

*To my parents,
with love.*

SYNTHESIS OF THE STAUROSPORINE AGLYCONE

a thesis presented by

KULSUM FAROUQ RAHIMTOOLA

in partial fulfilment of the requirements

for the award of

DOCTOR OF PHILOSOPHY

OF THE

UNIVERSITY OF LONDON

Hofmann Laboratory,
Department of Chemistry,
Imperial College of Science,
Technology, and Medicine,
London SW7 2AY.

September 1990

Abstract

The isolation, structure determination, biological activity, and synthesis of indolocarbazoles is reviewed.

The synthesis and Diels-Alder reactivity of the pyrano[4,3-*b*]indol-3-one system is described and compared with the known isomeric pyrano[3,4-*b*]indol-3-one system. The pyrano[4,3-*b*]indol-3-ones are stable indole-2,3-quinodimethane analogues. They undergo Diels-Alder reactions with alkynes to give, after spontaneous loss of carbon dioxide, substituted carbazoles. They are less reactive than the isomeric pyrano[3,4-*b*]indol-3-ones, but their reactivity may be increased by the presence of an electron-withdrawing *t*-butoxycarbonyl group on the indole nitrogen. They appear to exhibit the opposite regioselectivity to their isomeric counterparts. Factors which affect the reactivity and regiochemistry of these indole-2,3-quinodimethane type dienes are discussed.

The above chemical methodology has been applied to a highly convergent synthesis of the staurosporine aglycone. Model studies towards this goal are described. The key step involves an intramolecular Diels-Alder reaction of a pyrano[4,3-*b*]indol-3-one with either an alkyne or an alkene. In the case of alkynes, concomitant loss of carbon dioxide occurs to give the substituted carbazole in good yield. However, in the case of the alkenes, air oxidation is required to form the carbazole. Synthetic studies towards the staurosporine aglycone are described. These include a successful synthesis of the staurosporine aglycone without the use of protecting groups. The route involves an intramolecular Diels-Alder reaction of a pyrano[4,3-*b*]indol-3-one with an alkene, followed by a nitrene mediated cyclisation.

Acknowledgements

I would like to thank Professor Christopher J. Moody, my supervisor, for his help, guidance, and constant encouragement throughout my time at Imperial. I would also like to thank Professor Charles W. Rees for his helpful advice.

I am grateful to the excellent support staff at Imperial College and, in particular, would like to thank Pete Sulsh (technical assistance), Dick Sheppard and Paul Hammerton (NMR spectroscopy), John Bilton and Geoff Tucker (mass spectroscopy), and Ken Jones (microanalysis). I also wish to thank the S.E.R.C. mass spectrometry centre at Swansea for their efficient service.

I am indebted to William Wylie for the theoretical calculations and to Tony Beck, Peter Hunt, Graham Jones, Anita de La Motte, and Chris Moody for taking turns to synthesise ethyl 4-(2'-nitrophenyl)acetoacetate (to which I seem to have developed an allergy) and ethyl indol-2-ylacetate, the two starting materials without which this project really would not be possible! I am also grateful to Anita de La Motte for proof-reading this thesis. My thanks go to past and present members of the Hofmann Lab. for teaching me so much chemistry and for making my stay at Imperial so enjoyable.

Additionally, I wish to thank Glaxo Group Research for their generous financial support in the form of a studentship, Drs Barry Ross and Barry Porter at Glaxo for helpful discussions, and Dr Peter May and his colleagues in whose laboratory I worked during my period at Glaxo (Greenford).

Finally, I want to thank my parents and brothers for their unfailing confidence and constant support throughout my education.

Kulsum F. Rahimtoola,
London 1990.

Contents

	<u>page</u>
Abbreviations	6
 <u>Chapter 1</u> The chemistry of indolocarbazoles	
1.1 Introduction	9
1.2 Isolation and structure determination	10
1.3 Biological activity	17
1.4 Syntheses of indolocarbazoles and their derivatives	20
1.5 Conclusion	48
 <u>Chapter 2</u> Synthesis and Diels-Alder reactions of pyrano[4,3-<i>b</i>]indol-3-ones	
2.1 Introduction	50
2.2 Synthesis of pyrano[4,3- <i>b</i>]indol-3-ones	55
2.2.1 Synthesis of indol-2-ylacetic acid	55
2.2.2 Preparation of pyrano[4,3- <i>b</i>]indol-3-ones	65
2.3 Diels-Alder reactions of pyrano[4,3- <i>b</i>]indol-3-ones with alkynes	68
2.3.1 Results	68
2.3.2 Discussion	68
a) Reactivity	71
b) Regioselectivity	73
 <u>Chapter 3</u> Synthesis of the staurosporine aglycone	
3.1 Introduction	82
3.2 Initial approaches	84
3.3 Model studies	89
3.4 Synthetic studies towards the staurosporine aglycone	98

	<u>page</u>
3.4.1 Preparation of (<i>o</i> -nitrophenyl)propargylamine and its use towards a synthesis of the staurosporine aglycone	99
3.4.2 Preparation of (<i>o</i> -bromophenyl)propargylamine and its use towards a synthesis of the staurosporine aglycone	106
3.4.3 Attempted preparation of (<i>o</i> -azidophenyl)propargylamine	111
3.4.4 Preparation of <i>o</i> -nitrocinnamylamine and its use in a synthesis of the staurosporine aglycone	112
3.5 Conclusion	120
 <u>Chapter 4</u> Experimental section	
4.1 General information	122
4.1.1 Solvents and reagents	122
4.1.2 Chromatographic procedures	122
4.1.3 Spectroscopic techniques	123
4.1.4 Other data and instrumentation	124
4.2 Experimental for Chapter 2	125
4.3 Experimental for Chapter 3	137
4.3.1 Experimental for Section 3.3	137
4.3.2 Experimental for Section 3.4.1	149
4.3.3 Experimental for Section 3.4.2	153
4.3.4 Experimental for Section 3.4.4	158
 References	 165

Abbreviations

Ac	Acetyl
Ar	Aryl
ATP	Adenosine triphosphate
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
Bu	Butyl
cAMP	Cyclic adenosine monophosphate
DAG	Diacylglycerol
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulphoxide
DMF	N,N-Dimethylformamide
DNA	Deoxyribonucleic acid
Et	Ethyl
HMPA	Hexamethylphosphoramide
HMPT	Hexamethylphosphorus triamide
HOMO	Highest occupied molecular orbital
H.P.L.C.	High pressure liquid chromatography
IC ₅₀	Concentration required for 50% inhibition
IBCF	Isobutyl chloroformate
IP ₃	Inositol triphosphate
IR	Infra-red

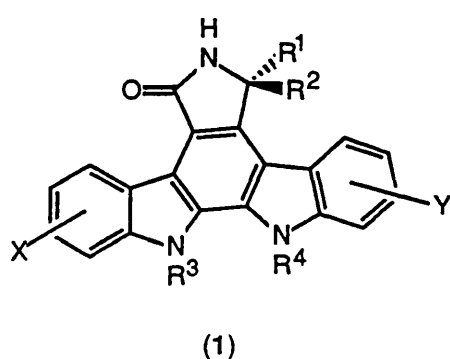
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
mCPBA	3-Chloroperbenzoic acid
Me	Methyl
MO	Molecular orbital
MOM	Methoxymethyl
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
PDC	Pyridinium dichromate
NPh	Phthalimido
Ph	Phenyl
PIP ₂	Phosphatidylinositol-4,5-bisphosphate
PKA	Protein kinase A
PKC	Protein kinase C
PPA	Polyphosphoric acid
PPSE	Polyphosphoric acid, trimethylsilyl ester
py	Pyridine
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl
TPA	12-O-Tetradecanoylphorbol-13-acetate
Ts	Tosyl
t.l.c.	Thin layer chromatography
UV	Ultra-violet

CHAPTER ONE

THE CHEMISTRY OF INDOLOCARBAZOLES

1.1 Introduction

Only a small group of natural products containing the indolocarbazole unit (1) have been isolated to date.



<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁴</u>
H	H	H	H
H	OH	Sugar	H
OH	H	H	Sugar
O	O	Sugar	Sugar

These indolocarbazoles can be divided into two subgroups. One group possesses a lactam in the "top" ring (such as staurosporine (2) and the K252 series (8-11)) and the other, a cyclic imide (such as rebeccamycin (7) and the arcyriflavins (5 and 6)). The majority of the indolocarbazoles are also linked to a sugar either *via* one or two N-glycosidic linkages to the indole nitrogens.

These compounds are of interest due to their significant biological activity. In particular, some of these indolocarbazoles are potent inhibitors of protein kinase C, an enzyme in the inositol phosphate pathway. This enzyme plays a crucial role in cellular signal transduction, cellular proliferation, and cellular differentiation. Investigation of this enzyme and its role using indolocarbazoles is an on-going area of research. This review will only attempt to give a brief over-view of the subject to illustrate the importance of these compounds.

Several syntheses of indolocarbazoles and their derivatives have been reported in the literature. These are all discussed and particular attention is given to the efficiency of the method and the ease with which it can be applied to make other indolocarbazoles. Where appropriate, the synthesis of the glycoside moiety and its subsequent attachment to the indolocarbazole aglycone is also discussed.

1.2 Isolation and structure determination

In 1977, a natural product with a novel structure was isolated from *Streptomyces staurosporeus*.¹ This was initially called AM-2282, and later named staurosporine (2). The structure of this new alkaloid could not be established completely until 1978 when the X-ray crystal structure of its methanol solvate was obtained.^{2,3} Staurosporine (2) consists of an unusual indolocarbazole unit linked by two N-glycosidic bonds to a sugar moiety.

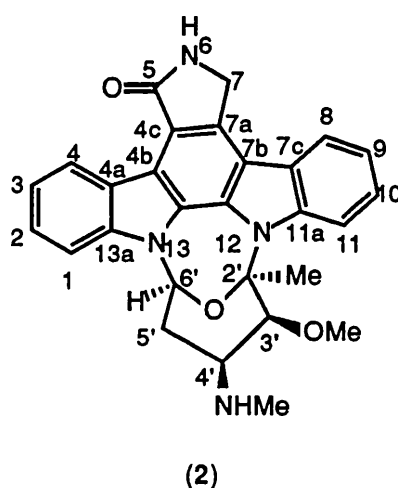


Figure 1.1 shows staurosporine (2) in ball and stick and space-filling representations. The aglycone is slightly bent, with the two terminal benzene rings making an angle of 7.5° with each other, due to steric hindrance between the methylamino group of the sugar and the aromatic system. The UV spectrum has a strong characteristic absorption at 292 nm^{-1} . Extensive NMR studies have resulted in the assignment of all the proton and carbon chemical shifts.⁴ As can be seen from Table 1.1, a chemical shift difference exists between the two halves of the indolocarbazole unit. In particular, it is worth noting the marked downfield shift of 4-H due to the shielding effect of the lactam carbonyl group. Staurosporine is soluble in DMSO and DMF, slightly soluble in methanol, ethyl acetate, and chloroform, and insoluble in water.^{1,4} This low solubility is a feature of all the indolocarbazoles and is responsible for a number of problems encountered during synthetic transformations on these compounds. Preliminary studies on the biosynthesis of staurosporine show that the aglycone moiety is made from two intact units of

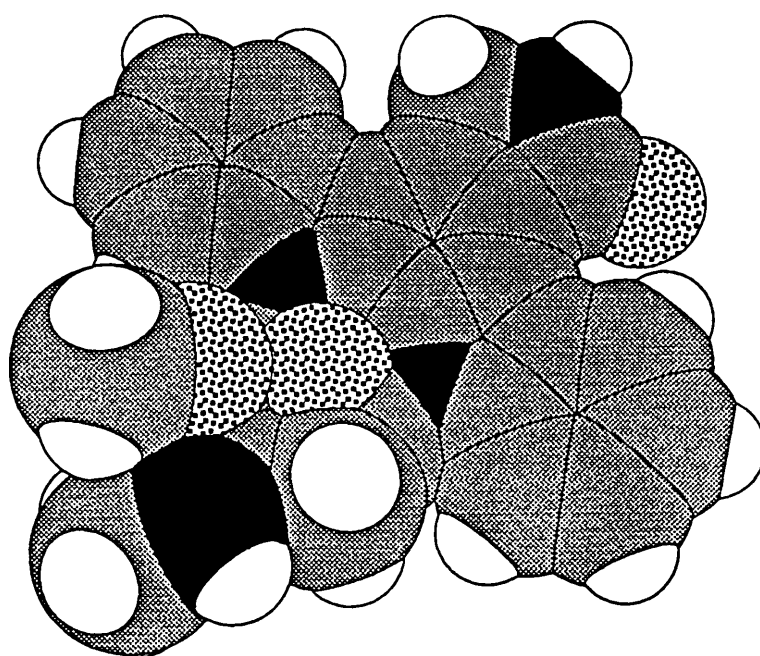
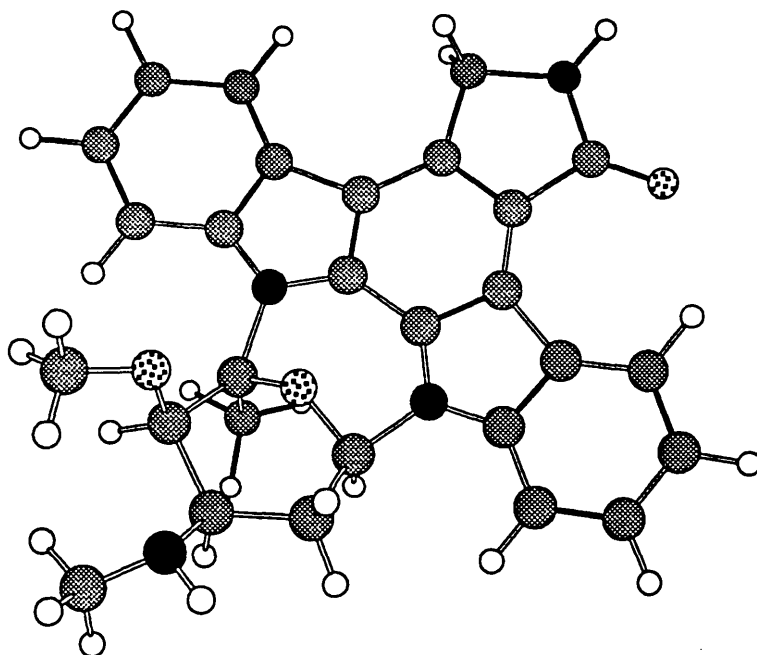


Figure 1.1 Staurosporine (2) in ball and stick and space-filling representations.

Key

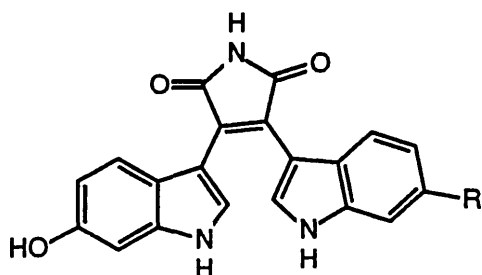
	Carbon
	Hydrogen
	Nitrogen
	Oxygen

Table 1.1 ^1H NMR data of staurosporine (2) and K-252c (10).

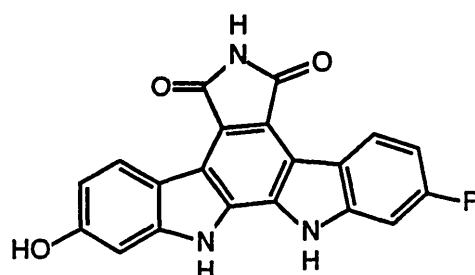
Chemical shift in ppm (J, Hz)		
proton	(2) ⁴	(10) ¹⁵
	CDCl_3	$(\text{CD}_3)_2\text{SO}$
1	7.26 (t, 7.6)	7.73 (d, 8.1)
2	7.46 (t, 7.6)	7.44 (br t)
3	7.35 (t, 7.6)	7.24 (br t)
4	9.42 (t, 7.6)	9.24 (d, 7.9)
6	6.81 (br s)	8.49 (br s)
7	4.99 (AB)	4.98 (s)
8	7.87 (d, 7.8)	8.05 (d, 7.8)
9	7.30 (t, 7.8)	7.31 (br t)
10	7.41 (t, 7.8)	7.48 (br t)
11	7.91 (d, 7.8)	7.79 (d, 8.1)
12		11.56 (br s)
13		11.38 (br s)
3'	3.86 (d, 3.6)	
4'	3.33 (t, 3.6)	
5'	2.71 (dd, 14.7, 3.6)	
5'	2.39 (ddd, 14.7, 5.2, 3.6)	
6'	6.52 (d, 5.2)	
Me	2.33 (s)	
OMe	3.37 (s)	
NMe	1.54 (s)	

tryptophan.⁵ However, the exact metabolic pathway is still under investigation.

The closely related arcylarubins (3 and 4) and arcylflavins (5 and 6) were isolated from the fruiting bodies of the slime mould *Arcyria denudata* by W. Steglich *et al.* in 1980.⁶ The arcylarubins have a distinct red colour, whereas the arcylflavins are yellow.



(3) R=H Arcylarubin B
(4) R=OH Arcylarubin C

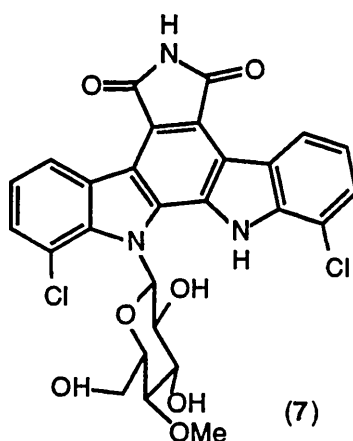


(5) R=H Arcylflavin B
(6) R=OH Arcylflavin C

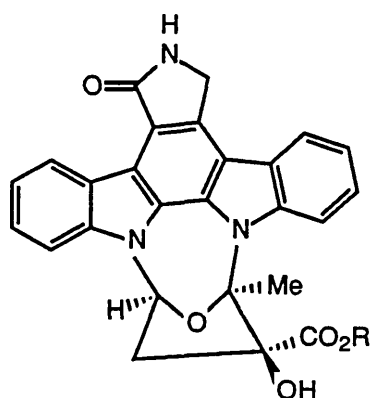
Steglich showed that it was possible to convert (4) into (6) on gentle heating in concentrated sulphuric acid, thus suggesting the formation of the 2,2'-indole bond as the final step in the biosynthetic pathway of these systems. This was later used by several groups as the final step in various syntheses of indolocarbazoles.⁷⁻¹⁰ The lactam ring in staurosporine has been oxidised to an imide in the arcylflavins. At least one hydroxyl group is also present at the 6-position of the indole moieties making up the aglycone.

After a gap of a few years, a handful of new indolocarbazoles were isolated in succession. The first of these was rebeccamycin (7), a yellow solid, isolated from *Nocardia aerocoligenes*, in 1985.¹¹ Analysis of spectroscopic data, together with X-ray crystallography, revealed that it possessed the same basic skeleton as the arcylflavins (5 and 6), containing an imide functionality in its structure, but was chlorinated at both the 7-positions of the indole moieties. Furthermore it had an N-glycosidic linkage to 4-O-methylglucose. The absolute stereochemistry of rebeccamycin (7) was only established after a total synthesis of this compound.⁸ Recently, investigations of the biosynthetic pathway showed that it is synthesised in cultures of *Saccharothrix aerocoligenes* (the new name of *Nocardia aerocoligenes*!) from two units of

tryptophan, one unit of glucose, and one of methionine.¹² However it appears that the imide nitrogen might be derived from a different source. Labelling experiments showed that ^{15}N was incorporated into the molecule when fermentation was done in the presence of ^{15}N -unlabelled tryptophan and ^{15}N -labelled ammonium sulphate.

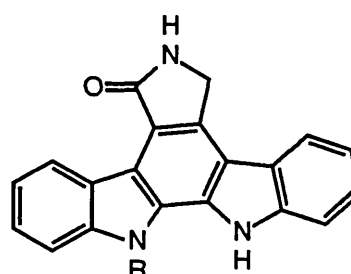


In the same year, Japanese workers reported the isolation and structure elucidation of SF2370 (8) from *Actinomadura*.¹³ The same compound was isolated the following year from *Nocardioopsis* sp. K-252 and was called K-252a (8).^{14,15} Another *Nocardioopsis* strain K-290 produced three other indolocarbazoles, K-252b (9), K-252c (10), and K-252d (11).^{15,16}

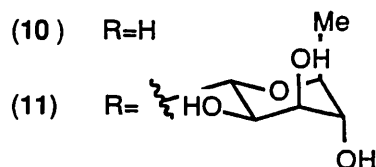


(8) R=Me

(9) R=H



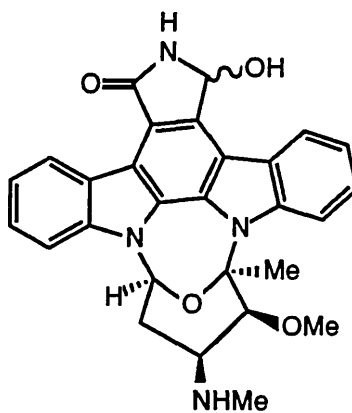
(10) R=H



(11) R=

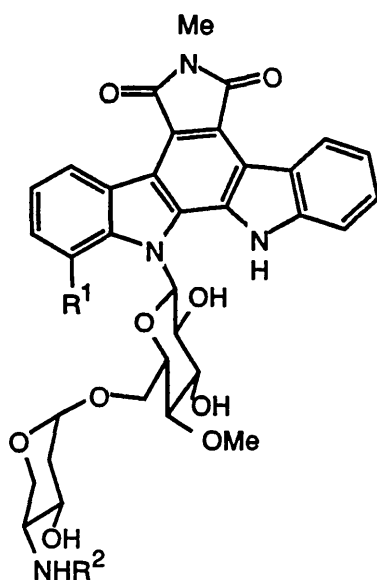
The distinct UV chromophore of these compounds suggested that they all possessed the same aglycone as staurosporine (2). Study of the spectroscopic data and an X-ray crystal enabled the assignment of the structure of K-252a (8). Yasuzawa *et al.* showed that hydrolysis of K-252a (8) gave K-252b (9).¹⁵ Furthermore, hydrolysis of K-252a (8) under drastic conditions gave K-252c (10), which was identical to the aglycone of staurosporine synthesised by Sarstedt and Winterfeldt.⁹ K-252c (10) is unusual in that it consists of only the staurosporine aglycone. Its ¹H NMR data are given in Table 1.1. K-252d (11) was hydrolysed to give a sugar, which was identical in all respects to naturally-occurring L- rhamnose. The spectroscopic data for these compounds were all consistent with the assigned structures.

UCN-01 (12) and UCN-02 (13) were isolated in 1987 from *Streptomyces* sp. N-126 during a screening program for new selective inhibitors of protein kinase C.¹⁷⁻¹⁹ Analysis of spectroscopic data showed that they were in fact stereoisomers of 7-hydroxystaurosporine. The absolute stereochemistry of UCN-01 and UCN-02 at C-7 has yet to be determined.



(12) and (13)

The full details of the isolation of the AT2433 series (14-17) from *Actinomadura melliaura* were next to be reported.^{20,21} These compounds had been referred to earlier as novel antibiotics, as well as antibacterial and antitumour agents, in a patent in 1986.²² Analysis of spectroscopic data, comparison with rebeccamycin (7), and degradation work enabled the structures to be assigned as shown below.



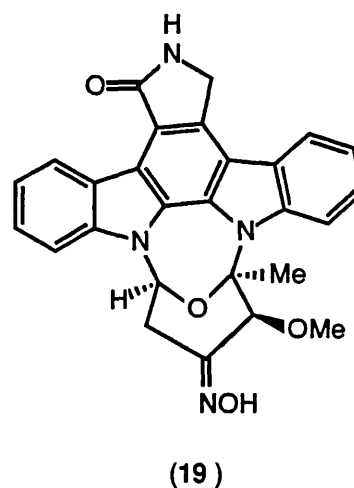
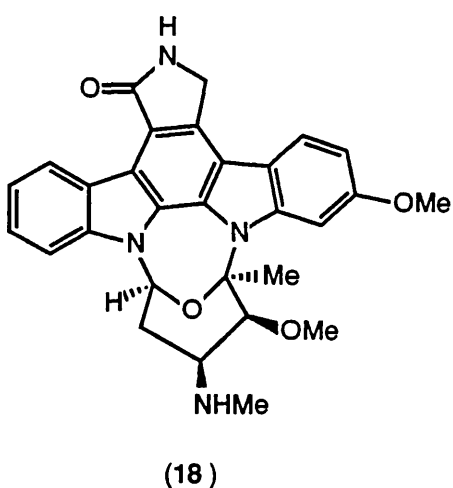
(14) AT2433-A1 $R^1 = \text{Cl}$ $R^2 = \text{Me}$

(15) AT2433-A2 $R^1 = \text{Cl}$ $R^2 = \text{H}$

(16) AT2433-B1 $R^1 = \text{H}$ $R^2 = \text{Me}$

(17) AT2433-B2 $R^1 = \text{H}$ $R^2 = \text{H}$

Recently, TAN-999 (18) and TAN-1030A (19) have been isolated from *Nocardioopsis* and *Streptomyces* respectively.²³ Comparison of spectroscopic data with staurosporine (2) showed that TAN-999 (18) was 10-methoxystaurosporine. TAN-1030A (19), however, differed from staurosporine (2) at the 4'-position in that it has an oxime functionality. This was confirmed by hydrogenation with Pt-black and subsequent acetylation with Ac_2O -pyridine to give an acetamide (-NHAc) at the 4'-position.



1.3 Biological activity

The indolocarbazoles are all biologically active compounds. Rebeccamycin (7) and the AT-2433 series (14-17) have all been patented as antitumour antibiotics.^{22,24} Studies show that rebeccamycin (7) produces single strand breaks in DNA.²⁵

Staurosporine (2) was originally patented as an antimicrobial and antifungal agent, which also showed hypertensive effects in rats.^{26,27} Since, it has been shown to inhibit platelet aggregation,²⁸ to activate macrophage function in mice,²³ and to show activity against a number of experimental tumours,²⁹⁻³¹ *e.g.* a cytotoxic effect on HeLa S3 cells.³⁰ It induced differentiation at low concentrations (20 nM) and cytotoxicity at high concentrations ($>0.21 \mu\text{M}$) on a human neuroblastoma cell line NB-1.³¹ Moreover, it is a potent inhibitor of protein kinase C (PKC), with an IC_{50} of 2.7 nM.³⁰ However, it appears to inhibit cAMP dependent protein kinases to a similar extent *e.g.* protein kinase A (IC_{50} 8.2 nM). It also is an inhibitor of tyrosine specific-protein kinase of P60 transforming protein of Rous sarcoma virus (IC_{50} 6.4 nM).³²

K-252a (8) and K-252b (9) are also protein kinase C inhibitors with IC_{50} of 32.9 nM and 38.3 nM respectively.^{14,16} K-252a (8) inhibits calmodulin activated enzymes to a lesser extent than PKC, and K-252b (9) to a similar extent as PKC. Interestingly, K-252c (10), the aglycone of staurosporine, also shows some PKC inhibitory activity (IC_{50} 214 nM),¹⁶ thus suggesting that the indolocarbazole skeleton is responsible for some interaction with the enzyme. K-252d (11) also shows weak inhibitory action (IC_{50} 337 nM) against PKC.¹⁶ All these K-252 compounds have been reported to affect seriously the function of various cells and tissues, such as platelets, mast cells, and vascular smooth muscle.^{14,16} Furthermore, K-252a (8) shows protective effects against rice plant disease in greenhouse tests.¹³

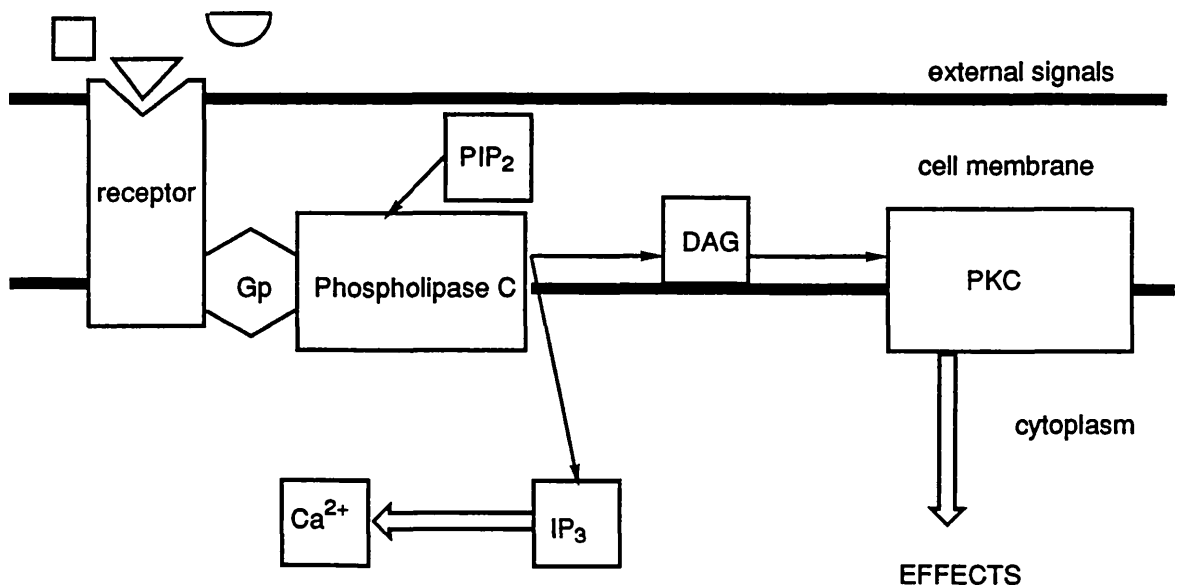
UCN-01 (12) is also a PKC inhibitor.¹⁹ Furthermore, it is more specific for PKC (IC_{50} 4.1 nM) over PKA (IC_{50} 42 nM). Interestingly, its stereoisomer, UCN-02 (13), also shows activity against PKC (IC_{50} 62 nM) and PKA (IC_{50} 0.25 mM), but to a lesser degree. They show cytotoxic effects on growth of HeLa S3 cells, as well as displaying anti-tumour activity against murine lymphotic leukaemia P388 *in vivo*.¹⁷

TAN-999 (18) and TAN-1030A (19) both appear to activate macrophage functions in mice.²³ Macrophages act as regulatory and effector cells in the host defence system. They are phagocytic and therefore protect the host from invasion by microorganisms and against development of tumours. Tanida *et al.* suggest that activation of macrophages may be controlled by protein kinases.

Protein kinases are enzymes which utilise adenosine triphosphate (ATP) to catalyse the phosphorylation of proteins and hence increase or decrease their functional activity. They are categorised by the amino acid residue being phosphorylated (usually serine and threonine, or tyrosine) and by the nature of their activators (*e.g.* cAMP, Ca^{2+} , phospholipids, *etc.*). Protein kinase C (PKC), in particular, is a family of enzymes that catalyse the phosphorylation of serine and threonine residues in the presence of Ca^{2+} and phospholipids. It is found in the cell membrane and appears to play an important part in the flow of extracellular informational signals from the cell surface to the cell interior, in cellular proliferation, and in cellular differentiation.

PKC is activated (Figure 1.2) by a series of events starting with the binding of an external agent at a receptor on the surface of the cell membrane.

Figure 1.2



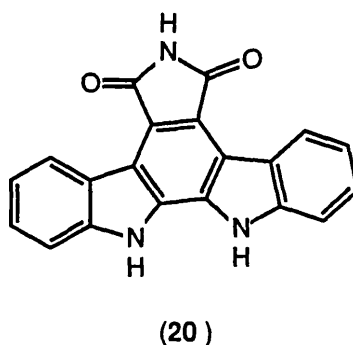
This receptor is coupled to a G protein which, in turn, activates the enzyme phospholipase C. This enzyme catalyses the hydrolysis of a membrane phospholipid, phosphatidylinositol-4,5-bisphosphate (PIP₂), to form two secondary messengers. The lipid portion, diacylglycerol (DAG), remains in the membrane and activates the membrane-attached PKC. The other product, inositol triphosphate (IP₃), is released into the cytoplasm where it causes the release of calcium ions from internal stores.

PKC has a regulatory and a catalytic domain. Thus several binding sites are available. The first is the binding site for the activator molecules, such as diacylglycerol, in the regulatory domain. Tumour-promoting phorbol esters, such as 12-O-tetradecanoylphorbol-13-acetate (TPA), bind at this site. The second region is the one responsible for maintaining the inactivity of the enzyme in the presence of activator molecules. The third region is the ATP binding site in the catalytic domain. This particular binding site is homologous to the ATP binding site in other protein kinases, thus inhibitors that bind at this site are generally not specific for PKC over other protein kinases.

Staurosporine (2) and the K252 compounds (8-11) inhibit the proteolytically-generated catalytic fragment of PKC, but have no effect on the binding of phorbol esters at the regulatory domain.³⁰ Thus they appear to bind at the ATP binding site. However, staurosporine exhibits biological potency at concentrations which are far lower than those required for competitive inhibition with ATP.³³ Thus the exact mechanism / site of interaction of these indolocarbazoles still remains in doubt. However, the indolocarbazoles are amongst the most potent inhibitors of PKC (IC₅₀ in nM range compared with mM range *e.g.* H-7 (12 mM), trifluoperazine (16 mM), chlorpromazine (24 mM), and R-24571 (5.3 mM)), and therefore of great importance in investigating the role of PKC at the cellular level.

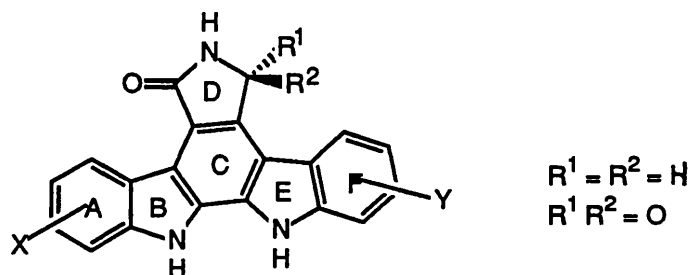
1.4 Syntheses of indolocarbazoles and their derivatives

A number of syntheses of indolocarbazoles have been reported in the literature.^{7-10, 34-36} However, the majority of these are of the N-protected aglycones. No mention is made in the papers for deprotection of these compounds, which will be a non-trivial matter due to the low solubility of the indolocarbazoles. Rebeccamycin (7) is the only sugar-containing indolocarbazole to be synthesized,⁸ and, in fact, the synthesis proved the absolute stereochemistry of the natural product. Arcyriaflavins A (20),³⁴ B (5),³⁵ and C (6),⁶ the



rebeccamycin aglycone,^{8, 34} K-252c (10) (the staurosporine aglycone),⁹ derivatives of the staurosporine aglycone,^{7, 35-36} and derivatives of the unusual staurosporine sugar ^{7, 37} have also been made. However, methodology has yet to be developed to link the staurosporine sugar *via* a double N-glycosidic linkage, stereospecifically and regiospecifically, to the aglycone.

Consider the indolocarbazole aglycone:

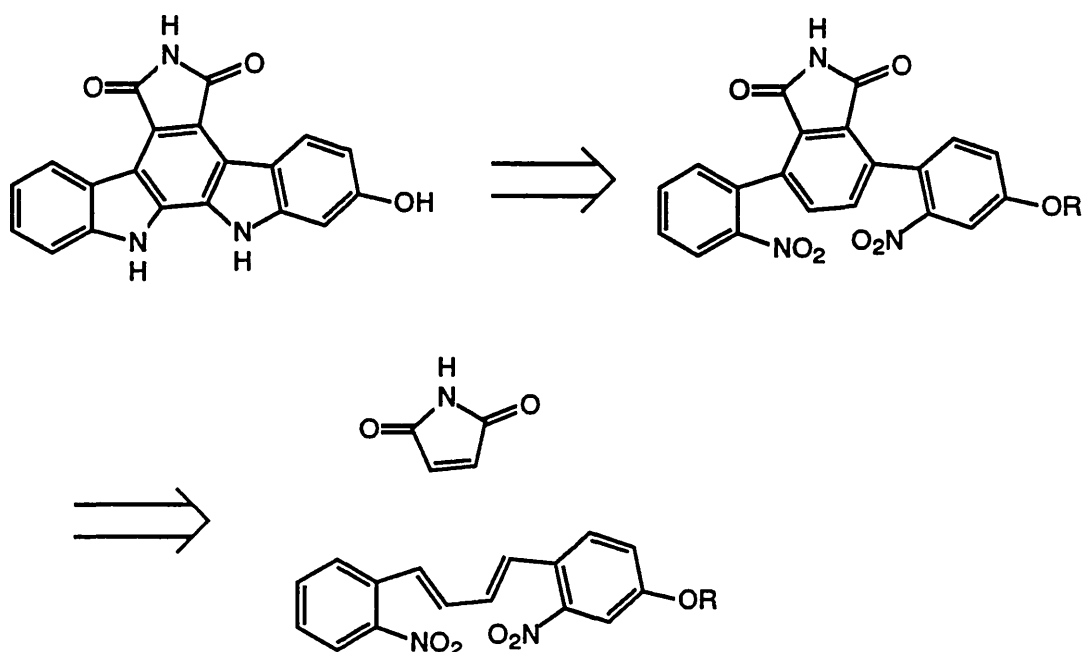


The syntheses, so far, can be divided into two main groups: those which involve formation of the indole B and E rings in the final step,³⁴⁻³⁵ and those which involve formation of the middle six-membered ring C.⁶⁻¹⁰ The exception is Magnus's approach which involves synthesis of the D ring as the final annulation.³⁶ However, the key step in his method is formation of the C ring *via* an intramolecular indole-2,3-quinodimethane reaction.

In the case of staurosporine, it is also worth noting the χ^{ncv} symmetry of the aglycone due to the lactam in the D ring. Some groups introduce this χ^{nc} symmetry at an early stage of the synthesis, whereas others concentrate on the symmetrical imide structure (1, $R^1 R^2 = O$) and only reduce it down to the lactam at a later stage in the synthesis. This is a non-trivial transformation. A variety of methods have been tried ($LiAlH_4$ and related metal hydrides only gave partial reduction, even under forcing conditions) and only Clemmensen reduction appears to give a satisfactory result.^{7, 35}

Two syntheses of indolocarbazole compounds use formation of the indole B and E rings in the final step. The first of these was a synthesis of arcyriflavin B reported by Hughes and Raphael in 1983.³⁵ The key disconnections (Scheme 1.1) were firstly the two indole rings, followed by the "middle" six-membered ring C.

Scheme 1.1

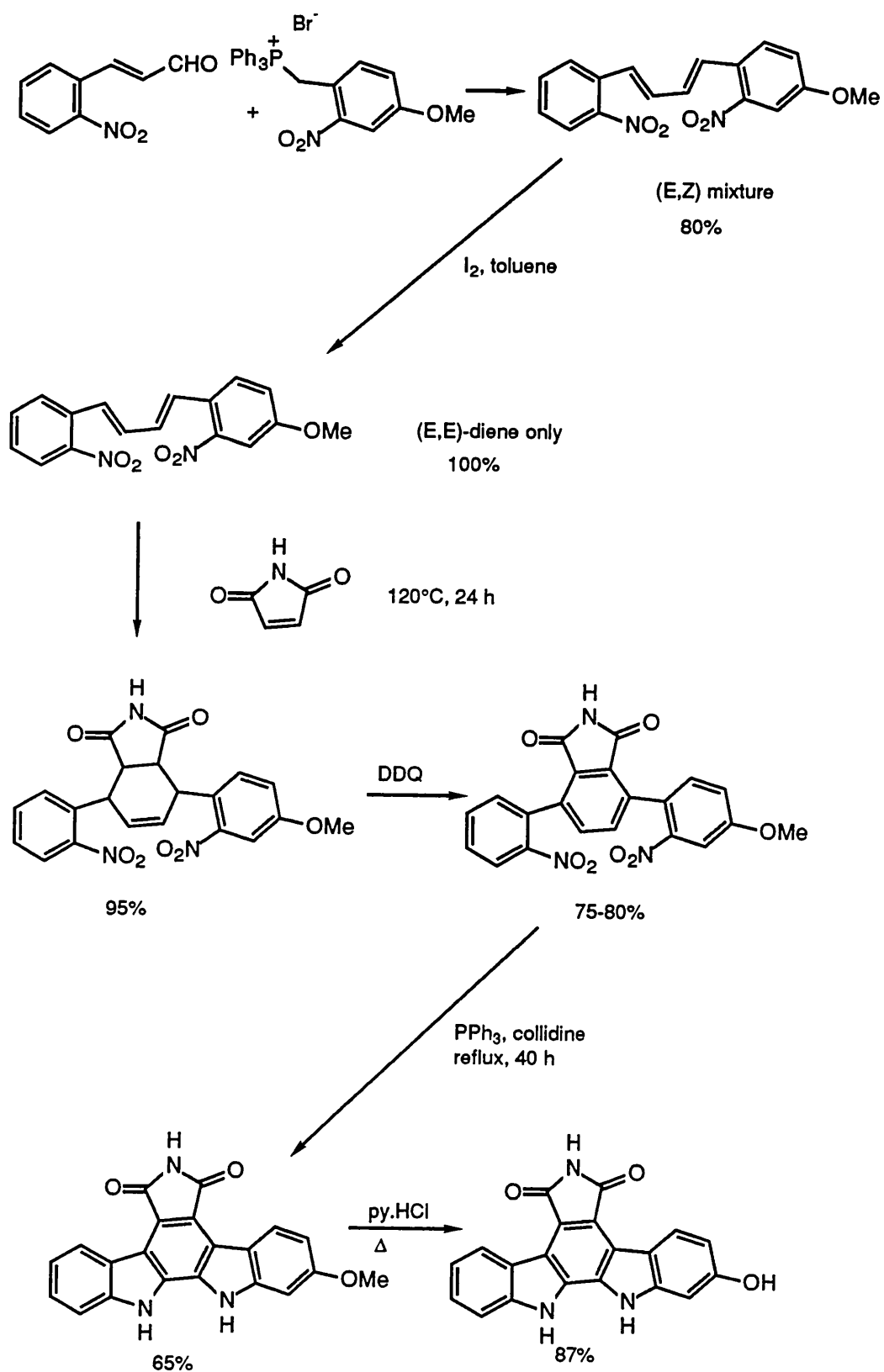


The first step was formation of the required diene from the appropriate ylid and *o*-nitrocinnamaldehyde (Scheme 1.2), followed by treatment with iodine to form the (E,E)-diene. The Diels-Alder reaction of this diene with neat maleimide proceeded in 95% yield. The Diels-Alder adduct was then dehydrogenated with DDQ. The next major step was formation of the two indole rings *via* a double nitrene insertion. This was achieved with triphenylphosphine in refluxing collidine for 40 h, in 65% yield. By-products of this reaction included both the mononitrene carbonyl insertion products. The final step was a demethylation with neat pyridine hydrochloride in a sealed tube reaction. The vigorous conditions required for this simple deprotection step were due to the low solubility of the indolocarbazole. Thus the overall yield of arcyrflavin B from 2-nitro-4-methoxybenzyl bromide was 27%.

Raphael and Hughes also used the same methodology to synthesize N-benzyl staurosporine.* In this case the asymmetry in the staurosporine aglycone is introduced at the end by Clemmensen reduction of the imide to a lactam.

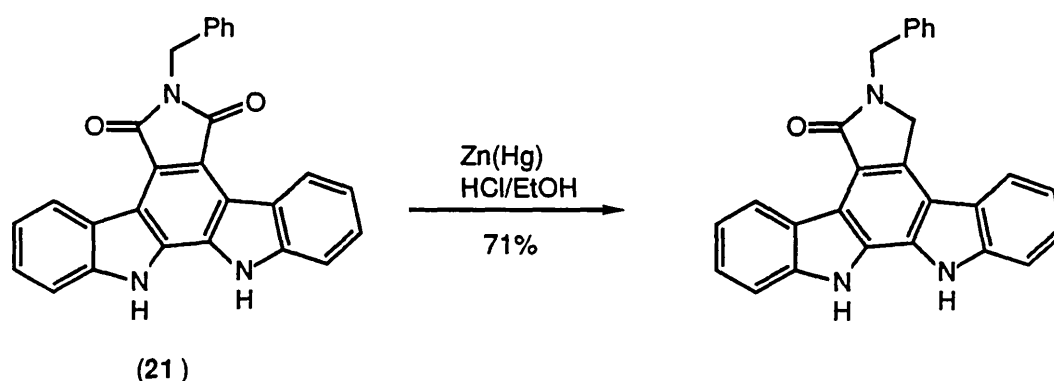
* Henceforth, "staurosporine" refers only to the aglycone.

Scheme 1.2



Thus Diels-Alder reaction of 1,4-di(*o*-nitrophenyl)butadiene with *N*-benzylmaleimide, followed by dehydrogenation and nitrene mediated insertion gave (21) in 55% overall yield. The authors also suggested a slightly different route which was more amenable to large scale preparation. This involves cycloaddition of the diene with dimethyl acetylenedicarboxylate, dehydrogenation with palladium black in mesitylene, formation of the *N*-benzylimide, followed by nitrene insertion to give (21). No yields are reported for this reaction sequence. Clemmensen reduction of (21) gave *N*-benzylstaurosporine in 71% yield.

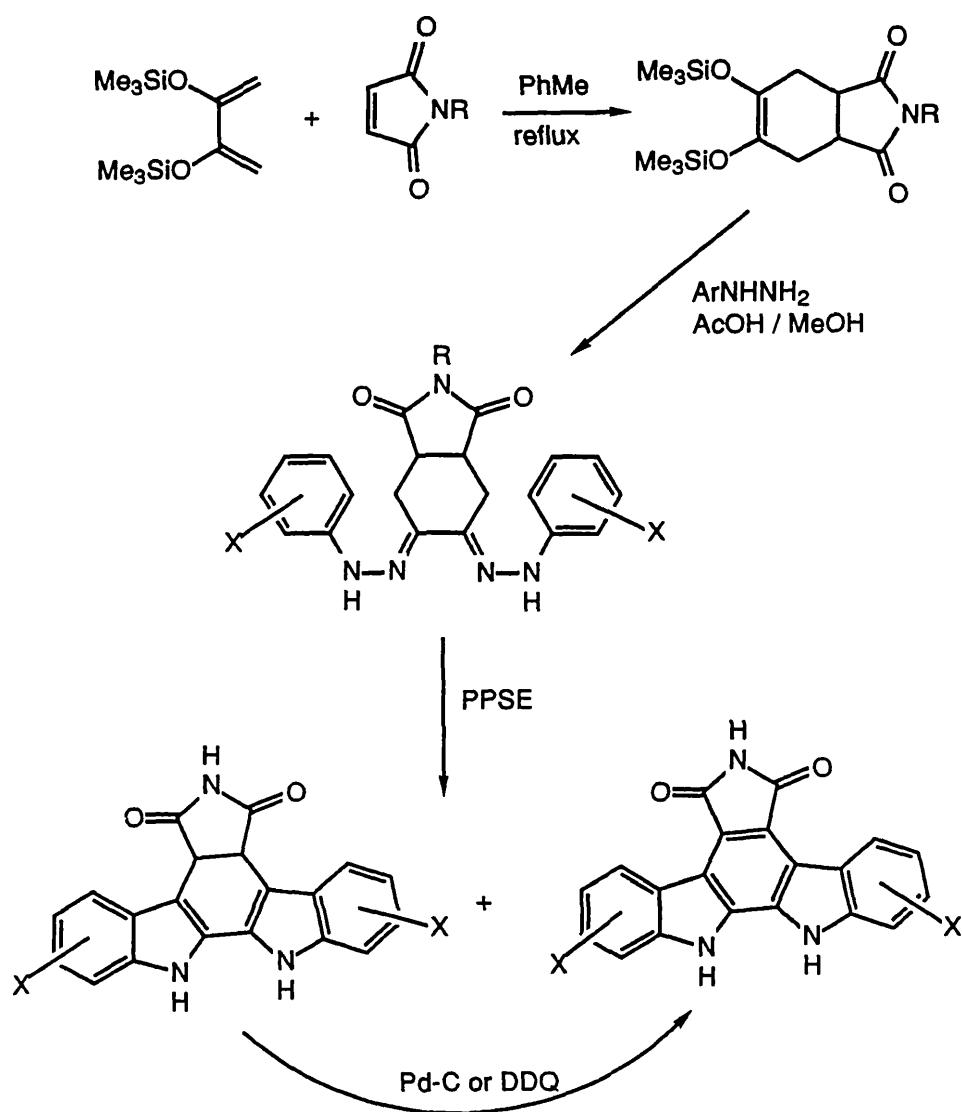
Scheme 1.3



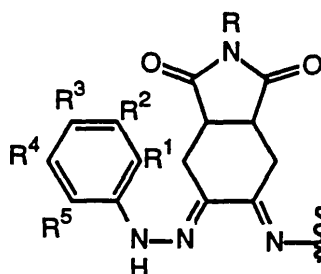
The second synthesis using the same disconnections was reported recently by Bergman *et al.* and involves a double Fischer indolisation to make the B and E rings.¹⁰ The previous key step again involves cycloaddition. Reaction of 2,3-bis[(trimethylsilyl)oxy]butadiene with maleimides (Scheme 1.4) gave bis(trimethylsilyl)-protected α -hydroxyketone cycloadducts in *ca.* 90% yield. These react readily with 3 equivalents of aryl hydrazine to give the required bis (phenylhydrazones). These could be cyclised in good yield to give mixtures of dihydroindolocarbazole and aromatic indolocarbazole when PPSE was used as catalyst. Conventional catalysts, such as HCl / EtOH, H_2SO_4 , PPA, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ / AcOH, *etc.*, all gave complex mixtures. After cyclisation, the crude reaction mixtures were directly aromatised by treatment with Pd-C in refluxing diglyme, or with DDQ. Thus arcyriflavin A and the

rebeccamycin aglycone were synthesized in 55.7% and 37.7% yield respectively from maleimide and 2,3-bis[(trimethylsilyl)oxy]butadiene, using appropriately substituted hydrazines.

Scheme 1.4



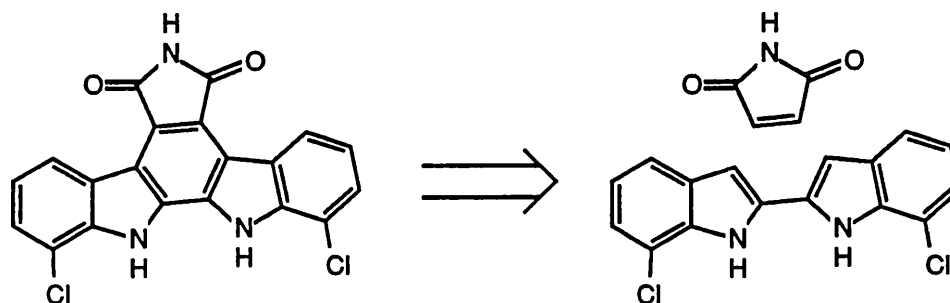
Bergman *et al.* made a variety of analogues to show the general nature of this method. The usual problem of regiospecificity of the Fischer indolisation process are mostly avoided.



