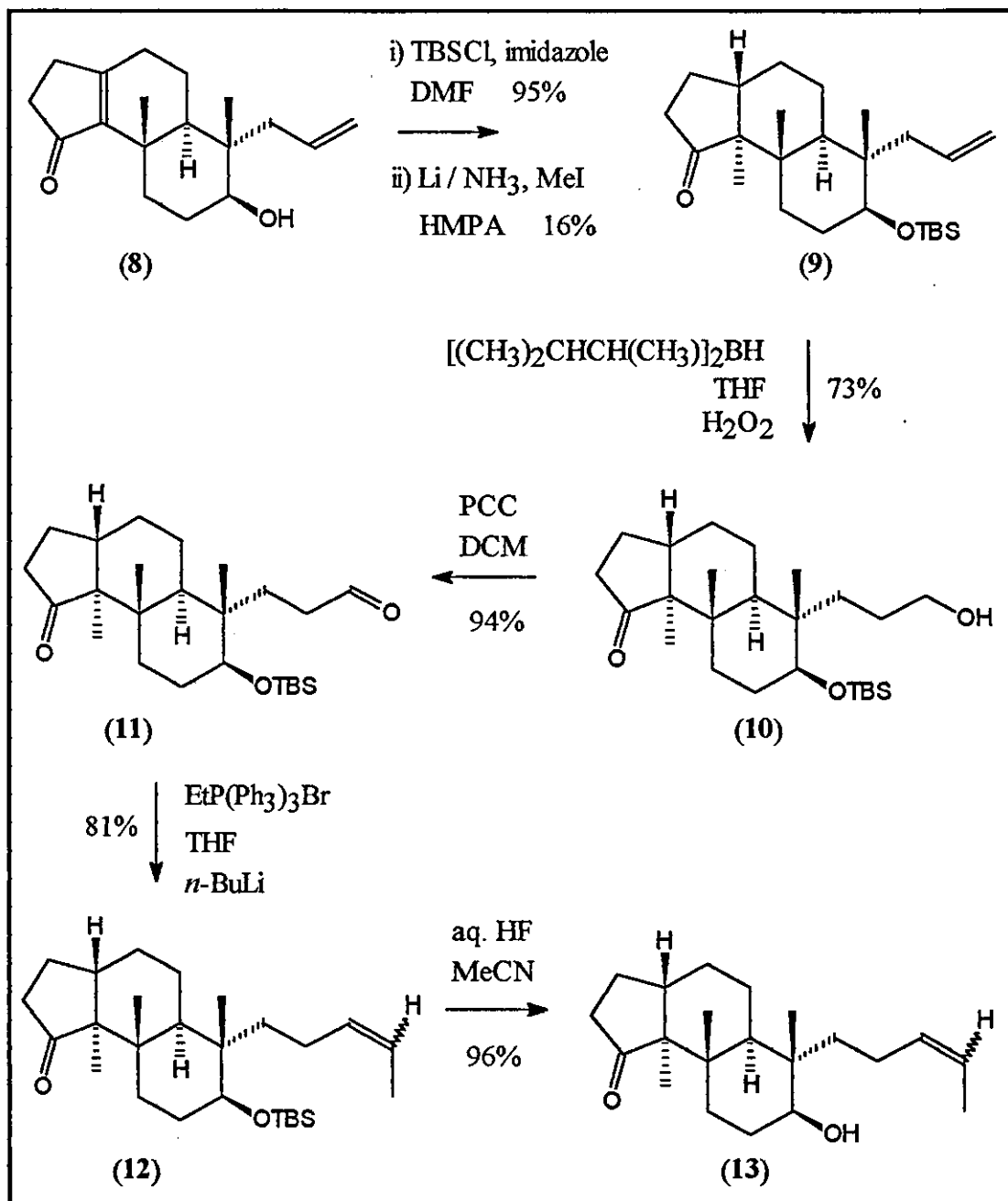
Scheme 1

Reductive alkylation of enone (3) with lithium in liquid ammonia and allyl bromide gave the ketone (4) (Scheme 2). Carbonyl reduction with sodium borohydride followed by deketalization gave a mixture of alcohols (5) which were separated by flash chromatography. The *S*-alcohol was treated with the lithium anion derived from the tetrahydropyranyl ether of propargyl alcohol to give a mixture of alkynes (6). Acidic hydrolysis of the protecting ether led to a mixture of triols (7) which cyclised upon more forcing acidic conditions to give the enone (8).³⁰



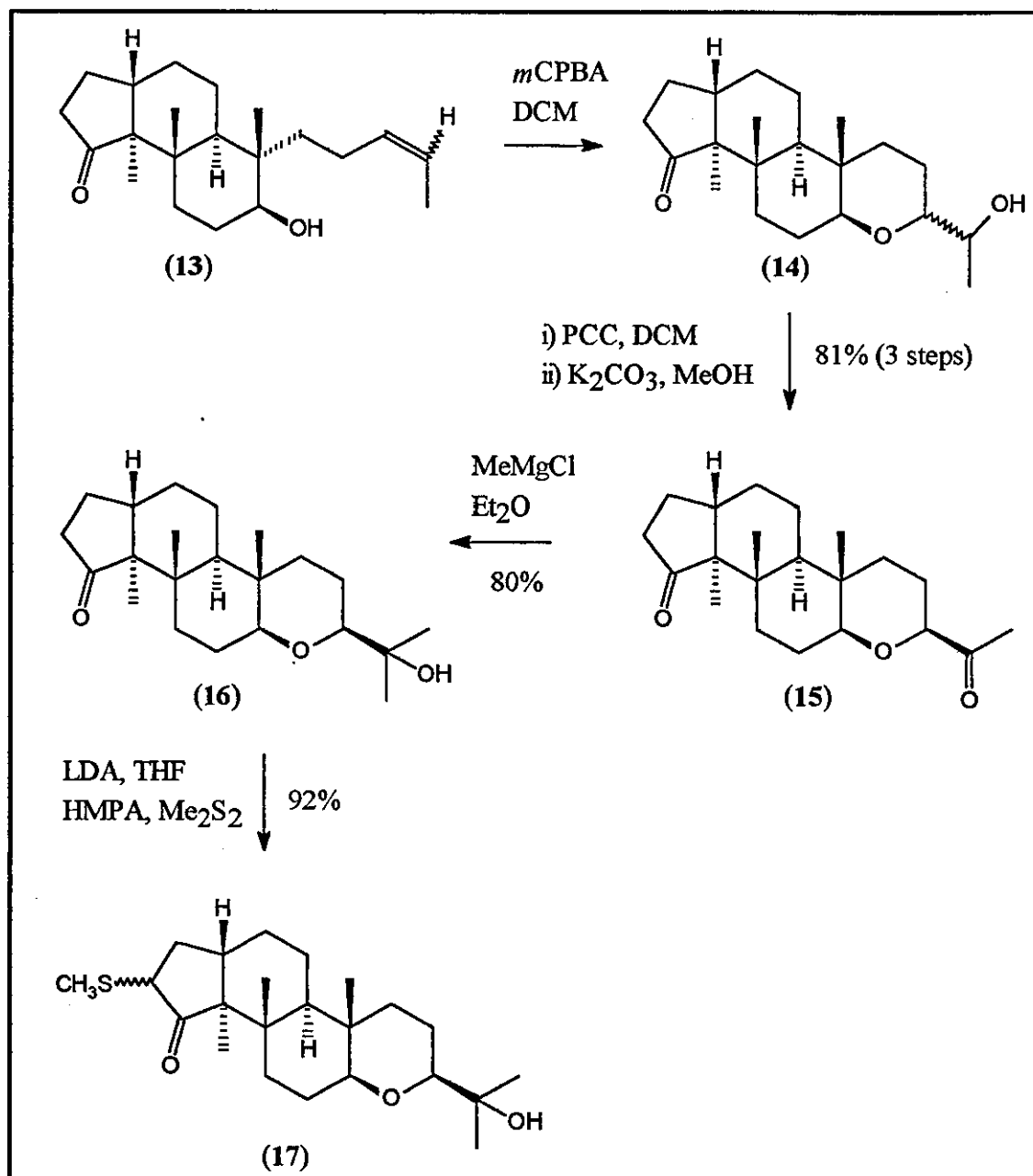
Scheme 2

Protection of the alcohol using chlorotributylsilane followed by reductive methylation of the enone double bond gave ketone (9). Hydroboration with disiamylborane followed by oxidation with hydrogen peroxide afforded the alcohol (10). Oxidation of the alcohol using pyridinium chlorochromate gave the aldehyde (11). Wittig reaction of the aldehyde (11) with (ethyl)triphenylphosphonium bromide gave the alkene (12). Acidic hydrolysis of the silyl ether gave the alcohol (13) (Scheme 3).



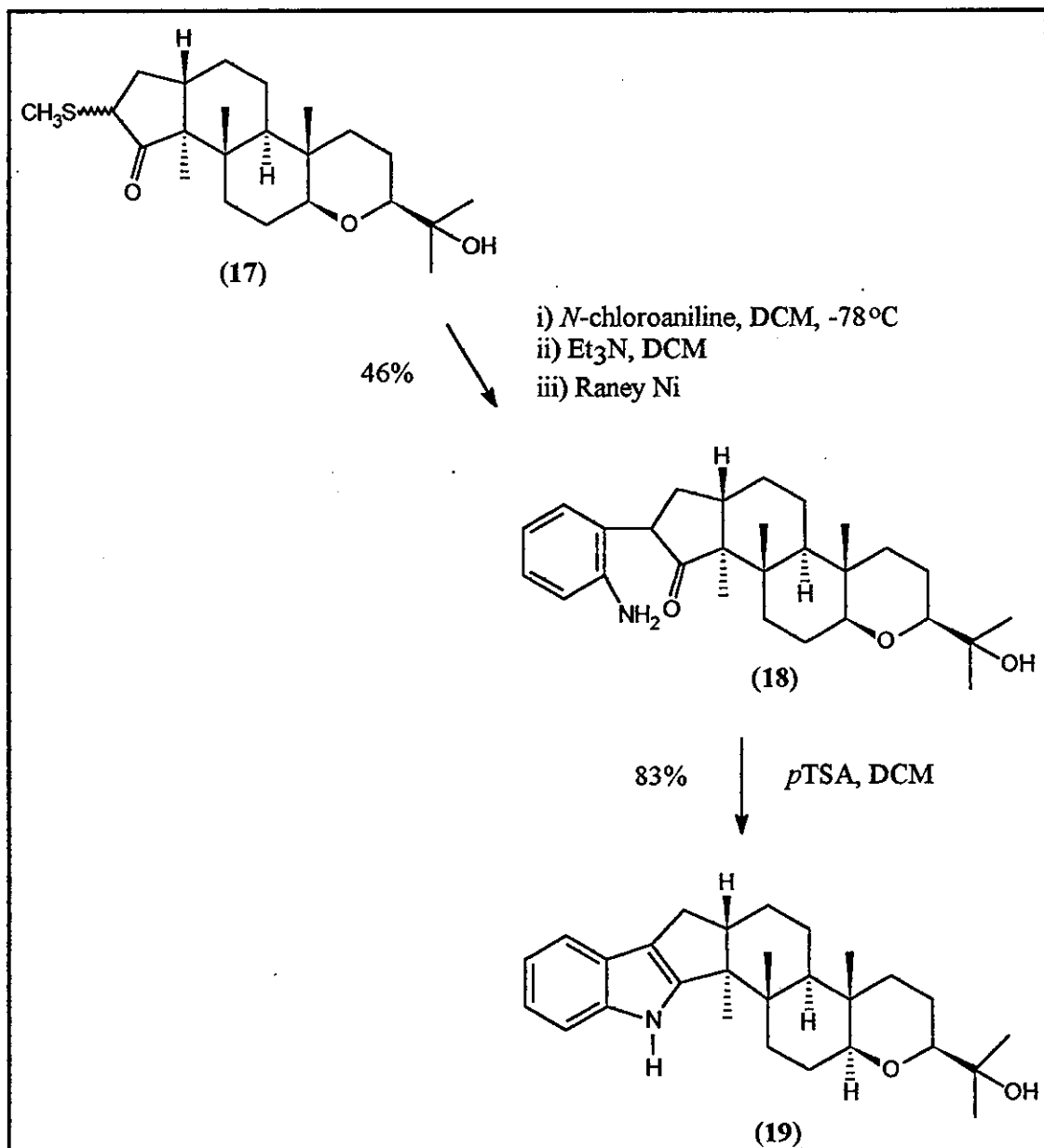
Scheme 3

Treatment of olefin (13) with *m*-chloroperbenzoic acid afforded a mixture of pyranyl alcohols (14). Oxidation of (14) using pyridinium chlorochromate followed by equilibration with base gave the diketone (15). Treatment with methylmagnesium chloride gave the tertiary alcohol (16). Construction of the indole portion of the nucleus was achieved via the Gassman procedure.³¹ The ketone (16) was treated with lithium diisopropylamide and alkylated with dimethyldisulfide to give the β -keto sulfide (17) (Scheme 4).



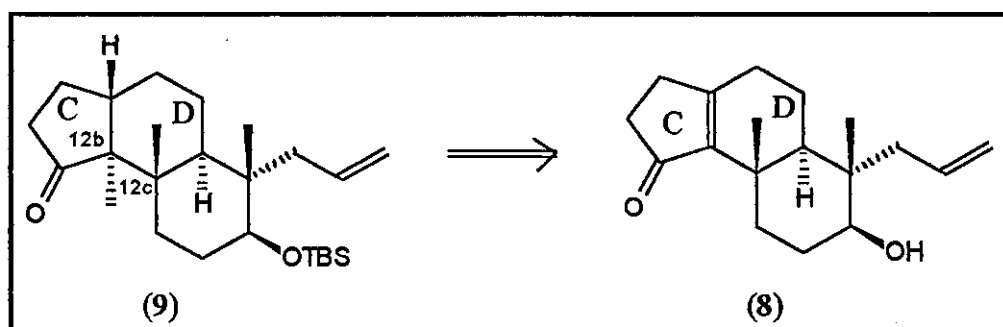
Scheme 4

The first bond of the indole was then formed via a [2,3]-sigmatropic rearrangement of the intermediate sulfur ylide, derived by reaction of *N*-chloroaniline with the β -keto sulfide (17) in the presence of triethylamine. Reductive desulfurization using Raney nickel gave the aniline (18). Acid catalysed cyclisation gave the target molecule (-)-paspaline (19) in an overall yield of 0.003% after 24 steps (Scheme 5).



Scheme 5

As can be seen from the above synthesis the cornerstone of the strategy was the reductive alkylation of enone (8) to (9) (Scheme 6).



Scheme 6

This transformation not only established the required *trans* C/D ring fusion but also introduced a quaternary methyl substituent at C12b *trans* to the vicinal methyl C12c, which is the key architectural feature of this class of compounds. However, the first attempt at this methylation via alkylation of the lithium enolate with methyl iodide at -78°C led to the new methyl group being disposed *cis* to the original methyl group which was not the desired transformation. The modification of the usual reductive process adopted above, i.e. inverse addition of the enolate to a solution of methyl iodide-HMPA at 50°C , led to a 2:1 mixture of *cis:trans* ketones in 50% yield which were separable by flash chromatography.

It is evident that this step requires optimisation or a different approach for the introduction of the C12b methyl group needs to be developed.

1.2.2 The indole nucleus of the tremorgenic indoles

Smith *et al.* next turned their attention to the introduction of the indole nucleus at an earlier stage in the synthesis.^{32,33} In conjunction with this strategy, they devised a different route to the *trans* fused hydrindane system. The object of their studies was the model compound shown in Figure 13, which would give the central portion of the tremorgenic indoles.

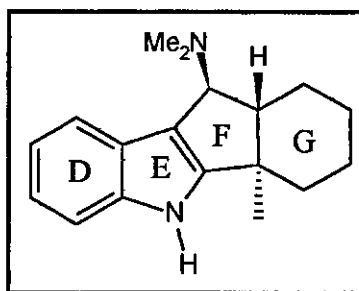
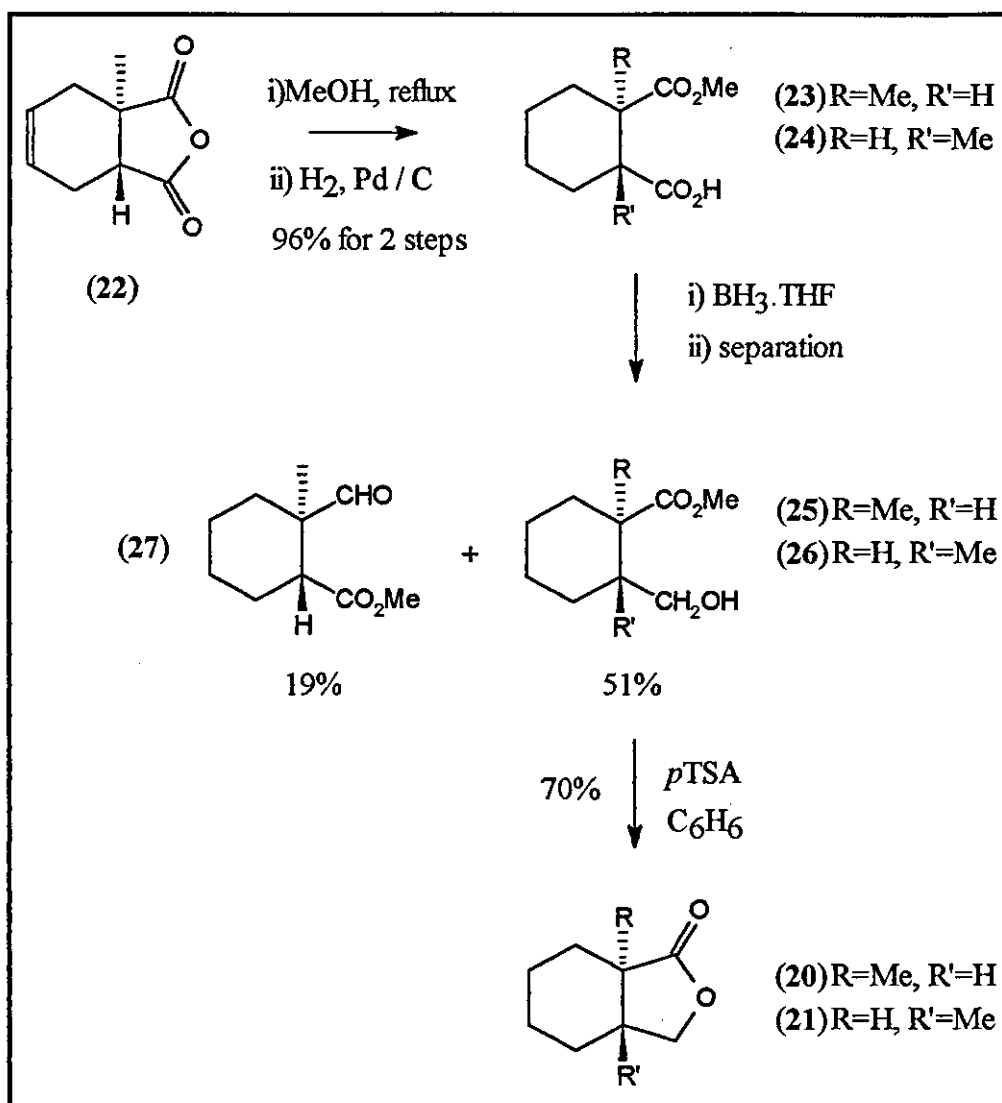


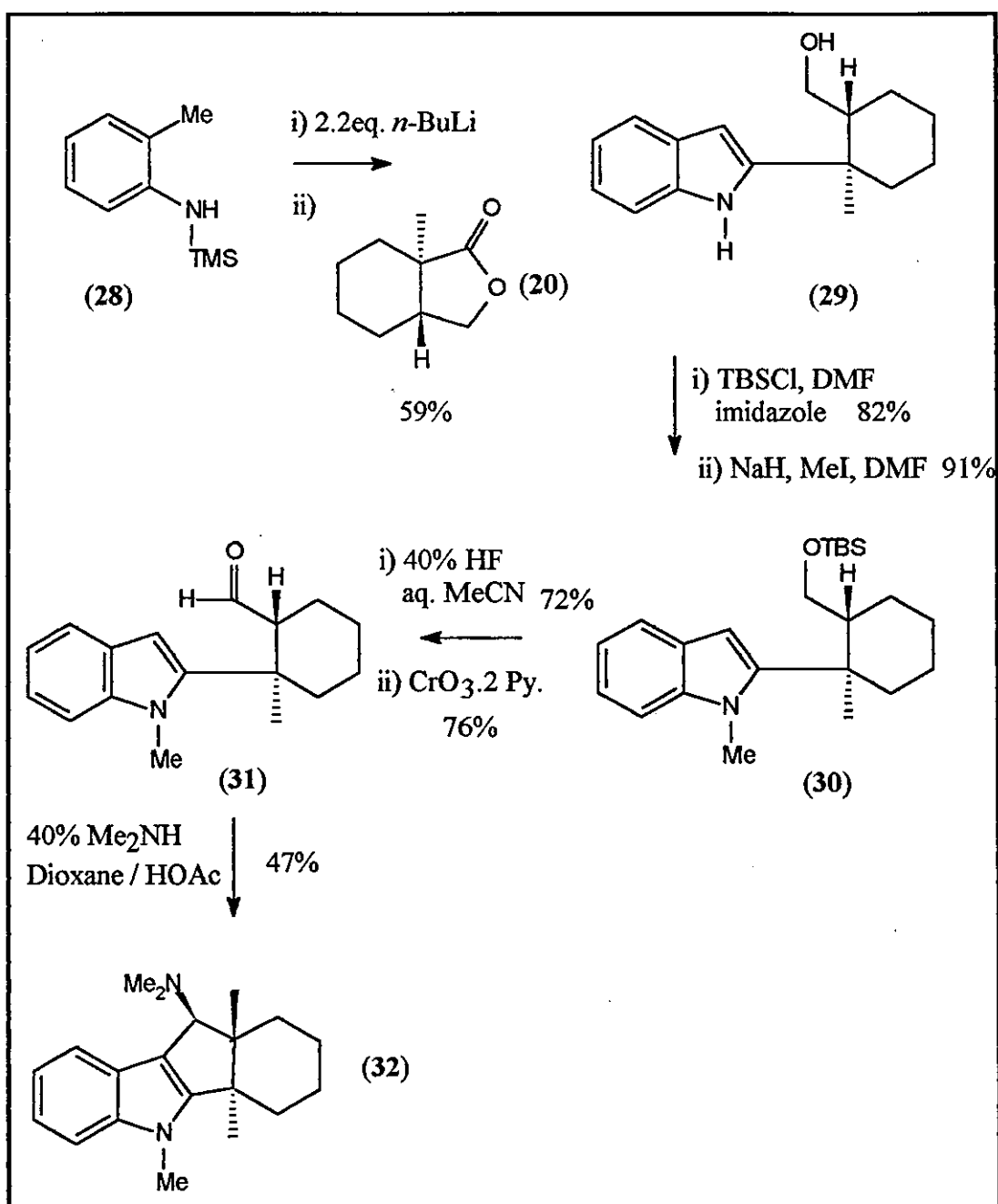
Figure 13: Central portion of the tremorgenic indoles.

The synthesis starts with the lactone (20) which was prepared from the anhydride (22) in 3 steps (Scheme 7). Methanolysis of the anhydride (22) gave a mixture of half esters which, without separation, were hydrogenated to give a 1:1 mixture of (23) and (24). Subsequent reduction with borane-tetrahydrofuran complex gave the hydroxy esters (25) and (26) plus the aldehyde (27). These were separated by flash chromatography and individual lactone formation under acidic conditions gave (20) and (21) from (25) and (26) respectively.



Scheme 7

Addition of the lactone (20) to the organolithium reagent derived from *N*-trimethylsilyl-*o*-toluidine (28) gave the indole (29). Protection of the alcohol was achieved using chlorotributylsilane and the indole nitrogen was methylated using methyl iodide and sodium hydride in tetrahydrofuran giving indole (30). Silyl ether hydrolysis followed by Collins oxidation afforded the aldehyde (31). Treatment of the aldehyde with dimethylamine in hot acetic acid (i.e. Mannich conditions) gave a single crystalline compound (32). The overall yield for the indole (32) was 19% for 5 steps (Scheme 8).



Scheme 8

This novel indole synthesis allows functional diversification at the C2 position of the indole nucleus with complete regio- and stereocontrol. Incorporation of the hydrindane into this route gives a model for the central portion of this class of compounds.

1.2.3 Synthesis of an indole-oxocane

Smith and co-workers investigated the synthesis of rings A-F of penitrem D (Figure 14) incorporating the routes described above.^{34,35}

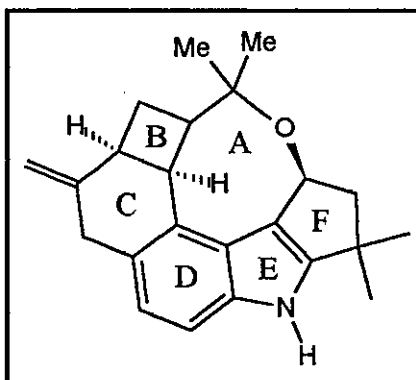
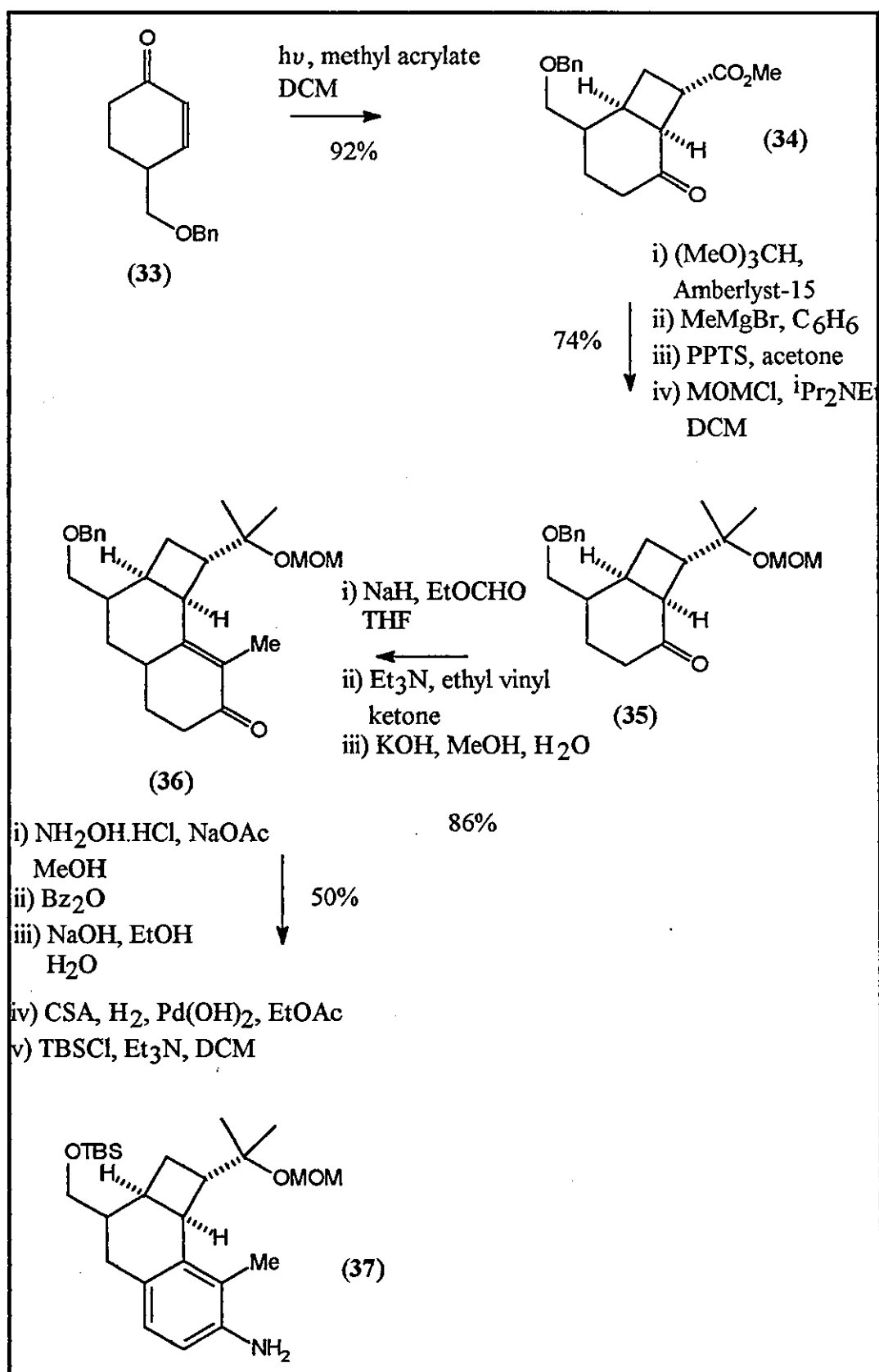


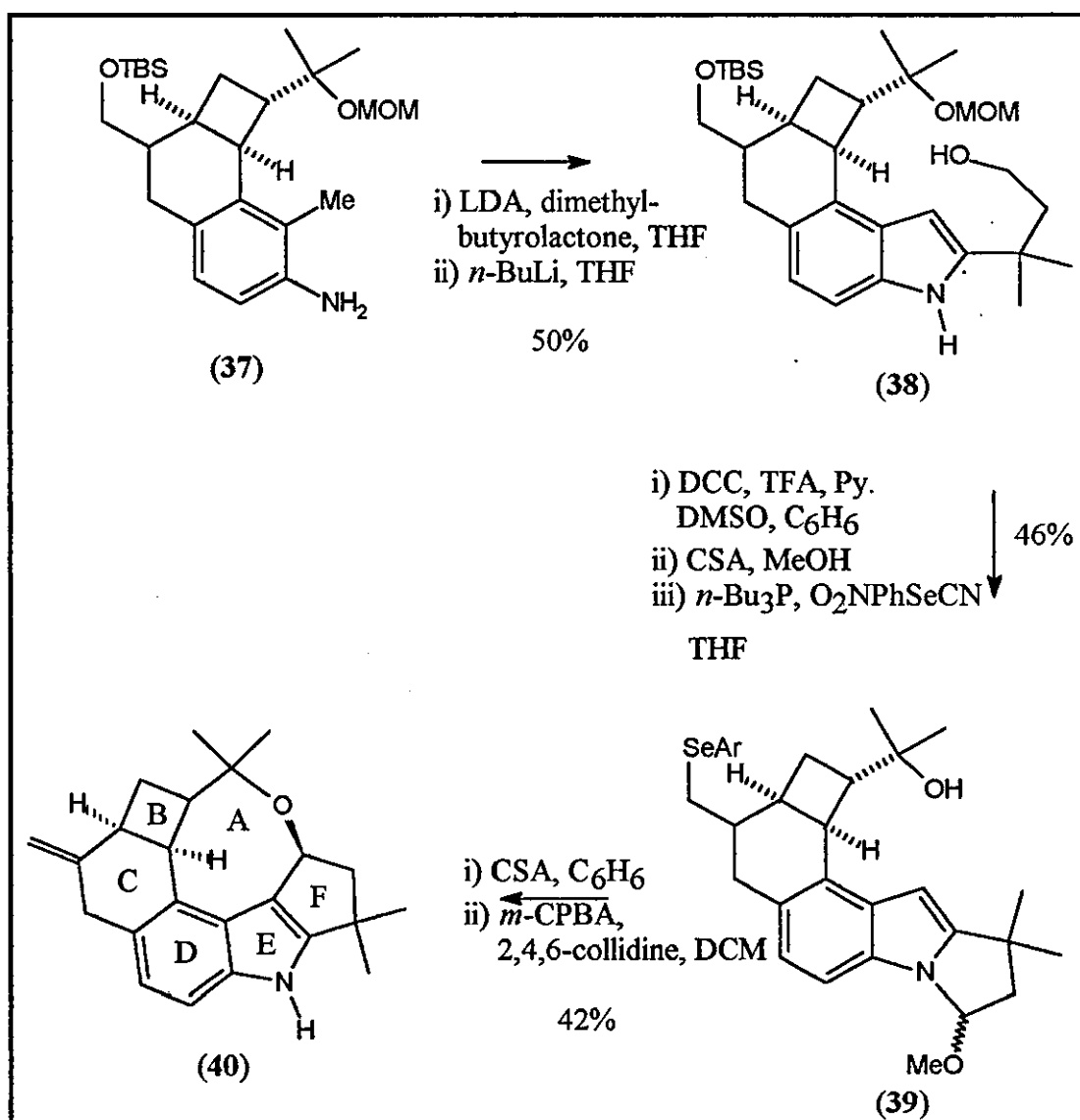
Figure 14: Rings A-F of Penitrem D.

The synthesis starts with the enone (33), itself prepared from 3-ethoxy-2-cyclohexenone via the method of Stork and Danheiser.³⁶ Irradiation of the enone (33) in the presence of excess methyl acrylate (DCM, uranium filter, 4°C) produced a mixture of photoproducts, of which (34) was the major product (Scheme 9). The mixture was subjected to the following sequence:- ketalization with trimethylorthoformate and Amberlyst-15, followed by treatment with excess methylmagnesium bromide and then deketalization with pyridinium *p*-toluenesulfonate in acetone and protection of the alcohol using chloromethyl methyl ether to give, after chromatographic separation, the ketone (35). Robinson annulation as modified by Woodward gave the enone (36).³⁷ The corresponding oxime was formed by reaction of the enone (36) with hydroxylamine hydrochloride and sodium acetate in methanol and then aromatisation by refluxing with benzoic anhydride in xylene. Basic hydrolysis of the resulting benzamide followed by conversion of the benzyl ether to the tributylsilyl ether gave the aniline (37). The change of protecting group was necessary as it was found that the benzyl ether was too labile under the conditions subsequently used for formation of the indole.



Scheme 9

The aniline (**37**) was acylated with dimethylbutyrolactone and then treated with *n*-butyl lithium to give the indole (**38**). The primary alcohol was oxidized to the aldehyde under Moffatt conditions and the protecting groups were removed under acidic conditions which also caused concomitant cyclisation to the pentacyclic system. The primary alcohol was selectively selenated using 2-nitrophenyl selenocyanate and *n*-tributylphosphine in tetrahydrofuran to give indole (**39**). Treatment of the indole with camphorsulfonic acid followed by *m*-chloroperbenzoic acid and 2,4,6-collidine gave the target molecule, rings A-F of penitrem D (**40**) (Scheme 10).



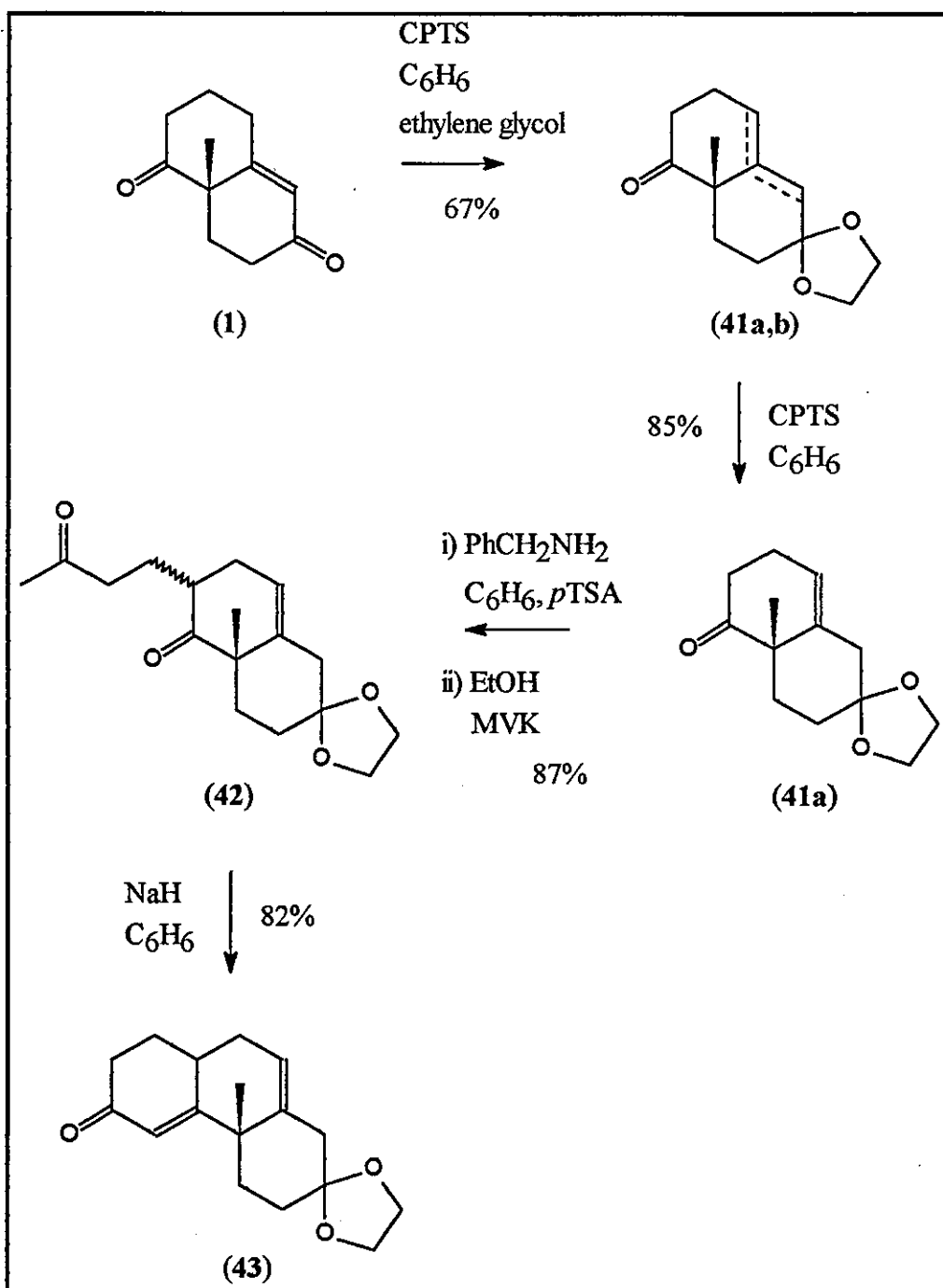
Scheme 10

This work showed the viability of Smith's novel route to the indole nucleus and its use in the formation of an oxocane system as in penitrem D. To date he has not published a total synthesis of penitrem D or indeed any syntheses of the tremorgenic mycotoxins using this indole route. He has however, published a route to rings G-I of penitrem D starting with the Wieland-Miescher ketone³⁸ and improved his route to the *trans* fused hydrindane system to give 32% yield of the desired isomer *en route* to a total synthesis of (+)-paspalicine and (+)-paspalinine using the Gassman procedure to obtain the indole nucleus.^{39a-b,40}

1.2.4 Improved route to the *trans* fused hydrindane portion

In order to overcome the low yield of *trans* hydrindane obtained by reductive alkylation using methyl iodide and lithium in ammonia (section 1.2.1), Smith and co-workers reinvestigated this step and decided to introduce the quarternary methyl at C12b directly via conjugate addition to the enone (43) (Scheme 11).^{39a} By performing the transformation on a 6,6-bicyclic system as opposed to a 6,5-bicyclic system one would expect only the *trans* isomer to be obtained as this is the thermodynamically favoured conformation for this system.

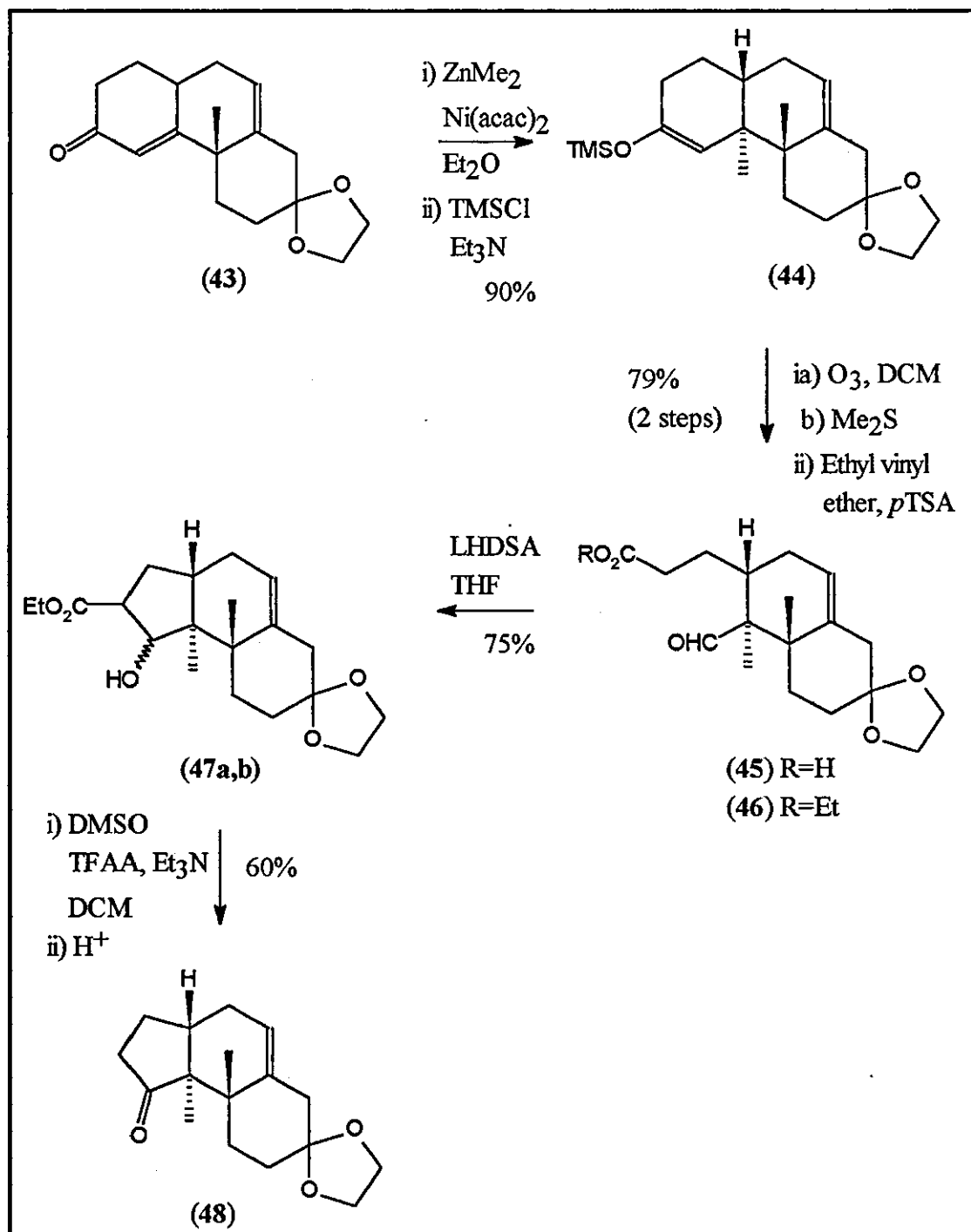
To this end, the enone (43) was prepared from Wieland-Miescher ketone in 4 steps, starting with ketalisation of the ketone (1) with ethylene glycol in the presence of collidinium *p*-toluenesulfonate giving a mixture of (41a) and (41b) (Scheme 11). Equilibration of the resulting mixture under acidic conditions afforded the thermodynamically more stable ketal (41a). Exposure of the ketal (41a) to benzylamine with a catalytic amount of *p*-toluenesulfonic acid gave the corresponding imine, which, on reaction with methyl vinyl ketone gave the diketone (42). Robinson annulation of the diketone (42) in the presence of sodium hydride gave the tricyclic enone (43).



Scheme 11

Conjugate addition to the enone (43) was achieved via treatment with dimethylzinc in diethyl ether containing nickel acetylacetonate, which gave, after quenching with trimethylsilyl chloride and triethylamine, the 1,4-adduct (44) (Scheme 12). Ozonolysis of the silyl enol ether (44), followed by dimethyl disulfide work-up, gave the aldehyde (45). Treatment of (45) with ethyl vinyl ether under acidic conditions gave the corresponding ester (46). Cyclisation to the five-membered ring was effected with lithium

hexamethyldisilazide affording the β -hydroxy esters (47a) and (47b). Swern oxidation of (47a) and (47b) gave the corresponding β -keto ester, decarboxylation of which, was achieved by treatment with dilute hydrochloric acid to give the cyclopentanone (48).



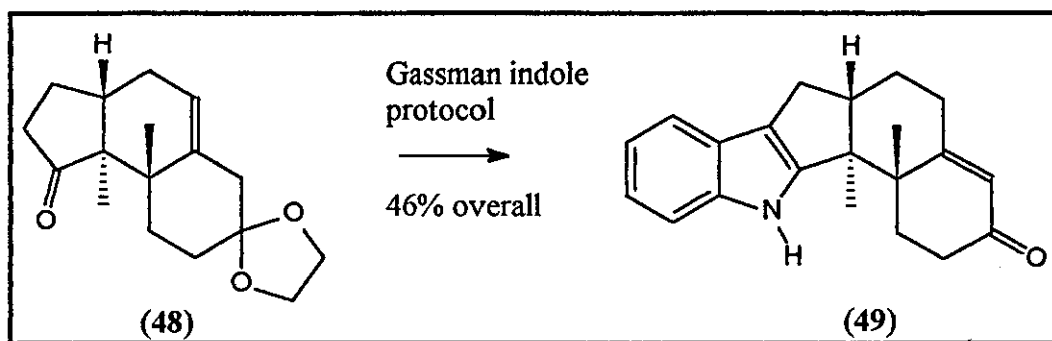
Scheme 12

This route is advantageous in terms of the amount of *trans* isomer obtained. In the original route (Scheme 3), the *trans* isomer was obtained in one step in 16% yield. In this improved route, the *trans* hydrindane (**48**) is obtained in 3 steps from the 6,6-bicyclic precursor (**44**) in 32% overall yield. The tetracyclic ketone (**48**) is also a common intermediate for the construction of all members of this class of compound.^{39b,40}

1.2.5 Total synthesis of (+)-paspalicine and (+)-paspalinine

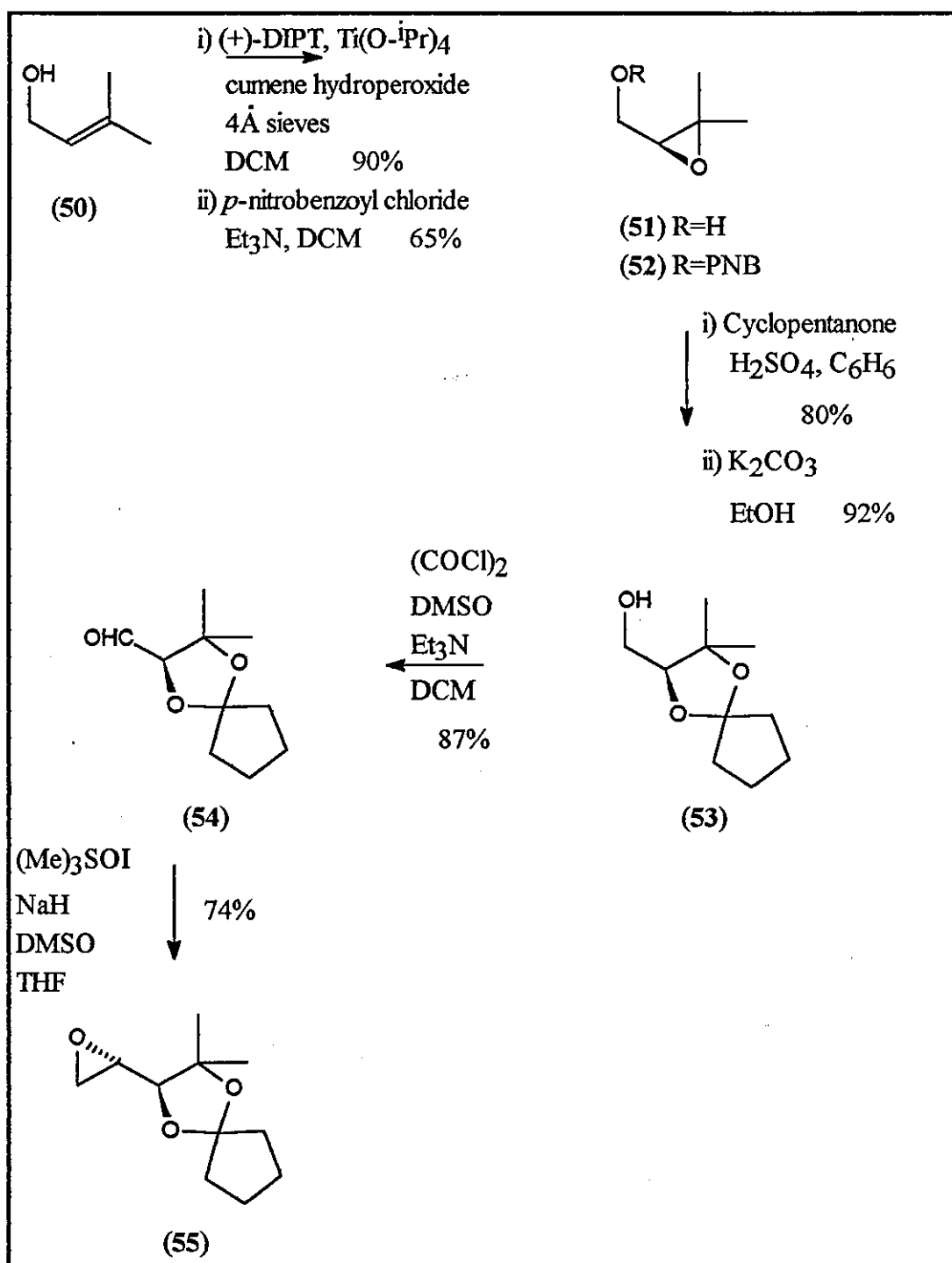
Making use of the tetracyclic ketone (**48**) obtained above (section 1.2.4), Smith and co-workers devised a convergent approach to (+)-paspalicine and (+)-paspalinine.^{39b,40}

The common left-hand portion (**49**) of the target molecules was prepared from ketone (**48**) (Scheme 13) via the Gassman indole protocol as described in Schemes 4-5.³¹



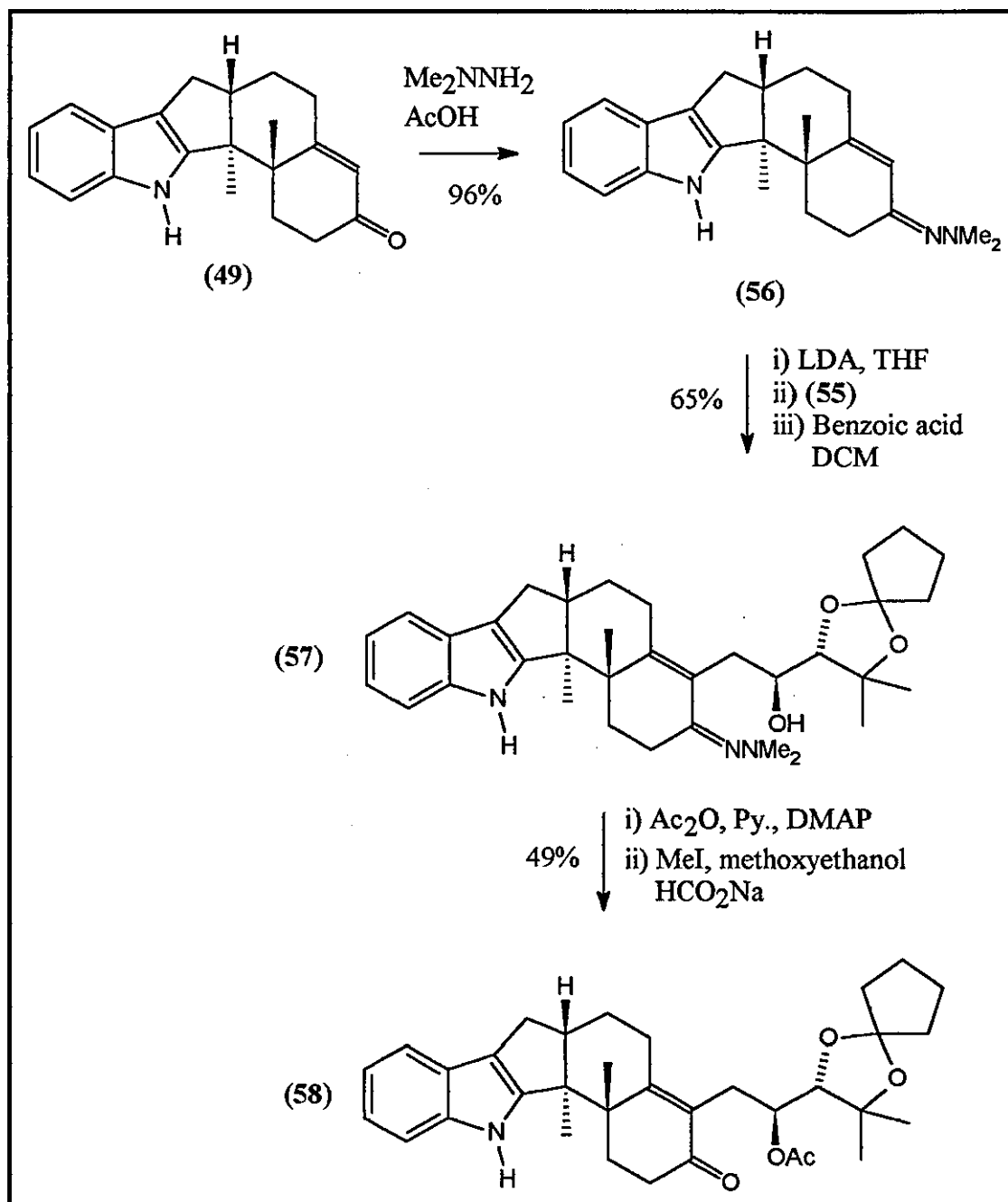
Scheme 13

The right-hand section of the metabolites was prepared as epoxide (**55**) (Scheme 14). The synthesis starts with Sharpless epoxidation of the allylic alcohol (**50**) to give the desired epoxy alcohol (**51**) in greater than 95% enantiomeric excess. The alcohol (**51**) was protected as the corresponding *p*-nitrobenzoate ester (**52**) under standard conditions. Ring opening of the epoxide under acidic conditions in the presence of cyclopentanone gave, after debenzoylation, the protected diol (**53**). Swern oxidation of the alcohol (**53**) afforded the aldehyde (**54**). Methylenation using Corey's conditions gave the epoxide (**55**) in a isomeric ratio of 98:2.^{40a}



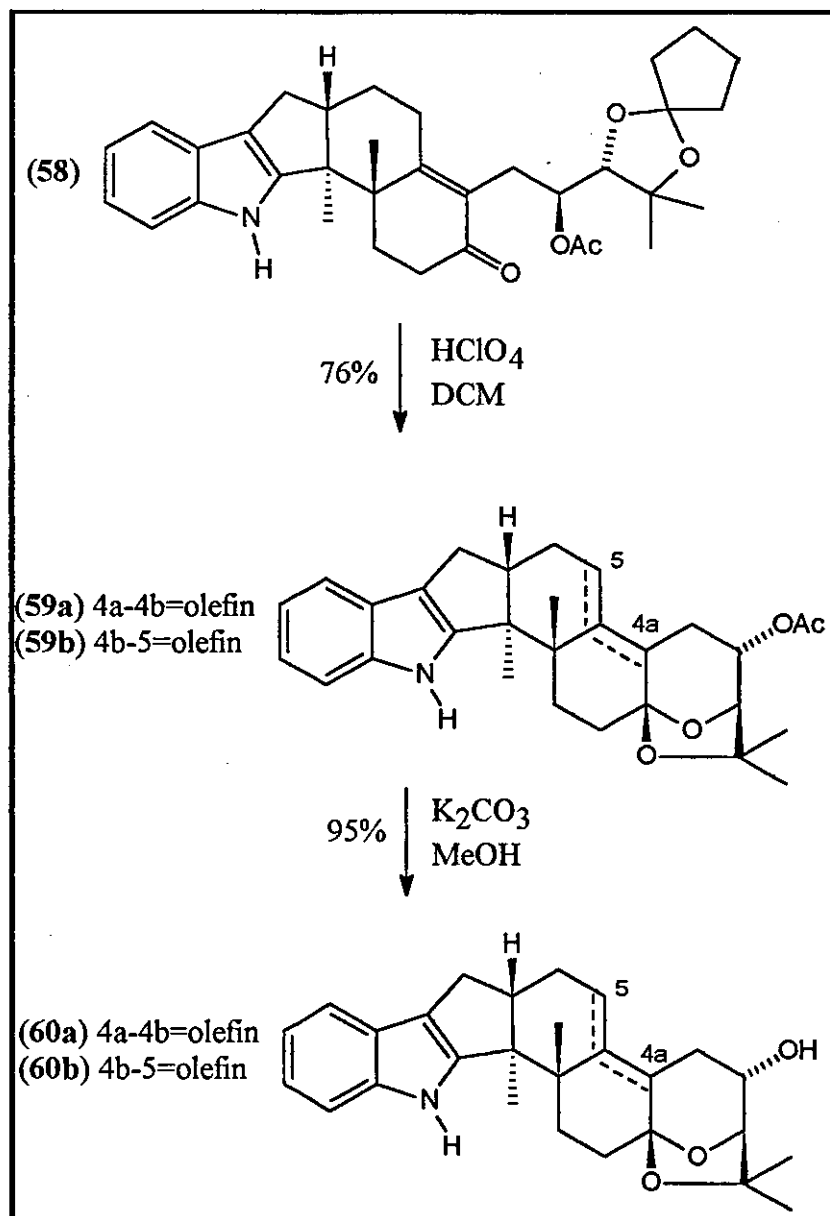
Scheme 14

Enone (49) and epoxide (55) were coupled in the following manner. The enone (49) was first converted to the hydrazone (56) (Scheme 15). Alkylation with the epoxide (55) using lithium diisopropylamide in tetrahydrofuran followed by isomerisation of the double bond with benzoic acid furnished the alcohol (57). Acetylation followed by removal of the hydrazone gave the enone (58).



