

Synthetic Routes to [cd]-Fused Indoles

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*To Bronwen,
and Mum and Dad.*

*Strange things I have in head that will to hand,
Which must be acted ere they may be scanned....
This deed I'll do before this purpose cool.*

Macbeth
William Shakespeare

Abstract

The Clavine Alkaloids, in particular clavicipitic acid and aurantioclavine, are reviewed, emphasis being placed on their biosynthesis. The published laboratory syntheses of these compounds are discussed, and briefly compared with their biosynthesis.

Two complementary methods of synthesising [cd]-fused indoles have been investigated. The first utilises vinyl nitrene chemistry to construct the pyrrole ring onto the existing rings of a bicyclic aromatic ketone. The methodology was successfully applied to the synthesis of a number of examples, whilst the attempted syntheses of some other [cd]-fused indoles met with failure. Reasons are suggested for the failure of the methodology in these cases, and possible solutions are discussed.

The photolysis of haloacetyltryptophan derivatives gives [cd]-fused indoles, and an extension of this reaction constitutes the second of the two synthetic methods. The syntheses and, where possible, the photolyses of α -chloro esters, amides and ketones are described, both for esters and amides derived from indole-3-alkanoic acids, and for the compounds derived from the corresponding indole-3-ethyl alcohol or amine. Problems encountered during the synthesis of these photolysis substrates are described, and solutions to these problems are discussed.

The application of the photocyclisation reaction to a novel strategy for the synthesis of clavicipitic acid and aurantioclavine is discussed, and the results of these synthetic studies are detailed, together with reasons for, and possible solutions to, the problems encountered.

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Anthony L. Beck

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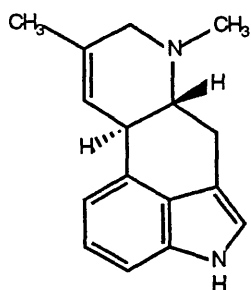
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ONE

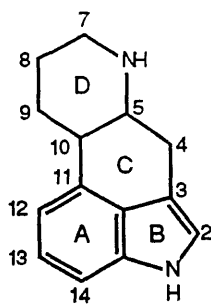
The Clavine Alkaloids

1.1 Introduction

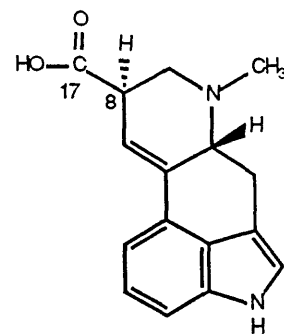
In 1951, Abe¹ isolated agroclavine (1) from the parasitic *Claviceps* fungus growing on *Agropyrum semicostatum* Nees and from saprophytic cultures of this *Claviceps* strain. Agroclavine was to be the first member of the new class of clavine alkaloids, most of which are found in various species of *Claviceps* such as *C. purpurea* and *C. paspali*. However, clavines have been isolated from other fungi, *e.g.* festuclavine and fumigaclavines A and B from *Aspergillus fumigatus*,² and also from higher plants of some genera in the Convolvulaceae family.^{3,4} The clavine alkaloids constitute a sub-section of the well-known group of ergot alkaloids, which is one of the largest known classes of nitrogenous fungal metabolites. All of the clavines share a common structural feature with the ergot alkaloids, *viz.* the [cd]-fused indole moiety which, in most of the alkaloids, forms part of the tetracyclic ergoline ring system (2). Notable exceptions to this are the chanoclavines, clavicipitic acid, and aurantioclavine. These are special cases of clavine alkaloid, the structures of which may shed some light on the biosynthesis of the ergoline ring system; they shall therefore be discussed in greater detail later in this review.



(1)



(2)



(3)

The biological properties of the clavine and indeed ergot alkaloids in general are well documented.⁵ Their effects were observed as long ago as the early middle ages when their consumption was responsible for epidemics of 'St. Anthony's fire' or ergotism, resulting in great loss of life. More beneficial effects were exploited in the early nineteenth century when the crude ergot drug was introduced into medicine in the United States. Today, ergot alkaloids are used to treat a wide variety of ailments from migraine to hypertension. Generally, however, these compounds lack specificity—their broad spectrum of action includes central, neurohumoral, and peripheral effects.⁶ Fortunately, modification of the structure alters these effects, and it is becoming increasingly clear that most of the pharmacological activity of these compounds is associated with the ergoline system and is largely independent of the amide portion of these lysergic acid (3) derivatives.⁷ It is for this reason that there is so much interest in these alkaloids and in the clavines in particular. This, together with the intriguing biosynthetic pathway and the problems associated with their laboratory synthesis, make the clavine alkaloids prime candidates for study by both chemists and biologists.

Firstly in this review the origin of the ergoline ring system and its biosynthesis will be examined, so that a comparison can be made between the laboratory synthesis and the biosynthesis of these compounds. Also the biosynthetic significance of the alkaloids clavicipitic acid and aurantioclavine will be discussed. Elaboration of the C-17 side chain to form the amide derivatives of lysergic acid is beyond the scope of this review and so will not be discussed in detail, other than to describe the biological oxidation of C-17 to the acid functionality. Finally, the published laboratory syntheses of clavicipitic acid and aurantioclavine will be reviewed.

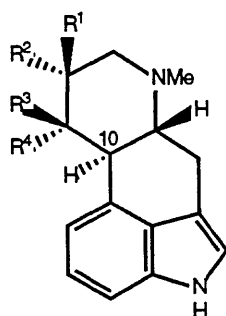
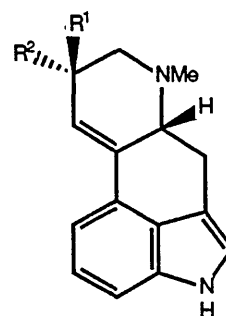
1.2 Structures of clavine alkaloids

As already mentioned, the clavines all contain the [cd]-fused indole system. This

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usually forms part of the ergoline skeleton, although a class of alkaloid, namely the 6,7-secoergolines, exists in which the D-ring remains unclosed. Alkaloids containing the ergoline ring system can be further divided into $\Delta^{8,9}$ -ergolenes or $\Delta^{9,10}$ -ergolenes, depending on the position of the olefinic double bond, or ergolines which contain a fully saturated D-ring. In addition, three other structurally different clavine alkaloids are known. The first of these, cycloclavine, retains the A-, B-, and C-rings of the ergoline system, but has a modified D-ring consisting of a fused [3,5]-system. The remaining two, clavicipitic acid and the closely related aurantioclavine are tricyclic [cd]-fused indoles containing an azepine ring which bears a 2-methyl-1-propenyl side chain. The structures of these alkaloids are shown in Figure 1 for comparison.⁷

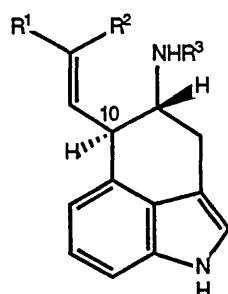
Ergolines:

 $\Delta^{9,10}$ -Ergolenes:

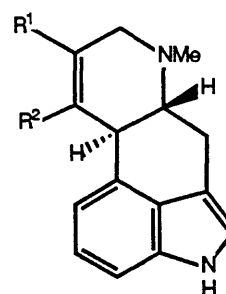
	R ¹	R ²	R ³	R ⁴		R ¹	R ²
Festucaclavine	CH ₃	H	H	H	Lysergine	CH ₃	H
Costaclavine	CH ₃	H	H	H	Lysergol	CH ₂ OH	H
(epimer at C-10)					Isolysergol	H	CH ₂ OH
Pyroclavine	H	CH ₃	H	H	D-Lysergic Acid	CO ₂ H	H
Dihydrolysergol-I	CH ₂ OH	H	H	H	Lysergene	—CH ₂ —	
Dihydrosetoclavine	CH ₃	OH	H	H	Setoclavine	CH ₃	OH
Fumigaclavine A	H	CH ₃	CH ₃ CO ₂	H	Isosetoclavine	OH	CH ₃
Fumigaclavine B	H	CH ₃	OH	H	Norsetoclavine	CH ₃	OH
Isofumigaclavine A					(NH instead of NMe)		
(Roquefortine A)	CH ₃	H	H	CH ₃ CO ₂	Penniclavine	CH ₂ OH	OH
Isofumigaclavine B					Isopenniclavine	OH	CH ₂ OH
(Roquefortine B)	CH ₃	H	H	OH			

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6,7-Secoergolines:



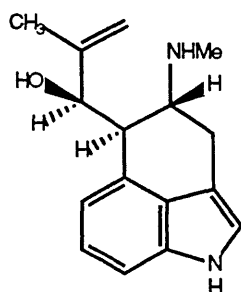
	R ¹	R ²	R ³
Chanoclavine-I	CH ₂ OH	CH ₃	CH ₃
Chanoclavine-II	CH ₂ OH	CH ₃	CH ₃
(epimer at C-10; plus enantiomer)			
Isochanoclavine-I	CH ₃	CH ₂ OH	CH ₃
Norchanoclavine-I	CH ₂ OH	CH ₃	H
Norchanoclavine-II	CH ₂ OH	CH ₃	H
(epimer at C-10; and/or enantiomer)			
Chanoclavine-I Acid	CO ₂ H	CH ₃	CH ₃

 $\Delta^{8,9}$ -Ergolenes:

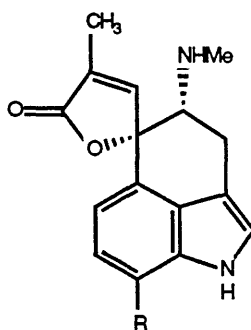
	R ¹	R ²
Agroclavine	CH ₃	H
Elymoclavine	CH ₂ OH	H
Molliclavine	CH ₂ OH	OH (?)
Paspalic Acid	CO ₂ H	H
Elymoclavine-O-		
β-D-fructoside	CH ₂ O-sugar	H

Rugulovasine A (R=H)

Paliclavine

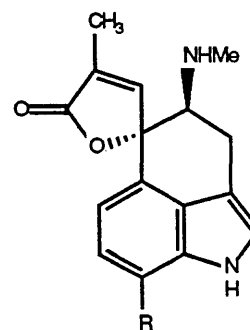


8-Chlororugulovasine A (R=Cl)



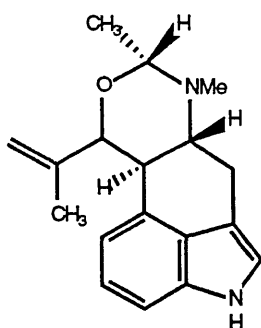
Rugulovasine B (R=H)

8-Chlororugulovasine A (R=Cl)

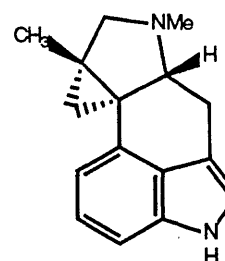


Others:

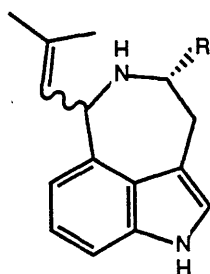
Paspoclavine



Cycloclavine



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Clavicipitic Acid ($R=CO_2H$)Aurantioclavine ($R=H$)

Dihydrochanoclavine-I

Isodihydrochanoclavine-I (epimer at C-8)

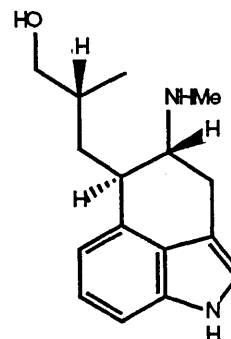


Figure 1. Structures of the Clavine Alkaloids and Secoergolines.

1.3 Biosynthesis of clavine alkaloids

1.3.1 Introduction.

The investigation of ergot alkaloid biosynthesis has caught the imagination of chemists and biochemists for more than 30 years. A wide range of chemical, microbiological, and biochemical techniques has been used to probe the biosynthetic pathways involved in the production of these compounds. Much is now known about the fascinating processes behind the biosynthesis of these alkaloids, although some important details still remain to be clarified, as this review will show. Detailed descriptions of labelling experiments will not be given, except where appropriate, nor will the early biosynthetic work be rigorously discussed—for this the reader is referred to the several reviews which have been published on the subject.⁸

1.3.2 The main biosynthetic pathway.

1.3.2.1 Biosynthetic origin of the ergoline system.

Seven different hypotheses on the biosynthetic origin of lysergic acid were published before any experiments were performed to investigate the question. All except one⁹ assumed that the indole rings A and B were derived from tryptophan. Other hypoth-

eses^{10,11} suggested that 5-hydroxytryptophan was a precursor and that the reactivity of the 4-position could be increased if a quinonimine species was an intermediate. The remainder of the ergoline system was envisaged as arising from a variety of sources including dihydronicotinic acid,¹⁰ acetonedicarboxylic acid and formaldehyde,¹¹ citric acid¹², α -ketoglutaric acid and a C₁ unit,¹³ succinic acid,¹⁴ and an isoprenoid C-5 unit.^{15,16}

Initial labelling experiments proved inconclusive—contradictory results were obtained which showed that tryptophan- β -¹⁴C was¹⁵ or was not¹⁷ an ergoline precursor. This amply illustrates the danger of relying on negative incorporation results during biosynthetic studies. Upon repetition of the feeding studies on both parasitic and, for the first time, saprophytic cultures, good incorporations (up to 39%) of tryptophan- β -¹⁴C into elymoclavine were obtained.¹⁸ Furthermore, it was soon found that tryptophan-(carboxyl-¹⁴C) gave negligible incorporation.^{18,19} These positive incorporation results have been confirmed and duplicated many times since, both for lysergic acid derivatives and for the clavines. Further labelling studies showed incorporation of the entire indole ring system.^{20,21,22} The conclusion drawn from this evidence is that the complete tryptophan molecule, except the carboxyl group and the hydrogen at C-4 of the indole ring, is incorporated intact into the ergoline system.

At about the same time as the incorporation results for tryptophan were published, evidence was obtained which showed that an isoprenoid unit, in the form of mevalonic acid, was also efficiently incorporated.^{19,23,24} These results also account for the observation^{18,23} that acetate-¹⁴C is incorporated into ergot alkaloids. It is interesting to note that this was the first demonstration that mevalonic acid is not only involved in the biosynthesis of typical isoprenoidal compounds, but also of alkaloids.⁷ Further studies showed that incorporation of mevalonate proceeded in a similar fashion to that for terpenes, *i.e. via* isopentenylpyrophosphate and dimethylallylpyrophosphate. It was found that C-1 of mevalonate was not incorporated, and that the incorporation of mevalonate-2-¹⁴C was reduced when fed jointly with isopentenyl- or γ,γ -dimethylallylpyrophosphate.²⁵

The *N*-methyl group was shown to be derived from methionine, although less significant incorporation of formate- ^{14}C was also observed.²⁶ Furthermore, L-methionine-(methyl- ^{14}C , ^3H) was incorporated with no change in the ^3H : ^{14}C ratio, showing that the methyl group is incorporated as an intact unit.

Other labelling studies have enabled the configuration of the biological precursors to be determined. It has been shown²⁷ that both D- and L-tryptophan can be utilised for alkaloid biosynthesis, the former by complete loss of the α -hydrogen and predominant loss of the amino nitrogen of the side chain. Thus, L-tryptophan is the immediate alkaloid precursor, while D-tryptophan is firstly converted to the L-isomer, possibly *via* indole pyruvate. Also, 3*R*-mevalonic acid is the only active isomer in *Claviceps*, as in other systems.²⁸ The biosynthetic origin of the ergoline ring system is summarised in Figure 2.

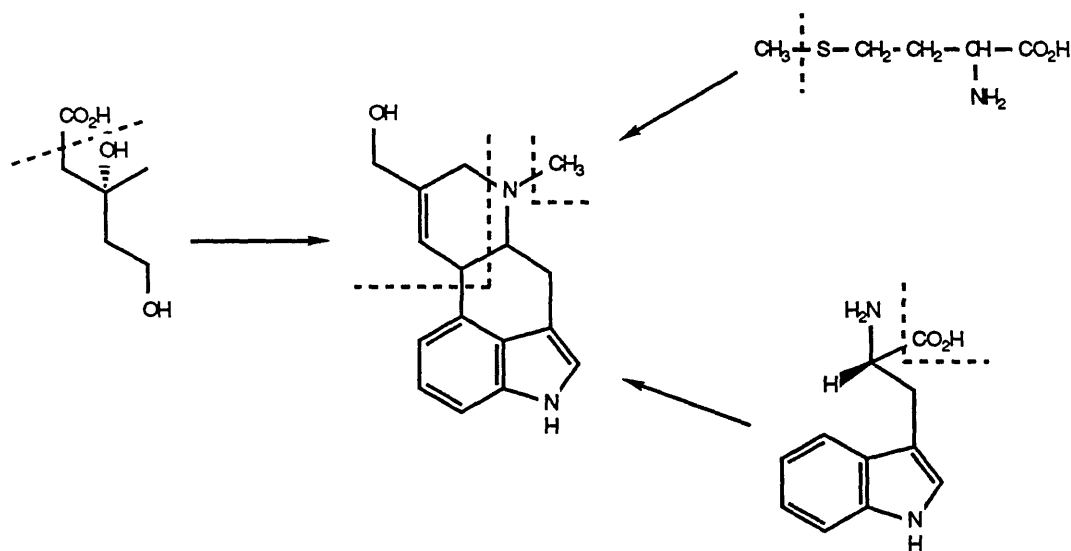


Figure 2. Biosynthetic origin of the ergoline ring system.

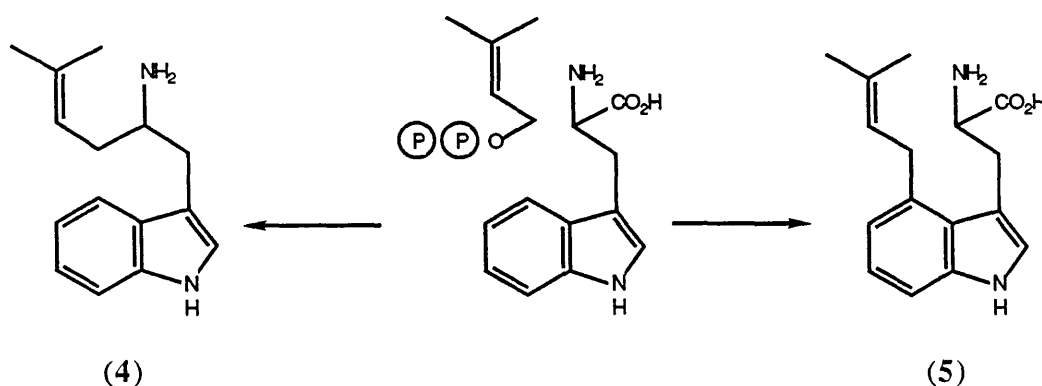
1.3.2.2 The first pathway specific reaction.

Once the biological precursors were firmly established, experiments were devised to determine the order of events during the initial stages of alkaloid biosynthesis. The construction of the ergoline ring system from its precursors obviously requires decarboxylation, isoprenylation, and *N*-methylation of the tryptophan molecule, but the

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order in which these reactions occur was uncertain. Tryptamine^{26a,29} and its N_ω -methyl derivative²⁹ were found to be not incorporated, so decarboxylation was not the first step. N_α -Methyltryptophan was found²⁹ to be slightly incorporated into elymoclavine, but double labelling studies³⁰ soon showed that this was due to demethylation to tryptophan. This suggested that isoprenylation of tryptophan was the first pathway-specific step, and various proposals such as activation by hydroxylation at C-4 or C-5 were suggested in order to overcome the problem of the relatively low reactivity of the indole 4-position towards electrophilic substitution. No supportive evidence for any of these suggestions has as yet been obtained, indeed most have now been disproved by labelling studies,^{20,21,31,32} leaving *direct* isoprenylation as the first step.

The structure of chanoclavine suggests that the initial reaction could involve an isoprenoidal allylic pyrophosphate group in an alkylation reaction of tryptophan at either the indole C-4 position or at the α -carbon of the tryptophan side chain—the latter possibility would involve simultaneous decarboxylation to account for the retention of the α -hydrogen (Scheme 1).

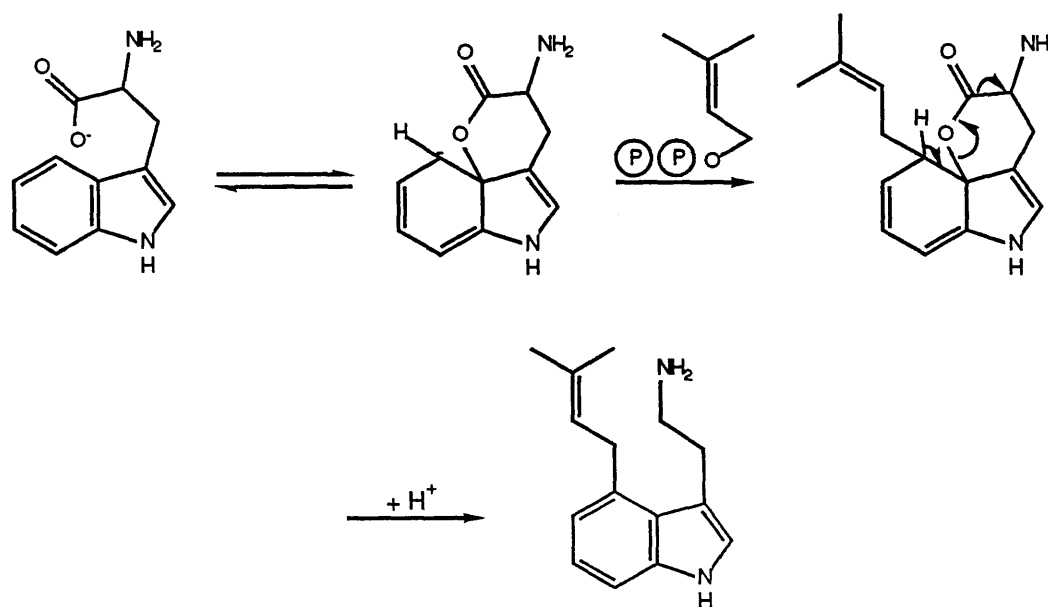


Scheme 1

Labelled versions of compounds (4)³³ and (5)³⁴ were synthesised, and it was eventually found³⁵ that (5) was incorporated to a much greater extent than (4). Further studies³⁶ showed that γ,γ -dimethylallyltryptophan (DMAT, 5) was incorporated intact into elymoclavine. More recently, (5) has been isolated from ergot cultures in which alkaloid

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synthesis had been inhibited by exclusion of oxygen or by addition of ethionine.³⁷ Additional conclusive evidence was obtained in 1971 when dimethylallylpyrophosphate:tryptophan dimethylallyl transferase, the enzyme catalysing the isoprenylation reaction, was isolated^{38a} and partially purified—purification to homogeneity was achieved in 1976.^{38b} This enzyme and its mechanism have been studied in great detail, but its mode of action is still relatively poorly understood. Several hypotheses have been proposed to explain the observed site of substitution on the indole ring. These included activation of the 4-position by 4- or 5-hydroxylation as mentioned earlier, anchimeric assistance of the carboxylate group (Scheme 2), or migration of the isoprene unit from the more nucleophilic 1- or 3-positions.⁷ However, no supporting evidence for any of these proposals has been obtained, either by feeding- or model-studies, so it seems that the enzyme facilitates *direct* attack at the 4-position and prevents attack at other more electronically favoured sites by proper alignment of the two substrates.^{38b}

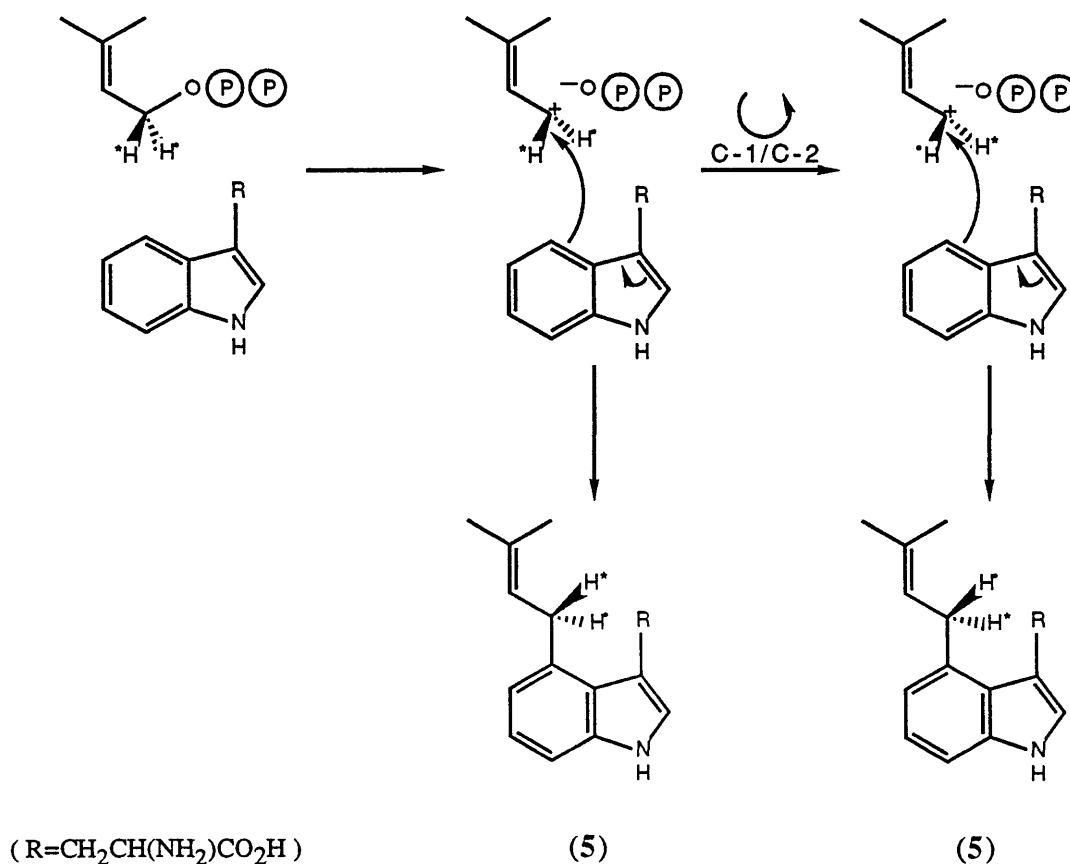


Scheme 2

An important observation, made repeatedly during labelling studies by several investigators,⁷ is that scrambling of the label from mevalonate-2-¹⁴C occurs such that the tetracyclic alkaloids agroclavine, elymoclavine, and lysergic acid contain the majority of the

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label at C-17, but up to 10% is also found at C-7. Since no scrambling was observed when synthetic labelled DMAT was fed, it must occur during the synthesis of DMAT. This has recently been confirmed by Floss and co-workers, who showed, surprisingly, that the scrambling occurred during the formation of dimethylallylpyrophosphate from mevalonate.³⁹ Furthermore, they also proved that the scrambling of C-2 of mevalonate was independent of another observed^{28b,d} scrambling process, this time between the two hydrogens derived from C-5 of mevalonate, when stereospecifically C-5-tritiated mevalonic acid was shown to retain up to 13.5% of tritium from the *pro*-5*R* position and up to 88% from the *pro*-5*S* position. On this basis, Floss *et al.*³⁹ proposed a plausible S_N1-type mechanism for the DMAT synthase reaction, in which dissociation of the C-1/pyrophosphate bond resulted in the formation of an ion pair or equivalent (Scheme 3).



Scheme 3

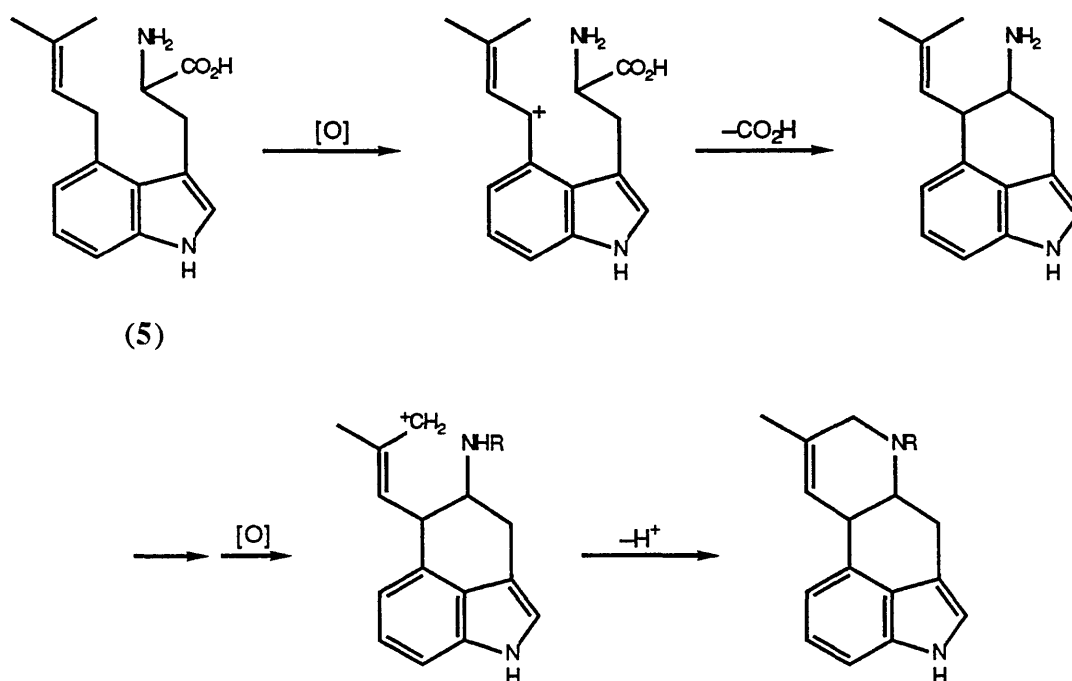
The ion pair would be approached by C-4 of an enzyme-bound tryptophan molecule from the opposite face to the departing pyrophosphate group and react to produce (5) with inversion at C-1 and retention of the geometry of the double bond. Any scrambling between the allylic hydrogens can be explained by rotation about the C-1/C-2 bond of the allylic carbocation prior to carbon-carbon bond formation; localisation of the positive charge at C-1 by interaction with the pyrophosphate counter ion would lower the energy barrier of this rotation.

1.3.2.3 The *N*-methylation step.

The timing of the methylation step remained a mystery for many years. Several proposals have been put forward,⁷ but until 1975, the only certainty was that *N*-norchanoclavine-I was not a biosynthetic intermediate,⁴⁰ implying that methylation occurred either prior to or during the formation of ring C, or at the stage of an unsuspected product of C-ring formation. In 1975, *N*-methyl-4-dimethylallyltryptophan was isolated from cultures of *Claviceps fusiformis* starved of oxygen.⁴¹ This was to be the first clue to the timing of *N*-methylation, although it was not established whether *N*-methyl-DMAT was in fact a true intermediate, or whether it was merely a product which accumulated under the anaerobic conditions. Further labelling experiments showed that *N*-methyl-DMAT was efficiently incorporated intact into both elymoclavine⁴² and agroclavine.⁴¹ Furthermore, decarboxylated *N*-methyl-DMAT was *not* incorporated into elymoclavine, indicating that methylation precedes decarboxylation.⁴² Another interesting observation was that a *Claviceps purpurea* mutant was found to produce DMAT normally, but was unable to methylate it.⁴³ As a consequence of this, the strain was found to be unable to elaborate DMAT to ergot alkaloids—however, when fed to the mutant, agroclavine was shown to be converted normally into lysergic acid derivatives. All the available evidence therefore points to the *N*-methylation step as the second pathway-specific step in ergot alkaloid biosynthesis. This in turn has important implications for the mechanism of C-ring formation, which shall be discussed next.

1.3.2.4 Formation of the C-ring.

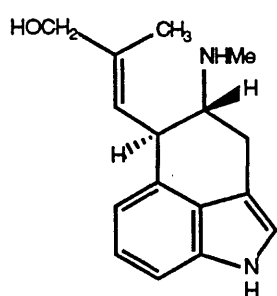
Early hypotheses on a number of aspects of ergoline biosynthesis have subsequently proved to be rather naïve and the biosynthetic pathway has been shown to be far more complex than first thought. This is particularly true in the case of C-ring formation, for which most authors invoked a series of allylic oxidations leading to allylic carbonium ions to facilitate ring closure (Scheme 4).⁷



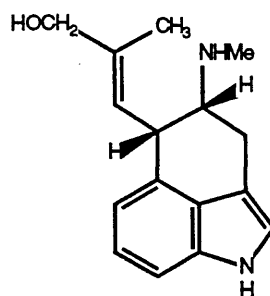
Scheme 4

The picture was further complicated by the fact that the key product of C-ring formation, chanoclavine, was later found⁴⁴ to exist in three different stereoisomeric forms, which led to a variety of inconsistent incorporation results.⁴⁵ This confusing state of affairs was clarified when three stereoisomers of chanoclavine, *viz.* chanoclavine-I (6), (-)- and (±)-chanoclavine-II (7), and isochanoclavine-I (8), were isolated from *Claviceps*.⁴⁴ The inconsistencies can be explained by the fact that *only* chanoclavine-I, but not (-)- and (±)-chanoclavine-II nor isochanoclavine-I, has been shown to be a precursor of the tetracyclic clavines;^{28a,46} a further consequence of this is that neither

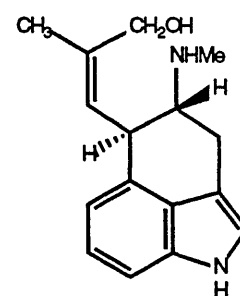
chanoclavine-II nor isochanoclavine-I can be converted to chanoclavine-I.



(6)

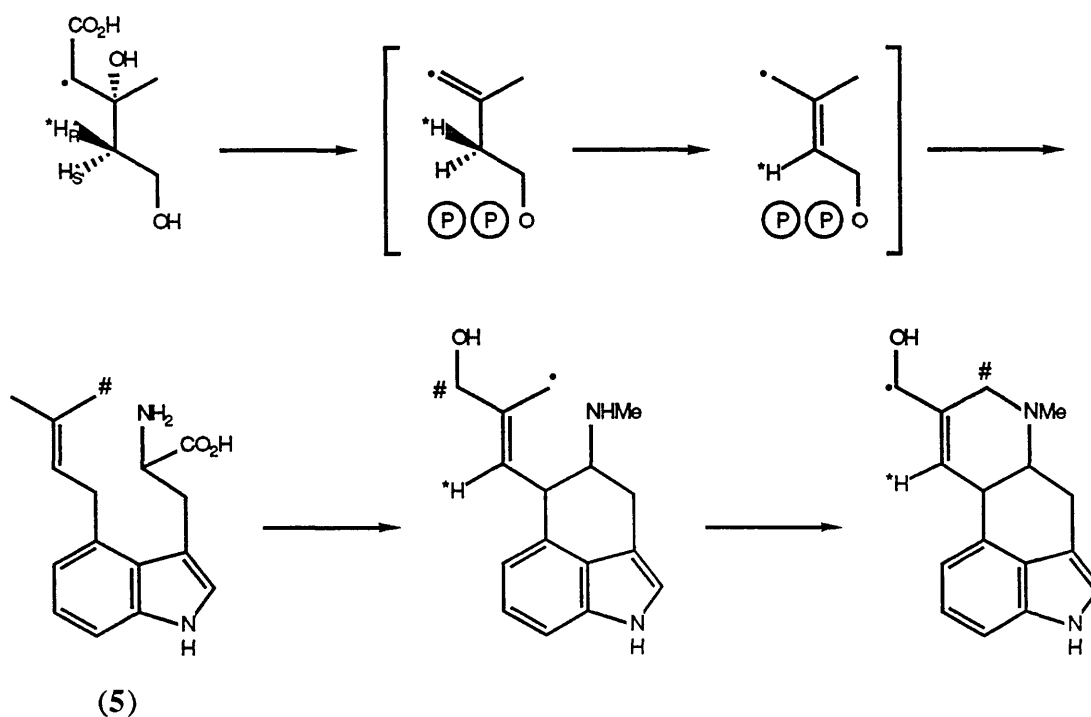


(7)



(8)

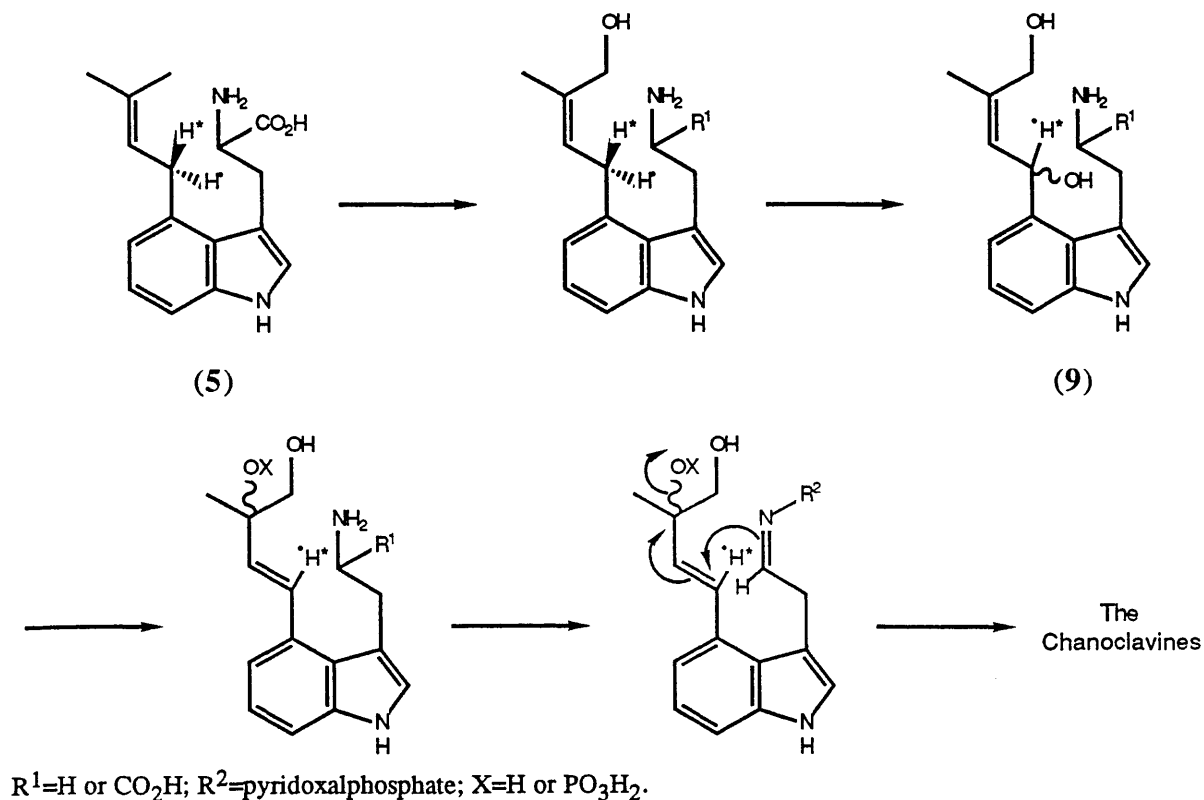
Despite these advances, the mechanism of C-ring formation is still uncertain, although a number of possibilities have been suggested. All invoke oxidation of the dimethylallyl side chain at some stage along the pathway. A further requirement is that they satisfactorily account for the observed⁴⁷ *cis-trans* isomerisation of the olefinic double bond between DMAT (5) and chanoclavine-I (Scheme 5).



Scheme 5

It should be remembered that the following proposals were put forward some years before the timing of the *N*-methylation step was firmly established. This obviously has an important bearing on the mechanism of C-ring formation and suggests that classical pyridoxal phosphate catalysis is extremely unlikely.⁴² Additional results showing the non-incorporation of nordeoxychanoclavine-I and deoxychanoclavine-I suggest that closure of ring C occurs *after* oxidation of the *cis*-methyl group of the isoprene unit.⁴⁷

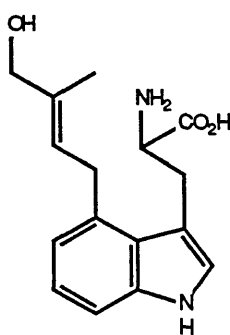
The first hypothesis^{28d} was published in 1972, and proposed that the 10-position was activated by hydroxylation, to give an intermediate (9), the stereochemistry of which would determine the stereochemistry of C-ring closure and therefore explain the stereoisomers of chanoclavine (Scheme 6). However, it was shown that all the clavines were formed with predominant retention of the *pro*-5*S* and loss of the *pro*-5*R* hydrogen of mevalonate, so no correlation appears to exist between the steric position of the hydrogen removed from C-10 and the stereochemistry of the resulting chanoclavine isomer.^{28d}



Scheme 6

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

Since closure of ring C was thought to occur after oxidation of an isoprenoid methyl group, it was assumed that this oxidation would be the next reaction after the formation of DMAT. Plieninger's group was the first to synthesise the *trans*-isomer of 4-hydroxylated DMAT (10), and study its incorporation.⁴⁸



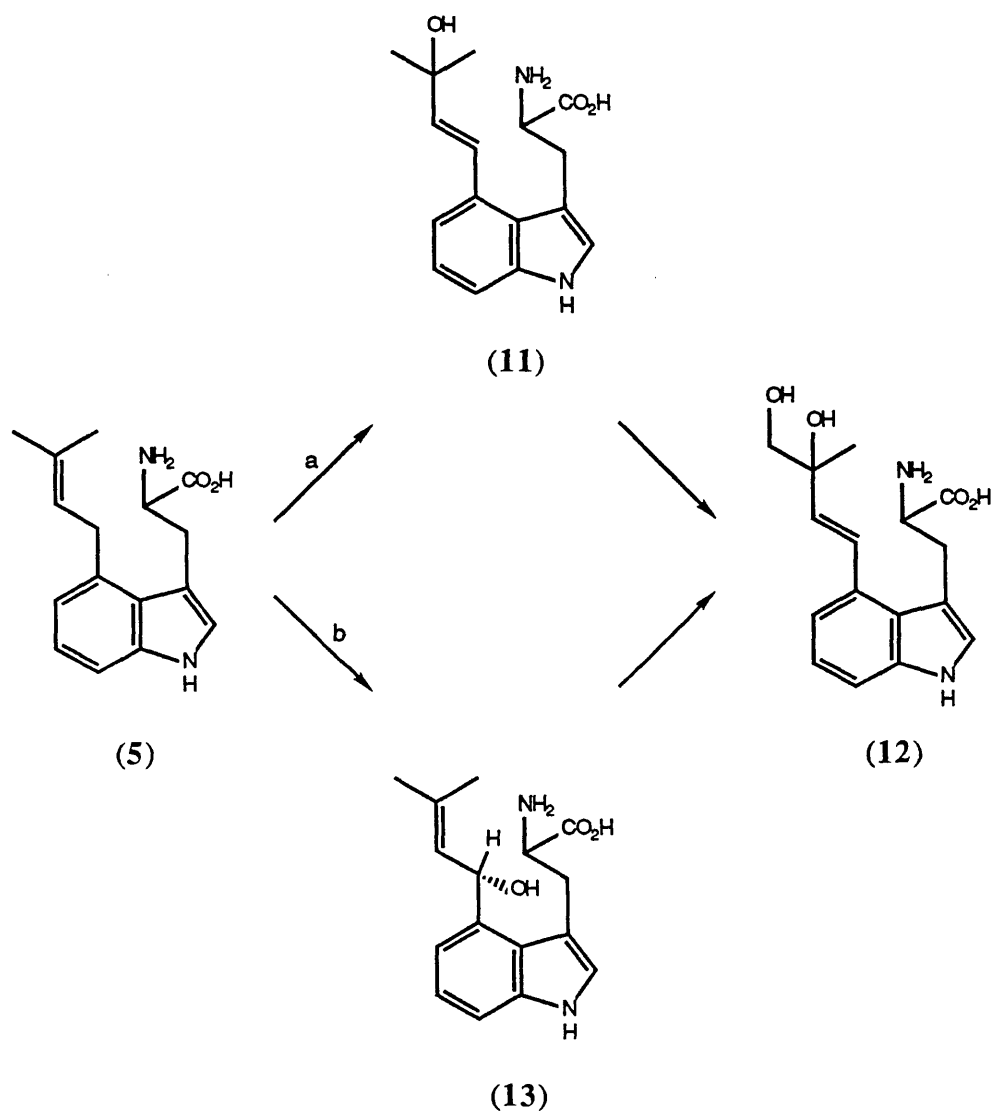
(10)

It was found that (10) was efficiently incorporated into elymoclavine, but *not* into agroclavine. Also, (10) labelled in the methyl group gave rise to elymoclavine labelled in the 7-position, which was known to be derived from the hydroxymethyl group of chanoclavine-I.^{7,47} Therefore, this compound was not an intermediate in the normal biosynthetic route from DMAT to elymoclavine *via* chanoclavine-I, but appears to be an intermediate in a secondary pathway from DMAT to elymoclavine. This is supported by the isolation of (10) from *Claviceps* species by two groups.⁴⁹

The negative results obtained with (10) led to the conclusion that oxidation of the methyl group was not the next step after formation of DMAT. Indeed, it is now known that at least one other step, *i.e.* methylation, precedes the oxidation step. Before this discovery, however, other possible oxidation sites, particularly the isoprenoid benzylic position (b)⁷ and the disubstituted olefinic carbon atom (α),⁵⁰ were considered (Scheme 7).

Since diol (12) could be an intermediate common to both routes, a labelled *N*-methylated version (since *N*-methylation precedes ring closure) was recently synthesised and fed to a *Claviceps* strain.⁵¹ No incorporation into elymoclavine was found, leading to the conclusion that (12) is *probably* not a biosynthetic intermediate.

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

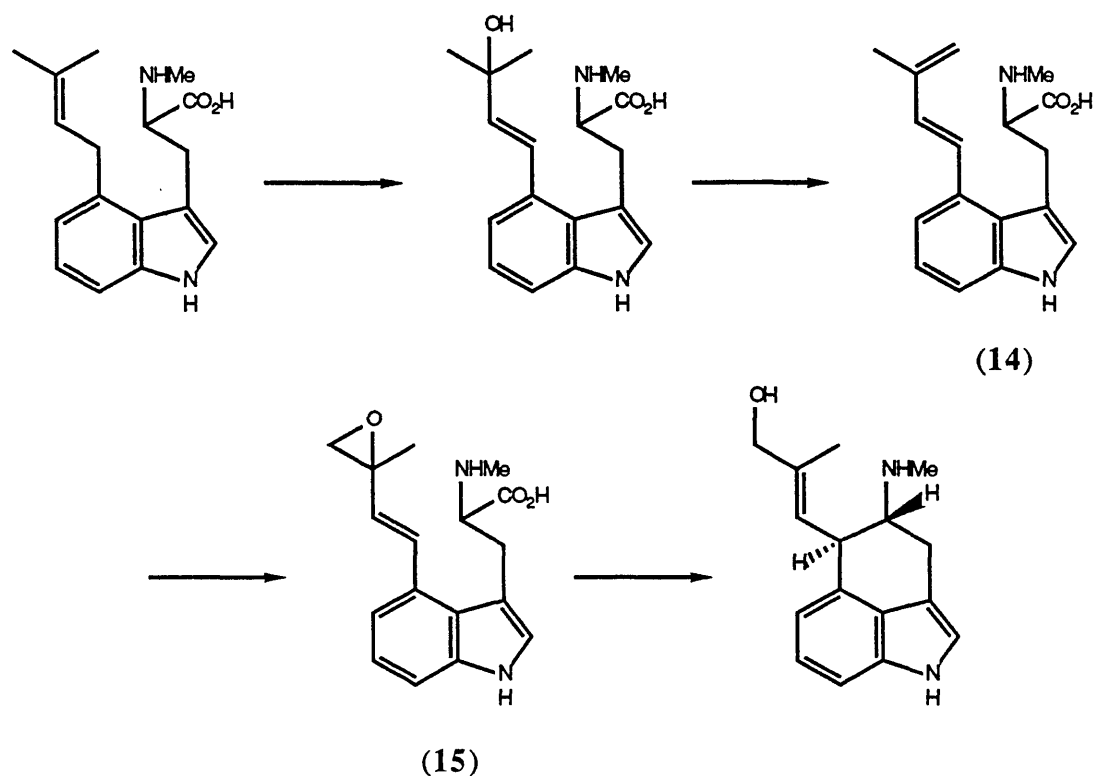


Scheme 7

Even more recent studies, this time with the tertiary allylic alcohol (11) have proved more fruitful.⁵² Good specific incorporation of the *N*-trideuteriomethyl derivative of (11) into elymoclavine was detected, suggesting a specific precursor rôle for this compound. Furthermore, mass spectral evidence was also obtained which suggested that diene (14) was also a probable intermediate—it was postulated that this could be epoxidised by cytochrome P-450 to give the vinyl oxirane (15) (Scheme 8). Cytochrome P-450 has been strongly implicated in ergoline biosynthesis⁵³ and interestingly, in 1975 epoxide (15) (without the *N*-methyl group) was proposed as a biosynthetic intermediate, albeit derived

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

from DMAT *via* a hydroperoxide.⁴⁷



Scheme 8

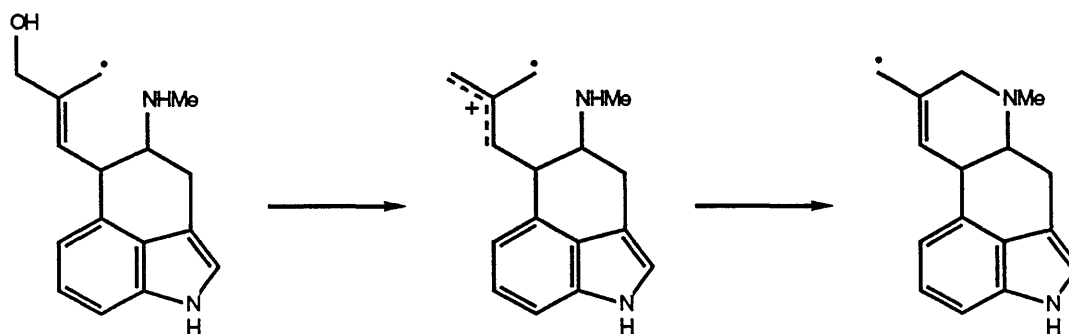
Additional supportive evidence for Scheme 8 comes in the form of a study which proves that the oxygen atom in chanoclavine-I is introduced by an oxygenase, and therefore originates from atmospheric oxygen.⁵⁴ Thus it would seem that the most plausible mechanism for C-ring formation, based on all the available evidence, is that shown in Scheme 8. However, it has still not yet been shown that (*N*-methylated) alcohol (11) is a true intermediate in this sequence, or whether diene (14) can be formed more directly from *N*-methyl-DMAT, hence the mechanism of C-ring formation is still not completely understood.

1.3.2.5 Formation of the D-ring.

At an early stage in the study of ergoline biosynthesis, it was found that the formation of ring D is accompanied by a *cis-trans* isomerisation at the allylic double bond.^{28a,46b}

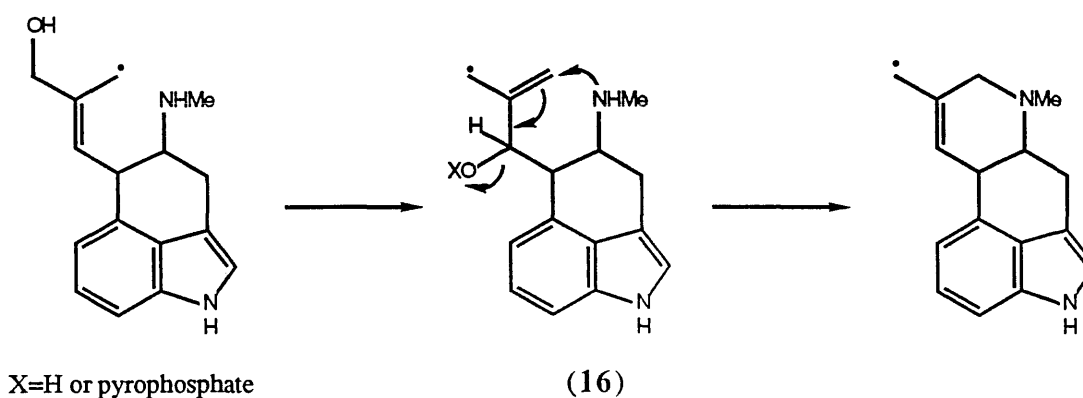
SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

Various mechanisms were proposed which accounted for this observation. The simplest invoked an allylic carbonium ion which supposedly had sufficient rotational freedom about the 8,9-double bond to facilitate cyclisation and simultaneous isomerisation (Scheme 9).^{8b,46c} This was ruled out by many subsequent results.



Scheme 9

More sophisticated alternatives were then suggested, such as allylic rearrangement followed by ring closure *via* an S_N2' process (Scheme 10).⁷ This idea was initially supported by the isolation of paliclavine, the C-9 epimer of (16) ($R=H$),⁵⁵ but again it was soon disproved by subsequent evidence. It is of interest to note that paliclavine does not arise from chanoclavine-I, nor is it converted into chanoclavine-I or isochanoclavine-I.⁵⁶

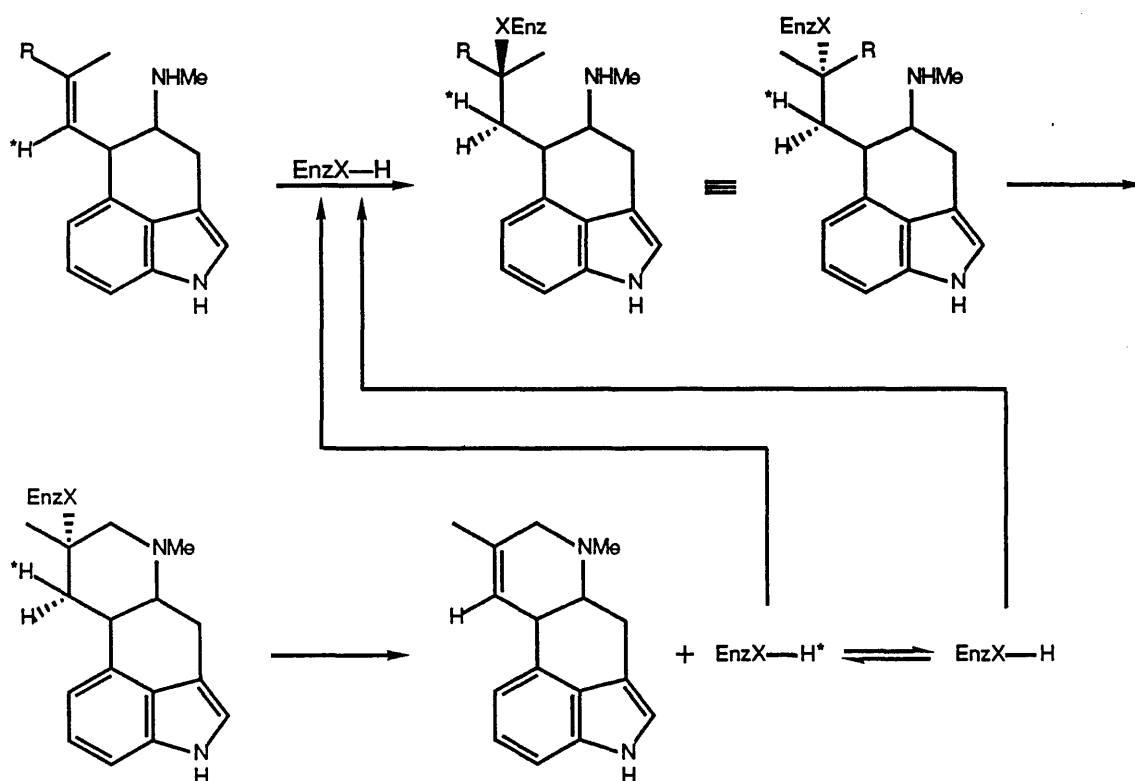


Scheme 10

It was not until 1974 that progress was made towards understanding the mechanism of D-ring formation.⁵⁷ At this time, little else was known about the process, except that the

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

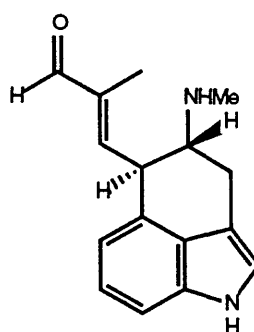
conversion of chanoclavine-I to agroclavine and elymoclavine proceeded with complete retention of the hydrogen at C-10, and only partial retention of that at C-9.^{8b,28a} It was then that labelling studies by Floss *et al.* revealed that the cyclisation involved an intermolecular transfer of the C-9 hydrogen to the same position of a new substrate molecule (Scheme 11).⁵⁷ This accounts for the isomerisation and the partial retention of the C-9 hydrogen.



Scheme 11

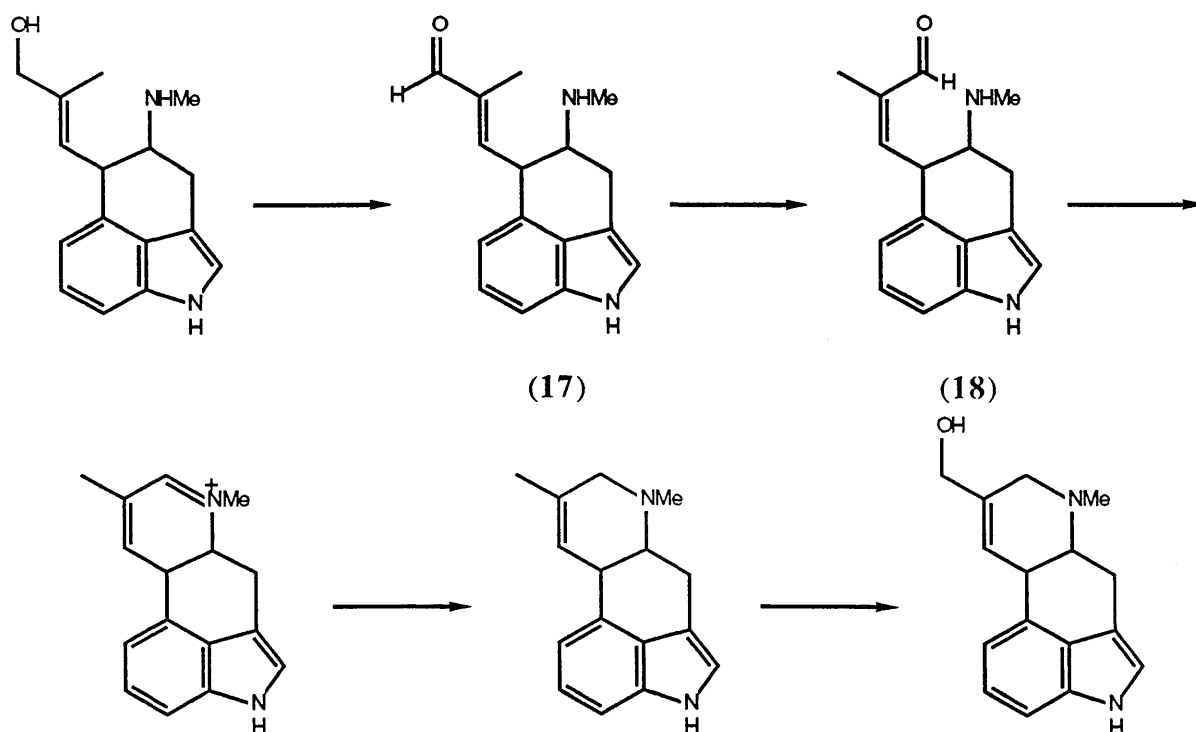
Also at this time, it was shown that chanoclavine-I-(17-³H) was incorporated into elymoclavine with only 53% tritium retention, showing that one of the hydrogens from C-17 is lost during cyclisation.⁵⁸ This implied that an intermediate exists which has only one hydrogen at C-17; a logical candidate was chanoclavine-I-aldehyde (17).

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES



(17)

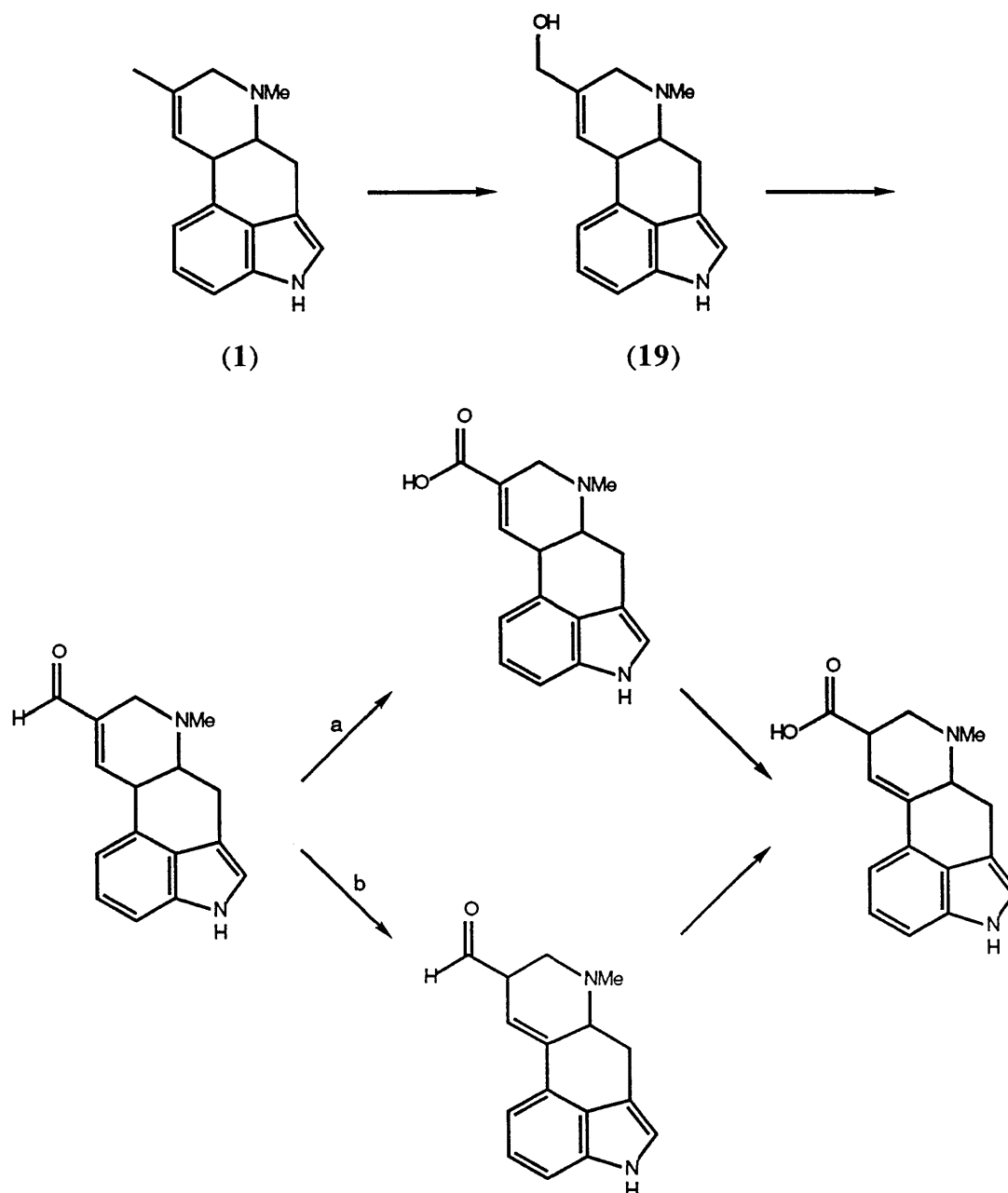
Aldehyde (17) was found to be incorporated into elymoclavine both specifically, with all the tritium from the aldehyde group appearing at C-7, and more efficiently than chanoclavine-I.⁵⁸ Also, virtually complete retention of the C-17 hydrogen was observed. Additional support for the intermediacy of chanoclavine-I-aldehyde is provided by the isolation in 1980 of this compound from a blocked mutant of *C. purpurea*.⁵⁹ These results are all consistent with (17) being an intermediate in the formation of ring D; the isomerisation shown in Scheme 11 probably occurs at the aldehyde stage ((17) $\rightarrow$ (18)) (Scheme 12).



Scheme 12

1.3.2.6 Formation of Lysergic Acid.

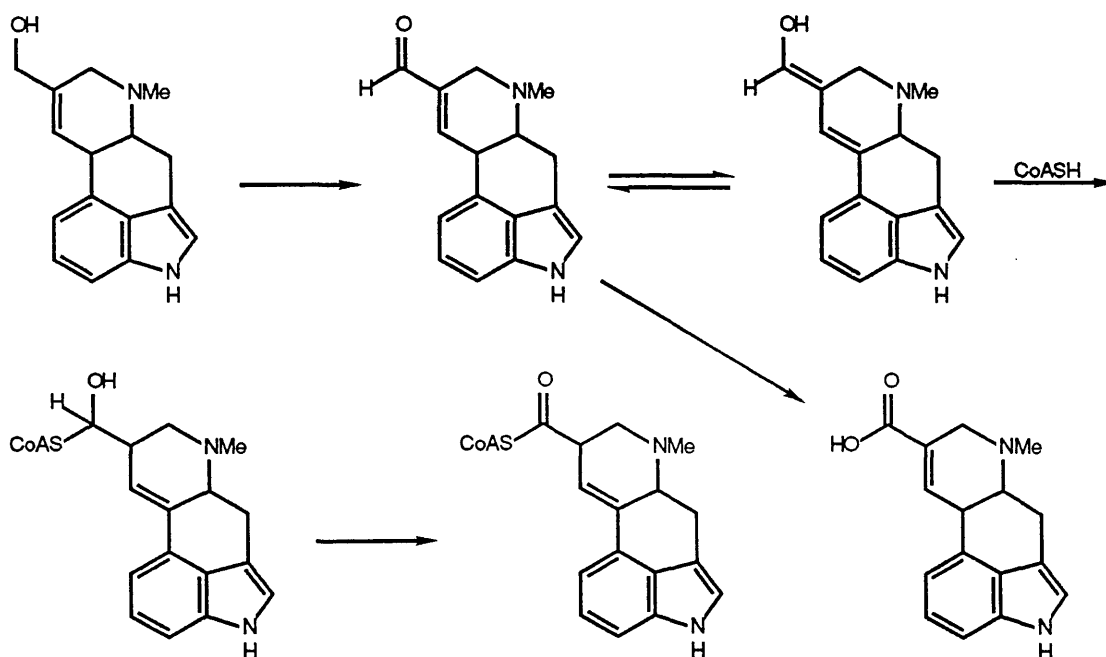
It is now well known that elymoclavine (19) (Scheme 13) is a precursor of lysergic acid.^{60,61} It therefore follows that the agroclavine (1) produced from the closure of ring D is oxidised at the C-17 methyl group to elymoclavine—indeed this conversion is found to be rapid, with the consequence that generally the ratio of agroclavine to elymoclavine is low in most *Claviceps* cultures.⁵



Scheme 13

A comparison of the structures of elymoclavine and lysergic acid (Figure 1) shows that a number of transformations are required for this conversion, *viz.* oxidation of the C-17 hydroxymethyl group and isomerisation of the $\Delta^{8,9}$ -double bond to the $\Delta^{9,10}$ -position. The detailed sequence of steps has not been fully elucidated, but it is known^{61a,b} that the process does not proceed through penniclavine or lysergol, hence isomerisation occurs *after* oxidation of the hydroxymethyl group. Labelled $\Delta^{8,9}$ -lysergic acid (natural paspalic acid) was found to be efficiently incorporated into $\Delta^{9,10}$ -lysergic acid amides, implying that the double bond isomerisation occurs at the acid oxidation level (path a, Scheme 13).⁶² However, it is known that $\Delta^{8,9}$ -lysergic acid spontaneously isomerises to the $\Delta^{9,10}$ -isomer, so the incorporation could be due to a non-enzymatic process. The alternative possibility is that the double bond shifts at the aldehyde stage (path b, Scheme 13), although the incorporation results for this aldehyde have not been reported.

A further problem is that virtually all natural derivatives of lysergic acid are amides, either peptidic or the simpler alkylamides. Their formation therefore requires activation of the carboxyl group, probably as a coenzyme A thiolester.



Scheme 14

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

Cell-free extracts of *Claviceps* can catalyse the formation of lysergyl-coenzyme A from lysergic acid,⁶³ but the possibility remains that oxidation of elymoclavine leads directly to an activated form of lysergic acid, for example the coenzyme A ester, and that the free acid is not an intermediate in the formation of the amide derivatives (Scheme 14).

