New Methods for the Synthesis of Heterocyclic Compounds

A Thesis submitted for the degree of
Doctor of Philosophy of the Australian National University

By,

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THE AUSTRALIAN NATIONAL UNIVERSITY

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Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2006-2009 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Alexander Bissember
November, 2009

"So we beat on, boats against the current, borne back ceaselessly into the past."

F. Scott. Fitzgerald

(The Great Gatsby, 1925)

Acknowledgements

The research described in this thesis and its ultimate success certainly derives from the valuable guidance, strong encouragement and tremendous accessibility of Professor Martin Banwell. I've particularly benefited from his firm support of my own ideas and his eagerness to pursue, and direct resources toward, a variety of related side-projects as they have arisen during my PhD studies. As a supervisor his overall philosophy and approach to chemistry, indeed science more generally, has both profoundly influenced and inspired my own professional development and outlook. Certainly, these special attributes when combined with a willingness to pick up a gourmet Silo sandwich on a Saturday morning definitely makes Martin worth his weight in gold, or more correctly, chicken Caesar rolls! A better person to work for is difficult to imagine.

Like countless students before me I've had the luxury of drawing upon the considerable expertise of the brilliant technical and administrative staff employed at The Research School of Chemistry; particularly, Stephen Lee, Tony Herlt, Christine Sharrad and John Allen. I'm also indebted to the members of the Banwell Group, both past and present, for their support and camaraderie over the years. I've definitely learnt a great deal from discussions with Okanya, Rajeev, Brett, Alison and Pat.

Without doubt my time at ANU would not have been as interesting, nor as enjoyable, were it not for the core of my Canberra family: Tom, Georgia, Matt, Jess, Lian, Naomi and Ivan. Their *penchant* for irony and the absurd, esoteric humour and acerbic wit never failed to find the wry side of even the most trying situations and ensured life was never taken too seriously.

And last but not least Mum and Dad... for everything. I'm wary of elaborating further, especially in print, as I'm sure to hear it recited back to me *verbatim* on a daily basis through a variety of media. That being said, their stubborn, if not at times wilful, belief in me has always made even the most Sisyphean tasks seemingly possible. I've never taken the opportunities available to me for granted.

Publications and Presentations

The following list details the publications[1] and presentations that have resulted from research performed during the candidature of the Doctor of Philosophy.

Publications Resulting From Research Described in this Thesis:

(i) Bissember, A.C.; Banwell, M.G. Preparation of Some Angularly Substituted and Highly Functionalized Quinolizidines as Building Blocks for the Synthesis of Various Alkaloids and Related Scaffolds of Medicinal Interest.
Tetrahedron, **2009**, *65*, 8222-8230.

(ii) Bissember, A.C.; Banwell, M.G. Microwave Assisted Trans-Halogenation Reactions of Various Chloro-, Bromo-, Trifluoromethanesulfonyloxy- and Nonafluoromethanesulfonyloxy-Substitued Quinolines, Isoquinolines, and Pyridines Leading to the Corresponding Iodinated Heterocycles.
Journal of Organic Chemistry, **2009**, *74*, 4893-4895.

(iii) Bissember, A.C.; Banwell, M.G. 4-Iodo-6-methoxyquinoline.
Organic Preparations and Procedures International, **2008**, *40*, 557-561.

(iv) Bissember, A.C.; Phillis, A.T.; Banwell, M.G.; Willis, A.C. Base Promoted Reactions of Dichlorocarbene Adducts of Cyclic Enamines: A New Route to Annulated Pyrroles.
Organic Letters, **2007**, *9*, 5421-5424.

Publications Resulting From Research Not Described in this Thesis:

(v) Menon, R.S.; Findlay, A.D.; Bissember, A.C.; Banwell, M.G. The Au(I)-Catalyzed Intramolecular Hydroarylation of Terminal Alkynes Under Mild Conditions: Application to the Synthesis of 2*H*-Chromenes, Coumarins, Benzofurans, and Dihydroquinolines.
Journal of Organic Chemistry, **2009**, *74*, 8901-8903.

(vi) Bissember, A.C. Methyl Cyanoformate (Mander's Reagent).
Synlett, **2009**, 681-682.

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[1] Reprints of these publications are contained within Appendix A.2.

Presentations:

(i) Bissember, A.C.; Banwell, M.G., Towards A Stereoselective Total Synthesis of Quinine.
Poster presentation at The 58th Gordon Research Conference on Natural Product Chemistry;
Tilton, NH, USA, July 2009.

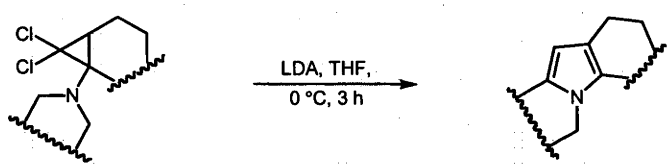
(ii) Bissember, A.C.; Banwell, M.G., Towards A Stereoselective Total Synthesis of Quinine.
Oral presentation at The Southern Highlands Conference on Heterocyclic Chemistry;
Moss Vale, NSW, Australia, September 2008.

(iii) Bissember, A.C.; Banwell, M.G.; Phillis, A.T.; Sharp, P.P. A New Method For the Synthesis of Annulated Pyrroles.
Poster presentation at The 22nd Royal Australian Chemical Institute Organic and 6th Royal Australian Chemical Institute Physical Chemistry Conference; Adelaide, SA, Australia, January 2007.

Abstract

Heterocycles comprise the largest class of organic compounds and the extraordinary diversity, multiplicity and significance of these structures is well established. This is most evident in Nature where these molecules are widely distributed and are essential to life. They are also readily accessible synthetically and many heterocycles thus formed are employed in an array of areas. The importance of this major class of organic compounds derives from its intrinsic complexity which is borne of its tremendous size. This ensures a seemingly limitless range of functionalised and structurally diverse molecular architectures that feature an assortment of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability, all of which can be readily exploited.[1]

This thesis reports on the development of new methods for the synthesis of heterocyclic compounds with the broad objective of exploring the scope, limitations and utility of these processes. In particular, the research presented in Part One dscribes the establishment of a new route to annulated pyrroles *via* the base-promoted reaction of *gem*-dihalogenocyclopropanes. The important features of this transformation were investigated in detail and extensions of this methodology also enabled the preparation of a structural analogue of the lamellarin alkaloids.

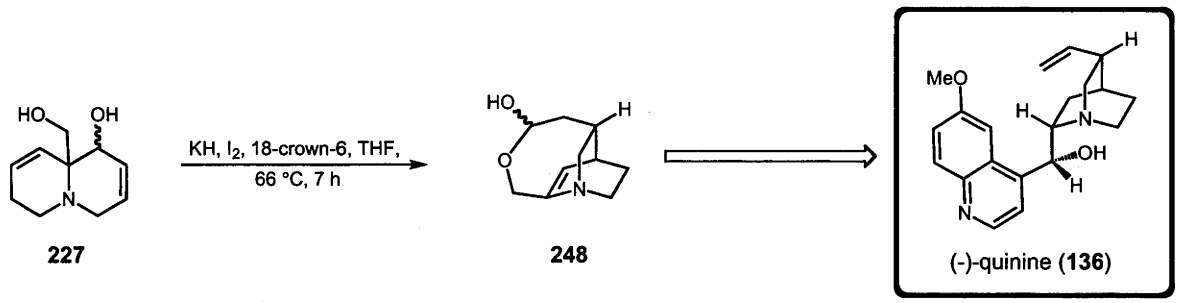


gem-dihalogenocyclopropanes
56, 65, 68, 69, 74

annulated pyrroles
57, 67, 76, 77, 80

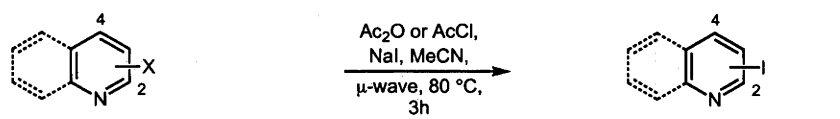
Part Two of this thesis describes studies directed towards the synthesis of the celebrated *Cinchona* alkaloid (-)-quinine (**136**). More specifically, this investigation sought to exploit an unusual and unprecedented anionic oxy-Cope rearrangement to construct the 1-azabicyclo[2.2.2.]octane framework of the natural product. The research, presented in Chapter Four, explored the capacity of model systems to engage in the abovementioned rearrangement. Significantly, the conversion of quinolizidine **227** into lactol **248** indicated that the key transformation could indeed form the centrepiece of an original and distinctive total synthesis of (-)-quinine (**136**).

[1] Katritzky, A.R.; Rees, C.W. *Comprehensive Heterocyclic Chemistry*, (Ed.: Meth-Cohn, O.), Pergamon Press, Oxford, **1984**, Vol. 1, Part 1, pVII.



227 **248** (-)-quinine (**136**)

As outlined in Chapters Five and Six, although initial attempts to install the quinoline substituent present within (-)-quinine (**136**) were unsuccessful, this work indirectly led to the development of a new microwave-assisted *trans*-halogenation procedure. This methodology allowed for the rapid and particularly efficient transformation of various chlorinated, brominated and pseudohalogenated quinolines, pyridines and isoquinolines into the corresponding iodinated heterocycles under mild conditions.



203, 267, 269, 271, 272, 274, 276, 277, 279, 280, 281, 287, 289, 292, 294, 295, 297
X = Cl, Br, OTf, ONf at C_2 and/or C_4

262, 268, 270, 273, 275, 278, 282, 288, 293, 296, 298
I at C_2 and/or C_4

Glossary

The following abbreviations have been used throughout this thesis:

°C	degrees Celsius
λ	wavelength (nm)
μg	microgram(s)
μL	microlitre(s)
Å	Ångstrom
$[\alpha]_D$	specific rotation at the sodium D-line
Ac	acetyl
Ad	adamant-1-yl
AcOH	acetic acid
APT	attached proton test (^{13}C NMR spectroscopy)
aq.	aqueous
Ar	unspecified aryl group
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Teoc	β-(trimethylsilyl)ethoxycarbonyl
br	broad
Bu	butyl
t-BuOK	potassium *tertiary*-butoxide
c	concentration (mol/L)
ca.	*circa* (approximately)
cat.	catalytic/catalyst
cf.	*confer* (compare)
cm	centimetre(s)
conc.	concentrated
d	doublet
Δ	heat
δ	chemical shift (parts per million)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine

DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dppm	1,1-bis(diphenylphosphino)methane
dppf	1,1'-bis(diphenylphosphino)ferrocene
E	entgegen
ee	enantiomeric excess
e.g.	*exempli gratia* (for example)
EI	electron impact (mass spectrometry)
equiv.	equivalent(s)
ES	electrospray (mass spectrometry)
Et	ethyl
et al.	*et alia* (and others)
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eV	electron volt(s)
FGI	functional group interconversion
g	gram
GCMS	gas chromatograpy mass spectrometry
gem	geminal
h	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i.e.	*id est* (that is)
IR	infrared
irr.	irradiation
J	1H-1H coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	litre(s)
LDA	lithium di*iso*propylamide
LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature value

LiTMP	lithium 2,2,6,6-tetramethylpiperidine
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
M^+	molecular ion
Me	methyl
MeOH	methanol
MIT	Massachusetts Institute of Technology
MOM	methoxymethyl
MHz	mega-Hertz
min	minute(s)
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point (°C)
MS	mass spectroscopy
μ-wave	microwave
m/z	mass-to-charge ratio
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
Nf	nonafluoromethanesulfonyl
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser enhancement spectroscopy
P	unspecified protecting group
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichlorochromate
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
i-PrMgBr	*iso*-propylmagnesium bromide
q	quartet
qu	quintet
quant.	quantitative

R	unspecified alkyl group
RCM	ring-closing metathesis
ref.	reference
R_f	thin layer chromatography retardation factor
R_t	retention time
RI	refractive index
r.t.	room temperature
s	singlet
s	secondary
salen	*N,N'*-bis(salicylidene)ethylenediamine
t	triplet
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEBAC	triethylbenzylammonium chloride
temp.	temperature (°C)
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
p-TsOH	*para*-toluenesulfonic acid
UV	ultra violet (spectroscopy)
viz.	*videlicit* (that is, namely)
vs.	*versus*
v/v	unit volume per unit volume (ratio)
W	watt(s)
WWI	World War I
WWII	World War II
w/v	unit weight per unit volume (%)
Z	zusammen

Table of Contents

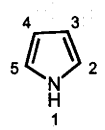
Chapter One

Studies Directed Towards a New Pyrrole Synthesis

"Pyrrole is a remarkable substance; it is highly reactive, versatile in that reactivity and is of crucial importance for living systems... What stands out plainly is the powerful effect substituents on the pyrrole nucleus have on the reactivity of the system, whether they be attached at carbon or nitrogen. Those who have worked personally with pyrrolic substances are acutely aware of this aspect of their chemistry, and for example, use it to steer safely along a synthetic route avoiding Scylla on the one hand and Charybdis on the other."[1]

1.1 Introduction

Pyrrole (**1**), represented in Figure 1.1.1, was first identified by Ferdinand Runge in 1834,[2] and its structure correctly elucidated by Adolf von Baeyer in 1870.[3] This fundamental aromatic heterocycle is an electron-rich, 'π–excessive' structure, with six electrons delocalised over the ring. As such it readily engages in electrophilic aromatic substitution processes:[⊥] including nitration, sulfonation and Friedel-Crafts acylation reactions. Indeed, the high electron density in the five-membered ring even enables pyrrole to undergo nitrosation, coupling with diazonium salts and the Reimer-Tiemann reaction - transformations that are characteristic of only the most reactive arenes. Pyrroles can also be oxidised, are capable of coordinating metals, and able to participate in both π–π stacking and hydrogen bonding interactions. Although nucleophilic addition reactions occur when the heterocycle is protonated, this type of reaction is essentially unknown in pyrrole itself.



1

Figure 1.1.1. *Structure and numbering of the pyrrole ring system.*

The abovementioned electronic and chemical features of pyrrole are readily encountered in various biological settings and responsible for the abundance of pyrrole-based structures found in nature.[4] The most celebrated and, arguably, the most important examples of these are the tetrapyrroles, the so-called, 'pigments of the life,'[5] which include

[⊥] Pyrrole undergoes electrophilic aromatic substitution preferentially at the 2- and 5-positions.

heme, chlorophyll, vitamin B_{12}, and the cytochromes. Beyond this well-known class of compounds are a particularly large number of structurally diverse and biologically active secondary metabolites each of which embodies the pyrrole motif. Distinct and potent pharmacological effects are elicited by a variety of such heterocycles, ranging from antibacterial, antiviral, anti-inflammatory, antitumoral activities to antioxidant behaviour.[6] The lamellarin alkaloids are representative and have been isolated from various marine organisms (Figure 1.1.2).[7] Almost all members of this class exhibit cytotoxicity against a wide range of cancer cell lines.[8]

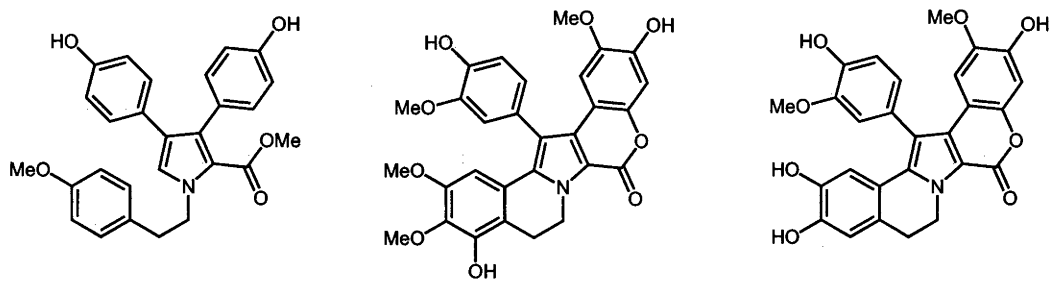


Figure 1.1.2. *Representative examples of the lamellarin alkaloids: lamellarins O (**2**), K (**3**) and D (**4**).*

Pyrroles are also readily accessible synthetically and represent highly flexible and versatile building blocks that have found use in a many diverse and unrelated areas:[9] in polymer[10] and materials science,[11] molecular optics[12] and electronics,[13] as gas sensors for organic compounds,[14] in molecular recognition applications[15] and, of course, as pharmaceutical agents.[16] The first synthetic routes to this fundamental class of aromatic heterocycle were established in the 19th century. The fact that new approaches continue to be developed not only reflects the enduring interest in pyrroles and their related structures, but also their general significance and continued relevance.

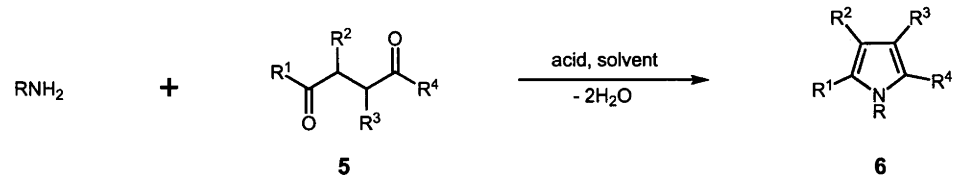
1.2 Established Methods for the Synthesis of Pyrroles

1.2.1 The Paal-Knorr Pyrrole Synthesis

The Paal-Knorr synthesis of subsitituted pyrroles, shown in Scheme 1.2.1, involves the Lewis- or Brønsted acid-catalysed condensation of 1,4-dicarbonyl compounds **5** (or their surrogates) with ammonia or primary amines.[⊥] Carl Paal and Ludwig Knorr first reported this process almost simultaneously in 1884.[17] This approach has become one of the most

[⊥] Aliphatic, aromatic and heterocyclic amines are all tolerated.

frequently employed methods for preparing functionalised pyrroles and continues to be utilised in organic synthesis.[18]

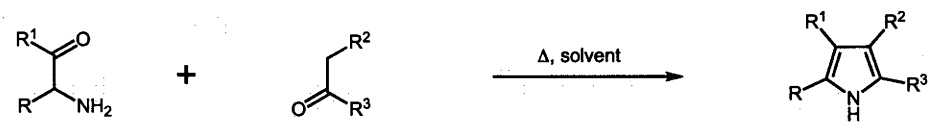


5 **6**

Scheme 1.2.1. *The Paal-Knorr pyrrole synthesis.*

1.2.2 *The Knorr Pyrrole Synthesis*

The condensation of an α-aminoketone (or an α-amino-β-ketoester) **7** with a carbonyl compound incorporating an 'active' methylene group is known as the Knorr pyrrole synthesis (Scheme 1.2.2). The process derives from investigations first undertaken by Knorr in 1886 who demonstrated that a substituted pyrrole could be synthesised by first nitrosating ethyl acetoacetate and then heating the mixture with zinc and glacial acetic acid.[19] The yield of the reaction is low unless ketone **8** contains a resonance-stabilising and electron-withdrawing substituent at the α–carbon atom.[20] This classic route has been extensively exploited to provide the necessary building blocks for preparing the tetrapyrroles. This is just one of the many useful applications of this methodology.[21]



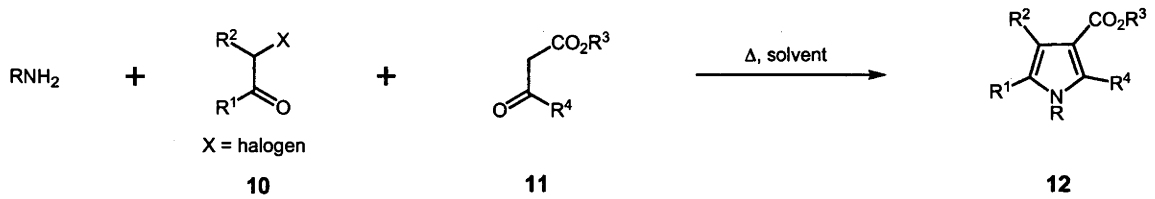
7 **8** **9**

Scheme 1.2.2. *The Knorr pyrrole synthesis.*

1.2.3 *The Hantzsch Pyrrole Synthesis*

The Hantzsch pyrrole synthesis, first reported in 1890 and shown in Scheme 1.2.3, features the reaction of α-haloketones (or aldehydes) **10** with β-diketones (or β-diketoesters) **11** in the presence of primary amines or ammonia.[22] Initial displacement of the halogen substituent in compound **10** by nucleophile **11** provides a 1,4-diketone that subsequently condenses with added amine to furnish the observed product **12**. This approach to structures incorporating this fundamental heterocycle continues to be employed and regularly so.[23] Furans are by-products of this reaction. In fact, if the amine is replaced with

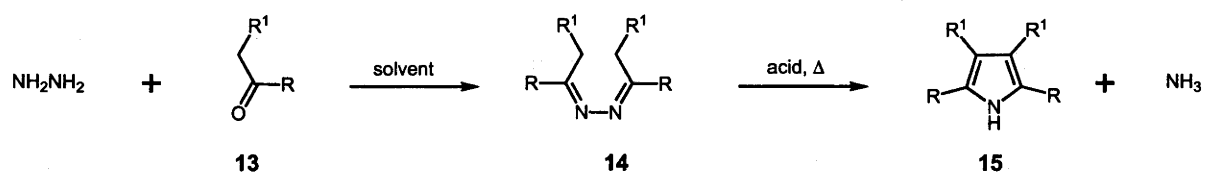
sodium hydroxide, a furan is formed, and the transformation referred to as the Feist-Bénary synthesis of furans.[24]



Scheme 1.2.3. *The Hantzsch pyrrole synthesis.*

1.2.4 *The Piloty-Robinson Pyrrole Synthesis*

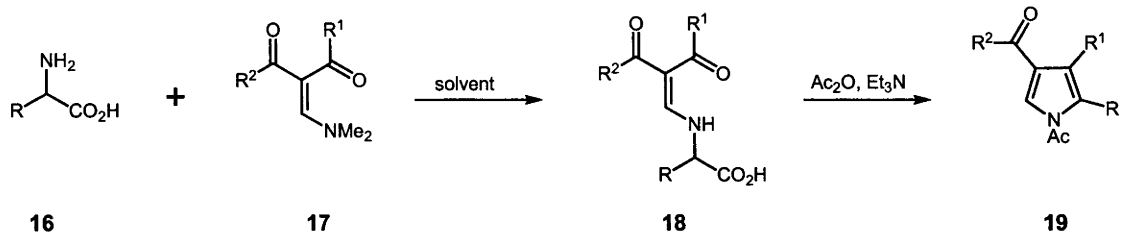
The condensation of hydrazine with two equivalents of an enolisable ketone **13** provides diimine **14** that, when treated with acid, tautomerises to the corresponding dienamine intermediate (Scheme 1.2.4). This last species undergoes a [3,3]-sigmatropic rearrangement, followed by a 5-*exo*-trig cyclisation that provides symmetrical pyrrole **15** with the accompanying loss of a molecule of ammonia. This process is known as the Piloty-Robinson pyrrole synthesis and was developed independently by Oskar Piloty and Robert Robinson in the early parts of the twentieth century.[25]



Scheme 1.2.4. *The Piloty-Robinson pyrrole synthesis.*

1.2.5 *The Zav'yalov Pyrrole Synthesis*

First described in 1973,[26] the Zav'yalov synthesis of pyrroles involves the substitution of the β-dimethylamino-moiety in β-dimethylaminomethylene ketones (acrylyl esters or both) **17** by an amino acid **16** to furnish enamine **18** (Scheme 1.2.5). Compound **18** then reacts with acetic anhydride to provide a species in which the enamine and acid functional groups are converted into alkenyl-acetamide and mixed anhydride substituents, respectively. This intermediate then undergoes a triethylamine-promoted cyclisation and a subsequent decarboxylation/elimination sequence provides functionalised pyrrole **19**. Modifications and variations of this methodology have recently been reported.[27]

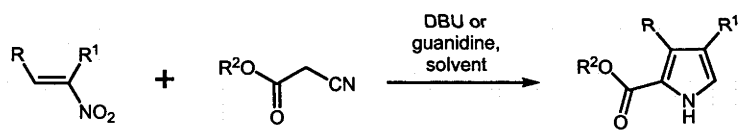


16 **17** **18** **19**

Scheme 1.2.5. *The Zav'yalov pyrrole synthesis.*

1.2.6 The Barton-Zard Pyrrole Synthesis

In 1985 Derek Barton and Samir Zard reported that various nitroolefins of the general form **20** could be reacted with α-cyanoacetate esters **21** in the presence of non-nucleophilic bases such as DBU or guanidine to yield pyrrole structures **22** that are able to be readily elaborated to a range of tetrapyrroles (Scheme 1.2.6).[28] This method exploits the ability of the nitro-substituent to activate olefins to towards Michael addition processes as well as its capacity to function as a leaving group. Because of the flexibility and efficiency of this approach it has subsequently been employed in a number of total syntheses including in the preparation of pyrrolostatin.[29]



20 **21** **22**

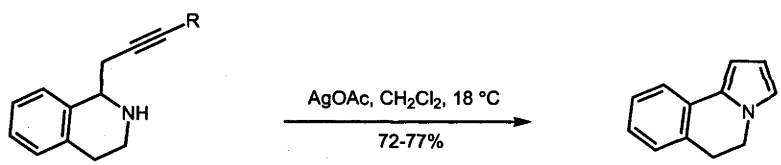
Scheme 1.2.6. *The Barton-Zard pyrrole synthesis.*

These well-established approaches to pyrroles have been studied extensively since they were first reported and are regularly employed to deliver members of this significant class of aromatic heterocycle. However, the considerable reactivity of pyrroles has dictated that novel methods for their synthesis continue to be developed so as to complement the abovementioned processes and thus allow for the preparation of structures with substitution patterns that are otherwise difficult to obtain. A number of such routes are described below.

1.3 New Methods for the Synthesis of Annulated Pyrroles

So great are the number of original approaches that have been developed to pyrroles it is not possible, to present and subsequently describe them all in this forum, especially since comprehensive reviews providing in depth discussions of a wide range of approaches to this class of aromatic heterocycle have been published.[9a,30] Accordingly, this commentary is restricted to recently established routes to annulated pyrroles and focuses on the important features of a variety of the more interesting and unprecedented examples.

Agarwal and Knölker reported the efficient preparation of annulated pyrroles **24** through the silver(I)-promoted oxidative cyclisation of homopropargylamines **23** at ambient temperature (Scheme 1.3.1).[31] Substrates such as **23** were easily synthesised, in one step and good yield, by the addition of a propargyl Grignard reagent to the appropriate imine. The authors proposed a mechanism for the pivotal transformation that involved initial silver-induced activation of the alkyne towards nucleophilic attack by the ring nitrogen.[⊥] Significantly, this novel reaction was not thwarted by the presence of a free amine substituent and its utility was underscored through its application to a total synthesis of the indolizidino[8,7-*b*]indole alkaloid (±)-harmicine.[32]

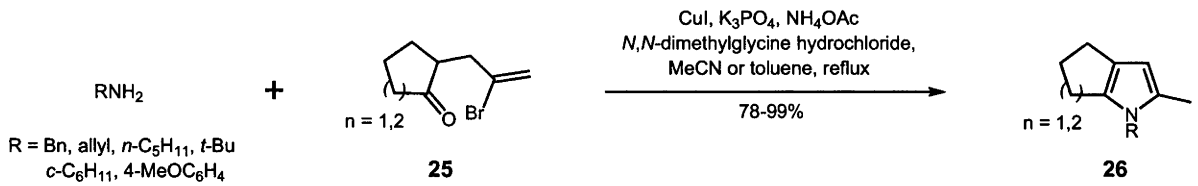


23 R = H, $SiMe_3$ **24**

Scheme 1.3.1. *The synthesis of annulated pyrrole* **24** *reported by Agarwal and Knölker.*[31]

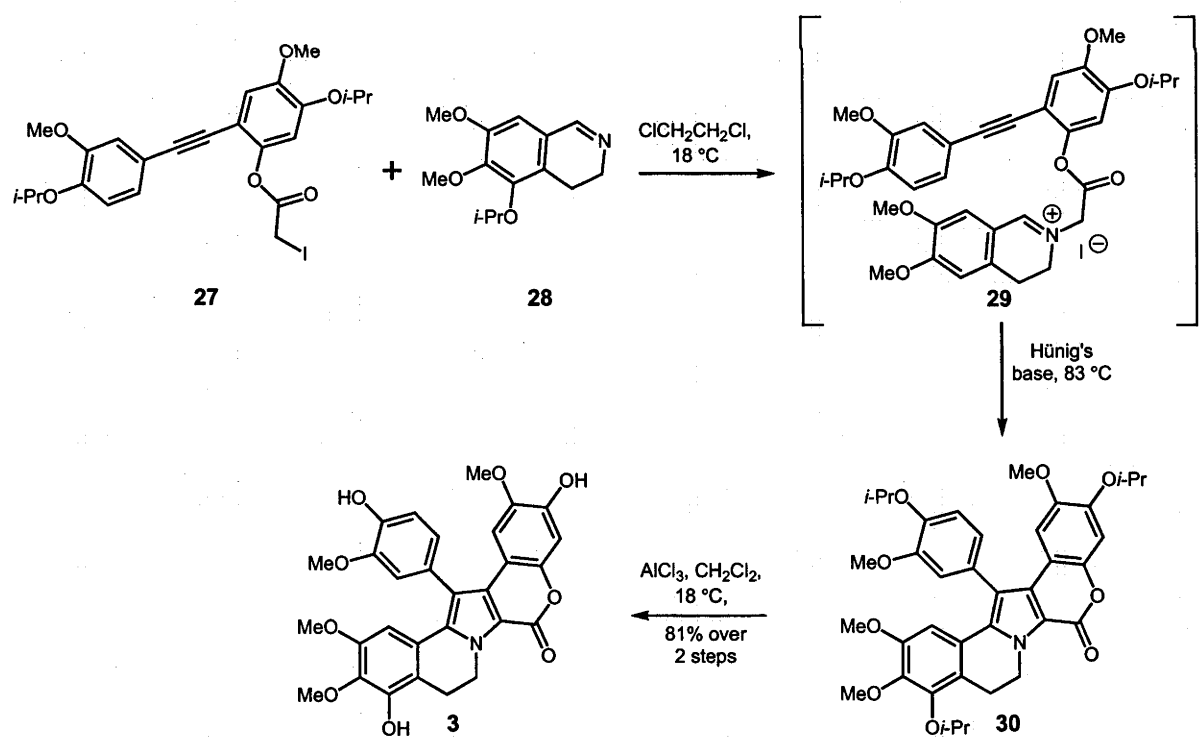
In 2007 Li and co-workers developed the copper(I)-catalysed reaction of a range of primary amines with γ-bromosubstituted γ,δ-unsaturated ketones **25** that provided various annulated pyrroles **26** in high yields (Scheme 1.3.2).[33] The first stage in this one-pot transformation is believed to be the condensation of the primary amine with the carbonyl group to provide an imine that tautomerises to the corresponding enamine that, in turn, engages in a copper-mediated intermolecular *N*-vinylation reaction. The resulting species is then thought to isomerise to the product pyrrole **26**.

[⊥] Protodesilylation by acetic acid occurs during the course of the reaction.



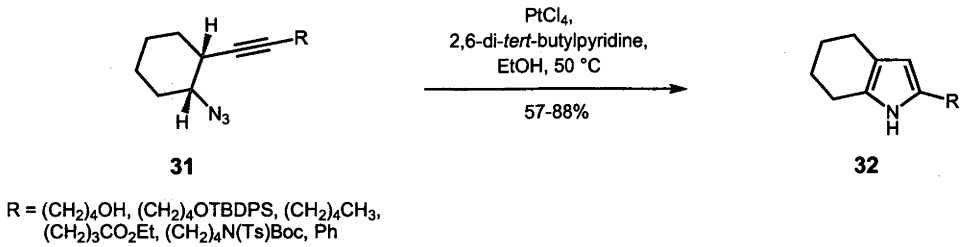
Scheme 1.3.2. *The synthesis of annulated pyrroles* **26** *reported by Li and co-workers.*[33]

In order to establish the first total synthesis of lamellarin K (**3**), Banwell and Flynn developed a novel method for the construction of the fused pentacyclic framework of this pyrrole-based marine natural product.[34] The relevant and final steps of the reaction sequence are shown in Scheme 1.3.3. This direct and efficient transformation provided heterocycle **30** *via* the intramolecular [3+2] cycloaddition reaction of dihydroisoquinolinium intermediate **29**. The highly convergent nature of this sequence established an unprecedented route to other members of the lamellerin alkaloid family and many analogues thereof. In 2007 Nygerges and co-workers reported a somewhat similar conversion that delivered a variety of related tricyclic pyrroles by a one-pot and sequential azomethine ylide 1,5-electrocyclisation–oxidation process.[35]



Scheme 1.3.3. *The final steps of the Banwell/Flynn total synthesis of Lamellarin K (***3***).*[34]

A novel $PtCl_4$-catalysed approach to annulated pyrroles **32** from homopropargylazide derivatives such as **31** is shown in Scheme 1.3.4 and was disclosed by Hiroya and co-workers in 2006.[36] The results of this study suggested that $PtCl_4$ was converted into an as yet unidentified active species that was responsible for the observed conversion. 2,5-Di-*tert*-butylpyridine needed to be present in the reaction mixture in order to buffer it and thus prevent decomposition of the pyrrolic product **32**.



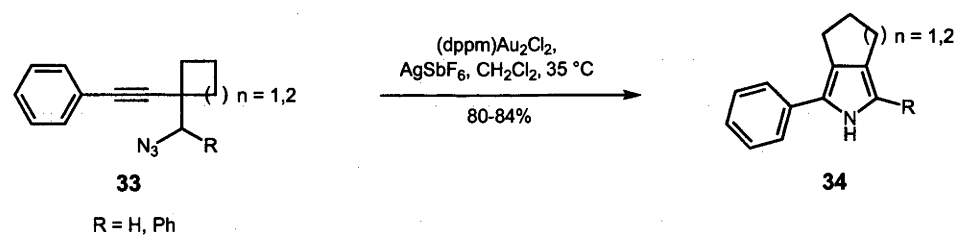
31

R = $(CH_2)_4OH$, $(CH_2)_4OTBDPS$, $(CH_2)_4CH_3$, $(CH_2)_3CO_2Et$, $(CH_2)_4N(Ts)Boc$, Ph

32

Scheme 1.3.4. *The synthesis of annulated pyrroles* **32** *reported by Hiroya and co-workers.*[36]

An analogous and more versatile gold(I)- and silver(I)-catalysed route to pyrroles **32** from homopropargylazides **31** was reported by Toste and co-workers prior to Hiroya's study.[37] Notably, Toste's catalyst system could also induce the rearrangement of cyclobutyl azides **33** to afford annulated pyrroles **34** (Scheme 1.3.5).[37] It is presumed the first step involves coordination of the gold catalyst to the alkyne and that this is followed by addition of the proximal nitrogen of the tethered azide. $AgSbF_6$ was needed to sequester chloride anions from the gold complex, thus making the catalyst more reactive and the process more facile and high yielding.



33

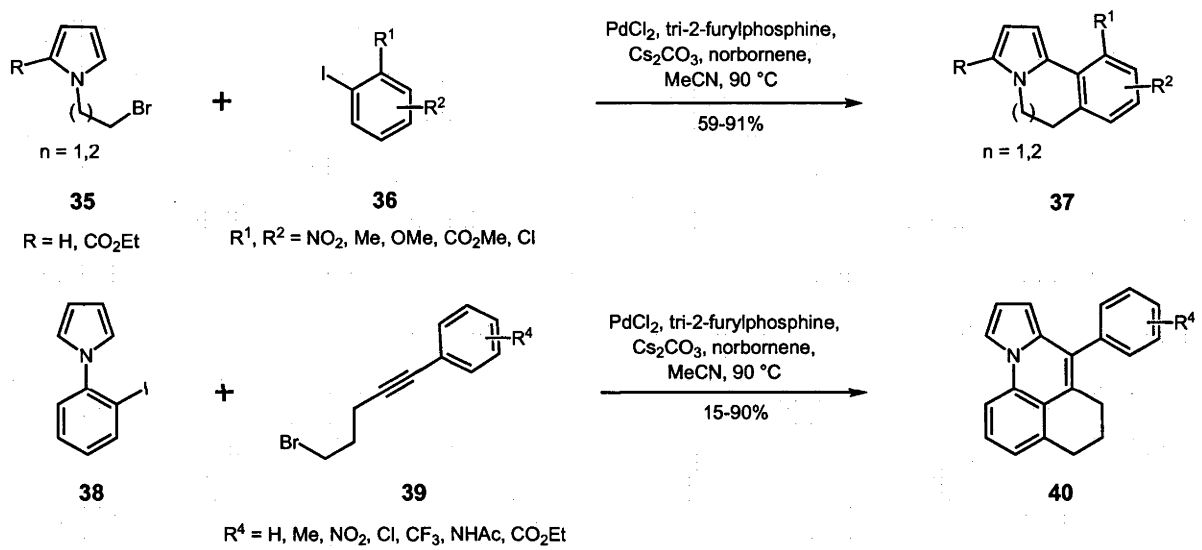
R = H, Ph

34

Scheme 1.3.5. *The synthesis of annulated pyrroles* **34** *reported by Toste and co-workers.* [37]

A number routes to annulated pyrroles have also been established in which the pyrrole ring was present prior to the construction of the requisite fused cyclic framework. For example, Lautens and co-workers developed a palladium-catalysed and norbornene-mediated coupling cascade involving an aromatic sp^2 C-H functionalisation as the

centrepiece (Scheme 1.3.6).[38] This unprecedented process, in which both alkyl-aryl and aryl-heteroaryl bonds were formed in a single step, allowed for the synthesis of a variety of six- and seven-membered annulated pyrroles **37**.[⊥] Norbornene is believed to facilitate both of these transformations at a number of stages, including during the crucial C-H functionalisation steps, by enabling the active palladium species to be 'relayed' across various bonds within the reactants. Mechanistic studies indicated that *ortho*-alkylation precedes aryl-heteroaryl coupling. Equally as impressive, when pyrrole **38** and a variety of alkynes **39** were reacted under the same conditions, a range of pyrrole-containing tetracyclic frameworks **40** was produced *via* a threefold domino reaction (Scheme 1.3.6).[39] Significantly, two of the C-C bonds formed by this approach were derived from the functionalisation of unactivated aryl C-H bonds.

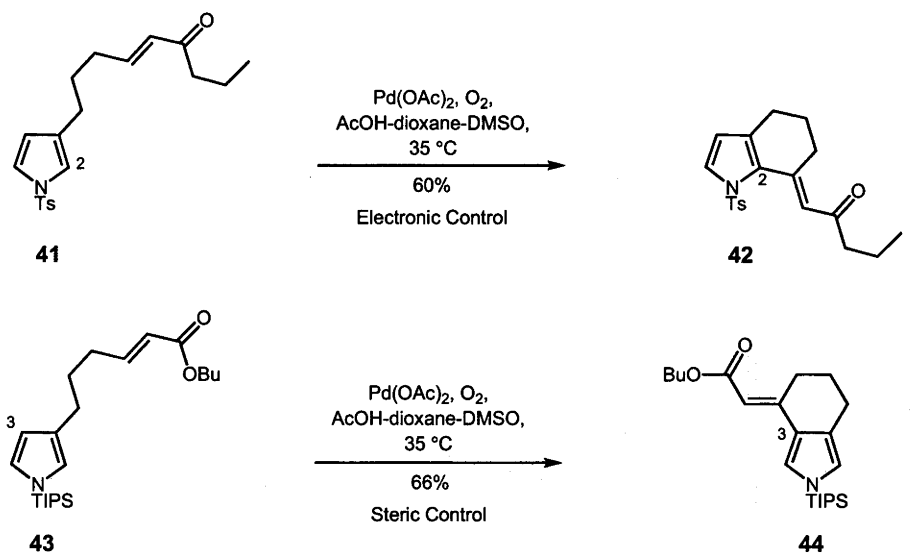


Scheme 1.3.6. *The syntheses of pyrroles* **37** *and* **40** *reported by Lautens and co-workers.*[38,39]

Gaunt and co-workers developed an alternative method for the regioselective and palladium-catalysed C-H activation and functionalisation of pyrroles under aerobic conditions.[40] In this way selective intramolecular pyrrole alkenylation at the 2- or 3-positions on the heterocyclic ring could be effected by the simple choice of electronic or sterically tuned *N*-protecting groups (Scheme 1.3.7). Cyclisation took place exclusively at the 2-position to provide heterocycle **42** when the electron-withdrawing *N*-tosyl protecting group was employed. In contrast, under the same conditions *N*-TIPS analogue **43** was selectively transformed into pyrrole **44**, because the sterically demanding nature of the silyl

[⊥] Pyrazoles could also be prepared by this methodology.

group prevented palladation at the proximal 2-position and thus C-H activation only occurred at the 3-position.

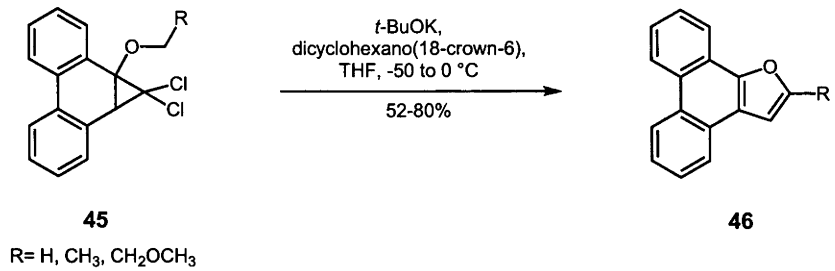


Scheme 1.3.7. *The synthesis of annulated pyrroles* **42** *and* **44** *reported by Gaunt and co-workers.*[40]

1.4 The Base-Promoted Conversion of *gem*-Dichlorocarbene Adducts of Enamines into Pyrroles

1.4.1 The Synthesis of Furans from gem*-Dichlorocarbene Adducts of Enol Ethers*

In work relevant to the synthesis of annulated pyrroles, the preparation of annulated furans by the base-promoted reactions of *gem*-dichlorocarbene adducts of enol ethers has been demonstrated. Indeed, Müller and Pautex were the first to show that ether-substituted dichlorocyclopropanes of the general form **45** could be converted into annulated furans **46** by treatment with *t*-BuOK (Scheme 1.4.1).[41] However, this brief study was limited to the base-induced elimination of dichlorocarbene adducts derived from 9-alkoxyphenanthrenes.



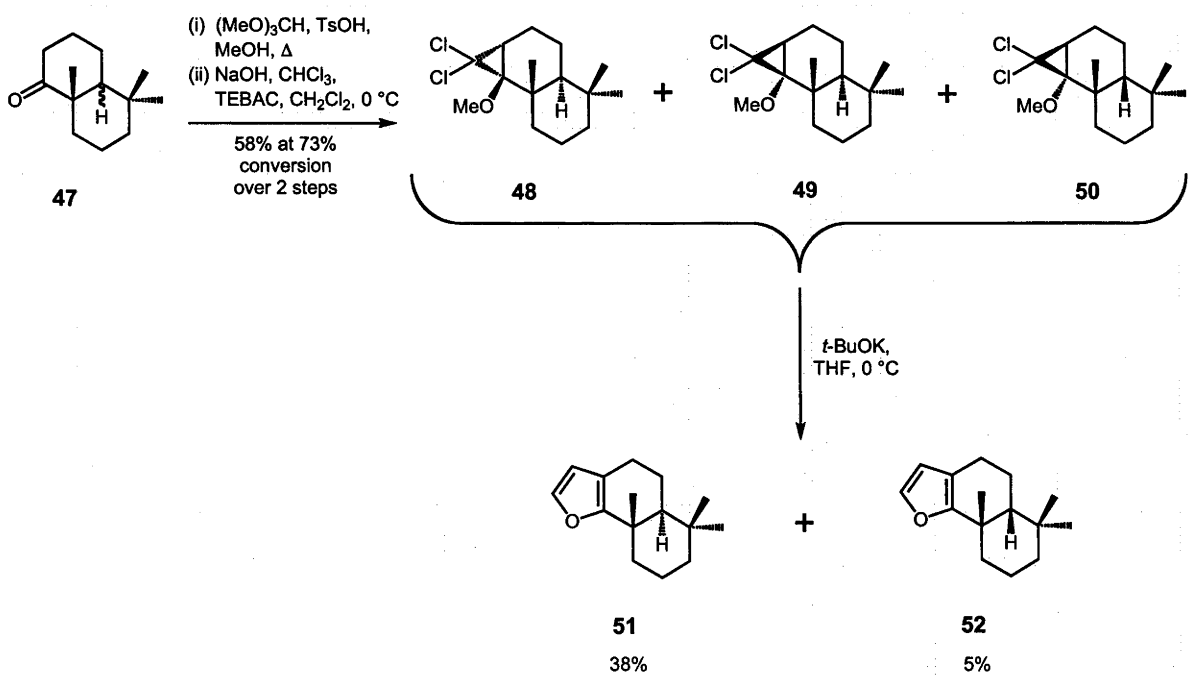
45

R= H, CH_3, CH_2OCH_3

46

Scheme 1.4.1. *The synthesis of annulated furans* ***46*** *reported by Müller and Pautex.*[41]

By exploiting a similar transformation to Müller and Pautex, Banwell and co-workers were recently able to develop a procedure enabling the three-step furannulation of various enolisable cyclic ketones.[42] This methodology was highlighted in 2006 during the course of a total synthesis of the furanosesquiterpenoid natural product (±)-pallescensin A.[43] The relevant and final steps of the reaction sequence are shown in Scheme 1.4.2. Thus, the methyl enol ether derivative of ketone **47** was prepared and converted directly into cyclopropanes **48-50** and these were then transformed into (±)-pallescensin A (**51**) and its *cis*-isomer **52** upon treatment with base. These tantalising findings suggested that an analogous base-promoted process might also provide pyrroles from the *gem*-dihalogenocarbene adducts of enamines.



47

48 **49** **50**

51

38%

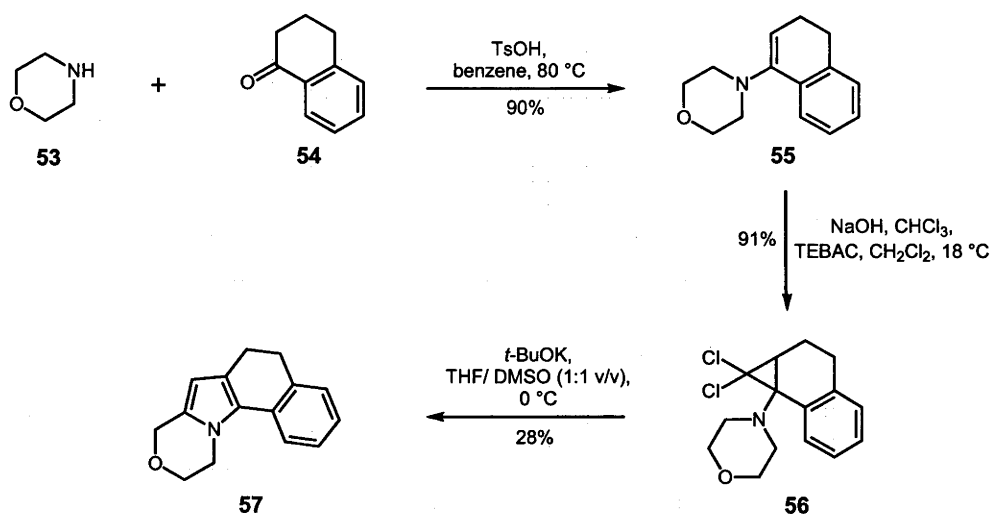
52

5%

Scheme 1.4.2. *The final steps of the total synthesis of (±)- pallescensin A (51).*[43]

1.4.2 *The Synthesis of Pyrroles from the* gem-*Dihalogenocarbene Adducts of Enamines*

Interestingly, although the *gem*-dihalogenocarbene adducts of enamines are known,[44] systematic studies of the base-induced reactions of such compounds have not been undertaken. However, Phillis and Banwell were able to demonstrate that the base-promoted reaction of amino-dichlorocyclopropane **56** gives the annulated pyrrole **57** in 28% yield.[42,45] The required substrate **56** was obtained *via* a two-step sequence from morpholine and 1-tetralone (Scheme 1.4.3). Thus, enamine **55** was formed by a traditional Stork synthesis and then a dichlorocarbene addition reaction provided cyclopropane **56** which was subsequently converted to the corresponding annulated pyrrole **57** by treatment with *t*-BuOK. Accordingly, it was anticipated that this process could be expanded to provide a range of pyrroles and, as such, allow for a new and hopefully general method for preparing this important class of compounds.



53 **54** **55** **56** **57**

Scheme 1.4.3. *Synthesis of annulated pyrrole* **57** *by Banwell and Phillis.*[42,45]

1.5 Aims of the Research Described in Part One of this Thesis

As the foregoing discussion has illustrated, because pyrroles are flexible and versatile building blocks with an array of valuable properties that can be exploited in diverse contexts, a vast number of synthetic approaches to these structures has been developed. However, the considerable reactivity of these heterocycles requires that new methods continue to be developed in order to efficiently provide such compounds featuring substitution patterns that might otherwise be difficult to obtain. Certainly, the opportunity to establish a new approach to this fundamental class of aromatic heterocycle was a particularly attractive prospect. Thus, the aim of the research described in the first part of this thesis was to undertake the first systematic study of the base-promoted reactions *gem*-dihalogenocarbene adducts of enamines and in this way develop a new and hopefully general route to pyrroles. If this could be achieved the intention was to highlight the utility of this novel methodology through the preparation of a natural product or a related compound. Such endeavours are described in Chapter Two.

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Chapter Two

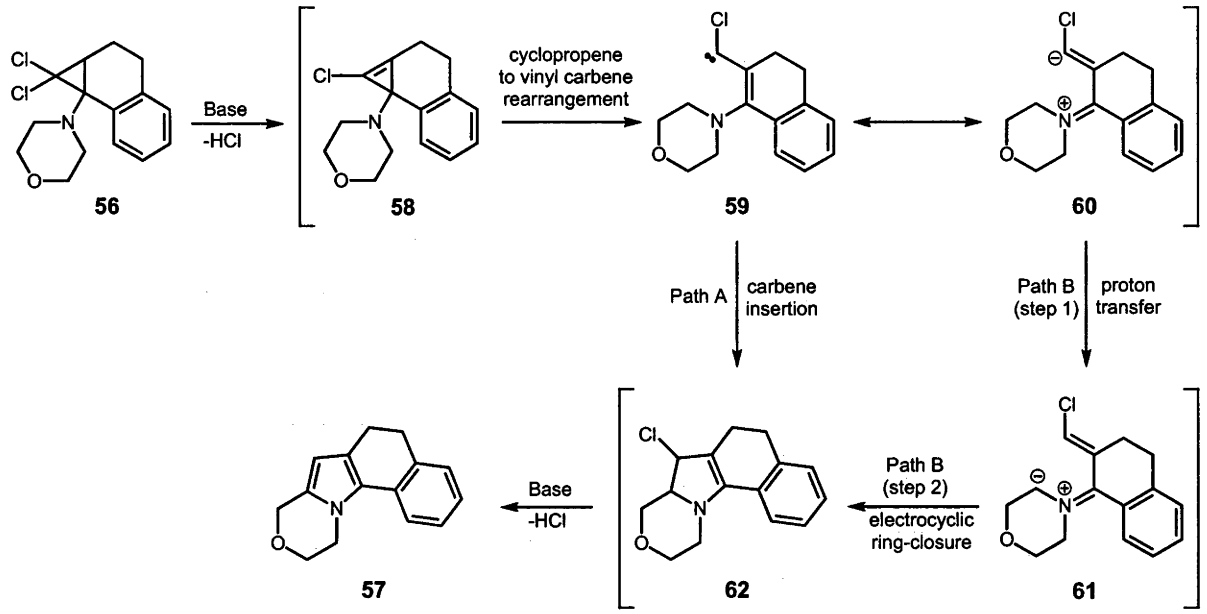
A New Route to Annulated Pyrroles

This chapter describes the development of a new route to annulated pyrroles. The outcomes of a comprehensive study investigating the scope, limitations and utility of this methodology are detailed. Extensions of the original process enabled the preparation of lamellarin analogue **96**. *It is anticipated that this pathway could provide access to more highly functionalised lamellarin-like structures and the results of the early stages of such endeavours are also discussed.*

2.1 Introduction

As noted in the preceding chapter, Phillis and Banwell first demonstrated that the base-promoted reaction of an amino-substituted *gem*-dichlorocyclopropane could provide an annulated pyrrole (Scheme 1.4.3).[1,2] At least two distinct reaction pathways may be envisaged for this conversion. Both of these (Paths A and B, Scheme 2.1.1) would involve dehydrochlorination of substrate **56** to provide the corresponding ring-fused cyclopropene **58**[⊥] that then isomerises to the corresponding vinylcarbene **59**/zwitterion **60**.[Ω] This species could undergo C-H insertion (Path A) to give the chlorinated dihydropyrrole **62** which loses a second equivalent of HCl to deliver the observed and fully aromatic product **57**. An alternate pathway (Path B) would involve intramolecular proton transfer to give the ylide **61**. Such a species might then be expected to undergo electrocyclic ring closure[3] to give dihydropyrrole **62**, the final intermediate in the reaction sequence and one that is common to both Paths A and B. A similar pathway was proposed to account for the equivalent furan-forming reaction[4] and mechanistic studies on related systems suggest that Path A is the more likely one.[5]

[⊥] These types of ring-fused cyclopropenes are readily trapped in Diels-Alder cycloaddition reactions.
[Ω] Zwitterion **60** is an equivalent resonance contributing form of structure **59**.



Scheme 2.1.1. *Possible reaction pathways leading to annulated pyrrole 57.*

In developing this encouraging precedent[1,2] that provided the previously unreported pyrrole **57**, the intention of work detailed herein was to systematically study this base-induced pyrrole-forming process with a view to investigating the key features of the chemistry and exploring the scope and utility of this concise and novel synthesis of pyrroles. Initial efforts to implement such ideas are described below.

2.2 Base-Promoted Reactions of the *gem*-Dihalogenocarbene Adducts of Enamines

2.2.1 *Preliminary Investigations*

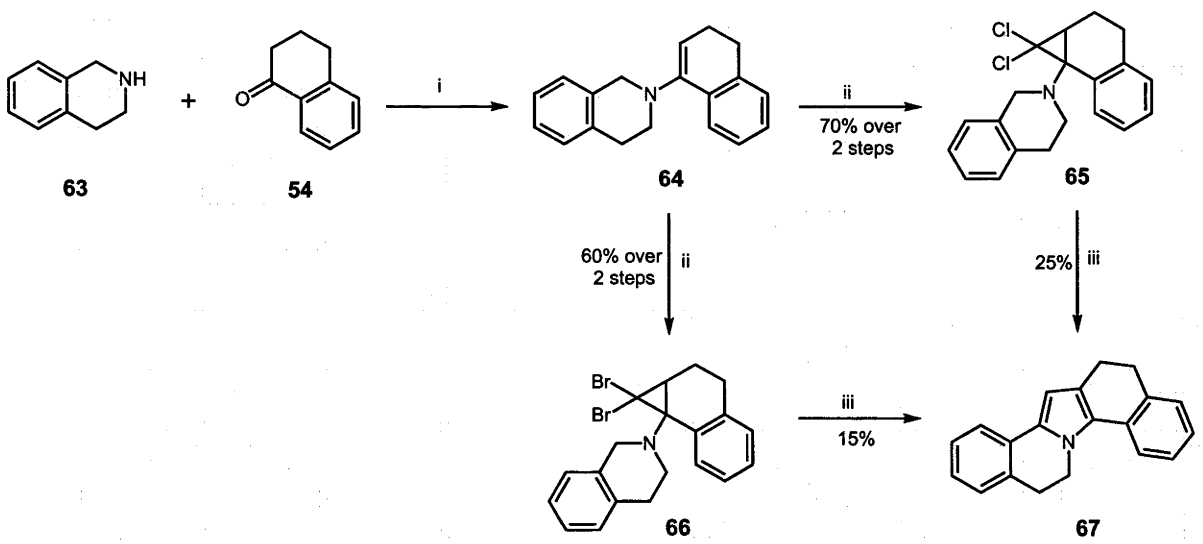
Before initiating studies of the base-promoted reaction an appropriate substrate needed to be identified. In the event, *gem*-dihalogenocyclopropanes **65** and **66** were selected for the preliminary studies as these enabled fundamental optimisation studies to be undertaken, while also permitting the investigation of a number of other pertinent features including:

(i) a comparison of the behaviour of both *gem*-dichloro- and *gem*-dibromocyclopropanes toward base-induced elimination and rearrangement;

(ii) the possibility of this transformation being regioselective as these substrates incorporate unsymmetrical amine components;

(iii) the effect that a bulky amine substituent may have on the outcome of the reaction.

In order to prepare the requisite *gem*-dihalogenocyclopropanes 1,2,3,4-tetrahydroisoquinoline was heated with 1-tetralone, 4 Å molecular sieves and *p*-TsOH (cat.) in toluene for 62 h with azeotropic removal of water (Scheme 2.2.1).[6] The resulting enamine **64** was not isolated but immediately converted into dichlorocyclopropane **65** by treatment with dichlorocarbene (generated from chloroform and NaOH, in the presence of the phase transfer catalyst TEBAC).[7] In this way compound **65** was obtained in 70% yield over two steps from 1-tetralone. Dibromocyclopropane **66** was prepared in 60% yield by an analogous process, save for the use of bromoform in the place of chloroform. All the spectroscopic and physical data obtained from the previously unreported compounds **65** and **66** were in accord with their assigned structures. It is worth noting that the synthesis of dibromocyclopropane **66** was neither as high yielding, nor as reliable, as the equivalent transformation leading to dichlorocyclopropane **65**.



Scheme 2.2.1. *Synthesis of pentacyclic annulated pyrrole* **67**.
Reagents and conditions: *(i) p-TsOH, 4 Å molecular sieves, toluene, 18 → 110 °C; (ii) TEBAC, NaOH, $CHCl_3$ or $CHBr_3$, CH_2Cl_2, sonication; (iii)* t-*BuOK, THF/DMSO (1:1 v/v), 0 °C.*

Gratifyingly, subjecting dichlorocyclopropane **65**, to the conditions first employed by Phillis provided annulated pyrrole **67** albeit in a low 25% yield. The 300 MHz ^{1}H NMR spectrum of pyrrole **67** (Figure 2.2.1) displayed all of the expected resonances and established that the product was the result of an anticipated benzylic C-H insertion reaction. Indeed, the most diagnostic features are the singlet at δ 6.47 that is attributed to the one and only pyrrolic proton and the triplet at δ 4.44 which is assigned to the methylene protons adjacent to the pyrrole nitrogen. The chemical shifts of pyrrolic protons in ^{1}H NMR spectra are generally observed in the range of δ 6-7, with α-proton signals usually shifted to higher frequencies than β-proton signals due to the inductive effect of the ring nitrogen. The 75

MHz ^{13}C NMR spectrum (Figure 2.2.2) displays the expected twenty carbon resonances and is fully consistent with the assigned structure. Furthermore, the EI mass spectrum displays a molecular ion at *m/z* 271 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{20}H_{17}N$.

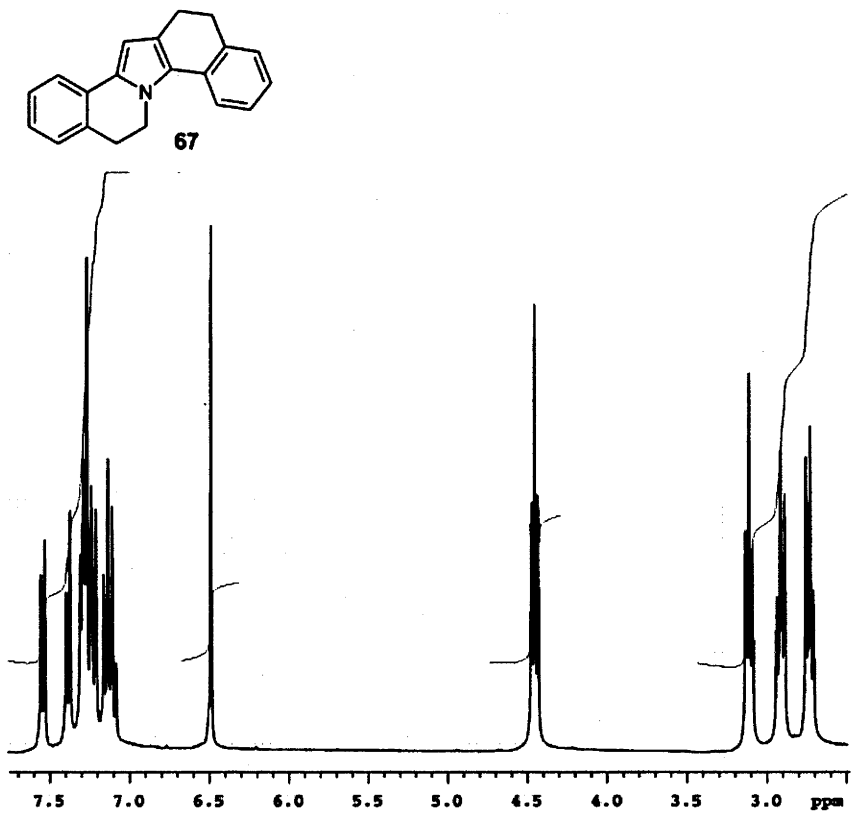


Figure 2.2.1. *300 MHz ^1H NMR spectrum of annulated pyrrole* **67** *(recorded in $CDCl_3$).*

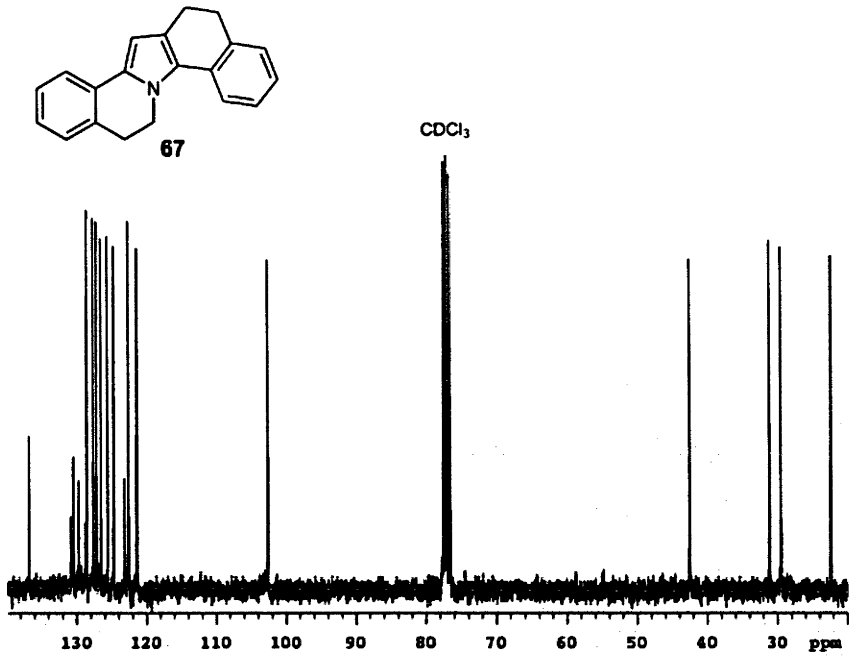


Figure 2.2.2. *75 MHz ^{13}C NMR spectrum of annulated pyrrole* **67** *(recorded in $CDCl_3$).*

In addition to obtaining a low yield of product **67** not all of the cyclopropane starting material was consumed in the reaction (10% was recovered after flash chromatography). In the analogous reaction, dibromocyclopropane **66** was converted into pyrrole **67** in a lower 15% yield. Indeed, the ^1H NMR analysis of crude product **67**, performed after work-up, also confirmed that employing dibromo-analogue **66** resulted in a much less efficient conversion into the final product. This result, coupled with the higher preparative yield of dichlorocyclopropane **65**, dictated its selection as the substrate from which subsequent studies of the base-promoted process would be undertaken.

2.2.2 *Optimisation Studies*

Following the successful synthesis of pentacyclic pyrrole **67** it was necessary to develop this methodology, with a particular view to improving the efficiency and yield in order to make the process synthetically viable. Consequently a thorough study of the base-induced reaction was required and effort was directed to optimising the conversion of **65** → **67** and thus identifying effective reaction conditions that could be applied to other substrates.

Preliminary studies centred on the effect of varying the THF/DMSO solvent ratio. As the results presented in Table 2.2.1 indicate, altering this ratio, from solely THF to exclusively DMSO had little effect on the yield of pyrrole **67** (Table 2.2.1, Entries 1-6). Furthermore, no reaction was observed when DMSO was replaced with either DMF or toluene (Table 2.2.1, Entries 7 and 8). Although these results indicated that the ratio of DMSO to THF did not influence the yield significantly, the rate was affected to some extent.

Thus, the reaction was fastest in DMSO (4 h) (Table 2.2.1, Entry 6) and slowest in solvent systems containing predominantly THF (16 h) (Table 2.2.1, Entry 5). This is a likely consequence of the differing pK_b associated with *t*-BuOK in these two very different solvent mixtures. The base strength of *t*-BuOK is greatest in the more polar DMSO (pK_a ~23) and significantly decreases in THF, where it exists largely as a tetrameric aggregate.[8] Interestingly, performing the reaction in the presence of 18-crown-6 did not markedly affect the rate and actually decreased the yield (Table 2.2.1, Entry 12). Although the effect of increasing the temperature was examined, it was found that while heating the reaction mixture increased the rate, it also decreased the yield of the pyrrolic product **67** (Table 2.2.1, Entry 10). These outcomes led to all subsequent experiments being conducted in THF.

Table 2.2.1: *Investigation of the base-promoted conversion* ***65*** → ***67***.

Entry	Base[a]	Solvent	Time (h)	Yield (%)
1	*t*-BuOK	THF/DMSO (1:1)	6	25
2	*t*-BuOK	THF/DMSO (1:3)	8	20
3	*t*-BuOK	THF/DMSO (2:1)	16	20
4	*t*-BuOK[b]	THF/DMSO (1:1)	18	25
5	*t*-BuOK	THF	16	25
6	*t*-BuOK	DMSO	4	15
7	*t*-BuOK	DMF	18	-
8	*t*-BuOK	Toluene	18	-
9	*t*-BuOK[c]	THF	18	20
10	*t*-BuOK[d]	THF/DMSO (1:1)	16	20
11	*t*-BuOK/*t*-BuOH (1:1)	THF	16	20
12	*t*-BuOK (sublimed)	THF	18	30
13	LiTMP[e]	THF	3	33
14	NaHMDS[e]	THF	3	-
15	LDA[e]	THF	3	45

[a]Unless otherwise stated 8 equiv. of base were used and the reactions performed at 18 °C. [b]3 equiv. of base used. [c]Reaction performed with 3 equiv. of 18-crown-6. [d]Reaction performed at 85 °C. [e]4 equiv. of base used and the reaction performed at 0 °C.

In all the experiments just described the alkoxide base was used as supplied by Sigma-Aldrich. However, the pronounced tendency of this base to absorb components from the air, thus forming both KOH and K_2CO_3 meant that it was very likely that *t*-BuOK employed in the earlier experiments contained significant impurities.[9] Accordingly, an investigation of the effect of using different forms of this base was undertaken. To such ends, *t*-BuOK (ex. Sigma-Aldrich) was sublimed in an effort to remove the aforementioned

impurities. Samples were prepared from potassium and *t*-butanol.[1] It was anticipated that these two different forms of *t*-BuOK might provide improved results.

Using the base prepared from *t*-butanol decreased the yield of pyrrole **67** significantly (Table 2.2.1, Entry 11). In contrast, employing freshly sublimed *t*-BuOK improved the outcome of the reaction (Table 2.2.1, Entry 12) and ^{1}H NMR analysis of the crude product, performed after work-up, indicated that the reaction was much more efficient. The possibility of preparing pyrrole **67** directly from enamine **64**, in one pot, utilising *t*-BuOK to form dichlorocyclopropane **65** and subsequently effecting conversion to pyrrole **67** *in situ* was also explored. Although a small amount of the pyrrole was isolated from such a process, it delivered dichlorocyclopropane **65** as the major product.

In order to investigate whether bases other than *t*-BuOK were capable of effecting the conversion **65** → **67**, the reaction was repeated using the amide bases NaHMDS, LiTMP and LDA. While NaHMDS gave no reaction, both LiTMP and LDA provided pyrrole **67** in improved yields (Table 2.2.1, Entries 13-15). These results demonstrated that LDA was superior to *t*-BuOK in promoting the key transformation - the yield was higher (45%), the reaction was faster (3 h) and ^{1}H NMR analysis of the crude material, performed after work-up, indicated that the reaction was considerably more efficient and proceeded to full conversion. The more efficient transformation employing LDA also raised the question of the loss of a significant amount of product during isolation by flash chromatography (silica). This was because both ^{1}H NMR and TLC analysis of the crude material, performed immediately after work-up, indicated that it contained primarily product while the mass of the crude reaction mixture suggested a high yield of pyrrole **67** (>80%). However, upon isolation by flash chromatography, the yield of the product pyrrole was much lower (45%) than expected. Thus, efforts to isolate pentacyclic pyrrole **67** by flash chromatography using both neutral and basic alumina, as well as preparative TLC, were made. Disappointingly, no significant improvement in the yield of isolated product was observed.

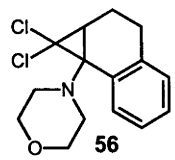
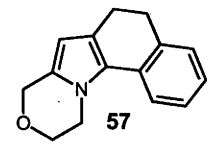
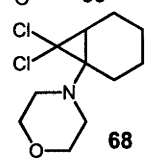
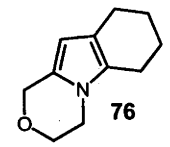
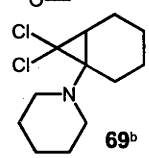
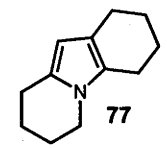
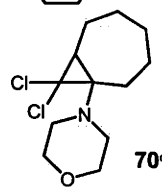
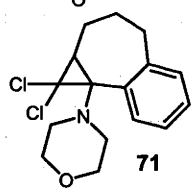
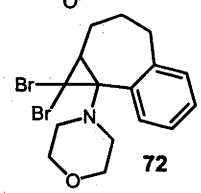
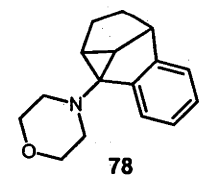
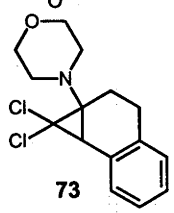
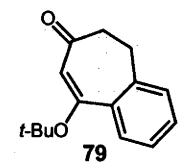
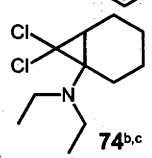
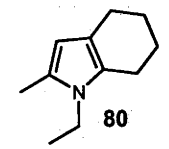
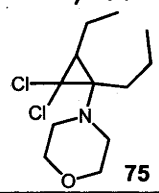
The findings of this thorough investigation of the base-promoted process of interest enabled the identification of optimised reaction conditions. These involved treating a THF solution of the *gem*-dichlorocyclopropane **65** with four equivalents of LDA at 0 °C for 3 h. In this manner, pyrrole **67** could be isolated in 67% yield.

[1] In this form, the base exists as a 1:1 mixture of *t*-BuOK and *t*-butanol.

2.2.3 *Scope of New Route to Annulated Pyrroles*

The establishment of standard reaction conditions allowed the scope of the new pyrrole-forming methodology to be explored. The results of this study are presented in Table 2.2.2. Thus, a wide range of substrates was prepared and despite the propensity of *gem*-dihalogenocyclopropanes carrying electron-donating substituents to undergo facile electrocyclic ring cleavage,[10] these adducts proved to be rather stable and generally crystalline materials. The majority of these cyclopropanes were synthesised by first heating the corresponding mixture of secondary amines and ketones with *p*-TsOH (cat.) and 4 Å molecular sieves in the presence of benzene/toluene under conditions involving azeotropic removal of water. The resulting enamines were immediately reacted with dihalocarbene (generated from chloroform/bromoform, NaOH and TEBAC) to then give the required cyclopropanes.

Table 2.2.2: *Investigation of the base-promoted reactions of various ring-fused* gem-*dihalogenocyclopropanes.*

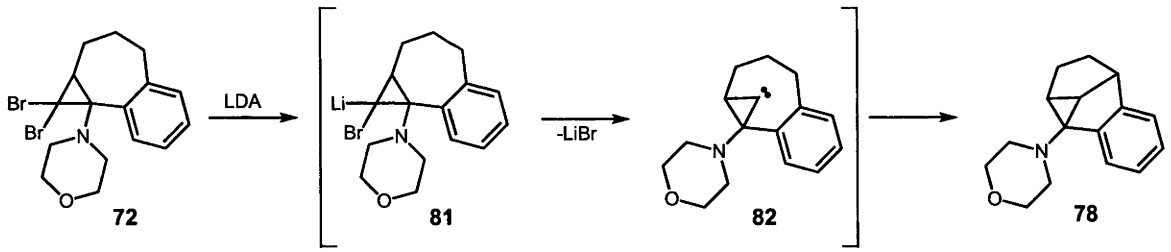
Entry	Substrate	Time (h)	Product[a]	Yield (%)
1	 **56**	5	 **57**	43
2	 **68**	3	 **76**	82
3	 **69**[b]	3	 **77**	66
4	 **70**[c]	8	No Reaction	-
5	 **71**	8	No Reaction	-
6	 **72**	3	 **78**	81
7	 **73**	22	 **79**	79[d]
8	 **74**[b,c]	3	 **80**	54
9	 **75**	8	No Reaction	-

[a]Unless otherwise stated, all products were prepared from the corresponding *gem*-dihalogenocyclopropanes by reaction with LDA at 0 °C. [b]Prepared by reaction with dichlorocarbene generated from $CHCl_3$ and *t*-BuOK. [c]Enamine precursor was prepared by reaction of the requisite secondary amine and ketone with $TiCl_4$. [d]Prepared by reaction with *t*-BuOK in THF at 18 °C.

The first dichlorocyclopropane synthesised was the original substrate **56** that Phillis had established could be converted into annulated pyrrole **57**.[1,2] Its subsequent preparation in 43% yield, compared to Phillis' 28% yield, underscored the abovementioned finding that LDA was superior to *t*-BuOK in promoting this process (Table 2.2.2, Entry 1). Gratifyingly, this transformation was not limited to either 1-tetralone- or morpholine-derived cyclopropanes. Indeed, substrates **68** and **69** were transformed into tricyclic annulated pyrroles **76** and **77** in 82% and 66% yields respectively (Table 2.2.2, Entries 2 and 3). Surprisingly, the route to piperidino-dichlorocyclopropane **69** was not entirely straightforward. The addition of dichlorocarbene, generated by standard means,[⊥] was unsuccessful despite repeated attempts and varied reaction conditions. This problem was overcome by synthesising cyclopropane **69**, albeit in a low 34% yield over two steps, following a known procedure in which *t*-BuOK was used to generate dichlorocarbene from chloroform.[11]

It was anticipated that cycloheptanone-derived dichlorocyclopropane **70** would also engage in the base-promoted process to provide the corresponding annulated pyrrole. Surprisingly, however, upon treatment with LDA no reaction was observed, even when extended reaction times (up to 8 h) were employed (Table 2.2.2, Entry 4). Treatment of substrate **70** with *t*-BuOK in THF at ambient temperature provided the same result, while heating the mixture to 60 °C only resulted in destruction of the starting material. Similarly, replacing this alkoxide base with lithium diethylamide and heating the reaction mixture in THF at 60 °C also only provided a complex mixture of products. This prompted the preparation of benzosuberone-derived dichlorocyclopropane **71** in order to investigate its behaviour under basic conditions. Disappointingly, as in the case of cyclopropane **70**, treatment with either LDA or *t*-BuOK gave no reaction (Table 2.2.2, Entry 5). When substrate **71** was heated with either *t*-BuOK or with lithium diethylamide in THF at 60 °C only a complex mixture of products was obtained. The origin of this divergent behaviour (relative to dichlorocyclopropane **56**) of both compounds **70** and **71** towards the reaction conditions remains unclear. Consequently, the *gem*-dibromo-analogue **72** of compound **71** was synthesised and subjected to the standard conditions and unexpectedly provided the diquinane **78** in 81% yield as a yellow oil (Table 2.2.2, Entry 6). Presumably this product arose through LDA-promoted lithium-for-bromine exchange at the apical cyclopropyl carbon to provide intermediate **81**, and this was followed by loss of the elements of LiBr to give the corresponding cyclopropylidene **82** (Scheme 2.2.2). This last species then underwent transannular insertion into the remote and *syn*-orientated benzylic C-H bond to afford the observed product **78**.[12]

[⊥] Generated from $CHCl_3$ and NaOH, in the presence of TEBAC (cat.).



Scheme 2.2.2. *Possible reaction pathway leading to diquinane 78.*

The 300 MHz ^{1}H NMR spectrum of diquinane **78** (Figure 2.2.3) displays all of the expected resonances. Similarly, the 75 MHz APT ^{13}C NMR spectrum (Figure 2.2.4) features the expected fourteen carbon resonances and is fully consistent with the assigned structure. Indeed, the most diagnostic features are the three signals at δ 47.7, 45.4 and 37.3 which are attributed to the three tertiary carbons. Furthermore, the EI mass spectrum displays a molecular ion at *m/z* 241 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{16}H_{19}NO$. Unfortunately, because diquinane **78** was an oil its structure could not be confirmed by single-crystal X-ray analysis.

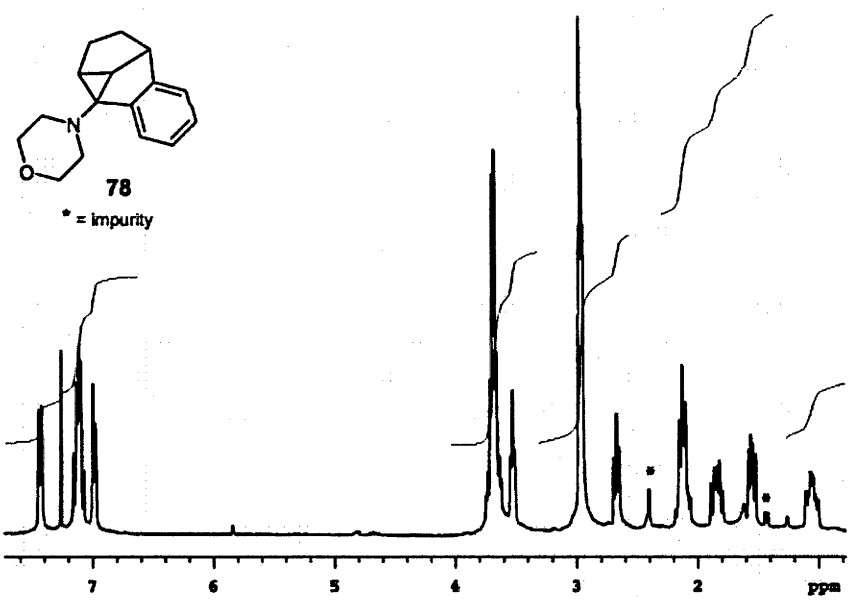


Figure 2.2.3. *300 MHz ^{1}H NMR spectrum of diquinane 78 (recorded in $CDCl_3$).*

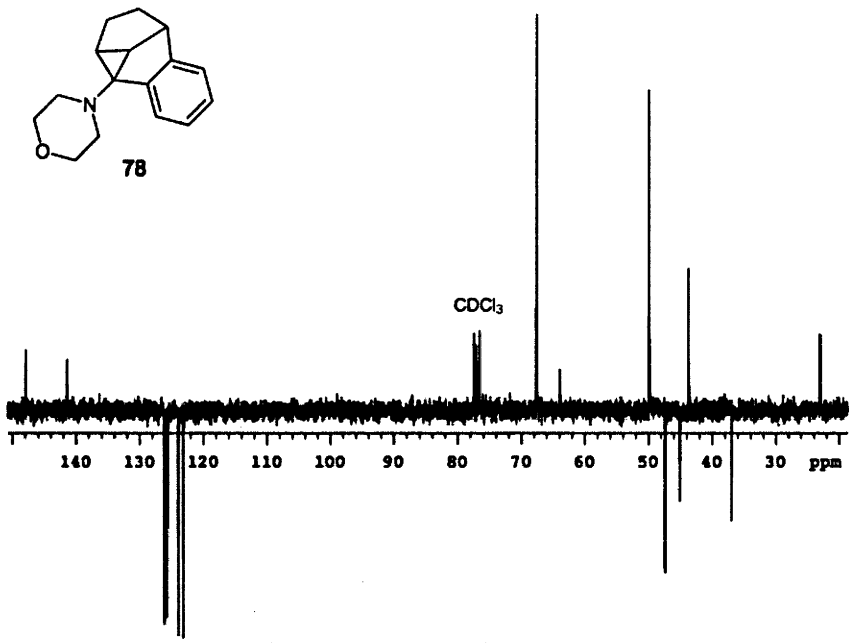
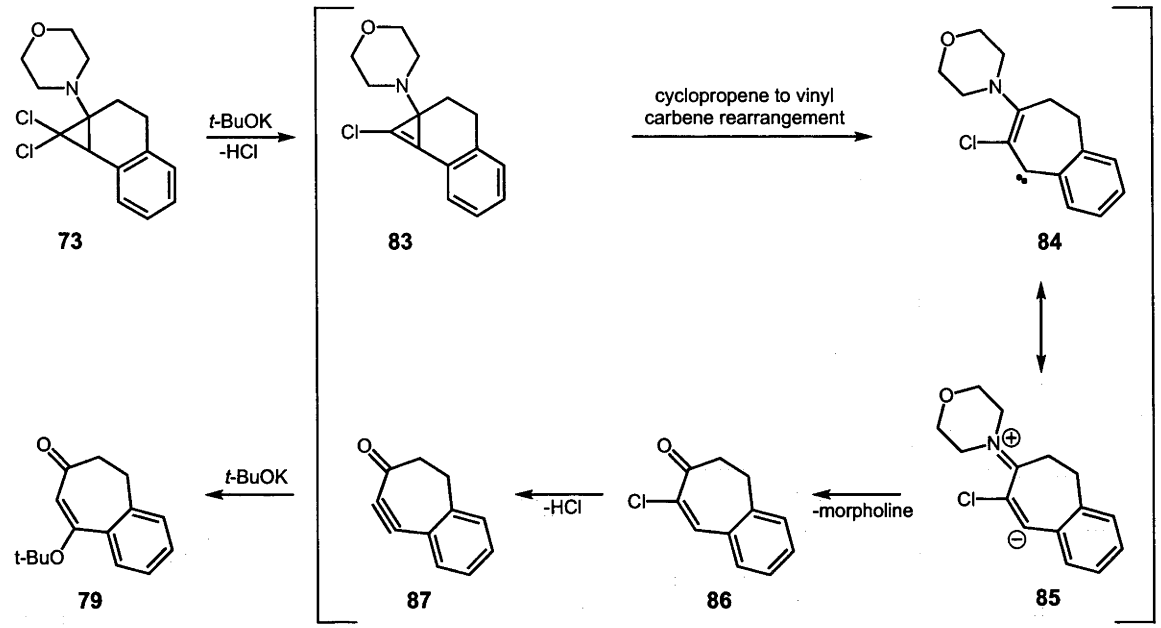


Figure 2.2.4. *75 MHz APT ^{13}C NMR spectrum of diquinane* **78** *(recorded in $CDCl_3$).*

It had been established that 1-tetralone-derived cyclopropanes could be converted into annulated pyrroles by treatment with various bases. It seemed appropriate, therefore, to examine the behaviour of 2-tetralone-derived cyclopropanes under analogous conditions. To such ends, dichlorocyclopropane **73**[1] was synthesised in 62% yield over two steps by a process analogous to that used in generating dichlorocyclopropane **56**. Disappointingly, treatment of this substrate with LDA did not provide the hoped-for annulated pyrrole. Rather, a complex mixture of products was obtained. However, when cyclopropane **73** was reacted with *t*-BuOK a ring-expansion process occurred, providing β-oxygenated cycloheptenone **79** in 79% yield (Table 2.2.2, Entry 7). The structure of ketone **79** was secured by single-crystal X-ray analysis (Appendix A.1.2). This product could conceivably arise through the dehydrochlorination of substrate **73** to provide the corresponding ring-fused cyclopropene **83** that then isomerises to the corresponding vinylcarbene **83**/zwitterion **85**. The strongly basic conditions would facilitate the loss of morpholine from species **85** to give α-chloroketone **86**. The subsequent elimination of the elements of HCl provides highly strained alkyne intermediate **87** that is susceptible to attack by *t*-butoxide in a Michael fashion and thus generating observed product **79**.

[1] The structure of which was confirmed by single-crystal X-ray analysis (Appendix A.1.1).



Scheme 2.2.3. *Possible reaction pathway leading to cycloheptenone 79.*

It was demonstrated that the base-promoted reaction of interest could also be applied successfully to cyclopropyl systems incorporating aliphatic secondary amine substituents by the synthesis of bicyclic pyrrole **80** in 54% yield from cyclopropane **74** (Table 2.2.2, Entry 8). Interestingly, the volatility of diethylamine necessitated *N,N*-diethylcyclohex-1-enamine, the precursor to cyclopropane **74**, be prepared at low temperatures. Thus, diethylamine and cyclohexanone were reacted with titanium tetrachloride at 0 °C to provide the requisite enamine which was immediately converted into cyclopropane **74** under the usual conditions.

Curiously, when the 4-heptanone-derived cyclopropane **75** was treated with either LDA or *t*-BuOK no reaction was observed even when extended reaction times were employed (Table 2.2.2, Entry 9). In contrast, treatment of the same substrate with either lithium diethylamide or *t*-BuOK in THF at 60 °C only led to a complex mixture of products. It should also be noted that despite extensive attempts to synthesise the cyclopropanes **88** and **89** (Figure 2.2.5) by the addition of dichlorocarbene to 4-cyclopentenylmorpholine and 4-(1*H*-inden-3-yl)morpholine respectively, neither was observed to form. This is presumably due to the high degree of ring strain associated with the desired products. Indeed, it has been reported that dichlorocarbene addition to 4-cyclopentenylmorpholine affords 2-chlorocyclohex-2-enone in 50% yield.[13]

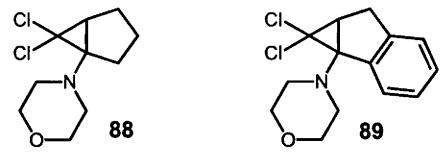
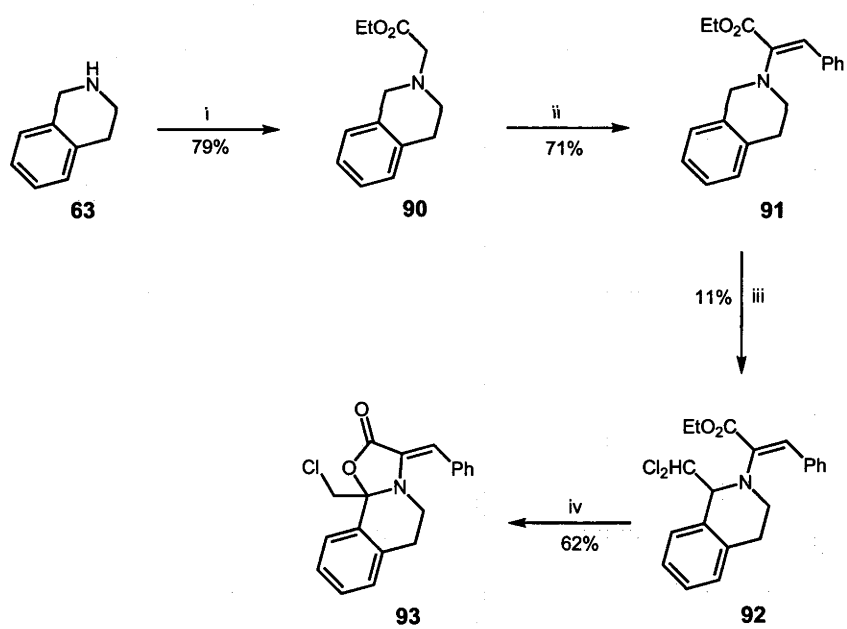


Figure 2.2.5. *Cyclopropanes 88 and 89 that were unable to be prepared.*

In an effort to investigate whether a highly substituted dichlorocyclopropane could also be converted into an annulated pyrrole, 1,2,3,4-tetrahydrosoquinoline was reacted with ethyl bromoacetate to provide ester **90** in 79% yield, which was subsequently converted into (Z)-α-aminocinnamate **91** in 71% by an aldol condensation (Scheme 2.2.4).[14] Interestingly, treating cinnamate **91** with chloroform, TEBAC, NaOH in dichloromethane did not deliver the anticipated *gem*-dichlorocyclopropane product. Rather, a complex mixture of products was obtained and the only isolable species was the carbene insertion product **92** (11%). On the basis that treatment of compound **92** with base might deliver an annulated pyrrole, this substrate was reacted with *t*-BuOK.[⊥] However, the product so formed was the unusual oxazolidinone **93** (63%), the structure of which followed from single-crystal X-ray analysis (Appendix A.1.3).

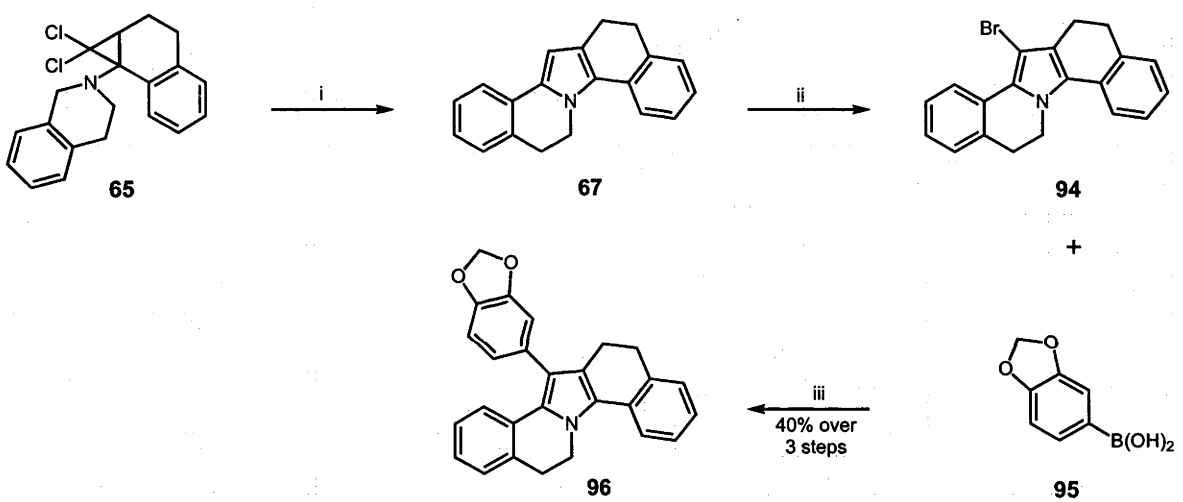


Scheme 2.2.4. *Synthesis of oxazolidinone 93.*
Reagents and conditions: *(i) ethyl bromoacetate, K_2CO_3, CH_2Cl_2, 0 → 18 °C; (ii) benzaldehyde,* t-*BuOK, THF, 0 → 18 °C; (iii) TEBAC, NaOH, $CHCl_3$, CH_2Cl_2, sonication; (iv)* t-*BuOK, THF, 0 → 18 °C.*

[⊥] Reaction with LDA only provided a complex mixture of products.

2.2.4 *Preparation of Lamellarin Analogue 96*

Standardised reaction conditions for the base-promoted pyrrole-forming process had been developed, the scope of this novel methodology successfully explored and its utility established. It was thus anticipated this chemistry could be exploited in preparing a structural analogue of the lamellarin class of marine alkaloids by further functionalising pyrrole **67**. To this end, cyclopropane **65** was converted into pyrrole **67** as before (Scheme 2.2.5). Due to the aforementioned concerns that a significant amount of pyrrole **67** was being lost during purification by flash chromatography, this product was not isolated. Rather, it was treated directly with NBS to provide bromide **94** which was immediately reacted with 3,4-methylenedioxyphenylboronic acid (**95**), under μ-wave irradiation, to furnish the Suzuki-Miyaura cross-coupled product **96** which was isolated in 40% yield over the three steps involved.[15]



Scheme 2.2.5. *Synthesis of lamellarin analogue 96.*
Reagents and conditions: *(i) LDA, THF, 0 °C; (ii) NBS, THF, 0 °C; (iii)* $Pd(PPh_3)_4$, K_2CO_3, *THF/* H_2O *(4:1 v/v), μ-wave irr., 18 → 100 °C.*

The structure of lamellarin analogue **96** was confirmed by single-crystal X-ray analysis (Figure 2.2.6 and Appendix A.1.4). All of the spectroscopic and physical data obtained from the previously unreported compounds **94** and **96** were in full accord with their assigned structures. Indeed, the 300 MHz ^{1}H NMR spectrum of pyrrole **96** (Figure 2.2.7) displays all of the expected resonances and is completely consistent with the proposed structure. The most diagnostic features are the singlet at δ 5.99 that is attributed to the methylenedioxy protons and the triplet at δ 4.41, assigned to the methylene protons adjacent to the pyrrole nitrogen. The 75 MHz ^{13}C NMR spectrum (Figure 2.2.8) displays the expected twenty-seven carbon resonances and is fully consistent with the assigned

structure. Furthermore, the 70eV EI mass spectrum displays a molecular ion at *m/z* 391 and an accurate mass measurement on this species established that it was of the expected composition, viz. $C_{27}H_{21}NO_2$.

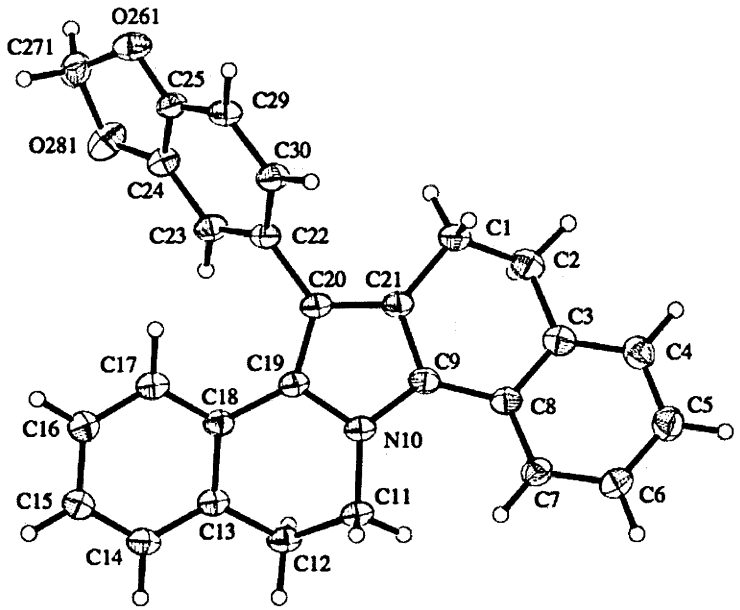


Figure 2.2.6. *ORTEP derived from the single-crystal X-ray analysis of lamellarin analogue* **96**.

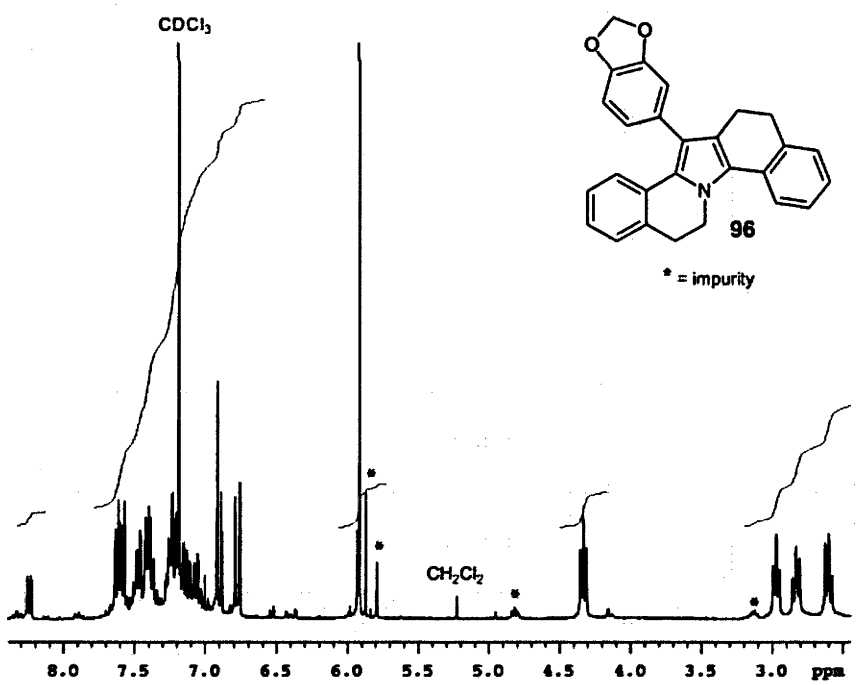


Figure 2.2.7. *300 MHz ^1H NMR spectrum of lamellarin analogue* **96** *(recorded in $CDCl_3$).*

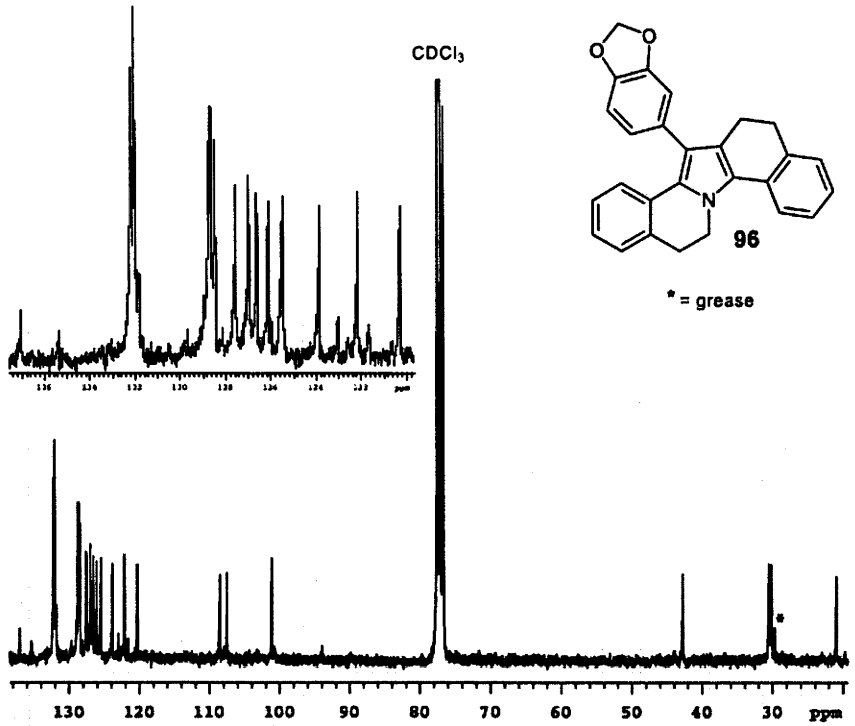
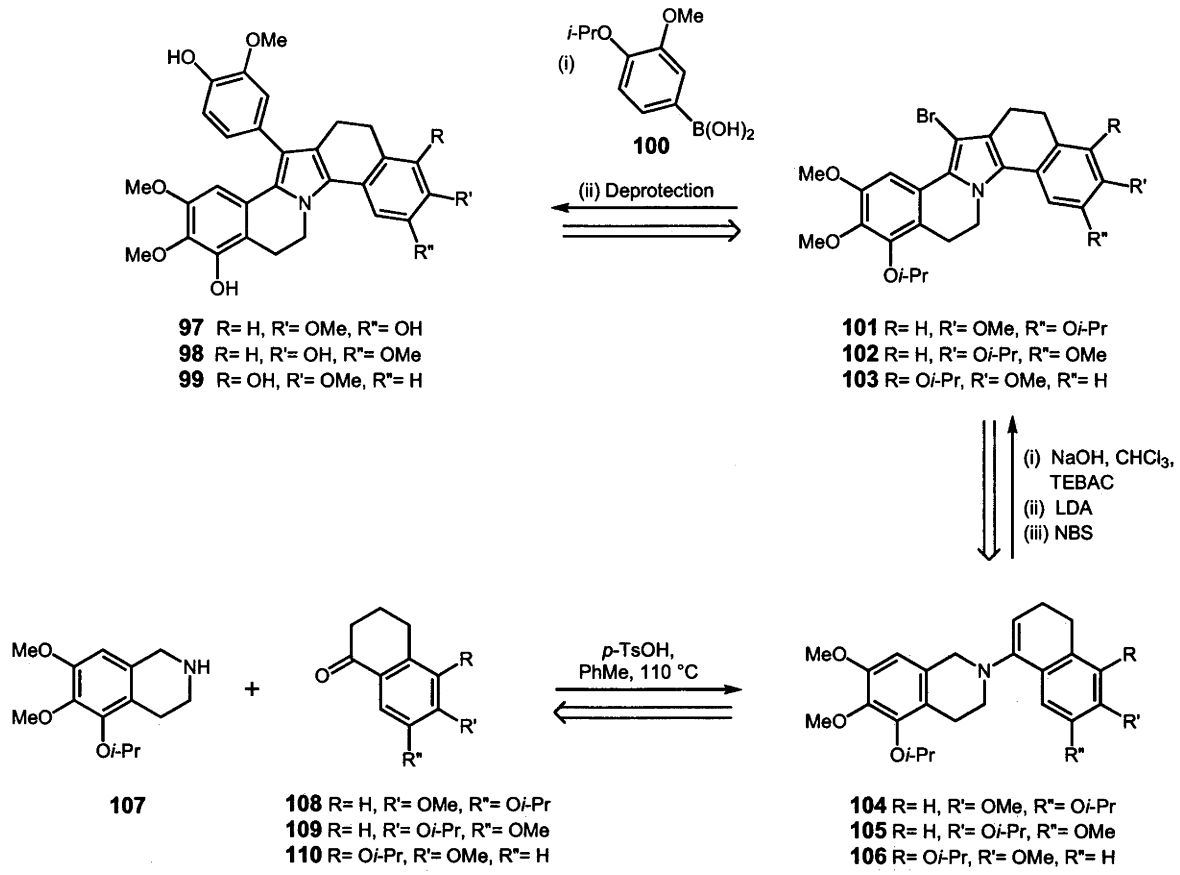


Figure 2.2.8. *75 MHz ^{13}C NMR spectrum of lamellarin analogue* ***96*** *(recorded in $CDCl_3$).*

2.3 Towards the Preparation of More Highly Functionalised Lamellarin Analogues

2.3.1 Introduction

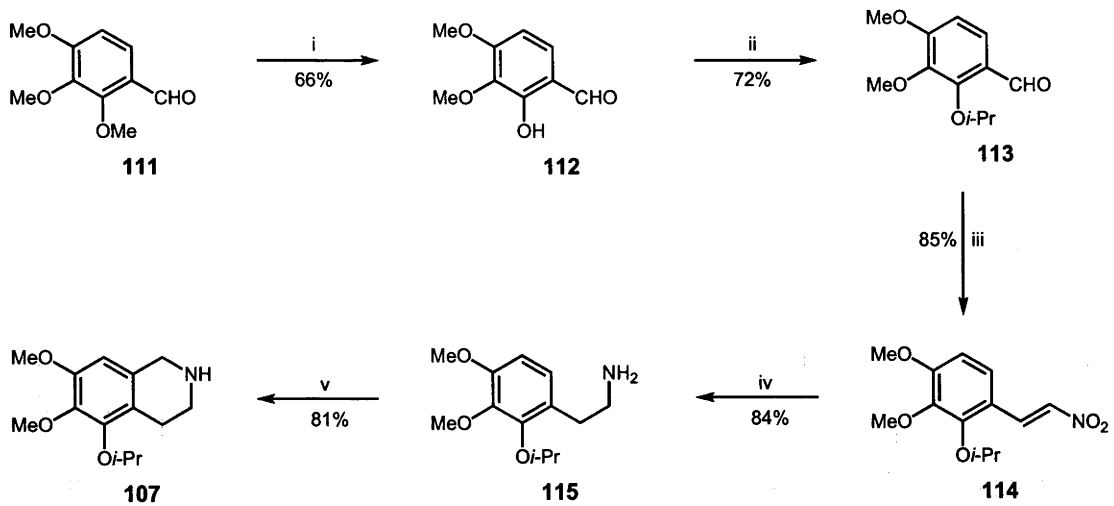
As a concise and efficient synthetic route to annulated pyrrole **96** had been devised, it was anticipated that the more highly functionalised lamellarin analogues **97-99** could be rapidly prepared using the same approach and these novel compounds would then be screened for potential biological activity (Scheme 2.3.1). Because almost all of the lamellarin alkaloids, some of which are depicted in Figure 1.1.2, exhibit cytotoxicity against a wide range of cancer cell lines[16] it is plausible that analogues **97-99** may also display similar valuable medicinal properties. However, in order to undertake the proposed syntheses tetrahydroisoquinoline **107** and 1-tetralones **108-110** needed to be prepared. These important building blocks were accessed *via* various traditional and well-established synthetic transformations as detailed in the following sections.



Scheme 2.3.1. *Retrosynthetic analysis of lamellarin analogues* **97-99**.

2.3.2 *Preparation of Isoquinoline 107*

The synthesis of isoquinoline **107** required a five-step reaction sequence involving generally straightforward transformations that began with commercially available 2,3,4,-trimethoxybenzaldehyde (**111**) (Scheme 2.3.2). The first step featured the regioselective demethylation of benzaldehyde **111** with aluminium chloride which delivered the known phenol **112** (66%).[17] The yield was improved to *ca.* 90% when the prescribed acid/base work-up was avoided and when this process was carried out on larger scales compound **112** was used without purification in the next step of the reaction sequence. Alkylation of structure **112** provided the isopropyl-protected benzaldehyde **113** in 72% yield. In principle, this yield could be improved and the reaction time significantly decreased by heating and replacing K_2CO_3 with Cs_2CO_3. In the following step compound **113** was subjected to a Henry reaction[18] using nitromethane and ammonium acetate in glacial acetic acid to provide, upon dehydration, nitrostyrene **114** in 85%. This product was then reduced using lithium aluminium hydride thus providing phenethylamine **115** in 84% yield.