If R^2 or R^4 is substituted, the ring formation will take place in such a way that R^2 or R^4 both end up in the indole 6-position. This is because the indole 4-position is quite sterically hindered due to the carbonyl oxygens of the imide. In fact, this is exactly what Bergman found when he tried the cyclisation with $R^4=OMe$, $R^1=R^2=R^3=R^5=H$. In the case where both R^2 and R^4 are substituted, it seems unlikely that the bis(hydrazone) will cyclise very readily. Bergman found that the nitro-substituted bis(hydrazone) ($R^3=NO_2$, $R^1=R^2=R^4=R^5=H$) was completely inert, probably due to the electron-withdrawal of the nitro groups. Furthermore, halogen-substituted ($R^4=Br$, $R^1=R^2=R^3=R^5=H$; $R^3=R^5=Cl$, $R^1=R^2=R^4=H$) hydrazones gave mixtures of indolocarbazoles due to migration or loss of halogen substituents. During the formation of one particular bis(hydrazone) ($R^1=R^2=R^3=R^4=R^5=H$), a small amount of monohydrazone was isolated. The authors showed that this could be reacted with a different hydrazine to give a mixed hydrazone. Thus this could be an attractive route for the formation of unsymmetrically substituted indolocarbazoles.

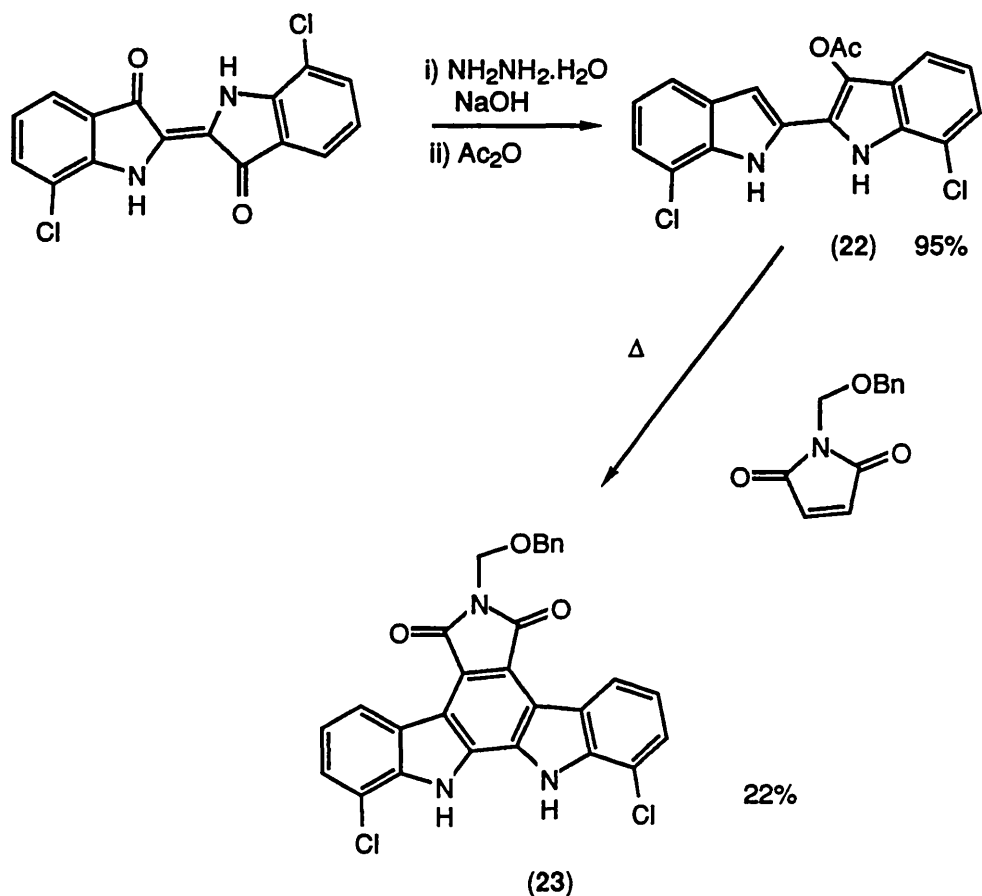
The remaining syntheses all concentrate on formation of the middle benzene ring C. The first approach is *via* cycloaddition as used by Kaneko and Wong to make rebeccamycin.⁸ Retrosynthetically, it involves disconnection of the middle benzene ring (Scheme 1.5). Thus the key step is a Diels-Alder reaction of maleimide and 2,2'-bisindole.

Scheme 1.5



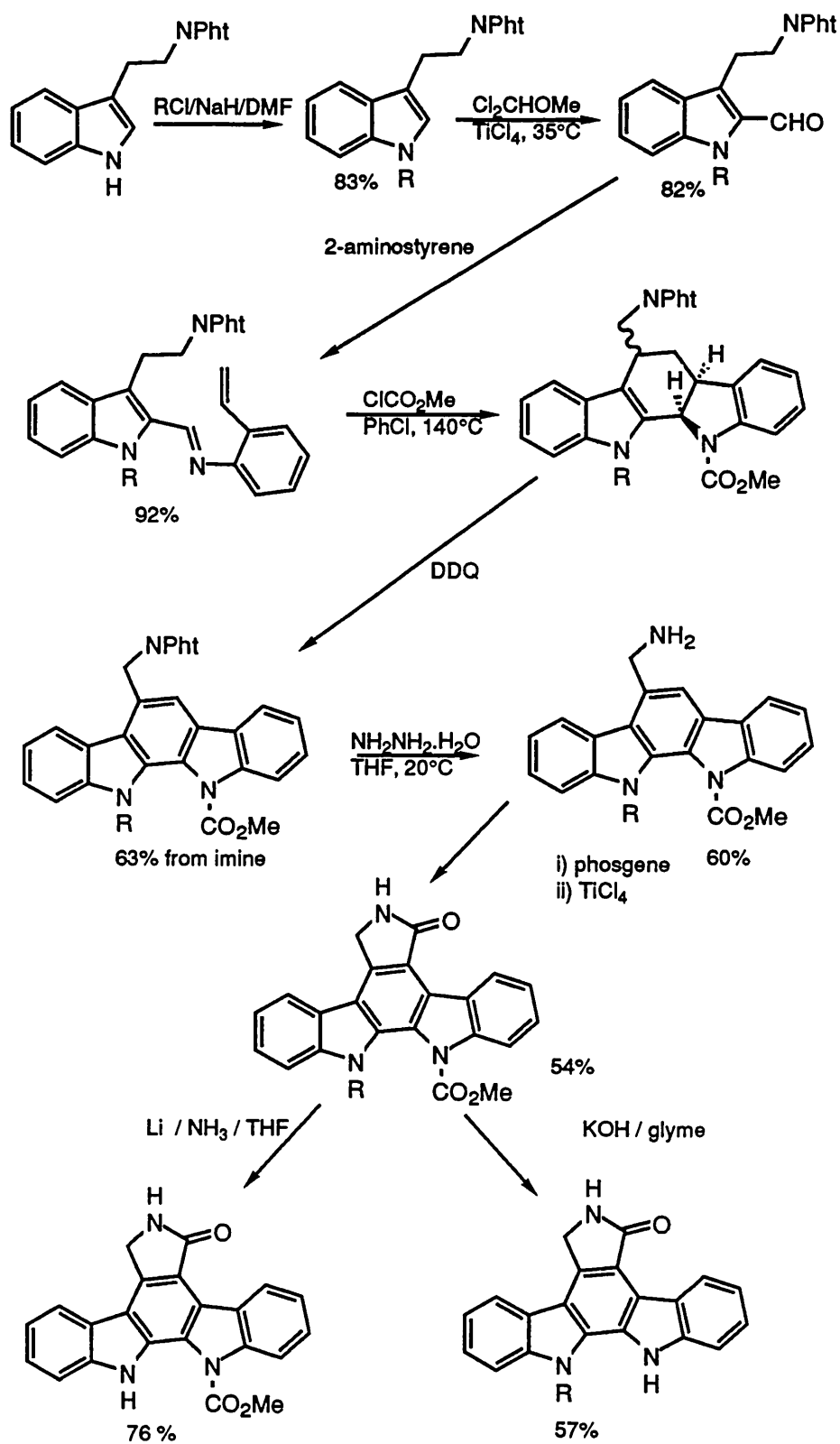
Due to problems with the synthesis of 7,7'-dichloro-2,2'-bisindole, readily available 7,7'-dichloroindigo (Scheme 1.6) was reduced and acetylated in 95% yield to give (22). This, on heating with N-benzyloxymethylmaleimide in a sealed tube at 105 °C for 8 days gave the intermediate (23) in 22% yield *via* a Diels-Alder reaction, elimination of acetic acid and dehydrogenation in one pot. Kaneko also synthesised (23) *via* a different route to rebeccamycin, and this is discussed later in the review.

Scheme 1.6



In Magnus and Sear's approach to the staurosporine aglycone, the key reaction is an indole-2,3-quinodimethane cyclisation to make the C ring.³⁶ This methodology makes it possible to protect differentially the two indole nitrogens and therefore might be of use in coupling sugars to the aglycone. Thus, starting with tryptamine, the first step was formation of the phthalimido derivative (Scheme 1.7). The indole nitrogen was protected next with a *p*-methoxybenzenesulphonyl group. The 2-position of indole was then formylated using α,α -dichloromethylmethyl ether, in good yield. This was condensed with 2-aminostyrene to give the required imine for cyclisation. The key indole-2,3-quinodimethane cyclisation was achieved in the presence of methyl chloroformate in refluxing chlorobenzene to give a 4:1 mixture of

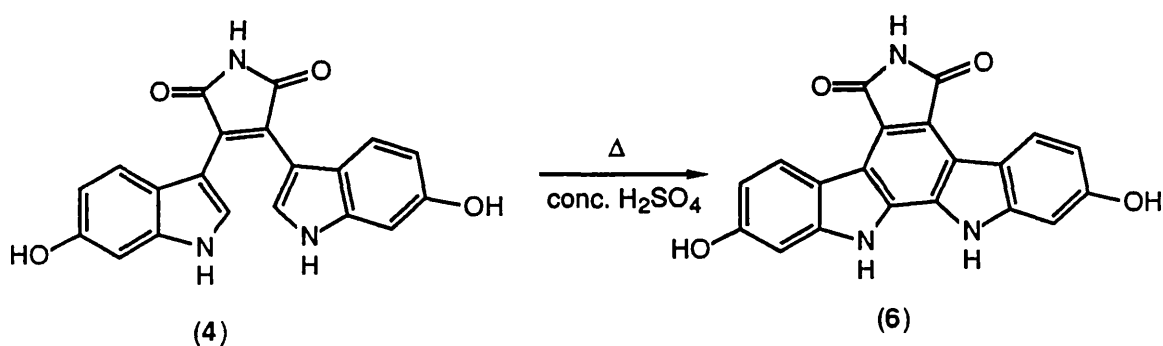
Scheme 1.7 (R=p-MeOC₆H₄SO₂⁻)



epimers at the methylenephthalimido group. This crude product was dehydrogenated with DDQ to give the corresponding aromatic compound in 63% from the imine. Finally, the top lactam ring was introduced by removal of the phthalimido protecting group and treatment with phosgene, followed by TiCl_4 . The overall yield to this derivative of staurosporine from N-phthaloyl tryptamine was 13.9%. Magnus *et al.* further showed that it was possible to remove each of the indole protecting groups to give selectively protected derivatives of the staurosporine aglycone. However, no mention is made of removing both the protecting groups.

The other approach to the middle ring involved disconnection of the 2,2'-indole bond. This was demonstrated to be a "viable" disconnection in the very first synthesis of an indolocarbazole by Steglich and coworkers when they found that on heating arcyriarubin C (4) in concentrated sulphuric acid, they obtained arcyriaflavin C (6).⁶

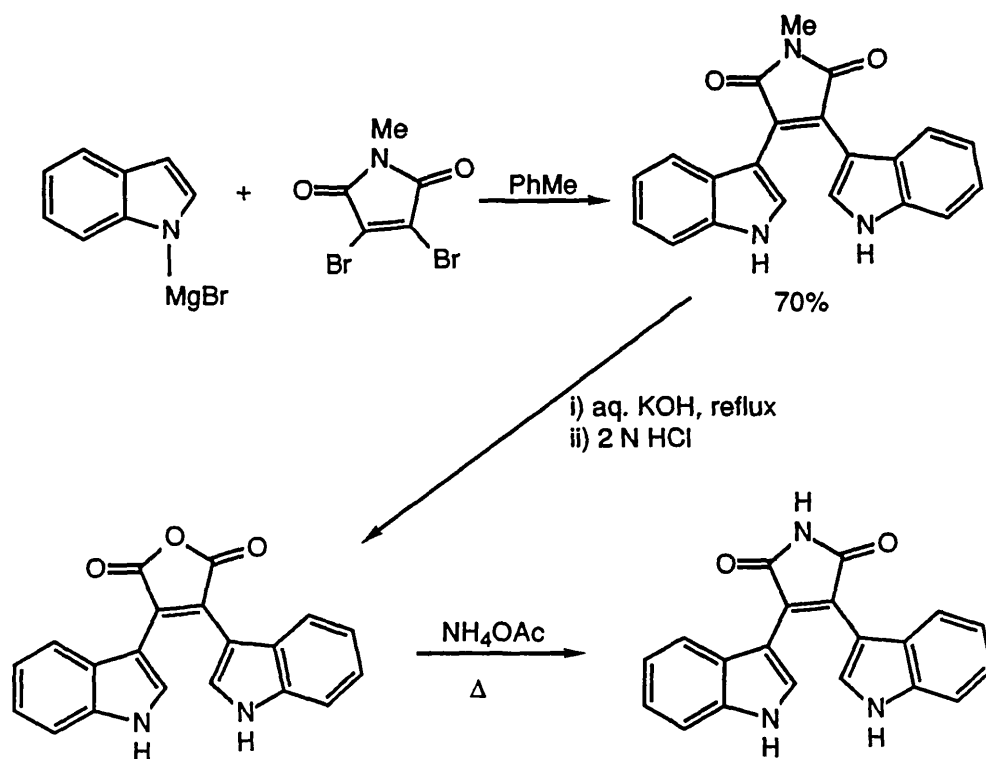
Scheme 1.8



Steglich also showed that a quick entry to the arcyriarubin skeleton was *via* reaction of indole Grignards with maleimides.³⁸ The crucial step in the synthesis of arcyriarubin A (Scheme 1.9) was reaction of indolylmagnesium bromide with 2,3-dibromo-N-methylmaleimide. This reaction was solvent dependent. In toluene, the bisindolyl compound is obtained in 70% yield, whereas in THF, it is possible to isolate the monosubstituted product in 74% yield. The latter needs to be N-protected before it is reacted with a different Grignard reagent to give differentially substituted arcyriarubins. Steglich also synthesised arcyriarubin B (3) using this

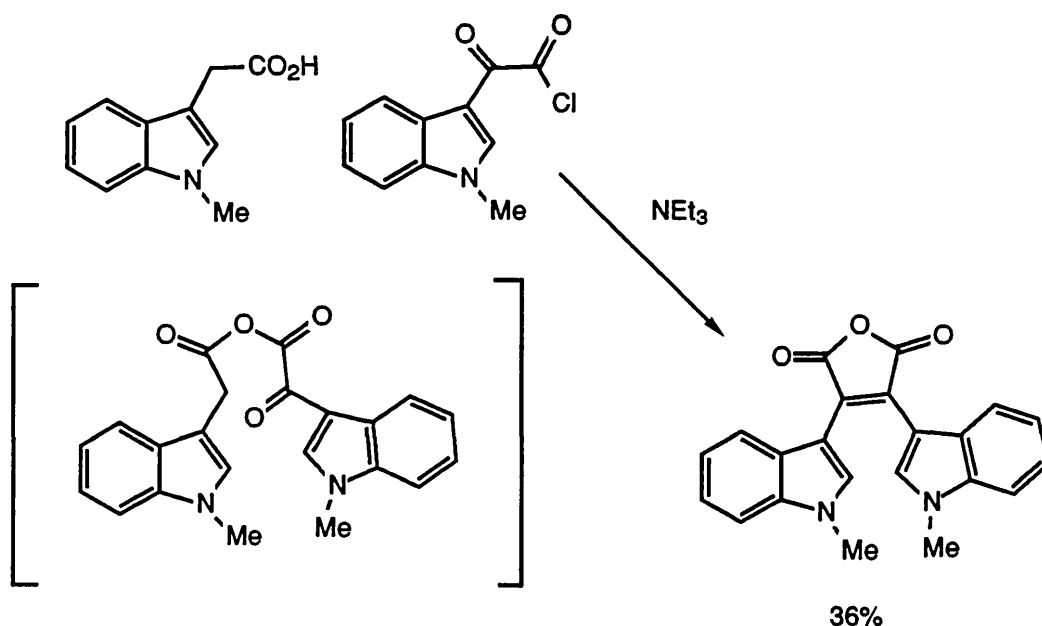
approach. Alkaline hydrolysis of the N-methyl imide, followed by treatment with ammonium acetate, yields the NH imide required.

Scheme 1.9



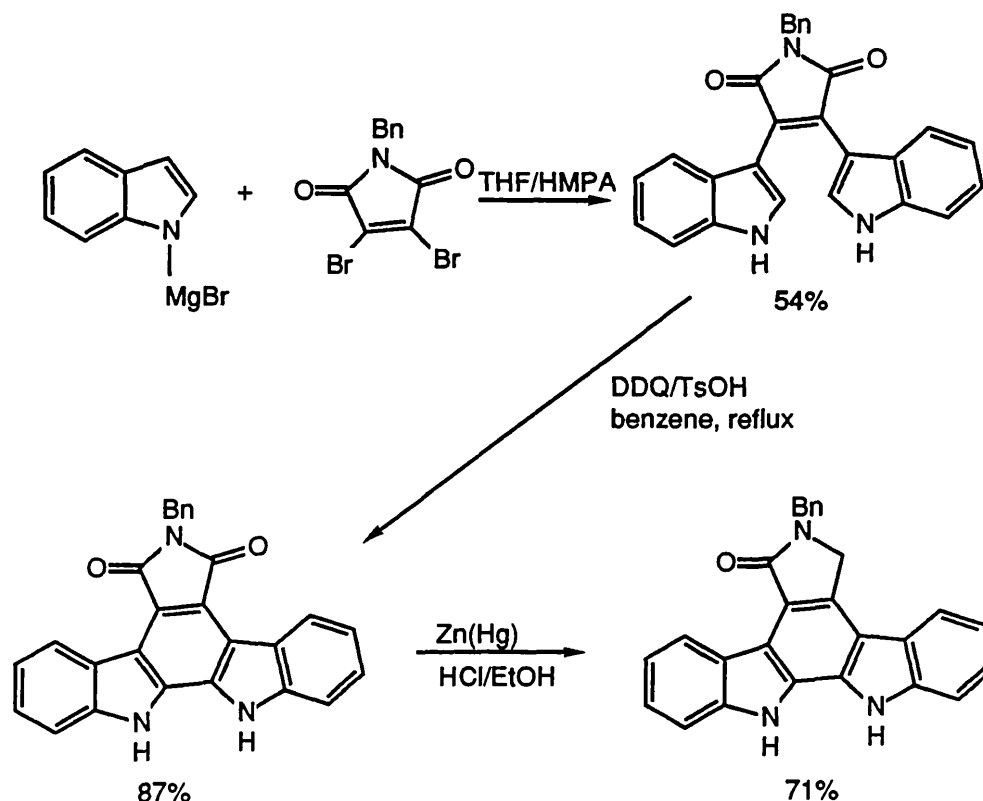
Since, a recently reported approach to similar systems as the arcylarubins has been patented.³⁹⁻⁴⁰ It involves treatment of N-methyl indole-3-acetic acid with N-methyl indole-3-glyoxalyl chloride (Scheme 1.10) in the presence of triethylamine, to give bis(1-methyl-3-indolyl)maleic anhydride in 36% yield. The authors feel that the reaction proceeds via formation of the mixed anhydride, followed by intramolecular Perkin condensation. However, there is no report of this method being taken further to synthesise indolocarbazoles.

Scheme 1.10



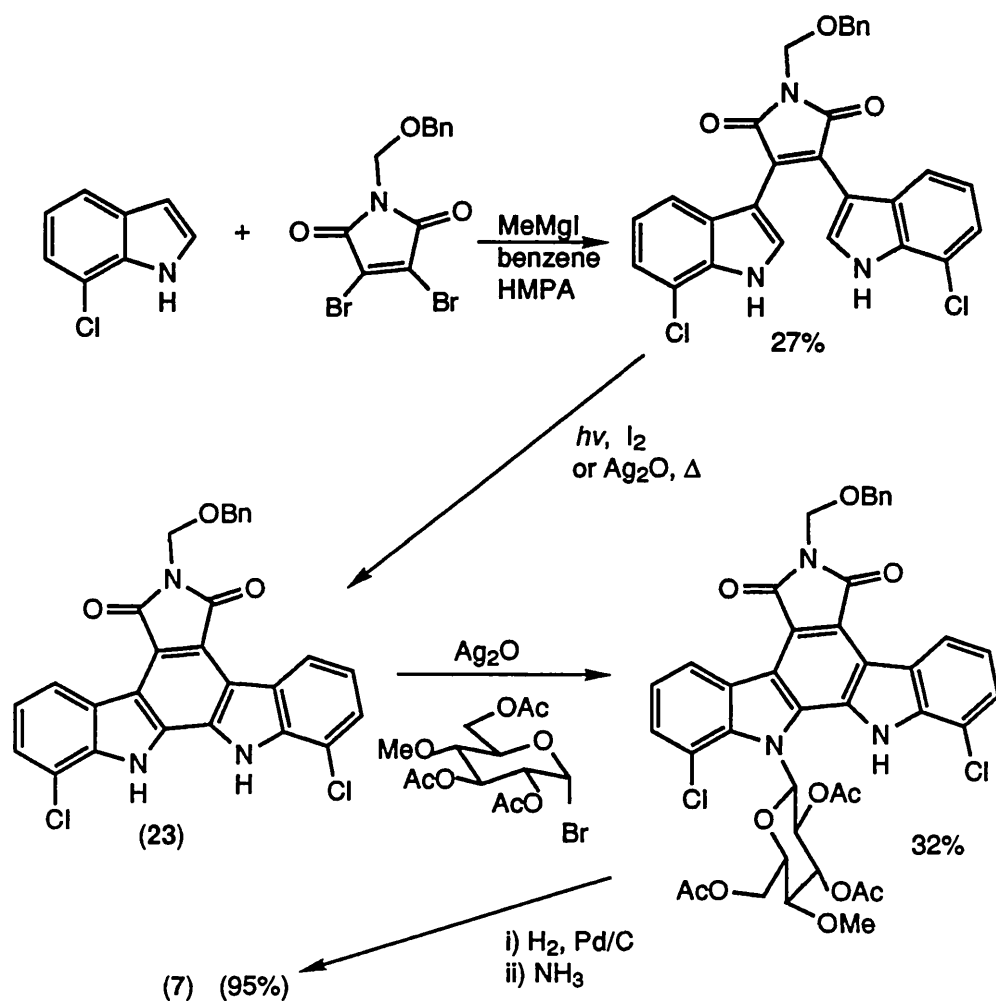
The Steglich approach to the arcylarubins was also used by Weinreb *et al.* in their synthesis of N-benzylstaurosporine.⁷ Reaction of N-benzyl-2,3-dibromomaleimide with indolylmagnesium bromide (Scheme 1.11) proceeded in 54% yield. The formation of the 2,2' indole bond was effected with a mixture of DDQ and *p*-toluenesulphonic acid in refluxing benzene, in excellent yield. Clemmensen reduction of the imide to the lactam using Raphael and Hughes's conditions furnished them with N-benzylstaurosporine. However, more importantly, they are the first and only group to date to publish a synthesis of derivatives of the staurosporine sugar. This is discussed later.

Scheme 1.11



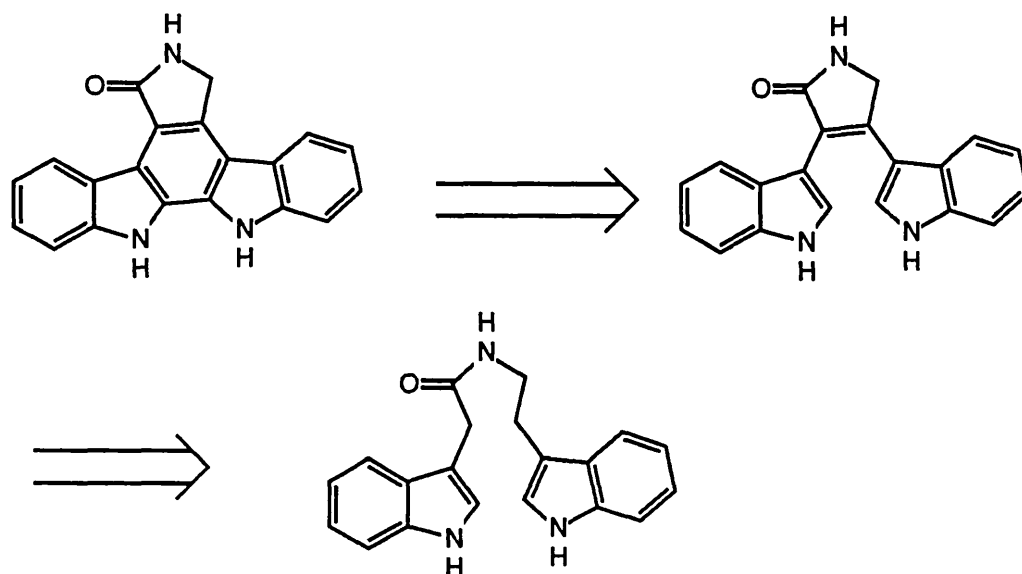
The second synthesis published by Kaneko and Wong of rebeccamycin also uses Steglich's indole Grignard method.⁸ 7-Chloroindole is treated with methylmagnesium iodide and N-benzyloxymethyl-2,3-dibromomaleimide (Scheme 1.12) in benzene containing a small amount of HMPA to give the required bisadduct in 27% yield. The formation of the 2,2' indole bond was effected with light in the presence of I_2 and air to give (23). However, it was more convenient to use refluxing benzene with a trace of silver oxide, since glycosidation could also be carried out under the same conditions. Thus the known sugar moiety, 1-bromo-2,3,6-tri-O-acetyl-4-O-methylglucose (prepared from glucose), was attached to the aglycone after cyclisation in 32% overall yield. Finally, removal of all the protecting groups by hydrogenation and ammonolysis gave rebeccamycin (7) in 8.2% overall yield.

Scheme 1.12



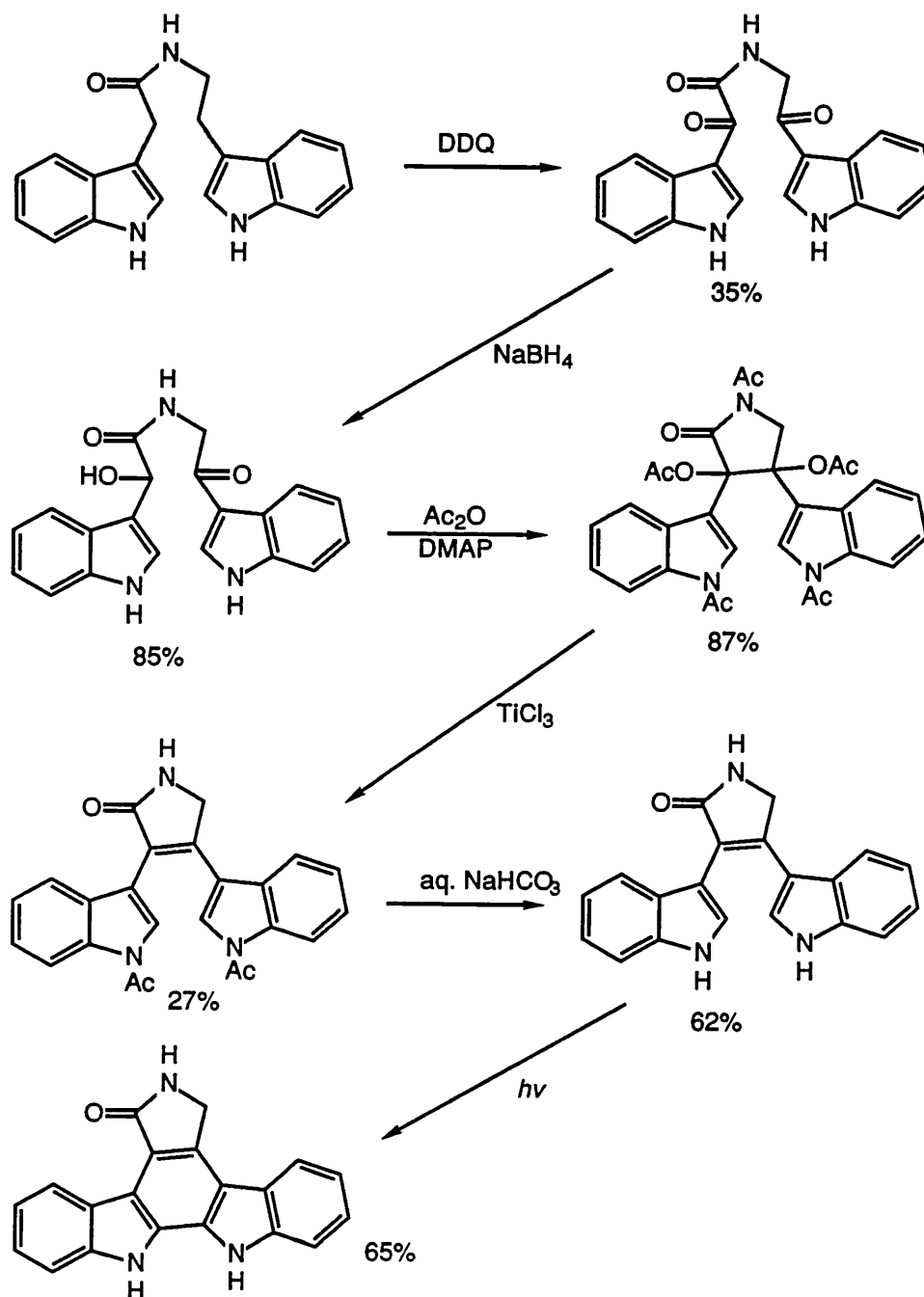
The first and, to date, only synthesis of the staurosporine aglycone was published in 1983 by Sarstedt and Winterfeldt.⁹ Retrosynthetically, the first disconnection again involves cleavage of the central bond connecting the 2 and 2' positions of the indole units (Scheme 1.13). The second disconnection, however, is cleavage of the lactam ring. This gives a product which can easily be formed from tryptamine and indole-3-acetyl chloride.

Scheme 1.13



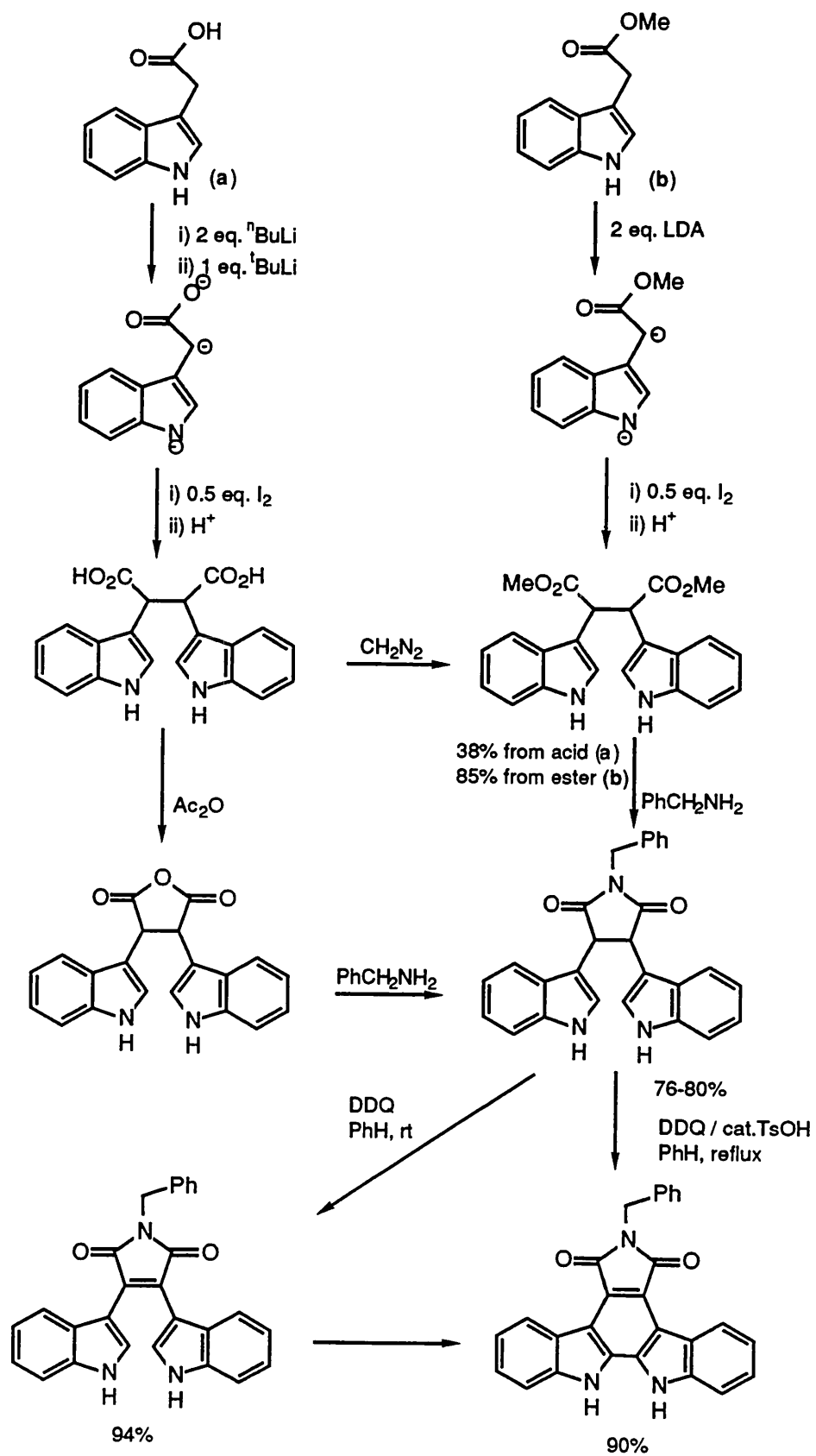
Thus starting with the amide (synthesized in 77% yield from tryptamine and indole-3-acetyl chloride), the first cyclisation was achieved in three steps (Scheme 1.14). The first of these was an oxidation to the diketone with DDQ, followed by selective reduction with borohydride and then treatment with acetic anhydride to effect ring closure. Reduction of the α -acetoxycarbonyl compound could only be achieved in acceptable yield with titanium (III) chloride in aqueous acetone. Photocyclisation was the chosen route to achieve the second cyclisation. It was not possible to photocyclise this N-diacetylated compound, but after deacetylation, the resultant compound cyclised readily to give the staurosporine aglycone in 2.2% overall yield from indole-3-acetyl chloride. It is interesting to note that the non- symmetry in the staurosporine aglycone is introduced in the very first step of the synthesis. Despite the low overall yield, this method allows unsymmetrically substituted indolocarbazoles to be formed with relative ease.

Scheme 1.14



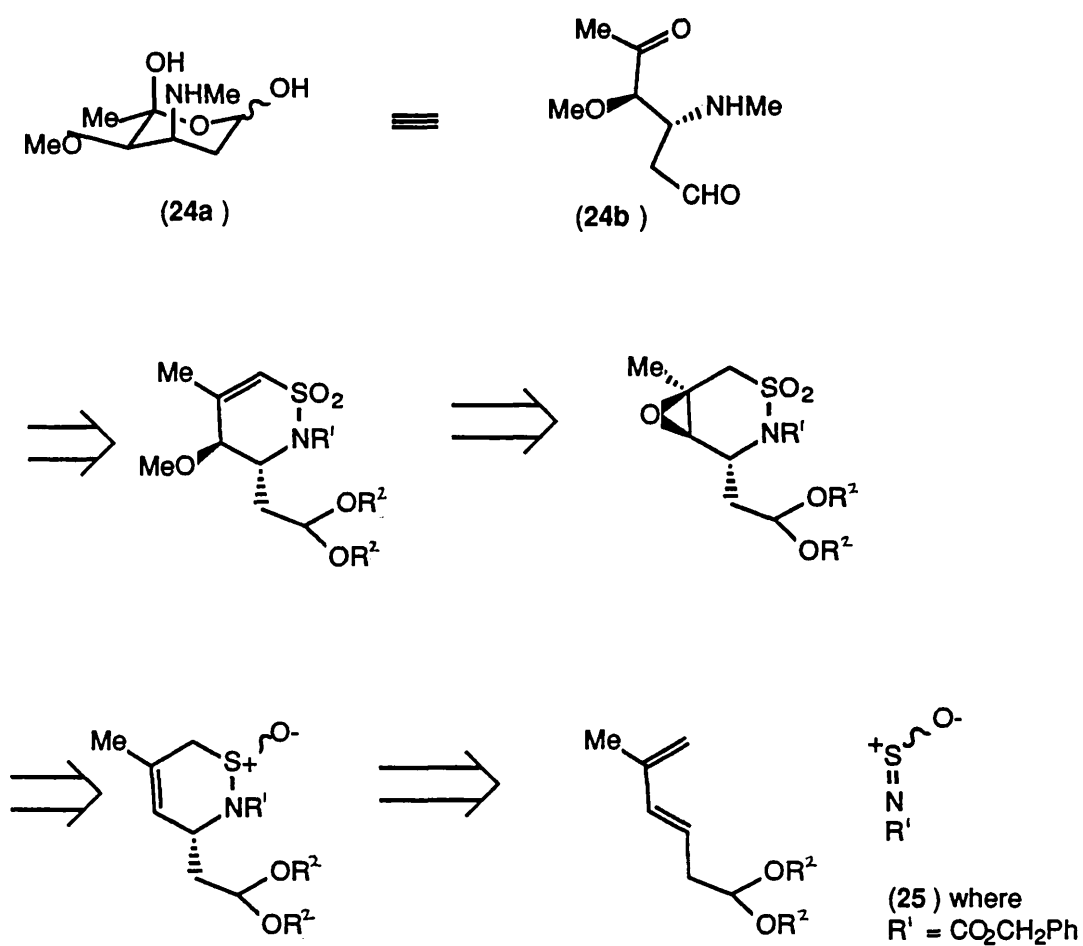
The second novel approach to indolocarbazoles reported by Bergman and co-workers is biomimetic (Scheme 1.15).¹⁰ Oxidative coupling of either the indole-3-acetic acid trianion or the methyl indole-3-acetate dianion gave the corresponding bisindole-3-succinic acid derivative. This could be heated with benzylamine to give the succinimide, which in turn could be oxidised with DDQ and *p*-toluenesulphonic acid to the indolocarbazole. Thus the indolocarbazole skeleton is accessed in three efficient steps. However, the use of this method to form unsymmetrically substituted indolocarbazoles is very limited.

Scheme 1.15



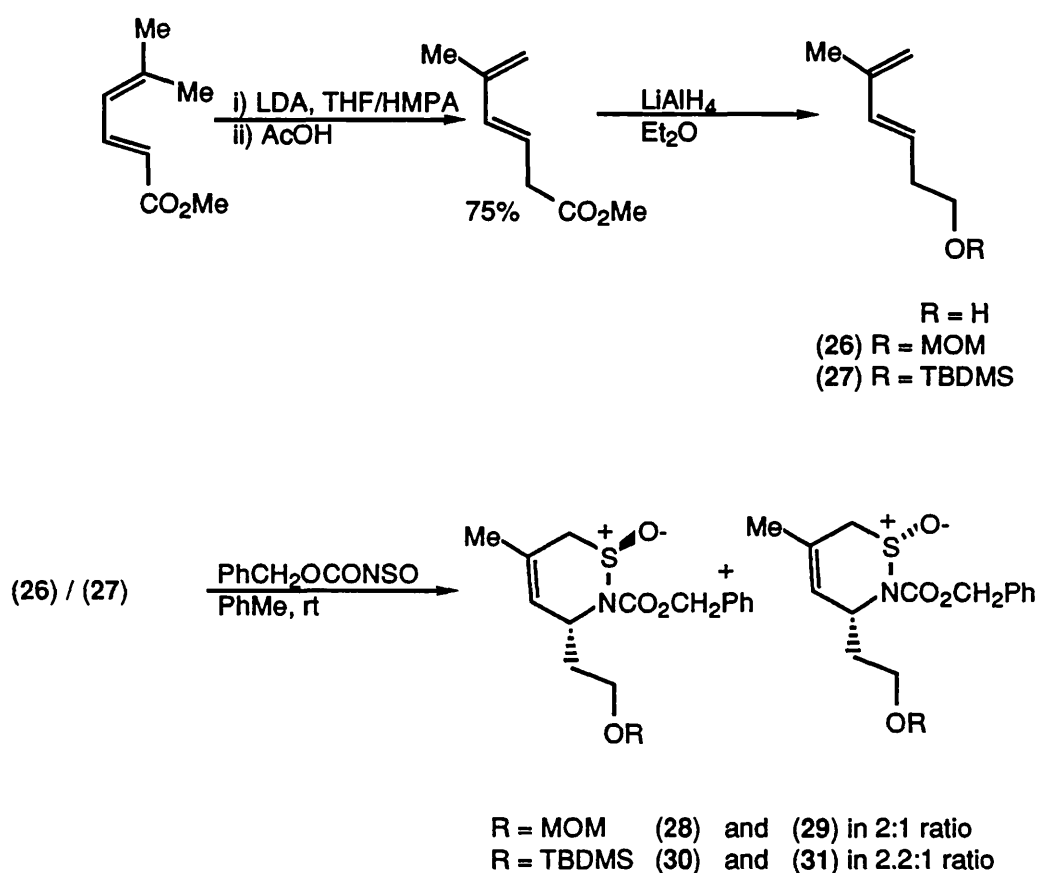
The only attempt at the staurosporine amino sugar (24) has been reported by Weinreb and co-workers.^{7, 37} Their strategy (Scheme 1.16) utilises Diels-Alder cycloadditions of benzyl sulphinyldicarbamate (25).

Scheme 1.16



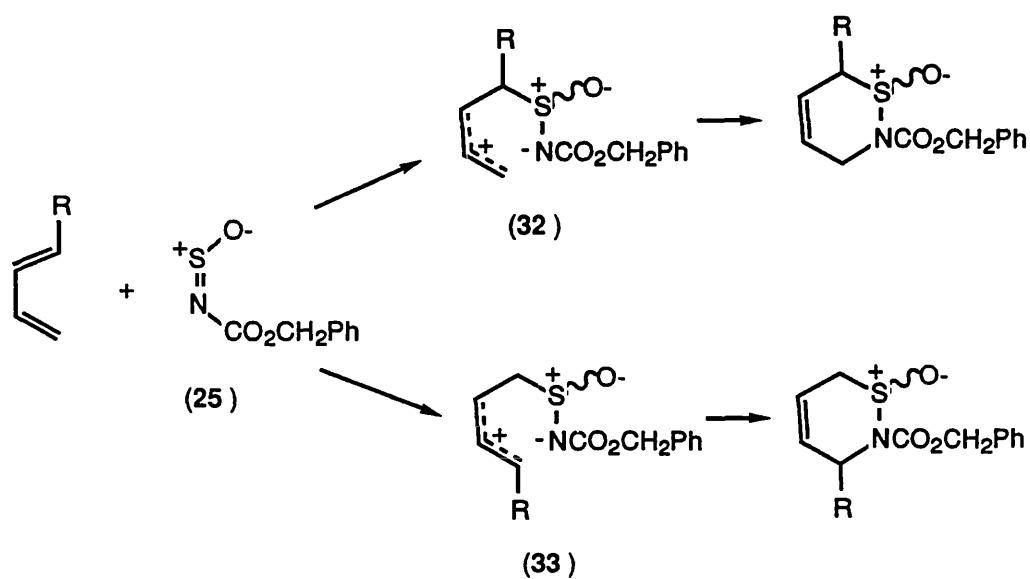
The dienes required were prepared efficiently, as shown in Scheme 1.17, by treatment of the conjugated ester with LDA and acetic acid to give the deconjugated ester. This ester was then reduced to the alcohol and protected as its MOM (26) and TBDMS (27) derivatives. These underwent cycloaddition with (25) in high yield to give a chromatographically separable mixture of epimers. No other regioisomers were detected.

Scheme 1.17



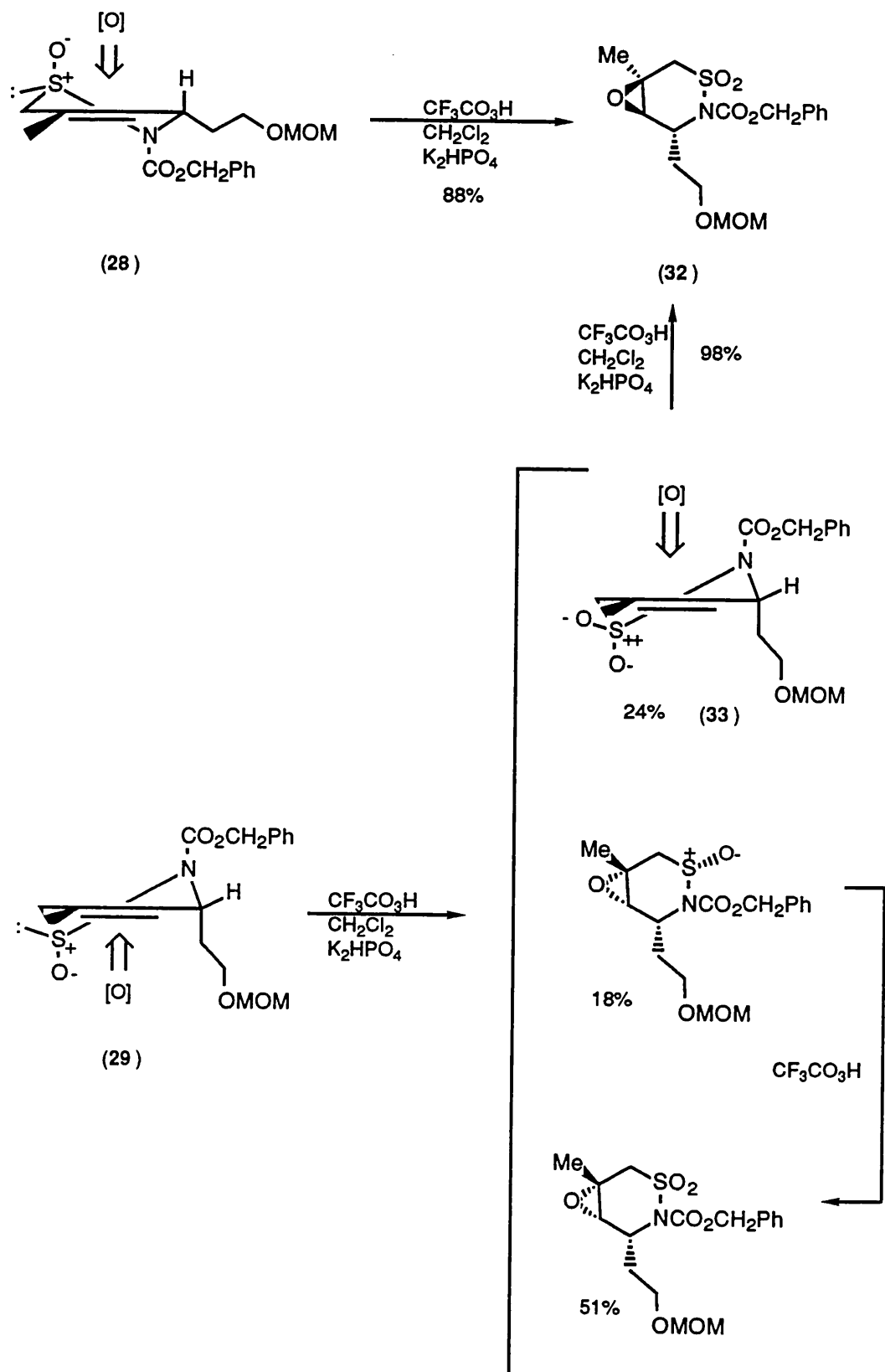
The regiochemistry of these additions was exactly as expected. Investigations reveal that these reactions probably proceed in a stepwise process, and may be rationalised by consideration of the relative stability of dipolar species such as (32) and (33) in Scheme 1.18.⁴¹

Scheme 1.18



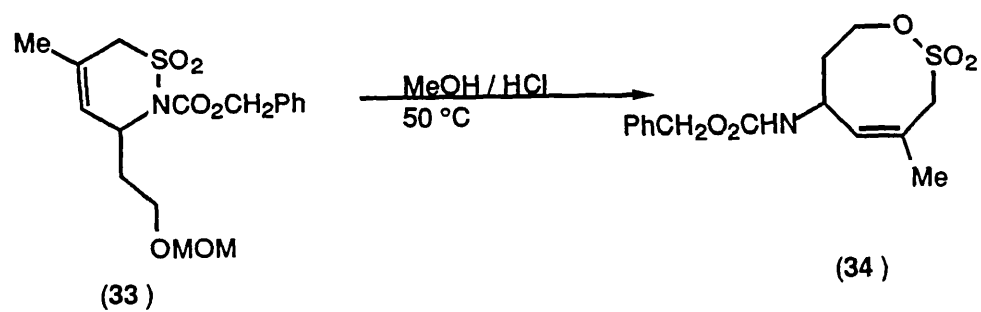
The next step was to introduce oxygen functionality with β -stereochemistry at C-4 of the adducts. So (28) was treated with trifluoroperacetic acid and gave exclusively the required β -epoxy sultam (32) (subsequent transformations established this stereochemistry). Similar treatment of (29) gave the mixture of products shown in Scheme 1.19. However, sultam (33), on epoxidation gave solely the β -epoxide (32). Thus, both the epimeric cycloadducts could be used to form the desired β -epoxy sultam by initial oxidation to the sultam followed by epoxidation. The stereospecificity of these epoxidations may be rationalised by assuming that the sulphur oxygen bond prefers to be quasi-axial and the sulphanyl oxygen in (28) can hydrogen bond to the trifluoroperacetic acid and so promote syn delivery to give the β -epoxide which is then oxidised at sulphur to give (32). In (29), the quasi-axial side chain interferes sterically with this syn delivery and competing sultam formation is fast. In (33) the less polar sultam oxygens probably do not hydrogen bond to the peracid, and so epoxidation occurs at the least congested face to give the β -epoxide.