1.3.2.7 Biogenetic relationships among clavine alkaloids.

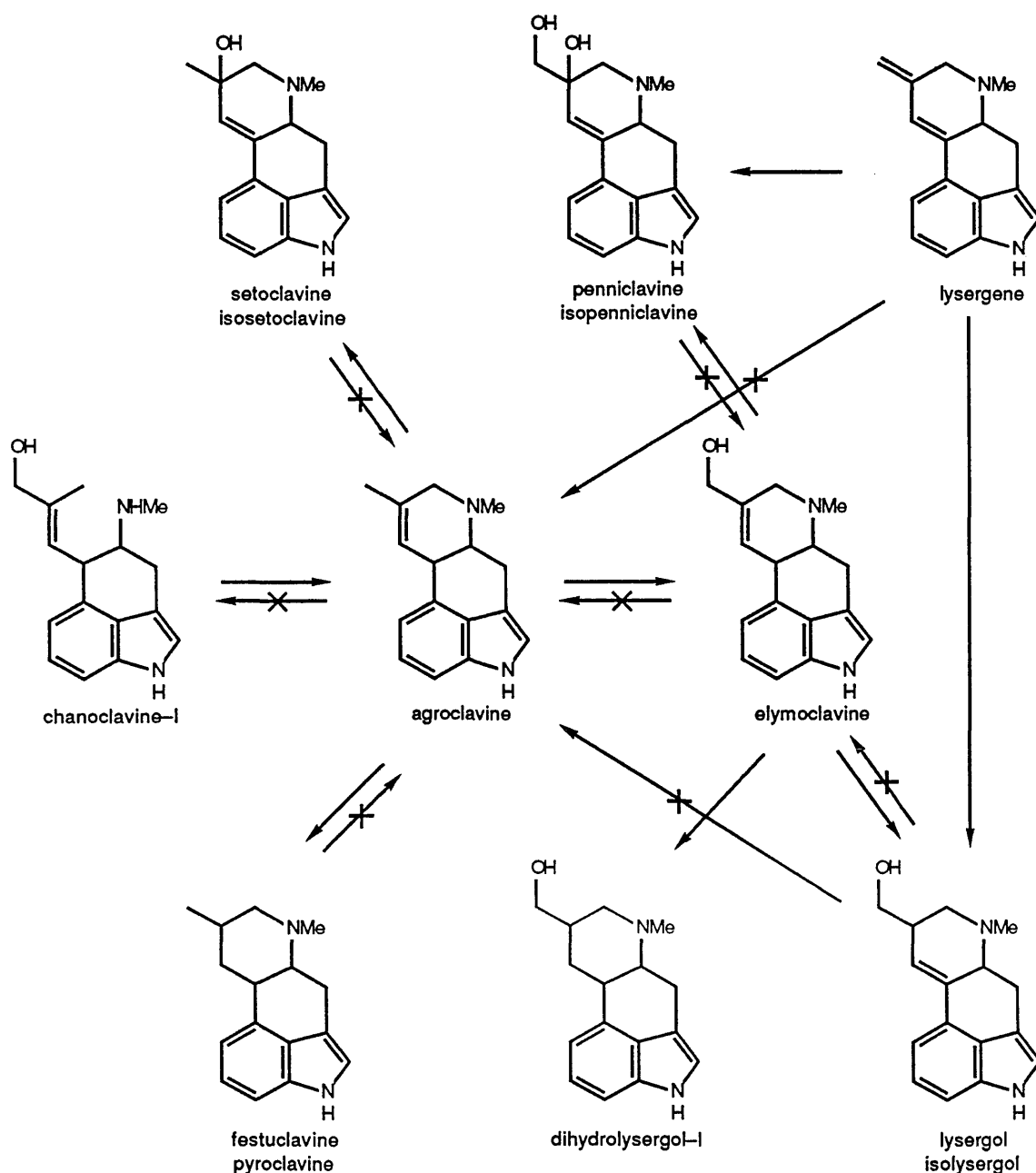


Figure 3

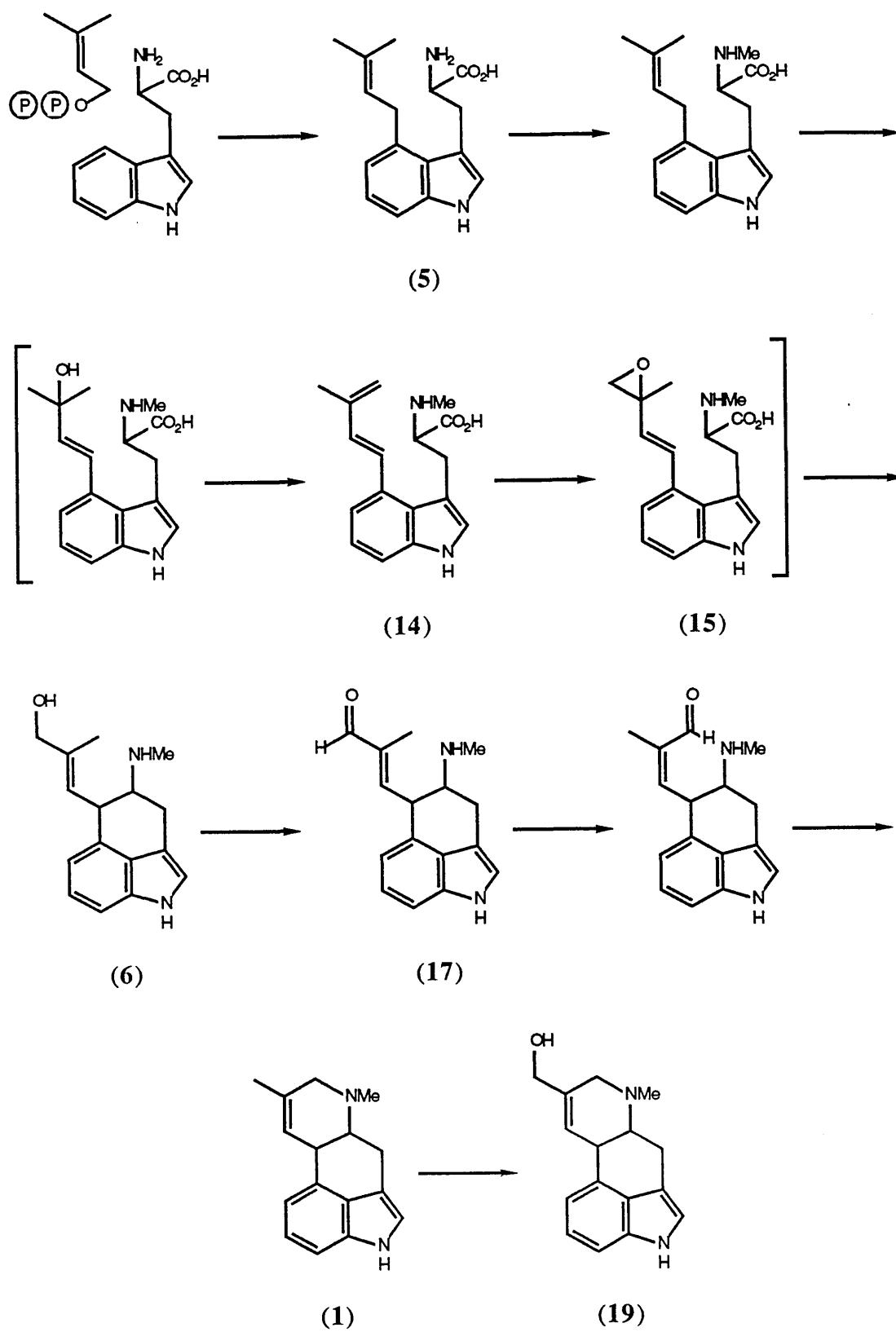
SYNTHETIC ROUTES TO [*cd*]-FUSED INDOLES

At an early stage in the investigation of the ergoline ring system, detailed and extensive studies using labelled alkaloids were carried out to ascertain the relationships between the various alkaloids.^{8b,45a,b,60,64} From these studies the sequence agroclavine → elymoclavine → lysergic acid derivatives was established. In addition, the relationships shown in Figure 3 were elucidated as a result of this work.^{8b,45a,b} The main types of process occurring during these interconversions are reduction of the $\Delta^{8,9}$ -double bond, isomerisation of this bond to the $\Delta^{9,10}$ -position, and hydroxylation at C-8 with a shift of the double bond to the $\Delta^{9,10}$ -position. The latter reaction is catalysed by peroxidase; the C-8 epimers are formed independently and are not interconvertible.

1.3.2.8 Summary.

The past thirty years have seen a great deal of work on the mechanistic aspects of ergoline biosynthesis. The last ten years or so have proved particularly fruitful, with new results making the biosynthetic pathway ever clearer. Plausible hypotheses now exist for the complete pathway from tryptophan to lysergic acid, although it must be said that the finer details of a few of these still require some clarification. Particularly intriguing is the mechanism of C-ring formation, which has possibly been solved thanks to the recent joint work of Kozikowski and Floss. However, more work needs to be done in order to investigate their hypothesis more fully, so it is perhaps dangerous to attach too much significance to their findings at this stage. That said, their results are in agreement with all the available evidence to date, and therefore their mechanism is the most plausible at this time. Thus the biosynthesis of the ergoline ring system is perhaps, at this stage, best represented as shown in Scheme 15, the stages in parentheses remaining somewhat uncertain.

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

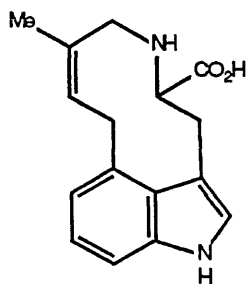


Scheme 15

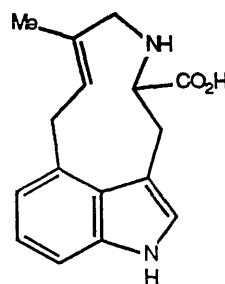
1.4 Clavicipitic acid and aurantioclavine

1.4.1 Introduction.

In 1969, a compound was isolated from submerged cultures of *Claviceps* which had been inhibited with ethionine to retard the *N*-methylation step.⁶⁵ The compound was named clavicipitic acid, and labelling studies showed that mevalonic acid-2-¹⁴C and tryptophan (alanine-3-¹⁴C) were incorporated in an analogous fashion to the ergoline alkaloids. It was also found, perhaps not surprisingly, that the methyl group from labelled methionine was not incorporated, so clavicipitic acid did not appear to contain an *N*-methyl group. Tryptophan (carboxyl-¹⁴C) was incorporated, so a carboxyl group at position 5 (ergoline numbering) was implicated. Tritium retention experiments using tryptophan (alanine-2-³H-carboxyl-¹⁴C) and mevalonic acid (2-¹⁴C-5-³H) showed that the α -hydrogen of tryptophan and the two hydrogens in position 5 of mevalonic acid were retained, so, unlike the clavines, there was no link between the carbon atoms derived from these positions. This, together with the presence of a vinylic proton, as evidenced by the NMR spectrum of a trimethyl derivative, led to the proposal of (20) as the structure of clavicipitic acid. Molecular models indicate that there are large steric interactions in (20), but these are greatly reduced in the double bond isomer (21).



(20)

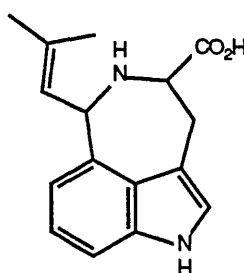


(21)

The evidence for this structure was by no means conclusive, the mass spectral fragmentation being particularly difficult to rationalise, and in 1973 a second paper on

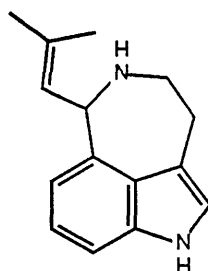
SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

clavicipitic acid was published.^{66a} This time the compound had been isolated from submerged cultures of *C. fusiformis* which had *not* been inhibited with ethionine, as well as from cultures which had. The isolated product could be resolved into two fractions, which were proposed to be diastereoisomers.^{66b} The authors could not prepare the previously reported trimethyl derivative,⁵⁶ but instead prepared the *N*-acetyl methyl ester derivative, from which an NMR spectrum could be obtained. This leaves no doubt that structure (20) (or (21)) is incorrect, and that the correct structure for clavicipitic acid is in fact (22). The compound contains a 3,4,5,6-tetrahydroazepino[5,4,3-*cd*]indole ring system, together with a 2-methyl-1-propenyl side chain, and is the first example of a natural compound with these two structural features.



(22)

More recently, this ring system has been found in aurantioclavine (23), a decarboxylated version of clavicipitic acid which was isolated from *Penicillium aurantio-virens*.⁶⁷



(23)

The remainder of this review will concentrate on clavicipitic acid. Although the compound is probably not an intermediate in ergoline biosynthesis, as will be shown later,

it does have important biological significance. This will be discussed briefly, and then the published laboratory syntheses of clavicipitic acid and aurantioclavine will be reviewed.

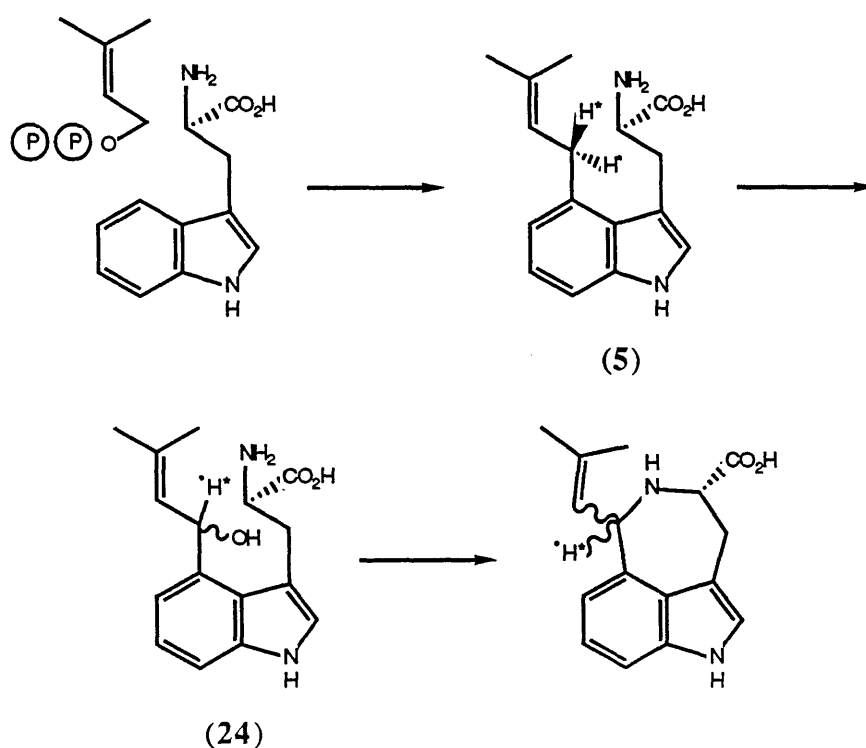
1.4.2 *Biological significance of clavicipitic acid.*

Whereas the biosynthesis of the clavine alkaloids has been studied at great length, this aspect of clavicipitic acid has received only comparatively scant attention. However, much is now known about both the biosynthetic origin of the compound and its probable relevance to ergoline biosynthesis.

When clavicipitic acid was first isolated, extensive labelling studies proved that, like the clavine alkaloids, the compound was derived from tryptophan and mevalonic acid.⁶⁵ Therefore, the logical conclusion was that the next intermediate was DMAT, (5), and this was confirmed by labelling experiments.⁶⁸ It was found that the conversion of DMAT to clavicipitic acid was favoured at high pH, and that oxygen but not cytochrome P-450 or any enzyme cofactor were required.^{68a} It was proposed^{68a} that the high pH increased the nucleophilicity of the amino nitrogen of DMAT, hence facilitating carbon-nitrogen bond formation, although this may be a rather simplistic view. Additionally, clavicipitic acid was found to be not significantly incorporated into elymoclavine, so it is probably not an intermediate in clavine biosynthesis.^{68a}

At this point, it was clear that the formation of clavicipitic acid was a major alternative to the production of alkaloids during the consumption of DMAT. Since agroclavine did not inhibit clavicipitic acid production,^{68b} there is apparently no feedback control of clavicipitic acid formation by alkaloids. The two pathways, clavicipitic acid production or ergoline alkaloid formation, may have developed to remove DMAT under different conditions—clavicipitic acid production is favoured during the rapid growth phase and at high pH, while ergoline alkaloids are produced during low or no growth and at near neutral pH. It is noteworthy that the production of these alkaloids under alkaline conditions would tend to maintain the high pH, while clavicipitic acid formation would tend to lower it.

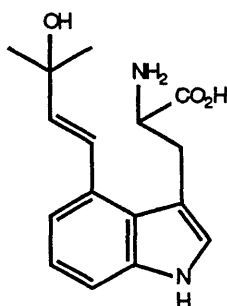
A further labelling study on clavicipitic acid revealed another surprising aspect of its formation.⁶⁹ It was found that the *pro*-5*S* hydrogen of mevalonate was completely retained, but only half of the *pro*-5*R* was retained. Since this observation again cast doubt on the structure of clavicipitic acid, X-ray crystallography was used to determine unequivocally the structure—this soon confirmed that clavicipitic acid was in fact (22). The unusual tritium retention was explained by proposing that clavicipitic acid is formed from DMAT *via* an intermediate (24) derived by hydroxylation of the benzylic position of DMAT (Scheme 16). It was suggested that the production of (24) proceeded with only partial discrimination between the two hydrogens at the benzylic position, and that the reaction involved an isotope effect.



Scheme 16

It is also possible that the formation of clavicipitic acid involves a similar intermediate to the production of the clavine alkaloids. It is perhaps significant that clavicipitic acid lacks a methyl group on the amino nitrogen, thus facilitating ring closure in a different mode to that

for alkaloid production. In view of the recent results obtained regarding the mechanism of C-ring closure in alkaloid biosynthesis, this would suggest that intermediates such as (11) should be synthesised and their possible incorporation into clavicipitic acid studied.



(11)

1.4.3 Laboratory syntheses of clavicipitic acid and aurantioclavine.

1.4.3.1 Introduction.

Chemists have, for a long time, attempted to mimic nature in the laboratory, and the field of clavine alkaloid synthesis is no exception. There have been numerous attempts to achieve 4-functionalisation of indoles already substituted, for example, in the 3-position, just like the isoprenylation of tryptophan described earlier, but, with a few exceptions,⁷⁰ the results have been largely unsuccessful. Since the eventual target is usually a [cd]-fused indole of some description, cyclisation of a suitable 3-substituted indole onto the (unsubstituted) 4-position has also been attempted. Success has been found for a few examples, notably *some* classical Friedel-Crafts type processes,⁷¹ and the photocyclisation of haloacetyltryptophan derivatives,⁷² or amino acid-tryptophan dipeptides.⁷³ Applications of the former reaction must be chosen with care, since yields can be very poor, and often an alternative cyclisation to the 2-position predominates or proceeds exclusively.^{71b} The second reaction will be discussed in more detail in Chapter 3.

Due to the difficulty in achieving this functionalisation, most laboratory syntheses of the clavine alkaloids start with a 4-functionalised indole which has been prepared *with that functionality built in*. This in itself is often not a trivial matter, due to the problems assoc-

iated with obtaining the correct regiochemistry during some of the classical indole syntheses, but it has been made considerably easier with the advent of methods such as the Leimgruber-Batcho indole synthesis.^{74a-e} Using this process, the ethyl and methyl esters of indole-4-carboxylic acid,^{74b} 4-cyanoindole,^{74b} 4-hydroxymethylindole,^{74b} and indole-4-carboxaldehyde (25)^{74c,d} have all been prepared, and the last two of these have been used to synthesise lysergic acid,^{75a} chanoclavine-I,^{75b} 6,7-secoagroclavine,^{75b} isochanoclavine-I,^{75b} costaclavine,^{75b} paliclavine,^{75b,c} the biosynthetic precursor DMAT,^{75d} and clavicipitic acid.^{75e}

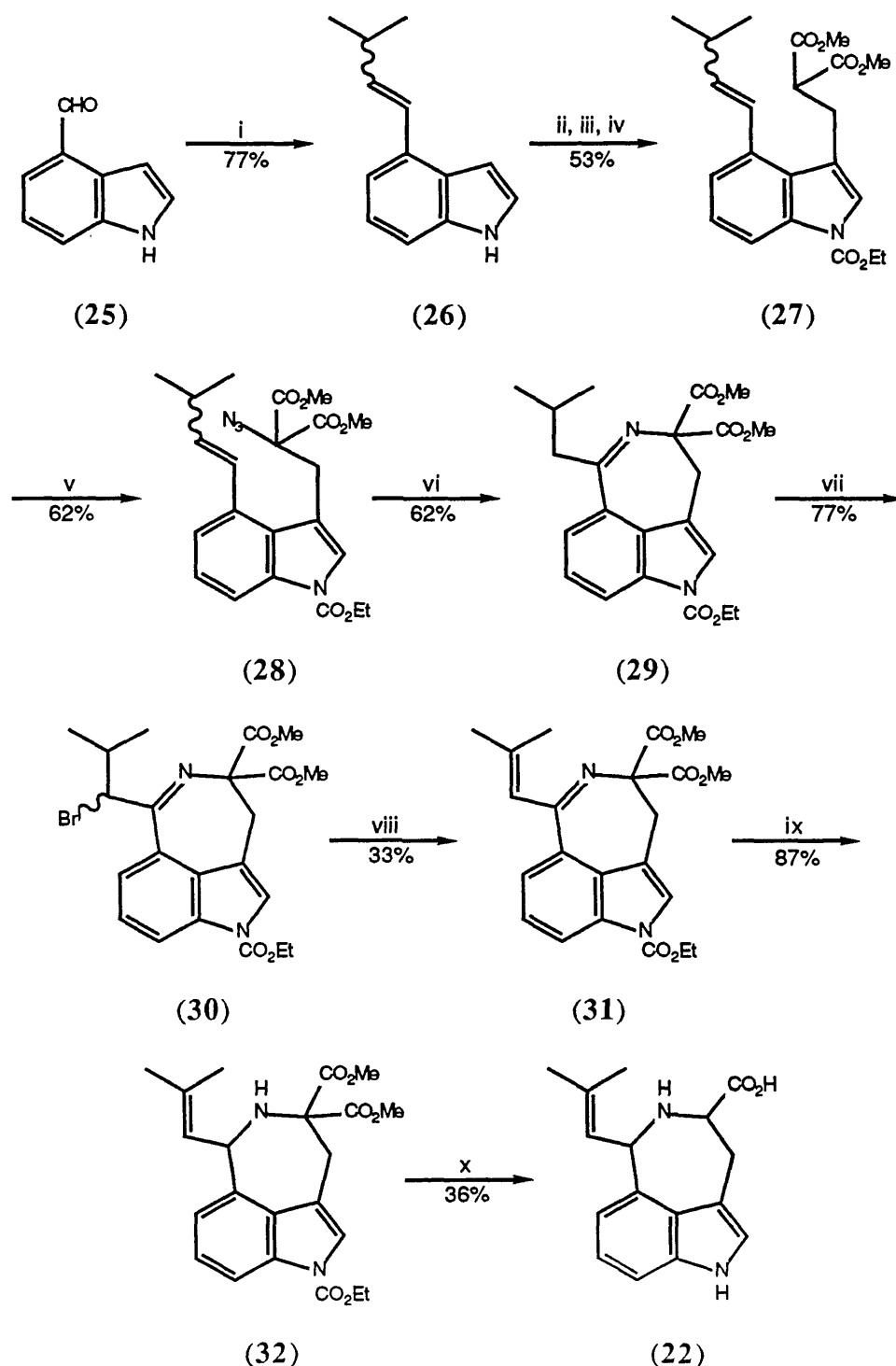
By far the majority of syntheses described below start from a 4-substituted indole, and the remainder of the functionality is built around this, usually producing a 3,4-disubstituted indole which then undergoes ring closure to construct the azepine ring. It is true that there are a few exceptions to this generalisation, but the fact remains that, at present, alternative methodology for the synthesis of this type of compound is rather limited.

1.4.3.2 Clavicipitic acid.

To date, there have been five total syntheses of clavicipitic acid reported in the literature,^{75e,76} together with one approach to the clavicipitic acid skeleton^{71f} and one formal synthesis.⁷⁷ The first synthesis of clavicipitic acid was published by Kozikowski and Greco in 1982,^{75e} and was based on their earlier reported approach⁷⁸ to the azepinoindole ring system using an intramolecular azide cycloaddition strategy (Scheme 17).

After several abortive 'stepwise' attempts to construct the azepine ring, the authors eventually used the cycloaddition method. Their first report of this process had described the synthesis of (29), and it was suggested that use of a more functionalised ylide in the first step would provide an efficient route to clavicipitic acid.⁷⁸ However, the synthesis described did not make use of this idea, instead the activating effect of the imine functionality was used to introduce the exocyclic double bond.

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

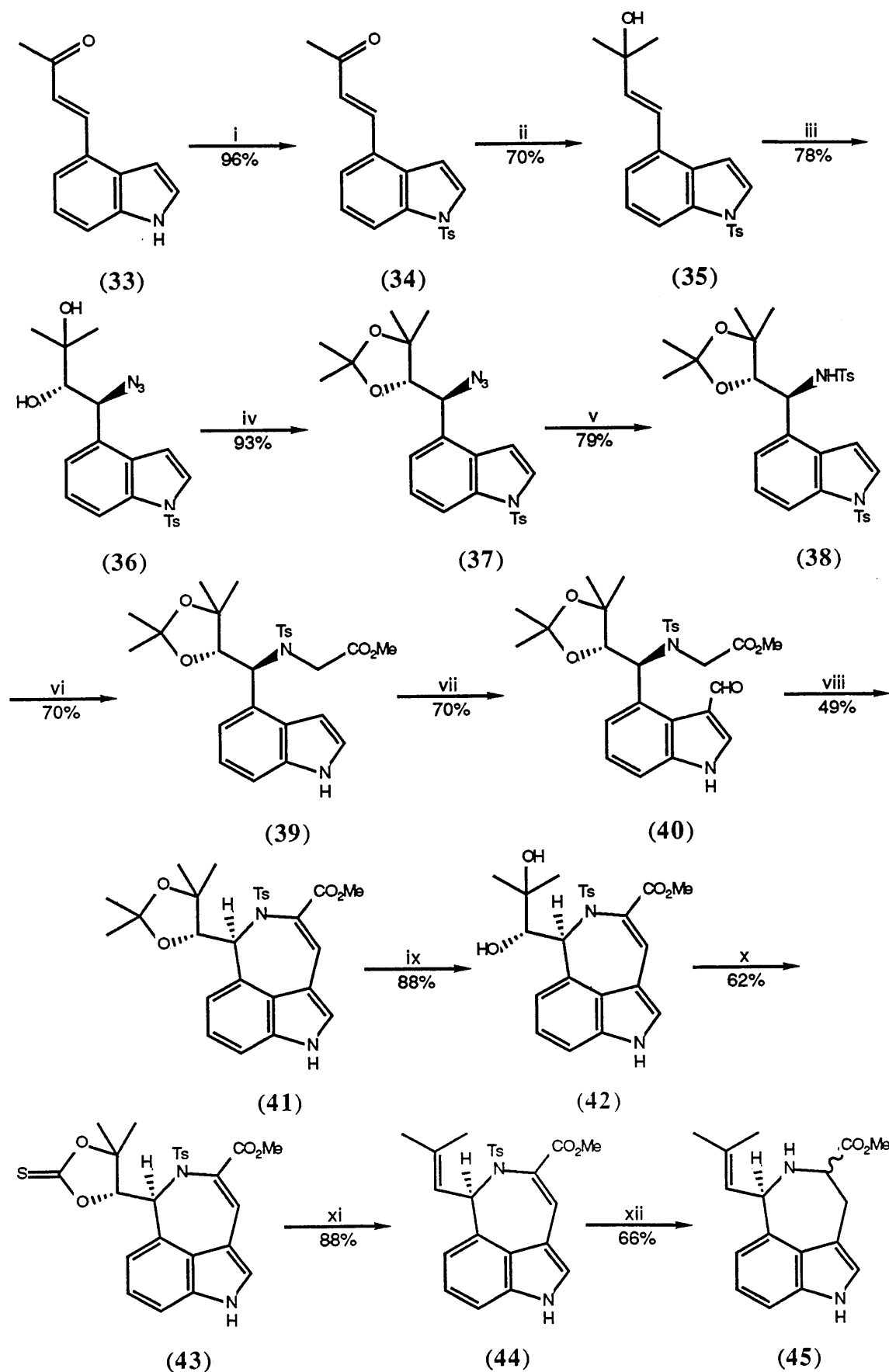


Scheme 17. Reagents: i, $i\text{-PrCH=PPh}_3$, THF; ii, $\text{Me}_2^+\text{N=CH}_2 \cdot \text{OAc}$, HOAc; iii, $\text{CH}_2(\text{CO}_2\text{Me})_2$, $n\text{-Bu}_3\text{P}$, MeCN; iv, EtO_2CCl , Et_3N , MeCN; v, NaH, TsN_3 , HMPA, THF; vi, $o\text{-di-chlorobenzene}$, reflux; vii, CuBr_2 , EtOAc, CHCl_3 ; viii, DBU, toluene, 80°C ; ix, catecholborane, CHCl_3 ; x, (a) KOH, MeOH, (b) dil. HCl.

Starting from indole-4-carboxaldehyde, standard Wittig chemistry gave the olefin (26) as a 3:1 *Z:E* mixture. This was converted to its gramine derivative using a conventional Mannich procedure, and reaction of this in turn with dimethyl malonate using tri-*n*-butylphosphine as catalyst introduced the required 3-functionality; protection of the indole nitrogen with ethyl chloroformate then gave (27) in 53% yield over three steps. Introduction of the azide group was achieved in reasonable yield using tosyl azide. Thermolysis of the product in refluxing *o*-dichlorobenzene effected cyclisation to a single imine, (29). No aziridine was produced, presumably due to the strain associated with a three-membered ring fused to the fairly constrained seven-membered, and the benzylic stabilisation which would favour the required hydrogen migration. It was found that this reaction proceeded poorly in toluene at the same temperature (sealed tube), and that other possible nitrene-derived products were absent, providing good support for an initial [3 + 2] cycloaddition reaction. Bromination of the imine with cupric bromide in chloroform/ethyl acetate gave (30) in good yield, but dehydrohalogenation of this proceeded poorly, with much starting material being recovered. It was not reported whether or not other reagents or conditions were investigated. However, vinyl imine (31) could be reduced smoothly to the olefin (32) with catecholborane. Simple hydrolysis and decarboxylation of (32) liberated clavicipitic acid as a 1:1 mixture of isomers. These were characterised using the previously reported⁶⁶ derivatisation conditions, but it was observed that in fact only one derivative was formed, and epimerisation was found to occur. It was found by another group^{76a} that under the conditions of derivatisation, the '*trans*'-isomer can readily convert to the more stable '*cis*'-isomer where the transannular interactions are minimised.

The second synthesis^{76a} of clavicipitic acid was both longer and less elegant than Kozikowski's—particularly so because the starting material (33) was prepared in seven steps from *N*-methoxycarbonylpyrrole (Scheme 18), instead of one step from indole-4-carboxaldehyde.⁵¹

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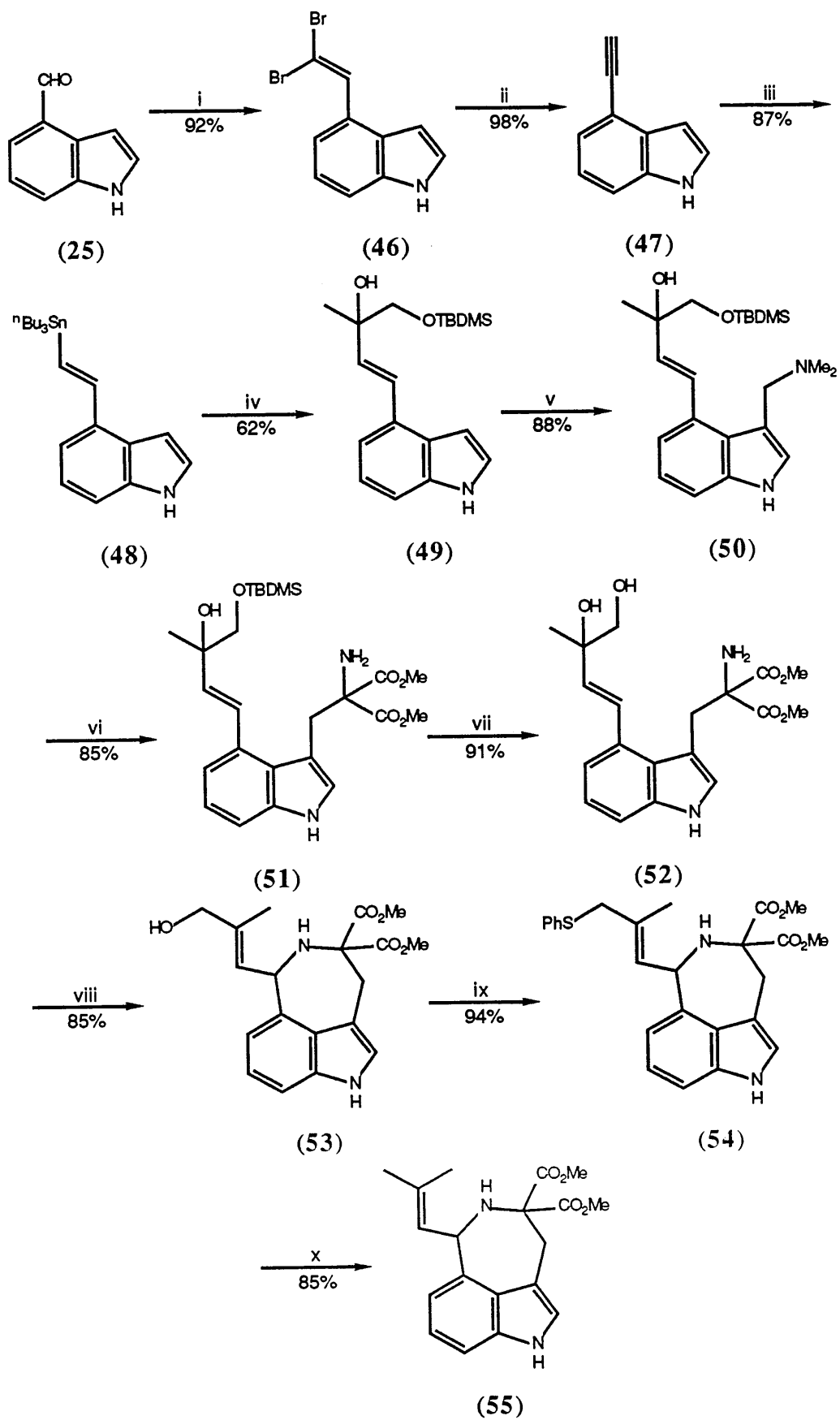
Scheme 18

Scheme 18. *Reagents:* i, K_2CO_3 , TsCl, EtOAc, reflux; ii, MeMgI, Et_2O/THF ; iii, (a) *m*-CPBA, DCM, (b) NaN_3 , aqueous dioxane, reflux; iv, $Me_2C(OMe)_2$, TsOH; v, (a) H_2 , PtO_2 , MeOH, (b) TsCl, Et_3N , $ClCH_2CH_2Cl$, reflux; vi, (a) $BrCH_2CO_2Me$, K_2CO_3 , DMF, (b) KOH, MeOH/DME/ H_2O (2:1:1), (c) CH_2N_2 in MeOH/ Et_2O ; vii, $POCl_3$, DMF, Et_2O ; viii, DBU, C_6H_6 , reflux; ix, HCl, MeOH, THF, H_2O ; x, $S=CCl_2$, DMAP, DCM; xi, $(MeO)_3P$, reflux; xii, $NaBH_4$, Na_2CO_3 , hv, MeOH/DME/ H_2O (4:2:1), $-70^\circ C$.

Tosylation of the indolic nitrogen of (33) proceeded in high yield, and reaction of the resulting tosyl derivative (34) with methylmagnesium iodide also proceeded smoothly to give the tertiary allylic alcohol (35) in 70% yield. Epoxidation of this with *m*-CPBA, followed by opening of the epoxide with azide ion under non-acidic conditions proceeded with the correct regiochemistry to give a 78% yield of the azido glycol (36). Protection of the diol as its acetonide (37) was followed by reduction of the azide group and tosylation to produce the monoprotected amine (38); treatment of this with methyl bromoacetate followed by alkaline deprotection of the indolic nitrogen and re-esterification gave the *N*-tosylglycine ester (39) in 51% yield from (36). Vilsmeier-Haack formylation introduced the required functionality in the 3-position (40), but cyclisation of this product to the seven-membered ring (41) proved disappointing, proceeding in at best 49% yield with the recovery of much starting material. Acidic cleavage of the acetonide protecting group gave the glycol (42) which could be converted to the olefin (44) *via* the thiocarbonate (43). Treatment of (42) with thiophosgene produced a mixture of 62% of (43) and 17% of the unwanted carbonate derivative. The olefin (44) was produced in 88% yield by refluxing (43) in neat trimethyl phosphite for 50 hours. Reduction of the conjugated double bond and simultaneous cleavage of the *N*-tosyl function gave a 66% yield of a mixture of the clavicipitic acid methyl esters (45), together with 17% of the corresponding *N*-tosyl derivatives. The esters (45) were hydrolysed to the free acids, and also acetylated to yield the *N*-acetyl clavicipitic acid methyl esters in order to compare their structures with authentic material.

An interesting approach to clavicipitic acid was described, again by Kozikowski, two

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Scheme 19

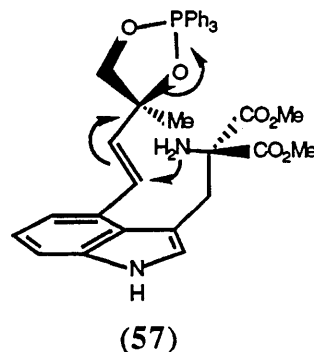
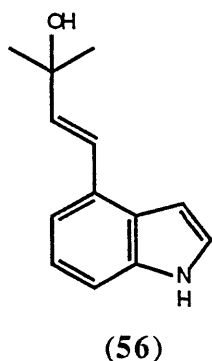
Scheme 19. *Reagents:* i, Ph_3P , CBr_4 , DCM, 0°C ; ii, $n\text{-BuLi}$, THF, -78°C ; iii, $n\text{-Bu}_3\text{SnH}$, AIBN, 90°C ; iv, (a) $n\text{-BuLi}$, THF, -78°C , (b) $\text{CH}_3\text{COCH}_2(\text{OTBDMS})$, Et_2O , -78°C ; v, $\text{Me}_2^+\text{N}=\text{CH}_2.\text{Cl}^-$, DCM, -20°C ; vi, $\text{CH}(\text{NH}_2)(\text{CO}_2\text{Me})_2$, $n\text{-Bu}_3\text{P}$, MeCN; vii, TBAF, THF; viii, DEAD, Ph_3P , THF, -78°C ; ix, N -thiophenylsuccinimide, $n\text{-Bu}_3\text{P}$, THF; x, Raney nickel, DMSO.

years later.^{76b} This consisted of a biomimetic approach to the azepine ring-closure reaction by utilising a slightly modified version of a previously proposed⁵⁰ intermediate in clavine alkaloid biosynthesis (Scheme 19).

The key intermediate for the scheme is the gramine derivative (50), a synthesis of which had been previously published by Kozikowski.⁵¹ This is ultimately derived from indole-4-carboxaldehyde (25) by production of the dibromo-olefin (46) which, on treatment with n -butyl-lithium gave 4-ethynylindole (47) in 90% overall yield from (25). Hydrostannylation of the alkyne produced a >95:5 mixture of *E*- and *Z*-vinylstannanes (48) in 87% yield. Transmetalation with n -butyl-lithium, followed by reaction with (*t*-butyldimethylsilyloxy)acetone produced the monoprotected diol (49), together with a small quantity of 4-vinylindole—the latter was probably formed by proton abstraction from the (silyloxy)acetone. Interestingly, reaction of the lithium or magnesium acetylides of (47) with the (silyloxy)acetone gave the predicted propargylic alcohol, but this could not be reduced to the required olefinic product (49). Use of the preformed dimethylmethylen ammonium chloride was required to achieve smooth formation of the gramine derivative of (49) in 88% yield. The key intermediate (50) now secured, all that remained was elaboration of the functionality in the 3-position and deprotection of the primary alcohol. This was achieved by condensation of (50) with dimethyl aminomalonate to afford only the product of carbon-carbon bond formation (51) in 85% yield; this was followed by desilylation using tetra- n -butylammonium fluoride to produce a 91% yield of (52). The ring-closing reaction of (52) proved interesting and is worthy of some comment. Reaction of (52) under Mitsunobu conditions achieved cyclisation to produce an 85% yield of the *E*-isomer (53), together with a mere 3% yield of the corresponding *Z*-compound.

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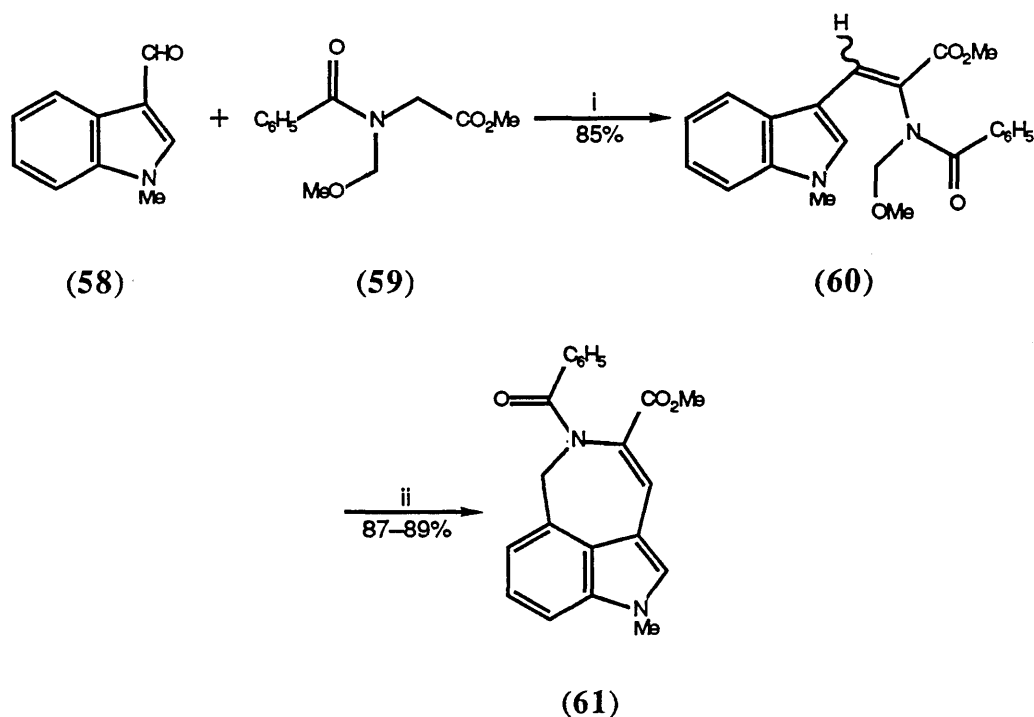
Previous studies with the related *N*-methylamino compounds had shown that this type of cyclisation failed to occur if the primary alcohol was not deprotected first,^{76b} suggesting the possible intermediacy of a vinyl oxirane similar to that proposed as an intermediate in the biosynthetic pathway. However, further investigations with the C-3 *unsubstituted* version of (52) failed to isolate the supposed epoxide intermediate. Furthermore, a simple carbonium ion mechanism can be discounted since reaction of the sensitive tertiary alcohol (56) under Mitsunobu conditions led only to the complete recovery of starting material. Further study of the reaction using ³¹P NMR showed the presence of a strong signal at -37.4 ppm, corresponding to a cyclic *O,O*-phosphorane, but no phosphorus resonance corresponding to triphenylphosphine oxide (+25 ppm) was observed. The authors therefore concluded that the reaction proceeded through S_N2' attack on a vinyl cyclic *O,O*-phosphorane (57), the stereochemistry being determined by the reduced steric crowding in the S_N2' transition state which leads to the more favoured *E*-isomer.



To complete the synthesis of clavicipitic acid, the hydroxyl group of (53) was replaced by a thiophenyl group, and the resulting sulphide (54) was desulphurised with Raney nickel in DMSO to give (55). The synthesis was concluded by simple basic hydrolysis and decarboxylation to yield the clavicipitic acids.

Perhaps one of the shortest and most remarkable syntheses of the clavicipitic acid azepinoindole ring system was that published in 1981 by Nakatsuka *et al.* (Scheme 20).^{71c}

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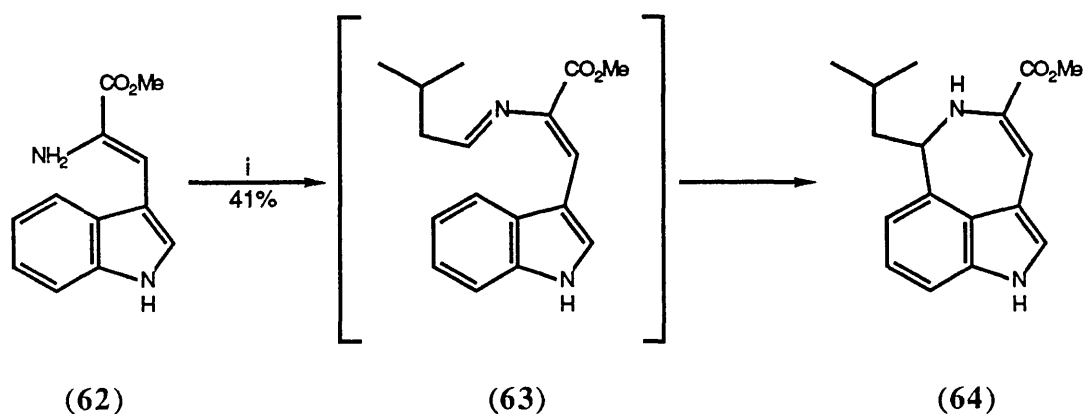


Scheme 20. Reagents: i, (a) LDA, (b) MsCl; ii, Ac₂O/HCO₂H, 80°C.

N-Benzoyl-*N*-methoxymethylglycine methyl ester (59) was prepared in 75% yield by reaction of the sodium salt of *N*-benzoylglycine methyl ester with chloromethyl methyl ether in DMF at -78°C. Knoevenagel condensation of (59) with *N*-methylindole-3-carboxaldehyde (58) using LDA followed by methanesulphonyl chloride gave predominantly the *Z*-dehydrotryptophan derivative (60) (77%), together with a small amount (8%) of the *E*-isomer. Treatment of either of these isomers with a 1:1 mixture of formic acid and acetic anhydride at 80°C gave an 87-89% yield of the 5,6-dihydroazepino[5,4,3-*cd*]indole derivative (61), the *E*-isomer presumably undergoing acid-catalysed isomerisation to the *Z*-compound before cyclisation. Interestingly, hydrogenation of the olefinic double bond of (60) produced the corresponding tryptophan derivative which, upon exposure to the same cyclisation conditions, gave rise to the Pictet Spengler-type cyclisation to the 2-position. The observed regiochemistry was explained by a combination of stereochemical and electronic effects. The transoid form of (60) would be expected to be more stable than the cisoid form, resulting in the methoxymethyl group

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being closer to the 4-position than to the 2-position, and also the conjugation between the ester carbonyl and the pyrrole ring would tend to diminish the reactivity of the 2-position of the indole nucleus. Either way, the olefinic double bond seems essential to the success of this cyclisation, and indeed the process is reported to be generally applicable to α,β -dehydrotryptophan derivatives.^{71c} This was amply illustrated by the application of this method to an approach towards the clavicipitic acid skeleton (Scheme 21).^{71f}

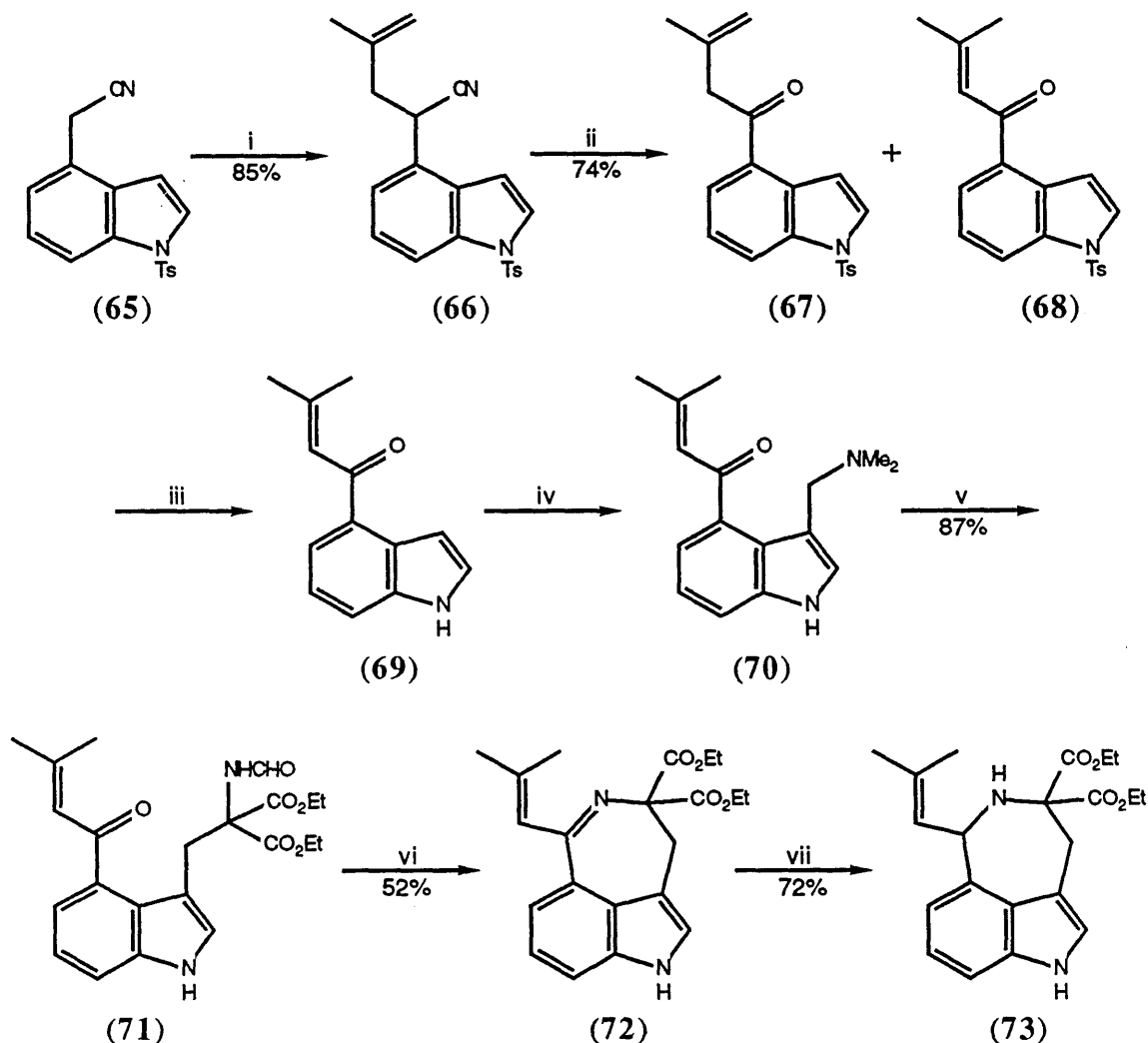


Scheme 21. Reagents: i, $(\text{CH}_3)_2\text{CHCH}_2\text{CHO}$, $\text{BF}_3 \cdot \text{OEt}_2$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, 80°C .

Dehydrotryptophan (62) was synthesised using a variation of a published⁸⁰ method involving Michael addition of indole to methyl α -nitro- β -ethoxyacrylate, followed by reduction of the nitro group with stannous chloride in anhydrous methanolic HCl. Condensation of (62) with isovaleraldehyde in the presence of boron trifluoride etherate directly produced a 41% yield of the cyclised product (64) from the supposed intermediate (63). Functionalisation of (64) in a similar fashion to that described for Kozikowski's synthesis shown in Scheme 17 could introduce the olefinic double bond of clavicipitic acid—alternatively, use of the corresponding α,β -unsaturated aldehyde might achieve this more directly. As yet, no further details about the completion of this synthesis of clavicipitic acid have been published.

One of the more recent syntheses of clavicipitic acid was published in 1987 (Scheme 22).^{26c} A 4-substituted indole in the form of 1-*p*-toluenesulphonyl-4-cyanomethylindole (65) was the starting material—this in turn had been prepared *via* a tortuous route involving

4-oxo-4,5,6,7-tetrahydroindole as intermediate.⁸¹



Scheme 22. Reagents: i, *n*-BuLi, TsOCH₂C(Me)=CH₂; ii, (a) *t*-BuOK, -78°C, (b) dry O₂; iii, NaOH, MeOH; iv, Me₂⁺N=CH₂.Cl⁻; v, OHCNHCH(CO₂Et)₂, MeO₂CC≡CCO₂Me, THF, 0°C; vi, 1.2N HCl, DME; vii, catecholborane, CHCl₃, 0°C.

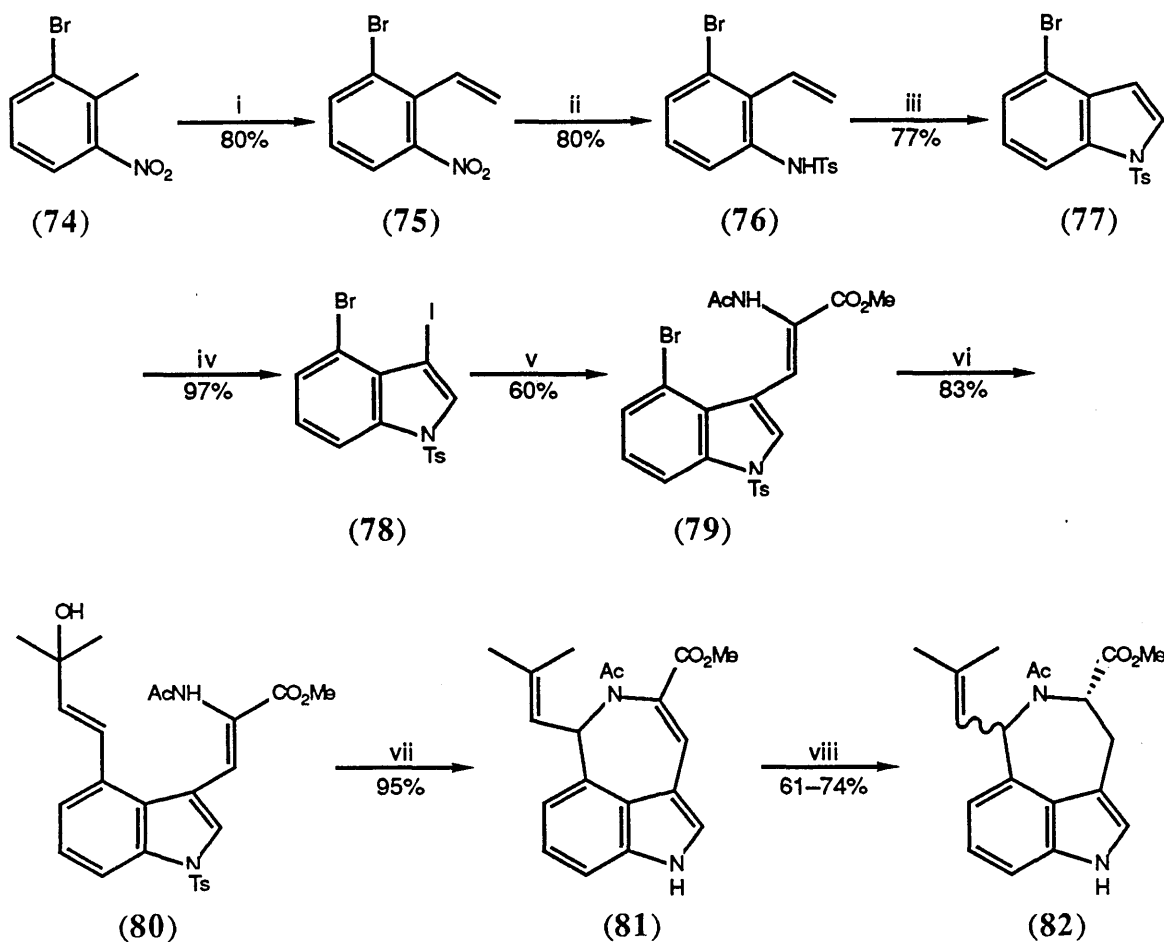
Elaboration of the C-4 side chain was achieved by formation of the anion of (65) and reaction of this with methallyl tosylate to yield 85% of (66). Aerobic oxidation of the anion of (66) removed the cyano group and produced isomeric ketones (67) and (68) in 43 and 31% yield, respectively. Alkaline deprotection of the mixture of the *N*-tosylindoles proceeded with simultaneous isomerisation of the olefinic double bond into conjugation with the carbonyl group, such that only one product (69) was obtained. The remainder of

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the synthesis, with the exception of the ring-closure step, is very similar to that of Kozikowski shown in Scheme 17, and requires little further comment. Introduction of the 3-substituent using the by now standard gramine chemistry proceeded smoothly. Hydrolysis of the *N*-formyl group of (71) revealed the primary amine function which, under the reaction conditions, cyclised to the carbonyl carbon in 52% yield. The more normal Michael addition observed between primary amines and α,β -unsaturated ketones did not occur, presumably due to steric factors, and due to the disfavoured formation of a 9-membered ring fused to the rigid indole system. The synthesis of clavicipitic acid from the tricyclic product (72) was completed exactly as in Kozikowski's process.

Palladium coupling chemistry has also been used in the synthesis of clavicipitic acid. The procedure of Hegedus *et al.* used this methodology four times, firstly to synthesise a suitable 3,4-disubstituted starting material, then to introduce the required 3- and 4-functionality, and finally to facilitate cyclisation of the azepine ring (Scheme 23).^{76d} The first three steps of the synthesis are concerned with the construction of the indole, and the details were published⁸² some years before the remainder of the work. Commercially available 2-bromo-6-nitrotoluene (74) was converted to the styrene derivative (75) by bromination and phosphonium salt formation followed by a Wittig reaction with formaldehyde. Reduction of (75) with iron in acetic acid produced the corresponding aniline which was *N*-tosylated to produce a high yield of styrene (76). Pd(II)-catalysed ring closure of (76) readily gave 4-bromo-1-tosylindole (77) in 77% yield. It is interesting to note that, although *p*-toluenesulphonamides are relatively poor nucleophiles, they do attack Pd(II)-coordinated olefins.⁸³ Indeed, the authors found that the tosyl group was the most effective for this transformation since the indole produced from the unprotected aniline decomposed under the reaction conditions, and the cyclisation of the corresponding acetanilide proceeded only very slowly.

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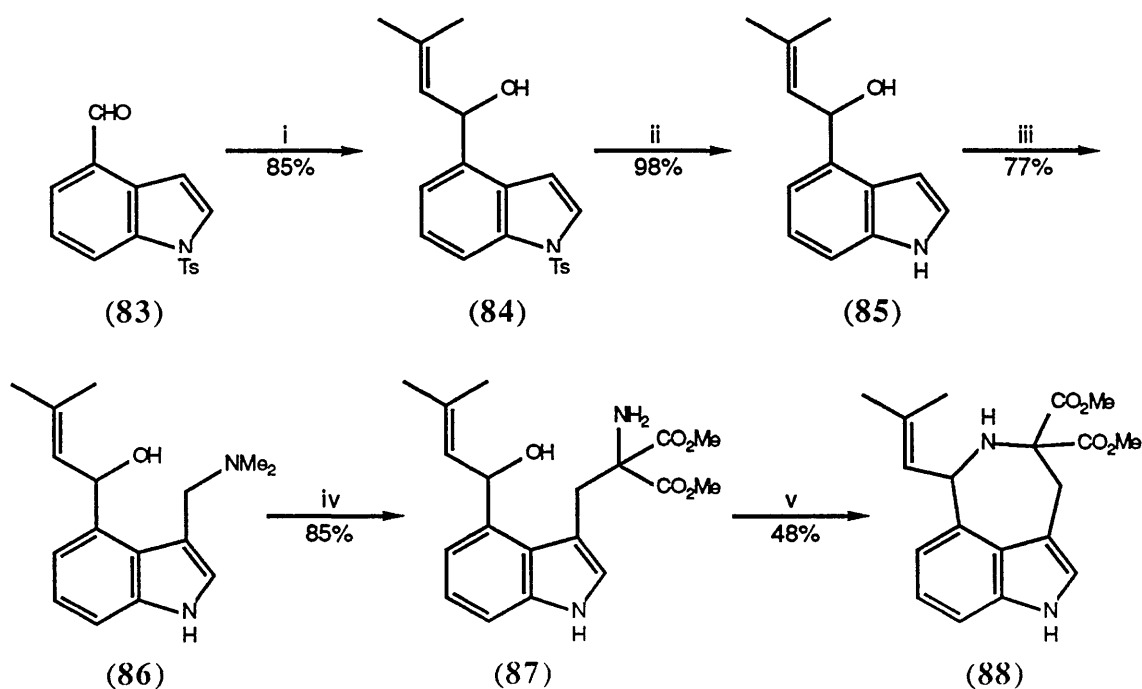


Scheme 23. *Reagents:* i, (a) Br₂, hv, CCl₄, (b) Ph₃P, (c) CH₂O_(g), Et₃N; ii, (a) Fe, HOAc, (b) TsCl, py; iii, 5% PdCl₂(MeCN)₂, benzoquinone; iv, (a) Hg(OAc)₂, HClO₄ cat., (b) I₂; v, methyl α-acetamidoacrylate, 5% Pd(OAc)₂, Et₃N, MeCN; vi, CH₂=CHC(Me)₂OH, 8% Pd(OAc)₂, (*o*-Tol)₃P, Et₃N, MeCN; vii, 15% PdCl₂(MeCN)₂, MeCN or TsOH, Δ; viii, NaBH₄, Na₂CO₃, hv, MeOH/DME/H₂O (4:2:1), -20°C.

To facilitate later insertion of a suitable 3-substituent, iodine was introduced into the 3-position of (77) by mercuriation followed by treatment with iodine in chloroform to give (78) in virtually quantitative yield. Heck arylation with methyl α-acetamidoacrylate produced exclusively the *Z*-isomer of (79) in 60% isolated yield. At the same time, approximately 20% of deiodinated product (77) was also obtained. A tertiary allylic alcohol side chain was similarly introduced into the 4-position to give (80) in 83% yield. Cyclisation of (80) to (81) was extremely facile—heating in acetonitrile at reflux for two hours with 15% PdCl₂(MeCN)₂ proved sufficient to achieve cyclisation virtually

quantitatively. The ease with which cyclisation occurred was ascribed to the *Z*-geometry of the acetamidoacrylate side chain, which holds the amide group in a favourable position for ring-closure. Selective reduction and simultaneous detosylation of (81) produced a good yield of *N*-acetyl clavicipitic acid methyl esters as a mixture of diastereoisomers. Interestingly, shorter reaction times (*ca.* 10 h) favoured the formation of *cis*-(82) in 61% yield, whereas longer reaction times (20.5 h) tended to produce 74% of a 1:1 mixture of diastereoisomers.

The final and most recent (formal) synthesis of clavicipitic acid appeared in 1988 and utilises alcohol (87) as an intermediate (Scheme 24). This alcohol is a functional equivalent of 10-hydroxylated DMAT, a compound which has been postulated several times as an intermediate in ergoline biosynthesis.⁷



Scheme 24. Reagents: i, $\text{BrCH}=\text{CMe}_2$, Mg , THF ; ii, Na/Hg , MeOH ; iii, H_2CO , Me_2NH , HOAc ; iv, $\text{H}_2\text{NCH}(\text{CO}_2\text{Me})_2$, $n\text{-Bu}_3\text{P}$, MeCN ; v, TsOH , MeCN .

The chemistry used to prepare the cyclisation precursor has been well used and is discussed in detail earlier in this review. Starting with the now familiar 1-*p*-toluene-

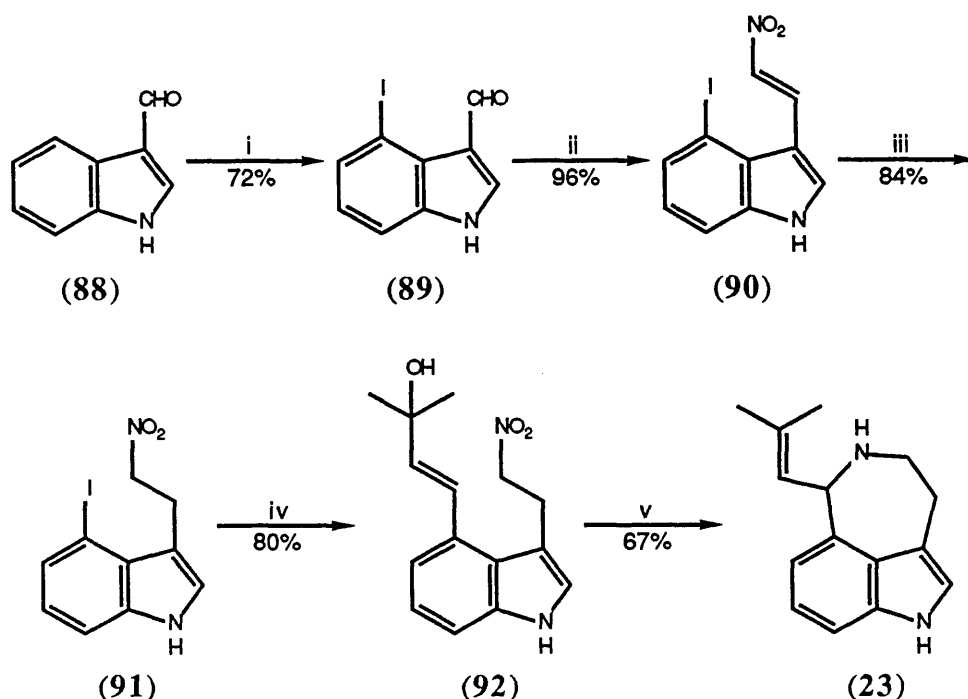
sulphonylindole-4-carboxaldehyde (83), the 2-methyl-1-propenyl group was introduced in 85% yield by means of a Grignard reaction. Virtually quantitative deprotection of the indolic nitrogen was achieved using Trost's buffered amalgam method; gramine formation followed by C-3 side chain elaboration exactly as described in Kozikowski's second synthesis^{76b} (Scheme 19) produced the cyclisation precursor (87). Simple treatment of this with *p*-toluenesulphonic acid in refluxing acetonitrile for 2 h promoted cyclisation to produce azepinoindole (55), which had previously been converted to clavicipitic acid by Kozikowski.^{76b} The presumed intermediate allylic benzylic carbocation is stable enough to allow its intramolecular reaction with any unprotonated amine. This formal synthesis of clavicipitic acid concludes the overview of laboratory syntheses of this compound.

1.4.3.3 Aurantioclavine.

Unlike the many syntheses of clavicipitic acid, the published syntheses of aurantio-clavine are only two in number.^{84a,84b} The first and shorter synthesis achieves 4-functionalisation of indole-3-carboxaldehyde (88) using thallium chemistry,^{70a} which allows the regioselective introduction of iodine into the 4-position (Scheme 25).^{84a} Treatment of indole (88) with thallium trifluoroacetate in trifluoroacetic acid at 25-30°C, followed by copper (I) iodide and iodine in DMF at ambient temperature, produced a 72% yield of the 4-iodinated material (89). Henry reaction of aldehyde (89) with nitromethane in the presence of ammonium acetate afforded the nitrovinyl indole (90) almost quantitatively. Simple reduction of this was achieved with sodium borohydride in the presence of silica gel; the resulting nitroethyl indole (91) was subjected to a Heck reaction with 2-methyl-3-buten-2-ol in DMF at 120°C to produce an 80% yield of the 3,4-disubstituted indole (92). A number of cyclisation conditions for the production of (23) from (92) were investigated, but only with amalgamated zinc in refluxing methanolic hydrochloric acid was this process successful, giving a 67% yield of aurantioclavine. It was suggested by the authors that the cyclisation occurred at the hydroxylamine stage since

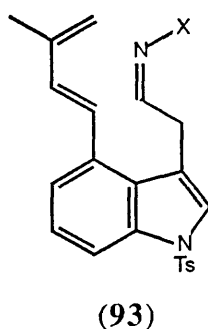
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the unstable hydroxylamine derivative of (23) was isolated after shorter reaction times.



Scheme 25. Reagents: i, (a) $\text{Ti}(\text{OCOCF}_3)_3$, TFA, 25-30°C, (b) I_2 , CuI, DMF, R.T.; ii, MeNO_2 , NH_4OAc ; iii, NaBH_4 , silica gel, *i*-PrOH, CHCl_3 ; iv, $\text{CH}_2=\text{CHC}(\text{Me})_2\text{OH}$, $n\text{-Bu}_4\text{N}^+\text{Br}^-$, $\text{Pd}(\text{OAc})_2$, DMF, 120°C; v, Zn/Hg , 2N HCl, MeOH, reflux.