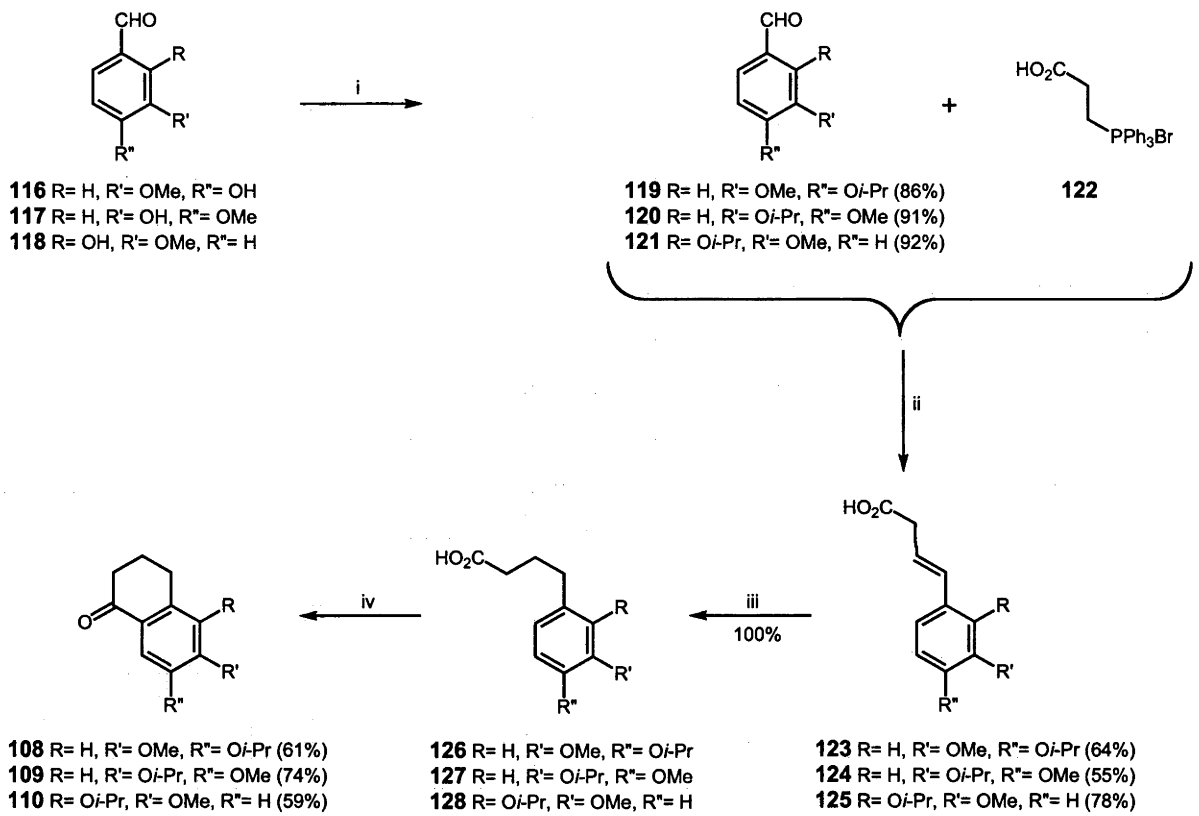
Scheme 2.3.2. *Synthesis of tetrahydroisoquinoline* **107**.
Reagents and conditions: *(i)* $AlCl_3$, *benzene; (ii) 2-bromopropane,* K_2CO_3, *DMF, 18 °C; (iii)* CH_3NO_2, NH_4OAc, *AcOH, 18 → 110 °C; (iv)* $LiAlH_4$, *THF, -50 → 0 °C; (v) paraformaldehyde, formic acid, 18 → 50 °C.*

The final step of the reaction sequence required to form isoquinoline **107** *via* a Pictet-Spengler reaction[19] was particularly problematic. Heating phenethylamine **115** with formalin in the presence of aqueous hydrochloric acid, resulted in a complex mixture of products while heating the substrate with paraformaldehyde in formic acid produced the same outcome. Attempting this transformation at ambient temperatures did not promote a reaction, while adding paraformaldehyde to a solution of the amine in formic acid at 0 °C and heating the mixture to 50 °C only provided isoquinoline **107** at low conversion after 18 h and also resulted in the formation of unidentified byproducts. The most suitable conditions that were eventually identified involved allowing the amine/paraformaldehyde/formic acid mixture to react at room temperature for 2 h, then warming to 50 °C and stirring for 40 h. In this manner isoquinoline **107** was obtained in 81% yield. Presumably, it is important that phenethylamine **115** first reacts with paraformaldehyde to form the corresponding Schiff base before the reaction mixture is then heated in order to promote the 6-*endo*-trig cyclisation reaction that finally leads to isoquinoline **107**.

2.3.3 *Preparation of 1-Tetralones 108-110*

Tetralones **108-110** were constructed by a four-step sequence involving established protocols, beginning with commercially available vanillin (**108**), isovanillin (**109**) and *o*-vanillin (**110**), respectively. Thus, in the first step isopropyl-protected benzaldehydes **116-118** were individually prepared through reaction of the relevant phenol with 2-bromopropane in DMF at 70 °C (Scheme 2.3.3). The next step involved a Wittig reaction[20]

using triphenylphosphonium bromide **122** which first had to be synthesised. Unfortunately, the initial attempt at this synthesis, which involved heating a 1.1:1 mixture of triphenylphosphine and 3-bromopropionic acid in benzene overnight, suffered from an inefficient and cumbersome work-up and yielded an intractable, glassy solid that proved difficult to handle.[21] However, altering the reaction conditions slightly,[22] employing acetonitrile as a solvent and modifying the isolation procedure allowed triphenylphosphonium bromide **122** to be obtained as a colourless, crystalline solid in 95% yield.



Scheme 2.3.3. *Synthesis of 1-tetralones* ***108-110.***
Reagents and conditions: *(i) 2-Bromopropane, K_2CO_3, DMF, 18 → 70 °C; (ii) NaH, THF/DMSO (1:1 v/v), 0 → 18 °C; (iii) H_2, Pd on charcoal, THF; (iv) PCl_5, 18 °C then $AlCl_3$, benzene, 0 → 18 °C then 2-bromopropane, K_2CO_3, DMF, 18 → 70 °C.*

It had been reported that the formation of β,γ-unsaturated acids *via* Wittig reactions can be low yielding,[21,23] and as such it was anticipated that these reactions would not be particularly efficient. Unconventional conditions were ultimately employed whereby the relevant benzaldehydes were dissolved in THF/DMSO[1] containing triphenylphosphonium

[1] DMSO was utilised as a co-solvent in order to ensure the solubility of the ylide and phosphobetaine intermediates associated with the process.

bromide **122** and the resulting solution added dropwise to NaH.[23] This ordering of events was necessary because the usual method of first preparing the ylide derived from compound **122** is extremely low yielding due to competing elimination of triphenylphosphine to form acrylic acid.[23] Using the modified protocol, the β,γ-unsaturated acids **123-125** were synthesised in 64%, 55% and 78% yields respectively.[⊥] The ensuing catalytic hydrogenation of unsaturated acids **123-125** delivered the required phenylbutanoic acids **126-128** quantitatively in each case.

Problems arose in the final Friedel-Crafts acylation[24] step due to the lability of the isopropyl protecting group under the acidic conditions required to effect the transformation. Consequently, the reaction had to be conducted under the mildest conditions possible - in particular, the use of strong acids and high temperatures had to be avoided. Indeed, reacting phenylbutanoic acid **126** in methanesulfonic acid or sulfuric acid at ambient temperature, while effecting the required acylation, also cleaved the isopropyl group and so the overall sequence was particularly inefficient. In an effort to circumvent such problems, tetralones **108-110** were prepared by treatment with phosphorous pentachloride to furnish the corresponding acid chlorides, followed by immediate reaction with aluminium chloride at ambient temperature. However, the respective yields for the final step were moderate largely due to continued significant isopropyl deprotection, which occurred during the course of the reaction, and as a result the cyclised tetralone products needed to be reprotected before being finally isolated by crystallisation. 1-Tetralones **108-110** were thus prepared in 61%, 74%, and 59% yields from phenylbutanoic acids **126-128** respectively. The physical and spectroscopic properties of compounds **126-128** were in full accord with the assigned structures and in agreement with the analogous data reported in the literature.[25]

2.3.4 *Towards the Preparation of Lamellarin Analogues 97-99*

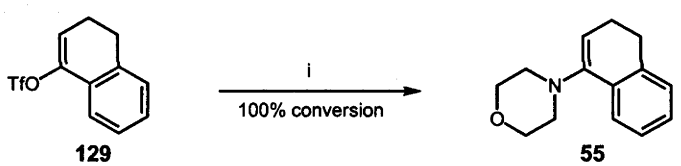
With tetrahydroisoquinoline **107** and 1-tetralones **108-110** in hand, it was anticipated that enamines **104-106** could be prepared by a similar approach to the one that had provided enamine **64**. Unfortunately, this process was not amenable to the synthesis of the target enamines with no reaction observed. Replacing toluene with higher boiling solvents such as xylene or mesitylene also failed to promote the desired transformation. Heating the starting materials (neat) in a μ-wave reactor in the presence of *p*-TsOH and 4 Å molecular sieves at either 100 or 200 °C was similarly unsuccessful.

These difficulties encountered in the preparation of enamines **104-106** from alkoxy-substituted 1-tetralones **108-110** may be understood by considering the successful reaction of 1-tetralone and 1,2,3,4-tetrahydroisoquinoline (Scheme 2.2.1). Formation of enamine **64**

[⊥] In each case the reaction did not proceed with full conversion. However, benzaldehydes **119-121** could be easily recovered and subsequently reused as required.

from these precursors occurred slowly (62 h) because of the unfavourable interaction between the α-methylene hydrogens of isoquinoline **63** and the aromatic peri-hydrogen (8-H) of 1-tetralone.[26] So, the effect of not only one, but two electron-donating alkoxy-substitutents on the respective aromatic rings of tetralones **108-110** might be expected to further lower the electrophilicity of the conjugated carbonyl group in system that was already reasonably inert.

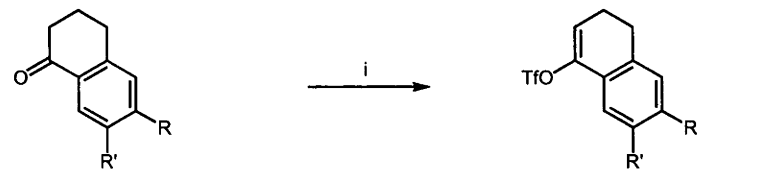
The Lewis acid-promoted approach to preparing enamines was explored. However, when tetrahydroisoquinoline **107** was reacted with 1-tetralone **108** in the presence of titanium tetrachloride enamine **104** was not formed. Disappointingly, replacing titanium tetrachloride with other Lewis acids, such as boron trifluoride, dibutyltin dichloride or tin tetrachloride, gave similar results. These findings dictated the synthetic strategy be revised and prompted the investigation of the utility of the Buchwald-Hartwig cross-coupling reaction to deliver enamines **104-106**.[27] The fact that Willis and Brace had established that a number of amines, including morpholine, and the 1-tetralone-derived alkenyl triflate **129** could be successfully coupled to provide enamine **55** at full conversion *via* the palladium-catalysed reaction was certainly encouraging (Scheme 2.3.4).[28] Although the authors noted that the increased the steric bulk of the amine had an adverse effect it seemed reasonable to expect that this approach could deliver enamines **104-106**.



129 **55**

Scheme 2.3.4. *The Buchwald-Hartwig cross-coupling to provide enamine* **55**.[28]
Reagents and conditions: *(i) $Pd(OAc)_2$ (2.5 mol%), BINAP (7.5 mol%), Cs_2CO_3, toluene, 80 °C.*

In order to test this hypothesis 1-tetralones **108** and **109** were converted into their respective alkenyl triflates **130** and **131**. Accordingly, the ability of both *N*-phenyltrifluoromethanesulfonimide and trifluoromethanesulfonic anhydride to effect the transformation of tetralone **108** into triflate **130** was investigated. *N*-Phenyl-bis(trifluoromethanesulfonimide) was used with a range of bases. Disappointingly, no reaction was observed when LDA and NaH were employed, while LiHMDS only delivered enol triflate **130** at low conversion. Although treating tetralone **108** with trifluoromethanesulfonic anhydride in the presence of pyridine provided alkenyl triflate **130**, the conversion was once again poor. Gratifyingly, employing the more sterically hindered 2,6-di-*tert*-butyl-4-methylpyridine base provided alkenyl triflates **130** and **131** in respectable yields, *viz.* 82% and 66%, respectively (Scheme 2.3.5).



108 R= OMe, R'= O*i*-Pr
109 R= O*i*-Pr, R'= OMe

130 R= OMe, R'= O*i*-Pr (82%)
131 R= O*i*-Pr, R'= OMe (66%)

Scheme 2.3.5. *Synthesis of alkenyl triflates* ***130*** *and* ***131****.*
Reagents and conditions: *(i)* Tf_2O, *2,6-di-*tert*-butyl-4-methylpyridine,* CH_2Cl_2, *0 °C.*

With alkenyl triflates **130** and **131** in hand, the pivotal Buchwald-Hartwig cross-coupling was investigated and the results of the relevant studies are presented in Table 2.3.1. The standard conditions disclosed by Willis and Brace[128] were employed initially, however, when triflate **130** was reacted with tetrahydroisoquinoline **107** the hoped-for enamine **104** was not observed, even after 40 h (Table 2.3.1, Entry 1). Performing the reaction at 100 °C gave the same result and, in fact, it was only after the process was performed at 110 °C that ^{1}H NMR analysis of the reaction mixture indicated enamine formation at *ca.* 40% conversion after 20 h (Table 2.3.1, Entries 2 and 3). Extended reaction times, up to 5 days, failed to improve matters. Increasing the catalyst and ligand loading up to 50 and 75 mol%, respectively, (Table 2.3.1, Entries 4-7) or replacing toluene with higher boiling solvents such as xylene and DMF also failed to deliver a better outcome (Table 2.3.1, Entries 18 and 19).

[1] $Pd(OAc)_2$ (5 mol%), BINAP (7.5 mol%), Cs_2CO_3, toluene, 80 °C.

Table 2.3.1. *Efforts to prepare enamines* ***104*** *and* ***105*** *by the Buchwald-Hartwig cross-coupling of tetrahydroisoquinoline* ***107*** *with triflates* ***130*** *and* ***131*** *and iodide* ***135****.*[a]

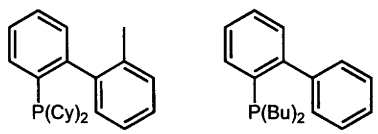
Entry	Catalyst (mol%)/Ligand (mol%)	Time (h)	Temperature (°C)	Conversion (%)
1	$Pd(OAc)_2$ (10)/BINAP (15)	40	80	-
2	$Pd(OAc)_2$ (10)/BINAP (15)	16	100	-
3	$Pd(OAc)_2$ (10)/BINAP (15)	22	110	*ca.* 40
4	$Pd(OAc)_2$ (10)/BINAP (15)	40	110	*ca.* 40
5	$Pd(OAc)_2$ (10)/BINAP (15)	66	110	*ca.* 40
6	$Pd(OAc)_2$ (25)/BINAP (38)	20	110	*ca.* 40
7	$Pd(OAc)_2$ (50)/BINAP (75)	20	110	*ca.* 40
8	$Pd(OAc)_2$ (10)/BINAP (15)	0.5	100 (μ-wave irr.)	-
9	$Pd(OAc)_2$ (10)/BINAP (15)	0.5	115 (μ-wave irr.)	-
10	$Pd(OAc)_2$ (10)/BINAP (15)	0.5	100 (μ-wave irr.)	-
11	$Pd_2(dba)_3$ (10)/BINAP (15)	20	110	*ca.* 40
12	$Pd(OAc)_2$ (10)/dppf (15)	18	110	-
13	$Pd_2(dba)_3$ (10)/**132** (15)	18	110	-
14	$Pd_2(dba)_3$ (10)/**133** (15)	16	110	-
15	$Pd(OAc)_2$ (10)/P(*o*-tolyl)$_3$ (15)	22	110	-
16	$Pd[P(t\text{-}Bu)_3]_2$ (10)	16	110	*ca.* 20
17	$Pd(OAc)_2$ (10)	16	110	-
18	$Pd(OAc)_2$ (10)/BINAP (15)	22	140	Trace
19	$Pd(OAc)_2$ (10)/BINAP (15)	20	120	-
20	$Pd(OAc)_2$ (10)/BINAP (15)	18	110	-
21	$Pd(OAc)_2$ (10)/BINAP (15)	18	110	-
22	$Pd(OAc)_2$ (10)/BINAP (15)	18	110	Trace
23	$Pd[P(t\text{-}Bu)_3]_2$ (10)	16	110	-
24	$Pd(OAc)_2$ (10)/BINAP (15)	0.5	100 (μ-wave irr.)	-

[a]All reactions employed triflate **130** except Entries 7, 10, 15, 16, 20, 21 where triflate **131** was used and Entries 22-24 where iodide **135** was used. All reactions were carried out in toluene, except Entries 10 and 24 where acetonitrile was used, Entry 18 where xylene was used and Entry 19 where DMF was used. All reactions employed Cs_2CO_3 as a base, except Entries 9 and 20 where *t*-BuOK was used and Entry 21 where DBU was used.

Employing $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ did not influence the outcome of the reaction and neither did preforming the active catalyst (Table 2.3.1, Entry 11).[⊥] Replacing BINAP with a variety of ligands was also explored, however, employing dppf, tri(*o*-tolyl)phosphine and biphenyl-based monophosphine ligands **132** and **133** (Figure 2.3.1) did

[⊥] This involved heating the palladium catalyst with the BINAP ligand in toluene before addition to the reaction mixture.

not provide the desired enamine, (Table 2.3.1, Entries 12-15). Although the tri(*t*-butyl)phosphine ligand successfully provided the target this was only achieved at *ca.* 20% conversion (Table 2.3.1, Entries 16).



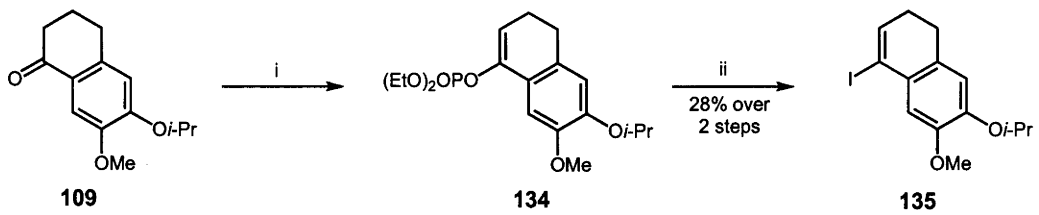
132 **133**

Figure 2.3.1. *Biphenyl-based monophosphine ligands* **132** *and* **133** *that were used in an attempt to promote the cross-coupling of tetrahydroisoquinoline* **107** *with triflate* **130** *(Table 2.3.1, Entries 13 and 14).*

Substituting Cs_2CO_3 for either DBU or *t*-BuOK also failed to improve matters (Table 2.3.1, Entries 20 and 21). Indeed, enamine **105** was not observed to form when DBU was used and only triflate cleavage leading to the corresponding enol[⊥] occurred when *t*-BuOK was employed. The effect of slow addition of the substrate to the reaction mixture was also investigated, whereby triflate **130** was added over 10 h (*via* syringe pump). Although a small amount of enamine **104** was generated under such circumstances, it was not significant. Attempting this process under μ-wave irradiation at various temperatures also failed to provide the required enamine, even in trace amounts (Table 2.3.1, Entries 8-10).

Due to the difficulties encountered in effecting the Buchwald-Hartwig cross-coupling between the respective alkenyl triflates **130** and **131** and tetrahydroisoquinoline **107**, it was postulated that the cross-coupling might be more successful if triflate **131** was replaced by its iodide analogue **135** in the pivotal cross-coupling reaction. Consequently compound **135** was prepared from the tetralone **109** by an unoptimised two-step sequence shown in Scheme 2.3.6. Thus, substrate **109** was treated with LDA and the resulting enolate trapped as diethylphosphonate ester **134**, which was not isolated, but immediately converted into alkenyl iodide **135** *via* a pseudo-Finkelstein reaction.[29] This process provided compound **135** in 28% yield over the two steps.

[⊥] As judged by ^{1}H NMR analysis of the crude reaction mixture.



109 134 135

Scheme 2.3.6. *Synthesis of iodide* **135**.
Reagents and conditions: *(i) LDA, diethyl chlorophosphonate, THF, -30 → 18 °C; (ii) TMSCl, NaI, MeCN, 18 °C.*

When the Buchwald-Hartwig cross-coupling reaction was attempted with iodide **135** ^{1}H NMR analysis of the reaction mixture after 20 h indicated that although the desired enamine had formed it was only present in trace amounts (Table 2.3.1, Entry 22). No product was observed when BINAP was replaced with tri(*t*-butyl)phosphine (Table 2.3.1, Entry 23), and when this process was attempted under μ-wave irradiation conditions, enamine **105** was not obtained (Table 2.3.1, Entry 24). Seemingly, then, iodide **135** is less reactive than triflates **130** and **131** towards the Buchwald-Hartwig cross-coupling. Certainly, it has been reported that alkenyl triflates are more reactive than alkenyl bromides by *ca.* four orders of magnitude towards the title reaction[30] and the results of this research clearly indicates that the triflates **130** and **131** are more reactive than iodide **135** in this instance.

The outcome of this thorough study allowed for identification of the best conditions for the Buchwald-Hartwig cross-coupling of either alkenyl triflate **130** or **131** with isoquinoline **107**. This involved the use of $Pd(OAc)_2$, BINAP and Cs_2CO_3 in toluene at 110 °C for 22 h. (Table 2.3.1, Entry 3). Because enamines **104** and **105** could be prepared at *ca.* 40% conversion by this approach it was anticipated that these products may be directly subjected to the subsequent carbene addition step and that the corresponding dichlorocyclopropane derivatives could then be isolated. Disappointingly, when this was undertaken only a complex mixture of products was obtained in each instance. As a consequence, the pursuit of the synthetic plan defined in Scheme 2.3.1 was abandoned.

2.4 Summary: Part One

Although the dichlorocarbene adducts of enamines are known,[11,13,31] no systematic studies of the base-promoted reactions of such compounds have been reported. However, the observation that novel annulated pyrrole **57** could be prepared in a single step from cyclopropane **56** by Banwell and Phillis[1,2] prompted a comprehensive investigation of this transformation. Gratifyingly, despite the propensity of *gem*-dihalogenocyclopropanes carrying electron-donating substituents to undergo facile electrocyclic ring cleavage,[11] these

adducts proved to be rather stable and generally crystalline materials.

A thorough optimisation study established that this transformation was most efficient when dichlorocyclopropanes were utilised as substrates and LDA employed as a base. Such findings enabled the scope and limitations of this unprecedented methodology to be explored. Research showed that cyclopropanes **56**, **65**, **68**, **69** and **74** provided the annulated pyrroles **57**, **67**, **76**, **77** and **80**, respectively, in yields ranging from 43-82%. This demonstrated that dihalogenocarbene adducts of enamines featuring a range of amine substituents, both aliphatic and cyclic, can be converted into pyrroles by this reaction. Unfortunately, there were a number of instances in which pyrrole formation was not observed. Thus, dichlorocyclopropanes **70**, **71** and **75** were inert to LDA, and dibromo-analogue **72** was converted into diquinane **78** under such conditions. Interestingly, subjecting compound **73**, the regioisomer of cyclopropane **56**, to reaction with *t*-BuOK failed to give the anticipated pyrrole - instead affording the β-oxygenated cycloheptanone **79**. Thus, it was established that this base-promoted process is restricted to *gem*-dihalogenocyclopropanes annulated to six-membered carbocycles.

The synthesis of pentacyclic annulated pyrrole **67**, and its subsequent conversion into cross-coupled derivative **96** provided the impetus to investigate whether this novel methodology could be exploited in the construction of more highly functionalised lamellarin analogues **97-99**. To such ends, isoquinoline **107** and tetralones **108-110** were prepared to test this hypothesis. Disappointingly, although the corresponding enamine intermediates **104** and **105** could be prepared, albeit at low conversion, they failed to engage in dichlorocarbene addition to give the corresponding dichlorocarbene adducts.

2.5 Conclusion: Part One

The development of a new method for the preparation of annulated pyrroles by the base-promoted reaction of *gem*-dihalogenocarbene adducts of enamines represents the most significant outcome of the studies described in Part One of this thesis and serves as a useful addition to the *repertoire* of procedures available for preparing these particularly important aromatic heterocycles. Certainly, the synthesis of lamellarin analogue **96** emphasises the potential of this methodology to deliver complex pyrrole-based structures bearing otherwise difficult to obtain substitution patterns both rapidly and efficiently.

Furthermore, the results of the first systematic study of the base-promoted reactions the *gem*-dihalogenocarbene adducts of enamines underscores the benefits of employing dihalogenocyclopropanes as building blocks for chemical synthesis.

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Chapter Three

Studies Directed Towards the Synthesis of Quinine

"If molecules were mythical figures, quinine would be chemistry's Helen of Troy - the structure that launched a thousand research projects. Louis Pasteur, William Henry Perkin, Robert Burns Woodward, Gilbert Stork - quinine has bewitched chemistry's brightest lights for more than 150 years."[1]

3.1 Introduction

3.1.1 The Cinchona *Alkaloids*

Quinine (**136**) occupies a central place among the many natural products used in medicine, chemistry and science more generally.[2] The *Cinchona* alkaloids, some of which are represented in Figure 3.1.1, are a class consisting of some thirty compounds, of which quinine is the best-known member. They are found in the bark of the *Cinchona* and *Remijia* species of evergreen trees native to the eastern slopes of the Andes ranging from Venezuela to Bolivia. These molecules constitute an extraordinarily versatile class of natural product, serving as medicinally important compounds, as both privileged catalysts and ligands for asymmetric catalysis,[3] while also being used in the food industry as the bitter principle of soft drinks.[⊥] Indeed, the *Cinchona* alkaloids are arguably the most commercially important alkaloid family. They are produced worldwide at an estimated 700 tonnes *per annum*.[Ω4]

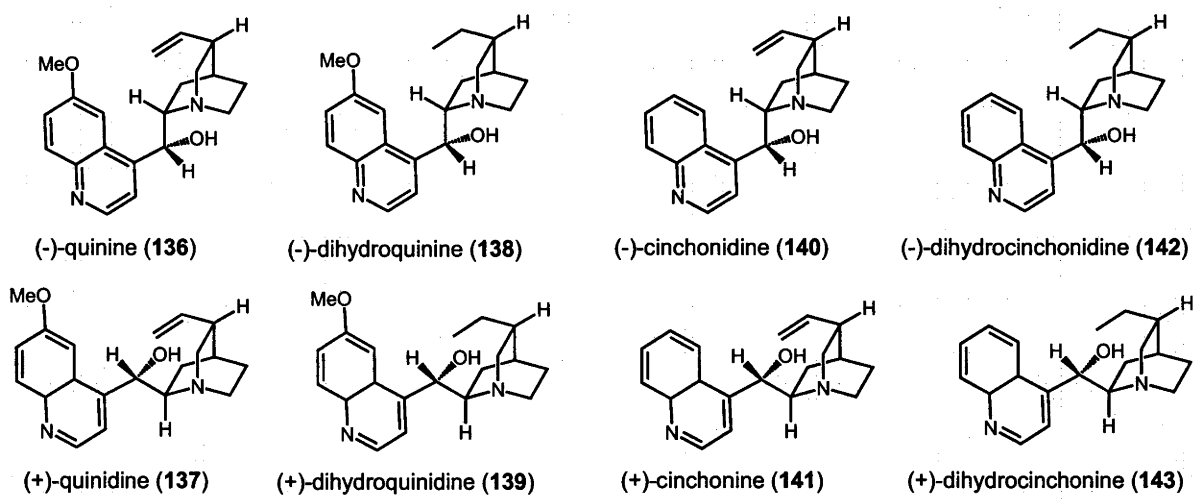


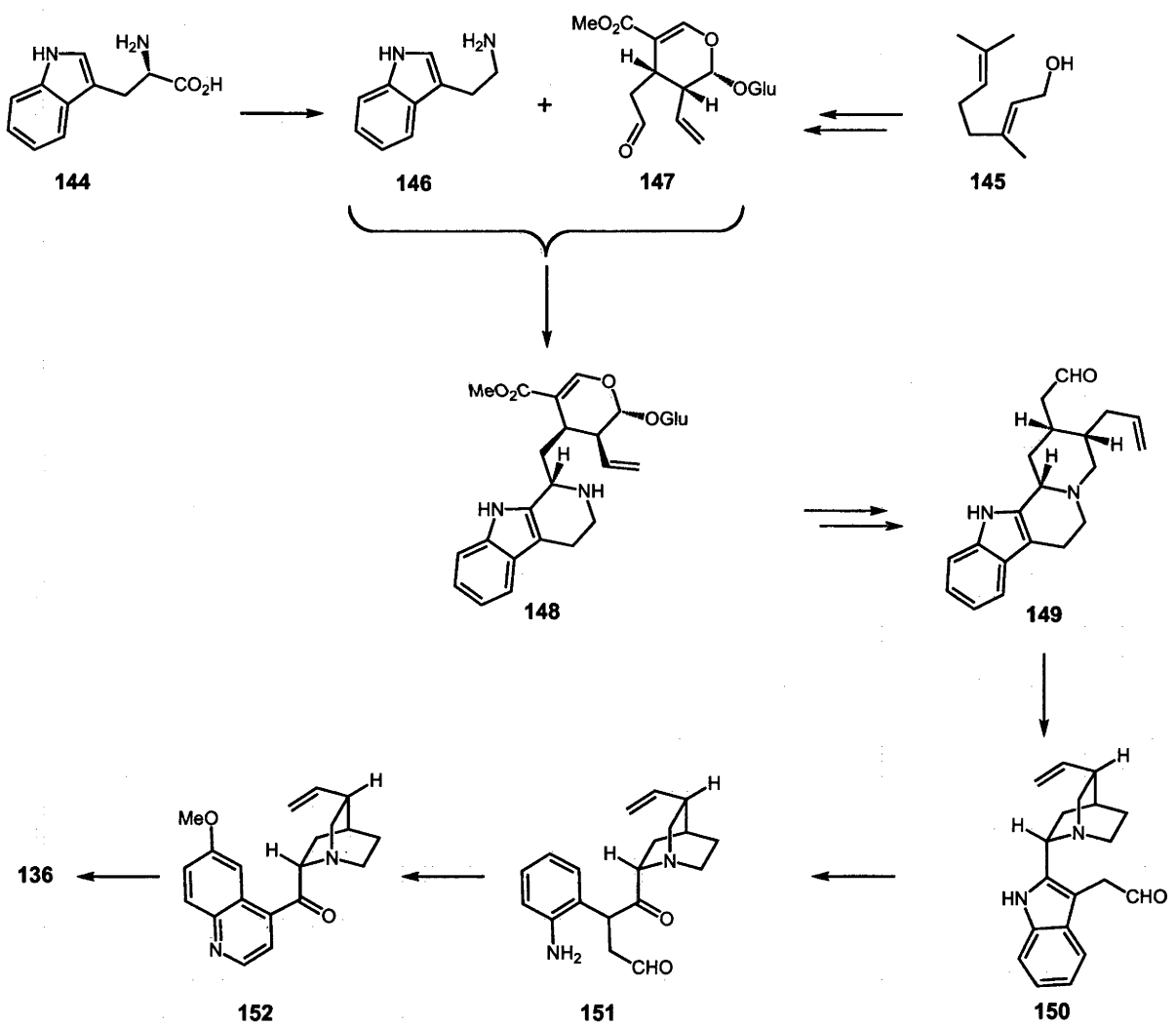
Figure 3.1.1. *The eight major* Cinchona *alkaloids.*

[⊥] Approximately 60% finds use in the food industry and 40% in the chemical/pharmaceutical industries.

[Ω] A significant proportion of the production involves quinine (**136**) and quinidine (**137**).

3.1.2 *Biosynthesis*

Some of the most remarkable examples of terpenoid indole alkaloid modifications are found in the *Cinchona* genus - mainly because the indolic nucleus is no longer present in this family of natural products, having been rearranged into the quinoline system. All terpene indole alkaloids are derived from tryptophan (**144**) and the iridoid terpene secologanin (**147**). The quinine biosynthetic pathway was established by feeding experiments performed by Alan Battersby and Ronald Parry in *Cinchona ledgeriana* (Scheme 3.1.1).[5] The first committed step of *Cinchona* alkaloid biosynthesis, and indeed that of all terpene indole alkaloids, involves the strictosidine synthase-catalysed, stereoselective Pictet-Spengler condensation between tryptamine (**146**) and secologanin to provide strictosidine (**148**).[6]



Scheme 3.1.1. *Proposed pathway for the biogenesis of (-)-quinine (136).*

It was confirmed that quinine is strictosidine-derived by carrying out feeding studies with radiolabelled tryptophan,[7] geraniol (**145**),[8] loganin[9] and strictosidine.[10] Incorporation of the corynantheal intermediate (**149**) suggests that the methoxycarbonyl group present in strictosidine is lost at an early stage. The next step in the sequence is believed to involve cleavage of the fused piperidine ring in corynantheal and formation of the quinuclidine ring in cinchoaminal (**150**). It is postulated that the indole framework is then ruptured to generate aniline **151**, featuring pendant aldehyde functionality. A Schiff base condensation reaction then provides the quinoline core. The installation of the methoxy substituent is thought to occur at a relatively late stage providing quininone **152**, which is selectively reduced to deliver (-)-quinine (**136**).

3.1.3 Biological Activity

Quinine is the classical treatment for malaria - an intractable ailment that has afflicted mankind since the foundation of recorded history and, surely, long before it.[11] This prevalent and life-threatening, vector-borne disease has been designated, *"The most significant disease for world civilisation over the past three centuries."*[12] Malaria kills between one to three million people annually - more than any disease except AIDS and tuberculosis.[13] For centuries quinine, as the major alkaloid present in *Cinchona* bark, was implicitly used to treat malaria and, after its identification as the active ingredient in the early nineteenth century, as a pure compound thereafter. However, after WWII chloroquine and various other more potent, synthetic anti-malarial drugs generally supplanted quinine for prophylaxis and routine treatment. This spared the *Cinchona* alkaloid widespread and prolonged use. Consequently, the high level resistance that has since been observed with most of these modern treatments has been slow to develop against quinine.

Malaria is caused by protozoal parasites of the genus *Plasmodium*, which enter red blood cells. The parasites then multiply and progressively break down the red blood cells. This has the effect of inducing bouts of fever and anaemia in infected individuals. These parasites are transmitted from an infected person to a healthy individual by mosquitoes of the *Anopheles* genus. Although the molecular basis of quinine's mode of action is not completely understood, it is thought to concentrate inside the parasite's digestive vacuole where it binds β-hematin, disrupting the detoxification of free heme and thus destroying it.[14] However, there is also some evidence that the alkaloid may function by inhibiting the parasite's uptake of haemoglobin from the host cell.[15]

In addition to its celebrated anti-malarial properties, quinine possesses analgesic, anti-inflammatory, antibacterial, antipyretic properties, finds use in the alleviation of muscle cramps and also acts as a cardiovascular stimulant.[16] Other members of the *Cinchona* alkaloid family display similar physiological activity. Quinidine (**137**), for example, is

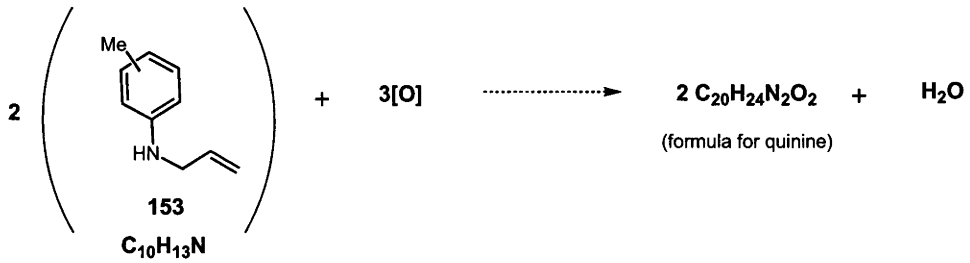
utilised as an anti-arrhythmic drug and, like cinchonidine (**140**) and cinchonine (**141**), is also a known anti-malarial agent.[17]

3.1.4 A Brief History of Quinine

Like morphine, atropine, coniine, and various other alkaloids, quinine was used by humans long before its structure was known. Accordingly, this legendary small molecule has profoundly shaped the development of modern society over the past four centuries. *"Its impact, direct or indirect, on human health, wealth and civilization is hardly equalled by any other chemical."*[18] Indeed, the natural product has been described as, *"The drug to have relieved more human suffering than any other in history."*[19] Western culture first became aware of quinine in the 1630s when Spanish missionaries stationed in present day Peru learnt of the antipyretic properties of *Cinchona* bark from the natives. Jesuits, notably Father Antonio de la Calancha and Cardinal Juan de Lugo, are credited with the introduction of *Cinchona* bark for medicinal use in Europe around 1640, after the perhaps fortuitous discovery of its anti-malarial properties in Peru.[20,21]

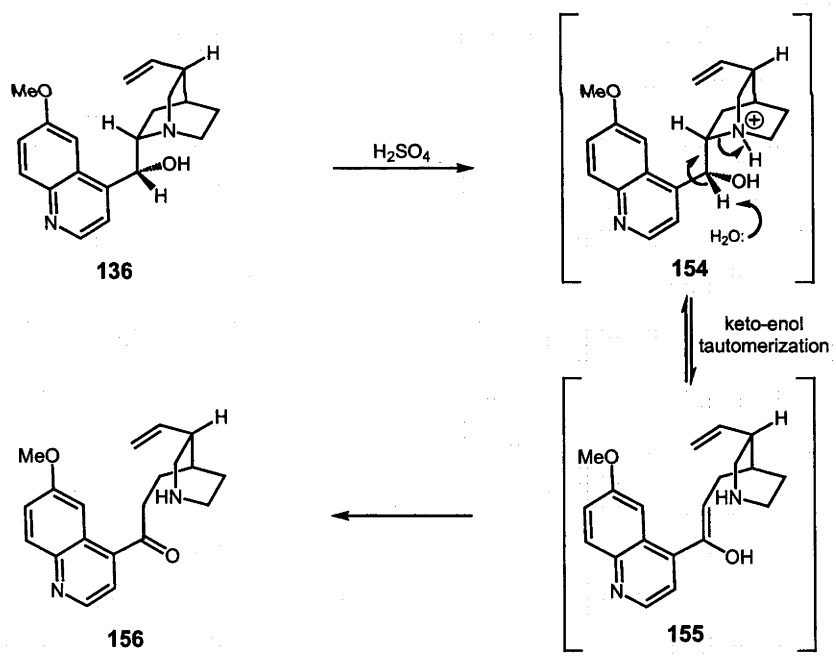
The great French pharmacists Pierre Pelletier and Joseph Caventou first isolated quinine in 1820,[22] which promptly led to the administration of a pure compound for the treatment of malaria for the first time. It should be noted that for over three centuries quinine was the only cure for malaria. However, it was a rare drug - a plant extract imported from South America at great expense. By the early nineteenth century the native *Cinchona* forests in the Andes were nearly exhausted so prices soared. Consequently, the British, Dutch and French, having established colonies in malaria-infested areas of the world, recognised that the prosperity of their respective empires would depend on their access to uninterrupted and abundant supplies of the valuable alkaloid. There were essentially two potential solutions: the establishment of new *Cinchona* plantations outside South America, or the preparation of quinine synthetically.

Accordingly, the total synthesis of this precious natural product arguably represented the 'Holy Grail' of synthetic chemistry during the 'Age of Empire' and unquestionably played a significant role in the development of organic chemistry. This may explain why unlike morphine, whose structural elucidation preceded its synthesis, attempts to prepare quinine began even before its structure was fully established. Certainly, the well-known story of August Wilhelm von Hofmann and his pupil William Henry Perkin who in 1856 sought to prepare quinine, in an ill-founded and quixotic attempt, by the oxidation of *N*-allyltoluidine (Scheme 3.1.2), has become part of the history and folklore of chemistry. Although, predictably unsuccessful in this aim, their research serendipitously led to the discovery of mauveine, the first synthetic dye, and with it the foundation of the global chemical industry.[23,24]



Scheme 3.1.2. *The assumption underpinning Hofmann and Perkin's famously unsuccessful* ***1856*** *attempt to prepare quinine (****136****).*

In 1853 the remarkable Louis Pasteur showed that treating quinine with sulfuric acid opened the quinuclidine ring to form quinotoxine (**156**) (Scheme 3.1.3) and, although he never deduced the molecular basis for the transformation,[⊥ Ω] this product enabled Pasteur to perform, in an experiment employing (±)-tartaric acid, the first chemical resolution.[25] These observations by this incredibly versatile scientist would not only influence the first rational synthetic approaches to quinine, some fifty years later, but also subsequent efforts extending well into the twentieth century.



Scheme 3.1.3. *Pasteur's acid-catalysed rearrangement of quinine (****136****) to quinotoxine (****156****) as first characterised by Rabe.*

[⊥] Rabe later deduced the structure of quinotoxine (**156**) (Rabe, P. *Liebigs Ann. Chem.*, **1909**, *365*, 366.).
[Ω] For an erudite and insightful analysis of this process see: Ireland, R.E. *Organic Synthesis*, Prentice-Hall, Englewood Cliffs, **1969**, p123.

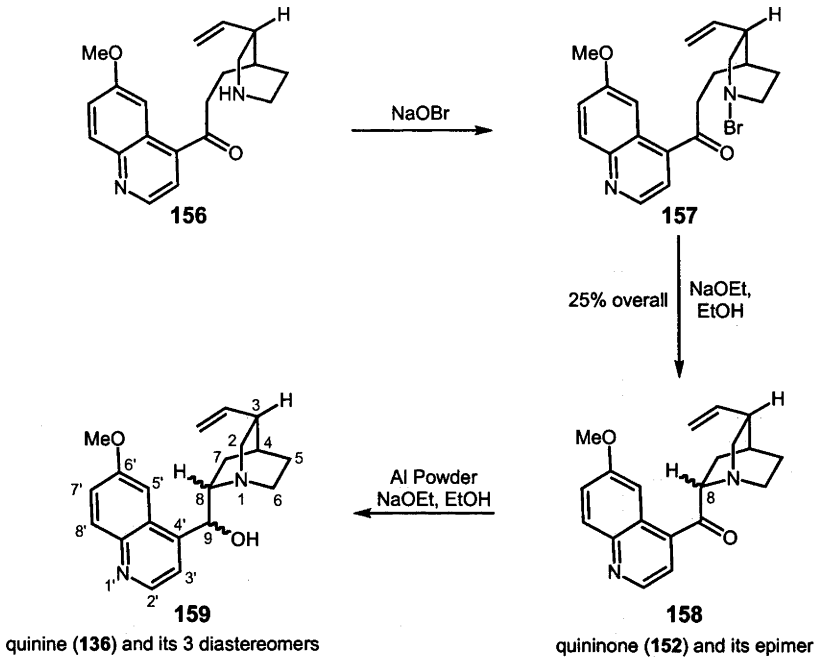
A year after Pasteur's seminal discovery Adolf Strecker established the empirical formula of quinine as $C_{20}H_{24}N_2O_2$.[26] However, the absence of sophisticated analytical tools at that time meant that determining quinine's structure remained a formidable and consequently protracted task. Adolf von Baeyer, Wilhelm Königs and Zdenko Skraup, amongst others,[2d,27] all made important progress to this end before Paul Rabe, who would become a central figure in the story of the synthesis of quinine, established the correct molecular connectivities of the alkaloid in 1908.[28] Obviously, because stereochemical analysis did not yet exist, the absolute configuration of quinine remained unknown. Nevertheless, Rabe's important advancement enabled more rationally designed synthetic studies than those initiated by Hofmann and Perkin.

3.2 Previous Syntheses of Quinine

3.2.1 *Partial Synthesis of (±)-Quinine: Rabe (1918)*

In 1918 Paul Rabe and his student Karl Kindler were able to prepare quinine from Pasteur's degradation product quinotoxine, which they reported in a terse communication containing only cursory experimental detail.[29] This sequence, shown in Scheme 3.2.1, was analogous to one that Rabe had developed to cinchonidinine (**140**) several years earlier as that featured an almost identical three-step sequence.[30] This previous approach was comprehensively outlined and complete experimental information provided, which may account for the brevity of the later publication on quinine.[⊥] Rabe and Kindler noted that following the bromination of quinotoxine (**156**) with sodium hypobromite, treatment of resultant product **157** with sodium ethoxide effected dehydrobromination to afford, in racemic form, a mixture of C_8 epimers **158**. After reduction with aluminium powder Rabe obtained a mixture of all four possible C_8-C_9 stereoisomers **159** namely, quinine (**136**) (12%), quinidine (**137**) (6%) and their respective C_9 epimers.[31] However, since stereochemical and conformational analysis were essentially unknown at the time Rabe could not have fully rationalised the collection of products he had obtained.[2b]

[⊥] In the view of the author, this report outlining the partial synthesis of quinine may have avoided rigorous refereeing as it was published during the latter stages of WWI.

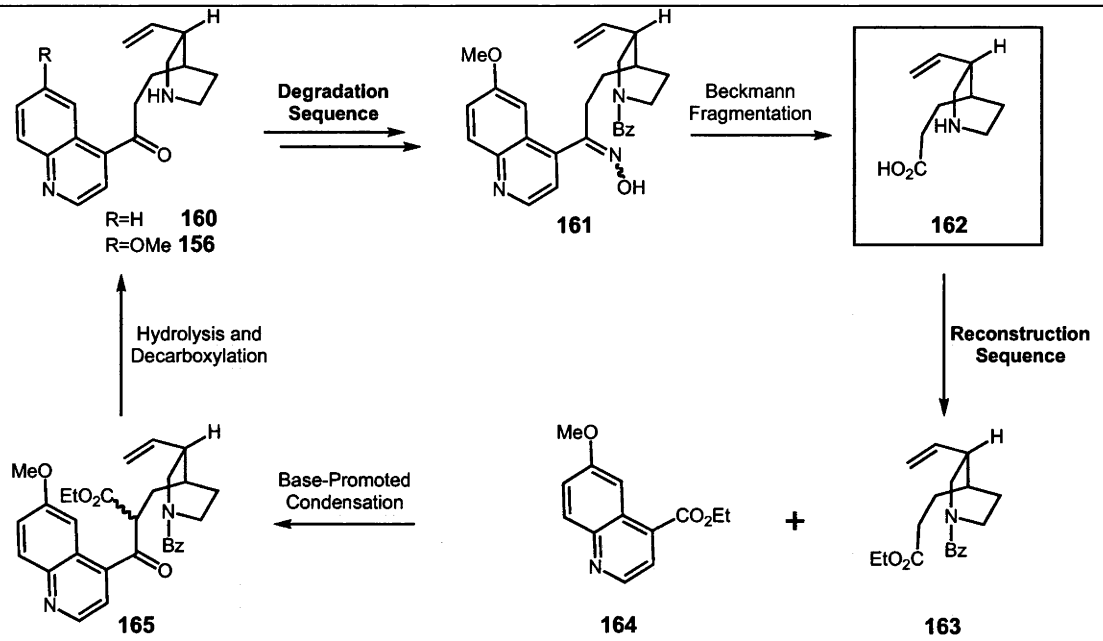


Scheme 3.2.1. *The reconstruction of (±)-quinine (136) from quinotoxine (156).*

In 1931 Rabe also reported a notable synthesis of dihydroquinine (**138**), complete with full experimental details, using essentially the same strategy as that employed in his earlier approach to quinine (**136**).[32] However, he never published the full experimental details associated with the transformation **156** → **159** and consequently lingering reservations regarding the reproducibility of this work would be raised publicly over eighty years later and instigating a polemical controversy that has become inextricably linked with the story of quinine.[33,34] Nevertheless, the strategy of forming the 1-azabicyclo[2.2.2.]octane framework of quinine, through creation of the N-C_8 bond has become known as the Rabe connection / disconnection or Rabe approach.

3.2.2 *Partial Synthesis of (±)-Quinine: Prelog (1943)*

In 1943 Vladimir Prelog and Mihovil Prošťenik were able to convert cinchotoxine (**160**) into the optically pure homomeroquinene (**162**) *via* the Beckmann degradation of related oxime intermediate **161** (Scheme 3.2.2.).[35] The condensation of homomeroquinene-derived ester **163** and ethyl quininate (**164**), followed by treatment with acid resulted in the conversion of β–ketoester **165** into quinotoxine (**156**). This linked their route with Rabe's aforementioned approach and so established a formal synthesis of quinine. Prelog's research illustrated that quinine could be prepared from homomeroquinene and certainly was important in guiding the strategy ultimately employed by Woodward that resulted in the historic and widely publicised first *de novo* synthesis of the *Cinchona* alkaloid.[36]



Scheme 3.2.2. *The degradation of cinchotoxine (160) and subsequent reconstruction of quinotoxine (156) by Prelog and Prošenik.*

3.2.3 *Formal Total Synthesis of (±)-Quinine: Woodward and Doering (1944)*

This milestone in organic synthesis must be understood in the context of WWII. The vast *Cinchona* plantations cultivated by the Dutch in Java formed the major source of European quinine supplies, which were stored in Amsterdam. However, these reserves were lost after Hitler conquered Holland in 1940. After the Japanese invasion and subsequent occupation of Java two years later the allied forces were completely cut off from their vital supply of quinine, which at that time remained indispensable in the treatment of malaria. Soldiers fighting the war in the Pacific were sorely in need of the precious alkaloid and research programs were frantically initiated with a view to developing alternative anti-malarial drugs.

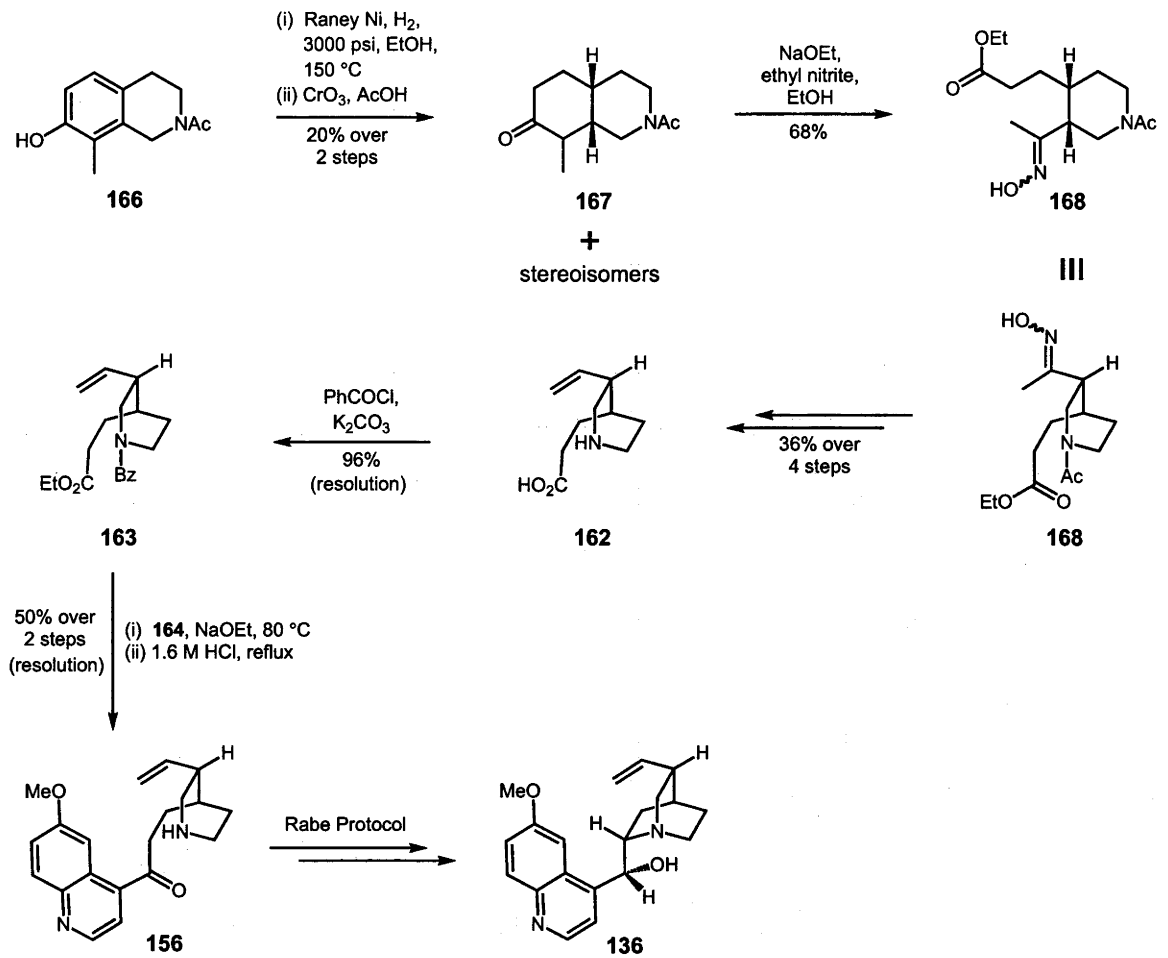
The Polaroid Corporation, which employed quinine iodosulfate as a light polarizer, was also looking for substitutes for the versatile natural product when the young, and at that time little known, Harvard-based Assistant Professor Robert Woodward swiftly solved this problem. The prodigy subsequently secured the company's support to fund a bold synthesis of quinine by an approach he began devising while still only a student at MIT. Woodward had realised, in an informal example of early retrosynthetic analysis,[37] that if he could devise a synthesis of homomeroquinene (**162**),[35] or a related derivative, a total synthesis of quinine would be achieved. To this end he developed an unusual and particularly novel solution to the problem.

The formation, modification, and eventual cleavage of carbocyclic frameworks to reveal new and distinct acyclic stereochemical elements at adjacent centres would become Woodward's distinctive personal signature and he used the synthesis of quinine to introduce this strategy.[2a,b] This was an approach which he would employ with increasing confidence and audacity in his subsequent, and structurally more complicated total syntheses including reserpine,[38] strychnine[39] and vitamin B_{12}.[40] With the aid of his student William Doering quinine quickly succumbed to synthesis for the first time - heralding the dawn of the Woodwardian Era of organic synthesis.[36] Arguably, the discipline was never quite the same again.

The details of the Woodward/Doering synthesis of quinine are shown in Scheme 3.2.3. Thus, tetrahydroisoquinoline **166** was prepared in 24% over five steps from 3-hydroxybenzaldehyde utilising standard transformations. Woodward then anticipated that in the subsequent reduction, hydrogen would be delivered to the heterocycle in a facially selective manner, however, double bond isomerisation which occurred at the elevated temperatures also gave rise to *trans*-fused products. Following oxidation of the reaction mixture decahydroisoquinoline **167** could be obtained as a racemic mixture of *cis*-fused isomers. The centrepiece of the approach involved exposure of compound **167** to ethyl nitrite in the presence of sodium ethoxide which converted the ketone functionality into an ester with the attendant oxidation of the adjacent carbon atom to oxime **168** by a remarkable process.[⊥2b] Novel transformations such as this one, which allowed for the rapid construction of the carbon frameworks of target molecules so elegantly and with such characteristic and breathtaking originality, reflected Woodward's stunning scientific intuition and unquestionable genius.[Ω41] Oxime **168** was then converted into homomeroquinene (**162**) after some functional group interconversions. This synthetic homomeroquinene was racemic but could be resolved after preparing the previously reported *N*-benzoylmeroquinene methyl ester (**163**). The final steps of the research then followed a similar sequence to that developed earlier by Prelog.[35] Amazingly, after only fourteen months of concerted application, Woodward and Doering succeeded in preparing quinotoxine (**156**) synthetically for the first time (obtaining 30 mg of the *D*-enantiomer).

[⊥] Despite the strongly basic conditions epimerisation did not occur due to the presence of the more acidic oxime proton which prevented additional proton abstraction and resultant imine-enamine tautomerisation.

[Ω] Professor A. Fredga introduced Woodward as the recipient of the Nobel Prize in Chemistry at the ceremony in 1965 by declaring, *"It is sometimes said that organic synthesis is at the same time an exact science and a fine art. Here nature is the uncontested master, but I dare say that the prize-winner of this year, Professor Woodward, is a good second." Nobel Lectures: Chemistry 1963-1970*, Elsevier, New York, **1972**, p96.



Scheme 3.2.3. *Woodward and Doering's formal total synthesis of (±)-quinine (136).*

Amidst the backdrop of WWII and because of the aforementioned scarcity of quinine supplies and the need to boost morale during wartime, reports of this breakthrough found their way into the mainstream press. The front page of The New York Times declared enthusiastically (and slightly misleadingly), *"Synthetic Quinine Produced, Ending Century Search. 2 Young Harvard Scientists Solve Baffling Chemical Jig-Saw Puzzle."*[42] More ardent and fanciful descriptions, such as the cartoon in Figure 3.2.1 and reports including this one, proclaiming, *"A promise of life and health for millions now suffering and dying from malaria,"* were also common.[43] This quinine synthesis and the ensuing 'hype' gave Woodward immense popularity, turned him into a veritable demigod in his own field and was the springboard that launched his remarkable career.

Figure 3.2.1. *A cartoon featured in the Oregon Journal, Portland, 28 May, 1944 depicting synthetic chemistry as America's wartime saviour in the face of losses of quinine, rubber and oil supplies*[44]

Clearly the Woodward-Doering sequence to quinine, as ingenious as it was in its classical design and brilliant execution, suffered from a lack of stereocontrol both in the hydrogenation step, and were it repeated, in Rabe's conversion of quinotoxine to quinine. Nevertheless this was an event of epochal importance, representing a watershed moment in chemistry, and arguably defined a new paradigm in organic synthesis.

Unfortunately Woodward and Doering didn't attempt to repeat the three-step sequence from quinotoxine to quinine reported by Rabe which would, unbeknownst to them, inadvertently call into question the legitimacy of their claims of a formal total synthesis in years to come because of the controversy surrounding the aforementioned reproducibility of Rabe's process. Doubts were initially raised privately by Gilbert Stork in a letter to Woodward in 1944[44] and then publicly for the first time over fifty years later.[33,34] Stork's assertion that because of this Woodward and Doering did not actually complete a formal total synthesis of quinine became a widely held view, endorsed by many others in the scientific community.[45] This prompted Jeffrey Seeman to conduct a meticulous review[44] of the large body of both published and unpublished material relating to Rabe's contentious sequence and Woodward's quinine research, after which he concluded that this formal total synthesis was a valid achievement. However, it was only following the unambiguous experimental results obtained by Robert Williams and Aaron Smith,[46] demonstrating the ready reproducibility of Rabe's experimental protocols, by carefully repeating the controversial transformation of quinotoxine (**156**) to quinine (**136**), that these reservations were essentially laid to rest once and for all by the mainstream academic community.[47]

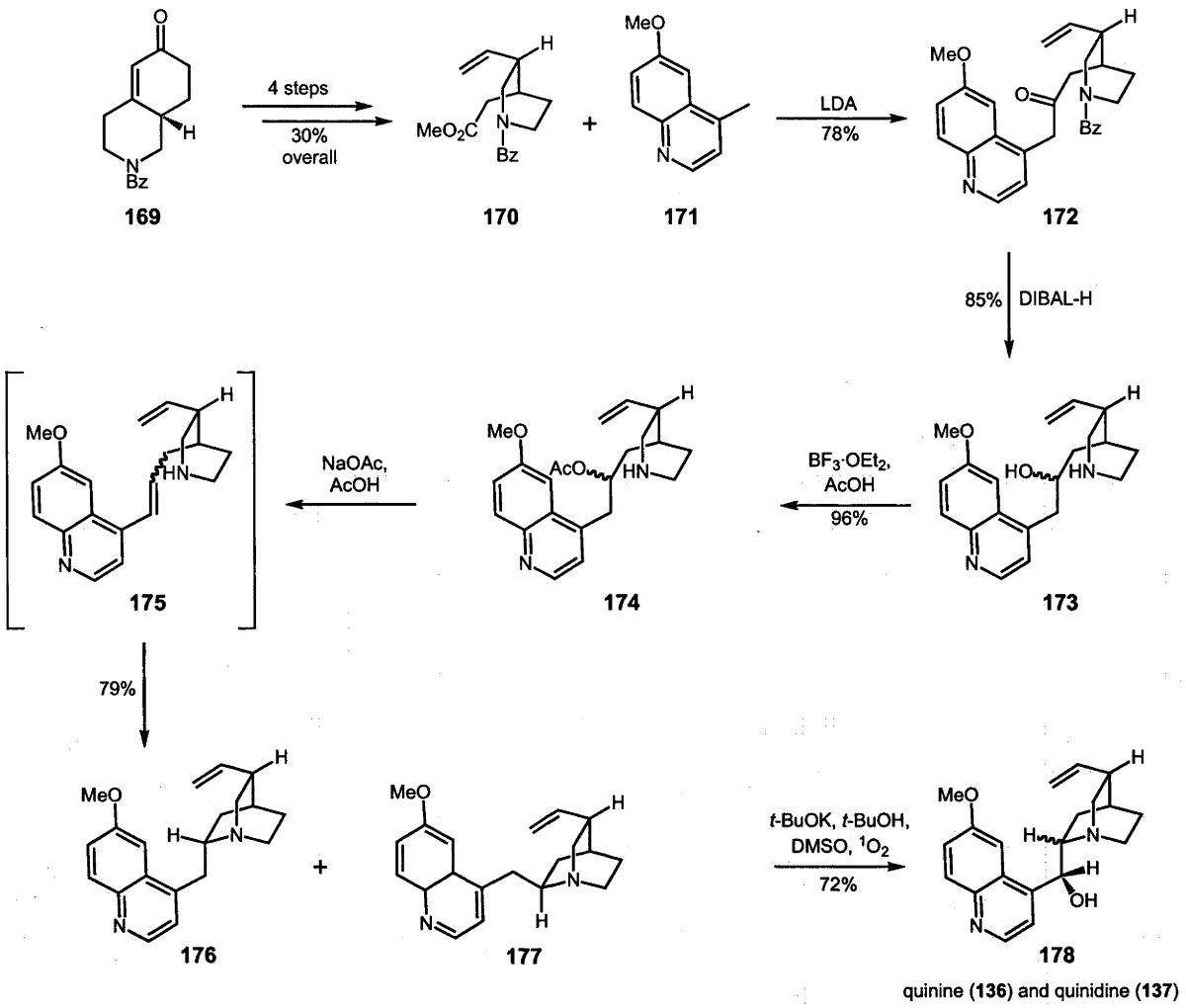
3.2.4 *Total Syntheses of (±)-Quinine: Uskoković (1970-1978)*

The next chapter in the epic story of quinine was written during the 1970s, and was the result of a thorough investigation, undertaken over more than a decade, by a team of researchers at the Hoffmann-La Roche Pharmacetical Group led by Milan Uskoković. The ultimate aim of such work was to develop a viable route to the valuable natural product allowing for its large-scale production, in addition to the preparation of novel analogues as potential antimalarial drug candidates. This rigorous and in-depth study focussed on the Rabe route to quinine, presumably because of the attractive structural simplification the N-C_8 disconnection ostensibly offered, and would come to illustrate the significant difficulties with such an approach.

The first total synthesis of quinine developed by the Hoffmann-La Roche workers, (Scheme 3.2.4) began with the stereoselective preparation of racemic *N*-benzoylmeroquinene methyl ester (**170**). This was achieved in four steps from the readily accessible *N*-benzoylhexahydroisoquinolone **169**.[⊥48] An LDA-promoted condensation of this 1,2-*cis*-functionalised piperidine and 6-methoxylepidine (**171**) led to *N*-benzoylquinoxtine (**172**).[49] A subsequent global reduction provided a mixture of diastereomeric alcohols **173**, which after resolution, enabled the isolation of the required 3*R*,4*S*-enantiomer. Chemoselective acetylation led to compound **174** which was then converted into desoxyquinine (**176**) and its C_8 epimer desoxyquinidine (**177**). These were obtained in a 57:43 ratio. This reaction proceeded *via* alkenylquinoline intermediate **175**, which was the product of *in situ* acetate elimination. A subsequent intramolecular conjugate addition process provided the observed products.[Ω]

[⊥] A partial synthesis of quinine was disclosed simultaneously by Gates, M. Sugavanam , B. Schreiber, W.L. *J. Am. Chem. Soc.*, **1970**, *92*, 205.

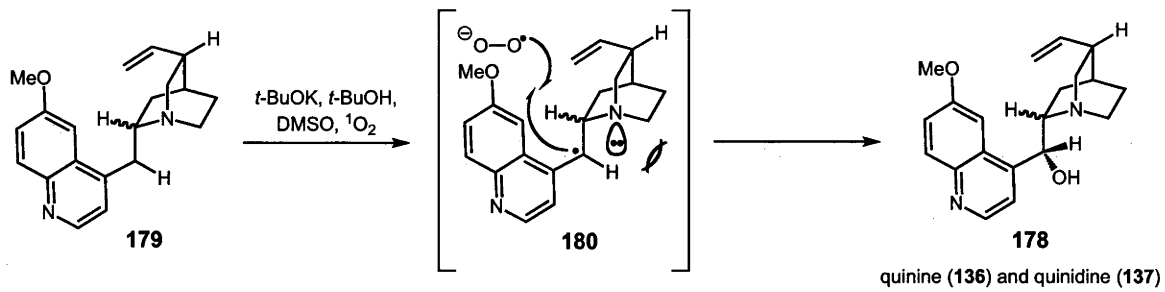
[Ω] Exposure of either pure desoxyquinine (**176**) or desoxyquinidine (**177**) to the reaction conditions provided a 1:1 mixture of C_8 isomers.



Scheme 3.2.4. *The first total synthesis of (±)-quinine (136) achieved by Uskoković and co-workers in 1970.*

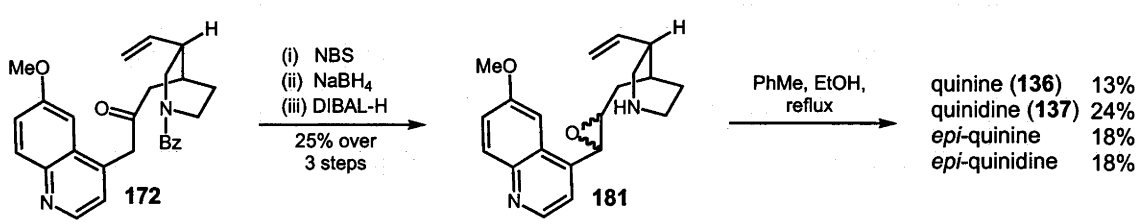
The entire synthetic strategy was predicated upon the hypothesis that in the final step the C_9-hydroxy group would be installed in a highly selective fashion. To that end, Uskoković and Gutzwiller employed *t*-BuOK and triplet oxygen to promote the autooxidation of desoxyquinine (**176**) and its C_8 epimer, desoxyquinidine (**177**), to provide a mixture consisting primarily of quinine (**136**) and quinidine (**137**), with a stereoselectivity of approximately 5:1 (Scheme 3.2.5). This result is presumed to occur because of the preference of the oxygen radical anion to approach intermediate **180** such that it avoids the repulsive force of the lone pair of electrons on the quinuclidine nitrogen.[50] Indeed, this process represents an extraordinary example of 1,2-asymmetric induction that does not involve carbonyl chemistry.[2a] Four years later, in 1974, Edward Taylor and Stephen Martin reported a selective synthesis of quinine that employed a similar strategy to that of the Hoffmann-La Roche researchers, including the abovementioned autooxidation process. However, their

sequence also lacked control of the C_8 stereocentre.[51] The highly selective final step also guided Gilbert Stork's approach to quinine and enabled his group to establish the first stereoselective total synthesis of the *Cinchona* alkaloid some three decades later.[34]



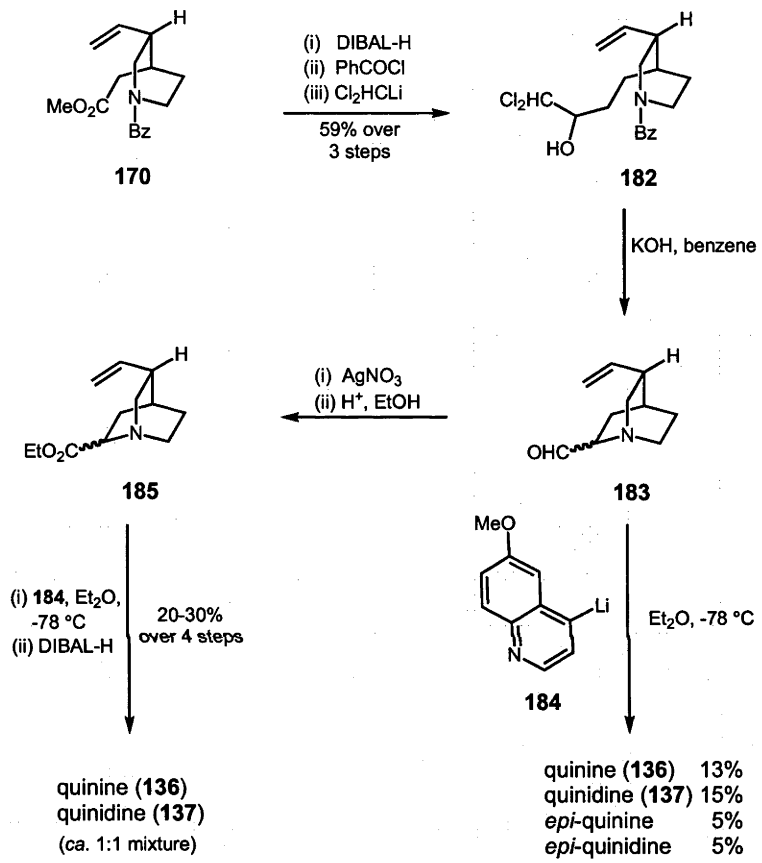
Scheme 3.2.5. *The mechanism proposed for the stereoselective oxidation of desoxyquinine (176) to quinine (136).*

The second route to quinine undertaken by Uskoković and his team lacked the elegance, efficiency and selectivity of their previous approach. Although the fundamental strategy was brilliant, their inability to selectively prepare epoxide **181** meant that the creation of the C_8 and C_9 stereocentres could not be controlled (Scheme 3.2.6). After bromination of *N*-benzoylquinoxtine (**172**), reduction of the resultant α-bromoketone formed a mixture of bromohydrins which spontaneously cyclised to provide epoxide **181**.[52] However, this sequence was low yielding and generated all four possible epoxides. Deprotection of the benzoyl group, followed by the thermally-assisted nucleophilic ring opening of the epoxide and concomitant cyclisation provided quinine (13%) in addition to the three other possible C_8 and C_9 diastereoisomers. While this approach was subject to improvement, complete selectivity could not be achieved.[50] Although not an efficient route at the time, this strategy would later be independently employed more successfully by both Eric Jacobsen and Yuichi Kobayashi in their respective stereoselective total syntheses of quinine disclosed in 2004.[53,54]



Scheme 3.2.6. *Synthesis of (±)-quinine (136) by the aminoepoxide ring closure approach achieved by Uskoković and co-workers in 1973.*

The third approach to quinine by the Hoffmann-La Roche group, which persisted with the Rabe strategy, unfortunately still lacked control of the C_8 and C_9 centres.[55] This new route involved the condensation of racemic aldehyde **183**, prepared in a short sequence from *N*-benzoylmeroquinene methyl ester (**170**), with lithiated quinoline **184** (Scheme 3.2.7). All four possible C_8 and C_9 diastereoisomers were isolated in a low yielding final step and a similar, albeit more selective, result was obtained by employing ethyl ester **185**.



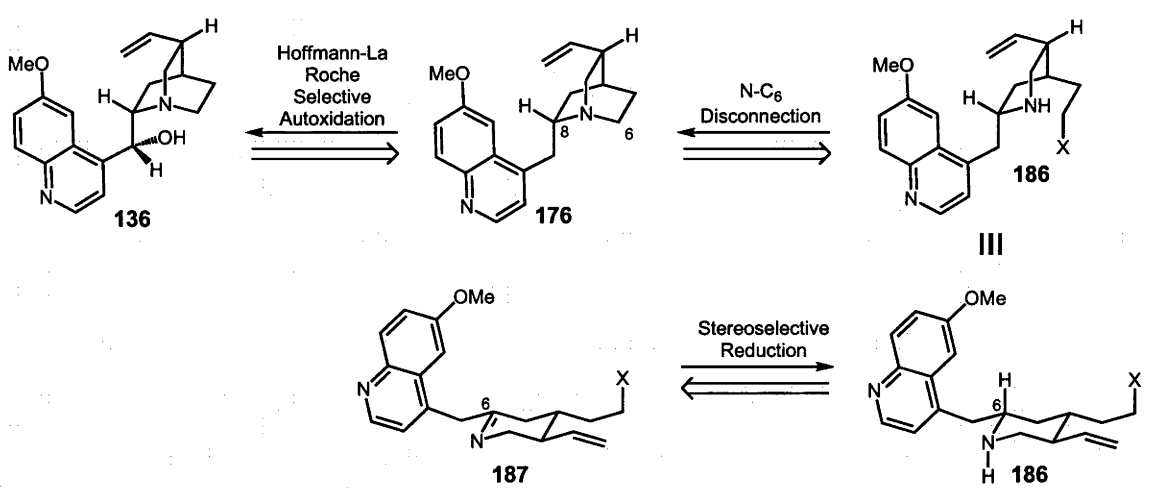
Scheme 3.2.7. *Synthesis of (±)-quinine (136)* via *the late stage installation of the quinoline substituent achieved by Uskoković and co-workers in 1978.*

Uskoković and co-workers were able to construct the quinuclidine core of quinine efficiently and somewhat selectively and their long study significantly contributed to a greater understanding of the synthetic challenges associated with preparing the natural product. Impressively, this extensive work provided three separate, stereocontrolled, if not completely stereoselective, approaches to quinine. That every subsequent synthesis of the elusive *Cinchona* alkaloid was influenced or guided by the outcomes of this long-running investigation is testament to the scope and quality of the research undertaken by Uskoković and his colleagues. Their findings certainly highlighted the inability to control stereochemistry, particularly at the C_8 position by employing the Rabe approach to quinine

and dictated that the solution to this complex synthetic problem would ultimately require a significant departure from this traditional and well-explored strategy.[⊥]

3.2.5 *Total Synthesis of (-)-Quinine: Stork (2001)*

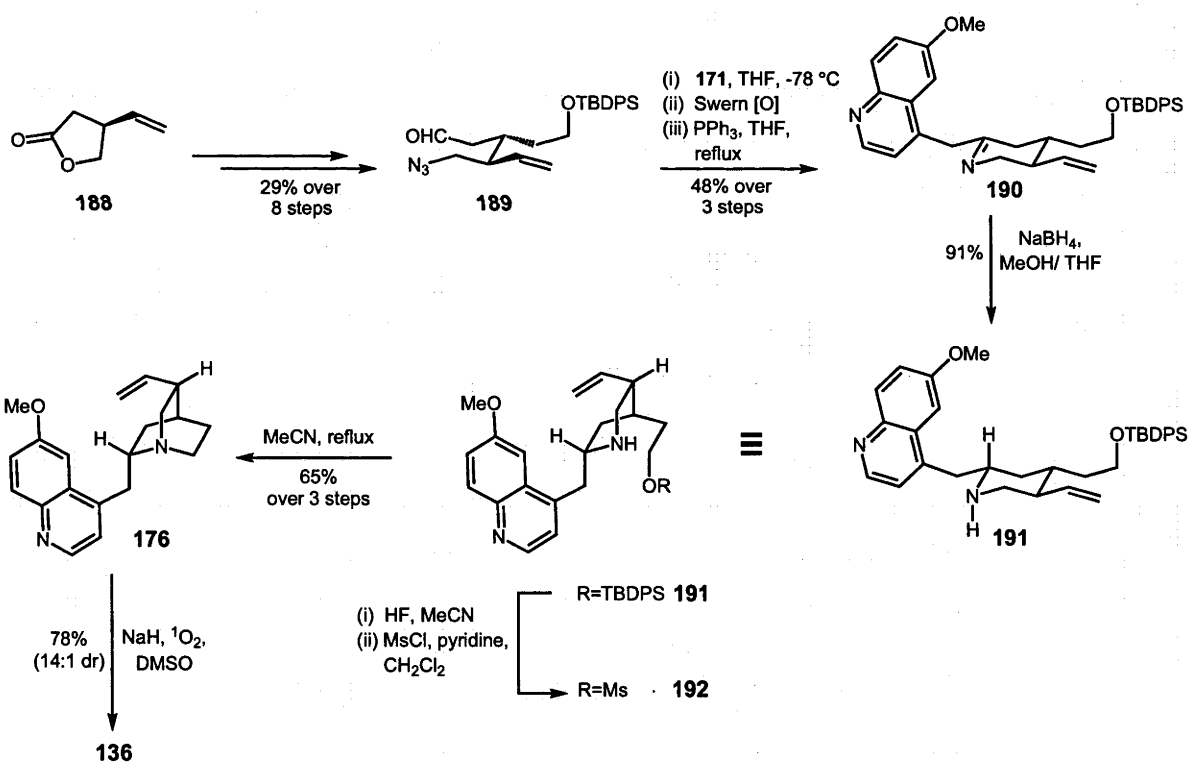
The aforementioned selective autooxidation reported by the Hoffmann-La Roche group[49] was duly noted by the Gilbert Stork, who realised that if a stereospecific synthesis of desoxyquinine (**176**) could be effected, it then followed that a stereoselective synthesis of quinine could finally be achieved. Consequently, Stork proposed abandoning the time-honoured Rabe route and adopting an original N-C_6 disconnection to construct the quinuclidine skeleton, thus avoiding the well-established pitfalls associated with the traditional method (Scheme 3.2.8). On the face of it this approach ostensibly provided more challenges than improvements - primarily, the more demanding stereoselective synthesis of a trisubstituted-piperidine as opposed to the requisite disubstituted-intermediate associated with the N-C_8 strategy. Robert Ireland's maxim that, "*All too often the most convenient way to draw a molecule on paper belies the most efficient synthetic approach,*" seemed appropriate in this instance.[2b] Indeed, representing piperidine **186** in its chair form clearly illustrates the logic behind this new approach - all three substituents are equatorially orientated in order to minimise 1,3-diaxial interactions. Accordingly, Stork predicted that the C_8 stereocentre might arise from the delivery of a hydride equivalent onto imine precursor **187** in an axial fashion.



Scheme 3.2.8. *The unprecedented N-C_6 disconnection proposed by Stork.*

[⊥] This was indeed true at that time when asymmetric catalysis was still in its embryonic state.

Fittingly, after inexorably working towards this goal on and off for over half a century the pioneer of stereocontrolled synthesis was ultimately successful. In 2001 Gilbert Stork disclosed the landmark first stereoselective total synthesis of (-)-quinine (**136**) that some would say he was destined to complete.[34] The sequence began with Taniguichi's chiral lactone (**188**)[⊥56] and a series of meticulously planned and well-executed transformations efficiently provided azido aldehyde **189** in 29% over 8 steps (Scheme 3.2.9). Condensation with 4-lithio-6-methoxylepidine (**171**),[50] followed by a Swern oxidation and a subsequent Staudinger reduction with concomitant cyclisation generated the strategically important imine **190**. As anticipated, axial hydride delivery formed trisubstituted-piperidine **191** stereoselectively, thus securing the lynchpin of this bold approach and the total synthesis was a *fait accompli*. The ensuing conversion of silyl ether **191** to mesylate **192** was followed by cyclisation to furnish desoxyquinine (**176**) in a completely selective manner. In the final step a variation of the Hoffmann-La Roche autooxidation protocol[49] selectively afforded (-)-quinine (**136**) in 78% yield. This was accompanied by only the smallest amounts of *epi*-quinine.



Scheme 3.2.9. *The first completely stereoselective total synthesis of (-)-quinine (136) achieved by Stork and co-workers in 2001.*

[⊥] Readily prepared by the condensation of but-2-ene-1,4-diol and triethylformate and obtained in optically pure form following resolution employing (*S*)-(-)-α-methylbenzylamine.

Stork's fully stereoselective synthesis of the celebrated *Cinchona* alkaloid, in a total of 16 steps (from Taniguichi's lactone) and 6% overall yield, by a route that conspicuously did not require modern or expensive reagents, validated the conceptual uniqueness and retrosynthetic novelty of his intrepid plan. Indeed, the widely acknowledged artistry and elegance of this inexorable approach[45] brought Paul Wender to compare it to a ballet: *"An inexperienced observer of a great performance might leave with a view that there are no new steps. But one schooled in the field will see an exquisite choreography, the remarkable timing, the efficiency of execution, and the economy of movement - and leave inspired."*[45a] This milestone total synthesis decisively solved a problem that had haunted chemistry for over 150 years and its significance transcended that of quinine itself. In fact Stork himself reflected that, *"The value of a quinine synthesis has essentially nothing to do with quinine. It is like the solution to a long-standing proof of an ancient theorem in mathematics: it advances the field."* [34]

3.2.6 *Total Synthesis of (-)-Quinine: Jacobsen (2004)*

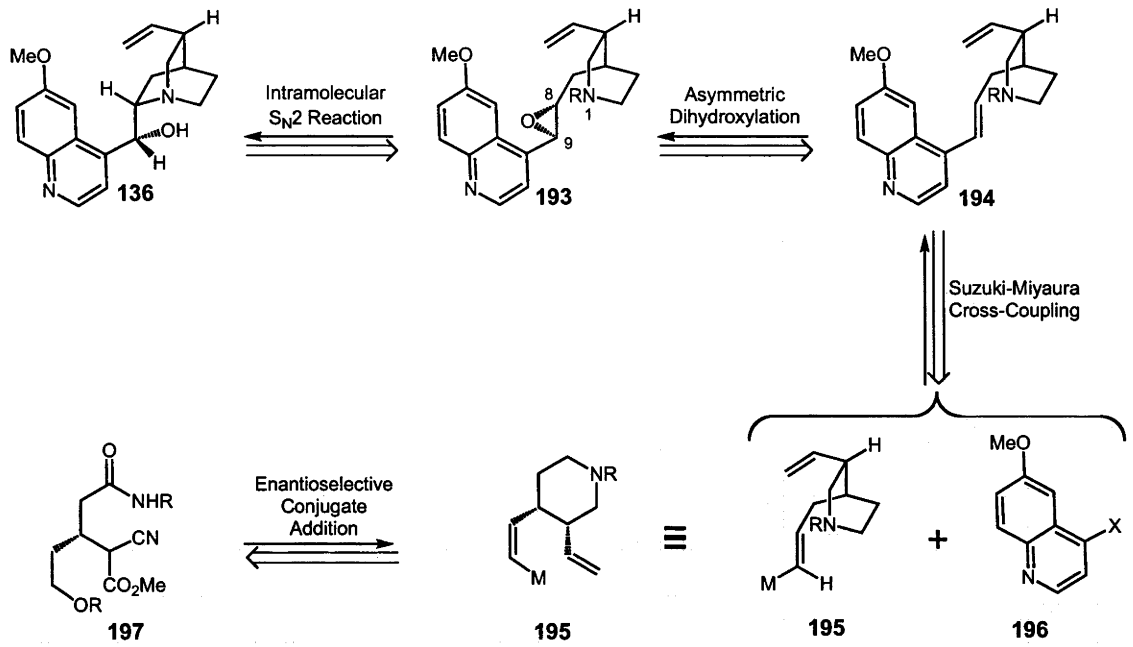
Three years after Stork's pioneering work Eric Jacobsen and co-workers reported the catalytic and asymmetric total syntheses of quinine (**136**) and quinidine (**137**), employing an impressive strategy that featured the legendary Rabe connection in a particularly efficient sequence.[53] This enabled the simultaneous control of the configuration at the C_8 and C_9 stereocentres. The ensuing enantiodivergent approach relied upon four fundamental bond-forming processes to selectively construct the target *Cinchona* alkaloid (Scheme 3.2.10):

(i) catalytic enantioselective conjugate addition to construct the C_4 stereocentre;

(ii) coupling of piperidine **195** with quinoline **196** by a Suzuki-Miyaura process;

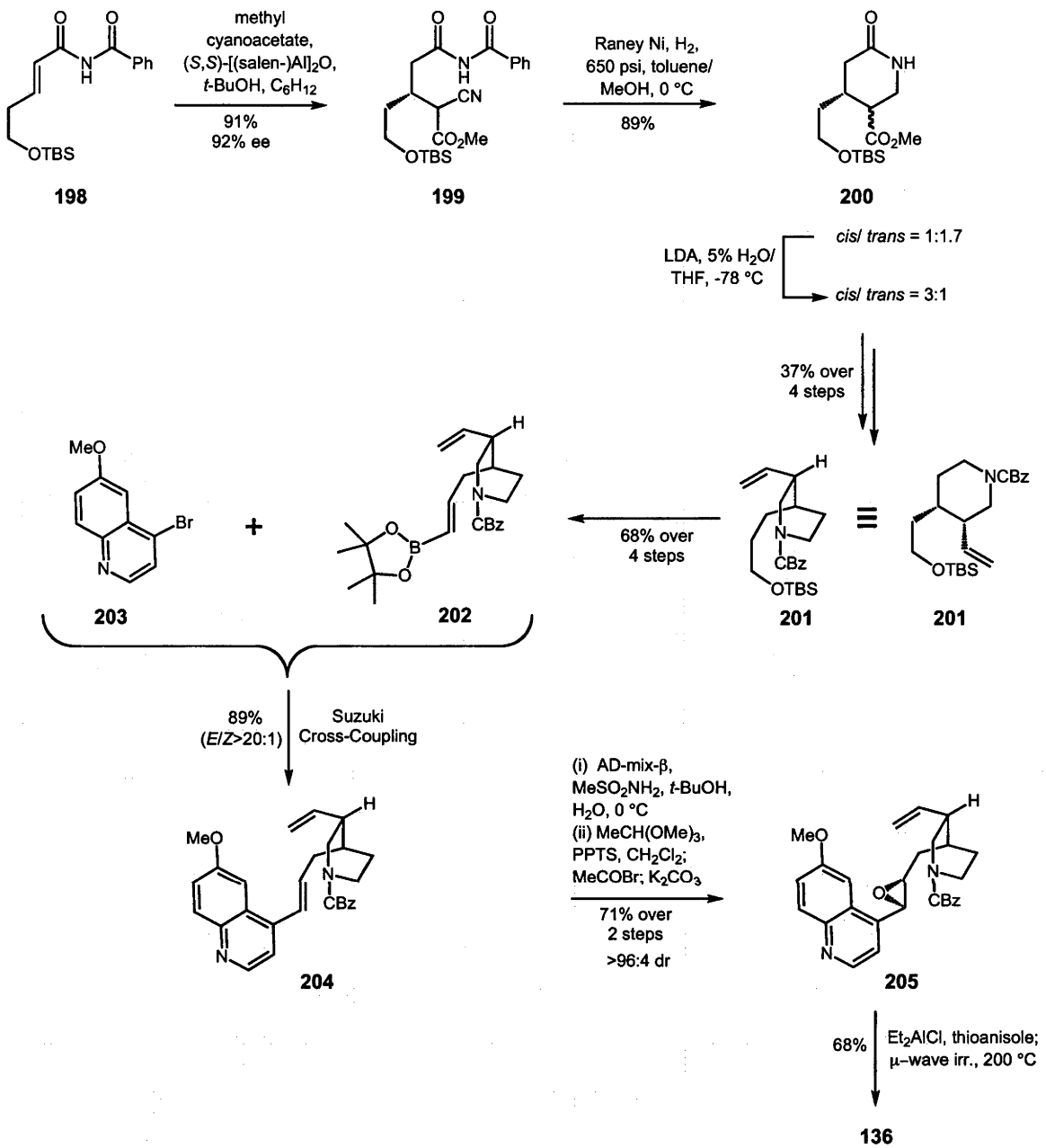
(iii) an asymmetric dihydroxylation to establish the C_8 and C_9 stereocentres;

(iv) and finally an aminoepoxide cyclisation to form the quinuclidine ring without the loss of stereochemistry at the C_8 centre.



Scheme 3.2.10. *Retrosynthetic analysis of (-)-quinine (136) by Jacobsen.*

The synthesis began with α,β-unsaturated imide **198** which was prepared, with high (*E*)-selectivity and in 84% chemical yield, by a Horner-Wadsworth-Emmons olefination (Scheme 3.2.11). The enantioselective conjugate addition of methyl cyanoacetate catalysed by a (salen)-aluminium complex then afforded compound **199** which, after a hydrogenative cyclisation, led on to lactam **200** with an undesirable 1:1.7 diastereomeric ratio of *cis*/*trans* isomers. A protonation/deprotonation sequence led to selective formation of the desired diastereoisomer with a 3:1 *cis*/*trans* ratio. A number of functional group manipulations eventually provided pinacolatoboronic ester **202** and a Suzuki-Miyaura cross-coupling with quinoline **203** then selectively delivered (*E*)-alkenyl quinoline **204**. Jacobsen and co-workers subsequently effected a Sharpless asymmetric dihydroxylation (AD) that ironically, employed the dihydroquinidine (**139**)-based AD-mix-β.[57] The product diol thus formed was converted into epoxide **205** and cleavage of the carbazole protecting group was followed by a μ-wave-assisted nucleophilic attack involving the resultant secondary amine to furnish the quinuclidine framework and thus quinine (**136**). This approach ultimately provided the natural product in 16 steps and a 5% overall yield.



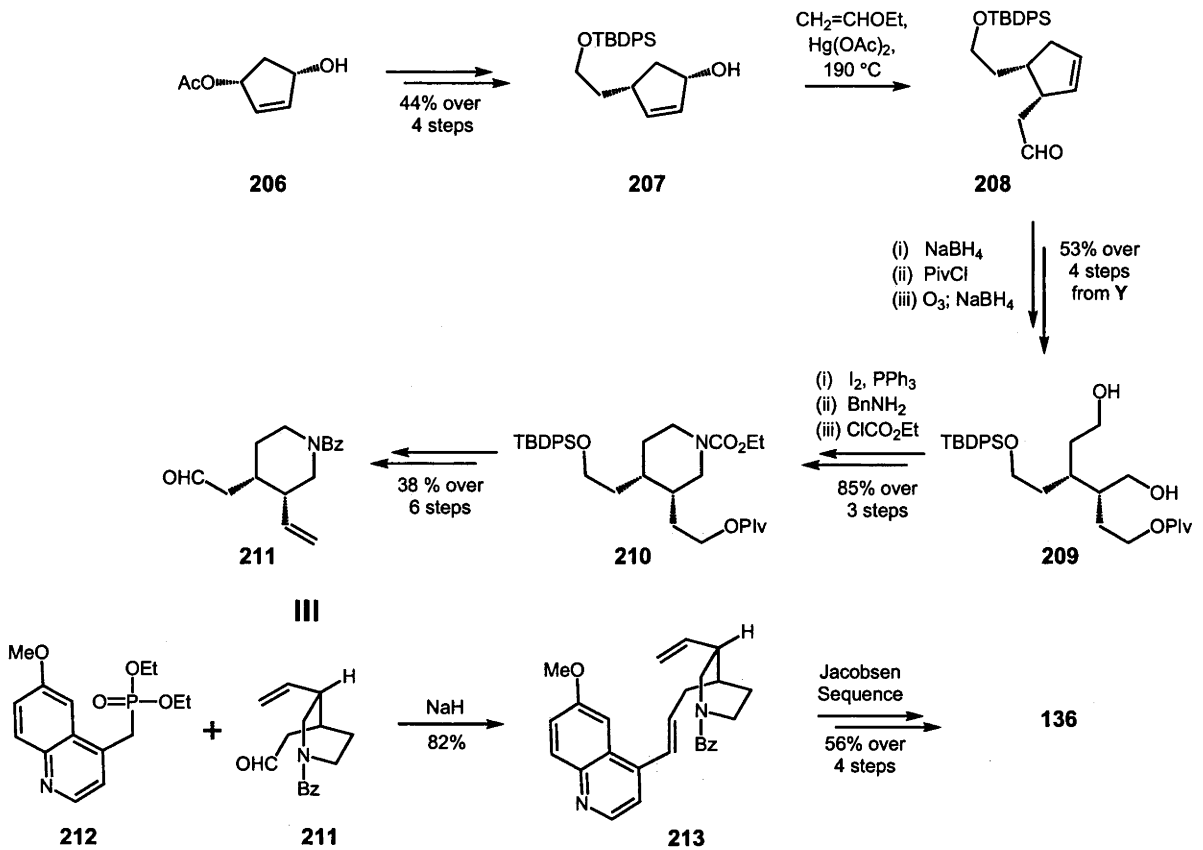
Scheme 3.2.11. *The catalytic asymmetric total synthesis of (-)-quinine (136) achieved by Jacobsen and co-workers in 2004.*

Impressively, this approach also allowed for the preparation of quinidine (**137**) by simply replacing AD-mix-β with the dihydroquinine (**138**)-based AD-mix-α as the chiral catalyst in the key dihydroxylation step. This total synthesis, like Stork's, benefited from the aforementioned earlier research by Uskoković and his group. Certainly, Jacobsen's fundamental strategy could be viewed as an asymmetric adaptation of the aminoepoxide cyclisation approach employed in the Hoffmann-La Roche group's second total synthesis of quinine (Scheme 3.2.6).[50,52] By establishing this selective route to the *Cinchona* alkaloid,

exploiting asymmetric catalytic processes and using modern and sophisticated reagents with aplomb, Jacobsen illustrated the progress that has been made in organic synthesis by the development of new synthetic methodology over the past thirty years. Recently, Krische and Webber[58] completed a formal total synthesis of (±)-quinine, preparing Jacobsen's alkenylquinoline intermediate **204**, *via* a merged Morita-Baylis-Hillman-Tsuji-Trost cycloallylation reaction.

3.2.7 *Total Synthesis of (-)-Quinine: Kobayashi (2004)*

Shortly after the abovementioned work by the Jacobsen Group was disclosed, Yuichi Kobayashi and co-workers reported the third stereocontrolled total synthesis of quinine (**136**) in which the quinuclidine framework of the natural product was prepared employing an analogous reaction sequence from the very similar (*E*)-alkenyl quinoline **212** (Scheme 3.2.12).[54a] However, the route to intermediate **212** exploited a much more classical synthetic approach than that employed by Jacobsen. Thus, the Kobayashi approach began with the known and easily accessible chiral monoacetate **206**[59] and various functional group manipulations then afforded alcohol **207** in 44% yield over 4 steps. After conversion to the corresponding vinyl ether, aldehyde **208** was prepared *via* a Claisen rearrangement, and this compound was subsequently transformed into diol **209** by a three-step sequence employing standard methods. Further elaboration provided piperidine **211** from which key alkenyl quinoline substrate **213** was secured, in 82% yield, through a Horner-Wadsworth-Emmons olefination. A very similar sequence to Jacobsen's then provided the target *Cinchona* alkaloid and this longer and less sophisticated approach ultimately provided quinine in 22 steps (from monoacetate **206**) and 3.5% overall yield. In 2005 Kobayashi and Igarashi reported an improved total synthesis of quinine that allowed for the more efficient preparation of the natural product by employing the Teoc-protected analogue of piperidine **211**.[54b]

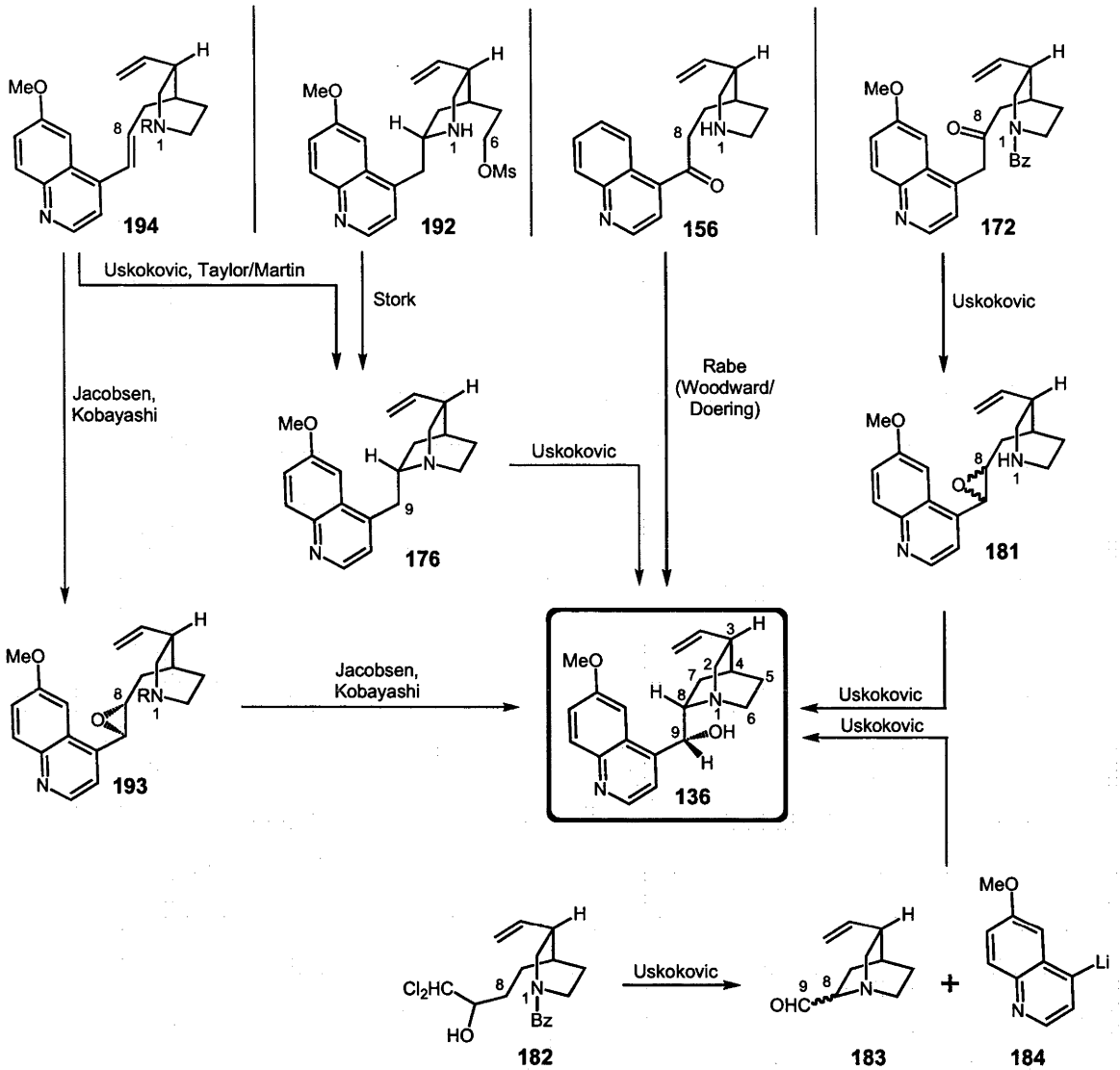


Scheme 3.2.12. *The stereoselective total synthesis of (-)-quinine (136) achieved by Kobayashi and co-workers in 2004.*

3.2.8 *Summary of the Successful Approaches to Quinine*

There have been a number of syntheses of quinine (**136**) by approaches that have evolved over the past century.[⊥] These routes are summarised in Scheme 3.2.13.[60] Interestingly, all but one of these many investigations, the Stork synthesis,[34] has employed the Rabe disconnection to prepare the natural product. Furthermore, only three of the various studies, those of Stork,[34] Jacobsen[53] and Kobayashi,[54] all of which were completed in the twenty-first century, were fully stereocontrolled. Indeed, these three impressive approaches allowed for highly selective, atom-economical and efficient syntheses of quinine. The shortest of these is Jacobsen's enantiodivergent approach, which succeeds in constructing the *Cinchona* alkaloid in a remarkable 16 steps and 5% overall yield.[Ω] Accordingly, as a target (-)-quinine (**136**) could be viewed as a barometer of the state of organic synthesis over the past century.

[⊥] All of these were discussed or at least referred to in the preceding sections.
[Ω] Jacobsen's is also the only one of the three strategies that does not employ a chiral starting material.



Scheme 3.2.13. *Summary of the multiple approaches to the total synthesis of quinine (136).*

3.3 Towards a Total Synthesis of (-)-Quinine

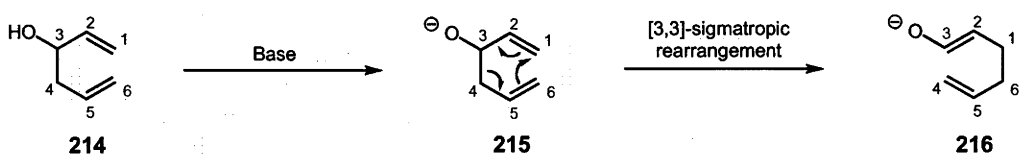
3.3.1 The C_3-C_4 Approach

As alluded to earlier, only three successful stereoselective approaches to (-)-quinine (**136**) have been achieved over the past 150 years and these featured the formation of the quinuclidine core by either Stork's novel N-C_6 disconnection[34] or the more traditional Rabe N-C_8 route.[53,54] Accordingly, the stereocontrolled synthesis of quinine that is proposed on the following pages seeks to exploit an unusual and wholly unprecedented anionic oxy-Cope rearrangement in constructing the 1-azabicyclo[2.2.2.]octane framework of the natural

product. This anticipated process would allow for a synthesis of the celebrated *Cinchona* alkaloid by what is essentially a C_3-C_4 strategy, and thereby clearly differentiating this work from the many approaches that have preceded it.[⊥]

3.3.3 *The Anionic Oxy-Cope Rearrangement*

The observation that the oxy-Cope rearrangement,[61] a [3,3]-sigmatropic process, may be facilitated by forming the appropriate oxy-anion was first reported by Evans and Golob in 1975 (Scheme 3.3.1).[62] Indeed, the capacity to effect transmission of stereochemistry with high fidelity,[Ω] as a consequence of a highly ordered cyclic, chair-like transition state,[Ψ] makes this process ideally suited to the predictable formation of many stereochemically complex compounds.[63,64] Both the thermal and anionic oxy-Cope variants share an irreversibility that distinguishes them from classical Cope reactions and extends their overall utility well beyond that customarily available to classical [3,3]-sigmatropic processes.[63] In the first case this stems from the greater thermodynamic stability of a carbonyl group relative to a C-C double bond. In the anionic oxy-Cope rearrangement, the formation of the resonance stabilised enolate anion **216** renders the process irreversible and also offers extraordinary rate enhancements of between 10-17 orders of magnitude relative to the parent process.[62,65] Potassium bases are typically used, and 18-crown-6 employed to effect greater charge separation, by sequestering the potassium cation, and thus maximising the rate acceleration. These features enable the base-promoted reaction to occur at moderate temperatures[ξ] and as a result, a wide range of functional groups may be tolerated, thereby greatly enhancing the utility of this reaction by allowing for the synthesis of multifunctional organic compounds.[63,64]



Scheme 3.3.1. *The anionic oxy-Cope rearrangement.*

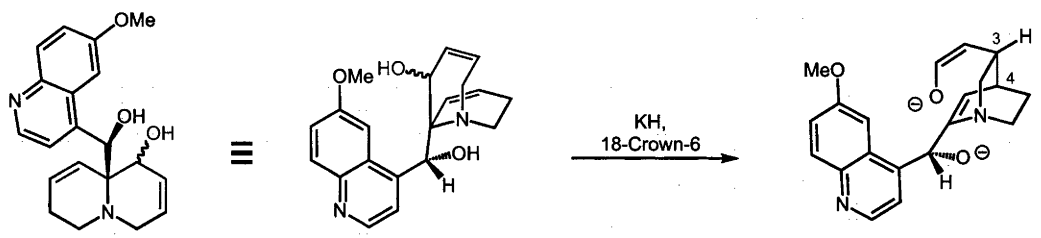
[⊥] The synthesis of 7-hydroxyquinine, featuring an unrelated C_3-C_4 disconnection, has been reported: Johns, D.M.; Mori, M.; Williams, R.M. *Org. Lett.*, **2006**, *8*, 4051.

[Ω] The anionic oxy-Cope rearrangement, like the parent Cope and oxy-Cope processes, is both stereospecific and stereoselective.

[Ψ] A boat-like transition state is energetically accessible if structurally imposed by the substrate.

[ξ] Anionic oxy-Cope rearrangements typically occur at temperatures between 60–100 °C while the parent thermal processes often require temperatures well in excess of 100 °C.

The abovementioned properties of the title rearrangement prompted its use in the present work. It was anticipated, in this unprecedented C_3-C_4 approach to quinine, that quinolizine **217** could, under suitable conditions, engage in the title rearrangement to form quinuclidine **218** (Scheme 3.3.2). Certainly, the high expectations held for this rearrangement, as the key step in constructing the fundamental 1-azabicyclo[2.2.2.]octane framework of quinine, appear legitimate as demonstrated in the following sections.



217 **217** **218**

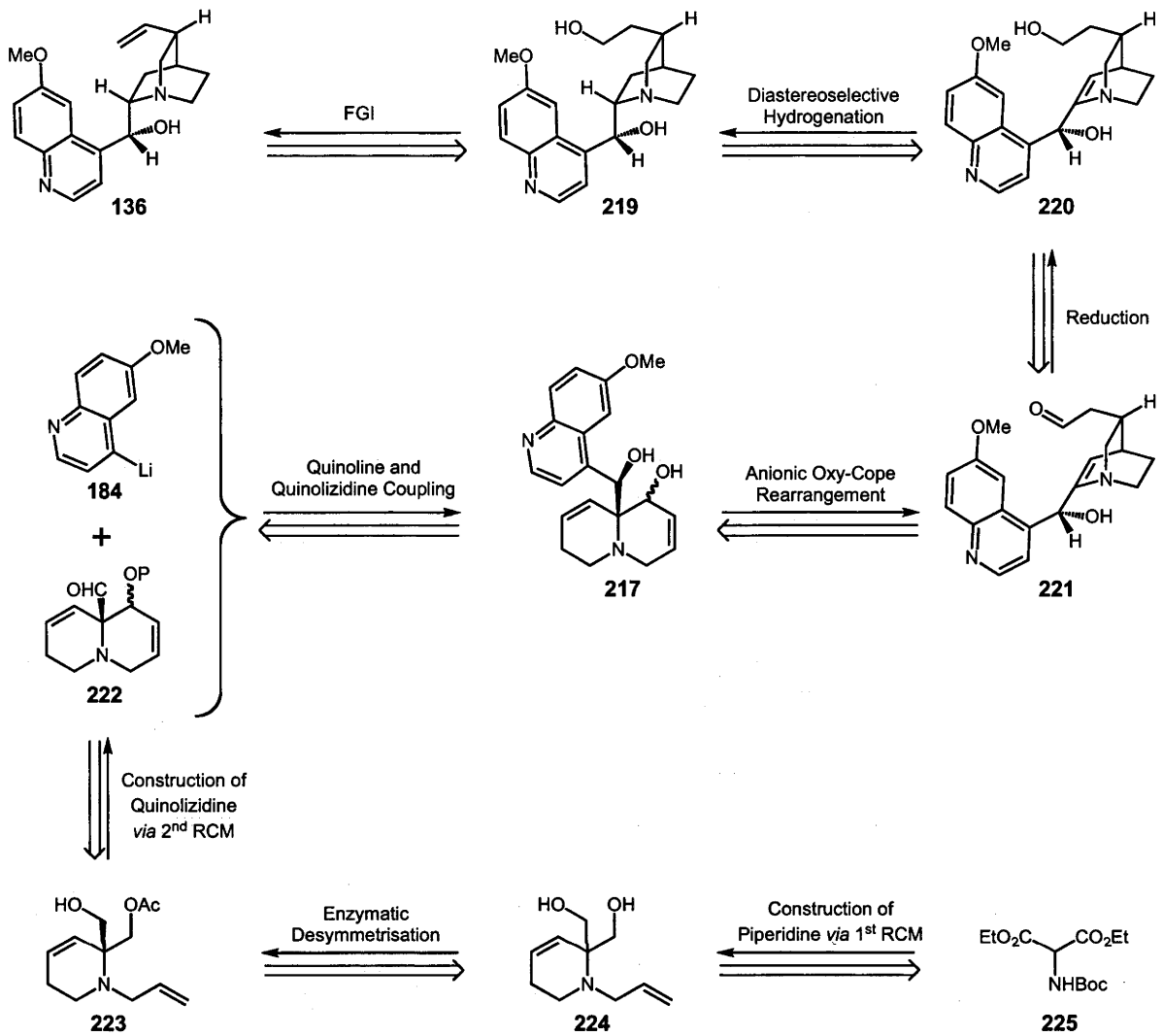
Scheme 3.3.2. *The pivotal anionic oxy-Cope rearrangement required to prepare the 1-azabicyclo[2.2.2.]octane framework of (-)-quinine (**136**).*

3.3.3 Retrosynthetic Analysis

(-)-Quinine (**136**) contains only four stereocentres,[⊥] however, the considerable challenges associated with their installation, particularly at the C_8 and C_9 positions, is well documented.[2a,b] These difficulties guided the synthetic strategy that was adopted here. In a reverse sense the proposed stereoselective approach to the *Cinchona* alkaloid required that it be prepared *via* a straightforward functional group interconversion from quinuclidine **219** (Scheme 3.3.3). It was anticipated that intermediate **219** would, in turn, be derived from the diastereoselective hydrogenation of unsaturated precursor **220**, by a transformation that would selectively create the stereochemistry at C_8.[Ω] Diol **220** would conceivably result from the reduction of aldehyde **221** - the expected product of the anionic oxy-Cope rearrangement.

