Towards the Assembly of the Binary *Vinca* Alkaloids: Strategies for the Synthesis of Analogues of the Indole-Indoline Core of (+)-Vinblastine

A thesis submitted for the degree of Doctor of Philosophy

of the Australian National University

by

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Canberra, Australia

June, 2006

Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2001-2005 and that it has not been presented for examination for any other degree. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive. This thesis is less than 100,000 words in length.

Michael John Harvey

June, 2006

"Chemists are a strange class of mortals, impelled by an almost maniacal impulse to seek their pleasures amongst smoke and vapour, soot and flames, poisons and poverty, yet despite these evils I seem to live so sweetly that I would rather die than change places with the King of Persia."

Johann Joachim Becher in *Physica Subterranea* (**1667**)

Acknowledgements

To begin with, I would like to thank my supervisor, Professor Martin Banwell, for his contributions towards my thesis. His advice and patience are valued. I also appreciate the opportunity he gave me to conduct my PhD research here in Canberra.

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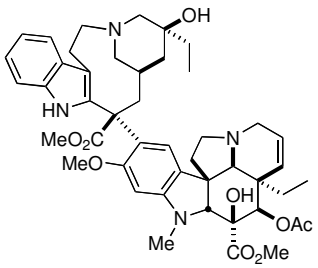
To the people that have been closest and most important to me personally during this period in my life – I thank you for your understanding, your support and your unfailing belief in me. Belinda, Kathy and Su Jing, your confidence and encouragement have given me strength.

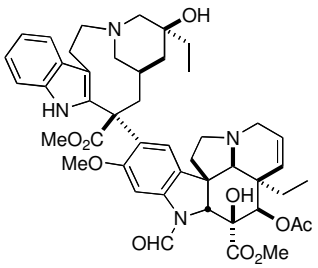
Finally, my family are the foundation where I came from, and I am grateful for everything that they have done for me so far, and in the future. I am thankful for my mother, father and brother having been encouraging and supportive and, most of all, a comfort, over the telephone during my sojourn in Australia's capital.

Abstract

The clinically important alkaloids (+)-vinblastine (**1**) and (+)-vincristine (**2**) both exhibit extraordinary potency as anti-mitotic agents and act by destabilising polymerised tubulin. While the development of a structure-activity-relationship (SAR) profile around these natural products should allow for the identification of the relevant pharmacophore, this task is especially daunting because of the structural complexity of these compounds. Indeed, most analogues of the *Vinca* alkaloids are obtained through modifications of the natural products rather than being generated *de novo* by "total synthesis".

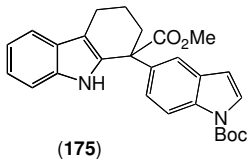


(**1**)



(**2**)

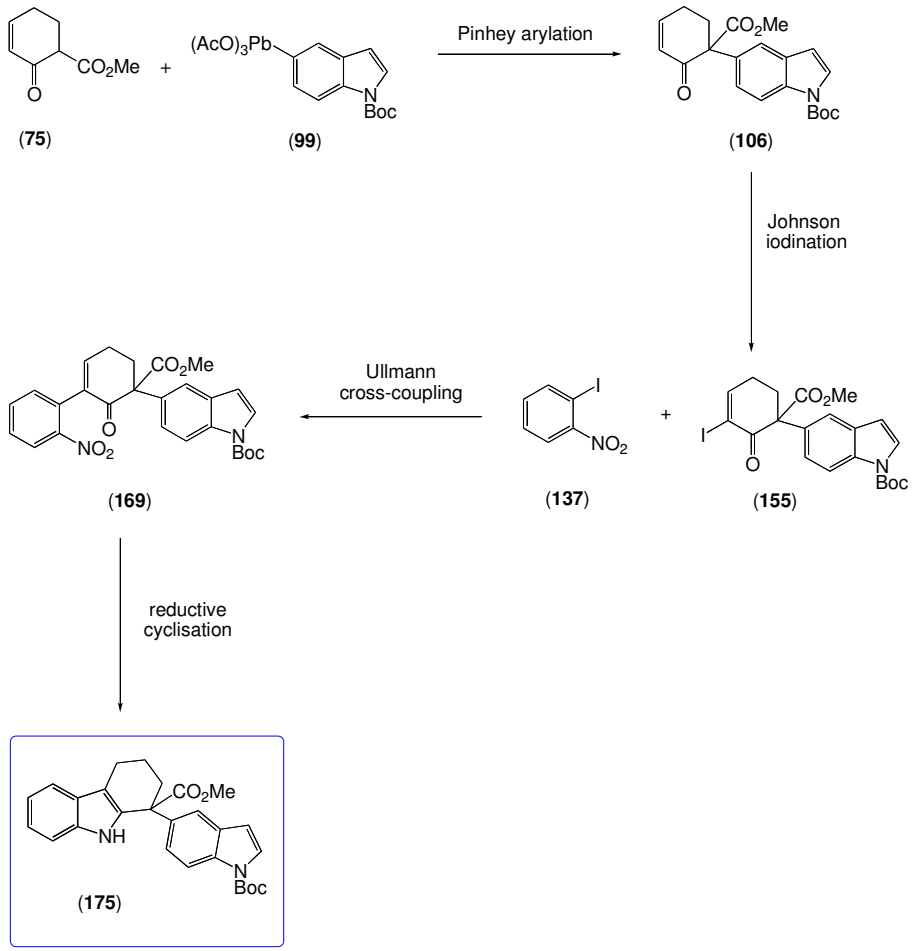
In principle, a useful starting point in generating small molecule analogues of the title alkaloids that may well retain useful biological properties would be to prepare a series of compounds mimicking the indole-indoline core of (+)-vinblastine (**1**) and involving a range of different pairings of aryl groups as surrogates for these heterocyclic units. This approach, which would lead to compounds such as **175**, requires establishing methods for the generation and appropriate linking of these units.



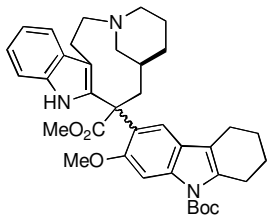
(**175**)

The methodology ultimately established for obtaining the abovementioned (+)-vinblastine analogues is detailed in Chapter Two and involved Pinhey-type arylation of α-carbomethoxylated cycloalkenones such as **75** with the relevant plumbated arenes, *e.g.* **99**. The resulting α-arylated cycloalkenone, *e.g.* **106**, was submitted to a Banwell-type indole synthesis involving α′-iodinaton of such compounds under conditions defined by Johnson and then subjecting the product of this process, *e.g.* **155**, to a

palladium[0]-catalysed Ullmann cross-coupling reaction with *o*-iodonitrobenzene (**137**). The resulting product, *e.g.* **169**, was then subjected to reductive cyclisation using dihydrogen in the presence of palladium on carbon, and so affording the target mimetics, *e.g.* **175**, of the indole-indoline core of alkaloids **1** and **2**

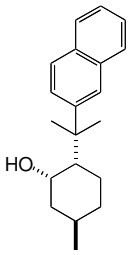


Attempts, as described in Chapter Three, were then made to extend such chemistry to the preparation of the *bis*-indole **44** containing a tetracyclic structure resembling the carbomethoxyvelbamine portion of (+)-vinblastine (**1**).



(**44**)

The following Chapter (Four) details attempts to extend the methodology introduced in Chapter Two to the enantioselective preparation of vinblastine analogues such as **175**. In particular, the carbomethoxy group associated with the α-carbomethoxycycloalkenone precursors, *e.g.* **75**, to such compounds were replaced by carboalkoxy groups incorporating chiral alcohol residues such as menthol, (1-methyl-1-phenylethyl)cyclohexanol, 8-β-naphthylmenthol and [*N*-benzenesulfonyl-*N*-(3,5-diphenyl)-amino]-2-bornanol and then seeking to effect the diastereoselective Pinhey arylation of these compounds. Some diastereoselection was achieved in this regard when the chiral auxiliary **244** was employed.



(**244**)

Publications and Presentations Carried Out During Period of Candidature

Publications:

"An Evaluation of Functional Group Tolerances in the Johnson-type Synthesis of ±-Haloenones and in their Palladium[0]-Catalysed Ullman Cross-Coupling Reactions with *o*-Halonitrobenzenes: Application to the Synthesis of a Simple Vinblastine Analogue". Banwell, M. G., Harvey, M. J., Lupton, D. W., manuscript in preparation, to be submitted to *Organic and Bimolecular Chemistry.*

Presentations:

"Towards the Assembly of the Binary Indole-Indoline Alkaloids: A Strategy for the Construction of the C-16′ to C-10 Linkage of (+)-Vinblastine". Poster presentation at the 39th National Organic Chemistry Symposium (NOS), The University of Utah, Salt Lake City, Utah, June 2005.

Glossary

The following abbreviations and symbols have been used throughout this thesis:

AcOH	acetic acid
Ac	acetyl
Ac_2O	acetic anhydride
Ar	Aryl
aq.	aqueous
atm.	atmosphere
BINAP	2,2-*bis*(diphenylphosphino)-1-1' binaphthyl
Bn	benzyl
bipy	2,2′-bipyridyl
Boc	*tert*-butoxycarbonyl
$(Boc)_2O$	di-*tert*-butyldicarbonate
b.p.	boiling point (°C)
Bu	butyl
n-BuLi	*n*-butyllithium
t-Bu	*tertiary*-butyl
t-BuLi	*tertiary*-butyllithium
c	concentration (g/100 mL)
ca.	*circa* (approximately)
conc.	concentrated
COSY	homonuclear ($^1H/^1H$) correlation spectroscopy
d	doublet
δ	chemical shift (parts per million)

DCM	dichloromethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement of polarisation transfer
DNA	deoxyribonucleic acid
dm	demimetre
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppp	1,4-*bis*(diphenylphosphino)propane
d.r.	diastereomeric ratio
e.g.	*exemplia gratia*
e.e.	enantiomeric excess
E	*entgegen* (opposite)
EI	electron impact
ether	diethyl ether
equiv. or eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
Et_3N	triethylamine
eV	electron volt
FTIR	fourier transform infrared
g	gram
h	hour(s)
$Hg(OTf)_2$	mercuric (II) triflate
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrum
Hz	Hertz

Im.	imidazole
IR	infrared
J	coupling constant (Hz)
Jones' reagent	Chromic and sulfuric acid in acetone
t-BuOK	potassium *tert*-butoxide
KHMDS	potassium hexamethyldisilazide
L	length (dm)
LDA	lithium diisopropylamide
lit.	literature
LiHMDS	lithium hexamethyldisilazide
M	Molar ($molL^{-1}$)
m	multiplet
$M^{+\bullet}$	molecular ion
Mander's reagent	methyl cyanoformate
Me	methyl
MeCN	acetonitrile
MeOH	methanol
min.	minute(s)
mg	milligram
mL	millilitre
mm	millimetre
mol	mole
mmol	millimole
m.p.	melting point (ºC)
MS	mass spectrum
MsCl	methanesulfonyl chloride

m/z	mass-to-charge ratio
nm	nanometre
NaHMDS	sodium hexamethyldisilazide
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
t-BuONa	sodium *tert*-butoxide
Ns	2-nitrobenzenesulfonyl
OMe	methoxy
ν_{max}	infrared absorption maxima (cm^{-1})
p	pentet
p-BQ	*para*-benzoquinone
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium[0]
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium[0]
Ph	phenyl
Piv	pivaloyl
i-Pr	isopropyl
i-Pr_2NH	diisopropylamine
py.	pyridine
q	quartet
R	*rectus*
RCM	ring closing metathesis
R_f	retardation factor
r.t.	room temperature (assumed to be ~18°C)
S	*sinister*
s	singlet
SAR	structure-activity-relationship

sat.	saturated
sept	septet
sex	sextet
$(Bu)_3SnSn(Bu)_3$	hexabutyl ditin
$(Bu)_3SnCl$	tri-*n*-tributylstannyl chloride
t	triplet
TBS	*tert*-butyldimethylsilyl
TBDMS	*tert*-butyldimethylsilyl
TIPS	tri*iso*propylsilyl
Tf	trifluoromethanesulfonyl
TfOH	trifluoromethanesulfonic acid
TFA	trifluoroacetyl
$(TfO)_2$	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
$TiCl_3$•THF	titanium trichloride tetrahydrofuran complex
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
UV	ultraviolet
v/v	volume ratio
Z	*zusammen* (together)
<	less than
>	greater than
°C	degrees Celsius
%	percentage
Δ	heating

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Corrigendum

(i) Page iv, Line 11 and Page 21, Line 6: replace “mimicing” with “mimicking”.

(ii) Page vii, Line 8: replace “to” with “in”.

(iii) Page xii, Line 12: The definition for TFA should read “trifluoroacetyl or trifluoroacetic acid”.

(iv) Page 1, Line 2: replace **“**amendable” with “amenable”.

(v) Page 3, Lines 2, 3 and 4: Should read, “Towards the end of the event, the microtubles begin to form and conglomerate towards the newly formed chromosomes. This event creates the mitotic spindles”.

(vi) Page 5, Fig 1.3: Insert reference number 5 at end of caption.

(vii) Page 8, Line 8, replace “exhibits” with “exhibit”.

(viii) Page 8, Line 22: remove “in”.

(ix) Page 12, Line 2, Page 198, Scheme A:1 and references 16, 34 and 35 in Chapter One: replace “Poiter” with “Potier”.

(x) Page 15, Line 4: replace “piperidine” with “nitrogen-containing”.

(xi) Page 29, Line 1: replace “Nillson” with “Nilsson”.

(xii) Page 45, Line 2: replace “tetrahydocarbazoles” with “tetrahydrocarbazoles”.

(xiii) Page 47, Line 1: replace “as” with “is”.

(xiv) Page 71, Line 18: replace “isolatable” with “isolable”.

(xv) Page 80, Table 3.5, Entry 8: replace “LIHMDS” with “LiHMDS”.

(xvi) Page 105, Line 23: replace “**273**” with “**265**”.

(xvii) Page 121: Compound **87** should be the free alcohol and not the triflate.

(xviii) Page 202, Scheme A.6: The product shown after step c should be the amide not the illustrated thioamide.

(xix) References: Replace “*Tetrahedron Ass”* with “*Tetrahedron: Asymmetry”*; “*Aus. J. Chem*.” with “*Aust. J. Chem.”* and “*Org. Prep. Proced. Int*.” with “*Org. Prep. Proceed. Int*.”

Chapter One

The Biological Activity of (+)-Vinblastine and Motives for the Synthesis of Small Molecule Analogues

1.1 Introduction

Malignant tumours represent one of the most common human diseases worldwide, and the subset of such cancers that are amenable to curative treatment is rather small. Although there has been tremendous progress in understanding the molecular events that lead to malignancy, the development of clinically innovative drugs remains slow. The recent and dramatic success of the natural product Taxol® in treating breast and ovarian cancers has refocussed attention on compounds that act as tubulin binding agents or spindle toxins and that can, therefore, stop the division of cancerous cells.

1.1.1 Tubulin and Microtubules

Every nucleated cell contains two similar spherical proteins, α- and β-tubulin. Through a series of events that are not yet fully understood, these two proteins couple to form heterodimers that can, in turn, combine in a head-to-tail arrangement to give a long protein fibre composed of alternating α-and β-tubulin subunits known as a protofilament. The protofilament then curls along a single axis to form a pipe-like assembly called a microtubule (Figure 1.1).

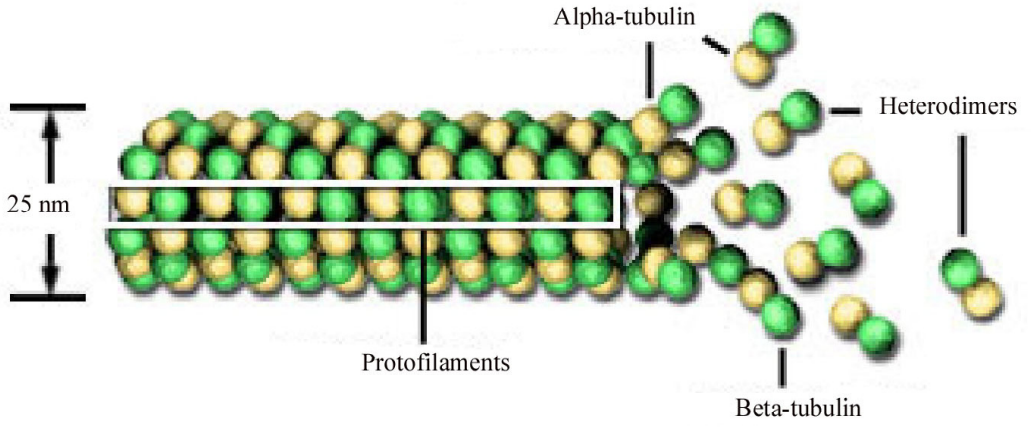


Figure 1.1: *The structure of the microtubule and its component parts*[1]

Once formed, these assemblies are not static. Rather, they exist in equilibrium, with the constituent heterodimers constantly adding to one end and leaving at the other. The resulting control of the length of the microtubules is vital for a number of their functions in the cell. Arguably, the most important role of microtubules is their formation into a bundle that grows towards the newly forming chromosomes. This bundle is known as the mitotic spindle, a structure that is intimately involved in cell replication.

Microtubules and Mitosis

During division the cell duplicates its internal components, including ordering its DNA into two identical sets of chromosomes that separate towards the opposite ends of the cell and are, thereby, ready to form the nuclei of the two new progenitor cells. Once fully separated, the cell splits forming two identical daughter cells. The events associated with the ordering and relocation of genetic material is known as mitosis. Four distinct phases are involved and these are illustrated in Figure 1.2.

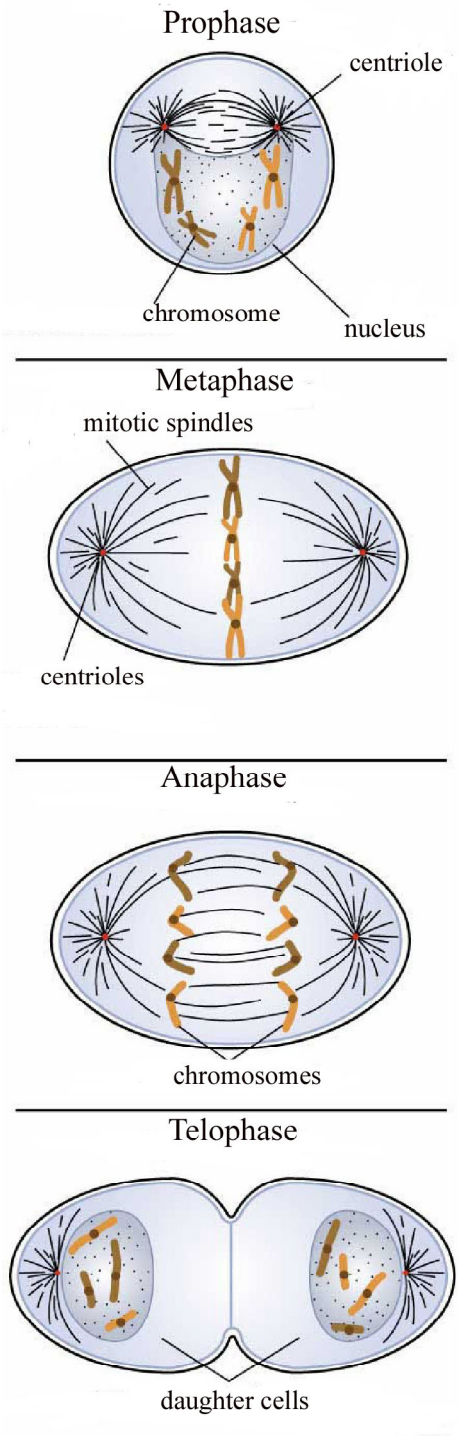


Figure 1.2: *The four stages of cellular mitosis*

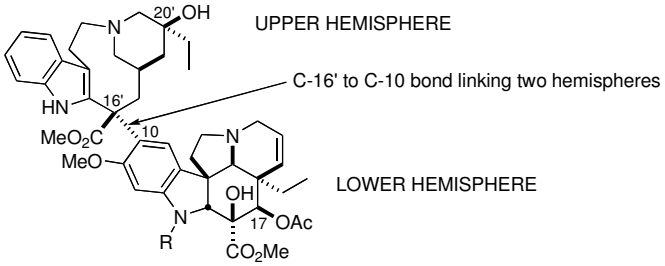
During the initial or prophase, DNA is replicated and organised into two sets of genetic material. Towards the end of this event, the microtubules begin to form and conglomerate towards the newly formed chromosomes. This event created the mitotic spindles.

The next stage, the metaphase, is where the chromosomes arrange vertically along the axis of microtubule bundles known as centrioles. Once this has occurred, the cell abruptly enters anaphase, where the daughter chromosomes begin to separate and the microtubules decay, thus drawing the daughter chromosomes apart and towards the opposite ends of the dividing cell.

During the final phase, the telophase, new nuclear envelopes form around the daughter chromosomes. This ends the cell division process, with microtubules having played a pivotal role by maintaining a structural scaffold that allows replication to occur. Accordingly, agents that interfere with the dynamics of tubulin/microtubule equilibrium may also act as inhibitors of mitosis. Thus, if microtubules in a tumour cell can be selectively prevented from forming, the chromosomes cannot separate, the cell cannot reproduce and, therefore, the tumour cannot grow.

The *Vinca* Alkaloid Binding Site on Tubulin

The alkaloids (+)-vinblastine (**1**) and (+)-vincristine (**2**) each destabilise polymerised tubulin by binding to a site on β-tubulin.[2] Both compounds have a high affinity for this protein[3] and so exhibit an extraordinary potency as anti-mitotic agents. It has been suggested that this destabilising effect arises from the prevention of polymerisation through the forming of a wedge between two tubulin molecules.[4]



1, R = Me, (+)-vinblastine
2, R = CHO, (+)-vincristine

Recently, the structural basis for the regulation of tubulin by (+)-vinblastine (**1**) has been explored. The X-ray structure of crystals of compound **1** attached to the *Vinca* alkaloid binding site of tubulin has been resolved to 4 Å.[5] This structure reveals that the *Vinca* alkaloid binding site of tubulin is comprised of residues that form a hydrophobic pocket. (+)-Vinblastine (**1**) is orientated so that its "upper" and "lower" hemispheres

each interact with both tubulin heterodimers to a similar extent. Key interactions of the binding site with (+)-vinblastine (**1**) probably include those between the tertiary alcohol attached to C-20′ of the alkaloid and the carboxyl carbonyl of the β222 proline residue. This alcohol functionality may also hydrogen bond with the β224 tyrosine residue. Another possible point of contact may be between the backbone amide of β329 asparagine and the carbonyl of the acetate attached to C-17. These interactions are illustrated in Figure 1.3.

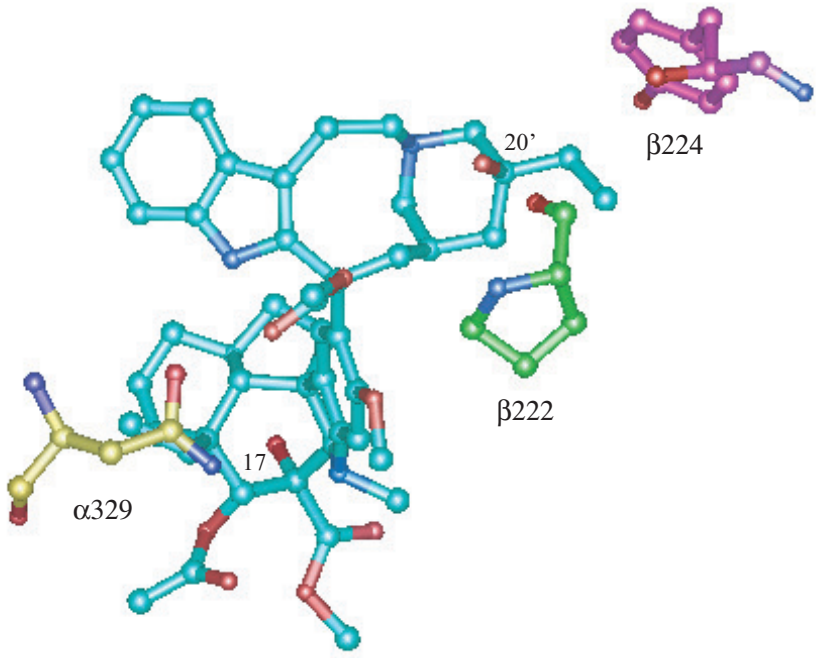


Figure 1.3: *Possible key interactions between (+)-vinblastine (**1**) (cyan) and proline β222 (green), tyrosine β224 (purple) and asparagine α329 (yellow) within the Vinca alkaloid binding site on tubulin*[5]

As the microtubule is a dynamic structure, constantly polymerising and depolymerising, *Vinca* alkaloid poisoned tubulin dimers could easily be incorporated into the microtubule polymer and so prevent further growth. Most studies of analogues of the *Vinca* alkaloids have been confined to ones involving modifications of the natural products. Accordingly, an approach involving synthetically-derived small molecule analogues of the *Vinca* alkaloids could provide important insights into the exact mode of action of this class of compounds because of the capacity it offers for the identification of precisely which functionalities within these natural products are pivotal for interaction with tubulin. While the drugs that interact with tubulin seem to differ greatly in structure,[6] analysis of a number of the compounds that inhibit polymerisation

of this protein, including (+)-vinblastine (**1**), reveals that they contain a "bridging region" between an "upper" and a "lower" hemisphere as shown in Figure 1.4.

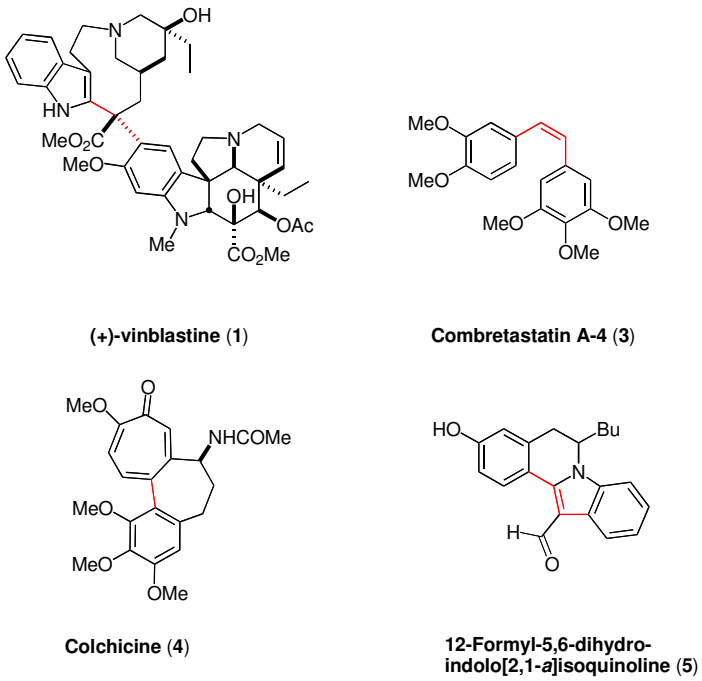


Figure 1.4: *"Bridging regions" (highlighted in red) present in known inhibitors of tubulin polymerisation*

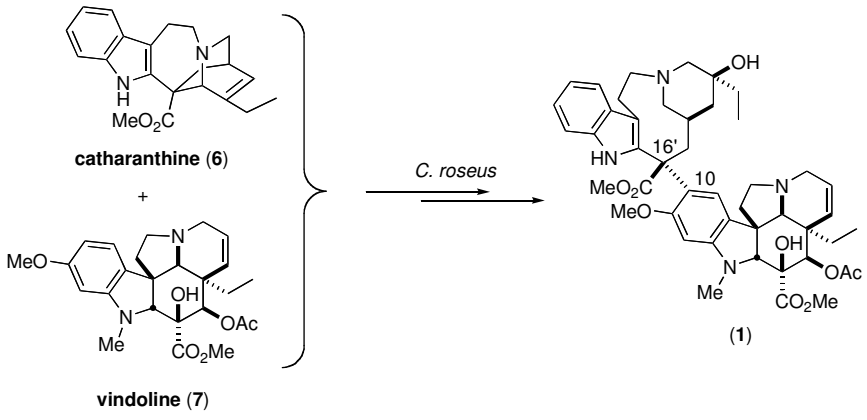
In principle, a series of compounds containing this "bridging region", and incorporating a range of different pairings of aryl groups, representing the "upper" and "lower" hemispheres of the natural product, might be able to be used to identify those functionalities that are responsible for the biological activity of (+)-vinblastine (**1**). Accordingly, the major focus of the work described in the body of this thesis was the development of chemistry that would allow for the assembly of such (+)-vinblastine analogues. However, before any discussion of such work, it is appropriate to highlight some key aspects of the chemistry that has been developed in connection with the total synthesis of (+)-vinblastine (**1**), as well as providing some indications of the structure-activity-relationship (SAR) work that has been carried out around this natural product. This is done in the following sections.

1.2 (+)-Vinblastine

In the late 1950's cellular extracts from the Madagascan periwinkle, *Catharanthus roseus* (L.) G. Don,[7] were found to dramatically suppress the growth of murine leukaemias. Fractionation of these extracts led to the isolation of a number of structurally novel binary alkaloids, including (+)-vinblastine (**1**) and (+)-vincristine (**2**) and from which the observed oncolytic activity was derived.[8]

Since their original isolation and structural elucidation, these particular binary alkaloids, which represent "exotic" members of the aspidosperma family, have risen to prominence as components of combinatorial therapies for the treatment of a range of cancers. These include Hodgkin's and non-Hodgkin's lymphoma, testicular cancer, bladder cancer and acute childhood leukaemia.[9] Although some SAR studies have been undertaken on these alkaloids,[10] thus far, essentially no structurally simpler analogues with clinical utility have been uncovered.

Biosynthetically speaking, the binary aspidosperma alkaloids are derived from a late-stage coupling of catharanthine (**6**) and (-)-vindoline (**7**). This pivotal coupling is followed by a series of functionalisation steps, not yet fully understood, that delivers the natural product **1** (Scheme 1.1).[7, 11-14]



Scheme 1.1: *The late stages of the biosynthesis of (+)-vinblastine (**1**)*

The biosynthetic relationship between the binary alkaloids and their monomeric precursors has been exploited by many research groups investigating the total synthesis of (+)-vinblastine (**1**) and related compounds.[15-22] In the most recent example of such an

approach, Fukuyama prepared (+)-vinblastine (**1**) by coupling (-)-vindoline (**7**) with a macrocyclic catharanthine precursor so as to provide a conjugate that was then readily elaborated to the natural product.[23] This approach was later extended to the preparation of (+)-vincristine (**2**).[24]

It is interesting to note that neither of the *in vivo* precursors to compounds **1** and **2**, namely catharanthine (**6**) and (-)-vindoline (**7**), exhibit cytotoxicity.[25] It is only when these subunits are coupled through a C-16′ to C-10 linkage, to form various binary indole-indoline alkaloids, that oncolytic activity is observed. Clearly, then, this dimerisation leads to the biological activity associated with these alkaloids. As part of an ongoing program within these laboratories that is directed towards developing an expeditious preparation of (+)-vinblastine (**1**) and various analogues, a synthetic protocol was sought for the assembly of the C-16′ to C-10 linkage between the "upper" and "lower" hemispheres of compounds related to the precursors of the alkaloids **1** and **2**. If identified, such a protocol could be used to prepare models of the "bridging region" within compounds **1** and **2** and these would be subject to biological evaluation in order to develop a SAR around a range of (+)-vinblastine substructures. The body of this thesis, therefore, details the development of protocols aimed at identifying an efficient and flexible method for establishing this pivotal linkage and for the preparation of analogues incorporating a biaryl core that might be used to help "pinpoint" the key functionalities responsible for the chemotherapeutic properties of (+)-vinblastine (**1**).

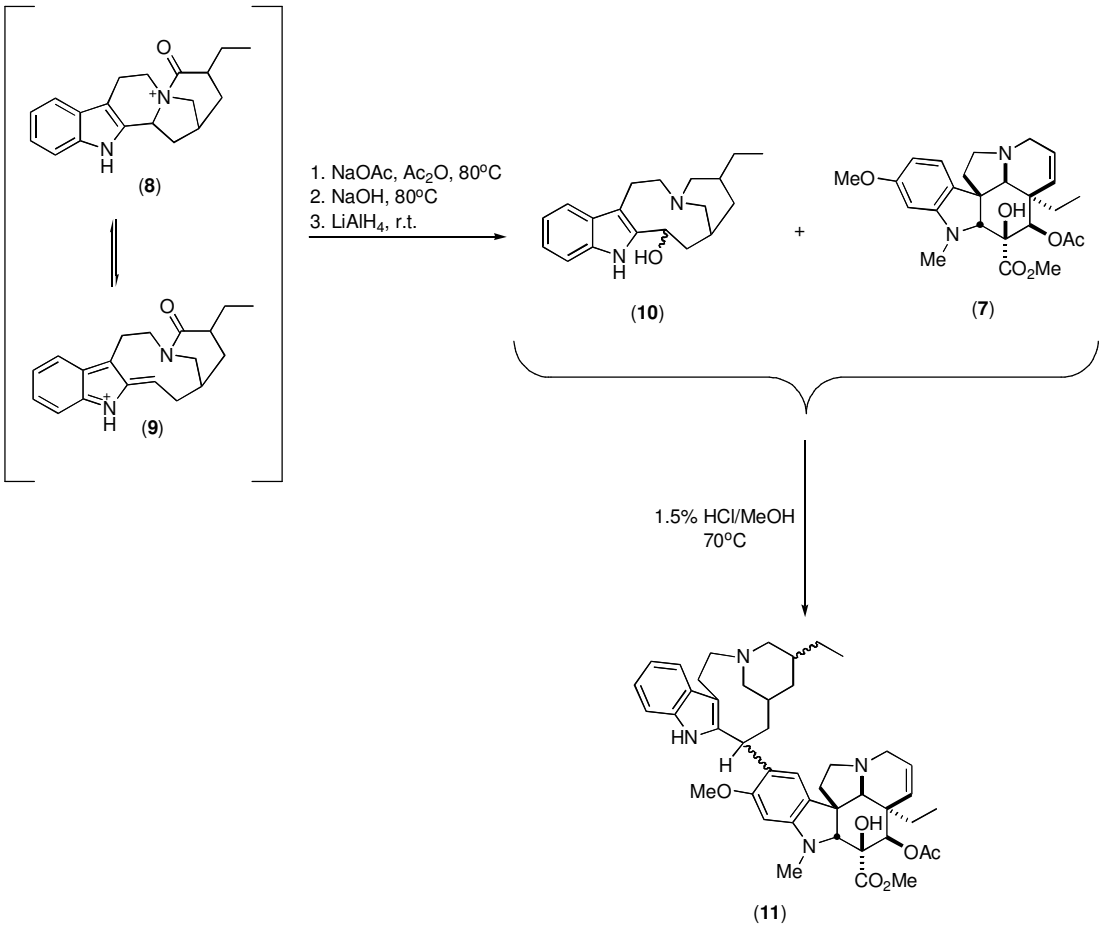
1.3 Studies on the C-16′ to C-10 Linkage of (+)-Vinblastine

Before discussing protocols that have been developed within these laboratories for the installation of the C-16′ to C-10 linkage, it is appropriate to survey the existing methods available for constructing this bond within (+)-vinblastine (**1**). Certainly, it has become well recognised that one of the major difficulties associated with the synthesis of such binary alkaloids is the need to control the absolute stereochemistry at C-16′, which must be *S*.[26] Significantly, analogues of compound **1** incorporating the *R*-configuration at this centre lack the therapeutically valuable cytotoxicity observed in the natural products.[27, 28] Only five total syntheses of (+)-vinblastine (**1**)[19-23] have been reported to date. In the key step, the formation of the C-16′ to C-10 linkage, the three different approaches reported all involve coupling of (-)-vindoline (**7**) to a precursor of the "upper" hemisphere of the target structure **1**.

A comprehensive review of each total and formal total synthesis of (+)-vinblastine (**1**) reported thus far is beyond the scope of this introduction, but summaries of such work are provided in Appendix A. However, a detailed commentary on each type of coupling strategy that has been used to link the two hemispheres of this natural product is presented in the following sections.

1.3.1 The Hydroxyindole Approach

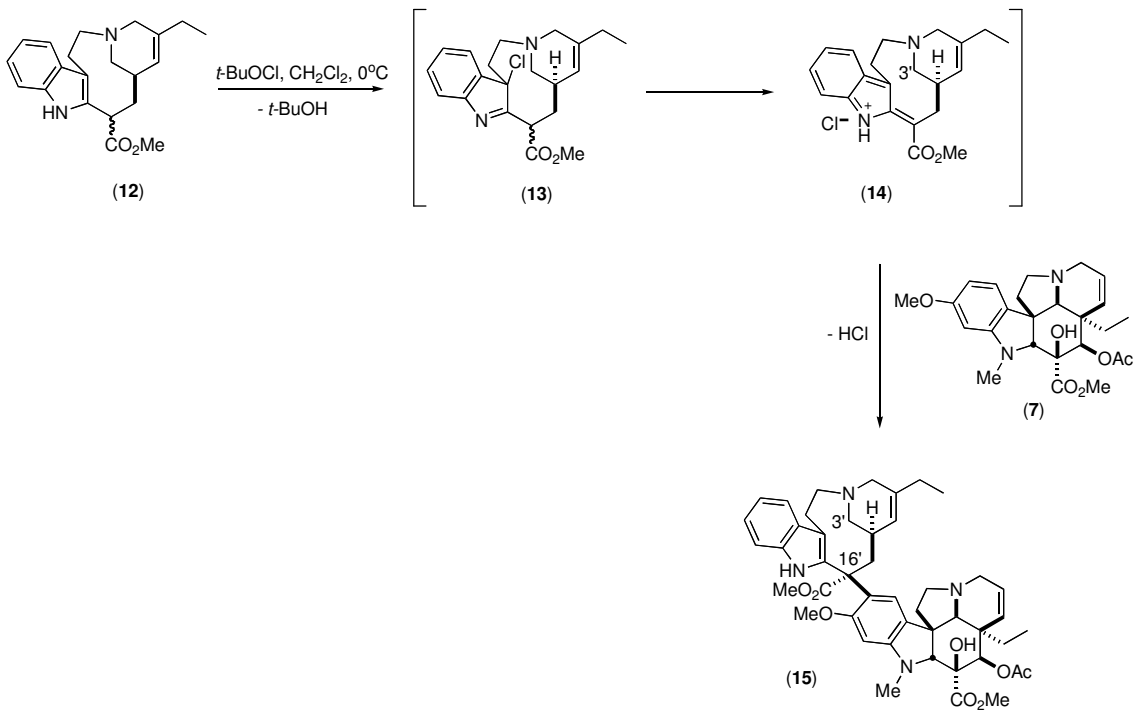
The earliest reported coupling reaction relevant to present discussion was based on the rapid self-condensation observed for 1-hydroxy-1,2,3,4-tetrahydrocarbazole in the presence of dilute acids.[29] This was extended to the ring opening of the pentacyclic *N*-acyl ammonium intermediate **8** and so forming iminium ion **9** (Scheme 1.2).[30] Trapping of the latter by an acetate ion, cleavage of the acetate group so introduced with base, followed by hydride reduction of the lactam function gave the coupling precursor **10** as a mixture of diastereoisomers. Treatment of alcohol **10** with 1.5% methanolic HCl in the presence of (-)-vindoline (**7**) then afforded the binary system **11**, lacking a C-16′ carbomethoxy moiety and obtained as an unspecified mixture of diasteroisomers. Surprisingly, the possibility of directly trapping the postulated iminium ions **8/9** with (-)-vindoline (**7**) was not investigated.



Scheme 1.2: *Key elements associated with the hydroxyindole approach to the binary indole-indoline alkaloids*

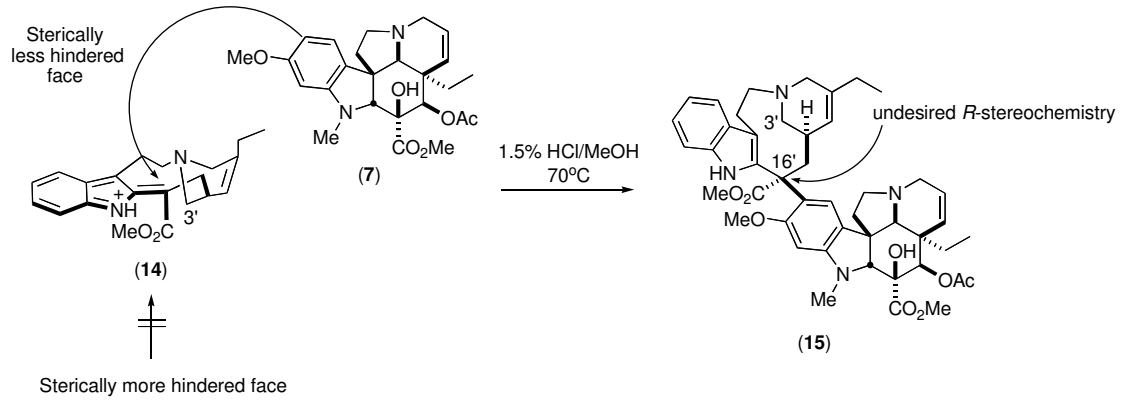
1.3.2 The Chloroindolenine Approach

In a strategy related to that outlined above, and developed almost simultaneously by Neuss[31] and Kutney[32] then extended by Atta-ur-Rahman,[33] the chloroindolenine approach (Scheme 1.3) involves the conversion of a mixture of the epimeric carbomethoxycleavamines **12** into the chloroindolenine **13** that readily rearranges to the azafulvene-type cation **14**. This last species then reacts with (-)-vindoline (**7**) at 70°C to afford 16′-*epi*-anhydrovinblastine (**15**), possessing the opposite stereochemistry to that required at C-16′. As a result, a total synthesis of (+)-vinblastine (**1**) could not be realised by such means. Nevertheless, these early studies of this coupling reaction provided important information about the mechanism of the process.



Scheme 1.3: *The chloroindoline approach to 16′-epi-anhydrovinblastine* ***(15)***

This undesired outcome is attributed to the steric hindrance exerted by the C-3′ methylene group, which retards the approach to the lower face of the nine-membered ring as would be required to establish the correct stereochemistry at C-16′ (Scheme 1.4).

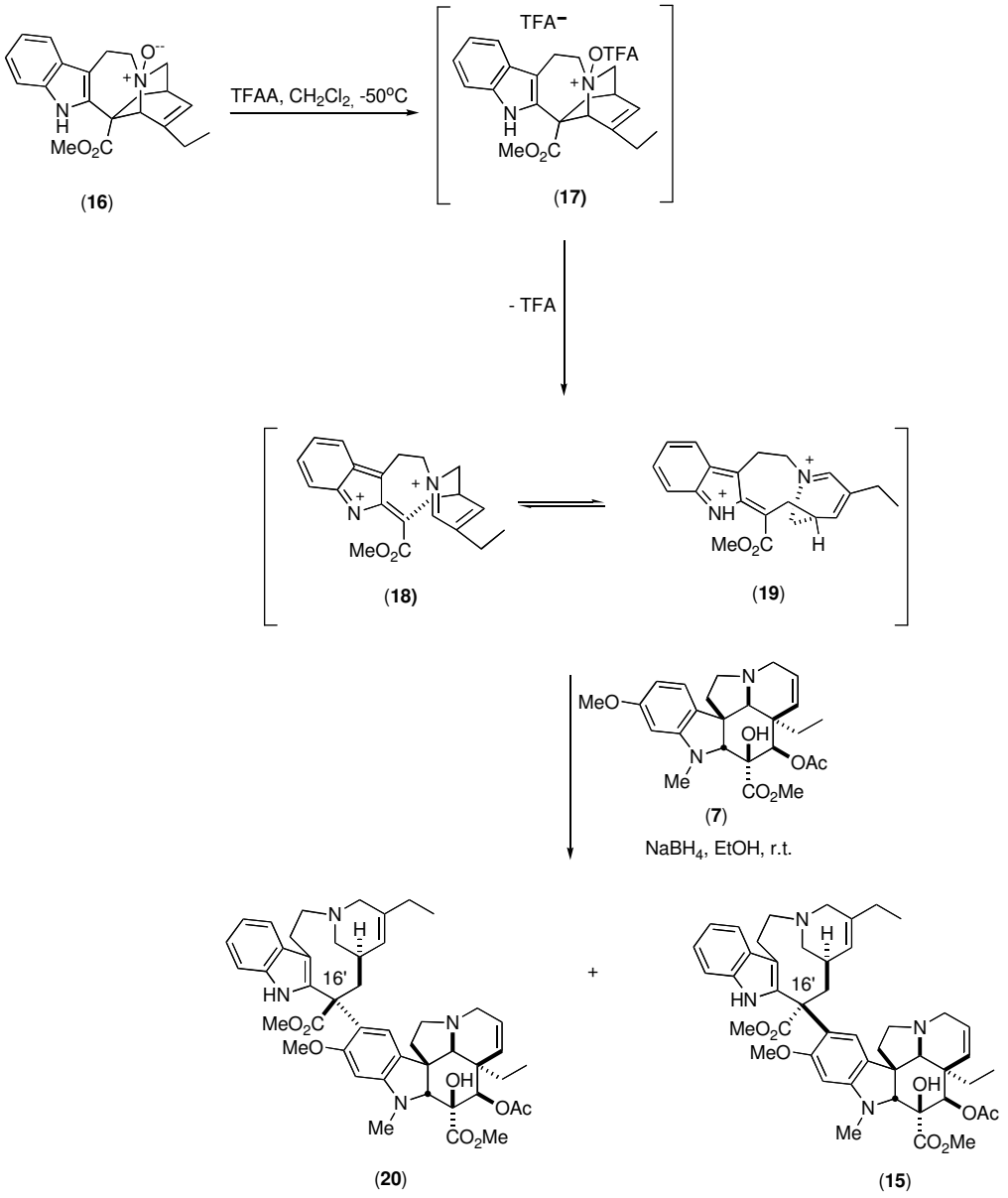


Scheme 1.4: *Preferred trajectory for the reaction of (-)-vindoline (**7**) with azafulvenium cation* ***14***

As explained in the following section, such problems associated with the chloroindolenine route were eventually solved and thus allowed Kuehne to establish a total synthesis of (+)-vinblastine (**1**).

1.3.3 The Biomimetic Approach

The breakthrough in studies directed towards the total synthesis of (+)-vinblastine (**1**) came with the work of Potier,[16, 34, 35] Kutney[18, 36, 37] and Atta-ur-Rahman.[33] Their basic premise involved the notion that, as noted earlier, binary alkaloids are formed in plants through the coupling of (-)-vindoline (**7**) and catharanthine (**6**) and one could use, therefore, a surrogate for compound **13** associated with the chloroindolenine approach. Utilising this concept, Potier[17] and Kutney[38] found a solution to the stereochemical problem by exploiting the Polonovski reaction.[35, 39, 40] Thus, catharanthine *N*-oxide (**16**) (Scheme 1.5) was treated with trifluoroacetic anhydride to give *N*-trifluoroacetoxy cathranthine (**17**) which underwent spontaneous fragmentation to form the *bis*-iminium ions **18/19** that were then trapped by (-)-vindoline (**7**) to furnish, after hydride reduction, either anhydrovinblastine (**20**) or 16′-*epi*-anhydrovinblastine (**15**). The stereochemical outcome at C-16′ was observed to be dependent upon reaction temperature. At –50°C, the natural or *S*-isomer is formed, while at 0°C, the *R*-isomer predominated.



Scheme 1.5: *Exploitation of the Polonovski rearrangement in generating vinblastine-like coupling products with defined stereochemistry at C-16´*

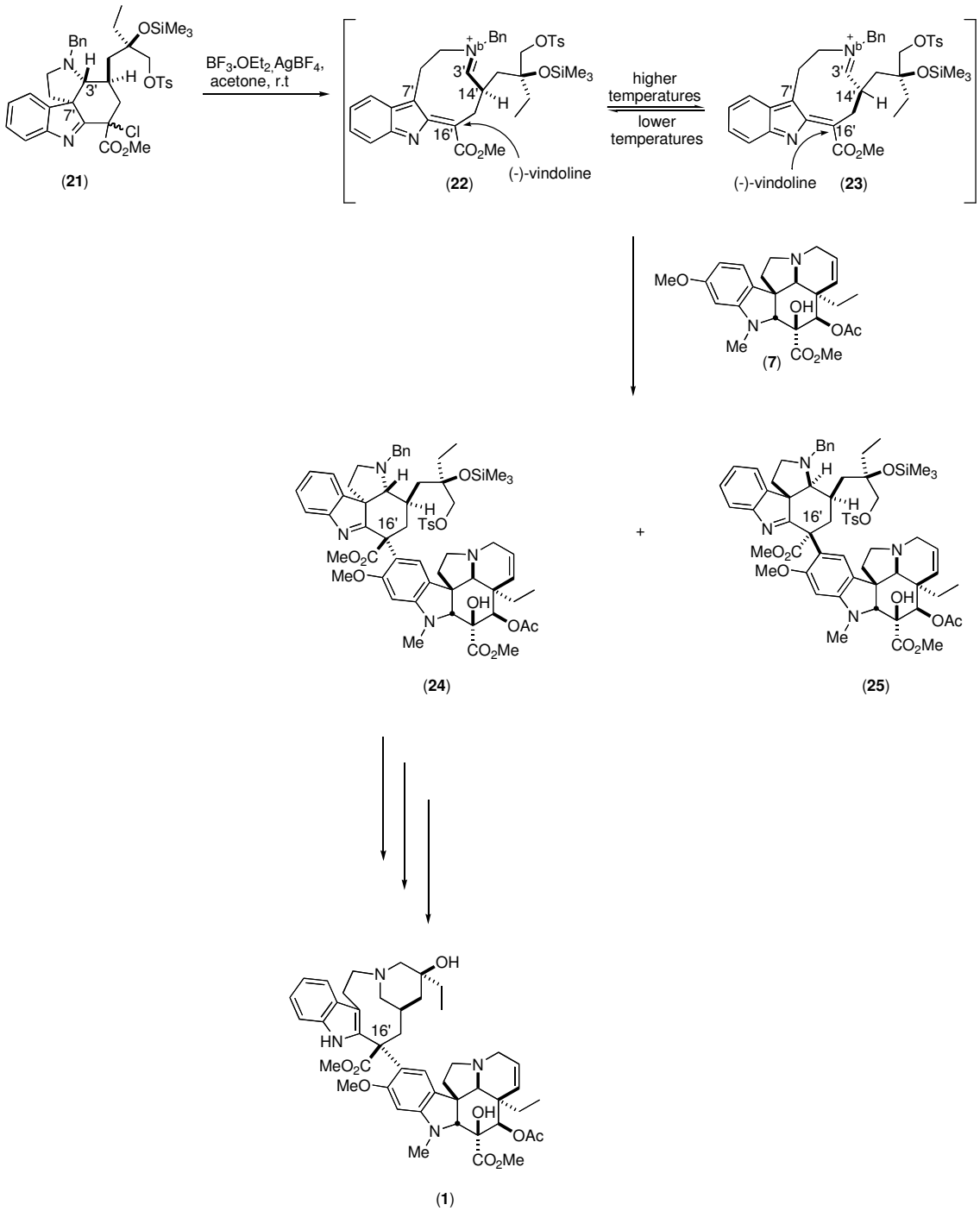
This temperature dependence on stereochemical outcome can be rationalised by invoking an alteration in the conformations of the intermediate iminium ions. At –50°C, ion **18** is generated from catharanthine *N*-oxide (**16**) and the conformation of this species resembles that associated with precursor **16** and so forces the electrophilic substitution reaction with (-)-vindoline (**7**) to take place from the less hindered α-face and thus producing the coupling product possessing the (correct) *S* stereochemistry at C-16′. At higher temperatures equilibration of ion **18** with congener **19** (closely related to the electrophile involved in the chloroindolenine route) becomes more rapid and results in (-)-vindoline (**7**) now attacking the latter intermediate and thus leading to the

formation of compound **15** incorporating the unnatural C-16′ stereochemistry. On the basis of these results, Keuhne was able to modify the chloroindolenine approach so as to generate (+)-vinblastine (**1)** in a stereoselective fashion. The following section details Kuehne's effort in this regard.

Total Synthesis of (+)-Vinblastine by Kuehne

Kuehne's enantioselective synthesis of (+)-vinblastine (**1**)[21] involved the coupling of the chlorinated vincadifformine intermediate **21** with (-)-vindoline (**7**) as shown in Scheme 1.6. The coupling was achieved by treating chloroindolenine **21** with silver tetrafluoroborate so as to generate the intermediate iminium salt **22**. This intermediate was then trapped with (-)-vindoline (**7**), resulting in the tetracyclic indolenine **24** possessing the correct stereochemistry at C-16′.

As suggested in the preceding section, the stereochemistry established at C-16′ is strongly dependent on temperature, with the yield of undesired stereoisomer **25** increasing as the reaction mixture is warmed up. While steric considerations can be used to explain the stereochemical outcome observed in the coupling of (-)-vindoline (**7**) with chloroindolenines (Scheme 1.4), stereoelectronic reasons explain why the correct stereochemistry is obtained when the appropriate chlorinated vincadifformine intermediates are used.



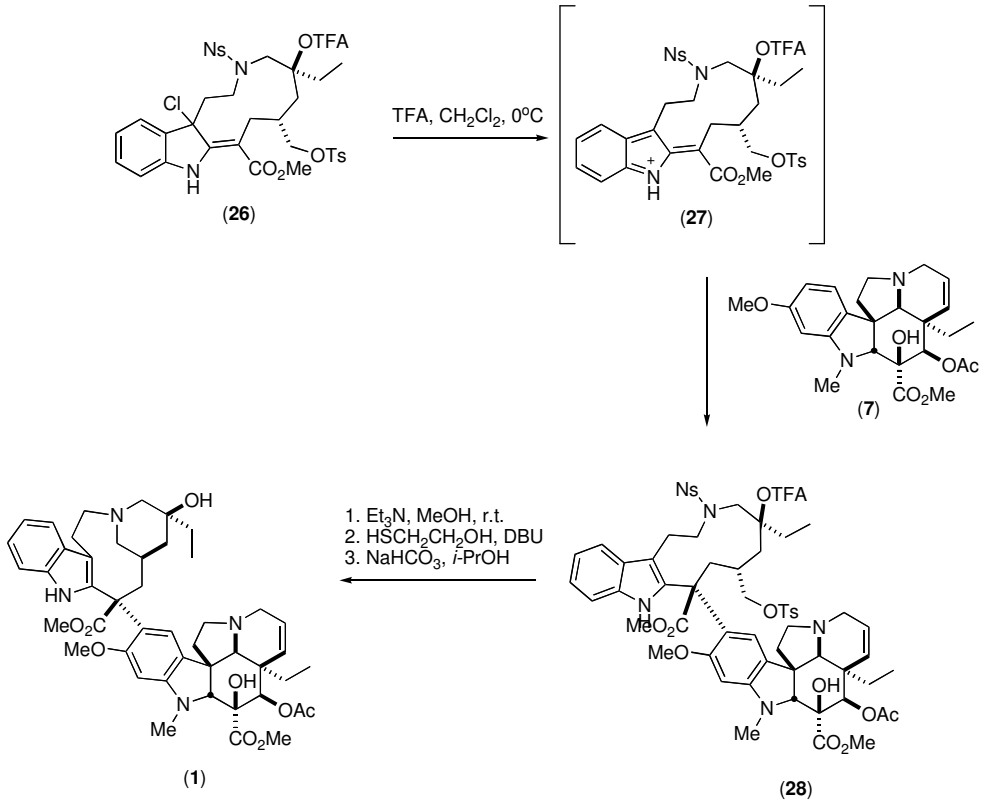
Scheme 1.6: *Kuehnes's use of the chloroindolenine approach in establishing a total synthesis of (+)-vinblastine (**1**)*

Thus, the success of the coupling is based on the ready cleavage of the C-7′ to C-3′ bond in intermediate **21** which is facilitated by the *trans*-periplanar orientation of this bond and the N^b lone pair and all while maintaining the desired C-3′ to C-14′ *trans*-substitution. This allows the ring to flip to a less strained conformation that then leads to establishment of the correct stereochemistry in compound **24**. At the point of formation of the pivotal bond from C-16′ of iminium ion **22** to C-10 of (-)-vindoline (**7**), the one-

sided interaction of the extended polyene, including at the reaction site C-16′, differs between the potentially interconverting iminium ions **22** and **23**. This is due to the reversible cleavage of the C-7′ to C-3′ bond in precursor **21** during the reaction, with the relative amount of the correct stereoisomer **24** arising from the maintenance of some semblance of the initial confirmation of this precursor in the product iminium ion. With increasing temperature, the yield of the correct stereoisomer **24** decreases because of the diminished stereoelectronic control exerted by the abovementioned factors.

Total Synthesis of (+)-Vinblastine by Fukuyama

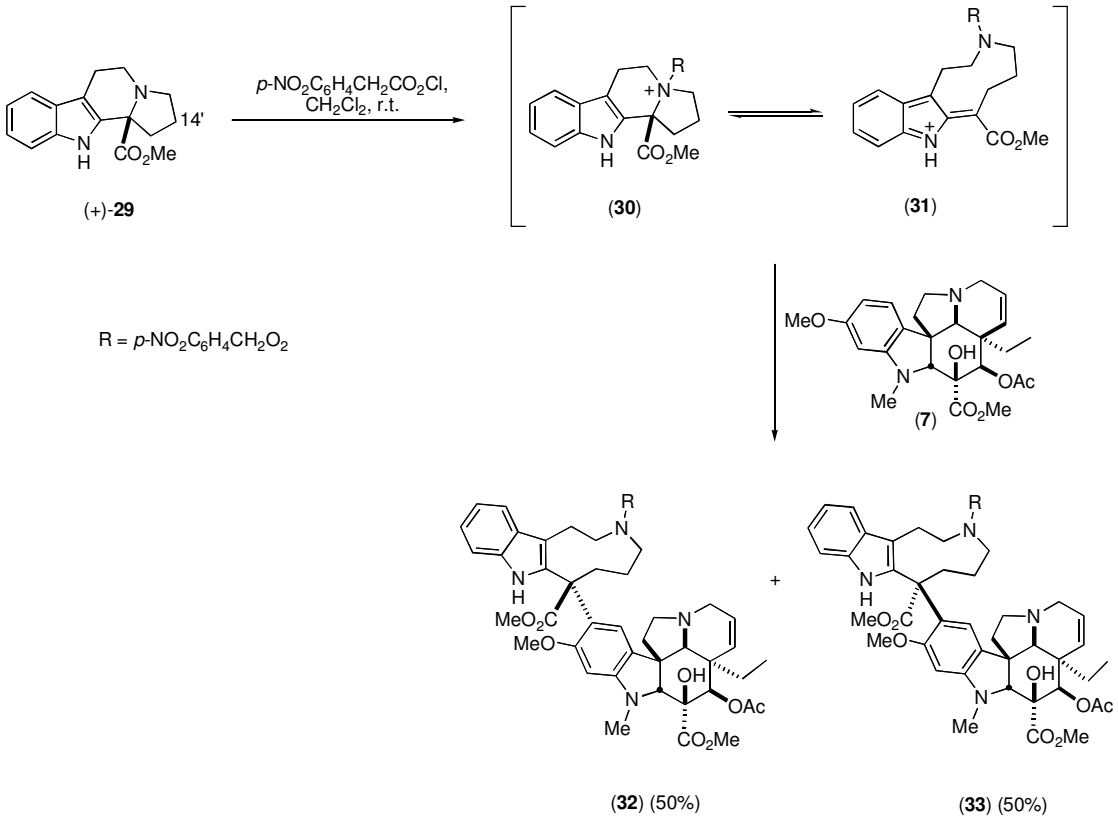
Fukuyama[23] has completed the most recently reported stereocontrolled total synthesis of (+)-vinblastine (**1**) by exploiting the coupling protocols established in Kuehne's synthesis.[21] The final stages in this total synthesis of (+)-vinblastine (**1**) are illustrated in Scheme 1.7. Thus, treatment of chloroindolenine **26** with (-)-vindoline (**7**) in the presence of trifluoroacetic acid, furnished, *via in situ* formation of cation **27**, the desired compound **28** as the sole reaction product and in 97% yield. After deprotection of the tertiary alcohol, the Ns group was then removed, under mild conditions, to liberate the corresponding secondary amine, which spontaneously formed a piperidine ring *via* transannular alkylation of nitrogen by the pendant tosyloxymethyl group. In this way the total synthesis of (+)-vinblastine (**1**) was completed.



Scheme 1.7: *The late stages of Fukuyama's stereocontrolled total synthesis of (+)-vinblastine (**1**) involving chloroindolenine **26** as a precursor to the coupling species **27***

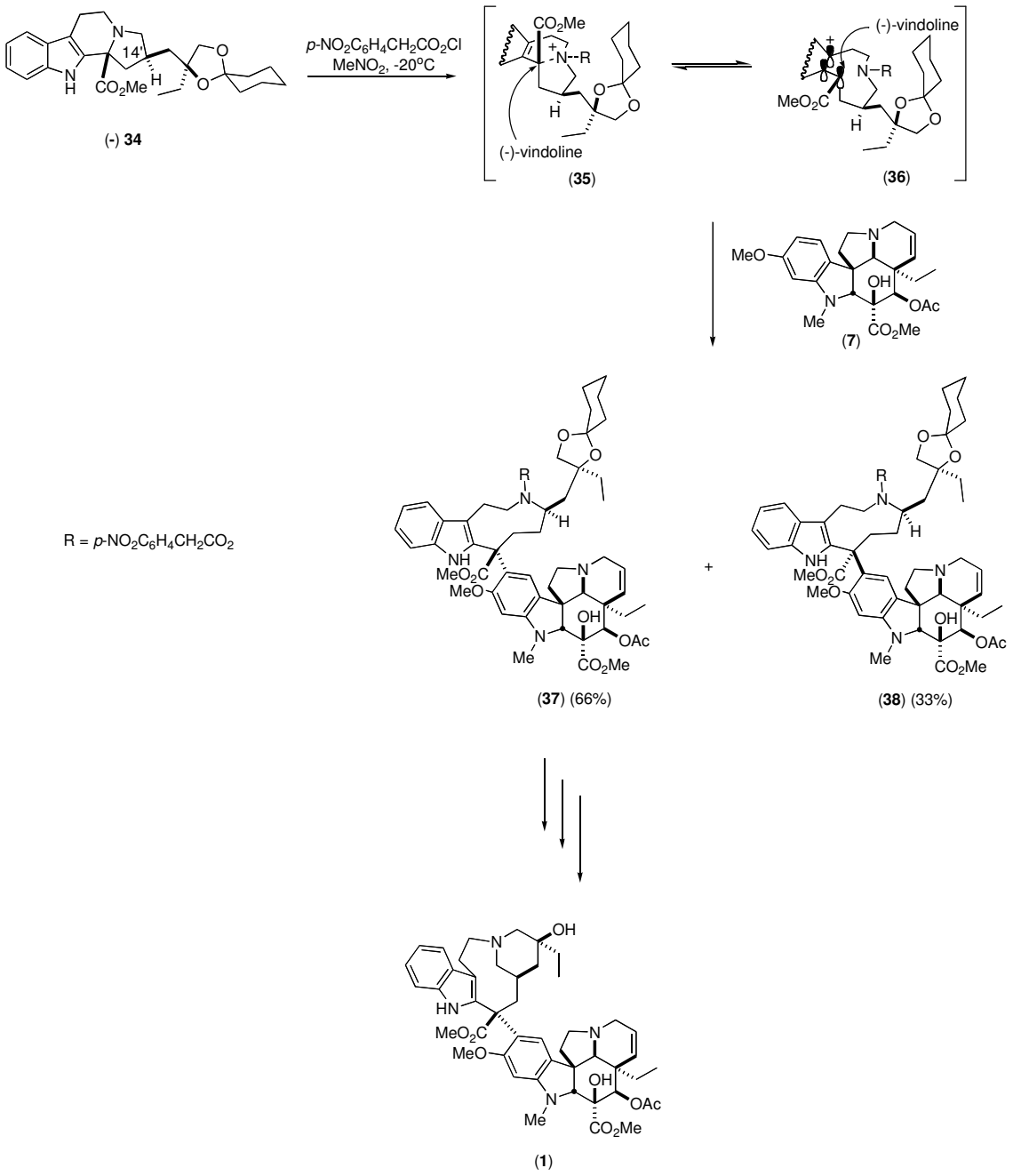
Total Synthesis of (+)-Vinblastine by Magnus

Magnus's group[22] was the first to exploit a new, nonoxidative coupling methodology in the preparation of (+)-vinblastine (**1**) and a novel solvent effect was used to attain the correct stereochemistry at the crucial C-16′ stereocentre. The key to this approach was the assumption that intermediate iminium ions such as **9**, **14**, **18/19** all contain a substituent at C-14′ that will exert some control on the stereochemistry at C-16′ in their coupling products with (-)-vindoline (**7**). Therefore, in preliminary work Magnus studied the reactions of a nine-membered ring iminium ion lacking such a substituent. To this end, tetracyclic amine (+)-**29** was synthesised. This compound was then treated with *p*-nitrobenzyl chloroformate to afford the intermediate **30** that underwent non-oxidative cleavage to generate the iminium ion which, in the presence of (-)-vindoline (**7**), was trapped at C-16′ to give a 1:1 mixture of the diastereomeric coupling products **32** and **33** (Scheme 1.8).



Scheme 1.8: *Magnus's model study on the non-oxidative coupling of tetracyclic amine (+)-**29** with (-)-vindoline (**7**)*

A major reason for obtaining a 1:1 mixture of epimers is that, remarkably, the electrophilic aromatic substitution reaction of the iminium ion **31** is reversible. Hence, when this process is slow, as is the case when (-)-vindoline (**7**) is the nucleophile, the iminium ion **31** undergoes equilibration with iminium ion **30** and so allowing for the formation of the observed diastereoisomeric forms of the final coupling product. However, this did not prove a problem, as the equivalent amine to (+)-**29** that would need to be used in the total synthesis study (Scheme 1.9) must have a sidechain at C-14′ that eventually becomes part of the piperidine ring. Fortuitously, this moiety slows the conformational inversion of the nine-membered ring and allows coupling with (-)-vindoline (**7**) to proceed with establishment of the required configuration at C-16′. Thus, treatment of amine (-)-**34** with *p*-nitrobenzyl chloroformate followed by (-)-vindoline (**7**) at –20°C in nitrobenzene and using 2,6-di-*tert*-butyl-4-methylpyridine as catalyst gave a 2:1 mixture of the 16′*S*-stereoisomer **37** and its epimer **38** (Scheme 1.9). The Magnus total synthesis (+)-vinblastine (**1**) was then completed through a series of relatively straightforward functionalisation steps and so affording (+)-vinblastine (**1**).