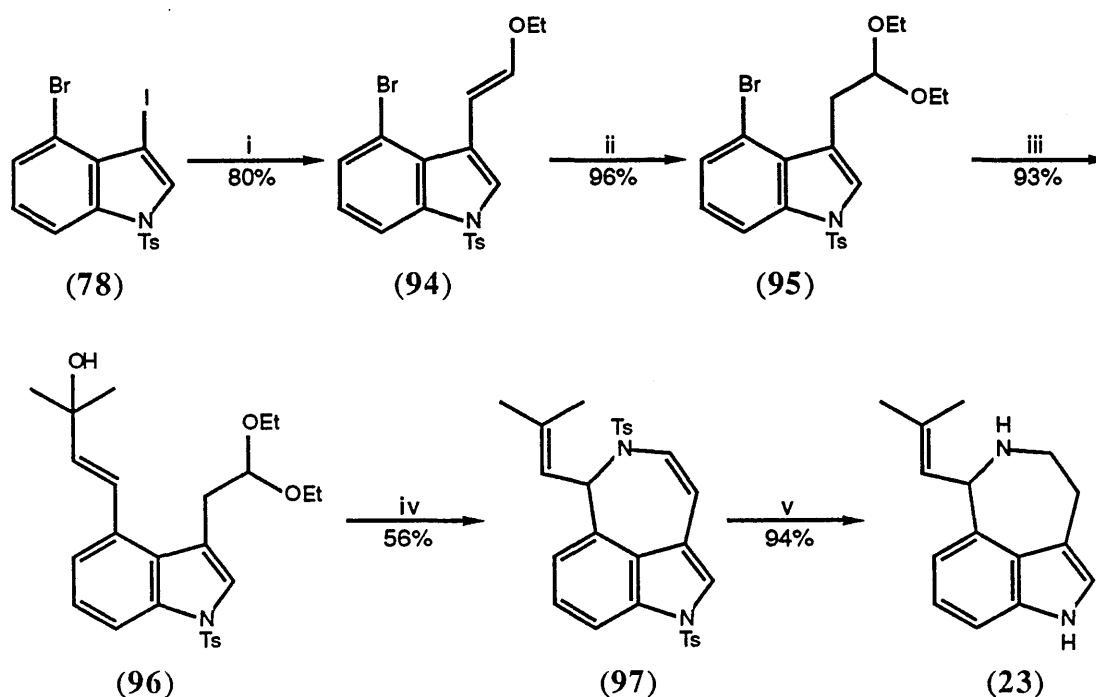
The second synthesis of aurantioclavine, by Hegedus *et al.*, arose largely as a result of an unsuccessful attempted synthesis of the ergoline skeleton.^{84b} This was to have proceeded *via* an intramolecular hetero Diels-Alder reaction of an imine-diene such as (93).



Unfortunately, it was found that when $\text{X}=\text{OMe}$, cyclisation would not occur, but when

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X was more electron withdrawing (benzyloxycarbonyl or *p*-toluenesulphonyl, for example) an alternative cyclisation, to form an azepine ring, proceeded exclusively (Scheme 26). However, this apparent failure was turned into a successful synthesis of aurantio-clavine.



Scheme 26. Reagents: **i**, $\text{Cp}_2\text{Zr}(\text{Cl})\text{CH}=\text{CH}(\text{OEt})$, $\text{Ni}(\text{Ph}_3\text{P})_4$, THF; **ii**, (a) $\text{BBr}_3 \cdot \text{SMe}_2$, DCM, (b) EtOH, NaHCO_3 ; **iii**, $\text{CH}_2=\text{CHC}(\text{Me})_2\text{OH}$, $\text{Pd}(\text{OAc})_2$, (*o*-Tol) $_3\text{P}$, Et_3N , MeCN; **iv**, TsNH_2 , TsOH , MeCN, 90°C ; **v**, NaBH_4 , hv, MeOH/DME/ H_2O (4:2:1).

The preparation of dihaloindole (78) by Hegedus *et al.* has already been discussed, since it was a key intermediate for their synthesis of clavicipitic acid (Scheme 23). Formation of the enol ether (94) from this proved troublesome, nickel (0)-catalysed oxidative addition-transmetallation from zirconium being required to achieve satisfactory yields (80%). Hydrolysis of (94) was generally sluggish, but the use of boron tribromide-dimethyl sulphide complex circumvented this problem. The resulting sensitive aldehyde was immediately converted to its diethyl acetal (95) in overall 96% yield. The tertiary allylic alcohol side chain was efficiently introduced under standard conditions, forming the pre-cyclisation intermediate (96). Condensation of this with *p*-toluenesulphonamide in the

presence of *p*-toluenesulphonic acid afforded a moderate yield (56%) of the dihydroazepinoindole derivative (97). It was suggested that this cyclisation occurred due to acid-catalysed *N*-alkylation of the (presumed) intermediate enamine by the tertiary allylic alcohol, probably *via* the delocalised allylic-benzylic cation. Borohydride reduction of (97) under photolytic conditions as used previously by these authors gave a 94% yield of aurantioclavine.

1.4.3.4 Summary.

Of the nine azepinoindole syntheses described above, two start with an indole which is not substituted in the 4-position, and only one of these succeeds in a direct cyclisation to that position, illustrating the noticeable gap in indole synthetic methodology. However, with suitably designed starting materials, this difficulty can usually be overcome. Palladium chemistry usually enables both the 3- and 4-substituents to be introduced intact, as two complete units. On the other hand, the use of compounds such as the important indole-4-carboxaldehyde has proved immensely useful in syntheses of this kind. The remainder of the 4-substituent is easily introduced using the versatile aldehyde functionality, and then the C-3 side chain can be added using standard gramine chemistry. These methods have been developed by necessity in order to circumvent rather than confront the difficulty of 4-functionalisation of indoles.

1.5 Conclusion

The clavine alkaloids have kept both chemists and biochemists busy for the last 30 years. Much is now known about their biosynthesis and also about efficient laboratory routes for their synthesis. As even more information about their biosynthesis emerges, doubtless many other chemical possibilities, both synthetic targets and methodology, will be revealed. This, together with their pharmaceutical potential, will ensure that interest in the clavine alkaloids will stay alive for years to come.

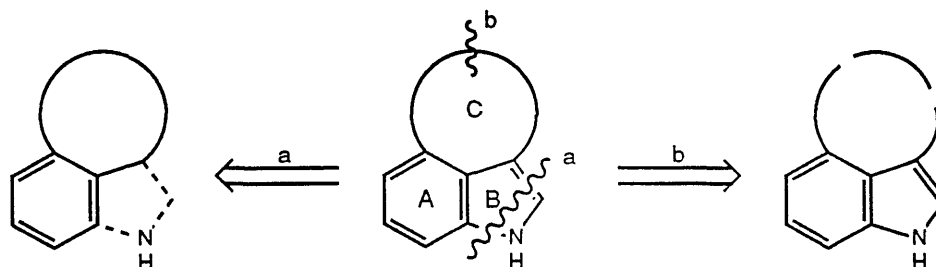
TWO

Nitrenes in Indole Synthesis

2.1 Introduction

The indole ring system is remarkably common in Nature, occurring in a wide variety of alkaloids, such as the aforementioned ergots and clavines, the hapalindoles,⁸⁵ and the trikentrins.⁸⁶ Of these, the $[cd]$ -fused compounds, which contain a bridge between the 3- and 4-positions, are the most common and most challenging synthetically. The preceding review illustrates how the $[cd]$ -ring systems are usually built up from a 3,4-disubstituted indole, which in turn is often prepared from a 4-substituted indole precursor. However, alternative strategies are possible, and it is the aim of this Chapter to detail the results of another approach to this class of indole.

To accomplish the synthesis of a $[cd]$ -fused indole system, it is necessary to form a number of carbon-carbon or carbon-nitrogen bonds. A brief retrosynthetic analysis presents us with several possibilities (Scheme 27).

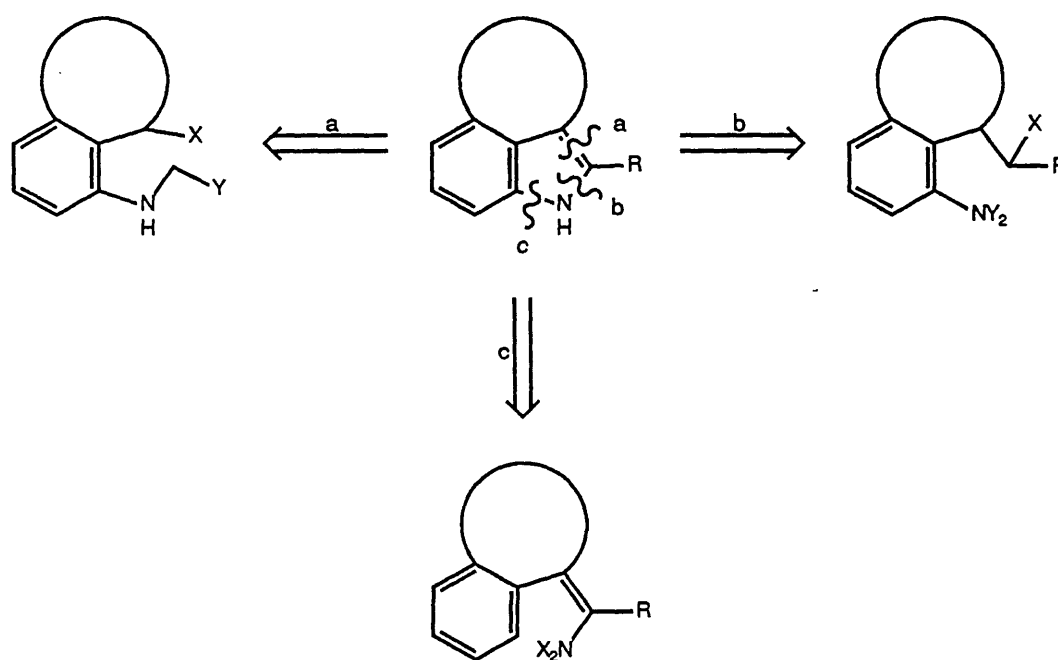


Scheme 27

Since disconnection of the benzene ring would leave a suitably functionalised 3,4-bridged pyrrole as a rather difficult synthetic target, effectively the problem is reduced to

the synthesis of either the pyrrole ring (a, Scheme 27), or the 3,4-bridging ring (b) from suitable bicyclic precursors. This Chapter is concerned with disconnection (a).

Formation of the pyrrole ring onto the bicyclic starting material leaves a choice of three bonds to form during the ring-closure step (Scheme 28). A closer look at the options available soon reveals that classical indole syntheses, such as the Fischer or Bischler methods,⁸⁷ are largely unsuitable for the preparation of these compounds due to the inaccessibility of the precursors.



Scheme 28

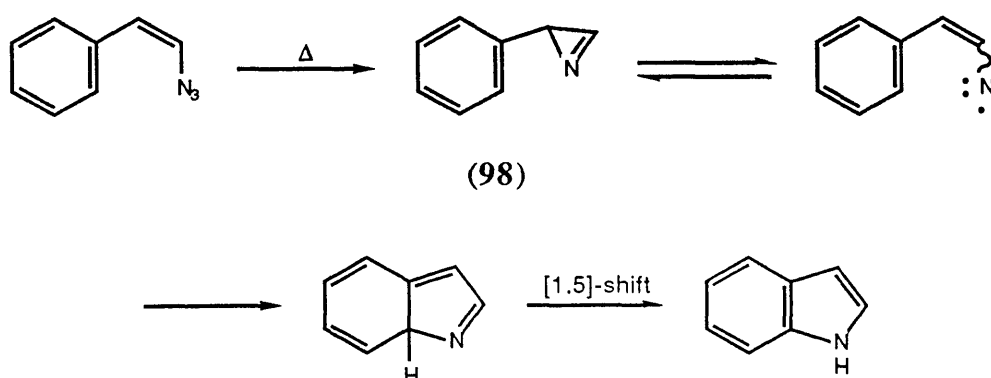
Disconnection (a) is of limited use, again due to the inaccessibility of the intermediates. Modifications of procedures such as the Leimgruber-Batcho^{74a-e} or Reissert^{74f} syntheses could be suitable for the second disconnection ((b), Scheme 28), although again the requisite functionalised bicyclic precursor would be the product of an extensive synthetic process. The third option, (c), described now, takes the rather unusual step of forming the benzene-nitrogen bond during the cyclisation process. One of the very few ways this can be readily achieved is by the use of vinyl nitrenes which in turn can be generated from vinyl

azides; there are numerous examples of this type of process applied to the synthesis of other types of indoles.

2.2 Background

The production of indoles by the thermolysis of azides was first reported by Smolinsky and Pryde in 1968,⁸⁸ and stemmed from an investigation of the formation of azirines from vinyl azides.⁸⁹ It was found that the thermolysis of 'terminal' vinyl azides, *i.e.* azidomethylene compounds, gave rise to, amongst other things, indoles. However, 'internal' vinyl azides consistently produced azirines in good yield.

Since this pioneering work, the results of a number of investigations into both the mechanism^{90a} of the reaction and the synthesis^{90b} of the vinyl azides have been reported. Although alternative mechanisms, such as a concerted process⁸⁸ or the intermediacy of a triazole⁸⁹ have been suggested, more recent studies indicate that a vinyl nitrene is the most likely intermediate.^{90a} Evidence in support of nitrene intermediates includes their successful generation from sources other than azides^{89,91a} and experiments where the intermediate nitrene was trapped as a phosphinimine.^{91b,c}



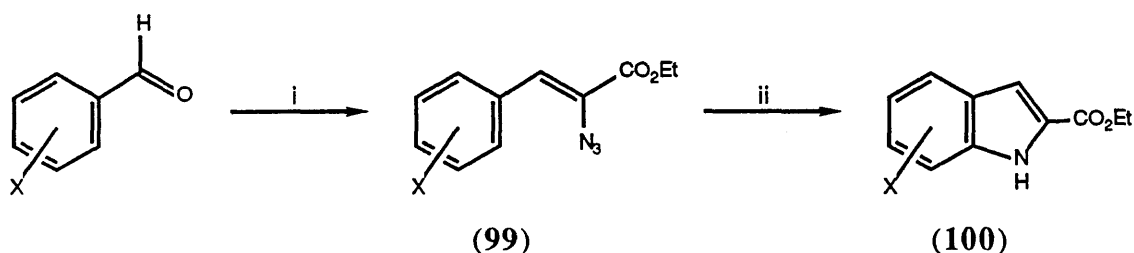
Scheme 29

The vinyl nitrene is in thermal equilibrium with an azirine (98), which provides a mechanism for *cis-trans* isomerisation of the vinylic bond; consequently the geometry of

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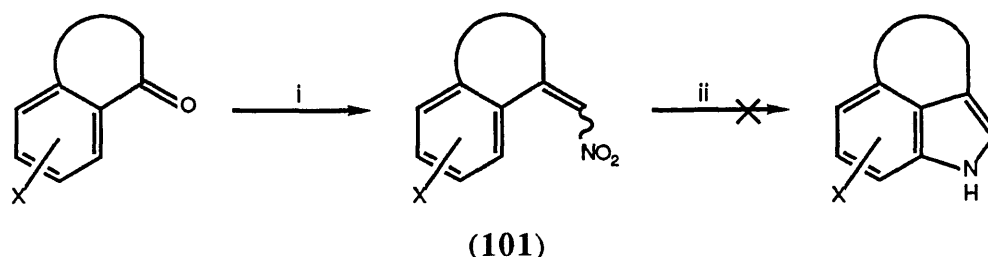
the vinyl azide is unimportant. Indole formation probably occurs *via* electrocyclicisation of the vinyl nitrene, followed by a [1,5]-hydrogen shift to achieve aromatisation, rather than a direct insertion into the *ortho*-C–H bond (Scheme 29).

The variety of methods available for synthesising the vinyl azides has increased dramatically over the years.^{90b} A major contribution was the discovery, in the early 1970's, that benzaldehydes undergo condensation with methyl or ethyl azidoacetate in the presence of the corresponding sodium alkoxide (Scheme 30).⁹² The resulting α -azido-cinnamates (**99**) readily undergo the thermolytic cyclisation to produce good yields of indole-2-carboxylates (**100**), provided that *ortho*-substituents which can interact with the vinyl nitrene are not present. This azidocinnamate methodology has been used to great effect in the synthesis of a number of indolic natural products.⁹³



Scheme 30. Reagents: i, $\text{EtO}_2\text{CCH}_2\text{N}_3$, NaOEt , EtOH , -15°C ; ii, toluene or xylene, reflux.

As mentioned earlier, nitrenes can be generated from sources other than azides. For example, isoxazoles^{91a} and aryl nitro compounds⁹⁴ have both been used as sources of nitrenes, the former by thermal or photochemical decomposition and the latter by deoxygenation using, for example, triethyl phosphite. Unfortunately, however, the readily-available vinyl nitro compounds (**101**) do not lend themselves as easily to this procedure, since their deoxygenation does not produce useful yields of indoles.⁹⁵ Consequently, the rapid, two-step synthesis of [cd]-fused indoles shown in Scheme 31 is doomed to failure in the last step. Therefore, an azide precursor of the vinyl nitrene seems the most attractive prospect.



Scheme 31. Reagents: i, $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ cat., CH_3NO_2 , reflux; ii, $(\text{EtO})_3\text{P}$, Δ .

2.3 Nitrene methodology in [cd]-fused indole synthesis

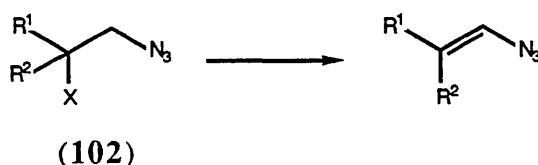
2.3.1 Introduction.

At first sight, the azidocinnamate methodology might be expected to be applicable to the synthesis of [cd]-fused indoles. However, the presence of the strong base during the condensation severely limits the generality of this reaction, due to problems associated with enolisation and self-condensation of the carbonyl substrate. The situation is further complicated by the instability of the ethyl azidoacetate anion, which can only be generated *in situ*, in the presence of the carbonyl substrate. It is found, as is common with such reactions, that the structure of the carbonyl component is restricted to one in which α -protons are absent—an aromatic aldehyde, for example. Whilst this is perfectly satisfactory for the synthesis of indoles *unsubstituted* at the 3-position, an extension of Scheme 30 to the preparation of [cd]-fused indoles would start from an aromatic ketone. This would generally contain protons α to the carbonyl group, and is therefore unsuitable for the reaction. In view of this, an alternative method of synthesising vinyl azides is required.

The preparative methods for the synthesis of vinyl azides are well established,^{90a,b} and fall into three categories. The first, introduction of the azide function onto an existing double bond, includes addition of hydrazoic acid to alkenes and vinylic substitution of vinyl halides. Since simple vinyl halides are extremely resistant to nucleophilic substitution, even with good nucleophiles such as azide ion, the success of the latter reaction requires the presence of an electron-withdrawing (*e.g.* ester, ketone, sulphone, cyanide

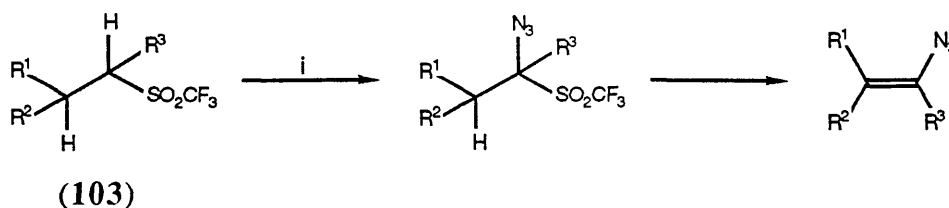
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or nitro) group at the β -carbon and a good leaving group at the α -position.^{90a} This greatly reduces the generality and consequently the applicability of this method to the present project. A second method, formation of the carbon-carbon double bond in the presence of the azide function, is probably the most reliable and general method of vinyl azide synthesis available. The process involves elimination of HX from a (usually) β -substituted azide (102) (Scheme 32); these compounds can be prepared by a variety of methods including addition of the extremely hazardous halogen azides to alkenes ($X=\text{Halide}$), ring-opening of epoxides with azide ion ($X=\text{OH}$), or from β -hydroxyalkyl azides ($X=\text{OH}$). The latter compounds are readily derived from α -bromocarbonyl compounds *via* displacement of bromide and borohydride reduction of the carbonyl group.

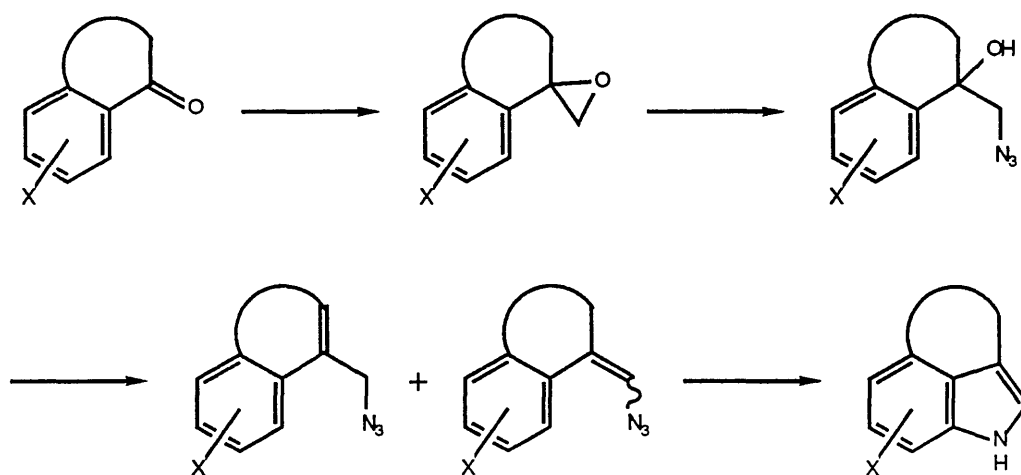


Scheme 32

The third, and possibly the least widely applicable synthesis of vinyl azides achieves the simultaneous introduction of the double bond and the azide group. Probably the most versatile example of this process makes use of the acidic α -hydrogen found in trifluoromethyl sulphones (103); this is removed with sodium hydride and the resulting anion quenched with *p*-toluenesulphonyl azide. Elimination of trifluoromethyl sulphinic acid produces the vinyl azide (Scheme 33).

Scheme 33. Reagents: i, NaH, TsN₃.

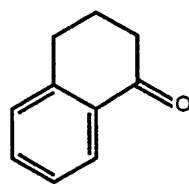
An examination of these syntheses soon reveals that the options open for the present problem are somewhat limited. An obvious requirement is that the precursors of the vinyl azides must be easily prepared, from readily available starting materials—this discounts a large number of the possibilities presented above. Since bi- or tri-cyclic aromatic ketones are readily available, they could be used to advantage in the present situation. All that is then required is a method of introducing a C-1 unit and the azide functionality. An obvious possibility therefore presents itself—the ketone can readily be converted to an epoxide, which introduces the C-1 unit; ring-opening of this with azide ion introduces the nitrogen atoms *and* produces an intermediate which should be easily dehydrated to the vinyl azide. Although two double bond regioisomers are possible, one *exo*- and the other *endo*-cyclic, it will be seen later that this did not usually present a problem since both isomers were readily separable. This formed the basis of a general reaction scheme (Scheme 34) which was to be applied to a number of starting materials.



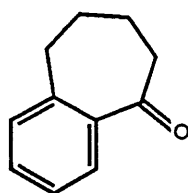
Scheme 34

A wide range of both commercially available and easily prepared aromatic ketones was chosen for investigation; these are shown in Figure 4.

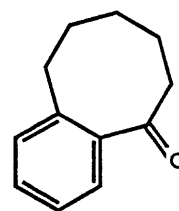
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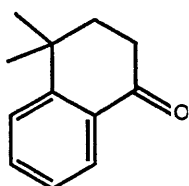
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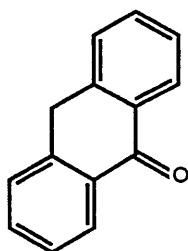
(105)



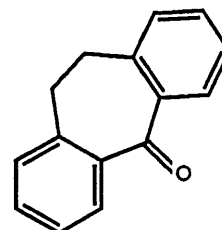
(106)



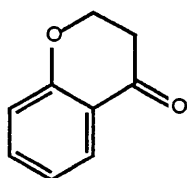
(107)



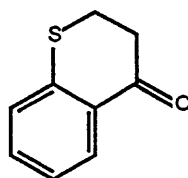
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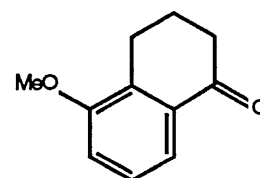
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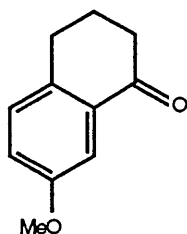
(110)



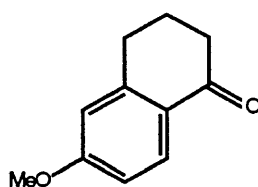
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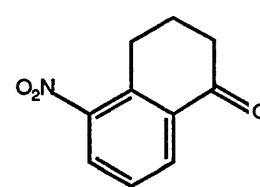
(112)



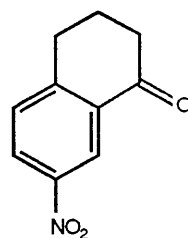
(113)



(114)



(115)

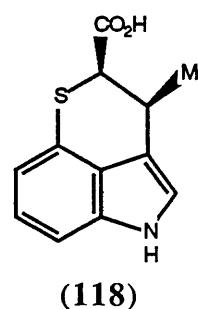
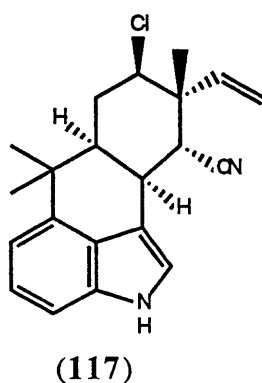


(116)

Figure 4

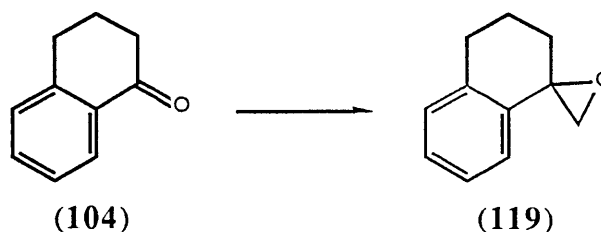
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The choice of starting materials was not entirely random—all of the ketones had to be readily available, but more importantly the examples should give as much information as possible about the feasibility of the Scheme, particularly regarding its possible application to the synthesis of natural product targets such as clavine alkaloids, the hapalindoles (*e.g.* (117)), and the antibiotic chuangxinmycin (118). Hence, some examples were chosen which would lead to [cd]-fused indole ring systems similar to those found in Nature.



2.3.2 Preparation of epoxides.

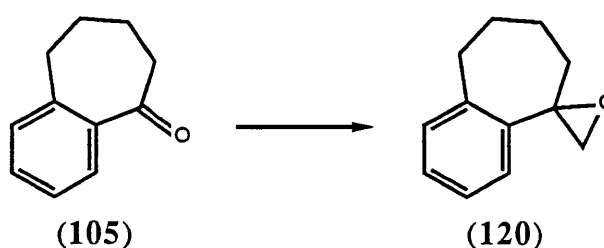
The conversion of ketones to epoxides by treatment with sulphur ylides has become a standard process since its discovery in 1965 by E. J. Corey *et al.*,⁹⁶ so it was logical to choose this reaction in order to effect the first transformation in Scheme 34. In order to start the investigation of the Scheme on a sound footing, α -tetralone was chosen as the first starting material, since its conversion into epoxide (119) has already been reported.⁹⁷



Dimethylsulphoxonium methylide⁹⁸ was readily prepared by the careful addition of dry DMSO to a slurry of trimethylsulphoxonium iodide and sodium hydride under nitrogen. Addition of α -tetralone (104) to the ylide slurry, followed by warming to not greater than

55°C overnight, resulted in the formation of a red-brown mixture from which a 65% yield of epoxide (**119**) could be isolated by standard extraction and purification techniques. The reaction was repeated five times, but the reported⁹⁷ 98% yield could never be reproduced.

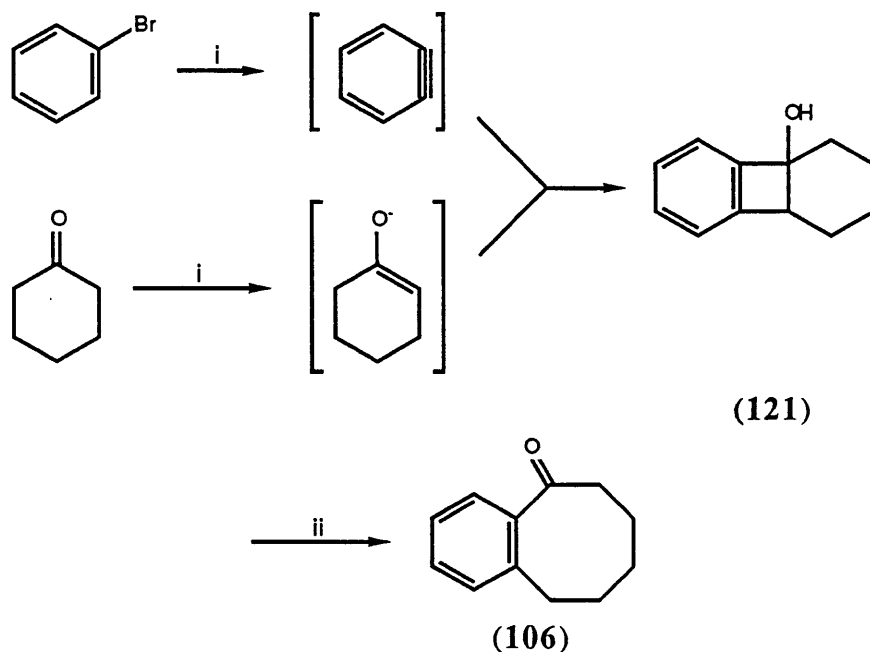
In order to investigate the effect of ring-size on the reactions, it had been decided to employ commercially available 1-benzosuberone and easily prepared benzocyclo-octanone⁹⁹ as starting materials. In an exactly analogous fashion to α -tetralone, epoxide (**120**) was prepared in 89% yield from 1-benzosuberone (**105**).



The preparation of the eight-membered cyclic ketone (**106**) has been reported several times in the literature. The most convenient method appeared to be that first described by Corbere¹⁰⁰ and later modified by Thies *et al.*,⁹⁹ which involved the condensation of benzyne with the enolate of cyclohexanone to give the intermediate alcohol (**121**); treatment of this with strong base facilitates ring expansion to ketone (**106**) (Scheme 35). However, in our hands it proved possible to simplify the process even further, and this is worthy of some comment.

The literature procedure⁹⁹ for the preparation of tricyclic alcohol (**121**) was followed up to the purification step. The published method stated that most of the excess cyclohexanone was removed by distillation at reduced pressure, followed by treatment of the crude solid with Girard's reagent T to completely remove the ketones. Standard separation techniques, followed by recrystallisation from hexane, were reported to give a 15% yield of alcohol (**121**).

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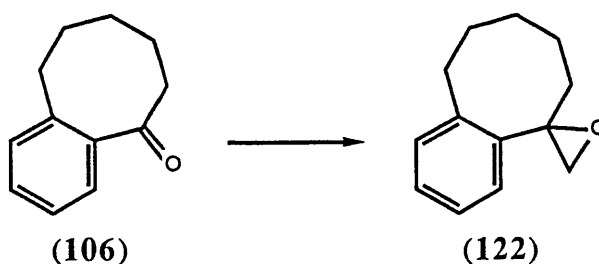


Scheme 35. Reagents: i, NaNH₂, THF, -5°C; ii, KH, hexane, THF.

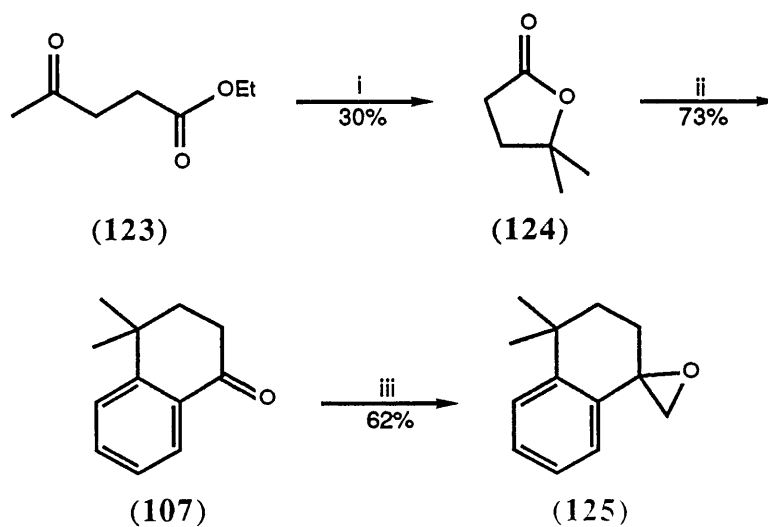
The simplified version of this procedure achieved removal of the excess cyclohexanone from the crude product by evaporation at reduced pressure to leave a pale yellow solid. This was not treated with Girard's reagent, but instead recrystallisation from petrol gave a crop of alcohol (121), whilst recrystallisation of the evaporated filtrate gave *directly* ketone (106). It was pleasing to note that the combined yield of (106) and (121) was significantly higher than quoted in the literature. The *in situ* conversion of some of alcohol (121) to ketone (106) is obviously due to the excess sodamide present in the reaction mixture, and probably also occurred during the reported literature preparation. It is ironic that the steps in the literature method designed to facilitate purification, namely the use of Girard's reagent, actually waste a significant quantity of product.

With useful quantities of benzocyclo-octanone in hand, the epoxide (122) could be prepared. This time, however, use of the more reactive dimethylsulphonium methylide⁹⁶ in DMSO/THF provided a more satisfactory yield of epoxide (122), although this was still only 52%.

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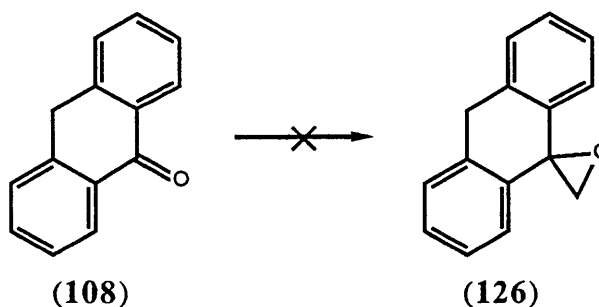
The effect of both aryl and alkyl substituents around the saturated ring was investigated using 4,4-dimethyl-1-tetralone¹⁰¹ (107), anthrone (108), and dibenzosuberone (109). Ketone (107) was prepared according to the procedure of Arnold *et al.* (Scheme 36).¹⁰¹ Treatment of an ether/benzene solution of ethyl levulinate (123) with methylmagnesium iodide produced an intermediate γ -hydroxy ester which readily lactonised to (124) upon treatment with acid. Friedel-Crafts reaction of lactone (124) with benzene gave a 73% yield of ketone (107). Reaction of this with dimethylsulphoxonium methylide under the same conditions as for α -tetralone produced epoxide (125) in 62% yield.



Scheme 36. *Reagents:* i, (a) MeMgI, C₆H₆/Et₂O, (b) dil. H₂SO₄, (c) 50% H₂SO₄; ii, AlCl₃, C₆H₆, 5°C→reflux; iii, Me₃S⁺O.I⁻, NaH, DMSO, 5°C→55°C.

The preparation of epoxide (126) from anthrone (108) met with great difficulties which eventually proved insurmountable.

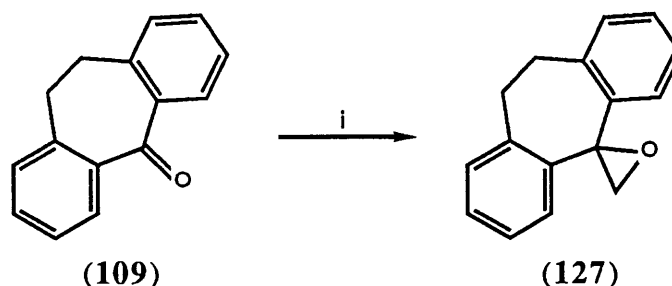
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Reaction of (108) with the sulfoxonium ylide under the usual conditions resulted in the isolation of starting material only. Use of the more reactive sulphonium ylide produced the same result. The problem was thought to be due to the ready enolisation of the anthrone, the ylide serving as a base producing an enolate which, of course, would be inert to condensation. The generation of ylides under reversible conditions is reported to overcome problems with the enolisation of the carbonyl substrate.¹⁰² Accordingly, both the sulphonium and sulfoxonium ylides were prepared in an aqueous system under phase transfer catalysed conditions, with tetra-*n*-butylammonium iodide as the catalyst.¹⁰³ Again, however, only starting material was recovered. At this stage it was becoming clear that epoxide (126) was unlikely to be obtained using sulphur ylide chemistry, so an alternative method was sought. At about this time a paper, describing the synthesis of epoxides from carbonyl compounds, bromochloromethane, and lithium metal under sonochemical conditions, appeared in the literature.¹⁰⁴ Since this seemed to be a mild method, it was decided to apply it to the present problem. Whilst repetition of the procedure on acetophenone gave similar results to those reported, the synthesis of (126) could not be achieved using this reaction. At this point, it was therefore decided to abandon the investigation of anthrone.

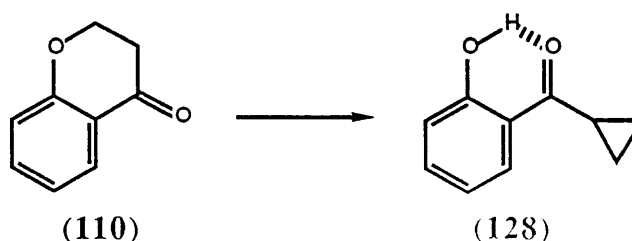
Epoxide (127), derived from dibenzosuberone (109), was described in a patent some 15 years ago.¹⁰⁵ However, its reported preparation using dimethylsulphoxonium methylide could not be reproduced, starting material being the only compound isolated. Fortunately, the difficulty was overcome by the use of the more reactive sulphonium ylide,

which gave a 90% yield of epoxide (127) (Scheme 37).



Scheme 37. *Reagents:* i, $\text{Me}_3\text{S}^+\text{I}^-$, NaH, DMSO/THF, $0^\circ\text{C} \rightarrow 20^\circ\text{C}$.

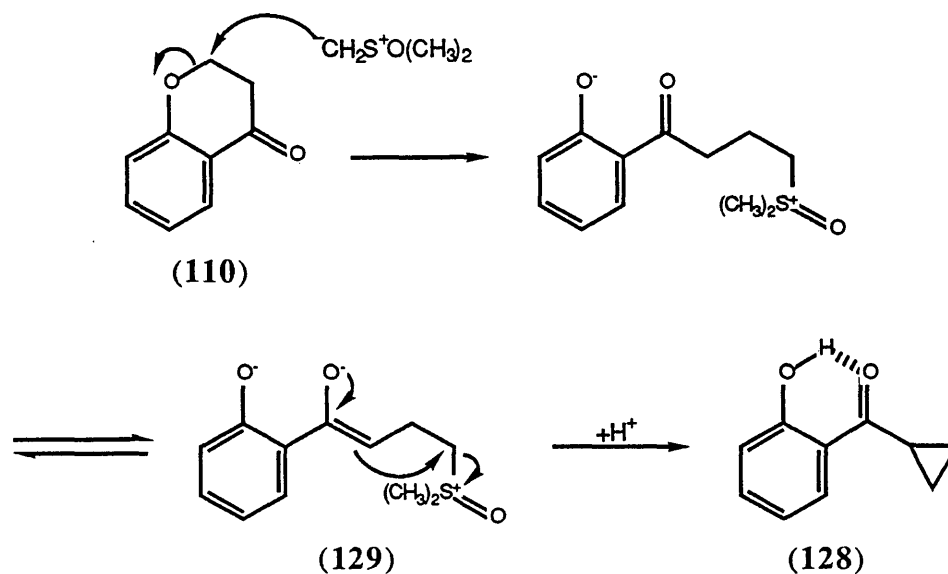
Another variable which it was hoped to investigate was the effect of placing a heteroatom such as oxygen or sulphur in the saturated ring. To this end, the application of the Scheme to chroman-4-one (110) and thiochroman-4-one (111) was to be an interesting extension of the methodology. Chroman-4-one, when reacted with the sulfoxonium ylide, failed to produce the epoxide—instead cyclopropyl ketone (128) was isolated in 29% yield. The structure of (128) follows from its spectra—the IR spectrum clearly shows the presence of a hydrogen-bonded carbonyl stretch at 1635 cm^{-1} , while the NMR spectrum contains high field cyclopropyl protons at $\delta\ 1.04\text{--}1.13\text{ ppm}$ and a low field hydrogen-bonded proton at $\delta\ 12.50\text{ ppm}$.



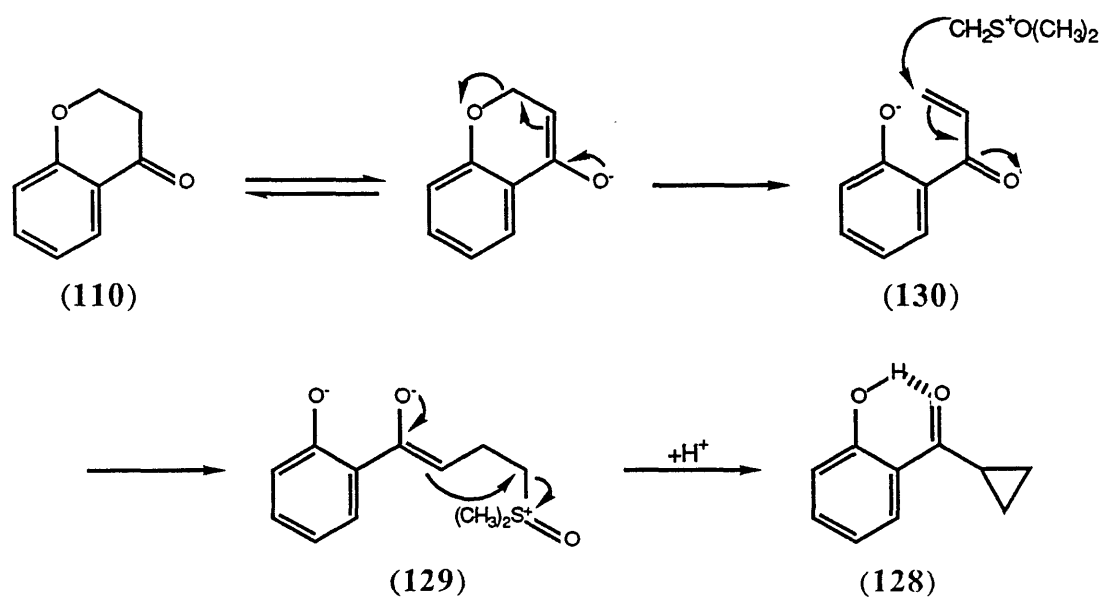
The mechanistic rationale for the formation of (128) consists of two possibilities, shown in Scheme 38.

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A:



B:



Scheme 38

It will be seen that both mechanisms proceed *via* the same intermediate (129), the derivation of which is the only difference between the two processes. In the first (Scheme 38, A), (129) is produced as a result of attack of the ylide on C-2, whilst in the second (Scheme 38, B) (129) is formed by Michael addition of the ylide to the ring-opened product derived from the enol form of (110). Sulphonium ylides react with α,β -un-

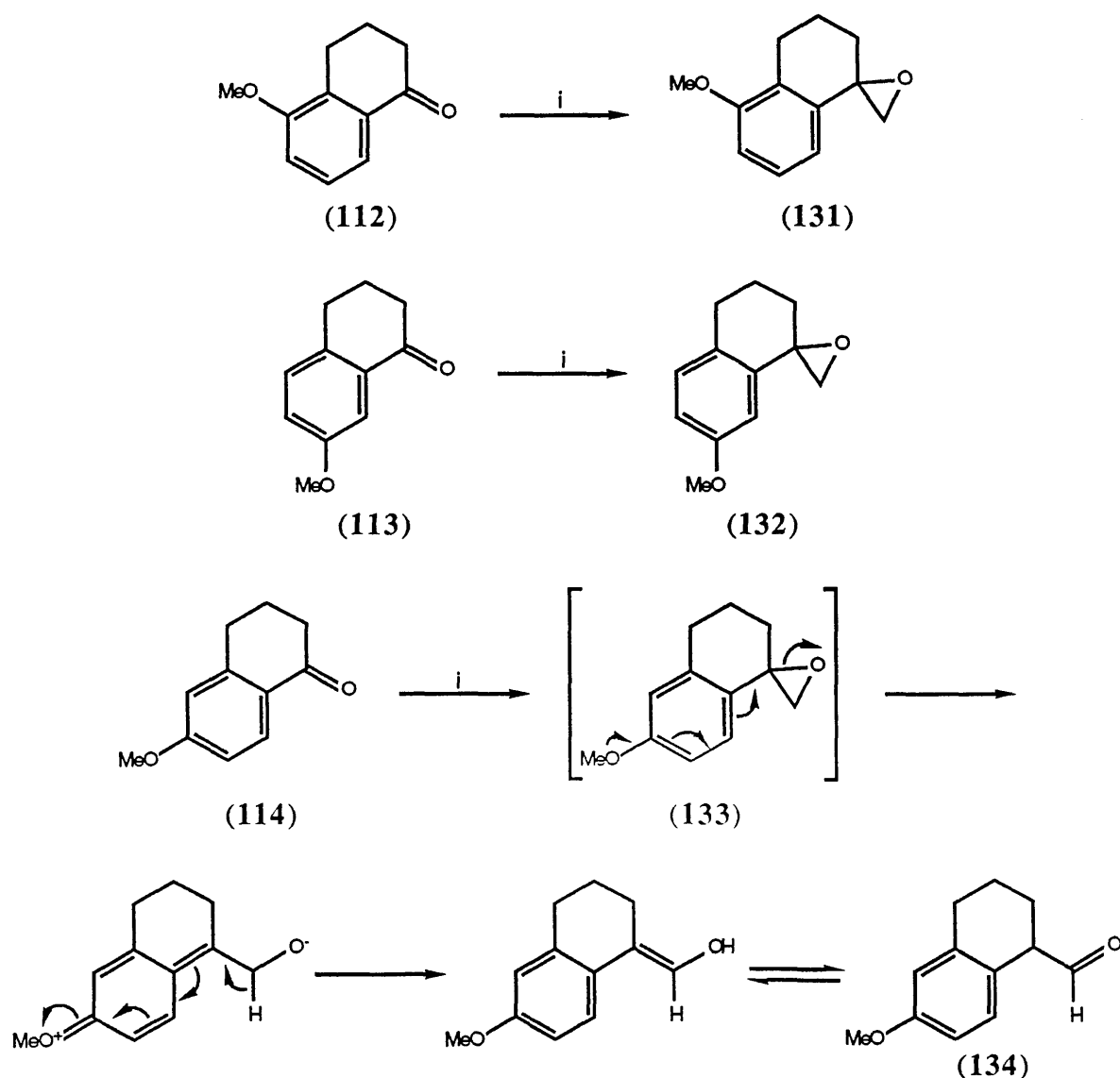
saturated carbonyl compounds exclusively at the carbonyl carbon to form epoxides and not in a Michael fashion to form cyclopropanes, whereas sulfoxonium ylides preferentially undergo Michael addition, producing cyclopropyl compounds.¹⁰² Therefore, if mechanism B in Scheme 38 is operating, the use of the sulphonium ylide might be expected to produce the epoxide derivative of enone (130). In practice, the use of dimethylsulphonium methylide made little change to the outcome of the reaction, and (128) was still isolated. Treatment of (110) with base under the same conditions, followed by aqueous work-up, produced only starting material and no trace of (protonated) (130). This, together with the result of the sulphonium ylide reaction, suggests that mechanism A is most likely, although the failure to isolate (130) under the conditions described would be expected if its formation from (110) was a reversible process.

Although of no synthetic value for the present purpose, the unexpected outcome of this reaction was rather interesting. It was soon found that the process had a number of literature precedents, for example with flavanones,^{106a} dihydroquinol-4-ones,^{106b} and thiochroman-4-ones.^{106c} The last example was of particular concern, since it meant that the attempted reaction with thiochroman-4-one (111) would probably be unsuccessful—indeed this was found to be the case. Furthermore, the attempted preparation of the epoxide from (110) using the variety of other conditions tried for anthrone, including phase transfer catalysis and the sonochemical method, proved unsuccessful. For this reason, it was concluded that the Scheme was limited to compounds *without* heteroatoms adjacent to the benzene ring, in the saturated ring.

Having chosen examples with varying substituents on, and sizes of, saturated ring, it seemed logical to investigate examples of starting materials bearing substituents around the benzene ring. The only commercially available α -tetralones substituted on the aromatic ring are the 5-, 6-, and 7-methoxy compounds. The reaction of each of these with sulphur ylides has been described,¹⁰⁷ but in all cases it was reported that the epoxides readily rearranged to the corresponding acetaldehyde derivatives,^{107b} resulting in the isolation of

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

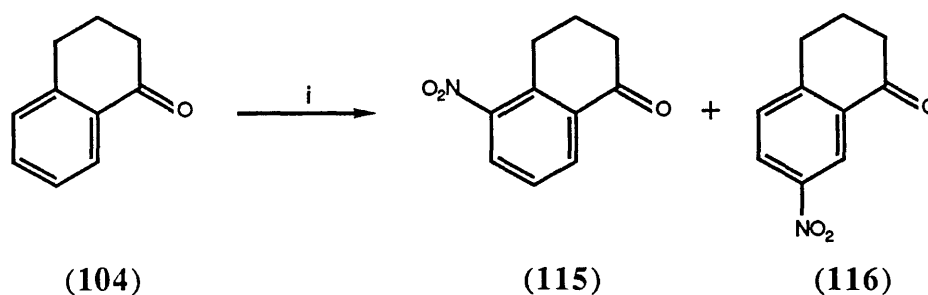
low yields of the epoxides (*ca.* 5%), together with other rearrangement products. The reason for the rearrangement of 6-methoxy-1-tetralone is obviously due to the electron releasing methoxy group *para* to the carbon atom bearing the epoxide, but the reason for the same rearrangement occurring with the 5- and 7-substituted compounds is less clear. It was therefore decided that the attempted preparation of epoxides (131) and (132) would be worthwhile, especially since the eventual cyclisation of the vinyl nitrene onto the electron-rich aromatic ring would hopefully proceed in high yield. Careful application of the standard sulfoxonium ylide conditions to tetralones (112) and (113) produced epoxides (131) and (132) in 59 and 48% yield, respectively.



Scheme 39. Reagents: *i*, Me₃S⁺O.I⁻, NaH, DMSO, 5°C→55°C.

To confirm the published observations regarding the 6-methoxy compound (114), the ylide reaction was performed as usual. Several products were obtained, including a significant quantity of aldehyde (134), but no trace of epoxide (133) was observed (Scheme 39).

The effect of an electron-withdrawing group on the cyclisation step would also be of interest. Possibly the simplest such group to put in place is the nitro group. Although at the time of the present work an effective direct nitration of α -tetralone had not been described, a more recent paper does report such a transformation.¹⁰⁸ Treatment of α -tetralone (104) with a mixture of fuming nitric acid and concentrated sulphuric acid produced a small but usable yield (29%) of an approximately 1:3 mixture of 5- and 7-nitrotetralones (115) and (116) respectively, which could be easily separated by column chromatography (Scheme 40). The exact substitution pattern, although predictable, was confirmed from the NMR spectra by an examination of the splitting patterns, and also by n.O.e. experiments.

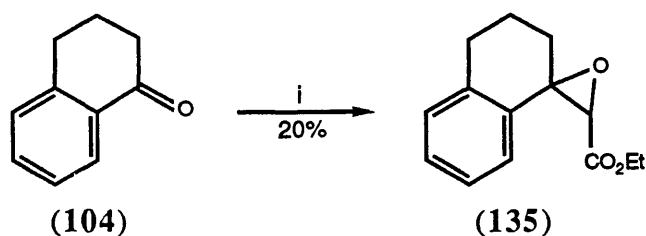


Scheme 40. Reagents: i, $\text{HNO}_3/\text{H}_2\text{SO}_4$, 0°C .

Unfortunately, attempted preparation of the epoxides from (115) and (116) using either the sulphonium or the sulfoxonium ylides at a variety of temperatures and dilutions resulted only in the formation of tars, and not the required epoxides. It is possible that the presence of the nitro group activated the benzylic protons in (115) and (116), so that self-condensation and polymerisation could occur, but this is only speculative. Possibly the use of phase transfer conditions would help to remedy the problem, but this was not investi-

gated.

The last compound to be investigated was the glycidic ester (135) derived from α -tetralone by means of the Darzens reaction (Scheme 41).¹⁰⁹



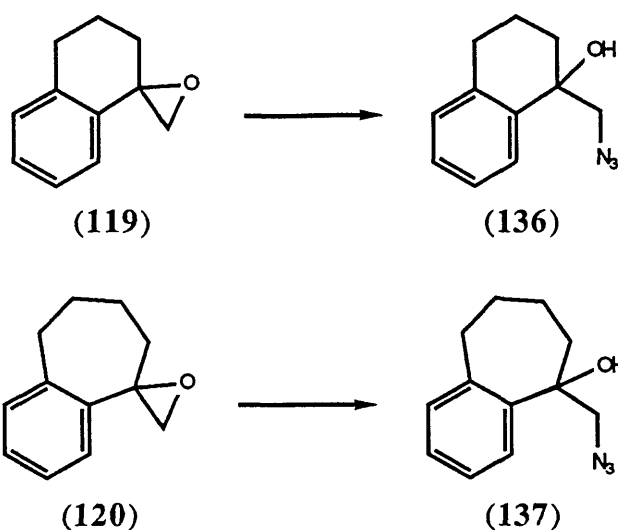
Scheme 41. Reagents: i, $\text{ClCH}_2\text{CO}_2\text{Et}$, NaOEt , EtOH , -5°C .

Although a mere 20% yield of (135) was obtained, this was sufficient for subsequent reactions. This would hopefully give some information regarding the effect of an electron-withdrawing group attached to the epoxide, and provide a route to [cd]-fused indole-2-carboxylates which was complementary to the azidocinnamate methodology. Furthermore, the dehydration of the α -hydroxy azide, which would hopefully be derived from (135), should proceed such that the olefinic double bond is in conjugation with the ester group, thus favouring the required unsaturated azide.

2.3.3 Introduction of azide.

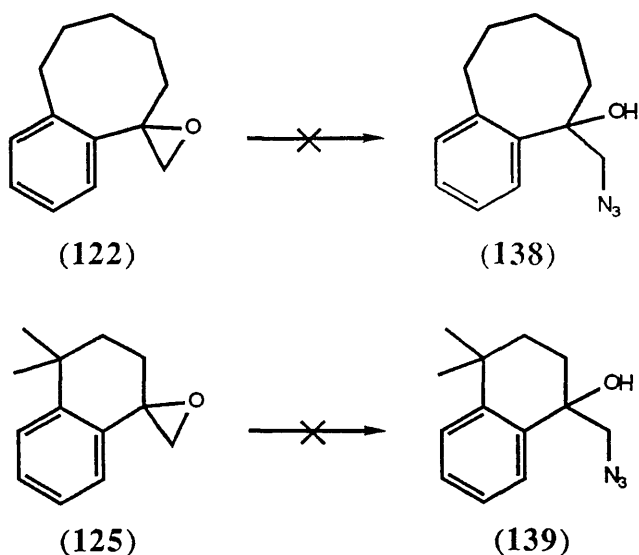
In view of the mass of literature regarding the reaction of azide ion with epoxides,¹¹⁰ the second step of Scheme 34 certainly had good precedent. However, in practice, this transformation often proved difficult to achieve. The first two epoxide examples, (119) and (120), could be converted to the corresponding α -hydroxy azides (136) and (137) in 53 and 71% yield, respectively, by treatment with a mixture of sodium azide and *anhydrous* lithium chloride in hot DMF. Epoxide (119) was found to undergo the reaction at 65°C for 15 h, whereas epoxide (120) required both a longer reaction time and a higher temperature, although the maximum temperature was kept to 100°C for fear of decomposing the potentially unstable product.

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The presence of the lithium chloride seems crucial for the success of the reaction, since without it (119) repeatedly failed to react. The reaction presumably proceeds *via* lithium azide which would be produced *in situ*—its advantages are two-fold. Firstly, it is noticeably more soluble in DMF than is sodium azide, and secondly the lithium cation probably co-ordinates to the epoxide oxygen. Other counter-ions had previously been investigated for a similar reaction,¹¹¹ but lithium was found to be superior. Stronger Lewis acids were thought to be unsuitable, since they would be expected to facilitate ring-opening in an S_N1 -fashion, resulting in the incorrect regiochemistry.

The problem was not so easily solved in the case of epoxides (122) and (125).



Reaction under conditions similar to those for (119) and (120) resulted in the isolation of starting material only. Reports in the literature describe the use of a variety of other solvents for nucleophilic attack on epoxides, so water,^{112a} aqueous dioxane,^{112b} aqueous acetone,^{112c} DMSO,^{112d} and methanol⁸⁸ were all tried, without success. Prolonged reaction times (*ca.* 5 days) resulted in significant decomposition.

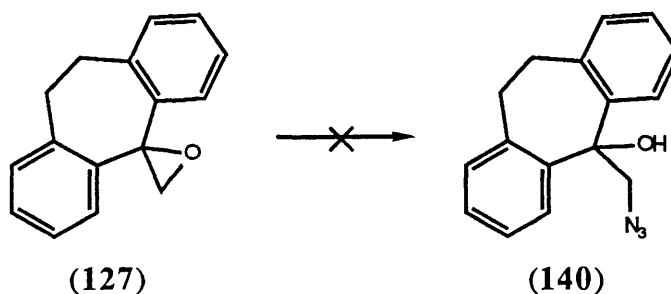


Table 1. Reaction of epoxide (127) with nucleophiles.

reagent	solvent	temp./°C	time/h	result	reference
NaN ₃ /LiCl	DMF	80→100	30	no reaction	—
NaN ₃ /LiCl	DMF	100	120	decomp.	—
NaN ₃ /LiCl	H ₂ O	reflux	30	no reaction	112a
NaN ₃ /LiCl	H ₂ O	reflux	120	decomp.	112a
NaN ₃ /LiCl	dioxane/H ₂ O	reflux	50	no reaction	112b
NaN ₃ /LiCl	acetone/H ₂ O	reflux	50	no reaction	112c
NaN ₃ /LiCl	DMSO	90	50	no reaction	112d
NaN ₃ /LiCl	MeOH	reflux	50	slight decomp.	88
LiN ₃ ^a	DMF	90	36	no reaction	—
KOH	DMSO/H ₂ O	90	50	trace of diol	112d
LiBr	DMF	90	36	no reaction	—

^a Prepared according to ref. 113.

The failure to isolate either α -hydroxy azide (138) or (139) meant that the reaction had to be investigated more fully. To prevent the wastage of epoxides (122) and (125), which had already taken a number of steps to synthesise, the reaction of the quickly- and efficiently-prepared epoxide (127) with azide ion (hopefully to produce (140)) and other nucleophiles was studied. The results are presented in Table 1.

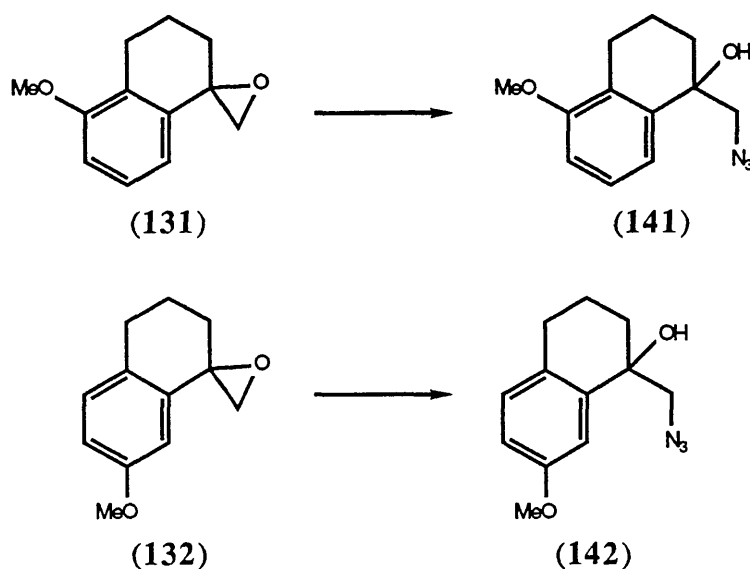
Since the NaN_3/LiCl system was unsuccessful in a variety of solvents, lithium azide was prepared and used in the hope that the pre-formed reagent would prove more satisfactory. However, this was not the case, no reaction being observed after 36 h in DMF at 90°C . Alkaline hydrolysis of (127) seemed to produce a trace of the corresponding diol, but in a yield that was not synthetically useful. If this had been successful, tosylation of the primary hydroxyl group, followed by displacement with azide, should have afforded the required α -hydroxy azide (140). Similarly, although admittedly a less powerful nucleophile than azide ion, reaction with bromide would have furnished the bromohydrin which again could have led to (140).

Having exhausted the possibilities with simple reagent and solvent systems, more exotic methods were investigated. Reaction of epoxides with trimethylsilyl azide in the presence of titanium tetra-isopropoxide or aluminium tri-isopropoxide in a variety of solvents was recently reported to produce *O*-silylated hydroxy azides.¹¹⁴ The reaction is thought to proceed through the intermediates $\text{Ti}(\text{O-}i\text{-Pr})_2(\text{N}_3)_2$ and $\text{Al}(\text{O-}i\text{-Pr})_2\text{N}_3$, which can also be pre-formed and used to facilitate the reaction.¹¹⁵ However, reaction of (127) with any of these reagent systems at best resulted in the formation of a minute trace of the incorrect regioisomer; prolonged reaction times (up to 3 weeks) made little difference to the amount of conversion observed.

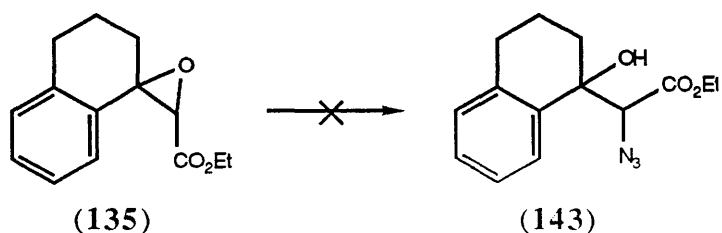
Tributyltin azide^{116a} and dibutyltin diazide^{116b} have been recently described as highly nucleophilic sources of azide ion. However, their reported reactions with the epoxide derived from benzaldehyde clearly shows that the secondary azide product predominates. Therefore, it was decided that the use of these reagents was likely to be unsuccessful for

the present problem.

Although the epoxide opening proved problematic for compounds modified in the saturated ring, substituents around the benzene ring apparently had little effect on the reaction. Thus, methoxy-substituted epoxides (131) and (132) could be converted into the corresponding azides (141) and (142) in reasonable yield (59 and 53%, respectively) by treatment with sodium azide/lithium chloride in DMF as before.



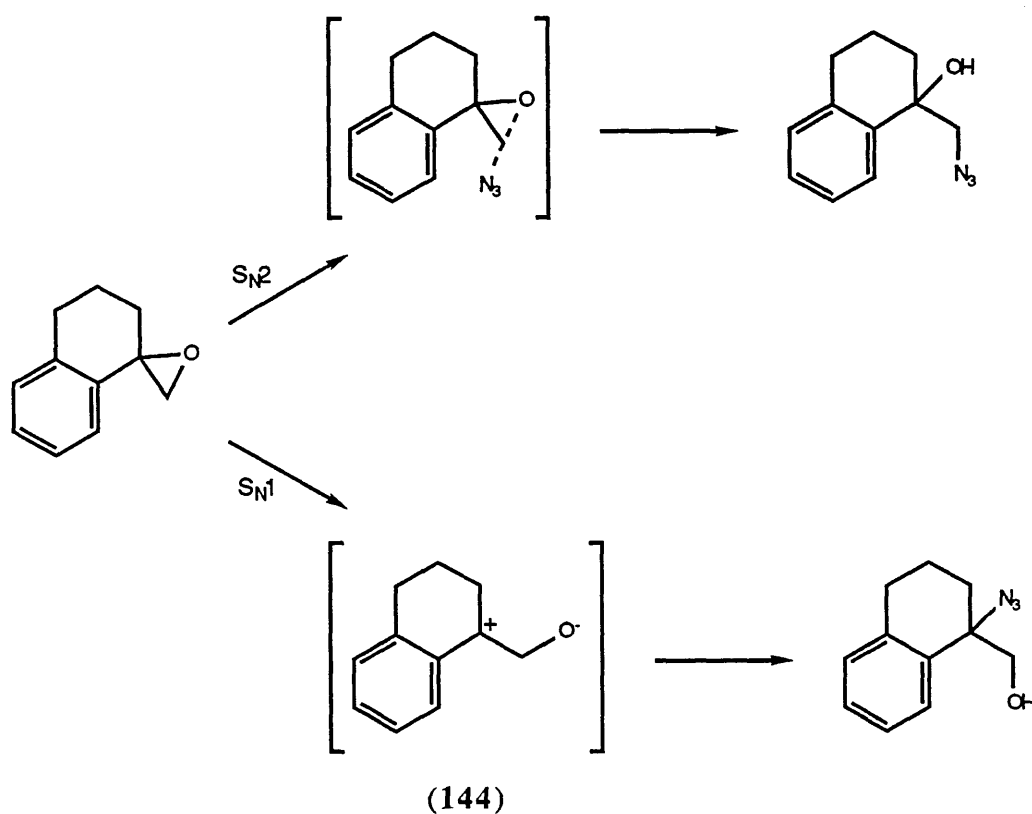
Unfortunately, however, glycidic ester (135) could not be converted to azide (143) by a variety of the methods previously described.



The failure of this reaction in so many cases obviously requires some comment. For the glycidic ester (135), the possibility exists that steric hindrance is to blame, since electronically the carbon atom α to the ester group should be the favoured site of attack. However, in the remainder of the cases, the reason is less clear. It is true that steric effects

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probably play a part where the larger rings are concerned, but this cannot be the complete story since the steric environment of the oxirane ring in the dimethyl-substituted epoxide (125) is little different to that in the unsubstituted analogue (119). The problem is probably largely concerned with the fact that the ring-opening process can occur by either an S_N1 - or S_N2 -type process, depending on the reaction conditions (Scheme 42).

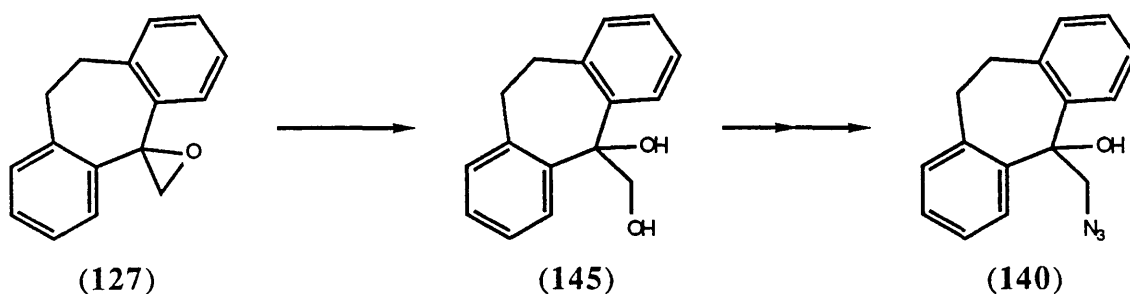


Scheme 42

The S_N1 -type process is favoured in the presence of protic or Lewis acids, and leads to the 'wrong' regiochemistry for the present requirements. The S_N2 -type process occurs somewhat less readily, but is favoured under neutral or non-acidic conditions and produces the required regiochemistry. There is obviously a fine divide between the two processes, especially when a comparatively mild Lewis acid catalyst such as lithium chloride is present. Furthermore, the (exaggerated) intermediate carbocation (144) represented in Scheme 42 is stabilised by the aromatic ring—this would play a major rôle in the case of the

doubly benzylic compound (127). Therefore, it seems likely that the problem is due to a combination of steric effects and, more importantly, to the fact that the reaction needs some sort of mild Lewis acid catalyst to proceed. However, too strong a catalyst would result in the unwanted S_N1 -type process, which is in any case favoured by the possibility of benzylic stabilisation. This may not be a complete explanation, particularly because it does not account for the success observed with the methoxy compounds, which are also able to slightly stabilise the benzylic carbocation, but it does show how the success or failure of the reaction is very finely balanced.