Scheme 1.19



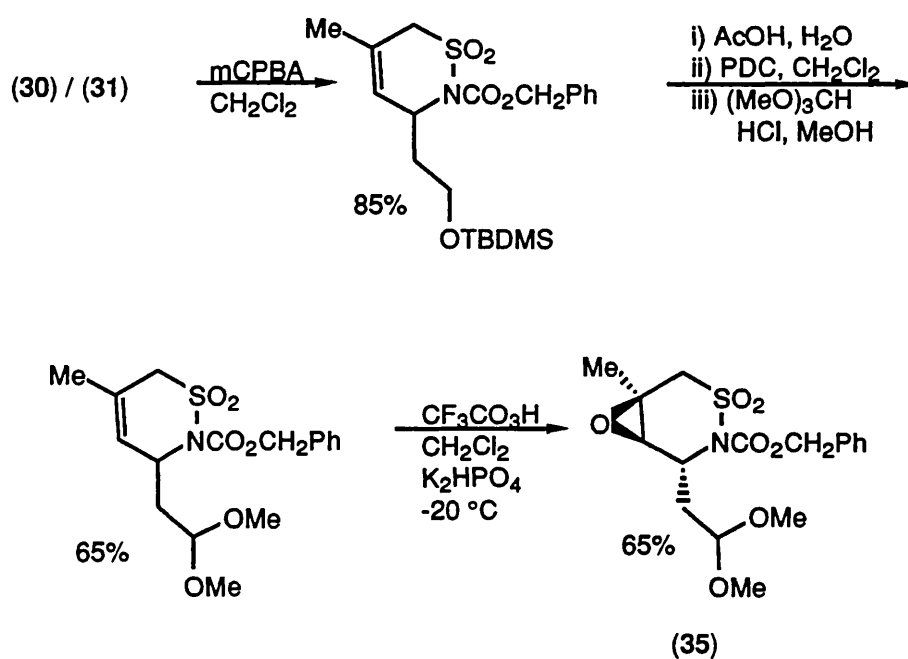
The next step was adjustment of the oxidation level of the side chain to the aldehyde. Treatment of (33) with methanolic HCl gave the unexpected cyclic sulphonate (34) in 70% yield (Scheme 1.20).

Scheme 1.20



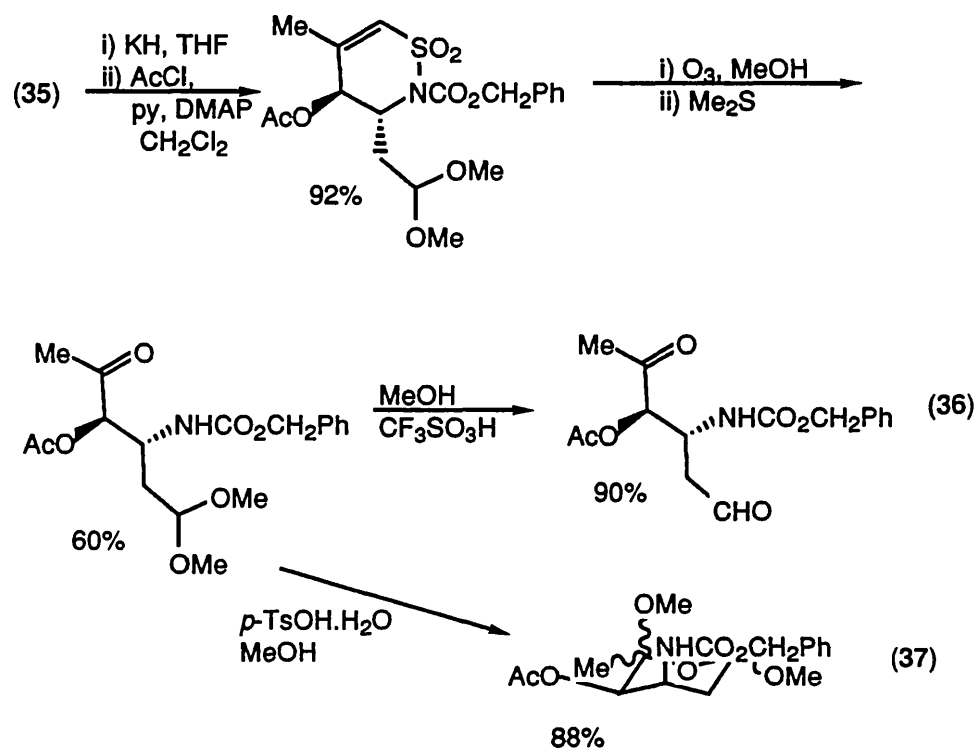
To avoid this problem, the TBDMS-protected adducts (30) and (31) were oxidised to the sultam (Scheme 1.21) with mCPBA, the alcohol was deprotected with mild acidic hydrolysis, oxidised up to the aldehyde, and reprotected as the dimethyl acetal. Epoxidation of the double bond gave the β -epoxide (35) stereospecifically.

Scheme 1.21



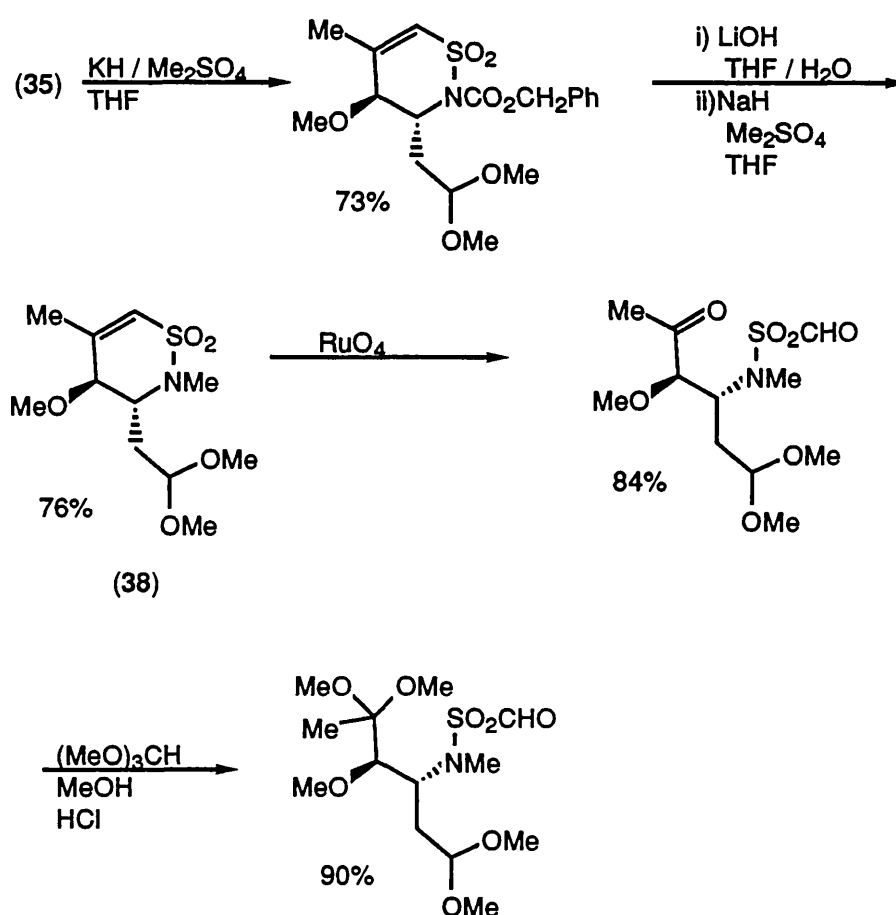
The epoxide (35) was then opened up using potassium hydride and the resulting alkoxide trapped with acetyl chloride (Scheme 1.22). The acetoxy derivative was ozonolysed to give the methyl ketone which was deprotected to give the sugar derivatives (36) and (37).

Scheme 1.22



However, the staurosporine sugar has O- and N-methyl substituents, and so (35) was also treated as shown in Scheme 1.23. The epoxide was opened up using potassium hydride and O-methylated *in situ*. Hydrolysis of the benzyl carbamate group and N-methylation gave (38). This sultam had to be cleaved with ruthenium tetroxide, as ozonolysis only gave intractable tars. Thus a route to derivatives of the unusual staurosporine aminohexose sugar has been developed.

Scheme 1.23



1.5 Conclusion

As has been illustrated, a variety of methods exist in the literature to synthesise this unusual class of natural products. However, in the case of staurosporine, only one complete synthesis of the aglycone has been reported (the other syntheses all make the N-protected product). Thus, a need to develop a new method for synthesising the staurosporine aglycone, without the use of protecting groups, still exists.

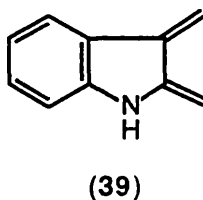
Weinreb and coworkers have developed an elegant approach to the staurosporine sugar. However, work still needs to be done to develop methodology to generate the bis-N-glycosidic bonds to the aglycone. Furthermore, nontrivial regiochemical and stereochemical considerations also need to be addressed.

CHAPTER TWO

SYNTHESIS AND DIELS-ALDER REACTIONS OF PYRANO[4,3-*b*]INDOL-3-ONES

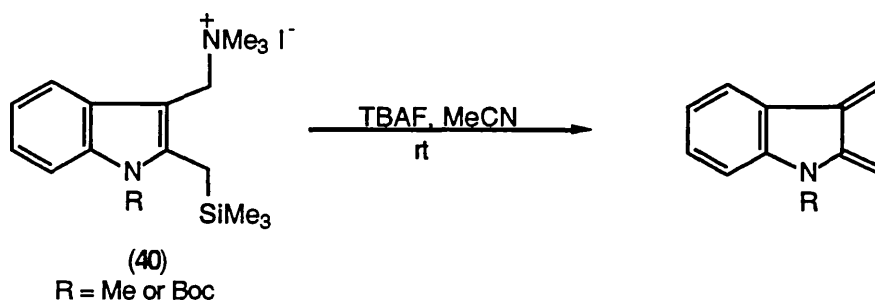
2.1 Introduction

In the last few years a considerable amount of work has been done on indole-2,3-quinodimethanes (39).

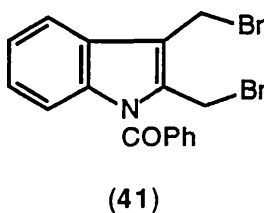


These reactive intermediates have to be generated *in situ*. Marinelli has reported intermolecular Diels-Alder reactions of simple indole-2,3-quinodimethanes, generated *via* fluoride-induced 1,4-elimination from ammonium salts (40) (Scheme 2.1).⁴²

Scheme 2.1

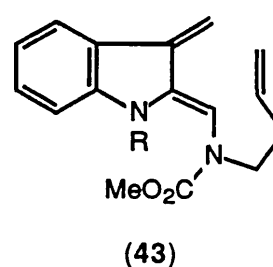
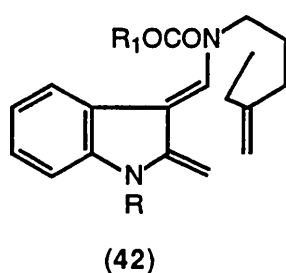


A similar approach is generation of the indole-2,3-quinodimethane from the dibromide (41) by treatment with sodium iodide.⁴³

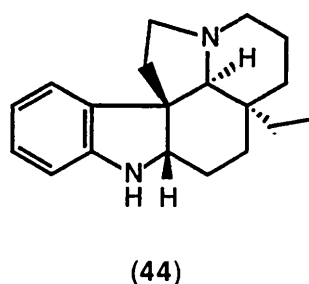


In both these cases, Diels-Alder reaction occurs with simple, highly reactive dienophiles such as N-phenylmaleimide in varying yields. Furthermore, protection of the indole nitrogen is necessary.

Work on the intramolecular reactions of derivatives of (39) has been dominated by Magnus and co-workers.⁴⁴⁻⁴⁷ An additional nitrogen atom is present in his final products since his methodology requires imine precursors to the *in situ* generated indole-2,3-quinodimethane derivatives, such as (42) and (43).

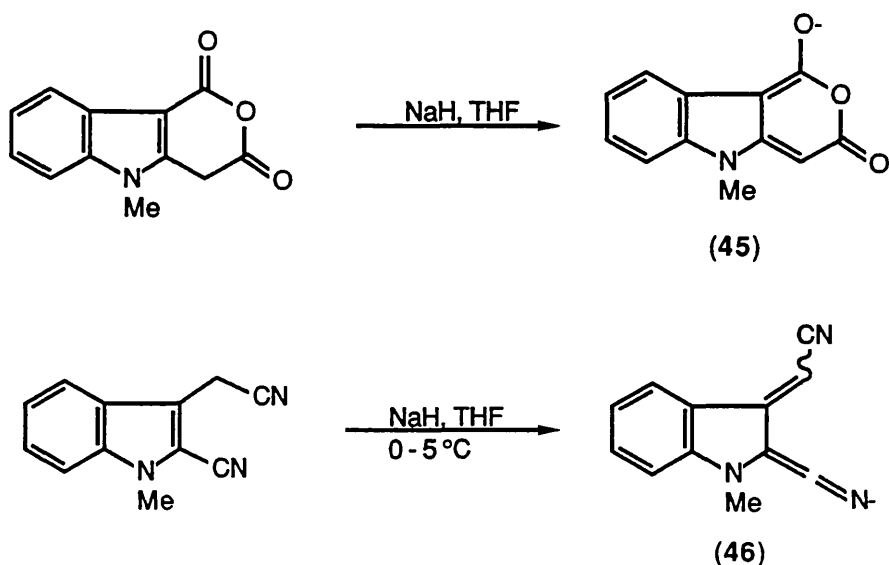


Magnus has utilised this methodology extremely successfully to form a variety of indole alkaloids, such as (*dl*)-aspidospermidine (44)^{46,48} and, of course, derivatives of the staurosporine aglycone³⁶ (described earlier in Section 1.4).

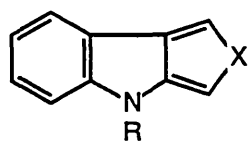


The anionic 2,3-quinodimethane-like intermediates (45)⁴⁹ and (46)⁵⁰ have also been generated by treatment of the corresponding indole with sodium hydride as illustrated in Scheme 2.2.

Scheme 2.2



Stable synthetic analogues of (39) have also received considerable attention. Cyclic systems, such as pyrrolo[3,4-*b*]indoles (47) ⁵¹ and (48) ⁵² and thieno- (49) ⁵³ , seleno- (50) ⁵³ , and furo-[3,4-*b*]indoles (51) ⁵⁴ have all been reported.



(47) X = NCH₂Ph, R = Ph

(48) X = NH or NCO₂Me, R = SO₂Ar

(49) X = S, R = C(=O)Ph

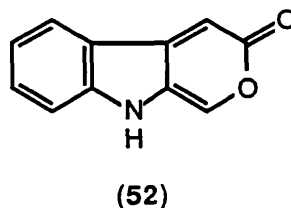
(50) X = Se, R = C(=O)Ph

(51) X = O, R = SO₂Ph

Diels-Alder reactions have been reported of all these systems with only simple and highly reactive dienophiles, such as dimethyl acetylenedicarboxylate (DMAD) and benzyne. Furthermore, all these systems, in common with the others mentioned above, need a

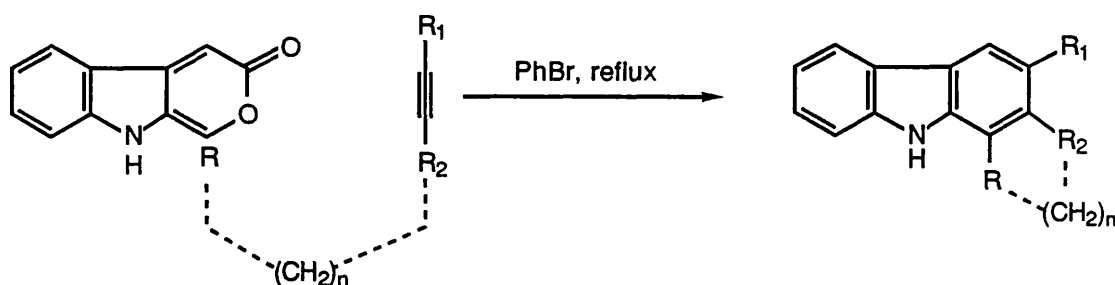
protecting group present on the indole nitrogen.

The most recent work in this field has been on the pyrano[3,4-*b*]indol-3-one system (52).



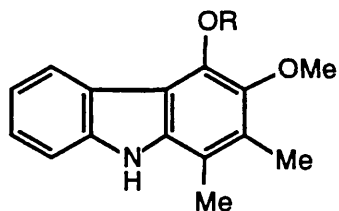
These indole-2,3-quinodimethane intermediates were first reported by Plieninger over a quarter of a century ago.⁵⁵ However, despite reporting the preparation of a variety of compounds, he describes only one Diels-Alder reaction of these compounds with an alkyne. The viability of these compounds as indole-2,3-quinodimethane analogues was extended initially by Moody,⁵⁶⁻⁵⁹ and since, by other groups.⁶⁰⁻⁶⁹ The ease of preparation of these compounds, together with their stability, is extremely attractive. Moreover, protection of the indole nitrogen is not necessary. These compounds are of great value as synthetic precursors to substituted carbazoles in particular, as on cycloaddition to alkynes, they spontaneously lose carbon dioxide to form the carbazole in one pot. Additionally, they may be utilised in intramolecular Diels-Alder reactions to form an all carbon framework (Scheme 2.3).

Scheme 2.3



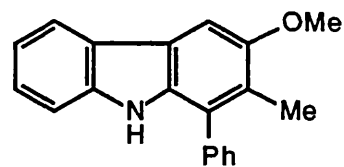
Moody and co-workers have used this methodology in concise syntheses of the carbazole alkaloids, carbazomycin A (53) and B (54),⁷⁰ hyellazole (55),⁷⁰ and carazostatin (56),⁷¹ as

well as the antitumour alkaloid ellipticine (57).⁷²

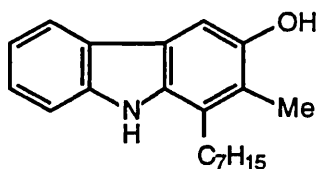


(53) R = Me

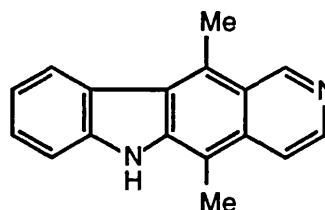
(54) R = H



(55)

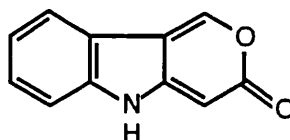


(56)



(57)

Thus it was of interest to us to investigate the "reverse" pyranoindolone system (58) *i.e.* the isomeric system with the carbon dioxide bridge reversed. In particular, we were interested in how the reversal of the carbon dioxide bridge would affect the regioselectivity of the Diels-Alder reaction with simple alkynes.

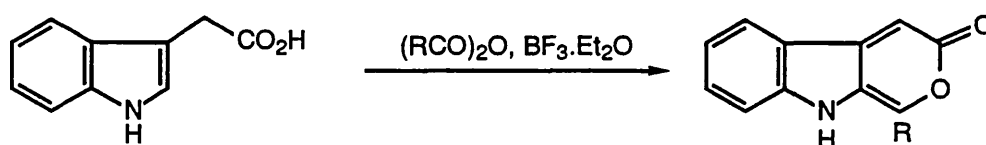


(58)

2.2 Synthesis of pyrano[4,3-*b*]indol-3-ones

Pyrano[3,4-*b*]indol-3-ones may be prepared easily (Scheme 2.4) from commercially available indol-3-ylacetic acid by treatment with the appropriate anhydride and boron trifluoride-diethyl ether. Thus our first task was to obtain indol-2-ylacetic acid, as we felt this would be a suitable precursor to the isomeric ring system (58).

Scheme 2.4

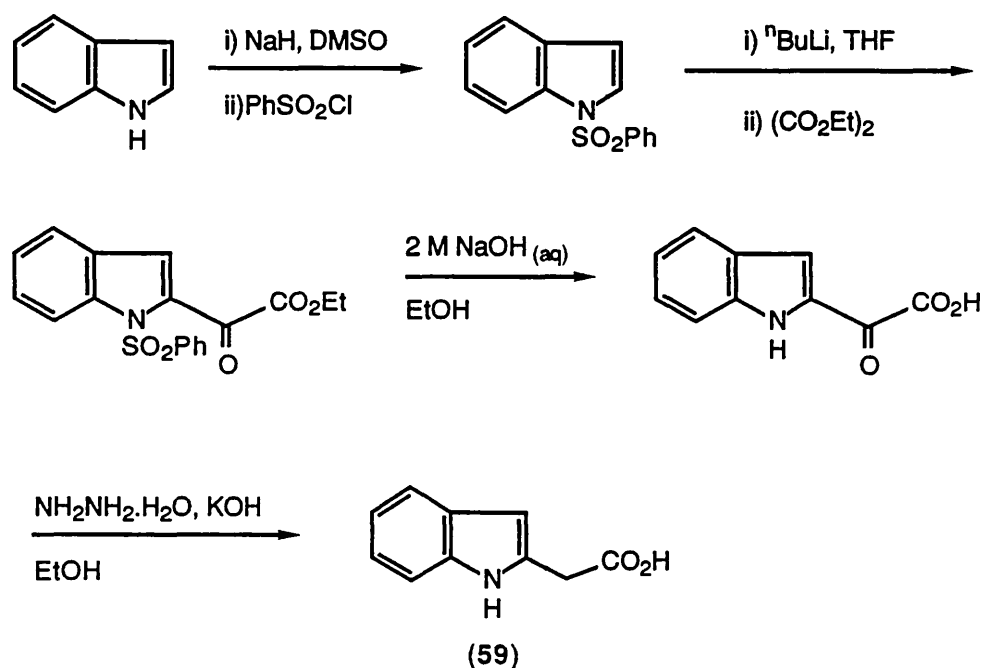


2.2.1 Synthesis of indol-2-ylacetic acid

Unlike indol-3-ylacetic acid, indol-2-ylacetic acid is not commercially available. However, a number of syntheses of the latter exist in the literature.⁷³⁻⁷⁷ These can be divided into two categories: those which involve indole ring synthesis⁷⁷ and those which involve modification of other indoles.⁷³⁻⁷⁶

Initially we attempted the latter approach. The following reported synthetic route (Scheme 2.5) was followed.^{73,74}

Scheme 2.5

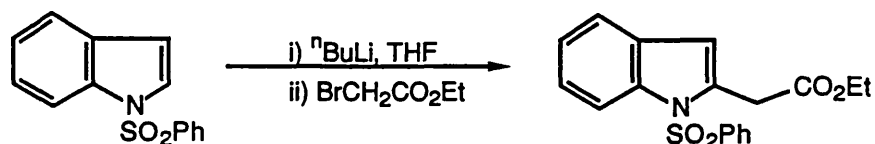


Thus, 1-phenylsulphonylindole was made in 96% yield from indole by reaction with dimethyl sodium and quenching with benzenesulphonyl chloride. This was treated with *n*butyl lithium to form the 2-lithioindole species, which was added to an excess of diethyl oxalate. Despite high reported yields for this inverse quenching, in our hands, this proved to be an extremely messy reaction. It was a lot easier to hydrolyse directly the crude reaction mixture and then crystallise out the acid. The yield for these two steps could not be improved above ca. 10%. The Wolff-Kishner reaction proceeded in excellent yield (87%) to furnish us with a sample of indol-2-ylacetic acid (59).

The low overall yield of indol-2-ylacetic acid prompted us to investigate similar synthetic routes in an attempt to increase the yield. Thus 2-lithio-1-phenylsulphonylindole was quenched

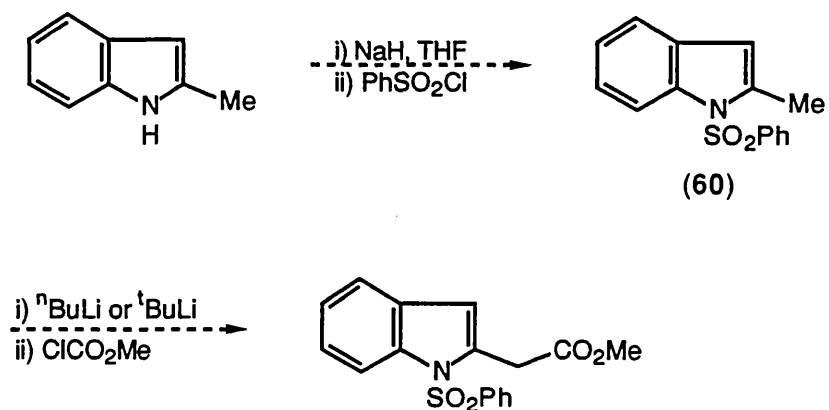
with bromoacetic ester (Scheme 2.6). This reaction, again, was not clean.

Scheme 2.6

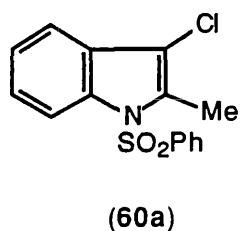


The extremely elegant synthesis of indol-2-ylacetic acid reported by Katritzky from 2-methylindole ⁷⁸ prompted us to also try the following route shown in Scheme 2.7.

Scheme 2.7

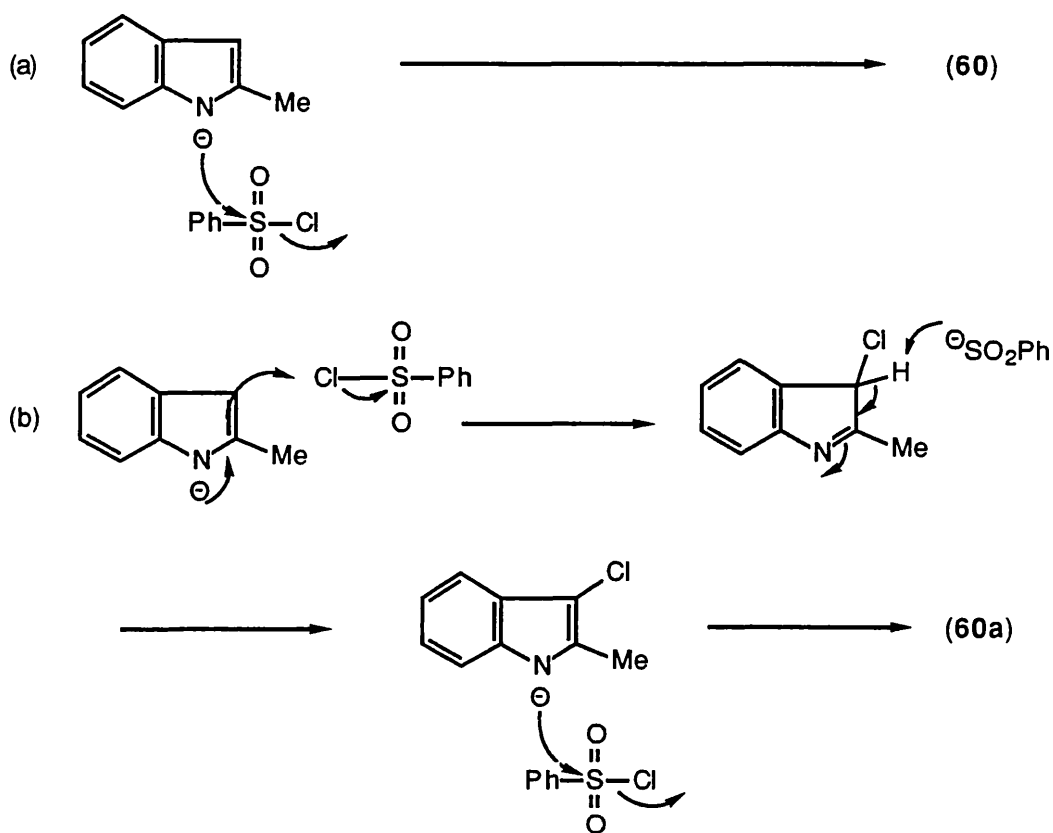


However, our attempt at protecting the indole nitrogen resulted in the unexpected isolation of a 4 : 1 mixture of 3-chloro-2-methyl-1-phenylsulphonylindole (60a) and 2-methyl-1-phenylsulphonylindole (60).



There appears to be some precedence for benzenesulphonyl chloride acting as a chlorinating agent with 2-lithiated thiophenes.⁷⁸ We can rationalise this result to a certain extent by consideration of the anion formed with sodium hydride. Reaction can occur either (a) at the nitrogen or (b) at the indole C-3 position. Nitrogen is a "hard" centre and carbon is "soft". The reacting electrophile is benzenesulphonyl chloride. Both Cl^- and PhSO_2^- are good leaving groups. The "soft" carbon prefers to attack at chlorine, whereas the "harder" nitrogen prefers to attack at sulphur. Scheme 2.8 shows the possible outcomes.

Scheme 2.8

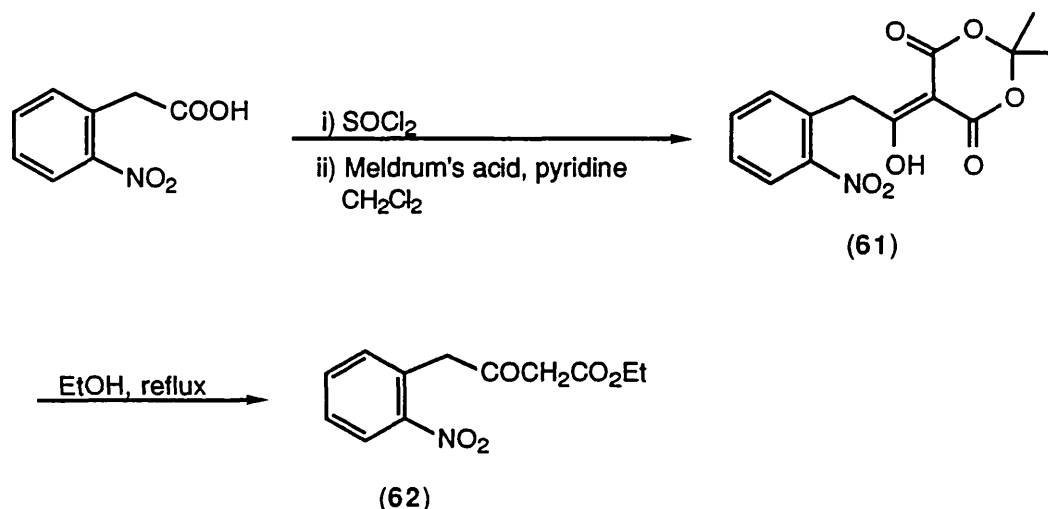


To avoid chlorination in the 3-position, we decided to formylate the 2-methylindole before protecting the indole nitrogen, since this compound could later be elaborated to the parent pyranoindolone. Thus, Vilsmeier formylation of 2-methylindole proceeded in 94% yield.

Treatment of this product with sodium hydride followed by benzenesulphonyl chloride gave a variety of products.

In our search for a quick and efficient route to indol-2-ylacetic acid (59), we also decided to try a ring synthesis approach. In the synthesis reported by Giuliano and Stein, ethyl 4-(2-nitrophenyl)acetoacetate is prepared from 2-nitrophenylacetyl chloride and the anion of acetoacetate, followed by treatment with ammonia. This is then hydrolysed and reductively cyclised using *sodium dithionite* to give (59).⁷⁷ We decided that a more modern approach to the β -ketoester using Meldrum's acid was preferable.⁷⁹ Thus acylation of Meldrum's acid with 2-nitrophenylacetyl chloride, in the presence of pyridine, followed by ethanolysis of (61) gave the β -ketoester (62) in yields of ca. 20% from 2-nitrophenylacetic acid.

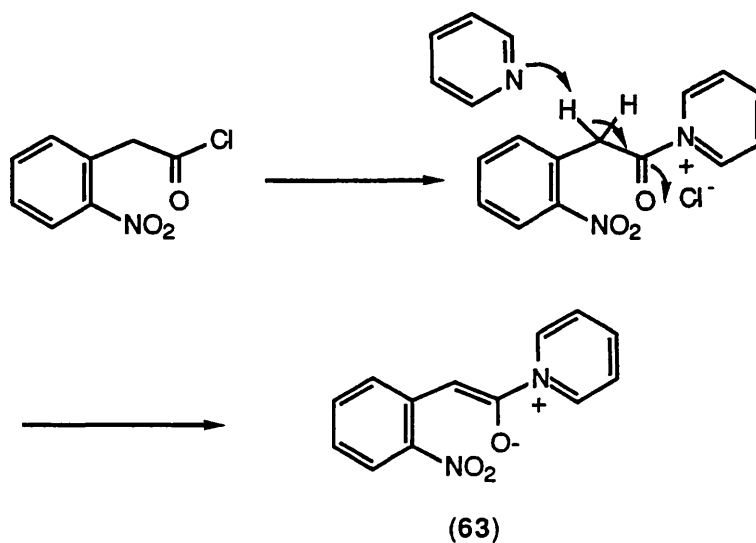
Scheme 2.9



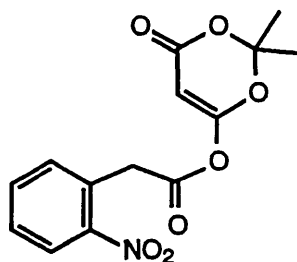
Despite the low yields, this appeared to be a promising route to indol-2-ylacetic acid as it was amenable to large scale preparation. We decided to try and optimise this procedure. A control experiment with phenylacetic acid gave much higher yields (ca. 80%) of the corresponding β -ketoester. Thus it appeared that the *o*-nitro group was responsible for the low yields. We feel that a possible explanation for this is the increased acidity of the α -hydrogens, together with the formation of the acyl-pyridinium complex, thus resulting in the formation of (63). This is inert to

attack by Meldrum's acid.

Scheme 2.10

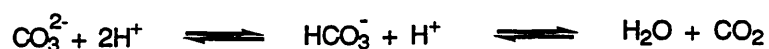


We decided that a change of base might result in a higher yielding reaction. Our initial thoughts were to pre-form the enolate of Meldrum's acid with sodium hydride, and then add the acid chloride. This, however, gave a completely different compound, which was tentatively assigned as the O-acylated product (64) on the basis of NMR. Thus the benzyl protons in (61) which occur as a singlet at δ 4.8 ppm are shifted upfield to 3.6 ppm in (64). Furthermore, the broad singlet corresponding to the enol proton in (61) at δ 15.5 ppm is replaced by a sharp singlet at 4.2 ppm in (64). O-Acylation does usually occur more readily than C-acylation on reaction with sodium salts of enolates.



(64)

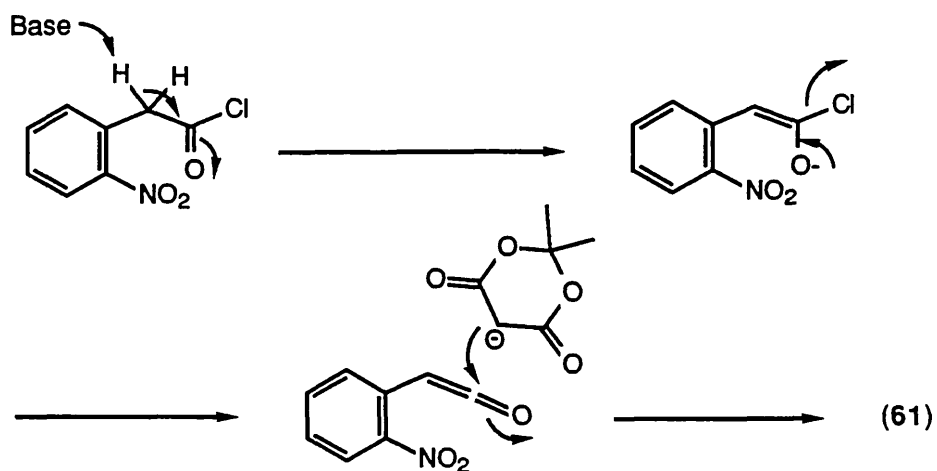
Our next thoughts were to use a heterogeneous base, such as sodium carbonate. We expected this to absorb HCl and deprotonate Meldrum's acid, but not to add nucleophilically to the acid chloride. The yield from this reaction was 50% recovered *o*-nitrophenylacetic acid and 50% of the required acyl-Meldrum's acid complex (61). Now, for every mole of Meldrum's acid anion formed, there is correspondingly half mole of water formed.



Under basic conditions, the acid chloride is converted quickly to the acid. Thus intrinsic problems exist with the choice of the base itself.

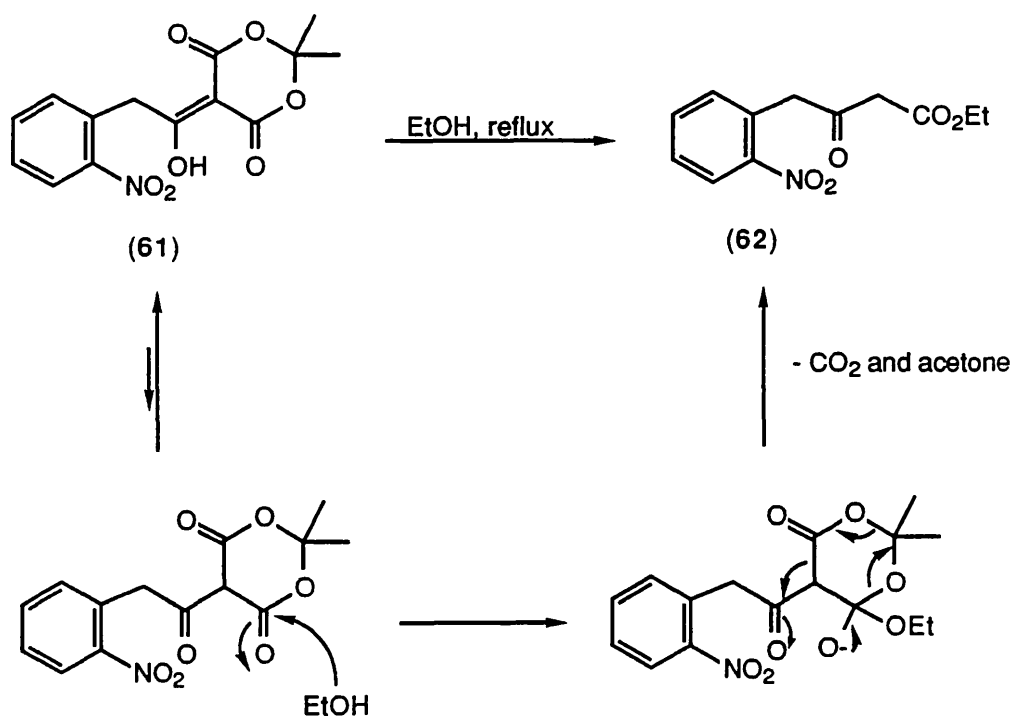
From these experiments, what we appeared to require was a non-nucleophilic, hindered base. Hünig's base (N,N-diisopropylethylamine) appeared to fulfil these criteria and therefore was tried next. Crude yields of the acyl-Meldrum's acid complex (61) were consistently in the 85-95% range. Hünig's base is a stronger base than pyridine and therefore this reaction might be proceeding *via* the ketene (Scheme 2.11).

Scheme 2.11



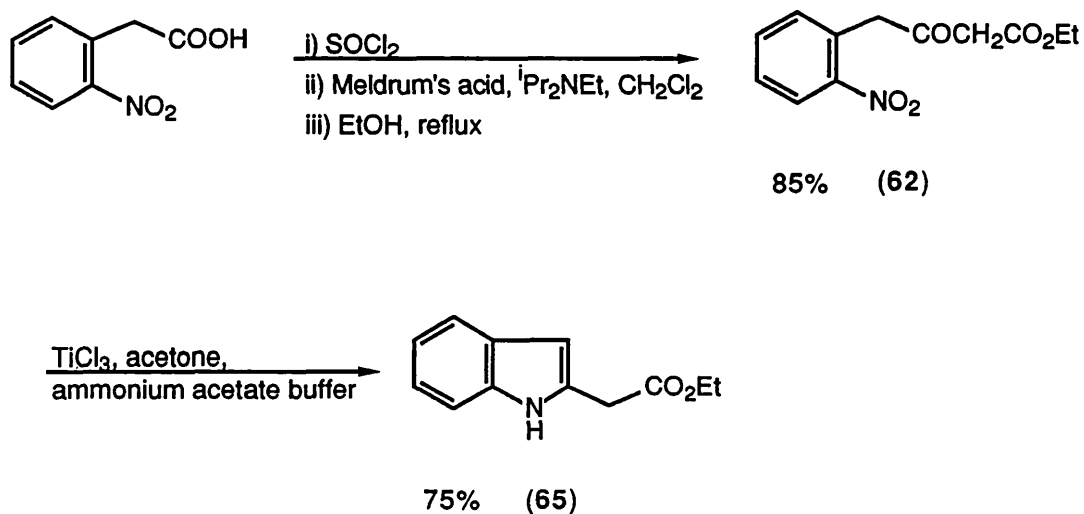
Refluxing this acyl-Meldrum's acid complex in ethanol gave the required β -ketoester (62) in 85% yield from 2-nitrophenylacetic acid.

Scheme 2.12



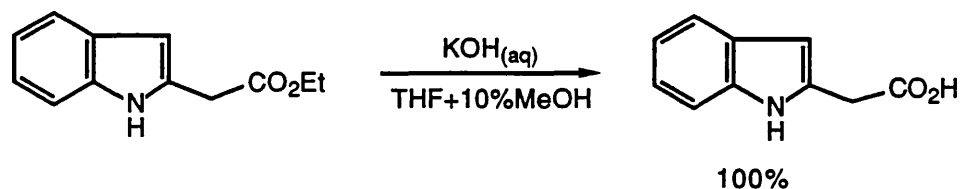
We now needed to reduce the nitro group and hence effect cyclisation. In Giuliano and Stein's original method, they failed to cyclise the ester directly to the indole with zinc and acetic acid.⁷⁷ We tried a variety of other methods. Hydrogenation (using palladium on carbon as catalyst) was not clean. This was presumably due to incomplete reduction. Similarly, the mild stannous chloride reduction conditions gave a variety of products.⁸⁰ However reduction using sodium dithionite was successful and gave us the required ethyl indol-2-ylacetate in 42% yield. A much higher yielding reaction (75%) was reduction with aqueous titanium (III) chloride, using an ammonium acetate buffer. Thus, our final route to ethyl indol-2-ylacetate (65) is as shown in Scheme 2.13.

Scheme 2.13



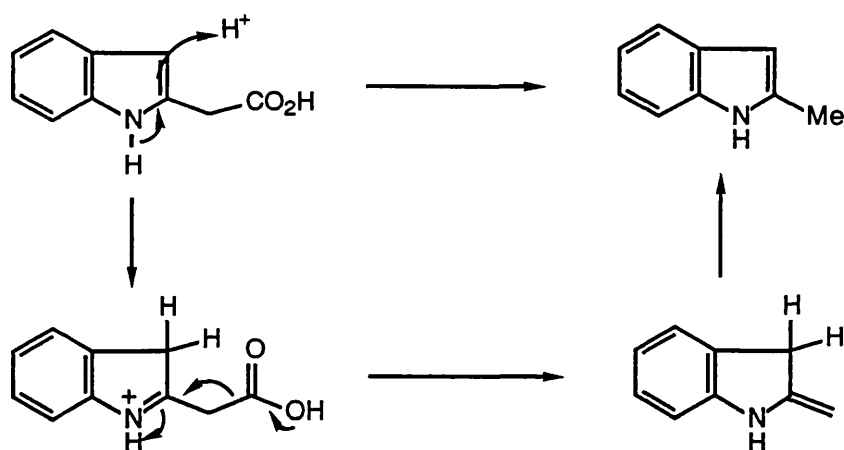
Ethyl indol-2-ylacetate (65) could be hydrolysed quantitatively to the corresponding acid (59).

Scheme 2.14



We found that a certain amount of care needed to be taken with indol-2-ylacetic acid as it decarboxylated quite easily. Protonation at the 3-position of the indole, followed by decarboxylation and migration of the double bond gives 2-methylindole (Scheme 2.15). In fact this is a side product in the reductive cyclisation with titanium (III) chloride.

Scheme 2.15

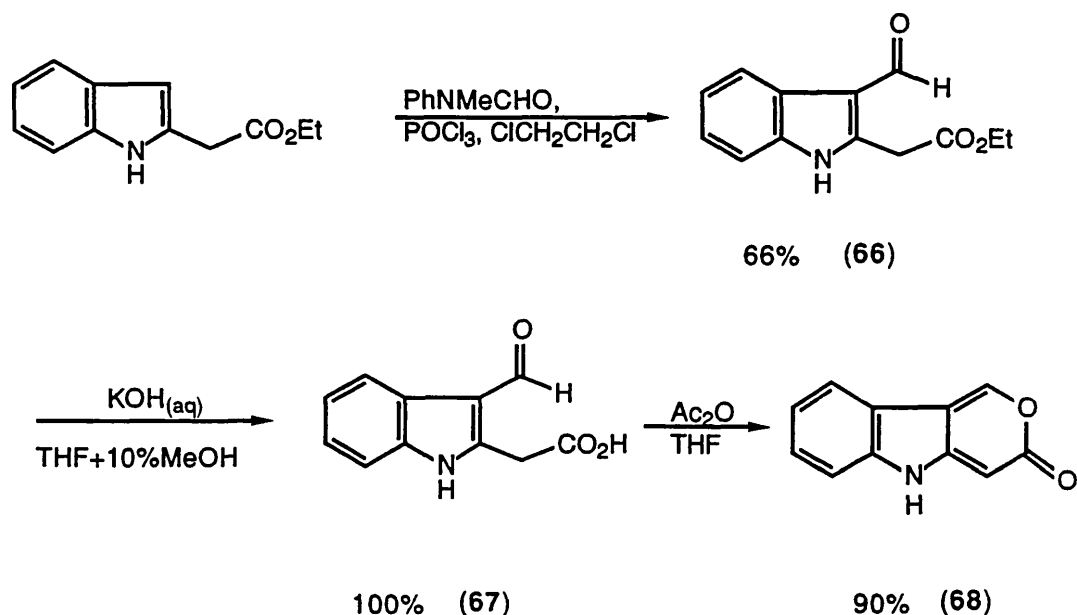


2.2.2 Preparation of pyrano[4,3-*b*]indol-3-ones

Having obtained indol-2-ylacetic acid, we tried to form 1-methylpyrano[4,3-*b*]indol-3-one using the conditions described by Plieninger, and subsequently by Moody.⁵⁵⁻⁵⁹ The result, however, was unsatisfactory. The ease with which indol-2-ylacetic acid decarboxylates might be an important factor, especially with the presence of boron trifluoride-diethyl ether in the reaction mixture. We therefore decided to employ a more systematic approach to the pyrano[4,3-*b*]indol-3-one system.

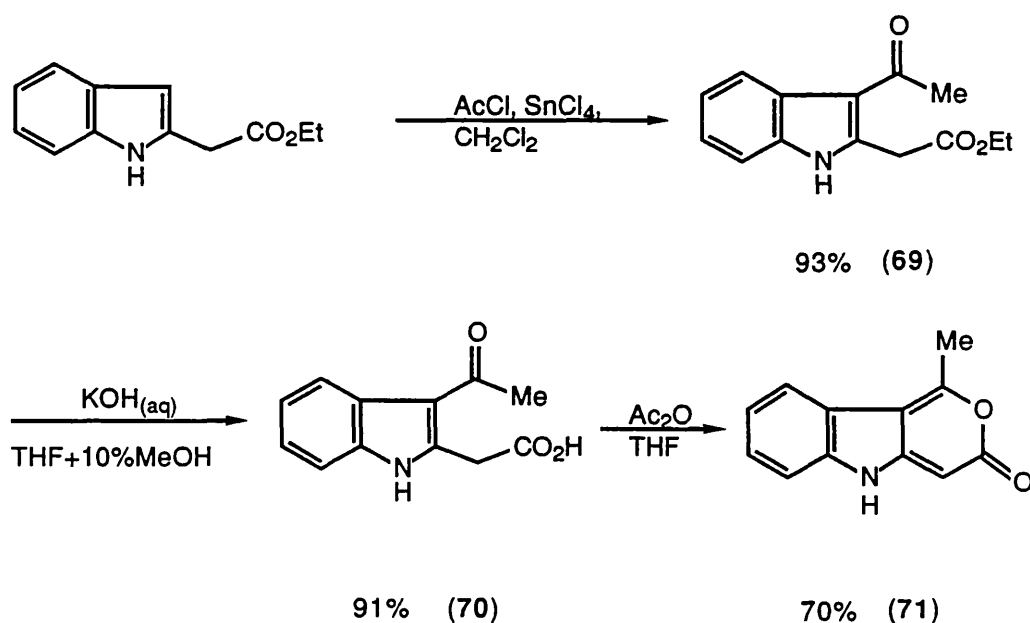
Vilsmeier formylation of ethyl indol-2-ylacetate (65), using *N*-methylformanilide and phosphorus oxychloride in 1,2-dichloroethane, gave ^{the} 3-formylindole (66) (Scheme 2.16). Hydrolysis of this gave 3-formylindol-2-ylacetic acid (67) in quantitative yield. Treatment of (67) with acetic anhydride resulted in cyclodehydration and furnished us with the parent pyrano[4,3-*b*]indol-3-one (68) in 90% yield.

Scheme 2.16



Similarly, ethyl indol-2-ylacetate could be acetylated with acetyl chloride in the presence of tin (IV) chloride to give (69) in 93% yield (Scheme 2.17). This was also hydrolysed to the acid (70) and cyclodehydrated as shown below to give 1-methylpyrano[4,3-*b*]indol-3-one (71). Attempts to directly cyclise (69) to (71) were unsuccessful. Treatment of (69) with sodium hydride in THF gave a polymeric mixture of products and treatment with acid (camphorsulphonic acid or sulphuric acid) resulted in the recovery of starting material.

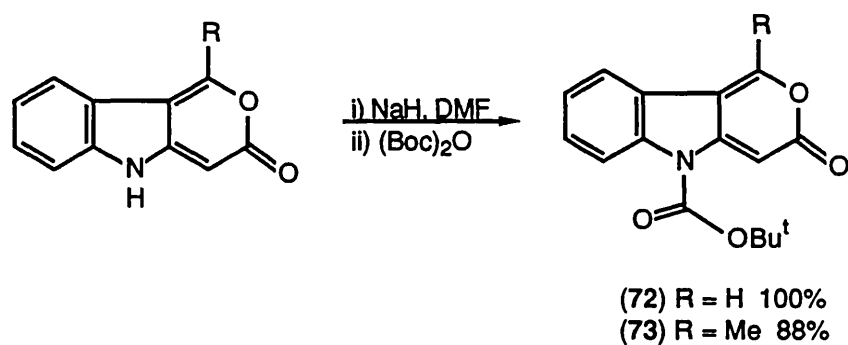
Scheme 2.17



The pyranoindolones (68) and (71) are stable solids. NOE difference spectroscopy was used to assign the ^1H NMR spectrum of the parent pyranoindolone (68). Thus pre-irradiation of the broad singlet at δ 10.2 (NH) caused enhancements of the singlet at δ 5.61 (4-H) and the doublet at δ 7.23 (6-H).

The N-t-butoxycarbonyl (NBoc) derivatives of pyranoindolones (68) and (71) were also prepared by reaction with di-t-butyl oxydicarbonate (Scheme 2.18).

