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.

I would also like to thank all the postdoctoral researchers who have been instrumental and influential during my time here at the Research School of Chemistry. In particular I would like to thank Dr Jens Renner for teaching the vagaries of good experimental practice, Dr Steffan Gross for our robust conversations on more theoretical matters and finally, Dr Michael Backes for his pragmatic approach to synthesis when I had a crazy idea to share.

Many research students have come and gone during my stay at the Australian National University and all have helped in some way. I would like to acknowledge the support of Dr David Lupton, who introduced me to the wonderful world of Ullmann and Mr Okanya Kokas who was always willing to listen and discuss ideas of a wide nature.

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”.

![Chemical Structures](attachment:image.png)

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.

![Chemical Structure](attachment:image.png)

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).
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 \( \alpha \)-carbomethoxycycloalkenone precursors, \textit{e.g.} 75, to such compounds were replaced by carboalkoxy groups incorporating chiral alcohol residues such as menthol, (1-methyl-1-phenylethyl)cyclohexanol, 8-\( \beta \)-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.
Publications and Presentations Carried Out During Period of Candidature

Publications:


Presentations:

## Glossary

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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH</td>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>Ac</td>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
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<td>Ar</td>
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</tr>
<tr>
<td>aq.</td>
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<td>atm.</td>
<td>atm.</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINAP</td>
<td>BINAP</td>
<td>2,2-\textit{bis}(diphenylphosphino)-1-1' binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>bipy</td>
<td>bipy</td>
<td>2,2′-bipyridyl</td>
</tr>
<tr>
<td>Boc</td>
<td>Boc</td>
<td>\textit{tert}-butoxycarbonyl</td>
</tr>
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<td>(Boc)₂O</td>
<td>(Boc)₂O</td>
<td>di-\textit{tert}-butyldicarbonate</td>
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<td>b.p.</td>
<td>b.p.</td>
<td>boiling point (°C)</td>
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<tr>
<td>Bu</td>
<td>Bu</td>
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<td>\textit{t}-Bu</td>
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<td>(c)</td>
<td>concentration (g/100 mL)</td>
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<tr>
<td>\textit{ca.},</td>
<td>\textit{ca.},</td>
<td>\textit{circa} (approximately)</td>
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<tr>
<td>conc.</td>
<td>conc.</td>
<td>concentrated</td>
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<tr>
<td>COSY</td>
<td>COSY</td>
<td>homonuclear ((^1\text{H}/^1\text{H})) correlation spectroscopy</td>
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<td>(d)</td>
<td>(d)</td>
<td>doublet</td>
</tr>
<tr>
<td>(\delta)</td>
<td>(\delta)</td>
<td>chemical shift (parts per million)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>DEPT</td>
<td>distortionless enhancement of polarisation transfer</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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</tr>
<tr>
<td>dm</td>
<td>demimetre</td>
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<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
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</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<td>dppp</td>
<td>1,4-bis(diphenylphosphino)propane</td>
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<td>d.r.</td>
<td>diastereomeric ratio</td>
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<tr>
<td>e.g.</td>
<td>exemplia gratia</td>
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<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
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<tr>
<td>E</td>
<td>entgegen (opposite)</td>
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<tr>
<td>EI</td>
<td>electron impact</td>
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<td>ether</td>
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<td>equiv. or eq.</td>
<td>equivalents</td>
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<td>electrospray ionisation</td>
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</tr>
<tr>
<td>eV</td>
<td>electron volt</td>
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<td>FTIR</td>
<td>fourier transform infrared</td>
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</tr>
<tr>
<td>g</td>
<td>gram</td>
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<tr>
<td>h</td>
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<td>Hg(OTf)₂</td>
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<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
<td></td>
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<tr>
<td>Hz</td>
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<tr>
<td>Im.</td>
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<td>infrared</td>
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<td>$J$</td>
<td>coupling constant (Hz)</td>
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<td>Jones’ reagent</td>
<td>Chromic and sulfuric acid in acetone</td>
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<td>$t$-BuOK</td>
<td>potassium $t$-butoxide</td>
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<td>potassium hexamethyldisilazide</td>
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</tr>
<tr>
<td>$L$</td>
<td>length (dm)</td>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
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<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<tr>
<td>M</td>
<td>Molar ($\text{molL}^{-1}$)</td>
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<tr>
<td>m</td>
<td>multiplet</td>
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<td>$M^{+*}$</td>
<td>molecular ion</td>
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<tr>
<td>MsCl</td>
<td>methanesulfonyl chloride</td>
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</table>
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

v_{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\(_2\)NH  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 trisopropylsilyl
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 microtubules 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.