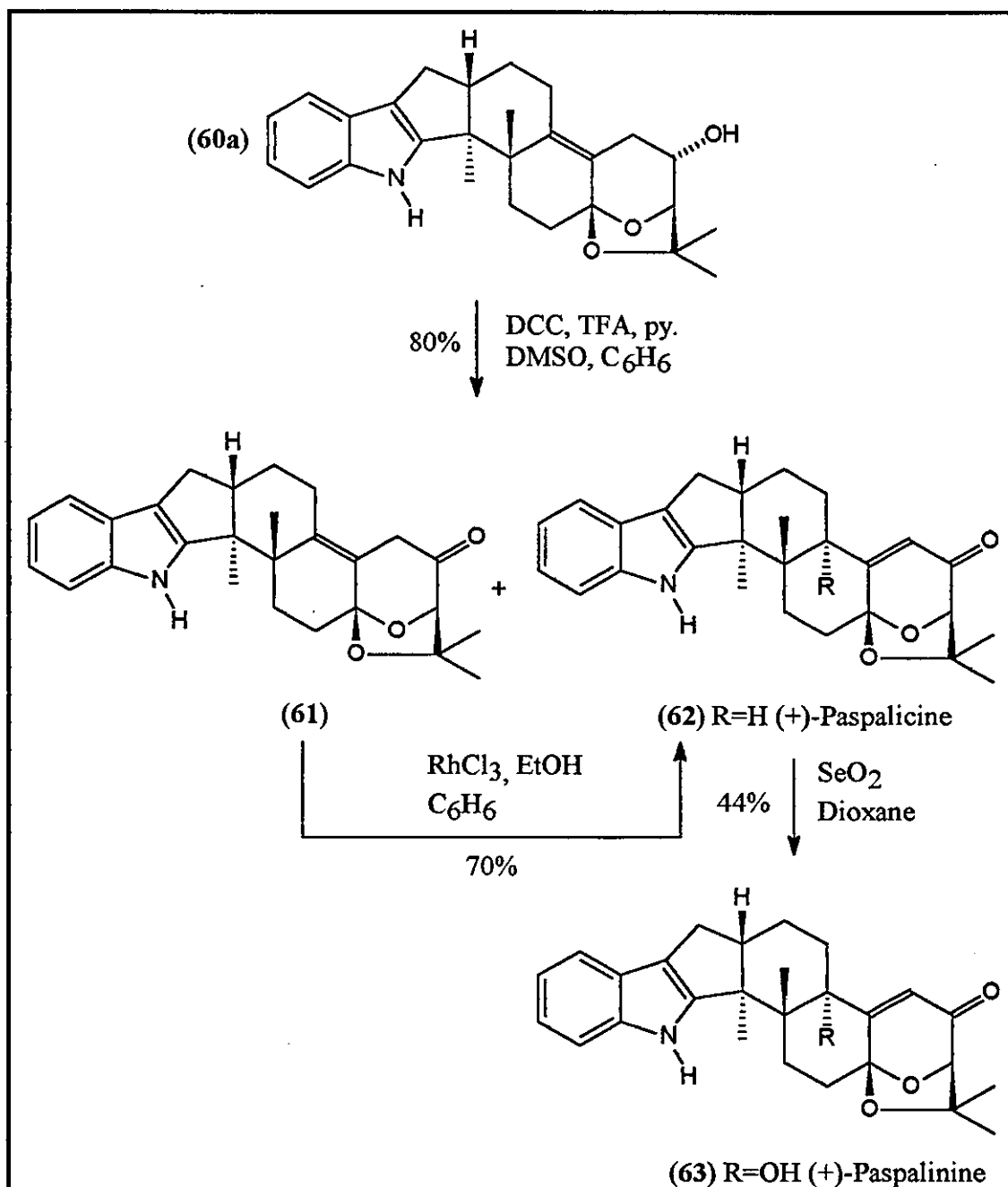
Scheme 15

Treatment of (58) with acid removed the cyclopentylidene moiety with concomitant cyclisation to give the bicyclic ketals (59a) and (59b). Deacetylation gave the alcohols (60a) and (60b) which were separable by flash chromatography (Scheme 16).



Scheme 16

Moffatt oxidation of (60a) gave a 5:1 mixture of β,γ -enone (61) and paspalicine (62), the former readily isomerised in the presence of rhodium (III) chloride to give (62) as the sole product (Scheme 17). Thus, the preparation of (+)-paspalidine (62) entailed 22 steps with an overall yield of 1.2%. Allylic oxidation of (62) with selenium dioxide afforded (+)-paspalinine (63) in 44% yield.



Scheme 17

1.2.6 Alternative route to the right-hand side of the tremorgenic indoles

Saxton *et al.* have published a modification to the synthesis of rings D-G of Paspalicine (Figure 15).⁴¹

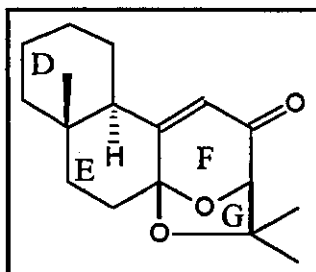
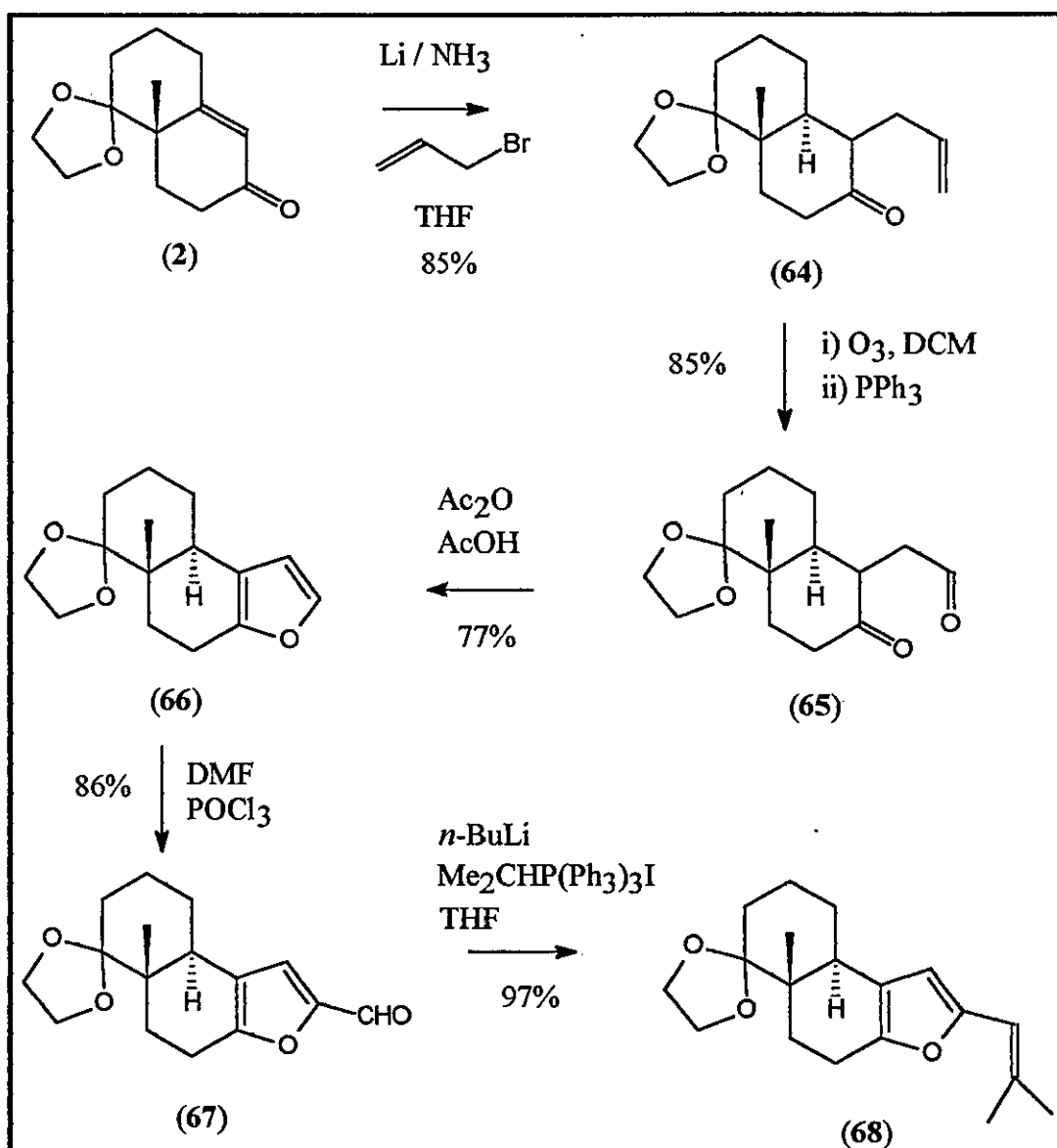


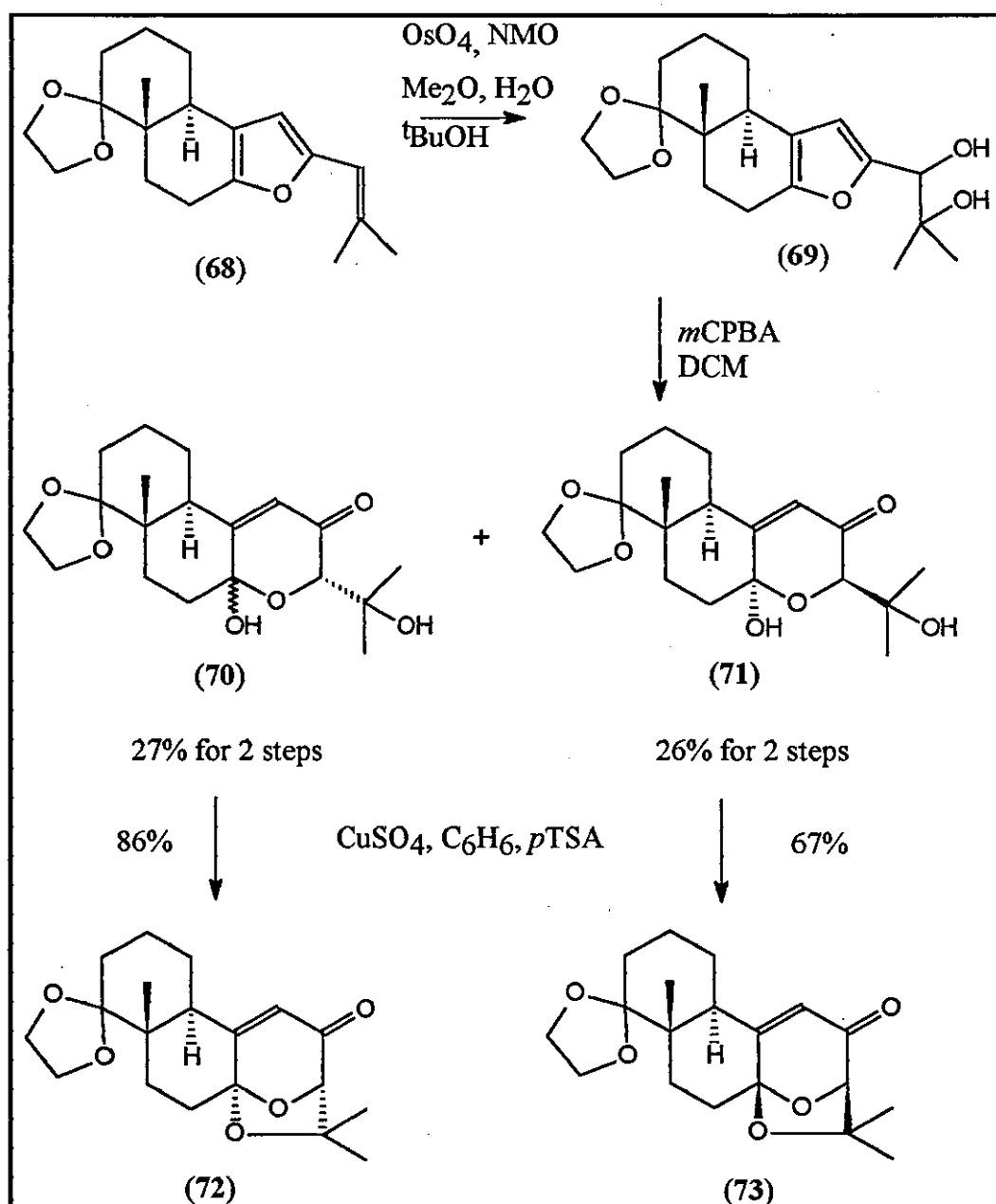
Figure 15: Rings D-G of Paspalicine.

This route starts with the reductive alkylation of enone (2) with lithium in liquid ammonia and allyl bromide to give the alkene (64). Ozonolysis of (64) gave the ketoaldehyde (65) which was efficiently cyclised to the furan (66) using acetic anhydride. Vilsmeier-Haack formylation of (66) gave the aldehyde (67) when acidic work-up conditions were avoided. Wittig reaction of the aldehyde (67) with isopropylidene triphenylphosphorane gave the isobutenylfuran derivative (68) (Scheme 18).



Scheme 18

Oxidation of the isobutenylfuran derivative (68) using osmium tetroxide and *N*-methylmorpholine *N*-oxide gave a mixture of diastereoisomeric diols (69) which were oxidatively ring expanded with *m*-chloroperbenzoic acid to give diols (70) and (71). The diols were cyclised in the presence of anhydrous copper sulfate to give the target molecules (72) and (73) (Scheme 19).



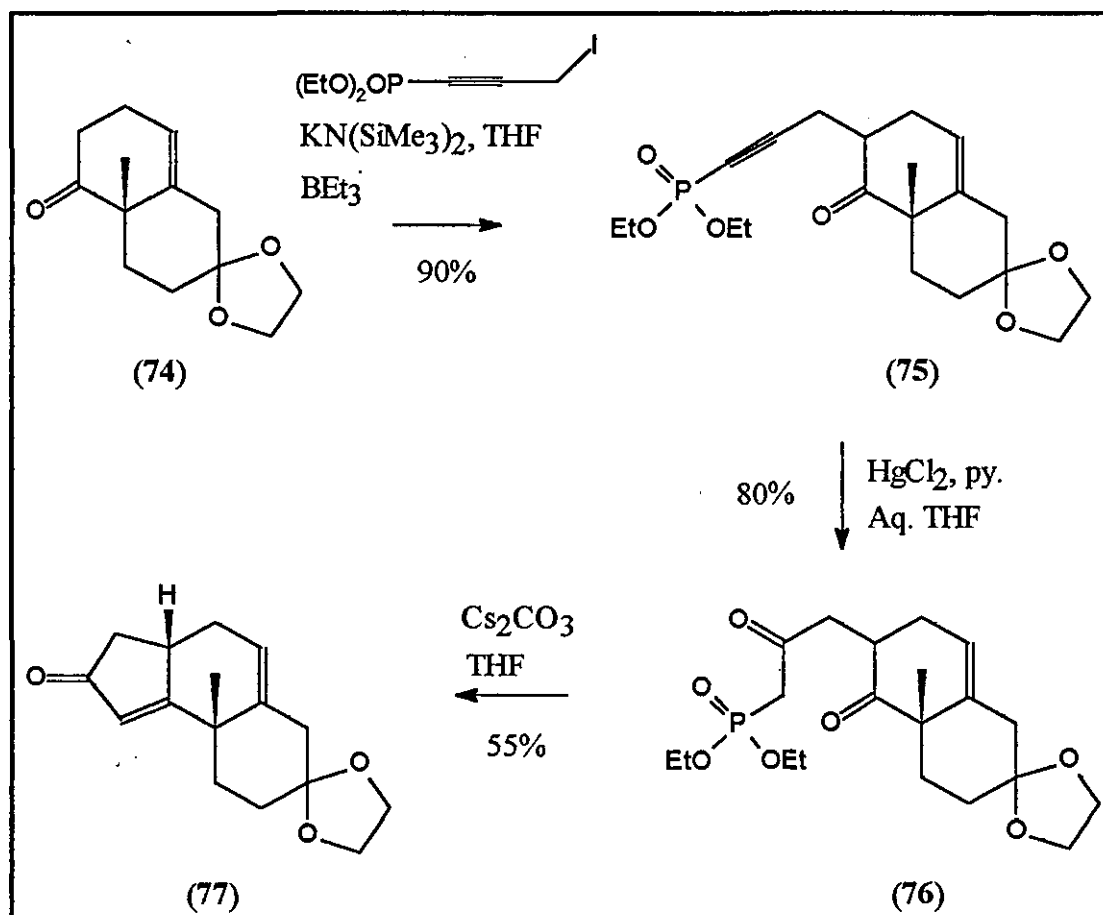
Scheme 19

Although there are fewer steps in this synthesis of the right-hand side of paspalicine, Smith *et al.*^{39b,40} start their synthesis with the indole moiety already intact, so in fact, there is no real advantage to this route. However, production of compounds (70) and (71) is particularly beneficial as modification of these isomers could provide a route to paspaline.

1.2.7 An alternative route to the *trans* fused hydrindane portion

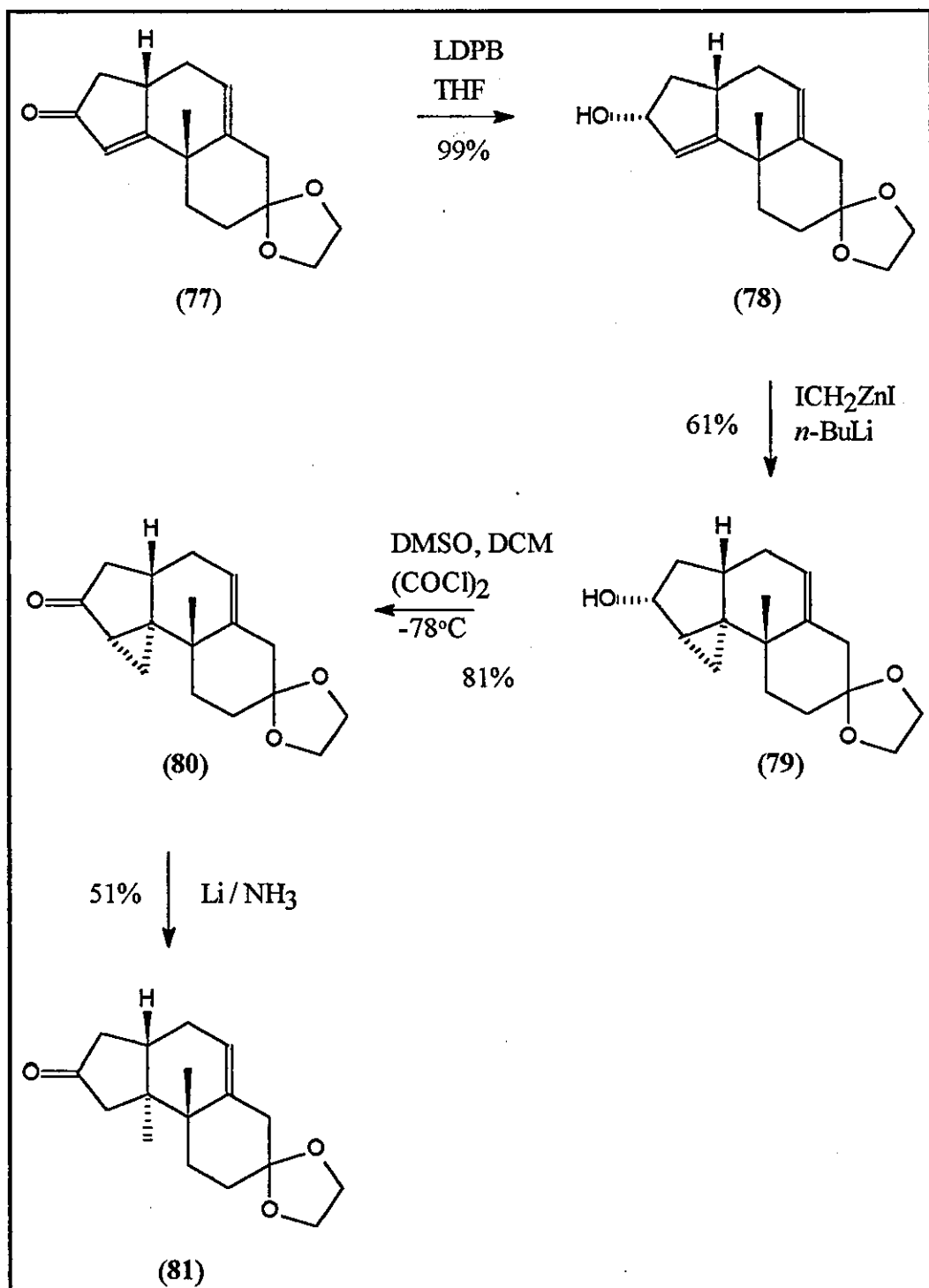
Saxton and co-workers investigated the development of a different route to the *trans* fused C-D rings of the tremorgenic indoles utilising phosphonate chemistry developed by Poss and Belter.^{42,43}

Thus, selective protection of Wieland-Miescher ketone (1) gave the monoketal (74) which was alkylated with diethyl 3-iodopropynyl phosphonate-potassium hexamethyldisilazide-tri-ethylborane,⁴⁴ to give the ketophosphonate (75). Hydration of (75) avoiding acidic reaction conditions gave the diketo phosphonate (76). Intramolecular Wadsworth-Emmons olefination gave the cyclopentanone derivative (77) - the workers state that this last step is very unreliable and the maximum yield obtained was 55% (Scheme 20).



Scheme 20

The cyclopentanone derivative (77) was reduced with lithium 1,2-dimethylpropylborohydride to give the allylic alcohol (78). Cyclopropanation using butyl lithium and diiodomethyl zinc gave the α -cyclopropane (79). Oxidation using Swern conditions afforded the ketone (80). The cyclopropane ring was cleaved using lithium in liquid ammonia to give the *trans* fused hydrindane system (81) (Scheme 21).



Scheme 21

This route shows another approach to the *trans* fused indane system. Again, the crucial steps give an overall yield of 25%, which is comparable with the 32% yield of *trans* fused indane system as obtained by Smith *et al* (section 1.2.4).^{39a}

The following chapters discuss our approaches to the synthesis of a *trans* fused hydrindane system. Model studies on its incorporation into the left-hand side of the tremorgenic mycotoxins, concentrating the efforts on lolitrem B, using Diels-Alder cycloadditions and Fischer indole chemistry are discussed.

CHAPTER 2

Hydrindane Studies

2.1 Disconnections

All of the tremorgenic indoles possess the same central indole moiety and have similar structures in the right-hand portion of the molecule. The main differences occur at the C4/C5 positions on the indole ring. Some work has been undertaken on the synthesis of the right hand portion of the tremorgenic indoles^{38,41} and much work has been carried out on the synthesis of the left hand portion of the more simple tremorgens^{26,27,39b} so it was decided to concentrate on the construction of the left hand portion (rings A-F) (Figure 16) of lolitrem B as no work has been published on its preparation to date.

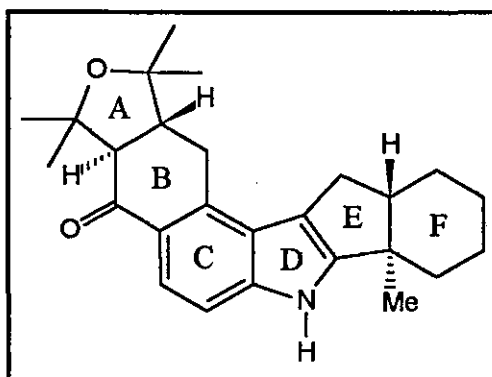
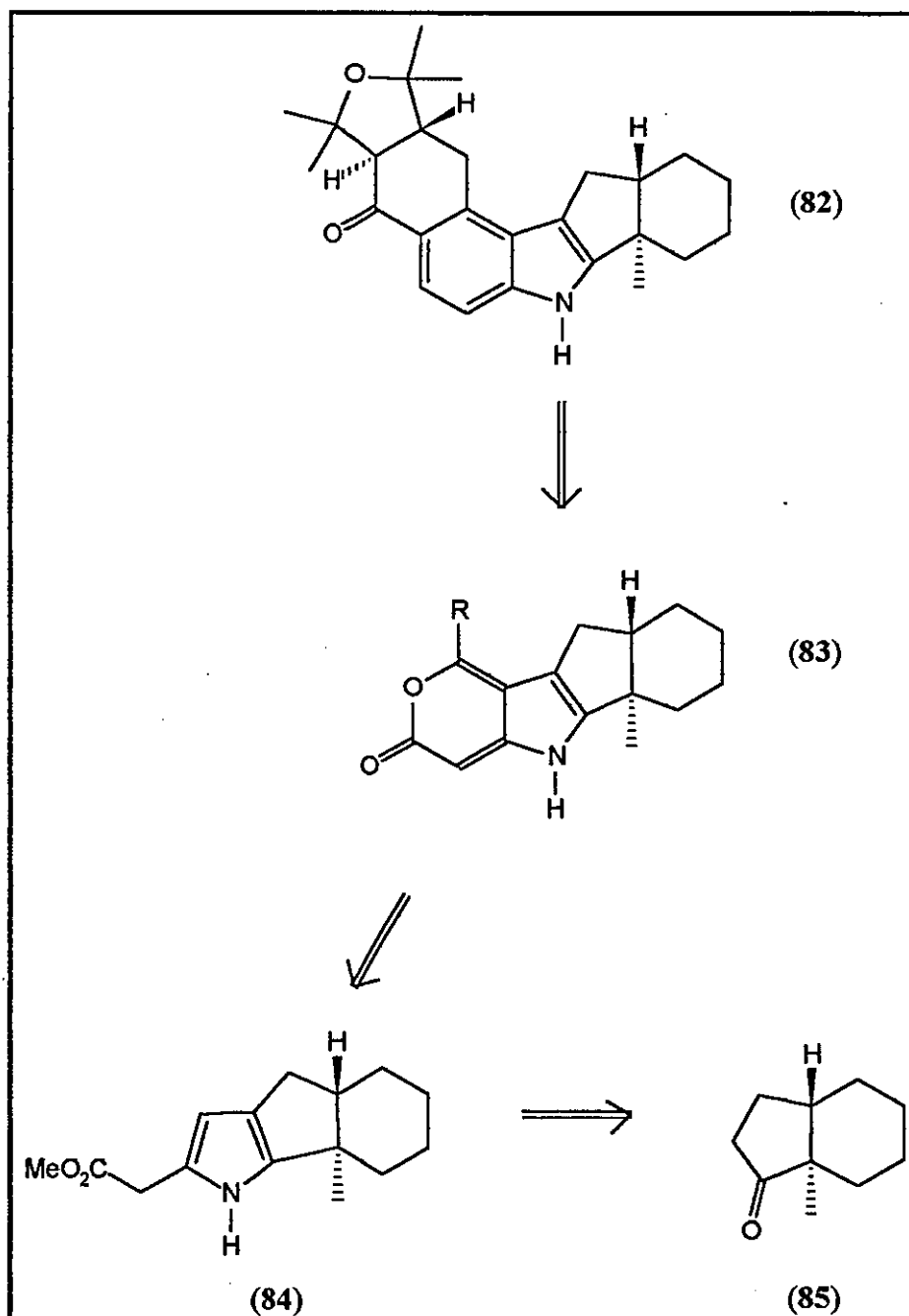


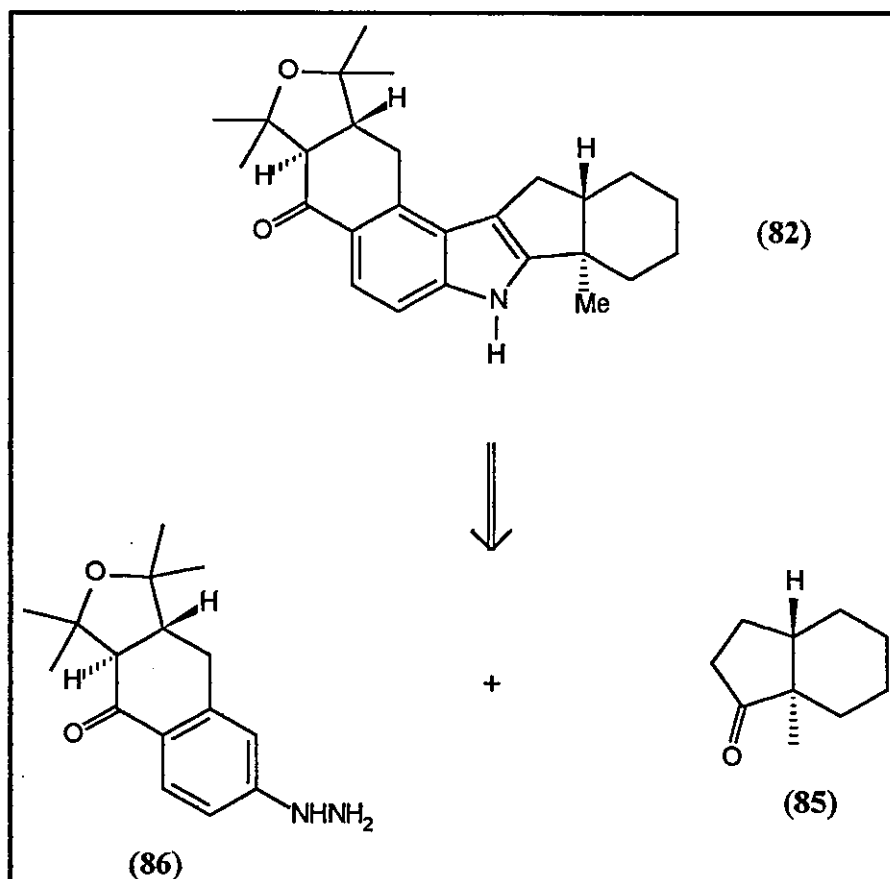
Figure 16: Rings A-F of Lolitrem B.

Scheme 22 shows the first disconnection where the indole moiety can be obtained from the pyranopyrrole (83) utilising Diels-Alder chemistry previously developed in our laboratories.^{45a-45c} The pyranopyrrole (83) is itself available from the *trans*-hydrindane (85) via the pyrrole (84). The *trans*-hydrindane (85) is a common intermediate for all the tremorgenic indoles.



Scheme 22

Alternatively, the hydrindane (85) could be reacted with hydrazine (86) to give the target molecule (82) (Scheme 23). Variation of the hydrazine used would allow development of an alternative route to other tremorgenic indoles.



Scheme 23

2.2 Introduction to Hydrindane Systems

The synthesis of hydrindane systems is well documented throughout the literature but obtaining the *trans* isomer has proved to be difficult. Figure 17 shows the numbering of indene and indane on which the hydrindanes are based.

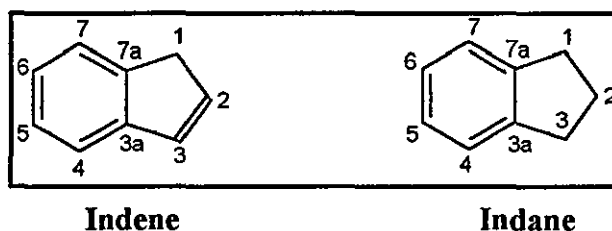


Figure 17: Indene and indane showing the numbering system.

There has been great interest in the synthesis of hydrindanes as they form the central core of many natural products of biological importance, for example: Vitamin D₃ and the tremorgenic indoles. The published routes to the *trans* isomer of such systems are briefly summarised below.

The classical route to the *trans* isomer of a hydrindane system is based on work aimed at preparing the BCD ring system of steroids (Figure 18).^{46a-c}

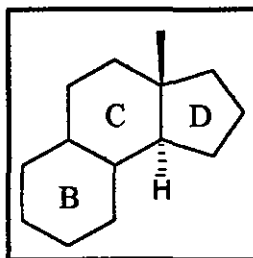
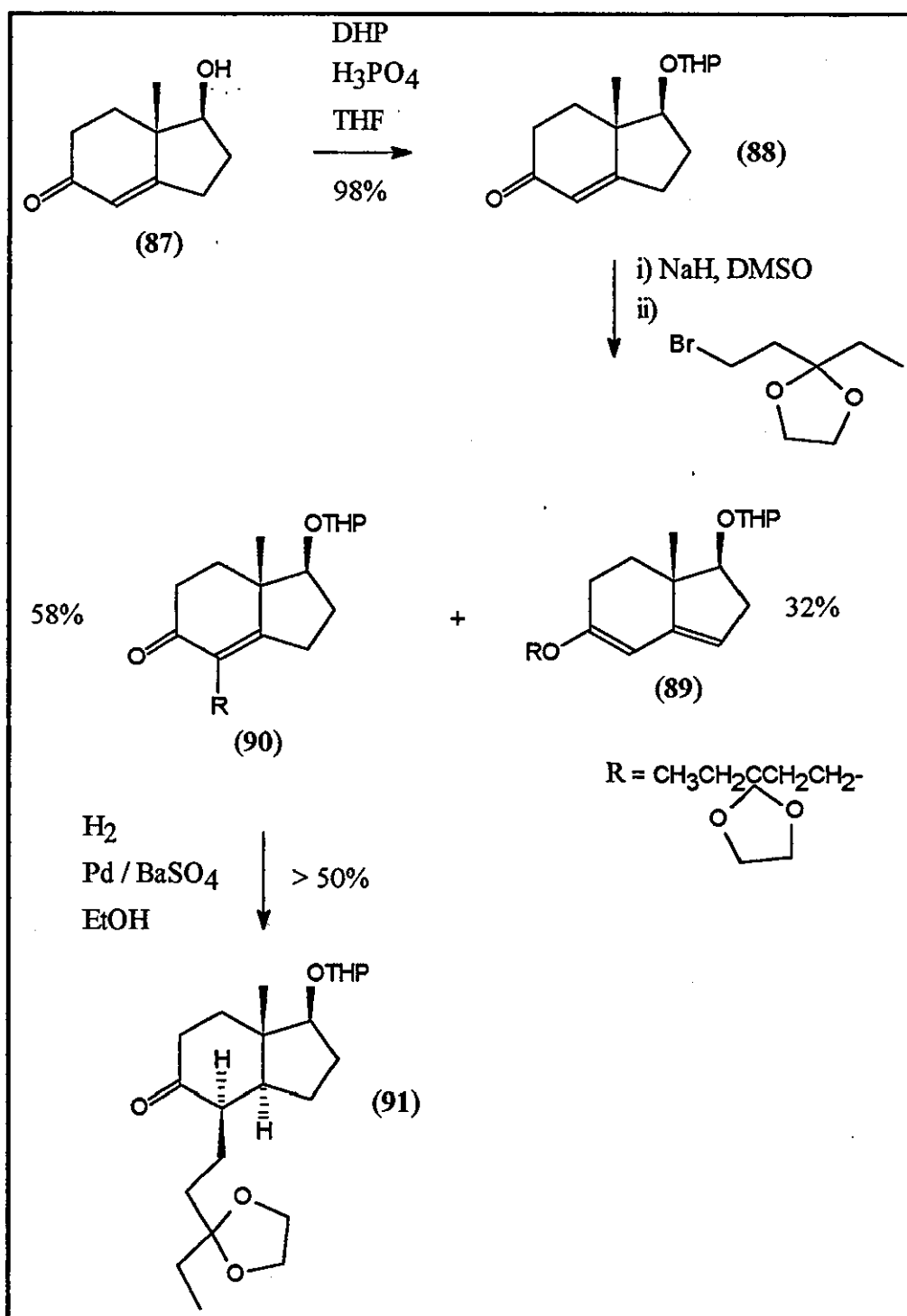


Figure 18: The BCD ring system of steroids.

Hajos *et al.*, proposed that the incorporation of a bulky group at the C4 position of a hydrindene system, a model for the BCD ring system of steroids, would induce hydrogenation from the less hindered face of the molecule to give the *trans* configuration across the ring junction.

To test this theory, the secondary alcohol (**87**) was protected as its tetrahydropyranyl ether (**88**) (Scheme 24). The anion, formed using sodium hydride and dimethyl sulfoxide,

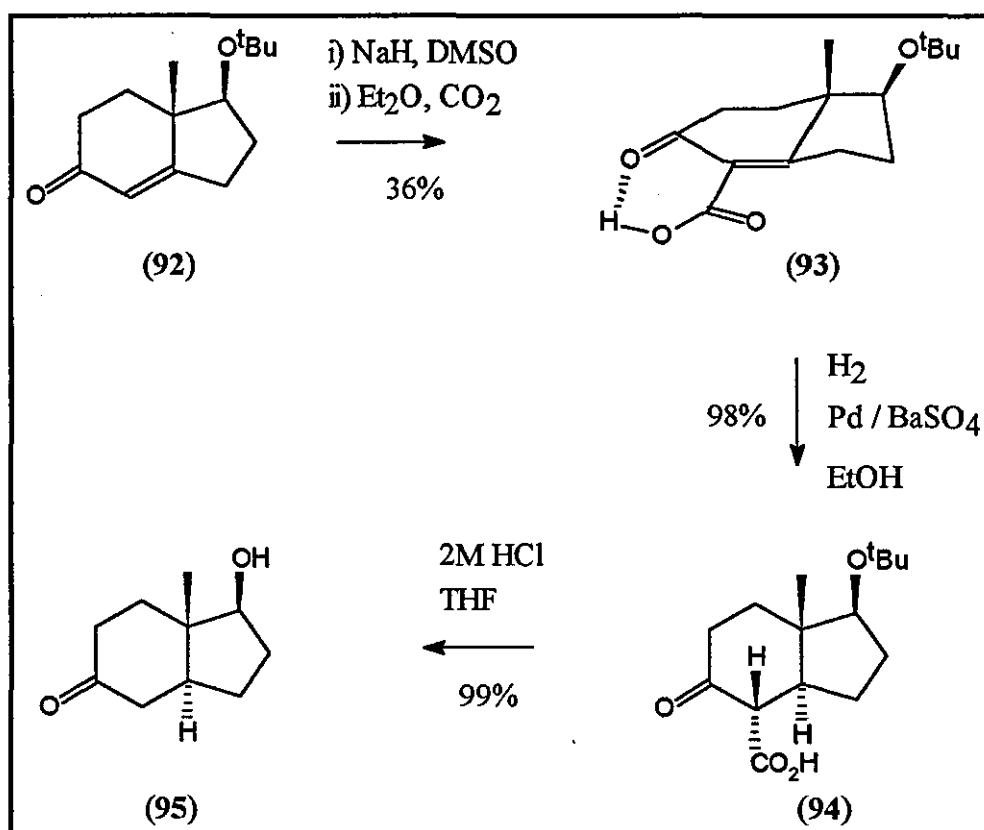
was quenched with 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane to give 32% *O*-alkylated product (89) and 58% of the desired *C*-alkylated product (90). Hydrogenation of (90) in the presence of 10% Pd/BaSO₄ in ethanol gave the desired *trans* isomer (91) in at least 50% purity. The side-chain was then cyclised onto the C5 position to form ring B of the steroid system.



Scheme 24

Hajos and co-workers subsequently moved on to the catalytic hydrogenation of a hydrindene system with a different substituent at the C4 position.^{47a-b} The reasoning for this was the assumption that if a substituent at C4 could interact with a substituent at C5 then a pseudo B ring of a steroid system would be formed and hence, hydrogenation would yield the *trans* isomer.

To this end, enone (92) was treated with sodium hydride and dimethyl sulfoxide to form the anion which was quenched with carbon dioxide to give the carboxylic acid (93) (Scheme 25). The hydroxyl group of the acid hydrogen-bonds with the carbonyl of the enone to form a pseudo B ring, which, on hydrogenation with 10% Pd/BaSO₄ in ethanol gave the *trans* β -keto-acid (94) in 98% yield and 94% purity. Decarboxylation and removal of the *tert*-butyl protecting group afforded the alcohol (95).



Scheme 25

Numerous groups have since utilised this technique for obtaining the *trans* isomer.⁴⁸⁻⁵² A Japanese group have modified this route and used a sulfone substituent or a silicon protected substituent instead of an acid substituent at the C4 position.⁵³⁻⁵⁴

Other approaches to the *trans* fused 6,5-bicyclic system include work by various groups on the conjugate reduction of the α,β -unsaturated ketone moiety of indenones using diisobutyl aluminium hydride, hexamethylphosphoramide with methyl copper as a catalyst to give the *trans* isomer.⁵⁵ Clive and co-workers have obtained the *trans* isomer via an alkylation-radical cyclization sequence of bicyclic lactones.⁵⁶ A Japanese group have utilised the thermal reaction of *trans* bis(diazo)diketones to obtain the desired isomer of hydrindenones.⁵⁷

An alternative approach used by an American group is that of photochemical degradation of vitamin D₃ analogs.⁵⁸ Stork and other workers have made use of homogeneous catalysis in the preparation of the *trans* isomer^{59a-c} and two groups have made use of π -allylpalladium chemistry in the search for an efficient route to the *trans* isomer of a hydrindane system.^{60a-c}

The work carried out above was on the commonly available enantiomer of these hydrindenones bearing a methyl group at C7a with *S*-configuration. For our purposes it was necessary to synthesise the uncommon enantiomer having the methyl at the C7a position in the *R*-configuration so that our model would correspond to the central portion of the target compounds. It was also desirable to find a shorter and more efficient route to the *trans* structure. Our studies towards the uncommon isomer of the hydrindane system are discussed in the following sections.

2.3 Synthetic Approaches

2.3.1 Hydrogenation

The first attempts at the formation of a *trans* fused hydrindane system involved the hydrogenation of an isolated double bond between C3a-C4 of the hydrindene skeletons (96) and (97) (Figure 19) during the synthesis of ketone (101) and ketone (106). Even though there have been reports that hydrogenation of an isolated double bond between either C3 and C3a or C3a and C4 gives only the *cis* isomer,^{47a} we were encouraged by reports that stated bulky substituents at C1 would induce hydrogenation such that the *trans* product is obtained.^{46c}

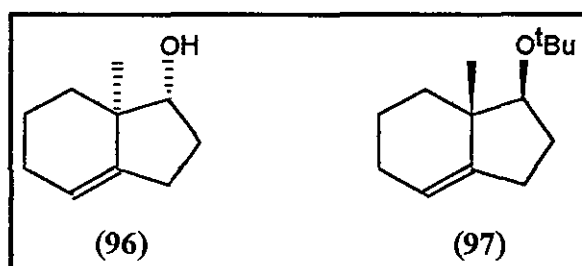
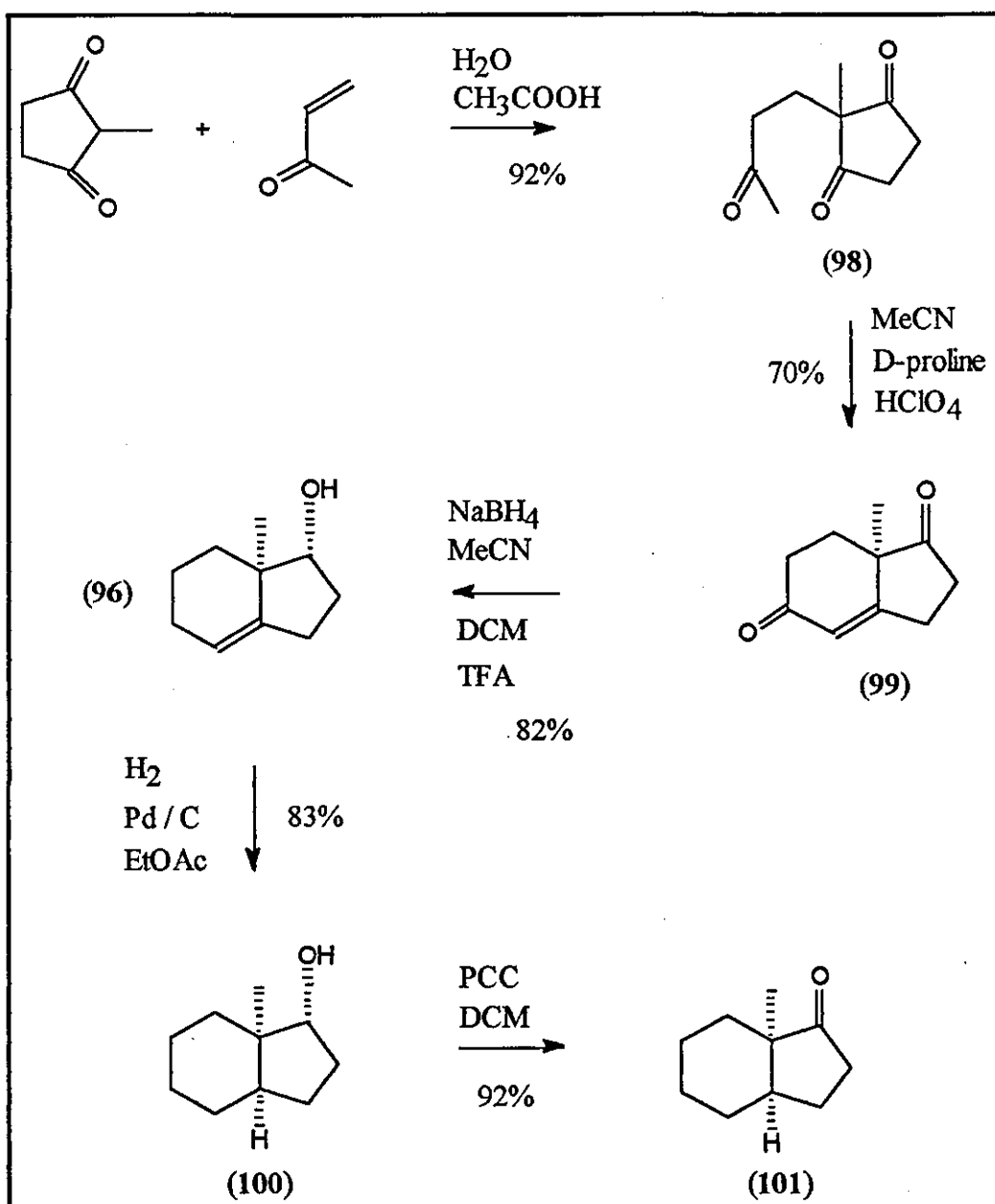


Figure 19: Hydrindene skeletons (96) and (97) showing isolated double bond between C3a-C4.

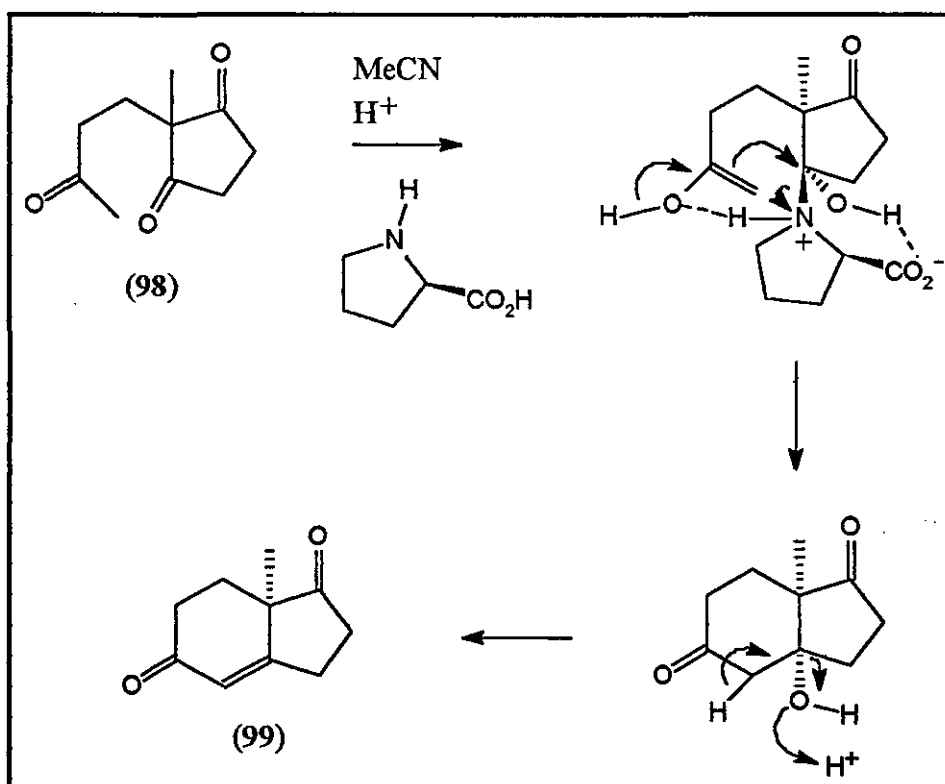
The uncommon hydrindene isomer bearing a 7a(*R*)-methyl group was synthesised using the following route.

Thus, Michael addition of 2-methylcyclopentane-1,3-dione, presumably in its enol form, to methyl vinyl ketone gave the triketone (98)^{28b} as an orange oil in 92% yield (Scheme 26). Robinson annulation of the triketone (98) in the presence of D-proline gave the diketone (99) as a colourless solid in 70% yield.^{28a,51} The mechanism of the annulation reaction (Scheme 27) is thought to proceed via attack of D-proline on one of the carbonyls of the cyclopentane ring.⁶¹ The use of D-proline gives the isomer (99) with *R*-configuration at C7a which is necessary for the model synthesis in order to give the required *S*-configuration at C7a in the target molecules.

Sodium borohydride reduction of the diketone (99) removed the enone carbonyl group and reduced the other carbonyl function to a secondary alcohol yielding the novel alcohol (96) as a colourless solid, m.p. 84-86°C in 82% yield.^{62,63} Hydrogenation of the alcohol (96) in the presence of 10%Pd/C afforded the saturated alcohol (100) as a colourless semi-solid in 83% yield. Careful examination of the ¹H NMR spectrum of the novel alcohol (100) showed the presence of an isomeric product. The methyl group of the major isomer resonates at 0.98 ppm which is characteristic of the *cis* isomer of comparable hydrindene systems,^{47a} downfield from the corresponding methyl singlet of the desired *trans* isomer at 0.74 ppm. The signal corresponding to the proton at C1 resonates at approximately 3.8 ppm in the major isomer and 3.6 ppm in the minor isomer, hence it can be deduced that the signal at 3.8 ppm is characteristic of the *cis* isomer. Integration of the methyl singlets shows that the *cis* isomer predominates in a ratio of 96:4. The isomers were not separable by flash chromatography and were hence reacted as a mixture. Pyridinium chlorochromate oxidation of the alcohol (100) gave the ketone (101)⁶⁴ as a pale yellow liquid in 92% yield - optimum results are obtained if the crude residue is chromatographed immediately after completion of the reaction.



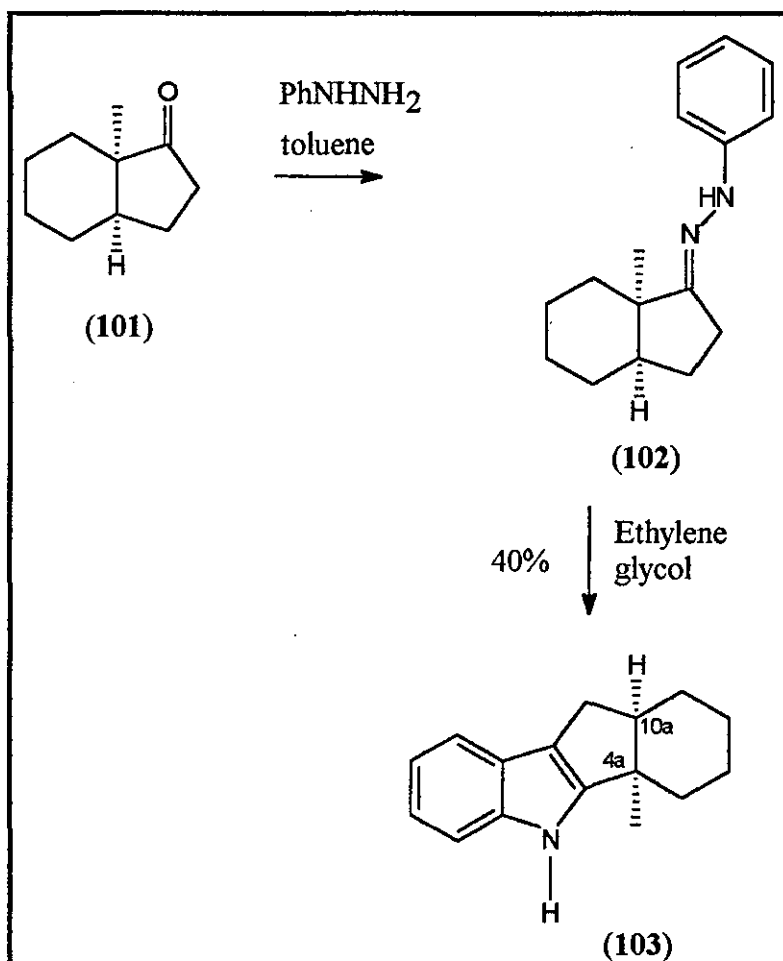
Scheme 26



Scheme 27

Despite the *cis* configuration across the ring junction in ketone (101) it was decided to employ the ketone (101) in a Fischer indole synthesis to provide a model for the central indole portion of the tremorgenic mycotoxins.

Accordingly, the ketone (101) was refluxed with phenylhydrazine in toluene to give the arylhydrazone (102) which was not isolated, but immediately thermally cyclised to give the novel indole (103) as a colourless solid in 40% yield, m.p. 95-96°C (Scheme 28).⁶⁵ Again, inspection of the proton NMR spectrum revealed the presence of an isomeric product. The methyl singlet for the major *cis* isomer resonates at 1.29 ppm, downfield from the methyl singlet of the desired minor isomer which resonates at 0.98 ppm. Integration of the methyl singlets shows that the ratio of enantiomers is 96:4 in favour of the *cis* isomer. The *cis* configuration across the ring junction is confirmed by NOE experiments. Irradiation of the methyl signal causes an enhancement at 2.49 ppm which corresponds to the proton at C10a of the indole (103). Correspondingly, irradiation of the signal at 2.49 ppm causes an enhancement of the methyl signal, thus the ring junction has the *cis* configuration.