Scheme 2.18



2.3 Diels-Alder reactions of pyrano[4,3-*b*]indol-3-ones with alkynes

2.3.1 Results

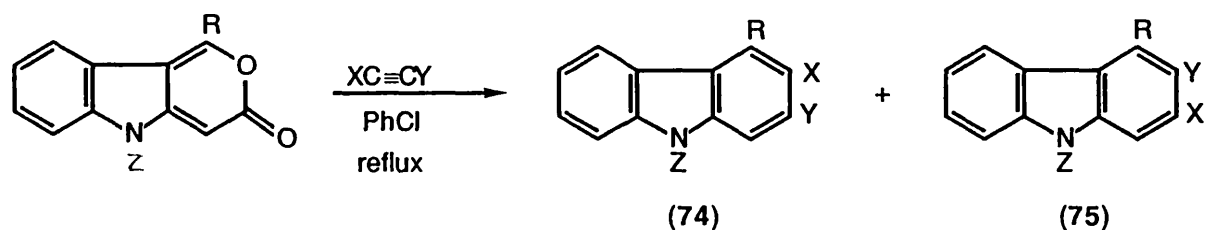
The pyranoindolones undergo Diels-Alder reaction with simple alkynes, followed by retro Diels-Alder reaction to lose carbon dioxide and give carbazoles (74) and (75) (Table 2.1). The cycloaddition reactions proceed in refluxing chlorobenzene. The pyranoindolones are insoluble or only sparingly soluble in most solvents, with the exception of THF, DMF, and DMSO. However they are soluble in refluxing chlorobenzene. Refluxing THF was also tried as a solvent in the reaction of pyrano[4,3-*b*]indol-3-one with DMAD but the reaction had still not gone to completion after 192 h. In comparison, the same reaction in chlorobenzene was over in 44 h. DMF at 90 °C was also tried as a solvent in the reaction of the parent pyranoindolone with ethyl propiolate. This, however, gave a variety of products, the majority of which contained an aldehyde functionality. This suggests that the DMF is facilitating the opening of the pyranone ring.

The NBoc pyranoindolones also undergo cycloadditions with alkynes, to give after loss of carbon dioxide, carbazoles. The results are slightly complicated since thermal removal of the Boc group from the pyranoindolone competes with cycloaddition to the alkyne. Moreover, thermal removal of the Boc group from the product carbazoles also occurs.

2.3.2 Discussion

Certain interesting points emerge when the results of these Diels-Alder reactions of pyrano[4,3-*b*]indol-3-ones with simple alkynes (Table 2.1) are compared with those reported by Moody and Shah for the pyrano[3,4-*b*]indol-3-one system (Table 2.2).^{57-58, 70}

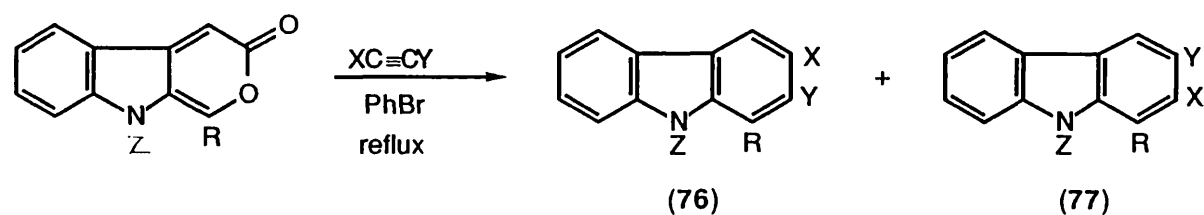
Table 2.1 Diels-Alder reactions of pyrano[4, 3-*b*]indol-3-ones with alkynes



Entry	R	Z	X	Y	Time (h)	(74)/(75)	Combined Yield (%)	Ratio (74):(75)	Notes
1	H	H	CO ₂ Me	CO ₂ Me	44	a	92	-	
2	H	Boc	CO ₂ Me	CO ₂ Me	20	b	82	-	a
3	Me	H	CO ₂ Me	CO ₂ Me	144	c	30	-	
4	H	H	H	CO ₂ Et	167	d	90	1:1.2	
5	H	Boc	H	CO ₂ Et	25	e	62	1.5:1	b
6	Me	H	H	CO ₂ Et	425	f	78	1:2	
7	H	H	Ph	CO ₂ Me	241	g	28	1:>20	c, d
8	H	Boc	Ph	CO ₂ Me	48	h	40	1:>20	d, e
9	H	H	SiMe ₃	CO ₂ Et	262	i	24	1:>20	d
10	H	H	Me	CO ₂ Me	528		0	-	
11	Me	H	SiMe ₃	CO ₂ Et	1344		0	-	
12	Me	Boc	SiMe ₃	CO ₂ Et	96		0	-	f

^aA mixture of NBoc and NH carbazoles was formed; this mixture was heated neat to give only the NH carbazole. ^bA mixture of NBoc (10%) and NH (52%) carbazoles was formed; ca. 35% NH pyranoindolone recovered. ^cCarried out in PhBr at 140°C. ^dOnly a single carbazole product observed by 270 MHz ¹H NMR. ^eca. 60% of NH pyranoindolone recovered. ^fca. 85% of NH pyranoindolone recovered.

Table 2.2 Diels-Alder reactions of pyrano[3, 4-*b*]indol-3-ones with alkynes ^{57, 58, 70}



Entry	R	Z	X	Y	Time (h)	Combined Yield (%)	Ratio (76):(77)	Notes
1	H	H	CO ₂ Me	CO ₂ Me	a	20-25	-	a
2	Me	H	CO ₂ Me	CO ₂ Me	3	81	-	
3	H	H	H	CO ₂ Et	10	23	1:1.6	b
4	Me	H	H	CO ₂ Et	10	74	1:1.7	
5	Me	CO ₂ Et	H	CO ₂ Et	24	86	1.4:1	
6	Me	H	Ph	CO ₂ Me	72	74	3.4:1	
7	Me	H	SiMe ₃	CO ₂ Et	48	77	>20:1	

^aCarried out in THF at room temperature for 20 h to give carbazole in 25% yield or in refluxing THF and toluene for 2 h to give carbazole in 20% yield.

^bCarried out in a mixture of THF and toluene at reflux.

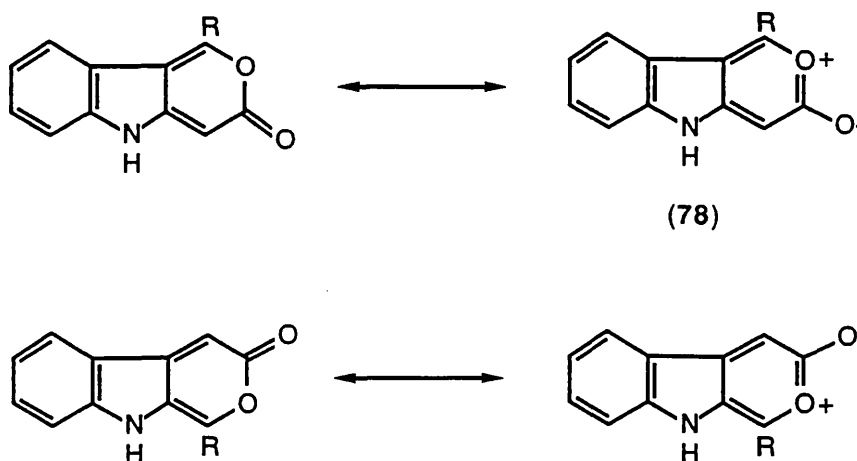
a) Reactivity

As can be seen from Table 2.1, the more electron - deficient alkynes react faster, thus suggesting that the Diels-Alder reactions of pyrano[4,3-*b*]indol-3-ones are "normal" electron demand reactions. This was also illustrated to be the case with Diels-Alder reactions of the isomeric pyrano[3,4-*b*]indol-3-ones with alkynes.⁵⁸ Thus in MO terms, it is the HOMO of the diene interacting with the LUMO of the dienophile.⁸¹

The pyrano[4,3-*b*]indol-3-ones are considerably less reactive than their isomeric counterparts (52). In some cases, no carbazole is obtained even after prolonged heating (Table 2.1, Entries 10-12). Furthermore, the parent pyrano[4,3-*b*]indol-3-one (68) is more reactive than 1-methylpyrano[4,3-*b*]indol-3-one (71) but less reactive than *t*-butyl 3-oxopyrano[4,3-*b*]indole-5-carboxylate (72) as shown by their respective reaction times with DMAD (Table 2.1, Entries 1-3) and ethyl propiolate (Table 2.1, Entries 4-6).

We feel that this decrease in reactivity is due to contributions from either (a) the aromatic *meso*meric form (78) shown in Scheme 2.19, or (b) the *meso*meric form (79) shown in Scheme 2.20.

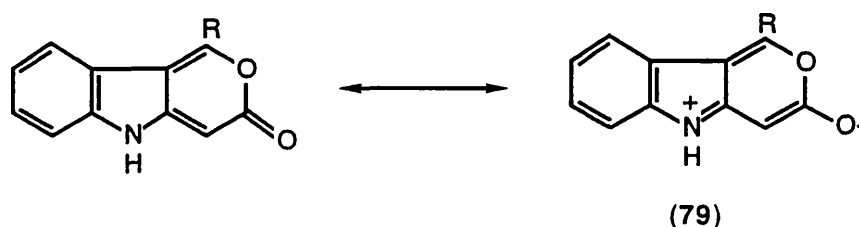
Scheme 2.19



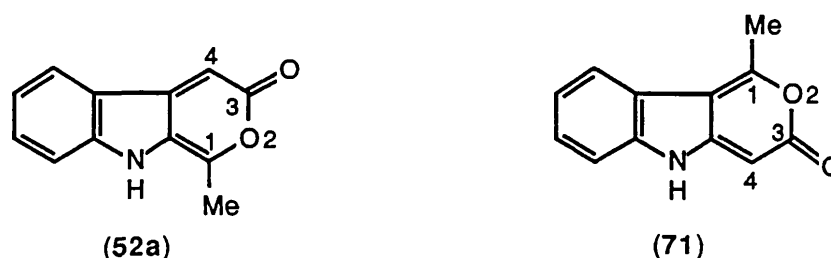
Scheme 2.19 shows the aromatic *meso*meric forms of both pyranoindolones (52) and (58). In both cases, the aromatic *meso*mer can be stabilised by the inductive effect of an alkyl substituent R. However, only in the case of the pyrano[4,3-*b*]indol-3-ones, the nitrogen lone pair also stabilises the aromatic *meso*mer (78).

Furthermore, as Scheme 2.20 shows, in the case of the pyrano[4,3-*b*]indol-3-ones, the nitrogen lone pair is conjugated through to the carbonyl group without disrupting the aromaticity of the benzene ring.

Scheme 2.20



Generally with 2-pyrones, the contribution from the aromatic *meso*mer is negligible.⁸² The spectroscopic data suggests that the main contribution to the pyrano[4,3-*b*]indol-3-ones (58) is from *meso*meric form (79) shown in Scheme 2.20.



Thus the carbonyl absorptions in the IR spectra for (52a) and (71) are 1695 and 1681 cm^{-1} respectively. The lower carbonyl stretching frequency in (71) suggests less carbonyl double bond character compared with (52a). The 4-H proton resonates at δ 5.46 ppm in (71) compared with δ 6.43 ppm in (52a). This again suggests a decrease in carbonyl double bond character. Additionally, the ^{13}C NMR spectra, which were assigned using gated broad band decoupling,

show resonances for C-4 and C-1 at δ 79.8 and 159.0 ppm for (71), and δ 95.5 and 144.3 ppm for (52a). So, in (71), C-4 is δ^- and C-1 is δ^+ compared with the corresponding carbons in (52a).

Thus it appears that the low reactivity of the pyrano[4,3-*b*]indol-3-ones compared with their isomeric counterparts (52) is simply due to less of the "diene" being available for cycloaddition. So placing an electron - withdrawing group on nitrogen in the pyrano[4,3-*b*]indol-3-ones should increase the reactivity of these compounds. This is exactly what happens as Entries 1 and 2, 4 and 5, and 7 and 8 illustrate in Table 2.1. The spectroscopic data are also consistent with this change in reactivity. On attachment of the electron - withdrawing Boc group to the indole nitrogen, the carbonyl stretching frequency in the IR spectrum increases and the NMR signal for 4-H is shifted downfield. Thus pyrano[4,3-*b*]indol-3-one (68) has a carbonyl stretching frequency of 1681 cm^{-1} , whereas the corresponding NBoc pyranoindolone (72) has a carbonyl stretching frequency of 1708 cm^{-1} . Additionally, the NMR signal for 4-H is at δ 5.61 ppm for (68) and at δ 6.65 ppm for (72). Similarly, the values in the IR spectra for the carbonyl stretch in (71) and (73) are 1681 and 1704 cm^{-1} respectively, and for the 4-H proton in the NMR spectra are δ 5.46 and 6.57 ppm respectively.

b) Regioselectivity

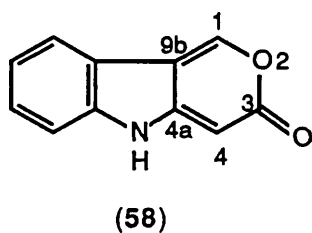
The Diels-Alder reaction of pyrano[4,3-*b*]indol-3-ones with ethyl propiolate results in a mixture of regioisomers (Table 2.1, Entries 4-6). This however appears to be a general result for Diels-Alder reactions of propiolic esters with 2-pyrones, in that they exhibit little or no regioselectivity, in contrast to other alkynes.^{83, 84} This lack of regioselectivity also occurs with pyrano[3,4-*b*]indol-3-ones (Table 2.2, Entries 3-5) and, in fact, Moody and Shah have shown that steric effects dominate in this reaction.⁵⁸ As the size of alkyl substituent R at C-1 increases, the selectivity of the reaction increases in favour of the less sterically crowded carbazole 3-ester.

In the reaction of pyrano[4,3-*b*]indol-3-one (68) with ethyl trimethylsilylpropynoate (Table 2.1, Entry 9), only the carbazole 3-ester (75i) is obtained. The structure of (75i) was proved by

NOE difference spectroscopy. Pre-irradiation of the singlet at δ 7.86 ppm (1-H) caused enhancements of the singlet at 0.36 (SiMe₃) and the broad singlet at 10.65 (NH). The structure was further confirmed by proto-desilylation to the known ethyl carbazole-3-carboxylate (75d). Unfortunately, due to the low reactivity of 1-methylpyrano[4,3-*b*]indol-3-one (71), no carbazole was isolated even after prolonged heating with the alkyne (Table 2.1, Entry 11). The correspondingly more reactive NBoc pyranoindolone (73) also did not yield any carbazole products, since thermal removal of the Boc group occurred preferentially to Diels-Alder reaction with the alkyne (Table 2.1, Entry 12). In contrast, 1-methylpyrano[3,4-*b*]indol-3-one (52a) gives the carbazole 2-ester as the sole product on reaction with the same alkyne (Table 2.2, Entry 7).⁷⁰ Similarly, in the reaction with methyl phenylpropiolate, (68) and (72) both react to give only one detectable isomer (Table 2.1, Entries 7 and 8). This is the carbazole 3-ester (75g). However, the carbazole 2-ester is the major product when (52a) is reacted with the same alkyne (Table 2.2, Entry 6).⁵⁸

Unlike the pyrano[3,4-*b*]indol-3-ones, there is no doubt as to the directing effect of the pyrano[4,3-*b*]indol-3-ones. In "arrow-pushing" terms, the nitrogen and the pyrone ring oxygen both direct the same way. Furthermore, calculation of the atomic charges, using zero differential overlap, indicates the diene is polarised in the same direction as predicted by our simple explanation, with charges 0.201 and -0.210 at C-1 and C-4 respectively (Figure 2.1). The ¹³C NMR data are also consistent with these calculated values, with signals at δ 159.0 and 79.8 ppm corresponding to C-1 and C-4 respectively. We have also calculated the HOMO coefficients, using the MNDO Hamiltonian within MOPAC 5, as shown in Figure 2.1.⁸⁵ These give the HOMO coefficient as 0.34 at C-1 and 0.42 at C-4. Pindur has also done some calculations of this system using the π -SCF-MO method from Allinger (Iris-workstation)/Sprague in the MMX packet from Serena Software Ltd. (U.S.A.).⁸⁶ This method takes only the π molecular orbitals into account. However, these calculations also give a larger HOMO coefficient at C-4 (0.51) compared with C-1 (0.34).

Figure 2.1

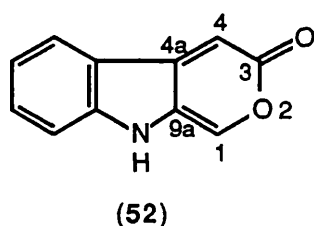


Atom	Atomic charge	HOMO coefficient
1	0.201	0.34
2	-0.251	
3	0.381	
4	-0.210	-0.42
4a	0.144	-0.09
9b	-0.193	0.30

$$\Delta H_{\text{form.}} = -19.76 \text{ kcal mol}^{-1}, E_{\text{HOMO}} = -8.68 \text{ eV}, E_{\text{LUMO}} = -0.87 \text{ eV}.$$

Analysis of the directing effect of pyrano[3,4-*b*]indol-3-ones is quite complicated. In "arrow-pushing" terms, the nitrogen and the pyrone ring oxygen direct in opposite directions. However, calculations of atomic charges, using zero differential overlap, suggest that the diene is polarised in the opposite direction, though to a lesser extent, than the corresponding pyrano[4,3-*b*]indol-3-one system. Thus the charges at C-1 and C-4 are 0.143 and -0.134 respectively (Figure 2.2). This is also borne out in the ^{13}C NMR data. The chemical shifts are 144.3 and 95.5 for C-1 and C-4 respectively. The discrepancy, however, arises on calculation of the coefficients of the HOMO in the parent pyranoindolone. Our calculations, using the MNDO Hamiltonian in MOPAC 5 (precise option used),⁸⁵ showed that the coefficients at C-1 and C-4 were very similar as indicated in Figure 2.2, with the coefficient at C-4 being marginally larger (0.40 compared with 0.38). Pindur's calculations using the MNDO package ($\Delta H_{\text{form.}} = +4.47 \text{ kcal mol}^{-1}$ as opposed to $-17.07 \text{ kcal mol}^{-1}$ in our calculations) gives the C-4 coefficient as 0.33, but the C-1 coefficient as 0.41.⁶⁴ Furthermore, his calculations using the π -VSCF method (only π -orbitals taken into consideration) gives values of 0.34 and 0.49 for the C-4 and C-1 coefficients respectively.⁸⁶

Figure 2.2



Atom	Atomic charge	HOMO coefficient
1	0.143	0.38
2	-0.244	
3	0.366	
4	-0.134	-0.40
4a	0.060	-0.11
9a	-0.125	0.31

$$\Delta H_{\text{form.}} = -17.07 \text{ kcal mol}^{-1}, E_{\text{HOMO}} = -8.77 \text{ eV}, E_{\text{LUMO}} = -1.09 \text{ eV}.$$

Various authors give different explanations for the regioselectivity of pyrano[3,4-*b*]indol-3-ones with alkenes and alkynes. Pindur claims that these cycloadditions are frontier orbital-controlled in the case of terminal alkynes and alkenes. He accounts for the discrepancies by saying that in the case of ethyl phenylpropiolate, the reaction is controlled by the polarisation of the diene (*i.e.* charge-controlled), since the difference in the LUMO coefficients at the ends of the alkyne are small.⁶⁴ However, in a later review, he says that in general the results of Moody and Shah of Diels-Alder reactions of (52a) with disubstituted alkynes are influenced by steric factors.⁶⁶ We have calculated the atomic charges and the LUMO coefficients of three alkynes (80; XCCCO₂R): ethyl propiolate, ethyl trimethylsilylpropynoate, and methyl phenylpropiolate (Figure 2.3).

Figure 2.3

	Atom	Atomic charge	LUMO coefficient
$\text{H}-\overset{3}{\text{C}}\equiv\overset{2}{\text{C}}-\text{CO}_2\text{Et}$	2	-0.181	0.38
	3	-0.021	-0.55
	Atom	Atomic charge	LUMO coefficient
$\text{Me}_3\text{Si}-\overset{3}{\text{C}}\equiv\overset{2}{\text{C}}-\text{CO}_2\text{Et}$	2	-0.123	-0.41
	3	-0.346	0.55
	Atom	Atomic charge	LUMO coefficient
$\text{Ph}-\overset{3}{\text{C}}\equiv\overset{2}{\text{C}}-\text{CO}_2\text{Me}$	2	-0.165	-0.35
	3	0.015	0.32

(80) X=H, R=Et $\Delta H_{\text{form.}} = -34.54 \text{ kcal mol}^{-1}$, $E_{\text{HOMO}} = -11.48 \text{ eV}$, $E_{\text{LUMO}} = +0.26 \text{ eV}$.

(80) X=TMS, R=Et $\Delta H_{\text{form.}} = -101.53 \text{ kcal mol}^{-1}$, $E_{\text{HOMO}} = -11.17 \text{ eV}$, $E_{\text{LUMO}} = +0.09 \text{ eV}$.

(80) X=Ph, R=Me $\Delta H_{\text{form.}} = -13.25 \text{ kcal mol}^{-1}$, $E_{\text{HOMO}} = -9.46 \text{ eV}$, $E_{\text{LUMO}} = -0.67 \text{ eV}$.

Firstly, as can be seen from the E_{HOMO} and E_{LUMO} differences, E_{HOMO} (pyranoindolone) - E_{LUMO} (alkyne) (Table 2.3) is indeed smaller than E_{HOMO} (alkyne) - E_{LUMO} (pyranoindolone) (Table 2.4). Thus the calculations are consistent with our observations that these Diels-Alder reactions are "normal" electron demand reactions.

Table 2.3 E_{HOMO} (pyranoindolone) - E_{LUMO} (alkyne) in eV.

	(80) X=H, R=Et	(80) X=TMS, R=Et	(80) X=Ph, R=Me
(58)	8.94	8.77	8.01
(52)	9.03	8.86	8.10

Table 2.4 E_{HOMO} (alkyne) - E_{LUMO} (pyranoindolone) in eV.

	(80) X=H, R=Et	(80) X=TMS, R=Et	(80) X=Ph, R=Me
(58)	10.61	10.30	8.59
(52)	10.39	10.08	8.37

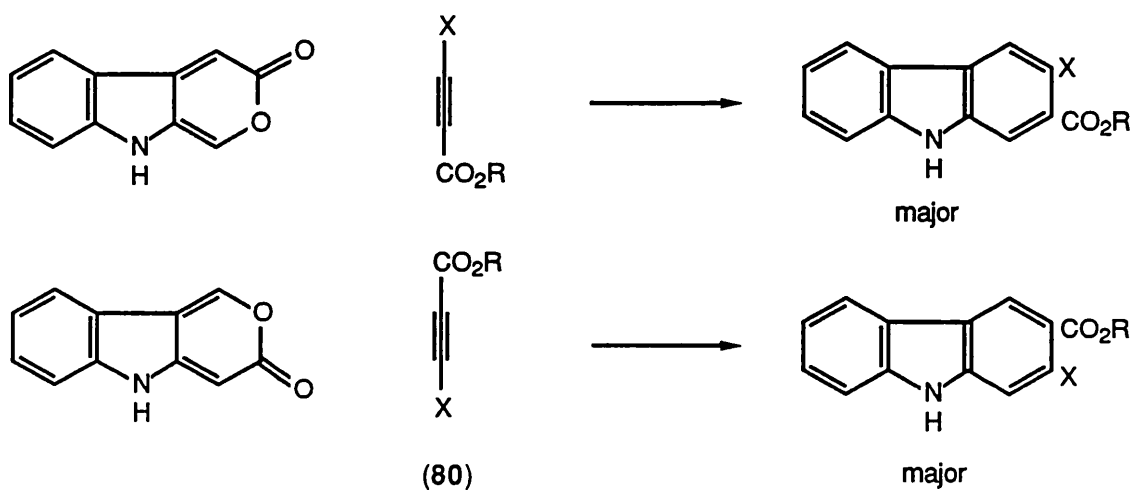
The experimental result which gives the carbazole 2-ester as the major product in the cycloaddition with methyl phenylpropiolate (Table 2.2, Entry 6) probably can be explained by a charge argument, and further strengthened by a steric argument. However, if one considers the coefficients of the HOMO of Pindur's diene and the coefficients of the LUMO of the alkyne, there appears to be no need for him to invoke steric or charge arguments to explain the results. In the case of ethyl trimethylsilylpropynoate, steric factors probably dominate due to the size of the TMS group, thus giving the carbazole 2-ester. We could arrive at the same result by consideration of our calculated frontier orbital coefficients. However, the difference in size of the coefficients of the diene are so small that it is unlikely that this plays an important role in determining the regioselectivity. The slight preference for the carbazole 3-ester in the reaction

with ethyl propiolate can only be explained by a steric argument, since both the atomic charges and our HOMO coefficients suggest that the carbazole 2-ester should be the major product. As discussed earlier, propiolic acid esters are unusual cases and modelling of the transition state might provide a better understanding of their lack of regioselectivity.

Consideration of the reaction of these pyranoindolones (52) with alkenes also gives some interesting results. Narasimham and Gokhale report isolation of the 3-substituted product in THF of α -activated chloroalkenes, but they obtain a mixture of regioisomers in collidine at 80 °C.⁶⁰ Now using Pindur's MO calculations, one can talk about this reaction being frontier molecular orbital-controlled. However, concerted pericyclic reactions are solvent independent. Thus, we feel that this result can be explained in terms of steric and charge factors. Steric factors dominate to give the 3-substituted carbazole. However, in the more polar solvent, charge factors become important and therefore the 2-substituted product is also formed. Similarly, the reactions with alkenes reported by Van Doren *et al.* can also be explained by considering steric effects.^{67, 68} Thus the 3-substituted product is predominant. When trisubstituted alkenes are used, the 2-disubstituted products are predominant. This may be due to the fact that the reaction is done in "neat" alkene, which is, in this case, quite a polar medium. Thus charge effects become important. Furthermore, the authors feel that these reactions probably occur *via* a stepwise mechanism, with the less sterically crowded centres first being linked.

Since the HOMO molecular coefficients are so similar, we feel that most of the reactions of pyrano[3,4-*b*]indol-3-ones are probably charge-controlled. Thus most simply, the regioselectivity of the reactions in Tables 2.1 and 2.2 can be explained by considering the directing effect of the pyrone ring oxygen. Thus pyrano[3,4-*b*]indol-3-ones give predominantly the carbazole 2-ester and pyrano[4,3-*b*]indol-3-ones give predominantly the carbazole 3-ester in cycloaddition reactions with acetylenic esters (80; X not H).

Scheme 2.21



However, all this analysis has only shown that it is not possible to make sweeping statements about the regioselectivity of these reactions, and that modelling of the transition state is required to obtain a better computer model in order to predict the regioselectivities. Thus whether our simple model holds up to further scrutiny remains to be seen.

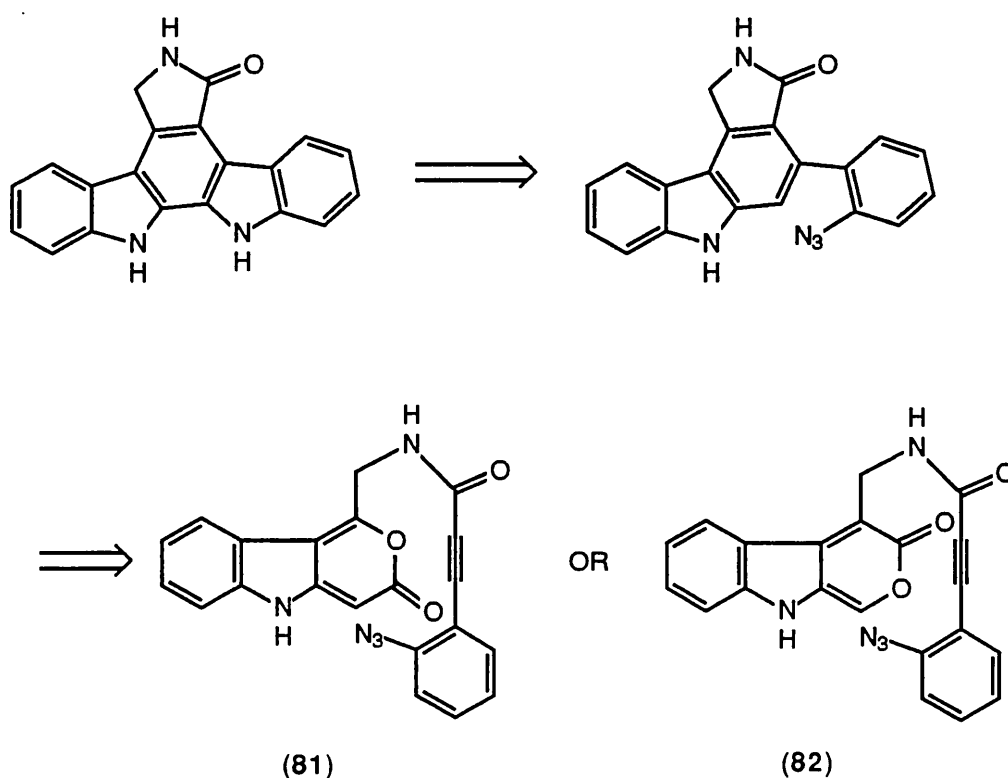
CHAPTER THREE

SYNTHESIS OF THE STAUROSPORINE AGLYCONE

3.1 Introduction

As has already been discussed in Chapter 1, a synthesis of the staurosporine aglycone, without the use of any protecting groups, still remains a synthetic target. The methodology described in Chapter 2 provides a route to substituted carbazoles, without the use of any protecting groups. Thus we felt that the two may be combined to give us a concise synthesis of the staurosporine aglycone. Scheme 3.1 shows a possible retrosynthetic analysis from the staurosporine aglycone back to a pyrano[4,3-*b*]indol-3-one system (81) and a pyrano[3,4-*b*]indol-3-one system (82).

Scheme 3.1

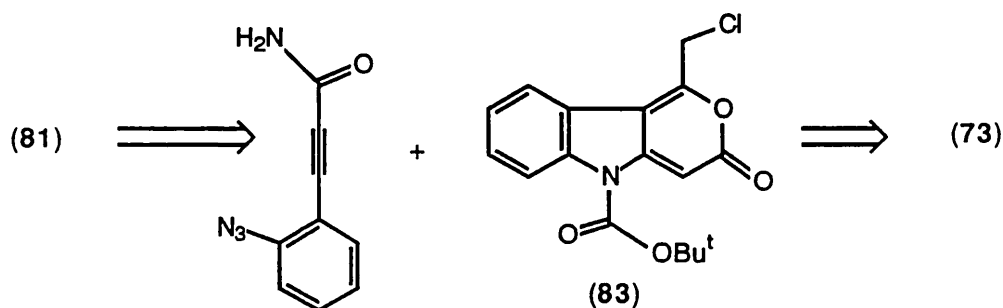


Thus the initial disconnection is of one of the indole rings to give us a tetracyclic carbazole. This, in turn, can be made from an intramolecular Diels-Alder reaction, followed by loss of carbon dioxide, of a pyranoindolone and an alkyne. Our original intention for making the pyrano[4,3-*b*]indol-3-one system was because we felt that pyranoindolone (81) could easily be made by reacting the appropriate anhydride with indol-2-ylacetic acid. However, as we have already discussed in Chapter 2, this method of synthesis was unsatisfactory and a more systematic approach was required. Despite this fact, as well as the lower reactivity of the pyrano[4,3-*b*]indol-3-one system, we decided initially to persevere with this pyranoindolone, rather than the isomeric system (82). We felt that the intramolecular reaction ought to be intrinsically faster, and therefore the lower reactivity of this ring system ought to pose less of a problem than it did in the intermolecular reactions described in Chapter 2.

3.2 Initial approaches

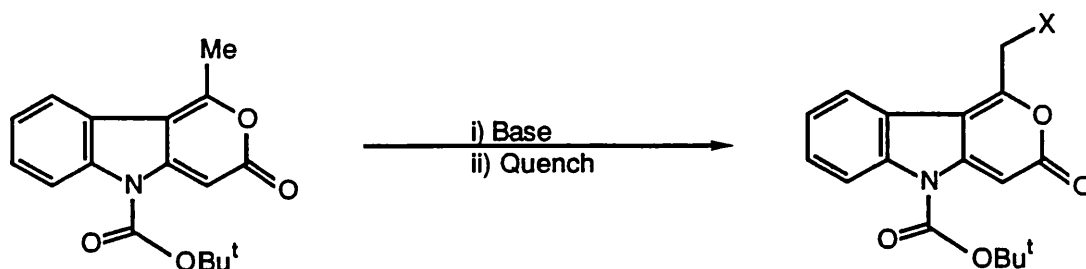
Our initial approach to the pyranoindolone (81) was to disconnect back to pyranoindolone (83), which in turn could be obtained from previously synthesised pyranoindolone (73).

Scheme 3.2



However, attempts to make (83) from *t*-butyl 1-methyl-3-oxopyrano[4,3-*b*]indole-5-carboxylate (73) by deprotonation at the methyl group with either LDA or n BuLi, and quenching with either carbon tetrachloride or hexachloroethane failed (Table 3.1). We were certain that deprotonation at the methyl group was occurring, since quenching with D₂O resulted in significant deuteration at the methyl group of (73), as indicated by the integration in the ¹H NMR spectrum. In the one case where we did obtain a second compound, as indicated by t.l.c., chromatography of the reaction mixture resulted in the isolation of a mixture of two compounds. NMR revealed that this mixture was composed of mainly starting pyranoindolone (73).

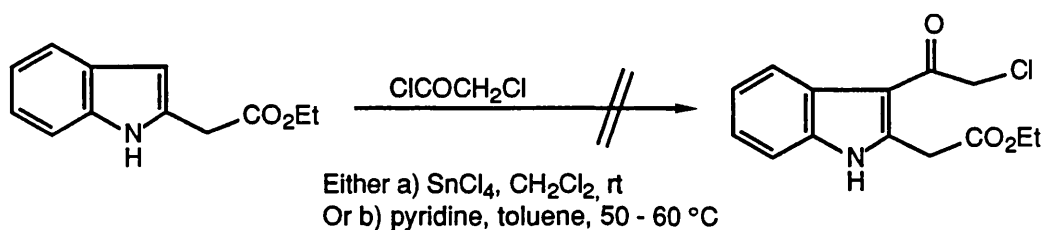
Table 3.1



Base	Quench	X
LDA, THF, -78 to 0 °C	CCl ₄ , 0 to 20 °C	H
ⁿ BuLi, THF, -78 to -12 °C	CCl ₄ , 0 to 20 °C overnight	H
ⁿ BuLi, THF, -78 to 0 °C, 2h	C ₂ Cl ₆ , 0 °C, 23 h	H + Cl?
ⁿ BuLi, THF, -78 to 0 °C, 2h	C ₂ Cl ₆ , 0 to 50 °C	–
ⁿ BuLi, THF, -78 to 0 °C, 2h	D ₂ O, rt, 20 h	D

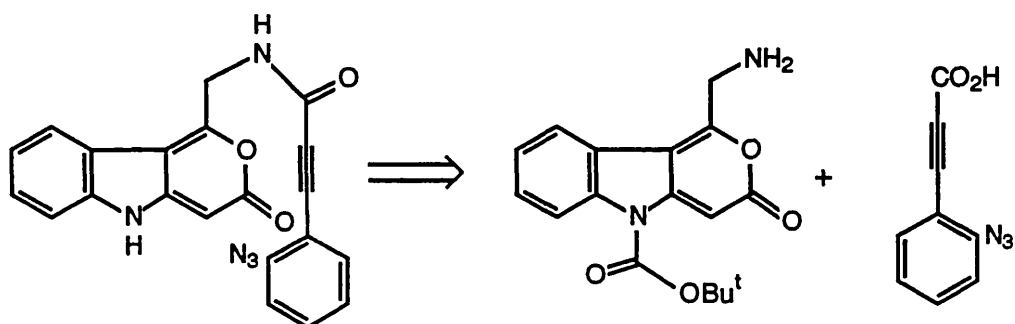
Other attempts to make (83) by the introduction of the chlorine at an earlier stage also failed. Attempts to acylate ethyl indol-2-ylacetate (65) with chloroacetyl chloride using tin (IV) chloride as Lewis acid, gave a variety of products. A milder method using (65), chloroacetyl chloride, and pyridine in toluene at 50 °C, resulted in the isolation of only starting material.⁸⁷

Scheme 3.3



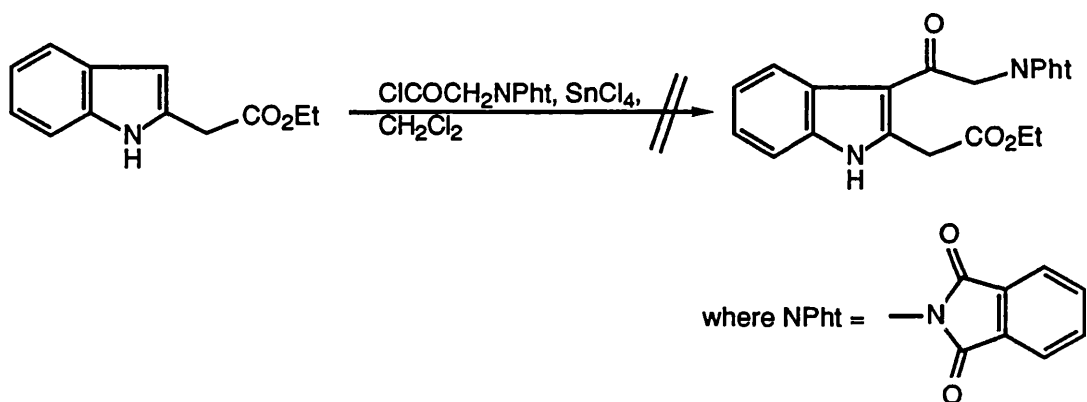
Our next thought was to try the more usual disconnection at the amide.

Scheme 3.4



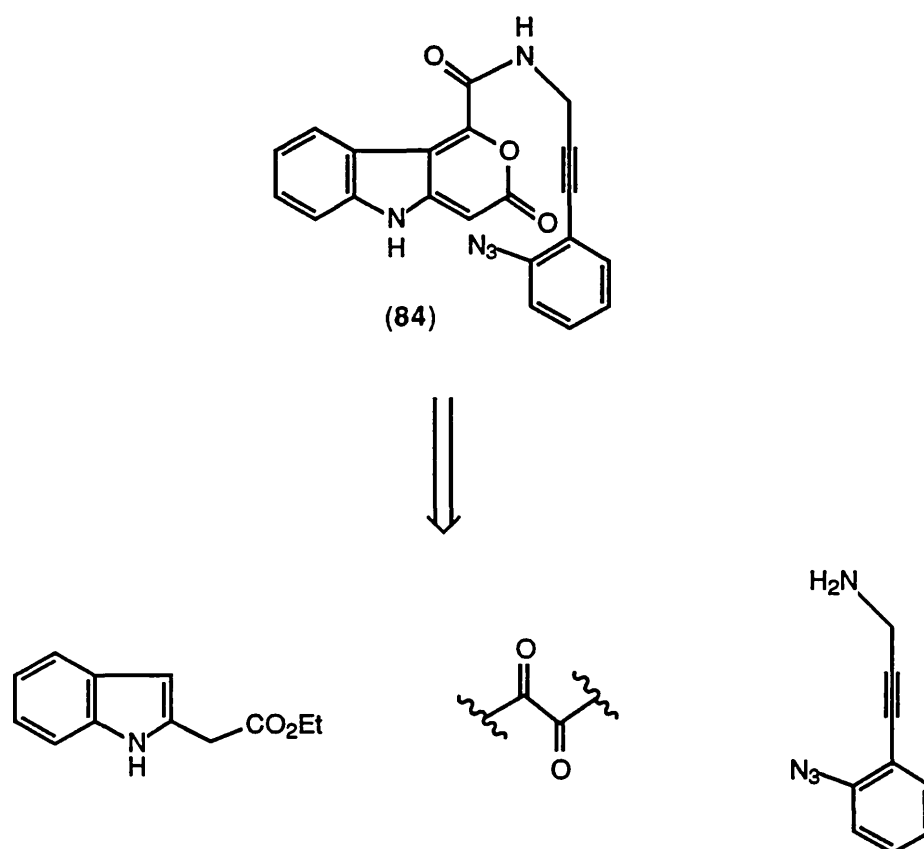
However the acylation reaction with the acid chloride of N-phthaloylglycine and ethyl indol-2-ylacetate was messy.

Scheme 3.5



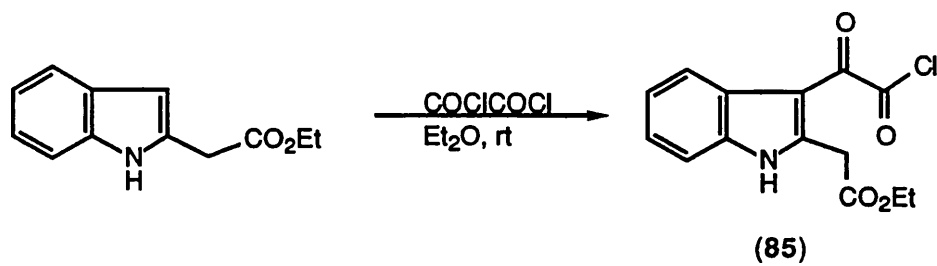
Now, we could rewrite the required pyranoindolone (81) with the amide carbonyl directly attached to the pyrone, as shown below in Scheme 3.6. Thus disconnecting (84) back to ethyl indol-2-ylacetate gives an amine and a synthon which could be obtained from oxalyl chloride.

Scheme 3.6



Giua, in 1924, reported that acylation of indoles with oxalyl chloride occurred remarkably easily.⁸⁸ Furthermore, trapping of this indole-3-glyoxalyl chloride with amines, followed by reduction of the carbonyl groups, has been the basis of a variety of substituted tryptamine syntheses.⁸⁹ We tried this reaction with ethyl indol-2-ylacetate (65) and found that the corresponding indole-3-glyoxalyl chloride (85) was formed within a few minutes, on the addition of excess oxalyl chloride to (65) in sodium dry ether, at room temperature. No Lewis acid was necessary.

Scheme 3.7

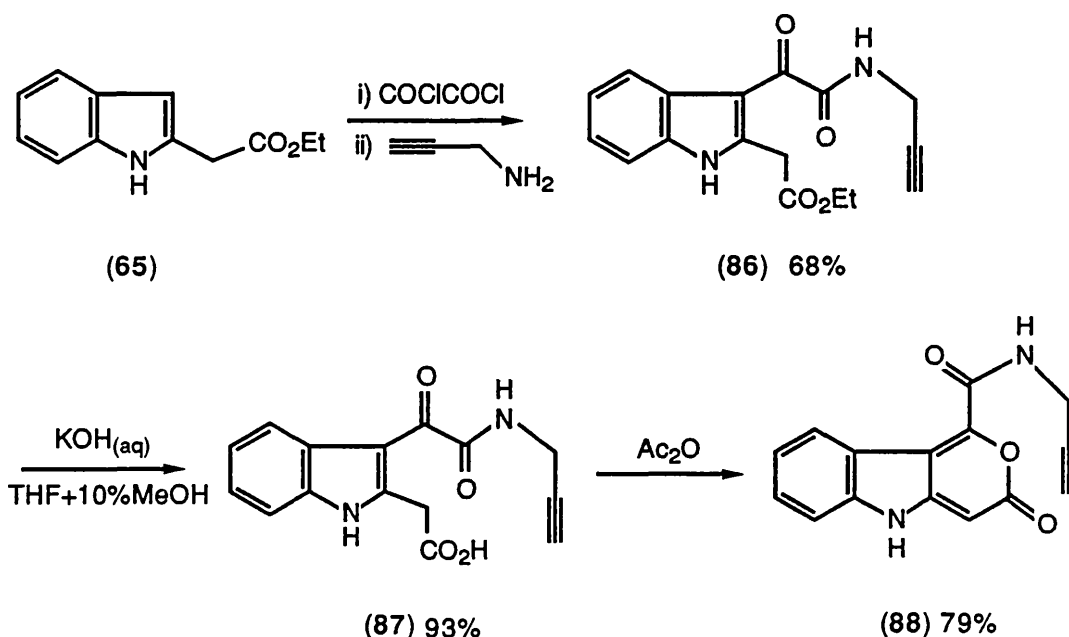


However, unlike indole-3-glyoxalyl chloride, this was not a stable solid but a red oil. We felt that we needed to trap this intermediate immediately with an appropriate amine. Thus model studies were undertaken to investigate the potential of this route to the staurosporine aglycone.

3.3 Model studies

Four different amines were used to trap the indole-3-glyoxalyl chloride intermediate (85). The first of these was propargylamine to give ester (86) in 68% yield (Scheme 3.8). Selective base hydrolysis of the ester over the amide, using a 2 M solution of potassium hydroxide, proceeded smoothly to give the acid (87) in 93% yield. This was cyclodehydrated by stirring in acetic anhydride at room temperature for 45 h. The pyranoindolone (88) precipitated out during the course of the reaction. This was filtered off and washed with ether.

Scheme 3.8

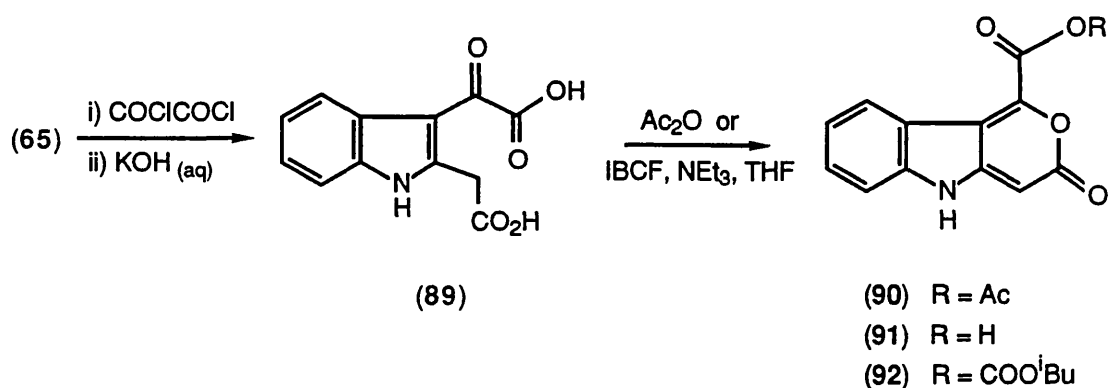


The pyranoindolone (88) was very different from the pyrano[4,3-*b*]indol-3-ones (58) described in Chapter 2. It was bright yellow in colour. The 4-H proton in the ^1H NMR spectrum had a chemical shift of δ 5.85 ppm and the lactone carbonyl stretch in the IR spectrum was at 1693 cm^{-1} . Furthermore, it was insoluble in most solvents and only appreciably soluble in THF, DMSO, and DMF. It was also fluorescent in solution, unlike (58). Thus (88) appeared to be

comparable in terms of physical properties and spectroscopic data to the pyrano[3,4-*b*]indol-3-ones (52). Another interesting detail in the ^1H NMR spectrum was the large downfield shift of 9-H in (88) compared with in (87). The same effect is seen in the chemical shift of 4-H in staurosporine. This is presumably due to the shielding effect of the amide carbonyl on 9-H, once the pyrone ring is formed.

A slightly modified route was also attempted to synthesise (88). Thus, ethyl indol-2-ylacetate was treated with oxalyl chloride and the resulting glyoxalyl chloride (85) was hydrolysed directly to the diacid (89) by treatment with aqueous potassium hydroxide. This was difficult to purify because of its high polarity. Nevertheless, we stirred the crude reaction mixture in acetic anhydride and obtained a mixture of two compounds which we tentatively assigned as (90) and (91) on the basis of their spectroscopic data (Scheme 3.9). The mixture was again extremely difficult to purify due to its insolubility and high polarity. We also tried treating (89) with either one or two equivalents of isobutyl chloroformate to form either (91) or (92) respectively (Scheme 3.9). The result, on using two equivalents of isobutyl chloroformate, was a messy reaction mixture. When one equivalent of isobutyl chloroformate was used, (91) was formed. However the reaction was not particularly clean, and it was difficult to purify the product.

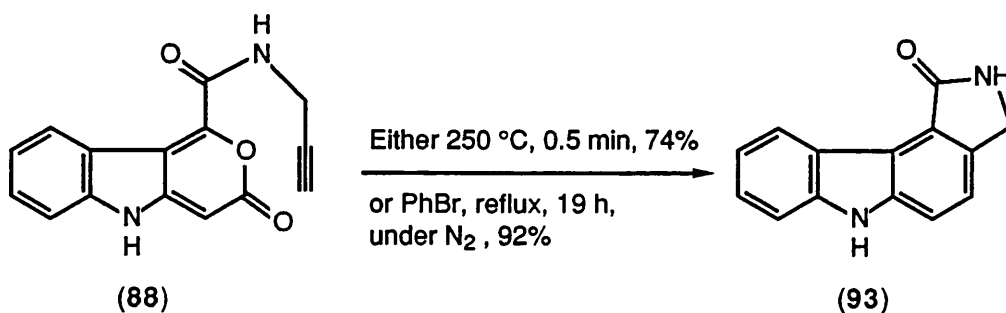
Scheme 3.9



Both the mixture obtained from the reaction with acetic anhydride, and the impure compound obtained from the IBCF reaction were stirred with propargylamine and DCC, to try and form (88). Unfortunately, these reactions were both unsatisfactory. The pyranoindolone from the IBCF reaction gave no product at all; and the mixture of (90) and (91) gave less than 10% of (88). Thus we felt that it was not worth pursuing this route further, and that the method shown in Scheme 3.8 was preferable.

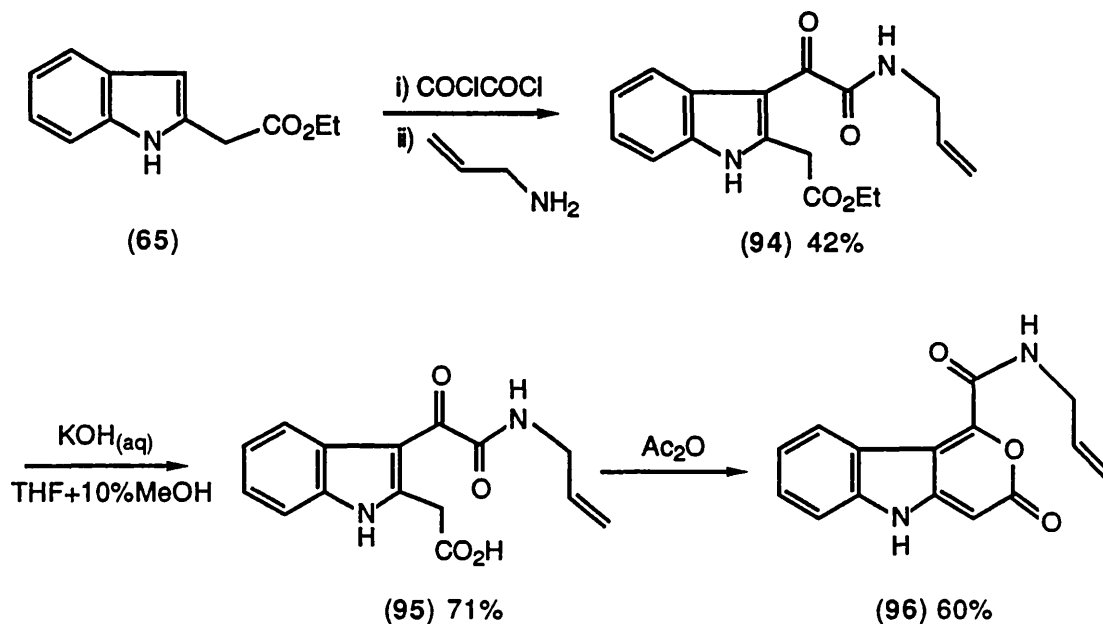
Having synthesised (88), we tried the intramolecular Diels-Alder reaction by refluxing the pyranoindolone in chlorobenzene. However, after 48 h in refluxing chlorobenzene only starting material was recovered. The pyranoindolone (88) was not soluble in chlorobenzene, even at reflux. Refluxing (88) in acetic anhydride, however, did yield carbazole products, although NMR revealed extensive N-acetylation had occurred. We initially got over this problem by heating the pyranoindolone (88) "neat" for 0.5 min at 250 °C using a Wood's metal bath. Chromatography of the residue gave the required carbazole (93) in 74% yield. We subsequently discovered that the pyranoindolone (88) was soluble in refluxing bromobenzene. Thus refluxing the pyranoindolone (88) in bromobenzene, under nitrogen, for 19 h, furnished us with carbazole (93) in a much cleaner reaction in 92% yield.