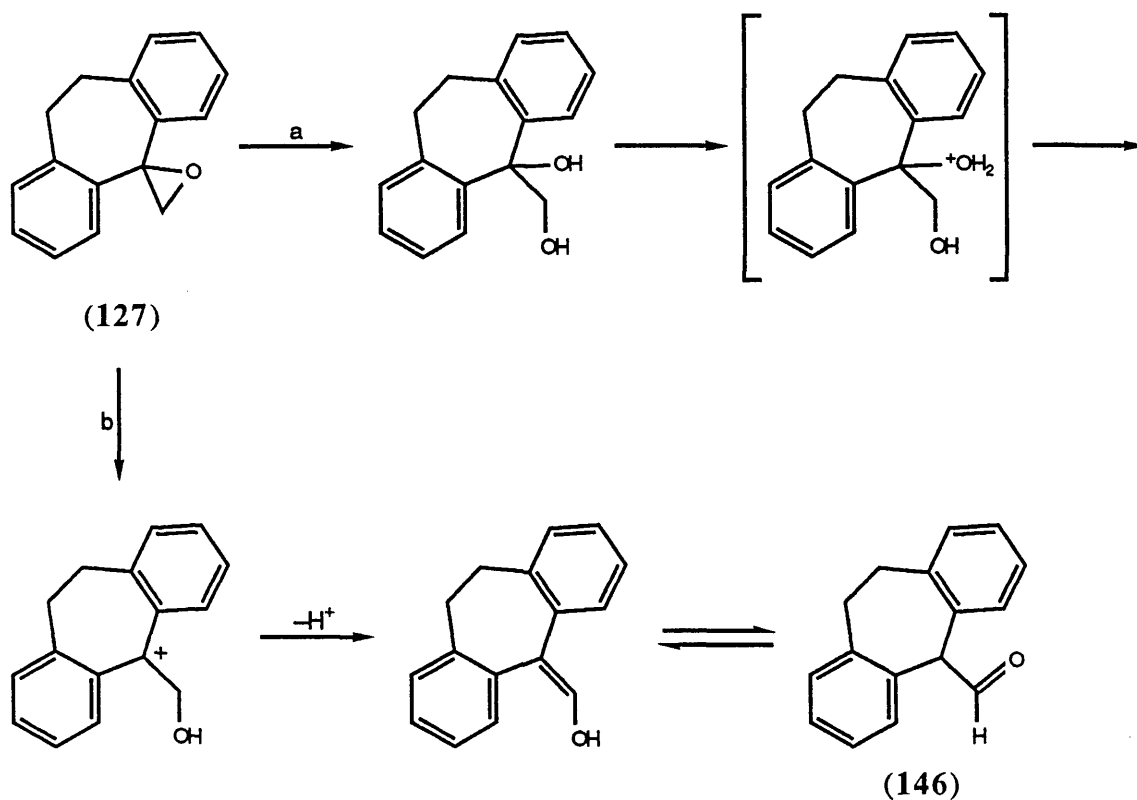
Having failed to achieve *nucleophilic* ring-opening with some examples, it was logical to attempt acid-catalysed ring-opening (Scheme 43). The intermediate diol (145) would be selectively monotosylated, and converted to the required azide (140) by simple S_N2 -displacement.



Scheme 43

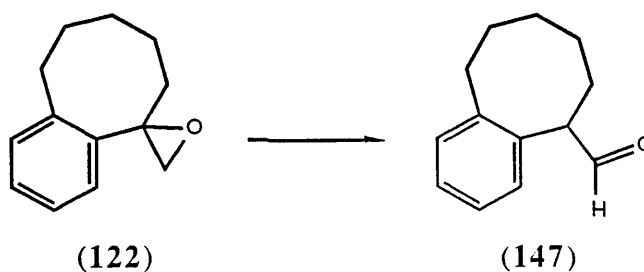
Unfortunately, upon treatment of epoxide (127) with perchloric acid, again the benzylic stabilisation came into play, resulting in the isolation of significant quantities of aldehyde (146), presumably *via* mechanism a or b shown in Scheme 44.

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES



Scheme 44

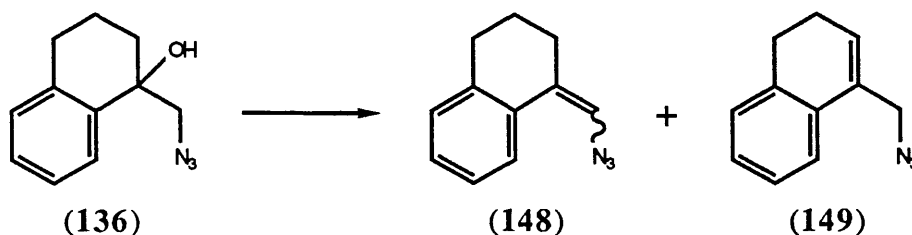
Since the failure of the reaction with (127) could be due to the *double* benzylic stabilisation, the process was attempted on epoxide (122). Again, however, the reaction met with failure—this time several other unidentified products in addition to aldehyde (147) were obtained.



2.3.4 Dehydration of azido alcohols.

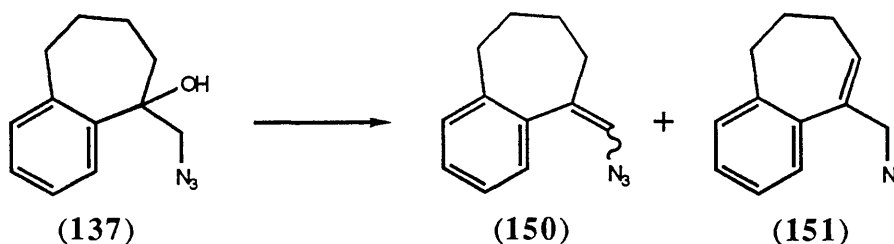
The failures associated with the preceding step had now reduced the compounds being investigated to four. The dehydration of the four α -hydroxy azides was carried out under

the conditions previously found to be best for this transformation.¹¹¹ Treatment of hydroxy azide (136) with thionyl chloride in pyridine at room temperature for 15 min produced a 71% yield of the expected mixture (*ca.* 4:1) of double bond regioisomers, (148) and (149).

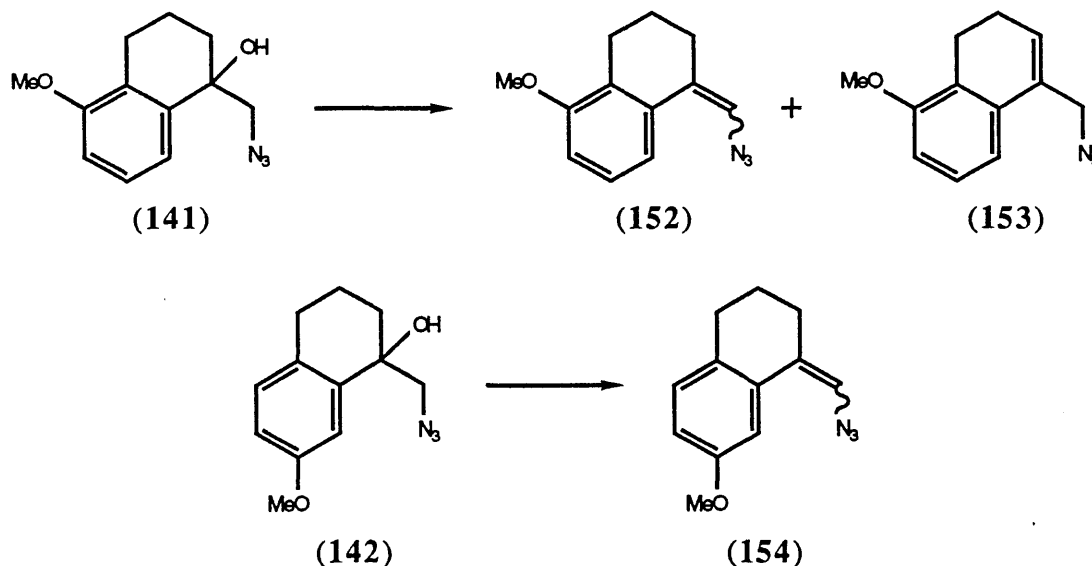


The two alkenes could be readily separated by chromatography down a short silica column, the vinyl azide being eluted first. Since simple vinyl azides are generally unstable, (148), as with all the vinyl azides prepared, was characterised only on the basis of IR and NMR data, and then immediately used for the next step. Also due to the instability of these compounds, no attempt was made to isomerise (149) to (148).

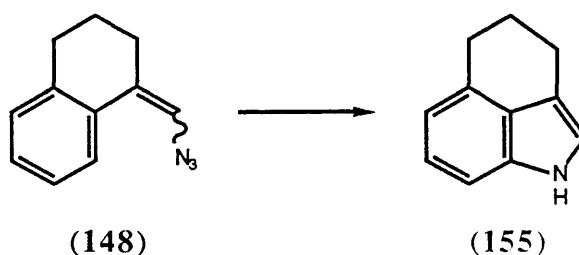
Similar results were obtained with hydroxy azides (137), (141), and (142), although it is noteworthy that (142) produced only the required vinyl azide in 71% yield on dehydration, no trace of the *endo* double-bond isomer being observed. This is in marked contrast to hydroxy azide (141), for which, unfortunately, the undesired *endo*-compound was found to predominate. The reason for this apparent anomaly is not clear, but it is unlikely to be an electronic effect, nor does it seem likely that the methoxy group in (142) has an effect on the steric requirements of the reaction.



SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

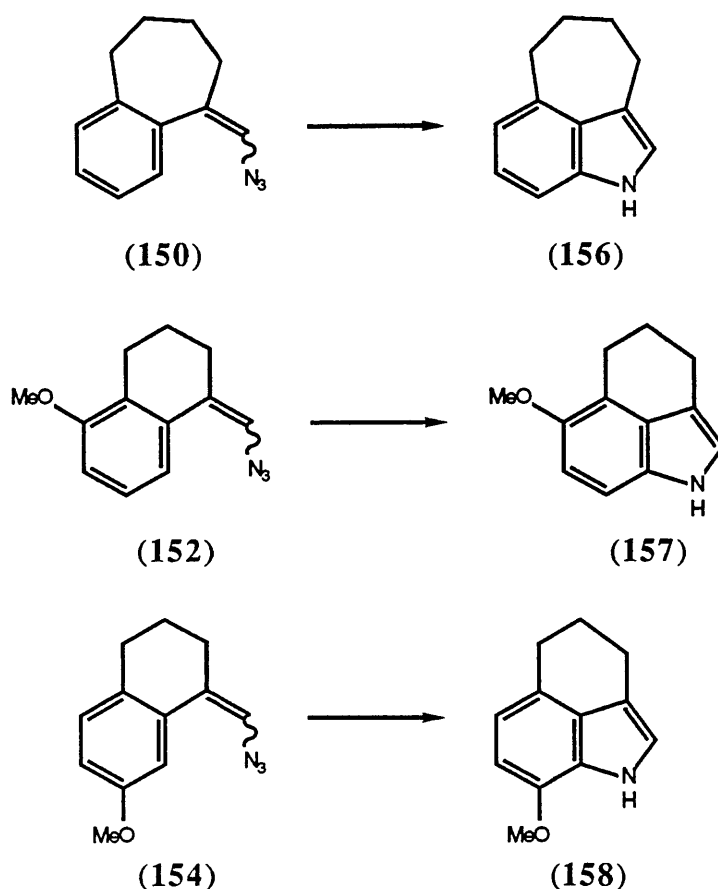
2.3.5 *Thermolysis of vinyl azides.*

With the requisite vinyl azides in hand, all that remained was to convert them to the corresponding indoles. To this end, vinyl azide (148), freshly prepared and purified, was dissolved in redistilled mesitylene, and the flask purged with nitrogen. The flask, fitted with a reflux condenser, was placed into a Woods metal bath preheated to 200°C, which quickly brought the solvent to reflux. After 45 min, the reaction was complete, and the previously reported¹¹⁷ tetrahydrobenz[cd]indole (155) could be isolated in 67% yield.



In a similar fashion, vinyl azides (150), (152), and (154) were converted to the previously unknown tetrahydrocyclohept[cd]indole (156) (72%), the 6-methoxy-tetrahydrobenz[cd]indole (157) (70%), and the known¹¹⁸ 8-methoxy derivative (158) (67%), respectively.

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES



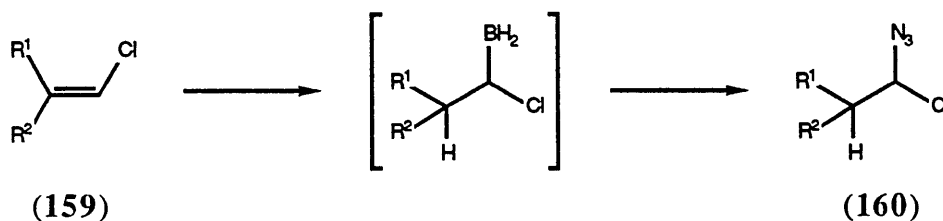
The *endo* double bond isomers (149), (151) and (153) were not heated, since these simple alkyl azides are expected to undergo insertion into the α -carbon hydrogen bond, resulting in the formation of an imine which could be hydrolysed to the aldehyde upon work-up.¹¹⁹

2.3.6 Other methods of introducing azide.

The most troublesome step associated with Scheme 34 is clearly the epoxide-opening step. Therefore, alternative methods of introducing the azide functionality were considered. A paper published in 1976 describes the efficient synthesis of alkyl azides from alkenes *via* hydroboration.¹²⁰ It was therefore thought that if a substituted alkene, for example a vinyl chloride (159), was to undergo the reaction, an alkyl azide (160) would be produced (Scheme 45). This alkyl azide would contain a chlorine atom capable

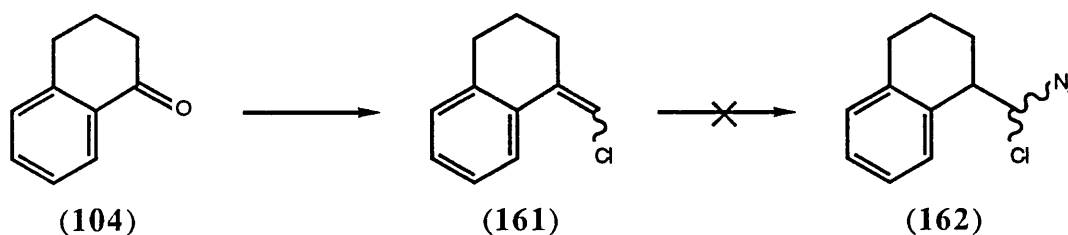
SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

of being eliminated to form a vinyl azide; since the chlorine atom in (160) is attached to the same carbon atom as the azide group, elimination of HCl would be expected to selectively produce only the required vinyl azide. A survey of the literature indicated that the hydroboration of terminal vinyl chlorides could be expected to proceed such that the major regioisomer contains the boron in the α -position,¹²¹ the correct regiochemistry for Scheme 45.

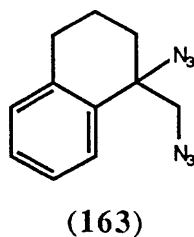


Scheme 45

It was decided to investigate the process first with α -tetralone (104).



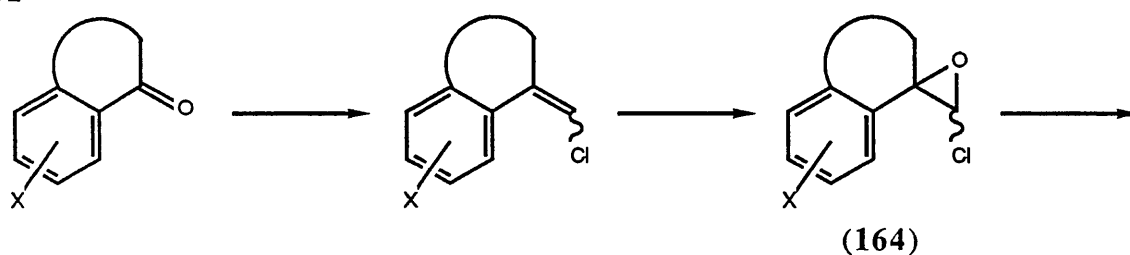
Standard phosphorus ylide chemistry gave an 83% yield of vinyl chloride (161) as a *ca.* 4:1 mixture of *E*- and *Z*-isomers, although the use of phenyl-lithium as base was necessary to ensure high yields by reducing the amount of metal-halogen exchange. Treatment of (161) with iron (III) azide, generated *in situ* from sodium azide and iron (III) sulphate behind a blast screen, and hydrogen peroxide did achieve introduction of azide into the molecule. Unfortunately, however, the compound isolated was not chloro-azide (162), but diazide (163).



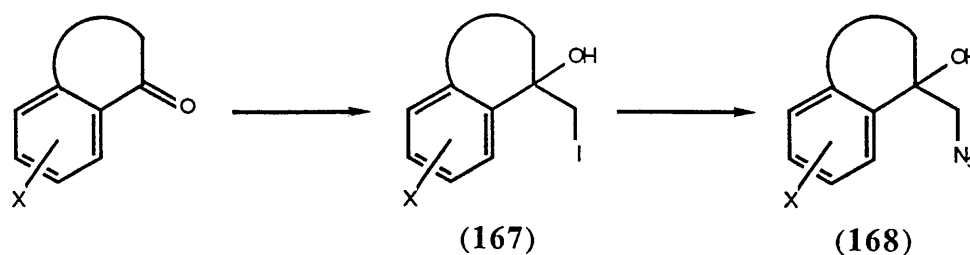
The structure was confirmed by a DEPT 135 ^{13}C NMR sequence, which firmly established the position of the azide groups. Consequently, the hydroboration reaction most probably proceeded in the opposite fashion to that shown in Scheme 45, the chlorine atom being displaced at some point after hydroboration. With the benefit of hindsight, the latter reaction was predictable, but the regiochemistry of the former process was something of a surprise. Because of the unexpected outcome of this reaction, the method appeared unsuitable for the present purpose and was consequently abandoned. Although this was the last azide insertion method investigated, it is worthwhile discussing other possibilities for this rather enigmatic problem.

The substrate for the azide introduction process must be readily available, and suitable for further elaboration when the azide functionality is in place. Two possibilities which fulfill these criteria are shown in Scheme 46.

A:



B:



Scheme 46

The first in a way combines both the epoxide and vinyl chloride routes. Vinyl chlorides are readily available from ketones *via* standard phosphorus ylide chemistry. If a vinyl chloride was to be epoxidised, for example with *m*-CPBA, the chlorine would then be attached to an sp³-centre (164), and could therefore undergo S_N2-displacement with azide ion to give an epoxy azide (165). The epoxide can be expected to be reasonably resistant to treatment with *sodium* azide in view of the results described earlier. Epoxides can be deoxygenated to olefins by a number of reagents,¹²² so by choosing a mild process such as treatment with aluminium tri-iodide,^{122b} the vinyl azide (166) could be produced from (165).

The second possibility utilises the reaction¹²³ between a carbonyl compound and diiodomethane, in the presence of samarium iodide, to produce an iodomethyl alcohol (167). Simple S_N2-displacement of the iodine with azide would readily produce the α-hydroxy azide (168), which could be dehydrated as before. Although neither of these methods was investigated, one of them *may* provide an answer to the difficult problem of introducing the azide group.

2.3.7 Summary.

A new synthetic route to [cd]-fused indoles has been developed, utilising a novel approach whereby the pyrrole ring is built onto the existing rings of a bicyclic aromatic ketone. The route consists of conversion of the ketone to its epoxide, ring-opening with azide ion followed by dehydration to a vinyl azide and thermolysis of these resulting vinyl azides. This is the first time nitrene chemistry has been applied to the specific problem of [cd]-fused indole synthesis. Although the epoxide-opening step was sometimes troublesome, the methodology was successfully applied to the synthesis of a number of indole examples. Reasons for the failure of the epoxide-opening have been suggested, together with possible solutions to the problem.

2.4 Conclusion

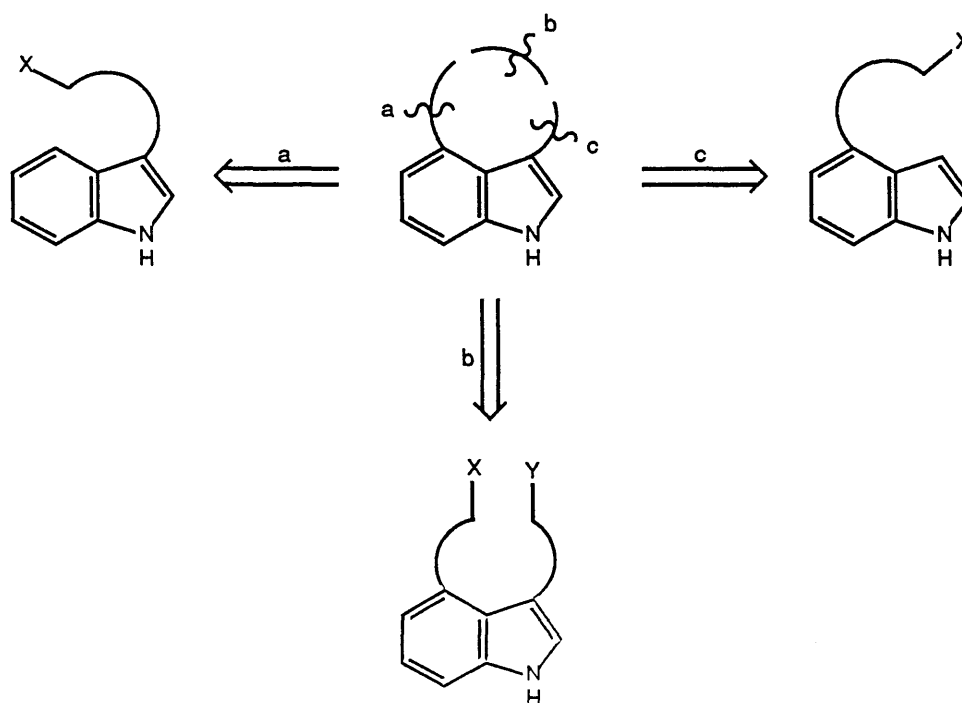
The vinyl nitrene methodology provides a simple, rapid route to indoles, and this methodology has now been extended and applied to the often difficult problem of [cd]-fused indole synthesis. The chosen route was not without its problems, but nevertheless the method did prove suitable for the synthesis of some previously reported and also some new [cd]-fused indoles. It seems that the size and presence of substitution of the alkyl ring are of prime importance for the epoxide-opening reaction, since large (7- or 8-membered) and substituted rings often fail to undergo the reaction. However, substituents on the aryl ring may have little effect on the progress of this reaction, although it must be said that detailed data on this is rather limited due to the small number of examples successfully synthesised. Alternative methods of introducing the azide group look interesting since they *may* provide a solution to the problems encountered. Additionally, the vinyl chloride/epoxide route, if successful, would overcome the slight disadvantage associated with the formation of *two* double-bond regioisomers during the dehydration of the α -hydroxy azide.

THREE

Photocyclisations in Indole Synthesis

3.1 Introduction

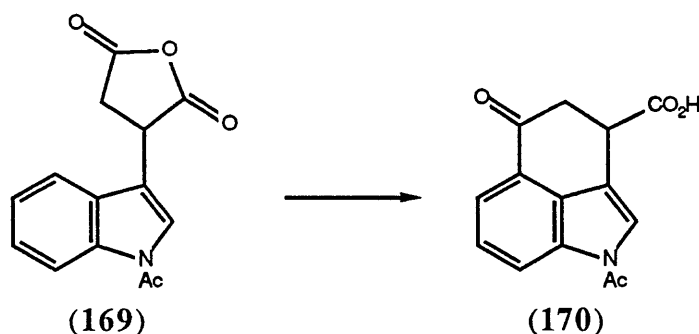
The second disconnection presented in Scheme 27 (Chapter 2) uses a suitably functionalised indole in order to form the bridging 'C'-ring. This, in turn, can be achieved in three ways (Scheme 47).



Scheme 47

Disconnection (b) has been seen many times in Chapter 1—indeed it is the standard, most common method for synthesising *[cd]*-fused indoles such as chuangxinmycin,

clavicipitic acid, and aurantioclavine, which contain a heteroatom in the 'C'-ring. The cyclisation of a suitably functionalised 4-substituted indole onto the nucleophilic 3-position, as illustrated by disconnection (c), although usually efficient, is much less common, with only a few examples known. This is presumably due to the fact that 4-substituted indoles can often be difficult to synthesise, although their increasing availability may mean that this strategy will become more widely used in the future. Disconnection (a), whereby the 'C'-ring is constructed by the *direct* cyclisation of a 3-substituted indole onto the 4-position, has also been applied, the reactions used to effect this transformation consisting of either Friedel-Crafts or photocyclisation processes. The former has been extensively studied and its limitations well-documented. The process was first discovered in 1963, when treatment of anhydride (169) with aluminium chloride gave [cd]-fused indole (170) in 68% yield.^{71a}



However, this transformation was soon shown not to be general, the cyclisation of compounds analogous to (169) usually proceeding to the 2-position unless it was blocked with, for example, an ethoxycarbonyl group.^{71b}

Another example of this type of reaction, cyclisation of dehydrotryptophan derivatives, has already been discussed during the review of clavicipitic acid syntheses in Chapter 1 (Schemes 20 and 21).

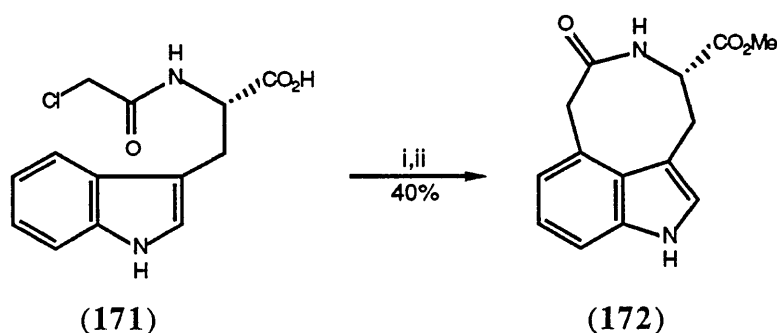
The second type of process, photocyclisation reactions of haloacetyltryptophan derivatives, has also been studied and its application extended. However, its application to the specific problem of [cd]-fused indole synthesis has been the subject of only limited

study, a significant proportion of which has been performed in our laboratory.¹²⁴ Therefore, further study of this methodology for the synthesis of these compounds seemed desirable, and this Chapter is concerned with the results of such a study.

3.2 Background

3.2.1 Introduction.

In 1966, Witkop and co-workers reported a photoreduction of tryptophan with sodium borohydride in aqueous solution.^{72a} However, when this process was extended to *N*-chloroacetyltryptophan (171), the major product isolated was lactam (172) (Scheme 48).



Scheme 48. Reagents: i, hv, H₂O, 45 min; ii, CH₂N₂.

The selectivity for the indole 4-position was notable, the process being one of the very few methods of achieving this transformation. In view of this, the reaction was studied further, particularly with regard to its mechanism, and also its application to non-indolic substrates.

3.2.2 Mechanism.

In their original paper, the authors suggested that the reaction proceeded *via* photolytic homolysis of the chlorine-carbon bond and intramolecular aromatic substitution by a free-radical at C-4 of the indole nucleus.^{72a} However, they did not discount the possibility of a

concerted intramolecular cyclisation with extrusion of chloride ion. Subsequent results have shown that their first hypothesis is a very simplified explanation of the *probable* mechanism, which is in fact much more complex than was first imagined.

The absorption of light by a molecule produces an electronically excited species, which is susceptible to energy loss by a variety of processes. Firstly, inter- or intra-molecular energy transfer can lead to an alternative, second excited species which can go on to lose energy by the same variety of processes. Chemical change, which often accompanies light absorption, can come about either as a result of direct reaction of the excited species, by dissociation of the excited species into reactive fragments, or by spontaneous isomerisation of the excited species. Radiative loss of energy from the excited species gives rise to luminescence phenomena such as fluorescence, which occurs between excited and ground states of the same multiplicity, or phosphorescence, between states of differing multiplicities. Physical quenching is also a method by which energy loss can occur. Here, a second atom or molecule can accept the excess energy of the excited state, initially as excitation energy, but in doing so its chemical behaviour must remain unchanged, otherwise the process constitutes a simple intermolecular energy transfer.

Upon irradiation of an aromatic chromophore, a π -electron is promoted from the ground state to the singlet first excited state. This results in the molecule attaining the $^1(\pi, \pi^*)$ state, either by non-radiative vibrational relaxation, fluorescence, intersystem crossing to the $^3(\pi, \pi^*)$ state, or by intermolecular energy transfer. Indoles, amongst other compounds such as anisole, are able to lose energy from their excited states by fluorescence. However, when certain other molecules such as chloroacetamide and ethyl chloroacetate are present, they act as quenching agents, relieving the excited indole of its excess energy. This results in a much weaker fluorescence spectrum when these compounds are present.¹²⁵ Similarly, intramolecular quenching is observed in the case of *N*-chloroacetyltryptamine, with the result that its fluorescence spectrum is weaker than that of the corresponding non-chlorinated compound.¹²⁵ It therefore follows that the carbon-

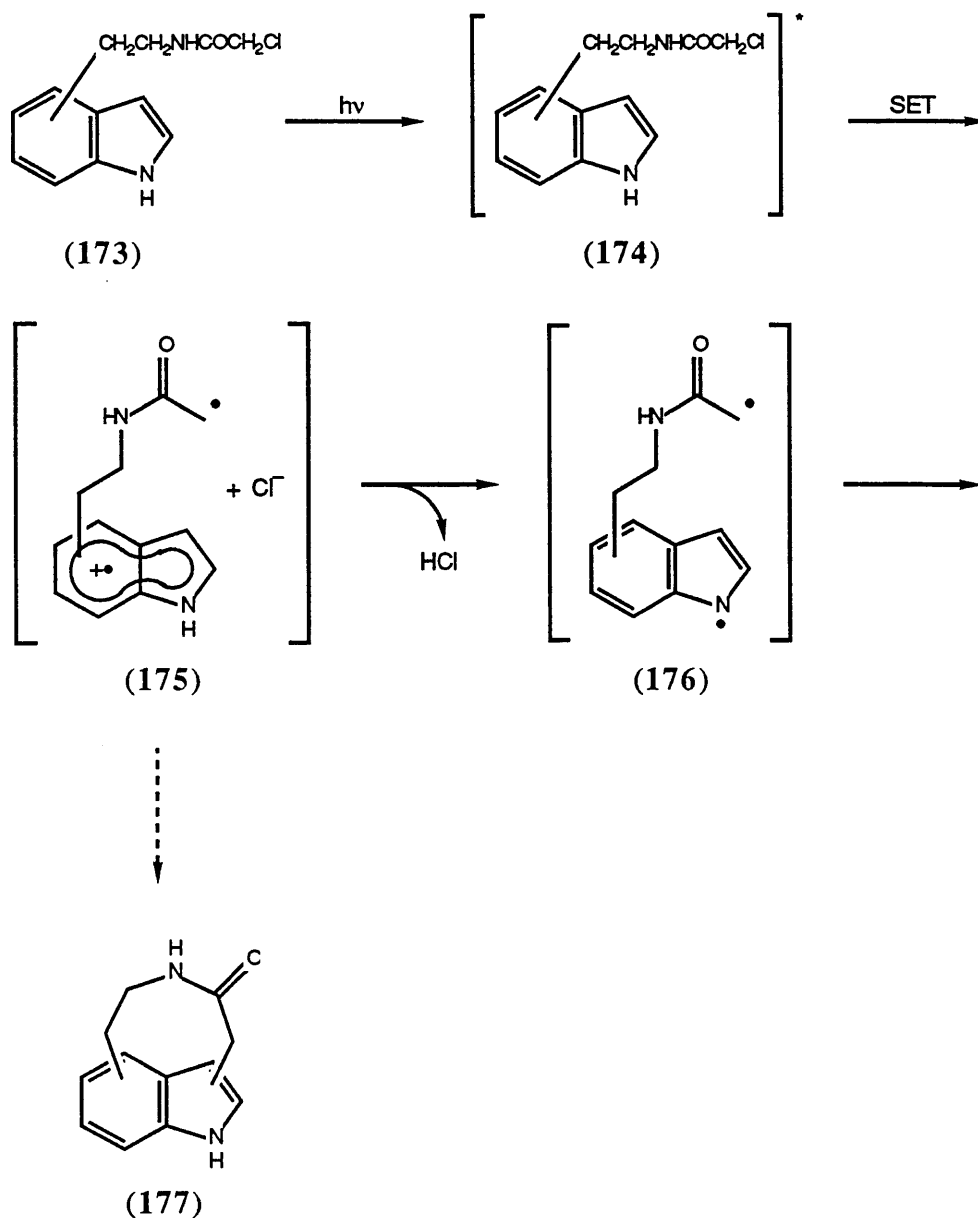
chlorine bond somehow facilitates this energy transfer, the magnitude of which may in turn be sufficient to dissociate the bond.

It has been shown that electrons are expelled from indole,^{126a} tryptophan,^{126b} and other aromatic compounds such as anisole.^{126c} This, together with a study on the effect of the solvent dielectric constant, which showed that the cyclisation was favoured in polar solvents,^{126d} strongly implicates an ionic intermediate in the cyclisation mechanism.

The mechanism was probed further by the synthesis and irradiation of the *N*-chloroacetyl derivatives of the seven isomeric aminoethylindoles.¹²⁷ The quantum yields for the disappearance of each of the starting materials and the formation of products were calculated, and from these the relative reactivity at each position of the indole ring was shown to be C-3>6,4>7,2>5>1. However, for 1-unsubstituted indoles, the electron densities of the singly occupied molecular orbitals of the indole radical cation, as calculated by INDO, did not correspond well with the quantum yields for product formation. A better correlation was found, though, with the SOMO-ED values of the indole-1-radical. This in turn agrees well with the known instability of the indole radical cation, which readily rearranges to the indole-1-radical with the loss of a proton.¹²⁸ Therefore, it may be supposed that the indole-1-radical is an intermediate.

On the basis of all this evidence, a reasonable mechanism can be formulated as shown in Scheme 49. Upon irradiating indole chloroacetamides (173), they are promoted to the singlet first excited state (174). This is rapidly followed by the expulsion of an electron which is captured by the chloroacetyl group, causing heterolysis of the carbon-chlorine bond to produce radical cation (175). In the case of 1-unsubstituted indoles, this readily loses a proton, giving the indole-1-radical (176). Cyclisation of this forms the tricyclic products (177). For 1-substituted compounds, (176) is not an intermediate, and (175) presumably cyclises directly, followed by the loss of a proton.

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES



Scheme 49

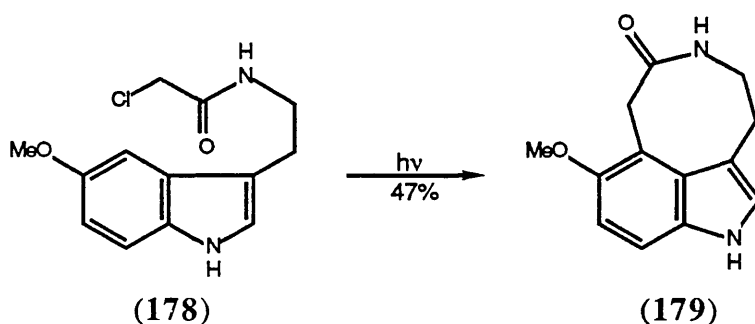
3.2.3 Applications.

The photocyclisation reaction described above has been applied to a number of substrates such as indoles, mescaline and other phenethylamines,¹²⁹ tyrosine derivatives,¹³⁰ and amino acid-tryptophan dipeptides.⁷³ Although the non-indolic studies represent an important extension of the reaction, they will not be discussed here since this work has been adequately reviewed elsewhere.¹²⁴ However, it is instructive to briefly

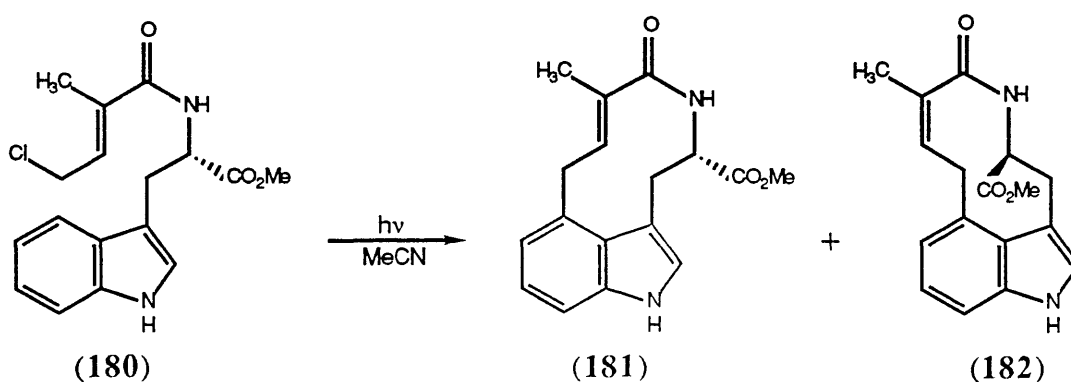
SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

discuss the application of the reaction to indolic substrates, in order to place the present work in context.

Besides the mechanistic studies with the aminoethylindole derivatives described above, which incidentally produced a number of novel azepino- and azocino-indoles,¹²⁷ the reaction has also been applied to the more structured syntheses of other target molecules. The first of these, published in 1969, concerned the synthesis of tricyclic melatonin analogues.^{131a} Thus, on irradiation of an aqueous THF solution of the methoxy tryptamine derivative (178), a 47% yield of azocinoindole (179) was obtained.



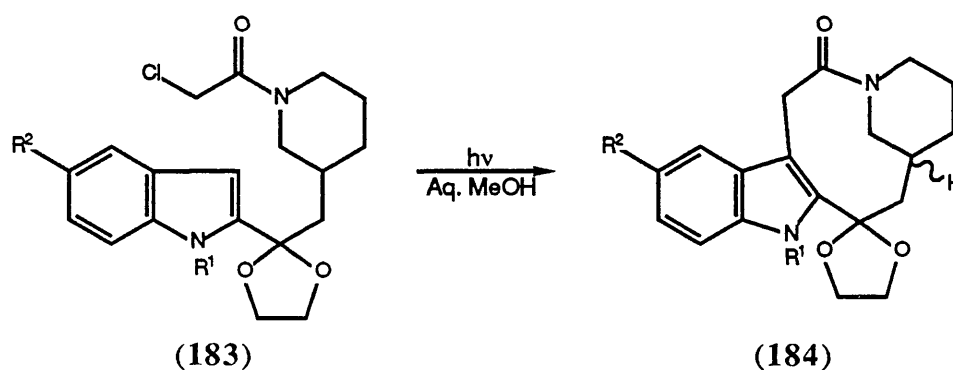
A significant extension of the methodology was reported in 1977, when *N*-(4-chlorotiglyl)tryptophan methyl ester (180) was prepared and irradiated to give the two ten-membered ergolinoid lactams (181) and (182) in 33 and 19% yield, respectively.^{131b}



The success of the reaction for this example is probably largely due to the restriction imposed on the indole 3-side chain by the conjugated amide, which ensures that the chloromethyl group is closer to C-4 than to any other indole carbon atom.

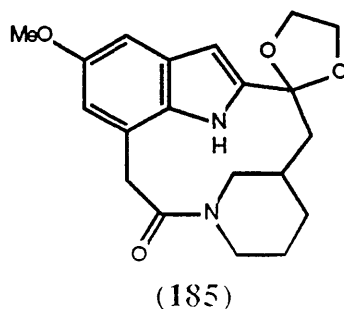
SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

The reaction has also been applied to the synthesis of 2,3-bridged indoles by cyclisation of a 2-substituted indole onto the 3-position. This approach was used in the synthesis of the quebrachamine and cleavamine ring system, derived by acid-catalysed cleavage of the dimeric *vinca* alkaloids.^{131c}



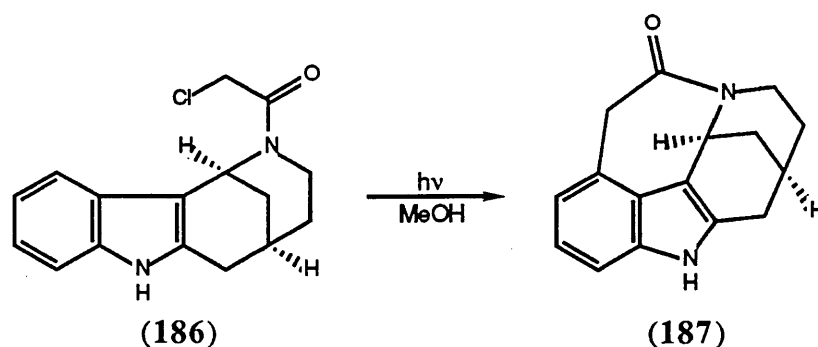
- (a) $R^1=R^2=H$
 (b) $R^1=CH_3$; $R^2=H$
 (c) $R^1=H$; $R^2=MeO$

Photolysis of (183) in aqueous methanol produced the desired products (184) in 35-50% yield. However, it was found that photolysis of (183c) also produced a trace of (185), the product of cyclisation to the 7-position of the indole ring.

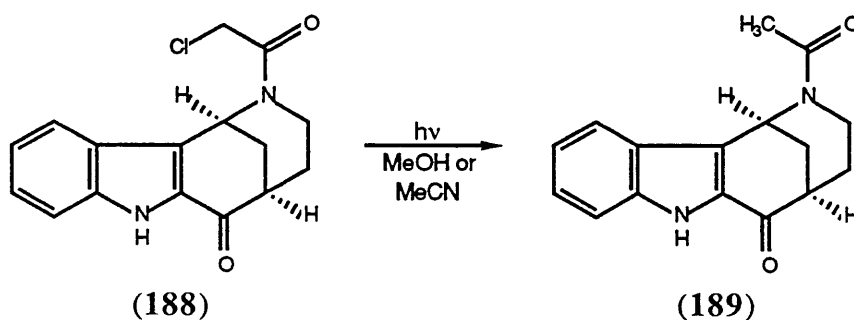


Some years later, the reaction was used again, this time in an unsuccessful attempt to synthesise the *Strychnos* alkaloid ring system.^{131d} Photolysis of (186) gave, amongst other products, a 28% yield of (187) by cyclisation to the 4-position, instead of the desired product of cyclisation to the 3-*ipso* position.

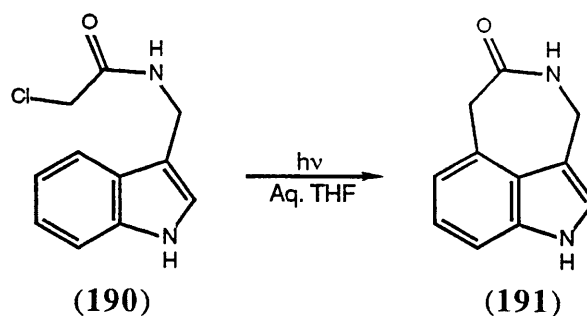
SYNTHETIC ROUTES TO [cd]-FUSED INDOLES



An interesting observation was that cyclisation *failed* to occur if the methylene group attached to indole C-2 was replaced by a carbonyl group. Thus, (188), upon irradiation, gave a 20% yield of (189) as the only isolable product, reflecting the deactivation caused by the carbonyl group conjugated with the indole ring.

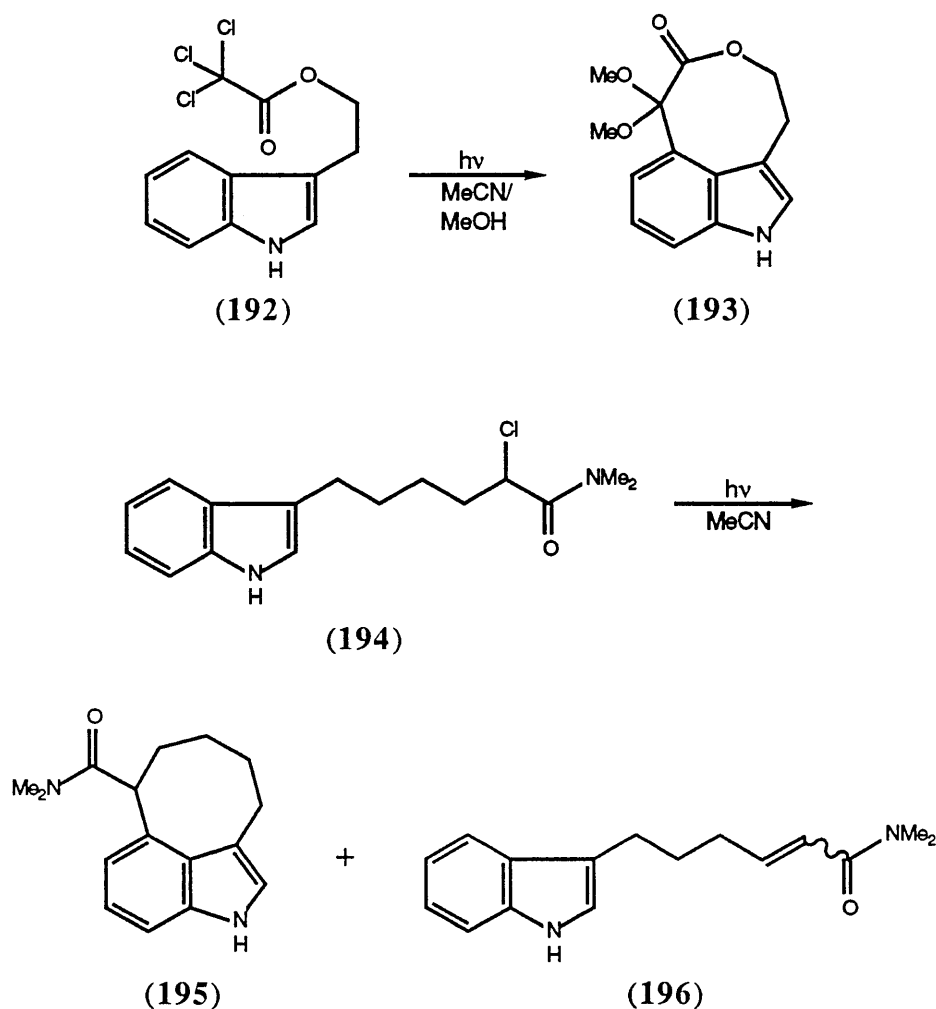


The photocyclisation has recently been used in the synthesis of serotonin receptor agonists containing the azepino[3,4,5-*cd*]indole system.^{131e} Photolysis of (190) and its 5-methoxy derivative produced the corresponding azepinoindole (191) and the 8-methoxy derivative in 48 and 46% yield, respectively.



SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

This was to be the last reported use of the reaction in the synthesis of indoles, other than the work done in our laboratory. Although this is discussed in detail elsewhere,¹²⁴ it is fitting to summarise very briefly some of the results obtained from this work. The cyclisation was successfully applied to the synthesis of indolactam V and an analogue of serotobenine, but, more significantly for the present work, adaptation of the methodology was initiated in order to apply the synthesis to different ring systems. Two examples of importance here are the photolysis of tryptophyl trichloroacetate (192) in methanolic acetonitrile to give a 45% yield of lactone (193), and the similar reaction of α -chloroamide (194) to give cyclo-octaindole (195) as a minor product (13%), accompanied with significant quantities (21%) of α,β -unsaturated amide (196) (Scheme 50).



Scheme 50

This completes the brief overview of the photocyclisation as applied to indole substrates. It has been shown that, although the reaction presents many interesting possibilities, save for the work done in our laboratory, these have been largely ignored, particularly with regard to [cd]-fused indole synthesis. This Chapter will now detail the results of further investigations into the application of the methodology to the synthesis of these compounds.

3.3 Photocyclisations in [cd]-fused indole synthesis

3.3.1 Introduction.

The basic requirement of the reaction appears to be the presence of an α -chloro- or polychloro-carbonyl group attached by an alkyl chain to the 3-position. This presents two general possibilities which can be classified as 'endo' compounds, where the carbonyl group is *endo* to the closing ring, or 'exo' compounds, where the group is *exo* to the closing ring (Figure 5).

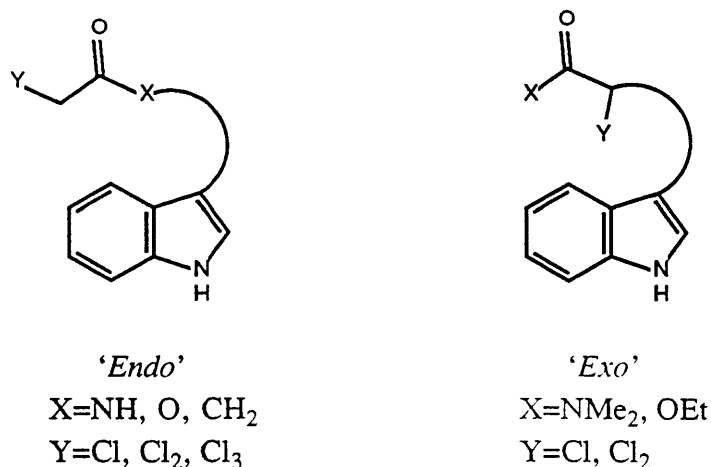


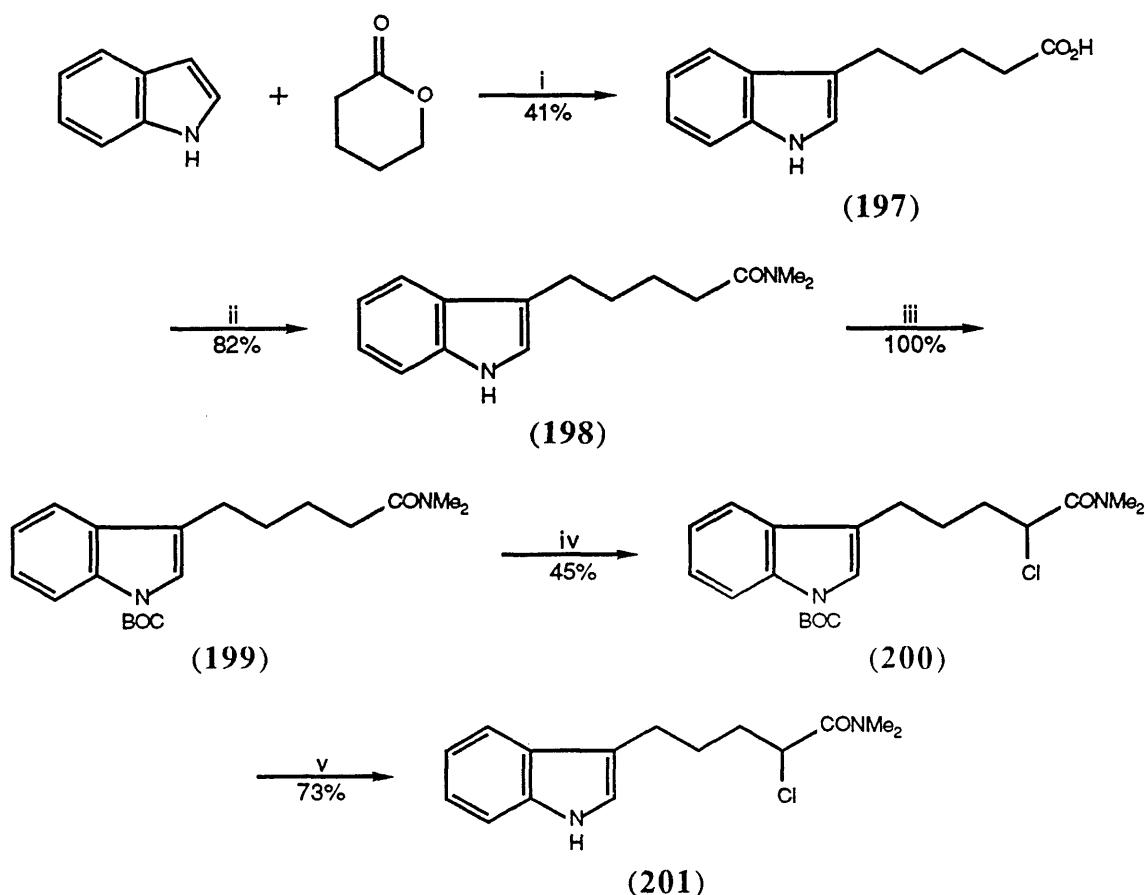
Figure 5

It can be seen that the general requirement of a α -chlorocarbonyl group leads to a variety of possibilities, namely chloro-amides, -esters, and -ketones. The results of the syntheses and, where possible, the photolyses of these compounds will now be discussed.

3.3.2 *exo Compounds.*

3.3.2.1 Amides.

All of the reported investigations of the photocyclisation of indoles had concentrated on the study of chloroacetyl derivatives of indole alkylamines such as tryptamine and tryptophan. It therefore seemed logical to see what effect the alternative approach of using α -chloroamide derivatives of indole-3-alkanoic acids would have on the cyclisation. Initial results in our laboratory had indicated that simple photoelimination of HCl could be an unwanted side-reaction, which for the example chosen did actually predominate (see Section 3.2.3).¹²⁴ However, it was felt that if the cyclisation was made more competitive, for instance by reducing the size of the ring to be formed, the yield of tricyclic product would hopefully increase at the expense of the elimination product. For this reason, the synthesis of the indole-3-pentanoic acid derivative was instigated (Scheme 51).



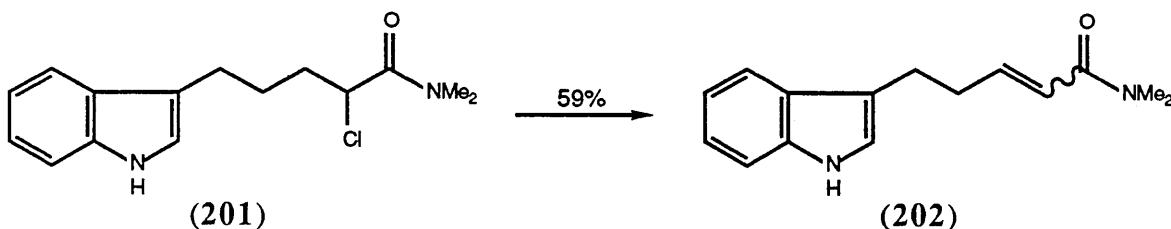
Scheme 51. Reagents: i, KOH, *p*-cymene, reflux; ii, (a) $\text{ClCO}_2i\text{-Bu}$, Et_3N , THF, 0°C , (b) $\text{Me}_2\text{NH}/\text{IMS}$, 0°C ; iii, $(\text{BOC})_2\text{O}$, DMAP, MeCN; iv, (a) LiICA, THF, -78°C , (b) CCl_4 , THF, -78°C ; v, TFA, DCM.

A simple, efficient synthesis of indole-3-alkanoic acids consists of the base-catalysed reaction of lactones with indole.¹³² Accordingly, the known indole-3-pentanoic acid (197) was prepared by prolonged treatment of a mixture of indole and δ -valerolactone with potassium hydroxide in *p*-cymene at reflux. Acid (197) was readily converted into its dimethylamide derivative (198) by treatment with triethylamine and isobutyl chloroformate, followed by alcoholic dimethylamine solution. It was hoped to chlorinate (198) directly by forming the enolate with two equivalents of LDA and quenching the resulting dianion with carbon tetrachloride.¹³³ However, reaction under a variety of conditions, and the use of hexachloroethane as an alternative source of chlorine all proved unsuccessful, resulting either in the recovery of starting material or the formation of many products, none of which appeared to be the required chloro-compound. It was felt that the deprotonated indole nucleus could be the source of the problem, so to preclude this possibility the *N*-BOC derivative (199) of indole (198) was prepared in quantitative yield by treatment with di-*tert*-butyl dicarbonate and a catalytic quantity of 4-dimethylaminopyridine in dry acetonitrile.¹³⁴ Attempted chlorination of (199) still proved troublesome, and a deuteration study resulted in decomposition of (199), implying that the deprotonation and *not* the quench was the source of the problem. The use of the base lithium *N*-isopropylcyclohexylamide (LiICA) as an LDA substitute for the deprotonation of esters was reported to give superior results, and halogenation of the resulting enolates was also said to proceed smoothly.¹³⁵ Upon running two deuteration studies side-by-side, one using LDA and the other using LiICA, it was found that the use of LiICA resulted in the successful deuteration of (199), while LDA formed a variety of unidentified products. Eventually, suitable conditions for the chlorination were found. Use of LiICA was essential, but it also proved necessary to add the anion solution at -78°C *via* a catheter to a THF solution of the carbon tetrachloride quench, which was itself held at -78°C and stirred vigorously. Using these conditions, a reproducible 40-45% yield of chloroamide (200) could be obtained. Simple deprotection of the indole nitrogen under standard conditions afforded the rather sensitive

chloroamide (201) in 73% yield.

Obviously, other methods do exist for the preparation of α -halo acid derivatives—a notable example is the classical Hell-Volhard-Zelinski reaction. However this and other methods were considered unsuitable for the present purpose due to the rather harsh conditions of the reaction. The enolate methodology provided a mild alternative to these reactions, and proved most suitable for the present requirements.

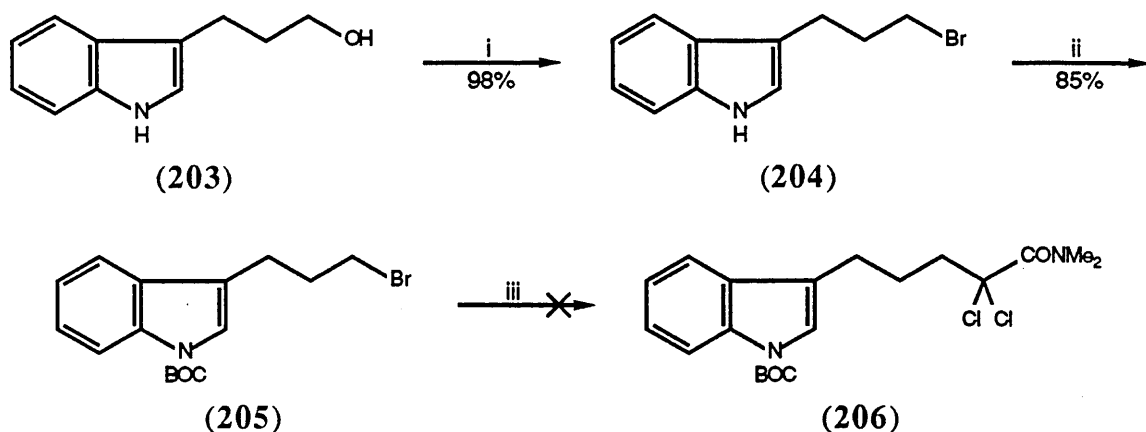
Having obtained chloroamide (201), it was irradiated in acetonitrile. The results proved to be disappointing, the elimination product (202) being the only product isolated, in 59% yield.



No trace of any other indolic products was observed. Previous studies^{124,131b,d} had shown that the choice of (polar) solvent had little effect on the outcome of the reaction, so it was not considered to be worth exploring this option. However, it had been found that the photolysis of *di*- or *tri*-chlorocarbonyl compounds generally proved superior to the corresponding monochloro derivatives, usually resulting in increased yields and improved regioselectivity. It was therefore decided to investigate the photocyclisation as applied to the *exo* class of dichloroamides.

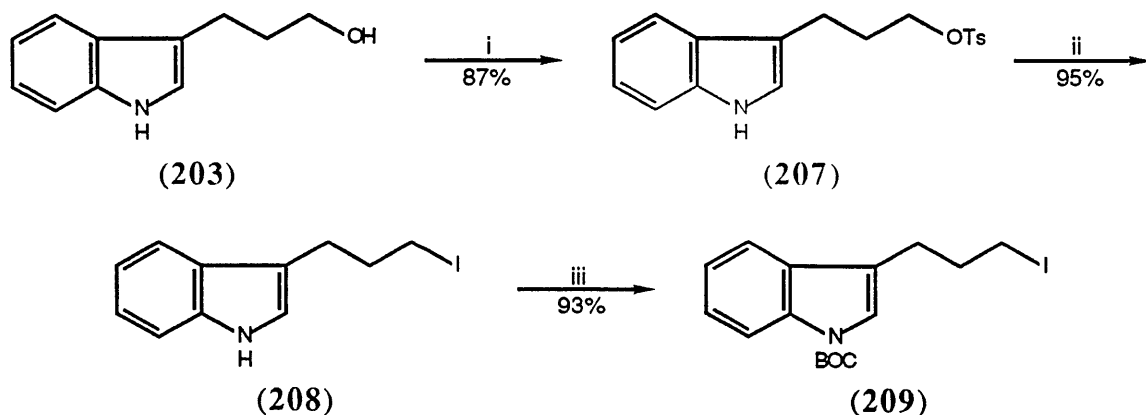
Initial studies soon made it clear that the carbon tetrachloride quench of an enolate was not going to be suitable for the preparation of the dichloro compound. However, the reaction of the anions derived from α,α -dichloroacetate esters with alkyl bromides was reported to give high yields of a variety of dichloroesters.¹³⁶ It was decided to try to apply this reaction to bromoalkylindole (204) and *N,N*-dimethyl- α,α -dichloroacetamide, which is readily prepared from dichloroacetyl chloride (Scheme 52).

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Scheme 52. Reagents: i, Ph_3P , CBr_4 , DCM; ii, $(\text{BOC})_2\text{O}$, DMAP, MeCN; iii, $\text{Li}^+\text{C}(\text{Cl})_2\text{CONMe}_2$, THF, -78°C .

Bromide (204) was prepared in 98% yield from homotryptophol (203) by treatment with triphenylphosphine and carbon tetrabromide in dry dichloromethane.¹³⁷ Bromide (204) has been prepared before, in only 24% yield, by treatment of (203) with phosphorus tribromide in diethyl ether.¹³⁸ Direct treatment of bromide (204) with the *N,N*-dimethyldichloroacetamide anion, prepared using LiICA, resulted in no reaction. To prevent any complication due to the indole NH, the *N*-BOC derivative (205) was prepared. Again, attempted reaction of (205) proved unsuccessful, and it was found, contrary to the reported¹³⁶ procedure, that the presence or absence of HMPA made little difference to the outcome of the reaction. It was therefore decided to make use of a more efficient alkylating agent in the form of the iodide.



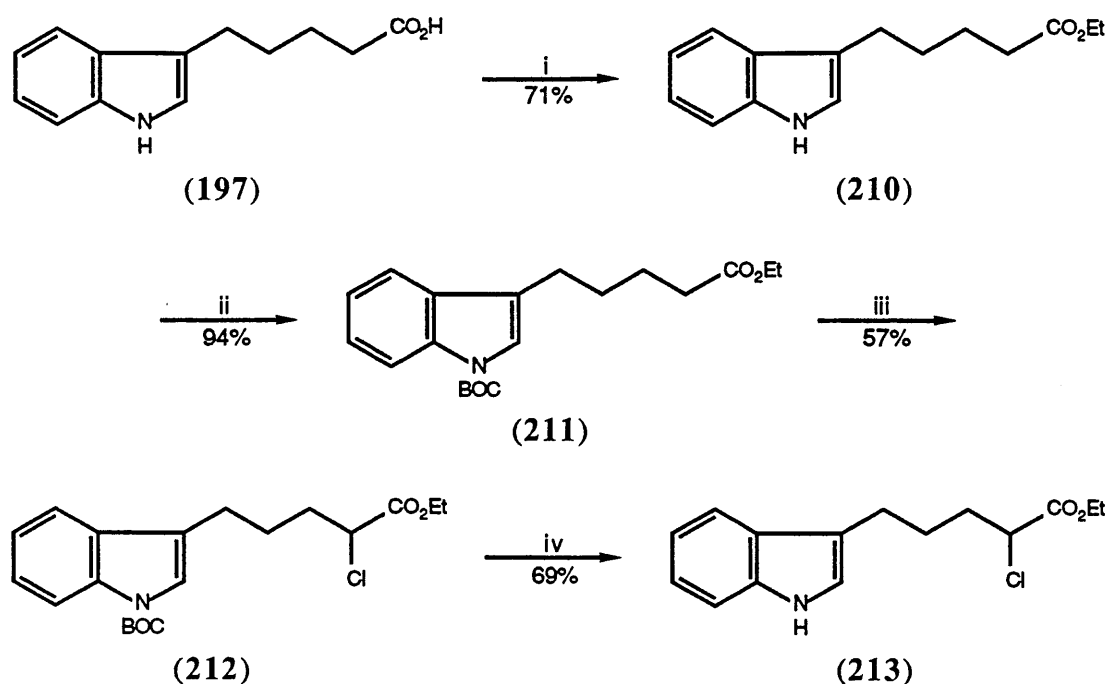
Scheme 53. Reagents: i, TsCl, pyridine, 0°C ; ii, NaI, Me_2CO ; iii, $(\text{BOC})_2\text{O}$, DMAP, MeCN.

Treatment of homotryptophol with triphenylphosphine and iodine in the presence of imidazole proved a disappointment in that only an approximate 20% yield of iodide (208) was obtained. However, it was found that formation of iodide (208) *via* the tosylate (207) was a superior method (Scheme 53). Protection of the NH as before gave the *N*-BOC indole (209).

Treatment of (209) with the *N,N*-dimethyldichloroacetamide anion, under the same conditions described earlier, again resulted in no reaction. In spite of several attempts to find the correct conditions for reaction, dichloroamide (206) could not be prepared. The failure was ascribed to the instability of the *N,N*-dimethyldichloroacetamide anion, which, if formed, would obviously be very susceptible to α -elimination. For this reason, the investigation of the photocyclisation of *exo* dichlorocarbonyl compounds was confined to dichloroesters, described in the next Section.

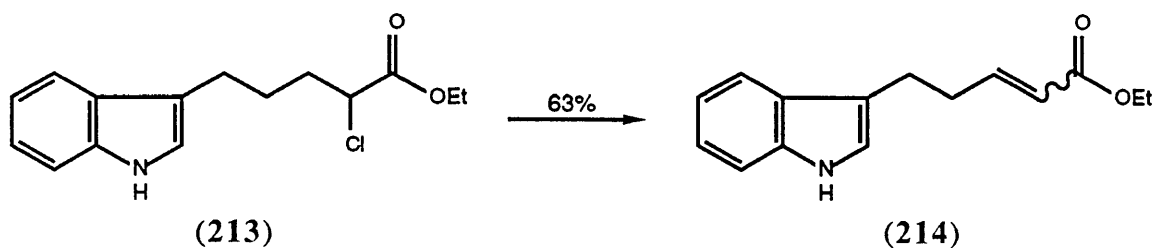
3.3.2.2 Esters.

Other than the one *endo* example of tryptophyl trichloroacetate, no examples of the application of the reaction to chloroesters have been reported. Therefore, the synthesis and photolysis of these compounds was a high priority. The preparation of acid (197) has been described earlier, and it was easily converted to the ethyl ester (210) *via* the acid chloride (Scheme 54). Again, NH-protection and the use of LiICA were found to be necessary for successful chlorination, so the *N*-BOC compound (211) was prepared as before, and chlorinated to give (212) in reasonable yield. Deprotection of this with trifluoroacetic acid in dichloromethane gave an acceptable yield of the required α -chloroester (213).

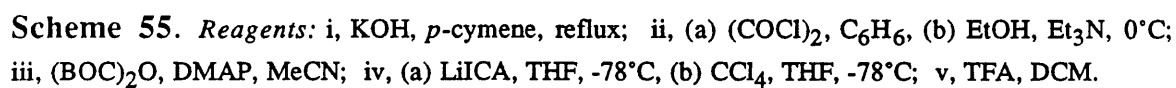
SYNTHETIC ROUTES TO [*cd*]-FUSED INDOLES

Scheme 54. Reagents: i, (a) $(\text{COCl})_2$, C_6H_6 , (b) EtOH , Et_3N , 0°C ; ii, $(\text{BOC})_2\text{O}$, DMAP, MeCN ; iii, (a) LiICA , THF , -78°C , (b) CCl_4 , THF , -78°C ; iv, TFA , DCM .

