
The Chemoenzymatic Synthesis of the Lycorine Framework and the Synthesis of C-3-Mono-Alkylated Oxindoles *via* the Palladium- Catalysed Ullmann Cross-Coupling Reaction.

A thesis submitted for the degree of Doctor of Philosophy
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by

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Declaration

I declare that the material published in this Thesis represents the result of original work carried out by me during the period 2005 – 2010 and has not been submitted for examination for any other degree. This Thesis is less than 100,000 words in length. Wherever possible, established procedures have been acknowledged by citation of the original publications from which they derive.

Matthew Jones
13 January 2013

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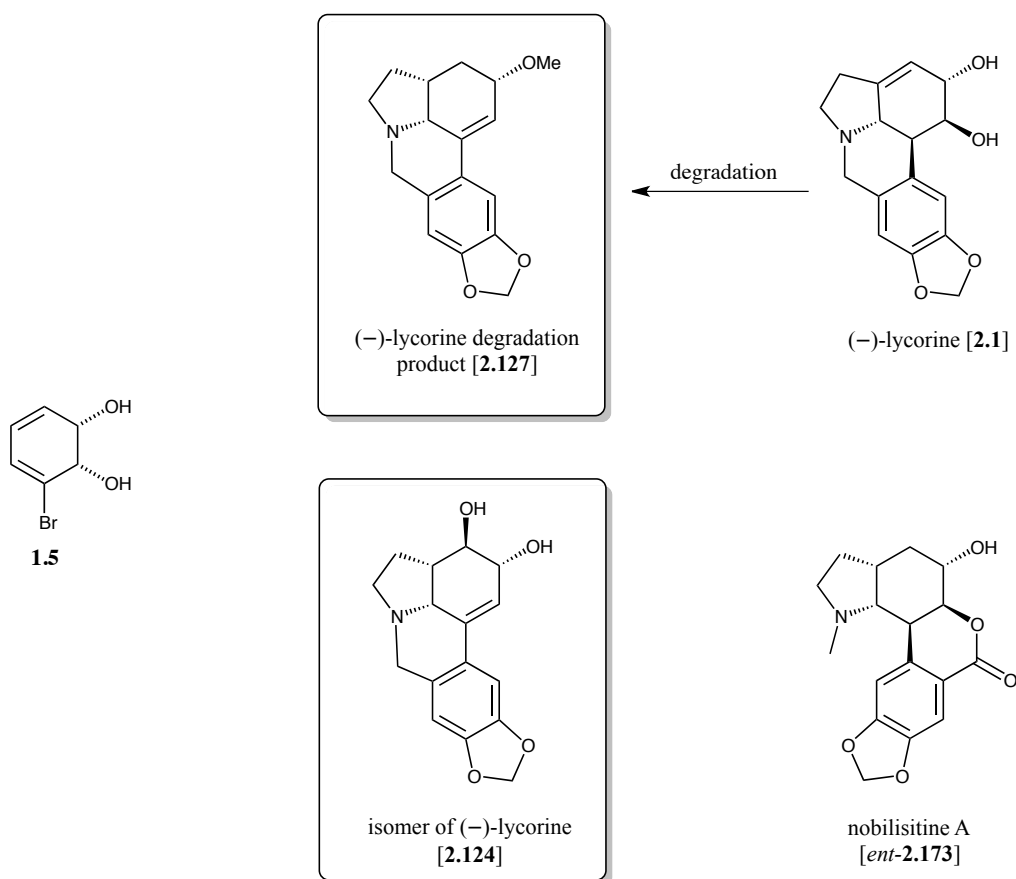
My research work would not have been possible without the assistance of the hard-working staff at the RSC and I am particularly grateful for the contributions of Dr Tony Willis, Mr Gordon Lockhart and Mr Paul Gugger. I should also like to acknowledge the help of the postdoctoral fellows Dr Jonathon Foot, Dr Jens Höegermeier and Dr Rajiv Menon.

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The following publications have resulted from the research work described in this Thesis.

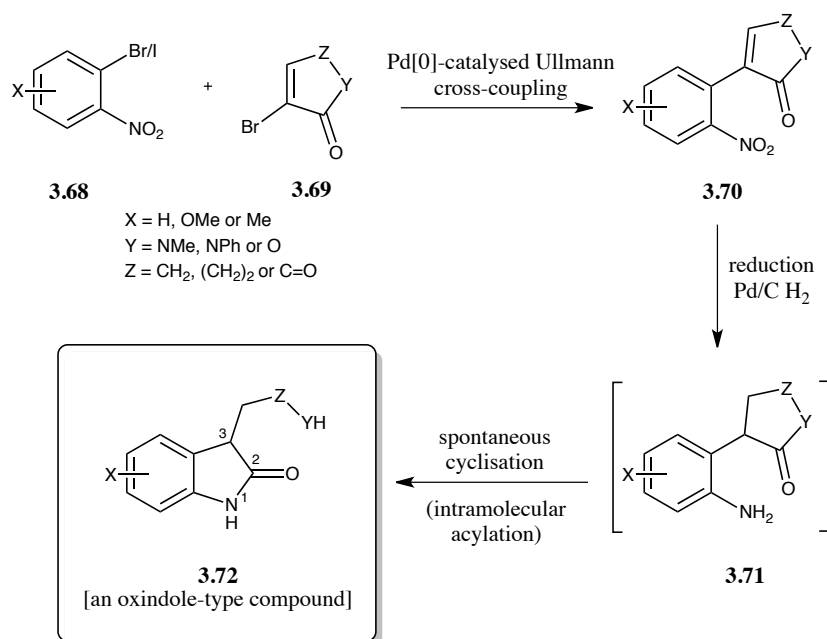
1. “New Protocols for the Synthesis of 3,4-Annulated and 4-Substituted Quinolines From β -Bromo- α,β -Unsaturated Aldehydes and 1-Bromo-2-Nitrobenzene or 2-Bromoacetanilide.” Some, S.; Ray J. K.; Banwell, M. G.; Jones, M. T. *Tetrahedron Letters*, **2007**, 48, 3609-3612.
2. “Rapid and Enantioselective Assembly of the Lycorine Framework Using Chemoenzymatic Techniques.” Jones, M. T.; Schwartz, B. D.; Willis, A. C.; Banwell, M. G. *Organic Letters*, **2009**, 11, 3506-3509.
3. “Synthesis of the Enantiomer of the Structure Assigned to the Natural Product Nobilisitine A.” Schwartz, B. D.; Jones, M. T.; Banwell, M. G.; Cade, I. A. *Organic Letters*, **2010**, 12, 5210-5213.
4. “A Pd[0]-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Approach to C-3 Mono-Alkylated Oxindoles and Related Compounds.” Banwell, M. G.; Jones, M. T.; Loong, D. T.; Lupton, D. W.; Pinkerton, D. M.; Ray, J. K; Willis, A. C. *Tetrahedron*, **2010**, 66, 9252-9262.
5. “The Palladium-Catalysed Ullmann Cross-Coupling Reaction.” Banwell, M. G.; Jones, M. T.; Rieke, T. A. *Chemistry in New Zealand*, **2011**, 75, 122-127.

Chapter One of this Thesis briefly describes the history and production of chiral starting materials of type-**1.5** (Scheme A.1) and summarises their synthetic attributes as well as providing several examples of their use in natural product synthesis. Chapter Two begins with a succinct review of the structural characteristics and biological properties of the *Amaryllidaceae* alkaloid (–)-lycorine [**2.1**] and describes several established synthetic approaches to compounds of this type. Thereafter, experimentally-based research leading to the development of a rapid and enantioselective synthesis of the lycorine framework, starting from the *cis*-1,2-dihydrocatechol **1.5**, and culminating in the first syntheses of the lycorine derivatives **2.127** and **2.124** is described (Scheme A.1). Additionally, the true structure of the *Amaryllidaceae* alkaloid nobilisitine A [*ent*-**2.173**] is disclosed.



Scheme A.1 Key Structures Associated with Research Work Described in Chapters One and Two of this Thesis.

Chapter Three provides a short review of the classic Ullmann bi-aryl synthesis and introduces the Pd[0]-catalysed variant. The synthesis of indoles and quinolones *via* a Pd[0]-catalysed Ullmann cross-coupling/reductive cyclisation approach is then described. Thereafter, research leading to the efficient synthesis of C-3 monoalkylated oxindoles of the general form **3.72** by such means is presented (Scheme A.2). Chapter Three also presents the results of methodological studies directed towards improving the efficiency of the Pd[0]-catalysed Ullmann cross-coupling reaction by using highly activated copper powders. This theme is developed further in Chapter Four.



Scheme A.2 The Pd[0]-Catalysed Ullmann Cross-Coupling/Reductive Cyclisation Approach to C-3 Mono-Alkylated Oxindoles.

The following abbreviations have been used throughout this Thesis:

A	absorbance
Å	Ångstrom (1×10^{-10} m)
Ac	acetyl
AIBN	2,2'-azo- <i>bis</i> -isobutyronitrile
$[\alpha]_D$	specific rotation of the sodium D-line
APT	attached proton test
aq.	aqueous
Ar	aryl
atm	atmosphere
BC	before Christ
Bn	benzyl
Boc	<i>tertiary</i> -butoxycarbonyl
brd	broad
Bu	butyl
Burgess reagent	methyl <i>N</i> -(triethylammoniumsulfonyl)carbamate
Bz	benzoyl
<i>c</i>	concentration (mol.L ⁻¹)
<i>ca.</i>	<i>circa</i> (approximately)
cat.	catalyst or catalytic quantity
CD	circular dichorism
cm	centimetre(s)
conc.	concentration (mol.L ⁻¹)
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
°C	degrees Celcius
Δ	heat (unless used in a compound name where Δ denotes olefin)
DIBAL-H	di- <i>iso</i> -butylaluminium hydride

DIPEA	di- <i>iso</i> -propylethylamine
DIPHOS	1,2- <i>bis</i> (diphenylphosphino)ethane
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	<i>N,N</i> -dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMSO	dimethylsulfoxide
DoM	directed <i>ortho</i> -metallation
dppf	1,1'-bis(diphenylphosphino)ferrocene
2D NMR	two-dimensional nuclear magnetic resonance
<i>E</i>	<i>entgegen</i> (opposite)
e.e.	enantiomeric excess
EI	electron impact ionisation (mass spectrometry)
<i>ent</i>	prefix used to indicate the enantiomer of a compound
equiv	equivalent
ESI	electrospray ionisation (mass spectrometry)
Et	ethyl
<i>et al.</i>	<i>et alia</i> (and others)
EtOH	ethanol
eV	electron Volt(s)
g	gram(s)
<i>gem</i>	geminal
h	hours(s)
HMPA	hexamethylphosphoric acid triamide (hexamethylphosphoramidate)
hν	irradiation with light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IMDA	intramolecular Diels-Alder (reaction)
^{<i>i</i>} Pr	<i>iso</i> -propyl
IR	infrared
<i>J</i>	coupling constant (Hz)

KHMDS	potassium <i>bis</i> (trimethylsilyl)amide
L	litre(s)
<i>l</i>	path length (cm)
λ	wavelength (nm)
λ_{max}	wavelength of maximum absorbance (nm)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
lit.	literature value
L-selectride	lithium tri- <i>sec</i> -butylborohydride
m	multiplet
M^{+}	molecular ion (arising from electron-impact ionisation)
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MeOH	methanol
mg	milligram(s)
μg	microgram(s)
MHz	mega-Hertz
min	minute(s)
mL	milliliter(s)
μL	microliter(s) microliter(s)
mm	millimetre(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
m.p.	melting point ($^{\circ}\text{C}$)
MS	mass spectrometry
μ -wave	microwave irradiation
<i>m/z</i>	mass:charge ratio
<i>n</i>	number of monomeric units in an oligomer
<i>n</i>	normal (e.g. an unbranched alkyl chain)
nm	nanometre(s) ($1 \times 10^{-9} \text{ m}$)
NMR	nuclear magnetic resonance
ν_{max}	infrared absorbance maxima

ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	pyridinium chlorochromate
Ph	phenyl
pH	logarithm of the reciprocal of the hydrogen ion concentration (i.e. – $\log_{10}[\text{H}^+]$)
PMB	<i>para</i> -methoxybenzyl
q	quartet
Raney-Co	Raney cobalt sponge-metal catalyst
Raney-Ni	Raney nickel sponge-metal catalyst
ref.	reference
Rieke-Cu	Rieke copper
®	registered trademark
R_f	retardation factor (chromatography)
s	singlet
<i>sec</i>	secondary
<i>sp.</i>	species
T	temperature (°C)
t	triplet
<i>tert</i>	tertiary
TBS	<i>tert</i> -butyldimethylsilyl
TDO	toluene dioxygenase
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Tf	trifluomethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	trade mark
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	tetramethylsilyl
trig	trigonal
Ts	<i>para</i> -toluenesulfonyl (or tosyl)
UV	ultraviolet (spectroscopy)
V	Volt(s)

<i>viz.</i>	<i>videlicet</i> ('that is' or 'namely')
<i>vs.</i>	<i>versus</i>
v/v	unit volume per unit volume (ratio)
W	Watt(s)
w/v	unit weight per unit volume
Z	zusammen ('together')
>	greater than
<	less than

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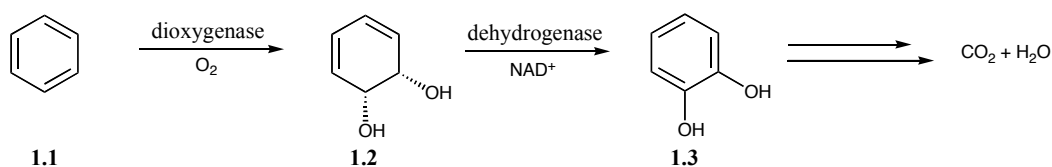
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cis-1,2-Dihydrocatechols: Versatile Starting Materials for the Stereoselective Synthesis of Natural Products

1.1 Introduction

It has long been recognized that certain micro-organisms are capable of the metabolic degradation of aromatic compounds *via* oxidative processes and that these organisms are widely distributed in the environment.^{1,2} Numerous examples of such bacterial (prokaryotic) and fungal (eukaryotic) species have been discovered.³ *Pseudomonas* bacteria constitute by far the most important genus of such prokaryotes (based on frequency of isolation from environmental samples) whilst the fungal genus *Candida* predominates amongst eukaryotes.⁴

In a seminal study published in 1968 Gibson and co-workers demonstrated that the soil bacterium *Pseudomonas putida* F1 metabolizes aromatic compounds *via cis*-1,2-dihydrocatechol derivatives of type **1.2** (Scheme 1.1).⁵ This metabolic process is fundamentally different from that of eukaryotic organisms including fungi, plants and animals, which metabolise arenes *via* the corresponding *trans*-1,2-dihydrocatechol derivatives.⁶ Cell extracts from *P. putida* F1 were found to contain a dehydrogenase enzyme that catalysed the conversion of *cis*-1,2-dihydrocatechol [**1.2**] into catechol [**1.3**], whereas *trans*-1,2-dihydrocatechol was not transformed in this way (Scheme 1.1).⁵ The dehydrogenase enzyme proved to be capable of converting synthetically generated *cis*-1,2-dihydrocatechol into catechol in the presence of the electron acceptor NAD⁺. In the wild-type organism the catechols are subjected to further oxidative degradation leading, ultimately, to carbon dioxide and water (Scheme 1.1).⁷



Scheme 1.1 *The Oxidative Degradation of Aromatic Compounds by Bacterial (Prokaryotic) Organisms such as Pseudomonas putida.*

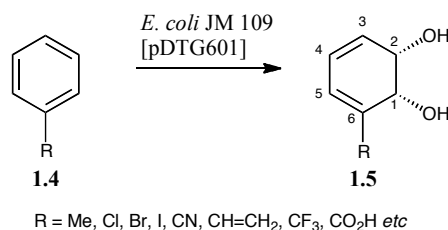
In subsequent experiments Gibson and co-workers treated *P. putida* F1 with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and thereby obtained several mutant strains. One of these, designated *P. putida* 39D, lacked the dehydrogenase enzyme that converts *cis*-1,2-

dihydrocatechols into the corresponding aromatic catechols. Due to the absence of the dehydrogenase enzyme in the mutant organism significant quantities of *cis*-1,2-dihydrocatechol substances accumulate during fermentation and these may be isolated and characterised.^{8,9}

The oxidation of arenes to *cis*-1,2-dihydrocatechols is catalysed by dioxygenase enzymes and several of these have been isolated from *P. putida* and other bacterial species. In the context of synthetic chemistry, by far the most important of these enzymes is toluene-dioxygenase (TDO) as this exhibits the greatest capacity to metabolise a wide range of substrates. Other significant dioxygenases include benzene- (BDO), naphthalene- (NDO), benzoate- (BZDO) and biphenyl-dioxygenase (BPDO). Experiments involving $^{18}\text{O}_2$ and mixtures of $^{16}\text{O}_2$ and $^{18}\text{O}_2$ have established that both of the oxygen atoms that TDO incorporates into *cis*-1,2-dihydrocatechol compounds are derived from a single molecule of dioxygen.^{8,9} The precise mechanism by which TDO cleaves the aromatic system is not yet understood but it is evident that the process takes place with the substrate bonded, *via* dioxygen, to iron at the catalytic site of the enzyme.

1.2 Biocatalytic Production of *cis*-1,2-Dihydrocatechols

The genes encoding for TDO in *P. putida* 39D and the mutant strain *P. putida* UV4 have been isolated, cloned and expressed in *Escherichia coli* JM109. The resulting recombinant organisms, *E. coli* JM109 [pDTG601] and *E. coli* JM109 [pKST11], as well as mutant strains of the parent organisms, have been employed in the biocatalytic conversion of a wide range of aromatic compounds into *cis*-1,2-dihydrocatechols. Production of *cis*-1,2-dihydrocatechols, whether by fermentation of arenes with mutant strains of *P. putida* or with recombinant organisms, can be conducted on a multi-kilogram scale. The metabolites are frequently obtained in essentially enantiomerically pure form (typically > 99.8% e.e.) and yields may be as high as 35 g per liter of fermentation broth. A wide range of functional groups is tolerated and, consequently, the process can be applied to a remarkable range of substrates. While more than 400 *cis*-1,2-dihydrocatechol metabolites have been reported, it is those derived from mono-nuclear substrates in which R = Me, Cl, Br or I (Scheme 1.2) that have served as the most useful as starting materials in synthetic chemistry.¹⁰



Scheme 1.2 The Oxidative Conversion of Mononuclear Arenes into *cis*-1,2-Dihydrocatechol Compounds by Recombinant forms of *E. coli* that Overexpress TDO.

1.3 The Synthetic Utility of *cis*-1,2-Dihydrocatechols

The biocatalytic production of *cis*-1,2-dihydrocatechols provides a range of versatile starting materials for chemical synthesis and these may be manipulated through various bond-forming or bond-cleavage reactions. Because the research work described in Chapter 2 of this Thesis employs the *cis*-1,2-dihydrocatechol that is derived from bromobenzene the following sections are focused upon the reactivity and synthetic utility of the halogenated variants of compounds of the general form **1.5** (R = Cl, Br, I).

1.3.1 Sites of Reactivity Associated With Halogenated *cis*-1,2-Dihydrocatechols

While the structures of halogenated *cis*-1,2-dihydrocatechols **1.5** are relatively simple, compounds of this type possess a remarkable combination of reactive functionalities each of which can be manipulated selectively (Figure 1.1).¹¹ The range of such characteristics is extensive but several are especially noteworthy. The hydroxyl substituents may be protected as a pair or they may be individually derivatised. In either case they serve as a means of exerting stereocontrol because reactions with the π -bonds of the associated diene tend to take place at the less hindered β -face of the molecule. The halogen substituent at C-6 differentiates the reactivity of the two olefinic bonds and the hydroxyl moieties of compounds of type-**1.5** through steric and electronic effects. Thus, when X = Br the C-3 – C-4 olefinic bond preferentially reacts with electrophilic species and it may be epoxidised with complete regioselectivity using, for example, the oxidizing agent *m*-CPBA. The remaining C-5 – C-6 double bond is then available for manipulation and it has been exploited as a site for dihydroxylation or ozonolysis. The latter process allows for ring-cleavage. Various ring-closure processes that result in overall ring-expansion or contraction can follow this. Both of these processes have been exploited in

the synthesis of carbohydrates and other polyoxygenated compounds from *cis*-1,2-dihydrocatechols.¹² Importantly, the C-3 – C-6 diene system can engage in various cycloaddition reactions.¹³ Finally, the halogen substituent can participate in transition-metal catalysed cross-coupling reactions or it may be removed by reduction (these normally involving metal-for-halogen exchange processes followed by protonation).

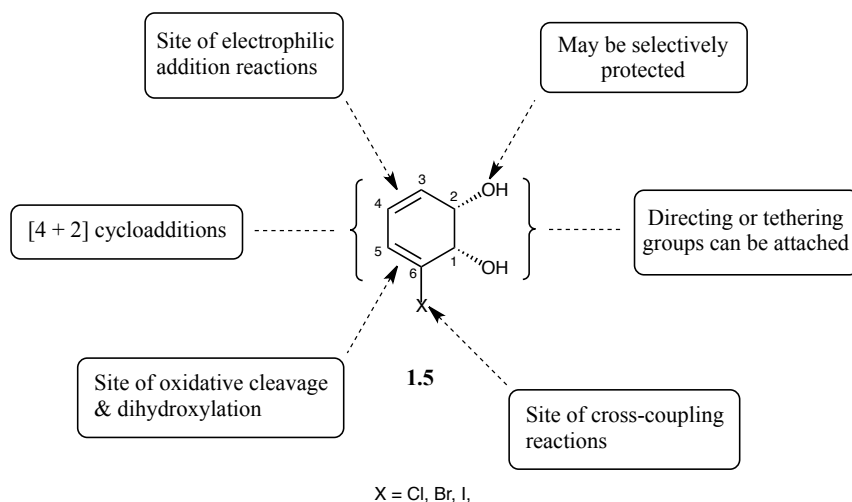
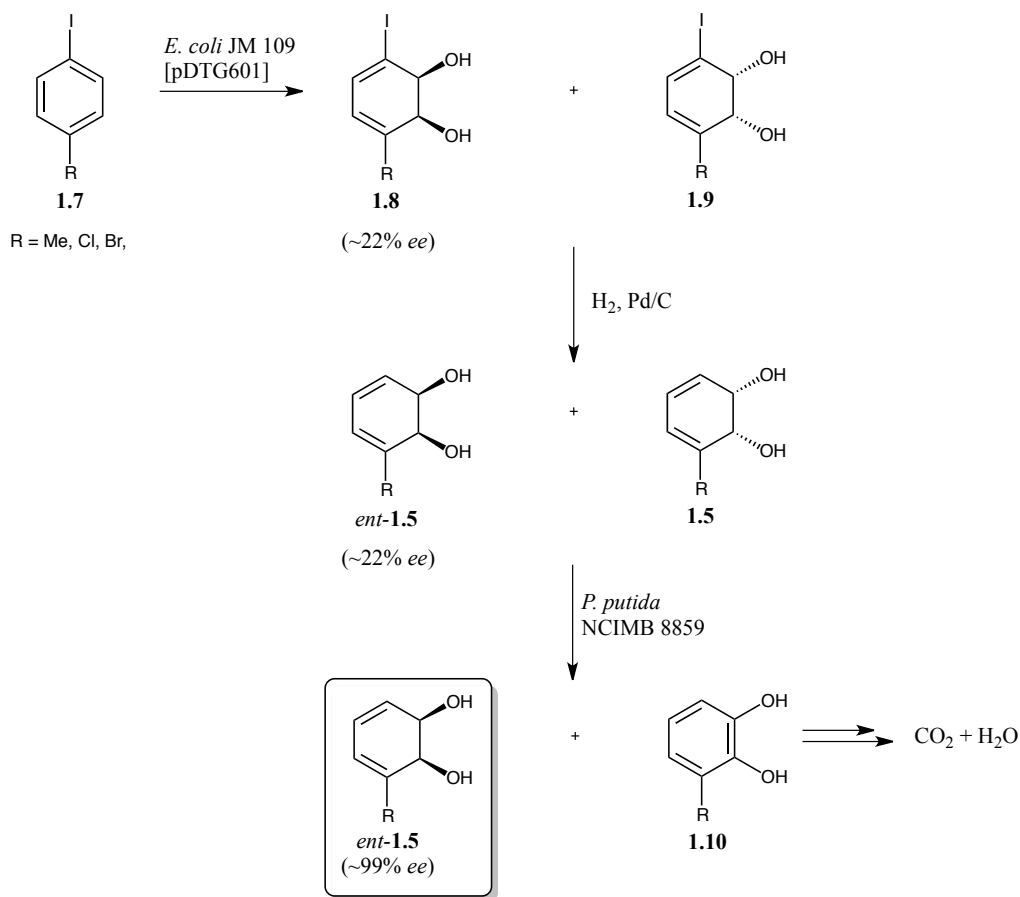


Figure 1.1 *Reactive Sites of Halogenated cis-1,2-Dihydrocatechols*

1.3.2 Accessing Either Enantiomeric Form of *cis*-1,2-Dihydrocatechols

A limitation of the biocatalytic production of *cis*-1,2-dihydrocatechols is that, with few exceptions, only one enantiomer of each compound is generated. As such, it might appear that the potential for enantioselective synthesis from such starting materials is severely restricted. Fortunately, Boyd and co-workers have developed a technique that directly addresses this problem and provides access to the other enantiomer (Scheme 3).¹⁴ Boyd describes this technique as “enantiomeric switching” which involves subjecting a *p*-iodinated benzene derivative **1.7** (R = Me, Cl, Br) to biocatalytic transformation with TDO (Scheme 1.3). This produces a mixture of compound **1.8** and its enantiomer **1.9** in which the former predominates due to the fact that the enzyme ‘recognises’ iodine as the larger substituent. This mixture of enantiomers is then subjected to Pd/C hydrogenolysis, which removes the labile iodine substituent whilst leaving the other substituent unaffected. Finally, the mixture is subjected to fermentation with a wild-type strain of *P. putida* producing a dehydrogenase enzyme and which, therefore, selectively metabolises the undesired substrate (in this case compound **1.5**)

leaving compound *ent*-**1.5** to accumulate. Obviously this technique has the disadvantage that a significant amount of compound **1.5** is wasted in order to obtain the target enantiomer but compounds of the type *ent*-**1.5** are much more difficult to obtain by other means.¹⁵



Scheme 1.3 The Acquisition of Compound *ent*-**1.5** Through Chemoenzymatic Methods.

1.4 Synthetic Applications of *cis*-1,2-Dihydrocatechols.

Synthetic chemists were slow to recognise the potential of *cis*-1,2-dihydrocatechols. It was not until 1983 that chemists working at ICI reported the use of bio-catalytically derived *meso-cis*-1,2-dihydrocatechol for the industrial-scale synthesis of polyphenylene.¹⁶ In 1987 Ley reported the synthesis of racemic pinitol [(±)-**1.14**] from *meso-cis*-1,2-dihydrocatechol [**1.11**] (Figure 1.2).¹⁷ This work was significant because it demonstrated the value of *cis*-1,2-dihydrocatechols as precursors to poly-oxygenated compounds.

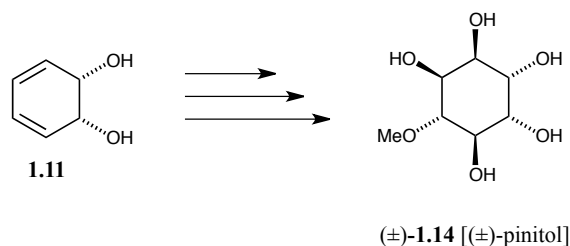


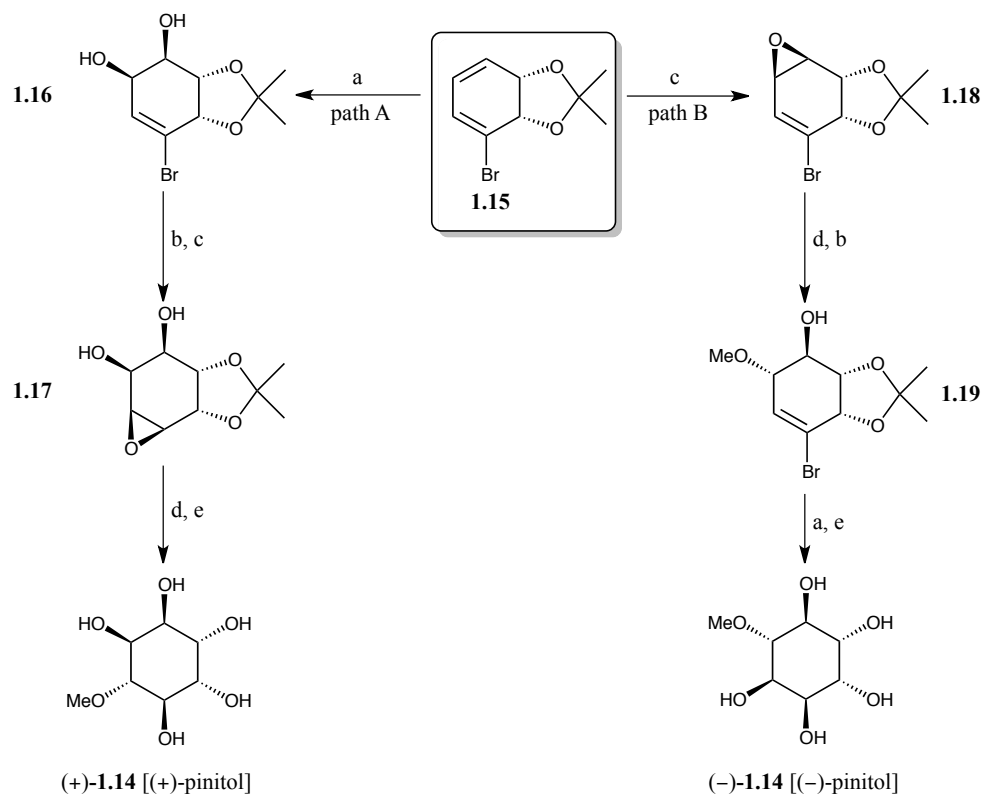
Figure 1.2 *Ley's Synthesis of (±)-1.14 [(±)-Pinitol]*

Following Ley's publication of the synthesis of (±)-pinitol numerous research groups have used *cis*-1,2-dihydrocatechols in various settings and the field continues to grow rapidly. A thorough summary of the current state of this work is well beyond the scope of this chapter but several such reviews have been published.¹¹ The examples presented below have been selected to illustrate various strategies by which the reactive properties of *cis*-1,2-dihydrocatechols of the general form **1.5** have been exploited. For the sake of brevity only the pertinent synthetic steps are described in detail. The reader is referred to the relevant publications for thorough descriptions of all aspects of the various syntheses.

1.4.1 *cis*-1,2-Dihydrocatechols as Precursors to Polyoxygenated Compounds. The Enantioselective Synthesis of (+)- & (–)-Pinitol.

Ley's synthesis of racemic (±)-pinitol highlighted the value of *cis*-1,2-dihydrocatechols as precursors to poly-oxygenated compounds. However, Hudlicky recognised that this capacity could be combined with the potential of *cis*-1,2-dihydrocatechols to serve as starting materials in enantiodivergent syntheses. In particular, Hudlicky developed the concept of "proenantiotopic symmetry" to describe how differentiated reactive sites of *cis*-1,2-dihydrocatechols could be exploited to selectively synthesize opposite enantiomers of a compound by varying the order of chemical steps in a reaction sequence.¹⁸ This concept was elegantly demonstrated through the development of concise syntheses of (+)- and (–)-pinitol from the readily available acetonide **1.15** (Scheme 1.4).¹⁹ The reaction sequence (path A) that affords (+)-**1.14** [(+)-pinitol] begins with the osmium–catalysed *cis*-dihydroxylation of the acetonide **1.15** to afford the diol **1.16**. The polarization of the 1,3-diene system induced by the bromine substituent and the steric effect of the acetonide moiety combine to ensure that the more electron-rich double bond is hydroxylated from the less congested *exo*-face of the molecule. The diol **1.16** was then subjected to reductive debromination with LiAlH_4

and the resulting dehalogenated olefin was epoxidised, stereoselectively, with *m*-CPBA. The ensuing oxirane **1.17** was then subjected to alumina-promoted methanolysis of the epoxide followed by acid-catalysed cleavage of the acetonide to generate the target (+)-**1.14** [(+)-pinitol].



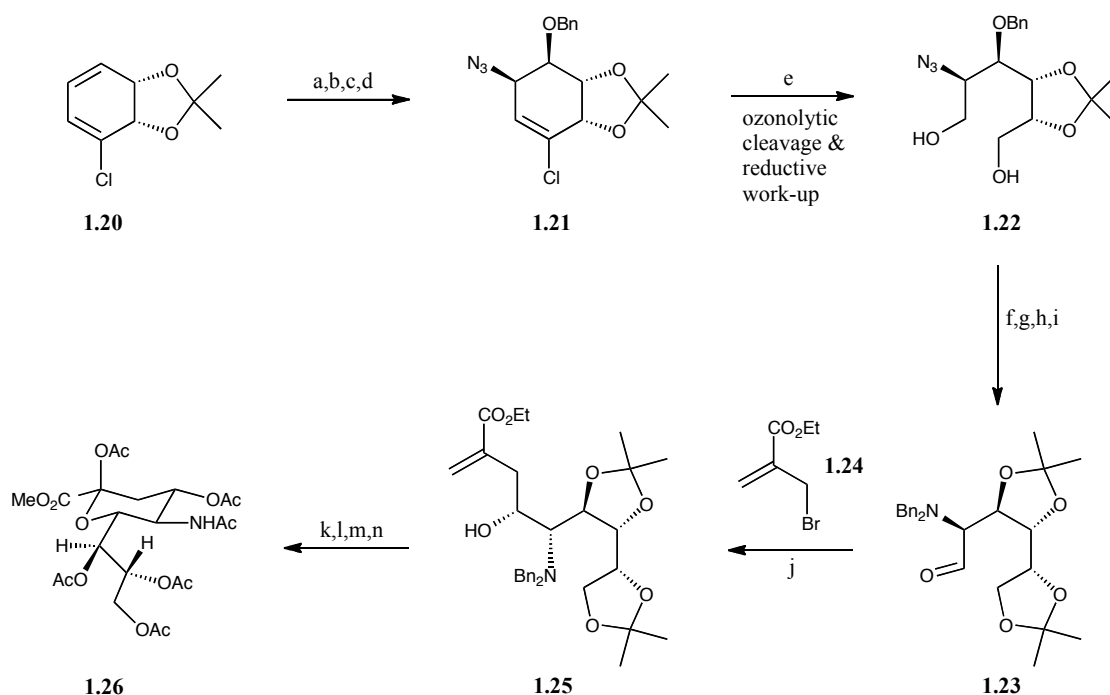
Scheme 1.4 Reaction conditions: (a) OsO₄, NMO; (b) LiAlH₄; (c) *m*-CPBA; (d) Al₂O₃, MeOH; (e) HCl, H₂O.

By changing the order of the reaction sequence (Path B) the proenantiotopic symmetry of substrate **1.15** was exploited so as to generate compound (-)-**1.14** [(-)-pinitol]. Each of the reaction steps has an exact counterpart in the alternative sequence and enantiodivergence was achieved solely by reordering of the sequence.

1.4.2 *cis*-1,2-Dihydrocatechols as Substrates for Oxidative Cleavage.

The utility of *cis*-1,2-dihydrocatechols as precursors to poly-oxygenated compounds is not limited to carbocyclic products since they have also proven to be excellent precursors to carbohydrates. Hudlicky was amongst the first to recognise this potential and he has demonstrated that almost any hexose derivative can be obtained from *cis*-1,2-dihydrocatechol precursors by means of ozonolytic cleavage of the C-5 – C-

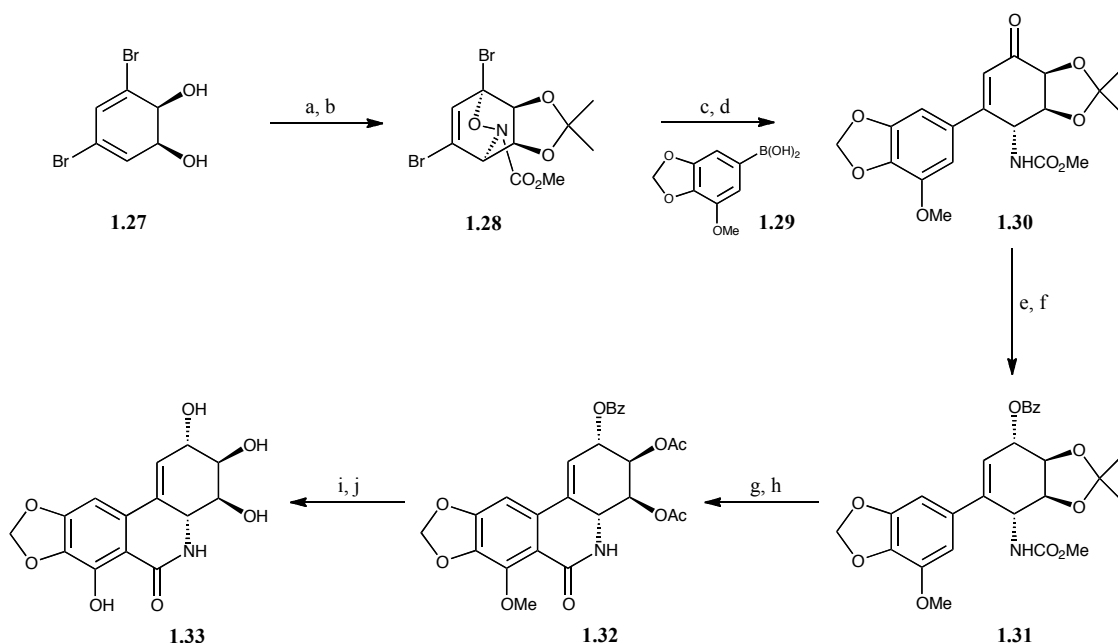
6 olefinic bond followed by reductive cyclisation.²⁰ Banwell has exploited the technique of ozonolytic cleavage and reductive cyclization for the synthesis of the *per*-acetylated derivative of (–)-*N*-acetylneuraminic acid **1.26** (Scheme 1.5).²¹ Thus, the reaction sequence began with the acetonide derivative, **1.20**, of the *cis*-1,2-dihydrocatechol **1.5** (R = Cl). Manipulation of compound **1.20** via a sequence of well-established reactions²² afforded the azide **1.21** and treatment of the latter compound with ozone resulted in cleavage of the carbocyclic ring at the C-5 – C-6 double bond and subsequent *in situ* reduction, with NaBH₄, gave the diol **1.22**. A sequence of protecting group manipulations furnished the aldehyde **1.23** that was condensed with the organozinc compound derived from the bromoacrylate **1.24** to afford the ester **1.25**. This material was then readily converted, over four conventional steps, into the *per*-acetylated derivative, **1.26**, of (–)-*N*-acetylneuraminic acid.



Scheme 1.5 Reaction conditions: (a,b,c) see reference 23; (d) NaH, THF, 0 °C, 0.75 h then BnBr, 0 - 18 °C, 4 h, 70% over 4 steps; (e) O₃, MeOH, -78 °C - 0 °C then NaBH₄ (9.0 mol equiv) 18 °C, 7 h, 70%; (f) H₂, (50 psi), Pd/C, MeOH, 18 °C, 7 h; (g) BnBr, K₂CO₃, 2:1 MeCN:H₂O, 60 °C, 16 h, 90% over 2 steps; (h) acetone, TfOH (cat) 0 °C, 3 h, 62%; (i) (COCl)₂, DMSO, DCM, -78 °C - 0 °C, 1 h then Et₃N, 100%; (j) Zn dust, sat. aq. NH₄Cl, THF, 0 - 18 °C, 0.75 h, 85%; (k) NaBH₄, EtOH, - 10° C, 4 h then TMSCl, HMDS, pyridine, 0 - 18 °C, 19 h, 60%; (l) AD-mix-α, Bu^tOH, H₂O, 18 °C, 22 h then Pb(OAc)₄, CaCO₃, DCM, 18 °C, 0.33 h, 89%, (m) 6% w/v HCl in MeOH, 18 °C, 18 h then Ac₂O, DMAP (trace), pyridine, 18 °C, 20h, 60%; (n) Pd black 5% w/v, HCO₂H, MeOH, 18 °C, 0.5 h then Ac₂O, DMAP (trace), pyridine, 18 °C, 20h, 75%.

1.4.3 *cis*-1,2-Dihydrocatechols as Substrates for Cross-coupling Reactions.

Amongst the most useful of modern techniques for C-C bond formation are the various methods of palladium-catalysed cross-coupling and Hudlicky has synthesised the *Amaryllidaceae* alkaloid (+)-narciclasine **1.33** by employing, as key features in his work, a Suzuki-Miyaura cross-coupling reaction and the *cis*-1,2-dihydrocatechol **1.27** as starting material (Scheme 1.6).²³ Thus, compound **1.27** was first protected as its acetonide derivative and this was subjected to a nitroso-Diels-Alder cyclisation reaction to afford the oxazine **1.28**. The oxazine was then engaged in a Suzuki-Miyaura cross-coupling reaction with the boronic acid **1.29** and, after formation of the α,β -unsaturated ketone by treatment with *tris*-trimethylsilane, the α -aminoconduritol **1.30** was obtained. Luche reduction of the enone moiety within compound **1.30** followed by epimerization of the ensuing allylic alcohol under Mitsunobu conditions then gave the benzoate **1.31**. This last compound was subjected to a series of protecting group manipulations and the resulting compound was engaged in a Bischler-Napieralski reaction to afford the protected form, **1.32**, of the target. A two-step deprotection sequence then afforded (+)-narciclasine itself.

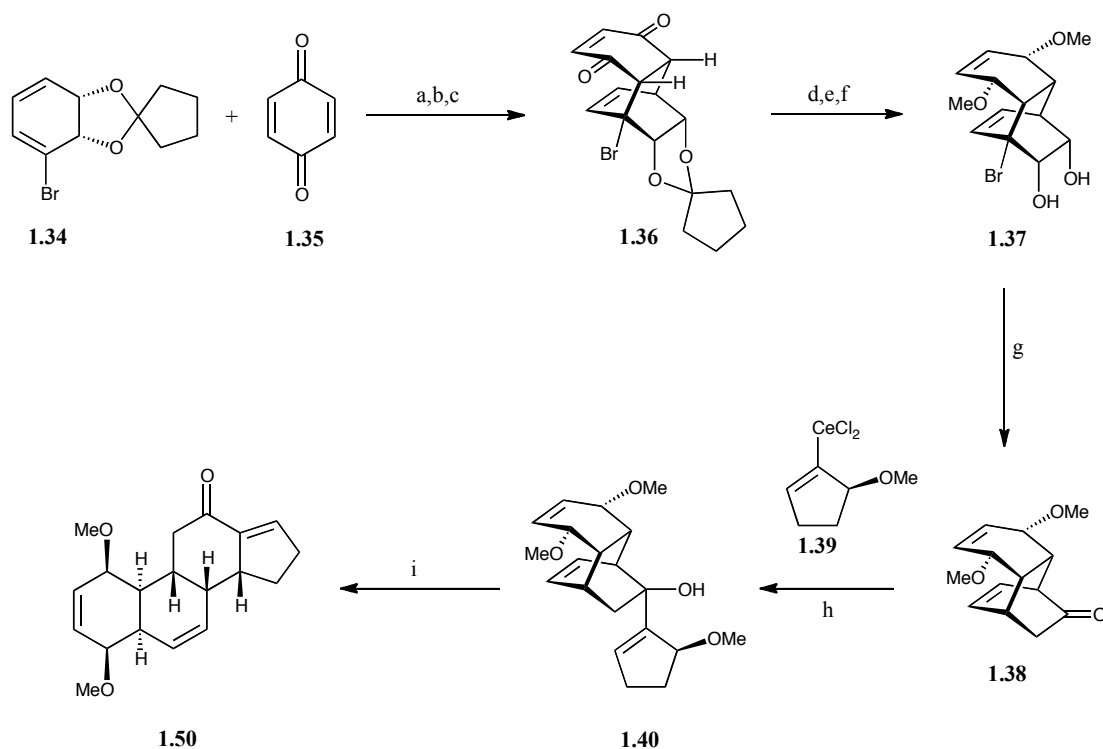


Scheme 1.6 Reaction conditions: (a) 2,2-DMP, *p*-TsOH; (b) MeCONHOH, NaIO₄, 78% over two steps; (c) Pd(PPh₃)₄, aq. Na₂CO₃, 80 °C, 30%, (d) TTMSS, AIBN, 80 °C, 80%, (e) NaBH₄, CeCl₃·7H₂O, 0° C, 80%; (f) BzOH, Bu₃P, DEAD, 65%; (g) Dowex 50X8-100 ion-exchange resin, MeOH; (h) Ac₂O, pyridine, DMAP, 70% over two steps; (i) Tf₂O, DMAP, 0 °C, 40%; (j) Amberlyst A21, MeOH then LiCl, 120 °C, 20% over two steps.

1.4.4 *cis*-1,2-Dihydrocatechols as Partners in Cycloaddition Reactions.

Halogenated *cis*-1,2-dihydrocatechols of the general form **1.5** have proven to be valuable as 4π addends in Diels-Alder cycloaddition reactions. Numerous highly functionalized bi- and tri-cyclic compounds have been synthesised by exploiting *cis*-1,2-dihydrocatechols in this manner²⁴ and Hudlicky's synthesis of (+)-narciclasine **1.33** (Scheme 1.6) provides an example of such an application. A wide range of *cis*-1,2-dihydrocatechols and their derivatives have been shown to engage in either inter- or intra-molecular Diels-Alder cycloaddition reactions. Halogenated *cis*-1,2-dihydrocatechols are particularly reactive when combined with suitably activated dieneophiles including alkenes, singlet-oxygen and nitroso compounds. This is due to the polarizing effect of the halogen substituent on the diene. Moreover, this polarity, in combination with the directing effects of the C-2 and C-3 oxygen substituents, dictates that cycloaddition processes proceed with high levels of regio- and stereo-control.²⁵

Banwell's synthesis of a highly functionalized steroidal nucleus (Scheme 1.7)²⁶ illustrates several of these characteristics. The reaction sequence begins with a Diels-Alder cycloaddition reaction between the cyclopentylidene derivative, **1.34**, of the *cis*-1,2-dihydrocatechol **1.5** ($X = \text{Br}$) and *p*-benzoquinone **1.35**. The configuration of the resulting crystalline product, **1.36**, was predicted on the basis that the dienophile would approach *via* the sterically less hindered face and that an *endo*-type transition state would be favoured. These predictions were confirmed by single-crystal X-ray analysis. The diketone **1.36** was subjected to several functional group interconversions to afford the diol **1.37** and this was itself manipulated to generate the ketone **1.38**. This ketone reacted with the chiral organocerium reagent **1.39** with complete diastereofacial selectivity to afford the tertiary alcohol **1.40**. When the latter compound was treated with KHMDS in refluxing THF/toluene it underwent an anionic oxy-Cope rearrangement to afford, *via* an intermediate enolate that loses a methoxide ion, compound **1.50** embodying the steroidal nucleus.



Scheme 1.7 Reaction conditions: (a) **1.34**, **1.35** (1.5 mol equiv.), C₆H₆, reflux, 18 h, 55%; (b) NaBH₄, CeCl₃·7H₂O, 1:1 v/v MeOH/CH₂Cl₂, 18 °C, 0.33 h; (c) NaH, MeI, THF, 18 °C, 1.5h, 62% over two steps; (d) 1:1 v/v MeCN:10% aq. HCl, 40 °C, 5 h, 72%; (e) 4-AcNHTEMPO, *p*-TsOH, CH₂Cl₂, 0 - 18 °C, 16 h, 82%; Ac₂O, pyridine, CH₂Cl₂, 18 °C, 1 h, 94%; (f) SmI₂, AcOH, THF, 0 - 18 °C, 0.25 h, 84%; (g) *n*-Bu₃SnH, AIBN (*cat.*), C₆H₆, reflux, 18 h, 84%; (h) **1.39** (5 mol equiv.), THF, -78 °C, 1 h, 80%; (i) KN(TMS)₂, THF/toluene, -78 - 66 °C, 2 h, 79%.

1.5 Aims of the Research Work Described in Chapter Two of This Thesis

As illustrated above, enzymatically-derived and enantiopure *cis*-1,2-dihydrocatechols of type-**1.5** (R = I, Br, Cl) are remarkably versatile starting materials for chemical synthesis. The Banwell research group maintains an ongoing program directed towards further exploiting these compounds in the *de novo* construction of natural products. Accordingly, the aim of the research work described in Chapter Two of this Thesis was to employ a *cis*-1,2-dihydrocatechol of the general form **1.5** in the synthesis of the structural framework of lycorine-type alkaloids. The motivations for pursuing such alkaloids as synthetic targets are presented in the following Chapter.

1.6 References.

- 1 Gray, P. H.; Thornton, H. G. *Zentralb. Bacteriol.*, [II], **1928**, 73, 74.
- 2 Atlas, R. M.; *Microbiol. Rev.*, **1981**, 45, 180.
- 3 ZoBell, C. E.; *Bacteriol. Rev.*, **1946**, 10, 49
- 4 Bartha, R.; Atlas, R. M. *Adv. Appl. Microbiol.*, **1977**, 22, 225.
- 5 Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry*, **1968**, 7, 2653.
- 6 Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Rep.*, **1998**, 15, 309.
- 7 (a) Gibson, D. T.; Subramanian, V. In *Microbial Degradation of Organic Compounds*; Gibson, D. T., Ed.; Marcel Dekker; New York, **1984**, pp 181 –252;
(b) Bayley, R. C.; Barbour, M. G.; in *Microbial Degradation of Organic Compounds*; Gibson, D. T., Ed.; Marcel Dekker; New York, **1984**, pp 253 – 294.
- 8 Gibson, D. T.; Cardini, G. E.; Maseles, F. C.; Kallio, R. E. *Biochemistry*, **1970**, 9, 1631.
- 9 Gibson, D. T. *CRC Crit. Rev. Microbiol.*, **1971**, 1, 199
- 10 Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH, Weinheim, **2007**, pp 218 – 219.
- 11 For reviews of the reactivity and synthetic applications of *cis*-1,2-dihydrocatechols see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta*, **1999**, 32, 35; (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.*, **2003**, 75, 223; (c) Johnson, R. A. *Org. React.* **2004**, 63, 117; (d) Hudlicky, T.; Reed, J. W. *Synlett.*, **2009**, 685; (e) Banwell, M. G. *Pure Appl. Chem.*, **2008**, 80, 669. Bon, D. J.; Lee, B.; Banwell, M. G.; Cade, I. A. *Chim. Oggi.*, **2012**, 30, 22.
- 12 Numerous examples are cited in: *Naturally Occurring Organohalogen Compounds - A Comprehensive Update*. Gribble, G. Springer - Verlag/Wein, New York, **2010**, pp 367 - 369.
- 13 Hudlicky, T.; Olivo, H. F.; McKibben, B.; *J. Am. Chem. Soc.*, **1994**, 116, 5108.
- 14 Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Sheldrake, G. N.; Taylor, S. C. *J. Chem. Soc., Chem Commun.*, **1995**, 117.
- 15 Examples of chemical syntheses of enantiomers of compound **1.5** include: (a) Akgun, H.; Hudlicky, T.: *Tetrahedron Lett.*, **1999**, 40, 3081, [synthesis of *ent*-**1.5** (R = SO₂Ph) in three steps from a tetrahydroperoxide precursor]; (b) Hanazawa, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.*, **2001**, 41, 5455. [Synthesis of

- acetone derivatives of *ent*-**1.5** (R = Me, Bu, Ph) in seven steps from advanced precursors.]
- 16 Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.*, **1983**, 954.
 - 17 Ley, S. V.; Sternfield, F.; Taylor, S. *Tetrahedron Lett.*, **1993**, 28, 225.
 - 18 (a) Hudlicky, T.; Thorpe, A. J. *Chem. Commun.*, **1996**, 1993; (b) Hudlicky, T.; Reed, J. W. in *Advances in Asymmetric Synthesis*, Vol. 1, Hassner, A.; Ed.; J.A.I. Press, Greenwich Connecticut, **1995**, 271.
 - 19 Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Price, J. D. *J. Am. Chem. Soc.*, **1990**, 112, 9439.
 - 20 Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.*, **1996**, 1195.
 - 21 Banwell, M. G.; De Savi, C.; Watson, K. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 2251.
 - 22 Nugent, T.; Hudlicky, T. *J. Org. Chem.*, **1998**, 63, 510
 - 23 Hudlicky, T.; Rinner, U.; Gonzales, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T.; Pettit, G. *J. Org. Chem.*, **2002**, 67, 8726.
 - 24 (a) Hudlicky, T.; Boros, C. H. *Tetrahedron Lett.*, **1993**, 34, 2557; (b) Banwell, M. G.; Dupuche, J. R.; Gable, R. W. *Aust. J. Chem.*, **1996**, 49, 639; (c) Hudlicky, T.; McKibben, B.; *J. Chem. Soc., Perkin Trans. 1*, **1994**, 485.
 - 25 (a) Hudlicky, T.; Boros, C. H.; Olivo, H. F.; Merola, J. S. *J. Org. Chem.*, **1992**, 57, 1026; (b) Ley, S. V.; Redgrave, A. J.; Taylor, S. C. Ahmed, S.; Ribbons, D. W. *Synlett.*, **1991**, 741.
 - 26 Banwell, M. G.; Hockless, D. C. R.; Holman, J. W.; Longmore, R. W.; McRae, K. J.; Pham, Ha T. T. *Synlett.*, **1999**, 1491.

Rapid and Enantioselective Assembly of the Lycorine Framework Using Chemoenzymatic Techniques

2.1 Introduction

2.1.1 A History of Lycorine Including its Structural Elucidation

The toxic alkaloid (–)-lycorine [2.1] is the most widely distributed secondary metabolite of the family of *Amaryllidaceae* plants. It was first isolated in 1877¹ from the bulbs of common daffodils (*Narcissus pseudonarcissus*) within which it constitutes as much as 1% of the dry weight of this portion of the plant.² Subsequently more than 500 structurally distinct alkaloids have been isolated from various *Amaryllidaceae* species, which is now regarded as one of the most important alkaloid-containing plant families. The three major classes of structurally distinct *Amaryllidaceae* alkaloids are the lycorine [2.1], galanthamine [2.2] and crinine [2.3] types.³

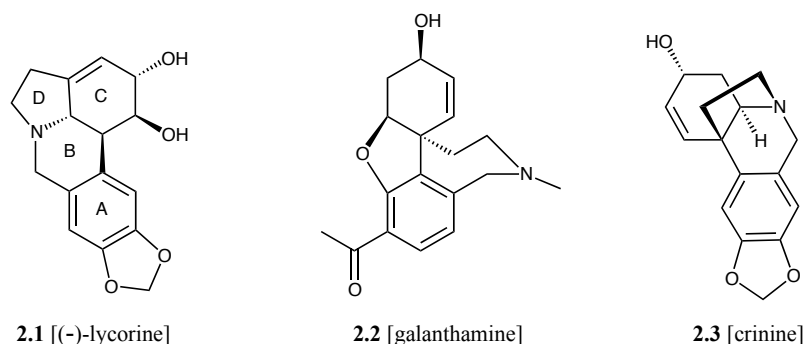
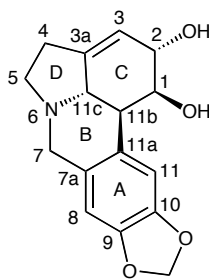


Figure 2.1.0 The Parent Members of the Three Major Classes of Structurally Distinct *Amaryllidaceae* Alkaloids

Derivatives of each of these classes of alkaloid may occur concurrently in individual plants of the same species but the lycorine class is almost ubiquitous. (–)-lycorine [2.1] is comprised of a five-membered polycyclic framework incorporating a phenanthridine residue. The constituent rings of lycorine-type compounds are defined as A, B, C and D with the aromatic component being the first of these. In keeping with most literature reports, the atom numbering scheme used throughout this chapter will follow the pattern depicted on the following page wherein the methylenedioxy ring is not denominated (Figure 2.1.2).⁴



2.1 [lycorine]

Figure 2.1.1 The Ring and Numbering Sequence for Lycorine Used in This Thesis.

It was not until 1910 that a systematic investigation into the structure of lycorine began and the complete elucidation of its structure took more than 50 years.⁵ The success of this effort rested, in large part, on the work of a number of Japanese research groups that undertook a monumental series of degradation studies. Foremost amongst these groups was that led by H. Kondo of the Itsuu Laboratory Research Foundation.

The correct molecular formula of lycorine ($C_{16}H_{17}NO_4$) was established in 1913⁶ and by 1920 it was clear that the structure contained an isoquinoline residue, a non-conjugated double bond and two non-phenolic hydroxyl groups.⁷ Subsequently, Kondo showed that zinc-mediated reduction of lycorine and several other *Amaryllidaceae* alkaloids afforded phenanthridine.⁸ By 1939 it was apparent to Kondo that lycorine was probably one or other of the isomeric systems **2.1b**, **2.4** or **2.5** (Figure 2.1.2) but the exact position of the double bond and of the hydroxyl groups remained unclear at this stage.⁹ At the time, Kondo favoured isomer **2.4** but further degradation studies and advances in UV/vis spectroscopic techniques in the early 1950's led Kondo to conclude that only arrangement **2.1b** was consistent with all the relevant data.¹⁰ Even at this stage the position of the double bond continued to be ambiguous and the matter of determining the correct stereochemistry of lycorine remained.

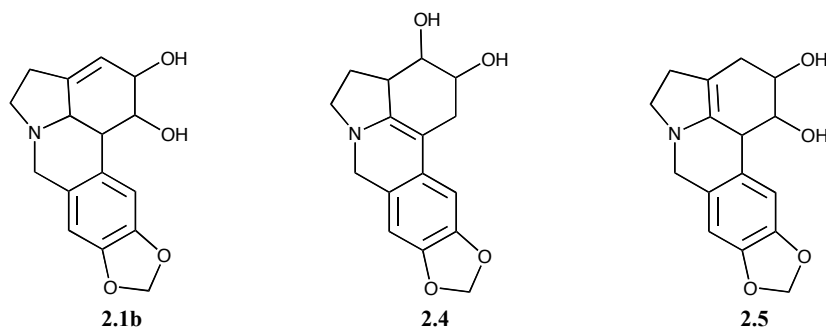


Figure 2.1.2 Possible Structures Considered for Lycorine.

During the mid-1950's Takeda and Kotera undertook degradation studies of (–)-dihydrolycorine [2.6] (obtained by catalytic hydrogenation of (–)-lycorine) and established that the hydroxyl substituents are vicinally related and *trans*-diaxial in arrangement. They were also able to assign a *trans*-B/C ring junction and established that there is a *cis*-C/D ring junction present in (–)-dihydrolycorine.¹¹

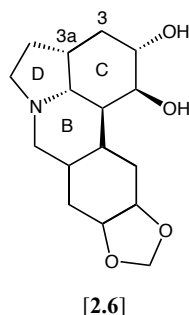


Figure 2.1.3 (–)-Dihydrolycorine

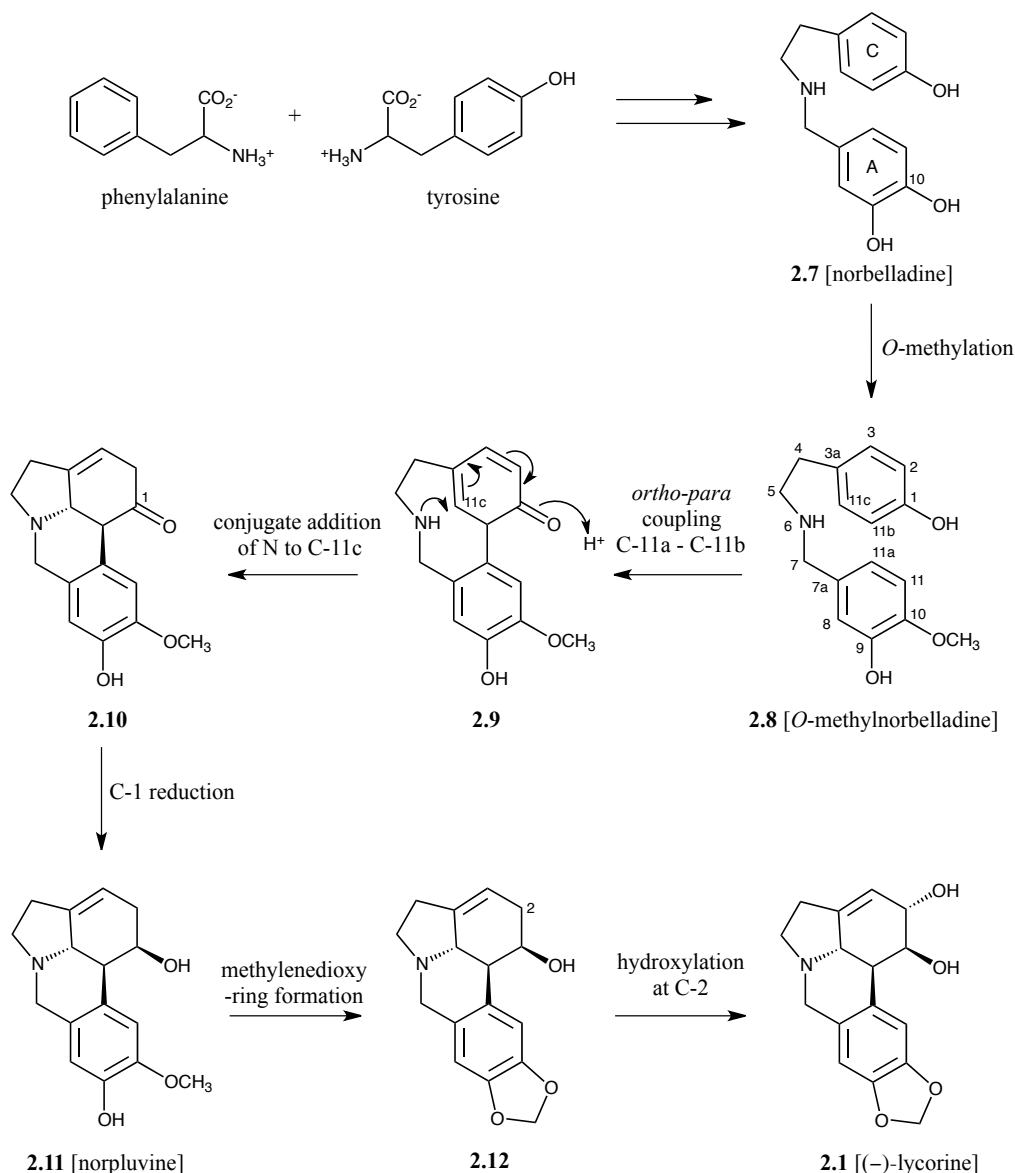
In 1959 Nakagawa and Uyeo unequivocally fixed the C-3 – C-3a position of the double bond of (–)-lycorine and, as a result, it was possible to define the structure of (–)-lycorine as either **2.1** or its enantiomer *ent*-**2.1**.¹² The matter of absolute stereochemistry was finally resolved in 1966 through the application of modern analytical techniques. In particular, Shiro, Sato and Koyama published a single-crystal X-ray analysis of the hydrobromide salt of (–)-dihydrolycorine, which, with the exception of the loss of the double bond, exhibited the same structure as **2.1**.¹³ At much the same time Kotera and co-workers undertook exhaustive NMR studies of (–)-lycorine and (–)-dihydrolycorine. By such means, that included nOe experiments and the application of the Karplus

equation, they were able to confirm the *trans*-B/C ring junction stereochemistry of both compounds¹⁴ and thus confirm the structure of (–)-lycorine as **2.1**.

2.1.2 Proposed biosynthesis of Lycorine

During the 1960's and early 1970's the biosynthetic origins of the *Amaryllidaceae* alkaloids was the subject of intense research by several groups.¹⁵ Sophisticated methods for precise radiolabeling were employed to unravel the biosynthetic origins of lycorine, narciclasine, galanthamine and other related alkaloids. The springboard for this research was the proposal, first articulated by Barton and Cohen in 1957, that lycorine and many other *Amaryllidaceae* alkaloids are derived from tyrosine and phenylalanine *via* a common intermediate, namely norbelladine [**2.7**].^{16,17} The proposed biosynthesis of (–)-lycorine is depicted in Scheme **2.1**. Thus, the C-10 position of norbelladine [**2.7**] is subjected to *O*-methylation to afford *O*-methylnorbelladine [**2.8**] (the *O*-methyl carbon is later incorporated into the methylenedioxy carbon of lycorine).¹⁸ The aromatic residues of *O*-methylnorbelladine are then enzymatically coupled in an *ortho-para* manner to give the intermediate **2.9**. Conjugate addition of the pendant amine nitrogen to the dienone system of the latter species then leads to the simultaneous formation of the B- and D- rings as manifest in product **2.10**. This event is followed by reduction of the carbonyl residue of ketone **2.10** to the corresponding β-alcohol and thereby generating norpluvine [**2.11**] (norpluvine has since proved to be an intermediate in the biosynthesis of several *Amaryllidaceae* alkaloids).¹⁵ Finally, closure of the methylenedioxy ring leads to compound **2.12** and hydroxylation at C-2 within this framework completes the biosynthesis of (–)-lycorine [**2.1**].

Feeding studies have demonstrated that radio-labeled tyrosine is incorporated by daffodils into norbelladine, norpluvine and lycorine.¹⁹ Furthermore, radio-labeled norbelladine is incorporated by daffodils into norpluvine and lycorine while radio-labeled norpluvine is incorporated into lycorine.²⁰



Scheme 2.1 The Biosynthesis of (-)-Lycorine

2.1.3. The Use of *Amaryllidaceae* Plant Extracts in Traditional Medicines

Plants of the *Amaryllidaceae* family are distributed throughout Europe, North Africa, Arabia, Persia, much of Asia as well as the Americas and they have a long history of use as traditional medicines, especially in the treatment of cancer.²¹ At least thirty species have been employed and the earliest record of their use dates back nearly 2500 years. Hippocrates of Kos (ca. 460 ~ 370 B.C.), often referred to as the “father of medicine”, employed pessaries prepared from the oil of *N. poeticus* to treat uterine tumors. Followers of the Hippocratic School of Medicine continued to employ this treatment for centuries after his death. The Roman philosopher Pliny the Elder (23 ~ 79 A.D.) recorded the use of extracts of *N. poeticus* and *N. pseudonarcissus* for the topical

treatment of skin cancers. Evidence also exists that extracts of *Amaryllidaceae* plants have been employed in China and the Arab world for the treatment of uterine, testicular, stomach, breast and skin cancers. Many such extracts also exhibit analgesic qualities and they have, therefore, been exploited in traditional medicines for this purpose. In fact, the name *Narcissus* has its origins in the ancient Greek word *narkosis* meaning numbing. Other traditional uses of *Amaryllidaceae* extracts include their application as antiseptics, for the relief of rheumatic pain, as anti-inflammatory agents, for the induction of labour and for use as emetics and poisons.

Current scientific evidence suggests that the therapeutic benefits of *Amaryllidaceae* extracts in traditional treatment of cancers are primarily due to the presence of the secondary metabolites lycorine, narciclasine and pancratistatin. The analgesic properties of these extracts are most likely due to the presence of galanthamine, which exhibits activity comparable to that of morphine.

2.1.4 The Biological Properties of Lycorine

During its initial isolation lycorine was recognised as potent emetic toxin.²² In 1958 it was discovered that it also exerts strong cytostatic effects on certain tumor cell lines.²³ The latter discovery and the knowledge that *Amaryllidaceae* extracts have been employed in traditional treatments of cancers have spurred intense investigations into the biological properties of lycorine. As a result it has been shown that the compound exhibits a large and diverse array of biological properties. For example, lycorine is active against poliovirus, smallpox virus and SARS-associated coronavirus. At therapeutic doses it kills the protozoan parasite *Trypanosoma brucei* that causes African trypanosomiasis (sleeping sickness) in humans and animals. Furthermore, it exhibits significant antimalarial properties due to its toxicity to the parasite *Plasmodium falciparum*.²⁴ Lycorine inhibits the biosynthesis of ascorbic acid in plants and it has proven to be a valuable tool for investigating this important process. It is also a strong inhibitor of growth and cell division in higher plants, algae and yeast due to its capacity to inhibit RNA, tRNA and protein synthesis. The long history of use lycorine-containing *Amaryllidaceae* plant extracts in the treatment of cancers underscores increasing evidence of the potential of the compound as a chemotherapeutic agent.²⁵ Lycorine is active as an antiproliferative agent at therapeutic doses against a number of cancer cell-lines and it has been shown to suppress the growth and division of leukemia cell-lines (HL-60) both *in vitro* and *in vivo*. When mice inoculated with leukemia HL-60 cells and,

therefore, exhibiting severe immuno-deficiency were treated with lycorine this resulted in decreased tumor growth and increased survival rates with no apparent adverse effects. Furthermore, lycorine inhibits the *in vivo* growth of a murine transplantable ascites tumor and it arrests the cell cycle and induces apoptosis of multiple myeloma (KM3) cells.²⁶

The chemotherapeutic potential of lycorine and its derivatives appears to be associated with the capacity of these compounds to induce apoptosis (programmed cell death) in cancer cells. This is known as the “proapoptotic effect”. Many cancerous conditions are characterised by cells that proliferate because they lack the normal intrinsic cellular mechanisms to induce apoptosis. Thus, chemotherapeutic agents that can selectively apply proapoptotic stimuli to cancer cells are of great interest and recently this capacity of lycorine has been studied in more detail. Lycorine, in common with the *Amaryllidaceae* alkaloid narciclasine, exerts its apoptotic effect by disrupting the formation of the actin cytoskeleton of cancer cells and in this respect it is at least 15 times more active in cancer cells than in healthy cells. Importantly, it is able to cross the blood/brain barrier and the *in vivo* toxicity of lycorine at therapeutic doses is lower than that of narciclasine and the chemotherapeutic agent Cisplatin (*cis*-diamminedichloroplatinum).²⁷ The methylenedioxy unit of lycorine may be replaced with 9-hydroxy and 10-methoxy substituents without affecting the induction of apoptosis. The presence of the C-3–C-3a double bond is not critical for induction of apoptosis as dihydrolycorine is also active. However, the hydroxyl substituents at the C-1 and C-2 positions appear to be crucial since protection of one or other or both of these with silyl or acetate units significantly reduces the apoptotic effect.²⁸

Recently, Hayden and colleagues have demonstrated a novel mode of anti-tumour activity of lycorine in combating chronic lymphocytic leukemia (CLL).²⁹ Most people suffering this disease are elderly and, therefore, unable to withstand the acute toxic side effects of the potent chemotherapeutic agents that are active against CLL. Thus, the disease is effectively incurable for most patients and there is a need to develop a less toxic therapeutic regime. One promising therapy involves the drugs bezafibrate and medroxyprogesterone acetate (MPA) which, when administered concurrently, induce rapid apoptosis of lymphocytic tumor cell-lines *in vitro*. The toxicity of these compounds is relatively low, but in the tumor microenvironment, *in vivo*, the activity of this therapeutic combination is strongly inhibited by the CD40 ligand that is expressed by T-cells in the lymph nodes. Remarkably, the addition of lycorine at therapeutic concentrations to the mixture of bezafibrate and MPA restores the capacity of this

combination to induce apoptosis of tumorous lymphocytes in the presence of the CD40 ligand. This represents a promising lead for the development of effective anti-cancer therapies based on lycorine-type compounds.

It is clear from the combination of historical records and increasing scientific evidence that lycorine is a suitable lead for the synthesis of compounds to treat cancers that suppress normal cellular apoptosis such as myeloma, melanoma, non-small-cell lung cancers and chronic lymphocytic leukemia.

2.2 Previous Studies on the Synthesis of Lycorine and the Assembly of the Lycorine Framework

2.2.1 Overview

The diverse range of biological properties and the distinctive structural characteristics of lycorine-type compounds have prompted a great deal of research directed towards the development of practical syntheses of lycorine and its congeners. While lycoricidine, narciclasine and pancratistatin have been synthesised in their natural and unnatural enantiomeric configurations *via* several distinct routes, lycorine has proven to be a far greater challenge. The earliest studies directed towards the synthesis of lycorine date from 1962 and numerous approaches to the pentacyclic framework of this alkaloid have been developed in the interim.^{30,31} Although several syntheses of the racemic form of the alkaloid were reported during the 1970's and 1980's, the efficient and stereoselective functionalisation of the C-ring proved very difficult.³² A relay synthesis of (–)-lycorine was described by Tsuda and co-workers in 1975 but this relied upon an optically pure starting material that was itself a degradation product of (–)-lycorine.³³ In 1996 Schultz and co-workers synthesised *ent*-lycorine and *ent*-deoxylycorine³⁴ but it was not until 2009 that Tomioka and co-workers achieved the first asymmetric total synthesis of (–)-lycorine.³⁵ Since a thorough review of this large body of work is beyond the scope of this Thesis only selected approaches to the lycorine framework and to lycorine itself are presented on the following pages. These various strategies have been selected as representing some of the more elegant and successful approaches as well as to illustrate some of the limitations of the work carried out to date.

2.2.2 Irie and Uyeo's Synthesis of ($\pm$)- α -, β - and δ -lycorane

During the 1970's the Japanese researchers Irie and Uyeo of Kyoto University developed an effective technique for the synthesis of ($\pm$)-dihydrolycorine³⁶ as well as the racemic forms of α -, β - and δ -lycorane (**2.13** – **2.15** respectively).³⁷

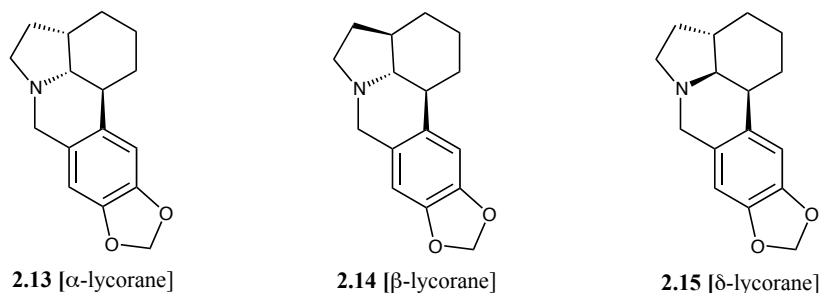
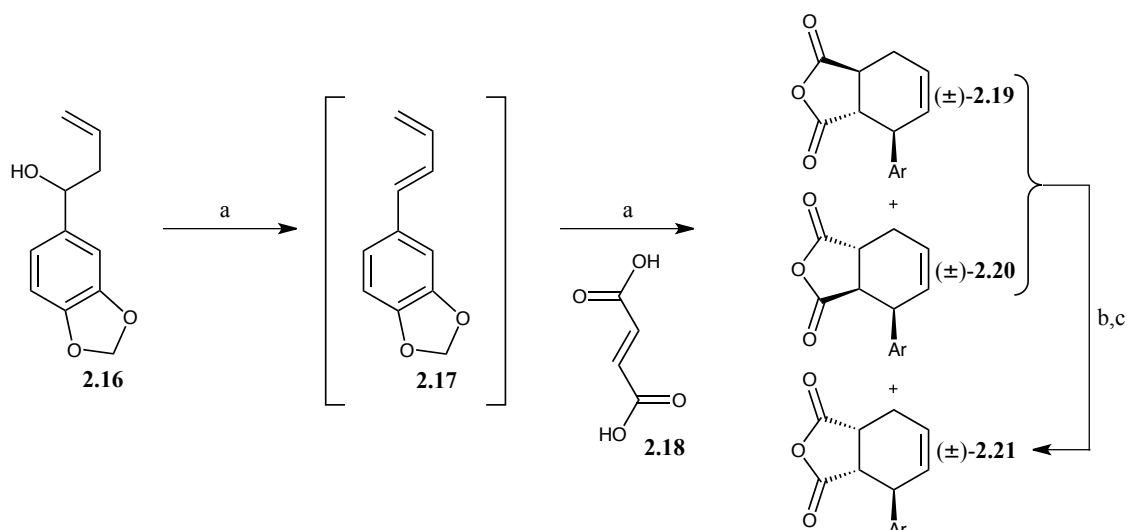


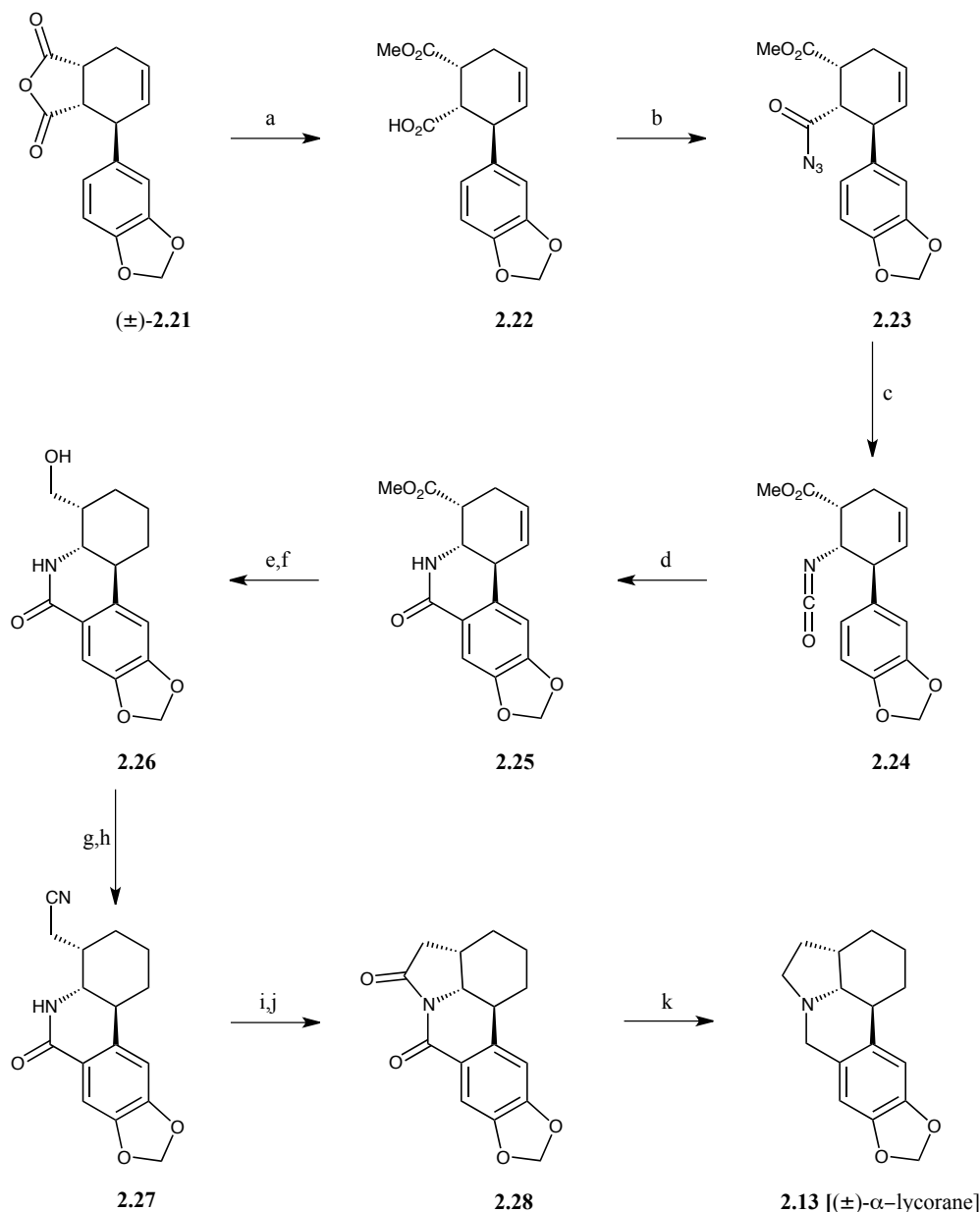
Figure 2.2.1 α -, β - and δ -Lycorane

The key intermediate required for the synthesis of ($\pm$)- α -lycorane, as well as ($\pm$)-dihydrolycorine and ($\pm$)-lycorine (see below), was the *trans,cis*-anhydride ($\pm$)-**2.21** that was obtained *via* the reaction sequence depicted in Scheme 2.2. Thus, the alcohol **2.16** (prepared by allylation of piperonal³⁶) was subjected to dehydration with acetic anhydride to afford the diene **2.17**. The Diels-Alder reaction of the compound **2.17** with fumaric acid [**2.18**] in the presence of acetic anhydride furnished a mixture of the anhydrides ($\pm$)-**2.19**, ($\pm$)-**2.20** and ($\pm$)-**2.21**. The first two of these products were obtained as the major ones (32% each) and only small amounts (yield 4%) of the requisite anhydride, ($\pm$)-**2.21**, could be isolated. However, the anhydrides ($\pm$)-**2.19** and ($\pm$)-**2.20** were readily converted into the anhydride ($\pm$)-**2.21** as follows: the crude product-mixture was heated under reflux with aqueous sodium hydroxide and then it was acidified with concentrated hydrochloric acid to afford a mixture of the corresponding dicarboxylic acids. Subjection of this mixture to reaction with refluxing acetic anhydride then gave the requisite *trans,cis*- anhydride ($\pm$)-**2.21** good yield (55% from the alcohol **2.16**).