Scheme 3.10



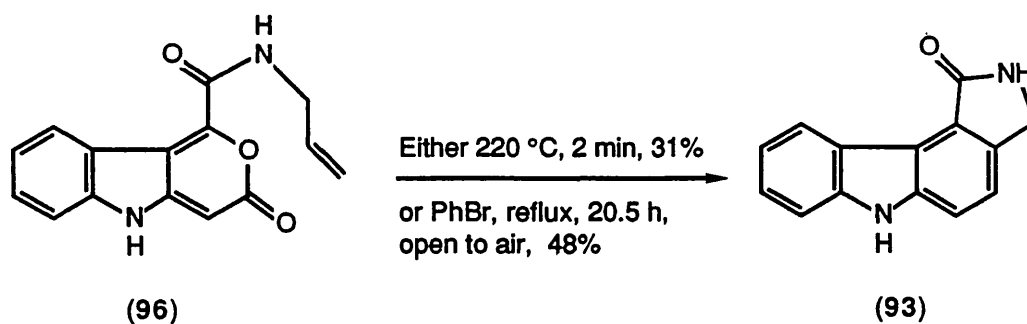
The second amine we tried in these model studies was allylamine. In this case the ester (94) was formed in 42% yield. Hydrolysis of (94) gave the acid (95) in 71% yield, which on dehydration gave the pyranoindolone (96).

Scheme 3.11

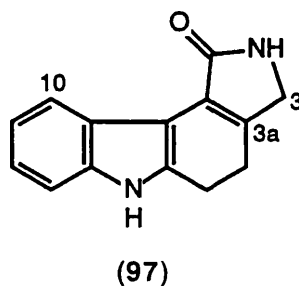


Now, in this case, Diels-Alder reaction followed by retro Diels-Alder reaction, to lose carbon dioxide, gives a dihydrocarbazole. Van Doren *et al.* have referred to the ease of oxidation of these compounds and we felt that air oxidation ought to be sufficient to form the carbazole.⁶⁷ Thus, we heated pyranoindolone (96) "neat" for 2 min at 220 °C in the presence of air. Chromatography of the residue gave the required carbazole (93) in only 31% yield. Refluxing pyranoindolone (96) in bromobenzene, in the presence of air, for 20.5 h gave (93) in 48% yield after chromatography.

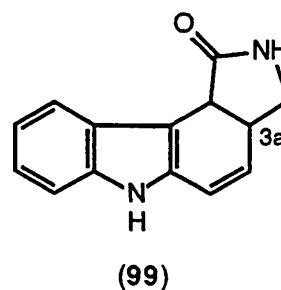
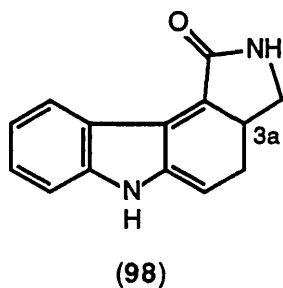
Scheme 3.12



Interestingly, heating pyranoindolone (96) in refluxing bromobenzene, under nitrogen, resulted in the isolation of a different compound, assigned as the dihydrocarbazole (97).

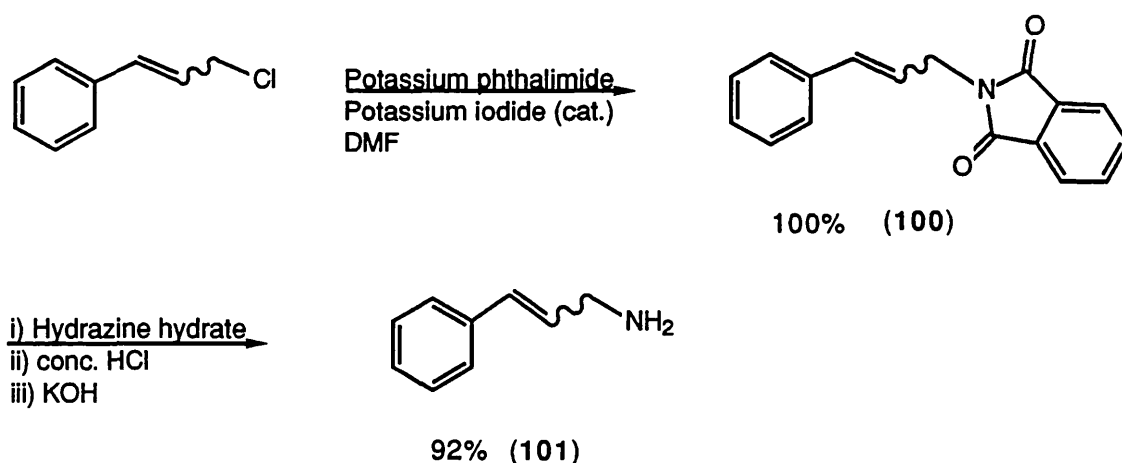


Presumably, this arises due to initial Diels-Alder reaction, loss of carbon dioxide, and [1,5] - hydrogen shift to give the more conjugated product. The ^1H NMR ruled out the alternative structures (98) and (99) due to lack of coupling between 3a-H and the methylene protons. It is particularly interesting to note the upfield shift of the 10-H proton to δ 8.51 ppm from δ 9.25 ppm in (93), thus suggesting that it is no longer in the plane of the carbonyl group. This may be due to twisting of the 6-membered ring, and hence of the adjoining 5-membered ring, by the saturated bridge.



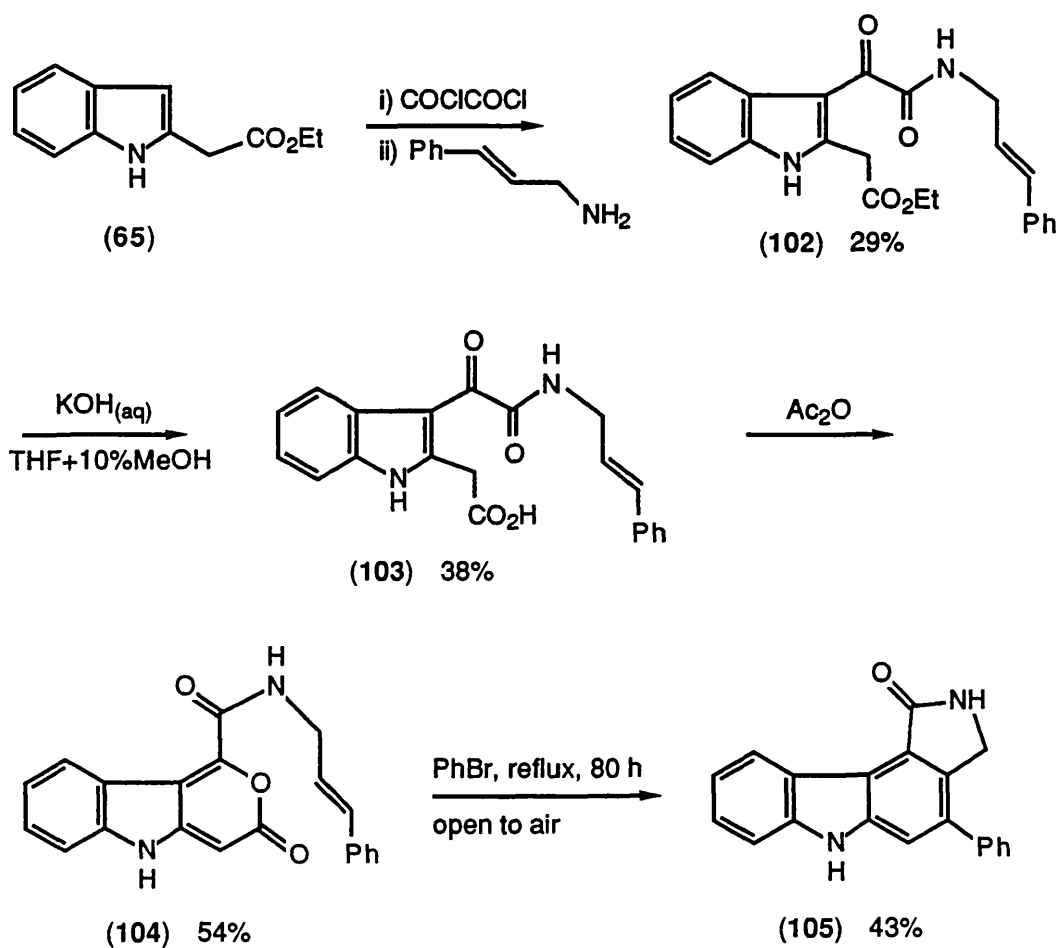
Cinnamylamine was also used as a trap for glyoxalyl chloride (85). It was made using standard procedures from cinnamyl chloride.⁹⁰ Thus cinnamyl chloride was reacted with potassium phthalimide in DMF, with a catalytic amount of potassium iodide, to give cinnamyl phthalimide (100) in quantitative yield. Deprotection of this phthalimide (100) using methylamine was attempted, but was unsatisfactory. However, deprotection using the Ing-Manske procedure, with hydrazine hydrate, yielded cinnamylamine (101).

Scheme 3.13



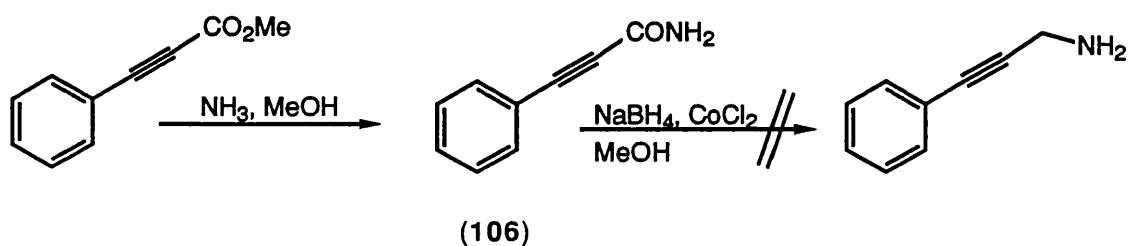
This was used directly in the formation of ester (102). The yield for this reaction was only 29%. Cinnamylamine is very reactive and in fact reacts very rapidly with even carbon dioxide from the air to form the carbamate.⁹¹ The hydrolysis step was also not clean and recrystallisation was necessary to purify the acid (103). The pyranoindolone (104) was formed under the same conditions as described previously, in 54% yield. Refluxing (104) in bromobenzene for 80 h, open to the air, gave carbazole (105) in 43% yield after chromatography.

Scheme 3.14



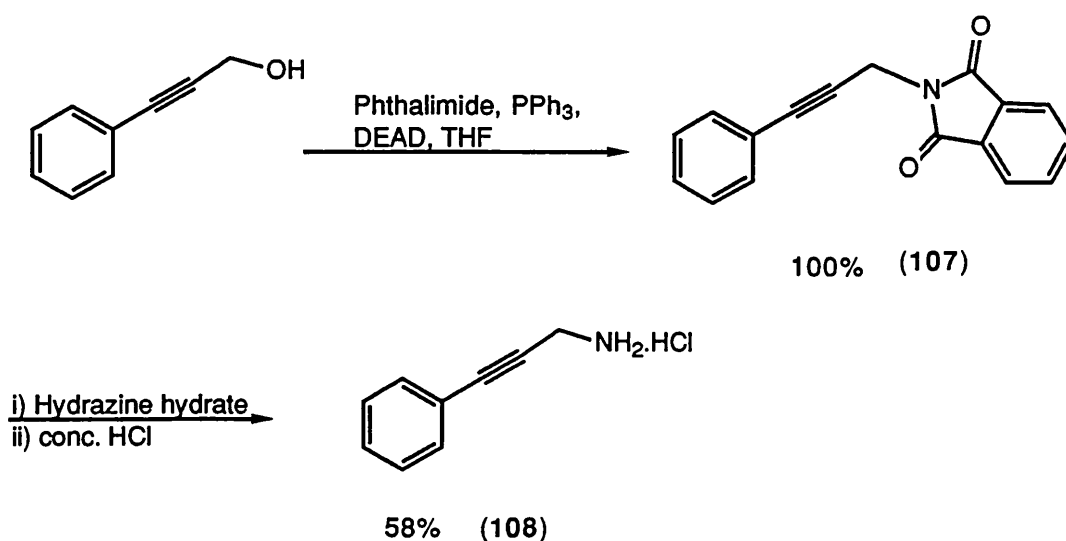
Our next task was to synthesise phenylpropargylamine. We tried initially to form phenylpropargyl chloride by treatment of the alcohol with thionyl chloride and pyridine.⁹² This however was unsatisfactory. We then formed the amide (106), by treatment of methyl phenylpropiolate with ammonia, but attempted reduction of this amide to the amine with sodium borohydride and cobalt (II) chloride failed.⁹³

Scheme 3.15



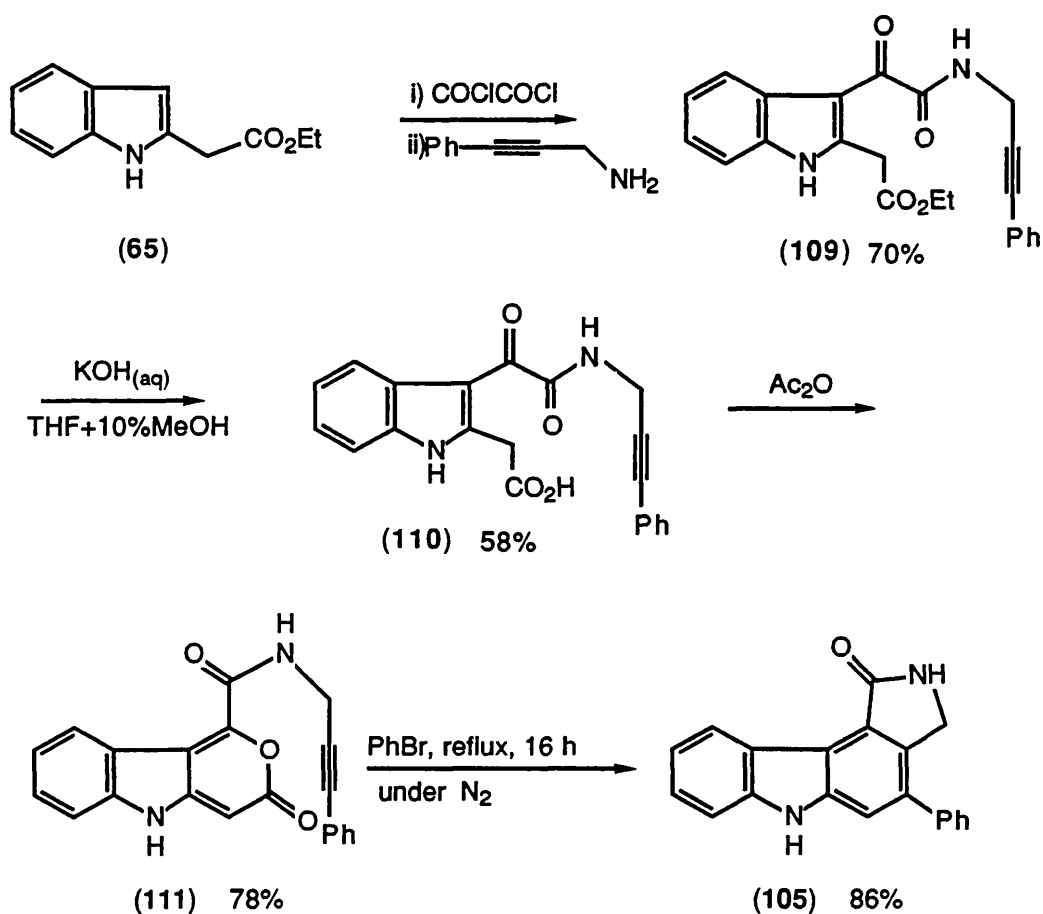
Finally, Mitsunobu reaction of phenylpropargyl alcohol and phthalimide gave phenylpropargylphthalimide (107).⁹⁴ This was deprotected on treatment with hydrazine hydrate to furnish us with phenylpropargylamine hydrochloride (108).

Scheme 3.16



This was treated with base to generate the free amine, which in turn was trapped with (85), to give (109) (70%). Hydrolysis and recrystallisation of the product gave pure acid (110) in 58% yield. The pyranoindolone (111) was again formed by dehydration with acetic anhydride in 78% yield. This, on refluxing in bromobenzene under nitrogen for 16 h, gave carbazole (105) in 86% yield.

Scheme 3.17



From these model studies, it would appear that the alkyne amines are preferable to the alkene amines. The former give better yields for ester formation compared to the latter. Furthermore, the carbazole is obtained in a cleaner reaction and in higher yield with the former.

3.4 Synthetic studies towards the staurosporine aglycone

The success of the model studies described in Section 3.3 prompted us to attempt a synthesis of the staurosporine aglycone. Thus we required an amine with appropriate *ortho* functionality, which could eventually be converted to a nitrene or a nitrene-type intermediate, to enable us to effect ring closure to form the second indole ring.

An azide as this *ortho* functionality is, of course, the obvious choice. Furthermore, we felt that if we could make the pyranoindolone (84), we could probably achieve the Diels-Alder reaction and subsequent aromatisation by loss of carbon dioxide at a low temperature, and the nitrene generation and subsequent insertion at a higher temperature, by choice of an appropriate solvent. Thus three rings would be made in one pot.

The alternative to the azide is an *o*-nitro functionality. This may be deoxygenated using a phosphorus reagent and the nitrene-type intermediate formed would presumably undergo insertion into the aryl CH bond to give an indolocarbazole.

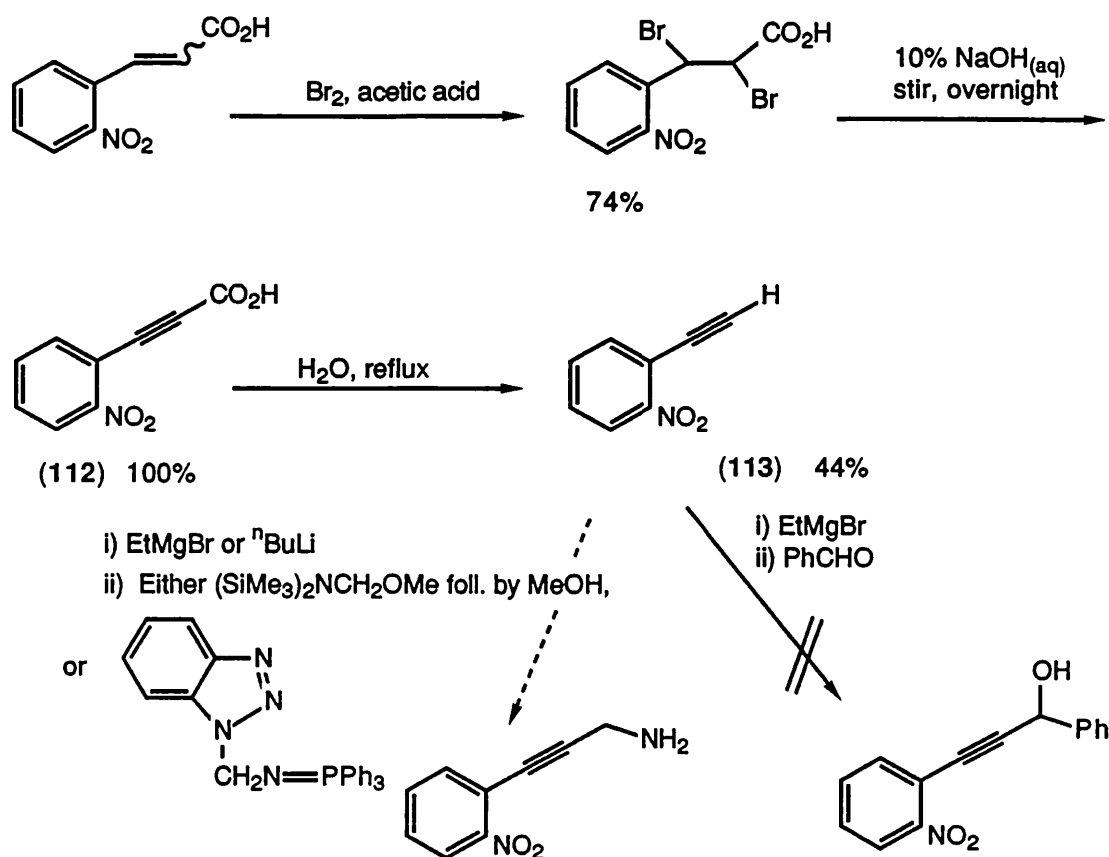
The third alternative is formation of the *o*-bromo compound and conversion of this, after formation of the carbazole, to the *o*-azido carbazole. Thus the nitrene may be generated, either on heating or by photochemical means, and ought to undergo CH insertion to form the staurosporine aglycone.

Now, for the intramolecular Diels-Alder reaction either an alkene or an alkyne may be used. The model studies in Section 3.3 have shown that an alkyne is probably preferable. Thus our first choice was formation of the appropriate alkyne amine.

3.4.1 Preparation of (*o*-nitrophenyl)propargylamine and its use towards a synthesis of the staurosporine aglycone

Our first target was to synthesise (*o*-nitrophenyl)propargylamine. We felt that we could probably achieve this by making *o*-nitrophenylacetylene, from *o*-nitrophenylpropionic acid, by using the procedure of Schofield and Simpson.⁹⁵ Our intention was to form the Grignard reagent of this terminal acetylene and quench this with an appropriate " $+CH_2NH_2$ " equivalent. The recently reported aminomethylating reagents shown in Scheme 3.18 appear to be suitable for these purposes.^{96, 97} Thus bromination of *o*-nitrocinnamic acid, followed by dehydrobromination on treatment with base, furnished us with *o*-nitrophenylpropionic acid (112) (74%).⁹⁵ This was easily decarboxylated on refluxing overnight in water, to give us *o*-nitrophenylacetylene (113) in 44% yield.⁹⁵ Before attempting the aminomethylation reaction, we first tried to form the Grignard with ethylmagnesium bromide and quenched the reaction mixture with benzaldehyde. Only unreacted benzaldehyde could be recovered from the reaction mixture. We suspected that this was due to the Grignard of *o*-nitrophenylacetylene probably being incompatible with the aromatic nitro group in the same molecule. Since both the aminomethylating reagents require formation of either a Grignard or an aryl lithium, we decided that this route was unlikely to be successful.

Scheme 3.18



However, we felt that we might be able to trap the anion of *o*-nitrophenylacetylene, generated on decarboxylation of *o*-nitrophenylpropionic acid (112), *in situ* with formaldehyde. But, as one would expect, refluxing *o*-nitrophenylpropionic acid in formaldehyde only resulted in a polymeric mixture being formed.

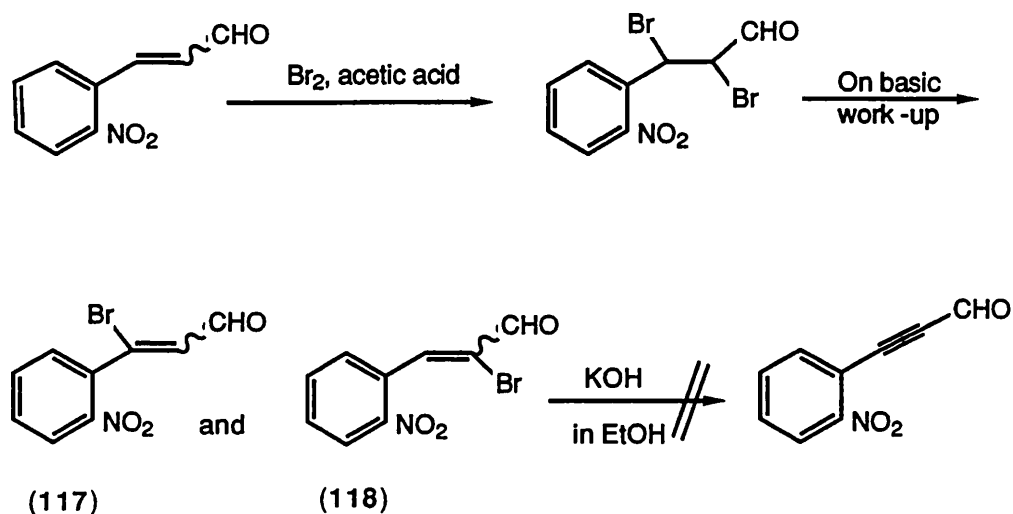
We decided that since *o*-nitrophenylpropionic acid had the correct carbon chain length, we ought to try and reduce the carboxylic acid to the correct oxidation level, instead of decarboxylation to (113). With this in view, we formed the methyl ester (114) of *o*-nitrophenylpropionic acid, but reduction of this with lithium aluminium hydride was unsatisfactory. However, formation of the acid chloride of *o*-nitrophenylpropionic acid with thionyl chloride and reduction with sodium borohydride was successful. This reaction, though, was not consistently reproducible. The side product (*o*-nitrophenylacetylene) was often the major or the sole

product. HCl also easily added across the double bond. We felt, therefore, that we needed a more reliable procedure to form this alcohol. Initially, we tried to form the acid chloride at room temperature with oxalyl chloride. This, however, was unsuccessful, so we used DMF as a catalyst.⁹⁸ This did succeed in forming the acid chloride in only a few minutes, however, HCl added across the triple bond very easily. We also tried to eliminate the HCl generated under the reaction conditions by forming the sodium salt of *o*-nitrophenylpropionic acid with sodium hydride, before adding oxalyl chloride or thionyl chloride to generate the acid chloride. However, the starting acid was regenerated, presumably due to the residual HCl present in the oxalyl chloride and thionyl chloride. Along the same lines, we also tried to make the TBDMS ester (115) of *o*-nitrophenylpropionic acid so that we could subsequently convert it to the acid chloride under neutral conditions.⁹⁹ However, the reaction to form the ester was unsatisfactory. We also tried to form the mixed anhydride (116) of *o*-nitrophenylpropionic acid (112) with isobutyl chloroformate, as we felt that we could also reduce this to the alcohol with borohydride. Unfortunately, the reaction to form the mixed anhydride was not clean.

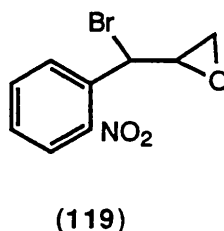
We felt that the combination of a triple bond and an *o*-nitro group was probably responsible for most of our problems with this compound. So we decided to reduce the nitro group to the amine and trap this *in situ* with acetic anhydride. Thus treatment with ammonia and zinc of *o*-nitrophenylpropionic acid (112) gave us a compound which was bright blue in ethereal solution. We thought that this was probably the nitroso compound. So the slightly more powerful combination of zinc and ammonium chloride solution was tried, and the reaction mixture was treated with acetic anhydride and pyridine to acetylate any amine *in situ*. The result was a very messy reaction.

Our next idea was to "protect" the triple bond by adding bromine across the corresponding double bond compound and to delay generation of the triple bond to a later stage. However, treatment of *o*-nitrocinnamaldehyde with bromine gave what tentatively could be assigned as the partially dehydrobrominated products (117) and (118), on work up. Treatment of this mixture with ethanolic potassium hydroxide was not successful in generating the alkyne aldehyde.

Scheme 3.19



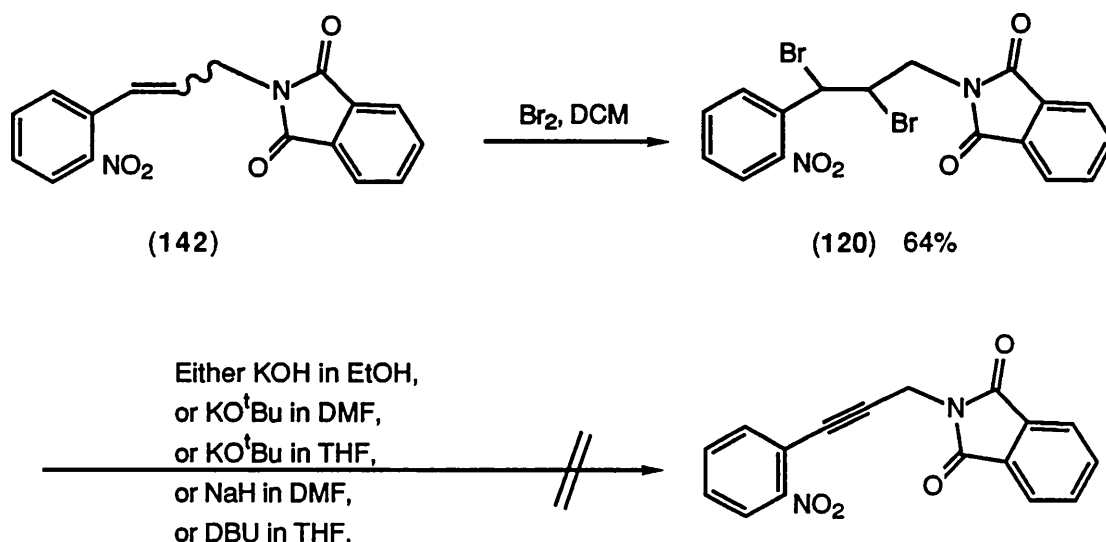
o-Nitrocinnamyl alcohol (141) (the synthesis of which is described in Section 3.4.4) was also treated with bromine. However, a mixture of products was again generated. We felt that this mixture probably included the epoxide (119), despite the neutral conditions.



Treatment of *o*-nitrocinnamyl phthalimide (142) (the synthesis of which is described in Section 3.4.4) with bromine did proceed cleanly to furnish us with the corresponding dibromocompound (120) in 64% yield. However, a variety of methods were tried to dehydrobrominate (120) but they were all unsuccessful. Potassium *t*-butoxide in THF was unsuccessful, as was ethanolic potassium hydroxide and sodium hydride in DMF. But DBU in THF underwent clean reaction with phthalimide (120). The product, however, was difficult to characterise but was clearly not the alkyne. The recently reported procedure by Grattan and

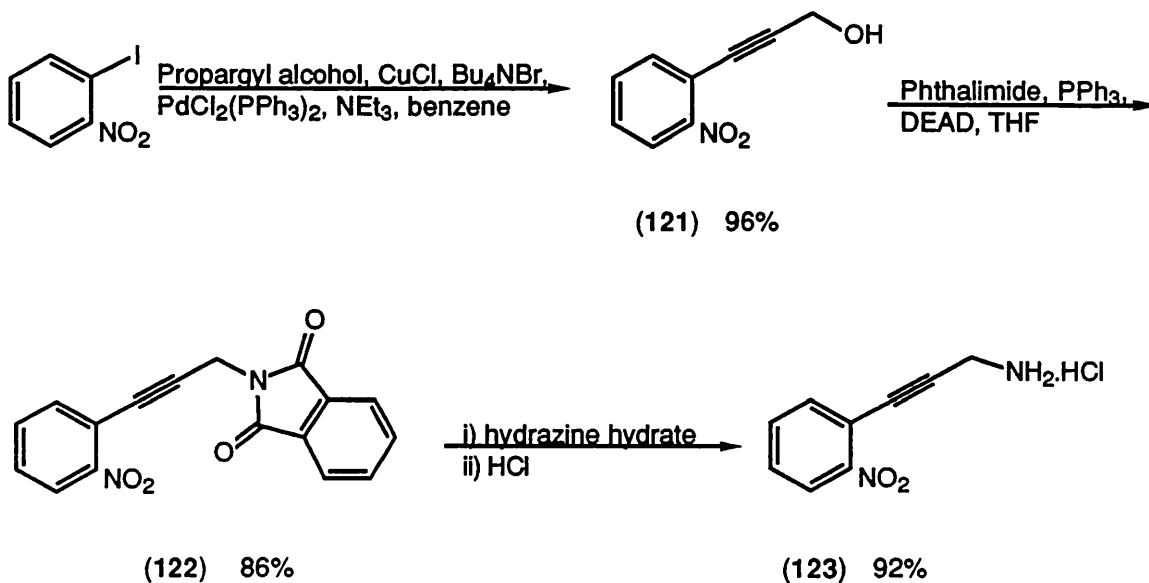
Whitehurst using potassium t-butoxide in DMF to generate an alkyne was also tried, but was not successful.¹⁰⁰

Scheme 3.20



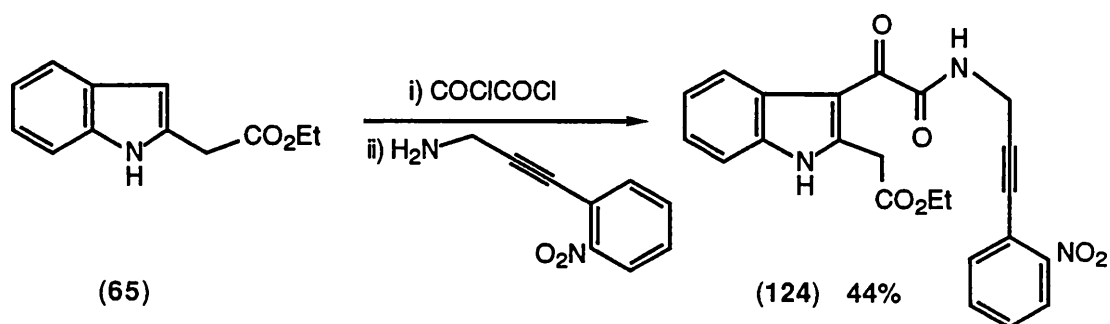
A literature search revealed that whilst the amine was not known, (o-nitrophenyl)propargyl alcohol (121) was a known compound. It had been made by some Russian workers using palladium coupling.¹⁰¹ They did not report any data on this compound, but a French patent, using the same methodology did report the NMR data.¹⁰² By following the procedure reported by Boomageen and Ponomarev, we were successfully able to synthesise (121) in 96% yield consistently. The alcohol could be converted to the phthalimide (122) using the excellent Mitsunobu conditions in 86% yield. Deprotection with hydrazine hydrate finally furnished us with (o-nitrophenyl)propargylamine (123).

Scheme 3.21



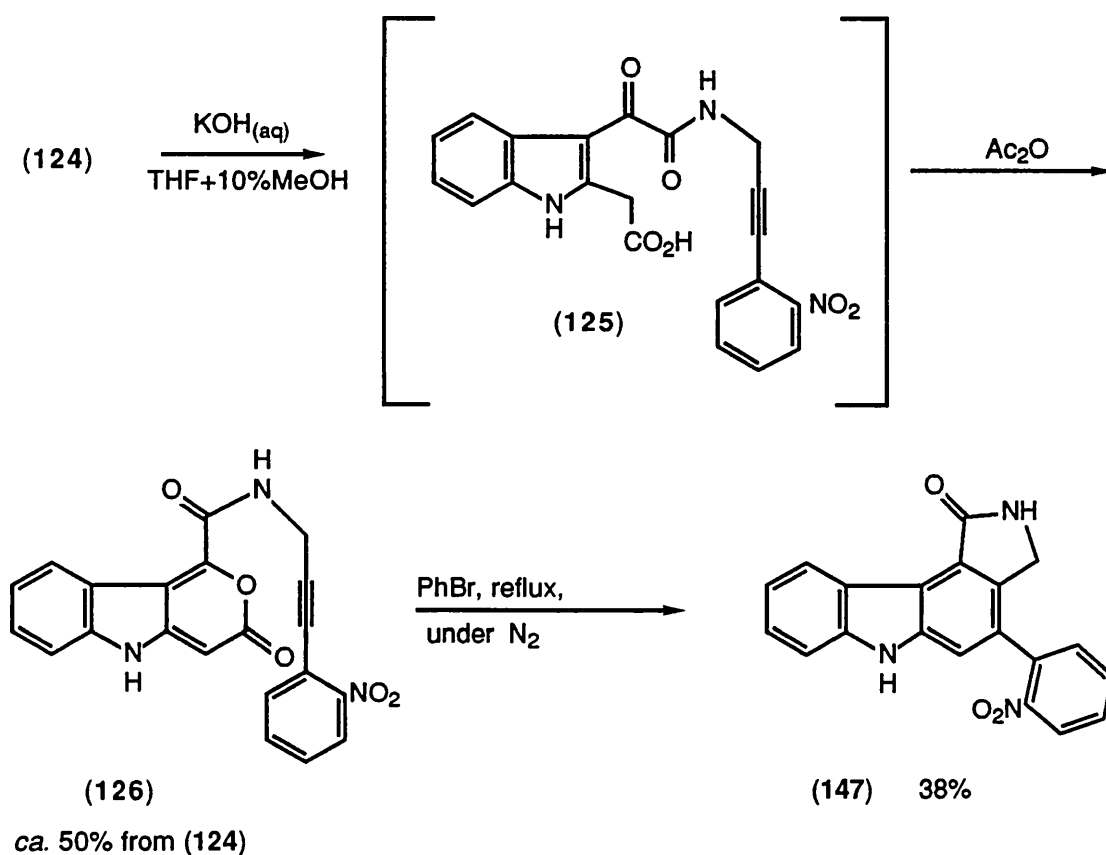
Having made the amine (123), it was directly used to quench the glyoxalyl chloride derivative (85). Despite half-a-dozen attempts at this reaction, the required acylated indole ester (124) could only be obtained in *ca.* 20% yield, after chromatography. We thought that perhaps this product was unstable to silica and therefore the reaction was repeated and the crude product obtained was directly recrystallised from ethanol. This resulted in an increase in the yield to 44%.

Scheme 3.22



The next step was hydrolysis of the ester. The usual procedure was used, but was unsatisfactory. We tried to vary the concentration of potassium hydroxide solution, but this appeared to make no difference. Dealkylation conditions, using trimethylsilyl chloride and sodium iodide, were also tried but did not give the required acid (125).¹⁰³ Milder hydrolysis conditions, using lithium hydroxide at 5 °C, did work, but were not reproducible. In the one instance that these conditions did work, the crude reaction mixture containing some acid (125) was directly dissolved in THF and stirred in the presence of acetic anhydride to give a product, which on the basis of NMR, was assigned as the pyranoindolone (126). This on heating in bromobenzene gave a product which we were later (Section 3.4.4) able to assign as the carbazole (147), in only 38% yield after chromatography.

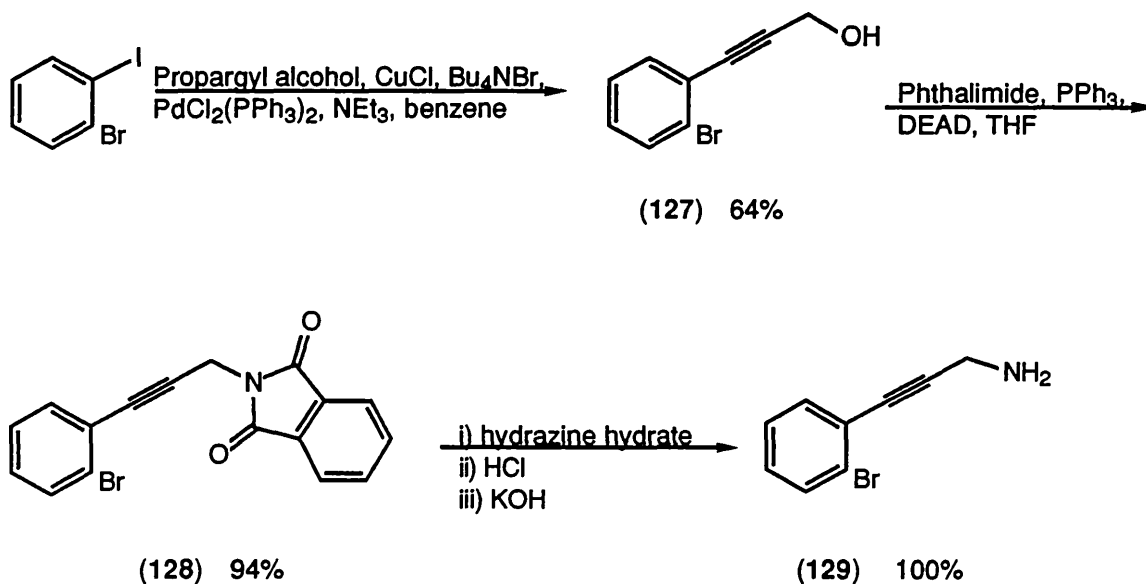
Scheme 3.23



3.4.2 Preparation of (o-bromophenyl)propargylamine and its use towards a synthesis of the staurosporine aglycone

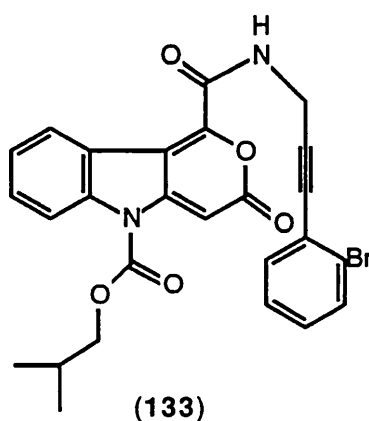
Having discovered a route to synthesise (o-nitrophenyl)propargylamine, we were easily able to synthesise (o-bromophenyl)propargylamine using the same methodology. Thus propargyl alcohol was coupled to 1-bromo-2-iodobenzene to furnish us with (o-bromophenyl)propargyl alcohol (127) in 64% yield. It proved surprisingly difficult to get this reaction to go to completion, and 1-bromo-2-iodobenzene was always recovered. The yield of (o-bromophenyl)propargyl alcohol was 95% if this recovered starting material was taken into account. This alcohol could be converted into the phthalimide (128) using Mitsunobu conditions in excellent yield (94%), and subsequent deprotection with hydrazine hydrate, furnished us with (o-bromophenyl)propargylamine (129).

Scheme 3.24

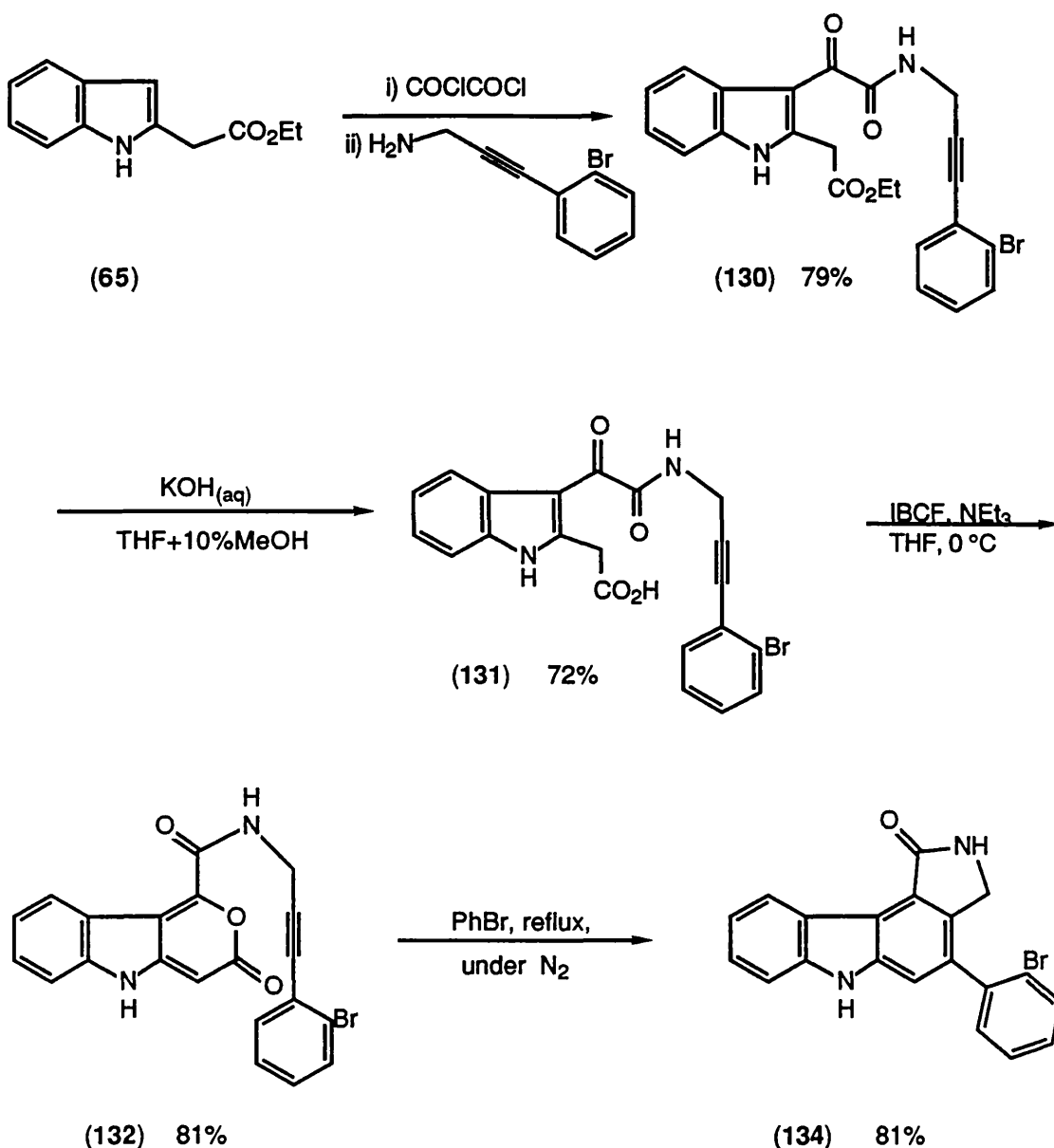


This was immediately coupled to the indole-3-glyoxalyl chloride (85) to give us the required acylated indole ester (130) in 79% yield. Hydrolysis proceeded smoothly in 72% yield. This

does suggest that it is the combination of a triple bond and an aromatic nitro group which is responsible for the unusual properties of the corresponding *o*-nitro ester (124). The pyranoindolone (132) could be made by stirring this acid (131) in THF with acetic anhydride at room temperature for 7 days. However the reaction was slow and even after 7 days did not go to completion. This resulted in the mixed anhydride contaminating the pyranoindolone (132). We found that a much cleaner and faster route to the pyranoindolone (81%) was by treatment of the acid (131) with isobutyl chloroformate and triethylamine in THF at 0 °C. The reaction was complete in 2 h. Since a slight excess of IBCF was used (1.05 equivalents), the main impurity was the N-protected pyranoindolone (133). Refluxing pyranoindolone (132) in bromobenzene under nitrogen for 76 h gave us the carbazole (134) in 81% yield.



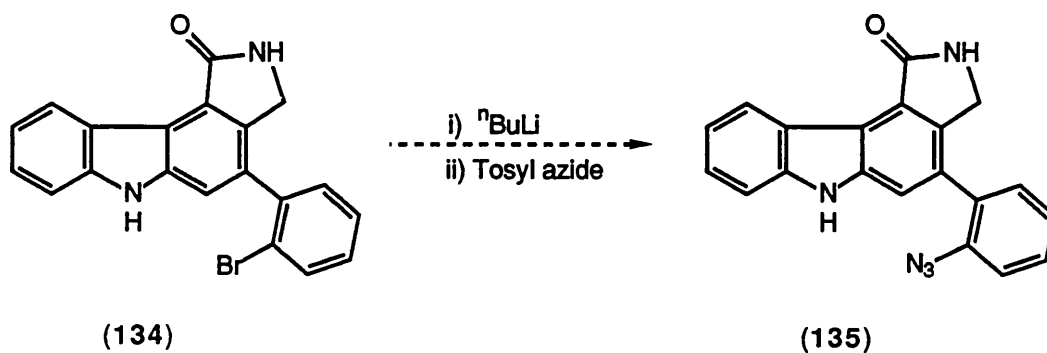
Scheme 3.25



Having obtained this carbazole in good overall yield (37.3%) from ethyl indol-2-ylacetate (65), the next step was to replace the bromine with an azide group. We felt that we could probably achieve this by halogen-metal exchange, followed by azido-de-metallation by treatment with an appropriate electrophilic azide reagent. Since we were trying to avoid protecting groups altogether, we felt that we could perhaps use three equivalents of *n*-butyl lithium to remove the amide and indole protons and replace the bromine; and then quenching

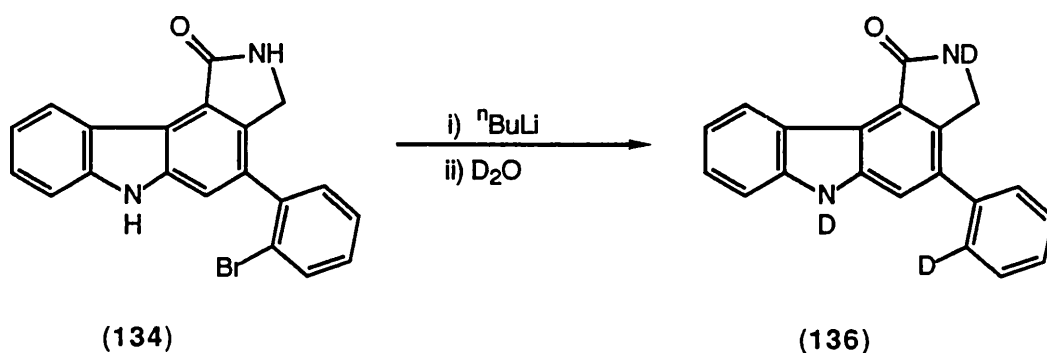
of this aryl lithium with one equivalent of tosyl azide ought to give us 4-(2'-azidophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (135) on work-up.

Scheme 3.26

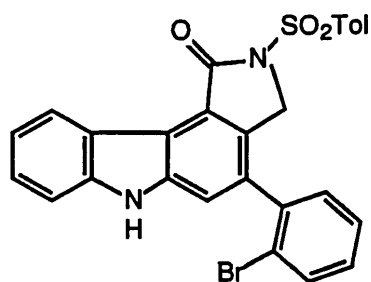


Since these carbazoles are fairly insoluble, we felt that there might be a problem with the insolubility of this "trianion". However, when excess *n*-butyl lithium was used and the reaction quenched with D_2O , the deuterated carbazole (136) was formed quantitatively.

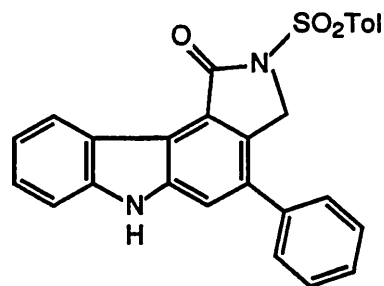
Scheme 3.27



So we proceeded with our intended reaction scheme shown in Scheme 3.26. The quenching with tosyl azide was not clean. A variety of products were formed in the reaction mixture. The major spot by t.l.c. was isolated and was tentatively assigned as a mixture of *N*-tosylated starting material (137) and *N*-tosylated carbazole (138). Starting material was also isolated.