[⊥] The quinuclidine nitrogen and C_4 constitute a single asymmetric unit due to their bridgehead location.

[Ω] This also enables enantiodivergency at a late stage in the sequence as hydrogen delivery from the α-face would allow for the synthesis of quinidine (**137**).



Scheme 3.3.3. *Retrosynthetic analysis of (-)-quinine (136).*

Certainly, this powerful [3,3]-sigmatropic process represents the centrepiece of the present synthetic strategy and in one single step would address a number of stereochemical issues that have dogged earlier routes to (-)-quinine (**136**):

(i) by mechanistic necessity the aldehyde residue in the rearrangement product **221** is established with the stereochemistry required for its ultimate elaboration into the vinyl group at the C_3 position (Scheme 3.3.2);

(ii) simultaneously, the requisite stereochemistry of the N-C_4 asymmetric unit is created;

(iii) and also the sidechain at the C_8 position featuring the 6-methoxyquinoline substituent is installed.

Moreover, either epimeric form of quinolizidine **217** can react affording quinuclidine **221** and one additional stereocentre (C_3) is essentially created for 'free' as a consequence of the pivotal process. It was envisaged that key substrate **217** involved in the anionic oxy-Cope rearrangement could be prepared *via* the condensation of quinoline **184** and quinolizidine **222**. The decision to incorporate the requisite quinoline motif prior to the formation of the quinuclidine framework was guided by the aforementioned outcomes of the third total synthesis of quinine (**136**) disclosed by Uskoković and co-workers that illustrated it could not be installed stereoselectively at a later stage.[55] Angularly substituted quinolizidine **222**, featuring the two well defined double bonds required to participate in the pivotal [3,3]-sigmatropic process was anticipated to originate from piperidine **223** through a sequence that ultimately exploits a RCM reaction.[⊥66] Chiral monoacetate **223** was expected to arise from the enzymatic desymmetrisation of prochiral 1,3-diol **224**, which itself would be derived from another RCM procedure. This strategy would begin with the commercially available and inexpensive 2-[*N*-(*tert*-butoxycarbonyl)amino]-malonate (**225**).

3.4 Aims of the Research Described in Part Two of this Thesis

In light of the foregoing discussion it is clear that the completely stereocontrolled preparation of (-)-quinine (**136**) offers tremendous challenges as a synthetic target. That this epic feat was only achieved in 2001 certainly underscores this and reflects the difficulty such a task presents.[34] Accordingly, a novel and ambitious approach featuring an unprecedented method for constructing of the quinuclidine core of the celebrated *Cinchona* alkaloid was conceived. Thus, the aim of the research described in the second part of this thesis was to produce an original and stereoselective total synthesis of quinine (**136**) by exploiting the anionic oxy-Cope rearrangement to construct the 1-azabicyclo[2.2.2.]octane framework of the natural product (Scheme 3.3.2). Consequently, establishing an efficient route to the required quinolizidine substrate **222**, and promptly testing the validity of this fundamental proposal was crucial. Such endeavours, and the ultimate success or otherwise of the general synthetic strategy, are described in Chapters Four, Five and Six.

[⊥] Indeed, the construction of quinolizidine **222** without relying on metathesis processes to install at least one of the double bonds is difficult to contemplate.

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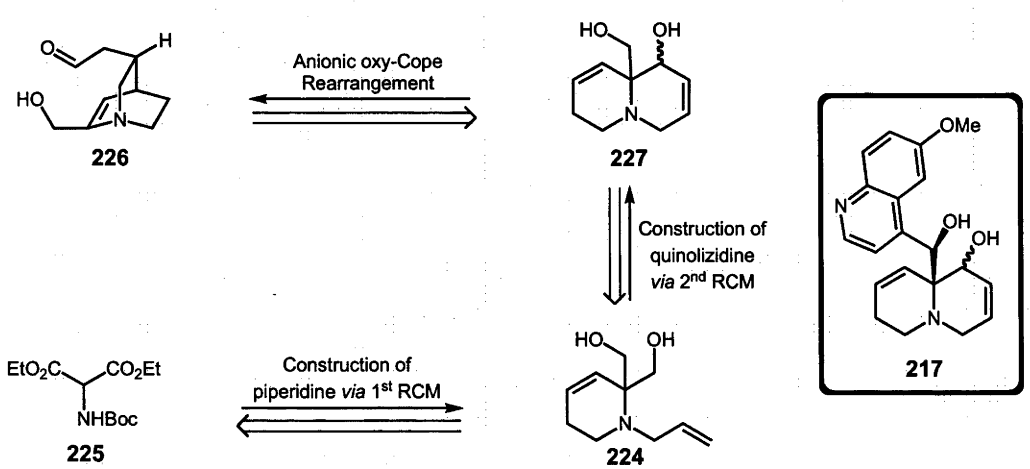
Chapter Four

Developing an Original Approach to (-)-Quinine

This chapter describes the development of a synthetic route to quinolizidines **245**, **246**, **256** *and* **257**. *The capacity of these substrates to engage in the pivotal anionic oxy-Cope rearrangement was comprehensively investigated and the outcomes of this study are discussed. The formation of lactol* **248** *supported the fundamental proposal and indicated that the key transformation could indeed form the centrepiece of an unprecedented total synthesis of (-)-quinine (***136**).

4.1 Introduction

As noted in the preceding chapter, the proposed but unprecedented anionic oxy-Cope rearrangement of quinolizidine **217** completely underpinned the success of the proposed route to (-)-quinine (**136**) (Scheme 3.3.2). Thus, it was particularly important to test the validity of this key step before directly focussing on synthesising the final target. To this end quinolizidine **227** (Scheme 4.1.1) was identified as a relevant model system from which the transformation's potential to construct the 1-azabicyclo[2.2.2.]octane framework of (-)-quinine (**136**) could be assessed. Compound **227** was nominated as a suitable structure for two reasons. Firstly, this diol (**227**) represents the least sophisticated, and therefore, the most easily accessible model for key substrate **217**. Secondly, it was likely that this investigation would ultimately aid in any resulting synthesis of intermediate **217** as both were to be derived from piperidine **224** (Schemes 3.3.3 and 4.1.1).



Scheme 4.1.1. *Retrosynthetic analysis of quinuclidine* **226**.

Although it was anticipated that the first stereocentre associated with (-)-quinine (**136**) would arise from the enzymatic desymmetrisation of prochiral diol **224** this process was not investigated in the first instance simply because the principal need was to confirm that substrate **227** could engage in the anionic oxy-Cope rearrangement to provide quinuclidine **226**. Accordingly, the preliminary aim of the research was to prepare quinolizidine **227** in racemic form and then test the validity of the pivotal anionic oxy-Cope rearrangement. The outcomes of such endeavours are discussed below.

4.2 Synthesis of Quinolizidine 227

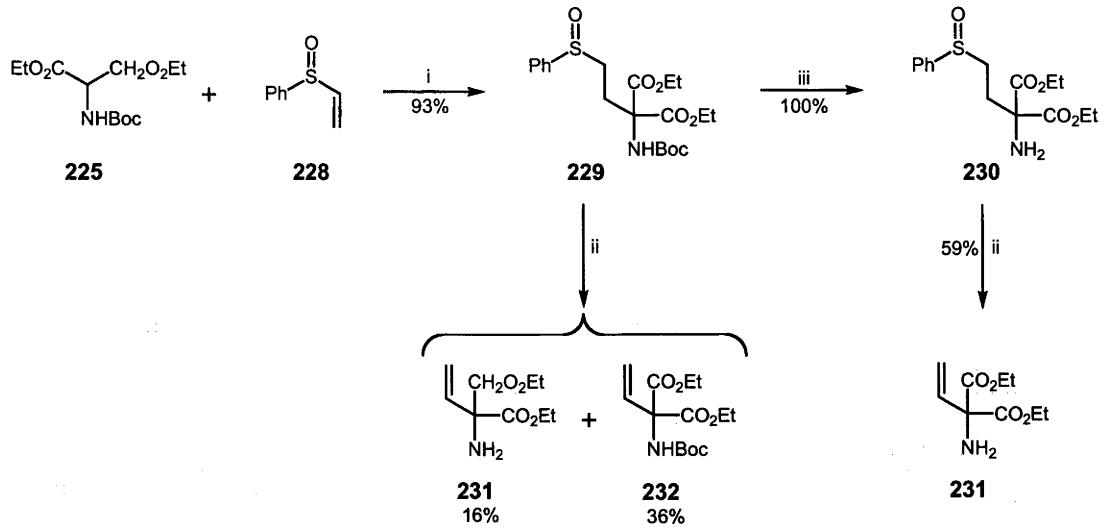
4.2.1 Synthesis of Piperidine 224

The first step of the sequence ultimately leading to target **227** involved the conjugate addition of the anion derived from the commercially available malonate **225** to the similarly accessible vinyl sulfoxide **228** (Scheme 4.2.1). This process provided adduct **229** in 93% yield.[⊥1] The isolation of product **229** by flash chromatography from a number of unidentified impurities was a particularly difficult and tedious exercise partly because the compound is insoluble in many organic solvents which, coupled with the abovementioned purification issues, makes it a rather intractable substance. In the subsequent transformation sulfoxide **229** was heated, neat, at 160 °C for 14 h. This led to the thermal elimination of the elements of phenylsulfenic acid,[Ω] providing Boc-deprotected α-amino-α-vinylmalonate **231** albeit in only 27% yield. Furthermore, this was accompanied by significant quantities of unidentified decomposition products. Interestingly, when the reaction was carried out at 150 °C, for 14 h, only a small amount of desired product **231** could be formed.[Ψ] Sulfoxide **229** was also heated in the presence of pyridine with a view to exploiting the base-promoted variant of this process.[2] In this case, however, only traces of product **232** were observed.[Ψ]

[⊥] This was the first of many instances in which the malonate group within this and subsequent substrates played a role, direct or otherwise, in transformations that ultimately led to quinolizidine **227**.

[Ω] The thermally-induced elimination of phenylsulfenic acid from the acetamido-analogue of compound **229** has been described: Galons, H.; Labidalle, S.; Miocque, M.; Ligniere, B.; Bram, G. *Phosphorous, Sulfur Silicon Relat. Elem.*, **1988**, *39*, 73.

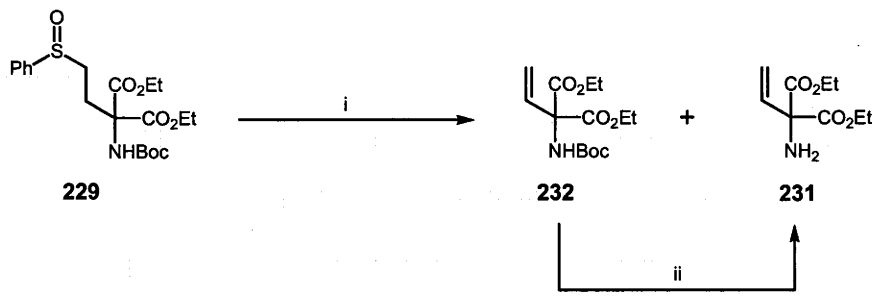
[Ψ] As judged by ^{1}H NMR analysis of the crude reaction mixture.



Scheme 4.2.1. *Synthesis of α-vinylmalonates* **231** *and* **232**.
Reagents and conditions: *(i) NaOEt, 0 → 18 °C; (ii) neat, μ-wave irr., 18 → 160 °C; (iii) TFA, CH_2Cl_2, 0 → 18 °C.*

The thermal elimination of sulfoxides under μ–wave irradiation, employing solvent-free conditions and a basic alumina/KF solid support, has been disclosed.[3] The excellent yields (>90%) and short reaction times (4 min) associated with this protocol prompted an investigation of its utility to provide desired products **231**/**232**. However, upon subjecting compound **229** to such conditions at 160 °C for 0.5 h no significant reaction occurred. In contrast, reacting sulfoxide **229**, neat, in this same fashion, gave a *ca.* 1:2 mixture of α-amino- and α-*N*-Boc-α-vinylmalonates **231** (16%) and **232** (36%), respectively. At temperatures below 160 °C this μ–wave-promoted thermal elimination only provided compounds **231** or **232** with poor conversion. Disappointingly, heating substrate **229** with pyridine in DMF also only gave a mixture of the starting material **229** and products **231** and **232**, while only a complex mixture of products was obtained when sulfoxide **229** was reacted in DBU at a range of temperatures up to 120°C. This illustrated that the best results were obtained by simply heating sulfoxide **229**, neat, at 160 °C for 0.5 h in a μ–wave reactor. However, because partial thermal cleavage of the Boc-group was also occurring under these conditions, and thus giving rise to both compounds **231** and **232**, amine **230** was employed as the substrate for this elimination process so as to generate a single product. Consequently, the Boc-protecting group within adduct **229** was removed using TFA and the resulting 1° amine **230** (quantitative yield) was subjected to heating at 160 °C under μ–wave irradiation, thus providing α-amino-α-vinylmalonate derivative **231** in 59% yield. This was suitable for synthesising small quantities of compound **231** (*ca.* 100 mg) but not particularly

convenient for preparing large amounts.[⊥] A useful modification to the early parts of the sequence just described involved taking crude samples of sulfoxide **229** and subjecting them to μ–wave irradiation (Scheme 4.2.2). In this way varying mixtures of the chromatographically separable amine **231** and its Boc-protected congener **232** could be obtained. The latter product was contaminated with significant quantities of phenylsulfenic acid as well as other impurities but upon deprotection with TFA and subjection of the crude reaction mixture to chromatography then further quantities of purified samples of compound **231** could be obtained. This was found to be a more convenient and practical means for generating preparatively useful quantities of compound **231** than the protocol originally devised and shown in Scheme 4.2.1.



229 **232** **231**

Scheme 4.2.2. *Synthesis of preparatively useful quantities of α-amino-α-vinylmalonate* **231**. Reagents and conditions: *(i) neat, μ-wave irr., 160 °C; (ii) TFA, CH_2Cl_2, 0 → 18 °C.*

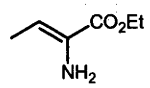
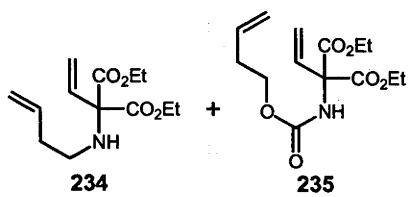
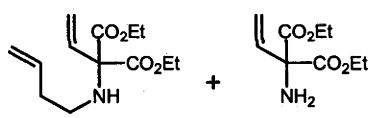
The ostensibly straightforward *N*-homoallylation of amine **231** with 4-bromo-1-butene also posed considerable difficulties. There were concerns regarding the potential for concomitant overalkylation of substrate **231**, a common problem encountered when reacting 1°-amines with alkyl haides. Accordingly, the first conditions that were investigated utilised $CsOH \bullet H_2O$ (in DMF at ambient temperature). This base reportedly[4] provides high selectivity in the monoalkylation of various 1°-amines with up to 9:1 mixtures of monoalkylated or dialkylated products being obtained with a range of alkylating agents. Unfortunately, this protocol did not provide the anticipated 2°-amine and only decarboxylated product **233** (26%) was able to be isolated and characterised (Table, 4.2.1, Entry 1). The observed formation of compound **233** suggested that less nucleophilic bases should be employed in further experiments. Accordingly, the alkylation process was attempted using DBU, Cs_2CO_3, $NaHCO_3$ and K_2CO_3. However, in all cases no reaction was observed (Table, 4.2.1, Entries 2-6).[Ω] Ironically, the problem being faced did not relate to the

[⊥] This is due to the abovementioned difficulties regarding the purification and handling of sulfoxide **229**.

[Ω] The reaction of Boc-protected amine **232** with 4-bromo-1-butene employing either NaH or KH similarly did not provide the Boc-protected analogue of diene **234**.

overalkylation of substrate **231**, rather, no reaction was occurring between amine **231** and 4-bromo-1-butene. Such behaviour is almost certainly a function of the considerable electron-withdrawing effect of the α-malonate group within compound **231** that significantly reduces the nucleophilicity of the amine moiety.[⊥]

Table 4.2.1: *Efforts to prepare diene* **234** *by the reaction of amine* **231** *with 4-bromo-1-butene.*[a]

Entry	Base	Solvent	Time (h)	Product(s)	Yield (%)
1	$CsOH \cdot H_2O$	DMF[b]	18	 **233**	26
2	DBU	DMF[b]	18	No reaction	-
3	Cs_2CO_3	DMF[b]	16	No reaction	-
4	$NaHCO_3$	MeCN	16	No reaction	-
5	K_2CO_3	MeCN	16	No reaction	-
6	K_2CO_3	DMF[c]	16	No reaction	-
7	K_2CO_3[d]	DMF	18	 **234** **235**	35[e] (**234**) 35 (**235**)
8	Na_2CO_3[f]	DMF	41	 **234** **231**	57 (**234**) 30 (**231**)

[a]Unless otherwise stated all reactions were performed at 80 °C. [b]Reaction performed at 18 °C. [c]Significant decomposition of amine **231** was observed at temperatures above 100 °C. [d]TBAI added (1.2 equiv.). [e]Unreacted amine **231** was also recovered (10%). [f]NaI added (1.2 equiv.).

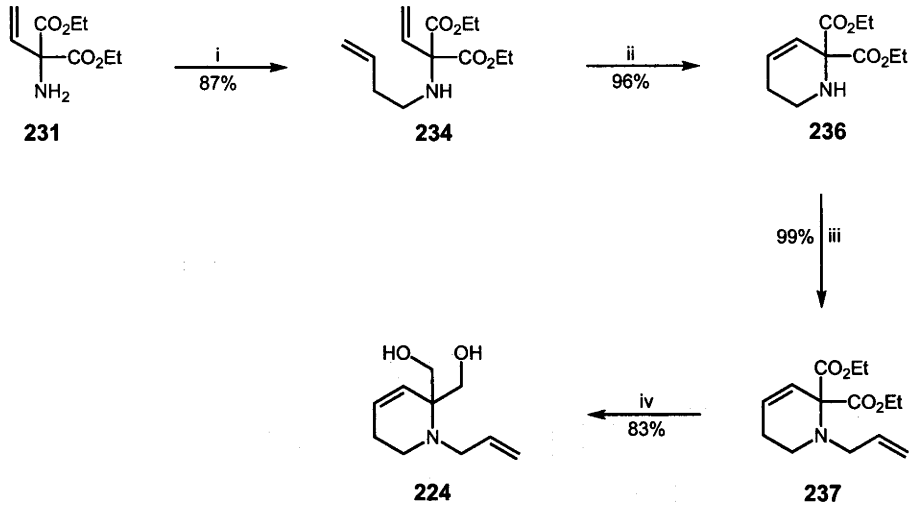
Obviously it was necessary to develop conditions that would facilitate the desired *N*-homoallylation process. Unfortunately, it was found that heating amine **231** in DMF at high temperatures (>100 °C), in the presence of various bases, resulted in significant decomposition of the substrate. Consequently, it was considered important that the reaction be carried out at more moderate temperatures (*ca.* 80 °C). With this in mind, it seemed plausible that adding a source of iodide to the reaction mixture, thus forming 4-iodo-1-butene *in situ*, by a Finkelstein reaction,[5] could assist in the formation of target diene **234**. Although product **234** was finally able to be synthesised, using K_2CO_3 and TBAI, carbamate **235** was also formed in equal amounts (Table, 4.2.1, Entry 7). Despite research illustrating

[⊥] It should also be noted that unlike its homologue allyl bromide, 4-bromo-1-butene is an unactivated alkylating agent.

that carbamates can be prepared by the reaction of amines with K_2CO_3 and alkyl halides in DMF,[6] earlier investigations demonstrated that compound **235** was not formed in the absence of TBAI (Table, 4.2.1, Entry 6).[⊥] However, it is known that tetraethylammonium hydrogen carbonate enables the transformation of amines into carbamates.[7] Accordingly, it was postulated that under the reaction conditions K_2CO_3 and TBAI were combining to produce a similar reagent that was capable of effecting such a process. Gratifyingly, when TBAI was replaced with NaI then diene **234** could be obtained in 87% yield at 70% conversion (Table, 4.2.1, Entry 8).[Ω]

Amine **234** was protected as its HCl-salt which was then treated with Grubbs' second generation catalyst.[8] Under such conditions, and after basic work-up, mono-unsaturated piperidine **236** (96%) was obtained (Scheme 4.2.3).[Ψ] It should be noted that the malonate group present within diene **234** accelerates the rate of this ring-closing metathesis process *via* the Thorpe-Ingold effect.[§9] Substrate **236** was subsequently alkylated with allyl bromide in DMF at 30 °C (44 h) to give diene **237** in 99% yield at 81% conversion. Although performing this transformation at higher temperatures reduced the time of the reaction and enabled it to proceed to completion, the yield decreased noticeably (by *ca.* 10%). The subsequent reduction of both ester residues within compound **237**, which was accomplished using lithium aluminium hydride, afforded the bis-hydroxymethylated piperidine **224** in 83% yield.

[⊥] This research undertaken by Butcher also showed that employing Na_2CO_3 decreases the carbamate yield while Cs_2CO_3 results in an increase.
[Ω] Reaction times greater than *ca.* 40 h did not appreciably improve conversion to amine **234**.
[Ψ] No reaction was observed when the HCl-salt of amine **234** was treated with Grubbs' first generation catalyst.
[§] When a dichloromethane solution of *tert*-butyl allyl(but-3-enyl)carbamate was reacted with Grubbs' second generation catalyst (5 mol%) the reaction had to be performed at a higher concentration (0.1 M) and at reflux in order to facilitate an efficient the ring-closing metathesis process.



Scheme 4.2.3. *Synthesis of diol 224.*
Reagents and conditions: *(i) 4-bromo-1-butene, Na_2CO_3, NaI, DMF, 18 → 80 °C; (ii) HCl, Et_2O, 0 → 18 °C then 5 mol% Grubbs' II catalyst, CH_2Cl_2, 18 → 25 °C; (iii) allyl bromide, K_2CO_3, DMF, 18 → 30 °C; (iv) $LiAlH_4$, THF, 0 → 18 °C.*

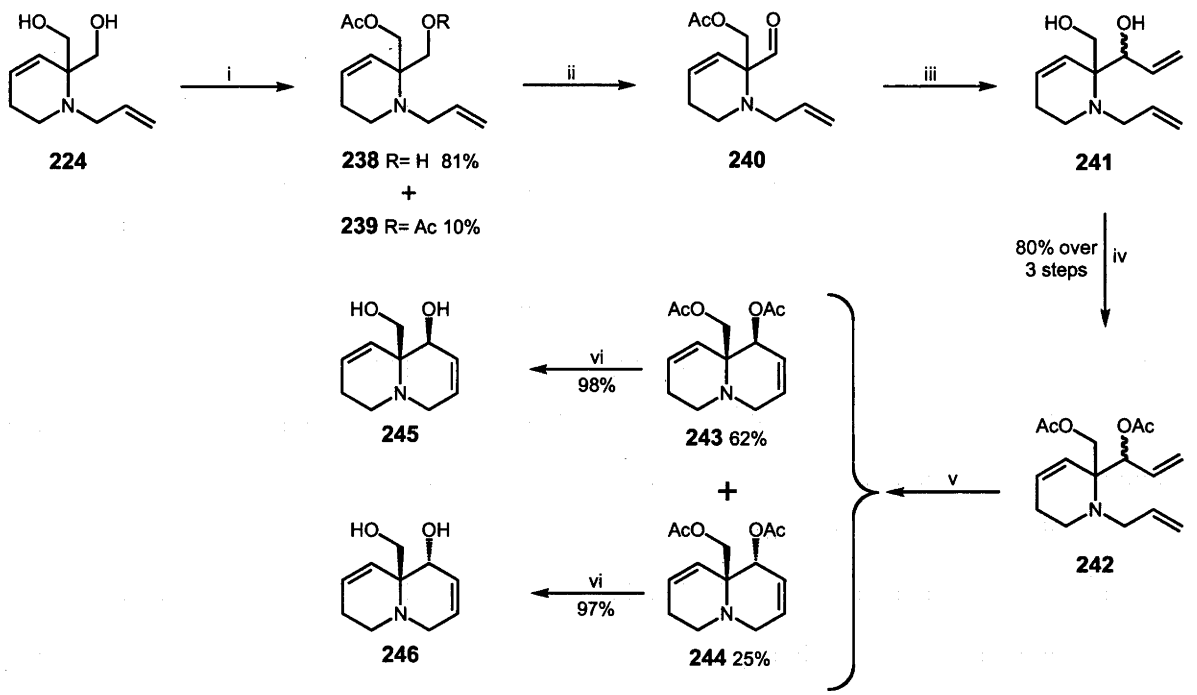
In this manner intermediate **224** was able to synthesised in 7 steps and a 38% overall yield. The spectroscopic data acquired on this material were fully consistent with the assigned structure. In particular, the 300 MHz ^{1}H NMR spectrum displayed two doublets at δ 3.65 and 3.43 (J = 11.1 Hz) that corresponded to the two equivalent pairs of AB-coupled methylene protons within the prochiral hydroxymethylene moieties and a broad singlet at δ 2.42 arising from the two hydroxyl protons. The 75 MHz ^{13}C NMR spectrum displays the expected nine carbon resonances and the ESI mass spectrum displays a protonated molecular ion (M + H) at m/z 184. Furthermore, an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{10}H_{17}NO_2$.

4.2.2 *Synthesis of Quinolizidines 245 and 246.*

In order to complete the synthesis of quinolizidine **227**, diol **224** was acetylated under conventional conditions to give a *ca.* 8:1 mixture of the chromatographically separable mono- and di-acetates **238** (81%) and **239** (10%), respectively (Scheme 4.2.4).[⊥] However, the subsequent oxidation of alcohol **238** proved to be particularly problematic. Although reacting substrate **238** with PCC provided aldehyde **240**, this was only in trace amounts and was accompanied by various unidentified decomposition products.[Ω] Similarly, performing a Ley-Griffith oxidation[10] while successful in delivering adduct **240**

[⊥] Di-acetate **239** could be converted back into diol **224**, essentially quantitatively, by treatment with K_2CO_3 in methanol and thus reused to prepare mono-acetate **238**.
[Ω] The milder, less acidic oxidant PDC gave similar unsatisfactory results.

(25%) also gave numerous unidentified side-products. Compounding this poor result, the TPAP-mediated transformation of **238** → **240** often did not proceed to completion.



Scheme 4.2.4. *Synthesis of quinolizidines* **245** *and* **246**.
Reagents and conditions: *(i)* Ac_2O, Et_2O, 18 °C; *(ii)* $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 → 18 °C; *(iii) vinylmagnesium bromide, THF, -78 → 18 °C; (iv)* Ac_2O, Et_2O, 18 °C; *(v) 10 mol% Grubbs' II catalyst, DMSO,* CH_2Cl_2, 18 °C; *(vi)* K_2CO_3, *MeOH, 18 °C.*

When a Dess-Martin oxidation[11] of compound **238** was attempted, at ambient temperature in dichloromethane, aldehyde **240** was only isolated in 30% yield and as one of a number of products. Carrying out the reaction in the presence of pyridine,[⊥] at 0 °C, provided compound **240** in an improved 46% yield after isolation by flash chromatography. Curiously, the ^{1}H NMR spectrum of the crude reaction mixture did not reflect this low yield and sparked concerns that the poor result was a consequence of the inherent instability of aldehyde **240** under flash chromatographic conditions. This hypothesis was confirmed when alcohol **238** was subjected to a Swern oxidation.[12] ^{1}H NMR and TLC analysis of the reaction mixture suggested that compound **240** was the exclusive product of the reaction. However, when the reaction mixture was subjected to flash chromatography various decomposition products were isolated along with target **240**. Fortunately, the Swern conditions allowed for such a clean conversion of **238** → **240** that, following a mildly basic work-up, product **240** was sufficiently pure and could be subjected, in a direct manner, to the required vinylation reaction.

[⊥] Pyridine was used to neutralise the residual acetic acid present in Dess-Martin periodinane.

In the event, reaction of aldehyde **240** with the Grignard reagent[13] vinylmagnesium bromide gave a *ca.* 2:1 mixture of the epimeric forms of diol **241**.[⊥] Disappointingly, reaction of triene **241** with either Grubbs' first or second generation catalysts in dichloromethane, at ambient temperature, gave no reaction. The transformation was attempted using HCl as a protecting group in order to investigate whether the basic nitrogen atom within substrate **241** was binding the catalyst. However, this was also unsuccessful and heating compound **241** with the Grubbs' second generation catalyst in toluene at 80 °C also failed to provide quinolizidine **227**. Presumably, in each case, ring-closing metathesis was not occurring because the diol group within substrate **241** had chelated the active ruthenium complex and sequestered it. Indeed, it had been reported[14] that when an analogous substrate, containing an allylic alchohol moiety, had been subjected to similar conditions no product could be obtained. For this reason, both hydroxyl groups within compound **241** were protected as their acetates and di-acetate **242** thus became the substrate for the ring-closing metathesis process.

Gratifyingly, reacting a mixture of triene di-acetates **242** with 10 mol% Grubbs' second generation catalyst provided the diastereoisomeric quinolizidines **243** (62%) and **244** (25%) which could be readily separated by flash chromatography.[Ω] In order to obtain the abovementioned species in pure form, it was imperative that DMSO was added to the reaction mixture after the transformation **242** → **243** + **244** was complete.[15] If such treatment was omitted, products **243** and **244** could not be chromatographically separated from various co-produced ruthenium impurities. While other methods could be employed[16] to remove such impurities, this simple protocol proved the most reliable and effective.

Although quinolizidines **243** and **244** were then each subjected to extensive spectroscopic characterisation the relative stereochemistries of compounds **243** and **244** was not explicitly established. However, an equivalent analysis of related compounds (*vide infra*) suggests that the major product **243** possesses the illustrated *cis*-relationship between the acetoxy and acetoxymethyl groups. This is consistent with the notion that a chelation-controlled process[17] is operating in the addition reaction **240** → **241** that establishes the relevant stereogenic centre. Independent hydrolysis of each of compounds **243** and **244** employing K_2CO_3 in methanol led to the target diols **245** (98%) and **246** (97%), respectively. In this way, key diastereoisomers **245** and **246** were able to synthesised in 6 steps (from piperidine **224**) and a combined 55% overall yield. As with all of the precursors to these compounds except sulfoxide **229** they were each obtained as oils.

The 300 MHz ^{1}H NMR spectrum of quinolizidine **245** (Figure 4.2.1) displays all of the expected resonances. Indeed, the most diagnostic features are the four signals in the region δ 6.21-5.59 that are attributed to the four olefinic protons, the two doublets at δ 3.89 and 3.42

[⊥] Under the basic reaction conditions cleavage of the acetate group within aldehyde **240** occurred.
[Ω] When less than 10 mol% of catalyst was used the rate of the reaction decreased considerably and the process was unable to proceed to completion.

(J = 11.4 Hz) that correspond to the two AB-coupled protons within the angular methylene moiety, the singlet at δ 3.67 that is derived from the oxymethine proton and the broad singlet at δ 1.85 which is assigned to the two hydroxyl protons. The 75 MHz ^{13}C NMR spectrum (Figure 4.2.2) displays the expected ten carbon resonances and is fully consistent with the assigned structure. Furthermore, the ESI mass spectrum displays a protonated molecular ion (M + H) at *m/z* 182 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{10}H_{15}NO_2$.[1]

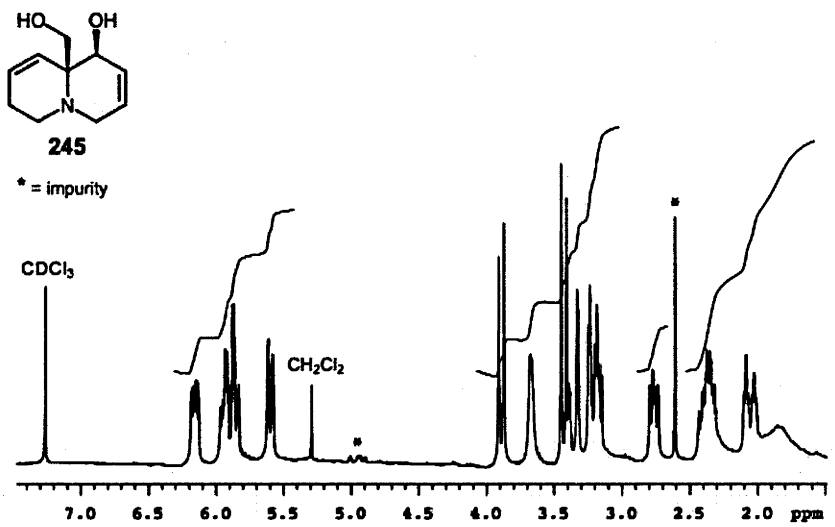


Figure 4.2.1. *300 MHz ^1H NMR spectrum of quinolizidine* **245** *(recorded in $CDCl_3$).*

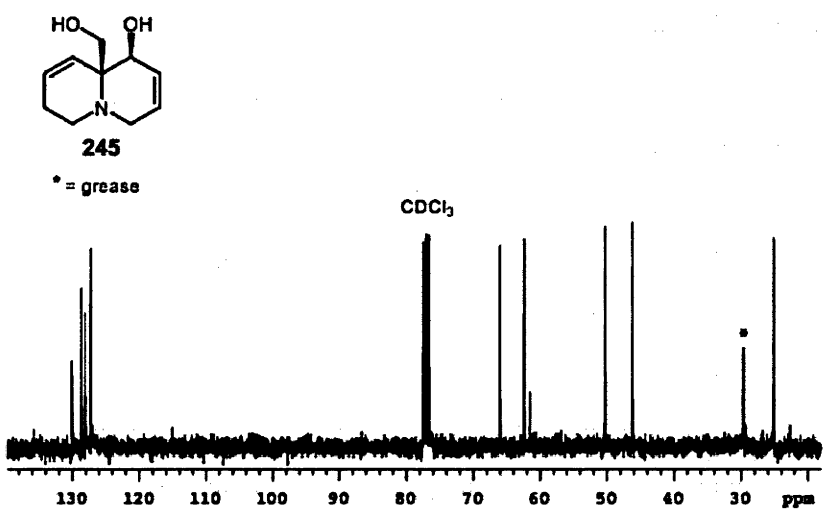


Figure 4.2.2. *75 MHz ^{13}C NMR spectrum of quinolizidine* **245** *(recorded in $CDCl_3$).*

[1] The equivalent spectroscopic data obtained on diastereoisomer **246** were very similar to those of compound **245** and, as such, have not been discussed explicitly.

4.3 Investigating the Anionic Oxy-Cope Rearrangement of Quinolizidines 245 and 246

4.3.1 Results

With quinolizidines **245** and **246** in hand the anionic oxy-Cope rearrangement[18] could at last be explored and its potential to provide a route to the 1-azabicyclo[2.2.2.]octane framework of (-)-quinine (**136**) investigated. Initial studies of this key step employed diastereoisomer **245** simply because it was the major one. In keeping with many other studies of this type,[19] KH was used to effect the title rearrangement. Certainly, it was important that a potassium base be used because the degree of cation coordination at the oxy anionic centre plays a pivotal role in the rate acceleration associated with this process.[18] The reactivity trend is potassium > sodium > lithium. Preliminary treatment of a commercial sample of KH (ex. Sigma-Aldrich) with iodine,[20] so as to destroy the putative potassium and potassium superoxide contaminants, was always undertaken before a solution containing substrate **245** was added.[⊥] In the first experiment a mixture of diol **245** and KH in THF was heated at 66 °C for 20 h but no reaction occurred. Significantly, when this reaction was repeated in the presence of the potassium complexing agent 18-crown-6[Ω18] then GCMS analysis of the reaction mixture, undertaken after 7 h, showed that quinolizidine **245** had been completely converted into a new product. The chromatogram (Figure 4.3.1) suggested an efficient transformation had taken place. The peak due to starting material **245**, observed at *ca.* 14.8 min, was conspicuously absent and a new one, believed to correspond to the hoped-for quinuclidine **226**, was seen at *ca.* 13.5 min.

[⊥] This is reported to result in improved and highly reproducible yields.
[Ω] Cation chelation is generally necessary when alignment of the double bonds within the 1,5-dien-3-ol moiety is not very good and/or the transformation does not result in strain release.

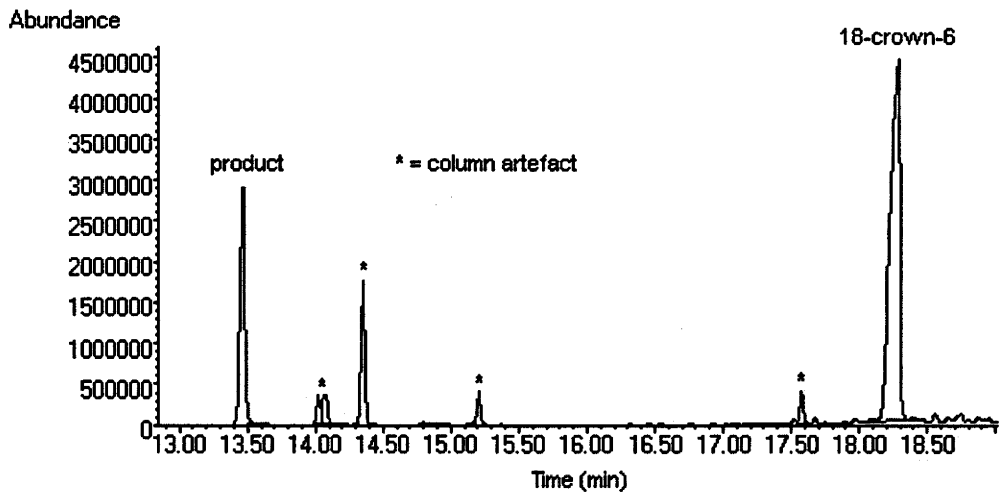


Figure 4.3.1. *GCMS chromatogram of the reaction mixture from the anionic oxy-Cope rearrangement of* **245** *(analysis performed after 7 h).*[⊥]

The notion that the anionic oxy-Cope rearrangement had been successful was supported by mass spectral analysis (Figure 4.3.2) of the product. Thus, the molecular ion is clearly observed at *m/z* 181 and the spectrum is noticeably different from that associated with diol precursor **245** (Figure 4.3.3). The mass spectrum associated with the product, shown in Figure 4.3.2, displays a cluster of peaks at, and slightly above, *m/z* 150 which is thought to arise from a retro-Diels-Alder fragmentation process that leads to loss of ethylene from the product.[Ω] The signal at *m/z* 132 and the base peak at *m/z* 122 correspond to the loss of water and methanol, respectively, from the abovementioned fragment. The major fragment ion appearing at *m/z* 108 is assigned to a pyridinylmethanol species thought to result from an alternative retro-Diels-Alder fragmentation of the product and the peak at *m/z* 94 is attributed to methyl pyridine. Substrate **245** features a distinctive fragmentation pattern and does not display the molecular ion (*m/z* 181) and the base peak appears at *m/z* 150. So, these results were quite encouraging and suggested that the desired rearrangement may indeed have taken place.

[⊥] No other signals were observed over the 0.5 h runtime.
[Ω] Fragmentation in this manner would provide a 1,3-disubstituted dihydropyridine which, upon aromatisation, would give rise to the peak at *m/z* 151.

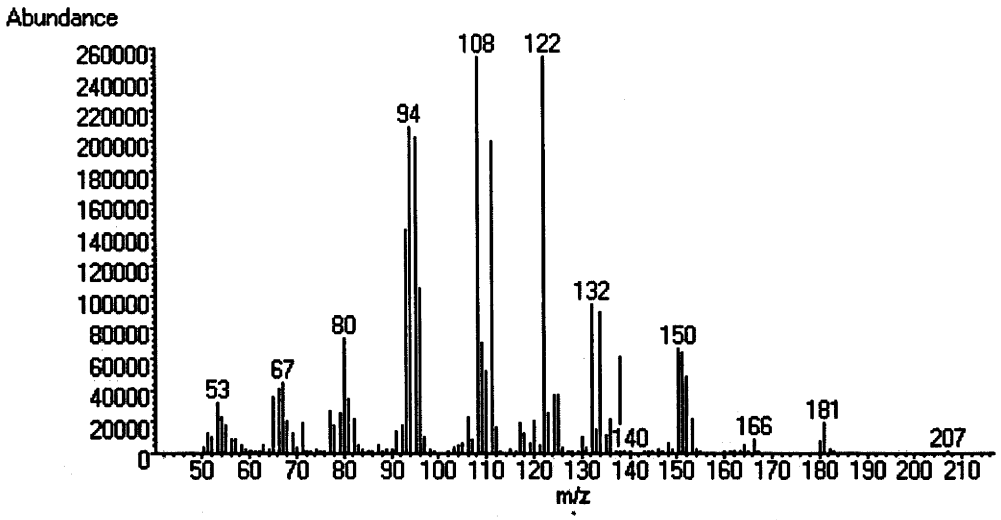


Figure 4.3.2. *GCMS (EI, 70 eV) of the signal observed at* ca. *13.5 min in the chromatogram (Figure 4.3.1) which is believed to correspond to the product of the anionic oxy-Cope rearrangement of quinolizidine* **245** *($M^+ = 181$).*

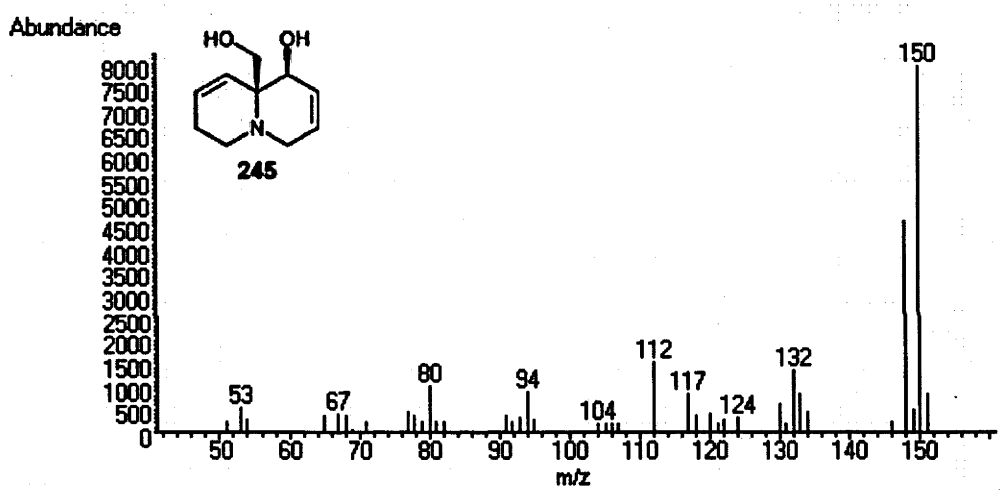
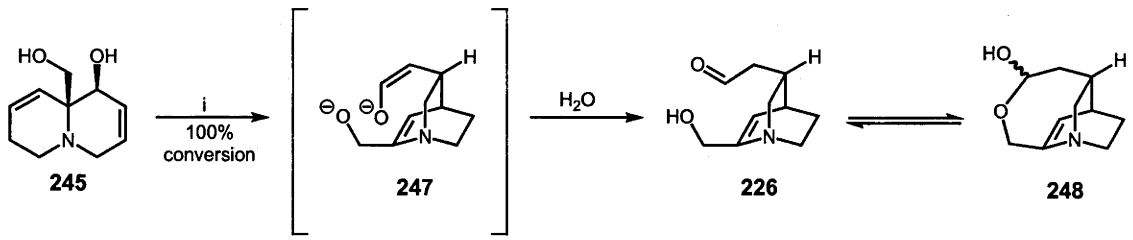


Figure 4.3.3. *GCMS (EI, 70 eV) of the signal corresponding to quinolizidine* **245** *($M^+ = 181$) which, although not visible in the chromatogram shown in Figure 4.3.1, is observed at* ca. *14.8 min when present in the reaction mixture.*

Considerable problems were encountered when attempting to isolate the highly polar product of the abovementioned transformation by flash chromatography. In fact, it was only after performing reverse phase, semi-preparative HPLC that a purified sample was obtained.[⊥] In this way, the product of this pivotal step was tentatively assigned as lactol **248** (Scheme 4.3.1). It was postulated that, as anticipated, diol **245** had engaged in the rearrangement to form enolate **247** and that, upon work-up, this intermediate spontaneously cyclised to provide lactol **248**. It should be noted that the *trans*-double bond

[⊥] Because the product does not have a chromophore that absorbs light in the UV range during HPLC it could only be isolated using RI detection. This precluded gradient elution of the sample **248** and necessitated premixing of the mobile phase. Consequently establishing a suitable method was particularly time consuming and further complicated the purification of this material.

present at a bridgehead position in proposed product **248** exists within an eight-membered ring, which is of sufficient size to accommodate it, and thus satisfying Bredt's rule.[⊥21]



Scheme 4.3.1. *Synthesis of lactol* **248**.
Reagents and conditions: *(i) KH, I_2, 18-crown-6, THF, 18 → 66 °C.*

The 300 MHz ^{1}H NMR spectrum of lactol **248** (Figure 4.3.4) is consistent with the proposed structure and all fifteen protons are observed. The most diagnostic features are the three signals in the region δ 6.10-5.50 that are believed to correspond to the oxymethine proton, the olefinic proton and the hydroxyl proton, respectively, that are present within molecule **248**. The two sets of doublets [at δ 5.12 and 4.79 (J = 6.0 Hz) and δ 4.26 and 3.58 (J = 10.2 Hz)] attributed to the two pairs of AB-coupled protons present within the C_9 methylene moiety and the C_2 methylene group, respectively, are also visible. Unfortunately, heterocycle **248** appeared to gradually decompose in $CDCl_3$, possibly because of the sensitivity of the lactol linkage within structure **248** to the traces of acid present in the deuterated solvent. This apparent instability of species **248** precluded the acquisition of a clean ^{13}C NMR spectrum. When the ^{13}C NMR experiment was performed significant decomposition of compound **248** occurred during the extended time (16 h) and thus did not allow for any sensible analysis of the acquired data. It should be noted that the IR spectrum of lactol **248** does not display a strong stretching band between 1600-1900 cm^{-1}, suggesting the absence of a carbonyl group in the rearrangement product and further supporting the assignment of structure **248** to this rearrangement product.

[⊥] The ring-strain associated with such a structure does not appear to be significant. Indeed, this was supported, although obviously not rigorously, when a molecular model of lactol **248** was constructed.

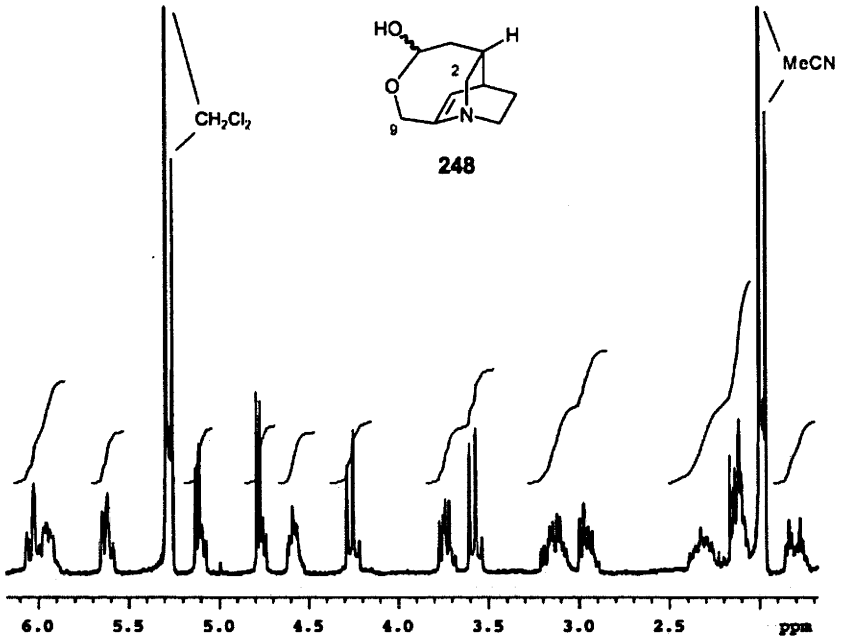


Figure 4.3.4. *300 MHz ^1H NMR spectrum of lactol* **248** *(recorded in $CDCl_3$).*[⊥]

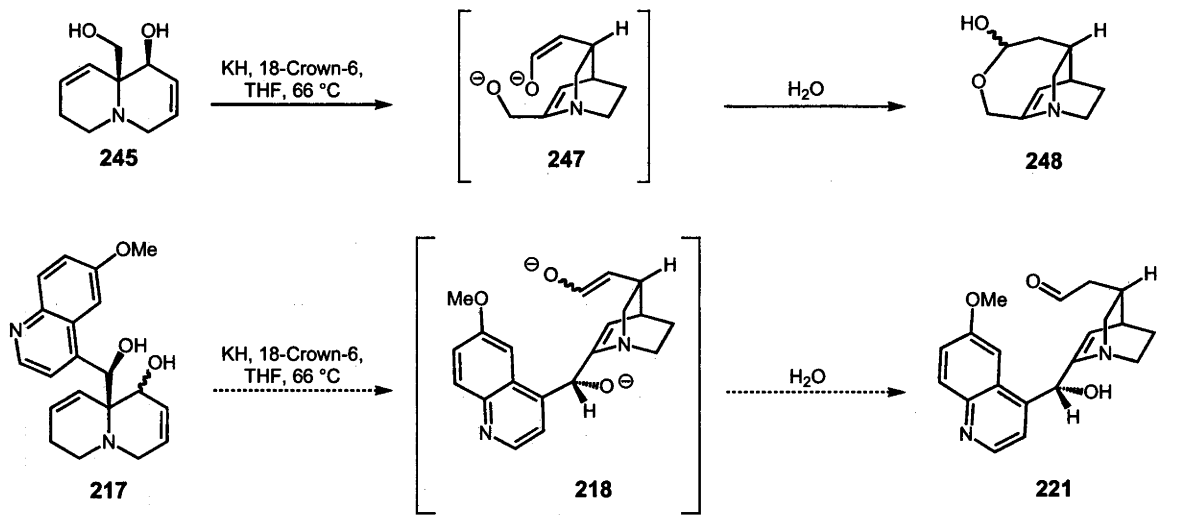
Further investigation of this anionic oxy-Cope process showed that the diastereoisomeric quinolizidine **246** was able to undergo key rearrangement and, as expected, behaved no differently to congener **245**. Attempting to promote the rearrangement under μ–wave irradiation (1 h) only returned starting material **245**. When 18-crown-6 was replaced with HMPA the reaction provided, after 20 h, a *ca.* 3:1 mixture of product **248** and starting material **245**, respectively.[Ω] Interestingly, when adduct **245** was reacted in THF at ambient temperature, in the presence of 18-crown-6, the process required *ca.* 70 h to proceed to near complete conversion. The ability of substrates **243** and **245** to participate in the thermally-induced oxy-Cope rearrangement was also briefly studied. Various experiments were performed at a range of temperatures (up to 350 °C) all of which were unsuccessful. In all cases either no reaction occurred or the decomposition of quinolizidines **243** and **245** was observed.

4.3.2 Conclusions

The results obtained from the anionic oxy-Cope rearrangement of diol **245** suggested that the product of the reaction was lactol **248** and consequently there was confidence in an analogous process ultimately providing quinuclidine **221** (or its tautomer) from substrate **217** (Scheme 4.3.2). However, before explicitly attempting to synthesise compound **217** this

[⊥] There were indications that lactol **248** was reasonably volatile and thus the complete removal of dichloromethane and acetonitrile *in vacuo* was not attempted. Consequently, when performing the ^1H NMR experiment locking the sample was difficult and the signals, particularly those corresponding to the solvents (deuterochloroform, dichloromethane and acetonitrile), were visibly duplicated.
[Ω] As judged by GCMS analysis of the reaction mixture.

key step was studied in more detail. Indeed, in light of the abovementioned difficulties concerning species **248** it was anticipated that protecting the 1° alcohol within substrate **245** could potentially address some of these issues by preventing the formation of a lactol product.



Scheme 4.3.2. *The anionic oxy-Cope rearrangement of diol* **245** *that provided lactol* **248** *and the anticipated transformation of quinolizidine* **217** *to quinuclidine* **221**.

4.4 Investigating the Anionic Oxy-Cope Rearrangement of Quinolizidines 256 and 257

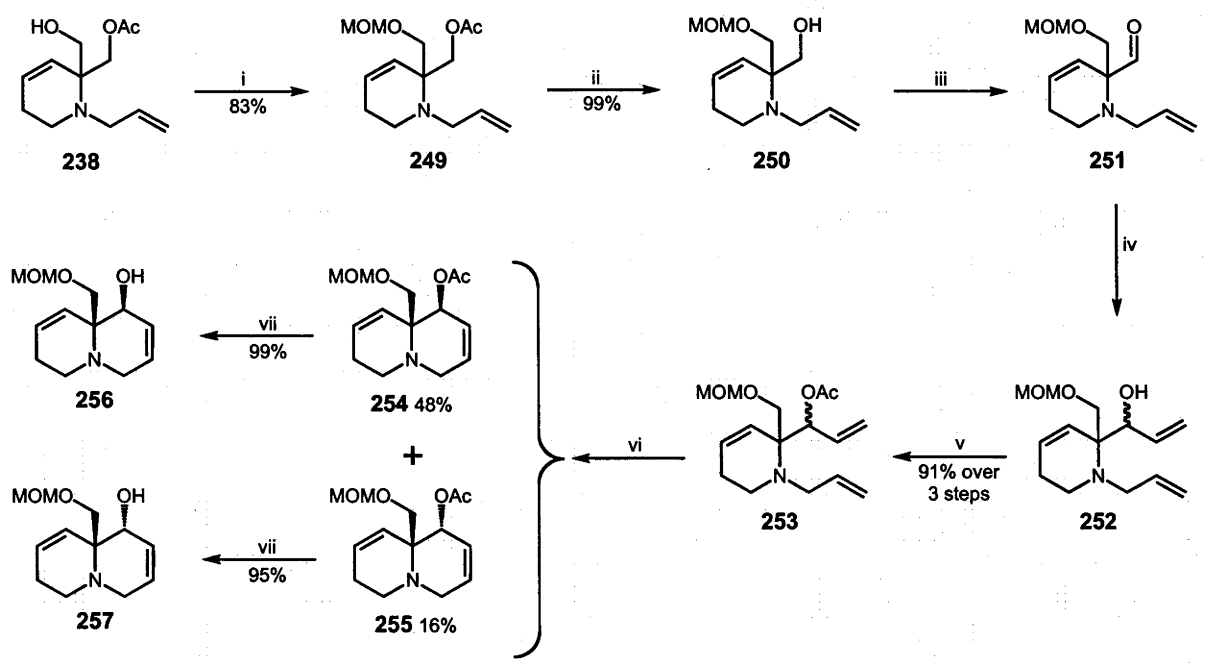
4.4.1 Synthesis of Quinolizidines 256 and 257

Unfortunately diol **245** (or **246**) could not be selectively protected at the 1° position. Consequently, it was necessary to repeat the synthetic sequence, as outlined in Scheme 4.2.4, with an appropriate derivate of alcohol **238** that featured a base-stable protecting group. This was because the acetate moiety within aldehyde **240** was cleaved during the Grignard addition reaction, thus preventing the preparation of a mono-ol derivative of intermediate **241**. It was anticipated that suitable congeners of quinolizidine **245** and **246** could be synthesised by employing the particularly base-stable MOM protecting group.

A simple variation on the reaction sequence shown in Scheme 4.2.4 allowed for the preparation of mono-protected derivatives of compounds **245** and **246**. Thus, as shown in Scheme 4.4.1, reaction of acetate **238** with chloromethyl methyl ether[1] in the presence of Hünig's base then treatment of resulting ether **249** (83%) with K_2CO_3 in methanol afforded

[1] A large excess of chloromethyl methyl ether (*ca.* 2.5 equiv.) was required to drive the reaction to completion.

the expected alcohol **250** (99%) that could be oxidised to the corresponding aldehyde **251**[⊥] under Swern conditions. Vinylation of this last compound in the same manner as employed earlier gave a *ca.* 3:1 mixture of the epimeric allylic alcohols **252** that were not separated but committed, as a mixture, to acetylation under conventional conditions. The resulting mixture of the diasteroisomeric forms of acetate **253** (91% from **250**) was then subjected to the conditions that successfully enabled the ring-closing metathesis of trienes **242**. Surprisingly, TLC analysis of the reaction mixture indicated there was considerable amount of starting material present, even after 31 h. However, it was found that performing this process in refluxing dichloromethane improved the conversion of **253** → **254** + **255** and so afforded a chromatographically separable mixture of the quinolizidine derivatives **254** (48% at 57% conversion) and **255** (16% at 57% conversion). Although this step was not optimised, subsequent experiments indicated that when the reaction was performed in toluene at 80 °C the conversion of **253** → **254** + **255** improved significantly (>90%). Each of the product quinolizidines **254** and **255** was then independently treated with K_2CO_3 in methanol and thereby afforded the target mono-ols **256** (99%) and **257** (95%), respectively.



Scheme 4.4.1. *Synthesis of quinolizidines* **256** *and* **257**.
Reagents and conditions: *(i) MOMCl, Hünig's Base, DMAP, CH_2Cl_2, 18 °C; (ii) K_2CO_3, MeOH, 18 °C; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 → 18 °C; (iv) vinylmagnesium bromide, THF, -78 → 18 °C; (v) Ac_2O, Et_2O, 18 °C; (vi) 10 mol% Grubbs' II catalyst, DMSO, NEt_3, CH_2Cl_2, 18 → 40 °C; (vii) K_2CO_3, MeOH, 18 °C.*

[⊥] Aldehyde **251**, like congener **240**, is unstable to purification by flash chromatography.

The illustrated stereochemistries in structures **254** and **255** were established using NOESY techniques. In particular, in the former isomer a strong interaction was observed between the proton resonance due to the acetoxymethyl group and that due to the methyl group of the MOM ether. As expected, the equivalent interaction in compound **255** was much less pronounced. These results served to establish the illustrated (relative) configurations for compounds **243-246**, and **254-257**. The 300 MHz ^{1}H NMR spectrum of quinolizidine **256** (Figure 4.4.1) displayed all of the expected resonances. Indeed, the most diagnostic features are the four signals in the region δ 6.01-5.72. These are attributed to the four olefinic protons. The two sets of doublets [at δ 4.59 and 4.54 (J = 6.6 Hz) and δ 3.76 and 3.53 (J = 9.3 Hz)] correspond to the two pairs of AB-coupled protons present within the MOM-methylene group and the angular methylene moiety, respectively. The singlet at δ 3.32, representing the three MOM-methyl protons, and the broad singlet δ 2.35,[⊥] which is assigned to the single hydroxyl proton, were also considered diagnostic. The 75 MHz ^{13}C NMR spectrum (Figure 4.4.2) displays the expected twelve carbon resonances and is completely consistent with the assigned structure. Furthermore, the ESI mass spectrum displays a protonated molecular ion (M + H) at *m/z* 226 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{12}H_{19}NO_3$.[Ω]

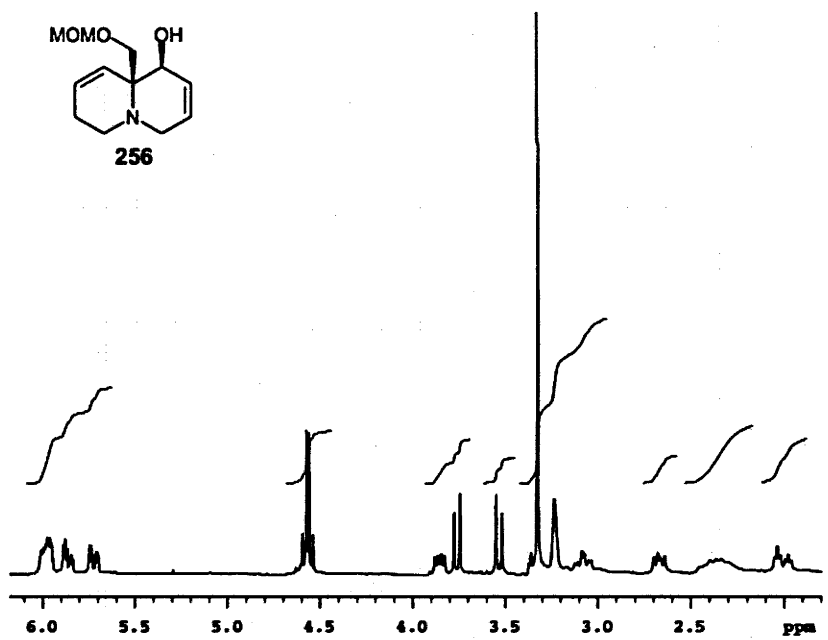


Figure 4.4.1. *300 MHz ^{1}H NMR spectrum of quinolizidine* **256** *in (recorded in $CDCl_3$).*

[⊥] This signal obscures a peak corresponding to another proton within quinolizidine **256**.
[Ω] The equivalent spectroscopic data obtained on diastereoisomer **257** were very similar to those of compound **256** and, as such, have not been discussed explicitly.

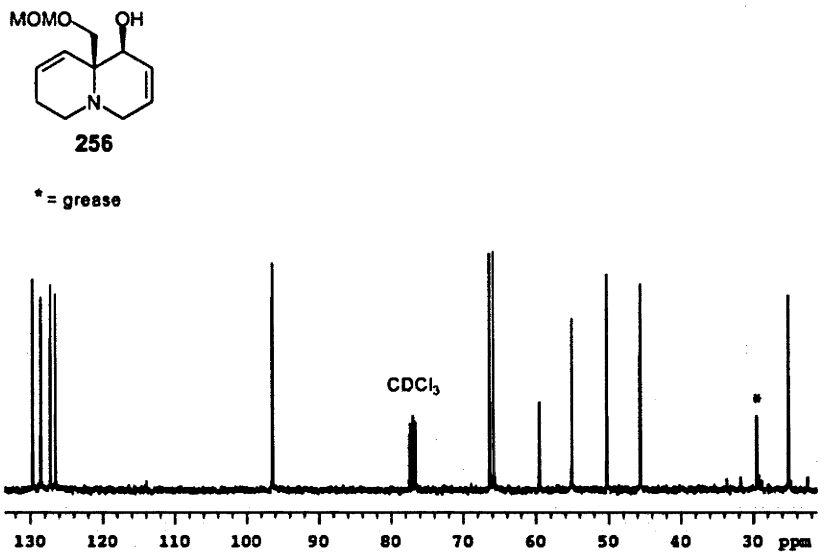
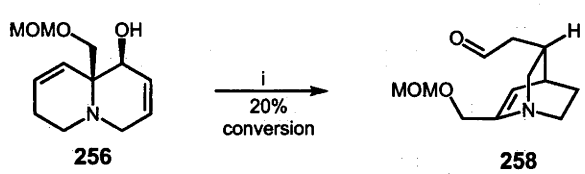


Figure 4.4.2. *75 MHz ^{13}C NMR spectrum of quinolizidine* **256** *(recorded in $CDCl_3$).*

4.4.2 *The Anionic Oxy-Cope Rearrangement of Quinolizidines 256 and 257*

With quinolizidines **256** and **257** in hand the capacity of these substrates to engage in the anionic oxy-Cope rearrangement was investigated. Disappointingly, and despite repeated attempts, when substrate **256** was subjected to the conditions[⊥] that had led to the efficient generation of lactol **248** GCMS analysis, undertaken after 18 h, suggested that the transformation had proceeded to only *ca.* 20% conversion (Scheme 4.4.2). This did not appreciably improve even after 70 h. The ^1H NMR spectrum of the crude reaction mixture, obtained after work-up, displayed a signal (δ 9.65) that was believed to correspond to the aldehydic proton associated with structure **258**. However, with the exception of the GCMS data no other evidence for product **258** could be obtained and this product was not characterised.[Ω] As expected the reaction of quinolizidine **257** under the standard conditions[⊥] provided similar results to those observed with diastereoisomer **256**.

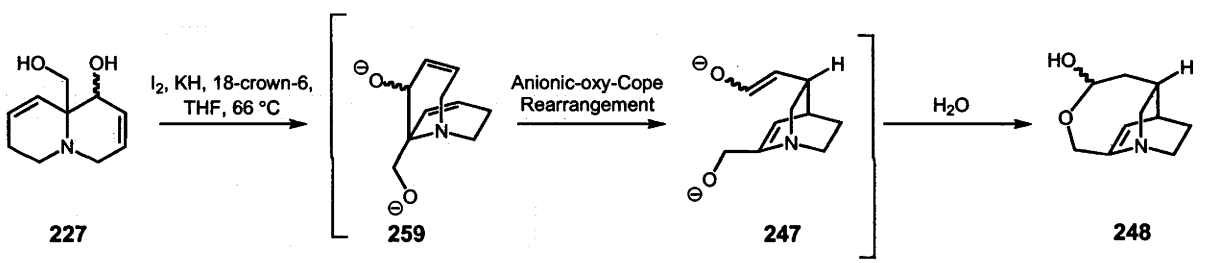


Scheme 4.4.2. *The anionic oxy-Cope rearrangement of quinolizidine* **256**.
Reagents and conditions: *(i) KH, I_2, 18-crown-6, THF, 18 → 66 °C.*

[⊥] KH, 18-crown-6, THF, 66 °C.
[Ω] Unfortunately, the product could not be isolated by flash chromatography.

The spectacular rate enhancement that the anionic oxy-Cope rearrangement provides relative to the parent thermal process is well established.[18,22] Indeed, the creation of a thermodynamically more favourable resonance stabilised enolate anion renders the process irreversible and also offers extraordinary rate acceleration. However, the outcomes of the abovementioned study suggest that the ability of quinolizidines **245** and **246** to efficiently undergo the transformation is not exclusively dependent on this intrinsic property of the pericyclic reaction. The presence of a second oxy-anion substituent within substrate **259** was ostensibly crucial to delivering product **248** (Scheme 4.4.3). Conceivably, repulsion of the negatively charged and proximal oxyanionic groups within compound **259** prompts the substrate to adopt a conformation that minimises this force. Auspiciously, this leads to an intermediate that features improved alignment of the 1,5-diene moiety and, by definition, enhanced orbital overlap of the π-system, which is essential for facilitating the key [3,3]-sigmatropic rearrangement.

It should also be noted that the oxy-anion and enolate residues within product **247** are considerably further apart than the oxy-anion substituents within starting material **259**[⊥] and thus further lowering the energy associated with species **247** relative to structure **259**.



Scheme 4.4.3. *The additional rate enhancement provided by the second oxy-anion substituent present within compound* **259**.

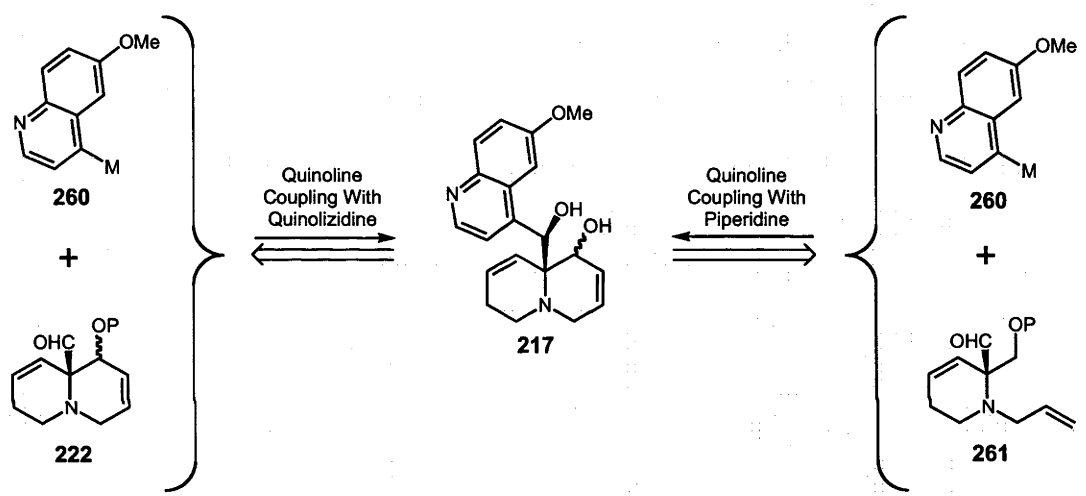
4.5 Designing an Approach to Quinolizidine 217

The outcomes of the research outlined in this chapter confirmed the validity of the fundamental proposal and indicated that the anionic oxy-Cope rearrangement could form the centrepiece of an unprecedented approach to the total synthesis of (-)-quinine (**136**). Consequently, a more specific strategy for preparing target *Cinchona* alkaloid **136** had to be designed. An appropriate quinolizidine capable of participating in this transformation needed to be identified. As noted in Chapter Three, such a structure must incorporate the quinoline motif because it cannot be installed stereoselectively after the quinuclidine

[⊥] In compound **259** the two oxy-anion groups are separated by three atoms, while in structure **247** the enolate and oxy-anion residues are seven atoms apart.

framework has been established.[23] In addition, the observed dianion rate enhancement of the pivotal transformation dictated that the unprotected 1,3-hydroxyl moiety had to be present within this adduct. These criteria were satisfied by compound **217** - originally suggested as the rearrangement substrate in the retrosynthetic analysis of (-)-quinine (**136**) shown in Scheme 3.3.3.

Structure **217** could conceivably be prepared by one of essentially two distinct approaches; namely by the addition of metallated quinoline **260** to either quinolizidine **222** or piperidine **261** (Scheme 4.5.1). Accordingly, the aim of the research described in Chapters Five and Six was to conduct a comprehensive investigation to determine which of these two strategies would provide better results and ultimately enable a more concise and efficient route to heterocycle **217**.



Scheme 4.5.1. *The two fundamental strategies for preparing key anionic oxy-Cope rearrangement substrate* **217**.

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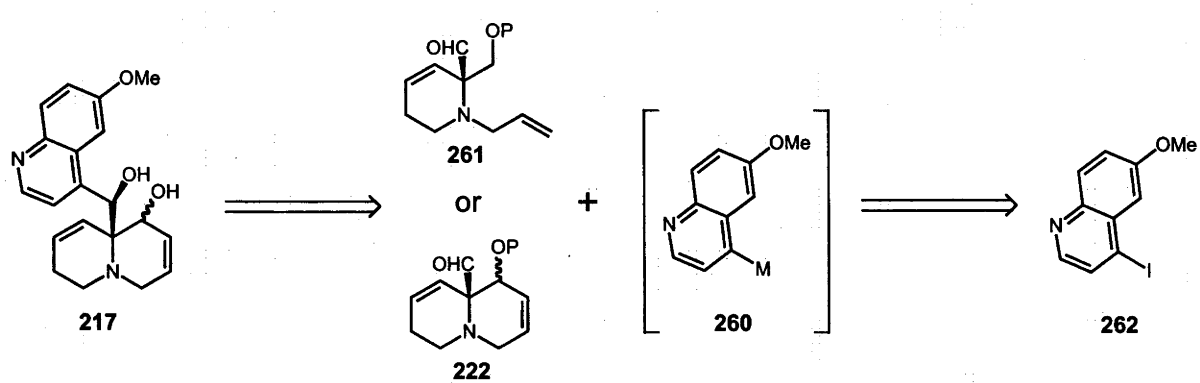
Chapter Five

Synthesis of Iodide 262 via *a New* trans-*Halogenation Procedure*

*This chapter describes the synthesis of 4-iodo-6-methoxyquinoline (**262**). Significantly, this led to the development of a new microwave-assisted* trans-*halogenation procedure for the transformation of various chloro-, bromo- trifluoromethanesulfonyloxy- and nonafluorobutanesulfonyloxy-substituted quinolines, isoquinolines, and pyridines into their corresponding iodinated derivatives. The results of a comprehensive study investigating the scope, limitations and utility of this methodology are detailed.*

5.1 Introduction

Because of the encouraging results arising from the model studies described in the previous chapter, the focus of efforts directed towards the synthesis (-)-quinine (**136**) shifted to explicitly preparing the key anionic oxy-Cope rearrangement substrate **217** (Scheme 5.1.1). However, before this investigation could be undertaken an appropriately substituted quinoline, that could be used to prepare quinolizidine **217**, needed to be synthesised. It was anticipated that structure **217** would derive from the addition of metallated intermediate **260** to either aldehyde **222** or **261** and, as such, 4-iodo-6-methoxyquinoline (**262**) was deemed a suitable precursor. Heterocycle **262** represents a more flexible building block than its bromo-congener since the weakness of the C-I bond relative to the C-Br bond allows for the more facile preparation of various organometallic species **260** by a range of processes. Thus, the aim of the research presented in this chapter was to synthesise iodide **262**.

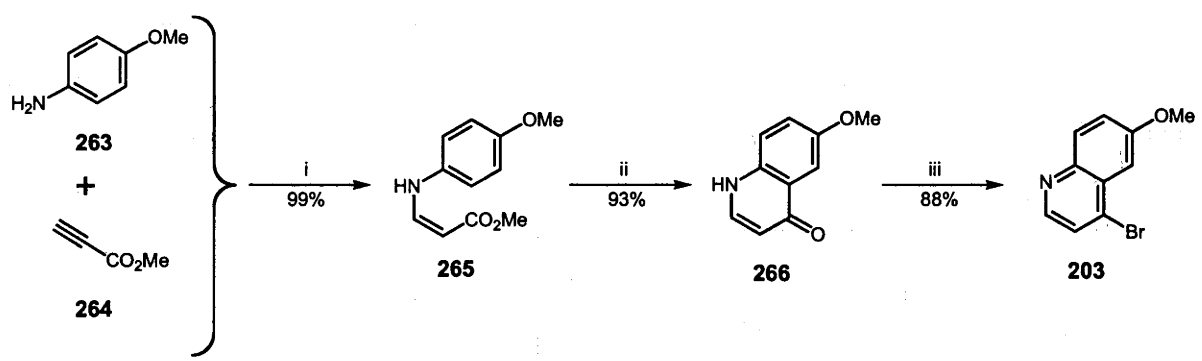


Scheme 5.1.1: *Retrosynthetic analysis of quinolizidine **217** and identification of quinoline **262** as a key precursor.*

5.2 Synthesis of 4-Iodo-6-methoxyquinoline (262)

5.2.1 *Synthesis of 4-Bromo-6-methoxyquinoline (203)*

A suitable approach to iodide **262** had to be developed and it was anticipated that such a species could be derived from 4-bromo-6-methoxyquinoline (**203**). An examination of the relevant literature suggested that bromide **203** should be accessible by one of at least two distinct and relatively efficient routes.[1,2] In the event, heterocycle **203** was prepared *via* a concise, three-step sequence, although a number of significant modifications to the originally reported procedures was required to ensure that an efficient process was established.[3] The route used to obtain quinoline **203** is presented in Scheme 5.2.1 and began with the stereoselective Michael addition of *p*-anisidine (**263**) to methyl propiolate (**264**).[1a] Interestingly, when this reaction was conducted at 18 °C a *ca.* 9:1 mixture of acrylate **265** and its corresponding (*E*)-isomer was obtained. In contrast, when the same reaction was carried out at 30 °C compound **265** was essentially the only product and was obtained in near quantitative yield. Presumably, the (Z)-stereoselectivity observed in the reaction of **263** + **264** → **265** derives from the stability associated with the formation of a hydrogen bond between the N-H proton and the carbonyl moiety present within product **265**. This seems likely since similar interactions have been reported in related systems.[4]



Scheme 5.2.1. *Synthesis of 4-bromo-6-methoxyquinoline (203).*
Reagents and conditions: *(i) MeOH, 30 °C; (ii) Ph_2O, 260 °C; (iii) PBr_3, DMF, 0 → 18 °C.*

Following a reported procedure[1a] that was expected to result in *p*-anilinoacrylate **265** undergoing a Conrad-Limpach reaction[5] to give 4-quinolone **266**, a *ca.* 0.4 M solution of substrate **265** in diphenyl ether was heated at *ca.* 260 °C for 0.5 h. However, under such conditions only polymeric products were obtained. After a great deal of experimentation, it was established that heating a five-fold diluted solution of the substrate under the same conditions led to an efficient cyclisation reaction thus providing the target 4-quinolone **266**

in 93% yield. The conversion of this compound into bromide **203** proceeded smoothly when phosphorus tribromide in DMF was employed[2] and desired product (**203**) was obtained in 88% yield. The physical and spectroscopic properties of this material were in full accord with the assigned structure and in agreement with the equivalent data reported in the literature.[1,2]

5.2.2 *Synthesis of 4-Iodo-6-methoxyquinoline (262)*

Iodide **262** needed to be prepared from precursor **203** and it was thought best to do this using a *trans*-halogenation protocol. It should be noted that aryl iodides are often difficult to obtain, especially if the halogen is attached to a nitrogen-containing heteroaromatic framework.[6] *trans*-Halogenation protocols (sometimes characterised as aromatic Finkelstein reactions)[7] involving a bromo- or chloro-precursor to the target iodide have been introduced in an effort to overcome such difficulties although many limitations still apply.[8]

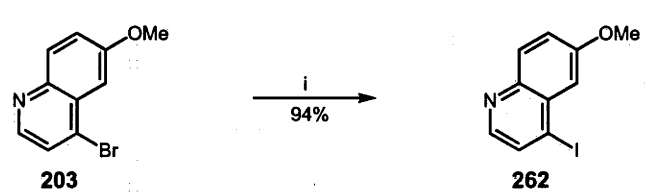
In 1947 Bruce demonstrated that a 2,4-di-iodinated pyridine could be prepared in quantitative yield by heating its dichloro-analogue with hydroiodic acid.[9] Variations on this sort of approach have been introduced over the intervening years wherein the ring nitrogen in pyridines has been activated through protonation,[10] silylation,[11] or acylation[12,13] and thereby facilitating a nucleophilic addition/elimination reaction (S_NAr reaction) involving iodide ion that leads to the target aryl halide.[14] The proton activation approach has been applied to quinolines[12,13,15] although Newkome[16] has shown that such conditions can lead to reductive dehalogenation when especially electron-deficient pyridines are involved. Nickel and copper-promoted *trans*-halogenation processes have been introduced over the last two decades[17] while, in 2002, Klapars and Buchwald reported[18] a copper-catalysed method for the conversion of aryl bromides into the corresponding iodides. Buchwald's group has since developed various relevant extensions of this chemistry.[19] Despite these useful advancements, high temperatures (>100 °C), extended reactions times (≥24 h), and/or strongly acidic conditions are often required and thus precluding the application of such techniques to substrates containing sensitive functionalities.

Attempting the ostensibly simple transformation of 4-bromoquinoline **203** into iodo-analogue **262** employing established *trans*-halogenation protocols was not a trivial undertaking. Thus, heating 4-bromoquinoline **203** in hydroiodic acid[20] only gave rise to a complex mixture of products, while treating compound **203** with *n*-BuLi and trapping the ensuing lithiated intermediate with iodine only afforded target **262** in 10% yield.[⊥,21] Unfortunately, when bromide **203** was subjected to the copper-catalysed protocol

[⊥] The latter procedure is obviously not a *trans*-halogenation protocol.

established by Buchwald[18] no reaction was observed even after 20 h.[⊥] Indeed, only when the catalyst loading was significantly increased,[Ω] and the transformation performed at 110 °C for 0.5 h in a μ-wave reactor, could the iodide product be generated, albeit only at *ca.* 40% conversion.[Ψ] Some decomposition of substrate **203** was also observed under these conditions. Disappointingly, increasing the catalyst and ligand loading four-fold provided a *ca.* 2:1:3 mixture of, 6-methoxyquinoline, bromide **203** and its derivative **262**, respectively. Since 4-iodo-6-methoxyquinoline (**262**) could not be chromatographically separated from precursor **203** it was unable to be purified. These unsatisfactory results necessitated the development of a new *trans*-halogenation procedure capable of facilitating the abovementioned process.

It has been reported[12] that certain halogen-substituted aromatic heterocycles can be activated towards nucleophilic addition/elimination reactions (S_NAr reactions) involving iodide ions by acylation, albeit in low yields (35-65%) and under extended reaction times (*ca.* 24 h) in refluxing acetonitrile. Consequently, a suspension of 4-bromoquinoline **203**, acetyl chloride and NaI in acetonitrile was subjected to μ-wave irradiation at 80 °C for 0.5 h. This provided the relevant chloro-, bromo- and iodo-quinolines in a *ca.* 10:1:9 ratio.[Ψ] Interestingly, replacing acetyl chloride with acetic anhydride provided bromide **203** and iodide **262** in a *ca.* 3:2 ratio after 0.75 h, which improved to *ca.* 1:2 after 1.5 h (Scheme 5.2.2). Gratifyingly, conducting the reaction for 3 h delivered 4-iodo-6-methoxyquinoline (**262**) as a colourless crystalline solid and as the sole product in 94% yield.[3] The spectral data obtained on compound **262** were in full accord with the assigned structure and the ESI mass spectrum displayed a protonated molecular ion (M + H) at *m/z* 285. Furthermore, both an accurate mass measurement and elemental analysis confirmed that the reaction product was of the expected composition, *viz.* $C_{10}H_8INO$. However, the melting point of this material was significantly higher (126 °C) than that reported (85 °C) for the material prepared by John and Andraschko in 1930.[22] The origins of this discrepancy remain unclear.



203 **262**

Scheme 5.2.2. *Synthesis of 4-iodo-6-methoxyquinoline (262).*
Reagents and conditions: *(i) NaI, Ac_2O, MeCN, μ-wave irr., 80 °C.*

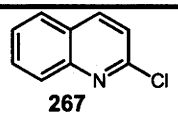
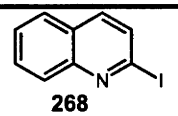
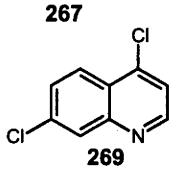
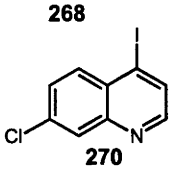
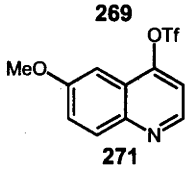
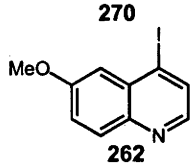
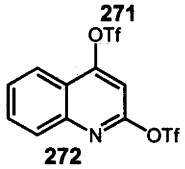
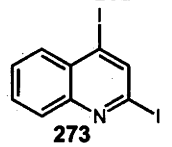
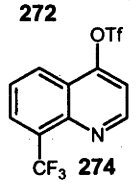
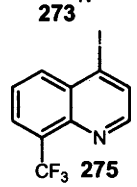
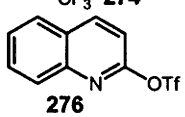
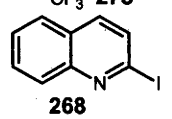
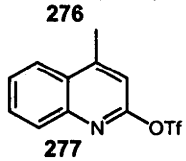
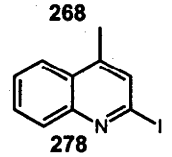
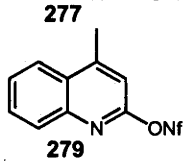
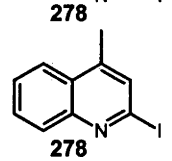
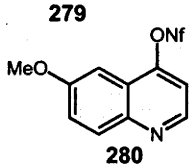
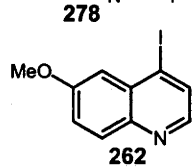
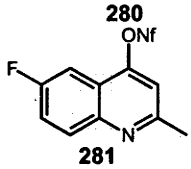
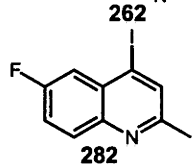
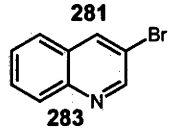
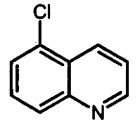
[⊥] This involved heating quinoline **203** with CuI (5 mol%), *N,N'*-dimethylethylenediamine (10 mol%) and NaI in dioxane at 110 °C.
[Ω] CuI (25 mol%), NaI, *N,N'*-dimethylethylenediamine (50 mol%).
[Ψ] As judged by GCMS analysis of the reaction mixture.

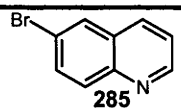
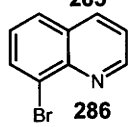
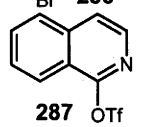
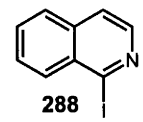
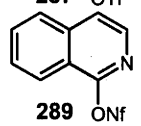
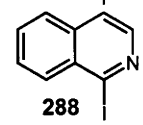
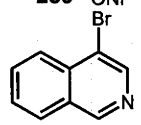
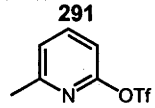
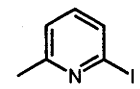
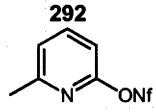
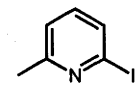
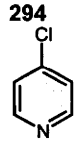
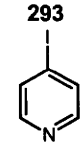
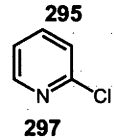
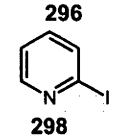
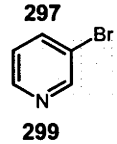
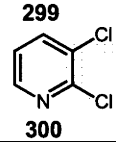
5.3 A New, Microwave-Assisted *trans*-Halogenation Protocol

The abovementioned difficulties encountered in preparing of 4-iodo-6-methoxyquinoline (**262**) from parent bromide **203** underscored the lack of mild, rapid and efficient methods available for the *trans*-halogenation of aromatic heterocycles. Accordingly, an extensive investigation of the abovementioned procedure was undertaken with a view to establishing the capacity of this methodology to provide a range of iodinated aromatic heterocycles.[23]

The successful *trans*-halogenation reactions are presented in Table 5.3.1 and involved treating acetonitrile solutions of quinolines **267**, **269**, **271**, **272**, **274**, **276**, **277**, **279**, **280**, and **281**, isoquinolines **287** and **289**, as well as pyridines **292**, **294**, **295**, and **297** with NaI and either acetic anhydride or acetyl chloride then subjecting the resulting mixtures to μ-wave irradiation at 80 °C for 3 h. The substrates used for these studies were either commercially available or in the case of triflates **271**, **272**, **274**, **276**, **277**, **287**, **292** and nonaflates **279-281**, **289**, **294** readily prepared by applying standard procedures to the commercially available hydroxy-precursors. Indeed, triflates **271**, **272**, **274**, **276**, **277**, **287**, **292** were synthesised in 43%, 16%, 86%, 86%, 78%, 89% and 79% yields respectively and nonaflates **279-281**, **289**, **294** were obtained in 28%, 33%, 17%, 23% and 83% yields respectively. The yields of the substrates prepared by such means were not optimised.

Table 5.3.1: *Outcomes of the* trans-*halogenation reactions of various substituted quinolines, isoquinolines and pyridines.*

Entry	Substrate	Product	Procedure[a]	Yield (%)
1	 **267**	 **268**	A	85
2	 **269**	 **270**	A	93
3	 **271**	 **262**	A	93
4	 **272**	 **273**	B	97
5	 **274**	 **275**	A	97
6	 **276**	 **268**	B	91
7	 **277**	 **278**	B	94
8	 **279**	 **278**	B	92
9	 **280**	 **262**	A	92
10	 **281**	 **282**	A	95
11	 **283**	No Reaction	A or B	-
12	 **284**	No Reaction	A or B	-

13	 **285**	No Reaction	A or B	-
14	 **286**	No Reaction	A or B	-
15	 **287**	 **288**	B	90
16	 **289**	 **288**	B	93
17	 **290**	No Reaction	A or B	-
18	 **291**	No Reaction	A or B	-
19	 **292**	 **293**	B	33
20	 **294**	 **293**	B	74
21	 **295**	 **296**	B	91
22	 **297**	 **298**	B	98
23	 **299**	No Reaction	A or B	-
24	 **300**	No Reaction	A or B	-

[a]Procedure A: Ac_2O, NaI, MeCN, μ-wave irr., 80 °C, 3 h. Procedure B: AcCl, NaI, acetonitrile, μ-wave irr., 80 °C, 3 h.

The results shown clearly demonstrate that quinolines carrying a leaving group at C_2 and/or C_4 readily engage in the desired *trans*-halogenation reaction(s) and thereby afford the corresponding iodides in generally excellent yields (Table 5.3.1, Entries 1-10). Significantly, compounds **269**, **271**, **274**, **280**, and **281** carrying potential leaving groups at C_6, C_7, or C_8 did not undergo iodination at these positions (Table 5.3.1, Entries 2, 3, 5, 9, 10). In

keeping with expectations, quinolines featuring halogen substituents at C_3, C_5, C_6 or C_8 all failed to engage in *trans*-halogenation reactions when subjected to the conditions defined by either procedure A or B (Table 5.3.1, Entries 11-14). In some instances it was found that using acetic anhydride as the activating agent (procedure A) provided better yields of product than when acetyl chloride was employed (procedure B) for the same purpose (Table 5.3.1, Entries 1-3, 5, 9, 10). This outcome was attributed to co-production of the corresponding aryl chloride when the latter activating agent was employed. Nevertheless, there were other cases where the latter procedure proved to be the superior one (Table 5.3.1, Entries 4, 6-10).

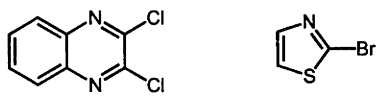
As expected, isoquinolines **287** and **289** carrying a potential leaving group at C_1 engaged in the *trans*-halogenation reaction to deliver iodide **288** in excellent yield (Table 5.3.1, Entries 15 and 16). Studies outlined below have established that C_1 is likely to be the only position on the isoquinoline framework where such a process can take place. (Table 5.3.1, Entries 17 and 18). A further interesting observation was that when 1-chloroisoquinoline, rather than isoquinolin-1-yl trifluoromethanesulfonate (**287**), was used as the substrate for the *trans*-halogenation reaction then the corresponding iodide was only prepared in 45% yield and this was accompanied by significant quantities of a byproduct tentatively identified as an unsymmetrical 1,*X*'-biisoquinoline.

Pyridines bearing a leaving group at C_2 or C_4 also participated in *trans*-halogenation reactions under the specified conditions, thus affording the anticipated iodinated products in generally good yield. The origins of the rather poor yield (33%) associated with the conversion of triflate **292** into iodide **293** (Table 5.3.1, Entry 19) were unclear but could, seemingly, be addressed by using the corresponding nonaflate (**294**) as substrate (Table 5.3.1, Entry 20). The lack of reaction of substrate **300** at C_2 was a little surprising given the successful *trans*-halogenation of 2-chloropyridine (Table 5.3.1, Entries 22 and 24) but clearly attributable to the presence of the C_3 chlorine substituent. It seems possible that the two chlorines attached to the pyridine ring in compound **300** inhibited the initial *N*-acylation process, thus precluding *trans*-halogenation under the established conditions. Of course, steric effects exerted by the two chlorines may have also contributed to the lack of reactivity of compound **300**.

The success of these reactions is clearly dependent upon the acylation of the ring-nitrogen and the resulting activation of the halogenated (or pseudohalogenated) carbon toward a S_NAr reaction involving iodide as nucleophile. To ensure complete reaction, a threefold excess of NaI was employed under those conditions involving acetic anhydride (procedure A) as the activating agent. When acetyl chloride was used for the same purpose (procedure B) then a tenfold excess of NaI was used so as to ensure a much higher iodide than chloride ion concentration in the reaction mixture. It is noteworthy that in all instances where an isoquinoline or pyridine was a substrate then the more vigorous conditions

defined by procedure B were required to achieve good conversions into the target iodide.

A brief investigation of the capacity of other aromatic nitrogen heterocycles to participate in the title process was undertaken. However, no useful outcomes were observed. Thus, for example, attempts to effect *trans*-halogenation of the commercially available substrates **301** and **302** (Figure 5.3.1) under either of the specified conditions failed and only the starting compounds were recovered in each instance.



301 **302**

Figure 5.3.1. *Heterocycles* ***301*** *and* ***302*** *that were inert to the* trans-*halogenation conditions.*

A final aspect of the present investigation was concerned with establishing if nucleophiles other than iodide could be induced to participate in S_NAr reactions under the conditions developed. However, upon exposing compound **270** to either acetic anhydride or acetyl chloride in the presence of various sources of fluoride, chloride, cyanide, and nitrite anions no evidence for the formation of the hoped-for substitution products could be obtained.

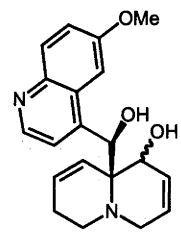
5.4 Summary and Conclusions

The comprehensive study investigating the scope, limitations and utility of this new *trans*-halogenation methodology established that quinolines bearing a leaving group at C_2 and/or C_4 readily engaged in the desired *trans*-halogenation process providing the corresponding iodides in generally excellent yields. The C_1 position was the only location on the isoquinoline framework where such a transformation could take place. Pyridines featuring a halogen/pseudohalogen substituent at C_2 or C_4 also participated in the reaction affording the anticipated iodinated products in generally good yields. In some circumstances it was found that using acetic anhydride as the activating agent provided better yields of product than when acetyl chloride was employed for the same purpose. Indeed in, all instances where isoquinolines or pyridines were substrates acetyl chloride was required to achieve good conversions into the target iodides.

Certainly, this newly established protocol provides a useful means for effecting the rather rapid and efficient *trans*-halogenation of various chlorinated, brominated, or pseudohalogenated quinolines, isoquinolines, and pyridines under mild conditions. The reaction pathways involved mean that the regioselectivities of these processes are entirely predictable. As such this methodology should provide a useful addition to the *repertoire* of

procedures available for preparing a variety of iodinated aromatic nitrogen heterocycles.

The development of the abovementioned *trans*-halogenation methodology enabled the concise and efficient preparation of 4-iodo-6-methoxyquinoline (**262**) in 4 steps and 76% overall yield. With this key building block in hand studies directed towards the synthesis of key quinolizidine **217** (Figure 5.4.1) could commence. Accordingly, the aim of the research described in Chapter Six was to exploit the chemistry that had been established and described in both this and the preceding chapter to generate heterocycle **217**, from which the centrepiece anionic oxy-Cope rearrangement could be investigated.



217

Figure 5.4.1: *Key anionic oxy-Cope rearrangement substrate* **217.**

5.5 References

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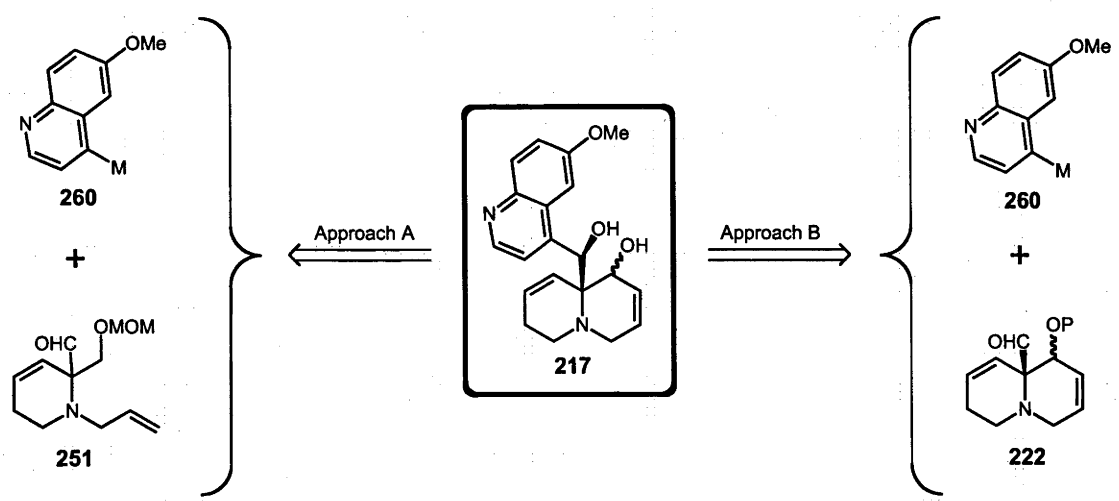
Chapter Six

Evolution of the Synthetic Strategy Leading to (-)-Quinine

This chapter describes efforts to prepare quinolizidine **217** via *two fundamental approaches. The outcomes of this investigation and its bearing on the development of the strategy leading to (-)-quinine (***136***) are outlined.*

6.1 Introduction

As noted in Chapters 4 and 5, there are conceivably two distinct routes that could be employed in gaining access to the key anionic oxy-Cope rearrangement substrate **217**, namely approaches A and B as shown in Scheme 6.1.1. The former pathway would involve the addition of metallated quinoline **260** to piperidine **251**, while the latter would require the coupling of heterocycle **260** with quinolizidine **222**. However, because piperidine **251** essentially constitutes a synthetic intermediate *en route* to structure **222** the former was selected to form the basis of preliminary investigations directed towards the installation of quinoline **260**. Such a decision directly reflected the fundamental need to promptly establish suitable conditions capable of effecting this important transformation.



Scheme 6.1.1. *The two fundamental strategies for preparing key anionic oxy-Cope rearrangement substrate* **217**.

Indeed, with the exception of the centrepiece rearrangement, this addition reaction probably represents the most crucial step associated with the proposed synthesis of (-)-

quinine (**136**).[⊥] Certainly, if this step were unsuccessful then the synthetic strategy would need to be drastically redefined. It should be noted that this approach to quinolizidine **217** features a challenging coupling of 'neopentyl' aldehyde **251** with the bulky and thus weakly nucleophilic quinoline **260**.[Ω] Accordingly, compound **251** was chosen to study the coupling reaction because of the small size of the MOM-protecting group contained within it and the inertness of this moiety to basic conditions. The aim of the research presented in this chapter was to develop conditions that would allow for the incorporation of fragment **261** and to then devise a route that would enable the preparation of heterocycle **217**. The outcomes of such endeavours are discussed herein. Of course, the ultimate aim of such efforts was to establish a total synthesis of (-)-quinine (**136**).

6.2 Investigation of Approach A

6.2.1 Installation of the Quinoline Substituent

With 4-bromo-6-methoxyquinoline (**203**) and 4-iodo-6-methoxyquinoline (**262**) in hand, the important coupling reaction could be investigated. To this end, bromide **203** was treated with *n*-BuLi and intermediate **184** thus formed was added to a THF solution of aldehyde **251** maintained at -78 °C. The ensuing mixture was then allowed to slowly warm to ambient temperature over *ca.* 20 h. However, no reaction occurred despite numerous attempts. It was postulated that residual impurities associated with the oxidation of alcohol **250** to compound **251** may have been interfering with this addition process and a favourable result might be achieved if heterocycle **251** could be obtained in a purer form.[Ψ] Although not essential when reacting vinylmagnesium bromide with compound **251** (Scheme 4.4.1), presumably the poorer nucleophilicity of lithiated quinoline **184** necessitated such a modification in this instance.

The inherent instability of aldehyde **251** to flash chromatography precluded the use of this technique for its purification and dictated that an alternative method needed to be developed. Thus, the addition of ether to the crude samples of compound **251**, obtained after work-up, ultimately allowed for insoluble impurities[ξ] to precipitate out of solution. Subsequent filtration of the mixture through a pad of magnesium sulfate and concentration of the resulting filtrate provided material of adequate purity.[Θ] This was evidenced by the

[⊥] It might also be argued that the success of either of the ring-closing metathesis steps in the sequence is just as crucial because if one of these transformations were to fail the synthetic strategy would need to be altered significantly.

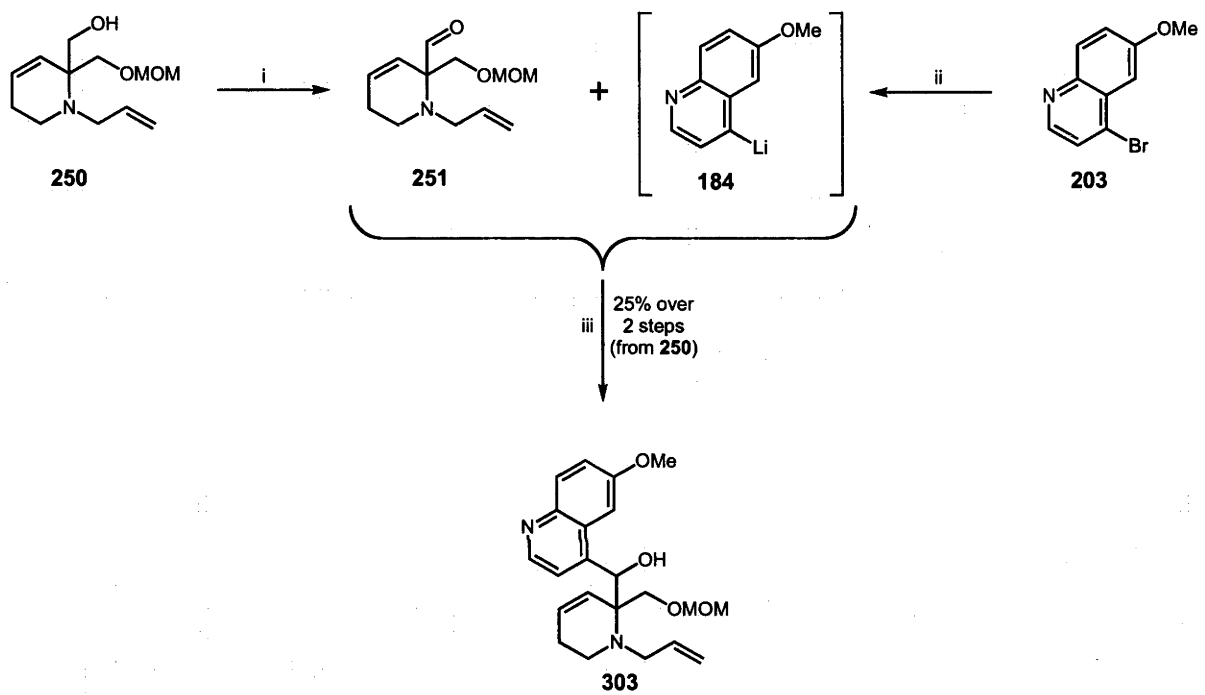
[Ω] These challenges are also a feature of approach B.

[Ψ] Because of the significant yield loss associated with the purification of aldehyde **251** by flash chromatography, which was previously discussed in Chapter 4, compound **251** was not isolated.

[ξ] Identification of these impurities was not undertaken.

[Θ] The ^{1}H NMR spectrum corresponding to this material displayed the expected signals assigned to aldehyde **251**, in addition to a peak corresponding to residual DMSO, and only some very minor signals arising from trace impurities.

fact that when a THF solution of aldehyde **251** obtained in this manner was treated with quinoline **184**, then alcohol **303** was provided as a single diastereoisomer,[⊥] albeit in only 25% yield over two steps from alcohol **250** (Scheme 6.2.1). Clearly, then, the addition reaction was particularly inefficient and this presumably derives from the aforementioned properties of compounds **251** and **184** which are responsible for their attenuated reactivities. In addition to this, the instability of intermediate **184** at temperatures above -50 °C, as reported[1] by Uskoković and co-workers during their third total synthesis of quinine (**136**), may have also contributed to this disappointing result.



Scheme 6.2.1. *The preparation of quinoline* ***303****.*
Reagents and conditions: *(i)* $(COCl)_2$, *DMSO,* Et_3N, CH_2Cl_2, *-78 → 18 °C; (ii)* n-*BuLi, THF, -78 °C; (iii) THF, -78 → 18 °C.*

The 300 MHz ^{1}H NMR spectrum of heterocycle **303** (Figure 6.2.1) displayed all of the expected resonances. Indeed, the most diagnostic features are the four doublets and the singlet in the region δ 8.75-6.95 that correspond to the five individual quinoline protons and the multiplets at δ 6.00 and 5.17 that are assigned to three protons present within the vinyl group. A pair of doublets at δ 4.13 and 3.90[Ω] (J = 10.5 Hz) that arise from the two AB-coupled protons within the aliphatic methylene group (alpha to the OMOM moiety) are also observed. The singlets at δ 5.56, 4.79, 3.92 and 3.44 that are attributed to the oxymethine proton, the two MOM-methylene protons, the three quinoline-methoxyl protons and the

[⊥] The relative stereochemistry of compound **303** was not explicitly established.
[Ω] The doublet at δ 3.90 overlaps the singlet at δ 3.92.

three MOM-methoxyl protons, respectively, are also visible. The signals corresponding to the two olefinic protons contained in the piperidine ring are not observed in the expected chemical shift range (δ 5.5-6.5). It is postulated that the electron density of quinoline ring heavily shields these protons, causing the corresponding to be shifted well upfield where they are obscured by other spectral features. The 75 MHz ^{13}C NMR spectrum (Figure 6.2.2) displays the expected twenty-two carbon resonances and is fully consistent with the assigned structure. Furthermore, the ESI mass spectrum displays a protonated molecular ion (M + H) at *m/z* 385 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{22}H_{28}N_2O_4$.

