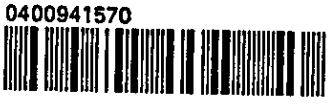

SYNTHETIC APPROACHES TOWARDS NOVEL INDOLE ALKALOIDS.

By

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CONTENTS

ABSTRACT

This thesis describes several synthetic approaches to some novel indole alkaloids. The Introduction (Chapter One) outlines the need for continuous discovery of new antibiotics in todays environment. The family of Kinamycin antibiotics is described along with their biosynthesis and the evidence of the novel biosynthetic precursor known as Pre-Kinamycin.

Chapter Two (2.1) deals with a retrosynthetic analysis leading to a study of Tandem Directed *Ortho*- Metallation reactions and a proposed synthesis of Pre-Kinamycin. Section 2.2 describes the study of stable analogues of indole-2,3-quinodimethane and the Diels-Alder reactions therof. Also Diels-Alder reactions of pyrano[3,4-*b*]indol-3-ones with benzyne and the subsequent manipulation of the carbazole-based products are detailed. Section 2.3 outlines the study of the Friedel-Crafts acylation reaction with respect to the indole nucleus and the application of such a reaction to the synthesis of the Pre-Kinamycin skeleton. Investigations into acid mediated cyclisations to form quinones and the use of Weinreb amides as acylating agents are also described.

Chapter Three (3.1) examines the problems of iron overload diseases (haemochromatosis) and the efforts to produce effective iron chelators. Section 3.2 describes the discovery of four novel indole alkaloids known as Uvarindoles and their possible consideration as iron chelators. Section 3.3 examines two retrosynthetic analyses towards Uvarindole B and the investigation into the synthesis thereof, involving similar methodology as that developed in section 2.3.

Chapter Four describes the relevant experimental details for the intermediates described in sections 2.1 through 3.3 and the respective spectroscopic data obtained.

Chapter Five gives the references for all the relevant work quoted in above sections.

ACKNOWLEDGEMENTS

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* Big cheers to :Scouse, Paul, Lynchy, The family Farrell, Bob & Jean, Sean, Tiff, Mark & Ann, Keith & Tina, Philthy Phil and the rest of the crowd (who know who they are).

ABBREVIATIONS

The abbreviations used in this thesis are as follows :

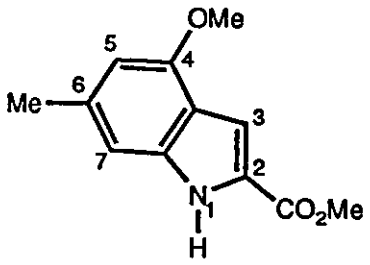
Ac_2O	acetic anhydride
aq.	aqueous
ATCC	American Type Culture Collection
BuLi	n-butyllithium
CoA	co-enzyme A
CSA	camphor-10-sulfonic acid
CSI	N-chlorosulfonyl isocyanate
d-	deuterio -
dec.	decomposition
DCC	*N, N* -dicyclohexylcarbodiimide
DMAP	*N, N* -dimethylaminopyridine
DMF	*N, N* -dimethylformamide
DMG	directed metallation groups
DMSO	dimethyl sulfoxide
DoM	directed ortho metallation
eq.	equivalents
Et	ethyl
EtOH	ethanol
Et_2O	diethyl ether
FDA	Food & Drugs Administration
FGI	Functional group interconversion
h	hours
HOAc	acetic acid
i.r.	infra-red
LiCa	lithium iso-propylcyclohexylamide
LiTMP	lithium tetramethylpipridide

m.p.	melting point
MAPA	N-methylamino pyridyl amide
Me	methyl
MeOH	methanol
min	minutes
MOM	methoxymethyl
NBS	N-bromosuccinimide
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
PPA	polyphosphoric acid
Py	pyridine
RT	ambient or room temperature
THF	tetrahydrofuran
tlc.	thin layer chromatography
TMEDA	*N, N, N, N* -tetramethylethylene diamine
TMSCl	trimethylsilyl chloride
TsOH	*para* - toluenesulfonic acid

NOMENCLATURE

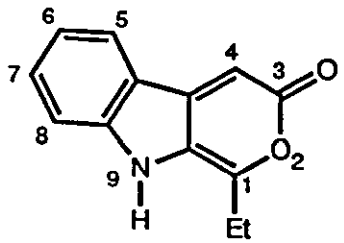
For ease of description, the following numbering system has been adopted.

For indoles:



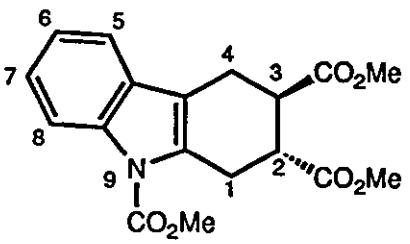
i.e. Methyl 4-methoxy - 6-methylindole-2-carboxylate

For Pyranoindolones:



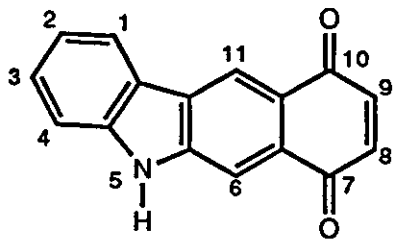
i.e. 1-Ethylpyrano[3,4-*b*]indol-3-one.

For Carbazoles:



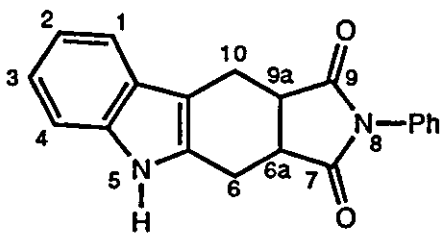
i.e. *trans*-Trimethyl 1,2,3,4-tetrahydrocarbazole-2,3,9-tricarboxylate.

For Benzocarbazoles:



i.e. 5H-Benzo[*b*]carbazole-7,10-dione.

For Pyrrolocarbazoles:



i.e. 8-Phenyl-6,6a,9a,10-tetrahydro-5H-pyrrolo[3,4-*b*]carbazole-7,9-dione.

Chapter 1

1.1 Introduction

An analogy can be drawn between the search for new antibiotics and the case of the Red Queen where we must "keep running in order to stand still."

The widespread development of multiple antibiotic resistance is well known and represents a serious challenge to modern medicine. The most well known and probably mis-used antibiotic is still Penicillin G,[1a] which was discovered by Fleming in 1928. The antibiotic was shown to have a pronounced effect against many Gram negative bacteria and was used to dramatic effect against *Staphylococcus aureus* in the Second World War. It is, however, unfortunate to note that nowadays nearly all strains of *S.aureus* are resistant to Penicillin G, which now only has limited use in the treatment of some Gram positive bacterial infections. The lack of knowledge of antibiotic resistance unfortunately led to this scenario in the case of Penicillin G, as a result of general mis-use. The discovery of plasmids in the bacterial cell led to a better understanding of mechanisms of resistance and a realisation of the magnitude of the problem to be faced.

Plasmids[1b,c] are individual circles of DNA that are not part of the main chromosome but exist separately. Therefore, the plasmid can be inherited by a following generation without being linked to the chromosome. The properties that a particular plasmid can confer to the host are many-fold, so to the bacterium, plasmids represent a evolutionary advantage which to man is a disadvantage in all but a few cases. For example, Col plasmids can enable the host to produce antibacterial colicins which can degrade competing bacteria, virulence plasmids which increase the pathogenicity of the strain and R plasmids which allow resistance to local pathogens (*e.g.* antibiotics) by a number of methods. The plasmids themselves are transferred by a number of routes and in the case of R plasmids, a strain of antibiotic resistant bacteria can be established.

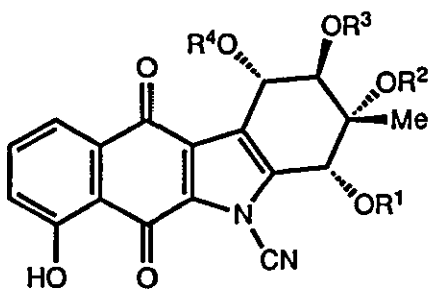
Ironically, the place where the most resistant bacteria originate are hospitals where the levels of antibiotics are generally high and thus surviving bacteria have a good chance of developing

resistance. It is therefore of the utmost importance to eliminate all of the bacteria in a given place (or subject) on the very first exposure of a new antibiotic to effectively remove the possibility of survivors developing resistance. Failure to do this can ultimately lead to new strains of "super bacteria" and subsequently render antibiotics, for example Penicillin G, redundant.
The problem faced by doctors and medical staff is to administer a level of antibiotic that will guarantee elimination of bacteria in a given subject. While this in itself is a trivial operation in hospitalised patients, less serious cases receiving treatment at home represent a problem as the symptoms of bacterial infection disappear long before the elimination of the cause and therefore the chances of the subject completing the necessary course whilst not under supervision are not guaranteed. The problem of multiple resistance is a growing one and requires much attention to avoid a return to a situation where the medical profession is unable to treat a large number of infections with often fatal consequences. At present the number of untreatable strains of bacteria remains small (but are being discovered *cf.* pesticide immunity in insects) and most infections can be treated with one antibiotic or another. Nevertheless, care must be taken with all new antibiotics to avoid a reversal of this current situation.

1.2. Pre-Kinamycin and the Kinamycin Antibiotics

Omura *et al.* first isolated and characterised a series of intensely coloured natural products[2] from *Streptomyces murayamaensis* which were shown to possess antibacterial properties[3] and in some cases antitumour activity. These agents were extensively analysed by Gould *et al* . and shown to be a novel family of structurally unique benzo[*b*]carbazoloquinones.[4,5]

By careful manipulation of the composition of the fermentation medium and subsequent nuclear magnetic resonance experiments, the structures were assigned and a biosynthetic pathway proposed. The structure of the Kinamycins (A - F) **1** were assigned as in Figure 1;

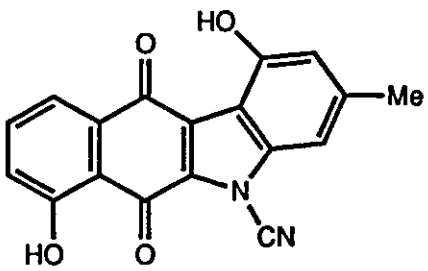


Kinamycin (A-F)
1

Figure 1

	R^1	R^2	R^3	R^4
A	Ac	Ac	Ac	H
B	H	Ac	H	H
C	Ac	H	Ac	Ac
D	Ac	H	Ac	H
E	Ac	H	H	H

The biosynthetic precursor known as 'Pre-Kinamycin' **2** was assigned, see below ;



Pre-Kinamycin

2

The structure of Pre-Kinamycin was determined on the basis of its spectroscopic data.[6] Hence, infra-red spectroscopy showed the presence of a quinone and a hydroxyl group and also a signal at 2162 cm^{-1} which was later proven to be a cyanamide group. Examination of the nmr. spectrum leads provisionally to the structure **2** (Figure.2);

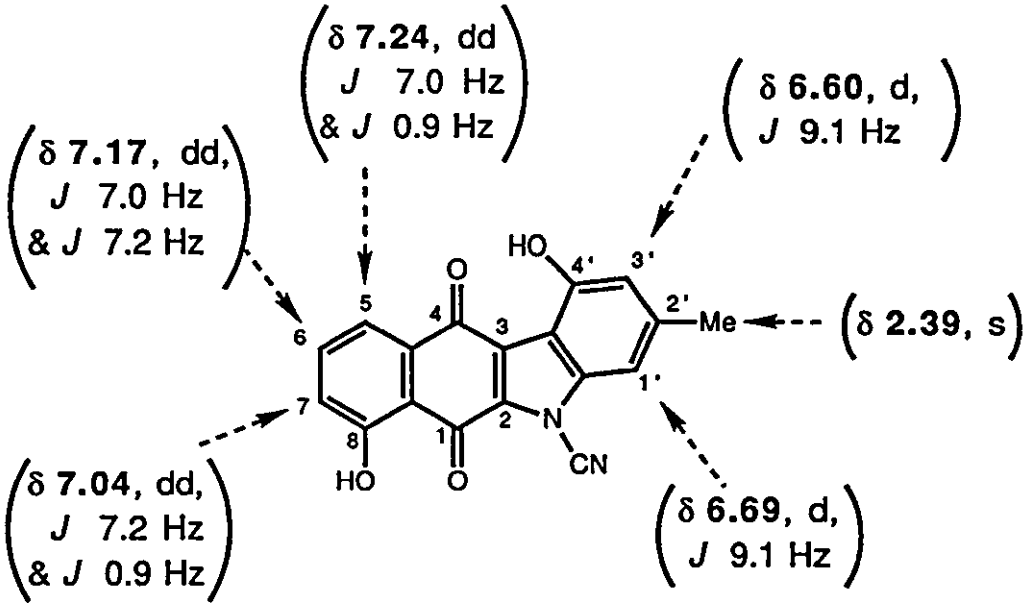
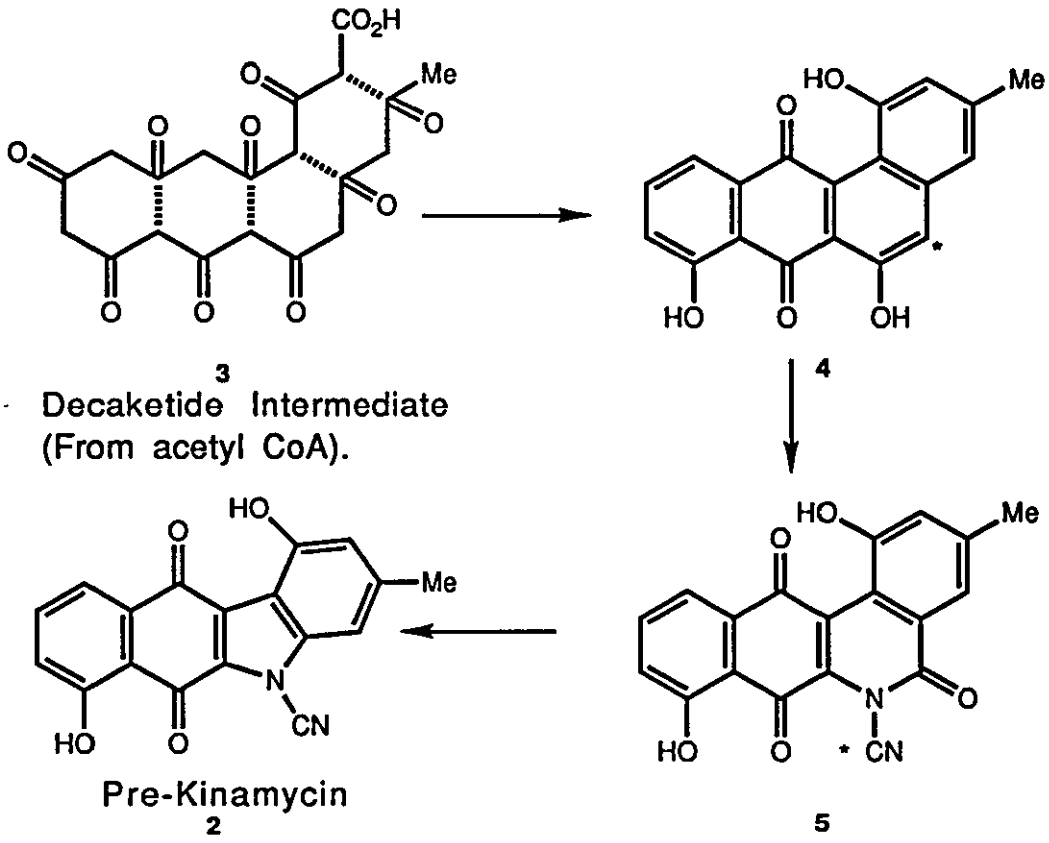


Figure.2

The two resonances at δ 6.60 and 6.69 were assigned to the *meta*-protons H-1' and H-3' on the tetra-substituted aromatic ring. The two hydrogens showed an nOe effect upon irradiation of the methyl signal at δ 2.39 but the coupling constant between H-1' and H-3' of

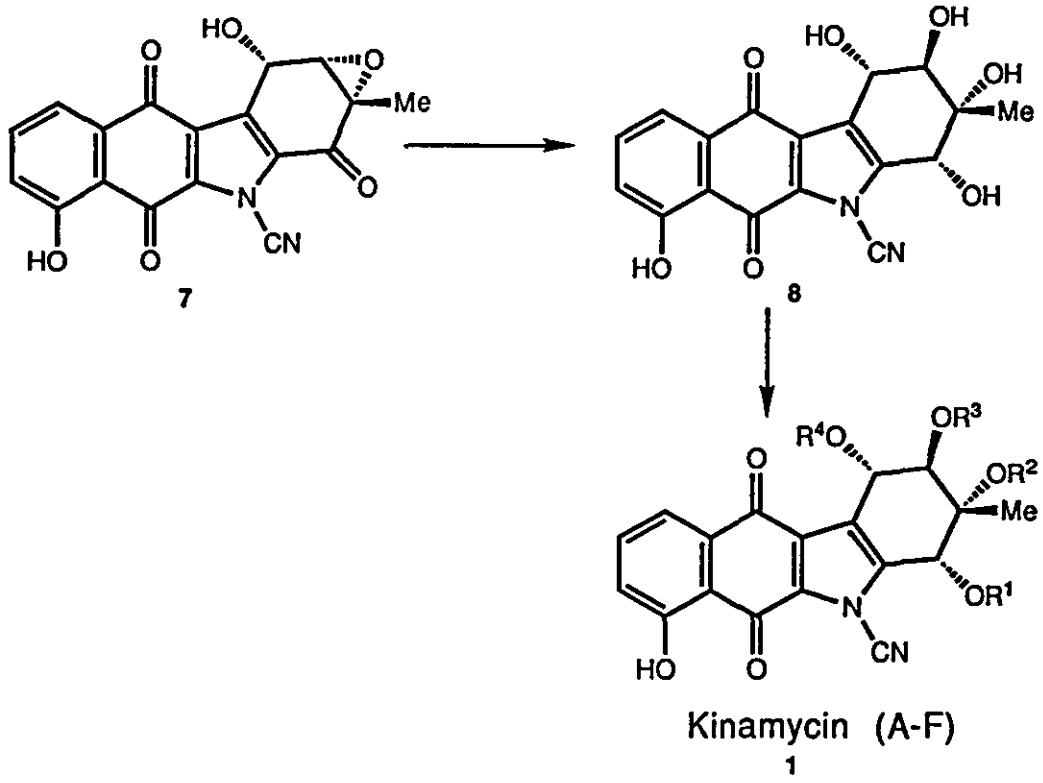
9.1 Hz appeared to be too large for simple *meta*- coupling (typically J ~ 1.0 Hz). This observation casts some doubt as to the assignment of the structure in Figure 2 and required an independent synthesis of the quinone proposed by Omura in order to investigate the apparent anomaly. The three remaining aromatic signals at δ 7.24, 7.17 and 7.04 were shown to be typical of that of three hydrogen atoms on a trisubstituted aromatic system i.e. H-5, H-6 & H-7 and each of the resonances showed the appropriate coupling constants to each other. The two hydroxyl signals at δ 11.60 and 12.32 were assigned to the two hydrogen bonded hydroxyl substituents at the C-4' and C-8 positions. The quinone carbonyls were observed in the ^{13}C spectrum of the diacetate at δ 174.14 and 192.48 and the cyanamide carbon resonance at δ 83.71.

Scheme 1[4] outlines the proposed biosynthetic pathway. A decaketide intermediate **3** leads directly to the benzanthraquinone **4**. A unique process of oxidation, nitrogen insertion and ring contraction leads to the benzo[*b*]carbazoloquinone skeleton of Pre-Kinamycin **2**.



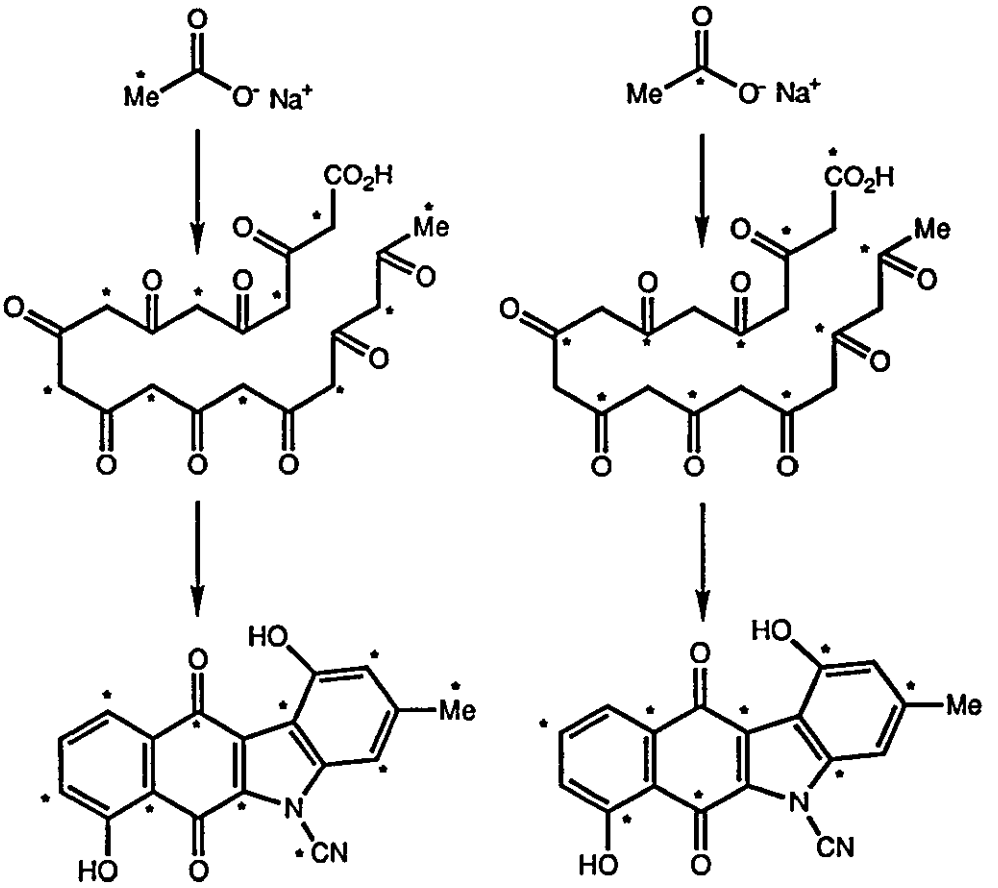
Scheme 1

The scheme continues below (Scheme 2) through a series of isolated intermediates to the final Kinamycin structure.



Scheme 2

The benzanthraquinone 4 proceeds through the previously mentioned oxidation / nitrogen insertion / ring contraction to afford the benzo[b]carbazoloquinone and although the exact mechanism of this remarkable process is as yet a matter of speculation, labelling experiments to determine the origins of the carbon atoms in the cyanamide portion have been carried out. Carbon-13 labelled sodium acetate (NaO_2C^*Me and NaO_2CMe^*) were fed independently into culture media in order to determine the origin of the cyanamide carbon and from the results it was noted that the CN group showed ^{13}C enrichment only from the broth spiked with NaO_2CMe^* (see Scheme 3) .



Scheme 3

From the distribution of the labels above, the existence of the intermediate pyridone **5** was postulated. As yet, a synthesis of the benzanthraquinone **4** with a single label * has not been accomplished so the precise mechanism of the ring contraction is still a matter of speculation.

Isolation and Extraction of the Kinamycins

Optimum production of Kinamycins A - D were achieved as follows; a sample of the patent strain of *S. murayamaensis* (ATCC 21414) from a Krainsky's agar slant, was pre-incubated in the following medium (glucose , 2.0 % , soybean meal , 2.0 % , NaCl , 0.3 %) for 48 hours at 26 - 27°C , to produce the most effective seed culture for future fermentation. A 5 % inoculum level was used in a culture consisting of either a glycerol-asparagine medium (glycerol 3% , L-asparagine 0.1% , $K_2HPO_4 \cdot 3H_2O$ 0.1% , $MgSO_4 \cdot 7H_2O$ 0.04% , $FeSO_4 \cdot 7H_2O$ 0.01% in distilled water), or an identical soybean medium to that of the pre-incubation system. All cultures were

incubated at pH8 at 26-27°C for approximately 48 hours with pH control every 8 hours.
Isolation of a typical broth is shown in Figure.4

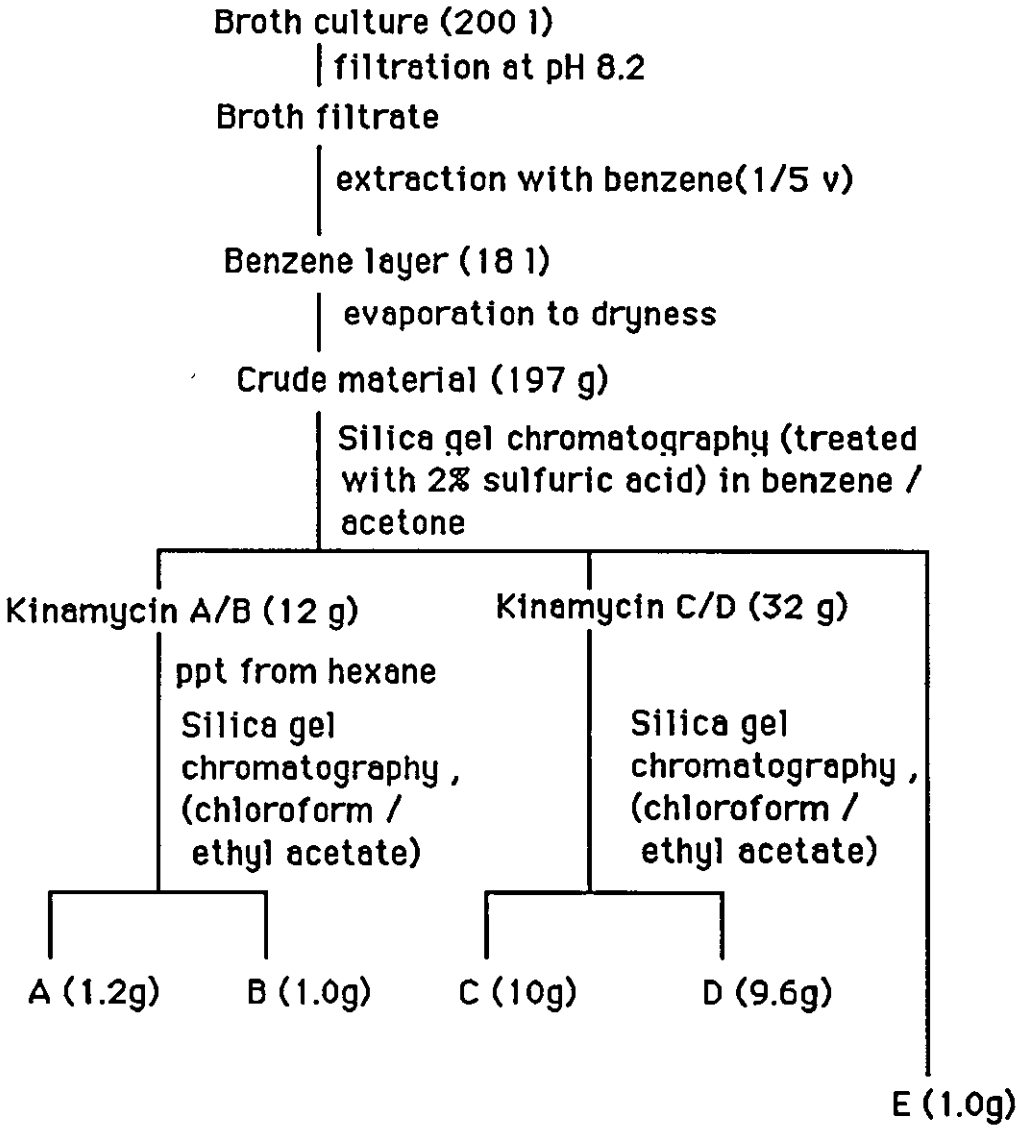


Figure.4

A.- Yellow needles (crystallised from EtOAc) m.p. 139-142°C
B.- Orange needles (crystallised from $CHCl_3$) m.p. 190-193°C
C.- Yellow needles (crystallised from EtOAc) m.p. 150-153°C
D.- Orange needles (crystallised from EtOAc) m.p. 170-175°C
E.- Minor metabolites **4**, **7**, **8** and Pre-Kinamycin, **2**.

The distribution of products in the broth during incubation is best represented by the thin layer chromatogram represented in Figure 5.

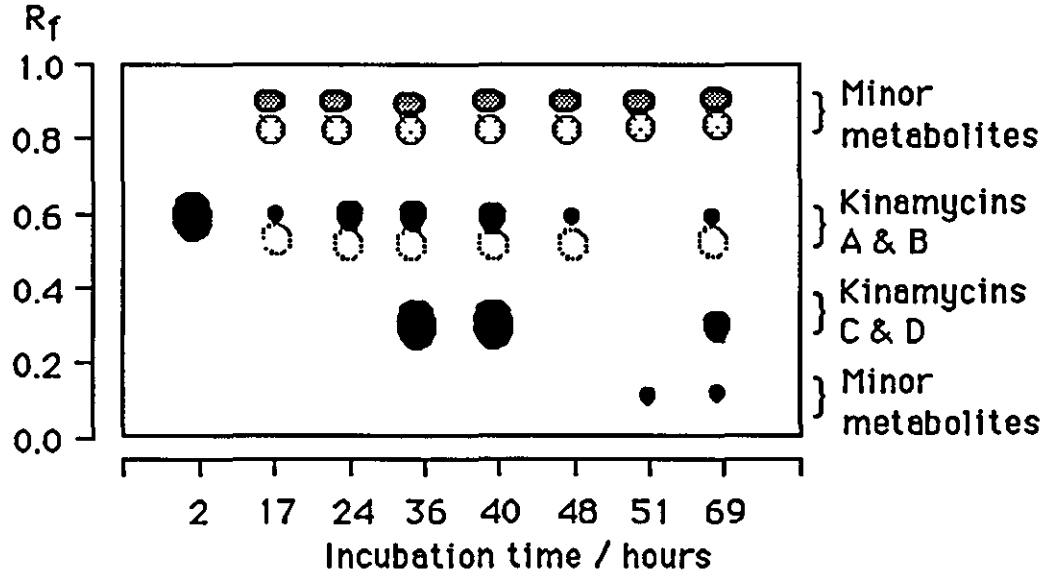


Figure 5

Adsorbent : silica gel (treated with H_2SO_4)
Developer : benzene / acetone (5 : 1)
Detection : UV lamp (254 nm) and visible colour.

The spectrum of activity of the Kinamycins against the most commonly challenged organisms is shown in Figure 6.

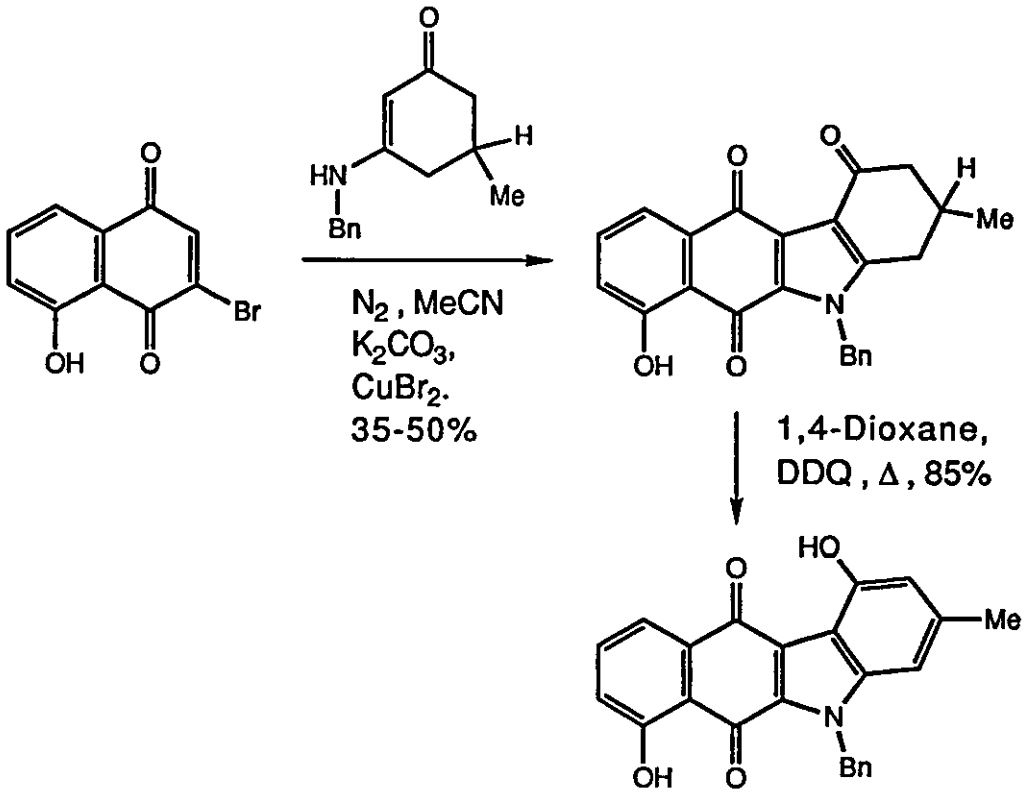
Test organism	M.I.C†. / μml^{-1} A	B	C	D
Bacillus subtilis PCI-219	0.024	0.012	0.19	0.012
Bacillus anthracis	0.19	0.012	0.19	0.024
Staphylococcus aureus *	0.78	0.012	0.78	0.024
Staphylococcus aureus SM-R	1.56	0.006	0.39	0.024
Staphylococcus albus	0.024	0.012	0.39	0.024
Staphylococcus haemolyticus	100	12.5	12.5	50
Mycobacterium 607	25	6.25	6.25	6.25
Eschericia coli NIHJ	>100	3.12	100	12.5

Figure 6

* FDA 209P

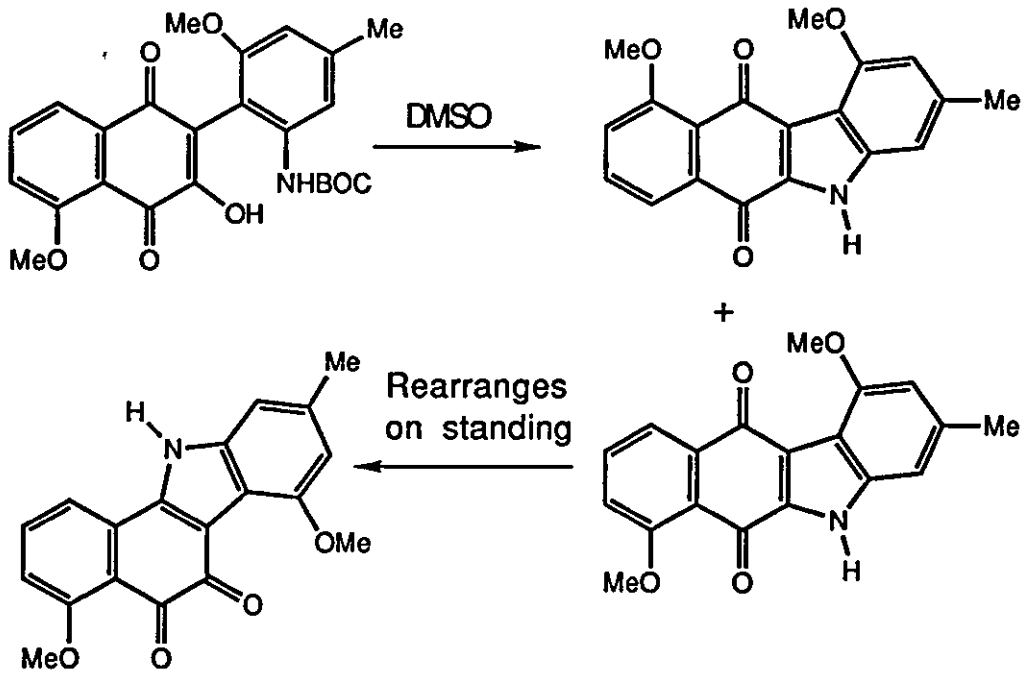
† Minimum inhibitory concentration

Two independant synthetic approaches have been recently published by Murphy *et al*[7] and Echavarren *et al*[8] in an attempt to elucidate the structure of Pre-Kinamycin.
The route of Murphy *et al* uses a bromonaphthoquinone and its coupling with an enamino ketone to construct the indoloquinone structure of the Kinamycin antibiotics (Scheme 4), although the work has yet to be applied to Pre-Kinamycin itself.



Scheme 4

The method of Echavarren *et al* has been applied directly to the synthesis of Pre-Kinamycin (Scheme 5) and yields a product that has physical and spectral properties different to that of the reported structure and confirms the ambiguity of the assignment. The synthesis however, does yield an unexpected rearrangement product and therefore the route cannot be declared unambiguous until the rearrangement has been exhaustively studied.



Scheme 5

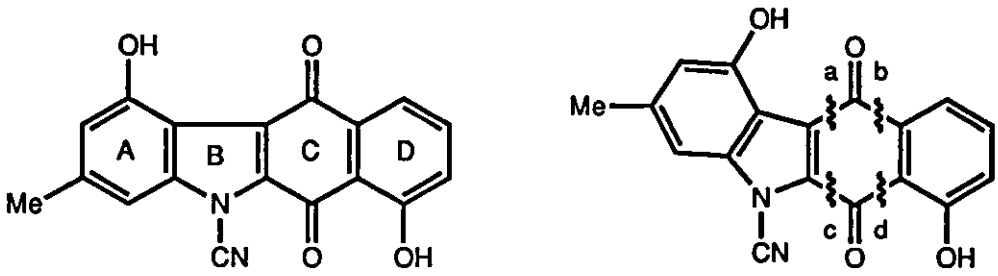
In conclusion, there is a need for an unambiguous synthesis of the novel indoloquinone Pre-Kinamycin to either prove or disprove the structure proposed by Omura and also to compare the regiochemistry and properties of the structure synthesised by Echavarren.

Chapter 2

2.1. Discussion & Results.

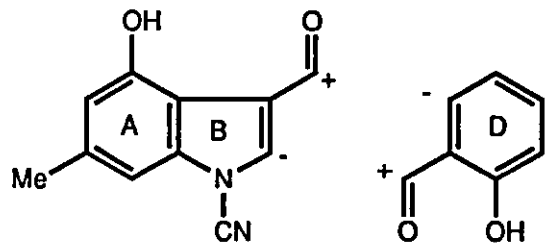
The four rings of the tetracyclic target molecule will be arbitrarily labelled A, B, C & D here and throughout this text. Retrosynthetic analyses on the target molecule are many and varied but due to considerable precedent concerning indole and quinone syntheses the main disconnections were carried out across bonds a, b, c and d (Scheme 6).

Target Molecule

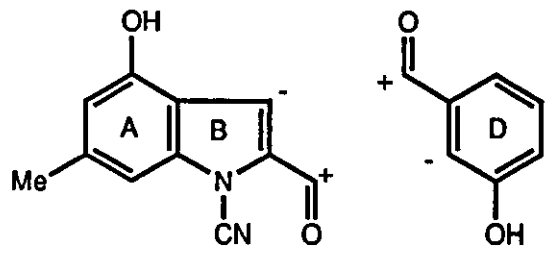


Disconnections :

i. b / c



ii. a / d

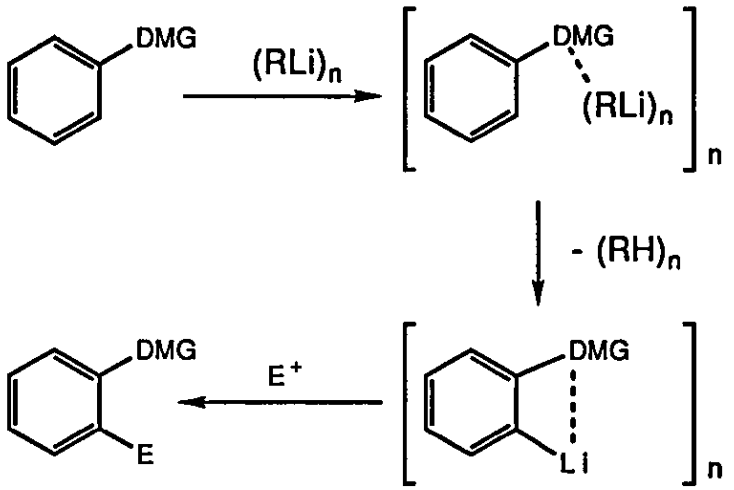


Scheme 6.

The disconnections i and ii both lead to useful synthons which have been the subject of considerable study by Gilman, Wittig and Fuhrman[9-12] in the past and in more recent years by several groups including that of Snieckus.

Directed metallation reactions (DoM) - scope and influences

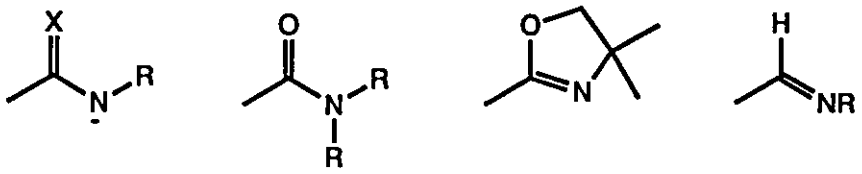
The reaction takes its usefulness from the ability to predict the deprotonation site of an aromatic system when treated with a strong base. In general, when an aromatic system bearing a heteroatom-containing directed metallation group (DMG) is treated with a strong base (usually an alkyllithium reagent), the site of deprotonation is *ortho* to the DMG. Thus, upon quenching with a suitable electrophile, 1, 2-disubstituted products are obtained[13] (scheme 7).



Scheme 7.

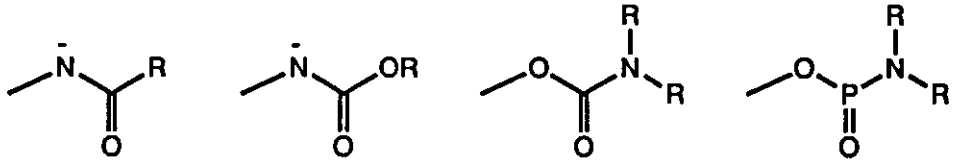
One of the simplest and most effective metallating systems is sec-BuLi / TMEDA, which effects deprotonation of $SiMe_4$ some 1000 times faster than n-BuLi / TMEDA[14] and to date, is the most popular system used. The nature of the DMG must be twofold and act both as a good coordination site for alkyllithium and a poor electrophile towards the strong base. A heteroatom therefore, is an obligatory component of a useful DMG (Figure 7).

Carbon based:

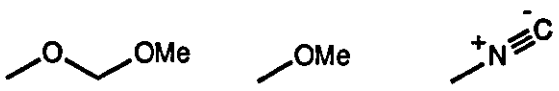


Ref: 15,16,17 18 19 20

Heteroatom based:



Ref: 21 22 23 24



Ref: 25,26 15 27

Figure 7

The usefulness of DMG's is further exemplified by observing the cooperative effect of a second DMG in a 1, 3-disubstituted aromatic where the selectivity of the metallation procedure is considerable. Several examples of this effect are shown in Figure 8. With respect to anthraquinone syntheses, the ambiguity often found in Friedel-Crafts approaches (Scheme 8) is overcome.

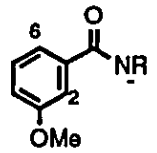
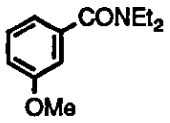
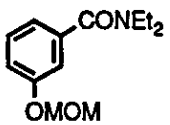
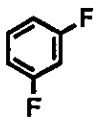
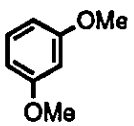
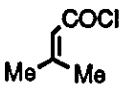
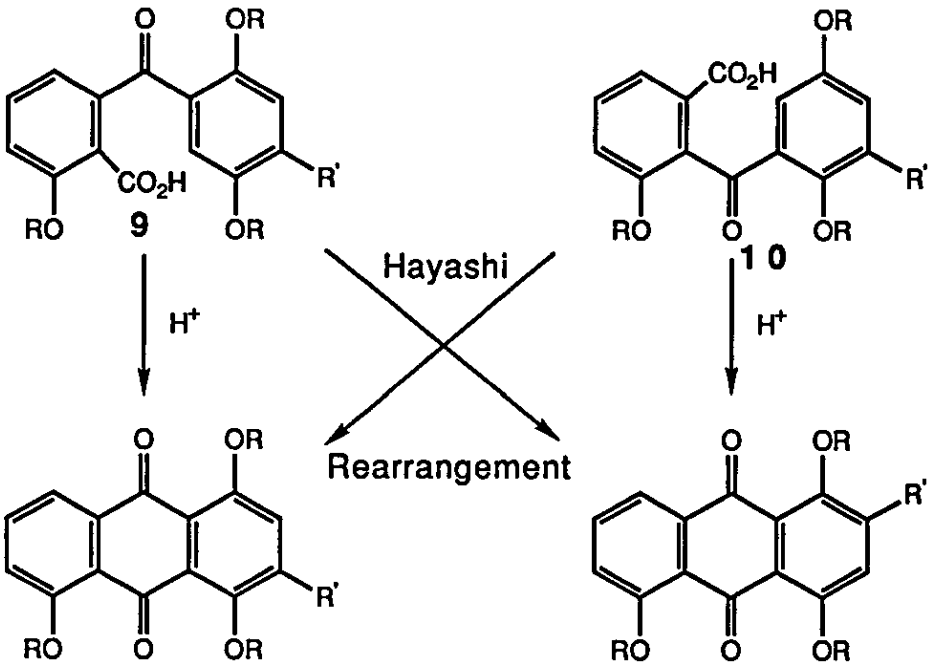
	Substrate	Conditions	E+	Yield %	Selectivity C_2:C_6	Ref.
1.		n-BuLi / TMEDA / THF / -78°C → -10°C	ArCHO	48	95 : 5	28
			Ph_2CO	79	95 : 5	29
2.		s-BuLi / TMEDA / THF / -78°C	D_2O / TMSCl	90	95 : 5	30
3.		t-BuLi / Et_2O -78°C		35	95 : 5	31
4.		n-BuLi / THF -65°C	CO_2	88	95 : 5	15
5.		n-BuLi / THF 35 → -78°C		78	95 : 5	32

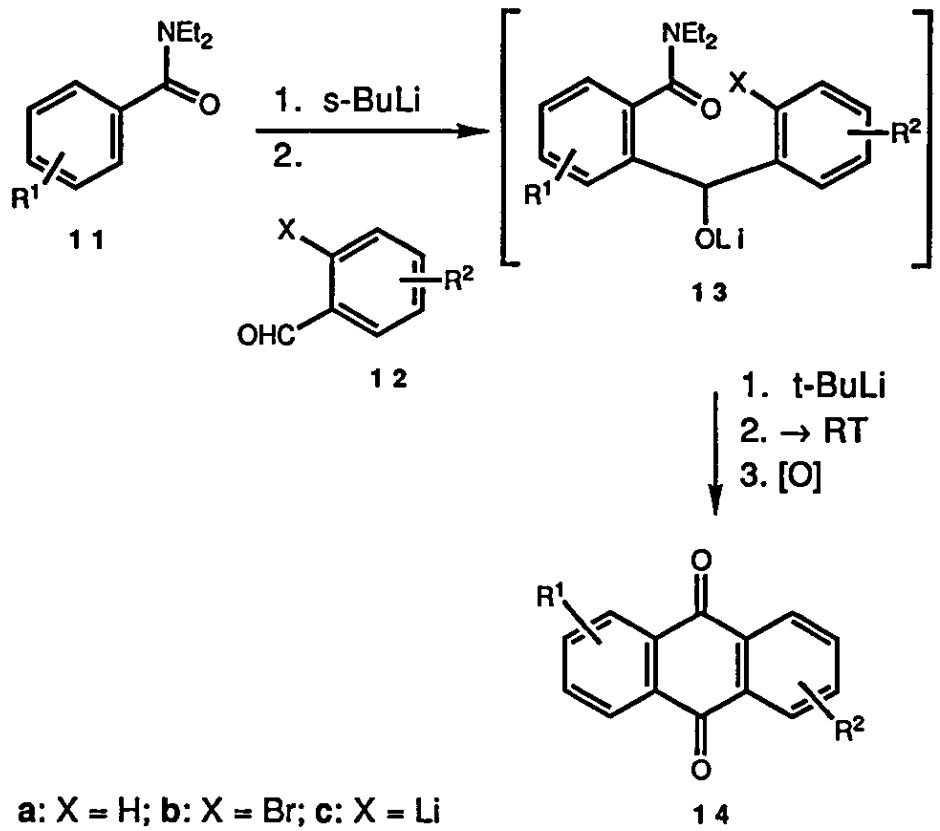
Figure 8



Scheme 8

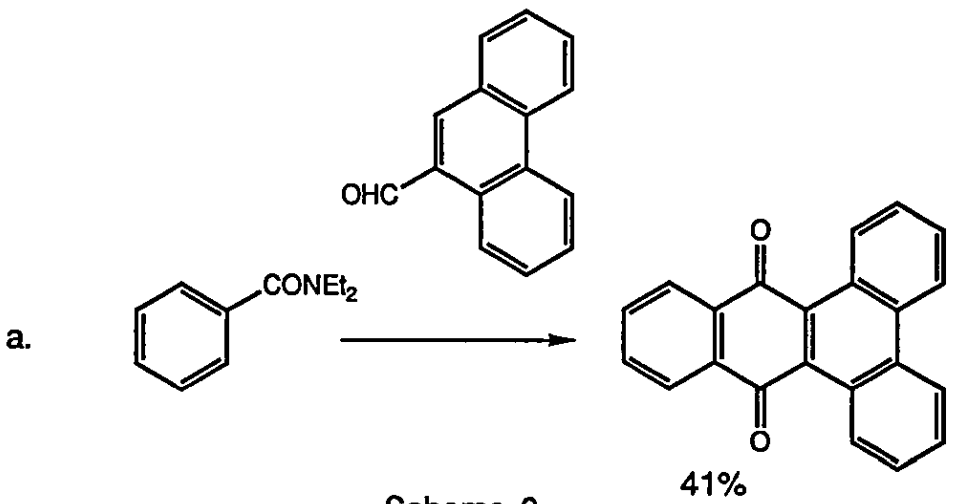
Here, the reaction is restricted by the potential Hayashi rearrangements of the acylium ions formed from **9** and **10** and the inefficiency of the process due to the electron-withdrawing *ortho* -benzoyl substituent.

The tandem DoM reaction has been extensively used in several elegant anthraquinone syntheses of interest[33] (Scheme 9).Snieckus and Watanabe[34,35] described syntheses of simple and more complex annelated anthraquinones by a novel tandem directed *ortho* metallation sequence **11** + **12a** → **13a** → **14** (Scheme 7).

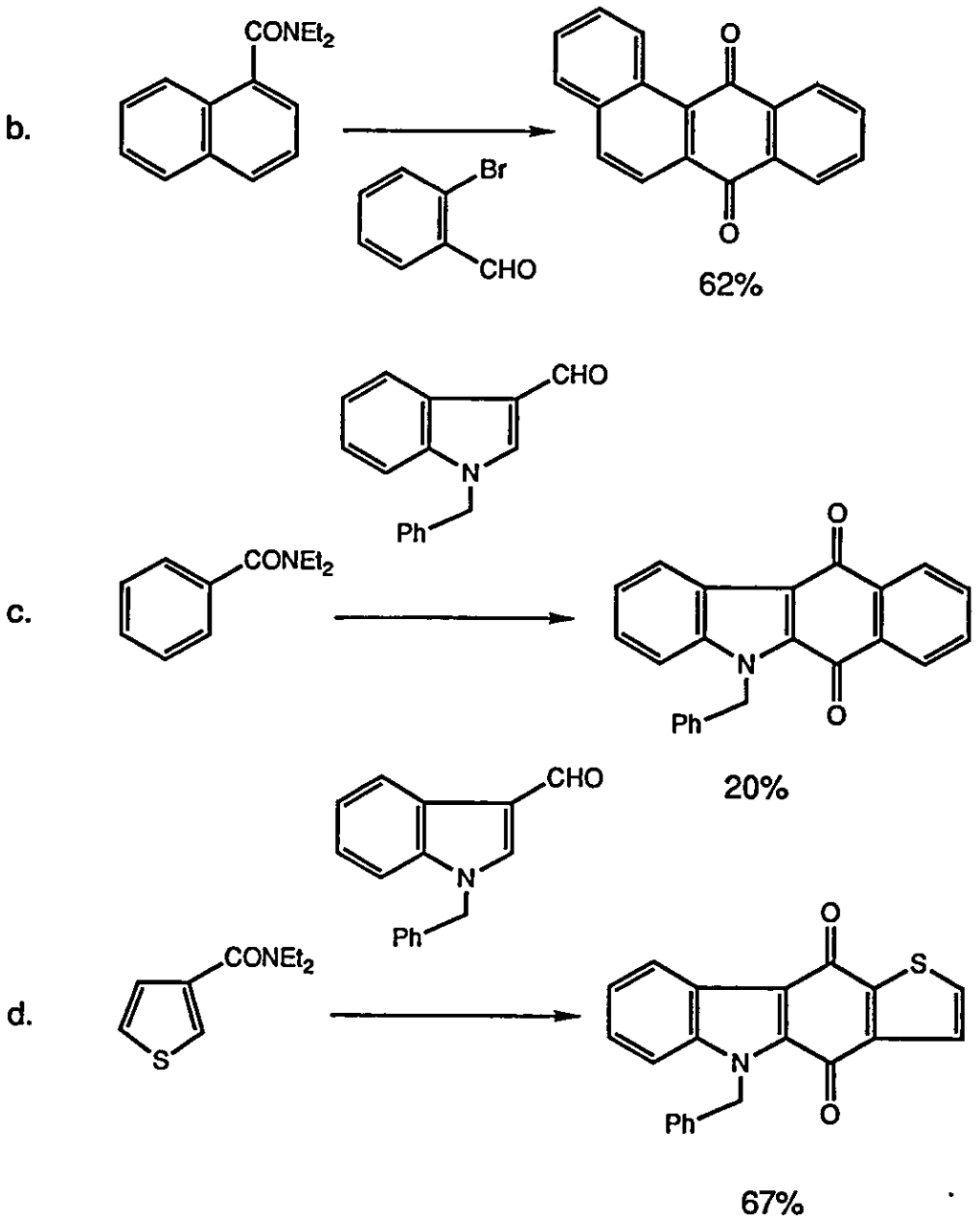


Scheme 7a

A recent review[36] gives extensive details as to the scope of the reaction and the many influencing factors.