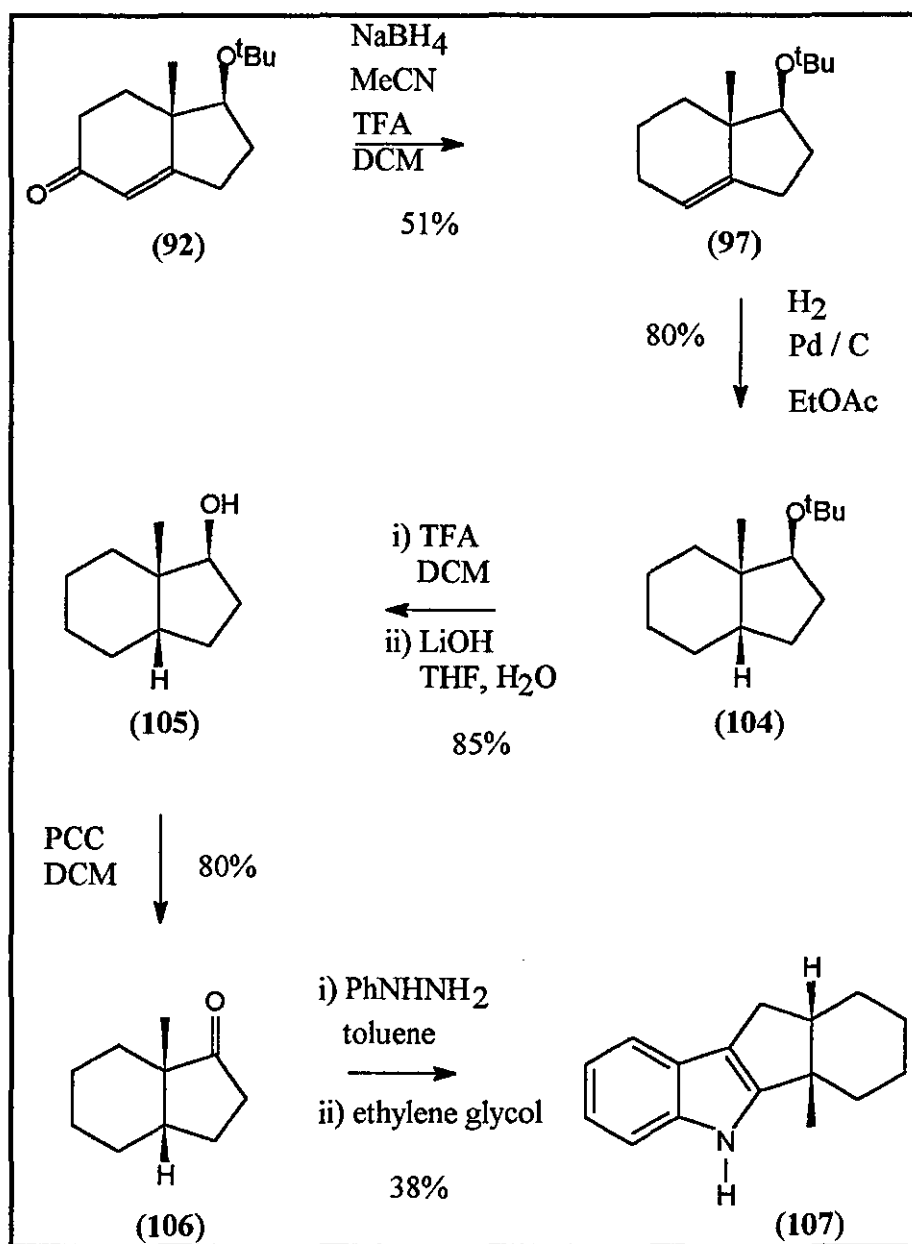


Scheme 28

In order to test whether a more bulky substituent adjacent to the quaternary methyl in the hydrindene (96) would induce hydrogenation such that the *trans* product was obtained, a sample of material obtained from Schering,⁶⁶ having a *tert*-butyl group adjacent to the quaternary methyl group, was employed in the same series of reactions as above.

Accordingly, the *tert*-butoxy enone (92) was treated with sodium borohydride as previously to give the hydrindene (97) as a yellow liquid in 51% yield. Hydrogenation using 10%Pd/C in ethyl acetate gave the hydrindane (104) as a yellow liquid in 53% yield. Examination of the proton NMR spectrum of the novel hydrogenation product (104) revealed the presence of a second isomer. The methyl group of the major isomer resonates at 0.98 ppm whereas the methyl singlet corresponding to the minor isomer appears upfield at 0.74 ppm. As stated for the alcohol (100) the signal corresponding to the proton at C1 resonates at 3.8 ppm for the major isomer and 3.6 ppm for the minor isomer. Thus it can be deduced that the major component is again the *cis* isomer. Integration of the methyl singlets shows that the *cis* isomer predominates in the ratio 85:15. The presence of a bulky

substituent adjacent to the quaternary methyl group does indeed improve the ratio of *trans:cis* isomers obtained. Unfortunately the increase in *trans* isomer obtained is not sufficient to be of synthetic use. Removal of the *tert*-butoxy group was achieved by treatment with trifluoroacetic acid followed by lithium hydroxide to give the alcohol (105) as a colourless semi-solid in 85% yield.⁶³ Pyridinium chlorochromate oxidation gave the ketone (106) as a colourless oil in 80% yield.^{63,64} The ketone (106) was reacted with phenylhydrazine as previously to give the novel indole (107) as a colourless solid in 38% yield and 98% purity after flash chromatography, m.p. 93-95°C. The purity is determined from the relative integral heights of the methyl singlets for the *cis* and *trans* isomers at 1.32 ppm and 1.00 ppm respectively. NOE experiments as for indole (103) confirmed the ring junction of the hydrindane to be *cis* (Scheme 29). Thus, as the starting material had the C7a methyl group in the *S*-configuration which is opposite to the previously prepared compounds, then it would be expected that the indole (107) would exhibit opposite chiroptical properties ($[\alpha]_D^{20} +45^\circ$) to the enantiomeric indole (103) ($[\alpha]_D^{20} -41^\circ$) and this is indeed found to be the case.

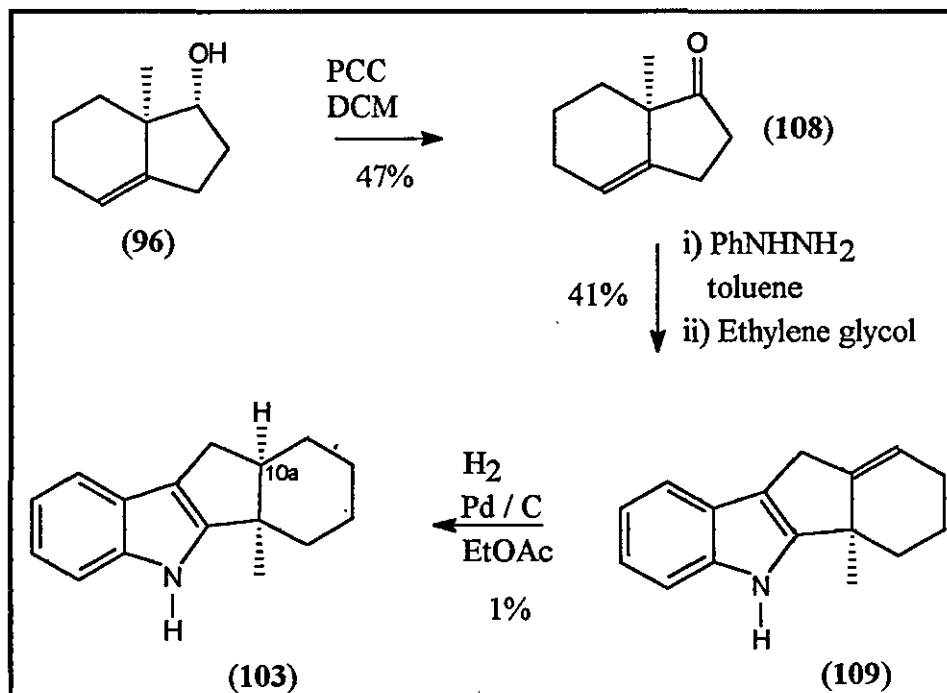


Scheme 29

The next approach to this route was to hydrogenate the olefin after it had been incorporated into the indole to test whether the inherent rigidity of the tetracyclic system would improve the ratio of isomers obtained.

Thus, pyridinium chlorochromate oxidation of the alcohol (96) gave the unsaturated ketone (108) as a yellow liquid in 47% yield, which, on reaction with phenylhydrazine gave the novel indole (109) in 41% yield, m.p. 110-112°C (Scheme 30). Hydrogenation of the indole proved to be troublesome with isomerisation of the double bond being a major by-product, but enough material was obtained for NMR study. Only one product was observed

in the proton NMR spectrum with the methyl signal resonating at 1.32 ppm thus indicating that the *cis* isomer had been formed. NOE data confirmed this as irradiation of the methyl singlet caused an enhancement at 2.47 ppm which corresponds to the proton at C10a and irradiation of this signal causes an enhancement of the methyl peak. Hence, the system is *cis*-fused.



Scheme 30

As there were problems with heterogeneous catalytic hydrogenation, it was decided to employ techniques that involved homogeneous catalysis.

2.3.2 Directed hydrogenation

This technique involves the use of polar functional groups in proximity to the double bond which remain bound to the metal during the catalytic cycle and hence control the direction of hydrogenation through chelation.^{59a} Hydroxyl groups are often used as the polar functional group and one such catalyst is Crabtree's catalyst, (Tricyclohexylphosphine) (1,5-cyclooctadiene) (pyridine) iridium(I)hexafluorophosphate; [Ir(cod)py(PCy₃)]PF₆ (Figure 20). It has been used to obtain the *trans* isomer of hydrindane systems as shown in the literature by Stork *et al.*^{59b} However, a later report by Mourino *et al.*,^{59c} states that

they only obtained the *cis* isomer of such systems when using Crabtree's catalyst, but they did obtain the *trans* isomer in a ratio of 2:1 *trans:cis* using Wilkinson's catalyst.

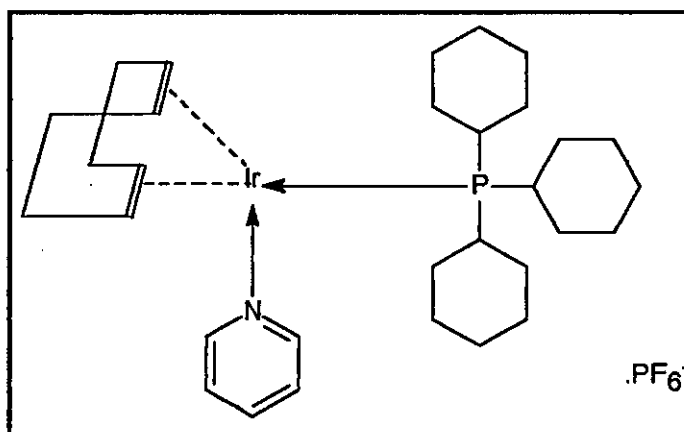


Figure 20: Crabtree's catalyst.

It was envisaged that the hydroxyl group of the hydrindene alcohol (**96**) would provide a suitable chelation site for Crabtree's catalyst. In order to obtain the *trans* hydrogenation product, the catalyst needs to chelate to the opposite face of the molecule from the methyl group. In hydrindene (**96**) the hydroxyl and methyl groups are on the same face of the molecule so the hydroxyl group would need to be inverted before hydrogenation could take place (Figure 21). This inversion was attempted using triphenylphosphine, diethyl azodicarboxylate and benzoic acid (Mitsunobu conditions)⁶⁷ but unfortunately all attempts at the inversion were unsuccessful. There have been reports in the literature that confirm the difficulty of inversion about this sterically hindered centre.⁶⁸

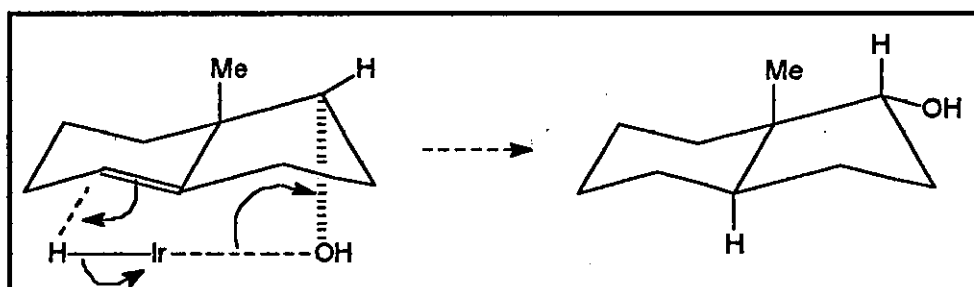
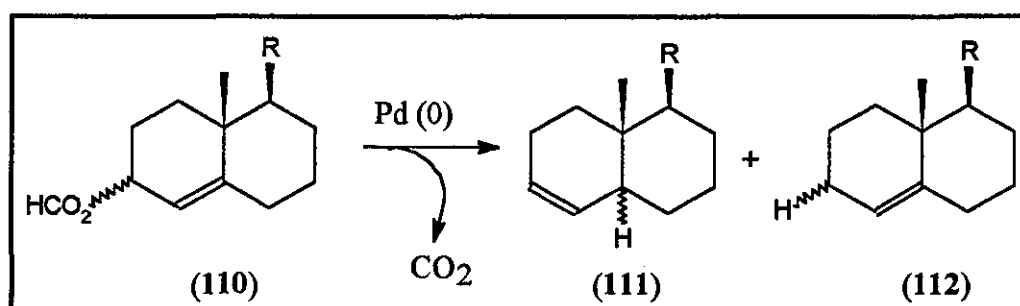


Figure 21: Mode of action of directed hydrogenation.

2.3.3 π -Allyl complex hydrogenolysis

Various groups have used π -allyl complexes in the hydrogenolysis of hydrindane and decalin systems and obtained the desired *trans* isomer.^{60a-c}

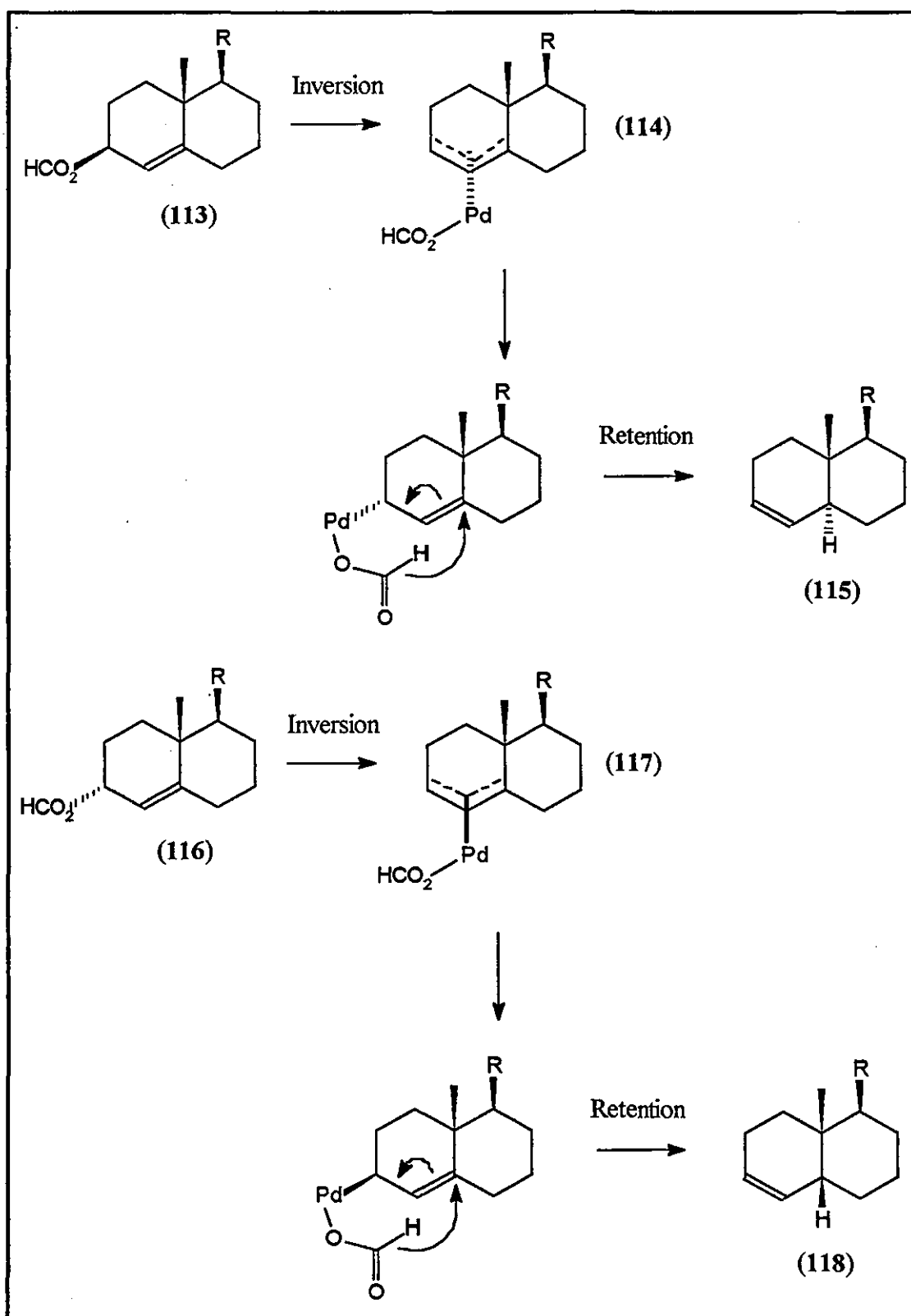
Background work to this route was performed by Mandai and Tsuji *et al.* on terminal allylic compounds giving terminal olefins. Developing their method for use with internal allylic compounds they expected high regio- and stereoselectivities using palladium and allyl formates.^{60a,b} It was found that the hydride attacks the more substituted carbon of the allyl system (110) in a bicyclic system and concerted decarboxylation gives olefin (111) rather than olefin (112) (Scheme 31).



Scheme 31

The expected stereoselectivities were based on the following mechanistic considerations:- in palladium-catalysed allylation reactions of nucleophiles via π -allylpalladium complexes, it is well established that the initial step of π -allylpalladium complex formation involves inversion of stereochemistry.^{69a-c} The subsequent addition of a soft carbon nucleophile to the π -allyl system takes place from the side opposite to the palladium resulting in a net retention of configuration. On the other hand, addition of a hard nucleophile to a π -allylpalladium complex proceeds from the same side as the palladium, hence net inversion of configuration results.

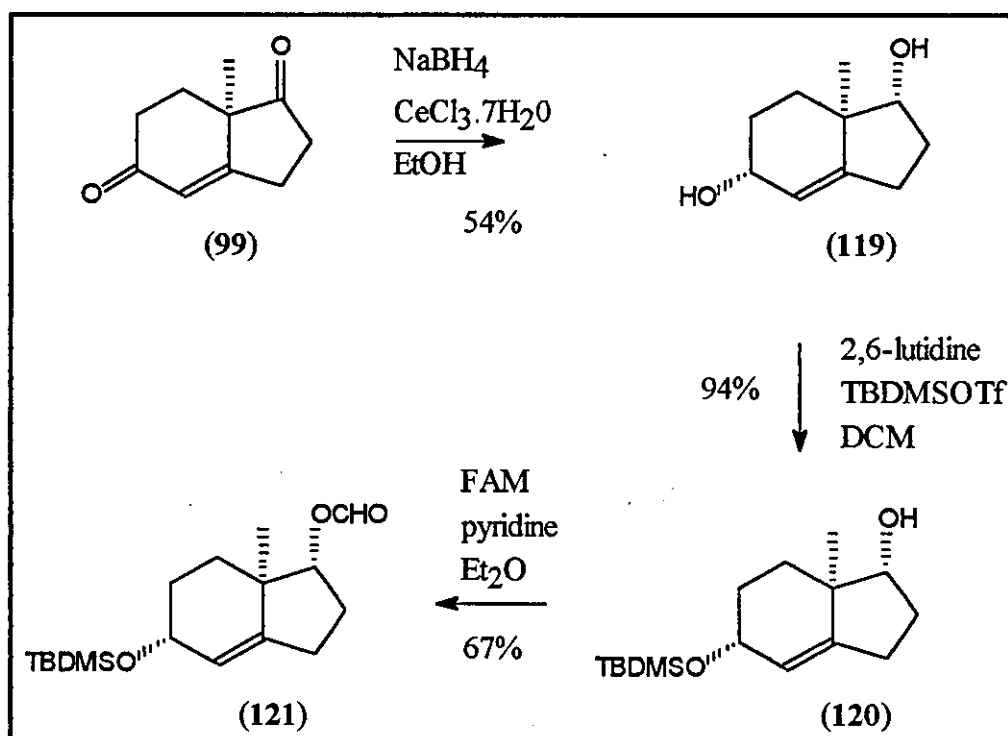
Based on these considerations, it was postulated that attack of Pd(0) on a decalin β -formate (113) to give a π -allylpalladium formate (114) in which the palladium has an α orientation (inversion), followed by attack of a hard nucleophile (retention), would give overall inversion of configuration to give a *trans* decalin (115). Conversely, attack of Pd(0) on a decalin α -formate (116) to give a π -allylpalladium formate (117) in which the palladium has an β orientation (inversion), followed by attack of a hard nucleophile (retention), would give overall inversion of configuration to give a *cis* decalin (118) (Scheme 32).



Scheme 32

It was decided to utilise such palladium chemistry in the formation of the desired *trans* hydrindane. The requisite α -formate should be accessible via the selectively protected diol obtained from the reduction of the diketone (99). Mandai *et al.* obtained the α -formate via Mitsunobu inversion of the corresponding β -alcohol.

Accordingly, the diketone (99), prepared as described previously, (Scheme 26)^{28a,51} was reduced using sodium borohydride and cerium (III) chloride (Luche's conditions)^{59c,70} to give the diol (119) as a colourless liquid in 54% yield. Selective protection of a secondary alcohol in the presence of an α,β -unsaturated alcohol has been achieved by Danishefsky⁷¹ and hence, the diol (119) was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of 2,6-lutidine at -78°C , to afford the alcohol (120) as a colourless solid, m.p. $101\text{--}103^\circ\text{C}$, in 94% yield. Without further investigation, the alcohol (120) was formylated using formic acid-acetic anhydride mixture^{72a,b} to give the formate (121) as a colourless liquid in 67% yield (Scheme 33). In the proton NMR spectrum for diol (119) the signal corresponding to the proton at C1 resonates at 3.59 ppm, upfield from the signal for the proton at C5 which resonates at 4.28 ppm due to α,β -unsaturation. Protection with the silyl group causes no change in the chemical shifts of these two protons. Formylation, however, causes the signal at 3.59 ppm to shift markedly downfield to 4.76 ppm thus indicating that it was the allylic alcohol that was protected as the silyl ether and the alcohol at C1 that was formylated.

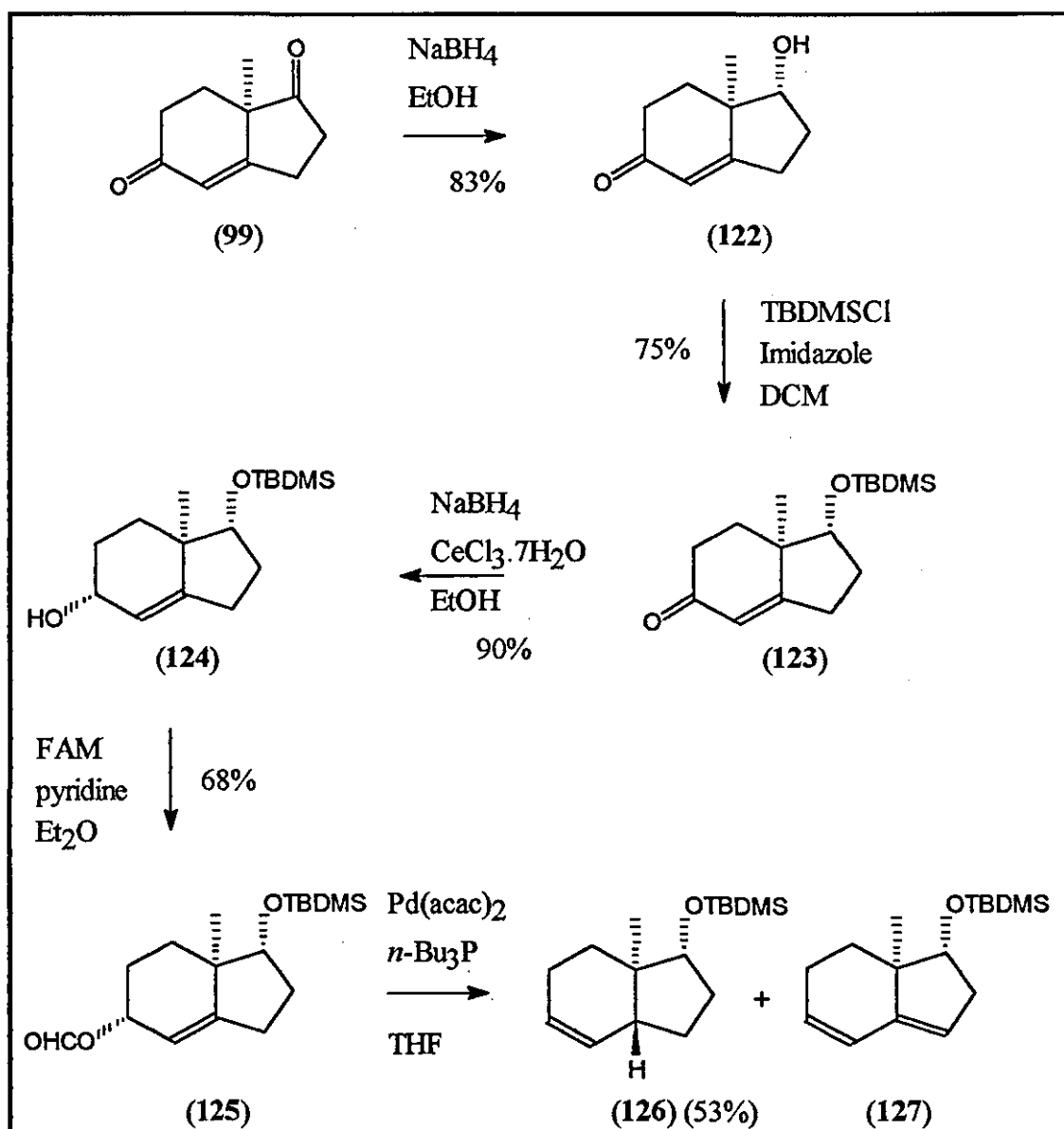


Scheme 33

As the wrong isomer had been obtained another route to the desired hydrindene formate was investigated. Accordingly, the diketone (99) was selectively reduced using sodium borohydride in ethanol at -10°C ,⁴⁸ to give the enone (122), as a colourless semisolid in 83% yield (Scheme 34). Initial attempts at protection of the alcohol (122) using *tert*-butyldimethylsilyl trifluoromethanesulfonate and either 2,6-lutidine or pyridine as the base only gave the silyl ether (123) in a modest yield of 44% yield. Upon changing the base to imidazole and using *tert*-butyldimethylsilyl chloride instead of *tert*-butyldimethylsilyl trifluoromethanesulfonate, the novel enone (123), was isolated as a pale yellow liquid in 75% yield. Reduction of the carbonyl group under Luche's conditions gave the enantiomerically pure alcohol (124) ($[\alpha]_{\text{D}}^{20} +18^{\circ}$) as a colourless semisolid in 90% yield. Formylation of the alcohol (124) using formic acid-acetic anhydride mixture and pyridine gave the desired α -formate (125) as a colourless liquid in 68% yield. The formylation reaction shows variable yields and timescale of reaction. The optimum yield of 68% shown was obtained after stirring at room temperature for 7 days.

With the α -formate in hand, attention was turned to the palladium catalysed hydrogenation. The catalyst was prepared by reaction of fresh palladium acetylacetonate and freshly distilled tributyl phosphine in dry tetrahydrofuran at room temperature. The catalyst was added dropwise to the α -formate (125) in dry tetrahydrofuran and the mixture stirred at room temperature. The desired olefin (126) was obtained as a colourless liquid in an optimum yield of 53%. Preparation of the catalyst is crucial - it must be prepared immediately before use or the yields of desired olefin (126) are greatly reduced, sometimes it is not obtained at all and the only product obtained is the diene by-product (127).

This represents the first synthesis of the hydrindene (126) although its enantiomer is known.^{60a,b} As expected, the ^1H NMR data for (126) is in close agreement with the literature data for its enantiomer. For example, the proton at C1 of (126) gives rise to a multiplet at 3.63 ppm, the corresponding C1 proton of the enantiomer resonates as a multiplet at 3.65 ppm. The methyl singlet for (126) resonates at 0.7 ppm and at 0.73 ppm in the corresponding enantiomer. This data and the previous NMR data for the hydrindene systems (100) and (104) serves to confirm that the hydrogenation product is indeed *trans*. Had the hydrogenation product been *cis* then the signals for the proton at C1 and the methyl group would have been shifted downfield to 3.8 ppm and 0.89 ppm respectively.



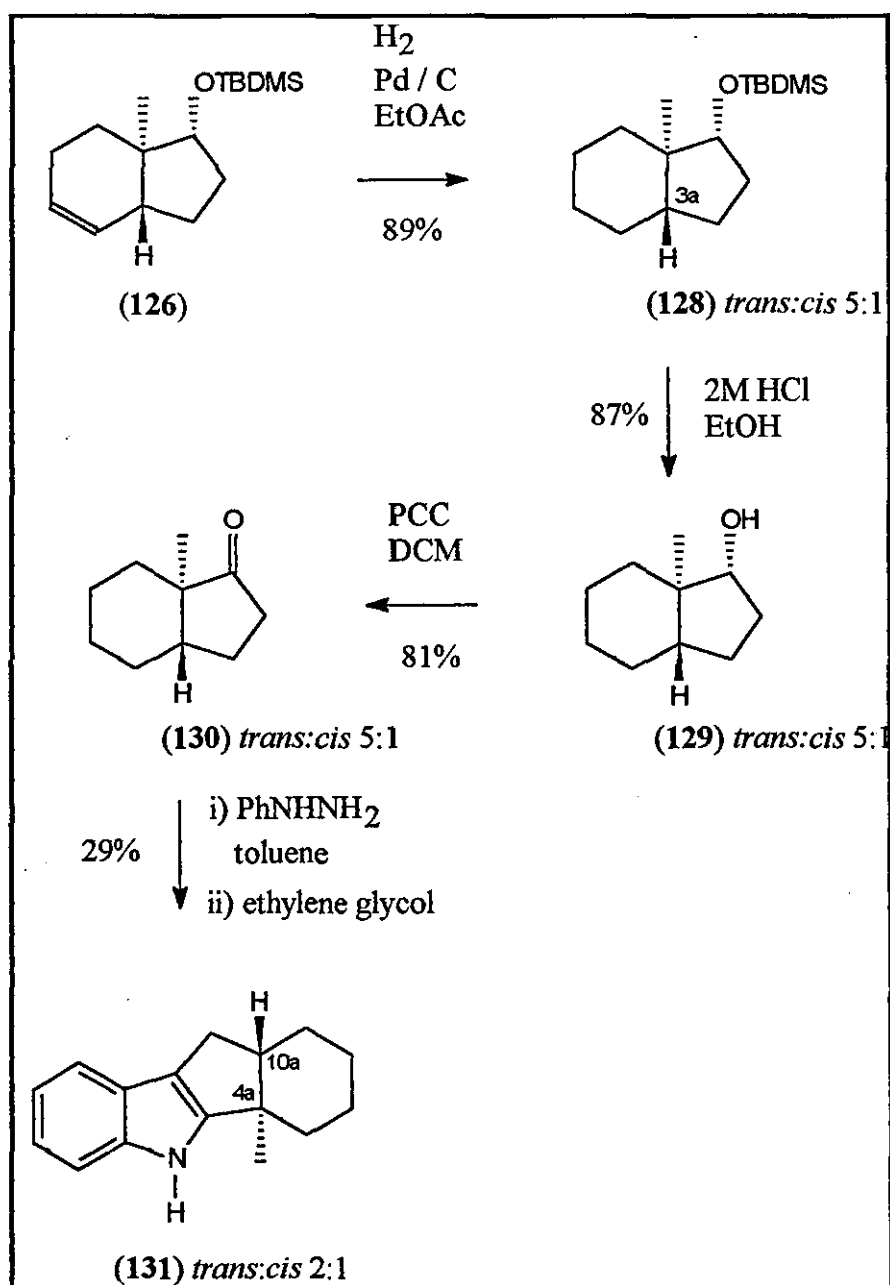
Scheme 34

A German group have stated that they did not obtain the *trans* isomer under the conditions described above but they have obtained the desired isomer using a palladium catalyst in refluxing dioxane.^{60c} In our hands, it was found that both sets of conditions gave the desired isomer, the latter conditions however, gave (126) in lower yield.

The Japanese and German groups that used palladium chemistry to obtain the *trans* isomer in the enantiomeric hydriindene system did not publish any further reactions on the system. It was necessary for our purposes, however, to obtain the *trans* ketone (130) and

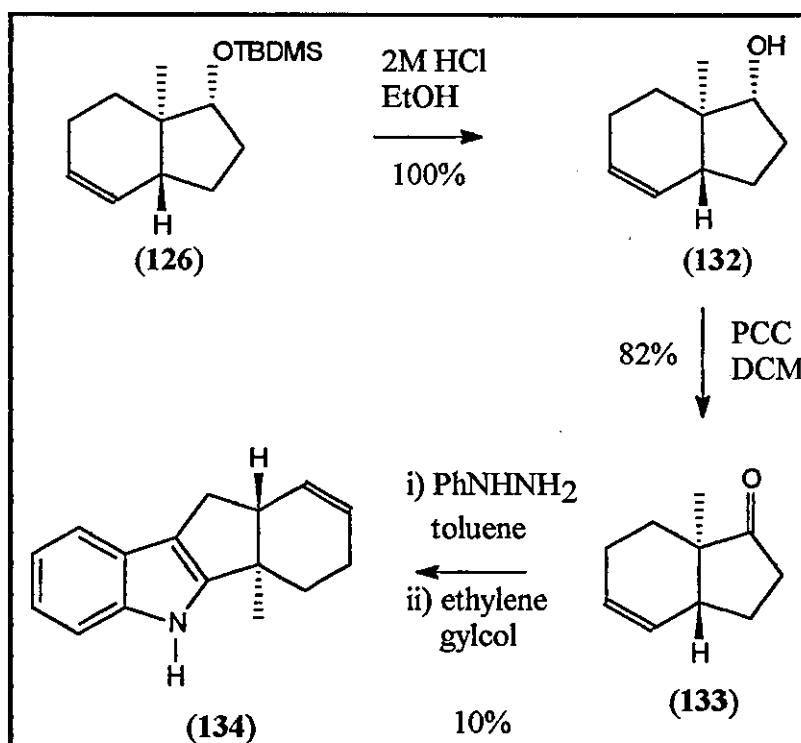
incorporate this into the Fischer indole synthesis in order to obtain the central indole moiety of the tremorgenic indoles.

To this end, the olefin (**126**) was hydrogenated using 10% Pd/C in ethyl acetate to give hydrindane (**128**) as a colourless liquid in 89% yield. At this stage there was also an amount of the *cis* isomer produced where partial isomerisation at C3a had occurred. In the proton NMR spectrum the signal for the proton at C1 of the major isomer appears at 3.57 ppm whereas the corresponding signal for the minor isomer is observed at 3.86 ppm. As stated previously this indicates that the major component is the *trans* isomer and integration of these peaks showed the ratio to be 5:1 *trans:cis*. In an attempt to improve the 5:1 *trans:cis* ratio, the hydrogenation step was reinvestigated. However, variation of solvent and/or catalyst did not improve the ratio of isomers obtained. The isomers were chromatographically indistinguishable and hence were reacted as a mixture. Removal of the silyl protecting group was achieved with 2M hydrochloric acid in ethanol at room temperature to give the alcohol (**129**) as a colourless semisolid in 87% yield. Pyridinium chlorochromate oxidation of the alcohol (**129**) gave the ketone (**130**) as a pale yellow liquid in 81% yield. The ketone was reacted with phenylhydrazine as previously and the indole (**131**) was obtained as a yellow solid in 29% yield after flash chromatography (Scheme 35). Unfortunately, analysis of spectroscopic data showed the compound to be a mixture of *trans* and *cis* isomers in a ratio of 2:1. The IR spectrum showed the presence of two NH stretches at 3472 and 3408 cm^{-1} . The proton NMR spectrum showed the *trans* and *cis* methyl singlets at 0.99 ppm and 1.31 ppm respectively in a ratio of 2:1 and two NH peaks at 7.7 and 7.8 ppm. The carbon NMR spectrum showed doubling up of the peaks in the aliphatic region with two methyl signals and two CH signals corresponding to the proton at C10a in the indole (**131**).



Scheme 35

In order to obtain optically pure *trans* ketone and employ it in a Fischer indole reaction, it was decided to keep the olefin intact. Preliminary studies were undertaken as follows. The hydrindene (126) was treated with ethanolic hydrochloric acid as previously to give the novel alcohol (132) as a colourless semi-solid in quantitative yield. Pyridinium chlorochromate oxidation of the alcohol (132) gave the ketone (133) as a colourless liquid in 82% yield. Reaction of the ketone (133) with phenylhydrazine in refluxing toluene followed by cyclisation in refluxing ethylene glycol gave the novel indole (134) as an orange solid in 10% yield, m.p. 93-95°C (Scheme 36).



Scheme 36

2.4 Conclusions

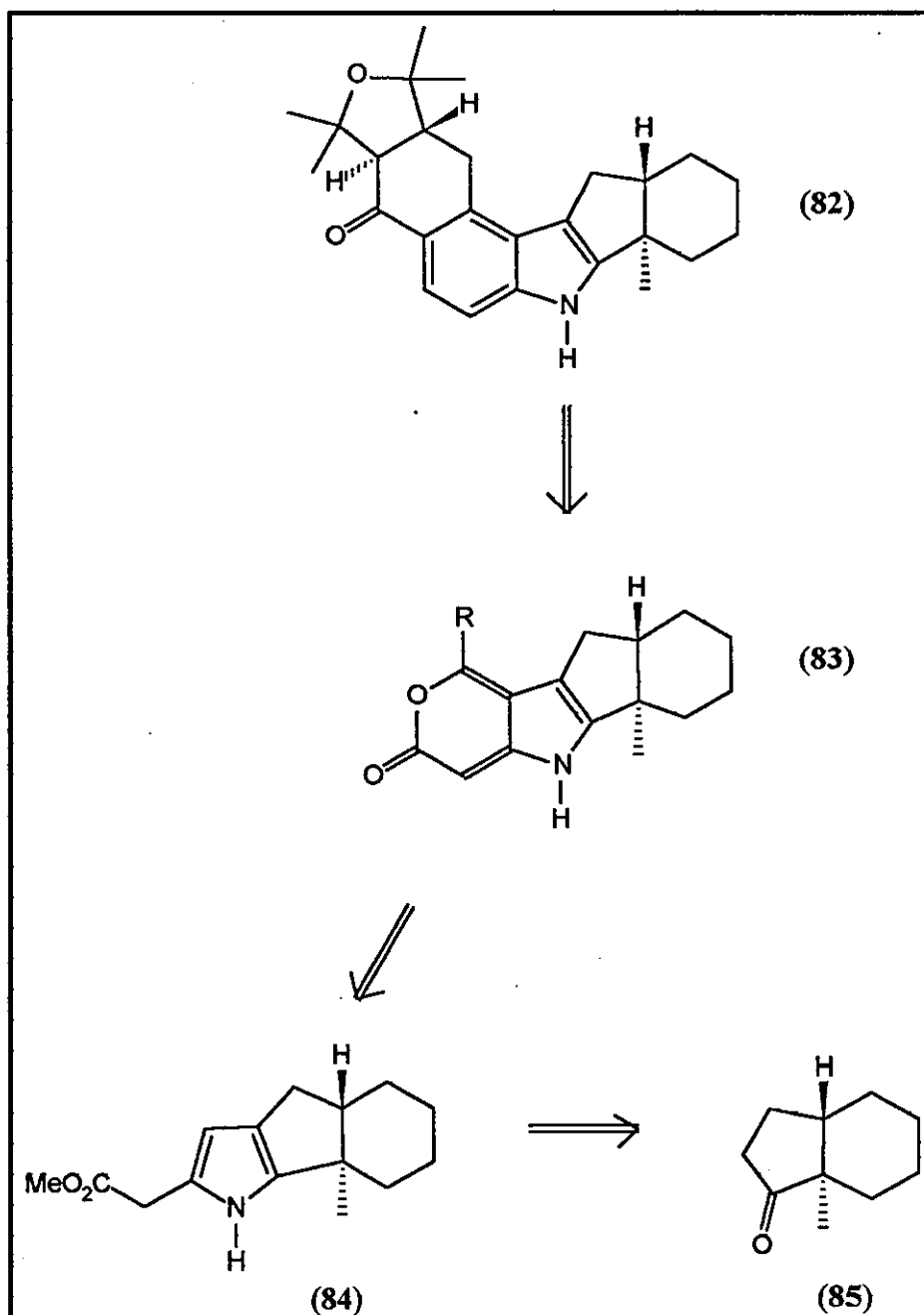
We have achieved our objective of obtaining the *trans* isomer of the hydrindane and its incorporation into the central portion of the tremorgenic indoles. The tetracyclic indole (134) was prepared with *trans* stereochemistry in 10 steps starting from methyl vinyl ketone and 2-methylcyclopentane-1,3-dione. Our work does however, illustrate that the difficulty of obtaining the *trans* isomer of 6,5-bicyclic systems via catalytic heterogeneous hydrogenation is not easily overcome.

CHAPTER 3

Pyrrole and Tetrahydrofuran Studies

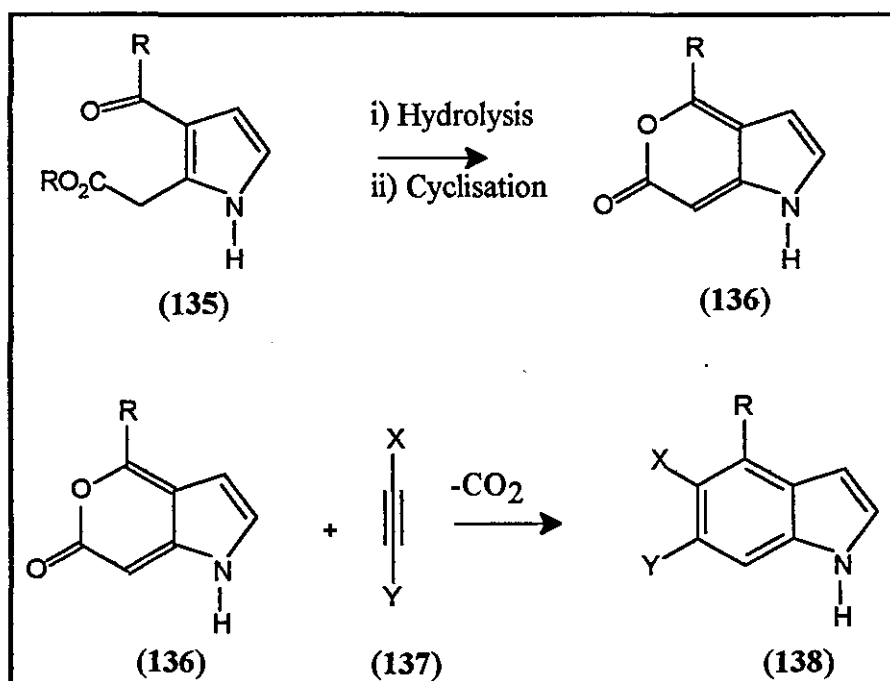
3.1 Introduction

As shown in Chapter 2, the central indole moiety of the tremorgenic indoles can be obtained from the pyranopyrrole (83) (Scheme 37). The pyranopyrrole (83) is itself available from the *trans*-hydrindane (85) via the pyrrole (84). This is a novel route to indoles from pyrroles utilising Diels-Alder chemistry previously developed in our laboratories.^{45a-45c,73,74} If the R group on pyranopyrrole (83) is a substituted tetrahydrofuran then the left-hand side of lolitrem B (82) is readily available.



Scheme 37

To this end, it is essential for the synthetic strategy that the pyrrole is obtained with an acetic ester substituent at either the 2- or 3- position. This allows further functionalisation of the vacant position on the pyrrole ring to give a compound such as (135). The α -pyranone (136) is formed via hydrolysis of the ester to the corresponding acid followed by cyclisation. Diels-Alder reactions on (136) with the spontaneous loss of carbon dioxide produce substituted indoles (138). The choice of dienophile (137) will determine which functionalities are on the indole and thus give an approach to the tremorgenic indoles (Scheme 38).



Scheme 38

If the R group on pyranopyrrole (136) is a substituted tetrahydrofuran then the left-hand side of lolitrem B (82) is accessible via an intramolecular approach. If, however, the R group is a simple substituent and the dienophile (137) supports groups that can be modified to allow the incorporation of a tetrahydrofuran moiety onto the indole ring then the left-hand portion of lolitrem B (82) is accessible via intermolecular Diels-Alder chemistry. Other members of the tremorgenic mycotoxin family could also be prepared via this methodology.

There are many examples of syntheses where direct attachment of an ester group to the pyrrole ring is possible from a carbonyl precursor, for example; the Hantzsch synthesis - reaction between an α -haloketone and a β -ketoester and the Knorr synthesis - reaction between an α -aminoketone and a carbonyl compound.⁷⁵ However, the extra methylene group in the ester substituent needed for this synthetic route was the major stumbling block

in the preparation of the pyrrole ring. Previous studies showed that simple homologation of a pyrrole ring was unsuccessful.⁷³ Recent reports state that this can be achieved via selective homolytic substitution on the pyrrole ring,⁷⁶ however, a twelve-fold excess of the starting pyrrole is required and this would be impractical as a synthetic route.

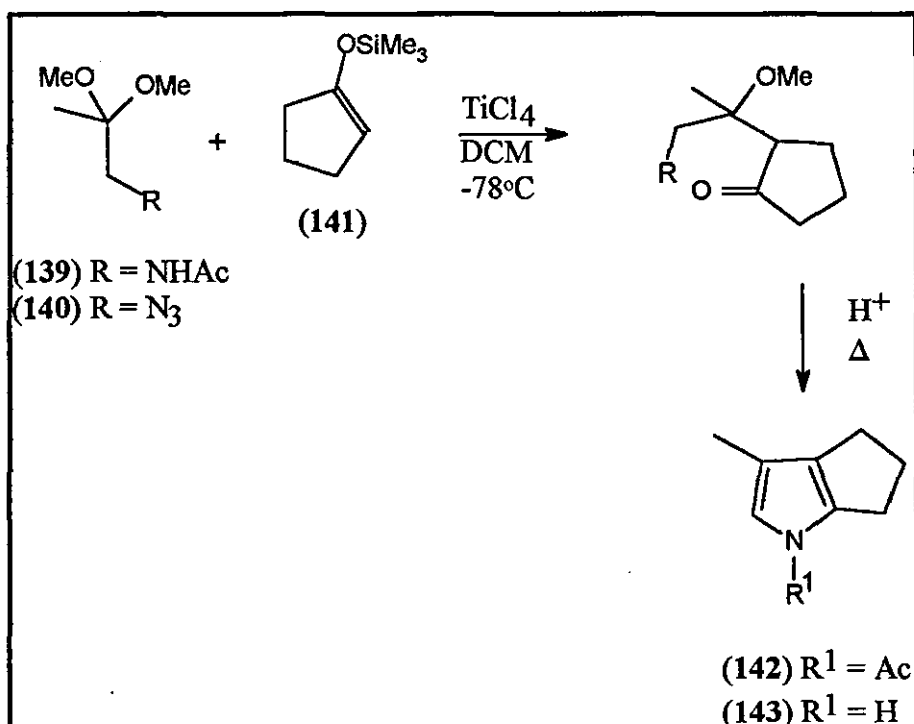
The synthetic routes are discussed in terms of the routes undertaken for the formation of 2- and 3- substituted pyrroles and whether the C3-C4 or C2-N bond is formed first. In all of these studies, cyclopentanone is used as a model for the five-membered ring ketone of the hydrindane (85).

3.2 Synthetic Approaches

3-Substituted Pyrroles

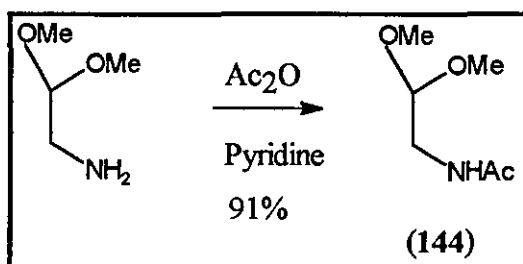
3.2.1 Initial formation of C3-C4 bond

The first attempted route to the pyrrole was based on the Mukaiyama crossed aldol synthesis⁷⁷ - reports in the literature showed that a silyl enol ether (141) could be reacted with an amide (139) or azide (140) in the presence of a Lewis acid to give pyrroles (142) or (143) respectively (Scheme 39).⁷⁸



Scheme 39

To test this route, various substrates were prepared. The simplest substrate was the amide (144) prepared from the reaction of aminoacetaldehyde dimethylacetal and acetic anhydride in pyridine (Scheme 40). This would furnish a pyrrole with a hydrogen at the C3 position.

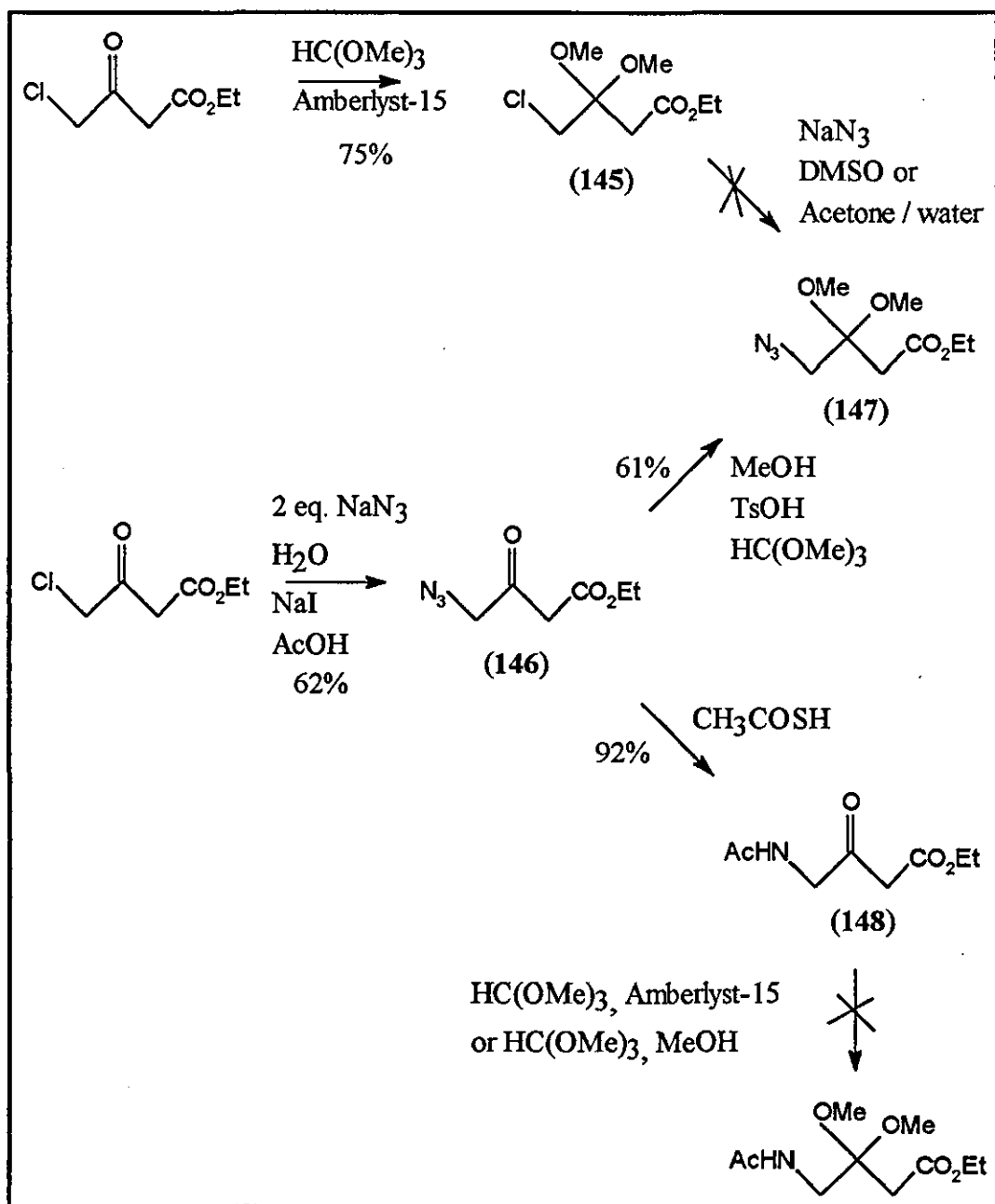


Scheme 40

Incorporation of the methylene ester into the system to lead to the formation of the desired acetic ester substituted pyrrole proved troublesome. The target molecules were the ketal protected amide and azide of ethyl 4-chloro-3-oxobutanoate. Ketal protection of ethyl 4-chloro-3-oxobutanoate was achieved by reaction of the ketone with trimethyl orthoformate in the presence of Amberlyst-15 ion exchange resin giving the butanoate (145) as an orange liquid in 75% yield. Nucleophilic displacement of the chloride with sodium azide did not take place in either dimethyl sulfoxide or acetone/water. It was decided to form the azide first and then protect the ketone functionality (Scheme 41).

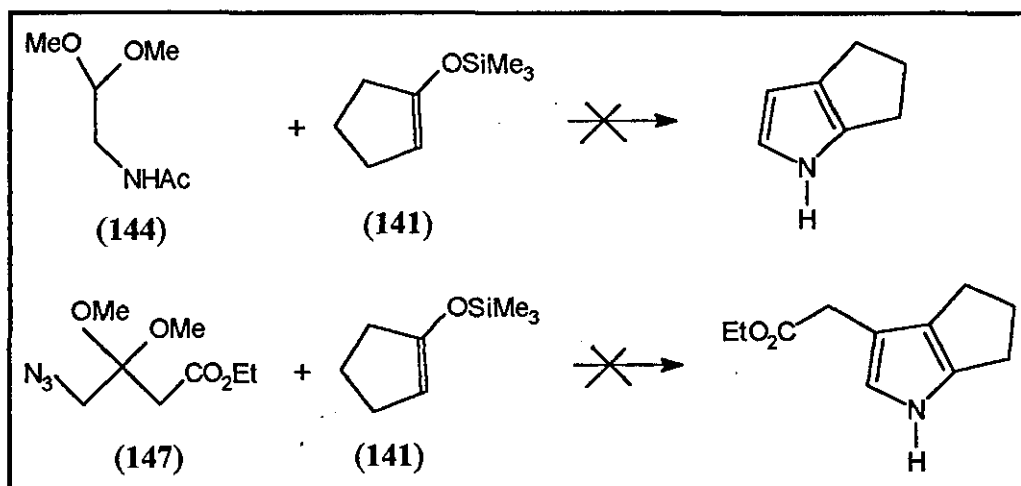
The initial attempts at forming the azide from the non-protected chloride by refluxing with sodium azide in either dimethyl sulfoxide, *N,N*-dimethylformamide or water gave the azide (146) in modest yield ranging from 23-55%. Optimum conditions were achieved by refluxing with two equivalents of sodium azide in water with catalytic amounts of sodium iodide and acetic acid. This afforded the azide (146) as a pale yellow liquid in 62% yield. Subsequent protection of the carbonyl functionality was achieved using trimethyl orthoformate and methanol to give the azide (147) as a pale yellow liquid in 61% yield.

Azide (146) was converted directly into the amide (148) as an orange solid in 92% yield, m.p. 42-44°C, by stirring with thioacetic acid.⁷⁹ Protection of the carbonyl functionality could not be achieved using either trimethyl orthoformate in the presence of Amberlyst-15 or trimethyl orthoformate and methanol.



Scheme 41

The amide (144) and azide (147) were reacted with trimethylsiloxy-cyclopentene (141)^{80a,b} but all attempts at the Mukaiyama reaction failed, and only decomposition products were obtained (Scheme 42). Thus, another approach to the desired pyrrole was required.