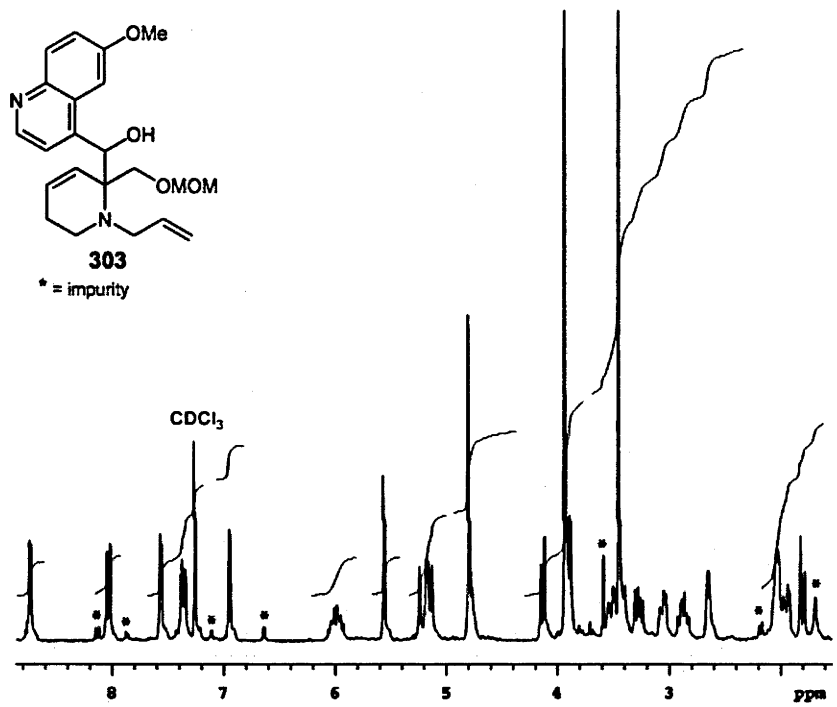


Figure 6.2.1. *300 MHz ^1H NMR spectrum of product* ***303*** *(recorded in $CDCl_3$).*

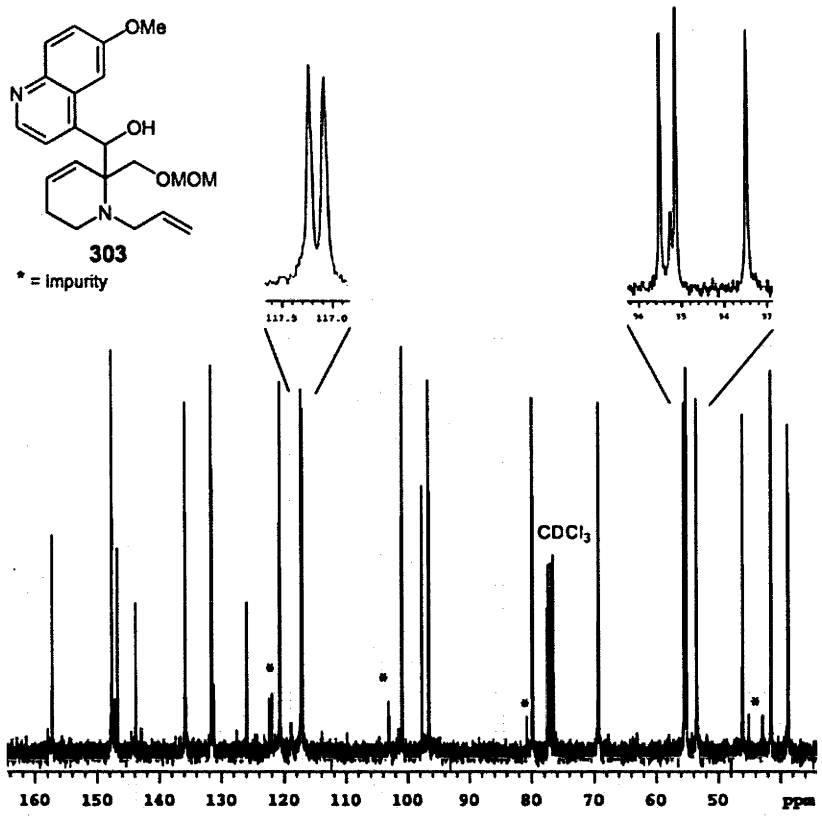


Figure 6.2.2. *75 MHz ^{13}C NMR spectrum of product 303 (recorded in $CDCl_3$).*

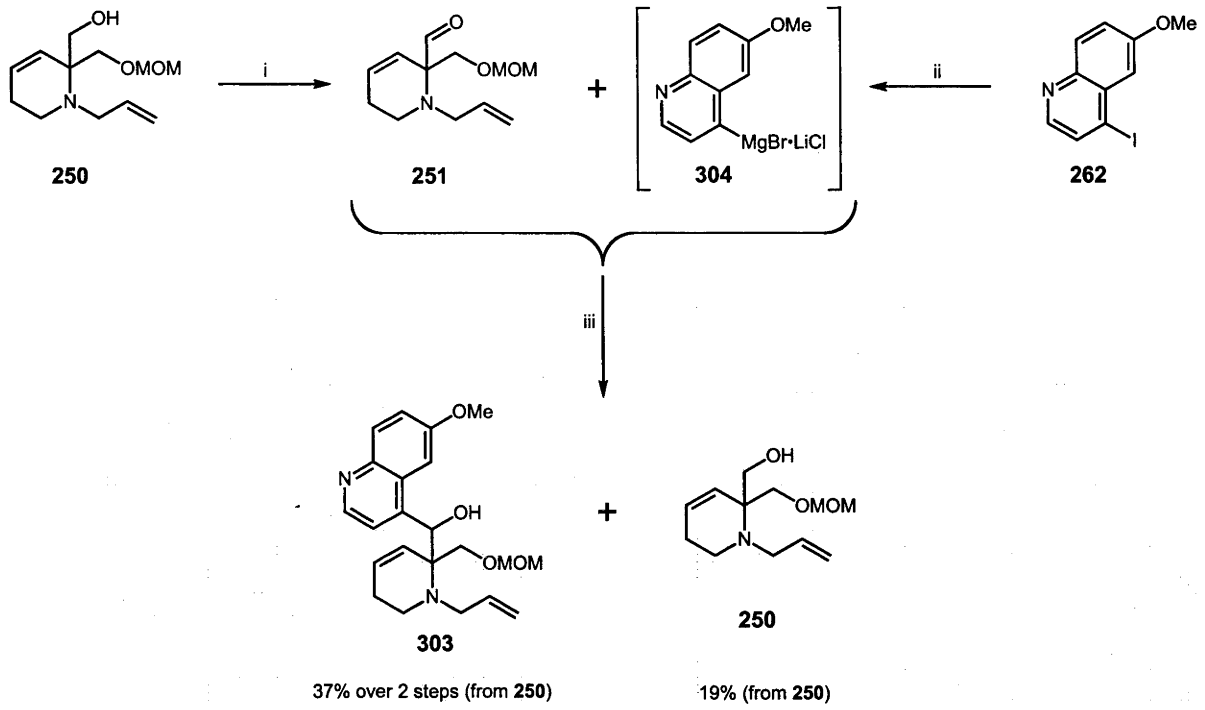
The low yield associated with the transformation of **251** + **184** → **303** obviously required that optimisation studies be undertaken. With this in mind, the reaction was repeated employing lithium-complexing reagents (HMPA and DMPU) but, surprisingly, in both cases compound **303** was not isolated. These disappointing results prompted an investigation of the capacity of a various transmetallation processes to provide target **303**. Thus, intermediate **184** was treated with $CeCl_3$ so as to generate the corresponding organocerium derivative. However, treatment of the latter species with aldehyde **251** gave only a complex mixture of products. Similar results were obtained in analogous reactions involving the organotitanium derivative of species **184**, prepared from chlorotriisopropoxytitanium(IV), and the analogous organozinc reactant synthesised using $ZnBr_2$. Interestingly, when organolithium **184** was treated with CuI then aldehyde **251** under a range of conditions no reaction occurred. Certainly, an inherent problem encountered when analysing the results of the abovementioned transmetallation processes was establishing whether the requisite intermediate was actually being formed from organolithium **184**.[⊥] As such, the failure to synthesise heterocycle **303** by these means may, or may not, have been due to an inability to generate the requisite metallated-derivatives of quinoline **184**.

[⊥] This is a problem encountered when analysing the results of unsuccessful transmetallation reactions more generally.

These poor results led to an investigation of the ability of the relevant organomagnesium derivatives of quinoline **184** to provide product **303**. The preparation of the quinoline-based Grignard[2] reagents by traditional direct magnesiation protocols is complicated by their instability at moderate temperatures. This is possibly related to the low LUMO levels of the aromatic heterocycle which makes various positions on the ring susceptible to nucleophilic attack.[3] Fortunately, Knochel has developed an impressive range of procedures[4] for the insertion of magnesium between carbon-halogen bonds under mild conditions. Thus, it was anticipated that such methodology could provide the desired Grignard derivative from iodoquinoline **262**. More specifically, Knochel has shown[4] that the direct magnesiation of bromopyridines can be effected at ambient temperature in the presence of LiCl. This salt serves a number of purposes - solubilising the resultant organomagnesium product and hence constantly providing a 'clean' metal surface or promoting initial electron transfer by the electrophilic activation of the aromatic ring through complexation.[5] The high ionic strength of LiCl solutions also facilitates charge separation and thus accelerating metal insertion.[6]

When iodide **262** was subjected to the abovementioned direct magnesiation protocol,[4] the corresponding Grignard could be generated after 1.5 h at ambient temperature but no reaction occurred when this intermediate was then reacted with aldehyde **251**. However, Knochel has also reported procedures[7] that allow for the preparation of 4-bromoquinoline-derived Grignard reagents by using *i*-PrMgCl•LiCl to promote bromine/magnesium exchange reactions. Accordingly, treatment of 4-iodo-6-methoxyquinoline (**262**) with *i*-PrMgBr•LiCl efficiently delivered compound **304** after 0.5 h at -78 °C (Scheme 6.2.2).[⊥] When quinoline **304** was added to a THF solution of aldehyde **251** maintained at -78 °C and the mixture allowed to gradually warm to ambient temperatures over *ca.* 20 h, this provided heterocycle **303** (37%), as a single diastereoisomer, along with alcohol **250** (19%). As the yield improvement reflects, this transformation was more efficient than the analogous organolithium-mediated process. This may be attributed to the greater stability of Grignard **304** relative to lithiated quinoline **184**.

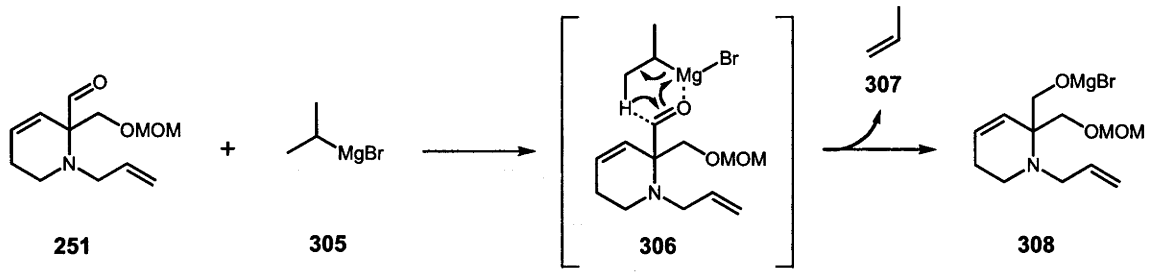
[⊥] When this transformation attempted using bromide **203** the exchange process only proceeded at low conversion (*ca.* <10%) after 2 h at -50 °C. This did not appreciably improve with extended reaction times and was accompanied by decomposition of quinoline **203** at higher temperatures.



Scheme 6.2.2. *The preparation of quinoline 303.*
Reagents and conditions: *(i)* $(COCl)_2$, *DMSO*, Et_3N, CH_2Cl_2, *-78 → 18 °C; (ii)* i-*PrMgBr•LiCl*, *THF, -78 °C; (iii) THF, -78 → 18 °C.*

The isolation of compound **250** from the transformation **251** + **304** → **303** + **250**, was an unexpected outcome. However, it has been reported[8] that both isopropyl and *t*-butyl Grignard reagents, which contain β-hydrogen atoms, are capable of reducing carbonyl groups. Thus, it is highly unlikely that intermediate **304** was responsible for the observed reduction of structure **251**. Rather, it is more probable that this outcome is due to the reversibility of the magnesium/iodine exchange process that generates Grignard **304**.[⊥] Thus, *i*-PrMgBr would be regenerated and a possible mechanism for the reduction of compound **251** that involves this species is shown in Scheme 6.2.3. The coordination of the magnesium atom within Grignard **305** to the carbonyl oxygen present in aldehyde **251** would form intermediate **306**. The subsequent elimination of propene (**307**) provides magnesium alkoxide **308** that upon work-up could give alcohol **250**.

[⊥] When reagent **304** was prepared from *i*-PrMgBr•LiCl an excess of iodide **262** was used.



251 305 306 308

Scheme 6.2.3. *A possible mechanism for the reduction of aldehyde* **251**.

Unfortunately, and despite extensive attempts, the transformation **251** + **304** → **303** + **250** could not be reproduced. Curiously, subsequent efforts only provided unreacted aldehyde **251**, alcohol **250** and various decomposition products. Furthermore, when *i*-PrMgBr•LiCl was prepared from different sources of magnesium and LiCl similar results were obtained. Atomic absorption spectroscopy performed on all of the magnesium and LiCl samples that were used indicated that they did not contain significant metal impurities. As such, the reasons for the irreproducibility of this addition process could not be determined.

It was anticipated that more success might be achieved by engaging the zinc-analogue of species **304** in reaction with aldehyde **251**. It was postulated that this could be achieved utilising established methodology that enables the preparation of zincated heterocycles from their corresponding iodinated derivatives *via* direct zinc insertion.[9] Accordingly, a *N,N*-dimethylacetamide solution of iodide **262** was reacted with zinc dust at ambient temperature.[⊥] While this gave no reaction (after 2 h), upon warming to 50 °C a *ca.* 1:5 mixture of the organozinc product and quinoline **262** was obtained after 3 h.[Ω] Unfortunately, the conversion did not improve appreciably with extended reaction times, while heating the reactants at 70 °C generated a number of unidentified byproducts. Because it has been reported[10] that zinc insertion processes can be promoted at lower temperatures in the presence of LiCl this was also attempted. However, such a modification gave similarly poor results, while employing Rieke zinc[11] also made little difference. Accordingly, the inability to adequately prepare the requisite zincated derivative of iodide **262** precluded further attempts to reinvestigate the reaction of interest. The utility of the Nozaki-Hiyama-Kishi reaction[12] to provide heterocycle **303** was briefly explored but the required chromium analogue of quinoline **262** could only be synthesised in trace amounts.

The outcomes of these studies focussed on preparation of compound **303** reflected the difficulties associated the strategy for incorporating the quinoline substituent. These

[⊥] Zinc dust was pretreated with 1,2-dibromoethane and chlorotrimethylsilane. This is a well known method for the activation of zinc, first reported by Erdik, E. *Tetrahedron*, **1987**, *43*, 2203.
[Ω] As judged by GCMS analysis of the reaction mixture.

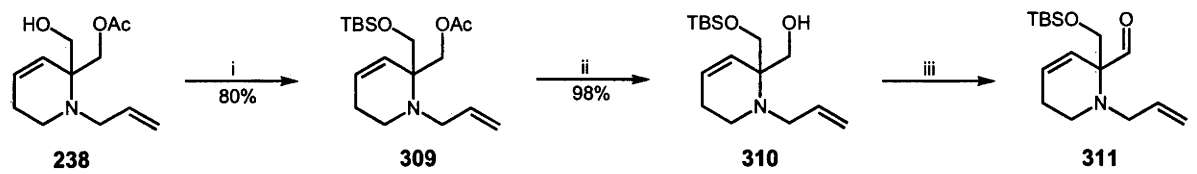
issues relate to the problem of coupling poorly nucleophilic heterocycle **184**, and its derivatives, with 'neopentyl' aldehyde **251**. Because of the irreproducibility of the Grignard addition to compound **251** the lower yielding process using organolithium **184** constituted the only successful, albeit inefficient, method for generating necessary product **303** (25% over two steps from alcohol **250**).

6.2.2 *Further Investigation of Approach A*

Attempts to elaborate heterocycle **303** to quinolizidine **217** followed but were restricted by both the poor nucleophilicity of the 2° alcohol moiety and the robust nature of MOM protecting group present within compound **303**.[⊥] Certainly, when ether **303** was treated with TFA under anhydrous conditions no reaction was observed. Similar results were obtained when either boron trifluoride or aqueous acetic acid were employed. Disappointingly, when a mixture of heterocycle **303** and HCl in aqueous methanol was heated at reflux this only led to decomposition of substrate **303**. In addition, treating species **303** with either bromotrimethylsilane or triphenylcarbenium tetrafluoroborate did not provide the relevant diol.

This inability to deprotect the MOM group within substrate **303** prompted the decision to investigate whether the reaction of TBS-protected congener of aldehyde **251** and quinoline **184** could provide the relevant TBS-derivative of coupled product **303**. With this in mind, the TBS-analogue **311** was prepared in 78% yield over two steps from acetate **238** by standard transformations (Scheme 6.2.4). Surprisingly, when compound **310** was subjected to the Swern oxidation conditions[13] that had successfully provided aldehydes **240** and **251**, product **311** was contaminated with numerous unidentified byproducts. Although the precise origins of this divergent behaviour are unknown, it is possible that this was the result of the sensitivity of TBS group within structure **310** to the HCl produced during the oxidation process. Fortunately, shortening the reaction time and adding more equivalents of triethylamine allowed for the smooth conversion of alcohol **310** into target **311**. However, when aldehyde **311** was reacted with quinoline **184** a complex mixture of products was obtained and despite repeated attempts the hoped-for addition product was not obtained.

[⊥] Compound **303** contains a 1° MOM group, which is particularly acid stable and thus it was anticipated that harsh conditions would be required for its removal.



Scheme 6.2.4. *Synthesis of aldehyde* ***311****.*
Reagents and conditions: *(i) TBSCl, imidazole, CH_2Cl_2, 18 °C; (ii) K_2CO_3, MeOH, 18 °C; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 → 18 °C.*

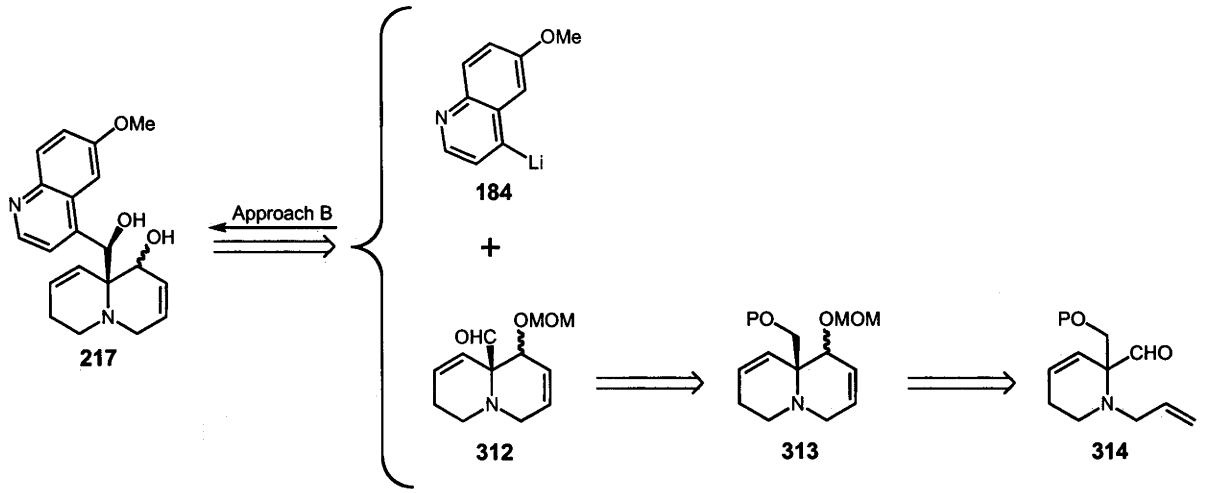
Although various suitably protected derivatives of aldehyde **311** could have been prepared and subsequently treated with quinoline **184** such a study was not undertaken.[⊥] The limited success of the crucial addition reaction reflected the sensitivity of this process and guided the decision to shift the focus of the research to studying the viability of approach B as defined earlier (see Scheme 6.1.1).

6.2.3 Summary and Conclusions

The outcomes of the investigation of approach A showed that the quinoline fragment could be incorporated to generate heterocycle **303**, as a single distereoisomer, albeit in a poor yield (25% over two steps from alcohol **250**).[Ω] The abovementioned research also illustrated the various problems associated with the strategy of attempting to prepare quinolizidine **217** *via* the coupling of aldehyde **251** and quinoline **184**. The fundamental reason for these difficulties almost certainly derives from the sensitivity of the crucial transformation **251** + **184** → **303** and this had ramifications on the development of the general approach to (-)-quinine (**136**). Because product **303** was unable to be elaborated into target **217** it was envisaged that the establishment the quinolizidine framework prior to the coupling reaction could allow for the construction of compound **217**.

Consequently, it was anticipated that an approach to key substrate **217**, *via* path B, by a sequence involving the addition of organolithium **184** to heterocycle **312** (Scheme 6.2.5), would be more successful. Provided an appropriate base-stable protecting-group is present within aldehyde **314** then the vinylation of this compound would appear to be more straightforward than the incorporation of the quinoline fragment at the equivalent stage. In addition to this, the ultimate removal of the MOM moiety to generate quinolizidine **217** would presumably be more facile in such a system than the analogous deprotection of compound **303**. This is because the relevant MOM group would be attached to a 2° and allylic oxygen substituent.

[⊥] The reaction of acetate-protected aldehyde **240** with quinoline **184** only provided a complex mixture of products.
[Ω] Heterocycle **303** was prepared in 37% yield by reaction with Grignard **304**, however, this result could not be reproduced.



Scheme 6.2.5. *Retrosynthetic analysis of quinolizdine 217 by approach B.*

6.3 Investigation of Approach B

6.3.1 Synthesis of Quinolizidines 322 and 323

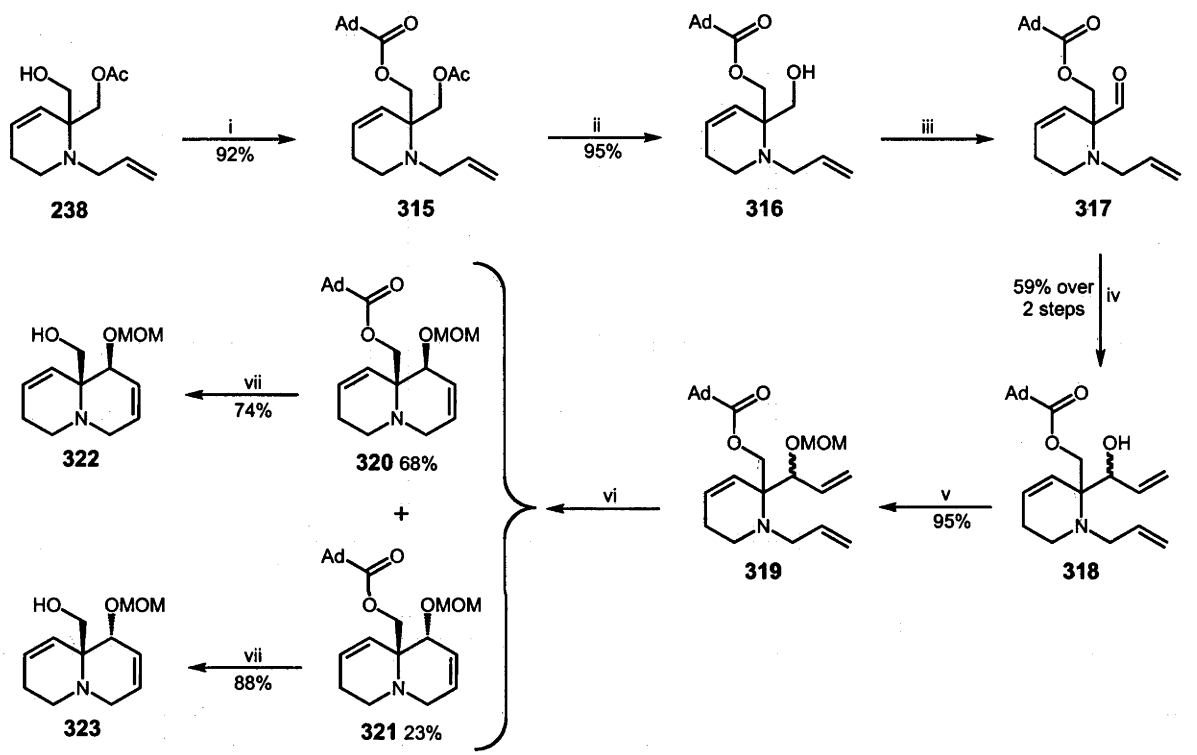
Identifying a suitable protecting group within aldehyde **314** that would enable an efficient vinylation process to occur was not a straightforward undertaking. Although it was anticipated that this could be achieved utilising the abovementioned TBS-protected aldehyde **311** (Scheme 6.2.4.), treatment with vinylmagnesium bromide provided a complex mixture of products and only traces of the desired allylic alcohol. Despite extensive attempts, this transformation was unable to be performed efficiently. Unfortunately, this problem could not be solved with the use of substituted ether-protecting groups. Indeed, the 1-ethoxyethyl moiety could not be introduced despite employing numerous established procedures.[14] These issues were finally resolved by preparing the adamantoate-protected analogue of aldehyde **314** and this allowed for the synthesis of quinolizidines **322** and **323** as shown in Scheme 6.3.1. Thus, reaction of acetate **238** with 1-adamantoyl chloride[⊥] in the presence of pyridine followed by treatment of resulting adamantoate **315** (obtained in 92% yield at 92% conversion) with K_2CO_3 in methanol at 0 °C[Ω] afforded expected alcohol **316** (95%). Compound **316** was then oxidised to the aldehyde **317** under Swern conditions.[Ψ] Reaction of structure **317** with vinylmagnesium bromide gave a *ca.* 2:1 mixture of the chromatographically inseparable epimeric allylic alcohols **318** (59% over two steps from

[⊥] A large excess of 1-adamantoyl chloride (*ca.* 2.5 equiv.) was required in order for the reaction to proceed with good conversion.

[Ω] When this reaction was performed at ambient temperature cleavage of the adamantoate group also occurred. Presumably neighbouring group participation involving the alcohol present within compound **316** is responsible for this outcome.

[Ψ] Aldehyde **317**, like congeners **251** and **240**, is also unstable to purification by flash chromatography.

316). Trienes **318** were then reacted with chloromethyl methyl ether in the presence of Hünig's base to afford a chromatographically inseparable mixture of the diastereoisomeric forms of adamantoate **319** (95% at 87% conversion).[⊥] The ring-closing metathesis of epimers **319** employing Grubbs' second generation catalyst[15] provided a chromatographically separable mixture of quinolizidine derivatives **320** (68%) and **321** (23%). Each of product heterocycles **320** and **321** was then independently treated with lithium aluminium hydride and thereby generating the target mono-ols **322** (74%) and **323** (88%), respectively.



Scheme 6.3.1. *Synthesis of quinolizidines* **322** *and* **323**.
Reagents and conditions: *(i) 1-adamantoyl chloride, pyridine, DMAP, CH_2Cl_2, 0 → 18 °C; (ii) K_2CO_3, MeOH, 0 °C; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 → 18 °C; (iv) vinylmagnesium bromide, THF, -78 → 0 °C; (v) MOMCl, Hünig's Base, DMAP, CH_2Cl_2, 18 °C; (vi) 10 mol% Grubbs' II, DMSO, NEt_3, PhMe, 18 → 60 °C; (vii) $LiAlH_4$, THF, 0 → 18 °C.*

[⊥] A very large excess of chloromethyl methyl ether (*ca.* 17.4 equiv.) and an extended reaction time (46 h) was required in order for the reaction to proceed with good conversion. Presumably this is due to the poor nucleophilicity of this sterically hindered 2° alcohol.

The 300 MHz ^{1}H NMR spectrum of quinolizidine **322** (Figure 6.3.1) displayed all of the expected resonances. Indeed, the most diagnostic features are the three signals in the region δ 6.09-5.55 that are attributed to the four olefinic protons and the set of doublets at δ 4.72 and 4.62 (J = 6.3 Hz) that correspond to the pair of AB-coupled protons present within the MOM-methylene group. The singlet at δ 3.38 representing the three MOM-methyl protons and the broad singlet δ 1.90 which is assigned to the single hydroxyl proton were also considered diagnostic. The 75 MHz ^{13}C NMR spectrum (Figure 6.3.2) displays the expected twelve carbon resonances and is completely consistent with the assigned structure. Furthermore, the ESI mass spectrum displays a protonated molecular ion (M + H) at *m/z* 226 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $C_{12}H_{19}NO_3$.[⊥]

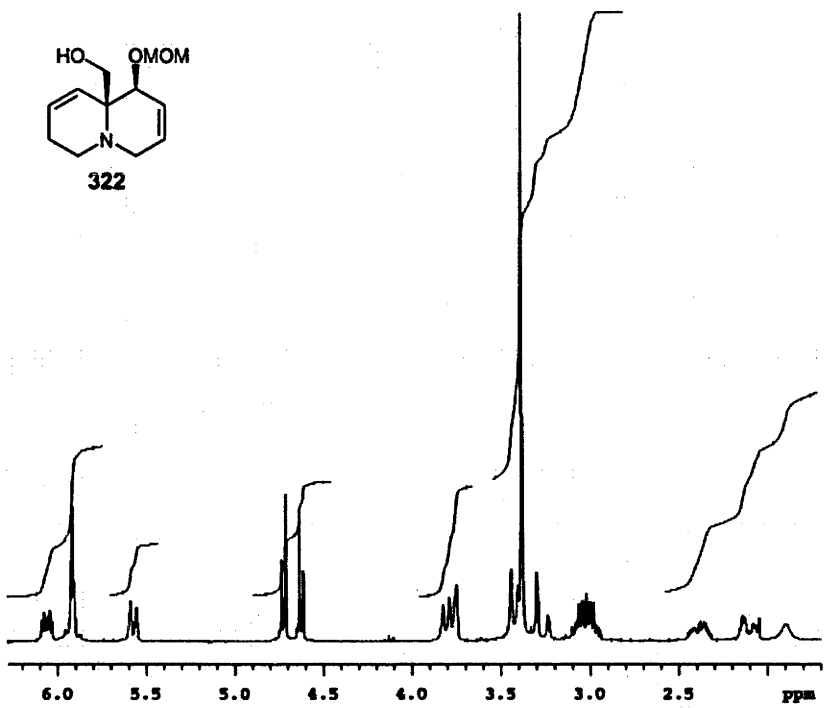


Figure 6.3.1. *300 MHz ^{1}H NMR spectrum of quinolizidine* **322** *(recorded in $CDCl_3$).*

[⊥] The equivalent spectroscopic data obtained on diastereoisomer **323** were very similar to those of compound **322** and, as such, have not been discussed explicitly.

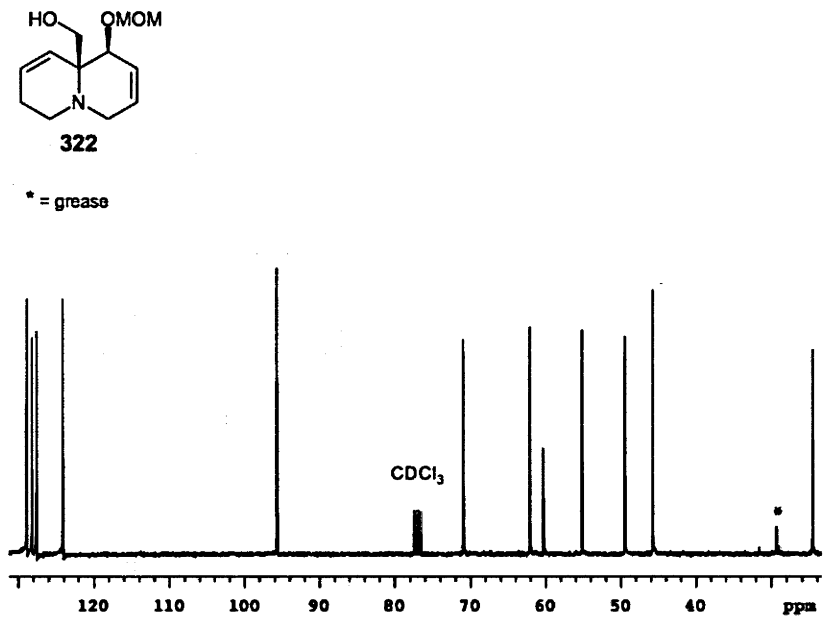
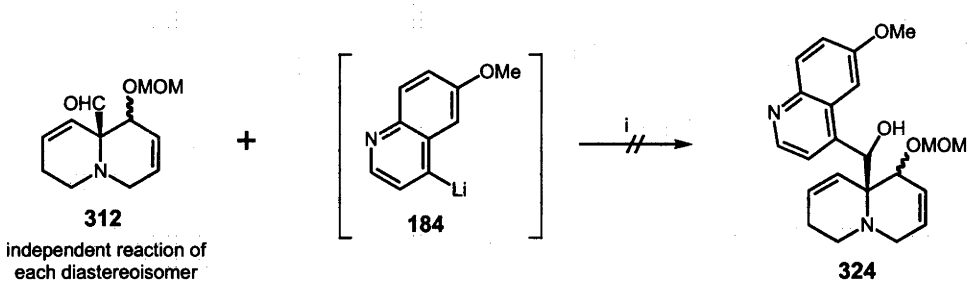


Figure 6.3.2. *75 MHz ^{13}C NMR spectrum of quinolizidine 322 (recorded in $CDCl_3$).*

6.3.2 *Investigation of Approach B*

With diastereoisomers **322** and **323** in hand, approach B could be investigated. To this end, alcohols **322** and **323** were independently subjected to the Swern oxidation[13] conditions that had successfully provided compounds **240** and **251** and the respective aldehydes **312** thus formed were each reacted with lithiated quinoline **184** (Scheme 6.3.2.).[⊥] In both cases only a complex mixture of products was obtained and desired heterocycles **324** were not formed. Presumably these disappointing results derived from the greater steric hindrance of aldehdyes **312** relative to piperidine **251** which led to the complete suppression of the desired nucleophilic addition process. As a consequence, the research effort directed towards the preparation of quinolizidine **217** *via* approach B was abandoned.



Scheme 6.3.2. *The failed reaction of aldehydes 312 with lithiated quinoline 184.*
Reagents and conditions: *(i) THF, -78 → 18 °C.*

[⊥] The conditions that successfully enabled the transformation of **251** + **184** → **303** were employed.

6.4 Future Work

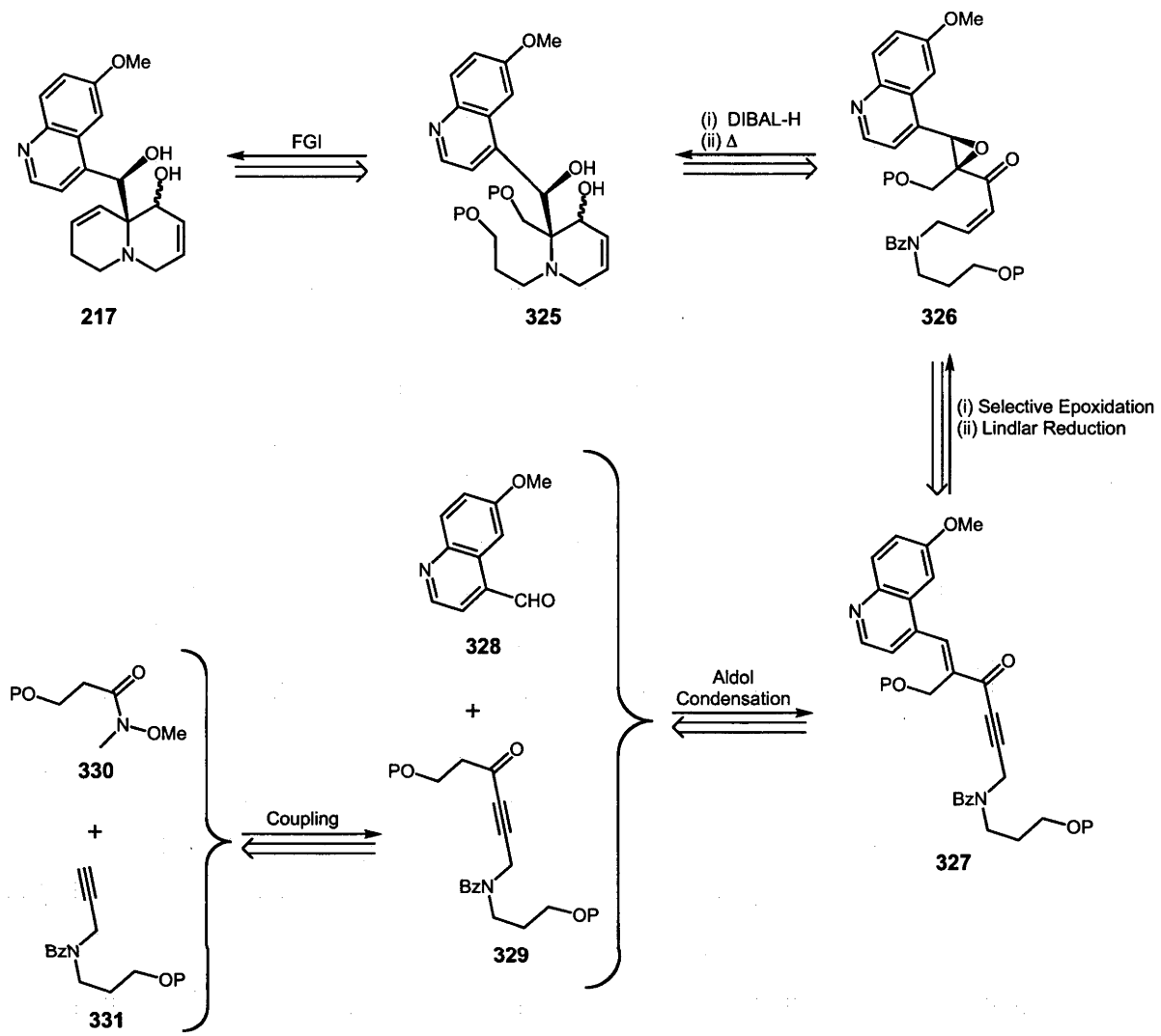
The abovementioned difficulties associated with the synthetic strategies leading to quinolizidine **217** illustrate that if this key intermediate is to be prepared a completely different approach is probably required. Thus, a new route to structure **217**, shown Scheme 6.4.1, is proposed that should avoid the problems that were encountered with the installation of the quinoline substituent. In a reverse sense the proposed sequence to compound **217** requires that it be prepared *via* functional group interconversions from piperidine **325**.[⊥] It is anticipated that intermediate **325** would, in turn, be derived from the global reduction and subsequent thermally-assisted intramolecular nucelophilic ring-opening of epoxide **326**. α,β-Unsaturated ketone **326** can, in turn, conceivably result from the selective oxidation/Lindlar reduction[16] of olefin **327**. Certainly, the stereo- and chemo-selective installation of the epoxide functional group poses the most significant obstacle to the success of this route to quinolizidine **217**. Accordingly, the most sensible strategy would involve a two-step sequence involving the Sharpless asymmetric dihydroxylation[17] of alkene **327** and subsequent conversion of the product diol into the relevant epoxide. This transformaton is well established and has been utilised to enantioselectively prepare a multitude of vicinal diols. Furthermore, such reactions occur almost exclusively with alkenes.[Ω18] Such an approach certainly appears more straightforward than attempting the direct epoxidation of alkene **327** utilising either the Jacobsen-Katsuki[19] or Shi[20] methodologies or by performing a Sharpless asymmetric epoxidation[21] on the corresponding allylic alcohol derivative. It is envisaged that quinoline **327** can be prepared *via* the aldol condensation of commercially available aldehyde **328** and α,β-unsaturated ketone **329**.[Ψ] Intermediate **329** could arise by the nucleophilic addition of the anion derived from propargylic amide **331** to Weinreb amide **330**.[§]

[⊥] It is envisaged that this double bond can ultimately be installed *via* a ring-closing metathesis process. The requisite triene substrate may be synthesised by the double-Wittig reaction of the relevant di-aldehyde precursor after elaboration of the protected primary alcohol moieties. Establishing the necessary olefin in this fashion rather than relying on a base-promoted β-elimination process is a response to concerns regarding the basic piperidine nitrogen complicating such a transformation.

[Ω] Thus, the alkyne moiety should be inert to the reaction conditions.

[Ψ] Presumably the inverse addition of Michael acceptor **329** to an appropriate base will be required in order to avoid the 1,4-addition of the enolate derived from ketone **329** to starting material **329**.

[§] It is anticipated that amide **331** can be derived from the commercially available *N*-(prop-2-ynyl)benzamide.



Scheme 6.4.1. *Retrosynthetic analysis of quinolizidine* **217**.

6.5 Summary: Part Two

Only three successful stereoselective approaches to (-)-quinine (**136**) have been achieved over the past 150 years and these featured the formation of the quinuclidine core by either the novel N-C_6 disconnection[22] or the traditional Rabe N-C_8 route.[23,24] Accordingly, this study sought to investigate the potential for an unusual and wholly unprecedented anionic oxy-Cope rearrangement[25] to construct the 1-azabicyclo[2.2.2.]octane framework of the *Cinchona* alkaloid by a distinctive C_3-C_4 disconnection strategy.[⊥]

In order to test the validity of this hypothesis, model quinolizidines **245**, **246**, **256** and **257** were prepared as described in Chapter Four.[26] The capacity of these substrates to engage in the pivotal anionic oxy-Cope rearrangement was comprehensively investigated

[⊥] Of course the ultimate aim of this research was to complete a total synthesis of (-)-quinine (**136**).

and the formation of lactol **248** supported the fundamental proposal. These encouraging findings indicated that the key transformation could form the centrepiece of an original and distinctive total synthesis of (-)-quinine (**136**). Significantly, the observed dianionic rate enhancement of the rearrangement of adducts **245** and **246** led to the identification of quinolizidine **217** as the key intermediate *en route* to (-)-quinine (**136**). Unfortunately, structure **217** was ultimately unable to be prepared despite extensive attempts to do so. This was a result of problems associated with the installation of the quinoline substitutent. However, difficulty generating 4-iodo-6-methoxyquinoline (**262**) led to the development of a new protocol that provides a useful means for effecting the efficient and rather rapid *trans*-halogenation of various chlorinated, brominated, or pseudohalogenated quinolines, isoquinolines, and pyridines under mild conditions.[27] A comprehensive study investigating the scope, limitations and utility of this novel *trans*-halogenation methodology was undertaken and outlined in Chapter 5.

6.6 Conclusion: Part Two

The fabled story of (-)-quinine (**136**) is essentially as old as organic synthesis itself. Certainly, because of quinine's versatility and utility as a molecule of both chemical and medicinal interest, the classic struggle to synthesise it, and the controversy that is inextricably linked to its legend, the celebrated *Cinchona* alkaloid maintains a significant and hallowed place in chemistry, its history and folklore. The quinuclidine-based natural product contains only four stereocentres,[⊥] however, its ostensibly simple structure belies the formidable challenge its synthesis has presented generations of highly skilled chemical practitioners. Indeed, such difficulties are reflected in the outcomes of research described in Part Two of this thesis.

Arguably, the evolution of the synthetic approaches to this fascinating natural product is a microcosm of the progress that has been made in organic synthesis from its humble beginnings at the turn of the twentieth century to its current sophistication. Rabe's pioneering synthesis[28] of quinine (**136**), disclosed in 1918, is generally acknowledged[29] as one of the primary events that constituted the inception of total synthesis as the discipline it became in the 1950s. The classical design and genuine artistry of Woodward and Doering's audacious route[30] to the *Cinchona* alkaloid epitomised the largely unsystematic approach to total synthesis, in which complex targets were prepared as individual masterpieces, during an era that the former defined. Stork's *tour de force*,[22] a prodigious and enduring effort, which itself spanned over half of the twentieth century, elegantly showcased the significant advancements that stereochemical, conformational and retrosynthetic analysis offered -

[⊥] The quinuclidine nitrogen and C_4 constitute a single asymmetric unit due to their bridgehead location.

developments which significantly contributed to the discipline's metamorphosis into an exact science.[1] Jacobsen's subsequent and equally impressive total synthesis of (-)-quinine (**136**) in 2004,[23] employing both modern reagents and techniques, illustrated the power and efficiency of contemporary organic synthesis and highlighted the integral role that asymmetric catalysis has played in such improvements. The research outlined in this thesis suggests, at least to some extent, that despite the significant progress that has been made in synthetic chemistry over the past century the discipline is far from fully mature and new frontiers and challenges still exist.

As a result of the investigation described in Part Two it is anticipated that if quinolizidine **217** can be prepared, possibly *via* the approach proposed in Scheme 6.4.1, this substrate should engage in the anionic oxy-Cope rearrangement. There is confidence that such a strategy can ultimately provide (-)-quinine (**136**). Certainly, if this route were to prove successful it would represent a completely unprecedented and distinctive total synthesis of this celebrated natural product and comprise the next chapter in the epic story of quinine; the remarkable *Cinchona* alkaloid which like a mythical Siren continues to bewitch and beguile synthetic chemists and maintains a tantalising aura of elusiveness.

[1] The formulation of detailed electronic mechanisms for fundamental organic reactions, the development of spectroscopic and other physical methods for structure analysis and the use of chromatographic methods of analysis and separation were also responsible for the advancement of organic synthesis. (Corey, E.J.; Cheng, X.M. *The Logic of Chemical Synthesis*, Wiley, New York, **1995**.)

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Chapter Seven

Experimental Procedures

"The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both."[1]

7.1 General Procedures

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied or, occasionally, recrystallised or distilled. Inorganic salts were purchased from Sigma-Aldrich, AJAX, BDH or Unilab Chemical companies.

Tetrahydrofuran (THF), diethyl ether (Et_2O) and benzene were distilled, under nitrogen, from sodium benzophenone ketyl. Toluene was distilled, through a Vigreux column, from molten sodium metal. Methanol (MeOH) and ethanol (EtOH) were distilled from their respective magnesium alkoxide salts. Dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) were distilled under nitrogen, through Vigreux columns, from calcium hydride. After March 2008 the abovementioned solvents, with the exception of ethanol, were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs.[2] Pyridine, triethylamine (Et_3N) and diisopropylamine were stored over anhydrous 4 Å molecular sieves that had previously been dried using a conventional microwave oven, then cooled under high vacuum and stored under anhydrous nitrogen or argon.

Glassware was soaked in a base bath (Pyroneg® in water) before being rinsed with water then acetone and oven-dried at 120 °C. Assembled apparatus was evacuated (<0.1 mm Hg) and flushed three times with dry nitrogen, prior to use. All reaction mixtures were manipulated under nitrogen using standard Schlenk techniques and, unless otherwise specified, stirred magnetically. Deoxygenated solutions were obtained by bubbling nitrogen through the relevant solution for at least 15 min.

Ambient temperature was assumed to be *ca.* 18 °C. Temperatures higher than ambient were attained using thermostated oil baths (or electrothermal heating mantles for temperatures greater than 200 °C). To attain temperatures lower than ambient, a cooled, water circulating bath (0 to 10 °C) or relevant cryostats (ice/water, 0 °C; dry ice/acetone, -78 °C; liquid nitrogen/MeOH, -100 °C) were used.

Organic solutions (extracts) obtained from the work-up of reaction mixtures were dried with sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before filtration and

concentration under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 40 °C unless otherwise specified.

All microwave irradiation experiments were carried out in a CEM Explorer™ microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilising the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL sealed Pyrex vessels with a working volume of 7 mL and equipped with a magnetic stirrer. The temperature was measured with a fibre optic temperature sensor immersed in the reaction vessel. After the irradiation period, the reaction vessel was cooled rapidly (1–2 min) to ambient temperature by jet cooling using nitrogen gas.

Flash column chromatography[3] was performed using analytical grade solvents and silica gel 60 (230–400 mesh, 0.040–0.0063 mm) as supplied by Merck.

Analytical thin layer chromatography (TLC) was performed on self-indicating aluminium backed 0.2 mm thick silica gel 60 GF254 plates as supplied by Merck. Similarly, preparative layer chromatography (PLC) was performed on self-indicating glass-backed 1.0 mm thick silica gel 60 GF254 plates, as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included: a) phosphomolybdic acid : cerium sulfate : sulfuric acid (conc.) : water (15 g : 2.5 g : 15 mL : 485 mL); b) potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL); c) anisaldehyde : sulfuric acid (conc.) : ethanol (3 mL : 4.5 mL : 200 mL); d) vanillin : ethanol : sulfuric acid (conc.) : water (18 g : 285 mL : 3 mL : 15 mL); e) ninhydrin : ethanol : glacial acetic acid (4.5 g : 300 mL : 9 mL).

Melting points were measured on a Stanford Research Systems Optimelt – Automated Melting Point System or on a Reichert hot-stage microscope apparatus and are uncorrected.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 20 °C in base-filtered deuterochloroform ($CDCl_3$) on a Varian Mercury 300 or Varian Inova 300 NMR spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Signals arising from the residual protio-forms of the solvent were used as the internal standard. Chemical shifts are recorded as δ values in parts per million (ppm). ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; qu = quintet; p = pentet; m=multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra, the data are given as: chemical shift (δ). The assignment of signals observed in proton and carbon NMR spectra was assisted by conducting complementary connectivity and/or proximity experiments. Connectivity experiments used included the attached proton test (APT), homonuclear (^{1}H/^{1}H) correlation

spectroscopy (COSY) and/or heteronuclear ($^{1}H/^{13}C$) correlation spectroscopy [heteronuclear multiple quantum coherence (HMQC) and/or heteronuclear multiple-bond correlation (HMQC)]. Proximity experiments included one or two-dimensional nuclear Overhauser effect and exchange spectroscopy (NOESY) experiments.

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

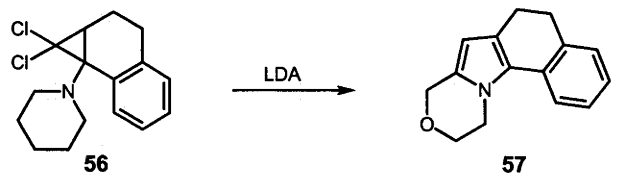
Mass spectrometry was performed by The Australian National University's Mass Spectrometric Services Unit located in The Research School of Chemistry, Canberra, Australia. Low and high resolution electron impact (EI) spectra were obtained on a VG Fisions AutoSpec M series three-sector (E/B/E) double-focussing mass spectrometer (located at The Australian National University). Low and high resolution electrospray (ES) mass spectra were recorded on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-MS or a VG Quattro II triple quadrupole MS instrument (both located at The Australian National University) operating in positive and/or negative ionisation mode. Gas chromatographic analysis and mass spectrometry (GCMS) were performed using, respectively, Varian 3400 Gas Chromatograph or an Agilent/HP 6890-5973 instrument (both located at The Australian National University) fitted with a capillary column. Peaks were detected using a flame ionisation detector operating at 300 °C and helium was employed as the carrier gas (flow rate *ca.* 35 $cm.s^{-1}$) with an isothermal temperature programme of 50 °C.

Analytical and semi-preparative high performance liquid chromatography (HPLC) was carried out using Waters Alliance 2695 separation module and Waters 2414 refractive index detector interfaced with Empower 2 chromatography software. In addition, semi-preparative HPLC separations were carried out using a Waters 600E solvent delivery system and a Rheodyne 7725i injection valve with a 5 mL sample loop. Analytical HPLC separations were carried out using a Waters XBridge C18 (5 μm) 4.6 mm (internal diameter) x 150 mm HPLC column (1 $mL.min^{-1}$ flow rate). Semi-preparative HPLC was carried out using a Waters XBridge C18 (5 μm) 19 mm (internal diameter) x 150 mm column (8.5 $mL.min^{-1}$ flow rate).

Elemental analyses were performed by The Australian National University's Microanalytical Services Unit based at The Research School of Chemistry, Canberra, Australia, using a Carbo Erba EA 1106 CHN-O automatic elemental analyser.

7.2 Experimental Procedures for Chapter Two

4,5-Dihydro-1*H*-benzo-1,3-oxazino-indole (57)



56 **57**

n-BuLi (1.00 mL of a 1.6 M solution in hexane, 1.61 mmol) was added to a magnetically stirred solution of diisopropylamine (0.23 mL, 1.61 mmol) in THF (7 mL) maintained under nitrogen at –20 °C. After 0.33 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 0.5 h then cooled to –60 °C and a solution of dichlorocyclopropane **56** (120 mg, 0.40 mmol, ex. Andrew Phillis, Banwell group) in THF (3 mL) was added. The ensuing reaction mixture was warmed, over 0.5 h, to 0 °C and maintained at this temperature for a further 5 h then NH_4Cl (5 mL of a saturated aqueous solution) was added and the separated aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 4:1 *v/v* hexane / EtOAc). Concentration of the appropriate fractions (R_f = 0.3) gave the *title pyrrole* **57** (39 mg, 43%) as a red, crystalline solid, m.p. 88–92 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.4 Hz, 1H), 7.26–7.16 (complex m, 2H), 7.04 (dt, *J* = 7.5 and 1.2 Hz, 1H), 5.80 (s, 1H), 4.91 (s, 2H), 4.29 (m, 2H), 4.06 (m, 2H), 2.86 (m, 2H), 2.65 (m, 2H).

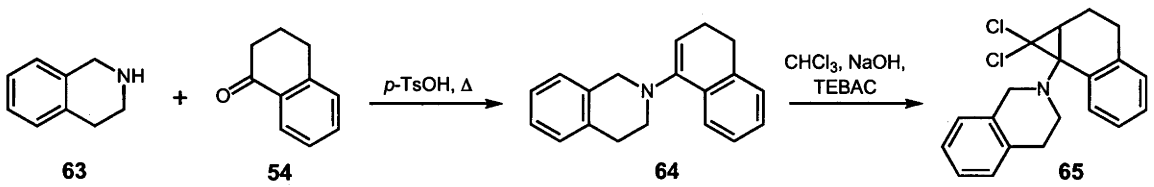
^{13}C NMR (75MHz, $CDCl_3$) δ 135.9, 129.9, 128.5, 127.1, 126.8, 126.5, 124.4, 122.0, 119.9, 101.2, 65.2, 64.6, 45.1, 31.1, 22.2.

IR υ_{max} (NaCl) 2834, 1489, 1427, 1383, 1338, 1301, 1114, 1089, 980, 876, 787, 753, 692 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 225 ($M^{+\bullet}$, 100%), 224 (80), 195 (63), 194 (66), 180 (17), 167 (25), 152 (14), 139 (13), 128 (9), 112 (20), 97 (15).

HREIMS Found: $M^{+\bullet}$, 225.1154. $C_{15}H_{15}NO$ requires $M^{+\bullet}$, 225.1154.

2-(1,1-Dichloro-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalen-7b-yl)-1,2,3,4-tetrahydroisoquinoline (65)



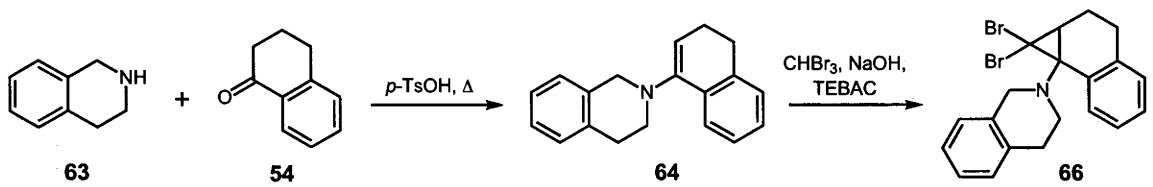
63 54 64 65

Step i: *p*-TsOH (131 mg, 0.69 mmol) was added to a magnetically stirred solution of 1-tetralone (**54**) (2.28 mL, 17.2 mmol) and 1,2,3,4-tetrahydroisoquinoline (**63**) (4.35 mL, 34.3 mmol) in toluene (15 mL) maintained under nitrogen at 18 °C and containing molecular sieves (1 g of 8-12 mesh 4 Å material). The ensuing mixture was heated at reflux for 62 h in a reaction flask fitted with a Dean-Stark trap topped by a Liebig condenser. The cooled reaction mixture was passed through filter paper and the filtrate concentrated under reduced pressure to give 2-(3,4-dihydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (**64**) as a clear, dark-green oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph.

Step ii: A magnetically stirred solution of 2-(3,4-dihydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (**64**) in $CHCl_3$ (25 mL) maintained under nitrogen at 18 °C was treated with powdered NaOH (4.13 g, 0.10 mol) and TEBAC (78 mg, 0.34 mmol) then subjected to sonication in a water bath. After 1 h the reaction mixture was filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with CH_2Cl_2 (150 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.3) afforded the *title dichlorocyclopropane* ***65*** (5.90 g, 70% over two steps) as a yellow, crystalline solid, m.p. 126 °C.

^{1}H NMR (300 MHz) δ 7.45 (m, 1H), 7.30–7.02 (complex m, 6H) 6.95 (m, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.51 (m, 2H), 3.15–2.74 (complex m, 4H), 2.54 (m, 2H), 2.16 (m, 1H), 1.67 (m, 1H).
^{13}C NMR (75 MHz) δ 141.2, 134.9, 134.7, 130.1, 129.1, 129.0, 128.5, 128.0, 126.5, 126.4, 126.1, 125.6, 72.6, 52.6, 51.0, 48.8, 37.5, 30.1, 28.9, 23.5.
IR υ_{max} (NaCl) 2927, 1487, 1453, 1383, 1276, 1141, 1099, 1050, 819, 747 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 347, 345 and 343 ($M^{+\bullet}$, 5, 22 and 30%), 310 and 308 (56 and 97), 261 (96), 260 (94), 141 (75), 131 (82), 130 (85), 117 (100), 115 (90), 91 (67).
HREIMS Found: $M^{+\bullet}$, 343.0893. $C_{20}H_{19}{}^{35}Cl_2N$ requires $M^{+\bullet}$, 343.0895.

2-(1,1-Dibromo-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalen-7b-yl)-1,2,3,4-tetrahydroisoquinoline (66)



63 54 64 66

A magnetically stirred solution of 2-(3,4-dihydronaphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (**64**) (1.00 g, 3.81 mmol), prepared from 1-tetralone (**54**) and 1,2,3,4-tetrahydroisoquinoline (**63**) as described above, and $CHBr_3$ (1.00 mL, 11.4 mmol) in CH_2Cl_2 (10 mL) maintained under nitrogen at 18 °C was treated with powdered NaOH (914 mg, 22.9 mmol) and TEBAC (17 mg, 0.8 mmol) then subjected to sonication in a water bath. After 0.5 h the reaction mixture was filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained were washed with CH_2Cl_2 (50 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.2) afforded the *title dibromocyclopropane* ***66*** (990 mg, 60% over two steps) as a yellow, crystalline solid, m.p. 38 °C.

^{1}H NMR (300 MHz) δ 7.42 (d, *J* = 7.0 Hz, 1H), 7.30-7.06 (complex m, 6H), 6.95 (d, *J* = 5.0 Hz, 1H), 3.87 (d, *J* = 14.0 Hz, 1H), 3.50 (m, 2H), 3.21-2.49 (complex m, 6H), 2.17 (dt, *J* = 7.0 and 3.0 Hz, 1H), 1.60 (m, 1H).

^{13}C NMR (75 MHz) δ 141.4, 135.1, 135.0, 130.3, 130.0, 129.3, 128.7, 128.2, 126.7, 126.6, 126.3, 125.8, 52.0, 51.4, 48.6, 48.2, 38.7, 30.3, 29.1, 26.0.

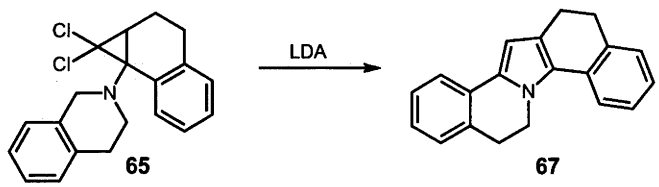
IR υ_{max} (NaCl) 3021, 2927, 1602, 1487, 1453, 1275, 1139, 1045, 940, 908, 740 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 434, 432 and 430 (5, 6 and 4%), 354 and 352 [$(M\text{-}Br^{\bullet})^+$, 15 and 25], 272 (39), 260 (100).

HREIMS Found: $(M - Br^{\bullet})^+$, 354.0674. $C_{20}H_{19}{}^{81}BrN$ requires $(M\text{-}Br^{\bullet})^+$, 354.0680.

Found: $(M - Br^{\bullet})^+$, 352.0696. $C_{20}H_{19}{}^{79}BrN$ requires $(M\text{-}Br^{\bullet})^+$, 352.0701.

5,6,12,13-Tetrahydrobenzo[6,7]indolo[2,1-a]isoquinoline (67)



65 67

Pyrrole **67** was prepared in the same manner as described above for pyrrole **57** but now using dichlorocyclopropane **65** as the starting material. In this manner the *title pyrrole* ***67*** was obtained as a light-yellow, crystalline solid (176 mg, 45%), m.p. 156 °C.

^{1}H NMR (300 MHz) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.30–7.17 (complex m, 4H), 7.15–7.05 (complex m, 2H), 6.47 (s, 1H), 4.44 (t, *J* = 6.0 Hz, 2H), 3.10 (t, *J* = 6.0 Hz, 2H), 2.89 (m, 2H), 2.71 (m, 2H).

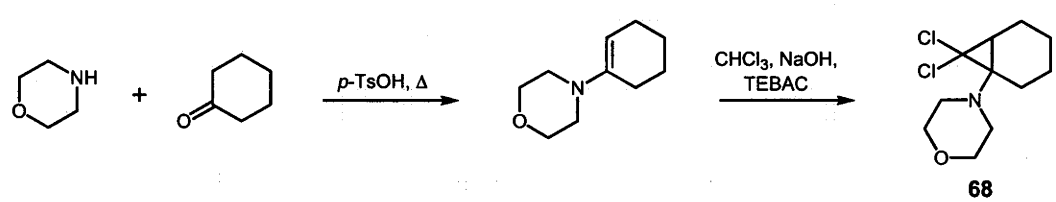
^{13}C NMR (75 MHz) δ 136.9, 130.9, 130.6, 129.9, 129.8, 128.9, 128.6, 127.8, 126.3, 126.7, 125.7, 124.8, 123.3, 122.7, 121.5, 102.7, 42.7, 31.3, 29.6, 22.5.

IR υ_{max} (NaCl) 3047, 2932, 2888, 1602, 1501, 1457, 1333, 1304, 1250, 1136, 1048, 909, 803, 758, 731 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 271 ($M^{+\bullet}$, 100%), 270 (51), 179 (29), 149 (40) 131 (63), 69 (45), 57 (46), 43 (42).

HREIMS Found: $M^{+\bullet}$, 271.1364. $C_{20}H_{17}N$ requires $M^{+\bullet}$, 271.1361.

4-(7,7-Dichlorobicyclo[4.1.0]heptan-1-yl)morpholine (68)



68

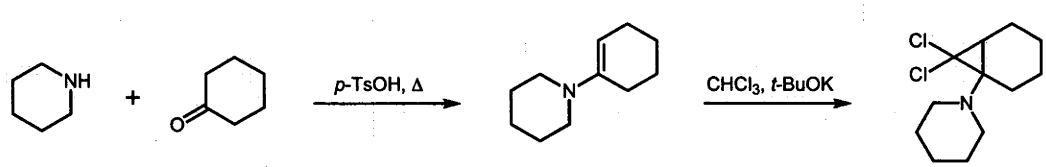
Step i: *p*-TsOH (73 mg, 0.39 mmol) was added to a magnetically stirred solution of cyclohexanone (1.00 mL, 9.65 mmol) and morpholine (1.27 mL, 14.5 mmol) in benzene (10 mL) maintained under nitrogen at 18 °C and containing molecular sieves (500 mg of 8–12 mesh 4 Å material). The ensuing mixture was heated at reflux for 21 h in a reaction flask fitted with a Dean–Stark trap topped by a Liebig condenser. The cooled reaction mixture was passed through filter paper and the filtrate concentrated under reduced pressure to give 4-(1-cyclohexen-1-yl)morpholine[4] as a clear, yellow oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph.

Step ii: A magnetically stirred solution of 4-(1-cyclohexen-1-yl)morpholine and $CHCl_3$ (2.30 mL, 29.0 mmol) in CH_2Cl_2 (10 mL) and maintained under nitrogen at 18 °C was treated with powdered NaOH (2.32 g, 57.9 mmol) and TEBAC (44 mg, 0.19 mmol) then subjected to sonication in a water bath. After 0.75 h, the reaction mixture was cooled then filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with CH_2Cl_2 (50 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* toluene/EtOAc). Concentration of the appropriate fractions (R_f = 0.2) afforded the title dichlorocyclopropane **68** (1.47 g, 61% over two steps) as a white, crystalline solid, m.p. 81°C (lit.[5] m.p. 84–85°C).

The physical data presented above matched the equivalent information reported in the literature.[5] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

^{1}H NMR (300 MHz) δ 3.70 (m, 4H), 2.66 (m, 4H), 2.14–1.88 (complex m, 2H), 1.70 (m, 2H), 1.58–1.18 (complex m, 5H).
^{13}C NMR (75 MHz) δ 72.3, 67.3, 50.0, 48.5, 33.5, 21.8, 20.4, 19.4, 17.0.
IR υ_{max} (NaCl) 2945, 2854, 1450, 1266, 1115, 1014, 869 cm^{-1}.
Mass Spectrum (ESI) *m/z* 252, 250 and 248 [$(M + H)^+$, 5, 19 and 26%], 166 (25), 149 (53), 105 (84), 43 (100).
HREIMS (EI) Found: $(M - H^\bullet)^+$, 248.0611. $C_{11}H_{17}{}^{35}Cl_2NO$ requires $(M - H^\bullet)^+$, 248.0609.

1-(7,7-Dichlorobicyclo[4.1.0]heptan-1-yl)piperidine (69)



69

Step i: *p*-TsOH (37 mg, 0.14 mmol) was added to a magnetically stirred solution of cyclohexanone (1.00 mL, 9.65 mmol) and piperidine (1.34 mL, 13.5 mmol) in toluene (10 mL) maintained under nitrogen at 18 °C and containing molecular sieves (500 mg of 8–12 mesh 4 Å material). The ensuing mixture was heated at reflux for 21 h in a reaction flask fitted with a Dean–Stark trap topped by a Liebig condenser. The cooled reaction mixture was passed through filter paper and the filtrate concentrated under reduced pressure to give 1-(1-cyclohexen-1-yl)piperidine[6] as a clear, yellow oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph.

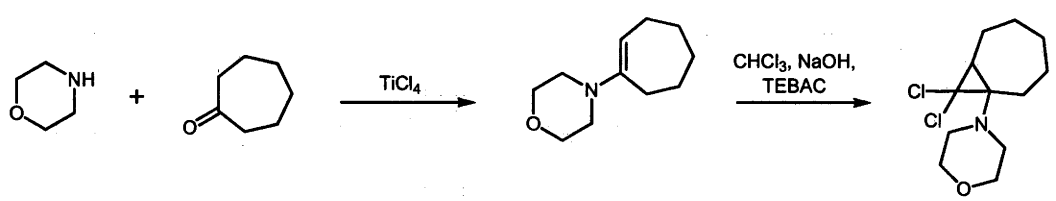
Step ii: A magnetically stirred solution of 1-(1-cyclohexen-1-yl)piperidine in CH_2Cl_2 (10 mL) maintained under nitrogen at 0 °C was treated with *t*-BuOK (1.14 g, 10.1 mmol) then $CHCl_3$ (0.84 mL, 10.6 mmol) was added dropwise. After 1 h the reaction mixture was warmed to 18 °C, maintained at this temperature for a further 2 h then treated with water (5 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc acetate) and concentration of the appropriate fractions (R_f = 0.4) afforded the title dichlorocyclopropane **69** (811 mg, 34% over two steps) as a pale-yellow solid, m.p. 29 °C (lit.[7] m.p. 31–32 °C).

^{1}H NMR (300 MHz) δ 2.50 (broad m, 4H), 2.06 (m, 1H), 1.91 (m, 1H), 1.73–1.13 (complex m, 13H).

The data presented above matched the equivalent spectral information reported in the literature.[7] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

^{13}C NMR (75 MHz) δ 73.0, 50.6, 49.4, 33.7, 26.1, 24.7, 21.9, 20.4, 19.4, 16.7.
IR υ_{max} (NaCl) 2936, 2854, 1442, 1378, 1272, 1119, 1034, 866, 842, 827, 803 cm^{-1}.
Mass Spectrum (ESI) *m/z* 252, 250 and 248 [$(M + H^{\bullet})^+$, 7, 30 and 61%], 216 and 214 (4 and 9), 165 and 163 (20 and 28), 86 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 248.0968. $C_{12}H_{19}{}^{35}Cl_2N$ requires $(M + H^{\bullet})^+$, 248.0973.

4-(8,8-Dichlorobicyclo[5.1.0]octan-1-yl)morpholine (70)



70

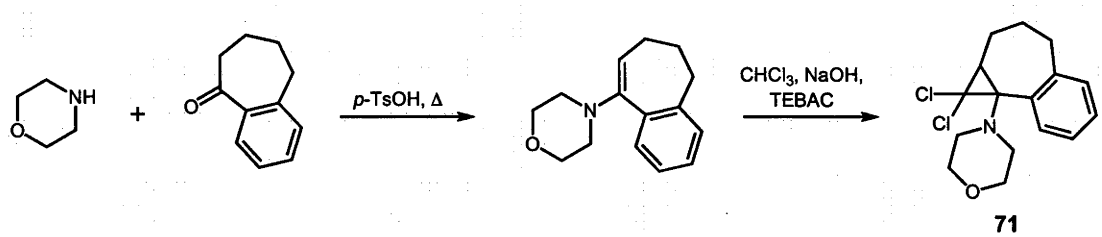
Step i: $TiCl_4$ (0.46 mL, 4.24 mmol) was added dropwise to a magnetically stirred solution of cycloheptanone (1.00 mL, 8.48 mmol) and morpholine (2.23 mL, 25.4 mmol) in toluene (15 mL) maintained under nitrogen at –30 °C. The ensuing mixture was warmed, over 3 h, to 18 °C and maintained at this temperature for 24 h. After this time the reaction mixture was filtered through Celite™ (~2 cm deep pad contained in a sintered glass funnel) and the solids thus retained were washed with hexane (100 mL). The combined filtrates

were concentrated under reduced pressure to give 4-(1-cyclohepten-1-yl)morpholine[4] as a clear, brown oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph

Step ii: A magnetically stirred solution of 4-(-1-cyclohepten-1-yl)morpholine and $CHCl_3$ (2.02 mL, 25.4 mmol) in CH_2Cl_2 (10 mL), maintained under nitrogen at 18 °C, was treated with powdered NaOH (2.04 g, 50.9 mmol) and TEBAC (39 mg, 0.17 mmol) then subjected to sonication in a water bath. After 0.75 h the reaction mixture was filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained were washed with CH_2Cl_2 (50 mL). The filtrate was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* toluene/EtOAc). Concentration of the appropriate fractions (R_f = 0.1) afforded the title dichlorocyclopropane **70** (1.47 g, 66% over two steps) as a white, crystalline solid, m.p. 65 °C. Although dichlorocyclopropane **70** is known[8] no spectral data has been reported. Accordingly, the following data were acquired on this compound.

^{1}H NMR (300 MHz) δ 3.67 (br s, 4H), 2.82 (br s, 4H), 2.38–2.21 (complex m, 2H), 1.89–1.74 (complex m, 2H), 1.64–1.52 (complex m, 3H), 1.33–1.10 (complex m, 4H).
^{13}C NMR (75 MHz) δ 74.6, 67.9 (broadened signal), 56.6, 49.8 (broadened signal), 40.7, 32.4, 28.3, 27.4, 27.3, 26.5.
IR υ_{max} (NaCl) 2926, 2852, 1457, 1374, 1269, 1223, 1115, 1010, 822 cm^{-1}.
Mass Spectrum (ESI) *m/z* 266 and 264 [$(M + H^{\bullet})^+$, 65 and 100%], 230 and 228 (6 and 20), 141 (38), 105 (76), 88 (75).
HRESIMS Found: $(M + H^{\bullet})^+$, 264.0927. $C_{12}H_{19}{}^{37}Cl^{35}ClNO$ requires $(M + H^{\bullet})^+$, 264.0922.

4-(6,6-Dichloro-6a,7,8,9-tetrahydro-5*H*-cycloprop[*a*]benzo[7]annulen-5-yl)morpholine (71)



71

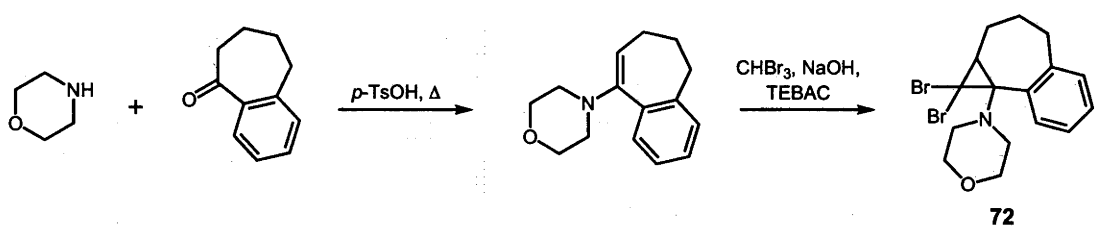
Step i: *p*-TsOH (57 mg, 0.27 mmol) was added to a magnetically stirred solution of 1-benzosuberone (1.00 mL, 6.68 mmol) and morpholine (1.27 mL, 14.5 mmol) in toluene (10 mL) maintained under nitrogen at 18 °C and containing molecular sieves (500 mg of 8–12 mesh 4 Å material). The ensuing mixture was heated at reflux for 62 h in a reaction flask fitted with a Dean–Stark trap topped by a Liebig condenser. The cooled reaction mixture was passed through filter paper and the filtrate concentrated under reduced pressure to

give 4-(6,7-dihydro-5*H*-benzocyclohepten-9-yl)morpholine[9] as a clear, brown oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph.

Step ii: A magnetically stirred solution of 4-(6,7-dihydro-5*H*-benzocyclohepten-9-yl)morpholine and $CHCl_3$ (1.59 mL, 20.0 mmol) in CH_2Cl_2 (10 mL), maintained under nitrogen at 18 °C, was treated with powdered NaOH (1.60 g, 40.1 mmol) and TEBAC (30 mg, 0.13 mmol) then subjected to sonication in a water bath. After 0.5 h the reaction mixture was cooled then filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with CH_2Cl_2 (50 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown solid recrystallised from methanol to furnish the *title dichlorocyclopropane* ***71*** (1.24 g, 69% over two steps) as a white, crystalline solid, m.p. 138 °C.

^{1}H NMR (300 MHz) δ 7.26 (m, 3H), 7.15 (m, 1H), 3.70 (t, J = 5.0 Hz, 4H), 3.15 (m, 1H), 2.74 (m, 4H), 2.59 (m, 1H), 2.04 (m, 1H), 1.91 (m, 2H), 1.76 (m, 1H), 0.98 (m, 1H).
^{13}C NMR (75 MHz) δ 140.8, 133.3, 130.7, 129.1, 128.7, 125.8, 71.1, 67.2, 56.4, 49.7, 36.7, 31.0, 23.3, 22.5.
IR υ_{max} (NaCl) 2939, 2854, 1451, 1266, 1116, 1074, 894, 881, 866 cm^{-1}.
Mass Spectrum (ESI) *m/z* 316, 314 and 312 [$(M + H^{\bullet})^+$, 10, 57 and 100%], 250 (13), 227 and 225 (22 and 36), 189 (92).
HRESIMS Found: $(M + H^{\bullet})^+$, 312.0931. $C_{16}H_{19}{}^{35}Cl_2NO$ requires $(M + H^{\bullet})^+$, 312.0922.

4-(6,6-Dibromo-6a,7,8,9-tetrahydro-5*H*-cycloprop[*a*]benzo[7]annulen-5-yl)morpholine (72)



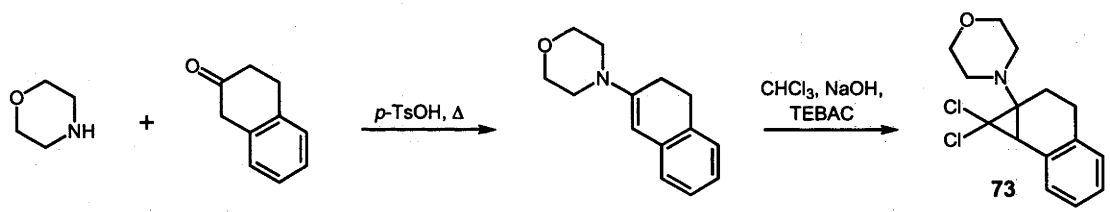
72

A magnetically stirred solution of 4-(6,7-dihydro-5*H*-benzocyclohepten-9-yl)morpholine (1.75 mL, 20.0 mmol), prepared from 1-benzosuberone and morpholine as described above, and $CHBr_3$ (1.75 mL, 20.0 mmol) in CH_2Cl_2 (10 mL) maintained under nitrogen at 18 °C was treated with powdered NaOH (1.60 g, 40.1 mmol) and TEBAC (30 mg, 0.13 mmol) then subjected to sonication in a water bath. After 0.5 h the reaction mixture was filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained were washed with CH_2Cl_2 (50 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash

chromatography (silica, 19:1 *v/v* toluene / EtOAc). Concentration of the appropriate fractions (R_f = 0.1) afforded the *title dibromocyclopropane* **72** (1.53 g, 57% over two steps) as a white, crystalline solid, m.p. 134–137 °C.

^{1}H NMR (300 MHz) δ 7.29–7.23 (complex m, 3H), 7.14 (m, 1H), 3.70 (t, J = 5.0 Hz, 4H), 2.95 (m, 1H), 2.62 (m, 4H), 2.57 (m, 1H), 2.12 (m, 1H), 1.96–1.68 (m, 3H), 0.94 (m, 1H).
^{13}C NMR (75 MHz) δ 140.7, 133.3, 130.8, 129.5, 128.7, 125.7, 67.3, 55.4, 49.7, 46.7, 37.8, 31.2, 26.5, 22.7.
IR υ_{max} (NaCl) 2938, 2855, 1451, 1265, 1116, 1071, 1021, 891, 872, 765, 742 cm^{-1}.
Mass Spectrum (ESI) *m/z* 404, 402 and 400 [(M + H$^•$)$^+$, 44, 90 and 47%], 315 (17), 235 and 233 (86 and 87), 154 (100).
HRESIMS Found: (M + H$^•$)$^+$, 399.9908. $C_{16}H_{19}{}^{79}Br_2NO$ requires (M + H$^•$)$^+$, 399.9912.

4-(1,1-Dichloro-1a,2,3,7b-tetrahydro-1*H*-cyclopropa[*a*]naphthalen-1a-yl)morpholine (73)



Step i: *p*-TsOH (13 mg, 0.07 mmol) was added to a magnetically stirred solution of 2-tetralone (0.45 mL, 3.42 mmol) and morpholine (0.90 mL, 10.3 mmol) in benzene (10 mL) maintained under nitrogen at 18 °C and containing molecular sieves (500 mg of 8–12 mesh 4 Å material). The ensuing mixture was heated at reflux for 5 h in a reaction flask fitted with a Dean–Stark trap topped by a Liebig condenser. The cooled reaction mixture was passed through filter paper and the filtrate concentrated under reduced pressure to give 4-(3,4-dihydro-2-naphthalenyl)morpholine[10] as a clear, yellow oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described immediately below.

Step ii: A magnetically stirred solution of 4-(3,4-dihydro-2-naphthalenyl)morpholine and $CHCl_3$ (0.82 mL, 10.3 mmol) in CH_2Cl_2 (10 mL), maintained under nitrogen at 18 °C, was treated with powdered NaOH (820 mg, 20.5 mmol) and TEBAC (16 mg, 0.07 mmol) then subjected to sonication in a water bath. After 1 h the reaction mixture was cooled to 18 °C, filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with CH_2Cl_2 (30 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1 *v/v* hexane / EtOAc). Concentration of the appropriate fractions (R_f = 0.3) afforded

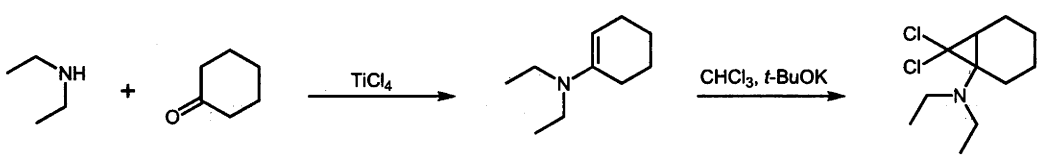
the title dichlorocyclopropane **73** (630 mg, 62% over two steps) as a white, crystalline solid, m.p. 110–114 °C (lit.[10] m.p. 118–120 °C).

^{1}H NMR (300 MHz) δ 7.38–7.00 (complex m, 4H), 3.74 (t, J = 4.0 Hz, 4H), 2.82–2.71 (complex m, 6H), 2.59 (s, 1H), 2.45 (m, 1H), 2.10 (m, 1H).

The data presented above matched the equivalent spectral information reported in the literature.[10] In addition, the following data was acquired on this compound, particularly because such spectral information is not available in the literature.

^{13}C NMR (75 MHz) δ 136.8, 130.6, 130.3, 128.5, 127.8, 126.7, 72.8, 67.3, 53.2, 48.7, 38.0, 28.5, 18.5.

7,7-Dichloro-*N*,*N*-diethylbicyclo[4.1.0]heptan-1-amine (74)



74

Step i: $TiCl_4$ (0.53 mL, 4.83 mmol) was added, dropwise, to a magnetically stirred solution of cyclohexanone (1.00 mL, 9.65 mmol) and diethylamine (4.00 mL, 39.4 mmol) in toluene (15 mL) maintained under nitrogen at –30 °C. The ensuing mixture was warmed, over 3 h, to 18 °C, stirred at this temperature for 16 h then filtered through Celite™ (~2 cm deep pad contained in a sintered glass funnel). The solids thus retained were washed with hexane (100 mL) and the combined filtrates concentrated under reduced pressure to give *N*,*N*-diethyl-1-cyclohexen-1-amine[11] as a yellow oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph.

Step ii: A magnetically stirred solution of *N*,*N*-diethyl-1-cyclohexen-1-amine in CH_2Cl_2 (15 mL) maintained under nitrogen at 0 °C was treated with *t*-BuOK (1.19 g, 10.6 mmol), then $CHCl_3$ (0.92 mL, 11.6 mmol) was added dropwise. After 3 h the reaction mixture was treated with brine (10 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.4) afforded the *title dichlorocyclopropane* **74** (659 mg, 29% over two steps) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 2.58 (q, *J* = 7.0 Hz, 4H), 2.06–1.89 (complex m, 2H), 1.79–1.58 (complex m, 3H), 1.50–1.19 (complex m, 4H), 1.09 (t, *J* = 7.0 Hz, 6H).

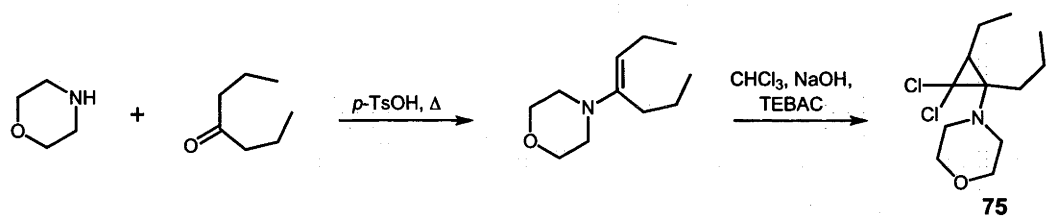
^{13}C NMR (75 MHz) δ 73.0, 50.3, 46.2 (broadened signal), 34.7, 21.8, 20.1, 19.2, 18.3, 14.2 (broadened signal).

IR υ_{max} (NaCl) 2963, 2937, 2857, 1448, 1381, 1298, 1221, 1176, 1116, 1069, 868, 842, 808 cm^{-1}.

Mass Spectrum (ESI) *m/z* 240, 238 and 236 [$(M + H^{\bullet})^+$, 11, 63 and 100%], 200 (5), 153 (25).

HRESIMS Found: $(M + H^{\bullet})^+$, 236.0969. $C_{11}H_{19}{}^{35}Cl_2N$ requires $(M + H^{\bullet})^+$, 236.0973.

4-(2,2-Dichloro-3-ethyl-1-propylcyclopropyl)morpholine (75)



75

Step i: *p*-TsOH (54 mg, 0.29 mmol) was added to a magnetically stirred solution of 4-heptanone (1.00 mL, 7.15 mmol) and morpholine (1.57 mL, 17.9 mmol) in toluene (10 mL), maintained under nitrogen at 18 °C and containing molecular sieves (500 mg of 8–12 mesh 4 Å material). The ensuing mixture was heated at reflux for 92 h in a reaction flask fitted with a Dean–Stark trap topped by a Liebig condenser. The cooled reaction mixture was passed through filter paper and the filtrate concentrated under reduced pressure to give 4-(1-propyl-1-butenyl)morpholine[12] as a clear, brown oil. This somewhat unstable material was immediately subjected to dichlorocarbene addition as described in the following paragraph

Step ii: A magnetically stirred solution of 4-(1-propyl-1-butenyl)morpholine and $CHCl_3$ (1.71 mL, 21.5 mmol) in CH_2Cl_2 (10 mL) and maintained under nitrogen at 18 °C was treated with powdered NaOH (1.72 g, 42.9 mmol) and TEBAC (33 mg, 0.14 mmol) then subjected to sonication in a water bath. After 0.25 h the reaction mixture was cooled then filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with CH_2Cl_2 (100 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, toluene). Concentration of the appropriate fractions (R_f = 0.2) afforded the *title dichlorocyclopropane* **75** (557 mg, 29% over two steps) as a clear, rose-coloured oil.

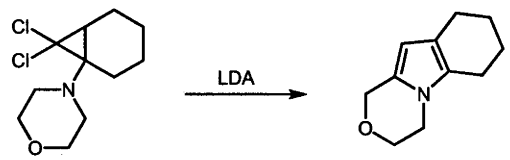
^{1}H NMR (300 MHz) δ 3.69 (t, *J* = 7.0 Hz, 4H), 2.95 (m, 2H), 2.83 (m, 2H), 1.78–1.41 (complex m, 6H), 1.06 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H),

^{13}C NMR (75 MHz) δ 71.9, 67.5, 55.1, 49.4, 42.2, 28.9, 20.6, 19.2, 15.0, 12.9.

IR υ_{max} (NaCl) 2965, 2854, 1456, 1374, 1269, 1116 cm^{-1}.

Mass Spectrum (ESI) *m/z* 270, 268 and 266 [$(M + H^{\bullet})^+$, 6, 30 and 48%], 232 and 230 (5 and 13), 143 (22), 107 (100), 88 (51).
HRESIMS Found: $(M + H^{\bullet})^+$, 266.1087. $C_{12}H_{21}{}^{35}Cl_2NO$ requires $(M + H^{\bullet})^+$, 266.1078.

3,4,6,7,8,9-Hexahydro-1*H*-[1,4]oxazino[4,3-*a*]indole (76)

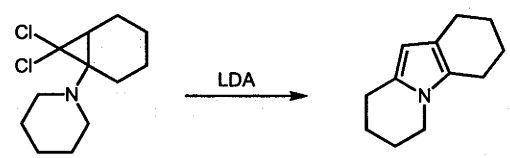


68 **76**

Pyrrole **76** was prepared in the same manner as described above for pyrrole **57** but now using dichlorocyclopropane **68** as the starting material. In this manner the *title pyrrole* ***76*** (116 mg, 82%) was obtained as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.65 (s, 1H), 4.79 (s, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 2.50 (br s, 4H), 1.90–1.72 (complex m, 4H).
^{13}C NMR (75 MHz) δ 126.4, 124.3, 117.0, 100.6, 65.1, 64.7, 41.6, 23.9, 23.3, 23.1, 21.1.
IR υ_{max} (NaCl) 2927, 2848, 1436, 1385, 1339, 1293, 1259, 1236, 1104, 1092, 977, 874 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 177 ($M^{+\bullet}$, 8%), 149 (25), 97 (26), 83 (37), 69 (70), 57 (80), 55 (75), 43 (100).
HREIMS Found: $M^{+\bullet}$, 177.1161. $C_{11}H_{15}NO$ requires $M^{+\bullet}$, 177.1154.

1,2,3,4,6,7,8,9-Octahydropyrido[1,2-*a*]indole (77)



69 **77**

Pyrrole **77** was prepared in the same manner as described above for pyrrole **57** but now using dichlorocyclopropane **69** as the starting material. In this manner the title pyrrole **77** (128 mg, 66%) as a clear, yellow oil.

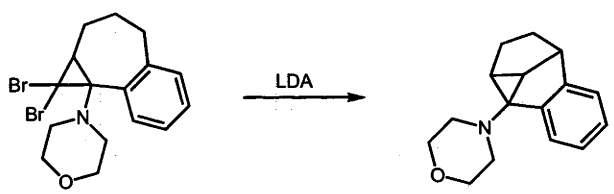
^{1}H NMR (300 MHz) δ 5.64 (s, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.49 (t, *J* = 6.0 Hz, 4H), 1.95–1.90 (complex m, 2H), 1.84–1.71 (complex m, 6H).

The data presented above matched the equivalent spectral information reported in the

literature.[13] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

^{13}C NMR (75 MHz) δ 127.5, 125.7, 116.5, 102.4, 42.2, 23.9, 23.7, 23.6, 23.4, 23.1, 21.4 (one signal obscured or overlapping).
IR υ_{max} (NaCl) 2927, 2841, 1434, 1380, 1348, 1327, 1291, 1131, 761 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 175 ($M^{+\bullet}$, 60%), 174 (50), 147 (100).
HREIMS Found: $M^{+\bullet}$, 175.1361. $C_{12}H_{17}N$ requires $M^{+\bullet}$, 175.1361.

1-(6,7-Benzo-1,2,8-cyclopropyl-bicyclo[3.2.1]octan-1-yl)morphline (78)

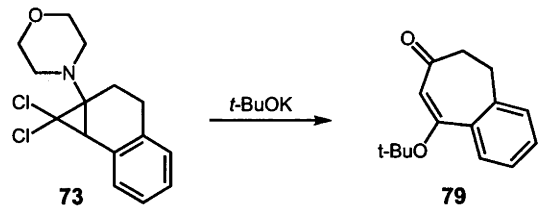


72 78

n-BuLi (1.24 mL of a 1.6 M solution in hexane, 2.00 mmol) was added to a magnetically stirred solution of diisopropylamine (0.28 mL, 2.00 mmol) in THF (10 mL) maintained under nitrogen at –20 °C. After 0.33 h the solution was warmed to 0 °C and maintained at this temperature for a further 0.5 h then cooled to –60 °C and a solution of dibromocyclopropane **72** (200 mg, 0.50 mmol) in THF (7 mL) added. The ensuing mixture was warmed, over 0.5 h, to 0 °C and maintained at this temperature for a further 3 h then NH_4Cl (10 mL of a saturated aqueous solution) was added and the separated aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.1) afforded the *title diquinane* **78** (98 mg, 81%) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 7.43 (d, *J* = 6.0 Hz, 1H), 7.15–7.07 (complex m, 2H), 6.99 (m, *J* = 6.0 Hz, 1H), 3.68 (m, 4H), 3.53 (t, *J* = 6.0 Hz, 1H), 2.96 (t, *J* = 7.0 Hz, 4H), 2.67 (t, *J* = 7.0 Hz, 1H), 2.11 (m, 2H), 1.84 (m, 1H), 1.55 (m, 1H), 1.06 (m, 1H).
^{13}C NMR (75 MHz) δ 148.2, 141.7, 126.4, 126.0, 124.2, 123.5, 67.9, 64.2, 50.2, 47.7, 45.4, 44.0, 37.3, 23.3.
IR υ_{max} (NaCl) 2944, 2853, 1474, 1453, 1361, 1264, 1115, 868, 856, 752 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 241 ($M^{+\bullet}$, 100%), 240 (67), 211 (31), 184 (32), 182 (37), 168 (22), 155 (66), 141 (16), 128 (34), 115 (30).
HREIMS Found: $M^{+\bullet}$, 241.1466. $C_{16}H_{19}NO$ requires $M^{+\bullet}$, 241.1467.

9-*tert*-Butoxy-5*H*-benzo[7]annulen-7(6*H*)-one (79)

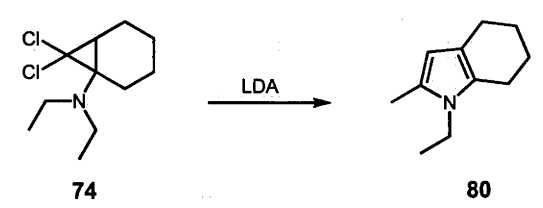


73 **79**

t-BuOK (301 mg, 2.68 mmol) was added to a magnetically stirred solution of cyclopropane **73** (67 mg, 0.22 mmol) in THF (15 mL) maintained under nitrogen at 0 °C. After 1 h the reaction mixture was warmed to 18 °C, maintained at this temperature for 22 h then NH_4Cl (10 mL of a saturated aqueous solution) was added and the separated aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing brown oil subjected to flash chromatography (silica, 17:3 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.1) afforded the *title compound* **79** (122 mg, 79%) as a yellow, crystalline solid, m.p. 43–45 °C.

^{1}H NMR (300 MHz) δ 7.72 (m, 1H), 7.34–7.11 (complex m, 3H), 5.99 (s, 1H), 2.98 (m, 2H), 2.66 (m, 2H), 1.54 (s, 9H).
^{13}C NMR (75 MHz) δ 201.7, 163.1, 141.1, 135.2, 130.3, 129.3, 128.6, 126.9, 112.7, 81.7, 43.5, 30.5, 28.9.
IR υ_{max} (NaCl) 2928, 1643, 1605, 1590, 1564, 1348, 1158, 1085, 846, 775, 752 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 230 ($M^{+\bullet}$, 25%), 175 (45), 174 (95), 157 (25), 146 (85), 133 (83), 132 (95), 129 (65), 115 (45), 104 (60), 57 (100).
HREIMS Found: $M^{+\bullet}$, 230.1308. $C_{15}H_{18}O_2$ requires $M^{+\bullet}$, 230.1307.

1-Ethyl-2-methyl-4,5,6,7-tetrahydro-1*H*-indole (80)



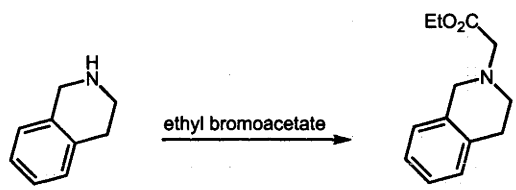
74 **80**

Pyrrole **80** was prepared in the same manner as described above for pyrrole **57** but now using dichlorocyclopropane **74** as the starting material. In this manner the title pyrrole **80** (54 mg, 54%) as a clear, yellow oil.

Although pyrrole **80** is a known compound[14] no spectral data has been reported. Accordingly, the following data were acquired on this compound.

^{1}H NMR (300 MHz) δ 5.68 (s, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H), 2.49 (t, *J* = 6.0 Hz, 2H), 2.24 (s, 3H), 1.83 (m, 2H), 1.73 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (75 MHz) δ 126.3, 120.4, 116.0, 104.8, 37.8, 23.9, 23.6, 23.1, 22.1, 16.4, 12.0.
IR υ_{max} (NaCl) 2926, 2852, 1443, 1403, 1298, 1260, 1095, 1076, 1019, 801 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 163 ($M^{+\bullet}$, 51%), 135 (75), 120 (15), 107 (13), 44 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 164.1435. $C_{11}H_{17}N$ requires $(M + H^{\bullet})^+$, 164.1439.

Ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (90)



63 **90**

A solution of ethyl bromoacetate (5.60 mL, 51 mmol) in CH_2Cl_2 (15 mL) was added to a magnetically stirred mixture of K_2CO_3 (7.00 g, 51 mmol) and 1,2,3,4-tetrahydroisoquinoline (**63**) (5.00 mL, 40 mmol) in CH_2Cl_2 (30 mL) maintained under nitrogen at 0 °C. After 1.5 h the mixture was warmed to 18 °C and maintained at this temperature for a further 14 h then filtered through Celite™ (~1 cm deep pad in a sintered glass funnel). The filtrate was extracted with HCl (2 x 50 mL of a 2M aqueous solution) then NaOH (150 mL of a 1M aqueous solution) was added to the combined aqueous phases until the solution became alkaline. The mixture was then extracted with CH_2Cl_2 (5 x 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title ester **90** (6.82 g, 79%) as a yellow oil. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 7.12-7.08 (complex m, 3H), 6.99 (m, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.80 (s, 2H), 3.41 (s, 2H), 2.94-2.88 (complex m, 4H), 1.29 (t, *J* = 7.0 Hz, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[15] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

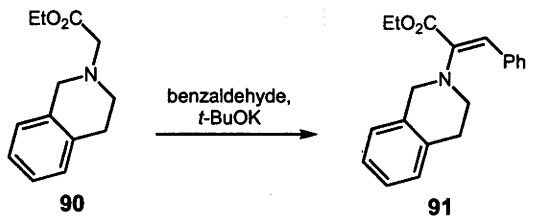
^{13}C NMR (75 MHz) δ 170.6, 134.5, 134.0, 128.9, 126.7, 126.4, 125.8, 60.8, 59.2, 55.5, 50.8, 29.2, 14.5.

IR υ_{max} (NaCl) 2980, 2922, 2806, 1750, 1498, 1455, 1388, 1185, 1153, 1103, 1031, 936, 743 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 219 ($M^{+\bullet}$, 12%), 190 (20), 147 (53), 146 (55), 132 (100).

HREIMS Found: $M^{+\bullet}$, 219.1253. $C_{13}H_{17}NO_2$ requires $M^{+\bullet}$, 219.1259.

(*Z*)-Ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-3-phenylacrylate (91)



90 **91**

A solution of ester **90** (1.35 g, 6.16 mmol) in THF (10 mL) was added, dropwise, to a magnetically stirred solution of *t*-BuOK (900 mg, 8.01 mmol) and benzaldehyde (0.62 mL, 6.16 mmol) in THF (20 mL) maintained under nitrogen at 0 °C. After 1 h the reaction mixture was warmed to 18 °C, maintained at this temperature for a further 3 h, then treated with brine (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title alkene* ***91*** (1.34 g, 71%) as a clear, yellow oil. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 7.71 (dm, *J* = 7.0 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.31–7.12 (complex m, 3H), 7.01–6.95 (complex m, 2H), 4.70 (s, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.13 (s, 2H), 3.28 (t, *J* = 6.0 Hz , 2H), 2.96 (t, *J* = 6.0 Hz , 2H), 1.34 (t, *J* = 7.0 Hz, 3H).

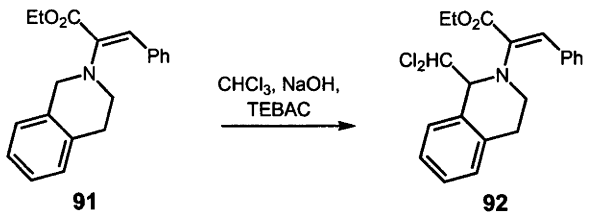
^{13}C NMR (75) MHz) 166.7, 141.2, 139.2, 135.1, 134.9, 134.5, 130.2, 129.0, 128.5, 128.4, 128.3, 128.2, 127.3, 126.8, 126.2, 125.9, 125.6, 64.8, 60.8, 51.6, 48.2, 29.3, 14.3 (5 signals presumed to correspond to the presence of benzyl alcohol).

IR υ_{max} (NaCl) 2925, 2847, 1707, 1608, 1448, 1386, 1232, 1142, 1101, 1026, 747, 696 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 307 ($M^{+\bullet}$, 38%), 278 (100), 218 (20), 105 (45), 91 (53).

HREIMS Found: $M^{+\bullet}$, 307.1570. $C_{20}H_{21}NO_2$ requires $M^{+\bullet}$, 307.1572.

(*Z*)-Ethyl 2-(1-(dichloromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-phenylacrylate (92)



A magnetically stirred solution of alkene **91** (900 mg, 2.93 mmol) and $CHCl_3$ (0.70 mL, 8.79 mmol) in CH_2Cl_2 (15 mL) maintained under nitrogen at 18 °C was treated with powdered NaOH (703 mg, 17.6 mmol) and TEBAC (27 mg, 0.12 mmol). After 16 h the reaction mixture was filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with CH_2Cl_2 (100 mL). The combined filtrates were concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.1) afforded the *title dichloride* **92** (121 mg, 11%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.45–7.22 (complex m, 9H), 5.88 (d, *J* = 2.0 Hz, 1H), 4.82 (d, *J* = 2.0 Hz, 1H), 4.25 (m, 2H), 3.53 (m, 1H), 3.20 (m, 2H), 2.84 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H).

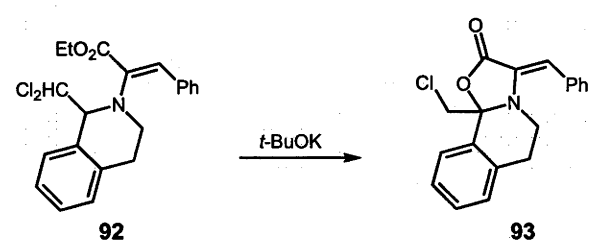
^{13}C NMR (75 MHz) δ 166.4, 138.3, 137.3, 133.9, 132.4, 132.2, 130.8, 129.6, 128.7, 128.4, 128.2, 127.8, 126.1, 78.1, 68.4, 61.2, 48.2, 30.0, 14.2.

IR υ_{max} (NaCl) 2980, 1705, 1620, 1447, 1239, 1203, 1136, 1101, 1027, 751, 693 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 391 and 389 ($M^{+\bullet}$, 2 and 4%), 306 [(M – $HCl_2C^{\bullet}$)$^+$, 100], 278 (11).

HREIMS Found: $M^{+\bullet}$, 389.0949. $C_{21}H_{21}{}^{35}Cl_2NO_2$ requires M^+, 389.0949.

(*Z*)-3-Benzylidene-10b-(chloromethyl)-3,5,6,10b-tetrahydro-2*H*-oxazolo[2,3-*a*]isoquinolin-2-one (93)



t-BuOK (95 mg, 0.85 mmol) was added to a magnetically stirred solution of dichloride **92** (42 mg, 0.21 mmol) in THF (5 mL) maintained under nitrogen at 0 °C. After 1 h the reaction mixture was warmed to 18 °C and maintained at this temperature for a further 16 h then NH_4Cl (3 mL of a saturated aqueous solution) was added and the

separated aqueous phase extracted with Et_2O (2 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 4:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.1) afforded the *title oxalolidinone* **93** (42 mg, 62%) as a white, crystalline solid, m.p. 138–140 °C.

^{1}H NMR (300 MHz) δ 7.59 (m, 1H), 7.53 (d, *J* = 5.0 Hz, 2H), 7.43–7.27 (complex m, 5H), 7.19 (m, 1H), 6.66 (s, 1H), 3.95 (d, *J* = 12.0 Hz, 1H), 3.81 (m, 2H), 3.72 (d, *J* = 12.0 Hz, 1H), 2.87 (m, 2H).

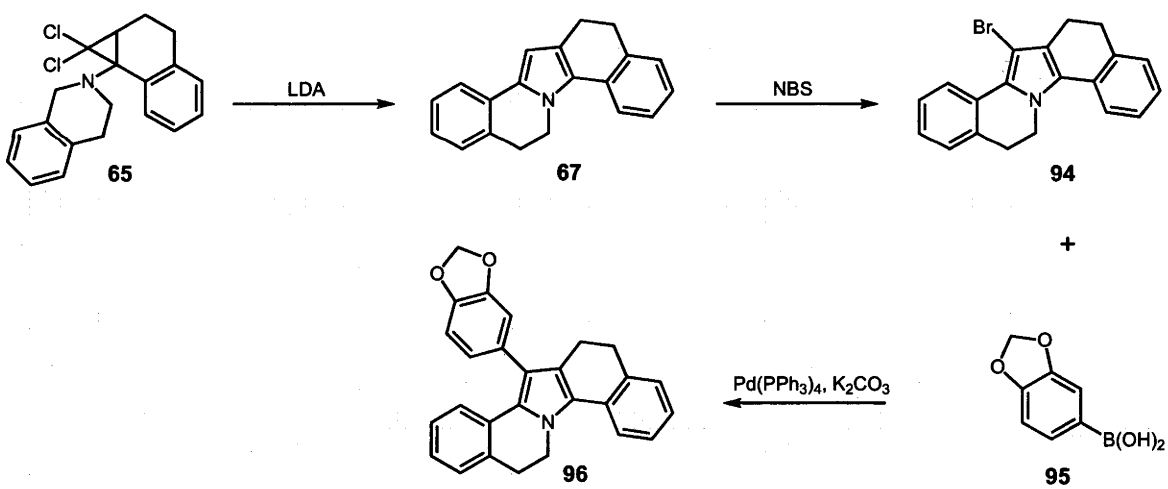
^{13}C NMR (75 MHz) δ 166.8, 135.3, 134.0, 132.2, 131.7, 129.7, 129.6, 128.6, 128.2, 128.0, 127.6, 126.6, 111.4, 93.7, 52.8, 44.5, 27.9.

IR υ_{max} (NaCl) 1777, 1648, 1492, 1448, 1400, 1367, 1264, 1186, 1150, 764, 747 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 325 ($M^{+\bullet}$, 13%), 276 (100), 248 (81).

HREIMS Found: $M^{+\bullet}$, 325.0870. $C_{19}H_{16}{}^{35}ClNO_2$ requires $M^{+\bullet}$, 325.0870.

14-(Benzo[d][1,3]dioxol-5-yl)-5,6,12,13-tetrahydrobenzo[6,7]indolo[2,1-a]isoquinoline (96)



Step i: *n*-BuLi (1.80 mL of a 1.6 M solution in hexane, 2.88 mmol) was added to a magnetically stirred solution of diisopropylamine (0.41 mL, 2.88 mmol) in THF (20 mL) maintained under nitrogen at –20 °C. After 0.33 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 0.5 h then cooled to –60 °C and a solution of dichlorocyclopropane **65** (250 mg, 0.72 mmol) in THF (10 mL) added. The ensuing reaction mixture was warmed, over 0.5 h, to 0 °C and maintained at this temperature for a further 3 h then NH_4Cl (15 mL of a saturated aqueous solution) was added and the separated aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the

ensuing residue, containing pyrrole **67**, immediately subjected to bromination as described in the following paragraph.

Step ii: NBS (155 mg, 0.87 mmol) was added to a magnetically stirred solution of pyrrole **67** in THF (12 mL) maintained under nitrogen at –60 °C. The solution was warmed to 0 °C, maintained at this temperature for a further 1 h then water (20 mL) was added and the separated aqueous phase extracted with Et_2O (4 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil.

Subjection of a sample of this material to flash chromatography (silica, 4:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.3) afforded the *title bromide* ***94*** as a light-yellow, crystalline solid, m.p. 119–122°C.