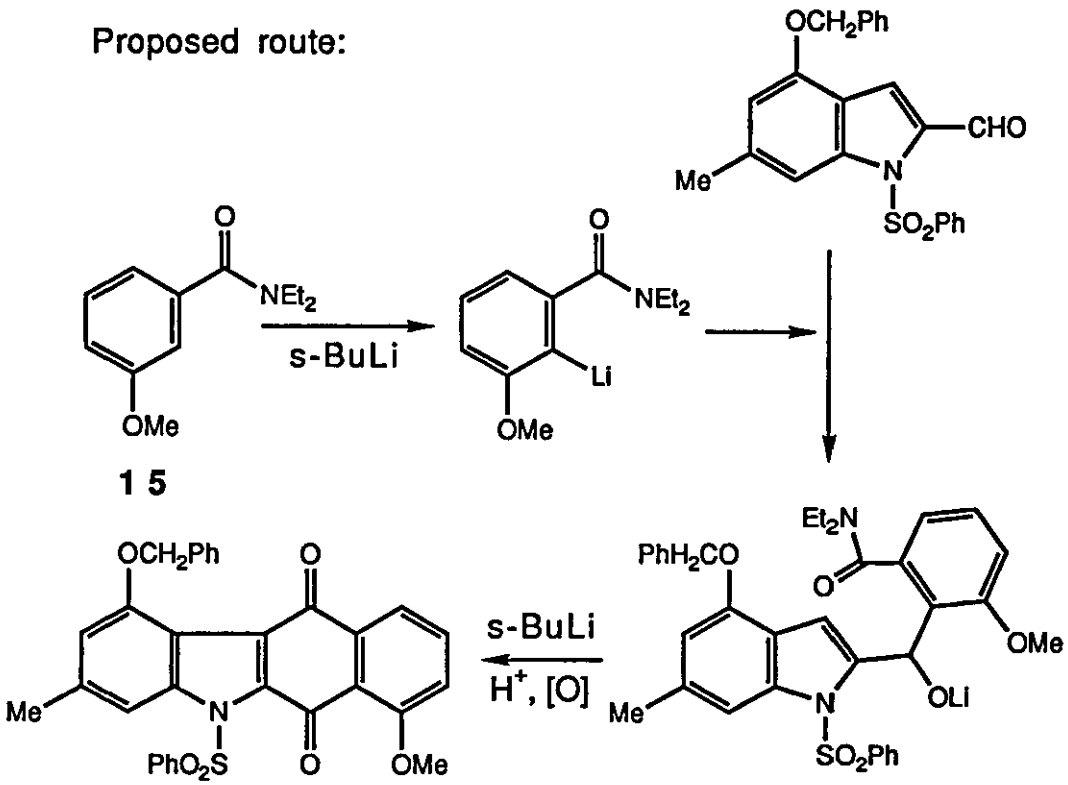
Scheme 9



Scheme 9 (continued)

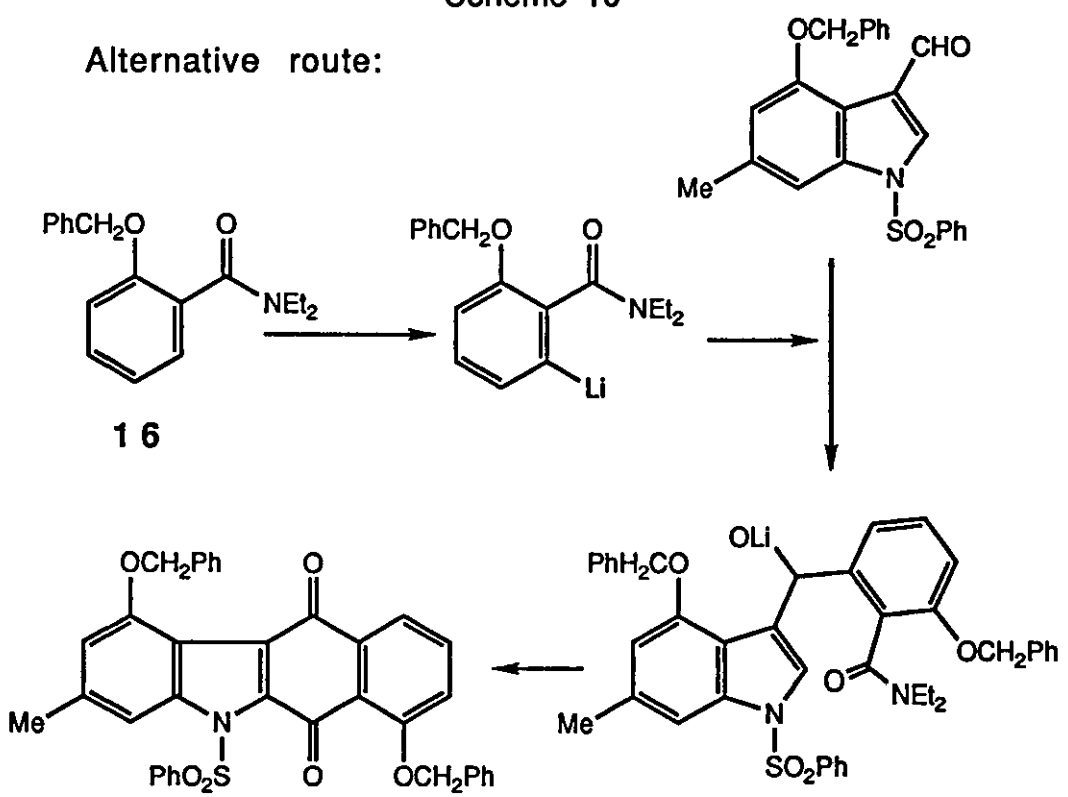
Reaction **c** was of particular interest despite the modest yield and appeared to require little modification for the synthesis of Pre-Kinamycin. Thus, two routes to Pre-Kinamycin were proposed as outlined in Schemes 10 and 11.

Proposed route:



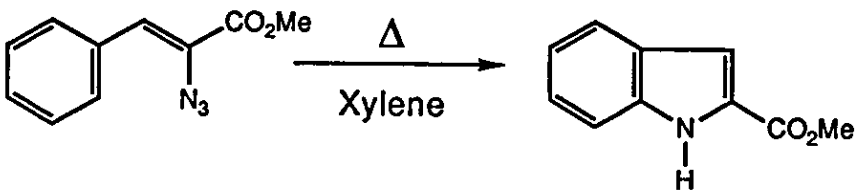
Scheme 10

Alternative route:



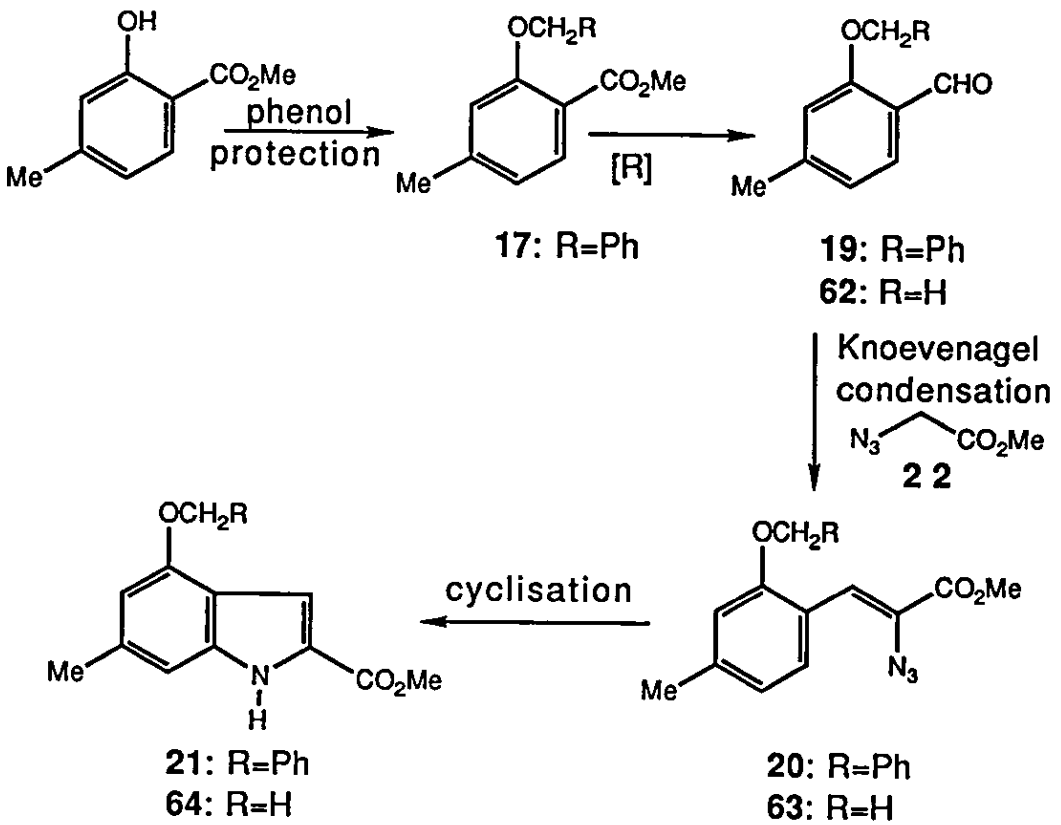
Scheme 11

The proposed synthesis in Scheme 10 required the pre-construction of the A and B rings with the appropriate substitution pattern i.e. 1-benzenesulfonyl-4-benzyloxy-6-methylindole-2-carboxaldehyde, which could also be the precursor for the isomeric indole in Scheme 11. Regiospecific indole synthesis has been the subject of much research and the number of routes available are considerable. The method of choice relies on the known thermal decomposition of phenyl vinyl azides (Scheme 12).



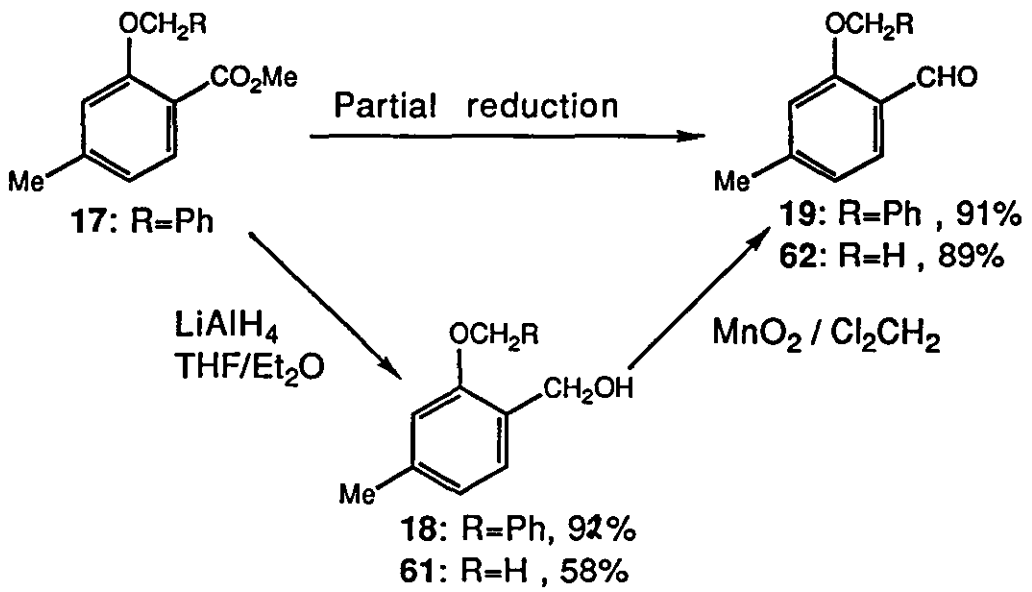
Scheme 12

In order to achieve an efficient synthesis of 1-benzenesulfonyl-4-benzyloxy-6-methylindole-2-carboxaldehyde by this methodology, scheme 13 was proposed, commencing with the commercially available methyl 4-methylsalicylate.



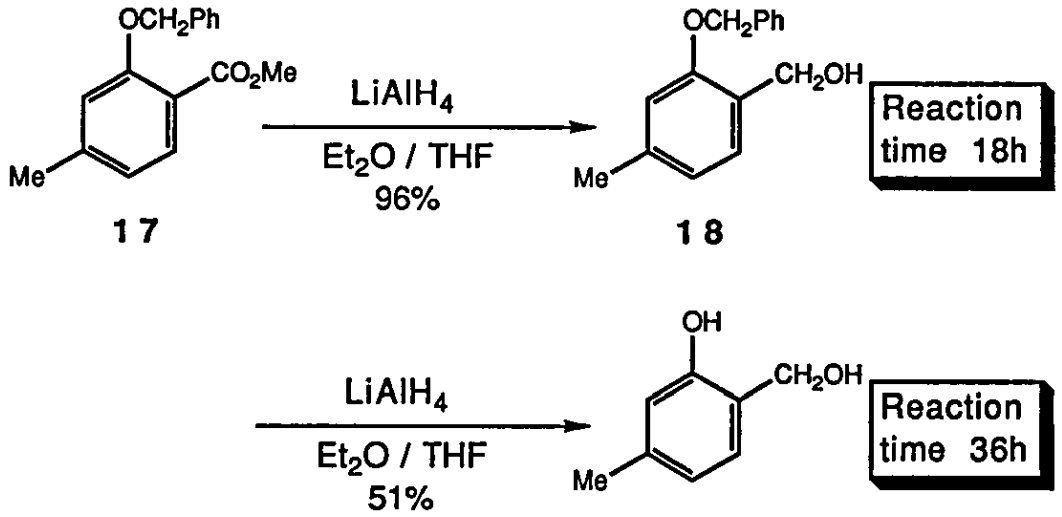
Scheme 13

Since the final indoles **21** and **64** represented versatile precursors to the indole aldehydes in schemes 10 and 11, both would rely on the successful construction of these intermediates.
Treatment of methyl 4-methylsalicylate with sodium hydride in DMF and *O*-alkylation with benzyl chloride gave a complex mixture of products and the deprotonation conditions judged too harsh. The preparation of **17** was carried out using milder conditions of potassium carbonate in acetone and alkylation with the more reactive benzyl bromide in 76% yield. The unpredictable nature of the partial reduction of aromatic esters to aldehydes led to the conversion of **17**→**19** and the preparation of **62** being carried out in two stages (scheme 14) via the fully reduced alcohols **18** and **61**.



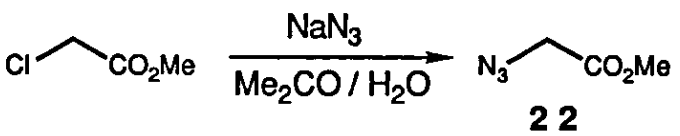
Scheme 14

Thus, reduction of the esters to, respectively **18** and **61** was carried out using lithium aluminium hydride in ether/THF over 2 and 18 hours respectively. The reaction time proved to be critical since in one case, where the reaction was allowed to continue for 36 hours the overreduced phenol was isolated as the major product from **17** (scheme 15).



Scheme 15

Partial oxidation of the alcohols **18** and **61** to the aldehydes **19** and **62** with freshly prepared manganese dioxide in methylene chloride proceeded without incident in good yield. The Knoevenagel condensation required the preparation of methyl azidoacetate **22** which was carried out by the nucleophilic substitution reaction of sodium azide (scheme 16) in aqueous acetone.

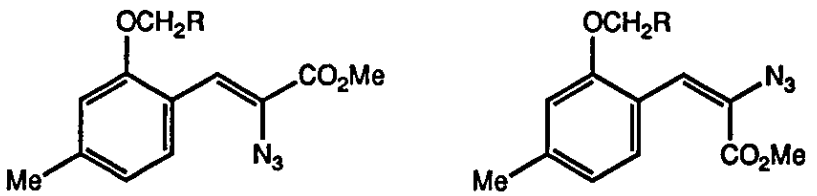


Scheme 16

Due to the explosive nature of azides, the oil isolated from the reaction was used without further purification. Nmr analysis of the crude azide showed a purity above 90% (the contaminant being unreacted chloromethyl acetate).

The conversions of both **19** to **20** (60% yield) and **62** to **63** (19% yield) required an inverse addition method where a pre-mixed solution of the azide **22** and aldehyde **19** (or **62**) in methanol was added to a freshly prepared solution of sodium methoxide in methanol at -12°C. The duration of the reaction was more critical and reaction times in excess of 4 hours resulted in severely reduced yields due to extensive decomposition of the azide **20** under strongly basic conditions.

The vinyl azides **20** and **63** have two possible configurations, the E and Z isomers (figure 9) and, in the case of **20** distinguishing between the two compounds is not trivial.

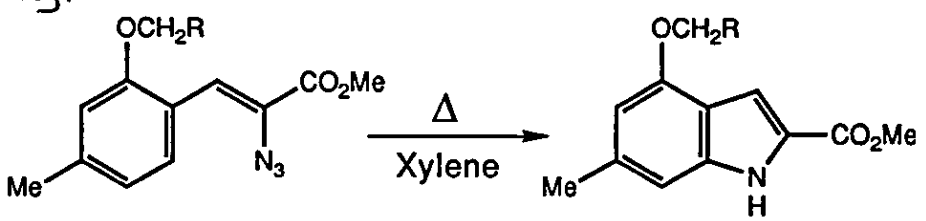


Z-**20** , R=Ph
Z-**63** , R=H

E-**20** , R=Ph
E-**63** , R=H

Figure 9

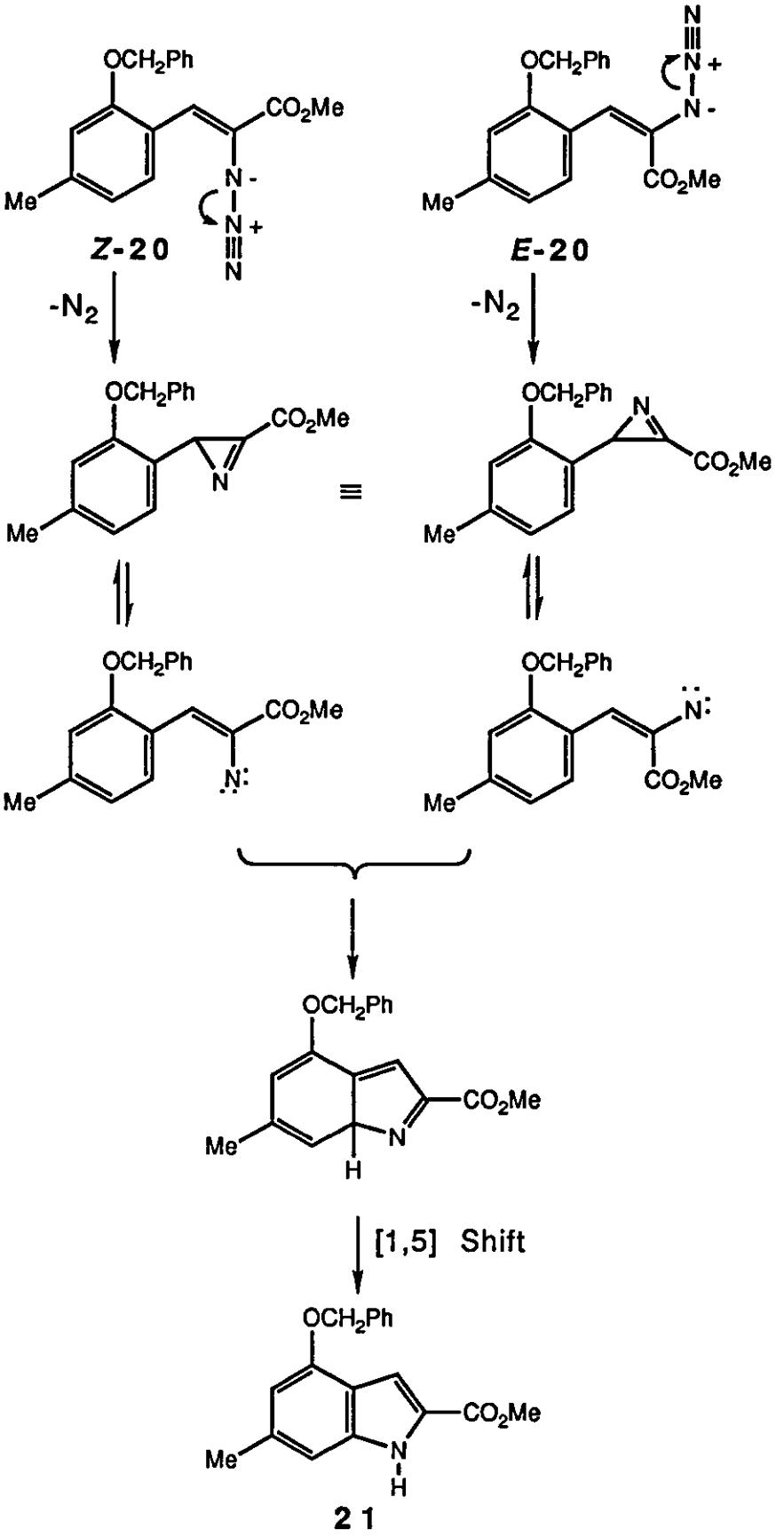
At first sight it appears that only the *Z* isomer is able to undergo cyclisation to the indole which would represent a considerable problem and thus a severely reduced yield. However, on close examination of the mechanism and the intermediates involved, these problems are shown to be non-existent.(Scheme 17b). The two possible azides *E*-**20** and *Z*-**20** initially decompose to nitrenes which are stabilised via the intermediate azirine.
The transitions between nitrene and azirine are reversible and it is at this stage that the original regiochemistry of the azides *E*-**20** and *Z*-**20** is lost and the reaction proceeds though a single intermediate to the indole **21** following a [1,5] H-shift.
Thus the cyclisations of **20**→**21** and **63**→**64** (Scheme 17a) were effected in refluxing xylene, in 40% and 60% yield (recrystallised), respectively.



20 , R=Ph
63 , R=H

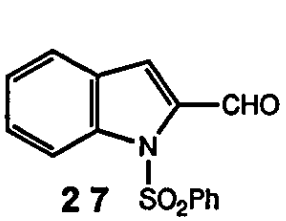
21 , R=Ph , 40%
64 , R=H , 60%

Scheme 17a

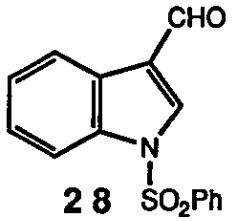


Scheme 17

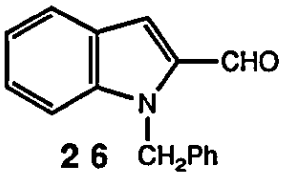
In order to evaluate the choice of protecting groups and the merits of schemes 10 & 11, four model compounds **26→29** were required i.e.



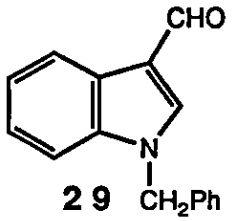
27



28

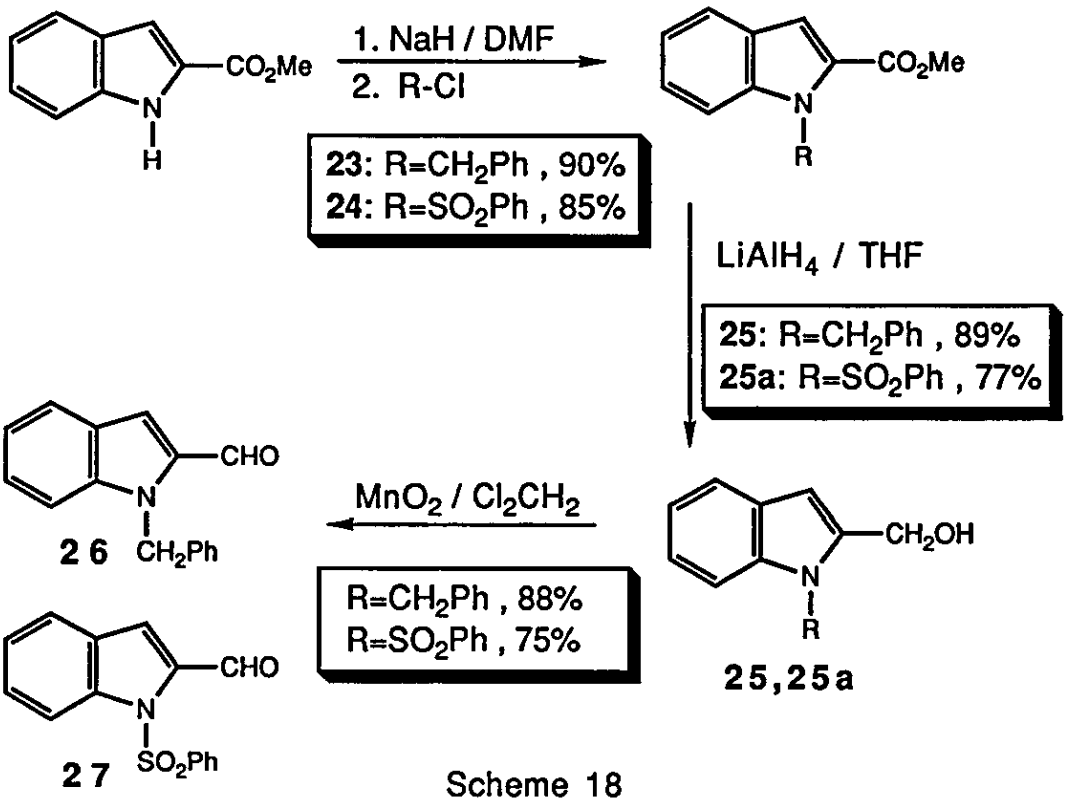


26



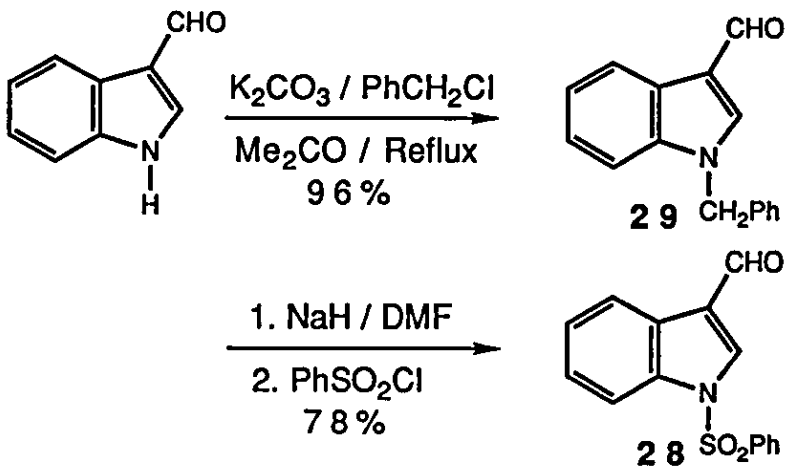
29

Indoles **27** & **26** were both synthesised from methyl indole-2-carboxylate (scheme 18) in good yield and the problem of partial reduction overcome again by complete reduction followed by mild oxidation of the ester function.

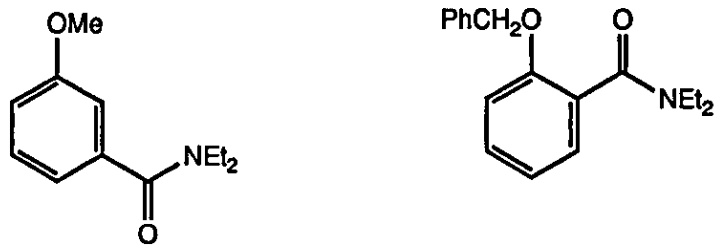


Scheme 18

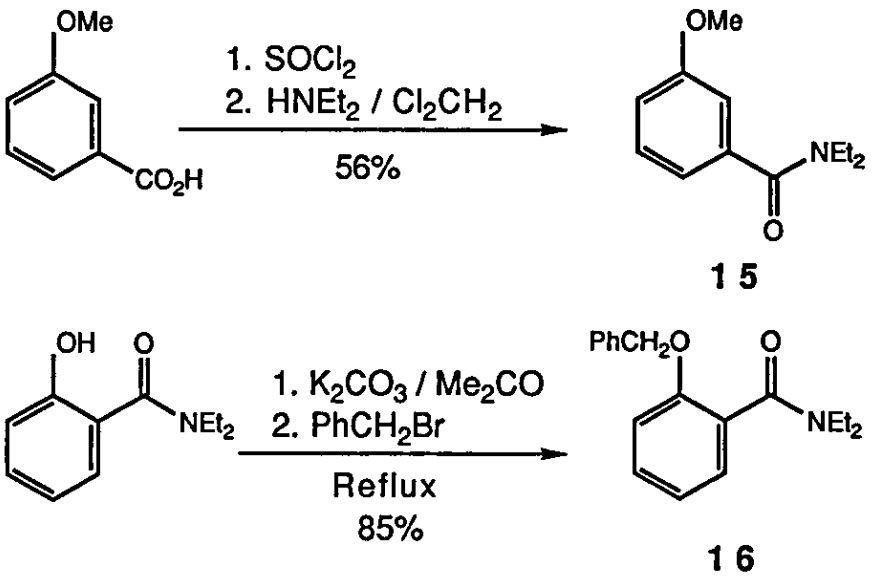
The remaining compounds **28** & **29** were synthesised from indole-3-carboxaldehyde (scheme 19).



Scheme 19

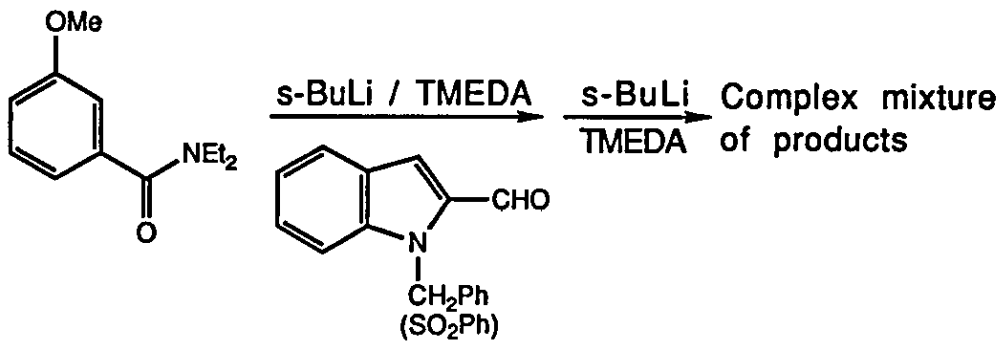


The two models **15** and **16** were also synthesised in good yield using standard manipulations (FGI's) (Scheme 20).

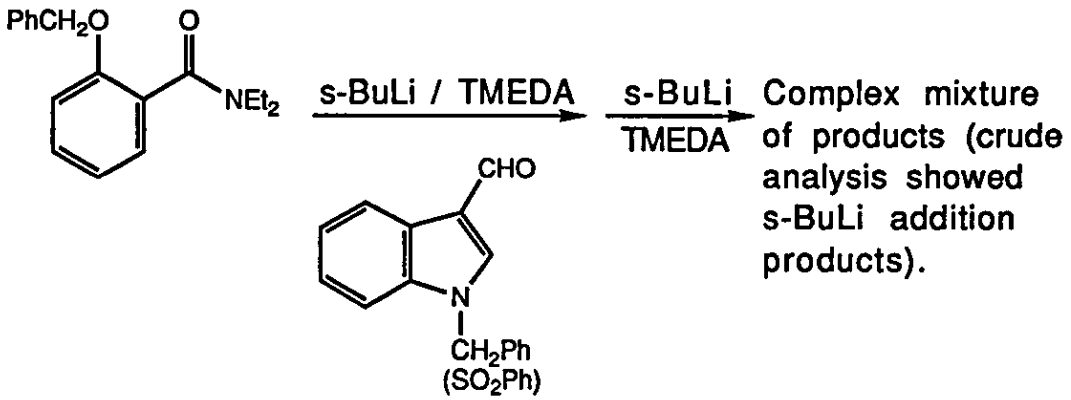


Scheme 20

Using the method of Snieckus (i.e. s-BuLi / TMEDA / -78°C) the two DMG containing heterocycles (**15** and **16**)were lithiated and quenched with each of the electrophiles (**26**→**29**) (Scheme 21,22)



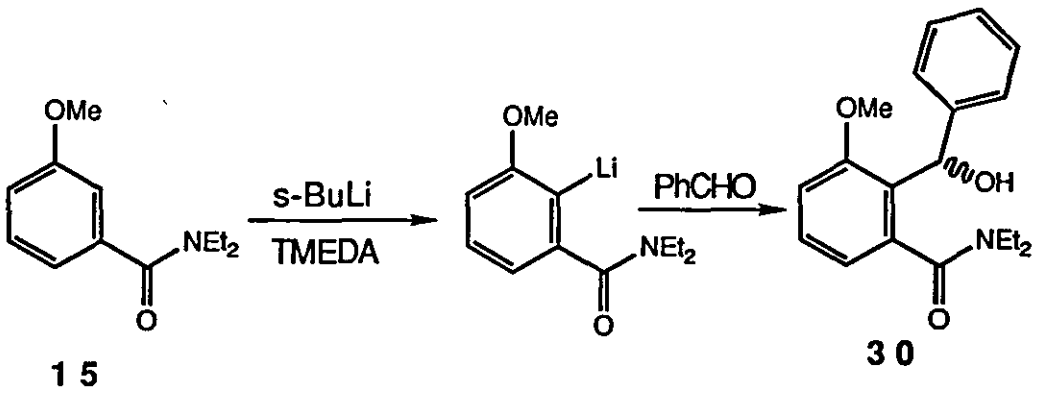
Scheme 21



Scheme 22

In light of these somewhat disappointing results, investigations were undertaken to determine at which stage the reaction was failing. To check that the anion of **15** was being formed under the reaction conditions, a simpler version of the reaction was carried out using identical conditions but replacing the electrophile with benzaldehyde (Scheme 23).

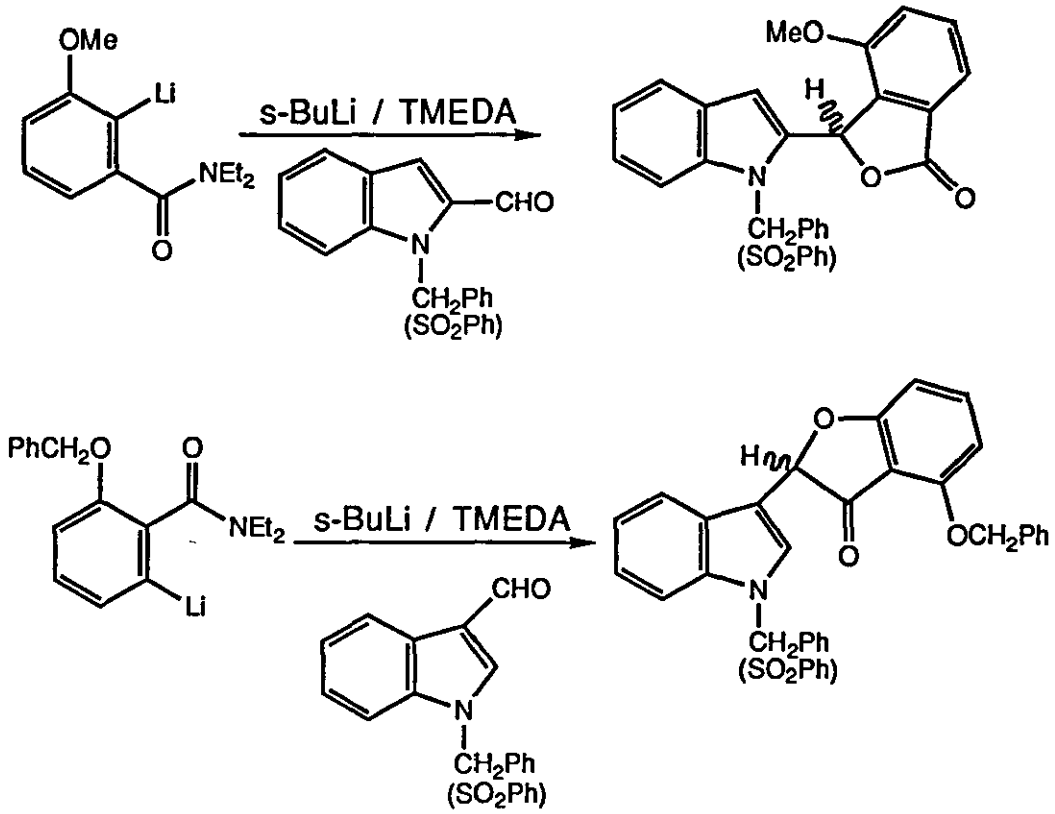
The carbinol **30** was isolated in a rather poor 25% yield which showed that the first two stages of the reaction were taking place. It was therefore feasible that the intermediate phthalides should be isolable from the first stage of the reaction which could be subsequently carried through to completion (Scheme 24).



15 30

Scheme 23

Unfortunately, attempts to synthesise any of the phthalides gave similar unproductive results and led to the abandoning of the routes. It was concluded that since the anions were being formed and were shown to quench with simpler electrophiles, then the indoles **26→29** were either too large to approach the anions or that the aldehydes were sufficiently deactivated by the indole nucleus to prevent the reaction proceeding further.

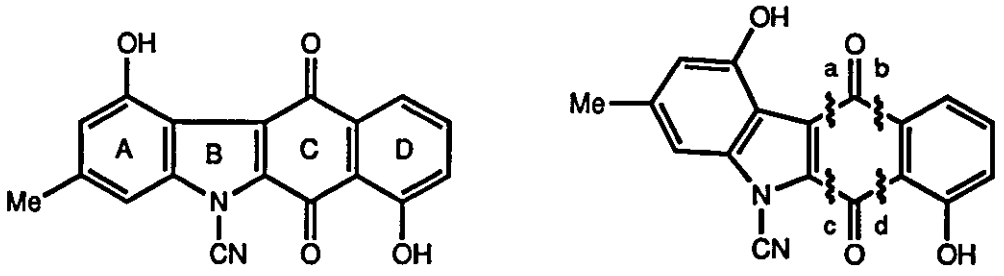


Scheme 24

2.2. Further Disconnections.

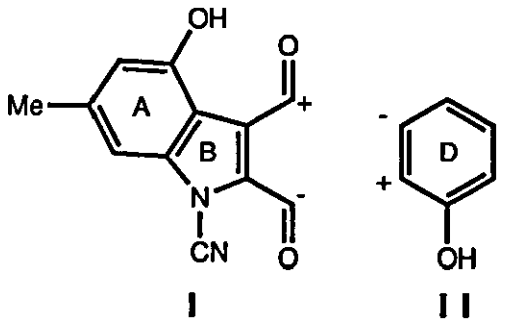
Returning to the target molecule in Scheme 6 there are several other disconnection possibilities to be investigated (Scheme 25).

Target Molecule



Disconnections:

b/d: ⟹

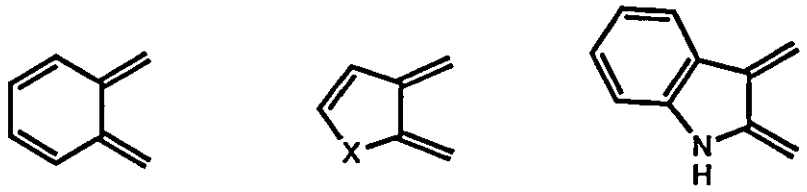


I II

Scheme 25

These unusual synthons **I** and **II**, upon examination lead to a study of cycloaddition reactions, of which the Diels-Alder cyclisation has proved to be one of the most important and versatile ring-building processes to date. The structures **I** and **II** do not appear to be easily transposable to that required for cycloaddition since the formation of a diene on either the B or D rings would involve a disruption of the aromatic system.

However, the presence of quinodimethanes (or *o*-xylylenes) at high temperature (Figure 10) has been the subject of some study and although these species have not been isolated their presence is evident from the isolation of reaction products arising from the Diels-Alder [4+2] cycloaddition reaction.



X= O, S, NR

Figure 10

These transient species have generated subsequent interest due to their synthetic potential and a number of stable precursors to ortho-quinodimethane itself have been made,[37-41] the most popular being shown in Figure 11.

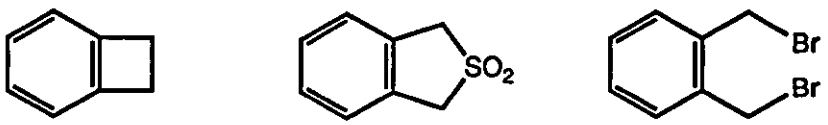
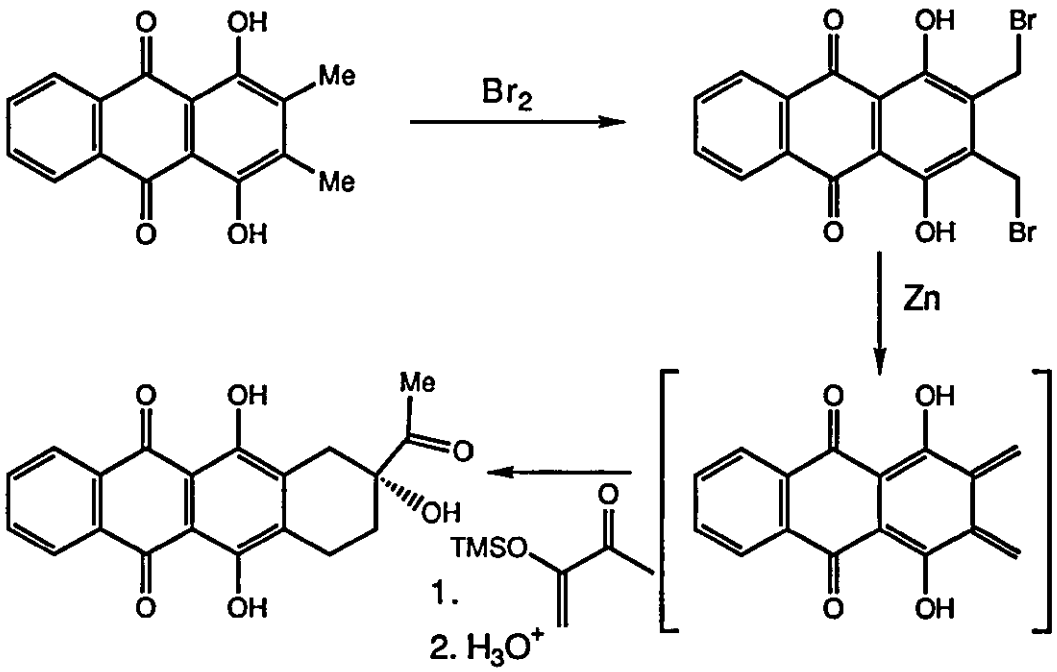


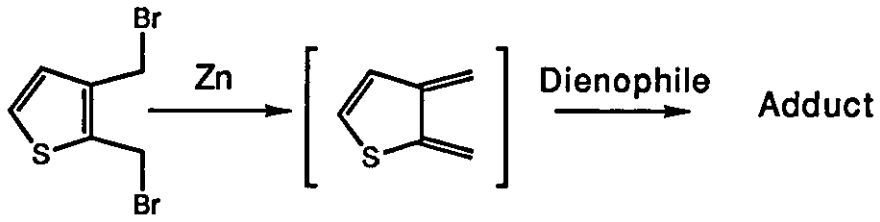
Figure 11.

Cava *et al*[37] used an anthraquinone-derived *o*-xylylene as the basis of a simple synthesis of the (±)4-demethoxydaunomycinone skeleton (Scheme 26).



Scheme 26

The thiophene analogue of *o*-xylylene has also been generated *in situ* by Chadwick[42] and Storr[43] and trapped by a series of dienophiles as their Diels-Alder adducts. The intermediate diene was generated from its dibromo derivative (Scheme 26, Figure 12) and also its trimethylsilyl oxazoline precursor (Scheme 27).



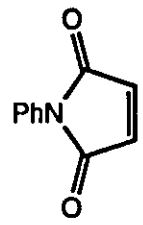
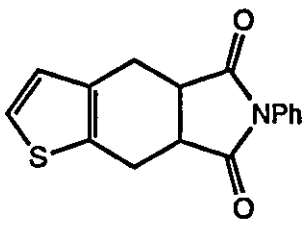
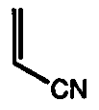
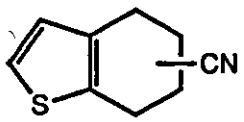
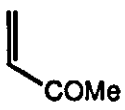
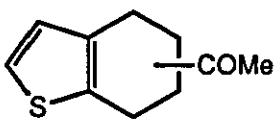
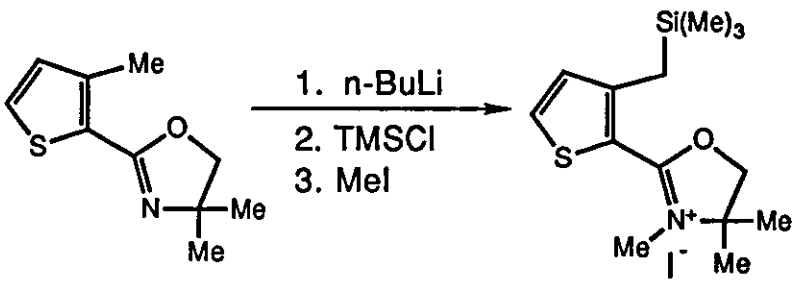
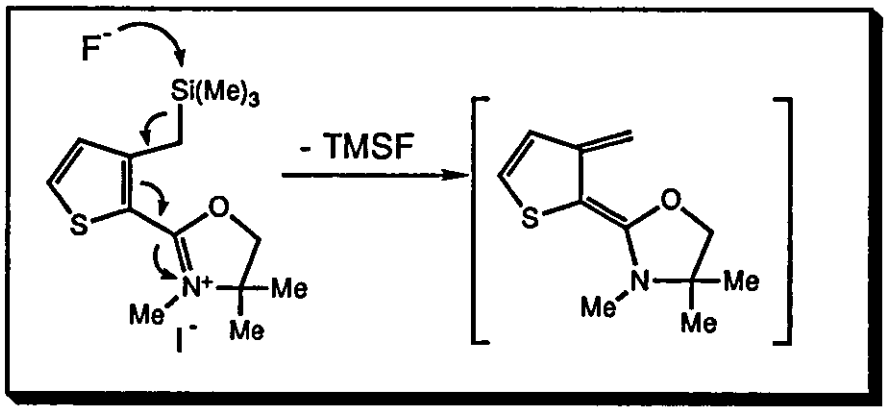
Dienophile	Product	Yield %
		60
		60
		50

Figure 12



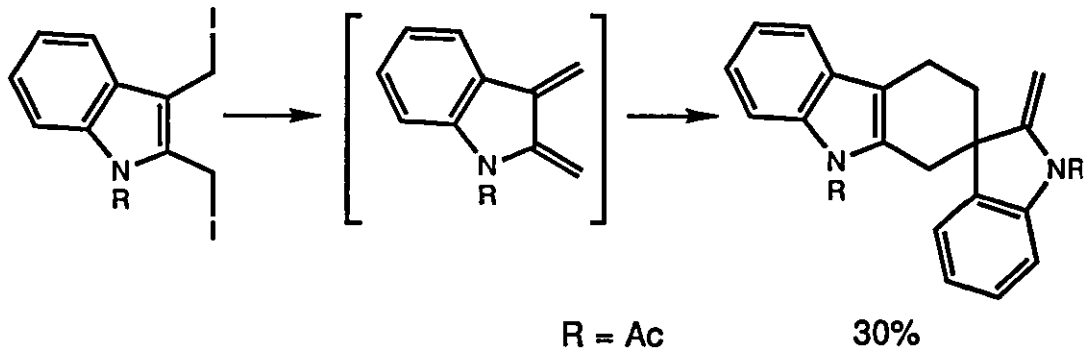
Scheme 27

The diene was generated *in situ* by fluoride induced elimination of the trimethyl silyl group from the quaternary ammonium salt (Scheme 28).



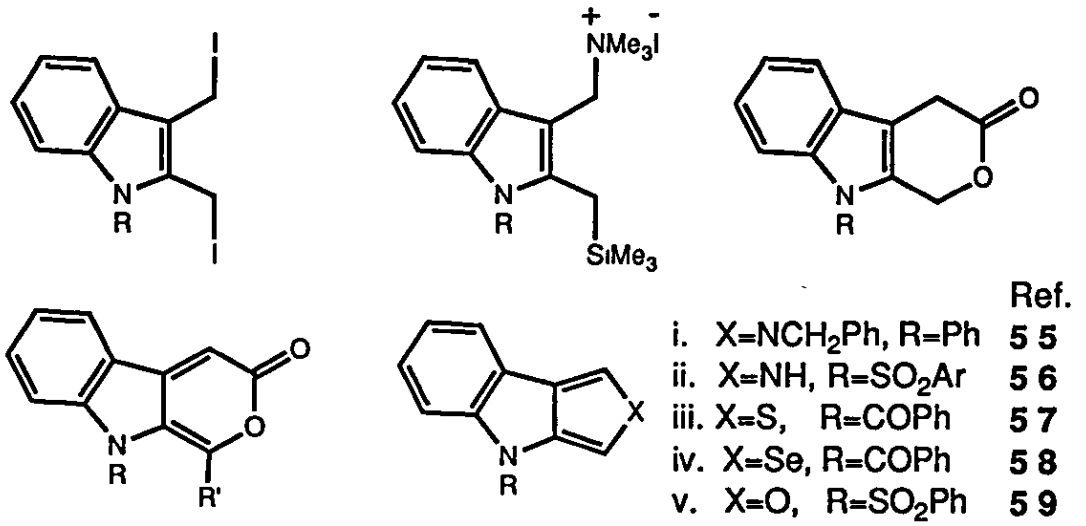
Scheme 28

Since the publishing of this pioneering work, the thiophene analogue of *o*-xylylene has found considerable use in the synthesis of thiophene containing natural products[44].
The furan *o*-quinodimethanes have also been extensively explored independently by several groups[45,46] and shown to have similar potential as versatile synthetic building blocks.
Of more relevance to this study however, is the case of indole-2,3-quinodimethanes which unsurprisingly, is also the subject of much past research. A short review by Dimitrienko[47] gives a good introduction to the methods of generation of the diene and some Diels-Alder reactions with unsymmetrical dienophiles, also the isolation of the dimer shown in Scheme 29.



Scheme 29

Once again, the synthetic potential of this chemistry led to this area of research attracting the attention of several groups since the original work by Plieninger,[48] including Magnus[49,50], Moody[51] and others.[52,53,54,54a]. The work outlined above covers both precursors to, and stable analogues of, indole-2,3-quinodimethane (Figure 12).



	Ref.
i. X=NCH_2Ph, R=Ph	55
ii. X=NH, R=SO_2Ar	56
iii. X=S, R=COPh	57
iv. X=Se, R=COPh	58
v. X=O, R=SO_2Ph	59

Figure 12

Our efforts focussed specifically on the 1,4-Dihydropyrano[3,4-*b*]indol-3-one (**III**) and its unsaturated analogue, pyrano[3,4-*b*]indol-3-one (**IV**). (Figure 13)

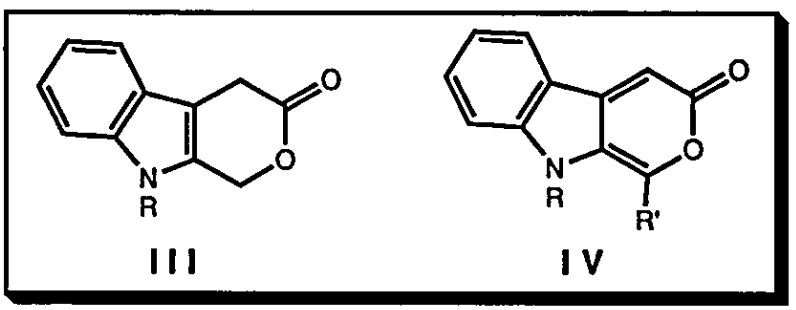
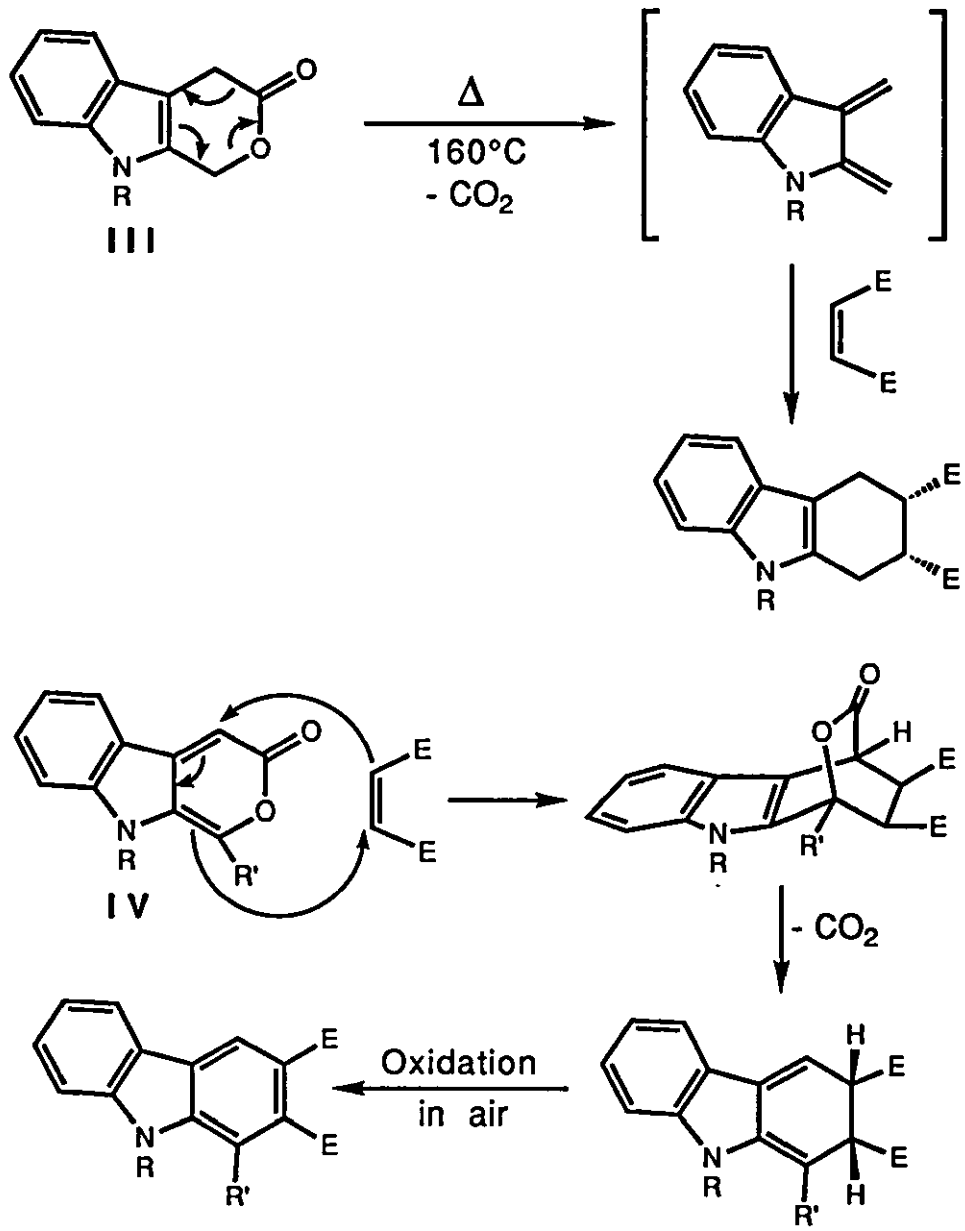


Figure 13

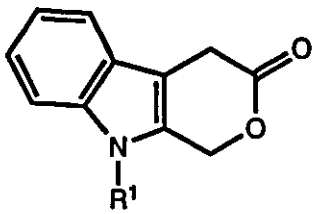
The Diels-Alder reactions of these two species give rise to adducts containing the 6-membered C ring (Scheme 6) but the precursors **III** and **IV** undergo the reactions in different ways.

The pyranone **III** loses CO_2 on heating to 160°C to give the unstable indole-2,3-quinodimethane (Figure 10) which is trapped in situ by a suitable dienophile to give products based on 1,2,3,4-tetrahydrocarbazole. The pyranone **IV** however is at a higher oxidation level and undergoes a Diels-Alder cycloaddition reaction followed by a loss of CO_2 to give products also at a higher oxidation state based on carbazole itself (Scheme 30).