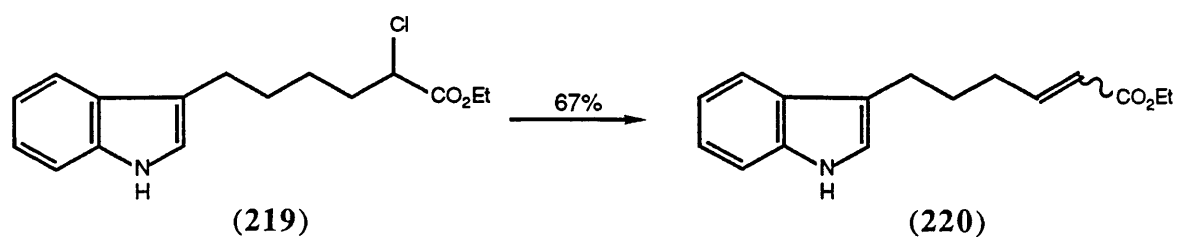
Upon photolysis of (213), photoelimination was again found to proceed exclusively, resulting in the formation of α,β -unsaturated ester (214). The reaction was performed three times, each using a different reaction time, but the outcome was always the same.



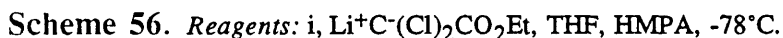
Since the cyclisation had already been shown to be successful when an *eight*-membered ring was being formed from an α -chloroamide (see Section 3.2.3), it was thought that some success *might* be achieved by investigating the corresponding α -chloroester. Acid (215) was therefore prepared according to the procedure described earlier (Scheme 55).



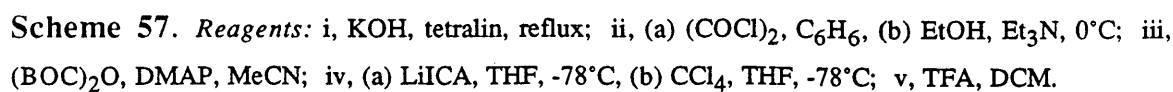
Photolysis of (219) again proceeded with exclusive photoelimination, (220) being the only indolic product isolated.



Since the preparation of the dichloroamide proved unsuccessful, no information on the photolysis of *exo* dichlorocarbonyl compounds had been obtained. Therefore, the preparation and photolysis of a dichloroester was desirable, so the literature method¹³⁶ for the production of these compounds was applied to the synthesis of (221) (Scheme 56).



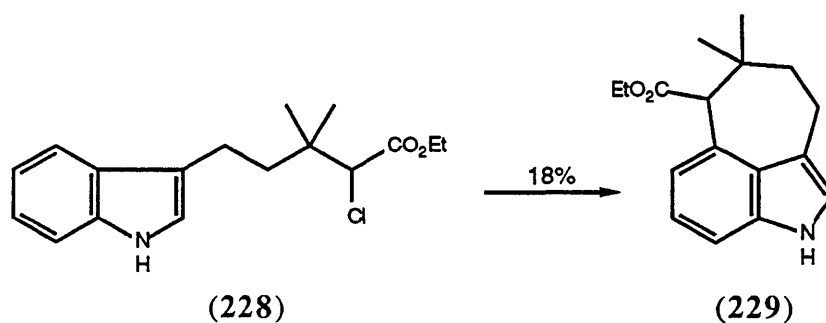
The obvious way of preventing photoelimination is to place two methyl groups β to the carbonyl group; this in turn means that the intermediate acid should be prepared from a 3,3-dimethyl-substituted lactone (Scheme 57).



SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

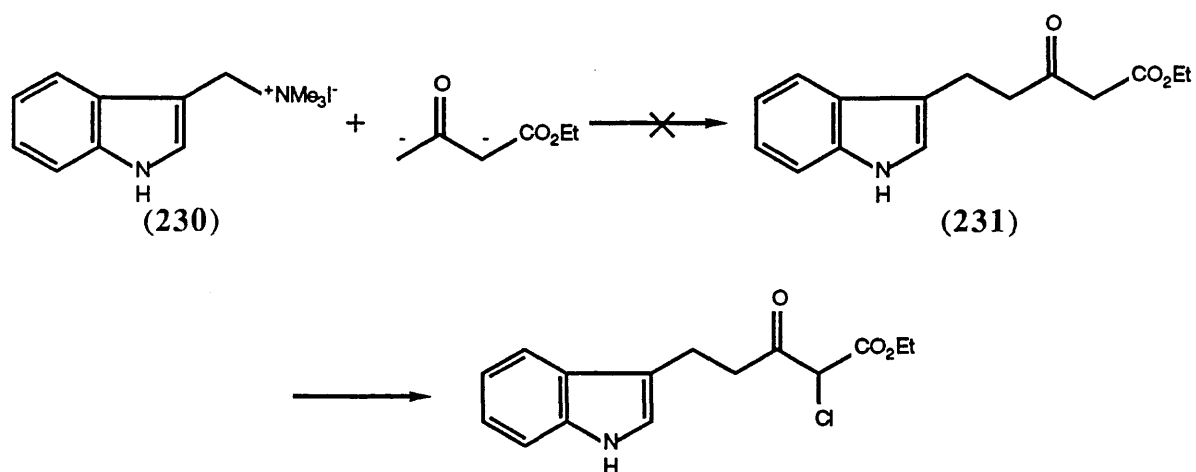
Lactone (223) was prepared from 3,3-dimethylglutaric anhydride by a literature procedure.¹³⁹ Treatment of (223) with indole and potassium hydroxide in tetralin as before produced the acid (224). However, purification of this acid proved difficult, so the crude product was esterified, and purified by column chromatography to give an acceptable yield of ester (225). Protection of the indole NH as the *N*-BOC derivative was easily achieved, giving a 97% yield of (226). Chlorination of (226), as described before, gave a 38% yield of chloroester (227), which could be deprotected to give indole (228) in 52% yield.

Photolysis of (228) did indeed result in cyclisation, a gratifying 18% yield of [cd]-fused indole (229) being obtained. Hence, when photoelimination is prevented, cyclisation *does* occur, even in the case of *exo* chloroesters.



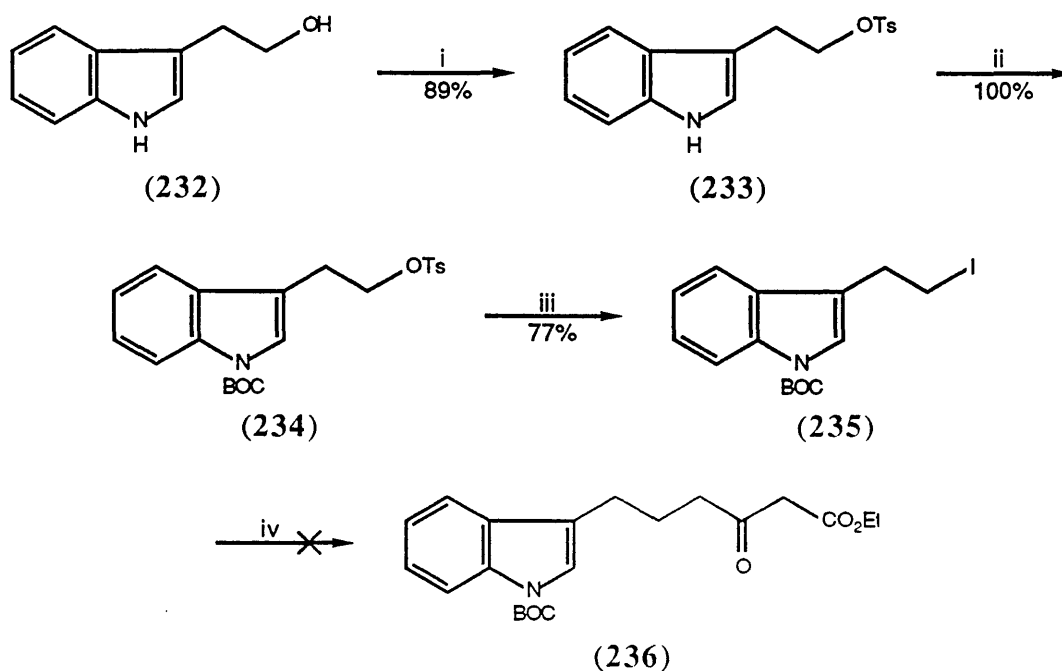
An alternative way of 'blocking' the β -position is by means of a carbonyl group, in the form of a β -ketoester which should also be easy to chlorinate. To prepare the cyclisation precursors for 7- and 8-membered ring formation, indoles bearing 1-C and 2-C side chains on the 3-position are required. A suitable candidate for the 1-C compound is gramine methiodide (230), which has been used to alkylate various carbon nucleophiles.¹⁴⁰ The methiodide was prepared according to a literature procedure,^{140d} and then used in an attempt to alkylate the dianion of ethyl acetoacetate (Scheme 58). It was found, however, that even performing the reaction under a variety of conditions failed to produce (231). Treatment of gramine itself with carbon nucleophiles in the presence of tri-*n*-butylphosphine is reported to be a mild method for the elaboration of the indole C-3 side chain.¹⁴¹ However, even this process proved unsuccessful for the preparation of (231).

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES



Scheme 58

The second option, preparation of an 8-membered cyclisation precursor, was therefore investigated. For this, the alkylating agent was to be the iodoethylindole (235), prepared from tryptophol (232) in a similar fashion to its previously described homologue (Scheme 59).



Scheme 59. *Reagents:* i, TsCl, pyridine, 0°C; ii, (BOC)₂O, DMAP, MeCN; iii, NaI, Me₂CO; iv, -CH₂COCH-CO₂Et, THF, -78°C→0°C.

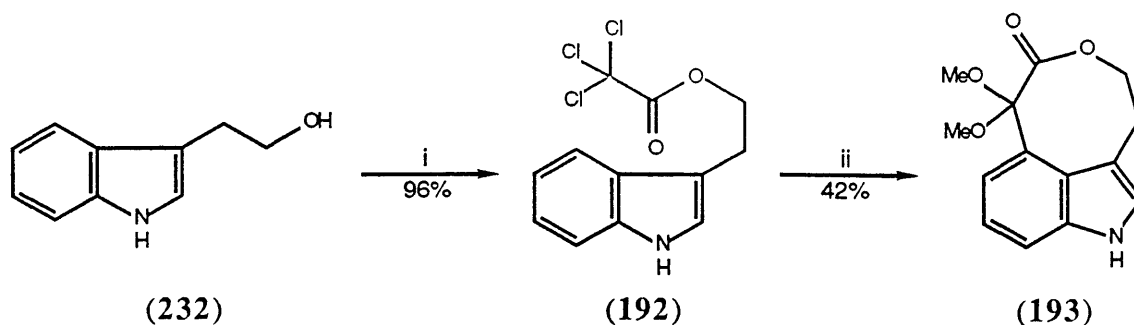
The known,¹⁴² sensitive tosylate (233) was prepared in 89% yield by a standard process. Conversion to the *N*-BOC derivative (234) proceeded smoothly, as did the conversion to the iodide (235). The *N*-protection step preceded the conversion to the iodide in order to stabilise the tosylate against intramolecular S_N2 displacement by the nucleophilic indole 3-position. However, upon reattempting the alkylation, the reaction again proved unsuccessful, with none of β -ketoester (236) being produced. Alteration of the reaction conditions would probably have resulted in a more successful outcome, but this was not pursued, the *endo* compounds being investigated instead.

3.3.3 *endo* Compounds.

3.3.3.1 Esters.

Although the photocyclisation has been applied to monochloroamides, for which it is often remarkably efficient, apart from the work from our laboratory the reaction has not been applied to esters, either *exo* or *endo*, or to poly-chlorinated compounds. It was therefore desirable to investigate both of these more fully. Initial studies¹²⁴ had shown that the cyclisation would work for the di- or tri-chloroacetyl derivatives of tryptophol, although in the former case ring-opening of the lactone product was observed. However, no further work had been done in this area.

The initial work with tryptophyl trichloroacetate (192) was repeated, and investigated further (Scheme 60).



Scheme 60. Reagents: i, Cl₃CCOCl, pyridine, DCM, 0°C; ii, hv, MeCN/MeOH.

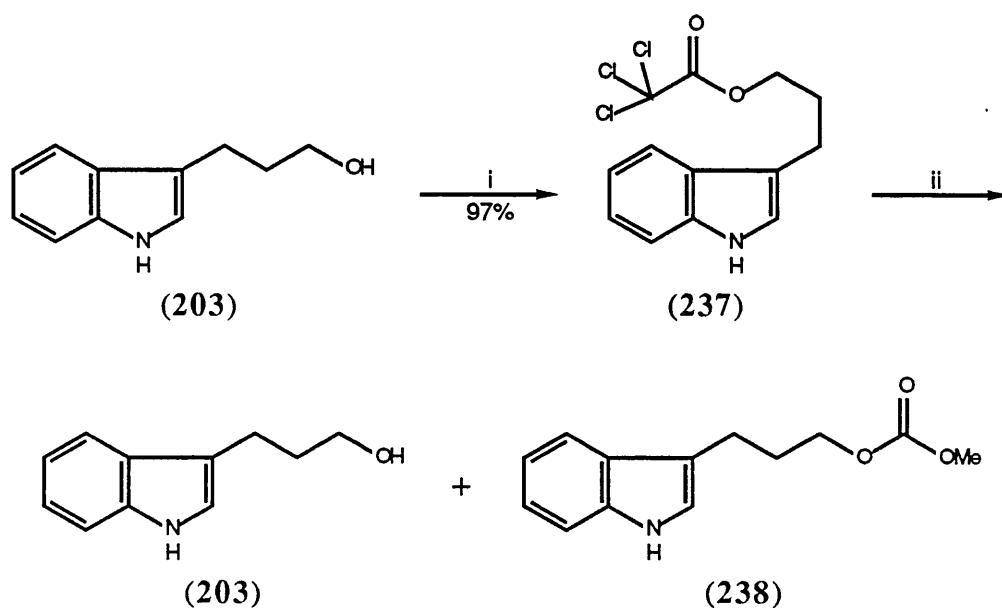
Trichloroester (192), easily prepared from tryptophol (232), was irradiated at 254 nm in methanolic acetonitrile to furnish lactone (193). However, more polar material was also observed repeatedly; this was isolated and found to be tryptophol, obviously derived by loss of the trichloroacetyl group, possibly by initial reaction of (192) with the methanol.

It is interesting to note that at no time was an alternative cyclisation to the 2-position ever observed, even though this would result in a more readily-formed seven-membered ring. This was to be a common feature of the photolysis of these trichloroacetate derivatives, and is presumably due to the closer proximity of the trichloroacetyl group to the indole 4-position than to the 2-position.

Previous attempts to perform a similar reaction in the absence of methanol had been unsuccessful—no single product could be isolated.¹²⁴ Varying the reaction time proved to have little effect on the relative amounts of lactone (193) and tryptophol isolated, shorter times merely reducing the yields of both compounds. Furthermore, irradiation at 350 nm was totally unsuccessful, no reaction being observed even after 3 h. Since it appeared that the reaction could not be readily improved, it was decided to accept the not unreasonable yield of 42%, and extend the reaction to other substrates.

Since tryptophyl trichloroacetate gave rise to an 8-membered ring on photolysis, it was decided to prepare homotryptophyl trichloroacetate, which *might* lead to the admittedly more ambitious nine-membered lactone. It had already been shown that polychloro compounds were generally superior for the reaction, so the photolysis of a trichloroester probably stood the best chance of success. Hence, trichloroester (237) was prepared from homotryptophol (203) and photolysed under the same conditions as before. Cyclisation did not occur, instead a 58% yield of homotryptophol, together with 11% of the methyl carbonate (238), was obtained (Scheme 61). The former compound presumably arises from a similar process to the tryptophol formed in the preceding example. The latter compound, (238), is formally derived by loss of chloroform from an adduct of methanol and the trichloroester. It is possible that (238) is produced as a result of methanolysis of

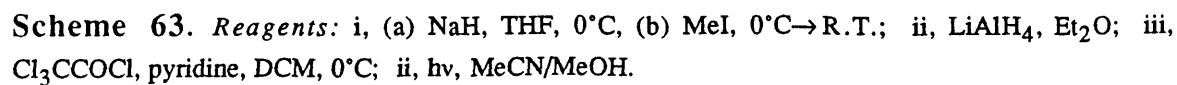
the trichloroacetyl group in (237)—the trichloromethyl group is not the most common leaving group, but it *is* known, for example in the generation of dichlorocarbene from chloroform. Upon performing the reaction in the absence of methanol, a reaction mixture was produced which showed a very poorly resolved TLC, and from which it proved impossible to isolate any identifiable product—certainly no trace of the nine-membered lactone was observed.



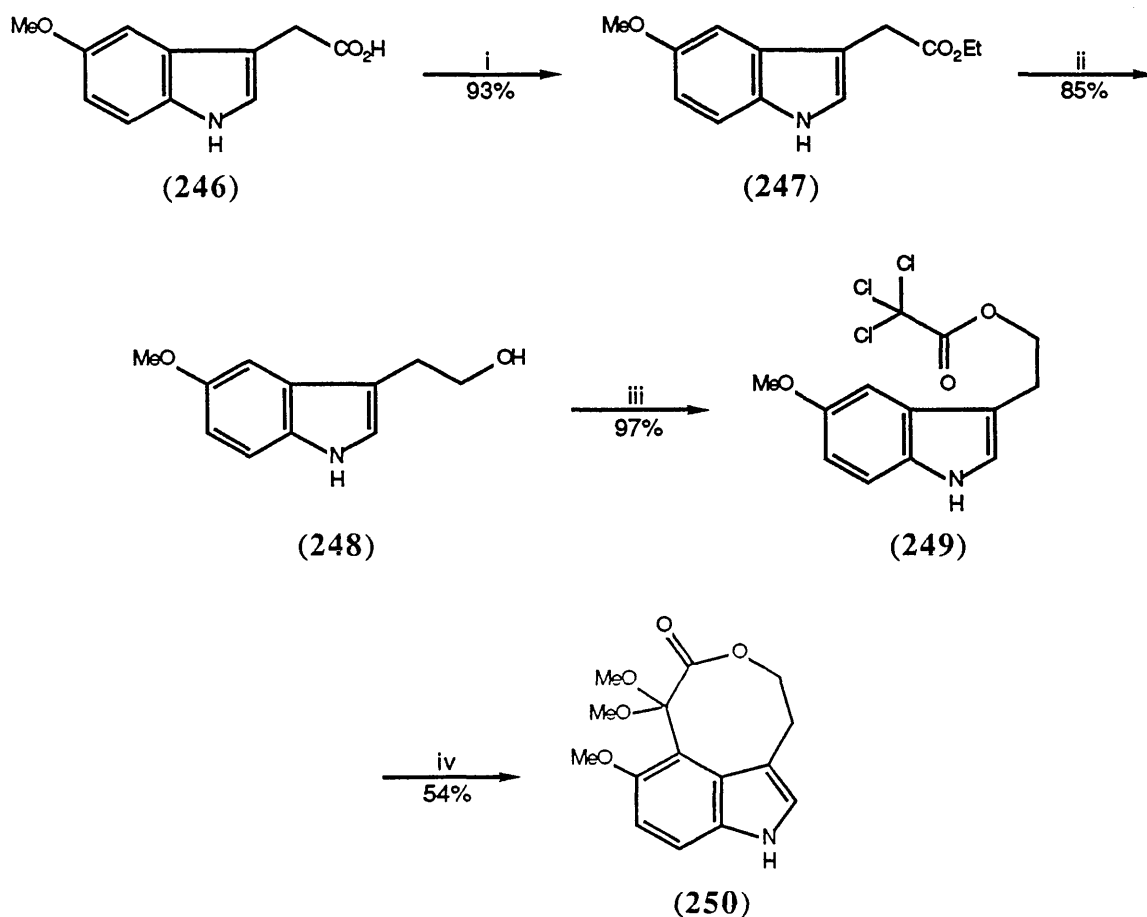
Scheme 61. Reagents: i, Cl_3CCOCl , pyridine, DCM, 0°C ; ii, $h\nu$, MeCN/MeOH.

In order to apply the reaction to the formation of a seven-membered lactone, indole-3-methanol would be required as a starting material. Derivatives of this alcohol are usually unstable, readily undergoing elimination of the oxygen function unless an electron-withdrawing group is attached to the indole nitrogen. Therefore, it was necessary to determine whether or not the photocyclisation would be successful if such a group was present. To this end, the *N*-BOC derivative (239) of tryptophyl trichloroacetate (192) was prepared and photolysed (Scheme 62). The result, although disappointing, was significant—*N*-BOC tryptophol (240) was isolated in 77% yield, showing that a reduction of the electron-density in the indole ring impedes cyclisation. This result obviously suggested that the *N*-protected indole-3-methanol example would be unsuccessful, so

In view of the previous results, the effect of a non electron-withdrawing group on the nitrogen atom was investigated by the synthesis and irradiation of the *N*-methyl derivative (244) (Scheme 63).



Attempts to form the *N*-methyl indole (244) by directly methylating the NH compound (192) were, perhaps not surprisingly, unsuccessful due to the rather sensitive trichloroester functionality. Therefore, a more piece-meal approach was adopted. Commercially available ethyl indole-3-acetate (241) was *N*-methylated under standard conditions to give a 51% yield of indole (242). Lithium aluminium hydride reduction of (242) proceeded smoothly to form the known¹⁴³ tryptophol derivative (243) in 97% yield. Trichloroacetylation of (243) gave a 96% yield of the required photolysis substrate (244). Irradiation of this resulted in successful cyclisation to form the *N*-methyl derivative (245) of the previously described lactone (193), illustrating that *N*-alkyl substituents do not significantly impede the cyclisation.



Scheme 64. Reagents: i, (a) DEAD, Et₂O, (b) Ph₃P, EtOH, Et₂O; ii, LiAlH₄, Et₂O; iii, Cl₃CCOCl, pyridine, DCM, 0°C; iv, hv, MeCN/MeOH.

Since the presence of an electron-withdrawing group results in the failure of the cyclisation, it was reasoned that the presence of an electron-releasing group might favour cyclisation. The 5-methoxytryptophol derivative (249) was therefore prepared starting from the commercially available 5-methoxyindole-3-acetic acid (246) (Scheme 64), in a similar fashion to the *N*-methyl compound described earlier.

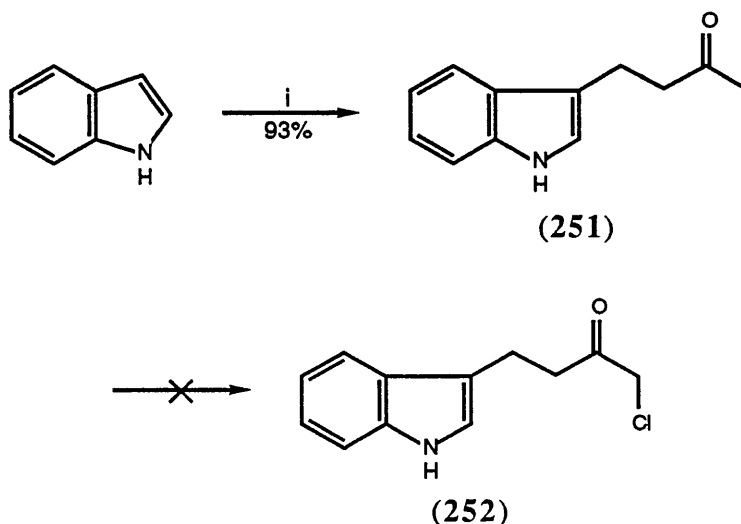
Direct reduction of acid (246) with diborane proved not to be a clean reaction, resulting in the formation of several compounds in addition to the required alcohol (248)—these were possibly derived from partial reduction of the pyrrole ring. For this reason, it was decided to proceed *via* reduction of the ester. Formation of the ethyl ester of (246) was effected by the Mitsunobu reaction¹⁴⁴ to give a 93% yield of ester (247). Although rather an exotic method for ester formation, the process when used did give consistently high yields, which was particularly important in this case due to the considerable expense of the starting acid (246).

Reduction of ester (247) with lithium aluminium hydride gave 5-methoxytryptophol (248) in 85% yield. Simple trichloroacetylation of this produced trichloroester (249), which on photolysis, cyclised to give a 54% yield of lactone (250). Possibly of more significance than the increased yield is the fact that the reaction was complete, and all starting material consumed, in *less than half the time taken for the complete reaction of tryptophyl trichloroacetate*. These two observations show that an increase in electron-density in the indole ring clearly favours the photocyclisation, most likely due to the increased ease with which electron-transfer can occur.

3.3.3.2 Ketones.

Although the photocyclisations of chloro-amides and -esters have now been investigated in some detail, no photocyclisations of α -chloroketoindoles have ever been reported. Investigation of these compounds would be interesting and potentially useful, since, if successful, a 3,4-bridging carbocyclic ring would result, leading to possibilities in the synthesis of clavine alkaloid analogues, for example.

The first example studied was a continuation of some earlier work in our laboratory,¹²⁴ in which α -chloroketone (252) was the synthetic target (Scheme 65). The parent ketone (251) had already been synthesised by Michael addition of indole to methyl vinyl ketone, and its chlorination attempted under a variety of conditions, without success.

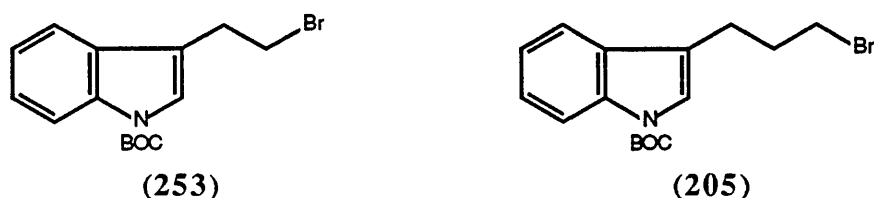


Scheme 65. Reagents: i, MVK, Ac₂O, AcOH.

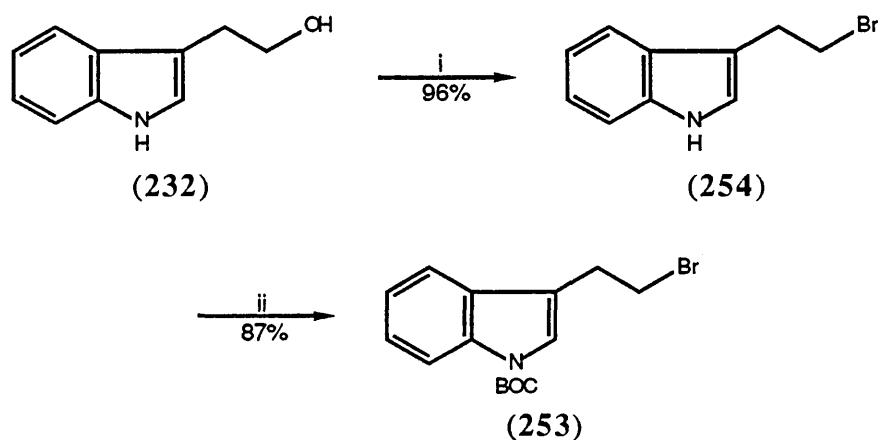
In view of the difficulties experienced with the chlorination of the esters and amide described in Section 3.3.2, and the eventual solution which was found, it was decided to attempt the chlorination with lithium isopropylcyclohexylamide as base. The results of this brief study were unsuccessful, using either (251), or its *N*-protected analogue. It was therefore decided to abandon the study of the monochloroketone, and try a totally different approach to dichloroketones.

A convenient synthesis of dichloroketones consists of the treatment of acetylenes with *N*-chlorosuccinimide in methanol to give intermediate dichlorodimethyl ketals, which can be hydrolysed to the corresponding ketones.¹⁴⁵ This reduces the problem to the synthesis of an indole with a terminal acetylene attached to the 3-position, although protection of the indole nitrogen as its *N*-BOC derivative will be required in order to divert the chlorine from the indole ring. Initial studies indicated that the introduction of the acetylene portion,

which was to be achieved by the well-documented¹⁴⁶ displacement of halide from an indole-3-alkyl halide, would also require the presence of a protecting group to prevent complications due to the NH group. In view of this, suitable intermediates for the preparation of the photocyclisation precursors to the 7- and 8-membered rings are the *N*-BOC bromoalkylindoles (253) and (205), respectively.



The preparation of (205) has already been discussed (Section 3.3.2.1), and (253) was prepared in a similar way from tryptophol (232) (Scheme 66).

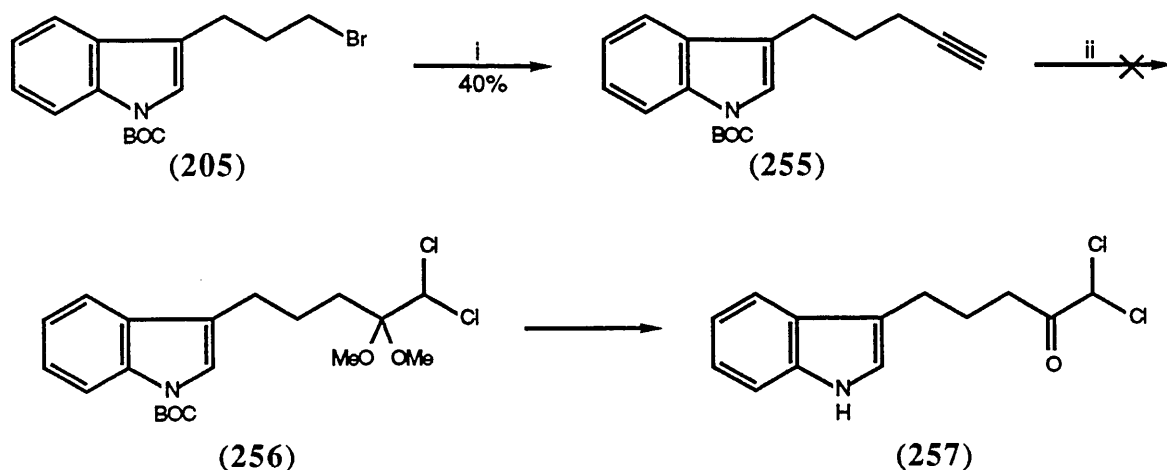


Scheme 66. Reagents: i, Ph_3P , CBr_4 , DCM; ii, $(\text{BOC})_2\text{O}$, DMAP, MeCN.

Treatment of tryptophol (232) with triphenylphosphine and carbon tetrabromide gave the known¹⁴⁷ bromoethylindole (254) in 96% yield; protection of this gave an 87% yield of the *N*-BOC compound (253).

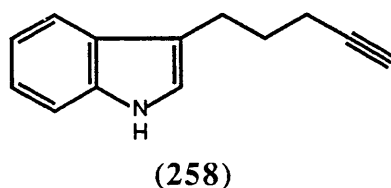
Since the bromopropyl compound (205) had already been prepared, this was to be elaborated first (Scheme 67).

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Scheme 67. Reagents: i, $\text{NaC}\equiv\text{CH}$, DMF, 0°C ; ii, NCS, MeOH.

Reaction of the bromide (205) with sodium acetylide in DMF at 0°C gave a 40% yield of acetylene (255), together with 30% of the deprotected compound (258), which could be reprotected to give (255) in 88% yield.

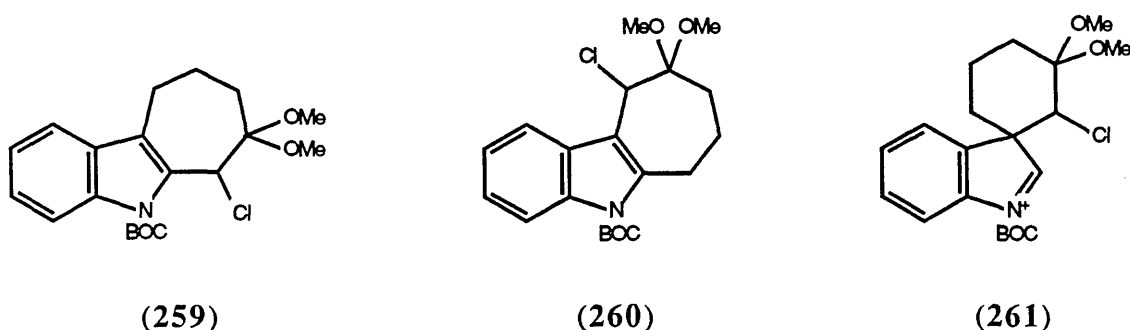


A variety of conditions, particularly with regard to the order of addition of reagents and temperature, were investigated in an attempt to reduce the amount of deprotection, but addition of the sodium acetylide to the bromide in DMF at 0°C proved to be the method of choice. In practice, the accompanying deprotection did not present a problem since the crude product from the reaction was simply treated with a suitable quantity (as judged by NMR) of di-*tert*-butyl dicarbonate and dimethylaminopyridine in acetonitrile, to enable the *N*-protected acetylene (255) to be isolated.

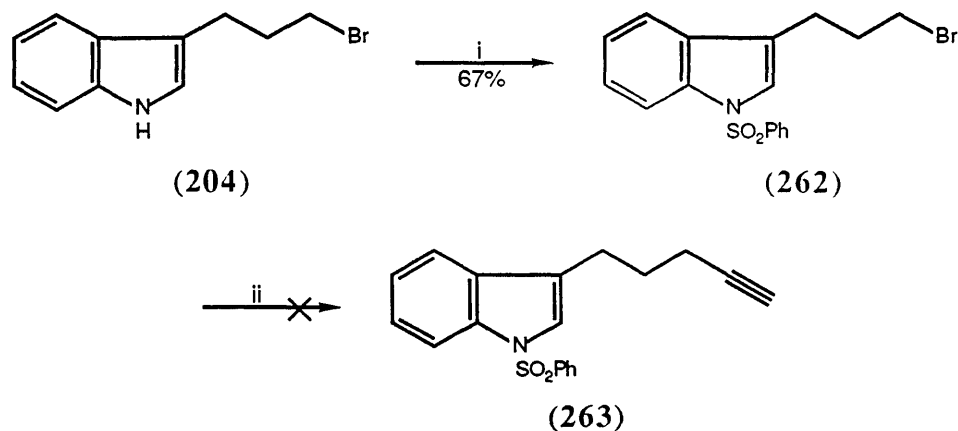
Problems were immediately encountered during the NCS step. The reaction was remarkably sluggish, and in dried methanol would not proceed at all. However, on heating the mixture, decomposition was observed. The use of a five-fold excess of NCS did effect

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a more rapid reaction, but the material isolated consisted of an approximately 1:1 mixture of unidentifiable oily products. The NMR spectra showed the absence of the indole 2-proton, but indicated that the *N*-BOC group was still present, together with two methoxy groups, while the mass spectra suggested that the molecular formula was $C_{20}H_{26}ClNO_4$ (M^+ 379/381) in each case. This corresponds to the required product (256), less HCl. All the available evidence therefore suggests that (259) and (260) *could* be the isolated compounds, possibly derived from (261), but no additional evidence is available to support this.



Regardless of the structures of the isolated products, the reaction had obviously been unsuccessful, and the loss of the indole 2-proton suggested that the reactivity of the ring needed to be decreased further in order to increase the chance of success. To this end, the more electron-withdrawing benzenesulphonyl group was used to protect the indole nitrogen.



Scheme 68. Reagents: i, NaH, $PhSO_2Cl$, C_6H_6 ; ii, $NaC\equiv CH$, DMF, $0^\circ C$.

Treatment of bromopropylindole (204) with a mixture of sodium hydride and benzenesulphonyl chloride in benzene gave a satisfactory yield of the protected indole (262) (Scheme 68).

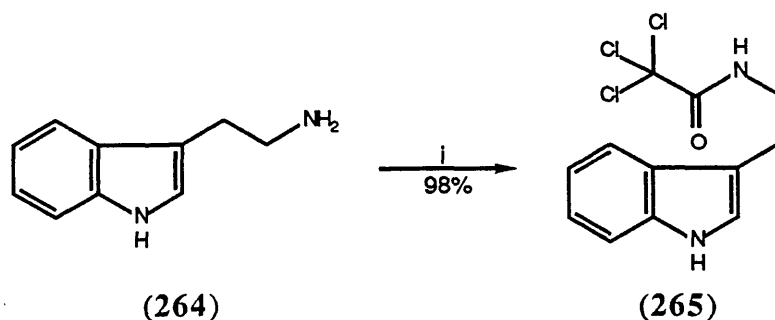
However, reaction of (262) with sodium acetylide failed to produce any of the *N*-protected acetylene (263). Instead a mere 27% yield of the deprotected acetylene (258) was obtained. Plans to reverse the stages and form the acetylene from the bromide *before* protection were thwarted by the discovery that it was not possible to reprotect indole (258) as the benzenesulphonyl compound. Several attempts resulted in either the isolation of starting material, or in decomposition to unidentified products. Since the NCS reaction was so problematic, it was decided that the chances of success with the synthesis of the photocyclisation precursor of the seven-membered ring were also remote. For this reason, the synthesis of α -chloroketones had to be abandoned to give precedence to further investigations which will now be discussed.

3.3.3.3 Amides.

Although extensive work has been done on *endo* monochloroamides, as evidenced in Section 3.2.3, with the exception of the work from our laboratory the extension of the reaction to polychloroamides has received little attention. As already mentioned, the photolysis of these polychloro compounds generally results in improved yields and regioselectivity—this was used to good effect in the synthesis of indolactam V, mentioned earlier. An additional advantage offered by a polychlorinated substrate is the increased degree of functionalisation in the product, introduced as a result of the presence of the extra chlorine atom(s). It was therefore desirable to apply the reaction to the synthesis of some other, more functionalised, azocinoindoles derived from indole trichloroacetamides.

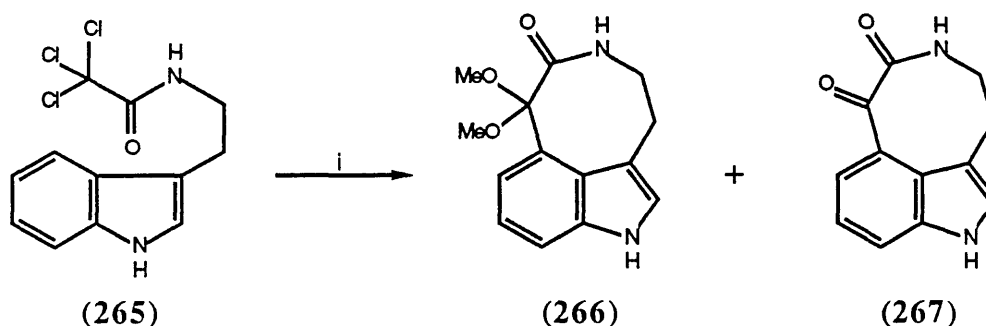
The example chosen was tryptamine trichloroacetamide (265), easily prepared in high yield by treatment of tryptamine (264) with trichloroacetyl chloride in the presence of pyridine in dichloromethane (Scheme 69).

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Scheme 69. *Reagents:* i, Cl_3CCOCl , pyridine, DCM, 0°C .

Photolysis of (265) in methanolic acetonitrile gave a 42% yield of the expected dimethoxy azocinoindole (266), together with 12% of the ketoamide (267) (Scheme 70).

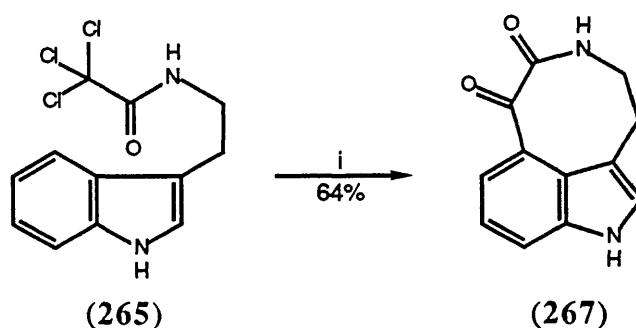


Scheme 70. *Reagents:* i, $h\nu$, MeCN/MeOH.

The ketoamide probably arose by hydrolysis of dimethyl ketal (266) during work-up, since both the methanol and the acetonitrile used had been dried prior to use. In addition, a trace of what looked by NMR to be the product of cyclisation to the 2-position was observed. However, the proportion of this compound was minimal, and sufficient could not be isolated for complete characterisation. It is instructive to compare this result with the photolysis of *N*-chloroacetyltryptophan, which was reported to cyclise to *both* the 2- and 4-positions, the former process accounting for *up to* 25% of the cyclised material produced from the reaction.¹²⁴

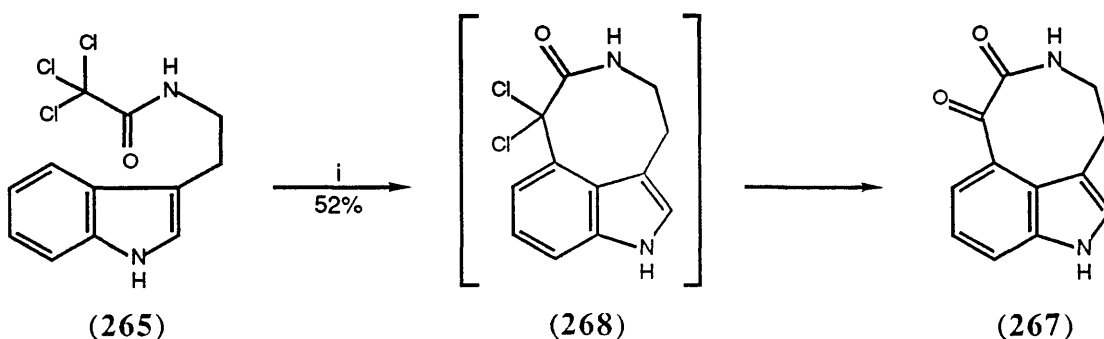
To increase the yield of the ketoamide (267), the photolysis of (265) was performed in aqueous acetonitrile, resulting in a 64% yield of (267) (Scheme 71).

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Scheme 71. Reagents: i, hv, MeCN/H₂O.

The reaction was repeated several times to try and optimise the yield of (267). Although the highest yields were obtained when the concentration of (265) was around 200 mg/100 ml, it was possible to increase the concentration to around 400 mg/100 ml before the yield of (267) suffered seriously. Also, the work-up procedure was greatly improved. Evaporation of the photolysis solution to approximately 20 ml was followed by the addition of *ca.* 50 ml of water to the dark green suspension. Thorough extraction of this mixture with dichloromethane resulted in a green-brown organic layer which was washed with brine. It was found to be necessary to re-extract the brine with dichloromethane, otherwise the yield was considerably reduced. The combined yellow-orange extracts were dried over magnesium sulphate, evaporated, and purified by column chromatography to give the product.



Scheme 72. Reagents: i, hv, MeCN.

In an attempt to try to isolate the intermediate *gem*-dichloro compound (268), trichloroacetamide (265) was photolysed in pure acetonitrile, without methanol or water present (Scheme 72). Upon work-up, no trace of (268) was found, instead ketoamide (267) was isolated in 52% yield.

It was possible that the dichloro compound had hydrolysed on work-up, so to investigate this possibility the reaction was repeated without the attempted isolation. The crude photolysis solution was evaporated to dryness, and a mass spectrum of a sample was recorded. However, again no trace of (268) could be observed, instead peaks corresponding to ketoamide (267) were found. It therefore seems likely that the *gem*-dichloro compound is unstable, and readily converted to the ketoamide under the conditions of the reaction.

This investigation, and particularly the optimisation of the work-up procedure and yield of ketoamide (265), was of direct relevance to the attempted synthesis of aurantioclavine, described in the next Chapter.

3.3.4 Conclusion.

This Chapter has detailed the results of the application of the photocyclisation reaction to the synthesis of a variety of [cd]-fused indoles. The generality has been greatly extended, and the reaction has now been applied to both *exo* and *endo* chloro- and polychloro-esters and the corresponding amides. Although the reaction proved a disappointment when applied to *exo* compounds, this was compensated for by the very promising results obtained with *endo* trichloroesters.

In general, it seems that the reaction is disrupted when β -elimination is possible, giving rise to α,β -unsaturated esters and amides. Also, the presence of an electron-withdrawing group attached to the indole nucleus impedes cyclisation, and results in side reactions. However, further activation of the indole ring, for example by the presence of a methoxy substituent, was shown to accelerate the cyclisation reaction, resulting in higher yields and shorter reaction times. This is largely to be expected, since the basis of the cyclisation is

the collapse of an electron-deficient radical onto an electron-rich ring system—increasing the electron density in the ring should favour the cyclisation, as is indeed the case. It is noticeable that trichloro compounds exhibit improved regioselectivity over the corresponding monochloro compounds, usually greatly favouring 4-cyclisation. The reason for this is not clear, although it *may* be a steric effect, the two chlorine atoms which remain in the radical cation intermediate disfavours the twisting of the C-3 side chain into a position suitable for reaction at the 2-position.

The reaction was successfully applied to the synthesis of a number of substituted azocinoindoles, and the reaction conditions for this process were optimised, with the result that ketoamide (267) can now be prepared in two steps from tryptamine in 63% overall yield. Ketoamide (267) is a crucial intermediate for a synthesis of aurantioclavine, discussed in the next Chapter.

FOUR

*Photocyclisations in
Aurantioclavine and Clavicipitic
Acid Syntheses*

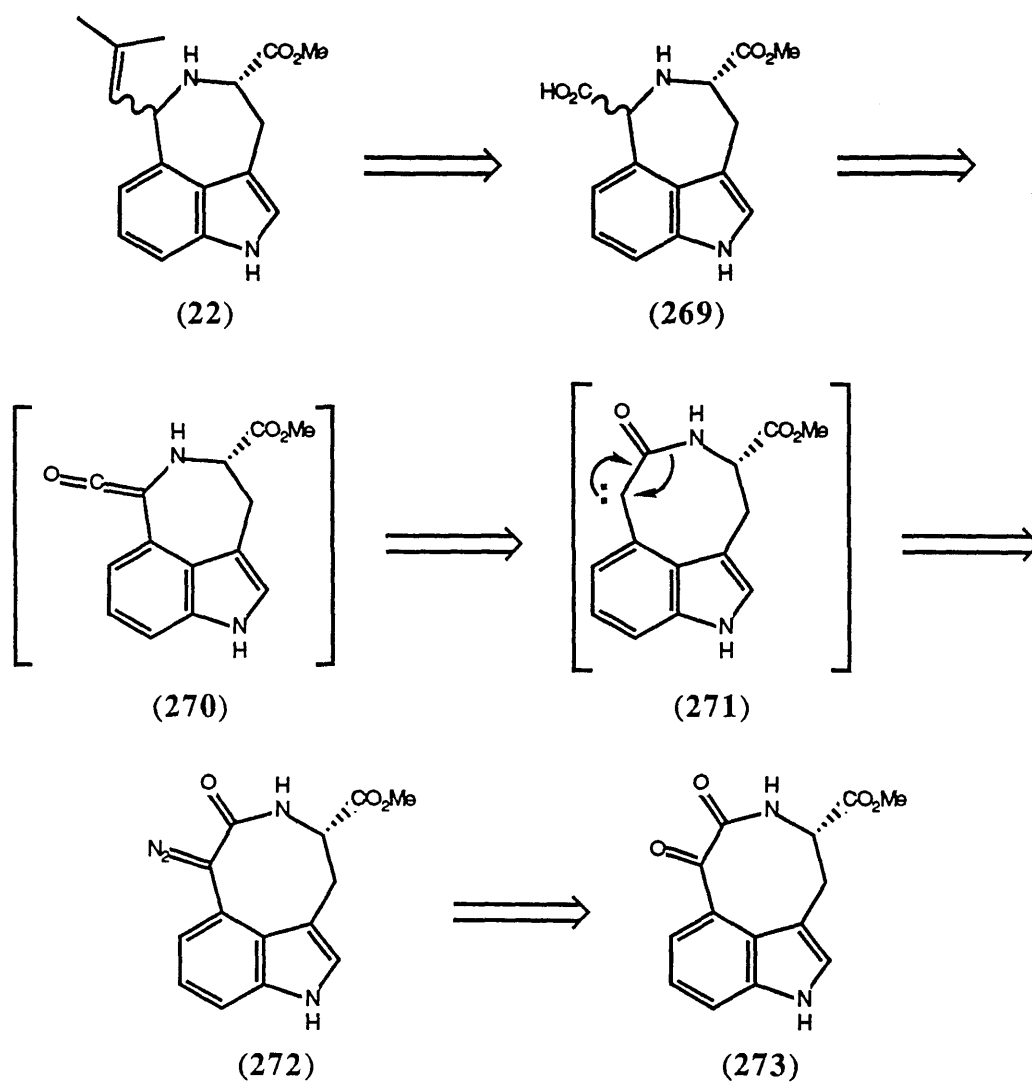
4.1 Introduction

The review in Chapter 1 clearly illustrated that the published laboratory syntheses of clavicipitic acid and aurantioclavine consist, almost without exception, of the ring-closure of a 3,4-disubstituted indole in order to form the bridging azepine ring. A novel, high-yielding approach would achieve a rapid entry to the clavicipitic acid ring-system by means of ring-contracting an azocinoindole, which in turn can be readily derived via the photocyclisation reaction. Scheme 73 shows the retrosynthetic analysis of such a strategy, applied to the more easily handled methyl ester of clavicipitic acid.

Simple functional group interconversion shows that the 2-methyl-1-propenyl side chain in (22) can be readily derived from a carboxylate function (269). Conversion of (269) to the aldehyde, followed by a Wittig reaction using the ylide derived from the known¹⁴⁸ isopropyltriphenylphosphonium iodide would be expected to give clavicipitic acid methyl ester. The crucial step in the synthetic scheme is the ring contraction which would give rise to acid (269). It was envisaged that this contraction could be achieved by a Wolff rearrangement of a diazocarbonyl compound, as shown in Scheme 73. Ketoamide (273), which can be derived by photocyclisation of *N*-trichloroacetyltryptophan methyl ester,¹²⁴ would be converted into the diazo compound (272). Hopefully, on photolysis, (272) would undergo a Wolff rearrangement to give the ring-contracted product (269); hydrol-

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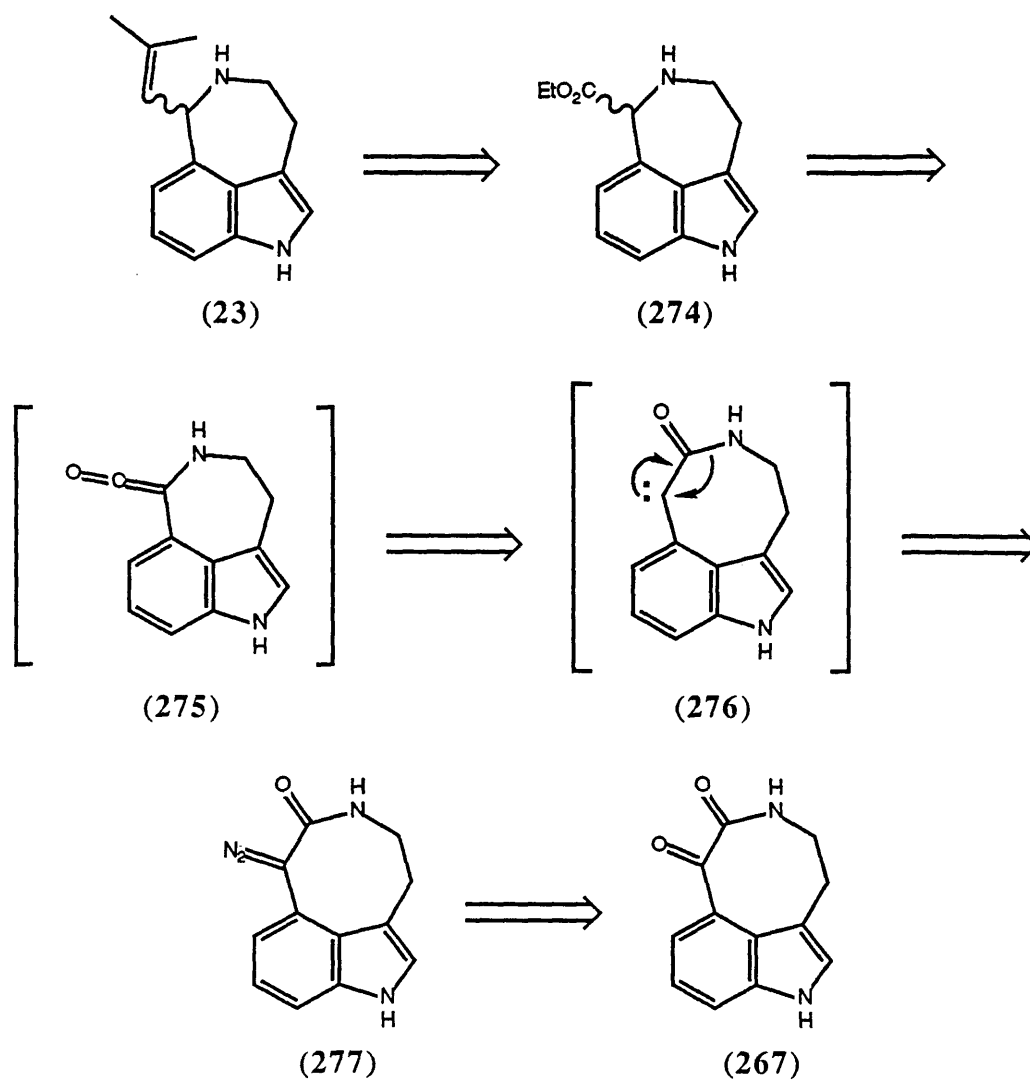
ysis of the intermediate ketene (270) would introduce the acid functionality. The carboxylic acid group was chosen so that it could be selectively transformed into the aldehyde in the presence of the methyl ester.



Scheme 73

The whole of Scheme 73 represents a completely new strategy in the synthesis of clavicipitic acid, and it was intended to apply the same idea to the synthesis of aurantio-clavine (Scheme 74). It was anticipated that this synthesis would be even simpler, since only one carboxylate group is present in the intermediate (274), thus negating the need for selective reductions.

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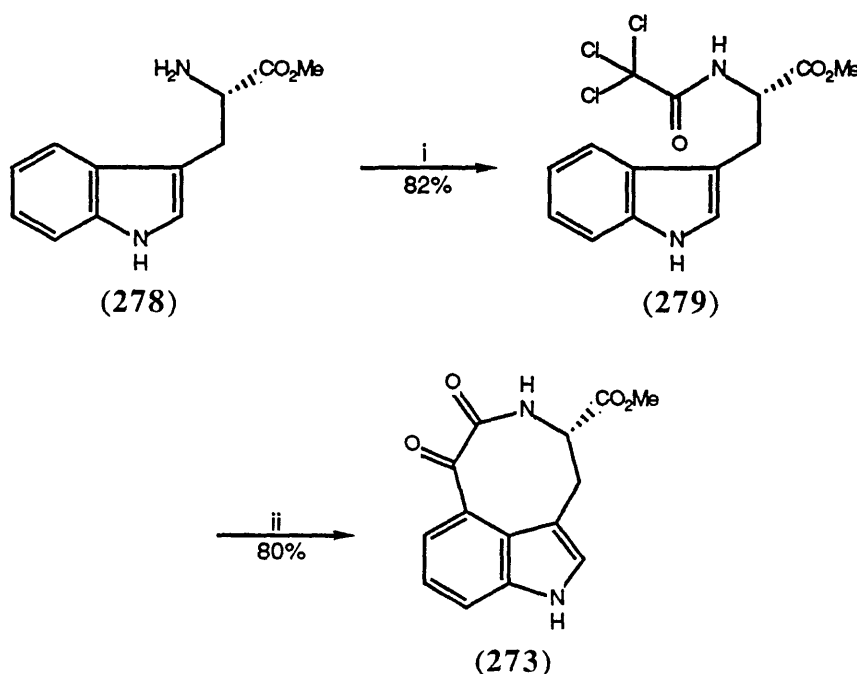
Scheme 74

The transformation of ester (274) to aurantioclavine would be achieved in a similar fashion to that described for clavicipitic acid, *i.e.* via the aldehyde and a Wittig reaction. Ester (274) would hopefully be derived from a Wolff rearrangement, as before, except that an ethanolic work-up would produce the ester functionality. The diazo precursor for this rearrangement would in turn come from ketoamide (267), the synthesis of which was described in Chapter 3.

The results of these synthetic studies are now presented, starting with clavicipitic acid.

4.2 Clavicipitic Acid

To achieve the synthesis of clavicipitic acid, suitable quantities of the azocinoindole (273) were required. This compound was prepared in 80% yield by the photolysis of *N*-trichloroacetyltryptophan methyl ester (279), itself readily obtained in high yield from tryptophan methyl ester (Scheme 75).



Scheme 75. Reagents: i, Cl_3CCOCl , pyridine, DCM, 0°C ; ii, $h\nu$, $\text{MeCN}/\text{H}_2\text{O}$.

The photolysis of (279) was studied extensively in order to optimise the yield of (273). Eventually, a reproducible 80% yield of (273) was obtainable from the photolysis of a 300 mg/100 ml solution of (279). It was also found that a work-up similar to that described for (267) (Section 3.3.3.3) resulted in both a higher yield of (273) and a simplified purification process.

The next stage of the synthesis was the preparation of the diazo compound (272) from ketoamide (273). One of the most versatile methods of converting carbonyl compounds to diazo compounds is the Bamford-Stevens reaction,¹⁴⁹ in which a carbonyl compound is treated with *p*-toluenesulphonyl hydrazine to form an intermediate tosyl hydrazone, which

is then cleaved with base to form the diazo compound. It was thought that this would be a more suitable method than reaction of hydrazine itself with (273), followed by oxidation of the hydrazone, since the hydrazine was likely to also react with the methyl ester function in (273).

The condensation of *p*-toluenesulphonyl hydrazine with carbonyl compounds is reported to occur under a variety of conditions, including acid catalysis. It was therefore decided to treat (273) with *p*-toluenesulphonyl hydrazine in methanol to which a few drops of hydrochloric acid had been added. No reaction was observed, but on warming, decomposition occurred, leading to intractable, polar products.

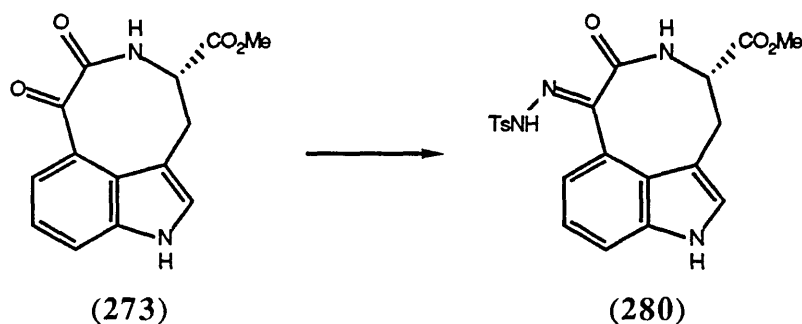


Table 2. Reaction of ketoamide (273) with *p*-toluenesulphonyl hydrazine.

catalyst	solvent	temp./°C	time/h	result	reference
none	MeOH	ambient	24	no reaction	150a
none	MeOH	reflux	24	no reaction	150b
dil. HCl	MeOH	ambient	48	no reaction	—
dil. HCl	MeOH	25→reflux	0.5	decomp.	150c
none	EtOH	reflux	24	no reaction	150d
AcOH	glac. AcOH	40→reflux	0.5	decomp.	150e
BF ₃ .OEt ₂	Et ₂ O	ambient	48	no reaction	—
BF ₃ .OEt ₂	THF	ambient	48	no reaction	—
BF ₃ .HOAc	THF	ambient	1	decomp.	—

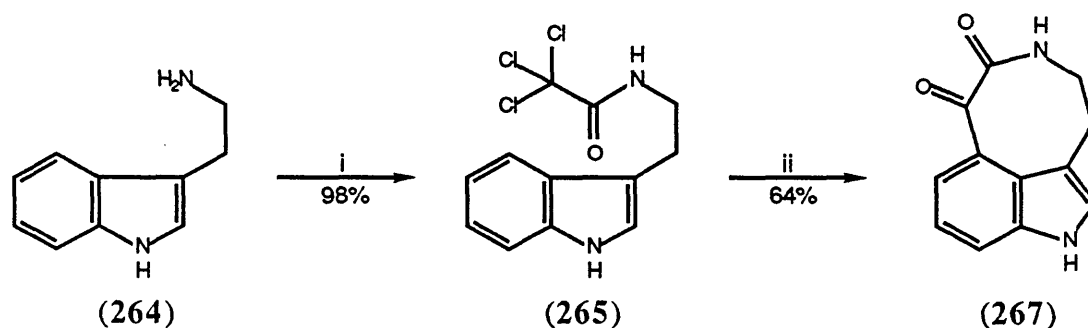
Some considerable time was therefore spent trying to find the correct conditions for reaction—the results of this investigation are presented in Table 2. During this study, two things became apparent. Firstly, no reaction was observed when a catalyst was not present, and secondly, heating the reaction mixture with an acid catalyst present led only to decomposition. Isolation of these rather polar decomposition products was attempted in a few cases, but without success. Since protic acids led to failure, Lewis acid catalysis was briefly investigated. Treatment of a suspension of (273) in ether with boron trifluoride etherate complex was unsuccessful, but this may have been due to the insolubility of (273) in ether. To circumvent this problem, the reaction was repeated in THF, in which (273) is noticeably more soluble. Again, however, no reaction was observed. Use of the harsher boron trifluoride-acetic acid complex led only to decomposition. The failure of this reaction is probably largely due to the presence of the methyl ester function, which provides another site for reaction of the *p*-toluenesulphonyl hydrazine. Models suggest that the ketoamide, although more reactive than the ester group, suffers from steric hindrance caused by the ester functionality. It seems likely, therefore, that any attempt to use more forcing reaction conditions will result in, at best, a mixture of products. In view of this rather disconcerting result, it was decided to investigate the synthesis of aurantioclavine.

4.3 Aurantioclavine

With the discovery of the problem associated with the synthesis of clavicipitic acid, attention was immediately turned to the synthesis of aurantioclavine. As already mentioned, the absence of the methyl ester in this compound was expected to make the synthesis easier, and it was hoped that the problem with the *p*-toluenesulphonyl hydrazine reaction would be either non-existent, or at least more readily overcome. Another option, not available for the synthesis of clavicipitic acid, might be possible for this synthesis, namely the use of hydrazine itself followed by oxidation to the hydrazone.

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The synthesis was to proceed *via* ketoamide (267) (Scheme 76), the preparation of which has already been described in detail (Section 3.3.3.3).



Scheme 76. Reagents: i, Cl_3CCOCl , pyridine, DCM, 0°C ; ii, $h\nu$, $\text{MeCN}/\text{H}_2\text{O}$.

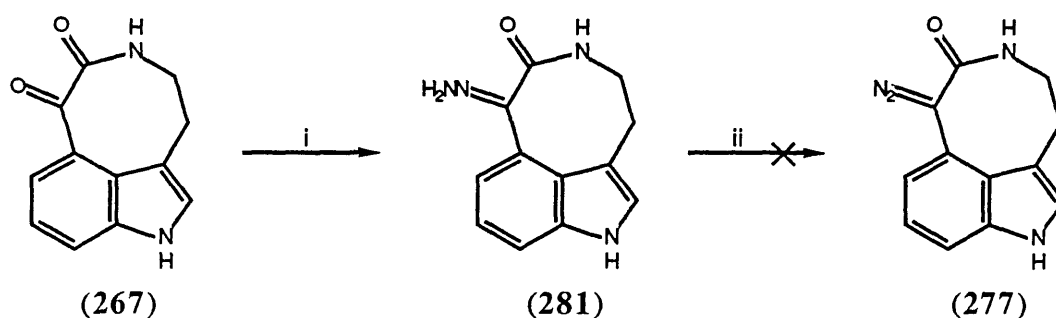
Table 3. Reaction of ketoamide (267) with hydrazines.

reagent	solvent/catalyst	temp./ $^\circ\text{C}$	time/h	result	reference
TsNHNH_2	MeOH/none	ambient	24	no reaction	150a
TsNHNH_2	MeOH/none	reflux	24	no reaction	150b
TsNHNH_2	$\text{MeOH}/\text{dil. HCl}$	ambient	72	no reaction	—
TsNHNH_2	$\text{MeOH}/\text{dil. HCl}$	$25 \rightarrow \text{reflux}$	1	decomp.	150c
TsNHNH_2	EtOH/none	reflux	48	no reaction	150d
TsNHNH_2	glac. AcOH	$40 \rightarrow \text{reflux}$	0.5	decomp.	150e
TsNHNH_2	DMF/none	100	24	no reaction	—
TsNHNH_2	$\text{DMF}/\text{dil. HCl}$	100	1	decomp.	—
$\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$	MeOH/none	ambient	1	no reaction	—
$\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$	$\text{H}_2\text{O}/\text{AcOH}$	ambient	18	no reaction	150f
NH_2NH_2	MeOH/none	ambient	24	no reaction	—
NH_2NH_2	none/none	ambient	1	reaction ^a	—
TsNHNH_2	$\text{Et}_2\text{O}/\text{BF}_3 \cdot \text{OEt}_2$	ambient	72	72% yield ^a	—
TsNHNH_2	$\text{THF}/\text{BF}_3 \cdot \text{OEt}_2$	ambient	72	43% yield	—
TsNHNH_2	$\text{THF}/\text{BF}_3 \cdot \text{HOAc}$	ambient	4	decomp.	—

^a See text.

Reaction of ketoamide (267) with either *p*-toluenesulphonyl hydrazine, or indeed with hydrazine itself, again proved problematic. A variety of conditions similar to those described in Section 4.2 were investigated (Table 3).

Again, the failure of protic acid catalysis soon became apparent. However, the option of using the more reactive hydrazine and obtaining the diazo compound (277) by oxidation of the intermediate hydrazone (281) still existed, so this was investigated more thoroughly (Scheme 77).



Scheme 77. Reagents: i, anhydrous NH₂NH₂, R.T.; ii, HgO, Na₂SO₄, Et₂O, KOH/EtOH.

Attempted reaction of ketoamide (267) with hydrazine hydrate or anhydrous hydrazine in a variety of solvents, with or without acid catalysis, proved unsuccessful, no reaction being observed. However, treatment of (267) with a large excess of neat anhydrous hydrazine, in the absence of a solvent, rapidly gave rise to a slightly exothermic reaction to produce a bright orange coloured, very polar oil. This proved to be insoluble in any common solvent, including water, so unfortunately an NMR spectrum could not be obtained. However, the IR spectrum was consistent with the structure of hydrazone (281), although the two carbonyl stretches in (267) do overlap, preventing confirmation that the ketonic vibration is absent in (281). Slightly more satisfactory evidence for the correct structure came in the form of the mass spectrum, which showed a peak corresponding to the molecular ion of (281), together with a plausible fragmentation pattern. However, in view of the limited evidence available, the structure of this compound

can at best only be tentatively claimed as (281); the validity of this is questioned further by the results of subsequent reactions on this compound.

One of the most common reagents for oxidising hydrazones to diazo compounds is mercuric oxide,¹⁵¹ although other reagents such as silver oxide have also been used.¹⁵¹ If the product of the hydrazine reaction was indeed hydrazone (281), oxidation of this would be expected to yield α -diazoamide (277), the IR spectrum of which would be very characteristic. Therefore, (281) was treated with mercuric oxide under standard conditions.¹⁵² However, the IR spectrum of the crude reaction product showed no trace of a diazo absorption, and even on repetition of the reaction the same result was obtained. Although no other oxidants were investigated, the result casts further doubt on the structure of the product of the reaction of ketoamide (267) with hydrazine.

At this stage, the structure of (267) itself was becoming questionable. Other than 2-cyclised products, it is difficult to imagine alternative products which could be produced as a result of the photolysis of the trichloroacetamide, and which would agree with the available spectroscopic data. However, the lack of reactivity exhibited by the ketone group in (267) was disconcerting, so crystals were grown and submitted for X-ray analysis, in the hope that this would reveal some information regarding the environment of the ketoamide functionality.

The X-ray crystal structure of (267) (Figure 6) clearly shows the planar amide group, and the ketone group which is twisted out of the plane of the indole ring. The rather confined steric environment of this carbonyl group, due to the two methylene groups of the opposite side of the azocine ring, is also apparent. Obviously, the conformation of the compound in solution will be constantly changing, and therefore different to that in the solid state—however, the most important thing to come from Figure 6 is the confirmation that the structure of (267) is indeed correct.