^{1}H NMR (300 MHz) δ 8.32 (d, *J* = 8.0 Hz, 1H), 7.35–7.10 (complex m, 7H), 4.41 (t, *J* = 7.0 Hz, 2H), 3.05 (t, *J* = 7.0 Hz, 2H), 2.91 (m, 2H), 2.67 (m, 2H).
^{13}C NMR (75 MHz) δ 137.2, 131.9, 129.1, 128.8, 128.3, 127.7, 127.1, 126.7, 126.2, 126.1, 125.6, 124.0, 123.2, 122.3, 94.1, 42.9, 30.7, 30.3, 21.1 (one signal obscured or overlapping).
IR υ_{max} (NaCl) 3060, 2931, 1603, 1542, 1501, 1455, 1389, 1331, 1260, 1099, 1058, 908, 801, 760, 737 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 351 and 349 ($M^{+\bullet}$, 76 and 77%), 270 (58), 269 (44), 127 (42), 85 (43), 71 (61), 57 (100), 43 (77).
HREIMS Found: $M^{+\bullet}$, 349.0466. $C_{20}H_{16}{}^{79}BrN$ requires $M^{+\bullet}$, 349.0466.

Step iii: A magnetically stirred solution of bromide **94**, prepared as described immediately above, in THF (4 mL), maintained at 18 °C, was treated with 3,4-methylenedioxyphenylboronic acid (**95**) (239 mg, 1.44 mmol, ex. Boron Molecular Pty Ltd, Melbourne), $Pd(Ph_3)_4$ (42 mg, 0.04 mmol) and K_2CO_3 (1 mL of a 3.6 M aqueous solution). The ensuing mixture was heated, for 0.5 h, at 100 °C in a μ-wave reactor then cooled and the separated aqueous phase extracted with Et_2O (2 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing brown oil subjected to flash chromatography (silica, 17:3 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.4) afforded *title pyrrole* ***96*** (110 mg, 40% over three steps) as a light-yellow, crystalline solid, m.p. 225–226 °C.

^{1}H NMR (300 MHz) δ 8.31 (d, *J* = 7.8 Hz, 1H), 7.71–7.05 (complex m, 6H), 6.97 (dm, *J* = 9.0 Hz, 2H), 6.85 (dm, *J* = 9.0 Hz, 2H), 5.99 (s, 2H), 4.41 (t, *J* = 7.0 Hz, 2H), 3.04 (t, *J* = 7.0 Hz, 2H), 2.91 (m, 2H), 2.68 (m, 2H).

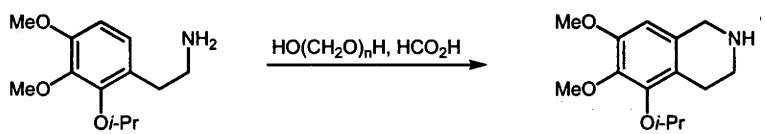
^{13}C NMR (75 MHz) δ 137.0, 135.3, 132.1, 132.0, 129.6, 128.7, 128.6, 128.4, 128.1, 127.5, 126.9, 126.6, 126.1, 125.9, 125.4, 123.8, 123.0, 122.1, 121.6, 120.3, 108.5, 107.5, 101.1, 42.7, 30.5, 30.1, 20.9.

IR υ_{max} (NaCl) 3059, 2929, 2890, 1603, 1501, 1477, 1437, 1392, 1230, 1195, 1118, 1038, 937, 803, 761, 721, 696 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 391 ($M^{+\bullet}$, 100%), 351 (10), 349 (9).

HREIMS Found: $M^{+\bullet}$, 391.1577. $C_{27}H_{21}NO_2$ requires $M^{+\bullet}$, 391.1572.

5-Isopropoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (107)



115 **107**

Amine **115** (17.9 g, 74.8 mmol) was added to magnetically stirred formic acid (60 mL) maintained under nitrogen at 0 °C. After 0.25 h paraformaldehyde (2.25 g, 74.8 mmol) was added and the ensuing reaction mixture warmed to 18 °C and kept at this temperature for a further 2 h. The mixture was then heated at 50 °C for 40 h in a flask fitted with a Liebig condenser, cooled and concentrated under reduced pressure. The ensuing residue was treated with NaOH (50 mL of a 2 M aqueous solution) and the aqueous mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were concentrated under reduced pressure and the ensuing oil was dissolved in Et_2O (70 mL) then extracted with HCl (5 x 30 mL of a 5 M aqueous solution). The combined aqueous phases were made alkaline with Na_2CO_3 (saturated aqueous solution) then extracted with CH_2Cl_2 (5 x 50 mL). The combined organic phases were washed with water (40 mL), dried ($MgSO_4$), filtered and then concentrated under reduced pressure to afford the *title tetrahydroisoquinoline* ***107*** (15.3 g, 81%) as a light-yellow oil. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.31 (s, 1H), 4.60 (septet, *J* = 6.0 Hz, 1H), 3.92 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.06 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.0 Hz, 2H), 1.83 (s, 1H), 1.26 (d, *J* = 6.0 Hz, 6H).

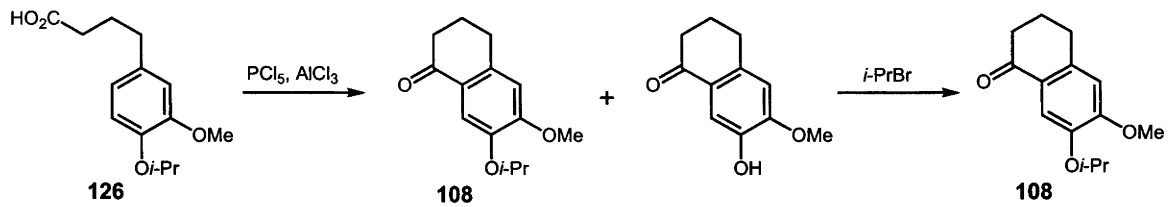
^{13}C NMR (75 MHz) δ 151.7, 149.6, 140.6, 131.2, 121.9, 104.6, 74.9, 60.7, 56.1, 48.4, 43.9, 24.1, 23.0.

IR υ_{max} (NaCl) 2973, 2933, 1601, 1492, 1451, 1424, 1380, 1323, 1237, 1115, 1025 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 251 ($M^{+\bullet}$, 77%), 208 (76), 192 (62), 180 (100), 166 (58).

HREIMS Found: $M^{+\bullet}$, 251.1520. $C_{14}H_{21}NO_3$ requires $M^{+\bullet}$, 251.1521.

7-Isopropoxy-6-methoxy-1-tetralone (108)



Step i: PCl_5 (22.9 g, 110 mmol) was added to a neat sample of acid **126** (25.2 g, 100 mmol) at 18 °C. After gas evolution had ceased (*ca.* 0.25 h) benzene (3 x 50 mL) was added and the mixture concentrated under reduced pressure. A solution of the ensuing oil in benzene (50 mL) was then added dropwise to a magnetically stirred suspension of $AlCl_3$ (16.0 g, 120 mmol) in benzene (50 mL) maintained under nitrogen at 0 °C. After 0.25 h the reaction mixture was warmed to 18 °C and kept at this temperature for a further 4 h. Et_2O (50 mL) was added and the reaction mixture was cooled to 0 °C then treated with HCl (100 mL of a 17% aqueous solution). The phases were separated, the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic phases were then washed with water (2 x 30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. CH_2Cl_2/hexane (100 mL of a 1:5 *v*/*v* solution) was added to the ensuing brown residue (consisting of a mixture of 1-tetralone **108** and 7-hydroxy-6-methoxytetralone), the mixture filtered, the filtrate concentrated under reduced pressure and the resulting solid recrystallised from Et_2O to give the title 1-tetralone **108** (1.90 g). The crude solids retained from the abovementioned filtration, containing 7-hydroxy-6-methoxytetralone, were immediately subjected to the alkylation reaction as described in the following paragraph.

Step ii: K_2CO_3 (16.9 g, 122 mmol) and 2-bromopropane (6.90 mL, 73.2 mmol) were added to a magnetically stirred solution of crude 7-hydroxy-6-methoxytetralone (obtained as described immediately above) in DMF (60 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 70 °C for 14 h in a flask fitted with a Liebig condenser then cooled. Water (70 mL) and Et_2O (50 mL) were added, the phases separated and the aqueous layer further extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing brown solid was recrystallised from Et_2O to afford the title 1-tetralone **108** (14.2 g in total and 61% over two steps) as a colourless, crystalline solid, m.p. 95 °C (lit.[16] m.p. 99-100 °C).

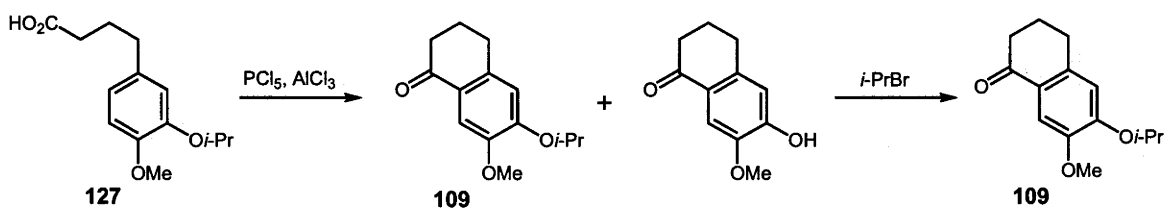
^{1}H NMR (300 MHz) δ 7.53 (s, 1H), 6.66 (s, 1H), 4.62 (septet, J = 6.0 Hz, 1H), 3.91 (s, 3H), 2.88 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 6.0 Hz, 2H), 2.11 (septet, J = 6.0 Hz, 2H), 1.37 (d, J = 6.0 Hz, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[16] In addition, the following data were acquired on

this compound, particularly because such spectral information is not available in the literature.

^{13}C NMR (75 MHz) δ 197.5, 154.9, 146.3, 139.4, 126.0, 112.2, 110.8, 71.3, 56.3, 38.8, 29.7, 23.9, 22.1.
IR υ_{max} (NaCl) 2975, 2934, 1671, 1596, 1506, 1447, 1352, 1267, 1216, 1114, 1031 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 234 ($M^{+\bullet}$, 35%), 192 (100), 164 (46), 136 (43).
HREIMS Found: $M^{+\bullet}$, 234.1259. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256.

6-Isopropoxy-7-methoxy-1-tetralone (109)



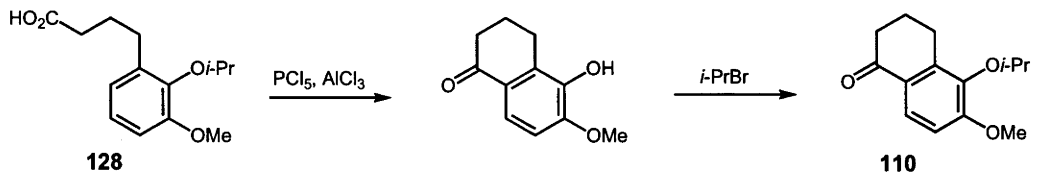
1-Tetralone **109** was prepared in the same manner as described immediately above for congener **108** but now using acid **127** as the starting material. In this manner the title 1-tetralone **109** (12.2 g, 74 %) was obtained as a colourless, crystalline solid, m.p. 98 °C (lit.[16] m.p. 101 °C).

^{1}H NMR (300 MHz) δ 7.50 (s, 1H), 6.66 (s, 1H), 4.64 (septet, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.10 (septet, *J* = 6.0 Hz, 2H), 1.41 (d, *J* = 6.0 Hz, 6H).

The data presented above matched the equivalent spectral information reported in the literature.[16] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

IR υ_{max} (NaCl) 2976, 2935, 1670, 1596, 1507, 1465, 1361, 1269, 1220, 1110, 1032 cm^{-1}.
^{13}C NMR (75 MHz) δ 197.3, 152.2, 148.8, 139.3, 125.6, 112.8, 109.0, 71.1, 56.1, 38.7, 29.6, 23.8, 22.0.
Mass Spectrum (EI, 70eV) *m/z* 234 ($M^{+\bullet}$, 17%), 192 (52), 164 (27), 32 (100).
HREIMS Found: $M^{+\bullet}$, 234.1257. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256.
Elemental Analysis Found: C, 71.83; H, 7.76%. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%.

5-Isopropoxy-6-methoxy-1-tetralone (110)



128 **110**

Step i: PCl_5 (30.9 g, 148 mmol) was added to a neat sample of acid **128** (34.0 g, 135 mmol) at 18 °C. After gas evolution had ceased (*ca.* 0.25 h) benzene (3 x 70 mL) was added and the mixture concentrated under reduced pressure. A solution of the ensuing oil in benzene (70 mL) was then added dropwise to a magnetically stirred suspension of $AlCl_3$ (21.6 g, 162 mmol) in benzene (70 mL) maintained under nitrogen at 0 °C. After 0.25 h the reaction mixture was warmed to 18 °C for and kept at this temperature for a further 4 h. Et_2O (100 mL) was added and the reaction mixture cooled to 0 °C and treated with HCl (150 mL of a 17% aqueous solution). The phases were separated, the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic phases were concentrated under reduced pressure to give 5-hydroxy-6-methoxytetralone which was immediately subjected to the alkylation reaction as described in the following paragraph.

Step ii: K_2CO_3 (37.3 g, 270 mmol) and 2-bromopropane (15.2 mL, 162 mmol) were added to a magnetically stirred solution of crude 5-hydroxy-6-methoxytetralone (obtained as described immediately above) in DMF (150 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 70 °C for 14 h in a flask fitted with a Liebig condenser then cooled. Water (70 mL) and Et_2O (70 mL) were added, the phases separated and the aqueous layer further extracted with Et_2O (3 x 70 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the ensuing red oil was subjected to flash chromatography (silica, 19:1 *v*/*v* hexane/EtOAc). Concentration of the appropriate fractions ($R_f = 0.1$) afforded the *title 1-tetralone* ***110*** (18.8 g, 59% yield) as a white, crystalline solid, m.p. 34-35 °C.

^{1}H NMR (300 MHz) δ 7.80 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.42 (septet, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 2.92 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H), 2.02 (septet, *J* = 6.0 Hz, 2H), 1.26 (d, *J* = 6.0 Hz, 6H).

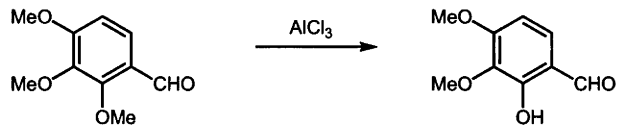
^{13}C NMR (75 MHz) δ 197.9, 157.2, 143.4, 139.6, 126.8, 124.2, 110.1, 74.9, 55.9, 39.0, 24.4, 23.2, 22.8.

IR υ_{max} (NaCl) 2972, 2937, 1678, 1588, 1487, 1463, 1323, 1279, 1217, 1109, 1079 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 234 ($M^{+\bullet}$, 23%), 192 (85), 164 (47), 69 (100).

HREIMS Found: $M^{+\bullet}$, 234.1252. $C_{14}H_{18}O_3$ requires $M^{+\bullet}$, 234.1256.

2-Hydroxy-3,4-dimethoxybenzaldehyde (112)



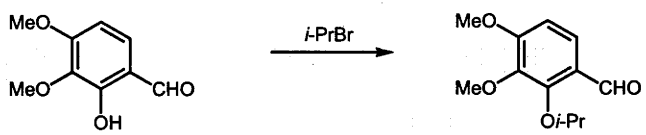
111 **112**

Phenol **112** was prepared using a protocol described by Chantimakorn.[17] Thus, anhydrous $AlCl_3$ (357 mg, 2.68 mmol) was added in 4 portions, over 0.5 h, to a magnetically stirred solution of 2,3,4-trimethoxybenzaldehyde (**111**) (500 mg, 2.55 mmol) in benzene (5 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at reflux for 4 h in a flask fitted with a Liebig condenser then cooled and treated with cold HCl (10 mL of a 5 M aqueous solution). The phases were separated and the aqueous layer was extracted with $CHCl_3$ (3 x 15 mL). The combined organic phases were extracted with NaOH (3 x 20 mL of a 2 M aqueous solution) then the combined aqueous phases were acidified with HCl (2 M aqueous solution). The aqueous mixture was then extracted with $CHCl_3$ (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow solid was subjected to flash chromatography (silica, 4:1 *v*/*v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.1) afforded the title phenol **112** (310 mg, 66%) as a colourless, crystalline solid, m.p. 72 °C (lit.[18] m.p. 76-77 °C).

^{1}H NMR (300 MHz) δ 11.19 (s, 1H), 9.72 (s, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[17]

2-Isopropoxy-3,4-dimethoxybenzaldehyde (113)



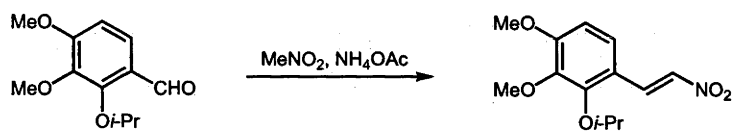
112 **113**

2-Bromopropane (20.6 mL, 0.22 mol) was added to a magnetically stirred solution of 2-hydroxy-3,4-dimethoxybenzaldehyde (**112**) (26.7 g, 0.15 mol) and K_2CO_3 (33.2 g, 0.24 mol) in DMF (100 mL) maintained under nitrogen at 18 °C. After 70 h water (100 mL) and Et_2O (100 mL) were added, the phases separated and the aqueous layer further extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with water (20 mL), dried

($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 4:1 *v*/*v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.2) afforded the *title ether* ***113*** (24.1 g, 72%) as a light-yellow oil.

^{1}H NMR (300 MHz) δ 10.20 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 4.64 (septet, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 1.25 (d, *J* = 6.0 Hz, 6H).
^{13}C NMR (75 MHz) δ 189.6, 159.4, 155.1, 142.1, 124.8, 124.0, 107.5, 76.9, 60.8, 56.4, 22.6.
IR υ_{max} (NaCl) 2975, 2936, 2857, 1680, 1587, 1495, 1455, 1427, 1382, 1335, 1289, 1260, 1092, 1034 cm^{-1}.
Mass Spectrum (EI, 70eV) *m*/*z* 224 ($M^{+\bullet}$, 43%), 182 (100), 167 (43), 149 (35), 139 (67), 136 (41).
HREIMS Found: $M^{+\bullet}$, 224.1054. $C_{12}H_{16}O_4$ requires $M^{+\bullet}$, 224.1049.
Elemental Analysis Found: C, 64.02; H, 7.33%. $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19%.

2-Isopropoxy-3,4-dimethoxy-1-[(*E*)-2-nitrovinyl]benzene (114)



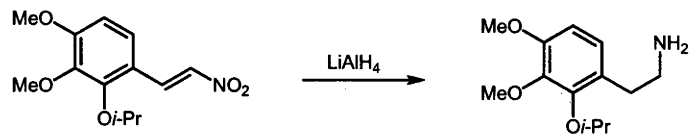
113 **114**

Nitromethane (0.07 mL, 1.34 mmol) was added to a magnetically stirred solution of aldehyde **113** (100 mg, 0.45 mmol) and ammonium acetate (87 mg, 23.1 mmol) in acetic acid (5 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at reflux for 4 h in a flask fitted with a Liebig condenser then cooled, diluted with water (10 mL) and CH_2Cl_2 (10 mL) and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with $NaHCO_3$ (15 mL of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, $CHCl_3$) and concentration of the appropriate fractions (R_f = 0.2) afforded the *title nitrostyrene* ***114*** (102 mg, 85%) as a bright-yellow solid, m.p. 72 °C.

^{1}H NMR (300 MHz) δ 8.16 (d, *J* = 14.0 Hz, 1H), 7.76 (d, *J* = 14.0 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 1H), 4.75 (septet, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 1.32 (d, *J* = 6.0 Hz, 6H).
^{13}C NMR (75 MHz) δ 157.4, 152.5, 142.8, 136.4, 136.0, 126.0, 118.5, 107.7, 76.9, 60.8, 56.4, 22.8.
IR υ_{max} (NaCl) 2976, 2936, 1627, 1592, 1510, 1494, 1453, 1339, 1284, 1095, 1040, 969 cm^{-1}.
Mass Spectrum (EI, 70eV) *m*/*z* 267 ($M^{+\bullet}$, 29%), 225 (18), 178 (100), 163 (57), 149 (19).
HREIMS Found: $M^{+\bullet}$, 267.1106. $C_{13}H_{17}NO_5$ requires $M^{+\bullet}$, 267.1107.

Elemental Analysis Found: C, 58.21; H, 6.55; N, 5.15%. $C_{13}H_{17}NO_5$ requires C, 58.42; H, 6.41; N, 5.24%.

2-(2-Isopropoxy-3,4-dimethoxyphenyl)ethanamine (115)



114 **115**

A solution of nitrostyrene **114** (400 mg, 1.50 mmol) in THF (6 mL) was added to a magnetically stirred suspension of $LiAlH_4$ (284 mg, 7.48 mmol) in THF (5 mL) kept under nitrogen at -78 °C. The ensuing mixture was warmed to 0 °C and after 0.5 h warmed to 18 °C then maintained at this temperature for a further 0.5 h. Rochelle's salt (15 mL of a saturated aqueous solution) was added, the phases separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic phases were extracted with HCl (3 x 10 mL of a 10% aqueous solution) then NaOH (2 M aqueous solution) was added to the combined aqueous layers until the solution became alkaline. The aqueous mixture was then extracted with Et_2O (4 x 20 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title amine* ***115*** (299 mg, 84%) as a colourless oil. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.78 (d, *J* = 9.0 Hz, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 4.55 (septet, *J* = 6.0 Hz, 1H), 3.77 (s, 6H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 1.44 (br s, 2H), 1.21 (d, *J* = 6.0 Hz, 6H).

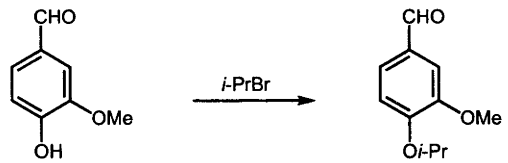
^{13}C NMR (75 MHz) δ 152.3, 150.0, 142.5, 126.7, 124.2, 106.8, 75.0, 60.6, 56.1, 42.9, 34.5, 22.9.

IR υ_{max} (NaCl) 2973, 2934, 1600, 1493, 1455, 1423, 1381, 1371, 1283, 1228, 1096, 1044, 982, 904 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 239 ($M^{+\bullet}$, 43%), 182 (84), 167 (100), 153 (62).

HREIMS Found: $M^{+\bullet}$, 239.1521. $C_{13}H_{21}NO_3$ requires $M^{+\bullet}$, 239.1521.

4-Isopropoxy-3-methoxybenzaldehyde (119)



116 **119**

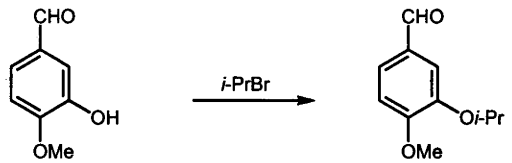
2-Bromopropane (18.5 mL, 197 mmol) was added to a magnetically stirred solution of vanillin (**116**) (25.0 g, 164 mmol) and K_2CO_3 (56.6 g, 410 mmol) in DMF (75 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 70 °C for 14 h in a flask fitted with a Liebig condenser then cooled. Water (100 mL) and Et_2O (50 mL) were added, the phases separated and the aqueous layer further extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing oil was subjected to flash chromatography (silica, 7:3 *v*/*v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.3) afforded the title aldehyde **119** (30.6 g, 96%) as a clear, tan-coloured oil.

^{1}H NMR (300 MHz) δ 9.84 (s, 1H), 7.40 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 4.69 (septet, *J* = 6.0 Hz, 1H), 3.94 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[19] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

^{13}C NMR (75 MHz) δ 190.9, 153.2, 150.4, 129.8, 126.7, 113.0, 109.6, 71.4, 56.0, 22.6.
Mass Spectrum (EI, 70eV) *m*/*z* 194 ($M^{+\bullet}$, 23%), 152 (100), 151, (90).
HREIMS Found: $M^{+\bullet}$, 194.0937. $C_{11}H_{14}O_3$ requires $M^{+\bullet}$, 194.0943.
Elemental Analysis Found: C, 67.80; H, 7.27%. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27%.

3-Isopropoxy-4-methoxybenzaldehyde (120)



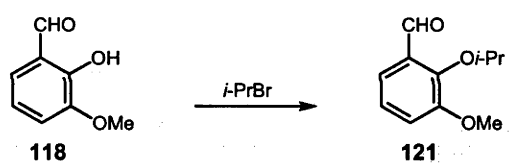
117 **120**

Aldehyde **120** was prepared in the same manner as described immediately above for congener **119** but now using isovanillin (**117**) as the starting material. In this manner the title aldehyde **120** (23.2 g, 91%) was obtained as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 9.84 (s, 1H), 7.43 (m, 2H), 6.98 (d, J = 8.0 Hz, 1H), 4.65 (septet, J = 6.0 Hz, 1H), 3.94 (s, 3H), 1.40 (d, J = 6.0 Hz, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[20]

2-Isopropoxy-3-methoxybenzaldehyde (121)



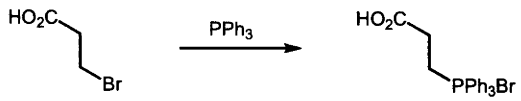
118 **121**

Aldehyde **121** was prepared in the same manner as described above for congener **119** but now using *o*-vanillin (**118**) as the starting material. In this manner the title aldehyde **121** (35.2 g, 92%) was obtained as a light-yellow colourless oil.

^{1}H NMR (300 MHz) δ 10.46 (s, 1H), 7.42 (m, 1H), 7.17 (m, 2H), 4.63 (septet, J = 6.0 Hz, 1H), 3.89 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[21]

3-Triphenylphosphonium propanoic acid bromide (122)



122

Triphenylphosphonium bromide **122** was prepared using a protocol described by Smith.[22] Thus, triphenylphosphine (8.57 g, 32.7 mmol) was added to a magnetically stirred solution of 3-bromopropionic acid (5.00 g, 32.7 mmol and MeCN (60 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at reflux for 69 h in a flask fitted with a Liebig condenser, then cooled and concentrated under reduced pressure. Benzene (30 mL) and MeCN (30 mL) were added and the magnetically stirred mixture maintained at 18 °C for a further for 43 h. The ensuing precipitate was removed by filtration and washed with benzene (20 mL) to afford the title triphenylphosphonium bromide **122** (12.9 g, 95%) as a white, crystalline solid, m.p. 196-197 °C (lit.[23] m.p. 196-197 °C).

^{1}H NMR (300 MHz) δ 7.85-7.69 (complex m, 15H), 3.72 (m, 2H), 3.12 (m, 2H) (signal due to CO_2H proton not observed).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[22] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

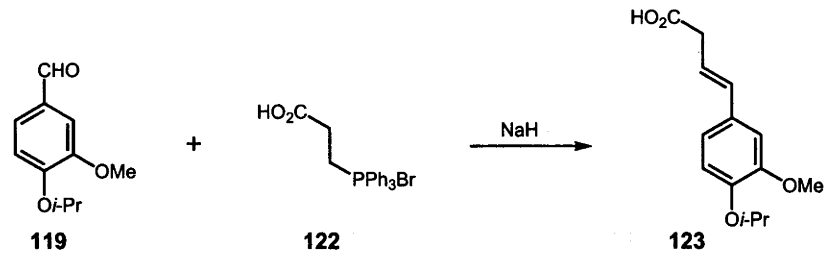
^{13}C NMR (75 MHz) δ 171.6, 171.4, 135.7, 135.6, 133.9, 133.8, 131.0, 130.8, 118.2, 117.0, 28.3, 19.4, 18.7.

Mass Spectrum (ESI) *m/z* 335 [$(M\text{-}Br^{\bullet})^+$, 100%}, 168 (6), 112, (7).

HRESIMS Found: $(M\text{-}Br^{\bullet})^+$, 335.1201. $C_{21}H_{20}O_2P$ requires $(M\text{-}Br^{\bullet})^+$, 335.1201.

Elemental Analysis Found: C, C, 60.92; H, 5.01; Br, 19.12; P, 7.37%. $C_{21}H_{20}BrO_2P$ requires C, 60.74; H, 4.85; Br, 19.24; O, 7.71; P, 7.46%.

(*E*)-4-(4-Isopropoxy-3-methoxyphenyl)but-3-enoic acid (123)



A solution of aldehyde **119** (31.2 g, 161 mmol) and triphenylphosphonium bromide **122** (66.7 g, 161 mmol) in THF/DMSO (400 mL of a 1:1 *v*/*v* solution) was added dropwise to NaH (9.66 g, 232 mmol) maintained under nitrogen at 0 °C. The ensuing mixture was then warmed to 18 °C and maintained at this temperature for 24 h. Water (200 mL) was added, the phases separated and the aqueous layer washed with Et_2O (3 x 80 mL) (to remove unreacted aldehyde **119**). The aqueous phase was acidified with HCl (2 M aqueous solution) and extracted with Et_2O (3 x 80 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 1:1 *v*/*v* hexane/Et_2O) and concentration of the appropriate fractions (R_f = 0.3) afforded the *title acid* ***123*** (24.7 g, 64%) as a white, crystalline solid, m.p. 80 °C.

^{1}H NMR (300 MHz) δ 6.93-6.81 (complex m, 3H), 6.44 (d, *J* = 15.0 Hz, 1H), 6.15 (dt, *J* = 15.0 Hz 1H), 4.52 (septet, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 3.28 (d, *J* = 7.0 Hz, 2H), 1.36 (d, *J* = 6.0 Hz, 6H) (signal due to CO_2H proton not observed).

^{13}C NMR (75 MHz) δ 178.5, 150.5, 147.3, 133.9, 130.2, 119.7, 119.0, 115.6, 109.6, 71.6, 56.1, 38.3, 22.2.

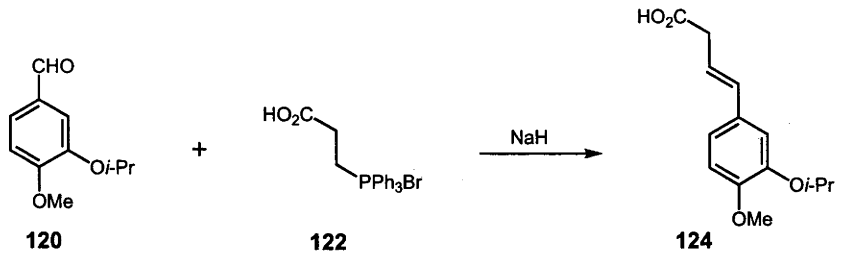
IR υ_{max} (NaCl) 2977, 2936, 1709, 1602, 1581, 1510, 1465, 1262, 1228, 1137 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 250 ($M^{+\bullet}$, 71%), 209 (27), 208 (98), 163, (55), 131 (100).

HREIMS Found: $M^{+\bullet}$, 250.1204. $C_{14}H_{18}O_4$ requires $M^{+\bullet}$, 250.1205.

Elemental Analysis Found: C, 67.08; H, 6.84%. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%.

(*E*)-4-(3-Isopropoxy-4-methoxyphenyl)but-3-enoic acid (124)



120 **122** **124**

Acid **124** was prepared in the same manner as described immediately above for congener **123** but now using aldehyde **120** as the starting material. In this manner the *title acid* ***124*** (10.5 g, 55%) was obtained as a white, crystalline solid, m.p. 82 °C.

^{1}H NMR (300 MHz) δ 6.96-6.80 (complex m, 3H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.11 (dt, *J* = 16.0 Hz, 1H), 4.54 (septet, *J* = 6.0 Hz, 1H), 3.84 (s, 3H), 3.27 (d, *J* = 7.0 Hz, 2H), 1.37 (d, *J* = 6.0 Hz, 6H) (signal due to CO_2H proton not observed).

^{13}C NMR (75 MHz) δ 178.2, 150.6, 147.5, 133.9, 129.9, 120.1, 118.9, 113.9, 112.1, 71.8, 56.2, 38.2, 22.3.

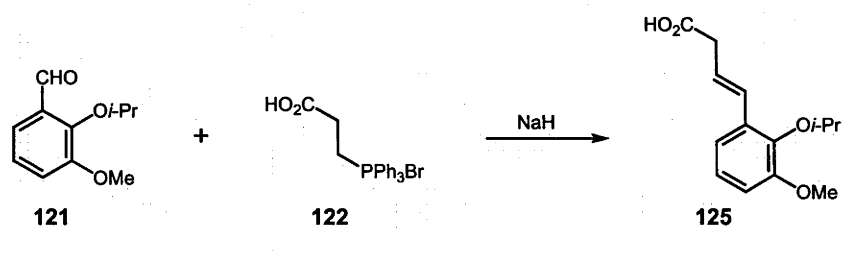
IR υ_{max} (NaCl) 2973, 2934, 1709, 1601, 1581, 1511, 1424, 1262, 1230, 1136 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 250 ($M^{+\bullet}$, 7%), 208 (13), 160 (97), 131, (28), 69 (100).

HREIMS Found: $M^{+\bullet}$, 250.1204. $C_{14}H_{18}O_4$ requires $M^{+\bullet}$, 250.1205.

Elemental Analysis Found: C, 66.91; H, 7.52%. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%.

(*E*)-4-(2-Isopropoxy-3-methoxyphenyl)but-3-enoic acid (125)



121 **122** **125**

Acid **125** was prepared in the same manner as described above for congener **123** but now using aldehyde **121** as the starting material. In this manner the *title acid* ***125*** (34.2 g, 78%) was obtained as a white, crystalline solid, m.p. 81 °C.

^{1}H NMR (300 MHz) δ 7.12-6.78 (complex m, 4H), 6.39 (dt, *J* = 16.0 and 7.2 Hz, 1H), 4.39 (septet, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 3.32 (d, *J* = 7.0 Hz, 2H), 1.27 (d, *J* = 6.0 Hz, 6H) (signal due to CO_2H proton not observed).

^{13}C NMR (75 MHz) δ 178.5, 153.4, 144.6, 132.0, 129.5, 123.8, 121.7, 118.3, 111.6, 75.7, 56.0, 38.7, 22.7.

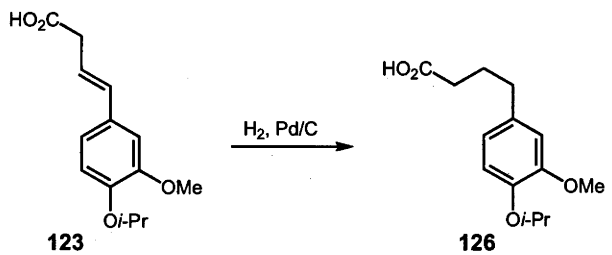
IR υ_{max} (NaCl) 2974, 2934, 1708, 1577, 1475, 1458, 1381, 1372, 1269, 1215, 1107, 1088 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 250 ($M^{+\bullet}$, 54%), 208 (78), 190 (89), 175, (100), 162 (65).

HREIMS Found: $M^{+\bullet}$, 250.1205. $C_{14}H_{18}O_4$ requires $M^{+\bullet}$, 250.1205.

Elemental Analysis Found: C, 67.02; H, 7.24%. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%.

4-(4-Isopropoxy-3-methoxyphenyl)butanoic acid (126)



123 **126**

A solution of alkene **123** (25.0 g, 100 mmol) in THF (150 mL) was treated with 10% palladium on carbon (850 mg) and the ensuing mixture maintained under a hydrogen atmosphere (1 atm) at 18 °C. After 16 h the reaction mixture was filtered through Celite™ (~3 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with Et_2O (150 mL). The combined filtrates were concentrated under reduced pressure to afford the *title acid* **126** as a light-yellow oil (25.2 g, 100%).

^{1}H NMR (300 MHz) δ 6.81 (d, *J* = 8.0 Hz, 1H), 6.68 (m, 2H), 4.47 (septet, *J* = 6.0 Hz, 1H), 3.84 (s, 3H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 1.94 (septet, *J* = 8.0 Hz, 2H), 1.35 (d, *J* = 6.0 Hz, 6H) (signal due to CO_2H proton not observed).

^{13}C NMR (75 MHz) δ 180.4, 150.5, 145.7, 134.5, 120.6, 116.2, 112.6, 71.7, 56.1, 34.9, 33.6, 26.6, 22.4.

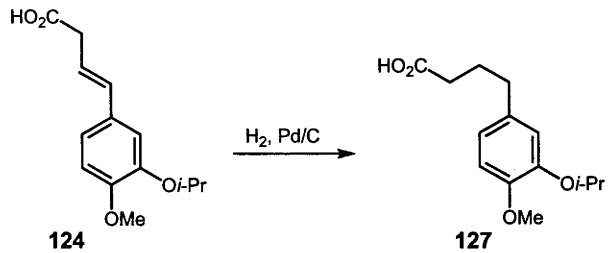
IR υ_{max} (NaCl) 2976, 1708, 1587, 1512, 1464, 1418, 1383, 1264, 1231, 1138, 1036, 954 cm^{-1}.

Mass Spectrum (EI, 70eV) *m/z* 252 ($M^{+\bullet}$, 28%), 210 (56), 150 (53), 137 (100).

HREIMS Found: $M^{+\bullet}$, 252.1360. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362.

Elemental Analysis Found: C, 66.83; H, 8.31%. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.99%.

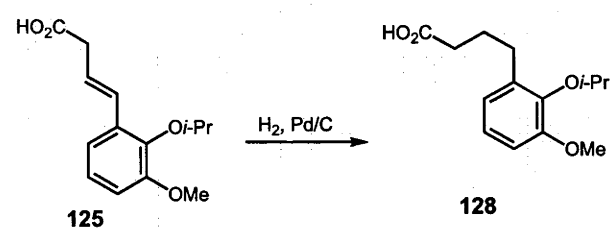
4-(3-Isopropoxy-4-methoxyphenyl)butanoic acid (127)



Acid **127** was prepared in the same manner as described immediately above for congener **126** but now using alkene **124** as the starting material. In this manner the *title acid* ***127*** (9.20 g, 100%) was obtained as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.80 (d, *J* = 8.0 Hz, 1H), 6.72 (m, 2H), 4.51 (septet, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 1.93 (septet, *J* = 8.0 Hz, 2H), 1.36 (d, *J* = 6.0 Hz, 6H) (signal due to CO_2H proton not observed).
^{13}C NMR (75 MHz) δ 180.2, 149.0, 147.3, 134.0, 121.2, 116.7, 112.3, 71.6, 56.2, 34.7, 33.5, 26.7, 22.3.
IR υ_{max} (NaCl) 2976, 1708, 1588, 1512, 1443, 1423, 1383, 1262, 1234, 1137, 1110, 1030 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 252 ($M^{+\bullet}$, 41%), 210 (69), 150 (76), 137 (100).
HREIMS Found: $M^{+\bullet}$, 252.1362. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362.

4-(2-Isopropoxy-3-methoxyphenyl)butanoic acid (128)

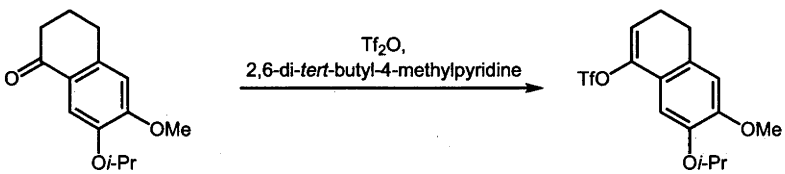


Acid **128** was prepared in the same manner as described above for congener **126** but now using alkene **125** as the starting material. In this manner the *title acid* ***128*** (34.3 g, 100 %) was obtained as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.96 (t, *J* = 7.0 Hz, 1H), 6.76 (m, 2H), 4.47 (septet, *J* = 6.0 Hz, 1H), 3.82 (s, 3H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.93 (septet, *J* = 7.0 Hz, 2H), 1.26 (d, *J* = 6.0 Hz, 6H) (signal due to CO_2H proton not observed).
^{13}C NMR (75 MHz) δ 180.7, 153.1, 145.1, 135.9, 123.6, 122.1, 110.5, 74.7, 55.8, 33.8, 29.7, 25.5, 22.9.

IR υ_{max} (NaCl) 2973, 1708, 1584, 1475, 1381, 1371, 1383, 1265, 1234, 1213, 1109, 1083 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 252 ($M^{+\bullet}$, 29%), 210 (28), 192 (56), 164 (33), 147 (40), 137 (100).
HREIMS Found: $M^{+\bullet}$, 252.1365. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362.

1,2-Dihydro-7-isopropoxy-6-methoxynaphthalen-4-yl trifluoromethanesulfonate (130)

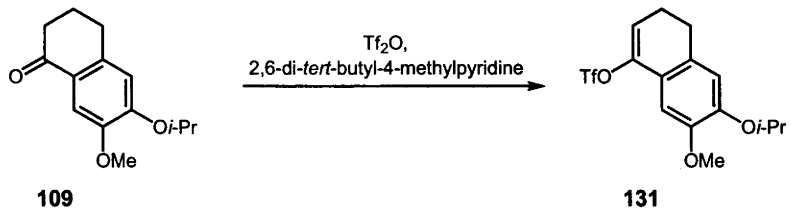


108 **130**

Trifluoromethanesulfonic anhydride (0.56 mL, 3.34 mmol) was added to a magnetically stirred solution of 1-tetralone **108** (400 mg, 1.67 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (686 mg, 3.34 mmol) in CH_2Cl_2 (15 mL) maintained under nitrogen at 0 °C. After 1 h the ensuing mixture was warmed to 18 °C and kept at this temperature for a further 0.5 h. Then hexane (10 mL) was added and the mixture filtered through Celite™ (~3 cm deep pad contained in a sintered glass funnel) and the solids thus retained were washed with hexane (20 mL). The combined filtrates were concentrated under reduced pressure and the ensuing purple residue subjected to flash chromatography (silica, 9:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.4) afforded the *title triflate* ***130*** (505 mg, 82%) as a colourless oil.

^{1}H NMR (300 MHz) δ 6.91 (s, 1H), 6.71 (s, 1H), 5.87 (t, *J* = 5.0 Hz, 1H), 4.49 (septet, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.47 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 6H).
^{13}C NMR (75 MHz) δ 151.1, 146.4, 146.0, 129.9, 121.4, 118.8 (q, *J* = 315 Hz), 115.2, 112.2, 109.8, 72.0, 56.3, 26.9, 22.8, 22.2.
IR υ_{max} (NaCl) 2977, 2939, 1512, 1418, 1367, 1278, 1248, 1212, 1142, 1123, 1058, 976 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 366 ($M^{+\bullet}$, 48%), 324 (100), 191 (46), 163 (54).
HREIMS Found: $M^{+\bullet}$, 366.0748. $C_{15}H_{17}F_3O_5S$ requires $M^{+\bullet}$, 366.0749.

1,2-Dihydro-6-isopropoxy-7-methoxynaphthalen-4-yl trifluoromethanesulfonate (131)

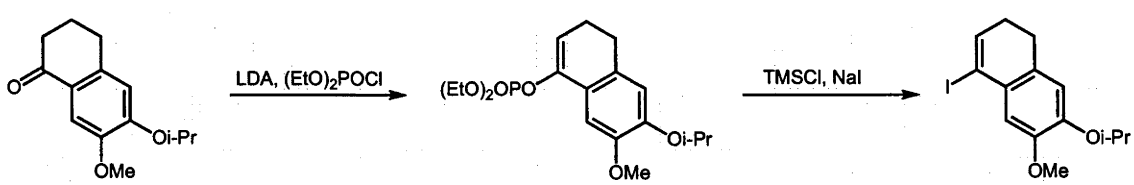


109 **131**

Triflate **131** was prepared in the same manner as described immediately above for congener **130** but now using 1-tetralone **109** as the starting material. In this manner the *title triflate **131*** (505 mg, 66%) was obtained as a colourless oil.

^{1}H NMR (300 MHz) δ 6.88 (s, 1H), 6.71 (s, 1H), 5.88 (t, *J* = 5.0 Hz, 1H), 4.55 (septet, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.47 (m, 2H), 1.38 (d, *J* = 6.0 Hz, 6H).
^{13}C NMR (75 MHz) δ 149.1, 148.1, 146.5, 129.4, 121.6, 118.8 (q, *J* = 318 Hz), 115.5, 115.4, 77.5, 71.8, 56.3, 26.8, 22.8, 22.3.
IR υ_{max} (NaCl) 2978, 2938, 1652, 1606, 1568, 1512, 1418, 1366, 1328, 1271, 1248, 1214, 1142, 1123, 1059, 1018, 988, 909 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 366 ($M^{+\bullet}$, 51%), 324 (100), 191 (46), 163 (70).
HREIMS Found: $M^{+\bullet}$, 366.0746. $C_{15}H_{17}F_3O_5S$ requires $M^{+\bullet}$, 366.0749.

1,2-Dihydro-4-iodo-6-isopropoxy-7-methoxynaphthalene (135)



109 **134** **135**

Step i: *n*-BuLi (3.90 mL, of a 1.6 M solution in hexane, 6.27 mmol) was added to a magnetically stirred solution of diisopropylamine (0.90 mL, 6.27 mmol) in THF (15 mL) maintained under nitrogen at -20 °C. After 0.33 h the ensuing mixture was warmed to 0 °C and maintained at this temperature for a further 0.5 h then a solution of 1-tetralone **109** (500 mg, 2.08 mmol) in THF (15 mL) was added dropwise over 1 h. After 0.33 h the ensuing mixture was cooled to -30 °C and diethyl chlorophosphonate (0.34 mL, 2.28 mmol) was added. The reaction mixture was warmed to 0 °C and maintained at this temperature for a further 1 h then warmed to 18 °C and, after 1 h, NH_4Cl (15 mL of a saturated aqueous solution) was added. The phases were separated, the aqueous phase extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated

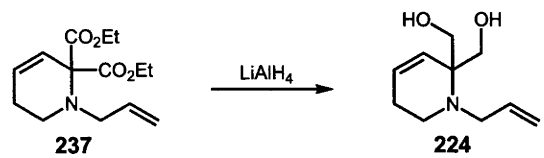
under reduced pressure to give phosphonate ester **134**. This somewhat unstable material was subjected to the pseudo-Finkelstein reaction as described in the following paragraph.

Step ii: TMSCl (0.80 mL, 6.24 mmol) was added to a magnetically stirred solution of crude phosphonate ester **134** (obtained as described immediately above) and NaI (935 mg, 6.24 mmol) in MeCN (12 mL) maintained under nitrogen at 18 °C. After 0.5 h $NaHCO_3$ (5 mL of a saturated aqueous solution) and Na_2SO_3 (5 mL of a saturated aqueous solution) were added the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried, filtered and concentrated under reduced pressure. The ensuing oil was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.2) afforded the *title iodide* ***135*** (183 mg, 28%) as a yellow oil.

^{1}H NMR (300 MHz) δ 7.02 (s, 1H), 6.69 (t, *J* = 5.0 Hz, 1H), 6.62 (s, 1H), 4.54 (septet, *J* = 6.0 Hz, 1H), 3.88 (s, 3H), 2.74 (t, *J* = 8.0 Hz, 2H), 2.31 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 6H).
^{13}C NMR (75 MHz) δ 149.0, 147.2, 138.0, 128.4, 127.8, 116.2, 115.3, 97.8, 71.8, 56.5, 27.7, 27.5, 22.4.
IR υ_{max} (NaCl) 2932, 2883, 1603, 1476, 1448, 1276, 938, 805, 756, 726 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 344 ($M^{+\bullet}$, 64%), 302 (100), 175 (99).
HREIMS Found: $M^{+\bullet}$, 344.0274. $C_{14}H_{17}{}^{127}IO_2$ requires $M^{+\bullet}$, 344.0273.

7.3 Experimental Procedures for Chapter Four

(1-Allyl-1,2,5,6-tetrahydropyridine-2,2-diyl)dimethanol (224)

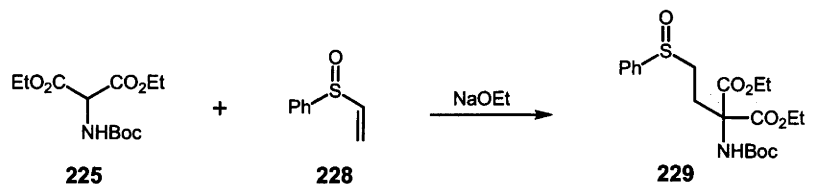


237 224

$LiAlH_4$ (19.5 mL of a 1.0 M solution in THF, 19.5 mmol) was added to a magnetically stirred solution of diester **237** (1.49 g, 5.54 mmol) in THF (53 mL) maintained under nitrogen at 0 °C. After 2 h the reaction mixture was warmed to 18 °C and maintained at this temperature for a further 6.5 h then THF (50 mL) was added. The ensuing mixture was cooled to 0 °C then water (0.75 mL), NaOH (0.75 mL of a 15% w/v aqueous solution), and water (2.25 mL) were added dropwise and in the specified order. The resulting mixture was warmed to 18 °C, maintained at this temperature for 0.25 h then dried ($MgSO_4$). After 0.25 h the reaction mixture was filtered and the solids thus retained were washed with THF (250 mL). The combined filtrates were concentrated under reduced pressure to afford the *title diol* ***224*** (850 mg, 83%) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 6.15 (dt, J = 6.0 and 3.9 Hz, 1H), 5.86–5.70 (m, 1H), 5.44 (d, J = 10.2 Hz, 1H), 5.26–5.10 (m, 2H), 3.65 (d, J = 11.1 Hz, 2H), 3.43 (d, J = 11.1 Hz, 2H), 3.28 (d, J = 6.0 Hz, 2H), 2.91 (t, J = 5.7 Hz, 2H), 2.42 (s, 2H), 2.14–2.05 (m, 2H).
^{13}C NMR (75 MHz) δ 136.4, 130.2, 129.2, 116.8, 63.0, 62.2, 51.2, 43.0, 25.0.
IR υ_{max} (NaCl) 3400, 2918, 1641, 1417, 1392, 1279, 1077, 1043, 992, 918, 830, 732 cm^{-1}.
Mass Spectrum (ESI) *m/z* 206 $[(M+Na^{\bullet})^+$, 7%], 184 $[(M+H^{\bullet})^+$, 44], 70 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 184.1339. $C_{10}H_{17}NO_2$ requires $(M + H^{\bullet})^+$, 184.1338.

Diethyl 2-(*tert*-butoxycarbonylamino)-2-(2-(phenylsulfinyl)ethyl)malonate (229)



Sodium metal (490 mg, 21.3 g atom) was added in four portions to magnetically stirred EtOH (30 mL) maintained under nitrogen at 18 °C. After all of the sodium had reacted the resulting solution of NaOEt in EtOH was cooled to 0 °C and 2-[*N*-(*tert*-butoxycarbonyl)amino]malonate (**225**) (4.79 mL, 17.8 mmol, ex. Sigma-Aldrich) was added. The resulting mixture was maintained at this temperature for 1 h then phenyl vinyl sulfoxide (**228**) (2.61 mL, 19.5 mmol, ex. Sigma-Aldrich) was added dropwise. The reaction mixture so-formed was maintained at this temperature for 2 h then warmed to 18 °C and maintained at this temperature for a further 2 h. After this time acetic acid was added until the solution became acidic and the reaction mixture was then concentrated under reduced pressure. The ensuing yellow oil was dissolved in EtOAc (50 mL) and the resulting solution was washed with $NaHCO_3$ (3 x 15 mL of saturated aqueous solution). The combined aqueous washings were extracted with EtOAc (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 97:2:1 *v/v/v* CH_2Cl_2/MeOH/Et_3N). Concentration of the appropriate fractions (R_f = 0.2) afforded the *title sulfoxide* **229** (7.08 g, 93%) as a white, crystalline solid, m.p. 72–75 °C.

^{1}H NMR (300 MHz) δ 7.62-7.56 (m, 2H), 7.55-7.42 (m, 3H), 5.91 (br s, 1H), 4 .19 (m, 4H), 2.85-2.44 (m, 4H), 1.40 (s, 9H), 1.20 (td, *J* = 7.2 and 0.9 Hz, 6H).

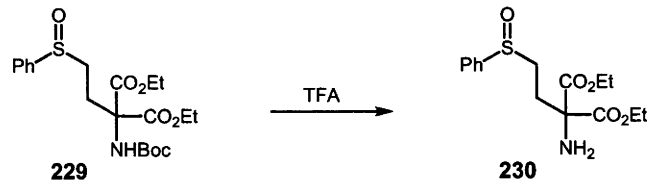
^{13}C NMR (75 MHz) δ 167.6, 167.5, 154.0, 143.4, 131.2, 129.3, 124.1, 80.7, 65.5, 62.9, 62.8, 52.0, 28.2, 26.2, 14.0(0), 13.9(8) (additional signals attributed to carbamate rotamers).

IR υ_{max} (NaCl) 3424, 2979, 1739, 1718, 1479, 1367, 1257, 1203, 1159, 1088, 1026 749 cm^{-1}.

Mass Spectrum (ESI) *m/z* 450 [(M+Na$^\bullet$)$^+$, 48%], 428 [(M+H$^\bullet$)$^+$, 8], 372 (9), 328 (100), 202 (20), 174 (48).

HRESIMS Found: (M + H$^\bullet$)$^+$, 428.1751. $C_{20}H_{29}NO_7S$ requires (M + H$^\bullet$)$^+$, 428.1743.

Diethyl 2-amino-2-(2-(phenylsulfinyl)ethyl)malonate (230)

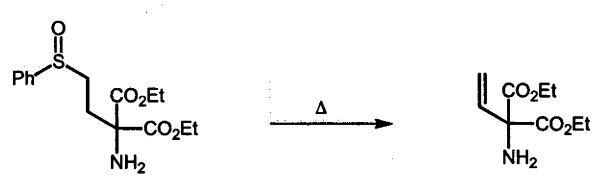


229 **230**

TFA (0.13 mL, 1.64 mmol) was added to a magnetically stirred solution of sulfoxide **229** (140 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was kept at this temperature for 0.5 h, then warmed to 18 °C and maintained at this temperature for a further 21 h. After this time $NaHCO_3$ (3 mL of a saturated aqueous solution) was added, the phases separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title amine* ***230*** (1.70 g, 100%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 7.64–7.56 (m, 2H), 7.54–7.44 (m, 3H), 4.18 (dq, J = 7.2 and 3.3 Hz, 4H), 3.12–2.96 (m, 1H), 2.90–2.80 (m, 1H), 2.40–2.28 (m, 1H), 2.20–2.08 (m, 1H), 1.92 (br s, 2H), 1.23(3) (t, J = 7.2 Hz, 3H), 1.22(7) (t, J = 7.2 Hz, 3H).
^{13}C NMR (75 MHz) δ 170.6, 143.2, 130.9, 129.2, 123.9, 64.7, 62.1, 51.1, 27.8, 13.9.
IR υ_{max} (NaCl) 3385, 2982, 1736, 1477, 1444, 1369,1250, 1206, 1188, 1086, 1037, 750, 693 cm^{-1}.
Mass Spectrum (ESI) *m/z* 350 [$(M+Na^{\bullet})^+$, 100%], 328 [$(M+H^{\bullet})^+$, 84], 256 (16), 202 (18), 174 (62).
HRESIMS Found: $(M + H^{\bullet})^+$, 328.1205. $C_{15}H_{21}NO_5S$ requires $(M + H^{\bullet})^+$, 328.1219.

Diethyl 2-amino-2-vinylmalonate (231)



230 **231**

A neat sample of sulfoxide **230** obtained as described immediately above, was heated at 160 °C for 0.5 h in a μ-wave reactor and, after cooling, the ensuing brown oil was subjected to flash chromatography (silica, 90:9:1 *v/v/v* hexane/EtOAc/Et_3N). Concentration of the appropriate fractions (R_f = 0.3 in 97:3 *v/v* CH_2Cl_2/MeOH) afforded *title amine* ***231*** (39 mg, 59%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.31 (dd, *J* = 17.4 and 10.5 Hz, 1H), 5.49 (dd, *J* = 17.4 and 0.6 Hz, 1H), 5.33 (dd, *J* = 10.5 and 0.6 Hz, 1H), 4.28–4.18 (m, 4H), 2.11 (br s, 2H), 1.27 (td, *J* = 7.2 and 0.3 Hz, 6H).

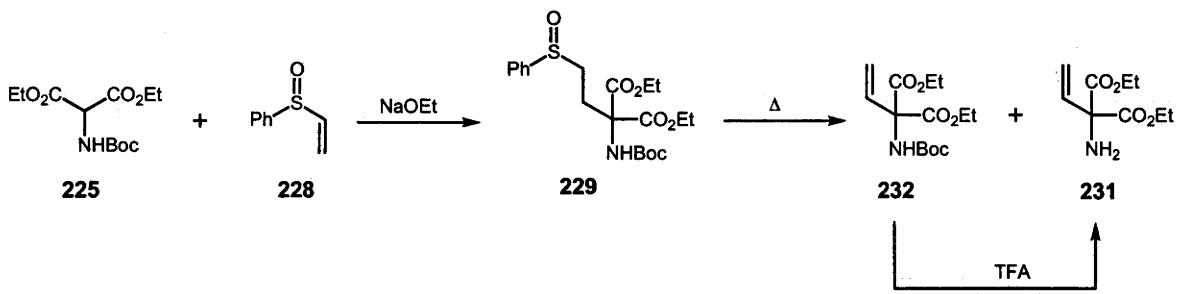
^{13}C NMR (75 MHz) δ 170.5, 134.8, 116.5, 67.1, 62.3, 14.1.

IR υ_{max} (NaCl) 3392, 2984, 1738, 1368, 1299, 1257, 1197, 1038 cm^{-1}.

Mass Spectrum (ESI) *m/z* 224 [$(M+Na^{\bullet})^+$, 100%], 202 [$(M+H^{\bullet})^+$, 20], 128 (80), 102 (84), 100 (88).

HRESIMS Found: $(M + H^{\bullet})^+$, 202.1070. $C_9H_{15}NO_4$ requires $(M + H^{\bullet})^+$, 202.1079.

Diethyl 2-amino-2-vinylmalonate (231) (Improved procedure)



Step i: Sodium metal (490 mg, 21.3 g atom) was added in four portions to magnetically stirred EtOH (30 mL) maintained under nitrogen at 18 °C. After all of the sodium had reacted the resulting solution of NaOEt in EtOH was cooled to 0 °C and 2-[*N*-(*tert*-butoxycarbonyl)amino]malonate (**225**) (4.79 mL, 17.8 mmol, ex. Sigma-Aldrich) was added and maintained at this temperature for 1 h then phenyl vinyl sulfoxide (**228**) (2.61 mL, 19.5 mmol, ex. Sigma-Aldrich) was added dropwise. The ensuing reaction mixture was maintained at this temperature for 2 h, then warmed to 18 °C and held at this temperature for a further 2 h. After this time acetic acid was added until the solution became acidic and the reaction mixture was then concentrated under reduced pressure. The ensuing yellow oil was dissolved in EtOAc (30 mL) and washed with $NaHCO_3$ (3 x 20 mL of a saturated aqueous solution). The aqueous washings were extracted with EtOAc (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material, which was presumed to contain sulfoxide **229**, was evenly divided between ten 10 mL Pyrex™ μ-wave reaction vials and these were then subjected (neat) to simultaneous μ-wave irradiation under the same conditions as described immediately above. The cooled reaction mixtures were then combined and subjected to flash chromatography (silica, 90:9:1 *v/v/v* hexane/EtOAc/Et_3N) affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 9:1 *v/v* CH_2Cl_2/EtOAc) afforded a *ca.* 2:3 mixture (as determined by ^{1}H NMR spectroscopic analysis) of carbamate **232** and

phenylsulfenic acid.

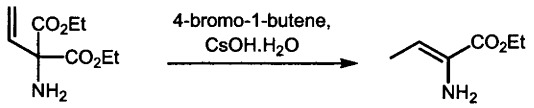
Concentration of fraction B (R_f = 0.3 in 97:3 *v/v* CH_2Cl_2/MeOH) afforded amine **231** as a light-yellow oil. This material was identical, in all respects, with an authentic sample obtained as described above.

Subjection of a portion of fraction A to flash chromatography (90:9:1 *v/v/v* hexane/EtOAc/Et_3N) and concentration of the appropriate fractions (R_f = 0.6 in 9:1 *v/v* CH_2Cl_2/EtOAc) gave a spectroscopically pure sample of *carbamate* **232** as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.50 (dd, *J* = 17.4 and 10.8 Hz, 1H), 6.09 (br s, 1H), 5.42–5.26 (m, 2H), 4.40–4.14 (m, 4H), 1.43 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 6H).
^{13}C NMR (75 MHz) δ 167.0, 153.6, 132.7, 116.3, 80.3, 67.1, 62.7, 28.1, 13.9.
IR υ_{max} (NaCl) 3435, 2981, 2937, 1743, 1724, 1484, 1368, 1271, 1254, 1205, 1166, 1059, 1022, 986 cm^{-1}.
Mass Spectrum (ESI) *m/z* 324 [$(M+Na^{\bullet})^+$, 46%], 246 (40), 202 (100), 128 (95).
HRESIMS Found: $(M + Na^{\bullet})^+$, 324.1426. $C_{14}H_{23}NO_6$ requires $(M + Na^{\bullet})^+$, 324.1423.

Step ii: A magnetically solution of the *ca.* 2:3 mixture of the carbamate **232** and phenylsulfenic acid (obtained as described immediately above) in CH_2Cl_2 (50 mL) maintained at 0 °C was treated with TFA (7.5 mL, 97.4 mmol). After 0.5 h the reaction mixture was warmed to 18 °C, stirred at this temperature for 16 h then treated with $NaHCO_3$ (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (9:90:1 *v/v/v* EtOAc/hexane/Et_3N) and concentration of the relevant fractions (R_f = 0.3 in 97:3 *v/v* CH_2Cl_2/MeOH) gave amine **231** in sufficient quantities to sustain the synthetic procedures defined below. This material was identical, in all respects, with an authentic sample obtained as described above.

(Z)-Ethyl 2-aminobut-2-enoate (233)



231 **233**

$CsOH \bullet H_2O$ (263 mg, 1.57 mmol) was added to a magnetically stirred solution of DMF (4 mL) maintained under nitrogen at 18 °C and containing molecular sieves (2 g of 8-12 mesh 4 Å material). After 0.5 h a solution of amine **231** (300 mg, 1.49 mmol) in DMF (4 mL) was added and the ensuing mixture maintained at this temperature for a further 0.5 h then 4-bromo-1-butene (0.18 mL, 1.79 mmol) was added. After 16.5 h the reaction mixture was filtered through Celite™ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained were washed with EtOAc (40 mL). The combined organic phases were then washed with NaOH (3 x 10 mL of a 1 M aqueous solution) and water (10 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 89:10:1 *v/v/v* hexane/EtOAc/Et_3N) and concentration of the appropriate fractions (R_f = 0.2) afforded the title alkene **233** (50 mg, 26%) as a yellow oil.

^{1}H NMR (300 MHz) δ 5.68 (q, *J* = 7.5 Hz, 1H), 3.50 (br s, 2H), 4.21 (q, *J* = 6.9 Hz, 2H), 1.65 (d, *J* = 7.5 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 3H).

The data presented above matched the equivalent spectral information reported in the literature.[24] In addition, the following data were acquired on this compound, particularly because such spectral information is not available in the literature.

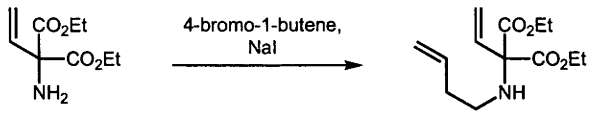
^{13}C NMR (75 MHz) δ 165.0, 133.2, 107.2, 60.9, 14.2, 11.5.

IR υ_{max} (NaCl) 3351, 2981, 1728, 1447, 1369, 1241, 1025 cm^{-1}.

Mass Spectrum (ESI) *m/z* 130 [$(M+H^{\bullet})^+$, 100%], 102 (37), 56 (28).

HRESIMS Found: $(M + H^{\bullet})^+$, 130.0863. $C_6H_{11}NO_2$ requires $(M + H^{\bullet})^+$, 130.0868.

Diethyl 2-(but-3-enylamino)-2-vinylmalonate (234)



231 **234**

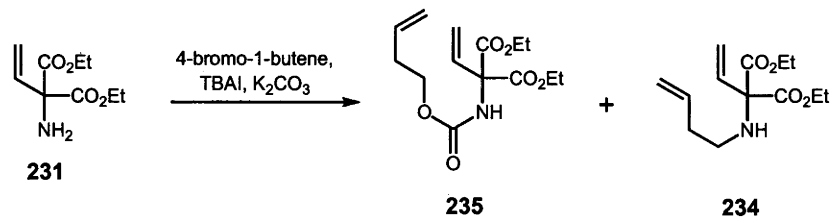
Na_2CO_3 (6.07 g, 57.3 mmol), NaI (5.14 g, 34.3 mmol), and 4-bromo-1-butene (5.81 mL, 57.3 mmol) were added to a magnetically stirred solution of amine **231** (5.76 mg, 28.6 mmol) in DMF (70 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 80 °C for 41 h in a reaction flask fitted with a Liebig condenser. After this time, the reaction mixture was cooled to 18 °C then diluted with CH_2Cl_2 (150 mL) and water (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 90:9:1 *v/v/v* hexane/EtOAc/Et_3N) and so affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 97:3 *v/v* CH_2Cl_2/MeOH) afforded the *title diene* **234** (4.45 g, 87% at 70% conversion) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.23 (dd, *J* = 17.4 and 10.5 Hz, 1H), 5.82–5.70 (m, 1H), 5.55 (dd *J* = 17.4 and 1.2 Hz, 1H), 5.40 (dd, *J* = 10.5 and 1.2 Hz, 1H), 5.18–5.00 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 4H), 2.50 (t, *J* = 6.6 Hz, 2H), 2.28 (q, *J* = 6.6 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 6H) (signal due to NH proton not observed).
^{13}C NMR (75 MHz) δ 169.2, 135.8, 132.5, 118.1, 116.6, 71.0, 61.8, 42.3, 34.3, 13.9.
IR υ_{max} (NaCl) 3352, 3078, 2981, 1738, 1640, 1465, 1447, 1391, 1367, 1255, 1198, 1047, 991, 936, 918, 860 cm^{-1}.
Mass Spectrum (ESI) *m/z* 278 $[(M+Na^{\bullet})^+$, 51%], 256 $[(M+H^{\bullet})^+$, 30], 182 (80), 108 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 256.1541. $C_{13}H_{21}NO_4$ requires $(M + H^{\bullet})^+$, 256.1549.

Concentration of fraction B (R_f = 0.3, 97:3 *v/v* CH_2Cl_2/MeOH) afforded starting amine **231** (1.75 g, 30% recovery) as a clear, light-yellow oil.

Diethyl 2-[(but-3-enyloxy)carbonylamino]-2-vinylmalonate (235)



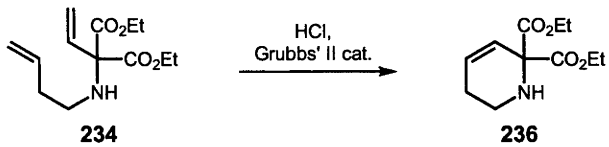
K_2CO_3 (296 mg, 2.14 mmol), TBAI (475 mg, 1.29 mmol), and 4-bromo-1-butene (0.22 mL, 2.14 mmol) were added to a magnetically stirred solution of amine **231** (215 mg, 1.07 mmol) in DMF (5 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 80 °C for 22 h in a reaction flask fitted with a Liebig condenser. After this time, the reaction mixture was cooled to 18 °C then diluted with CH_2Cl_2 (15 mL) and water (5 mL) and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 90:9:1 *v/v/v* hexane / EtOAc / Et_3N) and so affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 97:3 *v/v* CH_2Cl_2/MeOH) afforded diene **234** (95 mg, 35%) as a clear, light-yellow oil.

Concentration of fraction B (R_f = 0.4 in 97:3 *v/v* CH_2Cl_2/MeOH) afforded the *title carbamate* **235** (110 mg, 35%) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 6.47 (dd, *J* = 17.1 and 10.2 Hz, 1H), 6.23 (s, 1H), 5.82–5.68 (m, 1H), 5.33 (d, *J* = 17.1 Hz, 1H), 5.29 (d, *J* = 10.2 Hz, 1H), 5.05 (m, *J* = 10.5 and 6.3 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 4H), 4.08 (t, *J* = 6.6 Hz, 2H), 2.35 (q, *J* = 6.0 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 6H).
^{13}C NMR (75 MHz) δ 166.2, 153.7, 133.5, 132.1, 116.6, 115.8, 66.7, 63.7, 62.2, 32.9, 13.3.
IR υ_{max} (NaCl) 3429, 2983, 1733, 1492, 1251, 1092, 1054, 1465 cm^{-1}.
Mass Spectrum (ESI) *m/z* 322 [$(M+Na^{\bullet})^+$, 87%], 300 [$(M+H^{\bullet})^+$, 54], 226 (5), 130 (14), 102 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 300.1449. $C_{14}H_{21}NO_6$ requires $(M + H^{\bullet})^+$, 300.1447.

Diethyl 5,6-dihydropyridine-2,2(1*H*)-dicarboxylate (236)



234 **236**

HCl (0.03 mL of a 10 M aqueous solution) was added to a magnetically stirred solution of diene **234** (108 mg, 0.42 mmol) in Et_2O (1.5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was warmed to 18 °C and after 0.5 h at this temperature it was concentrated under reduced pressure. A magnetically stirred solution of the ensuing yellow oil in CH_2Cl_2 (7 mL) was treated with Grubbs' second generation catalyst (18 mg, 21.2 mmol) then warmed to 25 °C and maintained at this temperature for 40 h. After this time $NaHCO_3$ (3 mL of a saturated aqueous solution) was added to the reaction mixture and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a brown oil. This material was subjected to flash chromatography (silica, 90:9:1 *v/v/v* hexane / EtOAc / Et_3N) and concentration of the appropriate fractions (R_f = 0.2 in 9:1 *v/v* CH_2Cl_2 / EtOAc) afforded the *title piperidine* ***236*** (92 mg, 96%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.14 (dt, *J* = 10.2 and 3.6 Hz, 1H), 5.97 (td, *J* = 10.2 and 1.8 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 4H), 3.00 (t, *J* = 5.7 Hz, 2H), 2.84 (br s, 1H), 2.13–2.05 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 6H).

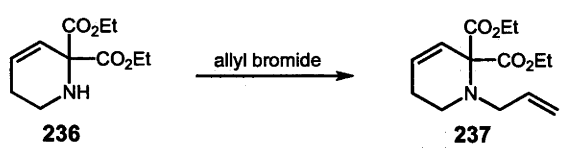
^{13}C NMR (75 MHz) δ 169.6, 129.7, 122.9, 66.4, 61.9, 39.8, 24.5, 13.9.

IR υ_{max} (NaCl) 3353, 2981, 1738, 1453, 1274, 1230, 1199, 1133, 1107, 1078, 1027 cm^{-1}.

Mass Spectrum (ESI) *m/z* 250 $[(M+Na^{\bullet})^+$, 14%], 228 $[(M+H^{\bullet})^+$, 58], 154 (100), 126 (89).

HRESIMS Found: $(M + H^{\bullet})^+$, 228.1225. $C_{11}H_{17}NO_4$ requires $(M + H^{\bullet})^+$, 228.1236.

Diethyl 1-allyl-5,6-dihydropyridine-2,2(1*H*)-dicarboxylate (237)



236 **237**

3-Bromo-1-propene (1.36 mL, 15.8 mmol) and potassium carbonate (2.28 g, 16.5 mmol) were added to a magnetically stirred solution of piperidine **236** (3.41 g, 15.0 mmol) in DMF (20 mL) maintained under nitrogen at 18 °C. The ensuing mixture was warmed to 30 °C and maintained at this temperature for 44 h then cooled and diluted with CH_2Cl_2 (40 mL)

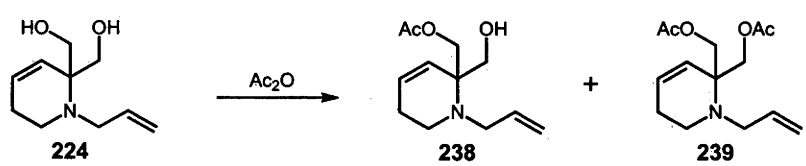
and water (10 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 9:1 *v/v* hexane/EtOAc) and thereby affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.3 in 9:1 *v/v* CH_2Cl_2/EtOAc) afforded the *title diene* **237** (3.25 g, 99% at 81% conversion) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 6.08–5.98 (m, 1H), 5.93–5.75 (m, 2H), 5.19 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.28–4.16 (m, 4H), 3.30 (d, *J* = 6.0 Hz, 2H), 2.83–2.76 (m, 2H), 2.24–2.10 (m, 2H), 1.32–1.23 (m, 6H).
^{13}C NMR (75 MHz) δ 168.8, 136.1, 128.7, 124.1, 116.1, 71.6, 61.0, 55.2, 42.6, 25.0, 13.8.
IR υ_{max} (NaCl) 2980, 2924, 1729, 1641, 1395, 1366, 1251, 1204, 1158, 1142, 1111, 1064, 1037 cm^{-1}.
Mass Spectrum (ESI) *m/z* 290 [(M+Na$^{\bullet}$)$^+$, 70%], 268 [(M+H$^{\bullet}$)$^+$, 23], 194 (100).
HRESIMS Found: (M + H$^{\bullet}$)$^+$, 268.1560. $C_{14}H_{21}NO_4$ requires (M + H$^{\bullet}$)$^+$, 268.1549.

Concentration of fraction B (R_f = 0.2 in 9:1 *v/v* CH_2Cl_2/EtOAc) afforded the starting piperdine **236** (658 mg, 19% recovery) as a clear, yellow oil.

[1-Allyl-2-(hydroxymethyl)-1,2,5,6-tetrahydropyridin-2-yl]methyl acetate (238) and (1-allyl-1,2,5,6-tetrahydropyridine-2,2-diyl)bis(methylene) diacetate (239)



224 **238** **239**

Acetic anhydride (0.46 mL, 4.91 mmol) was added to a magnetically stirred solution of diol **224** (900 mg, 4.91 mmol) in Et_2O (20 mL) maintained under nitrogen at 18 °C. After 12 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1/4:1 *v/v* hexane/EtOAc gradient elution) affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 9:1 *v/v* CH_2Cl_2/EtOAc) afforded the *title di-acetate* **239** (130 mg, 10%) as a clear, colourless oil.

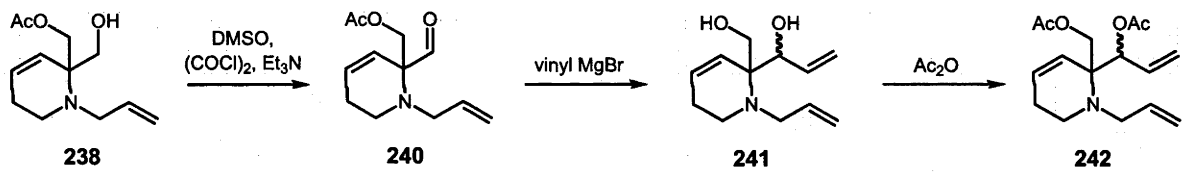
^{1}H NMR (300 MHz) δ 5.97 (dt, *J* = 9.9 and 3.9 Hz, 1H), 5.80–5.64 (m, 1H), 5.54 (dt, *J* = 10.2 and 2.1 Hz, 1H), 5.18 (dq, *J* = 17.1 and 1.5 Hz, 1H), 5.08 (dq, *J* = 9.9 and 1.5 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 2H), 4.08 (d, *J* = 11.4 Hz, 2H), 3.26 (dd, *J* = 5.7 and 1.2 Hz, 2H), 2.71 (t, *J* = 5.7 Hz, 2H), 2.10–2.00 (m, 2H), 2.05 (s, 6H).

^{13}C NMR (75 MHz) δ 170.6, 137.1, 129.0, 127.5, 116.3, 64.6, 58.7, 52.9, 43.1, 25.5, 20.9.
IR υ_{max} (NaCl) 2961, 2917, 2832, 1745, 1641, 1381, 1231, 1044, 916 cm^{-1}.
Mass Spectrum (ESI) *m/z* 268 [(M+H$^{\bullet}$)$^{+}$, 37%], 226 (6), 208 (5), 166 (7), 148 (71), 69 (100).
HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 268.1549. $C_{14}H_{21}NO_4$ requires (M + H$^{\bullet}$)$^{+}$, 268.1549.

Concentration of fraction B (R_f = 0.1 in 4:1 *v/v* hexane/EtOAc) gave the *title monoacetate* ***238*** (896 mg, 81%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.08–5.98 (m, 1H), 5.82–5.65 (m, 1H), 5.48–5.38 (m, 1H), 5.24–5.08 (m, 2H), 4.15 (d, *J* = 11.7 Hz, 1H), 4.08 (d, *J* = 11.7 Hz, 1H), 3.63–3.47 (m, 2H), 3.33 (d, *J* = 10.2 Hz, 2H), 2.99 (s, 1H), 2.94–2.82 (m, 1H), 2.68 (td, *J* = 11.1 and 3.9 Hz, 1H), 2.28–2.10 (m, 1H), 2.06 (s, 3H), 1.96 (d, *J* = 17.4 Hz, 1H).
^{13}C NMR (75 MHz) δ 170.6, 136.2, 129.6, 128.9, 117.0, 64.0, 62.3, 60.8, 51.4, 42.8, 25.4, 20.9.
IR υ_{max} (NaCl) 3444, 2918, 2833, 1742, 1641, 1381, 1236, 1043, 918 cm^{-1}.
Mass Spectrum (ESI) *m/z* 226 [(M+H$^{\bullet}$)$^{+}$, 85%], 166 (77), 148 (52), 136 (46), 70 (100).
HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 226.1432. $C_{12}H_{19}NO_3$ requires (M + H$^{\bullet}$)$^{+}$, 226.1443.

[2-(1-Acetoxyallyl)-1-allyl-1,2,5,6-tetrahydropyridin-2-yl]methyl acetate (242)



Step i: A solution of DMSO (0.24 mL, 3.33 mmol) in CH_2Cl_2 (10 mL) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (0.19 mL, 2.22 mmol) in CH_2Cl_2 (6 mL) maintained under nitrogen at -78 °C. After 0.25 h a solution of alcohol **238** (250 mg, 1.11 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 0.25 h. After 1 h a solution of Et_3N (0.62 mL, 4.44 mmol) in CH_2Cl_2 (10 mL) was added and the ensuing mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. $NaHCO_3$ (10 mL of a saturated aqueous solution) was then added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *aldehyde* ***240*** as a light-yellow oil.

Subjection of a portion of a sample of this material to flash chromatography gave a spectroscopically pure sample of aldehyde **240** as a clear, colourless oil (R_f = 0.7 in 9:1 *v/v* CH_2Cl_2/EtOAc).

^{1}H NMR (300 MHz) δ 9.20 (s, 1H), 6.24–6.16 (m, 1H), 5.82–5.68 (m, 1H), 5.32–5.23 (m, 1H),

5.22–5.08 (m, 2H), 4.45 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 3.32–3.20 (m, 1H), 3.18–3.06 (m, 1H), 2.97–2.88 (m, 1H), 2.74–2.62 (m, 1H), 2.35–2.20 (m, 1H), 2.14–2.07 (m, 1H), 2.03 (s, 3H).

^{13}C NMR (75 MHz) δ 199.9, 170.5, 136.0, 133.1, 122.3, 117.4, 68.8, 63.0, 54.3, 42.1, 26.1, 21.0.

IR υ_{max} (NaCl) 2921, 2817, 1746, 1377, 1234, 1078, 1045, 924, 711 cm^{-1}.

Mass Spectrum (ESI) *m/z* 246 [(M+Na$^{\bullet}$)$^{+}$, 20%], 224 [(M+H$^{\bullet}$)$^{+}$, 12], 178 (62), 164 (51), 109 (100).

HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 224.1285. $C_{12}H_{17}NO_3$ requires (M + H$^{\bullet}$)$^{+}$, 224.1287.

This somewhat unstable material was immediately subjected to the vinylation reaction as described in the following paragraph.

Step ii: Vinylmagnesium bromide (5.55 mL of a 1.0 M solution in THF, 5.55 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **240** (obtained as described immediately above) in THF (20 mL) maintained under nitrogen at -78 °C. After 0.5 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 2 h, then warmed to 18 °C. After 1 h the reaction mixture was cooled to 0 °C then water (4 mL) and NH_4Cl (2 mL of a saturated aqueous solution) were added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 2:1 mixture of the two diastereoisomeric forms of *diol* **241** as a light-yellow oil.

Subjection of a portion of a sample of this material to flash chromatography gave a spectroscopically pure sample of diol **241**.

^{1}H NMR (300 MHz) δ 6.30–5.65 (m, 3H), 5.50–4.90 (m, 5H), 4.26 (dd, J = 27.0 and 6.0 Hz, 1H), 3.85–3.10 (m, 4H), 3.20–2.50 (m, 2H), 2.25–1.80 (m, 4H).

^{13}C NMR (75 MHz) δ 137.6, 136.8, 136.5, 136.4, 132.3, 129.4, 127.4, 126.0, 117.5, 117.3, 116.7, 116.6, 75.2, 73.0, 64.7, 63.8, 63.4, 63.3, 51.3, 51.2, 43.8, 41.7, 25.4, 23.3.

IR υ_{max} (NaCl) 3400, 2919, 1641, 1417, 1279, 1066, 994, 918 cm^{-1}.

Mass Spectrum (ESI) *m/z* 232 [(M+Na$^{\bullet}$)$^{+}$, 6%], 210 [(M+H$^{\bullet}$)$^{+}$, 18], 192 (6), 70 (100).

HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 210.1492. $C_{12}H_{19}NO_2$ requires (M + H$^{\bullet}$)$^{+}$, 210.1494.

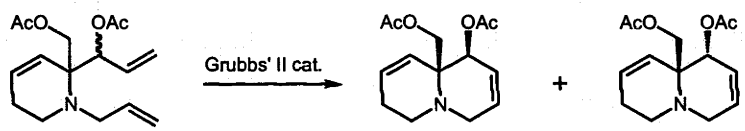
This material was immediately subjected to an acetylation reaction described in the following paragraph.

Step iii: Acetic anhydride (0.31 mL, 3.33 mmol) was added to a magnetically stirred solution of a *ca.* 2:1 mixture of the epimeric forms of diol **241** (obtained as described mmediately above) in Et_2O (10 mL) maintained under nitrogen at 18 °C. After 15 h the reaction mixture was concentrated was under reduced pressure and the ensuing yellow oil subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc). Concentration of the

appropriate fractions (R_f = 0.7 in 9:1 *v/v* CH_2Cl_2/EtOAc) afforded a *ca.* 2:1 mixture of the two diastereoisomeric forms of the *title triene* **242** (260 mg, 80% over 3 steps) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.10–5.40 (complex m, 5H), 5.30–5.00 (m, 3H), 4.40–3.95 (m, 2H), 3.67 (dm, *J* = 14.7 Hz, 1H), 3.10–2.75 (m, 2H), 2.63–2.48 (m, 1H), 2.08 (s, 3H - minor diastereoisomer), 2.06 (s, 3H - major diastereoisomer), 2.04 (s, 3H - minor diastereoisomer), 2.03 (s, 3H - major diastereoisomer), 2.10–1.80 (m, 3H).
^{13}C NMR (75 MHz) δ 170.8, 170.6, 169.9, 137.4, 136.9, 133.7, 133.0, 130.1, 130.0, 127.0, 125.7, 117.4, 117.3, 116.2, 115.9, 75.8, 72.8, 64.1 62.5, 61.8, 61.7, 52.9, 52.6, 43.3, 42.8, 25.8, 25.7, 21.2, 21.1, 21.0, 20.9 (one signal obscured or overlapping).
IR υ_{max} (NaCl) 2958, 2919, 2833, 1746, 1642, 1375, 1239, 1104, 1028, 918 cm^{-1}.
Mass Spectrum (ESI) *m/z* 316 [$(M+Na^{\bullet})^+$, 1%], 294 [$(M+H^{\bullet})^+$, 15], 234 (23), 174 (52), 104 (51), 70 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 294.1707. $C_{16}H_{23}NO_4$ requires $(M + H^{\bullet})^+$, 294.1705.

(1*R*, 9a*R*)-*rel*-(1-Acetoxy-4,6,7,9a-tetrahydro-1*H*-quinolizin-9a-yl)methyl acetate (243) and (1*S*, 9a*R*)-*rel*-(1-Acetoxy-4,6,7,9a-tetrahydro-1*H*-quinolizin-9a-yl)methyl acetate (244)



242 **243** **244**

Grubbs' second generation catalyst (87 mg, 0.10 mmol) was added to a magnetically stirred solution of a *ca.* 2:1 mixture of the epimeric forms of triene **242** (300 mg, 1.02 mmol) in CH_2Cl_2 (50 mL) kept under nitrogen at 18 °C. The ensuing mixture was maintained at this temperature for 23 h then DMSO (0.36 mL, 5.12 mmol) was added. After a further 22 h the reaction mixture was concentrated under reduced pressure and the ensuing brown residue was subjected to flash chromatography (silica, 9:1/4:1 *v/v* hexane/EtOAc gradient elution) and thereby affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.1, 9:1 *v/v* CH_2Cl_2/EtOAc) afforded the *title quinolizidine* **244** (69 mg, 25%) as a clear, light-yellow oil.

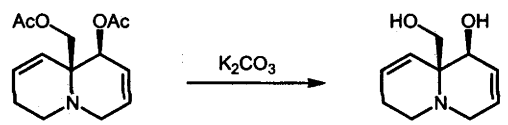
^{1}H NMR (300 MHz) δ 5.94–5.82 (m, 2H), 5.62–5.48 (m, 2H), 5.27 (br s, 1H), 4.40 (dd, *J* = 12.0 and 2.1 Hz, 1H), 4.33 (dd, *J* = 12.0 and 2.1 Hz, 1H), 3.38–3.13 (m, 3H), 2.76–2.64 (m, 1H), 2.42–2.40 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.05–1.94 (m, 1H).
^{13}C NMR (75 MHz) δ 170.3, 128.1, 127.5, 126.8, 125.2, 73.8, 61.9, 56.5, 50.0, 46.2, 25.2, 21.2 (two signals obscured or overlapping).

IR υ_{max} (NaCl) 2921, 2853, 1742, 1371, 1229, 1043 cm^{-1}.
Mass Spectrum (ESI) *m/z* 288 [$(M+Na^{\bullet})^+$, 5%], 266 [$(M+H^{\bullet})^+$, 41], 206 (24), 146 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 266.1393. $C_{14}H_{19}NO_4$ requires $(M + H^{\bullet})^+$, 266.1392.

Concentration of fraction B (R_f = 0.1 in 4:1 *v/v* CH_2Cl_2/EtOAc) afforded the *title quinolizidine* **243** (169 mg, 62%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.14–6.05 (m, 1H), 5.96–5.88 (m, 1H), 5.87–5.80 (m, 1H), 5.19 (d, *J* = 10.2, 1H), 5.10 (d, *J* = 4.5 Hz, 1H), 4.30 (d, *J* = 10.8 Hz, 1H), 4.16 (d, *J* = 10.8 Hz, 1H), 3.43–3.26 (m, 2H), 3.07–2.96 (m, 1H), 2.84–2.75 (m, 1H), 2.53–2.38 (m, 1H), 2.06 (s, 6H), 2.04–1.96 (m, 1H).
^{13}C NMR (75 MHz) δ 171.1, 170.8, 131.7, 127.5, 126.9, 122.2, 67.7, 62.7, 58.0, 49.7, 45.5, 25.0, 21.2, 21.0.
IR υ_{max} (NaCl) 2920, 2852, 1732, 1372, 1236, 1022, 974 cm^{-1}.
Mass Spectrum (ESI) *m/z* 288 [$(M+Na^{\bullet})^+$, 1%], 266 [$(M+H^{\bullet})^+$, 12], 206 (13), 146 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 266.1388. $C_{14}H_{19}NO_4$ requires $(M + H^{\bullet})^+$, 266.1392.

(1*R*, 9a*R*)-*rel*-9a-(Hydroxymethyl)-4,6,7,9a-tetrahydro-1*H*-quinolizin-1-ol (245)



243 **245**

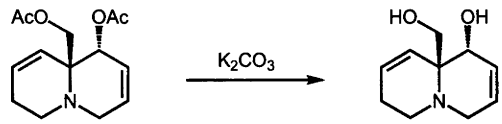
K_2CO_3 (94 mg, 0.68 mmol) was added to a magnetically stirred solution of di-acetate **243** (180 mg, 0.68 mmol) in MeOH (5 mL) maintained under nitrogen at 18 °C. After 19 h the reaction mixture was concentrated under reduced pressure then CH_2Cl_2 (5 mL) and water (1 mL) were added and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the title diol **245** (119 mg, 98%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.21–6.05 (m, 1H), 5.97–5.83 (m, 2H), 5.59 (dd, *J* = 10.2 and 0.9 Hz, 1H), 3.89 (d, *J* = 11.4 Hz, 1H), 3.42 (d, *J* = 11.4 Hz, 1H), 3.67 (br s, 1H), 3.36 (m, *J* = 16.5 Hz, 1H), 3.26–3.14 (m, 2H), 2.82–2.70 (m, 1H), 2.42–2.28 (m, 1H), 2.12–1.98 (m, 1H), 1.85 (br s, 2H).
^{13}C NMR (75 MHz) δ 130.1, 128.6, 128.1, 127.2, 66.0, 62.4, 61.5, 50.2, 46.2, 25.1.
IR υ_{max} (NaCl) 3386, 2922, 2852, 1467, 1341, 1286, 1140, 1109, 1075, 1050, 1028, 970, 730 cm^{-1}.
Mass Spectrum (ESI) *m/z* 204 [$(M+Na^{\bullet})^+$, 4%], 182 [$(M+H^{\bullet})^+$, 58], 164 (55), 146 (34), 134 (44),

112 (100).

HRESIMS Found: $(M + H^{\bullet})^+$, 182.1182. $C_{10}H_{15}NO_2$ requires $(M + H^{\bullet})^+$, 182.1181.

(1*S*, 9a*R*)-*rel*-9a-(Hydroxymethyl)-4,6,7,9a-tetrahydro-1*H*-quinolizin-1-ol (246)



244 **246**

Diol **246** was prepared in the same manner as described immediately above for congener **245** but now using di-acetate **244** as the starting material. In this manner the *title diol* ***246*** (46 mg, 97 %) was obtained as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.13–6.07 (m, 1H), 6.00–5.90 (m, 1H), 5.70–6.84 (m, 2H), 4.29 (s, 1H), 3.97 (d, J = 10.8 Hz, 1H), 3.76 (d, J = 10.8 Hz, 1H), 3.42–3.28 (m, 1H), 3.18–3.08 (m, 1H), 3.05–2.93 (m, 1H), 2.80–2.70 (m, 1H), 2.40–2.20 (m, 1H), 2.18–2.00 (m, 1H) (signals due to OH protons not observed).

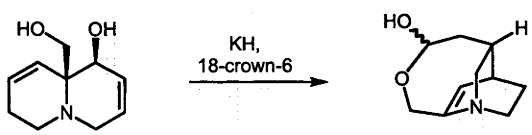
^{13}C NMR (75 MHz) δ 129.0, 128.8, 126.6, 126.0, 72.2, 60.7, 57.4, 49.9, 45.9, 25.3.

IR υ_{max} (NaCl) 3356, 2923, 2853, 1466, 1384, 1287, 1180, 1142, 1075, 1042, 990 cm^{-1}.

Mass Spectrum (ESI) *m/z* 182 [$(M+H^{\bullet})^+$, 100%], 164 (33), 146 (12), 134 (23).

HRESIMS Found: $(M + H^{\bullet})^+$, 182.1180. $C_{10}H_{15}NO_2$ requires $(M + H^{\bullet})^+$, 182.1181.

6-Oxa-1-azatricyclo[6.4.0.03,10]dodec-8-en-5-ol (248)



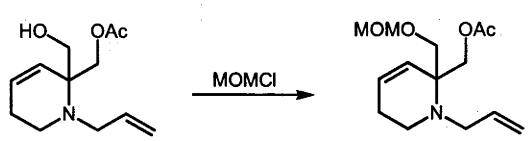
245 **248**

Iodine (28 mg, 0.11 mmol) was added to a mixture of KH (40 mg, 1.00 mmol) in THF (1.5 mL) maintained under nitrogen at 18 °C. After 0.25 h 18-crown-6 (88 mg, 0.33 mmol) and a solution of quinolizidine **245** (40 mg, 0.22 mmol) in THF (3 mL) were added and the ensuing mixture heated at reflux for 7 h then cooled and diluted with water (3 mL) and CH_2Cl_2 (10 mL). The phases were separated, the aqueous layer was further extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to semi-preparative HPLC (Waters XBridge C18 (5 μm) column, 19 mm x 150 mm, 2:3 *v/v* MeCN/H_2O containing 0.05% Et_3N). The appropriate fractions (R_t = 5.8 min) thus obtained

were concentrated under reduced pressure (to remove MeCN) and CH_2Cl_2 (5 mL) was added. The phases were separated, the aqueous layer was further extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title lactol* ***248*** (<5 mg, <13%) as a light-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07-5.91 (m, 2H), 5.63 (d, *J* = 8.1 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.27 (m, 1H), 3.59 (d, *J* = 10.2 Hz, 1H), 3.74 (dd, *J* = 9.6 and 6.9 Hz, 1H), 3.59 (d, *J* = 10.2 Hz, 1H), 3.14 (m, 1H), 2.96 (dd, *J* = 14.4 and 6.0 Hz, 1H), 2.33 (m, 1H), 2.12 (m, 1H), 1.81 (dt, *J* = 18.0 and 4.2 Hz, 1H), (signal due to OH proton not observed).
IR υ_{max} (NaCl) 2920, 2851, 1649, 1178, 1063, 1036, 938, cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 181 ($M^{+\bullet}$, 7%), 150 (23), 132 (37), 122 (100), 108 (99), 94 (77).

{1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methyl acetate (249)



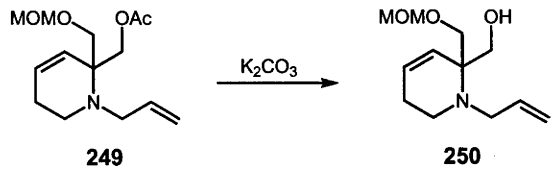
238 **249**

Chloromethyl methyl ether (0.35 mL, 4.66 mmol) was added in three equal portions over 2 h to a magnetically stirred solution of alcohol **238** (420 mg, 1.86 mmol), *N,N*-diisopropylethylamine (1.62 mL, 9.30 mmol) and DMAP (11 mg, 0.09 mmol) in CH_2Cl_2 (20 mL) maintained under nitrogen at 18 °C. After 21 h $NaHCO_3$ (5 mL of a saturated aqueous solution) was added to the reaction mixture and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 9:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.3, 9:1 *v/v* CH_2Cl_2/EtOAc) afforded the *title ether* ***249*** (418 mg, 83%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 5.94 (dt, *J* = 10.2 and 3.9 Hz, 1H), 5.82–5.68 (m, 1H), 5.58 (dt, *J* = 10.2 and 2.1 Hz, 1H), 5.18 (dq, *J* = 17.1 and 1.5 Hz, 1H), 5.07 (dq, *J* = 9.9 and 1.5 Hz, 1H), 4.59 (s, 2H), 3.68 (d, *J* = 11.4 Hz, 1H), 3.50 (d, *J* = 11.4 Hz, 1H), 3.68 (d, *J* = 9.9 Hz, 1H), 3.49 (d, *J* = 9.9 Hz, 1H), 3.38–3.20 (m, 3H), 3.34 (s, 3H), 2.93 (td, *J* = 6.0 and 1.2 Hz, 1H), 2.08–2.02 (m, 2H), 2.06 (s, 3H).
^{13}C NMR (75 MHz) δ 170.4, 137.3, 128.3, 127.9, 115.8, 96.4, 69.1, 64.6, 58.9, 55.0, 52.9, 43.0, 25.3, 20.8.
IR υ_{max} (NaCl) 2924, 2822, 1744, 1380, 1237, 1150, 1109, 1044, 918 cm^{-1}.

Mass Spectrum (ESI) *m/z* 270 [(M+H•)$^+$, 24%], 210 (62), 166 (4), 148 (80), 70 (100).
HRESIMS Found: (M + H•)$^+$, 270.1701. $C_{14}H_{23}NO_4$ requires (M + H•)$^+$, 270.1705.

{1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methanol (250)

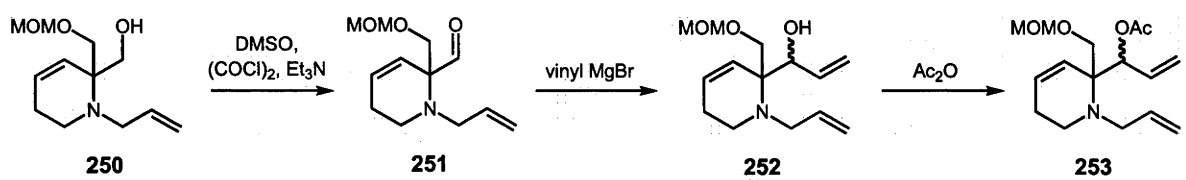


249 **250**

K_2CO_3 (254 mg, 1.84 mmol) was added to a magnetically stirred solution of acetate **249** in MeOH (15 mL) maintained under nitrogen at 18 °C. After 16.5 h the reaction mixture was concentrated under reduced pressure then CH_2Cl_2 (15 mL) and water (3 mL) were added and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title alcohol* ***250*** (410 mg, 99%) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 6.05–5.95 (m, 1H), 5.83–5.65 (m, 1H), 5.52 (dd, *J* = 9.9 and 1.5 Hz, 1H), 5.23– 5.08 (m, 2H), 4.58 (s, 2H), 3.67–3.50 (m, 3H), 3.40–3.33 (m, 2H), 3.35 (s, 3H), 3.10–3.04 (m, 1H), 2.95–2.84 (m, 2H), 2.72 (td, *J* = 10.5 and 3.9 Hz, 1H), 2.26–2.10 (m, 1H), 2.04–1.90 (m, 1H)
^{13}C NMR (75 MHz) δ 136.7, 130.0, 128.7, 116.6, 96.5, 68.2, 62.7, 61.3, 55.3, 51.5, 42.8, 25.4.
IR υ_{max} (NaCl) 3423, 2921, 1149, 1107, 1038, 917 cm^{-1}.
Mass Spectrum (ESI) *m/z* 250 [(M+Na•)$^+$, 19%], 228 [(M+H•)$^+$, 39], 196 (7), 166 (22), 148 (30), 70 (100).
HRESIMS Found: (M + H•)$^+$, 228.1592. $C_{12}H_{21}NO_3$ requires (M + H•)$^+$, 228.1600.

1-{1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}allyl acetate (253)



250 **251** **252** **253**

Step i: A solution of DMSO (1.51 mL, 21.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a magnetically stirred solution of oxalyl chloride (1.24 mL, 14.2 mmol) in CH_2Cl_2 (40 mL) maintained under nitrogen at -78 °C. After 0.25 h a solution of alcohol **250** (1.60 g, 7.10 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 0.25 h. After 1 h a solution

of Et_3N (3.95 mL, 28.4 mmol) in CH_2Cl_2 (15 mL) was added and the reaction mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. $NaHCO_3$ (20 mL of a saturated aqueous solution) was added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *aldehyde* ***251*** as a clear, colourless oil.

Subjection of a portion of a sample of this material to flash chromatography gave a spectroscopically pure sample of aldehyde **251**.

^{1}H NMR (300 MHz) δ 9.28 (s, 1H), 6.24–6.13 (m, 1H), 5.86–5.72 (m, 1H), 5.40–5.32 (m, 1H), 5.28–5.08 (m, 2H), 4.61 (s, 2H), 3.86 (d, J = 10.5 Hz, 1H), 3.80 (d, J = 10.5 Hz, 1H), 3.36 (s, 3H), 3.32–3.16 (m, 2H), 2.98–2.88 (m, 1H), 2.82–2.72 (m, 1H), 2.32–2.18 (m, 1H), 2.14–2.02 (m, 1H).
^{13}C NMR (75 MHz) δ 201.0, 136.4, 132.0, 123.3, 117.0, 96.7, 69.3, 67.3, 55.4, 54.3, 42.3, 25.9.
IR υ_{max} (NaCl) 3421, 2924, 1722, 1440, 1262, 1212, 1150, 1110, 1045, 919 cm^{-1}.
Mass Spectrum (ESI) *m/z* 248 [$(M+Na^{\bullet})^+$, 2%], 240, (100), 226 [$(M+H^{\bullet})^+$, 43], 210 (28), 194 (28), 178 (40), 164 (52), 146 (24), 109 (82).
HRESIMS Found: $(M + H^{\bullet})^+$, 226.1438. $C_{12}H_{19}NO_3$ requires $(M + H^{\bullet})^+$, 226.1443.

This somewhat unstable material was immediately subjected to the vinylation reaction as described in the following paragraph.

Step ii: Vinylmagnesium bromide (21.3 mL of a 1.0 M solution in THF, 21.3 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **251** (obtained as described immediately above) in THF (60 mL) maintained under nitrogen at -78 °C. After 0.5 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 2 h, then warmed to 18 °C. After a further 1 h the reaction mixture was cooled to 0 °C and water (12 mL) followed by NH_4Cl (8 mL of a saturated aqueous solution) were added then the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a *ca.* 3:1 mixture of the epimers of *alcohol* ***252*** as a light-yellow oil.

Subjection of a portion of a sample of this material to flash chromatography gave a spectroscopically pure sample of diol **252**.

^{1}H NMR (300 MHz) δ 6.10–5.90 (m, 1H), 5.75 (br s, 1H), 5.60 (dm, J = 10.2 Hz, 1H), 5.34 (dm, J = 17.4 Hz, 1H), 5.22–5.04 (m, 3H), 4.64 (d, J = 6.6 Hz, 1H), 4.61 (d, J = 6.6 Hz, 1H), 4.26 (s, 1H), 3.72 (s, 3H), 3.67 (s, 1H), 3.38 (s, 3H), 3.00–2.80 (m, 3H), 2.65 (m, 1H), 2.20–1.85 (m, 2H).
^{13}C NMR (75 MHz) δ 138.2, 136.9, 136.7, 136.1, 130.1, 129.2, 128.0, 126.6, 117.4, 116.7, 116.2, 115.4, 96.9, 96.8, 73.4, 71.1, 68.7, 67.8, 63.1, 55.6, 53.2, 51.7, 43.7, 43.4, 25.5, 24.9 (two signals obscured or overlapping).

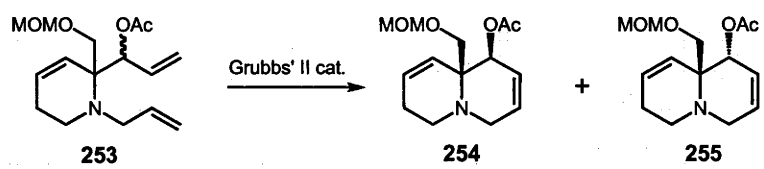
IR υ_{max} (NaCl) 3436, 2918, 1641, 1440, 1417, 1384, 1275, 1211, 1150, 1107, 1041, 916 cm^{-1}.
Mass Spectrum (ESI) *m/z* 254 [$(M+H^{\bullet})^+$, 100%], 228 (14), 210 (5).
HRESIMS Found: $(M + H^{\bullet})^+$, 254.1755. $C_{14}H_{23}NO_3$ requires $(M + H^{\bullet})^+$, 254.1756.

This material was immediately subjected to an acetylation reaction described in the following paragraph.

Step iii: Acetic anhydride (1.34 mL, 14.2 mmol) was added to a magnetically stirred solution of the abovementioned mixture of the epimeric forms of alcohol **252** (obtained as described immediately above) and DMAP (43 mg, 0.36 mmol) in Et_2O (30 mL) maintained under nitrogen at 18 °C. After 22 h the reaction mixture was concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 9:1 *v/v* hexane / EtOAc). Concentration of the appropriate fractions (R_f = 0.5, 9:1 *v/v* CH_2Cl_2 / EtOAc) afforded an indeterminable mixture of the epimers of the *title triene* **253** (1.99 g, 91% over 3 steps) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.05–5.90 (m, 2H), 5.75–5.60 (m, 2H), 5.60–5.45 (m, 1H), 5.20–5.00 (m, 3H), 4.60–4.50 (m, 2H), 3.75–3.60 (m, 2H), 3.51 (d, *J* = 10.5 Hz, 1H), 3.34 (s, 3H), 3.12–2.92 (m, 1H), 2.84–2.74 (m, 1H), 2.64–2.53 (m, 1H), 2.09 (s, 3H), 2.00–1.84 (m, 3H).
^{13}C NMR (75 MHz) δ 169.8, 137.3, 134.1, 129.2, 127.9, 126.7, 117.0, 115.7, 96.8, 95.4, 73.5, 68.7, 67.8, 62.0, 55.3, 52.8, 42.9, 25.7, 21.1 (thirteen signals obscured or overlapping).
IR υ_{max} (NaCl) 2925, 2825, 1743, 1641, 1370, 1238, 1149, 1109, 1039, 918 cm^{-1}.
Mass Spectrum (ESI) *m/z* 318 [$(M+Na^{\bullet})^+$, 5%], 296 [$(M+H^{\bullet})^+$, 29], 236 (66), 206 (14), 174 (51), 105 (63), 70 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 296.1863. $C_{16}H_{25}NO_4$ requires $(M + H^{\bullet})^+$, 296.1862.

(1*R*, 9a*R*)-*rel*-9a-[(methoxymethoxy)methyl)]-4,6,7,9a-tetrahydro-1*H*-quinolizin-1-yl acetate (254) and (1*S*, 9a*R*)-*rel*-9a-[(methoxymethoxy)methyl)]-4,6,7,9a-tetrahydro-1*H*-quinolizin-1-yl acetate (255)



253 **254** **255**

Grubbs' second generation catalyst (572 mg, 0.67 mmol) was added to a magnetically stirred solution of the epimeric forms of triene **253** (1.99 g, 6.74 mmol) in CH_2Cl_2 (335 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at reflux for 46 h then cooled and treated with DMSO (2.38 mL, 33.5 mmol) and Et_3N (4.66 mL, 33.5 mmol). After a further 23 h the reaction mixture was concentrated under reduced

pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1 / 4:1 *v/v* hexane / EtOAc) affording three major fractions, A,B, and C.

Concentration of fraction A (R_f = 0.6 in 9:1 *v/v* CH_2Cl_2 / EtOAc) afforded the starting triene **253** (847 mg, 43% recovery) as a clear, light-yellow oil.