Scheme 42

2-Substituted Pyrroles

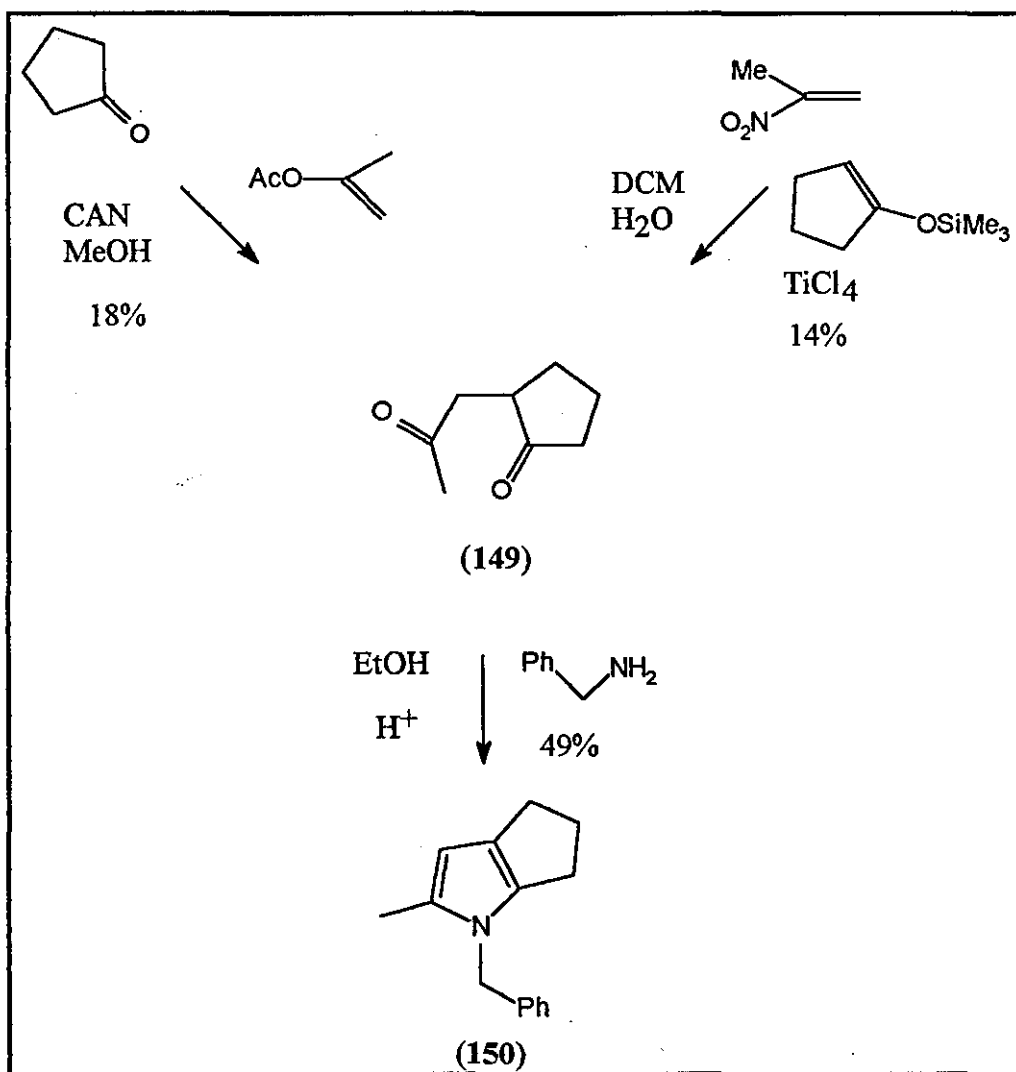
3.2.2 Initial formation of C3-C4 bond

The first attempts involved the preparation of 1,4-dicarbonyls for use in traditional Paal-Knorr pyrrole chemistry.

The simplest dicarbonyl to form would be the methyl substituted dicarbonyl (149) as it would be the key intermediate in the preparation of the simply substituted pyrrole (150) (Scheme 43). Two routes were employed, the first being the reaction between isopropenyl acetate and the radical of cyclopentanone generated by cerium (IV) ammonium nitrate.⁸¹ Dicarbonyl (149) was formed but in low yields (18%) and a twelve-fold excess of the ketone needed to be employed which would be unsatisfactory in a synthetic route.

The second preparation investigated was the use of a nitro compound,^{82a,b} as this functionality can be easily hydrolysed to a carbonyl group.^{82c} The silyl enol ether of cyclopentanone was reacted with 2-nitroprop-1-ene and there was evidence of the production of the dicarbonyl (149), but unfortunately there was insufficient material with which to carry on the synthesis.

Treatment of the available dicarbonyl (149) with benzylamine gave the pyrrole (150)⁸³ as a yellow oil in 49% yield. Thus, this methodology would be ideal in the formation of pyrroles but a more satisfactory route to the dicarbonyl (149) needs to be found.

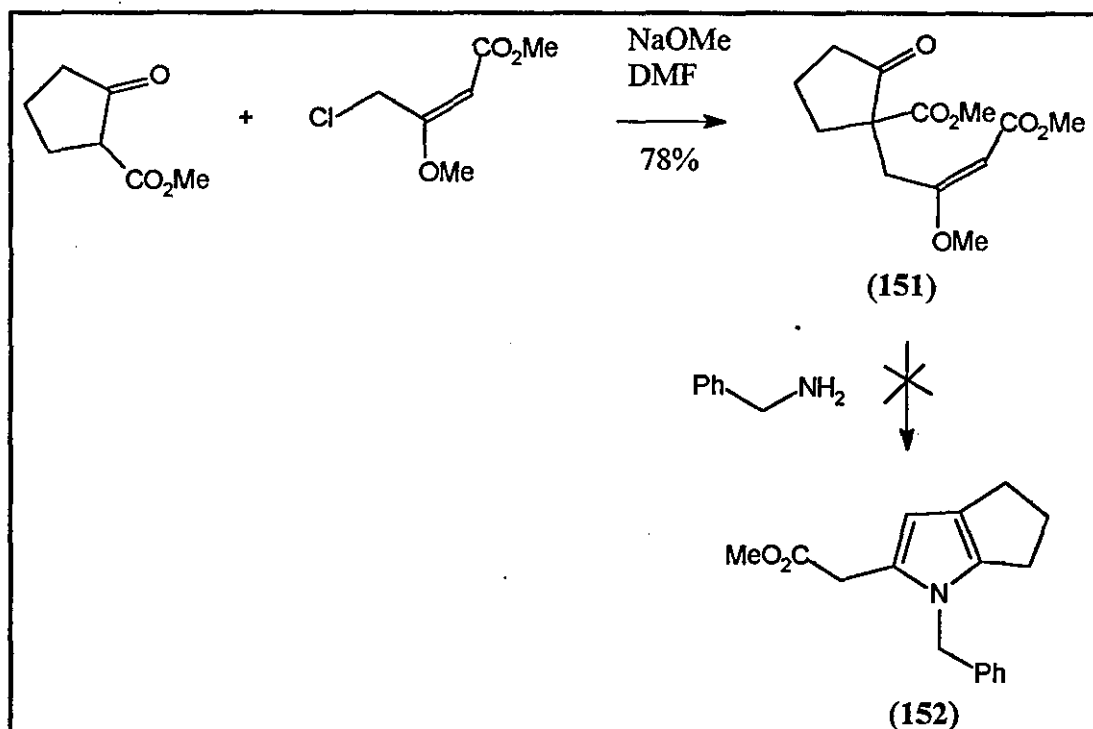


Scheme 43

An alternative route to the 1,4-dicarbonyl involves direct alkylation of the cyclopentanone ring. Alkylation of a cyclopentanone ring is notoriously difficult,⁸⁴ so it was decided to use an activated ring structure to make alkylation easier. In order to obtain the pyrrole with the desired acetic acid substituent, it was decided to use methyl 4-chloro-3-methoxy-2(*E*)-butenoate^{85a,b} as the alkylating agent as this would lead to a 1,4-dicarbonyl equivalent. Deprotection followed by cyclisation in the presence of an amine should lead to the desired pyrrole.

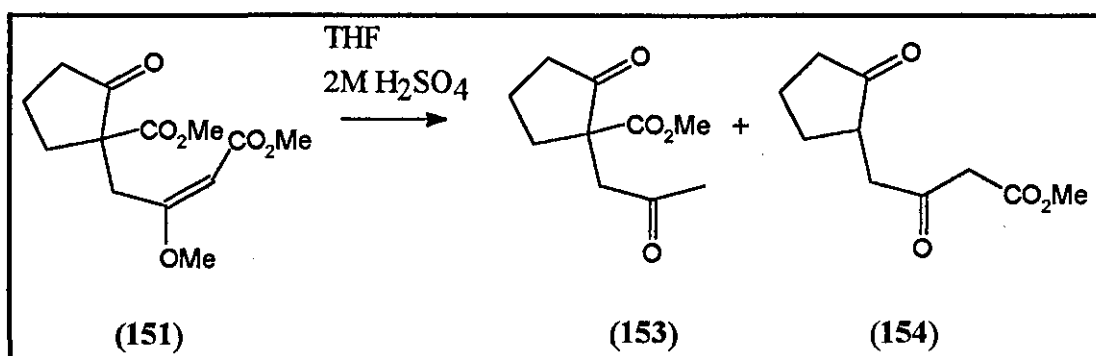
Accordingly, the anion of methyl 2-oxocyclopentanonecarboxylate was formed using sodium methoxide in *N,N*-dimethylformamide and this was reacted with methyl 4-chloro-3-methoxy-2(*E*)-butenoate^{85a,b,86} to give the novel carboxylate (**151**) as a yellow solid in 78% yield, m.p. 53-55°C (Scheme 44). Attempts to cyclise this compound in the presence

of benzylamine did not lead to the pyrrole (152) but stopped at the formation of the imine of the cyclopentanone ring.



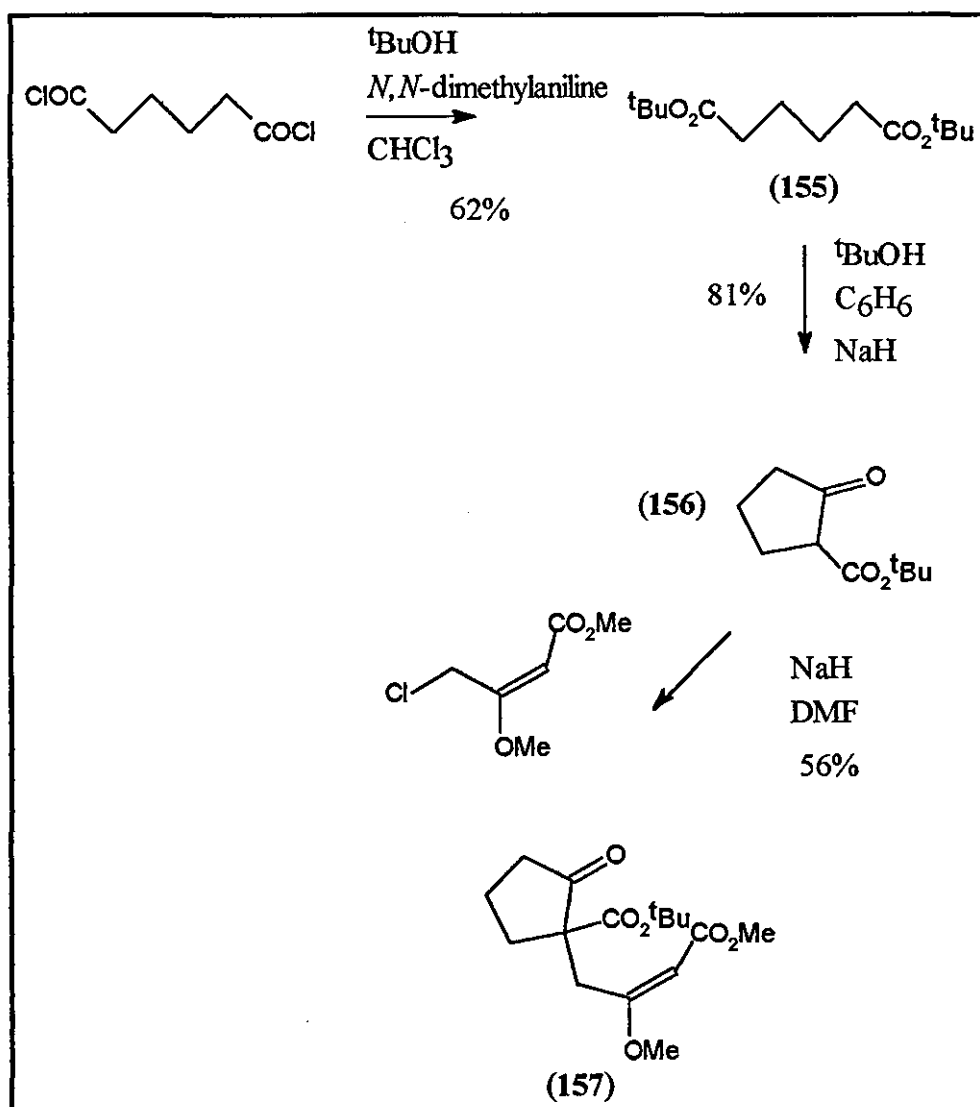
Scheme 44

It appeared that the activating group was preventing any cyclisation so it was decided to remove this group prior to reaction with benzylamine. Thus, acidic hydrolysis of compound (151) was undertaken and a mixture of products was obtained. Unfortunately, the desired dicarbonyl (154) was obtained only as the minor product with dicarbonyl (153) being formed as the major product (Scheme 45). This did not give sufficient quantities of the desired 1,4-dicarbonyl (154) so it was decided to use different activating groups as this should allow selective cleavage to give the dicarbonyl (154).



Scheme 45

It was decided to synthesise the corresponding tertiary butyl ester as this was expected to allow selective ester hydrolysis. The first step in the synthesis was the diprotection of hexanedioyl chloride as its tertiary butyl ester by reaction with *tert*-butanol and *N,N*-dimethylaniline. This gave di-*tert*-butyl-hexanedioate (**155**) as a colourless solid in 62% yield (Scheme 46). Cyclisation using sodium hydride in refluxing benzene gave the carboxylate (**156**)⁸⁷ as a colourless liquid in 81% yield. The activated cyclopentanone was reacted as previously with methyl 4-chloro-3-methoxy-2(*E*)-butenoate in *N,N*-dimethylformamide using sodium hydride as the base, to give the novel alkylated cyclopentanone (**157**) as a colourless liquid in 56% yield.

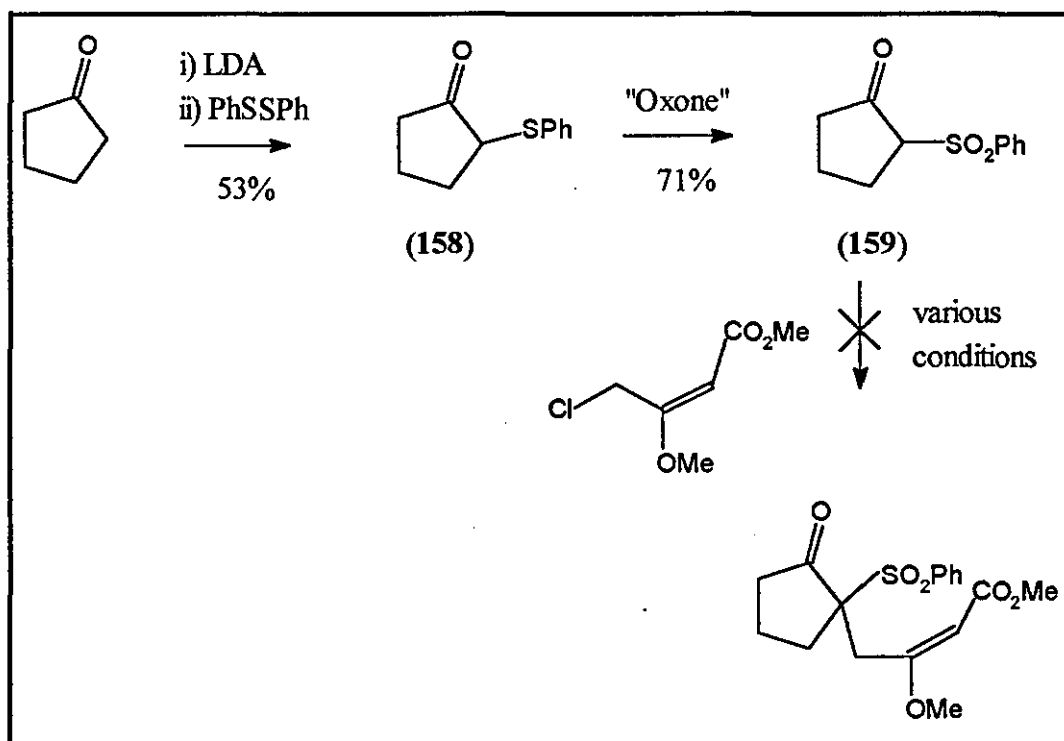


Scheme 46

Subsequent attempts at selective hydrolysis of the *tert*-butyl ester using sulfuric acid in methanol or trifluoroacetic acid did not give the desired dicarbonyl so a different activating group for the cyclopentanone ring was investigated.

Thus, the sulfone activating group was chosen as selective methods of its removal are well known.^{88a,b} Cyclopentanone was reacted with lithium diisopropylamide at -78°C and quenched with diphenyl disulfide at room temperature to give, after column chromatography, 2-phenylthiocyclopentanone (158)⁸⁹ as a yellow liquid in 53% yield. The sulfide was oxidised directly to the sulfone using "Oxone", potassium peroxymonosulfate, to give 2-oxocyclopentane-1-phenylsulfone (159)⁹⁰ as a colourless solid in 71% yield (Scheme 47). However, all attempts at alkylation of the sulfone with 4-chloro-3-methoxy-2(*E*)-butenoate using sodium hydride as the base in tetrahydrofuran or *N,N*-dimethylformamide

gave back starting materials; the use of sodium methoxide or potassium carbonate as the base in *N,N*-dimethylformamide gave back starting materials and the use of lithium diisopropylamide served to remove the sulfone group and not functionalise the ring.



Scheme 47

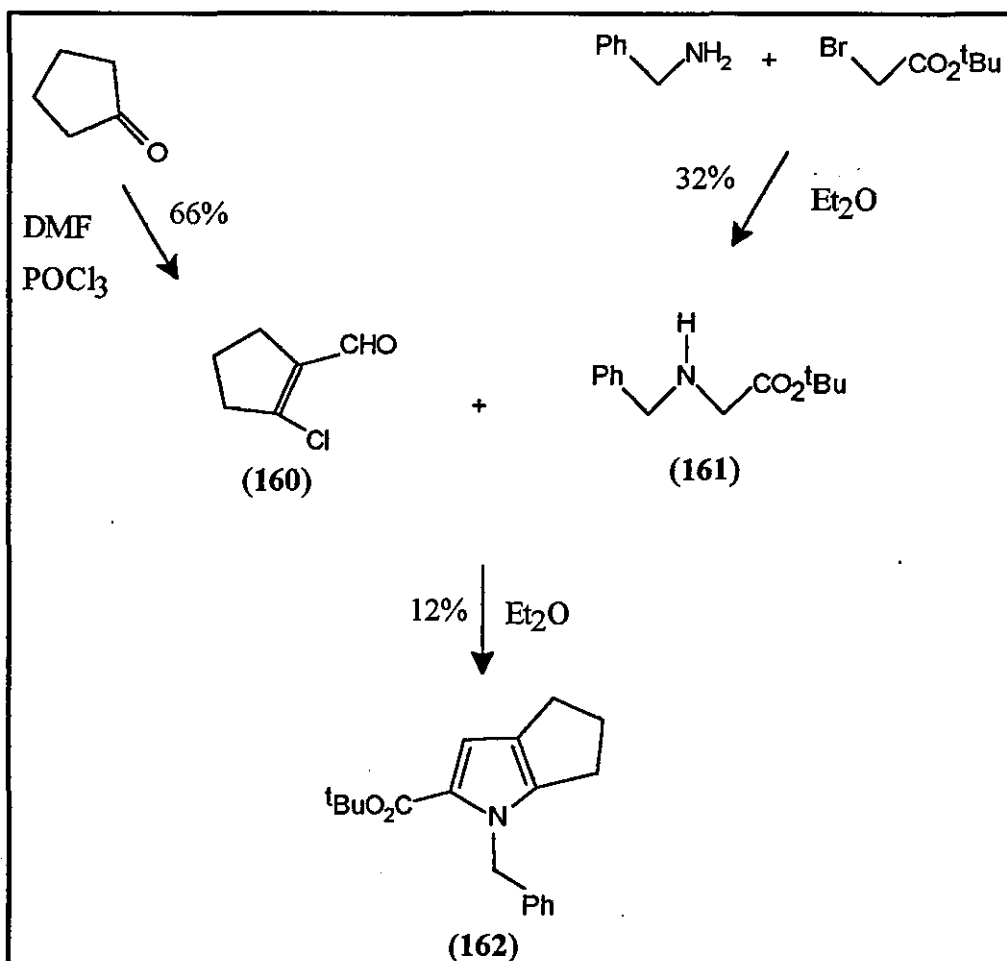
As a satisfactory route to the pyrrole via traditional Paal-Knorr chemistry could not be found, it was decided to return to a route which had been previously developed in these laboratories.⁷³

3.2.3 Initial formation of C2-N bond

This route is not ideal, as it is a lengthy synthesis and the first step is low yielding, however it does allow preparation of the 2-substituted pyrrole in gram quantities and thus development of a route to the indole portion of the tremorgenic mycotoxins.

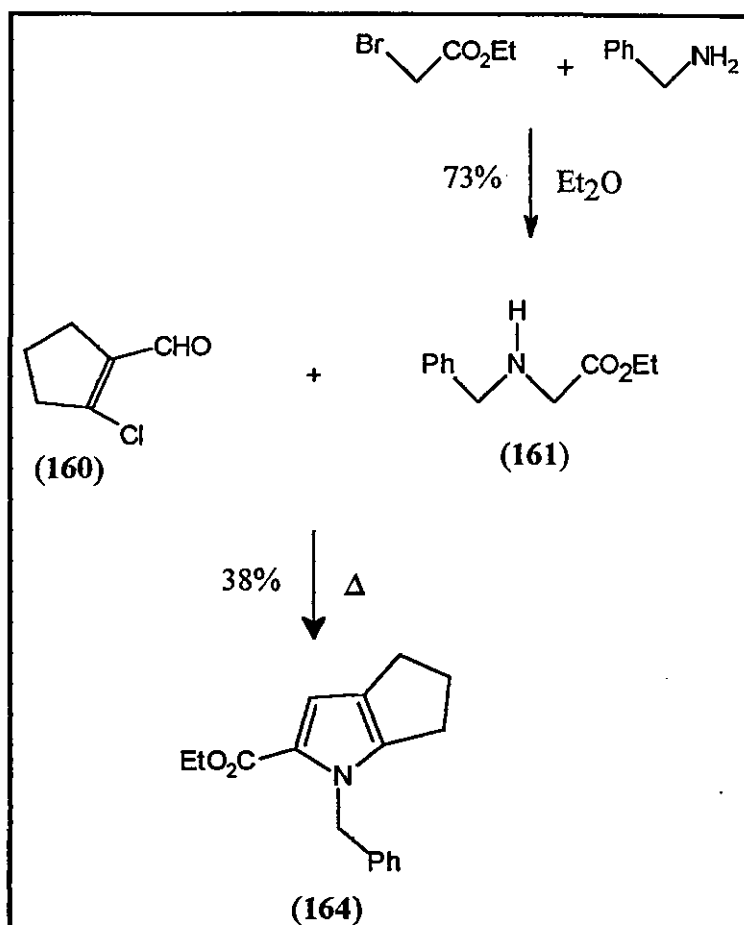
Accordingly, the reactive aldehyde (160)^{91a,b} was formed as a colourless liquid in 66% yield from the reaction of cyclopentanone with phosphorus oxychloride and *N,N*-dimethylformamide. The aldehyde must be used immediately after distillation or it decomposes giving off hydrochloric acid. Treatment of this aldehyde with a secondary

amine gives a 2-substituted cyclopent[*b*]pyrrole.⁹² The first amine to be reacted with the aldehyde, *tert*-butyl *N*-benzylglycinate (**161**) was prepared as a colourless liquid in 32% yield from benzylamine and *tert*-butyl bromoacetate. This however, only gave 12% yield of the novel pyrrole (**162**) (Scheme 48).



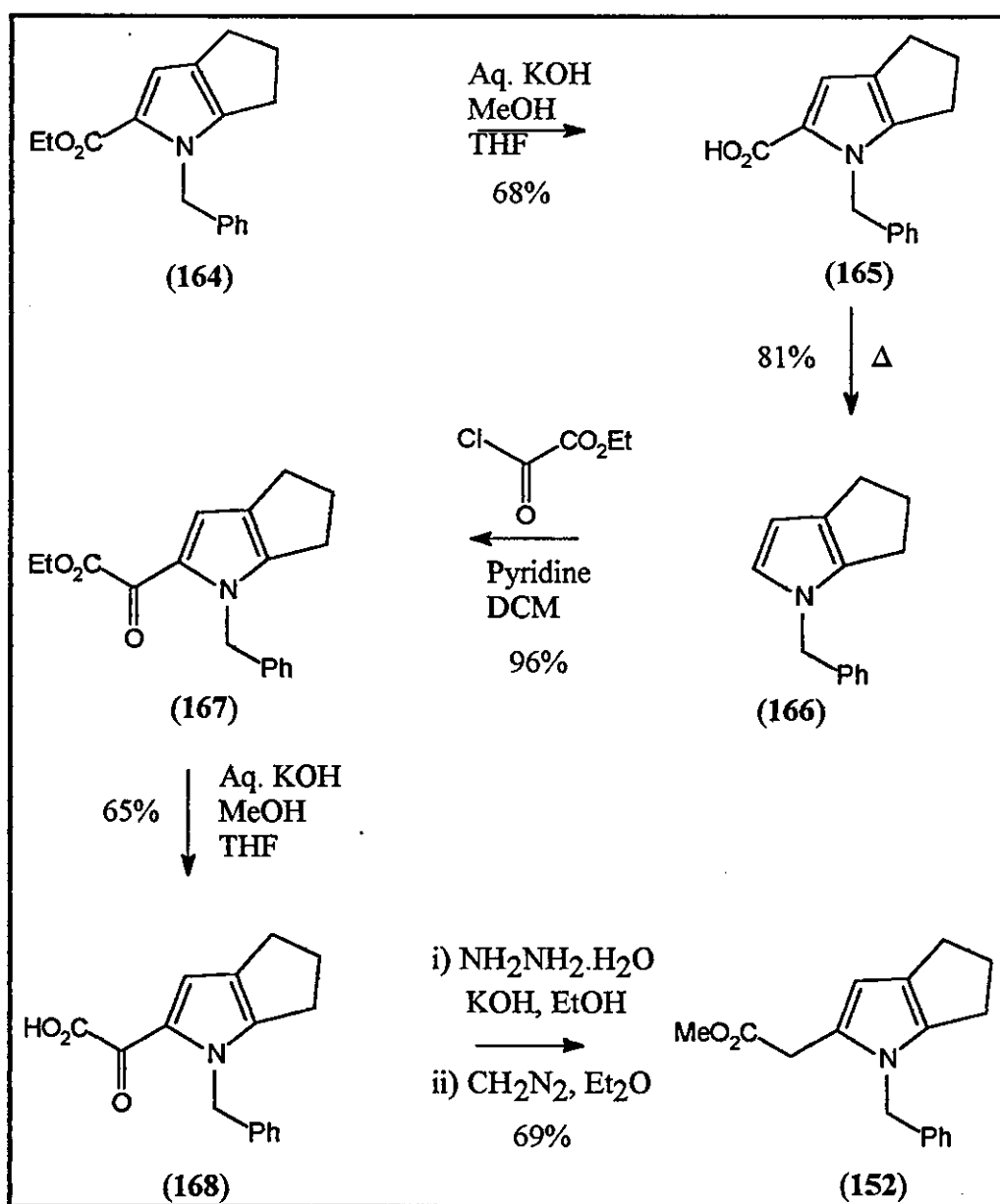
Scheme 48

The second amine to be used, ethyl *N*-benzylglycinate (**163**) was previously prepared in these laboratories.^{73,92} It is obtained as a colourless liquid in 73% yield from ethyl bromoacetate and benzylamine. Reaction of this amine with the aldehyde (**160**) gave the pyrrole (**164**) as a brown oil in 38% yield (Scheme 49).^{73,92}



Scheme 49

The conversion of pyrrole ester (164) into the desired pyrrole (152) was achieved via the following route.⁷³ Alkaline hydrolysis of the pyrrole ester (164), using aqueous potassium hydroxide in tetrahydrofuran and methanol gave the acid (165) as a brown solid in 68% yield (Scheme 50). Decarboxylation of the acid occurred smoothly at its melting point to give pyrrole (166) as a yellow oil in 81% yield. Immediate 2-acylation of the pyrrole (166) by treatment with ethyl oxalyl chloride and pyridine in dichloromethane gave the glyoxalate (167) as a brown oil in 96% yield. The glyoxalate (167) was hydrolysed using aqueous potassium hydroxide in tetrahydrofuran and methanol to give the acid (168) as a brown solid in 65% yield. Wolff-Kishner reduction of the acid (168) using ethanolic hydroxide and hydrazine hydrate, followed by esterification using diazomethane, gave the desired pyrrole ester (152) as a yellow oil in 69% yield. The yields throughout this route are variable, with the Wolff-Kishner reduction proving troublesome. The conditions of the reaction not only reduce the carbonyl to the corresponding methylene but also cause decarboxylation and loss of the side-chain to give the pyrrole (166). Hence, great reduction in yield often occurs.

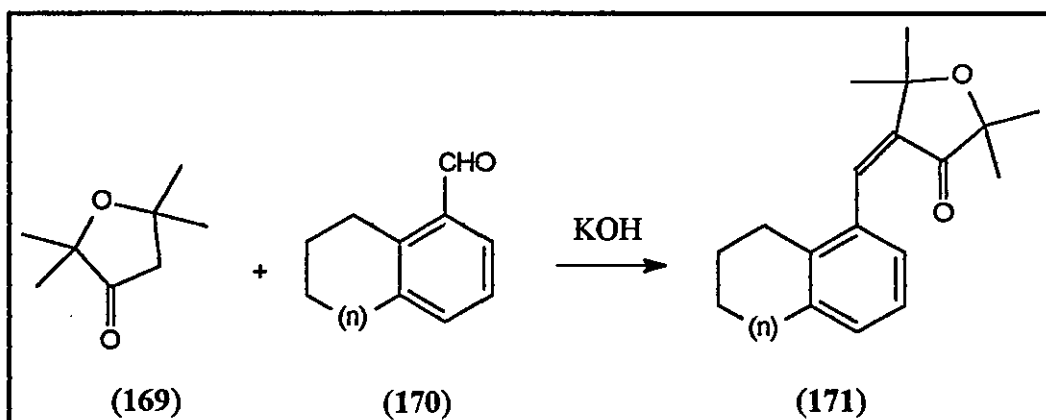


Scheme 50

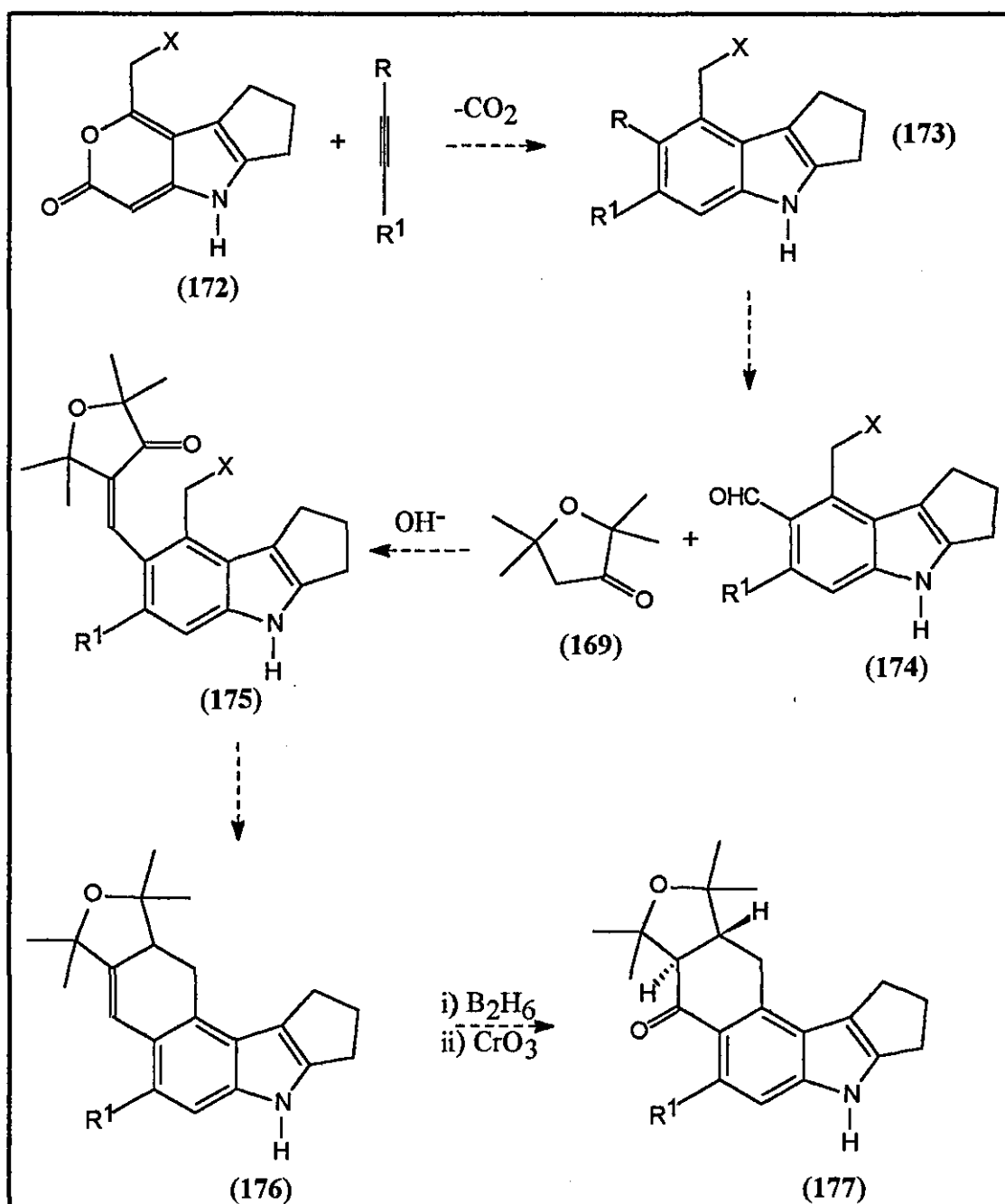
3.2.4 Pyranopyrrole and tetrahydrofuran studies

As stated in section 3.1, the correctedly substituted pyrrole can be acylated via a Friedel-Crafts reaction at the vacant carbon to give the precursor to the α -pyranone necessary for Diels-Alder cycloadditions.

In the intermolecular approach to the left-hand side of lolitrem B, the pyranone (172) can be reacted with a variety of known dienophiles which can be modified to allow incorporation of ring A onto the molecule. Ring A of lolitrem B is accessible from the tetrahydrofuranone (169). It is known that tetrahydrofuranone (169) reacts with a benzaldehyde (170) in an aldol condensation reaction to give the olefin (171) (Scheme 51).⁹³ It follows that if the reaction of the dienophiles and pyranone (172) give the indole (173) in which the substituents can be modified to give an aldehyde functionality on the indole ring (174) then it should be possible to attach the tetrahydrofuranone (169) to the central indole moiety to give olefin (175) (Scheme 52). If the group at the C4 position on the indole (175) is an activated functionality then it should be possible to cyclise the tetrahydrofuranone onto the indole ring giving the pentacyclic system (176). To obtain the precursor to rings A-E of lolitrem B (177) the olefin would need to be oxidised to a ketone, this could be achieved via organoborane chemistry.^{94a,b}



Scheme 51

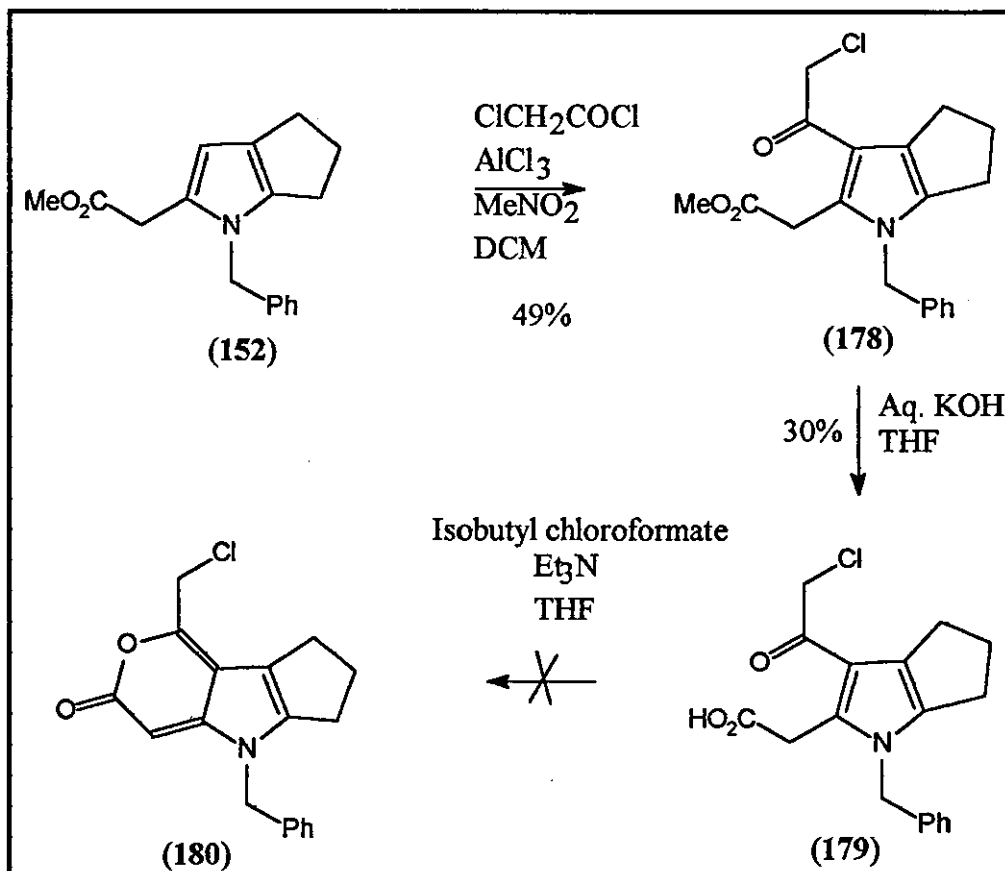


Scheme 52

It is crucial that the group on the dienophile that can be modified to give the aldehyde functionality finishes in the C5 position on the indole ring, *ortho* to the group at the C4 position from the α -pyranone in order for this methodology to be of any use.

Thus, it was decided to prepare an indole with a chloroacetyl substituent at the C4 position on the indole ring. Accordingly, the pyrrole (152) was reacted with chloroacetyl chloride in the presence of aluminium chloride to give the novel pyrrole (178) as a colourless solid in 49% yield, m.p. 136-138°C (Scheme 53). Alkaline hydrolysis of the ester

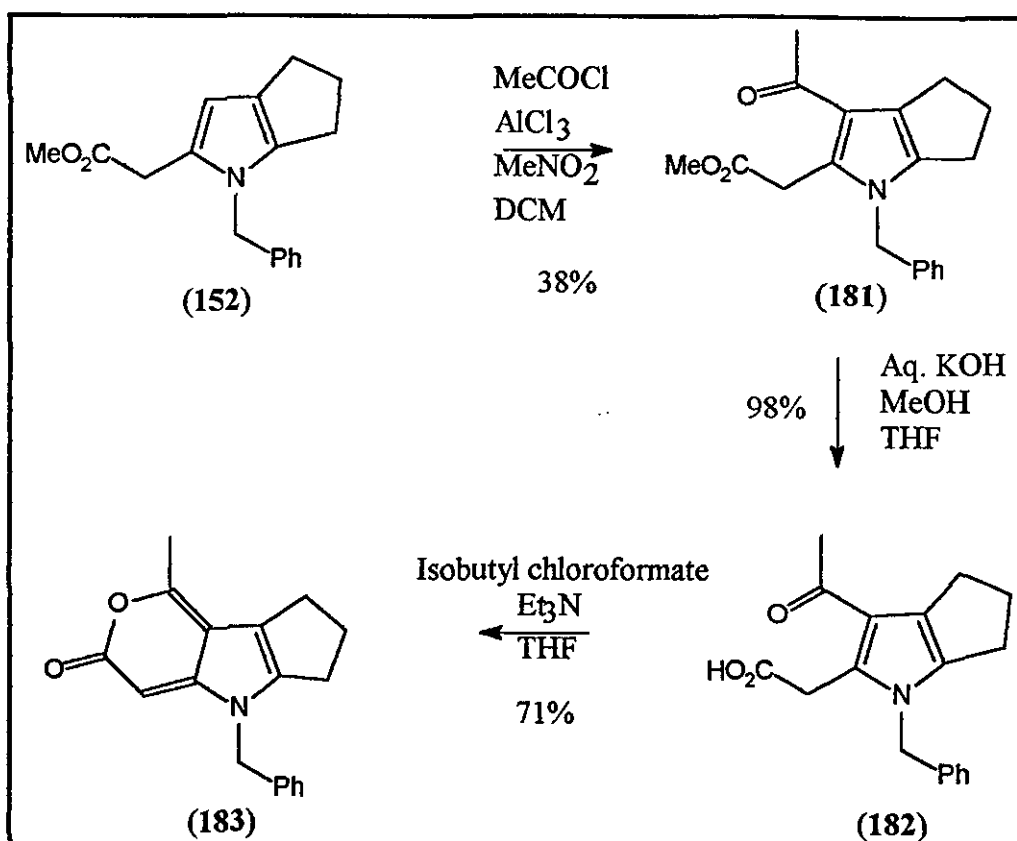
(178) was troublesome and gave the acid (179) as a brown solid in modest yield of 30%, m.p. 128-130°C. Cyclisation with isobutyl chloroformate in the presence of triethylamine however, did not afford the α -pyranone (180).



Scheme 53

As a satisfactory route to the pyranone could not be achieved, it was decided to return to an acylating agent that was known to proceed to the pyranone in good yield.

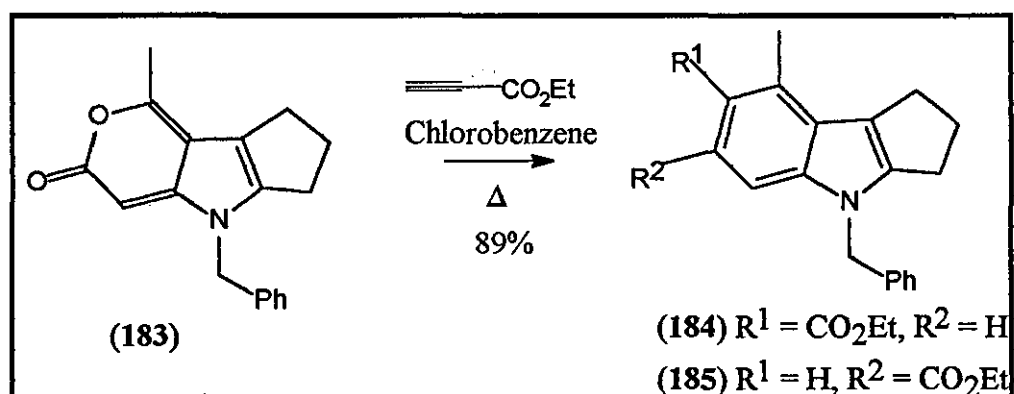
Thus, the pyrrole (152) was reacted with acetyl chloride in the presence of aluminium chloride to give the pyrrole (181) as a colourless solid in 38% yield (Scheme 54).⁷³ Alkaline hydrolysis of the ester (181) gave the acid (182) as a brown solid in quantitative yield. Cyclisation with isobutyl chloroformate in the presence of triethylamine afforded the α -pyranone (183) as a yellow solid in 71% yield.



Scheme 54

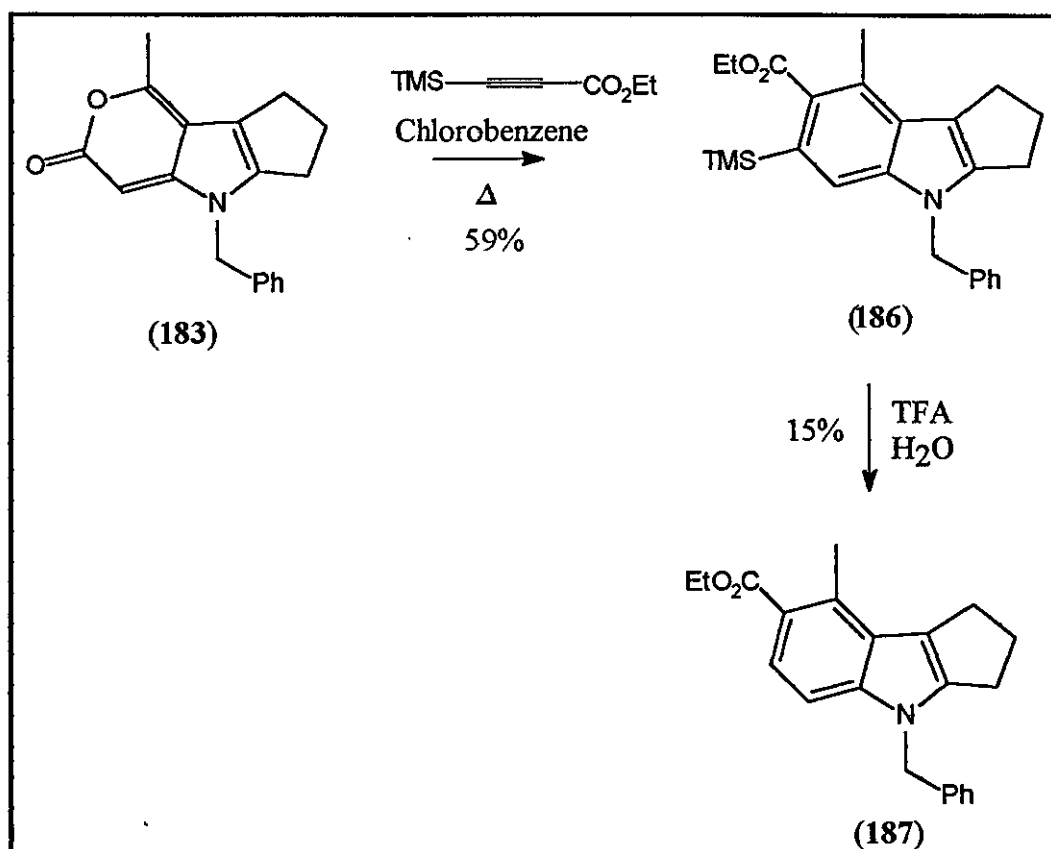
With the pyranone (183) in hand it was now possible to test whether the indole could be prepared with the substituents in the correct positions from the Diels-Alder reaction. The pyranone (183) was refluxed with ethyl propiolate for twelve hours affording a mixture of the novel indoles (184) and (185) (Scheme 55). The mixture of the two products is expected, as the unsymmetrical dienophile, ethyl propiolate, can add to the diene in two ways. The dienophile can add either with the ester functionality ending up *ortho* to the methyl group in the indole product (184) or *meta* to the methyl group in the indole product (185). The ratio of products can be determined by integration of the two methyl singlets. The singlet of the major isomer resonates at 2.59 ppm and the methyl singlet of the minor isomer resonates at 2.86 ppm. One would expect the methyl singlet of the *ortho* substituted indole to resonate downfield from the *meta* substituted product due to the deshielding effect of the ester group. This would indicate that the major isomer was the *meta* substituted indole which would give the isomers (184):(185) in a ratio of 1:1.8. Confirmation of the product structures can be obtained by examination of the aromatic region of the spectrum. For the isomer (185), where the methyl group is *meta* to the ester group, then one would expect two singlets for the remaining two aromatic protons and for isomer (184) one would expect a pair of doublets for the two *ortho* coupled aromatic protons. This is indeed found

to be the case and integration of the peaks shows that the isomers (184):(185) are in a ratio of 1:1.8. The isomers were extremely difficult to separate but sufficient material was obtained of isomer (184) for ^1H NMR studies to show conclusively that the methyl singlet for the *ortho* coupled isomer does resonate at 2.86 ppm and thus deduction of structure was correct. The ratio of products can be explained simply on steric grounds - the ester substituent prefers to lie away from the methyl substituent on the indole ring.



Scheme 55

This clearly does not give the desired substitution pattern for incorporation of the tetrahydrofuran portion of lolitrem B onto the indole ring. It is known from work previously undertaken in these laboratories that the presence of a bulky group on the other terminal of the dienophile forces the Diels-Alder reaction to be regiospecific and give an indole product with ester group *ortho* to the substituent from the pyranone. Thus, the pyranone (183) was refluxed with ethyl trimethylsilylpropiolate in chlorobenzene for 48 hours affording the novel indole (186) as a brown viscous oil in 59% yield (Scheme 56). Confirmation of the structure can be achieved by removal of the trimethylsilyl group. This proved troublesome with degradation of the product being a major problem, but sufficient material was obtained for proton NMR studies to be undertaken. The product obtained showed a shift in methyl signal from 2.51 ppm in indole (186) to 2.86 ppm in indole (187). This shift is comparable with the shift in methyl signal for the indoles (188) and (189) (Figure 22).⁷³ The aromatic region of the spectrum showed the appearance of a doublet at 7.67 ppm - identical to the spectrum obtained for indole (184), thus confirming that the presence of the bulky trimethylsilyl group forces the Diels-Alder reaction to be regiospecific giving the *ortho* ester substituted indole.



Scheme 56

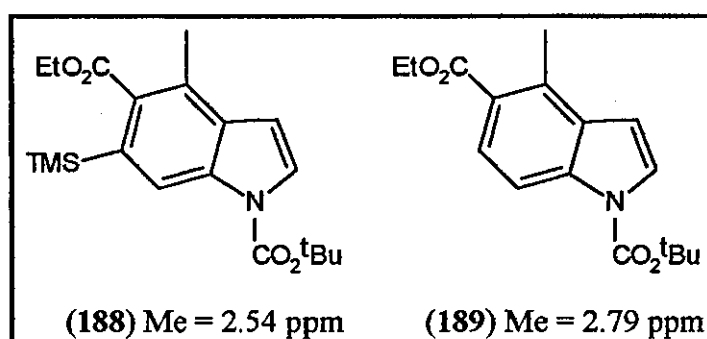
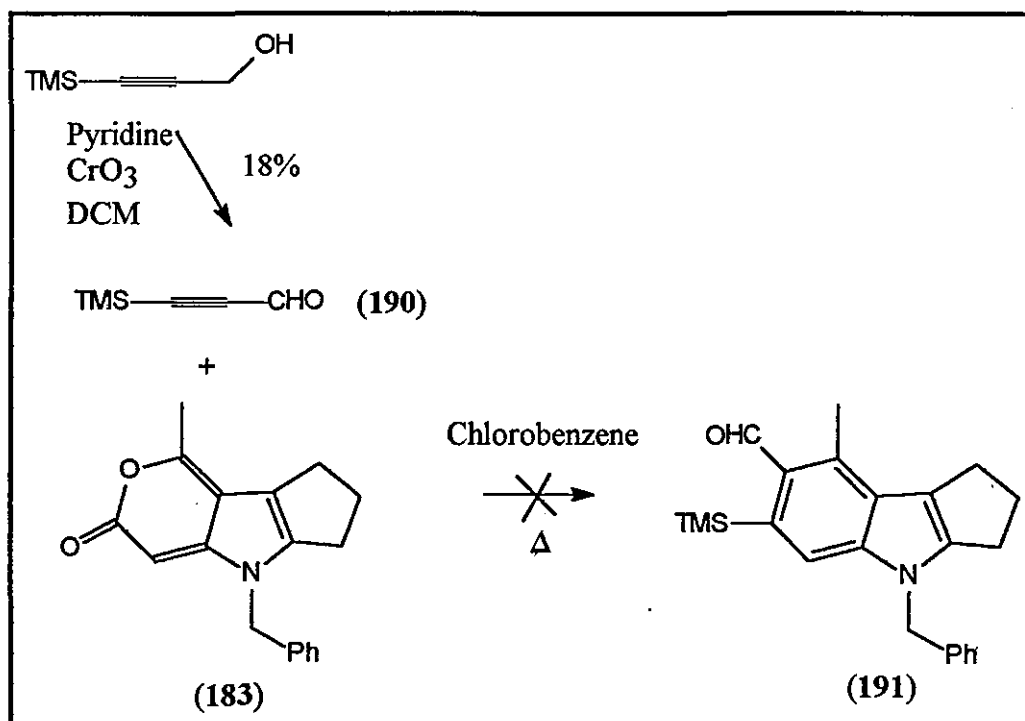


Figure 22: Indoles (188) and (189) showing shift in methyl signal on removal of trimethylsilyl group.

As it was now known that the Diels-Alder reaction could be controlled to give the desired substitution pattern on the indole ring it was decided to prepare the acetylene (190) by Collins oxidation of commercially available 3-trimethylsilyl-2-propyn-1-ol to give an approach to the indole with an aldehyde functionality at the C5 position on the indole ring. This would allow the tetrahydrofuran moiety to be attached to the central indole portion of

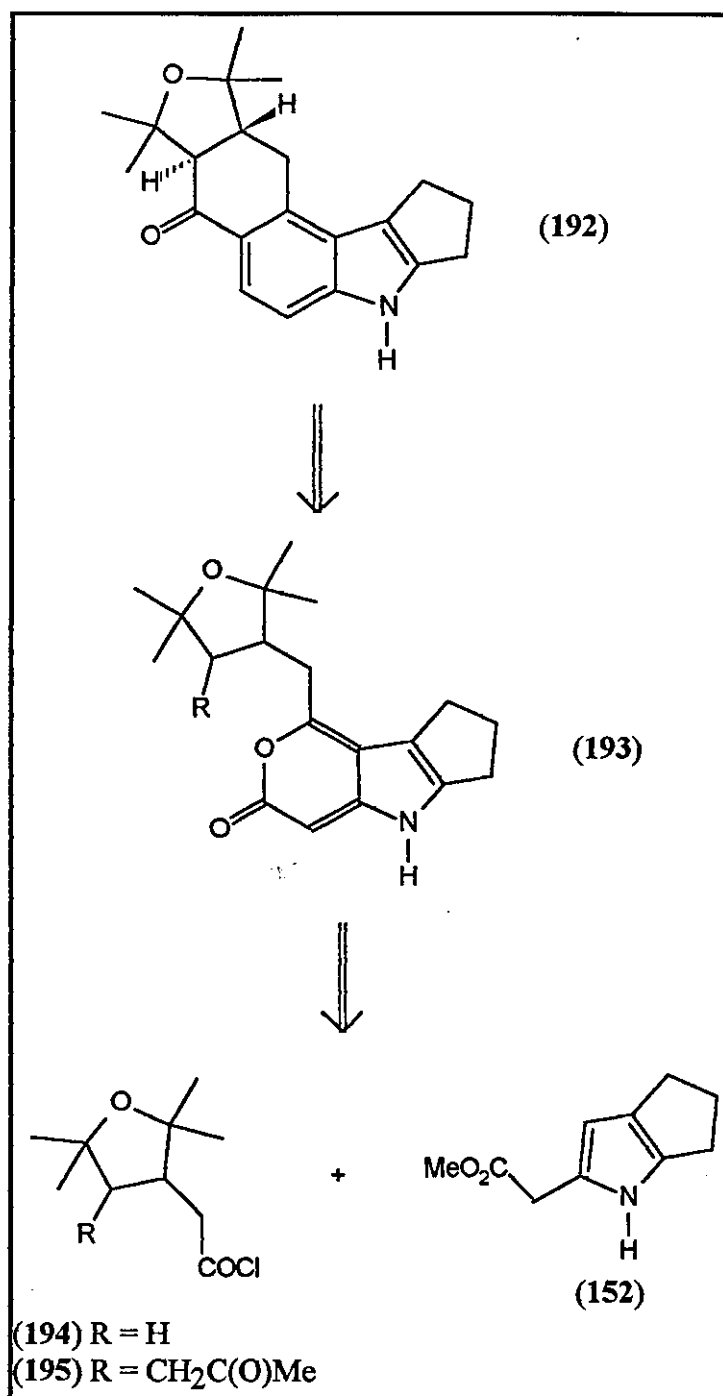
the molecule giving a precursor for lolitrem B. The acetylene (190) was refluxed with the pyranone (183) for 48 hours and the pyranone starting material was not visible by thin layer chromatography. However, the desired indole (191) was not formed (Scheme 57).