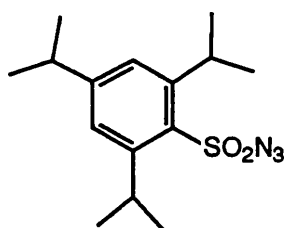


(137)



(138)

Thus we felt that the tosyl azide was probably too acidic and that rather than the metal being replaced by azide, the phenyl ring was being protonated. We felt that trisyl azide (139) would probably be more suited to our purposes, since it would eliminate this problem.



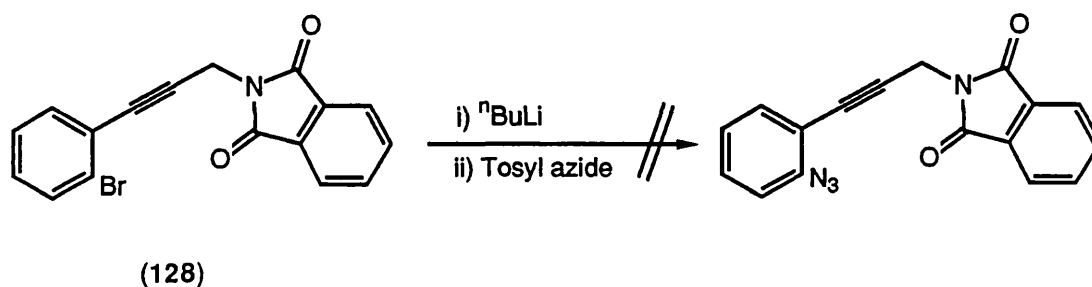
(139) Trisyl azide

Trisyl azide was made by following the usual procedure from 2,4,6-triisopropylbenzenesulphonyl chloride and sodium azide in excellent yield (100%).¹⁰⁴ 4-(2'-Bromophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (134) was treated with three equivalents of n-butyl lithium (which had been titrated to verify the molarity prior to use) and quenched with one equivalent of trisyl azide. Unfortunately, only starting material could be isolated from the reaction mixture. We also tried to form the trianion by using 6 equivalents of sodium hydride to remove any traces of water and to deprotonate the amide and indole protons, before adding 1.1 equivalent of n-butyl lithium at 0 °C. The reaction mixture was again quenched with trisyl azide. T.l.c. showed several fluorescent products. These were all isolated using column chromatography, but none showed an azide stretch in the IR spectra. The major compound isolated was starting material.

3.4.3 Attempted preparation of (*o*-azidophenyl)propargylamine

Since the *o*-nitro group appeared to be causing problems (Section 3.4.1), we felt that we ought to try forming the alternative *o*-azido compounds. We felt that it was best to try and introduce the azide at the phthalimide stage. However, treatment of N-((*o*-bromophenyl)propargyl) phthalimide (128) with one equivalent of *n*-butyl lithium and quenching with tosyl azide resulted in the recovery of tosyl azide and the isolation of a variety of baseline components. This does seem to suggest that the base is destroying the phthalimide rather than undergoing halogen-metal exchange.

Scheme 3.28



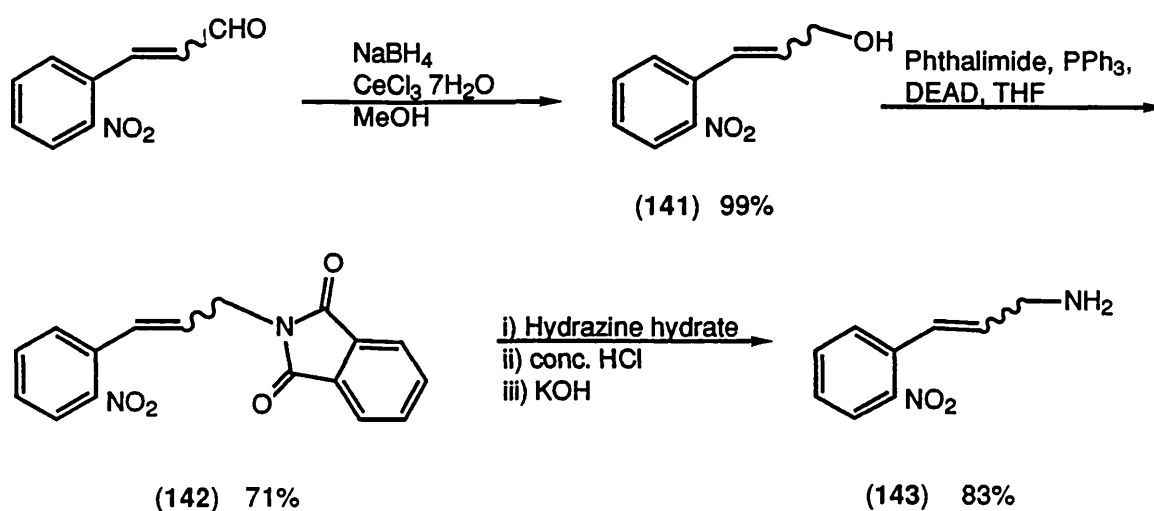
3.4.4 Preparation of *o*-nitrocinnamylamine and its use in a synthesis of the staurosporine aglycone

Despite the alkyne amines being preferable for the intramolecular Diels-Alder reaction, as discussed in Section 3.3, we also decided to try the reaction with *o*-nitrocinnamylamine. Thus our first task was to synthesise *o*-nitrocinnamylamine. Initially we tried to reductively aminate readily-available *o*-nitrocinnamaldehyde using ammonium acetate and sodium cyanoborohydride.¹⁰⁵ This however was unsuccessful.

Next, we tried to reduce the oxime (140) of *o*-nitrocinnamaldehyde with sodium borohydride and cobalt (II) chloride.⁹³ However, the reducing mixture was too powerful and it looked like the oxime, as well as the double bond and the aromatic nitro group were all being reduced. We did try the reaction at varying temperatures (0 °C, -15 to -5 °C, and -78 to -30 °C) but this did not appear to affect the outcome. The reaction probably proceeds *via* a boron-cobalt complex, which appears to be black in colour, and which seems to form at ca. -30 °C. However, if the reaction is worked up at this temperature, the same products are isolated, thus suggesting that it is too powerful a reducing mixture to selectively reduce the oxime.

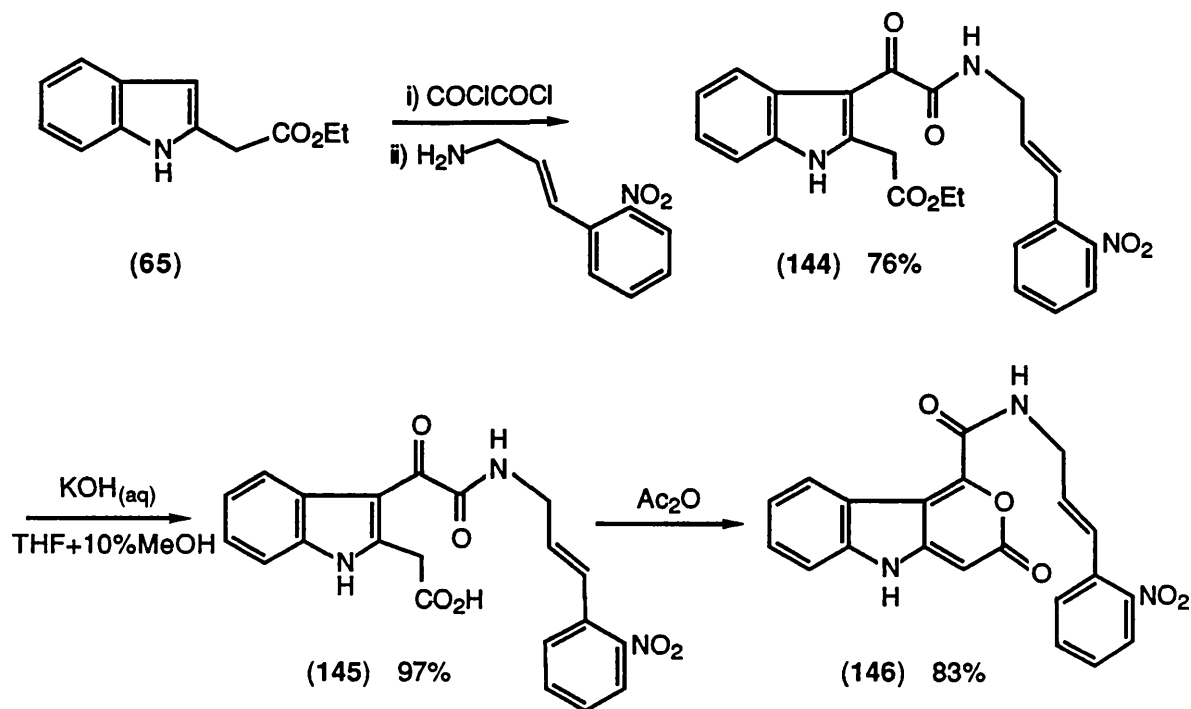
The third route we attempted to form *o*-nitrocinnamylamine did prove to be successful. Reduction of *o*-nitrocinnamaldehyde with sodium borohydride and cerium (III) chloride gave an excellent yield (99%) of *o*-nitrocinnamyl alcohol (141).¹⁰⁶ Treatment of this with phthalimide, triphenylphosphine, and diethyl azodicarboxylate in THF furnished us with the corresponding phthalimide (142). This was deprotected in the usual fashion with hydrazine hydrate to give *o*-nitrocinnamylamine (143) in 83% yield.

Scheme 3.29



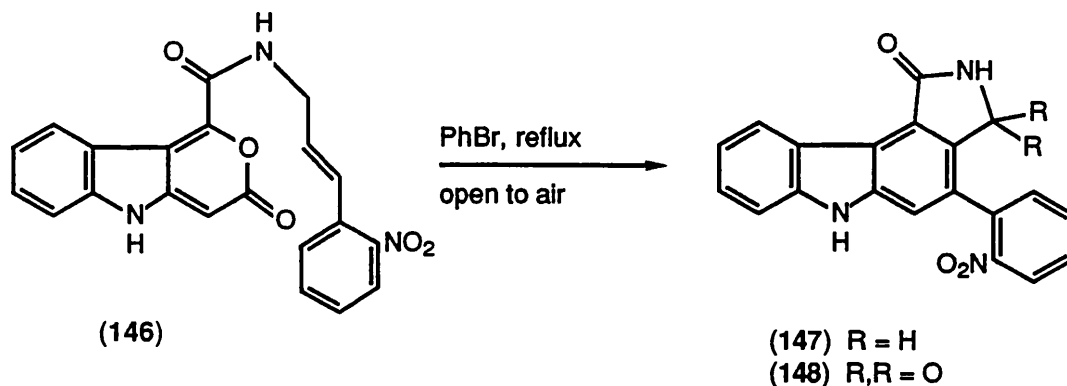
This was used directly as a quench for the indole-3-glyoxalyl chloride (85) to give ester (144). The yield of this reaction varied. If the reaction required chromatography, yields of *ca.* 40% were obtained. However, with practice, it was possible to obtain a clean reaction which did not require chromatography, and in this case, the yield was 76%. Hydrolysis of this ester proceeded smoothly in 97% yield. The corresponding pyranoindolone (146) could be formed on stirring the acid (145) in THF in the presence of acetic anhydride, at room temperature for 120 h. We also tried to form pyranoindolone (146) using IBCF, but the reaction was not as clean and the yield was also considerably lower (*ca.* 30%). If the reaction mixture was directly chromatographed the yield of the pyranoindolone was only *ca.* 50%. However, recrystallisation and chromatography of the filtrate to recover all the pyranoindolone gave a combined yield of *ca.* 80%. This does suggest that the pyranoindolone is decomposing to a certain extent on silica, as did the ester (144). The instability of ester (124) to silica, as well, suggests that the aromatic nitro group might be the cause of the problem.

Scheme 3.30



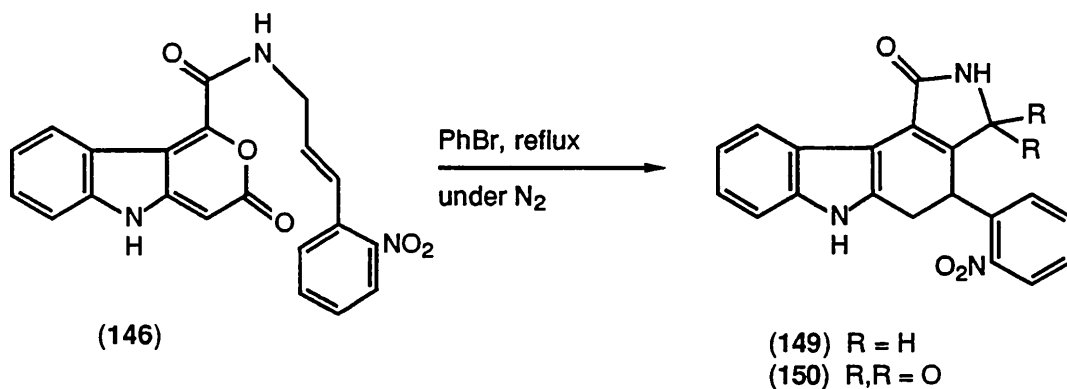
Pyranoindolone (**146**) was heated in refluxing bromobenzene, open to the air, to yield carbazole (**147**) after only 2 h. A major side product was the carbazole (**148**) in which the lactam had been oxidised to a cyclic imide. Both these carbazoles were unusual as they were not fluorescent under UV light. However, the spectroscopic data confirmed the structures. The reaction, however, was not clean and chromatography was required. This resulted in a yield of 72% still impure carbazole (**147**), which was further purified by reverse-phase H.P.L.C. The resulting yield was only 13%, due to decomposition of the carbazole.

Scheme 3.31



However, when the pyranoindolone was refluxed in bromobenzene under nitrogen, a new compound was isolated in a clean reaction. On the basis of spectroscopic data we assigned this as the dihydrocarbazole (149). This was formed in quantitative yield and none of the oxidised product (150) was present.

Scheme 3.32



We felt that we needed to investigate ways of oxidising (149) to the carbazole (147), in order to optimise this reaction. We required an oxidising agent that not only would oxidise (149) to the carbazole in a more controlled fashion, but would also not affect the readily oxidisable methylene group to form the cyclic imide (148). We felt that sulphur probably fulfilled these criteria, and so oxidations of (149) using sulphur under various reaction conditions were tried

(Table 3.2). We also investigated *in situ* oxidation of (149) by refluxing the pyranoindolone (146) and sulphur in various solvents (Table 3.3).

Table 3.2

Conditions	(149)
S (7 eq.), "neat", under N ₂ , 165-230 °C, 10 min.	ca. 4:1 of (149):(147) by NMR.
S (1 eq.), decalin, reflux (187-196 °C), under N ₂ , 30 min.	Only (147) by NMR.
S (4 eq.), 4-bromochlorobenzene, (m.p. 196 °C), under N ₂ , 10 min.	Only (147) by NMR, but "solvent" sublimes out of reaction mixture. Problems on large scale reaction.
S (1.8 eq.), PhCN, reflux (ca. 190 °C), under N ₂ , 30 min.	ca. 1:2 of (149):(147) by NMR.
S (7 eq.), PhCN, reflux (ca. 190 °C), under N ₂ , 2 h.	Mainly (147), but trace of (149) in NMR.

Table 3.3

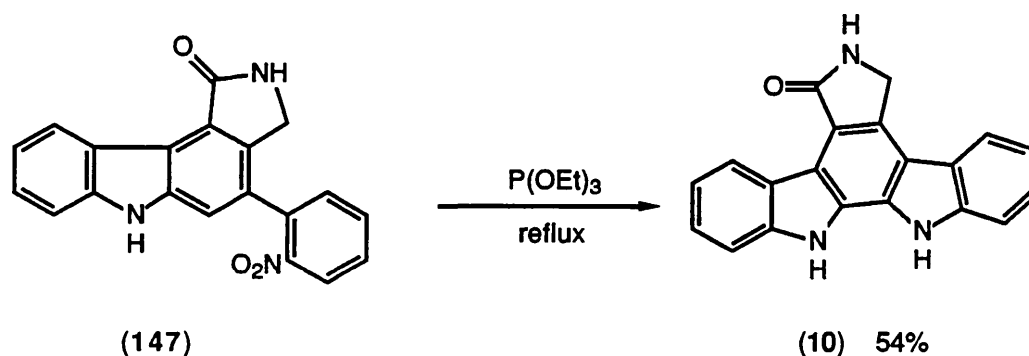
Conditions	(146)
S (1.3 eq.), PhCN, reflux (ca. 190 °C), under N ₂ , 15 min.	ca. 1:2:1 of (149):(147):(148) by NMR.
S (12 eq.), "neat", under Ar, 200-250 °C, 5 min.	ca. 1:2 of (147):(148) by NMR.
S (1 eq.), PhBr, reflux, under N ₂ , 1h.	Only (149) by NMR. Sulphur needs higher temperature to react.

As Tables 3.2 and 3.3 show, the oxidised carbazole (148) is always a side product when the pyranoindolone (146) is used, but there is no trace of it when the dihydrocarbazole (149) is used. Thus we felt that the simplest way of obtaining a higher yield of carbazole (147) was to first reflux the pyranoindolone (146) in bromobenzene under nitrogen, and then to reflux the resulting dihydrocarbazole (149) in bromobenzene, open to the air. This did indeed improve the yield of the reaction to 42% after chromatography. However, we still felt that carbazole (147) was being destroyed on the column since the reaction mixture before chromatography was much cleaner than indicated by the number of products isolated during chromatography. Thus we felt that it would be worth trying the next step on the crude reaction mixture to see if the overall yield was improved.

But firstly, we tried the insertion reaction on pure carbazole (147). Refluxing this in triethyl

phosphite for 1.5 h effected the final ring closure in 54% yield after chromatography to yield the staurosporine aglycone (10).¹⁰⁷

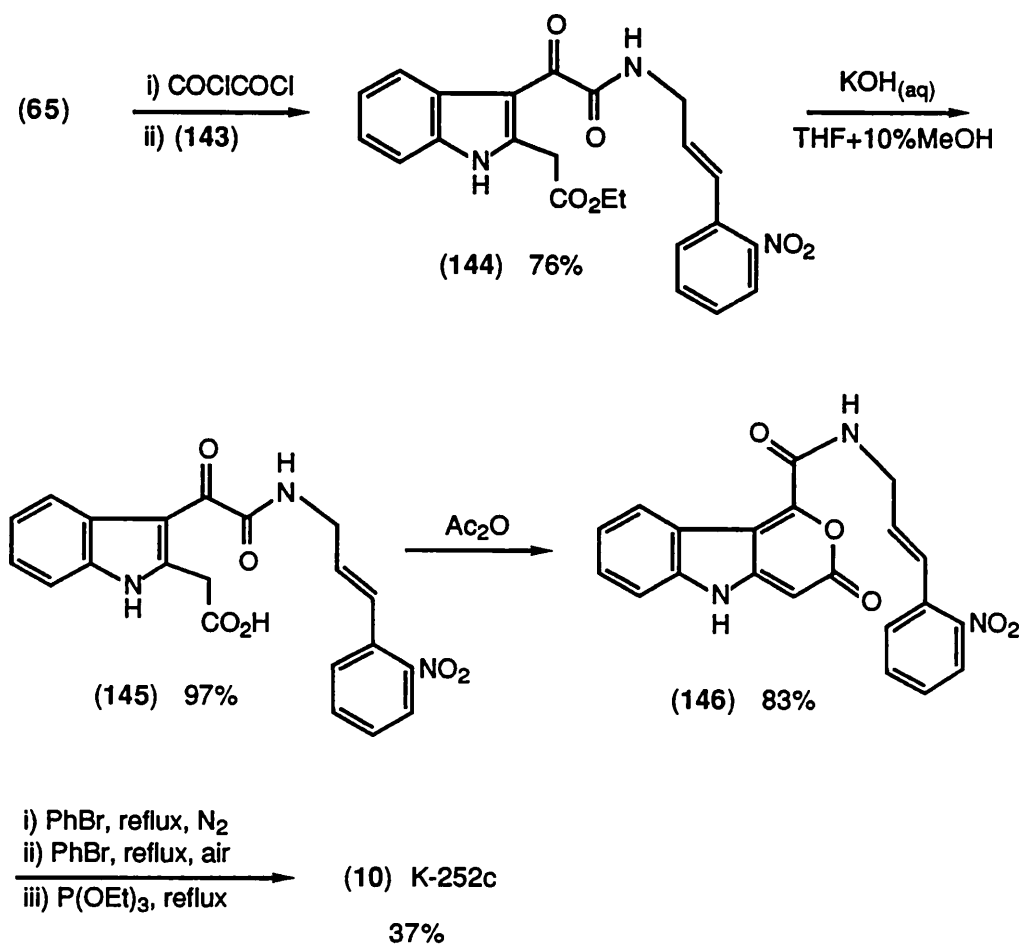
Scheme 3.33



Its spectroscopic properties closely matched those described in the literature. A trace of N-ethylation did also occur, but it was possible to purify the staurosporine aglycone by chromatography. When this final cyclisation was done on unpurified carbazole, the yield from the pyranoindolone (146) to the final product was increased to 37%. We decided that it was worth attempting the Diels-Alder reaction and this final ring closure in one pot. However, heating the pyranoindolone in triethyl phosphite at 110 °C to effect the Diels-Alder reaction and then at reflux to deoxygenate the nitro group resulted in a messy reaction mixture. Similarly, using 2.5 equivalents of triethyl phosphite in refluxing bromobenzene did not effect the ring closure in a clean reaction. We also investigated the use of triphenylphosphine, tributylphosphine, and HMPT as deoxygenating agents in bromobenzene respectively.¹⁰⁷ Unfortunately, triphenylphosphine was not reactive enough to deoxygenate the nitro group in refluxing bromobenzene even after 72 h. Tributylphosphine in refluxing bromobenzene also yielded only starting material. Using 2.2 equivalents of HMPT in refluxing bromobenzene resulted in the isolation of only starting material after 4 h. However, an excess of HMPT in refluxing bromobenzene showed only baseline material by t.l.c. after 0.5 h.

Thus our final route to the staurosporine aglycone is shown below (Scheme 3.34).

Scheme 3.34



3.5 Conclusion

We have described a concise synthesis of the staurosporine aglycone in Section 3.4.4 using a completely different approach to the indolocarbazole skeleton than those previously reported in the literature. Our synthesis does not use any protecting groups, and we are able to form the staurosporine aglycone in an acceptable yield of 22.6% in 6 steps from ethyl indol-2-ylacetate. This compares favourably with the only published synthesis to date of the aglycone reported by Sarstedt and Winterfeldt in 7 steps and 2.2% overall yield from indole-3-acetyl chloride.⁹ Furthermore, our methodology allows easy substitution of the indolocarbazole skeleton by varying either the starting indole or the amine or both to form differentially substituted indolocarbazoles.

CHAPTER FOUR

EXPERIMENTAL SECTION

4.1 General information

4.1.1 Solvents and reagents

Ether refers to diethyl ether which was dried by standing over sodium wire. Tetrahydrofuran was dried by standing over sodium wire, followed by distillation from potassium - benzophenone ketyl. Benzene and toluene were dried by standing over sodium wire. DMF was dried by stirring over anhydrous barium oxide at room temperature for 12 h, decanting, and distillation from oven dried alumina at reduced pressure. DMSO was dried by stirring over anhydrous barium oxide at room temperature for 2 h, decanting, and distillation at reduced pressure. Both dry DMF and DMSO were stored over 4 Å molecular sieves and under dry nitrogen. Chloroform, dichloromethane, and tetrachloromethane (unless required dry) were used as supplied. Dry dichloromethane, chloroform and tetrachloromethane were distilled from phosphorus pentoxide. Light petroleum refers to the fraction boiling in the range 40 - 60 °C, and was distilled before use. Triethylamine was distilled from sodium hydroxide. Hünig's base was dried by standing over potassium hydroxide. All other reagents and solvents were obtained from commercial suppliers and were used without purification.

4.1.2 Chromatographic procedures

Analytical thin layer chromatography (t.l.c.) was performed on Merck Kieselgel 60 GF₂₅₄ aluminium - backed plates, or Merck aluminium oxide 60 GF₂₅₄ neutral (Type E) aluminium backed plates. Visualisation was either by viewing under UV light (at 254 and / or 360 nm), or by staining with molybdate or permanganate dips, or with iodine vapour, or with Ehrlich's reagent.

Flash chromatography was carried out using either Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with either hand bellows or an aquarium pump. Gravity chromatography was carried out using Merck Kieselgel 60 (70 - 230 mesh) silica.

Samples were applied preadsorbed on silica or as a saturated solution in the appropriate solvent. Crystallisation of solids after isolation by chromatography was only attempted if necessary.

Analytical and preparative H.P.L.C. was carried out at Glaxo Group Research (Greenford); the latter in the Research Chromatography - Chemical Analysis Department.

4.1.3 Spectroscopic techniques

Infrared spectra were recorded using a Perkin Elmer 1710 FT spectrometer or a Nicolet 5SXC FT spectrometer, with internal calibration. Spectra were recorded as either solutions in chloroform or bromoform, or as thin films, or as nujol mulls. Thin films and nujol mulls were recorded between sodium chloride plates.

Ultraviolet - visible spectra were recorded using a Philips PU8740 UV / VIS scanning spectrophotometer. Pyranoindolone spectra were recorded in tetrahydrofuran solution and carbazole spectra were recorded in methanol solution.

Proton NMR spectra were recorded using Bruker WM 250 (250 MHz), Jeol GSX 270 (270 MHz), or Bruker AM 500 (500 MHz) instruments. All spectra employed a homonuclear lock (deuterium of the solvent). ^{13}C NMR spectra were recorded on a Bruker AM 500 (125 MHz) or Jeol GSX 270 (67.9 MHz). Signals are measured in ppm, and referenced to the residual peak of the solvent. In the case of proton spectra, this is 7.260 ppm for deuterio chloroform, 2.040 ppm for deuterio acetone, or 2.490 ppm for deuterio dimethyl sulphoxide. In the case of D_2O , DSS (sodium salt of 3-(trimethylsilyl)-1-propanesulphonic acid) was used as the reference peak at 0 ppm. They are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), double doublets (dd) etc.

Mass spectra were recorded at low resolutions using a VG Micromass 7070B instrument (Imperial College) or a VG Analytical ZAB-E instrument (courtesy of the SERC mass spectrometry centre at Swansea) in the electron impact mode at 70 eV, using a direct insertion probe. High resolution EI and FAB mass spectra were recorded on the same two instruments.

The matrix employed for obtaining FAB spectra is quoted.

4.1.4 Other data and Instrumentation

Melting points were determined on a Reichert Kofler hot stage apparatus, with thermometers as supplied, and are uncorrected.

Microanalyses were carried out by Mr. K. Jones and his staff in the Imperial College Chemistry Department microanalytical laboratory.

4.2 Experimental for Chapter 2

1-Methylpyrano[3,4-b]indol-3-one (52a).—For preparation, see reference 55; λ_{max} . (tetrahydrofuran) 243 (ϵ 29 329), 273 (17 622), 435 (7 195), and 462 nm (7 622); δ_{C} (67.9 MHz; $(\text{CD}_3)_2\text{SO}$) 16.4 (q, J_{CH} 130 Hz, CH_3), 95.5 (d, J_{CH} 171 Hz, 4-C), 111.3 (dd, J_{CH} 166 Hz, $^2J_{\text{CH}}$ 8 Hz, aromatic C), 118.9 (dd, J_{CH} 162 Hz, $^2J_{\text{CH}}$ 7 Hz, aromatic C), 119.3 (m, quaternary C), 124.4 (dd, J_{CH} 162 Hz, $^2J_{\text{CH}}$ 8 Hz, aromatic C), 124.9 (quintet, $^2J_{\text{CH}}$ 4 Hz, quaternary C), 132.9 (m, aromatic C), 144.3 (q, $^2J_{\text{CH}}$ 7 Hz, 1-C), 146.1 (m, quaternary C), 147.9 (m, quaternary C), and 162.5 (d, $^2J_{\text{CH}}$ 4 Hz, C=O).

2-Methyl-1-phenylsulphonylindole (60) and 3-Chloro-2-methyl-1-phenylsulphonylindole (60a).—To a cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 0.60 g) in tetrahydrofuran (10 ml), a solution of 2-methylindole (1.98 g, 15 mmol) in tetrahydrofuran (20 ml) was added. The solution was allowed to warm up to room temperature and left until hydrogen evolution ceased (about 1 h). The solution was then recooled to 0 °C, and benzenesulphonyl chloride (2.2 ml, 17 mmol) was added. After addition was complete, the reaction mixture was stirred for 10 min and then worked up by the addition of water. The mixture was extracted with ether. The ethereal extracts were dried (Na_2SO_4) and the solvent was evaporated to yield an oil. This was triturated with a 2:1 mixture of light petroleum and ether and cooled. The crystals obtained were recrystallised from a 1:1 mixture of dichloromethane and light petroleum to give a 4:1 mixture of (60a) and (60) (1.16 g, 26%). This mixture was inseparable by chromatography; ν_{max} (Nujol) 1595, 1238, 1220, 1189, 1151, 1120, 1101, 1022, and 954 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 2.60 (s, Me in (60)), 2.62 (s, Me in (60a)), 6.36 (s, indole 3-H in (60)), 7.18-7.60 (m, aromatic H), 7.75-7.80 (m, aromatic H), 8.16 (d, J 8 Hz, aromatic H in (60)), and 8.22 (~d, J 8 Hz, aromatic H in (60a)); m/z 307 / 305 (M^+ (60a), 15 / 40%), 271 (M^+ (60), 22%), 166 / 164 (M^+ (60a) - PhSO_2 , 33 / 100), and 130 (M^+ (60) - PhSO_2 , 39).

Ethyl 4-(2'-Nitrophenyl)acetoacetate (62).—Thionyl chloride (11.5 g, 96.4 mmol) was added to 2-nitrophenylacetic acid (8.72 g, 48.2 mmol) and the suspension was heated to 50 °C and stirred at this temperature until effervescence ceased. The resulting solution was concentrated *in vacuo* and the residue dissolved in dry dichloromethane (30 ml). This was added dropwise to a stirred solution of Meldrum's acid (6.94 g, 48.2 mmol) and Hünig's base (16.8 ml, 96.4 mmol) in dichloromethane (200 ml), under nitrogen, at 0 °C. After addition was complete, the solution was stirred for 1 h at 0 °C, then allowed to warm to room temperature and stirred for a further 1 h. The reaction mixture was poured into a separating funnel and washed, in turn, with dilute hydrochloric acid, water, brine, and dried (MgSO₄). The organic extracts were concentrated *in vacuo*. Absolute ethanol (200 ml) was added to the crude acyl-Meldrum's acid complex and the suspension refluxed until effervescence ceased. The solution was concentrated *in vacuo* and the resulting orange oil triturated with ethanol and left in the freezer overnight. The crude solid was recrystallised from ethanol to give the title compound (62) (10.28 g, 85%), as a beige powder, m.p. 55.5-57 °C (lit.,⁷⁷ m.p. 56 °C) (Found: C, 57.4; H, 5.0; N, 5.6. Calc. for C₁₂H₁₃NO₅: C, 57.4; H, 5.2; N, 5.6%); ν_{max} (Nujol) 1749 (ester C=O), 1723 (ketone C=O), 1613, 1579, 1522 (aromatic NO₂), 1409, 1347 (aromatic NO₂), 1308, 1275, 1204, 1152, 1067, and 1030 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.33 (3 H, t, *J* 7 Hz, ethoxy -CH₃), 3.63 (2 H, s, CH₂COOEt), 4.23 (2 H, q, *J* 7 Hz, ethoxy -CH₂), 4.26 (2 H, s, benzyl -CH₂), 7.31 (1 H, dd, *J* 8.6 and 1.6 Hz), 7.48 (1 H, td, *J* 8.6, 8.6, and 1.6 Hz), 7.61 (1 H, td, *J* 8.6, 8.6, and 1.6 Hz), and 8.14 (1 H, dd, *J* 8.6 and 1.6 Hz); *m/z* 251(*M*⁺, 1.4%), 164(21), 137(45), 120(53), 115(100), 87(32), 43(41), and 29(73).

Ethyl Indol-2-ylacetate (65).—Ethyl 4-(2'-nitrophenyl)acetoacetate (62) (2.68 g, 10.7 mmol) was dissolved in acetone (30 ml) and transferred to a separating funnel. Ammonium acetate solution (4 M; 288 ml) was added, followed by aqueous titanium (III) chloride (15% w/v; 77 ml). The mixture was shaken for 7 min. The resulting dark green solution was extracted with ether (4 x 100 ml) and the organic extracts washed with water, brine and dried (MgSO₄). The

ethereal extracts were concentrated *in vacuo* and the residue chromatographed (dichloromethane) to give the title compound (65) (1.63 g, 75%), m.p. 28-31 °C; ν_{max} .(film) 3461 (NH), 1729 (C=O), 1527, 1457, 1220, and 1029 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.30 (3 H, t, J 7 Hz, ethoxy -CH₃), 3.82 (2 H, s, CH₂COOEt), 4.24 (2 H, q, J 7 Hz, ethoxy -CH₂), 6.36 (1 H, s, 3-H), 7.08 (1 H, t, J 8 Hz), 7.16 (1 H, t, J 8 Hz), 7.36 (1 H, t, J 8 Hz), 7.54 (1 H, d, J 8 Hz), and 8.70 (1 H, br, NH); m/z 203(M^+ , 45%) and 130(100).

Indol-2-ylacetic acid (59).—Potassium hydroxide solution (2 M; 2.9 ml) was added to a solution of ethyl indol-2-ylacetate (65) (118 mg, 0.58 mmol) in tetrahydrofuran : methanol (9 : 1) (6 ml) and stirred at room temperature for 2.5 h. Water (100 ml) was added and the aqueous mixture extracted with ether. The aqueous phase was acidified (pH 1.5) with dilute hydrochloric acid and extracted with ethyl acetate. These extracts were washed with brine, dried (MgSO_4), and concentrated *in vacuo* to yield the title compound (59) (102 mg, 100%), m.p. 97-100 °C (dec.) (lit.,⁷⁷ m.p. 93 °C (dec.)); ν_{max} .(Nujol) 3393 (NH), 3400-2400 (br, COOH), 1720 (C=O), 1698, 1456, 1292, and 1252 cm^{-1} ; δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 3.83 (2 H, s, CH₂COOH), 6.33 (1 H, s, indole 3-H), 6.93-7.07 (2 H, m, aromatic H), 7.37 (1 H, d, J 8 Hz, aromatic H), 7.46 (1 H, d, J 8 Hz, aromatic H), and 10.1 (1 H, br, NH); m/z 175(M^+ , 11%), 131(72), and 130(100).

Ethyl 3-Formylindol-2-ylacetate (66).—N-Methylformanilide (0.59 ml, 4.79 mmol) and phosphorus oxychloride (0.44 ml, 4.79 mmol) were stirred at room temperature until the yellow Vilsmeier salt precipitated out. 1,2-Dichloroethane (5 ml) was added and the mixture cooled to 0 °C. Ethyl indol-2-ylacetate (65) (885 mg, 4.36 mmol) in 1,2-dichloroethane (20 ml) was added dropwise, the mixture heated to 50 °C and stirred for 0.5 h. On cooling, saturated sodium acetate solution (25 ml) was added and the reaction mixture extracted with ethyl acetate (4 x 25 ml). The organic extracts were washed with dilute hydrochloric acid, water, brine, and dried (MgSO_4). The solution was concentrated *in vacuo* to yield an orange oil which was triturated

with ether to give the *title compound* (66) (665 mg, 66%) as a yellow solid, m.p. 105-107 °C (Found: C, 67.6; H, 5.5; N, 6.1. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.7; N, 6.1%); $\nu_{\max}$.(Nujol) 3190 (NH), 1714 (C=O), 1630, 1585, 1499, 1468, and 1391 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 1.34 (3 H, t, J 7 Hz, ethoxy -CH₃), 4.29 (2 H, q, J 7 Hz, ethoxy -CH₂), 4.29 (2 H, s, CH₂COOEt), 7.28 (2 H, m), 7.42 (1 H, m), 8.16 (1 H, m), 9.86 (1 H, br, NH), and 10.26 (1 H, s, CHO); m/z 231 (M^+ , 82%), 185(100), 158(83), 130(36), 103(15), 77(17), and 29(18).

3-Formylindol-2-ylacetic Acid (67).—Potassium hydroxide solution (2 M; 14.4 ml) was added to a solution of ethyl 3-formylindol-2-ylacetate (66) (665 mg, 2.88 mmol) in tetrahydrofuran : methanol (9 : 1) (30 ml) and stirred at room temperature for 2 h. Water (100 ml) was added and the aqueous mixture extracted with ether (2 x 25 ml). The aqueous phase was acidified (pH 1.5) with dilute hydrochloric acid and extracted with ethyl acetate (4 x 30 ml). These extracts were washed with brine, dried (MgSO₄), and concentrated *in vacuo* to yield the *title compound* (67) (584 mg, 100%), m.p. 138-142 °C (Found: M^+ , 203.0581. $C_{11}H_9NO_3$ requires 203.0582); $\nu_{\max}$.(Nujol) 3200 (NH), 3600-2200 (br, COOH), 1714 (C=O), 1617, 1583, and 1248 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 4.3 (2 H, s, CH₂COOH), 7.2 (2 H, m), 7.5 (1 H, m), 8.2 (1 H, m), 10.3 (1 H, s, CHO), and 11.1 (1 H, br, NH); m/z 203 (M^+ , 5%), 158(100), 130(29), 103(12), 77(16), and 44(47).

Pyrano[4,3-b]indol-3-one (68).—Acetic anhydride (1 ml) was added to a solution of 3-formylindol-2-ylacetic acid (67) (157 mg, 77 mmol) in tetrahydrofuran (10 ml) and stirred at room temperature for 36 h. The solution was concentrated *in vacuo* and the resulting solid washed with ether and recrystallised from boiling ethyl acetate to give the *title compound* (68) (129 mg, 90%) as a brown powder, m.p. 158 °C (dec.) (Found: C, 71.1; H, 3.6; N, 7.5. $C_{11}H_7NO_2$ requires C, 71.35; H, 3.8; N, 7.6%); $\nu_{\max}$.(Nujol) 3160 (NH), 1681 (C=O), 1651, 1619, 1587, and 1207 cm^{-1} ; $\lambda_{\max}$. (tetrahydrofuran) 259 (ϵ 22 263), 269 (30 288), 305 (6 214), 317 (6 091), and 369 nm (2 840); δ_H (270 MHz; $(CD_3)_2CO$) 5.61 (1 H, d, J 1 Hz, 4-H), 7.12 (1 H, td, J 8, 8,

and 1 Hz, 8-H), 7.23 (1 H, d, J 8 Hz, 6-H), 7.35 (1 H, td, J 8, 8, and 1 Hz, 7-H), 7.82 (1 H, d, J 8 Hz, 9-H), 8.51 (1 H, d, J 1 Hz, 1-H), and 10.2 (1 H, br, NH); m/z 185(M^+ , 100%), 157(27), 129(37), and 126(57).

Ethyl 3-Acetylintol-2-ylacetate (69).—To a solution of ethyl indol-2-ylacetate (65) (517 mg, 2.55 mmol) in dichloromethane (50 ml) at 0 °C, under nitrogen, was added acetyl chloride (0.54 ml, 7.64 mmol), followed by a solution of tin (IV) chloride in dichloromethane (1.0 M; 23 ml). The mixture was stirred at room temperature, under nitrogen, for 60 h. Water (50 ml) was added and the mixture extracted with dichloromethane (4 x 50 ml). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the *title compound* (69) (580 mg, 93%) as a yellow oil (Found: M^+ , 245.1059. $C_{14}H_{15}NO_3$ requires 245.1052); ν_{max} .($CHCl_3$) 3397 (NH), 1729 (ester C=O), 1642 (α,β -unsaturated ketone C=O), 1530, 1489, 1459, 1450, 1375, 1328, and 1266 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 1.20 (3 H, t, J 7 Hz, ethoxy -CH₃), 2.60 (3 H, s, Ac), 4.12 (2 H, q, J 7 Hz, ethoxy -CH₂), 4.27 (2 H, s, CH₂COOEt), 7.20 (2 H, m), 7.50 (1 H, m), 8.00 (1 H, m), and 11.26 (1 H, br, NH); m/z 245(M^+ , 53%), 203(27), 199(100), 184(25), 171(43), and 130(58).

3-Acetylintol-2-ylacetic Acid (70).—Potassium hydroxide solution (2 M; 11.8 ml) was added to a solution of ethyl 3-acetylintol-2-ylacetate (69) (580 mg, 2.37 mmol) in tetrahydrofuran : methanol (9 : 1) (30 ml) and stirred at room temperature for 2 h. Water (100 ml) was added and the aqueous mixture extracted with ether (2 x 25 ml). The aqueous phase was acidified (pH 1.5) with dilute hydrochloric acid and extracted with ethyl acetate (4 x 30 ml). These extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield the *title compound* (70) (470 mg, 91%), m.p. 187 °C (dec.) (Found: C, 66.2; H, 5.1; N, 6.3. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%); ν_{max} .(Nujol) 3188 (NH), 3500-2300 (br, COOH), 1718 (C=O), 1626, 1544, 1491, 1426, 1328, 1224, and 1189 cm^{-1} ; δ_H (270 MHz;

(CD₃)₂CO) 2.6 (3 H, s, Ac), 4.3 (2 H, s, CH₂COOH), 7.2 (2 H, m), 7.5 (1 H, m), 8.0 (1 H, m), and 11.2 (1 H, br, NH); *m/z* 217(*M*⁺, 8%), 173(47), 158(100), 130(11), and 77(11).

1-Methylpyrano[4,3-*b*]indol-3-one (71).—Acetic anhydride (1 ml) was added to a solution of 3-acetylindol-2-ylacetic acid (70) (370 mg, 1.71 mmol) in tetrahydrofuran (10 ml) and stirred at room temperature for 36 h. the solution was concentrated *in vacuo* and the resulting solid washed with ether and recrystallised from boiling ethyl acetate to give the *title compound* (71) (236 mg, 70%) as a brown powder, m.p. 216 °C (dec.) (Found: C, 72.05; H, 4.5; N, 6.9. C₁₂H₉NO₂ requires C, 72.35; H, 4.55; N, 7.0%); $\nu_{\max}$. (Nujol) 3148 (NH), 1681 ((C=O), 1642, 1619, and 1587 cm⁻¹; $\lambda_{\max}$. (tetrahydrofuran) 259 (ϵ 41 436), 269 (55 479), 306 (10 053), 319 (13 298), 367 (4 681), and 386 nm (3 404); δ_{H} (270 MHz; (CD₃)₂CO) 2.68 (3 H, s, Me), 5.46 (1 H, s, 4-H), 7.14 (1 H, td, *J* 7, 7 and 1 Hz), 7.23 (1 H, dd, *J* 8 and 1 Hz), 7.33 (1 H, td, *J* 8, 8 and 1 Hz), 7.77 (1 H, d, *J* 7 Hz), and 10.13 (1 H, br, NH); δ_{C} (67.9 MHz; (CD₃)₂SO) 18.8 (q, *J*_{CH} 130 Hz, CH₃), 79.8 (d, *J*_{CH} 168 Hz, 4-C), 110.2 (m, quaternary C), 110.7 (dd, *J*_{CH} 162 Hz, ²*J*_{CH} 8 Hz, aromatic C), 120.9 (m, quaternary C), 121.2 (dd, *J*_{CH} 162 Hz, ²*J*_{CH} 7 Hz, aromatic C), 121.7 (dd, *J*_{CH} 161 Hz, ²*J*_{CH} 9 Hz, aromatic C), 127.6 (dd, *J*_{CH} 162 Hz, ²*J*_{CH} 8 Hz, aromatic C), 142.9 (td, ²*J*_{CH} 7, 7 and 5 Hz, quaternary C), 155.0 (d, ²*J*_{CH} 5 Hz, quaternary C), 159.0 (q, ²*J*_{CH} 7 Hz, 1-C), and 162.9 (d, ²*J*_{CH} 4 Hz, quaternary C); *m/z* 199(*M*⁺, 100%), 184(58), 171(46), 143(15), 128(23), 115(12), and 101(12).

***t*-Butyl 3-Oxopyrano[4,3-*b*]indole-5-carboxylate (72).**—To a cooled suspension (0 °C) of sodium hydride (12.9 mg, 0.32 mmol) in dimethylformamide (6 ml), was added dropwise a solution of pyrano[4,3-*b*]indol-3-one (68) (54 mg, 0.29 mmol) in dimethylformamide (10 ml). After addition was complete, the mixture was left to stir, under nitrogen, at room temperature for 0.5 h. The mixture was recooled to 0 °C and di-*tert*-butyl pyrocarbonate (326 mg, 1.47 mmol) in dimethylformamide (10 ml) was added. The mixture was allowed to warm to room temperature

and stirred for a further 2.5 h. Water (150 ml) was added and the solution extracted with ethyl acetate (3 x 50 ml). The organic extracts were washed with water, brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by chromatography (ether) to give the *title compound* (72) (83.2 mg, 100%) as a beige solid, m.p. 131 °C (dec.) (Found: C, 67.6; H, 5.6; N, 4.7. C₁₆H₁₅NO₄ requires C, 67.4; H, 5.3; N, 4.9%); ν_{max} (Nujol) 1736 (carbamate C=O), 1708 (pyrone C=O), 1666, 1575, 1410, 1335, 1311, 1240, 1199, 1153, and 1124 cm⁻¹; λ_{max} (tetrahydrofuran) 256 (ϵ 29 464), 265 (32 768), 297 (5 268), and 309 nm (4 821); δ_{H} (270 MHz; (CD₃)₂CO) 1.73 (9 H, s, t-Bu), 6.65 (1 H, d, *J* 1 Hz, 4-H), 7.31 (1 H, td, *J* 7, 7 and 1 Hz), 7.46 (1 H, td, *J* 7, 7 and 1 Hz), 7.86 (1 H, d, *J* 7 Hz), 8.07 (1 H, d, *J* 7 Hz), and 8.52 (1 H, d, *J* 1 Hz); *m/z* 285(*M*⁺, 9%), 229(22), 185(57), 157(10), 129(12), and 57(100).

t-Butyl 1-Methyl-3-Oxopyrano[4,3-*b*]indole-5-carboxylate (73).—To a cooled suspension (0 °C) of sodium hydride (32 mg, 0.80 mmol) in dimethylformamide (10 ml), was added dropwise a solution of 1-methylpyrano[4,3-*b*]indol-3-one (71) (131 mg, 0.66 mmol) in dimethylformamide (10 ml). After addition was complete, the mixture was left to stir, under nitrogen, at room temperature for 0.5 h. The mixture was recooled to 0 °C and di-*tert*-butyl pyrocarbonate (720 mg, 3.30 mmol) in dimethylformamide (15 ml) was added. The mixture was allowed to warm to room temperature and stirred for a further 2.5 h. Water (150 ml) was added and the solution extracted with ethyl acetate (3 x 50 ml). The organic extracts were washed with water, brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by chromatography (ether) to give the *title compound* (73) (173 mg, 88%) as a beige solid, m.p. 151 °C (dec.) (Found: C, 68.0; H, 5.7; N, 4.5. C₁₇H₁₇NO₄ requires C, 68.2; H, 5.7; N, 4.7%); ν_{max} (Nujol) 1737 (carbamate C=O), 1704 (pyrone C=O), 1597, 1577, 1296, and 1160 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 1.72 (9 H, s, t-Bu), 2.70 (3 H, s, Me), 6.57 (1 H, s, 4-H), 7.34 (1 H, td, *J* 7, 7 and 1 Hz), 7.45 (1 H, dt, *J* 8, 8 and 1 Hz), 7.82 (1 H, d, *J* 7 Hz), and 8.12 (1 H, d, *J* 8 Hz); *m/z* 299(*M*⁺, 4%), 243(17), 199(100), 184(47), 171(38), 128(18), and 57(37).

Dimethyl 9H-Carbazole-2,3-dicarboxylate (74a).—A mixture of pyrano[4,3-*b*]indol-3-one (68) (20.4 mg, 0.11 mmol) and dimethyl acetylenedicarboxylate (50 μ l, 0.41 mmol) in chlorobenzene was refluxed under nitrogen for 44 h. The solvent was evaporated and the residue chromatographed (ether) to give the title carbazole (74a) (28.6 mg, 92%) as a crystalline compound, m.p. 145.5-146.5 °C (lit.,¹⁰⁸ 136-137 °C) (Found: C, 67.9; H, 4.6; N, 4.9. Calc. for C₁₆H₁₃NO₄ : C, 67.8; H, 4.6; N, 4.9%); ν_{max} .(CHCl₃) 3465 (NH), 1718 (C=O), 1436, 1348, 1267, 1111, and 1070 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 3.87 (6 H, s, 2 x OMe), 7.28 (1 H, t, *J* 7 Hz), 7.50 (1 H, t, *J* 7 Hz), 7.61 (1 H, d, *J* 8 Hz), 7.80 (1 H, s, 1-H), 8.26 (1 H, d, *J* 8 Hz), 8.59 (1 H, s, 4-H), and 10.85 (1 H, br, NH); *m/z* 283(*M*⁺, 81%) and 252(100).

9-*t*-Butyl 2,3-Dimethyl 9H-Carbazole-2,3,9-tricarboxylate (74b).—A mixture of *t*-butyl 3-oxopyrano[4,3-*b*]indole-5-carboxylate (72) (47.6 mg, 0.17 mmol) and dimethyl acetylenedicarboxylate (72 μ l, 0.59 mmol) in chlorobenzene was refluxed under nitrogen for 20 h. The solvent was evaporated and the residue chromatographed (ether) to give a mixture of NH and NBoc carbazoles (74a and 74b). This mixture was heated neat for 2 h at 180 °C and then rechromatographed (ether) to give the NH carbazole (74a) (38.5 mg, 82%) as a crystalline compound.

Dimethyl 4-Methyl-9H-Carbazole-2,3-dicarboxylate (74c).—A mixture of 1-methylpyrano[4,3-*b*]indol-3-one (71) (17.2 mg, 0.09 mmol) and dimethyl acetylenedicarboxylate (25 μ l, 0.20 mmol) in chlorobenzene was refluxed under nitrogen for 144 h. The solvent was evaporated and the residue chromatographed (ether) to give the title carbazole (74c) (7.7 mg, 30%) as a crystalline compound, m.p. 130-131 °C (Found: C, 68.7; H, 5.0; N, 4.7. C₁₇H₁₅NO₄ requires C, 68.7; H, 5.1; N, 4.7%); ν_{max} .(CHCl₃) 3468 (NH), 1719 (C=O), 1438, 1342, 1259, and 1077 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 2.85 (3 H, s, Me), 3.88 (6 H, s, 2 x OMe), 7.28 (1 H, t, *J* 8 Hz), 7.51 (1 H, t, *J* 8 Hz), 7.63 (1 H, d, *J* 8 Hz), 8.01 (1 H, s, 1-

H), 8.29 (1 H, d, J 8 Hz), and 10.81 (1 H, br, NH); m/z 297(M^+ , 100%), 266(99), 265(73), 250(19), 207(62), and 179(31).