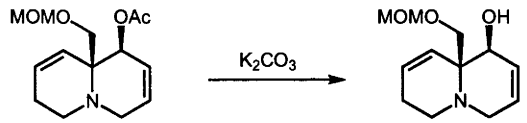
Concentration of fraction B (R_f = 0.2, 1:1 *v/v* hexane / EtOAc) afforded the *title quinolizidine* ***255*** (169 mg, 16% at 57% conversion) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 5.97–5.90 (m, 1H), 5.90–5.80 (m, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 5.50 (d, *J* = 10.2 Hz, 1H), 5.30 (s, 1H), 4.63 (d, *J* = 6.3 Hz, 1H), 4.58 (d, *J* = 6.3 Hz, 1H), 3.98 (d, *J* = 10.8 Hz, 1H), 3.62 (d, *J* = 10.8 Hz, 1H), 3.50–3.15 (m, 3H), 3.36 (s, 3H), 2.76–2.65 (m, 1H), 2.42–2.26 (m, 1H), 2.08 (s, 3H), 2.04–1.97 (m, 1H).
^{13}C NMR (75 MHz) δ 170.3, 128.3, 128.1, 127.0, 125.0, 96.7, 73.9, 66.0, 57.0, 55.3, 50.0, 46.4, 25.2, 21.2.
IR υ_{max} (NaCl) 2924, 1746, 1370, 1231, 1150, 1109, 1041 cm^{-1}.
Mass Spectrum (ESI) *m/z* 268 [$(M+H^{\bullet})^+$, 51%], 208 (12), 176 (21), 148 (51), 146 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 268.1549. $C_{14}H_{21}NO_4$ requires $(M + H^{\bullet})^+$, 268.1549.

Concentration of fraction C (R_f = 0.1 in 1:1 *v/v* hexane / EtOAc) afforded the *title quinolizidine* ***254*** (49 mg, 48% at 57% conversion) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ 6.03– 5.95 (m, 1H), 5.86–5.74 (m, 2H), 5.53 (d, *J* = 10.2 Hz, 1H), 5.30 (d, *J* = 5.1 Hz, 1H), 4.53 (d, *J* = 6.6 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 3.68 (d, *J* = 9.0 Hz, 1H), 3.54 (d, *J* = 9.0 Hz, 1H), 3.32–3.18 (m, 2H), 3.26 (s, 3H), 2.97 (td, *J* = 11.1 and 4.5 Hz, 1H), 2.76–2.66 (m, 1H), 2.46–2.30 (m, 1H), 2.06–1.91 (m, 1H), 1.99 (s, 3H).
^{13}C NMR (75 MHz) δ 170.9, 131.5, 128.2, 126.3, 122.3, 96.4, 67.8, 66.0, 58.4, 55.1, 49.6, 45.4, 24.9, 21.1.
IR υ_{max} (NaCl) 2922, 1731, 1370, 1241, 1140, 1109, 1041, 1022 cm^{-1}.
Mass Spectrum (ESI) *m/z* 290 [$(M+Na^{\bullet})^+$, 38%], 268 [$(M+H^{\bullet})^+$, 17], 236 (4), 208 (12), 148 (40), 146 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 268.1548. $C_{14}H_{21}NO_4$ requires $(M + H^{\bullet})^+$, 268.1549.

(1*R*, 9a*R*)-*rel*-9a-[(methoxymethoxy)methyl]-4,6,7,9a-tetrahydro-1*H*-quinolizin-1-ol (256)

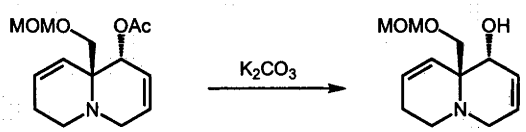


254 **256**

K_2CO_3 (54 mg, 0.39 mmol) was added to a magnetically stirred solution of quinolizidine **254** (105 mg, 0.39 mmol) in MeOH (5 mL) maintained under nitrogen at 18 °C. After 15.5 h the reaction mixture was concentrated under reduced pressure then CH_2Cl_2 (10 mL) and water (2 mL) were added to the residue and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title alcohol* ***256*** (88 mg, 99%) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 6.01–5.94 (m, 2H), 5.90–5.82 (m, 1H), 5.72 (d, *J* = 10.2 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 6.6 Hz, 1H), 3.90–3.82 (m, 1H), 3.76 (d, *J* = 9.3 Hz, 1H), 3.53 (d, *J* = 9.3 Hz, 1H), 3.32 (s, 3H), 3.28 (s, 2H), 3.09 (td, *J* = 11.1 and 4.2 Hz, 1H), 2.72–2.62 (m, 1H), 2.48–2.22 (m, 2H), 2.07–1.94 (m, 1H).
^{13}C NMR (75 MHz) δ 129.7, 128.6, 127.2, 126.5, 96.4, 66.4, 65.8, 59.5, 55.1, 50.2, 45.6, 25.1.
IR υ_{max} (NaCl) 3401, 2922, 1140, 1109, 1031, 732 cm^{-1}.
Mass Spectrum (ESI) *m/z* 248 [(M+Na$^\bullet$)$^+$, 12%], 226 [(M+H$^\bullet$)$^+$, 29], 208 (5), 176 (10), 156 (35), 148 (37), 146 (100).
HRESIMS Found: (M + H$^\bullet$)$^+$, 226.1432. $C_{12}H_{19}NO_3$ requires (M + H$^\bullet$)$^+$, 226.1443.

(1*S*, 9a*R*)-*rel*-9a-[(methoxymethoxy)methyl]-4,6,7,9a-tetrahydro-1*H*-quinolizin-1-ol (257)



255 **257**

Alcohol **257** was prepared in the same manner as described immediately above for congener **256** but now using quinolizidine **255** as the starting material. In this manner the *title alcohol* ***257*** (32 mg, 95%) was obtained as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 6.16–6.08 (m, 1H), 5.92–5.84 (m, 1H), 5.72 (s, 2H), 4.57 (s, 2H), 4.16–4.08 (m, 1H), 3.89 (d, *J* = 9.6 Hz, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.33 (s, 3H), 3.18 (d, *J* = 11.1 Hz, 2H), 3.02 (td, *J* = 11.1 and 4.2 Hz, 1H), 2.70–2.58 (m, 1H), 2.44–2.28 (m, 1H), 2.06–1.96 (m, 1H)

(signal due to OH proton not observed).

^{13}C NMR (75 MHz) δ 130.1, 128.7, 125.7, 125.4, 96.7, 73.2, 65.7, 56.7, 55.5, 50.2, 45.7, 25.3.

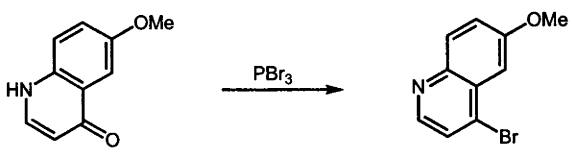
IR υ_{max} (NaCl) 3422, 3032, 2918, 2883, 1150, 1108, 1091, 1041, 761 cm^{-1}.

Mass Spectrum (ESI) *m/z* 248 [$(M+Na^{\bullet})^{+}$, 18%], 226 [$(M+H^{\bullet})^{+}$, 31], 208 (10), 176 (12), 148 (55), 146 (100).

HRESIMS Found: $(M + H^{\bullet})^{+}$, 226. 1437. $C_{12}H_{19}NO_3$ requires $(M + H^{\bullet})^{+}$, 226.1443.

7.4 Experimental Procedures for Chapter Five

4-Bromo-6-methoxyquinoline (203)



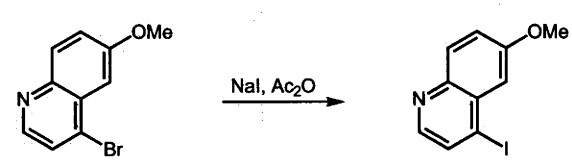
266 **203**

Bromide **203** was prepared using a protocol described by Margolis.[25] Thus, PBr_3 (1.10 mL, 1.18 mmol) was added to a magnetically stirred solution of quinolone **266** (200 mg, 1 .14 mmol) in DMF (5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was warmed to 18 °C and after 1 h at this temperature ice was added. After 0.5 h $NaHCO_3$ (5 mL of a saturated aqueous solution) and CH_2Cl_2 (15 mL) were added and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow residue was subjected to flash chromatography (silica, 4:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.3 in 1:1 *v/v* hexane/EtOAc) afforded the title bromide **203** (239 mg, 88%) as a light-yellow, crystalline solid, m.p. 86°C (lit.[26] m.p. 78-80 °C).

^{1}H NMR (300 MHz) δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.99 (m, 1H), 7.65 (d, *J* = 4.8 Hz, 1H), 7.42-7.38 (complex m, 2H), 3.98 (s, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[25,26]

4-Iodo-6-methoxyquinoline (262)



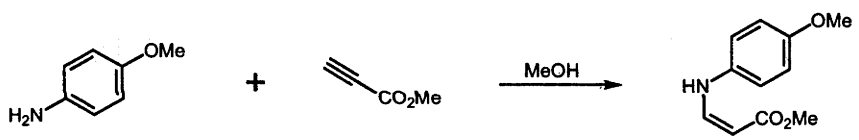
203 **262**

Acetic anhydride (300 μL, 3.15 mmol) was added to a magnetically stirred suspension of bromide **203** (300 mg, 1.26 mmol) and NaI (565 mg, 3.78 mmol) in MeCN (2 mL) maintained at 18 °C. The ensuing mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with K_2CO_3 (1.5 mL of a 10% w/v aqueous solution),

Na_2SO_3 (1.5 mL of a 5% w/v aqueous solution), $Na_2S_2O_3$ (1.5 mL of a saturated aqueous solution) and CH_2Cl_2 (10 mL). The phases were separated, the aqueous layer further extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow solid was subjected to flash chromatography (silica, 4:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.3 in 1:1 *v/v* hexane/ EtOAc) afforded the title iodide **262** (337 mg, 94%) as a colourless, crystalline solid, m.p. 126 °C (lit.[27] m.p. 85 °C).

^{1}H NMR (300 MHz) δ 8.29 (br s, 1H), 7.99-7.89 (complex m, 2H), 7.65 (dd, *J* = 9.0 and 2.7 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 1H), 3.95 (s, 3H).
^{13}C NMR (75 MHz) δ 158.9, 146.9, 143.7, 132.4, 131.4, 131.3, 122.9, 110.2, 109.2, 55.4.
IR υ_{max} (NaCl) 3344, 2953, 1617, 1555, 1498, 1452, 1423, 1350, 1264, 1232, 1159, 1028 cm^{-1}.
Mass Spectrum (EI, 70eV) *m/z* 285 ($M^{+\bullet}$, 100%).
HREIMS Found: $M^{+\bullet}$, 284.9651. $C_{10}H_8{}^{127}INO$ requires $M^{+\bullet}$, 284.9651.
Elemental Analysis Found: C, 42.45; H, 3.19; I, 44.22; N, 4.96%. $C_{10}H_8{}^{127}INO$ requires C, 42.13; H, 2.83; I, 44.51; N, 4.91%.

(Z)-Methyl 3-(4-methoxyphenylamino)acrylate (265)



263 **264** **265**

Acrylate **265** was prepared using the method detailed by Nicolaou[28] Thus, methyl propiolate (**264**) (4.45 mL, 49.9 mmol) was added to a magnetically stirred solution of *p*-anisidine (**263**) (6.15 g, 49.9 mmol) in MeOH (125 mL) maintained under nitrogen at 18°C. The ensuing mixture was warmed to 30 °C and after 15 h at this temperature it was cooled then concentrated under reduced pressure. The crude solid thus obtained was dissolved in boiling EtOAc (200 mL) and the resulting mixture filtered through silica (~5 cm deep pad contained in a sintered glass funnel). The solids thus retained were washed with EtOAc (150 mL) and the combined filtrates were concentrated under reduced pressure to afford the title acrylate **265**[28] (10.3 g, 99%) as a yellow solid, m.p. 126-128 °C.

^{1}H NMR (300 MHz) δ 9.79 (d, *J* = 12.0 Hz, 1H), 7.15 (dd, *J* = 12.0 and 8.1 Hz, 1H), 6.92-6.83 (AB system, *J* = 9.3 Hz, 4H), 4.78 (d, *J* = 8.1 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H).
^{13}C NMR (75 MHz) δ 170.8, 155.5, 144.2, 134.3, 116.9, 114.8, 85.5, 55.5, 50.5.
IR υ_{max} (NaCl) 3315, 2959, 2838, 1622, 1589, 1515, 1484, 1297,1233, 1207, 1180, 1034, 1017 828,

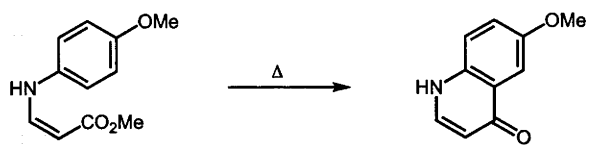
782 cm^{-1}.

Mass Spectrum (ESI) *m/z* 230 [(M+Na$^{\bullet}$)$^{+}$, 94%], 208 [(M+H$^{\bullet}$)$^{+}$, 9], 176 (100), 148 (30), 124 (36).

HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 208.0970. $C_{11}H_{13}NO_3$, requires (M + H$^{\bullet}$)$^{+}$, 208.0974.

Elemental Analysis Found: C, 63.72; H, 6.28; N, 6.79%. $C_{11}H_{13}NO_3$, requires C, 63.76; H, 6.32; N, 6.76%

6-Methoxy-1*H*-quinolin-4-one (266)



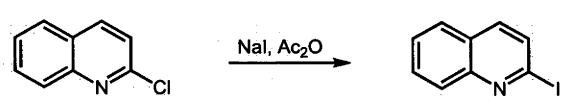
265 **266**

Quinolone **266** was prepared using a modification of a procedure described by Nicolaou.[28] Thus, acrylate **265** (4.70 g, 22.7 mmol) was added, in one portion, to a magnetically stirred solution of refluxing diphenyl ether (275 mL). After 0.5 h the reaction mixture was cooled to 18 °C then poured into hexane (300 mL). The ensuing precipitate was removed by filtration and washed with Et_2O (500 mL) to afford the title quinolone **266** (3.70 g, 93%) as a tan-coloured solid, m.p. 234-237 °C (lit.[28] m.p 237-238 °C).

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.57 (m, 1H), 7.48 (m, 1H), 7.33 (m, 1H), 6.16 (d, *J* = 7.2 Hz, 1H), 3.82, (s, 3H), 3.53 (br s, 1H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[28]

2-Iodoquinoline (268)



267 **268**

The previously reported iodide **268**[29] was prepared in the same manner as described above for compound **262** but now using chloride **267** as the starting material. In this manner the title iodide **268** (165 mg, 85%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 50 °C (after recrystallisation from hexane) (lit.[29] m.p. = 53–54 °C) (R_f = 0.2 in 19:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.05 (dm, *J* = 8.4 Hz, 1H), 7.81–7.69 (complex m, 4H), 7.57 (m, 1H).

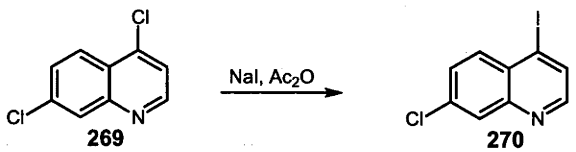
^{13}C NMR (75 MHz) δ 149.5, 137.1, 131.9, 130.3, 128.8, 127.8, 127.1, 119.0 (one signal obscured or overlapping).

IR υ_{max} 1617, 1579, 1560, 1548, 1488, 1447, 1416, 1329, 1284, 1146, 1118, 1075, 936, 822, 780 cm^{-1}.

Mass Spectrum (ESI) *m/z* 256 [(M+H$^{\bullet}$)$^{+}$, 100%], 129 (10), 102 (63).

HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 255.9623. $C_9H_6{}^{127}IN$ requires (M + H$^{\bullet}$)$^{+}$, 255.9623.

7-Chloro-4-iodoquinoline (270)



The previously reported iodide **270**[30] was prepared in the same manner as described above for compound **262** but now using chloride **269** as the starting material. In this manner the title iodide **270** (340 mg, 93%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 124 °C (lit.[30] m.p. = 120–122 °C) (R_f = 0.3 in 4:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.44 (d, *J* = 3.9 Hz, 1H), 8.06 (m, 1H), 7.99–7.94 (complex m, 2H), 7.56 (dm, *J* = 9.0 Hz, 1H).

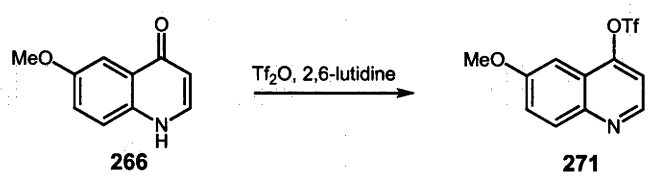
^{13}C NMR (75 MHz) δ 150.7, 148.1, 136.4, 133.1, 132.7, 129.1, 128.8, 111.5 (one signal obscured or overlapping).

IR υ_{max} 1605, 1549, 1482, 1439, 1360, 1335, 1288, 1076, 956, 873, 829, 809, 799 cm^{-1}.

Mass Spectrum (ESI) *m/z* 292 and 290 [(M+H$^{\bullet}$)$^{+}$, 29 and 100%], 165 (11), 163 (4), 102 (85).

HRESIMS Found: (M + H$^{\bullet}$)$^{+}$, 289.9235. $C_9H_5{}^{35}Cl{}^{127}IN$ requires (M + H$^{\bullet}$)$^{+}$, 289.9234.

6-Methoxyquinolin-4-yl trifluoromethanesulfonate (271)

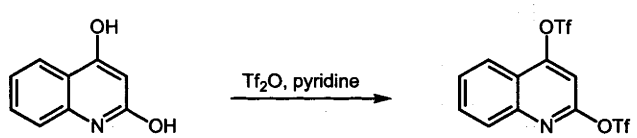


Trifluoromethanesulfonic anhydride (250 μL, 1.51 mmol) was added to a magnetically stirred suspension of quinolone **266** (200 mg, 1.26 mmol), 2,6-lutidine (210 μL, 1.76 mmol) and DMAP (31 mg, 0.15 mmol) in CH_2Cl_2 (17 mL) maintained at 0 °C. After 2 h the reaction mixture was warmed to 18 °C, maintained at this temperature for a further 2 h and then treated with water (5 mL) and the phases separated. The aqueous layer was extracted with

CH_2Cl_2 (3 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 19:1 *v/v* CH_2Cl_2/Et_2O) and concentration of the appropriate fractions (R_f = 0.5) afforded the title triflate **271**[31] (150 mg, 43%) as a light-yellow oil.

^{1}H NMR (300 MHz) δ 8.80 (d, *J* = 5.1 Hz, 1H), 8.07 (d, *J* = 9.3 Hz, 1H), 7.46 (dd, *J* = 9.3 and 3.0 Hz, 1H), 7.37 (d, *J* = 5.1 Hz, 1H), 7.25 (d, *J* = 3.0 Hz, 1H), 3.96 (s, 3H).
^{13}C NMR (75 MHz) δ 159.1, 151.7, 147.6, 146.7, 131.2, 124.1, 122.3, 118.6 (q, *J* = 319 Hz), 112.2, 97.7, 55.5.
IR υ_{max} 1627, 1605, 1500, 1477, 1429, 1363, 1252, 1234, 1215, 1176, 1140, 1069, 1018, 921, 827, 838, 807 cm^{-1}.
Mass Spectrum (ESI) *m/z* 308 $[(M+H^{\bullet})^+$, 15%], 198 (66), 176 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 308.0203. $C_{11}H_8F_3NO_4S$ requires $(M + H^{\bullet})^+$, 308.0204.

Quinoline-2,4-diyl bis(trifluoromethanesulfonate) (272)



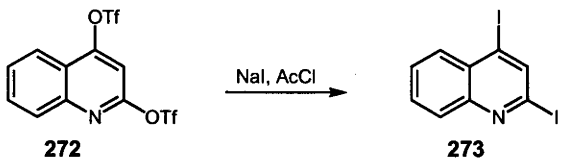
272

Trifluoromethanesulfonic anhydride (1.26 mL, 7.50 mmol) was added to a magnetically stirred solution of quinoline-2,4-diol (483 mg, 3.00 mmol) in pyridine (6 mL) maintained at 0 °C. After 0.5 h the reaction mixture was warmed to 18 °C, maintained at this temperature for a further 15 h and then treated with water (3 mL) and CH_2Cl_2 (20 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 9:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.5) under reduced pressure afforded the *title triflate* **272** (160 mg, 13%) as a colourless, crystalline solid, m.p. = 51 °C.

^{1}H NMR (300 MHz) δ 8.12 (t, *J* = 8.4 Hz, 2H), 7.94 (dt, *J* = 8.4 and 1.2 Hz, 1H), 7.79 (dt, *J* = 8.4 and 1.2 Hz, 1H), 7.29 (s, 1H).
^{13}C NMR (75 MHz) δ 155.3, 152.9, 146.9, 133.0, 129.4, 129.2, 121.0, 120.7, 118.6 (q, *J* = 319 Hz), 104.9 (one signal obscured or overlapping).
IR υ_{max} 1624, 1606, 1578, 1508, 1431, 1318, 1247, 1225, 1136, 1044, 1022, 974, 900, 834, 803, 765 cm^{-1}.
Mass Spectrum (ESI) *m/z* 426 $[(M+H^{\bullet})^+$, 25%], 74 (100).

HRESIMS Found: $(M + H^{\bullet})^+$, 425.9528. $C_{11}H_5F_6NO_6S_2$ requires $(M + H^{\bullet})^+$, 425.9541.

2,4-Diiodoquinoline (273)

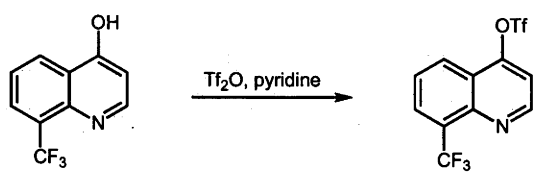


272 **273**

Acetyl chloride (48 μL, 0.67 mmol) was added to a magnetically stirred suspension of triflate **272** (190 mg, 0.45 mmol) and NaI (674 mg, 4.50 mmol) in MeCN (1 mL) maintained at 18 °C. The ensuing reaction mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with K_2CO_3 (1.5 mL of a 10% w/v aqueous solution), Na_2SO_3 (1.5 mL of a 5% w/v aqueous solution), $Na_2S_2O_3$ (1.5 mL of a saturated aqueous solution) and CH_2Cl_2 (10 mL). The phases were separated, the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.7) afforded the *title iodide* **273** (165 mg, 97%) as a colourless, crystalline solid, m.p. = 90 °C.

^{1}H NMR (300 MHz) δ 8.32 (s, 1H), 7.96 (m, 2H), 7.72 (tm, *J* = 6.9 Hz, 1H), 7.61 (tm, *J* = 6.9 Hz, 1H).
^{13}C NMR (75 MHz) δ 148.8, 141.5, 131.8, 131.1, 129.4, 129.3, 128.5, 117.8, 112.3.
IR υ_{max} 1547, 1535, 1477, 1379, 1236, 1138, 1083, 948, 842, 827, 794, 752 cm^{-1}.
Mass Spectrum (ESI) *m/z* 382 [$(M+H^{\bullet})^+$, 35%], 71 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 381.8590. $C_9H_5N^{127}I_2$ requires $(M + H^{\bullet})^+$, 381.8590.

8-(Trifluoromethyl)quinolin-4-yl trifluoromethanesulfonate (274)



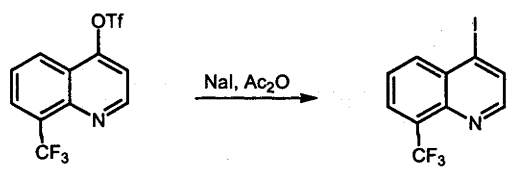
274

Trifluoromethanesulfonic anhydride (630 μL, 3.75 mmol) was added to a magnetically stirred solution of 8-(trifluoromethyl)quinolin-4-ol (400 mg, 1.88 mmol) in pyridine (5 mL) maintained at 0 °C. After 0.5 h the reaction mixture was warmed to 18 °C, maintained at this temperature for a further 22 h and then treated with water (3 mL) and CH_2Cl_2 (20 mL) and

the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 9:1 *v/v* hexane / EtOAc) and concentration of the appropriate fractions (R_f = 0.7) under reduced pressure afforded the *title triflate* **274** (560 mg, 86%) as a colourless, crystalline solid, m.p. = 64–65 °C.

^{1}H NMR (300 MHz) δ 9.14 (d, *J* = 4.8 Hz, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 7.78 (br t, *J* = *ca.* 7.8 Hz, 1H), 7.54 (d, *J* = 4.8 Hz, 1H).
^{13}C NMR (75 MHz) δ 152.7, 151.6, 146.6, 129.5 (q, *J* = 6 Hz), 128.3 (q, *J* = 30 Hz), 127.1, 125.0, 123.6 (q, *J* = 264 Hz), 121.7, 118.6 (q, *J* = 319 Hz), 112.2.
IR υ_{max} 1625, 1608, 1578, 1496, 1416, 1319, 1297, 1254, 1212, 1132, 903, 863, 824, 812, 770, 761 cm^{-1}.
Mass Spectrum (ESI) *m/z* 346 [$(M+H^{\bullet})^+$, 100%], 214 (50), 194 (26).
HRESIMS Found: $(M + H^{\bullet})^+$, 345.9968. $C_{11}H_5F_6NO_3S$ requires $(M + H^{\bullet})^+$, 345.9973.

4-Iodo-8-(trifluoromethyl)quinoline (275)

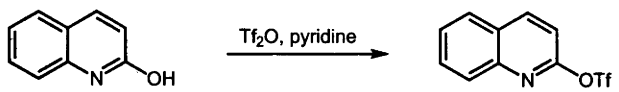


274 **275**

Iodide **275** was prepared in the same manner as described above for compound **262** but now using triflate **274** as the starting material. In this manner the *title iodide* **275** (198 mg, 97%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 110 °C (R_f = 0.6 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.59 (d, *J* = 4.8 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.09–8.14 (complex m, 2H), 7.66 (t, *J* = 8.4 Hz, 1H).
^{13}C NMR (75 MHz) δ 150.2, 144.3, 136.2, 133.4, 130.4, 128.8 (q, *J* = 6 Hz), 128.0 (q, *J* = 30 Hz), 126.5, 123.5 (q, *J* = 272 Hz), 111.7.
IR υ_{max} 1568, 1486, 1307, 1286, 1214, 1187, 1123, 1080, 836 cm^{-1}.
Mass Spectrum (ESI) *m/z* 346 [$(M+Na^{\bullet})^+$, 4%], 324 [$(M+H^{\bullet})^+$, 59], 304 (48), 129 (37), 99 (59), 71 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 323.9495. $C_{10}H_5NF_3{}^{127}I$ requires $(M + H^{\bullet})^+$, 323.9497.

Quinolin-2-yl trifluoromethanesulfonate (276)

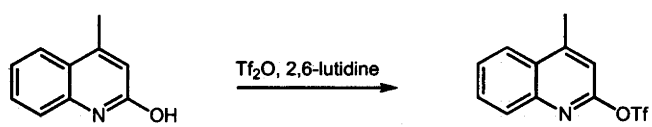


276

The previously reported triflate **276**[32] was prepared in the same manner as described above for compound **274** but now using quinolin-2-ol as the starting material. In this manner the title triflate **276** (660 mg, 86%) was isolated by flash chromatography, as a clear, colourless oil (R_f = 0.5 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.35 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.81 (dm, *J* = 8.4 Hz, 1H), 7.64 (dm, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H).
^{13}C NMR (75 MHz) δ 153.5, 145.6, 141.8, 131.0, 128.5, 127.6, 127.5, 118.7 (q, *J* = 319 Hz), 112.8 (one signal obscured or overlapping).
IR υ_{max} 1620, 1598, 1582, 1507, 1423, 1214, 1162, 1136, 1106, 961, 913, 845 cm^{-1}.
Mass Spectrum (ESI) *m/z* 300 [(M+Na$^{\bullet}$)$^+$, 11%], 278, [(M+H$^{\bullet}$)$^+$, 5], 145 (100), 128 (37).
HRESIMS Found: (M + H$^{\bullet}$)$^+$, 278.0099. $C_{10}H_6F_3NO_3S$ requires (M + H$^{\bullet}$)$^+$, 278.0099.

4-Methylquinolin-2-yl trifluoromethanesulfonate (277)

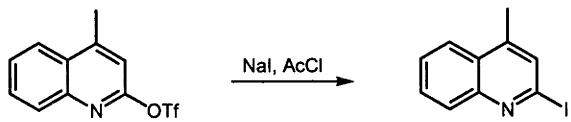


277

The previously reported triflate **277**[33] was prepared in the same manner as described above for compound **274** but now using 4-methylquinolin-2-ol as the starting material. In this manner the title triflate **277** (715 mg, 78%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 72 °C (R_f = 0.7 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.03 (m, 2H), 7.79 (dm, *J* = 8.4 Hz, 1H), 7.65 (dm, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 2.78 (s, 3H).
^{13}C NMR (75 MHz) δ 153.5, 151.4, 145.4, 130.7, 129.1, 127.5, 127.3, 123.7, 118.6 (q, *J* = 319 Hz), 112.9, 18.6.
IR υ_{max} 1591, 1518, 1451, 1443, 1410, 1387, 1326, 1217, 1142, 977, 838, 763 cm^{-1}.
Mass Spectrum (ESI) *m/z* 292 [(M+H$^{\bullet}$)$^+$, 5%], 73 (100).
HRESIMS Found: (M + H$^{\bullet}$)$^+$, 292.0258. $C_{11}H_8F_3NO_3S$ requires (M + H$^{\bullet}$)$^+$, 292.0255.

2-Iodo-4-methylquinoline (278)

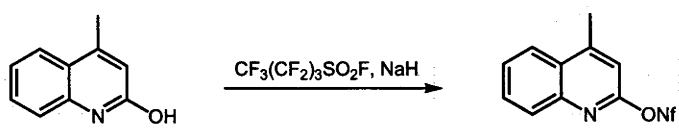


277 **278**

Acetyl chloride (67 μL, 0.95 mmol) was added to a magnetically stirred suspension of triflate **277** (183 mg, 0.63 mmol) and NaI (944 mg, 12.6 mmol) in MeCN (1 mL) maintained at 18 °C. The ensuing reaction mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with K_2CO_3 (1.5 mL of a 10% w/v aqueous solution), Na_2SO_3 (1.5 mL of a 5% w/v aqueous solution), $Na_2S_2O_3$ (1.5 mL of a saturated aqueous solution) and CH_2Cl_2 (10 mL). The phases were separated, the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.6) afforded the title iodide **278** (159 mg, 94%) as a colourless, crystalline solid, m.p. = 88 °C (lit.[34] m.p. = 87–89 °C).

^{1}H NMR (300 MHz) δ 8.02 (dm, *J* = 7.8 Hz, 1H), 7.93 (dm, *J* = 7.8 Hz, 1H), 7.68 (m, 1H), 7.59 (s, 1H), 7.56 (m, 1H), 2.61 (s, 3H).
^{13}C NMR (75 MHz) δ 148.8, 145.6, 131.9, 129.7, 129.0, 127.0, 126.6, 123.9, 119.4, 17.9.
IR υ_{max} 1579, 1544, 1504, 1443, 1409, 1278, 1143, 1092, 877, 831, 755, 750 cm^{-1}.
Mass Spectrum (ESI) *m/z* 270 [$(M+H^{\bullet})^+$, 100%], 142 (15), 71 (38).
HRESIMS Found: $(M + H^{\bullet})^+$, 269.9779. $C_{10}H_8N^{127}I$ requires $(M + H^{\bullet})^+$, 269.9780.

4-Methylquinolin-2-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (279)



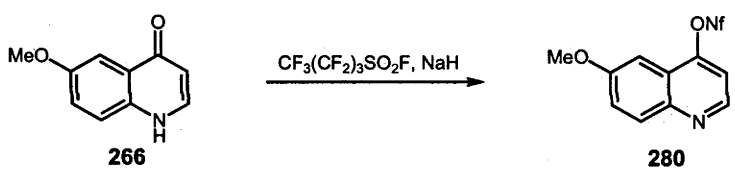
279

NaH (250 mg of a 60% dispersion in mineral oil, 6.28 mmol) was added to a magnetically stirred solution of 4-methylquinolin-2-ol (3.14 mmol) in DMF (10 mL) maintained at 0 °C. The ensuing reaction mixture was warmed to 18 °C and after 0.25 h perfluoro-1-butane-sulfonyl fluoride (1.11 mL, 6.28 mmol) was added dropwise. After 15 h brine (5 mL of a saturated solution) and CH_2Cl_2 (20 mL) were added. The phases were

separated, the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 19:1 *v/v* hexane/EtOAc) and concentration of the appropriate fractions (R_f = 0.5) under reduced pressure afforded the title nonaflate **279** (385 mg, 28%) as a colourless, crystalline solid, m.p. = 59 °C (lit.[35] m.p. = 61–62 °C) (R_f = 0.5 in 19:1 *v/v* hexane/EtOAc).

^{1}H NMR (300 MHz) δ 8.01 (t, *J* = 8.4 Hz, 2H), 7.77 (dm, *J* = 6.6 Hz, 1H), 7.62 (dm, *J* = 6.6 Hz, 1H), 7.06 (s, 1H), 2.75 (s, 3H).
^{13}C NMR (75 MHz) δ 153.7, 151.3, 145.7, 130.8, 129.5, 127.8, 127.5, 123.9, 113.1, 19.0 (signals due to carbons of nonaflate group not observed).
IR υ_{max} 1618, 1589, 1515, 1422, 1405, 1353, 1318, 1241, 1202, 1145, 1116, 1033, 1010, 959, 909 cm^{-1}.
Mass Spectrum (ESI) *m/z* 464 [(M+Na$^{\bullet}$)$^+$, 71%], 442 [(M+H$^{\bullet}$)$^+$, 13], 413 (15), 160 (13), 142 (100).
HRESIMS Found: (M + Na$^{\bullet}$)$^+$, 463.9974. $C_{14}H_8F_9NO_3S$ requires (M + Na$^{\bullet}$)$^+$, 463.9979.

6-Methoxyquinolin-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (280)

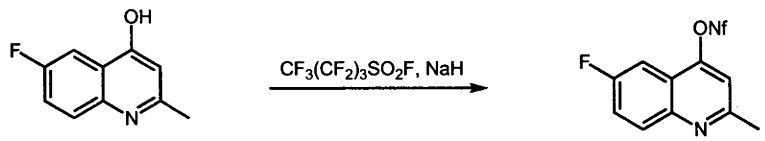


266 **280**

Nonaflate **280** was prepared in the same manner as described immediately above for compound **279** but now using quinolone **266** as the starting material. In this manner the *title nonaflate **280*** (190 mg, 33%) was isolated by flash chromatography, as a clear, colourless oil (R_f = 0.2 in 9:1 *v/v* EtOAc).

^{1}H NMR (300 MHz) δ 8.81 (dm, *J* = 5.1 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 7.47 (dm, *J* = 9.3 Hz, 1H), 7.40 (d, *J* = 5.1 Hz, 1H), 7.27 (m, 1H), 3.97 (s, 3H).
^{13}C NMR (75 MHz) δ 159.2, 152.0, 147.6, 146.8, 131.3, 124.2, 122.3, 112.1, 97.8, 55.5 (signals due to carbons of nonaflate group not observed).
IR υ_{max} 3013, 2964, 2939, 1628, 1605, 1500, 1477, 1430, 1353, 1236, 1206, 1145, 1070, 1032, 1018, 921, 899, 874, 839 cm^{-1}.
Mass Spectrum (ESI) *m/z* 458 [(M+H$^{\bullet}$)$^+$, 71%], 175 (100).
HRESIMS Found: (M + H$^{\bullet}$)$^+$, 458.0103. $C_{14}H_8F_9NO_4S$ requires (M + H$^{\bullet}$)$^+$, 458.0109.

6-Fluoro-2-methylquinolin-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (281)



281

Nonaflate **281** was prepared in the same manner as described immediately above for compound **279** but now using 6-fluoro-2-methylquinolin-4-ol as the starting material. In this manner the *title nonaflate 281* (131 mg, 17%) was isolated by flash chromatography, as a clear, colourless oil (R_f = 0.6 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.10 (dd, *J* = 9.0 and 5.1 Hz, 1H), 7.58 (m, 2H), 7.34 (s, 1H), 2.80 (s, 3H).

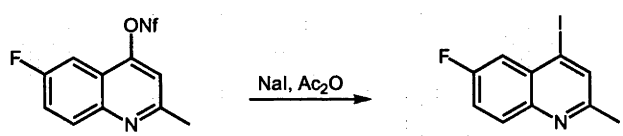
^{13}C NMR (75 MHz) δ 162.6, 159.2, 152.5, 147.0, 131.7 (d, *J* = 9 Hz), 121.3 (d, *J* = 27 Hz), 120.3 (d, *J* = 9 Hz), 113.1, 104.6 (d, *J* = 25 Hz), 25.4 (signals due to carbons of nonaflate group not observed).

IR υ_{max} 2919, 1617, 1561, 1500, 1479, 1430, 1384, 1237, 1201, 1144, 1038, 970, 931 cm^{-1}.

Mass Spectrum (ESI) *m/z* 460 $[(M+H^{\bullet})^+$, 18%], 200 (53), 178 (100).

HRESIMS Found: $(M + H^{\bullet})^+$, 460.0062. $C_{14}H_7F_{10}NO_3S$ requires $(M + H^{\bullet})^+$, 460.0065.

6-Fluoro-4-iodo-2-methylquinoline (282)



281 **282**

Iodide **282** was prepared in the same manner as described above for compound **262** but now using nonaflate **281** as the starting material. In this manner the *title iodide 282* (80 mg, 95%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 132–134 °C (R_f = 0.5 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 7.95 (dd, *J* = 9.3 and 5.4 Hz, 1H), 7.91 (s, 1H), 7.65 (dd, *J* = 9.3 and 2.7 Hz, 1H), 7.66 (m, 1H), 2.67 (s, 3H).

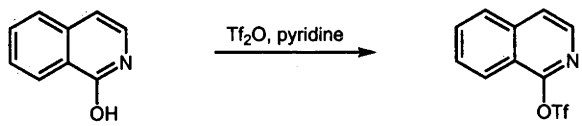
^{13}C NMR (75 MHz) δ 162.6, 159.3, 157.9 (d, *J* = 3 Hz), 144.3, 133.9, 131.8 (d, *J* = 9 Hz), 120.3 (d, *J* = 25 Hz), 115.0 (d, *J* = 24 Hz), 110.4 (d, *J* = 6 Hz), 24.3.

IR υ_{max} 1583, 1493, 1384, 1145, 1111, 1047, 878, 848, 823, 800 cm^{-1}.

Mass Spectrum (ESI) *m/z* 288 $[(M+H^{\bullet})^+$, 100%], 71 (80).

HRESIMS Found: $(M + H^{\bullet})^+$, 287.9687. $C_{10}H_7NF^{127}I$ requires $(M + H^{\bullet})^+$, 287.9686.

Isoquinolin-1-yl trifluoromethanesulfonate (287)

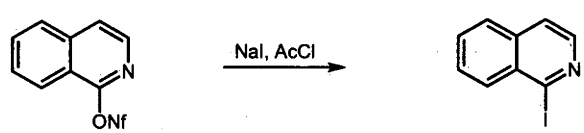


287

The previously reported triflate **287**[36] was prepared in the same manner as described above for compound **274** but now using isoquinolin-1-ol as the starting material. In this manner the title triflate **287** (510 mg, 89%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 42–43 °C (lit.[36] m.p. = 41–43 °C) (R_f = 0.5 in 19:1 *v/v* hexane/EtOAc).

^{1}H NMR (300 MHz) δ 8.19 (d, *J* = 6.0 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.81 (br t, *J* = 6.9 Hz, 1H), 7.68–7.75 (complex m, 2H).
^{13}C NMR (75 MHz) δ 152.7, 139.2, 139.1, 131.8, 129.0, 126.7, 122.4, 121.9, 119.6, 118.6 (q, *J* = 318 Hz).
IR υ_{max} 1635, 1593, 1571, 1496, 1419, 1343, 1212, 1134, 1033, 1013, 898, 824 cm^{-1}.
Mass Spectrum (ESI) *m/z* 300 [$(M+Na^{\bullet})^+$, 6%], 278 [$(M+H^{\bullet})^+$, 4], 146 (25), 145 (100), 128 (45).
HRESIMS Found: $(M + Na^{\bullet})^+$, 299.9906. $C_{10}H_6F_3NO_3S$ requires $(M + Na^{\bullet})^+$, 299.9918.

1-Iodoisoquinoline (288)



289 **288**

The previously reported iodide **288**[29] was prepared in the same manner as described above for compound **278** but now using nonaflate **289** as the starting material. In this manner the title iodide **288** (88 mg, 93%) was isolated by flash chromatography, as a light-yellow, crystalline solid, m.p. = 72–74 °C (lit.[29] m.p. = 75.5–76.5 °C) (R_f = 0.1 in 250:12:1 *v/v/v* hexane/EtOAc /Et_3N).

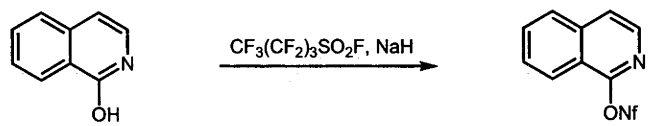
^{1}H NMR (300 MHz) δ 8.21 (d, *J* = 5.7, 1H), 8.04 (m, 1H), 7.68–7.60 (complex m, 3H), 7.53 (dm, *J* = 5.7, 1H).
^{13}C NMR (75 MHz) δ 142.9, 136.0, 132.7, 131.8, 131.0, 128.9, 127.4, 127.2, 121.2.

IR υ_{max} 3051, 1619, 1578, 1543, 1491, 1445, 1368, 1311, 1303, 1251, 1218, 1179, 1139, 955, 867, 823, 788, 745 cm^{-1}.

Mass Spectrum (ESI) *m/z* 256 [$(M+H^{\bullet})^+$, 100%], 128 (11).

HRESIMS Found: $(M + H^{\bullet})^+$, 255.9628. $C_9H_7{}^{127}IN$ requires $(M + H^{\bullet})^+$, 255.9623.

Isoquinolin-1-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (289)



289

Nonaflate **289** was prepared in the same manner as described immediately above for compound **279** but now using isoquinolin-1-ol as the starting material. In this manner the *title nonaflate* ***289*** (200 mg, 23%) was isolated by flash chromatography, as a colourless, crystalline solid, m.p. = 87–90 °C (R_f = 0.6 in 19:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.39 (dm, *J* = 8.1 Hz, 1H), 7.77 (tm, *J* = 8.1 Hz, 1H), 7.45–7.61 (complex m, 3H), 6.60 (d, *J* = 8.1 Hz, 1H).

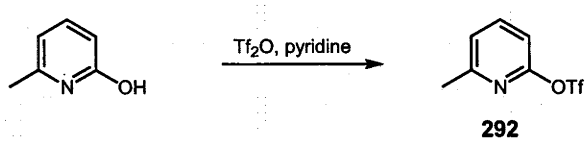
^{13}C NMR (75 MHz) δ 160.5, 135.8, 135.2, 129.0, 128.9, 126.8, 125.7, 125.1, 109.7 (signals due to carbons of nonaflate group not observed).

IR υ_{max} 1706, 1697, 1639, 1423, 1401, 1352, 1246, 1194, 1145, 1051, 1028 cm^{-1}.

Mass Spectrum (ESI) *m/z* 427 [$(M + H^{\bullet})^+$, 60%], 363 (12), 144 (89), 128 (55), 116 (100).

HRESIMS Found: $(M + H^{\bullet})^+$, 426.9928. $C_{13}H_6F_9NO_3S$ requires $(M + H^{\bullet})^+$, 426.9925.

6-Methylpyridin-2-yl trifluoromethanesulfonate (292)



292

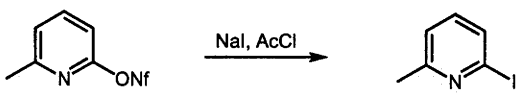
The previously reported triflate **292**[37] was prepared in the same manner as described above for compound **274** but now using 6-methylpyridin-2-ol as the starting material. In this manner the title triflate **292** (571 mg, 79%) was isolated by flash chromatography, as a clear, colourless oil (R_f = 0.2 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 7.75 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 2.54 (s, 3H).

^{13}C NMR (75 MHz) δ 159.0, 155.1, 140.9, 123.7, 118.6 (q, *J* = 318 Hz), 111.6, 23.6.

IR υ_{max} 1610, 1567, 1458, 1423, 1212, 1180, 1138, 1087, 1006, 989, 933, 844 cm^{-1}.
Mass Spectrum (ESI) *m/z* 242 [$(M+H^{\bullet})^+$, 11%], 109 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 242.0098. $C_7H_6F_3NO_3S$ requires $(M + H^{\bullet})^+$, 242.0099.

2-Iodo-6-methylpyridine (293)

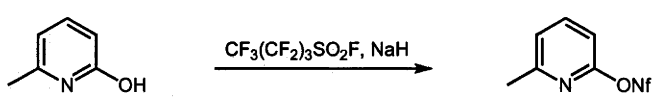


294 **293**

The previously reported iodide **293**[38] was prepared in the same manner as described above for compound **278** but now using nonaflate **294** as the starting material. In this manner the title iodide **293** (205 mg, 74%) was isolated by flash chromatography, as a light-yellow oil (R_f = 0.3 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 7.48 (dm, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.97 (dm, *J* = 7.8 Hz, 1H), 2.47 (s, 3H).
^{13}C NMR (75 MHz) δ 160.5, 137.7, 131.9, 122.5, 117.4, 24.3.
IR υ_{max} 3056, 2922, 1577, 1549, 1433, 1389, 1161, 1115, 1081, 991, 971, 827 cm^{-1}.
Mass Spectrum (ESI) *m/z* 220 [$(M+H^{\bullet})^+$, 13%], 149 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 219.9624. $C_6H_6N^{127}I$ requires $(M + H^{\bullet})^+$, 219.9623.

6-Methylpyridin-2-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (294)



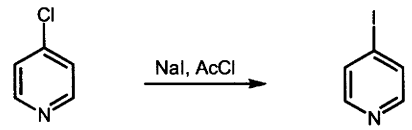
294

Nonaflate **294** was prepared in the same manner as described immediately above for compound **279** but now using 6-methylpyridin-2-ol as the starting material. In this manner the *title nonaflate* ***294*** (970 mg, 83%) was isolated by flash chromatography, as a clear, light-yellow oil (R_f = 0.3 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 7.75 (t, *J* = 7.8 Hz, 1H), 7.22 (dm, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 2.54 (s, 3H).
^{13}C NMR (75 MHz) δ 159.1, 155.2, 140.9, 123.7, 111.7, 23.8 (signals due to carbons of nonaflate group not observed).
IR υ_{max} 1610, 1567, 1458, 1425, 1353, 1239, 1205, 1177, 1144, 1033, 1008, 933, 851, 794 cm^{-1}.

Mass Spectrum (ESI) *m/z* 414 [(M+Na•)$^+$, 45%], 392 [(M+H•)$^+$, 33], 109 (100).
HRESIMS Found: (M + H•)$^+$, 391.9999. $C_{10}H_6F_9NO_3S$ requires (M + H•)$^+$, 392.0003.

4-Iodopyridine (296)

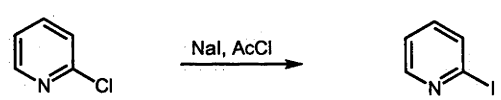


295 **296**

The previously reported iodide **296**[39] was prepared in the same manner as described above for compound **278** but now using triflate **295** as the starting material. In this manner the title iodide **296** (235 mg, 91%) was isolated by flash chromatography, as a light-yellow, crystalline solid, m.p. = 98–100 °C (lit.[14] m.p. = 100 °C) (R_f = 0.1 in 9:1 *v/v* hexane / EtOAc).

^{1}H NMR (300 MHz) δ 8.21 (d, *J* = 4.2, 2H), 7.62 (d, *J* = 4.2 Hz, 2H).
^{13}C NMR (75 MHz) δ 150.0, 132.9, 105.3.
IR υ_{max} 1560, 1542, 1471, 1399, 1209, 1057 cm^{-1}.
Mass Spectrum (ESI) *m/z* 206 [(M+H•)$^+$, 38%], 102 (100).
HRESIMS Found: (M + H•)$^+$, 205.9467. $C_5H_5{}^{127}IN$ requires (M + H•)$^+$, 205.9467.

2-Iodopyridine (298)



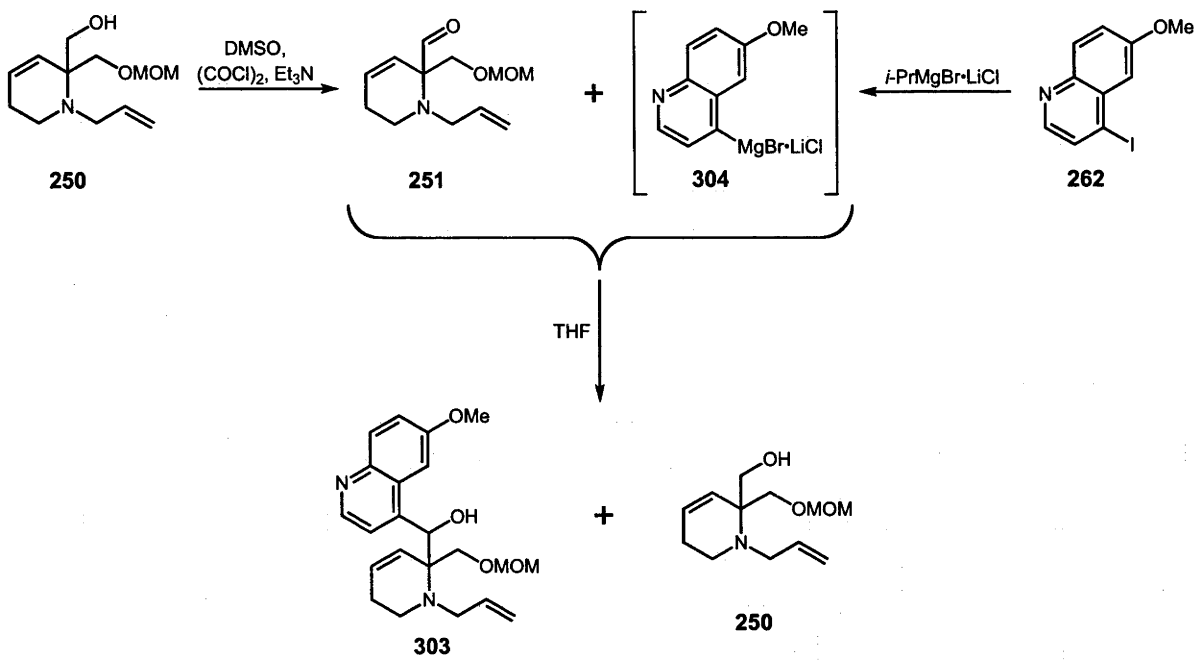
297 **298**

The previously reported iodide **298**[34] was prepared in the same manner as described above for compound **278** but now using triflate **297** as the starting material. In this manner the title iodide **298** (253 mg, 98%) was isolated by flash chromatography, as a clear, colourless oil (R_f = 0.3 in 19:1 *v/v* CH_2Cl_2 / Et_2O).

^{1}H NMR (300 MHz) δ 8.55 (m, 1H), 7.73 (dm, *J* = 7.8 Hz, 1H), 7.38–7.23 (complex m, 2H).
^{13}C NMR (75 MHz) δ 150.6, 137.5, 134.8, 122.8, 118.0.
IR υ_{max} 1564, 1555, 1443, 1411, 1094, 1067, 1038, 983, 754, 685 cm^{-1}.
Mass Spectrum (ESI) *m/z* 206 [(M+H•)$^+$, 21%], 102 (100).
HRESIMS Found: (M + H•)$^+$, 205.9472. $C_5H_4{}^{127}IN$ requires (M + H•)$^+$, 205.9467.

7.5 Experimental Procedures for Chapter Six

(*R*)-*rel*-{(*R*)-1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}(6-methoxyquinolin-4-yl)methanol (303)



Step i: A solution of DMSO (0.30 mL, 4.16 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a magnetically stirred solution of oxalyl chloride (0.24 mL, 2.78 mmol) in CH_2Cl_2 (15 mL) maintained under nitrogen at -78 °C. After 0.25 h a solution of alcohol **250** (315 mg, 1.39 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 0.25 h. After 1 h a solution of Et_3N (0.77 mL, 5.56 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. $NaHCO_3$ (10 mL of a saturated aqueous solution) was added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was treated with Et_2O (10 mL) and mixture was filtered through $MgSO_4$ (~1 cm deep pad contained in a sintered glass funnel) and the solids thus retained washed with Et_2O (30 mL). The combined filtrates were concentrated under reduced pressure to give aldehyde **251** as a clear, light-yellow oil.

This somewhat unstable material was immediately subjected to the addition reaction as described in the following paragraph.

Step ii: i-PrMgBr•LiCl (**304**) (4.17 mL of a 0.7 M solution in THF, 2.92 mmol) [Prepared by making the relevant modification to the protocol described by Knochel[40] for the synthesis of *i*-PrMgCl•LiCl. Thus, 2-bromopropane (1.40 mL, 15.0 mmol) was added,

dropwise, to a magnetically stirred solution of magnesium turnings (400 mg, 16.45) and anhydrous LiCl (634 mg, 15.0 mL) in THF (10 mL). After 16 h the ensuing mixture was transferred, *via* cannula, into a clean flask to provide *i*-PrMgBr•LiCl (**304**) as a 0.7 M THF solution. The concentration was determined using salicylaldehyde phenylhydrazone as a titrant.[41]] was added, dropwise, to a magnetically stirred solution of quinoline **262** (871 mg, 3.06 mmol) in THF (60 mL) maintained under nitrogen at -78 °C. After 0.5 h the mixture was added, *via* cannula, to aldehyde **251** (obtained as described immediately above) in THF (10 mL) maintained under nitrogen at -78 °C and the mixture slowly warmed to 18 °C over 20 h. Water (10 mL) followed by NH_4Cl (10 mL of a saturated aqueous solution) were added, the phases separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 90:10:1/60:40:1 *v/v* hexane/EtOAc/Et_3N gradient elution) thereby affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 1:1 hexane/EtOAc) afforded alcohol **250** (60 mg, 19%) as a clear, yellow oil.

Concentration of fraction B (R_f = 0.1 in EtOAc) afforded the *title quinoline* ***303*** (200 mg, 37%) as a clear, yellow oil.

^{1}H NMR (300 MHz) δ 8.74 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 9.3 and 1.2 Hz, 1H), 7.56 (d, *J* = 4.5 Hz, 1H), 7.36 (d, *J* = 9.3 and 1.8 Hz, 1H), 6.95 (s, 1H), 6.01 (m, 1H), 5.56 (s, 1H), 5.24-5.13 (m, 2H), 4.79 (s, 2H), 4.13 (d, *J* = 9.9 Hz, 1H), 3.92 (s, 3H), 3.90 (d, *J* = 9.9 Hz, 1H), 3.54 (m, 1H), 3.44 (s, 3H), 3.31-3.24 (m, 1H), 3.05 (m, 1H), 2.87 (m, 1H), 2.65 (m, 1H), 2.04 (m, 2H), 1.95 (m, 1H), 1.80 (d, *J* = 11.1 Hz, 1H).

^{13}C NMR (75 MHz) δ 157.2, 147.6, 146.8, 143.8, 135.8, 131.6, 125.9, 120.7, 117.2, 117.1, 100.9, 97.7, 96.6, 79.9, 69.3, 55.5, 55.3, 55.1, 53.5, 46.0, 14.5, 38.7.

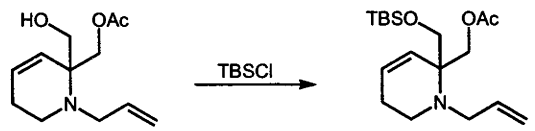
IR υ_{max} (NaCl) 3395, 2926, 1621, 1494, 1452, 1262, 1228, 1150, 1107, 1049, 915 cm^{-1}.

Mass Spectrum (ESI) *m/z* 407 [$(M+Na^{\bullet})^+$, 20%], 385 [$(M+H^{\bullet})^+$, 100], 196 (98).

HRESIMS Found: $(M + H^{\bullet})^+$, 385.2126. $C_{22}H_{28}N_2O_4$ requires $(M + H^{\bullet})^+$, 385.2127.

Found: $(M + Na^{\bullet})^+$, 407.1946. $C_{22}H_{28}N_2O_4$ requires $(M + Na^{\bullet})^+$, 407.1947.

{1-Allyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methyl acetate (309)

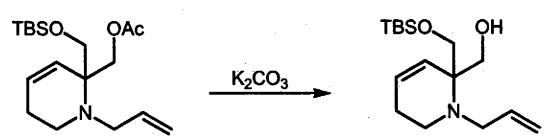


238 **309**

tert-Butyldimethylsilyl chloride (936 mg, 6.21 mmol) was added to a magnetically stirred solution of alcohol (**238**) (700 mg, 3.11 mmol) and imidazole (846 mg, 5.33 mmol) in CH_2Cl_2 (60 mL) maintained under nitrogen at 18 °C. After 21 h $NaHCO_3$ (10 mL of a saturated aqueous solution) was added to the reaction mixture and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 49:1 *v/v* hexane/EtOAc). Concentration of the appropriate fractions (R_f = 0.4 in 9:1 CH_2Cl_2/EtOAc) afforded the *title acetate* ***309*** (840 mg, 80%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.96 (m, 1H), 5.75 (m, 1H), 5.59 (dt, *J* = 9.9 and 2.1 Hz, 1H), 5.12 (m, 2H), 4.30 (d, *J* = 11.1 Hz, 1H), 4.12 (d, *J* = 11.1 Hz, 1H), 3.81 (d, *J* = 9.9 Hz, 1H), 3.47 (d, *J* = 9.9 Hz, 1H), 3.32 (dq, *J* = 14.4 and 5.7 Hz, 2H), 2.70 (t, *J* = 5.7 Hz, 2H), 2.08-2.02 (m, 2H), 2.05 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H).
^{13}C NMR (75 MHz) δ 170.6, 137.7, 128.6, 127.7, 115.8, 64.7, 64.4, 59.7, 53.4, 43.3, 25.7, 25.6, 21.0, 18.0, -5.8.
IR υ_{max} 2955, 2929, 2857, 1746, 1471, 1381, 1236, 1208, 1096, 837 cm^{-1}.
Mass Spectrum (ESI) *m/z* 340 [(M+ H$^{\bullet}$)$^+$, 90%], 280 (10), 208 (8), 148 (100).
HRESIMS Found: (M + H$^{\bullet}$)$^+$, 340.2311. $C_{18}H_{33}NO_3Si$ requires (M + H$^{\bullet}$)$^+$, 340.2308.

{1-Allyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methanol (310)



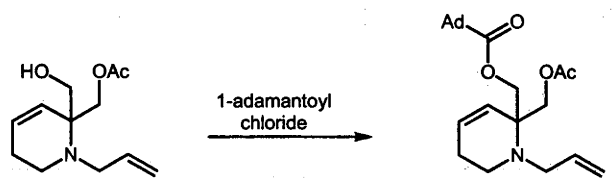
309 **310**

K_2CO_3 (180 mg, 1.30 mmol) was added to a magnetically stirred solution of acetate **309** (495 mg, 1.84 mmol) in MeOH (10 mL) maintained under nitrogen at 18 °C. After 19 h the reaction mixture was concentrated under reduced pressure then CH_2Cl_2 (10 mL) and

water (2 mL) were added and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title alcohol* ***310*** (378 mg, 98%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.99 (m, 1H), 5.76 (m, 1H), 5.47 (d, *J* = 10.2 Hz, 1H), 5.18 (m, 2H), 3.56-3.71 (m, 4H), 3.37 (m, 1H), 3.14-2.68 (m, 4H), 2.18 (br s, 1H), 1.99 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H).
^{13}C NMR (75 MHz) δ 137.0, 130.3, 128.4, 116.3, 63.4, 62.5, 62.1, 51.7, 42.9, 25.6, 25.4, 17.9, -5.8.
IR υ_{max} 3435, 2954, 2928, 2856, 1471, 1387, 1255, 1097, 1049, 837 cm^{-1}.
Mass Spectrum (ESI) *m/z* 298 [(M+ H$^•$)$^+$, 83%], 280 (8), 208 (6), 166, (84), 148 (100).
HRESIMS Found: (M + H$^•$)$^+$, 298.2203. $C_{16}H_{31}NO_2Si$ requires (M + H$^•$)$^+$, 298.2202.

[2-(Acetoxymethyl)-1-allyl-1,2,5,6-tetrahydropyridin-2-yl]methyl adamantane-1-carboxylate (315)



238 **315**

A solution of 1-adamantoyl chloride (2.65 mL, 13.3 mmol) in CH_2Cl_2 (15 mL) was added, in three equal portions over 2 h, to a magnetically stirred solution of alcohol **238** (1.20 g, 5.33 mmol), pyridine (4.31 mL, 53.3 mmol) and DMAP (65 mg, 0.53 mmol) in CH_2Cl_2 (45 mL) maintained under nitrogen at 0 °C. The ensuing mixture was warmed to 18 °C and after 18 h $NaHCO_3$ (10 mL of a saturated aqueous solution) was added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 200:6:1/80:20:1 *v/v* hexane/EtOAc/Et_3N gradient elution) thereby affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 1:1 *v/v* hexane/EtOAc) afforded the *title adamantoate* ***315*** (2.06 g, 92% at 92% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.96 (dt, *J* = 10.5 and 3.6 Hz, 1H), 5.80–5.67 (m, 1H), 5.58 (dt, *J* = 10.2 and 1.5 Hz, 1H), 5.18 (dt, *J* = 17.7 and 1.8 Hz, 1H), 5.07 (dt, *J* = 10.2 and 1.8 Hz, 1H), 4.23 (t, *J* = 11.1 Hz, 2H), 4.08 (d, *J* = 3.6 Hz, 1H), 4.04 (d, *J* = 4.2 Hz, 1H), 3.26 (d, *J* = 6.0 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.05 (s, 3H), 2.00 (m, 5H), 1.85 (m, 6H), 1.69 (m, 6H).

^{13}C NMR (75 MHz) δ 177.1, 170.6, 137.1, 128.8, 127.6, 116.3, 64.6, 64.0, 58.9, 53.0, 43.0, 40.6, 38.7, 36.3, 27.8, 25.5, 20.9.

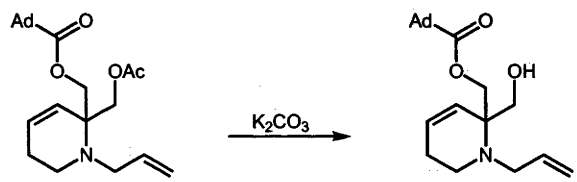
IR υ_{max} (NaCl) 2907, 2852, 1745, 1729, 1453, 1380, 1230, 1237, 1075, 1041 cm^{-1}.

Mass Spectrum (ESI) *m/z* 410 (42%), 388 [$(M+H^{\bullet})^+$, 100], 328 (11), 208 (6), 148 (44).

HRESIMS Found: $(M + H^{\bullet})^+$, 388.2492. $C_{23}H_{33}NO_4$ requires $(M + H^{\bullet})^+$, 388.2488.

Concentration of fraction B (R_f = 0.7 in 9:1 *v/v* CH_2Cl_2/EtOAc) afforded starting alcohol **238** (100 mg, 8% recovery) as a clear, colourless oil.

[1-Allyl-2-(hydroxymethyl)-1,2,5,6-tetrahydropyridin-2-yl]methyl adamantane-1-carboxylate (316)



315 **316**

K_2CO_3 (64 mg, 0.46 mmol) was added to a magnetically stirred solution of acetate **315** (180 mg, 0.46 mmol) in MeOH (5 mL) maintained under nitrogen at 0 °C. After 2.5 h NH_4Cl (3 mL of a saturated aqueous solution) and CH_2Cl_2 (10 mL) were added and the phases separated. The aqueous layer was further extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 95:5:1 *v/v* hexane/EtOAc/Et_3N) and concentration of the appropriate fractions (R_f = 0.4 in 1:1 *v/v* hexane/EtOAc) afforded the *title alcohol **316*** (140 mg, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.03-5.98 (m, 1H), 5.81–5.68 (m, 1H), 5.58 (dt, *J* = 9.9 and 1.8 Hz, 1H), 5.19 (d, *J* = 17.7 Hz, 1H), 5.13 (d, *J* = 11.1 Hz, 1H), 4.14 (d, *J* = 11.7 Hz, 1H), 4.03 (d, *J* = 11.7 Hz, 1H), 3.63 (d, *J* = 9.9 Hz, 1H), 3.54 (d, *J* = 14.7 Hz, 1H), 3.34 (t, *J* = 11.1 Hz, 1H), 3.00-2.83 (m, 3H), 2.69 (td, *J* = 11.1 and 4.2 Hz, 1H), 2.25-2.14 (m, 1H), 1.99 (m, 3H), 1.85 (m, 6H), 1.69 (m, 6H) (signal due to OH proton not observed).

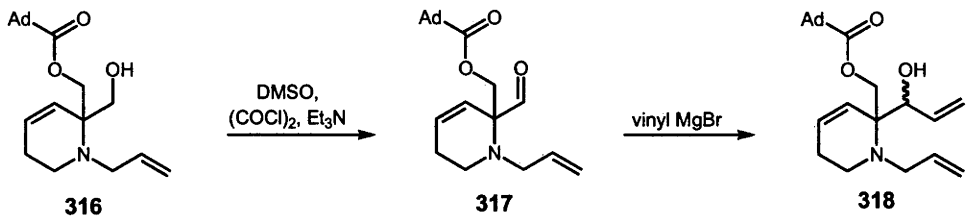
^{13}C NMR (75 MHz) δ 177.0, 136.3, 129.3, 128.9, 116.8, 63.3, 62.3, 61.0, 51.6, 42.7, 40.6, 38.7, 36.2, 27.7, 25.3.

IR υ_{max} (NaCl) 2907, 2852, 1727, 1452, 1231, 1103, 1077 cm^{-1}.

Mass Spectrum (ESI) *m/z* 368 (100%), 346 [$(M+H^{\bullet})^+$, 91], 166 (53).

HRESIMS Found: $(M + H^{\bullet})^+$, 346.2384. $C_{21}H_{31}NO_3$ requires $(M + H^{\bullet})^+$, 346.2382.

[1-Allyl-2-(1-hydroxyallyl)-1,2,5,6-tetrahydropyridin-2-yl]methyl adamantane-1-carboxylate (318)



316 317 318

Step i: A solution of DMSO (0.25 mL, 3.50 mmol) in CH_2Cl_2 (1.5 mL) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (0.20 mL, 2.34 mmol) in CH_2Cl_2 (30 mL) maintained under nitrogen at -78 °C. After 0.25 h a solution of alcohol **316** (370 mg, 1.07 mmol) in CH_2Cl_2 (7 mL) was added dropwise over 0.25 h. After 1 h a solution of Et_3N (0.65 mL, 4.68 mmol) in CH_2Cl_2 (2 mL) was added and the ensuing mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. $NaHCO_3$ (10 mL of a saturated aqueous solution) was then added and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *aldehyde* ***317*** as a light-yellow oil.

Subjection of a portion of a sample of this material to flash chromatography gave a spectroscopically pure sample of aldehyde **317** as a clear, colourless oil (R_f = 0.7 in 1:1 *v/v* hexane/EtOAc).

^{1}H NMR (300 MHz) δ 9.24 (s, 1H), 6.22-6.16 (m, 1H), 5.82–5.70 (m, 1H), 5.29-5.21 (m, 2H), 5.14 (d, *J* = 9.9 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.27 (d, *J* = 11.7 Hz, 1H), 3.29 (dd, *J* = 14.1 and 4.8 Hz, 1H), 3.13 (dd, *J* = 14.1 and 6.9 Hz, 1H), 3.34 (ddd, *J* = 11.1, 6.0 and 2.4 Hz, 1H), 2.72 (td, *J* = 11.7 and 4.2 Hz, 1H), 2.35-2.23 (m, 1H), 2.12-2.06 (m, 1H), 1.99 (m, 3H), 1.85 (m, 6H), 1.69 (m, 6H).

^{13}C NMR (75 MHz) δ 200.0, 177.1, 136.1, 132.7, 122.5, 117.4, 69.1, 62.6, 54.5, 42.1, 40.7, 38.8, 36.4, 27.9, 26.0.

IR υ_{max} (NaCl) 2907, 2852, 1730, 1453, 1265, 1230, 1075 cm^{-1}.

Mass Spectrum (ESI) *m/z* 366 (51%), 344 $[(M+H^{\bullet})^+$, 60], 164 (41).

HRESIMS Found: $(M + H^{\bullet})^+$, 344.2226. $C_{21}H_{29}NO_3$ requires $(M + H^{\bullet})^+$, 344.2226.

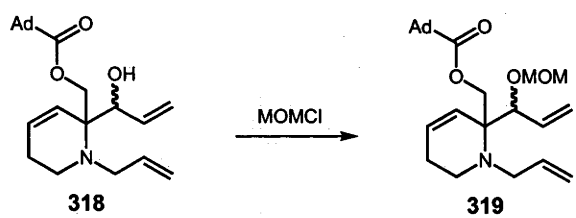
This somewhat unstable material was immediately subjected to the vinylation reaction as described in the following paragraph.

Step ii: Vinylmagnesium bromide (5.85 mL of a 0.6 M solution in THF, 3.51 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **317** (obtained as described immediately above) in THF (30 mL) maintained under nitrogen at -78 °C. After 1

h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 0.5 h, then water (5 mL) and NH_4Cl (5 mL of a saturated aqueous solution) were added. The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 95:5:1 *v/v* hexane/EtOAc/Et_3N) and concentration of the appropriate fractions (R_f = 0.7 in 1:1 *v/v* hexane/EtOAc) afforded a *ca.* 2:1 mixture of the two diastereoisomeric of the *title triene 318* (235 mg, 59% over 2 steps) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.10–5.67 (m, 5H), 5.55–5.10 (complex m, 3H), 4.37–3.97 (m, 3H), 3.76 (d, *J* = 14.7 Hz, 1H - minor diastereoisomer), 3.62 (d, *J* = 14.7 Hz, 1H - major diastereoisomer), 3.38–2.62 (m, 3H), 2.30–1.90 (m, 2H), 2.02 (m, 3H), 1.88 (m, 6H), 1.72 (m, 6H) (signal due to OH proton not observed).
^{13}C NMR (75 MHz) δ 177.2, 176.8, 137.8, 136.5, 136.1, 135.4, 130.5, 128.4, 127.9, 125.4, 117.7, 116.9, 116.2, 115.5, 72.9, 70.7, 63.6, 63.4, 62.7, 62.5, 52.9, 51.6, 43.3, 43.0, 40.5, 38.7, 36.2, 27.7, 27.6, 25.3, 24.6 (three signals obscured or overlapping).
IR υ_{max} (NaCl) 2907, 2852, 1727, 1452, 1231, 1103, 1077 cm^{-1}.
Mass Spectrum (ESI) *m/z* 394 (10%), 372 [$(M+H^{\bullet})^+$, 52], 314 (12), 314 (53), 250 (20), 192 (23), 136 (23).
HRESIMS Found: $(M + H^{\bullet})^+$, 372.2536. $C_{23}H_{33}NO_3$ requires $(M + H^{\bullet})^+$, 372.2539.

{1-Allyl-2-[1-(methoxymethoxy)allyl]-1,2,5,6-tetrahydropyridin-2-yl}methyl adamantane-1-carboxylate (319)



318 **319**

Chloromethyl methyl ether (0.82 mL, 10.8 mmol) was added in three equal portions over 2 h to a magnetically stirred solution of an undetermined mixture of the epimeric forms of alcohol **318** (420 mg, 1.86 mmol), *N,N*-diisopropylethylamine (3.75 mL, 21.5 mmol) and DMAP (33 mg, 0.27 mmol) in CH_2Cl_2 (25 mL) maintained under nitrogen at 18 °C. After 20 h *N,N*-diisopropylethylamine (3.75 mL, 21.5 mmol) was added, followed by chloromethyl methyl ether (0.82 mL, 10.8 mmol), in three equal portions over 2 h. After a further 6 h chloromethyl methyl ether (0.82 mL, 10.8 mmol) was added in three equal portions over 2 h. After 14 h $NaHCO_3$ (10 mL of a saturated aqueous solution) was added to the reaction mixture and the phases separated. The aqueous layer was extracted with

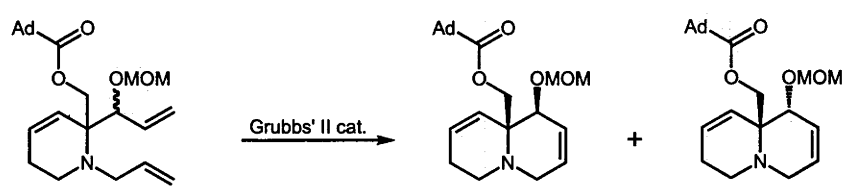
CH_2Cl_2 (3 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing red oil was subjected to flash chromatography (silica, 200:6:1/95:5:1 *v/v* hexane/EtOAc/Et_3N gradient elution) affording two major fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 1:1 *v/v* hexane/EtOAc) afforded an indeterminable mixture of epimers of the *title ether* ***319*** (930 mg, 95% at 87% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.00–5.59 (m, 4H), 5.41–5.02 (complex m, 4H), 4.70–4.12 (m, 5H), 3.92 (d, *J* = 14.7 Hz, 1H), 3.35 (s, 3H), 3.12–2.74 (m, 2H), 2.65 (td, *J* = 11.7 and 4.2 Hz, 1H), 2.17-1.90 (m, 2H), 2.01 (m, 3H), 1.89 (m, 6H), 1.71 (m, 6H).
^{13}C NMR (75 MHz) δ 177.3, 137.7, 137.2, 135.1, 134.7, 129.1, 128.8, 128.1, 126.3, 118.4, 118.0, 115.9, 115.3, 94.5, 94.0, 81.9, 77.6, 64.3, 63.9, 62.2, 61.9, 56.0, 53.4, 52.7, 43.7, 42.6, 40.6, 38.8, 36.4, 27.8, 25.7, 25.6 (six signals obscured or overlapping).
IR υ_{max} (NaCl) 2906, 2851, 1726, 1641, 1453, 1232, 1184, 1150, 1076, 1027, 918 cm^{-1}.
Mass Spectrum (ESI) *m/z* 438 [$(M+Na^{\bullet})^+$, 53%], 416 [$(M+H^{\bullet})^+$, 100], 354 (6), 236 (20), 174 (12).
HRESIMS Found: $(M + H^{\bullet})^+$, 416.2801. $C_{25}H_{37}NO_4$ requires $(M + H^{\bullet})^+$, 416.2801.
Found: $(M + Na^{\bullet})^+$, 438.2619. $C_{25}H_{37}NO_4$ requires $(M + Na^{\bullet})^+$, 438.2620.

Concentration of fraction B (R_f = 0.7 in 9:1 *v/v* hexane/EtOAc) afforded starting alcohol **318** (126 mg, 13% recovery) as a clear, colourless oil.

(1*R*, 9a*R*)-*rel*-1-[(Methoxymethoxy)methyl)]-4,6,7,9a-tetrahydro-1*H*-quinolizin-9a-yl adamantane-1-carboxylate (320) and (1*S*, 9a*R*)-*rel*-1-[(methoxymethoxy)methyl)]-4,6,7,9a-tetrahydro-1*H*-quinolizin-9a-yl adamantane-1-carboxylate (321)



319 **320** **321**

Grubbs' second generation catalyst (39 mg, 0.05 mmol) was added to a magnetically stirred solution of an undetermined mixture of the epimeric forms of triene **319** (190 mg, 0.46 mmol) in toluene (23 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 60 °C for 20 h then treated with DMSO (0.16 mL, 2.30 mmol) and Et_3N (0.31 mL, 2.30 mmol). After 24 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 95:5:1/90:10:1 *v/v* hexane/EtOAc/Et_3N gradient elution) affording two major fractions, A and B.

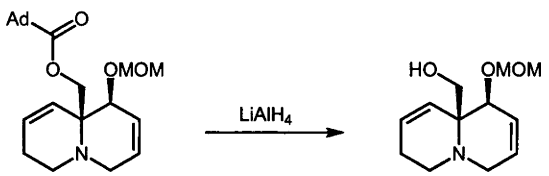
Concentration of fraction A (R_f = 0.3 in 1:1 *v/v* hexane/EtOAc) afforded the *title quinolizidine* ***321*** (40 mg, 23%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) 5.92-5.68 (m, 4H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 1H), 4.03 (s, 1H), 3.40 (s, 3H), 3.33-3.13 (m, 3H), 2.67 (dd, *J* = 11.1 and 7.2 Hz, 1H), 2.45-2.27 (m, 1H), 2.19 (d, *J* = 6.6 Hz, 1H), 2.00 (m, 3H), 1.85 (m, 6H), 1.69 (m, 6H).
^{13}C NMR (75 MHz) δ 177.5, 127.6, 127.3, 126.6, 126.5, 96.7, 79.0, 61.1, 58.0, 55.7, 50.3, 46.4, 40.6, 38.9, 36.5, 27.9, 25.1.
IR υ_{max} (NaCl) 2906, 2851, 1726, 1452, 1231, 1183, 1147, 1102, 1076, 1033, 919 cm^{-1}.
Mass Spectrum (ESI) *m/z* 410 [$(M+Na^{\bullet})^+$, 20%], 388 [$(M+H^{\bullet})^+$, 93], 356 (13), 326 (20), 208 (22), 146 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 388.2489. $C_{23}H_{33}NO_4$ requires $(M + H^{\bullet})^+$, 388.2488.
Found: $(M + Na^{\bullet})^+$, 410.2309. $C_{23}H_{33}NO_4$ requires $(M + Na^{\bullet})^+$, 410.2307.

Concentration of fraction B (R_f = 0.1 in 1:1 *v/v* hexane/EtOAc) afforded the *title quinolizidine* ***320*** (120 mg, 68%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) 6.00-5.87 (m, 3H), 5.55 (dd, *J* = 9.9 and 1.5 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 4.20 (d, *J* = 10.5 Hz, 1H), 4.11 (d, *J* = 10.5 Hz, 1H), 3.87 (d, *J* = 4.5 Hz, 1H), 3.40-3.20 (m, 2H), 3.37 (s, 3H), 3.03 (td, *J* = 11.1 and 4.8 Hz, 1H), 2.74 (dd, *J* = 11.1 and 6.6 Hz, 1H), 2.55-2.43 (m, 1H), 2.02-1.92 (m, 1H), 2.00 (m, 3H), 1.85 (m, 6H), 1.70 (m, 6H).
^{13}C NMR (75 MHz) δ 177.1, 129.8, 127.9, 126.2, 123.9, 95.7, 71.5, 62.4, 58.7, 55.3, 50.0, 45.5, 40.5, 38.6, 36.2, 27.7, 24.7.
IR υ_{max} (NaCl) 2906, 2852, 1727, 1453, 1230, 1148, 1102, 1076, 1041, 918 cm^{-1}.
Mass Spectrum (ESI) *m/z* 410 [$(M+Na^{\bullet})^+$, 41%], 388 [$(M+H^{\bullet})^+$, 78], 356 (10), 326 (18), 208 (27), 146 (100).
HRESIMS Found: $(M + H^{\bullet})^+$, 388.2491. $C_{23}H_{33}NO_4$ requires $(M + H^{\bullet})^+$, 388.2488.
Found: $(M + Na^{\bullet})^+$, 410.2310. $C_{23}H_{33}NO_4$ requires $(M + Na^{\bullet})^+$, 410.2307.

(1*R*,9a*R*)-*rel*-1-(Methoxymethoxy)-4,6,7,9a-tetrahydro-1*H*-quinolizin-9a-yl)methanol (322)



320 **322**

$LiAlH_4$ (2.35 mL of a 1.0 M solution in THF, 2.35 mmol) was added to a magnetically stirred solution of adamantoate **320** (520 mg, 1.34 mmol) in THF (20 mL) maintained under nitrogen at 0 °C. After 0.5 h the ensuing mixture was warmed to 18 °C and maintained at this temperature for a further 6 h then THF (15 mL) was added. The ensuing mixture was cooled to 0 °C then water (0.09 mL), NaOH (0.09 mL of a 15% w/v aqueous solution), and water (0.27 mL) were added dropwise and in the specified order. The resulting mixture was warmed to 18 °C, maintained at this temperature for 0.25 h then dried ($MgSO_4$). After 0.25 h the reaction mixture was filtered and the solids thus retained were washed with CH_2Cl_2 (80 mL). The combined filtrates were concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 50:50:1 *v/v* hexane/EtOAc/Et_3N) and concentration of the appropriate fractions (R_f = 0.1 in 1:9 *v/v* MeOH/EtOAc) afforded the *title alcohol* **322** (225 mg, 74%) as a clear, yellow oil.

^{1}H NMR (300 MHz) 5.96 (dt, *J* = 10.5 and 4.5 Hz, 1H), 5.92 (m, 2H), 5.61 (dt, *J* = 9.9 and 1.8 Hz, 1H), 4.72 (d, *J* = 6.3 Hz, 1H), 4.62 (d, *J* = 6.3 Hz, 1H), 3.81 (d, *J* = 10.5 Hz, 1H), 3.75 (m, 1H), 3.42 (d, *J* = 10.5 Hz, 1H), 3.38 (s, 3H), 3.30 (m, 1H), 3.24 (d, *J* = 3.0 Hz, 1H), 3.10-2.94 (m, 2H), 2.44-2.32 (m, 1H), 2.16-2.04 (m, 1H), 1.90 (br s, 1H).

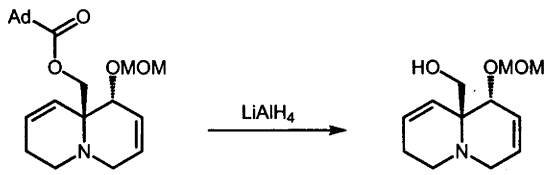
^{13}C NMR (75 MHz) δ 128.9, 128.2, 127.6, 124.1, 95.7, 70.9, 62.1, 60.3, 55.1, 49.5, 45.8, 246.

IR υ_{max} (NaCl) 3410, 2918, 1289, 1256, 1115, 1041 cm^{-1}.

Mass Spectrum (ESI) *m/z* 248, (5%), 226 [$(M+H^{\bullet})^+$, 22], 194 (9), 164 (70), 146 (17), 134 (22), 112 (100).

HRESIMS Found: $(M + H^{\bullet})^+$, 226.1442. $C_{12}H_{19}NO_3$ requires $(M + H^{\bullet})^+$, 226.1443.

(1*S*,9a*R*)-*rel*-1-(Methoxymethoxy)-4,6,7,9a-tetrahydro-1*H*-quinolizin-9a-yl)methanol (323)



321 **323**

Alcohol **323** was prepared in the same manner as described immediately above for congener **322** but now using adamantoate **321** as the starting material. In this manner the *title alcohol* **323** (88%) was isolated by flash chromatography (silica, 60:40:1 *v/v* hexane/EtOAc/Et_3N), as a clear, yellow oil (R_f = 0.2 in 1:9 *v/v* MeOH/EtOAc).

^{1}H NMR (300 MHz) 5.96 (m, 2H), 5.84-5.72 (m, 2H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.19 (s, 1H), 3.84 (dd, *J* = 10.5 and 4.2 Hz, 1H), 3.72 (dd, *J* = 10.5 and 4.2 Hz, 1H), 3.48-3.39 (m, 1H), 3.41 (s, 3H), 3.08-3.00 (m, 1H), 2.99-2.90 (m, 1H), 2.86-2.78 (m, 1H), 2.42 (t, *J* = 5.4 Hz, 1H), 2.30-2.10 (m, 2H).

^{13}C NMR (75 MHz) δ 129.4, 127.2, 126.9, 125.8, 96.7, 77.8, 60.8, 58.1, 55.8, 50.0, 46.5, 26.5.

IR υ_{max} (NaCl) 3435, 2922, 1146, 1099, 1041, 999, 918 cm^{-1}.

Mass Spectrum (ESI) *m/z* 226 [$(M+H^{\bullet})^+$, 100%], 164 (73), 146 (42), 134 (43).

HRESIMS Found: $(M + H^{\bullet})^+$, 226.1438. $C_{12}H_{19}NO_3$ requires $(M + H^{\bullet})^+$, 226.1443.

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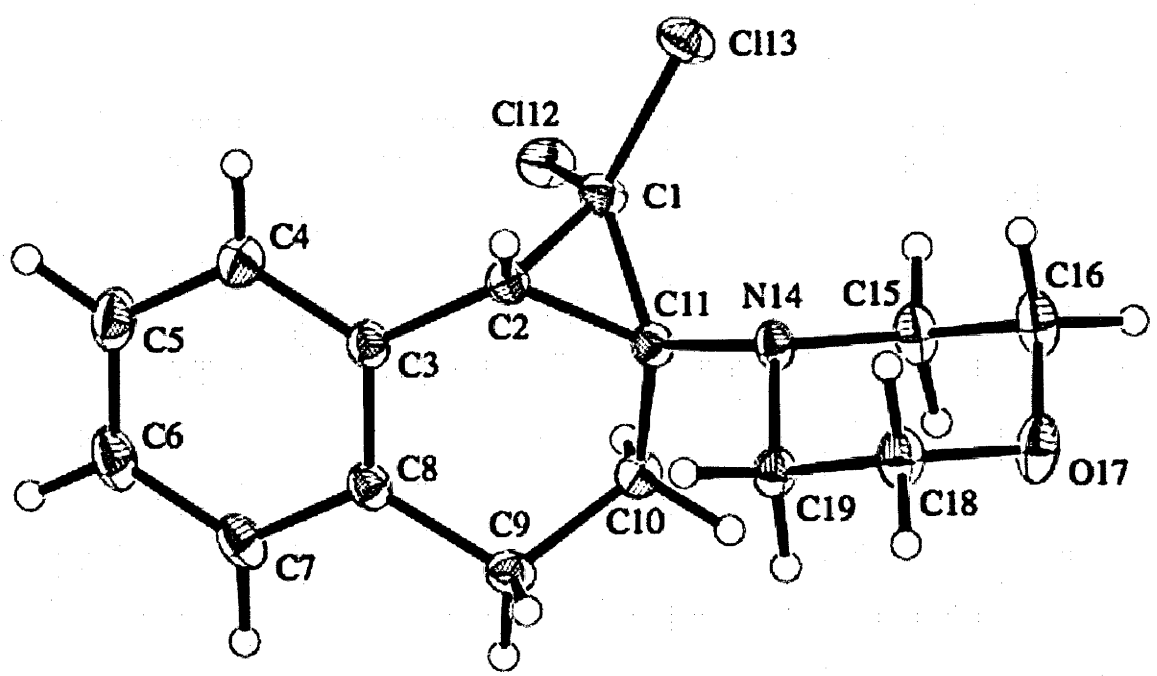
A.1 X-Ray Crystallographic Information

A.1.1 X-Ray Crystal Structure Report for Compound 73



10 Apr 2006

Crystal structure of $C_{15}H_{17}Cl_2NO$ –ban0611

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Abstract

The crystal structure of $C_{15}H_{17}Cl_2NO$ is reported.

Comment

The crystallographic asymmetric unit consists of two molecules of $C_{15}H_{17}Cl_2NO$.

The largest peaks in the final difference electron density map are located near Cl atoms or between C atoms and have no chemical significance.

Experimental

The compound was prepared by ACB and recrystallized from methanol. The sample ID is AB-11.

Crystal data

$C_{15}H_{17}Cl_2NO$
$M_r = 298.21$
Monoclinic
$P2_1/c$
$a = 11.1383\,(2)$ Å
$b = 20.8602\,(3)$ Å
$c = 12.2758\,(2)$ Å
$\beta = 90.0844\,(10)°$
$V = 2852.24\,(8)$ Å^3
$Z = 8$
$D_x = 1.389$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å

Cell parameters from 28948 reflections
$\theta = 3$–$27°$
$\mu = 0.446$ mm^{-1}
$T = 200$ K
Block
Colourless
0.38 × 0.30 × 0.30 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer

φ and ω scans with CCD

Absorption correction:

by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)

$T_{min} = 0.852$, $T_{max} = 0.888$

36822 measured reflections

6510 independent reflections

4162 reflections with

$I > 3.0\sigma(I)$

$R_{int} = 0.037$

$\theta_{max} = 27.5°$

$h = -14 \rightarrow 14$

$k = -27 \rightarrow 27$

$l = -15 \rightarrow 15$

Refinement

Refinement on F

$R = 0.0258$

$wR = 0.0308$

$S = 1.0862$

4162 reflections

445 parameters

Only coordinates of H atoms refined

Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982)

[weight] = $1.0/[A_0{*}T_0(x) + A_1{*}T_1(x) \ldots + A_{n-1}]{*}T_{n-1}(x)]$

where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are: 0.685 0.192 0.456

$(\Delta/\sigma)_{max} = 0.001275$

$\Delta\rho_{max} = 0.24$ e Å^{-3}

$\Delta\rho_{min} = -0.19$ e Å^{-3}

Extinction correction: none

Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

Table 1. *Selected geometric parameters (Å, °)*

Cl12—C1	1.7613 (15)	C6—C7	1.382 (3)
Cl13—C1	1.7518 (15)	C7—C8	1.395 (2)
Cl112—C101	1.7520 (15)	C8—C9	1.503 (2)
Cl113—C101	1.7636 (16)	C9—C10	1.528 (2)
O17—C16	1.428 (2)	C10—C11	1.530 (2)
O17—C18	1.426 (2)	C15—C16	1.511 (2)
O117—C116	1.426 (2)	C18—C19	1.514 (2)
O117—C118	1.428 (2)	C101—C102	1.509 (2)
N14—C11	1.4451 (18)	C101—C111	1.516 (2)
N14—C15	1.466 (2)	C102—C103	1.496 (2)
N14—C19	1.4694 (19)	C102—C111	1.521 (2)
N114—C111	1.4441 (18)	C103—C104	1.391 (2)
N114—C115	1.465 (2)	C103—C108	1.400 (2)
N114—C119	1.4670 (19)	C104—C105	1.392 (2)
C1—C2	1.506 (2)	C105—C106	1.381 (3)
C1—C11	1.513 (2)	C106—C107	1.381 (3)
C2—C3	1.491 (2)	C107—C108	1.397 (2)
C2—C11	1.525 (2)	C108—C109	1.506 (2)
C3—C4	1.393 (2)	C109—C110	1.529 (2)
C3—C8	1.398 (2)	C110—C111	1.529 (2)
C4—C5	1.390 (3)	C115—C116	1.518 (2)
C5—C6	1.380 (3)	C118—C119	1.507 (2)

C16—O17—C18	109.86 (13)	N14—C15—C16	109.39 (14)
C116—O117—C118	109.96 (13)	C15—C16—O17	110.55 (15)
C11—N14—C15	111.80 (12)	O17—C18—C19	111.28 (14)
C11—N14—C19	113.24 (12)	C18—C19—N14	108.76 (13)
C15—N14—C19	110.20 (13)	Cl113—C101—Cl112	111.04 (9)
C111—N114—C115	113.36 (12)	Cl113—C101—C102	118.80 (11)
C111—N114—C119	113.04 (12)	Cl112—C101—C102	118.77 (11)
C115—N114—C119	110.45 (12)	Cl113—C101—C111	118.67 (10)
Cl12—C1—Cl13	110.57 (8)	Cl112—C101—C111	120.91 (11)
Cl12—C1—C2	120.04 (10)	C102—C101—C111	60.40 (10)
Cl13—C1—C2	117.17 (11)	C101—C102—C103	119.22 (12)
Cl12—C1—C11	120.18 (11)	C101—C102—C111	60.03 (10)
Cl13—C1—C11	120.26 (10)	C103—C102—C111	118.35 (13)
C2—C1—C11	60.67 (10)	C102—C103—C104	121.07 (15)
C1—C2—C3	118.75 (12)	C102—C103—C108	119.05 (14)
C1—C2—C11	59.89 (10)	C104—C103—C108	119.85 (15)
C3—C2—C11	118.48 (13)	C103—C104—C105	120.38 (17)
C2—C3—C4	120.86 (15)	C104—C105—C106	119.79 (16)
C2—C3—C8	119.31 (14)	C105—C106—C107	120.27 (16)
C4—C3—C8	119.76 (15)	C106—C107—C108	120.69 (17)
C3—C4—C5	120.12 (18)	C103—C108—C107	119.01 (15)
C4—C5—C6	120.21 (17)	C103—C108—C109	119.21 (14)
C5—C6—C7	119.97 (16)	C107—C108—C109	121.77 (15)
C6—C7—C8	120.75 (17)	C108—C109—C110	110.75 (14)
C3—C8—C7	119.17 (15)	C109—C110—C111	110.21 (13)
C3—C8—C9	118.69 (13)	C110—C111—C102	115.91 (12)
C7—C8—C9	122.12 (15)	C110—C111—C101	120.42 (13)
C8—C9—C10	110.34 (13)	C102—C111—C101	59.57 (10)
C9—C10—C11	110.45 (13)	C110—C111—N114	118.71 (13)
C10—C11—C2	114.95 (12)	C102—C111—N114	114.80 (12)
C10—C11—C1	120.08 (12)	C101—C111—N114	113.73 (12)
C2—C11—C1	59.44 (10)	N114—C115—C116	108.29 (14)
C10—C11—N14	117.87 (13)	C115—C116—O117	110.86 (14)
C2—C11—N14	117.21 (12)	O117—C118—C119	111.66 (13)
C1—C11—N14	114.27 (12)	C118—C119—N114	108.64 (13)

All H atoms were observed in a difference electron density map prior to their inclusion. They were added at calculated positions, and then refined positionally.

Data collection: *COLLECT* (Nonius BV, 1997). Cell refinement: Denzo/Scalepack . Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR*92 (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*2003). Molecular graphics: *ORTEP*–II (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* .