Scheme 2.2 Reaction conditions: (a) Ac₂O, reflux, **2.18**, (**2.19**, 32%), (**2.20**, 32%), (**2.20**, 4%); (b) NaOH_(aq) reflux then HCl_(aq); (c) Ac₂O, reflux, 80% over 2 steps.

The synthesis of (±)- α -lycorane **2.13** from the anhydride (±)-**2.21** is shown in Scheme 2.3. So, treatment of anhydride (±)-**2.21** with methanol and pyridine in benzene afforded a 7:3 mixture of half-esters with compound **2.22** predominating (63% yield). The latter compound was reacted with thionyl chloride and then sodium azide to afford the acyl-azide **2.23**. When this last compound was heated in refluxing benzene it underwent a Curtius rearrangement to generate the isocyanate **2.24**. Treatment of compound **2.24** with SnCl₄ facilitated an intra-molecular Friedel-Crafts acylation to give the lactam **2.25** (57% yield over 3 steps). Catalytic hydrogenation of the olefinic bond of product **2.25** and subsequent hydride-mediated reduction of this ester afforded the alcohol **2.26** in 50% yield. Compound **2.26** was converted into the corresponding tosylate, which was, in turn, reacted with potassium cyanide in DMSO to furnish the nitrile **2.27** (52% yield over 2 steps). Hydrolysis of the nitrile function within the latter compound using concentrated hydrochloric acid followed by cyclisation of the resulting acid with acetic anhydride afforded the imide **2.28** (52% yield over 2 steps). Finally, lithium aluminium hydride-mediated reduction of the carbonyl moieties of compound **2.28** gave (±)- α -lycorane [**2.13**] in 30% yield. By applying the reaction sequence described above to anhydride (±)-**2.19** Irie and co-workers obtained (±)- β -lycorane [**2.14**]. Similarly, anhydride (±)-**2.20** was converted into (±)- δ -lycorane [**2.15**].

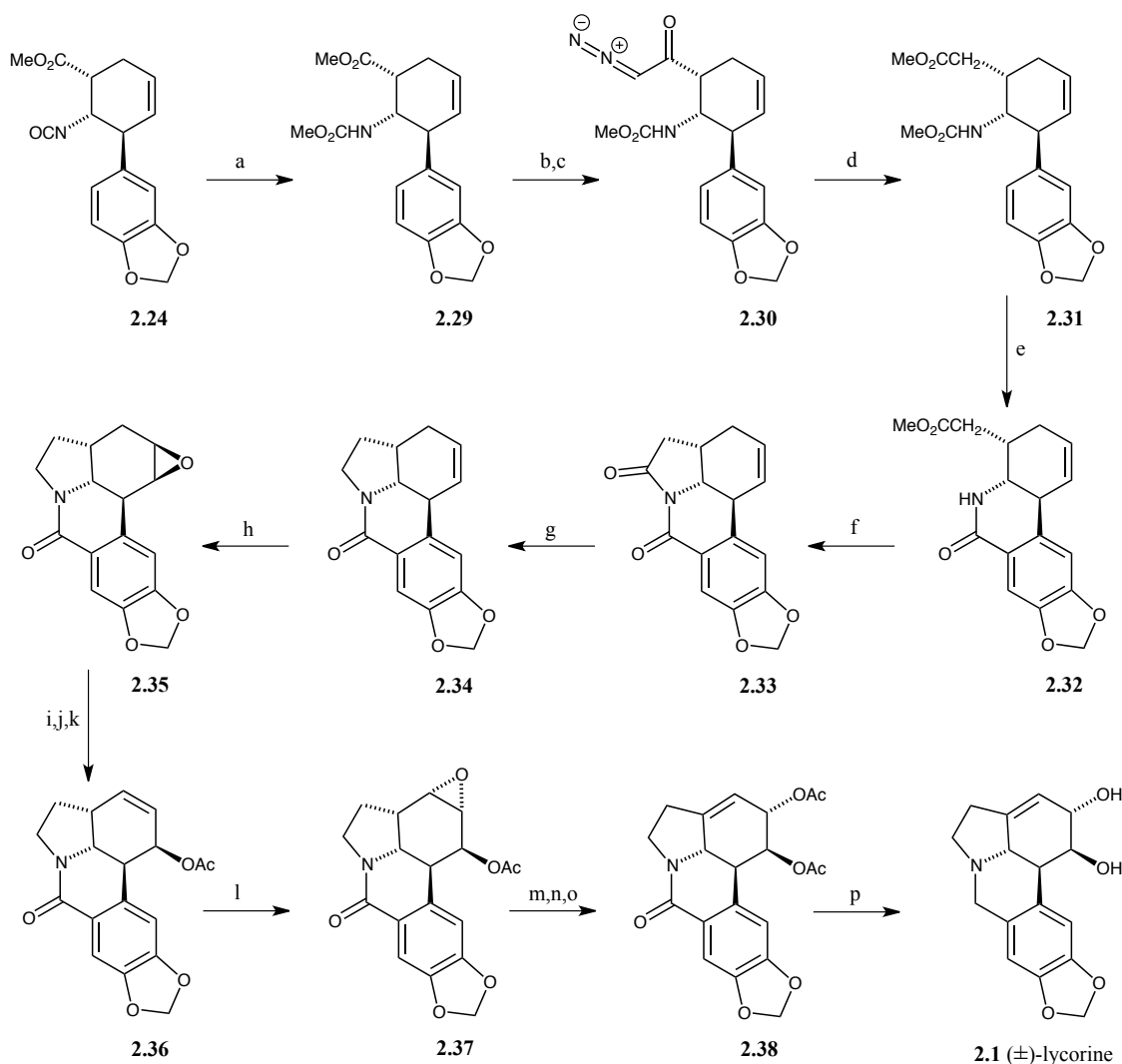


Scheme 2.3 Reaction conditions: (a) MeOH, pyridine, benzene, 20 °C, 63%; (b) SOCl₂, benzene, reflux then NaN₃, 20 °C; (c) benzene, reflux; (d) SnCl₄, CH₂Cl₂, 20 °C, 57% over 3 steps; (e) PtO₂, H₂, 65%; (f) LiAlH₄, THF, 0 °C, then NaBH₄, 78%; (g) *p*-TsCl, pyridine, 20 °C; (h) KCN, DMSO, 70 °C, 52% over 2 steps; (i) HCl, acetic acid 50 °C; (j) Ac₂O 100 °C, 52% over 2 steps; (k) LiAlH₄, THF, reflux, 30%.

2.2.3 Tsuda, Takagi and Irie's Total Synthesis of (±)-Lycorine

Tsuda, Takagi and Irie synthesised (±)-lycorine [(±)-**2.1**]³⁸ by building upon the strategy that had been developed by Irie and Uyeo for the synthesis of the lycoranes (as detailed above). The success of their approach depended upon the repeated application of Sharpless' method for the conversion of epoxides into allylic alcohols by treatment of the former motif with phenyl selenide followed by oxidative elimination.³⁹ The starting

material for the synthesis of (±)-lycorine [(±)-**2.1**] was the isocyanate **2.24**, which was itself obtained according to the procedures developed by Irie and Uyeo (see above). As shown in Scheme 2.4, this compound was reacted with methanol to afford the urethane **2.29** and the ester residue within the latter compound was subjected to an Arndt-Eistert homologation sequence. Thus, compound **2.29** was converted into the corresponding acid chloride that was, in turn, converted into diazoketone **2.30** and this was subjected to a Wolff rearrangement through treatment with silver benzoate and triethylamine in methanol to afford the homologated methyl ester **2.31**. Reaction of compound **2.31** with phosphorous oxychloride followed by treatment with tin tetrachloride furnished compound **2.32**. Hydrolysis of the methyl ester moiety within the last compound followed by cyclisation of the resulting acid using acetic anhydride gave the lactam **2.33** that was selectively reduced with lithium aluminium hydride to afford lactam **2.34**. Stereoselective oxidation of the olefinic bond of compound **2.34** with *m*-CPBA gave the α -epoxy **2.35** as the sole product of the reaction. Nucleophilic opening of the epoxide at C-2 with phenyl selenide afforded a hydroxy selenide that, upon treatment with sodium periodate, underwent oxidative elimination of the selenide substituent. Acetylation of the resulting allylic alcohol then gave the acetate **2.36**. The ester moiety within compound **2.36** effectively blocks the α -face of the molecule and, consequently, epoxidation of the associated olefinic bond of this compound resulted in the exclusive formation of β -epoxide **2.37**. Nucleophilic opening of epoxide moiety of the latter compound with phenyl selenide took place at C-3 and oxidative elimination of the resulting hydroxy selenide then gave the lactam **2.38**. Finally, acetylation of compound **2.38** followed by reduction with lithium aluminium hydride furnished (±)-lycorine [(±)-**2.1**].

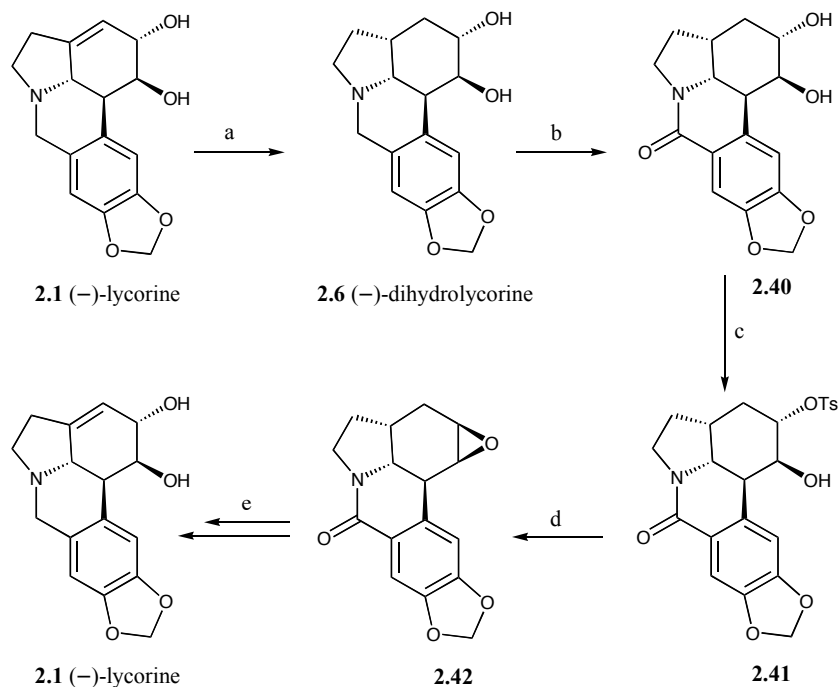


Scheme 2.4 Reaction conditions: (a) MeOH, reflux, 72%; (b) SOCl₂, benzene, reflux; (c) diazomethane, benzene, 20 °C, 61% over 2 steps; (d) Ag₂O, benzene, 40 °C, 73%; (e) POCl₃, reflux, then SnCl₄, 0 °C, 60%; (f) conc HCl, acetic acid, reflux, then Ac₂O, 100 °C, 95%; (g) LiAlH₄, Et₂O, 0 °C, 80%; (h) mCPBA, CH₂Cl₂, 5 °C, 97%; (i) diphenyl diselenide, NaBH₄, EtOH, reflux; (j) NaIO₄, 40 °C, 70% over 2 steps; (k) Ac₂O, pyridine; (l) *m*-CPBA, CHCl₃, 20 °C, 80% over 2 steps; (m,n,o) as for i,j,k, 40% over 3 steps; (p) LiAlH₄, THF, reflux, 40%.

2.2.4 Tsuda's Relay Synthesis of (-)-Lycorine

Tsuda and co-workers were able to achieve a relay synthesis of (-)-lycorine [**2.1**] by substituting into the sequence, depicted in Scheme 2.4, the optically pure α -epoxide **2.42** in place of its congener ($\pm$)-**2.35**. The epoxide **2.42** was itself readily prepared from naturally occurring (-)-lycorine by the reaction sequence shown in Scheme 2.5. Thus, naturally occurring (-)-lycorine [**2.1**] was subjected to catalytic hydrogenation to give (-)-dihydrolycorine [**2.6**] and this was, in turn, oxidized with potassium permanganate to afford the dihydrolycorine lactam **2.40**. Tosylation of

compound **2.40** afforded the monotosylate **2.41** and treatment of this compound with sodium acetate in methanol furnished the requisite optically pure α -epoxide **2.42**. (Scheme 2.14)



Scheme 2.5 Reaction conditions: (a) $\text{PtO}_2 \cdot \text{H}_2\text{O}$, H_2 , MeOH, 87%; (b) KMnO_4 , MgSO_4 , acetone, water, 61%; (c) *p*-TsCl, pyridine, CH_2Cl_2 , 84%; (d) NaOAc, acetone, water, 70%; (e) conversion to (-)-lycorine via steps i - p of Scheme 2.15.

The method developed by Irie and Uyeo for the synthesis of various lycorine-type compounds has proven the most effective means for accessing this important class of alkaloids. In addition to the syntheses described above, the method has been adapted to the preparation of ($\pm$)-dihydrolycorine, ($\pm$)-clivonine, ($\pm$)-clividine, ($\pm$)-zephyranthine and ($\pm$)-dihydrocaranine.^{40,41} No other approach has proven to be anywhere near as general. However, the method has been limited to the total synthesis of racemic mixtures and to a relay synthesis. It has not been successfully modified for the enantioselective total synthesis of lycorine-type compounds.

2.2.5 Stork's Stereospecific Synthesis of the Lycorine Framework via an Intramolecular Diels-Alder Reaction.

An efficient and stereospecific entry to the lycorine framework was developed by Stork⁴² who recognised that the position of the double bond in lycorine suggested a synthetic approach based on a [4+2] cycloaddition reaction such as the conversion shown in Figure 2.2.4. The difficulty with this approach is that the normal *endo*-course of such a cycloaddition reaction would result in an inappropriate *cis* relationship between H-11b and H-11c.

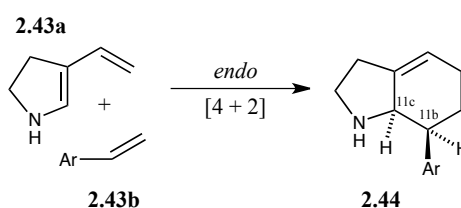


Figure 2.2.4 Intermolecular [4+2] Cycloaddition Reaction Between a Vinylated-4,5-Dihydropyrrole and a Styrene Proceeds via an *endo*-Transition State and Leads to an Inappropriate *cis*-Relationship Between C-11b – C-11c in Adduct 2.44.

This problem was avoided by tethering the two fragments through a conformationally rigid amide bond that constrains the cycloaddition reaction to proceed through an *exo*-transition state (2.45 → 2.46) and thereby establishing the requisite *trans*-relationship between the hydrogens associated with the C-11b – C-11c bond (Figure 2.2.5).⁴³

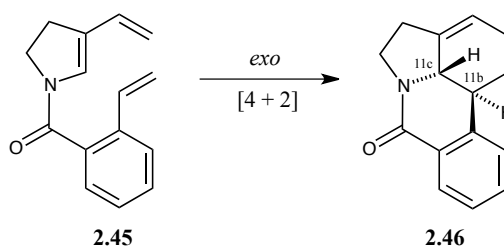
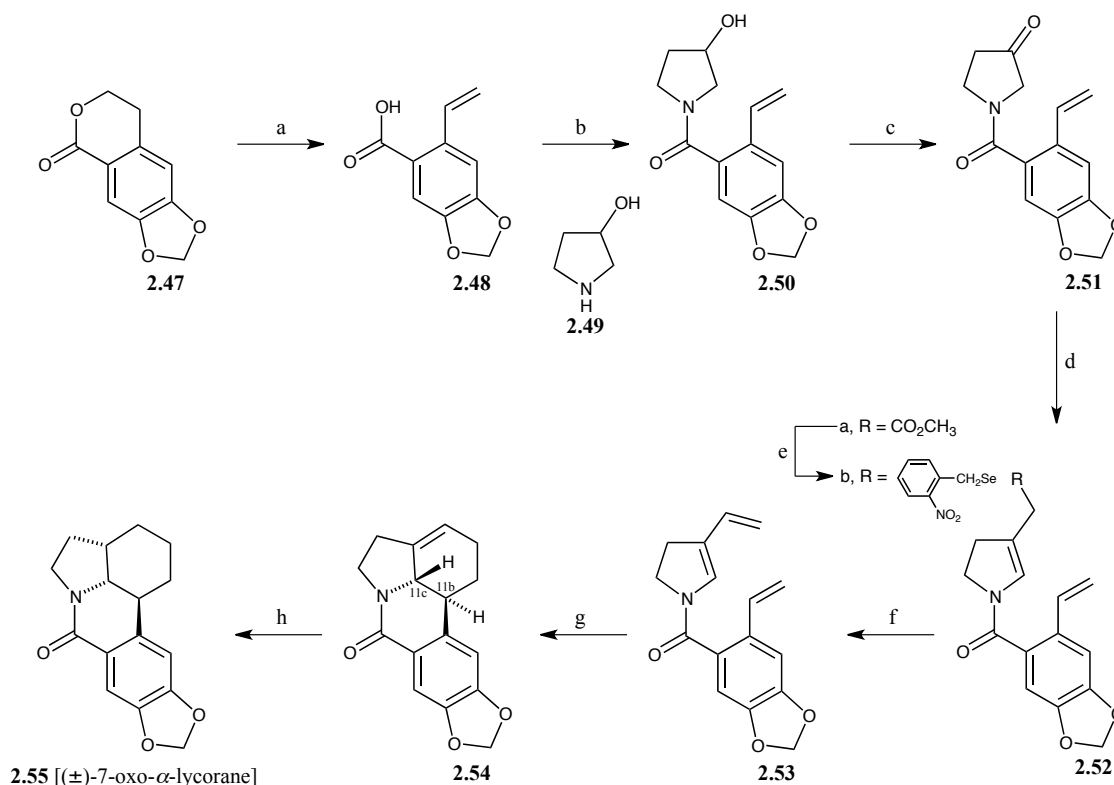


Figure 2.2.5 Intramolecular [4+2] Cycloaddition Reaction of an Amide Linked Compound Proceeds via an *exo*-Transition State and Results in a *trans*-Relationship Between H-11b and H-11c in Adduct 2.44.

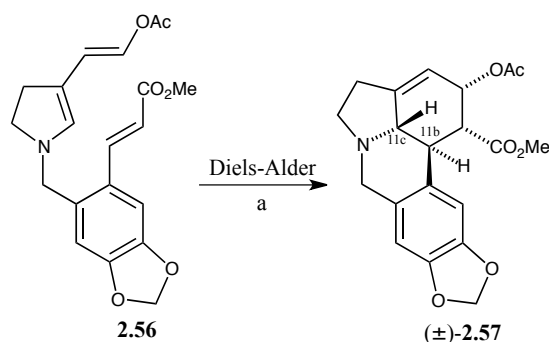
Stork's synthesis of ($\pm$)-7-oxo- α -lycorane [2.55] (Scheme 2.6) began with the isocoumarin **2.47** which was treated with $\text{LiN}(\text{SiMe}_3)_2$ in HMPA to afford the carboxylic acid **2.48** in 90 – 95% yield. The latter compound was coupled with 3-pyrrolidinol **2.49** in the presence of Ph_3P and CCl_4 to give the amide **2.50** in 93% yield. Oxidation of the alcohol moiety within compound **2.50** using pyridine- SO_3 complex in DMSO afforded the corresponding ketone **2.51** (79%) that was elaborated to the β,γ -unsaturated ester **2.52a** in 57% yield through a Horner-Wadsworth-Emmons olefination reaction. Reduction of compound **2.52a** with LiBH_4 followed by treatment of the resulting alcohol with *o*-nitrophenylselenocyanate and Bu_3P afforded the corresponding selenyl derivative **2.52b** (50 – 55%). This last compound was subjected to oxidative elimination under carefully controlled conditions to give, in 94% yield, the substrate **2.53** required for the intra-molecular Diels-Alder reaction. The critical cycloaddition reaction was conducted



Scheme 2.6 Reaction conditions: (a) $\text{LiN}(\text{SiMe}_3)_2$, HMPA, -78°C , 90%; (b) Ph_3P , CCl_4 , MeCN 0°C , 93%; (c) pyridine- SO_3 , DMSO then Et_3N , DMSO, 79%; (d) $(\text{EtO}_2)\text{P}(\text{O})\text{-CH}_2\text{CO}_2\text{CH}_3$, NaH, glyme, 0°C , 57%; (e) LiBH_4 , THF, 20°C then *o*-nitrophenylselenocyanate, Bu_3P , CH_2Cl_2 , 20°C , 55% over two steps; (f) NaIO_4 , THF, MeOH, H_2O , 20°C , 94%; (g) PhCl , 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide, *O,N*-bis(trimethylsilyl)acetamide, 140°C , 51%; (h) EtOAc , Pd/C, H_2 , 1 atm, 25°C , 100%.

at low concentration in refluxing chlorobenzene (140 °C) in the presence of a radical inhibitor to furnish the compound **2.54** (51%) that incorporates the required *trans*-B/C and *cis*-C/D ring-junctions. Catalytic hydrogenation of compound **2.54** then afforded the target ($\pm$)-7-oxo- α -lycorane [**2.55**], which was obtained in quantitative yield.

Despite the succinct nature of the reaction sequence developed by Stork it has not been exploited to any great extent. Several years after Stork's initial publication, Boeckman and co-workers reported the synthesis of an unnatural lycorine-type compound ($\pm$)-**2.57** using a related intra-molecular Diels-Alder reaction involving compound **2.56** as the substrate (Scheme 2.7). By this means they succeeded in functionalising the C-ring of the lycorine framework. Boeckman's cycloaddition product ($\pm$)-**2.57** incorporated the *trans*-B/C and *cis*-C/D ring-junctions of naturally occurring lycorine-type compounds, but the vicinally related acetoxy and carbomethoxy groups of the C-ring were in the (unnatural) *cis*-arrangement.

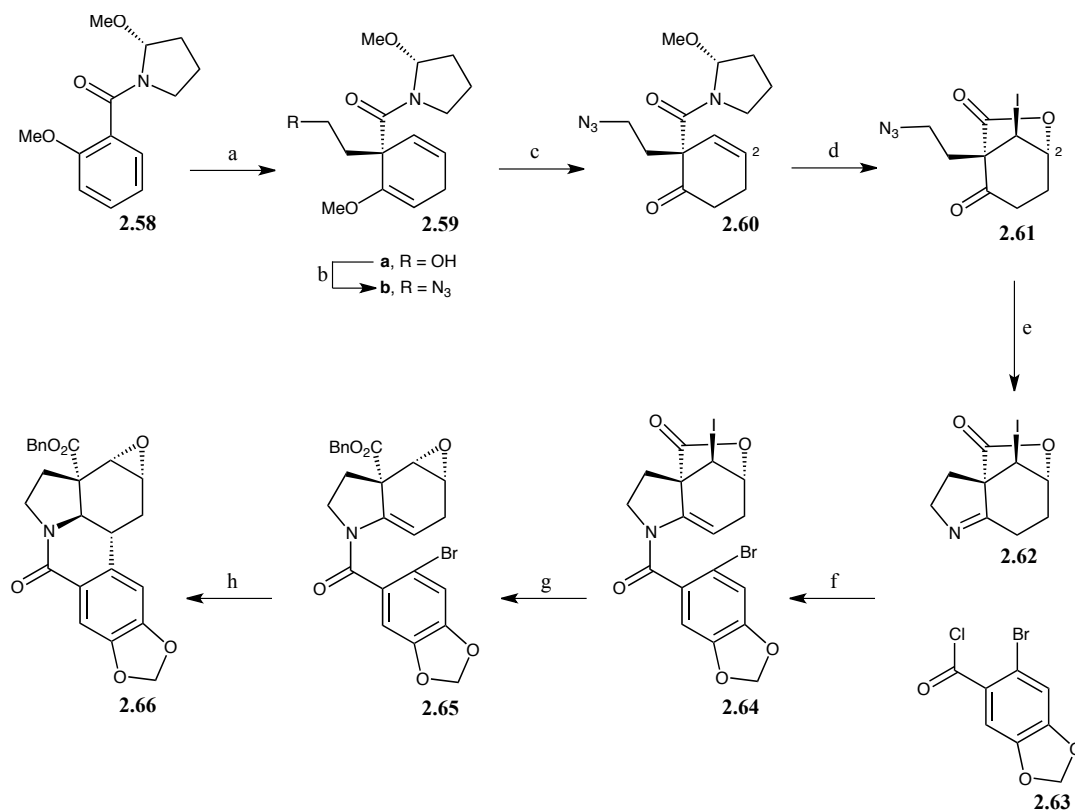


Scheme 2.7 Reaction conditions: (a) toluene, BHT, 110 °C, 64%.

2.2.6 Schultz' Asymmetric Synthesis of (+)-Lycorine

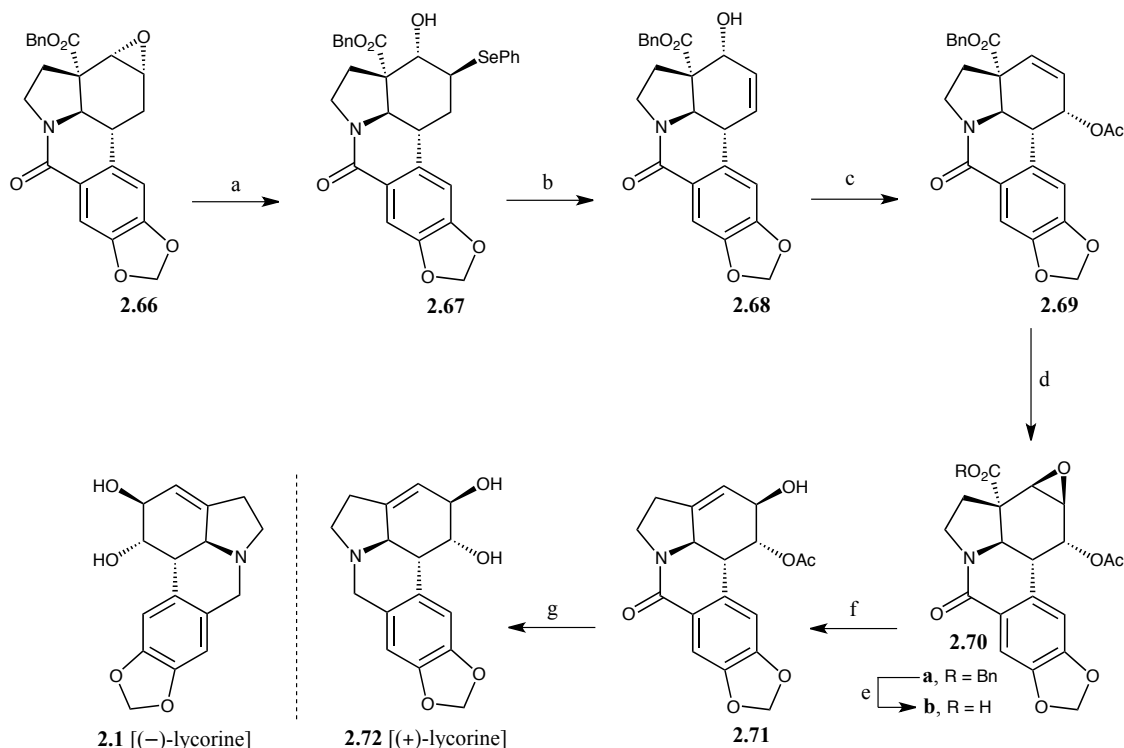
Although several methods were developed during the 1970's and 1980's for the synthesis of racemic modifications of lycorine-type alkaloids it was not until 1993 that the first asymmetric synthesis of such a compound was reported.⁴⁴ In that year Schultz, Holoboski and Smyth achieved the first asymmetric synthesis of (+)-deoxylycorine and in 1996 they reported an extension of this work to the asymmetric synthesis of (+)-lycorine [**2.72**], the non-natural enantiomer of (–)-lycorine [**2.1**].⁴⁵ The stereoselective functionalisation of the C-ring of these compounds was the focus of their attention and achieving this critical objective relied upon two key features in their synthetic design. Firstly, Schultz and co-workers had earlier developed a method for the enantioselective reductive alkylation of chiral benzamides to afford compounds that could be converted

into enantiomerically pure chiral cyclohexanes that had served as highly effective precursors for the asymmetric synthesis of various oxygenated natural products.⁴⁶ Secondly, Schultz was able to exploit a completely regio- and stereo-selective radical cyclisation reaction to generate a product containing the critical *trans*-B/C ring junction. Thus, both (+)-deoxylycorine and (+)-lycorine [2.72] were synthesised from a common intermediate, **2.66**, that was constructed as shown in Scheme 2.8. In particular, the commercially available chiral benzamide **2.58** was subjected to Birch reduction followed by alkylation with 2-bromoethyl acetate. Subsequent saponification gave the alcohol **2.59a** in high yield (96%) and as a single diastereomer. This alcohol was converted into the corresponding azide, **2.59b**, which underwent acidic enol-ether hydrolysis to afford amide **2.60**. Iodo-lactonisation of the latter compound delivered the lactone **2.61**. This step also effected introduction of a surrogate hydroxyl group at C-2 with complete stereocontrol while simultaneously releasing the now superfluous chiral auxiliary. Treatment of compound **2.61** with triphenylphosphine then gave the enantiomerically pure imine **2.62** in 50% overall yield from compound **2.59a**.



Scheme 2.8 Reaction conditions: (a) K, NH₃, *t*BuOH, -78 °C then BrCH₂CH₂OAc, -78 °C to 25 °C, KOH, MeOH, 96%; (b) DEAD, (PhO)₂P(O)N₃, THF; (c) HCL, MeOH; (d) I₂, THF, H₂O; (e) PPh₃, THF, reflux, 50% over three steps; (f) ArCOCl, Et₃N, CH₂Cl₂, 98%; (g) BnOH, nBuLi, THF, -78 °C to 25 °C, 53%; (h) AIBN, Bu₃SnH, benzene, reflux, 53%.

The enamide, **2.64**, obtained in 98% yield by acylation of compound **2.62** with 2-bromopiperonyl chloride [**2.63**] was reacted with the lithiated anion of benzyl alcohol to afford the substrate, **2.65** (53%), that was required for the subsequent radical cyclisation reaction. In the event, treatment of compound **2.65** with AIBN and Bu₃SnH in refluxing benzene produced the crystalline lactam **2.66** (53%) incorporating the requisite *trans*-B/C and *cis*-C/D ring connections, albeit in the opposite enantiomeric configuration to that of naturally occurring lycorine alkaloids. Conversion of compound **2.66** into (+)-lycorine [**2.72**] required installation of the C-2 allylic alcohol group that is characteristic of the C-ring of lycorine (see Scheme 2.18). Schultz described this challenge as being “more difficult than initially expected” and several seemingly promising leads failed. Ultimately, (+)-lycorine [**2.72**] was obtained as follows: the epoxide **2.66** was converted into phenyl selenide **2.67** (97%) and the latter compound was subjected to oxidative elimination using sodium periodate to give the allylic alcohol **2.68** (83%). Using conditions first described by Torssell,⁴⁷ this alcohol was heated at 50 °C in a mixture of benzoic acid, acetic anhydride and sulfuric acid to effect its rearrangement to the allylic benzoate **2.69** (34%). The olefinic bond of the benzoate was epoxidised using dimethyldioxirane to furnish the epoxide **2.70a** (46%) as the only characterisable product of the reaction. Catalytic hydrogenation of compound **2.70a** removed the benzyl moiety to afford the corresponding carboxylic acid **2.70b** (90%) and photochemically-promoted decarboxylation of the latter furnished the lactam **2.71** in 50% yield incorporating the requisite allylic alcohol at the C-2 position. The final step involved reduction of compound **2.71** with LiAlH₄ to afford (+)-lycorine [**2.72**] (70%). Schultz’s synthesis of (+)-lycorine [**2.72**] required fifteen steps and was achieved in an overall yield of 0.5% from the chiral benzamide **2.58**.

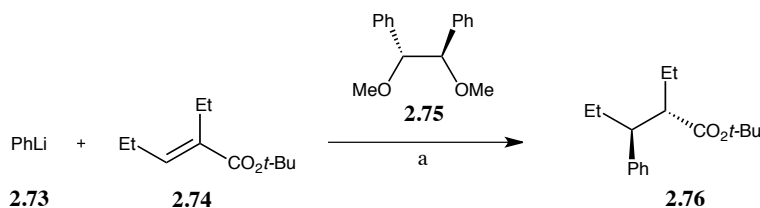


Scheme 2.18 Reaction conditions: (a) NaBH₄, EtOH, PhSeSePh, 20 °C, 93%; (b) NaIO₄, H₂O, THF, 20 °C, 87%; (c) AcOH, Ac₂O, H₂SO₄, 50 °C, 34%; (d) dimethyldioxirane, acetone, 0 °C, 46%; (e) 10% Pd/C, H₂ (1 atm), EtOH, 20 °C, 90%; (f) hν, acridine, benzene, *t*-BuSH, 50%; (g) LiAlH₄, THF, 70%.

2.2.7 Tomioka's Synthesis of (-)-Lycorine by an Asymmetric Conjugate Addition Cascade.

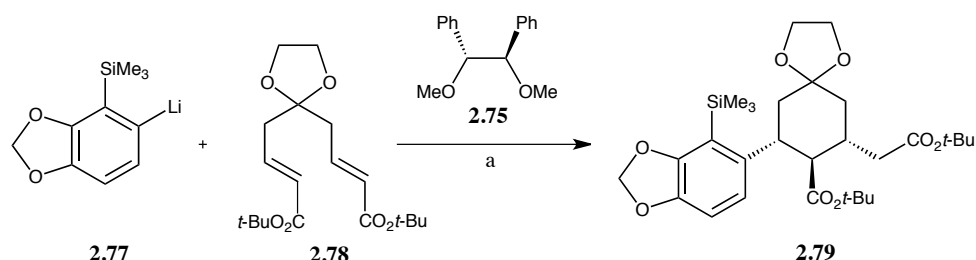
As noted earlier, over the past century Japanese researchers have made outstanding contributions to our knowledge of the *Amaryllidaceae* alkaloids and much of this work was conducted at Kyoto University. Accordingly, it is fitting that the first asymmetric synthesis of (-)-lycorine [2.1] was achieved by Kiyoshi Tomioka and co-workers in the laboratories of that institution.⁴⁸

Tomioka's synthesis of (-)-lycorine [2.1] was accomplished by means of an enantioselective chiral ligand-controlled conjugate addition cascade. The foundation of this synthesis was a method, developed by Tomioka, for the asymmetric addition of organolithium compounds to alkeneoates mediated by the chiral ligand **2.75** (Scheme 2.19).⁴⁹ The resulting 3-substituted alkanoates, such as compound **2.76**, are thereby obtained in good yield and high enantiomeric excess.



Scheme 2.19 Reaction conditions: (a) toluene, $-78\text{ }^{\circ}\text{C}$, 0.5 h, 83%, 92% ee.

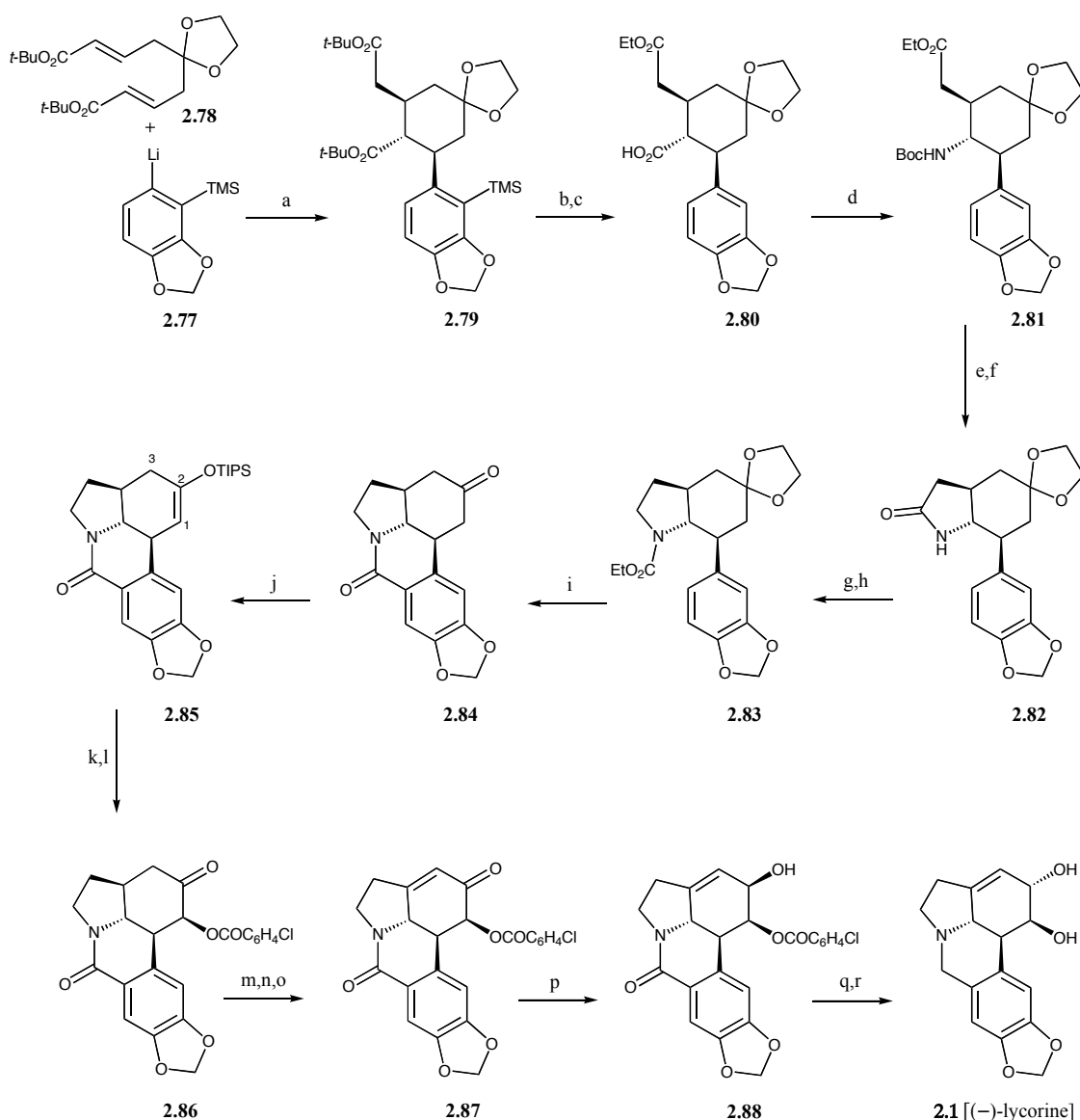
When the symmetric di-alkenoate **2.78** (Scheme 2.20) is employed a conjugate addition cascade ensues to afford a functionalised cyclohexene compound containing three contiguous stereogenic centers. The predominant diastereomer, **2.79**, produced by this means incorporates three stereo-centers in an *all-trans* arrangement.



Scheme 2.20 Reaction conditions: (a) toluene, $-78\text{ }^{\circ}\text{C}$, 0.5 h, 97%, 92% ee.

Tomoika's strategy for the synthesis of (–)-lycorine [**2.1**] involved manipulation of the arylcyclohexane **2.79** to generate a stereoselectively functionalised C-ring (Scheme 2.21). Thus, reaction of the 9:1 mixture of compound **2.79** and its diastereomer in refluxing ethanolic HCl removed the TMS and *t*-butyl groups. These conversions were accompanied by esterification of the less hindered carboxylic acid moiety. After re-ketalisation, the monocarboxylic acid **2.80** was obtained in 70% yield over these two steps. Compound **2.80** was readily separated from the co-produced diethyl ester arising from the minor diastereomer. A nitrogen atom was introduced by treatment with diphenylphosphoryl azide and the ensuing acyl azide was subjected to a Curtius rearrangement in refluxing *t*-BuOH to give the Boc-protected amine **2.81** (88%). Reductive alkylation of the nitrogen function furnished the lycorine D-ring as a component of the lactam **2.82** which was reacted with ethyl chloroformate to give the corresponding carbamate **2.83** (81% over two steps). This carbamate was engaged in a Bischler Napieralski reaction to establish the B-ring and deliver the keto-lactam **2.84** in

95% yield. The latter compound was converted, in 58% yield, into the corresponding TIPS enol-ether **2.85** in which a C-1–C-2 double bond is present. This process also resulted in the formation of the regioisomer of compound **2.85** in which the olefinic bond is located between C-2 and C-3. This regioisomer was obtained in 41% yield but it was readily separated from the required compound **2.85** and could be converted back into the requisite keto-lactam **2.84** by treatment with aqueous HF. Thus, compound **2.84** was converted into compound **2.85** in good yield by repeating these transformations twice. The enol-ether **2.85** so formed was converted into the *m*-chlorobenzoate derivative **2.86** using a procedure reported by Magnus in his synthesis of the *Amaryllidaceae* alkaloid (+)-pancratistatin.⁵⁰ The ketone moiety associated with compound **2.86** was transformed into the corresponding TMS enol-ether and subsequent dehydrogenation between the C-3 and C-3a, achieved through phenylselenation followed by oxidative elimination, gave the enone **2.87** in 52% yield. A Luche reduction afforded the allylic alcohol **2.88** in a stereoselective manner and in 90% yield. The stereo-configuration at C-2 was inverted by a modified Mitsunobu reaction⁵¹ and the synthesis of (–)-lycorine [**2.1**] was then completed by reduction with LiAlH₄ (62% over two steps).



Scheme 2.21 Reaction conditions: (a) ligand **2.75**, TMSCl, toluene, $-78\text{ }^{\circ}\text{C}$, 97%, 92% ee, dr = 9:1; (b) 40% HCl in EtOH, reflux; (c) ethylene glycol, *p*-TsOH, reflux, 77% over two steps; (d) DPPA, Et₃N, MS 4 Å, toluene, reflux then *t*-BuOH, reflux, 88%; (e) TFA, PhSMc, 18 $^{\circ}\text{C}$; (f) NaOMe, MeOH, rt, 81% over two steps; (g) LiAlH₄, THF, reflux; (h) ClCO₂Et, Et₃N, CH₂Cl₂, 18 $^{\circ}\text{C}$, 69% over two steps; (i) POCl₃, 90 $^{\circ}\text{C}$, 95%; (j) TIPSOTf, Et₃N, CH₂Cl₂, 18 $^{\circ}\text{C}$, 58% plus regioisomer 41%; (k) *m*-CPBA, CH₂Cl₂, imidazole, 18 $^{\circ}\text{C}$, 67%; (l) 48% HF in MeCN, 18 $^{\circ}\text{C}$, 95%; (m) TIPSOTf, Et₃N, CH₂Cl₂, 18 $^{\circ}\text{C}$; (n) PhSeCl, CH₂Cl₂, 18 $^{\circ}\text{C}$; (o) NaIO₄, H₂O, THF, 18 $^{\circ}\text{C}$, 52% over three steps; (p) NaBH₄, CeCl₃•7H₂O, MeOH, 0 $^{\circ}\text{C}$, 90%; (q) *p*-nitrobenzoic acid, PPh₃, DEAD, benzene, 18 $^{\circ}\text{C}$; (r) LiAlH₄, THF, reflux then NaOH, H₂O, 18 $^{\circ}\text{C}$, 62% over two steps.

Tomioka's synthesis of (-)-lycorine [**2.1**] *via* a chiral ligand-controlled asymmetric conjugate addition cascade methodology employs readily available coupling partners and a chiral ligand that is easily prepared from commercial starting materials. The method allows for the formation of two C–C bonds and three stereogenic centers in one pot and it provides a solution to the challenge of the stereoselective introduction of the C-ring substituents early in the sequence. Taken as a whole, the synthesis is not

especially succinct (18 steps), but the processes involved are conventional and do not require the use of exotic reagents or techniques. The overall yield was approximately 4%. Tomioka has demonstrated the potential for this method to be adapted to the syntheses of other lycorine derivatives through his construction of the unnatural lycorine isomer (–)-2-*epi*-lycorine.⁴⁸

2.2.8 Banwell and Matveenko's Chemoenzymatic Synthesis of *ent*-Narciclasine *via* an Overman Rearrangement

Recent efforts within the Banwell group directed towards the preparation of *Amaryllidaceae* alkaloids employing *cis*-1,2-dihydrocatechol compounds as starting materials have resulted in the synthesis of *ent*-narciclasine [2.89].

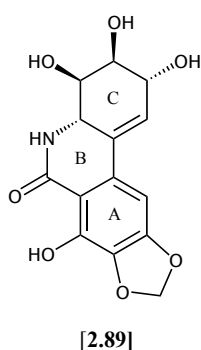
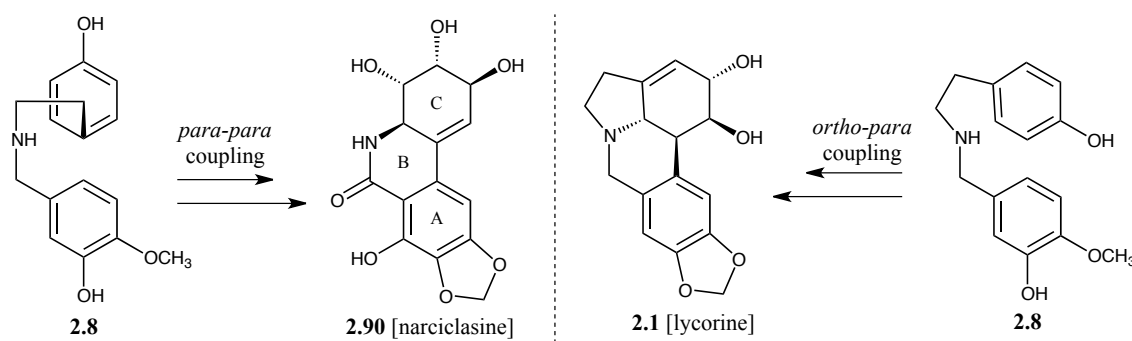


Figure 2.2.3 *ent*-Narciclasine

A description of the synthesis of *ent*-narciclasine [2.89] by Banwell and Matveenko is included in this Chapter because this employs the same starting materials and has several techniques in common with the work of the author as detailed on the following pages. That having been said, significant differences exist in the approach to formation of the B-ring as well as the use of molecular rearrangements as key synthetic steps.

Narciclasine and lycorine frequently co-occur in the same *Amaryllidaceae* species such as common daffodils although the concentration of narciclasine is usually much lower. For instance, lycorine may account for as much as 1% of the weight of dry daffodil bulbs but the concentration of narciclasine in daffodils is typically about 20mg/kg of dry bulbs. Both lycorine and narciclasine are derived from the same biosynthetic precursor, namely *O*-methylnorbelladine [2.8]. The biosynthesis of narciclasine [2.90] proceeds *via* a *para-para* coupling of the two aromatic components of *O*-methylnorbelladine [2.8] rather than the *ortho-para* coupling leading to lycorine 2.1

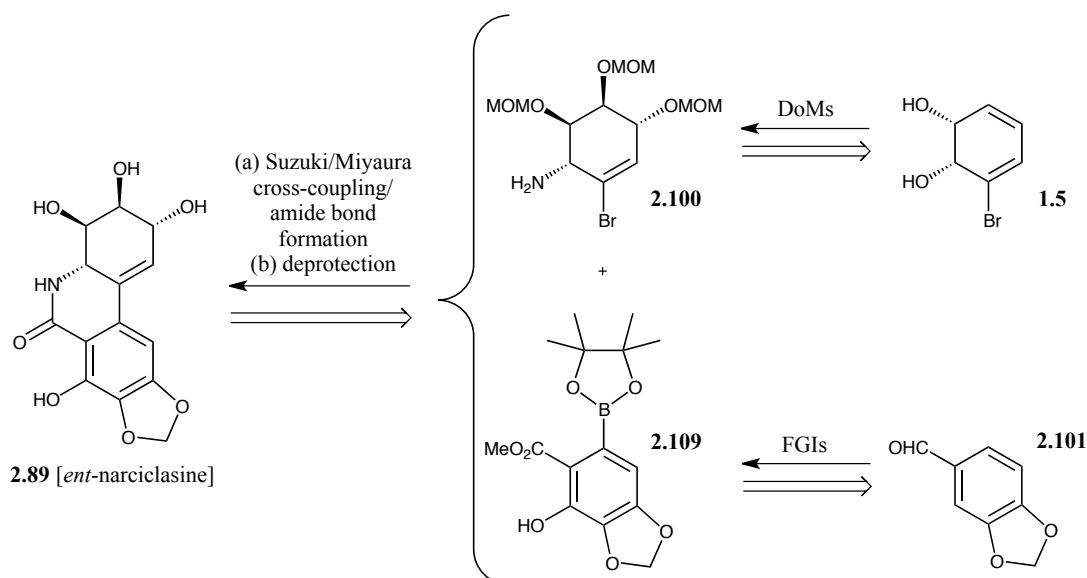
(Scheme 2.22). This leads to the significant structural differences between narciclasine [2.90] and lycorine [2.1].



Scheme 2.22 The Biosynthesis of Narciclasine [2.90] and Lycorine [2.1] from the Common Precursor O-Methylnorbelladine [2.8].

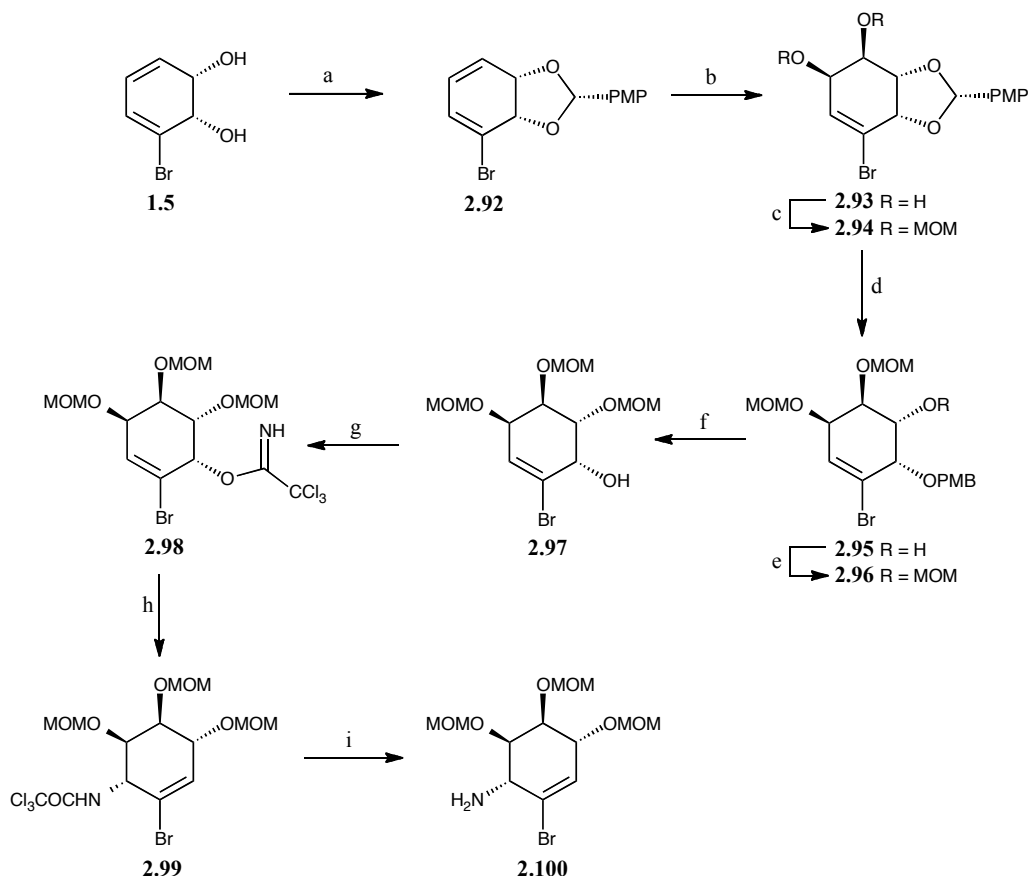
Narciclasine has been found to exhibit a wide range of potent biological activities, many being comparable to those of lycorine or, in some instances, exceeding it. This has spurred a great deal of research directed towards the synthesis of narciclasine and its congeners and numerous total syntheses of these compounds have been reported.⁵² One obvious conclusion to be drawn from the relatively large number of syntheses of narciclasine is that construction of the narciclasine C-ring does not present the formidable challenge associated with the construction of the C-ring of lycorine.

Banwell and Matveenko's approach to *ent*-narciclasine [2.89] exploits a tandem Suzuki-Miyaura cross-coupling/amide bond forming process between the aminoconduritol **2.100** and the aryl boronate **2.109** (see Scheme 2.23). This conversion involves both a Suzuki-Miyaura cross-coupling reaction and the formation of an amide bond but it is unclear as to the ordering of these events. Exhaustive cleavage of the MOM-ether residues within the product lactam then affords the target compound *ent*-narciclasine [2.89].



Scheme 2.23 Banwell and Matveenko's Synthetic Approach to *ent*-Narciclasine [**2.89**]

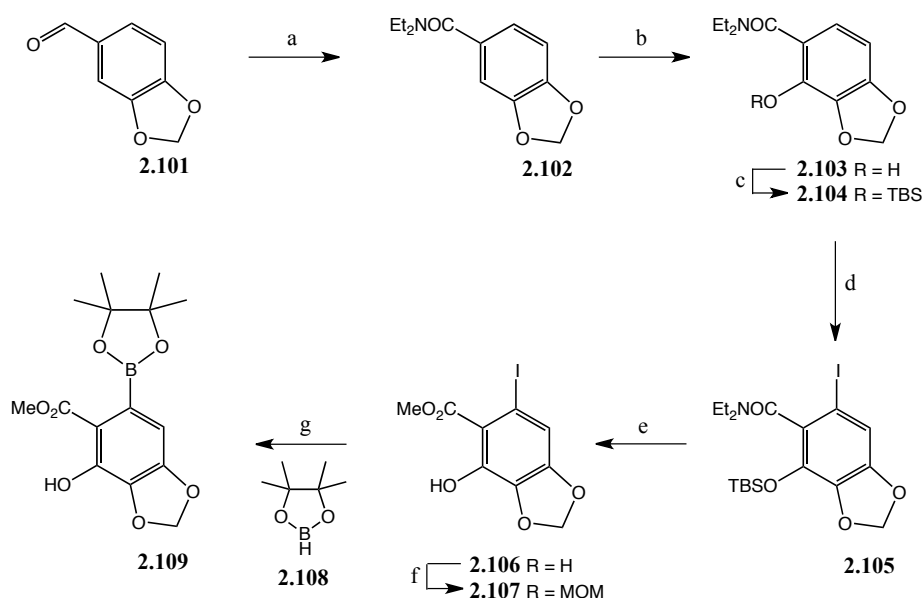
The aminoconduritol building block **2.100** was synthesised from 3-bromo-*cis*-1,2-dihydrocatechol **1.5** via an Overman rearrangement as shown in Scheme 2.24. Thus, the *cis*-diol **1.5** was converted into the corresponding *p*-methoxybenzylidene acetal **2.92**, which was obtained predominantly in the illustrated diastereomeric form. Acetal **2.92** was itself subjected to *cis*-1,2-dihydroxylation, under conditions defined by UpJohn,⁵³ to afford the diol **2.93** with excellent regio- and diastereo-control (65% over two steps). It is noteworthy that the dihydroxylation reaction takes place at the non-halogenated and, therefore, more nucleophilic double bond, and that the hydroxyl groups are introduced from the less congested *exo*-face. The hydroxyl groups within compound **2.93** were protected as MOM-ethers and the resulting *bis*-ether **2.94** was subjected to reductive cleavage of the PMP-acetal moiety with DIBAL-H to afford the *tris*-ether **2.95** in high yield. The regioselectivity observed in this last conversion is likely to be the result of coordination of the DIBAL-H to the acetal-oxygen that is further removed from the bulky bromine substituent. The free hydroxyl of compound **2.95** was protected as a MOM-ether and the PMB-group was removed by treatment with DDQ to give the alcohol **2.97**. Reaction of the latter compound with trichloroacetonitrile in the presence of DBU gave an acetimidate **2.98** that upon heating under microwave irradiation underwent an Overman rearrangement to afford the amide **2.99** (78% over two steps). Reduction of the last compound with DIBAL-H then furnished the requisite aminoconduritol **2.100** (89%).



Scheme 2.24 Reaction conditions: (a) *p*-MBDMA, CSA·H₂O, -20 °C; (b) OsO₄, NMO, 65% over two steps; (c) MOMCl, NaH, Et₃N, 91%; (d) DIBAL-H, -78 °C to -40 °C, 84%; (e) MOMCl, NaH, Et₃N, 90%; (f) DDQ, H₂O, 90%; (g) Cl₃CCN, DBU; (h) K₂CO₃, μ wave, 165 °C, 78% over two steps; (i) DIBAL-H, 89%.

The aryl boronate **2.109** (as introduced in Scheme 2.23) was derived from piperonal **2.101** via a series of directed *o*-metallation (DoM) processes as shown in the first parts of Scheme 2.25. Thus, piperonal **2.101** was treated with a mixture of sodium cyanide and manganese dioxide in neat diethylamine according to protocols described by Gilman⁵⁴ to afford the diethylamide **2.102** (58%). The diethylcarboxamide group of this last compound served as a directing group for *O*-metallation with *sec*-BuLi and treatment of the ensuing *O*-lithiated derivative with trimethyl borate followed by hydrogen peroxide/acetic acid afforded the phenolic compound **2.103** in high yield (90%) and with complete regioselectivity. The hydroxyl group of compound **2.103** was protected as the TBS-ether **2.104** and this itself was reacted with *sec*-BuLi followed by molecular iodine to give the aryl iodide **2.105** in 90% yield. Reaction of the last compound with Meerwein's reagent in the presence of dibasic sodium phosphate had the effect of methanolyzing the diethylcarboxamide group as well as cleaving the TMS-ether

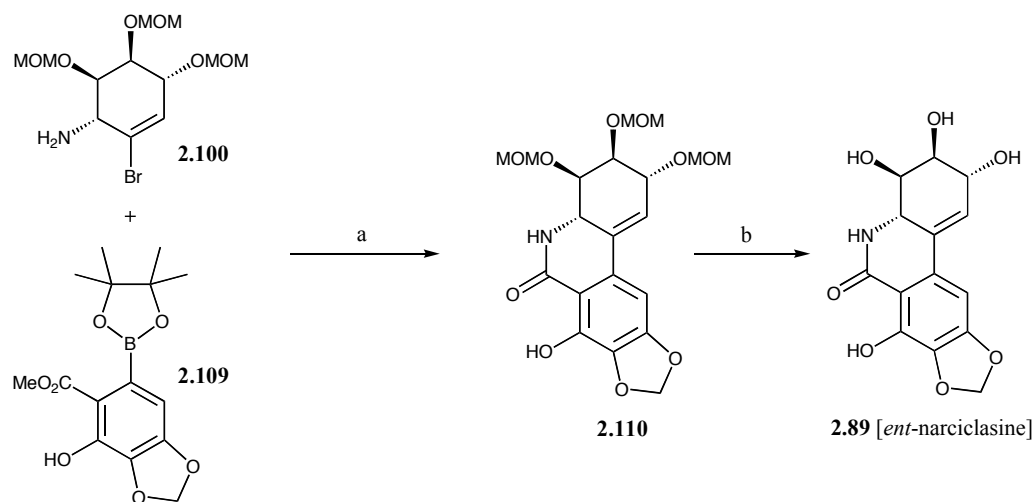
substituent to afford the methyl salicylate **2.106** (62%). Finally, the hydroxyl group of compound **2.106** was protected as the corresponding MOM-ether, **2.107**, which was itself subjected to Miyaura borylation using pinacolborane [**2.108**] in the presence of $\text{PdCl}_2\cdot\text{dppf}$ to afford the requisite arylboronate **2.109**.



Scheme 2.25 Reaction conditions: (a) NaCN , MnO_2 , Et_2NH (neat), 58%; (b) *sec*-BuLi, $\text{B}(\text{OMe})_3$, H_2O_2 , acetic acid, 90%; (c) TBSCl, imidazole, 94%; (d) *sec*-BuLi, I_2 , TMEDA, 90%; (e) $\text{Me}_3\text{O}^+\text{BF}_4^-$, Na_2HPO_4 , 62%; (f) MOMCl, NaH, Et_3N , 90%; (g) **2.108**, $\text{PdCl}_2\cdot\text{dppf}$, 44%.

Assembly of the narciclasine framework was completed (Scheme 2.26) by subjecting the arylboronate **2.109** and the aminoconduritol **2.100** to Suzuki-Miyaura cross-coupling conditions and thus generating the *tris*-MOM ether of *ent*-narciclasine, **2.110**, in 63% yield. Finally, cleavage of the MOM protecting groups using trimethylsilyl bromide in dichloromethane produced *ent*-narciclasine **2.89** in 48% yield.

Banwell and Matveenko's synthesis of *ent*-narciclasine involved 18 steps and was completed with an overall yield of 7%. The use of an Overmann rearrangement as a key step in the assembly of the aminoconduritol proved to be an effective method. Interestingly, Hudlicky and co-workers have reported a synthesis of (+)-narciclasine⁵⁵ that was completed in 11 steps from a similar *cis*-1,2-dihydrocatechol compound albeit in significantly lower yield (0.7%).



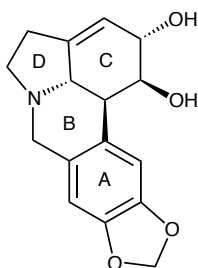
Scheme 2.26 Reaction conditions: (a) Pd(PPh₃)₄, K₂CO₃, TBAB, toluene/H₂O, μ wave, 120 °C, 63%; (b) TMS-Br, 48%.

2.3 An Enantioselective and General Synthetic Approach to the Lycorine Framework

The synthetic approaches to the lycorine framework and to lycorine itself as described above as well as recent publications concerning the anti-cancer activity of lycorine and its congeners represent the culmination of almost 100 years of research. However, despite this long history there remains the need for efficient and flexible approaches to these compounds that may be adapted to the synthesis of lycorine analogues as candidates for drug development. Tomioka's synthesis of (–)-lycorine *via* his chiral ligand-controlled asymmetric conjugate addition cascade methodology provides one such approach, but the development of alternative methods has both scientific and practical merit. This situation, combined with the Banwell Group's continuing interest in deploying *cis*-1,2-dihydrocatechol compounds as starting materials for the preparation of *Amaryllidaceae* alkaloids prompted the development of an enantioselective and general synthetic approach to the lycorine framework. The outcome of such studies is described in the following Sections of this Thesis.

2.4 Retrosynthetic Analysis and Strategy

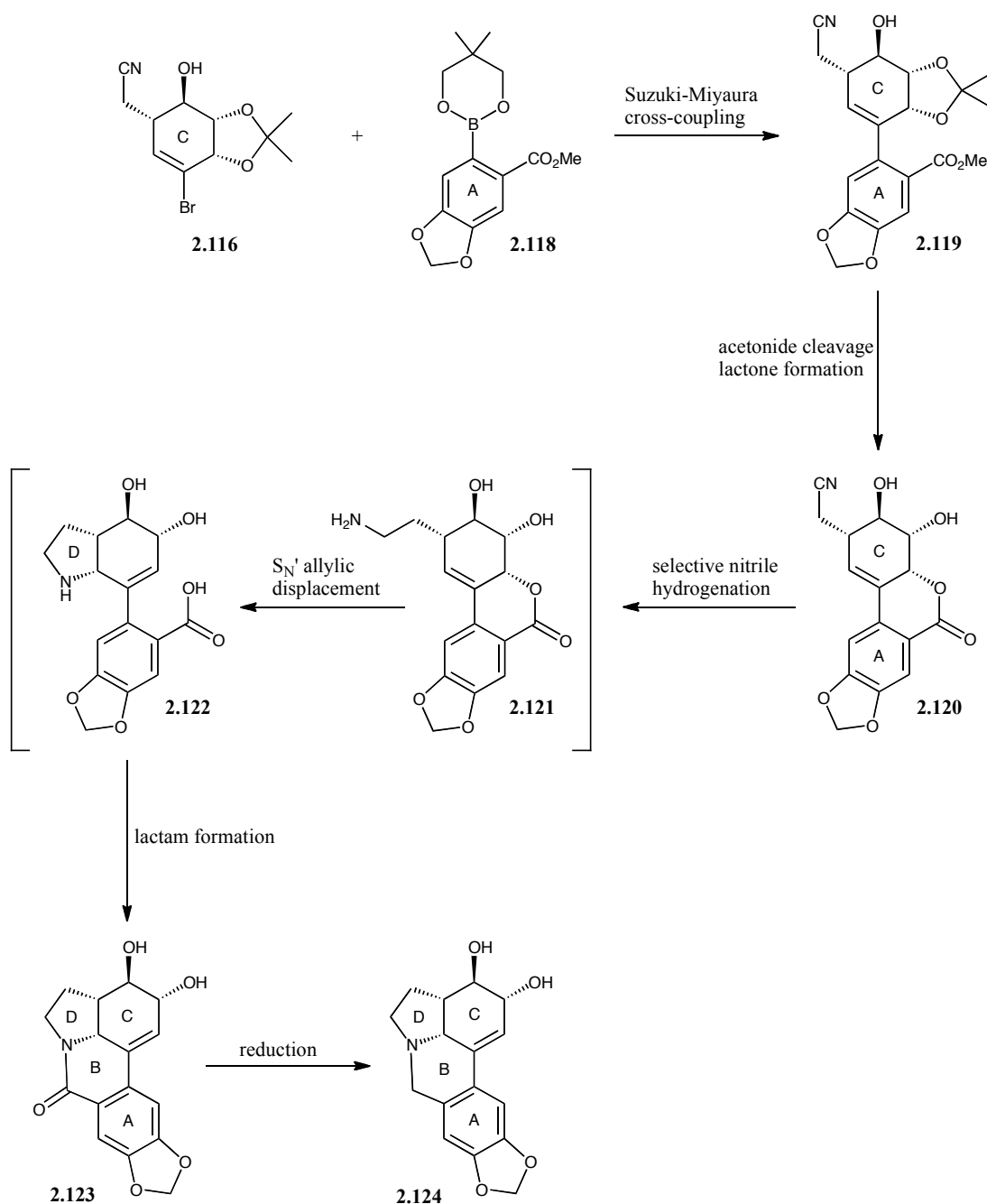
Analysis of the structure of the lycorine framework (Figure 2.4.1) and consideration of previous syntheses suggested that a convergent approach was likely to be the most effective one. Such an approach could be based on an enantioselective construction of an appropriately functionalised C-ring building block and a concise synthesis of a suitable aromatic A-ring building block. The two components could then be cross-coupled *via* a Suzuki-Miyaura reaction.^{56,57,58} The B- and D-rings of the lycorine framework would then be formed by manipulation of reactive sites within such a cross-coupled ensemble. Banwell and Matveenko employed a similar strategy in their synthesis of *ent*-narciclasine [2.89].



2.1 [lycorine]

Figure 2.4.1 The Ring Labeling Scheme for Lycorine.

On this basis, an approach to the lycorine framework was devised (Scheme 2.29) involving the Suzuki-Miyaura cross-coupling of arylboronate **2.118** with the γ -hydroxynitrile **2.116** which might be expected to afford the arylcyclohexene compound **2.119**. It was anticipated that the arylboronate **2.118** could be readily obtained from piperonal *via* standard chemical transformations including one involving a Miyaura borylation procedure.⁵⁹ However, the key challenge in synthesis of lycorine-type compounds is the efficient construction of the C-ring and its multiple stereocentres. It was proposed that this could be constructed using a chiral-pool approach from the enantiomerically pure *cis*-1,2-dihydrocatechol **1.5** which is itself obtained *via* the whole-cell biotransformation of bromobenzene.^{60,61} The choice of such a brominated starting material was significant because this would ensure that the C-ring cross-coupling partner would incorporate an alkenyl-bromide moiety as the substrate for a Suzuki-Miyaura cross-coupling reaction. Alkenylbromides are especially well suited to this reaction.⁵⁷

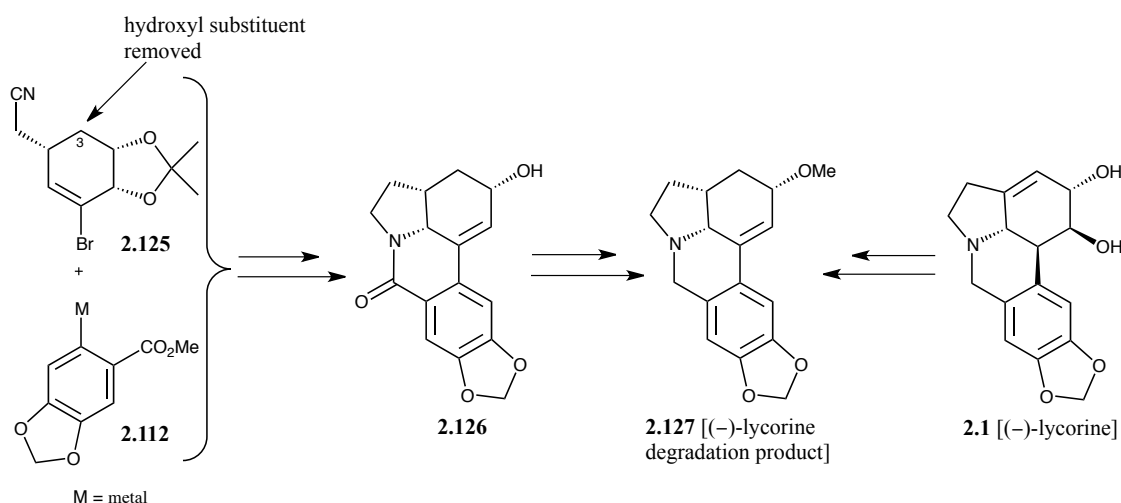


Scheme 2.29 Proposed Synthesis of the Lycorine Framework **2.124**.

The acetonide residue of the product, **2.119**, of the cross-coupling reaction would be subjected to acid-catalysed hydrolysis to reveal an allylic alcohol which it was anticipated would engage in a spontaneous lactonisation reaction with the adjacent aryl-ester residue to generate the lactone **2.120**. Selective reduction of the nitrile moiety within the latter compound would reveal a primary amine, **2.121**, that might be expected to engage in an S_N' displacement^{62,63} of the pendant lactone and so establishing the

lycorine D-ring manifest in compound **2.122**. Subsequent rotation about the C-11a – C-11b bond will bring the carboxylic residue of the aryl system and the nitrogen of the D-ring into close proximity and a spontaneous lactamisation reaction would be expected occur and thus generating the B-ring of compound **2.123**. Finally, reduction of the lactam carbonyl with a suitable hydride donor should afford the pentacyclic compound **2.124**, an (unnatural) isomer of lycorine.

Because each of the coupling partners associated with the proposed synthesis has the potential for structural manipulation, the approach described above is divergent and should allow for the synthesis of a variety of lycorine-type compounds. For instance, the C-3 hydroxyl substituent of the γ -hydroxynitrile **2.116** could be removed *via* the Barton–McCombie radical deoxygenation protocol to afford the nitrile **2.125** (Scheme 2.30). Substitution of this compound in Scheme 2.29 should lead to the lycorine-type compound **2.126**. This compound is closely related to the lycorine degradation product **2.127** reported by Takeda and Kotera in 1957.⁶⁴ Conversion of compound **2.126** into the lycorine degradation product **2.127** would require formation of an *O*-methyl ether and reduction of the lactam carbonyl.



Scheme 2.30 Proposed Synthesis of the Lycorine Degradation Product **2.127**.

Accordingly, the synthesis of the unnatural lycorine isomer **2.124** and the lycorine degradation product **2.127** were chosen as specific targets for the preliminary synthetic studies described below. The additional steps involved in the synthesis of the target **2.127** ensured that it would be the more challenging objective and it was, therefore, the central focus of this research. The work is set within the context of the

establishing an enantioselective and general synthetic route to the lycorine framework by employing *cis*-1,2-dihydrocatechol compounds as starting materials.

2.5 Synthesis of a Lycorine Degradation Product

As outlined in Section 2.4, the proposed strategy for the synthesis of the lycorine degradation product **2.127** requires that two building blocks be synthesised, namely the C-ring precursor **2.125** and the arylboronate **2.118**. Developing a synthesis of the C-ring precursor **2.125** was given priority. Details of studies on this matter are presented in the following section.

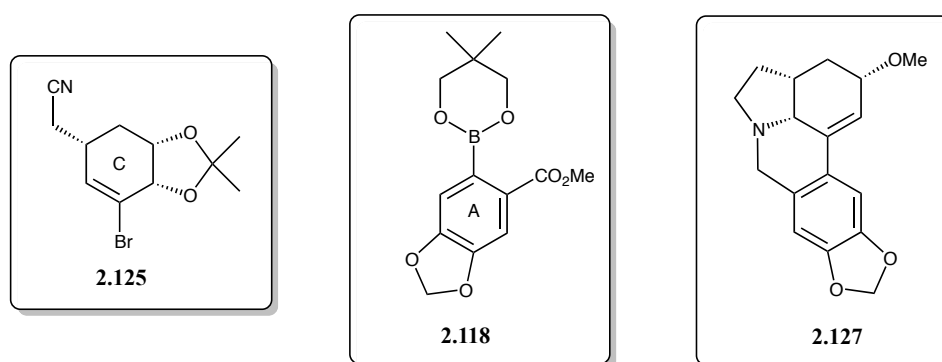


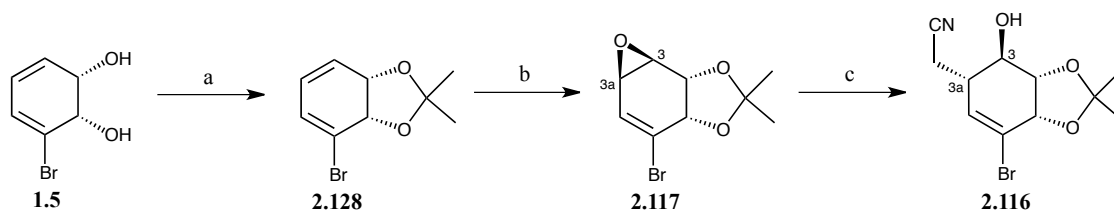
Figure 2.5.1 Key Building Blocks Used for Assembling the Lycorine Framework and the Lycorine Degradation Product **2.127**.

2.5.1 Acquisition of the C-Ring Precursor **2.125**

The first steps taken towards the acquisition of the *cis*-1,2-dihydrocatechol derivative **2.125** followed well-established protocols (Scheme 2.31). Thus, the *cis*-1,2-dihydrocatechol **1.5** was protected as the corresponding acetonide **2.128** (93%) and the latter compound was subjected to oxidation with *m*-CPBA at $-5\text{ }^{\circ}\text{C}$ to afford, in a stereoselective manner, the previously reported epoxide **2.117**⁶⁵ which was obtained in 95% yield. The epoxidation reaction takes place at the more nucleophilic (non-halogenated) bond and proceeds exclusively from the less sterically-congested *exo*-face of the substrate when the reaction temperature is maintained below $0\text{ }^{\circ}\text{C}$. It is noteworthy that when this epoxidation procedure is conducted at room temperature ($18\text{ }^{\circ}\text{C} \sim 20\text{ }^{\circ}\text{C}$) the product is contaminated with a trace of the alternate diastereomer.

The generation of the γ -hydroxynitrile **2.116** involves the nucleophilic attack of the anion derived from acetonitrile at the allylic carbon, C-3a, of epoxide **2.117**.⁶⁶ Similar

transformations of mono epoxide derivatives of cyclohexa-1,3-diene have been reported in which the requisite anion was obtained by treatment of a solution of acetonitrile in THF with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$.⁶⁷ Bordwell and co-workers have determined the equilibrium acidities of a wide range of compounds in DMSO⁶⁸ and have shown that the $\text{p}K_a$ of acetonitrile in pure DMSO is 31.3 whereas the typical $\text{p}K_a$ values of alkyl-lithium compounds are greater than 45 and with the $\text{p}K_a$ of alkyl-hydrocarbons (carbon acids) being greater than 50. Thus, *n*-BuLi is stable as a solution in hexane but it will readily abstract a proton from acetonitrile. Indeed at room temperature *n*-BuLi will abstract protons situated in the α -position in THF. However, at low temperatures the oxygen of THF acts as a very strong ligand for lithium and a tetrameric molecular complex (*n*-BuLi·THF)₄ is formed.⁶⁹ Thus, as long as sufficiently low temperatures are maintained this complex is reasonably stable with respect to THF and yet highly reactive towards compounds of lower $\text{p}K_a$. In the event, the slow addition of a solution of epoxide **2.117** in THF to a 1:7 v/v mixture of acetonitrile and THF and *n*-BuLi (1.5 equivalents) at temperatures maintained below $-60\text{ }^{\circ}\text{C}$ afforded, as the only product, the γ -hydroxynitrile **2.116** in 95% yield. The success of this transformation was readily confirmed by the appearance of an absorption band in the IR spectrum corresponding to the newly formed hydroxyl group. Evidently, nucleophilic attack by the acetonitrile anion has taken place exclusively at the less hindered carbon, C-3a, of the epoxide ring and from the more congested *endo*-face of the molecule, *anti* to the epoxide oxygen.



Scheme 2.31 Reaction conditions: (a) 2,2-DMP, *p*-TsOH (catalytic), 93%; (b) MCPBA, $-5\text{ }^{\circ}\text{C}$, 95%; (c) *n*-BuLi, THF/MeCN, $-60\text{ }^{\circ}\text{C}$, 95%.

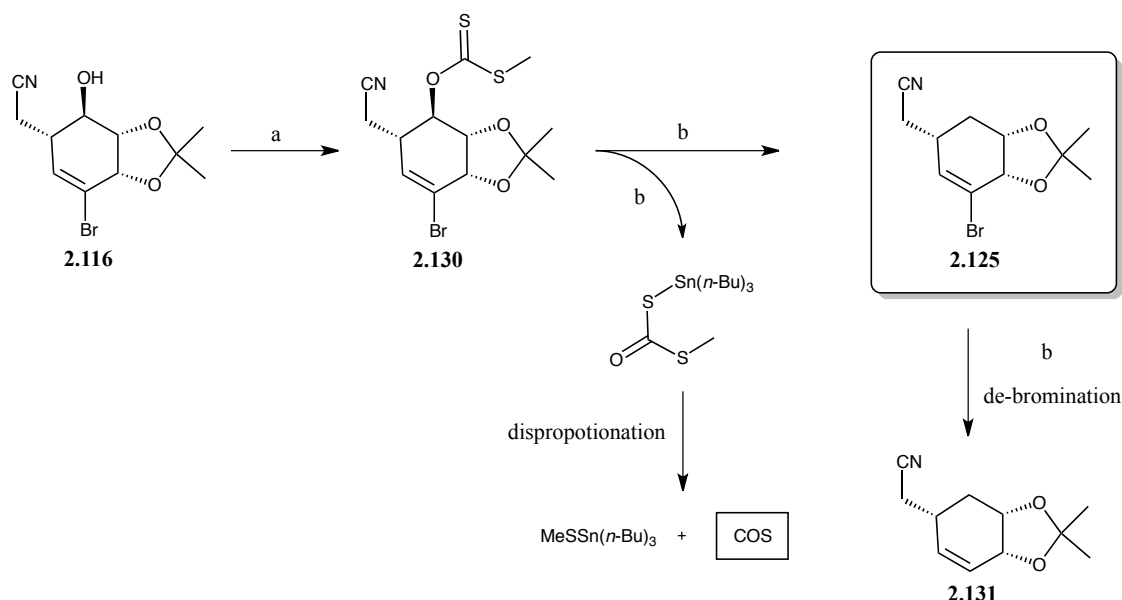
Removal of the hydroxyl group from compound **2.116** was achieved using the Barton-McCombie radical deoxygenation protocol.⁷⁰ The process followed the standard approach (Scheme 2.32) whereby the hydroxyl was first converted into the corresponding xanthate ester **2.130** and this was subsequently exposed to *n*-Bu₃SnH and the radical

initiator AIBN in refluxing benzene. However, despite the numerous precedents for the use of the Barton McCombie protocol in the synthesis of natural products⁷¹ the optimization of the procedure for the deoxygenation of compound **2.116** proved to be challenging. Early attempts to generate the xanthate ester were met with modest yields of the product and were accompanied by significant degradation of the starting material. Investigations of this problem revealed that the use of excess of carbon disulfide in this step led to degradation of the starting material and, thereby, unsatisfactory yields of the xanthate ester. It is not clear why this reaction was so sensitive to stoichiometry, but high yields (90 – 95%) of the xanthate ester **2.130** were reliably obtained by the use of a 1:1:1 ratio of compound **2.116**, CS₂ and MeI.