Scheme 1.9: *Late stages of Magnus's total synthesis of (+)-vinblastine (**1**)*

Initially, dichloromethane was used as the solvent in a coupling reaction that was conducted at room temperature. However, this led to the incorrect stereochemistry at C-16′. Magnus explained this outcome by invoking the establishment of an equilibrium between cations **35** and **36**. Under these reaction conditions the equilibration is faster than the coupling reaction. Nevertheless, the rate of the coupling reaction relative to the conformational equilibration could be increased by either decreasing the reaction temperature or by varying the polarity of the solvent. Thus, when the coupling was carried out –20°C and nitromethane used as solvent then the product possessing the

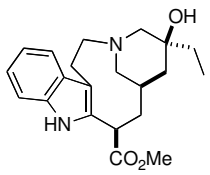
correct stereochemistry at C-16' was observed as the major product of the reaction. Magnus attributed the stereochemical consequences of replacing dichloromethane with nitromethane to a preferential solvation of the "closed" iminium ion **35** over the more delocalised and "open" iminium ion **36**. The localised charge in the "closed" ion should be lowered by solvation with nitromethane compared with that in the delocalised "open" ion. The "closed" ion is of a shape that allows electrophilic attack by (-)-vindoline (**7**) from the less hindered α-face and so leading to the desired stereochemistry in the coupling product.

To summarise, then, although there have been five total syntheses of (+)-vinblastine (**1**) reported, only three distinct approaches to the title alkaloid have been developed and these all involve the direct coupling of (-)-vindoline (**7**) with catharanthine (**6**) or an equivalent thereof. (-)-Vindoline (**7**) invariably acts as the nucleophile in such coupling processes.

The remainder of this introduction details a new synthetic strategy for the preparation of (+)-vinblastine analogues that mimic the "bridging region" between the "upper" indole and "lower" indoline hemispheres of the natural product.

1.4 Towards a Synthesis of "Bridging Region" Analogues of (+)-Vinblastine

Traditionally, (+)-vinblastine (**1**) has been constructed by coupling (-)-vindoline (**7**), which acts as a nucleophile, to a suitable carbomethoxyvelbamine precursor that acts as an electrophile. Such an approach is required because coupling of carbomethoxyvelbamine (**39**) itself to (-)-vindoline (**7**) gives the incorrect stereochemistry at C-16′ in the reaction product.[20]



(**39**)

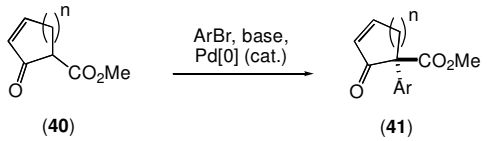
The coupling strategy developed as part of the work described below involved a nucleophilic synthetic equivalent for carbomethoxyvelbamine (**39**) and an electrophilic equivalent for (-)-vindoline (**7**). This approach represents a reversal of the polarity associated with biomimetic coupling of those units that has been used in all approaches to (+)-vinblastine (**1**) reported to date. Nevertheless, it provided a capacity to gain ready access to a series of small molecule analogues mimicking the indole-indoline core or "bridging region" of (+)-vinblastine (**1**). These analogues should allow for the probing of the key functionalities responsible for the biological activity of the title natural product. In principle, this approach could also be employed to explore key aspects of a potentially new strategy for the synthesis of (+)-vinblastine (**1**). As matters turned out, at no stage during the work reported in this thesis were efforts made to prepare (+)-vinblastine (**1**) itself. However, through such work the possibility of successfully tackling such a formidable problem has been greatly enhanced.

1.5 Aims of the Research Described in this Thesis

The three key areas studied, and reported upon in the body of this thesis, are introduced below. These involve, (i) the preparation of "bridging region" or indole-indoline analogues of (+)-vinblastine (**1**), (ii) attempts to develop a synthesis of the carbomethoxyvelbamine framework representing the "upper" hemisphere of (+)-vinblastine (**1**) and (iii) the use of chiral auxiliaries to develop a diastereoselective arylation reaction pivotal for the construction of the aforementioned analogues.

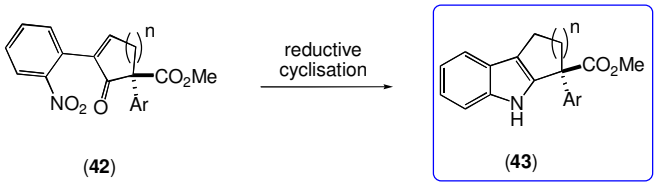
1.5.1 Preparation of "Bridging Region" Analogues of (+)-Vinblastine

The primary aim of this project was the development of a methodology for forming a series of "bridging region" or indole-indoline analogues of (+)-vinblastine (**1**). The approach required the initial preparation of an α-arylated β-ketoester **41**, perhaps *via* an enantioselective and Pd[0]-catalysed arylation reaction[41-46] of the corresponding non-arylated precursor **40** (Scheme 1.10).



Scheme 1.10: *Key Pd-catalysed arylation reaction associated with the initial stages of proposed approach to "bridging region" analogues of (+)-vinblastine*

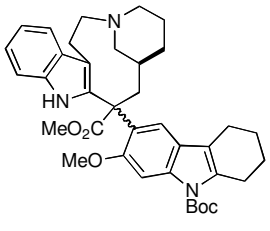
The motivation for seeking an enone like **41** was the development, within these laboratories,[47] of protocols for converting such compounds into their α′-(*o*-nitrophenyl) derivatives (e.g. **42**) that can undergo reductive cyclisation to give the corresponding indoles, (e.g. **43**) (Scheme 1.11). Provided that the original aryl group (Ar) was an appropriate one, these last compounds could be regarded as representing the desired (+)-vinblastine analogues. Studies aimed at the implementation of such ideas are described in Chapter Two.



Scheme 1.11: *Key indole-forming reaction associated with the final stage of a proposed approach to "bridging region" analogues of (+)-vinblastine*

1.5.2 Development of Carbomethoxyvelbamine Framework

The second aim of the work detailed in this thesis was to develop a method for constructing the carbomethoxyvelbamine framework of (+)-vinblastine (**1**). A model study involving attempts to prepare *bis*-indole **44** that contains a tetracyclic structure similar to that of the "upper" hemisphere of (+)-vinblastine (**1**) represented the initial objective in this area. The results of studies on this topic are detailed in Chapter Three.



1.5.3 Controlling the Stereochemistry of C-16´ to C-10 Linkage in the Targetted (+)-Vinblastine Analogues

In contemplating the preparation of a series of " bridging region" analogues of (+)-vinblastine, it is clear that the correct stereochemistry at the equivalent to C-16´ in such compounds would need to be established through a stereoselective arylation reaction. Accordingly, the third aim of this project was to develop a method, utilising chiral auxiliaries, for controlling the stereoselectivity of this key bond forming process. Relevant work directed towards this end is described in Chapter Four.

1.5 References

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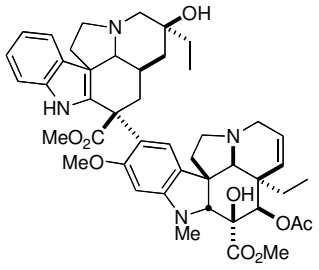
The Synthesis of Analogues of the Indole-Indoline Core of (+)-Vinblastine

2.1 Introduction

2.1.1 Overview and Context

In an effort to identify the key functionalities that are responsible for the biological activity of (+)-vinblastine (**1**), a series of analogues corresponding to the indole-indoline core of this natural product but incorporating a range of different aryl groups was sought.



(**1**)

Initially, attention was directed to constructing the link between the indole and indoline units, or their surrogates, and that would, therefore, mimic the C-16′ to C-10 bond present in *Vinca* alkaloid **1**. To this end, it was envisaged (Figure 2.1) that a β-ketoester such as **45** would first be α-arylated to form a derivative of the general form **46**. It was hoped this latter compound could then be transformed into the corresponding α′-iodinated enone, for example **47**, and that this would, in turn, engage in a Pd[0]-catalysed Ullmann cross coupling reaction[1] with, for example, *o*-nitroiodobenzene to give a product such as **48**. Finally, reductive cyclisation should afford the desired vinblastine analogue of the general type **49** that embodies the ABC-ring system of the alkaloid together with a "mimic" of the indoline portion of this natural product.

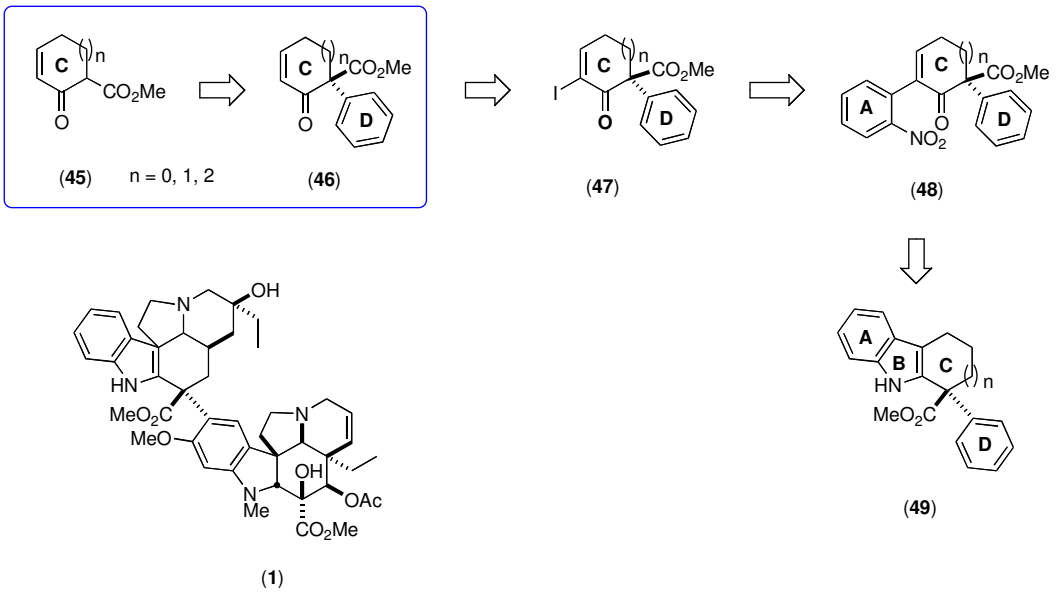


Figure 2.1: *Proposed route to the target vinblastine analogues* ***49***

A key feature of this approach is the need to effect the α-arylation of a β-ketoester such as **45** and to then use Pd[0]-catalysed Ullmann cross-coupling chemistry to install the D-ring of the requisite analogues. The product, e.g. **48**, of such a sequence would then be elaborated to a target of the general type **49**. This Chapter details the development of a method to prepare enones of the general form **46**, and how such systems were then converted into the desired analogues, e.g. **49**, of (+)-vinblastine.

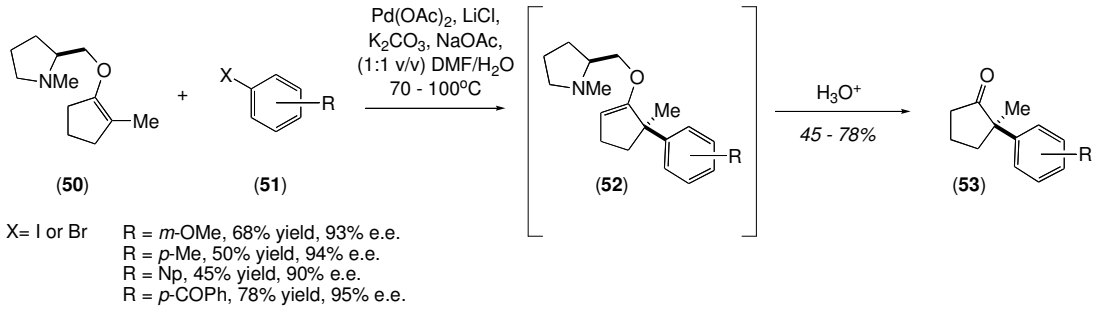
2.2 *α*-Arylation of β-Ketoesters

2.2.1 Background

Unlike alkyl halides and their equivalents, aryl halides do not normally react with metal enolates to give α-arylated carbonyl compounds.[2-4] Therefore, finding an efficient and reliable way to form a bond between an arene and the α-carbon of an enolisable carbonyl unit has been a challenging problem in organic synthesis. Of course, this type of conversion represents one of the key steps (see **45** → **46** in Figure 2.1) associated with the proposed route to the required (+)-vinblastine (**1**) analogues. It is appropriate, therefore, to review those methods currently available for this purpose.

Chelation-controlled Heck Reactions

In an example of a chelation-controlled Heck reaction, Nilsson[5] arylated the prolinol vinyl ether **50** with a range of aryl halides **51** using catalytic quantities of palladium acetate. The initial arylation products engaged in a syn-selective β-elimination reaction and so forming compounds of the type **52** that were not isolated. Rather they were subjected to acid hydrolysis and by such means gave products of the general form **53** in high e.e. (90 – 95%) and in yields in the range of 45 to 78% (Scheme 2.1).

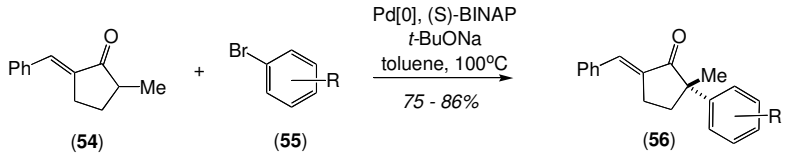


Scheme 2.1: *Asymmetric, chelation-controlled Heck arylation of prolinol vinyl ether* ***50*** *with a range of aryl halides* ***51***

The disadvantage associated with this protocol is that the preparation of the prolinol vinyl ether **50** involves an acid-catalysed acetalization-elimination sequence that is not regioselective and leads to nearly equal quantities of two possible regioisomeric enol ethers. This lack of selectivity is clearly undesirable, so another palladium-mediated technique was sought for the present purposes.

Buchwald/Hartwig Palladium Mediated α-Arylations

Buchwald[6-8] and Hartwig[9-11] have independently reported the synthesis of α-aryl ketones from ketones and aryl bromides using catalytic amounts of a Pd[0] species that is stabilised by bulky dialkylphosphino-binaphthyl ligands. Inorganic bases are utilised in these reactions which can proceed enantioselectively, a quality required in the present studies in order to establish the correct absolute stereochemistry at the equivalent of C-16′ in the proposed analogues. The Buchwald chemistry is exemplified in Scheme 2.2. Thus, a series of 2-alkylcyclopentanones **54** was treated with a range of aryl bromides (**55**), (*S*)-BINAP, sodium *tert*-butoxide and a Pd[0] catalyst so as to generate the corresponding series of aryl-2-alkylcyclopentanones **56**.



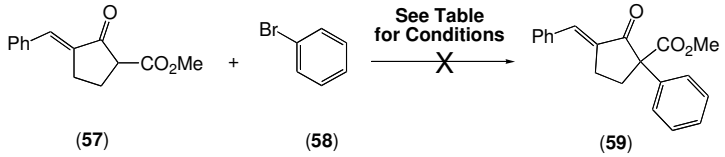
R = *m*-Me, 80% yield, 94% e.e.
R = *m*-1,3 dioxolane, 86% yield, 95% e.e.
R = *p*-*t*-Bu, 75% yield, 98% e.e.

Scheme 2.2: *Buchwald/Hartwig α-arylation of cyclic ketone* ***54***

It should be noted, however, that a blocking group was required to prevent arylation occurring at what would otherwise be the less substituted α-carbon of the ketone. In substrate **54** this blocking group is an aryl-substituted methylene unit. After 3 hours at 100°C, the products illustrated were formed in yields ranging from 75 to 86% and with e.e.'s from 86 – 98%.

On the basis of such reports, an investigation of the α-arylation of the known β-ketoester **57**[12] with bromobenzene (**58**) was undertaken and in the expectation that this would generate the corresponding arylated β-ketoester **59**. However, even though a range of bases, solvents and palladium sources was used (Table 2.1) it was not possible to generate the desired product **59**. Indeed, despite employing, in certain cases, rather forcing reaction conditions, only starting material was recovered in each instance.

Table 2.1: *Attempted Buchwald-type α-arylations of β-ketoester* ***57***



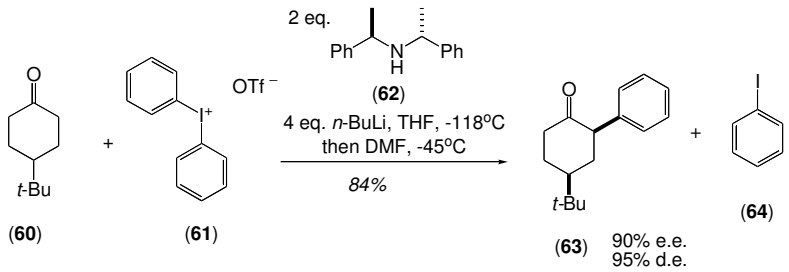
(**57**) (**58**) (**59**)

entry	catalyst[a]	ligand[b]	base	solvent	temp (°C) /time (h)	product
1	$Pd(OAc)_2$	*rac*-BINAP	*t*-BuONa	toluene	100/3	*No reaction*
2	$Pd(OAc)_2$	*rac*-BINAP	*t*-BuONa	toluene	100/12	*No reaction*
3	$Pd(PPh_3)_4$	*rac*-BINAP	*t*-BuONa	toluene	100/3	*No reaction*
4	$Pd_2(dba)_3$	*rac*-BINAP	*t*-BuONa	toluene	100/3	*No reaction*
5	$Pd_2(dba)_3$	*rac*-BINAP	*t*-BuONa	toluene	100/3	*No reaction*
6	$Pd_2(dba)_3$	*rac*-BINAP	*t*-BuONa	THF	70/12	*No reaction*
7	$Pd_2(dba)_3$	*rac*-BINAP	NaHMDS	THF	70/3	*No reaction*
8	$Pd_2(dba)_3$	*rac*-BINAP	*t*-BuOK	THF	70/3	*No reaction*

[a]catalyst loading: 10 mol%. [b]Pd/ligand ratio 1.25.

Direct Asymmetric α-Arylations Using Diaryl Iodonium Salts

Recently, high-valent iodonium salts have been exploited in a variety of contexts as equivalents of aryl iodides.[13] Aggarwal and Olofsson[14] have, for example, developed a method for the direct asymmetric α-arylation of 4-(*tert*-butyl)cyclohexanone (**60**) that involves the asymmetric enolisation of this substrate using the chiral base **62**. Reaction of the resulting enolate with the diphenyl iodonium salt **61** then afforded the *cis*-configured and α-arylated product **63** in 84% chemical yield, 90% e.e. and 95% d.e. (Scheme 2.3).

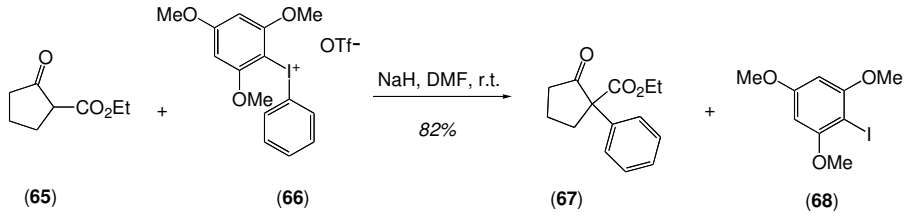


(**60**) (**61**) (**62**) (**63**) 90% e.e. 95% d.e. (**64**)

Scheme 2.3: *Asymmetric α-arylation of 4-(*tert*-butyl)cyclohexanone (**60**) with diphenyl iodonium salt **61** employing chiral base **62***

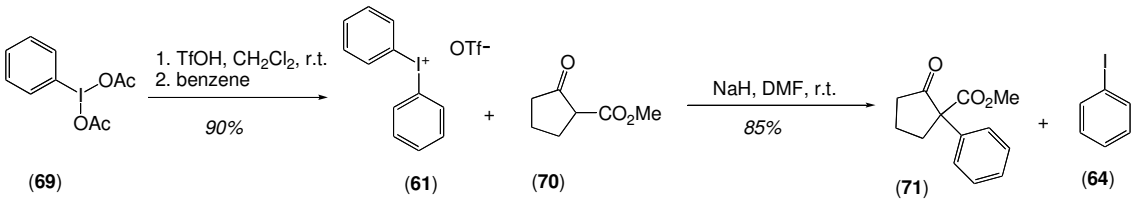
However, applications of this protocol are somewhat restricted by the need to employ a symmetrical carbonyl-containing compound.

Oh, during studies directed towards the total synthesis of the sesquiterpene laurene,[15] demonstrated that the sodium salt of ethyl 2-oxocyclopentanecarboxylate (**65**) reacted smoothly with the iodonium salt **66** to afford, as shown in Scheme 2.4, the phenylated product **67** in 82% yield together with the expected by-product **68**.



Scheme 2.4: *Arylation of β-ketoester* ***65*** *with diaryl iodonium salt* ***66***

In order to investigate the utility of such a protocol for the present purposes, iodobenzene diacetate (**69**) was treated with trifluoromethanesulfonic acid then benzene so as to form the diphenyl iodonium salt **61** which was obtained in 90% yield (Scheme 2.5).[16] Methyl 2-oxocyclopentanecarboxylate (**70**) was then treated with this salt under conditions defined by Oh[15] and product **71** was obtained in 85% yield. Iodobenzene (**64**) was also isolated as the expected by-product of this reaction.

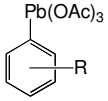


Scheme 2.5: *Arylation of methyl 2-oxocyclopentanecarboxylate (****70****) with diphenyl iodonium salt* ***61***

While this procedure is clearly quite effective when structurally simple products are being sought, it proved inapplicable in more complex cases because the yields of the required *bis*(heteroaryl) iodonium salts were poor due to their rapid decomposition under the acidic conditions required to generate them.[17]

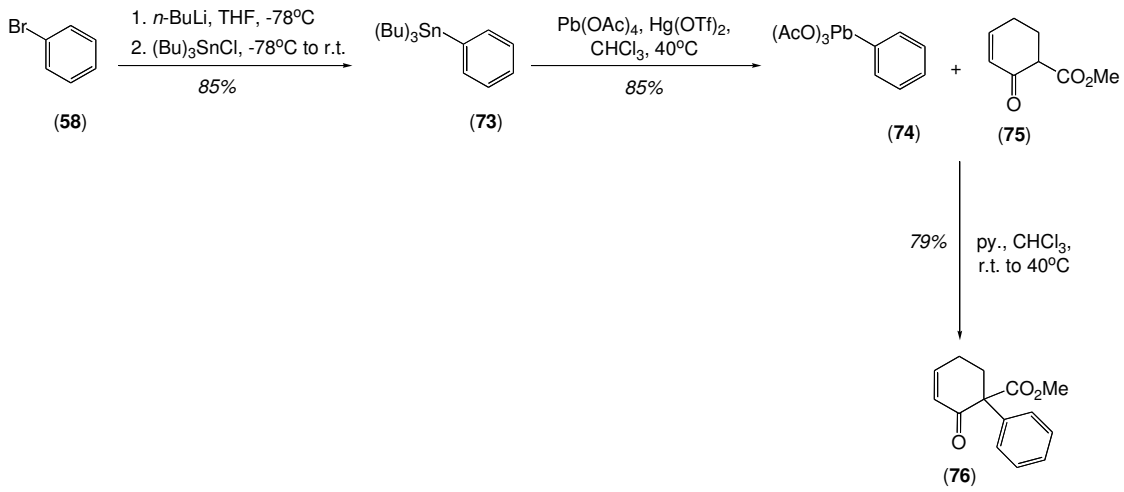
The Pinhey Reaction

Pinhey has shown that aryllead triacetates of the general form **72** react with various soft carbon-centred nucleophiles to deliver a range of *C*-arylation products. [18-22]



(**72**)

Essentially, such aryllead compounds behave as synthetic equivalents to aryl cations in reactions that are postulated to involve a ligand-coupling mechanism.[21, 23] In order to test the utility of aryllead triacetates in the proposed synthesis of the targetted analogues of (+)-vinblastine, bromobenzene (**58**) was treated (Scheme 2.6) with *n*-butyllithium and the resulting aryllithium was then reacted with tributyltin chloride to produce stannane **73**. Reaction of this last compound with lead tetraacetate in a mercury-catalysed tin-lead exchange process then gave phenyllead triacetate (**74**).[24] Compound **74** was, in turn, reacted with methyl 2-oxocyclohex-3-enecarboxylate (**75**), in the presence of three equivalents of pyridine and the α-arylated product methyl 2-oxo-1-phenylcyclohex-3-enecarboxylate (**76**) was generated in 79% yield (Scheme 2.6).



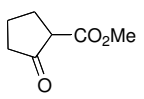
(**58**) (**73**) (**74**) (**75**) (**76**)

Scheme 2.6: *Pinhey arylation of methyl 2-oxocyclohex-3-ene carboxylate (**75**) with phenyllead triacetate (**74**)*

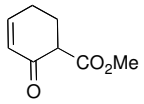
Based on these results the Pinhey arylation reaction seemed to offer a useful means of effecting the desired arylation reaction. Nevertheless, the scope of such a process needed to be investigated. Accordingly, a series of cyclic β-ketoesters of differing ring sizes was synthesised with a view to using these as the nucleophilic coupling partners in various Pinhey arylation reactions.

Preparation of Cyclic β-Ketoesters

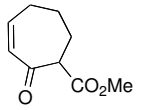
The substrates sought for use in a study of the scope of the Pinhey arylation process were the homologous series of cyclic β-ketoesters **70**, **75** and **79**.



(**70**)



(**75**)

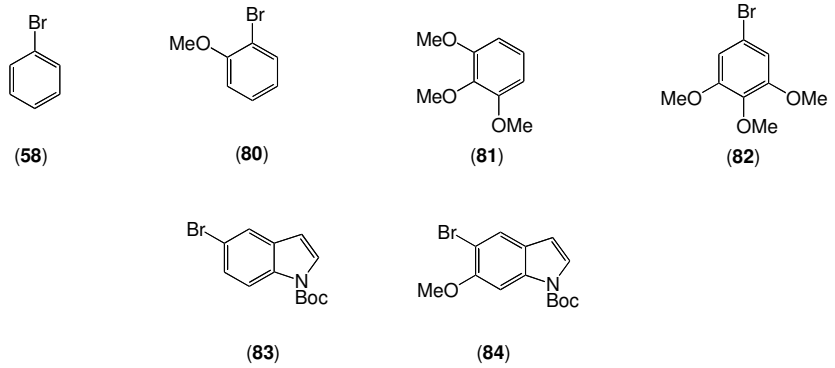


(**79**)

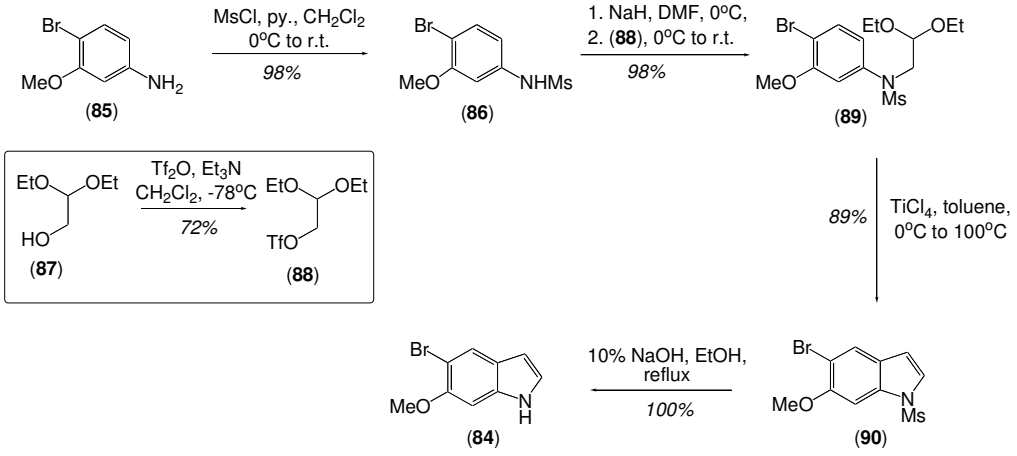
Compound **70** was commercially available, while higher homologues **75** and **79** were generated in 80 and 74% yield, respectively, by trapping the corresponding lithium enolates of 2-cyclohexen-1-one (**77**) and 2-cyclohepten-3-one (**78**) with methyl cyanoformate utilising chemistry developed by Mander and co-workers.[25] The saturated five-membered carbonyl compound was employed as attempts to generate the corresponding enone using the abovementioned chemistry only led to polymerisation products. The spectral data derived from compound **75** generated by such means were in full accord with those reported in the literature.[25] The 1,3-dicarbonyl compound **79** was new so full spectral characterisation was undertaken. Compound **79** exists as a mixture of keto-enol tautomers, with the keto-form predominating. In the ^{1}H NMR spectrum of this material a singlet was observed at δ 3.77 and this corresponds to the methyl group protons of the methyl ester unit. This assignment was further reinforced by the presence, in the ^{13}C NMR spectrum, of signals at δ 170.8 and 167.9 that are attributed to the ester carbonyl groups of the enol- and keto-forms, respectively. Signals appearing at δ 102.5 and 64.0 and being indicative of the α-carbon of the enol- and keto-forms of compound **79** were also observed. The IR spectrum exhibited bands at 1747 and 1653 cm^{-1} that are due to carbonyl stretching absorptions of the ester and α,β-unsaturated enone functionalities, respectively. Finally, the 70 eV electron impact mass spectrum showed the expected molecular ion at *m/z* 168. A fragment ion (30%) appearing at *m/z* 109 and arising from the loss of a carboxymethyl radical was also observed. This fragmentation is common for this class of compound. The base peak at *m/z* 81 is attributed to the loss of both carbon monoxide and a carboxymethyl radical from the molecular ion.

Preparation of Arylstannanes

The next stage of the proposed arylation study was to prepare the requisite aryllead triacetates for the use in the Pinhey arylation reaction. To this end, the precursor arylstannanes were required. These were chosen to mimic the "lower" hemisphere of (+)-vinblastine (**1**) and they proved accessible through elaboration of bromoarenes **58**, **80** – **84**.



Compounds **58**, **80** – **83** were readily obtained from chemical suppliers while congener **84** was prepared from the commercially available 3-methoxy-4-bromoaniline (**85**) using the Bischler indole synthesis (Scheme 2.7) as reported by Forbes.[26]

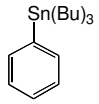


Scheme 2.7: *Bischler indole synthesis of indole* ***84***

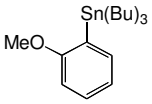
Thus, compound **85** was first converted, under standard conditions, into methanesulfonamide **86**. The ^{1}H NMR spectrum of this compound revealed a signal at δ 3.90 and this corresponds to the three methyl protons of the methanesulfonyl group, while the ^{13}C NMR spectrum showed a signal at δ 39.2 arising from the methanesulfonamide carbon. Electron impact mass spectral analysis revealed the

expected molecular ion at *m/z* 279. The base peak was observed at *m/z* 200 and corresponds to the loss of the methanesulfonyl radical from the parent ion. The triflate, **88**, derived from commercially available alcohol **87** was treated with the conjugate base of sulfonamide **86** to give the expected *N*-alkylated derivative **89** in 98% yield. The ^{1}H NMR spectrum of compound **89** showed various signals corresponding to the protons of the diethyloxyethyl group and these appeared as a triplet at δ 4.61 (J = 5.4 Hz), multiplets at δ 3.74 and 3.52 and a triplet at δ 1.16 (J = 7.0 Hz). In the ^{13}C NMR spectrum signals corresponding to the diethyloxyethyl carbons were observed at δ 110.9, 62.7, 53.3 and 15.3. In addition, the 70 eV electron impact mass spectrum showed the expected molecular ion at *m/z* 395, with a base peak appearing at *m/z* 103 and that is attributed to the loss of a diethyloxyethyl radical from the molecular ion. Compound **89** underwent the pivotal cyclisation reaction on exposure to titanium tetrachloride. Under such conditions the indole **90** was formed as the exclusive product of the reaction and obtained in 89% yield. The ^{1}H NMR spectrum of compound **90** showed a pair of mutually coupled doublets at δ 7.34 and 6.61 (J = 3.7 Hz) and these correspond to the H-2 and H-3 protons of the indole group. Furthermore, in the ^{13}C NMR spectrum of this indole, signals corresponding to the C-2 and C-3 indole carbons appeared at δ 125.6 and 96.7, respectively. The synthesis of the desired indole, **84**, was completed by alkaline hydrolysis of sulfonamide **90**. The ^{1}H NMR spectrum of product **84** so obtained was fully consistent with the assigned structure. In particular, the appearance of a broad signal at δ 7.80 that corresponds to the *N*-1 indolic proton indicated that hydrolysis of precursor **90** had been successful. Furthermore, the IR spectrum displayed a diagnostic absorption band at 3402 cm^{-1} that corresponds to NH stretching. An accurate mass measurement on the molecular ion observed at *m/z* 224 in the 70 eV electron impact mass spectrum established that this species had the expected composition, *viz* $C_9H_8{}^{79}BrNO$.

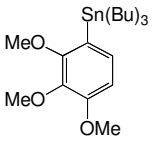
With the relevant bromoarene precursors in hand, the preparation of the required arylstannanes, **73** and **91** – **95**, could now be undertaken.



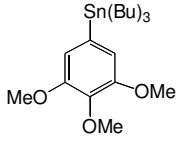
(**73**)



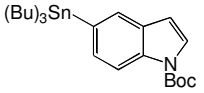
(**91**)



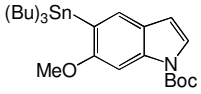
(**92**)



(**93**)



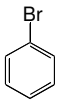
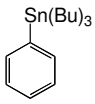
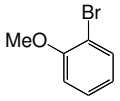
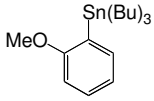
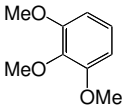
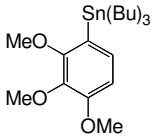
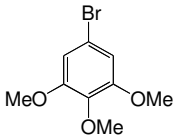
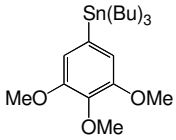
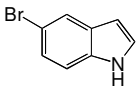
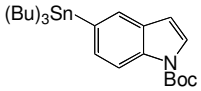
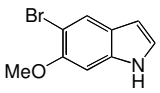
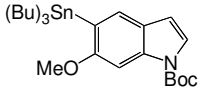
(**94**)



(**95**)

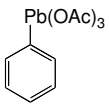
Stannanes **73** and **91** were prepared (Table 2.2.) by previously reported methods[24, 27] and the derived spectral data were in complete accord with the assigned structures. Compound **93** was synthesised by similar methods,[28] while compound **92** was prepared utilising a direct *ortho*-metallation of 1,2,3-trimethoxybenzene following the procedure of Sundburg.[29] Finally, indoles **94** and **95** were synthesised using a modification of a protocol developed by Konopelski *et al* during the course of a total synthesis of the alkaloid *N*-methylwelwitindolinone C isothiocyanate.[30] The ^{1}H NMR spectrum of each of these arylstannanes showed signals that are indicative of the constituent *n*-butyl protons at *ca.* δ 1.60 – 0.80, while resonances corresponding to the *n*-butyl carbons were always present in the ^{13}C NMR spectrum. In addition, 70 eV electron impact mass spectral analysis of these compounds revealed the expected cluster of molecular ions that reflects the natural distribution of tin isotopes. The base peak was always observed at *m/z* 57 and this is assigned to a butyl cation.

Table 2.2: *Preparation of arylstannanes* ***73, 91 – 95***

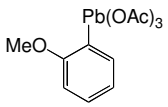
entry	starting material	procedure[a]	product	yield (%)
1	 (**58**)	Method A	 (**73**)	85
2	 (**80**)	Method A	 (**91**)	78
3	 (**81**)	Method A	 (**92**)	57
4	 (**82**)	Method A	 (**93**)	40
5	 (**83**)	Method B	 (**94**)	69
6	 (**84**)	Method C	 (**95**)	90

[a]**Method A:** (i) *n*-BuLi (1.1 eq.), diethyl ether, –78°C → r.t., 1 h; (ii) $(Bu)_3SnCl$ (1.1 eq,), –78°C → reflux, 3 h. **Method B:** (i) KH (1.1 eq.), diethyl ether, 0°C, 0.25 h; (ii) *t*-BuLi (1.1 eq.), –78°C, 1 h; (iii) $(Bu)_3SnCl$ (1.1 eq.), –78°C → r.t., 1 h; (iii) Boc_2O (1.1 eq.), CH_2Cl_2, r.t., 1 h. **Method C:** (i) KH (1.1 eq.), THF, 0°C, 0.25 h; (ii) *t*-BuLi (1.1 eq.), –78°C, 1 h; (iii) HMPA, $(Bu)_3SnCl$ (1.1 eq.), –78°C → reflux, 3 h; (iv) Boc_2O (1.1 eq.), CH_2Cl_2, r.t., 1 h.

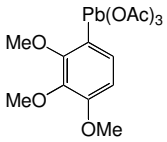
With the required arylstannanes in hand, the next step was to form the corresponding aryllead triacetates, **74** and **96 – 100**, that were to act as substrates in the Pinhey arylation process.



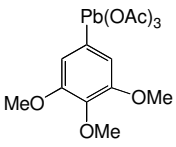
(**74**)



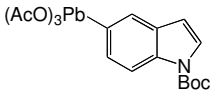
(**96**)



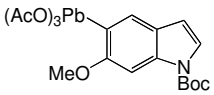
(**97**)



(**98**)



(**99**)



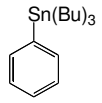
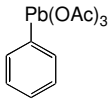
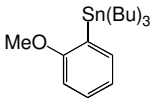
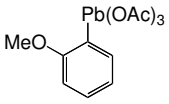
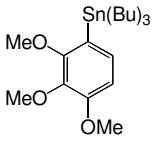
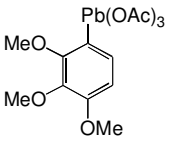
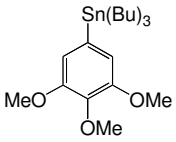
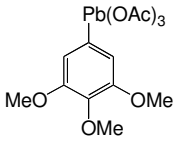
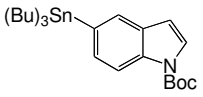
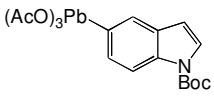
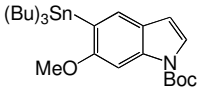
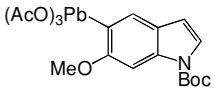
(**100**)

Preparation of Aryllead Triacetates

The abovementioned aryllead triacetates **74** and **96 – 99** were each prepared in good to excellent yields from the corresponding arylstannanes *via* a transmetallation reaction utilising lead tetraacetate and with mercuric triflate present as catalyst (Table 2.3). The mechanism of this reaction involves electrophilic *ipso*-substitution of the tin by mercury followed by a mercury-lead exchange reaction. Disappointingly, although this transmetallation process permitted the conversion of the stannane **95** into the lead derivative **100**, the latter material decomposed on work-up. Therefore, the crude samples of aryllead triacetate **100** so obtained were used directly in the studies of the Pinhey arylation reaction.

Compounds **74** and **96** have been described previously[24, 27] and the derived spectral data matched those reported. Thus, the ^{1}H NMR spectrum of each of these arylleads displayed a singlet in the region of δ 2.00 that corresponds to the acetate protons while in the ^{13}C NMR spectrum a signal assigned to the acetate carbonyls was always present at *ca*. δ 180.0. In addition, electron impact mass spectral analysis always revealed the expected cluster of molecular ions and reflecting the natural distribution of the isotopes of lead.

Table 2.3: *Preparation of aryllead triacetates* ***74, 96 – 100*** *required for the Pinhey arylation reaction*

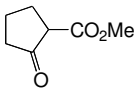
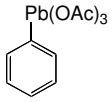
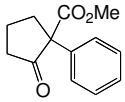
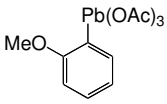
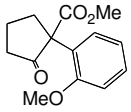
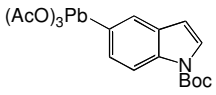
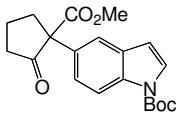
entry	starting material	product[a]	yield (%)
1	 (**73**)	 (**74**)	85
2	 (**91**)	 (**96**)	70
3	 (**92**)	 (**97**)	75
4	 (**93**)	 (**98**)	81
5	 (**94**)	 (**99**)	78
6	 (**95**)	 (**100**)	–[b]

[a]**Method:** $Pb(OAc)_4$ (1.1 eq.), $Hg(OTf)_2$ (10 mol%), $CHCl_3$, 40°C, 12 h. [b]Compound **100** was not isolated immediately and was subjected to the relevant Pinhey arylation reaction (see Experimental Section)

Arylation of β-Ketoesters

Investigations into the scope of the Pinhey arylation of β-ketoesters involved treating the β-ketoesters **70**, **75** and **79** with the aryllead triacetates **74**, **96** – **100** using three equivalents of pyridine in chloroform at 40°C. Gratifyingly, under such conditions the five-membered ring β-ketoester **70** coupled with the corresponding aryllead triacetates to give the expected products in good yields (Table 2.4).

Table 2.4: *Pinhey arylation of 5-membered ring β-ketoester* ***70*** *with aryllead triacetates* ***74, 96*** *and* ***99***

entry	β-ketoester	arylead triacetate	product of arylation[a]	yield (%)
1	 (**70**)	 (**74**)	 (**71**)	82
2	(**70**)	 (**96**)	 (**101**)	72
3	(**70**)	 (**99**)	 (**102**)	81

[a]**Method:** (i) β-ketoester (1.1 eq.), py. (3.0 eq.), $CHCl_3$, 0.5 h; (ii) aryllead triacetate (1.1 eq.), 40°C, 12 h.

Product **71** had been described previously and the derived spectroscopic data compared favourably with those reported.[31] Hitherto, compounds **101** and **102** had not been prepared and these were, therefore, subject to the usual range of characterisation protocols. In the ^{13}C NMR spectrum of each of these compounds a signal that corresponds to the quaternary α-carbon bearing the carboxymethyl and aryl groups was observed at *ca.* δ 65.0. The ^{1}H and ^{13}C NMR spectra of α-arylated ketone **102** are indicative and shown in Figures 2.2 and 2.3, respectively.

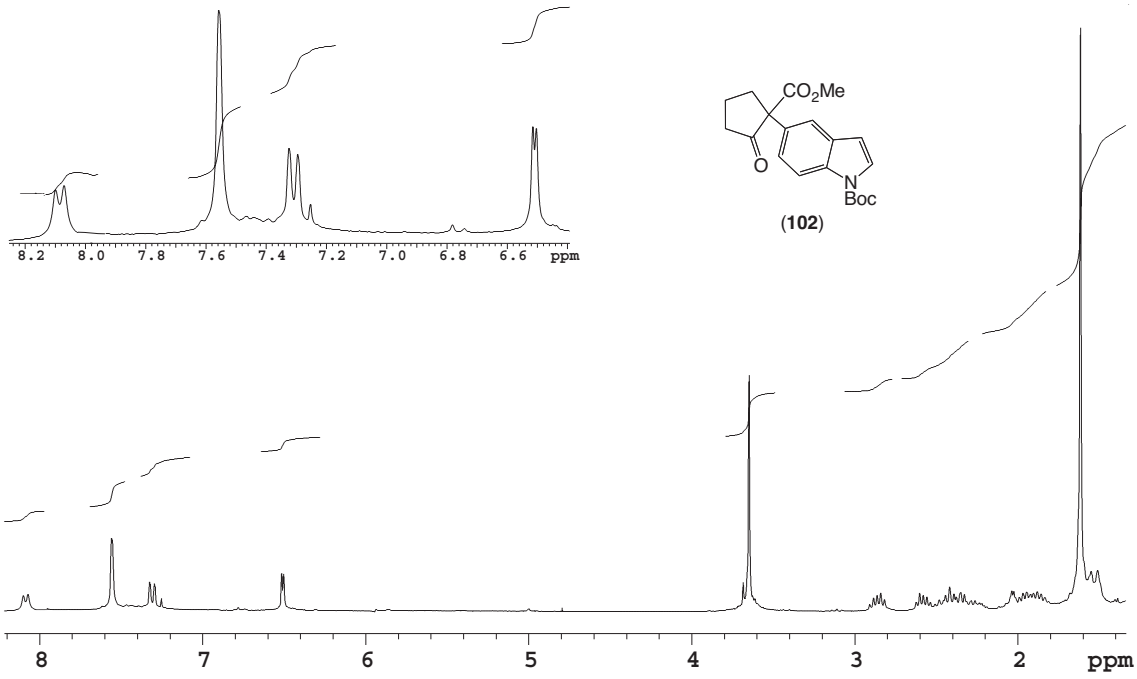


Figure 2.2: *300 MHz ^{1}H NMR spectrum of α-arylated β-ketoester* ***102*** *recorded in $CDCl_3$ at 18 ℃ (line broadening attributed to the presence of carbamate rotomers)*

INDEX	FREQUENCY	PPM	HEIGHT
1	15992.798	211.961	18.6
2	12916.420	171.188	20.0
3	11262.860	149.273	9.0
4	10118.880	134.111	8.3
5	9836.607	130.370	17.4
6	9805.116	129.952	21.8
7	9517.690	126.143	25.6
8	9305.842	123.335	34.2
9	9015.552	119.488	33.3
10	8676.596	114.995	35.3
11	8085.139	107.157	31.9
12	6299.316	83.488	19.0
13	5841.839	77.425	20.7
14	5809.775	77.000	21.5
15	5777.139	76.567	20.7
16	4870.773	64.555	29.3
17	3970.132	52.618	38.2
18	2822.717	37.411	33.8
19	2631.481	34.876	34.9
20	2097.280	27.796	130.0
21	1433.108	18.994	35.3

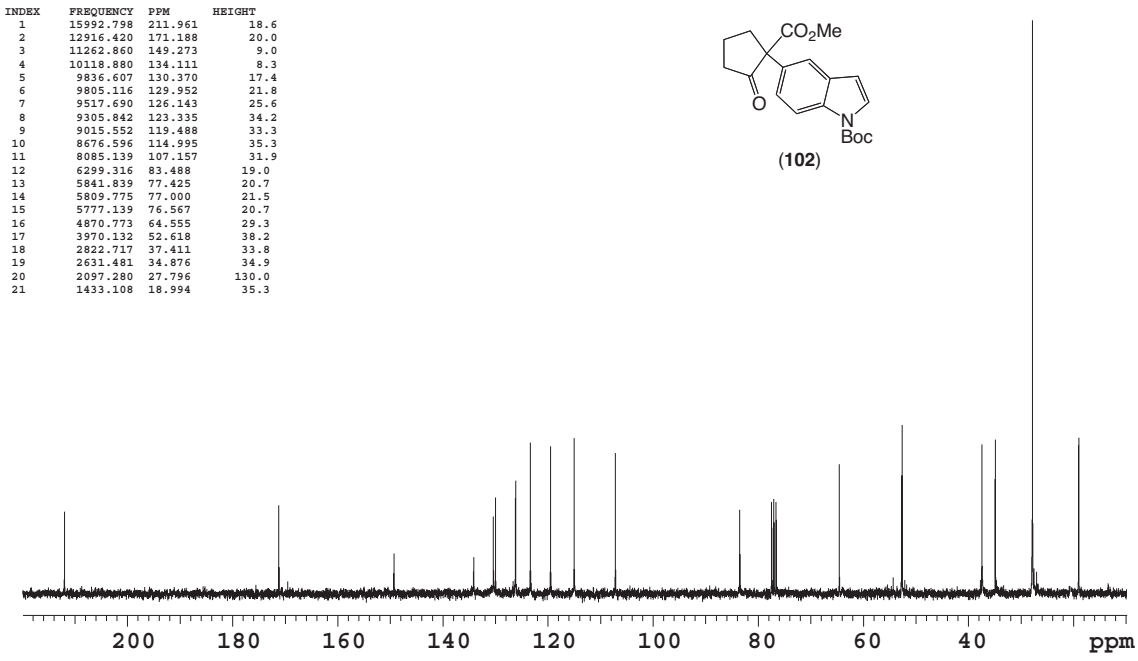
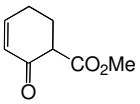
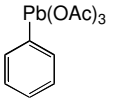
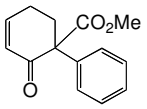
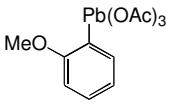
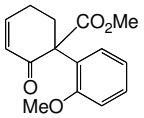
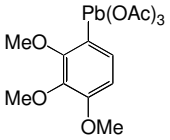
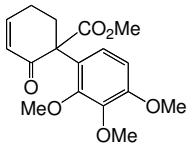
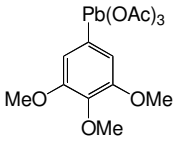
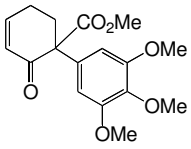
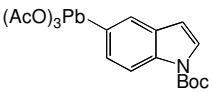
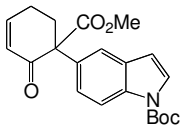
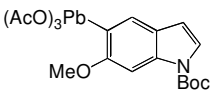
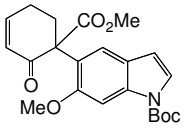


Figure 2.3: *75 MHz ^{13}C NMR spectrum of α-arylated β-ketoester* ***102*** *recorded in $CDCl_3$ at 18 ℃*

The higher homologue of compound **70**, namely 2-oxocyclohex-3-ene carboxylate (**75**), also coupled with the corresponding arylead triacetates to give products **76** and **103** – **107** in good yields (Table 2.5).

Table 2.5: *Pinhey arylation of 6-membered ring β-ketoester* ***75*** *with aryllead triacetates* ***74, 96 – 100***

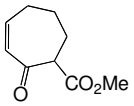
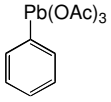
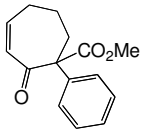
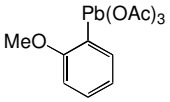
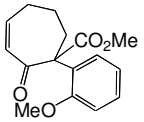
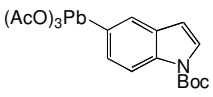
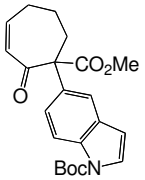
entry	β-ketoester	aryllead triacetate	product of arylation[a]	yield (%)
1	 (**75**)	 (**74**)	 (**76**)	79
2	(**75**)	 (**96**)	 (**103**)	76
3	(**75**)	 (**97**)	 (**104**)	75
4	(**75**)	 (**98**)	 (**105**)	84
5	(**75**)	 (**99**)	 (**106**)	71
6	(**75**)	 (**100**)	 (**107**)	82[b]

[a]**Method:** β-ketoester (1.1 eq.), py. (3.0 eq.), $CHCl_3$, 0.5 h; (ii) aryllead triacetate (1.1 eq.), 40°C, 12 h. [b]Yield over two steps.

These products had not been prepared previously and were, therefore, fully characterised.

The seven-membered ring compound **79** was also investigated as a potential coupling partner in the Pinhey arylation reaction in order to determine the applicability of this protocol to larger ring sizes as would be required in a synthesis of (+)-vinblastine (**1**). As can be seen from the results presented in Table 2.6, substrate **79** underwent α-arylation in preparatively useful yields.

Table 2.6: *Pinhey arylation of 7-membered ring β-ketoester* ***79*** *with aryllead triacetates* ***74, 96*** *and* ***99***

entry	β-ketoester	aryllead triacetate	product of arylation[a]	yield (%)
1	 (**79**)	 (**74**)	 (**108**)	63
2	(**79**)	 (**96**)	 (**109**)	70
12	(**79**)	 (**99**)	 (**110**)	71

[a]**Method:** β-ketoester (1.1 eq.), py. (3.0 eq.), $CHCl_3$, 0.5 h; (ii) aryllead triacetate (1.1 eq.), 40°C, 12 h.

Compounds **108** – **110** had not been prepared previously and were, therefore, fully characterised.

The successful arylations detailed above clearly demonstrates that a range of aryllead triacetates and cyclic β-ketoesters of varying ring sizes can participate in the Pinhey arylation reaction to give the desired products. The conversion of these Pinhey arylation products into the desired range of analogues of (+)-vinblastine is detailed in the following section.

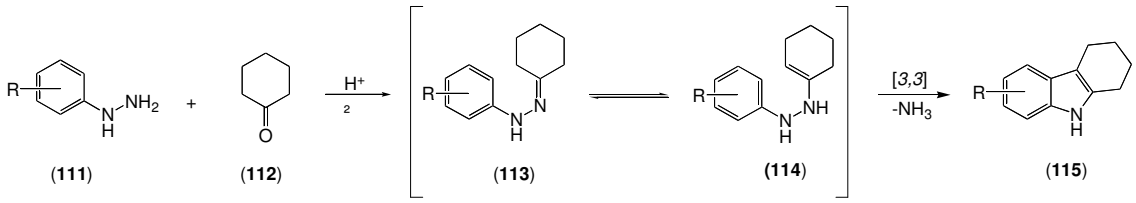
2.3 Synthesis of "Bridging Region" or Indole-Indoline Analogues of (+)-Vinblastine

2.3.1 Background

Although there is a wide range of methods available for the preparation of indoles and tetrahydrocarbazoles,[32-34] only a few of these, as detailed below, utilise cyclic ketones as starting materials and are, therefore, compatible with the synthetic strategy outlined in Figure 2.1.

Fischer's Indole Synthesis

In 1883, Emil Fischer developed the first and still most commonly utilised method for the synthesis of indoles.[35] This involves the reaction of various arylhydrazines **111** with an enolisable ketone, e.g. cyclohexanone (**112**), to generate the corresponding arylhydrazones **113**, that, under forcing conditions, tautomerise to unstable ene-hydrazines **114** that then undergo [3,3]-sigmatropic rearrangement to form, through a series of proton shifts and the loss of ammonia, tetrahydrocarbazoles of the general form **115** (Scheme 2.8).

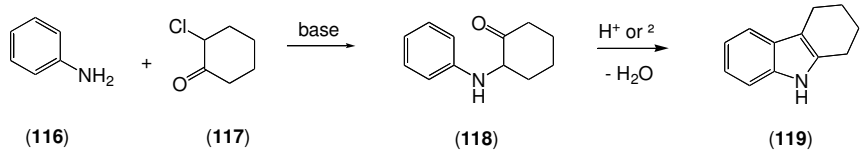


Scheme 2.8: *The Fischer indole synthesis*

The reaction usually requires high temperatures (180 – 250°C) and an acid catalyst. The likely instability of α-arylated ketones such as **102** to these conditions meant that this approach to the target analogues was not considered.

The Bischler-Mohlau Indole Synthesis

In 1892, Bischler discovered that indoles and tetrahydrocarbazoles can be formed by first reacting an aniline (e.g. **116**) with an α-chloroketone (e.g. **117**) in the presence of a base and thus generating the corresponding 2-phenylaminoketone **118**.[36] Such a product can be cyclized, using either acid or at high temperatures (70 – 160°C), to give, through a cyclocondensation process, the desired tetrahydrocarbazole **119** (Scheme 2.9).



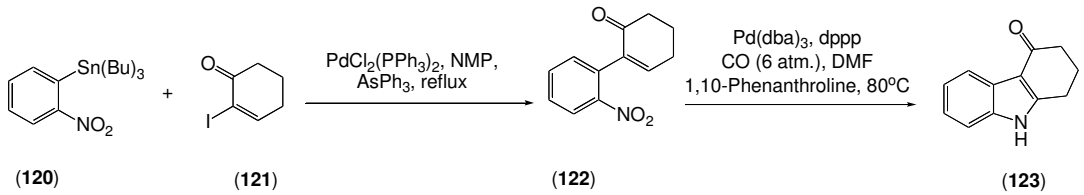
(**116**) (**117**) (**118**) (**119**)

Scheme 2.9: *The Bischler-Mohlau indole synthesis*

Unfortunately, these represent rather forcing conditions and, in addition, the protocol would not lead to the mode of indole ring-fusion required in the targetted analogues. Accordingly, this approach to such compounds was not considered in the first instance.

Soderberg's Indole Synthesis

Scott and Soderberg have recently reported that under Stille cross-coupling conditions stannane **120** reacts with α-iodocyclohexenone **121** to give product **122**[37] and, further, that this last compound engages in a novel palladium-catalysed reductive *N*-heteroannulation to give the 1,2-dihydro-4-(3*H*)-carbazolone (**123**) as illustrated in Scheme 2.10.



(**120**) (**121**) (**122**) (**123**)

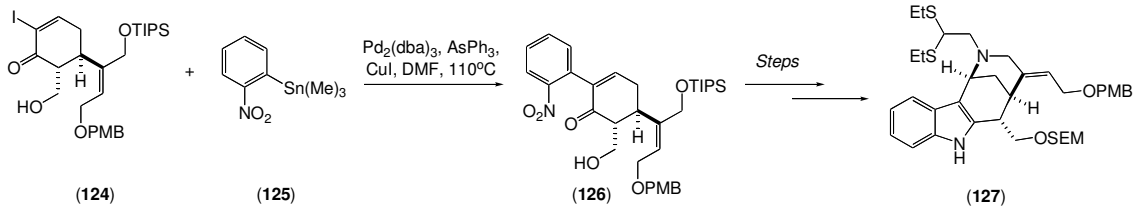
Scheme 2.10: *Soderberg's synthesis of 1,2-dihydro-4-(3*H*)-carbazolone (**123**)*

In terms of the synthetic strategy outlined in Figure 2.1, this annulation protocol would also lead to the wrong mode of indole ring-fusion. However, the first step of this

method could, in principle, be applied to the approach being proposed and is emphasised in the following sections.

Indole Annulation in Shibasaki's Synthesis of (-)-Strychnine

Shibasaki has reported a total synthesis of the alkaloid (-)-strychnine wherein the associated indole skeleton was assembled using a two-step process.[38] Thus, the α-iodocycloalkenone **124** was coupled with stannane **125** to afford nitro-arene **126** and this last compound was then converted, through a series of steps including a reductive cyclisation reaction using zinc and ammonium chloride, into indole **127** (Scheme 2.11).

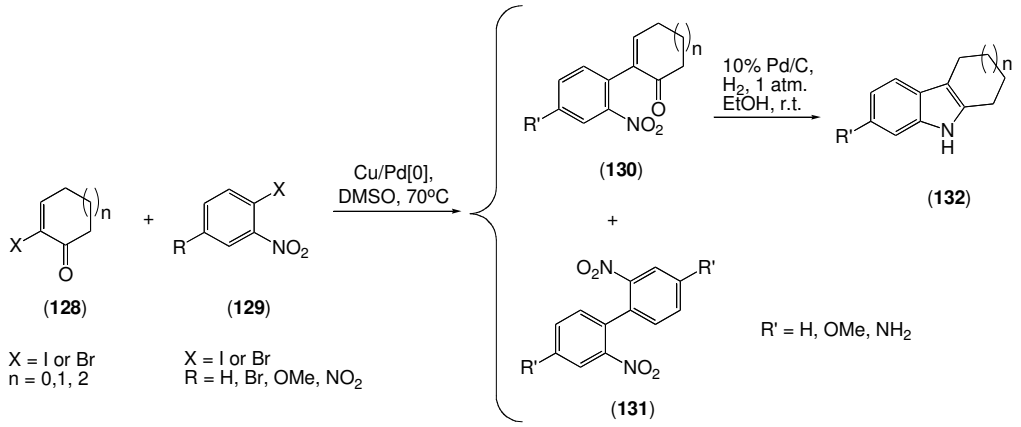


Scheme 2.11: *The indole annulation step associated with Shibasaki's (-)-strychnine synthesis*

However, unlike that used in original Soderberg's work (*vide supra*), the reductive cyclisation method employed by Shibasaki leads to indole ring-fusion in the same sense as required for obtaining the targetted analogues of (+)-vinblastine.

Banwell's Synthesis of Indoles

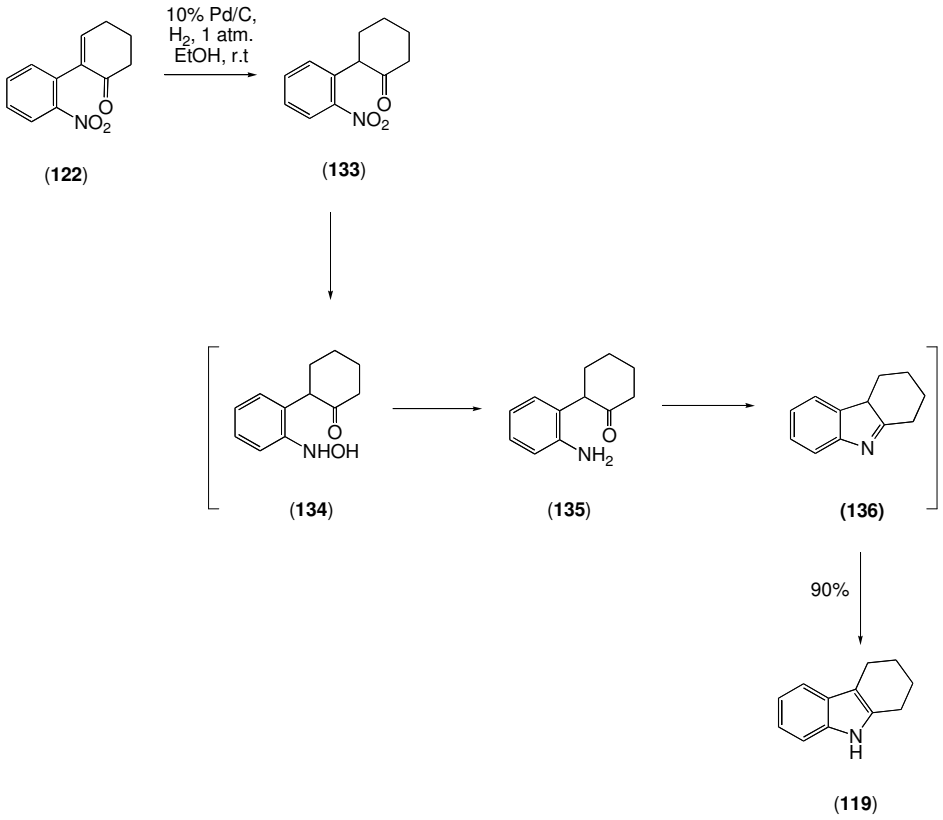
The Shibasaki chemistry detailed above required the use of stannylated precursors at an early stage of the synthetic sequence. This situation was deemed undesirable from both an economic and environmental standpoint and so other cross-coupling protocols were considered. Recently, Banwell *et al* have examined the utility of the Pd[0]-catalysed Ullmann cross-coupling reaction, wherein a range of α-halocycloalkenones **128** was reacted with *o*-halonitrobenzenes of the general type **129** using five equivalents of copper and Pd[0] as a catalyst.[1] Gratifyingly, in most cases the reaction went to completion generating the desired cross-coupled products **130** in high yield. Small quantities of the homo-coupled products of the general form **131** were also obtained but analogous homo-coupling of the enone **128** was not observed (Scheme 2.12).



Scheme 2.12: *Banwell's synthesis of indoles*

In all cases, the α-arylated enones **130** so obtained could be reductively cyclized, using palladium on charcoal under an atmosphere of dihydrogen, to give the corresponding indoles **132** in excellent yields.

A proposed mechanism for the reductive cyclisation of nitro-arene **122** to indole **119** is shown in Scheme 2.13. Thus, the first step is thought to involve the reduction of the enone moiety to provide the corresponding ketone **133**. The nitro-group is then reduced, probably, *via* an intermediate *N*-hydroxyamine **134**, to the corresponding aniline **135**, which engages in an intramolecular Schiff-base condensation reaction with the tethered ketone to give, after tautomerisation of the resulting imine **136**, the observed tetrahydrocarbazole **119**.

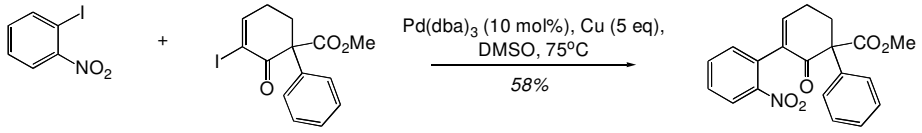


Scheme 2.13: *Proposed mechanism associated with the reductive cyclisation of nitro-arene* ***122*** *to tetrahydrocarbazole* ***119***

Such results clearly indicate that the Pd[0]-catalysed Ullmann cross-coupling reaction, followed by reductive cyclisation of the coupling product, could provide a simple and effective route to the required analogues of (+)-vinblastine.

2.4 Application of the Pd[0]-catalysed Ullmann Cross-Coupling Reaction in Preparing "Bridging Region" Analogues of (+)-Vinblastine

In order to determine if the Pd[0]-catalysed Ullmann cross-coupling route to indoles, as described above, could be applied to the present study, *o*-iodonitrobenzene (**137**) was cross-coupled with α-arylated α′-iodinated enone **138** (prepared as described in the following section) using conditions defined by Banwell *et al* (Scheme 2.14). Pleasingly, the desired coupling product, **139**, was obtained in 58% yield.



(**137**) (**138**) (**139**)

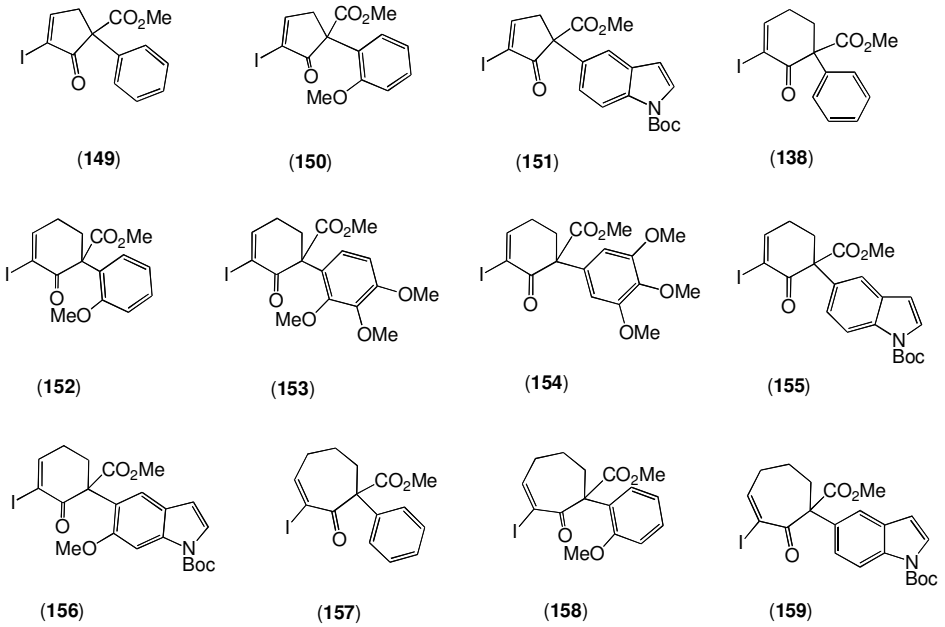
Scheme 2.14: *Pd[0]-catalysed Ullmann cross-coupling of* o-*iodonitrobenzene (**137**) with α-arylated enone **138***

These conditions were then applied to a range of other potential cross-coupling partners in order to test the utility of the title reaction in generating the relevant precursors to the targetted indole-indoline analogues of (+)-vinblastine.

2.4.1 Examining the Scope of Pd[0]-catalysed Ullmann Cross-Coupling Reaction

The aromatic coupling partner used to investigate the scope of Pd[0]-catalysed Ullmann cross-coupling reaction was *o*-iodonitrobenzene (**137**), a commercially available compound.

The non-aromatic cross-coupling partners investigated in this study were also chosen to allow for an examination of the range of "vinblastine relevant" functionalities that could survive this pivotal carbon-carbon bond forming step. The cyclic α′-iodinated enones **138**, **149**, **150**, **152 – 154**, **157** and **158** as well as the indole-containing cyclic α′-iodinated enones **151**, **155**, **156** and **159** were selected for this purpose.