It was then that Lewis acid catalysis in the reaction of (267) with *p*-toluenesulphonyl hydrazine was investigated. It was thought that the lack of reactivity shown by the ketone was a result of steric effects caused by the twisting of the 8-membered ring. By encourag-

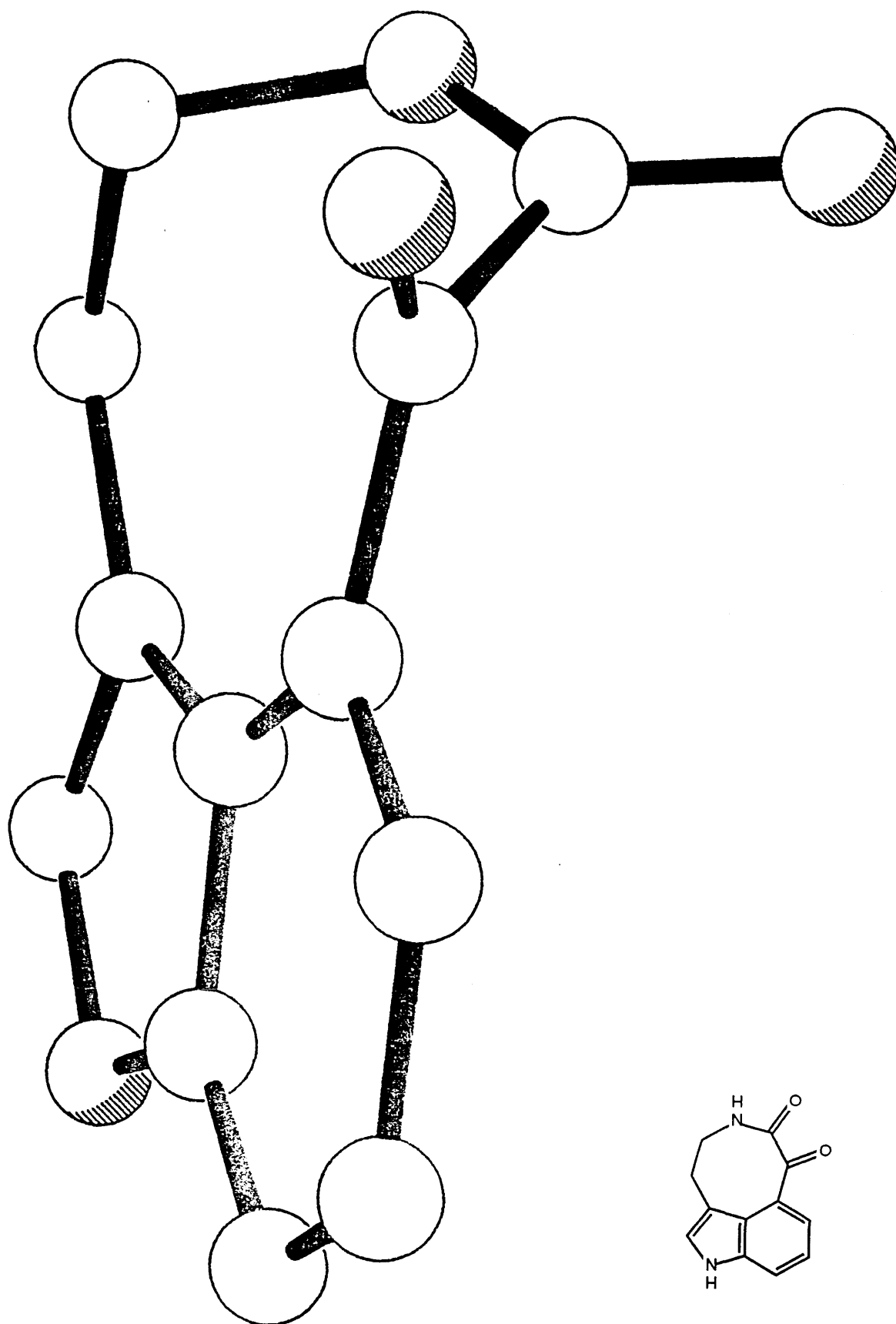
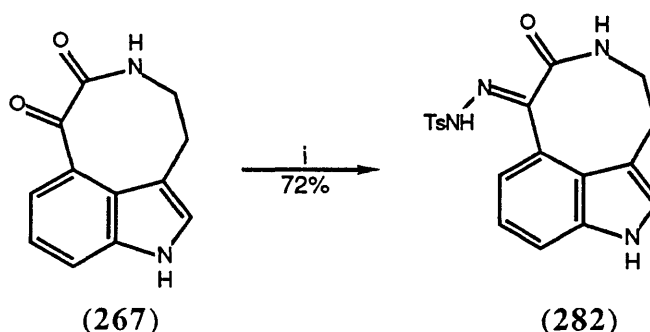


Figure 6. X-ray crystal structure of compound (267)

ing the ring to twist into a conformation more suitable for reaction, it was reasoned that the steric effects could be reduced, resulting in a greater chance of success. It was hoped that this twisting would be effected if the two oxygen atoms in (267) were complexed with a Lewis acid. Therefore, a golden-yellow suspension of (267) in ether was treated with 3 equivalents of boron trifluoride etherate complex. A colour change to dark green and partial dissolution of the solid material was immediately observed. *p*-Toluenesulphonyl hydrazine was then added to the mixture, which was stirred for a further 3 days. Standard work-up procedures afforded a 72% yield of *p*-toluenesulphonyl hydrazone (282) (Scheme 78). As is common with tosyl hydrazones, the mass spectrum of (282) showed no molecular ion, instead what was effectively a pyrolysis spectrum was obtained.

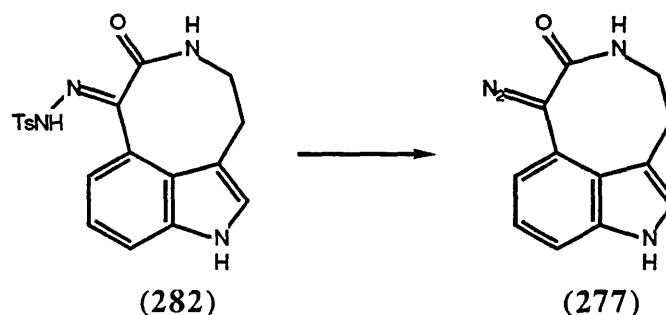


Scheme 78. Reagents: i, $\text{BF}_3 \cdot \text{OEt}_2$, TsNHNH_2 , Et_2O , R.T.

In order to try and reduce the conversion time, the reaction was studied further, particularly with regard to the solvent, the amount of boron trifluoride etherate complex, and the temperature. Changing the solvent to THF, in which (267) is very much more soluble, actually decreased the yield of (282) obtained. It was also found that increasing the amount of boron trifluoride etherate complex to 5 equivalents had little effect, but increasing the quantity beyond this resulted in decreased yield. Increasing the temperature by performing the reaction in refluxing ether resulted in a slightly diminished yield. However, it was found that by placing the reaction vessel in an ultrasonic bath after the addition of the boron trifluoride etherate complex, and sonicating the mixture for up to 30 min, the yield could be improved so that a reproducible 78% yield of (282) could be

obtained. The use of alternative oxophilic Lewis acids was another possibility, but this was not investigated, the 78% yield of (282) being quite acceptable.

With useful quantities of (282) now in hand, attention was turned to the conversion of (282) to the diazo compound, (277) (Scheme 79).



Scheme 79

There have been a variety of bases used for this purpose, but probably the most mild method is the use of basic alumina in dichloromethane or ethyl acetate.^{153a} On a small (10 mg) scale this method did appear to work, as judged by the IR spectrum of the crude product. However, this reagent proved unsuitable for larger scale reactions, no trace of the desired product being observed.

Table 4. Treatment of tosyl hydrazone (282) with bases.

reagent	solvent	temp./°C	time/h	result	reference
Basic Al ₂ O ₃	DCM	ambient	24	no reaction ^a	153a
NaOEt	EtOH	25→60	24	no reaction	149
NaO(CH ₂) ₂ OH	HO(CH ₂) ₂ OH	25→100	24	no reaction	149
NaOH	H ₂ O	25→60	24	no reaction	153b
NaOMe	pyridine	60	6	no reaction	150e
<i>n</i> -BuLi	THF	-78→0	1	decomp.	—

^a See text.

Further investigation of the reaction, using a variety of other reagents, was therefore initiated (Table 4), but without success.

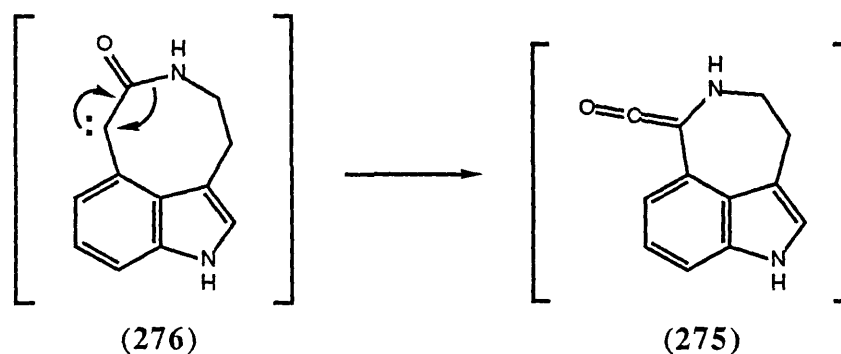
In view of the unsuccessful attempts to prepare *and isolate* the α -diazoamide (277), it was decided to form the anion of (282) with excess sodium hydride in THF and then photolyse the reaction mixture directly, in the hope that the diazo compound would be formed *in situ* and immediately undergo further reaction. A work-up with ethanol would ensure that if the reaction had been successful, the intermediate ketene (275) would be converted to the ethyl ester. Treatment of a solution of (282) in THF with 5 equivalents of sodium hydride produced a greyish suspension which was irradiated at 254 nm for 1.5 h. Upon work-up, a 27% mass return of a polar substance was obtained. Whilst the mass spectrum suggested that the molecular weight of this could be 200, the IR and NMR spectra were less clear. The NMR spectrum indicated that the material was in fact composed of at least two compounds, and also clearly showed the presence of an ethyl group. The presence of the indole ring was also indicated, suggesting that it had survived the reaction conditions. The IR spectrum on the other hand showed no peaks corresponding to a carboxylic ester, so it can be said with some certainty that the reaction was unsuccessful. However, little more information could be obtained from these spectra without further purification of the compounds, so this was attempted several times using column chromatography. Unfortunately, this proved unsuccessful, and purification could not be achieved by this or other methods. Also, regrettably, recrystallisation of a sample for X-ray analysis could not be achieved, and the synthesis had to be abandoned due to lack of time and material.

4.4 Conclusion

In the light of the rather negative outcome of these syntheses, little can be said regarding the application of this methodology to the synthesis of similar azepinoindole ring

systems. The initial problem associated with the attempted synthesis of clavicipitic acid *may* be overcome by the use of a protecting group to prevent unwanted reaction at the ester function. However, the difficulty associated with the ring-contraction step is a more complex problem. If a suitable method for the preparation of the α -diazamide is found, the difficulty may be simplified. If, however, the ring-contraction failed because of a more fundamental property of the ring system, then this would suggest that a modification is required in order to achieve success.

One possible source of the problem could be the amide group, which contains a certain amount of double bond character between the nitrogen atom and the carbonyl portion of this group. This would be expected to disfavour the crucial ring-contraction step (276) to (275) (Scheme 80).



Scheme 80

A possible way round this problem is to attach an electron withdrawing group, such as an acetyl or even a benzenesulphonyl group, to the azocine nitrogen. This would hopefully reduce the carbonyl-nitrogen electron density, resulting in less double bond character and therefore a greater chance of a successful ring contraction, however this was not investigated.

FIVE

*Experimental***5.1 Introduction****5.1.1 *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 of petroleum ether boiling between 40°C and 60°C, and was distilled through a 36 cm Vigreux column before use. 'Ether' refers to diethyl ether; this, together with benzene and toluene, was dried where necessary by standing over sodium wire for several days. THF was distilled from potassium benzophenone ketyl under nitrogen prior to use. Dichloromethane and carbon tetrachloride were dried where necessary by distillation from phosphorus pentoxide. DMSO and DMF were stirred for 15 h over barium oxide, decanted, and distilled under reduced pressure before storing over activated 4Å molecular sieves, under nitrogen. Pyridine, triethylamine, di-isopropylamine, and *N*-isopropylcyclohexylamine were each distilled from, and stored over, potassium hydroxide pellets. Mesitylene was distilled and stored over activated 4Å molecular sieves before use. Acetonitrile for photolyses was purified as follows: The reagent grade solvent was dried by stirring for 15 h over finely ground calcium hydride, and then distilled. Phosphorus pentoxide (5 g/l) was added, and the mixture was stirred for a further 15 h before being redistilled through a 30 cm glass-packed column. 'Tryptophan' in all cases refers to natural S-(-)-tryptophan, which was purchased from the Aldrich Chemical Company and used without further purification.

5.1.2 *Photochemistry.*

Photolyses were performed in a Rayonet type RS preparative photochemical reactor. Eight RUL 2537 Å lamps were used, giving a total output of 120 W predominantly (>99%) at 254 nm. Solutions of the substrates were placed in a quartz vessel, and degassed by passing a steady stream of dry nitrogen through the solution for at least 30 min prior to, and during, irradiation.

5.1.3 *Chromatography.*

Analytical thin layer chromatography was carried out on Merck Kieselgel 60 GF₂₅₄ aluminium-backed plates. Visualisation was achieved using u.v. light at 254 and 360 nm, iodine, and, in the case of indoles, by lightly spraying the plate with Ehrlich's reagent followed by gentle heating to produce a usually blue-purple colour. Ehrlich's reagent was prepared by adding 1 g of *p*-(dimethylamino)benzaldehyde to 100 ml of a 25% solution of concentrated hydrochloric acid in absolute ethanol. 'Column chromatography' refers to the technique described by Still,¹⁵⁴ and was performed on Merck Kieselgel 60 H, using medium pressure provided by means of hand-bellows. The sample mixture was applied to the top of the column as a solution in a small amount of the column eluant, or by preadsorption onto silica.

5.1.4 *Characterisation.*

Melting points (m.p.) were determined on a Kofler hot-stage microscope and are uncorrected.

Infra-red spectra ($\nu_{\max.}$) were recorded on either a Perkin-Elmer model 1710 or 883 Fourier transform infra-red spectrometer, the samples being analysed as thin films, Nujol mulls, or in solution, as indicated.

Ultra-violet/visible spectra ($\lambda_{\max.}$) were obtained using a Philips PU 8740 scanning spectrophotometer, the samples being dissolved in spectroscopic grade methanol.

Fourier transform proton nuclear magnetic resonance spectra (δ_{H}) were recorded on either a Bruker WM 200 (200 MHz), Bruker WM 250 (250 MHz), Jeol GSX 270 (270 MHz), or Bruker AM 500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million downfield of tetramethylsilane by referencing to the residual protons of the respective solvents. Coupling constants (J) in Hertz are included where possible. ^{13}C -Spectra (δ_{C}) were recorded on either the Jeol GSX 270 (67.9 MHz) or the Bruker WM 250 (62.9 MHz) instruments, and referenced to the solvent.

Electron impact ionisation mass spectra (m/z) were performed at Imperial College in the Organic Mass Spectrometry Laboratory, on an AEI MS 12 or a VG Micromass 7070 B mass spectrometer at an ionisation potential of 70 eV unless otherwise stated. Some accurate mass measurements were recorded by the Science and Engineering Research Council Mass Spectrometry Service Centre, University College, Swansea.

Elemental analyses were carried out in the Department of Chemistry, Imperial College, by the Departmental Micro-analytical Laboratory.

The X-ray crystal structure was determined by Dr. D. J. Williams and his group, in the Department of Chemistry, Imperial College.

5.2 Relating to Chapter Two

Spiro[1,2,3,4-*tetrahydronaphthalene*-1,2'-*oxirane*] (119).—Sodium hydride dispersion in mineral oil (60%; 0.88 g, 22.1 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (4.9 g, 22.1 mmol) was added, followed by dry DMSO (20 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 1-tetralone (2.50 g, 17.1 mmol) in dry DMSO (10 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (20 ml)

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was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a brown oil which was distilled in a Kugelröhr apparatus (oven temperature, 110°C , 0.45 mmHg) (lit.,⁹⁷ no b.p. given) to give the title compound (119) (1.77 g, 65%) as a colourless liquid (Found: C, 82.5; H, 7.8. Calc. for $\text{C}_{11}\text{H}_{12}\text{O}$, C, 82.5; H, 7.6%); ν_{max} (film) 2 940, 2 863, 1 493, 1 457, 1 039, 918, 841, 786, 759, and 724 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.82-1.91 (1 H, m, 2-CH), 2.00-2.24 (3 H, m, 2-CH and 3- CH_2), 2.90-2.98 (2 H, m, 4- CH_2), 3.03 (1 H, d, J 5 Hz, 3'-CH), 3.07 (1 H, d, J 5 Hz, 3'-CH), and 7.10-7.25 (4 H, m, 5-, 6-, 7- and 8-H); m/z 160 (M^+ , 40%), 159 (24), 132 (24), 131 (100, $M-\text{CHO}$), 129 (50), 128 (26), 115 (27), and 91 (25, C_7H_7^+).

Spiro[6,7,8,9-tetrahydro-5H-benzocycloheptene-5,2'-oxirane] (120).—Sodium hydride dispersion in mineral oil (60%; 1.13 g, 28.2 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (6.20 g, 28.2 mmol) was added, followed by dry DMSO (40 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 1-benzosuberone (3.47 g, 21.7 mmol) in dry DMSO (10 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (40 ml) was cautiously added. The resulting solution was extracted with ether (3 x 50 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a yellow oil which was distilled in a Kugelröhr apparatus (oven temperature, 80°C , 0.20 mmHg) to give the title compound (120) (3.35 g, 89%) as a colourless liquid (Found: C, 82.8; H, 8.4. $\text{C}_{12}\text{H}_{14}\text{O}$ requires C, 82.7; H, 8.1%); ν_{max} (film) 2 928, 2 854, 1 489, 1 444, 942, 876, 761, and 748 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.42-2.07 (6 H, m, 6-, 7- and 8- CH_2), 2.74 (1 H, dd, J 5.5 and 1.2 Hz, 3'-CH), 2.80-2.89 (2 H, m, 9- CH_2), 2.96 (1 H, d, J

5.5 Hz, 3'-CH), 7.08 (1 H, m, 3-H), 7.15 (1 H, d, J 3.5 Hz, 4-H), 7.17 (1 H, d, J 3.5 Hz, 1-H), and 7.36 (1 H, m, 2-H); m/z 174 (M^+ , 47%), 173 (72), 145 (100, M -CHO), 143 (21), 129 (49), 128 (32), 115 (29), and 91 (19, $C_7H_7^+$).

7,8-Benzobicyclo[4.2.0]oct-7-en-1-ol (121).—To a mechanically stirred solution of iron (III) nitrate nonahydrate (0.70 g, 1.73 mmol) in *ca.* 1.2 l of liquid ammonia at -70°C were added small pieces of sodium metal (2.3 g, 0.1 mol). Air was bubbled through the solution until the blue colour disappeared, then small pieces of sodium metal (55.7 g, 2.42 mol) were added. The mixture was stirred until the colour had changed from blue to grey (*ca.* 1.5 h), and then the ammonia was evaporated under a stream of nitrogen. THF (800 ml) was added, followed by a solution of cyclohexanone (100 ml, 0.97 mol) in THF (200 ml), which was added dropwise so as to maintain a temperature of 30 – 35°C . The solution was warmed to 40°C for 2 h, and then cooled to -5°C while bromobenzene (56 g, 0.36 mol) was added portionwise over 5 min. The mixture was stirred at -5°C for 15 h, then water (100 ml) was added dropwise very slowly to keep the temperature below 0°C (CAUTION). The mixture was poured onto ice and concentrated hydrochloric acid (300 ml), and this was then extracted with ether (1 x 500 ml, 1 x 250 ml). The organic phase was washed with water (2 x 1000 ml), 5% hydrochloric acid (800 ml), 10% aqueous sodium bicarbonate (2 x 300 ml), followed by brine (100 ml). The slightly yellow solution was dried (MgSO_4) and evaporated to give a pale yellow solid. One recrystallisation from 60 – 80°C petrol gave the title compound (121) (10.62 g, 17%) as a colourless crystalline solid, m.p. 109 – 110°C (lit.,⁹⁹ 108.5 – 109.5°C); (Found: C, 82.4; H, 8.4. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}$, C, 82.7; H, 8.1%); ν_{max} (film) 3 219, 2 926, 2 854, 1 457, 1 164, 1 081, 753, and 666 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.07–2.10 (8 H, m, 2-, 3-, 4-, and 5- CH_2), 2.26 (1 H, s, OH), 3.39 (1 H, t, J 5.1 Hz, 6-CH), and 7.13–7.32 (4 H, m, aromatic H); m/z 174 (M^+ , 19%), 146 (26), 145 (100), 132 (37), 131 (53), 128 (38), 117 (20), 115 (21), and 91 (20, $C_7H_7^+$). Evaporation of the recrystallisation filtrates,

followed by a second recrystallisation from 60-80°C petrol, afforded a crop of 7,8,9,10-tetrahydrobenzocyclo-octen-5(6*H*)-one (**106**) (2.60 g, 4%) as a colourless crystalline solid, m.p. 55-56.5°C (lit.,⁹⁹ 54-55°C); (Found: C, 82.6; H, 8.2. Calc. for C₁₂H₁₄O, C, 82.7; H, 8.1%); $\nu_{\max}$ (film) 3 031, 2 926, 2 855, 1 700, 1 461, 1 377, 758, and 701 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.78-1.88 (2 H, m, 9-CH₂), 1.97-2.26 (4 H, m, 7- and 8-CH₂), 2.39-2.59 (2 H, m, 6-CH₂), 3.60 (2 H, t, *J* 5.4 Hz, 10-CH₂), 7.12-7.16 (1 H, m, 2-H), and 7.25-7.37 (3 H, m, 1-, 3-, and 4-H); *m/z* 174 (*M*⁺, 52%), 131 (14), 130 (100), 117 (36), 115 (9), 104 (24), and 91 (20, C₇H₇⁺).

Spiro[7,8,9,10-tetrahydrobenzocyclo-octene-5,2'-oxirane] (**122**).—Sodium hydride dispersion in mineral oil (60%; 0.149 g, 3.73 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphonium iodide (0.76 g, 3.73 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 7,8,9,10-tetrahydrobenzocyclo-octen-5(6*H*)-one (**106**) (0.50 g, 2.87 mmol) in dry DMSO (5 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (20 ml) was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a brown oil which was distilled in a Kugelröhr apparatus (oven temperature, 100°C, 0.34 mmHg) to give the *title compound* (**122**) (0.28 g, 52%) as a colourless liquid (Found: C, 82.7; H, 8.6. C₁₃H₁₆O requires C, 82.9; H, 8.6%); $\nu_{\max}$ (film) 2 932, 2 859, 1 495, 1 447, 964, 927, 813, 761, and 701 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.45-2.08 (8 H, m, 5-, 6-, 7- and 8-CH₂), 2.36 (2 H, d, *J* 4.9 Hz, 4-CH₂), 3.00 (1 H, d, *J* 3.7 Hz, 3'-CH), 3.04 (1 H, d, *J* 3.9 Hz, 3'-CH), and 7.23-7.37 (4 H, m, ArH); *m/z* 188 (*M*⁺, 39%), 159 (5, *M*-CHO), 131 (14), 129 (22), 117 (15),

115 (17), 94 (22), and 91 (100, C₇H₇⁺).

4,4-Dimethylbutyrolactone (124).—Methylmagnesium iodide was prepared by the addition of a solution of methyl iodide (22.29 g, 0.157 mol) in dry ether (150 ml) to magnesium turnings (3.82 g, 0.57 mol) in dry ether (150 ml). The solution of the Grignard reagent was added with vigorous stirring over 45 min to a solution of ethyl levulinate (20.44 g, 0.142 mol) in ether (75 ml) and benzene (75 ml), which was held at 0°C during the addition. The ether was then removed by slow distillation, and the resulting benzene solution was heated at reflux for 3 h. After hydrolysis with dilute sulphuric acid (10 ml), the organic layer was separated, and the aqueous phase extracted with ether. Treatment of the combined extracts at 0°C with a solution of sodium hydroxide (40 g) in water (200 ml) gave an alkaline layer from which the lactone was generated with 50% sulphuric acid. This solution was saturated with ammonium sulphate, and extracted with ether. Solvent removal *in vacuo*, followed by distillation at reduced pressure, gave the title compound (124) (4.92 g, 30%) as a very pale yellow liquid, b.p. 96-100°C (20 mmHg) (lit.,¹⁰¹ 201-206°C (760 mmHg)); (Found: C, 63.2; H, 8.9. Calc. for C₆H₁₀O₂, C, 63.1; H, 8.8%); $\nu_{\max}$.(film) 2 978, 1 772, 1 376, 1 277, 1 255, 1 168, 1 137, 1 111, 959, and 934 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.39 (3 H, s, CH₃), 1.40 (3 H, s, CH₃), 2.03 (2 H, t, *J* 8.3 Hz, 3-CH₂), and 2.59 (2 H, t, *J* 8.3 Hz, 2-CH₂); *m/z* 114 (*M*⁺, 6%), 99 (100, *M*-CH₃), 70 (24), 59 (29), 56 (43), 55 (30), and 43 (84).

4,4-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-one (107).—To a stirred mixture of aluminium trichloride (7.08 g, 53.1 mmol) and thiophene-free dry benzene (10 ml) held at 5°C was added, over *ca.* 45 min, a solution of 4,4-dimethylbutyrolactone (124) (2 g, 17.5 mmol) in dry benzene (5 ml). The mixture was warmed slowly to reflux, where it was held for 3 h. After this time, the dark brown solution was added to ice and dilute hydrochloric acid (20 ml). The organic phase was separated and washed successively with

dilute hydrochloric acid (20 ml), water (50 ml) and saturated sodium bicarbonate solution (30 ml), before drying (MgSO_4). Concentration *in vacuo* gave a bright red oil which was distilled in a Kugelröhr apparatus (oven temperature, 120°C, 6 mmHg) (lit.,¹⁰¹ 119–120°C, 6 mmHg) to give the title compound (107) (2.21 g, 73%) as a colourless liquid (Found: C, 82.8; H, 8.0. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}$, C, 82.7; H, 8.1%); ν_{max} (film) 2 962, 1 686, 1 600, 1 331, 1 284, 1 250, and 769 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.38 (6 H, s, $(\text{CH}_3)_2$), 2.01 (2 H, t, J 6.8 Hz, 3- CH_2), 2.72 (2 H, t, J 6.8 Hz, 2- CH_2), 7.24–7.31 (1 H, m, 7-H), 7.41 (1 H, dd, J 7.5 and 1.5 Hz, 5-H), 7.48–7.54 (1 H, m, 6-H), and 8.01 (1 H, dd, J 8, 2 Hz, 8-H); m/z 174 (M^+ , 55%), 160 (15), 159 (100, $M-\text{CH}_3$), 131 (43), 115 (11), and 91 (13, C_7H_7^+).

4,4-Dimethylspiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (125).—Sodium hydride dispersion in mineral oil (60%; 0.298 g, 7.46 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (1.64 g, 7.46 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 4,4-Dimethyl-3,4-dihydro-1(2H)-naphthalenone (107) (1.0 g, 5.74 mmol) in dry DMSO (2 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (20 ml) was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a golden oil which was distilled in a Kugelrohr apparatus (oven temperature, 100°C, 0.46 mmHg) to give the title compound (125) (0.79 g, 73%) as a colourless liquid (Found: C, 82.95; H, 8.8. $\text{C}_{13}\text{H}_{16}\text{O}$ requires C, 82.9; H, 8.6%); ν_{max} (film) 2 960, 2 865, 1 489, 1 455, 1 030, 979, 879, 856, and 762 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.33 (3 H, s, Me), 1.38 (3 H, s, Me), 1.61–1.72 (1 H, m, 2-CH), 1.80–

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1.95 (2 H, m, 3-CH₂), 2.21-2.35 (1 H, m, 2-CH), 2.91 (1 H, dd, *J* 5.4 and 1.5 Hz, 3'-CH), 2.97 (1 H, d, *J* 5.4 Hz, 3'-CH), 7.05 (1 H, dd, *J* 7.8 and 1.7 Hz, 8-H), 7.13 (1 H, td, *J* 7.3 and 1.5 Hz, 7-H), 7.22 (1 H, td, *J* 7.3 and 1.7 Hz, 6-H), and 7.31 (1 H, dd, *J* 7.8 and 1.5 Hz, 5-H); *m/z* 188 (*M*⁺, 26%), 159 (100, *M*-CHO), 143 (20), 129 (14), 128 (21), 117 (43), 115 (14), and 91 (14, C₇H₇⁺).

Spiro[10,11-*dihydro*-5H-*dibenzo*[ad]*cycloheptene*-5,2'-*oxirane*] (127).—Sodium hydride dispersion in mineral oil (60%; 1.25 g, 31.21 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Dry DMSO (50 ml) and THF (50 ml) were added, and the mixture was cooled to 0°C. Trimethylsulphonium iodide (6.37 g, 31.21 mmol) in dry DMSO (10 ml) was added over 3 min. The mixture was stirred at 0°C while dibenzosuberone (5.0 g, 24.01 mmol) in THF (10 ml) was added. The mixture gradually turned orange-brown in colour, the cooling bath was removed and stirring was continued at ambient temperature for a further 15 h. The pale brown solution was diluted with water (100 ml). The resulting solution was extracted with ether (3 x 100 ml), the combined extracts being washed with water (2 x 100 ml) and brine (100 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a pale yellow crystalline solid which was recrystallised from ether to give the *title compound* (127) (4.82 g, 90%) as a colourless crystalline solid, m.p. 80-81°C (Found: C, 86.5; H, 6.4. C₁₆H₁₄O requires C, 86.45; H, 6.35%); *v*_{max}.(film) 3 012, 1 489, 1 448, 1 302, 1 018, 924, 782, and 585 cm⁻¹; *δ*_H(270 MHz; CDCl₃) 2.97-3.10 (2 H, m, 10- and 11-CH), 3.10 (2 H, s, 3'-CH₂), 3.40-3.55 (2 H, m, 10- and 11-CH), 7.10-7.25 (6 H, m, 1-, 2-, 3-, 7-, 8- and 9-H), and 7.50-7.55 (2 H, m, 4- and 6-H); *m/z* 222 (*M*⁺, 46%), 221 (100), 193 (32, *M*-CHO), 192 (10), 191 (31), 189 (19), 178 (14), and 165 (12).

(2-*Hydroxyphenyl*)*cyclopropyl ketone* (128).—Sodium hydride dispersion in mineral oil (60%; 0.18 g, 4.39 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (0.97 g,

4.39 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 4-chromanone (0.50 g, 3.37 mmol) in dry DMSO (5 ml) was added slowly, producing a clear orange solution from the grey-white slurry. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 1 h. The solution was then allowed to cool and water (20 ml) was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a brown oil which was distilled in a Kugelröhr apparatus (oven temperature, 110°C, 0.46 mmHg) to give the *title compound* (128) (0.16 g, 29%) as a colourless oil (Found: C, 73.8; H, 6.35. C₁₀H₁₀O₂ requires C, 74.05; H, 6.2%); $\nu_{\max}$ (film) 3 011, 2 800-3 200 (H-bonded OH), 1 635 (C=O), 1 608, 1 489, 1 448, 1 404, 1 284, 1 209, 1 157, 994, and 753 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.04-1.13 (2 H, m, cyclopropyl CH₂), 1.26-1.32 (2 H, m, cyclopropyl CH₂), 2.63-2.75 (1 H, m, cyclopropyl CH(CH₂)₂), 6.89-6.99 (2 H, m, 3- and 5-H), 7.45 (1 H, td, *J* 6.8 and 1.5 Hz, 4-H), 7.96 (1 H, dd, *J* 7.8 and 1.5 Hz, 6-H), and 12.50 (1 H, s, OH); *m/z* 162 (*M*⁺, 74%), 161 (15), 134 (14), 121 (100, *M*-cyclopropyl), 93 (15), and 65 (20).

5-Methoxyspiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (131).—Sodium hydride dispersion in mineral oil (60%; 0.30 g, 7.38 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (1.62 g, 7.38 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 5-methoxy-1-tetralone (1.0 g, 5.67 mmol) in dry DMSO (5 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (30 ml) was cautiously added. The resulting solution was extracted with

ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a brown oil which was distilled in a Kugelröhr apparatus (oven temperature, 95°C , 0.30 mmHg) to give the *title compound* (131) (0.63 g, 59%) as a colourless liquid (Found: C, 75.5; H, 7.6. $\text{C}_{12}\text{H}_{14}\text{O}_2$ requires C, 75.8; H, 7.4%); ν_{max} (film) 2 941, 1 583, 1 474, 1 440, 1 341, 1 259, 1 186, 1 052, 780, and 718 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.70-1.78 (1 H, m, 2-CH), 1.92-2.15 (3 H, m, 2-CH and 3- CH_2), 2.83 (2 H, t, J 4.5 Hz, 4- CH_2), 2.96 (1 H, d, J 5.4 Hz, 3'-CH), 3.00 (1 H, dd, J 5.4 and 1.2 Hz, 3'-CH), 3.83 (3 H, s, OMe), 6.73 (1 H, d, J 8.1 Hz, 6-H), 6.74 (1 H, d, J 8.1 Hz, 8-H), and 7.15 (1 H, t, J 8.1 Hz, 7-H); m/z 190 (M^+ , 44%), 162 (18), 161 (100, $M-\text{CHO}$), 159 (17), 129 (10), 128 (10), 115 (16), and 91 (13, C_7H_7^+).

Spiro[7-methoxy-1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (132).—Sodium hydride dispersion in mineral oil (60%; 0.30 g, 7.38 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (1.62 g, 7.38 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 7-methoxy-1-tetralone (1.0 g, 5.67 mmol) in dry DMSO (5 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (20 ml) was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a brown oil which was distilled in a Kugelröhr apparatus (oven temperature, 110°C , 0.25 mmHg) to give the *title compound* (132) (0.51 g, 48%) as a colourless liquid (Found: C, 75.8; H, 7.6. $\text{C}_{12}\text{H}_{14}\text{O}_2$ requires C, 75.8; H, 7.4%); ν_{max} (film) 2 938, 2 861, 2 837, 1 614, 1 500, 1 466, 1 435, 1 296, 1 236, 1 044, 918, 837, and 810 cm^{-1} ; δ_{H} (270 MHz; CDCl_3)

1.78-2.00 (1 H, m, 2-CH), 1.95-2.12 (3 H, m, 2-CH and 3-CH₂), 2.79-2.85 (2 H, m, 4-CH₂), 2.96-2.97 (2 H, m, 3'-CH₂), 3.76 (3 H, s, OMe), 6.61 (1 H, d, *J* 2.9 Hz, 8-H), 6.77 (1 H, dd, *J* 8.3 and 2.9 Hz, 6-H), and 7.03 (1 H, d, *J* 8.3 Hz, 5-H); *m/z* 190 (*M*⁺, 30%), 176 (12), 162 (15), 161 (100, *M*-CHO), 146 (9), and 91 (9, C₇H₇⁺).

6-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxaldehyde (134).—Sodium hydride dispersion in mineral oil (60%; 0.30 g, 7.38 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (1.62 g, 7.38 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 6-methoxy-1-tetralone (1.0 g, 5.67 mmol) in dry DMSO (5 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (20 ml) was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a pale brown oil which was distilled in a Kugelröhr apparatus (oven temperature, 95°C, 0.3 mmHg) (lit.,¹⁰⁷ no data given) to give, amongst other unidentified products, the title compound (134) (0.292 g, 27%) as a colourless liquid (Found: C, 75.6; H, 7.5. Calc. for C₁₂H₁₄O₂, C, 75.8; H, 7.4%); *v*_{max}.(film) 1 724, 1 611, 1 504, 1 465, 1 282, 1 250, 1 126, and 1 040 cm⁻¹; *δ*_H(270 MHz; CDCl₃) 1.73-1.82 (2 H, m, 3-CH₂), 1.85-1.98 (1 H, m, 2-CH), 2.13-2.24 (1 H, m, 2-CH), 2.72 (2 H, t, *J* 6.2 Hz, 4-CH₂), 3.56 (1 H, br t, *J* 4.5 Hz, 1-CH), 3.79 (3 H, s, OMe), 6.68 (1 H, d, *J* 2.7 Hz, 5-H), 6.79 (1 H, dd, *J* 8.3 and 2.7 Hz, 7-H), 7.08 (1 H, d, *J* 8.3 Hz, 8-H), and 9.67 (1 H, d, *J* 2.2 Hz, CHO); *m/z* 190 (*M*⁺, 28%), 176 (7), 162 (14), 161 (100, *M*-CHO), 159 (7), 146 (9), 115 (8), and 91 (10, C₇H₇⁺). The title compound was also analysed as its 2,4-dinitrophenylhydrazone derivative, which was a bright red-orange crystalline solid, m.p. 162-163°C (Found: C, 58.3; H, 4.9; N, 15.1.

$C_{18}H_{18}N_4O_5$ requires C, 58.4; H, 4.9; N, 15.1%).

Nitration of 1,2,3,4-tetrahydronaphthalene-1-one.—A mixture of fuming nitric acid (2.5 ml) and concentrated sulphuric acid (30 ml) was prepared and held at 0°C, whilst 1,2,3,4-tetrahydronaphthalen-1-one (10 g, 68.4 mmol) was very slowly added dropwise with vigorous stirring. The mixture was allowed to warm slowly to 40°C, whereupon it darkened to a black-brown colour. This was added to ice (*ca.* 20 g), water (30 ml) was added, and the mixture was extracted with ether (3 x 75 ml), the combined extracts being washed with water (100 ml) and brine (30 ml) before drying ($MgSO_4$). The solution was filtered through a pad of silica to remove the majority of the baseline material, and the filtrates were evaporated to leave a solid brown residue. The brown solid was digested in hot 40–60°C petrol, and the resulting solution decanted from the remaining solid material. This procedure was repeated four times until the petrol extracts were virtually colourless. The combined extracts were evaporated to give a pale yellow solid (3.86 g, 29%), which was shown by NMR to be a mixture of two isomers. A 1.5 g portion of this solid was purified by column chromatography (50% dichloromethane–light petroleum) to give firstly 5-nitro-1,2,3,4-tetrahydronaphthalen-1-one (**115**) (0.233 g, 15% based on the 1.5 g sample) as a colourless crystalline solid, m.p. 102–103°C (lit.,¹⁰⁸ 106–108°C); (Found: C, 63.1; H, 4.7; N, 7.3. Calc. for $C_{10}H_9NO_3$, C, 62.8; H, 4.75; N, 7.3%); ν_{max} (Nujol) 1 682 (C=O), 1 608, 1 523, 1 424, 1 348, 1 265, and 741 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 2.13 (2 H, quintet, J 6.4 Hz, 3- CH_2), 2.68 (2 H, t, J 6.4 Hz, 2- CH_2), 3.16 (2 H, t, J 6.4 Hz, 4- CH_2), 7.44 (1 H, t, J 7.9 Hz, 7-H), 8.03 (1 H, dd, J 7.9 and 1.3 Hz, 8-H), and 8.28 (1 H, dd, J 7.9 and 1.5 Hz, 6-H); m/z 191 (M^+ , 100%), 117 (68), 116 (30), 115 (76), 103 (44), 91 (35), 89 (49), and 63 (45). Elution was continued, giving 7-nitro-1,2,3,4-tetrahydronaphthalen-1-one (**116**) (0.733 g, 49% based on the 1.5 g sample) as a colourless crystalline solid, m.p. 97–99°C (lit.,¹⁰⁸ no m.p. given); (Found: C, 63.0; H, 4.7; N, 7.2. Calc. for $C_{10}H_9NO_3$, C, 62.8; H, 4.75; N, 7.3%); ν_{max} (Nujol) 1 684

(C=O), 1 609, 1 522, 1 424, 1 347, and 1 265 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.12 (2 H, quintet, J 6.4 Hz, 3- CH_2), 2.63 (2 H, t, J 6.4 Hz, 2- CH_2), 3.02 (2 H, t, J 6.4 Hz, 4- CH_2), 7.40 (1 H, d, J 8.5 Hz, 5-H), 8.12 (1 H, dd, J 8.4 and 2.4 Hz, 6-H), and 8.58 (1 H, d, J 2.4 Hz, 8-H); m/z 191 (M^+ , 83%), 176 (12), 163 (100), 145 (11), 135 (19), 115 (27), 89 (28), and 63 (18). The identity of these regioisomers was further confirmed by n. O. e. experiments.

Attempted preparation of 5-nitrospiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane].—Sodium hydride dispersion in mineral oil (60%; 0.06 g, 1.56 mmol) was washed with light petroleum (3 x 5 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (0.34 g, 1.56 mmol) was added, followed by dry DMSO (5 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 5-nitro-1,2,3,4-tetrahydronaphthalen-1-one (115) (0.23 g, 1.2 mmol) in dry DMSO (3 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (20 ml) was cautiously added. The resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 20 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a brown tar which, on attempted distillation, gave no identifiable product. Similar results were obtained when the trimethylsulphoxonium iodide was replaced by trimethylsulphonium iodide.

Attempted preparation of 7-nitrospiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane].—Sodium hydride dispersion in mineral oil (60%; 0.188 g, 4.69 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Trimethylsulphoxonium iodide (1.03 g, 4.69 mmol) was added, followed by dry DMSO (10 ml), which was added dropwise over 30 min. After the ensuing effervescence had ceased, the mixture was stirred for a further 30 min, after which time 7-nitro-1,2,3,4-

tetrahydronaphthalen-1-one (116) (0.69 g, 3.61 mmol) in dry DMSO (5 ml) was added slowly. The mixture was stirred at ambient temperature for a further 15 min, then at 55°C for a further 15 h. The solution was allowed to cool and water (30 ml) was cautiously added. The resulting solution was extracted with ether (3 x 40 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a brown tar which, on attempted distillation, gave no identifiable product. Similar results were obtained when the trimethylsulphoxonium iodide was replaced by trimethylsulphonium iodide.

Ethyl spiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane]-3'-carboxylate (135).—To a mixture of 1-tetralone (5.0 g, 34.2 mmol) and ethyl chloroacetate (6.76 g, 55.1 mmol) under nitrogen at -10°C was added an ethanolic solution of sodium ethoxide, prepared by cautiously dissolving sodium metal (1.26 g, 54.7 mmol) in dry ethanol (10 ml). The mixture was stirred at -5°C for 3 days and then allowed to warm to ambient temperature. Water (30 ml) was cautiously added and the resulting solution was extracted with ether (3 x 50 ml), the combined extracts being washed with water (4 x 50 ml) and brine (30 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a brown oil which was distilled in a Kugelrohr apparatus (oven temperature, 130°C, 0.46 mmHg) to give the *title compound* (135) (1.58 g, 20%) as a colourless liquid (Found: C, 72.5; H, 7.1. C₁₄H₁₆O₃ requires C, 72.4; H, 6.9%); $\nu_{\max}$ (film) 2 940, 1 729 (ester C=O), 1 494, 1 452, 1 298, 1 250, 1 093, 1 046, and 744 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.31 (3 H, t, *J* 7.2 Hz, CH₂CH₃), 1.75-1.95 (2 H, m, 3-CH₂), 2.05-2.15 (2 H, m, 2-CH₂), 2.75-2.82 (2 H, m, 4-CH₂), 3.63 (1 H, s, 3'-CH), 4.30 (2 H, q, *J* 7.2 Hz, CH₂CH₃), 6.98-7.02 (1 H, m, 8-H), and 7.12-7.26 (3 H, m, 5-, 6- and 7-H); *m/z* 232 (*M*⁺, 17%), 132 (11), 131 (100), 130 (8), 129 (14), 115 (8), and 91 (13, C₇H₇⁺).

1-Azidomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (136).—To spiro[1,2,3,4-tetra-

hydronaphthalene-1,2'-oxirane] (119) (0.81 g, 5.1 mmol) was added lithium chloride (0.28 g, 6.5 mmol), followed by sodium azide (0.44 g, 6.7 mmol) and dry DMF (10 ml). The mixture was stirred and heated at 65°C for 15 h. The mixture was then allowed to cool, water (30 ml) was added, and the solution was extracted with ether (1 x 50, 2 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (30 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a green-brown oil which was purified by column chromatography (dichloromethane) to give the *title compound* (136) (0.55 g, 53%) as a pale brown oil (Found: M^+ , 147.0808. C₁₁H₁₃N₃O-CH₂N₃ requires 147.0810); $\nu_{\max}$.(film) 3 391 (OH), 2 938, 2 104 (N₃), 1 451, 1 387, 1 350, 1 279, 1 085, 795, 764, and 733 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.72-1.95 (3 H, m, 2-CH and 3-CH₂), 2.09 (1 H, s, OH), 2.19-2.28 (1 H, m, 2-CH), 2.76-2.83 (2 H, m, 4-CH₂), 3.41 (1 H, d, J 12 Hz, CHHN₃), 3.59 (1 H, d, J 12 Hz, CHHN₃), 7.06-7.11 (1 H, m, 5-H), 7.16-7.26 (2 H, m, 6-H and 7-H), and 7.53-7.57 (1 H, m, 8-H); m/z 147 (M^+ -CH₂N₃, 100%), 144 (94), 118 (66), 115 (48), 91 (31, C₇H₇⁺), 90 (31), and 89 (15).

5-Azidomethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (137).—To spiro-[6,7,8,9-tetrahydro-5H-benzocycloheptene-5,2'-oxirane] (120) (1.0 g, 5.74 mmol) was added lithium chloride (0.30 g, 7.08 mmol), followed by sodium azide (0.46 g, 7.08 mmol) and dry DMF (20 ml). The mixture was stirred and heated at 100°C for 48 h. The mixture was allowed to cool, water (50 ml) was added, and the solution was extracted with ether (1 x 50, 2 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (30 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a yellow oil which was purified by column chromatography (dichloromethane) to give the *title compound* (137) (0.88 g, 71%) as a pale yellow oil (Found: M^+ , 161.0963. C₁₂H₁₅N₃O-CH₂N₃ requires 161.0966); $\nu_{\max}$.(film) 3 451 (OH), 2 930, 2 857, 2 104 (N₃), 1 484, 1 447, 1 293, and 761 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.45-1.58 (1 H, m, 6-

CH), 1.73-1.96 (4 H, m, 7- and 8-CH₂), 2.10-2.19 (1 H, m, 6-CH), 2.22 (1 H, s, OH), 2.83-2.89 (2 H, m, 9-CH₂), 3.57 (1 H, d, *J* 12 Hz, CHHN₃), 3.66 (1 H, d, *J* 12 Hz, CHHN₃), 7.08 (1 H, dd, *J* 7.5 and 1.5 Hz, 1-H), 7.16 (1 H, td, *J* 7.5 and 1.5 Hz, 2-H), 7.23 (1 H, td, *J* 7.5 and 2 Hz, 3-H), and 7.69 (1 H, dd, *J* 7.5 and 2 Hz, 4-H); *m/z* 161 (*M*⁺-CH₂N₃, 100%), 160 (63), 132 (22), 131 (42), 117 (27), 104 (33), and 91 (68, C₇H₇⁺).

Attempted reaction of spiro[7,8,9,10-tetrahydrobenzocyclo-octene-5,2'-oxirane] (122) with sodium azide.—To spiro[7,8,9,10-tetrahydrobenzocyclo-octene-5,2'-oxirane] (122) (0.1 g, 0.53 mmol) was added lithium chloride (0.029 g, 0.69 mmol), followed by sodium azide (0.045 g, 0.69 mmol) and dry DMF (5 ml). The mixture was stirred and heated at 70°C for 2 days. The mixture was allowed to cool, water (20 ml) was added, and the solution was extracted with ether (1 x 30, 2 x 15 ml), the combined extracts being washed with water (2 x 10 ml) and brine (10 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a pale brown oil which was purified by column chromatography (dichloromethane) to give unreacted starting material (122) (0.085 g, 85%), the spectral properties of which were identical to authentic material. Repetition of the reaction in water, aqueous dioxane, aqueous acetone, DMSO, or methanol gave similar results.

Attempted reaction of 4,4-dimethylspiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (125) with sodium azide.—To 4,4-dimethylspiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (125) (0.266 g, 1.42 mmol) was added lithium chloride (0.078 g, 1.84 mmol), followed by sodium azide (0.12 g, 1.84 mmol) and dry DMF (5 ml). The mixture was stirred and heated at 70°C for 2 days. The mixture was allowed to cool, water (30 ml) was added, and the solution was extracted with ether (1 x 30, 2 x 20 ml), the combined extracts being washed with water (2 x 20 ml) and brine (10 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a brown oil which was purified by column

chromatography (dichloromethane) to give unreacted starting material (125) (0.21 g, 79%), the spectral properties of which were identical to authentic material. Repetition of the reaction in water, aqueous dioxane, aqueous acetone, DMSO, or methanol gave similar results.

Preparation of lithium azide.—The literature¹¹³ procedure was used, as follows. With gentle warming, sodium azide (6.50 g, 0.10 mol) and lithium sulphate (7.05 g, 55.1 mmol) were dissolved in distilled water (35 ml). Absolute ethanol (175 ml) was added, while the mixture was shaken gently. After 10 min the mixture was filtered to remove the colourless residue of sodium sulphate and lithium sulphate, the filtered solid being washed with absolute ethanol (2 x 50 ml). The filtrate and wash solutions were combined and evaporated to near dryness, the residue being dried over phosphorus pentoxide overnight in a dessicator. The crude product was digested with absolute ethanol (50 ml) at 35°C for 2 min, filtered, and the colourless solution was evaporated as before. The resulting colourless solid was dried *in vacuo* overnight to give the title compound (4.06 g, 83%) as a colourless microcrystalline solid.

Attempted reaction of spiro[10,11-dihydro-5H-dibenzo[ad]cycloheptene-5,2'-oxirane] (127) with sodium azide.—To spiro[10,11-dihydro-5H-dibenzo[ad]cycloheptene-5,2'-oxirane] (127) (0.80 g, 1.42 mmol) was added lithium chloride (0.198 g, 4.68 mmol), followed by sodium azide (0.304 g, 4.68 mmol) and dry DMF (10 ml). The mixture was stirred and heated at 70°C for 2 days. The mixture was allowed to cool, water (40 ml) was added, and the solution was extracted with ether (1 x 40, 2 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a pale brown oil which was purified by column chromatography (dichloromethane) to give unreacted starting material (127) (0.69 g, 86%), the spectral properties of which were identical to authentic material.

Repetition of the reaction under alternative conditions of temperature, reaction time, solvent, and source of nucleophile, as detailed in Table 1 Chapter 2, led to similar results.

Attempted reaction of spiro[10,11-dihydro-5H-dibenzo[ad]cycloheptene-5,2'-oxirane] (127) with trimethylsilyl azide in the presence of titanium tetra-isopropoxide.—To a solution of spiro[10,11-dihydro-5H-dibenzo[ad]cycloheptene-5,2'-oxirane] (127) (0.10 g, 0.45 mmol) in THF (5 ml) was added trimethylsilyl azide (0.069 g, 0.60 mmol) and titanium tetra-isopropoxide (2 mg, 7.04 μ mol), the resulting solution being stirred at ambient temperature for up to 3 weeks. The mixture was diluted with water (20 ml), and the resulting solution was extracted with ether (3 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a pale brown oil which was purified by column chromatography (dichloromethane) to give unreacted starting material (127) (0.67 g, 67%), the spectral properties of which were identical to authentic material. Repetition of the reaction using pre-formed $\text{Ti}(\text{O}-i\text{-Pr})_2(\text{N}_3)_2$ catalyst produced identical results.

1-Azidomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (141).—To 5-methoxy-oxyspiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (131) (0.54 g, 2.8 mmol) was added lithium chloride (0.16 g, 3.7 mmol), followed by sodium azide (0.24 g, 3.7 mmol) and dry DMF (10 ml). The mixture was stirred and heated at 65°C for 15 h. The mixture was allowed to cool and water (30 ml) was added. The solution was extracted with ether (1 x 50, 2 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (30 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a brown oil which was purified by column chromatography (dichloromethane) to give the *title compound* (141) (0.39 g, 59%) as a very pale brown oil which solidified *in vacuo* (Found: M^+ , 233.1169. $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$ requires 233.1164); ν_{max} (film) 3 571 (OH), 2 099 (N_3), 1 582, 1 345, 1 310, 1 261, 1 031, 937, 793, and 727 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.69-1.79 (2 H, m, 3- CH_2), 1.90-1.97 (1 H, m, 2-CH), 2.18 (1 H, s, OH), 2.18-2.25 (1

H, m, 2-CH), 2.64-2.72 (2 H, m, 4-CH₂), 3.41 (1 H, d, J 12.7 Hz, CHHN₃), 3.59 (1 H, d, J 12.7 Hz, CHHN₃), 3.83 (3 H, s, OMe), 6.78 (1 H, dd, J 7.3 and 2.0 Hz, 6-H), and 7.17-7.26 (2 H, m, 7-H and 8-H); m/z 233 (M^+ , 3%), 177 (M -CH₂N₃, 100%), 176 (26), 174 (14), 148 (13), 121 (29), and 91 (19, C₇H₇⁺).

1-Azidomethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-ol (142).—To spiro-[7-methoxy-1,2,3,4-tetrahydronaphthalene-1,2'-oxirane] (132) (0.10 g, 0.53 mmol) was added lithium chloride (29 mg, 0.68 mmol), followed by sodium azide (44 mg, 0.68 mmol) and dry DMF (10 ml). The mixture was stirred and heated at 65°C for 15 h, then allowed to cool and water (30 ml) was added. The solution was extracted with ether (1 x 50, 2 x 30 ml), the combined extracts being washed with water (2 x 30 ml) and brine (30 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a brown oil which was purified by column chromatography (dichloromethane) to give the *title compound* (142) (65 mg, 53%) as a pale brown oil (Found: M^+ , 233.1172. C₁₂H₁₅N₃O₂ requires 233.1164); $\nu_{\max}$ (film) 3 455 (OH), 2 936, 2 102 (N₃), 1 612, 1 500, 1 455, 1 283, 1 238, 1 042, 867, and 811 cm⁻¹; δ_H (270 MHz; CDCl₃) 1.77 (1 H, s, OH), 1.80-1.95 (2 H, m, 3-CH₂), 2.17-2.25 (2 H, m, 2-CH₂), 2.71-2.74 (2 H, m, 4-CH₂), 3.41 (1 H, d, J 12.7 Hz, CHHN₃), 3.59 (1 H, d, J 12.7 Hz, CHHN₃), 3.81 (3 H, s, OMe), 6.80 (1 H, dd, J 8.4 and 2.6 Hz, 6-H), 7.02 (1 H, d, J 8.5 Hz, 5-H), and 7.10 (1 H, d, J 2.6 Hz, 8-H); m/z 233 (M^+ , 9%), 178 (12), 177 (M -CH₂N₃⁺, 100%), 176 (17), 121 (19), 86 (13), 84 (21), and 49 (25).

Attempted reaction of ethyl spiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane]-3'-carboxylate (135) with sodium azide.—To ethyl spiro[1,2,3,4-tetrahydronaphthalene-1,2'-oxirane]-3'-carboxylate (135) (0.50 g, 1.42 mmol) was added lithium chloride (0.119 g, 2.80 mmol), followed by sodium azide (0.182 g, 2.80 mmol) and dry DMF (5 ml). The mixture was stirred and heated at 70°C for 2 days. The mixture was allowed to

cool, water (30 ml) was added, and the solution was extracted with ether (1 x 30, 2 x 20 ml), the combined extracts being washed with water (2 x 20 ml) and brine (10 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a brown oil which was purified by column chromatography (dichloromethane) to give unreacted starting material (135) (0.38 g, 76%), the spectral properties of which were identical to authentic material. Repetition of the reaction under a variety of other conditions, already described, gave similar results.

Reaction of spiro[10,11-dihydro-5H-dibenzo[ad]cycloheptene-5,2'-oxirane] (127) with aqueous perchloric acid.—To a solution of spiro[10,11-dihydro-5H-dibenzo[ad]cycloheptene-5,2'-oxirane] (127) (0.50 g, 2.25 mmol) in THF (10 ml) was added 2 ml of a 1:1 mixture of 60% perchloric acid and water. The solution was stirred at ambient temperature for 2 h, after which time no starting material was present. The solution was diluted with water (40 ml), and then extracted with ether (3 x 40 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a pale yellow oil which was purified by column chromatography (dichloromethane) to give 10,11-dihydro-5H-dibenzo[ad]cycloheptene-5-carboxaldehyde (146) (0.32 g, 64%) as a colourless oil (Found: C, 86.5; H, 6.3. $\text{C}_{16}\text{H}_{14}\text{O}$ requires C, 86.45; H, 6.35%); ν_{max} (film) 1 723 (C=O), 1 494, 1 445, 1 266, 759, 737, and 581 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.83-3.18 (4 H, m, 10- and 11- CH_2), 4.62 (1 H, s, 5-CH), 7.14-7.47 (6 H, m, 1-, 2-, 3-, 7-, 8-, and 9-H), 8.04 (2 H, dd, J 7.7 and 1.9 Hz, 4- and 6-H), and 9.89 (1 H, s, CHO); m/z 222 (M^+ , 16%), 209 (89), 208 (45), 206 (43), 193 (100), 192 (33), 191 (42), and 178 (67).

Reaction of spiro[7,8,9,10-tetrahydrobenzocyclo-octene-5,2'-oxirane] (122) with aqueous perchloric acid.—To a solution of spiro[7,8,9,10-tetrahydrobenzocyclo-octene-5,2'-oxirane] (122) (0.198 g, 1.05 mmol) in THF (10 ml) was added 2 ml of a 1:1

mixture of 60% perchloric acid and water. The solution was stirred at ambient temperature for 4 h, after which time only a trace of starting material was present. The solution was diluted with water (40 ml), and then extracted with ether (3 x 40 ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a pale yellow oil which was purified by column chromatography (dichloromethane) to give 7,8,9,10-tetrahydrobenzocyclo-octene-5-carboxaldehyde (**147**) (0.133 g, 67%) as a colourless oil (Found: M^+ , 188.1201. $\text{C}_{13}\text{H}_{16}\text{O}$ requires 188.1201); ν_{max} (film) 1 494 (C=O), 1 449, 1 267, 1 116, 1 055, 766, 738, and 702 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.40-2.00 (8 H, m, 6-, 7-, 8-, and 9- CH_2), 2.32 (2 H, t, J 8.9 Hz, 10- CH_2), 3.15 (1 H, m, 5-H), 7.17-7.41 (4 H, m, 1-, 2-, 3- and 4-H), and 9.45 (1 H, d, J 2.9 Hz, CHO); m/z 188 (M^+ , 60%), 131 (20), 129 (25), 117 (50), 115 (19), 104 (30), 92 (24), and 91 (20, C_7H_7^+).

Dehydration of 1-azidomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (136).—1-Azidomethyl-1,2,3,4-tetrahydronaphthalen-1-ol (**136**) (0.25 g, 1.23 mmol), dissolved in dry pyridine (10 ml), was treated at ambient temperature with thionyl chloride (0.25 ml, 3.44 mmol). The solution was stirred at ambient temperature for 15 min and then water (25 ml) was cautiously added. The mixture was extracted with ether (3 x 30 ml), the combined extracts being washed with water (3 x 30 ml), saturated copper sulphate solution (3 x 30 ml), water (2 x 30 ml) and brine (30 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a golden oil which was purified by column chromatography (light petroleum) to give firstly 1-azidomethylene-3,4-dihydronaphthalene (**148**) (0.13 g, 56%) as a very pale brown oil which was characterised on the basis of IR and NMR. data; ν_{max} (film) 2 936, 2 104 (N_3), 1 633, 1 450, 1 278, and 764 cm^{-1} ; δ_{H} (200 MHz; CDCl_3) 1.78 (2 H, quintet, J 6 Hz, 3- CH_2), 2.47 (2 H, td, J 6 and 2 Hz, 2- CH_2), 2.75 (2 H, t, J 6 Hz, 4- CH_2), 6.71 (1 H, t, J 2 Hz, $\text{C}=\text{CHN}_3$), 7.10-7.15 (3 H, m, 5-, 6- and 7-H), and 7.41 (1 H, dd, J 9 and 4 Hz, 8-H). This was followed by the isomeric

dehydration product, 1-azidomethyl-3,4-dihydronaphthalene (34 mg, 15%), obtained as a pale brown oil; $\nu_{\max}$ (film) 2 930, 2 099 (N_3), 1 573, 1 460, 1 265, and 789 cm^{-1} ; δ_{H} (200 MHz; CDCl_3) 2.36 (2 H, m, 3- CH_2), 2.80 (2 H, t, J 8 Hz, 4- CH_2), 4.11 (2 H, s, CH_2N_3), 6.13 (1 H, t, J 4.5 Hz, 2-CH), and 7.14-7.28 (4 H, m, 5-, 6-, 7- and 8-H).

Dehydration of 5-azidomethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (137).—5-Azidomethyl-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (137) (0.76 g, 3.5 mmol), dissolved in dry pyridine (10 ml), was treated at ambient temperature with thionyl chloride (0.72 ml, 9.81 mmol). The solution was stirred at ambient temperature for 2 h and then water (75 ml) was cautiously added. The mixture was extracted with ether (3 x 50 ml), the combined extracts being washed with water (3 x 50 ml), saturated copper sulphate solution (3 x 50 ml), water (2 x 50 ml) and brine (30 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a pale yellow oil which was purified by column chromatography (light petroleum) to give firstly 5-azidomethylene-6,7,8,9-tetrahydro-5H-benzocycloheptene (150) (0.23 g, 33%) as a pale yellow oil which was characterised on the basis of IR and NMR data; $\nu_{\max}$ (film) 2 927, 2 854, 2 104 (N_3), 1 635, 1 446, 1 297, 1 252, and 758 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.69-1.78 (4 H, m, 7- and 8- CH_2), 2.34-2.41 (2 H, m, 6- CH_2), 2.75 (2 H, t, J 5.2 Hz, 9- CH_2), 6.21 (1 H, s, $\text{C}=\text{CHN}_3$), and 7.09-7.20 (4 H, m, 1-, 2-, 3- and 4-H). This was followed by the isomeric dehydration product, 5-azidomethyl-8,9-dihydro-7H-benzocycloheptene (151) (0.12 g, 17%) obtained as a colourless oil; $\nu_{\max}$ (film) 2 931, 2 861, 2 108 (N_3), 1 602, 1 451, 1 209, and 815 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.32-2.39 (4 H, m, 7- and 8- CH_2), 2.89 (2 H, t, J 7.1 Hz, 9- CH_2), 4.13 (2 H, s, CH_2N_3), 6.26 (1 H, t, J 4.7 Hz, 6-H), and 7.07-7.30 (4 H, m, 1-, 2-, 3- and 4-H).

Dehydration of 1-azidomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (141).—1-Azidomethyl-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (141) (0.12 g,

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

0.52 mmol), dissolved in dry pyridine (10 ml), was treated at ambient temperature with thionyl chloride (0.68 ml, 9.28 mmol). The solution was stirred at ambient temperature for 1.5 h and then water (25 ml) was cautiously added. The mixture was extracted with ether (3 x 30 ml), the combined extracts being washed with water (3 x 30 ml), saturated copper sulphate solution (3 x 30 ml), water (2 x 30 ml) and brine (30 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a golden oil which was purified by column chromatography (light petroleum) to give firstly *1-azidomethylene-3,4-dihydro-5-methoxynaphthalene* (**152**) (35.4 mg, 32%) as a very pale brown oil which was characterised on the basis of IR and NMR data; ν_{max} (film) 2 924, 2 109 (N₃), 1 623, 1 572, 1 474, 1 455, 1 435, 1 328, 1 253, 1 127, and 780 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.79 (2 H, quintet, *J* 6.4 Hz, 3-CH₂), 2.45 (2 H, td, *J* 6.4 and 1.5 Hz, 2-CH₂), 2.71 (2 H, t, *J* 6.4 Hz, 4-CH₂), 3.82 (3 H, s, OMe), 6.70-6.74 (2 H, m, C=CHN₃ and 6-H), and 7.04-7.14 (2 H, m, 7- and 8-H). This was followed by the isomeric dehydration product, *1-azidomethyl-3,4-dihydro-5-methoxynaphthalene* (**153**) (50.5 mg, 46%), obtained as a pale brown oil; ν_{max} (film) 2 938, 2 099 (N₃), 1 574, 1 462, 1 439, 1 347, 1 325, 1 261, 1 048, and 781 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 2.30-2.38 (2 H, m, 3-CH₂), 2.81 (2 H, t, *J* 8.3 Hz, 4-CH₂), 3.85 (3 H, s, OMe), 4.12 (2 H, d, *J* 0.7 Hz, CH₂N₃), 6.15 (1 H, t, *J* 4.6 Hz, 2-H), 6.84 (1 H, d, *J* 8.3 Hz, 6-H), 6.94 (1 H, d, *J* 7.8 Hz, 8-H), and 7.20 (1 H, t, *J* 8.1 Hz, 7-H).

Dehydration of 1-azidomethyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (**142**).—*1-Azidomethyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol* (**142**) (17 mg, 0.076 mmol), dissolved in dry pyridine (5 ml), was treated at ambient temperature with thionyl chloride (0.10 ml, 1.37 mmol). The solution was stirred at ambient temperature for 1 h and then water (30 ml) was cautiously added. The mixture was extracted with ether (3 x 30 ml), the combined extracts being washed with water (3 x 30 ml), saturated copper sulphate solution (3 x 30 ml), water (2 x 30 ml) and brine (30 ml) before drying (MgSO₄). Evaporation under reduced pressure gave a pale brown oil which was purified by column

chromatography (dichloromethane) to give 1-azidomethylene-3,4-dihydro-7-methoxynaphthalene (154) (12 mg, 71%) as a pale brown oil which was characterised on the basis of IR and NMR data; $\nu_{\max}$ (film) 2 928, 2 099 (N_3), 1 627, 1 602, 1 497, 1 466, 1 274, 1 241, 1 223, and 1 044 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.72-1.82 (2 H, m, 3- CH_2), 2.45 (2 H, td, J 5.5 and 1.8 Hz, 2- CH_2), 2.69 (2 H, t, J 6.3 Hz, 4- CH_2), 3.80 (3 H, s, OMe), 6.71 (1 H, m, $\text{C}=\text{CHN}_3$), 6.74 (1 H, dd, J 8.5 and 2.7 Hz, 6-H), 6.94 (1 H, d, J 2.7 Hz, 8-H), and 7.01 (1 H, d, J 8.5 Hz, 5-H).

1,3,4,5-Tetrahydrobenz[cd]indole (155).—A solution of 1-azidomethylene-3,4-dihydronaphthalene (148) (72 mg, 0.39 mmol) in mesitylene (10 ml) under nitrogen was quickly heated to reflux for 45 min. The solution was allowed to cool and the solvent was removed under vacuum. The residue was chromatographed (dichloromethane) to give the title compound (115) (41 mg, 67%) as a colourless crystalline solid, m.p. 54-56°C (lit.,¹¹⁷ 55-56°C); $\nu_{\max}$ (Nujol) 3 411 (indole NH), 2 928, 1 606, 1 445, 1 345, 1 083, 1 028, 775, and 749 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.06 (2 H, quintet, J 6 Hz, 4- CH_2), 2.87 (2 H, td, J 6 and 1.2 Hz, 3- CH_2), 2.95 (2 H, t, J 6 Hz, 5- CH_2), 6.82 (1 H, d, J 1.2 Hz, 2-H), 6.84 (1 H, d, J 1 Hz, 6-H), 7.11 (2 H, m, 7- and 8-H), and 7.72 (1 H, br s, 1-H); m/z 157 (M^+ , 100%), 156 (90), 130 (23), 129 (35), 128 (16), and 104 (19).

3,4,5,6-Tetrahydrocyclohept[cd]indole (156).—A solution of 5-azidomethylene-6,7,8,9-tetrahydro-5H-benzocycloheptene (150) (0.21 g, 1.04 mmol) in mesitylene (10 ml) under nitrogen was quickly heated to reflux for 45 min. The solution was allowed to cool and the solvent was removed under vacuum. The residue was chromatographed (dichloromethane) to give the title compound (156) (0.13 g, 72%) as a colourless crystalline solid, m.p. 65-67°C (Found: M^+ , 171.1044. $\text{C}_{12}\text{H}_{13}\text{N}$ requires 171.1048); $\nu_{\max}$ (Nujol) 3 392 (indole NH), 2 926, 2 855, 1 462, 1 418, 1 378, 1 363, 775, and

748 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.90-2.08 (4 H, m, 4- and 5- CH_2), 2.97 (2 H, t, J 5.3 Hz, 3- CH_2), 3.17 (2 H, t, J 5.6 Hz, 6- CH_2), 6.91 (1 H, dd, J 7.5 and 1.3 Hz, 7-H), 6.98 (1 H, t, J 1.3 Hz, 2-H), 7.09 (1 H, t, J 7.5 Hz, 8-H), 7.19 (1 H, d, J 7.5 Hz, 9-H), and 7.94 (1 H, br s, 1-H); m/z 171 (M^+ , 100%), 170 (48), 143 (54), 130 (15), 115 (15), 77 (13), and 71 (14).