When a solution of the xanthate ester **2.130** in refluxing benzene was subjected to radical cleavage by treatment with 2.1 molar equivalents of *n*-Bu₃SnH and 5 mol % of the radical initiator AIBN the nitrile **2.125** was obtained in 75 – 82% yield. Careful monitoring of the reaction by TLC was essential in order to obtain such yields because the compound **2.125** was itself subject to radical debromination, albeit at a slower rate than the radical deoxygenation process. In practice, some of the debrominated by-product **2.131**, (5% – 15%), was always formed during the procedure. It was, therefore, necessary to quench the reaction when it was judged that the production of nitrile **2.125** was at its optimum with respect to maximum conversion of the starting material and minimum degradation of the target.

The nitrile **2.125** and the debrominated compound could be separated by column chromatography, but another contaminant made it necessary to subject the nitrile **2.125** to especially rigorous chromatographic purification. A by-product of the Barton-McCombie radical deoxygenation procedure is carbonyl sulfide⁷² (Scheme 2.31), which is readily hydrolysed to generate hydrogen sulfide. Both of these small molecules are notorious as catalyst poisons in the petrochemical industry.⁷³ The presence of carbonyl sulfide as a contaminant of nitrile **2.125** significantly lowered the yield of the palladium-catalysed Suzuki-Miyaura cross-coupling that is the next step in the reaction sequence. Fortunately, removal of carbonyl sulfide proved to be simple because it is very soluble in toluene⁷⁴ whereas, the nitrile **2.125** is only sparingly so. Thus, when a crude sample of compound **2.125** was loaded onto a silica gel column this was first flushed with toluene until the eluent no longer exhibited any sulfurous odour.⁷⁵ The eluting solvent was then changed

to a mixture of 3.0/0.5/96.5-v/v/v acetone/triethylamine/toluene, which allowed for isolation of compound **2.125** as a crystalline compound of high purity.^a



Scheme 2.31 Reaction conditions: (a) NaH, CS₂, MeI, 90%; (b) (*n*-Bu)₃SnH, AIBN, benzene, reflux, 82% of compound **2.125** plus 5% of compound **2.131**.

The most significant indication of the success of the Barton-McCombie radical deoxygenation reaction was obtained *via* the IR spectrum of compound **2.125** which lacked a hydroxyl absorption band. The ¹H nuclear magnetic resonance (¹H NMR) spectrum of nitrile **2.125** (Figure 2.5.2) exhibited two strong singlets at δ 1.47 and δ 1.38 each of which integrated for three protons and which correspond to the hydrogens of the acetonide-protecting group. A broad multiplet appearing at δ 2.06 and integrating for two protons is attributed to the methylene hydrogens of the cyclohexene ring. A broad singlet

^a As an aside, it is worth noting that this problem was not foreseen and early trials with the critical Suzuki-Miyaura cross-coupling were met with erratic results and, sometimes, outright failure. After many fruitless attempts to solve this problem the solution was literally 'sniffed out'! Both COS and H₂S exhibit a pungent odour that can be detected by the human nose at low levels and it became apparent that newly synthesised samples of nitrile **2.125** which exhibited a sulfurous odour would not engage in the palladium-catalysed cross-coupling reaction. On the other hand, samples of the nitrile that had been recovered from unsuccessful reactions and which exhibited no odour readily engaged in the cross-coupling reaction. Eventually the malodorous cause of the unreliable cross-coupling reaction was identified and a simple means of removing it was developed (*vide supra*).

observed at δ 2.64, and integrating for three protons, was assigned to the two methylene hydrogens of the pendant acetonitrile residue and the (single) hydrogen at C-6. The distinct one-proton multiplet at δ 4.44 and the one-proton doublet ($J = 5.4$ Hz) at δ 4.51 confirmed the presence of the two oxymethine hydrogens whilst the olefinic proton resonated at δ 6.24. The ^{13}C NMR data are also completely consistent with the proposed structure. The EI mass spectrum did not display a molecular ion, but two fragment ions at m/z 258 (59%) and 256 (60%) correspond to the loss of a methyl radical from the molecular ion. Accurate mass measurements on each of these species established that they were of the expected composition, *viz.* $\text{C}_{10}\text{H}_{11}\text{BrNO}_2$. The IR spectrum of this compound exhibited a sharp but rather weak absorption band at 2244 cm^{-1} characteristic of nitrile groups. The specific rotation, $[\alpha_D]$, of the compound was found to be $+90$ (c 1.0, CHCl_3). The acquisition of compound **2.125** completed the assembly of the C-ring precursor to the lycorine degradation product **2.127**.

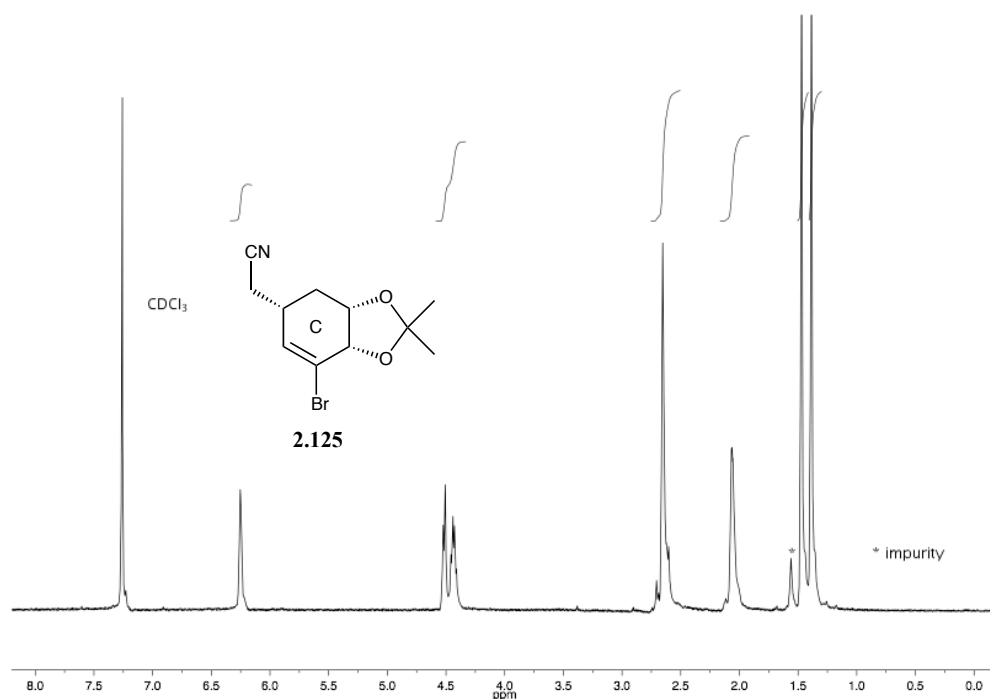
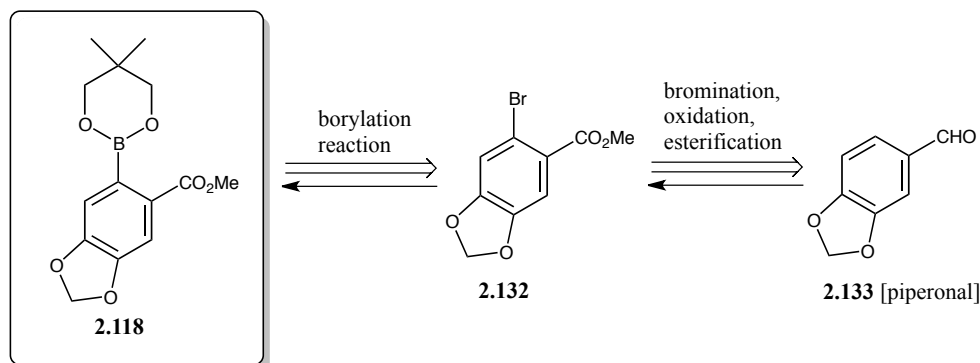


Figure 2.5.2 300 MHz ^1H NMR Spectrum of Nitrile **2.125** (Recorded in CDCl_3)

2.5.2 Assembly of the Aromatic Coupling Partner

With the C-ring precursor **2.125** in hand, attention was turned to the construction of the previously reported aromatic building block **2.118**.⁷⁶ The route to this compound started from piperonal **2.133** and is shown in retrosynthetic form in Scheme

2.32. This approach was strongly influenced by Tønder's earlier synthesis of this compound⁷⁶ and by the Banwell and Matveenکو synthesis of the structurally related arylboronate **2.109** (Scheme 2.25, Page 42) from piperonal.⁷⁷



Scheme 2.32 Retrosynthetic Analysis of the Aryl Coupling Partner.

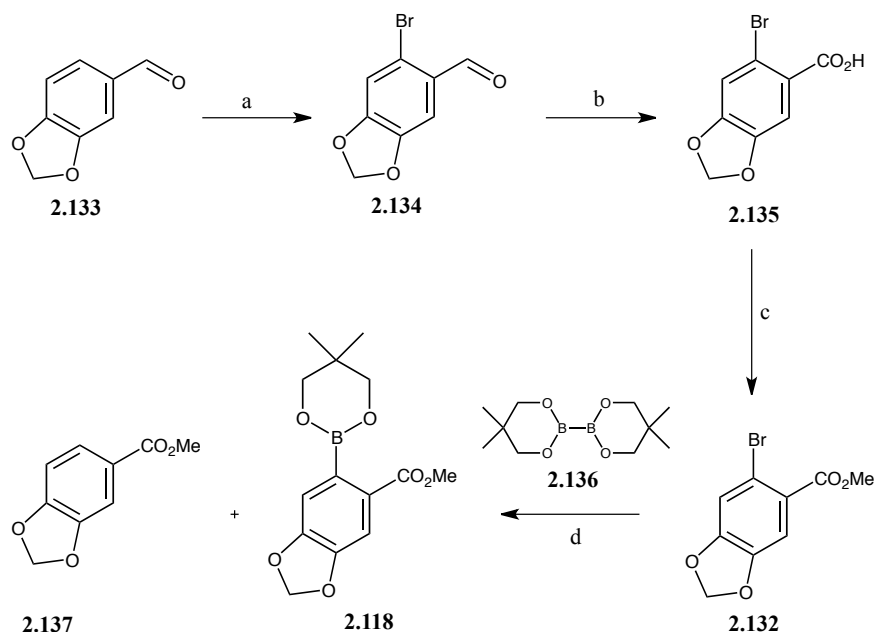
A difficulty that is encountered when attempting to install a boronate moiety *ortho* to an electron-withdrawing group such as an ester is that the process tends to suffer from competing reductive dehalogenation, a problem that results in low yields of the desired product.⁷⁸ Moreover, the steric hindrance imposed by an *ortho* substituent impedes the borylation of aryl halides.⁷⁹ Since aryl iodides are generally more reactive as substrates for organometallic reactions than aryl bromides, the synthesis the former type of halide seemed preferable. Banwell and Matveenکو explored such an approach, but when the iodo congener of compound **2.132** was subjected to reaction conditions required for palladium-catalysed borylation with either pinacolborane or bis(pinacolato)diborane, only modest yields of the corresponding arylboronate could be obtained. The product was invariably accompanied by a significant amount of reductively dehalogenated material, and in many instances the dehalogenated material predominated.⁸⁰ By contrast, Tønder⁷⁶ was able to obtain good yields of the arylboronate **2.118** by means of palladium-catalysed borylation of the aryl-bromide **2.132** employing pinacolborane, Et₃N, dioxane and a catalyst derived from Pd(OAc)₂ and the ligand 2-(dicyclohexylphosphino)-biphenyl. Tønder's success demonstrated the suitability of a brominated derivative of piperonal as a substrate for the borylation process. However, the requisite ligand was not available in Australia at the time the research described in this thesis was conducted. Fortunately, Wang and co-workers have reported a high yielding method for the borylation of a wide range of *ortho*-substituted aryl bromides including methyl 2-bromobenzoate.⁸¹ Their method employs the readily available borylating agent

bis(neopentyl glycolato)diboron [2.136] and common palladium catalysts such as Pd(PPh₃)₄ or PdCl₂(dppf)·CH₂Cl₂. Wang attributes the high yields afforded by this technique to the lower steric bulk of the neopentyl-glycolato boronic ester relative to that of pinacol-boronic ester. Accordingly, it was decided to synthesise the arylbromide 2.132 from piperonal and to conduct the subsequent borylation reaction using Wang's technique.

ortho-Bromination of piperonal was achieved by the time-tested method of stirring this substrate for several days at room temperature with a suspension of iron powder in a mixture of acetic acid and molecular bromine.⁸² The regiochemistry of this electrophilic aromatic substitution is dominated by the activating effect of the oxy-methylene substituent at the 3-position, which directs the introduction of bromine to the 6-position. The process delivered 6-bromopiperonal [2.134] in good yield but mass spectral analysis revealed that a small amount of dibrominated material was also produced. In practice, it was difficult to remove this impurity either by chromatography or by recrystallisation. By conducting the bromination reaction under milder conditions at lower temperatures and lower concentrations of bromine it was possible to suppress the production of the dibrominated product, but at the cost of lower yields of the product. Fortunately, a procedure disclosed by Khanapure and co-workers,⁸³ involving the addition of a catalytic quantity of iodine to a solution of piperonal and molecular bromine in glacial acetic acid and carbon disulfide (Scheme 2.23), afforded high yields (>80%) of 6-bromopiperonal [2.134] with no dibrominated impurity and in less than half the time required by the previous method. Furthermore, considerably less molecular bromine and no iron powder were required. Presumably, the presence of a catalytic quantity of iodine allows a small amount of IBr to be generated and this species serves as a more reactive electrophilic brominating agent than Br₂ itself.⁸⁴

The next step in the synthetic sequence is the conversion of the aldehyde group of piperonal into a methyl ester. Tønder achieved this by means of a one-pot oxidation/esterification procedure employing MnO₂ and sodium cyanide in the presence of methanol.⁸⁵ Banwell and Matveenko have also employed this technique to good effect. This approach is efficient and suitable for 'one-off' small-scale synthesis, but when multi-gram quantities of a product are required the use of larger amounts of sodium cyanide presents an unwelcome hazard, as does the repeated use of this substance. Moreover, a by-product of this reaction is HCN gas. Since it was expected that a considerable quantity of compound 2.118 would be required for various different

projects a less hazardous procedure was pursued. Thus, 6-bromopiperonal [**2.134**] was subjected to a Pinnick oxidation and the ensuing carboxylic acid [**2.135**] was treated with a mixture of thionyl chloride and methanol to afford methyl 6-bromopiperonate [**2.132**] in an overall yield of 74% (Scheme 2.23).



Scheme 2.33 Reaction conditions: (a) Br₂, I₂ (catalytic), CS₂, acetic acid, 81%; (b) NaClO₂, NaH₂PO₄, H₂O₂, then HCl (2.0M), 100%; (c) SOCl₂, MeOH, 85%; (d) PdCl₂(dppf)·CH₂Cl₂, KOAc, MeCN, 85% of compound **2.118** plus 5% of compound **2.137**.

Borylation of methyl 6-bromopiperonate [**2.132**] was readily achieved by employing the conditions disclosed by Wang and co-workers using anhydrous DMSO as a solvent. Yields in excess of 75% of the *bis*(neopentylglycolato)diboron derivative **2.118** could be obtained by such means, but the inconvenience of the need to carry out a thorough extraction of this compound from DMSO prompted an investigation into the use of various other solvents. Under similar conditions dioxane, which is a common solvent for palladium-catalysed borylation reactions,⁸⁶ afforded a lower yield (68%). In contrast, yields were negligible when either THF or toluene was employed. Fortunately, acetonitrile proved an excellent solvent for the purpose, and under reflux conditions afforded comparable yields to those obtained with DMSO but now allowing for ready extraction of the product. Separately dissolving the borylating agent in a small quantity of acetonitrile and injecting the resulting solution into the reaction vessel over one hour

further improved the process. This refinement minimised degradation of the borylating agent in the hot reaction mixture and reliably afforded yields in excess of 85% of the arylboronate **2.118** and approximately 5% yield of the debrominated compound **2.137** (Scheme 2.33). When this technique was combined with the use of freshly recrystallised⁸⁷ $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ the arylboronate **2.118** could be obtained in 92% yield.

The spectral data obtained on compound **2.118** were entirely consistent with the assigned structure and in close accord with those obtained by Tønder for the structurally related pinacolato-boronate. In particular, the ^{13}C NMR spectrum of compound **2.118** (Figure 2.5.3) displayed eleven signals including six (with one signal obscured or overlapping) in the region above δ 105 and corresponding to the sp^2 -hybridised carbons within the structure. The most significant components of the spectrum were those corresponding to the neopentyl-glycolato moiety. Thus, a strong signal is observed at δ 72.7 arising from the two equivalent methylene oxycarbons whilst the signal at δ 31.9 is due to the isolated quaternary carbon. The two equivalent methyl group carbons resonated at δ 22.2 while the carbonyl carbon of the ester residue resonated at δ 168.6. The signal due to methylenedioxy carbon was observed at δ 101.7 and the signal arising from methyl carbon of the ester-moiety appeared at δ 52.8.

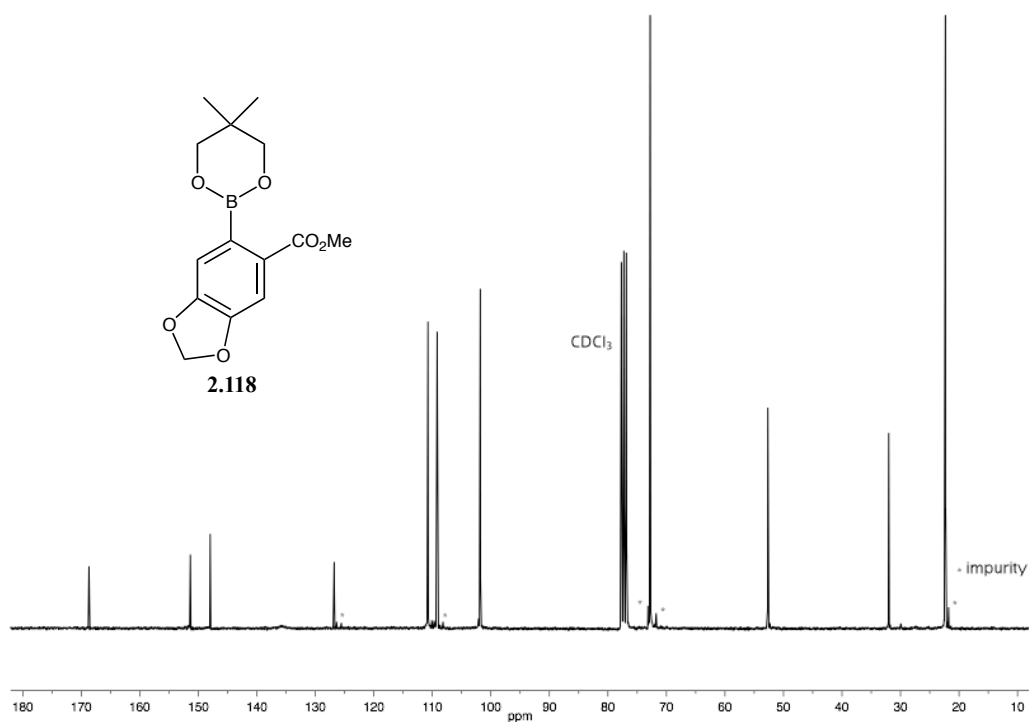


Figure 2.5.3 75 MHz ^{13}C NMR Spectrum of Compound **2.118** (Recorded in CDCl_3)

2.5.3 Suzuki-Miyaura Cross-coupling of the *cis*-1,2-Dihydrocatechol Derivative **2.125** and the Arylboronate **2.118**.

With the potential reaction partners **2.125** and **2.118** to hand, an investigation of their capacity to engage in the pivotal Suzuki-Miyaura cross-coupling could be pursued. The generally accepted mechanism of this type of Pd[0]-catalysed reaction is depicted in general terms in Figure 2.5.4.⁸⁸ Thus, oxidative addition of the simplified cyclohexenyl bromide **2.139** to Pd[0] generates the Pd[II] complex **2.140**. This event is followed by exchange of the Br[−] ion attached to the palladium for the anion of the base [M⁺(OR[−])] in a process referred to as metathesis. The ensuing Pd[II] species **2.141** and the alkylborate complex **2.143** then undergo transmetallation to afford an intermediate **2.144**, which itself engages in a reductive elimination with formation of the C – C bond of the product **2.145**. This is accompanied by regeneration of the Pd[0] catalyst **2.146**.

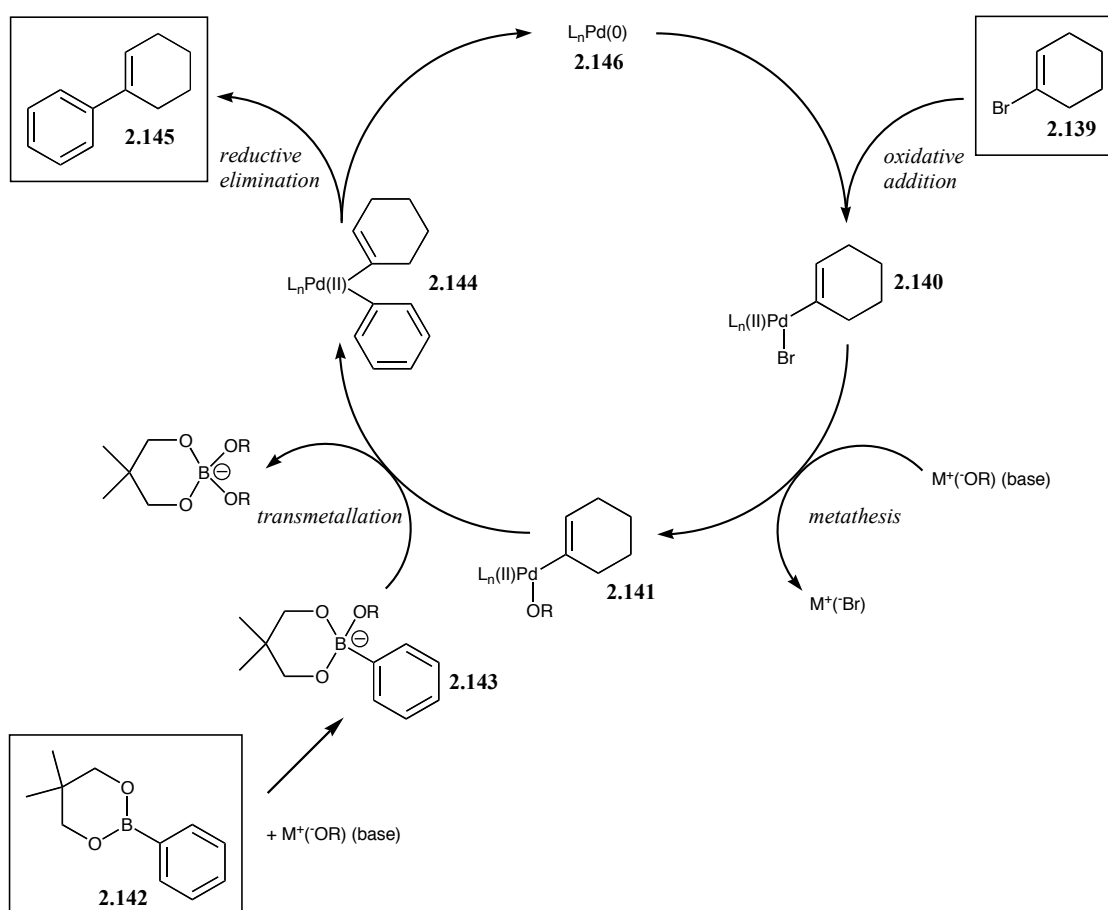


Figure 2.5.4 The Catalytic Cycle Associated with the Suzuki-Miyaura Cross-coupling Reaction.⁸⁸

The Suzuki-Miyaura cross-coupling reaction is a reliable and versatile method of effecting C-C bond formation but optimal yields depend upon the careful selection of the solvent, base, and palladium catalyst. A thorough discussion of these factors is beyond the scope of this Thesis but several important factors are summarised here.⁹⁴ Suzuki-Miyaura cross-coupling reactions are typically conducted at elevated temperatures and employing solvents such as DMF, DME, DMSO, dioxane or THF. Mixtures of water and THF are commonly used and bi-phasic mixtures of toluene and water may be employed, although in the latter case it is necessary to add a phase-transfer catalyst such as *tetra*-butylammonium bromide to overcome the immiscibility of the solvents.

It is apparent from the catalytic cycle as shown in Figure 2.5.4 that the base plays a key role in the reaction and, therefore, in the yields and selectivity of it. A wide range of bases has been employed but amongst the most common are NaHCO₃, K₂CO₃, KOAc, CsCO₃ as well as the organic bases, triethylamine and *i*-PrNEt₂.

Perhaps the most important factor for a successful Suzuki-Miyaura cross-coupling reaction is the choice of a palladium catalyst and the ligands used to stabilize it.⁸⁹ Fortunately, the readily available palladium complexes Pd(PPh₃)₄ and PdCl₂(dppf)·CH₂Cl₂ are effective catalysts in many instances. Catalysts derived from Pd(OAc)₂ and bulky electron-rich ligands such as P(*t*-Bu)₃ or 2-dicyclohexylphosphino-2'-methylbiphenyl⁹⁰ can facilitate coupling of otherwise unreactive substrates and may overcome competitive binding of moieties such as free amines. As a counterpoint, it is worth noting that highly effective 'ligandless' conditions involving Pd(OAc)₂ and coordinating solvents such as DMSO have been reported.⁹¹

In order to establish suitable conditions for the cross-coupling reaction a series of small-scale tests was conducted. The reaction conditions utilized for these experiments employed 0.20 mmol of each coupling partner (*viz.* compounds **2.118** and **2.125**) and 5 ml of a 4:1 v/v mixture of THF and water, plus Pd(PPh₃)₄ (5 mole % loading) and 0.60 mmol (three molar equivalents) of base. The reaction mixture was heated at 70°C until TLC analysis indicated that no further reaction was taking place or for a maximum of four hours. No reaction was observed with potassium carbonate or potassium phosphate as the base but potassium acetate gave a yield of 41% of the cross-coupled product **2.138** whilst CsCO₃ afforded a yield of 48%. TLC and NMR analysis revealed that a significant proportion of the arylboronate was being consumed through reductive deborylation processes but no method was found to prevent this phenomenon altogether. However, by

adding two molar equivalents of the arylboronate to the reaction mixture and using CsCO_3 as a base, yields in excess of 55% of the cross-coupled product were obtained. Several other solvents were investigated under similar conditions including DMF, DMSO, dioxane, MeCN and a 1:1 v/v mixture of toluene and water. No reaction was observed with the toluene and water mixture or MeCN whilst DMF and dioxane were inferior to the THF/water solvent mixture. On the other hand, DMSO proved to be an effective solvent and when the optimum reaction conditions so developed were employed an apparent yield of 64% of cross-coupled product **2.138** was obtained. However, the product was contaminated with the triphenylphosphine ligand, which tended to co-elute during chromatographic separation. This problem was overcome by employing $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ as a catalyst. By this means a yield of 62% of cross-coupled product **2.138** was obtained at good levels of purity.

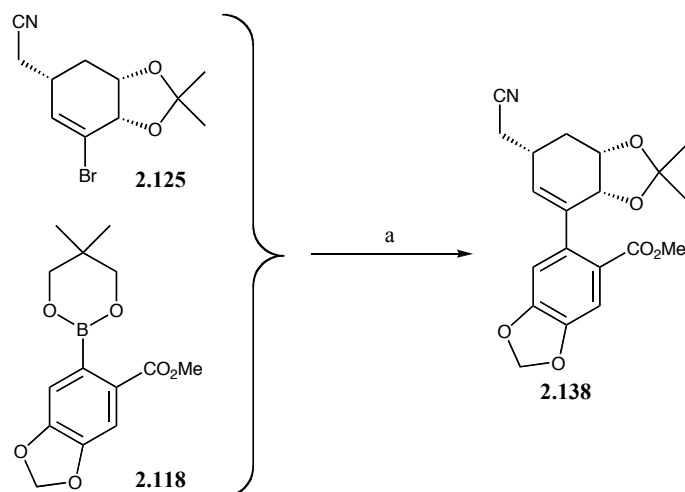
Through previous experience and from literature reports it was known that microwave irradiation is frequently superior to conventional heating for promoting the Suzuki-Miyaura cross-coupling reaction.⁹² This is most likely due to superheating effects that result from the direct coupling of microwave electromagnetic radiation with the molecules (solvents, reagents, catalysts) that are present in the reaction mixture.⁹³ Microwave irradiation raises the temperature of the bulk reaction mixture very rapidly and it has been shown that almost isothermal conditions are achieved during microwave heating.⁹⁴ By contrast, conventional heating, which relies upon conduction of heat from the reaction vessel walls, causes large temperature gradients within the bulk reaction mixture prior to the establishment of thermal equilibrium and is a comparatively slow and inefficient method of transferring energy.

One of the most important parameters for microwave-enhanced transformations is the choice of the solvent. The capacity of a solvent to convert microwave energy into heat is determined by the dielectric loss tangent ($\tan\delta$), which provides a useful guide for the choice of a suitable solvent system (Table 2.1). A solvent with a medium to high $\tan\delta$ value (> 0.1) is required for efficient microwave heating. On this basis DMSO is an excellent solvent for microwave-heated reactions. Moreover, a mixture of water and THF may be employed as a solvent. Transfer of energy from the water molecules, which readily interact with microwave irradiation, heats such a mixture.

Solvent	$\tan\delta$	Solvent	$\tan\delta$
Ethylene glycol	1.350	Water	0.123
Ethanol	0.941	Chlorobenzene	0.101
DMSO	0.825	Chloroform	0.091
2-Propanol	0.799	Acetonitrile	0.062
Formic acid	0.722	Ethyl Acetate	0.059
Methanol	0.659	Acetone	0.054
Nitrobenzene	0.589	THF	0.047
1-Butanol	0.571	Dichloromethane	0.042
2-Butanol	0.447	Toluene	0.040
1,2-dichlorobenzene	0.280	Hexane	0.020
DMF	0.161	Dioxane	~0
1,2-dichloroethane	0.127	Benzene	~0

Table 2.1 Dielectric Loss Tangents ($\tan\delta$) of Different Solvents.⁹⁵

The reaction conditions established as described above were reinvestigated under microwave irradiation, but DMSO proved to be an inappropriate solvent. When the solid bases KOAc and CsCO₃ were employed with this solvent they tended to gel as an amorphous mass at the bottom of the reaction vessel. This prevented the dispersal of the base throughout the reaction mixture and, as a consequence, yields were poor or erratic. Tests of the liquid organic bases triethylamine and *i*-PrNEt₂ in conjunction with DMSO afforded only modest yields. Fortunately, a 4:1 v/v mixture of THF and water proved to be an effective medium and a yield of 71% was obtained after 1 h of microwave irradiation at 80°C and employing CsCO₃ as a base. Replacing CsCO₃ with triethylamine and using a 9:1 v/v mixture of THF and water further improved the yield. Thus, subjection of the arylboronate **2.125** and the *cis*-1,2-dihydrocatechol derivative **2.118** under optimized cross-coupling conditions (Scheme 2.36) in a microwave reactor at 90 °C for 1.5 h provided the required cross-coupled product **2.138** in 75% yield.



Scheme 2.36 Reaction conditions: (a) $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$, Et_3N , $\text{THF}:\text{H}_2\text{O}$ 9:1 v/v, 90°C μ -wave 1.5 h, 75%.

The spectral data derived from compound **2.138** were entirely consistent with the proposed structure. For example, the ^{13}C NMR spectrum of compound **2.138** (Figure 2.5.5) displayed twenty signals including eleven in the region above δ 109. Eight of these arise from the sp^2 -hybridised carbons within the structure whilst the sp -hybridised carbon of the nitrile substituent, the quaternary carbon of the acetonide group and the carbonyl carbon each give rise to a signal in this region. The signal due to the methylenedioxy carbon was observed at δ 102.0 while the two oxymethine carbons gave rise to signals at δ 73.6 and δ 73.1. The methyl group carbon of the ester residue resonated at δ 52.8. The three remaining methylene and two methyl carbons were observed in the range δ 30.7 to δ 23.1.

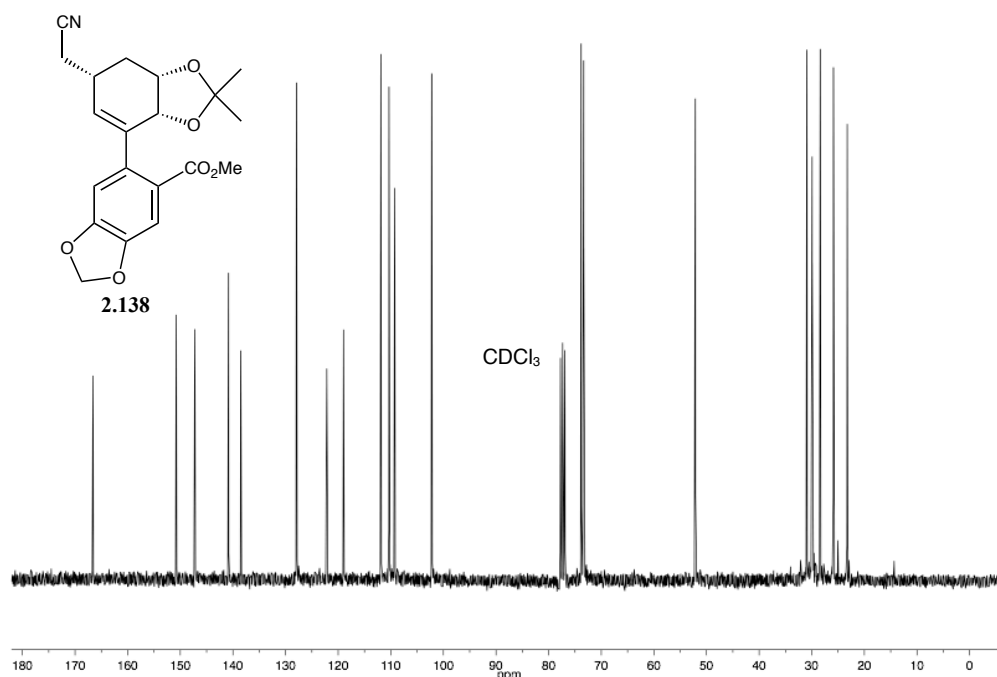


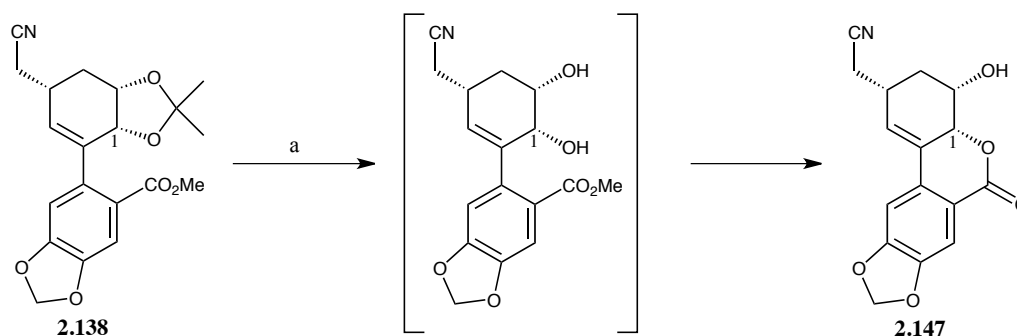
Figure 2.5.5 75 MHz ^{13}C NMR Spectrum of Compound **2.138** (Recorded in CDCl_3)

The ^1H NMR spectrum of this material displayed two three-proton singlets at δ 1.48 and δ 1.30 corresponding to the methyl group hydrogens of the acetonide moiety. Two broad, one-proton singlets at δ 1.95 and δ 2.14 were attributed to the methylene hydrogens of the cyclohexene ring. A broad singlet at δ 2.67, and integrating for three protons, corresponds to the pair of methylene hydrogens of the pendant acetonitrile residue and the single hydrogen at C-6. The protons of the methyl ester were observed as a singlet at δ 3.80. The distinct one-proton multiplet at δ 4.50 and one-proton doublet ($J = 6.0$ Hz) at δ 4.79 confirmed the presence of the two oxymethine hydrogens whilst the single olefinic proton resonated at δ 5.62. The geminal methylenedioxy protons appeared as a multiplet at δ 6.03 whilst the aromatic protons gave rise to two isolated one-proton signals at δ 6.71 and δ 7.40. The IR spectrum exhibited an absorption band at 2248 cm^{-1} that is characteristic of the $\text{-C}\equiv\text{N}$ stretching of a nitrile and a strong carbonyl absorption peak at 1717 cm^{-1} arose from the aryl ester. The EI mass spectrum of compound **2.138** displayed a molecular ion at m/z 371 whilst an accurate mass measurement confirms that this was of the expected composition, *viz.* $\text{C}_{20}\text{H}_{21}\text{NO}_6$.

2.5.4 Hydrolysis of the Acetonide Protecting Group and Accompanying Lactone Formation

In order to form the B- and D-rings of the lycorine framework (see Figure 2.1.1) it first was necessary to prepare a precursor that incorporated a lactone-ring in which the carboxylate leaving group was attached at C-1 (Scheme 2.37). It was anticipated that the lactone, **2.147**, would be obtained by acid-catalysed hydrolysis of the acetonide protecting group of the cross-coupled compound **2.138** to reveal an allylic alcohol at C-1 that would engage in spontaneous lactonisation with the pendant aryl ester moiety.

Numerous methods are available for the acid-catalysed hydrolysis of acetonides⁹⁶ and three of these were tested. Heating the acetonide-protected compound **2.138** at 90 °C for four days in a suspension of acidified Dowex-50WX8-100 ion-exchange resin in a 9:1 v/v mixture of methanol and water afforded the lactone **2.147** in 95% yield. In an effort to establish a more rapid process, experiments were conducted in which compound **2.138** was treated with aqueous HCl at various concentrations and temperatures but these proved to be unsatisfactory. Thus, only low yields of the desired product were obtained and significant degradation of the starting material occurred. Subsequently, it was found that treatment of compound **2.138** with a 4:1 v/v mixture of glacial acetic acid and water at 80 °C for 1 h afforded the lactone **2.147** in 89% yield (Scheme 2.37).



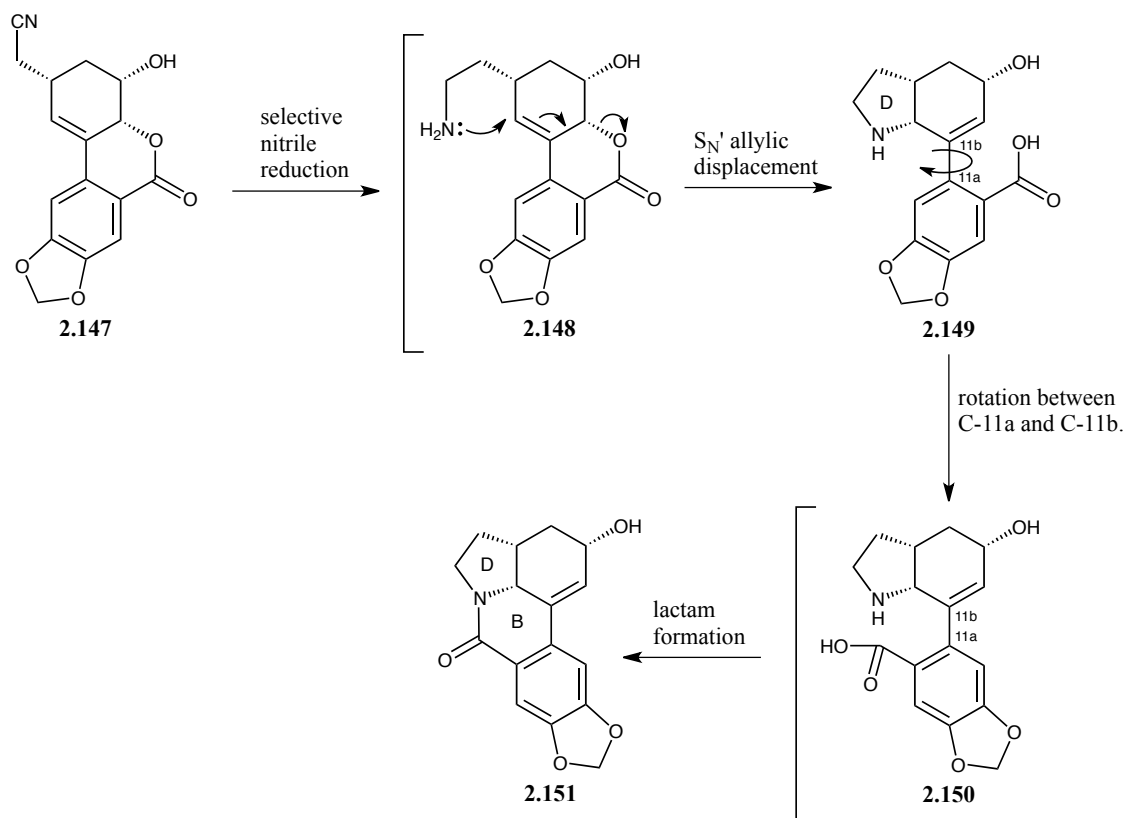
Scheme 2.37 Reaction conditions: (a) 4:1 v/v acetic acid/water, 80 °C, 1 h, 89%.

The spectral data obtained on the lactone **2.147** were completely consistent with the proposed structure. In particular, the signals corresponding to the acetonide protecting group of the cross-coupled compound **2.138** were absent from the ¹H and ¹³C NMR spectra of lactone **2.147**. A peak corresponding to the oxymethine proton attached to C-1 appeared in the ¹H NMR spectrum at δ 5.06 whereas the equivalent proton in the

precursor **2.138** gave rise to a resonance at δ 4.79. The ^{13}C NMR spectrum of compound **2.147** displayed sixteen signals including eleven above δ 102. An OH stretching band appeared in the IR spectrum of lactone **2.147** at 3448 cm^{-1} whereas no such band was observed in the IR spectrum of the precursor **2.138**. The characteristic nitrile stretching band appeared at 2245 cm^{-1} in the same spectrum. The EI mass spectrum of compound **2.147** displayed a molecular ion at m/z 299 whilst an accurate mass measurement confirmed that this was of the expected composition, *viz.* $\text{C}_{16}\text{H}_{13}\text{NO}_5$.

2.5.5 Annulation of the D- and B-rings

With the lactone precursor **2.147** in hand it was now possible to investigate the formation of the D- and B-rings of the lycorine framework *via* the proposed intramolecular S_{N}' allylic displacement and (subsequent) lactamisation reaction sequence (Scheme 2.38). This unusual and demanding step was to be initiated by the selective reduction of the nitrile group within substrate **2.147** to afford the corresponding primary amine as a component of the intermediate **2.148**. Once formed this was expected to act as an internal nucleophile and engage in an intramolecular S_{N}' allylic displacement of the pendant lactone residue and so furnishing compound **2.149** incorporating the D-ring. Rotation about the C-11a – C-11b bond within this aromatic acid would bring the carboxylic residue of the aryl system and the nitrogen of the D-ring into close proximity and thereby allow for a spontaneous lactamisation reaction to generate compound **2.151** and so deliver the B-ring and, indeed, the complete framework of the natural product.



Scheme 2.38 Proposed Formation of the D- and B-rings of the Lycorine Framework via Intramolecular S_N' Allylic Displacement and Subsequent (Spontaneous) Lactamisation Reactions.

2.5.6 The Intramolecular S_N' Allylic Displacement Reaction

As discussed below, practical methods for the selective catalytic hydrogenation of nitriles to primary amines are well established, but the critical ring-forming intramolecular S_N' allylic displacement reaction merits further comment. Paquette and Stirling have provided a useful review of intramolecular allylic displacement reactions,⁹⁷ whilst an earlier review by Magid details examples of the equivalent intermolecular processes.⁹⁸ In the intramolecular allylic displacement reaction the nucleophile is tethered to the allylic system (Figure 2.5.6). For the purposes of this discussion only nucleophiles tethered to C_γ and attacking at C_γ will be considered because, (i), this structural arrangement is observed in the intermediate compound **2.148** and, (ii), other arrangements are much less common.

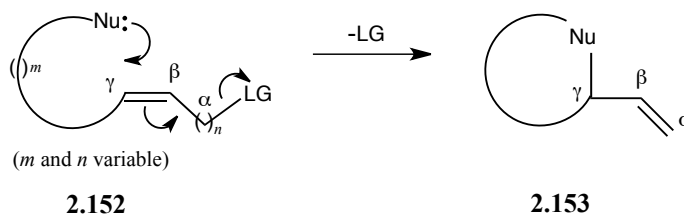


Figure 2.5.6 The General Form of the Intramolecular S_N' reaction.

There are two possible ways that attack by the nucleophile at C_γ can form a new bond. The process may be similar to an S_N2 reaction with attachment of the nucleophile at C_γ and simultaneous departure of the leaving group. Alternatively, it may be similar to an S_N1 reaction with dissociation of the leaving group and subsequent (rapid) attachment of the nucleophile. Unfortunately, no systematic research has been undertaken into the mechanistic aspects of intramolecular ring-forming allylic displacement reactions and it is not yet clear how these proceed. Accordingly, such reactions are simply designated as S_N' ('nucleophilic substitution with rearrangement'). The majority of intramolecular S_N' reactions are, to use Baldwin's terminology,⁹⁹ *exo-trig* processes with the formation of 5-membered rings being especially favourable. It will be seen in Scheme 2.38 that the proposed intramolecular ring-forming S_N' reaction is of this kind.

In a compound with the general structure **2.152** (Figure 2.5.6) the intramolecular S_N' reaction produces a new stereocentre at C_γ whilst the double bond migrates to the C_α – C_β position. In principle, there are two possible alignments of the approaching nucleophile and the leaving group, namely *syn* or *anti*. In reality the *syn* process (Figure 2.5.7) is the only functional one regardless of whether an inter- or intra-molecular variant is involved.

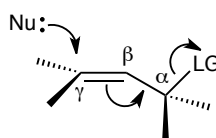


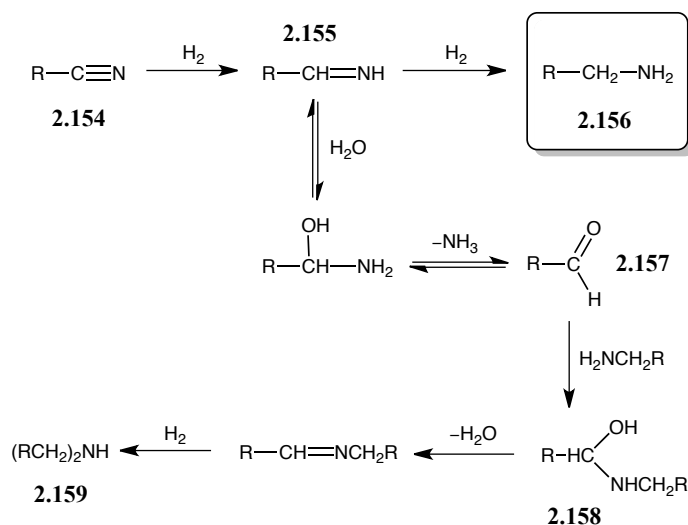
Figure 2.5.7 The Favourable *syn*-Alignment of the Nucleophile and the Leaving Group

2.5.7 The Selective Catalytic Hydrogenation of Nitriles

The hydrogenation of nitriles over metal catalysts is of great importance for the preparation of amines due to its broad industrial and pharmacological applications.¹⁰⁰

The selective hydrogenation of nitriles is generally carried out with Raney-Ni or Raney-Co sponge-metal catalysts and using ammoniacal methanol as a solvent at temperatures up to 100 °C and pressures in the range of 200 – 5,000 kPa. Other suitable catalysts include Pt, Pd and Rh. By carefully adjusting the reaction conditions it is usually possible to selectively hydrogenate nitriles without affecting other potentially reducible groups.¹⁰¹

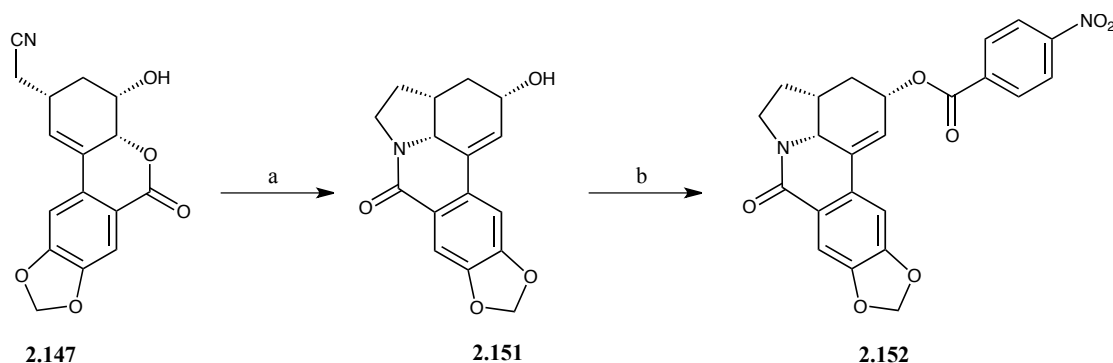
The catalytic hydrogenation of nitriles is depicted in a simplified form in Scheme 2.39.¹⁰² The addition of two hydrogen molecules to the carbon-nitrogen triple bond proceeds in a stepwise fashion to yield the amine **2.156**. An intermediate in this sequence is the highly reactive imine **2.155** and the addition of water to this may lead to formation of an aldehyde **2.157** (with the accompanying loss of ammonia). The aldehyde **2.157** may itself react with a primary amine leading to formation of a secondary amine by-product, *viz.* compound **2.158**. This secondary amine may react further to form a tertiary amine **2.159**. The suppression of secondary- and tertiary-amine forming processes is achieved by saturating the methanolic solvent with ammonia (an application of Le Châtelier's principle).



Scheme 2.39 *Competing Reaction Pathways Associated With the Catalytic Hydrogenation of Nitriles.*

Experiments directed towards establishing the optimum conditions for the pivotal (selective) nitrile reduction and attendant formation of the D- and B-rings (as depicted in Scheme 2.38) revealed that Raney-Co was an effective catalyst for this process. Thus, under optimized conditions the lactam **2.151** was obtained in 68% yield from a Raney-Co catalysed reaction (Scheme 2.40). In contrast, the use of Raney-Ni

catalyst resulted in complex mixtures of products with only low yields of the lactam **2.151** being obtained. It was also apparent that in order to obtain good yields of the lactam it was necessary to saturate the methanolic solvent with ammonia. Thus, when an experiment was carried out in which no ammonia was added a complex mixture of products was obtained and the lactam could not be isolated. Moreover, the use of methanol that was not fully saturated with ammonia resulted in lower yields of the target compound.



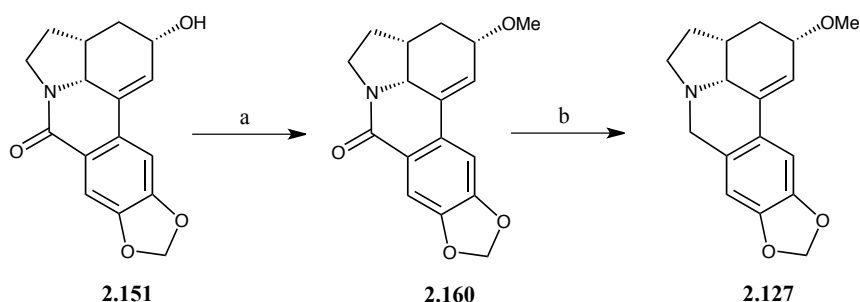
Scheme 2.40 Reaction conditions: (a) Raney-Co, MeOH/NH₃, H₂, 3000 kPa, 2.5 h, 68%; (b) *p*-nitrobenzoyl chloride, DMAP, CH₂Cl₂, reflux, 4.5 h, 46%.

The various spectra recorded on the lactam **2.151** were in full accord with the proposed structure. In particular, the IR spectrum lacked an absorption band around 2250 cm⁻¹, as would be expected for a process leading to loss of the nitrile substituent. Furthermore, the carbonyl band appearing at 1634 cm⁻¹ is consistent with the presence of a δ -lactam and stands in contrast to the carbonyl stretching band seen at 1711 cm⁻¹ in the IR spectrum of the precursor **2.147**. The ¹³C NMR spectrum of compound **2.151** exhibited the expected sixteen signals including eight above δ 106. In the ¹H NMR spectrum the signal corresponding to the olefinic proton appeared at δ 5.96 (the equivalent proton appeared at δ 6.38 in the precursor). This up-field shift is consistent with the change in position of the double bond in which the olefinic proton is now in closer proximity to the remaining hydroxyl moiety. The EI mass spectrum of compound **2.151** displayed a molecular ion at m/z 285 whilst an accurate mass measurement confirmed that this was of the expected composition, viz. C₁₆H₁₅NO₄. The structure of compound **2.151** was confirmed through the single-crystal X-ray analysis of the corresponding *p*-nitrobenzoate derivative **2.152**, which was readily prepared by reaction

of lactam **2.151** with *p*-nitrobenzoyl chloride in the presence of DMAP (Scheme 2.40). The resulting ORTEP is shown in Appendix Two.

2.5.8 Final Steps: Preparation of the of the Lycorine Degradation Product

The final steps in the synthetic sequence leading to the lycorine degradation product **2.127**⁶⁴ involved *O*-methylation of the lactam **2.151** followed by reductive elimination of the carbonyl moiety. To such ends, compound **2.151** was treated with trimethyloxonium tetrafluoroborate in the presence of Proton-sponge™ to afford the corresponding *O*-methyl ether **2.160** in 95% yield (Scheme 2.41). The success of this transformation was readily confirmed by the presence of a three-proton singlet in the ¹H NMR spectrum of the product at δ 3.44 (and obviously arising from the newly formed methyl ether moiety). The ¹³C NMR spectrum of this material exhibited, as expected, seventeen signals including one at δ 56.3 due to the same group. The EI mass spectrum of compound **2.160** displayed a molecular ion at *m/z* 299 and an accurate mass measurement established that this was of the expected composition, viz. C₁₇H₁₇NO₄.



Scheme 2.41 Reaction conditions: (a) Me₃OBf₄, Proton-sponge™, 95%; (b) LiAlH₄, THF, reflux 89%.

The lactam carbonyl of compound **2.160** was removed by its treatment with LiAlH₄ in refluxing THF (Scheme 2.42) and this afforded the target 3°-amine **2.127** (89% yield). This crystalline solid was subjected to single-crystal X-ray analysis and the resulting ORTEP is shown in Figure 2.5.7.

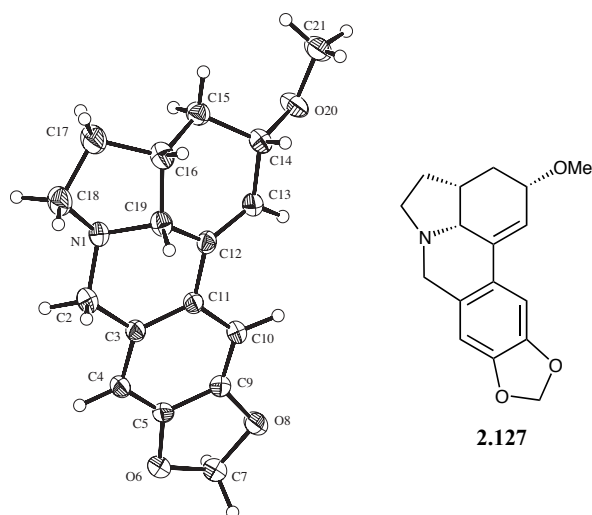


Figure 2.5.7 ORTEP Derived From Single-Crystal X-ray Analysis of Compound **2.127** With Labeling of Selected Atoms. (Thermal Ellipsoids are Drawn at the 50% Probability Level.)

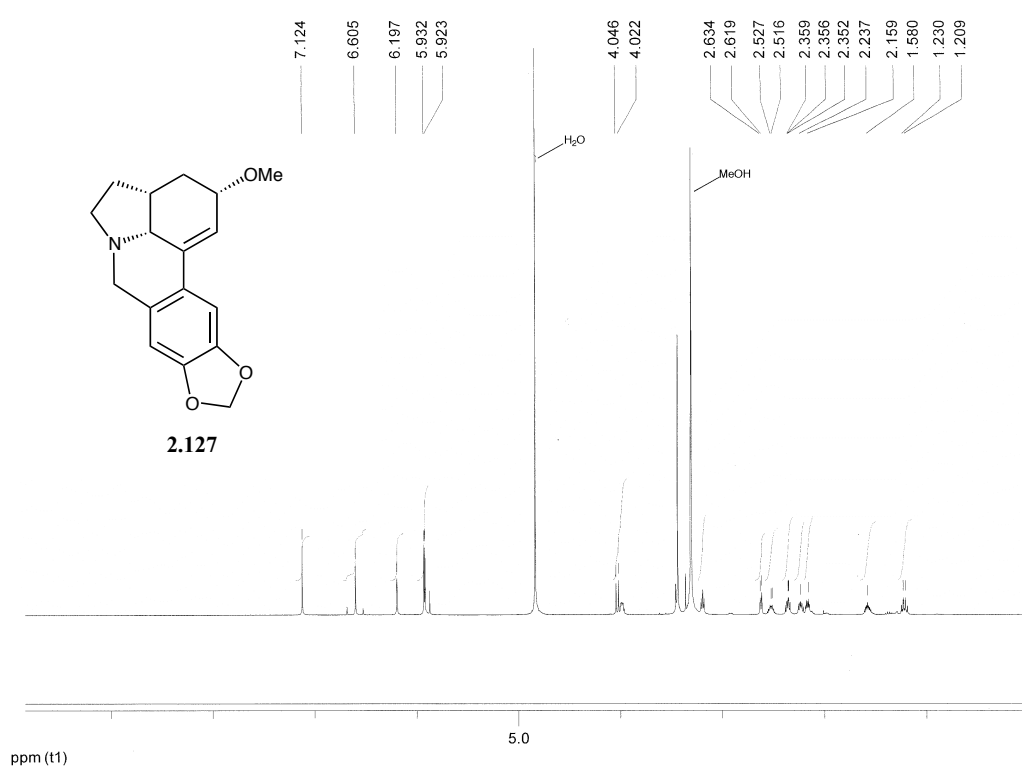


Figure 2.5.8 600 MHz ^1H NMR Spectrum of Compound **2.127** (Recorded in CD_3OD)

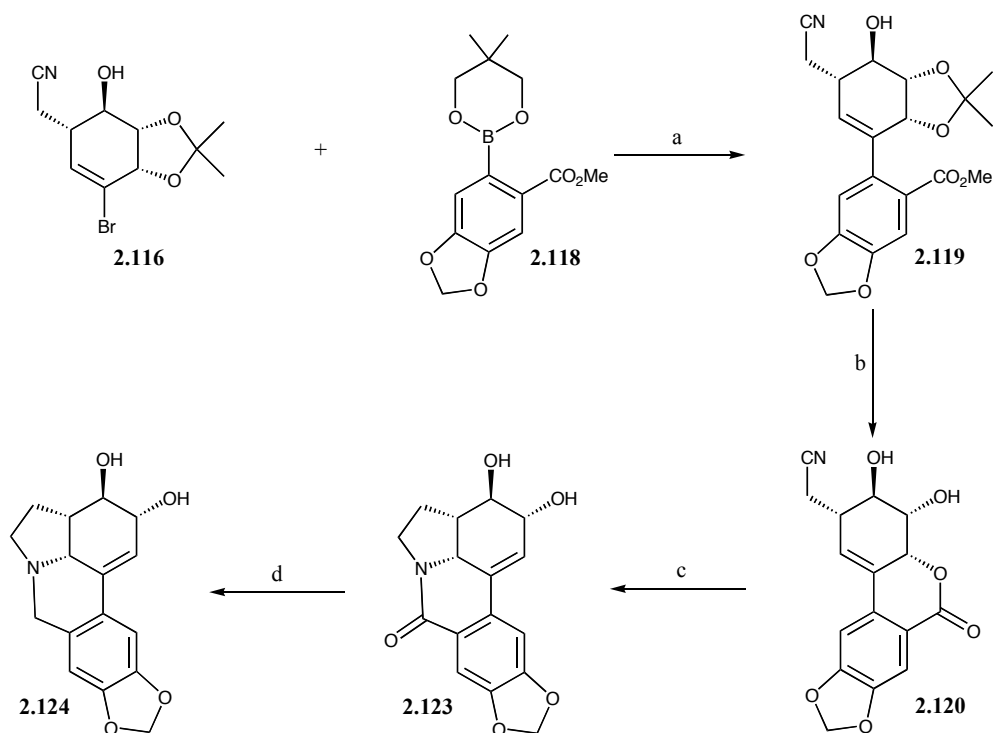
The 600 MHz ^1H NMR spectrum of compound **2.127** displayed all the expected features (Figure 2.5.8) whilst the 150 MHz ^{13}C NMR spectrum showed the anticipated

seventeen resonances. The melting point (mp 154–157 °C), specific rotation $\{[\alpha]_{\text{D}} -64$ (c 0.9, EtOH) $\}$ and UV spectrum of compound **2.127** were in good agreement with those recorded by Takeda and Kotera $\{\text{mp } 155\text{--}156$ °C, $[\alpha]_{\text{D}} -80$ (c 1.0, EtOH) $\}$ for the compound they obtained by manipulating lycorine and to which they assigned the structure **2.127**. The EI mass spectrum of the author's sample of compound **2.127** displayed a molecular ion at m/z 285 whilst an accurate mass measurement confirmed that this was of the expected composition, *viz.* C₁₇H₁₉NO₃.

2.6 Synthesis of an Isomer of Lycorine

The strategy employed for the synthesis of the lycorine degradation product **2.127** was adapted so as to allow for the synthesis of an unnatural isomer **2.124** of lycorine (a compound of interest in connection with developing a structure/activity relationship (SAR) profile of this class of compounds). The synthesis of this isomer required that the hydroxyl group at C-3 of the γ -hydroxynitrile **2.116** remain in place, in contrast to the synthetic process detailed above where it was removed as part of the reaction sequence leading to the compound **2.127**.

The synthesis of the target analogue, **2.124**, of lycorine (Scheme 2.42) began with a Suzuki-Miyaura cross-coupling reaction between the γ -hydroxynitrile **2.116** and the arylboronate **2.118**. This was conducted under conventional heating conditions in a medium comprised of 10:1 v/v THF/H₂O and using a mixture of 3 molar equivalents of CsCO₃ and 1.5 molar equivalents of KOAc. By such means the expected arylcyclohexene **2.119** was obtained in 79% yield. Experiments involving microwave promoted Suzuki-Miyaura cross-coupling of compounds **2.116** and **2.118** (under otherwise identical conditions) afforded lower yields (62 – 69%) of compound **2.119** and no significant advantage was gained by the use of microwave irradiation in this case. Treatment of the arylcyclohexene **2.119** with a 4:1 v/v mixture of glacial acetic acid and water at 80 °C for 1 h afforded the lactone **2.120** in yields ranging from 65 to 82% (the origins of this variability were not determined). Subjection of the lactone **2.120** to dihydrogen in the presence of Raney-Co afforded the lactam **2.123** in 51% yield. The final step involved the reduction of the carbonyl moiety of the lactam **2.123** with LiAlH₄ in refluxing THF to give the unnatural isomer **2.124** of lycorine in 78% yield.



Scheme 2.42 Reaction conditions: (a) $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$, KOAc, THF:H₂O 10:1, 66 °C, 3.0 h, 79%; (b) 80% acetic acid, 65 - 82%; (c) Raney-Co, MeOH/NH₃, H₂, 3500 kPa, 65 °C, 2.5 h, 51%; (d) LiAlH₄, THF, reflux 78%.

The 75 MHz ^{13}C NMR spectrum of compound **2.124** (Figure 2.6.1) displayed sixteen signals, as would be expected from the proposed structure. The most significant features of this spectrum were the eight signals in the region above δ 104 which are attributed to the sp^2 -hybridised carbons of the product and the signals appearing at δ 74.1 and 77.5 due to the mono-oxygenated sp^3 -hybridised carbons C-2 and C-3. As expected, the IR spectrum exhibited a strong absorption band at 3344 cm^{-1} arising from the hydroxyl moieties. The EI mass spectrum of compound **2.124** displayed a molecular ion at m/z 287 whilst an accurate mass measurement on this species confirmed that it was of the expected composition, *viz.* $\text{C}_{16}\text{H}_{17}\text{NO}_4$.

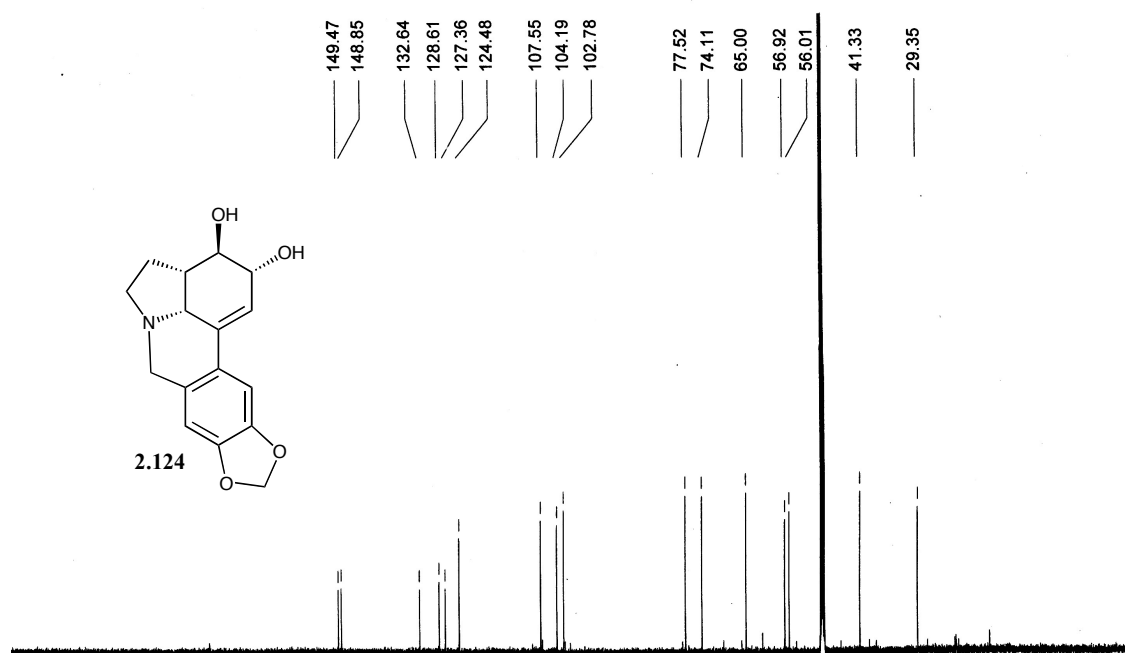
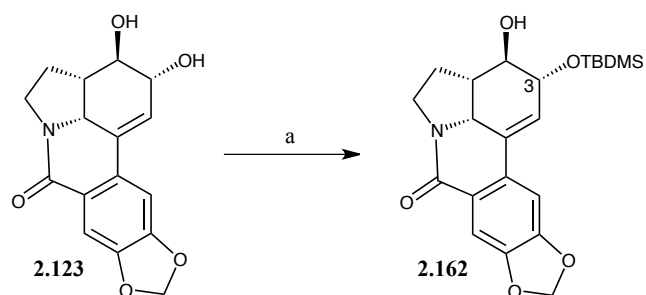


Figure 2.6.1 600 MHz ^{13}C NMR Spectrum of Compound **2.124** (Recorded in CD_3OD)

The successful extension of the method developed for the annulation of the D- and B-rings of the lycorine framework demonstrates the potential of this technique for generating a variety of polyfunctionalised lycorine frameworks. Moreover, the two *trans*-configured hydroxyl substituents associated with the lycorine isomer **2.124** are in different chemical environments and this raised the possibility of being able to selectively manipulate one or other of them. To test this possibility, a sample of the lactam **2.123** was treated with one molar equivalent of *tert*-butyldimethylsilyl triflate (TBDMSOTf) in the presence of triethylamine (Scheme 2.43) and this gave, in 48% yield, the monosilyl ether **2.162** as a crystalline solid. A single-crystal X-ray analysis of this material confirmed that the C-3 hydroxyl within compound **2.123** had been selectively derivatised (Figure 2.6.2). As a consequence of this result there is now the potential for creating a library of analogues of lycorine. Such a collection would assist in the establishment of the structure/activity relationship (SAR) profile within the lycorine class of alkaloids.



Scheme 2.43 Reaction conditions: (a) TBDMSOTf, Et₃N, -78 °C, 1 h, 48%.

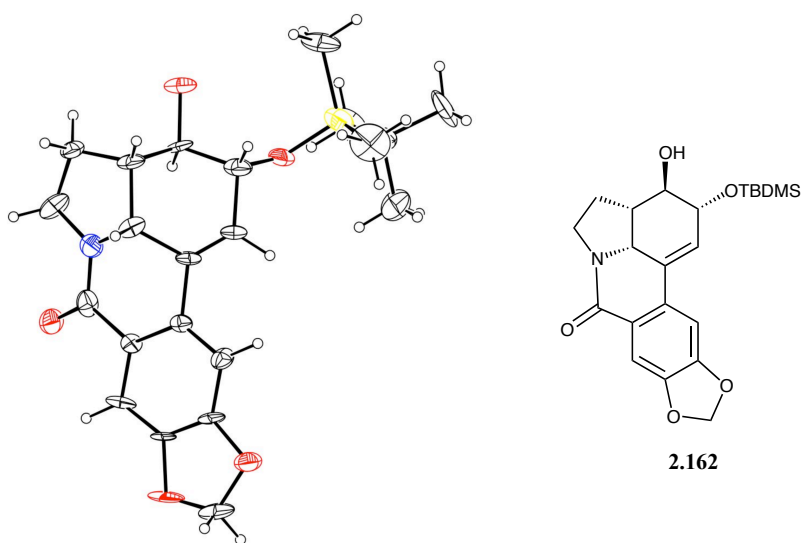
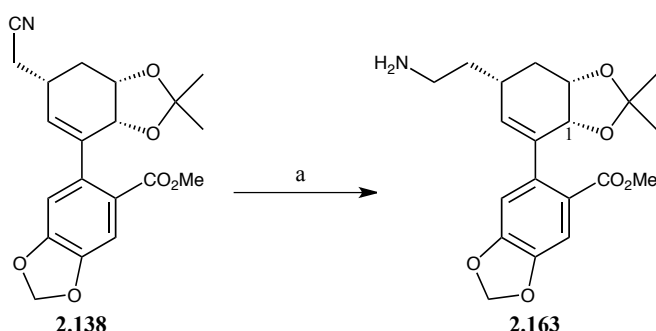


Figure 2.6.2 ORTEP Derived from Single-Crystal X-ray Analysis of Compound **2.162**. (Thermal Ellipsoids are Drawn at the 50% Probability Level)

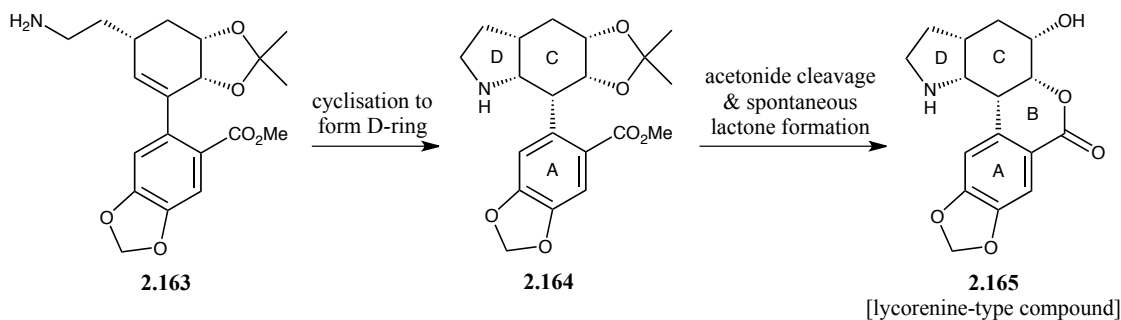
2.7 Synthesis of the Enantiomer of the Structure Assigned to the Lycorenine Alkaloid Nobilisitine A

A key intermediate in the synthesis of the lycorine degradation product **2.127** is the arylated-cyclohexene **2.138**. Investigations into the chemical properties of this compound revealed that it could be reduced, by catalytic hydrogenation over Raney-Co, to the corresponding primary amine **2.163** in a completely chemoselective manner and in quantitative yield (Scheme 2.44).



Scheme 2.44 Reaction conditions: (a) Raney-Co (5 mol%), MeOH/NH₃, H₂, 6000 kPa, 45 °C, 2 h, 100%

The primary amine **2.163** is stable and it does not undergo an intramolecular S_N' allylic displacement reaction because the acetonide protected oxygen in the allylic (C-1) position is not a particularly effective leaving group. The availability of this compound raised the intriguing possibility of using it as the starting material for the synthesis of lycorenine-type alkaloids in which the B-ring is comprised of a lactone structure (Scheme 2.45). In principle, such a structure could be obtained by closure of the D-ring *via* a radical cyclisation procedure to give compound **2.164**. This compound could then be subjected to acid-catalysed cleavage of the acetonide protecting group to reveal hydroxyl groups at C-1 and C-2. The C-1 hydroxyl group should spontaneously react with the adjacent methyl ester to form a lactone and, thereby, the B-ring of compound **2.165** (Scheme 2.45) which embodies the framework of the lycorenine-type alkaloids.



Scheme 2.45 Proposed Synthesis of a Lycorenine-type Compound.

A representative member of the lycorenine-type class of alkaloids is (–)-clividine **2.166** which was originally isolated in 1971 from the South African lilly *Clivia miniata*.¹⁰³ In 1999 Evidente and colleagues reported the isolation of the stereoisomeric natural product nobilisitine A from the related Egyptian ornamental plant *Clivia nobilis*.¹⁰⁴ On the basis of the recorded NMR, infrared and mass spectral data they concluded that the compound possessed structure **2.167**, which represents a diastereomer of (–)-clividine [**2.166**] and embodies an “all-*cis*” arrangement of the non-hydrogen substituents about the cyclohexene C-ring. As highlighted in Figure 2.7.1, the stereo-configuration of the structure assigned to nobilisitine A [**2.167**] is enantiomeric with compound **2.165** save for the fact that the latter compound lacks an *N*-methyl group.

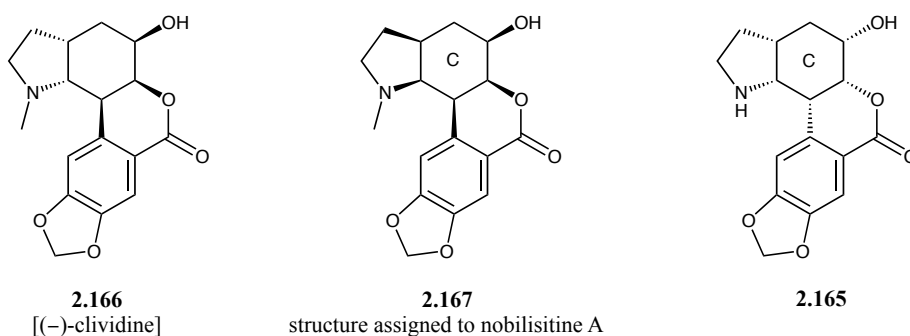


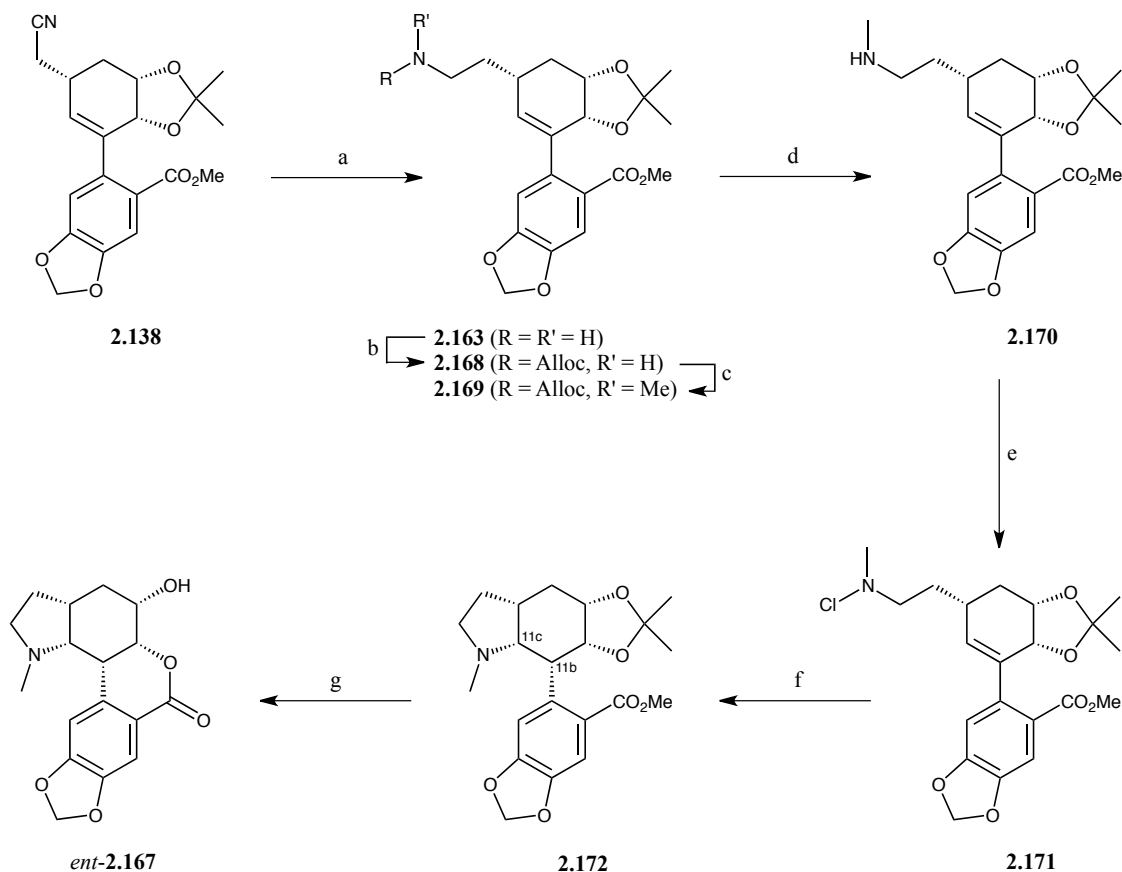
Figure 2.7.1 The Lycorenine-Type Alkaloid (–)-Clividine [**2.166**] and the Enantiomeric Relationship Between the Structure Assigned to Nobilisitine A [**2.167**] and the Structure of Compound **2.165**.

On this basis, and in keeping with our interest in developing new methods for the synthesis of biogenetically and structurally related *Amaryllidaceae* alkaloids and for the

purpose of checking Evidente's structural assignment a total synthesis of the compound *ent*-**2.167** was undertaken.¹⁰⁵ This work, which is detailed below, was conducted in collaboration with Dr. B. Schwartz, a Postdoctoral Research Fellow at the Research School of Chemistry, Australian National University.

The pivotal step in the proposed synthesis of compound *ent*-**2.167** was the formation of the D-ring complete with its associated *N*-methyl substituent (Scheme 2.46). It was envisaged that this would be achieved by means of a nitrogen-centered radical cyclisation process.¹⁰⁶ The substrate required for this purpose was prepared as shown in Scheme 2.46. Thus, reaction of the primary amine **2.163** with allyl chloroformate in the presence of pyridine gave the carbamate **2.168** in 88% yield. *N*-methylation of the latter compound was achieved by successive treatment of it with lithium hexamethyldisilazide (LiHMDS) and methyl iodide to afford compound **2.169** in 98% yield. The Alloc group associated with compound **2.169** was removed by treating it with Pd(PPh₃)₄ in the presence of excess dimedone¹⁰⁷ and the resulting secondary amine **2.170** (99%) was then subjected to chlorination, at nitrogen, using *N*-chloro-succinimide (NCS) to afford the *N*-chloramine **2.171** in 88% yield. The *N*-chloramine **2.171** was itself treated with *n*-Bu₃-SnH (1.1 mol equiv) and the radical initiator AIBN (5 mol%) in refluxing benzene. This resulted in the co-production of the chromatographically separable reductive cyclisation product **2.172** (23% or 77% based on recovered **2.170**) and the direct reduction product **2.170** (71% recovery).