Scheme 57

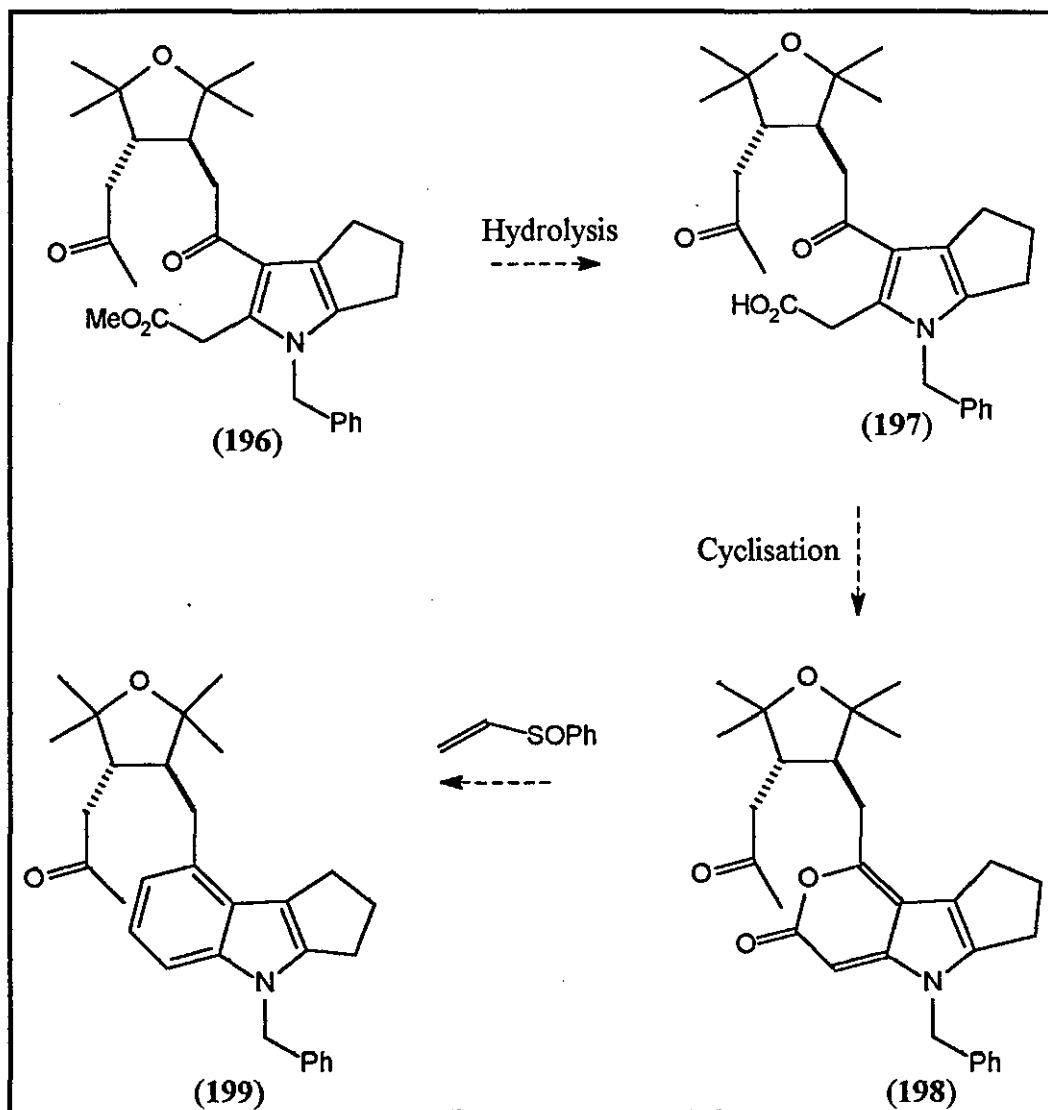
It has been shown that the Diels-Alder reaction can be controlled to give the desired substitution pattern on the indole ring. If further development on the preparation of the desired pyranone (180) and reaction with the acetylene (190) are undertaken then the left-hand side of lolitrem B should be accessible via the route shown in Scheme 52.

In the intramolecular approach to rings A-E of lolitrem B (192) the tetrahydrofuran portion of the molecule can be prepared as a substituted acid chloride (194) where R=H is a simple model for the system or (195) where the tetrahydrofuran supports the desired side-chain, which could be used in the Friedel-Crafts acylation of pyrrole (152) to give a pyranone (193), which after Diels-Alder reaction and cyclisation would give the target molecule (192) (Scheme 58).



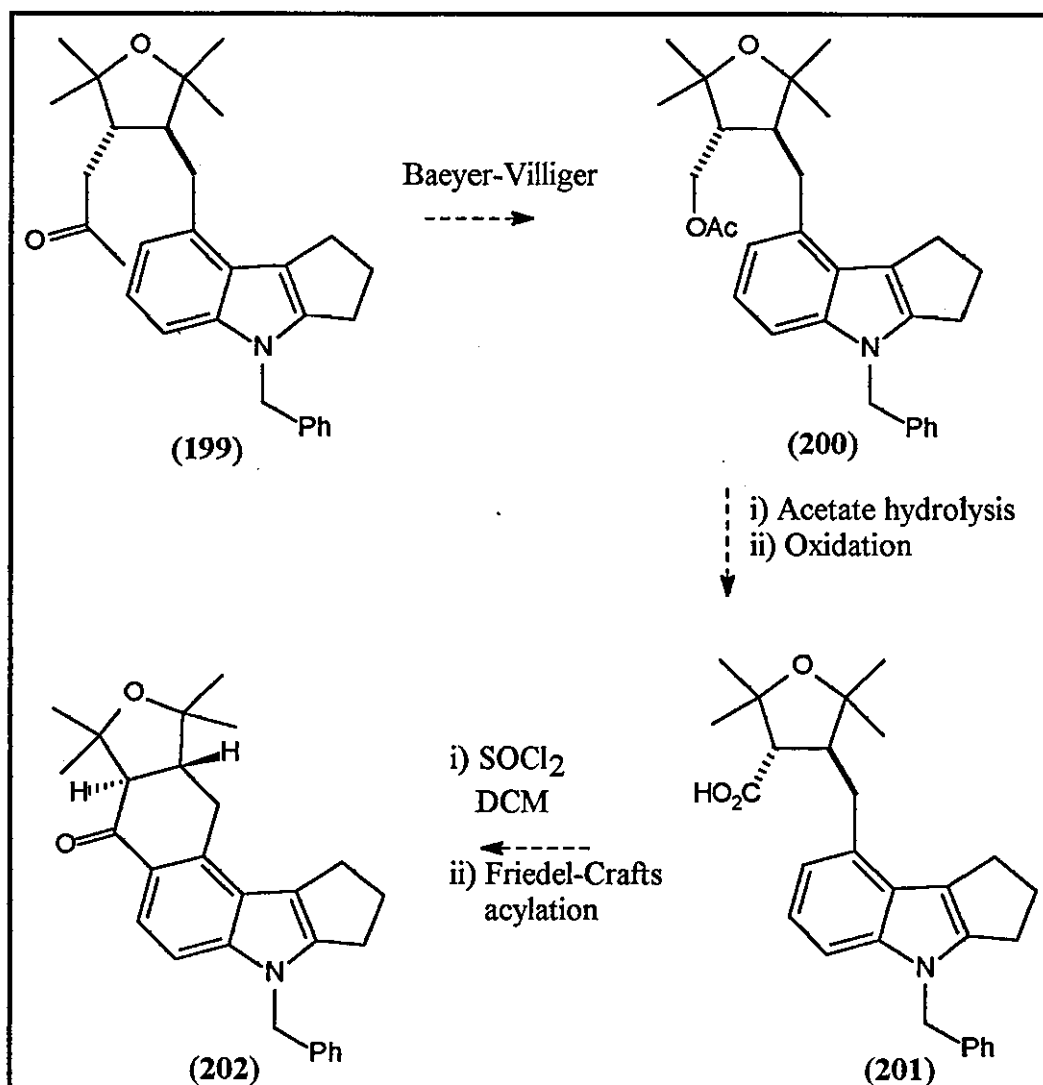
Scheme 58

When pyrrole (152) is acylated with tetrahydrofuran (195) giving pyrrole (196), then the α -pyranone (198) can be formed via the acid (197). Intermolecular Diels-Alder reaction using an acetylene equivalent would give the indole (199) (Scheme 59).



Scheme 59

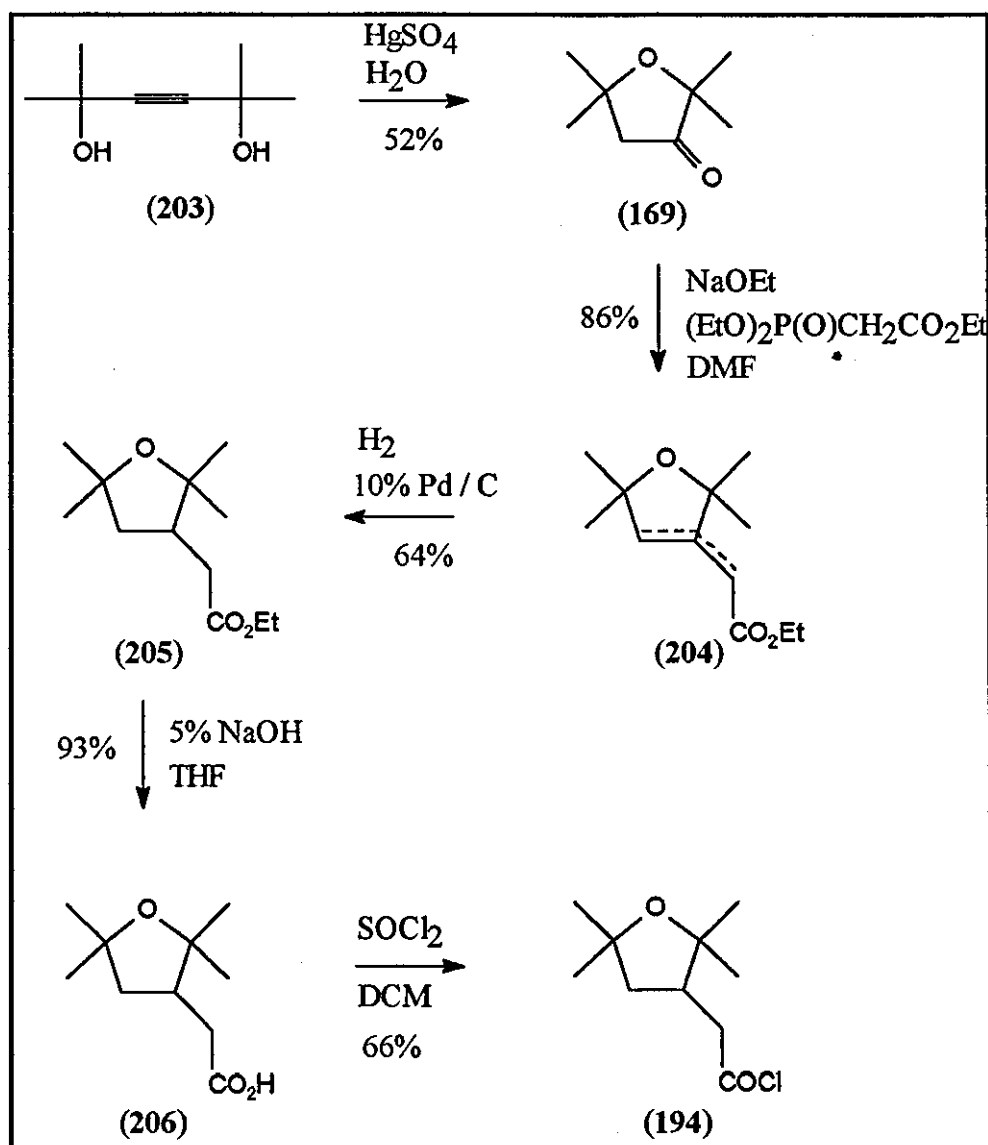
Baeyer-Villiger reaction on the methyl ketone (199) would give the acetate (200) and hydrolysis followed by oxidation would give the acid (201). Once obtained, the acid (201) could be converted to its corresponding acid chloride and cyclised onto the indole ring via a Friedel-Crafts reaction to give the pentacyclic compound (202) (Scheme 60). Removal of the benzyl group from the nitrogen would give rings A-E of lolitrem B (192).



Scheme 60

The tetrahydrofurans were prepared as follows. The model tetrahydrofuran (194) where R=H, is the acetyl chloride derivative of 2,2,5,5-tetramethyltetrahydrofuran. The first step in the synthesis of (194) is the mercuric sulfate catalysed alkyne hydration of 2,5-dimethyl-3-hexyne-2,5-diol (203) giving the cyclic furanone (169) (Scheme 61).⁹⁵ Wadsworth-Emmons olefination of the furanone (169) with triethyl phosphonoacetate using sodium ethoxide as the base and *N,N*-dimethylformamide as the solvent gave a mixture of

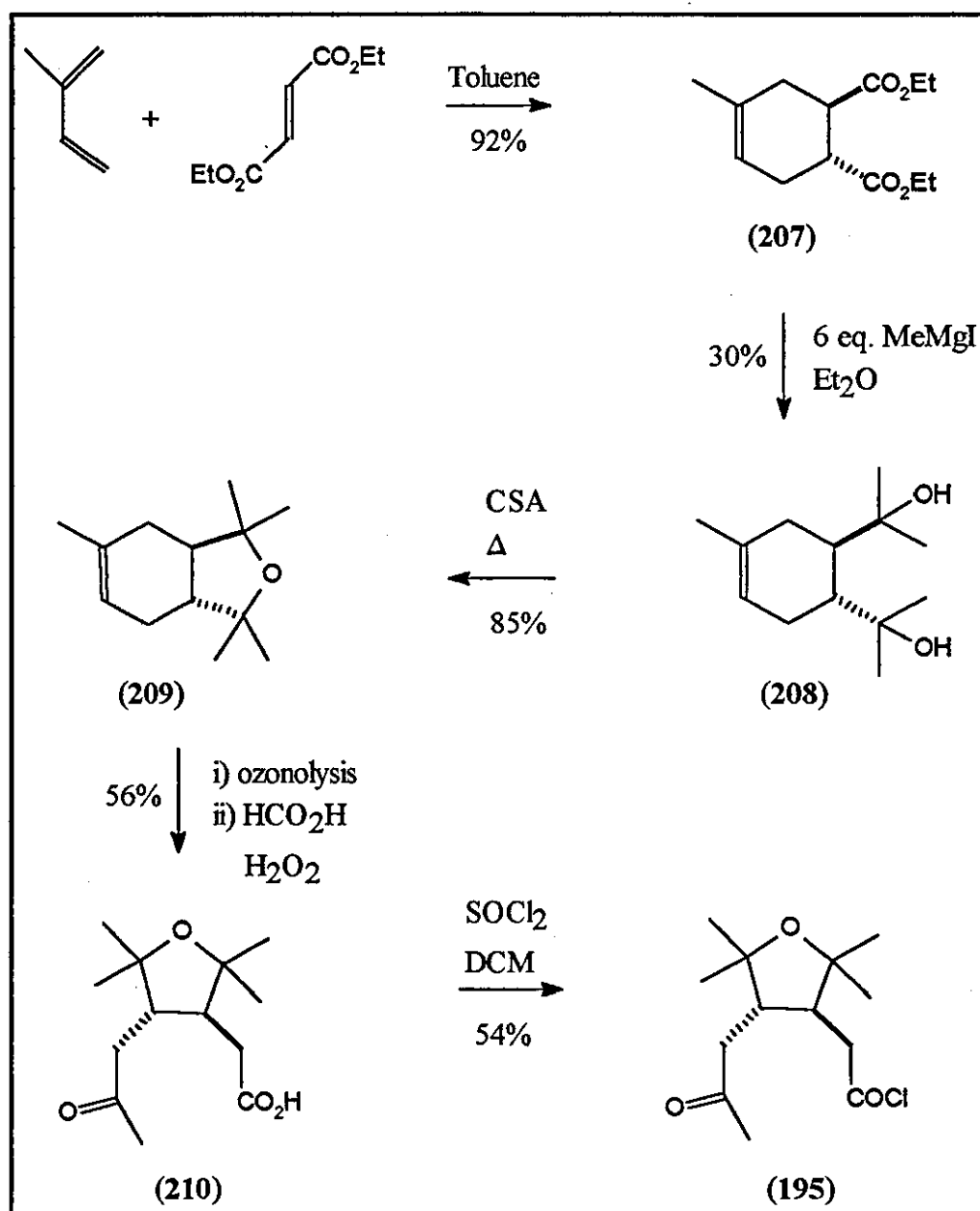
sodium ethoxide as the base and *N,N*-dimethylformamide as the solvent gave a mixture of unsaturated esters (**204**) as a colourless liquid in 86% yield.⁹⁶ Catalytic hydrogenation of the esters using 10% Pd/C gave the saturated ester (**205**) as a colourless liquid in 79% yield. Alkaline hydrolysis of the ester (**205**) using sodium hydroxide in tetrahydrofuran gave the corresponding acid (**206**) as a colourless solid in 93% yield. Subsequent conversion into the acid chloride (**194**) was achieved in 66% yield by refluxing in thionyl chloride and dichloromethane.



Scheme 61

The alternative tetrahydrofuran precursor (**195**), where $\text{R}=\text{CH}_2\text{C}(\text{O})\text{Me}$ was prepared following the procedure previously developed in these laboratories (Scheme 62).⁷³

Accordingly, Diels-Alder reaction of isoprene and diethyl fumarate gave the cyclohexene (207) as a colourless liquid in 92% yield. Reaction of the diester (207) with six equivalents of methylmagnesium iodide in refluxing diethyl ether gave the diol (208) as a colourless solid in 30% yield. Heating the diol (208) in the presence of camphorsulfonic acid resulted in cyclisation to the tetrahydrofuran (209) in 85% yield. Ozonolysis, followed by oxidative work-up with formic acid and hydrogen peroxide gave the acid (210) as a colourless solid in 56% yield. Reaction of the acid (210) with thionyl chloride gave the acid chloride (195) as a brown liquid in 54% yield.



Scheme 62

The acid chlorides (194) and (195) were reacted with the pyrrole (152) using the standard conditions shown previously and preliminary results indicate that reaction would be successful. However, optimum conditions need to be found. Unfortunately, as with the intermolecular approach to the left-hand portion of lolitrem B, there was insufficient material with which to carry on the synthesis.

3.3 Conclusions

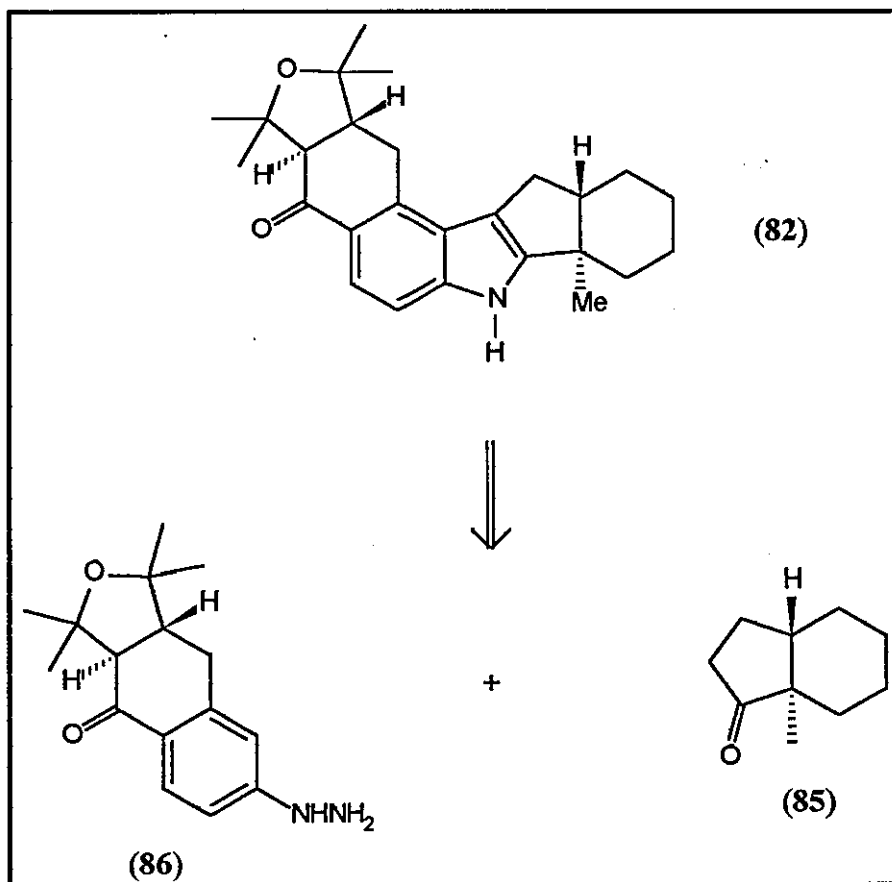
It has been shown that the incorporation of a methylene ester substituent directly into the synthesis of a pyrrole is not straight forward. However, utilising a route previously developed in these laboratories we have synthesised some novel indoles and shown that the Diels-Alder approach is applicable to the synthesis of the left-hand side of lolitrem B. We have carried out preliminary studies on the proposed route for the incorporation of the tetrahydrofuran portion of lolitrem B onto the central indole moiety. Further development is needed on both the route to the pyrrole and subsequent incorporation of the tetrahydrofuran moiety.

CHAPTER 4

Indole Studies

4.1 Introduction

As stated in Chapter 2, an alternative approach to the indole portion of lolitrem B is the reaction of the hydrindane (85) with hydrazine (86) to give the target molecule, rings A-F of lolitrem B, (82) (Scheme 63). Variation of the hydrazine used would allow development of an alternative route to other tremorgenic indoles.



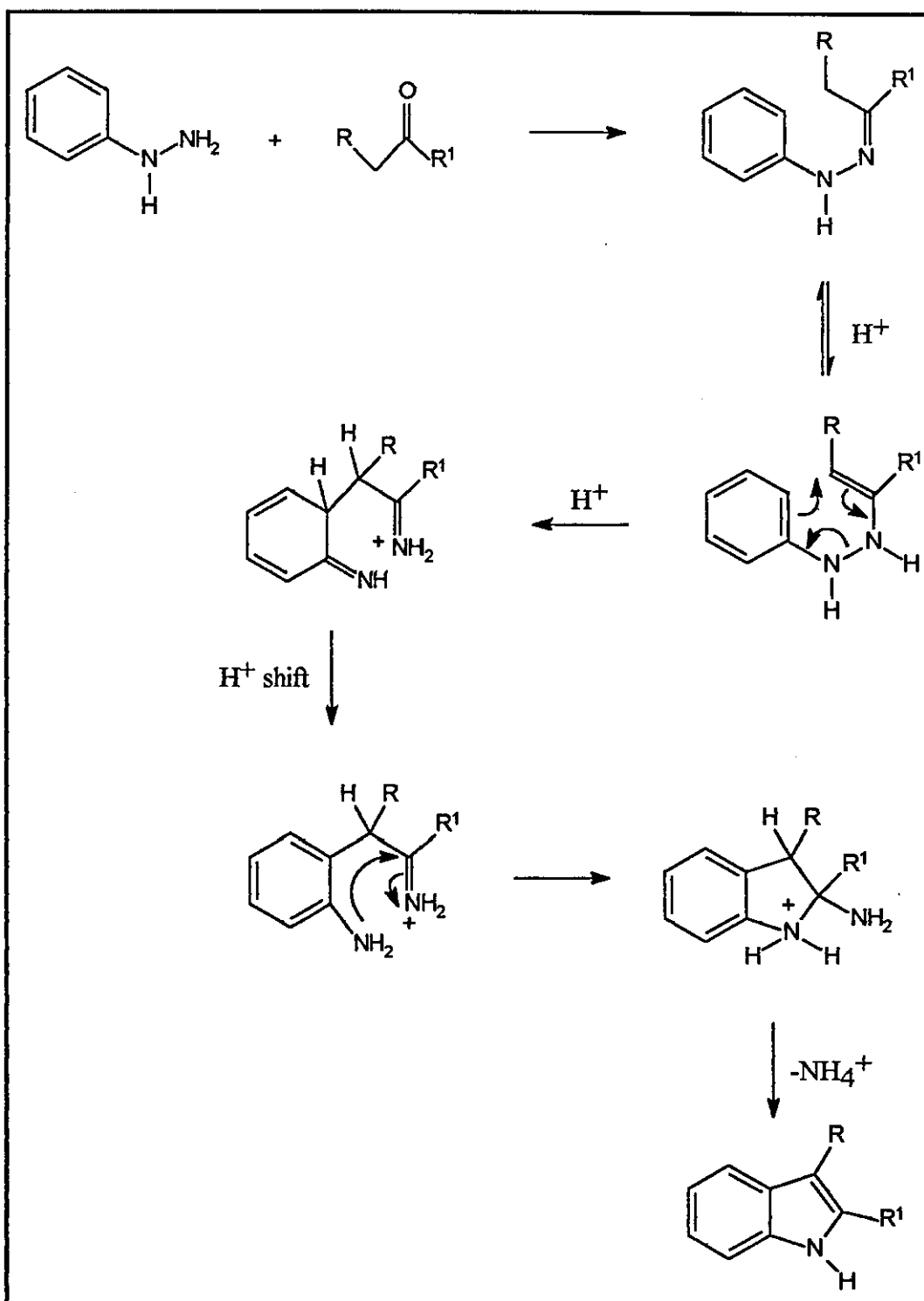
Scheme 63

Thus, in an attempt to prepare other members of the mycotoxin family, as well as lolitrem B, synthesis of the left-hand portion of these compounds directly from the five-membered ring ketone of the hydrindane (85) was investigated.

There are numerous routes to indoles, but only the historically most important method, the Fischer indole synthesis, is discussed here.^{97,98}

The Fischer indole synthesis was discovered by Hermann Emil Fischer in 1874 and is the reaction between an arylhydrazine and an aldehyde or ketone.

The proposed mechanism, many parts of which are still strongly debated, can be considered as the elimination of the elements of ammonia from the arylhydrazone of an aldehyde or ketone, bearing at least one hydrogen atom on a C-2 atom, by treatment with either a Brønsted or Lewis acid or by thermal cyclisation in a high boiling organic solvent (Scheme 64). The key step of the mechanism is a [3,3]-sigmatropic rearrangement.



Scheme 64

4.2 Synthetic Approaches

Even though Smith *et al.*, in their work on the indole portion of the tremorgens, state that no useful results were obtained with the Fischer indole synthesis,²⁷ it was decided to utilise this route as it was the most straightforward to use from the ketone precursor (85). In all of these studies, cyclopentanone is used as the model for the five-membered ring ketone of the hydrindane (85) and 1-indanone is used to give easy to handle crystalline derivatives.

The standard reaction conditions were refluxing the ketone and a phenylhydrazine in toluene with the continuous removal of water to give the hydrazone, this was immediately cyclised to the indole by refluxing in ethylene glycol.⁹⁹ These conditions were tested on cyclopentanone and 1-indanone with phenylhydrazine and gave cyclopent[*b*]indole (211)¹⁰⁰ and indeno[1,2-*b*]indole (212)¹⁰¹ (Figure 23) in 45% and 59% yield, respectively.

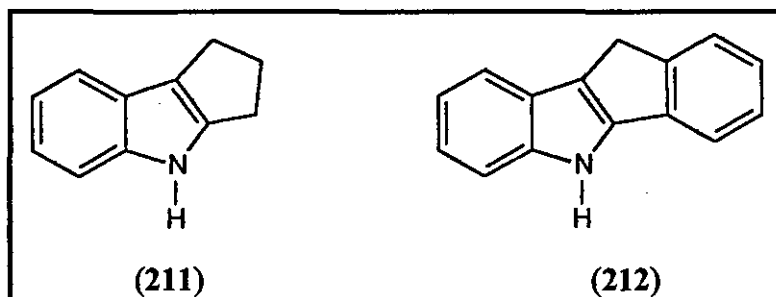


Figure 23: Cyclopent[*b*]indole (211) and indeno[1,2-*b*]indole (212).

4.2.1 The Claisen route

Synthesis of an indole with a hydroxyl functionality at the C5 position on the indole ring would allow modification to give the left-hand portion of alflatrem (213) and paspalitrem C (214) (Figure 24) via Claisen rearrangement of ethers (215) and (216), followed by dehydroxylation (Figure 25).

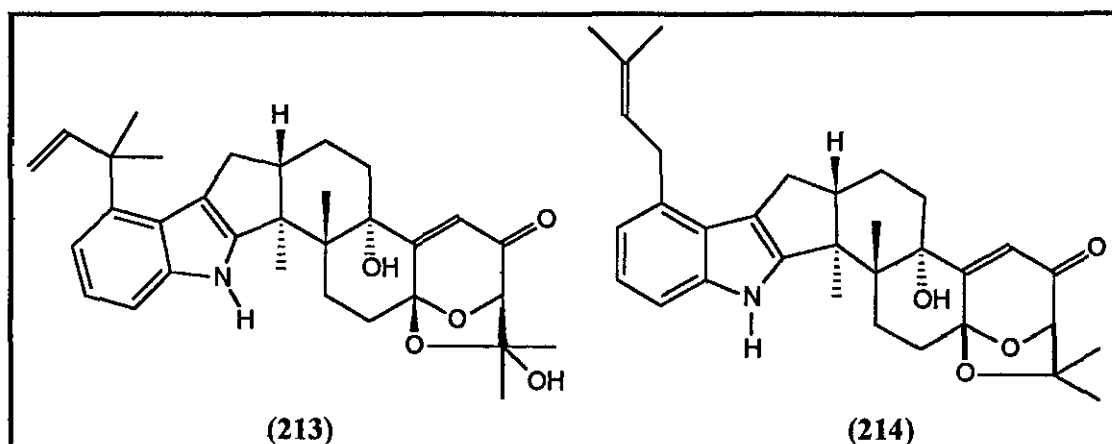


Figure 24: Alflatrem (213) and Paspalitrem C (214).

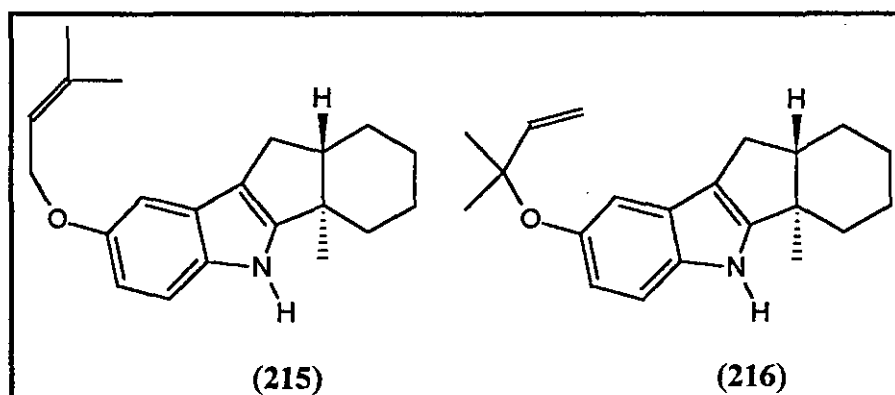


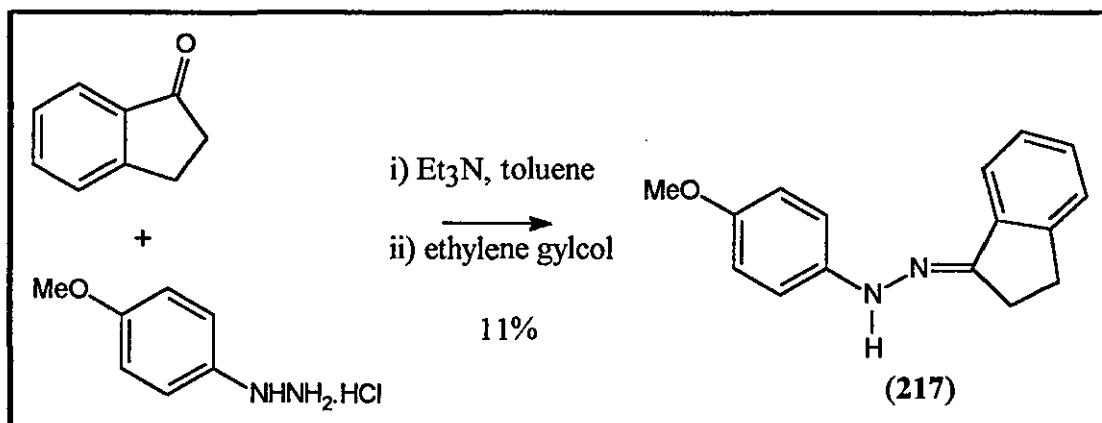
Figure 25: Ethers set up for Claisen rearrangement.

It is known that the Claisen rearrangement is regioselective and the ether substituent would migrate to the C4 position and not to the C6 position on the indole ring.¹⁰² After the Claisen rearrangement had been performed the hydroxyl group, trapped as an acetate due to the conditions of the reaction, would need removal. This could be achieved via hydrolysis of the acetate to give the phenol, conversion of the phenol to either a triflate or sulfonate and removal of these groups with palladium catalysis.^{103a-d}

In order to obtain a hydroxy group at C5 of the indole ring it was decided to prepare the corresponding methoxy derivative, followed by demethylation.

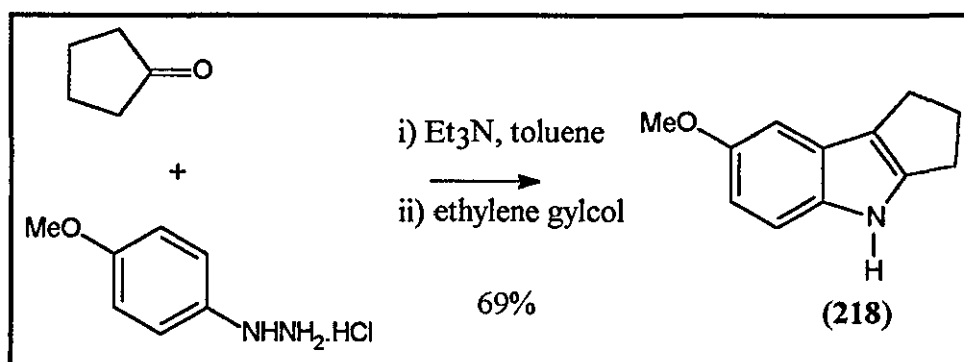
Accordingly, 1-indanone was reacted with 4-methoxyphenylhydrazine hydrochloride in the standard manner to give beige needles in 11% yield, m.p. 88-90°C (Scheme 65). The ¹H NMR spectrum showed the presence of four aliphatic protons and eight aromatic protons which indicate this to be the hydrazone (217) and not the desired indole. The structure was confirmed by elemental analysis data and mass spectral fragmentation. Further attempts at

cyclisation in refluxing ethanolic hydrochloric acid or refluxing concentrated sulfuric acid failed. Reports in the literature confirm the difficulty of cyclisation of hydrazones that are substituted by electron releasing groups.^{104a,b}



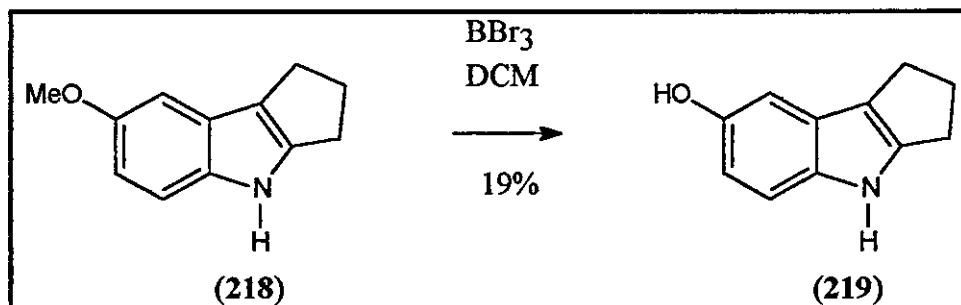
Scheme 65

As the indanone indole could not be obtained, it was decided to test the route on cyclopentanone. Thus, cyclopentanone was reacted with 4-methoxyphenylhydrazine hydrochloride in the standard manner to give a yellow solid in 69% yield (Scheme 66).¹⁰⁵ Proton and carbon NMR spectra showed only three aromatic protons present so cyclisation to the novel indole (218) had been achieved. Again the structure was confirmed by elemental analysis data and mass spectral fragmentation.



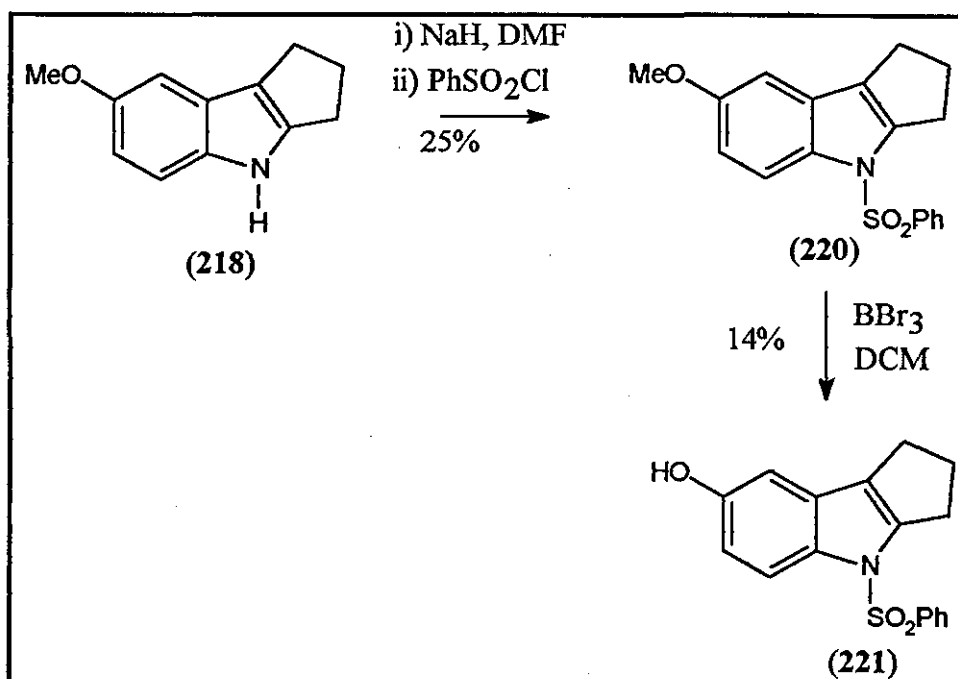
Scheme 66

With a route to the methoxy indole (218) in good yield the next step was demethylation to give the novel hydroxy indole (219). Initial attempts to remove the methyl group with either trimethylsilyl iodide or aluminium chloride as the Lewis acids gave back only starting material. The only Lewis acid that would remove the methyl group was boron tribromide after reflux for 4 hours.¹⁰⁶ This only gave 19% of the desired hydroxy indole (219) as a yellow solid, m.p. 155-158°C, no improvement on the yield could be made (Scheme 67). A recent report confirms the difficulty and low yields on demethylation of methoxy indoles.¹⁰⁷



Scheme 67

It was thought that if the indole nitrogen was protected the yields might improve. Hence, 7-methoxycyclopent[b]indole (218) was protected with benzenesulphonyl chloride using sodium hydride as the base and *N,N*-dimethylformamide as the solvent giving the indole (220) as a beige solid in 25% yield, m.p. 151-153°C. However, deprotection of the methoxy group gave only 14% yield of the *N*-protected hydroxy indole (221) (Scheme 68).

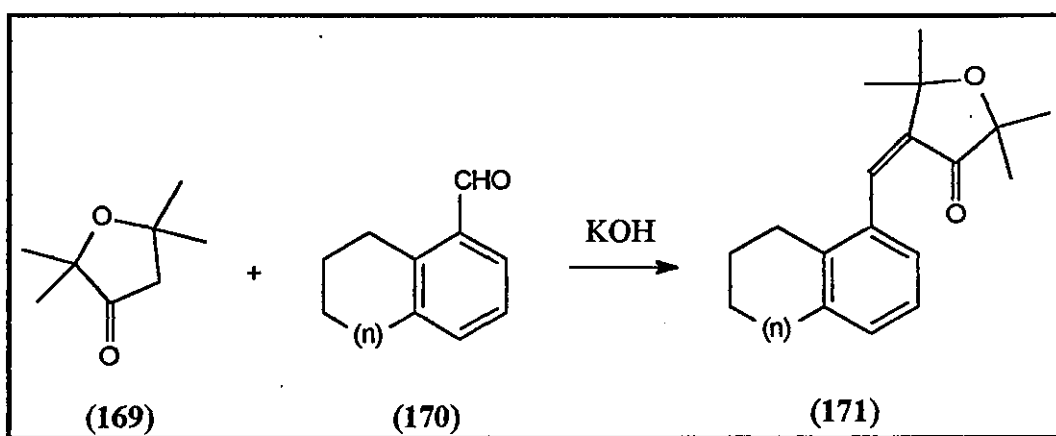


Scheme 68

As a suitable route to the hydroxy derivative could not be obtained, this work was not continued any further.

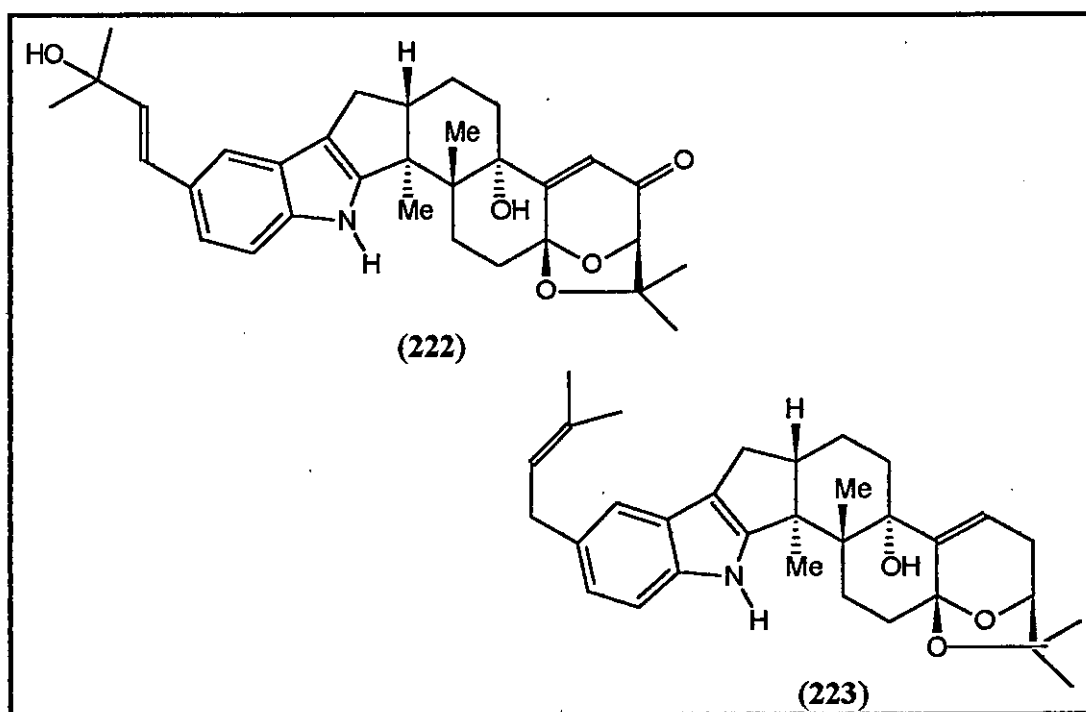
4.2.2 The bromoindole route

As shown in section 3.2.4, it is known that 2,2,5,5-tetramethyltetrahydrofuran-3-one (169) undergoes aldol condensation with a benzaldehyde (170) in the presence of base to give the alkene (171) (Scheme 69).⁹³ This could be utilised in the incorporation of 2,2,5,5-tetramethyltetrahydrofuran-3-one as ring A onto the left-hand portion of lolitrem B, by preparing an indole with an aldehyde functionality at the C5 position of the indole ring. It was envisaged that the aldehyde functionality would be accessible from the corresponding bromo derivative.



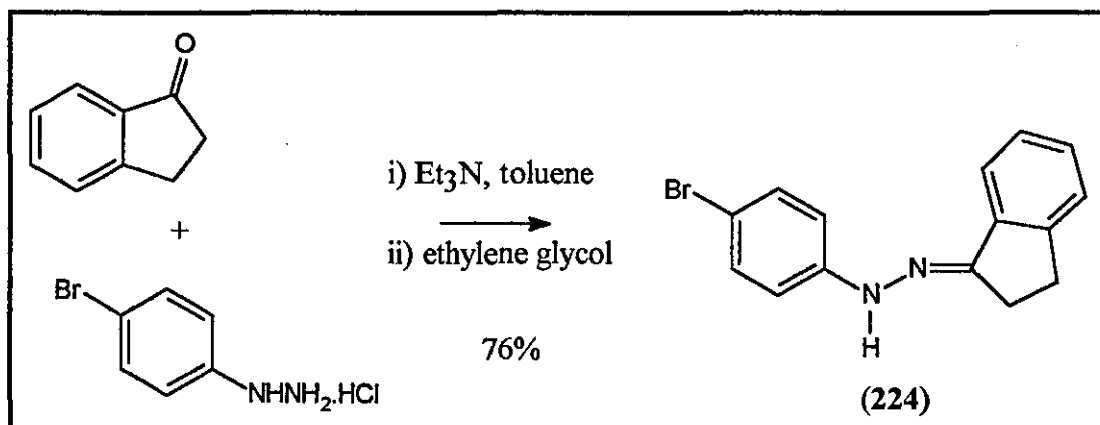
Scheme 69

Synthesis of an indole with a bromo functionality at the C5 position on the indole ring would allow modification to give the left-hand portion of paspalitrem B (**222**) via a Heck reaction and the left-hand portion of paspalitrem A (**223**) via lithiation followed by substitution (Figure 26).



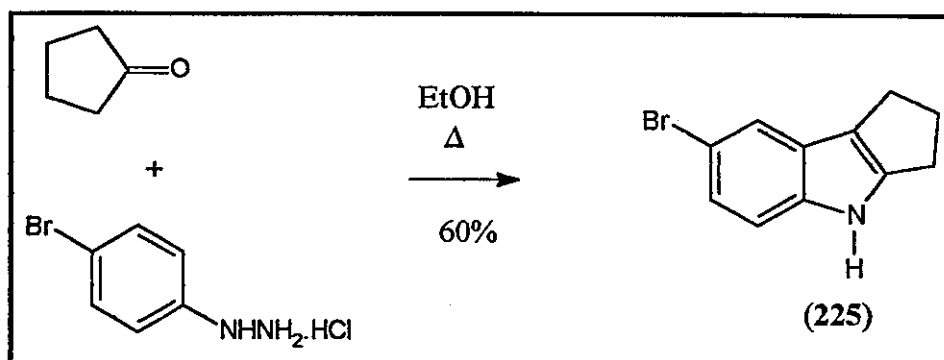
*Figure 26: Paspalitrem B (**222**) and Paspalitrem A (**223**).*

Attempts at the preparation of a bromo derivative are discussed below. Thus, 1-indanone was reacted with 4-bromophenylhydrazine hydrochloride in the standard manner to give yellow needles in 76% yield, m.p. 153-155°C (Scheme 70). The ^1H NMR spectrum showed the presence of four aliphatic protons and eight aromatic protons which indicate this to be the novel hydrazone (224) and not the desired indole. The structure was confirmed by elemental analysis data and mass spectral fragmentation. Further attempts at cyclisation failed.



Scheme 70

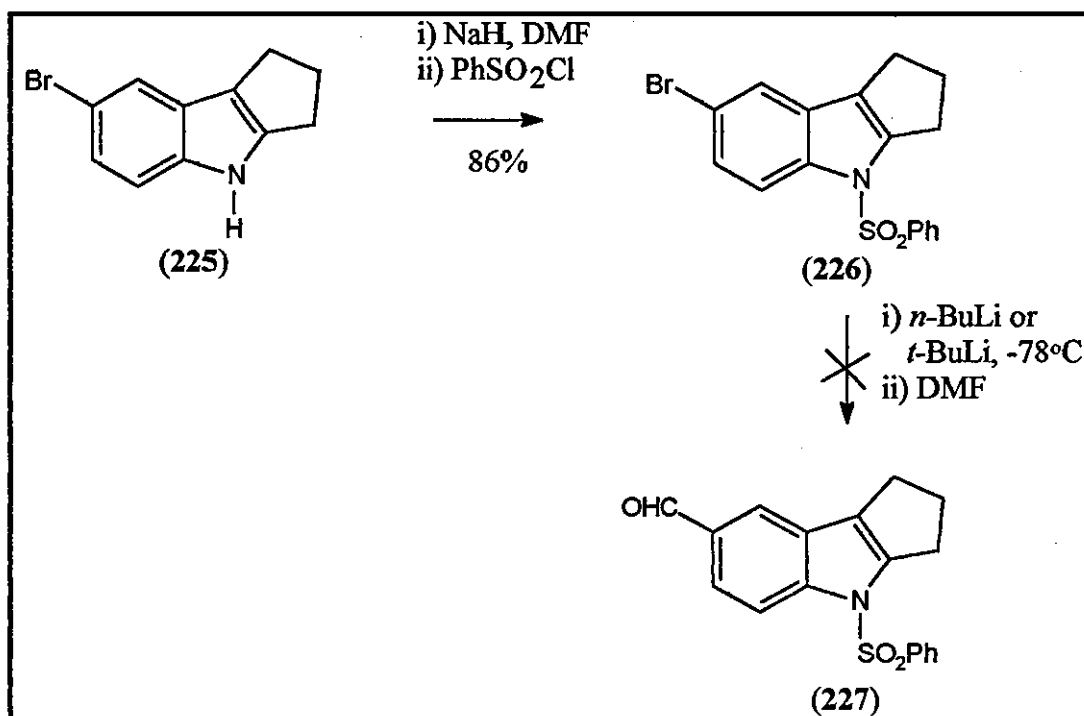
Again, due to the failure of cyclisation using indanone, the route was tested on cyclopentanone. Cyclopentanone was reacted with 4-bromophenylhydrazine hydrochloride in refluxing ethanol to give a brown solid in 60% yield, m.p. 136-137°C (Scheme 71). This is a different route to the standard conditions but gives comparable yields with just one step and does not need any base present to liberate the free phenylhydrazine. Proton and carbon NMR data showed only 3 aromatic protons present so cyclisation to the novel indole (225) had been achieved.



Scheme 71

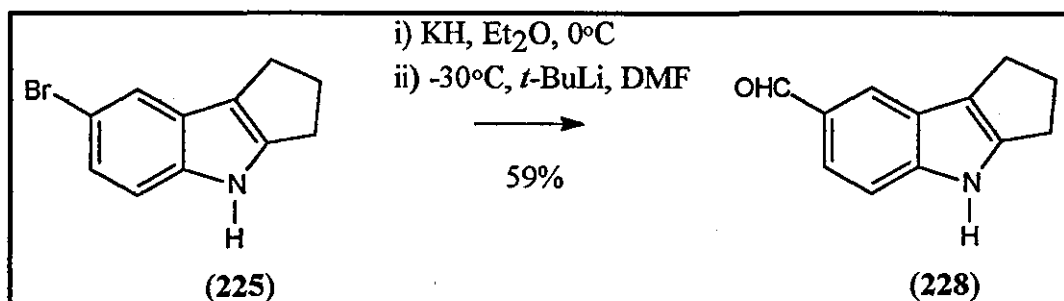
Having found a reliable, good yielding route to the bromoindole, substituting the bromo group for other functionalities on the benzene ring was the next stage in the synthesis of lolitrem B, paspalitrem A and paspalitrem B.

Preparation of the aldehyde (227) necessary for the synthesis of the left-hand side of lolitrem B was not as straightforward as it first seemed. Initially the *N*-protected bromoindole (226) was prepared as a brown solid in 86% yield, m.p. 170°C by reacting the bromoindole (225) with benzenesulfonyl chloride in the presence of sodium hydride as the base and *N,N*-dimethylformamide as the solvent. Attempts at lithiation of this species using firstly *n*-BuLi or *t*-BuLi at -78°C gave back only starting material (Scheme 72).



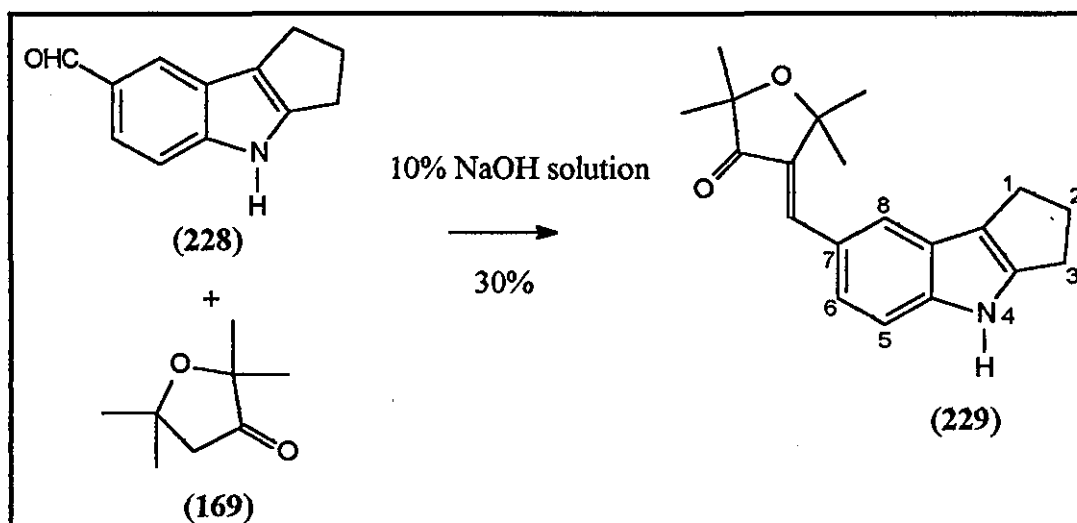
Scheme 72

It was decided to utilise a literature preparation that firstly generates the nitrogen anion by reaction with potassium hydride then lithiates with *t*-BuLi at -78°C and quenches with *N,N*-dimethylformamide to give the formyl indole.¹⁰⁸ However, the desired product was not obtained until the temperature was allowed to rise to -30°C , at this temperature the novel indole (**228**) was obtained as a yellow solid in 59% yield, m.p. $144\text{--}146^{\circ}\text{C}$ (Scheme 73).



Scheme 73

The indole (**228**) could now be reacted with tetrahydrofuranone (**169**) to give ring A of lolitrem B attached to the central indole moiety. Thus, the indole (**228**) was reacted with tetrahydrofuranone (**169**) in the presence of 10% sodium hydroxide solution to give the alkene (**229**) in a combined yield of 30% (Scheme 74).



Scheme 74

Prior to column chromatography there appeared only one spot other than the starting material, but during chromatographic separation, the product spot gave two close running

components. IR spectra of both components showed α,β -unsaturated ketones were present. Both of these compounds had the correct mass and the fragmentation pattern was identical. The proton NMR spectra however, were very different.