6-Methoxy-1,3,4,5-tetrahydrobenz[cd]indole (157).—A solution of 1-azidomethylene-3,4-dihydro-5-methoxynaphthalene (152) (20 mg, 0.093 mmol) in mesitylene (10 ml) under nitrogen was quickly heated to reflux for 45 min. The solution was allowed to cool and the solvent was removed under vacuum. The residue was chromatographed (dichloromethane) to give the *title compound* (157) (12.2 mg, 70%) as a colourless crystalline solid, m.p. 94-95°C (Found: M^+ , 187.0997. $\text{C}_{12}\text{H}_{13}\text{NO}$ requires 187.0997); ν_{max} (CHCl_3) 3 482 (indole NH), 3 053, 2 985, 2 937, 1 504, 1 440, 1 265, 1 240, 1 064, 783, and 757 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.99-2.08 (2 H, m, 4- CH_2), 2.83 (2 H, td, J 5.6 and 1.1 Hz, 3- CH_2), 2.91 (2 H, t, J 5.9 Hz, 5- CH_2), 3.87 (3 H, s, OMe), 6.84 (1 H, t, J 1.1 Hz, 2-H), 6.86 (1 H, d, J 8.4 Hz, 7-H), 7.10 (1 H, d, J 8.4 Hz, 8-H), and 7.67 (1 H, br s, 1-H); m/z 187 (M^+ , 77%), 172 (38), 157 (33), 156 (36), 150 (45), 57 (100), and 41 (48).

8-Methoxy-1,3,4,5-tetrahydrobenz[cd]indole (158).—A solution of 1-azidomethylene-3,4-dihydro-7-methoxynaphthalene (154) (12 mg, 0.053 mmol) in mesitylene (10 ml) under nitrogen was quickly heated to reflux for 45 min. The solution was allowed to cool and the solvent was removed under vacuum. The residue was chromatographed (dichloromethane) to give the *title compound* (158) (6.7 mg, 67%) as a colourless crystalline solid, m.p. 70-71°C (lit.,¹¹⁸ 71-72°C) (Found: M^+ , 187.1001. Calc. for $\text{C}_{12}\text{H}_{13}\text{NO}$, 187.0997); ν_{max} (Nujol) 3 481 (indole NH), 3 007, 2 936, 1 519, 1 404, 1 280, 1 255, 1 065, and 795 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.99-2.08 (2 H, m, 4- CH_2), 2.81-

2.86 (2 H, m, 3-CH₂), 2.86-2.91 (2 H, m, 5-CH₂), 3.93 (3 H, s, OMe), 6.56 (1 H, d, *J* 7.6 Hz, 7-H), 6.73 (1 H, dt, *J* 7.6 and 1.0 Hz, 6-H), 6.83 (1 H, t, *J* 1.0 Hz, 2-H), and 7.97 (1 H, br s, 1-H); *m/z* 187 (*M*⁺, 100%), 186 (17), 172 (45), 156 (8), 154 (9), 149 (28), and 144 (7).

(*E* and *Z*)-1-Chloromethylene-3,4-dihydronaphthalene (161).—Powdered (chloromethyl)triphenylphosphonium chloride (7.13 g, 20.5 mmol) was suspended in THF (50 ml) under nitrogen, and cooled to -78°C. Phenyl-lithium (2 M solution in cyclohexanether, 10.3 ml, 20.52 mmol) was added slowly, producing a yellow colouration. The solution was stirred at -78°C for a further 5 min, then allowed to warm to 0°C. The dark red-orange mixture was then cooled to -78°C again, and a solution of 1-tetralone (2 g, 13.68 mmol) in THF was added slowly such that the temperature remained below -60°C. The resulting mixture was stirred at -78°C for 2 h, and then allowed to warm to 0°C, where it was stirred for another 15 h. After this time water (100 ml) was added dropwise to the reddish solution, which was then extracted with ether (3 x 100 ml), the combined extracts being washed with water (2 x 100 ml) and brine (50 ml) before drying (MgSO₄). Evaporation followed by chromatography (dichloromethane) gave the title compound¹⁵⁵ (161) (2.03 g, 83%) as a pale yellow oil (Found: C, 74.0; H, 6.4. Calc. for C₁₁H₁₁Cl, C, 73.95; H, 6.2%); ν_{max} (film) 2 936, 2 866, 1 612, 1 483, 1 454, 818, 776, and 750 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.80-1.90 (2 H, m, *E* 3-CH₂), 1.89-1.99 (2 H, m, *Z* 3-CH₂), 2.47 (2 H, td, *J* 6.2 and 1.4 Hz, *Z* 2-CH₂), 2.68 (2 H, td, *J* 6.5 and 2.1 Hz, *E* 2-CH₂), 2.77 (2 H, t, *J* 6.1 Hz, *E* 4-CH₂), 2.88 (2 H, t, *J* 6.6 Hz, *Z* 4-CH₂), 6.11 (1 H, t, *J* 1.4 Hz, *Z* C=CHCl), 6.59 (1 H, t, *J* 2.1 Hz, *E* C=CHCl), 7.11-7.23 (3 H, m, *E* 5-, 6-, and 7-H), 7.13-7.24 (3 H, m, *Z* 5-, 6-, and 7-H), 7.44-7.48 (1 H, m, *E* 8-H), and 8.16-8.21 (1 H, m, *Z* 8-H); *m/z* 178 (*M*⁺, 100%), 143 (56), 141 (28), 129 (45), 128 (56), 127 (15), and 115 (38).

Reaction of (E- and Z)-1-Chloromethylene-3,4-dihydronaphthalene (161) with iron (III) azide and hydrogen peroxide.—To a solution of 1-chloromethylene-3,4-dihydronaphthalene (161) (0.50 g, 2.80 mmol) in THF (20 ml) at 0°C under nitrogen was added borane-THF complex (1.0 M solution, 0.63 ml, 0.63 mmol). The mixture was stirred at 0°C for 3 days, after which time the THF was removed under vacuum, and the flask refilled with nitrogen. The flask was placed behind a blast screen and iron (III) sulphate pentahydrate (2.06 g, 4.2 mmol) together with sodium azide (0.55 g, 8.4 mmol) and dry methanol (10 ml). The mixture was stirred at ambient temperature for 30 min, and then cooled in a water bath whilst hydrogen peroxide (30%, 1 ml) was added dropwise to the brown reaction mixture. The mixture was stirred at this temperature for a further 2 h, and then 15% sodium hydroxide (10 ml) and 30% hydrogen peroxide (2.5 ml) were added in order to decompose the residual organoboranes. The brown mixture was extracted with ether (3 x 50 ml), the combined extracts being washed with water (2 x 30 ml) before drying (MgSO₄) and evaporating. The crude product was obtained as a pale brown oil, which was purified by chromatography (light petroleum) to give 1-azido-1-azidomethyl-1,2,3,4-tetrahydronaphthalene (163) (0.312 g, 49%) as a pale yellow liquid (Found: C, 58.1; H, 5.4; N, 36.85. C₁₁H₁₂N₆O requires C, 57.9; H, 5.3; N, 36.8%); $\nu_{\max}$ (film) 2 104 (N₃), 1 489, 1 450, 1 255, 1 091, 908, 762, 736, and 667 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.84-2.11 (3 H, m, 2-CH and 3-CH₂), 2.24-2.29 (1 H, m, 2-CH), 2.81-2.89 (2 H, m, 4-CH₂), 3.47 (1 H, d, *J* 12.8 Hz, CHN₃), 3.57 (1 H, dd, *J* 12.9 and 0.5 Hz, CHN₃), 7.15-7.18 (1 H, m, 5-H), 7.24-7.29 (2 H, m, 6- and 7-H), and 7.43-7.47 (1 H, m, 8-H); δ_{C} (67.9 MHz DEPT sequence experiment: CDCl₃) 19.5 (2-C), 29.3 (3-C), 31.1 (4-C), 58.9 (CH₂N₃), 65.4 (1-C), 126.6 (6-C), 126.9 (7-C), 128.4 (5-C), 129.6 (8-C), 134.3 (4a-C), and 137.7 (8a-C); *m/z* 185 (*M*-HN₃, 9%), 172 (20, *M*-2N₂), 161 (20), 144 (100), 143 (35), 131 (93), 117 (36), and 116 (86).

5.3 Relating to Chapter Three

5-(Indol-3-yl)pentanoic acid (197).—Into a 3-necked flask equipped with overhead stirrer and Dean-Stark trap was placed indole (20 g, 0.171 mol), δ -valerolactone (19.66 g, 0.196 mol) and potassium hydroxide pellets (85% reagent, 16.90 g, 0.256 mol), together with *p*-cymene (100 ml). The mixture was stirred and heated to reflux, and this temperature was maintained until water production had ceased (96 h). After this time the mixture was allowed to cool, producing a brown solution and a pale brown gum. Water (*ca.* 50 ml) was added, and the mixture was stirred until the gummy substance had dissolved. The aqueous phase was separated and washed with light petroleum (3 x 30 ml), the combined organic extracts furnishing, on evaporation, mainly unreacted indole (5.56 g). The aqueous phase was cautiously acidified with concentrated hydrochloric acid, which produced a red-brown oil. The mixture was kept below 4°C for 2 days, after which time the oil had solidified. The solid material was filtered from the aqueous phase and washed with water (2 x 30 ml). The solid was dissolved in ether, producing a red solution and an oily residue. The ether layer was separated, washed with water (3 x 50 ml) which removed much of the red colouration, and then dried (MgSO₄). The ether solution was evaporated to approximately half its volume, and then kept at 0–4°C overnight. Crystallisation was completed by cooling in a cardice bath, the product was filtered and the solid washed with a small quantity of cold ether. Concentration of the recrystallisation filtrates afforded further crops of the title compound (197) (total yield 15.19 g, 41%) as an off-white powdery solid, m.p. 104–105°C (lit.¹³² 105–107°C) (Found: C, 72.0; H, 7.05; N, 6.35. Calc. for C₁₃H₁₅NO₂, C, 71.9; H, 7.0; N, 6.45%); $\nu_{\max}$ (Nujol) 3 500–2 500 (OH), 3 427 (indole NH), 1 690, 1 409, 1 299, 1 258, 1 200, 1 089, and 736 cm⁻¹; δ_{H} (20 MHz; CDCl₃) 1.76 (4 H, m, 3- and 4-CH₂), 2.40 (2 H, t, *J* 7.9 Hz, 2-CH₂), 2.79 (2 H, t, *J* 7.4 Hz, 5-CH₂), 6.97 (1 H, s, 2'-H), 7.14 (2 H, m, 5'- and 6'-H), 7.35 (1 H, d, *J* 7.1 Hz, 7'-H), 7.59 (1 H, d, *J* 7.5 Hz, 4'-H), and 7.90 (1 H, br s, 1'-H); *m/z* 217 (*M*⁺, 33%), 158 (7), 144 (11), 130 (100, ArCH₂⁺), 103 (12), and 77 (15).

N,N-Dimethyl 5-(indol-3-yl)pentanecarboxamide (198).—To a solution of 5-(indole-3-yl)pentanoic acid (197) (1.0 g, 4.60 mmol) and triethylamine (0.50 g, 4.94 mmol) in THF (20 ml) at 0°C under nitrogen was added *iso*-butyl chloroformate (0.70 g, 5.13 mmol), whereupon the solution went cloudy. The mixture was stirred at 0°C for 30 min, after which time it was added dropwise to a solution of dimethylamine in IMS (33% solution, 20 ml), also at 0°C. The mixture was allowed to warm to ambient temperature, whereupon a yellow solution was obtained. This was diluted with water (50 ml), and extracted with dichloromethane (3 x 50 ml), the combined extracts being washed with water (2 x 100 ml), dried (MgSO₄), and evaporated to give a colourless solid. The solid was recrystallised from dichloromethane/light petroleum to give the *title compound* (198) (0.92 g, 82%) as a colourless granular solid, m.p. 133-134°C (Found: C, 73.5; H, 8.35; N, 11.4. C₁₅H₂₀N₂O requires C, 73.7; H, 8.25; N, 11.5%); $\nu_{\max}$ (film) 3 192 (indole NH), 1 633 (C=O), 1 413, 1 330, 1 232, 1 152, 1 081, 778, 748, and 727 cm⁻¹; δ_{H} (200 MHz; CDCl₃) 1.76 (4 H, m, 3 and 4-CH₂), 2.35 (2 H, t, *J* 7.2 Hz, 2-CH₂), 2.79 (2 H, t *J* 7.4 Hz, 5-CH₂), 2.94 (3 H, s, NCH₃), 2.97 (3 H, s, NCH₃), 6.98 (1 H, d, *J* 2.7 Hz, 2'-H), 7.13 (2 H, m, 5'- and 6'-H), 7.34 (1 H, d, *J* 7.4 Hz, 7'-H), 7.60 (1 H, d, *J* 7.4 Hz, 4'-H), and 8.08 (1 H, br s, 1'-H); *m/z* 244 (*M*⁺, 26%), 199 (5), 157 (10), 143 (22), 130 (100, ArCH₂⁺), 117 (13), 87 (18), 72 (15), and 45 (16).

Attempted chlorination of N,N-Dimethyl 5-(indol-3-yl)pentanecarboxamide (198).—A solution of LDA was prepared by adding *n*-butyl-lithium (1.6 M solution in hexanes, 2.7 ml, 4.30 mmol) to di-isopropylamine (0.60 ml, 4.30 mmol) in THF (20 ml) at -78°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before recooling to -78°C. A solution of *N,N*-dimethyl 5-(indol-3-yl)pentanecarboxamide (198) (0.50 g, 2.05 mmol) in THF (10 ml) was added dropwise to the LDA solution. After 1 h, dry carbon tetrachloride (0.26 ml, 2.66 mmol) was added to the golden-brown solution, producing a dark green-brown colouration. After a further 10 min, acetic acid

(0.13 ml, 2.25 mmol) was added, and the resulting brown mixture was diluted with water (30 ml) and extracted with dichloromethane (3 x 40 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (2% methanol-dichloromethane), to give, amongst other unidentified products, unreacted starting material (198) (0.297 g, 59%), the spectral properties of which were identical to authentic material. Repetition of the reaction under alternative conditions of concentration or temperature led to similar results or to decomposition to a variety of unidentified products.

N,N-Dimethyl 5-(1-*t*-butoxycarbonylindol-3-yl)pentanecarboxamide (199).—To a suspension of *N,N*-dimethyl 5-(indol-3-yl)pentanecarboxamide (198) (0.40 g, 1.64 mmol) in dry acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (0.54 g, 2.46 mmol) and 4-dimethylaminopyridine (0.020 g, 0.164 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear pale yellow solution, which was then evaporated to leave a yellow-brown gum. This was purified by chromatography (dichloromethane) to give the *title compound* (199) (0.56 g, 100%) as a very pale yellow crystalline solid, m.p. 117-118°C (Found: C, 69.7; H, 8.3; N, 8.2. $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_3$ requires C, 69.7; H, 8.2; N, 8.1%); ν_{max} (Nujol) 1 732 (carbamate C=O), 1 650 (amide C=O), 1 276, 1 209, 1 161, 1 091, 1 034, 765, and 750 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.66 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.76 (4 H, quintet, J 3.7 Hz, 3- and 4- CH_2), 2.35 (2 H, m, 2- CH_2), 2.71 (2 H, m, 5- CH_2), 2.94 (3 H, s, NCH_3), 2.98 (3 H, s, NCH_3), 7.19-7.33 (2 H, m, 5'- and 6'-H), 7.35 (1 H, s, 2'-H), 7.51 (1 H, dd, J 7.6 and 1.2 Hz, 4'-H), and 8.11 (1 H, d, J 8.1 Hz, 7'-H); m/z 344 (M^+ , 43%), 244 (85), 199 (27), 143 (33), 130 (100, ArCH_2^+), 117 (31), 87 (31), and 57 (72).

N,N-Dimethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-2-chloropentanecarboxamide (200).—A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 0.60 ml, 0.087 mmol) to *N*-isopropylcyclohexylamine (145 μl , 0.087 mmol) in

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

THF (20 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of *N,N*-dimethyl 5-(1-*t*-butoxycarbonylindol-3-yl)pentanecarboxamide (**199**) (0.20 g, 0.058 mmol) in THF (5 ml) was added dropwise to the LiICA solution. After a further 10 min, the mixture was allowed to warm slowly to -20°C , producing a clear orange solution. This was cooled again to -78°C , and then added *via* a catheter to a solution of dry carbon tetrachloride (6 ml) in THF (10 ml), also at -78°C under nitrogen. The solution was stirred at -78°C for a further 10 min, and then allowed to warm slowly to ambient temperature, giving a pale yellow solution. After a further 20 min, acetic acid (0.5 ml) was added, and the resulting solution was diluted with water (30 ml) and extracted with dichloromethane (3 x 40 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (2% methanol-dichloromethane) to give the *title compound* (**200**) (0.100 g, 45%) as a pale brown oil (Found: M^+ , 378.1710. $\text{C}_{20}\text{H}_{27}\text{ClN}_2\text{O}_3$ requires 378.1710); $\nu_{\text{max.}}$ (film) 1 732 (carbamate C=O), 1 661 (amide C=O), 1 452, 1 371, 1 256, 1 157, 1 091, and 748 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.68 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.72-1.92 (2 H, m, 4- CH_2), 2.01-2.18 (2 H, m, 3- CH_2), 2.73-2.82 (2 H, m, 5- CH_2), 2.98 (3 H, s, NCH_3), 3.07 (3 H, s, NCH_3), 4.44 (1 H, t, J 7.6 Hz, 2-CH), 7.21-7.35 (2 H, m, 5'- and 6'-H), 7.39 (1 H, s, 2'-H), 7.52 (1 H, d, J 7.3 Hz, 4'-H), and 8.14 (1 H, br d, J 8.1 Hz, 7'-H); m/z 378 (M^+ , 13%), 278 (19), 170 (40), 143 (76), 130 (31, ArCH_2^+), 72 (22), 57 (100), and 41 (20).

N,N-Dimethyl 5-(indol-3-yl)-2-chloropentanecarboxamide (**201**).—To a solution of *N,N*-dimethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-2-chloropentanecarboxamide (**200**) (0.070 g, 0.185 mmol) in dichloromethane (15 ml) was added dropwise trifluoroacetic acid (200 μl). The slightly purple solution was stirred at ambient temperature for 1 h, and then evaporated under reduced pressure, leaving a purple oil. This was purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (**201**) (0.038 g, 73%) as a colourless oil (Found: M^+ , 278.1186. $\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}$ requires 278.1186); $\nu_{\text{max.}}$ (film) 3 470 (indole NH), 1 655 (amide C=O), 1 490, 1 454, 1 417, and 1 338

cm^{-1} ; λ_{max} (MeOH) 290 (log ϵ 3.17), 320infl, and 340infl nm; δ_{H} (270 MHz; CDCl_3) 1.74-1.93 (2 H, m, 4- CH_2), 1.98-2.19 (2 H, m, 3- CH_2), 2.82 (2 H, t, J 7.4 Hz, 5- CH_2), 2.96 (3 H, s, NCH_3), 3.01 (3 H, s, NCH_3), 4.40 (1 H, dd, J 7.6 and 6.3 Hz, 2-CH), 7.00 (1 H, d, J 2.0 Hz, 2'-H), 7.10 (1 H, td, J 7.5 and 1.0 Hz, 5'-H), 7.18 (1 H, td, J 7.5 and 1.1 Hz, 6'-H), 7.35 (1 H, d, J 8.0 Hz, 7'-H), 7.59 (1 H, d, J 8.0 Hz, 4'-H), and 8.20 (1 H, br s, 1'-H); m/z 278 (M^+ , 19%), 170 (40), 168 (17), 143 (76), 130 (31, ArCH_2^+), 72 (22), 57 (100), and 41 (20).

Irradiation of N,N-Dimethyl 5-(indol-3-yl)-2-chloropentanecarboxamide (201).—

A solution of *N,N*-dimethyl 5-(indol-3-yl)-2-chloropentanecarboxamide (201) (0.030 g, 0.108 mmol) in acetonitrile (30 ml) was irradiated for 20 min. The brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give *N,N*-dimethyl 5-(indol-3-yl)pent-2-enecarboxamide (202) (0.015 g, 59%) as a golden brown oil (Found: M^+ , 242.1419. $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$ requires 242.1419); ν_{max} (film) 3 481 (indole NH), 1 659 (amide $\text{C}=\text{O}$), 1 494, 1 457, 1 417, 1 401, and 1 149 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.58-2.68 (2 H, m, 4- CH_2), 2.73-2.82 (2 H, m, 5- CH_2), 2.91 (3 H, s, NCH_3), 3.00 (3 H, s, NCH_3), 5.95-5.98 (1 H, m, 2-CH), 6.25 (1 H, dt, J 15.1 and 1.6 Hz, 3-CH), 6.99 (1 H, d, J 2.0 Hz, 2'-H), 7.08-7.22 (2 H, m, 5'- and 6'-H), 7.35 (1 H, d, J 7.7 Hz, 7'-H), 7.60 (1 H, d, J 8.0 Hz, 4'-H), and 7.99 (1 H, br s, 1'-H); m/z 242 (M^+ , 20%), 170 (12), 168 (4), 131 (10), 130 (100, ArCH_2^+), 113 (8), 98 (5), and 77 (5).

*3-(3-Bromopropyl)indole (204).—*To a solution of homotryptophol (0.50 g, 2.85 mmol) and triphenylphosphine (0.90 g, 3.42 mmol) in dry dichloromethane (20 ml) at ambient temperature was very cautiously added dropwise a solution of carbon tetrabromide (0.95 g, 2.85 mmol) in dry dichloromethane (10 ml) (CAUTION-EXOTHERM). The resulting golden yellow solution was stirred at ambient temperature for 20 min, and was

then evaporated to leave a greenish-brown oil. This was purified by chromatography (dichloromethane) to give the title compound¹³⁸ (**204**) (0.667 g, 98%) as a green-brown oil (Found: C, 55.4; H, 5.1; N, 5.9. Calc. for $C_{11}H_{12}BrN$, C, 55.5; H, 5.1; N, 5.9%); $\nu_{\max}$.(film) 3 417 (indole NH), 1 456, 1 421, 1 338, 1 255, 1 237, 1 226, 1 092, and 744 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.27 (2 H, quintet, J 7.0 Hz, 2'- CH_2), 2.97 (2 H, td, J 7.2 and 0.7 Hz, 1'- CH_2), 3.46 (2 H, t, J 6.5 Hz, 3'- CH_2), 7.03 (1 H, d, J 2.4 Hz, 2-H), 7.15 (1 H, td, J 7.3 and 1.1 Hz, 5-H), 7.23 (1 H, td, J 7.6 and 1.3 Hz, 6-H), 7.37 (1 H, d, J 8.2 Hz, 7-H), 7.64 (1 H, d, J 7.8 Hz, 4-H), and 7.92 (1 H, br s, 1-H); m/z 237 (M^+ , 17%), 131 (11), 130 (100, ArCH_2^+), 129 (5), 128 (4), 103 (5), 102 (4), and 77 (8).

t-Butyl 3-(3-bromopropyl)indole-1-carboxylate (**205**).—To a suspension of 3-(3-bromopropyl)indole (**204**) (0.196 g, 0.823 mmol) in dry acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (0.27 g, 1.24 mmol) and 4-dimethylaminopyridine (0.015 g, 0.123 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (dichloromethane) to give the *title compound* (**205**) (0.238 g, 85%) as a pale yellow oil which darkened on standing (Found: C, 57.0; H, 6.05; N, 4.05. $C_{16}H_{20}BrNO_2$ requires C, 56.8; H, 6.0; N, 4.1%); $\nu_{\max}$.(film) 1 734 (carbamate C=O), 1 455, 1 376, 1 256, 1 159, 1 085, and 747 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 2.25 (2 H, quintet, J 6.9 Hz, 2'- CH_2), 2.87 (2 H, t, J 7.1 Hz, 1'- CH_2), 3.47 (2 H, t, J 6.6 Hz, 3'- CH_2), 7.24 (1 H, td, J 7.4 and 1.2 Hz, 5-H), 7.32 (1 H, td, J 6.3 and 1.3 Hz, 6-H), 7.40 (1 H, s, 2-H), 7.54 (1 H, d, J 7.1 Hz, 4-H), and 8.12 (1 H, br d, J 7.9 Hz, 7-H); m/z 337 (M^+ , 10%), 283 (35), 281 (35), 237 (11), 174 (15), 130 (65), 57 (100), and 41 (18).

Attempted reaction of t-butyl 3-(3-bromopropyl)indole-1-carboxylate (205) with

the anion of N,N-dimethyl- α,α -dichloroacetamide.—A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 0.46 ml, 0.692 mmol) to *N*-isopropylcyclohexylamine (115 μ l, 0.692 mmol) in THF (20 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of *N,N*-dimethyl- α,α -dichloroacetamide (0.108 g, 0.692 mmol) in THF (3 ml) was added to the LiICA solution, and the mixture was stirred at -78°C for 15 min. A solution of *t*-butyl 3-(3-bromopropyl)indole-1-carboxylate (205) (0.16 g, 0.473 mmol) in THF (5 ml) was added dropwise to the golden yellow solution, and the mixture was stirred at -78°C for 2 h. After this time, acetic acid (0.5 ml) was added, and the resulting solution was diluted with water (30 ml) and extracted with dichloromethane (3 x 40 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (dichloromethane) to give unreacted starting material (205) (0.123 g, 77%), the spectral properties of which were identical to authentic material.

1-(Indol-3-yl)propyl-3-(p-toluenesulphonate) (207).—To a yellow solution of homotryptophol (1.0 g, 5.71 mmol) in pyridine (5 ml) at 0°C was added *p*-toluenesulphonyl chloride (2.18 g, 11.4 mmol). Once all the *p*-toluenesulphonyl chloride had dissolved, the golden mixture was kept at 0°C for 24 h. After this time, crystals of pyridinium hydrochloride had formed, and the mixture was poured onto ice-water (*ca.* 50 ml). The mixture was then extracted with ether (3 x 75 ml), the combined extracts being washed with saturated copper (II) sulphate solution (*ca.* 4 x 30 ml), until no darkening of the copper sulphate solution was evident, followed by water (3 x 40 ml), and brine (30 ml), before drying (MgSO_4). The solution was evaporated at ambient temperature, leaving a yellowish solid which was purified by chromatography (dichloromethane) to give the title compound (207) (1.64 g, 87%) as a colourless crystalline solid, m.p. $98-100^{\circ}\text{C}$ (lit.,¹⁴² $97-98^{\circ}\text{C}$); (Found: C, 65.4; H, 5.7; N, 4.5. Calc. for $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{S}$, C, 65.6; H, 5.8; N, 4.25%); ν_{max} (Nujol) 3 386 (indole NH), 1 346, 1 172, 923, 817, 781, 750, and 554

cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.04 (2 H, quintet, J 6.7 Hz, 2- CH_2), 2.44 (3 H, s, CCH_3), 2.81 (2 H, t, J 7.1 Hz, 1- CH_2), 4.09 (2 H, t, J 6.2 Hz, 3- CH_2), 6.91 (1 H, d, J 2.5 Hz, 2'-H), 7.09 (1 H, td, J 7.1 and 1.4 Hz, 5'-H), 7.19 (1 H, td, J 7.5 and 1.4 Hz, 6'-H), 7.30-7.37 (3 H, m, 7'-H and CH_3CCHCH), 7.51 (1 H, d, J 7.8 Hz, 4'-H), 7.78 (2 H, d, J 8.3 Hz, CH_3CHCH), and 7.95 (1 H, br s, 1'-H); m/z 329 (M^+ , 28%), 157 (26), 156 (12), 144 (5), 131 (12), 130 (100, ArCH_2^+), 91 (12, C_7H_7^+), and 77 (9).

3-(3-Iodopropyl)indole (208).—

Method A. To a solution of homotryptophol (0.50 g, 2.85 mmol) in dry toluene (20 ml) at ambient temperature was added triphenylphosphine (2.25 g, 8.56 mmol), imidazole (0.583 g, 8.56 mmol), and resublimed iodine (1.45 g, 5.71 mmol). The resulting solution was stirred at ambient temperature for 20 min, after which time some tarry material had precipitated. The toluene was decanted from this, and the residue was washed with ether (3 x 50 ml). The combined organic solvents were washed with 5% aqueous sodium thiosulphate (40 ml) and water (2 x 40 ml) before drying (MgSO_4) and evaporating to leave a brown oily residue. This was purified by chromatography (50% dichloromethane-light petroleum) to give the *title compound* (208) (0.19 g, 23%) as a brown oil (Found: M^+ , 285.0014. $\text{C}_{11}\text{H}_{12}\text{IN}$ requires 285.0013); ν_{max} (film) 3 414 (indole NH), 1 605, 1 456, 1 338, 1 265, 1 213, 1 169, 1 093, 1 011, and 743 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.20 (2 H, quintet, J 7.0 Hz, 2'- CH_2), 2.90 (2 H, t, J 7.0 Hz, 1'- CH_2), 3.22 (2 H, t, J 7.0 Hz, 3'- CH_2), 7.05 (1 H, d, J 2.2 Hz, 2-H), 7.13 (1 H, td, J 7.1 and 1.0 Hz, 5-H), 7.21 (1 H, td, J 7.1 and 1.1 Hz, 6-H), 7.37 (1 H, d, J 8.0 Hz, 7-H), 7.62 (1 H, d, J 7.7 Hz, 4-H), and 7.98 (1 H, br s, 1-H); m/z 285 (M^+ , 47%), 148 (5), 131 (11), 130 (100, ArCH_2^+), 129 (6), 103 (6), 102 (5), and 77 (10).

Method B. To a solution of 1-(indol-3-yl)propyl-3-(*p*-toluenesulphonate) (207) (0.30 g, 0.911 mmol) in acetone (20 ml) at ambient temperature was added sodium iodide (0.683 g, 4.55 mmol). The resulting suspension was stirred at ambient temperature for 2 days, after

which time water (40 ml) was added to the pale yellow mixture. The resulting solution was extracted with ether (3 x 40 ml), the combined extracts being washed with water (30 ml) before drying (MgSO_4) and evaporating to leave a yellow oil. This was purified by chromatography (50% dichloromethane-light petroleum) to give the *title compound* (208) (0.247 g, 95%) as a brown oil, the spectroscopic properties of which were identical to those of material prepared by method A.

t-Butyl 3-(3-iodopropyl)indole-1-carboxylate (209).—To a suspension of 3-(3-iodopropyl)indole (208) (0.240 g, 0.842 mmol) in dry acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (0.276 g, 1.26 mmol) and 4-dimethylaminopyridine (0.010 g, 84.3 μmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (dichloromethane) to give the *title compound* (209) (0.301 g, 93%) as a yellow-brown oil which darkened on standing (Found: C, 49.8; H, 5.2; N, 3.6. $\text{C}_{16}\text{H}_{20}\text{INO}_2$ requires C, 49.9; H, 5.2; N, 3.6%); ν_{max} (film) 1 733 (carbamate C=O), 1 455, 1 371, 1 255, 1 159, 1 083, and 746 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 2.15–2.26 (2 H, m, 2'- CH_2), 2.82 (2 H, td, J 7.1 and 0.7 Hz, 1'- CH_2), 3.24 (2 H, t, J 6.7 Hz, 3'- CH_2), 7.24 (1 H, td, J 7.6 and 1.3 Hz, 5-H), 7.32 (1 H, td, J 7.8 and 1.3 Hz, 6-H), 7.41 (1 H, s, 2-H), 7.54 (1 H, d, J 7.8 Hz, 4-H), and 8.13 (1 H, br d, J 7.8 Hz, 7-H); m/z 385 (M^+ , 20%), 329 (60), 285 (14), 237 (12), 174 (18), 130 (80, ArCH_2^+), 57 (100), and 41 (22).

Ethyl 5-(indol-3-yl)pentanoate (210).—To a suspension of 5-(indol-3-yl)pentanoic acid (197) (1.0 g, 4.60 mmol) in dry benzene (20 ml) was added oxalyl chloride (4 ml, 46 mmol) and the mixture was stirred at ambient temperature for 30 min. After this time, all the solid had dissolved, forming a red-brown solution. This was evaporated to leave a red-brown oil which was cooled in an ice-bath whilst a mixture of ethanol (30 ml) and triethylamine (3 ml) was added dropwise. The mixture was stirred at 0°C for 30 min, after

which time it was diluted with water (75 ml) and extracted with ether (3 x 100 ml), the combined extracts being washed with water (2 x 100 ml), saturated aqueous sodium carbonate solution (2 x 75 ml), water (3 x 50 ml), and brine (30 ml) before being dried (MgSO_4), and evaporated to give a yellow oil. This was purified by chromatography (75% dichloromethane-light petroleum) to give the *title compound* (**210**) (0.80 g, 71%) as a colourless crystalline solid, m.p. 46.5-47.5°C (Found: C, 73.4; H, 7.7; N, 5.6. $\text{C}_{15}\text{H}_{19}\text{NO}_2$ requires C, 73.4; H, 7.8; N, 5.7%); ν_{max} (film) 3 320 (indole NH), 1 718 (C=O), 1 410, 1 243, 1 223, 1 189, 1 102, 785, 743, and 733 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.24 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.73-1.77 (4 H, m, 3- and 4- CH_2), 2.32-2.37 (2 H, m, 2- CH_2), 2.76-2.81 (2 H, m, 5- CH_2), 4.12 (2 H, q, J 7.1 Hz, OCH_2CH_3), 6.99 (1 H, d, J 2.4 Hz, 2'-H), 7.11 (1 H, td, J 6.9 and 1.2 Hz, 5'-H), 7.19 (1 H, td, J 7.5 and 1.2 Hz, 6'-H), 7.35 (1 H, d, J 8.1 Hz, 7'-H), 7.58-7.62 (1 H, m, 4'-H), and 7.91 (1 H, br s, 1'-H); m/z 245 (M^+ , 29%), 200 (11), 156 (6), 144 (6), 143 (7), 131 (14), and 130 (100, ArCH_2^+).

Ethyl 5-(1-t-butoxycarbonylindol-3-yl)pentanoate (**211**).—To a suspension of ethyl 5-(indol-3-yl)pentanoate (**210**) (0.76 g, 3.10 mmol) in dry acetonitrile (20 ml) was added di-*t*-butyl dicarbonate (1.014 g, 4.65 mmol) and 4-dimethylaminopyridine (0.038 g, 0.310 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear pale yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (**211**) (1.008 g, 94%) as a pale yellow oil (Found: C, 69.7; H, 8.0; N, 4.1. $\text{C}_{20}\text{H}_{27}\text{NO}_4$ requires C, 69.5; H, 7.9; N, 4.05%); ν_{max} (film) 1 734 (ester and carbamate C=O), 1 455, 1 377, 1 256, 1 162, 1 091, and 747 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.25 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.72-1.77 (4 H, m, 3- and 4- CH_2), 2.33-2.38 (2 H, m, 2- CH_2), 2.68-2.73 (2 H, m, 5- CH_2), 4.13 (2 H, q, J 7.2 Hz, OCH_2CH_3), 7.22 (1 H, td, J 6.2 and 1.2 Hz, 5'-H), 7.3 (1 H, td, J 6.3

and 1.2 Hz, 6'-H), 7.35 (1 H, s, 2'-H), 7.51 (1 H, d, J 8.0 Hz, 4'-H), and 8.12 (1 H, br d, J 8.0 Hz, 7'-H); m/z 345 (M^+ , 20%), 290 (1), 246 (10), 245 (59), 142 (6), 131 (15), 130 (100, ArCH_2^+), and 57 (81).

*Ethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-2-chloropentanoate (212).*—A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 1.2 ml, 1.74 mmol) to *N*-isopropylcyclohexylamine (286 μl , 1.74 mmol) in THF (50 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of ethyl 5-(1-*t*-butoxycarbonylindol-3-yl)pentanoate (211) (0.50 g, 1.45 mmol) in THF (15 ml) was added dropwise to the LiICA solution. After a further 10 min, the mixture was allowed to warm slowly to -20°C , producing a clear orange solution. This was cooled again to -78°C , and then added *via* a catheter to a solution of dry carbon tetrachloride (15 ml) in THF (25 ml), also at -78°C under nitrogen. The solution was stirred at -78°C for a further 10 min, and then allowed to warm slowly to ambient temperature, giving a pale yellow solution. After a further 20 min, acetic acid (1.5 ml) was added, and the resulting solution was diluted with water (60 ml) and extracted with dichloromethane (3 $\times$ 75 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (212) (0.314 g, 57%) as a colourless oil (Found: M^+ , 379.1550. $\text{C}_{20}\text{H}_{26}\text{ClNO}_4$ requires 379.1550); ν_{max} (film) 1 733 (ester and carbamate C=O), 1 455, 1 372, 1 256, 1 159, 1 092, and 747 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.28 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.82–2.08 (4 H, m, 3- and 4- CH_2), 2.74 (2 H, t, J 7.2 Hz, 5- CH_2), 4.22 (2 H, qd, J 6.6 and 0.5 Hz, OCH_2CH_3), 4.30 (1 H, dd, J 7.8 and 5.9 Hz, 2-CH), 7.23 (1 H, td, J 7.3 and 1.0 Hz, 5'-H), 7.31 (1 H, td, J 7.4 and 1.5 Hz, 6'-H), 7.37 (1 H, s, 2'-H), 7.50 (1 H, d, J 7.6 Hz, 4'-H), and 8.12 (1 H, br d, J 7.3 Hz, 7'-H); m/z 379 (M^+ , 18%), 325 (13), 323 (33), 281 (14), 279 (42), 131 (16), 130 (100, ArCH_2^+), and 57 (46).

Ethyl 5-(indol-3-yl)-2-chloropentanoate (213).—To a solution of ethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-2-chloropentanoate (212) (0.250 g, 0.658 mmol) in dichloromethane (25 ml) was added dropwise trifluoroacetic acid (800 μ l). The slightly red-brown solution was stirred at ambient temperature for 2 h, and then evaporated under reduced pressure, leaving a brown oil. This was purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (213) (0.127 g, 69%) as a colourless oil (Found: M^+ , 279.1026. $C_{15}H_{18}ClNO_2$ requires 279.1026); $\nu_{\max}$ (film) 3 415 (indole NH), 1 736 (C=O), 1 619, 1 458, 1 371, 1 340, 1 181, 1 095, and 743 cm^{-1} ; $\lambda_{\max}$ (MeOH) 274infl, 282 (log ϵ 3.73), and 290 (3.66) nm; δ_H (270 MHz; $CDCl_3$) 1.27 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.80–2.12 (4 H, m, 3- and 4- CH_2), 2.81 (2 H, t, J 7.3 Hz, 5- CH_2), 4.21 (2 H, qd, J 7.1 and 0.7 Hz, OCH_2CH_3), 4.30 (1 H, dd, J 7.8 and 5.9 Hz, 2-CH), 7.00 (1 H, d, J 2.2 Hz, 2'-H), 7.11 (1 H, td, J 8.0 and 1.2 Hz, 5'-H), 7.19 (1 H, td, J 7.0 and 1.2 Hz, 6'-H), 7.35 (1 H, d, J 8.0 Hz, 7'-H), 7.58 (1 H, d, J 8.5 Hz, 4'-H), and 7.95 (1 H, br s, 1'-H); m/z 279 (M^+ , 22%), 243 (3), 234 (2), 170 (9), 144 (6), 143 (12), 131 (11), and 130 (100, $ArCH_2^+$).

Irradiation of ethyl 5-(indol-3-yl)-2-chloropentanoate (213).—A solution of ethyl 5-(indol-3-yl)-2-chloropentanoate (213) (0.030 g, 0.107 mmol) in acetonitrile (30 ml) was irradiated for 15 min. The brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give *ethyl 5-(indol-3-yl)pent-2-enoate (214)* (0.016 g, 63%) as a golden brown oil (Found: M^+ , 243.1259. $C_{15}H_{17}NO_2$ requires 243.1259); $\nu_{\max}$ ($CHCl_3$) 3 481 (indole NH), 1 713 (C=O), 1 655, 1 457, 1 370, 1 091, and 910 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.28 (3 H, t, J 7.1 Hz, OCH_2CH_3), 2.58–2.67 (2 H, m, *E* 4- CH_2), 2.92 (2 H, t, J 7.4 Hz, *Z* 5- CH_2), 2.94 (2 H, td, J 7.3 and 0.5 Hz, *E* 5- CH_2), 3.08–3.13 (2 H, m, *Z* 4- CH_2), 4.16 (2 H, q, J 7.1 Hz, *Z* OCH_2CH_3), 4.18 (2 H, q, J 7.1 Hz, *E* OCH_2CH_3), 5.78 (1 H, dt, J 11.5 and 1.7 Hz, *Z* 2-CH), 5.88 (1 H, dt, J 15.8 and 1.6 Hz, *E* 2-CH), 6.31 (1 H, dt, J 11.5 and 7.2

Hz, Z 3-CH), 7.01 (1 H, d, J 2.2 Hz, 2'-H), 7.07 (1 H, dt, J 15.7 and 6.8 Hz, E 3-CH), 7.12 (1 H, td, J 7.0 and 1.2 Hz, 5'-H), 7.20 (1 H, td, J 7.3 and 1.3 Hz, 6'-H), 7.37 (1 H, d, J 8.1 Hz, 7'-H), 7.61 (1 H, d, J 7.8 Hz, 4'-H), and 7.95 (1 H, br s, 1'-H); m/z 243 (M^+ , 14%), 168 (5), 167 (4), 149 (8), 131 (11), 130 (100, ArCH_2^+), 129 (4), and 77 (4).

6-(indol-3-yl)hexanoic acid (215).—Into a 3-necked flask equipped with overhead stirrer and Dean-Stark trap was placed indole (20 g, 0.171 mol), ϵ -caprolactone (22.37 g, 0.196 mol) and potassium hydroxide pellets (85% reagent, 16.90 g, 0.256 mol), together with *p*-cymene (100 ml). The mixture was stirred and heated to reflux, and this temperature was maintained until water production had ceased (88 h). After this time the mixture was allowed to cool, producing a brown solution and a pale brown gum. Water (*ca.* 300 ml) was added, and the mixture was stirred until the gummy substance had dissolved. The golden aqueous phase was separated and washed with light petroleum (3 x 30 ml), the combined red organic extracts furnishing, on evaporation, mainly unreacted indole (12.10 g). The aqueous phase was cautiously acidified with concentrated hydrochloric acid, which produced a red-brown oil which gradually solidified. The mixture was kept below 4°C for 2 days, after which time precipitation was complete. The solid material was dissolved in ether (*ca.* 500 ml), and the acidic aqueous layer was extracted with ether (3 x 70 ml). The combined extracts were washed with water (3 x 150 ml), which removed much of the brownish colour. brine (70 ml), dried (MgSO_4), and evaporated to leave a foul-smelling yellow solid. This was recrystallised from benzene to give the title compound (215) (9.26 g, 23%) as a colourless powdery solid, m.p. 141–143°C (lit.,¹³² 143–144°C) (Found: C, 72.6; H, 7.5; N, 6.05. Calc. for $\text{C}_{14}\text{H}_{17}\text{NO}_2$, C, 72.7; H, 7.4; N, 6.1%); $\nu_{\text{max.}}$ (Nujol) 2 500–3 500 (OH), 3 372 (indole NH), 1 695 (C=O), 1 290, 1 254, 1 240, 1 198, 741, and 731 cm^{-1} ; δ_{H} (20 MHz; CDCl_3) 1.46 (2 H, m, 4- CH_2), 1.72 (4 H, m, 3- and 5- CH_2), 2.36 (2 H, t, J 7.3 Hz, 2- CH_2), 2.76 (2 H, t,

J 7.4 Hz, 6-CH₂), 6.96 (1 H, s, 2'-H), 7.11 (1 H, t, J 7.3 Hz, 5'-H), 7.19 (1 H, t, J 7.4 Hz, 6'-H), 7.34 (1 H, d, J 7.3 Hz, 7'-H), 7.60 (1 H, d, J 7.5 Hz, 4'-H), and 7.91 (1 H, br s, 1'-H); m/z 231 (M^+ , 29%), 158 (5), 144 (6), 130 (100, ArCH₂⁺), 102 (19), 73 (52), and 55 (44).

Ethyl 6-(indol-3-yl)hexanoate (216).—To a suspension of 6-(indol-3-yl)hexanoic acid (215) (1.0 g, 4.32 mmol) in dry benzene (20 ml) was added oxalyl chloride (4 ml, 46 mmol) and the mixture was stirred at ambient temperature for 1 h. After this time, all the solid had dissolved, forming a red-brown solution. This was evaporated to leave a red-brown oil which was cooled in an ice-bath whilst a mixture of ethanol (30 ml) and triethylamine (3 ml) was added dropwise. The mixture was stirred at 0°C for 30 min, after which time it was diluted with water (75 ml) and extracted with ether (3 x 100 ml), the combined extracts being washed with water (2 x 100 ml), saturated aqueous sodium carbonate solution (2 x 75 ml), water (3 x 50 ml), and brine (30 ml) before being dried (MgSO₄), and evaporated to give a yellow oil. This was purified by chromatography (75% dichloromethane-light petroleum) to give the *title compound* (216) (0.795 g, 71%) as a colourless crystalline solid, m.p. 60-61°C (Found: C, 74.0; H, 8.3; N, 5.25. C₁₆H₂₁NO₂ requires C, 74.1; H, 8.2; N, 5.4%); $\nu_{\max}$ (Nujol) 3 342 (indole NH), 1 710 (C=O), 1 354, 1 287, 1 252, 1 235, 1 220, 1 182, 1 096, 1 014, 748, and 668 cm⁻¹; δ_H (270 MHz; CDCl₃) 1.25 (3 H, t, J 7.2 Hz, OCH₂CH₃), 1.37-1.49 (2 H, m, 4-CH₂), 1.63-1.79 (4 H, m, 3- and 5-CH₂), 2.30 (2 H, t, J 7.3 Hz, 2-CH₂), 2.76 (2 H, t, J 7.3 Hz, 6-CH₂), 4.12 (2 H, q, J 7.1 Hz, OCH₂CH₃), 6.97 (1 H, d, J 2.2 Hz, 2'-H), 7.10 (1 H, td, J 6.7 and 1.2 Hz, 5'-H), 7.18 (1 H, td, J 6.7 and 1.2 Hz, 6'-H), 7.35 (1 H, d, J 6.7 Hz, 7'-H), 7.59 (1 H, d, J 7.7 Hz, 4'-H), and 7.91 (1 H, br s, 1'-H); m/z 259 (M^+ , 25%), 214 (7), 144 (4), 143 (3), 131 (15), 130 (100, ArCH₂⁺), 129 (3), and 77 (4).

Ethyl 6-(1-t-butoxycarbonylindol-3-yl)hexanoate (217).—To a suspension of ethyl 6-(indol-3-yl)hexanoate (216) (0.70 g, 2.70 mmol) in dry acetonitrile (20 ml) was added

di-*t*-butyl dicarbonate (0.884 g, 4.05 mmol) and 4-dimethylaminopyridine (0.033 g, 0.270 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear pale yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (217) (0.928 g, 96%) as a pale yellow oil (Found: C, 70.2; H, 8.1; N, 4.0. $C_{21}H_{29}NO_4$ requires C, 70.2; H, 8.1; N, 3.9%); $\nu_{\max}$ (film) 1 729 (ester and carbamate C=O), 1 456, 1 381, 1 309, 1 256, 1 225, 1 163, 1 094, and 747 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.25 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.40-1.49 (2 H, m, 4- CH_2), 1.62-1.76 (4 H, m, 5- and 7- CH_2), 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 2.31 (2 H, t, J 7.4 Hz, 2- CH_2), 2.68 (2 H, t, J 7.3 Hz, 6- CH_2), 4.12 (2 H, q, J 7.1 Hz, OCH_2CH_3), 7.22 (1 H, td, J 7.3 and 1.3 Hz, 5'-H), 7.31 (1 H, td, J 7.3 and 1.2 Hz, 6'-H), 7.34 (1 H, s, 2'-H), 7.51 (1 H, d, J 7.1 Hz, 4'-H), and 8.12 (1 H, br d, J 8.1 Hz, 7'-H); m/z 359 (M^+ , 13%), 315 (1), 260 (11), 259 (61), 143 (4), 131 (18), 130 (100, ArCH_2^+), and 57 (46).

*Ethyl 6-(1-*t*-butoxycarbonylindol-3-yl)-2-chlorohexanoate* (218).—A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 1.1 ml, 1.67 mmol) to *N*-isopropylcyclohexylamine (274 μl , 1.67 mmol) in THF (50 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of ethyl 6-(1-*t*-butoxycarbonylindol-3-yl)hexanoate (217) (0.50 g, 1.39 mmol) in THF (20 ml) was added dropwise to the LiICA solution. After a further 10 min, the mixture was allowed to warm slowly to -20°C , producing a clear orange solution. This was cooled again to -78°C , and then added *via* a catheter to a solution of dry carbon tetrachloride (15 ml) in THF (30 ml), also at -78°C under nitrogen. The solution was stirred at -78°C for a further 10 min, and then allowed to warm slowly to ambient temperature, giving a pale yellow solution. After a further 20 min, acetic acid (1.5 ml) was added, and the resulting solution was diluted with water (60 ml) and extracted with dichloromethane (3 x 75 ml). The combined extracts were dried (MgSO_4), evaporated, and

purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (218) (0.290 g, 53%) as a colourless oil (Found: M^+ , 393.1707. $C_{21}H_{28}ClNO_4$ requires 393.1707); $\nu_{\max}$ (film) 1 732 (ester and carbamate C=O), 1 455, 1 377, 1 309, 1 257, 1 161, 1 094, and 746 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.42-2.08 (6 H, m, 3-, 4-, and 5- CH_2), 1.67 (9 H, s, $C(CH_3)_3$), 2.70 (2 H, t, J 7.4 Hz, 6- CH_2), 4.22 (2 H, q, J 7.2 Hz, OCH_2CH_3), 4.27 (1 H, t, J 6.1 Hz, 2-CH), 7.23 (1 H, td, J 7.4 and 1.2 Hz, 5'-H), 7.31 (1 H, td, J 7.6 and 1.5 Hz, 6'-H), 7.35 (1 H, s, 2'-H), 7.50 (1 H, d, J 7.9 Hz, 4'-H), and 8.12 (1 H, br d, J 7.8 Hz, 7'-H); m/z 393 (M^+ , 4%), 293 (20), 184 (9), 131 (16), 130 (100, $ArCH_2^+$), 57 (51), 44 (8), and 41 (16).

Ethyl 6-(indol-3-yl)-2-chlorohexanoate (219).—To a solution of ethyl 6-(1-*t*-butoxycarbonylindol-3-yl)-2-chlorohexanoate (218) (0.250 g, 0.635 mmol) in dichloromethane (25 ml) was added dropwise trifluoroacetic acid (800 μ l). The slightly reddish solution was stirred at ambient temperature for 2 h, and then evaporated under reduced pressure, leaving a brown oil. This was purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (219) (0.121 g, 65%) as a colourless oil (Found: M^+ , 293.1183. $C_{16}H_{20}ClNO_2$ requires 293.1183); $\nu_{\max}$ ($CHCl_3$) 3 482 (indole NH), 1 736 (C=O), 1 457, 1 266, 1 227, 1 178, and 707 cm^{-1} ; $\lambda_{\max}$ (MeOH) 277infl, 283 (log ϵ 4.01), and 291 (3.91) nm; δ_H (270 MHz; $CDCl_3$) 1.28 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.43-1.63 (2 H, m, 4- CH_2), 1.71-1.79 (2 H, m, 5- CH_2), 1.95-2.07 (2 H, m, 3- CH_2), 2.78 (2 H, t, J 7.6 Hz, 6- CH_2), 4.22 (2 H, q, J 7.1 Hz, OCH_2CH_3), 4.25 (1 H, t, J 6.4 Hz, 2-CH), 6.98 (1 H, d, J 2.4 Hz, 2'-H), 7.11 (1 H, td, J 6.4 and 1.1 Hz, 5'-H), 7.19 (1 H, td, J 6.3 and 1.2 Hz, 6'-H), 7.36 (1 H, d, J 7.8 Hz, 7'-H), 7.59 (1 H, d, J 7.8 Hz, 4'-H), and 7.93 (1 H, br s, 1'-H); m/z 293 (M^+ , 21%), 212 (4), 149 (6), 131 (14), 130 (100, $ArCH_2^+$), 103 (3), 77 (7), and 57 (4).

Irradiation of ethyl 6-(indol-3-yl)-2-chlorohexanoate (219).—A solution of ethyl 6-

(indol-3-yl)-2-chlorohexanoate (219) (0.050 g, 0.170 mmol) in acetonitrile (50 ml) was irradiated for 15 min. The brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give *ethyl 6-(indol-3-yl)hex-2-enoate* (220) (0.029 g, 67%) as a golden brown oil (Found: M^+ , 257.1416. $C_{16}H_{19}NO_2$ requires 257.1416); $\nu_{\max.}(\text{CHCl}_3)$ 3 460 (indole NH), 1 713 (C=O), 1 369, 1 319, 1 301, 1 220, 1 187, and 1 144 cm^{-1} ; $\delta_{\text{H}}(270 \text{ MHz; CDCl}_3)$ 1.29 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.87 (2 H, m, 5- CH_2), 2.58-2.67 (2 H, m, 4- CH_2), 2.93 (2 H, t, J 7.5 Hz, 6- CH_2), 4.14 (2 H, q, J 7.1 Hz, OCH_2CH_3), 5.67-5.70 (1 H, m, 2-CH), 6.87 (1 H, dt, J 16.2 and 7.1 Hz, 3-CH), 7.00 (1 H, d, J 2.1 Hz, 2'-H), 7.10 (1 H, td, J 7.1 and 1.1 Hz, 5'-H), 7.18 (1 H, td, J 7.1 and 1.2 Hz, 6'-H), 7.35 (1 H, d, J 8.1 Hz, 7'-H), 7.61 (1 H, d, J 7.8 Hz, 4'-H), and 7.96 (1 H, br s, 1'-H); m/z 257 (M^+ , 6%), 231 (25), 170 (53), 168 (26), 143 (31), 130 (100, ArCH_2^+), 86 (29), and 84 (44).

Ethyl 5-(indol-3-yl)-2,2-dichloropentanoate (221).—A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 0.15 ml, 0.234 mmol) to *N*-isopropylcyclohexylamine (38 μl , 0.234 mmol) in a mixture of THF (20 ml) and HMPA (0.1 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of ethyl dichloroacetate (0.037 g, 0.234 mmol) in THF (3 ml) was added to the LiICA solution, and the mixture was stirred at -78°C for 15 min. A solution of *t*-butyl 3-(3-iodopropyl)indole-1-carboxylate (209) (0.10 g, 0.26 mmol) in THF (5 ml) was added dropwise to the yellow solution, and the mixture was stirred at -78°C for 2 h. After this time, acetic acid (2.0 ml) was added, and the resulting solution was diluted with water (30 ml) and extracted with dichloromethane (3 x 40 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (dichloromethane) to give the *title compound* (221) (0.018 g, 24%) as a pale yellow oil (Found: C, 57.5; H, 5.4; N, 4.7. $C_{15}H_{17}Cl_2NO_2$ requires C, 57.3; H, 5.5; N, 4.5%); $\nu_{\max.}(\text{film})$ 3 417 (indole NH), 1 743 (C=O), 1 457, 1 259, 1 094, 1 012, and 742

cm^{-1} ; λ_{max} (MeOH) 275infl, 282 (log ϵ 3.75), and 29 (3.68) nm; δ_{H} (270 MHz; CDCl_3) 1.30 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.97-2.09 (2 H, m, 4- CH_2), 2.50-2.56 (2 H, m, 3- CH_2), 2.86 (2 H, t, J 7.3 Hz, 5- CH_2), 4.28 (2 H, q, J 7.1 Hz, OCH_2CH_3), 7.02 (1 H, d, J 2.3 Hz, 2'-H), 7.12 (1 H, td, J 7.7 and 1.4 Hz, 5'-H), 7.20 (1 H, td, J 7.4 and 1.2 Hz, 6'-H), 7.36 (1 H, d, J 8.0 Hz, 7'-H), 7.60 (1 H, d, J 7.8 Hz, 4'-H), and 7.95 (1 H, br s, 1'-H); m/z 313 (M^+ , 15%), 243 (33), 241 (39), 193 (31), 170 (89), 168 (45), 167 (38), and 130 (100, ArCH_2^+).

Irradiation of ethyl 5-(indol-3-yl)-2,2-dichloropentanoate (221).—A solution of ethyl 5-(indol-3-yl)-2,2-dichloropentanoate (221) (0.012 g, 38.2 μmol) in acetonitrile (10 ml) was irradiated for 25 min. The brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give ethyl 5-(indol-3-yl)-2-chloropent-2-enoate (222) (0.006 g, 58%) as a golden brown oil (Found: M^+ , 277.0870. $\text{C}_{15}\text{H}_{16}\text{ClNO}_2$ requires 277.0870); ν_{max} (film) 3 480 (indole NH), 1 630 ($\text{C}=\text{O}$), 1 458, 1 419, 1 371, 1 183, 1 091, and 1 049 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.32 (3 H, t, J 7.2 Hz, OCH_2CH_3), 2.80 (2 H, td, J 7.0 and 1.0 Hz, 5- CH_2), 2.93-3.00 (2 H, m, 4- CH_2), 4.26 (2 H, q, J 7.1 Hz, OCH_2CH_3), 7.02 (1 H, d, J 2.4 Hz, 2'-H), 7.10-7.24 (3 H, m, 3-, 5'-, and 6'-H), 7.37 (1 H, d, J 7.8 Hz, 7'-H), 7.61 (1 H, d, J 7.8 Hz, 4'-H), and 7.97 (1 H, br s, 1'-H); m/z 277 (M^+ , 5%), 168 (3), 167 (3), 131 (10), 130 (100, ArCH_2^+), 129 (3), 108 (3), and 77 (4).

5-Hydroxy-3,3-dimethylpentanoic acid lactone (223).—To a suspension of sodium borohydride (4.0 g, 106 mmol) in THF (20 ml) at 0°C was added, over 30 min, a solution of 3,3-dimethylglutaric anhydride (10.0 g, 70.35 mmol) in THF (50 ml). The resulting solution was allowed to warm to ambient temperature, where it was stirred for 3.5 h. The solution was then recooled to 0°C, and was quenched by the addition of 6 M hydrochloric acid (35 ml). The resulting solution was washed with brine (5 x 50 ml), and then extracted

with ether (3 x 50 ml), the combined extracts being dried (MgSO_4) and evaporated to leave a pale yellow oil. Distillation of this in a Kugelröhr apparatus (oven temperature, 155°C , 24 mmHg) (lit.,¹³⁹ no b.p. given) gave the title compound (223) (5.90 g, 65%) as a colourless liquid $\nu_{\text{max.}}$ (film) 2 959, 1 746 ($\text{C}=\text{O}$), 1 404, 1 256, 1 226, 1 175, and 1 079 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.05 (6 H, s, $\text{C}(\text{CH}_3)_2$), 1.66 (2 H, t, J 6.1 Hz, 4- CH_2), 2.29 (2 H, s, 2- CH_2), and 4.33 (2 H, t, J 6.1 Hz, 5- CH_2); m/z 128 (M^+ , 20%), 83 (7), 70 (17), 69 (100), 56 (58), 55 (16), 41 (60), and 39 (16).

Ethyl 5-(indol-3-yl)-3,3-dimethylpentanoate (225).—Into a 3-necked flask equipped with overhead stirrer and Dean-Stark trap was placed indole (3.74 g, 31.89 mmol), 5-hydroxy-3,3-dimethylpentanoic acid lactone (223) (4.70 g, 36.67 mmol) and potassium hydroxide pellets (85% reagent, 3.16 g, 47.83 mmol), together with tetralin (100 ml). The mixture was stirred and heated to reflux, and this temperature was maintained until water production had ceased (96 h). After this time the mixture was allowed to cool, producing a brown solution and a pale brown gum. Water (ca. 50 ml) was added, and the mixture was stirred until the gummy substance had dissolved. The aqueous phase was separated and washed with light petroleum (3 x 30 ml), the combined organic extracts furnishing, on evaporation, mainly unreacted indole (1.3 g). The aqueous phase was cautiously acidified with concentrated hydrochloric acid, which produced a red-brown oil. The mixture was kept below 4°C for 2 days, after which time the oil still had not solidified. The oil was dissolved in dry benzene (20 ml) and oxalyl chloride (4 ml, 46 mmol) was added. The mixture was stirred at ambient temperature for 30 min, the the resulting red-brown solution was evaporated to leave a red-brown oil. This was cooled in an ice-bath whilst a mixture of ethanol (30 ml) and triethylamine (3 ml) was added dropwise. The mixture was stirred at 0°C for 30 min, after which time it was diluted with water (75 ml) and extracted with ether (3 x 100 ml), the combined extracts being washed with water (2 x 100 ml), saturated aqueous sodium carbonate solution (2 x 75 ml), water (3 x 50 ml), and brine (30 ml) before being dried (MgSO_4), and evaporated to give a yellow

oil. This was purified by chromatography (50% dichloromethane-light petroleum) to give the *title compound* (225) (0.398 g, 19% from (223)) as a colourless oil (Found: M^+ , 273.1729. $C_{17}H_{23}NO_2$ requires 273.1729); $\nu_{\max.}$ (film) 3 416 (indole NH), 1 732 (C=O), 1 458, 1 369, 1 337, 1 230, 1 115, 1 036, and 741 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.14 (6 H, s, $C(CH_3)_2$), 1.27 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.73-1.79 (2 H, m, 4- CH_2), 2.34 (2 H, s, 2- CH_2), 2.74-2.80 (2 H, m, 5- CH_2), 4.15 (2 H, q, J 7.2 Hz, OCH_2CH_3), 6.97 (1 H, d, J 2.2 Hz, 2'-H), 7.12 (1 H, td, J 7.1 and 1.2 Hz, 5'-H), 7.19 (1 H, td, J 7.4 and 1.2 Hz, 6'-H), 7.35 (1 H, d, J 7.7 Hz, 7'-H), 7.63 (1 H, d, J 7.9 Hz, 4'-H), and 7.93 (1 H, br s, 1'-H); m/z 273 (M^+ , 22%), 228 (8), 145 (5), 144 (41), 143 (8), 131 (11), 130 (100, $ArCH_2^+$), and 77 (5).

Ethyl 5-(1-t-butoxycarbonylindol-3-yl)-3,3-dimethylpentanoate (226).—To a suspension of ethyl 5-(indol-3-yl)-3,3-dimethylpentanoate (225) (0.371 g, 1.36 mmol) in dry acetonitrile (20 ml) was added di-*t*-butyl dicarbonate (0.44 g, 2.04 mmol) and 4-dimethylaminopyridine (0.017 g, 0.136 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear pale yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (70% dichloromethane-light petroleum) to give the *title compound* (226) (0.494 g, 97%) as a colourless oil (Found: C, 70.7; H, 8.7; N, 3.65. $C_{22}H_{31}NO_4$ requires C, 70.75; H, 8.37; N, 3.75%); $\nu_{\max.}$ (film) 1 729 (ester and carbamate C=O), 1 455, 1 371, 1 353, 1 256, 1 162, and 1 083 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.13 (6 H, s, $C(CH_3)_2$), 1.27 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.67 (9 H, s, $C(CH_3)_3$), 1.68-1.77 (2 H, m, 4- CH_2), 2.32 (2 H, s, 2- CH_2), 2.65-2.72 (2 H, m, 5- CH_2), 4.14 (2 H, q, J 7.2 Hz, OCH_2CH_3), 7.23 (1 H, td, J 7.6 and 1.3 Hz, 5'-H), 7.31 (1 H, td, J 8.2 and 1.3 Hz, 6'-H), 7.35 (1 H, s, 2'-H), 7.54 (1 H, d, J 7.6 Hz, 4'-H), and 8.12 (1 H, br d, J 7.8 Hz, 7'-H); m/z 373 (M^+ , 1%), 273 (23), 228 (8), 144 (44), 143 (10), 131 (11), 130 (100, $ArCH_2^+$), and 57 (17).

*Ethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-2-chloro-3,3-dimethylpentanoate (227).*—

A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 0.43 ml, 0.643 mmol) to *N*-isopropylcyclohexylamine (106 μ l, 0.643 mmol) in THF (20 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of ethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-3,3-dimethylpentanoate (226) (0.20 g, 0.536 mmol) in THF (10 ml) was added dropwise to the LiICA solution. After a further 10 min, the mixture was allowed to warm slowly to -20°C , producing a clear orange solution. This was cooled again to -78°C , and then added *via* a catheter to a solution of dry carbon tetrachloride (10 ml) in THF (25 ml), also at -78°C under nitrogen. The solution was stirred at -78°C for a further 10 min, and then allowed to warm slowly to ambient temperature, giving a pale yellow solution. After a further 20 min, acetic acid (1.5 ml) was added, and the resulting solution was diluted with water (60 ml) and extracted with dichloromethane (3 x 75 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (1% methanol-dichloromethane) to give the *title compound* (227) (0.083 g, 38%) as a colourless oil (Found: C, 65.05; H, 7.6; N, 3.1. $\text{C}_{22}\text{H}_{30}\text{ClNO}_4$ requires C, 64.8; H, 7.4; N, 3.4%); ν_{max} (film) 1 750 (ester C=O), 1 733 (carbamate C=O), 1 455, 1 371, 1 257, 1 157, 1 083, and 747 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.20 (6 H, s, $\text{C}(\text{CH}_3)_2$), 1.31 (3 H, t, J 7.2 Hz, OCH_2CH_3), 1.68 (9 H, s, $\text{C}(\text{CH}_3)_3$), 1.69–1.92 (2 H, m, 4- CH_2), 2.67–2.73 (2 H, m, 5- CH_2), 4.25 (2 H, qd, J 7.1 and 0.7 Hz, OCH_2CH_3), 4.30 (1 H, s, 2-CH), 7.24 (1 H, td, J 7.6 and 1.3 Hz, 5'-H), 7.29 (1 H, td, J 7.9 and 1.4 Hz, 6'-H), 7.36 (1 H, s, 2'-H), 7.53 (1 H, d, J 7.6 Hz, 4'-H), and 8.13 (1 H, br d, J 7.6 Hz, 7'-H); m/z 407 (M^+ , 17%), 351 (36), 188 (32), 144 (36), 130 (100, ArCH_2^+), 84 (27), 57 (96), and 41 (22).

Ethyl 5-(indol-3-yl)-2-chloro-3,3-dimethylpentanoate (228).—To a solution of

ethyl 5-(1-*t*-butoxycarbonylindol-3-yl)-2-chloro-3,3-dimethylpentanoate (227) (0.052 g, 0.127 mmol) in dichloromethane (15 ml) was added dropwise trifluoroacetic acid (200 μ l).

The slightly purple solution was stirred at ambient temperature for 2 h, and then evaporated under reduced pressure, leaving a brown oil. This was purified by chromatography (70% dichloromethane-light petroleum) to give the *title compound* (228) (0.020 g, 52%) as a colourless oil (Found: M^+ , 307.1339. $C_{17}H_{22}ClNO_2$ requires 307.1339); $\nu_{\max.}(\text{CHCl}_3)$ 3 481 (indole NH), 1 744 (C=O), 1 457, 1 371, 1 335, 1 269, 1 181, and 1 032 cm^{-1} ; $\lambda_{\max.}(\text{MeOH})$ 276infl, 282 (log ϵ 3.71), and 290 (3.65) nm; $\delta_{\text{H}}(270 \text{ MHz; CDCl}_3)$ 1.21 (6 H, s, $C(\text{CH}_3)_2$), 1.31 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.76-1.96 (2 H, m, 4- CH_2), 2.78 (2 H, t, J 8.3 Hz, 5- CH_2), 4.25 (2 H, qd, J 7.1 and 1.0 Hz, OCH_2CH_3), 4.32 (1 H, 2-CH), 6.98 (1 H, d, J 2.2 Hz, 2'-H), 7.13 (1 H, td, J 7.5 and 1.1 Hz, 5'-H), 7.21 (1 H, td, J 7.5 and 1.1 Hz, 6'-H), 7.37 (1 H, d, J 6.8 Hz, 7'-H), 7.61 (1 H, d, J 7.9 Hz, 4'-H), and 7.94 (1 H, br s, 1'-H); m/z 307 (M^+ , 8%), 223 (11), 213 (25), 149 (100), 144 (12), 130 (47, ArCH_2^+), 57 (22), and 41 (11).