(**149**) (**150**) (**151**) (**138**)

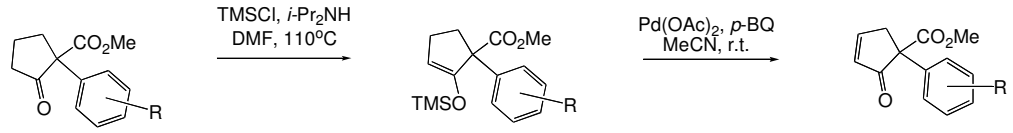
(**152**) (**153**) (**154**) (**155**)

(**156**) (**157**) (**158**) (**159**)

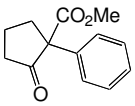
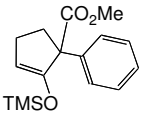
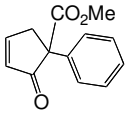
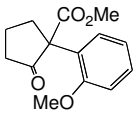
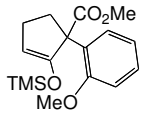
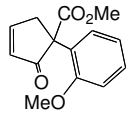
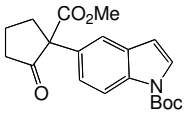
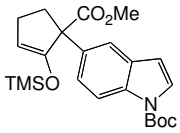
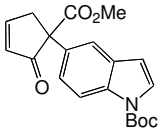
Preparation of α′-Iodinated Cross-Coupling Partners

The title substrates were all prepared by iodination of the corresponding non-iodinated systems using the protocols developed by Johnson[39] and others.[40-42] In the case of the 5-membered ring series, the ketones **71**, **101** and **102** were first transformed into the corresponding trimethylsilylenol ethers **143** – **145** and these were then subjected to Saegusa-type oxidation[43] with palladium acetate. In this manner, the requisite enones **146** – **148** were obtained in good overall yields (Table 2.7).

Table 2.7: *Preparation of the five-membered cyclic α-arylated enones* ***146 – 148***



(**140**) (**141**) (**142**)

entry	α-arylated cyclic ketone	trimethylsilylenol ether[a]	yield (%)	α-arylated cyclic enone[b]	yield (%)
1	 (**71**)	 (**143**)	72	 (**146**)	97
2	 (**101**)	 (**144**)	96	 (**147**)	61
3	 (**102**)	 (**145**)	72	 (**148**)	60

[a]**Method:** *i*-Pr_2NH (3.0 eq.), TMSCl (2.0 eq.), DMF, 110°C, 3 h. [b]**Method:** $Pd(OAc)_2$ (0.5 eq.), *p*-benzoquinone (0.5 eq.), MeCN, r.t, 3 h.

All the trimethylsilylenol ethers shown in Table 2.7 were previously unreported compounds and, therefore, subject to full spectroscopic characterisation. In the ^1H NMR spectrum of each of these compounds a triplet associated with the olefinic proton was always observed at *ca.* δ 4.90. Furthermore, in the corresponding ^{13}C NMR spectrum a signal that is attributed to the methyl carbons of the trimethylsilyl moiety was invariably

observed at *ca* δ -0.02. The ^{1}H and ^{13}C NMR spectra of compound **145**, as shown in Figures 2.4 and 2.5 respectively, are typical.

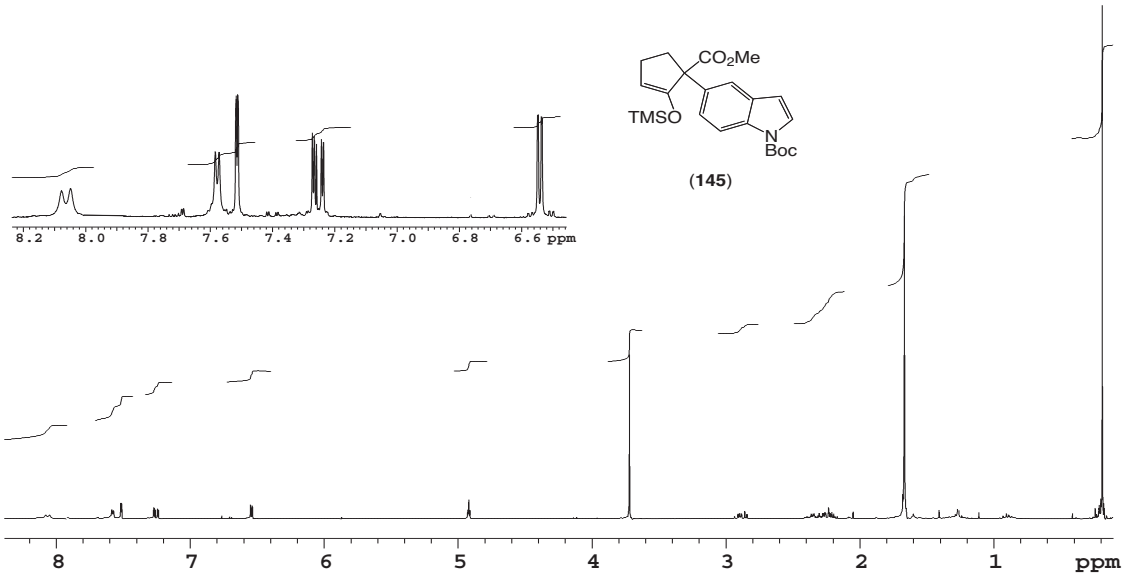


Figure 2.4: *300 MHz ^{1}H NMR spectrum of trimethylsilylenol ether **145** recorded in $CDCl_3$ at 18℃*

INDEX	FREQUENCY	PPM	HEIGHT
1	13202.128	174.975	12.7
2	11600.671	153.750	17.7
3	11298.930	149.751	5.8
4	10282.632	136.281	23.1
5	10096.549	133.815	4.9
6	9834.888	130.347	12.6
7	9502.229	125.938	22.3
8	9342.484	123.821	29.1
9	8997.229	119.245	27.5
10	8655.409	114.715	34.3
11	8110.330	107.490	32.7
12	7909.933	104.835	29.1
13	6298.742	83.481	15.0
14	5841.838	77.425	53.0
15	5809.774	77.000	56.0
16	5777.711	76.575	52.3
17	4795.766	63.561	23.0
18	3935.205	52.155	28.2
19	2813.555	37.290	34.4
20	2121.899	28.123	130.0
21	1952.993	25.884	33.3
22	-10.896	-0.144	80.1

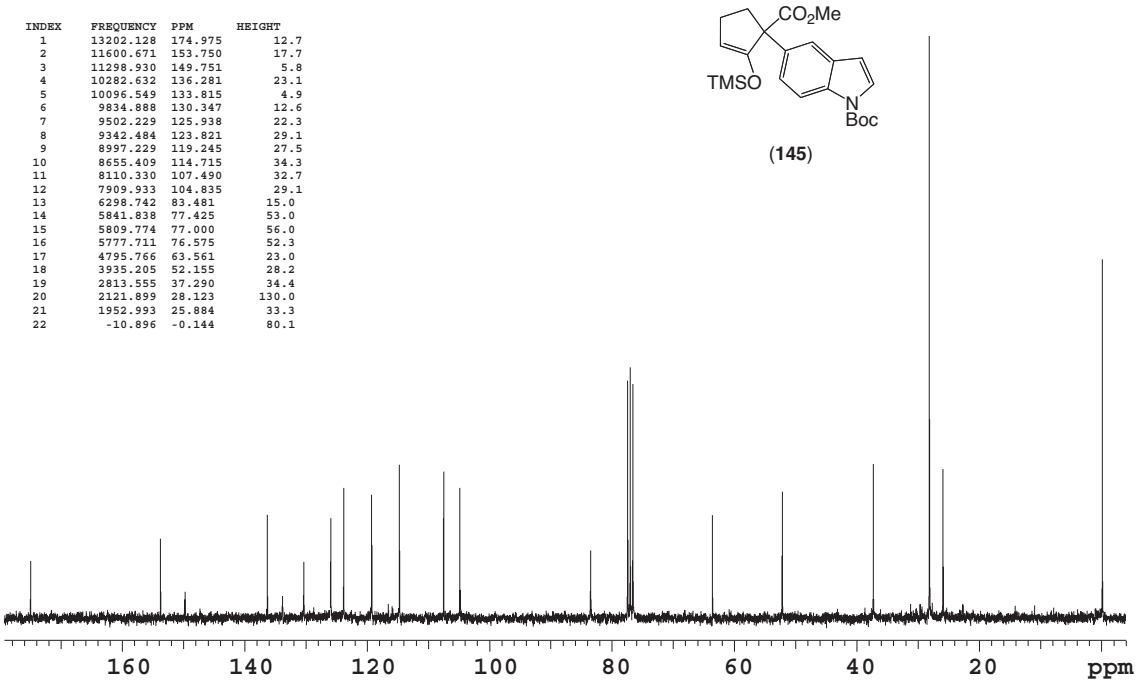


Figure 2.5: *75 MHz ^{13}C NMR spectrum of trimethylsilylenol ether **145** recorded in $CDCl_3$ at 18℃*

The cyclic enones shown in Table 2.7 were also new compounds and once again, fully characterised. In the ^{1}H NMR spectrum of each of these compounds, a pair of mutually coupled doublets of triplets (J = *ca.* 5.8 and 3.0 Hz) that are associated with the olefinic protons was always present in the regions of δ 7.80 and 6.25. Furthermore, in the ^{13}C NMR spectrum, a signal arising from the carbonyl moiety of the cyclic enone unit was invariably observed in the region of δ 200.0. The IR spectrum of each enone displayed intense absorption bands at *ca*. 1730 and 1705 cm^{-1} and these arise from stretching of the ester and α,β-unsaturated ketone carbonyl units, respectively. The ^{1}H and ^{13}C NMR spectra of enone **148**, as shown in Figures 2.6 and 2.7, are typical.

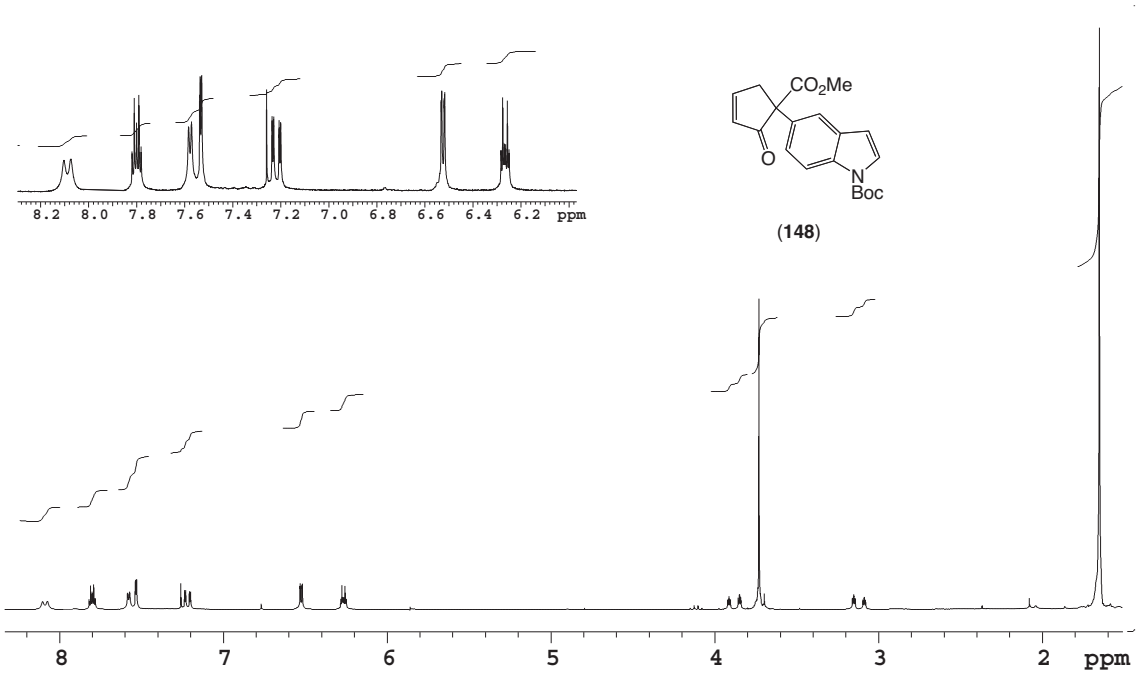
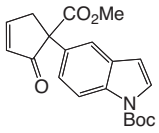


Figure 2.6: *300 MHz ^{1}H NMR spectrum of enone* ***148*** *recorded in $CDCl_3$ at 18 ℃*

INDEX	FREQUENCY	PPM	HEIGHT
1	15364.696	203.636	12.1
2	12891.799	170.862	12.0
3	12310.075	163.152	30.7
4	11285.761	149.576	6.0
5	10120.597	134.134	4.4
6	10030.704	132.942	14.9
7	9964.287	132.062	33.7
8	9854.928	130.613	10.8
9	9540.018	126.439	24.6
10	9324.735	123.586	32.0
11	9005.245	119.351	29.9
12	8709.803	115.436	34.6
13	8104.032	107.407	34.0
14	6322.217	83.792	14.0
15	5841.837	77.425	59.3
16	5809.774	77.000	61.4
17	5777.710	76.575	61.1
18	4719.043	62.544	14.9
19	4018.799	53.263	32.4
20	3322.563	44.036	32.8
21	2120.182	28.100	130.0

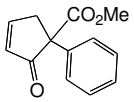
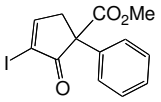
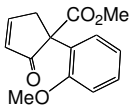
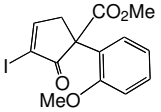
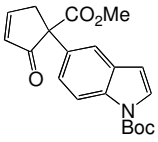
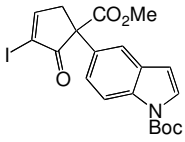


(**148**)

Figure 2.7: *75 MHz ^{13}C NMR spectrum of enone* ***148*** *recorded in $CDCl_3$ at 18 ℃*

With these five-membered cyclic enones now available, Johnson conditions were then applied to them and in order to form the α′-iodinated derivatives **149** – **151** (Table 2.8) required as cross-coupling partners in the foreshadowed Pd[0]-catalysed Ullmann cross-coupling reactions.

Table 2.8*: Preparation of 5-membered cyclic α′-iodinated α-arylated enones* ***149 – 151***

entry	starting material	product[a]	yield (%)
1	 (**146**)	 (**149**)	60
2	 (**147**)	 (**150**)	96
3	 (**148**)	 (**151**)	93

[a]**Method:** I_2 (4.0 eq.), (1:1 v/v) CCl_4/pyridine

The ^1H and ^{13}C NMR spectra of compound **151** as shown in Figures 2.8 and 2.9, respectively are, once again, typical of compounds in this series.

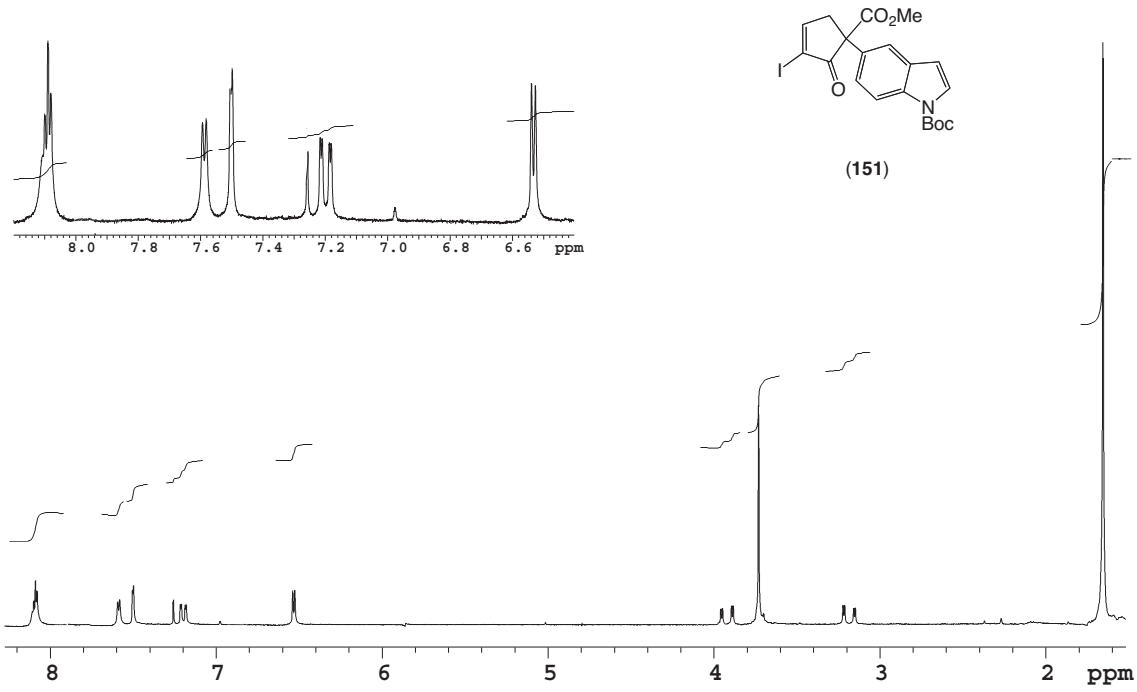


Figure 2.8: *300 MHz ^1H NMR spectrum of enone **151** recorded in $CDCl_3$ at 18℃*

INDEX	FREQUENCY	PPM	HEIGHT
1	15025.739	199.144	6.1
2	12849.429	170.300	10.5
3	11854.888	157.119	22.9
4	11290.342	149.637	5.7
5	11198.732	148.423	8.4
6	10706.328	141.897	12.2
7	10126.895	134.217	5.7
8	10051.316	133.215	24.1
9	10011.237	132.684	12.5
10	9931.651	131.629	23.5
11	9865.806	130.757	10.0
12	9781.067	129.634	24.0
13	9568.646	126.818	11.2
14	9541.163	126.454	18.8
15	9418.062	124.823	26.8
16	9321.872	123.548	23.1
17	9018.414	119.526	21.7
18	8716.101	115.519	25.4
19	8116.055	107.566	24.6
20	6323.362	83.807	11.0
21	5841.837	77.425	128.4
22	5809.774	77.000	130.0
23	5777.710	76.575	123.7
24	4799.774	63.614	15.9
25	4037.693	53.514	21.3
26	3192.018	42.306	21.7
27	2123.044	28.138	88.9

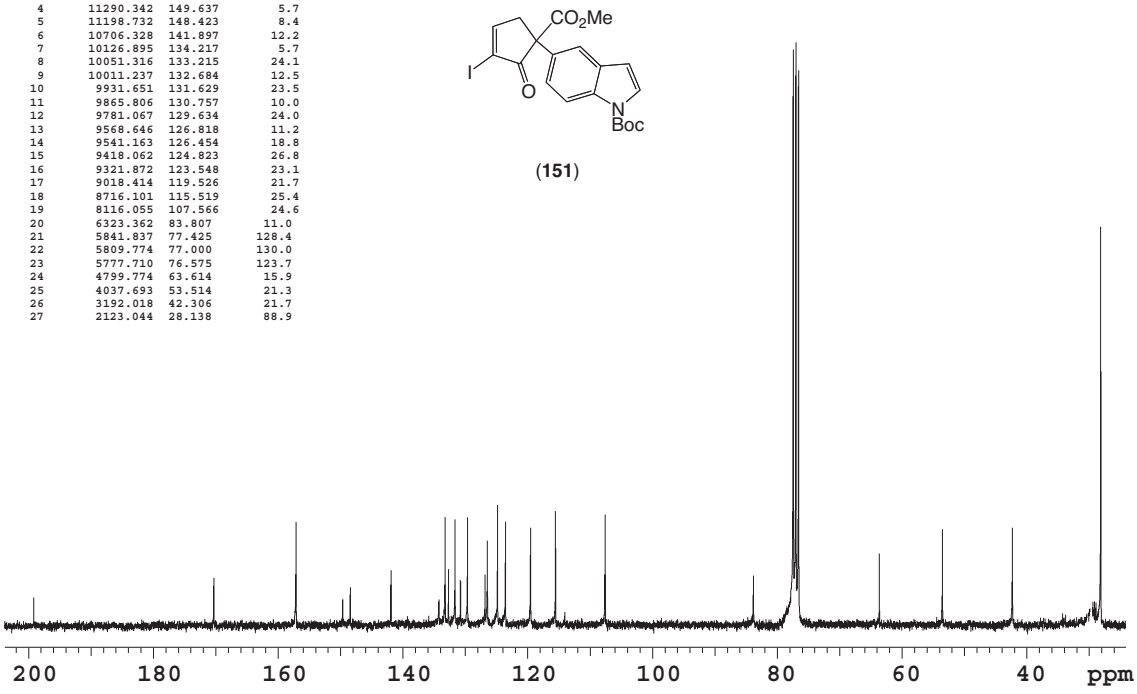
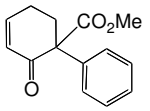
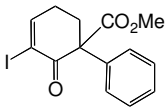
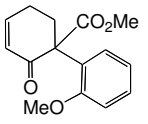
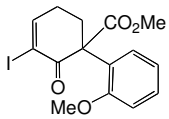
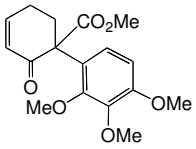
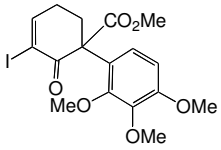
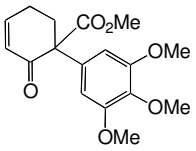
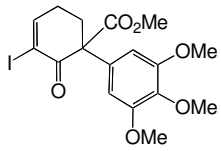
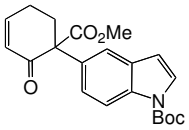
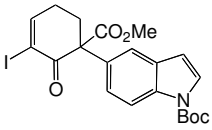
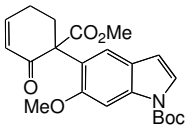
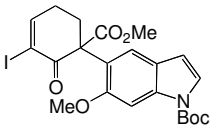


Figure 2.9: *75 MHz ^{13}C NMR spectrum of enone **151** recorded in $CDCl_3$ at 18℃*

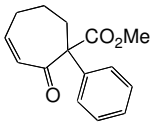
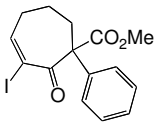
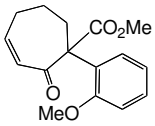
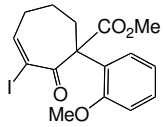
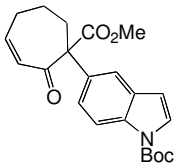
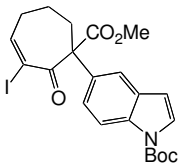
With the successful preparation of the five-membered α′-iodinated cross-coupling partners, the same approach was extended to the six- and seven-membered ring series (see Tables 2.9 and 2.10, respectively). All the compounds shown in these Tables were novel and, therefore, fully characterised. In the ^{1}H NMR spectrum of each of these compounds the mutually coupled signals associated with the olefinic protons of the precursor α,β-unsaturated enones were replaced with a triplet appearing at *ca*. δ 7.80 and arising from the β-olefinic proton. In addition, in the ^{13}C NMR spectra the signals associated with the olefinic α-carbon of the precursor were supplanted by a resonance for the carbon bonded to iodine that appeared in the region δ 100.0.

Table 2.9: *Preparation of the 6-membered cyclic α′-iodinated α-arylated enones* ***138, 152 – 156***

entry	starting material	product[a]	yield (%)
1	 (**76**)	 (**138**)	60
2	 (**103**)	 (**152**)	60
3	 (**104**)	 (**153**)	75
4	 (**105**)	 (**154**)	98
5	 (**106**)	 (**155**)	73
6	 (**107**)	 (**156**)	70

[a]**Method:** I_2 (4.0 eq.), (1:1 v/v) CCl_4/pyridine

Table 2.10: *Preparation of the 7-membered cyclic α′-iodinated α-arylated enones* ***157 – 159***

entry	starting material	product[a]	yield (%)
1	 (**108**)	 (**157**)	58
2	 (**109**)	 (**158**)	68
3	 (**110**)	 (**159**)	61

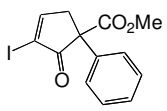
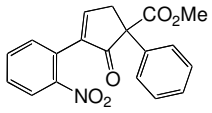
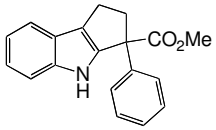
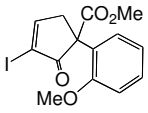
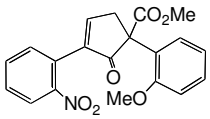
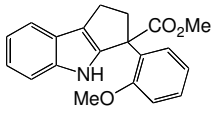
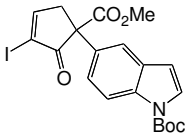
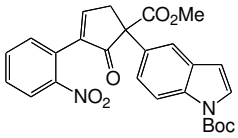
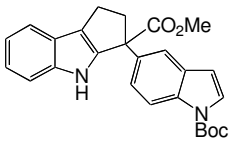
[a]**Method:** I_2 (4.0 eq.), (1:1 v/v) CCl_4/pyridine

With the requisite cyclic α′-iodinated enone substrates in hand, their capacity to engage in the Pd[0]-catalysed Ullmann cross-coupling reaction could be examined. Details of the outcomes of relevant studies are provided in the following section.

Cross-Coupling and Reductive Cyclisation

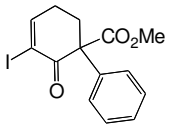
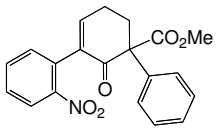
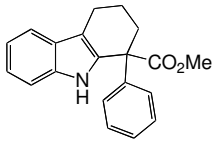
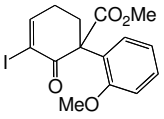
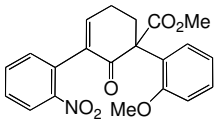
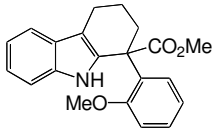
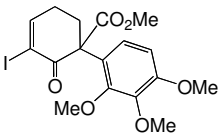
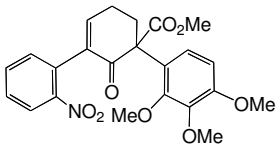
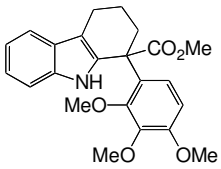
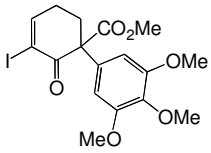
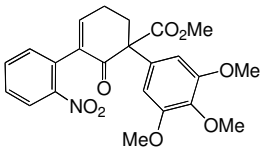
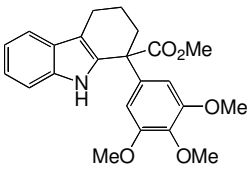
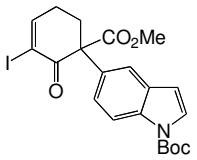
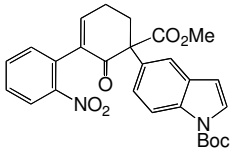
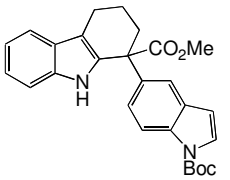
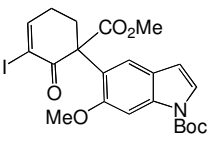
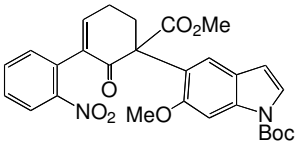
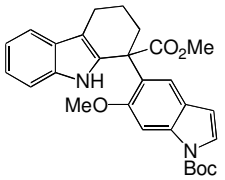
As can be seen in Tables 2.11 – 2.13, all of the abovementioned α′-iodinated cyclic enones coupled with *o*-iodonitrobenzene (**137**) in good to excellent yields. In each case, these previously unreported coupling products were accompanied by similar amounts of the chromatographically separable dimeric species **131** (R = H).

***Table 2.11**: Pd[0]-catalysed Ullmann cross-coupling of 5-membered cyclic α′-iodinated α-arylated enones **149 – 151** with* o*-iodonitrobenzene (**137**) and subsequent reductive cyclisation of the products*

entry	coupling partners[a]	coupling product[b]	yield[c] (%)	indole	yield (%)
1	 (**149**)	 (**160**)	60	 (**163**)	97
2	 (**150**)	 (**161**)	58	 (**164**)	98
3	 (**151**)	 (**162**)	86	 (**165**)	87

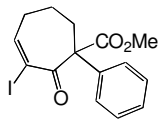
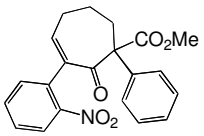
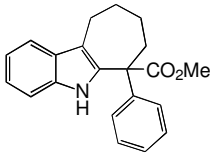
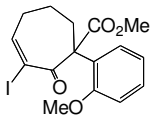
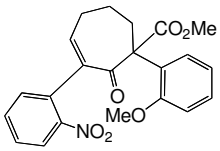
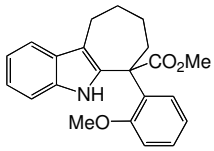
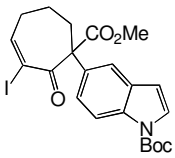
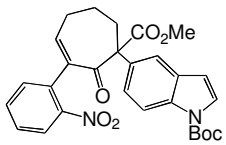
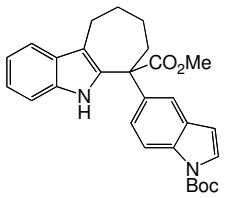
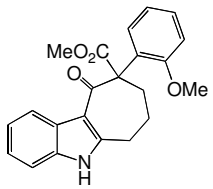
[a]All enones were coupled with **137**, [b]The reaction conditions defined by Banwell and co-workers were employed for the Pd[0]-catalysed Ullmann cross-coupling and in all cases dimer **131** (R = H) was isolated in *ca*. 50% yield based on arene **137**. [c]Yield calculation based on non-aromatic coupling partner.

Table 2.12: *Pd[0]-catalysed Ullmann cross-coupling of 6-membered cyclic α′-iodinated α-arylated enones* ***138, 152 – 156*** *with* o-*iodonitrobenzene (****137****) and subsequent reductive cyclisation of the products*

entry	coupling partners[a]	coupling product[b]	yield (%)[c]	indole	yield (%)
1	 (**138**)	 (**139**)	58	 (**171**)	95
5	 (**152**)	 (**166**)	66	 (**172**)	95
6	 (**153**)	 (**167**)	56	 (**173**)	67[d,e]
7	 (**154**)	 (**168**)	56	 (**174**)	95
8	 (**155**)	 (**169**)	62	 (**175**)	87
9	 (**156**)	 (**170**)	91	 (**176**)	75

[a]All enones were coupled with **137**, [b]The reaction conditions defined by Banwell and co-workers were employed for the Pd[0]-catalysed Ullmann cross-coupling and in all cases dimer **131** (R = H) was isolated in *ca*. 50% yield based on arene **137**. [c]Yield calculation based on non-aromatic coupling partner. [c]The *N*-hydroxyindole **177** was also isolated in 12% yield.[e]Indole **173** was formed as the exclusive product in 92% yield when reaction time increased to 24 h.

***Table 2.13**: Pd[0]-catalysed Ullmann cross-coupling of 7-membered cyclic α′-iodinated α-arylated enones **157 – 159** with o-iodonitrobenzene (**137**) and subsequent reductive cyclisation of the products*

entry	coupling partners[a]	coupling product[b]	yield (%)	indole	yield (%)
1	 (**157**)	 (**178**)	68	 (**181**)	71[d]
2	 (**158**)	 (**179**)	56	 (**182**)	95[d]
3	 (**159**)	 (**180**)	56	 (**183**)	88[d]
4	(**158**)	(**179**)	56	 (**184**)	68[e]

[a]All enones were coupled with **137**, [b]The reaction conditions defined by Banwell and co-workers were employed for the Pd[0]-catalysed Ullmann cross-coupling and in all cases dimer **131** (R = H) was isolated in *ca*. 50% yield based on arene **136**. [c]Yield calculation based on non-aromatic coupling partner. [d]Compounds **178** – **180** were reductively cyclised using 3 atmospheres of H_2. [e]Compound **179** was reductively cyclised using $TiCl_3$•THF.

In the IR spectrum of each of these cross-coupled materials, an absorption band was always observed in the region of 1520 cm^{-1} and this corresponds to a stretching vibration of the nitro group. Furthermore, in the ^1H NMR spectrum a doublet in the region of δ 8.15 was always present and this is attributed to the aromatic proton adjacent to the nitro-functionality. The ^1H and ^{13}C NMR spectra of nitro-arene **162** shown in Figures 2.10 and 2.11, respectively, are typical of this series.

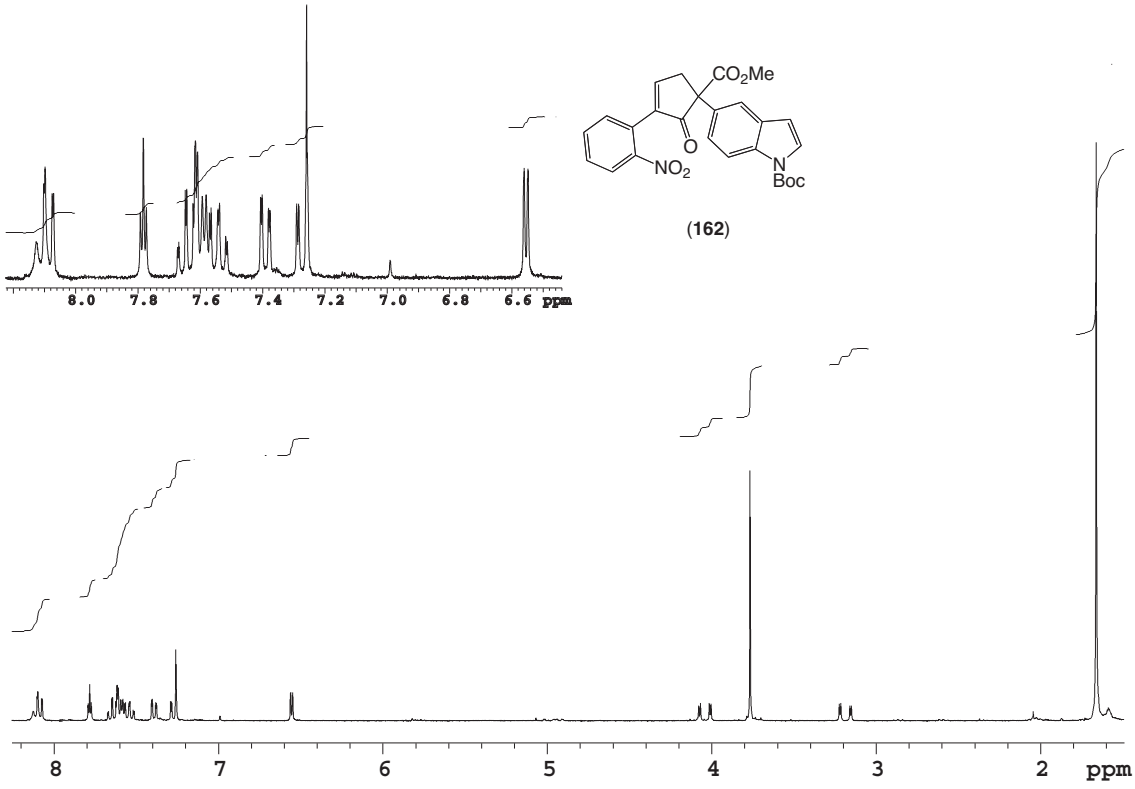


Figure 2.10: *300 MHz ^{1}H NMR spectrum of nitro-arene* ***162*** *recorded in $CDCl_3$ at 18 ℃*

INDEX	FREQUENCY	PPM	HEIGHT
1	14943.290	198.051	9.9
2	12831.680	170.065	12.0
3	12657.621	167.758	36.7
4	11282.326	149.531	6.8
5	10134.338	134.316	4.9
6	9969.440	132.130	14.8
7	9859.508	130.673	12.6
8	9554.905	126.636	25.8
9	9300.687	123.267	36.8
10	9000.664	119.291	34.5
11	8720.109	115.572	39.5
12	8102.886	107.392	38.1
13	7493.107	99.310	15.2
14	6330.806	83.906	15.8
15	5841.265	77.417	90.2
16	5809.774	77.000	89.1
17	5777.710	76.575	89.8
18	4523.226	59.949	16.9
19	4038.266	53.521	32.7
20	3474.292	46.047	33.4
21	2121.899	28.123	130.0

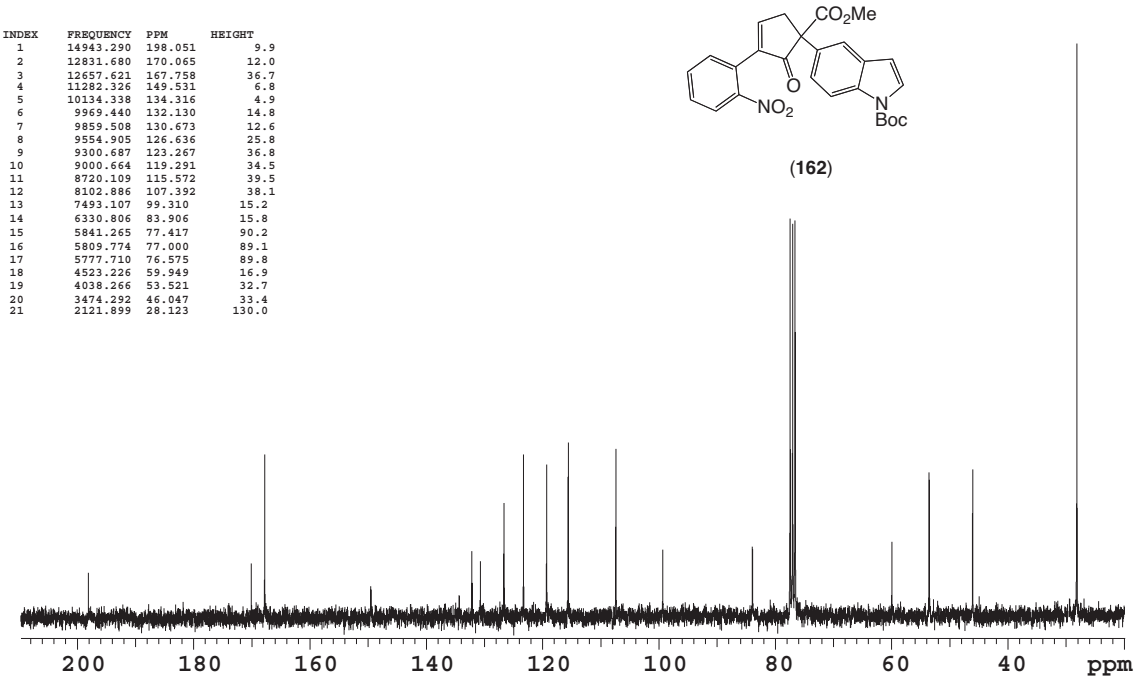
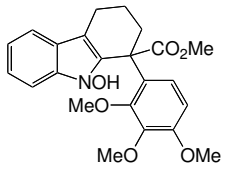


Figure 2.11: *75 MHz ^{13}C NMR spectrum of nitro-arene* ***162*** *recorded in $CDCl_3$ at 18 ℃*

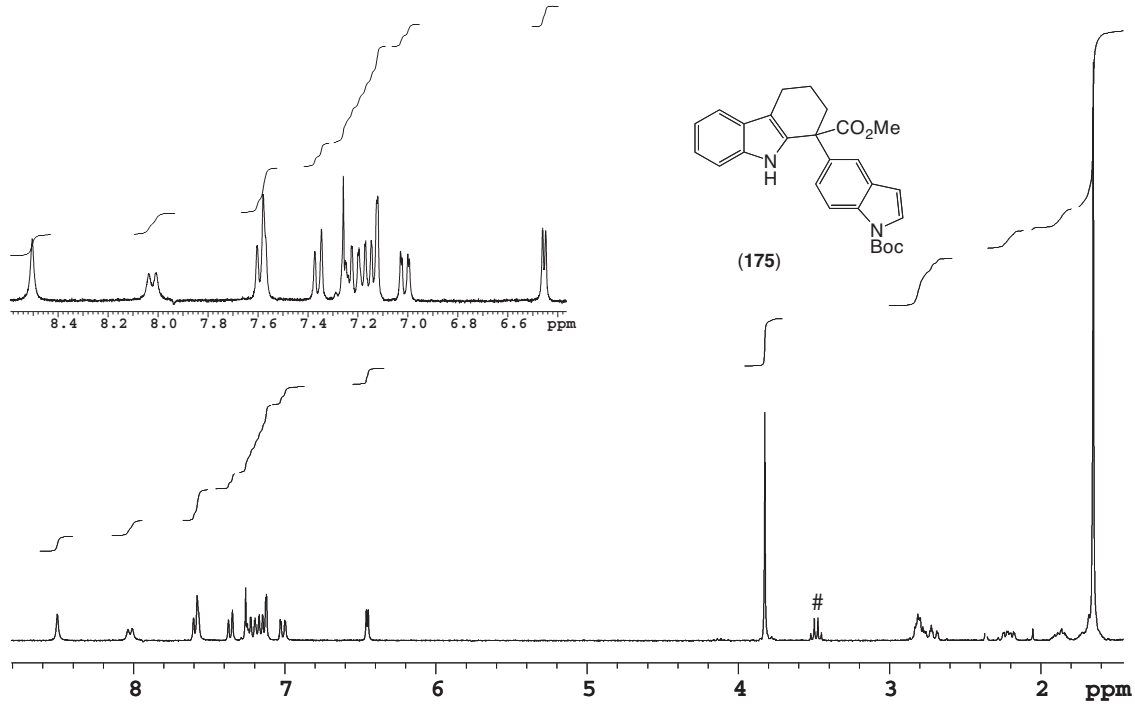
Having prepared the cross-coupled products, their reductive cyclisation, using dihydrogen in the presence of palladium on charcoal, was investigated. Pleasingly, under these conditions the target indoles **163** – **165** were each obtained in excellent yields. In the ^{1}H NMR spectrum of each of these indoles a broad signal was observed at *ca.* δ 8.20 and this is assigned to the hydrogen attached to the indolic nitrogen. Furthermore, signals attributed to the aromatic protons within these indoles appeared at significantly higher field, relative to those due to the corresponding hydrogens in the nitro-arene precursors.

The reductive cyclisation protocol was then extended to the six-membered ring series (Table 2.12) and under these conditions the indoles **171 – 176** were obtained in excellent yields. The ^{1}H and ^{13}C NMR spectra of indole **175** are presented in Figures 2.12 and 2.13, respectively, and are typical of this series. Interestingly, the reduction of compound **167** was accompanied by quantities of the chromatographically separable *N*-hydroxyindole **177** that was isolated in 12% yield.



(**177**)

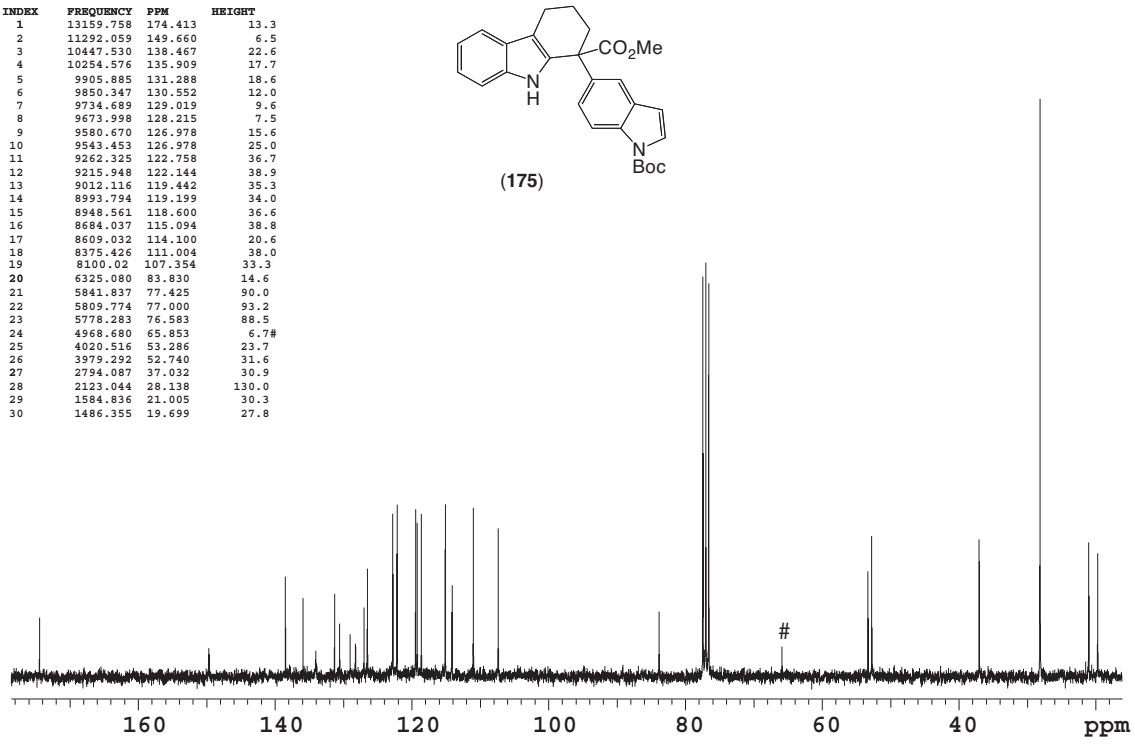
In the ^{1}H NMR spectrum of this by-product, there was a sharp signal at δ 9.27 and this is assigned to the hydroxyl hydrogen attached to nitrogen. Increasing the reaction time for the reductive cyclisation of compound **167** resulted in the formation of indole **173** as the exclusive product of the reaction and so suggesting the *N*-hydroxyindole **177** was an intermediate in the process leading to target **173**.



= diethyl ether

Figure 2.12: *300 MHz ^{1}H NMR spectrum of indole* ***175*** *recorded in $CDCl_3$ at 18℃*

INDEX	FREQUENCY	PPM	HEIGHT
1	13159.758	174.413	13.3
2	11292.059	149.660	6.5
3	10447.530	138.467	22.6
4	10254.576	135.909	17.7
5	9905.885	131.288	18.6
6	9850.347	130.552	12.0
7	9734.689	129.019	9.6
8	9673.998	128.215	7.5
9	9580.670	126.978	15.6
10	9543.453	126.978	25.0
11	9262.325	122.758	36.7
12	9215.948	122.144	38.9
13	9012.116	119.442	35.3
14	8993.794	119.199	34.0
15	8948.561	118.600	36.6
16	8684.037	115.094	38.8
17	8609.032	114.100	20.6
18	8375.426	111.004	38.0
19	8100.02	107.354	33.3
20	6325.080	83.830	14.6
21	5841.837	77.425	90.0
22	5809.774	77.000	93.2
23	5778.283	76.583	88.5
24	4968.680	65.853	6.7#
25	4020.516	53.286	23.7
26	3979.292	52.740	31.6
27	2794.087	37.032	30.9
28	2123.044	28.138	130.0
29	1584.836	21.005	30.3
30	1486.355	19.699	27.8

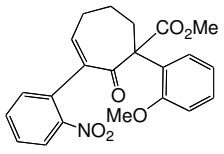


= diethyl ether

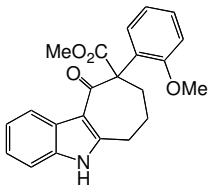
Figure 2.13: *75 MHz ^{13}C NMR spectrum of indole* ***175*** *recorded in $CDCl_3$ at 18℃*

Finally, the reductive cyclisation of the seven-membered ring α′-(*o*-nitrophenyl) enones was investigated and the results of this study are compiled in Table 2.13 (page 61). The cross-coupled products were reductively cyclised using palladium on charcoal under three atmospheres of dihydrogen. The use of lower pressures led to incomplete reaction.

A titanium trichloride-mediated reductive cyclisation[33] of substrate **179** was also attempted, but in this case a product, **184**, involving the wrong mode of indole ring-fusion was obtained. The unexpected synthesis of this indolone can be rationalised by a reversal in the order of reduction steps when compared to the reductive cyclisation employing palladium on charcoal and dihydrogen (Scheme 2.13). Thus, in the titanium trichloride-mediated reductive cyclisation process, it is presumed that the nitrophenyl unit is first reduced to the corresponding *N*-hydroxyaniline. Complexation of titanium to the carbonyl of the α,β-unsaturated enone then activates the associated double bond and allows for a Michael-type addition reaction to take place and so leading to the *N*-hydroxyindolone. Elimination of the elements of water from such a species would then give the observed product **184**. The IR spectrum of this indolone displayed absorption bands at 1732 and 1600 cm^{-1} and these correspond to the stretching vibrations of the ester and indolone carbonyl moieties, respectively. Furthermore, the ^{13}C NMR spectrum displayed the two carbonyl carbon resonances at δ 196.0 and 173.6. In addition, the 70 eV high resolution electron impact mass spectrum gave the expected molecular ion at *m/z* 363.1470 with the base peak appearing at *m/z* 43.



(**179**)



(**184**)

2.5 Summary

As part of investigations into methods to prepare indole-indoline analogues of (+)-vinblastine (**1**) a flexible protocol was developed for installing linkages that mimic the C-16′ to C-10 bond in the natural product. The important steps in this approach were the synthesis of a series of α-arylated β-ketoesters using chemistry developed by Pinhey and the subsequent utilisation of the Pd[0]-catalysed Ullmann cross-coupling reaction to

install all the indole rings of the targetted “bridging region” analogues of (+)-vinblastine. This route to the desired analogues has proven very robust and flexible with a variety of aryl groups and ring sizes being compatible with the reaction conditions used. This suggests that such chemistry might be applicable to the development of a total synthesis of (+)-vinblastine (**1**). Some very preliminary steps directed toward such ends are detailed in the following Chapter.

2.6 References

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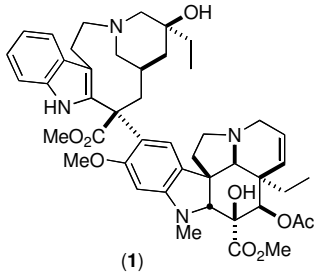
Chapter Three

Approaches to the Synthesis of a (+)-Vinblastine Analogue Incorporating a Carbomethoxyvelbamine Framework

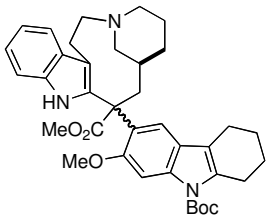
3.1 Introduction

3.1.1 Overview and Context

The preceding chapter described the use of a combination of the Pinhey arylation and Pd[0]-catalysed Ullmann cross-coupling reactions for the synthesis of α,α′-diarylated enones that could then be manipulated so as to generate a series of analogues of the indole-indoline core present in (+)-vinblastine (**1**). This chapter details attempts to extend this approach by developing a synthesis of compound **44** incorporating a framework resembling the "upper" carbomethoxyvelbamine hemisphere of (+)-vinblastine (**1**).



(**1**)



(**44**)

The acquisition and biological testing of such a compound could provide additional insights into the structure-activity-relationship (SAR) profile of (+)-vinblastine (**1**). Furthermore, the lessons learnt during the course of preparing a compound such as **44** could also be highly relevant in terms of ultimately achieving an efficient total synthesis of (+)-vinblastine (**1**).

3.2 Synthetic Strategy for the Preparation of a (+)-Vinblastine Analogue Incorporating a Carbomethoxyvelbamine Framework

The first approach to the compound **44** (Figure 3.1) centred on acquiring the previously unreported cyclic enone **186**. This latter compound would be expected to undergo a Johnson iodination reaction[1] and the product of this process could then be engaged in a Pd[0]-catalysed Ullmann cross-coupling reaction[2] to form the nitro-arene **185**. Reductive cyclisation of this last compound should then give the targetted *bis*-indole **44**. In principle, compound **186** could be obtained through a ring-closing metathesis (RCM) reaction,[3, 4] while the precursor, **187**, required for such a process could, in turn, be derived from the α-alkylated β-ketoester (3*S*)-**188** *via* a Pinhey arylation reaction[5] (**Section 2.2.1**) involving the aryllead triacetate **189**. It was believed that compound (3*S*)-**188** itself could be accessed by *C*-alkylation at the 2-position of the known 1,3-dicarbonyl compound **190**[6] using the easily accessible bromoalkylpiperidine **191**[7] as an electrophile. The β-ketoester **190** should itself be available in two steps through an aldol condensation reaction between (*E*)-crotylaldehyde (**192**) and commercially available methyl acetate (**193**) followed by Jones' oxidation of the resulting allylic alcohol.[8]

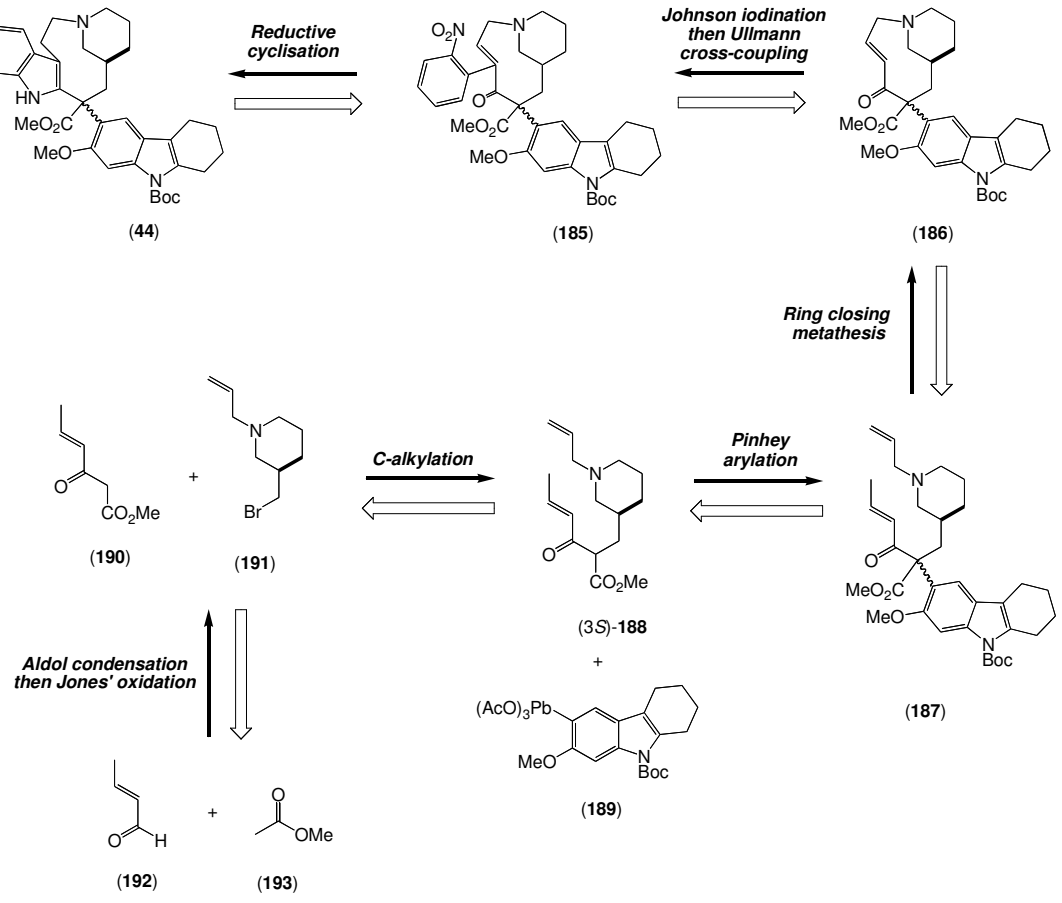


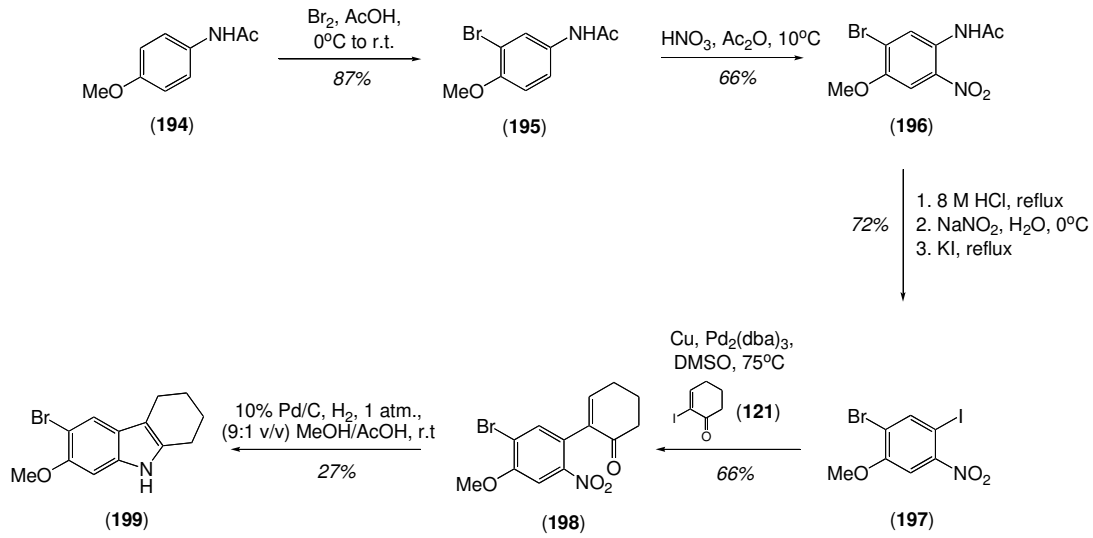
Figure 3.1: *Retrosynthetic analysis of the* bis-*indole* ***44***

As part of the initial campaign to put such ideas into effect, the bromoindole **199** was sought. Efforts directed towards such ends are described in the following section.

3.3 Synthesis of the Indole Fragment 189

3.3.1 Pd[0]-catalysed Ullmann Cross-Coupling Approach

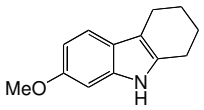
Based on the research described in the preceding chapter, tetrahydrocarbazole **199** seemed the logical precursor to the plumbated indole **189**. The former compound should be accessible *via* the reaction sequence shown in Scheme 3.1 and involving the previously described Pd[0]-catalysed Ullmann cross-coupling reaction as the key step.



Scheme 3.1: *Pd[0]-catalysed Ullmann cross-coupling approach to tetrahydrocarbazole* ***199***

To such ends, 4-methoxyphenylacetamide (**194**) was subjected to bromination under the conditions described by Lauer.[9] Recrystallisation of the crude reaction product from ethanol then gave arylbromide **195** in 87% yield. The spectroscopic properties of this compound compared favourably with those reported in the literature.[10] Electrophilic aromatic nitration of compound **195** then afforded arene **196** as the only isolable reaction product and in 66% yield.[11] The IR spectrum of this compound showed an absorption band at 1529 cm^{-1} that arises from the presence of the nitro moiety. Employing chemistry developed by Soderburg and Scott,[12] the nitro-acetamide **196** was hydrolysed under acidic conditions and the ensuing aniline subjected to a Sandmeyer-type reaction using potassium iodide and so giving the aryl iodide **197** in 72% yield

over the three steps. The ^{1}H NMR spectrum of product **197** lacked a signal at δ 2.23 that corresponds to the acetyl methyl protons of the starting material **196**. More importantly, the accurate mass measurement on the molecular ion appearing as the base beak at *m/z* 357 in the 70 eV electron impact mass spectrum of compound **197** showed that this aryl iodide had the expected molecular composition, *viz.* $C_7H_5{}^{79}Br^{126}INO_3$. Coupling compound **197** with iodoenone **121** using the Pd[0]-catalysed Ullmann cross-coupling process[2] gave the desired α′-arylated enone **198** in 66% yield. The ^{13}C NMR spectrum of this product showed all the signals expected of the desired structure including one at δ 196.5 that corresponds to the carbonyl of the enone moiety. The IR spectrum displayed a strong absorption band at 1525 cm^{-1} and this is, once again, attributed to the presence of the nitro-unit. Taken together, these data clearly indicate that the desired cross-coupling reaction had occurred. With compound **198** in hand, its reductive cyclisation to tetrahydrocarbazole **199** could be examined. Since, at higher pH, palladium on charcoal also has the capacity to catalyse the hydrogenolysis of bromoarenes, the reaction was performed in an acidic medium, but the desired product was only obtained in 27% yield, the major product still being the debrominated material **200**.

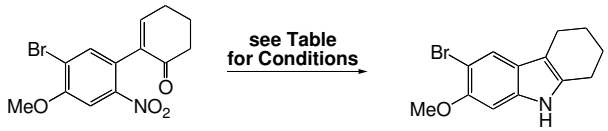


(**200**)

The ^{1}H NMR spectrum of tetrahydrocarbazole **199** featured a singlet at δ 6.84 that is attributed to the H-4 proton, which, as expected, had moved up field considerably when compared to the chemical shift of the signal of the equivalent proton in the precursor nitro-arene. The resonance assigned to the *N*-1 indolic proton appeared as a broad singlet at δ 7.59. The ^{13}C NMR spectrum is fully consistent with the assigned structure with resonances observed at δ 135.2 and 125.5 and corresponding to the C-4a and C-1a carbons of the tetrahydrocarbazole, respectively, and so indicating that reductive cyclisation had indeed taken place. The IR spectrum showed a prominent absorption band at 3357 cm^{-1} that is attributed to NH stretching.

A variety of other conditions was examined[13-15] in an attempt to reductively cyclise compound **198** in a more efficient manner and these are presented in Table 3.1.

Table 3.1: *Reductive cyclisation of nitro-arene* ***198*** *to tetrahydrocarbazole* ***199***



(**198**) (**199**)

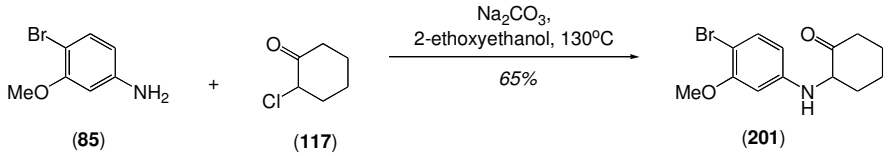
entry	conditions	yield (%)
1	1 atm. H_2, Pd/C, (9:1 v/v) MeOH/AcOH, r.t.	27[a]
2	Fe, NH_4Cl, (1:1 v/v) MeOH/H_2O, reflux	30
3	Zn, HCl, EtOH, reflux	32
4	$NaBH_4$, $SnCl_2$, EtOH, 60°C	33
5	$TiCl_3$•THF, NH_4OAc, (3:1 v/v) acetone/H_2O, r.t.	37

[a]debrominated material **200** also isolated

Unfortunately, all proved unsatisfactory since although nitro-arene **198** could be reduced to the tetrahydrocarbazole **199** under all these conditions, the isolated yields of the target compound were invariably poor. Though this survey of reductive cyclisation conditions was far from exhaustive, enough work was carried out to indicate that this route shown in Scheme 3.1 was unlikely to provide a serviceable means of obtaining tetrahydrocarbazole **199**. Consequently, an alternative strategy, as described in the following section, was investigated.

3.3.2 Bischler-Mohlau Approach

Having been unable to obtain reasonable yields of compound **199** by the means detailed above, a second and, as it transpired, a more direct approach was pursued. Of all the methods potentially available for effecting the synthesis of compound **199**, the Bischler-Mohlau tetrahydrocarbazole synthesis had the greatest appeal because of its apparent simplicity. Accordingly, 5-bromo-2-methoxyaniline (**85**) was treated with 2-chlorocyclohexanone (**117**)[16] in the presence of Na_2CO_3 and so generating the 2-arylaminoketone **201** in 65% yield (Scheme 3.2).[17]

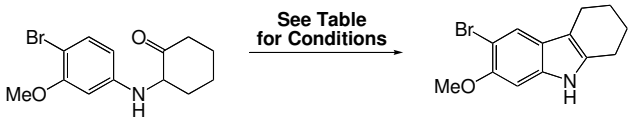


(**85**) (**117**) (**201**)

Scheme 3.2: *Synthesis of 2-arylaminoketone* ***201***

The spectral data obtained on this material were completely consistent with the assigned structure. For example, the IR spectrum of product **201** revealed a sharp absorption band at 1714 cm^{-1} and this corresponds to the carbonyl stretching frequency of the cyclic ketone. The full set of signals was observed in the ^{13}C NMR spectrum including one at δ 208.0 that is due to the ketone carbonyl functionality. So, with the 2-arylaminoketone **201** quite clearly in hand this was then subjected to a range of acidic conditions in an effort to achieve ring-closure to the target indole (Table 3.2).[18]

Table 3.2: *Acid-catalysed ring closure conditions*



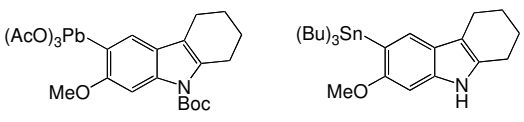
(**201**) (**199**)

entry	catalyst	solvent	temperature (°C)	reaction time (h)	yield (%)
1	$ZnCl_2$	EtOH	78	12	0[a]
2	$ZnCl_2$	AcOH	118	1	17[a]
3	$ZnCl_2$	2-methoxyethanol	125	12	21[a]
4	$ZnCl_2$	2-ethoxyethanol	140	1	28[a]
5	H_2SO_4	2-ethoxyethanol	140	4	36[b]
6	$MgCl_2/C_6H_5NH_2$	AcOH	118	4	48
7	$MgCl_2$	2-ethoxyethanol	140	1	57

[a]debrominated material **200** also isolated. [b]decomposition products also observed.

Ultimately, $MgCl_2$ proved to be the most effective reagent for this purpose and the required indole **199** was thus obtained in 57% yield. This material proved identical with that obtained by the longer route described in the preceding section.

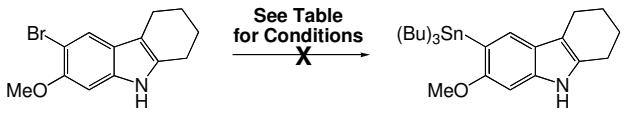
Having prepared tetrahydrocarbazole **199** in increased yield, it was now possible to investigate its conversion into the arylstannane **202** that would be expected to undergo transmetallation to afford the desired aryllead triacetate **189**.



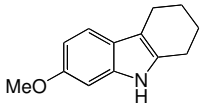
(**189**) (**202**)

The conditions examined in attempts to achieve the required transmetallation reaction are summarised in Table 3.3.[19, 20]

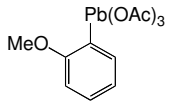
Table 3.3: *Attempted synthesis of arylstannane* ***202***



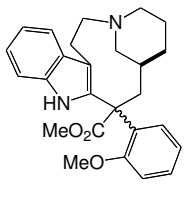
(**199**) (**202**)

entry	conditions	product
1	KH, ether, *t*-BuLi, $(Bu)_3SnCl$, -78°C → r.t.	*No reaction*
2	KH, THF, *t*-BuLi, $(Bu)_3SnCl$, -78°C → r.t.	 (**200**)
3	KH, (1:1 v/v) THF/HMPA, *t*-BuLi, $(Bu)_3SnCl$, -78°C → r.t.	(**200**)
4	KH, (1:1 v/v) THF/HMPA, *t*-BuLi, $(Bu)_3SnCl$, -78°C → reflux	(**200**)
5	$Pd(PPh_3)_4$, toluene, $Bu_3SnSnBu_3$, reflux	*No reaction*

Unfortunately, all such attempts failed. This was a surprising situation, considering the successful implementation of closely related chemistry as outlined in Chapter Two. The recovery of the debrominated material, **200**, from many of the reaction mixtures suggested that the initial lithium-for-bromine exchange had occurred but that the subsequent transmetallation step was failing. As a consequence of these difficulties, it was decided to use *o*-methoxyphenyllead triacetate (**96**) in place of the more complex but thus far inaccessible congener **189** and so as to generate a new target indole (3*S*)-**203**. This last compound now incorporates the *o*-methoxyphenyl unit as a surrogate for the "lower" hemisphere of (+)-vinblastine (**1**) while retaining the carbomethoxyvelbamine subunit associated with the originally targeted analogue **44**.