Ethyl 9H-Carbazole-2-carboxylate (74d) and Ethyl 9H-Carbazole-3-carboxylate (75d).—A mixture of pyrano[4,3-*b*]indol-3-one (68) (36.7 mg, 0.20 mmol) and ethyl propiolate (0.40 ml, 3.9 mmol) in chlorobenzene was refluxed under nitrogen for 167 h. The solvent was evaporated and the residue chromatographed (dichloromethane) to give the title carbazoles (74d : 75d) in a 1 : 1.2 ratio, (42.8 mg, 90%); $\nu_{\max}$.(CHCl₃) 3471 (NH), 1704 (C=O), 1254, and 1097 cm⁻¹; δ_H (270 MHz; (CD₃)₂CO) 1.33-1.40 (m, ethoxy -CH₃, both isomers), 4.38 (q, J 7 Hz, -OCH₂-, both isomers), 7.19-7.30 (m, both isomers), 7.40-7.50 (m, both isomers), 7.53-7.60 (m, both isomers), 7.87 (dd, J 8.3 and 1.5 Hz, minor isomer), 8.08 (dd, J 8.3 and 2 Hz, major isomer), 8.15-8.25 (m, both isomers), 8.82 (d, J 2 Hz, major isomer, 4-H), 10.60 (br, minor isomer, NH), and 10.71 (br, major isomer, NH); m/z 239(M^+ , 100%), 194(65), and 166(27).

*9-*t*-Butyl 2-Ethyl 9H-Carbazole-2,9-dicarboxylate (74e) and 9-*t*-Butyl 3-Ethyl 9H-Carbazole-3,9-dicarboxylate (75e).*—A mixture of *t*-butyl 3-oxopyrano[4,3-*b*]indole-5-carboxylate (72) (29.5 mg, 0.10 mmol) and ethyl propiolate (0.21 ml, 2.1 mmol) in chlorobenzene was refluxed under nitrogen for 25 h. The solvent was evaporated and the residue chromatographed (dichloromethane and methanol) to give pyrano[4,3-*b*]indol-3-one (68) (6.7 mg, 35%); a mixture of ethyl 9H-carbazole-2-carboxylate (74d) and ethyl 9H-carbazole-3-carboxylate (75d) in a 1 : 1 ratio (12.8 mg, 52%) and the *title carbazoles* (74e : 75e) in a 1.5 : 1 ratio, (3.5 mg, 10%); $\nu_{\max}$.(CHCl₃) 1713 (C=O), 1371, 1330, 1245, and 1156 cm⁻¹; δ_H (270 MHz; (CD₃)₂CO) 1.39-1.44 (m, ethoxy -CH₃, both isomers), 1.79 (9 H, s, minor isomer, *t*-Bu), 1.81 (9 H, s, major isomer, *t*-Bu), 4.40 (q, J 7 Hz, -OCH₂-, both isomers), 7.41-7.47 (m, both isomers), 7.53-7.63 (m, both isomers), 8.05 (1 H, dd, J 8 and 1 Hz, major isomer),

8.15-8.43 (m, both isomers), 8.75 (1 H, d, J 1 Hz, minor isomer), and 9.05 (1 H, d, J 1 Hz, major isomer); m/z 339(M^+ , 22%), 283(52), 239(70), and 57(100). This mixture of NBoc carbazoles was heated neat for 6 h at 140 °C to give the corresponding NH carbazoles (74d : 75d) in a 1.5 : 1 ratio.

Ethyl 4-Methyl-9H-carbazole-2-carboxylate (74f) and Ethyl 4-Methyl-9H-carbazole-3-carboxylate (75f).—A mixture of 1-methylpyrano[4,3-*b*]indol-3-one (71) (30.2 mg, 0.15 mmol) and ethyl propiolate (0.31 ml, 3.1 mmol) in chlorobenzene was refluxed under nitrogen for 425 h. The solvent was evaporated and the residue chromatographed (dichloromethane + 10% ethyl acetate) to give the *title carbazoles* (74f : 75f) in a 1 : 2 ratio, (30.0 mg, 78%) (Found: C, 75.8; H, 6.0; N, 5.4. $C_{16}H_{15}NO_2$ requires C, 75.9; H, 6.0; N, 5.5%); $\nu_{\max}$ (CHCl₃) 3470 (NH), 1703 (C=O), 1602, 1331, 1250, and 1073 cm^{-1} ; δ_H (270 MHz; (CD₃)₂CO) 1.39 (t, J 7 Hz, ethoxy -CH₃, both isomers), 2.90 (s, minor isomer, Me), 3.16 (s, major isomer, Me), 4.35 (m, -OCH₂-, both isomers), 7.22-7.29 (m, both isomers), 7.39-7.50 (m, both isomers), 7.56-7.63 (m, both isomers), 7.66 (s, minor isomer), 7.96 (d, J 8 Hz, major isomer), 8.06 (s, minor isomer), 8.23 (d, J 8 Hz, minor isomer), 8.30 (d, J 8 Hz, major isomer), 10.60 (br, minor isomer, NH), and 10.70 (br, major isomer, NH); m/z 253(M^+ , 100%), 225(14), 208(52), 180(31), and 104(12).

Methyl 2-Phenyl-9H-carbazole-3-carboxylate (75g).—A mixture of pyrano[4,3-*b*]indol-3-one (68) (40.7 mg, 0.22 mmol) and methyl phenylpropiolate (87.5 mg, 0.55 mmol) in bromobenzene was heated (140 °C) under nitrogen for 241 h. The solvent was evaporated and the residue chromatographed (dichloromethane + 5% light petroleum) to give the *title carbazole* (75g) (18.4 mg, 28%) as a crystalline compound, m.p. 165-166 °C (Found: C, 79.5; H, 4.9; N, 4.5. $C_{20}H_{15}NO_2$ requires C, 79.7; H, 5.0; N, 4.65%); $\nu_{\max}$ (CHCl₃) 3468 (NH), 1712 (C=O), 1633, 1610, 1494, 1467, 1434, 1347, 1259, 1243, and 1093 cm^{-1} ; δ_H (270 MHz; (CD₃)₂CO) 3.61 (3 H, s, OMe), 7.2-7.6 (9 H, m), 8.24 (1 H, d, J 8 Hz), 8.64 (1 H, s, 4-H), and

10.70 (1 H, br, NH); m/z 301(M^+ , 100%), 270(68), 241(26), and 121(19).

*Reaction of t-Butyl 3-Oxopyrano[4,3-*b*]indole-5-carboxylate (72) with methyl phenylpropiolate.*—A mixture of t-butyl 3-oxopyrano[4,3-*b*]indole-5-carboxylate (72) (28 mg, 0.10 mmol) and methyl phenylpropiolate (31.4 mg, 0.20 mmol) in chlorobenzene was refluxed under nitrogen for 48 h. The solvent was evaporated and the residue chromatographed (dichloromethane + 5% methanol) to give methyl 2-phenyl-9H-carbazole-3-carboxylate (75g) (11.8 mg, 40%) and pyrano[4,3-*b*]indol-3-one (68) (10.9 mg, 60%).

Ethyl 2-Trimethylsilyl-9H-carbazole-3-carboxylate (75l).—A mixture of pyrano[4,3-*b*]indol-3-one (68) (30.5 mg, 0.16 mmol) and ethyl 3-trimethylsilylpropynoate (82.9 mg, 0.49 mmol) in chlorobenzene was refluxed under nitrogen for 262 h. The solvent was evaporated and the residue chromatographed (dichloromethane) to give the *title carbazole* (75l) (12.5 mg, 24%) as a crystalline compound, m.p. 120.5-123 °C (Found: M^+ , 311.1340. $C_{18}H_{21}NO_2Si$ requires 311.1342); ν_{max} .($CHCl_3$) 3469 (NH), 1704 (C=O), 1605, 1467, 1371, 1335, 1245, 1104, and 844 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 0.36 (9 H, s, SiMe₃), 1.42 (3 H, t, J 7 Hz, ethoxy -CH₃), 4.40 (2 H, q, J 7 Hz, ethoxy -CH₂), 7.25 (1 H, t, J 8 Hz), 7.45 (1 H, t, J 8 Hz), 7.58 (1 H, d, J 8 Hz, 8-H), 7.86 (1 H, s, 1-H), 8.21 (1 H, d, J 8 Hz, 5-H), 8.88 (1 H, s, 4-H), and 10.65 (1 H, br, NH); m/z 311(M^+ , 19%), 296(100), and 268(76).

Ethyl 9H-Carbazole-3-carboxylate (75d).—Ethyl 2-trimethylsilyl-9H-carbazole-3-carboxylate (75l) (9.7 mg, 0.03 mmol) was dissolved in trifluoroacetic acid : water (2 : 1) (3 ml) and heated at 70 °C for 2 h. The reaction mixture was then cooled to room temperature and allowed to stand for 14 h. The mixture was diluted with water (30 ml) and extracted with ether (3 x 20 ml). The ethereal extracts were washed with saturated sodium hydrogen carbonate solution until the washings remained basic, then with water, brine and dried (MgSO₄). The solution was

concentrated *in vacuo* to give the *title compound* (75d) (6.1 mg, 82%), m.p. 165-168 °C (lit., 109 165-167 °C); $\nu_{\text{max.}}$ (CHCl₃) 3470 (NH), 1703 (C=O), 1252, and 1098 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 1.40 (3 H, t, *J* 7 Hz, ethoxy -CH₃), 4.38 (2 H, q, *J* 7 Hz, -OCH₂-), 7.26 (1 H, td, *J* 8,8 and 1 Hz), 7.45 (1 H, td, *J* 8, 8 and 1 Hz), 7.57 (1 H, dd, *J* 8 and 1 Hz), 8.08 (1 H, dd, *J* 8 and 2 Hz), 8.23 (1 H, dd, *J* 8 and 2 Hz), 8.82 (1 H, s, 4-H), and 10.73 (1 H, br, NH); *m/z* 239(*M*⁺, 100%), 194(91), and 166(31).

*Reaction of pyrano[4,3-*b*]indol-3-one (68) with methyl tetrolate*—A mixture of pyrano[4,3-*b*]indol-3-one (68) (60 mg, 0.32 mmol) and methyl tetrolate (0.13 ml, 1.3 mmol) in chlorobenzene was refluxed under nitrogen for 528 h. No carbazole products were detected by t.l.c. and so the reaction was abandoned.

*Reaction of 1-methylpyrano[4,3-*b*]indol-3-one (71) with ethyl 3-trimethylsilylpropynoate*—A mixture of 1-methylpyrano[4,3-*b*]indol-3-one (71) (27.7 mg, 0.14 mmol) and ethyl 3-trimethylsilylpropynoate (41.3 mg, 0.24 mmol) in chlorobenzene was refluxed under nitrogen for 1344 h. No carbazole products were detected by t.l.c. and so the reaction was abandoned.

*Reaction of t-butyl 1-methyl-3-oxopyrano[4,3-*b*]indole-5-carboxylate (73) with ethyl 3-trimethylsilylpropynoate*—A mixture of t-butyl 1-methyl-3-oxopyrano[4,3-*b*]indole-5-carboxylate (73) (14.2 mg, 0.05 mmol) and ethyl 3-trimethylsilylpropynoate (16 mg, 0.09 mmol) in chlorobenzene was refluxed under nitrogen for 96 h. The solvent was evaporated and the residue chromatographed (ether + 5% methanol) to give 1-methylpyrano[4,3-*b*]indol-3-one (72) (8.1 mg, 86%). No carbazole products were isolated.

4.3 Experimental for Chapter 3

4.3.1 Experimental for Section 3.3

Ethyl 3-[(N-Propargyl)aminoglyoxyl]indol-2-ylacetate (86).—Oxalyl chloride was added to a solution of ethyl indol-2-ylacetate (65) (2.54 g, 12.5 mmol) in dry ether. This was stirred for 10 min and then concentrated *in vacuo*. Dry ether was added and the solution was cooled using an ice / salt bath. Propargylamine (1.71 ml, 25 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 3 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, water, brine, and dried (MgSO_4). The solvent was evaporated and the crude product was recrystallised from hot ethanol to give the *title compound* (86) (2.65 g, 68%) as a yellow solid, m.p. 150-153 °C (Found: C, 65.2; H, 5.1; N, 9.3. $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ requires C, 65.4; H, 5.2; N, 9.0%); ν_{max} (Nujol) 3320 (alkyne H), 3275 (NH), 1709 (ester C=O), 1657 (ketone C=O), 1631 (amide C=O), 1530 (amide C=O), 1493, 1332, 1249, 1224, and 1184 cm^{-1} ; δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 1.22 (3 H, t, J 7 Hz, ethoxy $-\text{CH}_3$), 2.73 (1 H, t, J 2.5 Hz, acetylene H), 4.14 (2 H, q, J 7 Hz, ethoxy $-\text{CH}_2$), 4.19 (2 H, dd, J 6 and 2.5 Hz, CONHCH_2), 4.28 (2 H, s, CH_2COOEt), 7.15-7.25 (2 H, m, aromatic H), 7.45-7.50 (1 H, m, aromatic H), 8.11-8.15 (1 H, m, indole 4-H), 8.25 (1 H, br, amide NH), and 11.23 (1 H, br, indole NH); m/z 312(M^+ , 21%), 230(100), 202(32), 184(17), and 174(47).

3-[(N-Propargyl)aminoglyoxyl]indol-2-ylacetic acid (87).—Ethyl 3-[(N-propargyl)aminoglyoxyl]indol-2-ylacetate (86) (2.58 g, 8.27 mmol) was dissolved in tetrahydrofuran (55 ml) and methanol (6 ml). Potassium hydroxide solution (2 M, 21 ml) was added and the mixture stirred at room temperature for 2 h. Water (400 ml) was added and the basic solution was extracted with ether. The organic layer was discarded. The aqueous layer was

acidified (pH 1.5) with concentrated hydrochloric acid and then extracted with ethyl acetate (3 x 100 ml). The organic extracts were washed with brine, dried (MgSO₄), and concentrated *in vacuo* to give the *title compound* (87) (2.19 g, 93%) as a yellow crystalline solid, m.p. 166 °C (dec.) (Found: C, 63.3; H, 4.0; N, 9.8. C₁₅H₁₂N₂O₄ requires C, 63.4; H, 4.25; N, 9.85%); ν_{max} .(Nujol) 3400-2400 (br, COOH), 3309 (alkyne H), 3226 (NH), 2627 (alkyne), 1724 (acid C=O), 1662 (ketone C=O), 1580 (amide C=O), 1547, 1528, 1491, 1264, 1245, and 1185 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 2.72 (1 H, t, *J* 2.4 Hz, acetylene H), 4.19 (2 H, dd, *J* 5.8 and 2.4 Hz, CONHCH₂), 4.29 (2 H, s, CH₂COOH), 7.15-7.25 (2 H, m, aromatic H), 7.47-7.51 (1 H, m, aromatic H), 8.10-8.15 (1 H, m, indole 4-H), 8.25 (1 H, br, amide NH), and 11.26 (1 H, br, indole NH); *m/z* 284(*M*⁺, 0.1%), 240(9), 158(100), 130(8), 103(6), and 77(8).

N-Propargyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (88).—Acetic anhydride (100 ml) was added to 3-[(*N*-propargyl)aminoglyoxyl]indol-2-ylacetic acid (87) (1.98 g, 6.97 mmol) and the mixture was stirred for 45 h at room temperature. After 24 h, the acid went into solution and after a further 21 h, a bright yellow solid precipitated out. This solid was filtered and washed with ether under suction to give the *title pyranone* (88) (1.46 g, 79%) as a bright yellow solid, m.p. 229-231 °C (dec.) (Found: C, 67.4; H, 3.8; N, 10.3. C₁₅H₁₀N₂O₃ requires C, 67.7; H, 3.8; N, 10.5%); ν_{max} .(Nujol) 3304 (alkyne H), 3259 (NH), 1693 (pyranone C=O), 1652 (amide C=O), 1603, 1538 (amide C=O), 1298, and 1227 cm⁻¹; λ_{max} .(tetrahydrofuran) 278 (ϵ 47 635), 310 (6 697), 339 (4 311), and 418 nm (3 642); δ_{H} (270 MHz; (CD₃)₂CO) 2.71 (1 H, t, *J* 2.6 Hz, acetylene H), 4.29 (2 H, dd, *J* 5.9 and 2.4 Hz, CONHCH₂), 5.85 (1 H, s, 4-H), 7.15 (1 H, td, *J* 7 and 1 Hz, aromatic H), 7.24 (1 H, dd, *J* 7 and 1 Hz, aromatic H), 7.43 (1 H, td, *J* 7 and 1 Hz, aromatic H), 8.70 (1 H, br, amide NH), 8.96 (1 H, dd, *J* 7 and 1 Hz, 9-H), and 10.4 (1 H, br, indole NH); *m/z* 266(*M*⁺, 25%), 222(*M*⁺ - CO₂, 51), 221(19), 194(25), 184(100), 128(21), and 101(11).

2,3-Dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (93) from Diels-Alder reaction of (88).—N-Propargyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (88) (86.2 mg, 0.32 mmol) was placed in a Wood's metal bath at 250 °C for 0.5 min. The reaction mixture was chromatographed (ethyl acetate) to give the *title carbazole* (53.3 mg, 74%) as a yellow solid, m.p. 244 °C (dec.) (Found: M^+ , 222.0793. $C_{14}H_{10}N_2O$ requires 222.0793); $\nu_{\max}$. (Nujol) 3410 (lactam NH), 3160 (carbazole NH), 1693 (lactam C=O), and 1324 cm^{-1} ; $\lambda_{\max}$. (methanol) 220 (ϵ 43 590), 249 (24 100), and 312 nm (15 330); δ_H (270 MHz; $(CD_3)_2CO$) 4.59 (2 H, s, CH_2), 7.20 (1 H, ~t, J 8 Hz, aromatic H), 7.42 (1 H, ~t, J 8 Hz, aromatic H), 7.52 (2 H, m, aromatic H), 7.59 (1 H, br, amide NH), 7.76 (1 H, d, J 8 Hz, aromatic H), 9.25 (1 H, d, J 8 Hz, 10-H), and 10.63 (1 H, br, carbazole NH); m/z 222(M^+ , 100%), 221(36), 194(42), 193(22), 166(17), 139(10), and 111(11).

2,3-Dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (93) from Diels-Alder reaction of (88).—N-Propargyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (88) (37 mg, 0.14 mmol) in bromobenzene (5 ml) was refluxed, under nitrogen, for 19 h. The solution was concentrated under reduced pressure and the residue was chromatographed (ether + 5% methanol) to yield the *title compound* (28.5 mg, 92%) as a pale yellow solid.

Ethyl 3-[(N-Allyl)aminoglyoxy]indol-2-ylacetate (94).—Oxalyl chloride (2 ml, excess) was added to a solution of ethyl indol-2-ylacetate (65) (1.06 g, 5.22 mmol) in sodium dry ether (30 ml). This was stirred for 10 min at room temperature and then concentrated *in vacuo*. Dry ether (50 ml) was added and the solution was cooled using an ice / salt bath. Allylamine (0.85 ml, 11.3 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 3 h. Dilute hydrochloric acid (30 ml) was added and the reaction mixture was poured into a separating funnel and extracted with ethyl acetate. The organic extracts were combined and washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution, water, brine, and dried ($MgSO_4$). The solvent was

evaporated and the crude product was triturated with ethanol. The solid obtained was filtered and discarded, and the filtrate was concentrated *in vacuo* and chromatographed to give the *title compound* (94) (0.69 g, 42%) as a solid, m.p. 98-100 °C (Found: C, 64.8; H, 5.7; N, 8.8. $C_{17}H_{18}N_2O_4$ requires C, 65.0; H, 5.8; N, 8.9%); $\nu_{\max}$. (Nujol) 3317 (NH), 3280 (NH), 1708 (ester C=O), 1658 (ketone C=O), 1631 (amide C=O), 1574, 1531 (amide C=O), 1492, 1331, 1296, 1249, 1221, and 1183 cm^{-1} ; δ_H (270 MHz; $(\text{CD}_3)_2\text{CO}$) 1.21 (3 H, t, J 7 Hz, ethoxy - CH_3), 4.01 (2 H, tt, J 6 and 2 Hz, CONHCH_2), 4.12 (2 H, q, J 7 Hz, ethoxy - CH_2), 4.28 (2 H, s, CH_2COOEt), 5.12 (1 H, ddd, J 10, 3.5, and 1.5 Hz, terminal alkene H , *cis* to H), 5.28 (1 H, ddd, J 17, 3.5, and 1.5 Hz, terminal alkene H , *trans* to H), 5.96 (1 H, ddt, J 17, 10, and 5 Hz, CH_2CH), 7.15-7.24 (2 H, m, aromatic H), 7.44-7.50 (1 H, m, aromatic H), 7.98 (1 H, br, amide NH), 8.10-8.16 (1 H, m, indole 4-H), and 11.20 (1 H, br, indole NH); m/z 314(M^+ , 18%), 230(100), 224(17), 202(45), 184(27), 174(48), and 128(16).

3-[(*N*-Allyl)aminoglyoxyl]indol-2-ylacetic acid (95).—Ethyl 3-[(*N*-allyl)aminoglyoxyl]indol-2-ylacetate (94) (0.37 g, 1.18 mmol) was dissolved in tetrahydrofuran (9 ml) and methanol (1 ml). Potassium hydroxide solution (2 M, 6 ml) was added and the mixture stirred at room temperature for 2.5 h. Water was added and the basic solution was extracted with ether. The organic layer was discarded. The aqueous layer was acidified (pH 1.5) with concentrated hydrochloric acid and then extracted with ethyl acetate. These organic extracts were washed with brine, dried (MgSO_4), and concentrated *in vacuo* to give the *title compound* (95) (0.24 g, 71%) as a brown solid. This was recrystallised from ethyl acetate to yield pure acid (0.10 g, 30 %), m.p. 128 °C (dec.) (Found: C, 62.8; H, 4.9; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%); $\nu_{\max}$. (Nujol) 3328 (NH), 3277 (NH), 2400-3400 (COOH), 1718 (acid C=O), 1645 (ketone C=O), 1613 (amide C=O), 1553, 1529, 1493, 1396, 1296, 1252, 1202, 1181, 1170, and 1148 cm^{-1} ; δ_H (270 MHz; $(\text{CD}_3)_2\text{CO}$) 4.02 (2 H, m, CONHCH_2), 4.28 (2 H, s, CH_2COOH), 5.12 (1 H, ddd, J 10, 3, and 1.5 Hz, terminal H on alkene, *cis* to H), 5.28 (1 H, ddd, J 17, 3, and 1.5 Hz, terminal H on alkene, *trans* to H), 5.96 (1 H, ddt, J 17, 10, and 5.5 Hz, CH_2CH), 7.14-7.24 (2 H, m, aromatic H), 7.47-7.50 (1 H, m, aromatic H), 8.0 (1 H, br, amide

NH), 8.09-8.15 (1 H, m, indole 4-H), and 11.25 (1 H, br, indole NH); m/z 286(M^+ , 1%), 242(8), 202(4), 174(4), 158(100), 130(9), and 103(6).

*N-Allyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (96).*—Acetic anhydride (5 ml) was added to 3-[(*N*-allyl)aminoglyoxyl]indol-2-ylacetic acid (95) (93.2 mg, 0.33 mmol) and the mixture was stirred for 98 h at room temperature. The mixture was filtered to yield a *bright yellow solid* which was washed with ether under suction and then dried under vacuum to yield the *title pyranone* (52 mg, 60%), m.p. 219 °C (dec.) (Found: C, 66.9; H, 4.4; N, 10.2. $C_{15}H_{12}N_2O_3$ requires C, 67.15; H, 4.5; N, 10.4%); $\nu_{\max}$.(Nujol) 3280 (NH), 3160 (NH), 1697 (pyranone C=O), 1646 (amide C=O), 1593, 1542, 1299, and 1227 cm^{-1} ; $\lambda_{\max}$. (tetrahydrofuran) 272 (ϵ 84 430), 277 (88 320), 322 (7 250), 338 (6 540), and 415 nm (8 320); δ_H (270 MHz; $(CD_3)_2CO$) 4.09 (2 H, dddd, J 5.5, 5.5, 1.5, and 1.5 Hz, CONHCH₂), 5.12 (1 H, ddd, J 10, 3, and 1.5 Hz, terminal *H* on alkene, *cis* to H), 5.27 (1 H, ddd, J 17, 3, and 1.5 Hz, terminal *H* on alkene, *trans* to H), 5.81 (1 H, s, 4-H), 5.99 (1 H, ddt, J 17, 10, and 5.5 Hz, CH₂CH), 7.12 (1 H, m, aromatic H), 7.23 (1 H, m, aromatic H), 7.42 (1 H, m, aromatic H), 8.60 (1 H, br, amide NH), 8.92 (1 H, ~d, J 8 Hz, 9-H), and 10.97 (1 H, br, indole NH); m/z 268(M^+ , 30%) 224(M^+ - CO₂, 13), 222(M^+ - CO₂ - H₂, 13), 184(100), 149(10), and 128(16).

*2,3-Dihydro-2H, 6H-pyrrolo[3,4-*c*]carbazol-1-one (93) from Diels-Alder reaction of (96).*—*N*-Allyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (96) (22.5 mg, 0.08 mmol) was placed in a Wood's metal bath at 220 °C for 2 min. After cooling, the reaction mixture was chromatographed (ether + 5% methanol) to give the *title carbazole* (93) (5.8 mg, 31%) as a yellow solid.

*2,3-Dihydro-2H, 6H-pyrrolo[3,4-*c*]carbazol-1-one (93) from Diels-Alder reaction of*

(96).—N-Allyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (96) (15 mg, 0.06 mmol) was refluxed in bromobenzene (5 ml) for 20.5 h. The solvent was evaporated and the residue was chromatographed (ethyl acetate) to yield required *carbazole* (93) (6 mg, 48%).

2,3,4,5-Tetrahydro-2*H*, 6*H*-pyrrolo[3,4-*c*]carbazol-1-one (97).—N-Allyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (96) (11.3 mg, 0.04 mmol) was refluxed in bromobenzene (4 ml), under argon, for 6 h. The solution was cooled under argon, and the solvent was evaporated to give a *brown solid* (9.4 mg, 100%), m.p. 193-197 °C (dec.) (Found: MH^+ , 225.1028. $C_{14}H_{13}N_2O$ requires 225.1028.); ν_{max} (Nujol) 3250 (br, NH), 1665 (lactam C=O), 1459, and 1324 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 2.76 (2 H, t, J 9 Hz, CH_2), 3.08 (2 H, t, J 9 Hz, CH_2), 4.06 (2 H, s, CONHCH $_2$), 6.97-7.02 (2 H, m, aromatic H), 7.02 (1 H, br, amide NH), 7.27-7.36 (1 H, m, aromatic H), 8.51 (1 H, m, 10-H), and 10.30 (1 H, br, carbazole NH); m/z (FAB, matrix NOBA) 225(MH^+ , 17%), 224(M^+ , 16), 223(15), 167(11), 165(12), 152(15), 150(11), 139(14), 131(11), 124(14), 121(17), 120(18), 115(17), 113(16), 108(13), 106(11), and 105(14).

***N*-(Cinnamyl) Phthalimide (100).**—Cinnamyl chloride (15.44 g, 101 mmol), potassium phthalimide (37.48 g, 202 mmol), and potassium iodide (1 spatula full, catalyst) in DMF (75 ml) were heated to 85-90 °C, under nitrogen, for 8h. The mixture was cooled, diluted with water (1000 ml), and extracted with dichloromethane (4 x 250 ml). The organic extracts were washed with sodium hydroxide solution (3 x 150 ml, 0.2 M), water, brine, and dried ($MgSO_4$). The solvent was evaporated to give a solid (100) (26.56 g, 100%), m.p. 155-157 °C (lit.,¹¹⁰ 156 °C); ν_{max} (Nujol) 1771 (imide C=O), 1708 (imide C=O), 1498, 1428, 1397, 1323, and 1108 cm^{-1} ; δ_H (270 MHz; $CDCl_3$) 4.45 (2 H, dd, J 6.5 and 1.5 Hz, CH_2), 6.26 (1 H, dt, J 16 and 6 Hz, $CHCH_2$), 6.66 (1 H, d, J 16 Hz, ArCH), 7.19-7.42 (5 H, m, aromatic H), 7.71-7.76 (2 H, m, phthalimide H), and 7.83-7.90 (2 H, m, phthalimide H); m/z 263(M^+ , 21%), 245(10), 148(41),

130(14), and 116(100).

Cinnamylamine (101).—N-(Cinnamyl) phthalimide (100) (1.22 g, 4.64 mmol) and hydrazine hydrate (0.25 ml, 5.1 mmol) in methanol (20 ml) were refluxed for 1.5 h. The reaction mixture was cooled and concentrated HCl (3 ml) was added. The reaction mixture was refluxed for a further 0.5 h. The mixture was recooled and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue dissolved in ethanol. This was refiltered to remove final traces of phthalhydrazide and concentrated under reduced pressure. The residue was dissolved in water, basified with KOH pellets (pH>10), and extracted with ether. These ethereal extracts were dried (K₂CO₃) and the solvent evaporated to yield a yellow oil (101) (0.57 g, 92%). This was used directly to prepare (102); δ_{H} (250 MHz; CDCl₃) 3.5 (2 H, dd, *J* 7.5 and 2 Hz, CH₂), 6.3 (1 H, dt, *J* 15 and 7.5 Hz, CHCH₂), 6.5 (1 H, dd, *J* 15 and 2 Hz, ArCH), and 7.2-7.5 (5 H, m, aromatic H).

Ethyl 3-[(N-Cinnamyl)aminoglyoxy]indol-2-ylacetate (102).—Oxalyl chloride (1 ml, excess) was added to a solution of ethyl indol-2-ylacetate (65) (0.54 g, 2.67 mmol) in dry ether (10 ml). This was stirred for 15 min at room temperature and then concentrated *in vacuo*. Dry ether (10 ml) was added and the solution was cooled using an ice / salt bath. Freshly-made cinnamylamine (101) (0.72 g, 5.4 mmol) in ether (5 ml) was added dropwise. The solution was allowed to warm to room temperature and stirred for 2 h. Dilute hydrochloric acid was added and the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate solution, water, brine, and dried (MgSO₄). The solvent was evaporated and the resultant oil was triturated with ethanol to give the *title compound* (102) (0.30 g, 29%) as a solid, m.p. 139-141 °C (Found: C, 71.0; H, 5.75; N, 7.3. C₂₃H₂₃N₂O₄ requires C, 70.75; H, 5.7; N, 7.2%); ν_{max} (Nujol) 3398 (NH), 1720 (ester C=O), 1678 (ketone C=O), 1620 (amide C=O), 1524, 1510, and 1447 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.31 (3 H, t, *J* 7 Hz, ethoxy -CH₃), 4.23 (2 H, td, *J* 6 and 1.5 Hz, CONHCH₂), 4.25 (2 H, q, *J* 7

Hz, ethoxy -CH₂), 4.36 (2 H, s, CH₂COOEt), 6.27 (1 H, dt, *J* 16 and 6 Hz, CH₂CH), 6.64 (1 H, d, *J* 16 Hz, PhCH), 7.14-7.42 (8 H, m, aromatic H), 7.65 (1 H, br, amide NH), 8.18-8.21 (1 H, m, 4-H indole), and 10.25 (1 H, br, indole NH); *m/z* 390(*M*⁺, 7%), 230(100), 202(32), 174(36), 158(11), 117(25), and 115(20).

3-[(*N*-Cinnamyl)aminoglyoxyl]indol-2-ylacetic acid (103).—Ethyl 3-[(*N*-cinnamyl)aminoglyoxyl]indol-2-ylacetate (102) (0.26 g, 0.67 mmol) was dissolved in tetrahydrofuran (9 ml) and methanol (1 ml). Potassium hydroxide solution (2 M, 0.4 ml) was added and the mixture stirred at room temperature for 2 h. Water was added, but the product was not completely soluble in the basic aqueous solution. So the solution was acidified (pH 1) with concentrated hydrochloric acid and then extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO₄), and concentrated *in vacuo* to yield a coloured solid. This was recrystallised from ethyl acetate to give the *title compound* (103) (90.8 mg, 38%) as a solid, m.p. 184-185 °C (Found: C, 69.55; H, 5.0; N, 7.7. C₂₁H₁₈N₂O₄ requires C, 69.6; H, 5.0; N, 7.7%); *v*_{max}. (Nujol) 3288 (NH), 2400-3400 (COOH), 1738 (acid C=O), 1646 (ketone C=O), 1594 (amide C=O), 1573, 1483, 1242, and 1192 cm⁻¹; *δ*_H (270 MHz; (CD₃)₂CO) 4.18 (2 H, td, *J* 6 and 1.5 Hz, CONHCH₂), 4.31 (2 H, s, CH₂COOH), 6.40 (1 H, dt, *J* 16 and 6 Hz, CHCH₂), 6.68 (1 H, d, *J* 16 Hz, PhCH), 7.10-7.55 (8 H, m, aromatic H), 8.12 (1 H, br, amide NH), 8.14 (1 H, m, 4-H indole), and 11.25 (1 H, br, indole NH); *m/z* 318(*M*⁺ - CO₂, 5%), 158(100), 132(3), 130(6), and 117(5).

***N*-Cinnamyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (104).**—Acetic anhydride (5 ml) was added to 3-[(*N*-cinnamyl)aminoglyoxyl]indol-2-ylacetic acid (103) (67 mg, 0.19 mmol) and the mixture was stirred for 45 h at room temperature. The mixture was filtered and the bright yellow solid obtained was washed with ether under suction and then dried to give the *title pyranone* (34.4 mg, 54%), m.p. 172 °C (dec.) (Found: C, 73.2; H, 5.0; N, 7.85. C₂₁H₁₆N₂O₃

requires C, 73.2; H, 4.7; N, 8.1%); $\nu_{\max}$. (Nujol) 3287 (NH), 1650 (br) (pyranone and amide C=O), 1589, 1525, 1297, and 1215 cm^{-1} ; $\lambda_{\max}$. (tetrahydrofuran) 270 (ϵ 73 900), 277 (83 120), 322 (8 350), 338 (6 930), and 419 nm (5 830); δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 4.27-4.32 (2 H, m, CONHCH_2), 5.84 (1 H, s, 4-H), 6.44 (1 H, dt, J 16 and 6 Hz, CH_2CH), 6.70 (1 H, d, J 16 Hz, PhCH), 7.12-7.47 (8 H, m, aromatic H), 8.6 (1 H, br, amide NH), 8.99 (1 H, d, J 8 Hz, 9-H), and 10.4 (1 H, br, indole NH); m/z 344(M^+ , 4%), 300($M^+ - \text{CO}_2$, 100), 209(51), 184(35), and 158(75).

4-Phenyl-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (105) from Diels-Alder reaction of (104).—N-Cinnamyl 3-oxopyrano[4,3-*b*]indole-1-carboxamide (104) (20.8 mg, 0.06 mmol) was refluxed in bromobenzene (4 ml) for 80 h. The solution was concentrated *in vacuo* and chromatographed (dichloromethane + 10% methanol) to give the *title carbazole* (105) (7.8 mg, 43%) as a solid, m.p. 247 °C (dec.) (Found: M^+ , 298.1099. $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$ requires 298.1106); $\nu_{\max}$. (Nujol) 3233 (br, NH), 1672 (lactam C=O), and 1326 cm^{-1} ; $\lambda_{\max}$. (methanol) 212 (ϵ 27 560), 262 (24 530), and 322 nm (14 220); δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 4.60 (2 H, s, CH_2), 7.20 (1 H, t, J 6 Hz, aromatic H), 7.23-7.73 (7 H, m, aromatic H), 7.75 (1 H, s, 5-H), 8.05 (1 H, br, amide NH), 9.27 (1 H, d, J 8 Hz, 10-H), and 11.18 (1 H, br, carbazole NH); m/z 298(M^+ , 100%), 269(50), 241(13), and 135(11).

Phenylpropiolamide (106).—Ammonia (0.880, 6.25 ml) was added to a solution of methyl phenylpropiolate (1.10 g, 6.9 mmol) in methanol (5 ml). The solution was stirred at room temperature for 6 h, cooled, and the resulting crystals were filtered off to yield the required amide (0.78 g, 78%), m.p. 108-110 °C (lit.,¹¹¹ 108 °C); $\nu_{\max}$. (Nujol) 3384 (amide NH), 3181 (amide NH), 2225 (alkyne), 1654 (amide C=O), 1613 (amide C=O), 1492, and 1121 cm^{-1} ; δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 6.9 (br, NH_2) and 7.4-7.6 (m, aromatic H); m/z 145(M^+ , 64%) and 129(100).

***N*-(Phenylpropargyl) Phthalimide (107).**—To a solution of phenylpropargyl alcohol (5.51 g, 41.7 mmol), triphenylphosphine (11.1 g, 42.3 mmol), and phthalimide (6.65 g, 45.2 mmol) in dry THF (40 ml), diethyl azodicarboxylate (6.70 ml, 42.3 mmol) was added. The reaction mixture was stirred at room temperature for 24.5 h. H.P.L.C. showed the presence of starting material, so 2.0 ml of diethyl azodicarboxylate was added and the mixture was stirred for a further 22 h. The solvent was removed *in vacuo* to yield a semi-solid. This was chromatographed (dichloromethane + 5% light petroleum) to give a pale yellow solid (107) (10.9 g, 100%), m.p. 157-160 °C (lit.,¹¹² 158-160 °C); ν_{max} (Nujol) 1773 (imide C=O), 1710 (imide C=O), 1425, 1394, and 1114 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 4.70 (2 H, s, CH_2), 7.20-7.30 (3 H, m, aromatic H), 7.35-7.45 (2 H, m, aromatic H), 7.70-7.80 (2 H, m, phthalimide H), and 7.85-7.95 (2 H, m, phthalimide H); m/z 261 (M^+ , 100%), 232(46), 204(29), 178(11), 165(10), 115(14), 114(11), and 107(17).

Phenylpropargylamine Hydrochloride (108).—*N*-(Phenylpropargyl) phthalimide (107) (4.32 g, 16.6 mmol) and hydrazine hydrate (0.91 ml, 98%) in methanol (40 ml) were refluxed for 2.5 h. The reaction mixture was cooled and concentrated HCl (12 ml) was added. The reaction mixture was refluxed for a further 0.5 h. The mixture was recooled and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue extracted with ethanol (25 ml), refiltered to remove final traces of phthalhydrazide, and concentrated *in vacuo*. The solid residue was recrystallised from isopropanol (25 ml) to yield the title compound as white crystals (108) (1.61 g, 58%), m.p. darkens 208 °C, melts 216-217 °C (lit.,¹¹³ 216-217 °C); δ_{H} (270 MHz; D_2O + DSS) 4.77 (2 H, s, CH_2) and 7.39-7.57 (5 H, m, aromatic H).

Ethyl 3-[(N-Phenylpropargyl)aminoglyoxyl]indol-2-ylacetate (109).—Oxalyl chloride was added to a solution of ethyl indol-2-ylacetate (65) (0.83 g, 4.09 mmol) in dry ether. This was

stirred for 15 min and then concentrated *in vacuo*. Dry ether was added and the solution was cooled using an ice / salt bath. To an aqueous solution of phenylpropargylamine hydrochloride (108) (1.52 g, 9.07 mmol), KOH pellets were added (pH>10). The solution was extracted with ether. The ethereal extracts were washed with brine and dried (K_2CO_3). The solvent was evaporated to yield phenylpropargylamine as a pale yellow oil (1.18 g, 9.04 mmol). This freshly-made amine was redissolved in ether and was added dropwise to the acylated indole solution. The reaction mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temperature and stirred for a further 2 h. Dilute hydrochloric acid was added and the reaction mixture was extracted with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the resultant oil was triturated with ethanol to give the *title compound* (109) (0.49 g, 31%) as a solid. The filtrate was concentrated and chromatographed (ether) to give a further 0.62 g, thus giving a total yield of 70%, m.p. 141-144 °C (Found: C, 71.1; H, 5.25; N, 7.2. $C_{23}H_{20}N_2O_4$ requires C, 71.1; H, 5.2; N, 7.2%); ν_{max} (Nujol) 3317 (NH), 3286 (NH), 1710 (ester C=O), 1659 (ketone C=O), 1629 (amide C=O), 1529, 1492, 1333, 1222, and 1184 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 1.20 (3 H, t, J 7 Hz, ethoxy -CH₃), 4.12 (2 H, q, J 7 Hz, ethoxy -CH₂), 4.30 (2 H, s, CH_2COOEt), 4.42 (2 H, ~d, J 6 Hz, CONHCH₂), 7.13-7.24 (2 H, m, aromatic H), 7.32-7.54 (6 H, m, aromatic H), 8.15 (1 H, d, J 8 Hz, 4-H indole), 8.35 (1 H, br, amide NH), and 11.25 (1 H, br, indole NH); m/z 388(M^+ , 6%), 230(100), 202(30), 174(34), 130(19), and 115(45).

3-[(*N*-Phenylpropargyl)aminoglyoxy]indol-2-ylacetic acid (110).—Ethyl 3-[(*N*-phenylpropargyl)aminoglyoxy]indol-2-ylacetate (109) (0.39 g, 1.0 mmol) was dissolved in tetrahydrofuran (9 ml) and methanol (1 ml). Potassium hydroxide solution (2 M, 5 ml) was added and the mixture stirred at room temperature for 2 h. Water was added, but the product was not completely soluble in the basic aqueous solution. So the solution was acidified (pH 1) with concentrated hydrochloric acid and then extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield a coloured solid. This

was recrystallised from ethyl acetate to give the *title compound* (110) (0.21 g, 58%) as a solid, m.p. 183-185 °C (Found: C, 69.9; H, 4.5; N, 7.7. C₂₁H₁₆N₂O₄ requires C, 70.0; H, 4.5; N, 7.8%); ν_{max} (Nujol) 3290 (NH), 2400-3400 (COOH), 1736 (acid C=O), 1651 (ketone C=O), 1595 (amide C=O), 1572, 1484, 1241, 1196, and 1117 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 4.31 (2 H, s, CH₂COOH), 4.43 (2 H, dd, *J* 4 and 2 Hz, CONHCH₂), 7.10-7.25 (6 H, m, aromatic H), 7.30-7.50 (2 H, m, aromatic H), 8.13 (1 H, dd, *J* 8 and 2 Hz, 4-H indole), 8.35 (1 H, br, amide NH), and 11.30 (1 H, br, indole NH); *m/z* 316(*M*⁺ - CO₂, 11%), 211(5), 158(100), 130(15), and 115(26).

N-(Phenylpropargyl) 3-oxopyrano[4,3-*b*]indole-1-carboxamide (111).—Acetic anhydride (5 ml) was added to 3-[(*N*-phenylpropargyl)aminoglyoxyl]indol-2-ylacetic acid (110) (128 mg, 0.36 mmol) and the mixture was stirred for 25 h at room temperature. The mixture was filtered and the bright yellow solid obtained was washed with ether under suction and then dried to give the *title pyranone* (95.4 mg, 78%), m.p. 207-209 °C (Found: C, 73.4; H, 4.1; N, 8.1. C₂₁H₁₄N₂O₃ requires C, 73.7; H, 4.1; N, 8.2%); ν_{max} (Nujol) 3300 (NH), 1693 (pyranone C=O), 1646 (amide C=O), 1599, 1532, 1295, and 1222 cm⁻¹; λ_{max} (tetrahydrofuran) 272 (ϵ 88 730), 277 (96 110), 324 (7 860), 338 (6 880), and 418 nm (8 440); δ_{H} (270 MHz; (CD₃)₂CO) 4.49 (2 H, m, CONHCH₂), 5.83 (1 H, s, 4-H), 7.13 (1 H, ~t, *J* 8 Hz, aromatic H), 7.22 (1 H, ~d, *J* 8 Hz, aromatic H), 7.32-7.47 (6 H, m, aromatic H), 8.93 (1 H, ~d, *J* 8 Hz, 9-H), 9.02 (1 H, br, amide NH), and 11.0 (1 H, br, indole NH); *m/z* 342(*M*⁺, 4%), 298(*M*⁺ - CO₂, 100), 269(42), 241(12), 184(42), and 128(12).

4-Phenyl-2,3-dihydro-2*H*, 6*H*-pyrrolo[3,4-*c*]carbazol-1-one (105) from Diels-Alder reaction of (111).—*N*-(Phenylpropargyl) 3-oxopyrano[4,3-*b*]indole-1-carboxamide (111) (42 mg, 0.12 mmol) was refluxed in bromobenzene (15 ml) for 16 h. The solution was concentrated *in vacuo* to give the *title carbazole* (31.4 mg, 86%) as a solid.

4.3.2 Experimental for Section 3.4.1

Methyl (2'-Nitrophenyl)propiolate (114).—*o*-Nitrophenylpropionic acid (2.02 g, 10.6 mmol) was heated in an excess of thionyl chloride (10 ml) for 1 h at 50 °C. The mixture was cooled and concentrated *in vacuo*. Methanol was added to the residue and the reaction was stirred overnight at room temperature. The solvent was removed and the resulting solid was washed with ether and methanol to yield the title ester as a yellow crystalline solid (0.54 g, 25%), m.p. 86-88 °C (lit.,¹¹⁴ 87-88 °C); ν_{max} (Nujol) 2226 (alkyne), 1714 (ester C=O), 1608, 1571, 1525, 1436, 1347, 1316, 1295, 1213, and 1182 cm^{-1} ; δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 3.84 (3 H, s, Me), 7.80-7.96 (3 H, m, aromatic H), and 8.25 (1 H, ~d, J 8 Hz, aromatic H *ortho* to NO_2).

1-(2,3-Dibromo-3-(2'-nitrophenyl)-propyl) Phthalimide (120).—N-(2'-Nitrocinnamyl) phthalimide (142) (2.07 g, 6.7 mmol) and bromine (0.35 ml, 6.8 mmol) in dichloromethane were stirred at room temperature for 24 h. Saturated sodium sulphite solution was added and the organic layer was separated. The aqueous portion was extracted with dichloromethane, the organic fractions were combined, and dried (MgSO_4). The solvent was evaporated, and the resulting oil was chromatographed (dichloromethane) to yield the *title compound* as yellow crystals (2.0 g, 64%), m.p. 63-64 °C (Found: (M^+ - Br), 386.9980. $\text{C}_{17}\text{H}_{12}\text{BrN}_2\text{O}_4$ requires 386.9980); ν_{max} (Nujol) 1773 (imide C=O), 1713 (imide C=O), 1610, 1527, and 1396 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 4.29 (1 H, dd, J 14 and 10 Hz, CH_2), 4.63 (1 H, dd, J 14 and 4 Hz, CH_2), 5.06 (1 H, td, J 10, 10, and 4 Hz, 2-H), 6.03 (1 H, d, J 10 Hz, 3-H), 7.46-7.54 (2 H, m, aromatic H), and 7.65-7.94 (6 H, m, aromatic H); m/z 389/387 (M^+ - Br, 6%), 290(6), 289(6), and 160(100).

(2'-Nitrophenyl)propargyl Alcohol (121).—1-Iodo-2-nitrobenzene (2.18 g, 8.76 mmol), triethylamine (2.44 ml, 17.5 mmol), propargyl alcohol (0.61 ml, 10.5 mmol), tetrabutylammonium

bromide (0.30 g, 0.93 mmol), copper (I) chloride (0.12 g, 1.21 mmol), and bis(triphenylphosphine)palladium dichloride (64 mg, 0.09 mmol) were heated in sodium dry benzene (20 ml), under argon, for 20 min at 60-70 °C. The reaction mixture was cooled and the solvent was evaporated. The residue was dissolved in acetone and filtered through celite. The filtrate was concentrated *in vacuo*, preadsorbed, and chromatographed (ether) to yield the title compound as a solid (1.48 g, 96%), m.p. 66-67.5 °C (lit.,¹⁰¹ not reported); ν_{max} (Nujol) 2500-3500 (br, OH), 1609, 1567, 1523 (NO₂), 1464, 1346 (NO₂), 1303, 1262, 1148, 1084, and 1035 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 4.46 (2 H, s, CH₂), 7.59-7.76 (3 H, m, aromatic H), and 8.04 (1 H, d, *J* 7 Hz, aromatic H *ortho* to NO₂); *m/z* 177(*M*⁺, 26%), 148(39), 132(50), 104(45), and 77(100).

N-[(2'-Nitrophenyl)propargyl] Phthalimide (122).—To a solution of (2'-nitrophenyl)propargyl alcohol (121) (1.48 g, 8.36 mmol), triphenylphosphine (2.21 g, 8.44 mmol), and phthalimide (1.27 g, 8.64 mmol) in dry tetrahydrofuran (40 ml), diethyl azodicarboxylate (1.32 ml, 8.34 mmol) was added. The reaction mixture was stirred at room temperature for 26 h. The solvent was removed *in vacuo* to yield a semi-solid. This was chromatographed (dichloromethane) to give a *yellow solid* (122) (2.20 g, 86%), m.p. 170-172.5 °C (Found: C, 66.6; H, 3.2; N, 9.15. C₁₇H₁₀N₂O₄ requires C, 66.7; H, 3.3; N, 9.15%); ν_{max} (Nujol) 1778 (imide C=O), 1769 (imide C=O), 1724 (imide C=O), 1611, 1568, 1520 (NO₂), 1415, 1392 (NO₂), 1344, 1319, 1310, 1192, 1116, 1087, and 938 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 4.75 (2 H, s, CH₂), 7.41-7.62 (3 H, m, aromatic H), 7.72-7.79 (2 H, m, phthalimide H), 7.88-7.94 (2 H, m, phthalimide H), and 8.02 (1 H, dd, *J* 8 and 1.5 Hz, aromatic H *ortho* to NO₂); *m/z* 306(*M*⁺, 0.6%), 289(100), 261(17), 233(11), 160(68), 149(27), 130(40), 104(88), and 76(53).

(2'-Nitrophenyl)propargylamine (123).—*N*-[(2'-Nitrophenyl)propargyl] phthalimide (122) (0.64 g, 2.09 mmol) and hydrazine hydrate (0.11 ml, 98%) in methanol (15 ml) were refluxed for

1.5 h. The reaction mixture was cooled and concentrated HCl (3 ml) was added. The reaction mixture was refluxed for a further 10 min. The mixture was cooled and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated to yield the *amine hydrochloride* (0.41 g, 92%). A small portion of the amine hydrochloride was dissolved in water and KOH pellets were added (pH>10). The resulting oil was extracted with ether, dried (K₂CO₃) and concentrated *in vacuo* to yield a *pale yellow solid* (123) which darkened (to red) on standing; $\nu_{\text{max.}}$ (Nujol) 3363 (NH), 3286 (NH), 1608, 1568, 1519 (NO₂), 1346 (NO₂), 1305, and 1246 cm⁻¹; δ_{H} (270 MHz; (CD₃)₂CO) 2.8 (2 H, br, NH₂), 4.29 (2 H, s, CH₂), 7.57-7.74 (3 H, m, aromatic H), and 8.02 (1 H, d, *J* 8 Hz, aromatic H *ortho* to NO₂).