The stereochemistries of the two new stereogenic centers, C-11_b and C-11_c associated with product **2.172** were initially predicted by comparison with analogous cyclisation processes involving carbon-centered radicals.¹⁰⁸ Thus, the formation of a *cis*-ring-fused system would be expected. Furthermore, the benzylic radical created by such a process would be expected to react with *n*-Bu₃-SnH at the less congested β -face, thereby establishing the illustrated α -orientation of the aryl group at C-11_b in compound **2.172**. Conversion of acetone **2.172** into the target *ent*-**2.167** was achieved in 93% yield by treatment of the former compound with acidified Dowex-50WX8-100 ion-exchange resin in water/methanol.



Scheme 2.46 Reaction conditions: (a) Raney-Co, MeOH/NH₃, H₂, 6000 kPa, 45 °C, 2 h, 100%; (b) Alloc-Cl, pyridine, 0 °C, 0.25 h, 88%; (c) LiHMDS, THF –78 °C, 0.33 h, then MeI, –78 °C, 0.5 h, 98%; (d) THF, dimedone, Pd(PPh₃)₄, 18 °C, 0.33 h, 99%; (e) CH₂Cl₂, NCS, –30 °C, 0.5 h, 88%; (f) *n*-Bu₃-SnH (1.1 mol equiv), benzene, AIBN, reflux, 1 h, 23% of compound **2.172** plus 71% of compound **2.170**; (g) Dowex-50WX8-100 ion-exchange resin, 1:1 v/v water/methanol, reflux, 12 h, 93%.

All of the spectral data obtained on compound *ent*-**2.167** were in complete accord with the assigned structure and the relative stereochemistry was confirmed by single-crystal X-ray analysis. The ORTEP arising from this analysis is shown in Figure 2.7.2.

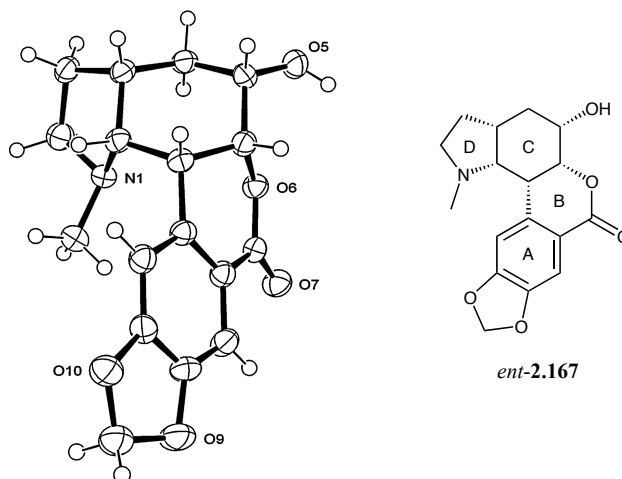


Figure 2.7.2: ORTEP Derived from the Single-crystal X-ray Analysis of the Compound *ent*-**2.167** (Thermal Ellipsoids are Drawn at the 50% Probability Level.)

A comparison of the ^1H and ^{13}C NMR spectral data obtained on the synthetically-derived compound *ent*-**2.167** and the data reported for nobilisitine A is presented in Table 2.2. It is apparent from this that the two compounds are different and, therefore, that the structure assigned to nobilisitine A is incorrect. The most significant difference is seen in the chemical shifts of the resonances reported for the *N*-methyl protons (δ_{H} 1.45 for *ent*-**2.167** vs. δ_{H} 2.24 for nobilisitine A). The high-field shift of the former signal can be attributed to the shielding effect of the arene *B*-ring on the adjacent *cis*-related *N*-methyl group of *ent*-**2.167**. On the basis of this analysis it was concluded that if the lycorenine-type framework assigned to nobilisitine A is correct, then a *trans*-relationship should exist between the equivalent moieties of nobilisitine A. Thus, the structure of nobilisitine A should comprise a *cis* B/C *anti*, *cis* C/D arrangement.

Table 2.2: Comparison of the ^{13}C and ^1H NMR Data Obtained on **ent-2.167** with the Analogous Data Reported for the Natural Product Nobilisitine A.

^{13}C NMR (δ_{C})		^1H NMR (δ_{H})	
ent-2.167 ^a	nobilisitine A ^b	ent-2.167 ^c	nobilisitine A ^d
164.7	164.0	7.54, s, 1H	7.53, s, 1H
151.9	152.6	6.70, s, 1H	7.05, s, 1H
147.6	147.2	6.05, m, 2H	6.05, broad s, 2H
137.8	137.3	4.61, t, $J = 2.5$ Hz, 1H	4.65, dd, $J = 6.6$ & 5.0 Hz, 1H
121.0	118.6	3.74, ddd, $J = 11.7, 3.7$ & 2.9 Hz, 1H	3.96, ddd, $J = 9.9, 6.6$ & 5.0 Hz, 1H
109.8	109.7	3.31, td, $J = 10.6$ & 6.8 Hz, 1H	3.34, dd, $J = 5.0$ & 5.0 Hz, 1H
106.6	106.5	2.87, dd, $J = 4.6$ & 3.0 Hz, 1H	3.24, ddd, $J = 13.6, 6.6$ & 5.0 Hz, 1H
101.9	102.0	2.60, t, $J = 4.9$ Hz, 1H	2.67, dd, $J = 5.8$ & 5.0 Hz, 1H
78.0	81.4	2.37-2.33, complex m, 1H	2.30, m, 1H
69.7	68.6	2.26-2.22, complex m, 1H	2.27, m, 1H
67.7	66.6	1.95-1.90, complex m, 1H	2.24, s, 3H (<i>N</i> -methyl protons)
55.0	54.9	1.88, q, $J = 12.4$ Hz, 1H	2.02, m, 1H
45.2	41.8	1.78, dt, $J = 10.3$ & 4.9 Hz, 1H	2.00, m, 1H
41.0	36.6	1.47-1.44, complex m, 1H	1.62, m, 2H
39.4	34.7	1.45, s, 3H (<i>N</i> -methyl protons)	—
30.9	33.7	OH proton signal not observed	OH proton signal not observed
29.8	30.1		

^a Data obtained from ref 105 and recorded in CDCl_3 at 200 MHz; ^b data obtained from ref. 104 recorded in CDCl_3 at unspecified field strength; ^c data obtained from ref 105 and recorded in CDCl_3 at 800 MHz; ^d data obtained from ref. 104 recorded in CDCl_3 at unspecified field strength

2.8 The True Structure of the Alkaloid Nobilisitine A

Following the revelation of the erroneous assignment of the structure of nobilisitine A by Evidente, and prompted by the prediction that a *trans*-relationship should exist between the arene B-ring and the adjacent *N*-methyl group, Lodewyk and Tantillo conducted a series of DFT calculations to predict the ^{13}C and ^1H NMR chemical shifts of the various diastereomeric forms of compound **2.167**.¹⁰⁹ Such an analysis led them to propose that the true structure of nobilisitine A is represented either by structure **2.173** or its enantiomer, *viz.* *ent*-**2.173** (Figure 2.8.1).

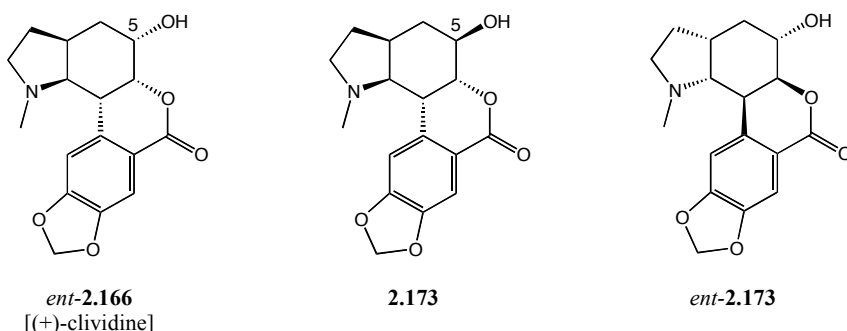


Figure 2.8.1: (+)-Clividine [*ent*-**2.166**] and the Structure of Nobilisitine A [**2.173**] Proposed by Lodewyk and Tantillo on the Basis of DFT Calculations.¹⁰⁹

At the time that Lodewyk and Tantillo were conducting their studies, members of the Banwell Research Group (namely Mr. L. White and Dr B. Schwartz) had completed a synthesis of the alkaloid (+)-clividine [*ent*-**2.166**].¹¹⁰ This compound is the enantiomer of the natural product (–)-clividine **2.166**. The synthesis of compound *ent*-**2.166** was achieved using chemistry that was originally developed for the preparation of compound *ent*-**2.167** (Section 2.7). It is apparent that (+)-clividine [*ent*-**2.166**] is the C-5-epimer of the structure, **2.173**, predicted by Lodewyk and Tantillo¹⁰⁹ for nobilisitine A (Figure 2.8.1). Accordingly, in an effort to determine if the new structure proposed for nobilisitine A was correct, Dr. B. Schwartz (Banwell research group) undertook the transformation of a sample of *ent*-**2.166** into compound **2.173**¹¹¹ by epimerizing the C-5 hydroxyl using a protocol developed by Zard and co-workers.¹¹² The spectral data derived from the compound so obtained were in complete accord with the proposed structure and confirmation of this followed from a single-crystal X-ray analysis. Comparisons of the ^{13}C and ^1H NMR spectral data obtained from the synthetically-derived compound **2.173** with those originally reported for nobilisitine A **2.167** are

presented in Table 2.3. These results clearly show that the compound **2.173** or (more likely) its enantiomer, *ent*-**2.173**, corresponds to the true structure of the lycorine alkaloid nobilisitine A.

Table 2.3: Comparison of the ^{13}C and ^1H NMR Data Obtained on Compound **2.173** With the Analogous Data Reported for the Natural Product Nobilisitine A.

^{13}C NMR (δ_{C})		^1H NMR (δ_{H})	
2.173 ^a	nobilisitine A ^b	2.173 ^c	nobilisitine A ^d
164.0	164.0	7.52, s, 1H	7.53, s, 1H
152.5	152.6	6.94, broad s, 1H ^e	7.05, s, 1H
147.2	147.2	6.05, broad s, 2H	6.05, broad s, 2H
137.3	137.3	4.65, dd, $J = 8.0$ and 4.0 Hz, 1H	4.65, dd, $J = 6.6$ & 5.0 Hz, 1H
118.6	118.6	3.97, m, 1H	3.96, ddd, $J = 9.9$, 6.6 & 5.0 Hz, 1H
109.7	109.7	3.37, broad s, 1H ^e	3.34, dd, $J = 5.0$ & 5.0 Hz, 1H
106.6	106.5	3.27, broad s, 1H ^e	3.24, ddd, $J = 13.6$, 6.6 & 5.0 Hz, 1H
102.0	102.0	2.69, t, $J = 4.0$ Hz, 1H	2.67, dd, $J = 5.8$ & 5.0 Hz, 1H
81.3	81.4	2.32, m, 1H	2.30, m, 1H
68.6	68.6	2.30, m, 1H	2.27, m, 1H
66.7	66.6	2.25, s, 3H	2.24, s, 3H
54.9	54.9	2.02, m, 1H	2.02, m, 1H
41.8	41.8	1.97, m, 1H	2.00, m, 1H
36.5	36.6	1.62, m, 2H	1.62, m, 2H
34.8	34.7	OH proton signal not observed	OH proton signal not observed
33.6	33.7		
30.2	30.1		

^aData obtained from ref 111 and recorded in CDCl_3 at 100 MHz; ^b data obtained from ref. 104 and recorded in CDCl_3 at unspecified field strength; ^c data obtained from ref 111 and recorded in CDCl_3 at 400 MHz; ^d data obtained from ref. 104 and recorded in CDCl_3 at unspecified field strength. ^e The ‘shape’ of this resonance varied somewhat from run-to-run.

2.9 Conclusions

The most significant outcome of the studies described in this Chapter is the acquisition of the lycorine alkaloid framework *via* the synthetic strategy defined above (Chapter 2, Sections 2.4 and 2.5). The synthesis of the lycorine degradation product **2.127** and the unnatural isomer of lycorine **2.124** demonstrate the utility of the developed methodology and it is anticipated that a variety of related lycorine-type compounds will be synthesized in analogous ways so as to provide a library compounds for biological testing. Additionally, by altering the order of various synthetic steps, a complimentary strategy has been developed for the synthesis of structurally related lycorenine-type compounds such as the compound *ent*-**2.167**. On the basis of these synthetic studies it became apparent that the structure **2.167** had been incorrectly assigned to the naturally occurring lycorenine alkaloid nobilisitine A. Thanks to a fruitful exchange of information with Lodewyk and Tantillo, members of the Banwell research group have now established the true structure of this alkaloid.

The research described in this Chapter also highlights the versatility of biosynthetically derived *cis*-1,2-dihydrocatechols as starting materials for the synthesis of a range of *Amaryllidaceae* alkaloids and their analogues, particularly those of the lycorine-type. Extensions of such work are now underway in the Banwell research group.

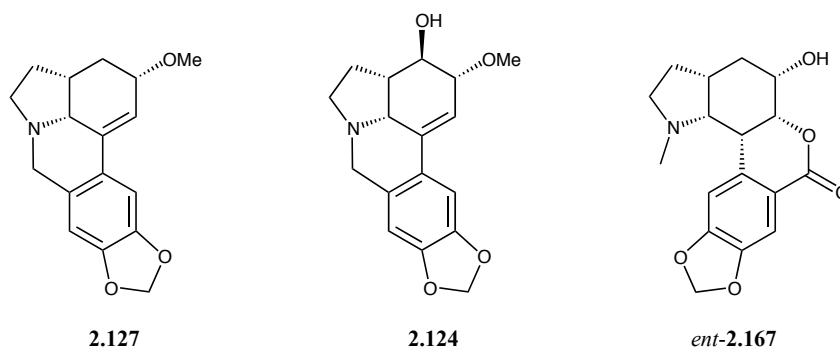


Figure 2.8.2: The Lycorine Degradation Product [**2.127**], an Isomer of Lycorine [**2.124**] and the Lycorenine-type Compound [*ent*-**2.167**].

2.10 References

- 1 Rinner, U.; Hudlicky, T. *Synlett.*, **2005**, 365.
- 1 Gerrard, A. W. *Pharm. J.*, **1877**, 8, 214.
- 2 (a) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, **1952**; Vol. 2, p 331; (b) Dalton, D. R. *The Alkaloids: The Fundamental Chemistry – A Biogenetic Approach*; Marcel Dekker: New York, **1979**; p 290.
- 3 Jin, Z. *Nat. Prod. Rep.*, **2005**, 22, 111.
- 4 (a) Kotera, K.; Hamada, Y.; Tori, K.; Aono, K.; Kuriyama, K. *Tetrahedron Lett.*, **1966**, 7, 2009; (b) Shiro, M.; Sato, T. *Chem. Ind.*, **1966**, 1229.
- 5 (a) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, **1952**; Vol. 2, p 331; (b) Dalton, D. R. *The Alkaloids: The Fundamental Chemistry – A Biogenetic Approach*; Marcel Dekker: New York, **1979**; p 290.
- 6 Asahina, Y.; Sugii, Y. *Chem. Zentr.*, **1913**, II, 1493.
- 7 (a) Gorter, K., *Chem. Zentr.*, **1920**, III, 842; (b) Gorter, K., *Chem. Zentr.*, **1920**, III, 846.
- 8 (a) Kondo, H.; Uyeo, S., *Chem. Ber.*, **1935**, 68, 1756; (b) Kondo, H.; Ishiwata, S., *Chem. Ber.*, **1937**, 70, 2427. (c) Kondo, H.; Ikeda, T. *Chem. Ber.*, **1940**, 73, 867; (c) Spath, E.; Kahovec, L., *Chem. Ber.*, **1934**, 67, 1501.
- 9 Kondo, H.; Katsura, H., *Chem. Ber.*, **1940**, 73, 1424.
- 10 Humber, L. G.; Kondo, H.; Kotera, K.; Takagi, S.; Takeda, K.; Taylor, W. I.; Thomas, B. R.; Tsuda, Y.; Tsukamoto, K.; Uyeo, S.; Yajima, H.; Yanaihara, N. *J. Chem. Soc.*, **1954**, 4622.
- 11 (a) Takeda, K.; Kotera, K. *Chem. Ind.*, **1956**, 347. (b) Takeda, K.; Kotera, K. *Chem. Pharm. Bull.*, **1957**, 5, 234.
- 12 Nakagawa, Y.; Uyeo, S. *J. Chem. Soc.*, **1959**, 3736.
- 13 Shiro, M.; Sato, T. *Chem. Ind.*, **1966**, 1229.

- 14 Kotera, K.; Hamada, Y.; Tori, K.; Aono, K.; Kuriyama, K. *Tetrahedron Lett.*, **1966**, 7, 2009.
- 15 For a review of this area see: Seigler, D. S. *Plant Secondary Metabolism*, Kluwer Academic Publishers: Boston, **2002**.
- 16 Barton, D. H. R.; Cohen, T. in *Festschrift Arthur Stoll*, Birkhauser, Basel, **1957**, 144.
- 17 Geissman, T. A.; Crout, D. H. G. in *Organic Chemistry of Secondary Plant Metabolism*, Freeman, Cooper and Co, San Francisco, **1969**, 512.
- 18 Barton, D. H. R.; Kirby, G. W.; Taylor, J. B.; Thomas, G. M. *J. Chem. Soc.*, **1963**, 4545.
- 19 (a) Battersby, A. R.; Binks, R.; Wildman, W. C. *Proc. Chem. Soc.*, **1960**, 410. (b) Barton D. H. R.; Kirby, G. W. *Proc. Chem. Soc.*, **1960**, 392.
- 20 Fungati, C. "The Amaryllidaceae Alkaloids" in *The Alkaloids*, Manske, R. H. F. Ed.; Academic Press: New York, **1975**; Vol.15, pp. 83 - 164.
- 21 For a thorough review of this area see: Kornienko, A.; Evidente, A. *Chem. Rev.*, **2008**, 108, 1982.
- 22 Morishima, A. *Arch. Exptl. Path. Pharmacol.*, **1897**, 40, 221.
- 23 Fitzgerald, D.B.; Hartwell, J.L.; Leiter, J. *J. Natl. Cancer. Inst.*, **1958**, 20, 763.
- 24 Sener, B.; Orhan I.; Satayavivad, J. *J. Phytother. Res.*, **2003**, 1220.
- 25 For recent publications reporting on the anti-cancer properties of lycorine and its derivatives see: (a) Dickneite, G.; Schorlemmer, H. U.; Sedlacek, H. H. Ger. Offen. DE 3426109, Jan 23, **1986** (*Chem. Abstr.*, **1986**, 104, 161979); (b) Toriizuka, Y.; Kinoshita, E.; Kogure, N.; Kitajima, M.; Ishiyama, A.; Otoguro, K.; Yamada, H.; Ōmura, S.; Takayama, H. *Bioorg. Med. Chem.*, **2008**, 16, 10182 and references cited therein; (c) Liu, X.; Jiang, J.; Jiao, X.; Wu, Y.; Lin, J.; Cai, Y. *Cancer Lett.*, **2009**, 274, 16 and references cited therein.
- 26 Li, Y.; Jing, L.; Tang, L.; Shi, Y.; Ren, W.; Hu, W. *Oncology Reports*, **2007**, 17, 377.

- 27 Lamoral-Theyes, D.; Andolfi, A.; Van Goietsenoven, G.; Cimmino, A.; Le Calve, B.; Wauthoz, N.; Meglazzi, V.; Gras, T.; Bruyere, C.; Dubois, J.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. *J. Med. Chem.*, **2009**, *52*, 6244.
- 28 McNulty, J.; Nair, J. J.; Bastida, J.; Pandey, S.; Griffin, C. *Phytochemistry*, **2009**, *70*, 913
- 29 Hayden, R.; Pratt, G.; Drayson, M.; Bunce, C. *Haematologica*, **2010**, *95*, 1889.
- 30 Synthetic approaches to the tetracyclic framework of lycorine: (a) Hill, R. K.; Joule, J. A.; Loeffler, L. J. *J. Am. Chem. Soc.*, **1962**, *84*, 4951; (b) Hendrickson, J. B.; Alder, R. W.; Dalton, D. R.; Hey, D. G. *J. Org. Chem.*, **1969**, *34*, 2667; (c) Landeryou, V. A.; Grabowski, E. J. J.; Autrey, R. L. *Tetrahedron*, **1969**, *25*, 4307; (d) Irie, H.; Nishitani, Y.; Sugita, M.; Uyeo, S. *Chem Commun.*, **1970**, 1313; (e) Ganem, B. *Tetrahedron Lett.*, **1971**, *12*, 4105; (f) Dyke, S. F.; Sainsbury, M.; Evans, J. R. *Tetrahedron*, **1973**, *29*, 213; (g) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.*, **1974**, 499; (h) Tanaka, H.; Yasuo, N.; Hiroshi, I.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin. Trans. 1*, **1979**, 875; (i) Kissel, W. S.; Padwa, A. *Tetrahedron Lett.*, **1999**, *40*, 4003; (j) Ishizaki, M.; Kai, Y.; Hoshino, O. *Heterocycles*, **2002**, *57*, 2279.
- 31 Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1987**, Vol. 30, 265.
- 32 Total syntheses or formal total syntheses of (±)-lycorine: (a) Møller, O.; Steinberg, E.-M.; Torrsell, K. *Acta. Chem. Scand. B*, **1978**, *32*, 98; (b) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K. *Heterocycles*, **1979**, *12*, 1475; (c) Martin, S. F.; Tu, C.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.*, **1982**, *47*, 3634; (d) Boeckman, R. K., Jr., Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.*, **1988**, *110*, 8250; (e) Hoshino, O.; Ishizaki, M.; Kamei, K.; Taguchi, M.; Nagao, T.; Iwaoka, K.; Sawaki, S.; Umezawa, B.; Iitaka, Y. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 571.
- 33 Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Irie, H.; Tanaka, H.; Takagi, S.; Yamaki, M.; Murata, M. *J. Chem. Soc., Chem. Commun.*, **1975**, 933.
- 34 Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.*, **1996**, *118*, 6210 [(+)-lycorine].

- 35 Yamada, K.; Yamashita, M.; Sumiyoshi, T.; Nishimura, K.; Tomioka, K. *Org. Lett.*, **2009**, *11*, 1631 [(-)-lycorine].
- 36 Irie, H.; Nishitani, Y.; Sugita, M.; Uyeo, S. *J. Chem. Soc., Chem. Commun.*, **1970**, 1313.
- 37 Tanaka, H.; Yasuo, N.; Irie, H.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin. Trans. I*, **1979**, 875.
- 38 Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Irie, H.; Tanaka, H.; Takagi, S.; Yamaki, M.; Murata, M. *J. Chem. Soc., Chem. Commun.*, **1975**, 933.
- 39 Sharpless, K.; Lauer, R. *J. Am. Chem. Soc.*, **1973**, *95*, 2697.
- 40 Irie, H.; Nagai, Y.; Tamoto, K.; Tanaka, H. *J. Chem. Soc., Chem. Commun.*, **1973**, 302.
- 41 Takagi, S.; Tsuda, Y.; Irie, H. *J. Chem. Soc., Perkin. Trans. I*, **1979**, 1359.
- 42 Morgans, D. J.; Stork, G. *Tetrahedron Lett.*, **1979**, *20*, 1959.
- 43 Oppolzer, W. *Angew. Chem. Int. Ed.*, **1977**, *15*, 10
- 44 Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.*, **1993**, *115*, 7904.
- 45 Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.*, **1996**, *118*, 6210.
- 46 (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.*, **1988**, *110*, 7828; (b) Schultz, A. G. *Acc. Chem. Res.*, **1990**, *23*, 207.
- 47 Moller, O.; Steinberg, E. M.; Torssell, K. *Acta Chem. Scand. B.*, **1978**, *32*, 98.
- 48 Yamada, K.; Yamashita, M.; Sumiyoshi, T.; Nishimura, K.; Tomioka, K. *Org. Lett.*, **2009**, *11*, 1631.
- 49 Tomioka, K. *Synthesis*, **1990**, 541
- 50 Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.*, **1998**, *120*, 5341.
- 51 Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.*, **1991**, *32*, 3017.
- 52 For recent reviews concerning the biological properties and synthetic approaches to narciclasine and its congeners see: (a) Kornienko, A.; Evidente, A. *Chem. Rev.*,

- 2008**, 108, 1982; (b) Chapleur, Y.; Chretien, F.; Ibn Ahned, S.; Khaldi, M. *Curr. Org. Synth.*, **2006**, 3, 341.
- 53 VanRheenen V.; Kelly R. C.; Cha D. Y. *Tetrahedron Lett.*, **1976**, 1973.
- 54 Gilman, N. W. *J. Chem. Soc. Chem. Commun.*, **1971**, 733.
- 55 Hudlicky, T.; Gonzalez, D.; Martinot, T. *Tetrahedron Lett.*, **1999**, 3077.
- 56 Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.*, **1981**, 11, 513.
- 57 (a) Miyaura, N.; Suzuki, A. *Chem. Rev.*, **1995**, 95, 2457; (b) Suzuki, A. J. *Organomet. Chem.*, **1999**, 576, 147.
- 58 Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.*, **2006**, 4, 2337.
- 59 Kürti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: Amsterdam, **2005**, 296.
- 60 Compound **1.5** can be obtained from the Aldrich Chemical Co. (Catalogue Number 489492) or from Questor, Queen's University of Belfast, Northern Ireland. Questor Contact Page: <http://questor.qub.ac.uk/newsite/contact.htm>
- 61 (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta*, **1999**, 32, 35; (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.*, **2003**, 75, 223; (c) Johnson, R. A. *Org. React.* **2004**, 63, 117; (d) Hudlicky, T.; Reed, J. W. *Synlett*, **2009**, 685.
- 62 Magid, R. M. *Tetrahedron*, **1980**, 36, 1901.
- 63 Paquette, L. A.; Stirling, C. J. M. *Tetrahedron*, **1992**, 48, 7383.
- 64 Takeda, K.; Kotera, K. *Chem. Pharm. Bull.*, **1957**, 5, 234.
- 65 Hudlicky, T.; Price, J.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.*, **1990**, 112, 9439.
- 66 For related examples of this type of epoxide ring-opening process see: Banwell, M. G.; Haddad, N.; Hudlicky, T.; Nugent, T. C.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1779.

- 67 (a) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.*, **2003**, *125*, 14149; (b) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.*, **1986**, *51*, 2230.
- 68 (a) Bordwell, F. G. *Acc. Chem Res.*, **1988**, *21*, 456; (b) Taft, R. W.; Bordwell, F. G. *Acc. Chem Res.*, **1988**, *21*, 463.
- 69 Gessner, V. H.; Daschlein, C.; Strohmman, C. *Chem. Eur. J.*, **2009**, *15*, 3320.
- 70 Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.
- 71 Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: Amsterdam, **2005**, 46.
- 72 (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.*, **1990**, *31*, 3991; (b) Lopez, R.; Hays, D.; Fu, G. *J. Am. Chem. Soc.*, **1997**, *119*, 6949
- 73 Svoronos, P. D.; Bruno, T. J. *Ind. Eng. Chem. Res.*, **2002**, *41*, 5321.
- 74 Ferm, R. J. *Chem. Rev.*, **1957**, *57*, 11.
- 75 The detection threshold of the human nose for H₂S is less than 1:10⁶, Karrie, A.; Brennan, R.; Dorman, D. C. *Toxicol. Pathol.*, **2000**, *28*, 326.
- 76 Mentzel, U. V.; Tanner, D.; Tønder, J. E. *J. Org. Chem.*, **2006**, *71*, 5807.
- 77 (a) Matveenko, M.; Kokas, O. J.; Banwell, M. G.; Willis, A. C. *Org. Lett.*, **2007**, *9*, 3683; (b) Matveenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron*, **2008**, *64*, 4817.
- 78 (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett.*, **1992**, 207; (b) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scr.*, **1984**, *23*, 120; (c) Gronowitz, S.; Honfelt, A.; Yang, Y. *Chem. Scr.*, **1988**, *28*, 281; (d) Monovich, L. G.; Le Huerou, Y.; Ronn, M.; Molander, G. A. *J. Am. Chem. Soc.*, **2000**, *122*, 52.
- 79 (a) Thompson, W. J.; Gaudino, J. *J. Org. Chem.*, **1984**, *49*, 5237; (b) Muller, D.; Fleury, J. F. *Tetrahedron Lett.*, **1991**, *32*, 2229; (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett.*, **1992**, 207; (d) Broutin, P. E.; Leroux, F.; Colobert, F. *Org. Lett.*, **2004**, *6*, 4419.
- 80 (a) Matveenko, M. *The Chemoenzymatic Synthesis of Certain Amaryllidaceae Alkaloids*. PhD Thesis, Australian National University, February **2009**; (b) Attempts to obtain a boronic acid derivative either by transmetallation procedures or by palladium-catalysed methods were unsuccessful.

- 81 Fang, H.; Kaur, G.; Yan, J.; Wang, B. *Tetrahedron Lett.*, **2005**, 46, 1671.
- 82 (a) Parijs, A. H. *Recl. Trav. Chim. Pays-Bas.*, **1930**, 49, 27; (b) Raphael, R. A.; Becker, D.; Hughes, L. R. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1674; (c) Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.*, **1987**, 52, 586.
- 83 (a) Khanapure, S.; Garvey, D.; Young, D.; Ezawa, M.; Earl, R.; Gaston, R.; Fang, S.; Murty, M.; Martino, A.; Shumway, M.; Trocha, M.; Marek, P.; Tam, W.; Janero, D.; Letts, G. *J. Med. Chem.*, **2003**, 46, 5484; (b) Hertz, W.; Mylius, B. *Chem. Ber.*, **1906**, 39, 3816.
- 84 Lambourne, L.; Robertson, P. *J. Chem. Soc.*, **1947**, 1167.
- 85 (a) Keck, G. E.; Wager, T. T.; Rodriguez, J. F. D. *J. Am. Chem. Soc.*, **1999**, 121, 5176; (b) Lai, G.; Anderson, W. K. *Synth. Commun.*, **1997**, 27, 1281; (c) Corey, E. J.; Gilman, N. W.; Ganem, G. E. *J. Am. Chem. Soc.*, **1968**, 90, 5616.
- 86 Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.*, **2000**, 65, 164.
- 87 PdCl₂(dppf)·CH₂Cl₂ was recrystallised from hot EtOH to afford yellow/orange needles, m.p. 276 - 280 °C.
- 88 Kürti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: Amsterdam, **2005**, 448.
- 89 Miura, M. *Angew. Chem. Int. Ed.*, **2004**, 43, 2201.
- 90 Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.*, **2006**, 45, 3484.
- 91 Leadbeater, N. E.; Marco, M. *Org. Lett.*, **2002**, 4, 2973.
- 92 For a thorough review of this field see Kappe, C.O. *Angew. Chem. Int. Ed.*, **2004**, 43, 6250.
- 93 (a) Baghurst, D.; Mingos, D. J. *Chem. Soc., Chem. Commun.*, **1992**, 674; (b) Bond, G.; Moyes, R.; Pollington, S.; Whan, D. *Chem. Ind.*, **1991**, 686.
- 94 Schanche, J. S. *Mol. Diversity*, **2003**, 7, 293.
- 95 Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews NC, **2002**.

- 96 Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*. Third Edition, John Wiley & Sons, New York, **1999**, pp. 211 – 213.
- 97 Paquette, L. A.; Stirling, C. J. M. *Tetrahedron*, **1992**, 48, 7383.
- 98 Magid, R. M. *Tetrahedron*, **1980**, 36, 1901.
- 99 Baldwin, J. E. *J. Chem. Soc., Chem. Commun.*, **1976**, 734.
- 100 *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. ed., VCH Verlag, Weinheim, **1985**, Vol. A2, 5.
- 101 Kukula, P.; Studer, M.; Blaser, H. U. *Adv. Synth. Catal.*, **2004**, 346, 1487
- 102 De Bellefon, C.; Fouilloux, P. *Catal. Rev. Sci. Eng.*, **1994**, 36, pp 459 - 506
- 103 (a) Döpke, W.; Bienert, M. *Tetrahedron Lett.*, **1970**, 11, 3245; (b) Jeffs, P.W.; Hansen, J. F.; Döpke, W.; Bienert, M. *Tetrahedron*, **1971**, 27, 5065.
104. Evidente, A.; Abou-Donia, A. H.; Darwish, F. A.; Amer, M. E.; Kassem, F. F.; Hammoda, H. A. M.; Motta, A. *Phytochem.*, **1999**, 51, 1151.
- 105 Schwartz, B.; Jones, M.; Banwell, M.; Cade, I. *Org. Lett.*, **2010**, 12, 5210.
- 106 For relevant examples of nitrogen centered radical cyclisation processes, see, for example: Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem. Int. Ed.*, **2002**, 41, 1783; (b) Banwell, M. G.; Lupton, D. W. *Heterocycles*, **2006**, 68, 71.
- 107 Kunz, H.; Unverzagt, C. *Angew. Chem. Int. Ed.*, **1984**, 23, 436
- 108 Beckwith, A. L. J. *Tetrahedron*, **1981**, 37, 3073.
- 109 Lodewyck, M.; Tantillo, D. *J. Nat. Prod.*, **2011**, 74, 1339.
- 110 White, L.; Schwartz, B.; Banwell, M.; Willis, A. *J. Org. Chem.*, **2011**, 76, 6250.
- 111 Schwartz, B.; White, L.; Banwell, M.; Willis, A. *J. Org. Chem.*, **2011**, 76, 8560.
- 112 Boivin, J.; Henriët, E.; Zard, S. *J. Am. Chem. Soc.*, **1994**, 116, 9739.

A Pd[0]-catalysed Ullmann Cross-Coupling and Reductive Cyclisation Approach to C-3 Mono-alkylated Oxindole Compounds.

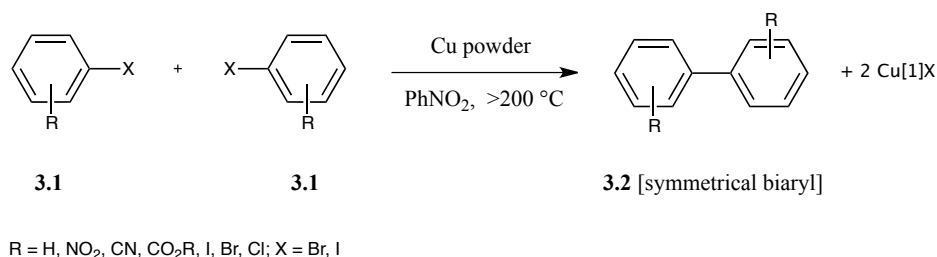
3.1 The Pd[0]-Catalysed Ullmann Cross-Coupling Reaction.

3.1.1 The Ullmann Biaryl Synthesis

The formation of aryl-aryl bonds is of fundamental importance in organic synthesis because the biaryl motif is a substructure encountered in many natural products, including alkaloids, as well as in numerous pharmaceuticals such as antibiotics, anti-inflammatories, anti-hypertensives, antifungal, anticancer and infertility treatments.¹ Agrochemicals and synthetic dyes frequently contain several aromatic rings and, increasingly, polyaromatic organic semiconductors are employed in electronic devices such as liquid crystal displays.² Moreover, *di*- and *tri*-aromatic ligands are found in some of the most efficient and selective asymmetric catalysts now known. A wide range of methods exist for the formation of aryl-aryl bonds, but in modern synthetic chemistry the palladium-catalysed Negishi, Stille and Suzuki reactions are at the forefront of techniques for creating carbon-carbon bonds including those that link aryl subunits to one another.³ Nevertheless, the Ullmann reaction, which is now more than 100 years old, remains a significant method for the formation of aryl-aryl bonds.

In 1901 Fritz Ullmann reported that the reaction of two equivalents of an aryl halide with one equivalent of finely divided copper at high temperature (above 200 °C) affords a symmetrical biaryl and copper halide as the associated by-product.⁴ Subsequently, the Ullmann biaryl synthesis or 'Ullmann reaction' has entered into the canon of organic chemistry as a fundamental method for synthesizing biaryl compounds. The general features of the reaction, as reported by Ullmann,⁵ may be summarized as follows: a limited range of substituents can be tolerated in the *ortho*, *meta* and *para* positions of the aryl substrates but the presence of an electron-withdrawing moiety (e.g., NO₂, CO₂Me, CHO) *ortho* to the halogen greatly increases the reactivity of the aryl halide. High boiling point solvents such as nitrobenzene or *p*-nitrotoluene are usually employed and in many cases a large excess of finely divided copper is required so as to

ensure that a satisfactory yield of the symmetrical biaryl product is obtained (Scheme 3.1).



Scheme 3.1 *The Ullmann Biaryl Synthesis.*

The coupling conditions originally reported are still widely used but more than a century of research has seen the development of numerous modifications. Several comprehensive reviews of the Ullmann reaction have been published recently and these describe, in detail, many of the innovations and applications of the reaction in modern organic synthesis.^{3,6} The scope of these reviews is large, but in the context of this thesis a brief description of certain important factors and some of the more significant modifications is warranted.

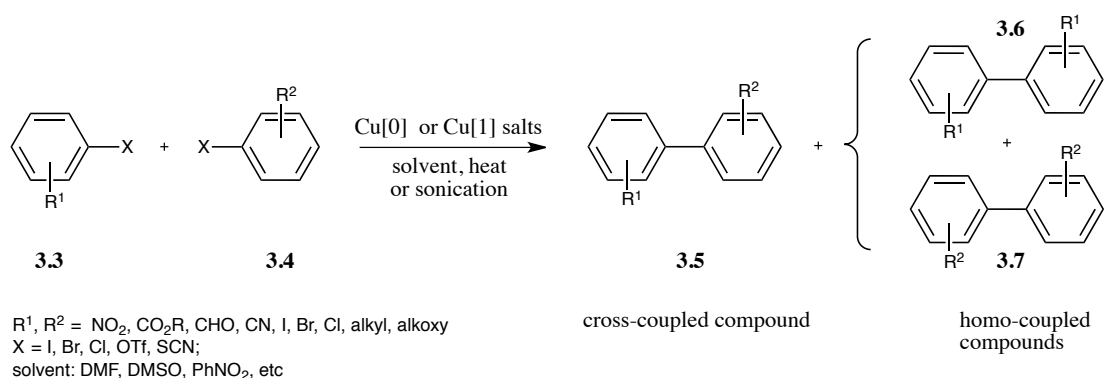
As already stated, substituents play an important part in determining the efficiency of the reaction with electron-withdrawing groups (especially -NO₂, -CO₂Me, -CHO groups) located *ortho* to the halogen having particularly beneficial effects. However, bulky *ortho*-substituents, which cause steric interference, tend to result in a lower yield of the biaryl and electron-donating groups located anywhere on either ring also usually diminish the yields of the coupling product. Certain unprotected functional groups (e.g., OH, NH₂, CO₂H, SO₂NH₂) that are open to alternative reaction pathways tend to inhibit the reaction as well.

Iodinated and brominated benzene derivatives are most commonly employed as substrates for biaryl formation *via* the Ullmann reaction, but chloro- and pseudo-halides such as triflates are also suitable in certain instances. The order of reactivity is I > Br > OTf >> Cl, whilst fluorinated aromatics are inert. Halogenated heteroaromatic compounds such as iodopyridine can also serve as substrates for the reaction.

The most common solvent used in modern Ullmann reactions is DMF but others including DMSO, nitrobenzene, NMP, *p*-nitrotoluene and quinolone have been used.⁷

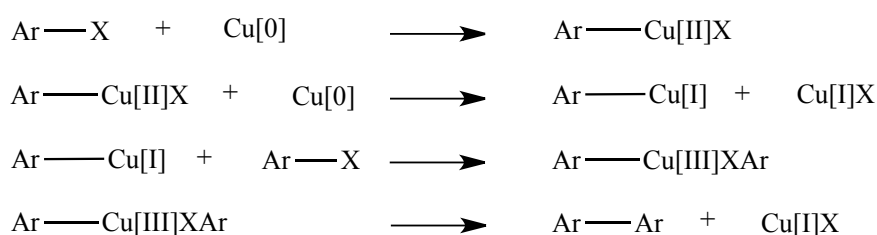
Activation of copper particles prior to their use in an Ullmann reaction leads to improved yields and often allows for the application of lower reaction temperatures, especially in conjunction with DMF or DMSO as solvent.^{8,9} Sonication of the reaction may improve the efficiency of the coupling, particularly when employed in conjunction with activated copper particles.¹⁰ Cu[I] salts such as Cu₂O and Cu₂S can mediate the reaction, although they are less reactive than activated copper metal.¹¹ Mild reaction conditions are sometimes possible when Ni[0] complexes are used in place of copper,¹² whilst the preparation of highly substituted biaryl compounds is best achieved by the use of pre-formed copper species (the so-called Ziegler modification of the Ullmann reaction).¹³

Both *inter*- and *intra*-molecular Ullmann couplings are possible and are not limited to the synthesis of symmetrical biaryl compounds. Halogenated benzene derivatives embodying various substitution patterns [3.4, 3.5] may be cross-coupled to give unsymmetrical biaryl products 3.6 (Scheme 3.2). However, such processes are almost always accompanied by some homo-coupling [3.6, 3.7] and this creates a degree of inefficiency although high yields of the cross-coupled product are possible if one coupling partner is electron-rich, whilst the other is electron-deficient.⁶ The alternative is to generate a magnesium, zinc, tin or boron derivative of one or other aromatic coupling partner and to then carry out a Kumada, Negishi, Stille or Suzuki cross-coupling reaction. Such reactions will generate the cross-coupled biaryl exclusively, but preparing the requisite precursor requires an extra step and this represents an inherent inefficiency in these modern processes. The sheer simplicity of conducting biaryl synthesis by means of the Ullmann reaction accounts for its ongoing use.



Scheme 3.2 Variations Associated with the Ullmann Biaryl Synthesis.

Despite extensive research, the mechanism of the Ullmann reaction is not well understood. The process or processes by which coupling takes place may involve either the formation of a series of discrete aryl-copper species or the formation of aryl radicals.⁶ Experimental evidence supporting a radical pathway is, at best, tenuous and ESR experiments do not suggest the involvement of radicals. The most widely accepted mechanism invokes the formation of aryl-copper intermediates, probably by complexation of the aryl π -system with the surface of Cu[0] metal followed by oxidative substitution of the copper. A reaction sequence involving disproportionation and reductive elimination then leads to the biaryl product (Scheme 3.3).^{14,15}



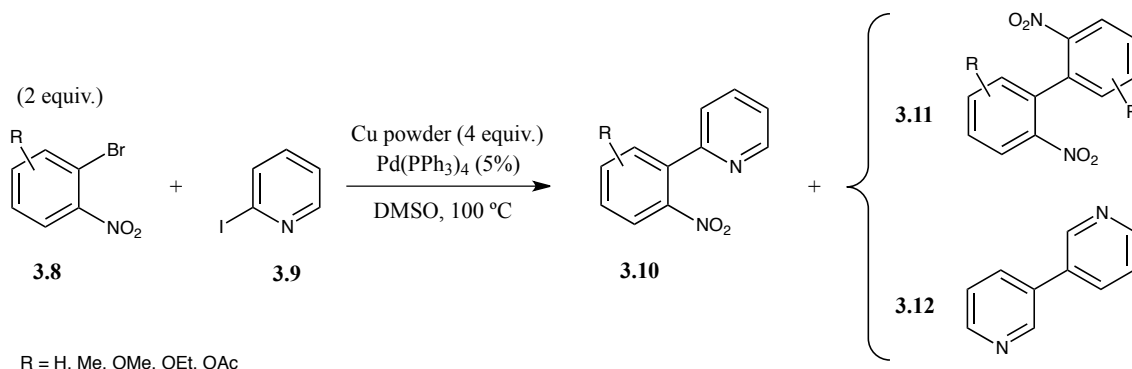
Scheme 3.3 *The Reaction Mechanism of the Ullmann Biaryl Synthesis.*

Most of the aryl-copper intermediates in this sequence are stable and they have been isolated and identified. Moreover, even moderate heating of these intermediates in the presence of aryl halides results in the formation of biaryl compounds.¹⁶ Vapour-phase experiments have allowed this reaction pathway to be studied in detail.¹⁵ However, just because a reaction that takes place *via* a particular sequence in the vapour-phase does not mean the same pathway is necessarily involved in the liquid-phase or where a heterogeneous reaction mixture is involved.

3.1.2 Palladium[0]-Catalysed Ullmann Cross-Coupling of 3-Iodopyridine With *o*-Bromonitrobenzene

An important modification of the Ullmann reaction was reported by Shimizu and co-workers of the Kowa Company, Japan, in 1993. This group demonstrated that a selective and efficient cross-coupling reaction could be achieved between 2-iodopyridine [3.9] and various derivatives of 2-bromonitrobenzene [3.8] in the presence of a Pd[0] catalyst.¹⁷ The resulting 2-nitrophenylpyridine derivatives [3.10] were obtained in high yields (78 - 94%) whereas the homocoupled nitrobenzene derivatives **3.11** that result from the conventional Ullmann biaryl synthesis were only obtained in moderate yields

(32 – 56%). Furthermore, only traces of 3,3'-bipyridine [**3.12**] were detected (Scheme 3.4).

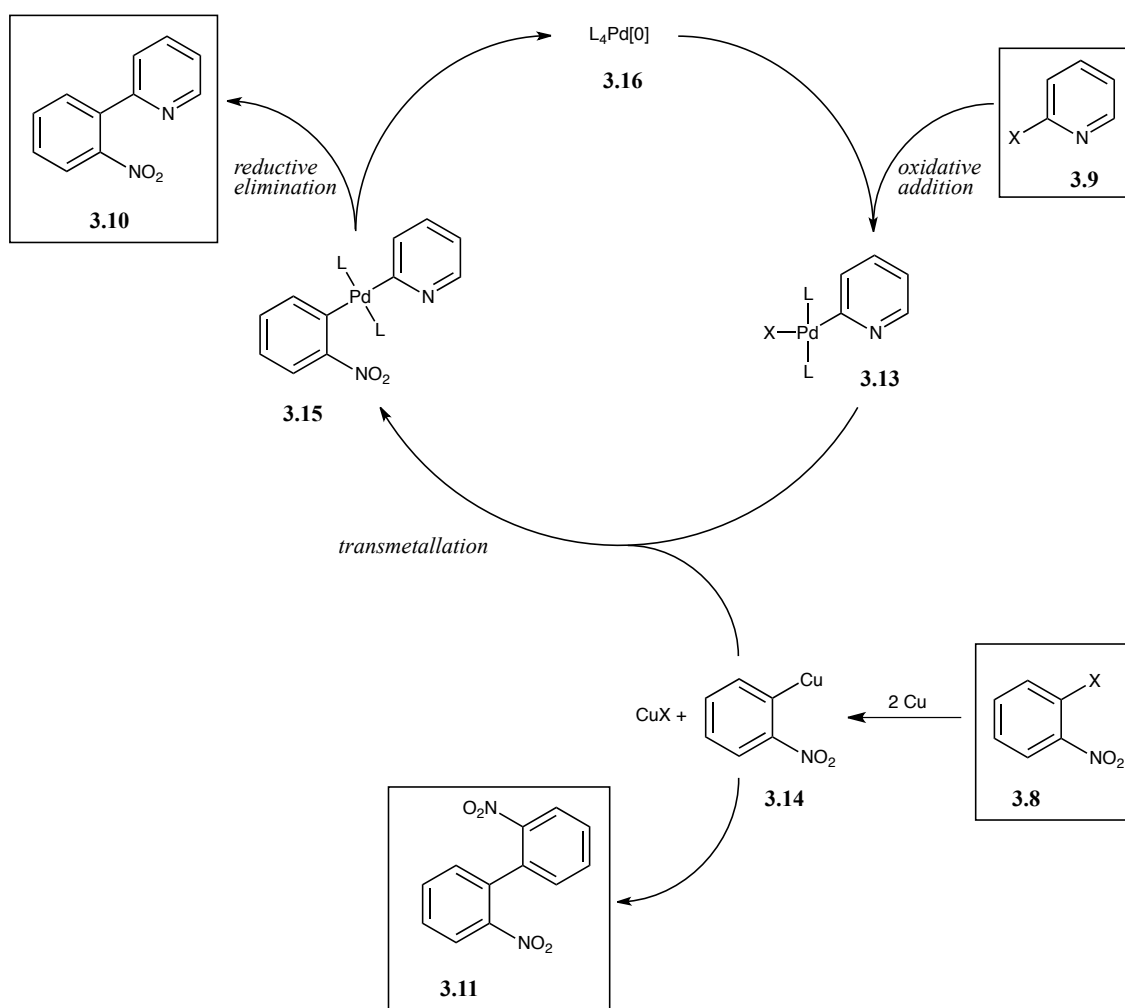


Scheme 3.4 *Pd[0]-Catalysed Ullmann Cross-Coupling of 2-Iodopyridine with 1-Bromo-2-nitrobenzene Derivatives.*

Although Pd[0]-catalysed Ullmann reactions had been reported previously,⁶ the significance of Shimizu's work lies in the fact that the reaction conditions favour cross-coupling over homocoupling to a significant extent. It is notable that in the absence of a zero-valent palladium catalyst negligible levels of the cross-coupled material were obtained and homocoupling of the nitrobenzene derivative proved to be the predominant process.

Shimizu and co-workers employed ¹H NMR techniques to investigate the relative reactivity of the aromatic coupling partners towards Pd(PPh₃)₄. These experiments indicated that the rate of reaction between the palladium complex and 2-iodopyridine [**3.9**] was approximately twenty times faster than that between the palladium complex and 2-bromo-4-ethoxy-1-nitrobenzene. On the other hand, 2-bromonitrobenzene derivatives are excellent substrates in the conventional Ullmann biaryl synthesis while 2-iodopyridine [**3.9**] is not. Thus, a high yielding cross-coupling reaction is feasible without the need to synthesise zinc, tin or boron derivatives of one of the cross-coupling partners. In other words, the inclusion of a palladium catalyst under conditions normally employed in the Ullmann reaction is sufficient to promote the cross-coupling in high yield. On the basis of these observations Shimizu proposed a catalytic cycle, as shown in Scheme 3.5, to account for the various facets of the reaction. Thus, the initial oxidative addition of Pd[0] across the carbon-halogen bond of 2-iodopyridine [**3.9**] gives the intermediate **3.13**. Transmetalation at Pd with the aryl-copper species **3.14**, formed from the reaction of the 2-halonitroarene [**3.8**] with copper, then affords the

intermediate **3.15**. This intermediate itself undergoes reductive elimination to deliver the observed product **3.10** and, simultaneously, regenerates the Pd[0] catalyst which is then available for the next cycle. Concurrently, there is the background formation of the homocoupled biaryl compound **3.11** *via* the conventional Ullmann reaction (Scheme 3.5).



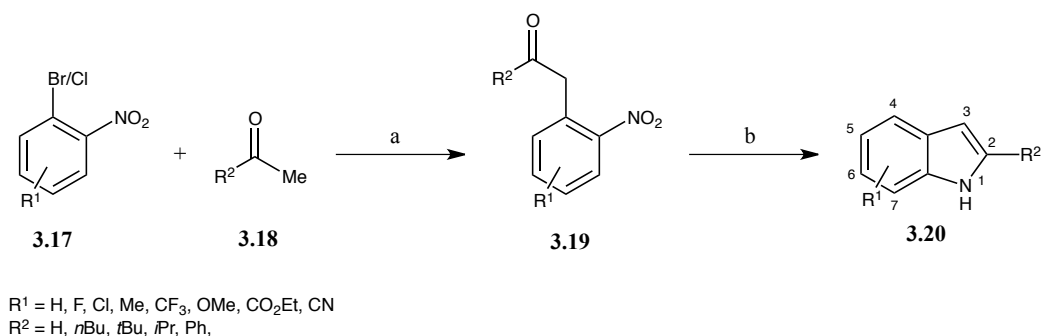
Scheme 3.5 Proposed Catalytic Cycle for the Pd[0]-Catalysed Ullmann Cross-Coupling Reaction

Several years after Shimizu's disclosure, Banwell and co-workers exploited the technique to effect a high yielding Pd[0]-catalysed Ullmann cross-coupling of 2-bromonitrobenzene with the pyrrole derivative 4-iodo-1*H*-pyrrole-2-carboxylate.¹⁸ The cross-coupled compound so obtained (42%) was employed in studies directed towards the synthesis of the alkaloid (±)-rhazinal. This extension of the Pd[0]-catalysed Ullmann

cross-coupling reaction to include coupling partners derived from pyrrole served to emphasise the potential versatility of the reaction.

3.1.3 Pd[0]-catalysed Ullmann Cross-Coupling and Reductive Cyclisation Approach to Indoles

In 2002 Buchwald reported a new method¹⁹ for the regioselective synthesis of 2-*n*-disubstituted indoles^a (Scheme 3.6). Buchwald's technique involved the Pd[0]-catalysed coupling of various enolisable methyl ketones [3.18] with 1-chloro- or 1-bromo-2-nitrobenzene derivatives 3.17 in the presence of phenol to deliver α -(*o*-nitroaryl)ketones 3.19. Upon exposure to TiCl₃/NH₄OAc these compounds underwent reductive cyclisation to give indoles of the general form 3.20.

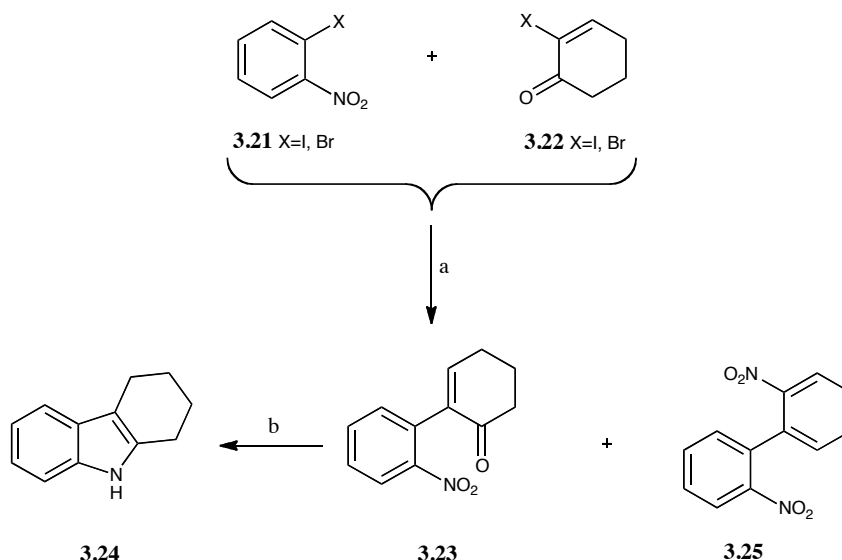


Scheme 3.6 Reaction conditions: (a) 1.0 equiv of 3.17, 2.2 equiv of 3.18, 0.2 equiv of phenol, Pd₂(dba)₃ 4%, 2 equiv of K₃PO₄, toluene, 35 – 80 °C; (b) 16.5 equiv of TiCl₃, 10 equiv of NH₄OAc, EtOH, 20 °C, 44 – 79% over two steps.

At the time of Buchwald's publication Banwell was seeking to develop a simple, mild and regioselective method for the synthesis of indoles employing ketones that can exist in more than one enolic form. The venerable Fischer indole synthesis does not meet these requirements because of the lack of regiocontrol that is available when using such ketones and because of the rather harsh reaction conditions that are needed to effect the necessary [3,3]-sigmatropic rearrangement of the initially produced hydrazone. Buchwald's reductive approach to the synthesis of indoles prompted Banwell to develop a complementary protocol (Scheme 3.7) involving the Pd[0]-catalysed

^a The aryl substituent R¹ may be variously located at the *n* = 4, 5, 6 or 7-position of the indole product 3.20 (Scheme 3.6).

Ullmann cross-coupling of an 1-iodo- or 2-bromo-2-nitrobenzene, *viz.* **3.21**, with α -halo- α,β -unsaturated enones such as compound **3.22**.²⁰ Reductive cyclisation of the ensuing coupling product, **3.23**, with dihydrogen in the presence of Pd/C then afforded the target indole **3.24**.



Scheme 3.7 Reaction conditions: (a) 2.0 equiv of **3.21**, 1.0 equiv of **3.22**, 5.0 equiv of Cu powder, Pd₂(dba)₃ 6 mol%, DMSO, 70 °C, 87%, plus **3.25** 46% with respect to **3.21**; (b) 10% Pd on C (20% by weight), H₂ 1 atm., MeOH, 20 °C, 0.75 h, 60%.

Preliminary studies were focused on optimising the coupling reaction **3.21** + **3.22** $\rightarrow$ **3.23** in order to find the most effective solvent, catalyst, temperature and stoichiometries. DMSO was identified as the best solvent and temperatures in the range of 50 – 70 °C were shown to be necessary. A variety of palladium catalysts could be employed including Pd(PPh₃)₄, Pd₂(dba)₃, PdCl₂(dppf) and Pd(OAc)₂, with the latter two presumably being reduced to Pd[0] by the copper powder introduced into the reaction mixture. The most effective catalyst was usually found to be Pd₂(dba)₃, which allowed for the efficient formation of the cross-coupled compound **3.23** at moderate temperatures. It was necessary to employ a large excess of copper powder and in a typical reaction 5 – 10 equiv (with respect to **3.21**) were required. The chromatographically separable homocoupled by-product **3.25** was always observed in yields ranging from 46% – 58% (with respect to **3.22**). Not surprisingly, the most efficient and rapid reactions were observed when iodinated versions of both coupling partners were employed, but the brominated congeners, either together or individually could also be employed. On the other hand, 1-chloro-2-nitrobenzene and 2-nitrophenyl triflate were found to be

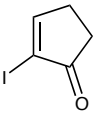
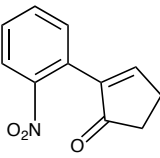
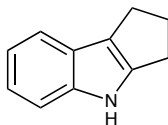
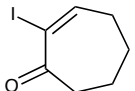
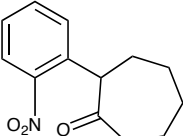
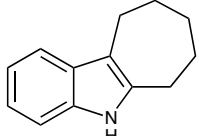
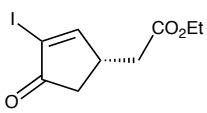
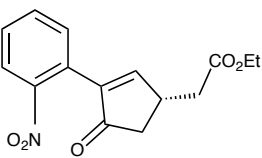
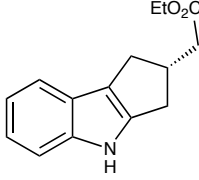
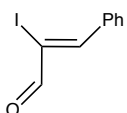
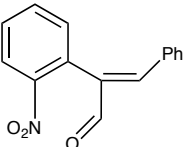
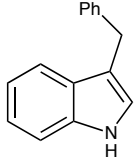
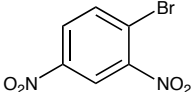
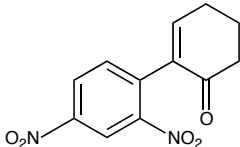
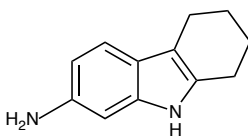
unreactive. As detailed in Scheme 3.7, under the optimized reaction conditions a yield of 87% of the cross-coupled compound **3.23** was obtained.

A variety of cyclic- and open-chain α -halo- α,β -unsaturated enones were found to readily engage in the Pd[0]-catalysed Ullmann cross-coupling process and, likewise, a range of substituted derivatives of 1-halo-2-nitrobenzene underwent efficient cross-coupling. The yields of cross-coupled compounds were in the range of 65 – 85%. Banwell considered that the mechanism of the cross-coupling process was consistent with the proposals advanced by Shimizu.

Reductive cyclisation of the arylated enone **3.23** to the annulated indole **3.24** was achieved in 60% yield by treatment of a methanolic solution of the former compound with dihydrogen at a pressure of 1 atmosphere in the presence of 10% Pd/C (20% by weight) for 0.75 h at 20 °C. This process was successfully applied to a range of cross-coupled compounds to afford the corresponding indoles in a reliable manner and high yield. The outcomes of such reactions are presented in Table 3.1 and provide a sense of the scope of the reaction.

It is noteworthy that the synthesis of indoles *via* the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach is operationally simple and involves mild reaction conditions. Moreover, the method obviates the need to prepare metallated cross-coupling partners such as zincates, stannanes or boronates. The procedure is versatile and reliable and it has been exploited in the synthesis of the relatively complex natural product aspidospermidine²¹ and in model studies directed towards the synthesis of Strychnos-type alkaloids.²²

Table 3.1 *Pd[0]–catalysed Ullmann Cross-Coupling and Reductive Cyclisation Reactions Leading to Ring-Fused Indoles.*

Entry	Coupling partner ^a	Product of cross-coupling ^b	Yield % ^c	Indole ^b	Yield %
1			75		90
	3.27	3.28		3.29	
2			66		72
	3.30	3.31		3.32	
3			68		90
	3.33	3.34		3.35	
4			67		88
	3.36	3.37		3.38	
5			82		80
	3.39	3.40		3.41	

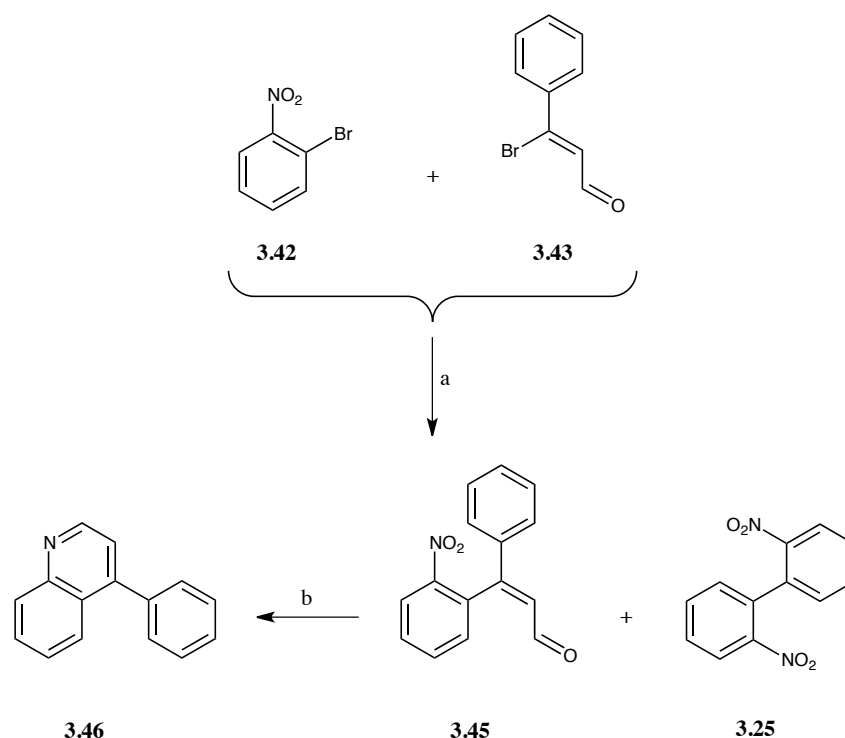
^a Entries 1 – 4: the other cross-coupling partner was 1-iodo-2-nitrobenzene [3.21]; Entry 5: the other cross-coupling partner was 2-iodocyclohex-2-eneone [3.22]. ^bThe reaction conditions defined in Scheme 3.7 were employed for the cross-coupling and reduction process. In all cases the homocoupled compound **3.25** was obtained in approximately 50% based on arene. ^cYield calculation based on α -iodo-enone.

3.1.4 The Pd[0]-catalysed Ullmann Cross-Coupling and Reductive Cyclisation Approach to Quinolines and Phenanthridines

Quinolines and related heterocyclic systems are ubiquitous substructures in biologically active natural products and medicinal compounds.²³ Consequently, numerous methods have been developed for their preparation.^{24,25,26} One of the most

effective of these is the Friedländer quinoline synthesis²⁷ in which an aminoarene incorporating an *ortho*-tethered enal moiety engages in an intramolecular Schiff base condensation reaction to deliver the quinoline heterocycle. However, the construction of the substrates required for this approach can be problematic and complimentary synthetic methods are desirable.²⁸

Banwell and co-workers were able to develop an effective two-step procedure for the synthesis of quinolines involving the Pd[0]-catalysed Ullmann cross-coupling of 1-bromo-2-nitroarenes with β -haloenals followed by reductive cyclisation of the products in the Friedländer mode.²⁹ An example of such a reaction sequence is depicted in Scheme 3.8.



Scheme 3.8 Reaction conditions: (a) 1.0 equiv of **3.42**, 1.0 equiv of **3.43**, 5.0 equiv of Cu powder, $\text{Pd}_2(\text{dba})_3$ 3%, DMSO, 80 °C, 68%, plus **3.25** <5% with respect to **3.21**; (b) 10% Pd on C (20% by weight), H_2 1 atm, MeOH, 20 °C, 0.75 h, 51%.

This new approach to quinolines was an extension of Banwell's method for the synthesis of indoles. It offered the same advantages of an operationally simple procedure and mild reaction conditions leading directly to the cross-coupled intermediate without the need to prepare metallated cross-coupling partners. Furthermore, since numerous 1-halo-2-nitroarenes are commercially available and because compounds of type **3.43** are

readily prepared *via* the Vilsmeier haloformylation³⁰ of the appropriate ketone, a wide range of β -nitroaryl-enals and corresponding quinolines may be synthesized by such means.

It is noteworthy that good yields of the cross-coupled compound **3.45** were obtained when a 1:1 stoichiometry was maintained between the arene [**3.42**] and the β -halo-enal [**3.43**] coupling partners. This differed from the situation observed with α -halo-enones, where it was necessary to employ at least 2 molar equivalents of the arene in order to optimize the yield of cross-coupled indole precursor (see above). In keeping with this observation, the yields of homo-coupled biaryl compounds of type **3.25** were very low (< 5%). Evidently, the cross-coupling reaction was taking place more rapidly than the corresponding homocoupling process. Banwell suggested that the Pd[0]-catalysed Ullmann cross-coupling reaction between 1-bromo-2-nitroarenes and β -haloenals was facilitated by the propensity of the latter to engage in nucleophilic addition-elimination reactions. The procedure is particularly well suited to the synthesis of [*b*]-annulated quinolines but it also allows for the synthesis of [*c*]-annulated quinolines which are difficult to obtain by other methods (Figure 3.1.1).^{29,31} Indeed, Banwell and co-workers have employed the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation reactions in the synthesis of the natural products trisphaeridine [**3.58**] and crinasiadine [**3.61**], each of which embodies such ring systems.^{29,32}

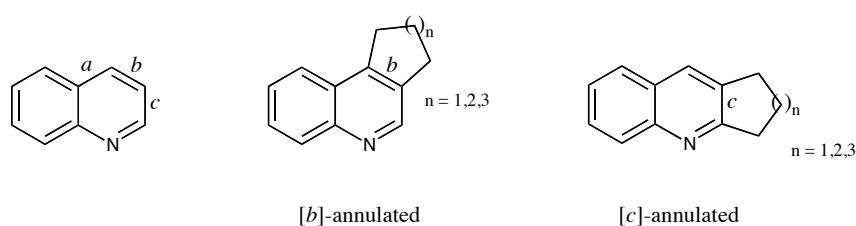
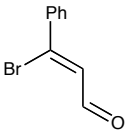
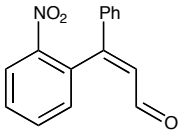
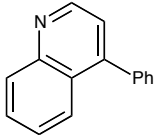
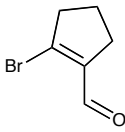
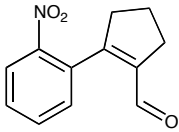
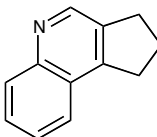
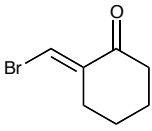
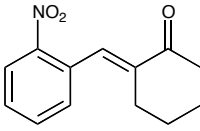
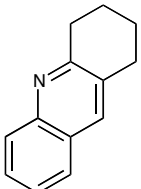
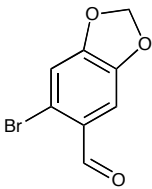
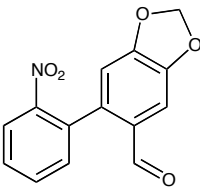
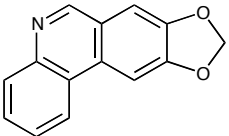
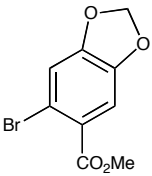
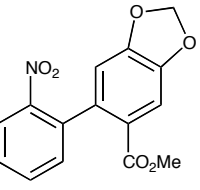
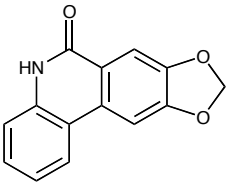


Figure 3.1.1 *Examples of Annulated Quinolines*

Table 3.2 depicts a selected range of coupling partners and the corresponding cross-coupled compounds as well as the quinolines that can be derived from these (see over).

Table 3.2 *Pd[0]–Catalysed Ullmann Cross-Coupling and Reductive Cyclisation to Afford Quinolines*

Entry	Coupling partner ^a	Product of cross-coupling ^b	Yield %	Quinoline	Yield %
1	 3.42	 3.43	68	 3.46	51
2	 3.47	 3.48	82	 3.49	92
3	 3.50	 3.51	71	 3.52	46
4	 3.56	 3.57	57	 3.58	68
5	 3.59	 3.60	40	 3.61	92

^aEntries 1 – 5: in all cases the other cross-coupling partner was 1-iodo-2-nitrobenzene [3.21]. ^bThe reaction conditions defined in Scheme 3.8 were employed for the cross-coupling and reduction process.

3.2 Pd[0]-Catalysed Ullmann Cross-Coupling and Reductive Cyclisation Approach to C-3 Mono-alkylated Oxindoles

3.2.1 Introduction

The oxindole or indolone motif [3.62] represents a privileged structure in medicinal chemistry.³³ For example, this heterocycle is encountered in antiproliferative agents,³⁴ in serotonergic agents,³⁵ in growth hormone secretagogues,³⁶ in the anti-Parkinsonian drug ropinirole [3.63],³⁷ in P-glycoprotein-mediated MDR inhibitors,³⁸ in non-opioid nociceptin receptor ligands³⁹ and in anti-inflammatory agents.⁴⁰ In addition, a number of prominent natural products embody oxindole substructures including welwitindolinone A isonitrile [3.64],^{41,42} rhynchophylline,⁴² horsfiline [3.65],⁴³ coerulescine,⁴⁴ elacomine [3.66],⁴⁵ gelsemine,⁴⁶ the gelsenicine-related oxindole alkaloids⁴⁷ and the spirotryprostatins [3.67] (Figure 3.1).^{37,48} Most of these display intriguing biological properties. Oxindoles also serve as precursors to a range of other heterocyclic compounds including indoles proper.⁴⁹ Accordingly, numerous routes to the title heterocyclic system have been developed and many of these have been summarized in recent reviews.^{42,50}

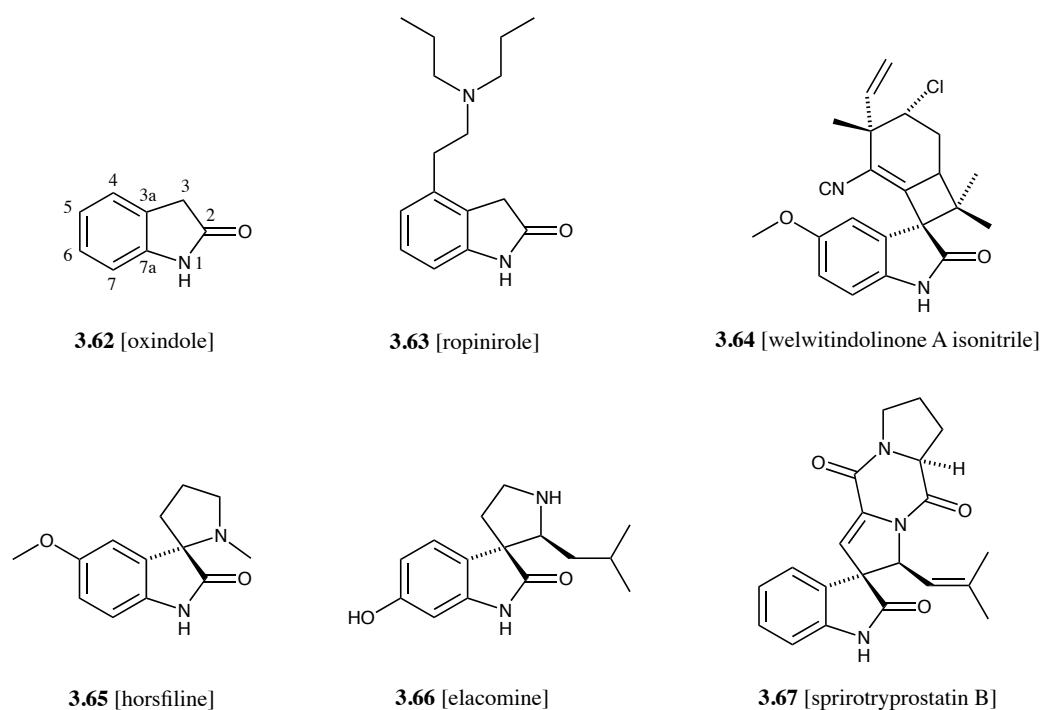


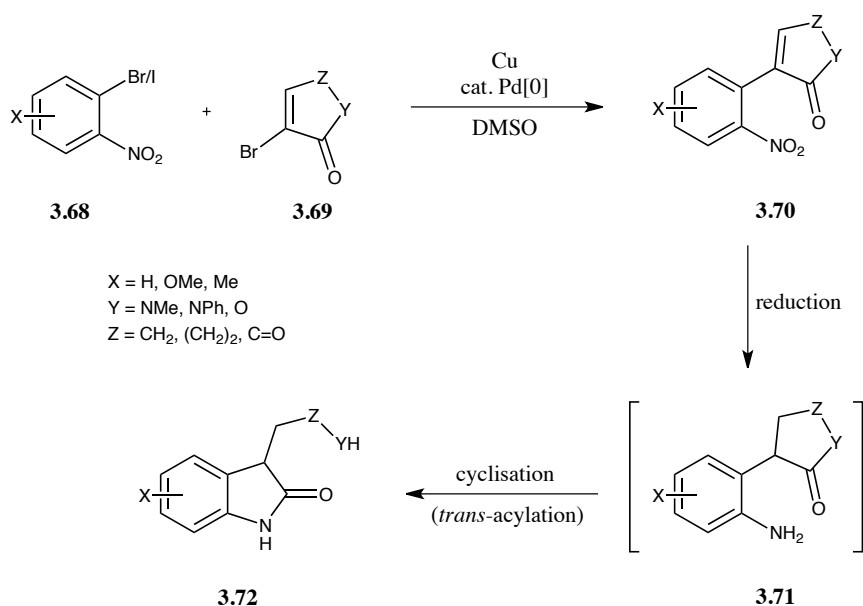
Figure 3.2.1 Oxindole [3.62] and Various Oxindole-containing Alkaloids.

Despite the impressive repertoire of methodologies available, the controlled assembly of C-3 mono-alkylated oxindoles remains a challenging matter.⁵¹ The following section describes research by the author leading to the efficient synthesis of such compounds. This was achieved by adapting Banwell's approach to indole and quinoline compounds using the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation sequence.

3.2.2 Background

The Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach to the synthesis of indole-type compounds and quinolines requires the use of a 1-bromo- or 1-iodo-2-nitroarene derivative as one of the cross-coupling partners. This is due, in part, to the requirement for the presence of a strong electron-withdrawing group *ortho* to the halogen. Additionally, the nitrogen atom of the nitro substituent is incorporated within the newly formed heterocycle during the reductive cyclisation process. In the examples described above the second coupling partner is a carbocyclic system of some form or another. Coupling partners derived from carbocyclic compounds have been of particular interest because they are amenable to the cross-coupling reaction and because they allow for the ready synthesis of annulated indoles and quinolines. Shimizu and Banwell have also shown that 1-bromo-2-nitroarene derivatives will engage in the Pd[0]-catalysed Ullmann cross-coupling reaction with halogenated aromatic heterocycles.^{17,18}

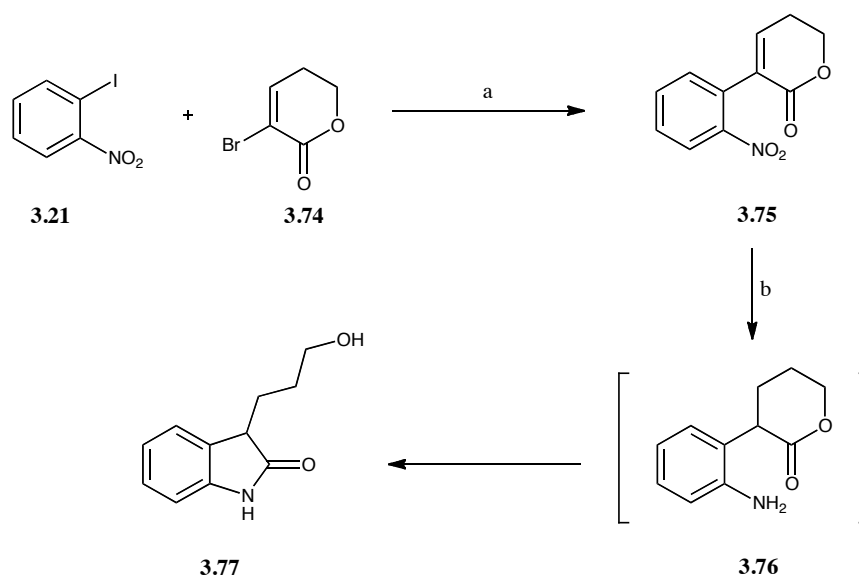
On the basis of this knowledge it was anticipated that 1-bromo- and 1-iodo-2-nitroarene derivatives of the general form **3.68** would engage in the Pd[0]-catalysed Ullmann cross-coupling reaction with various non-aromatic heterocycles including α -brominated α,β -unsaturated cycloimide, lactam and lactone compounds of the general form **3.69** (Scheme 3.9). It was expected that catalytic hydrogenation of the resulting cross-coupled compounds of type **3.70** would generate an intermediate **3.71** that would undergo spontaneous *trans*-acylation to afford the corresponding C-3 mono-alkylated oxindole **3.72**. The successful implementation of this approach is described below.



Scheme 3.9 Proposed Synthesis of C-3 Mono-Alkylated Oxindole Alkaloids via a Pd[0]-Catalysed Ullmann Cross-Coupling and Reductive Cyclisation Approach.

3.2.3 Preliminary Investigations

In the author's initial attempts to implement the synthetic plan defined immediately above, a sample of 3-bromo-5,6-dihydropyran-2-one⁵² [3.74] was prepared in 92% yield by treating 5,6-dihydropyran-2-one [3.73] with molecular bromine, followed by dehydrohalogenation of the crude dibromo-adduct with triethylamine. Reaction of compound 3.74 with 1-iodo-2-nitrobenzene [3.21] (Scheme 3.7) under Pd[0]-catalysed Ullmann cross-coupling conditions similar to those used for the preparation of indole precursors afforded the cross-coupled compound 3.75 in 42% yield. When a methanolic solution of compound 3.75 was exposed to 1 atmosphere of dihydrogen in the presence of 10% Pd on C this substrate underwent the expected cyclisation process, to give, presumably *via* intermediate 3.76, the known C-3 alkylated oxindole 3.77⁶⁷ in 74% yield (Scheme 3.10). This pleasing result confirmed that the synthetic plan was sound and a range of cross-coupling partners was therefore prepared in order to explore the scope of the process and to produce a library of C-3 mono-alkylated oxindoles.



Scheme 3.10 Reaction conditions: (a) 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.74**, 5.0 equivalents of Cu powder, Pd₂(dba)₃ 6 mol%, DMSO, 70 °C, 4 h, 42%; (b) 10% Pd on C (20% by weight), H₂ 1 atm, MeOH, 18 °C, 3 h, 74%.

3.2.4 Selection and Preparation of the Aromatic Coupling Partners.

The aromatic coupling partners used to investigate the scope of the Pd[0]-catalysed Ullmann cross-coupling approach to oxindoles included 2-iodonitrobenzene [**3.21**], 2-bromo-5-methoxy-1-nitrobenzene [**3.78**], 2-bromo-5-methyl-1-nitrobenzene [**3.79**] and 2-iodo-3-methoxy-1-nitrobenzene [**3.80**]. These compounds were considered to provide sufficient structural variation to allow for meaningful exploration of the scope of the cross-coupling reaction.

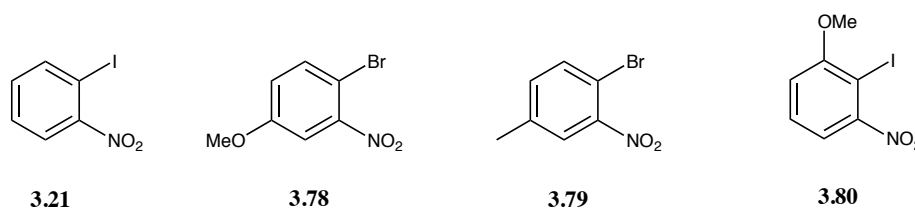
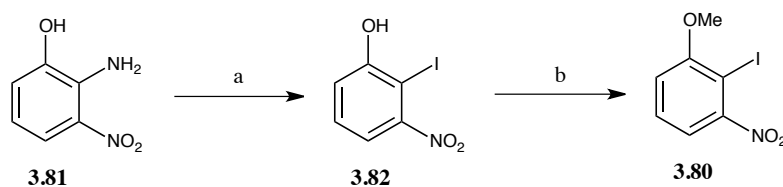


Figure 3.2.2 Aromatic Cross-Coupling Partners.