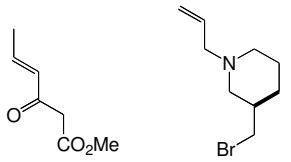


(**96**)



(3*S*)-**203**

The β-ketoester **190** required for implementing the plan defined in Figure 3.1 and to be used in an α-alkylation reaction with compound **191** now needed to be prepared. Details of how this was achieved are provided in the following section.

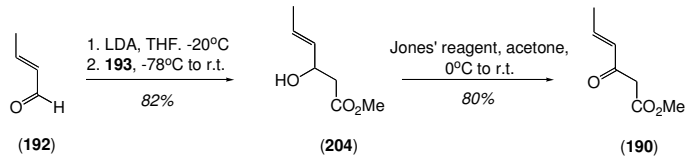


(**190**) (**191**)

3.4 Attempted Development of Carbomethoxyvelbamine Framework of (+)-Vinblastine

3.4.1 Synthesis of β-Ketoester 190

The chemistry of Zibuck,[8] as outlined in Scheme 3.3, was employed in order to generate the desired β-ketoester **190** and containing an olefinic residue as required for participation in the key ring-closing metathesis reaction as defined in the original synthetic plan (Figure 3.1). Thus, (*E*)-crotylaldehyde (**192**) was subject to a base-promoted aldol condensation reaction with methyl acetate (**193**) and thus affording methyl (*E)*-3-hydroxy-5-methyl-4-pentanoate (**204**). This β-hydroxyester was then subjected to a Jones' oxidation and in this way the requisite β-ketoester (*E*)-methyl 3-oxohex-4-enoate (**190**) was obtained in 65% overall yield.



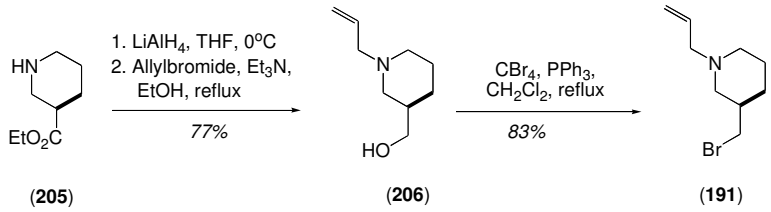
(**192**) (**204**) (**190**)

Scheme 3.3: *Synthesis of methyl (*E*)-3-oxohex-4-enoate (**190**)*

Both compounds **190**[6] and **204**[21] have been reported previously but only the latter material had been fully characterised. The spectral data obtained on compound **204** were in full accord with those reported in the literature.[21] The ^{1}H NMR spectrum of β-ketoester **190** showed, *inter alia*, a singlet at δ 3.53 that corresponds to the two equivalent α-protons while, the ^{13}C NMR spectrum contained the full set of signals including a resonance at δ 191.8 due to the newly formed ketone carbonyl unit.

Furthermore, the IR spectrum showed an absorption band at 1673 cm^{-1} that is indicative of the presence of an α,β-unsaturated enone carbonyl moiety.

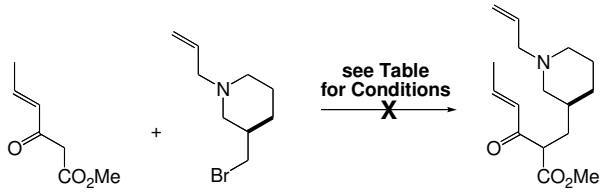
With the necessary β-ketoester **190** now clearly in hand, the next step in the development of the newly targetted vinblastine analogue (3*S*)-**203** was the α-alkylation of **190** with (*R*)-(+)-*N*-allyl-3-piperidinylmethyl bromide (**191**) so as to install the intact piperidine ring. Utilising a protocol used by Magnus[7] in his synthesis of desethyldihydronavelbine, commercially available (*R*)-(-)-ethyl nipecotate (**205**) was reduced to the corresponding alcohol and an allyl moiety then attached to the piperidine nitrogen so as to afford the *N*-allyl alcohol **206**. Alcohol **206** was then converted into the desired alkyl bromide **191** (Scheme 3.4) by standard methods. The spectroscopic data obtained on compounds **206** and **191** were in full accord with those recorded in the literature.[7]



Scheme 3.4: *Synthesis of alkyl halide* ***191***[7]

In order to affect the α-alkylation of β-ketoester **190** with halide **191** various reaction conditions were examined (Table 3.4). Standard conditions employing hydride bases at low temperatures resulted in starting material being recovered, while only decomposition of β-ketoester **190** was observed at higher temperatures. Amide bases were then used and even with HMPA as a co-solvent, no characterisable reaction products were generated (entry 9). Once again, only decomposition of the starting β-ketoester was observed under such conditions. Finally, the use of carbonates as bases was explored. Thus, a DMF solution of the starting materials was heated in the presence of potassium carbonate for 36 hours. Unfortunately, this also only led to the decomposition of the starting β-ketoester (entry 12).

Table 3.4: *Attempted α-alkylation of β-ketoester* ***190*** *with alkyl bromide* ***191***



(**190**) (**191**) (3*S*)-**188**

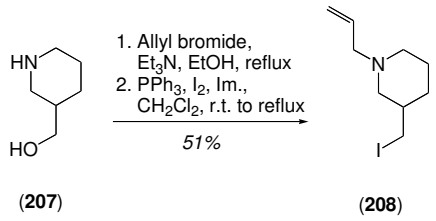
entry	base	solvent	temperature (°C)	product[a]
1	NaH	THF	0 → 18	*No reaction*
2	NaH	THF	0 → 70	*Decomposition*
3	NaH	DMF	0 → 18	*No reaction*
4	NaH	DMF	0 → 160	*Decomposition*
5	KH	THF	0 → 70	*Decomposition*
6	LDA	THF	0 → 70	*Decomposition*
7	LDA	ether	0 → 40	*No reaction*
8	LiHMDS	THF	0 → 70	*Decomposition*
9	LiHMDS	(1:1 v/v) THF/HMPA	0 → 70	*Decomposition*
10	NaHMDS	THF	0 → 70	*Decomposition*
11	KHMDS	THF	0 → 70	*Decomposition*
12	K_2CO_3	DMF	160	*Decomposition*
13	Cs_2CO_3	DCM	50	*No reaction*

[a]All reaction outcomes are judged by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

Due to the failure of these α-alkylation methods to affect the desired transformation, attention was now directed towards using a more reactive alkylating agent, in particular the corresponding alkyl iodide.

Synthesis of Alkyl Iodide 208

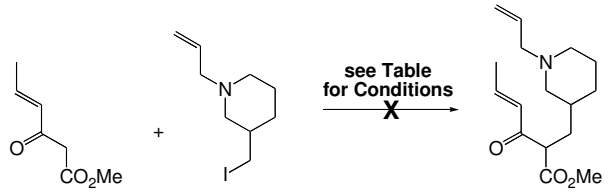
Due to the unexpected difficulties associated with trying to effect the pivotal α-alkylation reaction as described in the preceding section, the studies in the area were continued by utilising the more readily available racemic alcohol **207** that would be replaced with the enantiopure material if and when effective methodology had been developed. Accordingly, alcohol **207** was treated with allyl bromide and triethylamine to afford the *N*-allyl derivative. This crude product was then treated with triphenylphosphine, imidazole and molecular iodine. In this manner the required alkyl iodide **208** was formed in 51% yield over two steps as illustrated in Scheme 3.5.[22]



Scheme 3.5: *Synthesis of alkyl iodide* ***208***

The ^{1}H NMR spectrum of the product **208** lacked the broad singlet associated with the alcohol functionality of the starting material **207**. The 70 eV electron impact mass spectrum of alkyl iodide **208** displayed the expected molecular ion at *m/z* 265, while the base peak in this spectrum appeared at *m/z* 139 and corresponds to the loss of an iodine radical from the parent ion. With alkyl iodide **208** now readily available by such means, the key α-alkylation reaction was re-examined and with various alkylation conditions being investigated (Table 3.5).

Table 3.5: *Attempted α-alkylation of β-ketoester* ***190*** *with alkyl iodide* ***208***



(**190**) (**208**) (3*R/S*)-**188**

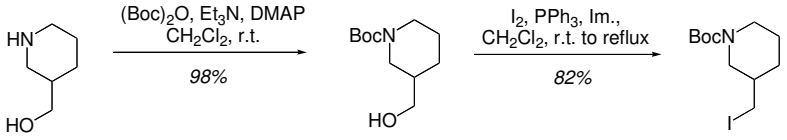
entry	base	solvent	temperature (°C)	product[a]
1	NaH	THF	0 → 18	*No reaction*
2	NaH	THF	0 → 70	*Decomposition*
3	NaH	DMF	0 → 160	*Decomposition*
4	KH	THF	0 → 70	*Decomposition*
5	*t*-BuOK	*t*-BuOH	90	*No reaction*
6	LDA	THF	0 → 70	*Decomposition*
7	LiHMDS	THF	0 → 70	*Decomposition*
8	LiHMDS	(1:1 v/v) THF/HMPA	0 → 70	*Decomposition*
9	NaHMDS	THF	0 → 70	*Decomposition*
10	KHMDS	THF	0 → 70	*Decomposition*
11	K_2CO_3	DMF	160	*Decomposition*
12	Cs_2CO_3	DCM	50	*No reaction*
13	*n*-BuLi	ether	0 → 40	*No reaction*

[a]All reaction outcomes are as judged by analysis of ^{1}H NMR spectrum of the crude reaction mixture.

As can be seen, a wide range of bases and solvents was employed but in all cases no product was observed even after prolonged reaction periods. Again, it was thought that the alkyl halide and/or the enolate derived from substrate **190** was/were too unreactive.

Preparation of a New Alkylation Partner

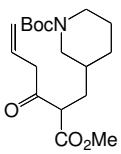
In a final effort to overcome the now significant difficulties that had been encountered in trying to alkylate the anion derived from the 1,3-dicarbonyl compound **190** with a piperidine-containing halomethyl electrophile, the *N*-Boc-protected compound **210** was sought (Scheme 3.6). To these ends, compound **207** was converted, in 79% yield over two steps, into the known, yet previously uncharacterised target halide **210**.[22] The ^{1}H NMR spectrum of this product showed a resonance at δ 1.46 that is due to the *tert*-butyl protons of the *tert*-butoxycarbonyl group, while the ^{13}C NMR spectrum displayed a signal at δ 154.7 that is attributed to the carbonyl unit of this same moiety. An accurate mass measurement on the molecular ion appearing at *m/z* 325 in the 70 eV electron impact mass spectrum showed that this compound was of the expected molecular composition. The base peak, at *m/z* 57, is assigned to the *tert*-butyl cation arising from cleavage of the Boc-group.



(**207**) (**209**) (**210**)

Scheme 3.6: *Synthesis of* N-*Boc-protected alkylation partner* ***210***

The α-alkylation was then undertaken with the new alkyl iodide **210** using the same conditions employed previously (Table 3.6). Once again, however, none of the desired alkylation product **211** formed. In partial contrast, at low reaction temperatures compound **212** was isolated. The acquisition of this compound reveals that an unexpected de-conjugation of the double bond in the sidechain had occurred during the course of the reaction.



(**212**)

Table 3.6**: Attempted α-alkylation of β-ketoester **190** using alkyl iodide **210

(**190**) (**210**) (**211**) (**212**)

entry	base	solvent	temperature (°C)	product (yield)
1	NaH	DMF	0 → 18	**212** (35%)
2	NaH	DMF	0 → 160	*Decomposition*
3	NaH	THF	0 → 70	*No reaction*
4	NaH	THF	0 → 70	*Decomposition*
5	KH	THF	0 → 18	**212** (28%)
6	LDA	THF	0 → 70	*Decomposition*
7	LDA	THF	0 → 18	**212** (80%)

The ^{1}H and ^{13}C NMR spectra of compound **212** are shown in Figures 3.2 and 3.3, respectively. The former spectrum features multiplets at δ 5.60 and 5.27 that integrate for one and two protons, respectively, and these are attributed to the protons associated with the terminal olefin. Furthermore, the doublet of doublets observed at δ 3.52 (J = 4.5 and 2.1 Hz) is assigned to the diastereotopic protons of the methylene group adjacent to the double bond. Another conspicuous feature was the lack of a signal associated with the methyl protons of the methyl unit of the starting material. The ^{13}C NMR spectrum showed resonances due to the terminal olefinic carbons at δ 135.1 and 119.8, while the signal at δ 55.0 is attributed to the methine α-carbon and thus indicating that α-alkylation had occurred.

Clearly, the acquisition of this deconjugated product (*viz.* β,γ-unsaturated enone **212**) precludes the foreshadowed use (Figure 3.1) of a RCM reaction to assemble the target carbomethoxyvelabamine core of analogues of (+)-vinblastine. Accordingly, new means for achieving such ends were sought. Details are provided in the following section.

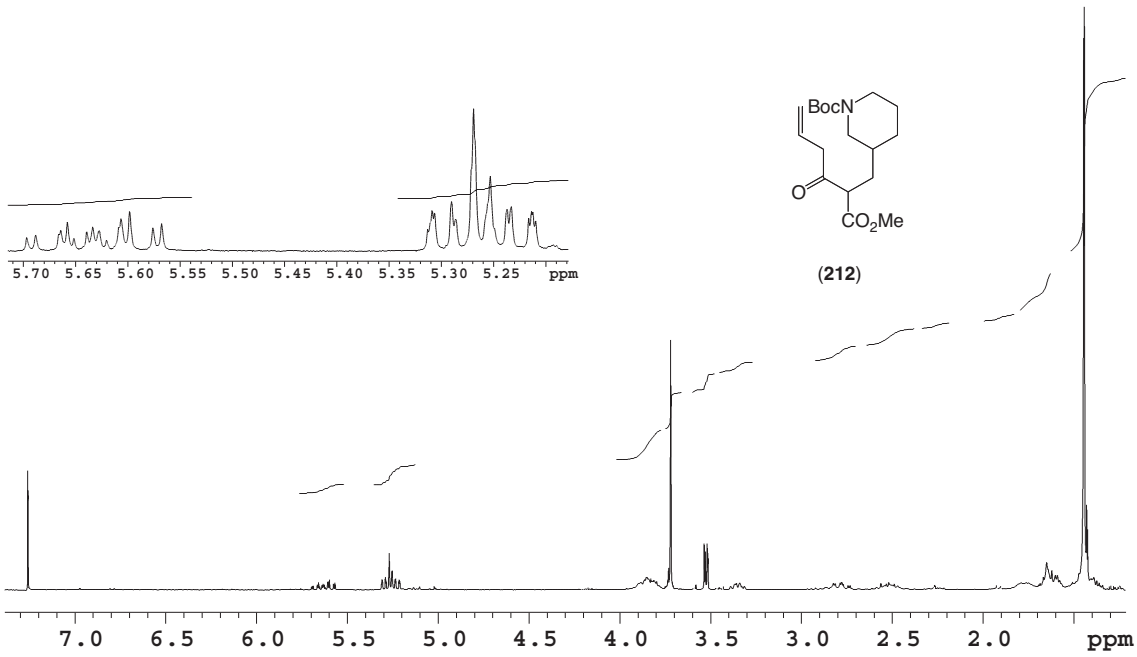


Figure 3.2: *300 MHz ^{1}H NMR spectrum of compound* ***212*** *recorded in $CDCl_3$ at 18℃*

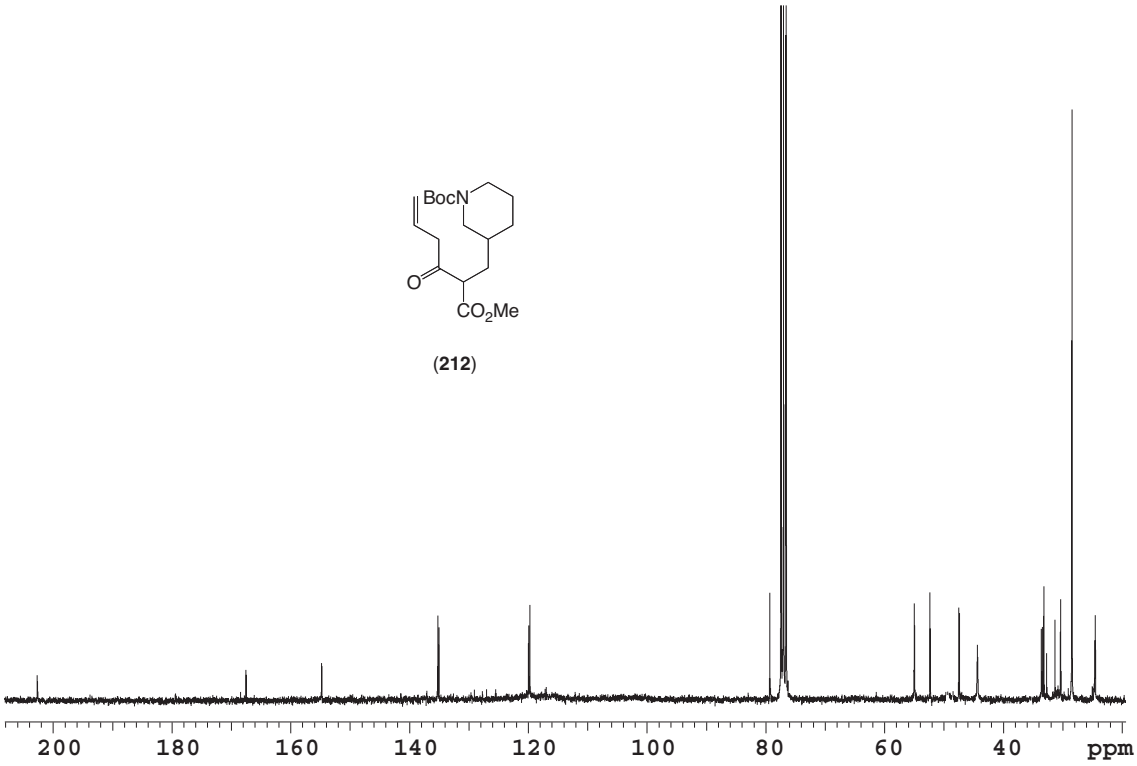


Figure 3.3: *75 MHz ^{12}C NMR spectrum of compound* ***212*** *recorded in $CDCl_3$ at 18℃ (doubling of signals attributed to the presence of carbamate rotomers)*

3.5 A Revised Synthetic Strategy

In the light of the results revealed in the preceding section, a modified reaction scheme that did not require a RCM reaction was considered in a final attempt to obtain the target vinblastine analogue, (3*R/S*)-**203**. In this new synthetic strategy, the RCM reaction associated with the original approach (Figure 3.1) was to be replaced by an intramolecular *N*-alkylation reaction and so leading to the formation of this carbomethoxyvelbamine substructure associated with the targetted (+)-vinblastine analogues (Figure 3.4).

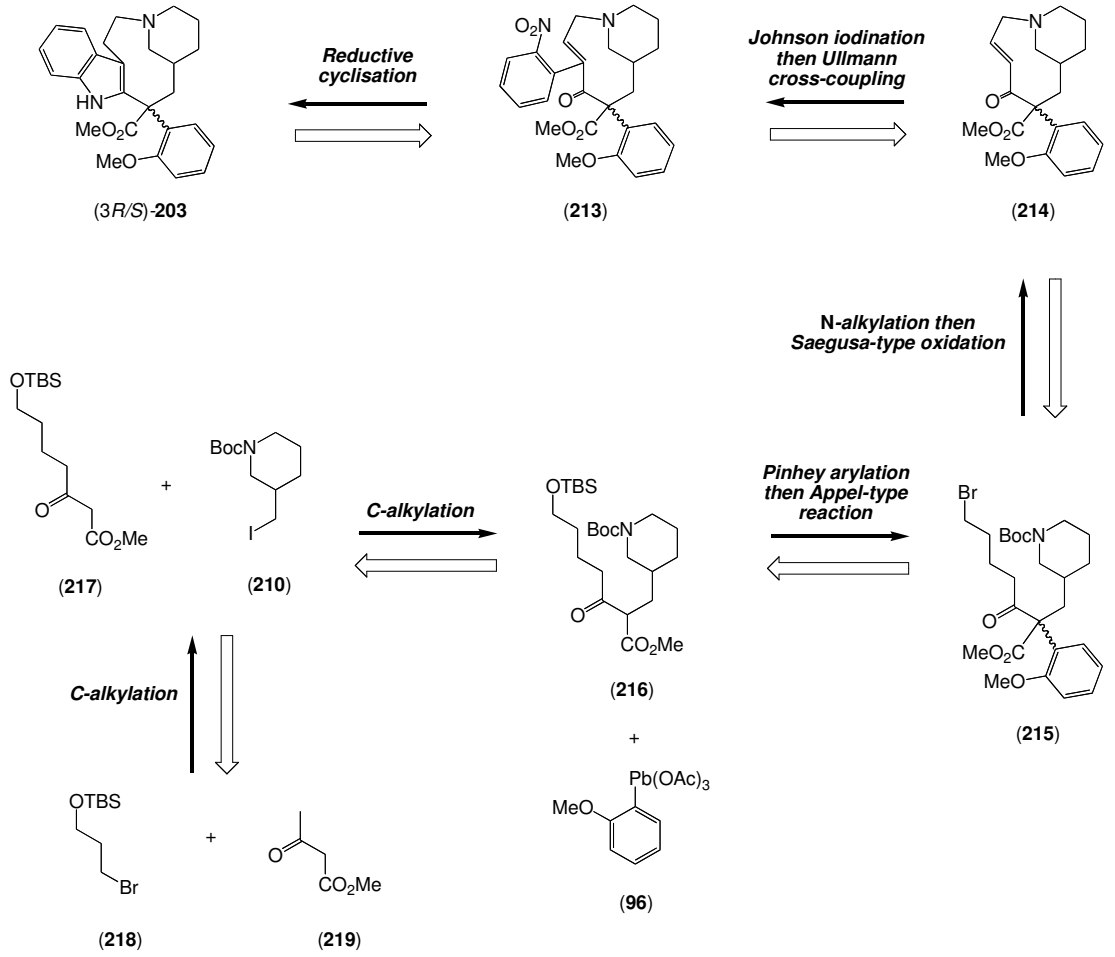
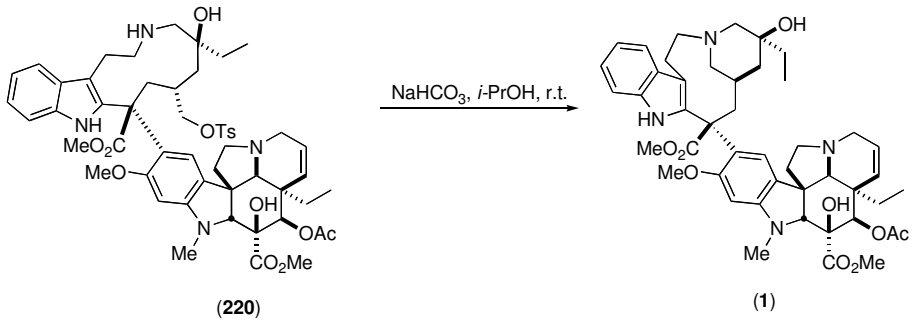


Figure 3.4: *Revised synthetic strategy for accessing the (+)-vinblastine analogue (3*R/S*)-**203***

This approach is related to the final stage of Fukuyama's stereocontrolled total synthesis of (+)-vinblastine (**1**) (**Section 1.3.3**) wherein the piperidine ring was formed through an intramolecular alkylation of nitrogen by the pendant tosyloxymethyl group in compound **220** and thus affording the natural product **1** (Scheme 3.7).

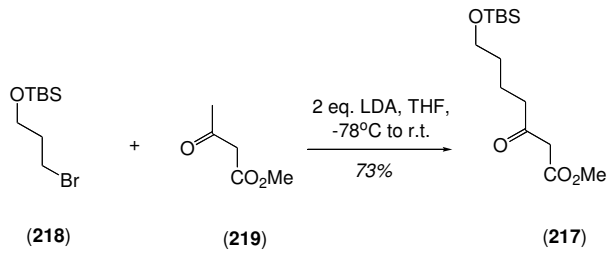


Scheme 3.7: *The final stage of Fukuyama's synthesis of (+)-vinblastine (**1**) incorporating an intramolecular* N*-alkylation*

The key intermediate, **214**, required in the revised approach was to be generated through an intramolecular *N*-alkylation reaction then a Saegusa-type oxidation to install the double bond required for the Banwell-type indole annulation process.[23] In order to attain this initial macrocyclic target, the alkyl halide **215** would be prepared using Appel-type chemistry described earlier (**Section 3.4.3**). Thus, the alkyl bromide **215** would be obtained from the β-ketoester **216** containing a protected alcohol functionality, that should, in turn, be accessible through the α-alkylation of β-ketoester **217**. The synthesis of this last compound and its subsequent manipulations are described in the following section.

3.5.1 Synthesis of β-Ketoester 217

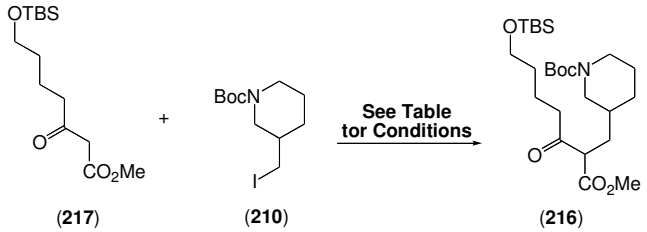
The first step in the development of a synthesis of the new vinblastine analogue (3*R/S*)-**203** was the preparation of known β-ketoester **217**[24] by the α′-alkylation of methyl acetoacetate (**219**) with (3-bromopropoxy)-*tert*-butyldimethylsilane (**218**) following the protocol of Moody (Scheme 3.8). The derived spectral data matched those reported.[24]



Scheme 3.8: *Synthesis of β-ketoester **217***

With compound **217** in hand, the next step was the α-alkylation of this β-ketoester with the *N*-Boc-protected alkyl iodide **210**. As with the α-alkylations already attempted, this reaction of β-ketoester **217** also proved problematic despite a range of bases and solvents being examined (Table 3.7).

Table 3.7: *α-Alkylation of β-ketoester* ***217*** *with alkyl iodide* ***210***



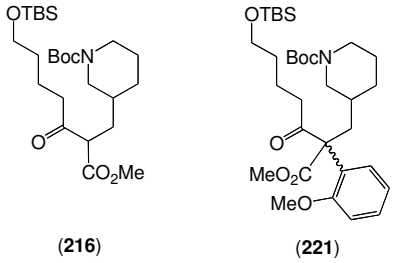
entry	base	solvent	temperature (°C)	yield (%)
1	NaH	DMF	0 → 18	4
2	NaH	DMF	0 → 90	12
3	LDA	THF	0 → 18	8
4	LDA	THF	0 → 70	16
5	LDA	(9:1 v/v) THF/HMPA	0 → 70	19
6	LiHMDS	THF	0 → 70	14
7	KHMDS	THF	0 → 70	35
8	K_2CO_3	DMF	18	25
9	K_2CO_3	DMF	90	75

Clearly, the standard alkylation conditions employed earlier led to poor yields of product. In contrast, when potassium carbonate was used as a base, the target compound **216** was obtained in 75% yield. The 300 MHz ^{1}H NMR spectrum of this new material lacked the singlet that is attributed to the two equivalent acidic α-protons of the starting material. Furthermore, the presence of a resonance at δ 2.52 that corresponds to the α′-methylene unit suggested α′-alkylation had not occurred. Finally, the singlets observed at δ 1.44, 0.87 and 0.03 indicated the compound contains a *tert*-butoxycarbonyl and a *tert*-butyldimethylsilyl protecting group. The DEPT ^{13}C NMR spectrum showed the associated methyl carbon resonances at δ 28.4, 25.9 and –5.4, while a signal at δ 56.2 is attributed to the methine α-carbon and thus indicating α-alkylation had taken place. The 70 eV mass spectrum displayed the expected molecular ion at *m/z* 485 and the base peak observed at *m/z* 57 corresponds to the *tert*-butyl cation. An accurate mass measurement on the molecular ion established that it was of the required composition,

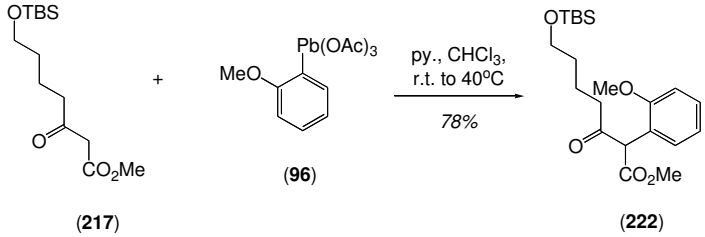
namely $C_{25}H_{47}NO_6Si$. With the key intermediate **216** now available, the Pinhey arylation reaction of this material was investigated and the outcomes of the relevant studies are presented in the following section.

3.5.2 Pinhey Arylation

As foreshadowed in the retrosynthetic analysis shown in Figure 3.4, the next step in the synthetic plan was to effect the Pinhey arylation of the β-ketoester **216** and so as to install a surrogate for the "lower" hemisphere of (+)-vinblastine (**1**) and thereby furnish the α-arylated product **221**. However, when this material was treated with the plumbated aryl **96** under standard conditions[5] only the starting nucleophile **216** was isolated from the reaction mixture.



In contrast, when the β-ketoester **217** was α-arylated with *o*-methoxyphenyllead triacetate (**96**), then the α-arylated product **222** was formed, as a mixture of keto-enol tautomers, in 78% yield (Scheme 3.9).



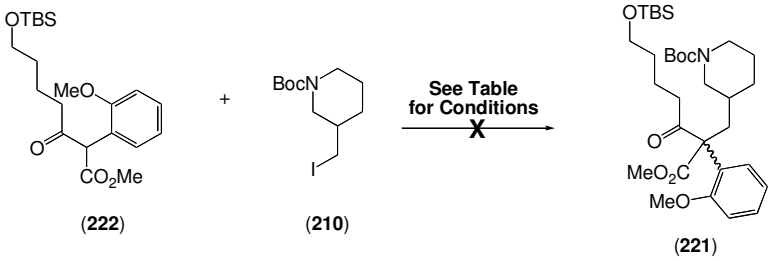
Scheme 3.9: *α-Arylation of β-ketoester **217** with* o*-methoxyphenyllead triacetate (**96**) to synthesise α-arylated β-ketoester **222***

The ^{1}H NMR spectrum of compound **222** displayed resonances at δ 2.48 and 2.05 that are assigned to the α′-methylene groups of its keto- and enol-forms, respectively. The keto-form predominates. The ^{13}C NMR spectrum showed a signal at δ 204.4 that is indicative of the ketone carbonyl of the keto-form, with the signal of the matching carbon of the enol form being seen at δ 176.8. The 70 eV electron impact mass spectrum displayed the expected molecular ion at *m/z* 394 with the base peak appearing

at *m/z* 337. This presumably arises through the loss of a *tert*-butyl radical from the parent ion.

The α-alkylation of compound **222** with alkyl halide **210** was then attempted but, as was the case with all the other α-alkylations tried, this also proved a disappointment (Table 3.8).

Table 3.8: *Attempted α-alkylation of β-ketoester* ***222*** *with alkyl iodide* ***210***



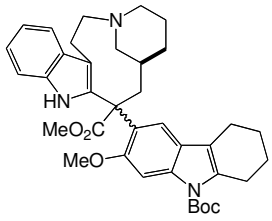
entry	base	solvent	temperature (°C)	product[a]
1	K_2CO_3	DMF	90	*Decomposition*
2	K_2CO_3	DMF	18	*No reaction*
3	K_2CO_3	(9:1 v/v) DMF/DMPU	90	*Decomposition*
4	K_2CO_3	DCM	50	*No reaction*
5	Cs_2CO_3	DCM	50	*No reaction*
6	LDA	THF	70	*Decomposition*
7	LDA	THF	0 → 18	*No reaction*
8	LDA	(1:1 v/v) THF/HMPA	0 → 18	*No reaction*
9	LiHMDS	(1:1 v/v) THF/HMPA	0 → 18	*No reaction*
10	KHMDS	(1:1 v/v) THF/HMPA	0 → 18	*No reaction*
11	NaHMDS	(1:1 v/v) THF/HMPA	0 → 18	*No reaction*
12	NaH	THF	0 → 70	*No reaction*
13	KH	THF	0 → 70	*No reaction*
14	NaH	DMF	0 → 18	*No reaction*
15	NaH	DMF	0 → 90	*Decomposition*

[a]All reaction outcomes are as judged by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

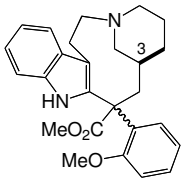
Due to the failure of these α-alkylation reactions, work in this area was abandoned.

3.6 Summary

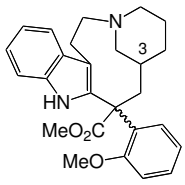
This chapter details two approaches to the (+)-vinblastine analogues **44**, (3*S*)-**203** and (3*R/S*)-**203** each of which incorporates the carbomethoxyvelbamine framework of the natural product **1**. In the first approach, a ring-closing metathesis was envisaged as the key step to be used in forming the macrocycles **44** and (3*S*)-**203**. Unfortunately, the requisite α-alkylated β-ketoester **211** could not be prepared. In a second approach the projected ring-closing metathesis step was replaced with one involving *N*-alkylation of the piperidine ring to generate the macrocycle (3*R/S*)-**203**. Again, problems were encountered in this strategy, with the α-alkylation of β-ketoester **217** proving problematic. In a final attempt to construct the requisite quaternary centre, a reaction sequence involving successive α-arylation then α-alkylation of β-ketoester **217** was attempted. Disappointingly, this also failed.



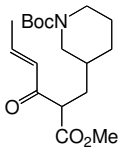
(**44**)



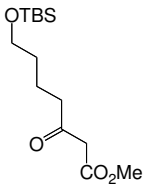
(3*S*)-**203**



(3*R/S*)-**203**



(**211**)



(**217**)

3.7 References

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Chapter Four

The Development of a Chiral Auxiliary-based Diasteroselective Pinhey Arylation of Cyclic β-Ketoesters

4.1 Introduction

4.1.1 Overview and Context

Chapter Two described the use of the Pinhey arylation reaction for the preparation of indole-indoline analogues of (+)-vinblastine (**1**). Such chemistry was then exploited, as described in Chapter Three, in an attempt to prepare analogues of (+)-vinblastine incorporating the carbomethoxyvelbamine hemisphere of this alkaloid.

As discussed in **Section 1.3**, one of the major difficulties associated with the synthesis of the dimeric *Vinca* alkaloids is the need to control the absolute stereochemistry at C-16′, which must be of the *S*-configuration.[1] Analogues of compound **1** incorporating the *R*-configuration at this centre lacked the therapeutically valuable cytotoxicity observed in the natural product.[2, 3] This chapter details the development of chemistry that should allow for the installation of the correct absolute configuration at the equivalent to this centre in the abovementioned indole-indoline analogues.

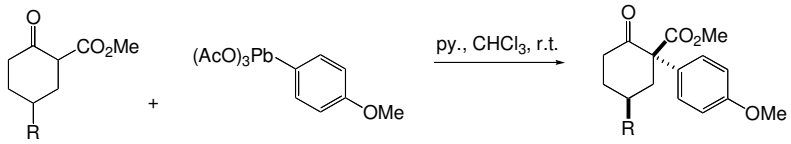
4.1.2 Background

The stereoselective introduction of electrophiles at the carbon α-related to an enolisable carbonyl group is a central topic in asymmetric synthesis. Although highly stereoselective α-alkylation reactions of ketones are now well known,[4-7] the analogous arylation processes remain underdeveloped. Following the studies described in **Section 2.2.1**, the Pinhey arylation reaction was seen as representing the best approach for achieving such ends and efforts to do so are discussed in the following section.

Diastereoselective Pinhey α-Arylations

One aspect of the Pinhey arylation reaction that has not been well studied is the control of the stereochemistry at a quaternary centre assembled by such means. Pinhey himself has described two examples of diastereoselective arylation reactions[8, 9] and Moloney[10, 11] has reported the same outcomes while preparing a series of glutamate analogues. Recently, Konopolski[12, 13] has investigated the diastereoselectivity of the reaction of 5-substituted methyl 2-oxo-cyclohexanecarboxylates **223** with *p*-methoxyphenyllead triacetate (**224**) as shown in Table 4.1.

Table 4.1: *Diastereoselectivity of the α-arylation of 5-substituted β-ketoesters* ***223*** *with* p-*methoxylead triacetate (****224****)*

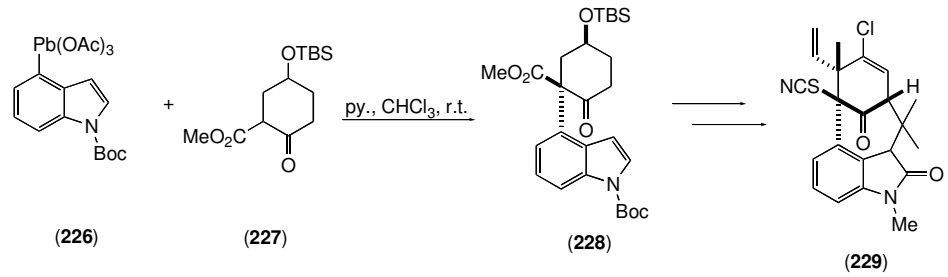


(**223**) (**224**) (**225**)

entry	R	yield (%)	d.r.
1	OMe	96	4:1
2	*t*-Bu	96	9:1
3	OTBDMS	97	20:1
4	OAc	64	4:1
5	OPiv	68	6:1
6	OTIPS	92	15:1
7	OTBDPS	95	99:1
8	OBn	85	6:1

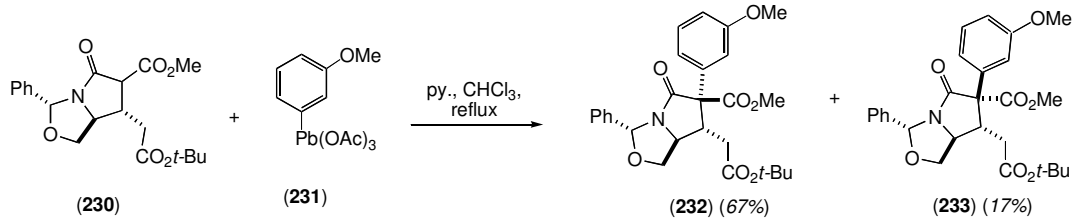
Clearly, the presence of more bulky R groups, especially silyl units, increased the stereoselectivity of this type of process. It has been postulated that the origin of this selectivity is an attractive electrostatic interaction and/or n, π* orbital overlap between the carbanionic centre of the β-ketoester and the distal silyl group.

Konopolski and Deng[14] have extended this approach to assemble, in a diastereoselective manner, the quaternary carbon centre associated with the alkaloid *N*-methylwelwitindolinone C isothiocyanate (**229**), a multidrug resistance reversal agent. As illustrated in Scheme 4.1, the indole-derived reagent **226** was treated, in chloroform containing three equivalents of pyridine, with the β-ketoester **227** and so forming product **228** in excellent yield (98%) and with very high diastereoselectivity (>30:1).



Scheme 4.1: *Use of aryllead triacetates in the diastereoselective formation of quaternary carbon centres*

Moloney[10, 11] has studied the Pinhey arylation of constrained glutamate analogues **230** (Scheme 4.2). In these systems, a diastereoselectivity of 4:1 for the desired product **232** was observed when *m*-methoxyphenyllead triacetate (**231**) was employed as the arylation partner.



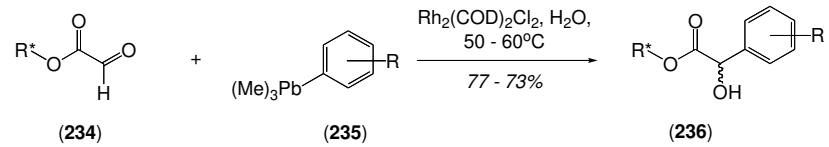
Scheme 4.2: *Diastereoselectivity of α-arylation of glutamate analogues **230** with* m-*methoxylead triacetate (**231**)*

Interestingly, these particular conversions required higher temperatures and longer reaction times than normally needed for this class of arylation process.

Another possible approach for establishing the desired stereochemistry would involve using β-ketoesters incorporating chiral alcohols since such systems might be expected to undergo diastereoselective Pinhey arylation reactions. Such possibilities are discussed in the next section.

4.2 The Use of Chiral Auxiliaries to Develop a Diastereoselective Pinhey Arylation of Cyclic β-Ketoesters

In a study relevant to the present discussion, Ding and co-workers[15] developed a rhodium-catalysed Barbier-Grignard-type arylation of chiral auxiliary-containing glyoxylates **234** with aryllead reagents **235**. A particular focus of this study was an examination of the level of diastereoselectivity induced by the presence of chiral auxiliaries on the electrophile (Scheme 4.3). Thus, treatment of the hydrate of glyoxylate **234** [R* = (-)-8-phenylmenthyl] with phenyltrimethyl lead **235** (R = H) afforded the expected product in a d.e. of 77%. This compares with a 3% d.e. observed when glyoxylate **234** [R* = (-)- menthyl] was employed as the electrophile.



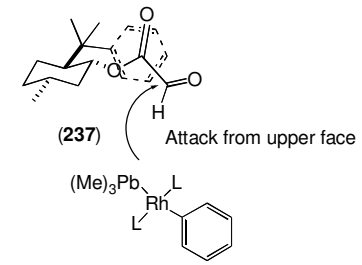
(**234**) (**235**) (**236**)

R* = (-)-menthyl
R* = (-)-8-phenylmenthyl

R = H, 75% yield, 3% d.e.
R = H, 73% yield, 77% d.e.
R = *m*-Cl, 76% yield, 67% d.e.
R = Np, 77% yield, 84% d.e.

Scheme 4.3: *Diastereoselective rhodium-catalysed arylation of glyoxylates* ***234*** *with aryltrimethyl leads* ***235***

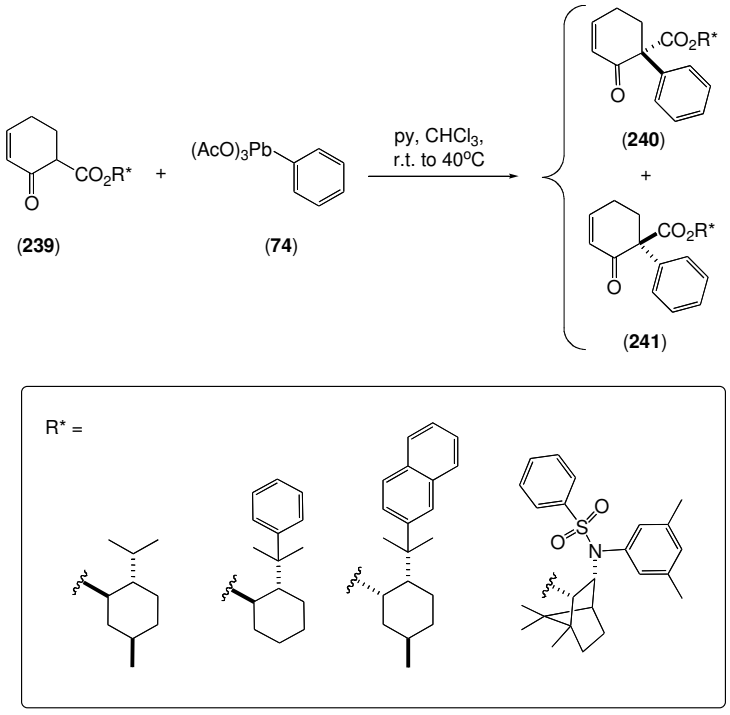
The high diastereoselectivity observed in the former case can be attributed to the phenyllead-Rh(I) complex **238** attacking that face of the aldehyde **237** that is not blocked by π-stacking of this moiety with the tethered phenyl residue (Figure 4.1).



(**237**) L = COD (**238**)

Figure 4.1: *Attack from upper face of (-)-8-phenylmenthyl glyoxylate (****237****) by the phenyltrimethyllead-Rh(I) complex* ***238***

Bearing such results in mind, chiral auxiliaries were applied to the present work and in attempts to effect a diastereoselective Pinhey arylation reaction and so produce the required stereochemistry in the targetted analogues of the indole-indoline core of (+)-vinblastine (**1**). In particular, a series of β-ketoesters, **239**, containing chiral alcohol residues was sought and these would then be subjected to arylation with phenyllead triacetate (**74**) and to generate, hopefully with some reasonable levels of diastereoselection, α-arylated products of the type **240** and **241** (Scheme 4.4). The synthesis of the relevant chiral auxiliaries is discussed in the next section.

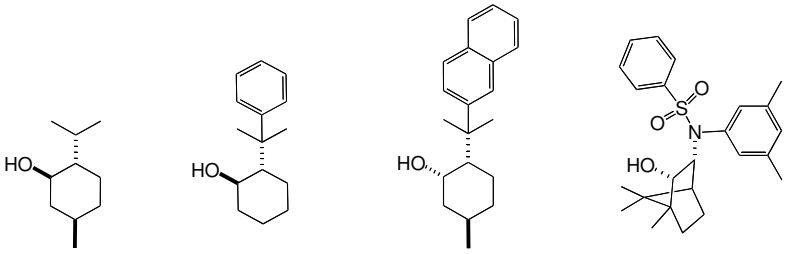


Scheme 4.4: *Proposed diastereoselective Pinhey arylation of chiral β-ketoesters* ***239*** *with phenyllead triacetate* ***(74)***

4.2.1 Preparation of Chiral Alcohols

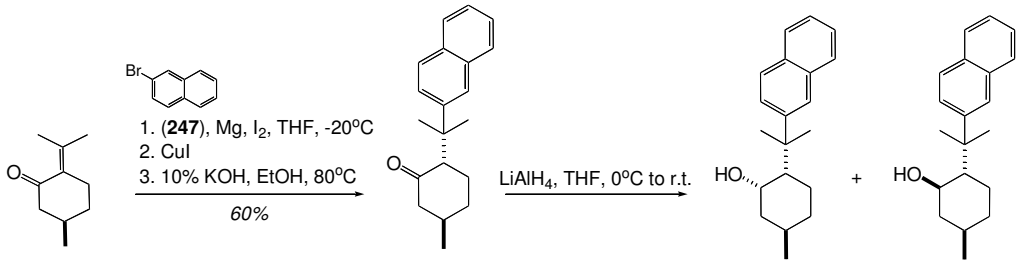
In order to investigate the utility of the abovementioned approach, 2-cyclohexen-1-one (**77**) would be acylated using a series of chiral cyanoformates to afford the desired auxiliary-containing β-ketoesters required for subjection to the Pinhey arylation reaction. Analogous protocols had been employed previously in the preparation of the racemic modifications of the cyclic β-ketoesters **75** and **79** (**Section 2.2.1**).

Based on the work of Ding,[15] (-)-menthol (**242**), (-)-*trans*-2-(1-methyl-1-phenylethyl)-cyclohexanol (**243**) and (+)-8-β-naphthyl*neo*menthol (**244**) were sought as the sources of chirality. (+)-3-[*N*-Benzenesulfonyl-*N*-(3,5-dimethylphenyl)-amino]-2-bornanol (**245**) was also used. These alcohols would first be converted into the corresponding chloroformates and then transformed into their respective cyanoformates to permit acylation of 2-cyclohexen-1-one (**77**). The use of cyanoformates rather than the precursor chloroformates in such reactions follows from the observation that use of the latter type of electrophile often affords mixtures of *O*- and *C*-acylated products.[16]



(**242**) (**243**) (**244**) (**245**)

Alcohols **242**, **243** and **245** were commercially available, while compound **244** was prepared using the protocol employed by Yang[17] (Scheme 4.5). Thus, commercially available (*R*)-(+)-pulegone (**246**) was subject to a Cu(I)-promoted 1,4-addition of the Grignard reagent derived from 2-bromonaphthalene (**247**). In this manner, a mixture of the *cis*- and *trans*-isomers of cyclohexanone **248** was obtained. This mixture was then treated with base to effect epimerisation and thus affording the desired *trans*-compound **248** in an exclusive manner. Cyclohexanone **248** was then reduced with lithium aluminium hydride to a 3:2 mixture of the corresponding alcohols **244** and **249**.



(**246**) (**248**) (**244**) (*60%*) (**249**) (*40%*)

Scheme 4.5: *Yang's protocol for the synthesis of alcohol* ***244***

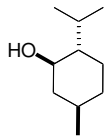
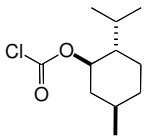
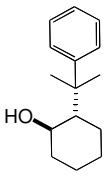
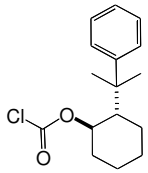
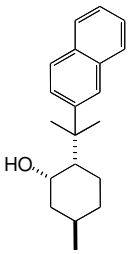
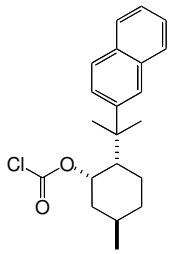
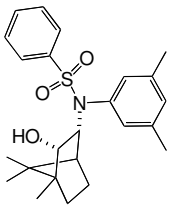
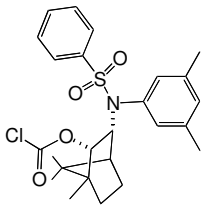
These alcohols could be separated chromatographically and the ^{1}H NMR spectrum of isomer **249** matched that reported in the literature,[18] while the analogous spectrum of the epimer **244** featured a diagnostic resonance at δ 3.85 that corresponds to the oxymethine proton. In the ^{13}C NMR spectrum of compound **244**, the associated carbon signal was observed at δ 68.3 and so indicating that reduction of the carbonyl moiety had occurred. Furthermore, the IR spectrum displayed a broad hydroxyl group absorption band at 3435 cm^{-1}. Finally, the 70 eV electron impact mass spectrum showed the expected molecular ion at *m/z* 282. The base peak observed at *m/z* 169 in this spectrum is attributed to a propan-2-yl-naphthalene cation arising from cleavage of the auxiliary.

With the desired chiral alcohols in hand, the next step in the preparation of the desired chiral β-ketoesters was the synthesis of the corresponding chloroformates. Relevant details are provided in the following section.

4.2.2 Preparation of Chiral Chloroformates

The standard procedure for preparing chloroformates from the corresponding alcohols is through reaction with phosgene gas,[19] a rather toxic reagent. Li has recently developed a much more convenient method for the synthesis of (-)-menthyl chloroformate involving replacement of phosgene gas by the synthetically equivalent triphosgene.[20] Accordingly, this protocol was applied to the present study and with pleasing results as shown in Table 4.2.

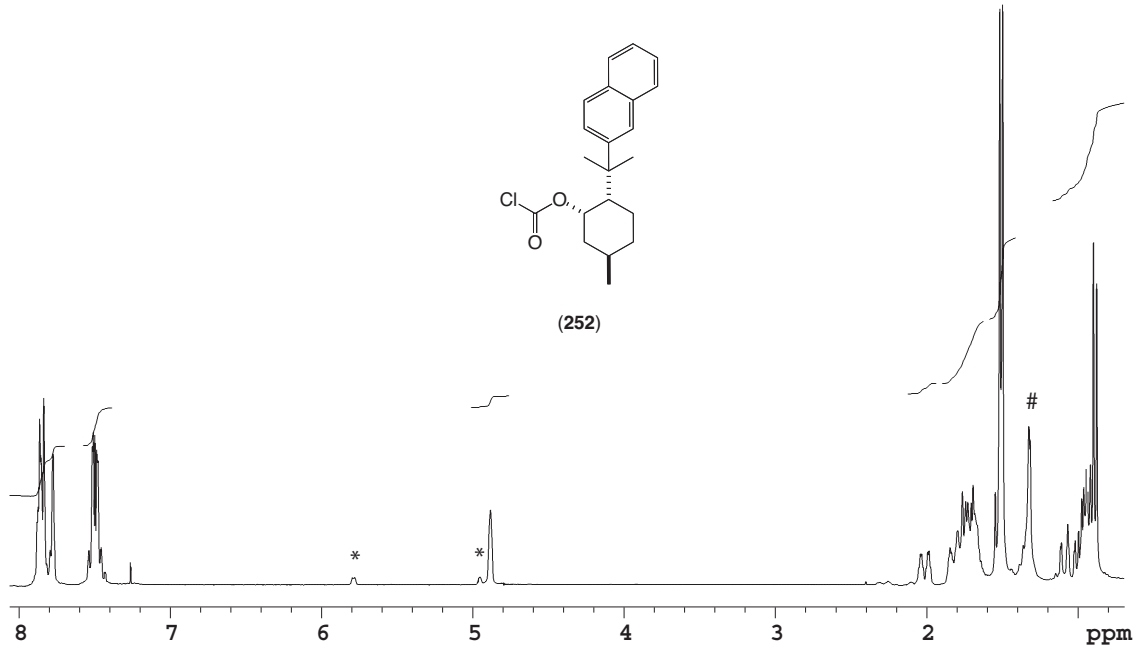
Table 4.2: *Preparation of chiral chloroformates* ***250 – 253***

entry	starting material	product[a]	yield (%)
1	 (**242**)	 (**250**)	82
2	 (**243**)	 (**251**)	70
3	 (**244**)	 (**252**)	83[b]
4	 (**245**)	 (**253**)	73

[a]**Method:** triphosgene (0.4 eq.), py. (3.0 eq.), CH_2Cl_2, -20°C → r.t., 12 h. [b](+)-2-(2-((*R*)-4-methylcyclohex-1-enyl)propan-2-yl)naphthalene (**254**) also produced as a side product in 13% yield.

While reference samples of chloroformate **250** were available through commercial suppliers, congeners **251** – **253**, have never been prepared previously and were, therefore, fully characterised. The IR spectrum of each of these compounds showed an absorption band in the region 1760 cm^{-1} and this corresponds to the stretching mode of the chloroformate carbonyl moiety. Furthermore, the ^1H NMR spectrum featured a signal in the region of δ 4.90 that corresponds to the methine proton attached to that ring-carbon bearing the chloroformate group. In the ^{13}C NMR spectrum the appearance of a signal at approximately δ 150.0 and corresponding to the oxygenated ring-carbon was taken as being indicative of the presence of a chloroformate carbonyl unit.

The ^{1}H and ^{13}C NMR spectra of chloroformate **252** are illustrated in Figures 4.2 and 4.3, respectively.



= water
* = unknown impurity

Figure 4.2: *300 MHz ^{1}H NMR spectrum of chloroformate* ***252*** *recorded in $CDCl_3$ at 18 ℃*

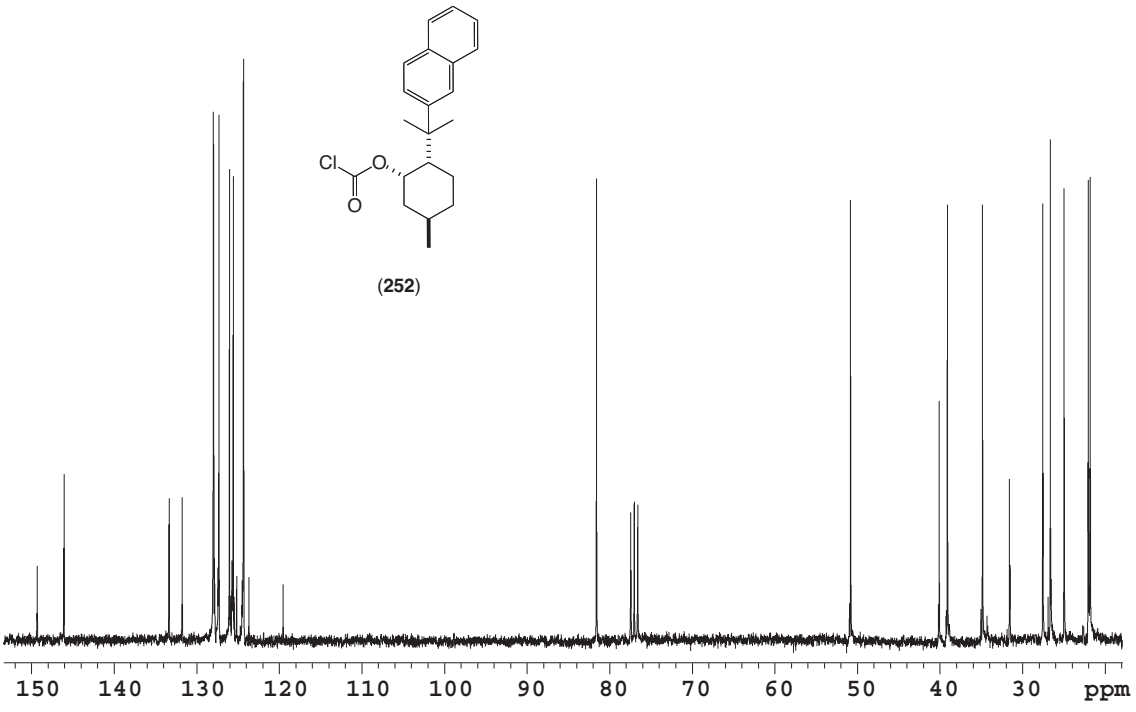


Figure 4.3: *75 MHz ^{13}C NMR spectrum of chloroformate* ***252*** *recorded in $CDCl_3$ at 18 ℃*

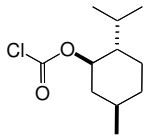
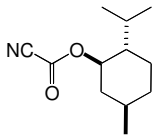
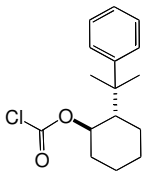
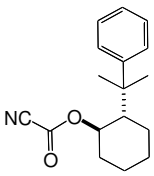
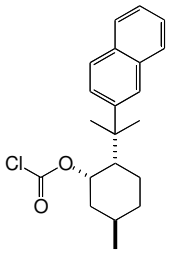
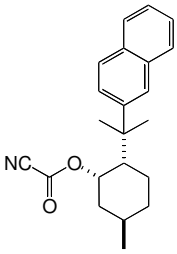
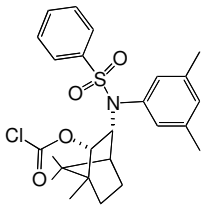
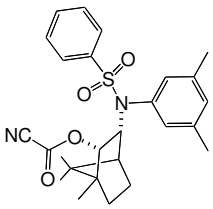
With these chiral chloroformates in hand, generation of the corresponding and targetted cyanoformates was then attempted. The protocols employed for this purpose are discussed in the following section.

4.2.3 Preparation of Chiral Cyanoformates

Following a procedure described by Kunish,[21] the optically active chloroformates **250** – **253** were transformed into their respective cyanoformates using conditions originally developed by Childs.[22] Thus, these substrates were treated with potassium cyanide in the presence of 18-crown-6 ether which acts as a phase transfer catalyst. In this way, the target cyanoformates **255** – **258** were each obtained in excellent yield (Table 4.3).

Compound **255** has been prepared previously, although not fully characterised,[23] while congeners **256** – **258** have not been described before in the chemical literature. Accordingly, they were subject to full spectroscopic characterisation. The IR spectrum of each of these cyanoformates displayed a sharp absorption band in the region of 1740 cm^{-1} that corresponds to the stretching mode of the carbonyl unit and this feature was used to monitor the progress of the formation of the target compound from the chloro-precursor, which displays a carbonyl absorption band at around 1760 cm^{-1}. Additionally, an absorption band in the region of 2240 cm^{-1} that is assigned to nitrile stretching was always observed for products **255** – **258**. Moreover, the ^{13}C NMR spectrum displayed a signal at *ca.* δ 110.0 and this is indicative of the presence of the nitrile moiety.

Table 4.3: *Preparation of chiral cyanoformates* ***255 – 258***

entry	starting material	product[a]	yield (%)
1	 (**250**)	 (**255**)	99
2	 (**251**)	 (**256**)	90
3	 (**252**)	 (**257**)	89
4	 (**253**)	 (**258**)	83

[a]**Method:** KCN (1.1 eq.), 18-crown-6 (0.4 eq.), CH_2Cl_2, r.t., 1 h.

The ^{1}H and ^{13}C NMR spectra of cyanoformate **257** are shown in Figures 4.4 and 4.5, respectively and are representative of the class as a whole.

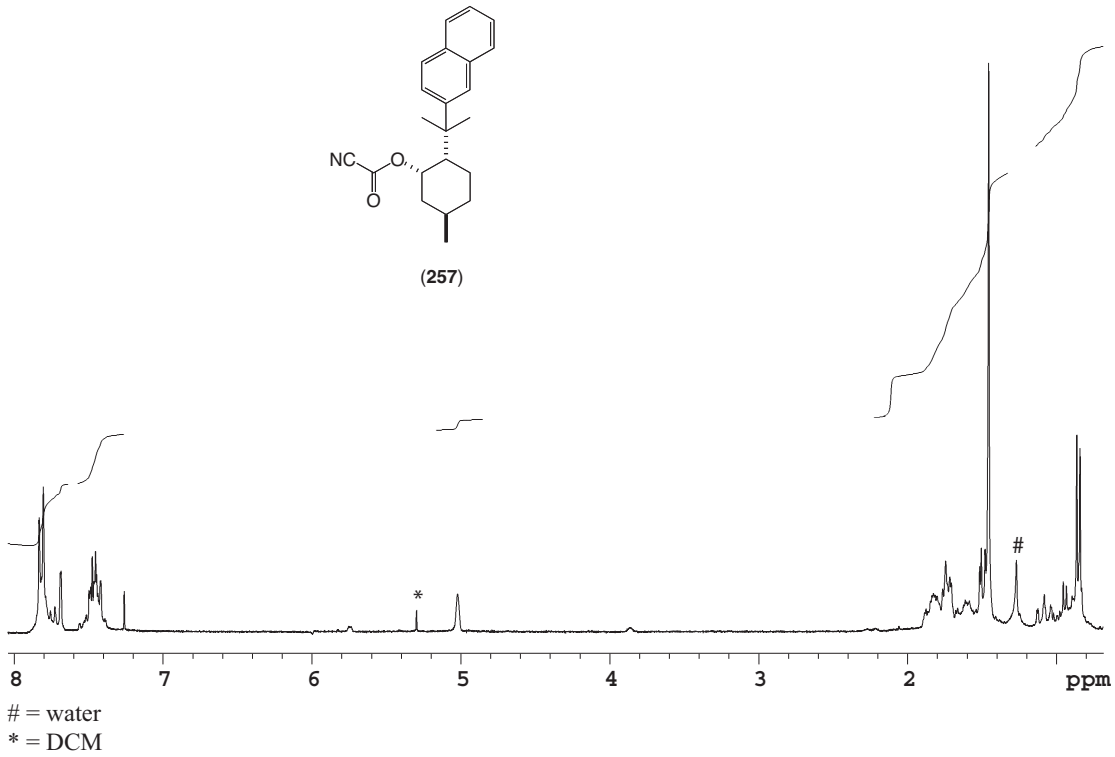


Figure 4.4: *300 MHz ^{1}H NMR spectrum of cyanoformate* ***257*** *recorded in $CDCl_3$ at 18 ℃*

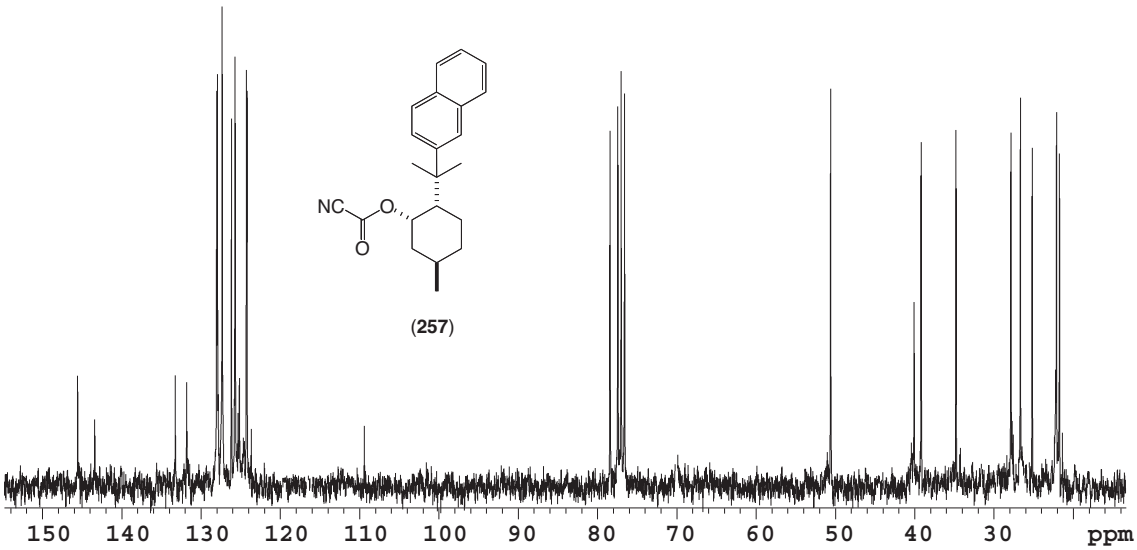


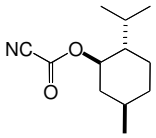
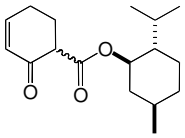
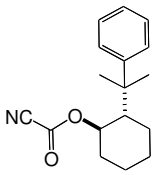
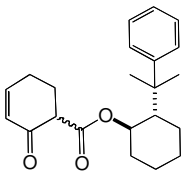
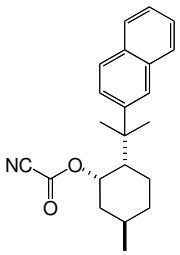
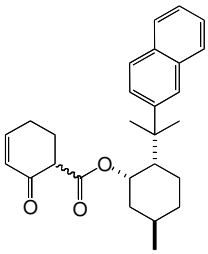
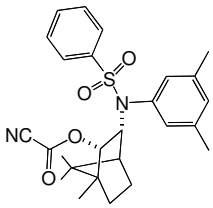
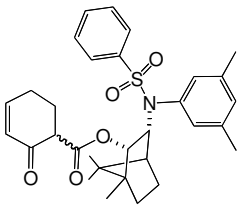
Figure 4.5*: 75 MHz ^{13}C NMR spectrum of cyanoformate* ***257*** *recorded in $CDCl_3$ at 18 ℃*

With the chiral cyanoformates now available, the synthesis of the derived β-ketoesters could be investigated. The outcomes of the relevant studies are outlined in the following section.

4.2.4 Preparation of Chiral β-Ketoesters

Following a protocol previously employed in the synthesis of cyclic β-ketoesters (**Section 2.1.2**), 2-cyclohexen-1-one (**77**) was acylated using the optically active cyanoformates **255** – **258** and so as to form the expected set of chiral β-ketoesters **259** - **262** and in preparatively useful yields (Table 4.4).

Table 4.4: *Preparation of chiral β-ketoesters* ***259 – 262***

entry	starting material	product[a]	yield (%)[b]
1	 (**255**)	 (**259**)	78
2	 (**256**)	 (**260**)	74
3	 (**257**)	 (**261**)	74
4	 (**258**)	 (**262**)	62

[a]**Method:** (i) *n*-BuLi (1.1 eq.), *i*-Pr_2NH (1.1 eq.), THF, -20°C, 0.5 h; (ii) 2-cyclohexen-1-one (**77**) (1.1 eq.), -78°C → 0°C, 1 h; (iii) HMPA (1.1 eq.), starting material (1.0 eq.), -78°C, 0.25 h; [b]product isolated as a mixture of diastereoisomers.