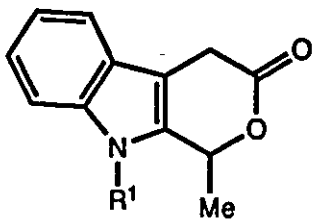
Scheme 30

The final aeriel oxidation is usually by-passed by using an acetylene instead of an olefin as the dienophile to give the carbazole directly. Before the use of *o*-xylylenes were applied to the synthesis in question there was an area of Diels-Alder chemistry to be clarified concerning the scope and limitations of the reaction and the influence of the indole protecting group. Thus, the aim was to synthesise the structures **35**, **36**, **39** and **40** (Figure 14) to study several examples.



35 R^1=H

36 R^1=CO_2Me

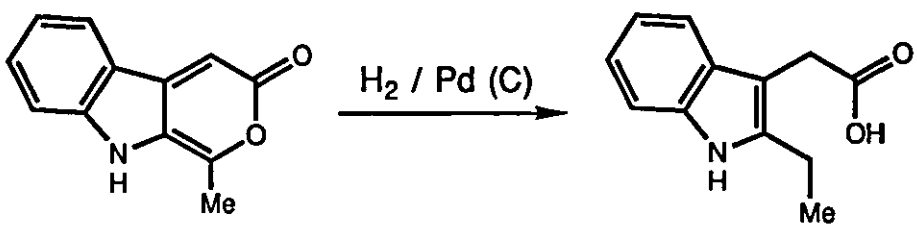


39 R^1=H

40 R^1=CO_2Me

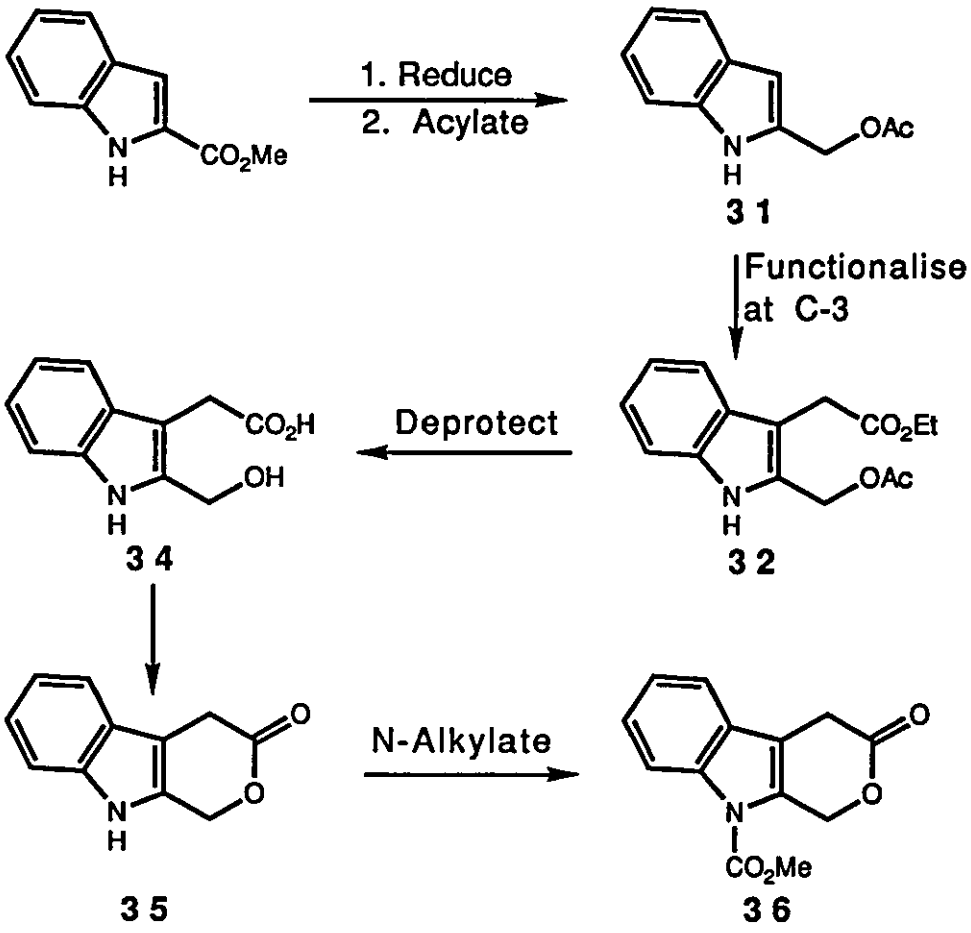
Figure 14

Structures **39** and **40** are the reduced forms of the pyrano[3,4-*b*]indol-3-one but simple hydrogenation of the parent structure leads to very poor yields and in most cases complete over-reduction[60] (Scheme 31).



Scheme 31

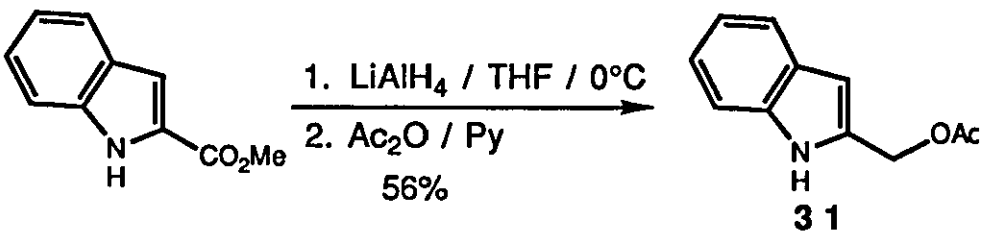
Since the hydrogenation was unpredictable and low yielding, the lactone had to be constructed from the commercially available methyl indole-2-carboxylate and the following scheme was proposed (Scheme 32).



Scheme 32

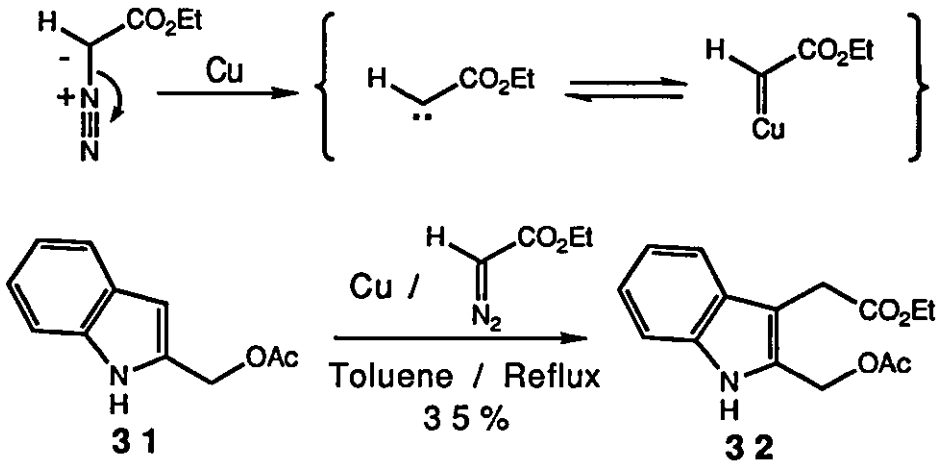
Reduction of methyl indole-2-carboxylate to indole-2-methanol was carried out using lithium aluminium hydride in dry THF / ether at 0°C in 87% yield. Indole-2-methanol was very unstable and extensive decomposition began as soon as the product was isolated, even at low temperatures. Subsequent batches were used directly in the next reaction where the presence of the acyl group gave a product that was stable and easily manipulated. Acylation of indole-2-methanol was effected with acetic anhydride in pyridine solution at room temperature to afford the acetate **31** in 64% yield. (Scheme 33)

Introduction of a 2-carbon fragment to the C-3 position of **31** proved to be low yielding (35%) despite efforts at optimisation of the process.



Scheme 33

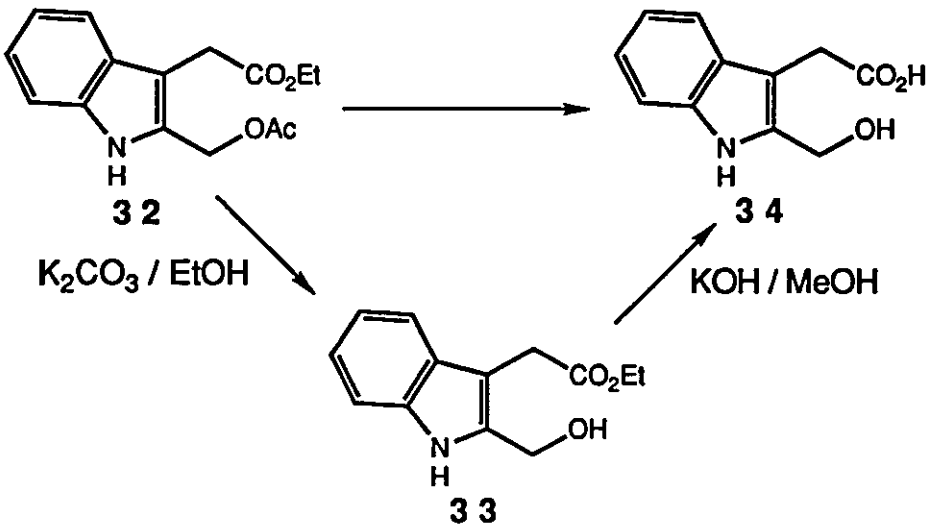
The copper catalysed decomposition of ethyl diazoacetate leads to the stabilised carbene which is then able to carry out an insertion reaction with, in this case an indole nucleus (Scheme 34).



Scheme 34

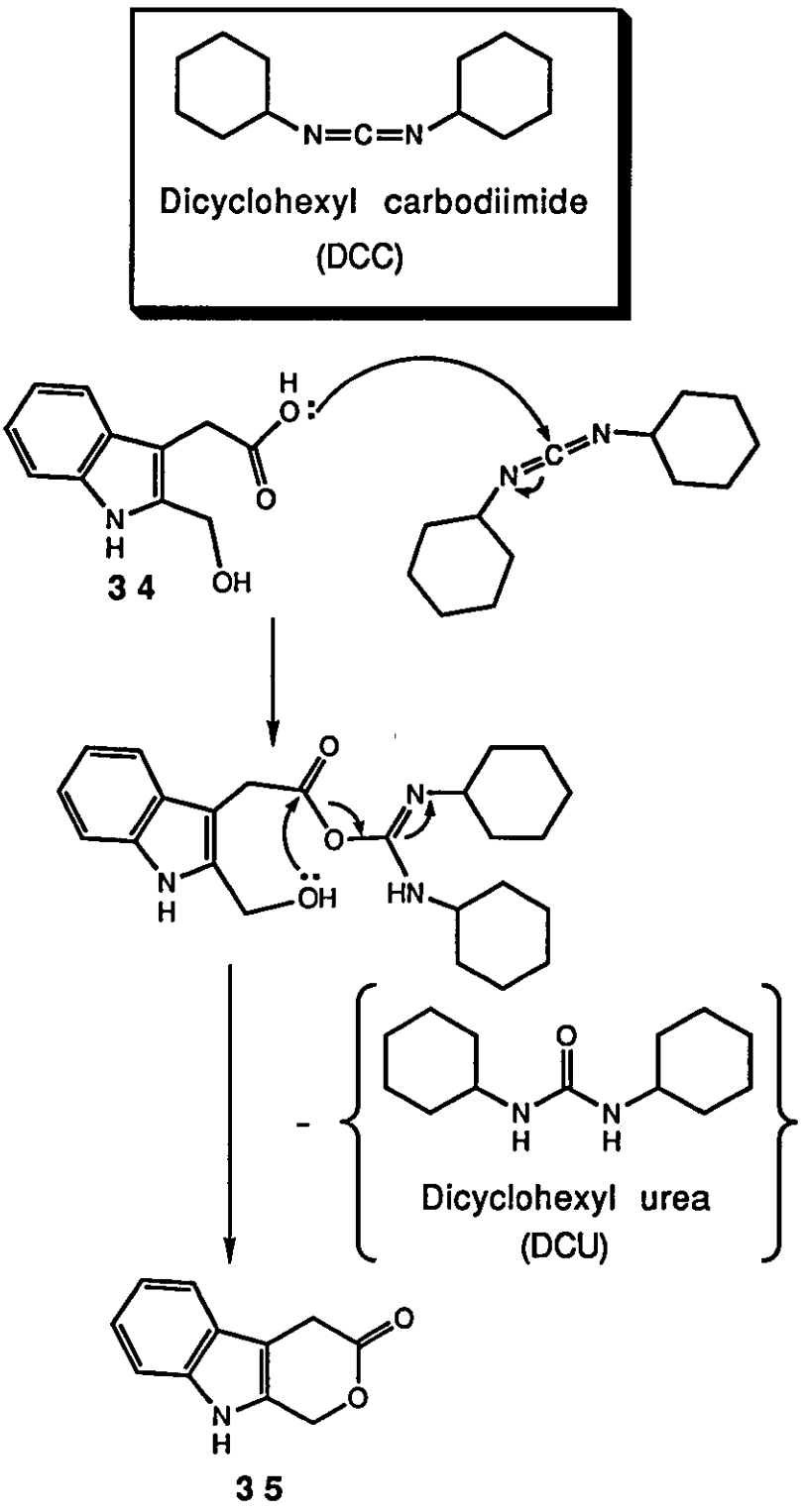
The reaction in Scheme 34 was carried out in refluxing distilled toluene using freshly precipitated copper as the catalyst for the decomposition. Attempts to improve the reaction using rhodium(II) acetate as an alternative catalyst were unsuccessful. Similarly unsuccessful was the attempted Reformatsky reaction using ethyl bromoacetate / zinc chloride and also the improved method using *bis*-trimethylsilylacetamide as an acid scavenger. With all the carbon atoms in place, there remained only the protecting groups to be removed for the cyclisation **34**→**35** to take place. However when **32** was treated with methanolic potassium hydroxide to hydrolyse both the ethyl ester and the acetate group only the characteristic bright red decomposition products were obtained. Judging the reaction conditions to be too harsh for the labile

hydroxymethyl group at the C-2 position the deprotection was carried out in two stages via an intermediate **33** to avoid the use of excess base (Scheme 35)



Scheme 35

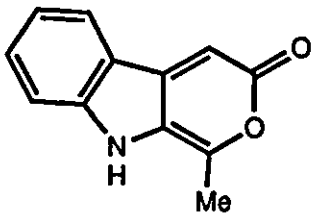
Unfortunately the inherent instability found in the structure **33** was also noted in the hydroxy acid **34** and attempts at extensive purification procedures resulted in severe decomposition. Subsequent batches were therefore used immediately with no further purification. Lactonisation of **34**→**35** has been carried out by Shah[60] previously, using *iso*-butyl chloroformate / triethylamine but in our hands the reaction proved to be unpredictable and invariably low yielding (~15%), and therefore a more efficient alternative was sought. Varying the reaction temperature and the base had little effect as did the formation of the mixed anhydride with trifluoroacetic anhydride. The problem was finally overcome by the use of the peptide coupling agent dicyclohexyl carbodiimide (DCC) in methylene chloride with pyridine as the base but since the levels of pyridine proved to be critical the reaction was carried out with pyridine as the solvent. The coupling reaction proceeds as shown in Scheme 36 with dehydration of the hydroxy acid **34** resulting in the formation of the lactone **35** and the hydrated form of DCC, dicyclohexyl urea (DCU).



Scheme 36

The lactonisation of **34→35** became slow as the DCU precipitated out of solution and to drive the reaction to completion it was necessary to add a catalytic amount of DMAP and warm the reaction to 50°C to give an overall yield for **34→35** of 40%.

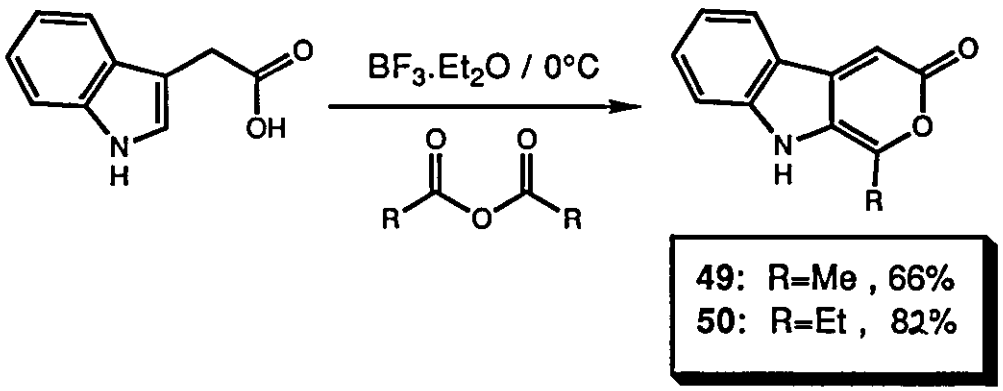
Acylation of **35** took place with dimethyl pyrocarbonate $(MeO_2C)_2O$ in acetonitrile with DMAP as the base to give **36** in 91% yield.
A similar route to **39** and **40** was discounted in favour of a simpler course starting from the easily accessible[61] pyranoindolone **49** (Figure 15).



49

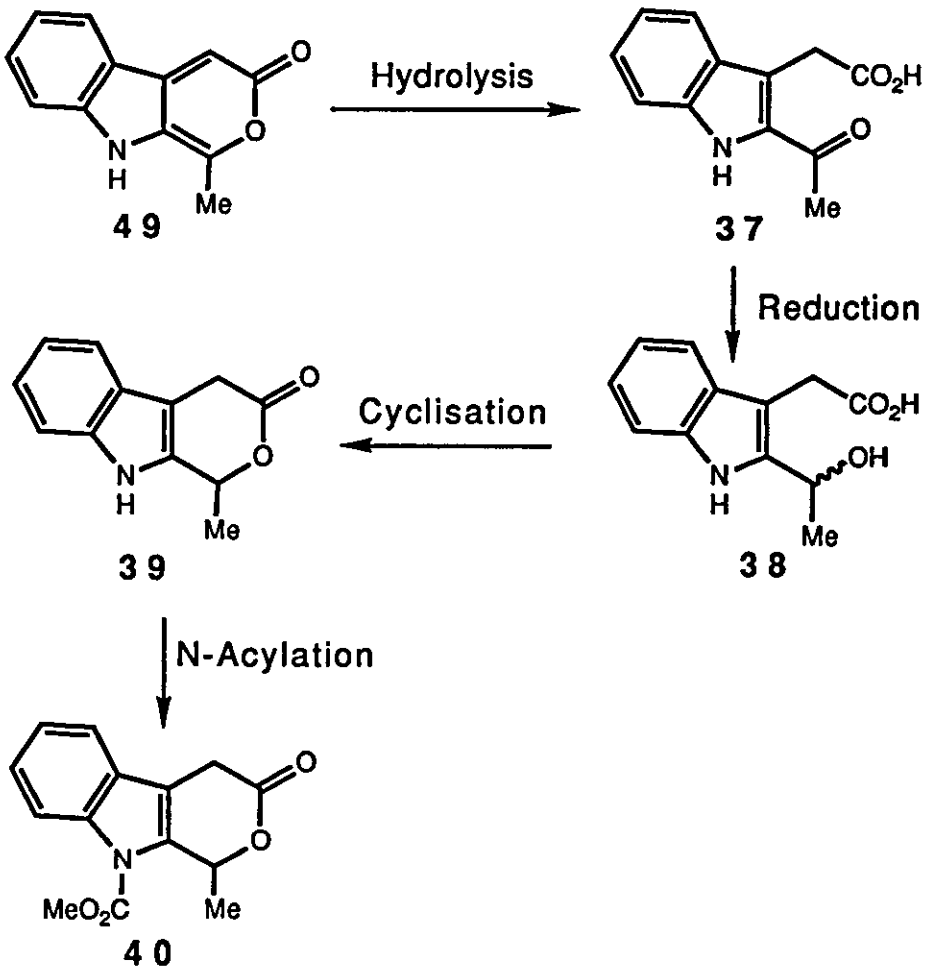
Figure 15

The pyranone **49** and other derivatives are easily prepared in good yield by the action of an aliphatic acid anhydride on indole-3-acetic acid in the presence of boron trifluoride etherate (Scheme 37).[60]



Scheme 37

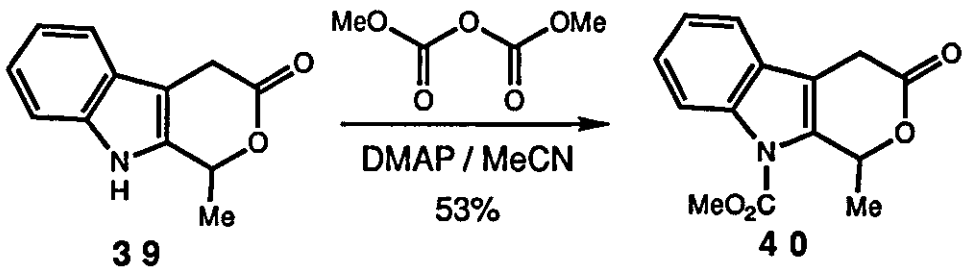
The reported syntheses of **49** and **50** proved to be reliable up to a 25g scale, and the following scheme for the synthesis of **39** and **40** was proposed starting from **49** (Scheme 38).



Scheme 38

Hydrolysis of the pyranone **49** was carried out with a refluxing aqueous sodium hydroxide / methanol solution to give **37** which was easily recrystallised in 90% yield. Mild reduction of the acetyl group at C-2 was effected with sodium borohydride in aqueous THF (to prevent reduction of the acetic acid group at C-3) to give **38** which proved to be as unstable as its counterpart **34** and as a result was used without purification immediately in the next reaction. Cyclisation of **38**→**39** with *iso*-butyl chloroformate failed altogether, so the method of cyclisation developed for the preparation of **35** using DCC was also used in this case.
The lactonisation proceeded without incident to give the 1,4-dihydropyranone **39**, and an overall yield for the conversion of **37**→**39** of 37%. Removal of the by-product, DCU, in this example was not trivial and required several purification steps and recrystallisations. Protection of the indole NH (Scheme 39) was

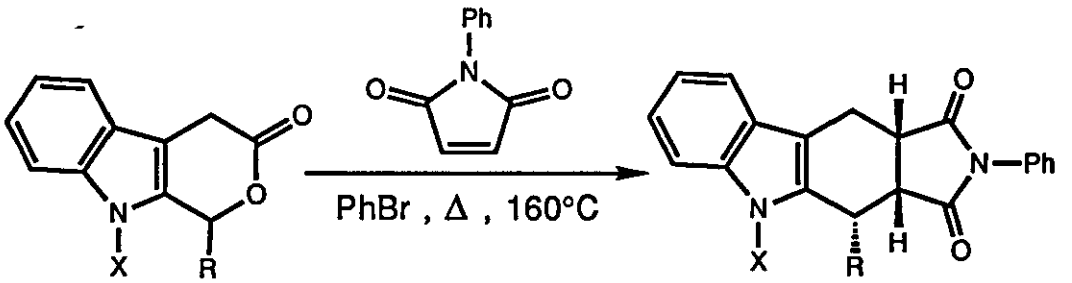
carried out using the same method as for the preparation of **40** in 53% yield, which contrasts sharply with the corresponding acetylation which was reported to proceed in only 9% yield.[47]



39 **40**

Scheme 39

For the study of the Diels-Alder cycloadditions[62] the dienophile was present in the reaction mixture while the CO_2 was being eliminated to ensure that the reactive diene was exposed to the dienophile for the maximum possible time. The dienophile chosen for the initial study was N-phenylmaleimide (NPM). (Scheme 40)



41-44

Scheme 40

The reactions were all carried out under dry nitrogen and the products isolated by silica gel flash chromatography. The results from the Diels-Alder reactions of **35**, **36**, **39** and **40** with NPM are summarised in Figure 16.

Indole lactone	X	R	Time / h	Product	Yield / %
35	H	H	5	**41**	58
36	CO_2Me	H	26	**42**	19
39	H	Me	1	**43**	50
40	CO_2Me	Me	6	**44**	86

Figure 16

The assignment of structures **41-44** (Scheme 40) were based on the nOe experiments carried out on **44** which clearly bears out the configuration shown in the part structure (Figure 17).

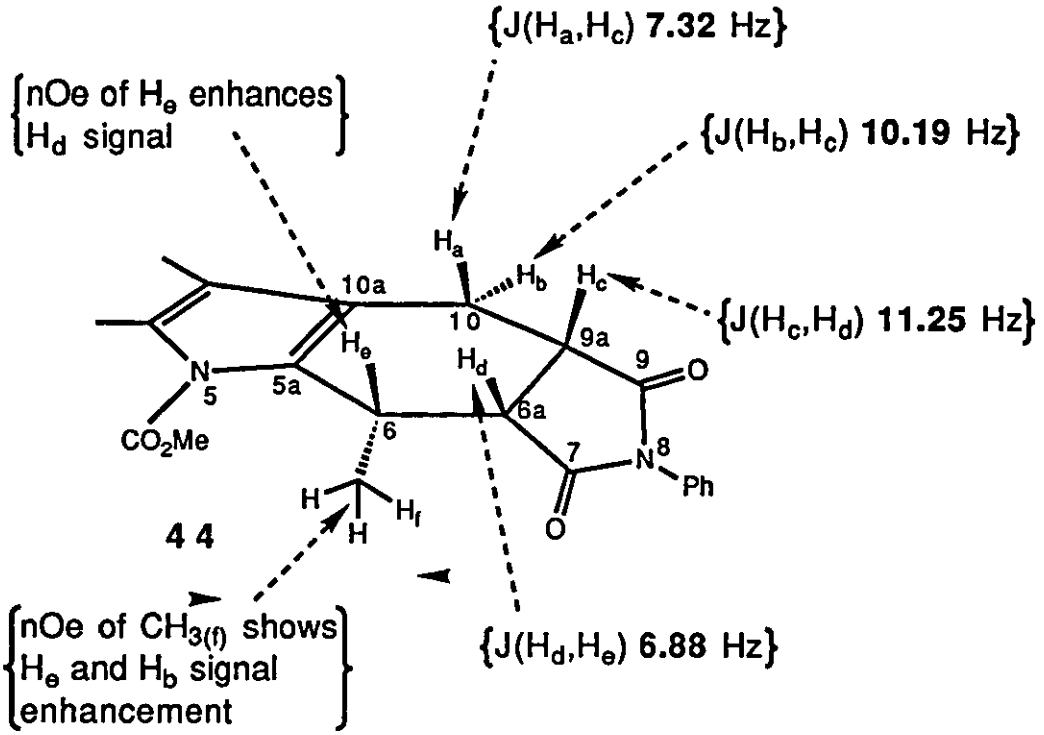
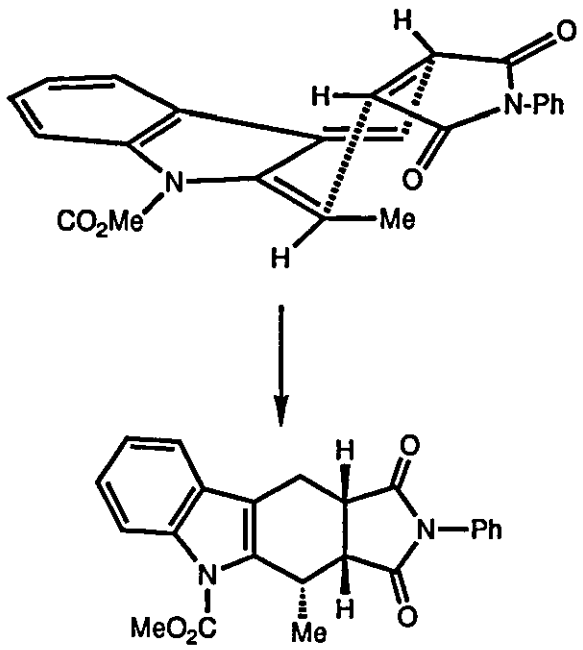


Figure 17

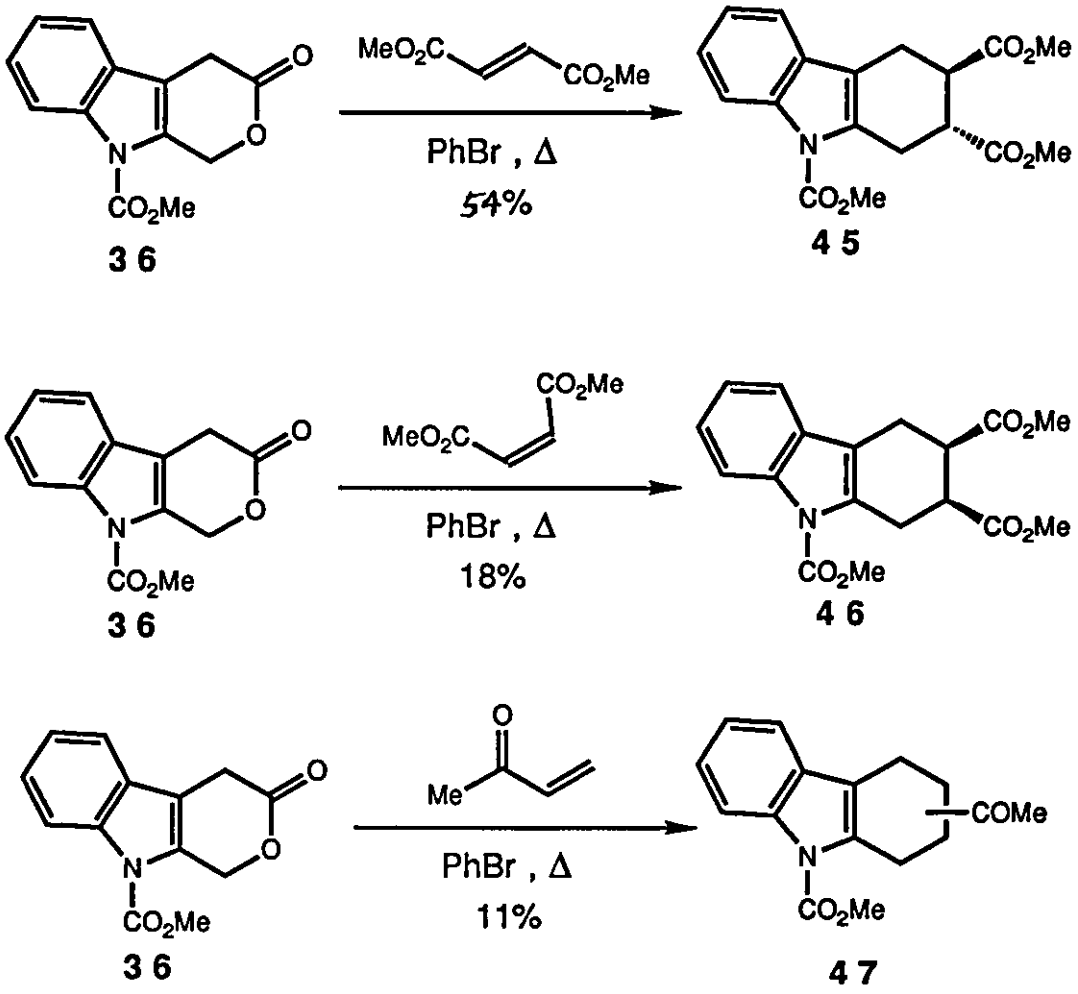
The unexpected coupling constants $J(H_a,H_c)$ and $J(H_b,H_c)$ suggest a bond distortion between C-9a and C-10 of ~15° from normal. Since only one isomer was isolated from the cycloaddition the reaction must have proceeded via the transition state shown (Figure 18) leading to the single product **44**.



44

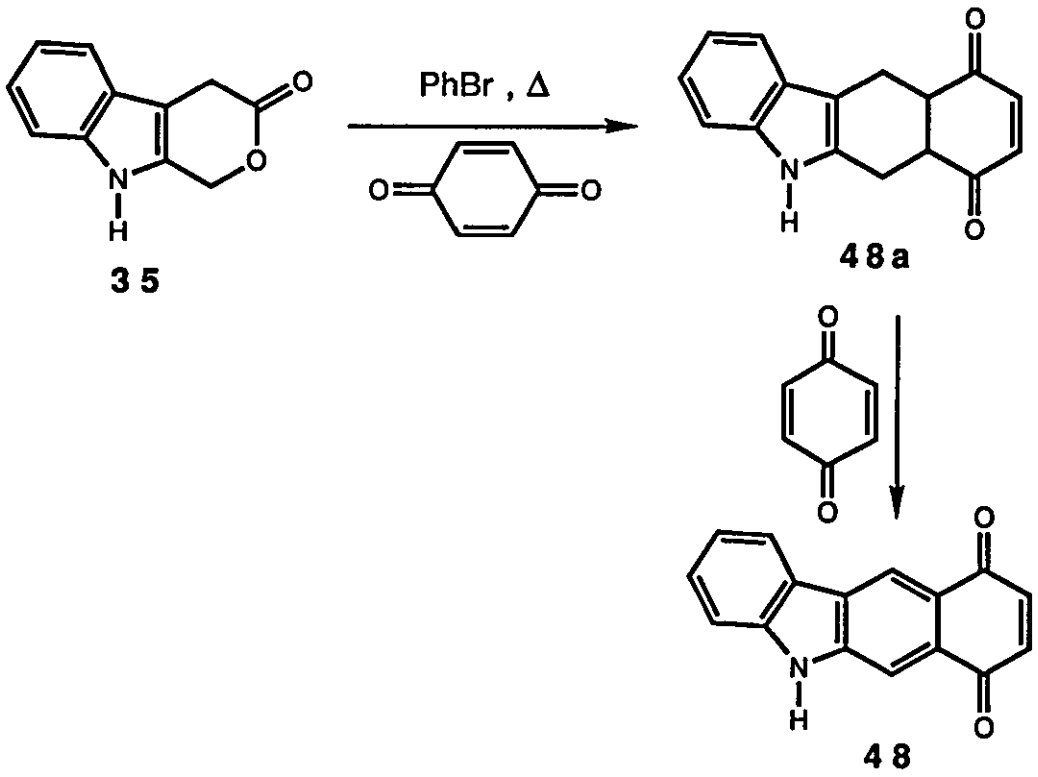
Figure 18

The trend revealed in Figure 16 concerning the N-methoxycarbonyl group was shown to hold true for other reactions, in that reactions proceeded much slower but the number of side products were less. Other reactions were carried out to investigate the scope of this reaction (Scheme 41) with several types of dienophile.
Reaction of **36** with both dimethyl fumarate and dimethyl maleate gave the expected adducts **45** and **46** with retention of the stereochemical integrity of the dienophiles. Distinction between the 2- and 3-acetyl tetrahydrocarbazoles **47** was uncertain and an accurate assignment could not be made.



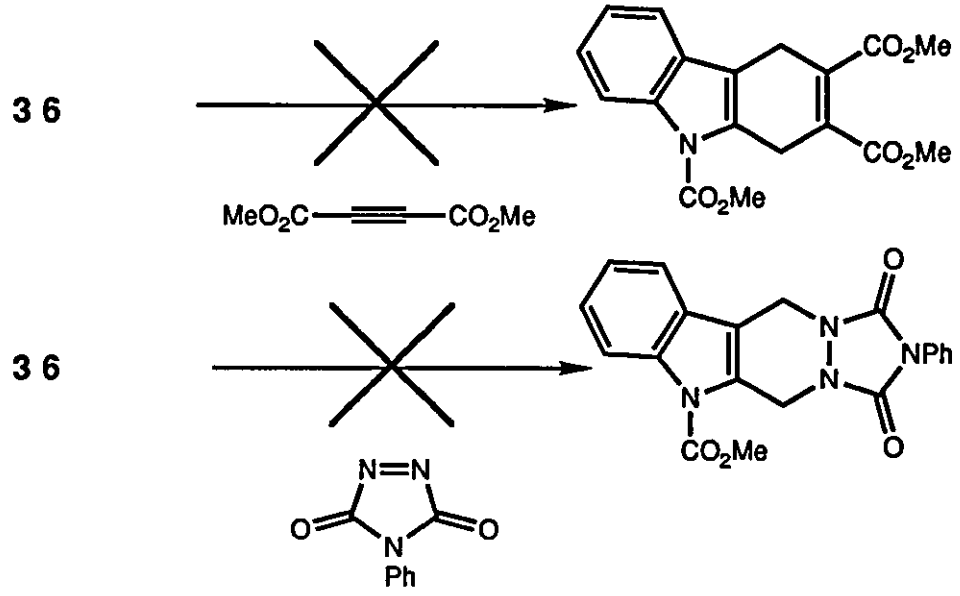
Scheme 41

Unfortunately the literature contains conflicting reports on related reactions, for example, the reaction of the N-acetyl derivative of **39** with methyl vinylketone is reported to give 2,9-diacetyl-1,2,3,4-tetrahydrocarbazole with 99:1 regioselectivity[47] whilst the N-benzoyl derivative of **35** is reported to give a 4:1 mixture of the corresponding 3- and 2-acetyl tetrahydrocarbazoles.[54] A comparison of the reactivities of **36** and **40** with the results in Scheme 41 was not possible since the reaction of **40** with dimethyl fumarate, dimethyl maleate or maleic anhydride led to the formation of complex mixtures. Reaction of **35** with 1,4-benzoquinone (3 equivalents) gave the benzo[*b*]carbazole **48** from oxidation of the intermediate tetrahydrobenzo[*b*]carbazole **48a** in 45% yield (Scheme 42)

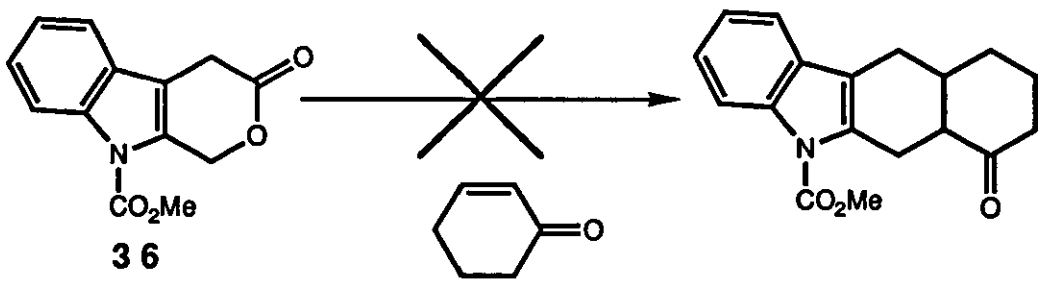


Scheme 42

Although the reactions outlined in Schemes 40-42 and Figures 16-18 proceeded to give the expected adducts with retention of dienophile stereochemistry, attempts to improve the yield or to widen the scope to a more synthetically useful area proved to be in vain (Scheme 43).



Scheme 43



Scheme 43 (continued)

The attempted reaction of **36** with 2-cyclohexen-1-one was of particular interest since the resulting tetracyclic product could be manipulated towards the quinone structure in question. Due to the failure of the initial reaction and the generally poor yields found in similar reactions, the use of these particular indole-2,3-dimethane precursors was rejected.

The generation of the aromatic benzo[*b*]carbazole **48** from the Diels-Alder reaction of **35** with 1,4-benzoquinone (Scheme 42) followed by further oxidation by the excess dienophile led to further considerations of cycloaddition reactions in particular the use of the pyrano[3,4-*b*]indol-3-one (**IV**) (Figure 13). On closer examination of the method of preparation, it is apparent that generation of the pyrano[3,4-*b*]indol-3-one with no substituent (Figure 19, R ≠ H) is far from trivial since the reaction requires a carboxylic acid anhydride.

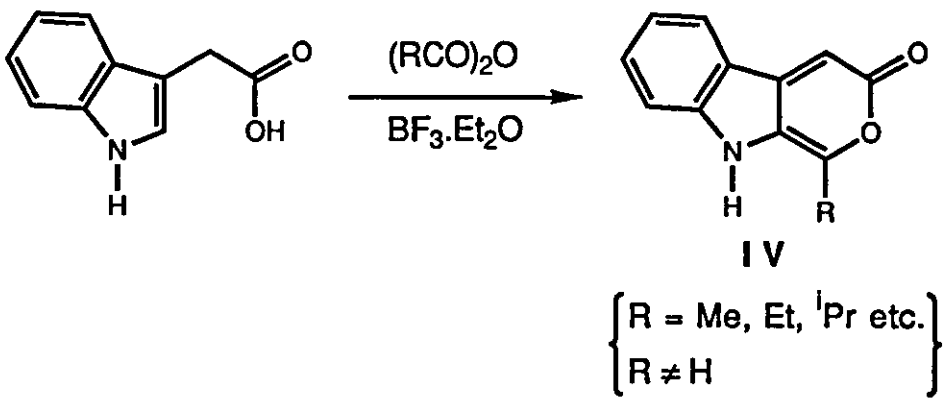
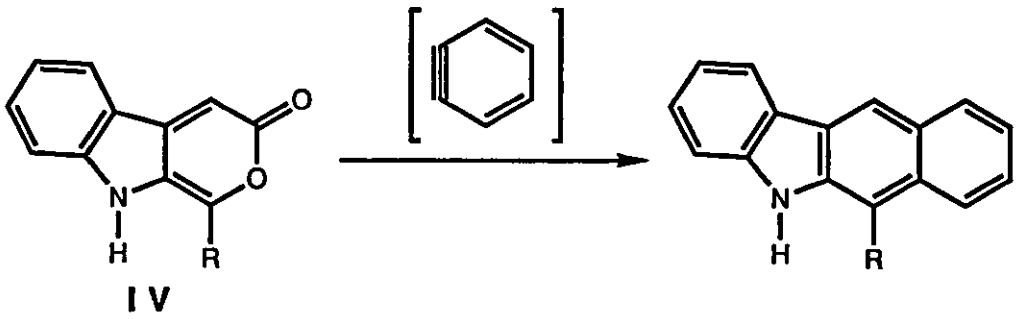


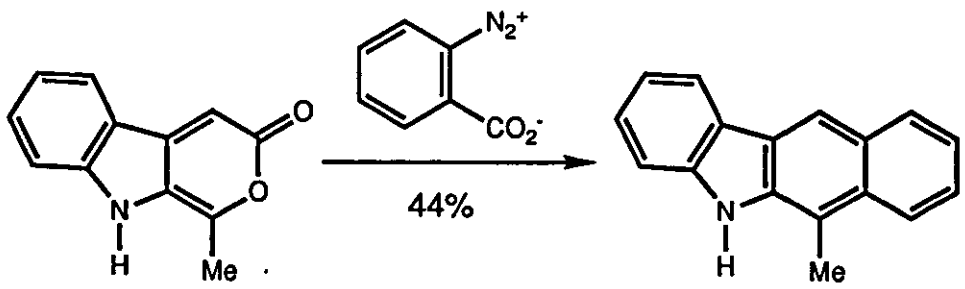
Figure 19

While this in itself is not a problem where most carboxylic acids are concerned there is, as yet, no evidence of the existence of formic anhydride other than as a formic-acetic mixed anhydride[63]. It is therefore necessary to consider the removal of the unwanted side chain in any proposed synthetic strategy. The scheme that was next considered involved the Diels-Alder reaction of the general pyrano[3,4-*b*]indol-3-one (IV) with the highly reactive dienophile benzyne (Scheme 44).



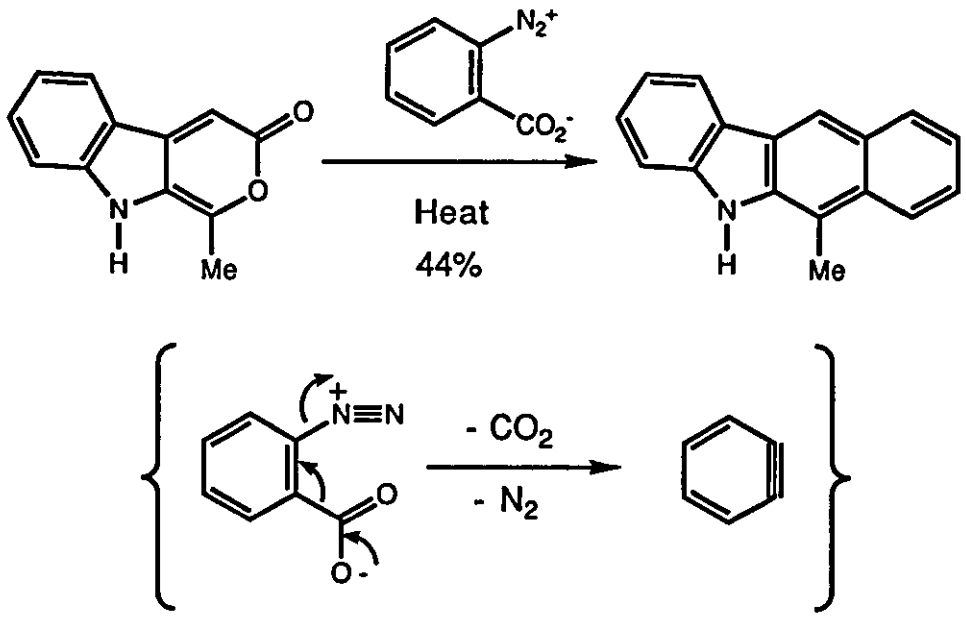
Scheme 44

Successful examples of this reaction have been demonstrated by Moody,[64] (Scheme 45) and benzyne generation methods improved by Simamura[65] (Scheme 46).



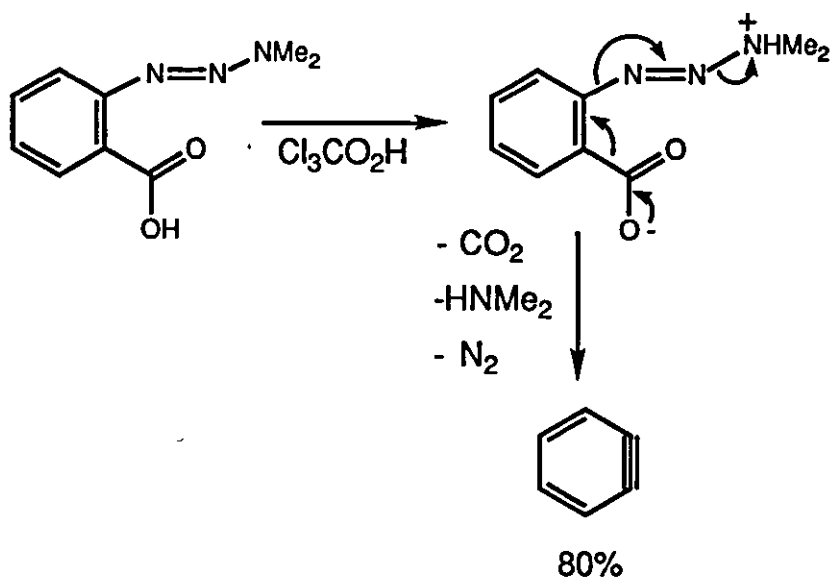
Scheme 45

Benzyne generation from anthranilic acid itself is seldom undertaken due to the explosive nature of the reaction and the work by Simamura *et al* showed that aromatic triazenes, although highly carcinogenic, are stable and efficient sources of benzyne.



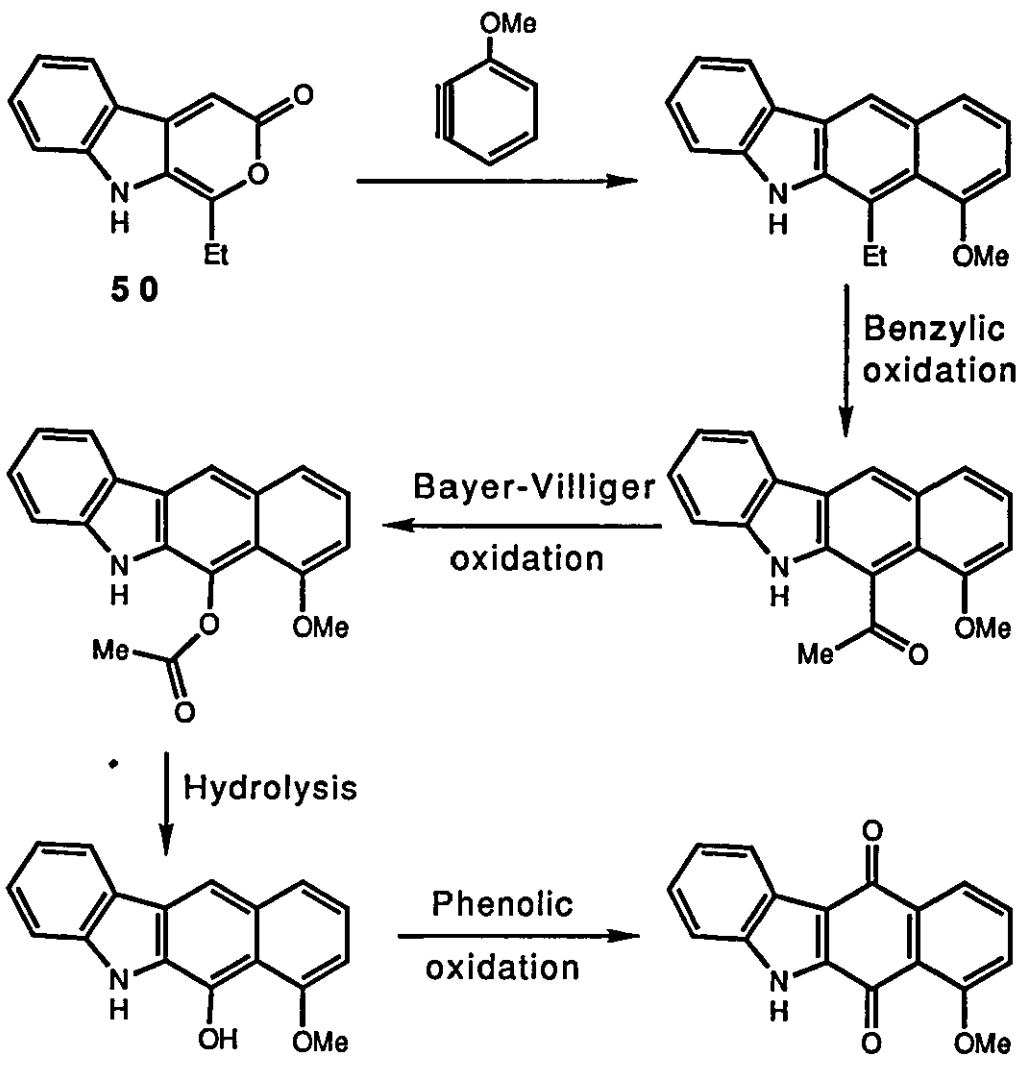
Scheme 46

The more effective precursor suggested by Simamura is 1-(2-carboxyphenyl)-3,3-dimethyltriazene, which is commercially available or easily prepared from anthranilic acid. Benzyne is generated by the decomposition of the triazene by trichloroacetic acid in benzene (Scheme 47).



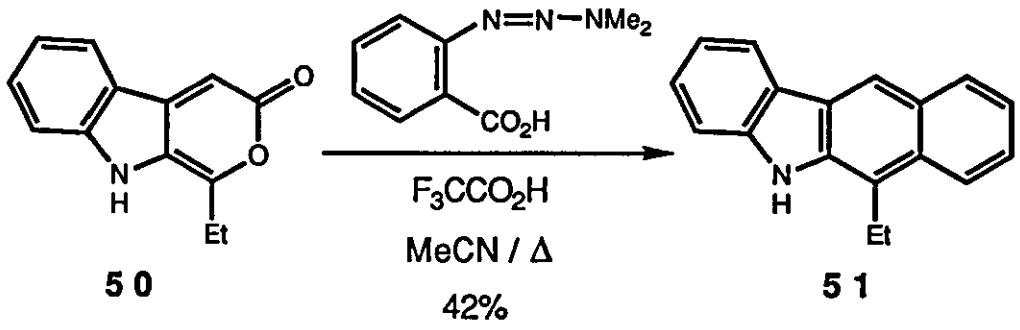
Scheme 47

On the basis of the precedent for the Diels-Alder reactions and the oxidations required the following scheme was considered (Scheme 48).



Scheme 48

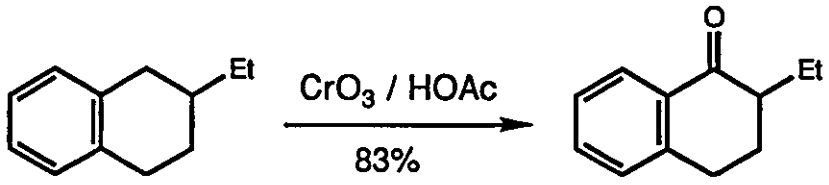
Before the problem of synthesising 3-methoxybenzyne was addressed, model studies on unsubstituted benzyne were undertaken. The 1-ethylpyrano[3,4-*b*]indol-3-one **50** was prepared under the standard conditions[60] of boron trifluoride etherate / propionic anhydride in 80% yield. The Diels-Alder cycloaddition of benzyne to the pyranone **50** was carried out with 1-(2-carboxyphenyl)-3,3-dimethyltriazene / trifluoroacetic acid in refluxing acetonitrile to give the characteristically fluorescent benzo[*b*]carbazole **51** in a modest 65% yield (Scheme 49).



50 **51**

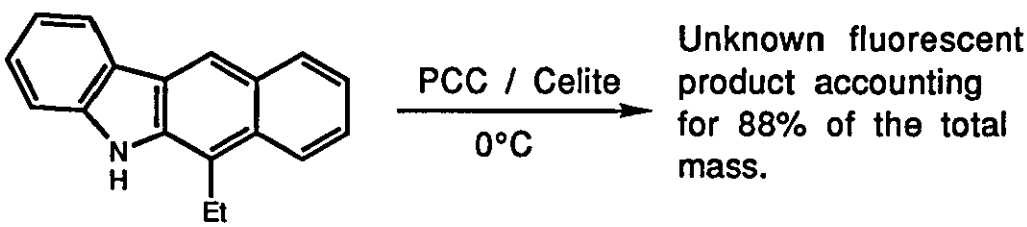
Scheme 49

Allylic and benzylic oxidations have been effectively carried out in the oxidation of tetralins using the aqueous CrO_3 / acetic acid[66] system in yields typically exceeding 65% (Scheme 50).



Scheme 50

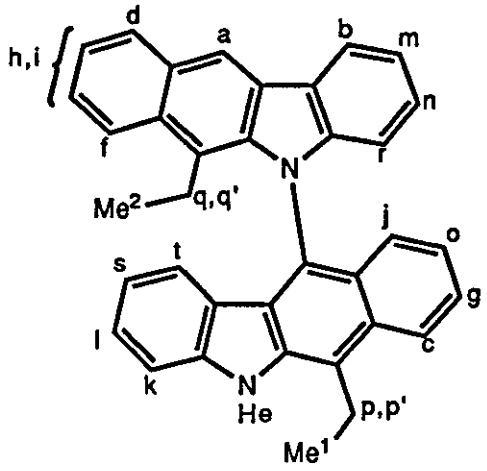
However, when the system described in Scheme 50 was applied to the benzo[*b*]carbazole **51**, the result was extensive decomposition despite attempts to moderate the conditions by diluting the chromic acid solution. A milder oxidising agent that has also found considerable use in tetralin and decalin oxidations is pyridinium chlorochromate[67] (PCC). In particular, the authors report the oxidation of ethylbenzene to acetophenone with PCC in 71% yield. The carbazole **51** was treated with PCC / Celite (Scheme 51) and a fluorescent product **52** obtained, the nmr analysis of which contained two sets of near identical signals.