Compounds **3.21**, **3.78** and **3.79** are commercially available whilst compound **3.80** was prepared by the route shown in Scheme 3.11. Thus, a solution of 2-amino-3-nitrophenol [**3.81**] in DMSO was treated with H₂SO₄ and NaNO₃ followed by KI to give, *via* a Sandmeyer reaction, 2-iodo-3-nitrophenol [**3.82**]. This compound was dissolved in

DMF and the resulting solution was treated with K_2CO_3 followed by MeI so as to generate 2-iodo-3-methoxy-1-nitrobenzene [**3.80**] which was obtained in 62% overall yield (Scheme 3.11).



Scheme 3.11. Reaction conditions: (a) DMSO, conc. H_2SO_4 , $NaNO_3$, $50\text{ }^\circ\text{C}$, 1 h then KI, H_2O , $0\text{ }^\circ\text{C}$ to $18\text{ }^\circ\text{C}$ 1.5 h; (b) DMF, K_2CO_3 , $18\text{ }^\circ\text{C}$, 0.25 h then MeI $18\text{ }^\circ\text{C}$ 5 h, 62% in two steps.

3.2.5 Selection and Preparation of the α -Brominated α,β -Unsaturated Heterocyclic Cross-Coupling Partners.

The above-mentioned α -brominated α,β -unsaturated heterocyclic cross-coupling partners required for the proposed study were also selected in order to investigate the range of substrates that the oxindole forming reaction sequence might tolerate. To such ends, the maleimides **3.83** and **3.84**, the lactones **3.85** and **3.74**, and the lactam **3.86** were identified as coupling partners. The syntheses of these compounds are detailed in the following section.

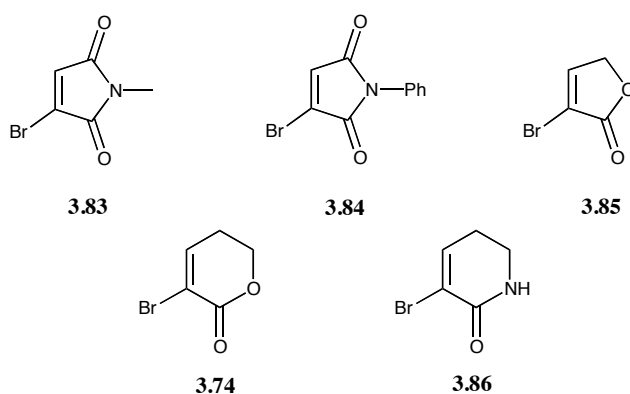


Figure 3.2.3 α -Brominated- α,β -unsaturated Heterocyclic Cross-Coupling Partners.

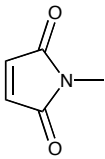
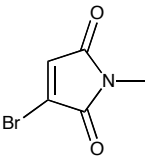
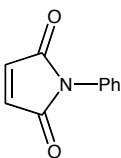
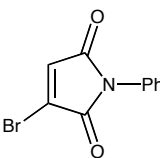
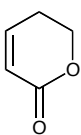
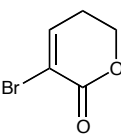
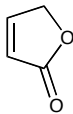
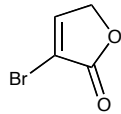
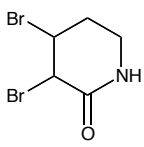
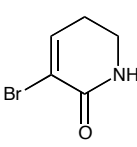
3.2.6 Preparation of the α -Brominated α,β -Unsaturated Heterocyclic Cross-Coupling Partners.

The α -brominated α,β -unsaturated heterocyclic cross-coupling partners were derived from their commercially available, or known and readily accessible unbrominated counterparts (Table 3.4). Thus, the compound 3-bromo-1-methyl-*1H*-pyrrole-2,5-dione⁵³ (3-bromo-1-methylmaleimide) [**3.83**] was synthesised in quantitative yield by treatment of 1-methylmaleimide [**3.87**] with molecular bromine, followed by dehydrohalogenation with triethylamine (Entry 1, Table 3.4). The compound 3-bromo-1-phenyl-*1H*-pyrrole-2,5-dione⁵⁴ (3-bromo-1-phenylmaleimide) [**3.84**] was obtained from the starting material 1-phenylmaleimide [**3.88**] in the same way and in 95% yield (Entry 2, Table 3.4).

The synthesis of 3-bromo-5,6-dihydropyran-2-one [**3.74**] has been described above (see also Entry 3, Table 3.4) and its homologue 3-bromofuran-(5*H*)-one⁵⁵ [**3.85**] was also required. It was expected that this compound could be derived from 2(5*H*)-furanone [**3.89**] *via* a similar bromination and dehydrobromination sequence but several attempts to effect this transformation failed and resulted in the complete degradation of the expensive starting material. Fortunately, as these studies were underway Boukouvalas and co-workers revealed that the key to the successful synthesis of 3-bromofuran-(5*H*)-one [**3.85**] from 2(5*H*)-furanone [**3.89**] *via* a bromination and dehydrohalogenation sequence is the rigorous exclusion of light from the reaction mixture.⁵⁶ By this means the target compound **3.85** was obtained in 73% yield (Entry 4, Table 3.4).

3-Bromo-5,6-dihydropyridin-2(*1H*)-one [**3.86**] was obtained by treatment of a heated solution of 3,3-dibromo-2-piperidinone [**3.90**]⁵⁷ in DMF with calcium carbonate, thereby effecting a dehydrohalogenation reaction and so delivering the target compound **3.86** in 65% yield (Entry 5, Table 3.5). All of the spectral and physical data obtained on this novel compound were in full accord with the assigned structure and are presented in Chapter 5.

Table 3.4 Preparation of α -Brominated α,β -Unsaturated Heterocyclic Substrates Required for Studying the Pd[0]-catalysed Ullmann Cross-coupling Reaction.

Entry	Starting material	Procedure	Product	Yield %
1	 3.87	Method A	 3.83	100
2	 3.88	Method A	 3.84	95
3	 3.73	Method B	 3.74	92
4	 3.89	Method C	 3.85	73
5	 3.90	Method D	 3.86	65

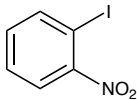
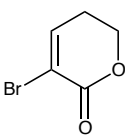
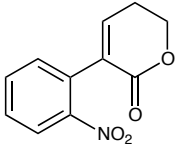
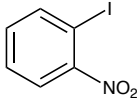
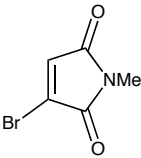
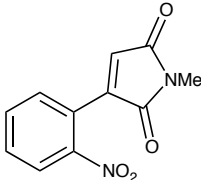
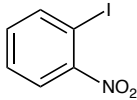
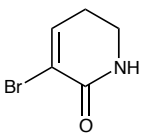
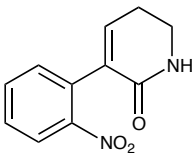
Method A. (i) Et₂O, Br₂, reflux 1 h; (ii) TEA, 0 °C 2 h. **Method B.** (i) CH₂Cl₂, Br₂, 18 °C, 1.5 h; (ii) TEA, 18 °C 0.75 h. **Method C.** (i) Reaction mixture protected from light, Et₂O, Br₂, reflux 4 h; (ii) TEA, 0 – 18 °C 1 h. **Method D.** DMF, CaCO₃, 80 °C, 36 h.

3.3 Optimisation of the Conditions for the Pd[0]-Catalysed Ullmann Cross-Coupling Reaction

3.3.1 Initial Investigations.

The initial investigations into the scope of the Pd[0]-catalysed Ullmann cross-coupling were conducted using reaction conditions adapted from Scheme 3.10 (Page 107). This work began with the cross-coupling of 1-iodo-2-nitrobenzene [**3.21**] with the α -brominated α,β -unsaturated heterocyclic compounds **3.74**, **3.83** and **3.86**. As can be seen in Table 3.5, these heterocyclic substrates engaged in the anticipated reaction with compound **3.21** although only delivering the expected products in modest yields.

Table 3.5 Pd[0]-Catalysed Ullmann Cross-Coupling of 1-Iodo-2-nitrobenzene [**3.21**] with Compounds **3.74**, **3.83**, **3.86** and **3.22** (initial results).

entry	2-nitrohaloarene	brominated heterocycle	cross-coupling product	yield (%)
1				42
	3.21	3.74	3.75	
2				47
	3.21	3.83	3.91	
3				36
	3.21	3.86	3.92	

Reaction conditions: 2.0 equiv of compound **3.21**, 1.0 equiv of brominated heterocycle, 5.0 equiv of 200 mesh Cu bronze powder, Pd₂(dba)₃ 6 mol%, DMSO, 70 °C, 2.0 h.

In all cases the homocoupled by-product **3.25**⁵⁸ was obtained in 50 – 55% yield. The yields of the heterocyclic cross-coupled products were somewhat disappointing and, to ensure that the procedure would provide a useful means of accessing C-3 mono-

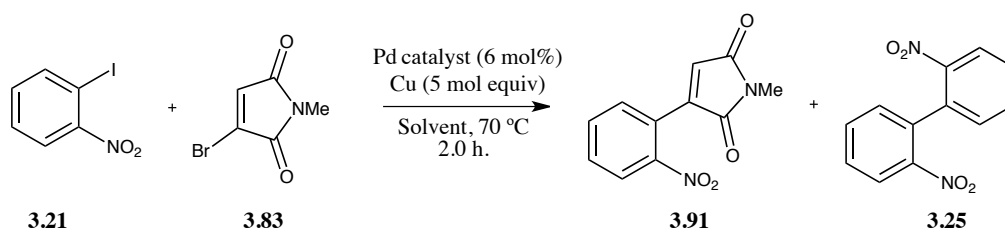
alkylated oxindoles, it was necessary to make improvements. Accordingly, the cross-coupling reaction between 1-iodo-2-nitrobenzene [**3.21**] and 3-bromo-1-methyl-1*H*-pyrrole-2,5-dione [**3.83**] was selected as a model system for further investigation (Entry 2, Table 3.5). Compound **3.21** is commercially available, whilst the brominated heterocycle **3.83** was readily synthesized, in quantitative yield and at the multi-gram scale, from a commercially available starting material (see above). Both of these substrates are stable for long periods when stored in refrigerator. For the purpose of this investigation a standard reaction mixture was employed. Thus, 1 mmol (190.0 mg) of the heterocycle **3.83** and 2 mmol (498.0 mg) of the arene **3.21** were dissolved in a suitable solvent (10.0 ml) and to this was added 5 mmol (318.0 mg) of copper and 6 mol% of palladium catalyst. Reactions were monitored by TLC and were judged to have run to completion when the heterocyclic coupling partner **3.83** was fully consumed.

Various facets of the cross-coupling reaction between compounds **3.83** and **3.21** were investigated including the role of the solvent, the catalyst, reaction temperature and the type of copper used. The outcome of this research is described in the following sections.

3.3.2 Effects of Solvent and catalyst.

Extensive research during the development of the Pd[0]-catalysed Ullmann cross-coupling reaction had established^{20,29} that the most effective solvent was DMSO. It had also been determined that Pd₂(dba)₃ was the most effective of the readily available palladium catalysts. Because of the importance of these factors they were reinvestigated using the substrates **3.21** and **3.83**. Various solvents that are commonly employed for Ullmann reactions including DMSO, DMF, NMP and nitrobenzene were tested under standard conditions. In keeping with the earlier research, the most effective solvent did indeed prove to be DMSO. In a similar manner, several palladium catalysts that are commonly employed for cross-coupling reactions were tested including Pd₂(dba)₃, Pd(PPh₃)₄, PdCl₂(PPh₃)₂, PdCl₂(dppf) and Pd(OAc)₂. Once again, the results of these experiments were consistent with earlier research.^{20,29} Thus, while the precise choice of the palladium catalyst was found to have relatively little effect on the outcome of the reaction, it was apparent that Pd₂(dba)₃ was the most effective.

Table 3.6: *The Effect of Various Solvents and Palladium Catalysts on the Pd[0]-Catalysed Ullmann Cross-Coupling of Substrates 3.21 and 3.83.*



Entry	Catalyst	Solvent	% Yield 3.91 ^a	% Yield 3.25 ^b
1	Pd ₂ (dba) ₃	nitrobenzene	0	32
2	Pd ₂ (dba) ₃	DMF	34	43
3	Pd ₂ (dba) ₃	NMP	38	46
4	Pd ₂ (dba) ₃	DMSO	47	55
5	Pd(PPh ₃) ₄	DMSO	41	57
6	PdCl ₂ (PPh ₃) ₂	DMSO	44	54
7	PdCl ₂ (dppf)	DMSO	44	56
8	Pd(OAc) ₂	DMSO	43	57

Reaction conditions: 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.83**, 5.0 equiv of -200 mesh Cu bronze powder, Pd catalyst 6 mol%, 70 °C, 2.0 h. ^aWith respect to compound **3.83**. ^bWith respect to compound **3.21**.

No improvement in the cross-coupling reaction between compounds **3.21** and **3.83** was achieved by changing the solvent or catalyst. Nevertheless, it was found that the loading of Pd₂(dba)₃ catalyst could be lowered to 5 mol% without adversely affecting the yield of target **3.91** (46%) and without the need to extend the reaction time (2 h). At a catalyst loading of 4 mol% the yield of compound **3.91** was slightly less (42%) but the reaction took nearly 4 h to run to completion. At a catalyst loading of 3 mol% the yield of compound **3.91** was significantly lower (28%) despite a reaction time of 12 h.

3.3.3 Temperature Effects.

*“Dans les champs de l'observation le hasard ne favorise que les esprits prepares.”*⁵⁹

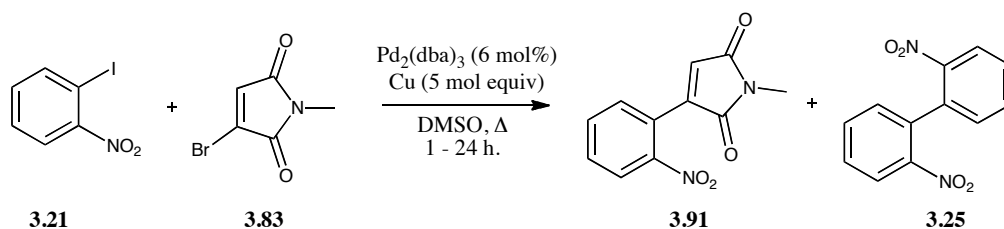
(In the fields of observation, chance favours only the prepared mind.)

Louis Pasteur, Inaugural Lecture, University of Lille, 1854.

Experimentalists know only too well that science is not entirely the product of rational and step-wise progress. Intangible factors, such as intuition, chance and accident play a significant role.⁶⁰ So it was, that the first clue to improving the Pd[0]-catalysed Ullmann cross-coupling reaction came by chance. A flask, charged with a ‘standard’ reaction mixture was inadvertently left unstirred for almost four days at approximately 35 °C. When the flask was rediscovered the reaction mixture was checked by TLC and it was apparent that the cross-coupling reaction had proceeded quite well, despite the unusual conditions. The reaction products were isolated and the yield of the cross-coupled compound, **3.91**, was found to be 51%. This was the best yield of compound **3.91** that had been obtained at that time. The yield of the homocoupled by-product **3.25** was 45%, which was lower than the typical yield observed for this compound (approximately 55%).

These chance observations prompted a systematic investigation into the effect of temperature on the Pd[0]-catalysed Ullmann cross-coupling of substrates **3.21** and **3.83**. This revealed that the yield of the homocoupled by-product **3.25** is strongly temperature dependant (Table 3.7). The use of higher temperatures resulted in higher yields of the by-product whereas the use of lower temperatures significantly diminished the yield of the material. Thus, at 20 °C the yield of compound **3.25** was just 20%, but at 90 °C it was 73%. On the other hand, the yield of the cross-coupled product **3.91** was not greatly affected by temperature within the range of 20 °C – 80 °C (the lower yield of the product **3.91** at 90 °C was due to degradation of the hetrocyclic starting material **3.83** at this temperature).

Table 3.7 *The Effect of Temperature on the Pd[0]-Catalysed Ullmann Cross-Coupling of Substrates 3.21 and 3.83.*



Entry	Temp °C	Time h	% Yield 3.91 ^a	% Yield 3.25 ^b
1	20	24.0	43	20
2	30	12.0	46	26
3	40	6.0	48	36
4	50	4.0	49	42
5	60	3.0	46	48
6	70	2.0	46	56
7	80	1.5	44	63
8	90	1.0	38	73

Reaction conditions: 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.83**, 5.0 equiv of -200 mesh Cu bronze powder, $\text{Pd}_2(\text{dba})_3$ 5 mol%, DMSO, 20 – 90 °C, 1 – 24 h. ^aWith respect to compound **3.83**. ^bWith respect to compound **3.21**.

The practical consequence of these observations was that in subsequent experiments a reaction temperature in the range of 40 – 50 °C was employed. Reaction temperatures in this range represent a sensible compromise between suppression of the homocoupling side-reaction and the need to conduct each reaction in a timely fashion. Importantly, when lower reaction temperatures were employed it was possible to use less than 2 molar equivalents of the aryl coupling partner because less of it was diverted into the homocoupling side-reaction. This represented a useful improvement in the overall atom-efficiency of the process, although it did not address the need to improve the yields of the cross-coupled products.

3.3.4 The Impact of Different Types of Copper.

The Pd[0]-catalysed Ullmann cross-coupling reaction is always accompanied by a certain amount of homocoupling of the aryl species due to the Ullmann reaction, which takes place concurrently. The formation of aryl-copper intermediates in this reaction

takes place at the surface of the copper metal (Schemes 3.3 & 3.5) and it is well-established that yields of the biaryl product are increased by the use of finely divided copper powder due to the very high surface area of such powders.⁸ The use of finely divided copper powder is especially effective if the powder is subjected to surface activation immediately prior to its addition to the reaction mixture.⁹

Experimental evidence from earlier research pointed towards the oxidative addition of the palladium complex to the non-aromatic substrate as the rate-limiting step in the Pd[0]-catalysed Ullmann cross-coupling.^{20,29} Therefore, it seemed possible that the use of copper with a relatively low surface area, combined with a lower reaction temperature (50 °C), might further suppress the homocoupling side-reaction (Ullmann biaryl synthesis) without having a detrimental effect on the cross-coupling pathway. Accordingly, a reaction was conducted at 50 °C and employing 5 molar equivalents of high purity copper foil (20 mm × 3 mm × 0.10 mm) instead of copper bronze powder. As can be seen in Table 3.8 (page 118), the substitution of copper foil in place of copper bronze powder had a negligible effect on the yield of either the cross-coupled product **3.93** or the homocoupled by-product **3.25** (Entry 2, Table 3.8). Following this somewhat surprising result the experiment was repeated, but on this occasion very fine 6 µm copper powder was employed. This experiment delivered a distinct improvement in yield of the cross-coupled product **3.93** (58%) whilst having little effect on the yield of homocoupled by-product **3.25** (45%) (Entry 3, Table 3.8).

With these interesting results to hand, a quantity of 3 µm dendritic copper dust was obtained. A sample of the minute particles of this dust were examined using a microscope and it was apparent that they were highly irregular in shape. Measurements of their size on a graticule established that they were in the range of 0.5 – 3 µm across the widest section. By contrast, the particles of 200-mesh copper bronze powder used in the standard process were found to be in the range of 50 – 70 µm across the widest section and were more uniformly shaped. Consequently, the 3 µm dendritic copper dust possesses a much larger surface area for a given mass of material than copper foil or copper bronze powder.⁶¹ A reaction conducted with 3 µm dendritic copper dust delivered the cross-coupled product in 69% yield. This represented a dramatic improvement in yield over the 48% obtained by using conventional copper bronze. The reaction was accompanied by a small increase in the yield of the by-product **3.25** (Entry 4). These

results suggested that activation of the copper dust might further improve the yield of the cross-coupled product.

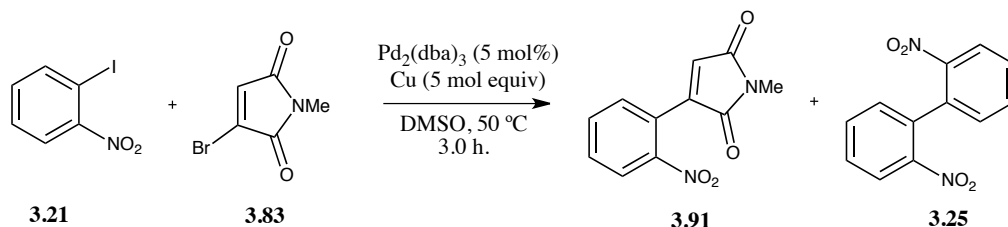
There are numerous methods available for the activation of copper powder and many of these have been exploited in the Ullmann biaryl synthesis.^{62,63} A simple and effective procedure for activating copper powder prior to its use in the Ullmann reaction involves washing the powder with aqueous EDTA solution.⁸ The procedure detailed below is adapted from this method and employs ultrasonication to further enhance the activation process.⁶⁴ Thus, 3 μm dendritic copper dust was subjected to ultrasonication for 20 min in EDTA (0.02 M aqueous solution). The supernatant fluid was decanted and the process was repeated twice more. The activated copper dust was rinsed successively with de-ionised water then methanol, ethanol and acetone. It was dried at low pressure (room temperature) on a rotary evaporator and then held under an atmosphere of N_2 or Ar gas. The activated copper so obtained possesses a pale salmon-pink colour and it was used promptly with minimal exposure to air. When this activated 3 μm dendritic copper dust was employed with the ‘standard reaction mixture’ the yield of the cross-coupled product **3.93** was increased to 77%, whilst the yield of the homocoupled by-product **3.25** was 52% (entry 4).^b

Careful observation of the reaction mixture revealed that the pale-pink colour that is characteristic of freshly activated copper dust was soon lost and the copper turned a dull grey-brown. This is probably due to contamination of the surface of the copper particles by a build-up of copper-halide salts and, perhaps, by deposition of palladium metal. Thus, in order to maintain a continuous supply of fresh uncontaminated copper in the reaction mixture, the activated 3 μm dendritic copper dust was slowly added over 1.5 hours. This was achieved by holding the activated copper and a measured quantity of DMSO under an inert atmosphere in a vessel equipped with a rubber septum. At appropriate intervals the vessel was vigorously shaken and an aliquot of the resulting suspension, equating to 1 molar equivalent of copper, was withdrawn and injected into the reaction mixture. In this way, 5 molar equivalents of activated 3 μm dendritic copper dust were added in 5 aliquots over 1.5 h. The reaction mixture was then heated for an additional 1.5 h (3 h in total). Under such conditions the yield of the product **3.91**

^b Activation of copper dust with dilute hydrochloric acid and dilute phosphoric acid was also tested. These dilute acids proved to be inferior to dilute EDTA solution for activating the metal. See Chapter 4 for details.

obtained by this process was 84%, whilst the yield of the homocoupled by-product **3.25** was 56% (Entry 6, Table 3.8).

Table 3.8 The Effect of Different Types of Copper on the Pd[0]-Catalysed Ullmann Cross-Coupling of Substrates **3.21** and **3.83**.



Entry	Copper type ^a	% Yield 3.91 ^b	% Yield 3.25 ^c
1	Copper bronze ^d	49	42
2	Copper foil	47	40
3	6µm Cu dust	58	45
4	3µm Cu dust	69	47
5	3µm Cu* dust	77	52
6	Slow addition 3µm Cu* dust ^e	84	56

^aCu* = activated copper. Reaction conditions (Entries 1 – 5): 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.83**, 5.0 equiv of Cu, $\text{Pd}_2(\text{dba})_3$ 5 mol%, DMSO, 50 °C, 3.0 h. ^bWith respect to compound **3.83**.

^cWith respect to compound **3.21**. ^d-200 mesh copper bronze powder ^eReaction conditions (Entry 6): As for entries 1 -5, but involving the addition of five × 1.0 ml aliquots of a suspension of the activated copper dust (Cu*) in DMSO (1.0 mmol Cu* per 1 ml DMSO) over 1.5 h.

Investigations into the effect of different loadings of copper revealed that the yield of the cross-coupled product **3.91** was not increased by the addition of more than 5 equivalents of activated 3 µm copper dust. For instance, the slow addition of 7.5 equivalents of activated 3 µm copper dust afforded compound **3.91** in 82% yield vs the 84% obtained earlier. In fact, the use of excessively high loadings of copper led to the formation of troublesome emulsions during the work-up process. On the other hand, the use of approximately 4.5 equivalents of copper dust was found to be the minimum that could be employed without loss of yield of the cross-coupled product. The requirement for a stoichiometric excess of copper dust is undoubtedly due to the contamination of the surface of the copper metal that occurs as the reaction progresses.⁶⁵ This contamination

builds up on the minute particles of copper to the extent that they become unreactive before they are fully consumed.⁶⁶

The high yield of cross-coupled product obtained by the slow addition of activated 3 μm dendritic copper dust addressed the requirement for improvement of the Pd[0]-catalysed Ullmann cross-coupling reaction. Accordingly, attention was turned, once again, to the synthesis of a variety of 2-nitroarylated heterocycles as potential precursors to the targeted oxindoles.

3.4 Synthesis of 2-Nitroarylated Heterocyclic Compounds (Precursors to Oxindoles) Using the Pd[0]-catalysed Ullmann Cross-Coupling Reaction.

The optimised conditions, defined above, for effecting the Pd[0]-catalysed Ullmann cross-coupling of 1-iodo-2-nitrobenzene [3.21] with 3-bromo-1-methyl-maleimide [3.83] to afford the *o*-nitroarylated heterocyclic product 1-methyl-3-(2-nitrophenyl)-1*H*-pyrrole-2,5-dione [3.93] were adapted to the synthesis of a variety of *o*-nitroarylated heterocyclic compounds. Thus, the expected, but previously unreported, products 3.75 and 3.91 – 3.97 were obtained by such means in good to excellent yield (Table 3.9). It is noteworthy that the optimised procedure delivered greatly improved yields of compounds 3.75, 3.91 and 3.92 when compared with the original (standard) procedure.

The spectral data obtained on each of these compounds were entirely consistent with the assigned structures. For instance, the ^{13}C NMR spectrum of compound 3.91 (Figure 3.4.1) displayed eleven signals including eight in the range δ 124 to 149 and corresponding to the sp^2 -hybridised carbons within the structure. Two signals were observed at δ 170.0 and 168.8 and these were assigned to the non-equivalent carbonyl carbons of the maleimide moiety. The resonance due to the *N*-methyl carbon appeared at δ 24.3. The ^1H NMR data were also consistent with the proposed structure 3.91. Furthermore, the EI mass spectrum displayed a molecular ion at m/z 232 (18%) and a fragment ion at m/z 186 (37%) corresponding to the loss of the nitro group ($\text{M}-\text{NO}_2$)⁺. An accurate mass measurement on the molecular ion confirmed that it was of the expected composition, viz. $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_4$.

Table 3.9: *Pd[0]-Catalysed Ullmann Cross-Coupling of o-Halonitroarenes with Brominated Heterocycles to Form o-Nitroarylated Heterocycles.*

Entry	2-Nitrohaloarene	Brominated heterocycle	Cross-coupling product	Yield (%) improved procedure	Yield (%) std procedure
1				84	47
2				82	
3				89	
4				78	42
5				77	
6				61	36
7				73	
8				61	

Reaction conditions: 2.0 equiv. of 2-halonitroarene, 1.0 equiv of brominated heterocycle, Pd₂(dba)₃ 5 mol%, slow addition of 5.0 equiv. activated 3 μm copper dust (3 μm Cu*) in DMSO over 1.5 h, 50 °C, 3.0 h.

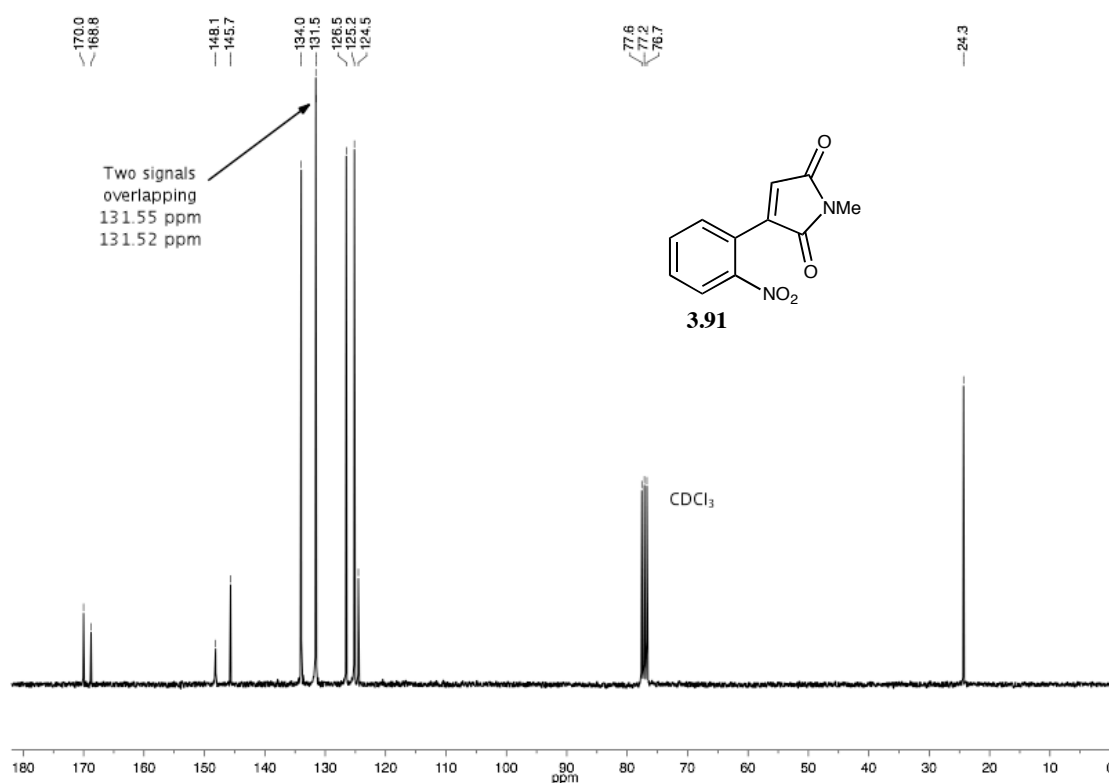
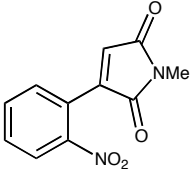
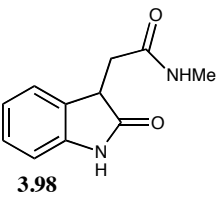
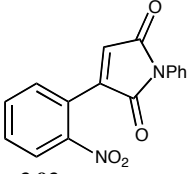
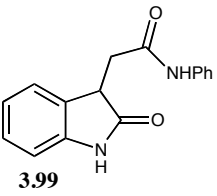
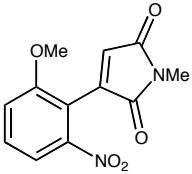
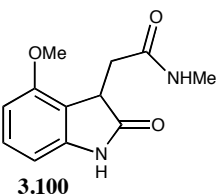
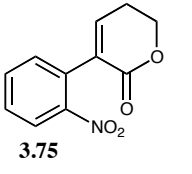
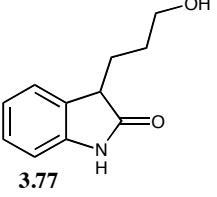
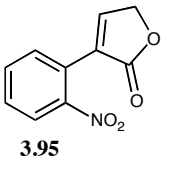
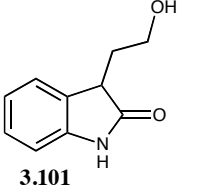
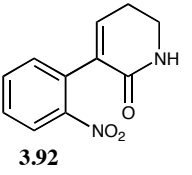
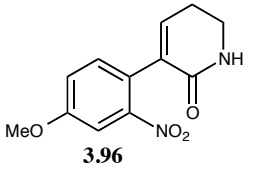
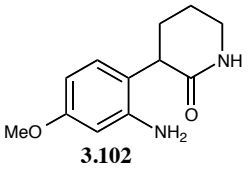
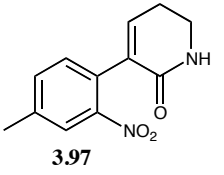
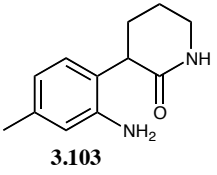


Figure 3.4.1 75 MHz ^{13}C NMR Spectrum of Compound **3.91** (Recorded in CDCl_3)

3.5 The Reductive Cyclisation Reaction. Formation of C-3 Mono-Alkylated Oxindoles.

With the requisite cross-coupling products to hand, an investigation of their capacities to engage in the desired reductive cyclization processes was undertaken. The outcomes of the relevant studies are shown in Table 3.10. Entries 1–5 reveal that upon exposure of a methanolic solution of each of the relevant cross-coupling products to an atmosphere of dihydrogen in the presence of 10% Pd on C (20% w/w) the anticipated conversions take place to afford the 3-substituted oxindoles **3.98** – **3.101** and **3.77** in good to excellent yields. The spectral data obtained on each of these oxindoles were fully consistent with the assigned structures. Compounds **3.99**,⁶⁷ **3.101**⁶⁸ and **3.77**⁶⁹ have been reported previously and where comparisons were possible the two sets of spectral data proved to be good matches. For instance, Table 3.11 presents a comparison of the spectral data obtained for compound **3.77** with the data reported by Hino and co-workers for 3-(2-hydroxypropyl)inolin-2-one. Clearly the two sets of data are in good agreement and it may be inferred that the compounds are one and the same.

Table 3.10: Catalytic Hydrogenation of Heterocycles **3.91- 3.97** and **3.75**.

Entry	Cross-coupling product	Oxindole	Yield (%)
1	 3.91	 3.98	87
2	 3.93	 3.99	99
3	 3.94	 3.100	77
4	 3.75	 3.77	74
5	 3.95	 3.101	96
6	 3.92	Complex mixture	
7	 3.96	 3.102	97
8	 3.97	 3.103	84

Reaction conditions: 10% Pd on C (20% by weight), H₂ 1 atm, MeOH, 18 °C, 3 h.

Table 3.11: Comparison of Various Spectral Data Obtained for Compound **3.77** With Those Reported for 3-(2-Hydroxypropyl)inolin-2-one.⁶⁹

3.77	3-(2-hydroxypropyl)inolin-2-one ⁶⁹
¹ H: NMR (δ_{H} in CDCl ₃ , 300 MHz)	¹ H: NMR (δ_{H} in CDCl ₃ , 100 MHz)
8.69 (broad s, 1H, NH)	9.2 (broad s, 1H, NH)
7.28 – 7.14 (m, 2H)	7.26 – 6.80 (m, 4H)
7.03 (t, $J = 7.8$ Hz, 1H)	
6.89 (d, $J = 7.8$ Hz, 1H)	
3.68 – 3.58 (m, 2H)	3.62 (t, 2H)
3.54 – 3.46 (m, 1H)	3.50 (t, 1H)
2.16 – 1.96 (m, 2H)	2.20 – 1.90 (m, 2H)
1.96 – 1.74 (broad s, 1H, OH)	2.68 (broad s, 1H, OH)
1.70 – 1.50 (m, 2H)	1.80 – 1.40 (m, 2H)
IR: (KBr, ν_{max} , cm ⁻¹)	IR: (KBr, cm ⁻¹)
3233 (NH, OH)	3420 – 3175 (NH, OH)
1701 (C=O)	1715 – 1685 (C=O)
MS: (EI, 70 eV, m/z _i)	MS: (EI, 70 eV, m/z _i)
191 (M ⁺ , 64%)	191 (M ⁺ , 65%)
173 (66%)	173 (55%)
146 (100%)	146 (100%)
145 (83%)	145 (90)
Melting point °C	Melting point °C
99 - 101	105.0 – 105.5

Note: the data listed in Table 3.11 for compound **3.77** is restricted to the range that may be directly compared with the range data reported by Hino for 3-(2-hydroxypropyl)inolin-2-one.⁶⁹ Consequently, ¹³C NMR spectral data for compound **3.77** are not included in this Table but may be found in Chapter 5, Section 5.3.5 .

The cross-coupled compounds **3.92**, **3.96** and **3.97** incorporate a dihydropyridinone moiety that is derived from the heterocyclic coupling partner 3-bromo-5,6-dihydropyridin-2(1*H*)-one **3.86**. It is apparent from Table 3.10 that subjection of these cross-coupled compounds to catalytic hydrogenation did not result in synthesis of the expected oxindoles. Rather, catalytic hydrogenation of the 2-nitroarylated heterocycle **3.92**, for example, resulted in a complex mixture of products consisting, for the most part, of tarry residues (Entry 6). On the other hand, Entries 7 and 8 of Table 3.10 reveal situations in which only the direct reduction products **3.102** and **3.103** were formed. In these cases, the ^{13}C NMR spectra displayed lactam carbonyl signals, at δ 173.8 (Figure 3.4.2) and 173.7 respectively, which indicated that the *trans*-acylation process required for oxindole formation had not taken place. Confirmation of this followed from a single-crystal X-ray analysis of compound **3.102** (See Appendix Five for details)

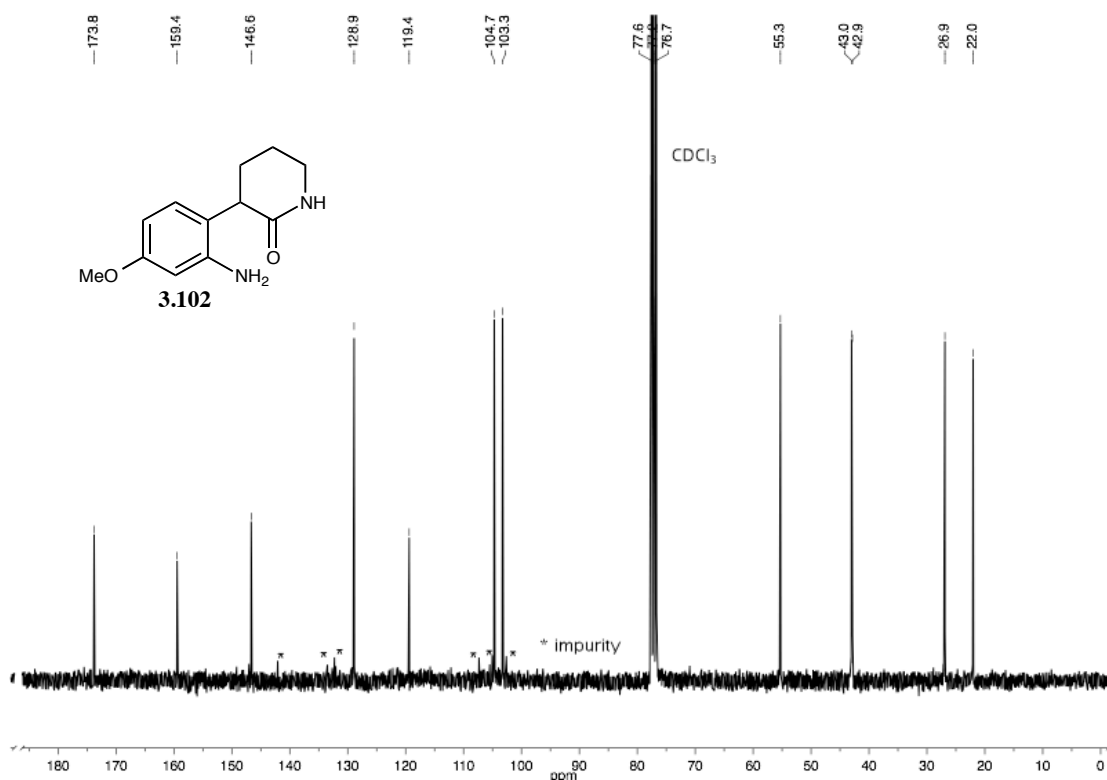
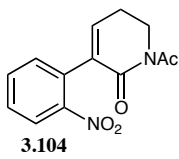
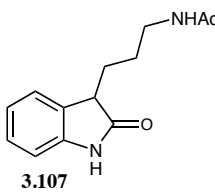
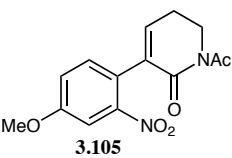
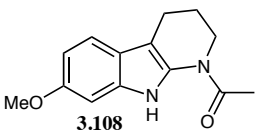
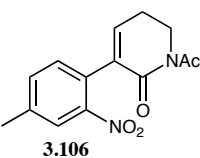
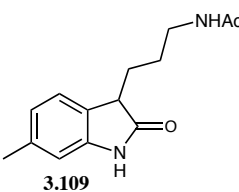


Figure 3.4.2 75 MHz ^{13}C NMR Spectrum of Compound **3.102** (Recorded in CDCl_3)

In order for the *trans*-acylation process to proceed (Scheme 3.9, page 106) it is essential that a sufficiently stable leaving group be formed by cleavage of the bond between the heteroatom and the carbonyl carbon of the heterocyclic moiety. The leaving group that would result from cleavage of the relevant bond of the dihydropyridinone moiety of reduction products **3.102** and **3.103** is the anion of an alkylamine, which is a rather poor leaving group.⁷⁰ It is likely that this factor accounts for the failure of compounds **3.102** and **3.103** to engage in the *trans*-acylation reaction. Moreover, the complex mixture that resulted from the catalytic hydrogenation of substrate **3.92** (Entry 6, Table 3.10) suggests that, in this case, polymerization of a reduction product had occurred instead of *trans*-acylation. It was anticipated, therefore, that in order to promote the *trans*-acylation reaction, the compounds **3.92**, **3.96** and **3.97** should first be converted into their *N*-acyl derivatives. The resulting imides would then be subjected to catalytic hydrogenation to afford the corresponding *N*-acyl substituted direct-reduction compounds as intermediates. During the ensuing *trans*-acylation reaction the leaving group would be the anion of an alkylamide. This represents a better leaving group than the anion of the corresponding alkylamine due to the capacity for delocalization of the negative charge in the former case.

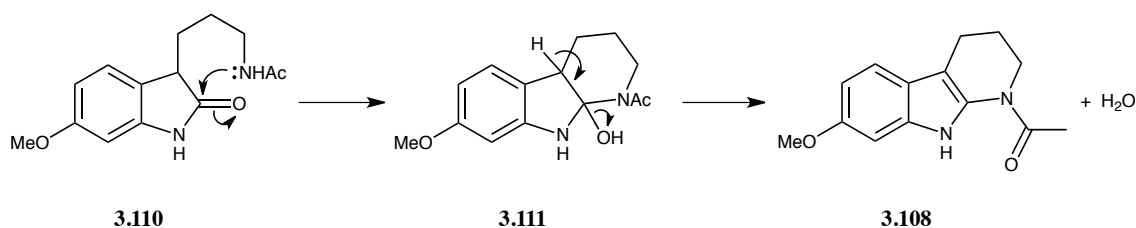
On the basis of the foregoing analysis, compounds **3.92**, **3.96** and **3.97** were converted, in high yields *via* a procedure described by Minami and co-workers,⁷¹ into their respective *N*-acyl derivatives. The resulting imides, namely compounds **3.104**, **3.105** and **3.106**, were then subjected to the standard reductive cyclisation conditions (Table 3.12). The first and third of these substrates gave the anticipated oxindoles **3.107** and **3.109**, respectively, in good yield. The spectral data derived from these were fully consistent with the assigned structures. Furthermore, the structure of product **3.107** was confirmed by single-crystal X-ray analysis (See Appendix Six for details).

Table 3.12: Outcomes of the Catalytic Hydrogenation of Imides **3.104** - **3.106**.

Entry	N-acyl compound	Oxindole	Yield (%)
1	 3.104	 3.107	72
2	 3.105	 3.108	93
3	 3.106	 3.109	60

Reaction conditions: 10% Pd on C (20% by weight), H₂ 1 atm, MeOH, 18 °C, 3 h.

The reductive cyclization of compound **3.105** afforded the annulated indole **3.108** in 93% yield (Entry 2, Table 3.12). This rather unstable product, the structure of which was also confirmed by single-crystal X-ray analysis (Figure 3.4.3 and Appendix Seven), presumably arises through cyclodehydration of the initially formed oxindole **3.110** (Scheme 3.12)



Scheme 3.12 Spontaneous Cyclodehydration of the Oxindole **3.110** Affords the Annulated Indole **3.108**

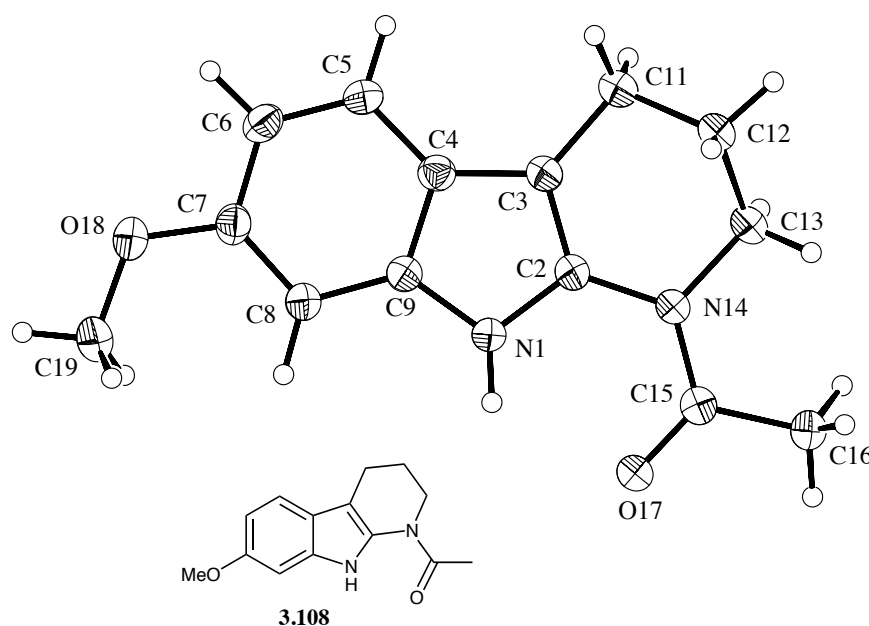


Figure 3.4.3 ORTEP Derived from Single-Crystal X-ray Analysis of Compound **3.108** with Labelling of Selected Atoms (Thermal Ellipsoids are Drawn at the 50% Probability Level).

3.6 Conclusions

A new method for the synthesis of C-3 mono-alkylated oxindoles has been developed.⁷² This involves the Pd[0]-catalyzed Ullmann cross-coupling of 2-nitrohaloarenes with various α -brominated α,β -unsaturated cycloimides, lactams or lactones followed by reductive cyclization of the coupling products. The cross-coupling process can be conducted in the presence of a useful range of functionalities and the reductive cyclization process proceeds smoothly provided that the *trans*-acylation step **3.71** $\rightarrow$ **3.72** involves a substrate possessing an imide- or lactone-containing side-chain. In keeping with expectations, when substrates incorporating a lactam-containing side-chain are involved then the conversion **3.71** $\rightarrow$ **3.72** fails to take place. The protocols described above offer various possibilities for assembling more complex oxindoles including natural products containing this motif. Work is now underway in the Banwell laboratories to exploit such possibilities.

3.7 References.

- 1 Horton, D.; Bourne, G.; Smythe, M. *Chem. Rev.*, **2003**, *103*, 893.
- 2 Türker, L.; Tapan, A.; Selcuk, G. *Polycyclic Aromatic Compounds*, **2009**, *3*, 123.
- 3 (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.*, **2002**, *102*, 1359; (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.*, **2008**, *108*, 3054; (c) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.*, **2009**, *48*, 6954.
- 4 Ullmann, F.; Bielecki, J. *Chem. Ber.*, **1901**, *34*, 2174.
- 5 Ullmann, F. *Ann.*, **1904**, *332*, 38.
- 6 Nelson, T.; Crouch, R. *Org. React.*, **2004**, *63*, 265.
- 7 Kornblum, N.; Kendall, D. *J. Am. Chem. Soc.*, **1952**, *74*, 5782.
- 8 Lewin, A.; Zovko, M.; Rosewater, W.; Cohen, T. *Chem. Comm.*, **1967**, *2*, 80.
- 9 Rieke, R.; Rhyne, L. *J. Org. Chem.*, **1979**, *44*, 3445.
- 10 Lindey, J.; Mason, T. *Ultrasonics*, **1986**, *24*, 292.
- 11 Bacon, R.; Pande, S. *J. Chem. Soc. C.*, **1970**, 1967.
- 12 Semmelhack, M.; Helquist, P.; Jones, L. *J. Am. Chem. Soc.*, **1971**, *93*, 5908.
- 13 Ziegler, F.; Fowler, K.; Kanfer, S. *J. Am. Chem. Soc.*, **1976**, *98*, 8282.
- 14 Nilsson, M.; Wennerström, O. *Tetrahedron Lett.*, **1968**, 3307.
- 15 Douglass, S.; Massey, S.; Woolard, S.; Zoellner, R. *Transition Met. Chem.*, **1990**, *15*, 317 and references therein.
- 16 Lewin, A.; Cohen, T. *Tetrahedron Lett.*, **1965**, 4531.
- 17 Shimizu, N.; Kitamura, T.; Watanabe, K.; Yamaguchi, T.; Shigyo, H.; Ohta, T. *Tetrahedron Lett.*, **1993**, *34*, 3421.
- 18 Banwell, M. G.; Smith, J. A. *Org. Biomol. Chem.*, **2003**, *1*, 296
- 19 Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2002**, *124*, 15168.
- 20 Banwell, M.; Kelly, B.; Kokas, O.; Lupton, D. *Org. Lett.*, **2003**, *5*, 2497.
- 21 Banwell, M.; Lupton, D.; Willis, A. *Aust. J. Chem.*, **2005**, *10*, 722.

- 22 Banwell, M.; Jones, M.; Reekie, T. *Chemistry in New Zealand*, **2011**, 75, 122.
- 23 (a) Balasubramanian, M.; Keay, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 245; (b) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.*, **2001**, 3, 1109; (c) Michael, J. P. *Nat. Prod. Rep.*, **2002**, 19, 742.
- 24 Jones, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds.; Pergamon Press: Oxford, **1996**; Vol. 2, pp 395-510.
- 25 For recent examples of the Friedländer approach to quinolines see: (a) Hsiao, Y.; Hughes, D.; Reider, P. *Org. Lett.*, **2001**, 3, 1101; (b) Arcardi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett.*, **2003**, 203; (c) Palmikar, S.; Siddiqui, S.; Daniel, T.; Lahoti, R.; Srinivasan, K. *J. Org. Chem.*, **2003**, 68, 9371; (d) McNaughton, B.; Miller, B.; *Org. Lett.*, **2003**, 5, 4257; (e) Dormer, P.; Eng, K.; Farr, R.; Humphrey, G.; Reider, P.; Sager, J.; Volante, R. *J. Org. Chem.*, **2003**, 68, 467.
- 26 For recently developed methods for the synthesis of quinolines (other than ones involving a Friedländer approach) see: (a) Pouységu, L.; Avellan, A.; Quideau, S. *J. Org. Chem.*, **2002**, 67, 3425; (b) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.*, **2003**, 5, 1455; (c) Mehta, B.; Yanagisawa, K.; Shiro, M.; Kotsuki, H.; *Org. Lett.*, **2003**, 5, 1605; (d) Du, W.; Curran, D.; *Org. Lett.*, **2003**, 5, 1765.
- 27 (a) Friedländer, P. *Ber.*, **1882**, 15, 2572; (b) Friedländer, P.; Gohring, *Chem. Ber.* **1883**, 16, 1833.
- 28 Cheng, C. C.; Yan, S. J. *Org. React.*, **1982**, 28, 37.
- 29 Banwell, M.; Lupton, D.; Ma, X.; Renner, J.; Sydnes, M.; *Org. Lett.*, **2004**, 6, 2741.
- 30 (a) Lilienkampf, A.; Johansson, M.; Wahala, K.; *Org. Lett.*, **2003**, 5, 3387 and references therein; (b) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.*, **1961**, 26, 3059; (c) Robertson, I.; Sharp, J. *Tetrahedron*, **1984**, 40, 3095.
- 31 Curran, D.; Kuo, S. *J. Org. Chem.*, **1984**, 49, 2063.
- 32 Banwell, M.; Cowden, C. *Aust. J. Chem.*, **1994**, 47, 2235.

- 33 For reviews see: (a) van den Hoogenband, A.; Lange, J. H. M.; Iwema-Bakker, W. I.; den Hartog, J. A. J.; van Schaik, J.; Feenstra, R. W.; Terpstra, J. W. *Tetrahedron Lett.*, **2006**, 47, 4361 and references cited therein; (b) Cerchiaro, G.; da Costa Ferreira, A. *J. Braz. Chem. Soc.*, **2006**, 17, 1473; (c) Peddibhotla, S. *Curr. Bioact. Compd.*, **2009**, 5, 20; (d) Rudrangi, S.; Bontha, V.; Manda, V.; Bethi, S. *Asian J. Chem. Res.*, **2011**, 4, 335.
- 34 See, for example: Roskoski Jr., R. *Biochem. Biophys. Res. Commun.*, **2007**, 356, 323.
- 35 (a) Kikuchi, C.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.*, **2002**, 12, 2549; (b) Mokrosz, M. J.; Duszyńska, B.; Misztal, S.; Kłodzińska, A.; Tatarczyńska, E.; Chojnacka-Wójcik, E.; Dziedzicka-Wasylewska, M. *Arch. Pharm. Pharm. Med. Chem.*, **1998**, 331, 325.
- 36 Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.*, **2001**, 44, 4641.
- 37 Gallagher Jr., G.; Lavanchy, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.*, **1985**, 28, 1533.
- 38 Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.*, **1995**, 47, 241.
- 39 Zaveri, N. T.; Jiang, F.; Olsen, C. M.; Deschamps, J. R.; Parrish, D.; Polgar, W.; Toll, L. *J. Med. Chem.*, **2004**, 47, 2973.
- 40 Alcaraz, M.-L.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowan, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.*, **2005**, 9, 555.
- 41 Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.*, **2008**, 130, 2087 and references therein.
- 42 For reviews on 3,3-spirooxindole natural products see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.*, **2003**, 2209; (b) Williams, R. M.; Cox, R. J. *Acc. Chem.*

- Res.*, **2003**, 36, 127; (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.*, **2007**, 46, 8748.
- 43 Trost, B. M.; Brennan, M. K. *Org. Lett.*, **2006**, 8, 2027 and references therein.
- 44 Chang, M.-Y.; Pai, C.-L.; Kung, Y.-H. *Tetrahedron Lett.*, **2005**, 46, 8463 and references therein.
- 45 Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.*, **2004**, 6, 711 and references therein.
- 46 Lin, H.; Danishefsky, S. J. *Angew. Chem. Int. Ed.*, **2003**, 42, 36 and references therein.
- 47 Kogure, N.; Ishii, N.; Kitajima, M.; Wongseripipatana, S.; Takayama, H. *Org. Lett.*, **2006**, 8, 3085 and references therein.
- 48 Trost, B. M.; Stiles, D. T. *Org. Lett.*, **2007**, 9, 2763 and references therein.
- 49 See, for example: (a) Wenkert, E.; Bernstein, B. S.; Udelhofen, J. H. *J. Am. Chem. Soc.*, **1958**, 80, 4899; (b) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginiwa, J.; *Tetrahedron*, **1973**, 29, 2015; (c) Kubo, A.; Nakai, T. *Synthesis*, **1980**, 365; (d) Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.*, **1983**, 24, 2437.
- 50 (a) Sundberg, R. J. *Indoles*, Academic Press: London, **1996**; (b) Porcs-Makkay, M.; Volk, B.; Kapiller-Dezsöfi, R.; Mezei, T.; Simig, G. *Monatsh. Chem.*, **2004**, 135, 697; (c) Russel, J. S.; Pelkey, E. T. In *Progress in Heterocyclic Chemistry Volume 20*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: London, **2009**; p 144 and earlier reviews in the series.
- 51 See, for example: (a) Volk, B.; Simig, G. *Eur. J. Org. Chem.*, **2003**, 3991; (b) Liu, K. G.; Robichaud, A. J. *Tetrahedron Lett.*, **2007**, 48, 461; (c) Krishnan, S.; Stoltz, B. M. *Tetrahedron Lett.*, **2007**, 48, 7571.
- 52 Posner, G.; Afarinkia, K.; Dai, H. *Org. Synth.*, **1996**, 73, 231.
- 53 (a) Monneret, C.; Dauzonne, D.; Hickman, J.; Pierre, A.; Kraus, B. L.; Pfeiffer, B.; Renard, P. *Chem. Abstr.*, **2005**, 142, 261336; (b) Burgess, K.; Lajkiewicz, N.; Sanyal, A.; Yan, W.; Snyder, J. *Org. Lett.*, **2005**, 7, 31.

- 54 Choi, D.; Huang, S.; Huang, M.; Barnard, T.; Adams, R. D.; Seminario, J.; Tour, J. *J. Org. Chem.*, **1998**, *63*, 2646.
- 55 Grossmann, G.; Poncioni, M.; Bornad, M.; Jolivet, B.; Neuburger, M.; Séquin, U. *Tetrahedron*, **2003**, *59*, 3237.
- 56 Boukouvalas, J.; Marion, O. *Synlett.*, **2006**, *10*, 1511.
- 57 D'Itri, F.; Popov, A. *J. Heterocycl. Chem.*, **1970**, *7*, 221.
- 58 (a) Fuson, R.; Cleveland, E. *Org. Synth.*, Coll. Vol. III, **1965**, 339.; (b) Gonzáles, R.; Liguori, L.; Martinez Carillo, A.; Bjørsvik, H. *J. Org. Chem.*, **2005**, *70*, 9591; (c) Thuruvikraman, S.; Suzuki, H. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 1597.
- 59 Pasteur, L.; Inaugural lecture, University of Lille, Douai, 7 December 1854. *Oeuvres de Pasteur*, Pasteur, V. Ed.; Masson, Paris, **1922 – 1939**, *7*, 130.
- 60 For a fascinating discussion of this area see: (a) Berson, J. *Chemical Discovery and the Logician's Program*. Wiley-VCH, Weinheim Germany, **2003**; (b) Berson, J. *Chemical Creativity*. Wiley-VCH, Weinheim Germany, **1999**.
- 61 Pavlovic, M.; Pavlovic, L.; Maksimovic, V.; Nikolic, N.; Popov, K. *Int. J. Electrochem. Sci.*, **2010**, *5*, 1862.
- 62 Fürstner, A. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 164 and references therein.
- 63 Nelson, T.; Crouch, R. *Org. React.*, **2004**, *63*, 274.
- 64 (a) Suslick, K.; Casadonte, D. *J. Am. Chem. Soc.*, **1987**, *109*, 3459; (b) Suslick, K.; Casadonte, D.; Green, M.; Thompson, M. *Ultrasonics*, **1987**, *25*, 56; (c) Suslick, K.; Casadonte, D.; Doktycz, S. *Chemistry of Materials*, **1989**, *1*, 6.
- 65 The stoichiometry of the reaction requires 4 equivalents of Cu[0] to convert the 2 equivalents of aryl halide **3.8** present in the reaction mixture into the aryl-copper species **3.14** (see Scheme 3.5).
- 66 A theme of Section 3.3 is the effect of inspiration, chance and accident on the course of scientific research. In this context, it is worth relating a final installment. The slow addition of activated copper dust had proven to be an effective method for improving the yields of the oxindole precursors. This was welcome, but the necessity to 'nurse' the reaction and periodically add aliquots of copper suspension was somewhat tedious. It occurred to the author that it might be possible to overcome the need to do this by adding an abrasive medium such as carborundum powder or sand to the reaction vessel along with the activated

copper. When agitated by an oversized magnetic stirring-bar the abrasive material would grind contaminants off the surface of the copper and thus expose fresh copper metal to the reaction medium. This procedure was tested with encouraging results. The yields of oxindole precursors arising from the 'abrasive method' were almost as good as those obtained by the 'slow addition' method. Unfortunately, the 'abrasive method' did not prove to be entirely reliable. A consequence of the procedure was severe scouring of the bottom of the glass reaction vessel by the abrasive material. Perhaps it was inevitable that on one occasion the base of a round bottom flask was worn so thin during a protracted reaction that it collapsed. The reaction vessel was immersed in a silicon oil heating-bath and the reaction mixture dropped into the hot silicon oil and, worse, the large stirring-bar was hurled against the side of the glass heating-bath and smashed it. The resulting mess was appalling and the purple language that followed this event does not bear repeating! Accordingly, the 'abrasive method' was abandoned.

- 67 Tacconi, G. *Gazz. Chim. Ital.*, **1968**, 98, 344.
- 68 (a) Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron*, **2006**, 62, 3040; (b) Volk, B.; Mezei, T.; Simig, G. *Synthesis*, **2002**, 5, 595 and references therein; (c) Rasmussen, H.; MacLeod, J. *J. Nat. Prod.*, **1997**, 60, 1152; (d) McEvoy, F.; Allen, G. *J. Org. Chem.*, **1973**, 38, 3350.
- 69 Hino, T.; Miura, H.; Murata, R.; Nakagawa, M. *Chem. Pharm. Bull.*, **1978**, 26, 3695.
- 70 Smith, M.; March, J. *March's Advanced Organic Chemistry.*, Wiley-Interscience, New York, 5th Ed., **2001**, 449.
- 71 Minami, N. K.; Reiner, J. E.; Semple, J. E. *Bioorg. Med. Chem. Lett.*, **1999**, 9, 2625.
- 72 Banwell, M.; Jones, M.; Loong, D.; Lupton, D.; Pinkerton, D.; Ray, J.; Willis, A. *Tetrahedron*, **2010**, 66, 9252.

Further Investigations into the Pd[0]-Catalysed Ullmann Cross-coupling Reaction

4.1 Introduction

The preceding chapter details research work in which the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach to indoles and quinolines was adapted to the synthesis of C-3 mono-alkylated oxindoles. The synthesis of oxindoles *via* this approach relies on the efficient cross-coupling of 1-bromo- and 1-iodo-2-nitrobenzene derivatives with various non-aromatic heterocyclic α -brominated α,β -unsaturated cycloimide, lactam and lactone coupling partners. These heterocyclic compounds were found to be less amenable to the Pd[0]-catalysed Ullmann cross-coupling reaction than the cyclic- and open-chain α - and β -halo- α,β -unsaturated enones employed for the synthesis of indoles and quinolines. Consequently, the ‘standard’ Pd[0]-catalysed Ullmann cross-coupling reaction conditions involving the use of copper-bronze particles as a reagent, delivered unsatisfactory yields of the requisite cross-coupled materials. This problem was solved upon discovering that the efficiency of the reaction is greatly enhanced when, instead of using copper-bronze, freshly activated 3 μm dendritic copper dust is slowly added to the reaction mixture. As shown in Table 3.9 (Page 120, Chapter 3), this simple modification to the procedure greatly improved the yields of cross-coupled products and, in some cases, almost doubled it.

The remarkable effectiveness of activated copper in the Pd[0]-catalysed Ullmann cross-coupling reaction prompted further investigations of this matter and raised the intriguing possibility of cross-coupling other, less-reactive compounds, and thereby gaining access to other heterocyclic systems. Section 4.2 (below) describes further research into the effects of highly active copper, whilst Section 4.3 describes work that was directed towards the synthesis of isoquinolines *via* a Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation sequence involving *o*-halo-benzonitriles as substrates.

4.2 The Effects of Activated Copper on the Pd[0]-catalysed Ullmann Cross-Coupling Reaction

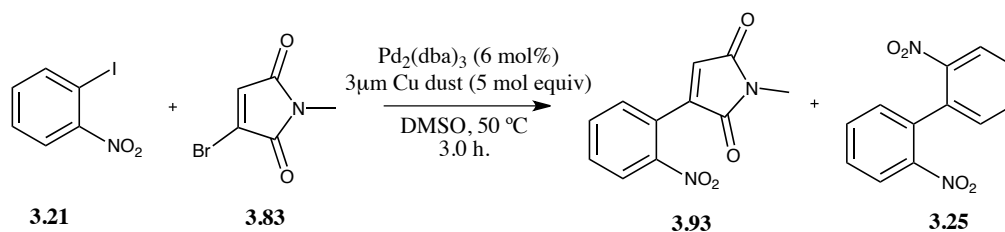
Lewin and Cohen's technique of activating copper powder by washing it with aqueous 0.02 M disodium EDTA¹ provides a simple and effective means of raising the yield of the Ullmann synthesis of biaryls. The successful application of this technique to the Pd[0]-catalysed Ullmann cross-coupling reaction, as described above, was gratifying on two counts. Firstly, and most importantly, improved yields of the cross-coupled products were obtained. Secondly, the simplicity of activating copper by this method is in keeping with the general simplicity of the Pd[0]-catalysed Ullmann cross-coupling reaction. Thus, both the activation of the copper powder and the cross-coupling reaction itself can be achieved using standard laboratory techniques employing reagents that are readily available and easy to handle.

In this spirit, various other simple methods of activating copper powder were investigated and the activated copper, so obtained, was tested in the Pd[0]-catalysed Ullmann cross-coupling reaction. The cross-coupling reaction between 1-iodo-2-nitrobenzene [3.21] and 3-bromo-1-methylmaleimide [3.83] was used in these tests.

4.2.1 Chemical Activation of Copper Powder

Several chemical activators were tested including hydrochloric acid, phosphoric acid, iodine and 1,2-dibromoethane. Whereas aqueous disodium EDTA is a complexing agent that removes Cu[I] and Cu[II] contaminants from the surface of the copper metal, these activators are 'corrosive' agents that react with the metal itself.²

Preliminary experiments with the two acids established that these should be used at low concentrations. Thus, activation of copper powder with dilute aqueous hydrochloric acid was tested at concentrations of 0.01, 0.02 and 0.05 M whilst activation with aqueous phosphoric acid was tested at 0.02 and 0.05 M concentrations. The activation procedure was the same as that used with 0.02 M disodium EDTA (see Chapter 3, Section 3.33) except, of course, that the acid was substituted for disodium EDTA. The yields of the products of the cross-coupling reactions employing the various samples of copper powder so prepared are shown in Table 4.1 (Entries 2 – 6). It is clear that activating the copper powder with dilute acids gives, at best, a small improvement in the yield of the cross-coupled product and that activating of copper powder with 0.02 M disodium EDTA solution delivers a significantly higher yield of the product.

Table 4.2.1: The Effect of Chemically Treated 3 μm Dendritic Copper Dust on the Pd[0]-Catalysed Ullmann Cross-Coupling of Substrates **3.21** and **3.83**.

Entry	Activating agent	% Yield (of 3.93)	Entry	Activating agent	% Yield (of 3.93)
1	none	69	6	H_3PO_4 (0.05M)	72
2	HCl (0.01M)	73	7	I_2/THF	65
2	HCl (0.02M)	64	8	$\text{I}_2/\text{acetone}/\text{HCl}$	75
4	HCl (0.05M)	58	9	$\text{CH}_2\text{BrCH}_2\text{Br}/\text{THF}$	68
5	H_3PO_4 (0.02M)	67	10	EDTA (0.02M)	77

Reaction conditions: 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.83**, 5.0 equiv of chemically treated 3 μm Cu dust, $\text{Pd}_2(\text{dba})_3$ 5 mol%, DMSO, 50 $^\circ\text{C}$, 3.0 h. The yield of the homocoupled by-product [**3.25**] was not determined.

A well-known method of activating magnesium powder for the purpose of preparing Grignard reagents is to stir it in hot THF or diethyl ether in the presence of a small amount of iodine.³ This technique was applied to 3 μm dendritic copper dust⁴ but the resulting material did not possess the salmon-pink colour that is characteristic of copper treated with dilute disodium EDTA solution and, when it was used in the cross-coupling process, it did not improve the yield of cross-coupled product **3.91** (Entry 7, Table 4.2.1). Interestingly, another form of activated copper was obtained by initially treating 3 μm dendritic copper dust with a dilute solution of iodine in acetone followed by washing the resulting solid material with a mixture of dilute hydrochloric acid and acetone, then water and then acetone. Finally, the activated metal was dried at reduced pressure.⁵ The copper so-formed exhibited a remarkably pale colour and delivered a comparable yield of the cross-coupled product to that obtained by using copper activated with dilute disodium EDTA solution (Entry 8, Table 4.2.1). However, the additional steps involved in this activation procedure did not warrant its ongoing use.

Treatment of 3 μm dendritic copper dust with a solution of 1,2-dibromoethane in THF, using a procedure described by Gaudemar,⁶ was not effective in activating the metal, as judged by the modest yield of the cross-coupled product (Entry 9, Table 4.2.1).

4.2.2 Rieke Copper

During the 1970's Rieke and co-workers developed several methods for the *in-situ* preparation of highly reactive metal powders by reduction of metal salts with alkali metals in an inert solvent such as THF.⁷ Many of the activated metal powders obtained in this way proved to be exceptionally reactive. However, their preparation by Rieke's original methods is somewhat hazardous because the reduction process, which typically involves potassium metal, may become violently exothermic. Moreover, some of these powders tend to agglomerate or sinter leading to rapid loss of reactivity. For example, the form of Rieke copper (Rieke-Cu) that is obtained by reduction of CuI with potassium in THF is especially susceptible to deterioration in quality.⁸ These problems were overcome when Rieke developed the technique of reducing metal salts with lithium in the presence of catalytic amounts of naphthalene dissolved in THF. This improved procedure is less hazardous because the reaction involving lithium does not tend to become uncontrollably exothermic. Furthermore, the metal powders prepared in this way proved no less reactive than the ones produced by the original method and were far less susceptible to sintering.⁹ As shown in Figure 4.2.1, naphthalene acts as an electron-transfer agent in these reduction processes.

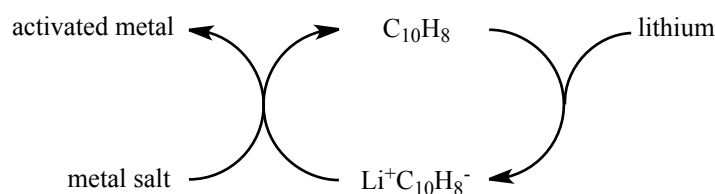


Figure 4.2.1 *The Catalytic Role of Naphthalene in the Formation of Rieke Metals.*

A range of highly reactive metal powders is available *via* this method including Rieke-Mg, -Zn, -Cu, -Ni, -Al, -U, -Sr, -Ba, -Ca and -In. Several of these types of highly activated metal powders have proven to be valuable reagents for synthesis, especially Rieke-Mg, -Zn and -Cu. A notable characteristic of these activated metals is their capacity to react with substrates that are unreactive towards less active metal powders. For instance, prior to the development of Rieke-Zn it was not possible to directly react

zinc with alkyl, aryl or vinyl bromides and chlorides. By contrast, Rieke-Zn will react directly with these substrates and is tolerant of a wide range of functional groups.⁹ Importantly, Rieke-Cu obtained by reduction of CuCl, CuI(PEt₃), CuCN·2LiBr or Cu(SMe₂)Cl with pre-formed lithium naphthalide is able to homocouple a range of aryl halides and thus deliver the corresponding bi-aryl species in high yields at moderate temperatures.^{9,10} This coupling takes place *via* the Ullmann reaction. Therefore, it was appropriate to test the effect of Rieke-Cu on the Pd[0]-catalysed Ullmann cross-coupling reaction. However, it is important to note that the preparation of Rieke-Cu adds a significant level of complexity to the process. Consequently, the ongoing use of Rieke-Cu would only be justified if it extended the scope of the reaction to include otherwise unreactive substrates or provided exceptionally high yields of cross-coupled products.

In the event, when a suspension of Rieke-Cu in THF was prepared by reduction of CuCN·2LiBr complex with pre-formed lithium naphthalide¹¹ and then added to a mixture of 1-iodo-2-nitrobenzene [**3.21**] (2.0 mmol), 3-bromo-1-methyl-1*H*-pyrrole-2,5-dione [**3.83**] (1.0 mmol) and Pd₂(dba)₃ (5 mol%) in THF, followed by stirring at 0 °C for 1.5 h the corresponding cross-coupled product **3.93** was not detected, even at trace levels. However, the homocoupled compound **3.25** was generated under such reaction conditions (and was isolated in 37% yield). This result demonstrated that the copper species present in the reaction mixture was able to mediate a conventional Ullmann reaction. A similar experiment was conducted at 20 °C but, once again, no cross-coupled product was observed although the homocoupled compound **3.25** was formed in 43% yield.

4.2.3 Copper Nano-Particles on Activated Charcoal

Reagents that are immobilized on inert carriers are commonly employed in laboratories and industry¹ in the form of ion-exchange resins and as zero-valent metal catalysts such as Pd or Pt bound to activated carbon. The use of such immobilized reagents has many advantages.¹² For instance, reagents comprised of sub-micron sized particles are easier to handle and are generally more stable when bound to an inert carrier. The workup of reaction mixtures is made easier because excess immobilized reagent can be removed by simple filtration rather than by extraction procedures. This also helps to improve yields. In addition, there may be concentration effects due to local

¹The explosive 'Dynamite' is undoubtedly most famous application of a chemical reagent absorbed onto an inert carrier. 'Dynamite' consists of nitroglycerine absorbed onto diatomaceous earth. It was invented by Alfred Nobel in 1866 and patented the following year. http://www.nobelprize.org/alfred_nobel/

enrichment of the bound reagent. Moreover, dissolved reagents that are charged or polarized or that contain π -electron systems can interact with the electrons of the conduction band of inert carriers such as carbon and graphite. These interactions can lead to a localized concentration of dissolved reagents at the phase boundary and to the lowering of activation energies.²

Various inert carriers are commonly employed including bentonite clays, diatomaceous earth, synthetic resins, silica, alumina, graphite and activated carbon. The last of these holds a special position because of its exceptionally high surface area per unit weight.¹² The microporous structure of activated carbon typically exhibits a surface area in excess of 500 m²/g and electron microscopy reveals that much of this is comprised of surfaces of graphite-like material separated by just a few nanometers. This provides an ideal environment for adsorption because the adsorbing material can intercalate between these planes and bind to both surfaces simultaneously through weak van der Waals forces.¹³

A simple method for the deposition of nano-sized particles of Cu[0] onto an inert carrier involves the treatment of a suspension of a suitable inert carrier in a solution of CuSO₄·5H₂O with the reducing agent NaBH₄.¹⁴ This method was employed for the deposition of nano-sized particles of Cu[0] onto activated carbon. Analysis of the resulting material by scanning electron microscopy (SEM) revealed that the copper is deposited on the surface of the activated carbon as sponge-like accretions (Figure 4.2.2). The diameter of the individual nodules and interconnecting strands of copper metal within these structures is in the range of 5 – 20 nm; averaging about 10 – 15 nm (Figure 4.2.3). The aggregated structures may be comprised of just a few distinct nodules or may grow to incorporate many thousands of these entities.

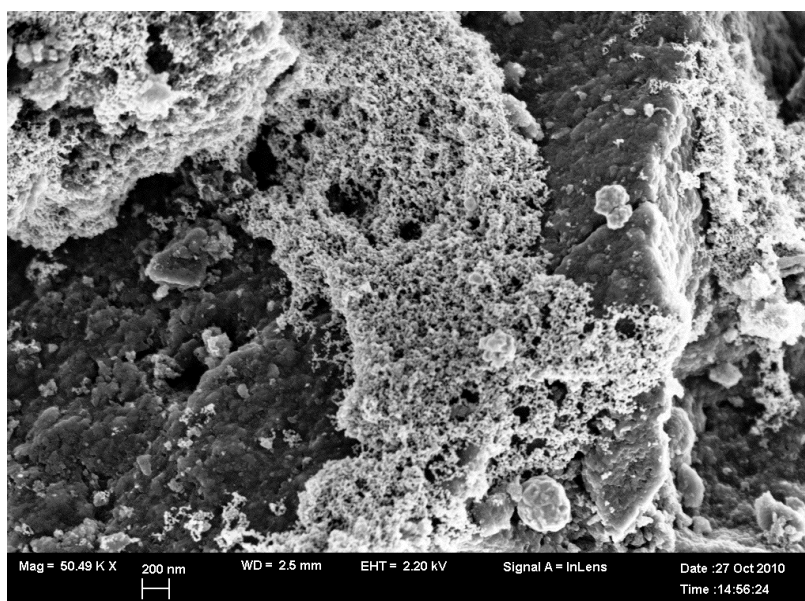


Figure 4.2.2 SEM Image of Copper Nano-Particles Deposited onto Activated Carbon. Magnification 50,490 $\times$. (The lighter coloured material is the activated copper.)

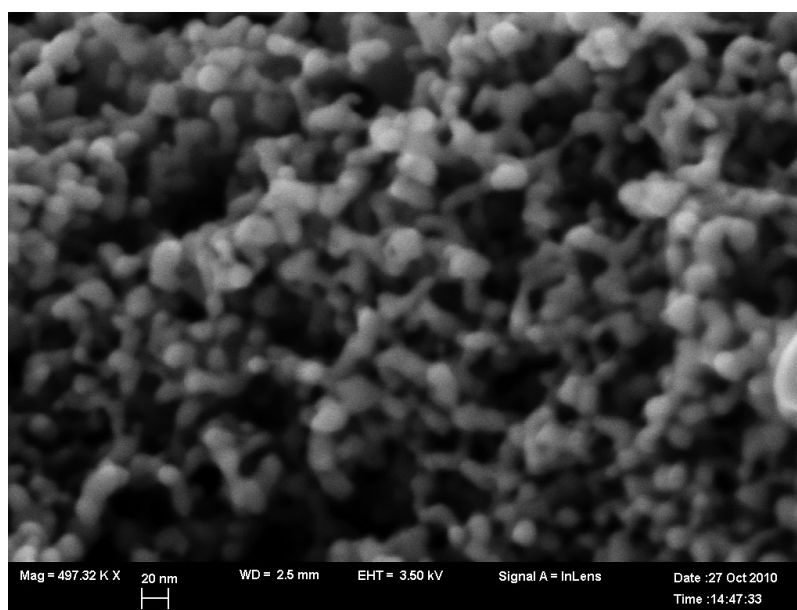


Figure 4.2.3 High magnification (497,320 $\times$) SEM Image of Copper Nano-Particles Deposited onto Activated Carbon.

Energy dispersive X-ray spectroscopy (EDS) reveals that, as expected, C and Cu are the predominant elements in the material (Figure 4.2.4).

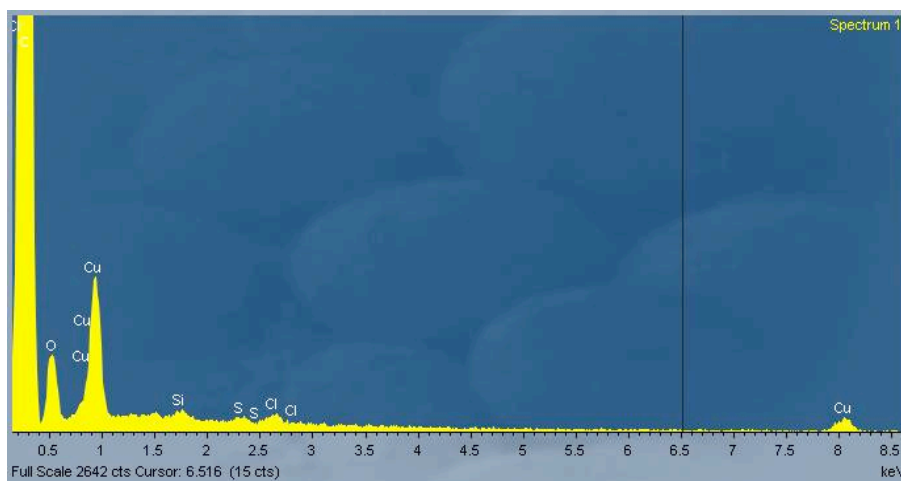
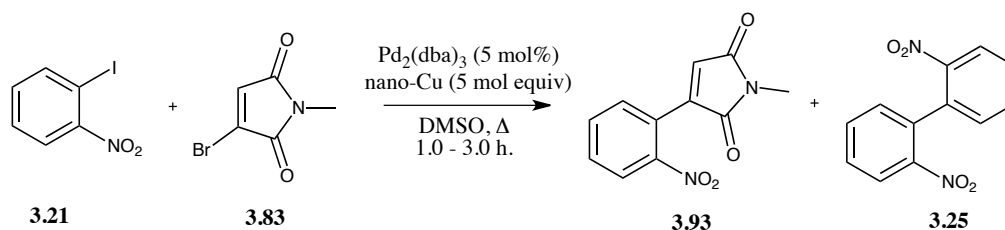


Figure 4.2.4 *Energy Dispersive X-ray Analysis of the Elemental Composition of Copper Nano-Particles Deposited onto Activated Carbon. (The signal at 0.1 - 0.4 keV is that of C, whilst Cu is observed at 0.7 - 1.1 keV.)*

The effect of copper nano-particles deposited onto activated carbon on the Pd[0]-catalysed Ullmann cross-coupling reaction was tested using the ‘standard’ reaction mixture that had been employed for previous investigations (see Chapter 3, Section 3.3.1). Thus, the flask containing the Cu[0] nano-particles was charged with 1-iodo-2-nitrobenzene [**3.21**] (2 mmol), 3-bromo-1-methyl-1*H*-pyrrole-2,5-dione [**3.83**] (1 mmol) and Pd₂(dba)₃ (5 mol%) and these were, in turn, suspended or dissolved in DMSO (10.0 ml). The ensuing mixture was stirred vigorously so as to ensure thorough suspension of the solid material and it was then heated at 40 °C for 1 h. After cooling, workup and isolation the cross-coupled compound **3.93** was obtained in 98% yield, whilst the yield of the homocoupled compound **3.25** was 51% (Table 4.2.2, Entry 1). This result indicated that Cu[0] nano-particles deposited on activated carbon are an especially effective source of copper in the Pd[0]-catalysed Ullmann cross-coupling reaction. Confirmation of this came from an experiment in which the reaction mixture was stirred at 20 °C (room temperature) for 4.5 h to afford compound **3.93** in 92% yield and compound **3.25** in 48% yield (Table 4.2.2, Entry 2).