Ethyl 3-[(N-(2'-Nitrophenyl)propargyl)aminoglyoxy]indol-2-ylacetate (124).—Oxalyl chloride (1 ml, excess) was added to a solution of ethyl indol-2-ylacetate (65) (0.16 g, 0.8 mmol) in sodium dry ether (15 ml). This was stirred for 10 min and then concentrated *in vacuo*. Dry ether (20 ml) was re-added and the solution was cooled using an ice / salt bath. Meanwhile, to an aqueous solution of (2'-nitrophenyl)propargylamine hydrochloride (0.41 g, 1.9 mmol), KOH pellets were added (pH>10). The solution was extracted with ether. The ethereal extracts were dried (K₂CO₃) and the solvent was evaporated to yield (2'-nitrophenyl)propargylamine (123). This was added to the cooled acylated indole solution. The solution was stirred at 0 °C for 1 h, and then was allowed to warm to room temperature and stirred for a further 17 h. Concentrated hydrochloric acid (5 ml) was added and the mixture was poured into water and extracted with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate solution, water, brine, and dried (MgSO₄). The solvent was evaporated and the resultant solid was recrystallised from ethanol to give the *title compound* (124) (0.15 g, 44%) as a pale yellow solid, m.p. 190-192 °C (dec.) (Found: C, 63.9; H, 4.5; N, 9.6. C₂₃H₁₉N₃O₆ requires C, 63.7; H, 4.4; N, 9.7%); $\nu_{\text{max.}}$ (Nujol) 3276 (NH), 1707 (ester C=O), 1661 (ketone C=O), 1628 (amide C=O), 1609, 1567 (amide C=O), 1522 (NO₂), 1493, and 1340 (NO₂) cm⁻¹;

δ_{H} (270 MHz; $(\text{CD}_3)_2\text{CO}$) 1.18 (3 H, t, J 7 Hz, ethoxy $-\text{CH}_3$), 4.11 (2 H, q, J 7 Hz, ethoxy $-\text{CH}_2$), 4.29 (2 H, s, CH_2COOEt), 4.49 (2 H, m, CONHCH_2), 7.13-7.24 (2 H, m, aromatic H), 7.48 (1 H, dd, J 7 and 2 Hz, aromatic H), 7.61-7.68 (1 H, m, aromatic H), 7.74-7.77 (2 H, m, aromatic H), 8.08 (1 H, d, J 8 Hz, aromatic H), 8.15 (1 H, dd, J 6 and 1.5 Hz, aromatic H), 8.42 (1 H, br, amide NH), and 11.25 (1 H, br, indole NH); m/z 433(M^+ , 3%), 415(19), 381(10), 360(39), 342(19), 339(24), 335(18), 326(13), 310(20), 294(10), 284(12), 270(16), 256(15), 230(74), 202(37), 184(28), 174(45), 160(29), 145(59), 130(36), 119(26), and 104(45).

4.3.3 Experimental for Section 3.4.2

(2'-Bromophenyl)propargyl Alcohol (127).—1-Bromo-2-iodobenzene (2.29 g, 8.09 mmol), triethylamine (2.59 ml, 18.6 mmol), propargyl alcohol (0.61 ml, 10.5 mmol), tetrabutylammonium bromide (0.27 g, 0.84 mmol), copper (I) chloride (0.10 g, 1.01 mmol), and bis(triphenylphosphine)-palladium dichloride (60 mg, 0.09 mmol) were heated in sodium dry benzene (25 ml), under argon, for 3 h at 60-70 °C. The reaction mixture was cooled and the solvent was evaporated. The residue was preadsorbed onto silica and chromatographed (ether) to yield recovered 1-bromo-2-iodobenzene (0.74 g, 32%) and the title compound (127) (1.1 g, 64%) as an oil; $\nu_{\text{max.}}$ (Film) 2600-3600 (br, OH), 2919, 2863, 1587, 1558, 1470, 1435, 1356, 1239, 1121, 1054, 1027, 956, and 754 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 1.78 (1 H, t, J 6 Hz, OH, disappears on shaking in D_2O), 4.55 (2 H, d, J 6 Hz, CH_2 , collapses to singlet on shaking in D_2O), 7.14-7.29 (2 H, m, aromatic H), 7.47 (1 H, dd, J 7 and 2 Hz, aromatic H), 7.58 (1 H, dd, J 8 and 1 Hz, aromatic H) (lit., $^{115}\delta_{\text{H}}$ (200 MHz; CDCl_3) 4.45 (2 H, s, CH_2) and 7.14-7.57 (m, aromatic H)); m/z 212/210(M^+ , 46%), 195/193(6), 182/180(12), 131(100), 103(47), 102(43), 101(23), and 77(31).

N-[(2'-Bromophenyl)propargyl] Phthalimide (128).—To a solution of (2'-bromophenyl)propargyl alcohol (127) (0.80 g, 3.79 mmol), triphenylphosphine (1.09 g, 4.16 mmol), and phthalimide (0.61 g, 4.15 mmol) in dry THF (20 ml), diethyl azodicarboxylate (0.66 ml, 4.17 mmol) was added. The reaction mixture was stirred at room temperature for 22 h. The solvent was removed *in vacuo* to yield a semi-solid. This was chromatographed (dichloromethane) to give a solid (128) (1.21 g, 94%), m.p. 189-191 °C (Found: C, 59.8; H, 2.75; N, 4.1. $\text{C}_{17}\text{H}_{10}\text{BrNO}_2$ requires C, 60.0; H, 3.0; N, 4.1%); $\nu_{\text{max.}}$ (Nujol) 1770 (imide C=O), 1723 (imide C=O), 1426, 1393, 1350, 1316, 1121, 947, 759, and 719 cm^{-1} ; δ_{H} (270 MHz; CDCl_3) 4.73 (2 H, s, CH_2), 7.14-7.25 (2 H, m, aromatic H), 7.44 (1 H, dd, J 7 and 2 Hz, aromatic H), 7.53 (1 H, dd, J 7 and 1.5 Hz, aromatic H), 7.73-7.76 (2 H, m, phthalimide H), and

7.89-7.92 (2 H, m, phthalimide H); m/z 341/339(M^+ , 25%), 313/311(3), 284/282(2), 232(19), 204(17), 149(13), 130(26), 113(10), and 104(18).

(2'-Bromophenyl)propargylamine (129).—N-[(2'-Bromophenyl)propargyl] phthalimide (128) (1.09 g, 3.21 mmol) and hydrazine hydrate (0.23 ml, 98%) in methanol (30 ml) were refluxed for 6.5 h. The reaction mixture was cooled and concentrated HCl (5 ml) was added. The reaction mixture was refluxed for a further 0.25 h. The mixture was re-cooled (0 °C) and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue dissolved in water and KOH pellets were added (pH>10). The solution was extracted with ether, the ethereal extracts were dried (K_2CO_3) and the solvent evaporated to yield an *oil* (129) (0.68 g, 100%), which was used directly to form (130).

Ethyl 3-[(N-(2'-Bromophenyl)propargyl)aminoglyoxy]indol-2-ylacetate (130).—Oxalyl chloride (1 ml, excess) was added to a solution of ethyl indol-2-ylacetate (65) (0.32 g, 1.6 mmol) in sodium dry ether (30 ml). This was stirred for 10 min and then concentrated *in vacuo*. Dry ether (30 ml) was re-added and the solution was cooled using an ice / salt bath. Freshly-made (2'-bromophenyl)propargylamine (129) (0.68 g, 3.2 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, and then was allowed to warm to room temperature and stirred for a further 4 h. Concentrated hydrochloric acid (5 ml) was added and the reaction mixture was poured into water and extracted with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the resultant solid was recrystallised from ethanol to give the *title compound* (130) (0.46 g, 62%) as a solid. The filtrate was concentrated *in vacuo* and chromatographed (ether) to give a further 0.13 g (18%) of product, m.p. 178.5-180.5 °C (Found: C, 59.2; H, 4.0; N, 5.8. $C_{23}H_{19}BrN_2O_4$ requires C, 59.1; H, 4.1; N, 6.0%); ν_{max} (Nujol) 3320 (NH), 3278 (NH), 1707 (ester C=O), 1657 (ketone C=O), 1628 (amide C=O), 1529 (amide C=O), 1492, 1332, 1183, 1028, and 744 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 1.18 (3

H, t, J 7 Hz, ethoxy -CH₃), 4.12 (2 H, q, J 7 Hz, ethoxy -CH₂), 4.30 (2 H, s, CH₂COOEt), 4.48 (2 H, m, CONHCH₂), 7.13-7.42 (4 H, m, aromatic H), 7.48 (1 H, dd, J 7 and 2 Hz, aromatic H), 7.55 (1 H, dd, J 7 and 1.5 Hz, aromatic H), 7.66 (1 H, dd, J 8 and 1.5 Hz, aromatic H), 8.15 (1 H, dd, J 7 and 1.5 Hz, indole 4-H), 8.39 (1 H, br, amide NH), and 11.25 (1 H, br, indole NH); m/z 468/466(M^+ , 1.5%), 378/376(7), 269(5), 230(100), 202(26), and 174(31).

3-[(*N*-(2'-Bromophenyl)propargyl)aminoglyoxyl]indol-2-ylacetic acid (131).—Ethyl 3-[(*N*-(2'-bromophenyl)propargyl)aminoglyoxyl]indol-2-ylacetate (130) (0.40 g, 0.86 mmol) was dissolved in tetrahydrofuran (9 ml) and methanol (1 ml). Potassium hydroxide solution (2 M, 4.3 ml) was added and the mixture stirred at room temperature for 4 h. Water (150 ml) was added and the mixture was extracted with ether. These ethereal extracts were discarded. The basic aqueous solution was then acidified with concentrated hydrochloric acid (pH 1) and saturated with solid sodium chloride. It was then extracted with ethyl acetate (3 x 50 ml). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The residue was recrystallised from ethyl acetate to give the required product as a *yellow solid* (131) (0.27 g, 72%), m.p. 182-192 °C (Found: C, 57.4; H, 3.25; N, 6.35. C₂₁H₁₅BrN₂O₄ requires C, 57.4; H, 3.4; N, 6.4%); $\nu_{\max}$ (Nujol) 3270 (NH), 2400-3400 (br, acid OH), 1719 (acid C=O), 1658 (ketone C=O), 1596 (amide C=O), 1527 (amide C=O), 1490, 1262, 1247, 1186, and 750 cm⁻¹; δ_H (270 MHz; (CD₃)₂CO) 4.31 (2 H, s, CH₂COOH), 4.49 (2 H, m, CONHCH₂), 7.12-7.41 (4 H, m, aromatic H), 7.48-7.51 (1 H, m, aromatic H), 7.55 (1 H, dd, J 7 and 1.5 Hz, aromatic H), 7.66 (1 H, dd, J 8 and 1.5 Hz, aromatic H), 8.12-8.16 (1 H, m, indole 4-H), 8.40 (1 H, br, amide NH), and 11.31 (1 H, br, indole NH); m/z 440/438(M^+ , 0.1%), 396/394(M^+ - CO₂, 4%), 202(2), 158(100), 130(6), 103(4), and 77(6).

N-[2'-Bromophenyl]propargyl 3-Oxopyrano[4,3-*b*]indole-1-carboxamide (132) and Isobutyl 1-[*N*-(2'-Bromophenyl)propargyl]carboxamide-3-oxopyrano[4,3-*b*]indole-5-

carboxylate (133).—Isobutyl chloroformate (85 ml, 0.65 mmol) was added to a solution of 3-[(N-(2'-bromophenyl)propargyl)aminoglyoxy]indol-2-ylacetic acid (131) (0.27 g, 0.62 mmol) and triethylamine (0.2 ml, 1.44 mmol) in tetrahydrofuran (25 ml), under nitrogen, at 0 °C. The solution was stirred for 2 h. Silica was added and the solution was concentrated *in vacuo* and chromatographed (ethyl acetate) to yield the *title pyranone* (132) (0.21 g, 81%) as a bright yellow solid, m.p. 189 °C (dec.) (Found: C, 59.7; H, 3.2; N, 6.6. C₂₁H₁₃BrN₂O₃ requires C, 59.9; H, 3.1; N, 6.65%); ν_{max} (Nujol) 3300 (NH), 1698 (pyranone C=O), 1650 (amide C=O), 1590, 1510, 1301, 1213, and 751 cm⁻¹; λ_{max} (tetrahydrofuran) 278 (ϵ 48 300), 324 (3 400), 340 (3 000), and 417 nm (3 300); δ_{H} (270 MHz; (CD₃)₂CO) 4.59 (2 H, m, CH₂), 5.86 (1 H, s, 4-H), 7.16 (1 H, ~t, *J* 7.5 Hz, aromatic H), 7.23-7.47 (4 H, m, aromatic H), 7.53 (1 H, dd, *J* 8 and 2 Hz, aromatic H), 7.64 (1 H, dd, *J* 8 and 1 Hz, aromatic H), 8.80 (1 H, br, amide NH), 8.98 (1 H, dd, *J* 7 and 1.5 Hz, 9-H), and 10.3 (1 H, br, indole NH); *m/z* 420/418(*M*⁺ - 2H⁺, 0.4%), 378/376(*M*⁺ - CO₂, 100/96), 297(12), 269(81), 241(20), and 158(87). Chromatography also yielded the *N-protected pyrone* (133) (32 mg, 11%) as a pale yellow solid, m.p. 172 °C (dec.) (Found: C, 59.95; H, 4.1; N, 5.3. C₂₆H₂₁BrN₂O₅ requires C, 59.9; H, 4.1; N, 5.4%); ν_{max} (CHCl₃) 3438 (NH), 3020 (NH), 2401 (alkyne), 1740 (carbamate C=O), 1713 (pyranone C=O), 1686 (amide C=O), 1577, 1511, 1460, 1387, and 1288 cm⁻¹; λ_{max} (tetrahydrofuran) 271 (ϵ 46 900) and 377 nm (4 800); δ_{H} (270 MHz; CDCl₃) 1.05 (6 H, d, *J* 8 Hz, 2Me), 2.2 (1 H, m, CHMe₂), 4.3 (2 H, d, *J* 8 Hz, CH₂), 4.6 (2 H, d, *J* 8 Hz, CH₂), 7.1-7.3 (3 H, m), 7.35 (1 H, t, *J* 8 Hz, aromatic H), 7.45-7.6 (4 H, m), 8.1 (1 H, d, *J* 8 Hz, aromatic H), and 9.15 (1 H, d, *J* 8 Hz, 9-H); *m/z* 478/476(*M*⁺ - CO₂, 44%), 422/420(12), 398(19), 378/376(40), 328(14), 326(24), 298(34), 297(26), 269(48), 268(35), 254(17), 241(16), and 240(17).

4-(2'-Bromophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (134).—N-(2'-Bromophenyl)propargyl 3-oxopyrano[4,3-b]indole-1-carboxamide (132) (0.13 g, 0.3 mmol) was refluxed in bromobenzene (10 ml) for 76 h. The solution was concentrated *in vacuo* and chromatographed (ether + 1% methanol) to give the *title carbazole* (134) (92 mg, 81%) as a

solid, m.p. 253-260 °C (dec.) (Found: M^+ , 376.0211. $C_{20}H_{13}BrN_2O$ requires 376.0211); $\nu_{\max}$.(Nujol) 3447 (NH), 3200 (NH), 1682 (amide C=O), 1318, and 763 cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 4.34 (2 H, s, CH_2), 7.23 (1 H, ~t, J 7 Hz, aromatic H), 7.35-7.55 (4 H, m, aromatic H), 7.59 (1 H, d, J 8 Hz, aromatic H), 7.63 (1 H, s, 5-H), 7.77 (2 H, ~d, J 8 Hz, aromatic H and amide NH), 9.31 (1 H, d, J 8 Hz, 10-H), and 10.79 (1 H, br, indole NH); m/z 378/376(M^+ , 51%), 297(6), 269(35), 241(11), 221(7), 199(16), and 149(18).

Trisyl Azide (139).—A warm solution (45 °C) of 2,4,6-triisopropylbenzenesulphonyl chloride (0.85 g, 2.8 mmol) in absolute ethanol (20 ml) was added to a solution of sodium azide (0.21 g, 3.2 mmol) in ethanol (4 ml) and water (2 ml). The mixture was stirred at room temperature for 4 h. Water was added and the solution was extracted with ether. The ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated to yield the title compound (139) (0.87 g, 100%) as an oil which solidified on cooling, m.p. 42-44 °C (lit.,¹¹⁶ 41-43 °C); $\nu_{\max}$.(Film) 2120 (azide), 1599, 1567, 1463, 1427, 1381, 1353, and 1169 cm^{-1} .

4.3.4 Experimental for Section 3.4.4

Oxime of 2-Nitrocinnamaldehyde (140).—A solution of hydroxylamine hydrochloride (0.73 g, 10.5 mmol) and sodium acetate (0.75 g, 9.1 mmol) in water (20 ml) was added to a suspension of 2-nitrocinnamaldehyde (1.07 g, 6.0 mmol) in methanol (20 ml). The reaction mixture was stirred overnight at room temperature. The resulting solid was filtered off, washed with water, and dried to give the title compound as a solid (140) (1.04 g, 90%), m.p. 124-134 °C (lit.,¹¹⁴ 134 °C (*E*-oxime) or 140 °C (*Z*-oxime)); ν_{max} (Nujol) 1520 (NO₂), 1359 (NO₂), 974, and 738 cm⁻¹.

2-Nitrocinnamyl Alcohol (141).—To a suspension of 2-nitrocinnamaldehyde (925 mg, 5.22 mmol) and cerium trichloride heptahydrate (2.04 g, 5.48 mmol) in methanol (13 ml), sodium borohydride (0.80 g, 21.1 mmol) was added. Violent effervescence was observed. The mixture was stirred at room temperature for 26 h. Dilute hydrochloric acid was added to work up the reaction. The methanol was removed on the rotary evaporator and the residue was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried (MgSO₄), and concentrated *in vacuo* to yield a solid (141) (0.93 g, 99%), m.p. 54-56 °C (Found: C, 60.2; H, 4.9; N, 7.75. C₉H₉NO₃ requires C, 60.3; H, 5.1; N, 7.8%); ν_{max} (Nujol) 3312 (br, OH), 1516 (aromatic NO₂), 1352 (aromatic NO₂), 1085, 1025, and 954 cm⁻¹; δ_{H} (270 MHz; CDCl₃) 1.78 (1 H, s, br, OH), 4.38 (2 H, dd, *J* 5.4 and 1.5 Hz, CH₂), 6.34 (1 H, dt, *J* 15.6, 5.4 and 5.4 Hz, CHCH₂), 7.08 (1 H, dd, *J* 15.6 and 1.5 Hz, ArCH), 7.39 (1 H, m, aromatic H), 7.53-7.62 (2 H, m, aromatic H), and 7.92 (1 H, d, *J* 8.8 Hz, aromatic H *ortho* to NO₂); *m/z* 179 (*M*⁺, 18%), 149(27), 148(28), 134(34), 132(44), 120(43), 104(49), 92(61), and 77(100).

N-(2-Nitrocinnamyl) Phthalimide (142).—To a solution of 2-nitrocinnamyl alcohol (141) (0.51 g, 2.85 mmol), triphenylphosphine (0.78 g, 2.98 mmol), and phthalimide (0.49 g, 3.33

mmol) in dry tetrahydrofuran (15 ml), diethyl azodicarboxylate (0.48 ml, 3.03 mmol) was added. The reaction mixture was stirred at room temperature for 26 h. The solvent was removed *in vacuo* to yield a semi-solid. This was chromatographed (dichloromethane) to give a *solid* (**142**) (0.62 g, 71%), m.p. 162-163 °C (Found: M^+ 308.0797 and $M^+ - OH$ 291.0765. $C_{17}H_{12}N_2O_4$ requires 308. 0797 and $C_{17}H_{11}N_2O_3$ requires 291.0770); ν_{max} (CHBr₃) 1770 (imide C=O), 1713 (imide C=O), 1523 (NO₂), 1393 (NO₂), and 1346 cm⁻¹; δ_H (270 MHz; CDCl₃) 4.50 (2 H, dd, J 6 and 1 Hz, CH₂), 6.24 (1 H, dt, J 15, 6, and 6 Hz, CHCH₂), 7.13 (1 H, d, J 15 Hz, ArCH), 7.35-7.42 (1 H, m, aromatic H), 7.50-7.57 (2 H, m, aromatic H), 7.70-7.77 (2 H, m, phthalimide H), 7.85-7.90 (2 H, m, phthalimide H), and 7.93 (1 H, d, J 8 Hz, aromatic H *ortho* to NO₂); m/z 291($M^+ - OH$, 3%), 279(2), 276(6), 263(3), 160(100), and 120(24).

2-Nitrocinnamylamine (143).—N-(2-Nitrocinnamyl) phthalimide (**142**) (3.76 g, 12.2 mmol) and hydrazine hydrate (0.67 ml, 98%) in methanol (40 ml) were refluxed for 21.5 h. The reaction mixture was cooled and concentrated HCl (10 ml) was added. The reaction mixture was refluxed for a further 0.5 h. The mixture was recooled (0 °C) and filtered to remove phthalhydrazide. The precipitate was washed with cold methanol. The filtrate was then concentrated and the residue dissolved in ethanol. This was refiltered to remove final traces of phthalhydrazide and the filtrate was concentrated *in vacuo*. The solid residue was dissolved in water and KOH pellets were added (pH>10). The resulting oil was extracted with ether and concentrated *in vacuo* to yield a *yellow oil* (**143**) (1.80 g, 83%). This was used directly to form (**144**); δ_H (250 MHz; CDCl₃) 3.55 (2 H, d, J 7 Hz, CH₂), 6.33 (1 H, dt, J 15, 7, and 7 Hz, CHCH₂), 6.97 (1 H, d, J 15 Hz, ArCH), 7.30-7.43 (1 H, m, aromatic H), 7.50-7.65 (2 H, m, aromatic H), and 7.90 (1 H, d, J 8 Hz, aromatic H *ortho* to NO₂); m/z 178(M^+ , 0.7%), 176(8), 161(13), 145(28), 129(10), 104(30), 103(17), 90(15), 89(12), 86(23), and 84(34).

Ethyl 3-[(N-(2'-Nitrocinnamyl)aminoglyoxy]indol-2-ylacetate (144).—Oxalyl chloride (2

ml, excess) was added to a solution of ethyl indol-2-ylacetate (65) (1.00 g, 4.93 mmol) in sodium dry ether (20 ml). This was stirred for 10 min and then concentrated *in vacuo*. Dry ether (60 ml) was re-added and the solution was cooled using an ice / salt bath. Freshly-made 2-nitrocinnamylamine (143) (1.80 g, 10.1 mmol) was added dropwise. The solution was stirred at 0 °C for 1 h, and then was allowed to warm to room temperature and stirred for a further 19.5 h. Concentrated hydrochloric acid (5 ml) was added and the reaction mixture was poured into water and extracted with ethyl acetate. The organic extracts were combined and washed with saturated sodium bicarbonate solution, water, brine, and dried (MgSO₄). The solvent was evaporated to give the *title compound* (144) (1.64 g, 76%) as a solid, m.p. 81-83 °C (Found: M^+ 435.1442. C₂₃H₂₁N₃O₆ requires 435.1430); ν_{max} (Nujol) 3372 (br, NH), 3215 (br, NH), 1739 (ester C=O), 1635 (ketone C=O), 1598 (amide C=O), 1574 (aromatic NO₂), 1523 (amide C=O), 1485 (aromatic NO₂), 1248, 1220, and 1188 cm⁻¹; δ_{H} (250 MHz; (CD₃)₂CO) 1.18 (3 H, t, J 7 Hz, ethoxy -CH₃), 4.10 (2 H, q, J 7 Hz, ethoxy -CH₂), 4.23 (2 H, ddd, J 6, 6, and 2 Hz, CONHCH₂), 4.29 (2 H, s, CH₂COOEt), 6.48 (1 H, dt, J 16 and 6 Hz, CH₂CH), 7.04 (1 H, d, J 16 Hz, ArCH), 7.15-7.24 (2 H, m, aromatic H), 7.46-7.56 (2 H, m, aromatic H), 7.70 (1 H, t, J 8 Hz, aromatic H), 7.82 (1 H, d, J 8 Hz, aromatic H), 7.93 (1 H, d, J 8 Hz, aromatic H), 8.13-8.25 (2 H, m, indole 4-H and amide NH), and 11.23 (1 H, br, indole NH); m/z 435(M^+ , 3%), 403(3), 230(100), 202(32), 184(16), 174(40), 145(12), and 130(16).

3-[(N-(2'-Nitrocinnamyl))aminoglyoxyl]indol-2-ylacetic acid (145).—Ethyl 3-[(N-(2'-nitrocinnamyl))aminoglyoxyl]indol-2-ylacetate (144) (0.45 g, 1.03 mmol) was dissolved in tetrahydrofuran (9 ml) and methanol (1 ml). Potassium hydroxide solution (2 M, 5 ml) was added and the mixture stirred at room temperature for 4 h. Water (150 ml) was added and the mixture was extracted with ether. These ethereal extracts were discarded. The basic aqueous solution was then acidified with concentrated hydrochloric acid (pH 1) and saturated with solid sodium chloride. It was then extracted with ethyl acetate (3 x 50 ml). The organic layer was dried (MgSO₄) and concentrated *in vacuo* to yield a *yellow solid* (145) (0.41 g, 97%), m.p. 181 - 183 °C (Found: C, 61.9; H, 4.3; N, 10.0. C₂₁H₁₇N₃O₆ requires C, 61.9; H, 4.2; N, 10.3%);

ν_{max} .(Nujol) 3300 (br, NH), 3270 (br, NH), 2400-3700 (COOH), 1719 (acid C=O), 1660 (ketone C=O), 1592 (amide C=O), 1519, 1490 (aromatic NO₂), 1342, 1245, and 1185 cm⁻¹; δ_{H} (250 MHz; (CD₃)₂CO) 4.20-4.30 (4 H, m, CONHCH₂ and CH₂COOH), 6.50 (1 H, dt, *J* 16 and 6 Hz, CHCH₂), 7.05 (1 H, d, *J* 16 Hz, ArCH), 7.10-7.25 (2 H, m, aromatic H), 7.45 (1 H, dd, *J* 8 and 2 Hz, aromatic H), 7.55 (1 H, d, *J* 8 Hz, aromatic H), 7.70 (1 H, t, *J* 8 Hz, aromatic H), 7.85 (1 H, d, *J* 8 Hz, aromatic H), 7.95 (1 H, d, *J* 8 Hz, aromatic H), 8.15 (1 H, dd, *J* 8 and 2 Hz, indole 4-H), 8.40 (1 H, br, amide NH), and 11.65 (1 H, br, indole NH); *m/z* 407(*M*⁺, 0.3%), 363(*M*⁺ - CO₂, 5%), 202(4), 158(100), 149(26), and 130(7).

N-(2'-Nitrocinnamyl) 3-oxopyrano[4,3-*b*]indole-1-carboxamide (146).—Acetic anhydride (1 ml) was added to a solution of 3-[(*N*-(2'-nitrocinnamyl))aminoglyoxy]indol-2-ylacetic acid (145) (300 mg, 0.74 mmol) in tetrahydrofuran (50 ml) and the solution was stirred for 120 h at room temperature. The reaction mixture was concentrated *in vacuo*, triturated with ether, and filtered to yield a *bright yellow solid* (146) (184 mg, 64%). The filtrate was concentrated *in vacuo* and chromatographed (ether + 1% methanol) to yield a further 55 mg of the *title pyranone*, thus making a total yield of 83%, m.p. 195 °C (dec.) (Found: *M*⁺ 389.1012. C₂₁H₁₅N₃O₅ requires 389.1012); ν_{max} .(Nujol) 3438 (NH), 1673 (pyranone C=O), 1646 (amide C=O), 1590, 1569, 1508 (aromatic NO₂), 1340, 1299, and 1217 cm⁻¹; λ_{max} . (tetrahydrofuran) 277 (ϵ 48 510), 323 (6 190), 338 (5 260), and 416 nm (3 540); δ_{H} (270 MHz; (CD₃)₂CO) 4.30 (2 H, ddd, *J* 6, 6, and 2 Hz, CONHCH₂), 5.83 (1 H, s, 4-H), 6.51 (1 H, dt, *J* 16 and 6 Hz, CH₂CH), 7.03 (1 H, d, *J* 16 Hz, ArCH), 7.12 (1 H, t, *J* 8 Hz, aromatic H), 7.23 (1 H, d, *J* 8 Hz, aromatic H), 7.41 (1 H, td, *J* 8 and 1.5 Hz, aromatic H), 7.51 (1 H, td, *J* 8 and 1.5 Hz, aromatic H), 7.68 (1 H, td, *J* 8 and 1.5 Hz, aromatic H), 7.83 (1 H, dd, *J* 8 and 1.5 Hz, aromatic H), 7.91 (1 H, dd, *J* 8 and 1 Hz, aromatic H), 8.90 (1 H, br, amide NH), 8.93 (1 H, d, *J* 9 Hz, 9-H), and 11.13 (1 H, br, indole NH); *m/z* 389(*M*⁺, 1%), 313(38), 311(42), 310(39), 309(67), 284(21), 269(30), 268(27), 255(24), and 184(39).

4-(2'-Nitrophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (147).—N-(2'-Nitrocinnamyl) 3-oxopyrano[4,3-b]indole-1-carboxamide (146) (58.7 mg, 0.15 mmol) was refluxed in bromobenzene (20 ml), under nitrogen, for 4 h. The solution was then cooled, the nitrogen inlet was removed, and the solution refluxed in air for 4 h. The solution was concentrated *in vacuo* and chromatographed (ether + 1% methanol) to give the *title carbazole* (147) (21.6 mg, 42%) as an oil, (Found: M^+ 343.0957. $C_{20}H_{13}N_3O_3$ requires 343.0957); $\nu_{\max}$. (Nujol) 3253 (NH), 1682 (amide C=O), 1609, 1524, 1459, 1349, and 1329 cm^{-1} ; $\lambda_{\max}$. (methanol) 220 (ϵ 45 770), 252 (29 940), and 317 nm (17 230); δ_H (270 MHz; $(CD_3)_2CO$) 4.35 (2 H, s, CH_2), 7.24 (1 H, ~t, J 8 Hz, aromatic H), 7.46 (1 H, ~t, J 8 Hz, aromatic H), 7.58 (1 H, d, J 8 Hz, aromatic H), 7.62 (1 H, s, 5-H), 7.71-7.78 (2 H, m, aromatic H), 7.86 (1 H, ~t, J 8 Hz, aromatic H), 8.11 (1 H, ~d, J 8 Hz, aromatic H), 9.28 (1 H, ~d, J 8 Hz, 10-H), and 10.7 (1 H, br, indole NH); m/z 343(M^+ , 22%), 310(30), 309(100), 293(37), 268(33), and 254(18).

4-(2'-Nitrophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (147) and 4-(2'-Nitrophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1,3-dione (148).—N-(2'-Nitrocinnamyl) 3-oxopyrano[4,3-b]indole-1-carboxamide (146) (40.7 mg, 0.1 mmol) was refluxed in bromobenzene (11 ml) for 2 h. The solution was concentrated *in vacuo* and chromatographed (ether + 5% methanol) to give (147) as an oil (26 mg, 72%) and (148) as a *yellow solid* (6 mg, 16%). (147) was purified further by H.P.L.C. to give a *solid* (4.7 mg, 13%), m.p. 168 °C (dec.). (148) did not require further purification, m.p. >300 °C (Found: M^+ 357.0750. $C_{20}H_{11}N_3O_4$ requires 357.0750); $\nu_{\max}$. (Nujol) 3360 (NH), 3200 (NH), 1758 (imide C=O), 1699, 1611, 1523, 1350, 1314, 1208, and 1147 cm^{-1} ; $\lambda_{\max}$. (methanol) 230 (ϵ 24 600), 274 (13 700), and 307 nm (13 500); δ_H (270 MHz; $(CD_3)_2CO$) 7.3-7.9 (7 H, m, aromatic H), 8.2 (1 H, ~d, J 8 Hz, aromatic H), 9.0 (1 H, ~d, J 8 Hz, 10-H), 9.9 (1 H, br, imide NH), and 11.2 (1 H, br, indole NH); m/z 357(M^+ , 9%), 325(44), 311(42), and 309(100).

2,3,4,5-Tetrahydro-4-(2'-nitrophenyl)-pyrrolo[3,4-c]carbazol-1-one (149).—N-(2'-Nitrocinnamyl) 3-oxopyrano[4,3-b]indole-1-carboxamide (146) (23.7 mg, 0.06 mmol) was refluxed in bromobenzene (5 ml), under argon, for 1 h. The solution was cooled under argon, and the solvent was evaporated to give a *brown solid* (21 mg, 100%), m.p. darkens ~200 °C (Found: MH^+ 346.1192. $C_{20}H_{16}N_3O_3$ requires 346.1192); ν_{max} (Nujol) 3200 (NH), 1673 (amide C=O), 1525 (NO_2), and 1348 (NO_2) cm^{-1} ; δ_H (270 MHz; $(CD_3)_2CO$) 3.28 (1 H, dd, J 17 and 7 Hz, 5-H), 3.69 (1 H, dd, J 17 and 10 Hz, 5-H), 3.92 (2 H, AB quartet, $CONHCH_2$), 4.72 (1 H, dd, J 10 and 7 Hz, 4-H), 7.01-7.07 (2 H, m, aromatic H), 7.18 (1 H, br, amide NH), 7.29-7.38 (1 H, m, aromatic H), 7.49-7.68 (3 H, m, aromatic H), 7.95 (1 H, ~d, J 8 Hz, aromatic H), 8.59 (1 H, m, 10-H), and 10.35 (1 H, br, indole NH); m/z (FAB, matrix MNBA(+)) 346(MH^+ , 11%), 345(M^+ , 9), and 307(9).

K252-c (Staurosporine aglycone) (10).—Triethyl phosphite (10 ml) was added to 4-(2'-Nitrophenyl)-2,3-dihydro-2H, 6H-pyrrolo[3,4-c]carbazol-1-one (147) (21.6 mg, 0.06 mmol) and the mixture was refluxed for 1.5 h. The solution was concentrated *in vacuo* and chromatographed (ether + 3% methanol) to yield the title compound (10.6 mg, 54%) as a yellow solid, m.p. > 300 °C (lit.,⁹ 323-326 °C (dec.)); ν_{max} (Nujol) 3437 (NH), 3315 (NH), 1650 (amide C=O), 1615, 1582, 1490, 1456, 1393, 1330, 1263, 1109, 1031, 939, and 736 cm^{-1} ; λ_{max} (methanol) 229 (ϵ 18 110), 289 (32 090), 324 (8 960), 333 (7 940), 344 (6 350), and 359 nm (4 450); δ_H (500 MHz; $(CD_3)_2SO$) 4.95 (2 H, s, CH_2), 7.22 (1 H, t, J 8 Hz, aromatic H), 7.30 (1 H, t, J 8 Hz, aromatic H), 7.42 (1 H, t, J 8 Hz, aromatic H), 7.46 (1 H, t, J 8 Hz, aromatic H), 7.71 (1 H, d, J 8 Hz, aromatic H), 7.78 (1 H, d, J 8 Hz, aromatic H), 8.03 (1 H, d, J 8 Hz, aromatic H), 8.48 (1 H, s, amide NH), 9.21 (1 H, d, J 8 Hz, 4-H), 11.35 (1 H, s, carbazole NH) and 11.52 (1 H, s, carbazole NH); δ_C (125 MHz; $(CD_3)_2SO$) 45.3 (CH_2), 111.3, 111.9, 114.1, 115.6, 118.9, 119.9, 121.1, 122.6, 122.8, 125.0, 125.2, 125.4, 127.9, 132.9, 139.1, 139.2, and 172.4 (C=O); m/z 311(M^+ , 67%), 309(17), 282(32), 255(16), 155(52), and 127(61).

K252-c (Staurosporine aglycone) (10).—N-(2'-Nitrocinnamyl) 3-oxopyrano[4,3-*b*]indole-1-carboxamide (146) (173 mg, 0.44 mmol) was refluxed in bromobenzene (25 ml), under nitrogen, for 1.5 h. The solution was then cooled, the nitrogen inlet was removed, and the solution refluxed in air for 3.5 h. The bromobenzene was removed on the rotary evaporator to yield a solid (170 mg). Triethyl phosphite (25 ml) was added to this solid (114.6 mg) and the mixture was refluxed under nitrogen for 2 h. The solvent was evaporated and the residue was chromatographed (ether + 3% methanol) to yield the staurosporine aglycone (35 mg, 37% over 2 steps).

REFERENCES

- 1 S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi, and R. Masuma, *J. Antibiot.*, 1977, 30, 275.
- 2 A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai, and S. Omura, *J. Chem. Soc., Chem. Commun.*, 1978, 800.
- 3 A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai, and S. Omura, *Bull. Chem. Soc. Jpn.*, 1982, 55, 3681.
- 4 D. Meksuriyen and G. A. Cordell, *J. Nat. Prod.*, 1988, 51, 884.
- 5 D. Meksuriyen and G. A. Cordell, *J. Nat. Prod.*, 1988, 51, 893.
- 6 W. Steglich, B. Steffan, L. Kopanski, and G. Eckhardt, *Angew. Chem., Int. Ed. Engl.*, 1980, 19, 459.
- 7 R. P. Joyce, J. A. Gainor, and S. M. Weinreb, *J. Org. Chem.*, 1987, 52, 1177.
- 8 T. Kaneko, H. Wong, K. T. Okamoto, and J. Clardy, *Tetrahedron Lett.*, 1985, 26, 4015.
- 9 B. Sarstedt and E. Winterfeldt, *Heterocycles*, 1983, 20, 469.
- 10 J. Bergman and B. Pelcman, *Tetrahedron Lett.*, 1987, 28, 4441.
- 11 D. E. Nettleton, T. W. Doyle, B. Krishnan, G. K. Matsumoto, and J. Clardy, *Tetrahedron Lett.*, 1985, 26, 4011.
- 12 C. J. Pearce, T. W. Doyle, S. Forenza, K. S. Lam, and D. R. Schroeder, *J. Nat. Prod.*, 1988, 51, 937.
- 13 M. Sezaki, T. Sasaki, T. Nakazawa, U. Takeda, M. Iwata, T. Watanabe, M. Koyama, F. Kai, T. Shomura, and M. Kojima, *J. Antibiot.*, 1985, 38, 1437.
- 14 H. Kase, K. Iwahashi, and Y. Matsuda, *J. Antibiot.*, 1986, 39, 1059.
- 15 T. Yasuzawa, T. Iida, M. Yoshida, N. Hirayama, M. Takahashi, K. Shirahata, and H. Sano, *J. Antibiot.*, 1986, 39, 1072.
- 16 S. Nakanishi, Y. Matsuda, K. Iwahashi, and H. Kase, *J. Antibiot.*, 1986, 39, 1066.
- 17 I. Takahashi, E. Kobayashi, K. Asano, M. Yoshida, and H. Nakano, *J. Antibiot.*, 1987, 40, 1782.

- 18 I. Takahashi, K. Asano, I. Kawamoto, T. Tamaoki, and H. Nakano, *J. Antibiot.*, 1989, 42, 564.
- 19 I. Takahashi, Y. Saitoh, M. Yoshida, H. Sano, H. Nakano, M. Morimoto, and T. Tamaoki, *J. Antibiot.*, 1989, 42, 571.
- 20 J. A. Matson, C. Claridge, J. A. Bush, J. Titus, W. T. Bradner, T. W. Doyle, A. C. Horan, and M. Patel, *J. Antibiot.*, 1989, 42, 1547.
- 21 J. Golik, T. W. Doyle, B. Krishnan, G. Dubay, and J. A. Matson, *J. Antibiot.*, 1989, 42, 1784.
- 22 A. C. Horan, J. Golik, J. A. Matson, and M. G. Patel, Eur. Pat., 1986, 175 284 [*Chem. Abs.*, 1986, 105, 5184j].
- 23 S. Tanida, M. Takizawa, T. Takahashi, S. Tsubotani, and S. Harada, *J. Antibiot.*, 1989, 42, 1619.
- 24 D. E. Nettleton, W. T. Bradner, J. A. Bush, and T. W. Doyle, Eur. Pat. Appl. EP 115,350 [*Chem. Abs.*, 1984, 102, 22793n].
- 25 J. A. Bush, B. H. Long, J. J. Catino, and W. T. Bradner, *J. Antibiot.*, 1987, 40, 668.
- 26 S. Omura, Y. Iwai, and A. Hirano, Ger. Offen. 2,754,326 [*Chem. Abs.*, 1978, 89, 58348y].
- 27 S. Omura, Y. Iwai, and A. Hirano, Japan. Kokai 78 73,501 [*Chem. Abs.*, 1978, 89, 178086h].
- 28 S. Oka, M. Kodama, H. Takeda, N. Tomizuka, and H. Suzuki, *Agric. Biol. Chem.*, 1986, 50, 2723.
- 29 H. Morioka, H. Shibai, Y. Yokogawa, M. Ishihara, T. Kida, and T. Suzuki, Jpn. Kokai Tokkyo Koho JP 60,185,719 [*Chem. Abs.*, 1986, 104, 18649u].
- 30 T. Tamaoki, H. Nomoto, I. Takahashi, Y. Kato, M. Morimoto, and F. Tomita, *Biochem. Biophys. Res. Commun.*, 1986, 135, 397.
- 31 H. Morioka, M. Ishihara, H. Shibai, and T. Suzuki, *Agric. Biol. Chem.*,

- 1985, 49, 1959.
- 32 H. Nakano, E. Kobayashi, I. Takahashi, T. Tamaoki, Y. Kuzuu, and H. Iba, *J. Antibiot.*, 1987, 40, 706.
- 33 U. T. Ruegg and G. M. Burgess, *Trends Pharmacol. Sci.*, 1989, 10, 218.
- 34 J. Bergman and B. Pelcman, *J. Org. Chem.*, 1989, 54, 824
- 35 I. Hughes and R. A. Raphael, *Tetrahedron Lett.*, 1983, 24, 1441.
- 36 P. D. Magnus and N. L. Sear, *Tetrahedron*, 1984, 40, 2795.
- 37 S. M. Weinreb, R. S. Garigipati, and J. A. Gainor, *Heterocycles*, 1984, 21, 309.
- 38 M. Brenner, H. Rexhausen, B. Steffan, and W. Steglich, *Tetrahedron*, 1988, 44, 2887.
- 39 P. D. Davis, R. A. Bit, and S. A. Hurst, *Tetrahedron Lett.*, 1990, 31, 2353.
- 40 P. D. Davis, C. H. Hill, and G. Lawton, Eur. Pat. Appl. EP 0 328 026 A1.
- 41 W. L. Mock and R. M. Nugent, *J. Am. Chem. Soc.*, 1975, 97, 6521 and 6526.
- 42 E. R. Marinelli, *Tetrahedron Lett.*, 1982, 23, 2745.
- 43 B. Saroja and P. C. Srinivasan, *Tetrahedron Lett.*, 1984, 25, 5429.
- 44 T. Gallagher and P. Magnus, *Tetrahedron*, 1981, 37, 3889.
- 45 P. Magnus, T. Gallagher, P. Brown, and P. Pappalardo, *Acc. Chem. Res.*, 1984, 17, 35.
- 46 C. Exon, T. Gallagher, and P. Magnus, *J. Am. Chem. Soc.*, 1983, 105, 4739.
- 47 P. Magnus, C. Exon, and N. L. Sear, *Tetrahedron*, 1983, 39, 3725.
- 48 T. Gallagher, P. Magnus, and J. C. Huffman, *J. Am. Chem. Soc.*, 1983, 105, 4750.
- 49 Y. Tamura, S. Mohri, H. Maeda, T. Tsugoshi, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, 1984, 25, 309.
- 50 T. Kurihara, M. Hanakawa, T. Wakita, and S. Harusawa, *Heterocycles*, 1985, 23, 2221.
- 51 W. M. Welch, *J. Org. Chem.*, 1976, 41, 2031.
- 52 C.-K. Sha, K.-S. Chuang, and J.-J. Young, *J. Chem. Soc., Chem. Commun.*, 1984, 1552.
- 53 A. Shafiee and S. Sattari, *J. Heterocycl. Chem.*, 1982, 19, 227.
- 54 M. G. Saulnier and G. W. Gribble, *Tetrahedron Lett.*, 1983, 24, 5435.
- 55 H. Plieninger, W. Muller, and K. Weinerth, *Chem. Ber.*, 1964, 97, 667.

- 56 C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 1984, 925.
- 57 C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2505.
- 58 C. J. Moody and P. Shah, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1407.
- 59 C. J. Moody, P. Shah, and P. Knowles, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3249.
- 60 N. S. Narasimham and S. M. Gokhale, *J. Chem. Soc., Chem. Commun.*, 1985, 86.
- 61 U. Pindur and H. Erfanian-Abdoust, *Liebigs Ann. Chem.*, 1988, 803.
- 62 U. Pindur and H. Erfanian-Abdoust, *Chimia*, 1988, 42, 180.
- 63 U. Pindur and H. Erfanian-Abdoust, *Liebigs Ann. Chem.*, 1989, 227.
- 64 U. Pindur, M. Eitel, and H. Erfanian-Abdoust, *Heterocycles*, 1989, 29, 11.
- 65 U. Pindur and H. Erfanian-Abdoust, *Heterocycles*, 1989, 29, 1709.
- 66 U. Pindur and H. Erfanian-Abdoust, *Chem. Rev.*, 1989, 89, 1681.
- 67 P. Van Doren, D. Vanderzande, S. Toppet, and G. Hoornaert, *Tetrahedron*, 1989, 45, 6761.
- 68 P. Van Doren, F. Compennolle, and G. Hoornaert, *Tetrahedron*, 1990, 46, 4023.
- 69 H. Nandin de Carvalho, G. I. Dmitrienko, and K. Neilson, *Tetrahedron*, 1990, 46, 5523.
- 70 C. J. Moody and P. Shah, *J. Chem. Soc., Perkin Trans. 1*, 1989, 376 and 2463.
- 71 P. M. Jackson and C. J. Moody, *Synlett*, 1990, 521.
- 72 a) C. May and C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 1984, 926. b) C. May and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1988, 247.
- 73 I. Hasan, E. R. Marinelli, L.-C. C. Lin, F. W. Fowler, and A. B. Levy, *J. Org. Chem.*, 1981, 46, 157.
- 74 D. D. Weller and D. W. Ford, *Tetrahedron Lett.*, 1984, 25, 2105.
- 75 W. Schindler, *Helv. Chim. Acta*, 1957, 40, 2156; *ibid.*, 1958, 41, 1441.
- 76 A. R. Katritzky and K. Akutagawa, *J. Am. Chem. Soc.*, 1986, 108, 6808.
- 77 R. Giuliano and M. L. Stein, *Ann. Chim. (Rome)*, 1958, 48, 1284.
- 78 D. W. Slocum and P. L. Gierer, *J. Org. Chem.*, 1976, 41, 3668.
- 79 Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, 1978, 43, 2087.
- 80 F. D. Bellamy and K. Ou, *Tetrahedron Lett.*, 1984, 25, 839.
- 81 a) I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions,' Wiley, Chichester, 1978.

- b) T. L. Gilchrist and R. C. Storr, 'Organic Reactions and Orbital Symmetry,' Cambridge University Press, 1979.
- 82 P. J. Brogden, C. D. Gabbutt, and J. D. Hepworth in 'Comprehensive Heterocyclic Chemistry,' ed. A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, vol. 3, p. 573.
- 83 J. A. Reed, C. L. Schilling, R. F. Tarvin, T. A. Rettig, and J. K. Stille, *J. Org. Chem.*, 1969, **34**, 2188.
- 84 J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, 1961, **44**, 540.
- 85 J. J. P. Stewart, MOPAC, Program 455, Quantum Chemistry Program Exchange, University of Indiana, Bloomington, USA.
- 86 U. Pindur, Personal communication to Professor C. J. Moody.
- 87 J. Bergman, J.-E. Backvall, and J.-O. Lindstrom, *Tetrahedron*, 1973, **29**, 971.
- 88 M. Giua, *Gazz. Chim. Ital.*, 1924, **54**, 593.
- 89 R. J. Sundberg, 'The Chemistry of Indoles' (vol. 18 in a series of monographs on Organic Chemistry, ed. Blomquist), Academic Press, 1970, p. 219.
- 90 M. S. Gibson and R. W. Bradshaw, *Angew. Chem. Int. Ed. Engl.*, 1968, **7**, 919.
- 91 T. Posner, *Ber.*, 1893, **26**, 1856.
- 92 L. H. Klemm, R. A. Klemm, P. S. Santhanam, and D. V. White, *J. Org. Chem.*, 1971, **36**, 2169.
- 93 T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Lett.*, 1969, 4552.
- 94 O. Mitsunobu, *Synthesis*, 1981, 1.
- 95 K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 1945, 512.
- 96 a) T. Morimoto, T. Takahashi, and M. Sekiya, *J. Chem. Soc., Chem. Commun.*, 1984, 794. b) H. J. Bestmann and G. Wölfel, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 53.
- 97 A. R. Katritzky, J. Jiang, and L. Urogdi, *Tetrahedron Lett.*, 1989, **30**, 3303.
- 98 H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653.
- 99 A. Wissner and C. V. Grudzinskas, *J. Org. Chem.*, 1978, **43**, 3972.

- 100 T. J. Grattan and J. S. Whitehurst, *J. Chem. Soc., Perkin Trans. 1*, 1990, 11.
- 101 N. A. Boomageen and A. B. Ponomarev, *Dokl. Akad. Nauk SSSR*, 1985, 283, 630.
- 102 A. Roloff and S. Farooq, Fr. Demande FR 2,471,966 [*Chem. Abs.*, 1982, 96, 6249s].
- 103 G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *J. Org. Chem.*, 1979, 44, 1247.
- 104 M. Regitz, J. Hocker, and A. Liedhegener, *Org. Synth.*, Coll. Vol. 5, 179.
- 105 R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, 93, 2897.
- 106 A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, 103, 5454.
- 107 J. I. G. Cadogan in 'Organophosphorus Reagents in Organic Synthesis,' ed. J. I. G. Cadogan, Academic Press, London, 1979, p. 269.
- 108 G. W. B. Reed, P. T. W. Cheng, and S. McLean, *Can. J. Chem.*, 1982, 60, 419.
- 109 R. W. G. Preston, S. H. Tucker, and J. M. L. Cameron, *J. Chem. Soc.*, 1942, 500.
- 110 E. Bergmann, *J. Chem. Soc.*, 1935, 1361.
- 111 E. Philippi and E. Spenner, *Monatsh.*, 1915, 36, 97.
- 112 CIBA Ltd. (R. P. Mull), Belg. 655,403, [*Chem. Abs.*, 1966, 64, 17481a].
- 113 L. H. Klemm, T. M. McGuire, and K. W. Gopinath, *J. Org. Chem.*, 1976, 41, 2571.
- 114 'Dictionary of Organic Compounds,' ed. J. Buckingham, 5th. edn., Chapman and Hall, New York, 1982.
- 115 G. Just and R. Singh, *Tetrahedron Lett.*, 1987, 28, 5981.
- 116 R. E. Harmon, G. Wellman, and S. K. Gupta, *J. Org. Chem.*, 1973, 38, 11.