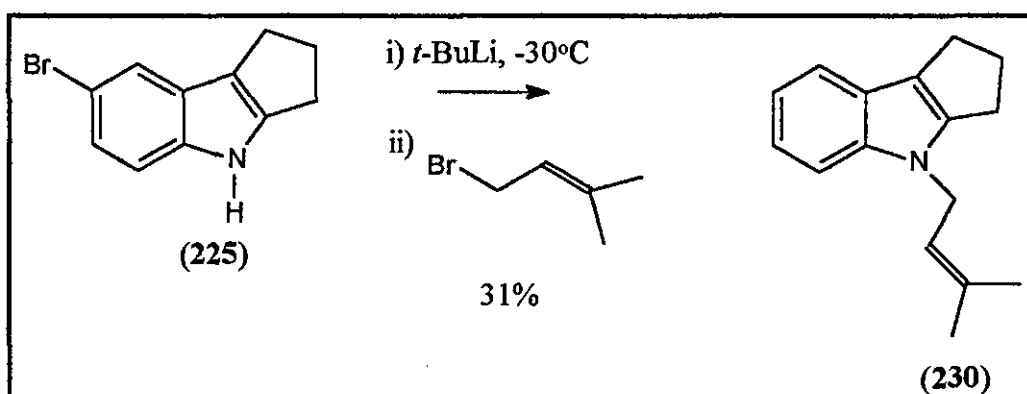
Compound 1, the highest running of the two spots and the minor product, had a more complicated aromatic region in the spectrum - a singlet (1 H) at 6.79 ppm, a double doublet (1 H, J 2.3, 8.6 Hz) at 7.29 ppm, a double doublet (1 H, J 1.7, 6.8 Hz) at 7.94 ppm and a doublet (1 H, J 1.1 Hz) at 9.27 ppm. The double doublets represent the two ortho coupled protons at C5 and C6 on the tricyclic structure. The proton at C5 is also coupled to the proton on the indole nitrogen, hence the *meta* coupling of 2.3 Hz. The proton at C6 is coupled to the proton at C8 hence giving the *meta* coupling of 1.7 Hz for the proton at C6 and the *meta* coupling of 1.1 Hz for the proton at C8. The carbon spectrum also showed doubling up of the peaks.

Compound 2, the major product, had, by comparison, a simple aromatic region - a singlet (2 H) at 7.30 ppm, a singlet (1 H) at 7.64 ppm and a singlet (1 H) at 7.67 ppm. The carbon spectrum was identical to the minor product but no doubling up of peaks was observed.

The compounds are geometric isomers, the major isomer, based on molecular modelling data, appears to be as shown in Scheme 74.

As there is no group at the C8 position on the tricyclic system it is not straightforward to cyclise the tetrahydrofuranone onto the indole ring. If however, the pyranopyrrole (**180**) in Chapter 3 bearing the activated side-chain at the C4 position of the indole ring could have been prepared and Diels-Alder chemistry would lead to an indole with an aldehyde functionality at the C5 position on the indole ring, then one can see that the left-hand portion of lolitrem B is accessible via this methodology.

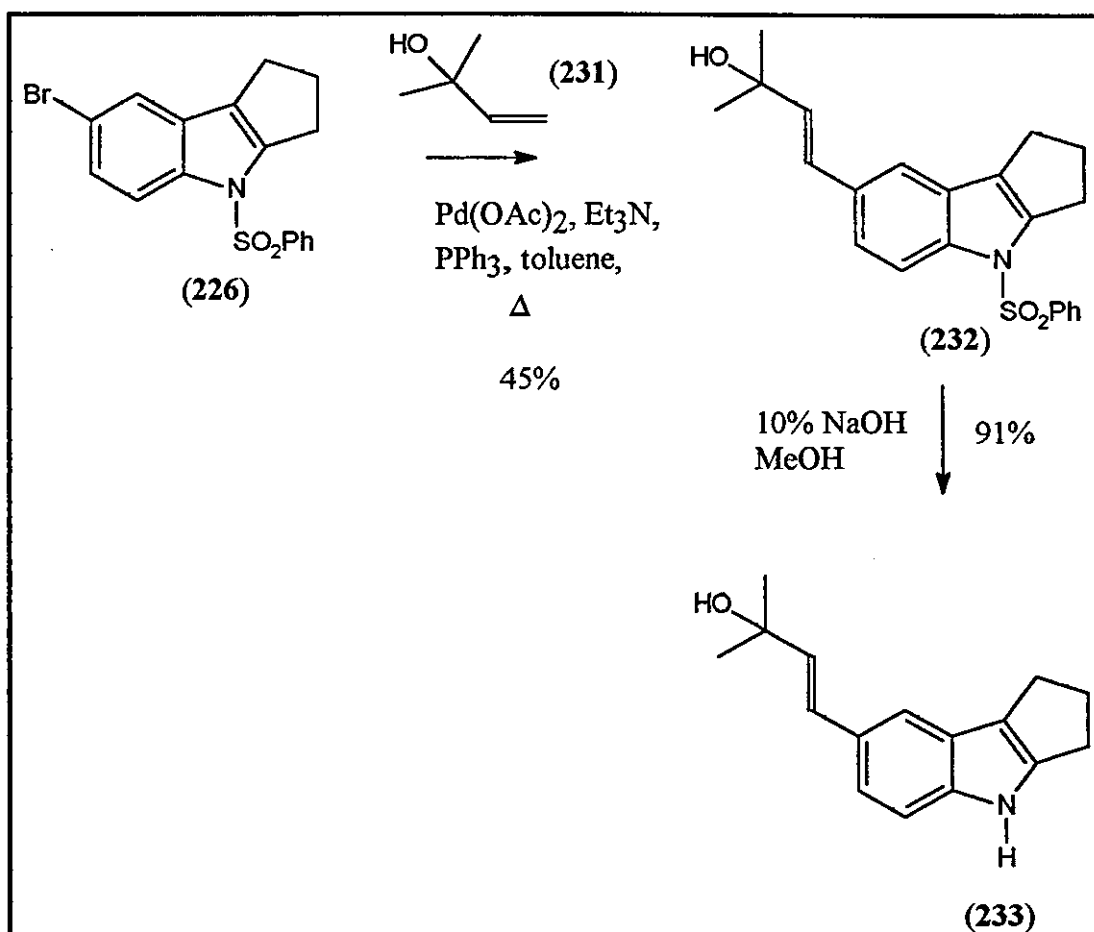
In order to synthesise paspalitrem A it was necessary to substitute the bromo group with a 3-methylbutenyl group. It was decided to use the conditions as above and lithiation of the bromoindole (**225**) followed by reaction with 4-bromo-2-methyl-2-butene afforded a yellow liquid in 31% yield (Scheme 75). The IR spectrum showed the absence of a NH stretch and the proton and carbon NMR spectra showed the presence of 4 aromatic protons. Thus, the indole (**230**) had been prepared and not the desired 7-substituted indole. The bromo group had been quenched by a proton source and the prenyl bromide had reacted at the indole nitrogen. Further work is required to obtain the optimum conditions for this reaction.



Scheme 75

In order to synthesise rings A-C of paspalitrem B (**233**), it was necessary to substitute the bromo group with the tertiary alcohol (**231**). It was envisaged that this could be achieved via a Heck reaction on the bromoindole using the commercially available tertiary alcohol, 3-methyl-1-buten-3-ol (**231**).

The first step in this synthesis was to protect the indole nitrogen with a benzenesulfonyl group as previously. Initial attempts at the Heck reaction, refluxing the indole (**226**) and the alcohol in the presence of a palladium catalyst in acetonitrile for 4 days failed, giving back starting material.¹⁰⁹ The conditions were modified, based on various reports in the literature, to heating the alcohol and indole in the presence of triethylamine, triphenylphosphine and palladium acetate in toluene in a sealed tube to 120°C for 60 hours.^{110a-c} This gave, after column chromatography, the desired novel indole (**232**) as a colourless solid in an optimum yield of 45%, m.p. 121-123°C. The reaction is not totally reproducible and the yields vary. After the product (**232**) was obtained, all that remained to obtain the left-hand portion of paspalitrem B (**233**) was to deprotect the nitrogen. This was achieved by refluxing the indole (**232**) in 10% sodium hydroxide solution to give the target molecule (**233**) as a colourless solid in 91% yield, m.p. 142-144°C (Scheme 76).



Scheme 76

4.3 Conclusions

Thus, some novel indoles have been prepared in our studies on the Fischer indole route to such tremorgenic compounds - further work is needed on the synthesis of paspalitrem A and the Claisen route to alflatrem and paspalitrem C. However, ring A of lolitrem B has been attached to rings C-E of lolitrem B and we have devised a synthetic route to rings A-C of paspalitrem B. If the *trans*-ketone prepared in Chapter 2 is used instead of cyclopentanone, in both the indole and pyrrole routes, one can see that the left-hand side of such compounds is accessible via this methodology.

CHAPTER 5

Experimental

5.1 General Information

Solvents and reagents. Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction boiling between 40 and 60°C, and was distilled from calcium chloride through a 36 cm Vigreux column before use. Diethyl ether and ethyl acetate were distilled from calcium chloride. Dichloromethane was distilled from phosphorus pentoxide and stored, where necessary, over 4Å molecular sieves under nitrogen. Diethyl ether was dried, where necessary, by storage over sodium wire for several days. THF was dried by distillation from sodium-benzophenone ketyl. Benzene was dried, where necessary, by storage over sodium wire for several days. Toluene was dried by distillation from calcium hydride and storing over sodium wire. DMF was dried by stirring over calcium hydride, distilling at reduced pressure, and storing over 4Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over, potassium hydroxide pellets. Methanol and ethanol were distilled from magnesium turnings and iodine, and stored over 4Å molecular sieves.

Chromatography. Analytical thin layer chromatography was carried out using Merck Kieselgel 60 F₂₅₄ aluminium-backed plates. Plates were visualised under UV light or by staining with molybdate or vanillin solution. Flash chromatography was carried out using Merck Kieselgel 60 H or Sorbsil C 60 silica.

Spectra. IR spectra were recorded in the range 4000-600 cm⁻¹ using a Nicolet FT-205 spectrometer, with internal calibration. ¹H and ¹³C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR spectroscopy Centre, Warwick) instruments. High- and low-resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (SERC mass spectrometry service, Swansea).

Other information. Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental Analyser. Melting points were determined using a Reichert Kofler hot stage apparatus or an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were determined using an Optical Activity Automatic Polarimeter AA100, values are recorded in units of degrees 10⁻¹ cm⁻¹ g⁻¹.

5.2 Experimental for Chapter 2

2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (98).^{28b}

To a solution of 2-methyl-1,3-cyclopentanedione (20 g, 0.18 mol) in deionised water (68 ml) was added glacial acetic acid (0.96 ml, 0.016 mol) and methyl vinyl ketone (29.6 ml, 0.35 mol). The system was shielded from light and heated under an atmosphere of nitrogen for 2 h at 70°C. After cooling, the mixture was extracted with dichloromethane and washed with brine. The combined brine extracts were washed with dichloromethane and the total dichloromethane extract was dried (Na₂SO₄). The solvent was removed under reduced pressure to give the title compound (98) (30 g, 92%) as an orange oil, $\nu_{\text{max}}(\text{film})$ 1760, and 1720 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.10 (3 H, s, CH₃), 1.90 (2 H, t, *J* 3.4 Hz), 2.10 (3 H, s, CH₃), 2.45 (2 H, t, *J* 5.9 Hz), and 2.79 (4 H, m)

(-)-(7aR)-7a-Methyl-2,3,7,7a-tetrahydro-inden-1,5-(6H)-dione (99).^{28a,51}

To a solution of the triketone (98) (15 g, 80 mmol) in acetonitrile (250 ml) was added D-proline (5 g, 40 mmol) and perchloric acid (1M, 24 ml, 24 mmol). The mixture was refluxed under an atmosphere of nitrogen for 22 h. After dilution with brine, the mixture was extracted with dichloromethane and dried (MgSO₄). The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 6:1 ethyl acetate:light petroleum) to give the title compound (99) (11.5 g, 70%) as colourless crystals with $[\alpha]_{\text{D}}^{20} -324^\circ$ (*c* 0.8, CHCl₃); m.p. 65-66°C (from light petroleum) (lit. m.p. 63-65°C);⁵¹ $\nu_{\text{max}}(\text{film CH}_2\text{Cl}_2)$ 1747, and 1667 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.32 (3 H, s, CH₃), 1.86 (1 H, m), 2.14 (1 H, m), 2.52 (3 H, m), 2.81 (3 H, m), and 5.97 (1 H, d, *J* 2.3 Hz, C=CH); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 20.58 (CH₃), 26.84 (CH₂), 29.19 (CH₂), 32.91 (CH₂), 35.88 (CH₂), 48.70 (4°C), 123.87 (C=CH), 169.82 (4°C, C=CH), 198.18 (C=C(H)CO), and 216.55 (CO); *m/z* 164 (M⁺, 64%), 122 (68), 107 (35), 79 (70), and 43 (100)

(-)-(1R,7aR)-7a-Methyl-2,3,5,6,7,7a-hexahydro-inden-1-ol (96).

Dry trifluoroacetic acid (28 ml, 0.36 mol) was added dropwise, with stirring, to a suspension of sodium borohydride (4.4 g, 0.12 mol) in dry acetonitrile (36 ml) and dry dichloromethane (28 ml) at -40°C under an atmosphere of nitrogen, so that temperature did not exceed -10°C. The solution was then recooled to -40°C and a solution of the diketone (99) (5 g, 0.03 mol) in dry dichloromethane (44 ml) was added dropwise, with stirring. The mixture was stirred at -40°C for 2 h and allowed to warm to room temperature and stirring continued overnight. The mixture was neutralised with sodium hydroxide solution (4M, ca. 80 ml) and extracted with dichloromethane. The combined dichloromethane extracts were washed with 2M sodium hydroxide solution and dried (MgSO₄). The solvent was removed

under reduced pressure to give the *title compound* (**96**) (3.9 g, 82%) as a colourless solid with $[\alpha]_{\text{D}}^{20} -65^{\circ}$ (*c* 0.5, CHCl_3) (lit. $[\alpha]_{\text{D}}^{24} +75^{\circ}$ (*c* 1.0, CHCl_3) for (1*S*,7*aS*)-isomer);⁶² m.p. 84-86°C (from diethyl ether/light petroleum) (lit. m.p. 86-88°C for (1*S*,7*aS*)-isomer);⁶² ν_{max} (film CH_2Cl_2) 3362, and 1676 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.94 (3 H, s, CH_3), 1.15 (1 H, m), 1.68 (4 H, m), 1.77 (1 H, m), 1.97 (4 H, m), 2.43 (1 H, m), 3.65 (1 H, dd, *J* 1.9, 7.8 Hz, $\text{CH}(\text{OH})$), and 5.35 (1 H, d, *J* 2.9 Hz, $\text{C}=\text{CH}$); δ_{C} (62.5 MHz; CDCl_3) 16.76 (CH_3), 18.70 (CH_2), 25.08 (CH_2), 25.87 (CH_2), 29.39 (CH_2), 34.46 (CH_2), 42.91 (4°C), 82.23 ($\text{CH}(\text{OH})$), 119.47 ($\text{C}=\text{CH}$), and 144.15 (4°C, $\text{C}=\text{CH}$); *m/z* 152 (M^+ , 43%), 134 (28), 110 (25), 108 (52), and 93 (100).

(-)-(1*R*,3*aR*,7*aR*)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-ol (**100**).

To a solution of the alcohol (**96**) (2 g, 13 mmol) in ethyl acetate (20 ml) was added 10%Pd/C (0.2 g) and a catalytic amount of 2M hydrochloric acid. The system was stirred overnight at room temperature under an atmosphere of hydrogen (45 psi). The mixture was filtered through Celite and washed with water. The ethyl acetate extracts were dried (MgSO_4) and the solvent removed under reduced pressure. The residue was distilled at 80-85°C, 0.5 mmHg to give the *title compound* (**100**) (1.7 g, 83%) as a colourless semi-solid with $[\alpha]_{\text{D}}^{20} -14^{\circ}$ (*c* 0.44 CHCl_3) (lit. $[\alpha]_{\text{D}}^{24} +20^{\circ}$ (*c* 1.0, CHCl_3) for (1*S*,3*aS*,7*aS*)-isomer);⁶⁴ ν_{max} (film) 3395 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.98 (3 H, s, CH_3), 1.16 (1 H, m), 1.45 (10 H, m), 1.79 (2 H, m), 2.18 (1 H, m), and 3.83 (0.95 H, dd, *J* 3.2, 3.7 Hz, $\text{CH}(\text{OH})$); δ_{C} (62.5 MHz; CDCl_3) 19.56 (CH_3), 21.71 (CH_2), 22.17 (CH_2), 25.90 (CH_2), 26.09 (CH_2), 31.33 (CH_2), 31.78 (CH_2), 41.85 (CH), 44.01 (4°C), and 79.93 ($\text{CH}(\text{OH})$); *m/z* 154 (M^+ , 64%), 110 (80), and 95 (100). Contaminated with 4% (1*R*,3*aS*,7*aR*)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-ol by proton NMR, δ_{H} (250 MHz; CDCl_3) 0.74 (3 H, s, CH_3), and 3.65 (1 H, m, $\text{CH}(\text{OH})$) - all other peaks obscured by major product

(-)-(3*aR*,7*aR*)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-one (**101**).⁶⁴

A mixture of the alcohol (**100**) (1.3 g, 8.4 mmol) and pyridinium chlorochromate (2.7 g, 12.6 mmol) in dichloromethane (30 ml) was stirred at room temperature for 90 min. The mixture was filtered through Celite and washed with water. The dichloromethane extracts were dried (MgSO_4) and the solvent removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (**101**) (1.2 g, 92%) as a pale yellow liquid with $[\alpha]_{\text{D}}^{20} -53^{\circ}$ (*c* 0.6 CHCl_3) (lit. $[\alpha]_{\text{D}}^{24} -57^{\circ}$ (*c* 1.0, CHCl_3);⁶⁴ (Found: M^+ 152.1201, $\text{C}_{10}\text{H}_{16}\text{O}$ requires *M* 152.1201); ν_{max} (film) 1736 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.04 (3 H, s, CH_3), 1.18 (1 H, m), 1.41 (5 H, m), 1.66 (3 H, m), 1.91 (2 H, m), and 2.37 (2 H, m); δ_{C} (62.5 MHz; CDCl_3) 20.92 (CH_3), 22.14 (CH_2), 22.35 (CH_2), 23.03 (CH_2), 26.72

(CH₂), 29.50 (CH₂), 34.95 (CH₂), 42.54 (CH), 48.30 (4°C), and 222.89 (CO); *m/z* 152 (M⁺, 20%), 110 (35), 96 (43), and 81 (100). Contaminated with 4% (3*a*S,7*a*R)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-one by proton NMR, δ_{H} (250 MHz; CDCl₃) 0.87 (3 H, s, CH₃) - all other peaks obscured by major product

*(-)-(4*a*R,10*a*R)-4*a*-Methyl-1,2,3,4,4*a*,5,10,10*a*-octahydro-5H-indenof[1,2-*b*]indole (103).*⁶⁵

A mixture of ketone (101) (1.2 g, 8 mmol) and phenylhydrazine (0.8 ml, 8 mmol) was refluxed overnight in dry toluene (10 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (13 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO₄). The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (103) (710 mg, 40%) as colourless crystals with $[\alpha]_{\text{D}}^{20}$ -41° (*c* 0.46, CHCl₃); m.p. 95-96°C (from light petroleum), (Found: C, 85.4; H, 9.1; N, 6.4; M⁺ 225.1523; C₁₆H₁₉N requires C, 84.8; H, 9.0; N, 6.2; *M* 225.1517); ν_{max} (film CH₂Cl₂) 3401, 3060, 2926, and 2851 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.29 (3 H, s), 1.42 (4 H, m), 1.58 (4 H, m), 2.49 (1 H, m, CH), 2.51 (1 H, m), 2.85 (1 H, m), 7.07 (2 H, m), 7.26 (1 H, m), 7.44 (1 H, m), and 7.63 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl₃) 21.67 (CH₂), 22.82 (CH₂), 24.54 (CH₃), 27.26 (CH₂), 28.89 (CH₂), 35.36 (CH₂), 41.28 (4°C), 50.60 (CH), 111.49 (CH), 115.55 (4°C), 118.51 (CH), 119.45 (CH), 120.14 (CH), 125.51 (4°C), 139.75 (4°C), and 151.89 (4°C); *m/z* 225 (M⁺, 77%), and 210 (100). Contaminated with 4% (4*a*R,10*a*S)-4*a*-Methyl-1,2,3,4,4*a*,5,10,10*a*-octahydro-5H-indenof[1,2-*b*]indole by proton NMR, δ_{H} (250 MHz; CDCl₃) 0.98 (3 H, s, CH₃) - all other peaks obscured by major product

*(+)-(1*S*,7*a*S)-1-tert-Butoxy-7*a*-methyl-2,3,5,6,7,7*a*-hexahydro-indene (97).*

Dry trifluoroacetic acid (17 ml, 0.22 mol) was added dropwise, with stirring, to a suspension of sodium borohydride (2.6 g, 0.07 mol) in dry acetonitrile (20 ml) and dry dichloromethane (16 ml) at -40°C under an atmosphere of nitrogen so that temperature did not exceed -10°C. The solution was then recooled to -40°C and a solution of enone (92) (4 g, 0.02 mol) in dry dichloromethane (30 ml) was added dropwise, with stirring. The mixture was stirred at -40°C for 2 h and allowed to warm to room temperature and stirring continued overnight. The mixture was neutralised with sodium hydroxide solution (4M, ca. 65 ml) and extracted with dichloromethane. The combined dichloromethane extracts were washed with 2M sodium hydroxide solution and dried (MgSO₄). The solvent was removed under reduced pressure which gave the *title compound* (97) (2.2 g, 51%) as a yellow liquid with $[\alpha]_{\text{D}}^{20}$ +70° (*c* 0.7, CHCl₃); (Found: M⁺ 208.1823; C₁₄H₂₄O requires *M* 208.1827);

ν_{max} (film CH_2Cl_2) 2977, and 2937 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.92 (3 H, s, CH_3), 1.17 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.86 (9 H, m), 2.42 (1 H, m), 3.41 (1 H, t, J 8.2 Hz, $\text{CH}(\text{O}^t\text{Bu})$), and 5.31 (1 H, s, $\text{C}=\text{CH}$); δ_{C} (62.5 MHz; CDCl_3) 17.45 (CH_3), 18.68 (CH_2), 25.18 (CH_2), 26.17 (CH_2), 28.59 ($\text{C}(\text{CH}_3)_3$), 29.78 (CH_2), 34.79 (CH_2), 42.33 (4°C), 72.44 (4°C , $\text{OC}(\text{CH}_3)_3$), 80.79 ($\text{CH}(\text{O}^t\text{Bu})$), 118.31 ($\text{C}=\text{CH}$), and 144.98 (4°C , $\text{C}=\text{CH}$); m/z 208 (M^+ , 5%), 152 (93), 133 (88), 109 (100), and 57 (80)

(+)-(1*S*,3*aS*,7*aS*)-1-*tert*-Butoxy-7*a*-methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-indene (**104**).

To a solution of the alkene (**97**) (1.5 g, 7.2 mmol) in ethyl acetate (10 ml) was added 10%Pd/C (0.2 g) and a catalytic amount of 2M hydrochloric acid. The system was stirred overnight at room temperature under an atmosphere of hydrogen (45 psi). The mixture was filtered through celite and washed with water. The ethyl acetate extracts were dried (MgSO_4) and the solvent removed under reduced pressure which gave the *title compound* (**104**) (0.8 g, 53%) as a yellow liquid with $[\alpha]_{\text{D}}^{20} +43^\circ$ (c 1.0, CHCl_3); ν_{max} (film) 2973, and 2926 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.88 (3 H, s, CH_3), 1.31 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.26-1.42 (11 H, m), 1.54 (1 H, m), 2.03 (1 H, m), and 3.73 (1 H, dd, J 2.5, 5.2 Hz, $\text{CH}(\text{O}^t\text{Bu})$); δ_{C} (62.5 MHz; CDCl_3) 21.80 (CH_3), 22.14 (CH_2), 23.86 (CH_2), 28.20 (CH_2), 28.69 ($\text{C}(\text{CH}_3)_3$), 31.63 (CH_2), 32.53 (CH_2), 43.16 (CH), 43.35 (4°C), 72.32 (4°C , $\text{C}(\text{CH}_3)_3$), and 76.51 ($\text{CH}(\text{O}^t\text{Bu})$); m/z 210 (M^+ , 10%), 154 (100), 135 (90), 109 (65), and 57 (70). Contaminated with 15% (1*S*,3*aR*,7*aS*)-1-*tert*-Butoxy-7*a*-methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-indene by proton NMR, δ_{H} (250 MHz; CDCl_3) 0.71 (3 H, s, CH_3), and 3.38 (1 H, dd, J 1.6, 7.4 Hz, $\text{CH}(\text{O}^t\text{Bu})$) - all other peaks obscured by major product

(+)-(1*S*,3*aS*,7*aS*)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-ol (**105**).⁶⁴

Trifluoroacetic acid (0.2 ml, 2.6 mmol) was added to hydrindane (**104**) (0.2 g, 0.9 mmol) in dichloromethane (4 ml) and the mixture stirred at room temperature overnight. The mixture was diluted with water, neutralised with 2M sodium hydroxide solution and extracted into dichloromethane. After removal of the solvent under reduced pressure the residue was treated with lithium hydroxide (0.2g, 4.8 mmol) in water (5 ml) and tetrahydrofuran (8 ml) and the mixture stirred at room temperature for 4 h. After acidification with 2M hydrochloric acid the mixture was extracted into dichloromethane. The solvent was removed under reduced pressure which gave the *title compound* (**105**) (130 mg, 85%) as a colourless semi-solid with $[\alpha]_{\text{D}}^{20} +11^\circ$ (c 0.10, CHCl_3) (lit. $[\alpha]_{\text{D}}^{24} +20^\circ$ (c 1.0, CHCl_3);⁶⁴ ν_{max} (film) 3428 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.98 (3 H, s, CH_3), 1.42 (11 H, m), 1.79 (2 H, m), 2.17 (1 H, m), and 3.85 (1 H, dd, J 1.1, 7.7 Hz, $\text{CH}(\text{OH})$); δ_{C} (62.5 MHz; CDCl_3) 19.47 (CH_3), 21.62 (CH_2), 22.08 (CH_2), 25.99 (CH_2), 26.09 (CH_2), 31.24 (CH_2), 31.68 (CH_2), 41.75 (CH), 43.92 (4°C), and 79.85 ($\text{CH}(\text{OH})$); m/z 154 (M^+ , 62%),

110 (80), 95 (100), and 81 (75). Contaminated with 10% *(1S,3aR,7aS)-7a-Methyl-2,3,3a,4,5,6,7,7a-octahydro-inden-1-ol* by proton NMR, δ_{H} (250 MHz; CDCl_3) 0.74 (3 H, s, CH_3), and 3.64 (1 H, dd, J 1.6, 7.4 Hz, $\text{CH}(\text{OH})$) - all other peaks obscured by major product

(+)-(3aS,7aS)-7a-Methyl-2,3,3a,4,5,6,7,7a-octahydro-inden-1-one (106).⁶⁴

A mixture of the alcohol (105) (0.8 g, 5 mmol) and pyridinium chlorochromate (1.7 g, 8 mmol) in dichloromethane (10 ml) was stirred at room temperature for 90 min. The mixture was filtered through celite and washed with water. The dichloromethane extracts were dried (MgSO_4) and the solvent removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane: light petroleum) to give the title compound (106) (640 mg, 80%) as a pale yellow liquid with $[\alpha]_{\text{D}}^{20} +47^\circ$ (c 0.19, CHCl_3) (lit. $[\alpha]_{\text{D}}^{24} +57^\circ$ (c 1.0, CHCl_3));⁶⁴ $\nu_{\text{max}}(\text{film})$ 1737 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.04 (3 H, s, CH_3), 1.28 (1 H, m), 1.46 (8 H, m), 1.92 (2 H, m), and 2.33 (2 H, m); δ_{C} (62.5 MHz; CDCl_3) 21.37 (CH_3), 22.14 (CH_2), 22.36 (CH_2), 23.04 (CH_2), 26.74 (CH_2), 29.52 (CH_2), 34.93 (CH_2), 42.57 (CH), and 48.37 (4°C); m/z 152 (M^+ , 65%), 108 (62), 96 (74), and 81 (100). Contaminated with 11% *(3aR,7aS)-7a-Methyl-2,3,3a,4,5,6,7,7a-octahydro-inden-1-one* by proton NMR, δ_{H} (250 MHz; CDCl_3) 0.87 (3 H, s, CH_3) - all other peaks obscured by major product

(+)-(4aS,10aS)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydro-5H-indeno[1,2-b]indole (107).

A mixture of ketone (106) (640 mg, 4 mmol) and phenylhydrazine (0.42 ml, 4 mmol) was refluxed overnight in dry toluene (10 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (10 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO_4). The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the title compound (107) (670 mg, 38%) as colourless crystals with $[\alpha]_{\text{D}}^{20} +45^\circ$ (c 0.3 CHCl_3); m.p. 93-95 $^\circ\text{C}$ (from light petroleum); (Found: C, 83.0; H, 8.3; N, 6.9; M^+ 225.1531, $\text{C}_{16}\text{H}_{19}\text{N}$ requires C, 84.8; H, 9.0; N, 6.2; M 225.1517); $\nu_{\text{max}}(\text{film } \text{CH}_2\text{Cl}_2)$ 3405 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.32 (3 H, s, CH_3), 1.43 (2 H, m), 1.54 (2 H, m), 1.62 (3 H, m), 1.75 (1 H, m), 2.47 (1 H, m, CH), 2.52 (1 H, m), 2.81 (1 H, m), 7.06 (2 H, m), 7.29 (1 H, m), 7.44 (1 H, m), and 7.73 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 21.69 (CH_2), 22.84 (CH_2), 24.60 (CH_3), 27.29 (CH_2), 28.92 (CH_2), 35.41 (CH_2), 41.33 (4°C), 50.63 (CH), 111.45 (CH), 115.57 (4°C), 118.53 (CH), 119.50 (CH), 120.20 (CH), 139.80 (4°C), 151.86 (4°C), and 159.33 (4°C); m/z 225 (M^+ , 77%), and 210 (100). Contaminated with 2% *(4aS,10aR)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydro-5H-indeno[1,2-b]indole* by

proton NMR, δ_{H} (250 MHz; CDCl_3) 1.03 (3 H, s, CH_3) - all other peaks obscured by major product. The elemental analysis data is not within the required limits for publication, but these are the values that were obtained.

(-)-(7aR)-7a-Methyl-2,3,5,6,7,7a-hexahydro-inden-1-one (108).

A mixture of the alcohol (96) (2 g, 13 mmol) and pyridinium chlorochromate (4.3 g, 20 mmol) in dichloromethane (30 ml) was stirred at room temperature for 90 min. The mixture was filtered through Celite and washed with water. The dichloromethane extracts were dried (MgSO_4) and the solvent removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (108) (950 mg, 47%) as a pale yellow liquid with $[\alpha]_{\text{D}}^{20}$ - 310° (c 0.28 CHCl_3); (Found: M^+ 150.1035; $\text{C}_{10}\text{H}_{14}\text{O}$ requires M 150.1045; ν_{max} (film) 1740, and 1685 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.12 (3 H, s, CH_3), 1.25 (1 H, m), 1.71 (3 H, m), 2.04 (2 H, m), 2.17 (1 H, m), 2.51 (3 H, m), and 5.58 (1 H, m, $\text{C}=\text{CH}$); δ_{C} (62.5 MHz; CDCl_3) 18.13 (CH_2), 21.79 (CH_3), 24.63 (CH_2), 26.86 (CH_2), 28.70 (CH_2), 36.75 (CH_2), 47.23 (4°C), 120.51 ($\text{C}=\text{CH}$), 141.52 (4°C , $\text{C}=\text{CH}$), and 221.06 (CO); m/z 150 (M^+ , 55%), 122 (15), 107 (34), and 93 (100)

(-)-(4aR)-4a-Methyl-2,3,4,4a,5,10-hexahydro-5H-indeno[1,2-b]indole (109).

A mixture of ketone (108) (950 mg, 6.2 mmol) and phenylhydrazine (0.61 ml, 6.2 mmol) was refluxed overnight in dry toluene (10 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (10 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO_4). The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (109) (570 mg, 41%) as colourless crystals with $[\alpha]_{\text{D}}^{20}$ - 7° (c 0.3, CHCl_3); m.p. 110-112°C (from light petroleum); (Found: C, 85.0; H, 8.2; N, 6.4; M^+ 223.1357; $\text{C}_{16}\text{H}_{17}\text{N}$ requires C, 85.6; H, 8.1; N, 6.2; M 223.1360); ν_{max} (film CH_2Cl_2) 3409, 3054, 2951, 2941, 2921, and 2837 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.30 (3 H, s), 1.68 (1 H, m), 1.91 (2 H, m), 2.03 (1 H, m), 2.11 (2 H, m), 3.30 and 3.36 (1 H, dd, J 0.9, 15.3 Hz, CH_2CH), 3.56 and 3.63 (1 H, dq, J 2.1, 14.2 Hz, CH_2CH), 5.56 (1 H, d, J 2.3 Hz, CH_2CH), 7.12 (2 H, m), 7.32 (1 H, m), 7.45 (1 H, m), and 7.83 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 18.31 (CH_2), 23.94 (CH_2), 24.29 (CH_3), 30.83 (CH_2), 32.25 (CH_2), 41.02 (4°C), 111.48 (CH), 114.30 (4°C), 118.72 (CH), 118.92 ($\text{C}=\text{CH}$), 119.62 (CH), 120.58 (CH), 124.54 (4°C), 139.52 (4°C), 148.20 (4°C), and 150.28 (4°C); m/z 223 (M^+ , 28%), and 208 (100)

(-)-(4aR,10aR)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydro-5H-indenof[1,2-b]indole (103) from (109).⁶⁵

A mixture of indole (109) (114 mg) and 10% Pd/C (15 mg) in ethanol (10 ml) was stirred overnight under an atmosphere of hydrogen (45 psi). The mixture was filtered and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:dichloromethane) to give the *title compound* (103)⁶⁵ (8 mg, 1%) as a colourless oil, $\nu_{\text{max}}(\text{film})$ 3387 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.32 (3 H, s, CH₃), 1.42 (4 H, m), 1.52 (4 H, m), 2.47 (1 H, m, CH), 2.56 (1 H, m), 2.81 (1 H, m), 7.07 (2 H, m), 7.32 (1 H, m), 7.44 (1 H, m), 7.75 (1 H, s, NH); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 21.70 (CH₂), 22.85 (CH₂), 24.60 (CH₃), 27.29 (CH₂), 28.92 (CH₂), 35.40 (CH₂), 41.33 (4°C), 50.63 (CH), 111.46 (CH), 118.53 (CH), 119.50 (CH), 120.20 (CH), 129.22 (4°C), 136.42 (4°C), 139.78 (4°C), and 151.88 (4°C)

(1R,5R,7aR)-7a-Methyl-2,3,7,7a-tetrahydro-inden-1,5-(6H)-diol (119).

Dione (99) (4.0 g, 20 mmol) and cerium (III) chloride heptahydrate (9.0 g, 20 mmol) were dissolved in absolute ethanol (30 ml) and the mixture cooled to 0°C. Sodium borohydride (1.9 g, 40 mmol) was added slowly. The reaction was stirred at room temperature for 10 min then quenched by the dropwise addition of water. The system was continuously extracted into diethyl ether for 24 h and the diethyl ether layer was dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 3:2 ethyl acetate:light petroleum) to give the *title compound* (119) (2.2 g, 54%) as a colourless liquid, (Found: M^+ 168.1150; C₁₀H₁₄O requires M 168.1150); $\nu_{\text{max}}(\text{film})$ 3355 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.02 (3 H, s, CH₃), 1.38 (1 H, m), 1.63 (2 H, m), 1.77 (1 H, m), 2.01 (4 H, m), 2.47 (1 H, m), 3.62 (1 H, dd J 1.9, 7.8 Hz, CH(OH)), 4.28 (1 H, m, C=C(H)CH(OH)), and 5.36 (1 H, s, C=CH); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 16.41 (CH₃), 25.38 (CH₂), 29.05 (CH₂), 29.36 (CH₂), 33.73 (CH₂), 43.61 (4°C), 68.43 (C=C(H)CH(OH)), 81.31 (CH(OH)), 123.03 (C=CH), and 148.49 (4°C, C=CH); m/z (M^+ 168, 20%), 151 (100), 121 (25), 106 (55), and 43 (55)

(+)-(1R,5R,7aR)-5-tert-Butyldimethylsiloxy-7a-methyl-2,3,7,7a-tetrahydro-inden-1-(6H)-ol (120).

Diol (119) (0.8 g, 4.8 mmol) in dry dichloromethane (45 ml) under an atmosphere of nitrogen was cooled to -78°C. A solution of 2,6-lutidine (1.5 ml, 12.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.4 ml, 6.1 mmol) in dry dichloromethane (9 ml) was added dropwise so that the temperature was maintained. The mixture was stirred at -78°C for 30 min and absolute methanol (0.2 ml) was added. The mixture was allowed to warm to room temperature and then washed with water and brine. The dichloromethane

layers were dried (MgSO_4) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**120**) (1.3 g, 94%) as a colourless solid with $[\alpha]_{\text{D}}^{20} +24^\circ$ (c 0.8 CHCl_3); m.p. 101–103°C; (Found: C, 67.8; H, 10.7; $\text{C}_{16}\text{H}_{30}\text{O}_2\text{Si}$ requires C, 68.1; H, 10.6); ν_{max} (film CH_2Cl_2) 3428 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.07 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3), 0.91 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.01 (3 H, s, CH_3), 1.25 (1 H, m), 1.60–1.74 (5 H, m), 2.04 (2 H, m), 2.46 (1 H, m), 3.59 (1 H, dd J 2.3, 7.8 Hz, $\text{CH}(\text{OH})$), 4.27 (1 H, m, $\text{CH}(\text{OSi})$), and 5.28 (1 H, s, $\text{C}=\text{CH}$); δ_{C} (62.5 MHz; CDCl_3) -4.52 (SiCH_3), -4.41 (SiCH_3), 16.41 (CH_3), 18.39 (4°C , $\text{C}(\text{CH}_3)_3$), 25.54 (CH_2), 26.04 ($\text{C}(\text{CH}_3)_3$), 29.39 (CH_2), 29.64 (CH_2), 33.95 (CH_2), 43.66 (4°C), 69.44 ($\text{CH}(\text{OSi})$), 81.61 ($\text{CH}(\text{OH})$), 124.29 ($\text{C}=\text{CH}$), and 147.08 (4°C , $\text{C}=\text{CH}$); m/z (M^+ 282, 5%), 265 (15), 225 (35), 151 (20), and 133 (100)

Preparation of formic acid-acetic anhydride mixture (FAM).^{72a,b}

Formic acid (96–98%) (0.18 ml, 4.8 mmol) was added dropwise to acetic anhydride (0.46 ml, 4.8 mmol) so that the temperature remained below 45°C. After complete addition of the acid, the mixture was heated at 45°C for 1 h. The mixture was cooled and used immediately.

(+)-(1R,5R,7aR)-5-tert-Butyldimethylsiloxy-7a-methyl-2,3,7,7a-tetrahydro-(6H)-inden-1-yl-formate (121).

The alcohol (**120**) (300 mg, 1 mmol) in the minimum amount of dry diethyl ether was added dropwise to a solution of pyridine (1 drop) and FAM (0.16 ml, 1.2 mmol) so that the temperature did not rise above 20°C. The mixture was stirred at room temperature for 3 days. The mixture was poured into sodium bicarbonate solution and extracted into diethyl ether. The organic extracts were dried (MgSO_4) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**121**) (220 mg, 67%) as a colourless liquid with $[\alpha]_{\text{D}}^{20} +51^\circ$ (c 0.7, CHCl_3); (Found: M^+ 310.1972; $\text{C}_{17}\text{H}_{30}\text{O}_3\text{Si}$ requires M 310.1964); ν_{max} (film) 1731 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.07 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3), 0.90 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.09 (3 H, s, CH_3), 1.48 (1 H, m), 1.60–1.75 (5 H, m), 2.14 (2 H, m), 2.54 (1 H, m), 4.28 (1 H, m, $\text{CH}(\text{OSi})$), 4.76 (1 H, t J 8.7 Hz, $\text{CH}(\text{OH})$), 5.34 (1 H, s, $\text{C}=\text{CH}$), and 8.09 (1 H, d J 0.7 Hz, CHO); δ_{C} (62.5 MHz; CDCl_3) -4.55 (SiCH_3), -4.43 (SiCH_3), 17.87 (CH_3), 18.36 (4°C , $\text{C}(\text{CH}_3)_3$), 25.67 (CH_2), 26.01 ($\text{C}(\text{CH}_3)_3$), 26.34 (CH_2), 29.52 (CH_2), 34.01 (CH_2), 43.24 (4°C), 69.15 ($\text{CH}(\text{OSi})$), 81.96 (CH), 125.06 ($\text{C}=\text{CH}$), 145.20 (4°C , $\text{C}=\text{CH}$), and 160.87 (CHO); m/z (M^+ 310, 8%), 253 (8), 133 (95), 91 (93), and 75 (100)

*(-)-(1R,7aR)-1-Hydroxy-7a-methyl-2,3,7,7a-tetrahydro-inden-1-ol-5-(6H)-one (122).*⁴⁸

Dione (**99**) (6 g, 37 mmol) was taken up in absolute ethanol (50 ml) and cooled to -10°C. A solution of sodium borohydride (0.4 g, 9.6 mmol) in absolute ethanol (36 ml) was added dropwise so that the temperature was maintained between -5°C and -10°C. The mixture was warmed to +5°C and then recooled to -10°C where the pH was adjusted to between 5-7 with 2M hydrochloric acid. The solvent was removed under reduced pressure and the aqueous layer extracted with ethyl acetate. The organic extracts were dried (MgSO₄) and the solvent removed under reduced pressure which gave the title compound (**122**) (5 g, 83%) as an colourless semisolid with $[\alpha]_D^{20}$ -69° (*c* 0.2, CHCl₃); (Found: C, 70.5; H, 8.8; *M*⁺ 166.0992; C₁₀H₁₄O₂ requires C, 70.6; H, 8.2; *M* 166.0993); $\nu_{\max}(\text{film})$ 3395, and 1642 cm⁻¹; δ_H (250 MHz; CDCl₃) 1.15 (3 H, s, CH₃), 1.83 (2 H, m), 2.15 (2 H, m), 2.42 (4 H, m), 2.70 (1 H, m), 3.86 (1 H, dd, *J* 2.7, 7.6 Hz, CH(OH)), and 5.79 (1 H, s, C=CH); δ_C (62.5 MHz; CDCl₃) 15.10 (CH₃), 26.49 (CH₂), 29.16 (CH₂), 33.32 (CH₂), 34.15 (CH₂), 45.24 (4°C), 80.65 (CH(OH)), 123.46 (C=CH), 175.22 (4°C, C=CH), and 199.37 (CO); *m/z* (*M*⁺ 166, 60%), 138 (35), 122 (45), and 109 (100)

(-)-(1R,7aR)-1-tert-Butyldimethylsiloxy-7a-methyl-2,3,7,7a-tetrahydro-inden-5-(6H)-one (123).

A mixture of enone (**122**) (6.0 g, 36 mmol), *tert*-butyldimethylsilyl chloride (8.6 g, 57 mmol) and imidazole (5.3 g, 78 mmol) in dry dichloromethane (20 ml) and dry *N,N*-dimethyl formamide (150 ml) was stirred under nitrogen for 24 h. After dilution with water the mixture was extracted into diethyl ether. The diethyl ether extracts were dried (MgSO₄) and the solvent reduced under reduced pressure. The residue was subjected to chromatography (silica, 4:1 light petroleum:ethyl acetate) to give the *title compound* (**123**) (7.6 g, 75%) as a pale yellow liquid with $[\alpha]_D^{20}$ -31° (*c* 0.2, CHCl₃); (Found: C, 64.8; H, 10.1; C₁₆H₂₈O₂Si requires C, 64.4; H, 10.1); $\nu_{\max}(\text{film})$ 1672 cm⁻¹; δ_H (250 MHz; CDCl₃) 0.05 (6 H, s, 2 x SiCH₃), 0.90 (9 H, s, C(CH₃)₃), 1.10 (3 H, s, CH₃), 1.75 (2 H, m), 1.99 (2 H, m), 2.37 - 2.70 (4 H, m), 3.75 (1 H, dd, *J* 2.5, 7.5 Hz, CH(OSi)), and 5.77 (1 H, s, C=CH); δ_C (62.5 MHz; CDCl₃) -4.88 (SiCH₃), -4.46 (SiCH₃), 15.27 (CH₃), 18.02 (4°C, C(CH₃)₃), 25.74 (C(CH₃)₃), 26.57 (CH₂), 29.59 (CH₂), 33.41 (CH₂), 34.40 (CH₂), 45.62 (4°C), 80.77 (CH(OSi)), 123.27 (C=CH), 175.24 (4°C, C=CH), and 199.42 (CO); *m/z* 223 (*M*⁺-*t*Bu, 100 %), and 75 (90)

(-)-(1R,5R,7aR)-1-tert-Butyldimethylsiloxy-7a-methyl-2,3,7,7a-tetrahydro-inden-5-(6H)-ol (124).

Enone (**123**) (2.0 g, 7.1 mmol) and cerium (III) chloride heptahydrate (2.6 g, 7.1 mmol) were dissolved in absolute ethanol (15 ml) and the mixture cooled to 0°C. Sodium

borohydride (0.52 g, 14 mmol) was added slowly. The reaction was stirred at room temperature for 10 min then quenched by the dropwise addition of water. The mixture was extracted into diethyl ether, dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**124**) (1.8 g, 90%) as a colourless semisolid with $[\alpha]_D^{20}$ -9° (*c* 0.35 CHCl₃); (Found: C, 67.4; H, 11.0; C₁₆H₃₀O₂Si requires C, 68.0; H, 10.7); $\nu_{\max}(\text{film})$ 3369 cm⁻¹; $\delta_H(250 \text{ MHz; CDCl}_3)$ 0.02 (6 H, s, 2 x SiCH₃), 0.88 (9 H, s, C(CH₃)₃), 0.98 (3 H, s, CH₃), 1.25 (1 H, m), 1.50-1.88 (5 H, m), 2.08 (2 H, m), 2.40 (1 H, m), 3.54 (1 H, dd, *J* 1.5, 8.0 Hz, CH(OSi)), 4.24 (1 H, m, CH(OH)), and 5.34 (1 H, d, *J* 1.0 Hz, CH=C); $\delta_C(62.5 \text{ MHz; CDCl}_3)$ -4.81 (SiCH₃), -4.43 (SiCH₃), 16.82 (CH₃), 18.07 (4°C, C(CH₃)₃), 25.66 (CH₂), 25.81 (C(CH₃)₃), 29.67 (CH₂), 29.78 (CH₂), 34.28 (CH₂), 44.18 (4°C), 68.80 (CH(OH)), 81.37 (CH(OSi)), 122.73 (CH=C), and 149.91 (4°C, C=CH); *m/z* 265 (M⁺-OH, 20%), 207 (20), 133 (90), 75 (100), and 41 (70)

(+)-(1R,5R,7aR)-1-tert-Butyldimethylsiloxy-7a-methyl-2,3,7,7a-tetrahydro-(6H)-inden-5-yl-formate (**125**).

Alcohol (**124**) (3.6 g, 12.6 mmol) in the minimum amount of dry diethyl ether was added dropwise to a solution of pyridine (0.11 ml, 0.14 mmol) and FAM (1.84 ml, 13.8 mmol) so that the temperature did not rise above 20°C. The mixture was stirred at room temperature for 7 days. The mixture was poured into sodium bicarbonate solution and extracted into diethyl ether. The organic extracts were dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**125**) (2.7 g, 68%) as a colourless liquid with $[\alpha]_D^{20}$ +18° (*c* 0.5 CHCl₃); (Found: C, 66.0; H, 9.9; C₁₇H₃₀O₃Si requires C, 65.8; H, 9.7); $\nu_{\max}(\text{film})$ 1726 cm⁻¹; $\delta_H(250 \text{ MHz; CDCl}_3)$ 0.02 (6 H, s, 2 x SiCH₃), 0.91 (9 H, s, C(CH₃)₃), 1.00 (3 H, s, CH₃), 1.25 (1 H, m), 1.64-1.89 (5 H, m), 2.08 (2 H, m), 2.41 (1 H, m), 3.57 (1 H, dd, *J* 1.6, 7.9 Hz, CH(OSi)), 5.31 (1 H, d, *J* 3.6 Hz, C=CH), 5.44 (1 H, s, CH(OCHO)), and 8.08 (1 H, d, *J* 1.1 Hz, CHO); $\delta_C(62.5 \text{ MHz; CDCl}_3)$ -4.83 (SiCH₃), -4.43 (SiCH₃), 16.60 (CH₃), 18.06 (4°C, C(CH₃)₃), 25.17 (CH₂), 25.76 (CH₂), 25.79 (C(CH₃)₃), 29.58 (CH₂), 33.90 (CH₂), 44.04 (4°C), 71.46 (CH(OCHO)), 81.20 (CH(OSi)), 117.92 (C=CH), 151.96 (4°C, C=CH), and 161.16 (C=O); *m/z* 265 (M⁺-OCHO, 10%), 207 (30), 133 (100), and 75 (25)

Preparation of Palladium catalyst.^{60a,60b}

To a solution of palladium (II) acetylacetonate (92 mg, 0.3 mmol) in dry tetrahydrofuran (4 ml) under nitrogen was added freshly distilled *n*-tri-butyl phosphine (0.07 ml, 0.3 mmol) dropwise. The catalyst was used immediately.

(-)-(1R,3aS,7aR)-1-tert-Butyldimethylsiloxy-7a-methyl-2,3,3a,6,7,7a-hexahydro-indene (126).

To a solution of hydrindene (125) (930 mg, 3.0 mmol) in dry tetrahydrofuran (3 ml) under nitrogen at room temperature was added dropwise the stock solution of catalyst (2.4 ml, 1.5 mmol). Stirring was continued for 1 h (the colour changes from yellow to dark brown during the course of the reaction). The compound was passed through a plug of florisil using diethyl ether (200 ml) as the eluant. The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, light petroleum) to give the *title compound* (126) (427 mg, 53%) as a colourless liquid with $[\alpha]_D^{20}$ -44° (*c* 0.25, CHCl₃); (Found: M^+ 266.2061; C₁₆H₃₀OSi requires *M* 266.2065); $\nu_{\max}(\text{film})$ 3020, 2957, 2929, and 2857 cm⁻¹; $\delta_H(250 \text{ MHz; CDCl}_3)$ 0.02 (6 H, s, 2 x SiCH₃), 0.7 (3 H, s, CH₃), 0.88 (9 H, s, C(CH₃)₃), 1.44-1.56 (4 H, m), 1.70 (1 H, m), 1.95 (2 H, m), 2.06 (2 H, m), 3.63 (1 H, dd, *J* 1.8, 6.9 Hz, CH(OSi)), and 5.53 (2 H, m, 2 x C=CH); $\delta_C(62.5 \text{ MHz; CDCl}_3)$ -4.58 (2 x SiCH₃), 10.51 (CH₃), 18.03 (4°C, C(CH₃)₃), 24.04 (CH₂), 24.22 (CH₂), 25.77 (C(CH₃)₃), 31.11 (CH₂), 33.88 (CH₂), 42.68 (CH), 80.27 (CH(OSi)), 126.56 (C=CH), and 128.06 (C=CH); *m/z* 266 (M^+ , 1%), 209 (35), 133 (40), and 75 (100)

(-)-(1R,7aR)-1-tert-Butyldimethylsiloxy-7a-methyl-2,6,7,7a-tetrahydro-indene (127)
(Contaminating by-product from reaction to give (126)).

Gives the *title compound* (127) as a colourless liquid, $\nu_{\max}(\text{film})$ 3028, 2956, 2926, and 2856 cm⁻¹; $\delta_H(250 \text{ MHz; CDCl}_3)$ -0.05 (1 H, s, SiCH₃), -0.03 (5 H, s, SiCH₃), 0.86 (12 H, s, CH₃ and C(CH₃)₃), 1.24 (2 H, m), 1.74 (1 H, m), 2.08 (2 H, m), 2.31 (1 H, m), 3.89 (1 H, m, CH(OSi)), 5.21 (1 H, s, C=CH), 5.68 (1 H, m, C=CH) and 6.06 (1 H, m, C=CH); $\delta_C(62.5 \text{ MHz; CDCl}_3)$ -4.83 (SiCH₃), -4.49 (SiCH₃), 15.18 (CH₃), 23.51 (CH₂), 25.84 (C(CH₃)₃), 34.02 (CH₂), 38.03 (CH₂), 82.23 (CH(OSi)), 118.68 (C=CH), 123.46 (C=CH), and 129.17 (C=CH)

(-)-(1R,3aS,7aR)-1-tert-Butyldimethylsiloxy-7a-methyl-2,3,3a,4,5,6,7,7a-octahydro-indene (128).

To a solution of the hydrindene (126) (140 mg, 0.5 mmol) in ethyl acetate (5 ml) was added 10%Pd/C (20 mg). The system was stirred for 2 h at room temperature under an atmosphere of hydrogen. The mixture was filtered and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, light petroleum) to give the *title compound* (128) (125 mg, 89%) as a colourless liquid with $[\alpha]_D^{20}$ -18° (*c* 0.08, CHCl₃); (Found: M^+ 268.2228, C₁₆H₃₂OSi requires *M* 266.2222); $\nu_{\max}(\text{film})$ 2955, 2927, and 2857 cm⁻¹; $\delta_H(250 \text{ MHz; CDCl}_3)$ 0.70 (3 H, s, CH₃), 0.90 (9 H, s, C(CH₃)₃), 1.31-1.51 (13 H, m), 1.68-1.74 (2 H, m), 1.90 (1 H, m), and 3.57 (1 H, dd, *J* 1.3, 7.2 Hz, CH(OSi)); $\delta_C(62.5 \text{ MHz; CDCl}_3)$ -4.80 (SiCH₃), -4.47 (SiCH₃), 10.42 (CH₃), 21.92

(CH₂), 25.88 (C(CH₃)₃), 25.93 (CH₂), 26.09 (CH₂), 30.45 (CH₂), 37.68 (CH₂), 44.74 (CH), and 82.04 (CH(OSi)); *m/z* 268 (M⁺, 1%), 211 (35), 135 (40), and 75 (100). Contaminated with 20% (1*R*,3*aR*,7*aR*)-1-*tert*-Butyldimethylsiloxy-7*a*-methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-indene by proton NMR, δ_{H} (250 MHz; CDCl₃) 3.86 (1 H, dd, *J* 2.8, 4.1 Hz, CH(OSi))- all other peaks obscured by major product

(-)-(1R,3aS,7aR)-7a-Methyl-2,3,3a,4,5,6,7,7a-octahydro-inden-1-ol (129).

A mixture of hydrindane (**128**) (230 mg) and 2% hydrochloric acid/ethanol solution was stirred at room temperature for 3 h. The mixture was extracted into diethyl ether and washed with sodium bicarbonate solution. The organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**129**) (115 mg, 87%) as a colourless semisolid with $[\alpha]_{\text{D}}^{20} -7^{\circ}$ (*c* 0.06, CHCl₃); (Found: M⁺ 154.1373, C₁₀H₁₈O requires *M* 154.1358); ν_{max} (film) 3350 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.73 (3 H, s, CH₃), 1.20-1.51 (11 H, m), 1.74 (2 H, m), 2.01 (1 H, m), and 3.64 (1 H, dd, *J* 1.0, 7.7 Hz, CH(OH)); δ_{C} (62.5 MHz; CDCl₃) 10.03 (CH₃), 21.32 (CH₂), 25.62 (CH₂), 25.80 (CH₂), 26.31 (CH₂), 29.89 (CH₂), 37.09 (CH₂), 42.69 (4°C), 44.93 (CH), and 82.01 (CH(OH)); *m/z* 154 (M⁺, 10%), 110 (20), 95 (35), 81 (35), and 44 (100). Contaminated with 20% (1*R*,3*aR*,7*aR*)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-ol by proton NMR, δ_{H} (250 MHz; CDCl₃) 3.80 (1 H, m, CH(OH))- all other peaks obscured by major product

(-)-(3aS,7aR)-7a-Methyl-2,3,3a,4,5,6,7,7a-octahydro-inden-1-one (130).