51 **52**

Scheme 51

Mass spectrometry of the sample revealed the structure to have a mass of twice that expected, so a dimerisation must have taken place. Detailed nOe, ^1H-^1H, and decoupling experiments finally revealed the structure of **52** to be a simple dimer of two unoxidised molecules of **51** (Figure 20).

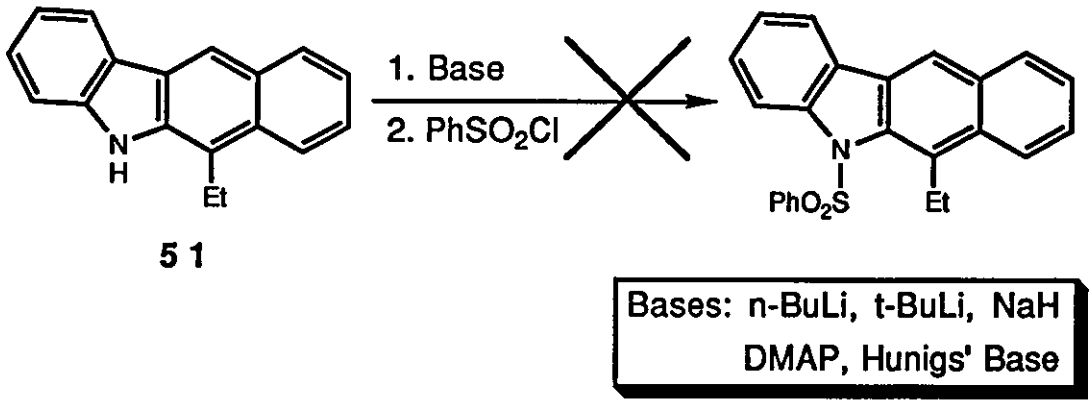


52

Figure 20

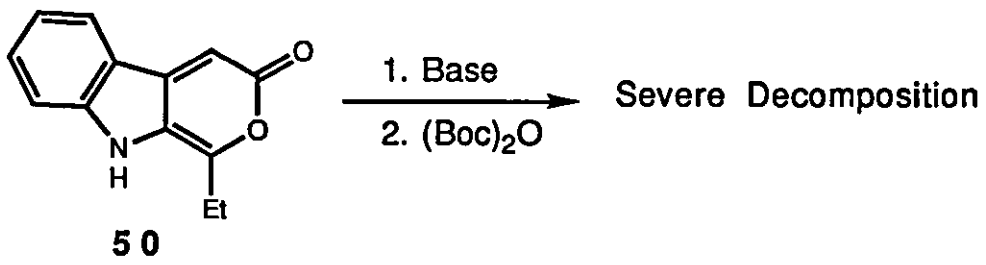
The dissimilarity of the methylene protons q and q' arise from the chirality that is a direct result of the doubly hindered inter-ring bond. The unexpectedly low frequencies of the signals r, s and t (δ 6.75-6.60) are due to paracyclophane type inter-ring shieldings. The near coincidence of the signals h and i lead to the unexpected complexity of resonances d and f.

The formation of the dimer **52** must have originated from coupling resulting from the radical conditions induced by the PCC, so to eliminate this, a protecting group for the indole NH must be incorporated. Endeavours to deprotonate the benzo[*b*]carbazole **51** with DMAP, Hunigs' base and sodium hydride (Scheme 52) were unsuccessful, yielding only unreacted starting materials. Stronger bases such as t-BuLi, n-BuLi and LDA resulted in deprotonation of the ethyl side chain and consequent decomposition. Efforts were then focussed on the synthesis of the carbazole **51** with an existing N-protecting group by incorporating a t-Boc group into the pyranone precursor **50**.

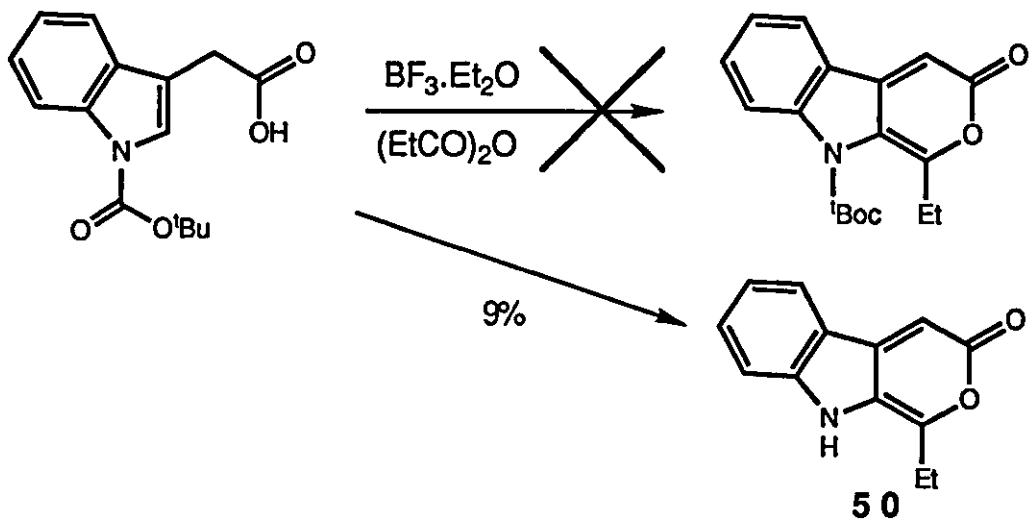


Scheme 52

Treatment of the pyranone **50** with a similar variety of bases also resulted in extensive decomposition (Scheme 53) and it was necessary to look back even further to N-protection of indole-3-acetic acid



Scheme 53



Scheme 54

A sample of 1-(*t*-butyloxycarbonyl)indole-3-acetic acid was

treated as in Scheme 37 with boron trifluoride etherate / $(EtCO)_2O$ in an attempt to form the Boc-protected pyranone (Scheme 54), but the conditions of the reaction facilitated deprotection and only the unprotected pyranone **50** was isolated in a very poor yield.
A protecting group that was resistant to conditions as harsh as $BF_3.Et_2O$ would be extremely difficult to remove at a later stage of the synthesis and since the question of 3-methoxybenzyne had not yet been addressed (probably not a trivial synthesis), work on this route was suspended.

2.3 Other Disconnections.

After the lack of success of the two bond disconnections discussed in **2.1→2.2**, our attention turned to single bond disconnections and the synthons derived from these. Considering the target molecule once more there are many possible retrosynthetic analyses from the breaking of bonds a, b, c and d. The first two considerations are outlined in Figure 21.

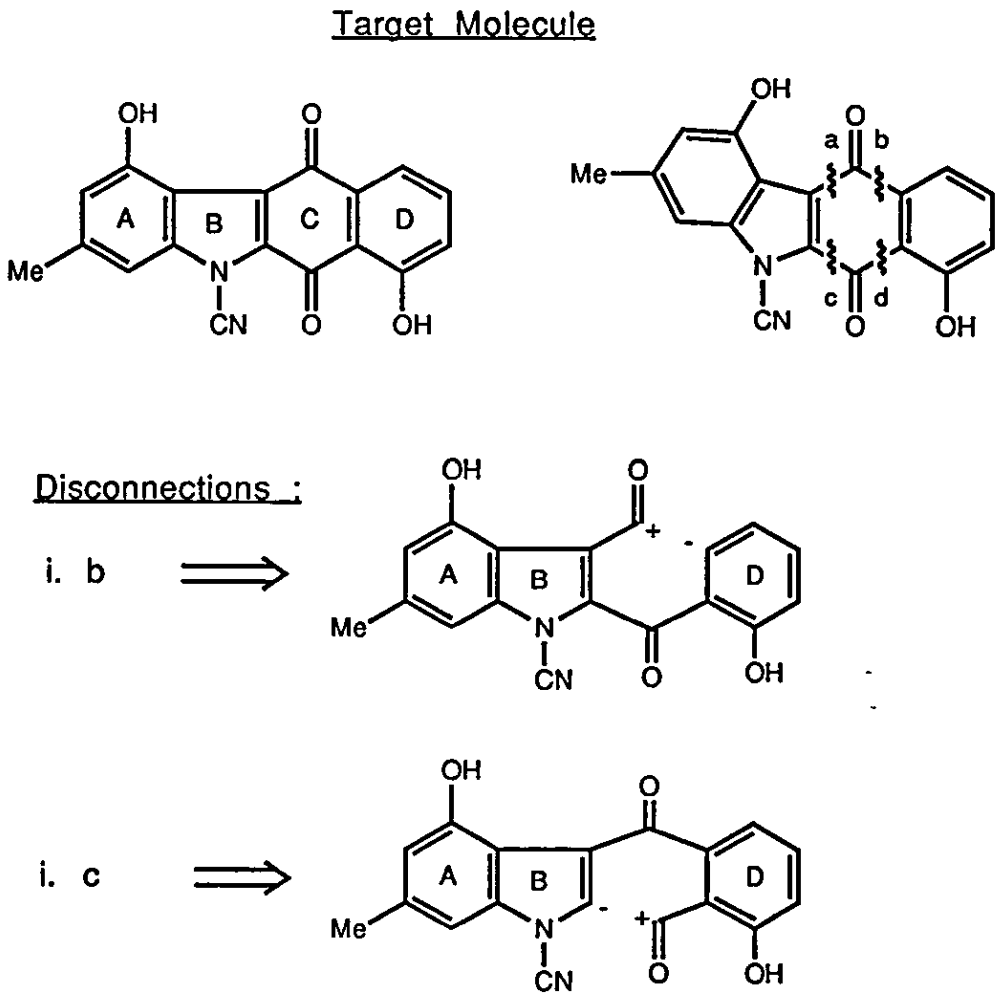
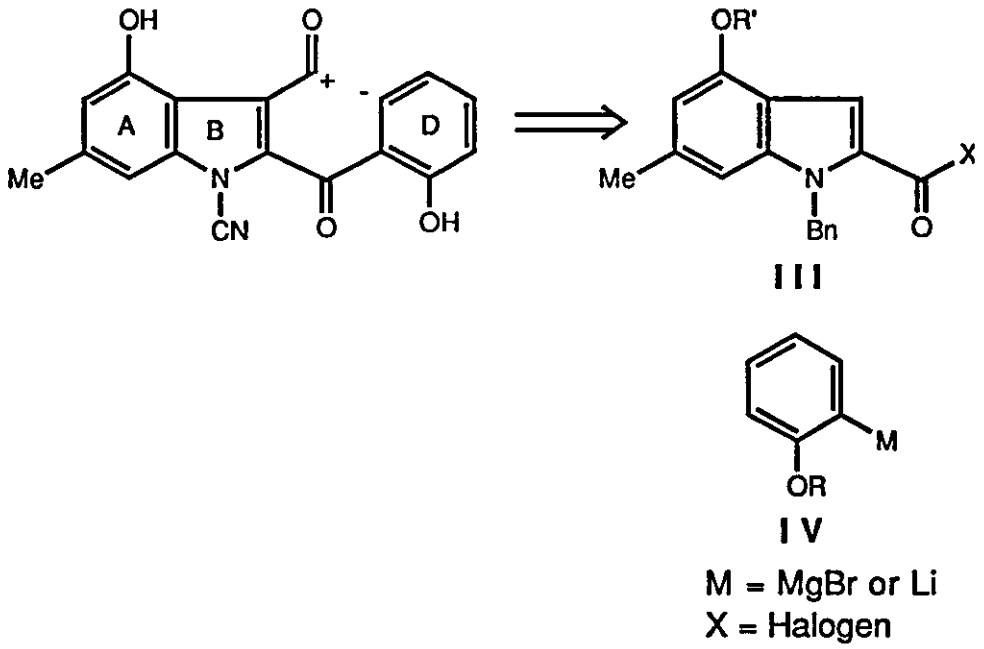


Figure 21

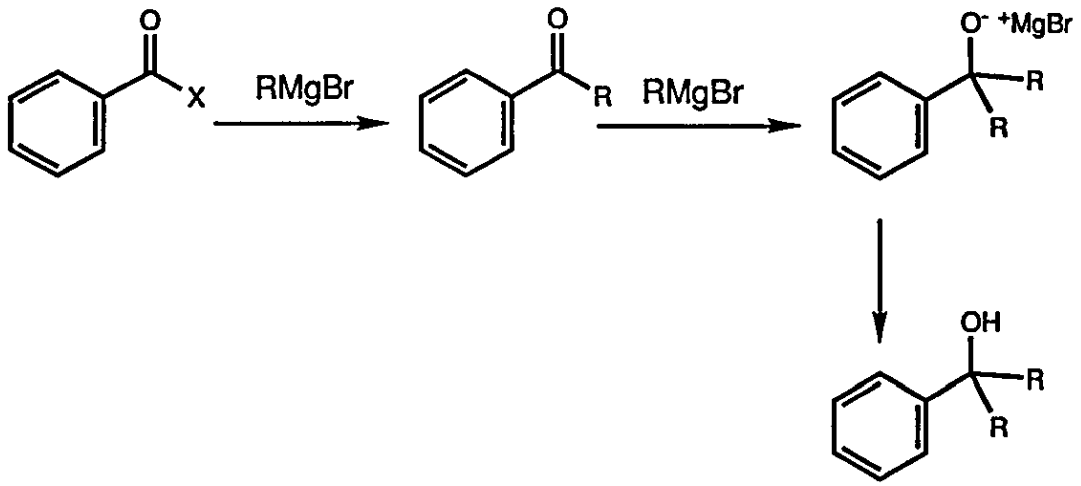
The disconnection b leads to a heavily functionalised indole intermediate bearing two acyl groups at C-2 and C-3. The incorporation of a single carbon fragment to an indole nucleus as

an aldehyde[68] or a cyano- group[69] has been extensively studied, whereas functionalising indole with a 2-acyl group is less common. Closer examination of the fragment from the disconnection b (Figure 21) suggests the use of a Grignard type reagent (Scheme 55).



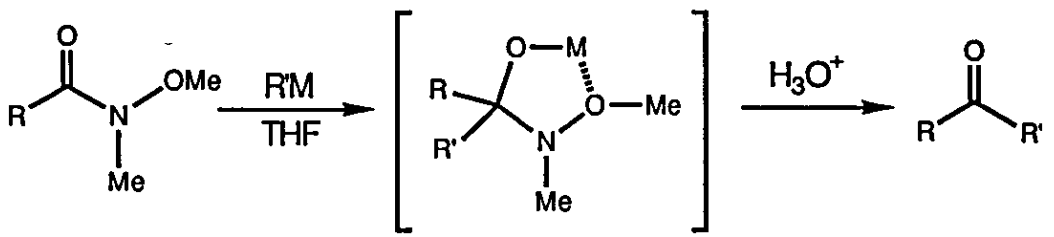
Scheme 55

The addition of Grignard and organolithium reagents to acid chlorides and activated esters has been used as a versatile method of forming ketones with a new carbon-carbon bond. The reaction does however, suffer with the more reactive Grignard and organolithium reagents tending to overadd to the substrate resulting in undesired tertiary alcohols (Scheme 56).
Several elegant solutions to this problem have been proposed for example, organocadmium/zinc[70] species and the use of N-methylamino pyridyl amides[71] (MAPA) which will not be discussed in detail here. The method that suited our needs best involved the acylating agents developed by Weinreb[72], namely N-methoxy, N-methylamides.



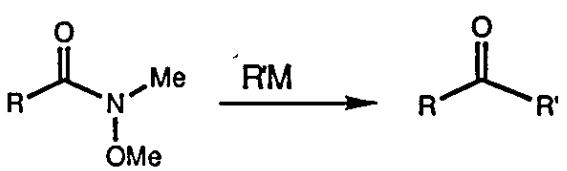
Scheme 56

The reluctancy of these N-methoxy, N-methylamides (Weinreb amides) to form tertiary alcohols from organometal overaddition is explained by the intermediate proposed by Weinreb (Scheme 57).



Scheme 57

The very stable metal-chelated intermediate formed from the first addition of the Grignard (or organolithium) to the amide is resistant to the reaction conditions and remains until acidic workup where the ketone is liberated as the chelate is hydrolysed. Several examples demonstrating the success of reactions carried out (Scheme 58) using these Weinreb amides are summarised in Figure 22



Scheme 58

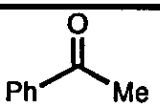
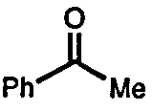
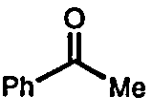
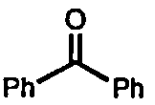
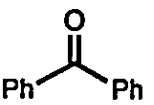
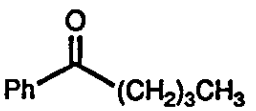
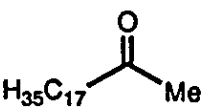
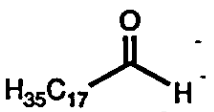
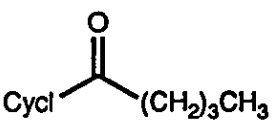
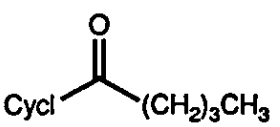
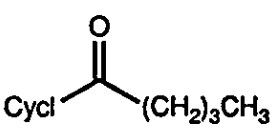
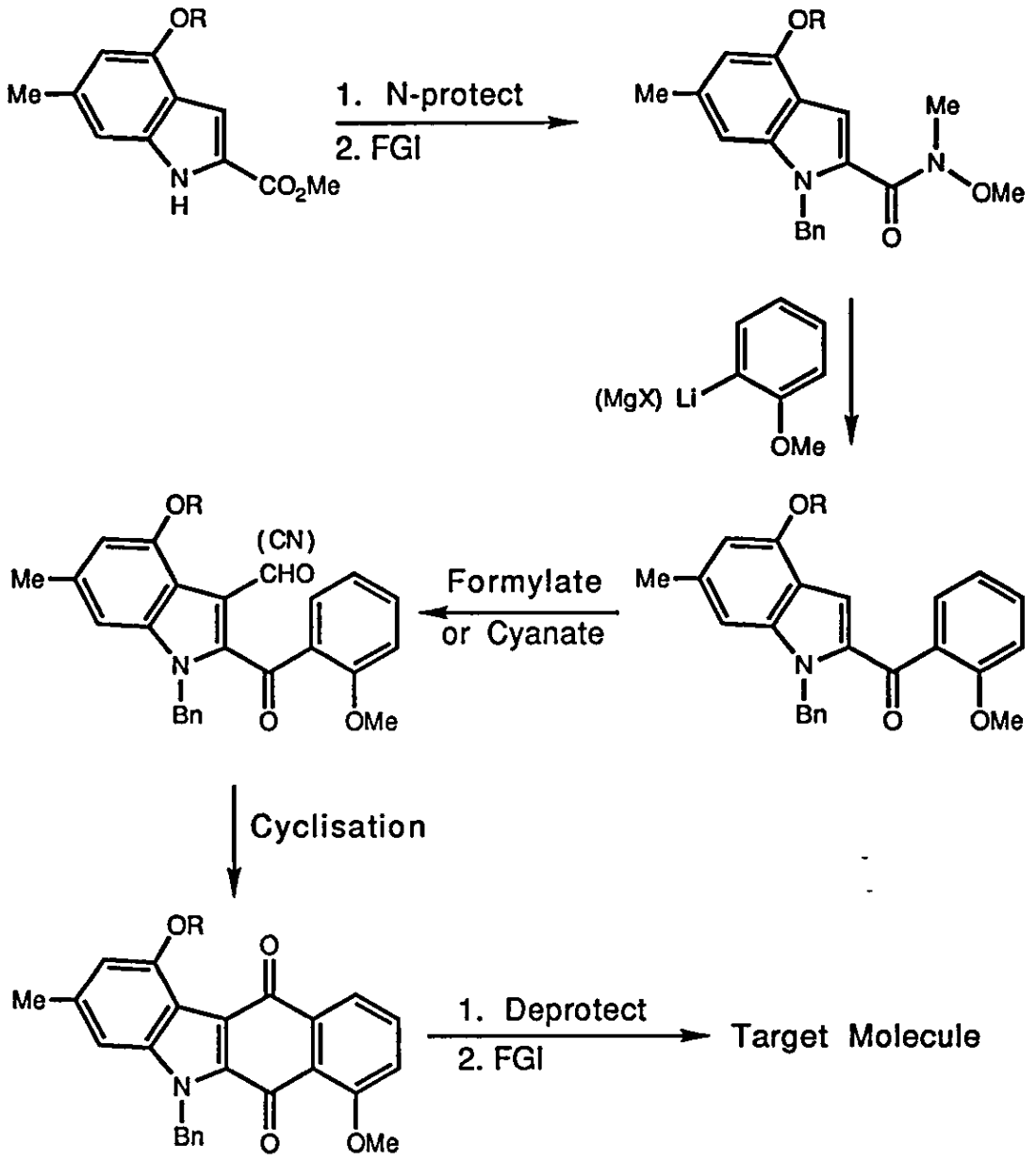
R	R'M	Equivalents of R'M	Product	Yield / %
Ph	MeMgBr	1.1		93
Ph	MeMgBr	3		95
Ph	MeMgBr	75		96
Ph	PhMgBr	3		93
Ph	PhLi	2		95
Ph	n-BuLi	2		84
n-$C_{17}H_{35}$	MeMgBr	2		94
n-$C_{17}H_{35}$	Dibal	1.5		71
Cyclohexyl	n-BuMgCl	1.5		97
Cyclohexyl	n-BuLi	1.5		86
Cyclohexyl	n-BuLi	15		94

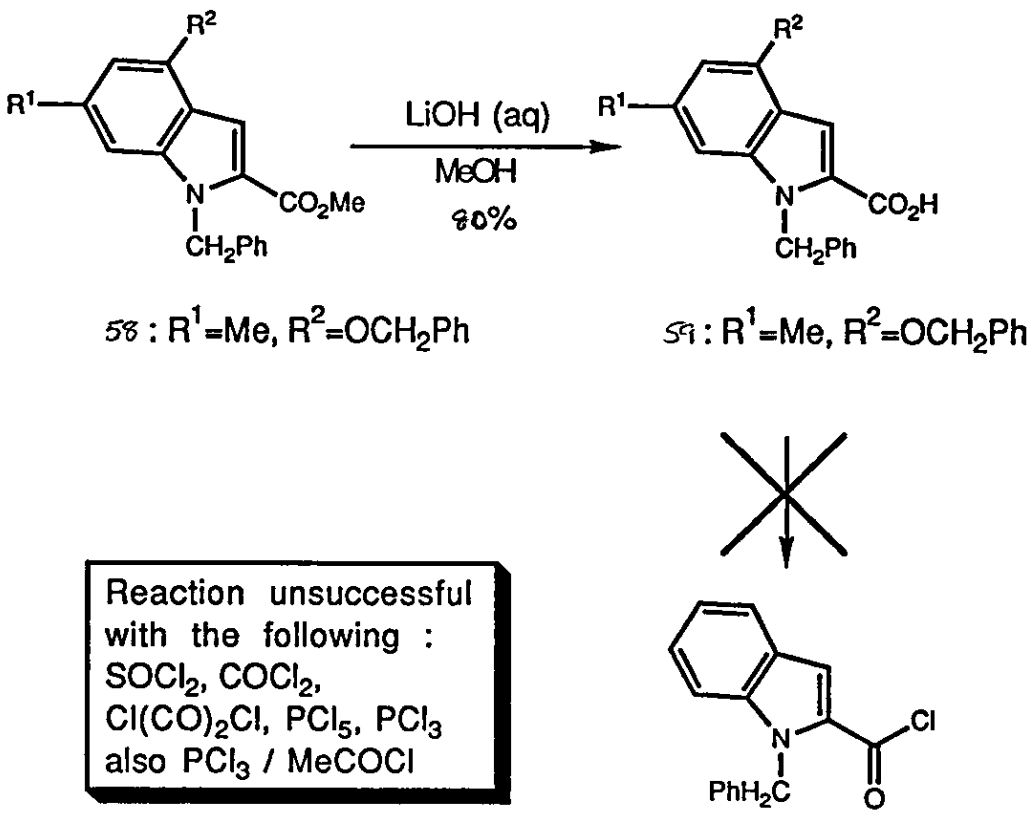
Figure 22

On the basis of these impressive results, the incorporation of the 2-acyl functionality was to be based on the use of Weinreb amides and the following scheme proposed for the synthesis of the required skeleton (Scheme 59).



Scheme 59

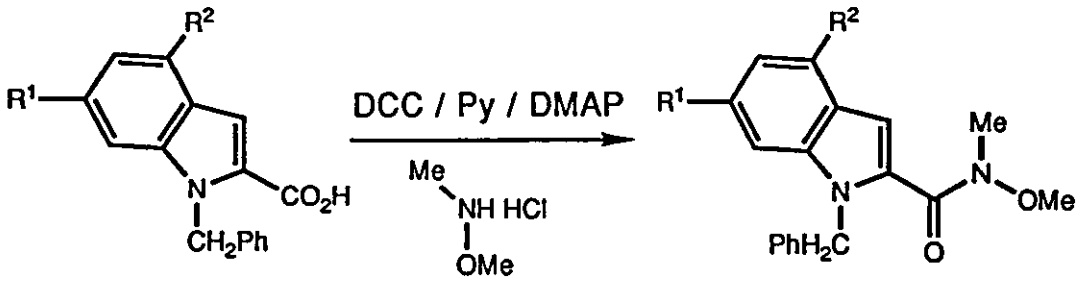
Working towards a model compound the synthesis was initiated from the previously constructed indoles **23** and **58**. The ester hydrolysis was carried out in aqueous methanolic lithium hydroxide solution in 98% to give the acids shown in (Scheme 60).



Scheme 60

All attempts to prepare the acid chloride resulted in severe decomposition, and efforts to trap the reactive species with an *in situ* nucleophile proved fruitless. Our efforts returned to the peptide coupling agent DCC, which made the process of amide formation possible without the need of the acid chloride (Scheme 61), using the commercially available N, O-dimethyl hydroxylamine hydrochloride.

The conversion of **59**→**60** and the preparation of **53** proceeded smoothly and the yield increased by the addition of a catalytic quantity of DMAP. Preparation of the organolithium reagent proved to be more effective with halogen-metal exchange of 2-bromoanisole than treatment of anisole itself. The lithiation proved more efficient with t-BuLi than s-BuLi and the exchange failed altogether with n-BuLi.



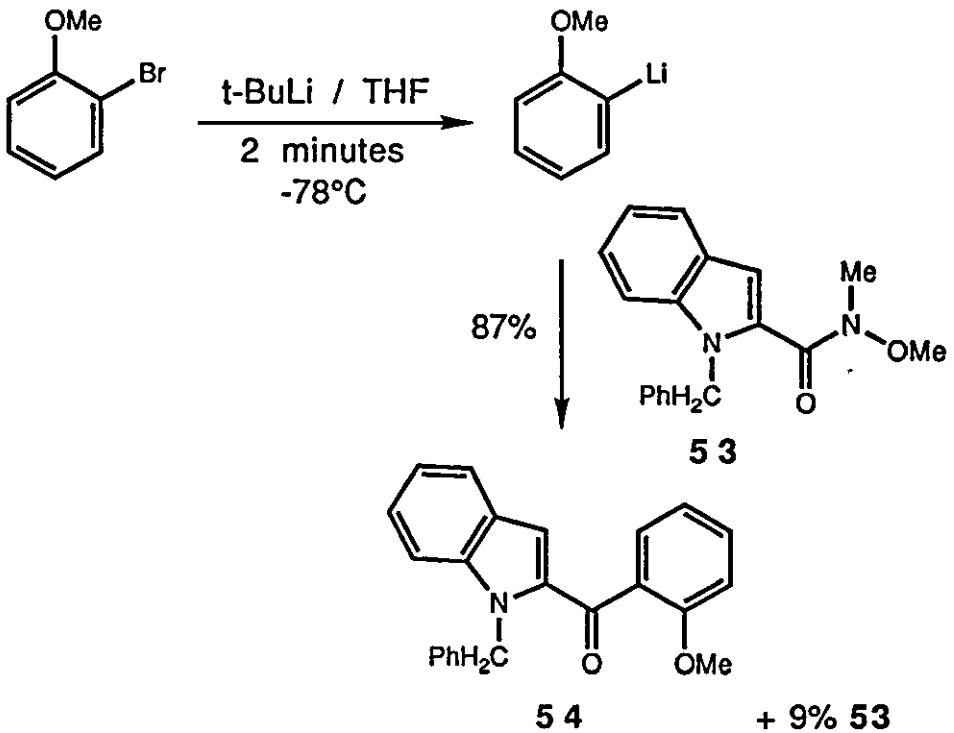
59: R^1=Me, R^2=OCH_2Ph

53: R^1=R^2=H , 70%

60: R^1=Me, R^2=OCH_2Ph , 54%

Scheme 61

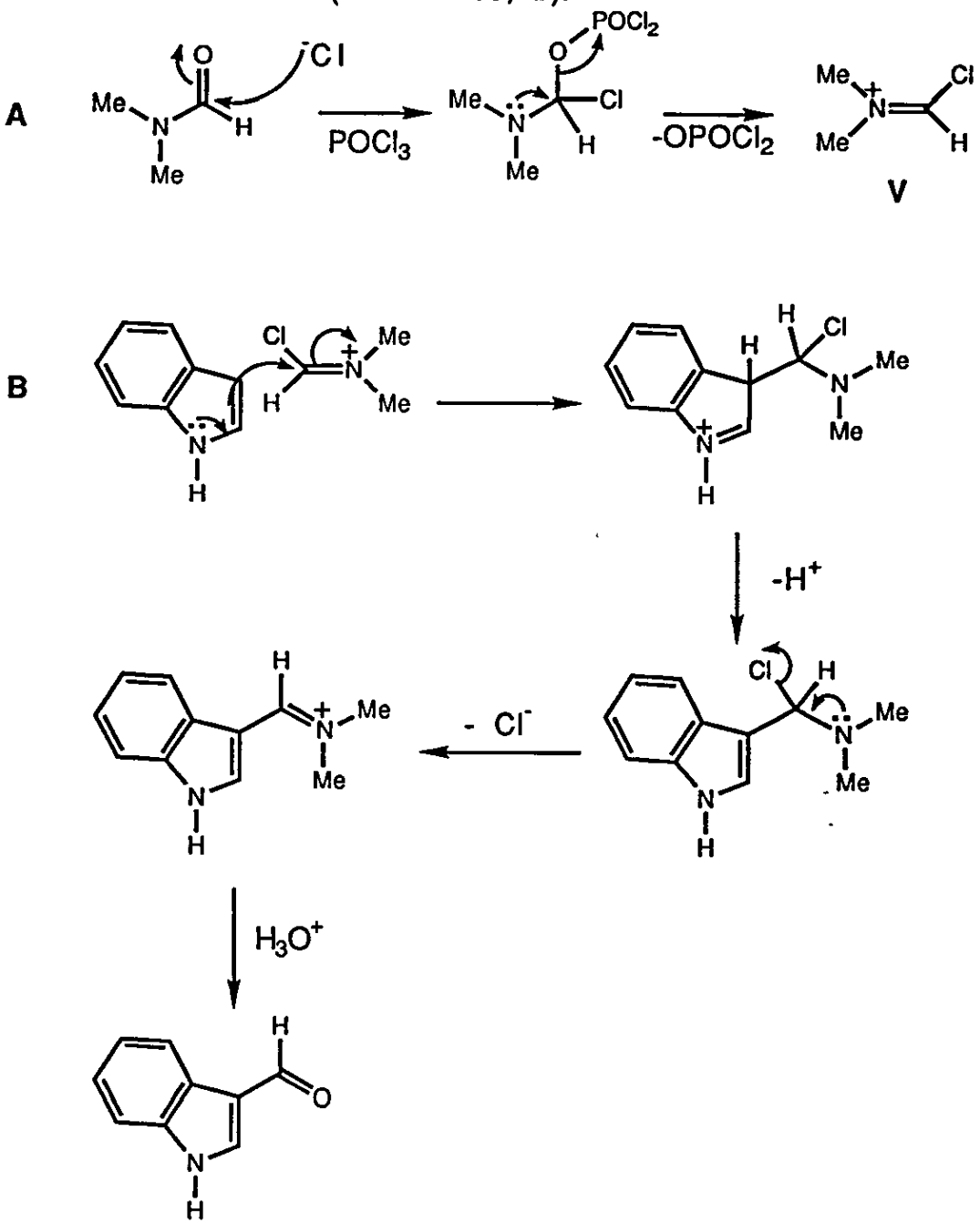
The halogen-metal exchange was almost instantaneous and the electrophile **53** was added after stirring the anion for only 2 minutes (Scheme 62). Subsequent experiments showed only reduced yields when the anion was stirred for a longer period or prepared at lower temperatures.



Scheme 62

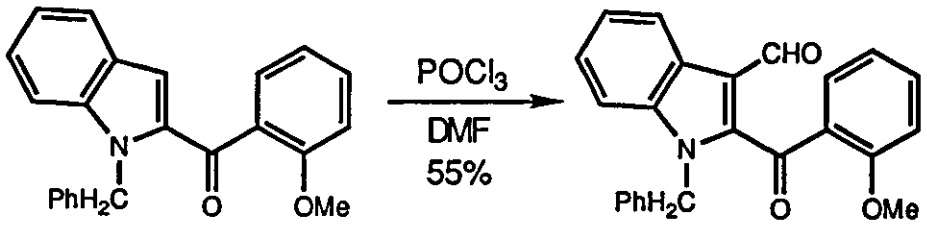
The product **54** was isolated in 87% after chromatography to remove the 9% of unreacted amide **53**.

The most established method of indole formylation is the Vilsmier reaction with typically, $POCl_3$ / DMF. The intermediate responsible for the reaction is formed from chlorination of the DMF to give the Vilsmier reagent **V** (Scheme 63, A). This potent electrophile then reacts with an indole via the C-3 position and the reaction proceeds as illustrated (Scheme 63, B).



Scheme 63

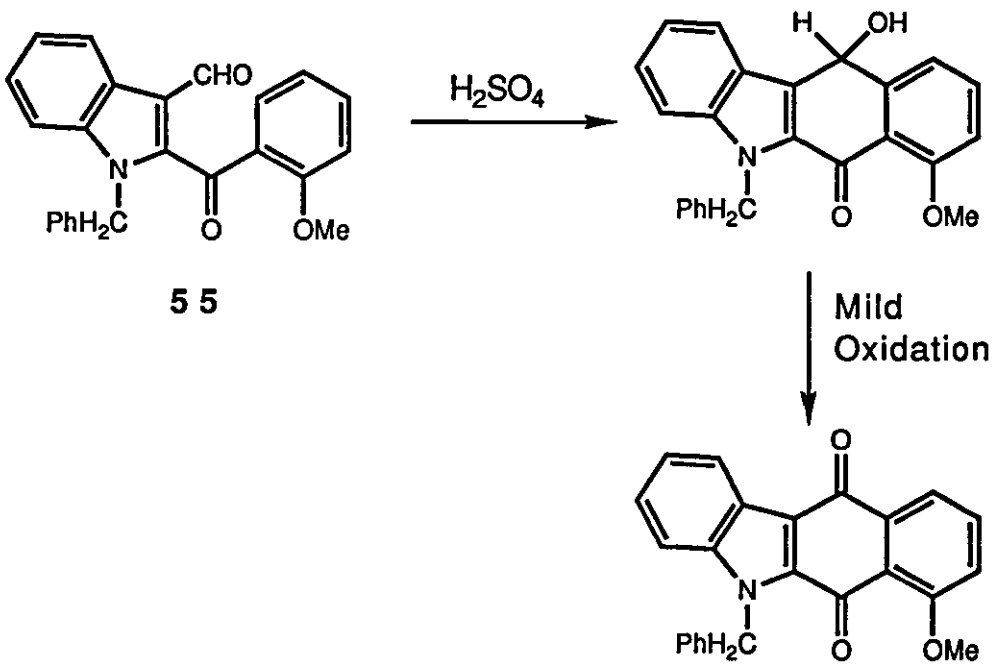
The reaction was attempted without modification and the product **55** was isolated in 55% yield (Scheme 64). The modest yield from the formylation was not improved by the use of N-methylformanilide which gave **55** in 41% yield with several unwanted side products.



54 55

Scheme 64

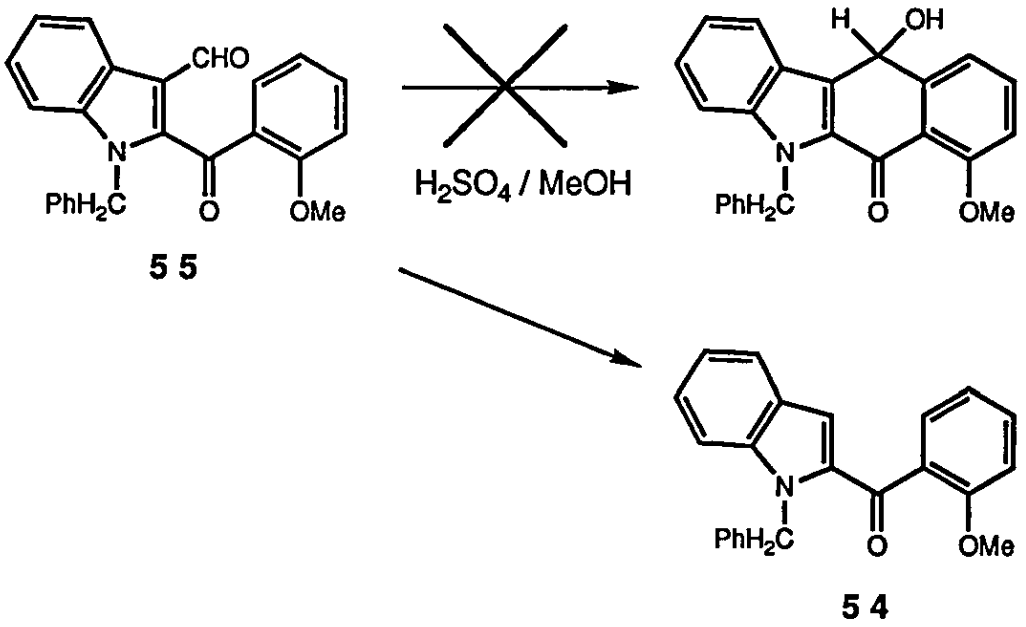
The aim was to complete the C-ring via acid mediated cyclisation followed by mild oxidation to the *p*-quinone (Scheme 65).



55

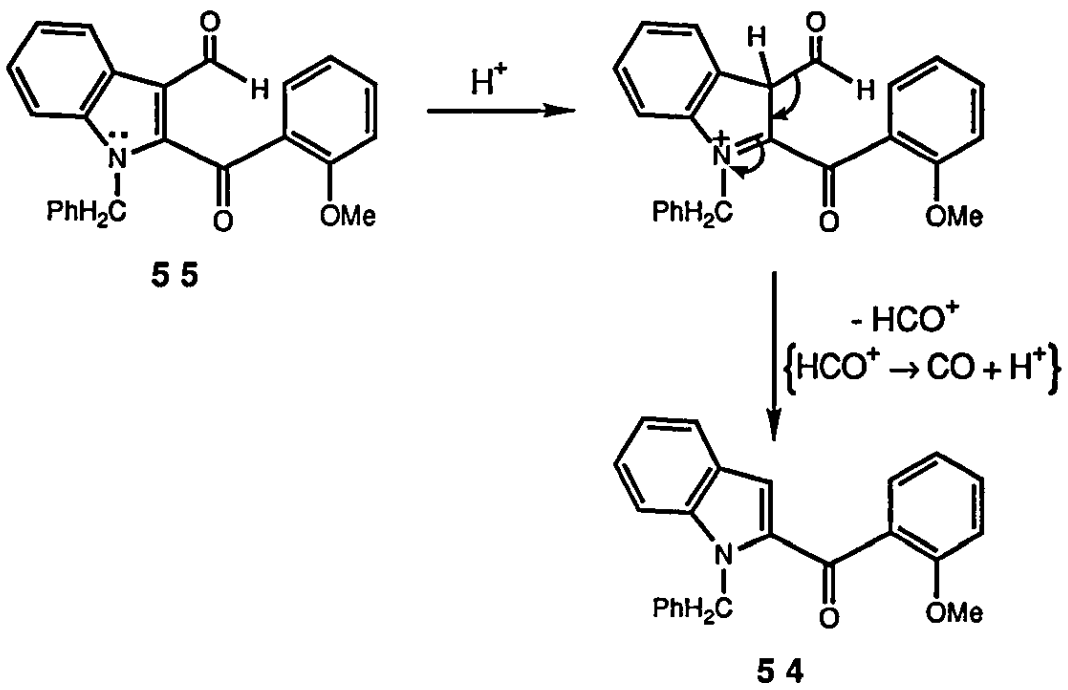
Scheme 65

The reaction was carried out using a 2M H_2SO_4 in methanol at reflux and a single product was isolated after all of the starting material **55**, was consumed. Upon analysis of the isolated product however, it became clear that the reaction had not proceeded in the desired fashion and the product exclusively formed was in fact, the precursor **54** (Scheme 66).



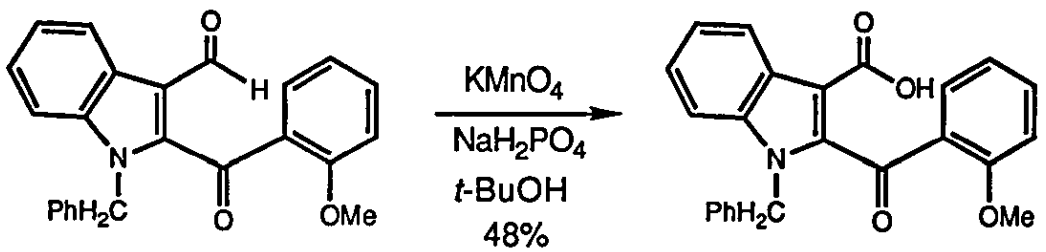
Scheme 66

The process that had taken place was in fact, a retro Gatterman-Koch reaction with elimination of a formyl group as carbon monoxide and a proton (Scheme 67).



Scheme 67

In order to avoid this unexpected reaction from taking place the aldehyde was oxidised to the carboxylic acid using the method of Masamune[73] i.e. a NaH_2PO_4 buffered solution of $KMnO_4$ in *t*-BuOH (Scheme 68).

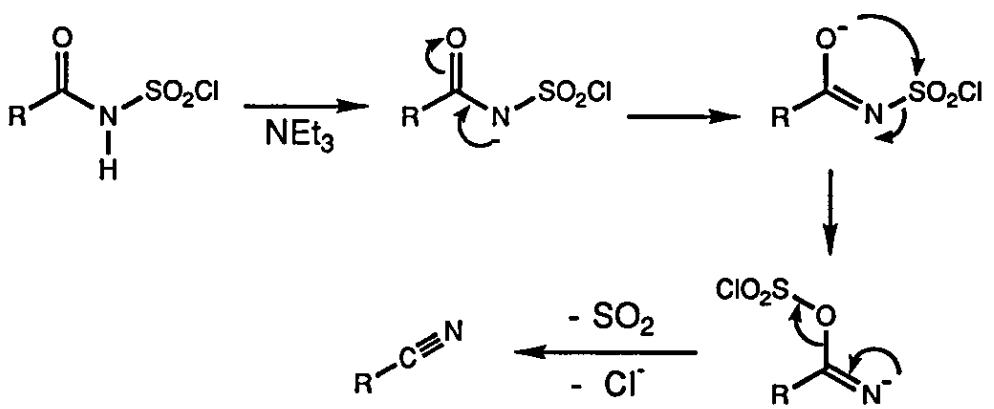


55 **57**

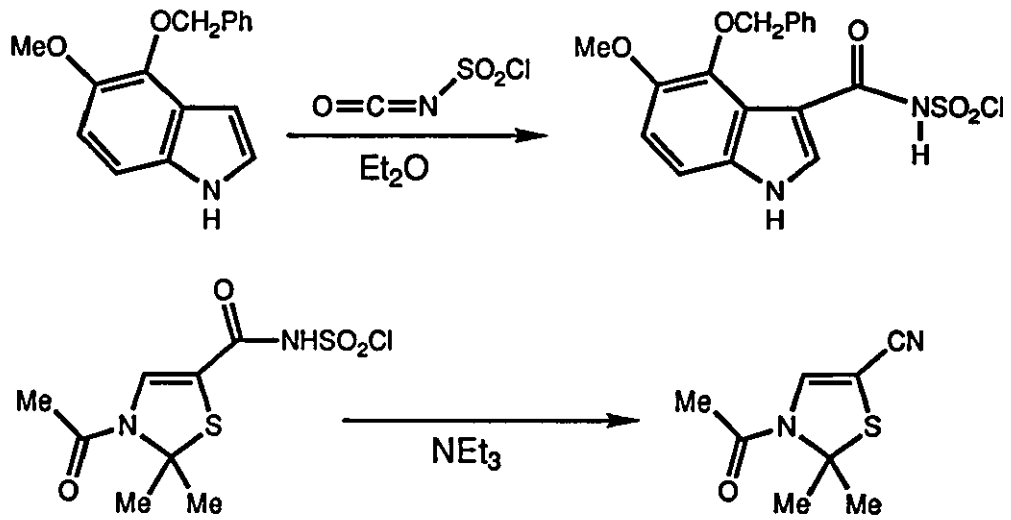
Scheme 68

The acid **57** was prepared in modest yield and the cyclisation attempted once more with the H_2SO_4 / MeOH system also polyphosphoric acid and trifluoroacetic anhydride / trifluoroacetic acid, all of which led to extensive decomposition with traces of the decarboxylated product **54**. It was clear that a different one carbon fragment would be needed if the reaction were to be successful. Friedel-Crafts reactions using nitriles as acylating agents have been studied in some detail in the past and have been shown to act efficiently in the presence of hydrogen and other metal halides.[74]

In order to investigate this possibility it was necessary to prepare the nitrile analogue of **56** which suggested the use of the reagent N-chlorosulfonyl isocyanate (CSI).

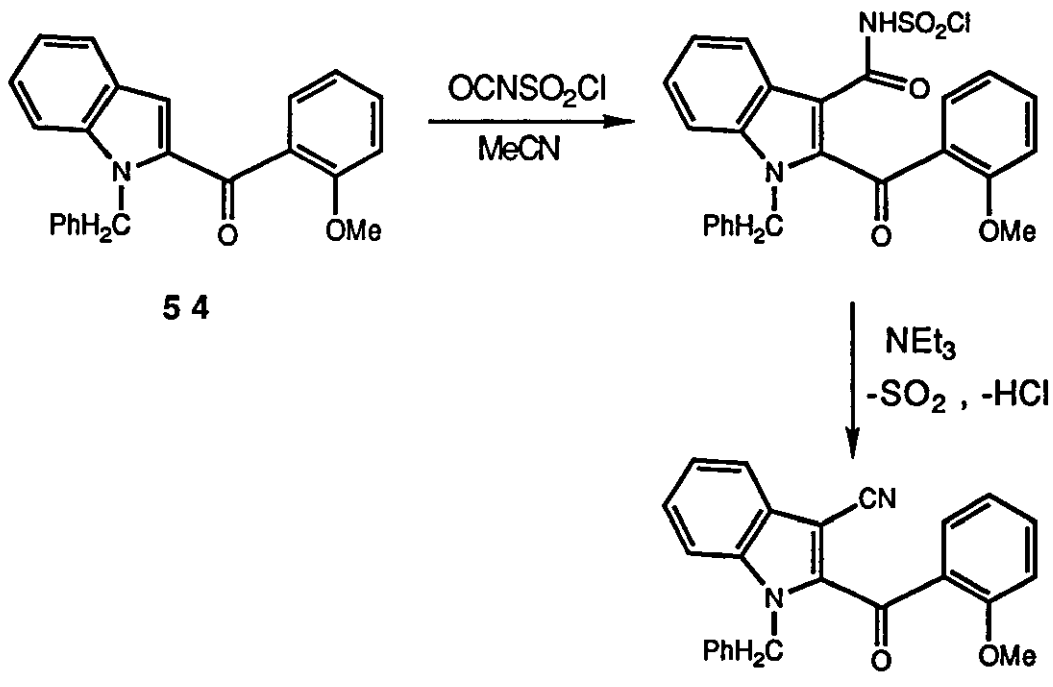


Scheme 69



Scheme 70

Usually used to prepare ß-lactams, the reaction can be stopped before completion at the N-chlorosulfonylamide stage and diverted to the nitrile in the presence of base (Scheme 70)[75].This unusual reaction proceeds via the mechanism suggested by Vorbrüggen[76] outlined in Scheme 69. The nitrile analogue **56**, was prepared from **54** by the method outlined in Scheme 70 using freshly distilled CSI.

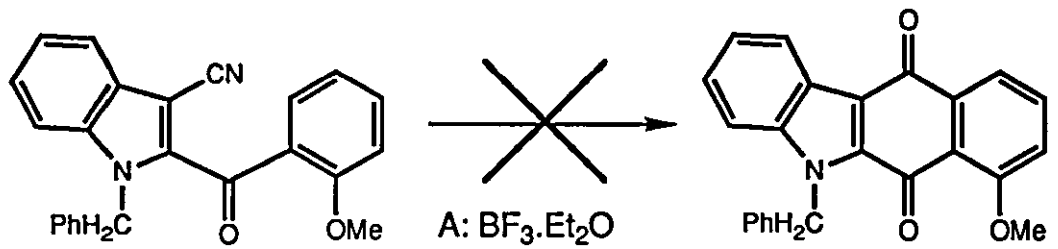


5 4

5 6

Scheme 71

The intermediate N-chlorosulfonylamide was not isolated and reaction simply treated with the triethylamine to afford the product **56** in 83% yield (Scheme 71).
Attempts at cyclisation with boron trifluoride etherate gave invariably an intractable tar but the milder version, BF_3.MeOH gave mostly decomposition with traces of the decyanated product **54**. Other Lewis acids such as zinc chloride gave **54** in very poor yield and weaker still Lewis acids gave no reaction.