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Supplementary data

Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
Cl12	1.00403 (4)	**0.390416** (19)	0.67937 (3)	0.0383
Cl13	0.92292 (4)	**0.403330** (19)	0.90162 (3)	0.0397
Cl112	0.49276 (4)	0.14379 (2)	0.39199 (3)	0.0365
Cl113	0.60361 (4)	**0.141417** (19)	0.17861 (3)	0.0362
O17	0.63544 (10)	0.60337 (6)	0.90649 (11)	0.0442
O117	0.85693 (10)	0.34581 (6)	0.12111 (10)	0.0392
N14	0.84197 (11)	0.53511 (6)	0.83783 (10)	0.0279
N114	0.66065 (11)	0.27829 (6)	0.21139 (10)	0.0279
C1	0.97490 (14)	0.44438 (7)	0.78647 (12)	0.0291
C2	1.05722 (13)	0.50055 (7)	0.80555 (12)	0.0277
C3	1.16057 (14)	0.51039 (7)	0.73030 (13)	0.0298
C4	1.26946 (15)	0.47913 (8)	0.74775 (16)	0.0388
C5	1.36312 (16)	0.48656 (10)	0.67412 (18)	0.0475
C6	1.34844 (17)	0.52445 (9)	0.58295 (17)	0.0447
C7	1.24076 (16)	0.55576 (8)	0.56529 (14)	0.0368
C8	1.14583 (14)	0.54923 (7)	0.63841 (12)	0.0293
C9	1.02687 (15)	0.58161 (8)	0.62062 (13)	0.0318
C10	0.92413 (15)	0.53511 (8)	0.64412 (12)	0.0297
C11	0.93058 (13)	0.51141 (7)	0.76198 (12)	0.0263
C15	0.72064 (15)	0.51357 (9)	0.80928 (15)	0.0372
C16	0.63362 (16)	0.53518 (10)	0.89614 (17)	0.0433
C18	0.75312 (15)	0.62428 (9)	0.93557 (15)	0.0379
C19	0.84426 (14)	0.60517 (7)	0.85013 (13)	0.0296
C101	0.53254 (13)	0.18936 (7)	0.27773 (12)	0.0284
C102	0.44931 (13)	0.24211 (7)	0.24066 (12)	0.0281
C103	0.33920 (14)	0.25642 (7)	0.30586 (12)	0.0293
C104	0.23255 (14)	0.22344 (8)	0.28759 (14)	0.0346
C105	0.13230 (15)	0.23540 (9)	0.35201 (15)	0.0390
C106	0.13907 (16)	0.27993 (9)	0.43507 (15)	0.0407
C107	0.24431 (16)	0.31333 (8)	0.45329 (14)	0.0377
C108	0.34555 (14)	0.30226 (8)	0.38891 (13)	0.0313
C109	0.46184 (16)	0.33743 (8)	0.40789 (15)	0.0364
C110	0.56856 (15)	0.29149 (8)	0.40087 (13)	0.0328
C111	0.57101 (13)	0.25872 (7)	0.28947 (12)	0.0272
C115	0.78380 (14)	0.26539 (8)	0.24726 (14)	0.0337
C116	0.86805 (15)	0.28045 (9)	0.15360 (16)	0.0391
C118	0.73650 (15)	0.35866 (9)	0.08761 (14)	0.0363
C119	0.64805 (14)	0.34542 (8)	0.17765 (13)	0.0307
H21	1.0712 (16)	0.5095 (8)	0.8823 (15)	0.0333
H41	1.2811 (18)	0.4518 (10)	0.8119 (17)	0.0466
H51	1.437 (2)	0.4635 (11)	0.6870 (18)	0.0570
H61	1.411 (2)	0.5278 (10)	0.5320 (18)	0.0537
H71	1.2282 (18)	0.5821 (10)	0.4991 (17)	0.0442
H91	1.0212 (17)	0.6185 (9)	0.6695 (16)	0.0382
H92	1.0211 (17)	0.5968 (9)	0.5458 (16)	0.0382
H101	0.8477 (17)	0.5557 (9)	0.6321 (14)	0.0357
H102	0.9270 (16)	0.4988 (9)	0.5934 (15)	0.0357
H151	0.6927 (18)	0.5317 (10)	0.7381 (17)	0.0446
H152	0.7187 (18)	0.4669 (10)	0.8050 (16)	0.0446
H161	0.658 (2)	0.5154 (10)	0.9683 (19)	0.0520
H162	0.551 (2)	0.5228 (10)	0.8762 (17)	0.0520
H181	0.7501 (18)	0.6706 (10)	0.9417 (16)	0.0455
H182	0.7755 (18)	0.6051 (9)	1.0097 (17)	0.0455
H191	0.9224 (18)	0.6169 (9)	0.8721 (15)	0.0355
H192	0.8245 (17)	0.6275 (9)	0.7813 (15)	0.0355
H1021	0.4440 (16)	0.2463 (9)	0.1600 (15)	0.0337
H1041	0.2277 (17)	0.1914 (10)	0.2295 (16)	0.0415

H1051	0.0597 (19)	0.2106 (10)	0.3404 (16)	0.0468
H1061	0.0714 (19)	0.2872 (10)	0.4821 (17)	0.0488
H1071	0.2487 (18)	0.3440 (10)	0.5101 (17)	0.0453
H1091	0.4588 (17)	0.3578 (10)	0.4769 (17)	0.0437
H1092	0.4696 (18)	0.3698 (10)	0.3513 (16)	0.0437
H1101	0.6434 (18)	0.3141 (9)	0.4109 (15)	0.0394
H1102	0.5627 (18)	0.2597 (9)	0.4569 (16)	0.0394
H1151	0.8060 (17)	0.2926 (10)	0.3100 (16)	0.0405
H1152	0.7918 (18)	0.2209 (10)	0.2669 (16)	0.0405
H1161	0.951 (2)	0.2736 (10)	0.1759 (16)	0.0469
H1162	0.8476 (19)	0.2517 (10)	0.0895 (18)	0.0469
H1181	0.7346 (18)	0.4040 (10)	0.0662 (16)	0.0436
H1182	0.7162 (18)	0.3322 (10)	0.0230 (17)	0.0436
H1191	0.6640 (17)	0.3743 (9)	0.2383 (15)	0.0368
H1192	0.5665 (18)	0.3522 (9)	0.1511 (15)	0.0368

Table *S2. Anisotropic displacement parameters* (Å^2)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl12	0.0517 (2)	0.03064 (19)	0.03276 (19)	0.00554 (17)	0.00873 (16)	−0.00497 (15)
Cl13	0.0511 (2)	0.0332 (2)	0.0347 (2)	0.00024 (17)	0.01593 (17)	0.00563 (15)
Cl112	0.0361 (2)	0.0391 (2)	0.0342 (2)	−0.00831 (16)	0.00125 (15)	0.01248 (16)
Cl113	0.0374 (2)	0.03278 (19)	0.0384 (2)	−0.00083 (16)	0.00504 (15)	−0.00143 (15)
O17	0.0272 (6)	0.0512 (8)	0.0543 (7)	0.0044 (5)	0.0049 (5)	−0.0199 (6)
O117	0.0258 (6)	0.0463 (7)	0.0457 (7)	−0.0076 (5)	0.0031 (5)	0.0130 (5)
N14	0.0231 (6)	0.0288 (6)	0.0318 (6)	−0.0012 (5)	0.0057 (5)	−0.0059 (5)
N114	0.0227 (6)	0.0301 (6)	0.0308 (6)	−0.0030 (5)	0.0018 (5)	0.0064 (5)
C1	0.0344 (8)	0.0278 (7)	0.0251 (7)	0.0011 (6)	0.0071 (6)	−0.0004 (6)
C2	0.0290 (8)	0.0293 (7)	0.0248 (7)	0.0021 (6)	0.0031 (6)	0.0007 (6)
C3	0.0271 (7)	0.0296 (7)	0.0328 (8)	0.0000 (6)	0.0048 (6)	−0.0026 (6)
C4	0.0322 (9)	0.0371 (9)	0.0473 (10)	0.0047 (7)	0.0022 (7)	0.0009 (7)
C5	0.0285 (9)	0.0448 (10)	0.0691 (13)	0.0067 (8)	0.0096 (8)	−0.0084 (9)
C6	0.0342 (9)	0.0453 (10)	0.0547 (11)	−0.0042 (8)	0.0200 (8)	−0.0100 (9)
C7	0.0381 (9)	0.0378 (9)	0.0346 (8)	−0.0068 (7)	0.0116 (7)	−0.0042 (7)
C8	0.0296 (8)	0.0280 (7)	0.0303 (8)	−0.0018 (6)	0.0060 (6)	−0.0029 (6)
C9	0.0372 (9)	0.0307 (8)	0.0276 (8)	0.0017 (6)	0.0050 (6)	0.0032 (6)
C10	0.0298 (8)	0.0326 (8)	0.0267 (7)	0.0027 (6)	−0.0003 (6)	−0.0010 (6)
C11	0.0268 (7)	0.0272 (7)	0.0250 (7)	0.0006 (6)	0.0038 (5)	−0.0020 (5)
C15	0.0278 (8)	0.0399 (9)	0.0439 (10)	−0.0053 (7)	0.0058 (7)	−0.0142 (7)
C16	0.0275 (9)	0.0511 (10)	0.0514 (11)	−0.0052 (8)	0.0098 (8)	−0.0136 (9)
C18	0.0330 (9)	0.0387 (9)	0.0420 (9)	0.0009 (7)	0.0051 (7)	−0.0139 (7)
C19	0.0272 (8)	0.0288 (7)	0.0328 (8)	0.0014 (6)	0.0014 (6)	−0.0062 (6)
C101	0.0269 (7)	0.0314 (8)	0.0270 (7)	−0.0045 (6)	0.0009 (6)	0.0040 (6)
C102	0.0267 (7)	0.0323 (7)	0.0253 (7)	−0.0052 (6)	0.0008 (6)	0.0024 (6)
C103	0.0256 (7)	0.0330 (8)	0.0293 (7)	−0.0002 (6)	0.0009 (6)	0.0069 (6)
C104	0.0284 (8)	0.0353 (8)	0.0401 (9)	−0.0017 (6)	−0.0004 (7)	0.0048 (7)
C105	0.0259 (8)	0.0402 (9)	0.0508 (10)	−0.0018 (7)	0.0027 (7)	0.0115 (8)
C106	0.0316 (9)	0.0426 (9)	0.0478 (10)	0.0084 (7)	0.0117 (7)	0.0129 (8)
C107	0.0382 (9)	0.0370 (9)	0.0381 (9)	0.0066 (7)	0.0068 (7)	0.0044 (7)
C108	0.0300 (8)	0.0330 (8)	0.0307 (8)	0.0001 (6)	0.0013 (6)	0.0055 (6)
C109	0.0382 (9)	0.0370 (9)	0.0341 (8)	−0.0032 (7)	0.0019 (7)	−0.0052 (7)
C110	0.0297 (8)	0.0387 (9)	0.0300 (8)	−0.0067 (7)	−0.0008 (6)	0.0001 (6)
C111	0.0235 (7)	0.0305 (7)	0.0276 (7)	−0.0031 (6)	0.0008 (6)	0.0044 (6)
C115	0.0258 (8)	0.0353 (8)	0.0402 (9)	−0.0002 (6)	0.0011 (6)	0.0092 (7)
C116	0.0233 (8)	0.0468 (10)	0.0472 (10)	0.0008 (7)	0.0036 (7)	0.0075 (8)
C118	0.0297 (8)	0.0417 (9)	0.0375 (9)	−0.0046 (7)	0.0030 (7)	0.0113 (7)
C119	0.0264 (8)	0.0321 (8)	0.0336 (8)	−0.0024 (6)	0.0012 (6)	0.0074 (6)

Table *S*3. *Geometric parameters (Å, °)*

Cl12—C1	1.7613 (15)	C16—H161	1.01 (2)
Cl13—C1	1.7518 (15)	C16—H162	0.98 (2)
Cl112—C101	1.7520 (15)	C18—C19	1.514 (2)
Cl113—C101	1.7636 (16)	C18—H181	0.97 (2)
O17—C16	1.428 (2)	C18—H182	1.02 (2)
O17—C18	1.426 (2)	C19—H191	0.944 (19)
O117—C116	1.426 (2)	C19—H192	0.989 (19)
O117—C118	1.428 (2)	C101—C102	1.509 (2)
N14—C11	1.4451 (18)	C101—C111	1.516 (2)
N14—C15	1.466 (2)	C102—C103	1.496 (2)
N14—C19	1.4694 (19)	C102—C111	1.521 (2)
N114—C111	1.4441 (18)	C102—H1021	0.996 (19)
N114—C115	1.465 (2)	C103—C104	1.391 (2)
N114—C119	1.4670 (19)	C103—C108	1.400 (2)
C1—C2	1.506 (2)	C104—C105	1.392 (2)
C1—C11	1.513 (2)	C104—H1041	0.98 (2)
C2—C3	1.491 (2)	C105—C106	1.381 (3)
C2—C11	1.525 (2)	C105—H1051	0.97 (2)
C2—H21	0.972 (18)	C106—C107	1.381 (3)
C3—C4	1.393 (2)	C106—H1061	0.96 (2)
C3—C8	1.398 (2)	C107—C108	1.397 (2)
C4—C5	1.390 (3)	C107—H1071	0.95 (2)
C4—H41	0.98 (2)	C108—C109	1.506 (2)
C5—C6	1.380 (3)	C109—C110	1.529 (2)
C5—H51	0.97 (2)	C109—H1091	0.95 (2)
C6—C7	1.382 (3)	C109—H1092	0.97 (2)
C6—H61	0.94 (2)	C110—C111	1.529 (2)
C7—C8	1.395 (2)	C110—H1101	0.97 (2)
C7—H71	0.99 (2)	C110—H1102	0.96 (2)
C8—C9	1.503 (2)	C115—C116	1.518 (2)
C9—C10	1.528 (2)	C115—H1151	0.99 (2)
C9—H91	0.978 (19)	C115—H1152	0.96 (2)
C9—H92	0.974 (19)	C116—H1161	0.97 (2)
C10—C11	1.530 (2)	C116—H1162	1.02 (2)
C10—H101	0.965 (19)	C118—C119	1.507 (2)
C10—H102	0.981 (19)	C118—H1181	0.98 (2)
C15—C16	1.511 (2)	C118—H1182	0.99 (2)
C15—H151	1.00 (2)	C119—H1191	0.974 (19)
C15—H152	0.98 (2)	C119—H1192	0.98 (2)
C16—O17—C18	109.86 (13)	C6—C5—H51	121.1 (13)
C116—O117—C118	109.96 (13)	C5—C6—C7	119.97 (16)
C11—N14—C15	111.80 (12)	C5—C6—H61	119.6 (13)
C11—N14—C19	113.24 (12)	C7—C6—H61	120.4 (13)
C15—N14—C19	110.20 (13)	C6—C7—C8	120.75 (17)
C111—N114—C115	113.36 (12)	C6—C7—H71	120.8 (12)
C111—N114—C119	113.04 (12)	C8—C7—H71	118.4 (12)
C115—N114—C119	110.45 (12)	C3—C8—C7	119.17 (15)
Cl12—C1—Cl13	110.57 (8)	C3—C8—C9	118.69 (13)
Cl12—C1—C2	120.04 (10)	C7—C8—C9	122.12 (15)
Cl13—C1—C2	117.17 (11)	C8—C9—C10	110.34 (13)
Cl12—C1—C11	120.18 (11)	C8—C9—H91	108.8 (11)
Cl13—C1—C11	120.26 (10)	C10—C9—H91	109.6 (11)
C2—C1—C11	60.67 (10)	C8—C9—H92	109.9 (11)
C1—C2—C3	118.75 (12)	C10—C9—H92	109.6 (11)
C1—C2—C11	59.89 (10)	H91—C9—H92	108.6 (16)
C3—C2—C11	118.48 (13)	C9—C10—C11	110.45 (13)
C1—C2—H21	113.3 (11)	C9—C10—H101	110.4 (11)
C3—C2—H21	116.8 (11)	C11—C10—H101	109.2 (11)
C11—C2—H21	117.3 (11)	C9—C10—H102	110.2 (11)
C2—C3—C4	120.86 (15)	C11—C10—H102	110.5 (11)
C2—C3—C8	119.31 (14)	H101—C10—H102	106.0 (15)
C4—C3—C8	119.76 (15)	C10—C11—C2	114.95 (12)
C3—C4—C5	120.12 (18)	C10—C11—C1	120.08 (12)
C3—C4—H41	120.6 (12)	C2—C11—C1	59.44 (10)
C5—C4—H41	119.2 (12)	C10—C11—N14	117.87 (13)
C4—C5—C6	120.21 (17)	C2—C11—N14	117.21 (12)
C4—C5—H51	118.6 (13)	C1—C11—N14	114.27 (12)

N14—C15—C16	109.39 (14)	C106—C107—C108	120.69 (17)
N14—C15—H151	112.2 (12)	C106—C107—H1071	120.2 (12)
C16—C15—H151	107.7 (12)	C108—C107—H1071	119.1 (12)
N14—C15—H152	109.9 (12)	C103—C108—C107	119.01 (15)
C16—C15—H152	108.8 (12)	C103—C108—C109	119.21 (14)
H151—C15—H152	108.8 (16)	C107—C108—C109	121.77 (15)
C15—C16—O17	110.55 (15)	C108—C109—C110	110.75 (14)
C15—C16—H161	109.0 (13)	C108—C109—H1091	108.9 (12)
O17—C16—H161	108.9 (12)	C110—C109—H1091	111.1 (12)
C15—C16—H162	110.2 (13)	C108—C109—H1092	107.8 (12)
O17—C16—H162	107.2 (13)	C110—C109—H1092	108.9 (12)
H161—C16—H162	111.0 (18)	H1091—C109—H1092	109.3 (16)
O17—C18—C19	111.28 (14)	C109—C110—C111	110.21 (13)
O17—C18—H181	107.0 (12)	C109—C110—H1101	110.9 (11)
C19—C18—H181	109.8 (12)	C111—C110—H1101	108.4 (11)
O17—C18—H182	109.0 (11)	C109—C110—H1102	109.9 (12)
C19—C18—H182	110.5 (11)	C111—C110—H1102	109.5 (12)
H181—C18—H182	109.2 (16)	H1101—C110—H1102	107.9 (16)
C18—C19—N14	108.76 (13)	C110—C111—C102	115.91 (12)
C18—C19—H191	110.6 (11)	C110—C111—C101	120.42 (13)
N14—C19—H191	107.7 (11)	C102—C111—C101	59.57 (10)
C18—C19—H192	108.6 (11)	C110—C111—N114	118.71 (13)
N14—C19—H192	112.1 (11)	C102—C111—N114	114.80 (12)
H191—C19—H192	109.0 (16)	C101—C111—N114	113.73 (12)
Cl113—C101—Cl112	111.04 (9)	N114—C115—C116	108.29 (14)
Cl113—C101—C102	118.80 (11)	N114—C115—H1151	111.2 (11)
Cl112—C101—C102	118.77 (11)	C116—C115—H1151	108.5 (11)
Cl113—C101—C111	118.67 (10)	N114—C115—H1152	109.8 (12)
Cl112—C101—C111	120.91 (11)	C116—C115—H1152	109.4 (12)
C102—C101—C111	60.40 (10)	H1151—C115—H1152	109.6 (16)
C101—C102—C103	119.22 (12)	C115—C116—O117	110.86 (14)
C101—C102—C111	60.03 (10)	C115—C116—H1161	110.1 (12)
C103—C102—C111	118.35 (13)	O117—C116—H1161	107.5 (12)
C101—C102—H1021	113.5 (10)	C115—C116—H1162	109.0 (12)
C103—C102—H1021	117.9 (11)	O117—C116—H1162	109.2 (12)
C111—C102—H1021	115.0 (11)	H1161—C116—H1162	110.1 (17)
C102—C103—C104	121.07 (15)	O117—C118—C119	111.66 (13)
C102—C103—C108	119.05 (14)	O117—C118—H1181	106.1 (12)
C104—C103—C108	119.85 (15)	C119—C118—H1181	111.0 (12)
C103—C104—C105	120.38 (17)	O117—C118—H1182	109.8 (12)
C103—C104—H1041	120.1 (11)	C119—C118—H1182	109.6 (12)
C105—C104—H1041	119.5 (11)	H1181—C118—H1182	108.5 (16)
C104—C105—C106	119.79 (16)	C118—C119—N114	108.64 (13)
C104—C105—H1051	119.4 (12)	C118—C119—H1191	109.2 (11)
C106—C105—H1051	120.8 (12)	N114—C119—H1191	111.0 (11)
C105—C106—C107	120.27 (16)	C118—C119—H1192	109.7 (11)
C105—C106—H1061	120.5 (12)	N114—C119—H1192	108.7 (11)
C107—C106—H1061	119.2 (12)	H1191—C119—H1192	109.6 (15)

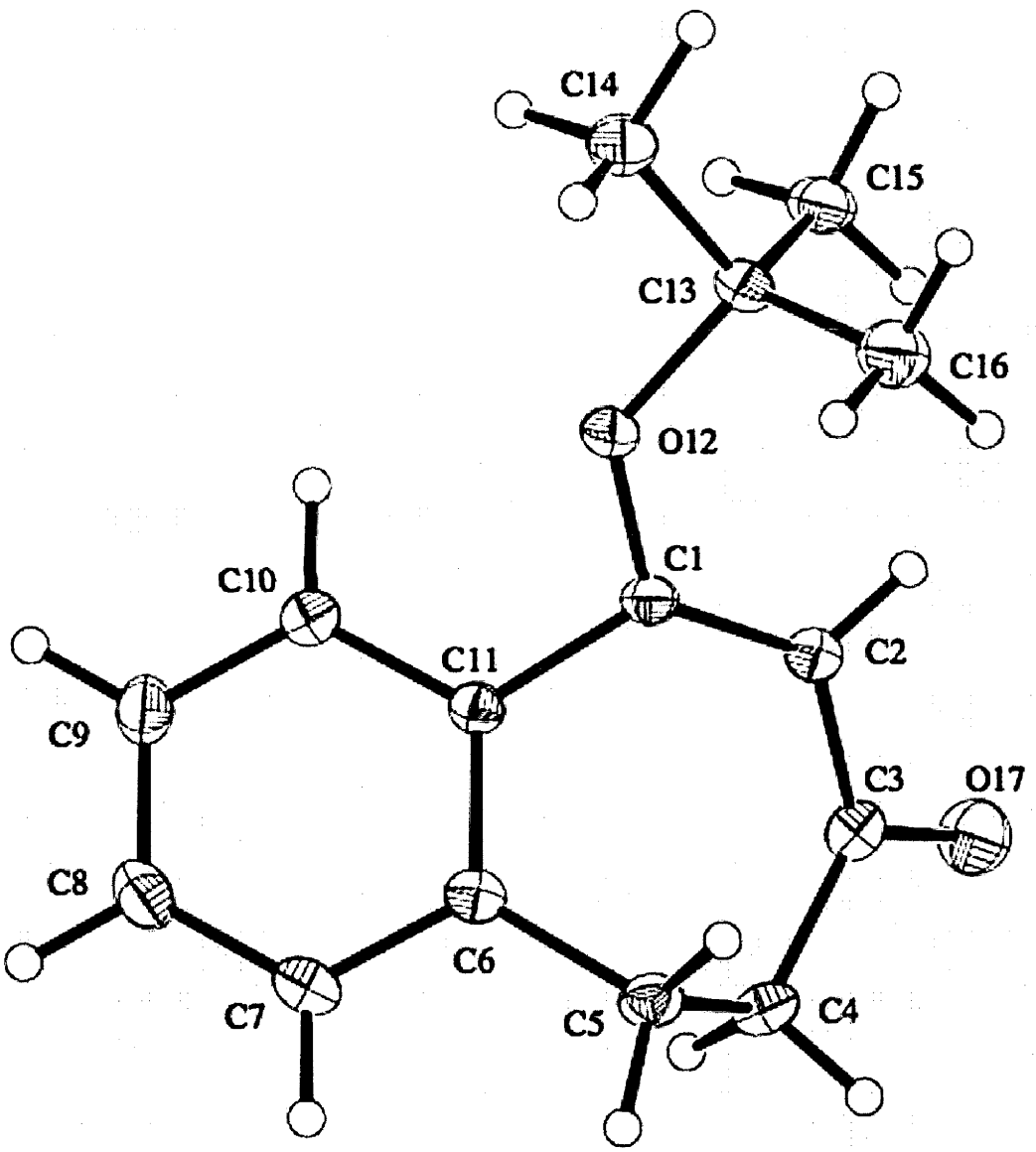
Cl12—C1—C2—C3	1.9 (2)	C4—C3—C8—C9	179.1 (1)
Cl12—C1—C2—C11	110.0 (1)	C4—C5—C6—C7	0.8 (3)
Cl12—C1—C11—N14	141.8 (1)	C5—C4—C3—C8	0.0 (3)
Cl12—C1—C11—C2	−109.7 (1)	C5—C6—C7—C8	−0.4 (3)
Cl12—C1—C11—C10	−6.8 (2)	C6—C7—C8—C9	−178.9 (2)
Cl13—C1—C2—C3	140.7 (1)	C7—C8—C9—C10	135.6 (2)
Cl13—C1—C2—C11	−111.2 (1)	C8—C3—C2—C11	22.1 (2)
Cl13—C1—C11—N14	−2.2 (2)	C8—C9—C10—C11	59.6 (2)
Cl13—C1—C11—C2	106.2 (1)	C10—C11—N14—C15	65.3 (2)
Cl13—C1—C11—C10	−150.9 (1)	C10—C11—N14—C19	−59.9 (2)
Cl112—C101—C102—C103	3.4 (2)	C11—N14—C15—C16	175.4 (1)
Cl112—C101—C102—C111	111.2 (1)	C11—N14—C19—C18	−176.9 (1)
Cl112—C101—C111—N114	146.4 (1)	C15—N14—C19—C18	57.0 (2)
Cl112—C101—C111—C102	−107.8 (1)	C15—C16—O17—C18	−59.9 (2)
Cl112—C101—C111—C110	−3.7 (2)	C16—O17—C18—C19	60.0 (2)
Cl113—C101—C102—C103	143.7 (1)	C16—C15—N14—C19	−57.7 (2)
Cl113—C101—C102—C111	−108.5 (1)	C101—C102—C103—C104	−87.0 (2)
Cl113—C101—C111—N114	2.8 (2)	C101—C102—C103—C108	90.8 (2)
Cl113—C101—C111—C102	108.7 (1)	C101—C102—C111—C110	−111.6 (1)
Cl113—C101—C111—C110	−147.2 (1)	C101—C111—N114—C115	−87.1 (2)
O17—C16—C15—N14	58.9 (2)	C101—C111—N114—C119	146.2 (1)
O17—C18—C19—N14	−58.4 (2)	C101—C111—C102—C103	109.2 (1)
O117—C116—C115—N114	59.3 (2)	C101—C111—C110—C109	−105.0 (2)
O117—C118—C119—N114	−57.9 (2)	C102—C101—C111—C110	104.1 (1)
N14—C11—C1—C2	−108.4 (1)	C102—C103—C104—C105	177.3 (2)
N14—C11—C2—C1	103.5 (1)	C102—C103—C108—C107	−176.9 (1)
N14—C11—C2—C3	−148.0 (1)	C102—C103—C108—C109	2.0 (2)
N14—C11—C10—C9	107.8 (2)	C102—C111—N114—C115	−153.2 (1)
N114—C111—C101—C102	−105.9 (1)	C102—C111—N114—C119	80.2 (2)
N114—C111—C102—C101	104.0 (1)	C102—C111—C110—C109	−36.5 (2)
N114—C111—C102—C103	−146.7 (1)	C103—C102—C101—C111	−107.8 (1)
N114—C111—C110—C109	106.4 (2)	C103—C102—C111—C110	−2.3 (2)
C1—C2—C3—C4	−85.6 (2)	C103—C104—C105—C106	−0.5 (3)
C1—C2—C3—C8	91.4 (2)	C103—C108—C107—C106	−0.4 (2)
C1—C2—C11—C10	−111.6 (1)	C103—C108—C109—C110	−42.3 (2)
C1—C11—N14—C15	−84.0 (2)	C104—C103—C102—C111	−156.6 (1)
C1—C11—N14—C19	150.8 (1)	C104—C103—C108—C107	0.9 (2)
C1—C11—C2—C3	108.6 (1)	C104—C103—C108—C109	179.8 (1)
C1—C11—C10—C9	−104.6 (2)	C104—C105—C106—C107	1.0 (3)
C2—C1—C11—C10	102.9 (1)	C105—C104—C103—C108	−0.5 (2)
C2—C3—C4—C5	177.1 (2)	C105—C106—C107—C108	−0.6 (3)
C2—C3—C8—C7	−176.8 (1)	C106—C107—C108—C109	−179.3 (2)
C2—C3—C8—C9	2.0 (2)	C107—C108—C109—C110	136.5 (2)
C2—C11—N14—C15	−150.7 (1)	C108—C103—C102—C111	21.2 (2)
C2—C11—N14—C19	84.1 (2)	C108—C109—C110—C111	58.2 (2)
C2—C11—C10—C9	−36.9 (2)	C110—C111—N114—C115	63.5 (2)
C3—C2—C1—C11	−108.1 (1)	C110—C111—N114—C119	−63.2 (2)
C3—C2—C11—C10	−3.0 (2)	C111—N114—C115—C116	173.3 (1)
C3—C4—C5—C6	−0.6 (3)	C111—N114—C119—C118	−173.8 (1)
C3—C8—C7—C6	−0.1 (2)	C115—N114—C119—C118	58.0 (2)
C3—C8—C9—C10	−43.2 (2)	C115—C116—O117—C118	−59.5 (2)
C4—C3—C2—C11	−154.9 (1)	C116—O117—C118—C119	59.0 (2)
C4—C3—C8—C7	0.3 (2)	C116—C115—N114—C119	−58.7 (2)

Table *S4. Contact distances (Å)*

Cl13···O117^{i}	3.041 (1)	O117···C2^{iv}	3.463 (2)
Cl13···C118^{i}	3.226 (2)	O117···C19^{iv}	3.499 (2)
Cl112···O17^{ii}	2.980 (1)	O117···C3^{iv}	3.516 (2)
Cl112···C18^{ii}	3.488 (2)	C6···C109^{iv}	3.575 (2)
O17···C119^{iii}	3.488 (2)	C9···C106^{iii}	3.496 (2)

Symmetry codes: (i) $x, y, 1+z$; (ii) $1-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iii) $1-x, 1-y, 1-z$; (iv) $2-x, 1-y, 1-z$.

A.1.2 X-Ray Crystal Structure Report for Compound 79



Crystal structure of $C_{15}H_{18}O_2$ — ban0730

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Abstract

The crystal structure of $C_{15}H_{18}O_2$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{15}H_{18}O_2$.

The largest peaks in the final difference electron density map are located along C—C bonds and have no chemical significance.

Experimental

The compound was prepared by ACB and recrystallized from hexane. The sample ID is AB-418.

Refinement

All hydrogen atoms were observed in difference electron density maps prior to their inclusion. They were added at calculated locations and refined positionally.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure:*SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0730)

Crystal data

$C_{15}H_{18}O_2$	$V = 1274.58\ (3)\ Å^3$
$M_r = 230.31$	$Z = 4$
Monoclinic, $P2_1/a$	Mo $K\alpha$

$a = 12.4990\ (2)$ Å	$\mu = 0.08\ mm^{-1}$
$b = 7.7906\ (1)$ Å	$T = 200$ K
$c = 13.1409\ (2)$ Å	0.30 × 0.26 × 0.12 mm
$\beta = 95.0722\ (11)°$	

Data collection

Nonius KappaCCD diffractometer	3735 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	2252 reflections with $I > 3.0\sigma(I)$
$T_{min} = 0.978$, $T_{max} = 0.991$	$R_{int} = 0.035$
36110 measured reflections	

Refinement

R = 0.034	208 parameters
wR = 0.042	Only H-atom coordinates refined
$S = 1.13$	$\Delta\rho_{max} = 0.20$ e Å^{-3}
2252 reflections	$\Delta\rho_{min} = -0.19$ e Å^{-3}

Selected geometric parameters (Å, °)

C1—C2	1.3520 (14)	C6—C11	1.4041 (14)
C1—C11	1.4879 (14)	C7—C8	1.3839 (18)
C1—O12	1.3579 (12)	C8—C9	1.3830 (19)
C2—C3	1.4674 (15)	C9—C10	1.3873 (17)
C3—C4	1.5097 (16)	C10—C11	1.4019 (15)
C3—O17	1.2302 (14)	O12—C13	1.4783 (13)
C4—C5	1.5203 (17)	C13—C14	1.5217 (18)
C5—C6	1.5005 (15)	C13—C15	1.5159 (19)
C6—C7	1.3950 (16)	C13—C16	1.5203 (18)
C2—C1—C11	126.29 (9)	C7—C8—C9	120.09 (11)
C2—C1—O12	125.51 (10)	C8—C9—C10	119.39 (12)
C11—C1—O12	108.05 (9)	C9—C10—C11	121.06 (11)
C1—C2—C3	126.93 (10)	C1—C11—C6	122.00 (9)
C2—C3—C4	122.74 (10)	C1—C11—C10	118.55 (9)
C2—C3—O17	118.88 (11)	C6—C11—C10	119.40 (10)
C4—C3—O17	118.32 (10)	C1—O12—C13	126.64 (8)
C3—C4—C5	115.86 (10)	O12—C13—C14	101.01 (9)
C4—C5—C6	110.85 (9)	O12—C13—C15	111.18 (10)
C5—C6—C7	120.27 (10)	C14—C13—C15	110.09 (12)
C5—C6—C11	121.22 (10)	O12—C13—C16	110.73 (10)
C7—C6—C11	118.49 (10)	C14—C13—C16	110.47 (12)
C6—C7—C8	121.55 (11)	C15—C13—C16	112.75 (11)

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Crystal structure of $C_{15}H_{18}O_2$ — ban0730

Alexander C. Bissember, Martin G. Banwell and Anthony C. Willis

(ban0730)

Crystal data

$C_{15}H_{18}O_2$	$F_{000} = 496$
$M_r = 230.31$	$D_x = 1.200$ Mg m^{-3}
Monoclinic, $P2_1/a$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 12.4990$ (2) Å	Cell parameters from 19191 reflections
$b = 7.7906$ (1) Å	$\theta = 2.6$–$30°$
$c = 13.1409$ (2) Å	$\mu = 0.08$ mm^{-1}
$\beta = 95.0722$ (11)°	$T = 200$ K
$V = 1274.58$ (3) Å^3	Block, yellow
$Z = 4$	0.30 × 0.26 × 0.12 mm

Data collection

Nonius KappaCCD diffractometer	2252 reflections with $I > 3.0\sigma(I)$
Monochromator: graphite	$R_{int} = 0.035$
$T = 200$ K	$\theta_{max} = 30.1°$
φ and ω scans with CCD	$\theta_{min} = 3.0°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	$h = -17 \rightarrow 17$
$T_{min} = 0.978$, $T_{max} = 0.991$	$k = -10 \rightarrow 10$
36110 measured reflections	$l = -18 \rightarrow 18$
3735 independent reflections	

Refinement

Refinement on F	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	Only H-atom coordinates refined
R = 0.034	Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982) [weight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ··· + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = F /Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(delta$F$/6*sigma$F$)^2]^2 A_i are: 0.811 0.478 0.487
wR = 0.042	$(\Delta/\sigma)_{max} = 0.004$
$S = 1.13$	$\Delta\rho_{max} = 0.20$ e Å^{-3}
2252 reflections	$\Delta\rho_{min} = -0.19$ e Å^{-3}

208 parameters
Primary atom site location: structure-invariant direct methods

Extinction correction: None

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	U_{iso}*/U_{eq}
C1	0.36863 (8)	0.48908 (13)	0.73374 (8)	0.0281
C2	0.39920 (9)	0.50921 (15)	0.63831 (8)	0.0312
C3	0.36739 (9)	0.64782 (15)	0.56630 (8)	0.0323
C4	0.25802 (9)	0.73126 (16)	0.56072 (9)	0.0353
C5	0.17542 (9)	0.64409 (16)	0.62152 (9)	0.0338
C6	0.20134 (8)	0.67179 (13)	0.73400 (8)	0.0286
C7	0.13382 (9)	0.77119 (15)	0.78919 (10)	0.0366
C8	0.15798 (11)	0.80488 (16)	0.89205 (10)	0.0418
C9	0.25092 (11)	0.73970 (17)	0.94264 (10)	0.0409
C10	0.31832 (10)	0.63788 (15)	0.88980 (8)	0.0346
C11	0.29494 (8)	0.60328 (13)	0.78551 (8)	0.0269
O12	0.40624 (7)	0.36725 (11)	0.80165 (6)	0.0382
C13	0.47333 (10)	0.21741 (14)	0.78038 (9)	0.0353
C14	0.47392 (15)	0.11962 (19)	0.88067 (11)	0.0510
C15	0.58650 (10)	0.27195 (18)	0.76221 (11)	0.0412
C16	0.41997 (12)	0.11124 (19)	0.69302 (12)	0.0467
O17	0.43061 (8)	0.69370 (14)	0.50500 (8)	0.0522
H21	0.4547 (11)	0.4388 (18)	0.6171 (10)	0.0374*
H41	0.2681 (12)	0.854 (2)	0.5836 (11)	0.0417*
H42	0.2339 (12)	0.7341 (19)	0.4891 (12)	0.0417*
H51	0.1038 (12)	0.6916 (18)	0.6003 (11)	0.0400*
H52	0.1734 (11)	0.519 (2)	0.6069 (11)	0.0400*
H71	0.0680 (12)	0.8172 (19)	0.7529 (11)	0.0439*
H81	0.1072 (13)	0.875 (2)	0.9305 (12)	0.0508*
H91	0.2669 (13)	0.760 (2)	1.0151 (13)	0.0493*
H101	0.3852 (12)	0.5884 (18)	0.9252 (11)	0.0414*
H141	0.5223 (14)	0.016 (2)	0.8788 (13)	0.0614*
H142	0.5018 (14)	0.196 (2)	0.9401 (14)	0.0614*
H143	0.4013 (15)	0.088 (2)	0.8883 (13)	0.0614*
H151	0.6305 (13)	0.170 (2)	0.7664 (12)	0.0490*
H152	0.6149 (13)	0.352 (2)	0.8156 (12)	0.0490*
H153	0.5914 (13)	0.326 (2)	0.6962 (13)	0.0490*
H161	0.4507 (13)	−0.006 (2)	0.6958 (12)	0.0554*
H162	0.3465 (14)	0.096 (2)	0.7033 (12)	0.0554*
H163	0.4266 (13)	0.160 (2)	0.6263 (13)	0.0554*

Atomic displacement parameters ($Å^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0265 (5)	0.0286 (5)	0.0286 (5)	0.0037 (4)	−0.0011 (4)	0.0014 (4)
C2	0.0287 (5)	0.0345 (5)	0.0302 (5)	0.0040 (4)	0.0018 (4)	0.0007 (4)
C3	0.0344 (5)	0.0344 (5)	0.0278 (5)	−0.0029 (4)	0.0013 (4)	0.0014 (4)

C4	0.0357 (6)	0.0391 (6)	0.0296 (5)	0.0017 (5)	−0.0049 (4)	0.0076 (5)
C5	0.0268 (5)	0.0384 (6)	0.0348 (5)	0.0011 (4)	−0.0049 (4)	0.0002 (4)
C6	0.0265 (5)	0.0254 (4)	0.0336 (5)	−0.0010 (4)	0.0009 (4)	0.0016 (4)
C7	0.0315 (5)	0.0317 (5)	0.0465 (7)	0.0061 (4)	0.0032 (5)	0.0008 (5)
C8	0.0449 (7)	0.0357 (6)	0.0465 (7)	0.0074 (5)	0.0137 (5)	−0.0034 (5)
C9	0.0514 (7)	0.0402 (6)	0.0317 (6)	0.0037 (5)	0.0077 (5)	−0.0037 (5)
C10	0.0385 (6)	0.0359 (5)	0.0292 (5)	0.0057 (4)	0.0011 (4)	0.0014 (4)
C11	0.0274 (5)	0.0251 (4)	0.0283 (5)	0.0012 (4)	0.0021 (4)	0.0014 (4)
O12	0.0473 (5)	0.0375 (4)	0.0301 (4)	0.0193 (4)	0.0047 (3)	0.0054 (3)
C13	0.0409 (6)	0.0303 (5)	0.0342 (6)	0.0127 (4)	0.0002 (4)	−0.0003 (4)
C14	0.0703 (10)	0.0414 (7)	0.0417 (7)	0.0218 (7)	0.0070 (6)	0.0100 (6)
C15	0.0382 (6)	0.0390 (6)	0.0449 (7)	0.0108 (5)	−0.0045 (5)	−0.0020 (5)
C16	0.0473 (7)	0.0412 (7)	0.0500 (8)	0.0031 (6)	−0.0047 (6)	−0.0074 (6)
O17	0.0526 (6)	0.0588 (6)	0.0477 (6)	0.0030 (5)	0.0186 (4)	0.0155 (5)

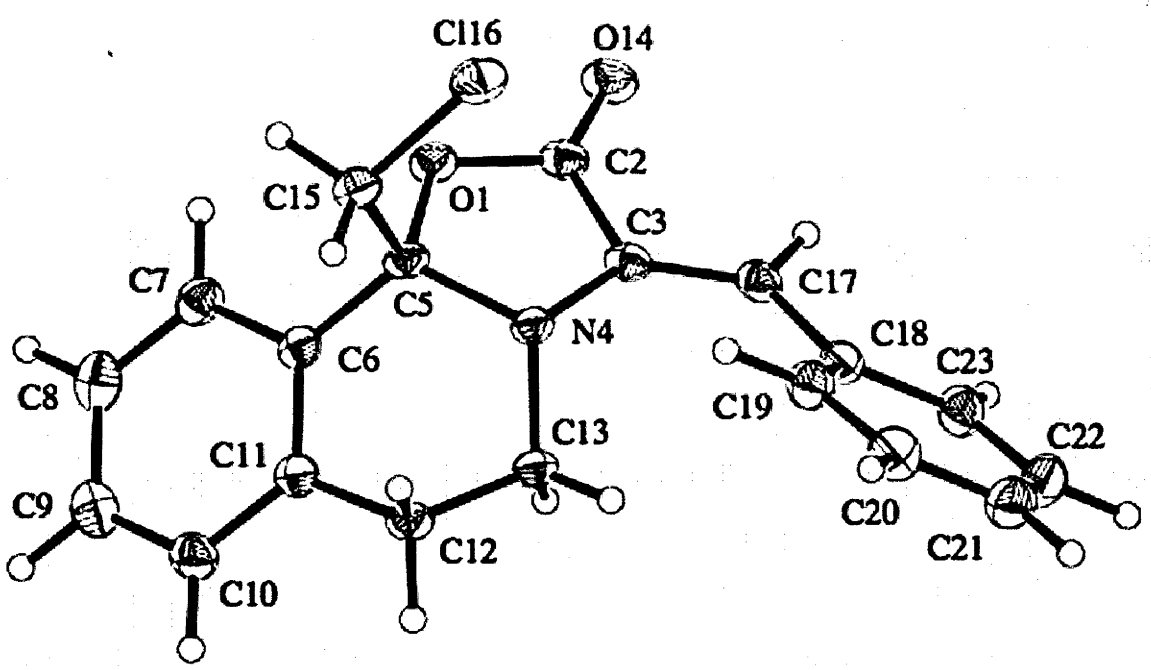
Geometric parameters (Å, °)

C1—C2	1.3520 (14)	C8—H81	1.006 (16)
C1—C11	1.4879 (14)	C9—C10	1.3873 (17)
C1—O12	1.3579 (12)	C9—H91	0.969 (17)
C2—C3	1.4674 (15)	C10—C11	1.4019 (15)
C2—H21	0.946 (14)	C10—H101	0.997 (14)
C3—C4	1.5097 (16)	O12—C13	1.4783 (13)
C3—O17	1.2302 (14)	C13—C14	1.5217 (18)
C4—C5	1.5203 (17)	C13—C15	1.5159 (19)
C4—H41	1.006 (15)	C13—C16	1.5203 (18)
C4—H42	0.963 (15)	C14—H141	1.011 (18)
C5—C6	1.5005 (15)	C14—H142	1.019 (18)
C5—H51	0.986 (15)	C14—H143	0.954 (18)
C5—H52	0.995 (15)	C15—H151	0.964 (17)
C6—C7	1.3950 (16)	C15—H152	0.980 (17)
C6—C11	1.4041 (14)	C15—H153	0.973 (16)
C7—C8	1.3839 (18)	C16—H161	0.988 (17)
C7—H71	0.982 (15)	C16—H162	0.948 (18)
C8—C9	1.3830 (19)	C16—H163	0.967 (17)
O17···C2^{i}	3.358 (2)	O17···C15^{i}	3.509 (2)
O17···O17^{i}	3.489 (2)	O17···C5^{ii}	3.532 (2)
C2—C1—C11	126.29 (9)	C10—C9—H91	120.4 (10)
C2—C1—O12	125.51 (10)	C9—C10—C11	121.06 (11)
C11—C1—O12	108.05 (9)	C9—C10—H101	120.5 (8)
C1—C2—C3	126.93 (10)	C11—C10—H101	118.4 (8)
C1—C2—H21	118.7 (8)	C1—C11—C6	122.00 (9)
C3—C2—H21	113.6 (8)	C1—C11—C10	118.55 (9)
C2—C3—C4	122.74 (10)	C6—C11—C10	119.40 (10)
C2—C3—O17	118.88 (11)	C1—O12—C13	126.64 (8)
C4—C3—O17	118.32 (10)	O12—C13—C14	101.01 (9)
C3—C4—C5	115.86 (10)	O12—C13—C15	111.18 (10)
C3—C4—H41	107.8 (8)	C14—C13—C15	110.09 (12)

C5—C4—H41	109.9 (8)	O12—C13—C16	110.73 (10)
C3—C4—H42	105.2 (9)	C14—C13—C16	110.47 (12)
C5—C4—H42	110.8 (9)	C15—C13—C16	112.75 (11)
H41—C4—H42	106.9 (12)	C13—C14—H141	109.7 (10)
C4—C5—C6	110.85 (9)	C13—C14—H142	110.3 (10)
C4—C5—H51	109.0 (8)	H141—C14—H142	108.7 (14)
C6—C5—H51	109.6 (8)	C13—C14—H143	106.8 (10)
C4—C5—H52	110.1 (8)	H141—C14—H143	111.8 (15)
C6—C5—H52	109.3 (8)	H142—C14—H143	109.5 (14)
H51—C5—H52	107.9 (12)	C13—C15—H151	107.2 (9)
C5—C6—C7	120.27 (10)	C13—C15—H152	110.4 (9)
C5—C6—C11	121.22 (10)	H151—C15—H152	108.2 (13)
C7—C6—C11	118.49 (10)	C13—C15—H153	113.3 (10)
C6—C7—C8	121.55 (11)	H151—C15—H153	109.2 (13)
C6—C7—H71	118.0 (9)	H152—C15—H153	108.4 (13)
C8—C7—H71	120.4 (9)	C13—C16—H161	109.3 (10)
C7—C8—C9	120.09 (11)	C13—C16—H162	109.1 (10)
C7—C8—H81	120.0 (9)	H161—C16—H162	104.8 (14)
C9—C8—H81	119.9 (9)	C13—C16—H163	113.8 (10)
C8—C9—C10	119.39 (12)	H161—C16—H163	109.4 (14)
C8—C9—H91	120.2 (10)	H162—C16—H163	110.0 (14)
O12—C1—C2—C3	−174.3 (1)	C2—C3—C4—C5	−9.9 (2)
O12—C1—C11—C6	−143.0 (1)	C3—C2—C1—C11	0.7 (2)
O12—C1—C11—C10	34.7 (1)	C3—C4—C5—C6	72.2 (1)
O17—C3—C2—C1	149.2 (1)	C4—C5—C6—C7	113.0 (1)
O17—C3—C4—C5	167.1 (1)	C4—C5—C6—C11	−65.1 (1)
C1—O12—C13—C14	−172.0 (1)	C5—C6—C7—C8	−177.3 (1)
C1—O12—C13—C15	71.2 (1)	C5—C6—C11—C10	177.5 (1)
C1—O12—C13—C16	−55.0 (1)	C6—C7—C8—C9	0.0 (2)
C1—C2—C3—C4	−33.8 (2)	C6—C11—C10—C9	−0.5 (2)
C1—C11—C6—C5	−4.8 (2)	C7—C6—C11—C10	−0.7 (2)
C1—C11—C6—C7	177.0 (1)	C7—C8—C9—C10	−1.2 (2)
C1—C11—C10—C9	−178.3 (1)	C8—C7—C6—C11	0.9 (2)
C2—C1—O12—C13	−10.6 (2)	C8—C9—C10—C11	1.5 (2)
C2—C1—C11—C6	41.3 (2)	C11—C1—O12—C13	173.65 (9)
C2—C1—C11—C10	−141.0 (1)		

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $x+1/2, -y+3/2, z$.

A.1.3 X-Ray Crystal Structure Report for Compound 93



Crystal structure of $C_{19}H_{16}ClNO_2$ — ban0722

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Abstract

The crystal structure of $C_{27}H_{21}NO_2$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{19}H_{16}ClNO_2$.

The largest peaks in the final difference electron density map are located along C—C bonds and have no chemical significance.

Experimental

The compound was prepared by ACB and recrystallized from methanol. The sample ID is AB-211.

Refinement

All hydrogen atoms were observed in difference electron density maps prior to their inclusion. They were added at calculated positions and ride on the atom to which they are bonded.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure:*SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0722)

Crystal data

$C_{19}H_{16}ClNO_2$	$V = 1572.20\ (5)$ Å^3
$M_r = 325.79$	$Z = 4$

Monoclinic, $P2_1/c$	Mo $K\alpha$
$a = 8.8875$ (2) Å	$\mu = 0.25$ mm^{-1}
$b = 19.4706$ (3) Å	$T = 200$ K
$c = 9.0930$ (1) Å	0.50 × 0.20 × 0.15 mm
$\beta = 92.3248$ (11)°	

Data collection

Nonius KappaCCD diffractometer	2782 independent reflections
Absorption correction: multi-scan multi-scan from symmetry-related measurements Sortav (Blessing 1995)	1987 reflections with $I > 3.0\sigma(I)$
$T_{min} = 0.794$, $T_{max} = 0.966$	$R_{int} = 0.052$
29715 measured reflections	

Refinement

R = 0.027	208 parameters
wR = 0.032	H-atom parameters not refined
$S = 1.13$	$\Delta\rho_{max} = 0.15$ e Å^{-3}
1987 reflections	$\Delta\rho_{min} = -0.17$ e Å^{-3}

Selected geometric parameters (Å, °)

Cl16—C15	1.7927 (16)	C7—C8	1.388 (3)
O1—C2	1.3640 (18)	C8—C9	1.384 (3)
O1—C5	1.4534 (16)	C9—C10	1.384 (2)
O14—C2	1.1995 (17)	C10—C11	1.393 (2)
N4—C3	1.4015 (18)	C11—C12	1.498 (2)
N4—C5	1.4678 (18)	C12—C13	1.516 (2)
N4—C13	1.4718 (17)	C17—C18	1.464 (2)
C2—C3	1.475 (2)	C18—C19	1.397 (2)
C3—C17	1.342 (2)	C18—C23	1.399 (2)
C5—C6	1.510 (2)	C19—C20	1.384 (2)
C5—C15	1.528 (2)	C20—C21	1.380 (3)
C6—C7	1.389 (2)	C21—C22	1.384 (3)
C6—C11	1.400 (2)	C22—C23	1.379 (3)
C2—O1—C5	110.13 (10)	C6—C7—C8	119.80 (15)
C3—N4—C5	108.20 (11)	C7—C8—C9	120.13 (16)
C3—N4—C13	117.32 (11)	C8—C9—C10	120.33 (16)
C5—N4—C13	118.41 (11)	C9—C10—C11	120.26 (15)
O1—C2—O14	121.52 (13)	C6—C11—C10	119.18 (14)
O1—C2—C3	108.13 (11)	C6—C11—C12	117.45 (13)
O14—C2—C3	130.35 (14)	C10—C11—C12	123.30 (13)
C2—C3—N4	107.70 (12)	C11—C12—C13	109.45 (11)
C2—C3—C17	121.90 (13)	C12—C13—N4	109.92 (12)
N4—C3—C17	130.40 (13)	C5—C15—Cl16	111.89 (10)

N4—C5—O1	105.52 (11)	C3—C17—C18	129.03 (13)
N4—C5—C6	114.64 (11)	C17—C18—C19	121.89 (14)
O1—C5—C6	109.82 (11)	C17—C18—C23	119.91 (14)
N4—C5—C15	111.90 (12)	C19—C18—C23	117.98 (15)
O1—C5—C15	106.92 (11)	C18—C19—C20	120.67 (15)
C6—C5—C15	107.77 (11)	C19—C20—C21	120.57 (17)
C5—C6—C7	121.06 (13)	C20—C21—C22	119.38 (16)
C5—C6—C11	118.52 (13)	C21—C22—C23	120.45 (16)
C7—C6—C11	120.30 (14)	C18—C23—C22	120.94 (16)

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Crystal structure of $C_{19}H_{16}ClNO_2$ — ban0722

Alexander C. Bissember, Martin G. Banwell and Anthony C. Willis

(ban0722)

Crystal data

$C_{19}H_{16}ClNO_2$	$F_{000} = 680$
$M_r = 325.79$	$D_x = 1.376$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 8.8875$ (2) Å	Cell parameters from 17526 reflections
$b = 19.4706$ (3) Å	$\theta = 2.6$–$25°$
$c = 9.0930$ (1) Å	$\mu = 0.25$ mm^{-1}
$\beta = 92.3248$ (11)°	$T = 200$ K
$V = 1572.20$ (5) Å^3	Needle, colourless
$Z = 4$	0.50 × 0.20 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer	1987 reflections with $I > 3.0\sigma(I)$
Monochromator: graphite	$R_{int} = 0.052$
$T = 200$ K	$\theta_{max} = 25.1°$
φ and ω scans with CCD	$\theta_{min} = 3.1°$
Absorption correction: multi-scan multi-scan from symmetry-related measurements Sortav (Blessing 1995)	$h = -10 \rightarrow 10$
$T_{min} = 0.794$, $T_{max} = 0.966$	$k = -23 \rightarrow 23$
29715 measured reflections	$l = -10 \rightarrow 10$
2782 independent reflections	

Refinement

Refinement on F	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters not refined
R = 0.027	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ··· + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F)^2]^2 A_i are: 0.642 0.320 0.360
wR = 0.032	$(\Delta/\sigma)_{max} = 0.001$
$S = 1.13$	$\Delta\rho_{max} = 0.15$ e Å^{-3}
1987 reflections	$\Delta\rho_{min} = -0.17$ e Å^{-3}

208 parameters
Primary atom site location: structure-invariant direct methods

Extinction correction: None

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$)

	x	y	z	U_{iso}*/U_{eq}
Cl16	0.23710 (5)	0.73938 (2)	0.39705 (5)	0.0461
O1	0.53157 (12)	0.66180 (5)	0.46983 (10)	0.0360
O14	0.47276 (14)	0.60192 (6)	0.66962 (11)	0.0457
N4	0.38111 (13)	0.60595 (6)	0.29207 (12)	0.0313
C2	0.45615 (17)	0.61109 (7)	0.53952 (15)	0.0348
C3	0.35926 (17)	0.57511 (7)	0.42883 (15)	0.0326
C5	0.48324 (16)	0.66454 (7)	0.31532 (14)	0.0317
C6	0.61897 (17)	0.66408 (7)	0.22069 (15)	0.0327
C7	0.75344 (19)	0.69461 (8)	0.26858 (18)	0.0420
C8	0.87396 (19)	0.69653 (9)	0.1762 (2)	0.0500
C9	0.8597 (2)	0.66877 (9)	0.0361 (2)	0.0488
C10	0.72585 (19)	0.63845 (8)	−0.01231 (17)	0.0420
C11	0.60393 (17)	0.63597 (7)	0.07918 (15)	0.0334
C12	0.45793 (18)	0.60139 (8)	0.03694 (15)	0.0360
C13	0.40478 (19)	0.56014 (8)	0.16635 (15)	0.0376
C15	0.40223 (17)	0.73309 (8)	0.29098 (16)	0.0367
C17	0.27056 (17)	0.52247 (7)	0.46492 (16)	0.0359
C18	0.15154 (17)	0.48840 (8)	0.37606 (16)	0.0361
C19	0.06550 (18)	0.52350 (8)	0.26826 (17)	0.0421
C20	−0.05411 (19)	0.49151 (10)	0.19391 (19)	0.0499
C21	−0.0899 (2)	0.42415 (10)	0.2242 (2)	0.0531
C22	−0.0060 (2)	0.38883 (9)	0.3312 (2)	0.0538
C23	0.11254 (19)	0.42044 (8)	0.40660 (19)	0.0446
H71	0.76342	0.71516	0.36929	0.0500*
H81	0.97127	0.71799	0.2109	0.0598*
H91	0.9465	0.67064	−0.0303	0.0587*
H101	0.71661	0.61825	−0.11337	0.0505*
H121	0.38073	0.63688	0.00869	0.0431*
H122	0.47273	0.57003	−0.04835	0.0431*
H131	0.48254	0.52497	0.19503	0.0453*
H132	0.30794	0.53665	0.13762	0.0453*
H151	0.47267	0.77120	0.32028	0.0439*
H152	0.37211	0.73761	0.18426	0.0439*
H171	0.28822	0.50394	0.56673	0.0432*
H191	0.09054	0.57223	0.24458	0.0505*
H201	−0.11507	0.51744	0.11754	0.0598*
H211	−0.1756	0.40107	0.1695	0.0638*
H221	−0.0315	0.34005	0.3539	0.0649*
H231	0.17150	0.39440	0.48423	0.0537*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl16	0.0447 (2)	0.0434 (2)	0.0498 (2)	0.00724 (17)	−0.00354 (16)	−0.00878 (18)
O1	0.0476 (6)	0.0369 (6)	0.0229 (5)	−0.0021 (4)	−0.0062 (4)	−0.0013 (4)
O14	0.0620 (7)	0.0502 (7)	0.0246 (5)	0.0029 (5)	−0.0025 (5)	0.0006 (5)
N4	0.0418 (7)	0.0278 (6)	0.0242 (6)	−0.0021 (5)	−0.0004 (5)	−0.0023 (4)
C2	0.0437 (8)	0.0346 (8)	0.0261 (7)	0.0055 (6)	−0.0001 (6)	−0.0011 (6)
C3	0.0407 (8)	0.0329 (8)	0.0242 (7)	0.0061 (6)	0.0017 (5)	0.0002 (6)
C5	0.0433 (8)	0.0295 (7)	0.0219 (6)	−0.0020 (6)	−0.0053 (6)	−0.0029 (5)
C6	0.0423 (8)	0.0257 (7)	0.0299 (7)	0.0008 (6)	−0.0031 (6)	0.0041 (5)
C7	0.0487 (9)	0.0370 (8)	0.0394 (8)	−0.0052 (7)	−0.0079 (7)	0.0024 (7)
C8	0.0422 (9)	0.0486 (10)	0.0587 (11)	−0.0070 (7)	−0.0037 (8)	0.0098 (8)
C9	0.0448 (9)	0.0492 (10)	0.0527 (10)	0.0005 (8)	0.0078 (7)	0.0091 (8)
C10	0.0518 (9)	0.0382 (8)	0.0363 (8)	0.0032 (7)	0.0059 (7)	0.0040 (7)
C11	0.0439 (8)	0.0279 (7)	0.0282 (7)	0.0032 (6)	−0.0006 (6)	0.0042 (6)
C12	0.0479 (9)	0.0368 (8)	0.0230 (7)	−0.0024 (6)	−0.0016 (6)	−0.0031 (6)
C13	0.0533 (9)	0.0327 (8)	0.0272 (7)	−0.0058 (7)	0.0039 (6)	−0.0067 (6)
C15	0.0461 (9)	0.0304 (7)	0.0333 (8)	0.0020 (6)	−0.0023 (6)	−0.0026 (6)
C17	0.0438 (8)	0.0341 (8)	0.0302 (7)	0.0033 (6)	0.0041 (6)	0.0037 (6)
C18	0.0407 (8)	0.0348 (8)	0.0334 (7)	0.0008 (6)	0.0088 (6)	0.0009 (6)
C19	0.0453 (9)	0.0391 (9)	0.0419 (9)	0.0004 (7)	0.0028 (7)	0.0032 (7)
C20	0.0439 (9)	0.0591 (11)	0.0465 (9)	−0.0007 (8)	−0.0011 (7)	0.0013 (8)
C21	0.0439 (9)	0.0556 (11)	0.0601 (11)	−0.0084 (8)	0.0055 (8)	−0.0126 (9)
C22	0.0544 (11)	0.0385 (9)	0.0693 (12)	−0.0090 (8)	0.0145 (9)	−0.0054 (8)
C23	0.0497 (9)	0.0369 (8)	0.0477 (9)	0.0007 (7)	0.0081 (7)	0.0063 (7)

Geometric parameters (Å, °)

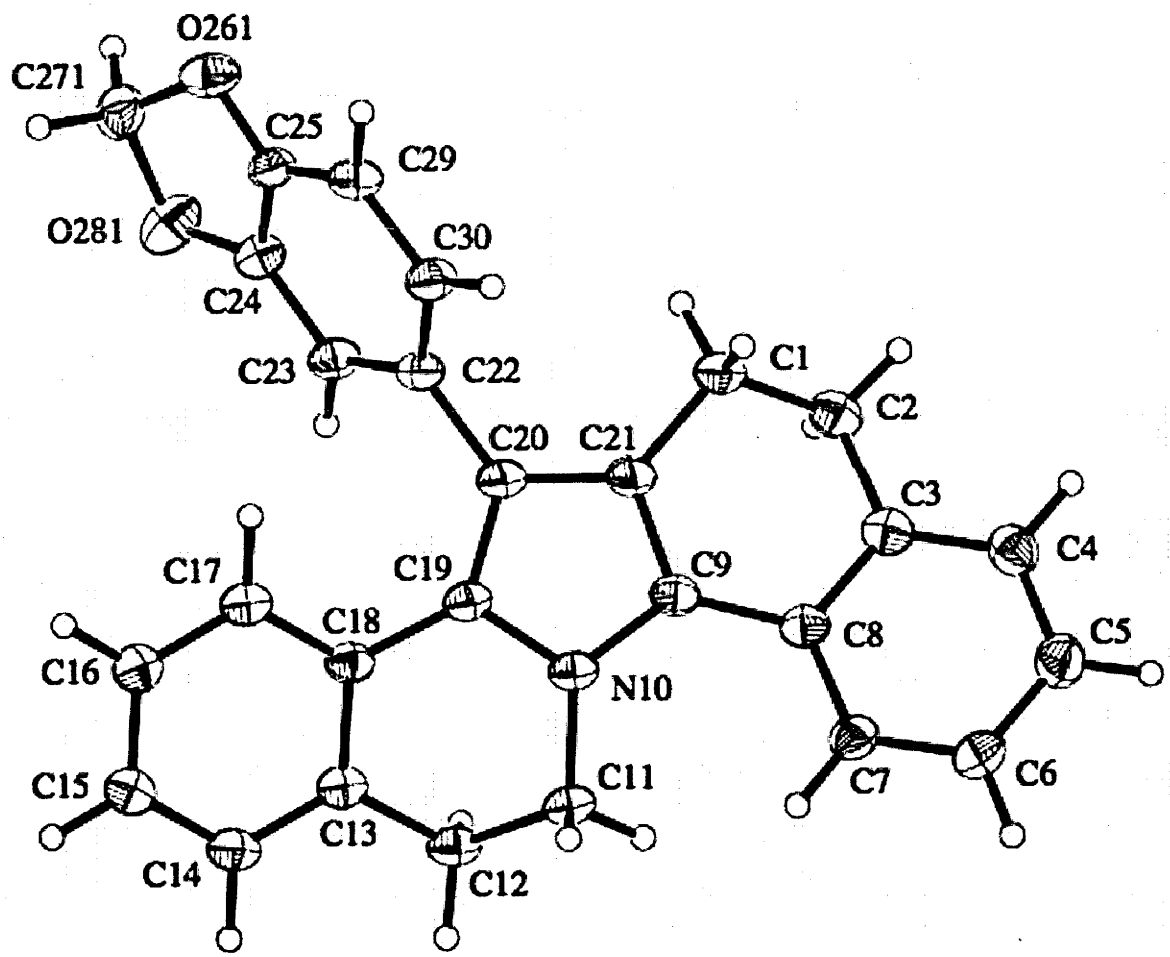
Cl16—C15	1.7927 (16)	C11—C12	1.498 (2)
O1—C2	1.3640 (18)	C12—C13	1.516 (2)
O1—C5	1.4534 (16)	C12—H121	1.000
O14—C2	1.1995 (17)	C12—H122	1.000
N4—C3	1.4015 (18)	C13—H131	1.000
N4—C5	1.4678 (18)	C13—H132	1.000
N4—C13	1.4718 (17)	C15—H151	1.000
C2—C3	1.475 (2)	C15—H152	1.000
C3—C17	1.342 (2)	C17—C18	1.464 (2)
C5—C6	1.510 (2)	C17—H171	1.000
C5—C15	1.528 (2)	C18—C19	1.397 (2)
C6—C7	1.389 (2)	C18—C23	1.399 (2)
C6—C11	1.400 (2)	C19—C20	1.384 (2)
C7—C8	1.388 (3)	C19—H191	1.000
C7—H71	1.000	C20—C21	1.380 (3)
C8—C9	1.384 (3)	C20—H201	1.000
C8—H81	1.000	C21—C22	1.384 (3)
C9—C10	1.384 (2)	C21—H211	1.000
C9—H91	1.000	C22—C23	1.379 (3)

C10—C11	1.393 (2)	C22—H221	1.000
C10—H101	1.000	C23—H231	1.000
O14···C12^{i}	3.348 (2)	C17···C21^{iv}	3.467 (2)
O14···C15^{ii}	3.462 (2)	C17···C22^{iv}	3.507 (2)
O14···C17^{iii}	3.577 (2)	C18···C23^{iv}	3.597 (2)
C2···C17^{iii}	3.560 (2)	C19···C23^{iv}	3.580 (2)
C2—O1—C5	110.13 (10)	C11—C12—H122	109.5
C3—N4—C5	108.20 (11)	C13—C12—H122	109.5
C3—N4—C13	117.32 (11)	H121—C12—H122	109.5
C5—N4—C13	118.41 (11)	C12—C13—N4	109.92 (12)
O1—C2—O14	121.52 (13)	C12—C13—H131	109.4
O1—C2—C3	108.13 (11)	N4—C13—H131	109.4
O14—C2—C3	130.35 (14)	C12—C13—H132	109.4
C2—C3—N4	107.70 (12)	N4—C13—H132	109.4
C2—C3—C17	121.90 (13)	H131—C13—H132	109.5
N4—C3—C17	130.40 (13)	C5—C15—Cl16	111.89 (10)
N4—C5—O1	105.52 (11)	C5—C15—H151	108.9
N4—C5—C6	114.64 (11)	Cl16—C15—H151	108.9
O1—C5—C6	109.82 (11)	C5—C15—H152	108.9
N4—C5—C15	111.90 (12)	Cl16—C15—H152	108.9
O1—C5—C15	106.92 (11)	H151—C15—H152	109.5
C6—C5—C15	107.77 (11)	C3—C17—C18	129.03 (13)
C5—C6—C7	121.06 (13)	C3—C17—H171	115.5
C5—C6—C11	118.52 (13)	C18—C17—H171	115.5
C7—C6—C11	120.30 (14)	C17—C18—C19	121.89 (14)
C6—C7—C8	119.80 (15)	C17—C18—C23	119.91 (14)
C6—C7—H71	120.1	C19—C18—C23	117.98 (15)
C8—C7—H71	120.1	C18—C19—C20	120.67 (15)
C7—C8—C9	120.13 (16)	C18—C19—H191	119.7
C7—C8—H81	119.9	C20—C19—H191	119.7
C9—C8—H81	119.9	C19—C20—C21	120.57 (17)
C8—C9—C10	120.33 (16)	C19—C20—H201	119.7
C8—C9—H91	119.8	C21—C20—H201	119.7
C10—C9—H91	119.8	C20—C21—C22	119.38 (16)
C9—C10—C11	120.26 (15)	C20—C21—H211	120.3
C9—C10—H101	119.9	C22—C21—H211	120.3
C11—C10—H101	119.9	C21—C22—C23	120.45 (16)
C6—C11—C10	119.18 (14)	C21—C22—H221	119.8
C6—C11—C12	117.45 (13)	C23—C22—H221	119.8
C10—C11—C12	123.30 (13)	C18—C23—C22	120.94 (16)
C11—C12—C13	109.45 (11)	C18—C23—H231	119.5
C11—C12—H121	109.5	C22—C23—H231	119.5
C13—C12—H121	109.5	C22i—H231i—.	.
Cl16—C15—C5—O1	−62.5 (1)	C5—N4—C3—C17	176.4 (2)
Cl16—C15—C5—N4	52.6 (1)	C5—N4—C13—C12	−35.6 (2)
Cl16—C15—C5—C6	179.48 (9)	C5—C6—C7—C8	−176.7 (1)
O1—C2—C3—N4	0.4 (2)	C5—C6—C11—C10	176.6 (1)

O1—C2—C3—C17	−179.8 (1)	C5—C6—C11—C12	−6.3 (2)
O1—C5—N4—C3	5.7 (1)	C6—C5—N4—C13	−10.0 (2)
O1—C5—N4—C13	−130.9 (1)	C6—C7—C8—C9	0.7 (2)
O1—C5—C6—C7	−32.6 (2)	C6—C11—C10—C9	−0.4 (2)
O1—C5—C6—C11	151.4 (1)	C6—C11—C12—C13	−40.2 (2)
O14—C2—O1—C5	−176.2 (1)	C7—C6—C5—C15	83.6 (2)
O14—C2—C3—N4	179.8 (2)	C7—C6—C11—C10	0.6 (2)
O14—C2—C3—C17	−0.5 (3)	C7—C6—C11—C12	177.6 (1)
N4—C3—C17—C18	−11.0 (3)	C7—C8—C9—C10	−0.5 (3)
N4—C5—O1—C2	−5.5 (1)	C8—C7—C6—C11	−0.7 (2)
N4—C5—C6—C7	−151.1 (1)	C8—C9—C10—C11	0.4 (2)
N4—C5—C6—C11	32.9 (2)	C9—C10—C11—C12	−177.3 (1)
N4—C13—C12—C11	60.6 (2)	C10—C11—C12—C13	136.7 (1)
C2—O1—C5—C6	−129.6 (1)	C11—C6—C5—C15	−92.4 (1)
C2—O1—C5—C15	113.8 (1)	C13—N4—C3—C17	−46.4 (2)
C2—C3—N4—C5	−3.9 (2)	C13—N4—C5—C15	113.1 (1)
C2—C3—N4—C13	133.3 (1)	C17—C18—C19—C20	−174.9 (2)
C2—C3—C17—C18	169.3 (1)	C17—C18—C23—C22	175.5 (2)
C3—N4—C5—C6	126.7 (1)	C18—C19—C20—C21	−0.5 (3)
C3—N4—C5—C15	−110.2 (1)	C18—C23—C22—C21	−0.6 (3)
C3—N4—C13—C12	−168.4 (1)	C19—C18—C23—C22	0.8 (2)
C3—C2—O1—C5	3.2 (2)	C19—C20—C21—C22	0.7 (3)
C3—C17—C18—C19	−30.6 (2)	C20—C19—C18—C23	−0.3 (2)
C3—C17—C18—C23	155.0 (2)	C20—C21—C22—C23	−0.2 (3)

Symmetry codes: (i) *x*, *y*, *z*+1; (ii) *x*, −*y*+3/2, *z*+1/2; (iii) −*x*+1, −*y*+1, −*z*+1; (iv) −*x*, −*y*+1, −*z*+1; i; i.

A.1.4 X-Ray Crystal Structure Report for Compound 96



Crystal structure of $C_{27}H_{21}NO_2$ — ban0720

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Abstract

The crystal structure of $C_{27}H_{21}NO_2$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{27}H_{21}NO_2$.

Disorder of the $C_7H_5O_2$ group was recognized, corresponding to an overlay of two images of the group rotated by 180° about the C20—C22 bond with respect to each other. Many sites are common to both images and are refined as single atoms of full occupancy, but others (mainly C27 and O28, and also, to a lesser degree, O26) do not overlay and so have partial occupancies. The relative populations were refined. Restraints were applied to distances and angles involving the minor sites so they tended to match the corresponding values for the major sites, and to their displacement parameters to match their neighbours'.

The largest peaks in the final difference electron density map are located away from the molecule and have no chemical significance.

Experimental

The compound was prepared by ACB and recrystallized from methanol. The sample ID is AB-285.

Refinement

Hydrogen atoms were added at calculated positions and ride on the atom to which they are bonded.

Computing details

Data collection: *COLLECT* (Nonius BV, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure:*SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003); molecular graphics: *ORTEP*II (Johnson 1976) in *TEXSAN* (MSC, 1992-1997); software used to prepare material for publication: *CRYSTALS* (Watkin *et al.* 2003).

(ban0720)

Crystal data

$C_{27}H_{21}NO_2$	$V = 1944.59\ (18)$ Å^3
$M_r = 391.47$	$Z = 4$
Monoclinic, $P2_1/a$	Mo $K\alpha$
$a = 9.7467\ (5)$ Å	$\mu = 0.08$ mm^{-1}
$b = 16.6619\ (9)$ Å	$T = 200$ K
$c = 12.1852\ (7)$ Å	0.25 × 0.20 × 0.03 mm
$\beta = 100.679\ (3)°$	

Data collection

Nonius KappaCCD diffractometer	3433 independent reflections
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	2546 reflections with $I > 2.0\sigma(I)$
$T_{min} = 0.982$, $T_{max} = 0.997$	$R_{int} = 0.073$
19189 measured reflections	

Refinement

R = 0.062	20 restraints
wR = 0.052	H-atom parameters not refined
$S = 1.12$	$\Delta\rho_{max} = 0.23$ e Å^{-3}
2546 reflections	$\Delta\rho_{min} = -0.29$ e Å^{-3}
299 parameters	

Selected geometric parameters (Å, °)

O26—C25	1.383 (3)	C8—C9	1.455 (3)
O26—C27	1.423 (5)	C9—C21	1.390 (3)
O28—C27	1.445 (3)	C11—C12	1.525 (3)
O28—C29	1.381 (2)	C12—C13	1.499 (3)
O261—C25	1.378 (10)	C13—C14	1.391 (3)
O261—C271	1.444 (9)	C13—C18	1.409 (3)
O281—C24	1.327 (7)	C14—C15	1.387 (3)
O281—C271	1.450 (8)	C15—C16	1.390 (3)
N10—C9	1.390 (3)	C16—C17	1.393 (3)
N10—C11	1.471 (2)	C17—C18	1.402 (3)
N10—C19	1.385 (3)	C18—C19	1.465 (3)
C1—C2	1.530 (3)	C19—C20	1.405 (3)
C1—C21	1.510 (3)	C20—C21	1.411 (3)
C2—C3	1.516 (3)	C20—C22	1.486 (3)
C3—C4	1.394 (3)	C22—C23	1.396 (3)

C3—C8	1.429 (3)	C22—C30	1.402 (3)
C4—C5	1.395 (3)	C23—C24	1.396 (3)
C5—C6	1.396 (3)	C24—C25	1.371 (3)
C6—C7	1.389 (3)	C25—C29	1.375 (3)
C7—C8	1.408 (3)	C29—C30	1.380 (3)
C25—O26—C27	104.1 (3)	C13—C18—C17	118.84 (19)
C27—O28—C29	104.63 (18)	C13—C18—C19	118.42 (18)
C25—O261—C271	100.2 (9)	C17—C18—C19	122.67 (17)
C24—O281—C271	106.4 (7)	C18—C19—N10	118.83 (16)
C9—N10—C11	128.76 (16)	C18—C19—C20	133.33 (18)
C9—N10—C19	109.49 (15)	N10—C19—C20	107.62 (18)
C11—N10—C19	121.72 (17)	C19—C20—C21	107.08 (17)
C2—C1—C21	109.27 (17)	C19—C20—C22	127.49 (19)
C1—C2—C3	112.59 (17)	C21—C20—C22	125.37 (17)
C2—C3—C4	121.5 (2)	C1—C21—C20	131.48 (18)
C2—C3—C8	118.9 (2)	C1—C21—C9	119.98 (19)
C4—C3—C8	119.6 (2)	C20—C21—C9	108.51 (17)
C3—C4—C5	121.4 (2)	C20—C22—C23	120.04 (17)
C4—C5—C6	119.1 (2)	C20—C22—C30	120.32 (19)
C5—C6—C7	120.7 (2)	C23—C22—C30	119.63 (19)
C6—C7—C8	121.0 (2)	C22—C23—C24	121.52 (19)
C3—C8—C7	118.2 (2)	C23—C24—O281	134.2 (4)
C3—C8—C9	115.75 (18)	C23—C24—C25	117.58 (19)
C7—C8—C9	125.84 (19)	O281—C24—C25	108.1 (4)
C8—C9—N10	129.24 (17)	O26—C25—C24	128.0 (2)
C8—C9—C21	123.38 (18)	O261—C25—C24	113.9 (7)
N10—C9—C21	107.29 (18)	O26—C25—C29	110.5 (2)
N10—C11—C12	109.31 (16)	O261—C25—C29	124.3 (6)
C11—C12—C13	111.39 (16)	C24—C25—C29	121.55 (18)
C12—C13—C14	122.83 (18)	O28—C27—O26	106.7 (2)
C12—C13—C18	117.40 (19)	O28—C29—C25	108.68 (19)
C14—C13—C18	119.76 (19)	O28—C29—C30	129.5 (2)
C13—C14—C15	121.28 (19)	C25—C29—C30	121.78 (19)
C14—C15—C16	119.0 (2)	C22—C30—C29	117.9 (2)
C15—C16—C17	120.8 (2)	O281—C271—O261	108.6 (9)
C16—C17—C18	120.26 (19)		

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Crystal structure of $C_{27}H_{21}NO_2$ — ban0720

Alexander C. Bissember, Martin G. Banwell and Anthony C. Willis

(ban0720)

Crystal data

$C_{27}H_{21}NO_2$	$F_{000} = 824$
$M_r = 391.47$	$D_x = 1.337$ Mg m^{-3}
Monoclinic, $P2_1/a$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 9.7467$ (5) Å	Cell parameters from 95841 reflections
$b = 16.6619$ (9) Å	$\theta = 2.6$–$25°$
$c = 12.1852$ (7) Å	$\mu = 0.08$ mm^{-1}
$\beta = 100.679$ (3)°	$T = 200$ K
$V = 1944.59$ (18) Å^3	Plate, yellow
$Z = 4$	0.25 × 0.20 × 0.03 mm

Data collection

Nonius KappaCCD diffractometer	2546 reflections with $I > 2.0\sigma(I)$
Monochromator: graphite	$R_{int} = 0.073$
$T = 200$ K	$\theta_{max} = 25.1°$
φ and ω scans with CCD	$\theta_{min} = 2.8°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (2000)	$h = -11 \rightarrow 11$
$T_{min} = 0.982$, $T_{max} = 0.997$	$k = -19 \rightarrow 19$
19189 measured reflections	$l = -14 \rightarrow 14$
3433 independent reflections	

Refinement

Refinement on F	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.062$	H-atom parameters not refined
$wR(F^2) = 0.052$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ··· + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = F /Fmax Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta$F$/6*sigma$F$)^2]^2 A_i are: 2.09 0.613 1.76
$S = 1.12$	$(\Delta/\sigma)_{max} = 0.007$

2546 reflections
299 parameters
20 restraints

$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.29$ e Å^{-3}
Extinction correction: None

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
O26	0.2922 (5)	0.4429 (4)	0.9866 (5)	0.0507	0.832 (4)
O28	0.14758 (19)	0.54740 (12)	0.91712 (15)	0.0569	0.832 (4)
O261	0.314 (3)	0.428 (2)	0.982 (2)	0.0577	0.168 (4)
O281	0.5079 (11)	0.3915 (6)	0.9032 (7)	0.0702	0.168 (4)
N10	0.48323 (17)	0.65344 (10)	0.46194 (13)	0.0408	
C1	0.1387 (2)	0.56627 (13)	0.46795 (18)	0.0463	
C2	0.1027 (2)	0.54609 (13)	0.34342 (19)	0.0520	
C3	0.1393 (2)	0.61351 (13)	0.27032 (18)	0.0453	
C4	0.0519 (2)	0.63390 (14)	0.17023 (19)	0.0529	
C5	0.0880 (3)	0.69418 (16)	0.1014 (2)	0.0602	
C6	0.2137 (2)	0.73525 (15)	0.13423 (19)	0.0557	
C7	0.3016 (2)	0.71696 (13)	0.23444 (16)	0.0465	
C8	0.2676 (2)	0.65584 (12)	0.30450 (17)	0.0402	
C9	0.3457 (2)	0.63555 (11)	0.41465 (17)	0.0396	
C11	0.5913 (2)	0.69148 (13)	0.40978 (17)	0.0445	
C12	0.7340 (2)	0.65816 (13)	0.46267 (18)	0.0461	
C13	0.7589 (2)	0.66493 (12)	0.58745 (17)	0.0421	
C14	0.8870 (2)	0.68737 (13)	0.65070 (19)	0.0480	
C15	0.9075 (2)	0.69082 (14)	0.76631 (19)	0.0529	
C16	0.7968 (2)	0.67245 (14)	0.81933 (19)	0.0531	
C17	0.6671 (2)	0.65080 (13)	0.75787 (18)	0.0476	
C18	0.6465 (2)	0.64654 (12)	0.64106 (17)	0.0407	
C19	0.5108 (2)	0.62751 (11)	0.57179 (17)	0.0399	
C20	0.3887 (2)	0.59155 (12)	0.59440 (17)	0.0410	
C21	0.2871 (2)	0.59669 (11)	0.49575 (17)	0.0402	
C22	0.3690 (2)	0.55189 (12)	0.69962 (17)	0.0414	
C23	0.4562 (2)	0.48879 (12)	0.74379 (17)	0.0434	
C24	0.4378 (2)	0.44859 (12)	0.84057 (18)	0.0462	
C25	0.3318 (2)	0.47407 (12)	0.89204 (17)	0.0438	
C27	0.2004 (3)	0.50189 (18)	1.0169 (2)	0.0539	0.832 (4)
C29	0.2455 (2)	0.53642 (13)	0.84983 (19)	0.0490	
C30	0.2611 (2)	0.57642 (13)	0.75376 (18)	0.0474	
C271	0.4443 (13)	0.3840 (8)	1.0013 (8)	0.0573	0.168 (4)
H11	0.0736 (2)	0.60861 (13)	0.48594 (18)	0.0567*	
H12	0.1293 (2)	0.51698 (13)	0.51280 (18)	0.0567*	
H21	0.0002 (2)	0.53528 (13)	0.32306 (19)	0.0626*	
H22	0.1557 (2)	0.49693 (13)	0.32924 (19)	0.0626*	
H41	−0.0385 (2)	0.60470 (14)	0.14731 (19)	0.0634*	
H51	0.0246 (3)	0.70779 (16)	0.0295 (2)	0.0719*	
H61	0.2408 (2)	0.77828 (15)	0.08513 (19)	0.0680*	
H71	0.3905 (2)	0.74769 (13)	0.25713 (16)	0.0569*	

H111	0.5899 (2)	0.75083 (13)	0.42167 (17)	0.0552*	
H112	0.5725 (2)	0.67973 (13)	0.32788 (17)	0.0552*	
H121	0.8080 (2)	0.68897 (13)	0.43389 (18)	0.0574*	
H122	0.7389 (2)	0.60035 (13)	0.44169 (18)	0.0574*	
H141	0.9658 (2)	0.70129 (13)	0.61205 (19)	0.0591*	
H151	1.0004 (2)	0.70629 (14)	0.81087 (19)	0.0634*	
H161	0.8106 (2)	0.67481 (14)	0.90265 (19)	0.0636*	
H171	0.5883 (2)	0.63824 (13)	0.79721 (18)	0.0584*	
H231	0.5336 (2)	0.47198 (12)	0.70524 (17)	0.0538*	
H241	0.4996 (2)	0.40287 (12)	0.87123 (18)	0.0562*	0.8320
H271	0.2521 (3)	0.53795 (18)	1.0761 (2)	0.0671*	0.832
H272	0.1216 (3)	0.47542 (18)	1.0452 (2)	0.0671*	0.832
H291	0.1694 (2)	0.55322 (13)	0.88985 (19)	0.0611*	0.1680
H301	0.1973 (2)	0.62150 (13)	0.72368 (18)	0.0585*	
H2711	0.5082 (13)	0.4067 (8)	1.0677 (8)	0.0675*	0.168
H2712	0.4262 (13)	0.3261 (8)	1.0150 (8)	0.0675*	0.168

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O26	0.0625 (18)	0.049 (3)	0.0466 (13)	0.0031 (11)	0.0268 (12)	0.0075 (15)
O28	0.0534 (12)	0.0711 (13)	0.0539 (12)	0.0109 (9)	0.0295 (9)	0.0094 (9)
O261	0.070 (7)	0.046 (9)	0.061 (7)	0.001 (5)	0.022 (6)	−0.002 (6)
O281	0.100 (8)	0.057 (6)	0.056 (6)	0.004 (5)	0.021 (5)	0.009 (5)
N10	0.0420 (10)	0.0410 (9)	0.0434 (10)	−0.0017 (7)	0.0178 (8)	0.0012 (7)
C1	0.0424 (11)	0.0440 (11)	0.0554 (13)	−0.0020 (9)	0.0166 (10)	0.0061 (10)
C2	0.0481 (13)	0.0461 (12)	0.0624 (14)	−0.0045 (10)	0.0119 (11)	−0.0017 (10)
C3	0.0482 (12)	0.0411 (11)	0.0495 (12)	0.0015 (9)	0.0168 (10)	−0.0087 (9)
C4	0.0492 (12)	0.0575 (14)	0.0519 (13)	−0.0021 (10)	0.0094 (11)	−0.0089 (11)
C5	0.0561 (14)	0.0756 (17)	0.0481 (13)	0.0027 (12)	0.0080 (11)	−0.0015 (12)
C6	0.0608 (14)	0.0664 (14)	0.0428 (12)	−0.0016 (11)	0.0174 (11)	0.0037 (11)
C7	0.0500 (12)	0.0537 (13)	0.0386 (12)	−0.0023 (9)	0.0156 (10)	−0.0015 (9)
C8	0.0441 (11)	0.0397 (10)	0.0406 (11)	0.0016 (8)	0.0172 (9)	−0.0054 (8)
C9	0.0390 (11)	0.0373 (10)	0.0455 (11)	0.0011 (8)	0.0152 (9)	−0.0020 (8)
C11	0.0487 (12)	0.0437 (11)	0.0456 (11)	−0.0026 (9)	0.0210 (9)	0.0040 (9)
C12	0.0445 (12)	0.0452 (11)	0.0539 (13)	0.0003 (9)	0.0229 (10)	0.0039 (9)
C13	0.0447 (12)	0.0369 (10)	0.0479 (12)	0.0014 (8)	0.0169 (10)	0.0025 (8)
C14	0.0438 (12)	0.0446 (11)	0.0592 (14)	−0.0020 (9)	0.0188 (10)	0.0060 (10)
C15	0.0478 (12)	0.0570 (14)	0.0536 (13)	−0.0092 (10)	0.0086 (10)	0.0027 (11)
C16	0.0536 (14)	0.0575 (14)	0.0480 (12)	−0.0066 (10)	0.0091 (11)	0.0024 (10)
C17	0.0491 (13)	0.0470 (12)	0.0499 (12)	−0.0037 (9)	0.0174 (10)	0.0039 (10)
C18	0.0419 (11)	0.0348 (10)	0.0476 (12)	0.0000 (8)	0.0143 (9)	0.0043 (8)
C19	0.0421 (11)	0.0382 (10)	0.0427 (11)	0.0017 (8)	0.0164 (9)	0.0039 (8)
C20	0.0429 (11)	0.0405 (11)	0.0439 (11)	−0.0011 (8)	0.0190 (9)	0.0027 (8)
C21	0.0412 (11)	0.0380 (10)	0.0445 (11)	0.0013 (8)	0.0156 (9)	0.0008 (8)
C22	0.0415 (11)	0.0421 (11)	0.0436 (11)	−0.0065 (8)	0.0157 (9)	−0.0005 (9)
C23	0.0489 (12)	0.0397 (11)	0.0459 (12)	0.0011 (9)	0.0197 (9)	0.0004 (9)
C24	0.0516 (13)	0.0437 (12)	0.0452 (12)	−0.0010 (9)	0.0142 (10)	0.0041 (9)

C25	0.0475 (12)	0.0472 (12)	0.0391 (11)	−0.0072 (9)	0.0141 (9)	0.0036 (9)
C27	0.0578 (16)	0.0637 (17)	0.0463 (16)	0.0047 (13)	0.0256 (13)	0.0088 (13)
C29	0.0452 (12)	0.0537 (13)	0.0536 (13)	−0.0016 (9)	0.0235 (10)	0.0010 (10)
C30	0.0464 (12)	0.0481 (11)	0.0517 (12)	0.0048 (9)	0.0195 (10)	0.0097 (10)
C271	0.065 (8)	0.064 (8)	0.041 (7)	−0.013 (6)	0.002 (6)	−0.006 (6)

Geometric parameters (Å, °)

O26—C25	1.383 (3)	C11—H112	1.000
O26—C27	1.423 (5)	C12—C13	1.499 (3)
O28—C27	1.445 (3)	C12—H121	1.000
O28—C29	1.381 (2)	C12—H122	1.000
O261—C25	1.378 (10)	C13—C14	1.391 (3)
O261—C271	1.444 (9)	C13—C18	1.409 (3)
O281—C24	1.327 (7)	C14—C15	1.387 (3)
O281—C271	1.450 (8)	C14—H141	1.000
N10—C9	1.390 (3)	C15—C16	1.390 (3)
N10—C11	1.471 (2)	C15—H151	1.000
N10—C19	1.385 (3)	C16—C17	1.393 (3)
C1—C2	1.530 (3)	C16—H161	1.000
C1—C21	1.510 (3)	C17—C18	1.402 (3)
C1—H11	1.000	C17—H171	1.000
C1—H12	1.000	C18—C19	1.465 (3)
C2—C3	1.516 (3)	C19—C20	1.405 (3)
C2—H21	1.000	C20—C21	1.411 (3)
C2—H22	1.000	C20—C22	1.486 (3)
C3—C4	1.394 (3)	C22—C23	1.396 (3)
C3—C8	1.429 (3)	C22—C30	1.402 (3)
C4—C5	1.395 (3)	C23—C24	1.396 (3)
C4—H41	1.000	C23—H231	1.000
C5—C6	1.396 (3)	C24—C25	1.371 (3)
C5—H51	1.000	C24—H241	1.000
C6—C7	1.389 (3)	C25—C29	1.375 (3)
C6—H61	1.000	C27—H271	1.000
C7—C8	1.408 (3)	C27—H272	1.000
C7—H71	1.000	C29—C30	1.380 (3)
C8—C9	1.455 (3)	C29—H291	1.000
C9—C21	1.390 (3)	C30—H301	1.000
C11—C12	1.525 (3)	C271—H2711	1.000
C11—H111	1.000	C271—H2712	1.000
O26···C16^{i}	3.286 (7)	N10···C23^{iv}	3.577 (3)
O26···C17^{i}	3.440 (7)	C4···C27^{v}	3.380 (4)
O26···O281^{i}	3.50 (1)	C5···C271^{vi}	3.39 (1)
O26···C24^{i}	3.546 (6)	C5···C27^{v}	3.598 (4)
O28···C5^{ii}	3.441 (3)	C6···C271^{vi}	3.21 (1)
O261···C16^{i}	3.29 (3)	C7···C11^{vii}	3.566 (3)
O261···C17^{i}	3.40 (3)	C8···C11^{vii}	3.448 (3)

O261···C6^{iii}	3.50 (3)	C11···C23^{iv}	3.524 (3)
O261···C24^{i}	3.58 (3)	C14···C19^{viii}	3.511 (3)
O281···C7^{iv}	3.27 (1)	C16···C27^{i}	3.522 (4)
O281···C27^{i}	3.34 (1)	C17···C271^{i}	3.36 (1)
O281···C6^{iii}	3.36 (1)	C24···C271^{i}	3.46 (1)
O281···C5^{iii}	3.42 (1)	C25···C271^{i}	3.32 (1)
O281···C25^{i}	3.498 (9)	C29···C271^{i}	3.49 (1)
O281···C6^{iv}	3.53 (1)		
C25—O26—C27	104.1 (3)	C14—C15—C16	119.0 (2)
C27—O28—C29	104.63 (18)	C14—C15—H151	120.5
C25—O261—C271	100.2 (9)	C16—C15—H151	120.5
C24—O281—C271	106.4 (7)	C15—C16—C17	120.8 (2)
C9—N10—C11	128.76 (16)	C15—C16—H161	119.6
C9—N10—C19	109.49 (15)	C17—C16—H161	119.6
C11—N10—C19	121.72 (17)	C16—C17—C18	120.26 (19)
C2—C1—C21	109.27 (17)	C16—C17—H171	119.9
C2—C1—H11	109.5	C18—C17—H171	119.9
C21—C1—H11	109.5	C13—C18—C17	118.84 (19)
C2—C1—H12	109.5	C13—C18—C19	118.42 (18)
C21—C1—H12	109.5	C17—C18—C19	122.67 (17)
H11—C1—H12	109.5	C18—C19—N10	118.83 (16)
C1—C2—C3	112.59 (17)	C18—C19—C20	133.33 (18)
C1—C2—H21	108.7	N10—C19—C20	107.62 (18)
C3—C2—H21	108.7	C19—C20—C21	107.08 (17)
C1—C2—H22	108.7	C19—C20—C22	127.49 (19)
C3—C2—H22	108.7	C21—C20—C22	125.37 (17)
H21—C2—H22	109.5	C1—C21—C20	131.48 (18)
C2—C3—C4	121.5 (2)	C1—C21—C9	119.98 (19)
C2—C3—C8	118.9 (2)	C20—C21—C9	108.51 (17)
C4—C3—C8	119.6 (2)	C20—C22—C23	120.04 (17)
C3—C4—C5	121.4 (2)	C20—C22—C30	120.32 (19)
C3—C4—H41	119.3	C23—C22—C30	119.63 (19)
C5—C4—H41	119.3	C22—C23—C24	121.52 (19)
C4—C5—C6	119.1 (2)	C22—C23—H231	119.2
C4—C5—H51	120.5	C24—C23—H231	119.2
C6—C5—H51	120.5	C23—C24—O281	134.2 (4)
C5—C6—C7	120.7 (2)	C23—C24—C25	117.58 (19)
C5—C6—H61	119.7	O281—C24—C25	108.1 (4)
C7—C6—H61	119.7	C23—C24—H241	121.2
C6—C7—C8	121.0 (2)	C25—C24—H241	121.2
C6—C7—H71	119.5	O26—C25—C24	128.0 (2)
C8—C7—H71	119.5	O261—C25—C24	113.9 (7)
C3—C8—C7	118.2 (2)	O26—C25—C29	110.5 (2)
C3—C8—C9	115.75 (18)	O261—C25—C29	124.3 (6)
C7—C8—C9	125.84 (19)	C24—C25—C29	121.55 (18)
C8—C9—N10	129.24 (17)	O28—C27—O26	106.7 (2)
C8—C9—C21	123.38 (18)	O28—C27—H271	110.2

N10—C9—C21	107.29 (18)	O26—C27—H271	110.2
N10—C11—C12	109.31 (16)	O28—C27—H272	110.2
N10—C11—H111	109.5	O26—C27—H272	110.2
C12—C11—H111	109.5	H271—C27—H272	109.5
N10—C11—H112	109.5	O28—C29—C25	108.68 (19)
C12—C11—H112	109.5	O28—C29—C30	129.5 (2)
H111—C11—H112	109.5	C25—C29—C30	121.78 (19)
C11—C12—C13	111.39 (16)	C25—C29—H291	119.1
C11—C12—H121	109.0	C30—C29—H291	119.1
C13—C12—H121	109.0	C22—C30—C29	117.9 (2)
C11—C12—H122	109.0	C22—C30—H301	121.0
C13—C12—H122	109.0	C29—C30—H301	121.0
H121—C12—H122	109.5	O281—C271—O261	108.6 (9)
C12—C13—C14	122.83 (18)	O281—C271—H2711	109.6
C12—C13—C18	117.40 (19)	O261—C271—H2711	109.7
C14—C13—C18	119.76 (19)	O281—C271—H2712	109.7
C13—C14—C15	121.28 (19)	O261—C271—H2712	109.7
C13—C14—H141	119.4	H2711—C271—H2712	109.5
C15—C14—H141	119.4		
O26—C25—C24—C23	178.6 (3)	C9—N10—C11—C12	−148.0 (2)
O26—C25—C29—O28	0.3 (3)	C9—N10—C19—C18	−174.7 (2)
O26—C25—C29—C30	−178.4 (3)	C9—N10—C19—C20	0.7 (2)
O26—C27—O28—C29	−22.7 (3)	C9—C21—C20—C19	−0.4 (2)
O28—C27—O26—C25	22.6 (4)	C9—C21—C20—C22	−177.9 (2)
O28—C29—C25—C24	178.7 (2)	C11—N10—C9—C21	177.4 (2)
O28—C29—C30—C22	−178.6 (2)	C11—N10—C19—C18	6.9 (3)
O261—C25—C24—O281	−9(1)	C11—N10—C19—C20	−177.8 (2)
O261—C25—C24—C23	176 (1)	C11—C12—C13—C14	−139.3 (2)
O261—C25—C29—C30	−174 (1)	C11—C12—C13—C18	41.5 (3)
O261—C271—O281—C24	12 (2)	C12—C11—N10—C19	30.1 (3)
O281—C24—C23—C22	−175.2 (6)	C12—C13—C14—C15	−178.1 (2)
O281—C24—C25—C29	176.3 (5)	C12—C13—C18—C17	178.8 (2)
O281—C271—O261—C25	−16 (2)	C12—C13—C18—C19	−4.1 (3)
O281—C271—O261—C27	−123 (4)	C13—C14—C15—C16	−0.9 (3)
N10—C9—C8—C3	165.9 (2)	C13—C18—C17—C16	−0.3 (3)
N10—C9—C8—C7	−19.5 (3)	C13—C18—C19—C20	164.6 (2)
N10—C9—C21—C1	−177.5 (2)	C14—C13—C18—C17	−0.5 (3)
N10—C9—C21—C20	0.8 (2)	C14—C13—C18—C19	176.6 (2)
N10—C11—C12—C13	−52.7 (2)	C14—C15—C16—C17	0.1 (3)
N10—C19—C18—C13	−21.5 (3)	C15—C14—C13—C18	1.1 (3)
N10—C19—C18—C17	155.5 (2)	C15—C16—C17—C18	0.5 (3)
N10—C19—C20—C21	−0.2 (2)	C16—C17—C18—C19	−177.3 (2)
N10—C19—C20—C22	177.3 (2)	C17—C18—C19—C20	−18.4 (3)
C1—C2—C3—C4	−140.1 (2)	C18—C19—C20—C21	174.3 (2)
C1—C2—C3—C8	41.0 (3)	C18—C19—C20—C22	−8.3 (4)
C1—C21—C9—C8	5.8 (3)	C19—N10—C9—C21	−0.9 (2)
C1—C21—C20—C19	177.6 (2)	C19—C20—C22—C23	−55.9 (3)
C1—C21—C20—C22	0.1 (4)	C19—C20—C22—C30	125.5 (2)
C2—C1—C21—C9	28.5 (3)	C20—C22—C23—C24	−178.0 (2)

C2—C1—C21—C20	−149.3 (2)	C20—C22—C30—C29	178.6 (2)
C2—C3—C4—C5	−177.9 (2)	C21—C20—C22—C23	121.2 (2)
C2—C3—C8—C7	178.5 (2)	C21—C20—C22—C30	−57.5 (3)
C2—C3—C8—C9	−6.5 (3)	C22—C23—C24—C25	−0.9 (3)
C3—C2—C1—C21	−49.7 (2)	C22—C30—C29—C25	−0.3 (3)
C3—C4—C5—C6	−0.6 (4)	C23—C22—C30—C29	−0.1 (3)
C3—C8—C7—C6	−0.6 (3)	C23—C24—O281—C271	172.2 (6)
C3—C8—C9—C21	−18.1 (3)	C23—C24—C25—C29	0.6 (3)
C4—C3—C8—C7	−0.4 (3)	C24—C23—C22—C30	0.7 (3)
C4—C3—C8—C9	174.6 (2)	C24—C25—O26—C27	167.3 (2)
C4—C5—C6—C7	−0.5 (4)	C24—C25—O261—C271	15 (2)
C5—C4—C3—C8	1.0 (4)	C24—C25—C29—C30	0.0 (3)
C5—C6—C7—C8	1.1 (4)	C25—C24—O281—C271	−2.5 (8)
C6—C7—C8—C9	−175.0 (2)	C25—C29—O28—C27	13.8 (2)
C7—C8—C9—C21	156.4 (2)	C27—O26—C25—C29	−14.5 (4)
C8—C9—N10—C11	−6.2 (3)	C27—O28—C29—C30	−167.7 (2)
C8—C9—N10—C19	175.5 (2)	C29—C25—O261—C271	−169.9 (8)
C8—C9—C21—C20	−175.9 (2)		

Symmetry codes: (i) $-x+1, -y+1, -z+2$; (ii) $x, y, z+1$; (iii) $-x+1/2, y-1/2, -z+1$; (iv) $-x+1, -y+1, -z+1$; (v) $x, y, z-1$; (vi) $-x+1/2, y+1/2, -z+1$; (vii) $x-1/2, -y+3/2, z$; (viii) $x+1/2, -y+3/2, z$.

A.2 Publications Resulting from Research Undertaken During PhD Candidature

The following list details the publications that have resulted from research performed during the candidature of the Doctor of Philosophy.

(i) Menon, R.S.; Findlay, A.D.; Bissember, A.C.; Banwell, M.G. The Au(I)-Catalyzed Intramolecular Hydroarylation of Terminal Alkynes Under Mild Conditions: Application to the Synthesis of *2H*-Chromenes, Coumarins, Benzofurans, and Dihydroquinolines.
Journal of Organic Chemistry, **2009**, *74*, 8901-8903.

(ii) Bissember, A.C.; Banwell, M.G. Preparation of Some Angularly Substituted and Highly Functionalized Quinolizidines as Building Blocks for the Synthesis of Various Alkaloids and Related Scaffolds of Medicinal Interest.
Tetrahedron, **2009**, *65*, 8222-8230.

(iii) Bissember, A.C.; Banwell, M.G. Microwave Assisted Trans-Halogenation Reactions of Various Chloro-, Bromo-, Trifluoromethanesulfonyloxy- and Nonafluoromethanesulfonyloxy-Substitued Quinolines, Isoquinolines, and Pyridines Leading to the Corresponding Iodinated Heterocycles.
Journal of Organic Chemistry, **2009**, *74*, 4893-4895.

(iv) Bissember, A.C. Methyl Cyanoformate (Mander's Reagent).
Synlett, **2009**, 681-682.

(v) Bissember, A.C.; Banwell, M.G. 4-Iodo-6-methoxyquinoline.
Organic Preparations and Procedures International, **2008**, *40*, 557-561.

(vi) Bissember, A.C.; Phillis, A.T.; Banwell, M.G.; Willis, A.C. Base Promoted Reactions of Dichlorocarbene Adducts of Cyclic Enamines: A New Route to Annulated Pyrroles.
Organic Letters, **2007**, *9*, 5421-5424.

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The Au(I)-Catalyzed Intramolecular Hydroarylation of Terminal Alkynes Under Mild Conditions: Application to the Synthesis of 2*H*-Chromenes, Coumarins, Benzofurans, and Dihydroquinolines

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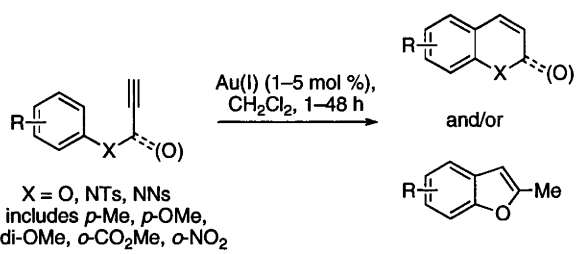
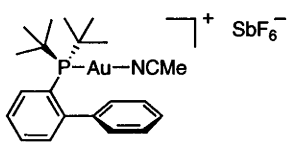


Operationally simple Au(I)-catalyzed intramolecular hydroarylation (IMHA) reactions of terminal alkynes that proceed in high yield and under very mild conditions are described. These processes involve low catalyst loadings, mild reaction temperatures, and short reaction times, require no cocatalysts or additives, and allow for the generation of a number of important heterocyclic motifs from readily accessible starting materials.

Cationic gold complexes are rapidly emerging as excellent catalysts for facilitating the assembly of a variety of carbon–carbon and carbon–heteroatom bonds with the result that powerful new methodologies based upon such processes are now being reported with increasing frequency.[1] Such complexes can be particularly effective in selectively activating alkynes toward nucleophilic addition and numerous reactions employing this strategy have been disclosed recently.[2] The majority of such processes require a cocatalyst, usually in the form of a silver salt, to activate the Au(I) species that is used. However, these silver salts are often hygroscopic, difficult to weigh accurately, and frequently result in an acidic reaction medium. Furthermore, the presence of a silver cocatalyst can promote unwanted side reactions.[3] Accordingly, a single-component Au(I) species that can activate alkynes toward nucleophilic attack offers numerous advantages over the conventional Au–Ag cocatalyst systems.

Recently, Echavarren and co-workers reported the synthesis of the stable Au(I) complex **1** possessing a weakly coordinating acetonitrile ligand that can, in the absence of silver and upon addition of a suitable substrate, be replaced by alkyne functionalities.[4] As a result this complex, which is able to be handled under standard benchtop conditions, has proven effective in catalyzing the cyclization of both enynes[2g,5a] and indole-tethered alkynes.[5b]



1

Our recent discovery of a highly efficient cascade reaction[6] that is catalyzed by complex **1** prompted us to investigate the capacity of this species to effect the intramolecular hydroarylation (IMHA) of alkynes. The latter process involves the formal addition of an arene unit and a hydrogen across the sp-hybridized carbons of a tethered alkyne.[7] While metals such as Pd,[8] Ru,[9] Ga,[10] Pt,[11] and Hg[12] as well as Tf_2NH[13] are

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(4) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(5) (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (b) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.

(6) Banwell, M. G.; Sharp. P. P. Unpublished results.

(7) Reviews: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (c) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (d) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111. For examples of the Au(I)-catalyzed IMHA reactions, see: (e) Reetz, M.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (f) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669.

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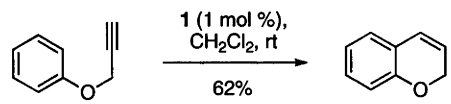
known to promote the IMHA reactions of alkynes, $AuCl_3$ is not effective[11d] in this regard. Among the isolated examples of Au(I)-catalyzed IMHA reactions of alkynes that have been reported, almost all require the use of a cocatalyst such as a Ag(I) salt or HBF_4.[3] We speculated that the now commercially available catalyst **1** would be ideal for effecting the IMHA reactions of a broad range of alkynes under mild conditions. As revealed herein, this has proved to be the case and allowed us to establish particularly convenient methods for the preparation of various 2*H*-chromenes, coumarins, benzofurans, and dihydroquinolines.

In a preliminary experiment designed to test our hypothesis, a dichloromethane solution of readily available phenyl propargyl ether (**2a**) maintained at ambient temperatures was treated with 1 mol % of complex **1**. Pleasingly, after 1 h the expected product, 2*H*-chromene (**3a**), was generated in 62% yield (Scheme 1).[14] Accordingly, we immediately sought

SCHEME 1. Au(I)-Catalyzed IMHA Reaction of Phenyl Propargyl Ether (2a)

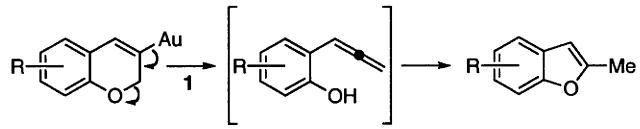


2a **3a**

to establish the scope and generality of this type of process. To that end a range of readily accessible aryl propargyl ethers was prepared and then subjected to the same reaction conditions. The outcomes of such studies are shown in Table 1, which reveals that the IMHA reactions effected by catalytic quantities of complex **1** are both broad in scope and highly efficient, even in instances where the arene ring incorporates electron-withdrawing groups (entries 3, 5, and 6). In cases involving nonsymmetrically substituted arene rings (entries 4 and 8) the cyclization reactions proceed regioselectively. Furthermore, when the ether tether was replaced with an ester linkage, as in the case of substrates **2k** and **2l** (entries 10 and 11, respectively), the corresponding coumarin-derived products **3k** and **3l** were obtained in good yield.

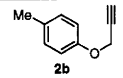
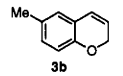
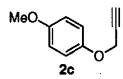
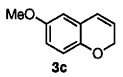
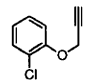
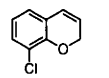
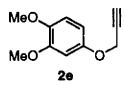
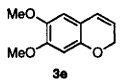
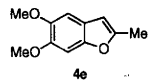
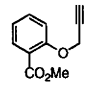
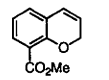
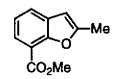
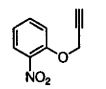
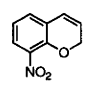
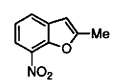
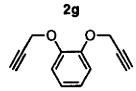
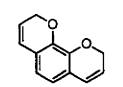
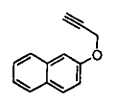
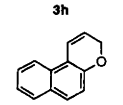
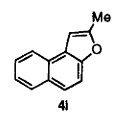
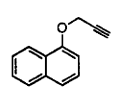
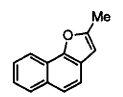
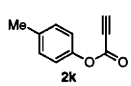
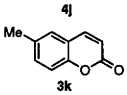
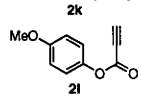
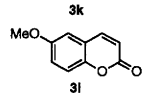
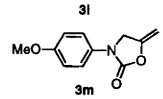
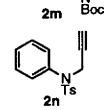
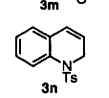
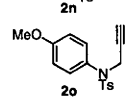
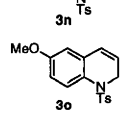
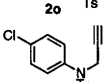
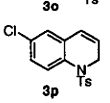
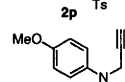
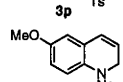
Benzofurans (**4**) were generated as coproducts (or as the only product) in a number of instances (entries 4, 5, 6, 8, and 9). Prior to the present study, the formation of benzofurans (**4**) from aryl propargyl ethers (**3**) had only been observed under much more forcing conditions (>200 °C, refluxing diethylaniline).[15] The formation of such coproducts in the present work may well involve fragmentation of the aurylated species **5**, a likely late-stage intermediate associated with the formation of the 2*H*-chromenes **3**, to give the allene **6** (Scheme 2), which engages in a 5-exo-dig cyclization reaction to give the observed product **4**.[16] This proposal is

SCHEME 2. Possible Pathway for the Formation of Benzofurans 4 from Substrates 3



5 **6** **4**

TABLE 1. Outcomes of Au(I)-Catalyzed IMHA Reactions of Certain Aryl Propargyl Ethers, Aryl Propargylates, and Aryl Propargyl Amine Derivatives

entry	substrate[a]	products[b]		yield[c] (%)
1	 **2b**	 **3b**		66
2	 **2c**	 **3c**		73
3	 **2d**	 **3d**		90
4	 **2e**	 **3e**	 **4e**	40 (**3e**) 13 (**4e**)
5	 **2f**	 **3f**	 **4f**	17 (**3f**) 80 (**4f**)
6	 **2g**	 **3g**	 **4g**	39 (**3g**) 39 (**4g**)
7	 **2h**	 **3h**		62
8	 **2i**	 **3i**	 **4i**	41 (**3i**) 31 (**4i**)
9	 **2j**	 **4j**		58
10	 **2k**	 **3k**		60
11	 **2l**	 **3l**		94
12	 **2m**	 **3m**		71
13	 **2n**	 **3n**		81
14	 **2o**	 **3o**		79
15	 **2p**	 **3p**		52
16	 **2q**	 **3q**		75

[a]The substrates were readily prepared by conventional methods (see the SI). [b]Conditions used for effecting the IMHA reactions shown are given in the Experimental Section and/or the SI. [c]All yields cited are of isolated and chromatographically purified materials.

(12) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563.

(13) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.

(14) See the Supporting Information for experimental details.

consistent with that of Echavarren,[5b] who has invoked related processes to account for the formation of 2-allenyl indoles from certain *N*-propargyl tryptophans in the presence of complex **1**.[5b]

When aryl propargyl amines are used as substrates for the IMHA reactions, the third group attached to nitrogen has a significant impact on the nature of the observed product. Thus, subjection of the *N*-Boc protected compound **2m** (entry 12) to the same reaction conditions as used earlier afforded oxazolidinone **3m**[17] in 71% yield and as the exclusive product of reaction. In contrast, replacement of the Boc group on nitrogen with a tosyl residue provided substrates that readily cyclized to the corresponding dihydroquinolines (see entries 13 and 14). Substrate **2p**, possessing an electron-withdrawing chloro-substituent on the aromatic ring, cyclized as expected to afford the corresponding dihydroquinoline derivative **3p** in 52% yield (entry 15). Compound **2q**, bearing a more easliy removed 2-nitrobenzenesulfonyl (Ns) nitrogen protecting group,[18] also reacted in the presence of complex **1** to give the corresponding dihydroquinoline derivative **3q** in good yield (75%, entry 16).

The protocols reported here provide an operationally simple method for effecting IMHA reactions that proceed under exceptionally mild conditions and in a time-efficient manner. A number of important heterocyclic motifs including 2*H*-chromenes, coumarins, benzofurans, and dihydroquinolines can thus be formed expeditiously from readily accessible starting materials.

(15) (a) Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. *Chem. Pharm. Bull.* **1992**, *40*, 1148. (b) Ishikawa, T.; Nagai, K.; Ohkubo, N.; Ishii, H. *Heterocycles* **1994**, *39*, 371.

(16) We thank a referee for useful suggestions regarding the reaction pathway proposed in Scheme 2.

(17) Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023.

(18) (a) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. (b) Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186.

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Experimental Section

Compound 3a. A magnetically stirred solution of aryl propargyl ether (**2a**)[19] (40 mg, 0.30 mmol) in CH_2Cl_2 (4 mL) maintained at 18 °C was treated with (acetonitrile)[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (**1**) (2.4 mg, 1 mol %). The resulting solution was stirred at 18 °C for 1 h then concentrated under reduced pressure and the ensuing yellow oil was subjected to flash column chromatography[20] (silica gel, hexane) to give, after concentration of the appropriate fractions (R_f 0.3 in 1:49 v/v ethyl acetate/hexane), chromene **3a**[21] (25 mg, 62%) as a clear, colorless oil. ^{1}H NMR (300 MHz) δ 7.13−7.08 (1H, m), 6.96−6.95 (1H, d, J = 7.2 Hz), 6.89−6.84 (1H, m), 6.78 (1H, d, J = 7.8 Hz), 6.43 (1H, d, J = 9.9 Hz), 5.80−5.74 (1H, m), 4.83 (2H, broad s); ^{13}C NMR (75 MHz) δ 154.0, 129.1, 126.5, 124.5, 122.3, 121.9, 121.3, 115.7, 65.5; IR ν_{max} (NaCl) 1640, 1608, 1488, 1458, 1229, 1201, 1117, 1043, 941, 756 cm^{-1}; MS (EI, 70 eV) *m*/*z* 132 ($M^{+\bullet}$, 96%), 131 (100), 103 (56), 77 (61), 51 (78); HRMS *m*/*z* calcd for C_9H_8O $M^{+\bullet}$ 132.0575, found 132.0572.

Acknowledgment. We thank the Institute of Advanced Studies at The Australian National University and the Australian Research Council (ARC) for generous financial support. R.S.M. is the grateful recipient of an ARC Australian Postdoctoral Fellowship.

Supporting Information Available: Detailed procedures and full characterization data for all new compounds and ^{1}H and ^{13}C NMR spectra for compounds **2g**, **2p**, **2q**, **3a**−**i**, **3k**−**q**, **4e**−**g**, **4i**, and **4j**. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

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Preparation of some angularly substituted and highly functionalized quinolizidines as building blocks for the synthesis of various alkaloids and related scaffolds of medicinal interest

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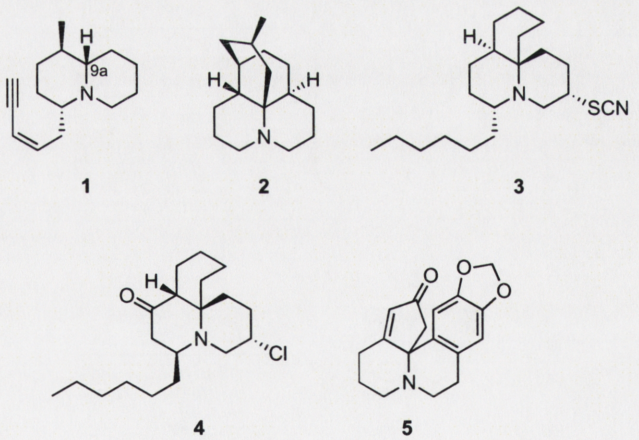
ABSTRACT

The epimeric forms of the angularly substituted quinolizidine **6**, representing potentially useful building blocks for the synthesis of various alkaloids, have been prepared via a pathway involving two consecutive ring-closing metathesis reactions. Variously hydroxy-protected derivatives (**21**, **22**, and **26–29**) of these compounds have also been generated.

1. Introduction

Many alkaloids incorporate the quinolizidine framework, and those variants lacking an angular substituent at C9a represent a large and important class of natural product that displays a range of interesting biological properties.[1,2] Such compounds have been isolated from both marine and terrestrial organisms including bacteria, fungi, higher plants, invertebrates, and vertebrates.[1,2] For example, quinolizidine 217A (**1**) is an amphibian alkaloid isolated from skin extracts of the Madagascan frog *Mantella baroni*.[3] Many additional and structurally more complex alkaloids incorporate an embedded quinolizidine unit. Representative examples of this type of system include lycopodine (**2**) (a lycopodium alkaloid that displays a curare-like paralyzing activity),[4] cylindricine B (**3**) (isolated from the ascidian *Clavelina cylindrical* collected off the East Coast of Tasmania),[5] and the structurally related fasicularin (**4**) (isolated from the marine invertebrate *Nephteis fasixcularis* and displaying selective activity against certain DNA repair-deficient organisms).[6] Embedded quinolizidines also represent scaffolds of interest from a medicinal chemistry perspective[7] and/or are encountered as precursors to other natural products.[8] For example, compound **5** has served as a key intermediate in a recently reported synthesis of the intriguing and cytotoxic alkaloid cephalotaxine,[8] derivatives of which have been subjected to clinical trails for the treatment of acute human leukemia.[9]



2. Results and discussion

As part of an ongoing program within our laboratories to establish synthetic routes to various classes of alkaloid,[10] we identified the epimeric forms of the angularly substituted quinolizidine **6** as potentially useful building blocks for the assembly of compounds

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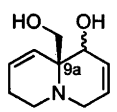
such as **2**–**5** as well as related systems. Thus, for example, manipulation of the angular hydroxymethyl group within compound **6** should provide a system that could engage in 6-*exo*-*trig* radical cyclization processes to give the tricyclic ring systems associated with alkaloids **3** and **4**. On the other hand, the enone generated by oxidation of the allylic alcohol moiety within compound **6** could engage in various cycloaddition reactions to give alternatively annulated systems, while the isomeric enone that would be accessible through the application of Wharton transposition chemistry[11] could engage in related processes to give benzannulated derivatives resembling the ABC-substructure associated with compound **5**. Furthermore, a combination of the radical cyclization and cycloaddition chemistries just mentioned could provide access to the complete tetracyclic framework of the same target.