A mixture of the alcohol (**129**) (95 mg, 6 mmol) and pyridinium chlorochromate (1.9 g, 9 mmol) in dichloromethane (15 ml) was stirred at room temperature for 90 min. The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (**130**) (76 mg, 81%) as a pale yellow liquid with $[\alpha]_{\text{D}}^{20} -77^{\circ}$ (*c* 0.09, CHCl₃); (Found: M⁺ 152.1202, C₁₀H₁₆O requires *M* 152.1202); ν_{max} (film) 1739 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.87 (3 H, s, CH₃), 1.27 (2 H, m), 1.38-1.51 (3 H, m), 1.58 (4 H, m), 1.73 (2 H, m), 1.79 (1 H, m), 1.98-2.13 (1 H, m), and 2.35-2.46 (1 H, m); δ_{C} (62.5 MHz; CDCl₃) 12.76 (CH₃), 21.03 (CH₂), 24.30 (CH₂), 25.62 (CH₂), 26.31 (CH₂), 32.05 (CH₂), 35.43 (CH₂), 45.85 (CH), 47.61 (4°C), and 221.48 (CO); *m/z* 152 (M⁺, 45%), 108 (40), 96 (60), and 81 (100). Contaminated with 20% (3*aR*,7*aR*)-7*a*-Methyl-2,3,3*a*,4,5,6,7,7*a*-octahydro-inden-1-one by proton NMR, δ_{H} (250 MHz; CDCl₃) 1.17 (3 H, s, CH₃) - all other peaks obscured by major product

(-)-(4aR,10aS)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydro-5H-indeno[1,2-b]indole (131).

A mixture of ketone (130) (62 mg, 0.4 mmol) and phenylhydrazine (0.05 ml, 0.4 mmol) was refluxed overnight in dry toluene (10 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (10 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO₄). The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (131) (27 mg, 29%) as a yellow tacky oil with $[\alpha]_D^{20} -19^\circ$ (*c* 0.1, CHCl₃); ν_{\max} (film CH₂Cl₂) 3472, 3019, 2932, and 2856 cm⁻¹; δ_H (250 MHz; CDCl₃) 0.99 (3 H, s, CH₃), 1.33-1.50 (2 H, m), 1.55-1.75 (8 H, m), 1.77-1.85 (1 H, m), 2.00-2.10 (1 H, m), 2.25-2.90 (5 H, m), 7.08-7.15 (2 H, m), 7.25-7.30 (1 H, m), 7.40-7.50 (1 H, m), and 7.83 (1 H, s, NH); δ_C (62.5 MHz; CDCl₃) 17.12 (CH₃), 21.31 (CH₂), 24.59 (CH₂), 26.80 (CH₂), 27.98 (CH₂), 34.87 (CH₂), 41.32 (4°C), 42.19 (4°C), 55.69 (CH), 111.47 (CH), 111.56 (CH), 116.80 (4°C), 118.53 (CH), 119.49 (CH), 119.56 (CH), 120.19 (CH), and 120.23 (CH). Contaminated with 50% *(-)-(4aR,10aR)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydro-5H-indeno[1,2-b]indole (103)*,⁶⁵ ν_{\max} (film CH₂Cl₂) 3408 cm⁻¹; δ_H (250 MHz; CDCl₃) 1.31 (3 H, s, CH₃), and 7.75 (1 H, s, NH); δ_C (62.5 MHz; CDCl₃) 21.69 (CH₂), 22.85 (CH₂), 24.71 (CH₃), 27.29 (CH₂), 28.92 (CH₂), 35.40 (CH₂), and 50.63 (CH) - all other peaks obscured by major product

(-)-(1R,3aS,7aR)-7a-Methyl-2,3,3a,6,7,7a-hexahydro-inden-1-ol (132).

A mixture of hydrindene (126) (360 mg) and 2% hydrochloric acid/ethanol solution was stirred at room temperature for 4 h. The mixture was extracted into diethyl ether and washed with sodium bicarbonate solution. The organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (132) (206 mg, 100%) as a colourless semisolid, with $[\alpha]_D^{20} -82^\circ$ (*c* 0.3, CHCl₃); ν_{\max} (film) 3316 cm⁻¹; δ_H (250 MHz; CDCl₃) 0.77 (3 H, s, CH₃), 1.43 (6 H, m), 1.85 (1 H, m), 2.13 (3 H, m), 3.74 (1 H, dd, *J* 2.0, 7.1 Hz, CH(OH)), and 5.59 (2 H, m); δ_C (62.5 MHz; CDCl₃) 10.18 (CH₃), 23.84 (CH₂), 24.04 (CH₂), 30.80 (CH₂), 33.46 (CH₂), 42.31 (4°C), 43.16 (CH), 80.40 (CH(OH)), 126.53 (CH), and 127.73 (CH)

(-)-(3aS,7aR)-7a-Methyl-2,3,3a,6,7,7a-hexahydro-inden-1-one (133).

A mixture of the alcohol (132) (68 mg, 0.4 mmol) and pyridinium chlorochromate (140 mg, 0.7 mmol) in dichloromethane (10 ml) was stirred at room temperature for 90 min. The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane: light petroleum) to give the *title compound*

(133) (55 mg, 82%) as a pale yellow liquid with $[\alpha]_{\text{D}}^{20} -89^\circ$ (c 0.17, CHCl_3); $\nu_{\text{max}}(\text{film})$ 3022, 2961, 2891, and 1740 cm^{-1} ; $\delta_{\text{H}}(250\text{ MHz; CDCl}_3)$ 0.89 (3 H, s, CH_3), 1.59 (3 H, m), 2.19 (4 H, m), 2.45 (2 H, m), and 5.66 (2 H, m); $\delta_{\text{C}}(62.5\text{ MHz; CDCl}_3)$ 12.88 (CH_3), 22.64 (CH_2), 23.76 (CH_2), 28.84 (CH_2), 36.15 (CH_2), 43.72 (CH), 47.22 (4°C), 126.44 (CH), and 128.06 (CH)

(-)-(4aS,10aR)-4a-Methyl-3,4,4a,5,10,10a-hexahydro-5H-indeno[1,2-b]indole (134).

A mixture of ketone (133) (13 mg, 0.09 mmol) and phenylhydrazine (0.01 ml, 0.09 mmol) was refluxed overnight in dry toluene (5 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (5 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO_4). The solvent was removed under reduced pressure to give a brown residue which was subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (134) (2 mg, 10%) as an orange solid with $[\alpha]_{\text{D}}^{20} -42^\circ$ (c 0.005, CHCl_3); m.p. $93-96^\circ\text{C}$ (from light petroleum); $\nu_{\text{max}}(\text{film CH}_2\text{Cl}_2)$ 3403, 3050, 3017, and 2957 cm^{-1} ; $\delta_{\text{H}}(250\text{ MHz; CDCl}_3)$ 0.98 (3 H, s, CH_3), 2.02 (2 H, m), 2.20 (2 H, m), 2.42 (1 H, m), 2.85 (1 H, m), 3.18 (1 H, m), 5.64 (1 H, m, $\text{C}=\text{CH}$), 5.90 (1 H, m, $\text{C}=\text{CH}$), 7.07 (2 H, m), 7.30 (2 H, m), 7.47 (1 H, m), and 7.85 (1 H, s, NH); $\delta_{\text{C}}(62.5\text{ MHz; CDCl}_3)$ 17.27 (CH_3), 23.66 (CH_2), 26.40 (CH_2), 31.88 (CH_2), 52.85 (CH), 111.51, 118.46, 119.62, 120.34, 126.58, and 127.58

5.3 Experimental for Chapter 3

Acetamidoacetaldehyde dimethylacetal (144).

A mixture of aminoacetaldehyde dimethylacetal (9.3 g, 0.09 mol), pyridine (15 g, 0.19 mol) and acetic anhydride (9.8 g, 0.09 mol) was stirred overnight at room temperature. Excess pyridine was removed under reduced pressure to give a yellow liquid. Distillation at 100-102°C, 0.5 mmHg gave the title compound (144) (11.9 g, 91%) as a colourless liquid, $\nu_{\max}(\text{film})$ 3300, 1718 and 1674 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 2.00 (3 H, s), 3.41 (8 H, s), 4.38 (1 H, t, J 5.2 Hz, $\text{CH}(\text{OCH}_3)_2$), and 6.17 (1 H, s, NH); $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 23.12 (CH_3), 41.03 (CH_2), 54.30 (OCH_3), 102.61 (CH), and 170.54 (CO)

Ethyl 4-chloro-3,3-dimethoxybutanoate (145).

A mixture of ethyl 4-chloro-3-oxobutanoate (5.6 g, 0.03 mol), trimethylorthoformate (20 ml, 0.18 mol) and Amberlyst-15 (2 g) was stirred at room temperature for 24 h. After filtration, the solvent was removed under reduced pressure to give title compound (145) (5.4 g, 75%) as an orange liquid, $\nu_{\max}(\text{film})$ 1736 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 1.25 (3 H, t, J 7.1 Hz, CH_2CH_3), 2.86 (2 H, s), 3.25 (6 H, s, 2 x OCH_3), 3.79 (2 H, s), and 4.21 (2 H, q, J 7.1 Hz, CH_2CH_3); $\delta_{\text{C}}(62.5 \text{ MHz; CDCl}_3)$ 14.13 (CH_3), 37.31 (CH_2), 42.92 (CH_2), 48.68 (OCH_3), 60.70 (CH_2), 100.53 (4°C) and 168.83 (CO)

Ethyl 4-azido-3-oxobutanoate (146).

To a suspension of sodium azide (4 g, 0.06 mol) in water (25 ml) was added ethyl 4-chloro-3-oxobutanoate (5.1 g, 0.03 mol), glacial acetic acid (0.25 ml) and sodium iodide (1 grain). The mixture was stirred at room temperature for 3 days. The mixture was extracted into ether, dried (Na_2SO_4) and the solvent removed under reduced pressure to give a red liquid. The residue was subjected to chromatography (silica, light petroleum then ethyl acetate) to give the title compound (146) (3.3 g, 62%) as a yellow liquid, $\nu_{\max}(\text{film})$ 2104, 1742 and 1724 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 1.27 (3 H, t, J 7.1 Hz, CH_2CH_3), 3.56 (2 H, s), 4.12 (2 H, s), and 4.20 (2 H, q, J 7.1 Hz, CH_2CH_3); $\delta_{\text{C}}(62.5 \text{ MHz; CDCl}_3)$ 14.07 (CH_3), 46.67 (CH_2), 57.73 (CH_2), 61.87 (CH_2), 166.41 (CO) and 197.29 (CO)

Ethyl 4-azido-3,3-dimethoxybutanoate (147).

A mixture of azide (146) (3.0 g, 17 mmol), trimethylorthoformate (5.7 ml, 52 mmol) and *p*-toluenesulfonic acid (180 mg) in methanol (12 ml) was stirred under reflux for 7 h. After cooling, the solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 3:1 light petroleum:diethyl ether) to give title compound (147) (2.3 g, 61%) as a pale yellow liquid, (Found: C, 44.4; H, 6.9; N, 19.0. $\text{C}_8\text{H}_{15}\text{N}_3\text{O}_4$ requires C, 44.2; H, 7.0; N 19.3); $\nu_{\max}(\text{film})$ 2105 and 1736 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 1.27 (3 H, t,

J 7.1 Hz, CH_2CH_3), 2.78 (2 H, s), 3.26 (6 H, s, 2 x OCH_3), 3.53 (2 H, s), and 4.15 (2 H, q, J 7.1 Hz, CH_2CH_3); δ_{C} (62.5 MHz; CDCl_3) 14.13 (CH_3), 38.08 (CH_2), 48.63 (OCH_3), 51.42 (CH_2), 60.79 (CH_2), 100.51 (4°C) and 168.94 (CO); m/z 161 ($\text{M}^+ - \text{CH}_2\text{N}_3$, 100%)

Ethyl 4-acetamido-3-oxobutanoate (148).

To azide (146) (3.2 g, 18 mmol) under an atmosphere of nitrogen was added thioacetic acid (4.8 ml, 75 mmol) dropwise, with stirring. After stirring at room temperature for 4 h the excess thioacetic acid was removed under reduced pressure to give an orange oil. The residue was subjected to chromatography (silica, 4:1 light petroleum:dichloromethane) to give the *title compound* (148) (3.2 g, 92%) as an orange solid, m.p. $42-44^\circ\text{C}$, (Found: $\text{M} + \text{NH}_4^+$ 205.1188; $\text{C}_8\text{H}_{13}\text{NO}_4 + \text{NH}_4^+$ requires M 205.1188); ν_{max} (film, CH_2Cl_2) 3304, 1747, 1740 and 1731 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.31 (3 H, t, J 7.2 Hz, CH_2CH_3), 2.09 (3 H, s), 3.52 (2 H, s), 4.21 (4 H, m, CH_2CH_3 , CH_2), and 6.61 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 14.07 (CH_3), 22.80 (CH_3), 46.72 (CH_2), 49.57 (CH_2), 61.74 (CH_2), 166.66 (CO), 170.53 (CO) and 198.57 (CO); m/z 205 ($\text{M} + \text{NH}_4^+$, 30%), and 188 (100)

Trimethylsiloxycyclopentene (141).^{80a,b}

To a solution of cyclopentanone (11.0 g, 0.13 mol), triethylamine (18.0 g, 0.18 mol) and chlorotrimethylsilane (18.8 g, 0.17 mol) was added dropwise, with stirring, a suspension of sodium iodide (26.0 g, 0.17 mol) in acetonitrile (125 ml) under nitrogen. The mixture was stirred overnight at room temperature. Cold light petroleum (200 ml) and water (200 ml) were added and the layers separated. The aqueous layer was extracted with light petroleum. The combined light petroleum extracts were washed with water until neutrality then dried (Na_2SO_4). The solvent was removed under reduced pressure to give a yellow liquid. Distillation at 40°C , 4 mmHg gave the *title compound* (141) (10.2 g, 61%) as a colourless liquid, ν_{max} (film) 1642 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.20 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 1.85 (2 H, m), 2.25 (4 H, m), and 4.61 (1 H, s, $\text{C}=\text{CH}$); δ_{C} (62.5 MHz; CDCl_3) 21.31 (CH_2), 28.73 (CH_2), 33.49 (CH_2), 102.08 ($\text{C}=\text{CH}$) and 154.99 (4°C , $\text{C}=\text{CH}$)

Procedure for the Mukaiyama reaction:⁷⁸

To a solution of azide (147) or amide (144) (1 equivalent) in dry dichloromethane at -78°C was added titanium (IV) chloride (4 equivalents) dropwise with stirring. To this was added silylenolether (141) (1 equivalent) in dry dichloromethane dropwise with stirring. After stirring at -78°C for 3 h and warming to ambient the mixture was hydrolysed with water and extracted with dichloromethane. The combined organic extracts were washed with water, dried (MgSO_4) and the solvent removed under reduced pressure to yield a black residue. The residue and a catalytic amount of *p*-toluenesulfonic acid was refluxed in toluene for 1 h using Dean and Stark apparatus. After cooling, the mixture was diluted with water and

extracted into dichloromethane. The combined organic extracts were dried (MgSO_4) and the solvent removed under reduced pressure to yield a black residue. All data showed no indication of pyrrole formation.

*2-(2-oxopropyl)cyclopentanone (149).*⁸¹

1. - To a mixture of cyclopentanone (20 ml, 0.23 mol) and isopropenylacetate (5 ml, 0.05 mol) in methanol (40 ml) was added cerium (IV) ammonium nitrate (10 g, 0.02 mol) with vigorous stirring. Stirring was continued at room temperature until disappearance of the CAN colour (ca. 40 min) when a solution of sodium hydrogencarbonate (1.5 g in 25 ml water) was added and the mixture heated at 40°C for 45 min. After cooling, the mixture was diluted with water and extracted into dichloromethane. The combined organic extracts were dried (MgSO_4) and the solvent removed under reduced pressure. The residue was distilled at 80-90°C, 1.5 mmHg to give the title compound (149) (450 mg, 18%) as a pale yellow liquid, $\nu_{\text{max}}(\text{film})$ 1735 and 1719 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.49 (2 H, m), 1.63 (2 H, m), 2.16 (3 H, s, CH_3), 2.23 (2 H, m), 2.47 (2 H, m), and 2.88 (1 H, dd, J 3.1, 14.3 Hz); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 20.80 (CH_2), 29.50 (CH_2), 30.03 (CH_3), 37.42 (CH_2), 43.33 (CH_2), 44.88 (CH), 206.60 (CO) and 220.12 (CO)

2. - 2-Nitropropene (475 mg, 4.5 mmol) was added rapidly to a dry dichloromethane solution of titanium (IV) chloride (0.33 ml, 3 mmol) under nitrogen at -78°C. The mixture was stirred at -78°C for 10 min. Trimethylsiloxycyclopentene (141) (527 mg, 3 mmol) was added dropwise with stirring and the mixture was stirred at -78°C for 1 h. After warming to ambient, water (5 ml) was added and the system heated under reflux for 2 h. After cooling, the mixture was extracted into ethyl acetate, the combined organic extracts were washed with water and brine. After drying (MgSO_4), the solvent removed under reduced pressure. The residue was distilled at 70°C, 0.5 mmHg to give the title compound (149) (65 mg, 14%) as a pale yellow liquid - data as above

*1-Benzyl-2-methyl-1,4,5,6-tetrahydrocyclopent[b]pyrrole (150).*⁸³

To a solution of the dicarbonyl (149) (213 mg, 1.7 mmol) in ethanol (3 ml) was added benzylamine (179 mg, 1.7 mmol) and a catalytic amount of 2M hydrochloric acid. The mixture was stirred under reflux for 3 h. The ethanol was removed under reduced pressure to yield a brown residue which was subjected to chromatography (silica, 2:1 light petroleum:diethyl ether) to give the title compound (150) (157 mg, 49%) as a yellow oil, $\nu_{\text{max}}(\text{film})$ 3087, 3063, 2927 and 2852 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 2.13 (3 H, s, CH_3), 2.37 (2 H, m), 2.59 (4 H, m), 4.93 (2 H, s, CH_2Ph), 7.01 (2 H, m), and 7.25 (4 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 12.67 (CH_3), 24.90 (CH_2), 25.81 (CH_2), 28.68 (CH_2), 48.57

(CH₂Ph), 101.81 (CH), 124.43 (4°C), 126.32 (CH), 127.09 (CH), 128.64 (CH), 131.17 (4°C), 137.27 (4°C) and 138.61 (4°C)

Methyl 1-(2-methoxy-3-methoxycarbonylprop-2(E)-en-1-yl)-2-oxocyclopentane-1-carboxylate (151).

A solution of sodium methoxide (3.9 g, 0.07 mol) in *N,N*-dimethylformamide (30 ml) was cooled in an ice-bath and methyl 2-oxocyclopentanecarboxylate, (9 ml, 0.07 mol) was added dropwise, with stirring, so that the temperature did not exceed 10°C. Stirring was continued for 10 min after which time a solution of methyl 4-chloro-3-methoxy-2(*E*)-butenoate (6 g, 0.035 mol) in *N,N*-dimethylformamide (10 ml) was added dropwise, with stirring. After stirring at room temperature for a further 2 h the solvent was removed under reduced pressure and the residue taken up in water and dichloromethane. The aqueous layer was neutralised with 2M hydrochloric acid and extracted into dichloromethane. The combined organic layers were dried (MgSO₄) and the solvent removed under reduced pressure to give an orange liquid. Distillation of the residue at 40°C, 1 mmHg for several hours removed excess starting materials and impurities and gave the *title compound (151)* (1.7 g, 78%) as a yellow solid m.p. 53-55°C (Found: C, 57.9; H, 6.7; C₁₃H₁₈O₆ requires C, 57.8; H, 6.7); ν_{\max} (film CH₂Cl₂) 1754, 1729, 1715 and 1628 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.76 (3 H, m), 2.21 (2 H, m), 2.33 (1 H, m), 3.08 (1 H, d, *J* 14.8 Hz, CH₂C=C), 3.45 (3 H, s), 3.53 (3 H, s), 3.57 (3 H, s), 3.59 (1 H, d, *J* 14.8 Hz, CH₂C=C), and 4.99 (1 H, s, C=CH); δ_{C} (62.5 MHz; CDCl₃) 19.56 (CH₂), 31.93 (CH₂), 34.66 (CH₂C=C), 37.59 (CH₂), 50.95 (CO₂CH₃), 52.63 (CO₂CH₃), 55.55 (OCH₃), 58.50 (4°C), 93.28 (C=CH), 167.67 (4°C), 171.01 (CO₂CH₃), 171.35 (CO₂CH₃), and 213.53 (CO); *m/z* 270 (M⁺, 15%), 238 (55), 207 (50), 182 (60), 154 (38), 130 (35), and 69 (100)

Methyl 1-(2-oxopropyl)-2-oxocyclopentane-1-carboxylate (153) and Methyl 4-(2-oxocyclopentyl)-3-oxobutanoate (154).

To ester (**151**) (144 mg, 0.56 mmol) in tetrahydrofuran (4 ml) was added 2M sulphuric acid (1 ml) and the mixture refluxed for 3 h. After dilution with water the mixture was extracted into dichloromethane. The combined organic extracts were dried (MgSO₄) and the solvent removed under reduced pressure to give the *title compounds (153)* and (**154**) (117 mg) as a brown viscous liquid, δ_{H} (250 MHz; CDCl₃) 2.08 (m), 2.14 (s), 2.47 (m), 3.00 (s), 3.18 (s), and 3.73 (s); δ_{C} (62.5 MHz; CDCl₃) (**153**) (major) 19.76, 29.95, 33.18, 37.65, 47.59, 52.84, 57.36, 171.01, 205.35 and 214.75, (**154**) (minor) 20.78, 29.48, 43.21, 44.88, 46.87, 48.79, 52.47, 169.70, 205.35 and 214.75

Di-tert-Butylhexanedioate (155).

A mixture of *tert*-butanol (33 g, 0.45 mol) and *N,N*-dimethylaniline (53 ml, 0.42 mol) was added slowly to hexanedioyl chloride (23 ml, 0.15 mol) in chloroform (26 ml) and the mixture refluxed for 3 h. The mixture was cooled and extracted into light petroleum. The combined light petroleum extracts were washed with 2M hydrochloric acid, water and saturated sodium hydrogen carbonate solution and dried (MgSO₄). The solvent was removed under reduced pressure which gave the title compound (155) (31 g, 62 %) as a colourless solid ν_{max} (film CH₂Cl₂) 1735 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.44 (18 H, s, 2 x C(CH₃)₃), 1.60 (4 H, m, 2 x CH₂), and 2.19 (4 H, m, 2 x CH₂CO₂^tBu); δ_{C} (62.5 MHz; CDCl₃) 24.57 (CH₂), 28.12 (C(CH₃)₃), 35.23 (CH₂CO₂^tBu), 80.01 (4°C, C(CH₃)₃), and 172.73 (CO₂^tBu)

*tert-Butyl 2-oxocyclopentanecarboxylate (156).*⁸⁷

A mixture of di-*tert*-butylhexanedioate (155) (1.5 g, 0.17 mol) and *tert*-butanol (50 mg) in dry benzene (4 ml) was added to sodium hydride (6.2 g, 0.5 mol) in refluxing benzene (190 ml). After 30 min a second portion of ester (155) (14 g, 1.5 mol) in dry benzene (20 ml) was added slowly over 30 min. The mixture was stirred vigorously under reflux for a further 5 h. After cooling to 0°C the mixture was neutralised with 4M acetic acid and extracted into diethyl ether. The combined diethyl ether extracts were washed with saturated sodium hydrogen carbonate solution and water and dried (MgSO₄). The solvent was removed under reduced pressure to give a yellow residue which on distillation at 95-100°C, 4 mmHg gave the title compound (156) (8.9 g, 81%) as a colourless liquid (lit. b.p. 80-85°C, 2 mmHg), ν_{max} (film) 1754, and 1723 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.46 (9 H, s, C(CH₃)₃), 1.81 (1 H, m), 2.17 (5 H, m), and 3.04 (1 H, t *J* 8.8 Hz, CH(CO₂^tBu)); δ_{C} (62.5 MHz; CDCl₃) 20.94 (CH₂), 27.46 (CH₂), 28.04 (C(CH₃)₃), 38.07 (CH₂), 55.75 (CH(CO₂^tBu)), 81.65 (4°C, C(CH₃)₃), 168.65 (CO₂^tBu), 212.74 (CO); *m/z* 184 (M⁺, 8%), 128 (33), 111 (83), 100 (42), and 57 (100)

tert-Butyl 1-(2-methoxy-3-methoxycarbonylprop-2(E)-en-1-yl)-2-oxocyclopentane-1-carboxylate (157).

To a suspension of freshly washed and dried sodium hydride (220 mg, 9 mmol) in *N,N*-dimethylformamide (20 ml) was added dropwise the cyclopentanone (156) (1.0 g, 5 mmol) in *N,N*-dimethylformamide (2 ml). When hydrogen evolution had ceased a solution of sodium iodide (80 mg) and methyl 4-chloro-3-methoxy-2(*E*)-butenoate (820 mg, 5 mmol) in *N,N*-dimethylformamide (2 ml) was added dropwise and the system stirred overnight at room temperature. After dilution with water the mixture was extracted into diethyl ether and the combined diethyl ether layers were dried (MgSO₄). The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 3:2 light

petroleum:diethyl ether) to give the *title compound* (**157**) (880 mg, 56%) as a colourless liquid, (Found: C, 61.3; H, 7.8; C₁₆H₂₄O₆ requires C, 61.2; H, 8.2); ν_{max} (film) 1753, 1713, and 1627 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.43 (9 H, s, C(CH₃)₃), 1.92 (3 H, m), 2.27 (3 H, m), 3.12 (1 H, d, *J* 15.0 Hz, CH₂C=C), 3.56 (3 H, s), 3.67 (3 H, s), 3.74 (1 H, d, *J* 15.0 Hz, CH₂C=C), and 5.09 (1 H, s, C=CH); δ_{C} (62.5 MHz; CDCl₃) 19.54 (CH₂), 27.81 (C(CH₃)₃), 32.31 (CH₂), 34.59 (CH₂), 37.51 (CH₂), 50.92 (CH₃), 55.23 (CH₃), 59.10 (4°C), 81.64 (4°C, C(CH₃)₃), 93.03 (C=CH), 167.69 (4°C, C=CH), 169.60 (CO₂^tBu), 171.98 (CO₂Me), and 213.85 (CO); *m/z* 312 (M⁺, 1%), 256 (35), 224 (65), and 207 (100)

2-Phenylthiocyclopentanone (**158**).⁸⁹

To dry tetrahydrofuran (60 ml) under nitrogen was added diisopropylamine (5 ml, 36 mmol). The solution was cooled to 0°C and *n*-butyl lithium (22 ml, 36 mmol) was added dropwise with stirring. After stirring for a further 10 min the mixture was cooled to -78°C and cyclopentanone (2.7 ml, 30 mmol) was added dropwise. The mixture was warmed to room temperature and diphenyldisulphide (20 g, 90 mmol) in tetrahydrofuran (30 ml) was added slowly. After stirring at room temperature for 2 h the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were dried (Na₂SO₄) and the solvent removed under reduced pressure to give a yellow residue. The residue was subjected to chromatography (silica, light petroleum then dichloromethane) to give the title compound (**158**) (3g, 53%) as a yellow liquid ν_{max} (film) 1738 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.03 (3 H, m), 2.28 (3 H, m), 3.57 (1 H, t, *J* 7.2 Hz, CH(SPh)), 7.30 (3 H, m), and 7.49 (2 H, m); δ_{C} (62.5 MHz; CDCl₃) 20.32 (CH₂), 30.63 (CH₂), 36.57 (CH₂), 52.36 (CH(SPh)), 123.99 (4°C), 127.73 (CH), 128.97 (CH), 132.53 (CH), and 213.81 (CO)

2-Phenylsulfonylcyclopentanone (**159**).⁹⁰

A 49.5% solution of "Oxone" (30 g, 65 ml water) was added slowly to a solution of sulfide (**158**) (3g, 0.01 mol) in methanol (65 ml) at 0°C and the resulting suspension stirred at room temperature for 4 h. The mixture was diluted with water and extracted into dichloromethane. The combined dichloromethane extracts were washed with water and brine and dried (MgSO₄). The solvent was removed under reduced pressure which gave the title compound (**159**) (2.5 g, 71 %) as a colourless solid, m.p. 113-114°C (lit. m.p. 114°C), ν_{max} (film CH₂Cl₂) 1750 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.86 (1 H, m), 2.27 (2 H, m), 2.44 (2 H, m), 2.67 (1 H, m), 3.76 (1 H, t, *J* 7.1 Hz, CH(SO₂Ph)), 7.65 (3 H, m), and 7.87 (2 H, m); δ_{C} (62.5 MHz; CDCl₃) 20.08 (CH₂), 25.01 (CH₂), 38.76 (CH₂), 69.43 (CH(SO₂Ph)), 129.04 (CH), 129.15 (CH), 134.15 (CH), 138.13 (4°C), and 207.19 (CO); *m/z* 224 (M⁺, 10%), 160 (55), 141 (70), 83 (65), and 77 (100)

2-Chlorocyclopentene-1-carbaldehyde (160).^{91a,b}

To a mixture of phosphorus oxychloride (5.3 ml, 56 mmol) in *N,N*-dimethylformamide (6.5 ml, 85 mmol) cooled in an ice-bath, was added cyclopentanone (5 ml, 56.5 mmol) dropwise, with stirring, so that the temperature did not exceed 60°C. The mixture was stirred at room temperature overnight. After careful quenching with saturated sodium acetate solution the mixture was extracted into diethyl ether. The combined ether layers were washed with saturated sodium hydrogencarbonate solution and water, dried (MgSO₄) and the solvent removed under reduced pressure. The residue was distilled at 50°C, 1 mmHg to give the title compound (160) (4.9 g, 66%) as a colourless liquid, $\nu_{\text{max}}(\text{film})$ 1678 and 1613 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 1.80-2.10 (2 H, m), 2.40-2.65 (2 H, m), 2.70-3.00 (2 H, m), and 10.10 (1 H, s, CHO)

tert-Butyl N-benzylglycinate (161).

To benzylamine (5.9 ml, 54 mmol) in diethyl ether (60 ml) was added *tert*-butyl bromoacetate (4.4 ml, 27 mmol) and the mixture stirred at room temperature overnight. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was distilled at 130-140°C, 0.3mmHg to give the *title compound* (161) (2.1 g, 32%) as a colourless liquid, (Found: MH⁺ 221.1416; C₁₃H₁₉NO₂ requires *M* 221.1416); $\nu_{\text{max}}(\text{film})$ 3342, and 1732 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 1.46 (9 H, s, C(CH₃)₃), 1.90 (1 H, s, NH), 3.30 (2 H, s), 3.78 (2 H, s), and 7.33 (5 H, s); $\delta_{\text{C}}(62.5 \text{ MHz; CDCl}_3)$ 28.12 (C(CH₃)₃), 50.94 (CH₂), 53.29 (CH₂), 81.15 (4°C, C(CH₃)₃), 127.09 (CH), 128.29 (CH), 128.43 (CH), 139.67 (4°C), and 171.68 (CO); *m/z* 221 (M⁺, 2%), 120 (85) and 91 (100)

tert-Butyl 1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrole-2-carboxylate (162).

To aldehyde (160) (73 mg, 0.6 mmol) was added amine (161) (199 mg, 1.0 mmol) and the mixture stirred overnight at room temperature. Water was added and the mixture extracted into diethyl ether. The ether layers were washed with brine and water then dried (MgSO₄). The solvent was removed under reduced pressure to give the *title compound* (162) (120 mg, 12%) as a beige solid, m.p. 73-75°C (from light petroleum), (Found: C, 77.0; H 7.8; N 4.5; C₁₉H₂₃NO₂ requires C 76.7; H 7.8; N, 4.7); $\nu_{\text{max}}(\text{film})$ 1740 and 1686 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz; CDCl}_3)$ 1.48 (9 H, s, C(CH₃)₃), 2.36 (2 H, m), 2.59 (4 H, m), 5.47 (2 H, s, CH₂Ph), 6.73 (1 H, s, H³), 7.05 (2 H, m), and 7.24 (3 H, m); $\delta_{\text{C}}(62.5 \text{ MHz; CDCl}_3)$ 24.81 (CH₂), 25.03 (CH₂), 28.39 (C(CH₃)₃), 28.51 (CH₂), 50.14 (CH₂), 79.79 (4°C, C(CH₃)₃), 112.64 (CH), 126.18 (4°C), 126.53 (CH), 126.98 (CH), 128.45 (CH), 138.69 (4°C), 146.62 (4°C) and 160.86 (CO₂^tBu); *m/z* 298 (MH⁺, 60%), 242 (100%), and 198 (50)

Ethyl N-benzylglycinate (163).^{73,92}

To benzylamine (39 g, 0.36 mol) in diethyl ether (500 ml) was added ethyl bromoacetate (30 g, 0.18 mol) and the mixture stirred at room temperature overnight. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was distilled at 130-135°C, 0.5mmHg to give the title compound (163) (25 g, 73%) as a colourless liquid, $\nu_{\text{max}}(\text{film})$ 3342 and 1737 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.25 (3 H, t, J 7.1 Hz, CH_2CH_3), 1.94 (1 H, s, NH), 3.39 (2 H, s), 3.79 (2 H, s), 4.16 (2 H, q, J 7.1 Hz, CH_2CH_3), and 7.30 (5 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 14.23 (CH_3), 50.10 (CH_2), 53.28 (CH_2), 60.38 (CH_2), 127.13 (CH), 128.26 (CH), 128.36 (CH), 139.56 (4°C) and 172.40 (CO); m/z 193 (M^+ , 3%), 120 (65), 106 (48) and 91 (100)

Ethyl 1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrole-2-carboxylate (164).^{73,92}

To aldehyde (160) (2.7 g, 20 mmol) was added amine (163) (8.0 g, 40 mmol) and the mixture stirred at 120°C under nitrogen for 5 min. Water was added immediately and the mixture extracted into diethyl ether. The diethyl ether layers were washed with brine and water then dried (MgSO_4). The solvent was removed under reduced pressure to give the title compound (164) (2.1 g, 38%) as a brown oil; $\nu_{\text{max}}(\text{film})$ 1685 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.26 (3 H, t, J 7.1 Hz, CH_2CH_3), 2.29 (2 H, m), 2.36 (4 H, m), 4.18 (2 H, q, J 7.1 Hz, CH_2CH_3), 5.48 (2 H, s, CH_2Ph), 6.79 (1 H, s, H^3), 7.05 (2 H, m), and 7.29 (3 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 14.41 (CH_3), 24.60 (CH_2), 25.00 (CH_2), 28.53 (CH_2), 50.20 (CH_2), 59.38 (CH_2), 112.81 (CH), 124.49 (4°C), 126.57 (CH), 127.06 (CH), 128.51 (CH), 138.53 (4°C), 147.26 (4°C) and 161.24 (CO); m/z 269 (M^+ , 35%), and 91 (100)

*1-Benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrole-2-carboxylic acid (165).*⁷³

Aqueous potassium hydroxide solution (5 M, 100 ml) was added to a stirred solution of pyrrole ester (164) (13.7 g) in tetrahydrofuran (100 ml) and methanol (100 ml) and the mixture heated under reflux for 4 h. After cooling to room temperature, the mixture was diluted with water, extracted into diethyl ether and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted into diethyl ether. The combined diethyl ether extracts were washed with water, brine and dried (MgSO_4). The solvent was removed under reduced pressure to give the title compound (165) (8.3 g, 68%) as a yellow solid, m.p. 137-138°C (decomp.) (from diethyl ether/light petroleum) (lit. m.p. 154-156°C (decomp.));⁷³ $\nu_{\text{max}}(\text{film } \text{CH}_2\text{Cl}_2)$ 3428, and 1641 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 2.40 (2 H, m), 2.61 (4 H, m), 5.47 (2 H, s, CH_2Ph), 6.68 (1 H, s, H^3), 7.08 (2 H, m), and 7.28 (3 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 24.77 (CH_2), 24.96 (CH_2), 28.46 (CH_2), 49.93 (CH_2), 113.16 (CH), 126.35 (4°C), 126.76 (CH), 126.98 (CH), 128.39 (CH), 138.66 (4°C), 147.17 (4°C), 162.95 (4°C) and 201.59 (CO_2H)

*1-Benzyl-1,2,3,4-tetrahydrocyclopent[b]pyrrole (166).*⁷³

The acid (165) (8.3 g) was heated under nitrogen until it melted (170°C) and evolution of carbon dioxide ceased (ca. 1 h). After cooling to room temperature, the residue was chromatographed (silica, 5:1 light petroleum:diethyl ether) to give the title compound (166) (5.5 g, 81%) as a pale yellow oil, $\nu_{\text{max}}(\text{film})$ 3096, 3063, 3030, 2946, 2901, and 2853 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 2.33 (2 H, m), 2.42 (2 H, m), 2.53 (2 H, m), 4.93 (2 H, s, CH_2Ph), 5.93 (1 H, d, J 2.5 Hz, H^2), 6.55 (1 H, d, J 2.9 Hz, H^3), 7.11 (2 H, m), and 7.30 (3 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 24.51 (CH_2), 25.68 (CH_2), 29.22 (CH_2), 51.87 (CH_2), 103.19 (CH^2), 123.41 (CH^3), 126.50 (4°C), 127.01 (CH), 127.42 (CH), 128.65 (CH), and 138.29 (4°C); m/z 197 (M^+ , 40%), and 91 (100)

*Ethyl 1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylglyoxylate (167).*⁷³

To a stirred solution of ethyl oxalyl chloride (3.5 ml, 0.03 mol) in dry dichloromethane (100 ml) under an atmosphere of nitrogen, was added pyridine (2.7 ml, 0.03 mol) and the mixture cooled to -78°C under nitrogen. A solution of the pyrrole (166) (5.5 g, 0.028 mol) in dry dichloromethane (50 ml) was added dropwise, with stirring, and the solution allowed to warm slowly to room temperature. After stirring overnight, the solution was washed with dilute hydrochloric acid, water, brine and dried (MgSO_4). The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 2:1 diethyl ether:light petroleum) to give the title compound (167) (8.1 g, 96%) as a brown oil, $\nu_{\text{max}}(\text{film})$ 1732, and 1631 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.37 (3 H, t, J 7.1 Hz, CH_2CH_3), 2.41 (2 H, m), 2.63 (4 H, m), 4.35 (2 H, q, J 7.1 Hz, CH_2CH_3), 5.53 (2 H, s, CH_2Ph), 7.04 (1 H, s, H^3), 7.14 (2 H, m), and 7.24 (3 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 14.04 (CH_3), 24.52 (CH_2), 24.77 (CH_2), 28.51 (CH_2), 51.00 (CH_2), 61.76 (CH_2), 119.65 (CH), 127.03 (CH), 127.37 (CH), 128.53 (CH), 129.43 (4°C), 130.59, 137.36, 153.96, 172.85 and 201.47 (CO_2Et); m/z 297 (M^+ , 15%), 224 (100), and 91 (100)

*1-Benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylglyoxylic acid (168).*⁷³

Aqueous potassium hydroxide solution (2 M, 150 ml) was added dropwise to a stirred solution of the ester (167) (8.1 g) in tetrahydrofuran (200 ml) and methanol (20 ml) and the mixture stirred at room temperature for 1 h. The mixture was diluted with water and extracted into ether and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted into ethyl acetate. The combined extracts were washed with water, brine and dried (MgSO_4). The solvent was removed under reduced pressure to give the title compound (168) (4.8 g, 65%) as a brown solid, m.p. $126\text{--}129^\circ\text{C}$ (from ethyl acetate/light petroleum) (lit. m.p. $133\text{--}136^\circ\text{C}$);⁷³ $\nu_{\text{max}}(\text{film } \text{CH}_2\text{Cl}_2)$ 3289, 1755, and 1607 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 2.44 (2 H, m), 2.68 (4 H, m), 5.53 (2 H, s, CH_2Ph), 7.06 (2 H, m), 7.30 (3 H, m), and 7.89 (1 H, s, H^3); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 24.54 (CH_2), 24.94

H, m), 7.30 (3 H, m), and 7.89 (1 H, s, H³); δ_C (62.5 MHz; CDCl₃) 24.54 (CH₂), 24.94 (CH₂), 28.51 (CH₂), 51.40 (CH₂), 123.47 (CH), 126.51 (CH), 127.63 (CH), 128.76 (CH), 129.97, 131.34, 137.03, 157.69, 161.08 and 167.55; m/z 269 (M⁺, 10%), 224 (40), and 91 (100)

*Methyl 1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylacetate (152).*⁷³

A mixture of the keto-acid (**168**) (4.8 g, 17.5 mmol), powdered potassium hydroxide (6.5 g, 115 mmol) and hydrazine hydrate (1.75 ml, 35.7 mmol) in ethanol (14 ml) was heated under nitrogen at 80°C for 1 h then at 150°C for 1 h. After cooling to room temperature, the mixture was diluted with water, acidified with dilute hydrochloric acid and extracted into diethyl ether. The combined extracts were washed with water, brine and dried (MgSO₄). The solvent was removed under reduced pressure and the residue dissolved in the minimum amount of dry diethyl ether. Ethereal diazomethane was added until the evolution of nitrogen ceased. The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 1:4 diethyl ether:light petroleum) to give the title compound (**152**) (3.3 g, 69%) as a yellow oil, ν_{\max} (film) 1738 cm⁻¹; δ_H (250 MHz; CDCl₃) 2.35 (2 H, m), 2.50 (2 H, m), 2.63 (2 H, m), 3.49 (2 H, s), 3.55 (3 H, s), 5.01 (2 H, s, CH₂Ph), 5.89 (1 H, s, H³), 6.98 (2 H, m), and 7.26 (3 H, m); δ_C (62.5 MHz; CDCl₃) 24.98 (CH₂), 25.77 (CH₂), 28.57 (CH₂), 33.32 (CH₂), 48.86 (CH₂), 52.00 (CH₃), 104.31 (CH), 125.01 (4°C), 126.27 (CH), 126.95 (CH), 127.21 (4°C), 128.65 (CH), 138.23 (4°C), 139.12 (4°C), and 171.29 (CO); m/z 269 (M⁺, 20%), 210 (58), and 91 (100)

Methyl 3-(chloro acetyl)-1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylacetate (178).

To a stirred solution of aluminium chloride (2.2 g, 16 mmol) and nitromethane (0.68 ml, 12 mmol) in dry dichloromethane (20 ml) at 0°C was added chloroacetyl chloride (0.44 ml, 5.5 mmol). The mixture was stirred at 0°C for 15 min. A solution of the pyrrole (**152**) (1.0 g, 3.7 mmol) in dry dichloromethane (5 ml) was added dropwise, with stirring. The mixture was allowed to warm to room temperature and stirred overnight. After quenching with water, the mixture was extracted into dichloromethane. The extracts were dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the title compound (**178**) (575 mg, 47%) as a colourless solid, m.p. 136-138°C (Found: C, 64.8; H, 5.5; N, 3.7; MH⁺ 346.1210; C₁₉H₂₀ClNO₃ requires C, 65.9; H, 5.8; N, 4.0; MH 346.1209); ν_{\max} (film CH₂Cl₂) 2930, 2864, 1727, and 1674 cm⁻¹; δ_H (250 MHz; CDCl₃) 2.45 (2 H, m), 2.53 (2 H, m), 2.85 (2 H, m), 3.61 (3 H, s, CO₂CH₃), 4.04 (2 H, s, CH₂CO₂CH₃), 4.45 (2 H, s, CH₂Cl), 5.00 (2 H, s, CH₂Ph), 7.01 (2 H, m), and 7.28 (3 H, m); δ_C (62.5 MHz; CDCl₃) 24.81 (CH₂), 27.65 (CH₂), 27.92 (CH₂), 31.78 (CH₂CO₂CH₃), 48.41 (CH₂Cl), 48.89 (CH₂Ph), 52.13 (CO₂CH₃), 125.26 (4°C), 126.31 (CH), 127.81 (CH), 128.86 (CH),

134.77 (4°C), 135.96 (4°C), 139.12 (4°C), 170.32 (CO), and 187.07 (CO); m/z 346 (MH^+ , 100%), 312 (20), and 91 (10). The elemental analysis data is not within the required limits for publication, but these are the values that were obtained.

3-(Chloro acetyl)-1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylacetic acid (179).

To a solution of the ester (178) (425 mg) in tetrahydrofuran (30 ml) was added aqueous potassium hydroxide solution (2 M, 10 ml) dropwise with stirring. The mixture was stirred at room temperature for 2 h. The mixture was diluted with water, extracted with diethyl ether and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted into ethyl acetate. The combined ethyl acetate extracts were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *title compound* (179) (122 mg, 30%) as a brown solid, m.p. 128-130°C (from ethyl acetate/light petroleum), (Found: C, 65.0; H, 5.4; N, 4.0; M^+ 331.1036; $C_{18}H_{18}ClNO_3$ requires C, 65.2; H, 5.5; N, 4.2; M 331.0975); ν_{max} (film CH_2Cl_2) 3249-3055, 1713, and 1671 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 2.47 (2 H, m), 2.55 (2 H, m), 2.86 (2 H, m), 3.88 (2 H, s, CH_2CO_2H), 4.51 (2 H, s, CH_2Cl), 5.12 (2 H, s, CH_2Ph), 7.02 (2 H, m), and 7.31 (3 H, m); δ_C (62.5 MHz; $CDCl_3$) 24.82 (CH_2), 27.32 (CH_2), 27.87 (CH_2), 33.96 (CH_2CO_2H), 47.53 (CH_2Cl), 48.99 (CH_2Ph), 125.77 (4°C), 126.30 (CH), 128.03 (CH), 128.65 (4°C), 128.71 (CH), 129.00 (4°C), 135.55 (4°C), 140.23 (4°C), and 170.85 (CO); m/z 331 (M^+ , 5%), 287 (20), 252 (25), and 91 (100)

Methyl 3-acetyl-1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylacetate (181).⁷³

To a stirred solution of aluminium chloride (0.2 g, 1.4 mmol) and nitromethane (0.06 ml, 1.1 mmol) in dry dichloromethane (2 ml) at 0°C was added acetyl chloride (0.04 ml, 0.5 mmol). The mixture was stirred at 0°C for 15 min. A solution of the pyrrole (152) (89 mg, 0.3 mmol) in dry dichloromethane (2 ml) was added dropwise, with stirring. The mixture was allowed to warm to room temperature and stirred overnight. After quenching with water, the mixture was extracted into dichloromethane. The extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (181) (39 mg, 38%) as a colourless solid, m.p. 117-118°C (lit. m.p. 118-119°C);⁷³ ν_{max} (film CH_2Cl_2) 1727 and 1648 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 2.36 (3 H, s, (CO) CH_3), 2.40 (2 H, m), 2.52 (2 H, m), 2.84 (2 H, m), 3.60 (3 H, s, CO_2CH_3), 4.04 (2 H, s), 4.99 (2 H, s, CH_2Ph), 6.99 (2 H, m), and 7.31 (3 H, m); δ_C (62.5 MHz; $CDCl_3$) 24.81 (CH_2), 27.71 (CH_2), 27.89 (CH_2), 29.76 ((CO) CH_3), 31.71 (CH_2), 48.68 (CH_2), 51.98 (CO_2CH_3), 118.37 (4°C), 126.30 (CH), 126.42 (4°C), 127.64 (CH), 128.78 (CH), 132.82 (4°C), 136.42 (4°C), 138.38 (4°C), 170.73 (CO), and 195.20 (CO); m/z 311 (M^+ , 20%), 279 (40), 252 (25), 188 (25), and 91 (100)

*3-Acetyl-1-benzyl-1,4,5,6-tetrahydrocyclopent[b]pyrrol-2-ylacetic acid (182).*⁷³

To a solution of the ester (**181**) (100 mg) in tetrahydrofuran (4 ml) and methanol (1 ml) was added aqueous potassium hydroxide solution (2 M, 3 ml) dropwise with stirring. The mixture was stirred at room temperature for 2 h. The mixture was diluted with water, extracted with diethyl ether and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted into ethyl acetate. The combined ethyl acetate extracts were washed with water and dried (MgSO₄). The solvent was removed under reduced pressure to give the title compound (**182**) (94 mg, 98%) as a brown solid, m.p. 174-176°C (from ethyl acetate/light petroleum) (lit. m.p. 170-172°C);⁷³ ν_{max} (film CH₂Cl₂) 1711 and 1643 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.46 (2 H, m), 2.48 (3 H, s, (CO)CH₃), 2.54 (2 H, m), 2.86 (2 H, m), 3.76 (2 H, s), 5.14 (2 H, s, CH₂Ph), 7.01 (2 H, m), and 7.31 (3 H, m); δ_{C} (62.5 MHz; CDCl₃) 24.79 (CH₂), 27.23 (CH₂), 27.85 (CH₂), 28.72 (CH₃), 34.84 (CH₂), 48.75 (CH₂), 118.98 (4°C), 126.23 (CH), 126.90 (4°C), 127.89 (CH), 128.94 (CH), 133.27 (4°C), 135.82 (4°C), 139.69 (4°C), 169.91 (CO), and 199.19 (CO); m/z 297 (M⁺, 5), 253 (85), 238 (25), 162 (30), and 91 (100)

*1-Benzyl-5-methyl-1,2,3,4,-tetrahydrocyclopent[d]pyrano[4,3-b]-pyrrol-7(1H)-one (183).*⁷³

To a solution of the acid (**182**) (129 mg, 0.4 mmol) and triethylamine (0.17 ml, 1.0 mmol) in dry tetrahydrofuran (10 ml) at 0°C under nitrogen was added isobutyl chloroformate (0.08 ml, 0.6 mmol) in dry tetrahydrofuran (4 ml) dropwise, with stirring. The mixture was allowed to warm to room temperature and stirring continued overnight. The mixture was poured into brine and extracted into ethyl acetate. The combined extracts were dried (MgSO₄), the solvent removed under reduced pressure and the residue subjected to chromatography (silica, 19:1 diethyl ether:methanol) to give the title compound (**183**) (86 mg, 71%) as a yellow solid, m.p. 157-160°C (lit. m.p. 158-161°C);⁷³ ν_{max} (film CH₂Cl₂) 1685 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.43 (3 H, s, CH₃), 2.46 (2 H, m), 2.57 (2 H, m), 2.74 (2 H, m), 4.81 (2 H, s, CH₂Ph), 5.48 (1 H, s), 7.14 (2 H, m), and 7.30 (3 H, m); δ_{C} (62.5 MHz; CDCl₃) 18.16 (CH₃), 25.05 (CH₂), 27.52 (CH₂), 48.15 (CH₂), 81.92 (CH), 116.52 (4°C), 126.85 (CH), 127.96 (CH), 128.89 (CH), 135.82, 150.14, 157.78, and 164.62; m/z 279 (M⁺, 5%), 91 (20), and 44 (100)

Mixture of Ethyl 4-benzyl-8-methyl-cyclopent[b]indole-7-carboxylate (184) and Ethyl 4-benzyl-8-methyl-cyclopent[b]indole-6-carboxylate (185).

A mixture of ethyl propiolate (0.07 ml, 0.7 mmol) and pyranopyrrole (**183**) (50 mg, 0.18 mmol) in chlorobenzene (5 ml) was refluxed under nitrogen for 12 h. The solvent was removed under reduced pressure to give the *title compounds* (**184**) and (**185**) (53 mg, 89%) as an orange semi-solid, (Found M⁺ 333.1734; C₂₂H₂₃NO₂ requires M 333.1734);

ν_{max} (film CH_2Cl_2) 3062, 3031, 2936, and 1702 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.40 (6 H, 2 x t, J 7.1 Hz, 2 x CH_2CH_3), 2.51 (4 H, m), 2.59 (3 H, s, CH_3 of **185**), 2.72 (4 H, m), 2.86 (3 H, s, CH_3 of **184**), 3.02 (4 H, m), 4.32 (4 H, 2 x q, J 7.1 Hz, 2 x CH_2CH_3), 5.17 (2 H, s, CH_2Ph), 5.25 (2 H, s, CH_2Ph), 7.06 (4 H, m), 7.26 (6 H, m), 7.54 (1 H, s), 7.67 (1 H, d, J 8.7 Hz), and 7.83 (1 H, s); δ_{C} (62.5 MHz; CDCl_3) 14.41 (CH_3), 17.68 (CH_3), 18.87 (CH_3), 24.76 (CH_2), 24.98 (CH_2), 25.85 (CH_2), 26.94 (CH_2), 28.31 (CH_2), 28.47 (CH_2), 48.30 (CH_2), 60.07 (CH_2), 60.40 (CH_2), 107.04 (CH), 109.79 (CH), 120.56 (CH), 122.22 (CH), 126.56 (CH), 127.45 (CH), 128.69 (CH), 167.00 (CO), and 169.00 (CO); m/z 333 (M^+ , 75%), 288 (10), and 91 (100). The residue was subjected to chromatography (silica, 2:1 light petroleum:diethyl ether) to give (**184**) (5 mg), δ_{H} (250 MHz; CDCl_3) 1.38 (3 H, t, J 7.1 Hz, CH_2CH_3), 2.51 (2 H, m), 2.70 (2 H, m), 2.87 (3 H, s, CH_3), 3.09 (2 H, m), 4.30 (2 H, q, J 7.1 Hz, CH_2CH_3), 5.21 (2 H, s, CH_2Ph), 7.06 (2 H, m), 7.25 (4 H, m), and 7.68 (1 H, d, J 8.7 Hz)

Ethyl 4-benzyl-8-methyl-cyclopent[b]indole-6-trimethylsilyl-7-carboxylate (186).

A mixture of ethyl 3-(trimethylsilyl)propynoate (0.05 ml, 0.3 mmol) and pyranopyrrole (**183**) (25 mg, 0.09 mmol) in chlorobenzene (5 ml) was refluxed under nitrogen for 48 h. The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 3:1 light petroleum:diethyl ether) to give the *title compound* (**186**) (19 mg, 53%) as a brown viscous oil, (Found M^+ 405.2124; $\text{C}_{25}\text{H}_{31}\text{NO}_2\text{Si}$ requires M 405.2124); ν_{max} (film) 3030, 2954, and 1709 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.14 (9 H, s, $(\text{CH}_3)_3$) 1.29 (3 H, t, J 7.7 Hz, CH_2CH_3), 2.40 (2 H, m), 2.51 (3 H, s, CH_3), 2.70 (2 H, m), 2.95 (2 H, m), 4.25 (4 H, q, J 7.1 Hz, CH_2CH_3), 5.11 (2 H, s, CH_2Ph), 6.97 (2 H, m), and 7.16 (4 H, m); δ_{C} (62.5 MHz; CDCl_3) 0.31 ($(\text{CH}_3)_3$), 14.26 (CH_3), 16.91 (CH_3), 24.89 (CH_2), 26.44 (CH_2), 28.44 (CH_2), 48.35 (CH_2), 60.63 (CH_2), 114.15 (CH), 118.95 (4°C), 126.77 (CH), 127.45 (CH), 128.07 (CH), 129.16 (CH), 129.27 (CH), 129.94 (4°C), 137.62 (4°C), 140.68 (4°C), 147.01 (4°C), and 171.95 (CO); m/z 405 (M^+ , 3%), 390 (15), 91 (100), 84 (20), and 49 (20)

Ethyl 4-benzyl-8-methyl-cyclopent[b]indole-7-carboxylate (187).

