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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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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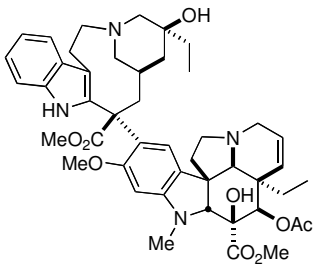
I would like to thank all the technical staff of the School. I am especially indebted to Tony Herlt (HPLC) and Chris Blake (NMR) for their technical wisdom. I would also like to thank Dr Aaron Oakley for his advice on biomolecular modelling.

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.

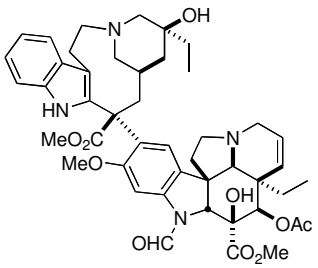
Finally, my family are the foundation where I came from, and I am grateful for everything that they have done for me so far, and in the future. I am thankful for my mother, father and brother having been encouraging and supportive and, most of all, a comfort, over the telephone during my sojourn in Australia's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

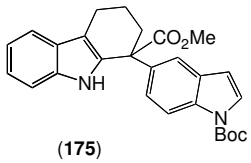


(**1**)



(**2**)

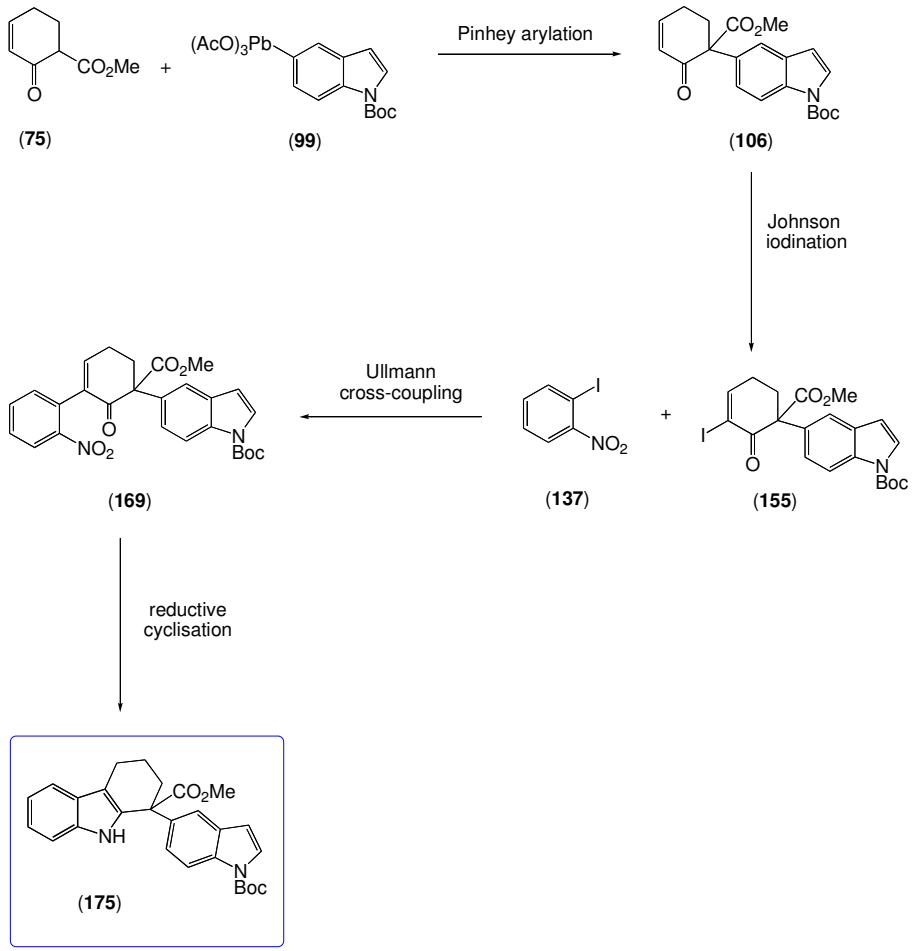
In principle, a useful starting point in generating small molecule analogues of the title alkaloids that may well retain useful biological properties would be to prepare a series of compounds mimicking the indole-indoline core of (+)-vinblastine (**1**) and involving a range of different pairings of 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.



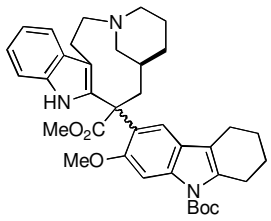
(**175**)

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**

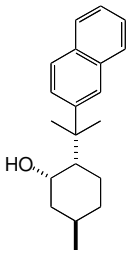


Attempts, as described in Chapter Three, were then made to extend such chemistry to the preparation of the *bis*-indole **44** containing a tetracyclic structure resembling the carbomethoxyvelbamine portion of (+)-vinblastine (**1**).



(**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*.”