Table 4.2.2 *The Effect of Various Supported Copper Nano-Particles on the Pd[0]-Catalysed Ullmann Cross-Coupling of Substrates 3.21 and 3.83.*



Entry	Inert Support	Temp °C	Time h	Yield 3.93 ^a	Yield 3.25 ^b
1	Carbon	40	1.0	98%	51%
2	Carbon	20	4.5	92%	48%
3	Montmorillonite	40	3.0	83%	46%
4	Alumina	40	1.5	0%	Trace

Reaction conditions: 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.83**, 5.0 equiv of Cu bronze, $\text{Pd}_2(\text{dba})_3$ 5%, DMSO, 20 – 40 °C, 1 – 4.5 h. ^aWith respect to compound **3.83**. ^bWith respect to compound **3.21**.

Copper nano-particles were also deposited onto K10-Montmorillonite and chromatographic-grade basic-alumina and the resulting powders were tested. Montmorillonite supported copper nano-particles did not prove to be as effective as Cu[0] nano-particles deposited onto activated carbon (Table 4.2.2, Entry 3) although, the activity of this material was comparable that of activated 3 μm dendritic copper dust. Alumina supported copper nano-particles were found to be unsuitable because this material tended to cohere into a paste that could not be properly dispersed throughout the reaction mixture (Table 4.2.2, Entry 4).

A range of coupling partners was subjected to the Pd[0]-catalysed Ullmann cross-coupling reaction in combination with Cu[0] nano-particles deposited onto activated carbon. Good to excellent yields of the corresponding cross-coupled compounds (Table 4.2.3) were obtained from reactions conducted at temperatures in the range of 20 – 40 °C. The yields of the cross-coupled compounds, so obtained, were generally a little higher than those obtained with activated 3 μm dendritic copper dust but these modest improvements in yields do not justify the additional steps and complexity involved in preparing and handling supported-Cu[0] nano-particles.

Table 4.2.3: The Effect of Supported Copper Nano-Particles on the Pd[0]-Catalysed Ullmann Cross-Coupling of Various Substrates.

Entry	<i>o</i> -Nitrohaloarene	Halogenated Heterocycle	Cross-coupling Product	Temperature	Time	Yield (%)
1				40 °C	1.0 h	98
2				20 °C	0.75 h	99
3				40 °C	3.0 h	67
4				20 °C	7.0 h	71
5				40 °C	1.5 h	87
6				40 °C	2.5 h	81

Reaction conditions: 2.0 equiv of 2-nitrohaloarene, 1.0 equiv of halogenated heterocycle, 5.0 equiv of Cu bronze, Pd₂(dba)₃ 5%, DMSO, 20 – 40 °C, 1 – 7 h. ^aWith respect to compound **3.83**. The yield of the homocoupled by-product was not determined.

The most significant features of the reactions depicted in Table 4.2.3 are the mild reaction temperatures involved. Those experiments summarised in Entries 2 and 4 were conducted at 20 °C (room temperature), whilst those associated with Entries 1, 3, 5 and 6 required only gentle heating at 40 °C. This could be advantageous if temperature-sensitive materials are to be cross-coupled. Moreover, these mild reaction temperatures clearly indicate that Cu[0] nano-particles deposited on activated carbon are far more

reactive than conventional sources of copper. Thus, the use of Cu[0] nano-particles deposited onto activated carbon in the Pd[0]-catalysed Ullmann cross-coupling reaction appeared to offer potential for expanding the scope of the reaction to include less reactive substrates. The pursuit of one such possibility is detailed in the remaining parts of this Chapter.

4.3 A Pd[0]-catalysed Ullmann Cross-coupling and Reductive Cyclisation Approach to 3,4-Annulated Isoquinolines

The isoquinoline alkaloids constitute one of the largest groups of naturally occurring alkaloids and more than 600 have been isolated from plant species.¹⁵ Several important pharmaceuticals are classed as isoquinoline derivatives including the analgesics morphine [4.2] and codeine, the anti-spasmodic agent papaverine [4.3], the anti-hypertensive quinapril [4.4] and the anti-parasitic praziquantel [4.5].¹⁶

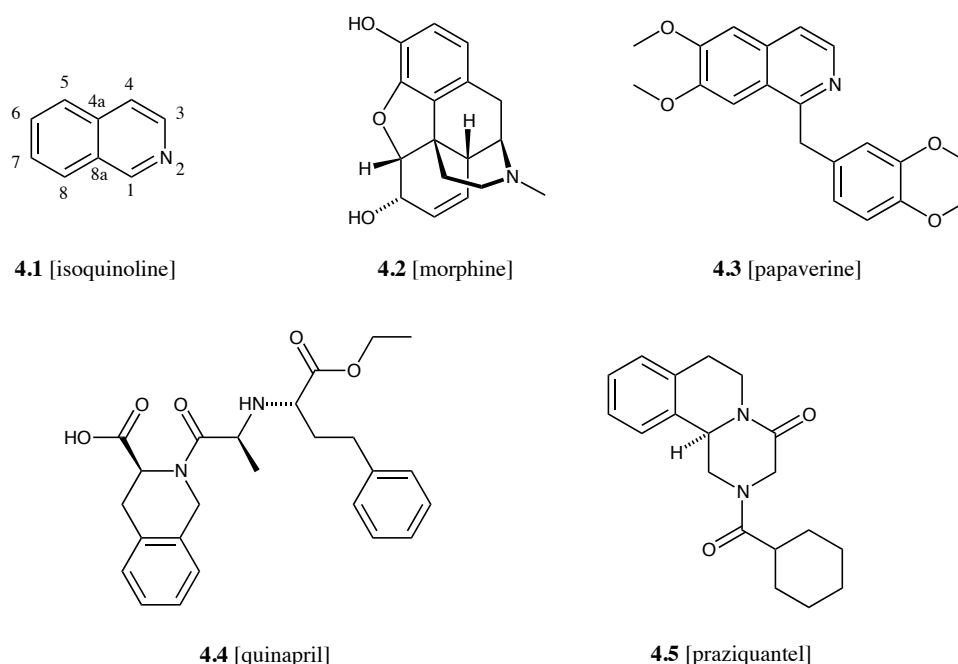


Figure 4.3.1 *Isoquinoline [4.1] and Several Pharmaceutical Compounds Derived From Isoquinoline Precursors.*

The abundance of naturally occurring isoquinoline alkaloids and the importance of pharmaceutical compounds derived from isoquinoline precursors have ensured the development of an impressive array of synthetic routes to this heterocyclic system. Foremost amongst these are the Bischler-Napieralski¹⁷ and the Pictet-Gams¹⁸ reactions

(in which the key bond-forming event takes place between C-8a and C-1), the Pictet-Spengler¹⁹ reaction (in which the key bond-forming event takes place between C-1 and N-2) and the Pommeranz-Fritsch²⁰ reaction (that joins C-4 and C-4a in the key step). These venerable methods have been widely used for the synthesis of isoquinolines but they suffer several limitations in terms of their widespread application. The key cyclisation step in the Bischler-Napieralski, Pictet-Gams and Pommeranz-Fritsch reactions involves an electrophilic aromatic substitution (S_EAr). This precludes the presence of strong electron-withdrawing substituents on the aromatic ring of the uncyclised precursor because such substituents deactivate the aromatic system towards S_EAr processes. Consequently, where a target incorporates a substituent such as a nitro-group, ester or aldehyde on the aromatic ring this must be installed after completing the cyclisation step. The Pomeranz-Fritsch reaction requires the use of strong acids, whilst the Bischler-Napieralski synthesis and Pictet-Gams reaction require the use of highly reactive dehydrating agents. Moreover, the use of high temperatures ($>100\text{ }^{\circ}\text{C}$) is often required in the aforementioned reactions. Finally, none of these reactions lends itself to the ready synthesis of 3,4-annulated isoquinolines and relatively few of these have been synthesised.²¹ Seemingly, the only general and simple method for the generation of annulated isoquinolines was developed by Kaneko and Naito and involves the 2 + 2 cycloaddition of heteroaromatics containing a β -alkoxyenone or δ -alkoxydienone moiety to alkenes, followed by elimination of an hydroxyl substituent from the adduct.²²

As highlighted in preceding parts of this Thesis (see Chapter 3, Sections 3.1.3 and 3.1.4), the synthesis of 2,3-annulated indoles, 2,3-annulated quinolines and 3-substituted oxindole compounds is readily accomplished under mild reaction conditions using the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach. Potentially, this approach could be employed for the synthesis of 3,4-annulated isoquinolines. Retrosynthetic analysis (Figure 4.3.2) of one of the simplest of these compounds, namely 1,2,3,4-tetrahydrophenanthridine [4.8], suggests that it might be obtained by reductive cyclisation of the substituted benzonitrile derivative 4.7. The latter compound would be the product of the Pd[0]-catalysed Ullmann cross-coupling of 2-iodo-benzonitrile [4.6] and 2-iodo-2-cyclohexen-1-one [3.22]. The synthesis of 3,4-annulated isoquinolines *via* the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation sequence would not only be an interesting challenge but, if successful, would provide a new synthetic route to an unusual and potentially valuable class of isoquinoline derivative.

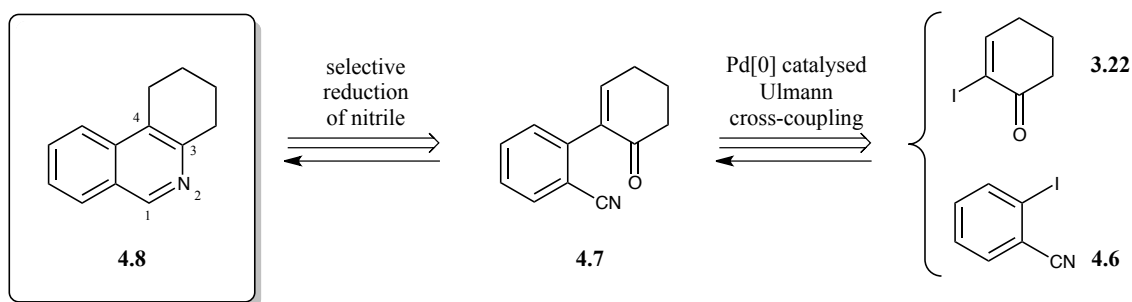


Figure 4.3.2 Retrosynthetic Analysis of the 3,4-Annulated-Isoquinoline Compound 1,2,3,4-Tetrahydrophenanthridine [4.8].

The proposed synthesis of 3,4-annulated isoquinoline compounds *via* such a sequence poses two challenges. Firstly, in order to facilitate the reductive cyclisation event it is essential that the nitrile substituent be selectively reduced to a primary amine without reduction of the carbonyl system of the cyclohexenone moiety. Fortunately, a variety of highly selective methods exist for the reduction of nitriles to primary amines. Foremost amongst these techniques is the hydrogenation of nitriles over Raney-Ni or Raney-Co catalysts. These processes are normally easy to implement and generally provide a high degree of selectivity.²³ The second and more challenging problem is that the nitrile substituent of 2-iodo-benzonitrile [4.6] does not display the same strong electron withdrawing effects as the nitro group that is present in the congener 3.21. A useful measure of the electron-withdrawing or electron-donating capacity of a functional group on an aryl compound is the Hammett substituent constant σ . This constant is obtained from the Hammett equation (Figure 4.3.3),²⁴ which relates the reaction rate k of a series of reactions of substituted benzene derivatives to the reaction rate k_0 of the unsubstituted compound.²⁵ In this equation σ is the Hammett substituent constant, which depends only on the specific substituent, and ρ is a reaction constant that relates only to the type of reaction being studied.

$$\log \frac{k}{k_0} = \sigma \rho$$

Figure 4.3.3 The Hammett Equation

The more positive the value of σ , the greater the electron-withdrawing capacity of the substituent, whilst a negative value indicates that the substituent is electron-

donating. Hydrogen (H) has the value 0.00 and is neutral in character (Table 4.3).²⁶ It is normally considered that Hammett constants only apply to *para*- (σ_{para}) and *meta*-substituents (σ_{meta}) because *ortho*-substituents exert steric effects that can alter normal electronic behavior. However, Meyers and Gellmann have shown that the Hammett equation is applicable to the Ullmann reaction²⁷ and it is clear that the order of reactivity follows the order of the Hammett σ_{para} constants. Thus, 1-iodo-2-nitrobenzene [3.21] is highly reactive towards the Ullmann biaryl synthesis whereas 2-iodo-benzonitrile [4.6] is less so. Consequently, it was expected that 2-iodo-benzonitrile derivatives would not be as reactive towards the Pd[0]-catalysed Ullmann cross-coupling as their nitro-containing counterparts.

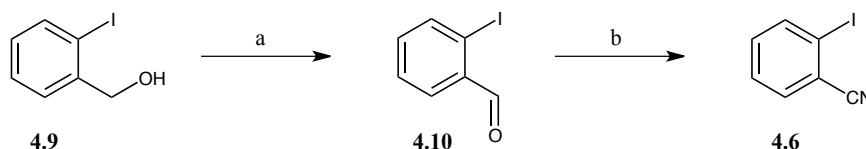
Table 4.3 Hammett σ_{para} Constants for Various Substituents.²⁶

Substituent	σ_{para}	Substituent	σ_{para}
NO ₂	0.78	Br	0.23
CN	0.66	H	0.00
COCH ₃	0.50	CH ₃	-0.17
CO ₂ R	0.45	OCH ₃	-0.27
CHO	0.42	NH ₂	-0.66

4.3.1 An Efficient Synthesis of 2-Iodobenzonitrile

At the time the research described in this thesis was being conducted the compound 2-iodobenzonitrile [4.6] was not readily available in Australia as a commercial product. Therefore, prior to investigating the synthesis of isoquinolines *via* the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach it was necessary to develop an efficient method for the synthesis of this compound. To such ends, it was soon determined that 2-iodobenzonitrile [4.6] could be prepared in good yield (79%), but only at small scale, by sequential reaction of 2-iodobenzoic acid with chlorosulfonyl isocyanate and *N,N*-dimethylformamide (DMF).²⁸ However, this procedure involved several time consuming steps and it was also difficult to thoroughly remove DMF residues from the product. Moreover, both chlorosulfonyl isocyanate and the gaseous by-product of the reaction, sulphur trioxide, are highly toxic. Accordingly, an alternative route was sought. A survey of the relevant literature revealed a procedure

disclosed by Fang and co-workers for the direct transformation of aldehydes into nitriles using I_2 in aqueous ammonia solution.^{29,30} This simple procedure allowed for the conversion of 2-iodobenzaldehyde [4.10] into 2-iodobenzonitrile [4.6] in quantitative yield and it was complimented by a method for the oxidation of 2-iodobenzylalcohol [4.9] to afford 2-iodobenzaldehyde [4.10] in high yield (85%) using silica-supported MnO_2 and microwave heating.³¹ Thus, by combining these two procedures the high-yielding conversion (85%) of 2-iodobenzylalcohol [4.9] into 2-iodobenzonitrile [4.6] was realised (Scheme 4.1). The spectral data obtained on the previously reported compound 4.6 proved entirely consistent with the assigned structure and matched those previously reported.³²



Scheme 4.1 Reaction conditions: (a) MnO_2 5.0 mmol, chromatographic grade silica 60/80 mesh 1.5 g, microwave (2×2 min), $80^\circ C$; (b) 4.10 1.0 mmol, I_2 1.0 mmol, NH_4OH (28% aq.) 10 ml, THF 1.0 ml, $20^\circ C$, 1 h, 85% over two steps.

4.3.2 Investigating the Pd[0]-Catalysed Ullmann Cross-Coupling of o-Iodobenzonitrile and 2-Iodocyclohex-2-enone

The Pd[0]-catalysed Ullmann cross-coupling of 2-iodobenzonitrile [4.6] and 2-iodo-2-cyclohex-2-enone [3.22] was initially tested using commercial copper bronze powder that had not been activated. Thus, 2-iodobenzonitrile [4.6] (4 mmol) and 2-iodo-2-cyclohexen-1-one [3.22] (1 mmol) were dissolved in DMSO (20ml) and heated for 2 h at $110^\circ C$ in the presence of copper bronze powder (20 mmol) and $Pd_2(dba)_3$ (0.20 mmol, 20 mol%) to afford the cross-coupled product 4.7 [2-(2-cyanophenyl)-2-cyclohexen-1-one] in just 40% yield (Entry 1, Table 4.4).

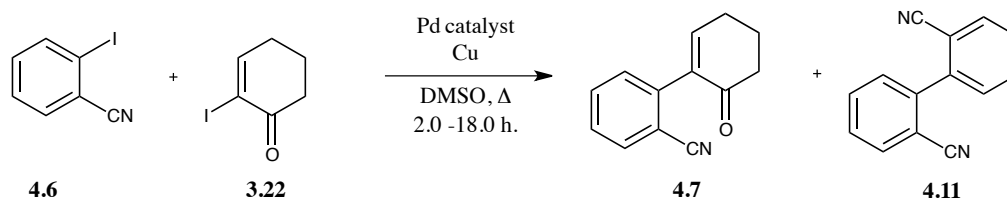
The spectral data obtained on the previously unreported compound 4.7 were completely consistent with the assigned structure. In particular, the ^{13}C NMR spectrum of compound 4.7 displayed, as expected, thirteen signals including ten in the region above δ 105 that correspond to the single sp - and nine sp^2 -hybridised carbons embodied within the structure. Additionally, the IR spectrum of compound 4.7 displayed an

absorption band at 2227 cm^{-1} that is characteristic of a nitrile moiety as well as a strong absorption band at 1663 cm^{-1} due to the carbonyl group.

The experimental results described above demonstrated the feasibility of the proposed Pd[0]-catalysed Ullmann cross-coupling, but the modest yield and relatively forceful conditions detracted from the process. Therefore, additional experiments were conducted in an effort to improve the efficiency of the process. In particular, the cross-coupling reaction was tested with activated $3\text{ }\mu\text{m}$ dendritic copper dust and with Cu[0] nano-particles deposited on activated carbon. In keeping with previous experience, it was found that the use of highly active copper allowed the Pd[0]-catalysed Ullmann cross-coupling to take place more readily and the more forceful conditions used earlier were now not required. The results of experiments directed towards optimizing the yield of the cross-coupled product are depicted in Table 4.4. Entries 2 – 10 define experiments in which catalytic quantities of Pd[0] were employed. Four common palladium catalysts were tested and each of these was capable of effecting the reaction, but it was apparent that $\text{Pd}_2(\text{dba})_3$ and $\text{PdCl}_2(\text{dppf})$ were the most promising. When catalytic quantities of Pd[0] were employed the best yield of compound **4.7** was 48% (Entry 7). This ‘optimum yield’ was obtained by adding five equal aliquots of a suspension of the activated $3\text{ }\mu\text{m}$ dendritic copper dust in DMSO and five equal aliquots of a solution of $\text{PdCl}_2(\text{dppf})$ in DMSO to the reaction mixture over 2.5 h. The use of Cu[0] nano-particles deposited on activated carbon afforded comparable yields of compound **4.7** (47% Entry 8 and 46% Entry 9) but the only notable advantage of this material over activated $3\text{ }\mu\text{m}$ dendritic copper dust was a shorter reaction time (4 vs 6 - 8 h).

As described in Section 4.3, it was anticipated that the ‘Achilles heal’ of this cross-coupling reaction would be the lower electron withdrawing capacity of the nitrile group. Thus, the modest yields of the cross-coupled product **4.7** (27 – 48%) were initially attributed to this factor. However, the yield of compound **4.7** was 85% when a catalyst loading of 110% of $\text{Pd}(\text{OAc})_2$ was employed (Entry 11).² Moreover, it was discovered that 2-iodobenzonitrile [**4.6**] readily engages in the Ullmann biaryl reaction when Cu[0] nano-particles deposited on activated carbon are employed as a source of copper and no Pd[0] catalyst is present. Thus, when 2-iodobenzonitrile [**4.6**] (2 mmol) and Cu[0] nano-particles deposited on activated carbon (5 mmol of Cu[0]) were

² $\text{Pd}(\text{OAc})_2$ was chosen for this somewhat extravagant experiment because it is the least expensive of the readily available palladium compounds.

Table 4.4 Optimization Studies into the Pd[0] Catalysed Ullmann Cross-Coupling of Substrates **4.6** and **3.22**.

Entry	Copper ^a	Cu mmol	4.6 mmol	Catalyst	Catalyst load	Temp.	Time	Yield ^{b,c} (of 4.7)
1 ^d	Cu-bronze	20.0	4.0	Pd ₂ (dba) ₃	20%	110 °C	2 h	40%
2	3 μm*	5.0	2.0	Pd ₂ (dba) ₃	5%	60 °C	18 h	32%
3	3 μm*	5.0	1.5	Pd ₂ (dba) ₃	5%	80 °C	6 h	38%
4	3 μm*	5.0	1.5	Pd(OAc) ₂	5%	80 °C	8 h	27%
5	3 μm*	5.0	1.5	Pd(PPh ₃) ₄	5%	80 °C	8 h	33%
6	3 μm*	5.0	1.5	PdCl ₂ (dppf)	5%	80 °C	8 h	40%
7 ^e	3 μm*	5.0	1.3	PdCl ₂ (dppf)	5%	80 °C	8 h	48%
8	nano-Cu	5.0	1.3	Pd ₂ (dba) ₃	5%	80 °C	4 h	47%
9	nano-Cu	5.0	1.3	PdCl ₂ (dppf)	5%	80 °C	4 h	46%
10	nano-Cu	5.0	1.3	Pd(OAc) ₂	5%	80 °C	6 h	36%
11 ^f	3 μm*	5.0	2.0	Pd(OAc) ₂	110%	75 °C	8 h	85%

Notes: 1.0 mmol of 2-iodocyclohex-2-enone [**3.22**] was employed for all experiments. ^a3 μm* = activated 3 μm dendritic copper dust. nano-Cu = copper nano-particles deposited on activated carbon. ^bYield of cross-coupled product **4.7** calculated with respect to compound **3.22**. ^cThe yield of the homocoupled by-product **4.11** was not accurately determined during these studies. Reaction conditions: (Entries 2 – 6 and 8 – 10): compound **4.6** quantity as indicated in table, compound **3.22** 1.0 mmol, Cu 5.0 mmol, Pd catalyst 5%, DMSO, N₂, Δ, 2.0 – 18.0 h. ^d(Entry 1) Reaction conditions: As for Entries 2 – 6, but involving 20.0 mmol of copper-bronze powder and a 20% catalyst loading. ^e(Entry 7) Reaction conditions: As for Entries 2 – 6, but involving the addition of 5 equal aliquots of a suspension of the activated copper dust (Cu*) in DMSO and 5 equal aliquots of a solution of PdCl₂(dppf) in DMSO over 2.5-h. ^f(Entry 11) Reaction conditions: As for Entries 2 – 6, but involving a 110% catalyst loading.

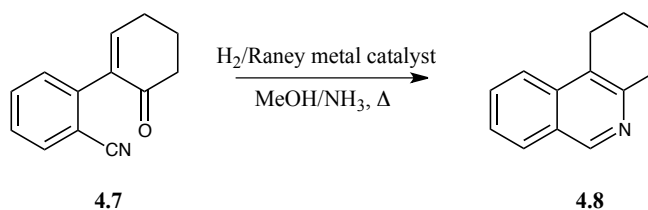
stirred together in dry DMSO (10 ml) at 80 °C for 2.0 h the homocoupled compound, viz. 1,1-biphenyl-2,2'-dicarbonitrile [**4.11**], was obtained in 92% yield. By way of contrast, the yield of the biaryl **4.11** as a by-product from the Pd[0]-catalysed Ullmann cross-coupling of 2-iodobenzonitrile [**4.6**] and 2-iodo-2-cyclohexen-1-one [**3.22**] was low (< 20%) and a significant proportion of unreacted 2-iodo-benzonitrile [**4.6**] was always

recovered. These observations suggest that the Pd[0] catalyst may actually be the ‘stumbling block’ in this process rather than the lower electron withdrawing capacity of the nitrile group. Work is currently underway within the Banwell research group to investigate this matter.

4.3.3 The Reductive Cyclisation Reaction. Synthesis of 1,2,3,4-Tetrahydrophenanthridine

With the cross-coupling product **4.7** in hand, an investigation of its capacity to engage in the reductive cyclization processes was undertaken. The outcomes of the relevant studies are shown in Table 4.5, which reveals that upon exposure of a solution of compound **4.7** in ammoniacal methanol to dihydrogen at 5000 kPa in the presence of Raney-Co (20% w/w) at 80 °C for 8 h the anticipated conversion took place to afford the somewhat unstable compound 1,2,3,4-tetrahydrophenanthridine [**4.8**] in 76% yield (Entry 1). Under similar conditions Raney-Ni afforded the same product in 68% yield (Entry 2). The omission of ammonia from the reaction mixture resulted in a complex mixture of inseparable residues (Entry 3), whilst hydrogenation over Raney-Co at lower pressure and temperature (415 kPa, 20 °C) proved to be ineffective (Entry 4). The spectral data obtained on compound **4.8** were entirely consistent with the assigned structure and matched those previously reported.^{33,34}

In summary, the synthesis of the 3,4-annulated isoquinoline **4.8** was achieved *via* the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach in two steps and an overall yield of 36%. At first-sight, this modest yield may appear unsatisfactory. Clearly, there is room for improvement. However, it is instructive to compare this result with the work of Pandey and Balakrishnan who recently reported the synthesis of compound **4.8** *via* a Suzuki/Miyaura cross-coupling and reductive cyclisation approach.³⁴ When the steps involved in the preparation of the requisite boronic acid are taken into account the overall yield associated with their synthesis was 37%. This highlights a fundamental advantage of the Pd[0]-catalysed Ullmann cross-coupling reaction in that, unlike the Suzuki/Miyaura, Stille and Negishi cross-coupling reactions, it allows for the direct cross-coupling of appropriate substrates without the prior preparation of a derivative.

Table 4.5 Reductive Cyclisation of **4.7** to Afford the 3,4-Annulated Isoquinoline 1,2,3,4-Tetrahydrophenanthridine [**4.8**].

Entry	Catalyst	Pressure H ₂	Solvent	Temp.	Time	Yield of 4.8
1	Raney-Co	5000 kPa	MeOH/NH ₃	80 °C	8.0 h	76%
2	Raney-Ni	5000 kPa	MeOH/NH ₃	80 °C	8.0 h	68%
3	Raney-Co	5000 kPa	MeOH	80 °C	6 h	Complex mixture
4	Raney-Co	415 kPa	MeOH/NH ₃	20 °C	48 h	Trace

Reaction conditions: (Entries 1,2 and 4.) Compound **4.7**, Raney sponge-metal catalyst 20% w/w, methanol saturated with gaseous ammonia, pressure, temperature and time as indicated. (Entry 3) As above, but methanol solvent not saturated with ammonia.

4.4 Conclusions

The use of very finely divided and highly activated elemental copper in the Pd[0]-catalysed Ullmann cross-coupling reaction improves the yields of cross-coupled products and allows the reaction to take place under mild conditions. These effects are further enhanced when the source of copper is in the form of Cu[0] nano-particles deposited on activated carbon.³⁵ The enhanced reactivity of these sources of copper has been exploited in the synthesis of the 3,4-annulated isoquinoline compound 1,2,3,4-tetrahydrophenanthridine [**4.8**], which was obtained *via* the Pd[0]-catalysed Ullmann cross-coupling and reductive cyclisation approach. The synthesis was readily achieved in two steps, under mild conditions, and in an overall yield of 36%. This approach provides a viable alternative to established methods that do not lend themselves to the ready synthesis of 3,4-annulated isoquinoline compounds. The Banwell Group continues to work on improving the efficiency of the process and to develop it for the synthesis of a diverse range of 3,4-annulated isoquinoline compounds.

4.5 References.

- 1 Lewin, A.; Zovko, M.; Rosewater, W.; Cohen, T. *Chem. Comm.*, **1967**, 2, 80.
- 2 Fürstner, A. *Angew. Chem. Int. Ed. Engl.*, **1993**, 32, 164.
- 3 Gilman, H.; Kirby, R. *Recl. Trav. Chim. Pays-Bas.*, **1935**, 54, 577
- 4 Lai, Y. *Synthesis*, **1981**, 586.
- 5 Kleiderer, E.; Adams, R. *J. Am. Chem. Soc.*, **1933**, 55, 4219.
- 6 Gaudemar, M. *Bull. Chim. Fr.*, **1962**, 974.
- 7 (a) Rieke, R.; Hudnall, P. *J. Am. Chem. Soc.*, **1972**, 94, 7178; (b) Rieke, R.; Hudnall, P.; Uhm, S. *J. Am. Chem. Soc.*, **1973**, 269.
- 8 Rieke, R.; Rhyne, L. *J. Org. Chem.*, **1979**, 44, 3445.
- 9 For a review of this field see: Rieke, R.; Sell, M.; Klein, W.; Chen, T.; Brown, J.; Hanson, M. in *Active Metals*. Ed.; Fürstner, A. VCH, New York, **1996**, pp. 1 – 55.
- 10 Rieke, R. *Science*, **1989**, 246, 1260.
- 11 Stack, D.; Dawson, B.; Rieke, R. *J. Am. Chem. Soc.*, **1991**, 113, 4672.
- 12 (a) Laszlo P. *Preparative Chemistry Using Supported Reagents*. Academic Press, New York, **1987**, pp. 3 – 12; (b) Varma, R. *Green Chem.*, **1999**, 1, 43 and references therein.
- 13 (a) Marsh, H.; Rodriguez-Reinoso, F. *Activated Carbon*, Elsevier, Amsterdam, **2006**, pp. 87 – 242; (b) Sircar, S.; Golden, T.; Rao, M. *Carbon*, **1996**, 34, 1.
- 14 Tandon, P.; Singh, S.; Srivastava, M. *Appl. Organometal. Chem.*, **2007**, 21, 264.
- 15 (a) For a comprehensive review of this field see: Bentley, K. *The Isoquinoline Alkaloids*. Harwood, London, **1998**; (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*. Wiley-VCH, Weinheim, **2003**, 348.
- 16 (a) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.*, **2000**, 8, 2629; (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic Publishers: Amsterdam, **1998**; Vol. 1.
- 17 Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: Amsterdam, **2005**, 62.
- 18 Li, J. *Name Reactions in Heterocyclic Chemistry*, Wiley, New York, **2005**, 457.
- 19 See reference 17, page 348.
- 20 See reference 17, page 358.

- 21 For some examples of the synthesis of 3,4-annulated isoquinolines see: (a) Bikram, K.; Le, Q.; Yang, S.; Van, H.; Cho, W. *Bioorg. Med. Chem.*, **2011**, *19*, 1924; (b) Ghorai, B.; Jiang, D.; Herndon, J. *Org. Lett.*, **2003**, *5*, 4261; (c) Liebeskind, L.; Zhang, J. *J. Org. Chem.*, **1991**, *56*, 6379; (d) Keneko, C.; Naito, T. *Heterocycles*, **1982**, *19*, 2183; (e) Rettig, W.; Wirz, J. *Helv. Chim. Acta.*, **1978**, *61*, 444; (f) Marsili, A.; Scartoni, V. *Chim. Ital.*, **1974**, *104*, 165; (g) Kessar, V.; Sobti, A.; Josi G. *J. Chem. Soc. C*, **1971**, *2*, 259; (h) Wawzonek, S.; Stowell, J.; Karli, J. *J. Org. Chem.*, **1966**, *31*, 1004.
- 22 Naito, T.; Kaneko, C. *Chem. Pharm. Bull.*, **1985**, *33*, 5328.
- 23 Medina, F.; Salagre, P.; Sueiras, J. *J. Mol. Catal.*, **1993**, *81* 363.
- 24 Hammett, L. *J. Am. Chem. Soc.*, **1937**, *59*, 96.
- 25 For a concise review of the effects of structure on reactivity see; Smith, M.; March, J. *March's Advanced Organic Chemistry*. 5th Edn., Wiley-Interscience, N.Y. **2001**, pp 363 – 380.
- 26 Hansch, S.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*. Wiley-Interscience, N.Y. **1979**, pp 49 – 52.
- 27 Meyers, J.; Gellman, A. *Surf. Sci.*, **1995**, *337*, 40.
- 28 Lohaus, J. *Org. Synth.*, **1970**, *50*, 18.
- 29 Talukdar, S.; Hsu, J.; Chou, T.; Fang, J. *Tetrahedron Lett.*, **2000**, *42*, 1103.
- 30 Under certain conditions it is possible for iodine and ammonia to react and produce nitrogen triiodide. The dry powder form of this compound is unstable and explodes readily. Therefore, excess iodine should not be used and the waste residues should be thoroughly diluted with water prior to disposal.
- 31 Varma, R.; Saini, R.; Dahiya, R. *Tetrahedron Lett.* **1997**, *38*, 7823.
- 32 Suzuki, Y.; Moriyama, K.; Togo, H. *Tetrahedron*, **2011**, *67*, 7956.
- 33 (a) Beugelmans, R.; Chastanet, J.; Roussi, G. *Tetrahedron*, **1984**, *40*, 311; (b) Masamune, T.; Ohno, M.; Koshi, M.; Ohuchi, S.; Iwadare, T. *J. Org. Chem.*, **1964**, *29*, 1419.
- 34 Pandey, G.; Balakrishnan, M. *J. Org. Chem.*, **2008**, *73*, 8128.
- 35 Banwell, M. G.; Jones, M. T.; Rieke, T. A. *Chemistry in New Zealand*, **2011**, *75*, 122.

Experimental Procedures for Chapters Two, Three and Four.

5.1 General Experimental Procedures

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in filtered base-treated CDCl_3 on a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In some cases a Varian Inova spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei or a Varian Inova 600 spectrometer operating at 600 MHz for proton and 150 MHz for carbon nuclei was used. The compound *ent*-**2.167** was analysed with a Bruker instrument operating at 800 MHz for proton and 200 MHz for carbon nuclei. Signals arising from the residual protonated form of the solvent were employed as the internal standards. Thus, the signal due to residual CHCl_3 appearing at δ 7.26 and the central resonance of the CDCl_3 ‘triplet’ appearing at δ 77.0 were used to reference ^1H and ^{13}C NMR spectra, respectively. ^1H 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; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Scanning electron microscopy was conducted using a Zeiss Ultraplus Analytical FESM instrument. A VG Fisons AutoSpec three-sector (E/B/E) double-focusing mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionization mode. Optical rotations were measured at 18 °C with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) at the concentrations (c) (g/100 ml) indicated using spectroscopic grade solvents. The measurements were conducted using a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_{\text{D}}$ were calculated according to the equation $[\alpha]_{\text{D}} = (100 \times a)/(c \times l)$ [units: $10^{-1} \cdot \text{deg} \cdot \text{cm}^2 \cdot \text{g}^{-1}$]. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F₂₅₄ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by

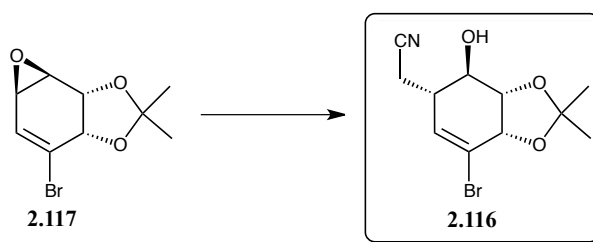
heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 ml) and potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 ml : 300 ml). Flash chromatographic separations were carried out following protocols defined by Still *et al.*¹ with silica gel 60 (0.0040-0.0063 mm) as the stationary phase and the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally supplied by the Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Pinacolborane and *bis*(neopentyl-glycolato)diboron were obtained from Boron Molecular Ltd (Melbourne, Australia). Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran, acetonitrile, methanol, toluene and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al.*² Benzene was distilled from sodium wire. Anhydrous DMSO was supplied by Sigma-Aldrich in a Sure-Seal™ bottle and was maintained under an argon atmosphere. Where necessary reactions were performed under a nitrogen or argon atmosphere. All microwave irradiation experiments were conducted using a CEM Explorer microwave apparatus, operating at a frequency of 2.45 GHz with continuous radiation power from 0 - 300 W, utilizing the standard absorbance level of 300 W. The reactions were carried out in 10 ml CEM Pyrex vessels fitted with CEM crimp tops, or in 80 ml CEM sealed Pyrex vessels. Both types of vessel were equipped with magnetic stirrers. Reaction temperatures were measured from the outer surface of the 10 ml vessels with an infrared sensor or with a fiber-optic infrared probe immersed in the reaction mixture of the 80 ml vessels. After the irradiation period the reaction vessels were cooled rapidly (1 – 2 minutes) to ambient temperature with a nitrogen jet.

5.2 Experimental Section for Chapter Two

Compounds **2.117**, **2.128**, **2.134** and **2.135** were prepared according to established procedures.^{3,4}

Compound **2.116**

[(3*aS*,4*R*,5*S*,7*aS*)-7-Bromo-3*a*,4,5,7*a*-tetrahydro-4-hydroxy-2,2-dimethyl-1,3-benzodioxole-5-acetonitrile]

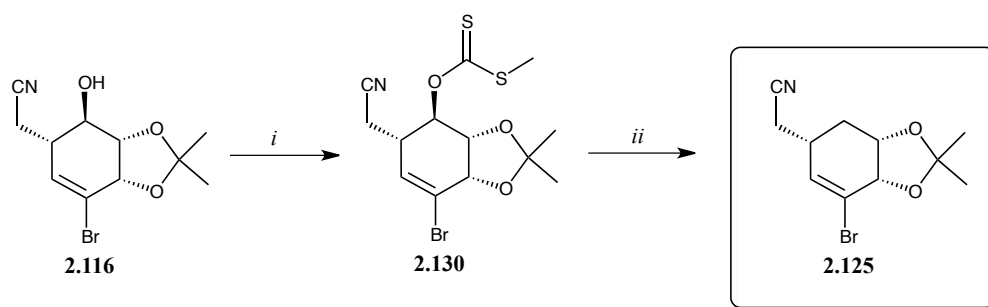


A magnetically stirred mixture of acetonitrile (5 mL, 95 mmol) in THF (35 mL), under a nitrogen atmosphere, was cooled to $-70\text{ }^{\circ}\text{C}$ (internal temperature, dry-ice/acetone bath) then treated with *n*-BuLi (18 mL of a 2 M solution in hexanes, 36 mmol) at such a rate as to maintain an internal temperature below $-60\text{ }^{\circ}\text{C}$. The resulting white suspension was treated, dropwise, with a solution of epoxide **2.117** (5.93 g, 24 mmol) in THF (25 mL) whilst maintaining the temperature of the reaction mixture at or below $-60\text{ }^{\circ}\text{C}$. The ensuing orange-colored suspension was stirred at -70 to $-75\text{ }^{\circ}\text{C}$ for 0.33 h then carefully poured into ice-cold ammonium chloride (150 mL of a half-saturated aqueous solution). The resulting mixture was diluted with ethyl acetate (25 mL) and the separated aqueous phase was acidified (with 1 M aqueous HCl) to pH 6. This was then extracted with additional ethyl acetate ($3 \times 25\text{ mL}$) and the combined organic phases were washed with sodium bicarbonate ($1 \times 25\text{ mL}$ of a saturated aqueous solution), water ($1 \times 25\text{ mL}$) and brine ($1 \times 25\text{ mL}$) before being dried (MgSO_4), filtered and concentrated under reduced pressure to an amber-colored oil. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) then gave the *title compound* **2.116** (6.67 g, 96%) as a light-yellow oil, $[\alpha]_D^{25} +27.9$ (c 3.0, chloroform- d) [Found: $(\text{M} - \text{CH}_3)^+$, 271.9922. $\text{C}_{11}\text{H}_{14}^{79}\text{BrNO}_3$ requires $(\text{M} - \text{CH}_3)^+$, 271.9922]. ^1H NMR (CDCl_3 , 300 MHz) δ 6.18 (1H, s), 4.70 (1H, d, $J = 6.2\text{ Hz}$), 4.09 (1H, m), 3.53 (1H, t, $J = 8.4\text{ Hz}$), 3.04 (1H, broad s), 2.79 (1H, m), 2.53–2.50 (2H, complex m), 1.54 (3H, s), 1.43 (3H, s); ^{13}C NMR (CDCl_3 , 75 MHz) δ

131.5, 120.5, 117.5, 110.5, 79.0, 77.1, 70.9, 39.5, 28.1, 25.8, 19.2; ν_{max} (KBr) 3447 (broad), 2987, 2934, 2249, 1382, 1245, 1218, 1162, 1075, 868 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 274 and 272 $[(M - \text{CH}_3)^+]$, 48 and 50%, 214 and 212 (15 and 16), 133 (26), 59 (27), 43 (100).

Compound **2.125**

[(3a*S*,5*R*,7a*S*)-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-5-acetonitrile]



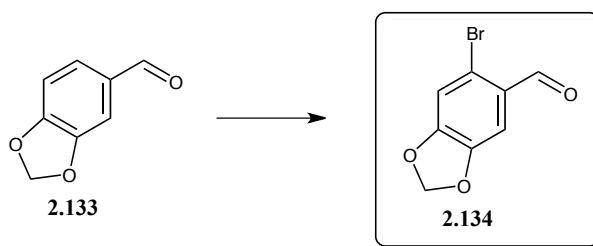
Step i: A magnetically stirred suspension of sodium hydride (prepared by washing 160 mg of a 60% dispersion in mineral oil with anhydrous hexane to give *ca.* 72 mg or 3 mmol of clean hydride) in THF (10 mL) maintained under nitrogen at 18 °C was treated, dropwise, with a solution of alcohol **2.116** (583 mg, 2.02 mmol) in THF (10 mL) (CAUTION: vigorous evolution of hydrogen gas – this was monitored using a silicon oil bubbler). The resulting suspension was stirred at 18 °C for 0.5 h then treated, in one portion, with a solution of carbon disulfide (120 mL, 2.02 mmol) in THF (1.5 mL). The ensuing reaction mixture was stirred at 18 °C for 0.33 h then cooled to 0 °C and treated with methyl iodide (312 mg, 2.2 mmol). Stirring was continued at 0 °C for 0.5 h then the reaction mixture was warmed to 18 °C over 0.5 h before being diluted with diethyl ether (40 mL) and poured into ammonium chloride (150 mL of a half-saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 × 20 mL) and the combined organic phases were washed with water (2 × 20 mL) and brine (1 × 20 mL) before being dried (MgSO_4) then filtered through a short plug of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to afford the *xanthate ester* **2.130** (720 mg, 94%) as an amber-colored oil. This unstable material was used, without purification, in the deoxygenation step described immediately below.

Step ii: A magnetically stirred solution of ester **2.130** (2.72 g, 7.2 mmol) in benzene (50 mL) maintained at 18 °C was treated, in one portion, with tri-*n*-butyltin

hydride (4.0 mL, 4.3 g, 14.8 mmol) and AIBN (60 mg, 0.37 mmol, 5 mole %). The ensuing mixture was heated rapidly to 80 °C and stirred at this temperature for 1.25–1.5 h (the reduction process was monitored very carefully by TLC so as to minimize the co-production of the reductively debrominated analogue of compound **2.125**). The cooled reaction mixture was diluted with water (40 mL) and the separated organic phase was dried (MgSO₄) then filtered and concentrated under reduced pressure. The resulting light-yellow oil was dissolved in acetonitrile (75 mL) and the solution thus obtained was washed with pentane (4 × 15 mL) (to remove alkyltin residues) and the acetonitrile phase was then concentrated under reduced pressure to give an amber-colored oil. This material was added to the top of a silica gel flash chromatography column that was then eluted with toluene until the eluent no longer smelt of sulfurous residues. The eluting solvent was then changed to 3:0.5:96.5 v/v/v acetone/triethylamine/toluene and concentration of the appropriate fractions ($R_f = 0.3$) then gave the *title compound* **2.125** (1.30 to 1.59 g, 67 to 82%) as a yellow oil that solidified on standing. Recrystallization (methanol) of a sample of this material gave analytically pure nitrile **2.125** as a white crystalline solid, mp 56–58 °C, $[\alpha]_D^{25} +90$ (c 1.0, CHCl₃) [Found: $(M - CH_3)^+$, 255.9977. C₁₁H₁₄⁷⁹BrNO₂ requires $(M - CH_3)^+$, 255.9973]. ¹H NMR (CDCl₃, 300 MHz) δ 6.24 (1H, broad s), 4.51 (1H, d, $J = 5.4$ Hz), 4.44 (1H, m), 2.64 (2H, broad s), 2.06 (2H, m), 1.47 (3H, s), 1.44 (1H, m), 1.38 (3H, s); ¹³C NMR (CDCl₃, 75 MHz) δ 131.9, 125.0, 118.4, 110.1, 75.9, 74.0, 32.8, 28.4, 28.0, 26.2, 22.7; ν_{max} (KBr) 2985, 2931, 2244, 1646, 1423, 1370, 1318, 1219, 1157, 1072, 1041, 986, 876 cm⁻¹; Mass spectrum (EI, 70 eV) m/z 258 and 256 [$(M - CH_3)^+$, 59 and 60%], 216 and 214 (13 and 14), 171 and 169 (17 each), 43 (100).

Compound **2.134**

[6-Bromobenzo[1,3]dioxole-5-carbaldehyde]

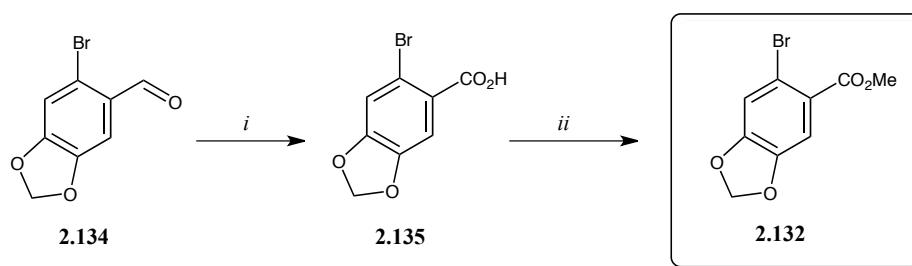


A magnetically stirred solution of piperonal [**2.133**] (12.04 g, 80.2 mmol) in glacial acetic acid (150 ml) maintained at 18 °C was treated dropwise with molecular

bromine (12.2 ml, 243 mmol) over 0.33 h. To this mixture was added a solution of molecular iodine (100 mg, 0.4 mmol) in carbon disulfide (15 ml). The resulting turbid red/brown mixture was stirred at 18 °C for 48 h and then the solvents and residual bromine were evaporated at reduced pressure. The solid material so obtained was dissolved in ethyl acetate (200 mL) and the resulting solution was stirred with saturated aqueous NaHCO₃ (500 ml) for 1 h. The separated organic phase was dried (MgSO₄) then filtered through a short plug of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to afford the *title compound* **2.134** (14.9 g, 81%) as an off-white solid. For the purpose of spectroscopic characterization a sample of this material was recrystallized (ethanol/water) to give white needles m.p = 129 – 131 °C, (lit.⁵ 131 °C) [Found: M⁺, 227.9423. C₈H₅⁷⁹BrO₃ requires M⁺, 227.9422]. ¹H NMR (CDCl₃, 300 MHz) δ 10.15 (1H, s), 7.33 (1H, s), 7.05 (1H, s), 6.09 (2H, s); ¹³C NMR (CDCl₃, 75 MHz) δ 190.3, 153.6, 148.2, 128.4, 121.3, 113.3, 108.3, 102.7; ν_{max} (KBr) 3032, 3011, 2982, 2904, 1672, 1612, 1467, 1388, 1238, 1206, 1100, 981 cm⁻¹; Mass spectrum (EI, 70 eV) m/z 228 and 230 [(M⁺, 100 and 95%), 201, 22%, 199, 28%, 143, 12%, 62, 24%].

Compound **2.132**

[6-Bromo-1,3-benzodioxole-5-carboxylic acid methyl ester]



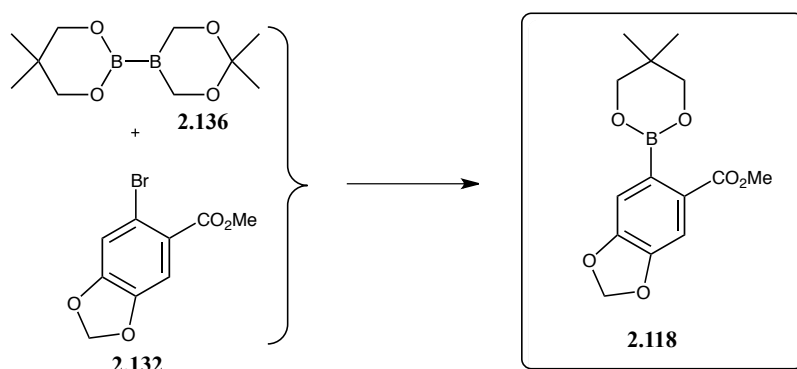
Step i: To a magnetically stirred solution of compound **2.134** (2.30 g, 10.0 mmol) in acetone (50 ml) maintained at 18 °C was added sodium dihydrogen orthophosphate (328 mg, 2.70 mmol) and 30% aqueous hydrogen peroxide (5 ml); then the mixture was treated with sodium chlorite (75% technical grade, 1.85 g, 15 mmol) over 2 h. The reaction mixture was stirred for 18 h and the resulting slurry was then treated with sodium sulfite (0.5 g) and stirred for 0.33 h. The slurry was acidified to pH 1 by addition of 2M HCl (approximately 8 ml) and it was extracted with ethyl acetate (4 × 50 mL). The organic phase was dried (MgSO₄) and then filtered through a short plug of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to afford the

title compound 2.135 (2.49g, 98%) as a white crystalline solid. This compound was used without further purification in the esterification step described immediately below.

Step ii: Magnetically stirred methanol (15ml) maintained at 0 °C was treated dropwise with thionyl chloride (0.55 ml, 7.5 mmol). To the ensuing mixture was added dropwise a solution of compound **2.135** (463 mg, 1.89 mmol) in methanol (15 ml). The resulting pale yellow mixture was stirred at 0 °C for 0.33 h and then it was warmed (0.5 h.) to 40 °C and it was stirred at this temperature for 10 h. The mixture was diluted with ethyl acetate (45 mL) and it was quenched with saturated aqueous NaHCO₃ (75 ml). The separated aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were washed with water (2 × 20 mL) and brine (1 × 20 mL) before being dried (MgSO₄) then filtered through a short plug of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to afford the *title compound 2.132* (360 mg, 74%) as a white crystalline solid. m.p = 83 – 85 °C, (lit.⁶ 84 – 85 °C) [Found: M⁺, 257.9529. C₉H₇⁷⁹BrO₄ requires M⁺, 257.9528]. ¹H NMR (CDCl₃, 300 MHz) δ 7.32 (1H, s), 7.09 (1H, s), 6.05 (2H, s), 3.89 (3H, s); ¹³C NMR (CDCl₃, 75 MHz) δ 165.7, 150.9, 147.2, 124.4, 114.9, 114.3, 110.8, 102.5, 52.4; ν_{max} (KBr) 3012, 2954, 2922, 1727, 1610, 1491, 1487, 1445, 1368, 1333, 1238, 1120, 1078, 971 cm⁻¹; Mass spectrum (EI, 70 eV) *m/z* 258 and 260 [(M⁺, 96 and 94%], 227 and 229 [(M – OCH₃)⁺, 100 and 98%], 199 and 201 (28 and 24%)

Compound **2.118**

[6-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-1,3-benzodioxole-5-carboxylic acid methyl ester]

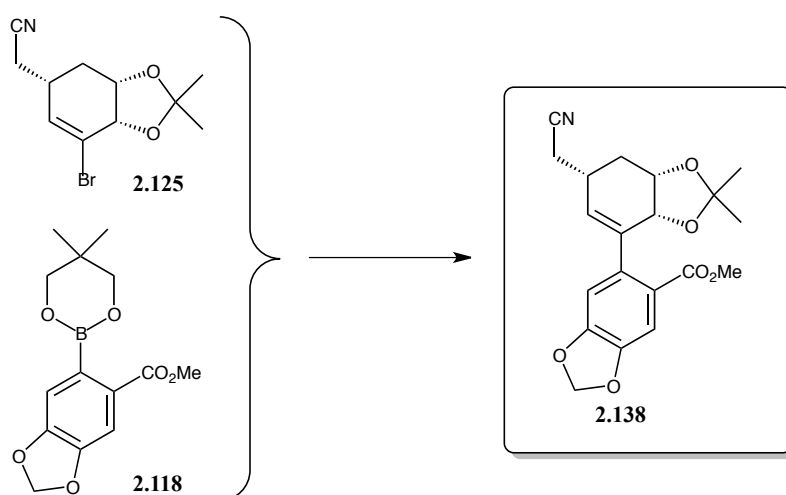


A magnetically stirred mixture of 6-bromopiperonylic acid methyl ester [**2.132**] (1.04 g, 4.0 mmol) and anhydrous potassium acetate (1.25 g, 12.74 mmol) in degassed

acetonitrile (20 mL) was treated, in one portion, with $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (164 mg, 0.22 mmol, *ca.* 5 mole %). The ensuing mixture was heated at reflux then treated, in 5 mL portions over a period of 1 h, with a solution of bis(neopentylglycolato)diboron **[2.136]** (1.36 g, 6.0 mmol) in acetonitrile (25 mL). The resulting solution was stirred at 82 °C for 1 h then cooled, diluted with ethyl acetate (100 mL) and filtered through a short plug of CeliteTM contained in a sintered-glass funnel. The filtrate was concentrated under reduced pressure and the resulting light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane). Concentration of the appropriate fractions ($R_f = 0.3$) then gave the *title compound 9* (1.03 g, 88%) as a low-melting, white crystalline solid (Found: M^+ , 292.1124. $\text{C}_{14}\text{H}_{17}\text{BO}_6$ requires M^+ , 292.1118). ^1H NMR (CDCl_3 , 300 MHz) δ 7.36 (1H, s), 6.89 (1H, s), 6.00 (2H, s), 3.89 (3H, s), 3.79 (4H, s), 1.10 (6H, s); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.6, 151.3, 147.9, 135.6 (broad), 126.7, 110.6, 109.1, 101.7, 72.7, 52.6, 31.9, 22.2; ν_{max} (KBr) 2960, 2927, 1702, 1607, 1508, 1473, 1446, 1425, 1411, 1366, 1292, 1268, 1243, 1217, 1140, 1113, 1034, 933, 878, 788 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 292 (M^+ , 66%), 291 (100), 290 (38), 207 (97), 206 (56), 175 (33), 149 (42), 148 (40).

Compound 2.138

[(3a*R*,6*R*,7a*S*)-6-(Cyanomethyl)-3a,6,7,7a-tetrahydro-2,2-dimethyl-4,5'-bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]

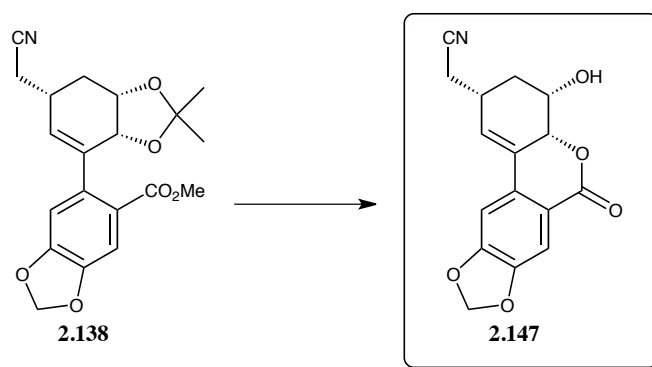


A mixture of acetone **2.125** (141 mg, 0.52 mmol) and boronate **2.118** (256 mg, 0.88 mmol, 1.7 mol equiv.), triethylamine (1 mL) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (24 mg, 0.03 mmol, 6 mole %) in THF/water (4 mL of a 9:1 v/v mixture) was sparged with nitrogen

for 5 min. then subjected to microwave irradiation at 90 °C for 1.5 h. The cooled reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (3 × 10 mL) then brine (1 × 5 mL) before being dried (MgSO₄) then filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane) to give, after concentration of the appropriate fractions (R_f = 0.2 in 2:3 v/v ethyl acetate/hexane), the *title compound* **2.138** (145 mg, 75%) as a clear, light-yellow oil, $[\alpha]_D^{+78}$ (c 1.0, CHCl₃) (Found: M^{+} , 371.1366. C₂₀H₂₁NO₆ requires M^{+} , 371.1369). ¹H NMR (CDCl₃, 300 MHz) δ 7.40 (1H, s), 6.71 (1H, s), 6.03 (2H, m), 5.62 (1H, broad s), 4.79 (1H, d, J = 6.0 Hz), 4.50 (1H, m), 3.80 (3H, s), 2.67 (3H, broad s), 2.14 (1H, m), 1.95 (1H, m), 1.48 (3H, s), 1.30 (3H, s); ¹³C NMR (CDCl₃, 75 MHz) δ 166.4, 150.6, 147.1, 140.7, 138.4, 127.7, 122.0, 118.8, 111.7, 110.2, 109.1, 102.0, 73.6, 73.2, 51.9, 30.7, 29.7, 28.2, 25.7, 23.1; ν_{max} (KBr) 2987, 2934, 2248, 1717, 1614, 1504, 1485, 1436, 1370, 1247, 1160, 1126, 1069, 1038, 928, 733 cm⁻¹; Mass spectrum (EI, 70 eV) m/z 371 (M^{+} , 25%), 356 (12), 313 (21), 282 (46), 264 (28), 254 (28), 241 (100), 213 (58).

Compound **2.147**

[(2*R*,4*S*,4*aR*)-2,4,4*a*,6-Tetrahydro-4-hydroxy-6-oxo-1*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-2-acetonitrile]

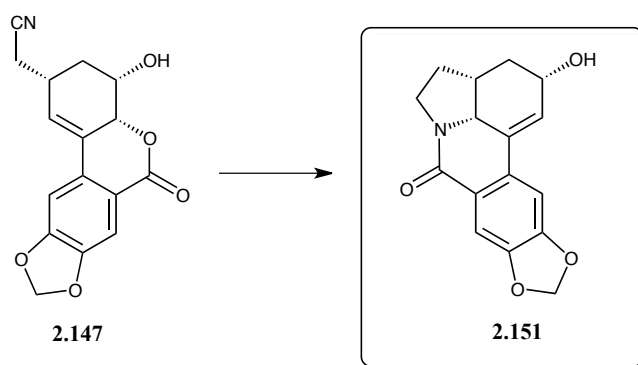


A magnetically stirred solution of compound **2.138** (98 mg, 0.26 mmol) in acetic acid/water (7.5 mL of a 4:1 v/v mixture) was heated at 80 °C for 1 h in a flask open to the atmosphere then cooled and concentrated under reduced pressure. The residue so obtained was dissolved in ethyl acetate (20 mL) and the resulting solution washed with sodium bicarbonate (3 × 15 mL of a saturated aqueous solution) then water (1 × 15 mL) and brine (2 × 15 mL) before being dried (MgSO₄), filtered and

concentrated under reduced pressure. The yellow oil so-obtained was subjected to flash chromatography (silica, 7:3 v/v ethyl acetate/hexane) to afford, after concentration of the appropriate fractions ($R_f = 0.3$), the title *compound 2.147* (71.2 mg, 89%) as a clear, colorless oil, $[\alpha]_D^{25} +216$ (c 1.0, CHCl_3) (Found: M^+ , 299.0794. $\text{C}_{16}\text{H}_{13}\text{NO}_5$ requires M^+ , 299.0794). ^1H NMR (CDCl_3 , 300 MHz) δ 7.51 (1H, s), 6.99 (1H, s), 6.38 (1H, broad s), 6.09 (2H, m), 5.06 (1H, m), 4.41 (1H, m), 2.84 (3H, broad s), 2.19 (1H, dd, $J = 15.0$ and 4.8 Hz), 2.10 (1H, broad s), 2.00 (1H, dm, $J = 15.0$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 163.7, 153.3, 148.8, 133.1, 127.0, 126.1, 119.3, 117.4, 109.1, 102.5, 102.4, 76.6, 65.2, 31.3, 29.3, 23.9; ν_{max} (KBr) 3448, 2921, 2245, 1711, 1616, 1503, 1481, 1394, 1278, 1246, 1123, 1083, 1035, 931, 861, 732 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 299 (M^+ , 95%), 259 (100), 255 (65), 215 (72).

Compound 2.151

[(2*S*,3*aR*,12*cR*)-2,3,3*a*,4,5,12*c*-Hexahydro-2-hydroxy-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one]

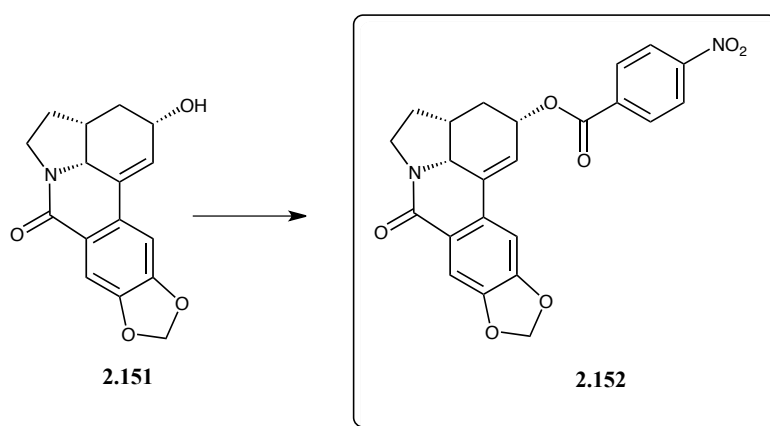


A magnetically stirred solution of compound **2.147** (148 mg, 0.49 mmol) in methanol (10 mL saturated with gaseous ammonia) contained in a Parr hydrogenation bomb was treated with Raney-Co⁷ (50 mg of wet material) and the resulting mixture was sparged with hydrogen for 5 min. The bomb was then pressurized under hydrogen at 3000 kPa and heated at 80 °C for 3 h. The cooled reaction mixture was poured from the opened bomb through a sintered-glass funnel. The filtrate was treated with flash chromatography-grade silica gel (400 mg) and the ensuing mixture was concentrated under reduced pressure to give a free-flowing light-yellow powder. This material was added, dry, to the top of a flash chromatography column that was eluted with 2:48 v/v methanol/ethyl acetate to give, after concentration of the appropriate fractions ($R_f = 0.3$),

the *title compound 2.151* (92 mg, 65%) as a white, crystalline solid, mp 171–173 °C, $[\alpha]_D -91$ (c 1.0, CHCl_3) (Found: M^{+} , 285.1002. $\text{C}_{16}\text{H}_{15}\text{NO}_4$ requires M^{+} , 285.1001). ^1H NMR (CDCl_3 , 300 MHz) δ 7.44 (1H, s), 6.67 (1H, s), 6.04 (2H, m), 5.96 (1H, broad s), 4.30 (1H, m), 4.02 (1H, d, $J = 7.5$ Hz), 3.80–3.60 (2H, complex m), 2.56 (1H, m), 2.46 (2H, broad s), 2.24 (1H, m), 2.06 (1H, m), 1.85 (1H, m); ^{13}C NMR (CDCl_3 , 75 MHz) δ 162.7, 150.8, 147.9, 133.2, 132.4, 131.0, 123.5, 107.6, 102.6, 101.9, 68.1, 56.5, 43.8, 36.1, 35.4, 29.1; ν_{max} (KBr) 3379, 2924, 1734, 1634, 1612, 1475, 1416, 1265, 1035, 931 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 285 (M^{+} , 100%), 268 (67), 241 (83), 240 (86), 228 (51).

Compound **2.152**

[(2*S*,3*aR*,12*cR*)-2,3,3*a*,4,5,12*c*-Hexahydro-2-[(4-nitrobenzoyl)oxy]-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one]

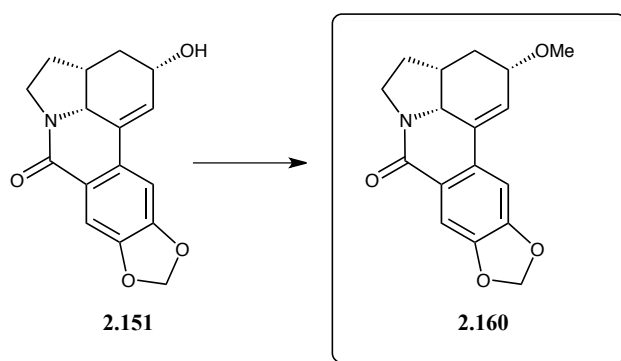


A magnetically stirred solution of compound **2.151** (52 mg, 0.18 mmol) and triethylamine (80 μL , 0.58 mmol) in dichloromethane (10 mL) was cooled to -5 °C then treated, dropwise, with a solution of *p*-nitrobenzoyl chloride (37.3 mg, 0.20 mmol) in dichloromethane (10 mL). The ensuing mixture was stirred at -5 °C for 0.33 h then at 0 °C for 0.75 h before being warmed to 25 °C over 1 h. TLC analysis of the resulting mixture indicated that significant quantities of the starting alcohol remained. Accordingly, the reaction mixture was treated with additional quantities of *p*-nitrobenzoyl chloride (75 mg, 0.40 mmol) as well as 4-(*N,N*-dimethylamino)pyridine (67 mg, 0.6 mmol) then heated at reflux for 4.5 h. The cooled reaction mixture was washed with water (2×10 mL) then dried (MgSO_4) and filtered. The filtrate was treated with flash chromatography-grade silica gel (500 mg) and the resulting mixture

concentrated under reduced pressure to give a free-flowing solid. This material was applied to the top of a dry silica gel flash chromatography column that was eluted with 7:3 v/v ethyl acetate/hexane. Concentration of the appropriate fractions ($R_f = 0.3$) then gave the *title compound* **2.152** (37 mg, 46%) as a bright-yellow, crystalline solid, mp 186–188 °C, $[\alpha]_D -57$ (c 1.0, CHCl_3) (Found: M^+ , 434.1111. $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_7$ requires M^+ , 434.1114). ^1H NMR (CDCl_3 , 300 MHz) δ 8.29 (2H, d, $J = 7.2$ Hz), 8.21 (2H, d, $J = 7.2$ Hz), 7.52 (1H, s), 6.89 (1H, s), 6.08 (1H, s), 6.03 (2H, m), 5.71 (1H, m), 4.23 (1H, d, $J = 7.5$ Hz), 3.80 (2H, m), 2.79 (1H, m), 2.42–2.20 (2H, complex m), 1.95 (1H, m), 1.72 (1H, broad s); ^{13}C NMR (CDCl_3 , 75 MHz) δ 164.3, 162.5, 151.0, 150.8, 148.5, 135.4, 134.6, 132.5, 130.9, 125.2, 124.5, 123.7, 108.0, 103.1, 102.0, 72.1, 56.4, 43.9, 34.9, 31.7, 29.2; ν_{max} (KBr) 2970, 1719, 1642, 1609, 1526, 1502, 1476, 1411, 1395, 1347, 1270, 1117, 1100, 1036, 1015, 934, 873, 838, 754, 719 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 434 (M^+ , 2%), 268 (38), 267 (100), 266 (52), 167 (19), 121 (9), 65 (15).

Compound **2.160**

[(2*S*,3*aR*,12*cR*)-2,3,3*a*,4,5,12*c*-Hexahydro-2-methoxy-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one]

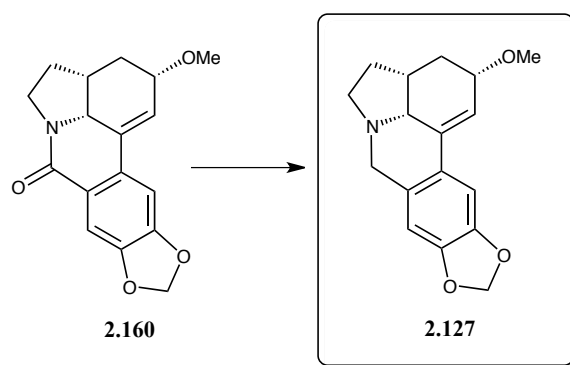


A magnetically stirred mixture of compound **2.151** (27 mg, 0.095 mmol), Proton-sponge[™] (214 mg, 1.0 mmol, 10.5 mol equiv.) and Me_3OBF_4 (56 mg, 0.38 mmol, 4 mol equiv.) in dichloromethane (5 mL) maintained under nitrogen was heated at reflux (internal temperature 45 °C) for 2.5 h. The cooled reaction mixture was diluted with dichloromethane (5 mL) and sodium bicarbonate (10 mL of a saturated aqueous solution) then the mixture was stirred at 18 °C for 0.33 h. The phases were separated and the organic one was stirred with citric acid (10 mL of a 10% w/v aqueous solution) for 0.33 h. The separated organic phase was dried (MgSO_4) and filtered then treated with

chromatographic-grade silica gel (400 mg) and the ensuing mixture was concentrated under reduced pressure to give a free-flowing light-yellow powder. This material was added, dry, to the top of a flash chromatography column that was eluted with ethyl acetate to give, after concentration of the appropriate fractions ($R_f = 0.3$), the *title compound* **2.160** (27 mg, 95%) as a white, crystalline solid, mp 128–131 °C, $[\alpha]_D -72$ (c 0.9, CHCl_3) (Found: M^+ , 299.1157. $\text{C}_{17}\text{H}_{17}\text{NO}_4$ requires M^+ , 299.1158). ^1H NMR (CDCl_3 , 300 MHz) δ 7.50 (1H, s), 6.87 (1H, s), 6.10 (1H, broad s), 6.02 (2H, m), 4.11 (1H, d, $J = 7.5$ Hz), 3.93 (1H, m), 3.82–3.66 (2H, complex m), 3.44 (3H, s), 2.59 (1H, m), 2.26 (1H, m), 2.12 (1H, m), 1.86 (1H, m), 1.23 (1H, m); ^{13}C NMR (CDCl_3 , 75 MHz) δ 162.5, 150.9, 148.1, 133.1, 132.6, 128.4, 124.3, 107.9, 103.0, 101.8, 77.0, 56.8, 56.3, 43.7, 35.3, 32.1, 29.4; ν_{max} (KBr) 2926, 2822, 1642, 1613, 1475, 1413, 1267, 1104, 1035, 931 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 299 (M^+ , 52%), 268 (52), 241 (30), 228 (26), 206 (24), 191 (100).

Compound **2.127**

[(2*S*,3*aR*,12*cR*)-2,3*a*,4,5,7,12*c*-Hexahydro-2-methoxy-3*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridine]

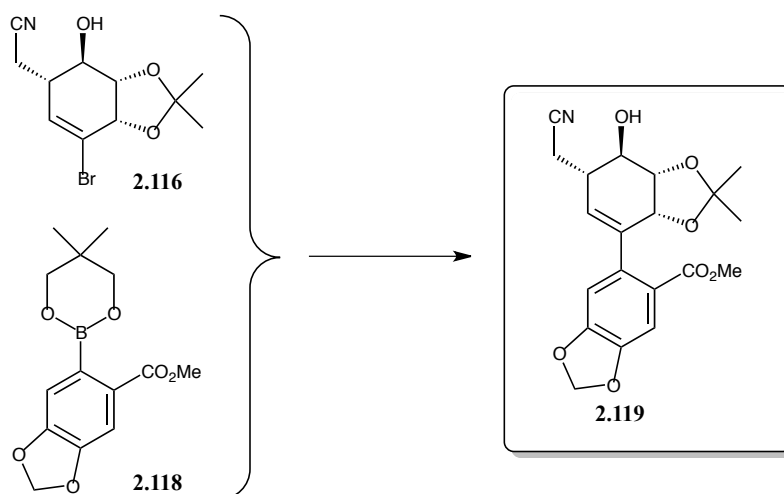


A magnetically stirred solution of lactam **2.160** (30 mg, 0.10 mmol) in THF (7.5 mL) maintained under a nitrogen atmosphere was treated with lithium aluminum hydride (0.6 mL of a 1 M solution in THF, 0.6 mmol) and the resulting mixture heated at reflux for 3 h. The cooled reaction mixture was diluted with water (0.5 mL) and it was stirred for 5 min at 18 °C, treated with sodium hydroxide (0.5 mL of 1 M aqueous solution), stirred for 5 min and then diluted with additional water (2 mL). The resulting mixture was treated with ethyl acetate (10 mL) and the separated aqueous phase was extracted with ethyl acetate (2 $\times$ 5 mL). The combined organic phases were dried (MgSO_4), filtered

and concentrated under reduced pressure. The resulting yellow oil rapidly solidified to give poor-quality crystals. Accordingly, this material was dissolved in HPLC-grade ethyl acetate (5 mL) and the resulting was solution treated with TLC-grade silica gel (250 mg). This mixture was concentrated under reduced pressure to give free-flowing light-yellow powder that was added to the top of a flash chromatography column which was then eluted with 5:1:94 v/v/v methanol/triethylamine/ethyl acetate to give, after concentration of the appropriate fractions ($R_f = 0.2$), the *title compound* **2.127**⁸ (25.5 mg, 89%) as a white, crystalline solid, mp 154–157 °C (lit.⁷ mp 155–156 °C), $[\alpha]_D -64$ (c 0.94, ethanol) {lit.⁷ $[\alpha]_D -80$ (c 1.0, ethanol)} (Found: M^{+} , 285.1360. $C_{17}H_{19}NO_3$ requires M^{+} , 285.1365). ^1H NMR (CD_3OD , 600 MHz) δ 7.12 (1H, s), 6.61 (1H, s), 6.20 (1H, s), 5.93 (2H, m), 4.03 (1H, d, $J = 22.8$ Hz), 3.99 (1H, m), 3.50 (1H, m), 3.44 (3H, s), 3.19 (1H, m), 2.63 (1H, d, $J = 9.0$ Hz), 2.52 (1H, m), 2.36 (1H, m), 2.24 (1H, m), 2.16 (1H, m), 1.58 (1H, m), 1.22 (1H, q, $J = 12.6$ Hz); ^{13}C NMR (CD_3OD , 150 MHz) δ 149.1, 148.6, 134.5, 129.8, 128.1, 123.7, 107.6, 104.0, 102.6, 79.0, 63.1, 57.5, 56.4, 56.1, 35.0, 34.3, 31.2; ν_{max} (KBr) 2958, 2924, 2910, 2822, 2774, 1651 (weak), 1501, 1479, 1439, 1361, 1348, 1331, 1311, 1245, 1235, 1211, 1109, 1090, 1039, 941, 900, 877 cm^{-1} ; λ_{max} (ethanol) 265 (log $\epsilon = 4.01$), 274 (shoulder, 3.94) and 309 (3.76) [lit.⁵ λ_{max} (ethanol) 265 (log $\epsilon = 4.09$) and 310 (3.84)]; Mass spectrum (EI, 70 eV) m/z 285 (M^{+} , 55%), 284 (93), 254 (100), 252 (50), 227 (20).

Compound **2.119**

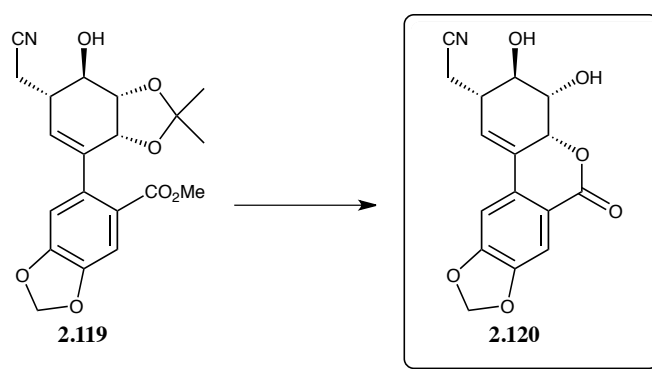
[(3*aR*,6*S*,7*R*,7*aS*)-6-(Cyanomethyl)-3*a*,6,7,7*a*-tetrahydro-7-hydroxy-2,2-dimethyl-4,5'-bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]



A solution of acetonide **2.116** (1.10 g, 3.82 mmol) in THF (30 mL) was treated with boronate **2.118** (1.34 g, 4.59 mmol, 1.2 mol equiv.), Cs₂CO₃ (3.51 g, 10.8 mol), potassium acetate (500 mg, 5.1 mmol) and water (3 mL). The ensuing mixture was sparged with nitrogen then treated PdCl₂(dppf)·CH₂Cl₂ (164 mg, 0.02 mmol, 5.3 mole %) then sparged again with nitrogen for 10 min. The ensuing mixture was heated at reflux for 3 h then cooled, diluted with ethyl acetate (75 mL) and washed with brine (1 × 20 mL) before being dried (MgSO₄) then filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane) to give, after concentration of the appropriate fractions (*R*_f = 0.33 in 2:3 v/v ethyl acetate/hexane), the *title compound* **2.119** (1.13 g, 79%) as a clear, light-yellow oil, [α]_D +44 (*c* 0.65, chloroform-*d*) (Found: *M*⁺, 387.1321. C₂₀H₂₁NO₇ requires *M*⁺, 387.1318). ¹H NMR (CDCl₃, 600 MHz) δ 7.43 (1H, s), 6.75 (1H, s), 6.05 (1H, d, *J* = 1.2 Hz), 6.03 (1H, d, *J* = 1.2 Hz), 5.55 (1H, d, *J* = 2.7 Hz), 4.84 (1H, d, *J* = 6.2 Hz), 4.29 (1H, t, *J* = 6.8 Hz), 3.82 (3H, s), 3.76 (1H, q, *J* = 7.2 Hz), 2.95 (1H, d, *J* = 5.5 Hz), 2.81–2.75 (1H, complex m), 2.71–2.64 (2H, complex m), 1.50 (3H, s), 1.32 (3H, s); ¹³C NMR (CDCl₃, 150 MHz) δ 166.5, 150.7, 147.3, 140.0, 138.0, 126.4, 121.7, 118.1, 111.4, 110.1, 110.0, 102.1, 78.4, 74.8, 71.0, 52.1, 37.9, 28.1, 25.6, 19.7; $\nu_{\max}$ (KBr) 3468, 2988, 2910, 2249, 1715, 1613, 1504, 1486, 1437, 1372, 1250, 1218, 1163, 1125, 1062, 1037, 872 cm⁻¹; Mass spectrum (EI, 70 eV) *m/z* 387 (*M*⁺, 55%), 372 (28), 329 (64), 297 (40), 280 (100), 270 (32), 257 (48), 251 (86), 228 (39).