5 6

Scheme 72

Thus, it seemed that only the stronger Lewis acids were able to facilitate reaction, but the reactivity of the C-3 position towards protonation led to severe lability of the cyano-, acid and aldehdye groups.
In light of these unproductive results and the many Friedel-Crafts possibilities still available, the synthesis was approached from a different angle. Returning to Figure 21 and the disconnection c (Figure 22), a new route was conceived (Scheme 73)

Disconnection c

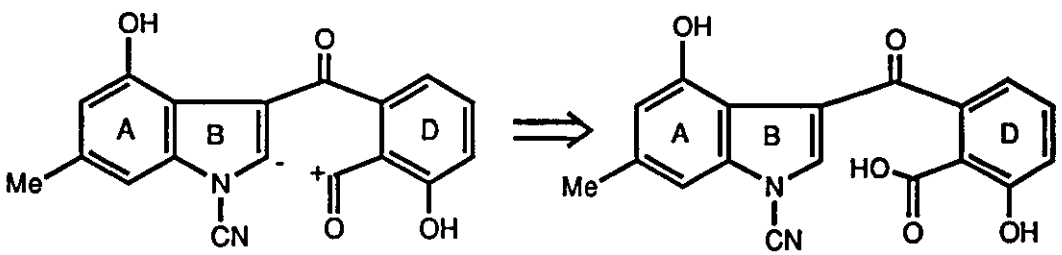
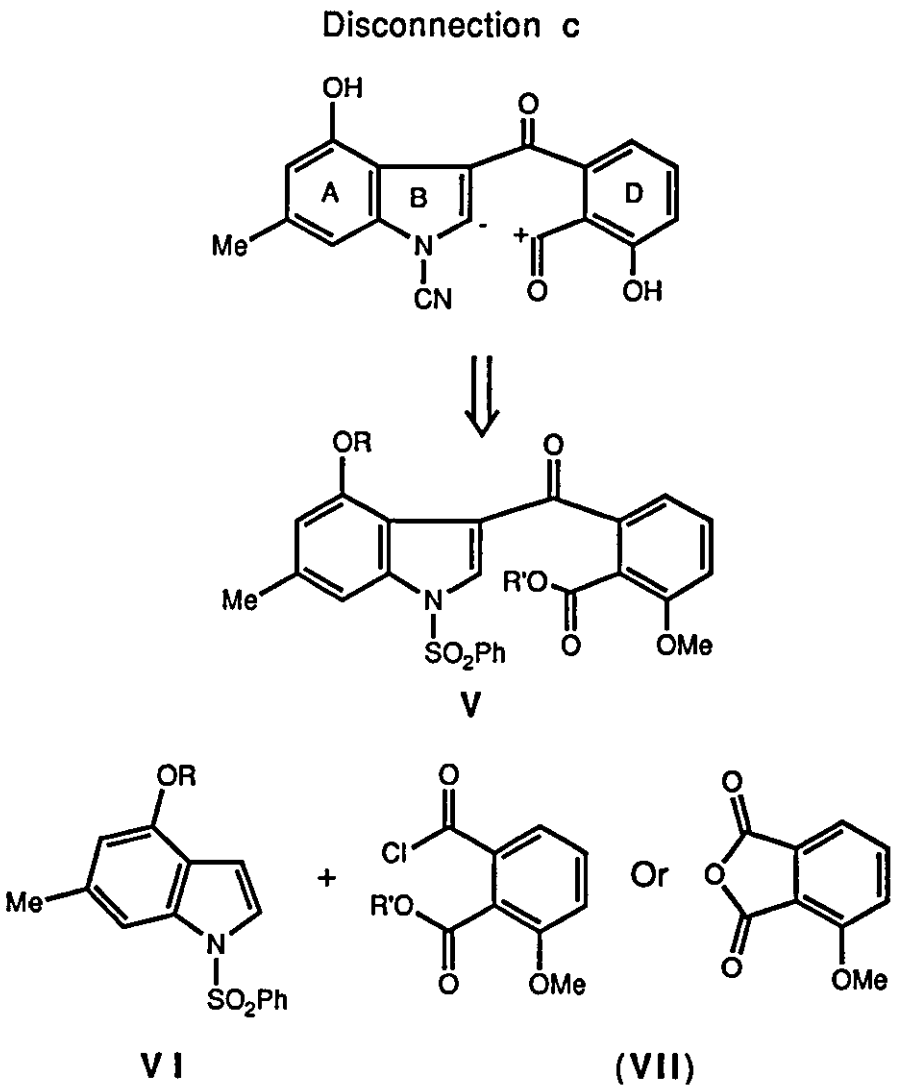
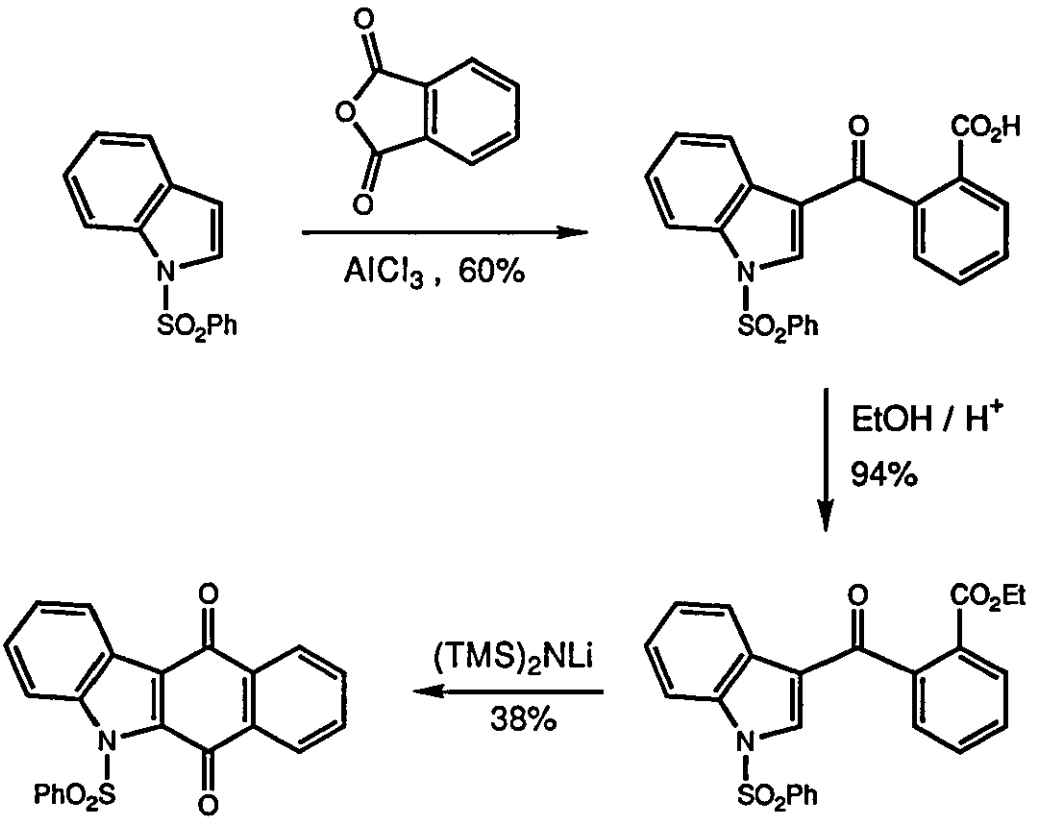


Figure 22



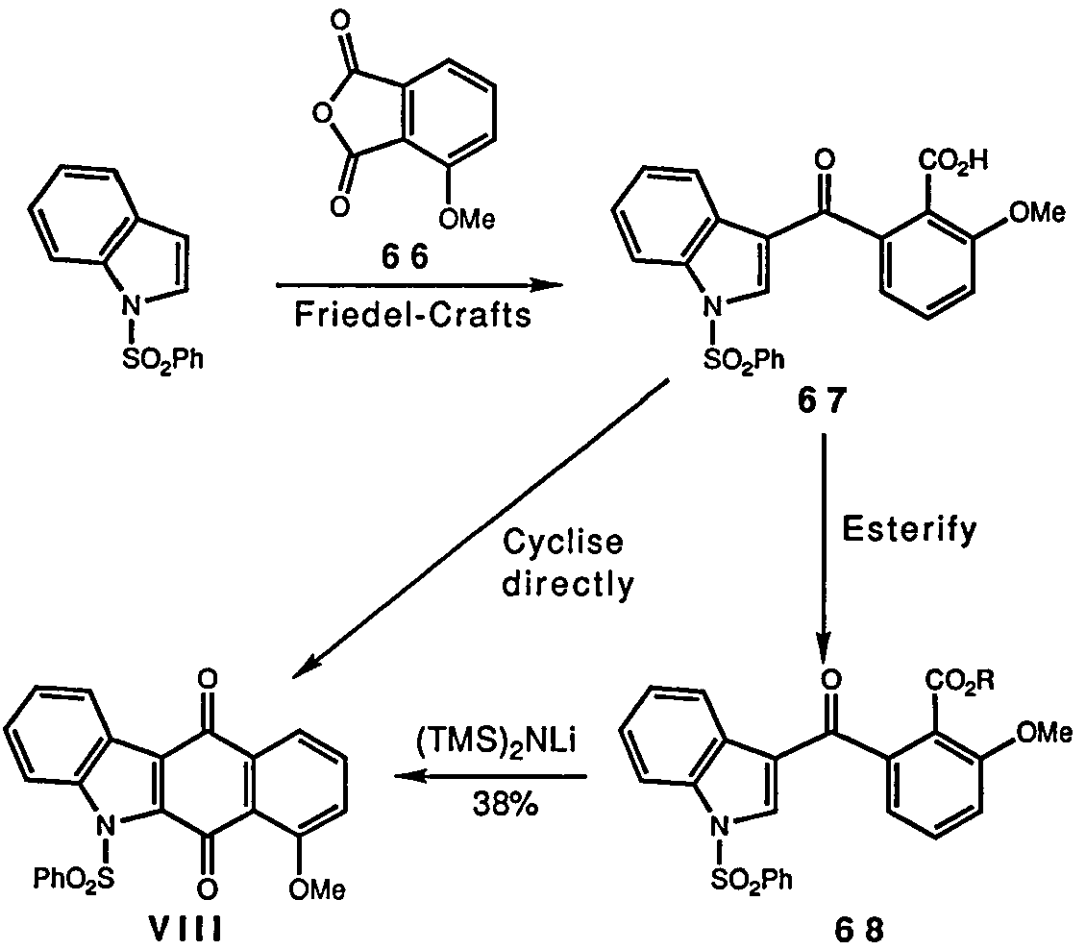
Scheme 73

One of the merits of Scheme 73 is that the inherent reactivity of the C-3 position of indole is used first then the less reactive C-2 position for the final cyclisation to the quinone. The need for the N-protecting group on the indole **VI** under acylating conditions is exemplified by Saxton[77] who found that acetylation of indole with acetic anhydride gave mainly 1,3-diacetylindole, with 1- and 3-monoacetylindole present only as minor products. Gribble[78] subsequently described several efficient syntheses of 3-acylindoles using the benzenesulfonyl group as an N-protecting group, including quinones based on ellipticine (Scheme 74).

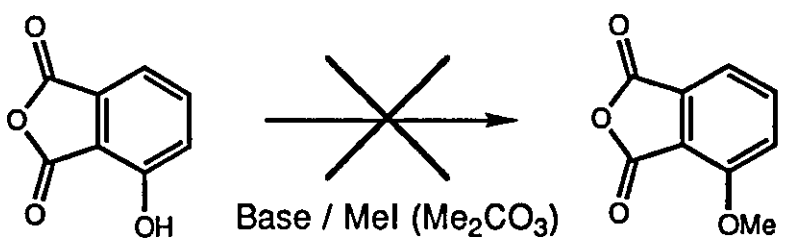


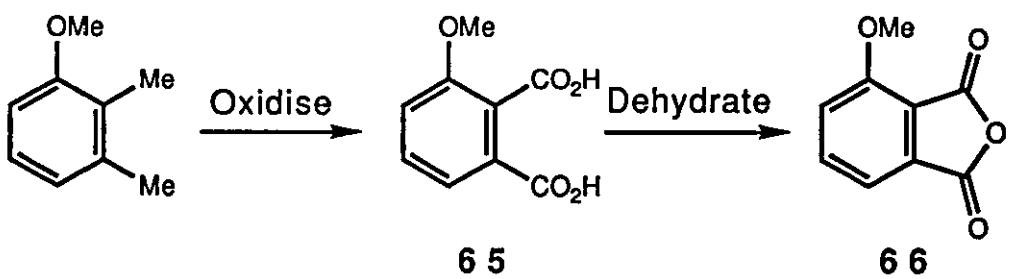
Scheme 74

The Friedel-Crafts acylation reaction with benzenesulfonylindole was possible with either an acid chloride or an anhydride (Scheme 73, **VII**). For the synthesis in question, use of the anhydride provided the second acid group without the inconvenience of preparing an acid chloride in the presence of an acid or ester.
On the basis of this successful synthesis, few modifications were needed for the following model synthesis of to be considered (Scheme 75). The problem first to be addressed was that of the synthesis of 3-methoxyphthalic anhydride **66**. Simple methylation of 3-hydroxyphthalic anhydride proved troublesome with such bases as potassium carbonate and sodium hydride so a simple route starting from 2,3-dimethylanisole was carried out. The oxidation of 2,3-dimethylanisole using potassium manganate(VII) in aqueous *t*-butanol according to the method of Leffler[79] gave the diacid **65** in, at best 38% (Scheme 76).
The low yield was attributed mainly to the difficulty in removing the product from the reaction mixture despite extractions of the aqueous concentrate at various pH levels.



Scheme 75





Scheme 76

The dehydration of the diacid **65** was effected by treatment with acetic anhydride giving 3-methoxyphthalic anhydride **66** in 73% yield.

Since 3-methoxyphthalic anhydride had two non-equivalent sites for reaction it was first necessary to clarify where the reaction would take place (Figure 23).

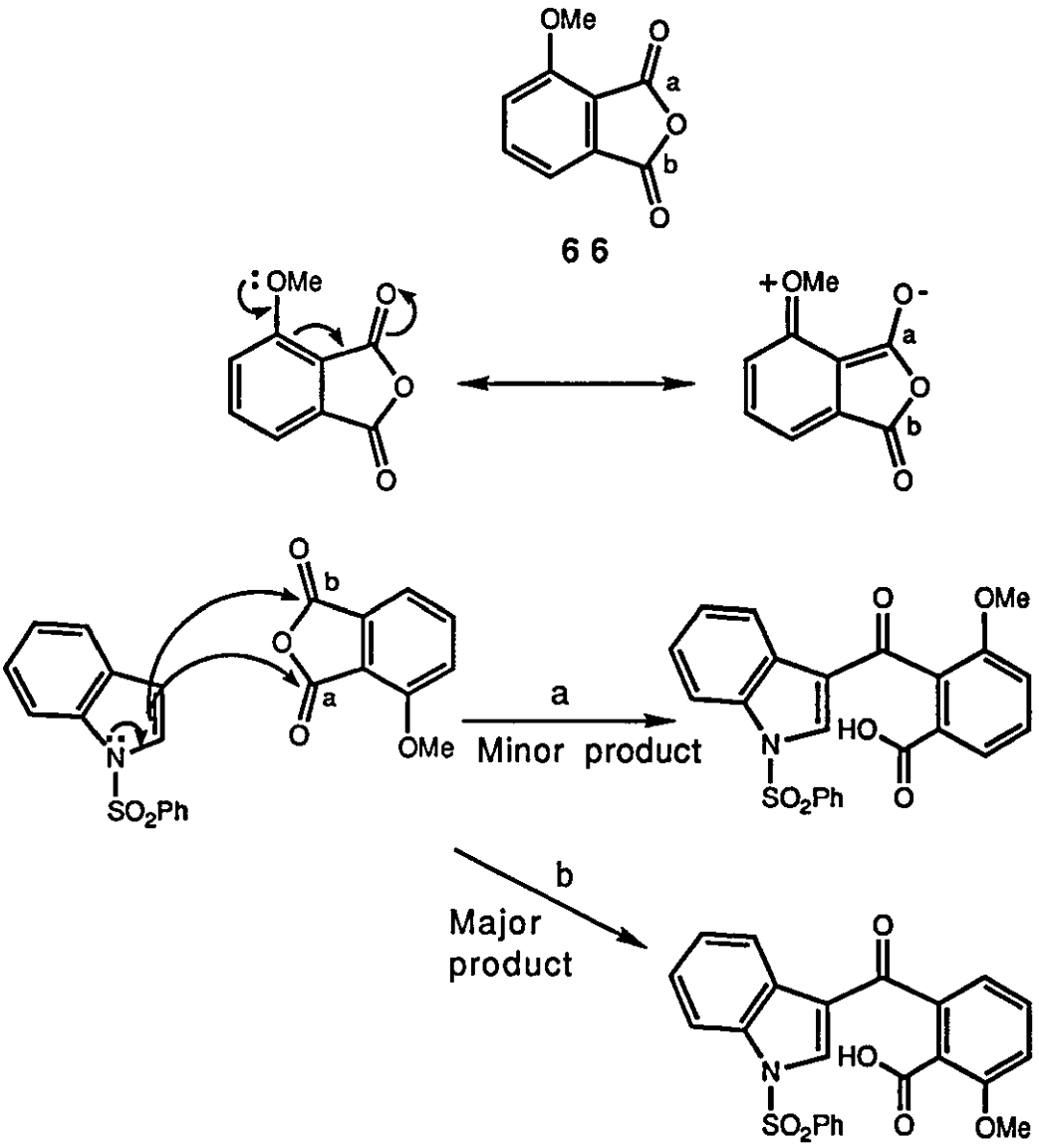


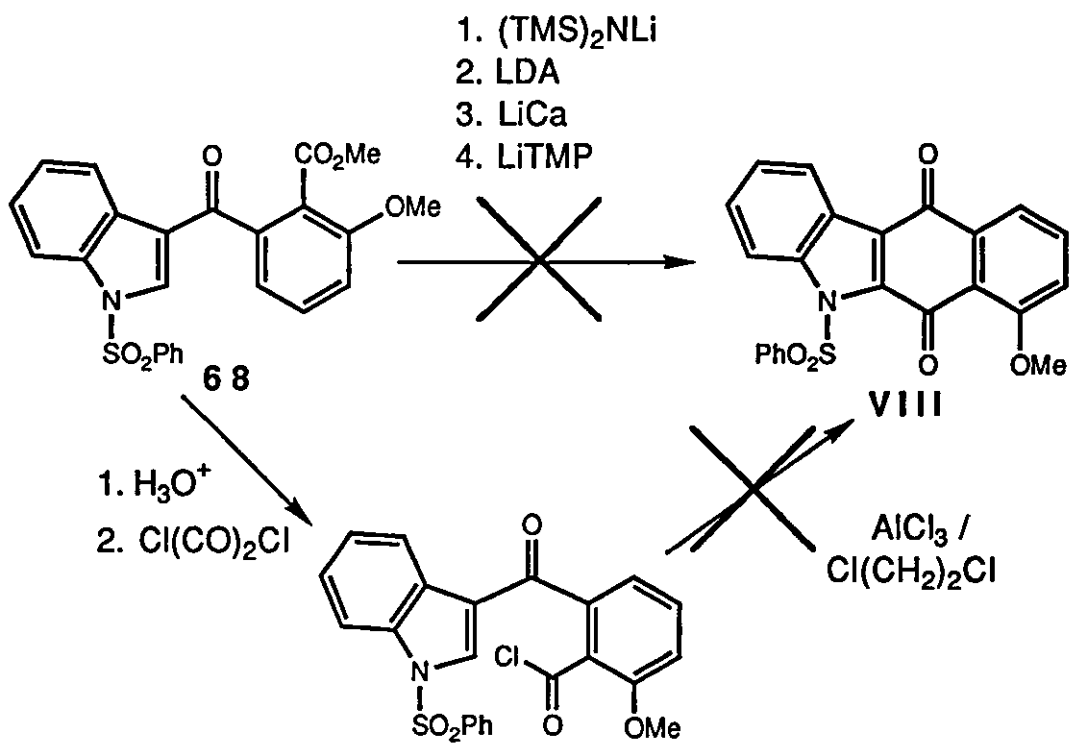
Figure 23

The importance of the mesomeric effect of the methoxy- group is illustrated in Figure 23 where the electron donation through the ring to the carbonyl group a deactivates that position towards nucleophilic attack. The attack would therefore be expected to

proceed via attack at the **b** carbonyl leading to the desired conformation.

1-Benzenesulfonylindole was easily prepared in 72% yield by treatment of indole itself with *n*-butyllithium and quenching with freshly prepared benzenesulfonyl chloride. The Friedel-Crafts acylation was carried out in 48% yield, by the anhydride **66** in ethylene chloride with aluminium chloride as the Lewis acid. Conversion of the resulting acid **67** to its methyl ester **68** in 65% was performed via the acid chloride which was not isolated but simply esterified with methanol / Hunigs' base.

There was some evidence for the absolute configuration of the structure **68** from several nmr decoupling experiments. The cyclisation of **68** to the target quinone **VIII** was attempted with several bases with little success (Scheme 77).

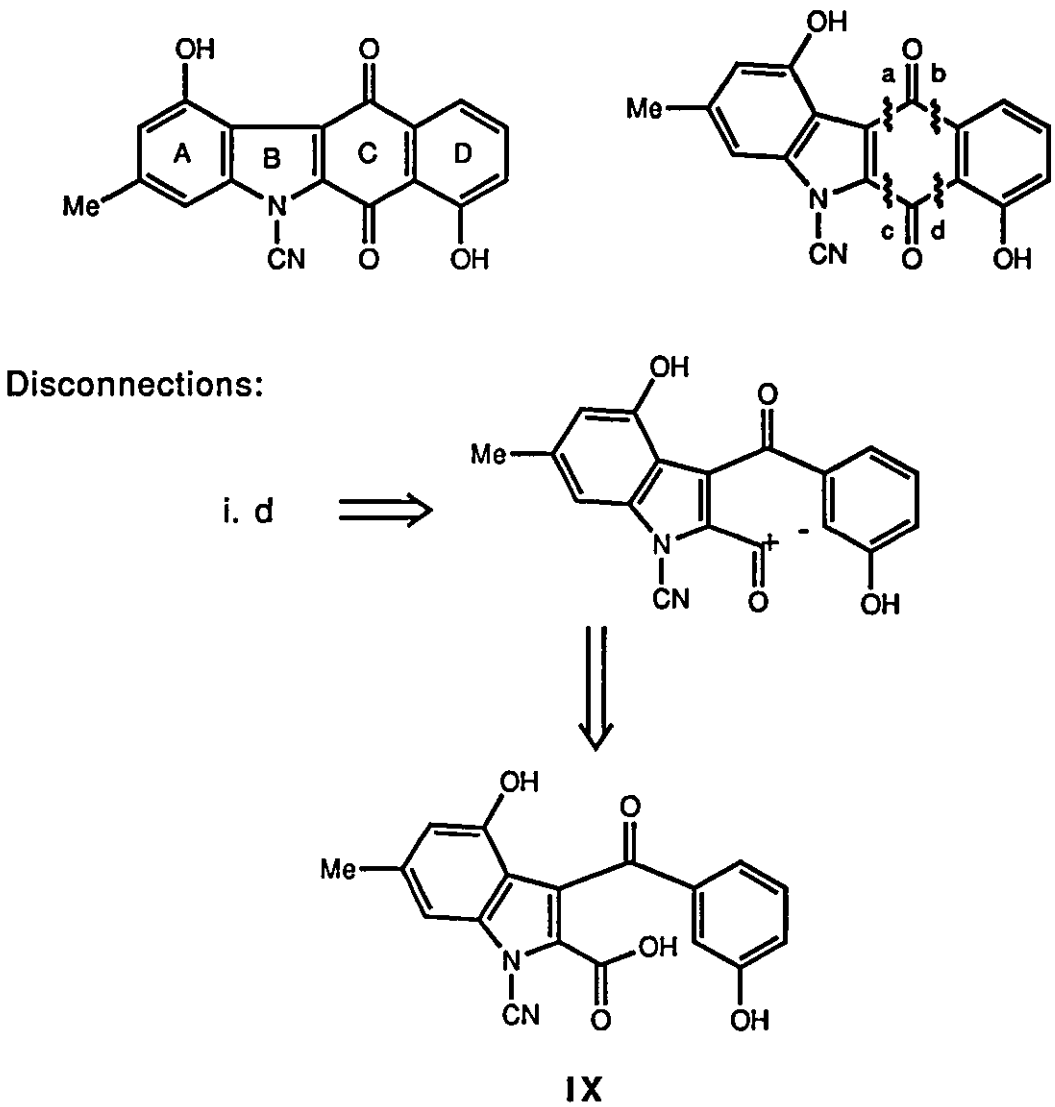


Scheme 77

Efforts to cyclise the acid **67** directly to the quinone with PPA and H_2SO_4 proved fruitless. The failure of this cyclisation was attributed to the electron withdrawing nature of the acyl group on the D ring. Another problem was due to the preference of an aromatic ring bearing a methoxy group to undergo electrophilic

substitution *ortho* or *para* to the directing group. With some regret, work on the route was suspended.

The final examination of the retrosynthetic strategy gave another similar approach (Figure 23).

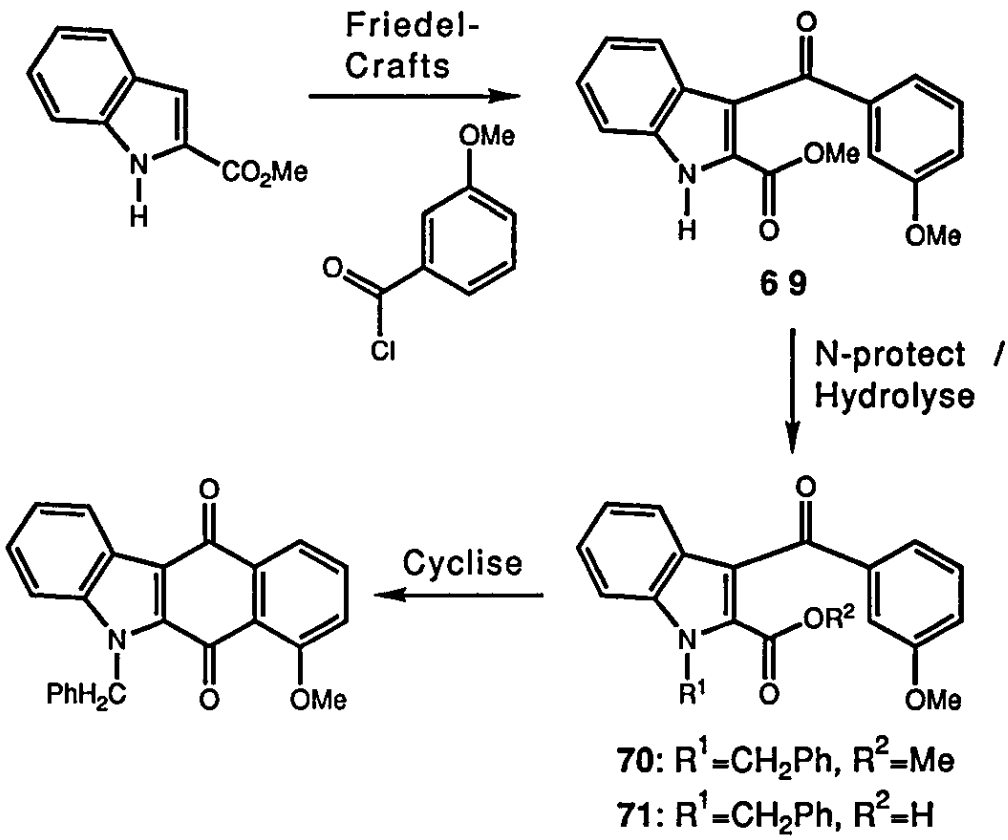


IX

Figure 23

The intermediate **IX** arising from the disconnection d is similar to the structure **V** described in Scheme 73 and the methodology for incorporation of the indole 3-acyl substituent similar. The route proposed (Scheme 78) was somewhat simpler since all the relevant carbon atoms were incorporated in one Friedel-Crafts acylation,

and despite the fact that an acyl group was still present the final cyclisation would take place in the preferred *ortho* position.



Scheme 78

m-Anisoyl chloride was prepared by treatment of the parent *m*-anisic acid with thionyl chloride and the product distilled to purity. The Friedel-Crafts reaction was attempted on methyl indole-2-carboxylate without the previously mentioned benzenesulfonyl group since any acylation at the N-position would be of benefit in the protection step **69**→**70**. The Friedel-Crafts reaction was carried out in ethylene chloride using aluminium chloride as the Lewis acid to give the 3-acyl indole **69** in 71% yield. Curiously, the acyl indole **69** was the sole product obtained and no N-acylation had taken place despite the twofold excess of *m*-anisoyl chloride required for successful reaction. The N-benzyl protecting group was subsequently incorporated by treatment of the N-H indole **69** with sodium hydride followed by benzyl bromide to afford the trisubstituted indole **70** in 93% yield. The carbomethoxy group at C-2 was hydrolysed to the acid **71** with

lithium hydroxide / THF (aq) in 70% yield. Examination of the structure **71** reveals two preferential sites in the D ring that are able to undergo electrophilic substitution, the C-2 and C-4 positions (Figure 24).

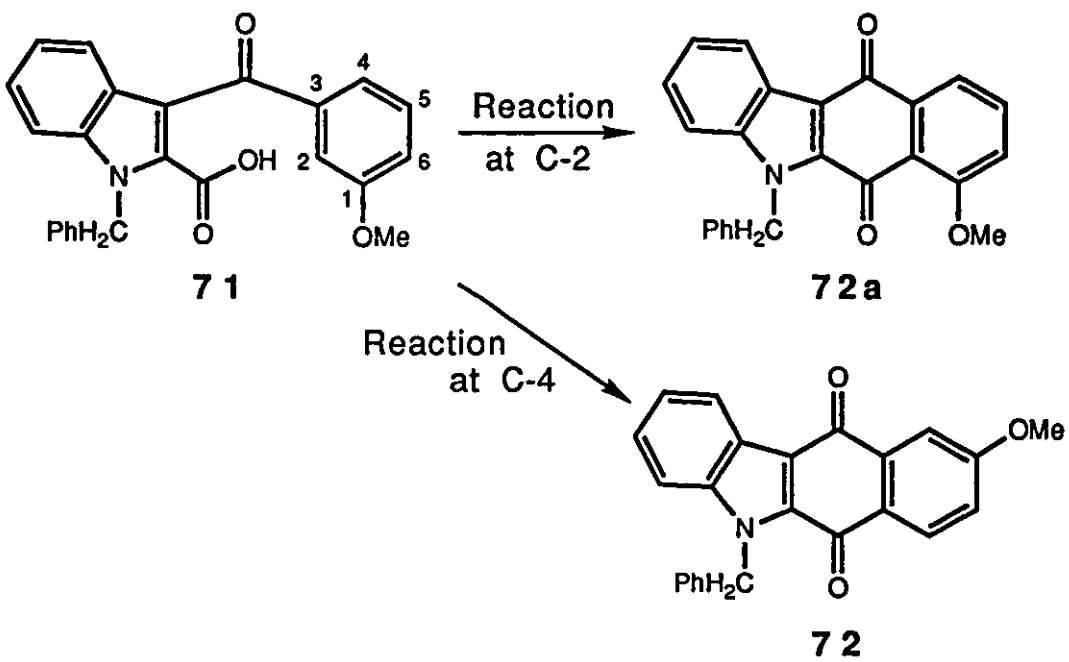


Figure 24

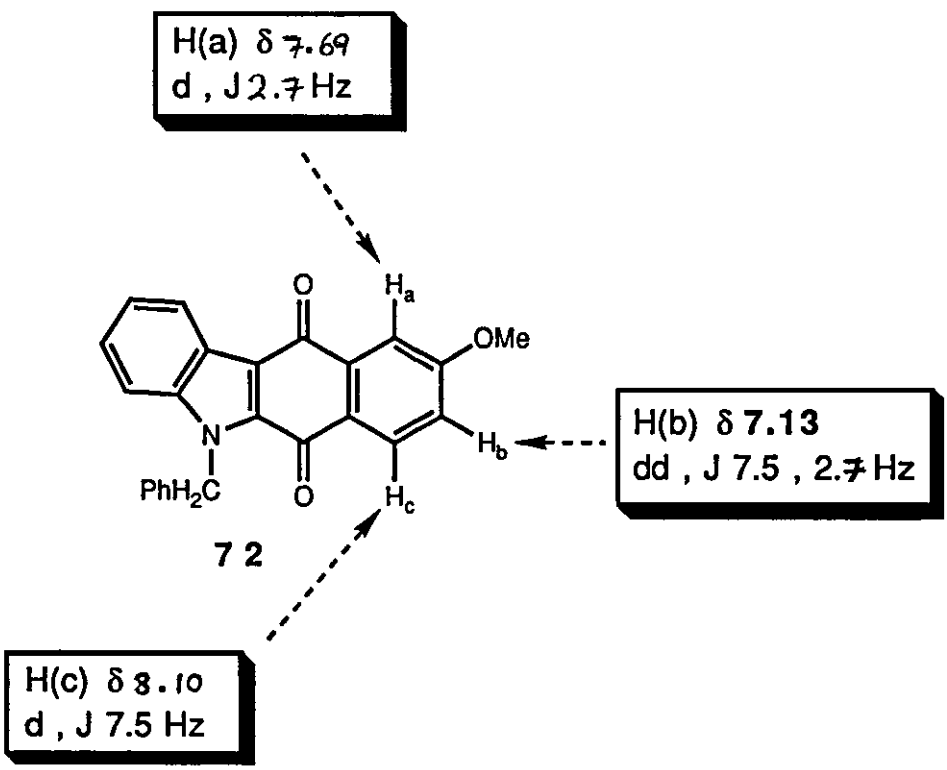
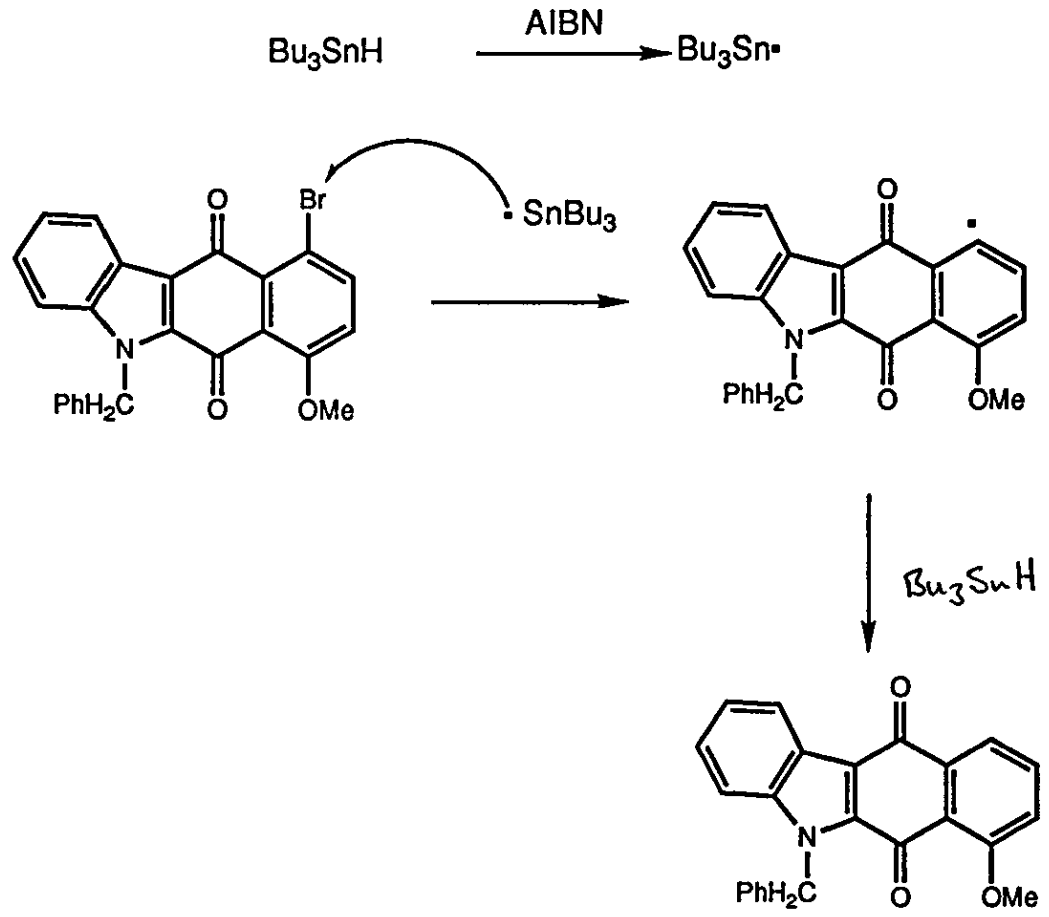


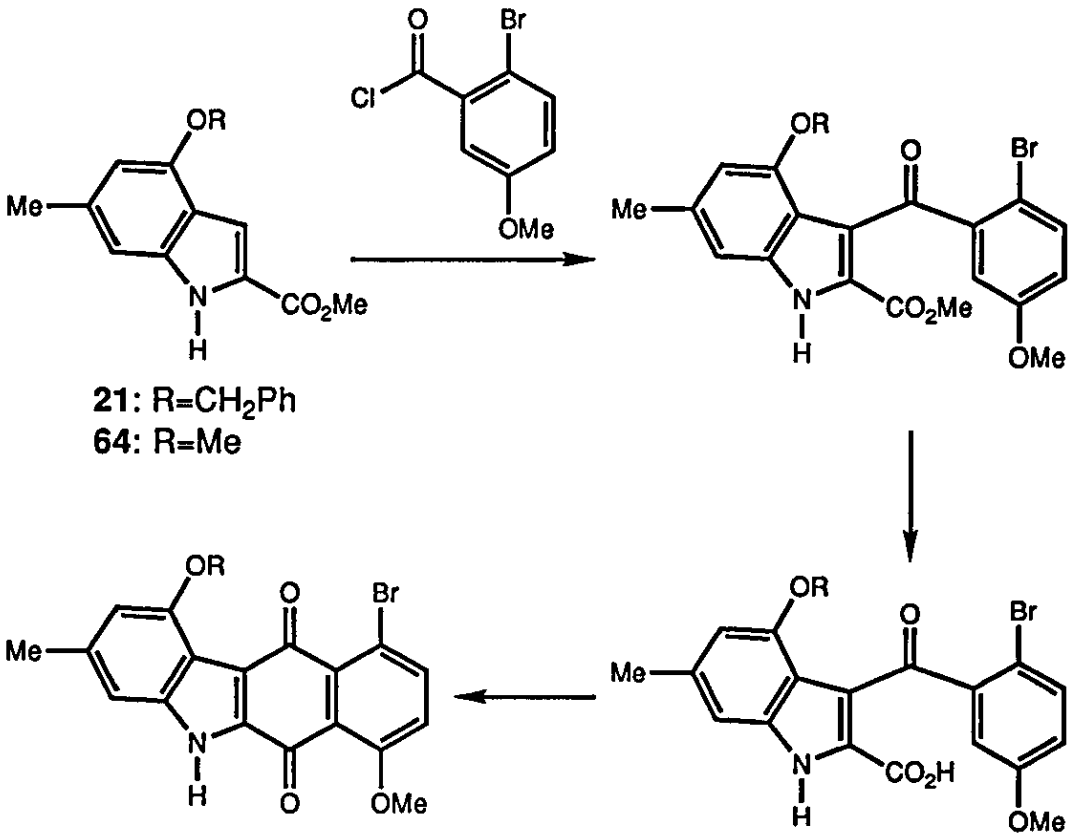
Figure 25

The cyclisation was undertaken in PPA at 60°C and a single fluorescent yellow product obtained. Nmr experiments revealed the structure to be the undesired isomer **72** (Figure 25)
The splitting patterns and the coupling constants shown in Figure 25 could only have arisen from the structure **72** and not **72a**.
The reason for the wrong isomer being formed is almost certainly steric, so in order to ensure that cyclisation only occurs at the desired site a blocking group is required. A bromine was chosen in this case, as simple treatment of the final product with tributyltin hydride should be sufficient to facilitate removal (Scheme 79).

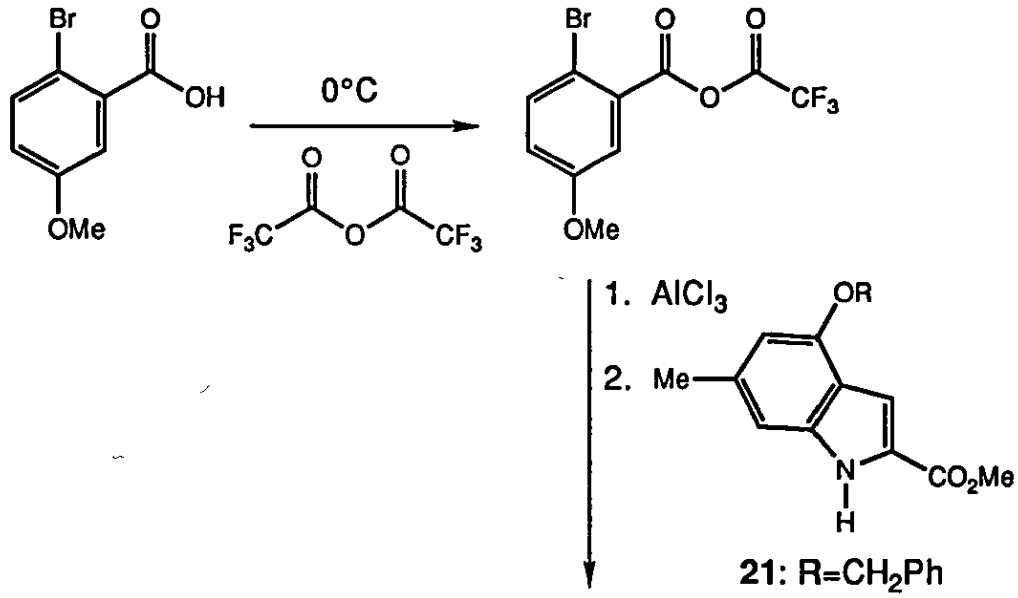


Scheme 79

Thus, a route based on Scheme 78 starting from the previously prepared indoles **21** and **64**, was undertaken to incorporate the bromine group into the final quinone thus ensuring that the correct isomer was formed (Scheme 80).



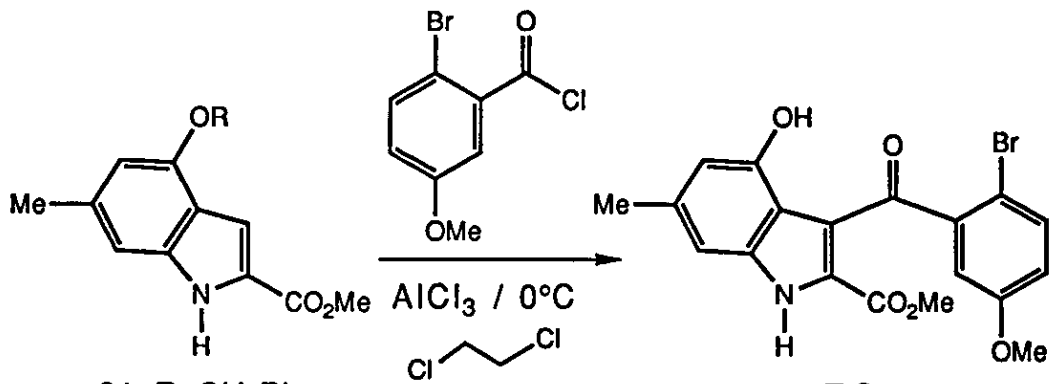
Scheme 80



Unreacted Starting Materials

Scheme 81

The commercially available 2-bromo-5-methoxybenzoic acid was chosen as the precursor to the acid chloride for the Friedel-Crafts reaction. Attempts to by-pass the preparation of the acid chloride by formation of a mixed trifluoroacetic anhydride led only to unreacted starting materials (Scheme 81).
2-Bromo-5-methoxybenzoyl chloride was eventually prepared as an unstable oil from treatment of the parent acid with thionyl chloride at 60°C and used immediately (Storage of the acid chloride in the freezer proved unsatisfactory).



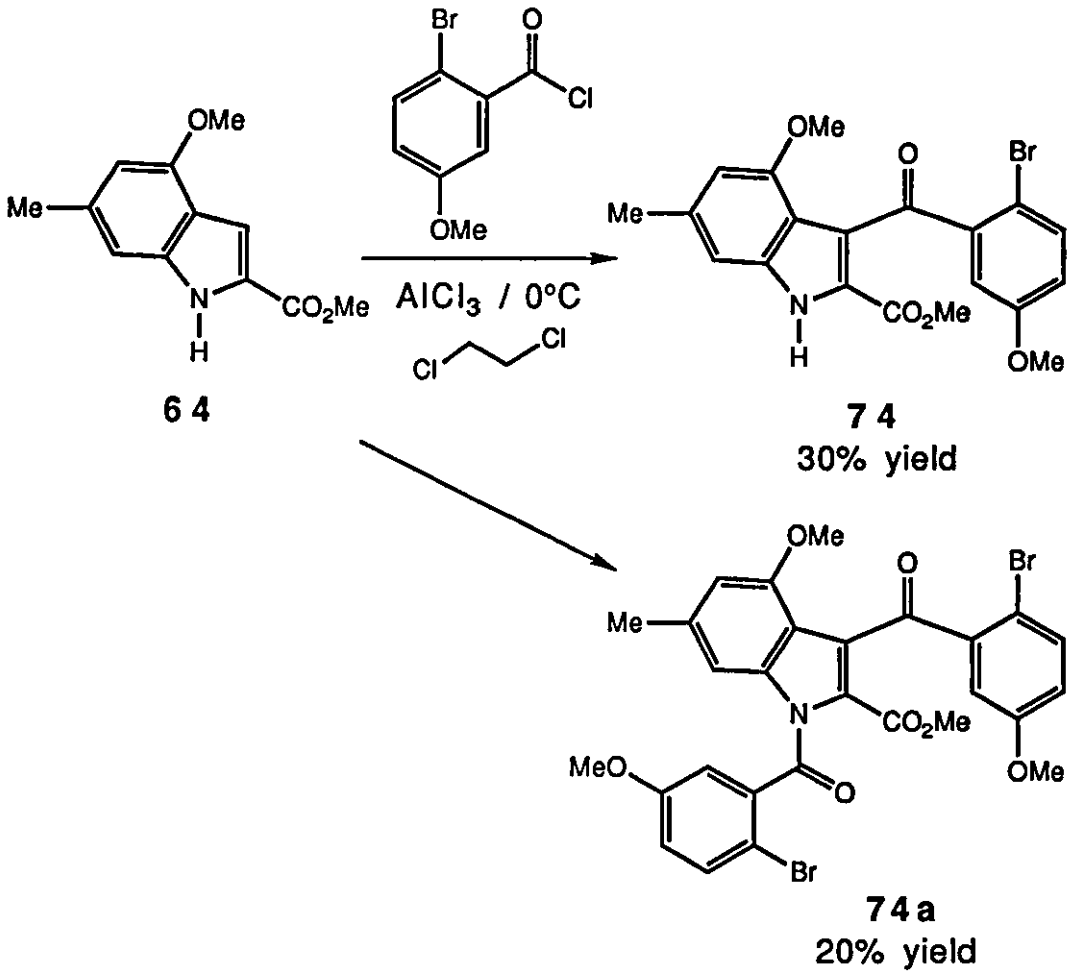
21: R=CH_2Ph

73

Isolated in 14% after extensive chromatography

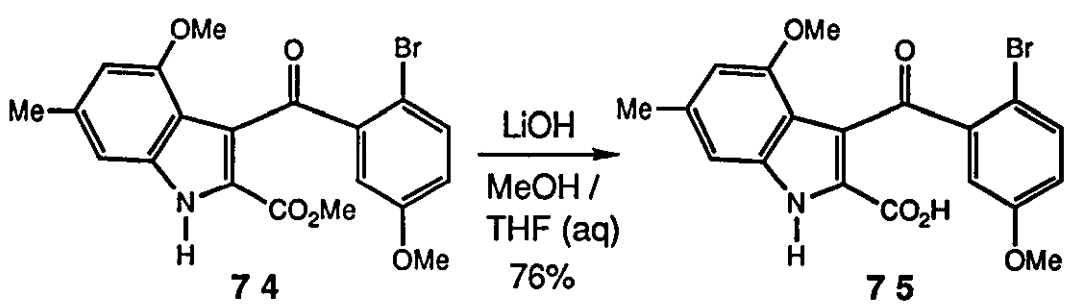
Scheme 82

The Friedel-Crafts reaction with the previously prepared **21** gave in excess of 10 products and after much chromatography the main product **73** was isolated.
The benzyl protecting group at C-4 of **21** had been removed by the Lewis acid in the reaction and even though the groups' removal was essential in the latter stages, some apprehension was had over the benefits of a free phenol group in the final cyclisation. It soon became apparent that the Friedel-Crafts reaction of **21**→**73** was far from reproducible and that extensive chromatography was unavoidable. Therefore, the indole **64** was used instead of **21** due to the increased stability of the methoxy group over the benzyloxy group under Lewis acid conditions. When the reaction was carried out under identical conditions (Scheme 83) another problem became apparent upon isolation of two major products **74** and **74a**.



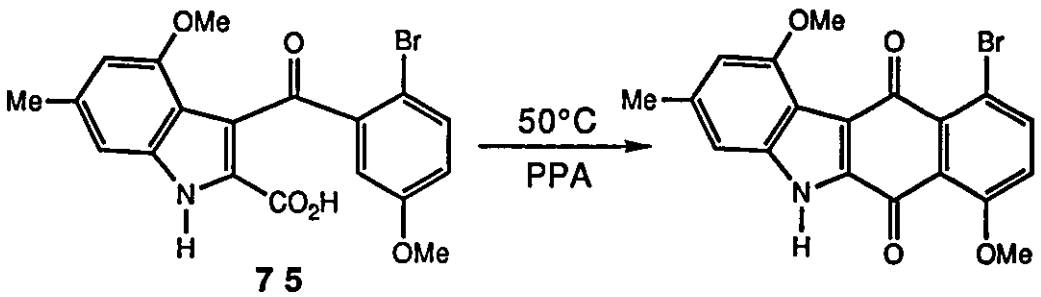
Scheme 83

The problem that had been feared earlier with 1,3-acylation competing with simple 3-acylation had accounted for a significant amount of starting material in the Friedel-Cratfs reaction. Despite the unwanted N-acyl group in **74a** the route was continued in the hope that the acyl group could be cleaved at a later stage.



Scheme 84

The 3-acylated product **74** was converted to the acid **75** by treatment with lithium hydroxide in aqueous THF / methanol in 76% yield (Scheme 84).



7 5

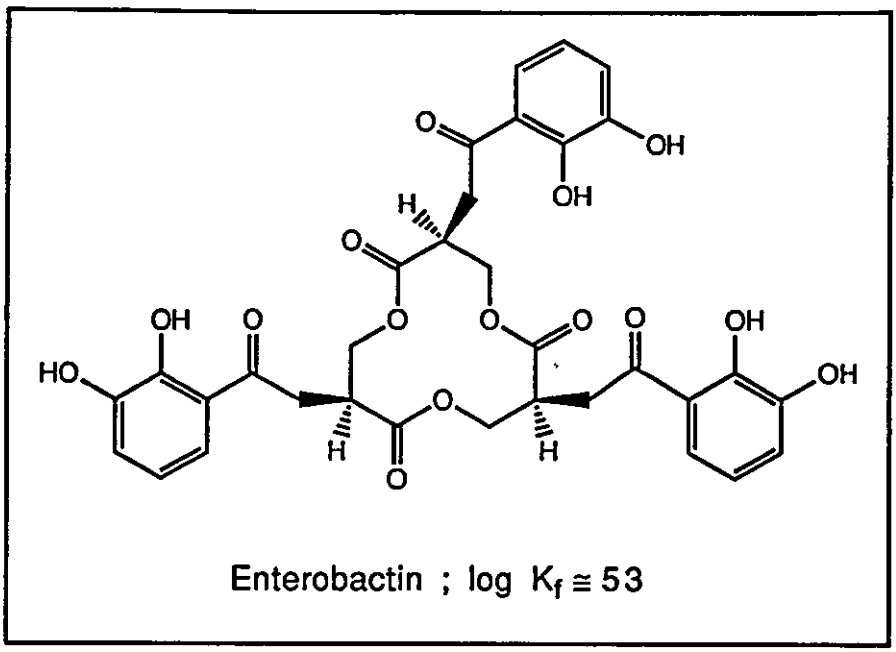
Scheme 85

Early attempts to cyclise the acid **75** at 50°C (Scheme 85) were unsuccessful but encouraging but it was at this stage that all work was suspended due to time restraints.
In conclusion the route outlined in chapter 3 was the most promising and likely to produce the Pre-Kinamycin skeleton due to the the success of the reactions shown in Figures 24 and 25.

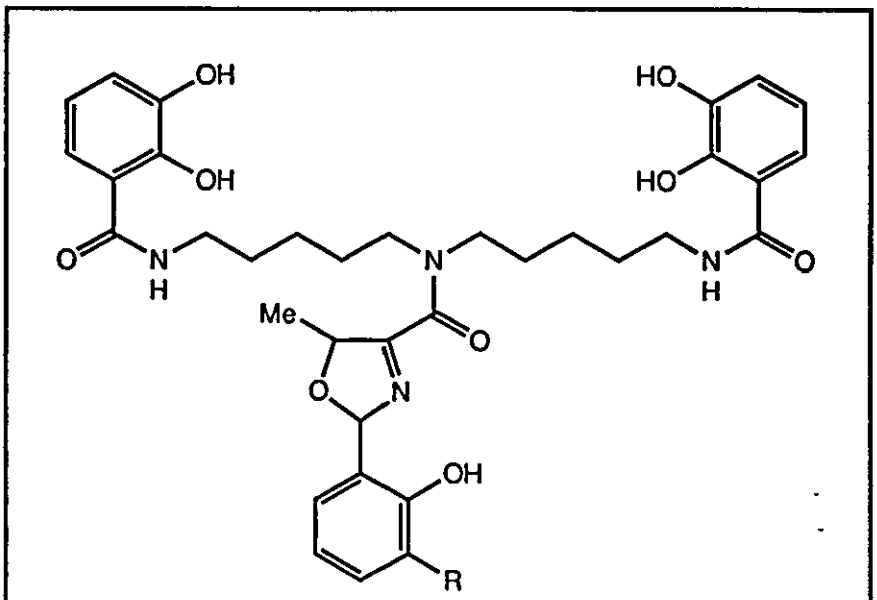
Chapter 3

3.1 Iron(III) - Chelation and Role in Overload Diseases.

Iron, in its' +3 oxidation state is essential to life in all forms except for a few species of lactobacilli and also plays a major role in infection processes. For this reason, and the fact the iron overload related diseases (hæmosiderosis and hæmochromatosis) are affecting some three million people world-wide, the study of effective iron chelators has attracted considerable interest.
A review by Neilands[81] details many natural 'siderophores' (Greek: iron bearer) and their affinity for the iron(III) species, most of which are produced by common bacteria when deprived of an iron source. Figure 26 shows the most effective siderophores known and the formation constants for their respective deferrisiderophores with the ferric ion.
Iron (III) has a low affinity for amine ligands and therefore an effective chelator must have coordinating groups based on oxygen. The natural siderophores shown in Figure 26 have previously been synthesised and an excellent review by Bergeron[82] deals comprehensively with the relevant synthetic research which will not be discussed here.
Unfortunately, the high formation constants shown for the siderophores (Figure 26) with Fe(III) are responsible for the toxicity of enterobactin and similar models in clinical trials against hæmosiderosis. This toxicity results from the siderophore delivering iron so efficiently to the subjects' resident flora that extreme sepsis and eventual death results. With hindsight, the failure could be predicted since the natural role of enterobactin under normal conditions is to effectively scavenge for iron to stimulate microbial growth. These results outline the need for a siderophore that cannot be used by the resident flora or foreign bacteria but still binds iron(III) efficiently enough to overcome the iron overload.



Enterobactin ; log $K_f \cong 53$



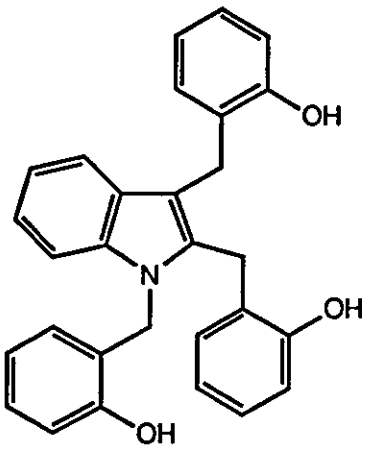
Agrobactin: R=OH ; log $K_f \cong 52$
Parabactin: R=H ; log $K_f \cong 52$ at neutral pH

Figure 26

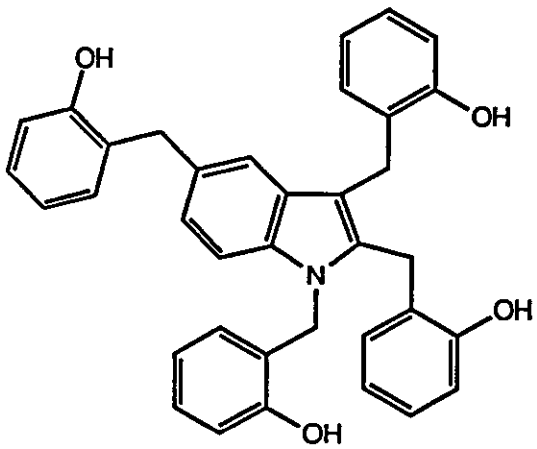
3.2 The Uvarindole Alkaloids.

Several indole-based natural products were considered as to their possible suitability as siderophores but the species discussed here were those first isolated by Waterman and Mohammad[80] from the

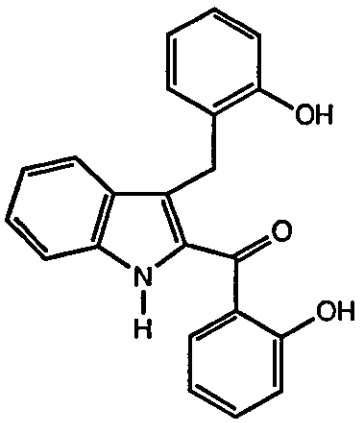
Uvaria angolensis stem bark. These four novel indoles were found to be extensively benzylated and detailed nmr and x-ray crystallography experiments revealed the structures, known as Uvarindoles (A-D) to be as illustrated in Figure 27.



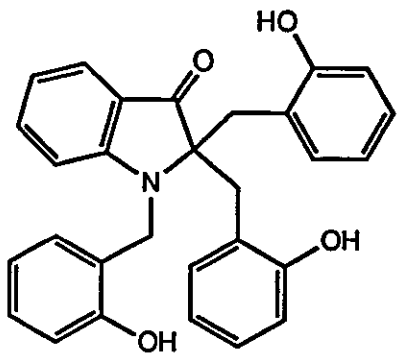
Uvarindole A



Uvarindole B



Uvarindole C



Uvarindole D

Figure 27

The orientation of the hydroxy groups on the benzyl substituents would be ideal for metal chelation, in particular the Uvarindoles A and B, since the separate coordination sites would bind the metal ion above or below the plane of the indole nucleus (Figure 28).