The β-ketoesters **259** – **262** were previously unreported and, therefore, subject to full characterisation. Each compound existed as a mixture of diastereoisomers with a resulting doubling of signals being observed in the relevant NMR spectra as would be expected for such a combination. Thus, the ^{1}H NMR spectrum of each compound displayed multiplets in the region of δ 3.20 and 3.00 arising from the diastereotopic and acidic α-protons. The ^{13}C NMR spectrum featured pairs of signals at approximately δ 190.0 and 170.0 arising from the carbonyl groups of the α,β-unsaturated enone and ester functionalities, respectively. Furthermore, a pair of signals appearing at *ca.* δ 56.0 was taken as being indicative of the methine α-carbon and so suggesting *C*-acylation had occurred. The IR spectrum displayed strong absorption bands in the region of 1735 and 1680 cm^{-1} that correspond to the carbonyl stretching frequencies of the ester and α,β-unsaturated enone units, respectively.

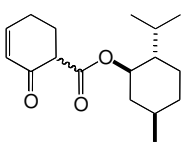
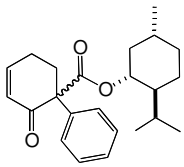
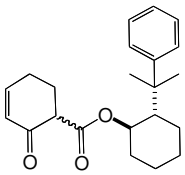
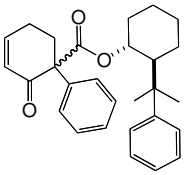
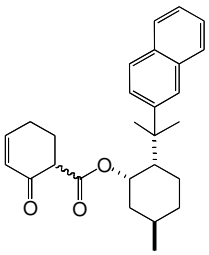
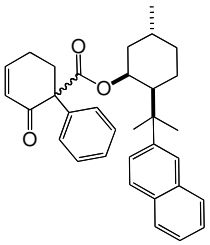
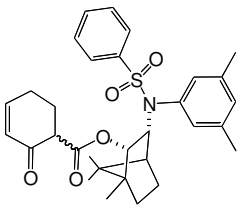
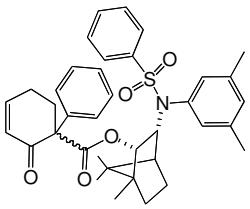
With the desired chiral β-ketoesters now quite clearly to hand, the diastereoselective Pinhey arylation reaction could be studied. Outcomes are detailed in the next section.

4.2.5 Diastereoselective Pinhey α-Arylations

Using standard Pinhey arylation reaction conditions,[8] chiral β-ketoesters **259** – **262** were treated with phenyllead triacetate (**74**) and the desired α-arylated β-ketoesters **263** – **266** thus generated in reasonable yields. In the case of the 8-arylmenthyl-containing β-ketoesters, good diastereomeric ratios were also observed (Table 4.5).

Compounds **263** – **266** had never been prepared before and were, therefore, fully characterised. The ^{13}C NMR spectrum of each compound featured a pair of signals at approximately δ 60.0 that is assigned to the new quaternary α-carbon having the carboalkoxy and phenyl groups attached. Doubling of signals indicated the presence of diastereoisomers. As an example, the ^{1}H and ^{13}C NMR spectra of α-arylated enone **265** are shown in Figures 4.6 and 4.7, respectively. The ratio of the product diastereoisomers was determined by the integration of the signals associated with the β-proton of the α,β-unsaturated enone functionality in the ^{1}H NMR spectrum of each mixture of α-arylated enones (See inset).

Table 4.5: *Diastereoselective Pinhey arylations of chiral β-ketoesters* ***263 – 266*** *with phenyllead triacetate (****74****)*

entry	starting material	product of arylation[a]	yield (%)[b]	d.r.[c]
1	 (**259**)	 (**263**)	57	50:50
2	 (**260**)	 (**264**)	56	87:13
3	 (**261**)	 (**265**)	76	90:10
4	 (**262**)	 (**266**)	90	66:34

[a]**Method:** py. (3.0 eq.), $CHCl_3$, 0.5 h; (ii) phenyllead triacetate (**74**) (1.1 eq.), 40°C, 12 h; [b]product isolated as a mixture of diastereoisomers; [c]As determined by integration of the signals for the respective β-olefinic protons in the ^{1}H NMR spectrum.

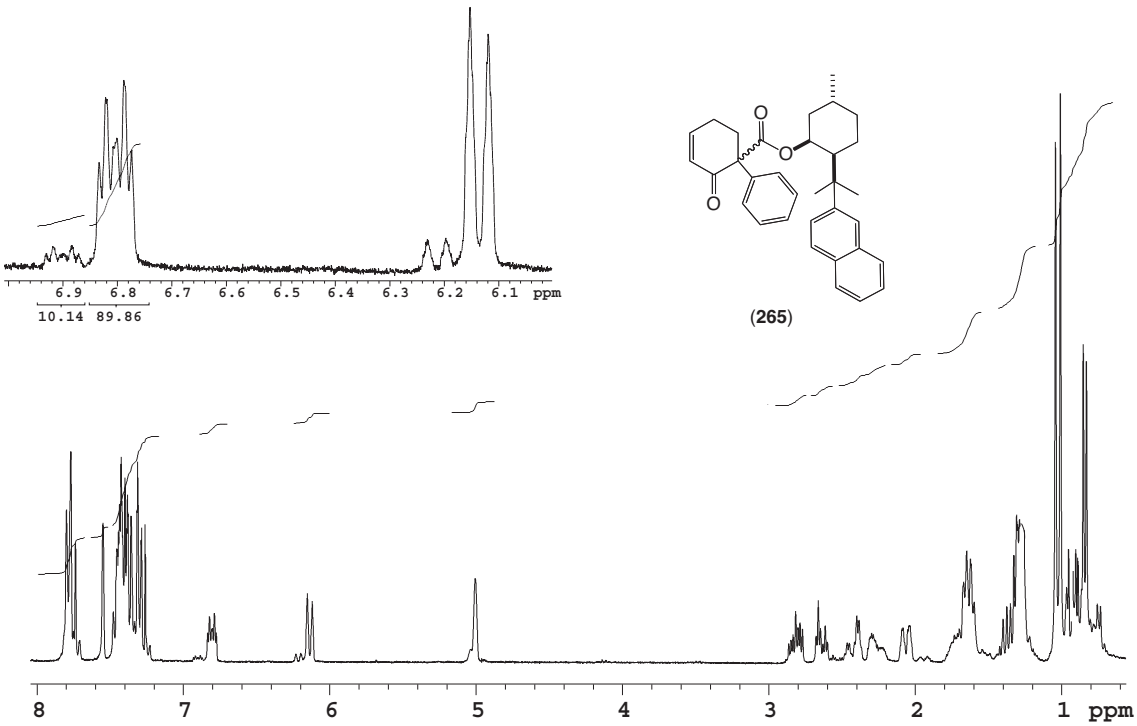


Figure 4.6: *300 MHz ^{1}H NMR spectrum of α-arylated enone* ***265*** *recorded in $CDCl_3$ at 18℃ (doubling of signals due to presence of diastereoisomers)*

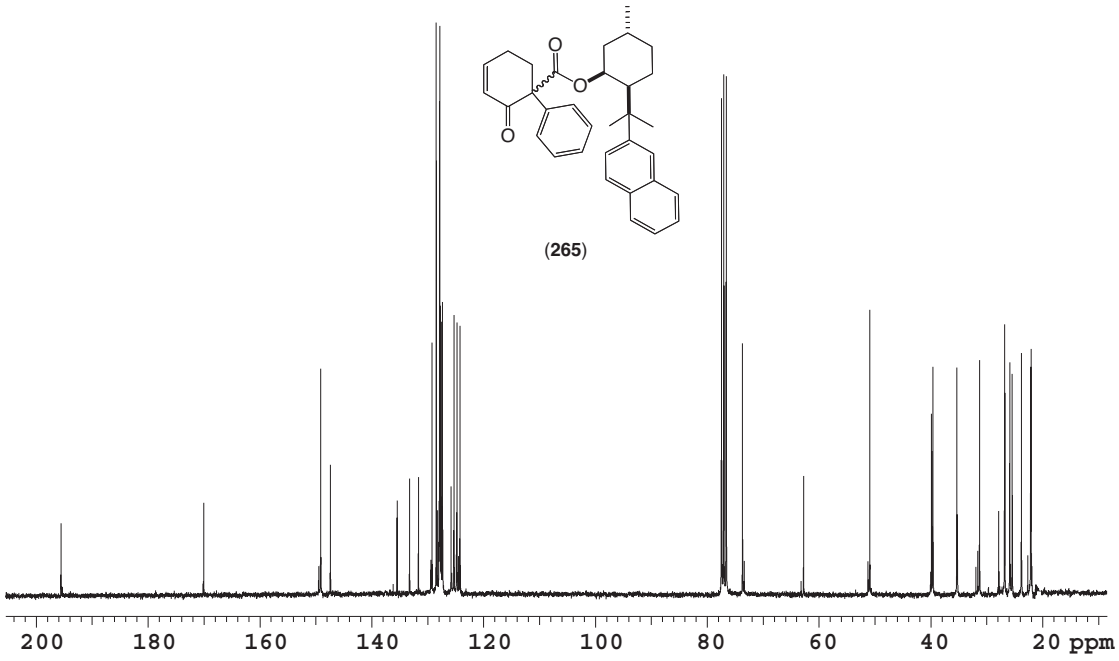
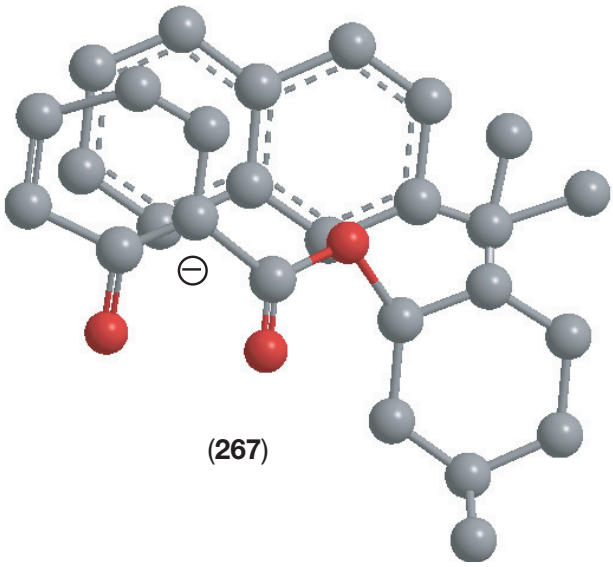


Figure 4.7: *75 MHz ^{13}C NMR spectrum of α-arylated enone* ***265*** *recorded in $CDCl_3$ at 18℃ (doubling of signals due to presence of diastereoisomers)*

Attempts to separate the diastereoisomers using chromatographic methods failed, with the result that the absolute stereochemistry of the major diasteromeric form of these arylation products remains undetermined in any rigorous sense.

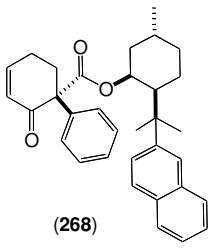
In terms of the diasteromeric ratio, increasing the steric bulk on the chiral auxiliary led to an increase in the propensity of one diastereoisomer to be formed over the other. It is proposed that the increased size of the chiral auxiliary allows attack by the phenyl carbocation to occur, to an increasing extent, from one face of the enolate **267**, so leading to one diastereoisomer being formed preferentially. In the case of the 8-β-naphthyl-containing chiral auxiliary a π-stacking interaction may facilitate the diastereoselectivity by shielding the lower face of enolate **267** (Figure 4.8).



(**267**)

Figure 4.8: *Proposed conformation of enolate* ***267*** *with a π-stacking interaction shielding the lower face*

It is therefore proposed that for the 8-β-naphthyl*neo*menthyl-containing system, the major product is compound **268**, wherein the phenyl carbocation derived from aryllead **74** attacked the face of the enolate **267** opposite to that shielded by the naphthyl ring.

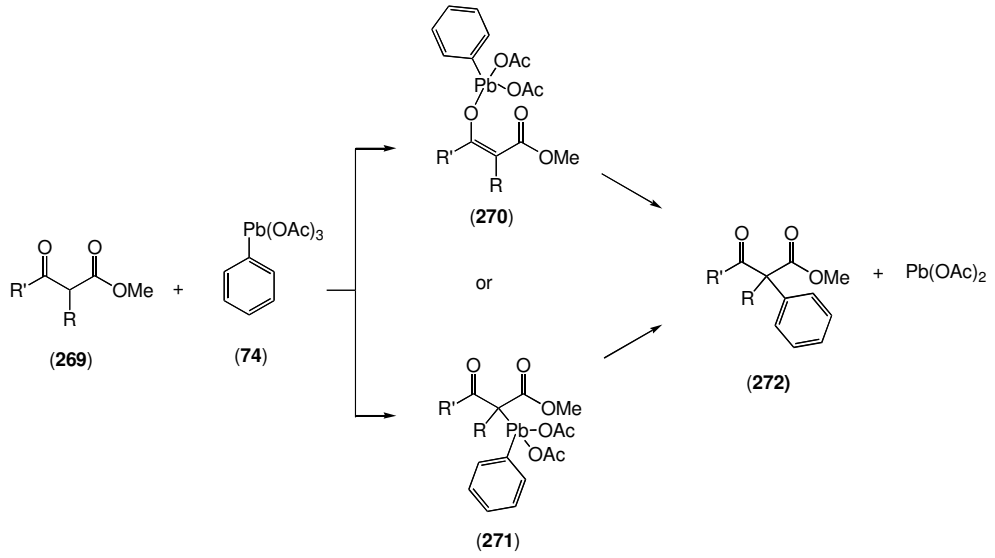


(**268**)

The stereochemistry at the quaternary α-carbon of compound **268** is opposite that of the desired absolute stereochemistry required in (+)-vinblastine (**1**) at C-16′. However, use of the chiral β-ketoester derived from, for example, chiral alcohol **249** should allow for installation of the correct absolute chemistry at this stereocentre through shielding the upper face of the enolate and so forcing attack of the phenyl carbocation from that face necessary to establish the correct stereochemistry.

Effect of Coordinating Base

A ligand-coupling mechanism has been proposed to explain the outcomes of the Pinhey arylation reaction.[24] For β-ketoesters of the general form **269** either an oxygen-lead intermediate **270** or a carbon-lead intermediate **271** is possible. In the second step, ligand coupling with accompanying reductive elimination of the elements of $Pb(OAc)_2$ occurs and so affording the product **272** as illustrated Scheme 4.6.

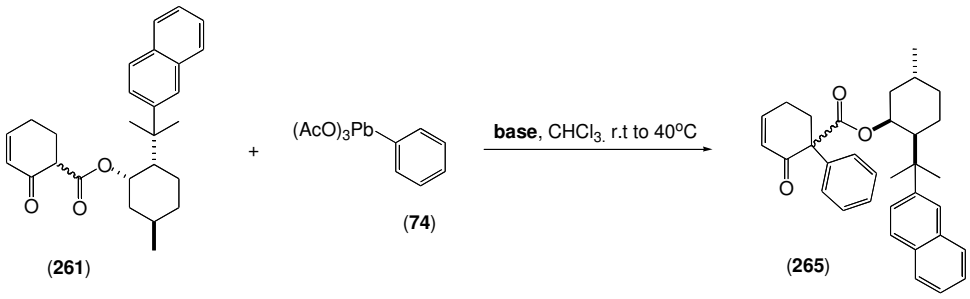


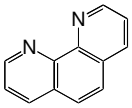
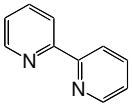
Scheme 4.6: *Alternative intermediates in the α-arylation of β-ketoesters **269** with phenyllead triacetate (**74**)*

A general feature of the arylation reaction with aryllead triacetates is the need for the presence of a coordinating base or solvent like DMSO. Therefore, in the case of a coordinating base, the intermediate involved in the arylation must have two nitrogen ligands attached to lead. It is envisaged that in the case of diastereoselective arylations, replacing pyridine (**273**) with a more sterically demanding base such as 1,10-phenanthroline (**274**) or 2,2′-bipyridine (**275**) might increase the steric crowding in the intermediate formed during the α-arylation of the β-ketoester **261** and thus lead to an increase in the diastereoselectivity observed.

However, as can clearly be seen from the results presented in Table 4.6, increasing the steric bulk of the coordinating base had little or no effect on the diastereoselectivity of the reaction and thus suggesting it is the choice of chiral auxiliary that determines the diastereoselectivity.

Table 4.6: *Effect of base on diastereoselectivity of Pinhey arylation between chiral β-ketoester* ***261*** *and phenyllead triacetate (****74****)*



entry	base[a]	d.r.[b]
1	 (**273**)	90:10
2	 (**274**)	89:11
3	 (**275**)	87:13

[a]Method same as Table 4.5 except with replacement of pyridine with 3 equivalents of the appropriate base. [c]As determined by integration of the signals for the respective β-olefinic protons in the ^{1}H NMR spectrum.

4.3 Summary

This chapter has detailed a method for controlling stereochemistry in a model system designed to mimic the indole-indoline core of (+)-vinblastine (**1**). A chiral auxiliary based on (+)-8-β-naphthyl*neo*menthol proved most effective, affording a 9:1 ratio of the diastereomeric arylation products. Although the absolute stereochemistry of the major diastereoisomer was unable to be determined, it is postulated that this is as shown in compound **268** and where attack of the phenyl carbocation on the precursor enolate **267** had occurred opposite to the face shielded by the bulky naphthyl ring. Compound **268** had the opposite stereochemistry of that desired for the indole-indoline analogues of (+)-vinblastine. However, with the ability to control the stereochemistry at this centre now possible, the implementation of the chiral β-ketoester derived from chiral alcohol **249** should allow for installation of the correct absolute chemistry at this stereocentre.

4.4 Conclusions

A series of small molecules resembling the indole-indoline core of (+)-vinblastine (**1**) was prepared by a process that involved a range of different pairings of aryl groups as surrogates for these heterocyclic units. A methodology was implemented and concerned, as its key steps, the Pinhey-type arylation of the appropriate cyclic β-ketoester with the suitable aryllead triacetates and then a Pd[0]-catalysed Ullmann cross-coupling reaction to form the corresponding α′-arylated enones. A reductive cyclisation reaction then led to the synthesis of the desired analogues of the indole-indoline core or "bridging region" of (+)-vinblastine (**1**). Studies on the installation of the correct stereochemistry at the equivalent of C-16′ of (+)-vinblastine (**1**) in these analogues led to the development of a diastereoselective Pinhey arylation reaction. Some success was achieved in the case of the 8-arylmenthol-based chiral auxiliaries. It is envisaged that the enantiomerically enriched analogues so formed will be tested to ascertain their value as anti-mitotic agents. The result reported herein also allow the possibility of developing more complex analogues of the *Vinca* alkaloid **1** and have greatly enhanced the prospects of developing a total synthesis of (+)-vinblastine (**1**).

4.5 References

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Chapter Five

Experimental Procedures Associated with Work Described in Chapters Two to Four

5.1 General Procedures

Unless otherwise indicated, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Signals arising from residual protio-forms of the solvent were used as the internal standard. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s), *J* Hz, relative integral] where multiplicity is defined as: s=singlet; d=doublet; t=triplet; q=quartet; p=pentet; sex=sextet; sept=septet; m=multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ 'triplet' was used as the reference in proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra, the data are given as: C=O = carbonyl; C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl. The assignment of the observed signals in various spectra was often assisted by conducting distortionless enhancement of polarisation transfer (DEPT), homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY) and/or nuclear Overhauser effect (NOE) experiments.

Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR spectrophotometer. Samples were analysed as thin films on NaCl plates.

A VG Fisons Autospec three-sector (E/B/E) double-focussing mass spectrometer was used to obtain both low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray mass spectra were obtained on a VG Quattro II triple quadrapole MS instrument operating in either positive and/or negative ionisation modes.

Unless otherwise stated, optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) and the concentrations (*c*) (g/100 mL) indicated using spectroscopic grade chloroform as solvent. The measurements were

carried out in a cell with a path length (*l*) of 1 dm. Specific rotations $[\alpha]_D^{20}$ were calculated at 18°C using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and given in 10^{-1}.deg.cm^2.g^{-1}.

Melting points were measured on a Reichart hot-stage microscope and are uncorrected.

Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based in the Research School of Chemistry.

Analytical thin layer chromatography (TLC) was performed on aluminium backed 0.5 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or *p*-anisaldehyde : sulfuric acid (conc) : glacial acetic acid : ethanol (3.7 mL : 5 mL : 1.5 mL : 135 mL). Flash chromatography was performed using the analytical grade solvents indicated and silica gel 60 (0.040-0.0063 mm) as supplied by Lomb Scientific.

Room temperature is assumed to be 18°C.

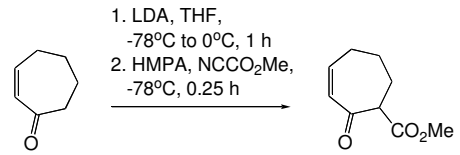
Starting materials and reagents were generally available from Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied or, in the case of some liquids, simply distilled prior to use.

Drying agents and other inorganic salts were purchased from AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Methanol and ethanol were distilled from their respective magnesium alkoxide salts. Acetonitrile, chloroform and dichloromethane were distilled from calcium hydride, while toluene was distilled from sodium. *N,N*-Dimethylformamide (DMF), pyridine, triethylamine, diisopropylamine were all distilled from and stored over potassium hydroxide pellets.

Organic solutions obtained from the work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$) then filtered and concentrated under reduced pressure on a rotary evaporator with the water bath not exceeding 30°C unless otherwise specified.

5.2 Procedures Associated with Work Described in Chapter Two

Methyl 2-oxo-cyclohept-3-ene carboxylate (79)



(**78**) (**79**)

Following a procedure developed by Mander *et al*,[1] a magnetically stirred solution of diisopropylamine (3.02 mL, 21.0 mmol) in THF (40 mL) maintained at –20°C (NaCl/ice bath) under a nitrogen atmosphere was treated, dropwise, with *n*-butyllithium (13.5 mL of a 1.6 M solution in hexanes, 21.0 mmol). The resulting mixture was stirred for 0.5 h at –20°C then the temperature was reduced to –78°C (dry-ice/acetone bath) and a solution of enone **78** (2.00 g, 18.5 mmol) in THF (10 mL) was added *via* cannula. The resulting solution was then warmed to 0°C (ice/water bath), stirred at this temperature for 1 h, cooled again to –78°C and HMPA (1.75 mL, 21.0 mmol) and methyl cyanoformate (1.79 mL, 21.0 mmol) were added. After stirring for an additional 0.25 h at –78°C, the reaction mixture was poured into cold water (150 mL) and extracted with ether (2 x 50 mL). The combined organic phases were washed with distilled water (3 x 50 mL) and the separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 5 → 20% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **79*** (2.29 g, 74%) as a clear, yellow oil.

R_f 0.6 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (enolic form-major isomer) δ 6.26 (dt, *J* = 12.2 and 4.2 Hz, 1H), 5.93 (dt, *J* = 14.4 and 2.1 Hz, 1H), 3.77 (s, 3H), 2.46–2.42 (complex m, 2H), 2.36–2.33 (complex m, 2H), 1.87–1.83 (complex m, 2H), (OH proton exchanges with solvent). (keto form-minor isomer) δ 6.62 (pd, *J* = 4.8 and 1.2 Hz, 1H), 6.05 (complex m, 1H), 3.73 (s, 3H), 3.64 (m, 1H), 2.21–1.98 (complex m, 6H).

^{13}C NMR (75 MHz) (enolic form-major isomer) δ 173.1 (C), 167.9 (C=O), 142.4 (CH), 125.8 (CH), 102.5 (C), 51.7 (CH_3), 32.1 (CH_2), 27.6 (CH_2), 24.2 (CH_2). (keto form-minor isomer) δ 198.6 (C=O), 170.8 (C=O), 146.7 (CH), 131.2 (CH), 58.8 (CH), 52.2 (CH_3), 29.9 (CH_2), 25.2 (CH_2), 24.5 (CH_2).

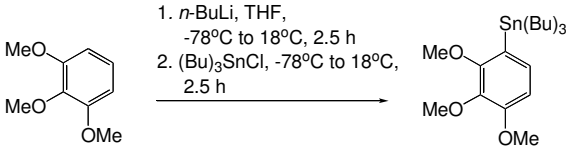
IR (NaCl, film) ν_{max} 2951, 2930, 1747 (C=O), 1653 (C=O), 1600, 1441, 1362, 1312, 1299, 1208, 1056, 834 cm^{-1}.

EIMS (70 eV) *m/z* 168 ($M^{+\bullet}$, 39%), 140 (55), 136 (42), 109 (30), 81 (100).

HRMS Found: $M^{+\bullet}$, 168.0785. $C_9H_{12}O_3$ requires $M^{+\bullet}$, 168.0786.

5.2.1 Synthesis of Arylstannanes 92 - 95

Tributyl(2,3,4-trimethoxyphenyl)stannane (92)



(**81**) (**92**)

Following a procedure developed by Sundburg *et al*,[2] a magnetically stirred solution of arene **81** (5.00 g, 29.9 mmol) in THF (50 mL) maintained at –78°C (dry-ice/acetone bath) under a nitrogen atmosphere was treated, *via* cannula, with *n*-BuLi (20.5 mL of a 1.6 M solution in hexane, 32.8 mmol). The resulting mixture was stirred for 0.5 h at –78°C, then warmed to 18°C and stirred at this temperature for 2 h, then cooled again to –78°C (dry-ice/acetone bath) and tri-*n*-butylstannyl chloride (8.20 mL, 30.0 mmol) was added dropwise. The resulting mixture was stirred for a further 0.5 h at –78°C then allowed to warmed to 18°C and stirred at this temperature for an additional 2 h, then quenched with ammonium chloride (1 x 20 mL of a saturated aqueous solution) and extracted with ether (2 x 50 mL). The combined organic phases were washed with KF (1 x 50 mL of a saturated aqueous solution) and distilled water (2 x 50 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 1 → 5% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound* ***92*** (7.68 g, 57%) as a clear, viscous oil.

R_f 0.3 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 6.98 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 1.51 (complex m, 6H), 1.32 (complex m, 6H), 1.02 (complex m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H).

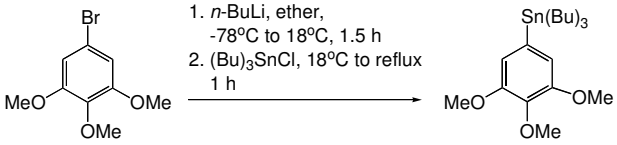
^{13}C NMR (75 MHz) δ 157.7 (C), 154.5 (C), 141.1 (C), 130.9 (CH), 126.1 (C), 107.9 (CH), 60.6 (CH_3), 60.5 (CH_3), 55.9 (CH_3), 29.1 (CH_2), 27.4 (CH_2), 13.7 (CH_2), 9.8 (CH_3).

IR (NaCl, film) ν_{max} 2955, 1578, 1482, 1267, 1093 cm^{-1}.

EIMS (70 eV) *m/z* 401 [(M–Bu•)$^+$, 100%], 345 (24), 287 (52).

HRMS Found: (M–Bu•)$^+$, 401.1139. $C_{17}H_{29}O_3{}^{120}Sn$ requires (M–Bu•)$^+$, 401.1139.

Tributyl(3,4,5-trimethoxyphenyl)stannane (93)



(**82**) (**93**)

Following a procedure developed by Suginome *et al*,[3] a magnetically stirred solution of bromoarene **82** (3.30 g, 13.0 mmol) in ether (50 mL) maintained at –78°C (dry-ice/acetone bath) under a nitrogen atmosphere was treated, *via* cannula, with *n*-BuLi (10.0 mL of a 1.6 M solution in hexane, 16.0 mmol). The resulting mixture was stirred for 0.5 h at –78°C then warmed to 18°C and stirred at this temperature for 1 h. Tri-*n*-butylstannyl chloride (3.52 mL, 13.0 mmol) was then added dropwise. The resulting mixture containing a yellow precipitate was heated to reflux and stirred at reflux for 1 h, then allowed to cooled to 18°C. The reaction mixture was then quenched with HCl (20 mL of a 1 M aqueous solution) and extracted with ether (1 x 100 mL). The organic phase was washed with $NaHCO_3$ (50 mL of a saturated aqueous solution) and distilled water (2 x 50 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 1 → 10% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound* ***93*** (2.40 g, 40%) as a clear, viscous oil.

R_f 0.3 (silica, 1:9 v/v ethyl acetate/hexane).

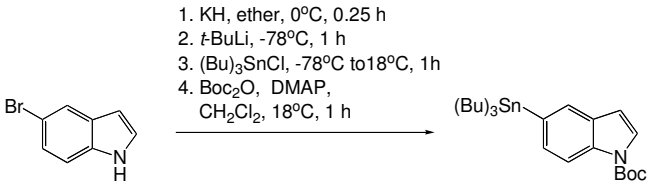
^{1}H NMR (300 MHz) δ 6.64 (s, 2H), 3.87 (s, 6H), 3.85 (s, 3H), 1.67–1.51 (complex m, 6H), 1.43–1.27 (complex m, 9H), 1.05 (complex m, 3H), 0.90 (t, J = 7.0 Hz, 9H).

^{13}C NMR (75 MHz) δ 152.9 (C), 138.1 (C), 136.7 (C), 112.7 (CH), 60.8 (CH_3), 56.1 (CH_3), 29.0 (CH_2), 27.3 (CH_2), 13.7 (CH_2), 9.7 (CH_3).

IR (NaCl, film) ν_{max} 2956, 1569, 1499, 1464, 1298, 1127 cm^{-1}.

EIMS (70 eV) *m/z* 458 ($M^{+\bullet}$, >1%), 401 (100), 345 (61), 287 (85).
HRMS Found: $M^{+\bullet}$, 458.1837. $C_{21}H_{38}O_3{}^{120}Sn$ requires $M^{+\bullet}$, 458.1843.

1-*tert*-Butoxycarbonyl-5-(tributylstannyl)-1*H*-indole (94)



(**83**) (**94**)

Following a procedure developed by Konopelski *et al*,[4] a magnetically stirred and chilled (ice/water bath) suspension of KH (1.57 g of a 30% suspension in mineral oil, 12.0 mmol) in ether (25 mL) maintained under a nitrogen atmosphere was treated, dropwise, over 0.25 h, with a solution of bromoindole **83** (1.96 g, 10.0 mmol) in ether (5 mL). After 0.5 h at *ca.* 0°C, the reaction mixture was cooled to –78°C (dry-ice/acetone bath) and treated, *via* cannula, with *t*-BuLi (11.8 mL of a 1.7 M solution in hexane, 20.1 mmol) that had been cooled to –78°C (dry-ice/acetone bath). A white precipitate formed and the reaction mixture was kept at –78°C for 1 h. Tri-*n*-butylstannyl chloride (6.57 g, 20.0 mmol) was then added in one portion. The resulting mixture was stirred at -78°C for an additional 1 h then allowed to warm to 18°C and quenched with ammonium chloride (1 x 20 mL of a saturated solution). The resulting solution was extracted with ether (2 x 25 mL) and the combined organic phases were washed with $NaHCO_3$ (2 x 25 mL of a saturated solution) and distilled water (2 x 25 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 5-(tributylstannyl)-1*H*-indole as a clear, yellow oil.

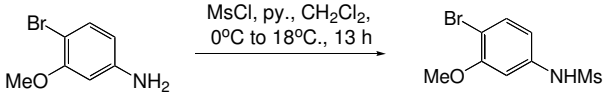
A solution of 5-(tributylstannyl)-1*H*-indole (prepared as described immediately above) in dichloromethane (5 mL) maintained under a nitrogen atmosphere was treated with Boc_2O (2.61 g, 12.0 mmol) and DMAP (121 mg, 1.00 mmol). The resulting mixture was stirred at 18°C for 1 h then concentrated under reduced pressure. The residue thus obtained was diluted with ether (25 mL) and the organic phase was washed with water (2 x 25 mL), $NaHCO_3$ (2 x 25 mL of a saturated aqueous solution) and brine (2 x 25 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give clear colourless oil. Subjection of this material to flash chromatography (silica, 2 → 5% v/v ethyl acetate/hexane gradient elution) provided,

after concentration of the appropriate fractions, the *title compound* ***94*** (3.50 g, 69%) as a clear, viscous oil.

R_f 0.6 (silica, 1:9 v/v ethyl acetate/hexane).
^{1}H NMR (300 MHz) δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.66 (s, 1H), 7.56 (d, *J* = 3.7 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 1.67 (s, 9H), 1.57 (complex m, 6H), 1.33 (p, *J* = 7.7 Hz, 6H), 1.90 (complex m, 6H), 0.89 (t, *J* = 7.2 Hz, 9H).
^{13}C NMR (75 MHz) δ 149.8 (C=O), 135.2 (C), 134.4 (C), 131.9 (CH), 130.7 (C), 129.0 (CH), 125.3 (CH), 114.8 (CH), 107.1 (CH), 83.4 (C), 29.1 (CH_2), 28.1 (CH_3), 27.4 (CH_2), 13.7 (CH_2), 9.6 (CH_3).
IR (NaCl, film) ν_{max} 2926, 1738 (C=O), 1532, 1452, 1362, 1251, 767 cm^{-1}.
EIMS (70 eV) *m/z* 507 ($M^{+\bullet}$, >1%), 450 [$(M–Bu\bullet)^+$, 75], 394 (26), 338 (19), 279 (48), 235 (35).
HRMS Found: $M^{+\bullet}$, 507.2159. $C_{25}H_{41}NO_2{}^{120}Sn$ requires $M^{+\bullet}$, 507.2159.

Preparation of 1-*tert*-Butoxycarbonyl-5-(tributylstannyl)-6-methoxy-1*H*-indole (95)

4-Bromo-3-methoxy-*N*-methylsulfonylanilide (86)



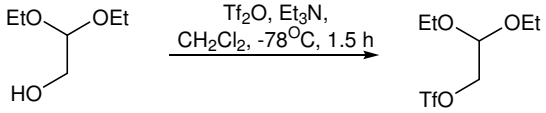
(**85**) (**86**)

Following a procedure developed by Forbes *et al*,[5] a magnetically stirred and chilled (ice/water bath) solution of aniline **85** (5.80 g, 28.7 mmol) and pyridine (2.40 mL, 28.7 mmol) in dichloromethane (50 mL) maintained under a nitrogen atmosphere was slowly treated with methanesulfonyl chloride (2.30 mL, 29.8 mmol). The reaction mixture was then warmed to 18°C, stirred at this temperature for 13 h, then diluted with dichloromethane (1 x 250 mL) and the organic phase was washed with distilled water (3 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound* ***86*** (8.81 g, 98%) as a light-brown solid.

R_f 0.5 (silica, 3:2 v/v ethyl acetate/hexane).
m.p. 120–122°C (lit. 121 – 123°C).[5]

^{1}H NMR (300 MHz) δ 7.47 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.68 (dd, *J* = 8.4 and 2.3 Hz, 1H), 3.90 (s, 3H), 3.02 (s, 3H). (NH proton exchanges with solvent).
^{13}C NMR (75 MHz) δ 156.7 (C), 137.2 (C), 133.8 (CH), 113.4 (CH), 107.9 (C), 104.9 (CH), 56.3 (CH_3), 39.2 (CH_3).
IR (NaCl, film) ν_{max} 3271 (NH), 1594, 1489, 1322, 1151, 1049, 977 cm^{-1}.
EIMS (70 eV) *m/z* 281 and 279 ($M^{+\bullet}$, 66%), 202 and 200 (100), 189 and 187 (16).
HRMS Found: $M^{+\bullet}$, 278.9566. $C_8H_{10}{}^{79}BrNSO_3$ requires $M^{+\bullet}$, 278.9565.

2,2-Diethoxyethyl)trifluoromethanesulfonate (88)

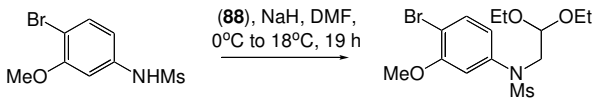


(**87**) (**88**)

A magnetically stirred solution of acetal **87** (6.05 g, 44.8 mmol) and Et_3N (7.05 mL, 50.0 mmol) in dichloromethane (50 mL) maintained at –78°C (dry-ice/acetone bath) under a nitrogen atmosphere was treated, dropwise, with a solution of trifluromethanesulfonic anhydride (13.9 g, 49.2 mmol) in dichloromethane (50 mL) over 0.5 h. Stirring was continued for a further 1.5 h at -78°C. The reaction mixture was quenched with water (1 x 50 mL) and the organic phase was washed with distilled water (2 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound **88*** (7.12 g, 72%) as a clear oil.

***R**$_f$* 0.4 (silica, 1:9 v/v ethyl acetate/hexane)
^{1}H NMR (300 MHz) δ 4.73 (d, *J* = 5.3 Hz, 1H), 4.75 (d, *J* = 5.3 Hz, 2H), 3.77–3.56 (complex m, 4H), 1.23 (t, *J* = 7.1 Hz, 6H).
^{13}C NMR (75 MHz) δ 120.6 (CF_3), 98.7 (CH), 73.9 (CH_2), 64.9 (CH_2), 15.1 (CH_3).
IR (NaCl, film) ν_{max} 2984, 2904, 1417, 1247, 1147, 972 cm^{-1}.
EIMS (70 eV) *m/z* 221 [$(M–EtO•)^+$, 36%], 193 (100).
HRMS Found: $(M–EtO•)^+$, 221.0081. $C_5H_8SF_3O_4$ requires $(M–EtO•)^+$, 221.0095.

4-Bromo-*N*-(2,2-diethoxyethyl)-3-methoxy-*N*-methylsulfonyl anilide (89)

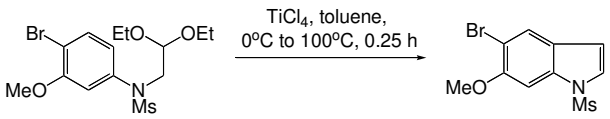


(**86**) (**89**)

Following a procedure developed by Forbes *et al*,[5] a magnetically stirred and chilled (ice/water bath) suspension of NaH (60% dispersion in oil, 800 mg, 20.0 mmol) in DMF (5 mL) maintained under a nitrogen atmosphere was treated with a solution of methylsulfonamide **85** (4.00 g, 14.29 mmol) in DMF (20 mL) over 0.5 h. After evolution of dihydrogen gas had ceased, trifluoromethanesulfonate **88** (4.60 g, 17.2 mmol) was quickly added and the resulting solution warmed to 18°C and stirred at this temperature for 6 h, further quantities of NaH (0.06 g, 2.50 mmol) and trifluoromethanesulfonate **88** (500 mg, 1.93 mmol) were then added and stirring was continued for an additional 13 h. The reaction mixture was then quenched with water (50 mL) and extracted with toluene (1 x 200 mL). The separated organic phase was washed with distilled water (1 x 100 mL) and brine (3 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Recrystallisation from ethanol of this material afforded the *title compound **89*** (4.42 g, 98%) as a light-brown solid.

***R**f* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).
m.p. 70–72°C (lit. 70 – 72°C).[5]
^{1}H NMR (300 MHz) δ 7.54 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.5 and 2.3 Hz, 1H), 4.61 (t, *J* = 5.5 Hz, 1H), 3.90 (s, 3H), 3.74 (d, *J* = 5.5 Hz, 2H), 3.69–3.48 (complex m, 4H), 2.96 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 6H).
^{13}C NMR (75 MHz) δ 156.4 (C), 140.6 (C), 133.4 (CH), 120.6 (CH), 113.3 (CH), 111.3 (C), 100.9 (CH), 62.7 (CH_2), 56.3 (CH_3), 55.3 (CH_2), 38.1 (CH_3), 15.3 (CH_3).
IR (NaCl, film) ν_{max} 2975, 1586, 1484, 1343, 1155, 968 cm^{-1}.
EIMS (70 eV) *m/z* 397 and 395 ($M^{+\bullet}$, 1%), 215 and 213 (27), 103 (100).
HRMS Found: $M^{+\bullet}$, 395.0395. $C_{14}H_{22}{}^{79}BrNO_5S$ requires $M^{+\bullet}$, 395.0402.

5-Bromo-6-methoxy-1-methylsulfonylindole (90)

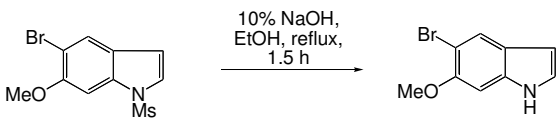


(**89**) (**90**)

Following a procedure developed by Forbes *et al*,[5] a magnetically stirred and chilled (ice/water bath) solution of anilide **89** (4.53 g, 11.4 mmol) in toluene (220 mL) maintained under a nitrogen atmosphere was treated, dropwise, with a solution of titanium tetrachloride (1.88 mL, 5.43 mmol) in toluene (100 mL). The reaction mixture was then heated to 100°C, stirred at this temperature for 0.25 h, then cooled and washed with $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution), HCl (1 x 100 mL of a 1 M aqueous solution) and distilled water (1 x 100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Recrystallisation from ether of this material afforded the *title compound **90*** (2.68 g, 89%) as a light-brown solid.

***R**f* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).
m.p. 121–124°C (lit. 126–129°C).[5]
^{1}H NMR (300 MHz) δ 7.79 (s, 1H), 7.48 (s, 1H), 6.34 (d, *J* = 3.7 Hz, 1H). 6.61 (d, *J* = 3.7 Hz, 1H), 3.97 (s, 3H), 3.08 (s, 3H).
^{13}C NMR (75 MHz) δ 153.8 (C), 134.8 (C), 125.6 (CH), 125.5 (CH), 125.0 (C), 108.7 (C), 108.3 (CH), 96.7 (CH), 56.6 (CH_3), 40.6 (CH_3).
IR (NaCl, film) ν_{max} 2926, 1610, 1473, 1365, 1167, 767 cm^{-1}.
EIMS (70 eV) *m/z* 305 and 303 ($M^{+\bullet}$, 62%), 226 and 224 (75), 211 and 209 (85), 102 (100).
HRMS Found: $M^{+\bullet}$, 302.9558. $C_{10}H_{10}{}^{79}BrNO_5S$ requires $M^{+\bullet}$, 302.9565.

5-Bromo-6-methoxy-1*H*-indole (84)



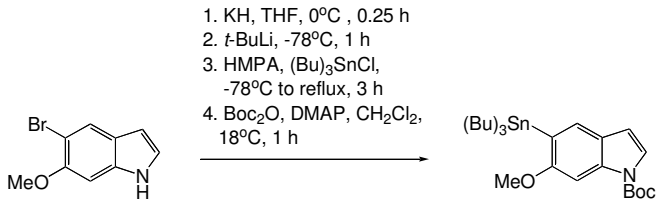
(**90**) (**84**)

Following a procedure developed by Forbes *et al*,[5] a magnetically stirred solution of sulfonamide **90** (1.42 g, 4.67 mmol) in a mixture of sodium hydroxide (10 mL of a 10% w/v aqueous solution) and ethanol (60 mL) was heated to reflux and stirred at reflux for

1.5 h. The cooled reaction mixture was concentrated under reduced pressure to near dryness and the residue, so obtained was dissolved in ethyl acetate (1 x 100 mL) and washed with distilled water (3 x 50 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown solid. Recrystallisation from ethanol afforded the *title compound* ***84*** (1.06 g, 100%) as a light-brown solid.

***R**f* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).
m.p. 110 –112°C (lit. 110–111°C).[5]
^{1}H NMR (300 MHz) δ 8.20 (s, 1H), 7.80 (s, 1H), 7.09 (t, *J* =3.9 Hz, 1H), 6.87 (s, 1H), 6.43 (m, 1H), 3.87 (s, 3H).
^{13}C NMR (75 MHz) δ 151.8 (C), 135.4 (C), 124.5 (CH), 123.8 (CH), 122.9 (C), 104.9 (C), 101.9 (CH), 94.5 (CH), 56.4 (CH_3).
IR (NaCl, film) ν_{max} 3402 (NH), 2925, 1619, 1454, 1307, 1164, 1039, 816 cm^{-1}.
EIMS *m/z* 227 and 225 ($M^{+\bullet}$, 100%), 212 and 210 (85), 184 and 182 (60).
HRMS Found: $M^{+\bullet}$, 224.9784. $C_9H_8{}^{79}BrNO$ requires $M^{+\bullet}$, 224.9789.

1-*tert*-Butoxycarbonyl-5-(tributylstannyl)-6-methoxy-1*H*-indole (95)



(**84**) (**95**)

A magnetically stirred and chilled (ice/water bath) suspension of KH (349 mg of a 30% suspension in mineral oil, 2.67 mmol) in THF (25 mL) maintained under a nitrogen atmosphere was treated, dropwise, over 0.25 h, with a solution of indole **84**[5] (500 mg, 2.25 mmol) in THF (5 mL). After stirring for an additional 0.5 h at *ca.* 0°C, the reaction mixture was cooled to –78°C (dry-ice/acetone bath) then treated, *via* cannula, with *t*-BuLi (2.61 mL of a 1.7 M solution in hexane, 4.44 mmol) that had been cooled to –78°C (dry-ice/acetone bath). A red precipitate formed and the reaction mixture was kept at -78°C for an additional 1 h. HMPA (1.15 mL, 13.8 mmol) followed by tri-*n*-butylstannyl chloride (1.21 mL, 4.44 mmol) were then added, each in one portion. The resulting solution was heated to reflux and stirred at reflux for 3 h, then cooled and quenched with ammonium chloride (1 x 20 mL of a saturated solution) then extracted

with dichloromethane (2 x 25 mL). The combined organic phases were washed with KF (1 x 25 mL of a saturated aqueous solution), $NaHCO_3$ (2 x 25 mL of a saturated aqueous solution) and distilled water (2 x 25 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 5-(tributylstannyl)-6-methoxy-1H-indole a clear, yellow oil.

A solution of 5-(tributyl-6-methoxy-1*H*-indole (prepared as described immediately above) in dichloromethane (5 mL) maintained under a nitrogen atmosphere was treated with Boc_2O (580 mg, 2.25 mmol) and DMAP (30 mg, 0.25 mmol). The resulting mixture was stirred at 18°C for 1 h and diluted with dichloromethane (25 mL). The organic phase was washed with KF (1 x 25 mL of a saturated aqueous solution), $NaHCO_3$ (2 x 25 mL of a saturated aqueous solution) and brine (2 x 25 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 1 → 5% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound* ***95*** (1.08 g, 90%) as a clear, viscous oil.

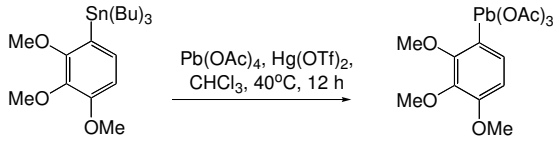
R_f 0.4 (silica, 5:95 v/v ethyl acetate/hexane).
^{1}H NMR (300 MHz) δ 7.66 (s, 1H), 7.48 (s, 1H), 7.43 (d, *J* = 3.7 Hz, 1H), 6.46 (d, *J* = 3.7 Hz, 1H), 3.83 (s, 3H), 1.66 (s, 9H), 1.52 (complex m, 6H), 1.32 (complex m, 6H), 1.02 (complex m, 6H), 0.87 (t, *J* = 7.3 Hz, 9H).
^{13}C NMR (75 MHz) δ 161.1 (C), 153.3 (C=O), 149.9 (C), 128.7 (CH), 125.5 (C), 124.8 (C), 123.9 (CH), 107.0 (CH), 96.3 (CH), 83.3 (C), 55.2 (CH_3), 29.2 (CH_2), 28.2 (CH_3), 27.4 (CH_2), 13.7 (CH_2), 9.8 (CH_3).
IR (NaCl, film) ν_{max} 2923, 1734 (C=O), 1456, 1359, 1148 cm^{-1}.
EIMS (70 eV) *m/z* 537 ($M^{+\bullet}$, 27%), 482 (76), 422 (80), 367 (49), 310 (100).
HRMS Found: $M^{+\bullet}$, 537.2272. $C_{26}H_{43}NO_3{}^{120}Sn$ requires $M^{+\bullet}$, 537.2265.

5.2.2 General Procedure for Synthesis of Aryllead Triacetates 97 – 99

Following a procedure developed by Pinhey *et al*,[6] a magnetically stirred solution of the appropriate arylstannane (1.00 mmol) in chloroform (5 mL) maintained under a nitrogen atmosphere was treated with lead (IV) tetraacetate (443 mg, 1.00 mmol) and mercury (II) trifluoroacetate (19.0 mg, 0.05 mmol). The reaction mixture was heated to 40°C, stirred at this temperature for 12 h, then cooled and filtered through a pad of

Celite™. The filtrate was then concentrated under reduced pressure to give viscous, yellow oil. The oil was washed with petroleum ether (5 x 20 mL) to afford the relevant aryllead triacetate as a pale yellow solid.

(2,3,4-Trimethoxyphenyl)lead triacetate (97)



(**92**) (**97**)

Yield 75%

m.p. 151–153°C.

^{1}H NMR (300 MHz) δ 7.46 (d, *J* = 8.9 Hz, 1H), 6.82 (d, *J* = 8.9 Hz, 1H), 4.04 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 2.10 (s, 9H).

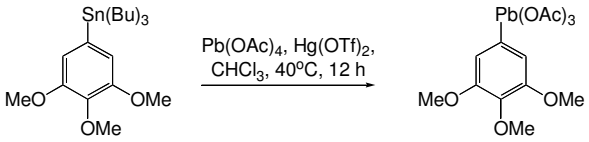
^{13}C NMR (75 MHz) δ 179.9 (C=O), 157.2 (C), 152.0 (C), 146.7 (C), 142.0 (C), 126.1 (CH), 108.7 (CH), 61.8 (CH_3), 61.0 (CH_3), 56.4 (CH_3), 20.4 (CH_3).

IR (NaCl, film) ν_{max} 2943, 1563 (C=O), 1406, 1085, 692 cm^{-1}.

EIMS (70 eV) *m/z* 493 [$(M–AcO•)^+$, >1%], 267 (100).

HRMS Found: $(M–AcO•)^+$, 493.0395. $C_{19}H_{13}O_8NPb$ requires $(M–AcO•)^+$, 493.0377.

(3,4,5-Trimethoxyphenyl)lead triacetate (98)



(**93**) (**98**)

Yield 81%

m.p. 125–127°C (lit. m.p. 123–125°C).[7]

^{1}H NMR (300 MHz) δ 6.88 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 2.13 (s, 9H).

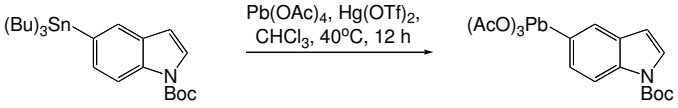
^{13}C NMR (75 MHz) δ 180.1 (C=O), 154.4 (C), 109.5 (C), 107.8 (CH), 106.1 (C), 61.0 (CH_3), 56.5 (CH_3), 20.4 (CH_3).

IR (NaCl, film) ν_{max} 2935, 1582 (C=O), 1492, 1403, 1232, 1122 cm^{-1}.

EIMS (70 eV) *m/z* 552 ($M^{+\bullet}$ >1%), 493 [$(M–AcO•)^+$, >1%], 267 (100).

HRMS Found: $(M–AcO•)^+$, 493.0739. $C_{19}H_{13}NO_8Pb$ requires $(M–AcO•)^+$, 493.0741.

1-tert-Butoxycarbonyl-5-indole lead triacetate (99)



(**94**) (**99**)

Yield 78%

m.p. 92–94°C.

^{1}H NMR (300 MHz) δ 8.35 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 1H), 7.71 (d, *J* = 3.9 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 6.64 (d, *J* = 3.9 Hz, 1H), 2.11 (s, 9H), 1.68 (s, 9H).

^{13}C NMR (75 MHz) δ 179.0 (C=O), 155.8 (C), 149.1 (C=O), 136.6 (C), 132.1 (C), 127.8 (CH), 125.2 (CH), 123.9 (CH), 117.3 (CH), 107.4 (CH), 84.7 (C), 28.1 (CH_3), 20.4 (CH_3).

IR (NaCl, film) ν_{max} 2979, 1738 (C=O), 1557, 1466, 1372, 1251, 1159, 1020 $cm^{-1.}$

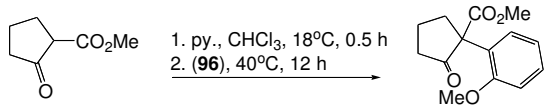
EIMS (70 eV) *m/z* 601 ($M^{+\bullet}$, >1%), 542 [$(M–AcO\bullet)^+$, 4], 267 (100).

Elemental Analysis Found: C, 36.90, H, 3.99, N, 2.44, Pb, 31.59. Calcd: $C_{19}H_{23}NO_8Pb$: C, 36.89, H, 4.07, N, 2.26, Pb, 33.49%.

5.2.3 General Procedure for Synthesis of Cyclic α-Arylated β-Ketoesters 76, 101 – 110

Following a procedure developed by Pinhey *et al*,[8] a magnetically stirred solution of the appropriate β-ketoester (1.00 mmol) in chloroform (2 mL) at 18°C under a nitrogen atmosphere was treated with pyridine (0.26 mL, 3.28 mmol) and the resulting mixture stirred for 0.5 h then treated with the appropriate aryllead triacetate (1.10 mmol). The resulting mixture was heated to 40°C and stirred at this temperature for 12 h, then cooled, quenched with HCl (drop of 1 M aqueous solution) and diluted with ethyl acetate (1 x 50 mL). The organic phase was washed with HCl (1 x 25 mL of a 1 M aqueous solution) and distilled water (2 x 25 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10 → 30% v/v ethyl acetate/petroleum spirit gradient elution) provided, after concentration of the appropriate fractions, the relevant cyclic α-arylated β-ketoester as either a colourless solid or oil.

Methyl 1-(2-methoxyphenyl)-2-oxocyclopentanecarboxylate (101)



(**70**) (**101**)

Colourless oil

Yield 72%

***R**f* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.28–7.22 (complex m, 1H), 6.92–6.86 (complex m, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 2.94 (p, *J* = 6.7 Hz, 1H), 2.47 (td, *J* = 7.6 and 3.3 Hz, 2H), 2.26 (p, *J* = 6.7 Hz, 1H), 2.00–1.85 (complex m, 2H).

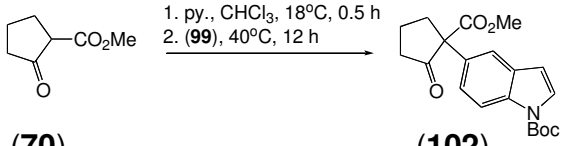
^{13}C NMR (75 MHz) δ 213.8 (C=O), 170.6 (C=O), 156.4 (C), 128.7 (CH), 128.5 (C), 127.5 (CH), 120.6 (CH), 111.7 (CH), 64.5 (C), 55.3 (CH_3), 52.7 (CH_3), 38.5 (CH_2), 35.2 (CH_2), 19.7 (CH_2).

IR (NaCl, film) ν_{max} 2953, 1751 (C=O), 1725 (C=O), 1493, 1241, 1107, 754 cm^{-1}.

EIMS (70 eV) *m/z* 248 ($M^{+\bullet}$, 100%), 189 (58), 133 (81).

HRMS Found: $M^{+\bullet}$, 248.1053. $C_{14}H_{16}O_4$ requires $M^{+\bullet}$, 248.1049.

N-tert-Butoxycarbonyl-5-(1-carbomethoxy-2-oxocyclopentyl)-1*H*-indole (102)



(**70**) (**102**)

Colourless oil

Yield 81%

***R**f* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.58 (s, 2H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 3.7 Hz, 1H), 3.66 (s, 3H), 2.89–2.83 (complex m, 1H), 2.61–2.57 (complex m, 1H), 2.50–2.33 (complex m, 2H), 2.00–1.84 (complex m, 2H), 1.62 (s, 9H).

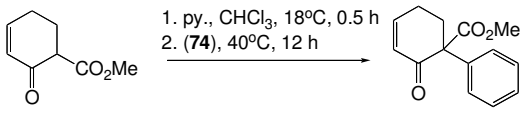
^{13}C NMR (75 MHz) δ 212.0 (C=O), 171.2 (C=O), 149.3 (C=O), 134.1 (C), 130.4 (C), 130.0 (C), 126.1 (CH), 123.3 (CH), 119.5 (CH), 115.0 (CH), 107.2 (CH), 83.5 (C), 64.6 (C), 52.6 (CH_3), 37.4 (CH_2), 34.9 (CH_2), 27.5 (CH_3), 19.0 (CH_2).

IR (NaCl, film) ν_{max} 2977, 1732 (C=O), 1371, 1164, 730 cm^{-1}.

EIMS (70 eV) *m/z* 357 ($M^{+\bullet}$, 24%), 301 (100), 257 (26).

HRMS Found: $M^{+\bullet}$, 357.1580. $C_{20}H_{23}NO_5$ requires $M^{+\bullet}$, 357.1576.

Methyl 2-oxo-1-phenyl-cyclohex-3-ene carboxylate (76)



(**75**) (**76**)

Colourless oil

Yield 79%

R_f 0.3 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.38–7.18 (complex m, 5H), 6.85 (dt, *J* = 10.2 and 4.1 Hz, 1H), 6.17 (dt, *J* = 10.2 and 1.9 Hz, 1H), 3.72 (s, 3H), 2.88–2.79 (complex m, 1H), 2.61–2.55 (complex m, 1H), 2.42–2.40 (complex m, 1H), 2.24–2.22 (complex m, 1H).

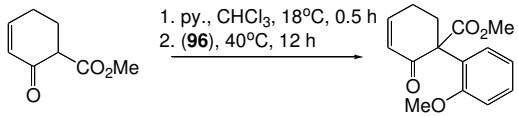
^{13}C NMR (75 MHz) δ 195.5 (C=O), 171.6 (C=O), 149.7 (CH), 136.0 (C), 129.1 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 62.8 (C), 52.7 (CH_3), 31.9 (CH_2), 23.7 (CH_2).

IR (NaCl, film) ν_{max} 2952, 1731 (C=O), 1677 (C=O), 1247, 1209, 698 cm^{-1}.

EIMS (70 eV) *m/z* 230 ($M^{+\bullet}$, 50%), 198 (11), 171 (33), 162 (42).

HRMS Found: $M^{+\bullet}$, 230.0942. $C_{14}H_{14}O_3$ requires $M^{+\bullet}$, 230.0943.

Methyl 1-(2-methoxyphenyl)-2-oxo-cyclohex-3-ene carboxylate (103)



(**75**) (**103**)

Colourless oil

Yield 76%

R_f 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 100–102°C.

^{1}H NMR (300 MHz) δ 7.30–7.24 (complex m, 1H), 6.97–6.86 (complex m, 4H), 6.20 (dt, *J* = 8.4 and 1.7 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 2.80–2.74 (complex m, 1H), 2.67–2.58 (complex m, 1H), 2.40–2.32 (complex m, 1H), 2.03–2.01 (complex m, 1H).

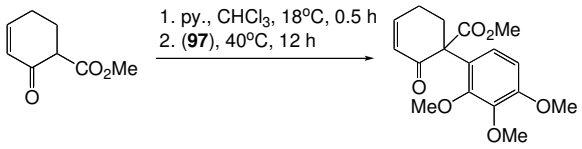
^{13}C NMR (75 MHz) δ 195.7 (C=O), 171.8 (C=O), 157.2 (C), 150.4 (CH), 129.5 (CH), 128.9 (CH), 127.8 (CH), 126.6 (C), 120.4 (CH), 111.6 (CH), 61.8 (C), 55.5 (CH_3), 52.4 (CH_3), 30.6 (CH_2), 23.8 (CH_2).

IR (NaCl, film) ν_{max} 2950, 1734 (C=O), 1678 (C=O), 1493, 1250, 754 cm^{-1}.

EIMS (70 eV) *m/z* 260 ($M^{+\bullet}$, 80%), 201 (36), 192 (100).

HRMS Found: $M^{+\bullet}$, 260.1053. $C_{15}H_{16}O_4$ requires $M^{+\bullet}$, 260.1049.

Methyl 1-(2,3,4-trimethoxyphenyl)-2-oxo-cyclocyclohex-3-ene carboxylate (104)



(**75**) (**104**)

Colourless oil

Yield 75%

***R**f* 0.5 (silica, 3:2 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 6.94–6.86 (complex m, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 6.14 (dt, *J* = 8.8 and 1.7 Hz, 1H), 3.80 (s, 6H), 3.78 (s, 3H), 3.72 (s, 3H), 2.65–2.56 (complex m, 2H), 2.34–2.32 (complex m, 1H), 2.11–2.00 (complex m, 1H).

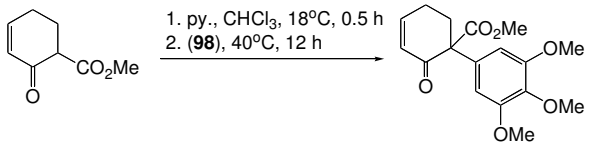
^{13}C NMR (75 MHz) δ 195.3 (C=O), 171.6 (C=O), 153.0 (C), 151.8 (C), 149.9 (CH), 141.8 (C), 129.3 (CH), 124.0 (C), 121.8 (CH), 105.9 (CH), 61.3 (C), 60.3 (CH_3), 60.1 (CH_3), 55.7 (CH_3), 52.4 (CH_3), 31.6 (CH_2), 23.8 (CH_2).

IR (NaCl, film) ν_{max} 2938, 1735 (C=O), 1680 (C=O), 1466, 1265, 732 cm^{-1}.

EIMS (70 eV) *m/z* 320 ($M^{+\bullet}$, 42%), 252 (100).

HRMS Found: $M^{+\bullet}$, 320.1265. $C_{17}H_{20}O_6$ requires $M^{+\bullet}$, 320.1260.

Methyl 1-(3,4,5-trimethoxyphenyl)-2-oxo-cyclocyclohex-3-ene carboxylate (105)



(**75**) (**105**)

Colourless oil

Yield 84%

***R**f* 0.4 (silica, 3:2 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 6.92–6.88 (complex m, 1H), 6.40 (s, 2H), 6.15 (dt, *J* = 10.2 and 1.8 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 6H), 3.74 (s, 3H), 2.86–2.80 (complex m, 1H), 2.56–2.31 (complex m, 3H).

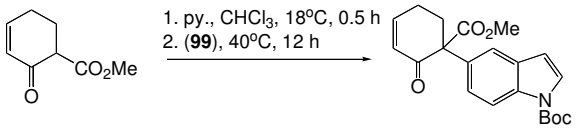
^{13}C NMR (75 MHz) δ 195.0 (C=O), 171.5 (C=O), 153.0 (C), 149.9 (CH), 137.0 (C), 131.5 (C), 129.2 (CH), 105.1 (CH), 62.7 (C), 60.8 (CH_3), 56.1 (CH_3), 52.9 (CH_3), 32.2 (CH_2), 23.8 (CH_2).

IR (NaCl, film) ν_{max} 2922, 1730 (C=O), 1677 (C=O), 1588, 1246, 1127 cm^{-1}.

EIMS (70 eV) *m/z* 320 ($M^{+\bullet}$, 33%), 252 (100), 237 (55).

HRMS Found: $M^{+\bullet}$, 320.1246. $C_{17}H_{20}O_6$ requires $M^{+\bullet}$, 320.1260.

1-*tert*-Butoxycarbonyl-5-(1-carbomethoxy-2-oxocyclohex-3-enyl-1*H*-indole (106)



(**75**) (**106**)

Colourless oil

Yield 71%

***R**$_f$* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 3.6 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.17 (dd, *J* = 8.4 and 2.0 Hz, 1H), 6.83 (dt, *J* = 10.1 and 4.1 Hz, 1H), 6.51 (d, *J* = 3.7 Hz, 1H), 6.15 (dt, *J* = 10.1 and 1.9 Hz, 1H), 3.71 (s, 3H), 2.87–2.83 (complex m, 1H), 2.69–2.64 (complex m, 1H), 2.40–2.37 (complex m, 1H), 2.23–2.19 (complex m, 1H), 1.64 (s, 9H).

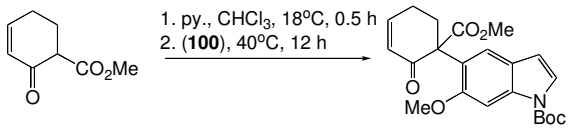
^{13}C NMR (75 MHz) δ 195.5 (C=O), 171.9 (C=O), 149.7 (CH), 149.5 (C=O), 134.3 (C), 130.4 (C), 130.0 (C), 129.9 (CH), 126.3 (CH), 123.6 (CH), 120.0 (CH), 115.0 (CH), 107.3 (CH), 83.7 (C), 62.6 (C), 52.6 (CH_3), 31.9 (CH_2), 28.0 (CH_3), 23.6 (CH_2).

IR (NaCl, film) ν_{max} 2953, 1731 (C=O), 1677 (C=O), 1470, 1371, 1166, 731 cm^{-1}.

EIMS (70 eV) *m/z* 369 ($M^{+\bullet}$, 17%), 313 (42), 245 (92), 201 (100).

HRMS Found: $M^{+\bullet}$, 369.1576. $C_{21}H_{23}NO_5$ requires $M^{+\bullet}$, 369.1576.

1-*tert*-Butoxycarbonyl-5-(1-carbomethoxy-2-oxocyclohex-3-enyl)-6-methoxy-1*H*-indole (107)



(**75**) (**107**)

Colourless oil

Yield[Ω] 82%

R$_f$ 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.74 (s, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 7.06 (s, 1H), 6.95 (complex m, 1H), 6.38 (d, *J* = 3.6 Hz, 1H), 6.19 (dt, *J* = 9.2 and 1.4 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 2.80–2.78 (complex m, 1H), 2.67–2.65 (complex m, 1H), 2.33–2.20 (complex m, 2H), 1.62 (s, 9H).

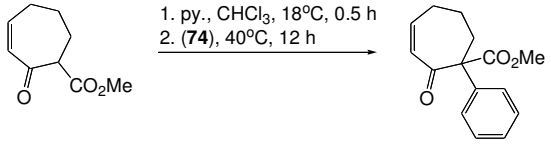
^{13}C NMR (75 MHz) δ 196.0 (C=O), 172.1 (C=O), 155.2 (C), 150.8 (C=O), 150.7 (CH), 149.5 (C), 129.4 (CH), 128.7 (C), 124.4 (CH), 122.3 (C), 119.8 (CH), 107.1 (CH), 98.8 (CH), 83.4 (C), 61.8 (C), 55.6 (CH_3), 52.3 (CH_3), 30.5 (CH_2), 27.9 (CH_3), 23.8 (CH_2).

IR (NaCl, film) ν_{max} 2951, 1734 (C=O), 1677 (C=O), 1474, 1156 cm^{-1}.

EIMS (70 eV) *m/z* 399 ($M^{+\bullet}$, 24%), 343 (67), 275 (100).

HRMS Found: $M^{+\bullet}$, 399.1683. $C_{22}H_{25}NO_6$ requires $M^{+\bullet}$, 399.1682.

Methyl 2-oxo-1-phenyl-cyclohept-3-ene carboxylate (108)



(**79**) (**108**)

Colourless oil

Yield 63%

***R**$_f$* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.37–7.17 (complex m, 5H), 6.37 (dt, *J* = 12.5 and 5.0 Hz, 1H), 6.15 (dt, *J* = 12.5 and 1.8 Hz, 1H), 3.72 (s, 3H), 2.75–2.65 (complex m, 1H), 2.46–2.34 (complex m, 3H), 1.93–1.83 (complex m, 2H).