Compound **2.120**

[(2*S*,3*R*,4*S*,4*aR*)-2,4,4*a*,6-Tetrahydro-3,4-dihydroxy-6-oxo-1*H*-[1,3]benzodioxolo[5,6-*c*][1]benzopyran-2-acetonitrile]

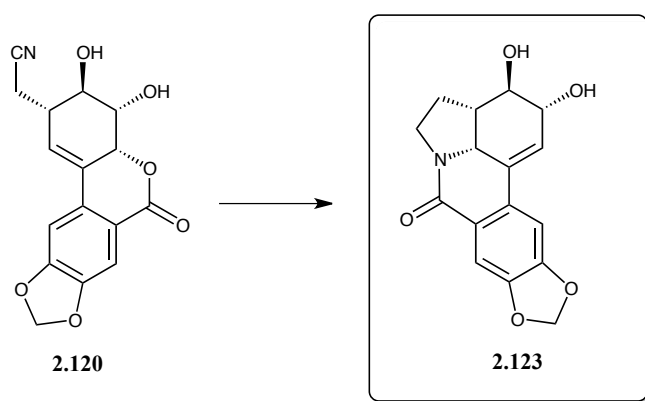


A magnetically stirred solution of compound **2.119** (265 mg, 0.68 mmol) in acetic acid/water (20 mL of a 4:1 v/v mixture) was heated at 45 °C for 2 h in a flask open

to the atmosphere then cooled and concentrated under reduced pressure. The residue so obtained was dissolved in ethyl acetate (25 mL) and the resulting solution washed with sodium bicarbonate (1 × 25 mL of a saturated aqueous solution) before being dried (MgSO₄), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1.5:98.5 v/v methanol/diethyl ether) to afford, after concentration of the appropriate fractions ($R_f = 0.3$), the *title compound* **2.120** (140 to 177 mg, 65 to 82%) as a white, crystalline solid, mp 162–164 °C (ex ethyl acetate), $[\alpha]_D^{+92}$ (c 0.4, CD₃COCD₃) (Found: M^{+} , 315.0744. C₁₆H₁₃NO₆ requires M^{+} , 315.0743). ¹H NMR (CD₃COCD₃, 600 MHz) δ 7.38 (1H, s), 7.24 (1H, s), 6.43–6.41 (1H, complex m), 6.16 (2H, d, $J = 10.3$ Hz), 5.28 (1H, m), 4.70 (1H, broad s), 4.64 (1H, d, $J = 3.5$ Hz), 4.30–4.26 (1H, complex m), 4.14 (1H, m), 2.96 (1H, dd, $J = 16.8$ and 8.6 Hz), 2.84 (1H, dd, $J = 16.8$ and 7.2 Hz), 2.73 (1H, m); ¹³C NMR (CD₃OD, 150 MHz) δ 165.0, 154.9, 150.5, 135.3, 128.7, 125.9, 120.7, 119.8, 109.9, 104.4, 104.1, 77.0, 71.2, 71.1, 42.1, 22.1; $\nu_{\max}$ (KBr) 3381, 2914, 2248, 1698, 1614, 1502, 1482, 1391, 1280, 1247, 1083, 1068, 1034, 931, 868 cm⁻¹; Mass spectrum (EI, 70 eV) m/z 315 (M^{+} , 47%), 256 (100), 255 (89), 227 (23), 215 (51).

Compound **2.123**

[(2*R*,3*R*,3*aS*,12*cR*)-2,3,3*a*,4,5,12*c*-Hexahydro-2,3-dihydroxy-7*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one]

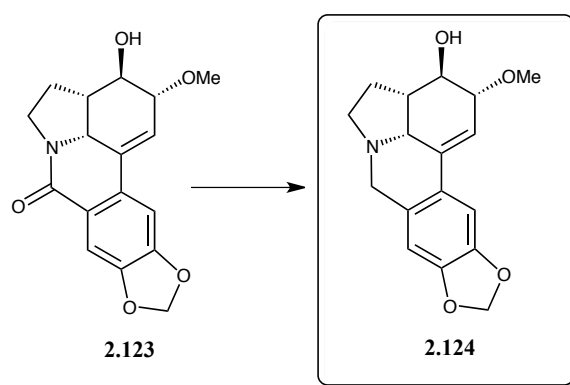


A magnetically stirred solution of compound **2.120** (170 mg, 0.54 mmol) in methanol (10 mL saturated with gaseous ammonia) contained in a Parr hydrogenation bomb was treated with Raney-Co⁶ (100 mg of wet material) and the resulting mixture was sparged with hydrogen for 5 min. The bomb was pressurized under hydrogen at

3500 kPa then heated at 65 °C for 2.5 h. The cooled reaction mixture was poured from the opened bomb through a sintered glass funnel. The filtrate was treated with TLC-grade silica gel (400 mg) and the ensuing mixture concentrated under reduced pressure to give free-flowing light-yellow powder. This material was added to the top of a flash chromatography column which was eluted with 15:85 v/v methanol/diethyl ether to give, after concentration of the appropriate fractions ($R_f = 0.4$), the *title compound* **2.123** (82 mg, 51%) as a white, crystalline solid, mp 138–141 °C, $[\alpha]_D -51.9$ (c 0.4, methanol) (Found: M^+ , 301.0948. $C_{16}H_{15}NO_5$ requires M^+ , 301.0950). ^1H NMR (CD_3OD , 600 MHz) δ 7.33 (1H, s), 7.04 (1H, s), 6.04 (1H, d, $J = 0.7$ Hz), 6.03 (1H, d, $J = 0.8$ Hz), 5.96 (1H, m), 4.38 (1H, d, $J = 7.7$ Hz), 4.13 (1H, dt, $J = 8.1$ and 1.8 Hz), 3.74–3.67 (2H, complex m), 3.19 (1H, dd, $J = 11.2$ and 8.2 Hz), 2.52 (1H, m), 2.34–2.18 (2H, complex m) (signals due to OH protons not observed); ^{13}C NMR (CD_3OD , 150 MHz) δ 164.4, 152.9, 149.8, 134.5, 132.3, 129.9, 124.5, 107.9, 104.3, 103.6, 74.5, 74.0, 59.6, 44.6, 43.5, 26.7; ν_{max} (KBr) 3343, 1633, 1609, 1598, 1479, 1417, 1270, 1035, 930 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 301 (M^+ , 100%), 265 (66), 264 (45), 241 (32), 231 (63).

Compound **2.124**

[(2*R*,3*R*,3*aS*,12*cR*)-2,3*a*,4,5,7,12*c*-Hexahydro-3*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]-2-methoxy-3-hydroxy-phenanthridine]

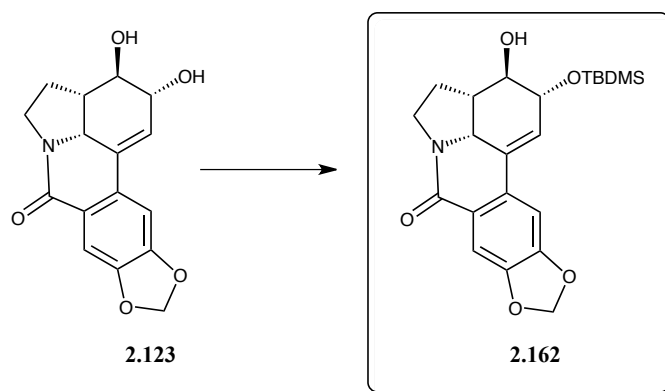


A magnetically stirred solution of lactam **2.123** (21 mg, 0.07 mmol) in THF (5 mL) maintained under a nitrogen atmosphere at 18 °C was treated with lithium aluminum hydride (0.6 mL of a 1 M solution in THF, 0.6 mmol) and the resulting mixture heated at reflux for 2 h. The cooled reaction mixture was poured into ammonium chloride (10 mL

of a saturated aqueous solution) and extracted with ethyl acetate (4×10 mL). The combined organic phases were washed with brine (1×10 mL) then dried (MgSO_4), filtered and concentrated under reduced pressure to give a light-yellow resin. Subjection of this material to flash chromatography (silica, 15:85 v/v methanol/diethyl ether elution) gave, after concentration of the appropriate fractions ($R_f = 0.3$), the *title compound 2.124* (15.5 mg, 78%) as a light-yellow resin, $[\alpha]_D -33.8$ (c 1.3, methanol) (Found: $(M - H)^+$, 286.1075. $\text{C}_{16}\text{H}_{17}\text{NO}_4$ requires $(M - H)^+$, 286.1079). ^1H NMR (CD_3OD , 600 MHz) δ 7.11 (1H, s), 6.63 (1H, s), 5.99 (1H, broad s), 5.95 (1H, d, $J = 0.9$ Hz), 5.94 (1H, d, $J = 0.9$ Hz), 4.15–4.12 (2H, complex m), 3.61 (1H, d, $J = 14.6$ Hz), 3.36–3.34 (1H, complex m), 3.27 (1H, dd, $J = 10.7$ and 8.5 Hz), 3.06 (1H, $J = 9.2$ Hz), 2.55 (1H, m), 2.42 (1H, m), 2.32–2.27 (1H, complex m), 1.87 (1H, m) (signals due to OH protons not observed); ^{13}C NMR (CD_3OD , 150 MHz) δ 149.5, 148.9, 132.6, 128.6, 127.4, 124.5, 107.6, 104.2, 102.8, 77.5, 74.1, 65.0, 56.9, 56.0, 41.3, 29.4; ν_{max} (KBr) 3344, 1503, 1483, 1245, 1072, 1037, 933, 920, 864 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 287 (M^+ , 85%), 286 [$(M - H)^+$, 100], 270 (51), 227 (19), 215 (42), 115 (15), 77 (13).

Compound 2.162

[(2*R*,3*R*,3*aS*,12*cR*)-2,3*a*,4,5,7,12*c*-Hexahydro-3*H*-[1,3]dioxolo[4,5-*j*]pyrrolo[3,2,1-*de*]-2-*O*-(*t*-butyl-dimethyl-silyl)-3-hydroxy-phenanthridine]

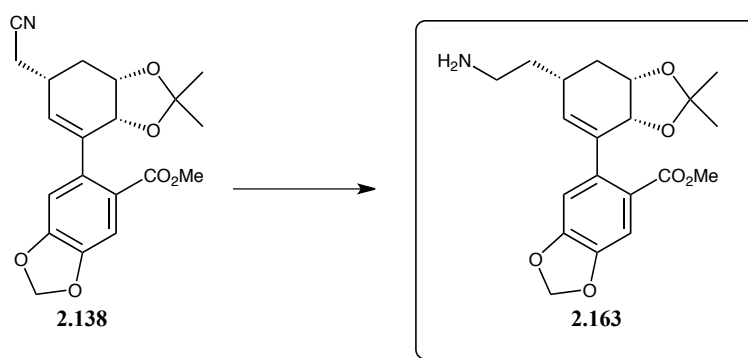


A magnetically stirred suspension of diol **2.123** (15 mg, 0.05 mmol) in anhydrous dichloromethane (2 mL) maintained at -78 °C was treated with triethylamine (17 μL , 0.13 mmol) and then, in one portion, with *tert*-butyldimethylsilyl triflate (TBDMSOTf) (12 μL , 0.05 mmol). The ensuing mixture was stirred at -78 °C for 1 h

after which time sodium bicarbonate (10 mL of a saturated aqueous solution) was added. The reaction mixture was then allowed to warm to 18 °C and extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure to afford a light-yellow oil that was subjected to flash chromatography (silica, ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.4) then gave the *silyl ether* **2.162** (10 mg, 48%) as a white, crystalline solid, mp 94 – 97 °C, $[\alpha]_D$ –122.4 (c 1.3, CDCl₃). (Found: M^{+} , 415.1813. C₂₂H₂₉NO₅Si requires M^{+} , 415.1815). ¹H NMR (CDCl₃, 600 MHz) δ 7.51 (1H, s), 6.84 (1H, s), 6.04 (1H, d, J = 1.4 Hz), 6.02 (1H, d, J = 1.4 Hz), 5.75 (1H, t, J = 1.8 Hz), 4.32 (1H, m, J = 8.2 Hz), 4.21 (1H, dt, J = 7.8 and 2.0 Hz), 3.82–3.70 (2H, complex m), 3.34 (1H, m), 2.56–2.51 (1H, complex m), 2.51 (1H, d, J = 2.0 Hz), 2.33–2.27 (1H, complex m), 2.24–2.17 (1H, complex m), 0.94 (9H, s), 0.19 (3H, s), 0.18 (3H, s); ¹³C NMR (CDCl₃, 150 MHz) δ 162.2, 150.7, 148.3, 132.1, 131.7, 127.4, 124.2, 107.8, 102.9, 101.8, 74.5, 73.6, 57.9, 43.6, 41.4, 25.8(2), 25.7(9), 18.1, –4.3, –4.6; $\nu_{\max}$ (KBr) 3289, 2929, 2856, 1638, 1601, 1502, 1479, 1465, 1418, 1396, 1360, 1270, 1250, 1086, 1036, 837, 777 cm^{–1}; Mass spectrum (EI, 70 eV) m/z 415 (M^{+} , 49%), 358 (100), 345 (25), 266 (87), 241 (22), 75 (58), 73 (41).

Compound **2.163**

[(3*aR*,6*R*,7*aS*)-6-(2-Aminoethyl)-3*a*,6,7,7*a*-tetrahydro-2,2-dimethyl-4,5'-bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]

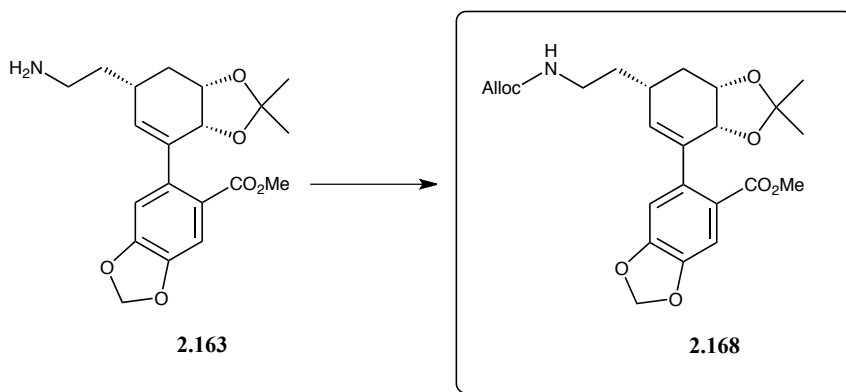


A magnetically stirred solution of compound **2.138** (990 mg, 2.67 mmol) in ammoniacal methanol (20 mL saturated) contained in a Parr hydrogenation bomb was treated with Raney-Co⁶ (400 mg of wet material) and the resulting mixture was sparged with hydrogen for 5 min. The bomb was then pressurized with hydrogen at 6000 kPa then heated at 45 °C for 2 h. The ensuing mixture was cooled, depressurized and the

supernatant liquid decanted. The residual Raney-Co was washed with methanol (20 mL). The combined methanolic solutions were concentrated under reduced pressure to give the *title compound* **2.163** (990 mg, quant.) as a colourless paste, $[\alpha]_D = +11.6$ (*c* 0.8, CDCl_3) (Found: $(M + H)^+$, 376.1760. $\text{C}_{20}\text{H}_{25}\text{NO}_6$ requires $(M + H)^+$, 376.1760). ^1H NMR (CDCl_3 , 400 MHz) δ 7.35 (s, 1H), 6.76 (s, 1H), 6.02 (d, $J = 1.4$ Hz, 1H), 6.01 (d, $J = 1.4$ Hz, 1H), 5.58 (d, $J = 2.6$ Hz, 1H), 4.69 (dd, $J = 5.9$ and 0.8 Hz, 1H), 4.37 (m, 1H), 3.78 (s, 3H), 2.86-2.75 (complex m, 2H), 2.34-2.24 (complex m, 1H), 1.97 (dt, $J = 12.5$ and 4.7 Hz, 1H), 1.70-1.56 (complex m, 2H), 1.51-1.43 (complex m, 1H), 1.47 (s, 3H), 1.42 (broad s, 2H, NH_2), 1.29 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) 167.0, 150.2, 146.7, 138.7, 136.7, 133.8, 122.6, 111.4, 109.9, 108.6, 101.8, 74.0, 73.8, 51.9, 39.8, 39.2, 32.0, 31.9, 28.5, 26.0; ν_{max} 3378, 2928, 1719, 1613, 1503, 1485, 1436, 1369, 1245, 1216, 1125, 1039 cm^{-1} ; Mass spectrum (ESI, +ve) 376 $[(M + H)^+]$, 15%, 318 (25), 300 (100), 268 (99), 251 (42). This material was used, without purification, in the next step of the reaction sequence.

Compound **2.168**

[(3*aR*,6*R*,7*aS*)-3*a*,6,7,7*a*-Tetrahydro-2,2-dimethyl-6-[2-[(2-propen-1-yloxy)-carbonyl]amino]ethyl]-4,5'-Bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]

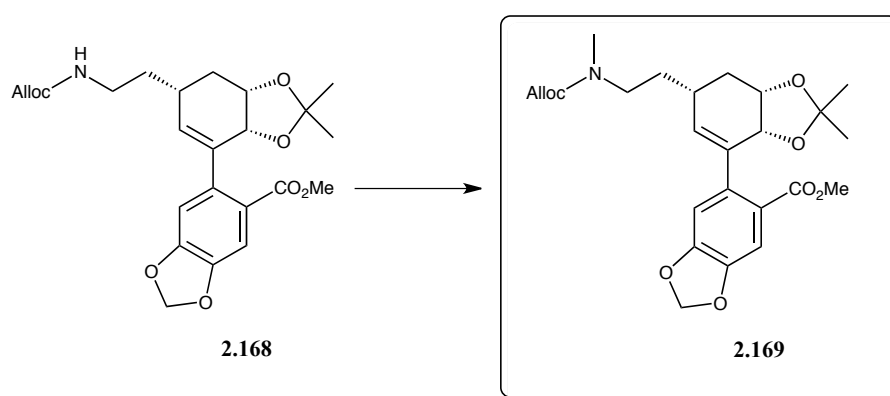


A magnetically stirred solution of the amine **2.163** (990 mg, 2.66 mmol), obtained as described above, in anhydrous pyridine (20 mL) maintained at 0 °C was treated, dropwise, with allyl chloroformate (330 μL , 3.07 mmol). After 0.25 h the reaction mixture was quenched with sodium hydrogen carbonate (20 mL of a saturated aqueous solution), stirred for 0.25 h at 0 °C then concentrated under reduced pressure. The ensuing residue was extracted with ethyl acetate (2×25 mL) and the combined

organic fractions were washed with brine (1 x 15 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica gel, 1:1 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions ($R_f = 0.4$ in 1:2 v/v ethyl acetate/hexane), the *title compound 2.168* (1.08 g, 88% from **2.138**) as a clear, colorless oil, $[\alpha]_D = +25.0$ (c 2.3, CDCl_3) (Found: $(M + \text{Na})^+$, 482.1791. $\text{C}_{24}\text{H}_{29}\text{NO}_8$ requires $(M + \text{Na})^+$, 482.1791). ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 6.74 (s, 1H), 6.03 (d, $J = 1.4$ Hz, 1H), 6.01 (d, $J = 1.4$ Hz, 1H), 5.91 (m, 1H), 5.58 (d, $J = 2.8$ Hz, 1H), 5.29 (m, 1H), 5.20 [m, 1H], 4.78 (broad s, 1H, NH), 4.71 (dd, $J = 6.0$, and 0.9 Hz, 1H), 4.55 (d, $J = 5.4$ Hz, 2H), 4.39 (ddd, $J = 8.9$, 5.9 and 4.6 Hz, 1H), 3.79 (s, 3H), 3.28 (m, 2H), 2.33-2.23 (complex m, 1H), 2.00 (dt, $J = 12.8$ and 4.8 Hz, 1H), 1.81-1.64 (complex m, 2H), 1.56 (dt, $J = 13.3$ and 8.8 Hz, 1H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 156.2, 150.2, 146.7, 138.7, 137.3, 132.7, 132.6, 122.5, 117.6, 111.5, 109.9, 108.7, 101.8, 73.9, 73.8, 65.4, 51.8, 38.9, 35.3, 31.7, 31.4, 28.4, 25.8; ν_{max} 3348, 2934, 1719, 1528, 1504, 1485, 1437, 1369, 1245, 1126, 1039 cm^{-1} ; Mass spectrum (ESI, +ve) 482 $[(M + \text{Na})^+]$, 100%, 305 (16), 304 (22).

Compound **2.169**

[(3*aR*,6*R*,7*aS*)-3*a*,6,7,7*a*-Tetrahydro-2,2-dimethyl-6-[2-[methyl[(2-propen-1-yloxy)-carbonyl]amino]ethyl]-4,5'-Bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]

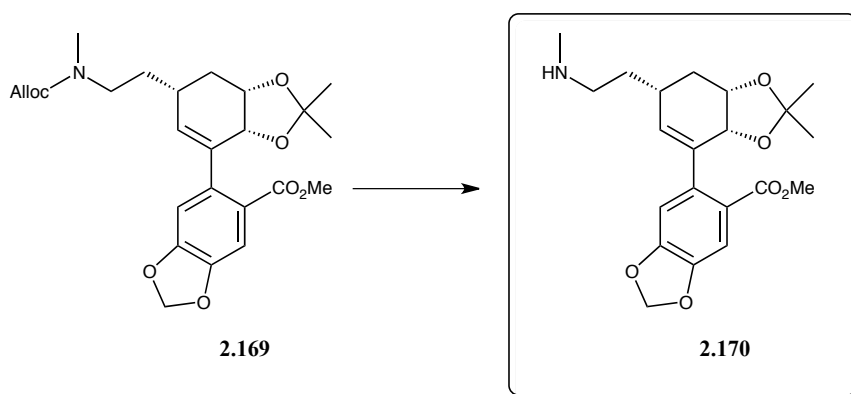


A magnetically stirred solution of compound **2.168** (601 mg, 1.31 mmol) in anhydrous THF (20 mL) at maintained at -78°C was treated, dropwise, with lithium hexamethyldisilazide (1.96 mL of a 1 M solution in hexanes, 1.96 mmol). The ensuing mixture was stirred at -78°C for 0.33 h then treated, dropwise, with methyl iodide (163 μL , 2.62 mmol) before being allow to warm to ambient temperatures. After 0.5 h the

reaction was treated with ammonium chloride (20 mL of a saturated aqueous solution) and the ensuing mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (1 × 20 mL) then dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f = 0.4 in 1:2 v/v ethyl acetate/hexane), the *title compound* **2.169** (610 mg, 98%) as a colorless paste, $[\alpha]_D^{25} = +23.1$ (c 6.7, CDCl₃) (Found: M^{+} , 473.2053. C₂₅H₃₁NO₈ requires M^{+} , 473.2050). ¹H NMR (400 MHz, CDCl₃) δ 7.36 (broad s, 1H), 6.75 (s, 1H), 6.04-6.03 (complex m, 2H), 5.98-5.85 (complex m, 1H), 5.63-5.56 (complex m, 1H), 5.32-5.24 (complex m, 1H), 5.22-5.14 (complex m, 1H), 4.71 (broad d, J = 6.0 Hz, 1H), 4.57 (dt, J = 6.0 and 1.4 Hz, 2H), 4.39 (ddd, J = 9.0, 6.0 and 4.6 Hz, 1H), 3.79 (s, 3H), 3.44-3.26 (complex m, 2H), 2.91 (s, 3H), 2.25-2.15 (complex m, 1H), 2.01 (m, 1H), 1.82-1.67 (complex m, 2H), 1.63-1.51 (complex m, 1H), 1.47 (s, 3H), 1.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (mixture of rotamers) 166.8, 156.0, 150.2, 146.7, 138.7, 137.3, 137.1, 133.1, 132.9, 132.7, 122.5, 117.3, 117.0, 111.5, 109.9, 108.6, 101.8, 73.9, 73.8, 65.8, 51.8, 47.0, 46.5, 34.4, 33.8, 33.3, 32.8, 31.8, 31.6, 28.4, 25.8; ν_{max} 2932, 1702, 1485, 1369, 1244, 1202, 1127, 1039 cm⁻¹; Mass spectrum (EI, 70 eV) m/z 473 (M^{+} , <1%), 458 (4), 415 (13), 397 (11), 383 (16), 366 (14), 342 (16), 308 (33), 298 (41), 282 (95), 269 (56), 267 (60), 255 (65), 238 (64), 128 (40), 84 (100).

Compound **2.170**

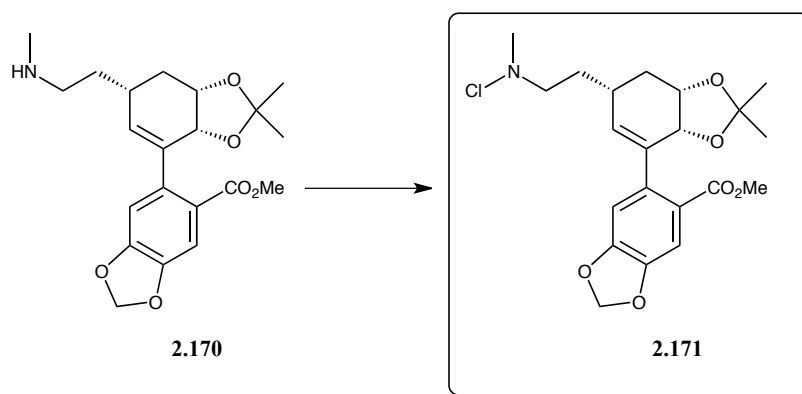
[(3*aR*,6*R*,7*aS*)-3*a*,6,7,7*a*-Tetrahydro-2,2-dimethyl-6-[2-(methylamino)ethyl]-4,5'-bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]



A magnetically stirred solution of carbamate **2.169** (637 mg, 1.35 mmol) in anhydrous and degassed THF (15 mL) was treated with dimedone (1.88 g, 13.5 mmol). After 5 minutes tetrakis(triphenylphosphine)palladium[0] (312 mg, 0.27 mmol) was added to the reaction mixture which was stirred at 18 °C for 0.33 h then diluted with CH₂Cl₂ (300 mL), washed with sodium hydrogen carbonate (3 × 20 mL of a saturated aqueous solution) then brine (1 x 30 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica, 1:10 v/v ammonia saturated methanol/CH₂Cl₂ elution) thereby affording, after concentration of the relevant fractions (*R*_f = 0.3), the amine **2.170** (520 mg, 99%) as a clear, colorless oil, [α]_D = +11.9 (*c* 2.0, CDCl₃) (Found: *M*⁺, 389.1835. C₂₁H₂₇NO₆ requires *M*⁺, 389.1838). ¹H NMR (400 MHz, CDCl₃) δ 7.33 (s, 1H), 6.75 (s, 1H), 6.00 (d, *J* = 1.4 Hz, 1H), 5.99 (d, *J* = 1.4 Hz, 1H), 5.57 (d, *J* = 2.7 Hz, 1H), 4.68 (dd, *J* = 5.9 and 1.1 Hz, 1H), 4.35 (ddd, *J* = 9.8, 5.8 and 4.8 Hz, 1H), 3.77 (s, 3H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.42 (s, 3H), 2.31-2.22 (complex m, 1H), 1.97 (dt, *J* = 12.6 and 4.7 Hz, 1H), 1.74-1.57 (complex m, 2H), 1.46 (dt, *J* = 12.6 and 9.6 Hz, 1H), 1.46 (s, 3H), 1.28 (s, 3H) (signal due to NH proton not observed); ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 150.1, 146.7, 138.7, 136.6, 133.8, 122.6, 111.4, 109.9, 108.6, 101.8, 74.0, 73.7, 51.8, 49.6, 36.5, 35.4, 32.2, 32.0, 28.5, 25.9; $\nu_{\max}$ 3418, 2984, 2930, 1719, 1614, 1503, 1485, 1436, 1369, 1245, 1124, 1039, 929, 872 cm⁻¹; Mass spectrum (EI, 70 eV) *m/z* 389 (*M*⁺, 30%), 374 (52), 314 (77), 277 (45), 238 (100).

Compound **2.171**

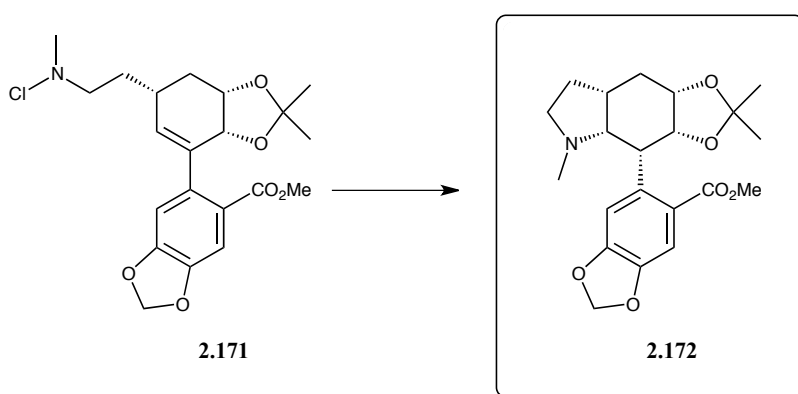
[(3*aR*,6*R*,7*aS*)-6-[2-(Chloromethylamino)ethyl]-3*a*,6,7,7*a*-tetrahydro-2,2-dimethyl-4,5'-bi-1,3-benzodioxole]-6'-carboxylic acid methyl ester]



A magnetically stirred solution of amine **15** (218 mg, 0.56 mmol) in CH_2Cl_2 maintained at $-30\text{ }^\circ\text{C}$ was treated, in one portion, with *N*-chlorosuccinimide (79 mg, 0.59 mmol). After 0.5 h the reaction mixture was diluted with ethyl acetate/hexane (40 mL of a 1:4 v/v mixture) then filtered through a pad of flash chromatography-grade silica gel contained in a sintered glass filter funnel. The pad was washed with ethyl acetate/hexane (50 mL of 1:4 v/v mixture) and the combined filtrates were concentrated under reduced pressure to afford the *title compound* **2.171** (211 mg, 88%) as a colorless foam, $[\alpha]_{\text{D}} = +17.4$ (c 2.0, CDCl_3), $R_{\text{f}} = 0.6$ (1:2 v/v ethyl acetate/hexane elution) (Found: M^+ , 423.1433. $\text{C}_{21}\text{H}_{26}\text{ClNO}_6$ requires M^+ , 423.1449). ^1H NMR (400 MHz, CDCl_3) δ 7.35 (s, 1H), 6.77 (s, 1H), 6.02 (s, 1H), 6.01 (s, 1H), 5.59 (d, $J = 2.6$ Hz, 1H), 4.70 (d, $J = 6.1$ Hz, 1H), 4.38 (m, 1H), 3.78 (s, 3H), 2.96 (t, $J = 7.1$ Hz, 2H), 2.93 (s, 3H), 2.38-2.28 (complex m, 1H), 1.99 (dt, $J = 12.5$ and 4.7 Hz, 1H), 1.93-1.85 (complex m, 1H), 1.83-1.75 (complex m, 1H), 1.51 (dt, $J = 12.5$ and 9.1 Hz, 1H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 150.2, 146.7, 138.7, 137.0, 133.3, 122.7, 111.4, 109.9, 108.7, 101.8, 74.0, 73.8, 63.8, 53.1, 51.8, 33.6, 31.8, 31.7, 28.4, 25.9; ν_{max} 2932, 1720, 1614, 1504, 1485, 1436, 1369, 1245, 1125, 1039 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 423 (M^+ , < 1%), 410 and 408 (2 and 5, respectively), 388 (14), 374 and 372 (10 and 30, respectively), 330 (13), 314 (21), 280 (29), 255 (50), 254 (100), 238 (44), 226 (25), 96 (65). All attempts to purify this compound using chromatographic techniques led to significant loss of material. Accordingly, it was used ‘as obtained’ in the next step of the reaction sequence.

Compound **2.172**

[6-[(3*aR*,4*R*,4*aR*,7*aR*,8*aS*)-Octahydro-2,2,5-trimethyl-4*H*-1,3-dioxolo[4,5-*f*]indol-4-yl]-1,3-benzodioxole-5-carboxylic acid methyl ester]



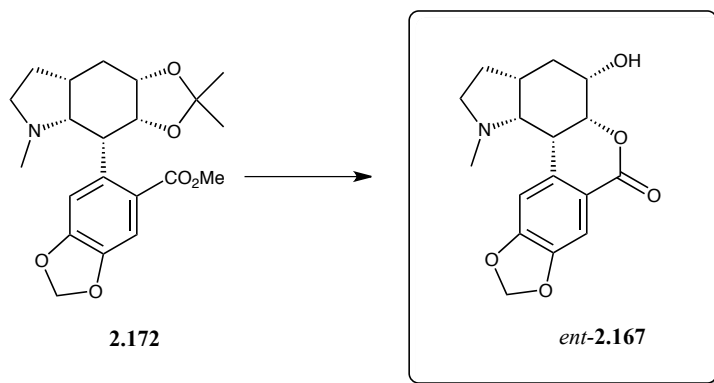
A magnetically stirred solution of *N*-chloroamine **2.171** (72 mg, 0.17 mmol) and tri-*n*-butyltin hydride (57 mg, 0.19 mmol) in anhydrous and degassed benzene (17 mL) was treated with AIBN (1.6 mg, 9.8 μ mol) and the mixture so obtained was heated under reflux for 1 h then cooled and frozen before the benzene was removed by vacuum sublimation. The residual oil was subjected to flash chromatography (silica, 1:20 v/v ammonia saturated methanol/CH₂Cl₂ elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:10 v/v ammonia saturated methanol/CH₂Cl₂) gave the *title compound* **2.172** (15 mg, 23% or 77% based on recovered **2.170**) as a clear, colorless oil, $[\alpha]_D = +5.8$ (c 0.8, CDCl₃) (Found: M^+ , 389.1838. C₂₁H₂₇NO₆ requires M^+ , 389.1838). ¹H NMR (400 MHz, C₆D₆) δ 8.42 (s, 1H), 7.57 (s, 1H), 5.28-5.23 (complex m, 2H), 4.37 (dd, J = 4.7 and 2.7 Hz, 1H), 4.30 (dd, J = 8.0 and 1.8 Hz, 1H), 4.11-4.03 (complex m, 1H), 3.48 (s, 3H), 3.13-2.99 (complex m, 2H), 2.53 (ddd, J = 22.3, 11.2 and 6.6 Hz, 1H), 2.47-2.35 (complex m, 1H), 2.01 (ddd, J = 11.5, 8.7 and 5.8 Hz, 1H), 1.87 (dt, J = 15.4 and 2.4 Hz, 1H), 1.84 (s, 3H), 1.63-1.57 (complex m, 2H), 1.55 (s, 3H), 1.12 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 167.5, 150.9, 146.3, 141.2, 122.9, 113.7, 110.2, 107.6, 101.6, 75.8, 73.7, 65.8, 57.8, 51.4, 44.6, 39.7, 36.6, 30.8, 27.7, 26.0, 23.2; ν_{max} 2904, 1713, 1617, 1505, 1486, 1434, 1378, 1345, 1253, 1229, 1203, 1119, 1039 cm⁻¹; Mass spectrum (EI, 70 eV) m/z 389 (M^+ , 25%), 374 (4), 358 (3), 314 (5), 300 (2), 126 (10), 96 (100), 83 (25), 82 (17).

Concentration of fraction B (R_f = 0.3 in 1:10 v/v ammonia saturated methanol/CH₂Cl₂) afforded the dechlorinated compound **2.170** (48 mg, 71%) as clear, colorless oil that was identical, in all respects, with an authentic sample.

Compound *ent*-**2.167**

[(3*aR*,5*S*,5*aR*,12*bR*,12*cR*)-2,3,3*a*,4,5,5*a*,12*b*,12*c*-Octahydro-5-hydroxy-1-methyl-1,3]dioxolo[6,7][2]benzopyrano[3,4-*g*]indol-7(1*H*)-one]



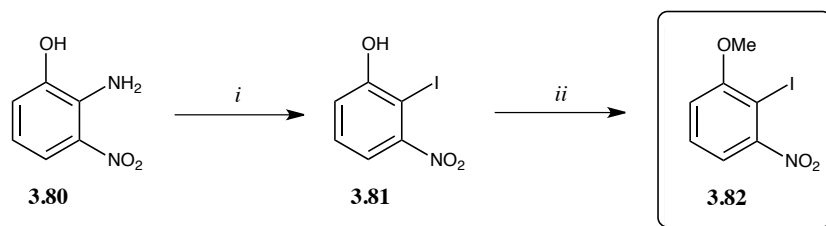
A solution of compound **2.172** (25 mg, 0.064 mmol) in methanol/water (3.0 mL of a 1:1 v/v mixture) was treated with DOWEX-50WX8-100 ion exchange resin (80 mg) and resulting mixture heated under reflux for 12 h. The cooled reaction mixture was diluted with CH₂Cl₂ (50 mL) then quenched with sodium hydrogen carbonate (2 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH₂Cl₂ (1 x 15 mL) then the combined organic phases were dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:20 v/v ammonia saturated methanol/CH₂Cl₂) and concentration of the appropriate fractions (*R_f* = 0.5 in 1:10 v/v ammonia saturated methanol/CH₂Cl₂) gave a clear, colorless oil that crystallized from CDCl₃ and thereby affording *compound ent*-**2.167** (19 mg, 93%) as a white crystalline solid, m.p. = 207-210 °C, [α]_D = +56.2 (*c* 0.4, CDCl₃) (Found: *M*⁺, 317.1263. C₁₇H₁₉NO₅ requires *M*⁺, 317.1265). ¹H NMR (800 MHz, CDCl₃) δ 7.54 (s, 1H), 6.70 (s, 1H), 6.05 (m, 2H), 4.61 (t, *J* = 2.5 Hz, 1H), 3.74 (ddd, *J* = 11.7, 3.7 and 2.9 Hz), 3.31 (td, *J* = 10.6 and 6.8 Hz, 1H), 2.87 (dd, *J* = 4.6 and 3.0 Hz), 2.60 (t, *J* = 4.9 Hz, 1H), 2.37-2.33 (complex m, 1H), 1.95-1.90, (complex m, 1H), 1.88 (q, *J* = 12.4 Hz, 1H), 1.78 (dt, *J* = 10.3 & 4.9 Hz, 1H), 1.47-1.44 (complex m, 1H), 1.45 (s, 3H); ¹³C NMR (200 MHz, CDCl₃) δ 164.7, 151.9, 147.6, 137.8, 121.0, 109.8, 106.6, 101.9, 78.0, 69.7, 67.7, 55.0, 45.2, 41.0, 39.4, 30.9, 29.8; $\nu_{\max}$ 3384, 2926, 2784, 1706, 1615, 1503, 1482, 1449, 1385, 1281, 1247, 1120, 1086 cm⁻¹; Mass spectrum (EI, 70 eV) *m/z* 317 (*M*⁺, 37%), 162 (6), 126 (6), 96 (75), 83 (100), 82 (45).

5.3 Experimental Section for Chapter Three

Compounds **3.21**, **3.78** and **3.79** were obtained from commercial sources.

Compound **3.82**

[2-Iodo-1-methoxy-3-nitrobenzene]



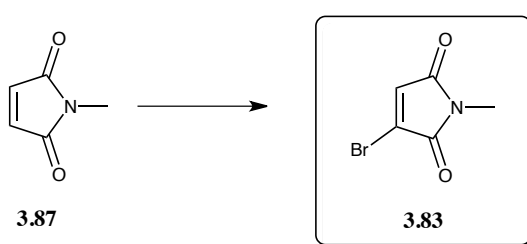
Step i: A mixture of DMSO (40 mL) and H₂SO₄ (40 mL of a 30% v/v aqueous solution) was treated with 2-amino-3-nitrophenol [**3.80**] (2.48 g, 16.1 mmol). The ensuing mixture stirred at 50 °C for 1 h then cooled to 0 °C and it was treated, over 5 min, with a solution of sodium nitrite (1.52 g, 22 mmol) in water (5 mL). The reaction mixture was stirred at 0 °C for 1 h then treated, in one portion, with potassium iodide (7.50 g, 45 mmol) in water (15 mL). After a further 1 h the reaction mixture was warmed to 18 °C, kept at this temperature for 0.5 h then extracted with diethyl ether (1 x 100 mL). The separated organic phase was washed with sodium thiosulfate (2 x 25 mL of a saturated aqueous solution), water (2 x 25 mL) then brine (1 x 25 mL) before being dried (MgSO₄), then filtered and concentrated under reduced pressure to give a crude sample of 2-iodo-3-nitrophenol⁹ [**3.81**] (3.46 g, *ca.* 81%) as an orange-brown solid. This material was used ‘as obtained’ in the next step of the reaction sequence.

Step ii: A solution of 2-iodo-3-nitrophenol [**3.81**] (2.48 g, 9.36 mmol) in DMF (15 mL) was treated with anhydrous K₂CO₃ (6.22 g, 45 mmol). The ensuing mixture was stirred vigorously at 18 °C for 0.25 h then methyl iodide (0.64 mL, 10.3 mmol) was added in one portion. The resulting mixture was stirred at 18 °C for 5 h under nitrogen then diluted with sodium hydroxide (15 mL of a 2 M aqueous solution) and diethyl ether (25 mL). The separated aqueous phase was acidified with HCl (2 M aqueous solution to pH 4) then extracted with diethyl ether (3 x 25 mL). The combined organic phases were washed with water (1 x 40 mL) and brine (1 x 40 mL) before being dried (MgSO₄) then filtered. The filtrate was treated silica (5 g of TLC-grade material) and the ensuing mixture concentrated under reduced pressure to give a free-flowing orange powder. This

material was added to the top of a flash chromatography column (silica), which was eluted with 1:4 v/v ethyl acetate/hexane. Concentration of the relevant fractions ($R_f = 0.25$) afforded the *title compound* **3.82**¹⁰ (2.02 g, 77%) as vivid-orange crystals, m.p. = 102-103 °C (lit.⁹ m.p. = 102.5-103.5 °C) (Found: M^+ , 278.9392. C, 30.40; H, 2.26; N, 4.96. $C_7H_6INO_3$ requires M^+ , 278.9392. C, 30.13; H, 2.17; N, 5.02%). ^1H NMR (DMSO- d_6 , 300 MHz) δ 7.55 (t, $J = 8.0$ Hz, 1H), 7.39 (dd, $J = 8.0$ and 1.2 Hz, 1H), 7.25 (dd, $J = 8.0$ and 1.2 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 160.3, 156.6, 131.7, 117.0, 115.2, 81.3, 58.3; $\nu_{max}(KBr)$ 3079, 2923, 2852, 1581, 1523, 1463, 1428, 1349, 1295, 1268, 1184, 1047, 1019, 900, 792, 734 cm^{-1} ; Mass spectrum (EI, 70 eV) m/z 279 (M^+ , 100%), 218 (37), 203 (37), 76 (26), 63 (21).

Compound 3.83

[3-Bromo-1-methyl-1H-pyrrole-2,5-dione]

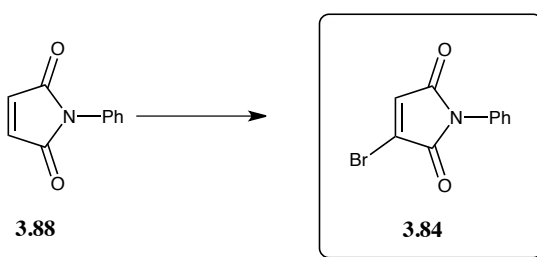


Molecular bromine (1 mL, 20 mmol) was added to magnetically stirred slurry of 1-methyl-1H-pyrrole-2,5-dione [**3.87**] (1.99 g, 18.0 mmol) in ether (25 mL). The ensuing mixture was heated at reflux for 1 h then cooled to 0°C and triethylamine (2.8 mL, 20 mmol) added. The reaction mixture was then stirred for a further 2 h at 0 °C before being warmed to 18°C and diluted with ethyl acetate (40 mL) and water (40 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic phases were washed with water (1 × 30 mL) and brine (1 × 30 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to a pale-brown solid. This material was rinsed with hexane and then dried under reduced pressure to afford the *title compound* **3.83**^{11, 12} (3.42 g, 100%) as pale-brown plates, m.p. = 86 -88°C (lit.¹⁰ m.p. = 88 - 89°C) (Found: C, 31.78; H, 2.34; N, 7.23. M^+ , 188.9428. $C_5H_4^{79}BrNO_2$ requires C, 31.61; H, 2.12, N, 7.37%. M^+ , 188.9425). ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 1H), 3.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 165.2, 131.8, 131.1, 24.4; $\nu_{max}(KBr)$ 3104, 1777, 1713, 1589, 1442, 1385, 1259, 1161, 1107, 968, 869, 826, 762, 184

706 cm^{-1} ; MS (EI, 70 eV) m/z 189 and 191 (M^{+} , both 98%), 162 and 160 (20), 134 and 132 (80), 106 and 104 (70), 53 (100).

Compound **3.84**

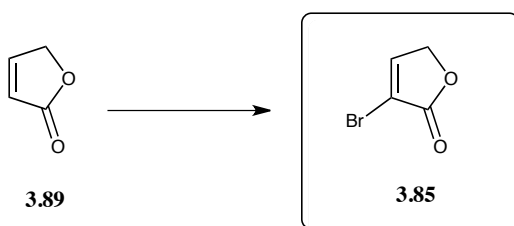
[3-Bromo-1-phenyl-1*H*-pyrrole-2,5-dione]



Bromination of 1-phenylmaleimide [**3.88**] in the same manner as described immediately above gave a brown solid on work up. Subjection of this material to flash chromatography (silica, 1:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) gave the *title compound* **3.84**¹³ (95%) as a white crystalline solid, m.p. = 157.5 - 158 °C (lit.¹² m.p. = 150 - 153 °C) (Found: M^{+} , 250.9579. C, 47.49; H, 2.37; N, 5.45. $\text{C}_{10}\text{H}_6^{79}\text{BrNO}_2$ requires M^{+} , 250.9582. C, 47.65; H, 2.40, N, 5.56%). ^1H NMR (300 MHz, CDCl_3) δ 7.55-7.30 (complex m, 6H); ^{13}C NMR (75 MHz, d_6 -DMSO) δ 168.0, 164.8, 132.7, 131.5, 130.9, 129.0, 128.2, 127.1; ν_{max} (KBr disk) 1719, 1591, 1504, 1398, 1193, 1149, 1048, 865, 848, 799, 751 cm^{-1} ; MS (EI, 70 eV) m/z 253 and 251 (M^{+} , 98 and 100%), 144 (25), 134 and 132 (32 and 34), 128 (46), 53 (52).

Compound **3.85**

[3-Bromofuran-2(5*H*)-one]

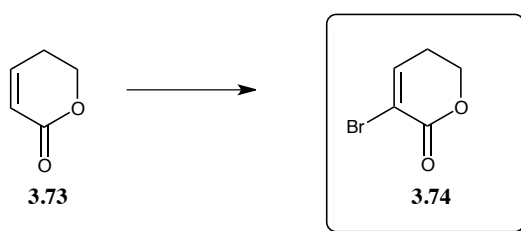


A magnetically stirred solution of 2(5*H*)-furanone [**3.89**] (2.11 g, 25.1 mmol) in diethyl ether (20 mL) that had been protected from light was treated, dropwise over 0.5 h,

with a solution of molecular bromine (1.5 mL, 4.81 g, 30 mmol) in diethyl ether (20 mL). The ensuing mixture was heated at reflux for 4 h then cooled to 18 °C. Excess bromine was removed by sparging the reaction mixture with nitrogen gas for 10 min. The resulting solution was cooled to -0°C (ice bath) treated, dropwise of over 10 min., with a solution of triethylamine (4.15 mL, 30 mmol) in diethyl ether (5.5 mL) then stirred for 1 h during which time it was allowed to warm to 18 °C. The ensuing mixture was washed with water (3 x 25 mL) and brine (1 x 25 mL) before being dried (MgSO₄) then filtered through a sintered glass funnel. The filtrate was treated with flash chromatography-grade silica gel (5 g) then concentrated, under reduced pressure, to a free-flowing powder. This was added to the top of a flash chromatography column, which was eluted with 1:2 v/v ethyl acetate/hexane. Concentration of the relevant fractions ($R_f = 0.3$) gave the *title lactone* **3.85**¹⁴ (2.96 g, 73%) as tan-colored crystals, m.p. = 57 - 58 °C (lit.¹³ m.p. = 56 - 58 °C) (Found: M^+ , 161.9316. C, 29.72; H, 1.99. C₄H₃⁷⁹BrO₂ requires M^+ , 161.9316. C, 29.48; H, 1.86%). ¹H NMR (CDCl₃, 300 MHz) δ 7.62 (t, $J = 1.9$ Hz, 1H), 4.86 (d, $J = 1.9$ Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.0, 149.7, 112.4, 71.5; $\nu_{\max}$ (KBr) 1785, 1758, 1605, 1453, 1346, 1279, 1156, 1048, 990, 830, 753, 719 cm⁻¹; MS (EI, 70 eV) m/z 164 and 162 (M^+ , 97 and 100%), 135 and 133 (36 and 37), 107 and 105 (both 22).

Compound 3.74

[3-Bromo-5,6-dihydropyran-2-one]

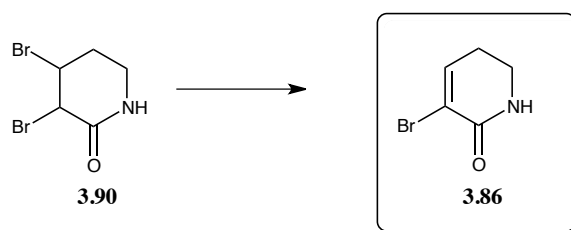


A magnetically solution of 5,6-dihydropyran-2-one [3.73] (1.0 g, 10.2 mmol) in dichloromethane (20 mL) maintained at 18 °C was treated, dropwise over 1.5 h, with a solution of molecular bromine (0.76 mL, 2.4 g, 15 mmol) in dichloromethane (15 mL). After a further 1.5 h the reaction mixture was treated, dropwise over 5 min, with a solution of triethylamine (2.2 mL, 11 mmol) in dichloromethane (20 mL). The ensuing mixture was stirred at 18 °C for 0.75 h washed with water (3 x 50 mL) and brine (1 x 50 mL) before being dried (MgSO₄), filtered and concentrated under reduced material to

give an amber-colored oil (2.02 g). This material was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane) and thus affording, after concentration of the appropriate fractions ($R_f = 0.25$) the *title lactone* **3.74**¹⁵ (1.66 g, 92%) as a pale-yellow solid, m.p. = 34 - 36 °C (lit.¹⁴ m.p. = 27 - 30 °C) (Found: M^+ , 175.9469. C, 33.97; H, 2.96. $C_5H_5^{79}BrO_2$ requires M^+ , 175.9473. C, 33.93; H, 2.85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 1H), 4.45 (t, $J = 6.0$ Hz, 2H), 2.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.4, 146.0, 113.8, 66.8, 26.7; $\nu_{max}(KBr)$ 2900, 1727, 1611, 1468, 1394, 1317, 1269, 1159, 1090, 1020, 965, 883, 850, 758 cm^{-1} ; MS (EI, 70 eV) m/z 178 and 176 (M^+ , 21 and 22%), 148 and 146 (40 and 38), 73 (65), 69 (100), 57 (76), 55 (80), 43 (95).

Compound **3.86**

[3-Bromo-5,6-dihydropyridin-2(1*H*)-one]



A magnetically stirred solution of 3,3-dibromo-2-piperidinone¹⁶ [**3.90**] (500 mg, 1.95 mmol) in DMF (15 mL) maintained under a nitrogen atmosphere was treated with $CaCO_3$ (250 mg, 2.50 mmol) and the resulting mixture heated at 80 °C for 36 h. The cooled reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic phases were washed with brine (3 x 50 mL) and water (1 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-brown oil was subjected to flash chromatography (silica, 3:97 v/v methanol/diethyl ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), the *title lactam* **3.86** (222 mg, 65%) as colourless needles, m.p. = 87.5 - 88 °C (Found: M^+ , 174.9633. C, 34.34; H, 3.44; N, 7.91. $C_5H_6^{79}BrNO$ requires M^+ , 174.9633. C, 34.12; H, 3.44; N, 7.96%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.04 (broad t, $J = 4.5$ Hz, 1H), 6.44 (broad s, 1H), 3.50 (m, 2H), 2.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 142.1, 118.1, 39.7, 26.4; $\nu_{max}(KBr)$ 3309, 3255, 3034, 2943, 2866, 1680, 1643, 1608, 1475, 1449, 1422, 1347, 1282, 1270, 1202, 1110, 1055, 1019, 994, 893, 878, 858, 845, 763, 704 cm^{-1} ; MS (EI, 70 eV) m/z 177 and

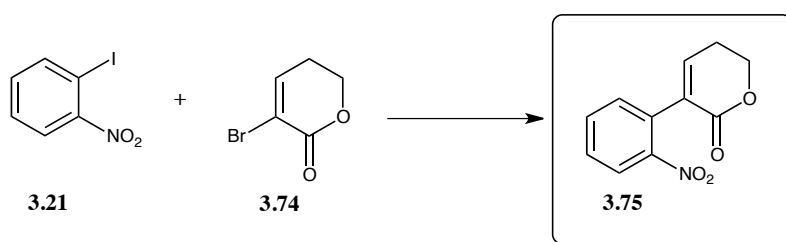
175 (M^{+} , 97 and 99%), 148 and 146 (97 and 100), 120 and 118 (41 and 42), 96 (43), 53 (31), 39 (66).

5.3.2 Standard Procedure for the Palladium[0]-catalysed Ullmann Cross-coupling Reaction Using Copper Bronze Powder. Formation of Compounds 3.75, 3.91 and 3.92.

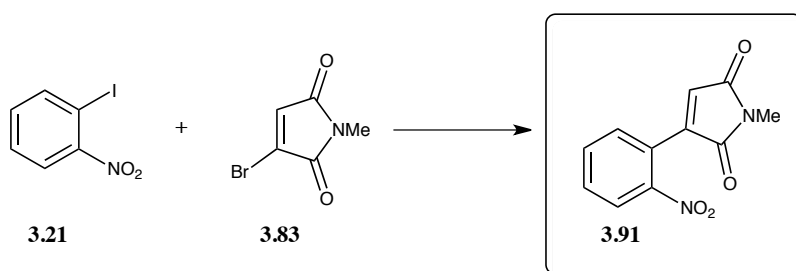
A magnetically stirred mixture of the arene **3.21** (498mg, 2.0 mmol) and the appropriate α -halo-enone (1.0 mmol), copper bronze powder (318 mg, 5.0 mmol of 200 mesh 99.5% material *ex* Aldrich Chemical Co.) and $Pd_2(dba)_3$ (55 mg, 6×10^{-5} mol, 6 mole %) in DMSO (10 ml) was heated at 70 °C for 2.0 h under a nitrogen atmosphere then cooled and diluted with ethyl acetate (25 ml). The resulting mixture was then filtered through a pad of Celite and the solids were rinsed with ethyl acetate (50 ml). The combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($MgSO_4$) and filtered. The resulting mixture was concentrated under reduced pressure to give an oily residue. Subjection of this material to flash chromatography (silica, ethyl acetate/hexane elution) and concentration of the appropriate fractions then afforded the title coupling products. Note: comprehensive characterization of these compounds is described in Section 5.3.4 (below).

Compound 3.75

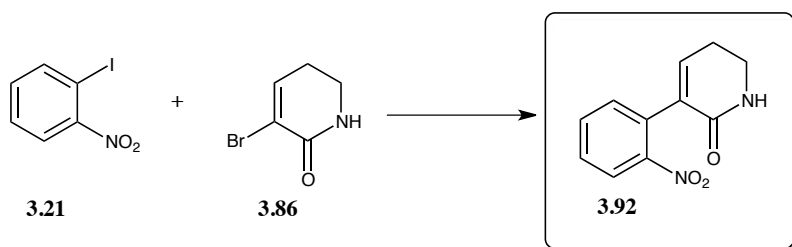
[5,6-Dihydro-3-(2-nitrophenyl)pyran-2-one]



Cross-coupling of arene **3.21** and heterocycle **3.74** under the conditions specified in the Standard Procedure 5.3.2 followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.25$) gave the *title compound* **3.75** (92 mg, 42%) as a pale-yellow, crystalline solid. See Section 5.3.4 (below) for full characterization.

Compound **3.91**[1-Methyl-3-(2-nitrophenyl)-1*H*-pyrrole-2,5-dione]

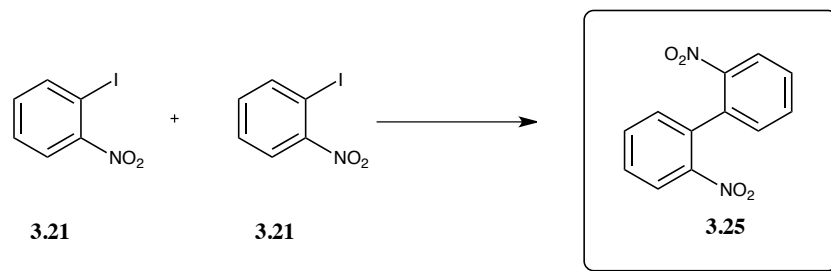
Cross-coupling of arene **3.21** and heterocycle **3.83** under the conditions specified in the General Procedure 5.3.3 followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.91** (110 mg, 47%) as a pale-yellow, crystalline solid. See Section 5.3.4 (below) for full characterization.

Compound **3.92**[5,6-Dihydro-3-(2-nitrophenyl)pyridin-2(1*H*)-one]

Cross-coupling of arene **3.21** and heterocycle **3.86** under the conditions specified in the General Procedure 5.3.3 followed by subjection of the crude product to flash chromatography (ethyl acetate) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.92** (79 mg, 36%) as a white, crystalline solid. See Section 5.3.4 (below) for full characterization.

Compound **3.25**

[2,2'-Dintro-1,1'-biphenyl]



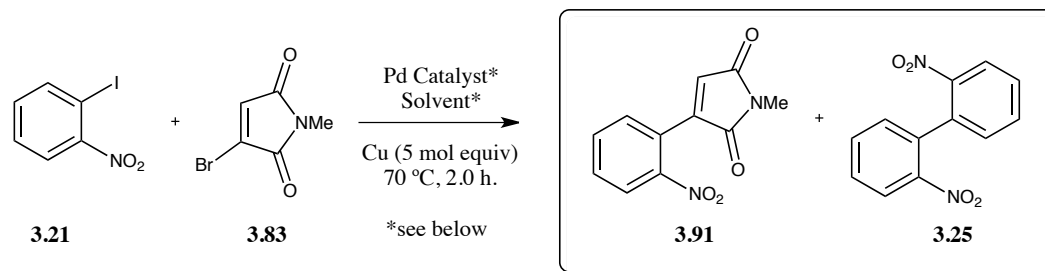
When conducted under the conditions specified in the Standard Procedure 5.3.2 the Pd[0]-catalysed Ullmann cross-coupling reaction was always accompanied by the homo-coupling of arene **3.21** to give compound **3.25** as a by-product. Subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.55$) gave the *title compound* **3.25**¹⁷ (yield 30 – 55%) as a pale-yellow, crystalline solid, m.p. = 123 –124 °C (lit.¹⁶ m.p. = 123.5 – 124.5 °C) (Found: M^+ , 244.0486. C, 59.04; H, 3.37; N, 11.45. $C_{12}H_8N_2O_4$ requires M^+ , 244.0484. C, 59.02; H, 3.30; N, 11.47%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (dd, $J = 8.2$ and 1.7 Hz, 1H), 7.70 (m, 2H), 7.59 (m, 2H), 7.30 (dd, $J = 8.2$ and 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 141.7, 135.1, 132.0, 124.7, 123.4; $\nu_{max}(KBr)$ 1607, 1566, 1524, 1470, 1461, 1436, 1410, 1365, 1320, 1301, 1266, 1167, 1144, 1106, 863, 785, 756, 747 cm^{-1} ; MS (EI, 70 eV) m/z 198 (100), 168 (38), 139 (50), 115 (33), 89 (11).

5.3.3 Optimisation of the Palladium[0]-catalysed Ullmann Cross-coupling Reaction

A magnetically stirred mixture of 1-iodo-2-nitrobenzene [**3.21**] (498 mg, 2.0 mmol), 3-bromo-1-methyl-1*H*-pyrrole-2,5-dione [**3.83**] (190 mg, 1.0 mmol), copper (318 mg, 5.0 mmol, type as indicted) and palladium catalyst (type and quantity as indicated) in DMSO (10 ml) was heated under a nitrogen atmosphere at the specified temperature for 2.0 h or until TLC analysis showed complete consumption of the heterocyclic starting material. The mixture was then cooled and diluted with ethyl acetate (25 ml) before being filtered through a pad of Celite. The solids thus retained were rinsed with ethyl acetate (50 ml) and the combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure to give an oily residue. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl

acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$) gave the cross-coupled product 1-methyl-3-(2-nitrophenyl)-1*H*-pyrrole-2,5-dione [**3.91**] and the homocoupled by-product 2,2'-dinitro-1,1'-biphenyl [**3.25**] in the yields indicted in the Tables presented on the following pages, viz. Tables **5.3.3 a,b,c** and **d**.

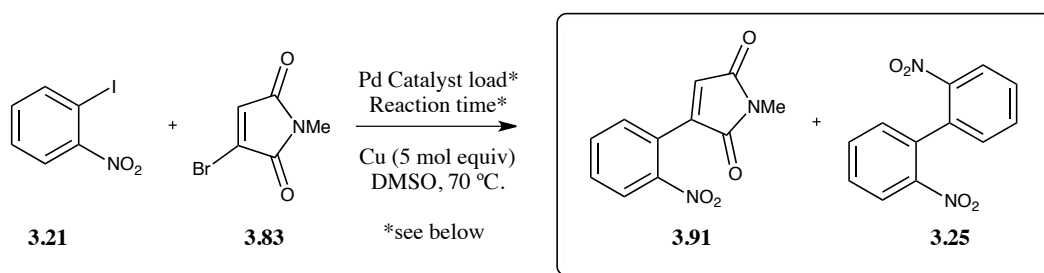
Table 5.3.3.a The Effect of Various Palladium Catalysts and Solvents on the Pd[0] Catalysed Ullmann Cross-Coupling of Substrates **3.21** and **3.83**.



Entry	Catalyst	Solvent	% Yield of 3.91 ^a	% Yield of 3.25 ^b
1	Pd ₂ (dba) ₃	nitrobenzene	0	32
2	Pd ₂ (dba) ₃	DMF	34	43
3	Pd ₂ (dba) ₃	NMP	38	46
4	Pd ₂ (dba) ₃	DMSO	47	55
5	Pd(PPh ₃) ₄	DMSO	41	57
6	PdCl ₂ (PPh ₃) ₂	DMSO	44	54
7	PdCl ₂ (dppf)	DMSO	44	56
8	Pd(OAc) ₂	DMSO	43	57

Reaction conditions: 5.0 equiv of Cu bronze powder (-200 mesh), Pd catalyst 6%, 70 °C, 2.0 h. ^aWith respect to compound **3.83**. ^bWith respect to compound **3.21**.

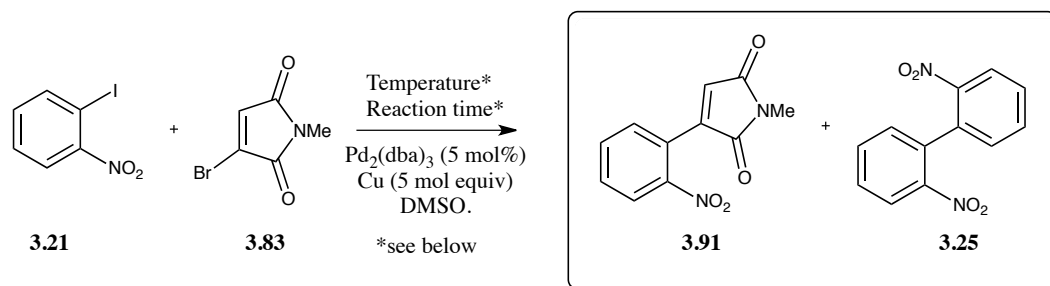
Table 5.3.3.b The Effect of Changing the Pd₂(dba)₃ Catalyst Load on the Pd[0] Catalysed Ullmann Cross-Coupling of Substrates **3.21** and **3.83**.



Entry	Catalyst	Load (mole%)	Time	% Yield of 3.91 ^a	% Yield of 3.25 ^b
1	Pd ₂ (dba) ₃	10%	2.0 h.	48	53
2	Pd ₂ (dba) ₃	6%	2.0 h.	47	55
3	Pd ₂ (dba) ₃	5%	2.0 h.	46	56
4	Pd ₂ (dba) ₃	4%	4.0 h.	42	61
5	Pd(PPh ₃) ₄	3%	12.0 h.	28	57

Reaction conditions: 5.0 equiv of Cu bronze powder (-200 mesh), 70 °C, 2.0 – 12.0 h. ^aWith respect to compound **3.83**. ^bWith respect to compound **3.21**.

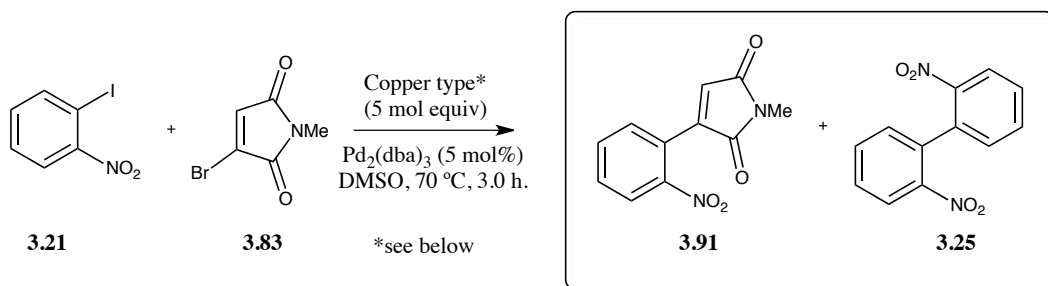
Table 5.3.3.c The Effect of Temperature on the Pd[0] Catalysed
Ullmann Cross-coupling of Substrates **3.21** and **3.83**.



Entry	Temp °C	Time h.	% Yield of 3.91 ^a	% Yield of 3.25 ^b
1	20	24.0	43	20
2	30	12.0	46	26
3	40	6.0	48	36
4	50	4.0	49	42
5	60	3.0	46	48
6	70	2.0	46	56
7	80	1.5	44	63
8	90	1.0	38	73

Reaction conditions: 5.0 equiv of Cu bronze powder (-200 mesh), Pd₂(dba)₃ 5%, DMSO, 20 – 90 °C, 1 – 24 h. ^aWith respect to compound **3.83**. ^bWith respect to compound **3.21**.

Table 5.3.3.d The Effect of Different Types of Copper on the Pd[0] Catalysed Ullmann Cross-Coupling of Substrates **3.21** and **3.83**.

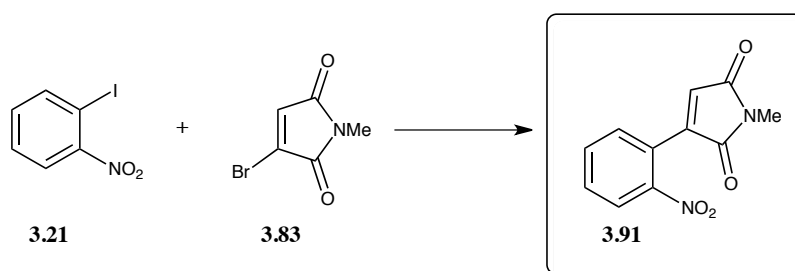


Entry	Copper type ^a	% Yield 3.91 ^b	% Yield 3.25 ^c
1	Copper bronze ^d	49	42
2	Copper foil	47	40
3	6µm Cu dust	58	45
4	3µm Cu dust	69	47
5	3µm Cu* dust	77	52
6	Slow addition	84	56

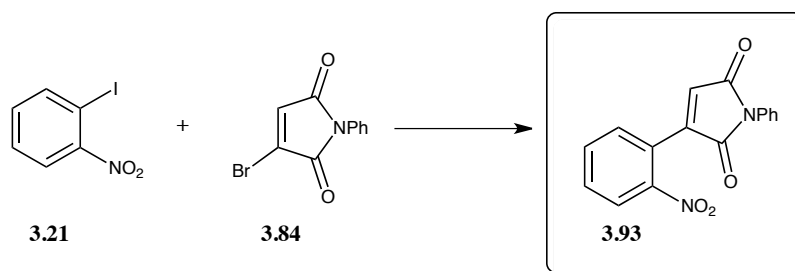
^aCu* = activated copper; see Section 5.3.3 below for a description of the preparation of this material. Reaction conditions (Entries 1 – 5): 5.0 equiv of Cu, Pd₂(dba)₃ 5 mole%, DMSO, 50 °C, total reaction time 3.0-h. ^bWith respect to compound **3.83**. ^cWith respect to compound **3.21**. ^d-200 mesh copper bronze powder ^eReaction conditions for Entry 6: as for entries 1-5, but involving the addition of five × 1.0 ml aliquots of a suspension of the activated copper dust (Cu*) in DMSO (ca. 65 mg Cu* per 1.0 ml DMSO) over 1.5 h.

5.3.4 General Procedure for the Palladium[0]-catalysed Ullmann Cross-coupling Reaction Using Activated 3 μ m Dendritic Copper Dust. Formation of Compounds 3.75 and 3.91 – 3.97.

A suspension of copper dust (400 mg of 3-micron dendritic material, *ex.* Aldrich Chemical Co.) in a solution of disodium-EDTA (100 mL of a 0.02 M solution in distilled water) was subjected to irradiation in a 100 W Watt Branson ultrasonication bath at 18 °C for 0.5 h. The copper dust was then allowed to settle and the supernatant was decanted. The residual solid was washed with de-ionized and deoxygenated water (4 x 25 mL) then acetone (3 x 25 mL) and methanol (2 x 25 mL). The material obtained after the final wash was transferred to a round-bottom flask and the residual methanol was removed by rotary evaporation and thus providing 320 - 350 mg of the activated metal. This was used promptly in the cross-coupling reaction. Thus, the activated material was suspended in dry DMSO (5 mL) and held under nitrogen. In a separate flask, a solution of the 2-halonitroarene **3.21**, **3.78**, **3.79**, or **3.82** (2 mmol) in DMSO (20 mL) was mixed with relevant heterocyclic cross-coupling partner **3.74** or **3.83–3.86** (1 mmol) and Pd₂(dba)₃ (47 mg, 5 x 10⁻⁵ mol, 5 mole %) and the resulting mixture was degassed then warmed, under a nitrogen atmosphere, to 40 - 50 °C then treated over 1.5 h with five x 1.0 ml aliquots of the suspension of the activated copper dust (Cu*) in DMSO over 1.5 h. Heating was continued for further 1.5–3.5 h then the reaction mixture was cooled to 18°C, diluted with ethyl acetate (25 mL) and filtered through a pad of Celite which was rinsed with ethyl acetate (50 mL). The combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (MgSO₄) and filtered. The filtrate was treated with flash chromatographic grade silica (1 g) and then concentrated under reduced pressure to a free-flowing powder. This was applied to the top of a flash chromatography column that was eluted with the appropriate combination of ethyl acetate and hexane (see below). Concentration of the appropriate fractions then gave the relevant cross-coupling product.

Compound **3.91**[1-Methyl-3-(2-nitrophenyl)-1*H*-pyrrole-2,5-dione]

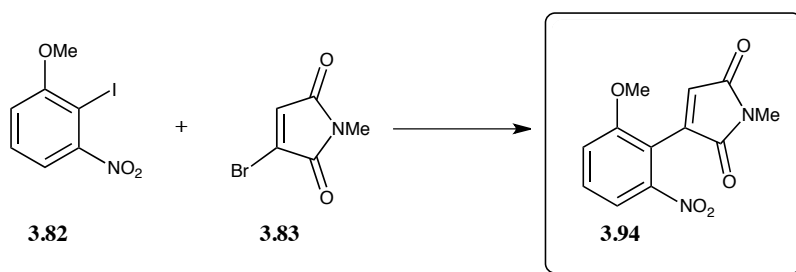
Cross-coupling of arene **3.21** and heterocycle **3.83** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.91** (197 mg, 85%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white, crystalline solid, m.p. = 148 - 149 °C (Found: M^+ , 232.0484. C, 56.71; H, 3.44; N, 12.05. $C_{11}H_8N_2O_4$ requires M^+ , 232.0484. C, 56.90; H, 3.47; N, 12.06%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (dd, $J = 8.1$ and 1.5 Hz, 1H), 7.71 (m, 2H), 7.47 (dd, $J = 7.5$ and 1.5 Hz, 1H), 6.70 (s, 1H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 168.6, 148.0, 145.5, 133.8, 131.4, 131.3, 126.4, 125.0, 124.4, 24.2; $\nu_{max}(KBr)$ 3109, 3072, 2962, 1768, 1705, 1602, 1571, 1521, 1441, 1387, 1345, 1265, 1247, 1117, 1096, 1059, 960, 879, 800, 726, 716, 686 cm^{-1} ; MS (EI, 70 eV) m/z 232 (M^+ , 16%), 186 (38), 175 (20), 147 (85), 146 (56), 130 (58), 119 (72), 103 (81), 89 (100), 76 (73), 75 (63).

Compound **3.93**[3-(2-Methoxy-6-nitrophenyl)-1-methyl-1*H*-pyrrole-2,5-dione]

Cross-coupling of arene **3.21** and heterocycle **3.84** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.93** (241 mg, 82%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white, crystalline solid, m.p. = 163 - 164 °C (Found: M^{+} , 294.0642. C, 65.62; H, 3.79; N, 9.52. $C_{16}H_{10}N_2O_4$ requires M^{+} , 294.0641. C, 65.31; H, 3.43; N, 9.52%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (dd, $J = 7.8$ and 1.2 Hz, 1H), 7.74 (m, 2H), 7.58-7.30 (complex m, 6H), 6.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 167.6, 148.3, 145.7, 134.1, 131.8, 131.7, 131.4, 129.3, 128.2, 126.5, 126.2, 125.4, 124.5; $\nu_{max}(KBr)$ 3092, 1714, 1641, 1597, 1572, 1531, 1518, 1500, 1457, 1382, 1349, 1201, 1144, 1128, 1030, 873, 858, 790, 753, 712, 699, 683 cm^{-1} ; MS (EI, 70 eV) m/z 295 [(M + H) $^{+}$, 28%], 294 (M^{+} , 100), 248 (16), 147 (43), 146 (32), 119 (52), 103 (48), 89 (46), 76 (35).

Compound **3.94**

[3-(2-Methoxy-6-nitrophenyl)-1-methyl-1*H*-pyrrole-2,5-dione]

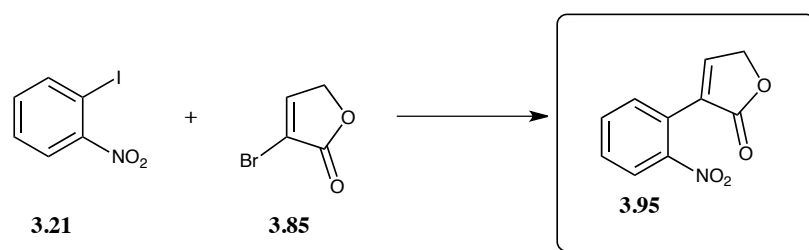


Cross-coupling of arene **3.82** and heterocycle **3.83** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.25$) gave the *title compound* **3.94** (233 mg, 89%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white, crystalline solid, m.p. = 126 - 127.5 °C (Found: M^{+} , 262.0594. C, 54.89; H, 3.94; N, 10.68. $C_{12}H_{10}N_2O_5$ requires M^{+} , 262.0590. C, 54.97; H, 3.84; N, 10.68%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (dd, $J = 8.4$ and 1.0 Hz, 1H), 7.56 (t, $J = 8.4$ Hz, 1H), 7.26 (dd, $J = 8.4$ and 1.0 Hz, 1H), 6.74 (s,

1H), 3.89 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 170.7, 169.6, 158.1, 149.6, 139.6, 131.5, 129.7, 116.8, 116.1, 112.9, 56.8, 24.3; $\nu_{\text{max}}(\text{KBr})$ 3097, 3026, 2950, 1775, 1714, 1630, 1599, 1566, 1531, 1437, 1381, 1356, 1277, 1254, 1165, 1117, 1053, 956, 910, 858, 810, 795, 780, 751, 724, 685 cm^{-1} ; MS (EI, 70 eV) m/z 263 [(M + H) $^+$, 13%], 262 (M^+ , 76), 216 (100), 177 (76), 147 (37), 133 (41), 132 (38), 105 (42), 104 (45), 103 (51), 76 (82), 62 (45).

Compound **3.95**

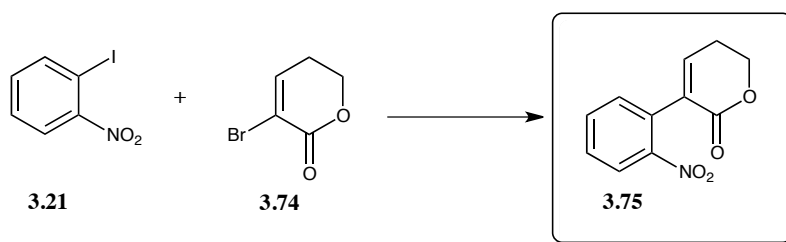
[3-(2-Nitrophenyl)furan-2(5H)-one]



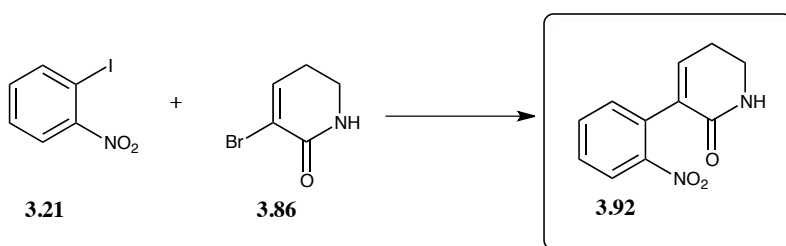
Cross-coupling of arene **3.21** and heterocycle **3.85** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (2:3 v/v ethyl acetate/hexane) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.95** (158 mg, 77%) as a white, crystalline solid, no m.p. (decomposes above 158 °C) (Found: M^+ , 205.0370. C, 58.73; H, 3.55; N, 6.83. Calculated for $\text{C}_{10}\text{H}_7\text{NO}_4$ M^+ , 205.0375. C, 58.54; H, 3.44, N, 6.83%). ^1H NMR (CDCl_3 , 300 MHz) δ 8.09 (dd, $J = 8.1$ and 1.2 Hz, 1H), 7.20-7.52 (complex m, 3 H), 7.46 (dd, $J = 7.5$ and 1.5 Hz, 1H), 5.04 (d, $J = 1.8$ Hz, 2H); ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) δ 171.3, 150.2, 148.0, 134.0, 132.2, 130.6, 129.7, 125.0, 124.7, 71.5; $\nu_{\text{max}}(\text{KBr})$ 3087, 2924, 1745, 1523, 1450, 1352, 1330, 1264, 1134, 1049, 1004, 965, 856, 841, 798, 738, 683 cm^{-1} ; MS (EI, 70 eV) m/z 205 (M^+ , 63%), 176 (42), 159 (85), 132 (41), 104 (51), 103 (60), 91 (50), 77 (100), 51 (66).

Compound **3.75**

[5,6-Dihydro-3-(2-nitrophenyl)pyran-2-one]



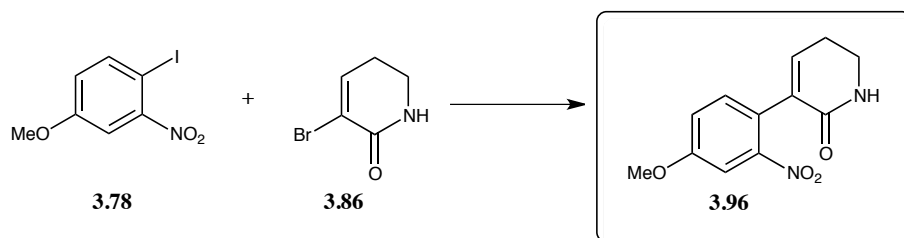
Cross-coupling of arene **3.21** and heterocycle **3.74** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.25$) gave the *title compound* **3.75** (171 mg, 78%) as a pale-yellow, crystalline solid. For the purposes of full characterization, a sample of this material was subjected to further flash chromatography (silica, 1:9 v/v acetone/toluene elution) and after concentration of the appropriate fractions ($R_f = 0.3$) an analytically pure sample of compound **3.75** was obtained as a white, crystalline solid, m.p. = 144 - 145 °C (Found: M^+ , 219.0532. C, 60.12; H, 4.33; N, 6.38. Calculated for $C_{11}H_9NO_4$ M^+ , 219.0532. C, 60.28; H, 4.14, N, 6.39%). ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11 (dd, $J = 8.1$ and 1.5 Hz, 1H), 7.65 (m, 1H), 7.53 (m, 1H), 7.38 (dd, $J = 7.8$ and 1.5 Hz, 1H), 6.93 (t, $J = 4.5$ Hz, 1H), 4.59 (m, 2H), 2.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 147.7, 140.3, 133.7, 132.6, 131.5, 131.3, 129.4, 124.6, 66.6, 24.4; $\nu_{max}(KBr)$ 3063, 2997, 2953, 2911, 1716, 1571, 1524, 1466, 1402, 1352, 1282, 1265, 1201, 1163, 1092, 1054, 1009, 980, 968, 891, 865, 846, 797, 785, 754, 722, 703 cm^{-1} ; MS (EI, 70 eV) m/z 219 (M^+ , 7%), 173 (100), 145 (45), 115 (48).

Compound **3.92**[5,6-Dihydro-3-(2-nitrophenyl)pyridin-2(1*H*)-one]

Cross-coupling of arene **3.21** and heterocycle **3.86** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (ethyl acetate) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.92** (133 mg, 61%) as a white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give white needles, no mp (decomposition above 191 °C) (Found: $(M-NO_2)^+$, 172.0764. C, 60.64; H, 4.34; N, 12.59. Calculated for $C_{11}H_{10}N_2O_3 (M-NO_2)^+$, 172.0762. C, 60.55; H, 4.62, N, 12.84%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dm, $J = 7.5$ Hz, 1H), 7.61 (tm, $J = 7.5$ Hz, 1H), 7.49 (tm, $J = 7.5$ Hz, 1H), 7.37 (dm, $J = 7.5$ Hz, 1H), 6.72 (t, $J = 4.5$ Hz, 1H), 5.84 (broad s, 1H), 3.64–3.54 (m, 2H), 2.60–2.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 148.7, 137.2, 135.2, 133.4, 132.4, 131.8, 129.0, 124.5, 39.8, 24.6; IR ν_{max} (KBr) 3435, 3193, 3060, 2890, 1681, 1671, 1617, 1524, 1487, 1356, 1288, 863, 746, 546 cm^{-1} ; MS (EI, 70 eV) m/z 172 $[(M-NO_2)^+]$, 100], 115 (19), 77 (19), 57 (27), 55 (34).