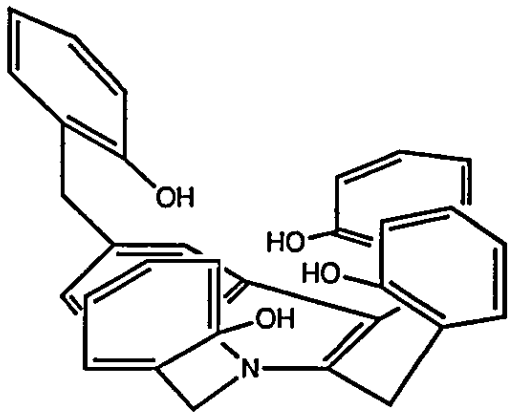


Figure 27

3.3 Retrosynthetic Analysis

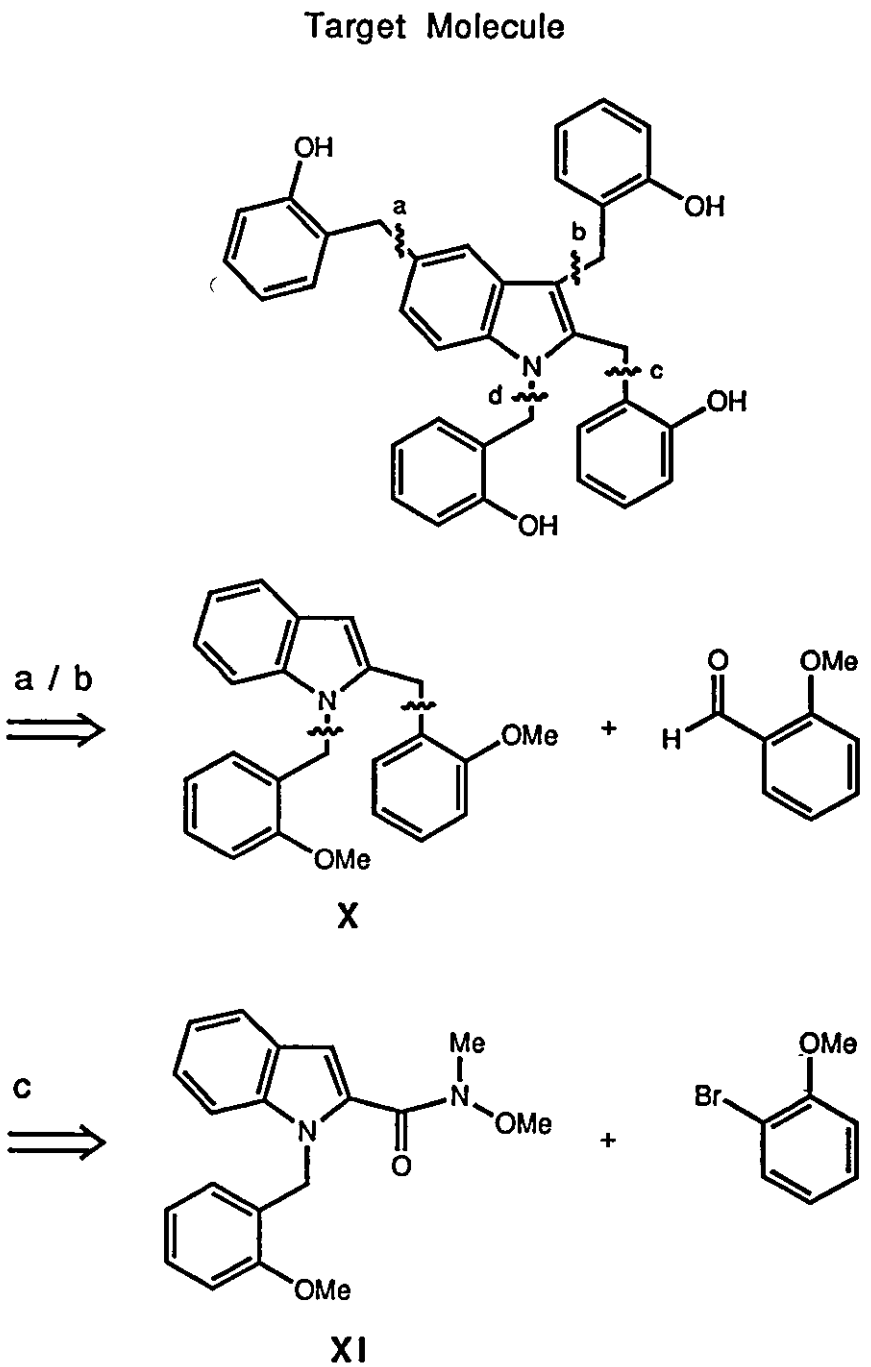


Figure 28

The initial disconnection leads to the 1,2-disubstituted indole **X** that on closer examination leads to a Weinreb amide **XI**, the general synthesis of which has been addressed previously in Chapter 3. The reductive alkylation procedure developed by Steele[83] shows how an

indole such as **X** can be converted to the 1,2,3-trisubstituted indole without the problems of dimerisation often experienced with similar indoles (Figure 29).

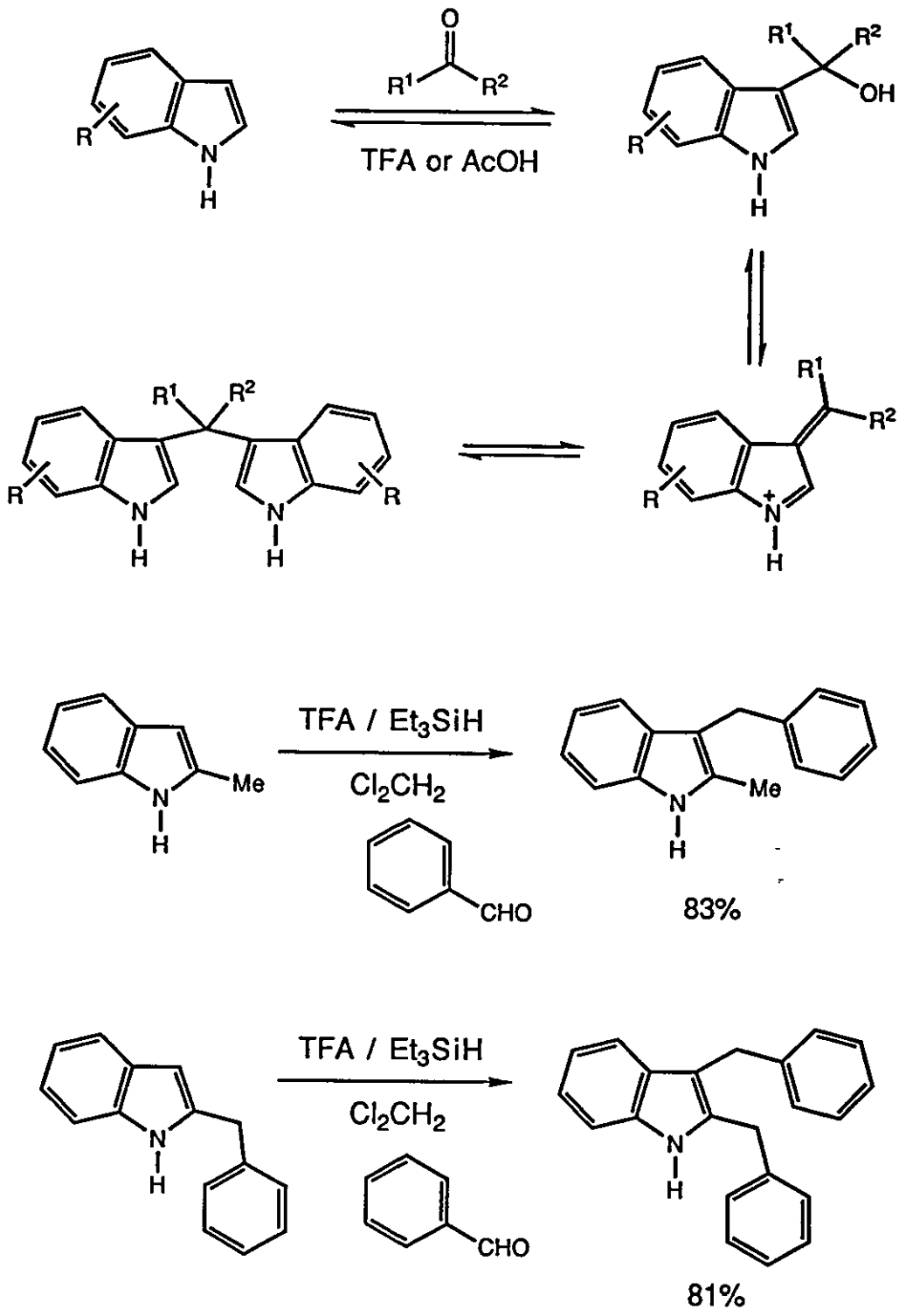
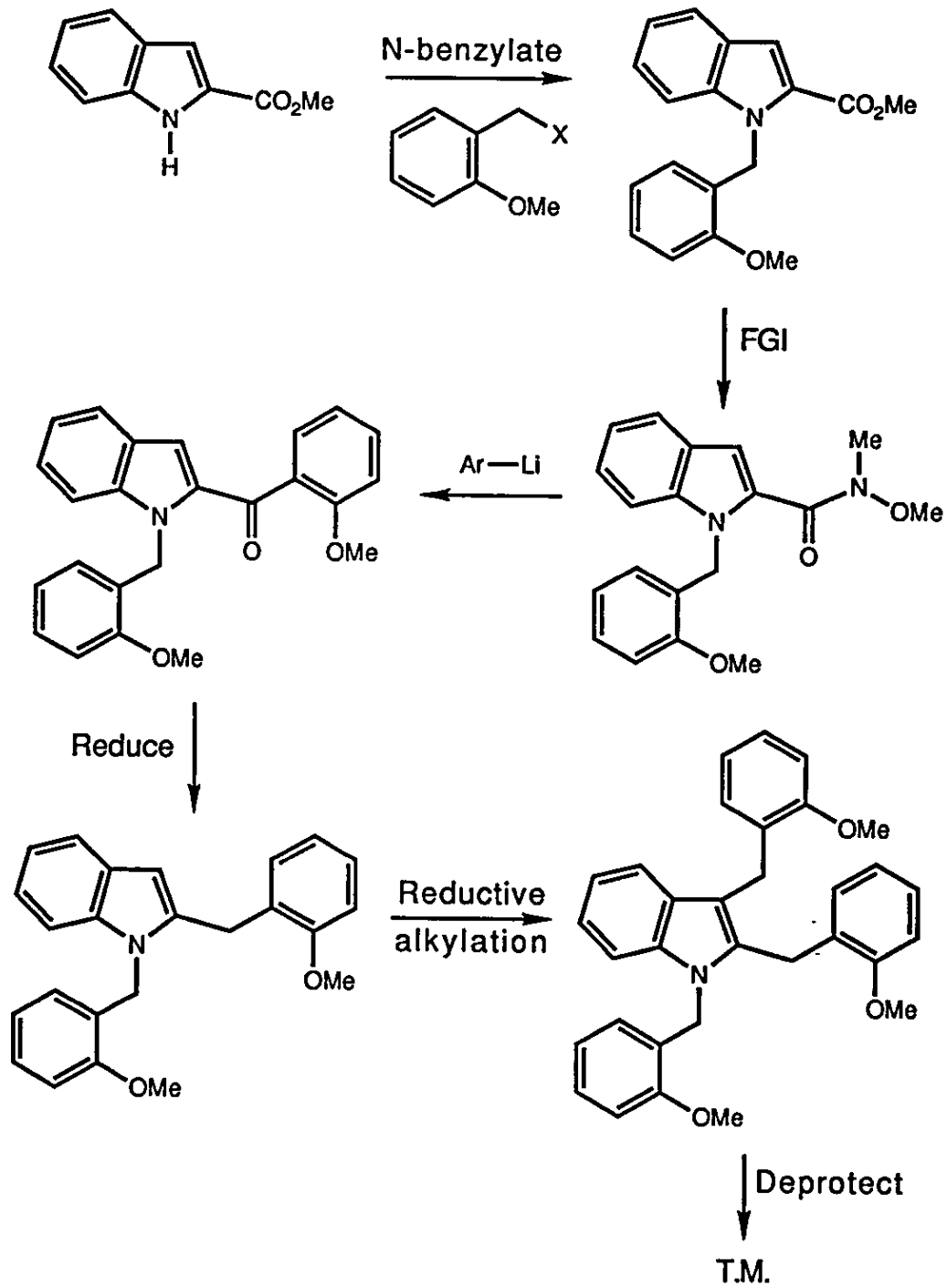


Figure 29

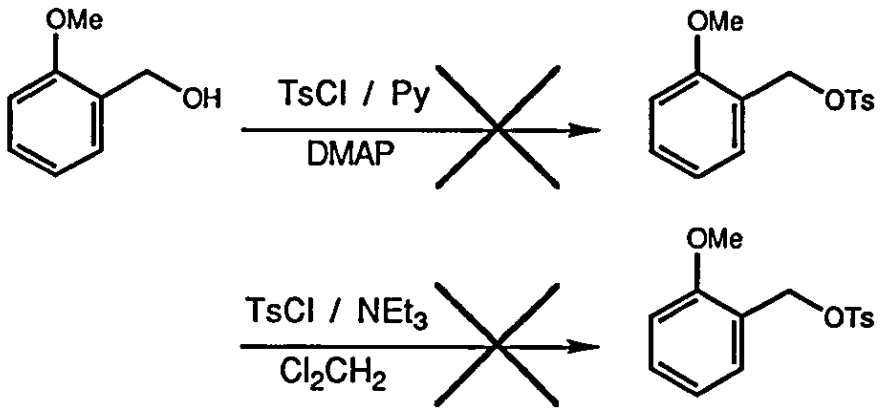
Thus, with the relevant chemistry established, the following scheme was proposed (Scheme 86).



Scheme 86

First, a 2-methoxybenzyl equivalent was required for the N-alkylation step, and the tosylate of 2-methoxybenzyl alcohol was deemed to be the reagent of choice.

Several attempts were carried out to synthesise such an alkylating agent, all of which proved fruitless, leading to an unstable polymeric material (Scheme 87)



Scheme 87

The tosyl group was considered too reactive for the product to be isolated, both the stability of the tosylate ion as a leaving group and the positive mesomeric effect of the neighbouring methoxy group being responsible for the polymerisation observed (Figure 30).

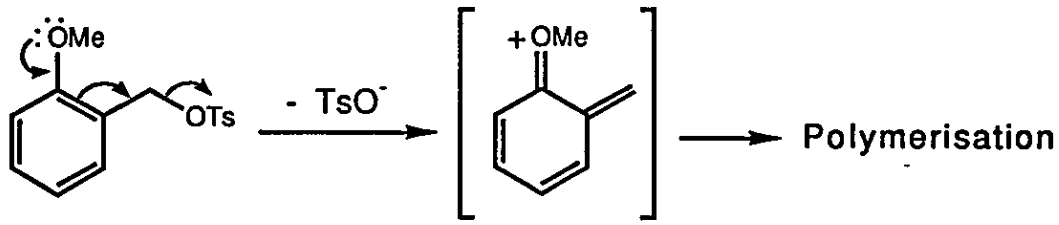


Figure 30

On the basis of this observation the tosyl group was replaced with a group less likely to leave so readily, i.e. a bromine group. Initial attempts at preparing 2-methoxybenzyl bromide were equally unsuccessful but finally the reagent was prepared with phosphorus tribromide (Figure 31).
The 2-methoxybenzyl bromide was isolated a crystalline solid but effective storage in a freezer was impossible as polymerisation became significant within 30 minutes of isolation.

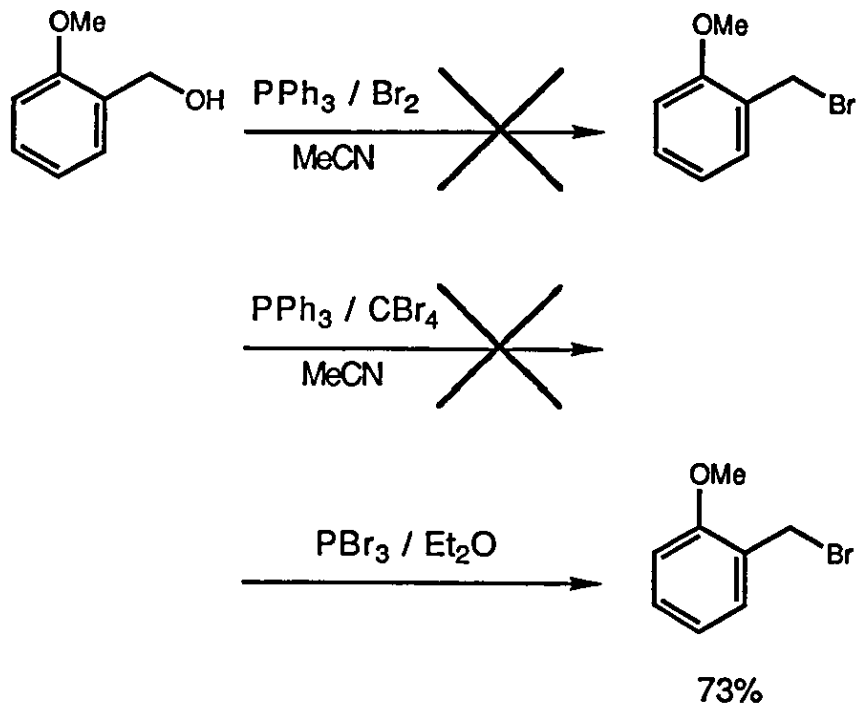
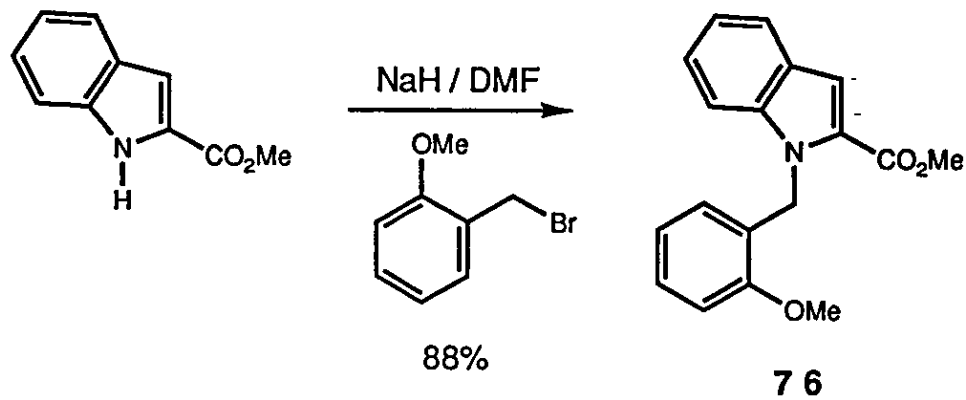


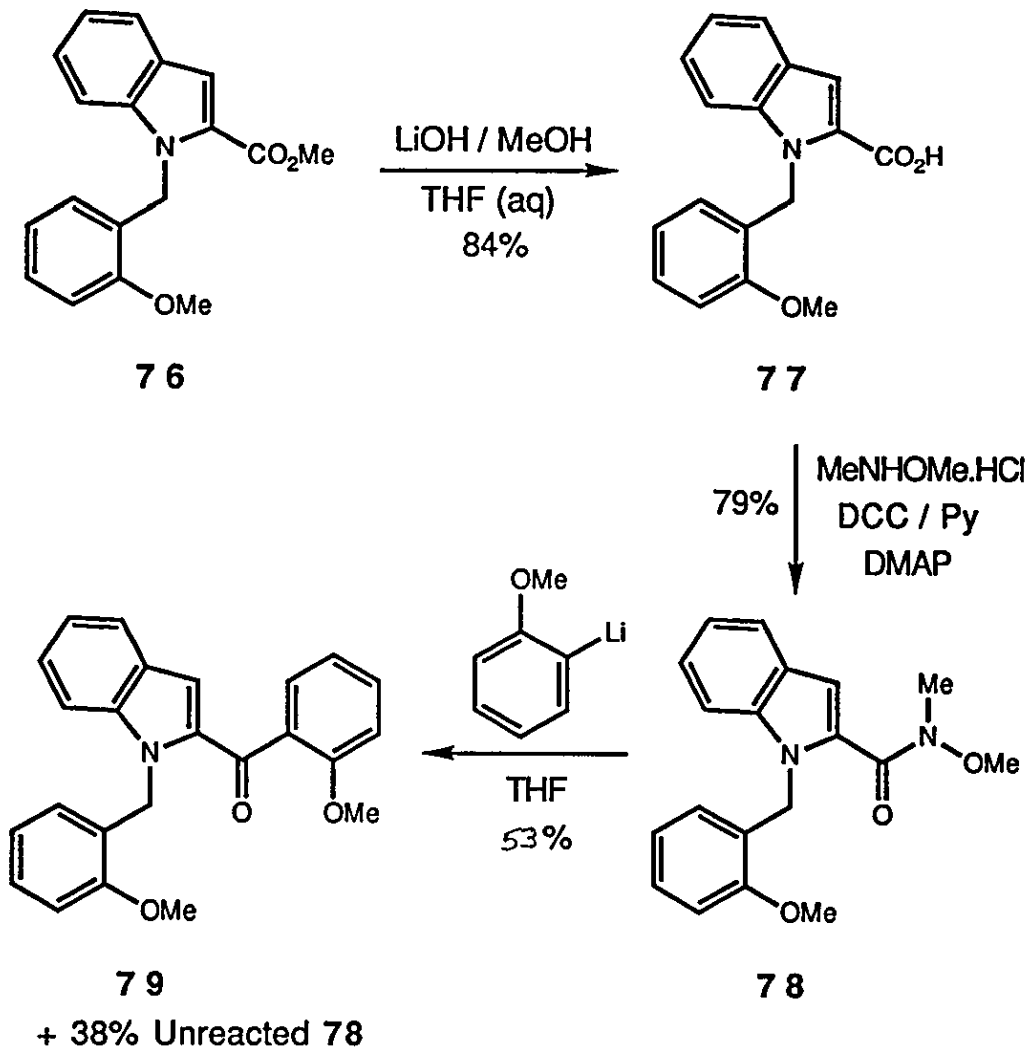
Figure 31

Having successfully synthesised the alkylating agent, methyl indole-2-carboxylate was N-protected by treatment with sodium hydride followed by 2-methoxybenzyl bromide to give **76** in 88% yield (Scheme 88).



Scheme 88

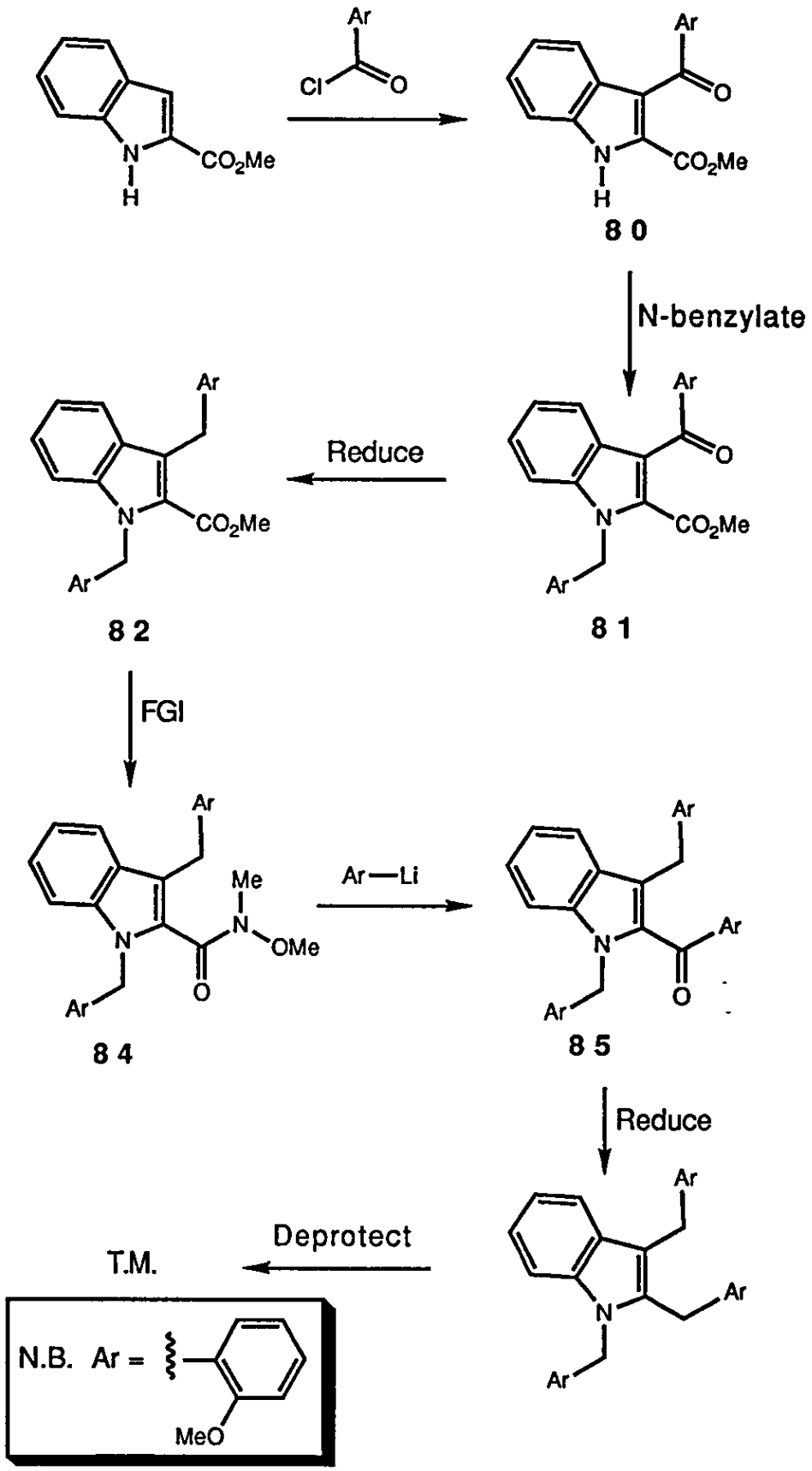
Similar methodology was used for the conversion of **76→79** as was used in Chapter 3 via the Weinreb amide **78** (Scheme 89). The conversion of **78→79** proceeded in a disappointing 53% yield but further optimisation experiments gave only poorer results.



Scheme 89

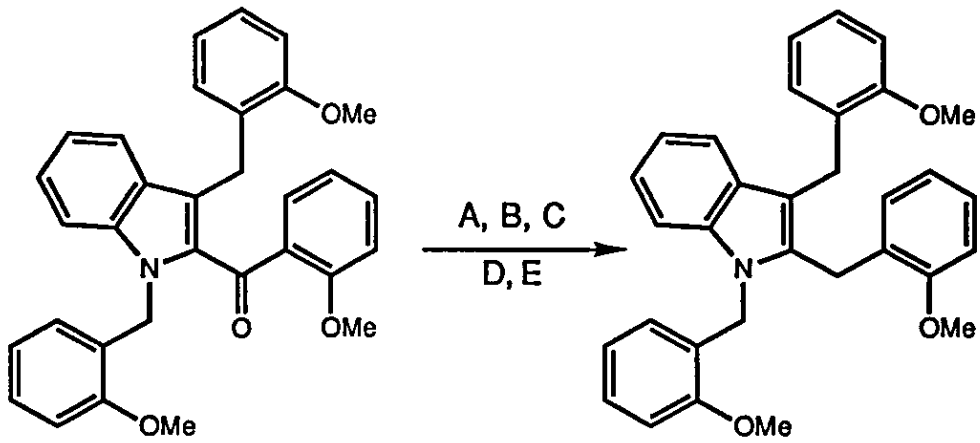
The reduction of the unwanted carbonyl group of **79** proved elusive despite the many approaches attempted. Treatment of **79** with $LiAlH_4$ proved too harsh and led to severe decomposition, likewise partial reduction with $NaBH_4$ yielded many unstable products when, upon hydrogenation of the crude material no identifiable products were obtained.

Since it was clear that reduction of this carbonyl group was not going to be a trivial matter a new, somewhat longer scheme was proposed that would make this operation the penultimate stage in the synthesis (Scheme 90).


Ar
Cl
O
CO2Me
N
H
80
N-benzylate
81
Reduce
82
FGI
84
Me
OMe
Ar—Li
85
Reduce
Deprotect
T.M.
N.B. Ar =
MeO

Scheme 90

The acylation of methyl indole-2-carboxylate was carried out using aluminium chloride and *o*-anisoyl chloride to give the 3-acylindole **80** in 65% yield (recrystallised) where fortunately, no N-acylation was observed. The second methoxybenzyl group was introduced by treatment of **80** with sodium hydride and benzylation with 2-methoxybenzyl bromide affording **81** in 91% yield. The complete reduction of the carbonyl group of **81** proved troublesome once more. Attempts to effect **81**→**82** included boron trifluoride / triethylsilane[84], lithium aluminium hydride and sodium borohydride, of which none proved to be successful. The problem was eventually overcome by catalytic hydrogenation using palladium on activated charcoal as the catalyst under high hydrogen pressure in a Parr shaker, where **82** was isolated in 65% yield at best. The reaction could not be driven to completion despite changes of solvent from ethyl acetate to ethanol and further acid catalysis. The reaction proved unreliable in yield and typically 25-50% of unreacted starting material **81** was isolated when the reaction was stopped. Attempts to boost the reaction turnover by removing spent catalyst and exposure to fresh Pd/C proved futile as did increasing the reaction time from 24 hours to 1 week. Only by recycling the unreacted starting material and repeating the reaction several times could an acceptable amount of material be brought through to the next stage of the synthesis. The acid **83** was prepared from basic hydrolysis of **82** in 69% yield using lithium hydroxide / methanol in aqueous THF. The corresponding Weinreb amide **84** was prepared in 54% yield using the method previously developed i.e. N, O-dimethyl hydroxylamine hydrochloride / DCC. The reaction of the amide **84** with 2-anisyllithium proved problematic due to the increased steric bulk of the electrophile, but the reaction was eventually carried out, giving **85** in 59% (with 20% unreacted **84**) by allowing the electrophile longer contact with the 2-anisyllithium at -78°C before warming to ambient temperature. The final problem of reducing the carbonyl group to its' parent alkyl group now remained to be addressed (Scheme 91).



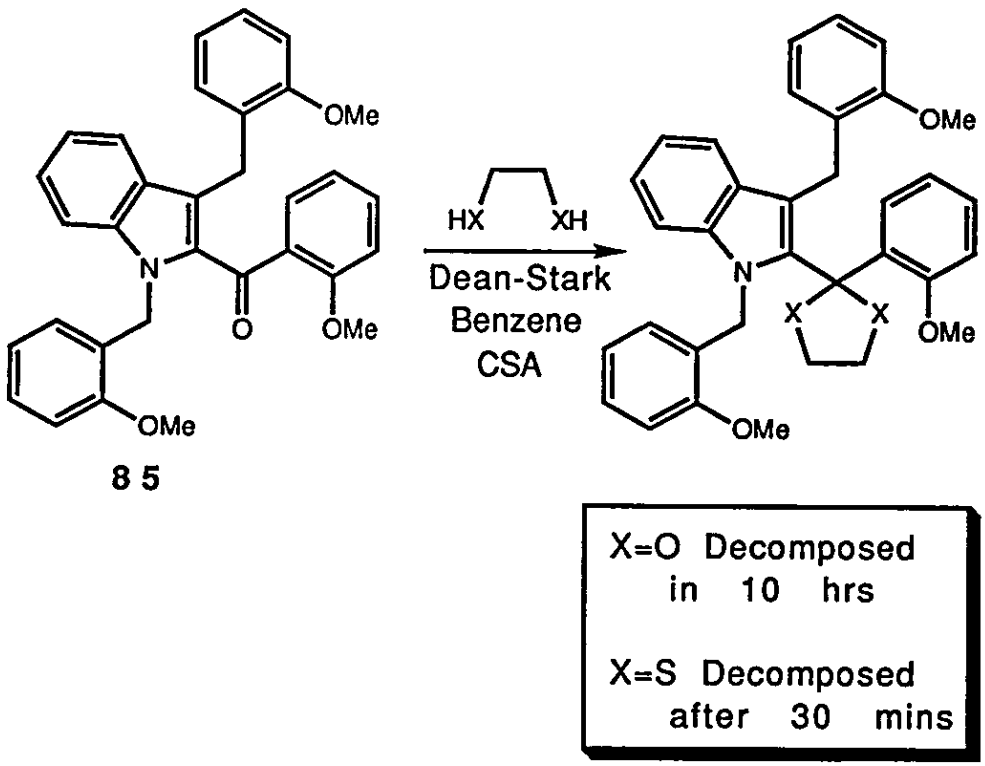
8 5

A: Diborane / Et_2O	- No reaction.
B: $BF_3.Et_2O$ / Et_3SiH / Cl_2CH_2	- No reaction at 0°C or at reflux.
C: $LiAlH_4$ / Et_2O	- Decomposed after 1 hour at 0°C with 0.25 eq.
D: $NaBH_4$ / MeOH	- Decomposed after 3 hours with 0.5 eq. at 0°C.
E: H_2 / Pd(C) / EtOH	- Many >9 products.

Scheme 91

None of the methods A→E in Scheme 91 showed any improvement when the conditions were altered, so attempts to form the ethylene and the dithioethylene ketals were investigated (Scheme 92).

The methods of Dean-Stark conditions in refluxing benzene with catalytic camphor-10-sulfonic acid gave similar results to that found in Scheme 91. The reactions were equally unsuccessful when 4Å molecular sieves were substituted for the Dean Stark conditions.



85

Scheme 92

The reactivity of the 2-acyl group on the indoles **79** and **85** was considerable and was thought to be a facet of both the neighbouring indole nucleus and the 2-methoxybenzyl substituent. The reactivity of this position is exemplified by the instability of indole-2-methanol towards mild acid or base, and 2-methoxybenzyl bromide itself polymerises on standing in approximately 30 minutes. Therefore with the two factors combined in the same molecule the inherent reactivities produce a species unstable to acid and base and also to most types of manipulation. At this stage time factors had become critical and work on all routes was terminated.

In conclusion, it has been demonstrated that indoles can be built up in a variety of ways both by direct incorporation into the N- and C-3 positions (Section 2.3) via Friedel-Crafts acylation. Construction of tetrahydrocarbazoles by Diels-Alder trapping of indole-2,3-quinodimethanes with dienophiles has also been demonstrated in Section 2.2, and modification of existing C-2 fragments has been investigated by reaction with aryllithium reagents (Section 2.3 and 3.3). Of the approaches carried out towards the synthesis of Pre-

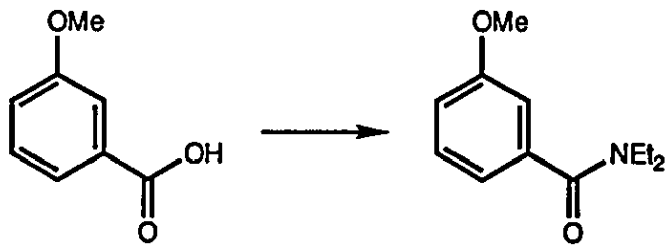
Kinamycin, the most promising route is that concerned with the Friedel-Crafts reactions of methyl indole-2-carboxylate (Section 2.3) which would need little modification to produce a workable synthetic scheme.

With regards to the Uvarindole syntheses, the problem of reducing the carbonyl group in the indole **85** remains to be overcome but there is little doubt that a successful scheme can be discovered since not all of the possible methods of carbonyl reduction were attempted in the time allotted for this part of the project.

Chapter 4

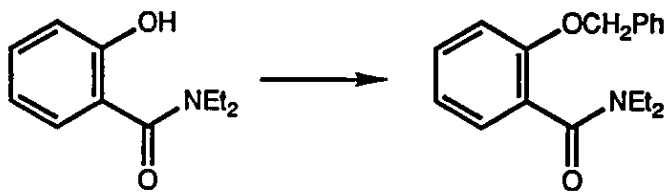
Experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction boiling between 40 and 60°C, and was distilled through a 36cm Vigreux column before use. Diethyl ether, xylene, benzene and toluene were dried where necessary by storage over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen prior to use. Methylene chloride was distilled from phosphorus pentoxide. DMF was dried by stirring over calcium hydride for 15h, decanted and distilled under reduced pressure before storage over 4 Å molecular sieves under nitrogen. Pyridine and triethylamine were distilled from, and stored over potassium hydroxide pellets. Methanol and ethanol were distilled from magnesium turnings and iodine and stored over activated 4Å molecular sieves under nitrogen.
Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{245}. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with Ehrlich's reagent or phospho-molybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60H silica or Matrex silica 60. Pressure was applied with hand bellows. Samples were applied pre-absorbed on silica or as a saturated solution in an appropriate solvent.
IR spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform, thin films or as KBr discs. Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental Analyser. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments; J values are recorded in Hz. High and low resolution mass spectra on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (SERC mass spectrometry service, Swansea). M.p.'s were measured on an Electrothermal digital melting point apparatus and are uncorrected.



N, N-Diethyl-3-methoxybenzamide. **(15)**

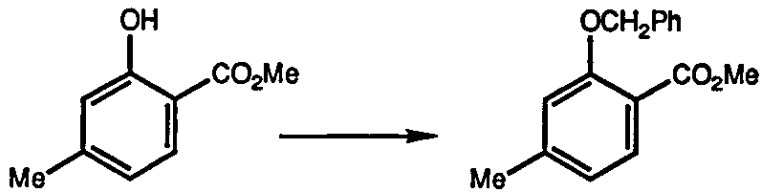
m-Anisic acid (10 g, 66 mmol) was dissolved in thionyl chloride (23.5 g, 197 mmol) at ambient temperature and stirred for 18 h. The remaining thionyl chloride was removed *in vacuo* and the crude acid chloride redissolved in methylene chloride (100 ml) and added dropwise to a solution of diethylamine (14.4 g, 197 mmol) in methylene chloride (150 ml) at ambient temperature.The reaction was stirred for 1 hour, poured into water and extracted with methylene chloride. The organic layers were recombined,washed with 2M hydrochloric acid,water,brine and dried and evaporated to give the *title compound* (**15**) as a tan oil (7.6 g, 56%). (Found: C, 69.04; H, 8.24; N, 6.76%. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%). υ_{max}(Nujol) 1616 cm^{-1}. δ_H(60 MHz, $CDCl_3$) 7.31-6.95(1H, m), 6.93-6.60(4H, m), 3.72(3H, s), 3.70-3.06(4H, m), 1.22(6H, t).



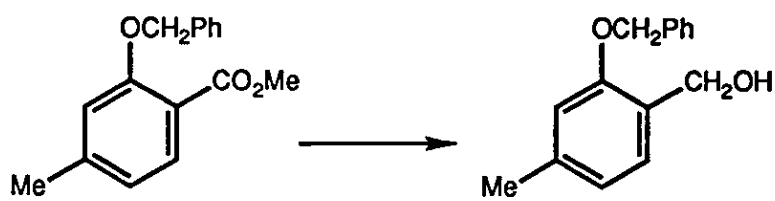
N, N-Diethyl 2-benzyloxybenzamide **(16)**

N, N-Diethylsalicylamide (5 g, 26 mmol) and benzyl bromide (4.87 g, 26 mmol) were dissolved in acetone (300 ml) and potassium carbonate (35.75 g, 260 mmol) was added in one portion. The reaction was brought to reflux for 18 h after which the acetone was removed *in vacuo*. The residue was redissolved in water (300 ml) and extracted with methylene chloride. The organic layers were combined, washed with sodium bicarbonate, water and brine then dried and evaporated to give a colourless oil which when triturated with cold ether gave the *title compound* (**16**) as a white crystalline solid (6.24 g, 85%). m.p. 69.4-69.8°C. (Found:C, 76.30;

H, 7.49; N, 4.91%; $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94%). υ_{max}(Nujol) 1614 cm^{-1}. δ_H(60 MHz, $CDCl_3$) 7.60-6.81(9H, m), 5.10(2H, s), 3.03-4.11(4H, m), 1.51-1.04(6H, m).

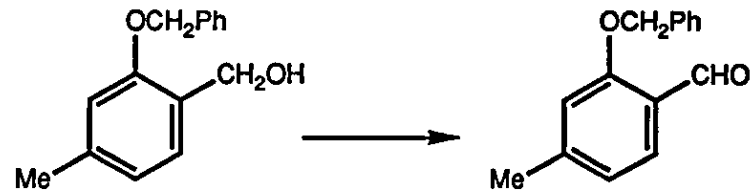


Methyl 2-Benzyloxy-4-methylbenzoate(**17**)
A mixture of benzyl bromide (11.3 g, 66 mmol), methyl 4-methylsalicylate (10 g, 60 mmol) and potassium carbonate (83.1 g, 600 mmol) were dissolved / suspended in acetone (500 ml) and brought to reflux for 18 h. On cooling the acetone was removed *in vacuo* and the residue dissolved in water (500 ml). The aqueous was extracted with ether (3 x 200 ml) and the organic layers combined, washed with sodium bicarbonate, water and brine, then dried (Na_2SO_4) and evaporated to give the *title compound* (**17**) (11.7 g, 76%), m.p.105-106.9°C. (Found C, 78.82; H, 7.04%. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29%), υ_{max}(Nujol) 1625 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 7.92-7.60(1H, d), 7.57- 7.22(5H, m), 6.65(2H, m), 5.13(2H, s), 3.92(3H, s), 2.32(3H, s).

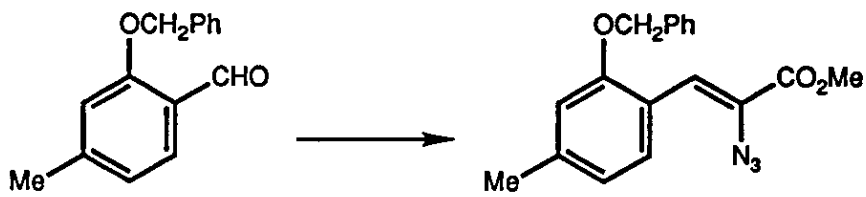


2-Benzyloxy-4-methylbenzylalcohol (**18**)
Lithium aluminium hydride (1.72 g, 45 mmol) was added gradually to a solution of **17** (10.6 g, 40 mmol) in THF (150 ml) at ambient temperature and the reaction stirred for 2 h. Water (15 ml) was added dropwise and the resulting solid removed by filtration and washed well with ether. The aqueous was extracted with ether and the organic layers combined, washed with sodium bicarbonate, water and brine then dried and evaporated *in vacuo* to give the *title compound* (**18**) (8.5 g, 92%), m.p. 49.6 - 49.8°C. (Found: C, 77.26, H, 6.78%. $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06%), υ_{max}($CHCl_3$) 3424 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 7.47- 7.25(5H, s), 7.21-7.13(1H, m), 6.81-

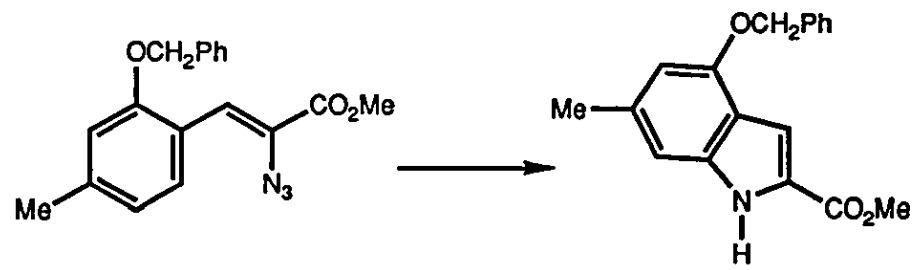
6.51(2H, m), 5.13(2H, s), 4.65(2H, s), 2.35(3H, s). m/z 228(M^+, 100%), 91(77).



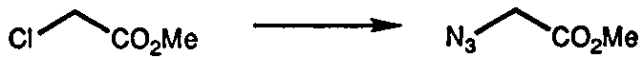
2-Benzyloxy-4-methylbenzaldehyde (**19**)
To a solution of **18** (1 g, 4.35 mmol) in methylene chloride (40 ml) was added manganese dioxide (3.78 g, 43.5 mmol) in one portion and the reaction stirred at ambient temperature for 1.5 h. The excess manganese dioxide was removed by filtration and the liquors evaporated *in vacuo* to give the *title compound* (**19**) (0.91 g, 91%) m.p. 86.4 - 86.6°C (Found: C, 79.61; H, 6.27%. $C_{15}H_{14}O_2$ requires C, 79.62; H, 6.24%). υ_{max}(Nujol) 1672 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 10.77(1H, s), 7.85-7.55(1H, d), 7.55-7.2 (5H, s), 7.05-6.63(2H, m), 5.15(2H, s), 2.35(3H, s). m/z 226(M^+, 100%), 91(77).



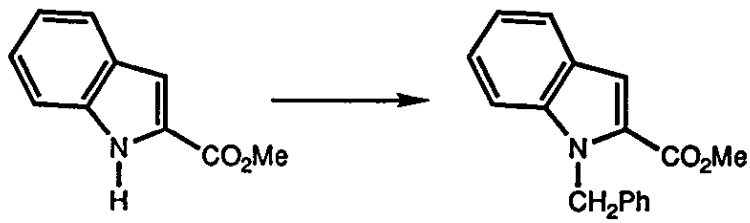
Methyl 2-azido-3-(2-benzyloxy-4-methylphenyl)propenoate (**20**)
Sodium metal (0.93 g, 39 mmol) was dissolved in dry methanol (25 ml) and cooled to -12°C. A mixture of **19** (2.31 g, 10 mmol), freshly prepared methyl azidoacetate **22** (4.65 g, 39 mmol), THF (10 ml) in methanol (10 ml) was added dropwise keeping the internal temperature below -10°C and the reaction allowed to warm to ambient temperature over 4 hours. Water (100 ml) was added gradually and the solids removed, redissolved in ethyl acetate and washed with water and brine, dried and evaporated to give the *title compound* (**20**) (1.93 g, 60%), m.p. 87-87.2 °C. υ_{max}(Nujol) 2124, 1700 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 8.11-7.94(1H, d), 7.42-7.07(6H, m), 6.78(1H, s), 5.05(2H, s), 3.75(3H, s), 2.25(3H, s); m/z 323(M^+, 2%), 295(100), 280(4), 263(5), 248(2).



Methyl 4-benzyloxy-6-methylindole-2-carboxylate (**21**)
A solution of the azide **20** (1.54 g, 4.64 mmol) in xylene (15 ml) was added dropwise over a period of 1 hour to refluxing xylene (163 ml). After refluxing for 15 min, the reaction was evaporated to minimum volume and the solids removed and washed with cold ether, leaving the *title compound* (**21**) (0.81 g, 40%) m.p. 195.5-195.8°C (Found: C, 73.40; H, 5.79; N, 4.69%. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%). υ_{max}(Nujol) 3332, 1688 cm^{-1}; δ_H(250 MHz, $CDCl_3$); m/z 295(M^+, 17%), 204(25), 172(20), 91(100).

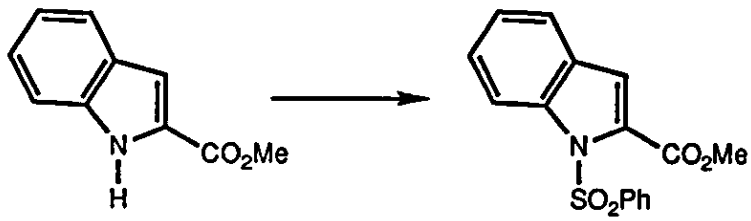


Methyl azidoacetate (**22**)
Methyl chloroacetate (20 g, 184 mmol) and sodium azide (15.08 g, 232 mmol) were dissolved in acetone (30 ml) and water (20 ml) and the reaction brought to reflux for 18 h (Care!). On cooling, the acetone was removed *in vacuo* at ambient temperature (no water bath heating) and the residue extracted with ether. The ether fractions were combined, washed with brine, dried and evaporated *in vacuo* at ambient temperature to give the *title compound* (**22**) as a tan oil (17.2 g, 81%). All analytical data found were identical with that of a reference sample.

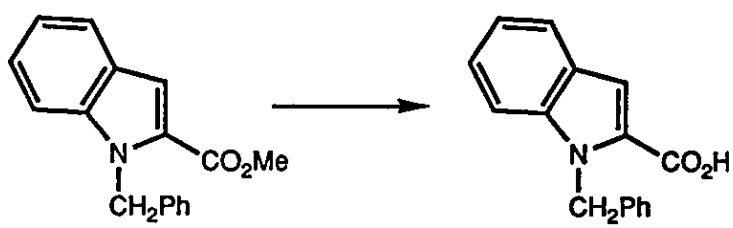


Methyl 1-benzylindole-2-carboxylate (**23**)
Sodium hydride (0.26 g, 10.7 mmol) was suspended in dry DMF (25 ml) and a solution of methyl indole-2-carboxylate (1.5 g, 8.6

mmol) in DMF (15 ml) added dropwise. The reaction was stirred at ambient temperature for 15 min, then benzyl bromide (1.61 g, 9.53 mmol) was added dropwise and the reaction stirred for 2 h. The reaction was poured into water (175 ml) and extracted with ethyl acetate. The combined organic layers were recombined, washed with sodium bicarbonate, water and brine, dried and evaporated *in vacuo* to give the *title compound* (**23**) as a pale oil (2.04 g, 90%). (Found: C, 76.90%; H, 5.65%; N, 5.24%, $C_{17}H_{15}NO_2$ requires; C, 76.91%; H, 5.70%; N, 5.26%). $\upsilon_{max}(CHCl_3)$ 1704 cm^{-1}; δ_H(60 MHz, $CHCl_3$) 7.62(1H, m), 7.44-6.90(9H, m), 5.74(2H, s), 3.75(3H, s).

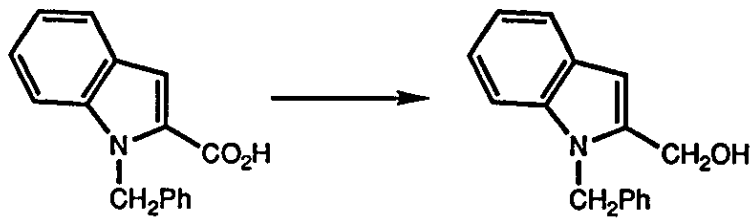


Methyl 1-benzenesulfonyl-indole-2-carboxylate (**24**)
Sodium hydride (0.38 g, 13 mmol) was suspended in dry DMF (20 ml) and to it was added a solution of methyl indole-2-carboxylate (2 g, 11 mmol) in DMF (10 ml). After stirring at ambient temperature for 5 min, a solution of benzenesulfonyl chloride (2.02 g, 11 mmol) in DMF (20 ml) was added dropwise and the reaction stirred for 2 h. Water (50 ml) was added dropwise and the aqueous extracted with methylene chloride. The organic layers were combined, washed with sodium bicarbonate, water and brine then dried and evaporated *in vacuo* to give the *title compound* (**24**) as a tan oil (3.04 g, 85%). $\upsilon_{max}(CHCl_3)$ 1674 cm^{-1}; δ_H(60 MHz, $CHCl_3$) 7.74(1H, m), 7.53-6.91(9H, m), 3.55(3H, s). Consistent with a reference sample.



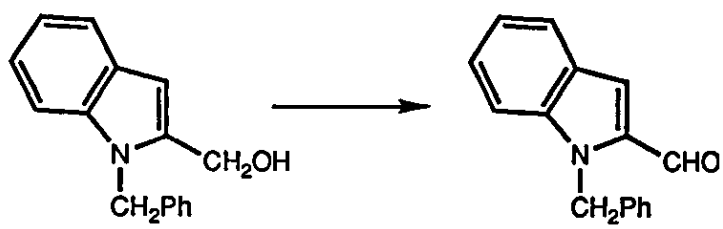
1-Benzylindole-2-carboxylic acid

Methyl 1-benzylindole-2-carboxylate (0.5 g, 1.89 mmol), lithium hydroxide (0.05 g, 2.08 mmol) methanol (2.5 ml) and water (2.5 ml) were all brought to reflux for 18 h where, on cooling the reaction was brought to pH2 with 2M H_2SO_4. The reaction was then extracted with ether and the organic layers combined, washed with water and brine, then dried and evaporated to give the*title compound* as a thick gum, used directly. (0.34 g, 72%). υ_{max}(Nujol) 1695 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 9.82(1H, broad s), 7.53(1H, m), 7.47-6.93(9H, m).



1-Benzyl-2-hydroxymethylindole (**25**)

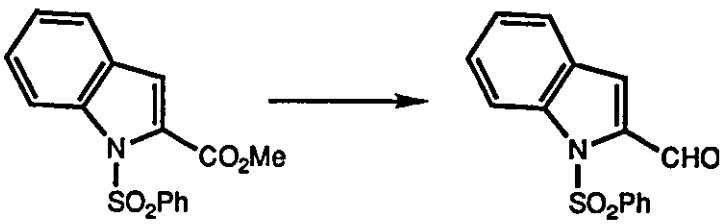
To a solution of 1-benzyl-indole-2-carboxylic acid (2 g, 7.55 mmol) in ether (20 ml) at 0 C was added lithium aluminium hydride (0.32 g, 8.3 mmol) gradually and the reaction stirred at 0°C for 1h. Water (5 ml) was added dropwise and the resulting solids were removed by filtration. The solids were washed well with ethyl acetate and the remaining aqueous extracted with more ethyl acetate. The organic layers were combined, washed with water and brine and dried (Na_2SO_4) and evaporated *in vacuo* to give the*title compound* (**25**) (1.6 g, 89%). m.p.100.2-100.9°C. (Found: C, 80.50%; H, 6.35%; N, 5.83%. $C_{16}H_{15}NO$ requires C, 80.98%; H, 6.37%; N, 5.90%). υ_{max}(Nujol) 3468 cm^{-1}. δ_H(60 MHz, $CDCl_3$) 8.51(1H, s), 7.15-6.92(8H, m), 6.81(1H, s), 5.72(2H, s), 5.45(2H, s).



1-Benzylindole-2-aldehyde (**26**)

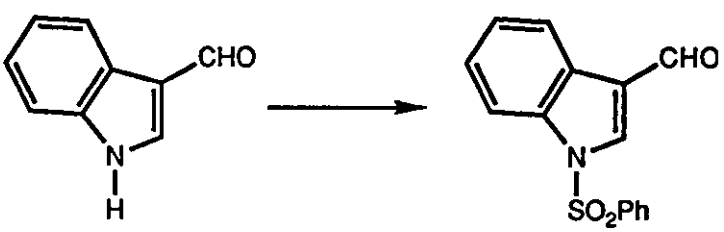
Manganese dioxide (1.84 g, 21.1 mmol) was added in one portion to a solution of **25** (0.5 g, 2.11 mmol) in methylene chloride (10 ml)

and the reaction stirred at ambient temperature for 18 h. The excess manganese dioxide was removed by filtration and the liquors evaporated *in vacuo* to give the *title compound* (**26**) as a pale oil (0.44 g, 89%). (Found: C, 81.20%; H, 5.58%; N, 5.88%; $C_{16}H_{13}NO$ requires C, 81.68%; H, 5.57%; N, 5.95%). υ_{max}(Nujol) 1664 cm^{-1}. δ_H(60 MHz, $CDCl_3$) 10.81(1H, s), 8.07(1H, d), 7.52- 7.03(9H, m), 5.81(2H, s).



1-Benzenesulfonylindole-2-aldehyde (**27**)

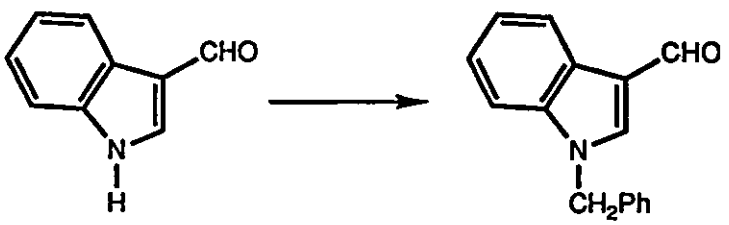
Lithium aluminium hydride (0.18 g, 4.75 mmol) was added gradually to a solution of **24** (1.5 g, 4.75 mmol) in ether / THF (2:1) (30 ml) and the reaction stirred vigorously for 20 mins. Water (1 ml) was added carefully and the solids removed by filtration. The liquors were washed with sodium bicarbonate, water and brine and after drying, redissolved in methylene chloride and poured onto manganese dioxide (4.13 g, 47.5 mmol) and stirred for 24 h. The excess manganese dioxide was removed by filtration and the liquors evaporated *in vacuo* to give the *title compound* (**27**) (0.66 g, 49%). (Found: C, 63.07%; H, 3.88%; N, 4.93% $C_{15}H_{11}NO_3S$ requires C, 63.15%; H, 3.89%; N, 4.91%). υ_{max}($CHCl_3$) 1674 cm^{-1}; δ_H(60 MHz, $CHCl_3$) 10.21(1H, s), 8.03(1H, d), 7.51-7.21(9H, m).