[Ω] Yield over two steps

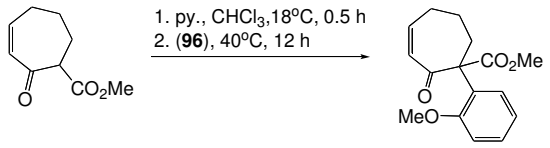
^{13}C NMR (75 MHz) δ 200.5 (C=O), 172.7 (C=O), 142.8 (CH), 138.5 (C), 131.4 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 68.9 (C), 52.7 (CH_3), 32.3 (CH_2), 31.0 (CH_2), 22.6 (CH_2).

IR (NaCl, film) ν_{max} 2927, 1733 (C=O), 1655 (C=O), 1448, 1230, 1018, 696 cm^{-1}.

EIMS (70 eV) *m/z* 244 ($M^{+\bullet}$, 7%), 216 (46), 185 (56), 103 (100).

HRMS Found: $M^{+\bullet}$, 244.1098. $C_{15}H_{16}O_3$ requires $M^{+\bullet}$, 244.1099.

Methyl 1-(2-methoxyphenyl)-2-oxocyclohept-3-ene carboxylate (109)



(**79**) (**109**)

Colourless solid

Yield 70%

***R**f* 0.3 (silica, 30:70 v/v ethyl acetate/hexane).

m.p. 81–83°C.

^{1}H NMR (300 MHz) δ 7.27 (td, *J* = 7.3 and 1.6 Hz, 1H), 7.02–6.88 (complex m, 3H), 6.40–6.33 (complex m, 1H), 6.15 (dt, *J* = 12.7 and 1.9 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 2.56–2.47 (complex m, 2H), 2.32–2.26 (complex m, 1H), 1.77–1.74 (complex m, 2H), 1.44–1.24 (m, 1H).

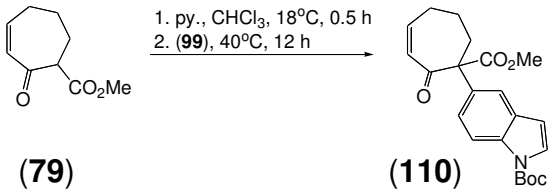
^{13}C NMR (75 MHz) δ 200.6 (C=O), 172.4 (C=O), 157.0 (C), 142.7 (CH), 131.5 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 120.6 (CH), 111.7 (CH), 67.3 (C), 55.5 (CH_3), 52.4 (CH_3), 31.0 (CH_2), 30.7 (CH_2), 21.9 (CH_2).

IR (NaCl, film) ν_{max} 2948, 1733 (C=O), 1660 (C=O), 1493, 1248, 1027, 755 cm^{-1}.

EIMS (70 eV) *m/z* 274 ($M^{+\bullet}$, 69%), 246 (36), 215 (46), 133 (100).

HRMS Found: $M^{+\bullet}$, 274.1205. $C_{16}H_{18}O_4$ requires $M^{+\bullet}$, 274.1205.

1-*tert*-Butoxycarbonyl-5-(1-carbomethoxy-2-oxocyclohept-3-enyl)-1*H*-indole (110)



(**79**) (**110**)

Colourless oil

Yield 71%

***R*$_f$** 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.36 (s, 1H), 7.14 (dd, *J* = 8.7 and 1.9 Hz, 1H), 6.52 (d, *J* = 3.7 Hz, 1H), 6.35 (dt, *J* = 12.4 and 4.8 Hz, 1H), 6.14 (*J* = 12.4 and 1.4 Hz, 1H), 3.70 (s, 3H), 2.72–2.68 (complex m, 1H), 2.52–1.85 (complex m, 5H), 1.64 (s, 9H).

^{13}C NMR (75 MHz) δ 200.7 (C=O), 172.8 (C=O), 149.5 (C=O), 142.7 (CH), 134.0 (C), 132.5 (C), 131.2 (CH), 130.3 (C), 126.2 (CH), 124.1 (CH), 120.2 (CH), 114.9 (CH), 107.3 (CH), 83.6 (C), 68.6 (C), 52.5 (CH_3), 32.0 (CH_2), 30.6 (CH_2), 28.0 (CH_3), 22.3 (CH_2).

IR (NaCl, film) ν_{max} 2951, 1732 (C=O), 1659 (C=O), 1470, 1371, 1257, 1164, 730 cm$^{-1.}$

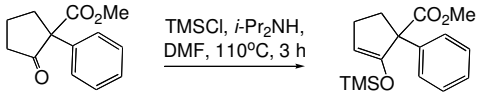
EIMS (70 eV) *m/z* 383 ($M^{+\bullet}$, 31%), 327 (36), 299 (40), 268 (74), 240, (100).

HRMS Found: $M^{+\bullet}$, 383.1729. $C_{22}H_{25}NO_5$ requires $M^{+\bullet}$, 383.1733.

5.2.4 General Procedure for Synthesis of Cyclic Arylated Trimethyl Silyl Enol Ethers 143 – 145

A magnetically stirred solution of diisopropylamine (0.50 mL, 3.53 mmol) and chlorotrimethylsilane (0.24 mL, 1.77 mmol) in DMF (2 mL) at 18°C under a nitrogen atmosphere was treated with a solution of the appropriate α-arylated cyclic ketone (1.00 mmol) in DMF (2 mL). The resulting mixture was heated to 110°C and stirred at this temperature for 3 h then cooled and diluted with pentane (2 x 50 mL). The combined organic phases were washed with $NaHCO_3$ (3 x 25 mL of a saturated aqueous solution), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 0 → 10% v/v ethyl acetate/petroleum spirit gradient elution) provided, after concentration of the appropriate fractions, the relevant arylated trimethyl silyl enol ether as a clear oil.

Methyl 1-phenyl-2-(trimethyl-silanoxy)-cyclopent-2-ene carboxylate (143)



(**71**) (**143**)

Yield 72%

R_f 0.3 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.32–7.28 (complex m, 5H), 4.89 (t, *J* = 2.5 Hz, 1H), 3.71 (s, 3H), 2.84–2.77 (complex m, 1H), 2.33 (complex m, 3H), 0.16 (s, 9H).

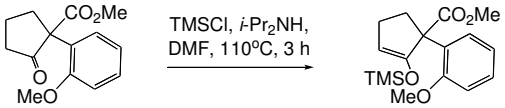
^{13}C NMR (75 MHz) δ 174.8 (C=O), 153.5 (C), 141.8 (C), 128.0 (CH), 127.2 (CH), 126.6 (CH), 104.8 (CH), 63.7 (C), 52.2 (CH_3), 37.0 (CH_2), 26.0 (CH_2), -0.2 (CH_3).

IR (NaCl, film) ν_{max} 2954, 1732 (C=O), 1645, 1435, 1253, 872, 698 cm^{-1}.

EIMS (EI, 70eV) *m/z* 290 ($M^{+\bullet}$, 9%), 231 (100), 218 (29).

HRMS Found: $M^{+\bullet}$, 290.1337. $C_{16}H_{22}O_3Si$ requires $M^{+\bullet}$, 290.1338.

Methyl 1-(2-methoxyphenyl)-2-(trimethyl-silanoxy)-cyclopent-2-ene carboxylate (144)



(**101**) (**144**)

Yield 96%

R_f 0.4 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.32–7.23 (complex m, 2H), 6.98–6.87 (complex m, 2H), 5.02 (t, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.16–3.09 (complex m, 1H), 2.37–2.35 (complex m, 1H), 2.17–2.13 (complex m, 1H), 1.92–1.87 (complex m, 1H), 0.26 (s, 9H).

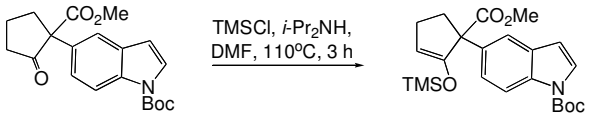
^{13}C NMR (75 MHz) δ 174.8 (C=O), 156.7 (C), 152.3 (C), 131.5 (C), 127.7 (CH), 127.3 (CH), 120.2 (CH), 110.7 (CH), 106.1, (CH), 61.4 (C), 55.1 (CH_3), 51.8 (CH_3), 34.9 (CH_2), 25.7 (CH_2), -0.3 (CH_3).

IR (NaCl, film) ν_{max} 2955, 1732 (C=O), 1646, 1491, 1246, 1030, 871 cm^{-1}.

EIMS (70 eV) *m/z* 320 ($M^{+\bullet}$, 30%), 305 (12), 261 [(M–$CO_2Me\bullet$)$^+$, 100].

HRMS Found: $M^{+\bullet}$, 320.1444. $C_{17}H_{24}O_4Si$ requires $M^{+\bullet}$, 320.1444.

1-*tert*-Butoxycarbonyl-5-(1-carbomethoxy-2-trimethyl-silanoxy-cyclopent-2-enyl)-*1H*-indole (145)



(**102**) (**145**)

Yield 72%

***R*$_f$** 0.5 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.25 (dd, *J* = 8.7 and 1.9 Hz, 1H), 6.54 (d, *J* = 3.7 Hz, 1H), 4.92 (t, *J* = 2.2 Hz, 1H), 3.72 (s, 3H), 2.94–2.84 (complex m, 1H), 2.40–2.29 (complex m, 3H), 1.67 (s, 9H), 0.19 (s, 9H).

^{13}C NMR (75 MHz) δ 175.0 (C=O), 153.8 (C), 149.8 (C=O), 136.3 (CH), 133.7 (C), 130.3 (C), 125.9 (C), 123.8 (CH), 119.2 (CH), 114.7 (CH), 107.5 (CH), 104.8 (CH), 83.5 (C), 63.6 (C), 52.2 (CH_3), 37.3 (CH_2), 28.1 (CH_3), 25.9 (CH_2), -0.1 (CH_3).

IR (NaCl, film) ν_{max} 2955, 1732 (C=O), 1645, 1470, 1327, 1164, 846 cm^{-1}.

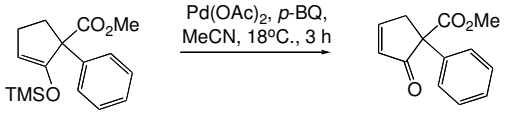
EIMS (70 eV) *m/z* 429 ($M^{+\bullet}$, 23%), 370 (40), 314 (100), 270 (65).

HRMS Found: $M^{+\bullet}$, 429.1963. $C_{23}H_{31}NO_5Si$ requires $M^{+\bullet}$, 429.1972.

5.2.5 General Procedure for Synthesis of Cyclic α-Arylated Enones 146 - 148

Following a procedure developed by Saegusa *et al*,[9] a magnetically stirred solution of $Pd(OAc)_2$ (112 mg, 0.50 mmol) and *p*-benzoquinone (54.0 mg, 0.50 mmol) in acetonitrile (5 mL) at 18°C under a nitrogen atmosphere was treated with the appropriate cyclic α-arylated trimethyl silyl enol ether (1.00 mmol). Stirring was continued at 18°C for 3 h then the solvent was then evaporated under reduced pressure. Subjection of this material to flash chromatography (silica, 40% v/v ethyl acetate/petroleum spirit elution) provided, after concentration of the appropriate fractions, the relevant cyclic α-arylated enone as either a clear, yellow oil or solid.

Methyl 2-oxo-1-phenylcyclopent-3-ene carboxylate (146)



(**143**) (**146**)

Clear, yellow oil

Yield 97%

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.81 (complex m, 1H), 7.35–7.28 (complex m, 5H), 6.26 (complex m, 1H), 3.83 (dt, *J* = 19.1 and 2.5 Hz, 1H), 3.74 (s, 3H), 3.07 (dt, *J* = 19.1 and 2.5 Hz, 1H).

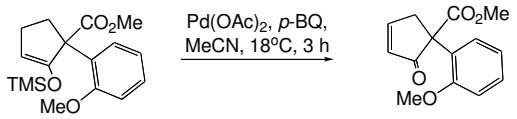
^{13}C NMR (75 MHz) δ 203.3 (C=O), 170.5 (C=O), 163.2 (CH), 138.6 (C), 132.1 (CH), 128.7 (CH), 127.5 (CH), 127.1 (CH), 62.7 (C), 53.3 (CH_3), 43.6 (CH_2).

IR (NaCl, film) ν_{max} 2954, 1738 (C=O), 1709 (C=O), 1594, 1207, 1154, 698 cm^{-1}.

EIMS (70eV) *m/z* 216 ($M^{+\bullet}$, 66%), 188 (7), 184 (27), 156 (100).

HRMS Found: $M^{+\bullet}$, 216.0784. $C_{13}H_{12}O_3$ requires $M^{+\bullet}$, 216.0786.

Methyl 1-(2-methoxyphenyl)-2-oxocyclopent-3-ene carboxylate (147)



(**144**) (**147**)

Yellow solid

Yield 61%

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 77–79°C.

^{1}H NMR (300 MHz) δ 7.79 (complex m, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 6.6 Hz, 1H), 6.90 (t, *J* = 7.7 Hz, 2H), 6.24 (complex m, 1H), 3.99 (dt, *J* = 19.9 and 2.2 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 2.68 (dt, *J* = 19.9 and 2.2 Hz, 1H).

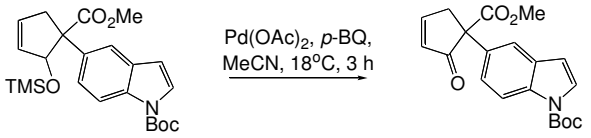
^{13}C NMR (75 MHz) δ 204.2 (C=O), 170.2 (C=O), 164.7 (CH), 157.1 (C), 131.5 (CH), 129.0 (C), 128.6 (CH), 127.1 (CH), 120.6 (CH), 110.9 (CH), 61.2 (C), 55.3 (CH_3), 53.0 (CH_3), 43.5 (CH_2).

IR (NaCl, film) ν_{max} 2951, 1729 (C=O), 1708 (C=O), 1492, 1256, 1154, 755 cm^{-1}.

EIMS (70 eV) *m/z* 246 ($M^{+\bullet}$, 100%), 214 (56), 186 (94), 171 (26).

HRMS Found: $M^{+\bullet}$, 246.0890. $C_{14}H_{14}O_4$ requires $M^{+\bullet}$, 246.0892.

1-*tert*-Butoxycarbonyl-5-(1-carbomethoxy-2-oxo-cyclopent-3-enyl)-*1H*-indole (148)



(**145**) (**148**)

Clear, yellow oil

Yield 60%

R_f 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.08 (d, *J* = 8.9 Hz, 1H), 7.80 (dt, *J* = 5.8 and 2.5 Hz, 1H), 7.58 (d, *J* = 3.6 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.22 (dd, *J* = 8.9 and 2.0 Hz, 1H), 6.52 (d, *J* = 3.6 Hz, 1H), 6.27 (dt, *J* = 5.8 and 2.5 Hz, 1H), 3.87 (dt, *J* = 19.6 and 2.7 Hz, 1H), 3.73 (s, 3H), 2.68 (dt, *J* = 19.6 and 2.7 Hz, 1H), 1.62 (s, 9H).

^{13}C NMR (75 MHz) δ 203.6 (C=O), 170.9 (C=O), 163.1 (CH), 149.6 (C=O), 133.8 (C), 133.0 (CH), 132.1 (C), 130.6 (C), 126.4 (CH), 123.6 (CH), 119.3 (CH), 115.4 (CH), 107.4 (CH), 83.8 (C), 62.5 (C), 53.3 (CH_3), 44.0 (CH_2), 28.1 (CH_3).

IR (NaCl, film) ν_{max} 2979, 1733 (C=O), 1371, 1257, 1166, 766 cm^{-1}.

EIMS (70 eV) *m/z* 355 ($M^{+\bullet}$, 20%), 299 (49), 255 (21), 239 (24), 195 (34), 57 (100).

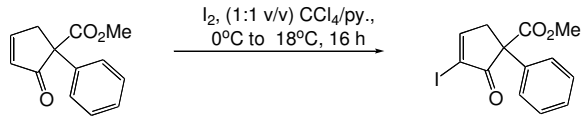
HRMS Found: $M^{+\bullet}$, 355.1419. $C_{20}H_{21}NO_5$ requires $M^{+\bullet}$, 355.1420.

5.2.6 General Procedure for Synthesis of α'-Iodinated Cyclic Enones 138, 149 - 159

Following a procedure developed by Johnson *et al*,[10] a magnetically stirred and cooled (ice/water bath) solution of the appropriate α-arylated cyclic enone (1.00 mmol) in 1:1 v/v pyridine/CCl_4 (4 mL) maintained under a nitrogen atmosphere was treated, dropwise, with a solution of molecular iodine (1.02 g, 4.00 mmol) dissolved in pyridine/CCl_4 (4 mL of a 1:1 v/v/ mixture). The resulting mixture was warmed to 18°C and stirred at this temperature for 16 h, then diluted with ether (1 x 100 mL). The organic phase was washed with HCl (2 x 50 mL of a 1 M aqueous solution), distilled water (1 x 50 mL) and Na_2SO_3 (1 x 50 mL of a 1 M solution). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10 →

30% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the relevant α′-iodinated cyclic enone as either a clear, yellow oil or colourless solid.

Methyl 3-iodo-2-oxo-1-phenylcyclopent-3-ene carboxylate (149)



(**146**) (**149**)

Clear, yellow oil

Yield 60%

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.09 (t, *J* = 3.0 Hz, 1H), 7.35-7.28 (complex m, 5H), 3.86 (dd, *J* = 22.2 and 3.0 Hz, 1H), 3.74 (s, 3H), 3.13 (dd, *J* = 22.2 and 3.0 Hz, 1H).

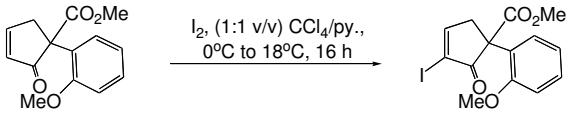
^{13}C NMR (75 MHz) δ 197.8 (C=O), 169.8 (C=O), 167.8 (CH), 137.8 (C), 128.8 (CH), 127.8 (CH), 127.0 (CH), 99.3 (C), 60.1 (C), 53.6 (CH_3), 45.6 (CH_2).

IR (NaCl, film) ν_{max} 2961, 2921, 1744 (C=O), 1720 (C=O), 1580, 1261, 800 cm^{-1}.

EIMS (70 eV) *m/z* 342 ($M^{+\bullet}$, 25%), 283 (39), 215 (58), 183 (100).

HRMS Found: $M^{+\bullet}$, 341.9750. $C_{13}H_{11}{}^{127}IO_3$ requires $M^{+\bullet}$, 241.9753.

Methyl 3-iodo-1-(2-methoxyphenyl)-2-oxocyclopent-3-ene carboxylate (150)



(**147**) (**150**)

Clear, yellow oil

Yield 96%

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.98 (t, *J* = 3.0 Hz, 1H), 7.22–7.20 (complex m, 1H), 6.91–6.80 (complex m, 3H), 3.95 (dd, *J* = 18.7 and 3.0 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 2.68 (dd, *J* = 18.7 and 3.0 Hz, 1H).

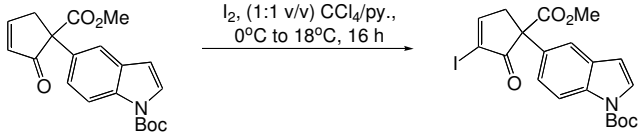
^{13}C NMR (75 MHz) δ 198.5 (C=O), 169.5 (C=O), 169.1 (CH), 156.8 (C), 129.0 (CH), 128.2 (C), 127.2 (CH), 120.8 (CH), 111.1 (CH), 98.2 (C), 58.9 (C), 55.4 (CH_3), 53.3 (CH_3), 45.6 (CH_2).

IR (NaCl, film) ν_{max} 2951, 1716 (C=O), 1493, 1255, 1027, 754 cm^{-1}.

EIMS (70 eV) *m/z* 372 ($M^{+\bullet}$, 46%), 340 (10), 313 (39), 245 (31). 213 (100).

HRMS Found: $M^{+\bullet}$, 371.9862. $C_{14}H_{13}{}^{127}IO_4$ requires $M^{+\bullet}$, 371.9859.

1-*tert*-Butoxycarbonyl-3-iodo-5-(1-carbomethoxy-2-oxocyclopent-3-enyl)-1*H*-indole (151)



(**148**) (**151**)

Clear, yellow oil

Yield 93%

***R**f* 0.2 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.10–8.08 (complex m, 2H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.50 (s, 1H), 7.20 (dd, *J* = 8.7 and 1.8 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 3.93 (dd, *J* = 19.3 and 2.8 Hz, 1H), 3.73 (s, 3H), 3.18 (dd, *J* = 19.3 and 2.8 Hz, 1H), 1.66 (s, 9H).

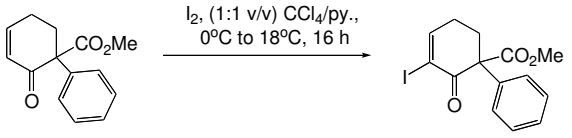
^{13}C NMR (75 MHz) δ 198.1 (C=O), 170.1 (C=O), 167.8 (CH), 149.5 (C=O), 134.3 (C), 132.1 (C), 130.7 (C), 126.6 (CH), 123.3 (CH), 119.3 (CH), 115.6 (CH), 107.4 (CH), 99.3 (C), 83.9 (C), 59.9 (C), 53.3 (CH_3), 46.0 (CH_2), 28.1 (CH_3).

IR (NaCl, film) ν_{max} 2978, 1732 (C=O), 1371, 1259, 1167, 730 cm^{-1}.

EIMS (70 eV) *m/z* 481 ($M^{+\bullet}$, 31%), 425 (63), 381 (29), 322 (26), 266 (41), 57 (100).

HRMS Found: $M^{+\bullet}$, 481.0390. $C_{20}H_{20}{}^{127}INO_5$ requires $M^{+\bullet}$, 481.0386.

Methyl 3-iodo-2-oxo-1-phenyl-cyclohex-3-ene carboxylate (138)



(**76**) (**138**)

Clear, yellow oil

Yield 60%

R_f 0.6 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.58 (t, *J* = 3.9 Hz, 1H), 7.39–7.33 (complex m, 3H), 7.15–7.12 (complex m, 2H), 3.73 (s, 3H), 2.91–2.86 (complex m, 1H), 2.69–2.64 (complex m, 1H), 2.52–2.50 (complex m, 1H), 2.43–2.31 (complex m, 1H).

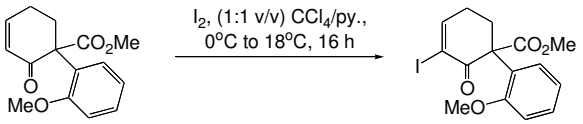
^{13}C NMR (75 MHz) δ 189.0 (C=O), 171.0 (C=O), 158.1 (CH), 135.3 (C), 128.5 (CH), 128.0 (CH), 127.3 (CH), 101.6 (C), 62.5 (C), 53.0 (CH_3), 31.5 (CH_2), 27.6 (CH_2).

IR (NaCl, film) ν_{max} 2951, 1734 (C=O), 1689 (C=O), 1447, 1247, 1048, 698 cm^{-1}.

EIMS (70 eV) *m/z* 356 ($M^{+\bullet}$, 51%), 297 (11), 194 (100).

HRMS Found: $M^{+\bullet}$, 355.9906. $C_{14}H_{13}{}^{127}IO_3$ requires $M^{+\bullet}$, 322.9910.

Methyl 3-iodo-1-(2-methoxyphenyl)-2-oxo-cyclohex-3-ene carboxylate (152)



(**103**) (**152**)

Clear, yellow oil

Yield 60%

R_f 0.2 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.66 (t, *J* = 3.7 Hz, 1H), 7.32–7.27 (complex m, 1H), 6.92–6.78 (complex m, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 2.88–2.82 (complex m, 1H), 2.72–2.66 (complex m, 1H), 2.44–2.33 (complex m, 1H), 2.13–2.04 (complex m, 1H).

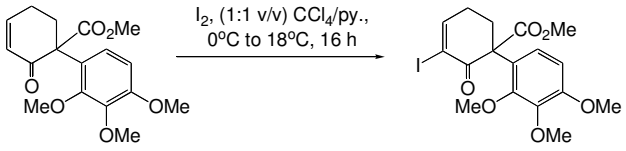
^{13}C NMR (75 MHz) δ 189.2 (C=O), 171.2 (C=O), 158.6 (CH), 157.0 (C), 129.2 (CH), 127.7 (CH), 126.0 (C), 120.6 (CH), 111.8 (CH), 102.3 (C), 61.4 (C), 55.6 (CH_3), 52.6 (CH_3), 30.6 (CH_2), 27.8 (CH_2).

IR (NaCl, film) ν_{max} 2950, 1733 (C=O), 1689 (C=O), 1493, 1251, 1022, 752 cm^{-1}.

EIMS (70 eV) *m/z* 386 ($M^{+\bullet}$, 77%), 326 (46), 192 (100).

HRMS Found: $M^{+\bullet}$, 386.0017. $C_{15}H_{15}{}^{127}IO_4$ requires $M^{+\bullet}$, 386.0015.

Methyl 3-iodo-1-(2,3,4-trimethoxyphenyl)-2-oxo-cyclohex-3-ene carboxylate (153)



(**104**) (**153**)

Clear, yellow oil

Yield 75%

***R*$_f$** 0.5 (silica, 3:2 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.56 (t, *J* = 4.1 Hz, 1H), 6.51 (complex m, 2H), 3.77 (s, 6H), 3.73 (s, 3H), 3.69 (s, 3H), 2.70–2.58 (complex m, 2H), 2.32–2.30 (complex m, 1H), 2.14–2.05 (complex m, 1H).

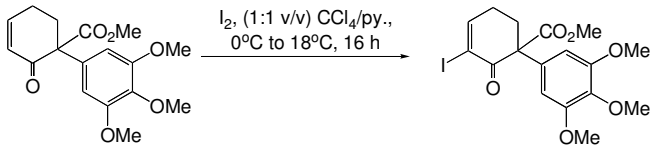
^{13}C NMR (75 MHz) δ 188.8 (C=O), 171.0 (C=O), 157.9 (CH), 153.4 (C), 151.5 (C), 141.7 (C), 123.3 (C), 121.5 (CH), 106.0 (CH), 102.0 (C), 60.7 (C), 60.3 (CH_3), 60.1 (CH_3), 55.6 (CH_3), 52.5 (CH_3), 31.4 (CH_2), 27.6 (CH_2).

IR (NaCl, film) ν_{max} 2945, 1734 (C=O), 1692 (C=O), 1495, 1235, 1074, 735 cm^{-1}.

EIMS (70 eV) *m/z* 446 ($M^{+\bullet}$, 100%), 259 (67), 252 (72).

HRMS Found: $M^{+\bullet}$, 446.0229. $C_{17}H_{19}{}^{127}IO_6$ requires $M^{+\bullet}$, 446.0226.

Methyl 3-iodo-1-(3,4,5-trimethoxyphenyl)-2-oxo-cyclohex-3-ene carboxylate (154)



(**105**) (**154**)

Colourless solid

Yield 98%

***R*$_f$** 0.4 (silica, 3:2 v/v ethyl acetate/hexane).

m.p. 81–83°C.

^{1}H NMR (300 MHz) δ 7.49 (t, *J* = 4.1 Hz, 1H), 6.23 (s, 2H), 3.75 (s, 3H), 3.73 (s, 6H), 3.66 (s, 3H), 2.83–2.76 (complex m, 1H), 2.60–2.54 (complex m, 1H), 2.39–2.27 (complex m, 2H).

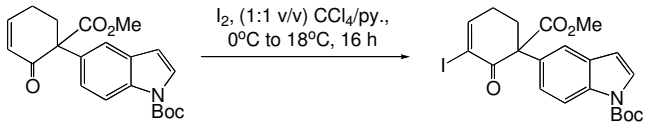
^{13}C NMR (75 MHz) δ 188.9 (C=O), 170.6 (C=O), 158.0 (C), 152.7 (CH), 137.4 (C), 130.3 (C), 104.6 (CH), 101.0 (C), 62.1 (C), 60.4 (CH_3), 55.8 (CH_3), 52.7 (CH_3), 31.1 (CH_2), 27.5 (CH_2).

IR (NaCl, film) ν_{max} 2922, 1735 (C=O), 1686 (C=O), 1590, 1257, 1129 cm^{-1}.

EIMS (70 eV) *m/z* 446 ($M^{+\bullet}$, 85%), 252 (100).

Elemental Analysis Found: C, 45.79, H, 4.45, I, 30.52. Calcd: $C_{17}H_{19}IO_6$, C, 45.76, H, 4.29, I, 28.44%.

1-*tert*-Butoxycarbonyl-3-iodo-5-(1-carbomethoxy-2-oxocyclohex-3-enyl)-1*H*-indole (155)



(**106**) (**155**)

Clear, yellow oil

Yield 73%

***R**$_f$* 0.7 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.10 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.54 (t, *J* = 4.1 Hz, 1H), 7.29 (s, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 3.6 Hz, 1H), 3.71 (s, 3H), 2.94–2.71 (complex m, 1H), 2.49–2.41 (complex m, 1H), 2.33–2.24 (complex m, 2H), 1.66 (s, 9H).

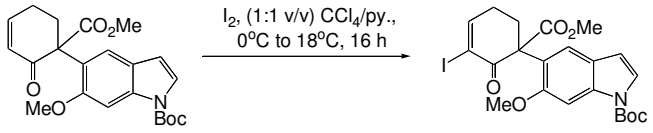
^{13}C NMR (75 MHz) δ 189.4 (C=O), 171.4 (C=O), 158.1 (CH), 149.5 (C=O), 134.4 (C), 130.5 (C), 129.2 (C), 126.5 (CH), 123.4 (CH), 119.8 (CH), 115.5 (CH), 107.3 (CH), 101.5 (C), 83.8 (C), 62.4 (C), 52.9 (CH_3), 31.5 (CH_2), 28.0 (CH_3), 27.6 (CH_2).

IR (NaCl, film) ν_{max} 2954, 1732 (C=O), 1471, 1258, 1166, 731 cm^{-1}.

EIMS *m/z* 495 ($M^{+\bullet}$, 13%), 439 (27), 395 (19), 201 (100).

HRMS Found: $M^{+\bullet}$, 495.0546. $C_{21}H_{22}{}^{127}INO_5$ requires $M^{+\bullet}$, 495.0543.

1-*tert*-Butoxycarbonyl-3-iodo-5-(1-carbomethoxy-2-oxocyclohex-3-enyl)-6-methoxy-1*H*-indole (156)



(**107**) (**156**)

Clear, yellow oil

Yield 70%

***R**f* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.76 (s, 1H), 7.65 (t, *J* = 4.3 Hz, 1H), 7.43 (d, *J* = 3.7 Hz, 1H), 6.92 (s, 1H), 6.43 (d, *J* = 3.7 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.88–2.83 (complex m, 1H), 2.71–2.69 (complex m, 1H), 2.38–2.35 (complex m, 1H), 2.09–2.06 (complex m, 1H), 1.64 (s, 9H).

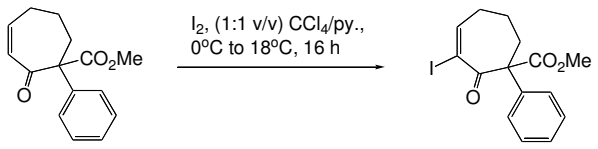
^{13}C NMR (75 MHz) δ 190.0 (C=O), 171.5 (C=O), 159.5 (C), 159.0 (CH), 155.0 (C), 149.5 (C=O), 124.7 (CH), 123.3 (C), 121.7 (CH), 119.8 (CH), 107.2 (C), 102.3 (C), 99.0 (CH), 83.6 (C), 61.6 (C), 55.8 (CH_3), 52.5 (CH_3), 30.6 (CH_2), 28.0 (CH_3), 27.8 (CH_2).

IR (NaCl, film) ν_{max} 2925, 1732 (C=O), 1684 (C=O), 1473, 1369, 1155 cm^{-1}.

EIMS (70 eV) *m/z* 525 ($M^{+\bullet}$, 24%), 469 (100), 275 (27)

HRMS Found: $M^{+\bullet}$, 525.0649. $C_{22}H_{24}{}^{127}INO_6$ requires $M^{+\bullet}$, 525.0648.

Methyl 3-iodo-2-oxo-1-phenyl-cyclohept-3-ene carboxylate (157)



(**108**) (**157**)

Clear, yellow oil

Yield 58%

***R**f* 0.2 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.39–7.23 (complex m, 5H), 7.10 (t, *J* = 5.0 Hz, 1H), 3.73 (s, 3H), 2.89–2.79 (complex m, 1H), 2.42–2.33 (complex m, 2H), 2.27–2.22 (complex m, 1H), 2.00–1.83 (complex m, 2H).

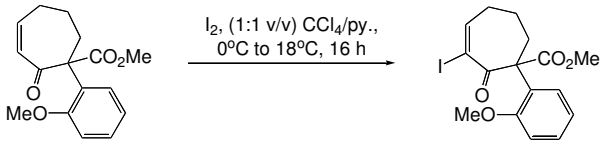
^{13}C NMR (75 MHz) δ 196.4 (C=O), 171.9 (C=O), 149.7 (CH), 137.8 (C), 128.7 (CH), 128.3 (CH), 128.0 (CH), 99.1 (C), 67.8 (C), 52.8 (CH_3), 33.0 (CH_2), 32.9 (CH_2), 22.9 (CH_2).

IR (NaCl, film) ν_{max} 2924, 2853, 1739 (C=O), 1447, 1238, 698 cm^{-1}.

EIMS (70 eV) *m/z* 310 [$(M–CO_2Me•)^+$, 9], 243 (24), 155 (100).

HRMS Found: $(M–CO_2Me•)^+$, Found 310.9934. $C_{13}H_{12}{}^{127}IO_2$ requires $(M–CO_2Me•)^+$, 310.9933.

Methyl 3-iodo-2-oxo-1-(2-methoxyphenyl)-2-cycloheptene carboxylate (158)



(**109**) (**158**)

Clear, yellow oil

Yield 68%

***R**$_f$* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.32–7.22 (complex m, 2H), 7.04–6.89 (complex m, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 2.66–2.43 (complex m, 2H), 2.24 (p, *J* = 6.1 Hz, 1H), 1.90–1.63 (complex m, 3H).

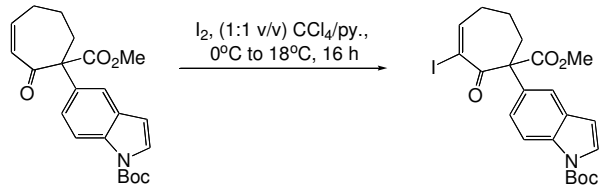
^{13}C NMR (75 MHz) δ 195.7 (C=O), 171.5 (C=O), 156.9 (C), 149.7 (CH), 129.0 (CH), 128.2 (C), 127.7 (CH), 120.6 (CH), 111.8 (CH), 102.6 (C), 65.4 (C), 55.7 (CH_3), 52.6 (CH_3), 32.2 (CH_2), 31.0 (CH_2), 21.9 (CH_2).

IR (NaCl, film) ν_{max} 2929, 1733 (C=O), 1691 (C=O), 1493, 1250, 1026, 754 $cm^{-1.}$

EIMS (70 eV) *m/z* 400 ($M^{+•}$, 16%), 313 (5), 274 (14) 213 (100).

HRMS Found: $M^{+•}$, 400.0176. $C_{16}H_{17}{}^{127}IO_4$ requires $M^{+•}$, 400.0172.

1-*tert*-Butoxycarbonyl-3-iodo-2-oxocyclohept-3-enyl-1*H*-indole-1-carboxylate (159)



(**110**) (**159**)

Clear, yellow oil

Yield 61%

R_f 0.3 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.20 (dd, *J* = 8.7 and 1.9 Hz, 1H), 7.08 (t, *J* = 5.6 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 3.70 (s, 3H), 2.88–2.83 (complex m, 1H), 2.51–2.44 (complex m, 1H), 2.35–2.31 (complex m, 1H), 2.23–2.19 (complex m, 1H), 1.99–1.87 (complex m, 2H), 1.66 (s, 9H).

^{13}C NMR (75 MHz) δ 196.8 (C=O), 171.1 (C=O), 149.7 (CH), 149.5 (C=O), 134.2 (C), 131.7 (C), 130.3 (C), 126.4 (CH), 124.3 (CH), 120.4 (CH), 114.8 (CH), 107.4 (CH), 99.3 (C), 83.8 (C), 67.5 (C), 52.7 (CH_3), 32.8 (CH_2), 31.6 (CH_2), 28.0 (CH_3), 22.7 (CH_2).

IR (NaCl, film) ν_{max} 2931, 1736 (C=O), 1469, 1371, 1164, 731 cm^{-1}.

EIMS (70 eV) *m/z* 509 ($M^{+\bullet}$, 53%), 453 (20), 409 (17), 350 (19), 326 (56), 298 (75), 266 (60), 222 (66), 194 (100).

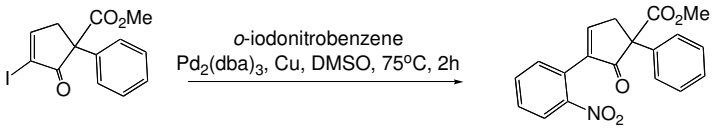
HRMS Found: $M^{+\bullet}$, 509.0701. $C_{22}H_{24}{}^{127}INO_5$ requires $M^{+\bullet}$, 509.0699.

5.2.7 General Procedure for Pd[0]-catalysed Ullmann Cross-Coupling

Following a procedure developed by Banwell *et al*,[11] a magnetically stirred mixture of *o*-iodonitrobenzene (**137**) (518 mg, 2.00 mmol), the appropriate α′-iodinated cyclic ketone (1.00 mmol), copper powder (310 mg of 99% material, CAS No. 7440-50-8, 5.00 mmol) and $Pd_2(dba)_3$ (10.0 mg, 10.0 μmol) in DMSO (8 mL) all maintained under a nitrogen atmosphere, was heated to 75°C and stirred at this temperature for 2 – 3 h, then cooled and diluted with ether (30 mL). The resulting mixture was then filtered through a pad of Celite™ and the solids thus retained washed with ether (1 x 80 mL). The combined filtrates were washed with distilled water (2 x 50 mL) and brine (1 x 50

mL) and the separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10 → 40% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the relevant Ullmann cross-coupling product as either a clear, yellow oil or solid.

Methyl 1-phenyl-3-(2-nitrophenyl)-2-oxocyclopent-3-ene carboxylate (160)



(**149**) (**160**)

Clear, yellow oil

Yield 60%

***R**f* 0.2 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.07 (dd, *J* = 8.1 and 1.2 Hz, 1H), 7.78 (t, *J* = 2.9 Hz, 1H), 7.64 (td, *J* = 7.5 and 1.2 Hz, 1H), 7.53 (td, *J* = 8.1 and 1.2 Hz, 1H), 7.39–7.29 (complex m, 6H), 3.97 (dd, *J* =19.5 and 3.0 Hz, 1H), 3.77 (s, 3H), 3.13 (dd, *J* = 19.5 and 3.0 Hz, 1H).

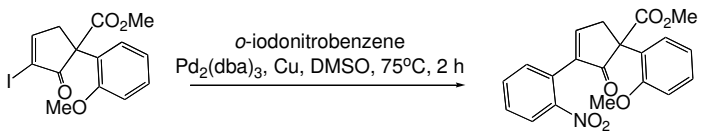
^{13}C NMR (75 MHz) δ 198.9 (C=O), 170.0 (C=O), 157.2 (CH), 148.3 (C), 141.9 (C), 138.3 (C), 133.2 (CH), 131.6 (CH), 129.7 (CH), 128.8 (CH), 127.5 (CH), 127.3 (CH), 126.7 (C), 124.8 (CH), 63.7 (C), 55.5 (CH_3), 41.9 (CH_2).

IR (NaCl, film) ν_{max} 2954, 1746 (C=O), 1722 (C=O), 1526 (NO_2), 1353, 699 cm^{-1}.

EIMS (70 eV) *m/z* 337 ($M^{+\bullet}$, >1%), 305 [$(M–CH_3OH)^+$, 100], 278 (28), 204 (52).

HRMS Found: $M^{+\bullet}$, 337.0958. $C_{19}H_{15}NO_5$ requires $M^{+\bullet}$, 337.0950.

Methyl 1-(2-methoxyphenyl)-3-(2-nitrophenyl)-2-oxocyclopent-3-ene carboxylate (161)



(**150**) (**161**)

Clear, yellow oil

Yield 58%

R$_f$ 0.2 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 2.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 6.6 Hz, 1H), 7.22 (d, *J* = 6.6 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 4.09 (dd, *J* =19.8 and 2.8 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.81 (dd, *J* = 19.8 and 2.8 Hz, 1H).

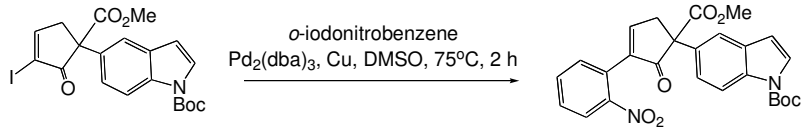
^{13}C NMR (75 MHz) δ 199.7 (C=O), 170.0 (C=O), 158.8 (CH), 157.0 (C), 148.4 (C), 141.4 (C), 133.2 (CH), 131.7 (CH), 129.5 (CH), 128.8 (C), 128.6 (CH), 127.5 (CH), 127.0 (C), 124.8 (CH), 121.0 (CH), 111.0 (CH), 62.2 (C), 55.5 (CH_3), 55.3 (CH_3), 41.8 (CH_2).

IR (NaCl, film) ν_{max} 2952, 1714 (C=O), 1527 (NO_2), 1354, 1248, 732 cm^{-1}.

EIMS (70 eV) *m/z* 367 ($M^{+\bullet}$, 35%), 335 (67), 308 (54), 290 (18), 135 (100).

HRMS Found: $M^{+\bullet}$, 367.1053. $C_{20}H_{17}NO_6$ requires $M^{+\bullet}$, 367.1056.

1-*tert*-Butoxycarbonyl-3-(2-nitrophenyl)-5-(1-carbomethoxy-2-oxo cyclopent-3-enyl)-1*H*-indole (162)



(**151**) (**162**)

Clear, yellow oil

Yield 86%

***R**$_f$* 0.3 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.10 (complex m, 2H), 7.79 (t, *J* = 2.8 Hz, 1H), 7.65 – 7.52 (complex m, 4H), 7.39 (dd, *J* = 7.6 and 1.9 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 6.55 (d, *J* = 3.7 Hz, 1H), 4.04 (dd, *J* = 19.2 and 3.0 Hz, 1H), 3.77 (s, 3H), 3.19 (dd, *J* = 19.2 and 3.0 Hz, 1H), 1.66 (s, 9H).

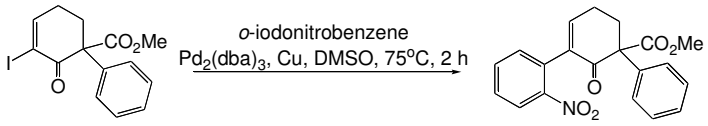
^{13}C NMR (75 MHz) δ 199.1 (C=O), 170.3 (C=O), 157.1 (CH), 149.6 (C), 148.4 (C=O), 141.9 (C), 134.2 (C), 133.2 (CH), 132.7 (C), 131.6 (CH), 130.7 (C), 129.6 (CH), 126.8 (C), 126.5 (CH), 124.8 (CH), 123.5 (CH), 119.5 (CH), 115.5 (CH), 107.6 (CH), 83.8 (C), 63.6 (C), 53.5 (CH_3), 42.3 (CH_2), 28.1 (CH_3).

IR (NaCl, film) ν_{max} 2925, 1732 (C=O), 1527 (NO_2), 1470, 1370, 1258, 1141, 730 cm^{-1}.

EIMS (70 eV) *m/z* 476 ($M^{+\bullet}$, 56%), 316 (100).

HRMS Found: $M^{+\bullet}$, 476.1584. $C_{26}H_{24}N_2O_7$ requires $M^{+\bullet}$, 476.1584.

Methyl 1-phenyl-3-(2-nitro-phenyl)-2-oxo-cyclohex-3-ene carboxylate (139)



(**138**) (**139**)

Clear, yellow solid

Yield 58%

***R**f* 0.2 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 161–163°C.

^{1}H NMR (300 MHz) δ 8.02 (d, *J* = 6.5 Hz, 1H), 7.61 (t, *J* = 6.5 Hz, 1H), 7.49 (t, *J* = 6.5 Hz, 1H), 7.39–7.19 (complex m, 6H), 6.94 (t, *J* = 4.0 Hz, 1H), 3.77 (s, 3H), 3.00–2.92 (complex m, 1H), 2.77–2.63 (complex m, 2H), 2.53–2.44 (complex m, 1H).

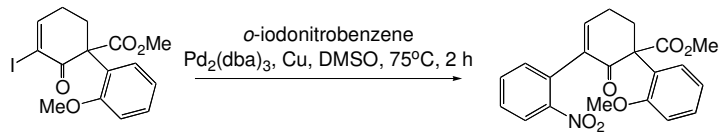
^{13}C NMR (75 MHz) δ 191.8 (C=O), 171.1 (C=O), 146.5 (CH), 138.8 (C), 136.4 (C), 133.1 (CH), 131.7 (CH), 131.5 (C), 129.0 (CH), 128.4 (CH), 127.8 (CH), 127.5 (CH), 124.8 (CH), 100.0 (C), 62.8 (C), 52.9 (CH_3), 32.1 (CH_2), 24.1 (CH_2).

IR (NaCl, film) ν_{max} 2927, 1733 (C=O), 1675 (C=O), 1525 (NO_2), 1353, 700 cm^{-1}.

EIMS (70 eV) *m/z* 351 ($M^{+\bullet}$, >1%), 292 (13), 275 (55), 230 (36), 215 (16), 115 (100).

HRMS Found: $M^{+\bullet}$, 351.1106. $C_{20}H_{17}NO_5$ requires $M^{+\bullet}$, 351.1107.

Methyl 1-(2-methoxyphenyl)-3-(2-nitrophenyl)-2-oxocyclohex-3-ene carboxylate (166)



(**152**) (**166**)

Yellow solid

Yield 56%

***R**f* 0.21 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 156–158°C.

^{1}H NMR (300 MHz) δ 8.01 (d, *J* = 6.4 Hz, 1H), 7.61 (t, *J* = 6.4 Hz, 1H), 7.48 (t, *J* = 6.4 Hz, 1H), 7.33–7.28 (complex m, 3H), 7.02 (m, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 2.90–2.60 (complex m, 3H), 2.37–2.35 (complex m, 1H).

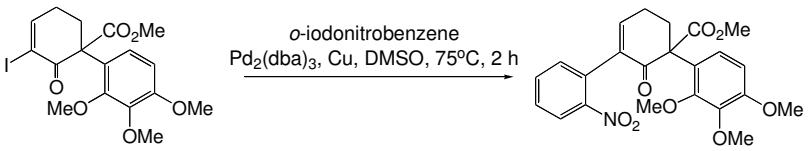
^{13}C NMR (75 MHz) δ 191.7 (C=O), 171.2 (C=O), 157.2 (C), 149.1 (C), 147.2 (CH), 138.8 (C), 132.9 (CH), 131.8 (CH), 131.7 (C), 129.0 (CH), 128.8 (CH), 127.9 (CH), 127.3 (C), 124.2 (CH), 120.6 (CH), 111.9 (CH), 61.7 (C), 55.6 (CH_3), 52.6 (CH_3), 30.8 (CH_2), 24.2 (CH_2).

IR (NaCl, film) ν_{max} 2950, 1734 (C=O), 1678 (C=O), 1527 (NO_2), 1251, 752 cm^{-1}.

EIMS (70 eV) *m/z* 381 ($M^{+\bullet}$, 27%), 349 (12), 322 (15), 305 (66), 276 (40), 145 (100).

HRMS Found: $M^{+\bullet}$, 381.1213. $C_{21}H_{19}NO_6$ requires $M^{+\bullet}$, 381.1212.

Methyl 1-(2,3,4-trimethoxyphenyl)-3-(2-nitrophenyl)-2-oxocyclohex-3-ene carboxylate (167)



(**153**) (**167**)

Clear, yellow oil

Yield 56%

R_f (0.4 (silica, 3:2 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 3.8 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.57 (d, *J* = 8.8 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.69 (s, 3H), 2.80–2.60 (complex m, 3H), 2.41–2.38 (complex m, 1H).

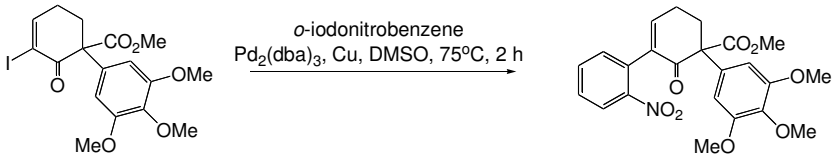
^{13}C NMR (75 MHz) δ 191.6 (C=O), 171.2 (C=O), 153.4 (C), 151.8 (C), 148.9 (C), 146.6 (CH), 141.9 (C), 138.7 (C), 132.9 (CH), 131.8 (CH), 131.7 (CH), 128.7 (C), 124.5 (C), 124.0 (CH), 121.8 (CH), 106.2 (CH), 61.7 (C), 60.4 (CH_3), 60.3 (CH_3), 55.8 (CH_3), 52.5 (CH_3), 31.8 (CH_2), 24.1 (CH_2).

IR (NaCl, film) ν_{max} 2947, 1734 (C=O), 1685 (C=O), 1527 (NO_2), 1354, 1103 cm^{-1}.

EIMS (70 eV) *m/z* 441 ($M^{+\bullet}$, 65%), 409 (33), 348 (35), 157 (100).

HRMS Found: $M^{+\bullet}$, 441.1422. $C_{23}H_{23}NO_8$ requires $M^{+\bullet}$, 441.1424.

Methyl 1-(3,4,5-trimethoxyphenyl)-3-(2-nitrophenyl)-2-oxocyclohex-3-ene carboxylate (168)



(**154**) (**168**)

Clear, yellow oil

Yield 56%

***R**f* 0.4 (silica, 3:2 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.00 (dd, *J* = 8.1 and 1.3 Hz, 1H), 7.59 (td, *J* = 7.6 and 1.3 Hz, 1H), 7.48 (td, *J* = 8.1 and 1.3 Hz, 1H), 7.24 (dd, *J* = 7.6 and 1.3 Hz, 1H), 6.99 (t, *J* = 4.0 Hz, 1H), 6.42 (s, 2H), 3.83 (s, 3H), 3.81 (s, 6H), 3.75 (s, 3H), 2.91 (complex m, 1H), 2.70–2.64 (complex m, 3H).

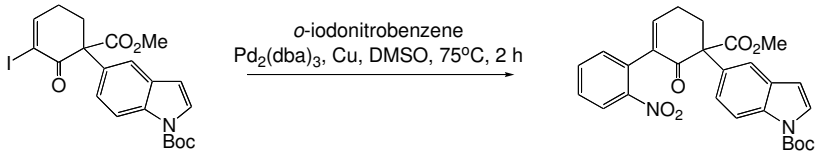
^{13}C NMR (75 MHz) δ 191.7 (C=O), 170.9 (C=O), 152.9 (C), 148.9 (C), 146.9 (CH), 138.8 (C), 137.5 (C), 133.1 (CH), 131.8 (C), 131.6 (CH), 131.4 (C), 129.0 (CH), 124.2 (CH), 105.0 (CH), 62.7 (C), 61.0 (CH_3), 56.1 (CH_3), 52.9 (CH_3), 32.5 (CH_2), 24.1 (CH_2).

IR (NaCl, film) ν_{max} 2932, 1733 (C=O), 1675 (C=O), 1527 (NO_2), 1251, 1128 cm^{-1}.

EIMS (70 eV) *m/z* 441 ($M^{+\bullet}$, 100%), 382 (27), 348 (25).

HRMS Found: $M^{+\bullet}$, 441.1418. $C_{23}H_{23}NO_8$ requires $M^{+\bullet}$, 441.1424.

1-*tert*-Butoxycarbonyl-3-(2-nitrophenyl)-5-(1-carbomethoxy-2-oxo cyclohex-3-enyl)-1*H*-indole (169)



(**155**) (**169**)

Clear, yellow oil

Yield 62%

***R**f* 0.3 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.10 (d, *J* = 8.7 Hz, 1H), 8.01 (dd, *J* = 8.1 and 1.4 Hz, 1H), 7.63–7.57 (complex m, 2H), 7.49 (td, *J* = 7.6 and 1.4 Hz, 1H), 7.40 (d, *J* = 8.1 and 1.4 Hz, 1H), 7.24 (dd, *J* = 7.6 and 1.4 Hz, 1H), 7.17 (dd, *J* = 8.7 and 1.4 Hz, 1H), 6.92 (t, *J*

= 3.8 Hz, 1H), 6.54 (d, *J* = 3.8 Hz, 1H), 3.76 (s, 3H), 3.06–2.99 (complex m, 1H), 2.85–2.64 (complex m, 2H), 2.52–2.50 (complex m, 1H), 1.66 (s, 9H).

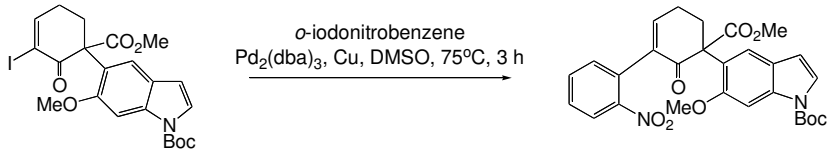
^{13}C NMR (75 MHz) δ 192.2 (C=O), 171.5 (C=O), 149.6 (C), 149.0 (C=O), 146.5 (CH), 138.7 (CH), 134.4 (C), 133.0 (CH), 131.7 (CH), 131.6 (C), 130.6 (C), 130.3 (C), 128.9 (CH), 126.4 (C), 124.2 (CH), 123.8 (CH), 120.1 (CH), 115.1 (CH), 107.4 (CH), 83.8 (C), 62.6 (C), 53.8 (CH_3), 32.0 (CH_2), 28.1 (CH_3), 24.1 (CH_2).

IR (NaCl, film) ν_{max} 2929, 1733 (C=O), 1688 (C=O). 1528 (NO_2), 1371, 731 cm^{-1}.

EIMS (70 eV) *m/z* 490 ($M^{+\bullet}$, 15%), 390 (11), 57 (100).

HRMS Found: $M^{+\bullet}$, 490.1742. $C_{27}H_{26}N_2O_7$ requires $M^{+\bullet}$, 490.1740.

1-*tert*-Butoxycarbonyl-3-(2-nitrophenyl)-5-(1-carbomethoxy-2-oxo cyclohex-3-enyl)-6-methoxy-1*H*-indole (170)



(**156**) (**170**)

Clear, yellow oil

Yield 91%

***R*$_f$** 0.2 (silica. 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.77 (s, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.51–7.43 (complex m, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 7.02 (t, *J* = 4.0 Hz, 1H), 6.45 (d, *J* = 4.0 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.99–2.96 (complex m, 1H), 2.86–2.81 (complex m, 1H), 2.57–2.30 (complex m, 2H), 1.65 (s, 9H).

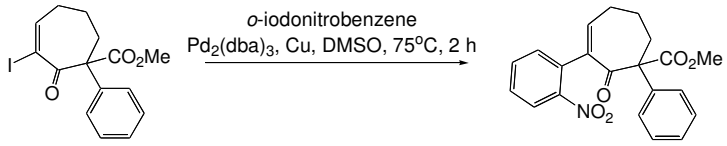
^{13}C NMR (75 MHz) δ 192.2 (C=O), 171.6 (C=O), 155.3 (C), 149.7 (C), 149.1 (C=O), 147.5 (CH), 138.8 (CH), 135.5 (C), 132.9 (CH), 131.9 (CH), 131.6 (C), 128.8 (CH), 124.6 (CH), 124.1 (CH), 123.5 (C), 123.0 (C), 120.0 (CH), 107.3 (C), 99.1 (CH), 83.5 (C), 61.8 (C), 55.8 (CH_3), 52.5 (CH_3), 30.9 (CH_2), 28.1 (CH_3), 24.2 (CH_2).

IR (NaCl, film) ν_{max} 2930, 1732 (C=O), 1676 (C=O), 1528 (NO_2), 1370, 1258 cm^{-1}.

EIMS (70 eV) *m/z* 520 ($M^{+\bullet}$, 36%), 464 (100), 420 (63).

HRMS Found: $M^{+\bullet}$, 520.1848. $C_{28}H_{28}N_2O_8$ requires $M^{+\bullet}$, 520.1846.

Methyl 1-phenyl-3-(2-nitro-phenyl)-2-oxo-cyclohept-3-ene carboxylate (178)



(**157**) (**178**)

Clear, yellow oil

Yield 68%

***R**f* 0.2 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.36–7.20 (complex m, 6H), 6.60 (t, *J* = 6.3 Hz, 1H), 3.72 (s, 3H), 2.88–2.81 (complex m, 1H), 2.72–2.63 (complex m, 1H), 2.44–2.22 (complex m, 2H), 2.07–1.91 (complex m, 2H).

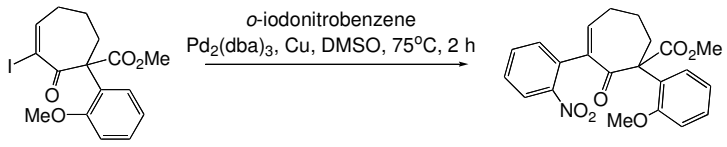
^{13}C NMR (75 MHz) δ 198.1 (C=O), 172.3 (C=O), 148.6 (C), 142.1 (CH), 141.1 (C), 137.7 (C), 135.0 (C), 132.9 (CH), 132.2 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 124.2 (CH), 68.0 (C), 52.7 (CH_3), 30.1 (CH_2), 27.3 (CH_2), 22.0 (CH_2).

IR (NaCl, film) ν_{max} 2951, 1734 (C=O), 1659 (C=O), 1562 (NO_2), 1233, 736 cm^{-1}.

EIMS (70 eV) *m/z* 365 ($M^{+\bullet}$, >1%), 288 (28), 115 (100).

HRMS Found: $M^{+\bullet}$, 365.1256. $C_{21}H_{19}NO_5$ requires $M^{+\bullet}$, 365.1263.

Methyl 1-(2-methoxyphenyl)-3-(2-nitro-phenyl)-2-oxo-cyclohept-3-ene carboxylate (179)



(**158**) (**179**)

Yellow solid

Yield 56%

***R**f* 0.2 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 92–94°C.

^{1}H NMR (300 MHz) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.36–7.30 (complex m, 2H), 7.05 (d, *J* = 6.6 Hz, 1H), 6.96–6.89 (complex m,

2H), 6.63 (complex m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 2.92–2.86 (complex m, 1H), 2.68–2.58 (complex m, 1H), 2.37–2.24 (complex m, 2H), 1.89–1.67 (complex m, 2H).

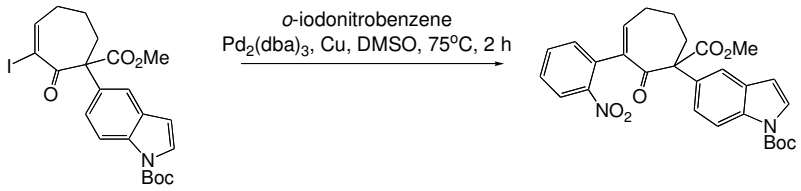
^{13}C NMR (75 MHz) δ 198.4 (C=O), 172.1 (C=O), 157.7 (C), 148.9 (C), 142.6 (CH), 141.2 (C), 135.5 (C), 132.8 (CH), 132.3 (CH), 133.1 (CH), 128.9 (CH), 128.4 (CH), 127.1 (C), 124.1 (CH), 120.8 (CH), 111.7 (CH), 66.7 (C), 55.6 (CH_3), 52.5 (CH_3), 29.0 (CH_2), 27.1 (CH_2), 21.0 (CH_2).

IR (NaCl, film) ν_{max} 2929, 1734 (C=O), 1658 (C=O), 1525 (NO_2), 1354, 1024 cm^{-1}.

EIMS (70 eV) *m/z* 395 ($M^{+\bullet}$, 10%), 318 (72), 274 (46), 146 (100).

HRMS Found: $M^{+\bullet}$, 395.1368. $C_{22}H_{21}NO_6$ requires $M^{+\bullet}$, 395.1369.

1-*tert*-Butoxycarbonyl-3-(2-nitrophenyl)-5-(1-carbomethoxy-2-oxo cyclohept-3-enyl)-1*H*-indole (180)



(**159**) (**180**)

Clear, yellow oil

Yield 56%

***R**$_f$* 0.3 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.08 (d, *J* = 8.5 Hz, 1H), 7.98 (dd, *J* = 8.1 and 1.2 Hz, 1H), 7.61–7.55 (complex m, 2H), 7.43 (td, *J* = 8.1 and 1.2 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.32 (dd, *J* = 7.6 and 1.5 Hz, 1H), 7.18 (dd, *J* = 8.5 and 1.9 Hz, 1H), 6.60 (t, *J* = 6.1 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 3.70 (s, 3H), 2.91–2.86 (complex m, 1H), 2.76–2.71 (complex m, 1H), 2.36–2.33 (complex m, 1H), 2.32–2.20 (complex m, 1H), 1.99–1.94 (complex m, 2H), 1.66 (s, 9H).

^{13}C NMR (75 MHz) δ 198.6 (C=O), 172.6 (C=O), 149.6 (C), 148.7 (C=O), 142.3 (CH), 141.1 (CH), 135.0 (C), 134.2 (C), 132.9 (CH), 132.2 (CH), 131.6 (C), 130.5 (C), 128.5 (CH), 126.3 (C), 124.3 (CH), 124.1 (CH), 120.3 (CH), 115.0 (CH), 107.5 (CH), 83.7 (C), 67.9 (C), 52.7 (CH_3), 30.0 (CH_2), 28.1 (CH_3), 27.2 (CH_2), 21.9 (CH_2).

IR (NaCl, film) ν_{max} 2978, 1733 (C=O), 1659 (C=O), 1527 (NO_2), 1166, 731 cm^{-1}.

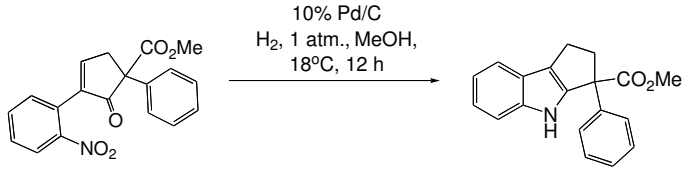
EIMS (70 eV) *m/z* 504 ($M^{+\bullet}$, 8%), 404 (4), 387 (13), 57 (100).

HRMS Found: $M^{+\bullet}$, 504.1894. $C_{28}H_{28}N_2O_7$ requires $M^{+\bullet}$, 504.1897.

5.2.8 General Procedure for Reductive Cyclisation of (o-Nitrophenyl)cycloalkenones 139, 160 – 163, 166 – 170 and 178 – 181

Following a procedure developed by Banwell *et al*,[11] a magnetically stirred solution of the appropriate Ullmann cross-coupling product (1.00 mmol) and 10% Pd/C (50.0 mg, 0.50 mmol) in methanol (5 mL) was treated with one to three atmospheres of dihydrogen at 18°C and stirred at this temperature for 1 – 24 h, then filtered through a pad of Celite™. The solids thus retained was washed with methanol (3 x 10 mL) and the combined filtrates were concentrated under reduced pressure to give a clear green oil. Subjection of this material to flash chromatography (silica, 30 → 70% v/v ethyl acetate/hexane gradient elution provided, after concentration of the appropriate fractions, the relevant indole as either a green solid or oil.

Methyl 1,2,3,4-tetrahydro-3-phenylcyclopenta[*b*]indole-3-carboxylate (163)



(**160**) (**163**)

Green oil

Yield 97%

***R**f* 0.6 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.23 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.30–7.08 (complex m, 7H), 3.77 (s, 3H), 3.51 (pd, *J* = 6.3 and 4.8 Hz, 1H), 2.91–2.82 (complex m, 2H), 2.68–2.61 (complex m, 1H).

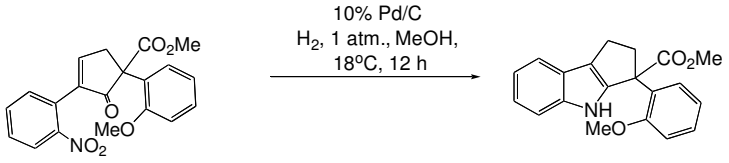
^{13}C NMR (75 MHz) δ 173.5 (C=O), 143.0 (C), 141.2 (C), 140.9 (C), 128.7 (CH), 127.2 (CH), 125.8 (CH), 124.1 (C), 121.83 (CH), 121.8 (C), 119.8 (CH), 119.3 (CH), 111.9 (CH), 59.6 (C), 52.7 (CH_3), 43.7 (CH_2), 22.8 (CH_2).

IR (NaCl, film) ν_{max} 3393 (NH), 2951, 1725 (C=O), 1449, 1232, 743 cm^{-1}.

EIMS (70 eV) *m/z* 291 ($M^{+\bullet}$, 56%), 232 (100).

HRMS Found: $M^{+\bullet}$, 291.1252. $C_{19}H_{17}NO_2$ requires $M^{+\bullet}$, 291.1259.

Methyl 1,2,3,4-tetrahydro-3-(2-methoxyphenyl)cyclopenta[*b*]indole-3-carboxylate (164)



(**161**) (**164**)

Green oil

Yield 98%

***R**f* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.13 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.15 (sept, *J* = 9.3 Hz, 3H), 6.94–6.82 (complex m, 3H), 3.82 (s, 3H), 3.71 (s, 3H), 3.71 (complex m, 1H), 3.00–2.96 (complex m, 1H), 2.88–2.86 (complex m, 1H), 2.61–2.56 (complex m, 1H).

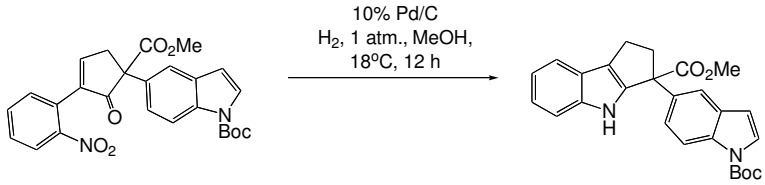
^{13}C NMR (75 MHz) δ 174.0 (C=O), 156.2 (C), 141.1 (C), 141.0 (C), 132.3 (C), 128.5 (CH), 126.9 (CH), 124.3 (C), 121.9 (C), 121.6 (CH), 120.7 (CH), 119.7 (CH), 119.3 (CH), 111.8 (CH), 111.1 (CH), 59.7 (C), 55.6 (CH_3), 52.4 (CH_2), 41.1 (CH_2), 23.2 (CH_2).

IR (NaCl, film) ν_{max} 3369 (NH), 2949, 1728 (C=O), 1490, 1246, 739 cm^{-1}.

EIMS (70 eV) *m/z* 321 ($M^{+\bullet}$, 40%), 262 (73), 84 (100).

HRMS Found: $M^{+\bullet}$, 321.1370. $C_{20}H_{19}NO_3$ requires $M^{+\bullet}$, 321.1365.