Compound **3.96**

[5,6-Dihydro-3-(4-methoxy-2-nitrophenyl)pyridin-2(1H)-one]

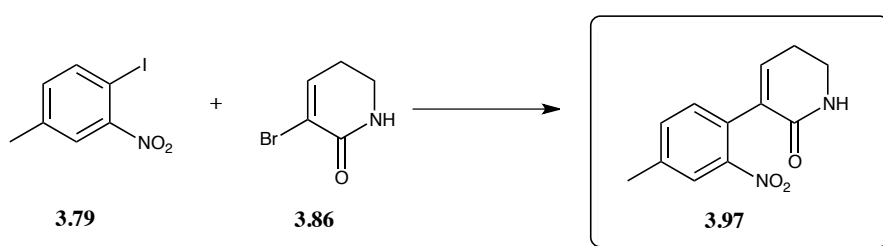


Cross-coupling of arene **3.78** and heterocycle **3.86** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (9:1 v/v ethyl acetate/hexane) and concentration of the relevant fractions ($R_f = 0.25$) gave the *title compound* **3.96** (209 mg, 73%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a cream-colored, crystalline solid, no mp (decomposition above 194 °C) (Found: M^+ , 248.0796. C, 58.02; H, 4.67; N, 11.28. Calculated for $C_{12}H_{12}N_2O_4 M^+$, 248.0797. C, 58.06; H, 4.87, N, 11.28%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, $J = 2.7$ Hz, 1H), 7.31–7.24 (m, 1H), 7.14 (dd, $J = 8.4$ and 2.7 Hz, 1H), 6.68 (t, $J = 4.5$ Hz, 1H), 6.17 (broad s, 1H), 3.89 (s, 3H), 3.62–3.52 (m, 2H),

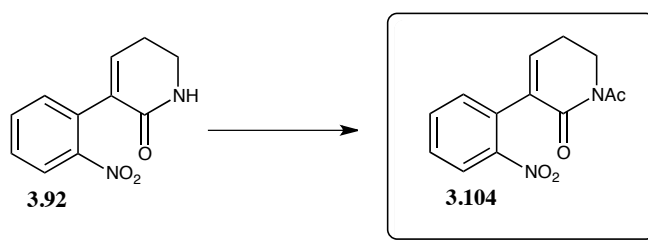
2.58–2.48 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 165.2, 159.8, 149.2, 136.6, 134.9, 132.6, 124.6, 119.8, 109.4, 56.0, 39.8, 24.6; IR ν_{max} (KBr) 3185, 3116, 3062, 2890, 1671, 1621, 1533, 1499, 1485, 1451, 1357, 1305, 1284, 1266, 1222, 1074, 1038, 1008, 917, 885, 869, 856, 822, 801 cm^{-1} ; MS (EI, 70 eV) m/z 248 ($\text{M}^{+\bullet}$, 4%), 203 (20), 202 [$(\text{M}-\text{NO}_2)^+$, 100].

Compound 3.97

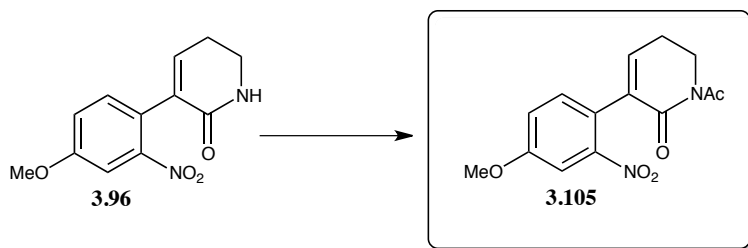
[3-(4-Methyl-2-nitrophenyl)-5,6-dihydropyridin-2(1H)-one]



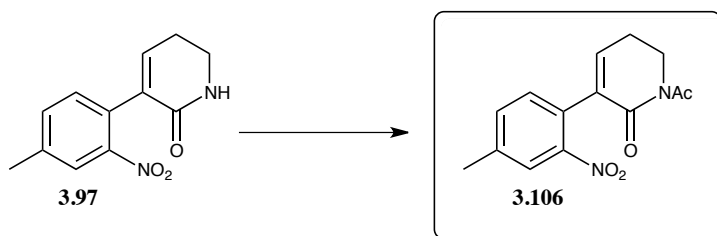
Cross-coupling of arene **3.79** and heterocycle **3.86** under the conditions specified in the General Procedure 5.3.4 followed by subjection of the crude product to flash chromatography (ethyl acetate) and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **3.97** (141 mg, 61%) as an off-white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give fine, white needles, mp = 199 - 200 °C (with decomposition) (Found: $(\text{M}-\text{NO}_2)^+$, 186.0919. C, 62.18; H, 5.10; N, 12.12. Calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ ($\text{M}-\text{NO}_2)^+$, 186.0919. C, 62.06; H, 5.21, N, 12.06%.) ^1H NMR (300 MHz, CDCl_3) δ 7.85 (s, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.28–7.20 (m, 1H), 6.69 (t, $J = 4.2$ Hz, 1H), 6.09 (broad s, 1H), 3.60–3.52 (m, 2H), 2.58–2.48 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.8, 148.3, 139.4, 136.5, 135.0, 133.9, 131.4, 129.4, 124.8, 39.7, 24.5, 20.9; IR ν_{max} (KBr) 3189, 3060, 2889, 1681, 1615, 1528, 1485, 1421, 1358, 1287, 1271, 1251, 1123, 1051, 1015, 888, 859, 830, 802, 760, 714, 675 cm^{-1} ; MS (EI) m/z 232 ($\text{M}^{+\bullet}$, <1%), 187 (22), 186 [$(\text{M}-\text{NO}_2)^+$, 100], 115 (15), 91 (15).

Compound **3.104**[1-Acetyl-3-(2-nitrophenyl)-5,6-dihydropyridin-2(1*H*)-one]

Following a procedure described by Minami and co-workers¹⁸ a magnetically stirred solution of lactam **3.92** (152 mg, 0.70 mmol) in acetic anhydride (10 mL) was treated with sodium acetate (160 mg, 1.95 mmol). The resulting mixture was heated at reflux for 1.5 h then cooled, diluted with ethyl acetate (50 mL) and the resulting solution poured into sodium hydrogen carbonate (200 mL of a saturated aqueous solution). The ensuing biphasic mixture was stirred vigorously for 0.3 h then the separated organic phase was washed with water (1 × 25 mL) and brine (1 × 25 mL) before being dried (MgSO₄) then filtered. The filtrate was treated with flash chromatography grade silica gel (1.0 g) and the resulting mixture then concentrated under reduced pressure. The free-flowing solid thus obtained was added to the top of a flash chromatography column. Elution of the column (with 2:3 v/v ethyl acetate/hexane) and concentration of the relevant fractions ($R_f = 0.3$) under reduced pressure afforded the *title compound* **3.104** (172 mg, 95%) as a colorless resin (Found: M^+ , 260.0795. Calculated for C₁₃H₁₂N₂O₄ M^+ , 260.0797). ¹H NMR (300 MHz, CDCl₃) δ 8.12 (broadened d, $J = 7.8$ Hz, 1H), 7.66 (broadened t, $J = 7.8$ Hz, 1H), 7.54 (td, $J = 7.8$ and 1.2 Hz, 1H), 7.37 (dd, $J = 7.8$ and 1.2 Hz, 1H), 6.94 (t, $J = 3.9$ Hz, 1H), 4.17 (broad s, 2H), 2.65–2.55 (m, 2H), 2.52 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.3, 164.8, 148.3, 140.8, 136.3, 133.8, 131.8, 129.5, 124.7, 40.9, 27.6, 24.8 (one signal obscured or overlapping); IR $\nu_{\max}$ (KBr) 2940, 1691, 1524, 1469, 1389, 1368, 1349, 1302, 1265, 1241, 1188, 1136, 1031 cm⁻¹; MS (EI, 70 eV) m/z 260 (M^+ , 2%), 214 (43), 172 (94), 115 (18).

Compound **3.105**[1-Acetyl-3-(4-methoxy-2-nitrophenyl)-5,6-dihydropyridin-2(1*H*)-one]

Following the procedure described immediately above, lactam **3.96** (135 mg, 0.55 mmol) was converted into the *title compound* **3.105** (131 mg, 83%), which was obtained as a pale-yellow solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethyl acetate/hexane) to give white needles, mp = 100 - 102 °C (Found: M^+ , 290.0901. C, 57.99; H, 5.05; N, 9.66. Calculated for $C_{14}H_{14}N_2O_5$ M^+ , 290.0903. C, 57.93; H, 4.86; N, 9.65%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 2.7 Hz, 1H), 7.30-7.26 (m, 1H), 7.18 (dd, J = 8.7 and 2.7 Hz, 1H), 6.90 (t, J = 4.5 Hz, 1H), 4.14 (broad s, 2H), 3.90 (s, 3H), 2.64-2.54 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 164.8, 159.9, 148.7, 140.3, 135.7, 132.6, 123.8, 119.7, 109.5, 55.9, 40.8, 27.4, 24.6; IR ν_{max} (KBr) 2940, 2842, 1692, 1620, 1531, 1466, 1388, 1368, 1349, 1303, 1273, 1227, 1188, 1135, 1035 cm^{-1} ; MS (EI, 70 eV) m/z 290 (M^+ , 5%), 244 (37), 202 (100).

Compound **3.106**[1-Acetyl-3-(4-methyl-2-nitrophenyl)-5,6-dihydropyridin-2(1*H*)-one]

Following the procedure described above for the conversion **3.92** $\rightarrow$ **3.104**, lactam **3.97** (116 mg, 0.50 mmol) was converted into the *title compound* **3.106** (133 mg, 97%) which was obtained as a pale-yellow solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (chloroform/hexane) to give

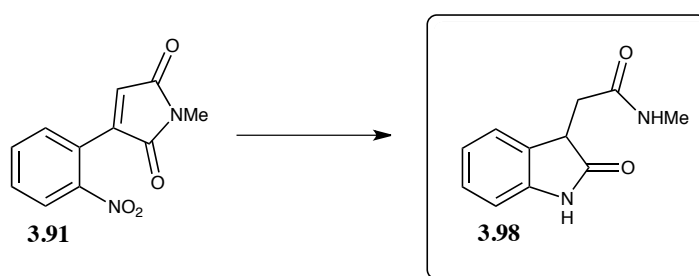
white needles, mp = 120 - 121 °C (Found: M^+ , 274.0960. C, 61.24; H, 5.01; N, 10.03. Calculated for $C_{14}H_{14}N_2O_4$ M^+ , 274.0954. C, 61.31; H, 5.14; N, 10.21%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (broad s, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.27–7.22 (partially obscured m, 1H), 6.90 (t, J = 4.8 Hz 1H), 4.16 (broad s, 2H), 2.61–2.54 (m, 2H), 2.51 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 164.9, 148.1, 140.3, 140.1, 136.3, 134.5, 131.6, 129.0, 125.1, 40.9, 27.6, 24.7, 21.1; IR ν_{max} (KBr) 3364, 2900, 1693, 1681, 1528, 1499, 1463, 1425, 1385, 1357, 1296, 1272, 1244, 1194, 1132, 1028 cm^{-1} ; MS (EI, 70 eV) m/z 274 (M^+ , 3%), 228 (50), 186 (100).

5.3.5 General Procedure for the Reduction and Cyclisation Reactions. Formation of Compounds 3.77 and 3.98–3.103.

A magnetically stirred solution of the relevant cross-coupled product **3.75** or **3.91** – **3.97** (1 mmol) in methanol (15 mL) was treated with 10% Pd on C (20% w/w wrt substrate) and the resulting mixture was sparged with dihydrogen and then maintained under an atmosphere of dihydrogen at 18 °C until TLC analysis indicated that all of the starting material had been consumed (*ca.* 2 – 4 h). The reaction mixture was filtered through a #3 porosity sintered-glass funnel and the solids were washed with methanol (15 mL). The combined filtrates were concentrated under reduced pressure and the residue taken up in ethyl acetate (20 mL). The solution thus obtained was filtered through a thin pad of TLC-grade silica gel that was rinsed with additional ethyl acetate (10 mL). The combined filtrates were concentrated under reduced pressure to give the relevant reduction product as specified under the individual headings shown below.

Oxindole **3.98**

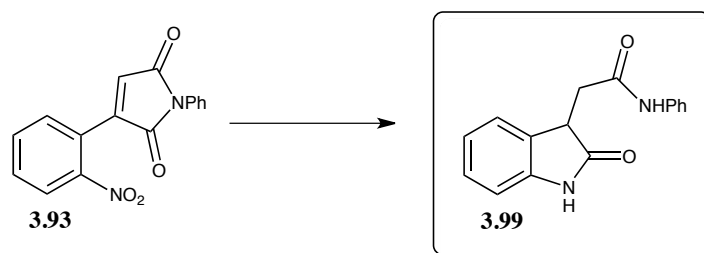
[*N*-Methyl-2-(2-oxoindolin-3-yl)acetamide]



Reductive cyclization of cross-coupling product **3.91** under the conditions specified in the general procedure gave *oxindole* **3.98** (178 mg, 87%) as a white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white, crystalline solid, mp = 101–103 °C (Found: M^{+} , 204.0903. C, 64.93; H, 5.93; N, 13.93. Calculated for $C_{11}H_{12}N_2O_2$ M^{+} , 204.0899. C, 64.69; H, 5.92, N, 13.72%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.17–7.09 (m, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.86–6.78 (m, 2H), 4.30–4.24 (m, 1H), 4.07 (broad s, 2H), 3.20–2.96 (complex m, 2H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 176.6, 145.5, 128.9, 126.0, 122.7, 119.9, 118.2, 41.2, 34.6, 25.2; IR ν_{max} (KBr) 3431, 3356, 2995, 2947, 1772, 1688, 1621, 1497, 1443, 1387, 1283, 1121, 1061, 951, 809, 786, 763, 697 cm^{-1} ; MS (EI, 70 eV) m/z 205 [$(M + H)^+$, 29%], 204 (M^{+} , 100), 146 (83), 145 (97), 128 (30), 119 (95), 118 (75), 117 (55), 91 (53).

Oxindole **3.99**

[2-(2-Oxindolin-3-yl)-*N*-phenylacetamide]

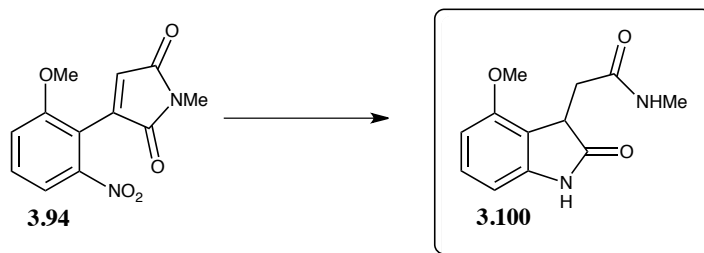


Reductive cyclization of cross-coupling product **3.93** under the conditions specified in the general procedure gave *oxindole* **3.99**¹⁹ (264 mg, 99%) as a pale-pink, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (acetone) to give a white, crystalline solid, no mp (decomposition above 184 °C) (lit.¹⁸ mp = 202 - 203 °C) (Found: M^{+} , 266.1055. C, 71.98; H, 5.49; N, 10.30. Calculated for $C_{16}H_{14}N_2O_2$ M^{+} , 266.1055. C, 72.17; H, 5.30, N, 10.52%). ^1H NMR (300 MHz, acetone- d_6) δ 9.47 (s, 1H), 9.42 (s, 1H), 7.66 (d, J = 7.5 Hz, 2H), 7.35–7.26 (m, 3H), 7.20–7.14 (m, 1H), 7.09–7.02 (m, 1H), 6.96–6.88 (m, 2H), 3.92–3.83 (m, 1H), 3.12 (dd, J = 15.9 and 4.5 Hz, 1H), 2.72 (dd, J = 15.9 and 8.7 Hz, 1H); ^{13}C NMR (75 MHz, acetone- d_6) δ 179.1, 179.0, 169.5, 169.4, 143.6, 143.4, 140.2, 140.1, 130.6, 129.5, 128.7, 125.1, 124.2, 122.4, 120.0, 119.9, 110.1(3), 110.0(8), 43.0, 38.3, 38.2 (additional signals due to the presence of amide rotamers); IR ν_{max} (KBr)

3315, 3213, 3092, 2875, 1702, 1679, 1623, 1600, 1551, 1498, 1472, 1446, 1346, 1317, 1184, 961, 7841, 692 cm^{-1} ; MS (EI, 70 eV) m/z 266 (M^{+} , 43), 173 (30), 146 (45), 145 (100), 132 (24), 117 (28), 93 (58), 77 (27).

Oxindole **3.100**

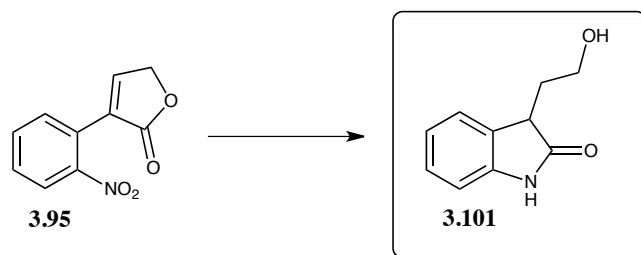
[2-(4-Methoxy-2-oxoindolin-3-yl)-*N*-methylacetamide]



Reductive cyclization of cross-coupling product **3.94** under the conditions specified in the general procedure gave *oxindole 3.100* (181 mg, 77%) as a pale-pink, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethanol) to give a white, crystalline solid, no mp (decomposition above 145 °C) (Found: M^{+} , 234.1004. C, 61.61; H, 6.11; N, 11.68. Calculated for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$ M^{+} , 234.1004. C, 61.53, H, 6.02, N, 11.96%). ^1H NMR (300 MHz, CDCl_3) δ 7.05 (t, J = 8.1 Hz, 1H), 6.44–6.32 (m, 2H), 4.08–3.98 (m, 1H), 3.67 (s, 3H), 3.65 (broad s, 2H), 3.06 (s, 3H), 3.06–2.96 (m, 1H), 2.73 (dd, J = 18.0 and 5.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 179.3, 177.2, 158.0, 145.8, 129.0, 111.7, 110.8, 102.4, 55.6, 37.4, 35.5, 24.9; IR ν_{max} (KBr) 1692, 1599, 1472, 1439, 1384, 1283, 1121, 1092, 951, 776 cm^{-1} ; MS (EI, 70 eV) m/z 234 (M^{+} , 100%), 176 (48), 175 (68), 149 (18), 134 (19).

Oxindole **3.101**

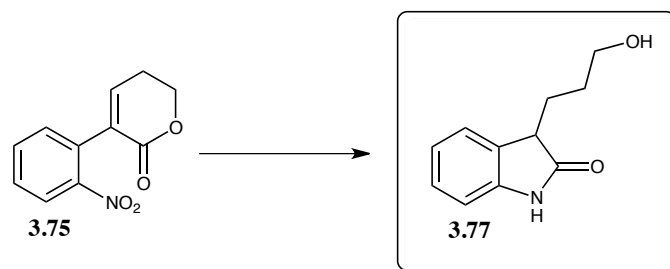
[3-(2-Hydroxyethyl)indolin-2-one]



Reductive cyclization of cross-coupling product **3.95** under the conditions specified in the general procedure gave *oxindole* **3.101**²⁰ (170 mg, 96%) as a pale-yellow oil that crystallized on standing. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (chloroform) to give a white, crystalline solid, mp = 109.5 - 111 °C (lit.¹⁹ mp = 109 - 111 °C) (Found: C, 67.77; H, 6.23; N, 7.78. M^{+} , 177.0786. Calculated for $C_{10}H_{11}NO_2$ C, 67.78, H, 6.26, N, 7.90%. M^{+} , 177.0790). ^1H NMR (300 MHz, $CDCl_3$) δ 9.14 (broad s, 1H), 7.28–7.18 (m, 2H), 7.07–6.99 (m, 1H), 6.93–6.87 (m, 1H), 3.94–3.84 (m, 2H), 3.66–3.58 (m, 1H), 3.47 (t, J = 6.0 Hz, 1H), 2.31–2.19 (m, 1H), 2.14–2.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 141.3, 129.4, 128.1, 123.9, 122.6, 110.0, 60.7, 44.8, 33.1; IR ν_{max} (KBr) 3353, 3157, 2953, 2884, 1688, 1618, 1472, 1348, 1298, 1213, 1183, 1108, 1037, 805, 761 cm^{-1} ; MS (EI, 70 eV) m/z 178 [$(M+H)^+$, 35%], 177 (M^{+} , 81), 159 (56), 146 (100), 144 (56), 133 (56), 130 (48), 77 (38).

Oxindole **3.77**

[3-(2-Hydroxypropyl)indolin-2-one]

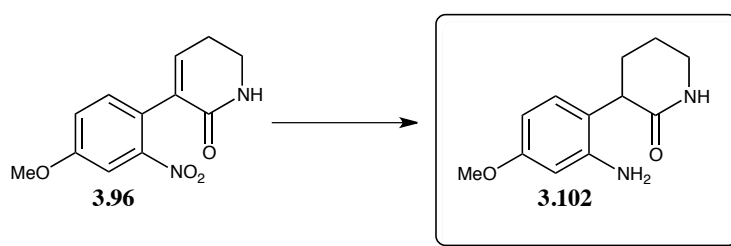


Reductive cyclization of cross-coupling product **3.75** under the conditions specified in the general procedure gave *oxindole* **3.77**²¹ (141 mg, 74%) as a clear,

colorless oil that slowly crystallized on standing. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethyl acetate/hexane) to give colorless needles, mp = 99 - 101 °C (lit.²⁰ mp = 105 - 105.5) (Found: M^{+} , 191.0946. Calculated for $C_{11}H_{13}NO_2$ M^{+} , 199.0946). ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (broad s, 1H), 7.28–7.14 (m, 2H), 7.03 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 3.68–3.58 (m, 2H), 3.54–3.46 (m, 1H), 2.16–1.96 (m, 2H), 1.70–1.50 (m, 2H) (signal due to OH group proton not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 141.6, 129.6, 128.1, 124.2, 122.6, 109.9, 62.5, 45.7, 28.9, 26.7; IR ν_{max} (KBr) 3233, 1701, 1621, 1471, 1338, 1221, 122.6, 109.9, 62.5, 45.7, 28.9, 26.7; IR ν_{max} (KBr) 3233, 1701, 1621, 1471, 1338, 1221, 1057, 751 cm^{-1} ; MS (EI, 70 eV) m/z 191 (M^{+} , 64%), 173 (66), 146 (100), 145 (83), 133 (40), 132 (53), 117 (39), 77 (30).

Compound **3.102**

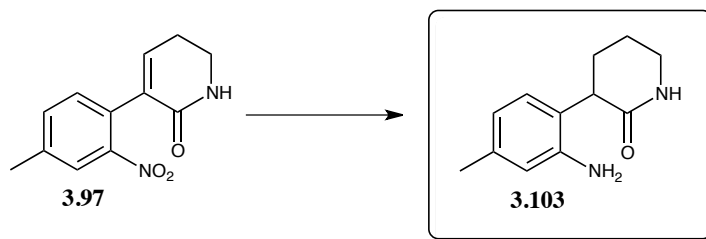
[3-(2-Amino-4-methoxyphenyl)piperidin-2-one]



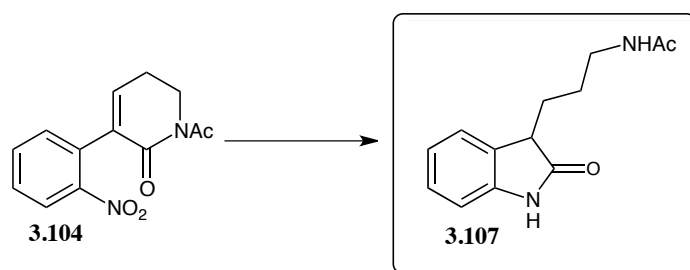
Reduction of cross-coupling product **3.96** under the conditions specified in the general procedure gave the *title compound* **3.102** (214 mg, 97%) as a pale-pink oil that crystallized on standing. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a pale-pink, crystalline solid, no mp (decomposition above 148 °C) (Found: M^{+} , 220.1208. C, 65.42; H, 7.22; N, 12.57. Calculated for $C_{12}H_{16}N_2O_2$ M^{+} , 220.1212. C, 65.43; H, 7.32, N, 12.72%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 8.4 Hz, 1H), 6.42–6.28 (complex m, 3H), 4.10 (broad s, 2H), 3.75 (s, 3H), 3.65 (dd, J = 9.0 and 6.0 Hz, 1H), 3.44–3.36 (m, 2H), 2.20–1.78 (complex m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.4, 146.7, 128.9, 119.4, 104.7, 103.2, 55.3, 43.0, 42.9, 26.9, 22.0; IR ν_{max} (KBr) 3407, 3343, 3178, 2933, 1660, 1614, 1583, 1514, 1496, 1455, 1416, 1325, 1294, 1264, 1218, 1170, 1147, 1031, 847, 799, 665 cm^{-1} ; MS (EI, 70 eV) m/z 221 [$(M + H)^+$, 32%], 220 (M^{+} , 96), 203 (47), 175 (100), 163 (53), 149 (62), 136 (66).

Compound **3.103**

[3-(2-Amino-4-methylphenyl)piperidin-2-one]



Reduction of cross-coupling product **3.97** under the conditions specified in the general procedure gave the *title compound* **3.103** (172 mg, 84%) as a honey-colored solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (acetone/diethyl ether) to give a white, crystalline solid, no mp (decomposition above 138 °C) (Found: M^{+} , 204.1265. Calculated for $C_{12}H_{16}N_2O$ M^{+} , 204.1263). ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 7.8 Hz, 1H), 6.64–6.55 (m, 2H), 6.10 (broad s, 1H), 3.92 (broad s, 2H), 3.72–3.64 (m, 1H), 3.46–3.34 (m, 2H), 2.24 (s, 3H), 2.20–1.94 (complex m, 3H), 1.92–1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 145.2, 137.7, 128.0, 123.9, 120.3, 118.4, 43.3, 42.8, 26.8, 22.0, 21.1; IR ν_{max} (KBr) 3342, 3233, 2944, 1655, 1510, 1490, 1447, 1355, 1319, 1110, 800, 730 cm^{-1} ; MS (EI, 70 eV) m/z 204 (M^{+} , 58%), 187 (33), 159 (47), 99 (100), 84 (56), 55 (78), 43 (78), 42 (98).

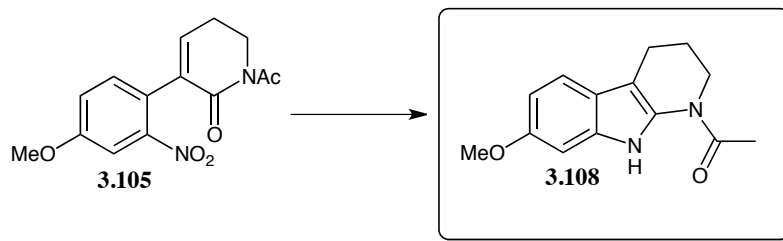
Oxindole **3.107**[*N*-[3-(2-Oxoindolin-3-yl)propyl]acetamide]

Reductive cyclization of cross-coupling product **3.104** (92 mg, 0.35 mmol) under the conditions specified in the general procedure gave a colorless and unstable resin. Subjection of this material to rapid flash chromatography (silica, 8:92 v/v

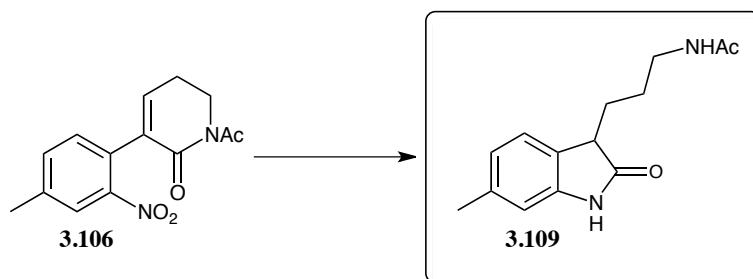
methanol/ethyl acetate) gave *oxindole* **3.107** (59 mg, 72%) as a clear, colorless resin, $R_f = 0.3$ (Found: M^+ , 232.1218. Calculated for $C_{13}H_{16}N_2O_2$ M^+ , 232.1212). ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.25–7.17 (m, 2H), 7.00 (t, $J = 7.5$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 5.83 (broad s, 1H), 3.30–3.15 (m, 2H), 2.06–1.92 (m, 3H), 1.95 (s, 3H), 1.62–1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 170.5, 141.8, 129.3, 128.2, 124.2, 122.6, 110.0, 45.6, 39.4, 27.6, 25.6, 23.4; IR ν_{max} (KBr) 3268, 2937, 2465, 1704, 1622, 1554, 1471, 1370, 1336, 1295, 1222, 1104 cm^{-1} ; MS (EI, 70 eV) m/z 232 (M^+ , 85%), 228 (52), 185 (36), 157 (57), 145 (78), 133 (50), 173 (100).

Indole **3.108**

[1-Acetyl-7-methoxy-2,3,4,9-tetrahydro-1*H*-pyrido[2,3-*b*]indole]



In a variation of the general procedure for reductive cyclization specified above, a magnetically stirred solution of the cross-coupling product **3.105** (65 mg, 0.22 mmol) in methanol (25 mL) was cooled to 10 °C then treated with 10% Pd on C (15 mg). The resulting mixture was deoxygenated then charged with dihydrogen (1 atmosphere) and stirred at 10 °C for 3 h. The reaction mixture was then filtered through a pad of Celite™ and the solids thus retained washed with methanol (25 mL). The combined filtrates were concentrated under reduced pressure to give a mauve-colored solid. Recrystallization (9:1 v/v *i*propanol/methanol) of this material gave the *title indole* **3.108** (51 mg, 93%) as white needles, no mp (decomposition above 129 °C), $R_f = 0.3$ (8:92 v/v methanol/ethyl acetate) (Found: M^+ , 244.1212. Calculated for $C_{14}H_{16}N_2O_2$ M^+ , 244.1212). ^1H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.30 (d, $J = 8.7$ Hz, 1H), 6.86 (d, $J = 2.1$ Hz, 1H), 6.76 (dd, $J = 8.7$ and 2.1 Hz, 1H), 3.84 (s, 3H), 3.83–3.78 (m, 2H), 2.75 (t, $J = 6.3$ Hz, 2H), 2.31 (s, 3H), 2.18–2.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 155.7, 132.9, 132.7, 120.2, 117.9, 109.2, 96.5, 95.1, 55.9, 47.0, 23.3, 23.2, 19.2; IR ν_{max} (KBr) 3350, 2935, 2846, 1647, 1621, 1585, 1573, 1486, 1394, 1344, 1242, 1206, 1146, 1118, 1027 cm^{-1} ; MS (EI, 70 eV) m/z 244 (M^+ , 100%), 229 (14), 201 (85), 187 (67), 173 (24).

Oxindole **3.109**[*N*-[3-(6-Methyl-2-oxoindolin-3-yl)propyl]acetamide]

Reductive cyclization of cross-coupling product **3.106** (105 mg, 0.38 mmol) under the conditions specified in the general procedure gave a colorless and unstable resin. Subjection of this material to rapid flash chromatography (silica, 6:94 v/v methanol/ethyl acetate) gave *oxindole* **3.109** (57 mg, 60%) as a clear, colorless resin, $R_f = 0.3$ (Found: M^{+} , 246.1369. Calculated for $C_{14}H_{18}N_2O_2$ M^{+} , 246.1368). ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.08 (d, $J = 7.5$ Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 6.72 (s, 1H), 5.76 (broad s, 1H), 3.46 (t, $J = 5.7$ Hz, 1H), 3.30–3.15 (m, 2H), 2.33 (s, 3H), 2.01–1.88 (m, 2H), 1.94 (s, 3H), 1.60–1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 170.3, 141.5, 138.3, 126.3, 124.0, 123.2, 110.7, 45.3, 39.4, 27.7, 25.7, 23.4, 21.7; IR ν_{max} (KBr) 3284, 2927, 2243, 1707, 1631, 1552, 1460, 1370, 1338, 1295, 1245, 1142, 1122 cm^{-1} ; MS (EI, 70 eV) m/z 246 (M^{+} , 82%), 204 (17), 187 (100), 159 (98), 146 (33).

5.4 Experimental Section for Chapter Four

Chemical Activation of 3 μm Dendritic Copper Dust.

The capacity for activation of 3 μm dendritic copper dust using dilute aqueous hydrochloric acid (0.01, 0.02 and 0.05 M) or dilute aqueous phosphoric acid (0.02 and 0.05 M) instead of disodium-EDTA 0.02 M solution was tested as follows.

(i) A suspension of copper dust (400 mg of 3 μm dendritic material, ex. Aldrich Chemical Co.) in the relevant activating solution (100 ml) was subjected to irradiation in a 100 W Watt Branson ultrasonication bath at 18 $^{\circ}C$ for 0.5 h. The copper dust was then allowed to settle and the supernatant liquid decanted. The solids thus retained were washed with de-ionized and deoxygenated water (4 x 25 mL) then acetone (3 x 25 mL) and methanol (2 x 25 mL). The material obtained after the final wash was transferred to a

round-bottom flask and the residual methanol was removed by rotary evaporation to provide 320 - 350 mg of the activated copper dust. This was used promptly in the cross-coupling reaction.

(ii) The activated copper dust obtained by the procedure described immediately above was suspended in dry DMSO (5 mL) and held under nitrogen. In a separate flask, a solution of 1-iodo-2-nitrobenzene [**3.21**] (498 mg, 2.0 mmol) and 3-bromo-1-methyl-1*H*-pyrrole-2,5-dione [**3.83**] (190 mg, 1.0 mmol) in DMSO (20 mL) was treated with Pd₂(dba)₃ (47 mg, 5 × 10⁻⁵ mol, 5 mole %) and the resulting mixture was degassed then warmed, under a nitrogen atmosphere, to 50 °C before being treated over 1.5 h with 5 × 1.0 ml aliquots of the suspension of the activated copper dust (Cu*) in DMSO. After the addition of the copper was complete, heating was continued for further 1.5 h then the reaction mixture was cooled to 18°C, diluted with ethyl acetate (25 mL) and filtered through a pad of Celite which was rinsed with ethyl acetate (50 mL). The combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (MgSO₄) and filtered. The resulting mixture was concentrated under reduced pressure to give an oily residue. Subjection of this to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (*R_f* = 0.3) gave the cross-coupled product 1-methyl-3-(2-nitrophenyl)-1*H*-pyrrole-2,5-dione [**3.91**] in the yields indicted in Table 5.4.1a

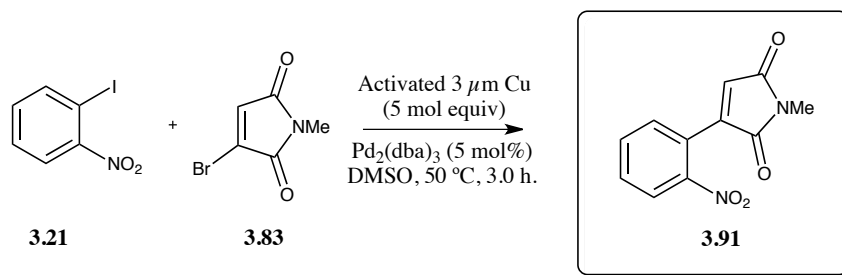
(iii) The activation of 3 µm dendritic copper dust using the technique described by Lai²² for the activation of magnesium turnings with iodine was adapted for the activation of copper and tested as follows: copper dust (350 mg, 5.5 mmol of 3-micron dendritic material, *ex.* Aldrich Chemical Co.) was added under nitrogen to dry THF (10 ml) followed by iodine (125 mg, 0.5 mmol) and the ensuing mixture was stirred at 20 °C for 1 h by which time the liquid phase had become colourless. The supernatant was decanted and the solids were washed with dry THF (2 x 10 mL) and the residual THF was removed by rotary evaporation to provide *ca.* 310 mg of activated copper dust. This was used promptly in the cross-coupling reaction as described above [5.4.1-(ii)].

(iv) A technique described by Kleiderer and Adams²³ for the activation of copper bronze with a dilute solution of iodine in acetone followed by washing with dilute hydrochloric acid was employed for the activation of 3 µm dendritic copper dust. Specifically, a magnetically stirred suspension of copper dust (350 mg, 5.5 mmol of 3

μm dendritic material *ex.* Aldrich Chemical Co.) in acetone (10 ml) maintained at 20 °C under nitrogen was treated with iodine (200 mg) and the ensuing mixture was stirred for 10 minutes at this temperature. The supernatant was decanted and the dull-grey coloured solids thus obtained were treated with dilute hydrochloric acid in acetone [20 ml of a 1:1 v/v mixture of aqueous HCl (0.1 M) and acetone]. The ensuing mixture was stirred for 10 minutes and then the supernatant was decanted and the solids were washed with water (2 x 10 mL) and acetone (2 x 10 mL) and the residual acetone was removed by rotary evaporation to provide *ca.* 330 mg of activated copper dust that exhibited a pale-pink colour. This material was used promptly in the cross-coupling reaction as described above [5.4.1-(ii)].

(v) A technique described by Gaudemar²⁴ for the activation of magnesium turnings with 1,2-dibromoethane was adapted for the activation of copper. Thus, a magnetically stirred suspension of copper dust (350 mg, 5.5 mmol of 3-micron dendritic material *ex.* Aldrich Chemical Co.) in dry THF (10 ml) at 20 °C under nitrogen was treated dropwise with 1,2-dibromoethane (0.5 ml, 1.1 g, 5.9 mmol) and the ensuing mixture was stirred at 20 °C for 2 h. The supernatant liquid was decanted and the solids thus obtained were washed with dry THF (2 x 10 ml) and the residual THF was removed by rotary evaporation to provide *ca.* 340 mg of copper dust. This was used promptly in the cross-coupling reaction as described above [5.4.1-(ii)].

Table 5.4.1a: The Effect of Chemically Treated 3 μ m Dendritic Copper Dust on the Pd[0] Catalysed Ullmann Cross-Coupling of Substrates **3.21** and **3.83**.



Entry	Activating agent	% Yield 3.91	Entry	Activating agent	% Yield 3.91
1	none	69	6	H ₃ PO ₄ (0.05M)	72
2	HCl (0.01M)	73	7	I ₂ /THF	65
2	HCl (0.02M)	64	8	I ₂ /acetone/HCl	75
4	HCl (0.05M)	58	9	CH ₂ BrCH ₂ Br/THF	68
5	H ₃ PO ₄ (0.02M)	67	10	EDTA (0.02M)	77

Reaction conditions: 2.0 equiv of compound **3.21**, 1.0 equiv of compound **3.83**, 5.0 equiv of chemically treated 3 μ m Cu dust, Pd₂(dba)₃ 6%, DMSO, 50 °C, 3.0 h. The yield of the homocoupled by-product **3.25** was not determined.

Rieke Copper

A method described by Rieke and co-workers for the formation of Rieke Copper²⁵ was employed. Thus, a mixture of Li (35 mg, 5.0 mmol) and naphthalene (960 mg, 7.5 mmol) in anhydrous THF (15 mL) was stirred under argon at 20 °C for 2 h during which time the metal was consumed. This mixture was then cooled to –78 °C. A suspension of CuCN (450 mg, 5.0 mmol) in anhydrous THF (15 mL) was treated with LiBr (955 mg, 11.0 mmol) and the ensuing mixture was stirred under argon at 20 °C for 1.5 h until the Cu[I] salt was solubilized. The resulting CuCN·2LiBr solution was cooled to –78 °C and it was transferred into the lithium naphthalide solution *via* cannula. The ensuing mixture was warmed to 0 °C and treated with 1-iodo-2-nitrobenzene [**3.21**] (498 mg, 2.0 mmol), 3-bromo-1-methyl-1*H*-pyrrole-2,5-dione [**3.83**] (190 mg, 1.0 mmol) and Pd₂(dba)₃ (46 mg, 0.05 mmol, 5 mol%). The ensuing mixture was stirred at 0 °C for 1.5 h then quenched with saturated NH₄Cl (10 mL of a saturated aqueous solution) and it

was diluted with ethyl acetate (25 ml) and then filtered through a pad of Celite. The solids thus retained were rinsed with ethyl acetate (50 ml) and the combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (MgSO_4) and filtered. The filtrate was concentrated under reduced pressure to give an oily residue and subjection of this to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) followed by concentration of the relevant fractions ($R_f = 0.6$) gave the homocoupled compound 2,2'-dinitro-1,1'-biphenyl [**3.25**] (181 mg, 37%) as a yellow crystalline solid. In a variation to this experiment, the mixture of $\text{CuCN} \cdot 2\text{LiBr}$ and lithium naphthalide was stirred at 20 °C for 1.5 h to afford compound **3.25** (210 mg, 43%).

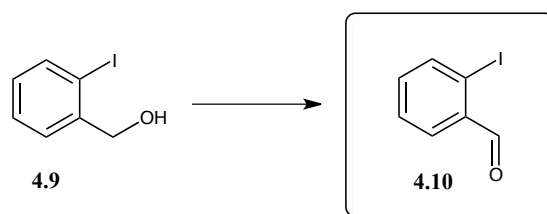
Copper Nano-Particles on Activated Charcoal

(i) A magnetically stirred solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (1.25 g, 5.0 mmol) in deionised water (20 mL) and maintained under an atmosphere of nitrogen was treated with activated charcoal dust (500 mg). The ensuing suspension was treated, dropwise over 10 minutes, with a solution of NaBH_4 (290 mg, 7.6 mmol) in deionised water (10 mL) and stirring was then continued at 20 °C for 0.5 h. The turbid mixture so formed was poured through a Büchner suction funnel fitted with a filter paper (Whatman grade 3) and the solids thus retained were washed successively with deionised water (4 x 25 mL) then ethanol (3 x 25 mL) and acetone (2 x 25 mL) whilst a vigorous flow of nitrogen gas was directed over the solid material. This material was transferred to a 50 mL r.b. flask and the residual acetone was removed under reduced pressure. The dry solids, consisting of activated copper nano-particles deposited on activated charcoal, were suspended in anhydrous DMSO (15 mL) and maintained under an atmosphere of nitrogen. This material was used promptly in the cross-coupling reaction (in a variation on this process K10-Montmorillonite powder was substituted for activated charcoal).

(ii) To a magnetically stirred suspension of copper nano-particles in anhydrous DMSO (15 mL) (see above) was added the 2-halonitroarene **3.21**, **3.78** or **3.79** (2 mmol) in DMSO (20 mL) and the relevant heterocyclic cross-coupling partner **3.74**, **3.83** and **3.86** (1 mmol) or 2-iodo-cyclohex-2-enone [**3.22**] (1 mmol) and $\text{Pd}_2(\text{dba})_3$ (47 mg, 5×10^{-5} mol, 5 mol%). The resulting mixture was warmed, under a nitrogen atmosphere, to 20-40 °C and stirred for 1 – 7 h, then the mixture was cooled to 18 °C, diluted with ethyl acetate (25 mL) and filtered through a pad of Celite which was rinsed with ethyl acetate (50 mL). The combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v

aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (MgSO_4) and filtered. The filtrate was treated with flash chromatographic grade silica (1 g) and then concentrated under reduced pressure to give a free-flowing powder. This was applied to the top of a flash chromatography column that was eluted with a suitable combination of ethyl acetate and hexane. Concentration of the appropriate fractions then gave the relevant cross-coupling product (Chapter 4, Table 4.2.3). See Section 5.3.4 for comprehensive characterization of the cross-coupled compounds **3.75**, **3.91**, **3.92**, **3.96** and **3.97**. The cross-coupled compound **3.23** has been reported previously²⁶ and the data obtained for this material were in complete agreement with the relevant literature.

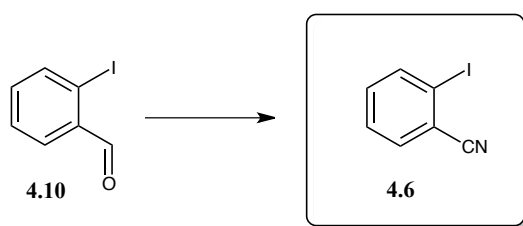
2-Iodobenzaldehyde [**4.10**]



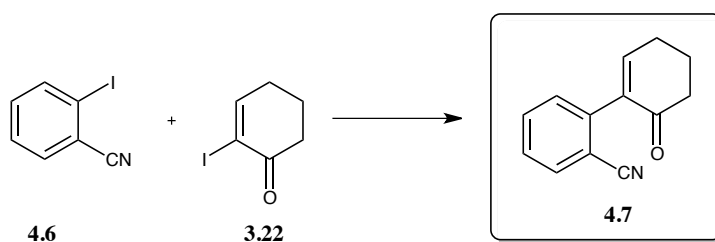
Following a procedure described by Varma and co-workers,²⁷ MnO_2 (870 mg, 10.0 mmol) and silica gel (1.5 g of 60 mesh material) were ground in a mortar until the MnO_2 was thoroughly dispersed into the silica gel. To this mixture was added 2-iodobenzylalcohol [**4.9**] (469 mg, 2.00 mmol), which was stirred into the MnO_2 /silica-gel. The dry reaction mixture was poured into a 10 mL CEM glass microwave reactor tube equipped with a crimp-top and was subjected to microwave irradiation at 80 °C for 2 minutes (ramp-time 1 min.). The mixture was cooled to 18 °C with a stream of nitrogen gas that was directed onto the surface of the reaction vessel and then it was subjected once more to microwave irradiation at 80 °C for 2 minutes (ramp-time 1 min.) before being cooled to 18 °C. The reaction mixture was poured onto a short plug of chromatographic grade silica-gel in a sintered glass funnel and the product was extracted with ethyl acetate/hexane (5 X 10ml of a 1:2 v/v mixture). After concentration at reduced pressure the *title compound* **4.10**²⁸ (384 mg, 83%) was obtained as a white, crystalline solid. The product, so obtained, may be employed for most purposes without additional purification. For the purpose of spectroscopic characterization, a sample of this material was recrystallized (ethyl acetate/hexane) to give white crystals, $R_f = 0.3$ (1:9 v/v ethyl acetate/hexane), mp = 37 – 38 °C (lit.²⁷ mp = 36 – 38), (Found: M^{+} , 231.9385.

Calculated for C_7H_5IO M^{+} , 231.9385). ^1H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.95 (d, $J = 7.9$ Hz, 1H), 7.87 (dd, $J = 7.9$ and 1.6 Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.28 (td, $J = 7.9$ and 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 140.7, 135.6, 135.1, 130.3, 128.8, 100.9; IR ν_{max} (KBr) 1697, 1580, 1450, 1401, 1260, 1199, 1014, 753 cm^{-1} ; MS (EI, 70 eV) m/z 232 (M^{+} , 91%), 231 (100), 204 (17), 203 (85), 128 (14), 127 (34), 105 (42), 104 (86) 77 (79), 76 (83).

2-Iodobenzonitrile [4.6]



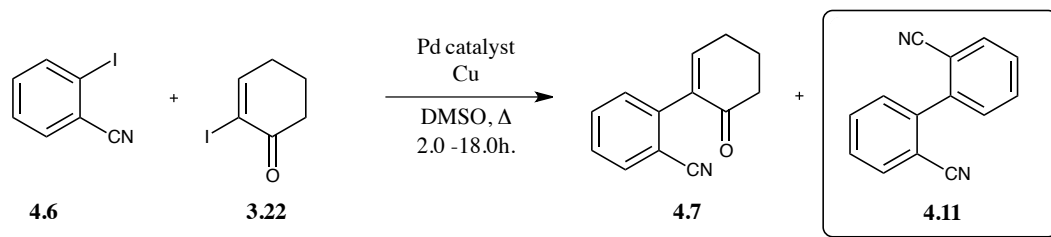
A magnetically stirred solution of 2-iodobenzaldehyde [4.10] (232 mg, 1.0 mmol) in ammonia (10 mL of 28% aqueous solution) and THF (1 mL) was treated with molecular iodine (254 mg, 1.0 mmol). The ensuing dark mixture was stirred (*ca.* 1 h) at 20 °C (room temperature) until it became colourless then diluted with diethyl ether (50 mL) and sodium thiosulfate (25 mL of 10% w/v aqueous solution). The phases were separated and the organic one was washed with water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure gave the *title compound* 4.6²⁹ (229 mg, 100%) as a white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethyl acetate/hexane) to give white needles, $R_f = 0.3$ (1:5 v/v ethyl acetate/hexane), mp = 54 – 55 °C (lit.²⁸ mp = 54 – 55) (Found: M^{+} , 228.9389. Calculated for C_7H_4IN M^{+} , 228.9389) ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, $J = 7.8$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 134.5, 134.0, 128.6, 120.8, 119.6, 98.7; IR ν_{max} (KBr) 2225, 1579, 1461, 1422, 1277, 1164, 1042, 1016, 755, 700, 644 cm^{-1} ; MS (EI, 70 eV) m/z 229 (M^{+} , 100%), 102 (64), 75 (21%).

Compound **4.7**[2-(2-Oxo-5,6-dihydro-2*H*-pyran-3-yl)-benzonitrile]

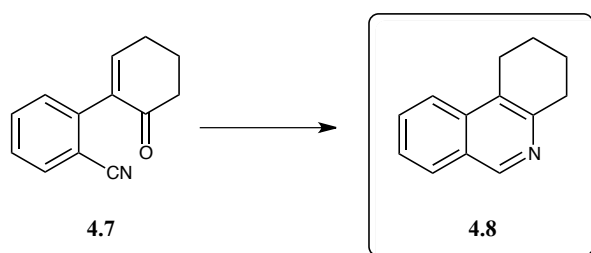
A magnetically stirred suspension of copper nano-particles in anhydrous DMSO (15 mL) (prepared as described above) was treated with 2-iodobenzonitrile [**4.6**] (298 mg, 1.3 mmol), 2-iodocyclohex-2-enone [**3.22**] (222 mg, 1 mmol) and $\text{Pd}_2(\text{dba})_3$ (47 mg, 5×10^{-5} mol, 5 mole %). The resulting mixture was stirred at 80 °C under a nitrogen atmosphere for 4 h then cooled to 18 °C and diluted with ethyl acetate (25 mL) before being filtered through a pad of Celite that was rinsed with ethyl acetate (50 mL). The combined filtrates were washed with ammonia (4 x 25 mL of a 5% w/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (MgSO_4) and filtered. The filtrate was treated with flash chromatographic grade silica (1 g) and then concentrated under reduced pressure to a free-flowing powder. This was applied to the top of a flash chromatography column (silica). Elution with 1:3 v/v ethyl acetate/hexane and concentration of the relevant fractions ($R_f = 0.3$) gave the *title compound* **4.7** (93 mg, 47%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (isopropanol) to give a white, crystalline solid, no m.p., decomposition above 115 °C (Found: M^+ , 197.0849. Calculated for $\text{C}_{13}\text{H}_{11}\text{NO}$ M^+ , 197.0841. ^1H NMR (CDCl_3 , 300 MHz) δ 7.67 (dd, $J = 7.5$ and 1.3 Hz, 1H), 7.57 (td, $J = 7.5$ and 1.3 Hz, 1H), 7.39 (td, $J = 7.5$ and 1.3 Hz, 1H), 7.30 (dd, $J = 7.5$ and 1.2 Hz, 1H), 7.15 (t, $J = 4.1$ Hz, 1H), 2.61 (m, 4H), 2.17 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 198.9, 141.4, 139.1, 136.4, 133.7, 132.8, 128.5, 127.6, 116.4, 110.1, 38.4, 26.6, 22.6; IR ν_{max} (KBr) 2958, 2921, 2227, 1663, 1594, 1483, 1445, 1358, 1280, 1264, 1155, 1129, 968, 841, 769 cm^{-1} ; MS (EI, 70 eV) m/z 197 (M^+ , 100%), 169 (97), 141 (93), 128 (35), 127 (33) 114 (39).

Compound **4.11**

[1,1'-Biphenyl-2,2'-dicarbonitrile]



The reaction conditions described above (for the synthesis of compound **4.7**) also resulted in the homo-coupling of arene **4.6** to give compound **4.11** as a by-product. Subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.65$) gave the *title compound* **4.11**³⁰ (yield 18 %) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (dichloromethane/isopropanol) to give a white, crystalline solid, mp = 172 - 174 °C (lit.²⁹ mp = 173 - 174) (Found: M^+ , 204.0689. Calculated for $C_{14}H_8N_2$ M^+ , 204.0687). ¹H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.73 (td, $J = 7.6$ and 1.4 Hz, 2H), 7.57 (m, 4H); ¹³C NMR (75 MHz, $CDCl_3$) δ 141.7, 133.7, 133.0, 130.7, 129.3, 117.7, 112.5; IR ν_{max} (KBr) 2224, 1591, 1475, 1428, 1261, 966, 765, 728, 555 cm^{-1} ; MS (EI, 70 eV) m/z 204 (M^+ , 100%), 203 (31), 177 (28), 150 (12), 75 (13).

1,2,3,4-Tetrahydrophenanthridine [**4.8**]

A magnetically stirred solution of compound **4.7** (121 mg, 0.61 mmol) in methanol (10 mL saturated with gaseous ammonia) contained in a Parr hydrogenation bomb was treated with Raney-Co⁷ (24 mg of wet material) and the resulting mixture was sparged with hydrogen for 5 min. The bomb was pressurized under hydrogen at 5000 kPa then heated at 80 °C for 8.0 h. The cooled reaction mixture was poured from the opened

bomb through a sintered glass funnel and the filtrate was treated with TLC-grade silica gel (400 mg) and the ensuing mixture concentrated under reduced pressure to give free-flowing light-yellow powder. This material was added to the top of a flash chromatography column which was eluted with 1:10 v/v acetone/toluene to give, after concentration of the appropriate fractions, the *title compound 4.8* ($R_f = 0.2$) as a clear colorless oil (85 mg, 76%) that slowly solidified to a white, crystalline material, no m.p. decomposition above 65 °C (lit.³¹ m.p. of picrate = 194 - 196 °C) (Found: M^{+} , 183.1049. Calculated for $C_{13}H_{13}N$, M^{+} , 183.1048.) ^1H NMR ($CDCl_3$, 300 MHz) δ 9.05 (s, 1H) 7.90 (m, 2H) 7.69 (td, $J = 8.5, 1.2$ Hz, 1H), 7.53 (td, $J = 8.5$ and 1.2 Hz, 1H), 3.08 (m, 4H) 1.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.9, 149.8, 135.6, 130.5, 128.4, 126.9, 126.1, 125.1, 122.1, 32.7, 24.9, 23.1, 22.7; IR ν_{max} (KBr) 2930, 2857, 1622, 1577, 1497, 1450, 1431, 1376, 1230, 1024, 884, 772, 749 cm^{-1} ; MS (EI, 70 eV) m/z 183 (M^{+} , 100%), 182 (77), 167 (21), 155 (47) 154 (33).

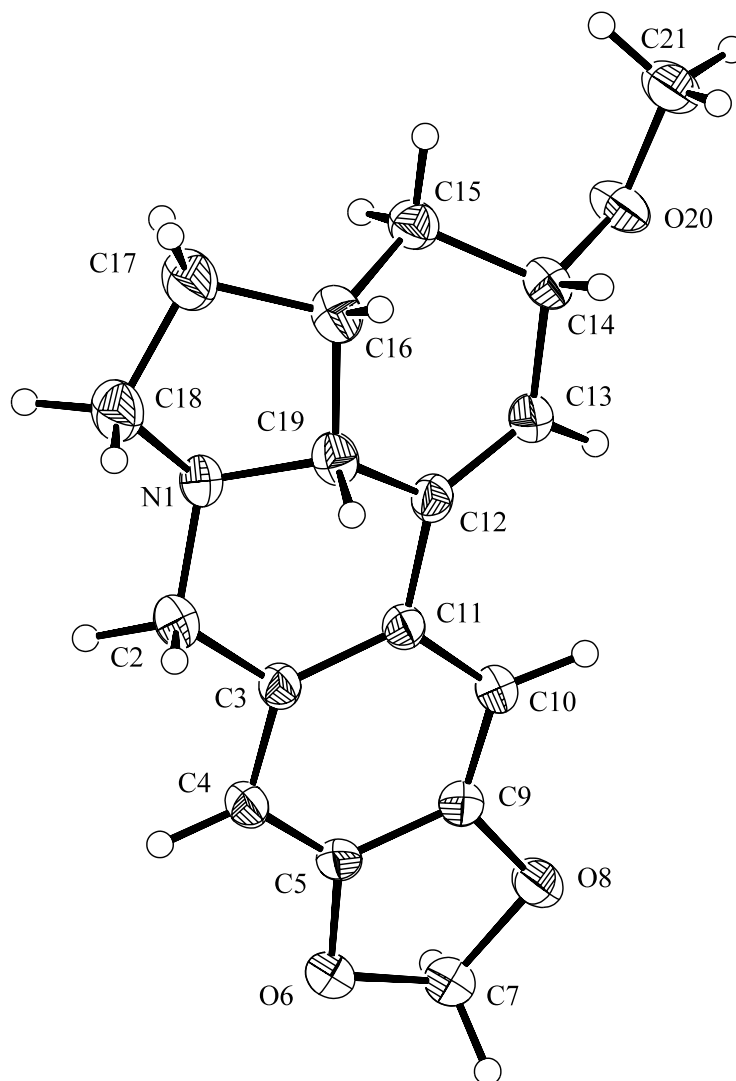
5.5 References.

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- 1 Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923.
 - 2 Pangborn, A.; Giardello, M.; Grubbs, R.; Rosen, R. *Organometallics*, **1996**, *15*, 1518.
 - 3 Hudlicky, T.; Price, J.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.*, **1990**, *112*, 9439.
 - 4 (a) Khanapure, S.; Garvey, D.; Young, D.; Ezawa, M.; Earl, R.; Gaston, R.; Fang, S.; Murty, M.; Martino, A.; Shumway, M.; Trocha, M.; Marek, P.; Tam, W.; Janero, D.; Letts, G. *J. Med. Chem.*, **2003**, *46*, 5484; (b) Dalconale, E.; Montonari, F. *J. Org. Chem.*, **1986**, *51*, 567.
 - 5 (a) Meyers, A.; Flisak, J.; Aitken, R. *J. Am. Chem. Soc.* **1987**, *109*, 5446; (b) Becker, D.; Hughes, L.; Raphael, R. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1674.
 - 6 Swenton, J.; Carpenter, J.; Chen, Y.; Kerns, M.; Morrow, G. *J. Org. Chem.*, **1993**, *58*, 3308.
 - 7 Adapted from a procedure described by Billica and Adkins for the preparation of Raney-Ni Type W-6 (Billica, H. R.; Adkins, H. In *Org. Synth.*, Wiley & Sons: New York, **1955**; Collect. Vol. III, 176).
 - 8 Takeda, K.; Kotera, K. *Chem. Pharm. Bull.*, **1957**, *5*, 234.
 - 9 Wawzonek, S.; Wang, S. *J. Org. Chem.*, **1951**, *16*, 1271.
 - 10 Scott, T.; Yu, X.; Gorugantula, S.; Carrero-Martinez, G.; Söderberg, B. *Tetrahedron* **2006**, *62*, 10835 and references cited therein.
 - 11 Monneret, C.; Dauzonne, D.; Hickman, J.; Pierre, A.; Kraus B.; Pfeiffer, B.; Renard, P. "Process for the preparation of new 9-aminopodophyllotoxin derivatives and antitumor pharmaceutical compositions containing them", *Fr. Demande*, 2005 (*Chem. Abstr.* **2005**, *142*, 261336).
 - 12 Burgess, K.; Lajkiewicz, N.; Sanyal, A.; Yan W.; Snyder, J. *Org. Lett.*, **2005**, *7*, 31.
 - 13 Choi D.; Huang, S.; Huang, M.; Barnard, T.; Adams, R.; Seminario J.; Tour, J. *J. Org. Chem.*, **1998**, *63*, 2646.

- 14 Bella, M.; Piancatelli G.; Squarcia, A. *Tetrahedron*, **2001**, 57, 4429.
- 15 Posner, G.; Afarinkia K.; Dai, H. *Org. Synth.*, **1996**, 73, 231.
- 16 Wineman, R.; Hus E.; Anagnostopoulos, C. *J. Am. Chem. Soc.*, **1958**, 80, 6233.
- 17 (a) Fuson, R.; Cleveland, E. *Org. Synth.*, Coll. Vol. III, **1965**, 339.; (b) Gonzáles, R.; Liguori, L.; Martinez Carillo, A.; Bjørsvik, H. *J. Org. Chem.*, **2005**, 70, 9591; (c) Thuruvikraman, S.; Suzuki, H. *Bull. Chem. Soc. Jpn.*, **1985**, 58, 1597.
- 18 Minami, N. K.; Reiner, J. E.; Semple, J. E. *Bioorg. Med. Chem. Lett.*, **1999**, 9, 2625.
- 19 Tacconi, G. *Gazz. Chim. Ital.*, **1968**, 98, 344.
- 20 Suárez-Castillo, O.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Castelán-Duarte, L.; Morales-Ríos M.; Joseph-Nathan, P. *Tetrahedron*, **2006**, 62, 3040.
- 21 Hino, T.; Miura, H.; Murata, R.; Nakagawa, M. *Chem. Pharm. Bull.*, **1978**, 26, 3695.
- 22 Lai, Y. *Synthesis*, **1981**, 586.
- 23 Kleiderer, E.; Adams, R. *J. Am. Chem. Soc.*, **1933**, 55, 4219.
- 24 Gaudemar, M. *Bull. Chim. Fr.*, **1962**, 974.
- 25 Stack, D.; Dawson, B.; Rieke, R. *J. Am. Chem. Soc.*, **1991**, 113, 4672.
- 26 Banwell, M.; Kelly, B.; Kokas, O.; Lupton, D. *Org. Lett.*, **2003**, 5, 2497.
- 27 Varma, R.; Saini, R.; Dahiya, R. *Tetrahedron Lett.*, **1997**, 38, 7823.
- 28 Olivera, R. SanMartin, R.; Dominiguez, E.; Solans, X.; Urtiaga, M. K. Arriortua, I. A. *J. Org. Chem.*, **2000**, 65, 6398.
- 29 Suzuki, Y.; Moriyama, K.; Togo, H. *Tetrahedron*, **2011**, 67, 7956.
- 30 (a) Cahiez, G. *Org. Lett.*, **2005**, 7, 1943; (b) Al-Awadi, H. *Tetrahedron*, **2007**, 63, 12948; (c) ; Hannon, J. *J. Chem. Soc.*, **1934**, 138; (d) Underwood, H. *J. Am. Chem. Soc.*, **1929**, 51, 583
- 31 Pandey, G.; Balakrishnan, M. *J. Org. Chem.*, **2008**, 73, 8128.

Appendix One

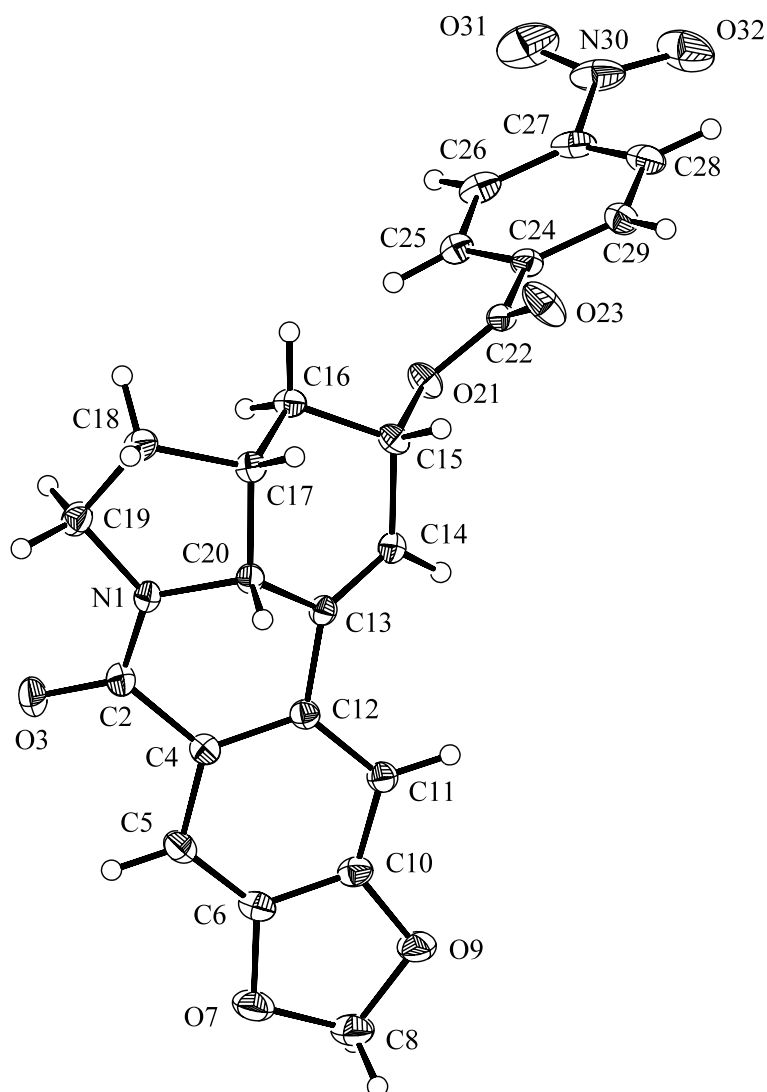
ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **2.127**.



A full X-ray crystallographic report for compound **2.127** (as compiled by Dr. A. C. Willis of the Research School of Chemistry, Australian National University) is provided in PDF-format in the compact disk found on the inside back cover of this Thesis.

Appendix Two

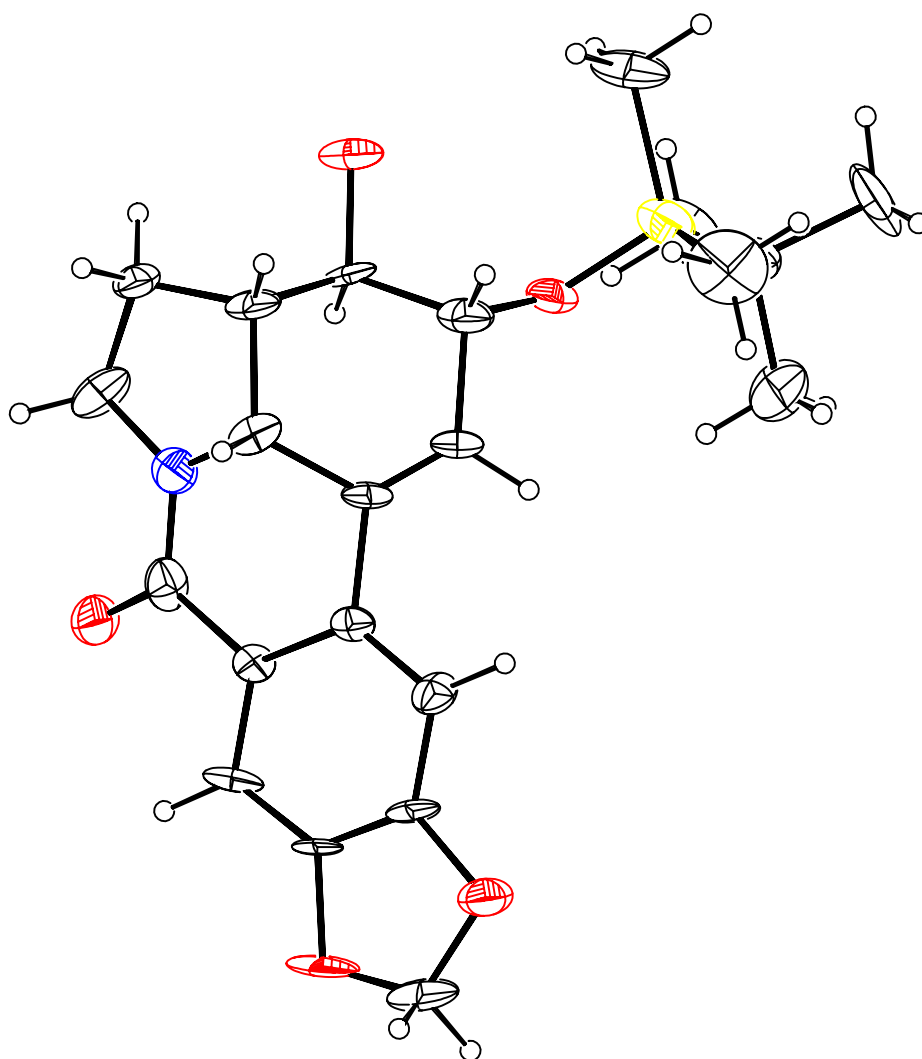
ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **2.152**.



A full X-ray crystallographic report for compound **2.152** (as compiled by Dr. A. C. Willis of the Research School of Chemistry, Australian National University) is provided in PDF-format in the compact disk found on the inside back cover of this Thesis.

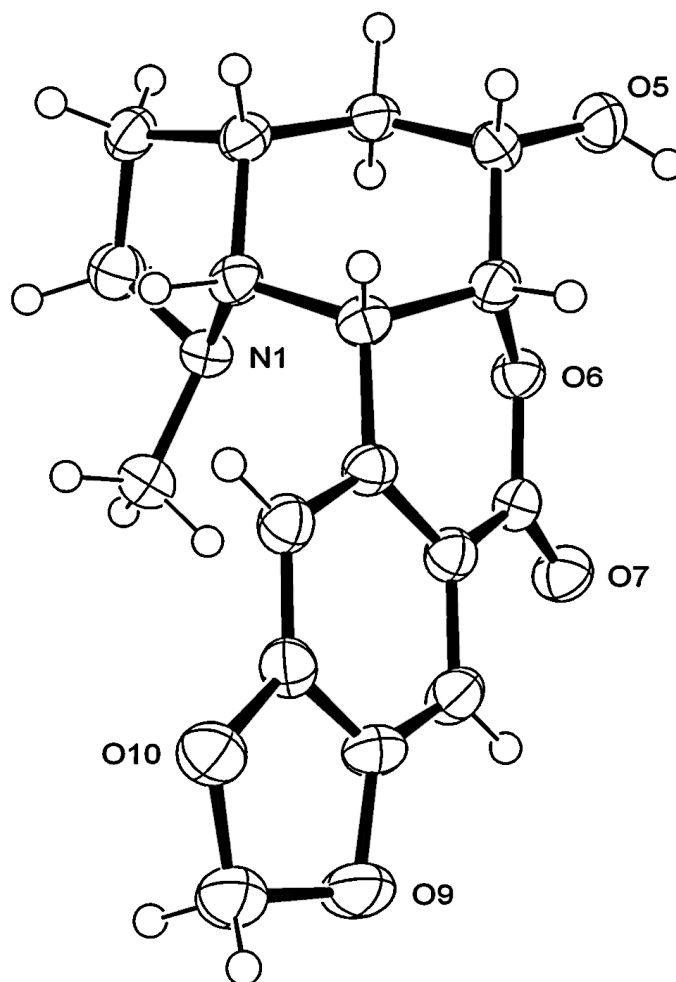
Appendix Three

ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **2.162**.



Appendix Four

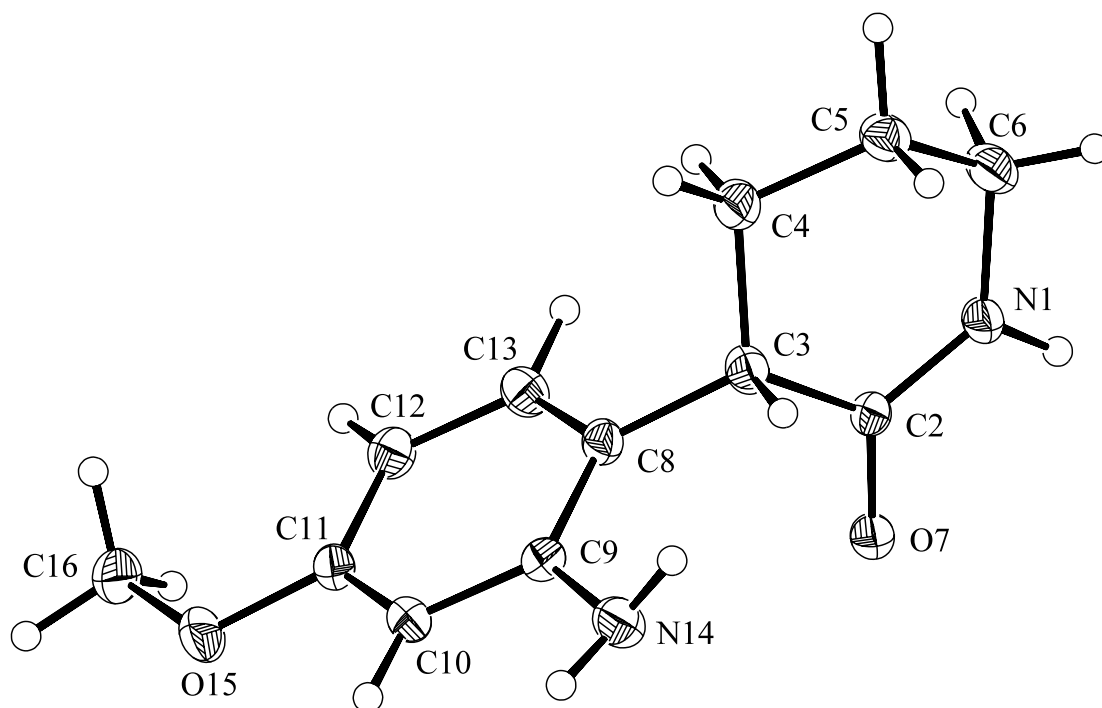
ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **ent-2.167**.



A full X-ray crystallographic report for compound **ent-2.167** (as compiled by Dr. I. A. Cade of the Research School of Chemistry, Australian National University) is provided in PDF-format in the compact disk found on the inside back cover of this Thesis.

Appendix Five

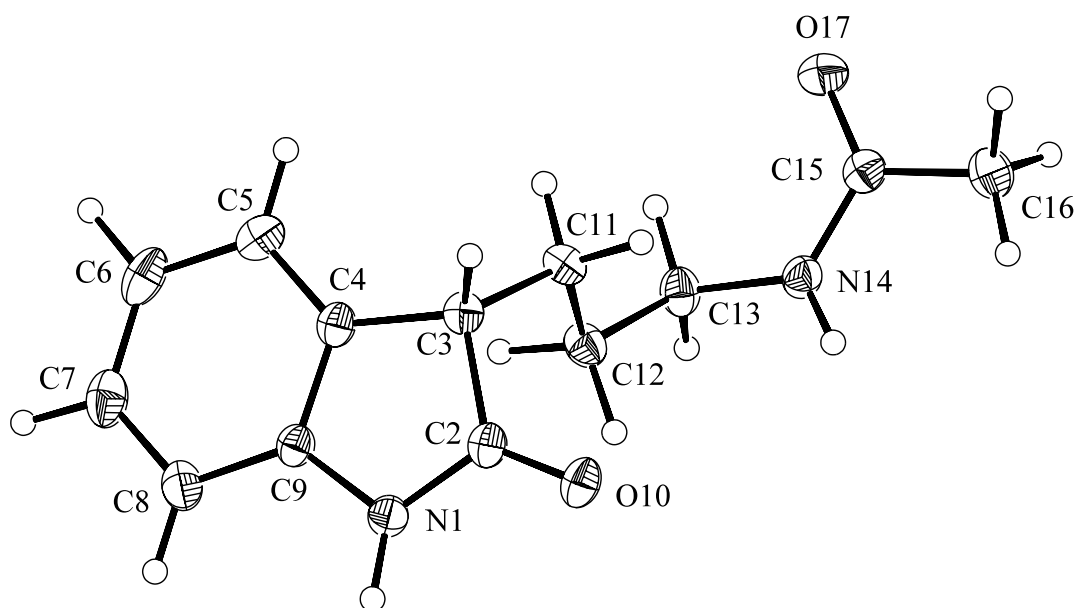
ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **3.102**.



A full X-ray crystallographic report for compound **3.102** (as compiled by Dr. I. A. Cade of the Research School of Chemistry, Australian National University) is provided in PDF-format in the compact disk found on the inside back cover of this Thesis.

Appendix Six

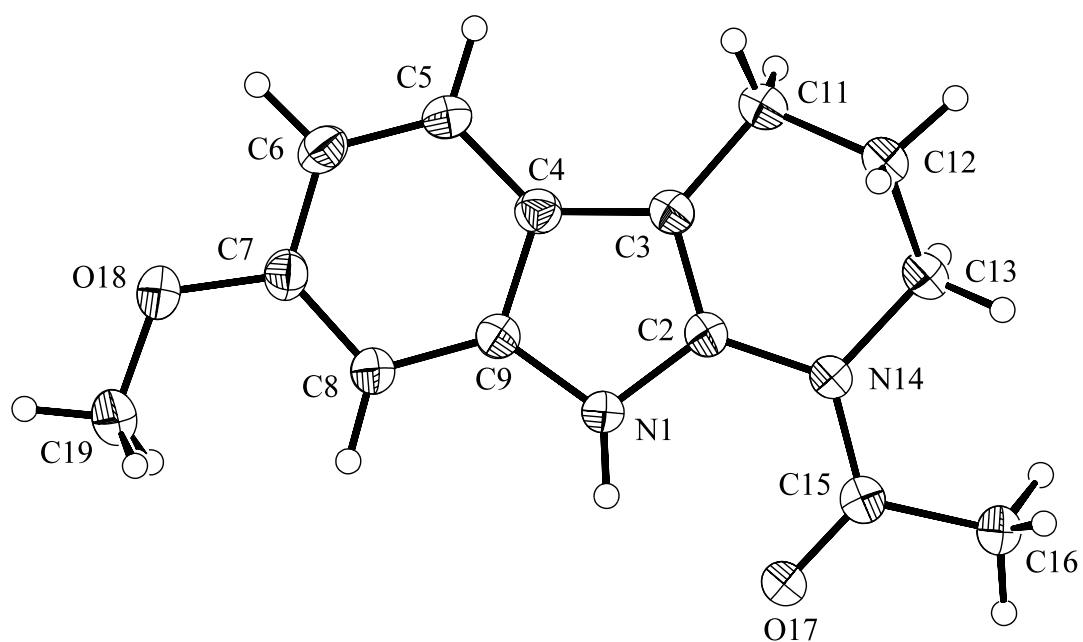
ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **3.107**.



A full X-ray crystallographic report for compound **3.107** (as compiled by Dr. A. C. Willis of the Research School of Chemistry, Australian National University) is provided in PDF-format in the compact disk found on the inside back cover of this Thesis.

Appendix Seven

ORTEP Derived From the Single-Crystal X-ray Analysis of Compound **3.108**.



A full X-ray crystallographic report for compound **3.108** (as compiled by Dr. A. C. Willis of the Research School of Chemistry, Australian National University) is provided in PDF-format in the compact disk found on the inside back cover of this Thesis.

Appendix Eight

This appendix contains reprints of publications arising from work reported in this Thesis.

1. "New Protocols for the Synthesis of 3,4-Annulated and 4-Substituted Quinolines From β -Bromo- α,β -Unsaturated Aldehydes and 1-Bromo-2-Nitrobenzene or 2-Bromoacetanilide." Some, S.; Ray J. K.; Banwell, M. G.; Jones, M. T. *Tetrahedron Letters*, **2007**, 48, 3609-3612.
2. "Rapid and Enantioselective Assembly of the Lycorine Framework Using Chemoenzymatic Techniques." Jones, M. T.; Schwartz, B. D.; Willis, A. C.; Banwell, M. G. *Organic Letters*, **2009**, 11, 3506-3509.
3. "Synthesis of the Enantiomer of the Structure Assigned to the Natural Product Nobilisitine A." Schwartz, B. D.; Jones, M. T.; Banwell, M. G.; Cade, I. A. *Organic Letters*, **2010**, 12, 5210-5213.
4. "A Pd[0]-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Approach to C-3 Mono-Alkylated Oxindoles and Related Compounds." Banwell, M. G.; Jones, M. T.; Loong, D. T.; Lupton, D. W.; Pinkerton, D. M.; Ray, J. K.; Willis, A. C. *Tetrahedron*, **2010**, 66, 9252-9262.
5. "The Palladium-Catalysed Ullmann Cross-Coupling Reaction." Banwell, M. G.; Jones, M. T.; Rieke, T. A. *Chemistry in New Zealand*, **2011**, 75, 122-127.