1-Benzenesulfonylindole-3-aldehyde (**28**)

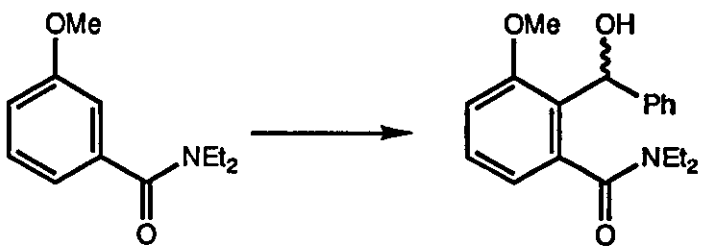
Sodium hydride (0.23 g, 7.59 mmol) was suspended in dry DMF (10 ml) and a solution of indole-3-aldehyde (1 g, 6.9 mmol) in DMF (10 ml) was added dropwise and after stirring for 5 min, benzenesulfonyl chloride (1.22 g, 6.9 mmol) was added dropwise.

The reaction was stirred at ambient temperature for 2h, poured into water (100 ml) and extracted with ethyl acetate. The organic layers were combined, washed with sodium bicarbonate, water and brine then dried and evaporated*in vacuo* to give the*title compound* (**28**) as a white semi-solid (1.53 g, 78%). υ_{max}(Nujol) 1674 cm^{-1}. δ_H(60 MHz, $CDCl_3$) 10.03(1H, s), 8.31-8.22(2H, m), 8.20-7.95(3H, m) 7.84-7.13(5H, m). Consistent with a reference sample.



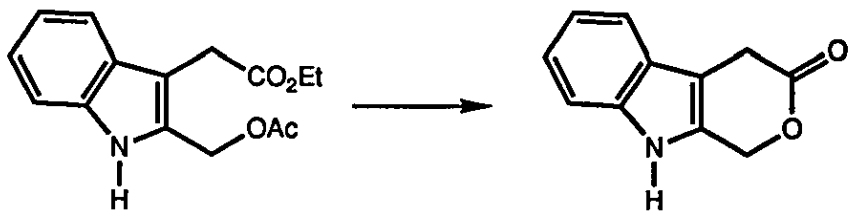
1-Benzylindole-3-aldehyde (**29**)

Benzyl chloride (2.88 g, 23 mmol), indole-3-aldehyde (3 g, 21 mmol) and potassium carbonate (28.5g, 210 mmol) were dissolved / suspended in acetone (150 ml) and the reaction brought to reflux for 18 h. On cooling, the acetone was removed *in vacuo* and the residue redissolved in water (150 ml). The aqueous was extracted with methylene chloride and the organic layers combined and washed with sodium bicarbonate, water and brine then dried and evaporated to give the *title compound* (**29**) as a buff solid (4.5 g, 96%) m.p. 123.0-124.5°C. υ_{max}($CHCl_3$) 1656 cm^{-1}; δ_H(60 MHz, $CHCl_3$) 9.94(1H, s), 8.37(1H, m), 7.51-7.11(8H, m), 3.25(3H, s).



1 Phenyl-1-(2-(N, N-diethylamido)-6-methoxy)methylalcohol (**30**). A solution of **15** (1 g, 4.83 mmol) in THF (10 ml) was cooled to -78°C and s-butyllithium (1.39 M) (3.82 ml, 5.31 mmol) was added dropwise. The reaction was allowed to warm to 0°C where benzaldehyde (0.56 g, 5.31 mmol) was added dropwise and the reaction allowed to warm overnight. Aqueous workup afforded the *title compound* as a buff oil(**30**) (0.37 g, 25%). (Found: C, 72.42; H,

7.30; N, 4.29%. $C_{19}H_{23}NO_3$ requires C, 73.29; H, 6.80; N, 4.50%). υ_{max}($CHCl_3$) 3460, 1624 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.41-6.82(9H, m), 6.35(1H, d, J 11.5 Hz), 5.30(1H, d, J 11.5 Hz), 3.85(3H, s), 3.18(2H, m), 2.81(1H, m), 2.43(1H, m), 0.91(6H, m). δ_C(62.5 MHz, $CDCl_3$) 171.6, 157.5, 144.3, 137.2, 131.2, 128.5, 127.6, 126.2, 125.7, 119.2, 112.1, 67.7, 56.0, 43.1, 39.1, 13.4, 12.4.

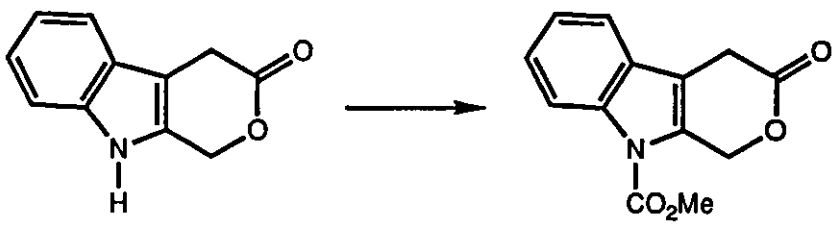


1,4-Dihydropyrano[3,4-b]indol-3-one (**35**)

Potassium carbonate (3.01 g, 21.82 mmol) was added in one portion to a stirred solution of ethyl 2-acetoxymethylindole-3-acetate **32** (2.00 g, 7.27 mmol) in ethanol (50 ml). After stirring at room temperature for 30 min, water (150 ml) was added, and the aqueous mixture extracted with ether (2 x 80 ml). The combined ethereal extracts were washed with water (2 x 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give (**33**) as a brown solid (1.61 g, 95%) m.p. 112-113.2°C. (Found: C, 67.1; H, 6.5; N, 6.0 $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%); υ_{max} (Nujol) 3472, 3226, 1714, 1031, 1008, 985, 739 cm^{-1}; δ_H(90 MHz, $CDCl_3$) 8.82(1H, br, NH), 7.68-7.45(1H, m), 7.30-7.05(3H, m), 4.68(2H, s), 4.12(2H, q, J 7 Hz), 3.74(2H, s), 3.35(1H, br, OH), 1.23(3H, t, J 7 Hz); m/z 233(M^+, 69%), 216(3), 204(8), 187(5), 160(100), 158(14), 146(42), 142(31), 130(28).

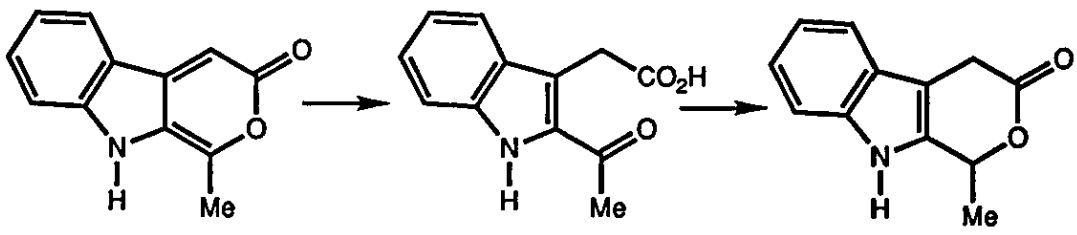
A mixture of potassium hydroxide (2 M, 20 ml) and methanol (30 ml) was added to the indole-ester (**33**) (2.16 g, 9.27 mmol) and the reaction stirred at room temperature for 15 min. Ether (100 ml) was added and the mixture acidified to pH2 with dilute phosphoric acid. The organic phase was separated and aqueous extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 2-hydroxymethylindole-3-acetic acid (**34**) as a pale brown gum (1.72 g, 91%).

The above crude product (1.72 g, 8.4 mmol) was dissolved in THF (100 ml) and the solution cooled to 0°C under nitrogen. Triethylamine (2.12 g, 21 mmol, 2.92 ml) was added followed by dropwise addition of iso-butyl chloroformate (1.2 g, 8.8 mmol, 1.14 ml) over a period of 10 min. After stirring for 2 h saturated ammonium chloride (100 ml) was added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated and the residue chromatographed (ethyl acetate-light petroleum) to give the *title compound* (**35**) (674 mg, 43%) m.p. 169-171°C (darkens, gas evolution observed on heating above 180°C), υ_{max} (Nujol) 3265, 1713, 1456, 1416, 1209, 1193, 1052, 747 cm^{-1}; δ_H[250 MHz, $(CD_3)_2CO$] 10.20(1H, br, NH), 7.48(1H, d, J 7.6 Hz), 7.41(1H, br d, J 7.6 Hz), 7.14(1H, ~ t, J 7.6 Hz), 7.05(1H, ~ t, J 7.6 Hz), 5.59(2H, t, J 1.7 Hz), 3.80(2H, t, J 1.7 Hz); m/z 187(M^+, 35%), 143(100).



Methyl 1,4-Dihydro-3-oxopyrano[3,4-b]indole-9-carboxylate (**36**)

Dimethyl pyrocarbonate (466 mg, 3.48 mmol) was added to a stirred solution of the dihydropyranoindole (**35**) (325 mg, 1.74 mmol) in acetonitrile (15 ml) followed by DMAP (25 mg, 0.2 mmol). After 20 min, the precipitate which had formed was filtered to give the *title compound* (**36**) (388 mg, 91%) m.p. 198-202°C, (Found: M^+ 245.0690. $C_{13}H_{11}NO_4$ requires M^+ 245.0688); υ_{max}(Nujol) 1736 sh, 1723 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 8.11(1H, br d, J 8 Hz), 7.43(1H, br d, J 8 Hz), 7.40-7.27(2H, m), 5.79(2H, t, J 3 Hz), 4.08 (3H, s), 3.78(2H, t, J 3Hz); δ_C(62.5 MHz, $CDCl_3$) 172.5, 163.1, 134.8, 133.0, 132.1, 129.9, 128.3, 123.8, 120.1, 116.2, 72.5, 59.4, 38.4; m/z 245(M^+, 100%), 201(72).

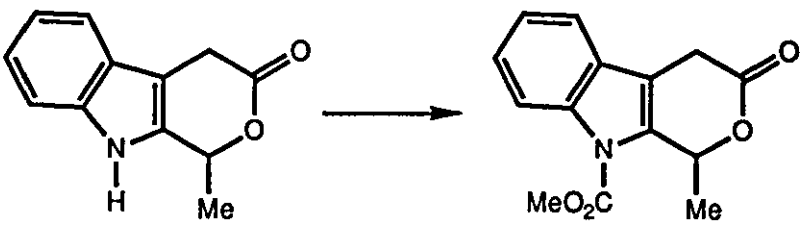


1-Methyl-1,4-dihydropyrano[3,4-b]indol-3-one (**39**)
1-Methylpyrano[3,4-*b*]indol-3-one (**49**) (3 g, 11.76 mmol) and sodium hydroxide (2M, 28.5 ml) were dissolved in methanol (28.5 ml), and the reaction mixture brought to reflux for 20 min. On cooling, the pH of the reaction mixture was brought to 1 with 2M hydrochloric acid and the brown solid filtered and recrystallised (methanol-water) to give 2-acetylindole-3-acetic acid (**37**) (2.9 g, 90%), m.p. 202-203°C (Found: M^+, 217.074; $C_{12}H_{11}NO_3$ requires M^+ 217.0738); υ_{max} ($CHCl_3$) 3500-2500, 1691, 1665 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 10.45 (1H, br), 7.50(1H, t, J 8.8 Hz), 7.24(1H, m), 7.15(1 H, t, J 7.5 Hz), 6.94(1H, t, J 7.5 Hz), 3.94(2H, s), 2.48(3H, s); m/z 218(MH^+, 100%), 200(50), 172(96), 158(29), 130(56).

To a stirred solution of the ketoacid (**37**) (0.3 g, 1.38 mmol) in aqueous THF (5:2) (6.1 ml) was added gradually sodium borohydride (0.157 g, 4.14 mmol) whilst maintaining the temperature at 20°C. After stirring at 20°C for 30 min, ether (30 ml) was added and the mixture acidified with phosphoric acid. The organic layer was removed and the aqueous further extracted with ether (30 ml). The organic fractions were recombined, washed with water, brine and dried (Na_2SO_4), then evaporated under reduced pressure to give the hydroxyacid (**38**) as an unstable buff oil which was used immediately in the next stage.

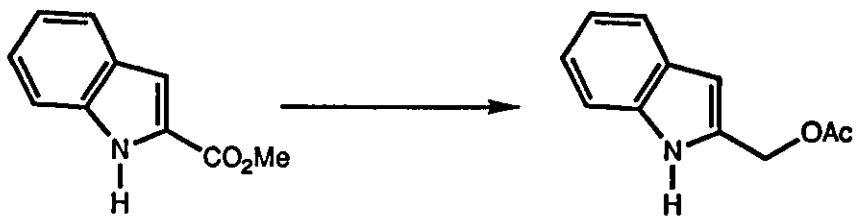
The above oil was dissolved in dry pyridine (15 ml) and DCC (0.29 g, 1.40 mmol) added. The reaction was stirred under dry nitrogen at ambient temperature for 18 h before the pyridine was removed under reduced pressure. The residue was resuspended in dichloromethane and the dicyclohexylurea (DCU) removed by filtration. The organic liquors were concentrated, passed through a short silica gel column and crystallised (ethyl acetate-

dichloromethane) to afford the *title compound* (**39**) as a crystalline solid (102 mg, 37%). m.p. 150-151°C (decomp. with loss of CO_2), (Found: M+, 201.0790. $C_{12}H_{11}NO_2$ requires M+ 201.0790); υ_{max}(Nujol) 3243, 1709 cm^{-1}; δ_H(250 MHz, d6-dmso) 11.20(1H, br, s), 7.45(1H, d, J 7.7 Hz), 7.37(1H, dt, J 8.5 Hz, 0.9 Hz), 7.11(1H, dt, J Hz, 1.2 Hz), 7.00(1H, dt, J 7.8 Hz, 1.2 Hz, 0.9 Hz), 5.81(1H, m), 3.84(1H, d, J 21 Hz, 2.3 Hz), 3.74(1H, dd, J 21 Hz, 2.3 Hz), 1.65(3H, d, J 6.7 Hz); δ_C(62.5 MHz, $CDCl_3$) 163.2, 141.9, 136.9, 130.1, 126.8, 124.2, 123.2, 116.6, 108.3, 78.6, 38.4, 26.6; m/z 202(MH+, 100%), 158(92), 144(15), 130(10).



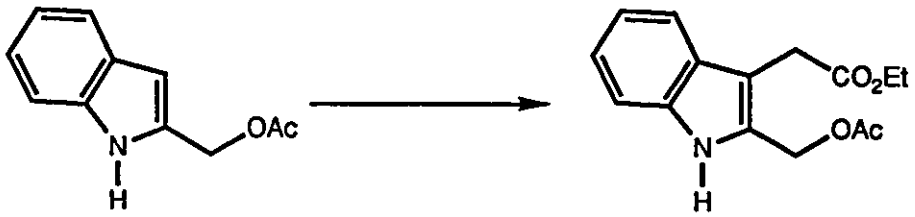
Methyl 1,4-Dihydro-1-methyl-3-oxopyrano[3,4-b]indole-9-carboxylate (**40**)

To a mixture of the lactone (**39**) (0.3 g, 0.15 mmol) and 4-dimethylaminopyridine (23 mg, 0.19 mmol) in acetonitrile (14 ml) was added dropwise dimethyl pyrocarbonate (0.44 g, 0.32 mmol). The mixture was stirred under a calcium chloride drying tube at ambient temperature for 15 min. The precipitate was filtered, the filtrate passed through a short flash silica column (dichloromethane), evaporated, and the residue crystallised (ethyl acetate-dichloromethane) to afford the *title compound* (**40**) (0.21 g, 53%), m.p. 158.4-158.7°C. (Found: C, 64.9; H, 5.3; N, 5.2. $C_{14}H_{13}NO_4$ requires C, 64.9; H, 5.1; N, 5.4%); (Found: M+, 259.0845. $C_{14}H_{13}NO_4$ requires M+ 259.0844); υ_{max}($CHCl_3$) 1737 (br) cm^{-1}; δ_H(250 MHz, $CDCl_3$) 8.10(1H, d, J 8 Hz), 7.44-7.26(3H, m), 6.17(1H, dt, J 8 Hz, 1.7 Hz), 4.09(3H, s), 3.77(2H, AB with additional fine splitting, J 21.2 Hz), 1.73(3H, d, J 6.4 Hz); m/z 259(M+, 80%), 215(100), 156(45), 144(44), 128(70).



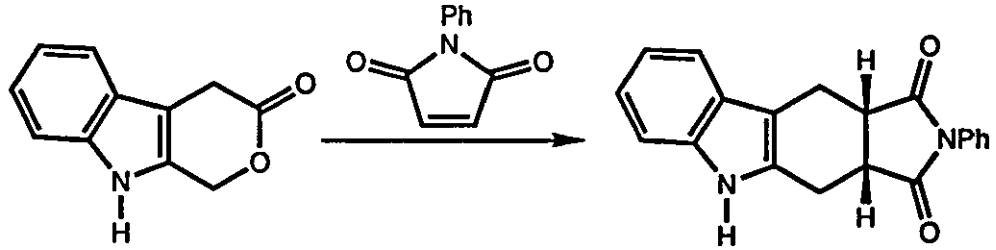
1-Acetoxy-1-(2'-indolyl)methanol (**31**)

To a solution of methyl indole-2-carboxylate (5 g, 28.6 mmol) in ether (200 ml) was added lithium aluminium hydride (1.33 g, 35 mmol) and the reaction stirred at ambient temperature for 2h. Water (50 ml) was added dropwise and the solids removed by filtration. The liquors were extracted with ether and the organic extracts combined, washed with water and brine then dried and evaporated *in vacuo* to an unstable oil (indole-2-methanol). The oil was immediately dissolved in dry pyridine (30 ml) and acetic anhydride (15 ml) added. The reaction was stirred at ambient temperature under nitrogen for 18h then water was added and the aqueous extracted with ethyl acetate. The organic extracts were combined, washed with saturated copper sulfate, water and brine, then dried and evaporated to give the *title compound* (**31**) as a buff solid (3 g, 56%) the data of which was identical to that of a pure reference sample.



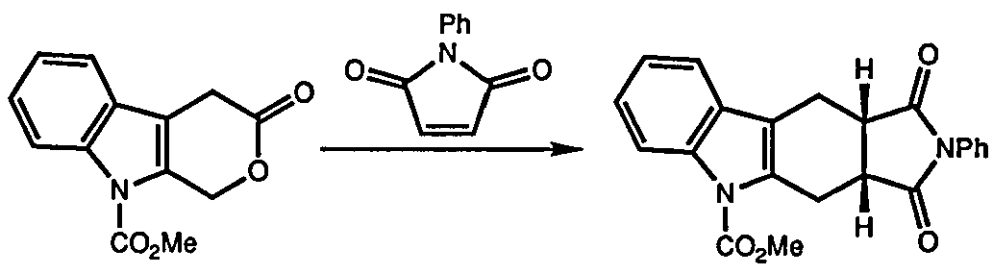
Ethyl 2-acetoxymethylindole-3-acetic acid (**32**)

The indole (**31**) (1 g, 5.3 mmol) was dissolved in toluene (25 ml) with catalytic copper (freshly prepared) and brought to reflux under nitrogen. Ethyl diazoacetate (1.25 ml) in toluene (25 ml) was added dropwise to the refluxing reaction over 1.5h and the reaction allowed to proceed for a further 1h. On cooling the toluene was removed *in vacuo* and the residue subjected to flash silica gel chromatography (ether / petrol) to give the *title compound* (**32**) as a buff oil, the data of which was identical to that of a pure reference sample (Ref: 60).



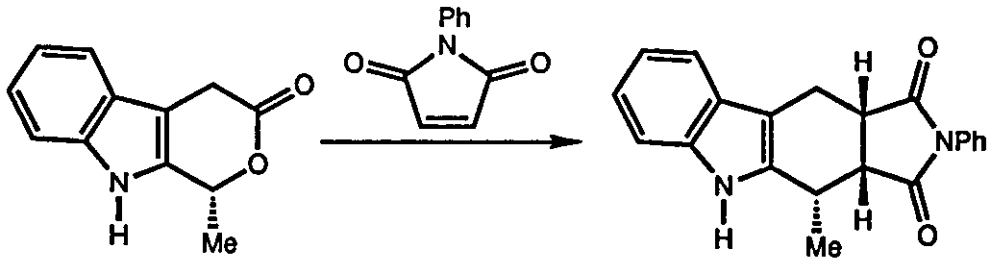
8-Phenyl-6,6a,9a,10-tetrahydro-5H-pyrrolo[3,4-b]carbazole-7,9-dione (**41**)

A mixture of the lactone (**35**) (55 mg, 0.29 mmol) and N-phenylmaleimide (61 mg, 0.35 mmol) in bromobenzene (5 ml) was heated under reflux under nitrogen for 5 h. The solvent was evaporated and the residue chromatographed (ethyl acetate-hexane) to give the *title compound* (**41**) (54 mg, 58%), m.p. 200-201°C, (Found: M^+, 316.1215. $C_{20}H_{16}N_2O_2$ requires M^+, 316.1212); υ_{max} (Nujol) 3393, 1697, 1497, 1392, 1312, 1188, 1142, 742 cm^{-1}; δ_H(500 MHz, $CDCl_3$) 7.98(1H, br, NH), 7.50(1H, d, J 7.5 Hz), 7.40-7.25(4H, m), 7.18-7.05(4H, m), 3.60-3.38(4H, m), 3.18-3.05(2H, m); m/z 316(M^+, 100%), 168(36), 143(89).

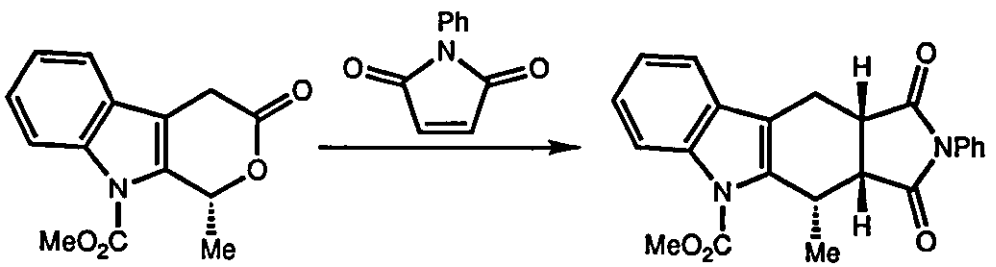


Methyl 7,9-Dioxo-8-phenyl-6,6a,9a,10-tetrahydropyrrolo[3,4-b]carbazole-5-carboxylate (**42**)

A mixture of the lactone (**36**) (50 mg, 0.21 mmol) and N-phenylmaleimide (38.8 mg, 0.22 mmol) was dissolved in bromobenzene (5 ml) and heated to reflux under dry nitrogen for 26 h. The solvent was evaporated under reduced pressure and the residue subjected to silica gel flash chromatography (ether-light petroleum) to afford the *title compound* (**42**) (14.5 mg, 19%) as a buff oil, (Found: M^+, 374.1267. $C_{22}H_{18}N_2O_4$ requires M^+, 374.1266); υ_{max} ($CHCl_3$) 3422, 1709 cm^{-1}, δ_H(250 MHz, $CDCl_3$) 8.05(1H, d), 7.40-7.06(8H, m), 4.04(3H, s), 3.59-3.31(6H, m); m/z 374 (M^+, 100%), 316(40), 201(23), 168(28), 167(45).

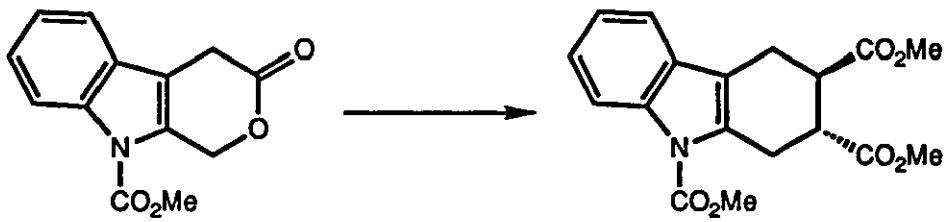


6-Methyl-8-phenyl-6,6a,9a,10-tetrahydropyrrolo[3,4,b]carbazole-7,9-dione (**43**)
The lactone (**39**) (50 mg, 0.249 mmol) and N-phenylmaleimide (0.116 g, 0.675 mmol) in bromobenzene (6 ml) was brought to reflux for 1 h. On cooling the residual solvent was removed under reduced pressure and the residue subjected to silica gel flash chromatography (ether-light petroleum) to afford the*title compound* (**43**) (41.1 mg, 50%) as a pale brown oil, (Found: M+ 330.1368; $C_{21}H_{18}N_2O_2$ requires M+ 330.1368); $\upsilon_{max}(CHCl_3)$ 3400 (br), 1702 (br) cm^{-1}; δ_H(250 MHz, $CDCl_3$) 10.64(1H, br, s), 7.93(1H, m), 7.83(4H, m), 7.54(2H, m), 7.48(2H, m), 4.15(1H, m), 4.02(2H, m), 3.78(1H, m), 3.56(1H, m), 1.97(3H, d, J 7.1 Hz); m/z 330(M+, 50%), 167(63), 157(100).



Methyl 7,9-Dioxo-6-methyl-8-phenyl-6,6a,9a,10-tetrahydropyrrolo[3,4-b]carbazole-5-carboxylate (**44**)
A mixture of the lactone (**40**) (50 mg, 0.25 mmol) and N-phenylmaleimide (117 mg, 0.68 mmol) in bromobenzene (6 ml) was heated under reflux for 6 h. On cooling the solvent was removed under reduced pressure and the residue subjected to flash chromatography on silica gel (ether-light petroleum) to give a crude product. Trituration of the crude with ether at 0°C afforded the *title compound* (**44**) as a white solid (70.6 mg, 86%), m.p. 181-182°C, (Found: M+, 388.1423; $C_{23}H_{20}N_2O_4$ requires M+, 388.1423); $\upsilon_{max}(CHCl_3)$ 1736, 1715, 1713 cm^{-1}; δ_H(250 MHz, d8-toluene) 8.24(1H, d, J 8.2 Hz), 7.42-7.39(2H, m), 7.25-7.13(6H, m), 4.41(1H,

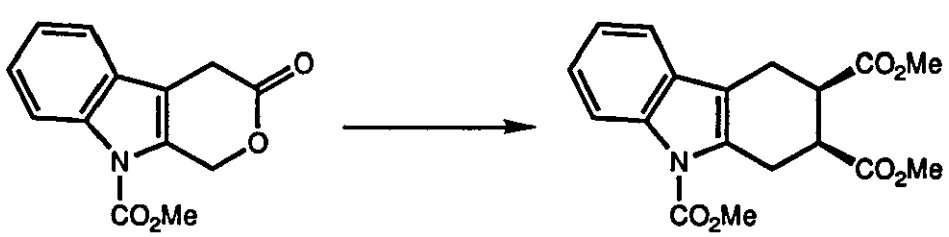
quint. J 6.9 Hz), 3.40(3H, s), 3.05-2.88(2H, m), 2.86-2.82(1H, m), 2.70-2.63(1H, m), 1.06(3H, d, J 6.9 Hz); δ_C(62.5 MHz, $CDCl_3$) 178.9, 176.6, 152.1, 138.3, 135.9, 131.6, 129.3, 128.7, 128.5, 126.4, 124.6, 123.3, 117.8, 115.9, 115.0, 53.7, 45.4, 38.7, 30.0, 17.8, 15.5; m/z 388(M^+, 100%), 373(20), 328(15), 215(56), 194(53), 189(58), 166(78).



trans-Trimethyl 1,2,3,4-tetrahydrocarbazole-2,3,9-tricarboxylate (**45**)

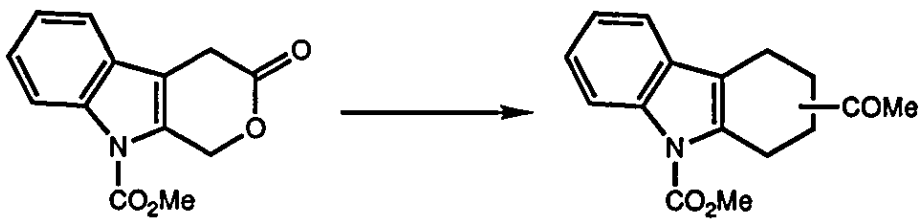
A mixture of the lactone (**36**) (75 mg, 0.31 mmol) and dimethyl fumarate (104 mg, 0.72 mmol) in bromobenzene (8 ml) was heated under reflux under nitrogen for 26 h. The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**45**) (57 mg, 54%), m.p. 88-88.5°C, (Found: C, 62.5; H, 5.5; N,4.0. $C_{18}H_{19}NO_6$ requires C, 62.5; H, 5.6; N, 4.1%); υ_{max}($CHCl_3$) 1735 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 8.11(1H, d, J 6.9 Hz), 7.39(1H, m), 7.36-7.20(2H, m), 3.86(3H, s), 3.75(6H, s), 3.55-3.50(1H, m), 3.23-3.08(4H, m), 2.86-2.78(1H, m); δ_C(100 MHz, $CDCl_3$) 174.6, 174.4, 152.2, 135.8, 132.3, 128.7, 124.2, 123.0, 117.6, 115.4, 115.0, 53.4, 52.1, 52.0, 42.3, 41.1, 27.5, 23.5; m/z 345(M^+, 48%), 285(47), 226(54), 194(50), 167(44), 47(100).

In a subsequent experiment carried out a smaller scale, the yield was 15%.



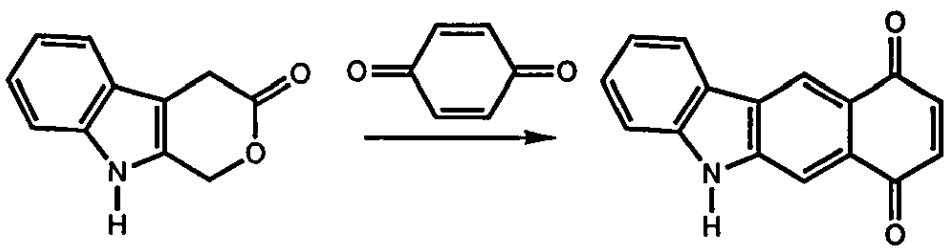
cis-Trimethyl 1,2,3,4-tetrahydrocarbazole-2,3,9-tricarboxylate (**46**)

The lactone (**36**) (50 mg, 0.21 mmol) was dissolved in dimethyl maleate (2 ml) and the mixture heated to reflux under dry nitrogen for 26 h. The excess dimethyl maleate was removed under reduced pressure and the residue subjected to preparative thin layer chromatography on silica gel (ether-light petroleum) to afford the *title compound* (**46**) (13 mg, 18%), m.p. 88-89°C, (Found: C, 62.6; H, 5.6; N,4.0. $C_{18}H_{19}NO_6$ requires C, 62.5; H, 5.6; N, 4.1%); $\upsilon_{max}(CHCl_3)$ 1735 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 8.10(1H, d, J 7.1 Hz), 7.44-7.40(1H, m), 7.29-7.23(2H, m), 4.02(3H, s), 3.71(3H, s), 3.70(3H, s), 3.62-3.57(1H, m), 3.37-3.15(4H, m), 3.03-2.96(1H, m); δ_C(100 MHz, $CDCl_3$) 173.1, 172.9, 152.2, 135.9, 132.7, 129.0, 124.0, 122.8, 117.7, 115.4, 115.2, 53.4, 52.0, 51.9, 40.9, 39.9, 26.1, 21.6.



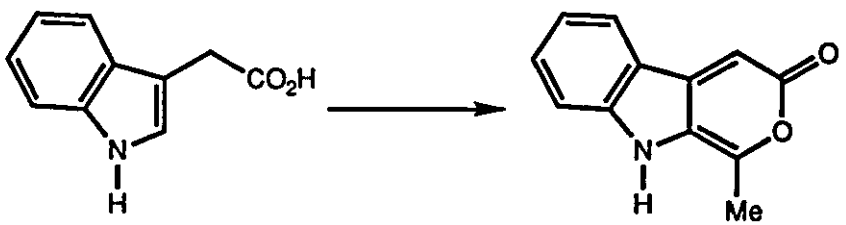
Methyl 2-acetyl-1,2,3,4-tetrahydrocarbazole-9-carboxylate or *methyl 3-acetyl-1,2,3,4 tetrahydrocarbazole-9-carboxylate* (**47**)

The lactone (**36**) (50 mg, 0.21 mmol) and methyl vinyl ketone (21.4 mg, 0.31 mmol) were dissolved in bromobenzene (5 ml) and heated to reflux for 16 h. On cooling the excess solvent and methyl vinyl ketone were removed under reduced pressure and the residue subjected to flash chromatography on silica gel (ether light petroleum) to afford a brown oil (**47**) (6 mg, 11%), (Found: M^+, 271.1208. $C_{16}H_{17}NO_3$ requires M^+, 271.1208); $\upsilon_{max}(CHCl_3)$ 1707, 1702, 1655, 1648, 1643, 1632 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 8.13-8.10(1H, m), 7.38-7.23(3H, m), 4.03(3H, s), 3.33-2.57(4H, m), 2.27(3H, s), 2.25-2.14(2H, m), 1.90-1.74(1H, m); m/z 271(M^+, 53%), 228(100), 167(40).



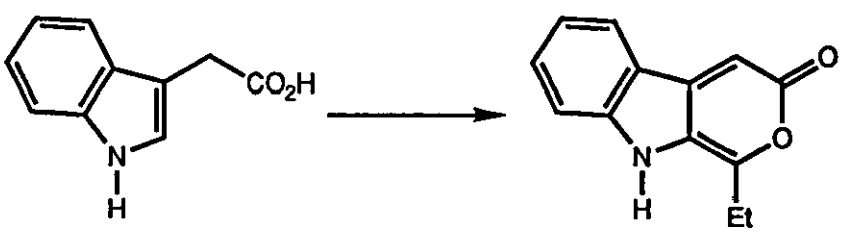
5H-Benzo[b]carbazole-7,10-dione (**48**)

A mixture of the lactone (**35**) (114 mg, 0.61 mmol) and 1,4-benzoquinone (197 mg, 1.82 mmol) in bromobenzene (15 ml) was heated under reflux under nitrogen for 2.5 h. The solvent was evaporated and the residue chromatographed (ether-dichloromethane) to give the *title compound* (**48**) (65 mg, 45%), m.p. darkens ~ 260°C, (Found: M^+, 247.0636. $C_{16}H_9NO_2$ requires M^+, 247.0633); υ_{max}(Nujol) 3313, 1658, 1622, 1593, 1357, 835, 751, 728 cm^{-1}; δ_H[270 MHz, $(CD_3)_2CO$] 11.13(1H, br, NH), 8.82(1H, s), 8.39(1H, d, J 8 Hz), 8.15(1H, s), 7.66(1H, d, J 8 Hz), 7.56(1H, ~ t, J 8 Hz), 7.34(1H, ~ t, J 8 Hz), 7.01(2H, s); m/z 247(M^+, 100%), 219(18), 191(20), 165(20).



1-Methyl pyrano[3,4-b]indol-3-one (**49**)

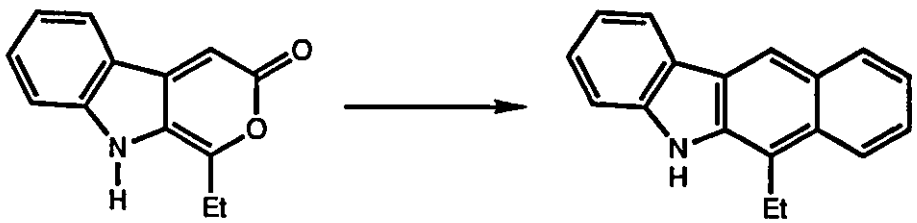
To a solution of indole-3-acetic acid (10 g, 57.1 mmol) in acetic anhydride (25 ml) at 0°C was added freshly distilled boron trifluoride etherate (10 ml) dropwise over 1h. The reaction was allowed to warm to ambient temperature over 2h then ether (100 ml) was added and the solid filtered, triturated with sodium bicarbonate, washed with water and ether. The solid was then dried *in vacuo* giving the *title compound* (**49**) (7.51 g, 66%). All data was found to be in accordance to that in Ref: 60.



1-Ethyl pyrano[3,4-b]indol-3-one (**50**)

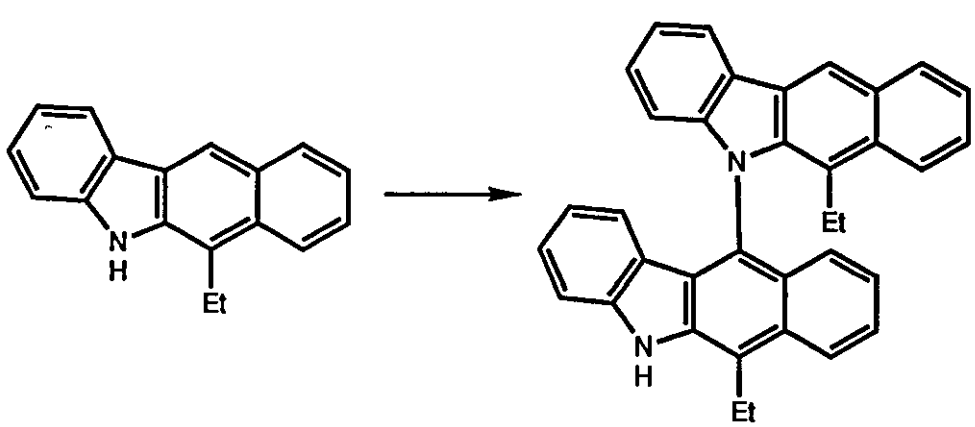
To a solution of indole-3-acetic acid (10.5 g, 60 mmol) in propanoic anhydride (30 ml) at 0°C was added freshly distilled boron

trifluoride etherate (10 ml) dropwise over 1h. The reaction was allowed to warm to ambient temperature over 2h then ether (300 ml) was added and the solid filtered, triturated with sodium bicarbonate, washed with water and ether. The solid was then dried *in vacuo* giving the *title compound* (**50**) (10.5 g, 82%). All data was found to be in accordance to that in Ref: 60.



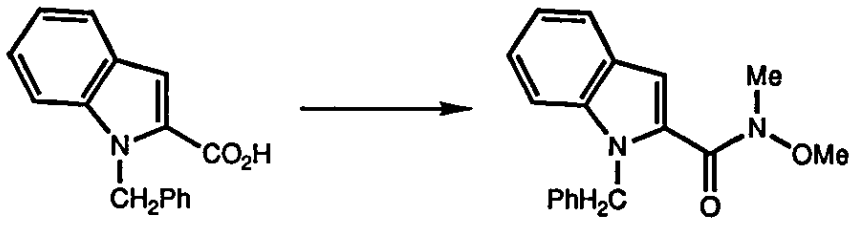
6-Ethyl-5H-benzo[b]carbazole (**51**)

The pyranoindolone (**50**) (1g, 4.87 mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (1.81g, 9.4 mmol) were dissolved in dry acetonitrile (100 ml) and 1 drop of trifluoroacetic acid added. The reaction was brought to reflux under nitrogen (care !) for 4h when, on cooling the excess solvent was removed *in vacuo* and the residue suspended in ether. The ether layer was washed with water, sodium bicarbonate, brine then dried and evaporated to a crude product. Flash silica gel chromatography (ether : light petrol) gave the *title compound* (**51**) (0.75g, 65%). m.p. 132.8-133.1°C. (Found: C, 88.16; H, 6.12; N 5.68%. $C_{18}H_{15}N$ requires C, 88.13; H, 6.16; N, 5.71%); υ_{max}(Nujol) 3033 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 8.46 (1H, s) 8.25-8.06(3H, m) 7.89(1H, s, broad) 7.58-7.40(5H, m) 3.33(2H, q, J 7.6 Hz) 1.44(3H, t, J 7.6 Hz); m/z 245(60), 230(M^+, 100), 202(9), 115(11), 92(10). Found: M^+, 245.1204; $C_{18}H_{15}N$ requires M^+, 245.1204.



5-[6-Ethyl-5H-benzo[b]carbazol-11-yl]-6-ethylbenzo[b]carbazole **(52)**

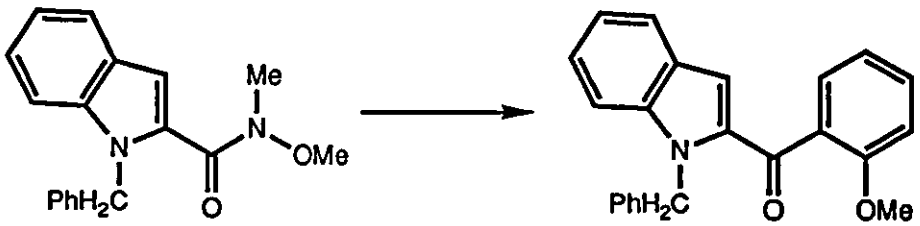
The carbazole **(51)** (100 mg, 0.41 mmol) was dissolved in dry benzene (10 ml) at 0°C and pyridinium chlorochromate (0.09 g, 0.41 mmol) and Celite (1 g) added. The reaction was stirred at 0°C for 1h when (tlc analysis showed no remaining starting material) the solids were removed by filtration and the residue concentrated *in vacuo* . Silica gel flash chromatography (ethyl acetate) gave the *title compound* **(52)** (0.65 g, 64%) as a pale semi-solid. $\upsilon_{max}(CHCl_3)$ 3431 1614 1604 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 8.74(1H, s), 8.41(1H, d, J 7.4 Hz), 8.30(1H, d, J 8.6 Hz), 8.19-8.15(1H, m), 8.10(1H, s, broad), 7.97-7.95(1H, m), 7.56(1H, ddd, J 7.5 Hz, 1.8 Hz, 1.5 Hz, 1.2 Hz), 7.46-7.41(3H, m), 7.39(1H, s), 7.33-7.27(2H, m), 7.24-7.18(2H, m), 6.75-6.70(2H, m), 6.60(1H, d, J 8 Hz), 3.6-3.4(2H, 2xsextet, J 7.4 Hz), 2.58(1H, sextet, J 7.4 Hz), 2.48(1H, sextet, J 7.4 Hz), 1.59(3H, t, J 7.6 Hz), 0.37(3H, t, J 7.5 Hz). m/z 488(M^+, 100), 473(21), 443(19), 244(33), 229(49).



N-Methoxy, N-methyl 1-benzylindole-2-amide **(53)**

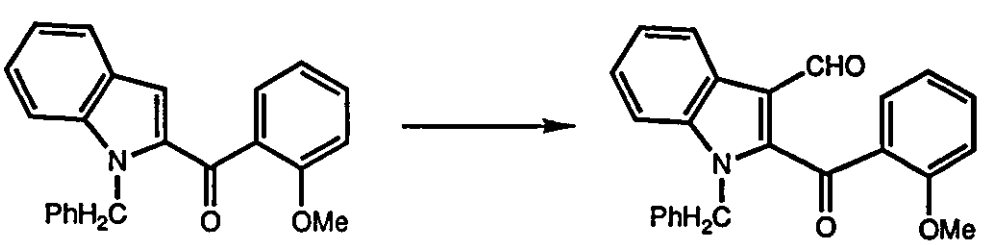
1-Benzylindole-2-carboxylic acid (0.43 g, 1.71 mmol), DCC (0.42 g, 2.05 mmol) and N, O-dimethylhydroxylamine hydrochloride (0.2 g, 2.05 mmol) were dissolved in dry pyridine and catalytic DMAP added. The reaction was stirred under nitrogen for 18h and concentrated *in vacuo*. The residue was suspended in methylene chloride and the precipitated DCU removed by filtration. The liquors were evaporated to a crude solid which upon silica gel flash chromatography (ether / methylene chloride) gave **(53)** (0.35 g, 70%) as a buff oil. υ_{max}(Nujol) 1624 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.74(1H, m), 7.44-7.10(9H, m), 5.76(2H, s), 3.54(3H, s), 3.34(3H, s). δ_C(62.5 MHz, $CDCl_3$) 196.5, 136.1, 135.8, 128.5, 127.2, 127.1, 127.0, 126.7, 126.6, 124.2, 122.2, 120.5, 110.5, 108.0, 61.2, 47.8, 38.9.

m/z 295(MH^+, 100), 265(11), 234(32), 206(8), 91(9); Found: M^+, 294.1368; $C_{18}H_{18}N_2O_2$ requires M^+, 294.1368.



1-Benzyl-2-(2'-methoxybenzoyl)indole (**54**)

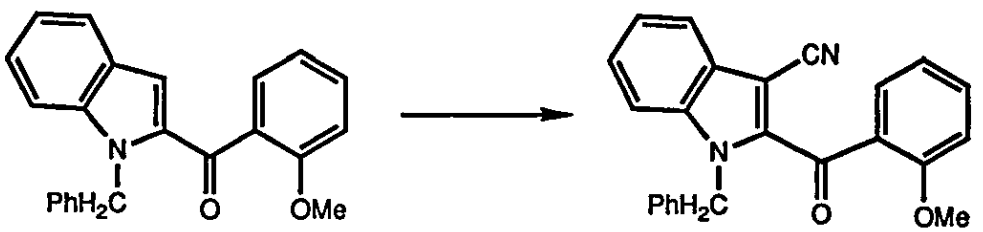
t-Butyllithium (1.7 M, 3.3 ml, 5.61 mmol) was added dropwise to a solution of 2-bromoanisole (0.95 g, 5.1 mmol) in THF (25 ml) at -78°C and stirred for 2 min at -78°C. The amide (**53**) (1 g, 3.4 mmol) in THF (25 ml) was added dropwise and the reaction allowed to warm to ambient temperature over 3h. The solvent was evaporated *in vacuo* and the residue subjected to silica gel flash chromatography (ether / petrol) to afford the *title compound* (**54**) (1.01 g, 87%) and unreacted (**53**) (0.09 g, 9%). υ_{max}(Nujol) 1681 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.65-7.62(1H, m), 7.44-6.92(13H, m), 5.99(2H, s), 3.77(3H, s). δ_C(62.5 MHz, $CDCl_3$) 187.8, 157.9, 140.3, 138.4, 136.4, 131.5, 129.4, 128.5, 127.1, 126.7, 126.3, 126.2, 123.1, 120.9, 120.0, 116.3, 111.5, 111.0, 55.7, 48.1. m/z 341(M^+, 41), 324(21), 310(38), 135(50), 91(100). (Found: M^+, 341.1416, $C_{23}H_{19}NO_2$ requires M^+, 341.1416).



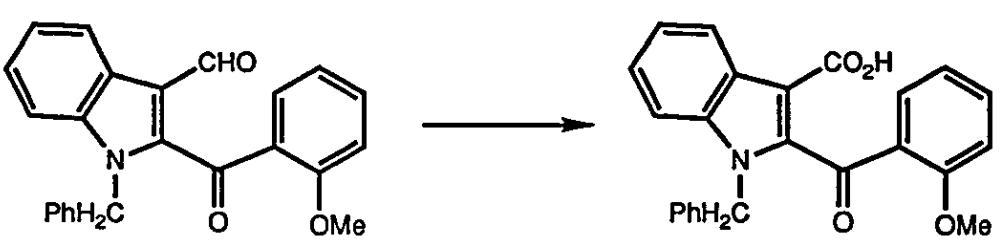
1-Benzyl-2-(2'-methoxybenzoyl)indole-3-aldehyde (**55**)

Phosphorus oxychloride (51 mg, 0.32 mmol) and DMF (95 mg, 1.29 mmol) were stirred at 0°C for 15 min under nitrogen. A solution of **54** (100 mg, 0.29 mmol) in DMF (2 ml) was added dropwise over 2 min and the reaction allowed to reach ambient temperature overnight. Water (50 ml) was added and the reaction extracted with ethyl acetate and the organic extracts combined and evaporated *in vacuo* to a crude brown solid. Silica gel flash chromatography (ether

/ petrol) gave **55** (60 mg, 55%) as a tan solid. m.p.193°C dec. υ_{max}(Nujol) 1661, 1635 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 9.64(1H, s), 8.46-8.43(1H, s), 7.56-7.53(2H, m), 7.40-6.76(10H, m), 5.61(2H, s), 3.56(3H, s). m/z 369(M^+, 15), 338(8), 278(10), 260(8), 232(7), 155(12), 135(14), 112(18), 91(100). (Found: MH^+, 370.1443, $C_{24}H_{19}NO_3$ requires MH^+, 370.1443).

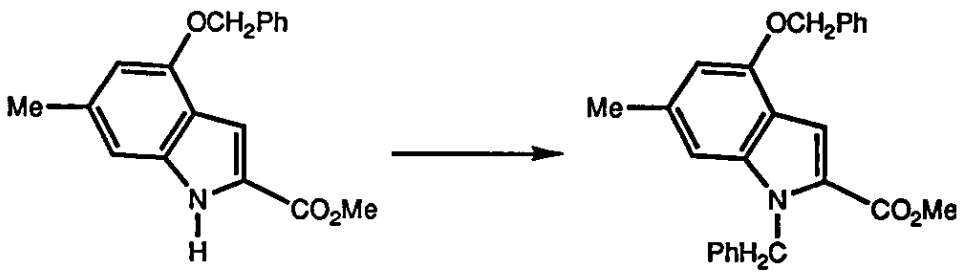


1-Benzyl-2-(2'-methoxybenzoyl)-3-cyanoindole (**56**)
The indole **54** (50 mg, 0.15 mmol) was dissolved in dry acetonitrile (5 ml) and cooled to 0°C under nitrogen. Chlorosulfonyl isocyanate (21 mg, 0.15 mmol) in acetonitrile (5 ml) was added over 15 min whilst the temperature was maintained below 2°C. The reaction was stired at 0°C for 0.5h before triethylamine (15 mg, 0.15 mmol) in acetonitrile (2 ml) was added and the reaction allowed to reach ambient temperature. The reaction was heated to 80°C for 4h and on cooling the solvent removed *in vacuo* and the residue subjected to silica gel flash chromatography to give the *title compound* (**56**) as a colourless oil (45 mg, 83%). υ_{max}(Nujol) 2223 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.79(1H, d, J 8 Hz), 7.47-7.10(11H, m), 6.99(1H, d, J 8Hz), 5.87(2H, s), 3.69(3H, s). δ_C(62.5 MHz, $CDCl_3$) 201.4, 158.7, 149.9, 143.6, 138.1, 136.6, 134.4, 130.3, 128.6, 128.2, 127.6, 127.1, 126.8, 126.6, 123.2, 121.1, 121.0, 95.9, 55.6, 40.5. m/z 336($M-H^+$, 4), 349(8), 335(18), 224(4), 135(19), 119(21), 91(100). (Found MH^+, 367.1447; $C_{24}H_{18}N_2O_2$ requires MH^+, 367.1446).

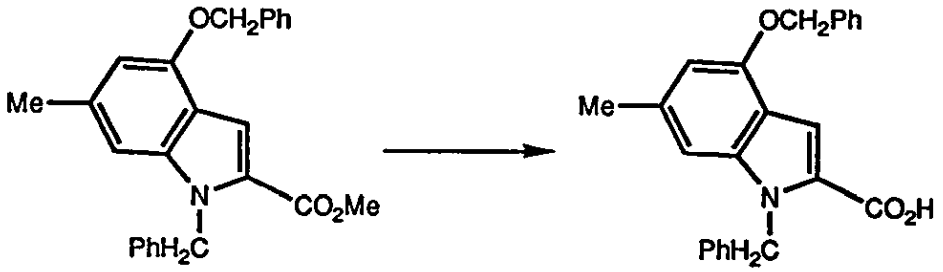


1-Benzyl-2-(2'-methoxybenzoyl)indole-3-carboxylic acid (**57**)

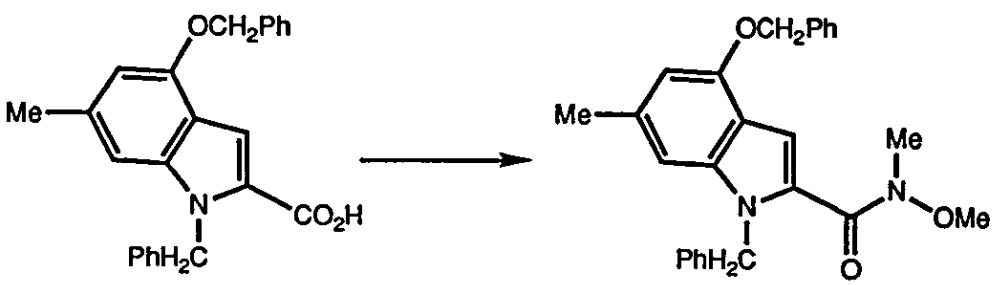
The indole aldehyde (**55**) (20 mg, 0.05 mmol) was dissolved in *t*-butanol (0.3 ml) and NaH_2PO_4 (1.25 M, 0.3 ml). Potasssium manganate(VII) (1 M, 0.3 ml) was added in one portion and the reaction stirred at ambient temperature for 4h. The reaction was concentrated *in vacuo* and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried and evaporated *in vacuo* to the *title compound* (**57**) as a buff oil (9.96 mg, 48%). υ_{max}(Nujol) 3214, 1637 cm^{-1}. δ_H(250 MHz, $CDCl_3$+dmso) 12.45(1H, s), 8.49-8.39(1H, s), 7.46-7.23(2H, m), 7.10-6.89(10H, m), 5.78(2H, s), 3.67(3H, s). m/z 383(M^+, 20), 339(57), 271(19), 260(3), 232(7), 155(25), 135(14), 112 (30), 91(100).



Methyl 1-benzyl-4-benzyloxy-6-methylindole-2-carboxylate (**58**) The indole (**21**) (0.5 g, 1.69 mmol) was dissolved in DMF (5 ml) and sodium hydride (0.08 g, 2.03 mmol) added in one portion. After stirring for 30 min at ambient temperature, benzyl bromide (0.29 g, 1.69 mmol) in DMF (15 ml) was added dropwise and the reaction stirred for a further 1h. The reaction was poured into water and extracted with ethyl acetate. The organic extracts were combined, washed with water and brine, then dried and evaporated *in vacuo* to give the *title compound* (**58**) as a crystalline solid (0.6 g, 92%) m.p. 121.5-122.8°C. υ_{max}(Nujol) 1702 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.51-7.01(11H, m), 6.75(1H, s), 6.43(1H, s), 5.77(2H, s), 5.26(2H, s), 3.81(3H, s), 2.40(3H, s). δ_C(62.5 MHz, $CDCl_3$) 200.2, 163.1, 163.0, 153.4, 141.4, 138.4, 137.1, 137.0, 128.5, 128.4, 127.9, 127.4, 127.0, 116.0, 109.1, 103.6, 103.3, 69.8, 51.4, 47.9, 22.7. m/z 385(M^+, 3), 294(6), 144(100), 129(89), 91(42), 73(61). (Found: M^+, 385.1678; $C_{25}H_{23}NO_3$ requires M^+, 385.1678).