Irradiation of ethyl 5-(indol-3-yl)-2-chloro-3,3-dimethylpentanoate (228).—A solution of ethyl 5-(indol-3-yl)-2-chloro-3,3-dimethylpentanoate (228) (0.014 g, 45.5 μmol) in acetonitrile (10 ml) was irradiated for 30 min. The brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give *ethyl 5,5-dimethyl-3,4,5,6-tetrahydrocyclohept[cd]indole-6-carboxylate* (229) (0.002 g, 18%) as a golden brown oil (Found: M^+ , 271.1572. $C_{17}H_{21}NO_2$ requires 271.1572); $\nu_{\max.}(\text{film})$ 3 478 (indole NH), 1 724 (C=O), 1 457, 1 423, 1 370, 1 227, 1 035, and 705 cm^{-1} ; $\delta_{\text{H}}(270 \text{ MHz; CDCl}_3)$ 1.18 (6 H, s, $C(\text{CH}_3)_2$), 1.22 (3 H, t, J 7.1 Hz, OCH_2CH_3), 1.76-1.80 (2 H, m, 4- CH_2), 2.65-2.87 (2 H, m, 3- CH_2), 4.05 (2 H, q, J 7.1 Hz, OCH_2CH_3), 4.92-5.02 (1 H, m, 6-CH), 6.98 (1 H, dd, J 7.8 and 1.2 Hz, 7-H), 7.03 (1 H, s, 2-H), 7.11 (1 H, t, J 7.8 Hz, 8-H), 7.21 (1 H, d, J 7.5 Hz, 9-H), and 8.09 (1 H, br s, 1-H); m/z 271 (M^+ , 31%), 198 (16), 185 (15), 184 (100), 182 (16), 169 (15), 168 (16), and 130 (54).

Attempted reaction of gramine methiodide with the dianion of ethyl acetoacetate.—

Sodium hydride dispersion in mineral oil (60%; 0.92 g, 23 mmol) was washed with light petroleum (3 x 10 ml) and allowed to dry under an atmosphere of nitrogen. Dry toluene (30 ml) was added and the resulting suspension cooled to -10°C. Ethyl acetoacetate (2.98 g, 23 mmol) was added and the mixture was stirred for 15 min before *n*-butyl-lithium (1.5 M solution in hexanes, 15.3 ml, 23 mmol) was added. Gramine methiodide (3.64 g, 11.5 mmol) was added, and the mixture was allowed to warm to ambient temperature for 15 min before it was heated to 80°C for 2 h. The mixture was then allowed to cool and water (50 ml) was very cautiously added dropwise. The organic phase was separated and the aqueous phase was extracted with ether (3 x 50 ml), the combined extracts being washed with water (50 ml) and brine (40 ml) before drying (MgSO₄) and evaporating to leave a brown oily residue. Purification of this by chromatography (dichloromethane) gave no recognisable products. Repetition of the reaction at a lower temperature (30°C) resulted in no reaction.

*Attempted reaction of gramine with ethyl acetoacetate in the presence of tri-*n*-*

*butylphosphine.—*To a stirred solution of gramine (1 g, 5.74 mmol) and ethyl acetoacetate (0.747 g, 5.74 mmol) in dry acetonitrile (20 ml) was added a solution of tri-*n*-butylphosphine (0.406 g, 2.00 mmol) in dry acetonitrile (5 ml). The mixture was stirred and heated to reflux under a nitrogen atmosphere for 4 h, and then cooled and evaporated leaving a brown oily residue. This was acidified by adding 1 M hydrochloric acid (20 ml) and the resulting brown mixture was extracted with dichloromethane (3 x 50 ml), the combined extracts being washed with water (2 x 30 ml), brine (30 ml) and dried (MgSO₄) before evaporation to leave a brownish residue. Attempted chromatography of this gave no recognisable product.

*1-(Indol-3-yl)ethyl-2-(p-toluenesulphonate) (233).—*To a yellow solution of tryp-

SYNTHETIC ROUTES TO [cd]-FUSED INDOLES

tophol (2.0 g, 12.41 mmol) in pyridine (10 ml) at 0°C was added *p*-toluenesulphonyl chloride (4.73 g, 24.8 mmol). Once all the *p*-toluenesulphonyl chloride had dissolved, the golden mixture was kept at 0°C for 24 h. After this time, crystals of pyridinium hydrochloride had formed, and the mixture was poured onto ice-water (*ca.* 50 ml). The mixture was then extracted with ether (3 x 75 ml), the combined extracts being washed with saturated copper (II) sulphate solution (*ca.* 4 x 30 ml), until no darkening of the copper sulphate solution was evident, followed by water (3 x 50 ml), and brine (30 ml), before drying (MgSO₄). The solution was evaporated at ambient temperature, leaving a yellowish solid which was recrystallised from ether-petrol to give the title compound (233) (3.47, 89%) as a colourless crystalline solid, m.p. 74-75°C (lit.,¹⁴² 77.5-79°C); (Found: C, 64.7; H, 5.4; N, 4.3. Calc. for C₁₇H₁₇NO₃S, C, 64.7; H, 5.4; N, 4.4%); $\nu_{\max}$ (Nujol) 3 423 (indole NH), 1 349, 1 188, 1 174, 976, 969, 904, 781, 753, and 663 cm⁻¹; δ_{H} (200 MHz; CDCl₃) 2.39 (3 H, s, CCH₃), 3.12 (2 H, t, *J* 7.1 Hz, 1-CH₂), 4.26 (2 H, t, *J* 7.1 Hz, 2-CH₂), 7.01 (1 H, d, *J* 2.5 Hz, 2'-H), 7.08 (1 H, dd, *J* 14 and 6.7 Hz, 5'-H), 7.15-7.26 (3 H, m, 6'-H and CH₃CCHCH), 7.34 (1 H, d, *J* 8.0 Hz, 7'-H), 7.42 (1 H, d, *J* 7.7 Hz, 4'-H), 7.68 (2 H, d, *J* 8.2 Hz, CH₃CCHCH), and 8.04 (1 H, br s, 1'-H); *m/z* 315 (*M*⁺, 1%), 172 (56), 155 (6), 143 (16), 130 (21, ArCH₂⁺), 107 (38), 91 (100, C₇H₇⁺), and 65 (50).

t-Butyl 3-(2-tosyloxyethyl)indole-1-carboxylate (234).—To a stirred solution of 1-(indol-3-yl)ethyl-2-(*p*-toluenesulphonate) (233) (0.50 g, 1.59 mmol) in dry acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (0.52 g, 2.38 mmol) and 4-dimethylaminopyridine (0.020 g, 0.16 mmol). The yellow-brown suspension was stirred at ambient temperature for 15 h, to give a clear yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (50% dichloromethane-light petroleum) to give the title compound (234) (0.66 g, 100%) as a yellow-brown oil (Found: C, 63.4; H, 6.1; N, 3.25. C₂₂H₂₅NO₅S requires C, 63.6; H, 6.1; N, 3.4%); $\nu_{\max}$ (film) 2 979, 2 929, 1 731 (C=O), 1 454, 1 368, 1 256, 1 188, 1 176, 1 159,

1 092, 767, 747, and 665 cm^{-1} ; δ_{H} (200 MHz; CDCl_3) 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 2.38 (3 H, s, CCH_3), 3.03 (2 H, t, J 6.8 Hz, 1'- CH_2), 4.28 (2 H, t, J 6.8 Hz, 2'- CH_2), 7.16 (2 H, d, J 7.9 Hz, CH_3CCHCH), 7.19 (1 H, m, 4-H), 7.32 (3 H, m, 2-, 5-, and 6-H), 7.63 (2 H, d, J 8.3 Hz, CH_3CCHCH), and 8.09 (1 H, d, J 8.0 Hz, 7-H); m/z 415 (M^+ , 5%), 359 (7), 342 (2), 315 (4), 187 (22), 143 (100), 130 (34, ArCH_2^+), and 57 (99).

t-Butyl 3-(2-iodoethyl)indole-1-carboxylate (235).—To a solution of *t*-butyl 3-(2-tosyloxyethyl)indole-1-carboxylate (234) (0.50 g, 1.20 mmol) in acetone (20 ml) at ambient temperature was added sodium iodide (0.902 g, 6.02 mmol). The resulting suspension was stirred at ambient temperature for 2 days, after which time water (40 ml) was added to the pale yellow mixture. The resulting solution was extracted with ether (3 x 40 ml), the combined extracts being washed with water (30 ml) before drying (MgSO_4) and evaporating to leave a yellow oil. This was purified by chromatography (50% dichloromethane-light petroleum) to give the *title compound* (235) (0.344 g, 77%) as a pale brown oil (Found: C, 48.8; H, 4.9; N, 3.65. $\text{C}_{15}\text{H}_{18}\text{INO}_2$ requires C, 48.5; H, 4.9; N, 3.8%); ν_{max} (Nujol) 1 724 ($\text{C}=\text{O}$), 1 451, 1 388, 1 356, 1 310, 1 250, and 1 161 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.67 (9 H, s, $\text{C}(\text{CH}_3)_3$), 3.30 (2 H, t, J 6.9 Hz, 2'- CH_2), 3.43 (2 H, td, J 7.2 and 1.2 Hz, 1'- CH_2), 7.25 (1 H, td, J 7.6 and 1.2 Hz, 5-H), 7.30 (1 H, td, J 7.6 and 1.3 Hz, 6-H), 7.47 (1 H, s, 2-H), 7.50 (1 H, d, J 7.6 Hz, 4-H), and 8.13 (1 H, br d, J 7.1 Hz, 7-H); m/z 371 (M^+ , 17%), 315 (33), 188 (31), 144 (71), 143 (19), 115 (14), 57 (100), and 41 (18).

Attempted reaction of t-butyl 3-(2-iodoethyl)indole-1-carboxylate (235) with the dianion of ethyl acetoacetate.—Sodium hydride dispersion in mineral oil (60%; 0.011 g, 0.269 mmol) was washed with light petroleum (3 x 5 ml) and allowed to dry under an atmosphere of nitrogen. THF (10 ml) was added and the resulting suspension cooled to

-10°C. Ethyl acetoacetate (0.035 g, 0.269 mmol) was added and the mixture was stirred for 15 min before *n*-butyl-lithium (1.5 M solution in hexanes, 0.2 ml, 0.269 mmol) was also added. *t*-Butyl 3-(2-iodoethyl)indole-1-carboxylate (235) (0.050 g, 0.135 mmol) was added, and the mixture was stirred at -10°C for 1 h before it was allowed to warm to ambient temperature. The mixture was then diluted with water (50 ml), and the resulting solution extracted with ether (3 x 50 ml), the combined extracts being washed with water (50 ml) and brine (40 ml) before drying (MgSO₄) and evaporating to leave a brown oily residue. Purification of this by chromatography (dichloromethane) gave unreacted starting material (0.039 g, 78%) as the only recognisable product.

2-(Indol-3-yl)ethyl trichloroacetate (192).—To a yellow solution of tryptophol (1.0 g, 6.20 mmol) and pyridine (0.49 g, 6.20 mmol) in dichloromethane (15 ml) at 0°C was added trichloroacetyl chloride (1.24 g, 6.82 mmol), whereupon the solution darkened slightly. The mixture was removed from the cold-bath and kept in the dark for 2.5 h, after which time the solvent was evaporated to give a brown oil. This was chromatographed (50% dichloromethane-light petroleum) to give the *title compound* (192) (1.82 g, 96%) as a pale yellow oil (Found: C, 47.3; H, 3.5; N, 4.4. C₁₂H₁₀Cl₃NO₂ requires C, 47.0; H, 3.3; N, 4.6%); $\nu_{\max}$.(film) 3 423 (indole NH), 1 764 (C=O), 1 458, 1 422, 1 255, 1 226, 984, 864, 827, 743, and 680 cm⁻¹; $\lambda_{\max}$.(MeOH) 275infl, 281 (log ϵ 3.74), and 290 (3.66) nm; δ_{H} (200 MHz; CDCl₃) 3.24 (2 H, t, *J* 7.1 Hz, 2-CH₂), 4.61 (2 H, t, *J* 7.1 Hz, 1-CH₂), 7.09 (1 H, d, *J* 2.7 Hz, 2'-H), 7.10-7.25 (2 H, m, 5'- and 6'-H), 7.37 (1 H, d, *J* 7.4 Hz, 7'-H), 7.64 (1 H, d, *J* 7.5 Hz, 4'-H), and 8.04 (1 H, br s, 1'-H); *m/z* 305 (*M*⁺, 8%), 144 (32), 143 (65), 130 (100, ArCH₂⁺), 115 (8), 103 (5), and 77 (7).

Irradiation of 2-(indol-3-yl)ethyl trichloroacetate (192).—A solution of 2-(indol-3-yl)ethyl trichloroacetate (192) (0.20 g, 0.652 mmol) in 20% methanol-acetonitrile (100 ml) was irradiated for 25 min. The golden brown solution was evaporated, and the residue

was purified by chromatography (2% methanol-dichloromethane) to give firstly 7,7-*dimethoxy-1,3,6,7-tetrahydro-[3]oxocino[4,5,6-cd]indol-6-one* (193) (0.071 g, 42%) as a pale yellow solid, m.p. 196-198°C; (Found: C, 64.1; H, 5.6; N, 5.5. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%); $\nu_{\max}$ (Nujol) 3 422 (indole NH), 1 752 (C=O), 1 262, 1 175, 1 128, 1 085, 1 055, 1 043, and 747 cm^{-1} ; $\lambda_{\max}$ (MeOH) 291infl, 296 (log ϵ 3.76), and 369 (3.24) nm; δ_H (270 MHz; CDCl_3) 3.06 (1 H, d, J 16.1 Hz, 3-CH), 3.35-3.48 (1 H, m, 3-CH), 3.51 (3 H, s, OMe), 3.75 (3 H, s, OMe), 4.17 (1 H, dt, J 11.7 and 3.2 Hz, 4-CH), 4.44 (1 H, t, J 11.8 Hz, 4-CH), 7.00 (1 H, br s, 2-H), 7.13 (1 H, t, J 7.7 Hz, 9-H), 7.22 (1 H, d, J 7.1 Hz, 8-H), 7.30 (1 H, d, J 8.1 Hz, 10-H), and 8.25 (1 H, br s, 1-H); m/z 261 (M^+ , 6%), 203 (11), 202 (83), 171 (14), 170 (100), 149 (11), 143 (11), and 115 (18). This was followed by tryptophol (0.051 g, 48%), the spectroscopic properties of which were identical to those of an authentic sample.

3-(Indol-3-yl)propyl trichloroacetate (237).—To a pale yellow solution of homo-tryptophol (1.0 g, 5.71 mmol) and pyridine (0.45 g, 5.71 mmol) in dichloromethane (15 ml) at 0°C was added trichloroacetyl chloride (1.14 g, 6.28 mmol), whereupon the solution became a brighter yellow colour. The mixture was removed from the cold-bath and kept in the dark for 2.5 h, after which time the solvent was evaporated to give a green-brown oil. This was chromatographed (50% dichloromethane-light petroleum) to give the *title compound* (237) (1.78 g, 97%) as a pale yellow solid, m.p. 81.5-82.5°C; (Found: C, 48.5; H, 3.7; N, 4.3. $C_{13}H_{12}Cl_3NO_2$ requires C, 48.7; H, 3.8; N, 4.4%); $\nu_{\max}$ (Nujol) 3 408 (indole NH), 2 954, 1 750 (C=O), 1 425, 1 266, 1 252, 1 012, 998, 896, 828, 749, and 681 cm^{-1} ; $\lambda_{\max}$ (MeOH) 275infl, 282 (log ϵ 3.84), and 290 (3.76) nm; δ_H (200 MHz; CDCl_3) 2.18 (2 H, quintet, J 7.0 Hz, 2- CH_2), 2.93 (2 H, t, J 7.3 Hz, 3- CH_2), 4.41 (2 H, t, J 6.3 Hz, 1- CH_2), 7.01 (1 H, d, J 1.6 Hz, 2'-H), 7.16 (2 H, m, 5'- and 6'-H), 7.37 (1 H, d, J 7.4 Hz, 7'-H), 7.60 (1 H, d, J 7.5 Hz, 4'-H), and 7.98 (1 H, br s, 1'-H); m/z 319 (M^+ , 10%), 158 (14), 130 (100, ArCH_2^+), 117 (3), 115 (3), 103 (4), and

77 (6).

Irradiation of 3-(indol-3-yl)propyl trichloroacetate (237).—A solution of 3-(indol-3-yl)propyl trichloroacetate (237) (0.20 g, 0.624 mmol) in 20% methanol-acetonitrile (100 ml) was irradiated for 25 min. The golden brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give firstly *methyl 3-(indol-3-yl)propyl carbonate (238)* (0.016 g, 11%) as a pale yellow oil (Found: C, 67.2; H, 6.7; N, 6.0. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%); $\nu_{\max}$ (film) 3 377 (indole NH), 1 732 (C=O), 1 444, 1 317, 1 286, 1 008, and 748 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 2.10 (2 H, quintet, J 7.1 Hz, 2- CH_2), 2.87 (2 H, t, J 7.1 Hz, 3- CH_2), 3.79 (3 H, s, OMe), 4.22 (2 H, t, J 7.1 Hz, 1- CH_2), 7.00 (1 H, d, J 2.4 Hz, 2'-H), 7.11 (1 H, td, J 7.6 and 1.0 Hz, 5'-H), 7.20 (1 H, td, J 7.4 and 1.2 Hz, 6'-H), 7.36 (1 H, d, J 8.0 Hz, 7'-H), 7.59 (1 H, d, J 7.8 Hz, 4'-H), and 7.95 (1 H, br s, 1'-H); m/z 233 (M^+ , 34%), 157 (25), 131 (13), 130 (100, $ArCH_2^+$), 86 (17), 84 (25), 51 (11), and 49 (33). This was followed by homotryptophol (0.063 g, 58%) which was isolated as a pale yellow oil, the spectral properties of which were identical to those of an authentic sample.

2-(1-t-butoxycarbonylindol-3-yl)ethyl trichloroacetate (239).—To a solution of 2-(indol-3-yl)ethyl trichloroacetate (192) (0.46 g, 1.50 mmol) in dry acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (0.491 g, 2.25 mmol) and 4-dimethylaminopyridine (0.018 g, 0.15 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear yellow solution, which was then evaporated to leave a yellow oily residue. This was purified by chromatography (dichloromethane) to give the *title compound (239)* (0.458 g, 75%) as a yellow oil (Found: C, 50.4; H, 4.7; N, 3.35. $C_{17}H_{18}Cl_3NO_4$ requires C, 50.2; H, 4.5; N, 3.4%); $\nu_{\max}$ (film) 1 767 (ester C=O), 1 736 (carbamate C=O), 1 456, 1 376, 1 256, 1 159, 1 093, 829, 747, and 682 cm^{-1} ; $\lambda_{\max}$ (MeOH) 258 (log ϵ 4.00), 262 (3.99), 274infl, 285 (3.74), and 293 (3.76) nm; δ_H (270 MHz; $CDCl_3$) 1.66 (9

H, s, C(CH₃)₃), 3.18 (2 H, td, *J* 6.8 and 1.1 Hz, 2-CH₂), 4.62 (2 H, t, *J* 6.8 Hz, 1-CH₂), 7.27 (1 H, td, *J* 7.5 and 1.2 Hz, 5'-H), 7.34 (1 H, td, *J* 7.5 and 1.3 Hz, 6'-H), 7.51 (1 H, s, 2'-H), 7.57 (1 H, dd, *J* 7.6 and 1.0 Hz, 4'-H), and 8.15 (1 H, br d, *J* 8.1 Hz, 7'-H); *m/z* 405 (*M*⁺, 6%), 349 (8), 305 (3), 187 (22), 143 (39), 130 (24, ArCH₂⁺), and 57 (100).

*Irradiation of 2-(1-*t*-butoxycarbonylindol-3-yl)ethyl trichloroacetate (239).*—A solution of 2-(1-*t*-butoxycarbonylindol-3-yl)ethyl trichloroacetate (239) (0.20 g, 0.49 mmol) in 20% methanol-acetonitrile (100 ml) was irradiated for 5 min. The yellow-brown solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give *t*-butyl 3-(2-hydroxyethyl)indole-1-carboxylate (240) (0.099 g, 77%) as a pale yellow oil (Found: C, 68.8; H, 7.5; N, 5.4. C₁₅H₁₉NO₃ requires C, 68.9; H, 7.3; N, 5.4%); *v*_{max} (film) 3 386 (OH), 1 733 (C=O), 1 455, 1 381, 1 310, 1 256, 1 159, and 1089 cm⁻¹; *δ*_H (270 MHz; CDCl₃) 1.54 (1 H, br s, OH), 1.67 (9 H, s, C(CH₃)₃), 2.97 (2 H, td, *J* 6.5 and 1.2 Hz, 1'-CH₂), 3.93 (2 H, br t, *J* 6.1 Hz, 2'-CH₂), 7.24 (1 H, td, *J* 7.6 and 1.3 Hz, 5-H), 7.33 (1 H, td, *J* 7.8 and 1.4 Hz, 6-H), 7.47 (1 H, s, 2-H), 7.55 (1 H, d, *J* 7.8 Hz, 4-H), and 8.15 (1 H, br d, *J* 8.5 Hz, 7-H); *m/z* 261 (*M*⁺, 26%), 205 (61), 174 (27), 149 (13), 131 (11), 130 (100, ArCH₂⁺), 57 (97), and 41 (20).

Ethyl 1-methylindole-3-acetate (242).—Sodium hydride dispersion in mineral oil (60%; 0.217 g, 5.41 mmol) was washed with light petroleum (3 x 5 ml) and allowed to dry under an atmosphere of nitrogen. THF (15 ml) was added, and the suspension was cooled to 0°C. A solution of ethyl indole-3-acetate (1.0 g, 4.92 mmol) in THF (10 ml) was added dropwise, and the mixture was stirred at 0°C for 30 min. After this time methyl iodide (0.30 ml, 4.92 mmol) was added, and the mixture was stirred at 0°C for 2 h before being allowed to warm to ambient temperature, where it was stirred for a further 15 h. The resulting mixture was cautiously diluted with water (40 ml) and extracted with ether (3 x 50

ml), the combined extracts being washed with water (2 x 30 ml) and brine (20 ml) before drying (MgSO_4). Evaporation under reduced pressure gave a golden brown residue which was purified by chromatography (dichloromethane) to give the *title compound* (242) (0.546 g, 51%) as a very pale yellow oil (Found: C, 71.6; H, 7.0; N, 6.6. $\text{C}_{13}\text{H}_{15}\text{NO}_2$ requires C, 71.9; H, 7.0; N, 6.45%); $\nu_{\text{max.}}$ (film) 3 053, 1 734 (C=O), 1 475, 1 376, 1 332, 1 250, 1 151, and 741 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.30 (3 H, t, J 7.1 Hz, OCH_2CH_3), 3.77 (3 H, s, NCH_3), 3.80 (2 H, td, J 4.3 and 0.8 Hz, 1'- CH_2), 4.20 (2 H, q, J 7.1 Hz, OCH_2CH_3), 7.07 (1 H, s, 2-H), 7.17 (1 H, td, J 7.2 and 1.1 Hz, 5-H), 7.28 (1 H, td, J 7.1 and 1.0 Hz, 6-H), 7.33 (1 H, d, J 7.6 Hz, 7-H), and 7.66 (1 H, d, J 8.1 Hz, 4-H); m/z 217 (M^+ , 19%), 203 (7), 145 (11), 144 (100, ArCH_2^+), 143 (5), 102 (3), 77 (4), and 72 (3).

3-(2-Hydroxyethyl)-1-methylindole (243).—To a suspension of lithium aluminium hydride (0.035 g, 0.921 mmol) in dry ether (10 ml) was added a solution of ethyl 1-methylindole-3-acetate (242) (0.20 g, 0.921 mmol) in dry ether (5 ml) at a rate sufficient to maintain a gentle reflux. The resulting yellow-grey suspension was heated at reflux for a further 30 min, and then allowed to cool. Water (0.2 ml) was cautiously added, followed by 15% aqueous sodium hydroxide (0.6 ml). The resulting granular precipitate was filtered from the very pale yellow solution, and washed thoroughly with ether (3 x 20 ml). The combined ethereal solutions were dried (MgSO_4) and evaporated to leave a pale yellow oil which was purified by chromatography (dichloromethane) to give the *title compound*¹⁴³ (243) (0.156 g, 97%) as a colourless oil (Found: C, 75.5; H, 7.5; N, 7.8. Calc. for $\text{C}_{11}\text{H}_{13}\text{NO}$, C, 75.4; H, 7.5; N, 8.0%); $\nu_{\text{max.}}$ (film) 1 615 (C=O), 1 474, 1 425, 1 378, 1 328, 1 046, 1 012, and 741 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.11 (1 H, br s, OH), 3.07 (2 H, td, J 6.5 and 0.7 Hz, 1'- CH_2), 3.77 (3 H, s, NCH_3), 3.92 (2 H, t, J 6.5 Hz, 2'- CH_2), 6.96 (1 H, s, 2-H), 7.22 (1 H, td, J 7.1 and 1.4 Hz, 5-H), 7.31 (1 H, td, J 7.1 and 1.2 Hz, 6-H), 7.37 (1 H, d, J 8.3 Hz, 7-H), and 7.68 (1 H, d, J 7.7 Hz, 4-H); m/z

175 (M^+ , 26%), 145 (11), 144 (100, ArCH_2^+), 143 (6), 115 (4), 103 (3), 102 (3), and 77 (5).

2-(1-Methylindol-3-yl)ethyl trichloroacetate (244).—To a pale yellow solution of 3-(2-hydroxyethyl)-1-methylindole (243) (0.156 g, 0.89 mmol) and pyridine (72 μl , 0.89 mmol) in dichloromethane (10 ml) at 0°C was added trichloroacetyl chloride (109 μl , 0.979 mmol), whereupon the solution darkened slightly. The mixture was removed from the cold-bath and kept in the dark for 2.5 h, after which time the solvent was evaporated to give a brown oil. This was chromatographed (dichloromethane) to give the *title compound* (244) (0.274 g, 96%) as a very pale yellow solid, m.p. 57–58°C, which readily turned purple on standing at room temperature (Found: C, 48.9; H, 3.7; N, 4.3. $\text{C}_{13}\text{H}_{12}\text{Cl}_3\text{NO}_2$ requires C, 48.7; H, 3.8; N, 4.4%); $\nu_{\text{max.}}$ (Nujol) 1 762 (C=O), 1 475, 1 240, 986, 828, 741, and 682 cm^{-1} ; $\lambda_{\text{max.}}$ (MeOH) 281infl and 287 (log ϵ 3.75) nm; δ_{H} (270 MHz; CDCl_3) 3.23 (2 H, td J 7.1 and 0.5 Hz, 2- CH_2), 3.77 (3 H, s, OMe), 4.59 (2 H, t, J 7.1 Hz, 1- CH_2), 6.96 (1 H, s, 2'-H), 7.15 (1 H, td, J 7.2 and 1.3 Hz, 5'-H), 7.26 (1 H, td, J 7.2 and 1.2 Hz, 6'-H), 7.32 (1 H, d, J 8.4 Hz, 7'-H), and 7.64 (1 H, d, J 8.1 Hz, 4'-H); m/z 319 (M^+ , 9%), 158 (21), 157 (30), 145 (11), 144 (100, ArCH_2^+), 143 (7), 115 (6), and 77 (5).

Irradiation of 2-(1-methylindol-3-yl)ethyl trichloroacetate (244).—A solution of 2-(1-methylindol-3-yl)ethyl trichloroacetate (244) (0.10 g, 0.312 mmol) in 20% methanol-acetonitrile (50 ml) was irradiated for 20 min. The golden yellow solution was evaporated, and the residue was purified by chromatography (2% methanol-dichloromethane) to give 1-methyl-7,7-dimethoxy-1,3,6,7-tetrahydro-[3]oxocino[4,5,6-cd]indol-6-one (245) (0.031 g, 36%) as a pale yellow solid, m.p. 141.5–143°C; (Found: M^+ , 275.1158. $\text{C}_{15}\text{H}_{17}\text{NO}_4$ requires 275.1158); $\nu_{\text{max.}}$ (CHCl_3) 1 745 (C=O), 1 459, 1 315, 1 263, 1 127, 1 092, and 1 044 cm^{-1} ; $\lambda_{\text{max.}}$ (MeOH) 299 (log ϵ 3.87) and 354infl nm; δ_{H} (270

MHz; CDCl_3) 3.05 (1 H, d, J 16.1 Hz, 3-CH), 3.35-3.48 (1 H, m, 3-CH), 3.50 (3 H, s, OMe), 3.74 (6 H, s, NCH_3 and OMe), 4.16 (1 H, dt, J 11.7 and 3.3 Hz, 4-CH), 4.44 (1 H, td, J 11.8 and 1.7 Hz, 4-CH), 7.12 (1 H, s, 2-H), 7.33 (1 H, t, J 8.0 Hz, 9-H), 7.61 (1 H, dd, J 8.0 and 1.7 Hz, 6-H), and 8.01 (1 H, dd, J 7.4 and 1.7 Hz, 10-H); m/z 275 (M^+ , 6%), 217 (12), 216 (82), 185 (16), 184 (100), 157 (15), 156 (10), 143 (8), and 115 (19).

Ethyl 5-methoxyindole-3-acetate (247).—A solution of triphenylphosphine (0.575 g, 2.19 mmol) and ethanol (0.2 ml, 3.41 mmol) in dry ether (10 ml) was added dropwise to a solution of diethyl azodicarboxylate (0.35 ml, 2.19 mmol) and 5-methoxyindole-3-acetic acid (0.30 g, 1.46 mmol) in dry ether (10 ml). The mixture rapidly turned cloudy, followed by some minutes later by the appearance of an oily material. The mixture was stirred for a further 30 min until all traces of the oily substance had disappeared, and then the resulting clear yellow solution was evaporated. The yellow-brown oily residue was purified by chromatography (dichloromethane) to give the *title compound (247)* (0.317 g, 93%) as a very pale solid, m.p. 89-91°C (Found: C, 67.0; H, 6.4; N, 6.0. $\text{C}_{13}\text{H}_{15}\text{NO}_3$ requires C, 66.9; H, 6.5; N, 6.0%); ν_{max} (Nujol) 3 349 (indole NH), 2 863, 1 712 (C=O), 1 488, 1 344, 1 311, 1 245, 1 218, 1 181, and 1 027 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.27 (3 H, t, J 7.1 Hz, OCH_2CH_3), 3.74 (2 H, s, 1'- CH_2), 3.86 (3 H, s, OMe), 4.18 (2 H, q, J 7.1 Hz, OCH_2CH_3), 6.86 (1 H, dd, J 8.6 and 2.1 Hz, 6-H), 7.07-7.09 (2 H, m, 2- and 4-H), 7.20 (1 H, d, J 8.6 Hz, 7-H), and 8.12 (1 H, br s, 1-H); m/z 233 (M^+ , 40%), 232 (5), 188 (6), 161 (12), 160 (100, ArCH_2^+), 159 (4), 145 (10), and 117 (6).

3-(2-Hydroxyethyl)-5-methoxyindole (248).—To a suspension of lithium aluminium hydride (0.033 g, 0.857 mmol) in dry ether (10 ml) was added a solution of ethyl 5-methoxyindole-3-acetate (247) (0.20 g, 0.857 mmol) in dry ether (5 ml) at a rate sufficient

to maintain a gentle reflux. The resulting yellow-grey suspension was heated at reflux for a further 30 min, and then allowed to cool. Water (0.2 ml) was cautiously added, followed by 15% aqueous sodium hydroxide (0.6 ml). The resulting granular precipitate was filtered from the very pale yellow solution, and washed thoroughly with ether (3 x 20 ml). The combined ethereal solutions were dried (MgSO_4) and evaporated to leave a pale yellow oil which was purified by chromatography (dichloromethane) to give the *title compound* (248) (0.140 g, 85%) as a colourless oil (Found: C, 69.15; H, 6.8; N, 7.3. $\text{C}_{11}\text{H}_{13}\text{NO}_2$ requires C, 69.1; H, 6.85; N, 7.3%); ν_{max} (film) 3 409 (indole NH), 1 625 (C=O), 1 585, 1 486, 1 456, 1 215, 1 172, 1 068, 1 044, and 798 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.10 (1 H, br s, OH), 2.99 (2 H, t, J 6.3 Hz, 1'- CH_2), 3.87 (3 H, s, OMe), 3.98 (2 H, t, J 6.3 Hz, 2'- CH_2), 6.88 (1 H, dd, J 8.7 and 2.4 Hz, 6-H), 6.98 (1 H, d, J 2.1 Hz, 2-H), 7.07 (1 H, d, J 2.4 Hz, 4-H), 7.22 (1 H, d, J 8.9 Hz, 7-H), and 8.25 (1 H, br s, 1-H); m/z 191 (M^+ , 24%), 173 (17), 161 (13), 160 (100, ArCH_2^+), 159 (8), 158 (9), 145 (15), and 117 (8).

2-(5-Methoxyindol-3-yl)ethyl trichloroacetate (249).—To a pale yellow solution of 3-(2-hydroxyethyl)-5-methoxyindole (248) (0.135 g, 0.706 mmol) and pyridine (57 μl , 0.706 mmol) in dichloromethane (10 ml) at 0°C was added trichloroacetyl chloride (87 μl , 0.777 mmol), whereupon the solution darkened slightly. The mixture was removed from the cold-bath and kept in the dark for 2.5 h, after which time the solvent was evaporated to give a yellow-brown oil. This was chromatographed (dichloromethane) to give the *title compound* (249) (0.231 g, 97%) as a colourless oil (Found: C, 46.2; H, 3.7; N, 4.25. $\text{C}_{13}\text{H}_{12}\text{Cl}_3\text{NO}_3$ requires C, 46.4; H, 3.6; N, 4.2%); ν_{max} (film) 3 421 (indole NH), 1 762 (C=O), 1 487, 1 456, 1 256, 985, 828, and 681 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 3.21 (2 H, td, J 7.1 and 0.7 Hz, 2- CH_2), 3.89 (3 H, s, OMe), 4.61 (2 H, t, J 7.1 Hz, 1- CH_2), 6.89 (1 H, dd, J 8.9 and 2.3 Hz, 6'-H), 7.08 (1 H, d, J 6.1 Hz, 4'-H), 7.09 (1 H, d, J 0.5 Hz, 2'-H), 7.27 (1 H, dd, J 8.8 and 0.5 Hz, 7'-H), and 7.98 (1 H, br s, 1'-

H); m/z 335 (M^+ , 11%), 174 (28), 173 (91), 172 (12), 160 (100, ArCH_2^+), 130 (23), 49 (13), and 36 (12).

Irradiation of 2-(5-methoxyindol-3-yl)ethyl trichloroacetate (249).—A solution of 2-(5-methoxyindol-3-yl)ethyl trichloroacetate (249) (0.090 g, 0.267 mmol) in 20% methanol-acetonitrile (50 ml) was irradiated for 10 min. The golden brown solution was evaporated, and the residue was purified by chromatography (1% methanol-dichloromethane) to give 7,7,8-trimethoxy-1,3,6,7-tetrahydro-[3]oxocino[4,5,6-cd]indol-6-one (250) (0.042 g, 54%) as a very pale yellow solid, m.p. 149–152°C (Found: M^+ , 291.1107. $\text{C}_{15}\text{H}_{17}\text{NO}_5$ requires 291.1107); $\nu_{\text{max.}}$ (CHCl_3) 3 479 (indole NH), 1 742 (C=O), 1 263, 1 243, 1 105, and 1 086 cm^{-1} ; $\lambda_{\text{max.}}$ (MeOH) 286 (log ϵ 3.56), 299infl, 319infl, and 360 (3.57) nm; δ_{H} (270 MHz; CDCl_3) 3.06 (1 H, d (with multiple fine splitting), J 17.3 Hz, 3-CH), 3.22–3.34 (1 H, m, 3-CH), 3.66 (3 H, s, 7-OMe), 3.74 (3 H, s, 7-OMe), 3.80 (3 H, s, 8-OMe), 4.14 (1 H, dt, J 11.7 and 3.7 Hz, 4-CH), 4.30 (1 H, td, J 11.7 and 2.0 Hz, 4-CH), 6.90 (1 H, d, J 8.8 Hz, 9-H), 7.03 (1 H, br s, 2-H), 7.30 (1 H, d, J 8.8 Hz, 10-H), and 8.01 (1 H, br s, 1-H); m/z 291 (M^+ , 2%), 260 (5), 232 (67), 201 (13), 200 (74), 185 (20), and 44 (27).

Attempted chlorination of 4-(indol-3-yl)butan-2-one (251).—A solution of LiICA was prepared by adding *n*-butyl-lithium (1.5 M solution in hexanes, 0.78 ml, 1.18 mmol) to *N*-isopropylcyclohexylamine (195 μl , 1.18 mmol) in THF (15 ml) at -20°C under nitrogen, and allowing the solution to warm to 0°C for 5 min before cooling to -78°C . A solution of 4-(indol-3-yl)butan-2-one (251) (0.10 g, 0.534 mmol) in THF (10 ml) was added dropwise to the LiICA solution. After a further 10 min, the mixture was allowed to warm slowly to -20°C , producing an orange coloured solution. This was cooled again to -78°C , and then added *via* a catheter to a solution of dry carbon tetrachloride (10 ml) in THF (25 ml), also at -78°C under nitrogen. The solution was stirred at -78°C for a further 10 min, and then allowed to warm slowly to ambient temperature, giving a golden yellow

solution. After a further 20 min, acetic acid (1.5 ml) was added, and the resulting solution was diluted with water (60 ml) and extracted with dichloromethane (3 x 75 ml). The combined extracts were dried (MgSO_4), evaporated, and purified by chromatography (1% methanol-dichloromethane) to give a complex mixture of products, the major component of which was unreacted starting material (251), the spectral properties of which were identical to those of authentic material.

3-(2-Bromoethyl)indole (254).—To a solution of tryptophol (0.50 g, 3.10 mmol) and triphenylphosphine (1.06 g, 4.03 mmol) in dry dichloromethane (20 ml) at ambient temperature was very cautiously added dropwise a solution of carbon tetrabromide (1.13 g, 3.41 mmol) in dry dichloromethane (10 ml) (CAUTION-EXOTHERM). The resulting golden yellow solution was stirred at ambient temperature for 20 min, and was then evaporated to leave a brown oil. This was purified by chromatography (dichloromethane) to give the title compound¹⁴⁷ (254) (0.667 g, 96%) as a colourless crystalline solid, m.p. 99.5–100°C (lit.,¹⁵⁶ 100–102°C), which turned yellow on standing (Found: C, 53.5; H, 4.4; N, 6.3. Calc. for $\text{C}_{10}\text{H}_{10}\text{BrN}$, C, 53.6; H, 4.5; N, 6.25%); ν_{max} (Nujol) 3 395 (indole NH), 1 243, 1 209, 1 092, 1 031, 826, 754, and 656 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 3.35 (2 H, t, J 7.7 Hz, 1'- CH_2), 3.65 (2 H, t, J 7.7 Hz, 2'- CH_2), 7.10 (1 H, d, J 2.2 Hz, 2-H), 7.14 (1 H, td, J 7.5 and 1.1 Hz, 5-H), 7.22 (1 H, td, J 7.0 and 1.3 Hz, 6-H), 7.39 (1 H, d, J 7.9 Hz, 7-H), 7.60 (1 H, d, J 7.9 Hz, 4-H), and 8.04 (1 H, br s, 1-H); m/z 223 (M^+ , 19%), 144 (22), 143 (11), 131 (10), 130 (100, ArCH_2^+), 115 (10), 89 (5), and 77 (5).

***t*-Butyl 3-(2-bromoethyl)indole-1-carboxylate (253).**—To a solution of 3-(2-bromoethyl)indole (254) (1.0 g, 4.46 mmol) in dry acetonitrile (25 ml) was added di-*t*-butyl dicarbonate (1.46 g, 6.69 mmol) and 4-dimethylaminopyridine (0.055 g, 0.446 mmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a

clear yellow solution, which was then evaporated to leave a yellow-brown residue. This was purified by chromatography (dichloromethane) to give the *title compound* (253) (1.255 g, 87%) as a colourless crystalline solid, m.p. 75-76°C (Found: C, 55.6; H, 5.3; N, 4.1. $C_{15}H_{18}BrNO_2$ requires C, 55.6; H, 5.6; N, 4.3%); $\nu_{\max}$ (Nujol) 1 724 (C=O), 1 452, 1 388, 1 358, 1 252, 1 164, and 749 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.68 (9 H, s, $C(CH_3)_3$), 3.28 (2 H, t, J 7.6 Hz, 1'-CH₂), 3.64 (2 H, t, J 7.6 Hz, 2'-CH₂), 7.25 (1 H, td, J 7.4 and 1.1 Hz, 5-H), 7.34 (1 H, td, J 7.7 and 1.3 Hz, 6-H), 7.48 (1 H, s, 2-H), 7.52 (1 H, d, J 7.7 Hz, 4-H), and 8.14 (1 H, br d, J 8.1 Hz, 7-H); m/z 323 (M^+ , 10%), 269 (31), 267 (32), 144 (14), 143 (17), 130 (58, $ArCH_2^+$), 57 (100), and 41 (17).

t-Butyl 3-(4-pentynyl)indole-1-carboxylate (255).—To a solution of *t*-butyl 3-(3-bromopropyl)indole-1-carboxylate (205) (0.978 g, 2.89 mmol) in DMF (20 ml) at 0°C under nitrogen was added a suspension of sodium acetylide (17.1% reagent in mineral oil, 1.2 ml, 4.34 mmol). The mixture was stirred at 0°C for 1.5 h, and then allowed to warm to ambient temperature where it was stirred for 1 h to form a black solution. Water (50 ml) was cautiously added, and the resulting dark brown solution was extracted with ether (3 x 50 ml), the combined extracts being washed with water (3 x 50 ml) and brine (30 ml) before drying ($MgSO_4$) and evaporating to leave a brown oil. This was purified by chromatography (50% dichloromethane-light petroleum) to give firstly the *title compound* (255) (0.323 g, 40%) as a colourless oil (Found: C, 76.2; H, 7.6; N, 4.9. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%); $\nu_{\max}$ (film) 1 733 (C=O), 1 455, 1 377, 1 255, 1 158, 1 088, and 747 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.67 (9 H, s, $C(CH_3)_3$), 1.94 (2 H, quintet, J 6.9 Hz, 2'-CH₂), 2.02 (1 H, t, J 2.7 Hz, 5'-CH), 2.28 (2 H, td, J 6.9 and 2.7 Hz, 3'-CH₂), 2.82 (2 H, td, J 7.7 and 1.1 Hz, 1'-CH₂), 7.23 (1 H, td, J 7.4 and 1.2 Hz, 5-H), 7.32 (1 H, td, J 7.4 and 1.2 Hz, 6-H), 7.39 (1 H, s, 2-H), 7.54 (1 H, d, J 8.1 Hz, 4-H), and 8.12 (1 H, br d, J 8.1 Hz, 7-H); m/z 283 (M^+ , 25%), 227 (54), 183 (26), 182 (22), 175 (19), 130 (45, $ArCH_2^+$), 57 (100), and 41 (18). This was followed

by 3-(4-pentynyl)indole (258) (0.16 g, 30%), which was also isolated as a colourless oil (Found: M^+ , 183.1048. $C_{13}H_{13}N$ requires 183.1048); $\nu_{\max}$ (film) 3 422 (indole NH), 3 299, 1 380, 1 309, 1 256, 1 158, 1 088, and 746 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.95 (2 H, quintet, J 6.8 Hz, 2'- CH_2), 2.01 (1 H, t, J 2.7 Hz, 5'-CH), 2.26 (2 H, td, J 7.0 and 2.4 Hz, 3'- CH_2), 2.90 (2 H, td, J 6.8 and 0.7 Hz, 1'- CH_2), 7.01 (1 H, d, J 2.4 Hz, 2-H), 7.12 (1 H, td, J 7.1 and 1.0 Hz, 5-H), 7.20 (1 H, td, J 7.1 and 1.2 Hz, 6-H), 7.37 (1 H, d, J 7.8 Hz, 7-H), 7.63 (1 H, d, J 7.8 Hz, 4-H), and 7.93 (1 H, br s, 1-H); m/z 183 (M^+ , 41%), 182 (23), 175 (13), 157 (12), 143 (11), 131 (22), 130 (100, ArCH_2^+), and 41 (15).

t-Butyl 3-(4-pentynyl)indole-1-carboxylate (255) (from 3-(4-pentynyl)indole (258)).—To a solution of 3-(4-pentynyl)indole (258) (0.150 g, 0.816 mmol) in dry acetonitrile (10 ml) was added di-*t*-butyl dicarbonate (0.267 g, 1.22 mmol) and 4-dimethylaminopyridine (0.010 g, 81.6 μmol). The colourless suspension was stirred at ambient temperature for 15 h, to give a clear solution, which was then evaporated to leave a yellowish residue. This was purified by chromatography (50% dichloromethane-light petroleum) to give the *title compound* (255) (0.203 g, 88%) as a colourless oil, the spectroscopic properties of which were identical to those of authentic material.

Reaction of t-Butyl 3-(4-pentynyl)indole-1-carboxylate (255) with *N*-chlorosuccinimide in methanol.—To a solution of *t*-butyl 3-(4-pentynyl)indole-1-carboxylate (255) (0.050 g, 0.176 mmol) in methanol (10 ml) was added *N*-chlorosuccinimide (0.118 g, 0.88 mmol). The resulting mixture was stirred at ambient temperature for 3 h, and then it was evaporated to leave a golden oil which consisted of a complex mixture of products.

1-Benzenesulphonyl-3-(3-bromopropyl)indole (262).—Sodium hydride dispersion

in mineral oil (60%; 0.28 g, 7.10 mmol) was washed with light petroleum (3 x 5 ml) and allowed to dry under an atmosphere of nitrogen. Dry benzene (20 ml) was added, followed by benzenesulphonyl chloride (1.45 g, 8.19 mmol). The mixture was stirred at ambient temperature whilst a solution of 3-(3-bromopropyl)indole (204) (1.3 g, 5.46 mmol) in dry benzene (5 ml) was added dropwise over *ca.* 30 min. The resulting mixture was stirred at ambient temperature for a further 15 h, causing the solution to become a pale brown colour. Water (50 ml) was cautiously added to the mixture, the organic phase was separated, and the aqueous phase was extracted with ether (3 x 30 ml). The combined organic layers were washed with water (2 x 30 ml), brine (30 ml) and dried (MgSO_4) before evaporating to leave a brown residue. This was purified by chromatography (70% dichloromethane-light petroleum) to give the *title compound* (262) (1.38 g, 67%) as a colourless crystalline solid, m.p. 118–120°C (Found: C, 53.8; H, 4.0; N, 3.6. $\text{C}_{17}\text{H}_{16}\text{BrNO}_2\text{S}$ requires C, 54.0; H, 4.3; N, 3.7%); $\nu_{\text{max.}}$ (Nujol) 1 448, 1 363, 1 176, 751, 723, and 601 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.20 (2 H, quintet, J 6.6 Hz, 2'- CH_2), 2.85 (2 H, td, J 7.2 and 1.1 Hz, 1'- CH_2), 3.37 (2 H, t, J 6.6 Hz, 3'- CH_2), 7.25 (1 H, td, J 7.3 and 1.3 Hz, 5-H), 7.33 (1 H, td, J 8.0 and 1.3 Hz, 6-H), 7.39 (1 H, t, J 1.0 Hz, 2-H), 7.42–7.52 (4 H, m, CHCHCSO_2 , CHCHCHCSO_2 , and 4-H), 7.85–7.89 (2 H, m, CHCSO_2), and 8.01 (1 H, d, J 8.3 Hz, 7-H); m/z 377 (M^+ , 64%), 271 (21), 270 (100), 157 (24), 156 (88), 130 (22), 129 (38), and 77 (57).

Reaction of 1-benzenesulphonyl-3-(3-bromopropyl)indole (262) with sodium acetylide.—To a solution of 1-benzenesulphonyl-3-(3-bromopropyl)indole (262) (0.20 g, 0.529 mmol) in DMF (20 ml) at 0°C under nitrogen was added a suspension of sodium acetylide (17.1% reagent in mineral oil, 0.30 ml, 1.06 mmol). The mixture was stirred at 0°C for 1.5 h, and then allowed to warm to ambient temperature where it was stirred for 1 h to form a black solution. Water (50 ml) was cautiously added, and the resulting brown solution was extracted with ether (3 x 50 ml), the combined extracts being washed with

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water (3 x 50 ml) and brine (30 ml) before drying (MgSO_4) and evaporating to leave a brown oil. This was purified by chromatography (50% dichloromethane-light petroleum) to give 3-(4-pentynyl)indole (258) (0.026 g, 27%) as a colourless oil, the spectral properties of which were identical to an authentic sample.

N-(3-Indolyethyl) trichloroacetamide (265).—To a solution of tryptamine (5.0 g, 31.2 mmol) and pyridine (2.5 ml, 31.2 mmol) in dry dichloromethane (50 ml) at 0°C was cautiously added dropwise trichloroacetyl chloride (3.8 ml, 34.3 mmol). The brown solution was stirred at ambient temperature for 1 h, and then evaporated to leave a yellow-brown solid. This was purified by chromatography (dichloromethane) to give the *title compound* (265) (9.31 g, 98%) as a colourless crystalline solid, m.p. 102–103°C (Found: C, 47.1; H, 3.45; N, 9.0. $\text{C}_{12}\text{H}_{11}\text{Cl}_3\text{N}_2\text{O}$ requires C, 47.2; H, 3.6; N, 9.2%); ν_{max} (Nujol) 3 412 (indole NH), 3 351 (amide NH), 1 715 (C=O), 1 695, 1 526, 1 257, 1 223, 1 208, 825, 807, and 742 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 3.09 (2 H, td, J 5.9 and 0.7 Hz, 1'- CH_2), 3.70 (2 H, dt, J 6.6 and 5.9 Hz, 2'- CH_2), 6.78 (1 H, br s, CH_2NHCO), 7.08 (1 H, d, J 2.4 Hz, 2-H), 7.16 (1 H, td, J 7.1 and 1.2 Hz, 5-H), 7.24 (1 H, td, J 6.8 and 1.2 Hz, 6-H), 7.40 (1 H, d, J 8.1 Hz, 7-H), 7.64 (1 H, d, J 7.8 Hz, 4-H), and 8.09 (1 H, br s, 1-H); m/z 304 (M^+ , 3%), 149 (6), 144 (9), 143 (38), 131 (11), 130 (100, ArCH_2^+), 84 (6), and 77 (8).

Irradiation of N-(3-indolyethyl) trichloroacetamide (265) in methanolic acetonitrile.—A solution of *N*-(3-indolyethyl) trichloroacetamide (265) (0.10 g, 0.327 mmol) in 20% methanol-acetonitrile (50 ml) was irradiated for 30 min. The green-brown solution was evaporated, and the residue was purified by chromatography (5% methanol-dichloromethane) to give firstly 7,7-dimethoxy-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocin-6-one (266) (0.036 g, 42%) as a yellow solid, m.p. 244–246°C (dec.) (Found: M^+ , 260.1161. $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ requires 260.1161); ν_{max} (CHCl_3) 3 479 (indole NH), 1 660 (C=O), 1 344, 1 223, 1 173, 1 123, 1 089, 666, and 559 cm^{-1} ;

λ_{max} (MeOH) 297 (log ϵ 3.76) nm; δ_{H} (270 MHz; CDCl_3) 3.03-3.09 (1 H, m, 3-CH), 3.19 (3 H, s, OMe), 3.21-3.29 (1 H, m, 3-CH), 3.42-3.49 (1 H, m, 4-CH), 3.56 (3 H, s, OMe), 4.08-4.17 (1 H, m, 4-CH), 5.76 (1 H, br s, 5-H), 7.05 (1 H, d, J 2.0 Hz, 2-H), 7.20 (1 H, t, J 7.7 Hz, 9-H), 7.35 (1 H, dd, J 8.0 and 1.0 Hz, 8-H), 7.64 (1 H, dd, J 7.5 and 1.0 Hz, 10-H), and 8.12 (1 H, br s, 1-H); m/z 260 (M^+ , 22%), 228 (65), 213 (44), 201 (44), 169 (96), 154 (44), 153 (100), and 129 (51). This was followed by 1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-6,7-dione (267) (0.008 g, 12%) which was isolated as a golden yellow solid, m.p. 274-278°C (dec.) (Found: C, 67.1; H, 4.8; N, 12.8. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_2$ requires C, 67.3; H, 4.71; N, 13.1%); ν_{max} (CHCl_3) 3 290 (indole NH), 1 658 (amide and ketone C=O), 1 607, 1 345, 1 251, 1 033, and 743 cm^{-1} ; λ_{max} (MeOH) 237 (log ϵ 3.50), 331infl, and 353 (4.13) nm; δ_{H} (270 MHz; acetone- d_6) 3.10-3.16 (1 H, m, 3-CH), 3.20-3.32 (2 H, m, 3- and 4-CH), 3.71-3.83 (1 H, m, 4-CH), 7.20 (1 H, t, J 7.5 Hz, 9-H), 7.35 (1 H, dd, J 7.3 and 1.2 Hz, 8-H), 7.43 (1 H, s (with multiple fine splitting), 2-H), 7.45-7.54 (1 H, br s, CH_2NHCO), 7.69 (1 H, dd, J 8.1 and 1.2 Hz, 10-H), and 7.86 (1 H, br s, 1-H); m/z 214 (M^+ , 33%), 186 (33), 158 (22), 157 (15), 143 (17), 130 (41), 129 (100), and 115 (18).

Irradiation of N-(3-indolyethyl) trichloroacetamide (265) in aqueous acetonitrile.—A solution of *N*-(3-indolyethyl) trichloroacetamide (265) (0.20 g, 0.654 mmol) in 20% water-acetonitrile (100 ml) was irradiated for 45 min. The green-brown solution was evaporated to approximately 20 ml and then water (*ca.* 50 ml) was added. The green-brown suspension was thoroughly extracted with dichloromethane (4 x 100 ml), the combined green-yellow extracts being washed with brine (50 ml) which removed much of the green colouration to leave a golden yellow solution. The brine solution was then re-extracted with dichloromethane (3 x 30 ml), and all the combined extracts were dried (MgSO_4) before evaporating to leave a golden brown solid. This was purified by chromatography (5% methanol-dichloromethane) to give 1,3,4,5,6,7-hexahydropyrrolo[4,3,2-

fg][3]benzazocine-6,7-dione (267) (0.089 g, 64%) as a golden yellow solid, m.p. 275-278°C (dec.) (Found: C, 67.1; H, 4.8; N, 12.8. $C_{12}H_{10}N_2O_2$ requires C, 67.3; H, 4.71; N, 13.1%); $\nu_{\max.}(\text{CHCl}_3)$ 3 290 (indole NH), 1 658 (amide and ketone C=O), 1 607, 1 345, 1 251, 1 033, and 743 cm^{-1} ; $\lambda_{\max.}(\text{MeOH})$ 237 (log ϵ 3.50), 331infl, and 353 (4.13) nm; $\delta_{\text{H}}(270 \text{ MHz; acetone-}d_6)$ 3.10-3.16 (1 H, m, 3-CH), 3.20-3.32 (2 H, m, 3- and 4-CH), 3.71-3.83 (1 H, m, 4-CH), 7.20 (1 H, t, J 7.5 Hz, 9-H), 7.35 (1 H, dd, J 7.3 and 1.2 Hz, 8-H), 7.43 (1 H, s (with multiple fine splitting), 2-H), 7.45-7.54 (1 H, br s, CH_2NHCO), 7.69 (1 H, dd, J 8.1 and 1.2 Hz, 10-H), and 7.86 (1 H, br s, 1-H); m/z 214 (M^+ , 33%), 186 (33), 158 (22), 157 (15), 143 (17), 130 (41), 129 (100), and 115 (18).

5.4 Relating to Chapter Four

N-Trichloroacetyl tryptophan methyl ester (279).—To a solution of tryptophan methyl ester (5.0 g, 22.9 mmol) and pyridine (1.85 ml, 22.9 mmol) in dry dichloromethane (50 ml) at 0°C was cautiously added dropwise trichloroacetyl chloride (2.8 ml, 25.2 mmol). The brown solution was stirred at ambient temperature for 1 h, and then water (100 ml) was added. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 50 ml), the combined dichloromethane solutions being washed with water (3 x 50 ml) and brine (30 ml) before being dried (MgSO_4) and evaporated to leave a yellow-brown solid. This was recrystallised from dichloromethane to give the title compound (279) (6.83 g, 82%) as a colourless crystalline solid, m.p. 178.5-179°C (lit.,¹²⁴ 176-178°C) (Found: C, 46.5; H, 3.5; N, 7.7. Calc. for $C_{14}H_{13}Cl_3N_2O_3$, C, 46.2; H, 3.6; N, 7.7%); $\nu_{\max.}(\text{Nujol})$ 3 351 (indole NH), 1 730 (ester C=O), 1 702 (amide C=O), 1 520, 1 446, 1 239, 1 218, 818, and 754 cm^{-1} ; $\lambda_{\max.}(\text{MeOH})$ 275infl, 281 (log ϵ 3.78), and 289 (3.71) nm; $\delta_{\text{H}}(270 \text{ MHz; acetone-}d_6)$ 3.38 (1 H, dd, J 14.9 and 7.6 Hz, 1'-CH), 3.47 (1 H, dd, J 14.9 and 5.4 Hz, 1'-CH), 3.72 (3 H, s, CO_2CH_3), 4.72-4.80

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(1 H, m, 2'-CH), 7.03 (1 H, td, J 7.2 and 1.1 Hz, 5-H), 7.10 (1 H, td, J 7.5 and 1.0 Hz, 6-H), 7.26 (1 H, s, 2-H), 7.38 (1 H, d, J 8.0 Hz, 7-H), 7.58 (1 H, d, J 7.9 Hz, 4-H), 8.10 (1 H, br s, CHNHCO), and 10.14 (1 H, br s, 1-H); m/z 362 (M^+ , 5%), 245 (3), 201 (6), 131 (10), 130 (100, ArCH_2^+), 129 (3), 77 (3), and 36 (3).

Methyl 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-4-carboxylate (273).—A solution of *N*-trichloroacetyl tryptophan methyl ester (279) (0.30 g, 0.825 mmol) in 20% water-acetonitrile (100 ml) was irradiated for 95 min. The golden brown solution was evaporated to approximately 30 ml and then water (*ca.* 50 ml) was added. The brown solution was thoroughly extracted with dichloromethane (4 x 100 ml), the combined yellow-brown extracts being washed with brine (50 ml) which removed much of the brown colouration to leave a golden yellow solution. The brine solution was then re-extracted with dichloromethane (3 x 30 ml), and all the combined extracts were dried (MgSO_4) before evaporating to leave a golden brown solid. This was purified by chromatography (5% methanol-dichloromethane) to give the title compound (273) (0.18 g, 80%) as a golden yellow solid, m.p. 254-256°C (dec.) (lit.,¹²⁴ 256-258°C (dec.)); $\nu_{\text{max.}}$ (CHCl_3) 3 691, 3472 (indole NH), 1 748 (ester C=O), 1 682 (amide and ketone C=O), 1 644, 1 603, 1 437, 1 236, and 705 cm^{-1} ; $\lambda_{\text{max.}}$ (MeOH) 325infl and 347 (log ϵ 3.71) nm; δ_{H} (270 MHz; acetone- d_6) 3.42 (1 H, dd, J 16.6 and 12.2 Hz, 3-CH), 3.58-3.63 (1 H, m, 3-CH), 3.80 (3 H, s, CO_2CH_3), 4.80-4.94 (1 H, m, 4-CH), 7.21 (1 H, t, J 7.8 Hz, 9-H), 7.33-7.42 (1 H, m, 8-H), 7.52 (1 H, s, 2-H), 7.72 (1 H, dd, J 8.1 and 1.4 Hz, 10-H), 7.89 (1 H, br s, 5-H), and 10.98 (1 H, br s, 1-H); m/z 272 (M^+ , 61%), 244 (28), 185 (100), 184 (20), 170 (36), 158 (76), 130 (64), and 129 (81).

Attempted reaction of methyl 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-4-carboxylate (273) with p-toluenesulphonylhydrazine.—To a solution of methyl 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-4-carboxylate (273) (0.015 g, 55.1 μmol) in methanol (5 ml) was added *p*-toluenesul-

phenylhydrazine (0.011 g, 60.6 μ mol). The mixture was stirred at ambient temperature for 24 h after which time the solution was evaporated and purified by chromatography (5% methanol-dichloromethane) to give unreacted starting material (273) (0.011 g, 73%), the spectral properties of which were identical to those of an authentic sample. Repetition of the reaction at higher temperature, or in the presence of an acid catalyst, led to the results detailed in Table 2, Section 4.2.

Reaction of 1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-6,7-dione (267) with hydrazine and attempted oxidation of the product.—To solid 1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-6,7-dione (267) (0.010 g, 46.7 μ mol) was added dropwise anhydrous hydrazine (0.2 ml). The mixture became slightly warm and turned a yellow colour. The mixture was cautiously evaporated to leave a very polar yellow-orange oil (0.016 g). Due to the polar nature of this material, further purification was not attempted, and since the substance was insoluble in any common solvent it proved impossible to obtain an NMR spectrum for this compound. However the IR and mass spectra were obtained: ν_{max} (film) 3 694, 3 443 (indole NH), 2 928, 1 686 (C=O), 1 603, 1 463, 1 380, and 1 330 cm^{-1} ; m/z 228 (M^+ , 9%), 171 (100), 170 (40), 169 (69), 155 (19), 144 (20), 143 (19), and 115 (17). The crude product from the reaction (0.016 g) was mixed with mercuric oxide (0.032 g, 0.147 mmol) and anhydrous sodium sulphate (0.010 g). The mixture was covered with dry ether (5 ml), and then a cold, saturated solution of ethanolic potassium hydroxide (0.2 ml) was added. The mixture was stirred vigorously for 1 h, and then it was filtered through Celite, the residue being washed with ether (3 x 5 ml). The ether solution was evaporated to dryness at ambient temperature, to leave a yellow oil. The IR spectrum of this crude material showed no diazo absorption, so further purification was not attempted.

Reaction of 1,3,4,5,6,7-hexahydropyrrolo[4,3,2-fg][3]benzazocine-6,7-dione

(267) with *p*-toluenesulphonylhydrazine in the presence of boron trifluoride-etherate complex.—To a golden yellow suspension of 1,3,4,5,6,7-hexahydropyrrolo[4,3,2-*fg*][3]benzazocine-6,7-dione (267) (0.124 g, 0.579 mmol) in dry ether (20 ml) was added boron trifluoride-etherate complex (210 μ l, 1.74 mmol), whereupon the mixture immediately turned dark green and the solid partially dissolved. The flask was placed in an ultrasonic bath and sonicated for 30 min, after which time *p*-toluenesulphonylhydrazine (0.14 g, 0.752 mmol) was added in one portion. The mixture was stirred vigorously for a further 3 days, and then water (30 ml) was cautiously added to the dark green mixture. The organic phase was separated and the aqueous phase was extracted with dichloromethane (4 x 50 ml), the combined organic solutions being washed with water (2 x 50 ml) and brine (30 ml) before drying (MgSO_4) and evaporating to leave a greenish solid. This was purified by chromatography (5% methanol-dichloromethane) to give 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-*fg*][3]benzazocine 7-(*p*-toluenesulphonylhydrazone) (282) (0.171 g, 78%) as a faintly greenish-yellow solid, m.p. 172–174°C (Found: C, 59.5; H, 4.8; N, 14.7. $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$ requires C, 59.7; H, 4.7; N, 14.65%); $\nu_{\text{max.}}(\text{CHCl}_3)$ 3 475 (indole NH), 3 400 (amide NH), 3 291, 1 673 (C=O), 1 216, 1 168, 1 094, and 814 cm^{-1} ; $\lambda_{\text{max.}}(\text{MeOH})$ 326 (log ϵ 3.88) nm; $\delta_{\text{H}}(270 \text{ MHz; acetone-}d_6)$ 2.44 (3 H, s, CCH_3), 3.14–3.18 (2 H, m, 3- CH_2), 3.63–3.70 (2 H, m, 4- CH_2), 6.91 (1 H, dd, J 7.3 and 1.2 Hz, 8-H), 7.04 (1 H, t, J 7.7 Hz, 9-H), 7.28 (1 H, s, 2-H), 7.44 (2 H, d, J 8.5 Hz, CHCHCSO_2), 7.49 (1 H, dd, J 8.1 and 1.2 Hz, 10-H), 7.73 (1 H, br t, J 6.2 Hz, 5-H), 7.91 (2 H, d, J 8.3 Hz, CHCSO_2), 9.20–9.25 (1 H, v br s, TsNH), and 10.53 (1 H, br s, 1-H); m/z 139 (51%), 124 (21), 123 (25), 92 (41), 91 (100, C_7H_7^+), 77 (19), 65 (36), and 39 (26).

*Treatment of 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-*fg*][3]benzazocine 7-(p-toluenesulphonylhydrazone) (282) with sodium ethoxide in ethanol.*—A solution of sodium ethoxide in ethanol was prepared by the careful addition of sodium metal (0.010 g,

0.435 mmol) to dry ethanol (2 ml). To this solution 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-*fg*][3]benzazocine 7-(*p*-toluenesulphonylhydrazone) (282) (0.028 g, 73.2 μ mol) was added, and the mixture stirred at 60°C for 24 h. The resulting colourless solution was diluted with water (5 ml) and extracted with dichloromethane (3 x 15 ml), the combined extracts being washed with water (2 x 10 ml) and brine (10 ml) before drying (MgSO_4) and evaporating to leave a yellowish solid. Purification of this by chromatography (5% methanol-dichloromethane) gave unreacted starting material (0.020 g, 71%), the spectral properties of which were identical to those of an authentic sample.

*Treatment of 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-*fg*][3]benzazocine 7-(p-toluenesulphonylhydrazone) (282) with sodium hydride and photolysis of the resulting mixture.*—Sodium hydride dispersion in mineral oil (60%; 0.063 g, 1.57 mmol) was washed with light petroleum (3 x 5 ml) and allowed to dry under an atmosphere of nitrogen. THF (20 ml) was added, followed by a solution of 6,7-dioxo-1,3,4,5,6,7-hexahydropyrrolo[4,3,2-*fg*][3]benzazocine 7-(*p*-toluenesulphonylhydrazone) (282) (0.120 g, 0.314 mmol) in THF (10 ml). The mixture was stirred at ambient temperature until effervescence had ceased (*ca.* 15 min), and then the greyish suspension was placed in a quartz tube, degassed, and irradiated for 90 min. To the resulting fluorescent green-brown solution was added absolute ethanol (20 ml) to give a golden brown solution, which was evaporated to leave a brownish solid. Chromatography of this (7% methanol-dichloromethane) gave a polar solid (0.032 g, 27% mass return), which was shown by NMR to be a complex mixture of several components. Further purification by chromatography using a high silica to compound ratio was attempted, without success. Due to lack of material, further identification of these compounds could not be achieved.

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Abbreviations

Å	Ångström unit
Ac	acetyl
AIBN	α,α' -azo- <i>iso</i> -butyronitrile
BOC	<i>t</i> -butoxycarbonyl
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
DBU	1,8-diazabicyclo[5.4.0]non-5-ene
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMAT	γ,γ -dimethylallyltryptophan
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulphoxide
HMPA	hexamethylphosphoric triamide
LDA	lithium di- <i>isopropyl</i> amide
LiICA	lithium <i>isopropylcyclohexyl</i> amide
MVK	methyl vinyl ketone (3-buten-2-one)
NCS	<i>N</i> -chlorosuccinimide
OPP	pyrophosphate
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>t</i> -butyl dimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
<i>o</i> -Tol	<i>o</i> -tolyl
Ts	<i>p</i> -toluenesulphonyl

Appendix 1

X-Ray Crystal Data For 1,3,4,5,6,7-Hexahydropyrrolo[4,3,2-*fg*][3]- benzazocine-6,7-dione (267)

Crystal data: $C_{12}H_{10}N_2O_2$, $M=214.2$, triclinic, $a=8.605(2)$, $b=9.898(2)$, $c=12.878(2)$ Å, $\alpha=89.12(2)$, $\beta=82.88(1)$, $\gamma=68.59(1)^\circ$, $V=1013$ Å³, space group P_1 , $Z=4$ (2 crystallographically independent molecules), $D_c=1.40$ gcm⁻³, Cu radiation, $\lambda=1.54178$ Å, $\mu(\text{Cu-K}\alpha)=8$ cm⁻¹, $F(000)=448$. Data were measured on a Nicolet R3m diffractometer with Cu-K α radiation (graphite monochromator) using ω -scans. A crystal of dimensions 0.10 x 0.17 x 0.67 mm was used. 2726 Independent reflections ($2\theta \leq 116^\circ$) were measured, of which 2456 had $|F_o| > 3\sigma(|F_o|)$, and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were located from a ΔF map. The positions of the C-H protons were idealised, C-H = 0.96 Å, assigned isotropic thermal parameters, $U(H)=1.2U_{eq}(C)$, and allowed to ride on their parent carbon atoms. The N-H hydrogens were refined isotropically subject to a N-H distance constraint. Refinement was by block-cascade full-matrix least-squares to $R=0.036$, $R_w=0.040$ [$w^{-1}=\sigma^2(F) + 0.00029F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.17 and -0.19 eÅ⁻³ respectively. The mean and maximum shift/error in the final refinement were 0.012 and 0.062 respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

What is now proved was once only imagin'd

The Marriage of Heaven and Hell,
William Blake.