Methyl 3-[1-(1-*tert*-Butoxycarbonyl)-1*H*-indol-5-yl]-1,2,3,4-tetrahydro cyclopenta[*b*]indole-3-carboxylate (165)



(**162**) (**165**)

Green oil

Yield 87%

***R**f* 0.6 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.28 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.58–7.54 (complex m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.24–7.09 (complex m, 4H), 6.46 (d, *J* = 3.7 Hz, 1H), 3.77 (s, 3H), 3.55 (complex m, 1H), 2.91–2.82 (complex m, 2H), 2.70–2.64 (complex m, 1H), 1.65 (s, 9H).

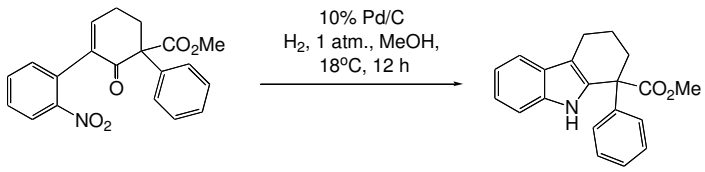
^{13}C NMR (75 MHz) δ 173.8 (C=O), 149.6 (C=O), 141.2 (CH), 137.4 (C), 134.1 (C), 130.8 (C), 127.5 (C), 126.5 (CH), 124.2 (C), 122.1 (CH), 121.8 (CH), 119.8 (CH), 119.3 (CH), 118.6 (C), 118.1 (CH), 115.4 (CH), 111.9 (CH), 107.3 (CH), 83.8 (C), 59.5 (C), 52.7 (CH_3), 44.0 (CH_2), 28.1 (CH_3), 22.8 (CH_2).

IR (NaCl, film) ν_{max} 3385 (NH), 2950, 1733 (C=O), 1467, 1371, 1257, 731 cm^{-1}.

EIMS (70 eV) *m/z* 430 ($M^{+\bullet}$, 16%), 371 (17), 315 (66).

HRMS Found: $M^{+\bullet}$, 430.1892. $C_{26}H_{26}N_2O_4$ requires $M^{+\bullet}$, 430.1893

Methyl 1-phenyl-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (171)



(**139**) (**171**)

Green solid

Yield 95%

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane)

m.p. 36–38°C.

^{1}H NMR (300 MHz) δ 8.74 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.35–7.00 (complex m, 8H), 3.81 (s, 3H), 2.97 (t, *J* = 7.7 Hz, 1H), 2.10 (complex m, 1H), 1.88–1.68 (complex m, 4H).

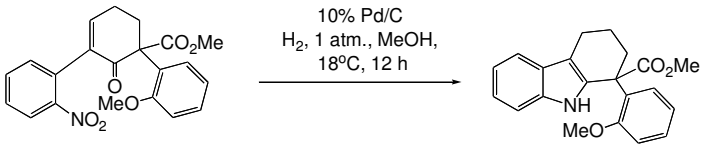
^{13}C NMR (75 MHz) δ 174.1 (C=O), 144.0 (C), 135.9 (C), 130.9 (C), 128.4 (CH), 127.1 (CH), 126.9 (C), 126.7 (CH), 122.2 (CH), 119.2 (CH), 118.6 (CH), 114.2 (C), 110.9 (CH), 53.4 (C), 52.7 (CH_3), 36.8 (CH_2), 20.9 (CH_2), 19.8 (CH_3).

IR (NaCl, film) ν_{max} 3410 (NH), 2934, 1732 (C=O), 1448, 1238, 1039, 743 cm^{-1}.

EIMS (70 eV) *m/z* 305 ($M^{+\bullet}$, 34%), 246 (100).

HRMS Found: $M^{+\bullet}$, 305.12419. $C_{20}H_{19}NO_2$ requires $M^{+\bullet}$, 305.1416.

Methyl 1-phenyl-2,3,4,9-tetrahydro-1-(2-methoxyphenyl)-1*H*-carbazole-1-carboxylate (172)



(**166**) (**172**)

Green solid

Yield 95%

***R*$_f$** 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 34–36°C.

^{1}H NMR (300 MHz) δ 8.22 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.32–7.09 (complex m, 3H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.76 (td, *J* = 7.7 and 1.4 Hz, 1H), 6.48 (dd, *J* = 7.7 and 1.4 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.09 (q, *J* = 7.4 Hz, 1H), 2.82–2.68 (complex m, 3H), 2.22–2.15 (complex m, 1H), 1.93–1.87 (complex m, 2H).

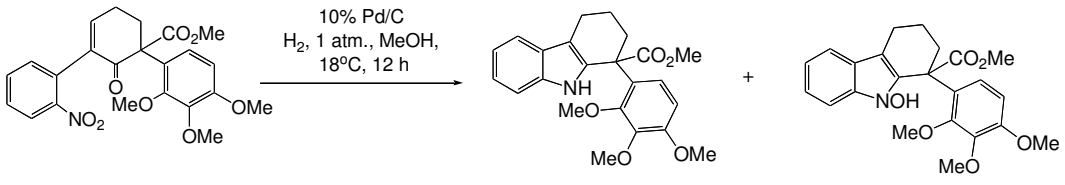
^{13}C NMR (75 MHz) δ 174.4 (C=O), 155.9 (CH), 135.8 (C), 132.7 (C), 130.4 (C), 129.9 (C), 129.8 (CH), 128.4 (CH), 127.2 (C), 122.1 (CH), 120.3 (CH), 119.2 (CH), 118.5 (CH), 114.3 (C), 110.9 (CH), 55.4 (C), 52.4 (CH_3), 50.8 (CH_3), 32.1 (CH_2), 21.0 (CH_2), 19.5 (CH_2).

IR (NaCl, film) ν_{max} 3387 (NH), 2947, 1729 (C=O), 1461, 1243, 1042, 738 cm^{-1}.

EIMS (70 eV) *m/z* 335 ($M^{+\bullet}$, 35%), 276 (100).

HRMS Found: $M^{+\bullet}$, 335.1522. $C_{21}H_{21}NO_3$ requires $M^{+\bullet}$, 335.1521.

Methyl 1-phenyl-2,3,4,9-tetrahydro-1-(2,3,4-trimethoxyphenyl)-1*H*-carbazole-1-carboxylate (173) and Methyl 1-phenyl-2,3,4,9-tetrahydro-1-(2,3,4-trimethoxyphenyl)-1-hydroxy-carbazole-1-carboxylate (177)



(**167**) (**173**) (**177**)

Compound 173:

Green solid

Yield 67%

***R*$_f$** 0.6 (silica, 3:2 v/v ethyl acetate/hexane).

m.p. 56–59°C.

^{1}H NMR (300 MHz) δ 8.26 (s, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.30–7.09 (complex m, 3H), 6.40 (d, *J* = 8.7 Hz, 1H), 6.19 (d, *J* = 8.7 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 2.80–2.71 (complex m, 4H), 2.11–1.91 (complex m, 2H).

^{13}C NMR (75 MHz) δ 174.7 (C=O), 153.1 (C), 150.4 (C), 141.6 (C), 135.8 (C), 130.7 (C), 130.2 (C), 127.1 (C), 123.8 (CH), 122.1 (CH), 119.2 (CH), 118.5 (C), 114.3 (CH), 110.9 (CH), 105.5 (CH), 60.5 (C), 60.4 (CH_3), 55.8 (CH_3), 52.5 (CH_3), 50.7 (CH_3), 33.5 (CH_2), 20.9 (CH_2), 19.5 (CH_2).

IR (NaCl, film) ν_{max} 3400 (NH), 2945, 1738 (C=O), 1493, 1274, 1101, 910, 734 cm^{-1}.

EIMS (70 eV) *m/z* 395 ($M^{+\bullet}$, 24%), 336 (100).

HRMS Found: $M^{+\bullet}$, 395.1736. $C_{23}H_{25}NO_5$ requires $M^{+\bullet}$, 395.1733.

Compound 177:

Green solid

Yield 12%

***R*$_f$** 0.6 (silica, 3:2 v/v ethyl acetate/hexane).

m.p. 68–71°C.

^{1}H NMR (300 MHz) δ 9.27 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.24 (m, 1H), 7.09 (m, 1H), 6.50 (d, *J* = 1.8 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 2.87–2.72 (complex m, 3H), 1.84–1.79 (complex m, 3H).

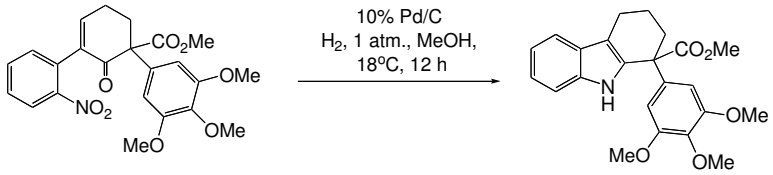
^{13}C NMR (75 MHz) δ 177.5 (C=O), 153.1 (C), 150.4 (C), 141.6 (C), 133.4 (C), 128.9 (C), 128.5 (C), 122.9 (CH), 122.3 (CH), 121.7 (C), 118.9 (CH), 118.2 (CH), 110.8 (C), 108.8 (CH), 106.4 (CH), 60.63 (C), 60.6 (CH_3), 55.8 (CH_3), 53.2 (CH_3), 51.0 (CH_3), 36.3 (CH_2), 21.11 (CH_2), 21.08 (CH_2).

IR (NaCl, film) ν_{max} 3234 (NOH), 2944, 1687 (C=O), 1493, 1287, 1101, 736 cm^{-1}.

EIMS (70 eV) *m/z* 411 ($M^{+\bullet}$, 92%), 351 (100), 336 (76), 243 (88).

HRMS Found: $M^{+\bullet}$, 411.1682. $C_{23}H_{25}NO_6$ requires $M^{+\bullet}$, 411.1682.

Methyl 1-phenyl-2,3,4,9-tetrahydro-1-(3,4,5-trimethoxyphenyl)-1*H*-carbazole-1-carboxylate (174)



(**168**) (**174**)

Green solid

Yield 95%

R_f 0.5 (silica, 3:2 v/v ethyl acetate/hexane).

m.p. 59–61°C.

^{1}H NMR (300 MHz) δ 8.46 (s, 1H), 7.58 (m, 1H), 7.34 (dt, *J* = 8.3 and 0.8 Hz, 1H), 7.21 (m, 1H), 7.14 (m, 1H), 6.23 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.70 (s, 6H), 2.82–2.64 (complex m, 3H), 2.18 – 2.05 (complex m, 1H), 1.89–1.78 (complex m, 2H).

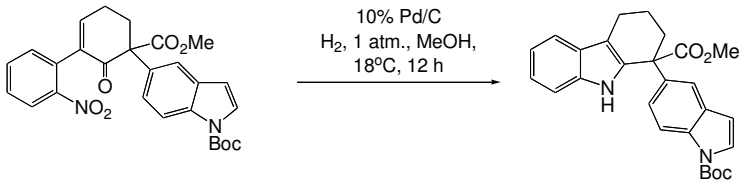
^{13}C NMR (75 MHz) δ 173.9 (C=O), 153.1 (C), 139.6 (C), 137.2 (C), 136.0 (C), 130.6 (C), 126.9 (C), 122.2 (CH), 119.2 (CH), 118.6 (CH), 114.4 (C), 110.9 (CH), 104.2 (CH), 60.8 (C), 56.2 (CH_3), 53.5 (CH_3), 52.7 (CH_3), 36.9 (CH_2), 20.9 (CH_2), 20.0 (CH_2).

IR (NaCl, film) ν_{max} 3401 (NOH), 2937, 1731 (C=O), 1589, 1455, 1239, 739 cm^{-1}.

EIMS (70 eV) *m/z* 395 ($M^{+\bullet}$, 82%), 336 (100).

HRMS Found: $M^{+\bullet}$, 395.1736. $C_{23}H_{25}NO_5$ requires $M^{+\bullet}$, 395.1733.

Methyl 1-[1-(1-*tert*-Butoxycarbonyl)-1*H*-indol-5-yl]-2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (175)



(**169**) (**175**)

Green oil

Yield 87%

R_f 0.6 (silica, 7:3 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.51 (s, 1H), 8.03 (d, *J* = 8.9 Hz, 1H), 7.60–7.58 (complex m, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.25–7.12 (complex m, 3H), 7.01 (dd, *J* = 8.9 and 1.8 Hz, 1H), 6.45 (d, *J* = 3.6 Hz, 1H), 3.83 (s, 3H), 2.81–2.69 (complex m, 4H), 2.21–2.05 (complex m, 1H), 1.86–1.68 (complex m, 1H), 1.65 (s, 9H).

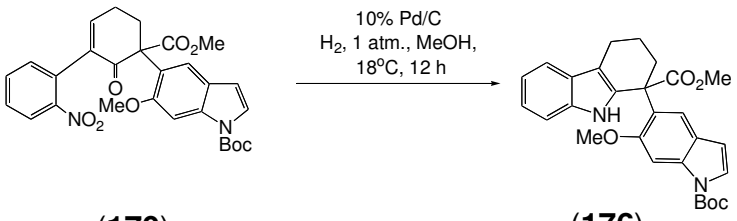
^{13}C NMR (75 MHz) δ 174.4 (C=O), 149.7 (C=O), 138.5 (CH), 135.9 (C), 131.3 (C), 130.5 (C), 129.0 (C), 127.0 (C), 126.5 (C), 122.8 (CH), 122.1 (CH), 119.4 (CH), 119.2 (CH), 118.6 (CH), 115.4 (CH), 114.1 (C), 111.0 (CH), 107.4 (CH), 83.8 (C), 53.3 (C), 52.7 (CH_3), 37.0 (CH_2), 28.1 (CH_3), 21.0 (CH_2), 19.7 (CH_2).

IR (NaCl, film) ν_{max} 3403 (NH), 2935, 1733 (C=O), 1464, 1371, 1255, 1143, 731 cm^{-1}.

EIMS *m/z* 444 ($M^{+\bullet}$, 88%), 385 (42), 329 (100).

HRMS Found: $M^{+\bullet}$, 444.2048. $C_{27}H_{28}N_2O_4$ requires $M^{+\bullet}$, 444.2049.

Methyl 1-[1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-4-yl]-2,3,4,9-tetra hydro-1*H*-carbazole-1-carboxylate (176)



(**170**) (**176**)

Green oil

Yield 75%

***R**f* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.27 (s, 1H), 7.80 (s, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 3.7 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.24–7.13 (complex m, 2H), 6.67 (s, 1H), 6.31 (d, *J* = 3.7 Hz, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 2.80–2.76 (complex m, 3H), 2.25 (complex m, 2H), 1.87 (complex m, 1H), 1.67 (s, 9H).

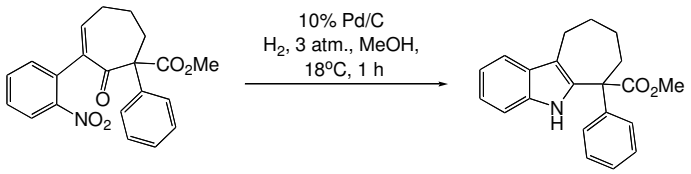
^{13}C NMR (75 MHz) δ 175.0 (C=O), 154.4 (C=O), 149.8 (C), 135.8 (C), 130.7 (C), 128.9 (C), 127.3 (C), 124.5 (CH), 123.3 (C), 122.0 (C), 121.8 (CH), 119.2 (CH), 118.5 (CH), 118.2 (C), 114.3 (CH), 111.0 (CH), 107.4 (CH), 98.3 (CH), 83.5 (C), 55.7 (C), 52.4 (CH_3), 51.0 (CH_3), 32.1 (CH_2), 28.1 (CH_3), 21.0 (CH_3), 19.3 (CH_2).

IR (NaCl, film) ν_{max} 3400 (NH), 2945, 1733 (C=O), 1623 (C=O), 1535, 1373 cm^{-1}.

EIMS (70 eV) *m/z* 474 ($M^{+\bullet}$, 91%), 415 (53), 374 (100), 359 (100).

HRMS Found: $M^{+\bullet}$, 474.2145. $C_{28}H_{30}N_2O_5$ requires $M^{+\bullet}$, 474.2155.

Methyl 5,6,7,8,9,10-hexahydro-6-phenylcyclohepta[*b*]indole-6-carboxylate (181)



(**178**) (**181**)

Green solid

Yield 71%

***R**f* 0.6 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 52–54°C.

^{1}H NMR (300 MHz) δ 8.24 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.33–7.03 (complex m, 8H), 3.81 (s, 3H), 2.90–2.85 (complex m, 2H), 2.66–2.27 (complex m, 4H), 1.86–1.62 (complex m, 2H).

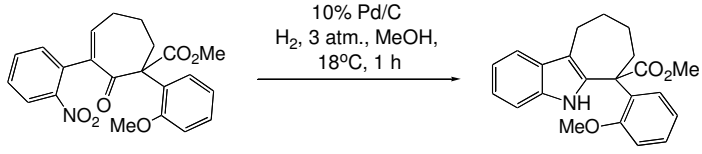
^{13}C NMR (75 MHz) δ 174.6 (C=O), 142.6 (C), 134.5 (C), 133.5 (C), 128.5 (CH), 127.8 (CH), 127.23 (CH), 127.19 (C), 121.8 (CH), 119.1 (CH), 118.4 (CH), 116.4 (C), 110.7 (CH), 58.1 (C), 52.8 (CH_3), 36.9 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 22.9 (CH_2).

IR (NaCl, film) ν_{max} 3401 (NH), 2924, 1733 (C=O), 1460, 1232 cm^{-1}.

EIMS (70 eV) *m/z* 319 ($M^{+\bullet}$, 30%), 260 (82).

HRMS Found: $M^{+\bullet}$, 319.1579. $C_{21}H_{21}NO_2$ requires $M^{+\bullet}$, 319.1572.

Methyl 5,6,7,8,9,10-hexahydro-6-(2-methoxyphenyl)cyclohept[*b*]indole-6-carboxylate (182)



(**179**) (**182**)

Green oil

Yield 95%

***R**f* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.37 (s, 1H), 7.58 (d, *J* = 6.7 Hz, 1H), 7.27–7.11 (complex m, 3H), 6.90 (d, *J* = 8.2 Hz, 2H), 6.77 (t, *J* = 7.7 Hz, 1H), 6.56 (dd, *J* = 7.7 and 1.5 Hz,

1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.94–2.90 (complex m, 2H), 2.71–2.69 (complex m, 2H), 1.80–1.72 (complex m, 4H).

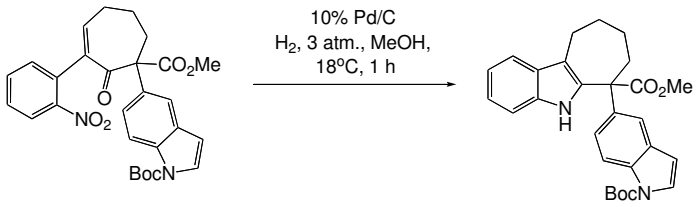
^{13}C NMR (75 MHz) δ 175.2 (C=O), 156.3 (C), 134.7 (C), 132.2 (C), 131.1 (C), 129.9 (CH), 128.4 (CH), 125.5 (C), 121.9 (CH), 120.4 (CH), 119.0 (CH), 118.4 (CH), 117.4 (C), 111.0 (CH), 110.7 (CH), 55.8 (C), 55.5 (CH_3), 52.5 (CH_3), 31.2 (CH_2), 26.2 (CH_2), 23.2 (CH_2), 21.7 (CH_2).

IR (NaCl, film) ν_{max} 3396 (NH), 2934, 1736 (C=O), 1460, 1244, 1028, 734 cm^{-1}.

EIMS (70 eV) *m/z* 349 ($M^{+\bullet}$, 51%), 290 [$(M–CO_2Me\bullet)^+$, 100].

HRMS Found: $M^{+\bullet}$, 349.1682. $C_{22}H_{23}NO_3$ requires $M^{+\bullet}$, 349.1678.

Methyl 6-[1-(1-*tert*-Butoxycarbonyl)-1*H*-indol-5-yl]-5,6,7,8,10-hexahydro hepta[*b*]indole-6-carboxylate (183)



(**180**) (**183**)

Green oil

Yield 88%

***R**$_f$* 0.7 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 8.28 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.60–7.58 (complex m, 2H), 7.24–7.03 (complex m, 5H), 6.48 (d, *J* = 3.6 Hz, 1H), 3.82 (s, 3H), 2.91–2.85 (complex m, 2H), 2.70–2.60 (complex m, 2H), 2.27–1.84 (complex m, 2H), 1.72–1.68 (complex m, 2H), 1.66 (s, 9H).

^{13}C NMR (75 MHz) δ 174.9 (C=O), 149.7 (C=O), 136.8 (C), 134.4 (C), 134.0 (C), 130.7 (C), 128.5 (C), 126.5 (CH), 125.5 (C), 123.3 (CH), 121.7 (CH), 119.8 (CH), 119.0 (CH), 118.4 (CH), 116.2 (C), 115.2 (CH), 110.7 (CH), 107.4 (CH), 83.9 (C), 57.9 (C), 52.9 (CH_3), 37.0 (CH_2), 28.1 (CH_3), 26.9 (CH_2), 25.0 (CH_2), 22.9 (CH_2).

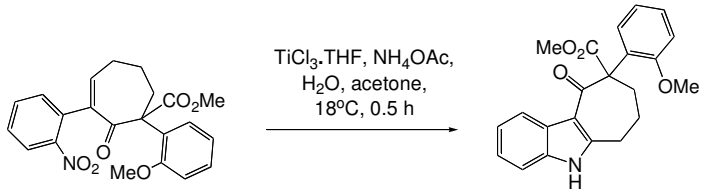
IR (NaCl, film) ν_{max} 3401 (NH), 2922, 1734 (C=O), 1462, 1371, 1143 cm^{-1}.

EIMS (70 eV) *m/z* 458 ($M^{+\bullet}$, >1%), 446 (1), 299 (24), 205 (100).

HRMS Found: $M^{+\bullet}$, 458.2214. $C_{28}H_{30}N_2O_4$ requires $M^{+\bullet}$, 458.2206.

5.2.9 Titanium Trichloride-mediated Reductive Cyclisation

Methyl 5,6,7,8,9,10-hexahydro-9-(2-methoxyphenyl)-10-oxocyclohepta[b] indole-9-carboxylate (184)



(**179**) (**184**)

Following a procedure developed by Rawal *et al*,[12] a magnetically stirred solution of titanium trichloride-tetrahydrofuran complex (750 mg, 1.80 mmol) in H_2O (2 mL) and maintained under a nitrogen atmosphere was treated with NH_4OAc (3.00 mL of a 2.5 M solution, 7.50 mmol) and acetone (3.5 mL) at 18°C, stirring was continued at this temperature for 0.25 h. The resulting dark blue solution was treated, dropwise, with a solution of α′-(*o*-nitrophenyl) enone **179** (90.0 mg, 0.23 mmol) in acetone (2.5 mL). After an additional 0.25 h the reaction mixture was diluted with water (1 x 5 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed with $NaHCO_3$ (2 x 50 mL of a saturated aqueous solution). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 20 → 40% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **184*** (57.0 mg, 68%) as a green solid.

***R**f* 0.1 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 46–48°C.

^{1}H NMR (300 MHz) δ 8.79 (s, 1H), 8.47 (dd, *J* = 6.7 and 1.8 Hz, 1H), 7.28–7.17 (complex m, 4H), 7.04 (dd, *J* = 7.7 and 1.8 Hz, 1H), 6.90 (dd, *J* = 8.3 and 1.0 Hz, 1H), 6.73 (td, *J* = 7.7 and 1.2 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 2.99 (dt, *J* = 14.8 and 4.7 Hz, 1H), 2.82–2.74 (complex m, 1H), 2.63–2.47 (complex m, 2H), 1.87–1.82 (complex m, 1H), 1.62–1.58 (complex m, 1H).

^{13}C NMR (75 MHz) δ 196.0 (C=O), 173.6 (C=O), 157.8 (C), 146.0 (C), 134.9 (C), 129.2 (CH), 128.7 (CH), 128.4 (C), 127.5 (C), 123.1 (CH), 122.5 (CH), 122.3 (CH), 120.8 (CH), 114.2 (C), 111.2 (CH), 110.5 (CH), 67.2 (C), 55.5 (CH_3), 52.4 (CH_3), 30.3 (CH_2), 27.3 (CH_2), 21.3 (CH_2).

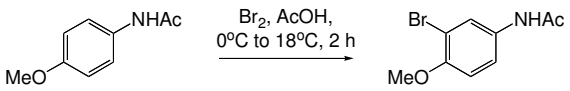
IR (NaCl, film) ν_{max} 3306 (NH), 2948, 1732 (C=O), 1600 (C=O), 1455, 1250, 752 cm^{-1}.
EIMS (70 eV) *m/z* 363 ($M^{+\bullet}$, 30%), 331 (10), 83 (95), 43 (100).
HRMS Found: $M^{+\bullet}$, 363.1470. $C_{22}H_{21}NO_4$ requires $M^{+\bullet}$, 363.1471.

5.3 Procedures Associated with Work Described in Chapter Three

*5.3.1 Synthesis of 3-Bromo-6,7,8,9-tetrahydro-2-methoxy-5*H*-carbazole (199)*

First Approach

N-(3-Bromo-4-methoxyphenyl)acetamide (195)



(**194**) (**195**)

Following a procedure developed by Lauer *et al*,[13] a magnetically stirred and cooled (ice/water bath) solution of acetanilide **194** (4.62 g, 28.0 mmol) in glacial acetic acid (13 mL) maintained under a nitrogen atmosphere was treated, dropwise, with molecular bromine (1.42 mL, 28.2 mmol) at such a rate that the internal temperature did not exceed 50°C. The resulting mixture was warmed to 18°C and stirred at this temperature for 2 h, at which time a yellow precipitate had formed. The mixture was then poured into ice water (140 mL) containing sodium bisulfite (500 mg) and the mixture stirred until the yellow colour had been discharged. The resulting solution was left to stand for 13 h at 0°C and filtered and the yellow solid retained. Recrystallisation from (4:1 v/v) ethanol/water afforded the *title compound* ***195*** (6.38 g, 87%) as a crystalline, white solid.

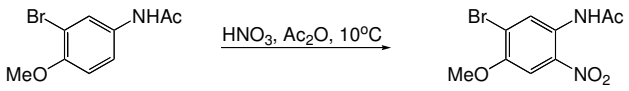
R_f 0.4 (silica, 3:7 v/v ethyl acetate/hexane).
m.p. 107–109°C (lit. 109–111°C).[13]
^{1}H NMR (300 MHz) δ 7.68 (d, *J* = 2.6 Hz, 1H), 7.44 (dd, *J* = 8.8 and 2.6 Hz, 1H), 7.09 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 3.87 (s, 3H), 2.16 (s, 3H).
^{13}C NMR (75 MHz) δ 168.2 (C=O), 152.8 (C), 131.6 (C), 125.5 (CH), 120.6 (CH), 111.9 (CH), 111.5 (CH), 56.5 (CH_3), 24.4 (CH_3).

IR (NaCl, film) ν_{max} 3306 (NH), 1663 (C=O), 1496, 1252, 1054 cm^{-1}.

EIMS (70 eV) *m/z* 245 and 243 ($M^{+\bullet}$, 68%), 203 and 201 [$(M–Ac\bullet)^{+}$, 71)], 186 and 188 (100).

HRMS Found: $M^{+\bullet}$, 244.9866. $C_9H_{10}{}^{81}BrNO_2$ requires $M^{+\bullet}$, 244.9874.

N-(5-Bromo-4-methoxy-2-nitrophenyl)acetamide (196)



(**195**) (**196**)

Following a procedure developed by Bindal *et al*,[14] a magnetically stirred and cooled (ice/water bath) solution of acetamide **195** (1.78 g, 7.28 mmol) in acetic anhydride (10 mL) maintained under a nitrogen atmosphere was treated, dropwise, with fuming nitric acid (0.82 mL, 11.9 mmol) at such a rate that the internal temperature did not exceed 10°C. The resulting mixture was poured into ice water (140 mL) and the yellow solid, thus obtained was filtered and washed with distilled water. Recrystallisation from ethanol afforded the *title compound **196*** (1.38 g, 66%) as yellow needles.

***R**f* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 173–175°C (lit. 175°C).[14]

^{1}H NMR (300 MHz) δ 9.09 (s, 1H), 7.67 (s, 1H), 3.95 (s, 3H), 2.23 (s, 3H). (NH proton exchanged with solvent).

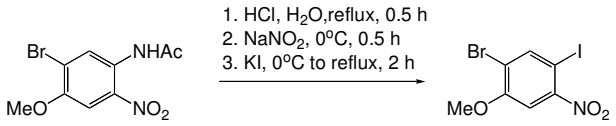
^{13}C NMR (75 MHz) δ 168.8 (C=O), 151.4 (C), 135.3 (C), 128.9 (C), 126.7 (CH), 121.6 (C), 106.7 (CH), 56.7 (CH_3), 25.5 (CH_3).

IR (NaCl, film) ν_{max} 3362 (NH), 2925, 1698 (C=O), 1579, 1506 (NO_2), 1306, 892 cm^{-1}.

EIMS (70 eV) *m/z* 290 and 288 ($M^{+\bullet}$, 28%), 248 and 246 (100), 233 and 231 (41).

HRMS Found: $M^{+\bullet}$, 287.9749. $C_9H_9{}^{79}BrNO_4$ requires $M^{+\bullet}$, 287.9746.

1-Bromo-5-iodo-2-methoxy-4-nitrobenzene (197)



(**196**) (**197**)

A magnetically stirred solution of acetamide **196** (1.15 g, 4.00 mmol) and HCl (1.00 mL of a concentrated aqueous solution), 12.0 mmol) in distilled water (1 mL) maintained under a nitrogen atmosphere was heated to reflux and stirred at reflux for 0.5 h, then cooled to 0°C (ice/water bath). The resulting reaction mixture was treated, dropwise, with a cold solution of sodium nitrite (340 mg, 4.80 mmol) in distilled water (6 mL). The solution was stirred at this temperature for an additional 0.5 h and then added dropwise to a solution of potassium iodide (960 mg, 6.00 mmol) in distilled water (6 mL). The resulting mixture was heated to reflux and stirred at reflux for 2 h then, cooled and diluted with ether (1 x 100 mL). The separated organic phase was washed with HCl (1 x 100 mL of a 1 M aqueous solution) and Na_2SO_3 solution (50 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 5 → 20% v/v ether/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **197*** (1.82 g, 72%) as a yellow solid.

***R**$_f$* 0.4 (silica, 1:9 v/v ethyl acetate/hexane).

m.p. 159–161°C.

^{1}H NMR (300 MHz) δ 8.19 (s, 1H), 7.46 (s, 1H), 3.96 (s, 3H).

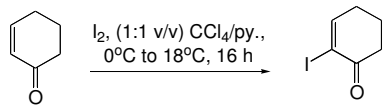
^{13}C NMR (75 MHz) δ 156.5 (C), 152.2 (C), 144.7 (CH), 118.0 (C), 108.8 (CH), 75.3 (C), 56.8 (CH_3).

IR (NaCl, film) ν_{max} 2930, 1520 (NO_2), 1471, 1300, 1055, 884 cm^{-1}.

EIMS (70 eV) *m/z* 357 and 359 ($M^{+\bullet}$, 100%), 311 and 313 (25), 296 and 298 (16), 184 and 186 (16).

HRMS Found: $M^{+\bullet}$, 356.8488. $C_7H_5{}^{79}Br^{127}INO_3$ requires $M^{+\bullet}$, 356.8498.

2-Iodocyclohexen-2-one (121)

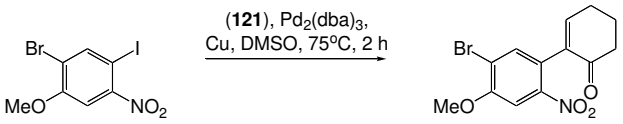


(**77**) (**121**)

Following a procedure developed by Johnson *et al*,[10] a magnetically stirred and cooled (ice/water bath) solution of the cyclohexanone (**77**) (960 mg, 10.0 mmol) in pyridine/CCl_4 (40 mL of a 1:1 v/v mixture) maintained under a nitrogen atmosphere was treated, dropwise, with a solution of molecular iodine (10.2 g, 40.0 mmol) dissolved in pyridine/CCl_4 (40 mL of 1:1 v/v/ mixture). The resulting mixture was warmed to 18°C and stirred at this temperature for 16 h, then diluted with ether (300 mL). The organic phase was washed with HCl (2 x 250 mL of a 1 M aqueous solution), distilled water (1 x 250 mL) and Na_2SO_3 (1 x 250 mL of a 1 M solution), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10 → 30% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **121*** (1.46 g, 66%) as a white solid.

***R**f* 0.4 (silica, 3:7 v/v ethyl acetate/hexane).
m.p. 44–46°C (lit. 47–49°C).[10]
^{1}H NMR (300 MHz) δ 7.26 (t, *J* = 4.4 Hz, 1H), 2.68–2.63 (complex m, 2H), 2.46–2.41 (complex m, 2H), 2.12–2.06 (complex m, 2H).
^{13}C NMR (75 MHz) δ 192.2 (C=O), 159.4 (CH), 103.8 (C), 37.2 (CH_2), 29.9 (CH_2), 22.8 (CH_2).
IR (NaCl, film) ν_{max} 2934, 1676 (C=O), 1585, 1422, 1315, 1121, 915 cm^{-1}.
EIMS (70 eV) *m/z* 222 ($M^{+\bullet}$, 87%), 193 (83), 67 (100).
HRMS Found: $M^{+\bullet}$, 221.9543. $C_6H_7{}^{127}IO$ requires $M^{+\bullet}$, 221.9542.

2-(5-Bromo-4-methoxy-2-nitrophenyl)cyclohex-2-enone (198)



(**197**) (**198**)

Following a procedure developed by Banwell *et al*,[11] a magnetically stirred mixture of nitrobenzene **197** (1.00 g, 2.80 mmol), iodoenone **121** (410 mg, 1.85 mmol), copper powder (590 mg of 99% material, CAS No. 7440-50-8), 9.25 mmol) and $Pd_2(dba)_3$ (85.0 mg, 85.0 μmol) in DMSO (10 mL) all maintained under a nitrogen atmosphere was heated to 75°C and stirred at this temperature for 2 h, then diluted with ether (50 mL). The resulting mixture was then filtered through a pad of Celite™ and the solids thus retained washed with ether (1 x 200 mL). The filtrate was washed with distilled water (2 x 100 mL) and brine (1 x 100 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 20 → 40% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **198*** (375 mg, 66%) as a yellow solid.

***R**f* 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 161–163°C.

^{1}H NMR (300 MHz) δ 7.57 (s, 1H), 7.45 (s, 1H), 6.99 (t, *J* = 7.0 Hz, 1H), 3.98 (s, 3H), 2.59–2.54 (complex m, 4H), 2.13 (t, *J* = 6.6 Hz, 2H).

^{13}C NMR (75 MHz) δ 196.5 (C=O), 155.8 (CH), 147.8 (C), 146.7 (C), 138.2 (C), 135.7 (CH), 125.3 (C), 117.4 (C), 107.4 (CH), 56.8 (CH_3), 38.2 (CH_2), 26.2 (CH_2), 22.5 (CH_2).

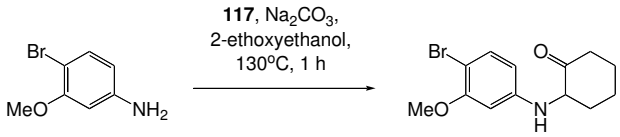
IR (NaCl, film) ν_{max} 2927, 1680 (C=O), 1525 (NO_2), 1490, 1346, 1240, 1038, 800 cm^{-1}.

EIMS (70 eV) *m/z* 327 and 325 ($M^{+\bullet}$, 45%), 280 and 278 (100).

HRMS Found: $M^{+\bullet}$, 324.9953. $C_{13}H_{12}{}^{79}BrNO_4$ requires $M^{+\bullet}$, 324.9950.

Second approach

2-(4-Bromo-3-methoxyphenylamino)cyclohexanone (201)



(**85**) (**201**)

Following a procedure developed by Campbell *et al*,[15] a magnetically stirred solution of methoxyaniline **85** (5.00 g, 25.0 mmol) in 2-ethoxyethanol (100 mL) maintained under a nitrogen atmosphere was treated with sodium carbonate (5.25 g, 50.0 mmol) and chlorocyclohexanone **117** (3.93 g, 30.0 mmol). The resulting mixture was heated to 130°C and stirred at this temperature for 1 h, then, cooled and filtered. The filtrate was concentrated under reduced pressure to give a viscous, brown oil. Subjection of this material to flash chromatography (silica, 2 → 5% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **201*** (4.83 g, 65%) as a white solid.

R_f 0.45 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 107–109°C.

^{1}H NMR (300 MHz) δ 7.26 (d, *J* = 8.5 Hz, 1H), 6.19 (d, *J* = 2.5 Hz, 1H), 6.07 (dd, *J* = 8.5 and 2.5 Hz, 1H), 3.98 (complex m, 1H), 3.83 (s, 3H), 2.67–2.55 (complex m, 2H), 2.43–2.41 (complex m, 1H), 2.19–2.14 (complex m, 1H), 1.91–1.68 (complex m, 3H), 1.43 (qd, *J* = 12.9 and 3.8 Hz, 1H), (NH proton exchanges for solvent).

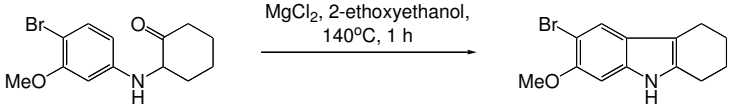
^{13}C NMR (75 MHz) δ 208.0 (C=O), 156.4 (C), 147.0 (C), 135.2 (C), 133.4 (CH), 105.5 (CH), 98.4 (CH), 61.6 (CH), 56.0 (CH_3), 41.1 (CH_2), 35.5 (CH_2), 28.0 (CH_2), 23.9 (CH_2).

IR (NaCl, film) ν_{max} 3379 (NH), 2935, 1714 (C=O), 1598, 1491, 1219, 818 cm^{-1}.

EIMS (70 eV) *m/z* 299 and 297 ($M^{+\bullet}$, 100%), 271 and 269 (67), 242 and 240 (76).

HRMS Found: $M^{+\bullet}$, 297.0372. $C_{13}H_{16}{}^{79}BrNO_2$ requires $M^{+\bullet}$, 297.0364.

3-Bromo-6,7,8,9-tetrahydro-2-methoxy-5*H*-carbazole (199)



(**201**) (**199**)

Following a procedure developed by Campiagne *et al*,[16] a magnetically stirred solution of cyclohexanone **201** (4.01 g, 13.5 mmol) in 2-ethoxyethanol (20 mL) maintained under a nitrogen atmosphere was treated with anhydrous magnesium chloride (2.50 g, 26.9 mmol). The resulting reaction mixture was heated to 140°C, stirred at this temperature for 1 h, then cooled and diluted with dichloromethane (200 mL). The organic phase was washed with distilled water (3 x 250 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10 → 20% v/v ethyl acetate/petroleum spirit gradient elution) provided, after concentration of the appropriate fractions, the *title compound **199*** (2.15 g, 57%) as a white solid.

***R**f* 0.52 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 135–137°C.

^{1}H NMR (300 MHz) δ 7.59 (s, 1H), 7.58 (s, 1H), 6.84 (s, 1H), 3.90 (s, 3H), 2.69 (t, *J* = 5.6 Hz, 2H), 2.62 (t, *J* = 5.6 Hz, 2H), 1.87 (complex m, 4H).

^{13}C NMR (75 MHz) δ 151.2 (C), 135.2 (C), 133.7 (C), 125.5 (C), 121.8 (CH), 109.6 (C), 103.8 (C), 94.7 (CH), 56.6 (CH_3), 23.2 (CH_2), 23.1 (CH_2), 23.0 (CH_2), 20.7 (CH_2).

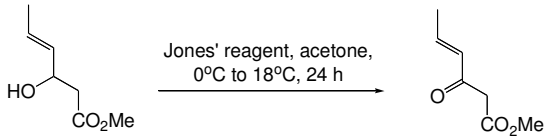
IR (NaCl, film) ν_{max} 3357 (NH), 2920, 1682, 1464, 1306, 1162 cm^{-1}.

EIMS (70 eV) *m/z* 281 and 279 ($M^{+\bullet}$, 100%), 266 and 264 (65).

HRMS Found: $M^{+\bullet}$, 279.0258. $C_{13}H_{14}{}^{79}BrNO$ requires $M^{+\bullet}$, 279.0259.

5.3.2 Synthesis of "Upper" Hemisphere Analogue

Methyl (*E*)-3-oxohex-4-enoate (190)



(**204**) (**190**)

Following a procedure developed by Zibuck *et al*,[17] Jones' reagent was prepared by the addition of H_2SO_4 (30.0 mL of a concentrated aqueous solution, 48.9 mmol) to a solution of chromium trioxide (33.5 g, 40.3 mol) in water (20 mL) followed by slow addition of distilled water to give 250 mL total volume. A magnetically stirred and chilled (ice/water bath) solution of β-hydroxyester **204**[18] (5.10 g, 36.0 mmol) in acetone (10 mL) maintained under a nitrogen atmosphere was treated, dropwise, with Jones' reagent (36.0 mL. 36.0 mmol). The reaction mixture was warmed to 18°C, stirred at this temperature for 24 h, then quenched with methanol (10 mL) and diluted with ether (1 x 200 mL). The separated organic phase was washed with distilled water (3 x 100 mL), $NaHCO_3$ (2 x 100 mL of a saturated aqueous solution) and brine (2 x 100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 5 → 10% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **190*** (4.90 g, 80%) as a clear, yellow oil.

***R**f* 0.3 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 6.85 (complex m, 1H), 6.08 (dd, *J* = 15.7 and 1.7 Hz, 1H), 4.92 (s, 2H), 3.68 (s, 3H), 1.88 (dd, *J* = 7.0 and 1.4 Hz, 3H).

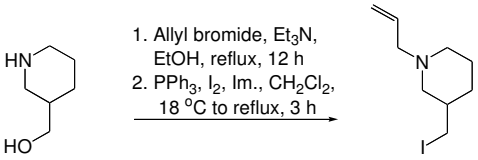
^{13}C NMR (75 MHz) δ 191.8 (C=O), 167.8 (C=O), 145.3 (CH), 131.0 (CH), 52.2 (CH_3), 46.3 (CH_2), 18.3 (CH_2).

IR (NaCl, film) ν_{max} 3323 (OH), 2955, 1745 (C=O), 1673 (C=O), 1433, 1240, 968 cm^{-1}.

EIMS (70 eV) *m/z* 142 ($M^{+\bullet}$, 100%), 127 (73), 101 (36).

HRMS Found: $M^{+\bullet}$, 142.0636. $C_7H_{10}O_3$ requires $M^{+\bullet}$, 142.0630.

1 – Allyl – 3 – (iodomethyl)piperidine (208)



(**207**) (**208**)

Following a procedure developed by Slusarchyk *et al*[19] and Magnus *et al*,[20] a magnetically stirred mixture of piperidinylmethanol **207** (1.15 g, 10.0 mmol) and triethylamine (14.0 mL, 100 mmol) in ethanol (20 mL) all maintained at 18°C under a nitrogen atmosphere was treated with allyl bromide (0.18 mL, 20.0 mmol) then heated to reflux and stirred at reflux for 12 h. After cooling, the reaction mixture was concentrated under reduced pressure, the residue dissolved in dichloromethane (200 mL) and the resulting solution washed with K_2CO_3 (3 x 300 mL of a 5% aqueous solution). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. A solution of this material in dichloromethane (50 mL) at 18°C under a nitrogen atmosphere was treated with triphenylphosphine (5.85 g, 22.5 mmol) and iodine (5.69 g, 22.5 mmol). The resulting reaction mixture was stirred for 0.25 h then imidazole (1.70 g, 25.0 mmol) was added in one portion and the resulting mixture heated to reflux and stirred at reflux for 3 h. After cooling, the reaction mixture was diluted with dichloromethane (1 x 200 mL) and washed with sodium thiosulfate (1 x 100 mL of a 5% aqueous solution) and brine (1 x 100 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10% v/v ethyl acetate/hexane 5% Et_3N elution) provided, after concentration of the appropriate fractions, the *title compound **208*** (1.35 g, 51%) as a clear, colourless, oil.

R_f 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 5.85 (complex m, 1H), 5.09 (complex m, 2H), 3.09 (complex m, 2H), 2.95 (complex m, 3H), 2.74 (d, J = 11.1 Hz, 1H), 1.93–1.54 (complex m, 6H), 1.05–0.98 (complex m, 1H).

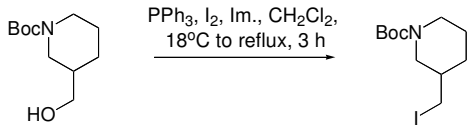
^{13}C NMR (75 MHz) δ 135.1 (CH), 117.8 (CH_2), 61.9 (CH_2), 59.7 (CH_2), 53.8 (CH_2), 38.2 (CH), 31.2 (CH_2), 24.7 (CH_2), 11.5 (CH_2).

IR (NaCl, film) ν_{max} 2931, 1464, 1191, 919 cm^{-1}.

EIMS (70 eV) *m/z* 265 ($M^{+\bullet}$, 5%), 138 (100).

HRMS Found: $M^{+\bullet}$, 265.0326. $C_9H_{16}{}^{127}IN$ requires $M^{+\bullet}$, 265.0328.

tert-Butyl 3-(iodomethyl)piperidine-1-carboxylate (210)



(**209**) (**210**)

Following a procedure developed by Slusarchyk *et al*,[19] a magnetically stirred solution of *tert*-butyl-3-(hydroxymethyl)piperidine-1-carboxylate (**209**) (2.15 g, 10.0 mmol) in dichloromethane (100 mL) at 18°C under a nitrogen atmosphere was treated with triphenylphosphine (5.85 g, 22.5 mmol) and iodine (5.69 g, 22.5 mmol). The reaction mixture was stirred for 0.25 h then imidazole (1.70 g, 25.0 mmol) was added in one portion and the resulting solution heated to reflux and stirred at reflux for 3 h. After cooling, the reaction mixture was diluted with dichloromethane (1 x 200 mL) and the organic phase washed with sodium thiosulfate (1 x 100 mL of a 5% aqueous solution) and brine (1 x 100 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10% v/v ethyl acetate/hexane 5% Et_3N elution) provided, after concentration of the appropriate fractions, the *title compound **210*** (2.67 g, 82%) as an opaque, white solid.

m.p 32–34°C.

R_f 0.3 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 4.04 (d. *J* = 10.6 Hz, 1H), 3.83 (dt, *J* = 13.3 and 3.8 Hz, 1H), 3.07 (d, *J* = 6.5 Hz, 2H), 2.84 (complex m, 1H), 2.60 (t, *J* = 9.9 Hz, 1H), 1.94–1.89 (complex m, 1H), 1.67–1.60 (complex m, 2H), 1.46 (s, 9H), 1.29–1.17 (complex m, 2H).

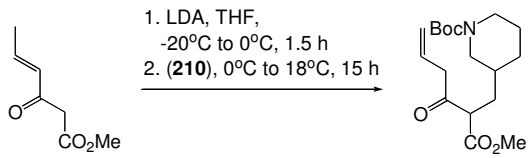
^{13}C NMR (75 MHz) δ 154.7 (C=O), 79.6 (C), 49.6 (CH_2), 41.1 (CH_2), 38.0 (CH_2), 31.4 (CH), 28.4 (CH_3), 24.3 (CH_2), 9.8 (CH_2).

IR (NaCl, film) ν_{max} 2930, 1693 (C=O), 1422, 1156 cm^{-1}.

EIMS (70 eV) *m/z* 325 ($M^{+\bullet}$, 20%), 269 (42), 199 (45), 57 (100).

HRMS Found: $M^{+\bullet}$, 325.0536. $C_{11}H_{20}{}^{127}INO_2$ requires $M^{+\bullet}$, 325.0539.

tert-Butyl-(2-(methoxycarbonyl)-3-oxohex-5-enyl)piperidine-1-carboxylate (212)



(**190**) (**212**)

A magnetically stirred solution of diisopropylamine (370 μL, 3.71 mmol) in THF (10 mL) maintained at –20°C (NaCl/ice bath) under a nitrogen atmosphere was treated, dropwise, with *n*-butyllithium (2.30 mL of a 1.6 M solution in hexanes, 3.68 mmol). The reaction mixture was stirred for an additional 0.5 h at –20°C. The resulting reaction mixture was treated, *via* cannula, with a solution of β-ketoester **190** (390 mg, 3.10 mmol) in THF (2 mL) and warmed to 0°C (ice/water bath), stirred at this temperature for 0.5 h then *tert*–butyl 3–(iodomethyl)piperidine-1-carboxylate (**210**) (1.00 g, 3.07 mmol) was added. The resulting solution was warmed to 18°C and stirred at this temperature for 15 h, then poured into a beaker of cold distilled water (150 mL) and extracted with ether (2 x 50 mL). The combined organic phases were washed with distilled water (3 x 50 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 5 → 20% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **212*** (806 mg, 80%) as a clear, colourless oil.

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (rotomers) δ 5.60 (complex m, 1H), 5.27 (complex m, 2H), 3.85 (complex m, 2H), 3.72 (s, 3H), 3.55 (dd, *J* = 4.5 and 2.1 Hz, 2H), 3.43 (complex m, 1H), 2.78 (complex m, 2H), 2.56–2.52 (complex m, 2H), 1.76 (complex m, 2H), 1.64–1.59 (complex m, 3H), 1.44 (s, 9H).

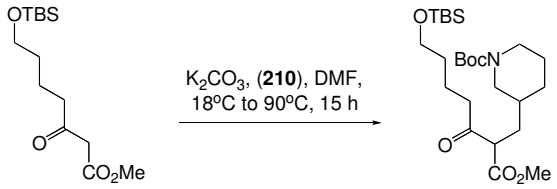
^{13}C NMR (75 MHz) (rotomers) δ 202.7 (C=O), 167.5 (C=O), 154.8 (C=O), 135.2 (CH), 135.0 (CH), 119.9 (CH), 119.7 (CH), 79.3 (C), 55.0 (CH), 54.9 (CH_3), 52.3 (CH_3), 47.5 (CH_2), 47.4 (CH_2), 33.6 (CH_2), 33.4 (CH_2), 33.2 (CH_2), 32.7 (CH_2), 31.3 (CH_2), 30.7 (CH_3), 28.4 (CH_3), 24.6 (CH_2), 24.5 (CH_2).

IR (NaCl, film) ν_{max} 2924, 1750 (C=O), 1688 (C=O), 1423, 1241, 1149 cm^{-1}.

ESIMS *m/z* 362 [$(M + Na)^+$, 100%], 325 (33), 283 (16).

HRMS (ESI) Found: $(M + Na)^+$, 362.1983. $C_{18}H_{29}NO_5Na$ requires $(M + Na)^+$, 362.1943.

tert-Butyl-3-(2-(methoxycarbonyl)-7-*tert*-butyl-dimethylsiloxy-3-oxocycloheptyl)piperidine-1-carboxylate (216)



(**217**) (**216**)

A magnetically stirred solution of β-ketoester **217** (600 mg, 2.10 mmol) in DMF (10 mL) at 18°C maintained under a nitrogen atmosphere was treated with potassium carbonate (238 mg, 2.50 mmol) and *tert*–butyl 3–(iodomethyl)piperidine-1-carboxylate (**210**) (715 mg, 2.20 mmol). The resulting reaction mixture was heated to 90°C, stirred at this temperature for 15 h, then cooled and poured into a beaker of cold distilled water (150 mL) and then extracted with dichloromethane (2 x 50 mL). The combined organic phases were washed with distilled water (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 5 → 20% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compound **216*** (765 mg, 75%) as a clear, colourless oil.

R_f 0.3 (1:9 v/v ethyl acetate/hexane),

^{1}H NMR (300 MHz) δ 3.73 (complex m, 2H), 3.72 (s, 3H), 3.59 (t, J = 6.3 Hz, 2H), 2.6–2.56 (complex m, 6H), 1.70 – 1.48 (complex m, 10H), 1.44 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H).

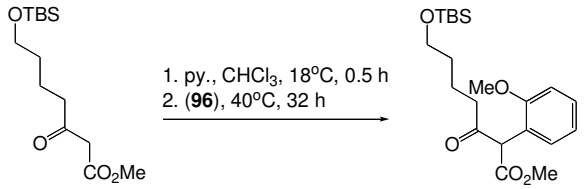
^{13}C NMR (75 MHz) (rotomers) δ 204.9 (C=O), 170.3 (C=O), 170.1 (C=O), 154.74 (C=O), 154.70 (C=O), 79.4 (C), 62.7 (CH_2), 61.7 (CH_2), 56.2 (CH), 56.0 (CH), 52.5 (CH_3), 52.3 (CH_3), 48.9 (CH_2), 42.0 (CH_2), 41.6 (CH_2), 33.74 (CH_2), 33.70 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 30.7 (CH_2), 30.6 (CH), 30.3 (CH), 28.43 (CH_3), 28.40 (CH_3), 25.9 (CH_3), 25.0 (CH_2), 24.9 (CH_2), 24.4 (CH_2), 24.3 (CH_2), 19.92 (C), 19.90 (C), -5.4 (CH_3).

IR (NaCl, film) ν_{max} 2930, 1743 (C=O), 1693 (C=O), 1427, 1366, 1256 cm^{-1}.

EIMS (70 eV) *m/z* 485 ($M^{+\bullet}$, >1%), 372 (73), 282 (57), 296 (100).

HRMS Found: $M^{+\bullet}$, 485.3172. $C_{25}H_{47}NO_6Si$ requires $M^{+\bullet}$, 485.3173.

Methyl 7-*tert*-butyldimethylsiloxy-2-(2-methoxyphenyl)-3-oxoheptane carboxylate (222)



(**217**) (**222**)

Following a procedure developed by Pinhey *et al*,[8] a magnetically stirred solution of β-ketoester **217** (600 mg, 2.10 mmol) in chloroform (3 mL) at 18°C maintained under a nitrogen atmosphere was treated with pyridine (0.50 mL, 6.30 mmol) and stirred for 0.5 h then treated with lead triacetate **96** (1.00 g, 2.11 mmol). The resulting mixture was heated to 40°C, stirred at this temperature for 32 h then cooled and quenched with HCl (drop of 1 M aqueous solution) and then diluted with ether (1 x 100 mL). The resulting solution was washed with HCl (1 x 100 mL of a 1 M aqueous solution) and distilled water (2 x 100 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 10 → 30% v/v ethyl acetate/petroleum spirit gradient elution) provided, after concentration of the appropriate fractions, the *title compound **222*** (640 mg, 78%) as a clear, colourless oil.

***R**_f* 0.44 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (keto form-major isomer) δ 7.28–7.24 (complex m, 1H), 6.97–6.92 (complex m, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.38 (t, *J* = 7.8 Hz, 2H), 1.58 (complex m, 2H), 1.43 (complex m, 2H), 0.86 (s, 9H), 0.01 (s, 6H). (enolic form-minor isomer) 5.22 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.48 (t, *J* = 6.3 Hz, 2H), 2.05 (complex m, 2H), 0.85 (s, 9H), -0.01 (s, 6H), (other signals overlapping).

^{13}C NMR (75 MHz) (keto form-major isomer) δ 204.4 (C=O), 169.5 (C=O), 156.7 (C), 129.9 (CH), 129.3 (CH), 121.4 (C), 120.9 (CH), 110.7 (CH), 62.7 (CH_2), 57.3 (CH), 55.6 (CH_3), 52.5 (CH_3), 41.4 (CH_2), 31.9 (CH_2), 25.9 (CH_3), 20.1 (CH_2), 18.3 (C), -5.4 (CH_2). (enolic form-minor isomer) δ 176.8 (C), 173.4 (C=O). 136.1 (CH), 130.6 (CH), 121.8 (C), 120.3 (CH), 102.1 (C), 55.4 (CH_3), 51.7 (CH_3), 32.3 (CH_2), 32.1 (CH_2), 22.7 (CH_2), (other signals overlapping).

IR (NaCl, film) ν_{max} 2953, 1751 (C=O), 1718 (C=O), 1464, 1248, 885 cm^{-1}.

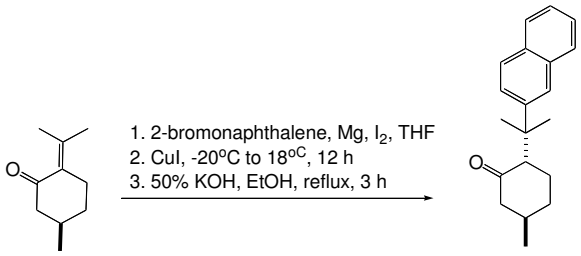
EIMS (70 eV) *m/z* 394 ($M^{+\bullet}$, 1%), 337 (100), 305 (91).

HRMS Found: $M^{+\bullet}$, 394.2178. $C_{21}H_{34}O_5Si$ requires $M^{+\bullet}$, 394.2176.

5.4 Procedures Associated with Work Described in Chapter Four

5.4.1 Preparation of (+)-(1R,2S,5R)-5-Methyl-2-(2-(naphthalen-3-yl) propan-2-yl)cyclohexyl)cyclohexanol (244)

(-)-(2*S*, 5*R*)-5-Methyl-2-[2-(naphthen-3-yl)propan-2-yl]cyclohexanone (248)



(**246**) (**248**)

Following a procedure developed by Yang *et al*,[21] a three-necked round bottomed flask equipped with a nitrogen inlet and an addition flask containing a solution of 2-bromonapthalene (3.45 g, 17.1 mmol) in THF (40 mL) maintained under a nitrogen atmosphere was treated with magnesium turnings (560 mg, 23.6 mmol), 2-bromonaphthalene (1.00 g, 4.85 mmol) in THF (5 mL) and a few crystals of iodine. As soon as the Grignard reagent began to form, the 2-bromonapthalene solution was added slowly. The reaction vessel was then cooled to –20°C (NaCl/ice bath) and treated with CuI (290 mg, 1.53 mmol). After stirring for 0.5 h at this temperature, the reaction mixture was treated, dropwise, with a solution of (*R*)-pulegone (**246**) (2.28 g, 15.0 mmol) in THF (20 mL). The resulting reaction mixture was warmed to 18°C, stirred at this temperature for 12 h then cooled to 0°C (ice/water bath) and quenched with ammonium chloride (1 x 20 mL of a saturated aqueous solution) and HCl (1 x 20 mL of a 6 M aqueous solution). The separated aqueous phase was extracted with ether (2 x 200 mL) and the combined organic phases were washed with brine (1 x 100 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to leave a clear, yellow oil.

A solution of this material in EtOH (50 mL) was treated with KOH (10 mL of a 50% aqueous solution) and the resulting solution heated to reflux and stirred at reflux for 3 h, cooled and treated with distilled water (30 mL) and then extracted with ether (2 x 150 mL). The combined organic phases were washed with HCl (1 x 100 mL of 1 M aqueous

solution), $NaHCO_3$ (1 x 100 mL of a saturated aqueous solution), distilled water (1 x 100 mL) and brine (1 x 100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless, yellow oil. Subjection of this material to flash chromatography provided, after concentration of the appropriate fractions, the *title compound* ***248*** (1.63 g, 60%) as a clear oil.

R_f 0.3 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.85–7.77 (complex m, 4H), 7.56 (complex m, 3H), 2.80 (dd, *J* = 13.0 and 4.8 Hz, 1H), 2.27 (ddd, *J* = 12.6, 4.2 and 1.2 Hz, 1H), 2.06 (td, *J* = 12.6 and 1.2 Hz, 1H), 1.80–1.73 (complex m, 2H), 1.60 (s, 3H), 1.55 (s, 3H), 1.55–1.16 (complex m, 3H), 0.88 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR (75 MHz) δ 211.2 (C=O), 147.3 (C), 133.2 (C), 131.6 (C), 128.0 (CH), 127.5 (CH), 127.3 (CH), 125.8 (CH), 125.3 (CH), 124.5 (CH), 124.1 (CH), 59.7 (CH), 52.3 (CH_2), 39.2 (C), 36.2 (CH_2), 34.6 (CH), 29.1 (CH_3), 26.7 (CH_3), 23.4 (CH_2), 22.2 (CH_3).

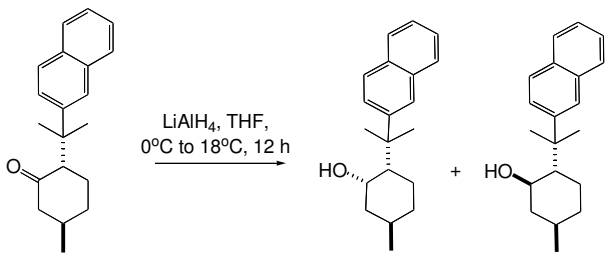
IR (NaCl, film) ν_{max} 2953, 1709 (C=O), 1454, 1120, 749 cm^{-1}.

EIMS (70 eV) *m/z* 280 ($M^{+\bullet}$, 91%), 170 (100).

HRMS Found: $M^{+\bullet}$, 280.1829. $C_{20}H_{24}O$ requires $M^{+\bullet}$, 280.1827.

Specific Rotation $[\alpha]_D$ -44.1 (*c* = 1.7, $CHCl_3$).

(+)-(1*S*,2*S*,5*R*)-5-Methyl-2-(2-(naphthalen-3-yl)propan-2-yl)cyclohexyl) cyclohexanol (244) and (-)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-(naphthalen-3-yl)propan-2-yl)cyclohexyl)cyclohexanol (249)



(**248**) (**244**) (**249**)

Following a procedure developed by Yang *et al*,[21] a magnetically stirred and cooled (ice/water bath) solution of cyclohexanone **248** (800 mg, 2.86 mmol) in THF (5 mL) under a nitrogen atmosphere was treated with $LiAlH_4$ (5.74 mL of a 1 M solution in THF, 5.74 mmol). The resulting mixture was warmed to 18°C, stirred at this temperature for 12 h, then quenched with ammonium chloride (1 x 5 mL of a saturated

aqueous solution) followed by HCl (1 x 10 mL of 2 M aqueous solution) and extracted with dichloromethane (2 x 100 mL). The combined organic phases were washed with distilled water (1 x 50 mL) and brine (1 x 50 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash chromatography (silica, 3 → 5% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the *title compounds* ***244*** (482 mg, 60%) and ***249*** (321 mg, 40%) as clear, colourless oils.

Compound 244

R_f 0.3 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.85–7.78 (complex m, 4H), 7.54 (dd, *J* = 8.9 and 1.8 Hz, 1H), 7.48–7.43 (complex m, 2H), 3.86 (complex m, 1H), 1.72–1.57 (complex m, 6H), 1.51 (s, 3H), 1.47 (s, 3H), 1.09–0.99 (complex m, 2H), 0.83 (d, *J* = 6.2 Hz, 3H), (OH proton exchanges with solvent).

^{13}C NMR (75 MHz) δ 147.5 (C), 133.3 (C), 131.6 (C), 128.0 (CH), 127.5 (CH), 127.3 (CH), 125.8 (CH), 125.3 (CH), 125.2 (CH), 124.3 (CH), 68.3 (CH), 51.8 (CH_2), 49.3 (CH), 40.4 (C), 35.6 (CH_2), 27.7 (CH_3), 26.2 (CH), 25.7 (CH_3), 22.2 (CH_2), 21.6 (CH_3).

IR (NaCl, film) ν_{max} 3435 (OH), 2919, 1455, 816, 745 cm^{-1}.

EIMS (70 eV) *m/z* 282 ($M^{+\bullet}$, 58%), 264 (24), 169 (100).

HRMS Found: $M^{+\bullet}$, 282.1984. $C_{20}H_{26}O$ requires $M^{+\bullet}$, 282.1984.

Specific Rotation $[\alpha]_D$ +28.4 (*c* = 1.0, $CHCl_3$).

Compound 249

R_f 0.2 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.83–7.77 (complex m, 4H), 7.54 (dd, *J* = 8.9 and 1.8 Hz, 1H), 7.49–7.43 (complex m, 2H), 3.60 (td, *J* = 10.1 and 4.1 Hz, 1H), 1.88–1.74 (complex m, 3H), 1.70–1.61 (m. 3H), 1.55 (s, 3H), 1.38 (s, 3H), 1.10–0.92 (complex m, 2H), 0.88 (d, *J* = 6.3 Hz, 3H), (OH proton exchanges solvent).

^{13}C NMR (75 MHz) δ 149.0 (C), 133.4 (C), 131.7 (C), 128.01 (CH), 127.96 (CH), 127.4 (CH), 126.0 (CH), 125.5 (CH), 125.2 (CH), 123.2 (CH), 73.3 (CH), 53.8 (CH_2), 45.4 (CH), 40.0 (C), 34.9 (CH_3), 31.5 (CH_3), 28.3 (CH), 26.6 (CH_2), 24.7 (CH_2), 22.0 (CH_3).

IR (NaCl, film) ν_{max} 3435 (OH), 2919, 1455, 816, 745 cm^{-1}.

EIMS (70 eV) *m/z* 282 ($M^{+\bullet}$, 58%), 262 (24), 170 (100).

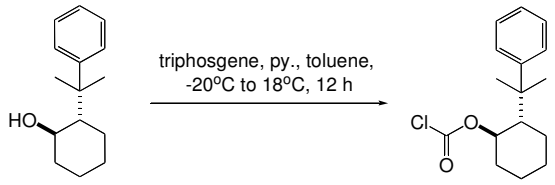
HRMS Found: $M^{+\bullet}$, 282.1984. $C_{20}H_{26}O$ requires $M^{+\bullet}$, 282.1984.

Specific Rotation $[\alpha]_D$ -28.2 (*c* = 1.0, $CHCl_3$).

5.4.2 General Procedure for Synthesis of Chiral Chloroformates 251 - 253

Following a procedure developed by Comins *et al*,[22] a magnetically stirred solution of triphosgene (126 mg, 0.43 mmol) in toluene (5 mL) maintained at –20°C (NaCl/ice bath) under a nitrogen atmosphere was treated with the appropriate chiral alcohol (1.00 mmol) then, over the period of 0.1 h, a solution of pyridine (0.14 mL, 1.10 mmol) in toluene (5 mL). The reaction mixture was then warmed to 18°C, stirred at this temperature for 12 h then filtered and the filtrate washed with distilled water (2 x 20 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 0 → 5% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the relevant chiral chloroformate as either a clear, colourless oil or white solid.

(-)-(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl chloroformate (251)



(**243**) (**251**)

Clear, colourless oil

R_f 0.3 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.35–7.18 (complex m, 5H), 4.77 (dt, *J* = 11.0 and 4.5 Hz, 1H), 2.06–2.04 (complex m, 2H), 1.70–1.64 (complex m, 4H), 1.37 (s, 3H), 1.31 (s, 3H), 1.29–1.07 (complex m, 3H).

^{13}C NMR (75 MHz) δ 151.8 (C=O), 149.8 (C), 128.2 (CH), 125.6 (CH), 125.4 (CH), 84.3 (CH), 51.0 (CH), 40.0 (C), 32.7 (CH_2), 27.2 (CH_2), 26.7 (CH_2), 26.6 (CH_3), 25.5 (CH_3), 24.5 (CH_2).