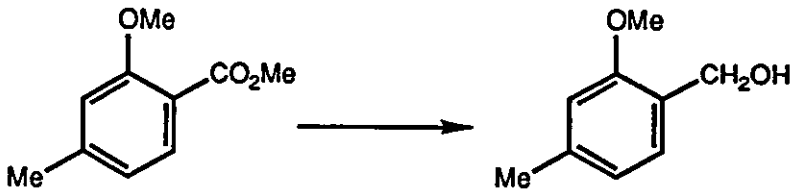


1-Benzyl-4-benzyloxy-6-methylindole-2-carboxylic acid (**59**)
The indole ester (**58**) (0.6 g, 1.56 mmol) was dissolved in THF : H_2O : MeOH (1:1:1, 15 ml) and lithium hydroxide (47 mg, 1.95 mmol) added in one portion. The reaction was brought to reflux for 18h and on cooling the pH was brought to 2 with 2M H_2SO_4 and extracted with ether. The organic extracts were washed well with water and brine then dried and evaporated *in vacuo* to give the *title compound* (**59**) (0.46 g, 80%) m.p. 143.5-144.9°C dec. υ_{max}(Nujol) 3423, 1662 cm^{-1}. δ_H(250 MHz, dmso) 7.57-7.04(11H, m), 6.76(1H, s), 6.44(1H, s), 5.80(2H, s), 5.20(2H, s), 2.40(3H, s); δ_C(62.5 MHz, dmso) 206.7, 163.2, 153.1, 141.3, 138.3, 137.0, 136.6, 128.3, 128.2, 127.6, 127.1, 126.8, 126.1, 125.2, 109.4, 103.5, 103.1, 69.5, 47.6, 22.4. m/z 371(M^+, 89), 327(38), 280(40), 91(100). (Found: M^+, 371.1521; $C_{24}H_{21}NO_3$ requires M^+, 371.1521).



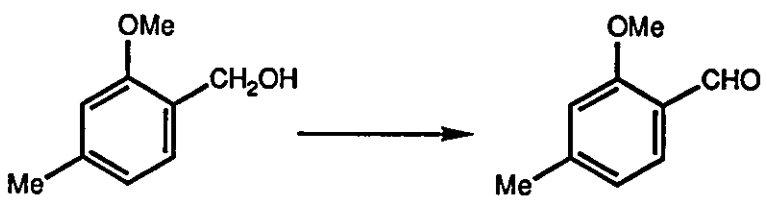
N-Methoxy, N-methyl 1-benzyl-4-benzyloxy-6-methylindole-2-amide (**60**)
The acid (**59**) (0.46 g, 1.24 mmol) and DCC (0.28 g, 1.36 mmol) were dissolved in dry pyridine (15 ml) under nitrogen and the N, O-dimethylhydroxylamine hydrochloride (0.25 g, 2.48 mmol) added followed by catalytic DMAP. The reaction was warmed to 60°C for 18h and on cooling the pyridine removed *in vacuo* and the residue suspended in methylene chloride. The DCU was removed by filtration and the residue passed through a short silica gel column to give the *title compound* (**60**) as a buff oil (0.28 g, 54%). υ_{max}(Nujol) 1624

cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.51-7.04(11H, m), 6.77(1H, s), 6.44(1H, s), 5.65(2H, s), 5.19(2H, s), 3.49(3H, s), 3.26(3H, s), 2.41(3H, s). δ_C(62.5 MHz, $CDCl_3$) 162.7, 153.1, 140.2, 138.7, 137.3, 135.7, 128.5, 128.4, 127.8, 127.4, 127.0, 126.5, 115.8, 106.1, 103.5, 103.2, 69.8, 61.0, 47.9, 34.1, 22.6. m/z 414(M^+, 13), 354(22), 323(20), 263(23), 120(9), 91(100), 61(41). (Found: M^+, 414.1943; $C_{26}H_{26}N_2O_3$ requires M^+, 414.1943).



2-Methoxy-4-methylbenzyl alcohol (**61**)

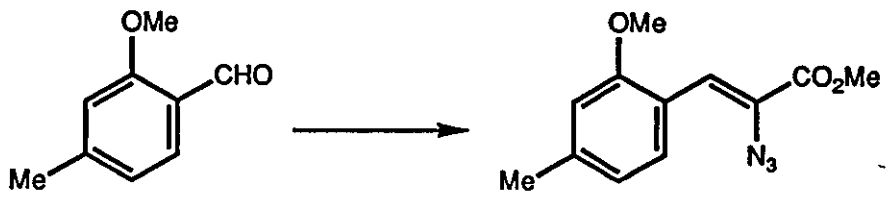
To a stirred solution of methyl 2-methoxy-4-methylbenzoate (24 g, 0.13 mol) in dry diethyl ether (250 ml) was added lithium aluminium hydride (2.5 g, 67 mg) in small portions. The reaction was stirred at ambient temperature for 18 h before the excess reducing agent was neutralised with water. The aqueous was extracted with ether and the organic layers washed with saturated sodium bicarbonate solution, water and brine. The solvent was evaporated (after drying over Na_2SO_4) to yield the *title compound* (**61**) as a buff oil (11.8 g, 58 %) (Found: M^+, 152.0837; $C_9H_{12}O_2$ requires M^+, 152.0837). υ_{max}(thin film) 3303 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.13(1H, d, J 7.5 Hz), 6.74(1H, d, J 7.5 Hz), 6.69(1H, s), 4.62(2H, s), 3.83(3H, s), 2.41(3H, s); δ_C(62.5 MHz, $CDCl_3$) 157.3, 138.9, 128.6, 126.2, 121.1, 111.2, 61.6, 21.6.



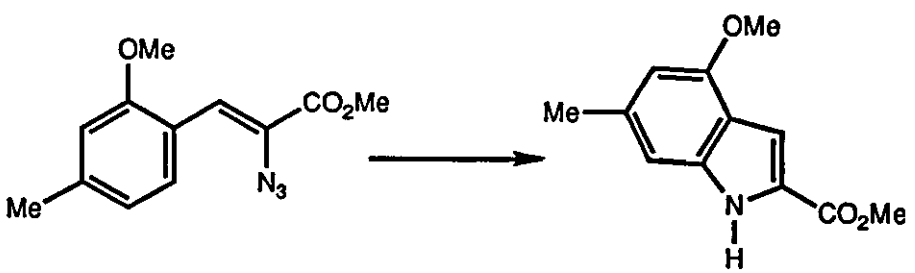
2-Methoxy-4-methylbenzaldehyde (**62**)

To a mechanically stirred solution of 2-methoxy-4-methylbenzyl alcohol (**61**) (11.8 g, 78 mmol) in dry methylene chloride (100 ml) was added manganese dioxide (67.48 g, 776 mmol) in one portion and the reaction stirred mechanically for 18h under dry nitrogen. The remaining manganese dioxide was removed by filtration and the

solvent evaporated to give the *title compound* (**62**) as a colourless oil (10.3 g, 89%). (Found MH^+, 151.0760; $C_9H_{10}O_2$ requires MH^+, 151.07599). υ_{max}(thin film) 1705 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 10.39(1H, s), 7.71(1H, d, J 7.8 Hz), 6.84-6.78(2H, m), 3.90(3H, s), 2.40(3H, s); δ_C(62.5 MHz, $CDCl_3$) 189.2, 161.8, 147.4, 128.4, 122.5, 121.5, 112.1, 55.4, 22.2.

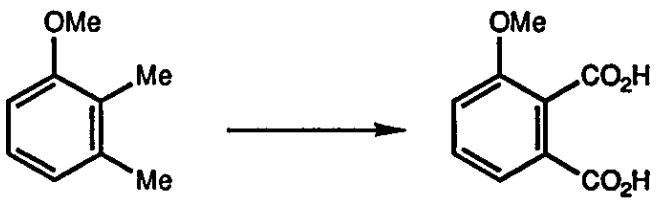


Methyl 2-azido-3-(2'-methoxy-4'-methylphenyl)propenoate (**63**)
Sodium (1.84 g, 80 mmol) was dissolved in dry methanol (75 ml) and cooled to -12°C under dry nitrogen where a mixture of 2-methoxy-4-methylbenzaldehyde (**62**) (3.0 g, 20 mmol) and methyl azidoacetate (**22**) (9.2 g, 80 mmol) in methanol (75 ml) was added over 0.5h. The reaction was stirred for 4h at -12°C and poured carefully into water. The crude product was removed by filtration, redissolved in ethyl acetate and washed with water and brine then dried and evaporated to give the *title compound* (**63**) as an oily liquid in poor yield (1.0 g, 20%). (Found: $M^+(-N_2)$, 219.0895; $C_{12}H_{13}N_3O_3$ requires $M^+(-N_2)$, 219.0895). υ_{max}(thin film) 2120, 1705 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 8.09(1H, d, J 8 Hz), 7.38(1H, s), 6.86-6.78(1H, m), 6.69(1H, t, J 6.7 Hz), 3.89(3H, s), 3.84(3H, s), 2.36(3H, s); δ_C(62.5 MHz, $CDCl_3$) 164.3, 157.5, 141.6, 130.3, 130.0, 124.0, 121.1, 119.8, 111.3, 55.4, 53.3, 21.9.



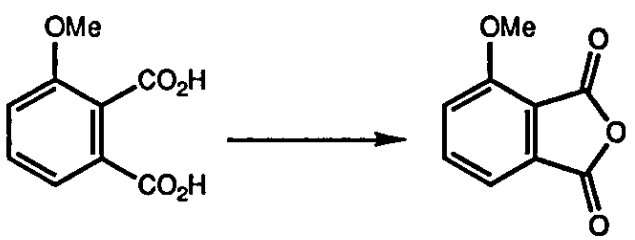
Methyl 4-methoxy-6-methylindole-2-carboxylate (**64**)
Xylene (250 ml) was brought to reflux under dry nitrogen where a solution of methyl 2-azido-3-(2'-methoxy-4'-methylphenyl)propenoate (**63**) (3.2 g, 13 mmol) in xylene (25 ml)

was added over 0.5h. The reaction was further refluxed for 2h where, on cooling the solvent was evaporated *in vacuo* to a yellow solid. Recrystallisation from ethyl acetate and silica gel flash chromatography of the liquors gave the *title compound* (**64**) as a buff crystalline solid (1.7 g, 60%) m.p. 129.3-130.9°C; υ_{max}(Nujol) 3335, 1689 cm^{-1}; d_H(250 MHz, $CDCl_3$) 8.88 (1H, s, br), 7.27 (1H, m), 6.80(1H, s), 6.33(1H, s), 3.93(3H, s), 2.44(3H, s); δ_C(62.5 MHz, $CDCl_3$) 162.6, 154.2, 138.7, 137.0, 125.2, 117.0, 106.6, 104.5, 102.0, 55.2, 22.5.



3-Methoxyphthalic acid (**65**)

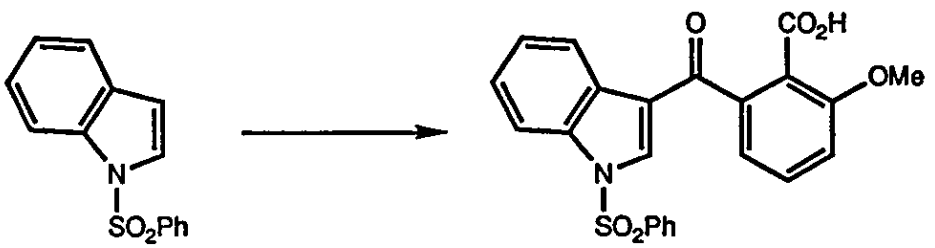
2,3-Dimethylanisole (1 g, 7.35 mmol) was dissolved in water (65 ml) along with potassium permanganate (5.53 g, 35 mmol) and the reaction brought to reflux over 1 hour. Reflux was maintained for 18 h and on cooling the reaction was filtered and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried and evaporated to give the *title compound* (**65**) (0.55 g, 38%). υ_{max}($CHCl_3$) 1686 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.11(1H, t), 6.90(1H, t) 6.71(1H, d) 3.39(3H, s) corresponding with data in Ref: 79.



3-Methoxyphthalic anhydride (**66**)

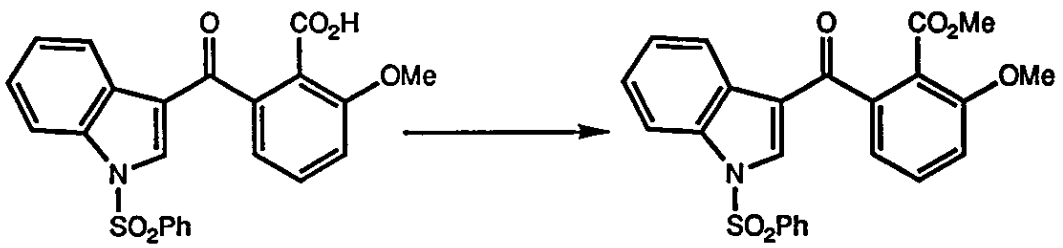
3-Methoxyphthalic acid (**65**) (0.5 g, 2.55 mmol) was suspended in distilled acetic anhydride (1 ml) and brought to reflux until the reaction became homogeneous. Reflux was then maintained for a further 2h where the reaction was left to cool overnight. The *title compound* was removed as a white crystalline solid (**66**) (0.33 g,

73%). υ_{max}(Nujol) 1848, 1774 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.85(1H, t), 7.57(1H, d), 7.33(1H, d), 4.08(3H, s) corresponding with Ref: 79.



1-Phenylsulfonylindol-3-yl 2'-carboxyl-3'-methoxy-1'-phenyl Ketone (**67**).

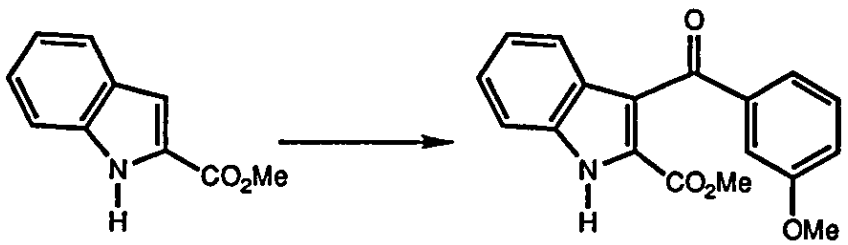
A solution of 3-methoxyphthalic anhydride (**66**) (0.5 g, 2.81 mmol) and aluminium chloride (0.65 g, 4.88 mmol) in ethylene chloride (20 ml) was stirred at ambient temperature for 1 hour when a solution of 1-benzenesulfonylindole (0.625 g, 2.43 mmol) in ethylene chloride (10 ml) was added in one portion and the reaction brought to reflux (84°C) for 24 h. The reaction was poured into water (100 ml) and the organic layer removed, washed with 2M hydrochloric acid (3 x 100 ml), water and brine then dried and subjected to silica gel flash chromatography in 1:1 (petrol / methylene chloride) to give the crude *title compound* (**67**) (0.51 g, 48%) which was used without further purification.



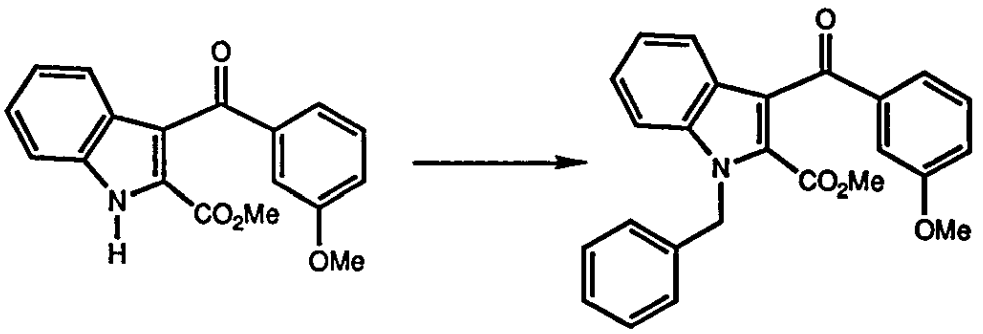
1-Phenylsulfonyl-indol-3-yl 2'-carbomethoxy-3'-methoxy-1'-phenyl ketone (**68**).

Crude (**67**) (0.18 g, 0.44 mmol) was dissolved in dry methylene choride (2 ml) and oxalyl chloride (0.06 g, 0.49 mmol) was added dropwise and the reaction stirred at ambient tremperature for 15 min. The excess oxalyl chloride was removed *in vacuo* and the residue suspended in N, N-diisopropylethylamine (0.045 g, 0.88

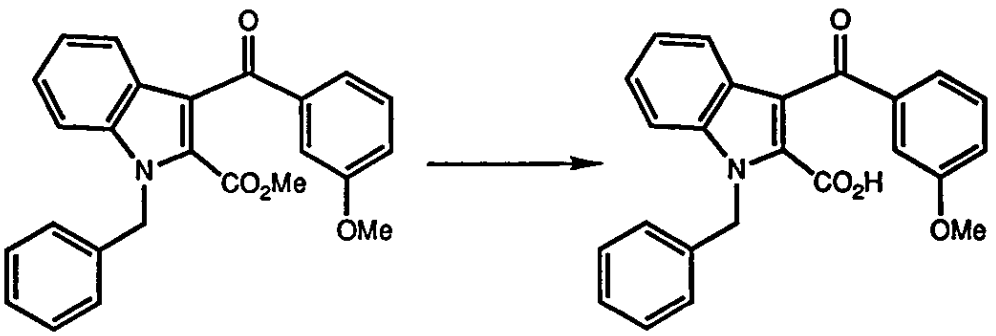
mmol) and stirred for 2 min where methanol (0.015 g, 0.44 mmol) was added dropwise and the reaction stirred at ambient temperature for a further 1 hour. The reaction was then evaporated *in vacuo* and the residue suspended in 1:1 ethyl acetate : water. The organic layers were combined, washed with water, sodium bicarbonate and brine then dried and evaporated *in vacuo* to give the *title compound* (68) as a buff oil (0.12 g, 65%). $\upsilon_{max}(CHCl_3)$ 1712 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 7.94(1H, d), 7.86(2H, d), 7.66-7.51(5H, m), 7.42(2H, t), 7.28(1H, t), 7.17(2H, m), 3.79(3H, s), 3.28(3H, s). m/z 449(M^+, 28), 418(41), 264(100), 77(62), 51(22).



Methyl 3-(3'-methoxybenzoyl)indole-2-carboxylate (69)
Aluminium chloride (1.22 g, 9.14 mmol) and *m*-methoxybenzoyl chloride (1.56 g, 9.14 mmol) were dissolved / suspended in dry ethylene chloride (20 ml) at 0°C and stirred for 0.5h. A solution of methyl indole-2-carboxylate (0.8 g, 4.57 mmol) in dry ethylene chloride (15 ml) was added dropwise whilst maintaining the temperature at 0°C. The reaction was stirred at 0°C for 1h and allowed to warm to ambient temperature over 4h. The reaction was quenched with ice / water and extracted with methylene chloride. The organic layers were washed with saturated sodium bicarbonate solution, water and brine, then dried and evaporated to a viscous yellow oil which upon trituration with ether at 0°C gave the *title compound* (69) as a buff crystalline solid.(1.0 g, 71%) m.pt 97.8-99.1°C. υ_{max}(Nujol) 3317, 1720, 1713 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 10.82(1H, s, br), 7.68(1H, d, J 8.2 Hz), 7.54-7.12(7H, m), 3.84(3H, s), 3.58(3H, s); δ_C(62.5 MHz, $CDCl_3$) 162.1, 159.6, 140.5, 135.5, 129.1, 127.2, 127.0, 126.2, 126.0, 122.6, 122.1, 122.0, 119.6, 112.7, 112.0, 96.0, 55.2, 52.0.

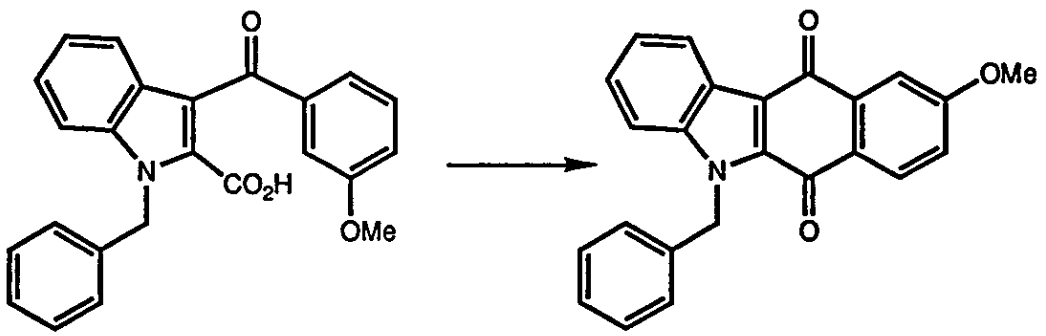


Methyl 3-(3'-methoxybenzoyl)-1-benzylindole-2-carboxylate (**70**) Sodium hydride (72 mg, 1.78 mmol) was suspended in dry DMF (5 ml) and a solution of methyl 3-(3'-methoxybenzoyl)-indole-2-carboxylate (**69**) (0.5 g, 1.62 mmol) in DMF added. The resulting solution was stirred at ambient temperature for 1h before a solution of benzyl bromide (0.28 g, 1.62 mmol) in DMF (10 ml) was added dropwise. The reaction was stirred for 2h, concentrated *in vacuo* and extracted with ethyl acetate. The organic extracts were combined, washed with saturated sodium bicarbonate solution, water and brine, then dried and evaporated to the *title compound* as a pale yellow oil (**70**) (0.6 g, 93%). υ_{max}(Nujol) 1720, 1718 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.81(1H, d, J 8.0 Hz), 7.45-7.19(8H, m), 7.08-7.05(4H, m), 5.74(2H, s), 3.83(3H, s), 3.30(3H, s). δ_C(62.5 MHz, $CDCl_3$) 162.1, 159.7, 141.2, 137.7, 136.6, 129.3, 128.7, 128.6, 127.5, 127.4, 126.3, 125.7, 122.5, 122.3, 121.7, 121.0, 119.3, 112.2, 110.8, 96.1, 55.1, 51.6, 48.0.

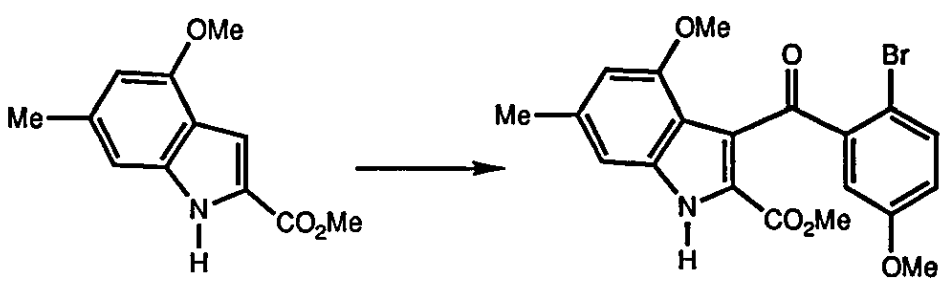


3-(3'-Methoxybenzoyl)-1-benzylindole-2-carboxylic acid (**71**) Methyl 3-(3'-methoxybenzoyl)-1-benzylindole-2-carboxylate (**70**) (0.6 g, 1.50 mmol) was dissolved in THF (5 ml) and added to a solution of lithium hydroxide (54 mg, 2.26 mmol) in (1:1) methanol / water (10 ml) and brought to reflux for 18h. On cooling the pH of the solution was lowered to pH1 with 2M H_2SO_4 and the aqueous

extracted with ether. The ether extracts were combined, washed with water and brine, dried and evaporated to afford the*title compound* (**71**) as a white solid (0.4 g, 70%) m.p. 177-178.6°C. υ_{max}(Nujol) 1715, 1713 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 11.11(1H, s, br), 7.45-6.82(12H, m), 5.96(2H, s), 3.80(3H, s).



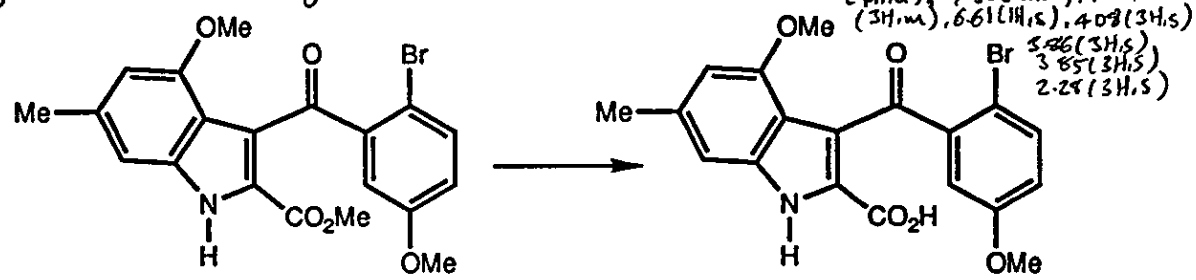
5-Benzyl-9-methoxybenzo[b]carbazole-6,11-dione (**72**)
3-(3'-methoxybenzoyl)-1-benzylindole-2-carboxylic acid (**71**) (200 mg, 0.52 mmol) was dissolved in neat polyphosphoric acid (~20 ml) in a Kugelrohr vessel and rotated at 70°C for 2h. On cooling, the crude acid was poured carefully into saturated sodium bicarbonate solution and extracted with ether. The ethereal extracts were combined, washed with brine, dried and evaporated to a yellow crude. The crude material was subjected to silica gel flash chromatography (ether / petrol) to afford the *title compound* (**72**) as a bright yellow solid (76 mg, 40%). (Found M^+, 367.1208; $C_{24}H_{17}NO_3$ requires M^+, 367.1208). υ_{max}(Nujol) 1728, 1655, 1596 cm^{-1}; δ_H(400 MHz, $CDCl_3$) 8.50-8.48(1H, m), 8.10(1H, d, J 7.5 Hz), 7.69(1H, d, J 2.7 Hz), 7.62-7.58(1H, m), 7.46-7.32(3H, m), 7.30-7.15(4H, m), 7.13(1H, dd, J 7.5 Hz, 2.7 Hz), 6.90(2H, s), 3.95(3H, s). δ_C(62.5 MHz, $CDCl_3$) 181.0, 178.3, 164.3, 139.5, 136.6, 136.5, 129.0, 128.8, 128.7, 127.8, 127.3, 127.2, 126.9, 126.7, 124.6, 124.2, 123.8, 118.7, 111.5, 110.3, 55.9, 48.4. m/z 367(M^+, 38), 290(9), 248(7), 177(10), 91(100), 65(20).



Methyl 3-(2'-bromo-5'-methoxybenzoyl)-4-methoxy-6-methylindole-2-carboxylate (74)

2-Bromo-5-methoxybenzoyl chloride (1.14 g, 4.57 mmol) was dissolved in dry ethylene chloride (15 ml) along with aluminium chloride (0.61 g, 4.57 mmol) and cooled to 0°C over 0.5h. The indole (64) (0.5 g, 2.28 mmol) in ethylene chloride (20 ml) was added and the reaction stirred at 0°C for 1h then warmed to ambient temperature over 2h. The reaction was poured onto ice and extracted with methylene chloride. The organic extracts were combined, washed with water, brine then dried and evaporated *in vacuo* to a crude oil. Flash silica gel chromatography (ether : methylene chloride) gave the *title compound* (74) (0.3 g, 30%) m.p. 151.1-152.4°C. υ_{max}(Nujol) 3429, 1789, 1730 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.61-7.19(3H, m), 6.82-6.75(1H, m), 6.26(1H, s), 3.93(3H, s), 3.81(3H, s), 3.72(3H, s), 2.23(3H, s). δ_C(62.5 MHz, $CDCl_3$) 195.5, 161.6, 159.3, 158.8, 158.6, 145.1, 143.1, 139.3, 134.2, 126.6, 117.7, 117.0, 116.9, 114.2, 113.0, 106.3, 105.3, 55.7, 55.6, 23.0.

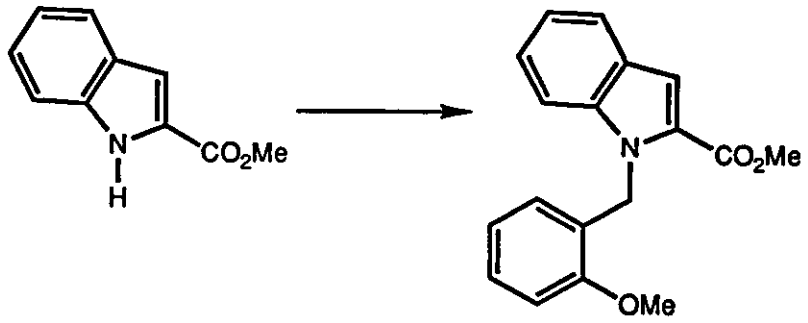
By-Product 74a as a yellow oil (0.59g, 20%). δ_H(250MHz, $CDCl_3$) 10.95(1H,s), 7.60(2H,d), 7.39 (3H,d), 7.35(1H,d), 7.04 (3H,m), 6.61(1H,s), 4.08(3H,s) 3.86(3H,s) 3.85(3H,s) 2.28(3H,s)



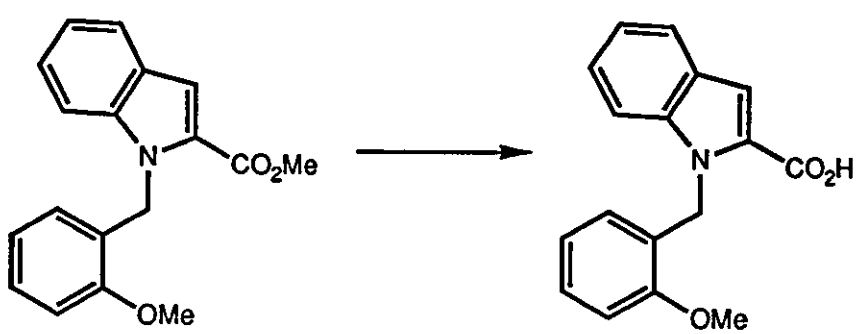
3-(2'-Bromo-5'-methoxybenzoyl)-4-methoxy-6-methylindole-2-carboxylic acid (75)

The indole ester(74) (74 mg, 17.1 mmol) was dissolved in THF (2 ml), water (2 ml) and methanol (2 ml) and lithium hydroxide (82 mg, 34.3 mmol) added. The reaction was brought to reflux for 4h and, on cooling the pH brought to 2 with 2M H_2SO_4. The aqueous was extracted with ether and the organic extracts washed with water and brine then dried and evaporated *in vacuo* to give the *title compound* (75) (55 mg, 76%) as a white crystalline solid m.p. 143.5-145°C dec.; υ_{max}(Nujol) 3422, 1735, 1689 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 13.30(1H, s, br), 10.89(1H, s, br), 7.60(2H, m), 7.26(1H, d, J 3 Hz), 7.15(1H, d, J 2 Hz), 6.62(1H, s), 3.78(3H, s), 3.77(3H, s), 2.07(3H, s). δ_C(62.5 MHz, $CDCl_3$) 200.0, 172.3, 167.1, 164.3, 163.4,

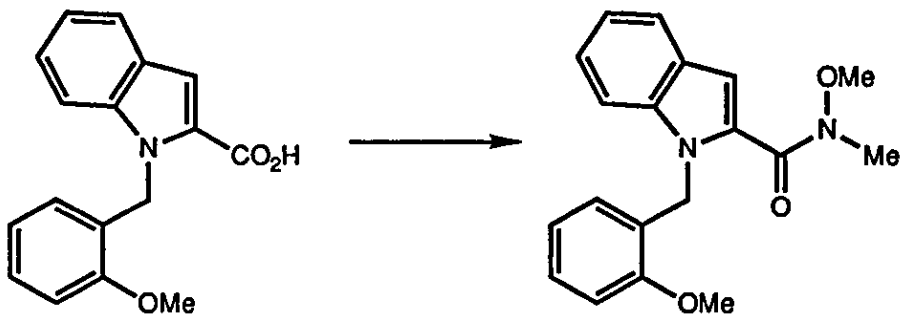
147.7, 143.6, 139.1, 132.6, 122.5, 120.7, 118.8, 118.4, 113.2, 111.1, 110.0, 61.1, 60.8.



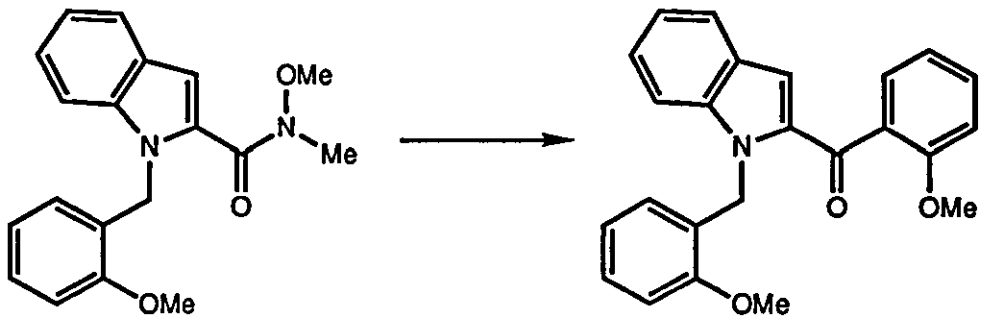
Methyl 1-(2'-methoxybenzyl)indole-2-carboxylate (**76**)
To a stirred suspension of sodium hydride (0.39g, 16.4 mmol) in DMF (20 ml) was added dropwise a solution of methyl indole-2-carboxylate (2.61 g, 14.9 mmol) in DMF (50 ml) and kept at room temperature for 1 hour. A solution of 2-methoxybenzyl bromide (3.0 g, 14.9 mmol) in DMF (50 ml) was added dropwise over 15 min and the reaction stirred for a further 1 hour. The reaction was concentrated *in vacuo*, poured into water (50 ml) and extracted with ether (3 x 100 ml). The ethereal extracts were washed with saturated sodium bicarbonate, brine, dried and evaporated to a pale yellow oil which was further purified by passing through a short silica column (petrol : ether) to give the *title compound* (**76**) as a white solid (3.88 g, 88%), m.pt. 67.5-68.1°C. (Found MH^+, 296.1287; $C_{18}H_{17}NO_3$ requires MH^+, 296.1287); υ_{max}(Nujol) 1709 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.71(1H, d, J 7.9 Hz), 7.38(1H, s), 7.29-7.11(5H, m), 6.89(1H, d, J 8.2 Hz), 6.69(1H, m), 6.32(1H, d, J 7.6 Hz), 5.85(2H, s), 3.92(3H, s), 3.85(3H, s). δ_C(62.5 MHz, $CDCl_3$) 202.2, 156.3, 139.6, 127.9, 126.5, 126.2, 126.0, 125.2, 122.6, 120.8, 120.5, 111.0, 109.8, 55.3, 51.7, 43.2. m/z 296(M^+, 100%), 188(62), 176(12), 138(10), 121(21), 91(5).



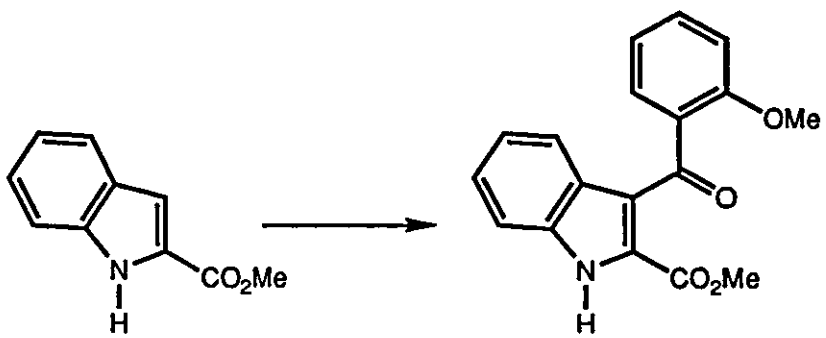
1-(2'-methoxybenzyl)indole-2-carboxylic acid (**77**)
A solution of (**76**) (3.88 g, 13.2 mmol) and lithium hydroxide (0.63 g, 26.3 mmol) in methanol (30 ml) was dissolved in THF / H_2O (1:1) (60 ml) and the reaction brought to reflux for 18 hours. On cooling the reaction was brought to pH1 with 2M HCl and extracted with ether (2 x 100 ml). The ether extracts were combined, washed with brine, dried and evaporated to give the *title compound* (**77**) as a buff oil (3.1 g, 84%) (Found MH^+, 282.1130, $C_{17}H_{15}NO_3$ requires MH^+, 282.1130); υ_{max}(Nujol) 1682 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.51-7.43(1H, m), 7.26-6.88(5H, m), 6.65(1H, d, J 8.2 Hz), 6.44(1H, t, J 7.4 Hz), 6.11(1H, d, J 7.4 Hz), 5.63(2H, s), 3.62(3H, s). δ_C(62.5 MHz, $CDCl_3$) 178.0, 163.3, 156.1, 139.0, 128.5, 127.7, 126.1, 124.6, 122.2, 120.4, 120.2, 110.8, 110.4, 109.6, 55.1, 42.6 .m/z 281(M^+, 22%), 143(20), 121(100), 91(75), 65(18).



N-methoxy, N-methyl 1-(2'-methoxybenzyl)indole-2-amide (**78**)
A solution of (**77**) (2.1 g, 7.5 mmol), N, N-dicyclohexylcarbodiimide (1.69 g, 8.22 mmol) and N,O-dimethyl hydroxylamine (1.45 g, 14.9 mmol) in pyridine (100 ml) was warmed to 60°C with catalytic 4-pyrrolidinopyridine for 24 hours. On cooling the pyridine was removed *in vacuo* and the residue subjected to silica gel flash chromatography (petrol / ether) to afford the *title compound* (**78**) as a buff oil (1.92 g, 80%). (Found: MH^+, 325.1552, $C_{19}H_{20}N_2O_3$ requires MH^+, 325.1552); υ_{max}(Nujol) 1630 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.75(1H, d, J 7.3 Hz), 7.40-7.18(5H, m), 6.90(1H, d, J 7.6 Hz), 6.77(1H, m), 6.57-6.54(1H, m), 5.78(2H, s), 3.88(3H, s), 3.59(3H, s), 3.36(3H, s); δ_C(62.5 MHz, $CDCl_3$) 197.0, 163.1, 157.5, 138.0, 129.9, 128.2, 128.0, 126.9, 126.8, 124.3, 121.3, 120.0, 111.2, 109.9, 107.2, 61.8, 55.0, 43.1, 34.0; m/z 325(MH+, 50), 295(100), 264(10), 217(8), 175(6), 121(13).

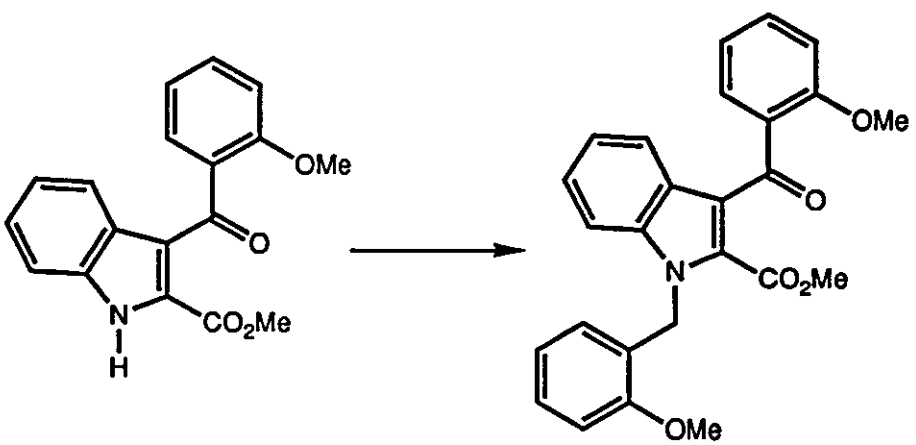


1-(2'-methoxybenzyl)-2-(2''-methoxybenzoyl)indole (**79**)
A solution of 2-bromoanisole (0.16 g, 0.83 mmol) in THF (5 ml) at -80°C was treated with t-butyllithium (1.7M, 0.49 ml, 0.83 mmol) and the resulting bright yellow anion stirred at -80°C for 30 minutes. A solution of the amide (**78**) (0.18 g, 0.56 mmol) in THF (10 ml) was added dropwise over 10 minutes and the reaction allowed to warm to ambient temperature over 4 hours. The solution was evaporated *in vacuo* and the residue subjected to silica gel flash chromatography (petrol / ether) to afford the *title compound* (**79**) as a colourless oil (0.11 g, 53%). (Found: MH^+, 372.1600, $C_{24}H_{21}NO_3$ requires MH^+, 372.1600). υ_{max}(Nujol) 1642 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.53(1H, d, J 8 Hz), 7.35-6.64(12H, m), 6.46(1H, d, J 1.5 Hz), 5.91(2H, s), 3.81(3H, s), 3.66(3H, s). δ_C(62.5 MHz, $CDCl_3$) 187.0, 157.3, 156.5, 140.4, 135.9, 131.4, 130.1, 129.4, 127.9, 126.7, 126.0, 122.9, 121.4, 120.7, 120.1, 119.9, 115.9, 111.4, 111.2, 109.9, 55.7, 55.3, 43.1. m/z 372(MH^+, 28), 149(30), 138(54), 124(100), 49(22).



Methyl 3-(2'-methoxybenzoyl)indole-2-carboxylate (**80**)
Aluminium chloride (2.85 g, 22 mmol) was suspended in dry ethylene chloride (20 ml) at 0°C and a solution of *o*-anisoyl chloride (3.71 g, 22 mmol) in ethylene chloride (20 ml) added dropwise. The resulting red solution was stirred at 0°C for 30 minutes and a

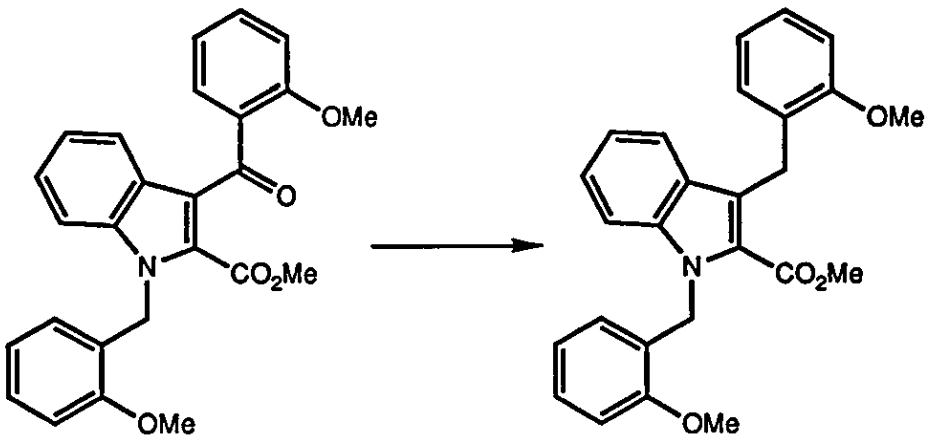
solution of methyl indole-2-carboxylate (1.9 g, 11 mmol) in ethylene chloride (50 ml) was added dropwise and the reaction allowed to warm to ambient temperature over 3 hours. The solution was poured into ice / water and extracted with methylene chloride. The organic extracts were combined, washed with saturated sodium bicarbonate, brine then dried and evaporated to a red oil which upon treatment with ether at 0°C afforded the *title compound* (**80**) as a buff crystalline solid (2.2 g, 65%). m.p. 152.3-155.1°C. (Found: MH+, 310.1079; $C_{18}H_{15}NO_4$ requires MH+, 310.1079). υ_{max}(Nujol) 3313, 1705, 1677 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 9.27(1H, s, br), 7.87(1H, d, J 4.1 Hz), 7.59-7.55(1H, m), 7.46-7.36(3H, m), 7.26-7.22(1H, m), 7.02-6.93(2H, m), 3.67(3H, s), 3.53(3H, s). δ_C(62.5 MHz, $CDCl_3$) 192.5, 162.0, 158.3, 135.2, 132.9, 130.9, 130.5, 127.3, 127.1, 125.8, 122.6, 122.5, 121.6, 120.3, 111.8, 111.5, 55.8, 52.1. m/z 309(MH+, 18), 250(40), 162(71), 135(100), 103(48), 91(98), 77(34).



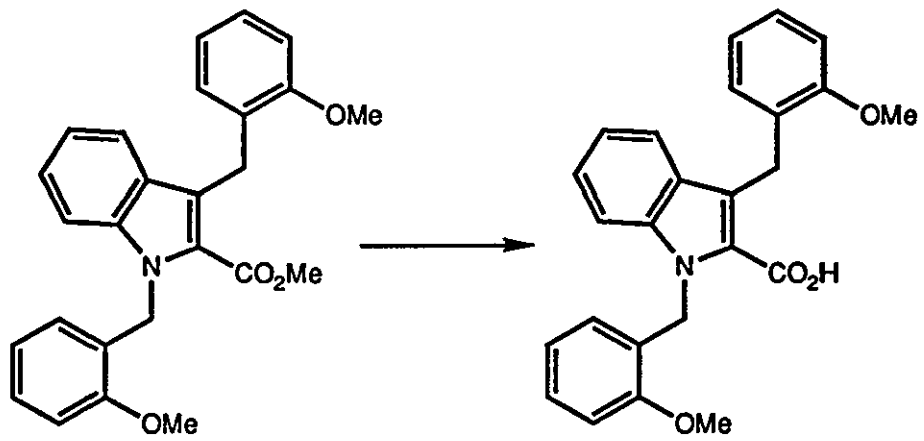
Methyl 1-(2'-methoxybenzyl)-3-(2''-methoxybenzoyl)indole-2-carboxylate (**81**)

To a suspension of sodium hydride (84 mg, 3.43 mmol) in DMF (10 ml) was added a solution of the indole (**80**) (0.96 g, 3.12 mmol) in DMF (20 ml) and the reaction stirred for 1 hour. 2-Methoxybenzyl bromide (0.69 g, 3.43 mmol) in DMF (15 ml) was added dropwise and the reaction stirred for a further 2 hours. The DMF was removed *in vacuo* and the residue purified by silica gel flash chromatography (petrol / ether) to afford the *title compound* (**81**) as a brown oil (1.1 g, 84%). (Found: MH+, 430.1654, $C_{26}H_{23}NO_5$ requires MH+, 430.1654). υ_{max}(Nujol) 1728, 1635 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 8.04(1H, d, J 6.8 Hz), 7.54-7.23(6H, m), 7.03-6.63(5H, m), 5.61(2H,

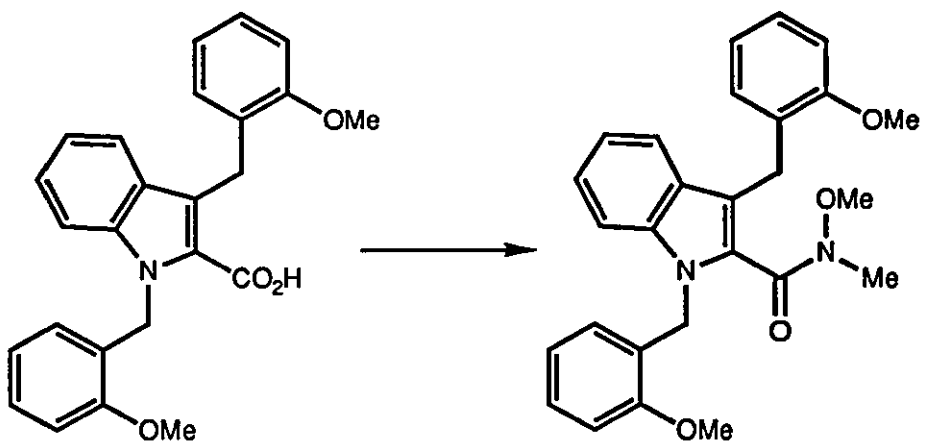
s), 3.83(3H, s) 3.71(3H, s), 3.27(3H, s); δ_C(62.5 MHz, $CDCl_3$) 191.0, 162.5, 157.5, 156.6, 137.2, 132.9, 132.2, 130.8, 130.3, 128.7, 127.2, 126.0, 124.9, 124.8, 122.9, 122.6, 120.5, 120.4, 120.1, 111.5, 111.0, 110.1, 55.7, 55.3, 51.9, 43.7; m/z 430(MH^+, 88), 212(20), 138(79), 121(87).



Methyl 1, 3-bis(2'-methoxybenzyl)indole-2-carboxylate (**82**)
The indole (**81**) (2.47 g, 5.78 mmol) was dissolved in ethyl acetate (50 ml) and 1 drop of conc. H_2SO_4 added. Activated palladium on charcoal (10 % wt) was added and the reaction shaken under an atmosphere of hydrogen for 4 days. The unreacted starting material was removed by silica gel flash chromatography to yield the *title compound* (**82**) as a colourless oil (1.5 g, 63 %). (Found: C, 75.18; H, 6.02; N, 3.37; $C_{26}H_{25}NO_4$ requires C, 75.13; H, 6.06; N, 3.33). υ_{max}(Nujol) 1715 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.59(1H, d, J 8 Hz), 7.26-7.00(5H, m), 6.89-6.72(5H, m), 6.45(1H, d, J 1.5 Hz), 6.32(2H, s), 4.50(2H, s), 3.89(3H, s), 3.88(3H, s), 3.75(3H, s); δ_C(62.5 MHz, $CDCl_3$) 163.0, 157.0, 156.3, 138.7, 129.5, 129.0, 127.8, 127.2, 126.8, 126.7, 126.3, 125.8, 125.2, 122.9, 121.3, 120.5, 120.3, 120.1, 110.7, 109.8, 109.7, 55.3, 55.2, 51.3, 43.6, 24.8; m/z 415(M^+, 40), 356 (21), 294(58), 121(100), 91(94).

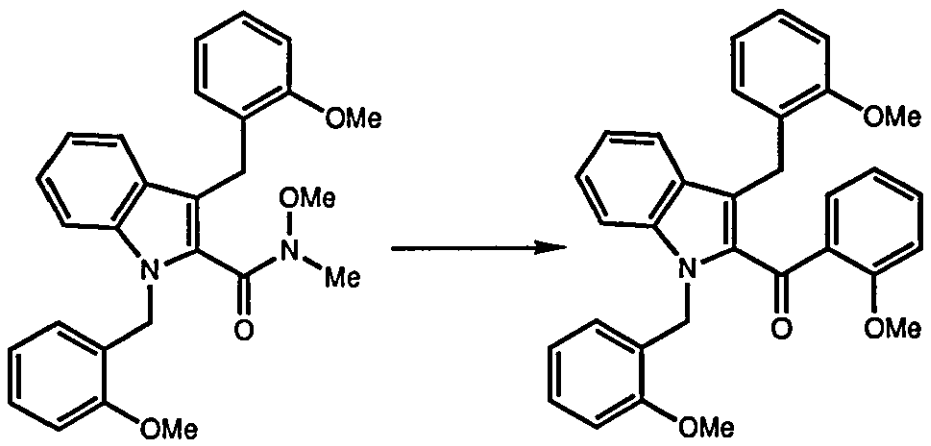


1, 3-bis(2'-Methoxybenzyl)indole-2-carboxylic acid (**83**)
A solution of methyl 1, 3-*bis*(2'-methoxybenzyl)indole-2-carboxylate (**82**) (600 mg, 1.45 mmol) in methanol (10 ml) was added to a solution of lithium hydroxide (52 mg, 2.17 mmol) in 1:1 THF / H_2O (20 ml) and brought to reflux for 18h. On cooling the pH of the solution was lowered to pH1 with 2M H_2SO_4 and the aqueous extracted with ether. The ether extracts were combined, washed with water and brine, dried and evaporated to afford the *title compound* (**83**) as a white solid (400 mg, 69%). (Found: M^+, 401.1627, $C_{25}H_{23}NO_4$ requires M^+, 401.1627); υ_{max}(Nujol) 3382, 1669 cm^{-1}; δ_H(250 MHz, $CDCl_3$+dmso) 7.50(1H, d, J 7.4 Hz), 7.19-6.70(10H, m), 6.39(1H, d, J 7.4 Hz), 5.81(2H, s), 4.50(2H, s), 3.90(3H, s), 3.88(3H, s); δ_C(62.5 MHz, $CDCl_3$+dmso) 164.0, 156.8, 156.2, 138.3, 129.4, 128.9, 127.6, 127.0, 126.6, 126.5, 126.4, 124.7, 122.1, 120.9, 120.2, 120.0, 119.7, 110.5, 109.7, 55.1, 43.1, 24.4; m/z 401(59, M^+), 357(38), 280(62), 121(100), 91(98).



N-Methoxy, N-methyl 1,3-bis(2'-methoxybenzyl)indole-2-amide (84)

1, 3-*bis*(2'-Methoxybenzyl)indole-2-carboxylic acid (83) (100 mg, 0.24 mmol) was added in one portion to a solution of N, N-dicyclohexylcarbodiimide (60 mg, 0.29 mmol) in pyridine (20 ml) and stirred under dry nitrogen for 15 minutes. N, O-dimethylhydroxylamine (50 mg, 0.48 mmol) in pyridine (5 ml) was added via cannula and the reaction warmed to 50°C where it was stirred for 18h (tlc analysis showed complete disappearance of starting acid). On cooling, the pyridine was removed *in vacuo* and the residue suspended in dry methylene chloride, where the precipitated N, N-dicyclohexylurea was removed by filtration. The residue on evaporation, was further purified by silica gel flash chromatography (ether) to afford the *title compound* (84) (60 mg, 54%) as a colourless oil. (Found: MH^+, 445.2127; $C_{27}H_{28}N_2O_4$ requires MH^+, 445.2127). υ_{max}(thin film) 1642.6 cm^{-1}; δ_H(250 MHz, $CDCl_3$) 7.49(1H, d, J 7.1 Hz), 7.32(1H, d, J 8.3 Hz), 7.24-7.03(4H, m), 6.84-6.69(6H, m), 5.46(2H, s), 4.16(2H, s), 3.84(3H, s), 3.79(3H, s); m/z 445(MH^+, 43%), 415(100), 295(40), 225(38), 150(22), 121(18).



2-(2'-Methoxybenzoyl)-1,3 bis-(2''-methoxybenzyl)indole (85)

t-Butyllithium (1.7 M, 1.2 ml, 2.03 mmol) was added to a solution of 2-bromoanisole (0.38 g, 2.03 mmol) in THF (15 ml) at -78°C under dry nitrogen and the resulting yellow anion stirred for 0.5h. The indole Weinreb amide (84) (0.6 g, 1.35 mmol) in THF (15 ml) was added dropwise via cannula whilst maintaining the temperature below -70°C and the reaction allowed to warm to ambient temperature over 3h. The reaction was concentrated and extracted

with ethyl acetate and the organic extracts washed with brine and evaporated to a yellow crude product. The crude was subjected to silica gel flash chromatography (petrol / ether) which gave the *title compound* (**85**) as a yellow oil. υ_{max}(Nujol) 1638 cm^{-1}. δ_H(250 MHz, $CDCl_3$) 7.80-6.67(16H, m), 5.83(2H, s), 4.08(2H, s), 3.89(3H, s), 3.73(3H, s), 3.71(3H, s). δ_C(62.5 MHz, $CDCl_3$) 189.5, 156.9, 156.5, 130.3, 129.3, 129.2, 128.2, 127.8, 127.7, 127.3, 127.2, 127.0, 125.5, 121.6, 120.5, 120.2, 120.1, 111.0, 109.9, 109.4, 55.3, 55.2, 55.0, 43.2, 24.4.

Chapter 5.

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