The indole (**186**) (16 mg) was refluxed in trifluoroacetic acid (1 ml) and water (0.5 ml) under nitrogen for 2 h. After dilution with water the mixture was extracted into diethyl ether. The diethyl ether extracts were washed with sodium hydrogen carbonate until the washings remained basic. The diethyl ether layers were dried (MgSO_4) and the solvent removed under reduced pressure. The residue subjected to chromatography (silica, 3:1 light petroleum:diethyl ether) to give the *title compound* (**187**) (2 mg, 15%) as a yellow oil, data as for (**184**) above

To a solution of pyridine (0.5 ml, 7 mmol) in dichloromethane (10 ml) was added chromium (VI) oxide (667 mg, 7 mmol) with rapid stirring. The alcohol 3-(trimethylsilyl)-2-propyn-1-ol (0.5 ml, 3.4 mmol) was added in one portion and the mixture stirred at room temperature for 30 min. The mixture was filtered through a plug of silica using diethyl ether as the eluant to give the title compound (**190**) (76 mg, 18%) as a yellow oil, $\nu_{\max}(\text{film})$ 2978, 2872, 2153, and 1666 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 0.25 (9 H, s, $(\text{CH}_3)_3$) and 9.15 (1 H, s, CHO); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 0.06 ($(\text{CH}_3)_3$), 103.13 ($^{\circ}\text{C}$), 103.91 ($^{\circ}\text{C}$), and 177.63 (CHO)

*2,2,5,5-Tetramethyltetrahydrofuran-3-one (169).*⁹⁵

To a solution of mercury (II) acetate (0.3 g, 0.09 mmol) in water (100 ml) was added c. sulfuric acid (1 ml) and 2,5-dimethyl-3-hexyne-2,5-diol (25 g, 0.18 mol). The mixture was heated using a Bunsen burner and when it turned cloudy the flask was immersed into cold water until an oil rose to the surface. The apparatus was set up for distillation and approximately 80 ml of the distillate was collected. The distillate was diluted with water and the layers separated. The aqueous layer was extracted into diethyl ether and the combined organic layers dried (MgSO_4). Removal of the solvent under reduced pressure gave a yellow liquid which, on distillation at 150°C gave the title compound (**169**) (13 g, 52 %) as a colourless liquid, $\nu_{\max}(\text{film})$ 1757 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.28 (6 H, s, 2 x CH_3), 1.39 (6 H, s, 2 x CH_3), and 2.51 (2 H, s, CH_2); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 26.42 (CH_3), 30.19 (CH_3), 48.52 (CH_2), 76.16 ($^{\circ}\text{C}$), 80.81 ($^{\circ}\text{C}$), and 218.81 (CO)

*Mixture of Ethyl-2,2,5,5-tetramethyltetrahydrofurylidene-3-acetate and Ethyl-2,2,5,5-tetramethyldihydrofuryl-3-acetate (204).*⁹⁶

To a suspension of sodium ethoxide (2 g, 30 mmol) in *N,N*-dimethylformamide (20 ml) under nitrogen was added triethyl phosphonoacetate (4.6 ml, 20 mmol) so that the temperature did not exceed 40°C . Once addition was complete, tetrahydrofuranone (**169**) (5 g, 0.03 mol) was added dropwise and the mixture heated at 100°C for 9 h. The mixture was poured into ice-water and extracted into diethyl ether. The combined diethyl ether extracts were dried (MgSO_4) and the solvent removed under reduced pressure to give a yellow liquid, distillation of the residue at 150°C , 16 mmHg gave the title compound (**204**) (4.2 g, 86%) as a colourless liquid, $\nu_{\max}(\text{film})$ 1740, 1715, and 1682 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.27 (30 H, m, 2 x CH_2CH_3 , 8 x CH_3), 2.98 (2 H, d, J 1.5 Hz, $\text{CH}_2\text{CO}_2\text{Et}$), 3.08 (2 H, d, J 2.5 Hz, $\text{CH}_2\text{C}=\text{C}$), 4.16 (4 H, m, 2 x CH_2CH_3), 5.59 (1 H, t, J 1.5 Hz, $\text{C}=\text{CH}$), and 5.67 (1 H, t, J 2.5 Hz, $\text{C}=\text{C}(\text{H})\text{CO}_2\text{Et}$); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 14.17 (CH_3), 14.32 (CH_3), 28.26 (CH_3), 29.63 (CH_3), 30.40 (CH_3), 32.52 (CH_2), 44.61 (CH_2), 59.99 (CH_2), 60.82 (CH_2), 79.82 ($^{\circ}\text{C}$), 83.03 ($^{\circ}\text{C}$), 85.05 ($^{\circ}\text{C}$), 87.60 ($^{\circ}\text{C}$), 110.95 ($\text{C}=\text{CH}$), 130.99 ($\text{C}=\text{CH}$), 137.00 ($^{\circ}\text{C}$, $\text{C}=\text{CH}$), 166.50 ($\text{C}=\text{C}(\text{H})\text{CO.OEt}$), and 171.00 ($\text{CH}_2\text{CO.OEt}$)

(CH₂), 79.82 (4°C), 83.03 (4°C), 85.05 (4°C), 87.60 (4°C), 110.95 (C=CH), 130.99 (C=CH), 137.00 (4°C, C=CH), 166.50 (C=C(H)CO.OEt), and 171.00 (CH₂CO.OEt)

*Ethyl-2,2,5,5-tetramethyltetrahydrofuryl-3-acetate (205).*⁹⁶

A mixture of the unsaturated esters (204) (6.7 g) and 10% Pd/C (700 mg) in ethyl acetate (20 ml) was stirred for 48 h at room temperature under an atmosphere of hydrogen (45 psi). After filtration of the catalyst the solvent was removed under reduced pressure to give the title compound (205) (5.4 g, 79%) as a colourless liquid, $\nu_{\text{max}}(\text{film})$ 1738 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.03 (3 H, s, CH₃), 1.21 (3 H, s, CH₃), 1.28 (9 H, m, 2 x CH₃, CH₂CH₃), 1.65 (1 H, t, *J* 12.2 Hz, CH), 2.03 (1 H, m), 2.19 (1 H m), 2.46 (2 H, m), and 4.16 (2 H, q, *J* 7.1 Hz, CH₂CH₃); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 14.24 (CH₃), 24.02 (CH₃), 28.92 (CH₃), 30.03 (CH₃), 30.65 (CH₃), 35.11 (CH₂), 44.73 (CH₂), 44.96 (CH), 60.44 (CH₂), 78.54 (4°C), 81.87 (4°C), and 172.67 (CO)

*2,2,5,5-Tetramethyltetrahydrofuryl-3-acetic acid (206).*⁹⁶

To tetrahydrofurylacetate (205) (100 mg) in tetrahydrofuran (6 ml) was added 5% sodium hydroxide solution (5 ml) and the mixture refluxed with vigorous stirring for 4 h. After cooling, the mixture was acidified with 2M hydrochloric acid and extracted into ethyl acetate. The combined ethyl acetate extracts were washed with water and dried (MgSO₄). The solvent was removed under reduced pressure to give the title compound (206) (81 mg, 93%) as a colourless solid, m.p. 159-161°C (lit. m.p. 159-160°C),⁹⁶ (Found: C, 64.4; H, 9.8; C₁₀H₁₈O₃ requires C, 64.5; H, 9.7); $\nu_{\text{max}}(\text{KBr disc})$ 1728 cm⁻¹; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.05 (3 H, s, CH₃), 1.22 (3 H, s, CH₃), 1.28 (3 H, s, CH₃), 1.30 (3 H, s, CH₃), 1.67 (1 H, t, *J* 12.3 Hz, CH), 2.20 (2 H, m), and 2.53 (2 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 24.02 (CH₃), 28.89 (CH₃), 30.02 (CH₃), 30.64 (CH₃), 34.97 (CH₂), 44.74 (CH₂), 44.87 (CH), 78.64 (4°C), 82.01 (4°C), and 175.31 (CO); *m/z* 186 (M⁺, 0.2%), 171 (68), 153 (55), 69 (56), and 43 (100)

2,2,5,5-Tetramethyltetrahydrofuryl-3-acetyl chloride (194).

To a solution of the acid (206) (0.8 g, 4 mmol) in dichloromethane (5 ml) was added thionyl chloride (1 ml, 10 mmol) and the mixture refluxed for 3 h. The solvent was removed under reduced pressure and the residue distilled at 90°C, 1 mm Hg to give the title compound (194) (0.56 g, 63%) as a colourless liquid, $\nu_{\text{max}}(\text{film})$ 1802 cm⁻¹

*Diethyl 1-methylcyclohexene-4,5-dicarboxylate (207).*⁷³

A mixture of isoprene (50.0 ml, 0.5 mol) and diethyl fumarate (20.0 ml, 0.12 mol) in toluene (100 ml) was refluxed for 72 h. The solvent was removed under reduced pressure and the residue distilled at 150°C, 4 mmHg to give the title compound (207) (27 g, 92%) as a

CH), 4.13 (4 H, m, 2 x CH₂CH₃), and 5.38 (1 H, m, C=CH); δ_C (62.5 MHz; CDCl₃) 14.18 (CH₃), 23.05, (CH₃), 28.19 (CH₂), 32.63 (CH₂), 41.30 (CH), 41.88 (CH), 60.55 (CH₂), 119.03 (C=CH), 132.27 (4°C, C=CH), 174.90 (CO), and 175.05 (CO)

*4,5-Di(2-hydroxyisopropyl)-1-methylcyclohexene (208).*⁷³

To a stirred suspension of magnesium turnings (4.04 g, 0.16 mol) in dry diethyl ether (50 ml) under nitrogen was added dropwise, methyl iodide (10 ml, 0.16 mol) in dry diethyl ether (50 ml). After addition was complete, the ester (207) (6.75 g, 0.028 mol) in dry diethyl ether (50 ml) was added dropwise and the mixture refluxed for 24 h. After cooling, the reaction was carefully quenched with ammonium chloride solution and extracted into diethyl ether. The ether extracts were dried (MgSO₄), the solvent removed under reduced pressure and the residue recrystallised from light petroleum to give the title compound (208) (2.04 g, 30%) as a colourless solid, m.p. 96-98°C (lit. m.p. 102-104 °C),⁷³ ν_{\max} (film CH₂Cl₂) 3229, 3043, and 2970 cm⁻¹; δ_H (250 MHz; CDCl₃) 1.11 (3 H, s, CH₃), 1.12 (3 H, s, CH₃), 1.26 (3 H, s, CH₃), 1.28 (3 H, s, CH₃), 1.70 (3 H, s, C=CCH₃), 1.82-2.07 (6 H, m, 2 x C=CCH₂, 2 x CH), 2.93 (2 H, s, 2 x OH), and 5.47 (1 H, s, C=CH); δ_C (62.5 MHz; CDCl₃) 23.24 (CH₃), 25.47 (CH₃), 25.78 (CH₃), 25.98 (CH₂), 30.22 (CH₃), 30.90 (CH₂), 42.94 (CH), 43.76 (CH), 73.73 (4°C), 73.79 (4°C), 120.92 (C=CH), and 134.94 (4°C, C=CH)

*1,1,3,3,5-Pentamethyl-3a,4,7,7a-tetrahydrophthalan (209).*⁷³

A mixture of the diol (208) (900 mg) and camphorsulfonic acid (90 mg) was heated to 150°C at 1 mmHg in a Kugelrohr apparatus. The distillate was subjected to chromatography (silica, 10:1 diethyl ether:light petroleum) to give the title compound (209) (703 mg, 85%) as a colourless liquid, ν_{\max} (film) 3027, 2969, 2903 and 2856 cm⁻¹; δ_H (250 MHz; CDCl₃) 1.04 (3 H, s, CH₃), 1.06 (3 H, s, CH₃), 1.26 (6 H, s, 2 x CH₃), 1.70 (3 H, s, C=CCH₃), 1.86 (6 H, m, 2 x C=CCH₂, 2 x CH), and 5.40 (1 H, s, C=CH); δ_C (62.5 MHz; CDCl₃) 23.40 (CH₃), 24.88 (CH₃), 26.32 (CH₂), 29.63 (CH₃), 31.55 (CH₂), 48.28 (CH), 48.92 (CH), 80.04 (4°C), 80.17 (4°C), 120.48 (C=CH), and 133.72 (4°C, C=CH)

*2,2,5,5-Tetramethyl-4-(2-oxopropyl)tetrahydrofuryl-3-acetic acid (210).*⁷³

The cyclohexene (209) (2.21 g) was dissolved in dry dichloromethane (80 ml) and cooled to -78°C. Ozone was bubbled through the solution until it turned blue. Excess ozone was blown out with nitrogen. The solution was warmed to room temperature and the solvent removed under reduced pressure. The residue was treated with formic acid (10 ml) and hydrogen peroxide solution (30%, 5 ml) and stirred at room temperature for 15 min then at 100°C for 30 min. After cooling, water was added and the mixture extracted into ethyl acetate. The extracts were dried (MgSO₄) and the solvent removed under reduced pressure.

100°C for 30 min. After cooling, water was added and the mixture extracted into ethyl acetate. The extracts were dried (MgSO_4) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, diethyl ether) to give the title compound (**210**) (1.55 mg, 56%) as a colourless solid, m.p. 130°C (decomp.) (lit. m.p. 127-129°C),⁷³ $\nu_{\text{max}}(\text{film})$ 3389-3143, and 1728 cm^{-1} ; $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$ 1.07 (3 H, s, CH_3), 1.10 (3 H, s, CH_3), 1.22 (3 H, s, CH_3), 1.24 (3 H, s, CH_3), 2.14 (3 H, s, COCH_3), 2.26 (1 H, m), 2.35 (1 H, m), 2.43 (3 H, m), and 2.68 (1 H, m); $\delta_{\text{C}}(62.5 \text{ MHz}; \text{CDCl}_3)$ 24.93 (CH_3), 25.17 (CH_3), 28.98 (CH_3), 29.92 (CH_3), 33.59 (CH_2), 43.43 (CH_2), 46.81 (CH), 48.72 (CH), 80.52 (4°C), 178.08 (CO_2H), and 207.95 (CO)

2,2,5,5-Tetramethyl-4-(2-oxopropyl)tetrahydrofuryl-3-acetyl chloride (195).

To a solution of the acid (**210**) (194 mg, 0.8 mmol) in dichloromethane (5 ml) was added thionyl chloride (0.2 ml, 3.2 mmol) and the mixture refluxed for 3 h. The solvent was removed under reduced pressure to give the *title compound* (**195**) (113 mg, 54%) as a colourless liquid, $\nu_{\text{max}}(\text{film})$ 1801, and 1722 cm^{-1}

5.4 Experimental for Chapter 4

*Cyclopent[b]indole (211).*¹⁰⁰

A mixture of cyclopentanone (2.1 ml, 20 mmol) and phenylhydrazine (2 ml, 20 mmol) was refluxed overnight in dry toluene (12 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (10 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO₄). The solvent was removed under reduced pressure which gave the title compound (211) (1.7 g, 45%) as a brown solid, m.p. 106-108°C (from methanol) (lit. m.p. 108°C),¹⁰⁰ ν_{max} (film CH₂Cl₂) 3477 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.50 (2 H, m), 2.75 (4 H, m), 7.06 (2 H, m), 7.15 (1 H, m), 7.39 (1 H, m), and 7.41 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl₃) 24.38 (CH₂), 25.73 (CH₂), 28.62 (CH₂), 111.33 (CH), 118.42 (CH), 119.41 (CH), 119.54 (4°C), 120.39 (CH), 124.68 (4°C), 140.89 (4°C), and 143.75 (4°C)

*Indeno[1,2-b]indole (212).*¹⁰¹

A mixture of 1-indanone (2 g, 15 mmol) and phenylhydrazine (1.5 ml, 15 mmol) was refluxed overnight in dry toluene (10 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (10 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO₄). The solvent was removed under reduced pressure which gave the title compound (212) (3 g, 96%) as a brown solid, m.p. 210°C (decomp.) (from methanol) (lit. m.p. decomp. 212-215°C),¹⁰¹ ν_{max} (film CH₂Cl₂) 3405 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 3.67 (2 H, s), 7.10 (3 H, m), 7.29 (1 H, m), 7.55 (4 H, m), and 10.87 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl₃) 30.07 (CH₂), 112.27 (CH), 117.71 (CH), 118.53 (CH), 119.36 (CH), 120.23 (4°C), 120.94 (CH), 124.33 (4°C), 124.43 (CH), 125.21 (CH), 126.40 (CH), 135.35 (4°C), 140.84 (4°C), 143.83 (4°C), and 147.56 (4°C)

1-Indanone (4-methoxy)phenylhydrazone (217).

A mixture of 1-indanone (2 g, 15 mmol), 4-methoxyphenylhydrazine hydrochloride (2.6 g, 15 mmol) and triethylamine (2.1 ml, 15 mmol) was refluxed overnight in dry toluene (20 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (20 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO₄). The solvent was removed under reduced pressure which gave the *title compound* (217) (430 mg, 11%) as yellow needles, m.p. 88-90°C (from methanol), (Found: C, 76.0; H, 6.5; N, 11.6; M⁺ 252.1281; C₁₆H₁₆N₂O

requires C, 75.8; H, 6.8; N, 11.0; M 252.1263); ν_{\max} (film CH_2Cl_2) 3351, 3054, 2987, 2956, and 2935 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 2.69 (2 H, m), 3.09 (2 H, m), 3.76 (3 H, s, OCH_3), 6.85 (3 H, m), 7.11 (2 H, d, J 8.9 Hz), 7.15 (3 H, m), and 7.79 (1 H, m, NH); δ_{C} (62.5 MHz; CDCl_3) 25.36 (CH_2), 28.53 (CH_2), 55.70 (CH_3), 114.23 (CH), 114.70 (CH), 120.84 (CH), 125.23 (CH), 126.96 (CH), 128.84 (CH), 138.93 (4°C), 139.74 (4°C), 146.40 (4°C), 151.34 (4°C), and 153.69 (4°C); m/z 252 (M^+ , 53%), and 122 (100)

7-Methoxycyclopent[b]indole (218).¹⁰⁵

A mixture of cyclopentanone (2.5 ml, 28 mmol), 4-methoxyphenylhydrazine hydrochloride (5 g, 28 mmol) and triethylamine (3.9 ml, 28 mmol) was refluxed for 3 h in dry toluene (40 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone and a few drops of 2M sulfuric acid was refluxed in ethane-1,2-diol (20 ml) for 5 h. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried (MgSO_4). The solvent was removed under reduced pressure which gave the title compound (218) (3.7 g, 69%) as beige needles, mp $120\text{--}123^\circ\text{C}$ (from methanol/water) (lit. m.p. $123\text{--}126^\circ\text{C}$).¹⁰⁵ (Found: C, 77.0; H, 6.9; N, 7.6; M^+ 187.0990; $\text{C}_{12}\text{H}_{13}\text{NO}$ requires C, 76.6; H, 7.4; N, 7.5; M 187.0997); ν_{\max} (film CH_2Cl_2) 3322, 3057, 2937, 2897, and 2851 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 2.55 (2 H, m), 2.76 (4 H, m), 3.79 (3 H, s, OCH_3), 6.72 (1 H, dd, J 2.5, 6.2 Hz), 6.90 (1 H, d, J 2.5 Hz), 7.12 (1 H, d, J 8.5 Hz), and 7.70 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 24.36 (CH_2), 25.85 (CH_2), 28.62 (CH_2), 55.89 (CH_3), 100.99 (CH), 110.00 (CH), 111.83 (CH), 119.56 (4°C), 125.04 (4°C), 136.04 (4°C), 144.71 (4°C), and 153.98 (4°C); m/z 187 (M^+ , 100%), 172 (27), and 144 (20)

7-Hydroxycyclopent[b]indole (219).

To a solution of indole (218) (1.0 g, 5.3 mmol) in dry dichloromethane under nitrogen at room temperature was added dropwise boron tribromide (1.0 M solution, 6.5 ml, 6.4 mmol). The mixture was stirred under reflux for 4 h then poured into ice salt-water. The mixture was extracted into dichloromethane and the combined dichloromethane layers dried (MgSO_4). The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the title compound (219) (180 mg, 19%) as beige needles, m.p. $155\text{--}158^\circ\text{C}$ (from methanol/water), (Found: C, 76.1; H, 6.4; N, 8.1; M^+ 173.0830; $\text{C}_{11}\text{H}_{11}\text{NO}$ requires C, 76.0; H, 6.8; N, 8.0; M 173.0840); ν_{\max} (film CH_2Cl_2) 3410, 3343, 3054, 2912, and 2852 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 2.52 (2 H, m), 2.76 (2 H, m), 2.82 (2 H, m), 4.40 (1 H, s, OH), 6.65 (1 H, dd, J 3.1, 6.1 Hz), 6.83 (1 H, d, J 2.5 Hz), 7.14 (1 H, d, J 8.6 Hz), and 7.68 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 24.29 (CH_2), 25.76 (CH_2), 28.55 (CH_2), 103.06 (CH), 109.67 (CH), 111.67 (CH),

118.14 (4°C), 125.15 (4°C), 135.82 (4°C), 144.87 (4°C), and 150.36 (4°C); m/z 173 (M^+ , 100%)

4-Benzenesulfonyl 7-methoxycyclopent[b]indole (220).

To a suspension of freshly washed and dried sodium hydride (272 mg, 6.9 mmol) in dry *N,N*-dimethylformamide (6 ml) was added a solution of indole (**218**) (1.2 g, 6.3 mmol) in dry *N,N*-dimethylformamide (4 ml). When hydrogen evolution had ceased, benzenesulfonyl chloride (0.9 ml, 6.9 mmol) was added dropwise. The mixture was stirred at room temperature for 3 h. After dilution with brine the mixture was extracted into dichloromethane and the combined dichloromethane layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue subjected to chromatography (silica, 2:1 dichloromethane:light petroleum) to give the *title compound* (**220**) (510 mg, 25%) as a colourless solid, m.p. 151-153°C (from methanol/water), (Found: C, 65.7; H, 5.1; N, 4.0; M^+ 327.0936; $C_{18}H_{17}NO_3S$ requires C, 65.8; H, 5.5; N, 4.3; M 327.0292); ν_{max} (film CH_2Cl_2) 3055, 2949, and 2912 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 2.54 (2 H, m), 2.69 (2 H, m), 3.10 (2 H, m), 3.81 (3 H, s, OCH_3), 6.81 (2 H, m), 7.44 (4 H, m), 7.81 (2 H, m), and 7.90 (1 H, d, J 8.9 Hz); δ_C (62.5 MHz; $CDCl_3$) 24.05 (CH_2), 27.40 (CH_2), 28.05 (CH_2), 55.61 (CH_3), 102.20 (CH), 111.52 (CH), 115.18 (CH), 126.46(CH), 126.95 (4°C), 128.25 (4°C), 129.18 (CH), 133.49 (CH), 134.84 (4°C), 136.59 (4°C), 138.65 (4°C), 144.15 (4°C), and 156.50 (4°C); m/z 327 (M^+ , 50%), 186 (100), 143 (25), and 77 (30)

1-Indanone (4-bromo)phenylhydrazone (224).

A mixture of 1-indanone (2 g, 15 mmol), 4-bromophenylhydrazine hydrochloride (3.4 g, 15 mmol) and triethylamine (2.1 ml, 15 mmol) was refluxed overnight in dry toluene (20 ml) using a Dean and Stark apparatus. After removal of the solvent, the resulting hydrazone was refluxed in ethane-1,2-diol (20 ml) for 5. After cooling, the mixture was diluted with water and extracted into diethyl ether. The combined diethyl ether extracts were washed with 2M hydrochloric acid and water, then dried ($MgSO_4$). The solvent was removed under reduced pressure which gave the *title compound* (**224**) (3.2 g, 76%) as yellow needles, m.p. 153-155°C (from methanol), (Found: C, 60.1; H, 4.3; N, 9.1; $C_{15}H_{13}BrN_2$ requires C, 59.7; H, 4.6; N, 9.3); ν_{max} (KBr disc) 3422, 3063, 3030, and 2910 cm^{-1} ; δ_H (250 MHz; $CDCl_3$) 2.68 (2 H, m), 3.10 (2 H, m), 7.26 (3 H, m), 7.35 (2 H, m), and 7.76 (1 H, m, NH); δ_C (62.5 MHz; $CDCl_3$) 25.38 (CH_2), 28.53 (CH_2), 111.57 (4°C), 114.57 (CH), 121.03 (CH), 125.30 (CH), 127.07 (CH), 129.28 (CH), 131.96 (CH), 138.61 (4°C), 144.51 (4°C), 146.63 (4°C), and 152.42 (4°C); m/z 302 (M^+ , 90%), 300 (M^+ , 100), 172 (50), 130 (50), and 91 (40)

7-Bromocyclopent[b]indole (**225**).

A mixture of 4-bromophenylhydrazine hydrochloride (3 g, 13 mmol) and cyclopentanone (1.2 ml, 13 mmol) were refluxed in dry ethanol for 4 h. After removal of ethanol under reduced pressure the residue was taken up in dichloromethane and washed with water. The organic layers were dried (MgSO₄) and the solvent was removed under reduced pressure which gave the *title compound* (**225**) (2.3 g, 60%) as a brown powder, m.p. 136-137°C (from methanol/water), (Found: C, 56.0; H, 4.2; N, 5.9; M⁺ 234.9997; C₁₁H₁₀BrN requires C, 56.0; H, 4.3; N, 5.9; M 234.9996); ν_{\max} (film CH₂Cl₂) 3464, 3054, and 2977 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.54 (2 H, m), 2.77 (4 H, m), 7.10 (2 H, s), 7.25 (1 H, s), and 7.87 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl₃) 24.18 (CH₂), 25.76 (CH₂), 28.50 (CH₂), 112.52 (CH), 112.63 (4°C), 119.38 (4°C), 121.03 (CH), 123.04 (CH), 126.30 (4°C), 139.47 (4°C), and 145.13 (4°C); *m/z* 235 (M⁺, 100%), and 154 (50)

4-Benzenesulfonyl 7-bromocyclopent[b]indole (**226**).

To a suspension of freshly washed and dried sodium hydride (130 mg, 3.4 mmol) in dry *N,N*-dimethylformamide (6 ml) was added a solution of indole (**225**) (600 mg, 2.8 mmol) in dry *N,N*-dimethylformamide (4 ml). When hydrogen evolution had ceased, benzenesulfonyl chloride (0.4 ml, 3.4 mmol) was added dropwise. The mixture was stirred at room temperature for 3 h. After dilution with brine the mixture was extracted into dichloromethane and the combined dichloromethane layers were dried (MgSO₄). The solvent was removed under reduced pressure which gave the *title compound* (**226**) (870 mg, 86%) as a brown powder, m.p. 170°C (decomp.) (from methanol/water), (Found: C, 54.2; H, 3.8; N, 3.8; C₁₇H₁₄BrNO₂S requires C, 54.3; H, 3.8; N, 3.7); ν_{\max} (film CH₂Cl₂) 3054, and 2987 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.51 (2 H, m), 2.68 (2 H, m), 3.13 (2 H, m), 7.33 (2 H, m), 7.46 (4 H, m), and 7.82 (2 H, m); δ_{C} (62.5 MHz; CDCl₃) 23.94 (CH₂), 27.42 (CH₂), 28.01 (CH₂), 115.73 (CH), 116.96 (4°C), 121.94 (CH), 126.06 (CH), 126.53 (CH), 128.26 (4°C), 128.90 (CH), 129.36 (CH), 133.83 (CH), 138.55 (4°C), 138.97 (4°C), and 145.17 (4°C); *m/z* 375 (M⁺, 35%), 234 (65), 154 (60), 127 (40), and 77 (100)

Cyclopent[b]indole-7-carbaldehyde (**228**).

To a suspension of freshly washed and dried potassium hydride (180 mg, 1.6 mmol) in dry diethyl ether (10 ml) at 0°C was added dropwise, a solution of indole (**225**) (370 mg, 1.6 mmol) in dry diethyl ether (15 ml). After stirring at 0°C for 15 min the mixture was cooled to -30°C and pre-cooled *t*-BuLi (1.85 ml, 1.6 mmol) was added so that the temperature did not rise above -30°C. After stirring at -30°C for a further 10 min, dry *N,N*-dimethylformamide (0.3 ml, 1.6 mmol) was added dropwise. The mixture was stirred at -30°C for 30 min and then allowed to warm to room temperature. The mixture was diluted with water and extracted into diethyl ether. The diethyl ether layers were washed with dilute

hydrochloric acid and dried (MgSO_4) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**228**) (166 mg, 57%) as an orange powder, m.p. 144-146°C (from methanol/water), (Found: C, 77.3; H, 6.0; N, 7.4; M^+ 185.0797; $\text{C}_{12}\text{H}_{11}\text{NO}$ requires C, 77.8; H, 6.0; N, 7.6; M 185.0840); ν_{max} (film CH_2Cl_2) 3296, 2851, 2818, and 1676 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 2.56 (2 H, m), 2.86 (4 H, m), 7.35 (1 H, d, J 8.4 Hz), 7.68 (1 H, dd, J 1.6, 6.8 Hz), 7.97 (1 H, s), 8.34 (1 H, s, NH), and 10.00 (1 H, s, CHO); δ_{C} (62.5 MHz; CDCl_3) 24.28 (CH_2), 25.83 (CH_2), 28.50 (CH_2), 111.70 (CH), 121.33 (CH), 121.41 (4°C), 123.23 (CH), 124.50 (4°C), 129.25 (4°C), 144.47 (4°C), 145.69 (4°C), and 192.74 (CHO); m/z 185 (M^+ , 100%), 173 (55), 156 (30), and 128 (25)

7-(2,2,5,5-Tetramethyltetrahydrofuran-4-ylidene-3-one)-cyclopent[b]indole (229).

To a mixture of indole (**228**) (62 mg, 0.38 mmol) and 2,2,5,5-tetramethyltetrahydrofuran-3-one (**169**) (120 mg, 0.76 mmol) in methanol (5 ml) was added 10% sodium hydroxide solution (10 ml). The system was stirred under reflux for 2 h. After cooling, the mixture was extracted into dichloromethane, dried (MgSO_4) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**229**) as two isomers: *minor isomer* (8 mg, 8%) as a yellow oil, (Found: 309.1741, $\text{C}_{20}\text{H}_{23}\text{NO}_2$ requires 309.1728); ν_{max} (film) 3342, and 1701 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.36 (6 H, s), 1.54 (6 H, s), 2.55 (2 H, m), 2.86 (4 H, m), 6.79 (1 H, s), 7.29 (1 H, dd, J 2.3, 8.6 Hz), 7.94 (1 H, dd, J 1.7, 6.8 Hz), 8.01 (1 H, s, NH), and 8.27 (1 H, d J 1.1 Hz); δ_{C} (62.5 MHz; CDCl_3) 24.18 (CH_2), 25.80 (CH_2), 26.35 (CH_3), 26.63 (CH_3), 28.53 (CH_2), 29.00 (CH_3), 31.71 (CH_3), 79.91 (4°C), 110.81 (CH), 111.33 (CH), 122.69 (CH), 123.17 (CH), 123.68 (CH), 124.62 (CH), 138.50 (CH) 141.55 (CH) and 201.51 (CO); m/z 309 (M^+ , 35%), 294 (100), 223 (25), and 43 (40); *major isomer* (23 mg, 22%) as a yellow solid, m.p. 110°C (decomp), (Found: 309.1728, $\text{C}_{20}\text{H}_{23}\text{NO}_2$ requires 309.1728); ν_{max} (film) 3285, and 1712 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.36 (6 H, s), 1.68 (6 H, s), 2.57 (2 H, m), 2.82 (4 H, m), 7.30 (2 H, s), 7.64 (1 H, s), 7.67 (1 H, s), and 8.22 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 24.25 (CH_2), 25.87 (CH_2), 26.23 (CH_3), 28.62 (CH_2), 29.08 (CH_3), 79.86 (4°C), 80.02 (4°C), 111.45 (CH), 120.56 (4°C), 122.83 (CH), 123.74 (CH), 124.90 (4°C), 125.02 (4°C), 133.04 (4°C), 136.15 (4°C), 138.69 (CH) 141.70 (4°C), 145.32 (4°C), and 207.60 (CO); m/z 309 (M^+ , 35%), 294 (100), 223 (23), and 43 (43)

4-(3-Methylbutenyl)-cyclopent[b]indole (230).

To a suspension of freshly washed and dried potassium hydride (180 mg, 1.6 mmol) in dry diethyl ether (10 ml) at 0°C was added dropwise, a solution of indole (**225**) (370 mg, 1.6 mmol) in dry diethyl ether (15 ml). After stirring at 0°C for 15 min the mixture was cooled

to -30°C and pre-cooled *t*-BuLi (1.85 ml, 1.6 mmol) was added so that the temperature did not rise above -30°C. After stirring at -30°C for a further 10 min, freshly distilled 4-bromo-2-methyl-2-butene (0.2 ml, 1.6 mmol) was added dropwise. The mixture was stirred at -30°C for 30 min and then allowed to warm to room temperature. The mixture was diluted with water and extracted into diethyl ether. The diethyl ether layers were washed with dilute hydrochloric acid and dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 light petroleum:diethyl ether) to give the *title compound* (**230**) (76 mg, 21%) as a pale yellow oil, (Found: M^+ 225.1520; C₁₆H₁₉N requires M 225.1517); ν_{\max} (film CH₂Cl₂) 3050, and 2927 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.70 (6 H, s), 1.81 (6 H, s), 2.51 (2 H, m), 2.80 (4 H, m), 4.58 (2 H, m), 5.28 (1 H, m), 7.08 (2 H, m), 7.22 (1 H, m), and 7.40 (1 H, m); δ_{C} (62.5 MHz; CDCl₃) 24.52 (CH₂), 25.14 (CH₂), 25.54 (CH₃), 28.37 (CH₂), 42.70 (CH₂), 109.59 (CH), 118.44 (CH), 118.76 (CH), 119.72 (CH), and 120.61 (CH); m/z 225 (M^+ , 30%), 157 (50), 69 (77), and 57 (100).

4-Benzenesulfonyl 7-(3-hydroxy-3-methylbut-2(E)-enyl)-cyclopent[b]indole (232).

A mixture of indole (**226**) (200 mg, 0.5 mmol), palladium (II) acetate (12 mg, 0.05 mmol), triphenylphosphine (28 mg, 0.1 mmol), 2-methyl-3-buten-2-ol (0.08 ml, 0.8 mmol) and dry triethylamine (0.14 ml, 1.0 mmol) were placed in a strong glass bottle with teflon screw cap, the system flushed with nitrogen and the bottle tightly sealed. The system was heated at 120°C for 60 h. After cooling, the residue was extracted into dichloromethane and washed with water. The organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. The residue was subjected to chromatography (silica, 1:1 diethyl ether:light petroleum) to give the *title compound* (**232**) (91 mg, 45%) as a colourless powder, m.p. 121-123°C (from methanol/water), (Found: C, 68.3; H, 6.0; N, 3.4; M^+ 381.1426; C₂₂H₂₃NO₃S requires C, 69.2; H, 6.1; N, 3.7; M 381.1398); ν_{\max} (film CH₂Cl₂) 3163, 3050, 2969, 2952, and 2857 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.41 (6 H, s, 2 x CH₃), 1.77 (1 H, s, OH), 2.50 (2 H, m), 2.67 (2 H, m), 3.10 (2 H, m), 6.29 (1 H, d, J 16.0 Hz, C=CH), 6.58 (1 H, d, J 16.1 Hz, C=CH), 7.24 (2 H, m), 7.42 (3 H, m), 7.81 (2 H, dd, J 1.5, 7.4 Hz), and 7.96 (1 H, d, J 8.6 Hz); δ_{C} (62.5 MHz; CDCl₃) 23.94 (CH₂), 27.35 (CH₂), 27.93 (CH₂), 29.86 (CH₃), 70.98 (4°C), 114.33 (CH), 116.90 (CH), 121.84 (CH), 126.35 (CH), 126.37 (CH), 126.40 (4°C), 126.87 (4°C), 129.16 (CH), 132.47 (4°C), 133.54 (CH), 136.76 (CH), 138.59 (4°C), 139.64 (4°C), and 144.15 (4°C); m/z 381 (M^+ , 20%), 363 (30), 222 (100), 77 (65), and 64 (20). The elemental analysis data is not within the required limits for publication, but these are the values that were obtained.

7-(3-Hydroxy-3-methylbut-2(E)-enyl)-cyclopent[b]indole (233).

Indole (**232**) (25 mg) was heated under reflux in a 10% sodium hydroxide/methanol solution for 2 h. The solution was diluted with water and extracted into dichloromethane. The

combined dichloromethane layers were dried (MgSO_4) and the solvent removed under reduced pressure to give the *title compound* (**233**) (14 mg, 91%) as a colourless solid, m.p. 142-144°C (from methanol/water), (Found: C, 78.6; H, 7.7; N, 5.7; M^+ 241.1470; $\text{C}_{16}\text{H}_{19}\text{NO}$ requires C, 79.6; H, 7.9; N, 5.8; M 241.1466); ν_{max} (film CH_2Cl_2) 3431, 3222, 3052, 2960 and 2848 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.43 (6 H, s, 2 x CH_3), 1.56 (1 H, s, OH), 2.50 (2 H, m), 2.79 (4 H, m), 6.28 (1 H, d, J 16.0 Hz, $\text{C}=\text{CH}$), 6.64 (1 H, d, J 16.0 Hz, $\text{C}=\text{CH}$), 7.15 (1 H, dd, J 1.6, 6.8 Hz), 7.20 (1 H, d, J 8.4 Hz), 7.43 (1 H, s), and 7.81 (1 H, s, NH); δ_{C} (62.5 MHz; CDCl_3) 24.24 (CH_2), 25.74 (CH_2), 28.49 (CH_2), 29.84 (CH_3), 71.02 (4°C), 111.19 (CH), 116.76 (CH), 119.04 (CH), 119.92 (4°C), 124.88 (4°C), 127.59 (CH), 128.47 (4°C), 134.27 (CH), 140.55 (4°C), and 144.17 (4°C); m/z 241 (M^+ , 25%), 223 (100), 208 (90), 194 (75), and 180 (80). The elemental analysis data is not within the required limits for publication, but these are the values that were obtained.

REFERENCES

- 1 R.J.Cole, J.W.Kirksey, J.M.Wells, *Can. J. Microbiol.*, (1974) **20**, 1159.
- 2 J.P.Springer, J.Clardy, J.M.Wells, R.J.Cole, J.W.Kirksey, *Tetrahedron Lett.*, (1975) **30**, 2531.
- 3 T.Fehr, W.Acklin, *Helv. Chim. Acta*, (1966) **49**, 1907.
- 4 J.P.Springer, J.Clardy, *Tetrahedron Lett.*, (1980) **21**, 231.
- 5 R.T.Gallagher, J.Finer, J.Clardy, *Tetrahedron Lett.*, (1980) **21**, 235.
- 6 B.J.Wilson, C.H.Wilson, A.W.Hayes, *Nature*, (1968) **220**, 77.
- 7 A.E.de Jesus, P.S.Steyn, F.R.van Heerden, R.Vleggaar, P.L.Wessels, W.E.Hull, *J. Chem. Soc., Chem. Commun.*, (1981) 289.
- 8 A.E.de Jesus, W.E.Hull, P.S.Steyn, F.R.van Heerden, R.Vleggaar, P.L.Wessels, *J. Chem. Soc., Chem. Commun.*, (1982) 837.
- 9 A.E.de Jesus, P.S.Steyn, F.R.van Heerden, R.Vleggaar, P.L.Wessels, W.E.Hull, *J. Chem. Soc., Perkin Trans. 1*, (1983) 1847.
- 10 A.E.de Jesus, P.S.Steyn, F.R.van Heerden, R.Vleggaar, P.L.Wessels, W.E.Hull, *J. Chem. Soc., Perkin Trans. 1*, (1983) 1857.
- 11 P.J.Norris, C.C.T.Smith, J.de Bellerocche, H.F.Bradford, P.G.Mantle, A.J.Thomas, R.H.C.Penny, *J. Neurochem.*, (1980) **34**, 33.
- 12 A. Horeau, *Tetrahedron Lett.*, (1961) **15**, 506.
- 13 P.S.Steyn, R.Vleggaar, *Fatschmitte*, (1985) **48**, 1.
- 14 B.J.Wilson, C.J.Wilson, *Science*, (1964) **144**, 177.
- 15 R.T.Gallagher, J.Clardy, B.J.Wilson, *Tetrahedron Lett.*, (1980) **21**, 239.
- 16 R.J.Cole, J.W.Dorner, J.A.Lamsden, R.H.Cox, C.Pape, B.Cunfer, S.S.Nicholson, D.M.Bedell, *J. Agric. Food Chem.*, (1977) **25**, 1197.
- 17 R.T.Gallagher, E.P.White, P.H.Mortimer, *N. Z. Vet. J.*, (1981) **29**, 189.
- 18a For large scale isolation of lolitrem B:- C.O.Miles, S.C.Munday, A.L.Wilkins, R.M.Ede, N.R.Towers, *J. Agric. Food Chem.*, (1994) **42**, 1488.
- 18b R.T.Gallagher, A.D.Hawkes, P.S.Steyn, R.Vleggaar, *J. Chem. Soc., Chem. Commun.*, (1984) 614.
- 19 C.O.Miles, A.L.Wilkins, R.T.Gallagher, A.D.Hawkes, S.C.Munday, N.R.Towers, *J. Agric. Food Chem.*, (1992) **40**, 234.
- 20 P.H.Mortimer, Academic Press, New York, (1978) 353.
- 21 *The Veterinary Record*, (1991) 419.
- 22 R.M.Ede, C.O.Miles, L.P.Meager, S.C.Munday, A.L.Wilkins, *J. Agric. Food Chem.*, (1994) **42**, 231.
- 23 J.A.Laakso, J.B.Gloer, D.T.Wicklowsky, P.F.Dowd, *J. Org. Chem.*, (1992) **57**, 138.
- 24 J.A.Laakso, J.B.Gloer, D.T.Wicklowsky, P.F.Dowd, *J. Org. Chem.*, (1992) **57**, 2066.
- 25 G.M.Staub, K.B.Gloer, J.B.Gloer, D.T.Wicklowsky, P.F.Dowd, *Tetrahedron Lett.*, (1993) **34**, 2569.

- 26 A.B.Smith III, R.Mewshaw, *J. Am. Chem. Soc.*, (1985) **107**, 1769.
- 27 R.E.Mewshaw, M.D.Taylor, A.B.Smith III, *J. Org. Chem.*, (1989) **54**, 3449.
- 28a U.Eder, G.Sauer, R.Wiechert, *Angew. Chem., Int. Ed. Engl.*, (1971) **10**, 496.
- 28b Z.G.Hajos, D.R.Parrish, *Org. Synth. Col. Vol. VII*, 363.
- 29 A.B.Smith III, R.Mewshaw, *J. Org. Chem.*, (1984) **49**, 3685.
- 30 G.A.MacAlpine, R.A.Raphael, A.Shaw, A.W.Taylor, H.J.Wild, *J. Chem. Soc., Perkin Trans. I*, (1976) 410.
- 31 P.G.Gassman, T.J.van Bergen, D.P.Gilbert, B.W.Cue Jr., *J. Am. Chem. Soc.*, (1974) **96**, 5495.
- 32 A.B.Smith III, M.Visnick, *Tetrahedron Lett.*, (1985) **26**, 3757.
- 33 A.B.Smith III, M.Visnick, J.N.Haseltine, P.A.Sprengeler, *Tetrahedron*, (1986) **42**, 2957.
- 34 J.N.Haseltine, M.Visnick, A.B.Smith III, *J. Org. Chem.*, (1988) **53**, 6160.
- 35 A.B.Smith III, J.N.Haseltine, M.Visnick, *Tetrahedron*, (1989) **45**, 2431.
- 36 G.Stork, R.L.Danheiser, *J. Org. Chem.*, (1973) **38**, 1775.
- 37 R.B.Woodward, F.Sondheimer, D.Taub, K.Heusler, W.M.McLamore, *J. Am. Chem. Soc.*, (1952) **74**, 4223.
- 38 A.B.Smith III, M.Ohta, W.M.Clark, J.W.Leahy, *Tetrahedron Lett.*, (1993) **34**, 3033.
- 39a A.B.Smith III, T.L.Leenay, *J. Am. Chem. Soc.*, (1989) **111**, 5761.
- 39b A.B.Smith III, J.Kingery-Wood, T.L.Leenay, E.G.Nolen, T.Sunazuka, *J. Am. Chem. Soc.*, (1992) **114**, 1438.
- 40 A.B.Smith III, T.Sunazuka, T.L.Leenay, J.Kingery-Wood, *J. Am. Chem. Soc.*, (1990) **112**, 8197.
- 40a E.J.Corey, M.Chaykovsky, *J. Am. Chem. Soc.*, (1965) **87**, 1353.
- 41 A.Ali, S.D.Guile, J.E.Saxton, M.Thornton-Pett, *Tetrahedron*, (1991) **47**, 6407.
- 42 S.D.Guile, J.E.Saxton, M.Thornton-Pett, *J. Chem. Soc., Perkin Trans. I*, (1992) 1763.
- 43 A.J.Poss, R.K.Belter, *J. Org. Chem.*, (1987) **52**, 4810.
- 44 E.J.Corey, S.C.Virgil, *J. Am. Chem. Soc.*, (1990) **112**, 6429.
- 45a P.M.Jackson, C.J.Moody, *J. Chem. Soc., Perkin Trans. I*, (1992) 2156.
- 45b P.M.Jackson, C.J.Moody, *Tetrahedron*, (1992) **48**, 7447.
- 45c J.F.P.Andrews, P.M.Jackson, C.J.Moody, *Tetrahedron*, (1993) **49**, 7353.
- 46a Z.G.Hajos, D.R.Parrish, E.P.Oliveto, *Tetrahedron Lett.*, (1966) **7**, 6495.
- 46b Z.G.Hajos, R.A.Micheli, D.R.Parrish, E.P.Oliveto, *J. Org. Chem.*, (1967) **32**, 3008.
- 46c Z.G.Hajos, D.R.Parrish, E.P.Oliveto, *Tetrahedron*, (1968) **24**, 2039.
- 46d C.B.C.Boyce, J.S.Whitehurst, *J. Chem. Soc.*, (1960) 4547.

- 47a Z.G.Hajos, D.R.Parrish, *J. Org. Chem.*, (1973) **38**, 3239.
- 47b R.A.Micheli, Z.G.Hajos, N.Cohen, D.R.Parrish, L.A.Portland, W.Sciamanna, M.A.Scott, P.A.Wehrli, *J. Org. Chem.*, (1975) **40**, 675.
- 48 J.N.Gardner, B.A.Anderson, E.P.Oliveto, *J. Org. Chem.*, (1969) **34**, 107.
- 49 P.A.Grieco, N.Fukamiya, M.Miyashita, *J. Chem. Soc., Chem. Commun.*, (1976) 573.
- 50 E.G.Baggiolini, J.A.Iacobelli, B.M.Hennessy, M.R.Uskokovic, *J. Am. Chem. Soc.*, (1982) **104**, 2945.
- 51 S.C.Rychnovsky, D.E.Mickus, *J. Org. Chem.*, (1992) **57**, 2732.
- 52 R.C.A.Isaacs, M.J.Di Grandi, S.J.Danishefsky, *J. Org. Chem.*, (1993) **58**, 3938.
- 53 H.Nemoto, H.Kurobe, K.Fukumoto, T.Kametani, *J. Org. Chem.*, (1986) **51**, 5311.
- 54 M.Ihara, Y.Tokunaga, N.Taniguchi, K.Fukumoto, *Tetrahedron*, (1991) **47**, 6635.
- 55 A.R.Daniewski, J.Kiegiel, *Syn. Commun.*, (1988) 115.
- 56 D.L.J.Clive, H.W.Manning, T.L.B.Boivin, M.H.D.Postema, *J. Org. Chem.*, (1993) **58**, 6857.
- 57 K.Nakatani, K.Takada, Y.Odagaki, S.Isoe, *J. Chem. Soc., Chem. Commun.*, (1993) 556.
- 58 W.G.Dauben, R.R.Ollmann Jr., S.C.Wu, *Tetrahedron Lett.*, (1994) **35**, 2149.
- 59a For a review: J.M.Brown, *Angew. Chem., Int. Ed. Engl.*, (1987) **26**, 190.
- 59b G.Stork, D.E.Khane, *J. Am. Chem. Soc.*, (1983) **105**, 1072.
- 59c B.Fernández, J.A.Martínez Pérez, J.R.Granja, L.Castedo, A.Mouriño, *J. Org. Chem.*, (1992) **57**, 3173.
- 60a T.Mandai, T.Matsumoto, M.Kawada, J.Tsuji, *J. Org. Chem.*, (1992) **57**, 1326.
- 60b T.Mandai, T.Matsumoto, M.Kawada, J.Tsuji, *Tetrahedron*, (1993) **49**, 5483.
- 60c L.F.Tietze, P.S.V.Subba Rao, *Synlett*, (1993) 291.
- 61 For a review: M.E.Jung, *Tetrahedron*, (1976) **32**, 3.
- 62 C.J.Moody, personal communication.
- 63 K.H.Baggaley, S.G.Brooks, J.Green, B.T.Redman, *J. Chem. Soc. (C)* (1971) 2671.
- 64 G.Demailly, G.Solladie, *Bull. Soc. Chim. Fr.*, (1975) 2128.
- 65 C.A.Harrison, R.Leineweber, C.J.Moody, J.M.J.Williams, *Tetrahedron Lett.*, (1993) **34**, 8527.
- 66 Sample kindly donated by Schering, Berlin.
- 67 O.Mitsunobu, *Synthesis*, (1981) 1.
- 68 M.Ando, S.Sayama, K.Takase, *J. Org. Chem.*, (1985) **50**, 251.
- 69a B.M.Trost, T.R.Verhoeven, *J. Org. Chem.*, (1976) **41**, 3215.
- 69b B.M.Trost, T.R.Verhoeven, *J. Am. Chem. Soc.*, (1980) **102**, 4730.

- 69c J.Fiaud, J.Legros, *J. Org. Chem.*, (1987) **52**, 1907.
- 70 J.Luche, *J. Am. Chem. Soc.*, (1978) **100**, 2226.
- 71 D.Askin, C.Angst, S.Danishefsky, *J. Org. Chem.*, (1987) **52**, 622.
- 72a W.Stevens, A.Van Es, *Recueil*, (1964) **83**, 1287.
- 72b A.Van Es, W.Stevens, *Recueil*, (1965) **84**, 704.
- 73 P.M.Jackson, *Doctoral Thesis*, Loughborough, 1991.
- 74 C.J.Moody, K.F.Rahimtoola, *J. Chem. Soc., Chem. Commun.* (1990) 1667.
- 75 For recent examples see: K.L.Baumann, D.E.Butler, C.F.Deering, K.F.Mennen, A.Miller, T.N.Nanninga, C.W.Palmer, B.D.Roth, *Tetrahedron Letters*, (1992) **33**, 2283.
- 76 E.Bacocchi, E.Muraglia, G.Sleiter, *J. Org. Chem.*, (1992) **57**, 6817.
- 77 T.Mukaiyama, *Pure Appl. Chem.*, (1983) **55**, 1749.
- 78 A.Meunier, *Doctoral Thesis*, University of Fribourg, Switzerland, 1989.
- 79 T.Rosen, I.M.Lico, D.T.W.Chu, *J. Org. Chem.*, (1988) **53**, 1580.
- 80a P.Cazeau, F.Duboudin, F.Moulines, O.Babot, J.Dunogues, *Tetrahedron*, (1987) 2075.
- 80b Y.Taniguchi, J.Inanaga, M.Yamaguchi, *Bull. Chem. Soc. Jpn.*, (1981) **54**, 3229.
- 81 E.Bacocchi, G.Civitarese, R.Ruzziconi, *Tetrahedron Letters*, (1987) **28**, 5357.
- 82a W.R.Bowman, S.W.Jackson, *Tetrahedron*, (1990) **46**, 7313.
- 82b M.Miyashita, T.Yanami, A.Yoshikoshi, *J. Am. Chem. Soc.*, (1976) **98**, 4679.
- 82c A.G.M.Barrett, G.G.Graboski, *Chem. Rev.*, (1986) **86**, 751.
- 83 M.AVolodina, V.G.Mishina, A.P.Terent'ev, G.V.Kiryushkina, *Zh. Obshch. Khim.*, (1962), **32**, 1922 - as in *Chem. Abs.*, **58**, 5612c.
- 84 G.H.Posner, C.M.Lentz, *J. Am. Chem. Soc.*, (1979) **101**, 934.
- 85a Sample kindly donated by Lonza Chemicals, Switzerland.
- 85b L.Duc, J.F.McGarrity, T.Meul, A.Warm, *Synthesis*, (1992) 391.
- 86 R.Fuchs, J.F.McGarrity, *Synthesis*, (1992) 373.
- 87 D.Henderson, K.A.Richardson, R.J.K.Taylor, *Synthesis*, (1983) 996.
- 88a B.Lygo, *Synlett*, (1992) 793.
- 88b M.J.Kurth, M.J.O'Brien, *J. Org. Chem.*, (1985) **50**, 3846.
- 89 D.Seebach, M.Teschner, *Chem. Ber.*, (1976) **109**, 1601.
- 90 B.M.Trost, D.P.Curran, *Tetrahedron Letters*, (1981) **22**, 1287.
- 91a W.Ziegenbein, W.Lang, *Chem. Ber.*, (1960) **93**, 2743.
- 91b T.Aubert, B.Tabyaoui, M.Farnier, R.Guilard, *J. Chem. Soc., Perkin Trans. 1*, (1989) 1369.
- 92 H.Urbach, R.Henning, *Tetrahedron Letters*, (1985) **26**, 1839.
- 93 E.Tamate, *Nippon Kagaku Zasshi*, (1959), **80**, 942 - as in *Chem. Abs.*, **55**, 4470i.
- 94a H.C.Brown, C.P.Garg, *J. Am. Chem. Soc.*, (1961) **83**, 2951.
- 94b R.N.Mirrington, K.J.Schmalzl, *J. Org. Chem.*, (1972) **37**, 2871.

- 95 M.S.Newman, W.R.Reichle, *Org. Synth., Coll. Vol. V*, 1024.
- 96 H.Hirai, K.Ueda, M.Matusi, *Agric. Biol. Chem.*, (1976) **40**, 153.
- 97 B.Robinson, *The Fischer Indole Synthesis*, *J.Wiley and Sons*, New York, 1982.
- 98 For a recent review see: D.L.Hughes, *Org. Prep. Proced. Int.*, (1993) 607.
- 99 B.Robinson, *J. Heterocycl. Chem.*, (1987) **24**, 1321.
- 100 W.H.Perkin, S.G.P.Plant, *J. Chem. Soc.*, (1923) **123**, 3242.
- 101 J.W.Armit, R.Robinson, *J. Chem. Soc.*, (1922) **121**, 827.
- 102 C.J.Moody, *J. Chem. Soc., Perkin Trans 1*, (1984) 1333.
- 103a Q-Y. Chen, Y-B. He, *Synthesis*, (1988) 896.
- 103b W.Cabri, S.De Bernardinis, F.Francalanci, S.Penco, R.Santi, *J. Org. Chem.*, (1990) **55**, 350.
- 103c S.Cacchi, P.G.Ciattini, E.Morera, G.Ortar, *Tetrahedron Letters*, (1986) **27**, 5541.
- 103d G.A.Peterson, F-A.Kunng, J.S.McCallum, W.D.Wulff, *Tetrahedron Letters*, (1987) **28**, 1381.
- 104a H.Ishii, H.Takeda, T.Hagiwara, M.Sakamoto, K.Kogusuri, Y.Murakami, *J. Chem. Soc., Perkin Trans 1*, (1989) 2407.
- 104b D.W.Brown, M.F.Mahon, A.Ninan, M.Sainsbury, H.G.Shertzer, *Tetrahedron*, (1993) **49**, 8919.
- 105 G.Kempter, M.Schwalba, W.Stoss, K.Walter, *J. Prakt. Chem.*, (1962), **18**, 39 - as in *Chem. Abs.*, **57**, 15052c.
- 106 E.H.Vickery, L.F.Pahler, E.J.Eisenbraun, *J. Org. Chem.*, (1979) **44**, 4444.
- 107 C.Caubère, P.Caubère, R.Renard, J-G.Bizot-Espiart, B.Jamart-Grégoire, *Synth. Commun.*, (1994) 1799.
- 108 M.P.Moyer, J.F.Shiurba, H.Rapoport, *J. Org. Chem.*, (1986) **51**, 5106.
- 109 J.B.Melpolder, R.F.Heck, *J. Org. Chem.*, (1976) **41**, 265.
- 110a W.C.Frank, Y.C.Kim, R.F.Heck, *J. Org. Chem.*, (1978) **43**, 2947.
- 110b R.W.Bates, C.J.Gabel, *Tetrahedron Letters*, (1993) **34**, 3547.
- 110c C.A.Busacca, R.E.Johnson, J.Swestock, *J. Org. Chem.*, (1993) **58**, 3299.