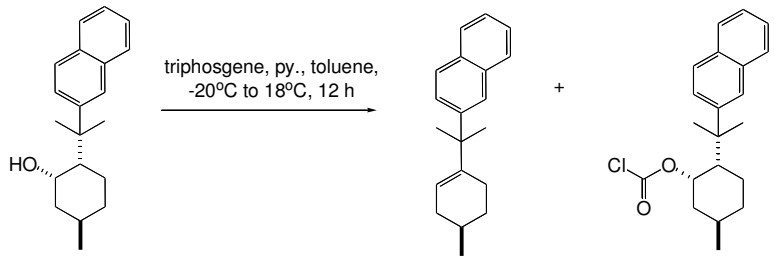
IR (NaCl, film) ν_{max} 2934, 1771 (C=O), 1170, 700 cm^{-1}.

EIMS (70 eV) *m/z* 280 ($M^{+\bullet}$, 6%), 200 (30), 119 (100).

HRMS Found: $M^{+\bullet}$, 280.1234. $C_{16}H_{21}{}^{35}ClO_2$ requires $M^{+\bullet}$, 280.1230.

Specific Rotation $[\alpha]_D$ -31.0 (*c* = 2.0, CH_3OH).

(+)-2-(2*R*)-4-Methylcyclohex-1-enyl)propan-2-yl)naphthalene (252) and (+)-(1*S*,2*S*,5*R*)-(-)-5-Methyl-2-[2-(naphthyl-3-yl)propan-2-yl]cyclohexyl chloroformate (254)



(**244**) (**252**) (**254**)

Compound 252

Clear, colourless oil

R_f 0.4 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.83–7.72 (complex m, 4H), 7.48–7.38 (complex m, 3H), 5.74 (t, *J* = 2.1 Hz, 1H), 2.20 (complex m, 1H), 1.81–1.52 (complex m, 6H), 1.50 (s, 3H), 1.46 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (75 MHz) δ 146.9 (C), 143.9 (C), 133.4 (C), 131.7 (C), 127.8 (CH), 127.41 (CH), 127.35 (CH), 125.75 (CH), 125.70 (CH), 125.2 (CH), 123.7 (CH), 119.6 (CH), 43.6 (C), 34.3 (CH_2), 31.5 (CH_2), 28.8 (CH), 28.4 (CH_3), 27.6 (CH_3), 25.6 (CH_2), 21.8 (CH_3).

IR (NaCl, film) ν_{max} 2948, 1599, 1363, 817, 744 cm^{-1}.

EIMS (70 eV) *m/z* 264 ($M^{+\bullet}$, 94%), 249 [$(M - Me\bullet)^+$, 100].

HRMS Found: $M^{+\bullet}$, 264.1880. $C_{20}H_{24}$ requires $M^{+\bullet}$, 264.1878.

Specific Rotation $[\alpha]_D$ +21.6 (*c* = 1.0, $CHCl_3$).

Compound 254

Clear, colourless oil

R_f 0.3 (silica 5% v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.88–7.77 (complex m, 4H), 7.53–7.45 (complex m, 3H), 4.88 (complex m, 1H), 2.01 (complex m, 1H), 1.84–1.68 (m. 4H), 1.51 (s, 3H), 1.49 (s, 3H), 1.11–0.91 (complex m, 3H), 0.88 (d, *J* = 6.3 Hz, 3H)

^{13}C NMR (75 MHz) δ 149.3 (C=O), 146.1 (C), 133.3 (C), 131.7 (C), 128.0 (CH), 127.9 (CH), 127.3 (CH), 126.0 (CH), 125.6 (CH), 124.3 (CH), 123.2 (CH), 81.6 (CH), 50.8 (CH), 40.1 (C), 40.0 (CH_2), 34.9 (CH_2), 27.5 (CH), 26.6 (CH_3), 25.0 (CH_3), 22.0 (CH_2), 21.8 (CH_3).

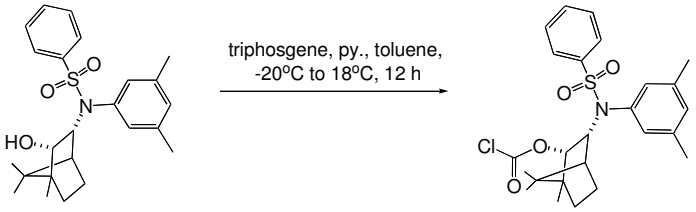
IR (NaCl, film) ν_{max} 2949, 1775 (C=O), 1129, 817 cm^{-1}.

EIMS (70 eV) *m/z* 344 ($M^{+\bullet}$, >1%), 264 (70), 249 (81), 169 (100).

HRMS Found: $M^{+\bullet}$, 344.1548. $C_{21}H_{25}{}^{35}ClO_2$ requires $M^{+\bullet}$, 344.1543.

Specific Rotation $[\alpha]_D$ +28.6 (*c* = 1.0, $CHCl_3$).

(+)-(1*R*,2*S*,3*R*)-3-[*N*-Benzenesulfonyl-*N*-(3,5-dimethylphenyl)-amino]-2-bornanyl chloroformate (253)



(**245**) (**253**)

White solid

***R**$_f$* 0.3 (silica, 1:4 v/v ethyl acetate/hexane).

m.p. 59–61°C.

^{1}H NMR (300 MHz) δ 7.48–7.29 (complex m, 6H), 6.80 (s, 2H), 5.88 (s, 1H), 5.07 (d, *J* = 7.0 Hz, 1H), 3.81 (d, *J* = 7.0 Hz, 1H), 2.17 (s, 3H), 2.00 (s, 3H), 1.91–1.48 (complex m, 2H), 1.24–1.16 (complex m, 2H), 0.83 (s, 3H), 0.79 (s, 3H), 0.54 (s, 3H).

^{13}C NMR (75 MHz) δ 150.3 (C=O), 138.4 (C), 136.7 (C), 132.8 (C), 129.7 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 89.0 (CH), 66.7 (CH), 50.5 (C), 48.4 (CH), 47.5 (C), 31.7 (CH_2), 27.6 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 11.1 (CH_3).

IR (NaCl, film) ν_{max} 2959, 1780 (C=O), 1354, 1169, 703 cm^{-1}.

EIMS (70 eV) *m/z* 475 ($M^{+\bullet}$, 1%), 413 (15), 334 (70), 254 (100).

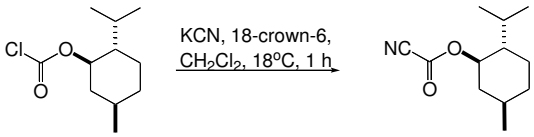
HRMS Found: $M^{+\bullet}$, 475.1587. $C_{25}H_{30}{}^{35}ClNO_4S$ requires $M^{+\bullet}$, 475.1584.

Specific Rotation $[\alpha]_D$ +25.0 (*c* = 0.5, $CHCl_3$).

5.4.3 General Procedure for Synthesis of Chiral Cyanoformates 255 - 258

Following a procedure developed by Childs *et al*,[23] a magnetically stirred solution of the appropriate chiral chloroformate (1.00 mmol) maintained at 18°C under a nitrogen atmosphere was treated with potassium cyanide (71.0 mg, 1.08 mmol) and 18-crown-6 (5.00 mg, 0.02 mmol) in dichloromethane (5 mL). The resulting reaction mixture was stirred at this temperature for 1 h then filtered and the filtrate was concentrated under reduced pressure to a give clear, yellow oil. Subjection of this material to Kugelrohr distillation or flash chromatography (silica, 0 → 10% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the relevant chiral cyanoformate as a either a clear, colourless oil or white solid.

(-)-(1*S*,2*R*,5S)-2-isopropyl-5-methylcyclohexyl cyanoformate (255)



(**250**) (**255**)

Clear, colourless oil

***R**f* 0.4 (silica, 1:9 v/v ethyl acetate/hexane).

b.p. 60 – 63°C (20 mm/Hg)

^{1}H NMR (300 MHz) δ 4.88 (dt, *J* = 11.0 and 4.3 Hz, 1H), 2.06–2.02 (complex m, 1H), 1.88–1.83 (complex m, 1H), 1.76–1.69 (complex m, 2H), 1.54–1.45 (complex m, 2H), 1.19–0.96 (complex m, 2H), 0.93 (complex m, 6H), 0.76 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz) δ 144.0 (C=O), 109.5 (CN), 80.7 (CH), 46.5 (CH), 40.1 (CH_2), 33.7 (CH_2), 31.4 (CH), 26.1 (CH), 23.1 (CH_2), 21.8 (CH_3), 20.6 (CH_3), 16.0 (CH_3).

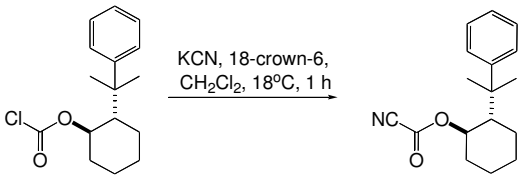
IR (NaCl, film) ν_{max} 2959, 2873, 2244 (CN), 1744 (C=O), 1456, 1251, 945 cm^{-1}.

EIMS (70 eV) *m/z* 138 [$(M–CO_2CN•)^+$, 56%], 123 (44), 81 (100).

HRMS Found: $(M–CO_2CN•)^+$, 138.1409. $C_{10}H_{18}$ requires $(M–CO_2CN•)^+$, 138.1409.

Specific Rotation $[\alpha]_D$ -42.0 (*c* = 1.0, $CHCl_3$).

(-)-(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)cyclohexyl cyanoformate (256)



(**251**) (**256**)

Clear, colourless oil

R_f 0.3 (silica, 1:99 v/v ethyl acetate/hexane)

^{1}H NMR (300 MHz) δ 7.37–7.19 (complex m, 5H), 4.96 (dt, *J* = 10.3 and 4.0 Hz, 1H), 2.16 (td, *J* = 11.1 and 3.9 Hz, 1H), 1.91–1.88 (complex m, 2H), 1.74–1.72 (complex m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 1.26–1.13 (complex m, 4H).

^{13}C NMR (75 MHz) δ 150.1 (C=O), 143.3 (C), 128.3 (CH), 126.1 (CH), 125.2 (CH), 109.0 (CN), 80.4 (CH), 50.7 (CH), 39.6 (C), 32.7 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 25.4 (CH_3), 24.4 (CH_3), 23.8 (CH_2).

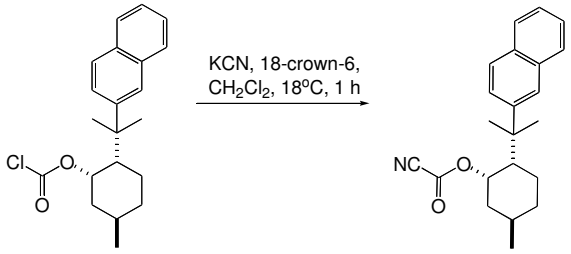
IR (NaCl, film) ν_{max} 2933, 2243 (CN), 1738 (C=O), 1252, 700 cm^{-1}.

EIMS (70 eV) *m/z* 271 ($M^{+\bullet}$, 21%), 200 (33), 119 (100).

HRMS Found: $M^{+\bullet}$, 271.1569. $C_{17}H_{21}NO_2$ requires $M^{+\bullet}$, 271.1572.

Specific Rotation $[\alpha]_D$ -31.0 (*c* = 1.8, CH_3OH).

(+)-(1*S*,2*S*,5*R*)-5-[2-(2-Naphthen-3-yl)propan-2-yl]cyclohexyl cyanoformate (257)



(**252**) (**257**)

Clear colourless oil

R_f 0.3 (silica, 5:95 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.83–7.68 (complex m, 4H), 7.48–7.41 (complex m, 3H), 5.02 (complex m, 1H), 1.82–1.47 (complex m, 6H), 1.45 (s, 6H), 1.08–0.89 (complex m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (75 MHz) δ 145.6 (C=O), 143.4 (C), 133.2 (C), 131.8 (C), 128.0 (CH), 127.9 (CH), 127.3 (CH), 126.2 (CH), 125.7 (CH), 124.3 (CH), 124.2 (CH), 109.4 (CN), 78.4 (CH), 50.6 (CH), 40.1 (C), 39.2 (CH_2), 34.8 (CH_2), 27.9 (CH), 26.7 (CH_3), 25.2 (CH_3), 22.1 (CH_2), 21.7 (CH_3)

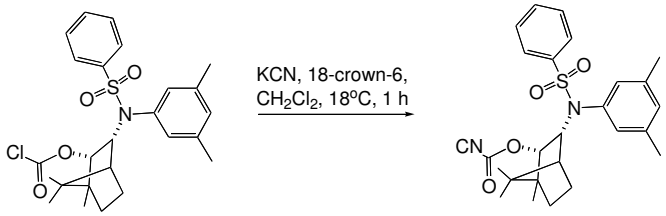
IR (NaCl, film) ν_{max} 2925, 2241 (CN), 1743 (C=O), 1248, 1112, 745 cm^{-1}.

EIMS (70 eV) *m/z* 335 ($M^{+\bullet}$, >1%), 264 (1), 169 (100).

HRMS Found: $M^{+\bullet}$, 335.1881. $C_{22}H_{25}NO_2$ requires $M^{+\bullet}$, 335.1885.

Specific Rotation $[\alpha]_D$ +34.9 (*c* = 1.6, $CHCl_3$).

(+)-(1*R*,2*S*,3*R*)-[*N*-Benzene-sulfonyl-*N*-(3,5-dimethylphenyl)-amino]-2-bornanyl cyanoformate (258)



(**253**) (**258**)

White solid

***R**f* 0.4 (silica, 1:4 v/v ethyl acetate/hexane).

m.p. 210–212°C.

^{1}H NMR (300 MHz) δ 7.57–7.36 (complex m, 6H), 6.90 (s, 2H), 6.00 (s, 1H), 5.28 (d, *J* = 7.0 Hz, 1H), 3.83 (d, *J* = 7.0 Hz, 1H), 2.26 (s, 3H), 2.09 (s, 3H), 1.75–1.69 (complex m, 1H), 1.60 (td, *J* = 13.0 and 3.4 Hz, 1H), 1.36–1.28 (complex m, 1H), 1.14–1.08 (complex m, 1H), 0.95 (s, 3H), 0.85 (complex m, 3H), 0.66 (s, 3H).

^{13}C NMR (75 MHz) δ 143.7 (C=O), 138.5 (C), 138.5 (C), 132.9 (CH), 129.7 (CH), 129.5 (C), 128.7 (C), 128.4 (CH), 128.3 (CH), 109.5 (CN), 85.3 (CH), 66.8 (CH), 50.4 (C), 48.5 (CH), 47.5 (C), 31.8 (C), 27.4 (CH_2), 21.0 (CH_2), 20.9 (CH_3), 20.6 (CH_3), 11.2 (CH_3).

IR (NaCl, film) ν_{max} 2921, 2243 (CN), 1751 (C=O), 1352, 1166, 703 cm^{-1}.

EIMS (70 eV) *m/z* 466 ($M^{+\bullet}$, 12%), 325 (33), 132 (100).

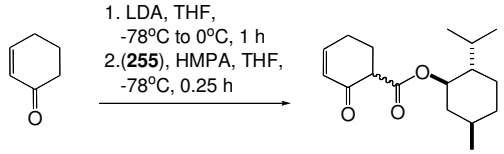
HRMS Found: $M^{+\bullet}$, 466.1922. $C_{26}H_{30}N_2O_4S$ requires $M^{+\bullet}$, 466.1926.

Specific Rotation $[\alpha]_D$ +36.0 (*c* = 1.0, $CHCl_3$).

5.4.4 General Procedure for Synthesis of Chiral β-Ketoesters 259 - 262

Following a procedure developed by Mander *et al*,[1] a magnetically stirred solution of diisopropylamine (0.18 mL, 1.20 mmol) in THF (10 mL) maintained at –20°C (NaCl/ice bath) under a nitrogen atmosphere was treated, dropwise, with *n*-butyllithium (0.70 mL of a 1.7 M solution in hexanes, 1.20 mmol). The resulting mixture was stirred at –20°C (NaCl/ice bath) for 0.5 h then the temperature was reduced to –78°C (dry-ice/acetone bath) and a solution of enone **77** (98.0 mg, 1.00 mmol) in THF (5 mL) was added *via* cannula. The resulting solution was warmed to 0°C (ice/water bath), stirred at this temperature for 1 h, then cooled to –78°C again and HMPA (0.10 mL 1.20 mmol) and the appropriate chiral cyanoformate (1.10 mmol) were added. After stirring for an additional 0.25 h at –78°C, the reaction mixture was poured into cold water (50 mL) and extracted with ether (2 x 50 mL). The combined organic phases were washed with distilled water (3 x 50 mL). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the relevant chiral β-ketoester as a mixture of diastereoisomers and as either clear, yellow oils or white solids.

(±)-(*R*/*S*)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-2-oxo-cyclohex-3-ene carboxylate (259)



(**77**) (**259**)

Clear, colourless oil

R_f 0.5 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 6.97 (complex m, 1H), 6.05 (complex m, 1H), 4.72 (dt, *J* = 11.0 and 4.3 Hz, 1H), 3.37 (complex m, 1H), 2.45–2.34 (complex m, 3H), 2.23–2.19 (complex m, 1H), 2.06–2.02 (complex m, 2H), 1.68–1.64 (complex m, 2H), 1.54–1.45 (complex m, 3H), 1.09–0.92 (complex m, 2H), 0.88 (complex m, 6H), 0.76 (complex m, 3H).

^{13}C NMR (75 MHz) δ 194.0 (C=O), 169.7 (C=O), 169.5 (C=O), 150.4 (CH), 129.2 (CH), 129.1 (CH), 75.3 (CH), 75.2 (CH), 53.7 (CH), 53.5 (CH), 46.8 (CH), 40.7 (CH_2), 40.6 (CH_2), 34.2 (CH_2), 31.4 (CH), 26.1 (CH), 26.0 (CH), 25.82 (CH_2), 25.77 (CH_2),

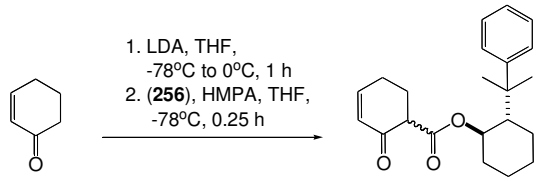
24.3 (CH_2), 24.2 (CH_2), 23.2 (CH), 23.0 (CH), 22.0 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 16.1 (CH_3), 15.9 (CH_3).

IR (NaCl, film) ν_{max} 2955, 2871, 1733 (C=O), 1683 (C=O), 1454, 1263 cm^{-1}.

EIMS (70 eV) *m/z* 278 ($M^{+\bullet}$, 1%), 138 (96), 123 (97), 96 (100).

HRMS Found: $M^{+\bullet}$, 278.1885. $C_{17}H_{26}O_3$ requires $M^{+\bullet}$, 278.1882.

(±)(*R/S*)-(1*R*,2*S*)-2-(2-phenylpropan-2-yl)cyclohexyl 2-oxocyclohex-3-ene carboxylate (260)



(**77**) (**260**)

Clear, colourless oil

R_f 0.5 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (major diastereoisomer) δ 7.31–7.23 (complex m, 5H), 7.13 (complex m, 1H), 6.02 (dt, *J* = 10.2 and 3.7 Hz, 1H), 4.83 (sept, *J* = 4.8 Hz, 1H), 2.90 (dd, *J*= 8.7 and 5.2 Hz, 1H), 2.43 – 1.90 (complex m, 8H), 1.70–1.60 (complex m, 3H), 1.30 (s, 3H), 1.19 (s, 3H), 1.07 (complex m, 2H). (minor diastereoisomer) δ 6.91 (complex m, 1H), 5.90 (ddd, *J* = 10.1, 2.5 and 1.6 Hz, 1H), 1.33 (s, 3H), 1.24 (s, 3H), 0.98 (complex m, 2H), (other signals overlapping).

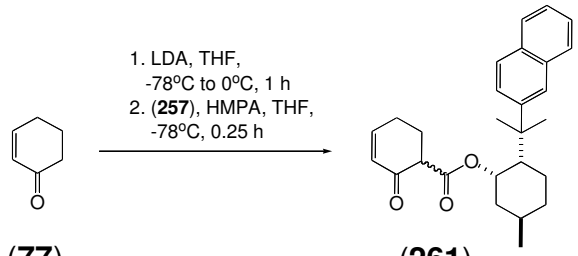
^{13}C NMR (75 MHz) (major diastereoisomer) δ 194.2 (C=O), 168.2 (C=O), 152.1 (C), 150.0 (CH), 129.0 (CH), 127.9 (CH), 125.4 (CH), 125.0 (CH), 75.4 (CH), 53.1 (CH), 50.5 (CH), 39.7 (C), 33.2 (CH_2), 28.7 (CH_3), 26.8 (CH_2), 25.9 (CH_2), 25.1 (CH_2), 24.6 (CH_2), 24.1 (CH_2), 23.9 (CH_3). (minor diastereoisomer) δ 194.1 (C=O), 151.4 (C), 150.2 (CH), 129.3 (CH), 127.8 (CH), 125.6 (CH), 124.7 (CH), 76.3 (CH), 53.5 (CH), 50.8 (CH), 40.0 (C), 33.1 (CH_2), 27.2 (CH_2), 26.7 (CH_2), 25.4 (CH_2), (other signals overlapping).

IR (NaCl, film) ν_{max} 2935, 1731 (C=O), 1681 (C=O), 1447, 1166, 701 cm^{-1}.

EIMS (70 eV) *m/z* 340 ($M^{+\bullet}$, 5%), 200 (73), 185 (24), 119 (100).

HRMS Found: $M^{+\bullet}$, 340.2036. $C_{22}H_{28}O_3$ requires $M^{+\bullet}$, 340.2038.

(±)(*R/S*)-(1*R*,2*S*,5*R*)-5-methyl-2-[2-(naphthalene-3-yl)propan-2-yl] cyclohexyl 2-oxocyclohex-3-ene carboxylate (261)



(**77**) (**261**)

Clear, colourless oil

R_f 0.6 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (major diastereoisomer) δ 7.82–7.69 (complex m, 4H), 7.50–7.40 (complex m, 3H), 7.02 (dt, *J* = 10.2 and 3.7 Hz, 1H), 6.12 (dt, *J* = 10.2 and 1.9 Hz, 1H), 5.10 (complex m, 1H), 3.06 (complex m, 1H), 2.42–1.92 (complex m, 4H), 1.72–1.44 (complex m, 6H), 1.42 (s, 3H), 1.40 (s, 3H), 0.92 (t, *J* =12.7 Hz, 2H), 0.90 (d, *J* = 5.4 Hz, 3H). (minor diastereoisomer) δ 6.94 (dt, *J* = 10.2 and 3.7 Hz, 1H), 6.03 (dt, *J* = 10.2 and 2.2 Hz, 1H), (other signals overlapping).

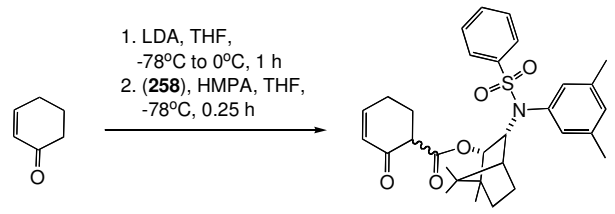
^{13}C NMR (75 MHz) δ 194.0 (C=O), 193.8 (C=O), 168.9 (C=O), 150.3 (CH), 150.2 (CH), 147.1 (C), 146.8 (C), 133.25 (C), 131.7 (C), 131.6 (C), 129.3 (CH), 129.2 (CH), 128.0 (CH), 127.33 (CH), 127.26 (CH), 125.8 (CH), 125.3 (CH), 125.1 (CH), 124.8 (CH), 124.5 (CH), 124.4 (CH), 72.7 (CH), 75.4 (CH), 53.9 (CH), 53.6 (CH), 51.1 (CH), 51.0 (CH), 40.2 (C), 40.1 (C), 39.82 (CH_2), 39.78 (CH_2), 35.5 (CH_2), 35.3 (CH_2), 31.6 (CH_2), 26.9 (CH), 26.8 (CH), 26.7 (CH_3), 26.6 (CH_3), 25.7 (CH_2), 25.5 (CH_2), 24.4 (CH_2), 24.3 (CH_2), 22.4 (CH_3), 22.1 (CH_3).

IR (NaCl, film) ν_{max} 2946, 1734 (C=O), 1679 (C=O), 1454, 1237, 747 cm^{-1}.

EIMS (70 eV) *m/z* 404 ($M^{+\bullet}$, 1%), 264 (12), 249 (12), 169 (100).

HRMS Found: $M^{+\bullet}$, 404.2359. $C_{27}H_{32}O_3$ requires $M^{+\bullet}$, 404.2351.

(±)(*R*/*S*)-(1*R*,2*S*,3*R*)-(+)-[*N*-benzene-sulfonyl-*N*-(3,5-dimethylphenyl)-amino]-2-bornanyl-2-cyclohex-3-ene carboxylate (262)



(**77**) (**262**)

White solid

R_f 0.6 (silica, 3:7 v/v ethyl acetate/hexane).

m.p. 223–225°C.

^{1}H NMR (300 MHz) (major diastereoisomer) δ 7.54–7.30 (complex m, 5H), 7.10 (complex m, 1H), 6.98 (complex m, 1H), 6.84 (s, 1H), 6.08 (complex m, 1H), 5.68 (s, 1H), 5.27 (d, *J* = 7.2 Hz, 1H), 3.83 (d, *J* = 7.2 Hz, 1H), 3.64 (complex m, 1H), 2.56–2.41 (complex m, 3H), 2.39 (s, 3H), 2.03 (s, 3H), 1.88–1.24 (complex m, 4H), 1.11–0.98 (complex m, 2H), 0.93 (s, 3H), 0.89 (s, 3H), 0.58 (s, 3H). (minor diastereoisomer) δ 6.20 (complex m, 1H), 3.76 (d, *J* = 7.2 Hz, 1H), 0.85 (s, 3H), 0.79 (s, 3H), 0.55 (s, 3H), (other signals overlapping).

^{13}C NMR (75 MHz) (major diastereoisomer) δ 194.5 (C=O), 169.6 (C=O), 150.9 (CH), 138.5 (C), 137.0 (C), 132.5 (CH), 129.3 (CH), 129.1 (CH), 128.7 (C), 128.2 (CH), 128.1 (CH), 82.0 (CH), 67.4 (CH), 57.3 (CH), 50.4 (CH), 48.4 (CH), 47.4 (C), 32.0 (CH_2), 27.7 (CH_2), 25.3 (CH_2), 24.4 (CH_2), 21.2 (CH_3), 20.7 (CH_3), 20.6 (CH_3), 11.2 (CH_3). (minor diastereoisomer) δ 168.9 (C=O), 151.2 (CH), 138.4 (C), 138.0 (C), 132.6 (CH), 129.6 (CH), 129.2 (CH), 128.4 (CH), 128.1 (CH), 81.8 (CH), 67.3 (CH), 54.2 (CH), 50.8 (CH), 48.6 (CH), 47.2 (C), 32.1 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 26.0 (CH_2), 21.1 (CH_3), 20.5 (CH_3), 19.3 (CH_3), 11.4 (CH_3), (other signals overlapping).

IR (NaCl, film) ν_{max} 2925, 1740 (C=O), 1680 (C=O), 1352, 1167, 718 cm^{-1}.

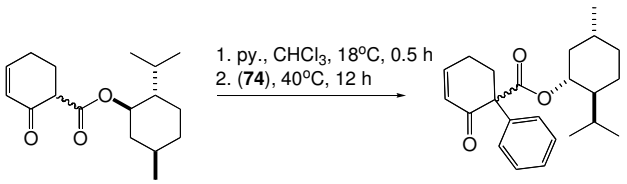
EIMS (70 eV) *m/z* 535 ($M^{+\bullet}$, >1%), 395 (18), 254 (100).

HRMS Found: $M^{+\bullet}$, 535.2391. $C_{31}H_{37}NO_5S$ requires $M^{+\bullet}$, 404.2392.

5.4.5 General Procedure for Synthesis of Chiral α-Arylated β-Ketoesters 263 -266

Following a procedure developed by Pinhey *et al*,[8] a magnetically stirred solution of the appropriate chiral auxiliary-containing β-ketoester (1.00 mmol) in chloroform (5 mL) at 18°C maintained under a nitrogen atmosphere was treated with pyridine (0.24 mL, 3.00 mmol) and stirred for 0.5 h then treated with phenyllead triacetate (**74**) (506 mg, 1.10 mmol). The resulting mixture was heated to 40°C, stirred at this temperature for 12 h, then cooled and quenched with HCl (drop of 1 M aqueous solution) and diluted with ether (20 mL). The organic phase was washed with HCl (1 x 25 mL of a 1 M aqueous solution) and distilled water (2 x 25 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, yellow oil. Subjection of this material to flash chromatography (silica, 5 → 20% v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions, the relevant chiral α-arylated β-ketoester as a mixture of diastereoisomers and as clear, colourless oils.

(±)-(1R/S)-(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-oxo-1-phenyl-cyclohex-3-ene carboxylate (263)



(**259**) (**263**)

R_f 0.3 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) δ 7.38–7.19 (complex m, 5H), 6.87 (complex m, 1H), 6.16 (dt, *J* = 10.2 and 1.9 Hz, 1H), 4.69 (complex m, 1H), 2.38–2.77 (complex m, 1H), 2.61–2.27 (complex m, 2H), 2.06–2.01 (complex m, 1H), 1.67–1.23 (complex m, 7H), 1.07–0.90 (complex m, 2H), 0.88 (complex m, 6H), 0.81–0.66 (complex m, 3H).

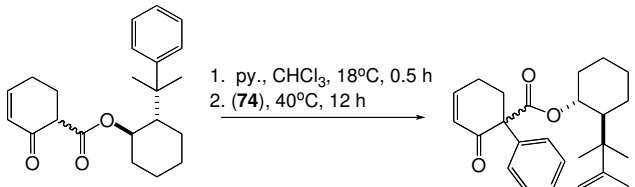
^{13}C NMR (75 MHz) δ 195.0 (C=O), 194.6 (C=O), 171.1 (C=O), 170.5 (C=O), 149.1 (CH), 149.0 (CH), 136.4 (C), 136.3 (C), 129.2 (CH), 129.1 (CH), 128.0 (CH), 127.32 (CH), 127.28 (C), 75.7 (CH), 62.6 (C), 62.4 (C), 46.42 (CH), 46.4 (CH), 40.0 (CH_2), 39.88 (CH_2), 33.9 (CH_2), 31.8 (CH_2), 31.7 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 27.6 (CH), 26.6 (CH), 25.4 (CH_2), 25.3 (CH_2), 23.8 (CH), 23.6 (CH), 22.7 (CH_3), 21.8 (CH_3), 20.51 (CH_3), 20.50 (CH_3), 15.5 (CH_3).

IR (NaCl, film) ν_{max} 2955, 1725 (C=O), 1683 (C=O), 1449, 1246, 1039, 696 cm^{-1}.

EIMS (70 eV) *m/z* 354 ($M^{+\bullet}$, 4%), 216 (56), 172 (100).

HRMS Found: $M^{+\bullet}$, 354.2199 Calcd for $C_{23}H_{30}O_3$ requires $M^{+\bullet}$, 354.2195.

(±)-(1R/S)-(1*R*,2*S*)-2-(2-Phenylpropan-2-yl)-cyclohexyl-2-oxo-1-phenyl-cyclohex-3-ene carboxylate (264)



(**260**) (**264**)

R_f 0.6 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (major diastereoisomer) δ 7.36–7.08 (complex m, 10H), 6.78 (complex m, 1H), 6.13 (dt, *J* = 10.0 and 1.8 Hz, 1H), 4.81 (td, *J* = 10.0 and 4.2 Hz, 1H), 2.50–2.28 (complex m, 2H), 2.10–2.07 (complex m, 2H), 1.85 (complex m, 1H), 1.64–1.47 (complex m, 2H), 1.37–1.14 (complex m, 6H), 1.12 (s, 3H), 0.96 (s, 3H), (minor diastereoisomer) δ 6.82 (complex m, 1H), 4.88 (td, *J* = 10.0 and 4.4 Hz, 1H), 1.14 (s, 3H), 0.95 (s, 3H), (other signals overlapping).

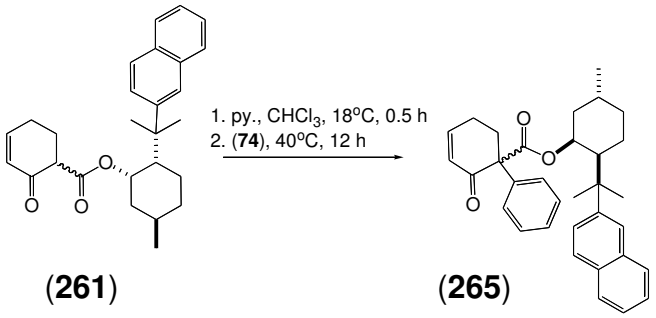
^{13}C NMR (75 MHz) (major diastereoisomer) δ 195.3 (C=O), 170.2 (C=O), 150.8 (C), 149.0 (CH), 135.4 (C), 129.2 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 125.7 (CH), 125.0 (CH), 77.5 (CH), 62.6 (C), 50.5 (CH), 40.2 (C), 32.8 (CH_2), 30.6 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 25.6 (CH_3), 24.4 (CH_3), 24.3 (CH_2), 23.7 (CH_2). (minor diastereoisomer) δ 195.2 (C=O), 170.3 (C=O), 149.6 (CH), 135.6 (C), 129.2 (CH), 128.3 125.15, 62.8 (C), 50.3 (CH), 40.25 (C), 32.6 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 27.8 (CH_2), 26.75 (CH_3), 24.5 (CH_3), 24.0 (CH_2), 23.5 (CH_2), (other signals overlapping).

IR (NaCl, film) ν_{max} 2931, 1720 (C=O), 1677 (C=O), 1244, 698 cm^{-1}.

EIMS (70 eV) *m/z* 416 ($M^{+\bullet}$, 1%), 269 (30), 119 (100).

HRMS Found: $M^{+\bullet}$, 416.2365. $C_{28}H_{32}O_3$ requires $M^{+\bullet}$, 416.2351.

(±)-(1R/S)-(1*S*,2*R*,5*S*)-5-Methyl-2-[2-(naphthalene-3-yl)propan-2-yl]-cyclohexyl 2-oxo-1-phenyl-cyclohex-3-ene carboxylate (265)



(**261**) (**265**)

R_f 0.2 (silica, 1:9 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (major diastereoisomer) δ 7.80–7.74 (complex m, 3H), 7.55–7.26 (complex m, 9H), 6.79 (complex m, 1H), 6.14 (d, *J* = 10.0 Hz, 1H), 5.00 (complex m, 1H), 2.81 (complex m, 1H), 2.77 (complex m, 1H), 2.66–2.30 (complex m, 2H), 2.08 (complex m, 1H), 1.73–1.35 (complex m, 2H), 1.30–1.26 (complex m, 5H), 1.02 (d, *J* = 10.0 Hz, 6H), 0.84 (d, *J* = 6.5 Hz, 3H). (minor diastereoisomer) 6.82 (complex m, 1H), 6.17 (d, *J* = 10.0 Hz, 1H), 5.05 (complex m, 1H), 1.95 (complex m, 1H), 1.01 (d, *J* = 10 Hz, 6H), 0.96 (s, 3H), 0.79 (d, *J* = 6.5 Hz, 3H), (other signals overlapping).

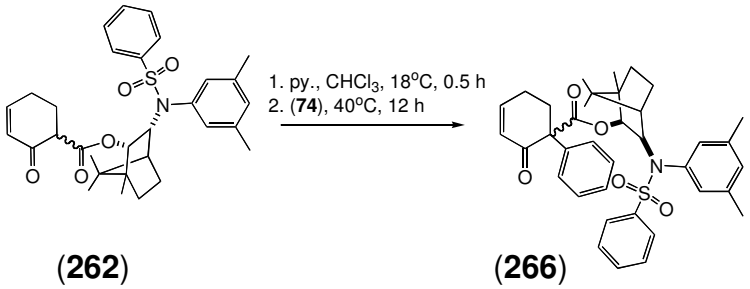
^{13}C NMR (75 MHz) (major diastereoisomer) δ 195.6 (C=O), 170.0 (C=O), 149.1 (CH), 147.4 (C), 135.4 (C), 133.2 (C), 131.6 (C), 129.2 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.73 (CH), 127.5 (CH), 127.3 (CH), 125.8 (CH), 125.3 (CH), 124.7 (CH), 124.2 (CH), 73.7 (CH), 62.7 (C), 50.9 (CH), 39.8 (C), 39.6 (CH_2), 35.3 (CH_2), 31.3 (CH_3), 26.7 (CH), 25.9 (CH_3), 25.4 (CH_3), 23.8 (CH_2), 22.1 (CH_3), 22.0 (CH_3). (minor diastereoisomer) δ 195.4 (C=O), 170.3 (C=O), 149.5 (CH), 136.2 (C), 129.4 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 124.9 (CH), 124.4 (CH), 73.4 (CH), 63.2 (C), 51.2 (CH), 40.1 (CH_2), 35.2 (CH_2), 29.7 (CH_3), 27.7 (CH), 25.7 (CH_3), 23.7 (CH_2), 22.6 (CH_3), 21.9 (CH_3), (other signals overlapping).

IR (NaCl, film) ν_{max} 2924, 1723 (C=O), 1676 (C=O), 1455, 1243, 697 cm^{-1}.

EIMS (70 eV) *m/z* 480 ($M^{+\bullet}$, >1%), 264 (15), 249 (18), 169 (100).

HRMS Found: $M^{+\bullet}$, 480.2664. $C_{33}H_{36}O_3$ requires $M^{+\bullet}$, 488.2664.

(±)-(1R/S)-(1*R*,2*S*,3*R*)-[*N*-Benzene-sulfonyl-*N*-(3,5-dimethylphenyl)-amino]-2-bornanyl-2-oxo-1-phenyl-cyclohex-3-ene carboxylate (266)



(**262**) (**266**)

R_f 0.4 (silica, 3:7 v/v ethyl acetate/hexane).

^{1}H NMR (300 MHz) (major diastereoisomer) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.59–7.27 (complex m, 12H), 6.80 (s, 1H), 6.10 (complex m, 1H), 5.37 (d, *J* = 7.0 Hz, 1H), 3.64 (d, *J* = 7.0 Hz, 1H), 3.25–3.16 (complex m, 2H), 2.98 (sept, *J* = 4.9 Hz, 1H), 2.33 (s, 3H), 2.04 (s, 3H), 1.88–0.97 (complex m, 6H), 0.93 (s, 3H), 0.90 (s, 3H), 0.41 (s, 3H). (minor diastereoisomer) δ 6.90 (s, 1H), 6.24 (dd, *J* = 10.0 and 2.5 Hz, 1H), 5.39 (d, *J* = 7.0 Hz, 1H), 3.76 (d, *J* = 7.1 Hz, 1H), 0.81 (s, 3H), 0.58 (s, 3H), (other signals overlapping).

^{13}C NMR (75 MHz) (major diastereoisomer) δ 196.0 (C=O), 171.2 (C=O), 149.6 (CH), 138.2 (C), 136.0 (C), 133.6 (C), 132.6 (CH), 129.4 (C), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 82.0 (CH), 67.2 (CH), 63.3 (C), 50.5 (CH), 48.4 (CH), 46.9 (C), 32.1 (CH_2), 27.9 (CH_2), 27.8 (C), 23.3 (CH_2), 23.1 (CH_3), 20.9 (CH_3), 20.6 (CH_3), 20.4 (CH_3), 11.5 (CH_3). (minor diastereoisomer) δ 171.1 (C=O), 150.8 (CH), 138.6 (C), 135.8 (C), 129.7 (C), 129.2 (CH), 128.8 (CH), 128.2 (CH), 127.1 (CH), 82.4 (CH), 67.6 (CH), 63.9 (C), 51.0 (CH), 48.7 (CH), 47.2 (C), 32.4 (CH_2), 28.0 (CH_2), 26.8 (C), 23.8 (CH_2), 23.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3), 11.4 (CH_3), (other signals overlapping).

IR (NaCl, film) ν_{max} 2957, 1736 (C=O), 1674 (C=O), 1352, 1167, 732 cm^{-1}.

EIMS (70 eV) *m/z* 611 ($M^{+\bullet}$, >1%), 470 (1), 254 (100).

HRMS Found: $M^{+\bullet}$, 611.2718. $C_{37}H_{41}NO_3S$ requires $M^{+\bullet}$, 611.2705.

5.5 References

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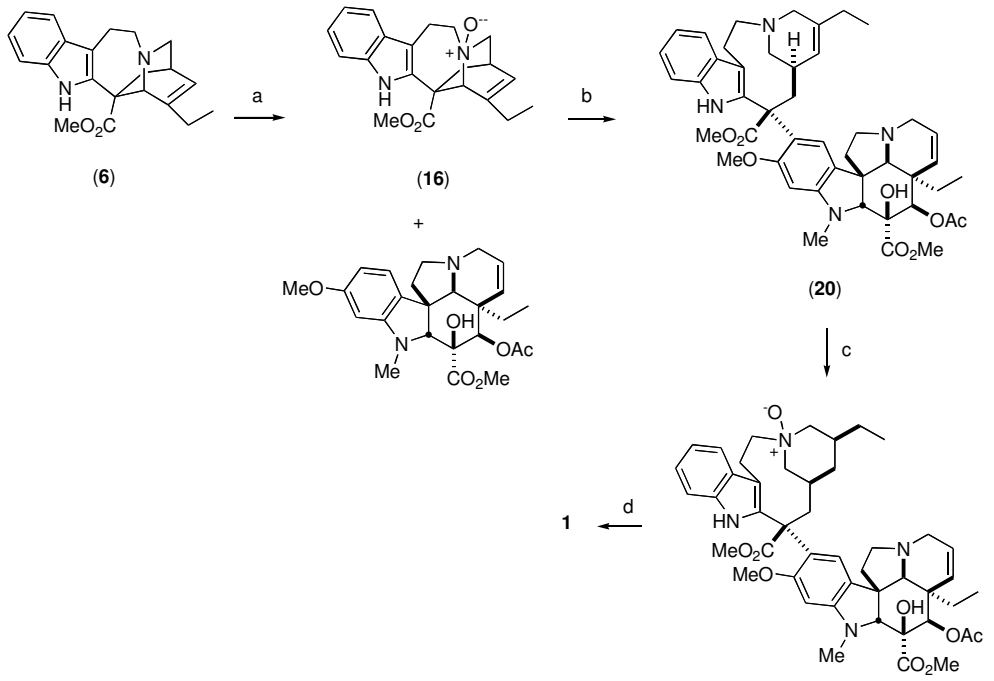
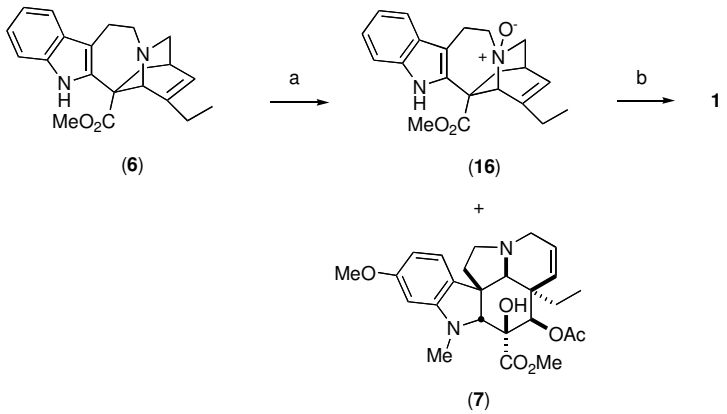
Appendix A:

Schemes Summarising Existing Syntheses of (+)-Vinblastine



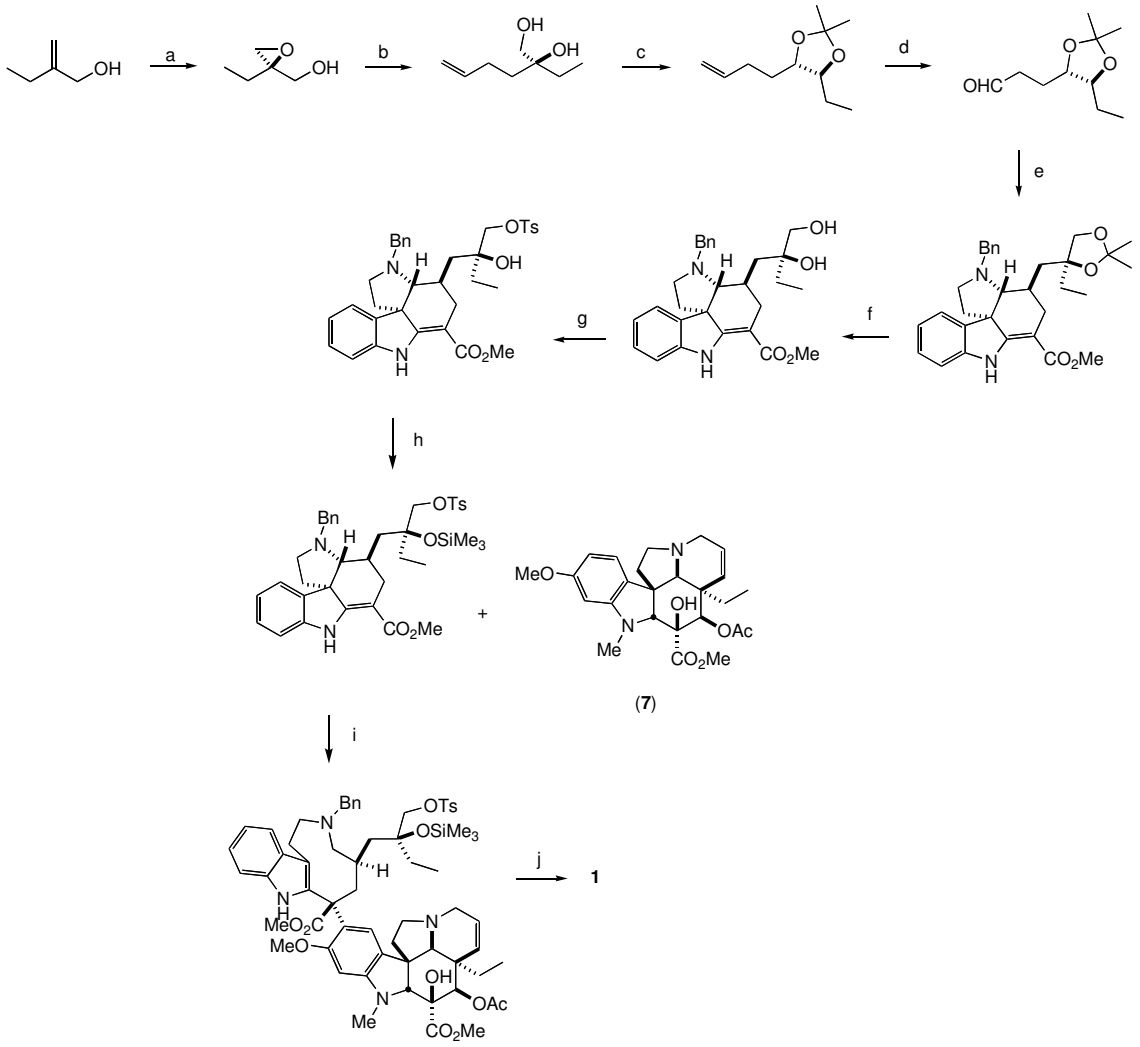
Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, -30°C; (b) i. TFAA, CH_2Cl_2, -50°C; ii. $NaBH_4$, EtOH, r.t.; (c) i. 10% Pd/C, H_2, 1 atm., EtOH, r.t.; ii. *m*CPBA, CH_2Cl_2, -30°C; iii. Ac_2O, CH_2Cl_2, 0°C; (d) i. $Tl(OAc)_3$, AcOH, 75°C; ii. $NaBH_4$, EtOH, r.t.

Scheme A.1: *Potiers's total synthesis of (+)-vinblastine (**1**)*



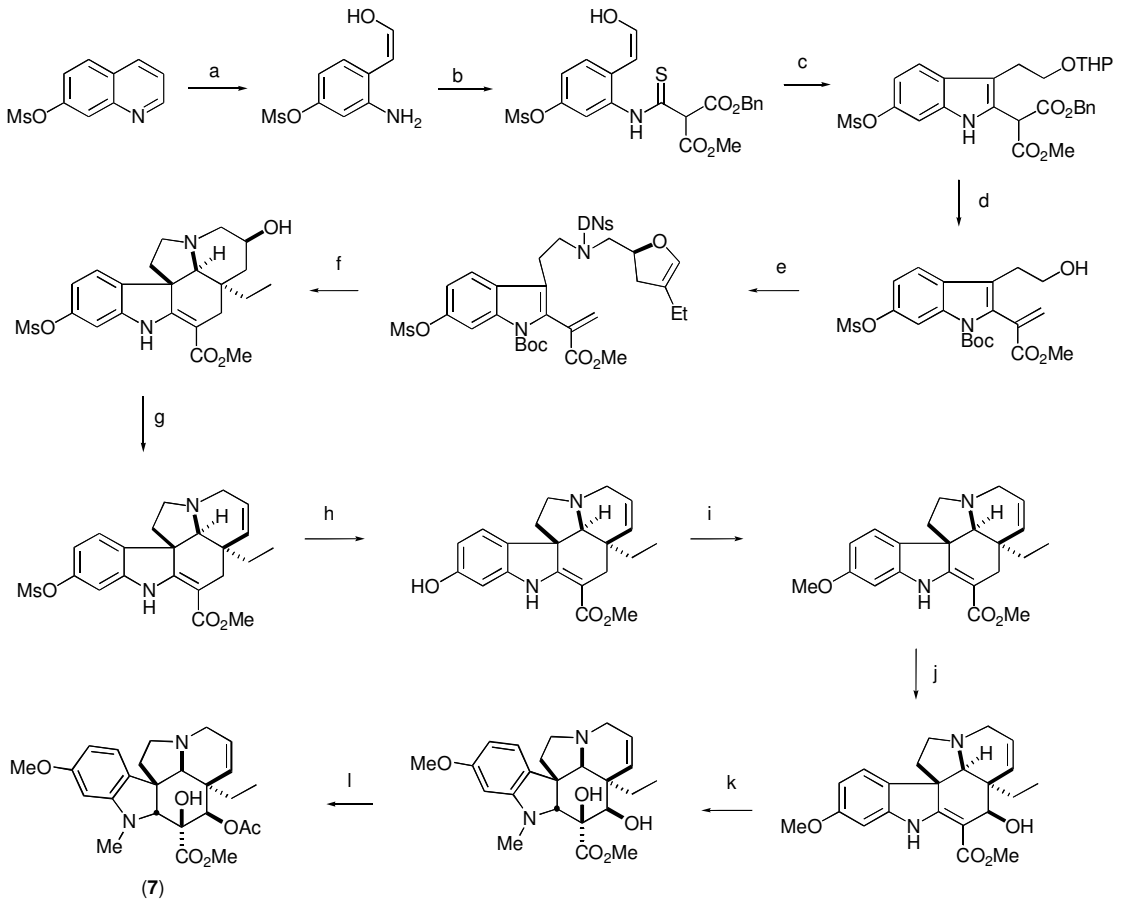
Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, -30°C (b) i. TFAA, CH_2Cl_2, -60°C; ii. β-NADH, MeOH, r.t.; iii. $FeCl_3$, O_2, MeOH, 0°C; iv. $NaBH_4$, MeOH, r.t.

Scheme A.2: *Kutney's biomimetic total synthesis of (+)-vinblastine (**1**)*



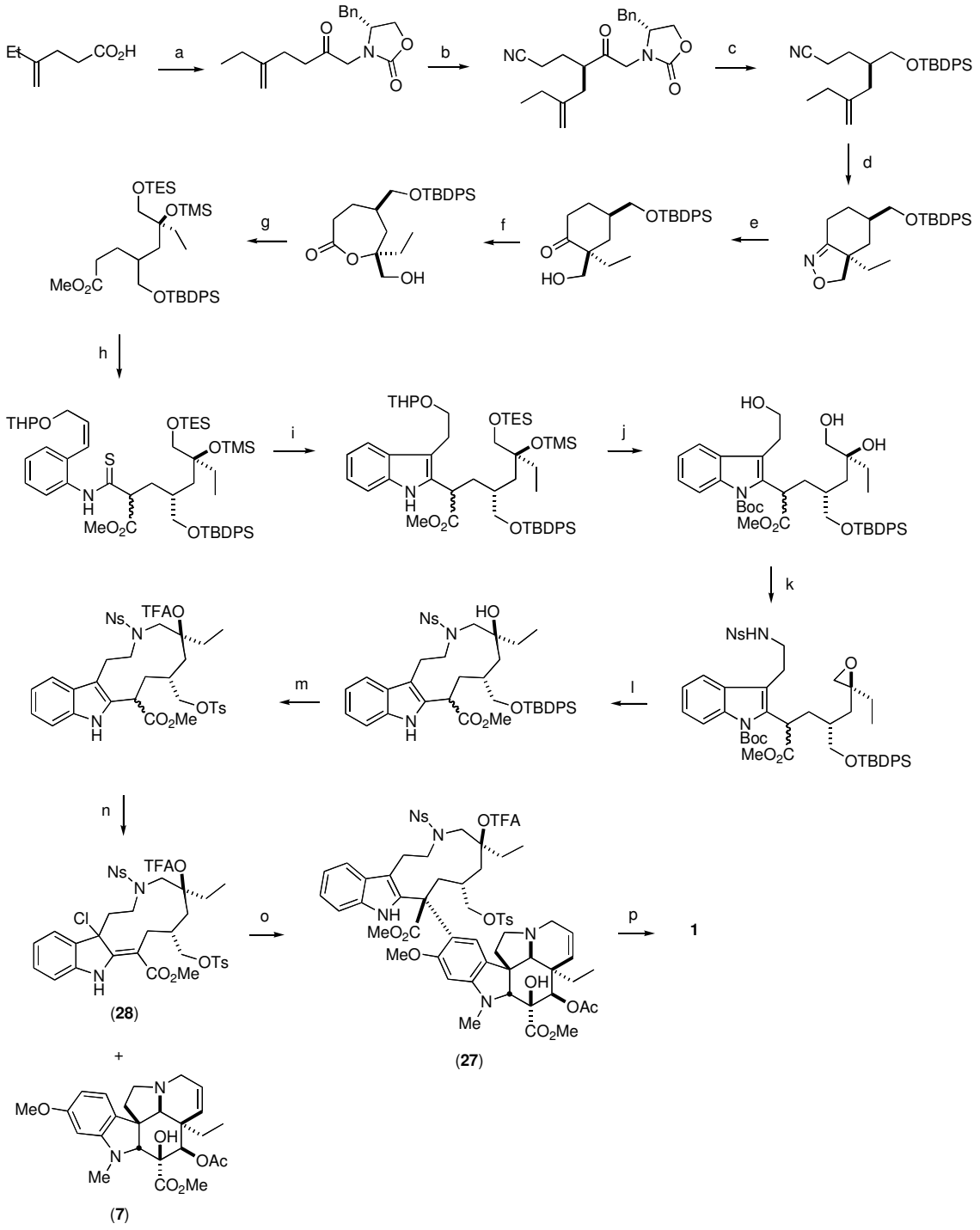
Reagents and conditions: (a) D-(-)-diethyl tartrate, Ti(*i*-PrO)$_4$, *t*-BuOOH, CH_2Cl_2, r.t. → -20°C; (b) CuI, allylmagnesium chloride, THF, -30°C; (c) TsOH, (9:1 v/v) acetone/DMP, r.t.; (d) ozone, PPh_3, CH_2Cl_2, -78°C → r.t.; (e) i. methyl 1,2,3,4,5,6-hexahydroazepino[4,5*b*]indole-5-carboxylate, THF, reflux; ii. BnBr, THF, reflux; iii. Et_3N, MeOH, reflux; (f) 10% HCl, MeOH, reflux; (g) Ts_2O, Et_3N, CH_2Cl_2, 0°C → r.t.; (h) TMS_2O, *i*-Pr_2EtN, THF, 0°C; (i) i. *t*-BuOCl, Et_3N, CH_2Cl_2, 0°C; ii. BF_3•OEt_2, $AgBF_4$, acetone, r.t.; iii. KBH_4, AcOH, r.t.; iv. reflux, MeOH; (j) i. 10% Pd/C, H_2, MeOH, r.t.; ii. TBAF, THF, r.t.

Scheme A.3: *Kuehne's total enantioselective total synthesis of (+)-vinblastine (**1**)*



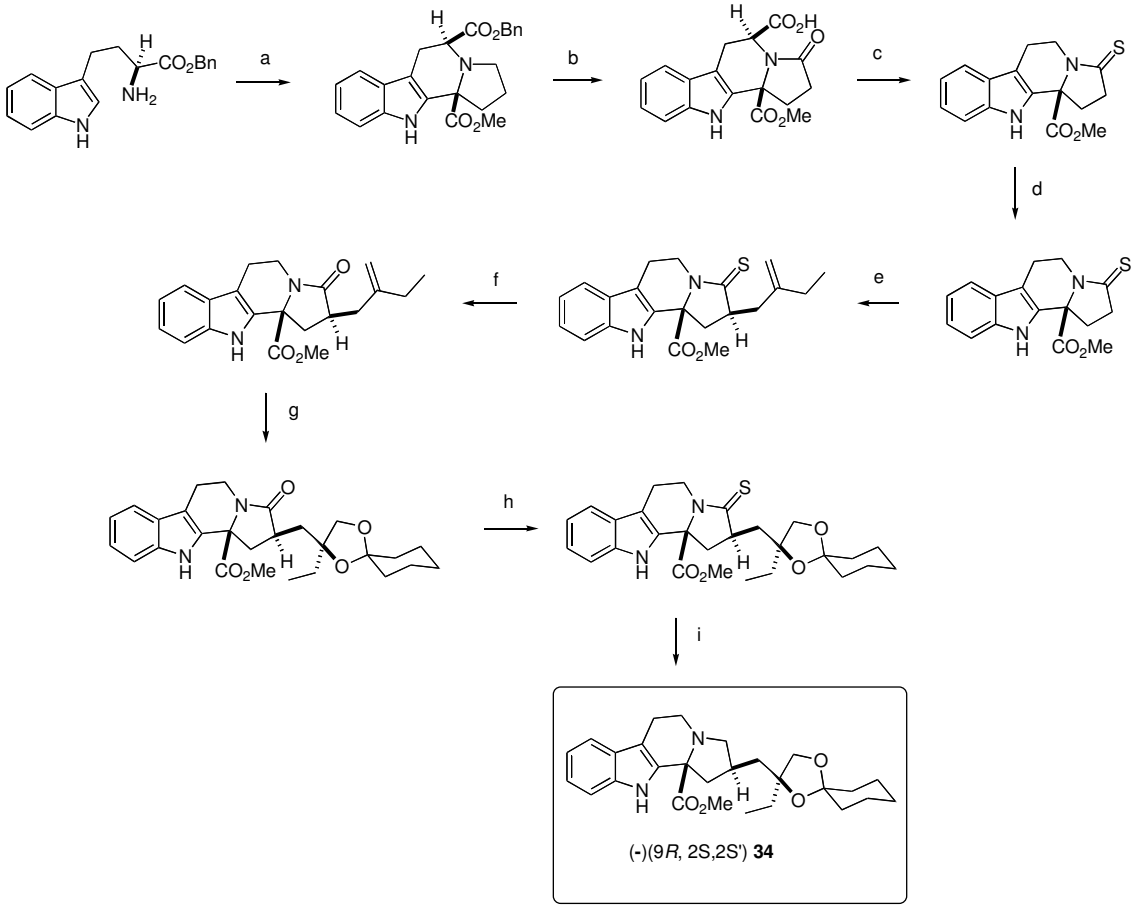
Reagents and conditions (a) i. thiophosgene, Na_2CO_3, THF, 0°C; ii. $NaBH_4$, MeOH, 0°C; (b) i. DHP, CSA, CH_2Cl_2, r.t.; ii. benzyl methyl malonate, NaH, THF, 0°C; (c) AIBN, Bu_3SnH, toluene, 110°C; (d) i. Boc_2O, Et_3N, DMAP, CH_2Cl_2, r.t.; ii. 10% Pd/C, H_2, EtOH, r.t.; iii. $Me_2NH{\bullet}HCl$, HCHO, NaOAc, AcOH, r.t.; iv. CSA, MeOH, r.t.; (e) (2*S*)-2-[[(2,4-dinitrobenzenesulfonyl)amino]methyl]-4-ethyl-2,3-dihydrofuran, DEAD, PPh_3, benzene, r.t.; (f) i. K_2CO_3, MeOH, r.t.; ii. TESCl, Im., DMF, r.t.; iii. TMSCl, DMF, r.t.; (g) PPh_3, CCl_4, MeCN, 70°C; (h) KOH, MeOH, 80°C; (i) MeI, *t*-BuOK, THF, 0°C; (j) $(PhSeO)_2O$, benzene, 80°C; (k) i. *m*CPBA, (1:9 v/v) $MeOH/CH_2Cl_2$, $NaHCO_3$ (aq), 0°C; ii. HCHO, $NaBH_3CN$, 10% HCl/MeOH, 0°C → r.t.; iii. Na_2CO_3, $NaHSO_3$, r.t.; (l) NaOAc, Ac_2O, r.t.

Scheme A.4: *Part one of Fukuyama's stereocontrolled synthesis of (+)-vinblastine (**1**)*



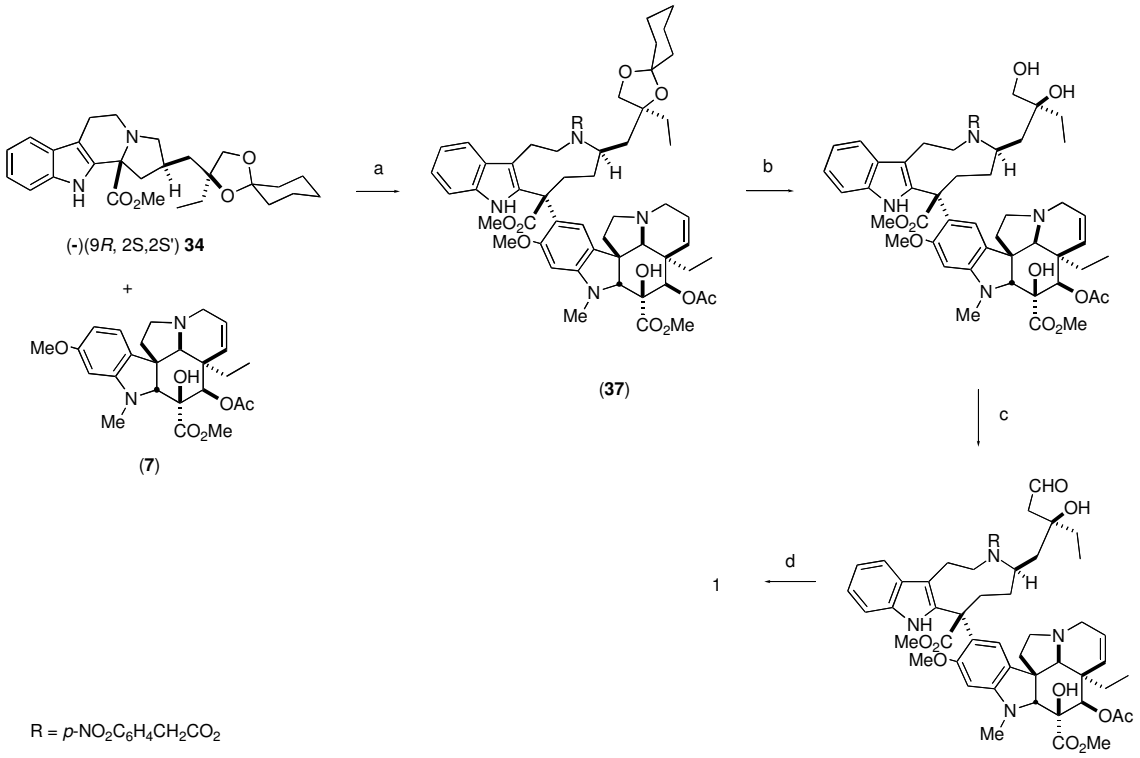
Reagents and conditions: (a) i. PivCl, Et_3N, Et_2O, 0°C; ii. *n*-BuLi, (*R*)-4-benzyl-2-oxazolidinone, THF, -78°C; (b) i. Ac_2O, py., r.t.; ii. (*i*-PrO)$TiCl_3$, *i*-Pr_2EtN, acrylnitrile, CH_2Cl_2, 0°C; (c) i. $NaBH_4$, THF, r.t.; ii. TBDPSCl, Im., DMF, r.t.; (d) i. DIBAL, CH_2Cl_2, -78°C; ii. H_2NOH•HCl, NaOAc, EtOH, r.t.; iii. NaOCl (aq), CH_2Cl_2, r.t.; (e) Zn, AcOH, r.t.; (f) *m*CPBA, AcOH, r.t.; (g) i. K_2CO_3, MeOH, r.t.; ii. TESCl, Im., DMF, r.t.; iii. TMSCl, DMF, r.t. (h) LDA, tetrahydro-2-[(*Z*)-3-(2-isothiocyanatophenyl)-2-propenyl]-oxy-2*H*-pyran, THF, -78°C → 0°C; i. Bu_3SnH, Et_3B, THF, r.t.; (j) i. Boc_2O, Et_3N, DMAP, CH_2Cl_2, r.t.; ii. AcOH, 80°C; (k) i. TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, r.t.; ii. $NaHCO_3$, DMF, 80°C; iii. $NsNH_2$, DEAD, PPh_3, toluene, r.t.; (l) K_2CO_3, DMF, 90°C; (m) i. TFA, CH_2Cl_2, r.t.; ii. TsCl, $Me_2N(CH_2)_3NMe_2$, (1:1 v/v) MeCN/toluene, r.t.; iii. TFAA, py., CH_2Cl_2, r.t.; (n) *t*-BuOCl, CH_2Cl_2, 0°C; (o) TFA, CH_2Cl_2, 0°C → r.t.; (p) i. Et_3N, MeOH, r.t.; ii. $HSCH_2CH_2OH$, DBU, MeCN, r.t.; iii. $NaHCO_3$, *i*-PrOH, r.t.

Scheme A.5: *Part two of Fukuyama's stereocontrolled synthesis of (+)-vinblastine (**1**)*



Reagents and conditions: (a) dimethyl α-ketoglutarate, THF, reflux; (b) 10% Pd/C, H_2, THF, r.t.; (c) i. *i*-Bu chloroformate, *N*-methylmorpholine, *N*-hydroxy-2-thiopyridone, Et_3N, THF; ii. *t*-BuSH, -20°C; iii. $h\nu$ 270W, 20°C; (d) Belleau's reagent, THF, r.t.; (e) (i) 2-(bromomethyl)but-2-ene, $MeNO_2$, r.t.; ii. DBU, THF, 5°C → 30°C; (f) *m*CPBA, CH_2Cl_2, 0°C → 25°C; (g) *N*-methylmorpholine *N*-oxide, OsO_4, acetone, 25°C; (h) Lawesson's reagent, toluene, 80°C → 25°C; (i) Raney nickel, THF, r.t.

Scheme A.6: *Part one of Magnus's enantioselective synthesis of (+)-vinblastine (**1**)*



Reagents and conditions: (a) 2,6-di-*tert*-butyl-4-methylpyridine, *p*-nitrobenzyl chloroformate, $MeNO_2$, -20°C; (b) 20% HCl (aq), THF, r.t.; (c) py•SO_3, Et_3N, DMSO, r.t.; (d) 10% Pd/C, H_2, MeOH, r.t.

Scheme A.7: *Part two of Magnus's enantioselective synthesis of (+)-vinblastine (**1**)*