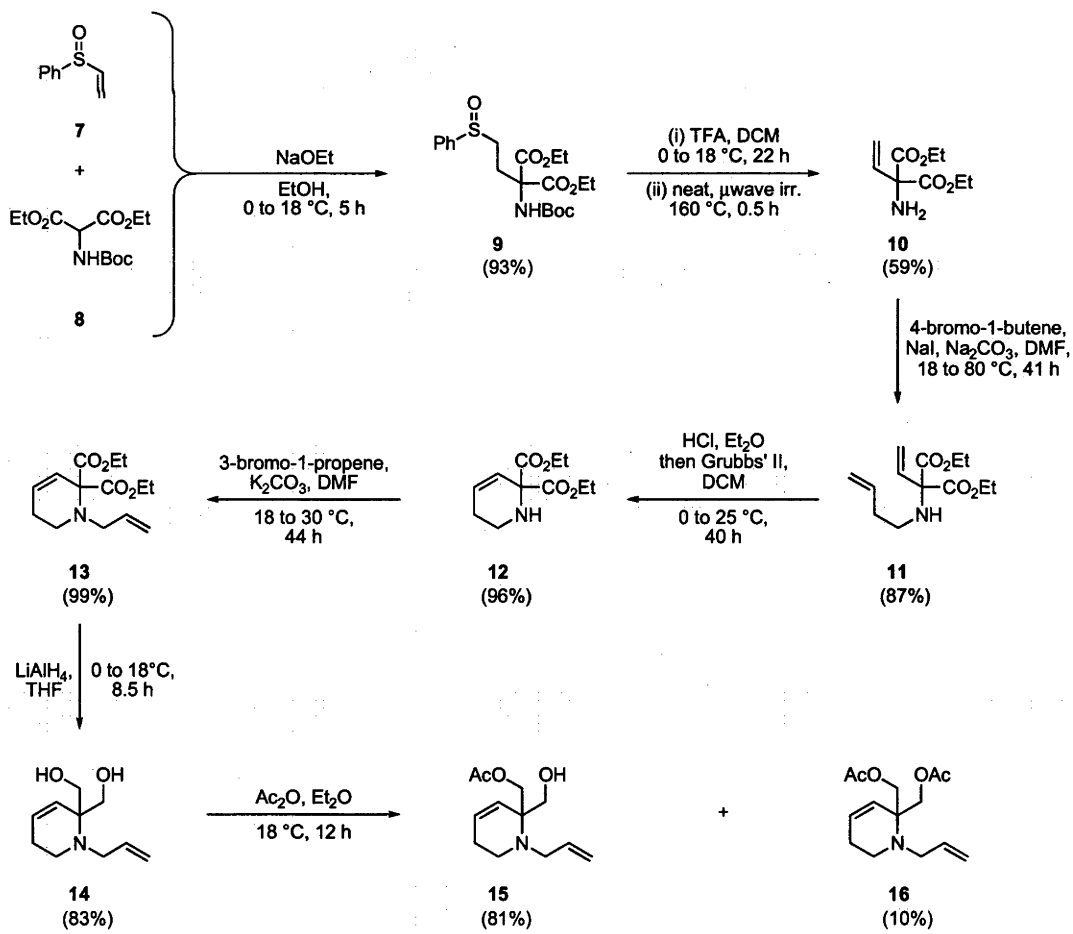
On the basis of the above-mentioned possibilities we sought to develop syntheses of two epimeric forms of the previously unreported but potentially versatile compound **6**, as well as certain hydroxy-protected precursors. Herein we describe such syntheses, which are capable of delivering the target compounds at useful scale and which should be readily adapted to the preparation of the homologous indolizidines. Furthermore, and as detailed below, the route that has been developed should be amenable to the synthesis of such systems in chiral, non-racemic form.



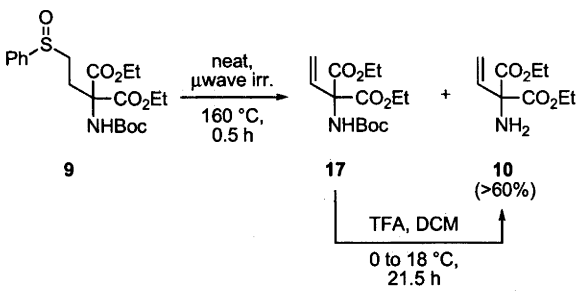
6

The initial steps of the synthetic route we have established, and that led to the racemic modification of compound **6**, are shown in Scheme 1. Thus, the sequence starts with the conjugate addition of the anion derived from the commercially available α-aminomalonate derivative **8** to the similarly accessible vinyl sulfoxide **7**. The Boc-protecting group within adduct **9**, which was obtained in near quantitative yield, could be removed using trifluoroacetic acid (TFA) and the resulting primary amine (quantitative yield) was subjected to heating at 160 °C in a microwave reactor. This led to the thermal elimination of the elements of phenylsulfenic acid[12] and the production of the α-amino-α-vinylmalonate derivative **10** in 59% yield. Reaction with 4-bromo-1-butene in the presence of base then provided diene **11** (87% yield at 70% conversion). Treatment of the HCl-salt of compound **11** with Grubbs' second generation catalyst[13] gave, after work-up with base, the monounsaturated piperidine **12** (96%) that could be *N*-allylated with allyl bromide to give diene **13** in 99% yield at 81% conversion. Reduction of both ester residues within compound **13** afforded the bis-hydroxymethylated compound **14** (83%) that was acetylated under conventional conditions to give a ca. 8:1 mixture of the chromatographically separable mono- and di-acetates, **15** (81%) and **16** (10%), respectively.

A useful modification to the early parts of the sequence just described involved (Scheme 2) taking the crude samples of malonate **9**, which has proven to be a rather intractable compound, and subjecting this to microwave irradiation. In this way varying mixtures of the chromatographically separable amine **10** and its Boc-protected congener **17** could be obtained. The latter product was contaminated with significant quantities of phenylsulfenic acid as well as other impurities but upon deprotection with TFA



Scheme 1.



9 17 10

Scheme 2.

and subjection of the crude reaction mixture to chromatography then additional quantities of pure samples of compound **10** could be obtained. This was found to be a more convenient and practical means for generating preparatively useful quantities of compound **10** than the protocol originally devised and shown in Scheme 1.

The completion of the syntheses of the epimeric forms of target **6** involved (Scheme 3) oxidation of mono-ol **15** under Swern conditions and reaction of the ensuing and rather unstable aldehyde **18** with vinyl magnesium bromide to give a ca. 2:1 mixture of the epimeric forms of the compound **19**. The mixture was immediately acetylated to give the corresponding mixture of triene di-acetates **20** (80% from **15**) that was then subjected to ring-closing metathesis using Grubbs' second generation catalyst.[13] The resulting quinolizidines **21** (62%) and **22** (25%) could be readily separated by flash chromatography and each was subjected to extensive spectroscopic characterization. An equivalent analysis of two related compounds (vide infra) suggests that the major product **21** possesses the illustrated *cis*-relationship between the acetoxy and acetoxymethyl groups. This is consistent with the notion that a chelation-controlled process[14] is preferred in the addition reaction **18**→**19** that establishes the relevant stereogenic center. Independent hydrolysis of each of compounds **21** and **22** using K_2CO_3 in methanol led to the target diols **6a** (98%) and **6b** (97%), respectively. As with all of the precursors to these compounds, except sulfoxide **9**, they were each obtained as oils.

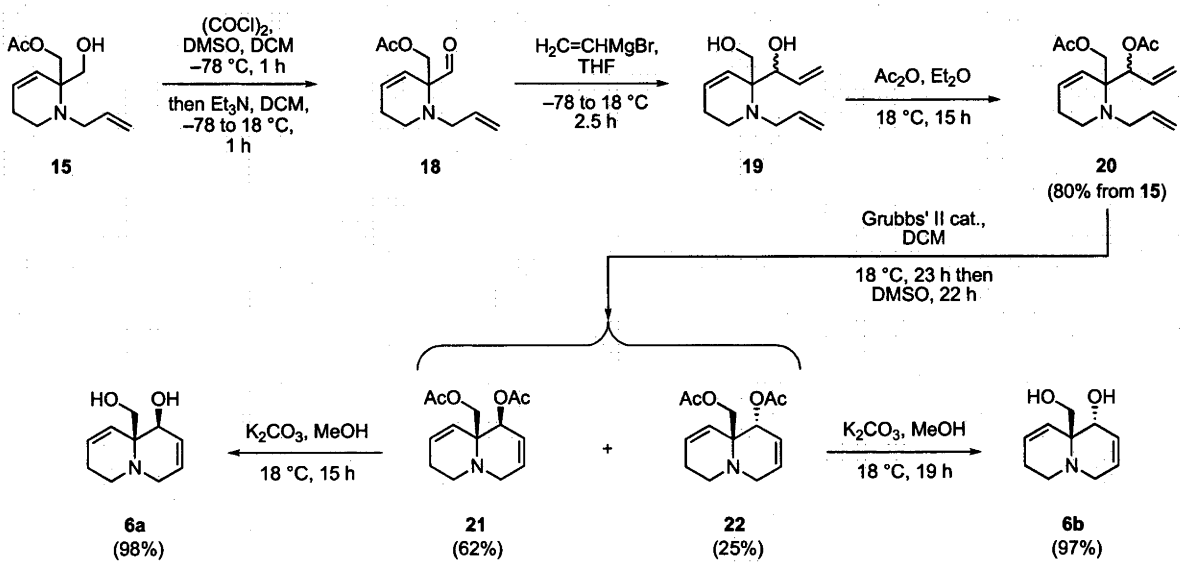
A simple variation on the reaction sequence shown in Scheme 3 has allowed for the preparation of mono-protected derivatives of compounds **6a** and **6b**. Thus, reaction of compound **15** with MOM-chloride in the presence of Hünig's base then treatment of the resulting ether/acetate (83%) with K_2CO_3 in methanol afforded the expected alcohol (99%) that could be oxidized to the corresponding aldehyde **23** under Swern conditions (Scheme 4). Vinylation of this last compound in the same manner as employed earlier gave a ca. 3:1 mixture of the epimeric allylic alcohols **24** that were not separated but committed, as a mixture, to acetylation under conventional conditions. The resulting ca. 3:1 mixture of the epimeric forms of acetate **25** (91% from **23**) was then subjected to ring-closing metathesis[13] and so affording a chromatographically separable mixture of the quinolizidine derivatives **26** (48% at 57% conversion) and **27** (16% at 57% conversion). Each of these was then independently treated with K_2CO_3 in methanol and thereby affording the target mono-ols **28** (99%) and **29** (95%), respectively. The illustrated stereochemistries in compounds **26** and **27** were established using NOESY techniques. In particular, in the former isomer a strong interaction was observed between the proton resonance due to the acetoxymethyl group and that due to the methyl group of the MOM ether. As expected, the equivalent interaction in compound **27** was much less pronounced. These results served to establish the illustrated (relative) configurations for compounds **6a**, **6b**, **21**, **22**, and **26**–**29**.

The reaction sequences shown in Schemes 3 and 4 would be capable of delivering enantiomerically pure forms of the title compounds **6a**, **6b**, **28**, and **29** if the enzymatic desymmetrization of either the diol **14** or diacetate **16** could be achieved. The prospects of achieving this seem rather good given the recent report by Donohoe and co-workers.[15] Accordingly, work directed toward such ends is now underway.

3. Experimental

3.1. General experimental procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ)[multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet or combinations of the above. The residual $CHCl_3$ peak (δ 7.26) was used as a reference for ^{1}H NMR spectra, and



15 18 19 20

6a (98%) 21 (62%) 22 (25%) 6b (97%)

Scheme 3.

the central peak (δ 77.0) of the $CDCl_3$ 'triplet' was used as a reference for proton-decoupled ^{13}C NMR spectra. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in positive ionization mode.

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 F_{254} plates as supplied by Merck. Eluted plates were visualized with ninhydrin. The retardation factor (R_f) was quoted to the nearest 0.1. Flash column chromatography[16] was performed using silica gel 60 (0.040–0.0063 mm) as the stationary phase and the analytical reagent (AR) or HPLC grade solvents indicated.

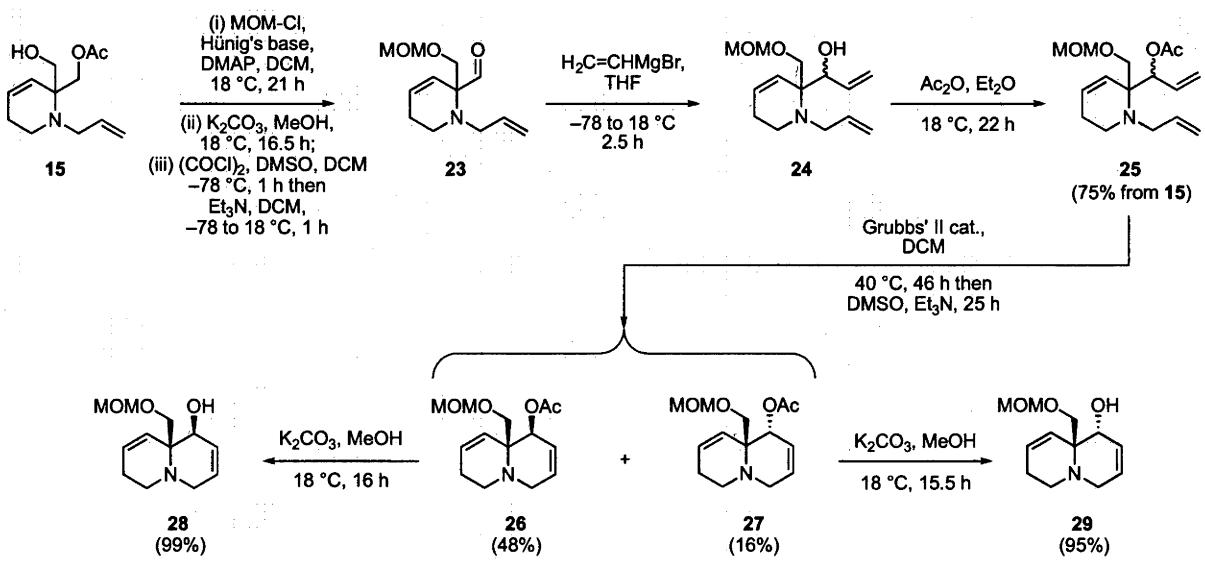
Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF) and diethyl ether (ether) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[17] Methanol was distilled from its magnesium alkoxide salt. CH_2Cl_2 was distilled from calcium hydride. Triethylamine was distilled from and stored over potassium hydroxide pellets.

3.2. Specific chemical conversions

3.2.1. Compound ***9***. Sodium metal (490 mg, 21.3 g atom) was added in four portions to magnetically stirred ethanol (30 mL) maintained under nitrogen at 18 °C. After all of the sodium had reacted the resulting solution of sodium ethoxide in ethanol was cooled to 0 °C and 2-[N-(*tert*-butoxycarbonyl)amino]malonate (**8**) (4.79 mL, 17.8 mmol, ex. Aldrich) was added. The resulting mixture was maintained at this temperature for 1 h then phenyl vinyl sulfoxide (**7**) (2.61 mL, 19.5 mmol, ex. Aldrich) was added dropwise. The reaction mixture so-formed was maintained at this temperature for 2 h then warmed to 18 °C and maintained at this temperature for a further 2 h. After this time acetic acid was added until the solution became acidic and the reaction mixture was then concentrated under reduced pressure. The ensuing yellow oil was dissolved in ethyl acetate (50 mL) and the resulting solution was washed with sodium bicarbonate (3×15 mL of a saturated solution). The combined aqueous washings were extracted with ethyl acetate (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 97:2:1 v/v/v dichloromethane/methanol/triethylamine elution). Concentration of the appropriate fractions (R_f=0.2) afforded *title compound* ***9*** (7.08 g, 93%) as a white, crystalline solid, mp=72–75 °C [Found: $(M+H)^+$, 428.1751. $C_{20}H_{29}NO_7S$ requires $(M+H)^+$, 428.1743]. ^1H NMR (300 MHz) δ 7.62–7.56 (m, 2H), 7.55–7.42 (m, 3H), 5.91 (br s, 1H), 4.19 (m, 4H), 2.85–2.44 (m, 4H), 1.40 (s, 9H), 1.20 (td, J=7.2 and 0.9 Hz, 6H); ^{13}C NMR (75 MHz) δ 167.6, 167.5, 154.0, 143.4, 131.2, 129.3, 124.1, 80.7, 65.5, 62.9, 62.8, 52.0, 28.2, 26.2, 14.0(0), 13.9(8) (additional signals attributed to carbamate rotamers); ν_{max} (NaCl) 3424, 2979, 1739, 1718, 1479, 1367, 1257, 1203, 1159, 1088, 1026, 749 cm^{-1}; MS (ESI) *m/z* 450 [$(M+Na)^+$, 48%], 428 [$(M+H)^+$, 8], 372 (9), 328 (100), 202 (20), 174 (48).

3.2.2. Compound ***10***. *Step i.* Trifluoroacetic acid (0.13 mL, 1.64 mmol) was added to a magnetically stirred solution of compound **9** (140 mg, 0.33 mmol) in dichloromethane (5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was kept at this temperature for 0.5 h, then warmed to 18 °C and maintained at this temperature for a further 21 h. After this time sodium bicarbonate (3 mL of a saturated aqueous solution) was added, the phases separated and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford *diethyl 2-amino-2-[2-(phenylsulfinyl)ethyl]malonate* (1.70 g, 100%) as a clear, light-yellow oil [Found: $(M+H)^+$, 328.1205. $C_{15}H_{21}NO_5S$ requires $(M+H)^+$, 328.1219]. ^1H NMR (300 MHz) δ 7.64–7.56 (m, 2H), 7.54–7.44 (m, 3H), 4.18 (dq, J=7.2, 3.3 Hz, 4H), 3.12–2.96 (m, 1H), 2.90–2.80 (m, 1H), 2.40–2.28 (m, 1H), 2.20–2.08 (m, 1H), 1.92 (br s, 2H), 1.23(3) (t, J=7.2 Hz, 3H), 1.22(7) (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 170.6, 143.2, 130.9, 129.2, 129.1, 123.9, 64.7, 62.1, 51.1, 27.8, 13.9; ν_{max} 3385, 2982, 1736, 1477, 1444, 1369, 1250, 1206, 1188, 1086, 1037, 750, 693 cm^{-1}; MS (ESI) *m/z* 350 [$(M+Na)^+$, 100%], 328 [$(M+H)^+$, 84], 256 (16), 202 (18), 174 (62).

Step ii. A neat sample of diethyl 2-amino-2-[2-(phenylsulfinyl)ethyl]malonate (107 mg, 0.33 mmol), obtained as described immediately above, was heated at 160 °C for 0.5 h in a microwave reactor and, after cooling, the ensuing brown oil was



Scheme 4.

subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution). Concentration of the appropriate fractions (R_f=0.3 in 97:3 v/v dichloromethane/methanol) afforded *title compound* **10** (39 mg, 59%) as a clear, light-yellow oil [Found: $(M+H)^+$, 202.1070. $C_9H_{15}NO_4$ requires $(M+H)^+$, 202.1079]. ^{1}H NMR (300 MHz) δ 6.31 (dd, J=17.4, 10.5 Hz, 1H), 5.49 (dd, J=17.4, 0.6 Hz, 1H), 5.33 (dd, J=10.5, 0.6 Hz, 1H), 4.28–4.18 (m, 4H), 2.11 (br s, 2H), 1.27 (td, J=7.2, 0.3 Hz, 6H); ^{13}C NMR (75 MHz) δ 170.5, 134.8, 116.5, 67.1, 62.3, 14.1; ν_{max} (NaCl) 3392, 2984, 1738, 1368, 1299, 1257, 1197, 1038 cm^{-1}; MS (ESI) m/z 224 [$(M+Na)^+$, 100%], 202 [$(M+H)^+$, 20], 128 (80), 102 (84), 100 (88).

3.2.3. Compound ***11***. Sodium carbonate (6.07 g, 57.3 mmol), sodium iodide (5.14 mg, 34.3 mmol), and 4-bromo-1-butene (5.81 mL, 57.3 mmol) were added to a magnetically stirred solution of compound **10** (5.76 mg, 28.6 mmol) in *N*,*N*-dimethylformamide (70 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at 80 °C for 41 h in a reaction flask fitted with a Liebig condenser. After this time, the reaction mixture was cooled to 18 °C then diluted with dichloromethane (150 mL) and water (30 mL). The separated aqueous layer was extracted with dichloromethane (3×50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution) and so affording two major fractions, A and B.

Concentration of fraction A (R_f=0.5, 97:3 v/v dichloromethane/methanol) afforded the *title compound* ***11*** (4.45 g, 87% at 70% conversion) as a clear, light-yellow oil [Found: $(M+H)^+$, 256.1541. $C_{13}H_{21}NO_4$ requires $(M+H)^+$, 256.1549]. ^{1}H NMR (300 MHz) δ 6.23 (dd, J=17.4, 10.5 Hz, 1H), 5.82–5.70 (m, 1H), 5.55 (dd, J=17.4, 1.2 Hz, 1H), 5.40 (dd, J=10.5, 1.2 Hz, 1H), 5.18–5.00 (m, 2H), 4.23 (q, J=7.2 Hz, 4H), 2.50 (t, J=6.6 Hz, 2H), 2.28 (q, J=6.6 Hz, 2H), 1.25 (t, J=7.2 Hz, 6H) (signal due to NH proton not observed); ^{13}C NMR (75 MHz) δ 169.2, 135.8, 132.5, 118.1, 116.6, 71.0, 61.8, 42.3, 34.3, 13.9; ν_{max} (NaCl) 3352, 3078, 2981, 1738, 1640, 1465, 1447, 1391, 1367, 1255, 1198, 1047, 991, 936, 918, 860 cm^{-1}. MS (ESI) m/z 278 [$(M+Na)^+$, 51%], 256 [$(M+H)^+$, 30], 182 (80), 108 (100).

Concentration of fraction B (R_f=0.3, 97:3 v/v dichloromethane/methanol) afforded the starting amine **10** (1.75 g, 30% recovery) as a clear, light-yellow oil.

3.2.4. Compound ***12***. Hydrochloric acid (0.03 mL of a 10 M aqueous solution) was added to a magnetically stirred solution of compound **11** (108 mg, 0.42 mmol) in diethyl ether (1.5 mL) maintained under nitrogen at 0 °C. The ensuing mixture was warmed to 18 °C and after 0.5 h at this temperature it was concentrated under reduced pressure. A magnetically stirred solution of the ensuing yellow oil in dichloromethane (7 mL) was treated with Grubbs' second generation catalyst (18 mg, 21.2 μmol) then warmed to 25 °C and maintained at this temperature for 40 h. After this time sodium bicarbonate (3 mL of a saturated solution) was added to the reaction mixture and the phases separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a brown oil. This material was subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution) and concentration of the appropriate fractions (R_f=0.2 in 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***12*** (92 mg, 96%) as a clear, colorless oil [Found: $(M+H)^+$, 228.1225. $C_{11}H_{17}NO_4$ requires $(M+H)^+$, 228.1236]. ^{1}H NMR (300 MHz) δ 6.14 (dt, J=10.2, 3.6 Hz, 1H), 5.97 (td, J=10.2, 1.8 Hz, 1H), 4.22 (q, J=7.2 Hz, 4H), 3.00 (t, J=5.7 Hz, 2H), 2.84 (br s, 1H), 2.13–2.05 (m, 2H), 1.26 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz) δ 169.6, 129.7, 122.9, 66.4, 61.9, 39.8, 24.5, 13.9; ν_{max} (NaCl) 3353, 2981, 1738, 1453, 1274, 1230, 1199, 1133, 1107, 1078, 1027 cm^{-1}; MS (ESI) m/z 250 [$(M+Na)^+$, 14%], 228 [$(M+H)^+$, 58], 154 (100), 126 (89).

3.2.5. Compound ***13***. 3-Bromo-1-propene (1.36 mL, 15.8 mmol) and potassium carbonate (2.28 g, 16.5 mmol) were added to a magnetically stirred solution of compound **12** (3.41 g, 15.0 mmol) in *N*,*N*-dimethylformamide (20 mL) maintained under nitrogen at 18 °C. The ensuing mixture was warmed to 30 °C and maintained at this temperature for 44 h then cooled and diluted with dichloromethane (40 mL) and water (10 mL). The separated aqueous layer was extracted with dichloromethane (3×20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and thereby affording two major fractions, A and B.

Concentration of fraction A (R_f=0.3, 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***13*** (3.25 g, 99% at 81% conversion) as a clear, yellow oil [Found: $(M+H)^+$, 268.1560. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^{1}H NMR (300 MHz) δ 6.08–5.98 (m, 1H), 5.93–5.75 (m, 2H), 5.19 (d, J=17.1 Hz, 1H), 5.10 (d, J=10.2 Hz, 1H), 4.28–4.16 (m, 4H), 3.30 (d, J=6.0 Hz, 2H), 2.83–2.76 (m, 2H), 2.24–2.10 (m, 2H), 1.32–1.23 (m, 6H); ^{13}C NMR (75 MHz) δ 168.8, 136.1, 128.7, 124.1, 116.1, 71.6, 61.0, 55.2, 42.6, 25.0, 13.8; ν_{max} 2980, 2924, 1729, 1641, 1395, 1366, 1251, 1204, 1158, 1142, 1111, 1064, 1037 cm^{-1}; MS (ESI) m/z 290 [$(M+Na)^+$, 70%], 268 [$(M+H)^+$, 23], 194 (100).

Concentration of fraction B (R_f=0.2, 9:1 v/v dichloromethane/ethyl acetate) afforded the starting piperidine **12** (658 mg, 19% recovery) as a clear, colorless oil.

3.2.6. Compound ***14***. Lithium aluminum hydride (19.5 mL of a 1.0 M solution in THF, 19.5 mmol) was added to a magnetically stirred solution of compound **13** (1.49 g, 5.54 mmol) in THF (53 mL) maintained under nitrogen at 0 °C. After 2 h the reaction mixture was warmed to 18 °C and maintained at this temperature for a further 6.5 h then THF (50 mL) was added. The ensuing mixture was cooled to 0 °C then water (0.75 mL), sodium hydroxide (0.75 mL of a 15% aqueous solution), and water (2.25 mL) were added dropwise and in the specified order. The resulting mixture was warmed to 18 °C, maintained at this temperature for 0.25 h then dried ($MgSO_4$). After 0.25 h the reaction mixture was filtered and the solids thus retained were washed with THF (250 mL). The combined filtrates were concentrated under reduced pressure to afford the *title diol* ***14*** (850 mg, 83%) as a clear, yellow oil [$(M+H)^+$, 184.1339. $C_{10}H_{17}NO_2$ requires $(M+H)^+$, 184.1338]. ^{1}H NMR (300 MHz) δ 6.15 (dt, J=6.0, 3.9 Hz, 1H), 5.86–5.70 (m, 1H), 5.44 (d, J=10.2 Hz, 1H), 5.26–5.10 (m, 2H), 3.65 (d, J=11.1 Hz, 2H), 3.43 (d, J=11.1 Hz, 2H), 3.28 (d, J=6.0 Hz, 2H), 2.91 (t, J=5.7 Hz, 2H), 2.42 (s, 2H), 2.14–2.05 (m, 2H); ^{13}C NMR (75 MHz) δ 136.4, 130.2, 129.2, 116.8, 63.0, 62.2, 51.2, 43.0, 25.0; ν_{max} (NaCl) 3400, 2918, 1641, 1417, 1392, 1279, 1077, 1043, 992, 918, 830, 732 cm^{-1}; MS (ESI) m/z 206 [$(M+Na)^+$, 7%], 184 [$(M+H)^+$, 44], 70 (100).

3.2.7. Compounds ***15*** *and* ***16***. Acetic anhydride (0.46 mL, 4.91 mmol) was added to a magnetically stirred solution of compound **14** (900 mg, 4.91 mmol) in diethyl ether (20 mL) maintained under nitrogen at 18 °C. After 12 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1→4:1 v/v hexane/ethyl acetate gradient elution) affording two major fractions, A and B.

Concentration of fraction A (R_f=0.7 in 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***16*** (130 mg, 10%) as a clear, colorless oil [Found: $(M+H)^+$, 268.1549. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^{1}H NMR (300 MHz) δ 5.97 (dt, J=9.9, 3.9 Hz, 1H), 5.80–5.64 (m, 1H), 5.54 (dt, J=10.2, 2.1 Hz, 1H), 5.18 (dq, J=17.1,

1.5 Hz, 1H), 5.08 (dq, J=9.9, 1.5 Hz, 1H), 4.24 (d, J=11.4 Hz, 2H), 4.08 (d, J=11.4 Hz, 2H), 3.26 (dd, J=5.7, 1.2 Hz, 2H), 2.71 (t, J=5.7 Hz, 2H), 2.10–2.00 (m, 2H), 2.05 (s, 6H); ^{13}C NMR (75 MHz) δ 170.6, 137.1, 129.0, 127.5, 116.3, 64.6, 58.7, 52.9, 43.1, 25.5, 20.9; ν_{max} (NaCl) 2961, 2917, 2832, 1745, 1641, 1381, 1231, 1044, 916 cm^{-1}; MS (ESI) m/z 268 [(M+H)$^+$, 37%], 226 (6), 208 (5), 166 (7), 148 (71), 69 (100).

Concentration of fraction B (R_f=0.1 in 4:1 v/v hexane/ethyl acetate) gave the *title compound* ***15*** (896 mg, 81%) as a clear, colorless oil [Found: (M+H)$^+$, 226.1432. $C_{12}H_{19}NO_3$ requires (M+H)$^+$, 226.1443]. ^{1}H NMR (300 MHz) δ 6.08–5.98 (m, 1H), 5.82–5.65 (m, 1H), 5.48–5.38 (m, 1H), 5.24–5.08 (m, 2H), 4.15 (d, J=11.7 Hz, 1H), 4.08 (d, J=11.7 Hz, 1H), 3.63–3.47 (m, 2H), 3.33 (d, J=10.2 Hz, 2H), 2.99 (s, 1H), 2.94–2.82 (m, 1H), 2.68 (td, J=11.1, 3.9 Hz, 1H), 2.28–2.10 (m, 1H), 2.06 (s, 3H), 1.96 (d, J=17.4 Hz, 1H); ^{13}C NMR (75 MHz) δ 170.6, 136.2, 129.6, 128.9, 117.0, 64.0, 62.3, 60.8, 51.4, 42.8, 25.4, 20.9; ν_{max} (NaCl) 3444, 2918, 2833, 1742, 1641, 1381, 1236, 1043, 918 cm^{-1}; MS (ESI) m/z 226 [(M+H)$^+$, 85%], 166 (77), 148 (52), 136 (46), 70 (100).

3.2.8. Improved procedure for the preparation of compound ***10****. Step i.* Sodium metal (490 mg, 21.3 g atom) was added in four portions to magnetically stirred ethanol (30 mL) maintained under nitrogen at 18 °C. After all of the sodium had reacted the resulting solution of sodium ethoxide in ethanol was cooled to 0 °C and 2-[*N*-(*tert*-butoxycarbonyl)-amino]malonate (**8**) (4.79 mL, 17.8 mmol, ex. Aldrich) was added and maintained at this temperature for 1 h then phenyl vinyl sulfoxide (**7**) (2.61 mL, 19.5 mmol, ex. Aldrich) was added dropwise. The ensuing reaction mixture was maintained at this temperature for 2 h, then warmed to 18 °C and held at this temperature for a further 2 h. After this time acetic acid was added until the solution became acidic and the reaction mixture was then concentrated under reduced pressure. The ensuing yellow oil was dissolved in ethyl acetate (30 mL) and washed with sodium bicarbonate (3×20 mL of a saturated aqueous solution). The aqueous washings were extracted with ethyl acetate (3×10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. This material, which was presumed to contain compound **9**, was evenly divided between ten 10 mL Pyrex™ microwave reaction vials and these were then subjected (neat) to simultaneous microwave irradiation under the same conditions as described earlier. The cooled reaction mixtures were then combined and subjected to flash chromatography (silica, 90:9:1 v/v/v hexane/ethyl acetate/triethylamine elution) affording two major fractions, A and B.

Concentration of fraction A (R_f=0.6 in 9:1 v/v dichloromethane/ethyl acetate) afforded a ca. 2:3 mixture (as determined by ^{1}H NMR spectroscopic analysis) of the compound **17** and phenylsulfenic acid.

Concentration of fraction B (R_f=0.3, 97:3 v/v dichloromethane/methanol) afforded the *title compound* ***10*** as a light-yellow oil. This material was identical, in all respects, with an authentic sample obtained as described above.

Subjection of a portion of fraction A to flash chromatography (9:90:1 v/v/v ethyl acetate/hexane/triethylamine elution) and concentration of the appropriate fractions (R_f=0.6 in 9:1 v/v dichloromethane/ethyl acetate) gave a spectroscopically pure sample of *compound* ***17*** as a clear, colorless oil [Found: (M+Na)$^+$, 324.1426. $C_{14}H_{23}NO_6$ requires (M+Na)$^+$, 324.1423]. ^{1}H NMR (300 MHz) δ 6.50 (dd, J=17.4, 10.8 Hz, 1H), 6.09 (br s, 1H), 5.42–5.26 (m, 2H), 4.40–4.14 (m, 4H), 1.43 (s, 9H), 1.26 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz) δ 167.0, 153.6, 132.7, 116.3, 80.3, 67.1, 62.7, 28.1, 13.9; ν_{max} (NaCl) 3435, 2981, 2937, 1743, 1724, 1484, 1368, 1271, 1254, 1205, 1166, 1059, 1022, 986 cm^{-1}; MS (ESI) m/z 324 [(M+Na)$^+$, 46%], 246 (40), 202 (100), 128 (95).

Step ii. A magnetically solution of the 2:3 mixture of the compound **17** and phenylsulfenic acid (obtained as described immediately above) in dichloromethane (50 mL) maintained at 0 °C was treated with trifluoroacetic acid (7.5 mL, 97.4 mmol). After 0.5 h the reaction mixture was warmed to 18 °C, stirred at this temperature for 16 h then treated with sodium bicarbonate (30 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3×30 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (9:90:1 v/v/v ethyl acetate/hexane/triethylamine elution) and concentration of the relevant fractions (R_f=0.3 in 97:3 v/v dichloromethane/methanol) gave compound **10** in sufficient quantities to sustain the synthetic procedures defined below. This material was identical, in all respects, with an authentic sample obtained as described above.

3.2.9. Compound ***18****.* A solution of dimethyl sulfoxide (0.24 mL, 3.33 mmol) in dichloromethane (10 mL) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (0.19 mL, 2.22 mmol) in dichloromethane (6 mL) maintained under nitrogen at −78 °C. After 0.25 h a solution of compound **15** (250 mg, 1.11 mmol) in dichloromethane (10 mL) was added dropwise over 0.25 h. After 1 h a solution of triethylamine (0.62 mL, 4.44 mmol) in dichloromethane (10 mL) was added and the ensuing mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. Sodium bicarbonate (10 mL of a saturated aqueous solution) was then added and the phases separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *compound* ***18*** as a light-yellow oil, R_f=0.7 (in 9:1 v/v dichloromethane/ethyl acetate) [Found: (M+H)$^+$, 224.1285. $C_{12}H_{17}NO_3$ requires (M+H)$^+$, 224.1287]. ^{1}H NMR (300 MHz) δ 9.20 (s, 1H), 6.24–6.16 (m, 1H), 5.82–5.68 (m, 1H), 5.32–5.23 (m, 1H), 5.22–5.08 (m, 2H), 4.45 (d, J=11.7 Hz, 1H), 4.31 (d, J=11.7 Hz, 1H), 3.32–3.20 (m, 1H), 3.18–3.06 (m, 1H), 2.97–2.88 (m, 1H), 2.74–2.62 (m, 1H), 2.35–2.20 (m, 1H), 2.14–2.07 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz) δ 199.9, 170.5, 136.0, 133.1, 122.3, 117.4, 68.8, 63.0, 54.3, 42.1, 26.1, 21.0; ν_{max} (NaCl) 2921, 2817, 1746, 1377, 1234, 1078, 1045, 924, 711 cm^{-1}; MS (ESI) m/z 246 [(M+Na)$^+$, 20%], 224 [(M+H)$^+$, 12], 178 (62), 164 (51), 109 (100).

This somewhat unstable aldehyde was immediately subjected to the vinylation reaction described directly below.

3.2.10. Compound ***19****.* Vinyl magnesium bromide (5.55 mL of a 1.0 M solution in THF, 5.55 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **18** (obtained as described immediately above) in THF (20 mL) maintained under nitrogen at −78 °C. After 0.5 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 2 h, then warmed to 18 °C. After 1 h the reaction mixture was cooled to 0 °C then water (4 mL) and ammonium chloride (2 mL of a saturated aqueous solution) were added. The separated aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 2:1 mixture of the two diastereoisomeric forms of *compound* ***19*** as a light-yellow oil [Found: (M+H)$^+$, 210.1492. $C_{12}H_{19}NO_2$ requires (M+H)$^+$, 210.1494]. ^{1}H NMR (300 MHz) δ 6.30–5.65 (m, 3H), 5.50–4.90 (m, 5H), 4.26 (dd, J=27.0, 6.0 Hz, 1H), 3.85–3.10 (m, 4H), 3.20–2.50 (m, 2H), 2.25–1.80 (m, 4H); ^{13}C NMR (75 MHz) δ 137.6, 136.8, 136.5, 136.4, 132.3, 129.4, 127.4, 126.0, 117.5, 117.3, 116.7, 116.6, 75.2, 73.0, 64.7, 63.8, 63.4, 63.3, 51.3, 51.2, 43.8, 41.7, 25.4, 23.3; ν_{max} (NaCl) 3400, 2919, 1641, 1417, 1279, 1066, 994, 918 cm^{-1}; MS (ESI) m/z 232 [(M+Na)$^+$, 6%], 210 [(M+H)$^+$, 18], 192 (6), 70 (100).

3.2.11. Compound ***20****.* Acetic anhydride (0.31 mL, 3.33 mmol) was added to a magnetically stirred solution of compound **19** in diethyl ether (10 mL) maintained under nitrogen at 18 °C. After 15 h the

reaction mixture was concentrated was under reduced pressure and the ensuing yellow oil subjected to flash chromatography (silica, 19:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f=0.7 in 9:1 v/v dichloromethane/ethyl acetate) afforded a ca. 2:1 mixture of the two diastereoisomeric forms of the *title compound* ***20*** (260 mg, 80% over 3 steps) as a clear, light-yellow oil [Found: $(M+H)^+$, 294.1707. $C_{16}H_{23}NO_4$ requires $(M+H)^+$, 294.1705]. ^{1}H NMR (300 MHz) δ 6.10–5.40 (complex m, 5H), 5.30–5.00 (m, 3H), 4.40–3.95 (m, 2H), 3.67 (dm, J=14.7 Hz, 1H), 3.10–2.75 (m, 2H), 2.63–2.48 (m, 1H), 2.08 (s, 3H—minor diastereoisomer), 2.06 (s, 3H—major diastereoisomer), 2.04 (s, 3H—minor diastereoisomer), 2.03 (s, 3H—major diastereoisomer), 2.10–1.80 (m, 3H); ^{13}C NMR (75 MHz) δ 170.8, 170.6, 169.9, 137.4, 136.9, 133.7, 133.0, 130.1, 130.0, 127.0, 125.7, 117.4, 117.3, 116.2, 115.9, 75.8, 72.8, 64.1 62.5, 61.8, 61.7, 52.9, 52.6, 43.3, 42.8, 25.8, 25.7, 21.2, 21.1, 21.0, 20.9 (one signal obscured or overlapping); ν_{max} (NaCl) 2958, 2919, 2833, 1746, 1642, 1375, 1239, 1104, 1028, 918 cm^{-1}; MS (ESI) m/z 316 [$(M+Na)^+$, 1%], 294 [$(M+H)^+$, 15], 234 (23), 174 (52), 104 (51), 70 (100).

*3.2.12. Compounds **21** and **22**.* Grubbs' second generation catalyst (87 mg, 0.10 mmol) was added to a magnetically stirred solution of a ca. 2:1 mixture of the epimeric forms of compound **20** (300 mg, 1.02 mmol) in dichloromethane (50 mL) kept under nitrogen at 18 °C. The ensuing mixture was maintained at this temperature for 23 h then dimethyl sulfoxide (0.36 mL, 5.12 mmol) was added. After a further 22 h the reaction mixture was concentrated under reduced pressure and the ensuing brown residue was subjected to flash chromatography (silica, 9:1→4:1 v/v hexane/ethyl acetate gradient elution) and thereby affording two major fractions, A and B.

Concentration of fraction A (R_f=0.1, 9:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***22*** (69 mg, 25%) as a clear, light-yellow oil [Found: $(M+H)^+$, 266.1393. $C_{14}H_{19}NO_4$ requires $(M+H)^+$, 266.1392]. ^{1}H NMR (300 MHz) δ 5.94–5.82 (m, 2H), 5.62–5.48 (m, 2H), 5.27 (br s, 1H), 4.40 (dd, J=12.0, 2.1 Hz, 1H), 4.33 (dd, J=12.0, 2.1 Hz, 1H), 3.38–3.13 (m, 3H), 2.76–2.64 (m, 1H), 2.42–2.40 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.05–1.94 (m, 1H); ^{13}C NMR (75 MHz) δ 170.3, 128.1, 127.5, 126.8, 125.2, 73.8, 61.9, 56.5, 50.0, 46.2, 25.2, 21.2 (two signals obscured or overlapping); ν_{max} (NaCl) 2921, 2853, 1742, 1371, 1229, 1043 cm^{-1}; MS (ESI) m/z 288 [$(M+Na)^+$, 5%], 266 [$(M+H)^+$, 41], 206 (24), 146 (100).

Concentration of fraction B (R_f=0.1 in 4:1 v/v dichloromethane/ethyl acetate) afforded the *title compound* ***21*** (169 mg, 62%) as a clear, light-yellow oil [Found: $(M+H)^+$, 266.1388. $C_{14}H_{19}NO_4$ requires $(M+H)^+$, 266.1392]. ^{1}H NMR (300 MHz) δ 6.14–6.05 (m, 1H), 5.96–5.88 (m, 1H), 5.87–5.80 (m, 1H), 5.19 (d, J=10.2, 1H), 5.10 (d, J=4.5 Hz, 1H), 4.30 (d, J=10.8 Hz, 1H), 4.16 (d, J=10.8 Hz, 1H), 3.43–3.26 (m, 2H), 3.07–2.96 (m, 1H), 2.84–2.75 (m, 1H), 2.53–2.38 (m, 1H), 2.06 (s, 6H), 2.04–1.96 (m, 1H); ^{13}C NMR (75 MHz) δ 171.1, 170.8, 131.7, 127.5, 126.9, 122.2, 67.7, 62.7, 58.0, 49.7, 45.5, 25.0, 21.2, 21.0; ν_{max} (NaCl) 2920, 2852, 1732, 1372, 1236, 1022, 974 cm^{-1}; MS (ESI) m/z 288 [$(M+Na)^+$, 1%], 266 [$(M+H)^+$, 12], 206 (13), 146 (100).

*3.2.13. Compound **6a**.* Potassium carbonate (94 mg, 0.68 mmol) was added to a magnetically stirred solution of compound **21** (180 mg, 0.68 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 19 h the reaction mixture was concentrated under reduced pressure then dichloromethane (5 mL) and water (1 mL) were added and the phases separated. The aqueous layer was further extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title compound* ***6a*** (119 mg, 98%) as a clear, light-yellow oil [Found: $(M+H)^+$, 182.1182. $C_{10}H_{15}NO_2$ requires $(M+H)^+$, 182.1181]. ^{1}H NMR (300 MHz) δ 6.21–6.05 (m, 1H), 5.97–5.83 (m, 2H), 5.59 (dd, J=10.2, 0.9 Hz, 1H), 3.89 (d, J=11.4 Hz, 1H), 3.42 (d, J=11.4 Hz, 1H), 3.67 (br s, 1H), 3.36 (m, J=16.5 Hz, 1H), 3.26–3.14 (m, 2H), 2.82–2.70 (m, 1H), 2.42–2.28 (m, 1H), 2.12–1.98 (m, 1H), 1.85 (br s, 2H); ^{13}C NMR (75 MHz) δ 130.1, 128.6, 128.1, 127.2, 66.0, 62.4, 61.5, 50.2, 46.2, 25.1; ν_{max} (NaCl) 3386, 2922, 2852, 1467, 1341, 1286, 1140, 1109, 1075, 1050, 1028, 970, 730 cm^{-1}; MS (ESI) m/z 204 [$(M+Na)^+$, 4%], 182 [$(M+H)^+$, 58], 164 (55), 146 (34), 134 (44), 112 (100).

*3.2.14. Compound **6b**.* Potassium carbonate (36 mg, 0.26 mmol) was added to a magnetically stirred solution of compound **22** (69 mg, 0.26 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 15 h the reaction mixture was concentrated under reduced pressure then dichloromethane (5 mL) and water (1 mL) were added and the phases separated. The aqueous layer was further extracted with dichloromethane (3×5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford *compound* ***6b*** (46 mg, 97%) as a clear, light-yellow oil [Found: $(M+H)^+$, 182.1180. $C_{10}H_{15}NO_2$ requires $(M+H)^+$, 182.1181]. ^{1}H NMR (300 MHz) δ 6.13–6.07 (m, 1H), 6.00–5.90 (m, 1H), 5.70–6.84 (m, 2H), 4.29 (s, 1H), 3.97 (d, J=10.8 Hz, 1H), 3.76 (d, J=10.8 Hz, 1H), 3.42–3.28 (m, 1H), 3.18–3.08 (m, 1H), 3.05–2.93 (m, 1H), 2.80–2.70 (m, 1H), 2.40–2.20 (m, 1H), 2.18–2.00 (m, 1H) (signals due to OH protons not observed); ^{13}C NMR (75 MHz) δ 129.0, 128.8, 126.6, 126.0, 72.2, 60.7, 57.4, 49.9, 45.9, 25.3; ν_{max} (NaCl) 3356, 2923, 2853, 1466, 1384, 1287, 1180, 1142, 1075, 1042, 990 cm^{-1}; MS (ESI) m/z 182 [$(M+H)^+$, 100], 164 (33), 146 (12), 134 (23).

*3.2.15. Compound **23**. Step i.* Chloromethyl methyl ether (0.35 mL, 4.66 mmol) was added in three equal portions over 2 h to a magnetically stirred solution of compound **15** (420 mg, 1.86 mmol), *N,N*-diisopropylethylamine (1.62 mL, 9.30 mmol) and 4-(*N,N*-dimethylamino)pyridine (11 mg, 0.09 mmol) in dichloromethane (20 mL) maintained under nitrogen at 18 °C. After 21 h sodium bicarbonate (5 mL of a saturated aqueous solution) was added to the reaction mixture and the phases separated. The aqueous layer was further extracted with dichloromethane (3×15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f=0.3, 9:1 v/v dichloromethane/ethyl acetate) afforded the expected *{1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methyl acetate* (418 mg, 83%) as a clear, light-yellow oil [Found: $(M+H)^+$, 270.1701. $C_{14}H_{23}NO_4$ requires $(M+H)^+$, 270.1705]. ^{1}H NMR (300 MHz) δ 5.94 (dt, J=10.2, 3.9 Hz, 1H), 5.82–5.68 (m, 1H), 5.58 (dt, J=10.2, 2.1 Hz, 1H), 5.18 (dq, J=17.1, 1.5 Hz, 1H), 5.07 (dq, J=9.9, 1.5 Hz, 1H), 4.59 (s, 2H), 3.68 (d, J=11.4 Hz, 1H), 3.50 (d, J=11.4 Hz, 1H), 3.68 (d, J=9.9 Hz, 1H), 3.49 (d, J=9.9 Hz, 1H), 3.38–3.20 (m, 3H), 3.34 (s, 3H), 2.93 (td, J=6.0, 1.2 Hz, 1H), 2.08–2.02 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz) δ 170.4, 137.3, 128.3, 127.9, 115.8, 96.4, 69.1, 64.6, 58.9, 55.0, 52.9, 43.0, 25.3, 20.8; ν_{max} (NaCl) 2924, 2822, 1744, 1380, 1237, 1150, 1109, 1044, 918 cm^{-1}; MS (ESI) m/z 270 [$(M+H)^+$, 24%], 210 (62), 166 (4), 148 (80), 70 (100).

Step ii. Potassium carbonate (254 mg, 1.84 mmol) was added to a magnetically stirred solution of the {1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methyl acetate (495 mg, 1.84 mmol) in methanol (15 mL) maintained under nitrogen at 18 °C. After 16.5 h the reaction mixture was concentrated under reduced pressure then dichloromethane (15 mL) and water (3 mL) were added and the phases separated. The aqueous layer was further extracted with dichloromethane (3×15 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the expected *{1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methanol*

(410 mg, 99%) as a clear, yellow oil [Found: $(M+H)^+$, 228.1592. $C_{12}H_{21}NO_3$ requires $(M+H)^+$, 228.1600]. ^1H NMR (300 MHz) δ 6.05–5.95 (m, 1H), 5.83–5.65 (m, 1H), 5.52 (dd, J=9.9, 1.5 Hz, 1H), 5.23–5.08 (m, 2H), 4.58 (s, 2H), 3.67–3.50 (m, 3H), 3.40–3.33 (m, 2H), 3.35 (s, 3H), 3.10–3.04 (m, 1H), 2.95–2.84 (m, 2H), 2.72 (td, J=10.5, 3.9 Hz, 1H), 2.26–2.10 (m, 1H), 2.04–1.90 (m, 1H); ^{13}C NMR (75 MHz) δ 136.7, 130.0, 128.7, 116.6, 96.5, 68.2, 62.7, 61.3, 55.3, 51.5, 42.8, 25.4; ν_{max} (NaCl) 3423, 2921, 1149, 1107, 1038, 917 cm^{-1}; MS (ESI) m/z 250 [$(M+Na)^+$, 19%], 228 [$(M+H)^+$, 39], 196 (7), 166 (22), 148 (30), 70 (100).

Step iii. A solution of dimethyl sulfoxide (1.51 mL, 21.3 mmol) in dichloromethane (5 mL) was added dropwise to a magnetically stirred solution of oxalyl chloride (1.24 mL, 14.2 mmol) in dichloromethane (40 mL) maintained under nitrogen at −78 °C. After 0.25 h a solution of the {1-allyl-2-[(methoxymethoxy)methyl]-1,2,5,6-tetrahydropyridin-2-yl}methanol (1.60 g, 7.10 mmol) in dichloromethane (30 mL) was added dropwise over 0.25 h. After 1 h a solution of triethylamine (3.95 mL, 28.4 mmol) in dichloromethane (15 mL) was added and the reaction mixture was then warmed to 18 °C and maintained at this temperature for a further 1 h. Sodium bicarbonate (20 mL of a saturated solution) was added and the phases separated. The aqueous layer was extracted with dichloromethane (3×30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *aldehyde* ***23*** as a clear, colorless oil [Found: $(M+H)^+$, 226.1438. $C_{12}H_{19}NO_3$ requires $(M+H)^+$, 226.1443]. ^1H NMR (300 MHz) δ 9.28 (s, 1H), 6.24–6.13 (m, 1H), 5.86–5.72 (m, 1H), 5.40–5.32 (m, 1H), 5.28–5.08 (m, 2H), 4.61 (s, 2H), 3.86 (d, J=10.5 Hz, 1H), 3.80 (d, J=10.5 Hz, 1H), 3.36 (s, 3H), 3.32–3.16 (m, 2H), 2.98–2.88 (m, 1H), 2.82–2.72 (m, 1H), 2.32–2.18 (m, 1H), 2.14–2.02 (m, 1H); ^{13}C NMR (75 MHz) δ 201.0, 136.4, 132.0, 127.9, 123.3, 117.0, 96.7, 69.3, 67.3, 55.4, 54.3, 42.3, 25.9; ν_{max} (NaCl) 3421, 2924, 1722, 1440, 1262, 1212, 1150, 1110, 1045, 919 cm^{-1}; MS (ESI) m/z 248 [$(M+Na)^+$, 2%], 240 (100), 226 [$(M+H)^+$, 43], 210 (28), 194 (28), 178 (40), 164 (52), 146 (24), 109 (82).

This somewhat unstable aldehyde was immediately subjected to the vinylation reaction described directly below.

3.2.16. Compound ***25****. Step i.* Vinyl magnesium bromide (21.3 mL of a 1.0 M solution in THF, 21.3 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde **23** (obtained as described immediately above) in THF (60 mL) maintained under nitrogen at −78 °C. After 0.5 h the reaction mixture was warmed to 0 °C and maintained at this temperature for a further 2 h, then warmed to 18 °C. After a further 1 h the reaction mixture was cooled to 0 °C and water (12 mL) followed by ammonium chloride (8 mL of a saturated aqueous solution) were added then the phases separated. The aqueous layer was extracted with dichloromethane (3×30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 3:1 mixture of the epimers of the *alcohol* ***24*** as a light-yellow oil [Found: $(M+H)^+$, 254.1755. $C_{14}H_{23}NO_3$ requires $(M+H)^+$, 254.1756]. ^1H NMR (300 MHz) δ 6.10–5.90 (m, 1H), 5.75 (br s, 1H), 5.60 (dm, J=10.2 Hz, 1H), 5.34 (dm, J=17.4 Hz, 1H), 5.22–5.04 (m, 3H), 4.61 (ABq, J=6.6 Hz, 2H), 4.26 (s, 1H), 3.72 (s, 3H), 3.67 (s, 1H), 3.38 (s, 3H), 3.00–2.80 (m, 3H), 2.65 (m, 1H), 2.20–1.85 (m, 2H); ^{13}C NMR (75 MHz) δ 138.2, 136.9, 136.7, 136.1, 130.1, 129.2, 128.0, 126.6, 117.4, 116.7, 116.2, 115.4, 96.9, 96.8, 73.4, 71.1, 68.7, 67.8, 63.1, 55.6, 53.2, 51.7, 43.7, 43.4, 25.5, 24.9 (two signals obscured or overlapping); ν_{max} (NaCl) 3436, 2918, 1641, 1440, 1417, 1384, 1275, 1211, 1150, 1107, 1041, 916 cm^{-1}; MS (ESI) m/z 254 [$(M+H)^+$, 100%], 228 (14), 210 (5).

This material was immediately subjected to an acetylation reaction described directly below.

Step ii. Acetic anhydride (1.34 mL, 14.2 mmol) was added to a magnetically stirred solution of the above-mentioned mixture of the epimeric forms of alcohol **24** (obtained as described immediately above) and 4-(*N*,*N*-dimethylamino)pyridine (43 mg, 0.36 mmol) in diethyl ether (30 mL) maintained under nitrogen at 18 °C. After 22 h the reaction mixture was concentrated under reduced pressure and the ensuing yellow oil was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f=0.5, 9:1 v/v dichloromethane/ethyl acetate) afforded an indeterminable mixture of the epimers of the *title compound* ***25*** (1.99 g, 91% over 3 steps) as a clear, light-yellow oil [Found: $(M+H)^+$, 296.1863. $C_{16}H_{25}NO_4$ requires $(M+H)^+$, 296.1862]. ^1H NMR (300 MHz) δ 6.05–5.90 (m, 2H), 5.75–5.60 (m, 2H), 5.60–5.45 (m, 1H), 5.20–5.00 (m, 3H), 4.60–4.50 (m, 2H), 3.75–3.60 (m, 2H), 3.51 (d, J=10.5 Hz, 1H), 3.34 (s, 3H), 3.12–2.92 (m, 1H), 2.84–2.74 (m, 1H), 2.64–2.53 (m, 1H), 2.09 (s, 3H), 2.00–1.84 (m, 3H); ^{13}C NMR (75 MHz) δ 169.8, 137.3, 134.1, 129.2, 127.9, 126.7, 117.0, 115.7, 96.8, 95.4, 73.5, 68.7, 67.8, 62.0, 55.3, 52.8, 42.9, 25.7, 21.1 (thirteen signals obscured or overlapping); ν_{max} (NaCl) 2925, 2825, 1743, 1641, 1370, 1238, 1149, 1109, 1039, 918 cm^{-1}; MS (ESI) m/z 318 [$(M+Na)^+$, 5%], 296 [$(M+H)^+$, 29], 236 (66), 206 (14), 174 (51), 105 (63), 70 (100).

3.2.17. Compounds ***26*** *and* ***27****.* Grubbs' second generation catalyst (572 mg, 0.67 mmol) was added to a magnetically stirred solution of the epimeric forms of compound **25** (1.99 g, 6.74 mmol) in dichloromethane (335 mL) maintained under nitrogen at 18 °C. The ensuing mixture was heated at reflux for 46 h then cooled and treated with dimethyl sulfoxide (2.38 mL, 33.5 mmol) and triethylamine (4.66 mL, 33.5 mmol). After a further 23 h the reaction mixture was concentrated under reduced pressure and the ensuing brown oil was subjected to flash chromatography (silica, 9:1→ 4:1 v/v hexane/ethyl acetate elution) affording three major fractions, A, B, and C.

Concentration of fraction A (R_f=0.6 in 9:1 v/v dichloromethane/ethyl acetate) afforded the starting triene **25** (847 mg, 43% recovery) as a clear, light-yellow oil.

Concentration of fraction B (R_f=0.2, 1:1 v/v hexane/ethyl acetate) afforded *title compound* ***27*** (169 mg, 16% at 57% conversion) as a clear, light-yellow oil (Found: $(M+H)^+$, 268.1549. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^1H NMR (300 MHz) δ 5.97–5.90 (m, 1H), 5.90–5.80 (m, 1H), 5.64 (d, J=9.6 Hz, 1H), 5.50 (d, J=10.2 Hz, 1H), 5.30 (s, 1H), 4.63 (d, J=6.3 Hz, 1H), 4.58 (d, J=6.3 Hz, 1H), 3.98 (d, J=10.8 Hz, 1H), 3.62 (d, J=10.8 Hz, 1H), 3.50–3.15 (m, 3H), 3.36 (s, 3H), 2.76–2.65 (m, 1H), 2.42–2.26 (m, 1H), 2.08 (s, 3H), 2.04–1.97 (m, 1H); ^{13}C NMR (75 MHz) δ 170.3, 128.3, 128.1, 127.0, 125.0, 96.7, 73.9, 66.0, 57.0, 55.3, 50.0, 46.4, 25.2, 21.2; ν_{max} (NaCl) 2924, 1746, 1370, 1231, 1150, 1109, 1041 cm^{-1}; MS (ESI) m/z 268 $[M+H)^+$, 51%], 208 (12), 176 (21), 148 (51), 146 (100).

Concentration of fraction C (R_f=0.1 in 1:1 v/v hexane/ethyl acetate) afforded the *title compound* ***26*** (49 mg, 48% at 57% conversion) as a clear, light-yellow oil [Found: $(M+H)^+$, 268.1548. $C_{14}H_{21}NO_4$ requires $(M+H)^+$, 268.1549]. ^1H NMR (300 MHz) δ 6.03–5.95 (m, 1H), 5.86–5.74 (m, 2H), 5.53 (d, J=10.2 Hz, 1H), 5.30 (d, J=5.1 Hz, 1H), 4.53 (d, J=6.6 Hz, 1H), 4.49 (d, J=6.6 Hz, 1H), 3.68 (d, J=9.0 Hz, 1H), 3.54 (d, J=9.0 Hz, 1H), 3.32–3.18 (m, 2H), 3.26 (s, 3H), 2.97 (td, J=11.1, 4.5 Hz, 1H), 2.76–2.66 (m, 1H), 2.46–2.30 (m, 1H), 2.06–1.91 (m, 1H), 1.99 (s, 3H); ^{13}C NMR (75 MHz) δ 170.9, 131.5, 128.2, 126.3, 122.3, 96.4, 67.8, 66.0, 58.4, 55.1, 49.6, 45.4, 24.9, 21.1; ν_{max} (NaCl) 2922, 1731, 1370, 1241, 1140, 1109, 1041, 1022 cm^{-1}; MS (ESI) m/z 290 [$(M+Na)^+$, 38%], 268 [$(M+H)^+$, 17], 236 (4), 208 (12), 148 (40), 146 (100).

3.2.18. Compound ***28****.* Potassium carbonate (54 mg, 0.39 mmol) was added to a magnetically stirred solution of compound **26** (105 mg, 0.39 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 15.5 h the reaction mixture was concentrated under reduced pressure then dichloromethane (10 mL) and water

(2 mL) were added to the residue and the phases separated. The aqueous layer was extracted with dichloromethane (3×10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the *title compound* ***28*** (88 mg, 99%) as a clear, yellow oil [Found: $(M+H)^+$, 226.1432. $C_{12}H_{19}NO_3$ requires $(M+H)^+$, 226.1443]. ^1H NMR (300 MHz) δ 6.01–5.94 (m, 2H), 5.90–5.82 (m, 1H), 5.72 (d, J=10.2 Hz, 1H), 4.59 (d, J=6.6 Hz, 1H), 4.54 (d, J=6.6 Hz, 1H), 3.90–3.82 (m, 1H), 3.76 (d, J=9.3 Hz, 1H), 3.53 (d, J=9.3 Hz, 1H), 3.32 (s, 3H), 3.28 (s, 2H), 3.09 (td, J=11.1, 4.2 Hz, 1H), 2.72–2.62 (m, 1H), 2.48–2.22 (m, 2H), 2.07–1.94 (m, 1H); ^{13}C NMR (75 MHz) δ 129.7, 128.6, 127.2, 126.5, 96.4, 66.4, 65.8, 59.5, 55.1, 50.2, 45.6, 25.1; ν_{max} 3401, 2922, 1140, 1109, 1031, 732 cm^{-1}; MS (ESI) m/z 248 [$(M+Na)^+$, 12%], 226 [$(M+H)^+$, 29], 208 (5), 176 (10), 156 (35), 148 (37), 146 (100).

3.2.19. Compound ***29***. Potassium carbonate (21 mg, 0.15 mmol) was added to a magnetically stirred solution of compound **27** (40 mg, 0.15 mmol) in methanol (5 mL) maintained under nitrogen at 18 °C. After 16 h the reaction mixture was concentrated under reduced pressure then dichloromethane (5 mL) and water (1 mL) were added to the residue and the phases separated. The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford *compound* ***29*** (32 mg, 95%) as a clear, yellow oil [Found: $(M+H)^+$, 226.1437. $C_{12}H_{19}NO_3$ requires $(M+H)^+$, 226.1443]. ^1H NMR (300 MHz) δ 6.16–6.08 (m, 1H), 5.92–5.84 (m, 1H), 5.72 (s, 2H), 4.57 (s, 2H), 4.16–4.08 (m, 1H), 3.89 (d, J=9.6 Hz, 1H), 3.72 (d, J=9.6 Hz, 1H), 3.33 (s, 3H), 3.18 (d, J=11.1 Hz, 2H), 3.02 (td, J=11.1, 4.2 Hz, 1H), 2.70–2.58 (m, 1H), 2.44–2.28 (m, 1H), 2.06–1.96 (m, 1H) (signal due to OH proton not observed); ^{13}C NMR (75 MHz) δ 130.1, 128.7, 125.7, 125.4, 96.7, 73.2, 65.7, 56.7, 55.5, 50.2, 45.7, 25.3; ν_{max} (NaCl) 3422, 3032, 2918, 2883, 1150, 1108, 1091, 1041, 761 cm^{-1}; MS (ESI) m/z 248 [$(M+Na)^+$, 18%], 226 [$(M+H)^+$, 31], 208 (10), 176 (12), 148 (55), 146 (100).

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JOC Note

Microwave-Assisted Trans-Halogenation Reactions of Various Chloro-, Bromo-, Trifluoromethanesulfonyloxy- and Nonafluorobutanesulfonyloxy-Substituted Quinolines, Isoquinolines, and Pyridines Leading to the Corresponding Iodinated Heterocycles†

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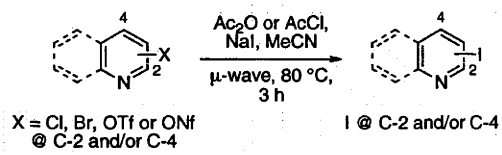

Microwave irradiation of certain chloro-, bromo-, trifluoromethanesulfonyloxy- and nonafluorobutanesulfonyloxy-substituted quinolines in the presence of acetic anhydride and sodium iodide leads, via a trans-halogenation process, to the corresponding iodides in high yield. Related conversions involving pyridines and isoquinolines can also be achieved under similar conditions.

The ready participation of aryl iodides in metalation processes and metal-catalyzed cross-coupling reactions has made them particularly valuable building blocks in medicinal chemistry, in materials science, and in total synthesis.[1] However, such compounds are often difficult to obtain, especially if the halogen is attached to a nitrogen-containing heteroaromatic framework.[2] Trans-halogenation protocols (sometimes characterized as aromatic Finkelstein reactions) involving a bromo- or chloro-precursor to the target iodide have been introduced in an effort to overcome such difficulties although many limitations still apply.[3] In 1947 Bruce demonstrated that a 2,4-di-iodinated pyridine could be prepared in quantitative yield by heating its dichloro-analogue with hydroiodic acid.[4] Variations on this sort of approach have been introduced over the intervening years wherein the ring nitrogen in pyridines has been activated through protonation,[5] silylation,[6] or acylation[7] and thereby facilitating a nucleophilic addition/elimination reaction (S_NAr reaction) involving iodide ion that leads to the target aryl halide.[8] The proton activation approach has been applied to quinolines[7,9] although Newkome[10] has shown that such conditions can lead to reductive dehalogenation when very electron-deficient pyridines are involved. Nickel- and copper-promoted trans-halogenation processes have been introduced over the last two decades[11] while, in 2002, Buchwald reported[12] a copper-catalyzed method for the conversion of aryl bromides into the corresponding iodides. Various relevant extensions of Buchwald's chemistry have since been introduced by his group.[13] Despite the useful advances involved, high reaction temperatures (i.e. >100 °C), extended reactions times (≥24 h), and/or strongly acidic conditions are often required and thus precluding the application of such techniques to substrates containing sensitive functionalities.

In connection with work directed toward the total synthesis of the alkaloid quinine, we recently reported a short and efficient synthesis of 4-iodo-6-methoxyquinoline.[14] The final step in the reaction sequence was the trans-halogenation of the corresponding bromide. The best conditions we could establish for effecting this conversion involved treating a solution of the substrate bromide in acetonitrile with sodium iodide and acetic anhydride and then subjecting the resulting mixture to microwave irradiation for 3 h at 80 °C. In this manner the desired iodo-compound was obtained in 94% yield. Since these sorts of conditions are much milder and involve shorter reaction times than those employed in many of the above-mentioned trans-halogenation protocols, we sought to investigate the scope of this method

† Strictly speaking, of course, the conversions of the title trifluoromethanesulfonyloxy- and nonafluorobutanesulfonyloxy-substituted systems into the corresponding iodides do not represent trans-halogenation processes, but since such substrates incorporate pseudohalogens it seems legitimate to apply this term to these cases as well as those true trans-halogenation processes detailed herein.

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for preparing a range of iodinated nitrogen-containing heterocyclic systems. The outcomes of such studies are reported here.

The successful trans-halogenation reactions are presented in Table 1 and involved treating acetonitrile solutions of quinolines **1**, **3**, **5**, **7**, **8**, **10**, **12**, **13**, **15**, **16**, and **17**, the isoquinolines **19** and **21**, as well as the pyridines **22**, **24**, **25**, and **27** with sodium iodide and either acetic anhydride or acetyl chloride then subjecting the resulting mixture to microwave irradiation at 80 °C for the specified period. The substrates used for these studies were either commercially available or readily prepared by applying standard procedures to commercially available precursors. The yields of the substrates prepared by such means were not optimized.

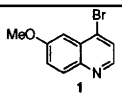
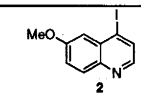
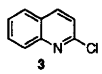
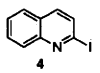
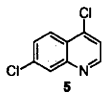
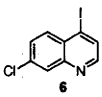
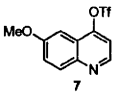
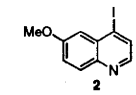
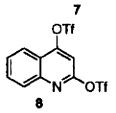
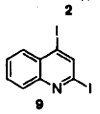
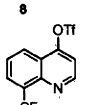
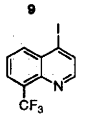
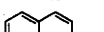
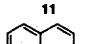
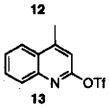
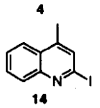
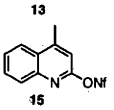
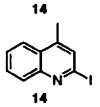
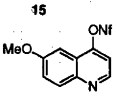
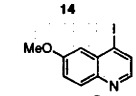
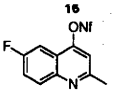
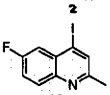
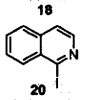
The results presented in Table 1 reveal that quinolines carrying a leaving group at C-2 and/or C-4 readily engage in the desired trans-halogenation reaction(s) and thereby afford the corresponding iodides in generally excellent yield. Significantly, compounds **5**, **7**, **10**, **16**, and **17** carrying potential leaving groups at C-6, C-7, or C-8 do not undergo iodination at these positions while additional results presented below also reveal (in keeping with expectations) a lack of reaction at C-3 and C-5 when these sites bear halogen substituents. In some instances it was found that using acetic anhydride as the activating agent (procedure A) provided better yields of product than when acetyl chloride was used for the same purpose (procedure B). This situation is attributed to coproduction of the corresponding aryl chloride when the latter activating agent was employed. Nevertheless, there were other cases where the latter procedure proved superior.

As expected, isoquinolines **19** and **21** carrying a potential leaving group at C-1 engage in the trans-halogenation reaction to give iodide **20** in excellent yield. Studies outlined below have established that C-1 is likely to be the only position on the isoquinoline framework where such a process can take place. Pyridines bearing a leaving group at C-2 or C-4 also participate in trans-halogenation reactions under the specified conditions, thus affording the anticipated iodinated products in generally good yield. The origins of the rather poor yield (33%) associated with the conversion of triflate **22** into iodide **23** remain unclear but can, seemingly, be addressed by using the corresponding nonaflate (**24**) as substrate. A further interesting observation is that when 1-chloroisoquinoline, rather than isoquinolin-1-yl trifluoromethanesulfonate (**19**), was used as the substrate for the trans-halogenation reaction then the yield of the corresponding iodide was only 45% and this was accompanied by significant quantities of a byproduct tentatively identified as an unsymmetrical 1,*X*′-biisoquinoline.

The success of these reactions is clearly dependent upon the acylation of the ring-nitrogen and the resulting activation of the halogenated (or pseudohalogenated) carbon toward a S_NAr reaction involving iodide as nucleophile. To ensure complete reaction, a 3-fold excess of sodium iodide was employed under those conditions involving acetic anhydride (procedure A) as the activating agent. When acetyl chloride was used for the same purpose (procedure B) then a 10-fold excess of sodium iodide was used so as to ensure a much higher iodide than chloride ion concentration in the reaction mixture. It is noteworthy that in all instances where an isoquinoline or pyridine was a substrate then the more vigorous conditions defined by procedure B were required to achieve good conversions into the target iodide.

In keeping with expectations, substrates **29**–**35** all failed to engage in trans-halogenation reactions when subjected to the conditions defined by procedure A or B. The lack of reaction of substrate **36** at C-2 is a little surprising given the successful trans-halogenation of 2-chloropyridine (see entry 17 of Table 1) but clearly attributable to the presence of the C-3 chlorine.

TABLE 1. Outcomes of the Trans-Halogenation Reactions of Certain Substituted Quinolines, Isoquinolines, and Pyridines

entry	substrate[a]	product	procedure[b]	yield[c] (%)
1	 1	 2	A	94
2	 3	 4	A	85
3	 5	 6	A	93
4	 7	 2	A	93
5	 8	 9	B	97
6	 10	 11	A	97
7	 12	 4	B	91
8	 13	 14	B	94
9	 15	 14	B	92
10	 16	 2	A	92
11	 17	 18	A	95
12	 19	 20	B	90
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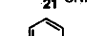
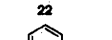
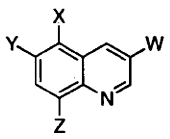
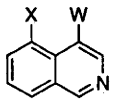
14	 22	 23	B	33
15	 24	 23	B	74
16	 25	 26	B	91
17	 27	 28	B	98

[a] The substrates used were either commercially available materials or readily prepared by conventional methods (see the SI). [b] Details of procedures A and B are provided in the SI. [c] All yields cited are of isolated and chromatographically purified materials.

It seems possible that the two chlorines attached to the pyridine ring in compound **36** inhibit the initial *N*-acylation process, thus precluding trans-halogenation under the conditions we report here. Of course, steric effects exerted by the two chlorines may also contribute to the lack of reactivity of compound **36**.



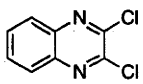
29 W = Br, X = Y = Z = H
30 X = Cl, W = Y = Z = H
31 Y = Br, W = X = Z = H
32 Z = Br, W = X = Y = H



33 W = Br, X = H
34 X = Br, W = H

35 X = Br, W = H
36 W = X = Cl

We have undertaken a brief investigation of the capacity of other aromatic nitrogen heterocycles to participate in the title process but no useful outcomes have been observed. Thus, for example, attempts to effect trans-halogenation of the commercially available compounds **37** and **38** under either of the specified conditions have failed and only the starting compounds were recovered.



37

38

A final aspect of the present investigation was concerned with establishing if nucleophiles other than iodide could be induced to participate in S_NAr reactions under the conditions developed. However, upon exposing compound **6** to either acetic anhydride or acetyl chloride in the presence of various sources of fluoride, chloride, cyanide, and nitrite anions no evidence for the formation of the hoped-for substitution products could be obtained.

The protocols defined here provide a useful means for effecting the rather rapid trans-halogenation of various chlorinated, brominated, or pseudohalogenated quinolines, isoquinolines, and pyridines under mild conditions. The reaction pathways involved mean that the regioselectivities of these processes are entirely predictable. As such they should find use in the preparation of a range of iodinated aromatic nitrogen heterocycles.

Experimental Section

Trans-Halogenation Studies: Procedure A. Acetic anhydride (300 μL, 3.15 mmol) was added to a magnetically stirred suspension of the appropriate quinoline (1.26 mmol) and sodium iodide (565 mg, 3.78 mmol) in acetonitrile (2 mL) maintained at 18 °C. The ensuing reaction mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with potassium carbonate (1.5 mL of a 10% aqueous solution), sodium sulfite (1.5 mL of a 5% w/v aqueous solution), sodium thiosulfate (1.5 mL of a saturated aqueous solution), and dichloromethane (10 mL). The phases were separated, the aqueous layer was extracted with dichloromethane (3 × 5 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography.[15]

Trans-Halogenation Studies: Procedure B. Acetyl chloride (134 μL, 1.89 mmol) was added to a magnetically stirred suspension of the appropriate pyridine, quinoline, or isoquinoline (1.26 mmol) and sodium iodide (1.88 g, 12.6 mmol) in acetonitrile (2 mL) maintained at 18 °C. The ensuing reaction mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with potassium carbonate (3 mL of a 10% w/v aqueous solution), sodium sulfite (3 mL of a 5% w/v aqueous solution), sodium thiosulfate (3 mL of a saturated aqueous solution), and dichloromethane (20 mL). The phases were separated, the aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography.[15]

4-Iodo-6-methoxyquinoline (2)—From Substrate 1 via Procedure A. The previously reported iodide **2**[14] was prepared in 94% yield from starting material **2** according to procedure A as specified above and isolated by, flash chromatography, as a colorless, crystalline solid, mp 126 °C (lit.[14] mp 126 °C) (R_f 0.2 in 4:1 v/v hexane/ethyl acetate). ^{1}H NMR (300 MHz) δ 8.29 (br s, 1H), 7.99−7.89 (complex m, 2H), 7.65 (dd, J = 9.0 and 2.7 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz) δ 158.9, 146.9, 143.7, 132.4, 131.4, 131.3, 122.9, 110.2, 109.2, 55.4; IR ν_{max} 3344, 2953, 1617, 1555, 1498, 1452, 1423, 1350, 1264, 1232, 1159, 1028 cm^{-1}; EI-MS *m/z* 285 ($M^{+\bullet}$,100%); HRMS *m/z* $M^{+\bullet}$ calcd for $C_{10}H_8{}^{127}INO$ 284.9651, found 284.9651. Anal. Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.83; I, 44.51; N, 4.91. Found: C, 42.45; H, 3.19; I, 44.22; N, 4.96.

Acknowledgment. We thank the Institute of Advanced Studies at the Australian National University and the Australian Research Council for generous financial support.

Supporting Information Available: Detailed procedures and full characterization data for all compounds and ^{1}H and ^{13}C NMR spectra for compounds **8**, **9**, **10**, **11**, **16**, **17**, **18**, **21**, and **24** (new compounds). This material is available free of charge via the Internet at http://pubs.acs.org.

JO9008386

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SYNLETT
Spotlight 268

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Methyl Cyanoformate (Mander's Reagent)

Compiled by Alex C. Bissember

Alex Bissember was born in London in 1983. He received a B.Sc. (Honors) in Chemistry from The Australian National University (ANU) in 2005 and is now working towards his Ph.D. under the supervision of Prof. Martin Banwell at The Research School of Chemistry (ANU). His current research is focused on the development of new methods for the synthesis of biologically active heterocycles.

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Introduction

Methyl cyanoformate, Mander's reagent (Figure 1), is most commonly employed to effect the regiocontrolled synthesis of β-keto esters through the C-acylation of preformed lithium enolates.[1,2] It is superior to more traditional reagents such as acyl halides, anhydrides and carbon dioxide because these can also produce variable amounts of the corresponding O-acylated products.[3] In addition to its aforementioned electrophilic behaviour, methyl cyanoformate has also been employed as a dipolarophile[4] that reacts with an α-diazo-β-imido ester and, in the presence of polyoxotungstate, as a radical cyanating agent.[5] Its homologue ethyl cyanoformate also behaves as a dipolarophile[6] and has been used to form substituted tetrazoles. It has also been employed in the preparation of α-keto esters.[7]

Methyl cyanoformate is a commercially available, colourless liquid that is readily prepared in small quantities (up to 30 g) by treating methyl chloroformate with potassium cyanide in the presence of a phase transfer catalyst such as 18-crown-6[8] or tetra-*n*-butylammonium bromide.[9]

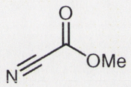
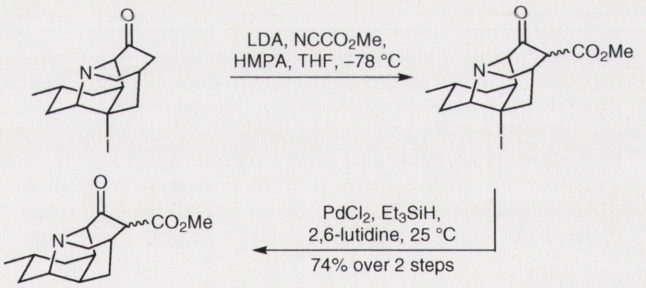


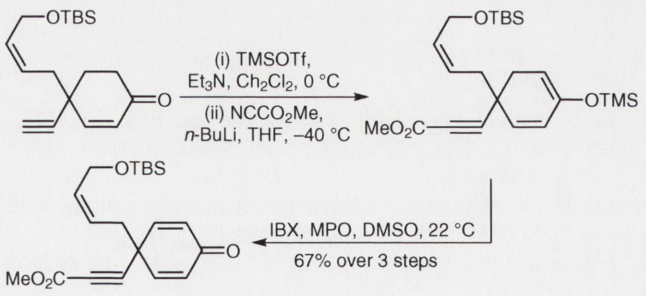
Figure 1 Methyl Cyanoformate

Abstracts

(A) Numerous syntheses of natural products and related compounds have featured the use of methyl cyanoformate to prepare β-keto esters. In the first total syntheses of (+)-lyconadin A and (–)-lyconadin B, Smith and co-workers[10] employed Mander's reagent for precisely this purpose.



(B) The title reagent was used to prepare an acetylenic ester that served as an early stage intermediate in the first asymmetric total synthesis of (–)-platensimycin reported by Nicolaou and co-workers.[11]



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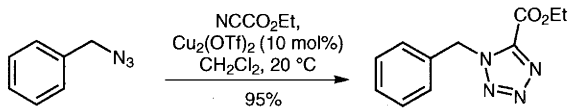
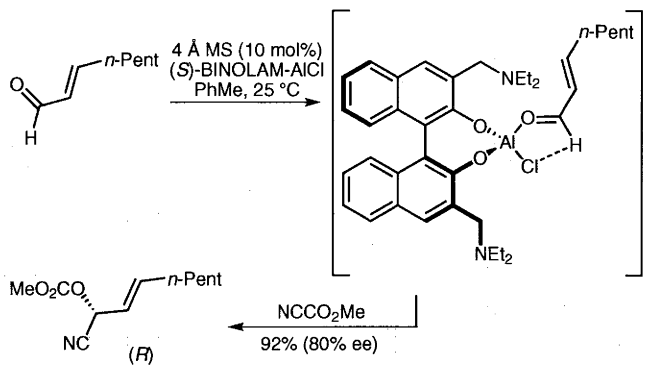
Advanced online publication: 16.02.2009
DOI: 10.1055/s-0028-1087716; Art ID: V27508ST

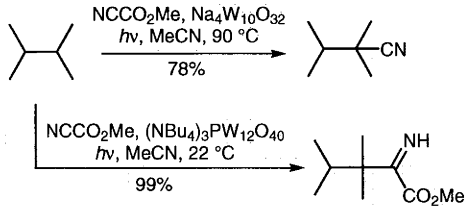
(C) Ethyl cyanoformate has been shown to engage in a copper(I)-catalyzed [3+2] dipolar cycloaddition with various organoazides, including benzylazide, to afford the corresponding 1,5-disubstituted tetrazoles.[6]



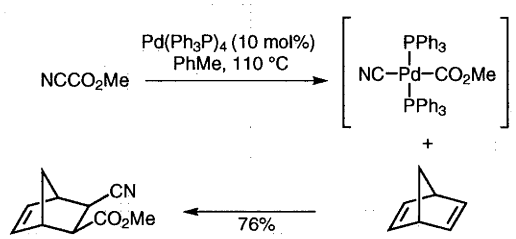
(D) Nájera and co-workers reported the one-step synthesis of various chiral cyanocarbonates from a range of aldehydes using the title reagent in the presence of chiral bifunctional catalysts such as *(R)*- or *(S)*-BINOLAM-AlCl.[12,13] It is believed that the catalytic cycle involves enantioselective hydrocyanation promoted by BINOLAM-AlCl, followed by the turnover-limiting O-alkoxycarbonylation step.



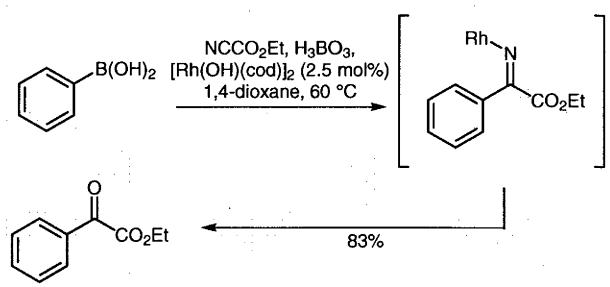
(E) Hill and Zheng have reported that irradiation ($\lambda > 280$ nm) of mixtures of various alkanes and methyl cyanoformate in the presence of either $W_{10}O_{32}^{4-}$ or $PW_{12}O_{40}^{3-}$ produces the corresponding nitrile or α-iminoester, respectively.[5] Such reactions can be highly selective if proper temperature controls are applied. An iminyl radical intermediate is thought to be involved in these conversions.



(F) Nishihara and co-workers have described the highly stereoselective and palladium-catalyzed addition of methyl cyanoformate across norbornene-type double bonds and so affording norbornanes bearing both cyano and ester groups.[14] It is believed that the complex *trans*-Pd(CN)(CO_2Me)(Ph_3P)$_2$ is an intermediate in the catalytic cycle associated with this cyanoesterification process.[15]



(G) Shimizu and Murakami have effected the selective formation of α-keto esters by the rhodium-catalyzed reaction of ethyl cyanoformate with arylboronic acids.[7] The observed conversion arises through preferential addition of an intermediate rhodium(I) species to the cyano group rather than to the ester carbonyl group. This conversion stands in sharp contrast to the outcomes observed when ethyl cyanoformate reacts with either phenyllithium or phenylmagnesium bromide so as to afford ethyl benzoate.[7]



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OPPI BRIEFS

4-IODO-6-METHOXYQUINOLINE

Submitted by Alex C. Bissember and Martin G. Banwell*
(08/06/08)

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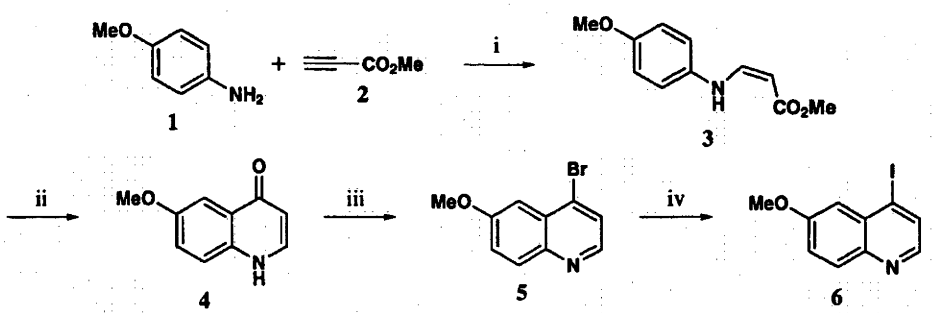
As part of a project directed towards establishing a fully stereocontrolled total synthesis of the anti-malarial agent quinine[1] we required access to the title compound (**6**). The only reported synthesis is a rather lengthy one published in 1930.[2] Accordingly we sought to establish a new route. An examination of the literature suggested the best approach might involve making the corresponding bromide **5**, a compound that appeared accessible by at least two distinct and relatively efficient routes,[3,4] then converting it into the target iodide (**6**) using one of a number of available *trans*-halogenation protocols.[5–7] In the event, this strategy proved successful although a number of significant modifications to reported procedures was required to ensure an efficient process was established. Details are provided herein.

The route used to obtain target **6** is shown in *Scheme 1* and started with the stereoselective Michael addition of *p*-anisidine (**1**) to methyl propiolate (**2**).[3] When this reaction was conducted at 18°C then a *ca.* 9:1 mixture of acrylate **3**[3] and the corresponding *E*-isomer was obtained. In contrast, when the same reaction was carried out at 30°C then compound **3** was essentially the only product of reaction and was obtained in near quantitative yield. Following a



i) MeOH, 18–30°C, 15 h; ii) Ph_2O, 260°C, 0.5 h; iii) PBr_3, DMF, 18°C, 1 h; iv) Ac_2O, NaI, MeCN, microwave irradiation, 80°C, 3 h.

Scheme 1

reported procedure[3] that was expected to result in the β-anilinoacrylate **3** undergoing a Conrad–Limpach reaction[8] to give 4-quinolone **4**, a *ca.* 0.4 M solution of compound **3** in diphenyl ether was heated at *ca.* 260°C for 0.5 h. However, under such conditions only polymeric products were obtained. After a great deal of experimentation, it was established that heating a *ca.* five-fold diluted solution of the substrate under the same conditions led to an efficient cyclization reaction thus providing the target 4-quinolone **4**[3,4] as a fine, tan-colored powder in 93% yield. The conversion of this compound into bromide **5** proceeded smoothly when PBr_3 in dimethylformamide (DMF) was used[4] and the desired product was obtained as a light-yellow crystalline solid in 88% yield. The physical and spectroscopic properties of this material were in full accord with the assigned structure and in agreement with the analogous data reported in the literature.[3,4]

Various protocols are available for the *trans*-halogenation of electron-deficient heterocycles.[5–7] For the purposes of effecting the conversion **5** → **6**, we chose to use that one involving a mixture of acetyl chloride and sodium iodide.[5,6] When the relevant reaction was carried out using microwave irradiation then the target compound **6** was indeed produced but the major product of reaction was the corresponding chloride. Accordingly, the acetyl chloride was replaced with acetic anhydride and while the ensuing reaction was a little slower, the required iodide could be obtained, after column chromatography, in 94% yield and as a crystalline solid. The spectral data of compound **6** were in full accord with the assigned structure but the melting point of this material was significantly higher (126°C) than that reported[2] (85°C) for the material prepared by John and Andraschko. The origins of this discrepancy remain unclear.

The time-efficient protocols described here should have utility in the preparation of other 4,6-disubstituted quinolines for which straightforward and rapid methods of access are lacking.[3b]

EXPERIMENTAL SECTION

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian Mercury or Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates. 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. Melting points were measured on an Optimelt automated melting point system and are uncorrected. All microwave irradiation experiments were carried out in the CEM Explorer™ microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W utilizing the standard absorbance level of 300 W maximum power. The reactions were carried out in 80 mL sealed Pyrex vessels (working volume of 50 mL) equipped with a magnetic stirrer. The temperature was measured with a fiber optic temperature sensor immersed in the reaction vessel. After the irradiation period, the reaction vessel was cooled rapidly (1–2 min) to ambient temperature by N_2 jet cooling.

(*Z*)-Methyl 3-(4-methoxyphenylamino)acrylate (3).- Compound **3** was prepared using the method detailed by Nicolaou *et al.*[3a] Thus, methyl propiolate (**2**) (4.45 mL, 49.9 mmol) was added to a magnetically stirred solution of *p*-anisidine (**1**) (6.15 g, 49.9 mmol) in methanol (125 mL) maintained under a nitrogen atmosphere at 18°C. The ensuing mixture was warmed to 30°C and after 15 h at this temperature it was cooled then concentrated under reduced pressure. The crude solid thus obtained was dissolved in boiling ethyl acetate (200 mL) and the resulting mixture filtered through a 5 cm deep pad of TLC-grade silica sitting on a sintered-glass funnel. The solids thus retained were washed with ethyl acetate (150 mL) and the combined filtrates were concentrated under reduced pressure to afford compound **3**[3a] (10.3 g, 99%) as a yellow solid, mp 126–128°C. ^{1}H NMR: δ 9.79 (d, J = 12.0 Hz, 1H), 7.15 (dd, J = 12.0 and 8.1 Hz, 1H), 6.92–6.83 (AB system, J = 9.3 Hz, 4H), 4.78 (d, J = 8.1 Hz, 1H), 3.77 (s, 3H), 3.70, (s, 3H); ^{13}C NMR δ 170.8, 155.5, 144.2, 134.3, 116.9, 114.8, 85.5, 55.5, 50.5; IR (NaCl): ν_{max} 3315, 2959, 2838, 1622, 1589, 1515, 1484, 1297, 1233, 1207, 1180, 1034, 1017 828, 782 cm^{-1}; MS: *m/z* 230 [(M + Na)$^+$, 94%], 208 [(M + H)$^+$, 9], 176 (100), 148 (30), 124 (36); HRMS: $C_{11}H_{13}NO_3$ requires (M + H)$^+$, 208.0974. Found: (M + H)$^+$, 208.0970.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76

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yellow, crystalline solid, mp 86°C (*lit.*[3b] mp 78–80°C), R_f 0.3 (in 1:1 v/v hexane/ethyl acetate). ^{1}H NMR: δ 8.52 (d, J = 4.8 Hz, 1H), 7.99 (m, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.42–7.38 (complex m, 2H), 3.98 (s, 3H); ^{13}C NMR δ 158.4, 146.7, 144.5, 132.0, 131.0, 128.5, 124.8, 122.8, 103.8, 55.3; IR (NaCl): ν_{max} 3083, 2961, 1618, 1622, 1573, 1558, 1497, 1424, 1352, 1263, 1231, 1160, 1064, 1028, 844, 817 cm^{-1}; MS (EI): *m/z* 239 and 237 ($M^{+\bullet}$, 39 and 38%), 207 (12), 194 (20), 158 (4), 149 (42); HRMS: $C_{10}H_8{}^{79}BrNO$ requires $M^{+\bullet}$, 236.9789. Found: $M^{+\bullet}$, 236.9793.

4-Iodo-6-methoxyquinoline (6).- Acetic anhydride (300 μL, 3.15 mmol) was added to a magnetically stirred suspension of 4-bromo-6-methoxyquinoline (**5**) (300 mg, 1.26 mmol) and sodium iodide (565 mg, 3.78 mmol) in acetonitrile (2 mL) maintained at 18°C. The ensuing reaction mixture was heated, for 3 h, at 80°C in a microwave reactor then cooled and treated with potassium carbonate (1.5 mL of a 10% aqueous solution), sodium sulfite (1.5 mL of a 5% aqueous solution) and dichloromethane (10 mL). The phases were separated, the aqueous layer extracted with dichloromethane (3 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow solid was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) and concentration of the appropriate fractions afforded title compound **6**[2] (337 mg, 94%) as a colorless, crystalline solid, mp 126°C (lit.[2] mp 85°C), R_f 0.3 (in 1:1 v/v hexane/ethyl acetate). ^{1}H NMR: δ 8.29 (br s, 1H), 7.99–7.89 (complex m, 2H), 7.65 (dd, J = 9.0 and 2.7 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR: δ 158.9, 146.9, 143.7, 132.4, 131.4, 131.3, 122.9, 110.2, 109.2, 55.4; IR (NaCl): ν_{max} 3344, 2953, 1617, 1555, 1498, 1452, 1423, 1350, 1264, 1232, 1159, 1028 cm^{-1}; MS (EI): *m/z* 285 ($M^{+\bullet}$, 100%); HRMS: $C_{10}H_8{}^{127}INO$ requires $M^{+\bullet}$, 284.9651. Found: $M^{+\bullet}$, 284.9651. *Anal.* Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.83; I, 44.51; N, 4.91. Found: C, 42.45; H, 3.19; I, 44.22; N, 4.96.

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A SHORT SYNTHESIS OF THE NATURALLY OCCURRING 2,3,3',4,4',5,5'-HEPTACHLORO- ("Q1") AND HEPTABROMO-1'-METHYL-1,2'-BIPYRROLES

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Of the more than 4,500 known naturally occurring organohalogen compounds[1] the halogenated bipyrroles are among the most interesting. For example, hexabromo-1,1'-dimethyl-2,2'-bipyrrole and 3,3',4,4'-tetrabromo-5,5'-dichloro-1,1'-dimethyl-2,2'-bipyrrole are present in the eggs of Pacific and Atlantic Ocean seabirds (albatross, puffin, gull, petrel, auklet) and in bald eagle liver samples,[2,3] and, more recently, 2,3,3',4,4',5,5'-heptachloro-1'-methyl-1,2'-bipyrrole (designated "Q1") (**1**) is found to be a ubiquitous marine natural product, detected in over 100 environmental marine samples from virtually all over the world (sea bird eggs, fish, the blubber of marine mammals, Antarctic air, and, remarkably, human milk from Eskimo women who consume whale blubber).[4] Although we established the structure of Q1 by total synthesis in 2002, the yield was very low due to the difficulty of synthesis and instability of the key intermediate 1,2'-bipyrrolyl **4**.[5] Subsequently, many mixed halogenated 1,2'-bipyrrolyls have been detected in a myriad of marine sources.[6] For example, 2,3,3',4,4',5,5'-heptabromo-1'-methyl-1,2'-bipyrrole (**2**) was tentatively identified in 2006.[6b,c]

To provide a more efficient synthesis of Q1 (**1**) for much needed analytical comparison and biological evaluation in view of its structural similarity to anthropogenic polychlorinated

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Base-Promoted Reactions of Dichlorocarbene Adducts of Cyclic Enamines: A New Route to Annulated Pyrroles

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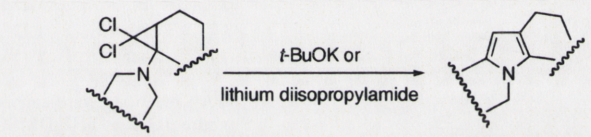
ABSTRACT



gem-dihalogenocyclopropanes
1–5

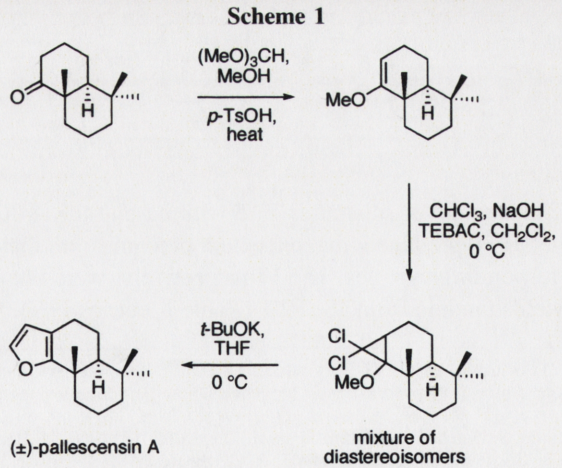
annulated pyrroles
13–17

Treatment of the *gem*-dihalogenocyclopropanes 1–5 with potassium *tert*-butoxide or LDA results in the formation of the corresponding and annulated pyrroles 13–17, respectively.

Recently, we reported that the dichlorocarbene adducts of various alkyl enol ethers react with strong base to give furans.[1] This process thus provides a method for the three-step furannulation of various enolizable ketones, and we have demonstrated the utility of it in the synthesis of the racemic modification of the furanosesquiterpenoid natural product pallescensin A.[1] The relevant reaction sequence is shown in Scheme 1, and the pathway by which the furan-forming step proceeds is the subject of ongoing studies within these laboratories.

In an effort to extend this type of chemistry, we were prompted to examine the base-promoted reactions of the corresponding dihalogenocarbene adducts of enamines. A major motivation for doing so was the expectation that these reactions might lead to pyrroles bearing otherwise difficult to obtain substitution patterns and so provide a useful addition to the repertoire of methods available for preparing these particularly important aromatic heterocycles.[2] Although the dichlorocarbene adducts of enamines are known,[3] we are not aware of any systematic studies of the base-promoted reactions of such compounds. Herein, therefore, we detail

Scheme 1



(±)-pallescensin A

mixture of diastereoisomers

our preliminary studies of this matter and report on the successful generation of a range of unusual pyrrolic systems[4].

The adducts **1**−**10** used in the present study were generally prepared (29−85%) by subjecting the relevant enamine to reaction with chloroform or bromoform and sodium hydroxide in the presence of the phase-transfer catalyst triethyl-

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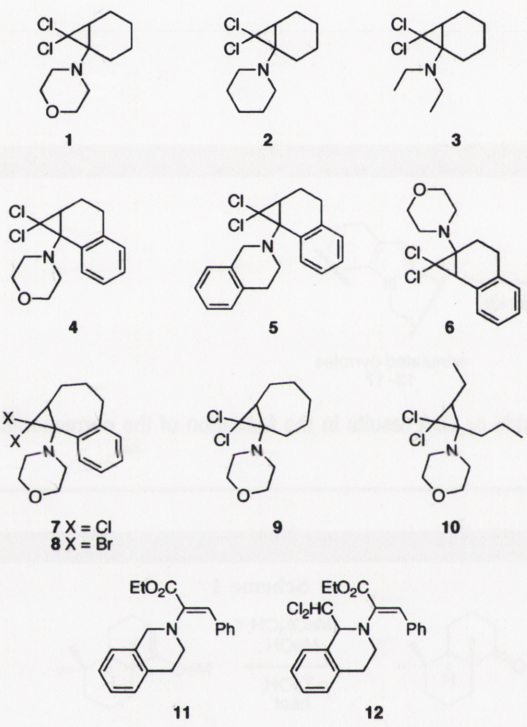
benzylammonium chloride (TEBAC) under conditions first defined by Mąkosza.[5] Despite the propensity of *gem*-dihalogenocyclopropanes carrying electron-donating substituents to undergo facile electrocyclic ring cleavage,[6] these adducts proved to be rather stable and generally crystalline materials. Indeed, the structures of compounds **4** and **6** were confirmed by single-crystal X-ray analysis.[7] In contrast, however, no success was had in efforts to isolate the dichlorocarbene adducts of the morpholino-based enamines derived from indan-1-one and cyclopentanone or the same types of adducts from the pyrrolidine-derived enamines of α-tetralone or cyclohexanone. In each instance only complex mixtures of materials were obtained. Interestingly, attempts to add dichlorocarbene to the double bond of the readily prepared amino-substituted cinnamate **11** delivered, as the only isolable material, what is tentatively identified as the dichlorocarbene insertion product **12** (11%).



The reaction of substrates **1**−**5** with base at 0−18 °C for 0.5−5.0 h produced the expected outcomes in that the corresponding pyrroles, **13**−**17** respectively, were obtained in yields ranging from 28−82% (Table 1, entries 1−7). Such

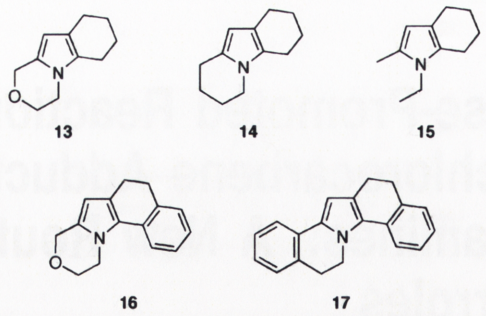


Table 1. Products Derived from Base-Promoted Reactions of Compounds **1**−**10**[a]

entry	substrate	base	temp (°C)	time (h)	product	yield (%)
1	**1**[b,c,d]	LDA	0	3	**13**	82
2	**2**[c,e]	LDA	0	3	**14**[f]	66
3	**3**	LDA	0	3	**15**[g]	54
4	**4**[d]	LDA	0	5	**16**	43
5	**4**	*t*-BuOK	0	0.5	**16**	28
6	**5**	LDA	0	3	**17**	45
7	**5**	*t*-BuOK	18	16	**17**	30−35
8	**6**[d,h]	*t*-BuOK	18	22	**18**	79
9	**7**	LDA	0	8	NR[i]	
10	**8**	LDA	0	3	**19**	81
11	**9**[d]	LDA	0	8	NR	
12	**10**	LDA	0	8	NR	

[a] All reactions were carried out using THF as solvent, except for entry 5 where 1:1 v/v THF/DMSO was used. [b] Reference 3a. [c] Reference 3e. [d] Reference 3f. [e] Reference 3b. [f] Reference 8. [g] Reference 9. [h] Reference 3c. [i] NR = no reaction.

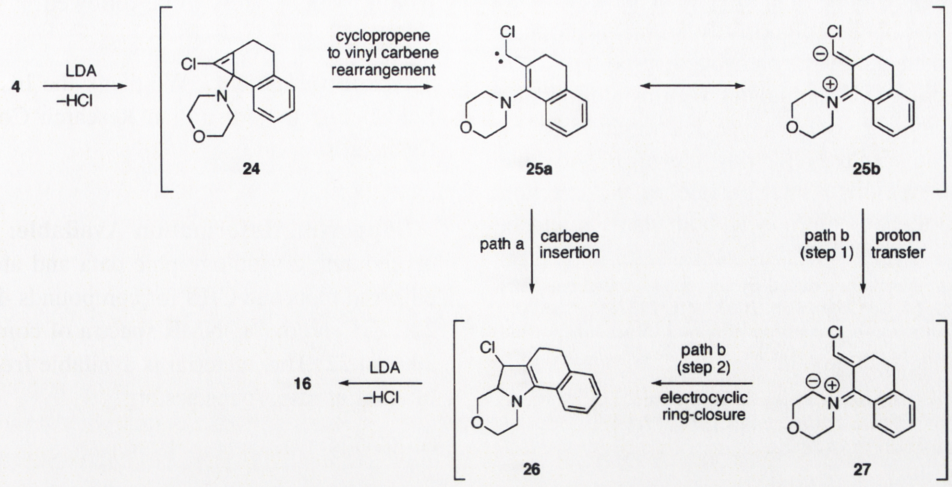
studies also revealed that lithium diisopropylamide (LDA) was a superior base to *t*-BuOK. The structures of the products were established by standard spectroscopic methods and confirmed through the single-crystal X-ray analyses of compound **16**[7] and a derivative of congener **17** (vide infra). The selective and efficient formation of the pyrrolo[2,1-*a*]-isoquinoline-type system **17** over its pyrrolo[1,2-*b*]isoquinoline-based isomer is noteworthy.

(2) For useful points of entry into the literature detailing new methods for the synthesis of pyrroles, their biogenesis, and their chemical manipulation, see: (a) Reisser, M.; Maas, G. *J. Org. Chem.* **2004**, *69*, 4913. (b) Agarwal, S.; Knölker, H.-J. *Org. Biomol. Chem.* **2004**, *2*, 3060. (c) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem.* **2005**, *9*, 1589. (d) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043. (e) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (f) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837. (g) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (h) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043. (i) Tóth, J.; Nedves, A.; Dancsó, A.; Blaskó, G.; Tőke, L.; Nyerges, M. *Synthesis* **2007**, 1003. (j) Pan, Y.; Lu, H.; Fang, Y.; Fang, X.; Chen, L.; Qian, J.; Wang, J.; Li, C. *Synthesis* **2007**, 1242.

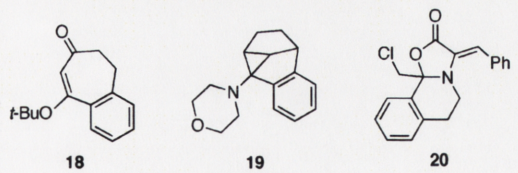
(3) (a) Ohno, M. *Tetrahedron Lett.* **1963**, 1753. (b) Wolinsky, J.; Chan, D.; Novak, R. *Chem. Ind. (London, UK)* **1965**, 720. (c) Pandit, U. K.; de Graaf, S. A. G.; Braams, C. T.; Raaphorst, J. S. T. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 799. (d) de Graaf, S. A. G.; Pandit, U. K. *Tetrahedron* **1973**, *29*, 2141. (e) Mąkosza, M.; Kacprowicz, A. *Bull. Acad. Pol. Sci., Chim.* **1974**, *22*, 467. (f) Graefe, J.; Adler, M.; Muehlstaedt, M. *Z. Chem.* **1975**, *15*, 14.

(4) This work was undertaken as part of a program within our group to exploit *gem*-dihalogenocyclopropanes as building blocks for chemical synthesis. For representative publications, see: (a) Banwell, M. G.; Gable, R. W.; Peters, S. C.; Phyland, J. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1395. (b) Banwell, M.; Edwards, A.; Harvey, J.; Hockless, D.; Willis, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2175. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R.; Wu, A. W. *J. Org. Chem.* **2000**, *65*, 4241. (d) Banwell, M. G.; Ebenbeck, W.; Edwards, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 114. (e) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2002. (f) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296. (g) Taylor, R. M. *Aust. J. Chem.* **2003**, *56*, 631. (h) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem.* **2004**, *57*, 537. (i) See reference 2b. (j) See reference 1. (k) Banwell, M. G.; Vogt, F.; Wu, A. W. *Aust. J. Chem.* **2006**, *59*, 415. (l) Banwell, M. G.; Phillis, A. T.; Willis, A. C. *Org. Lett.* **2006**, *8*, 5341. For a review of certain aspects of our work in this area, see reference 2c.

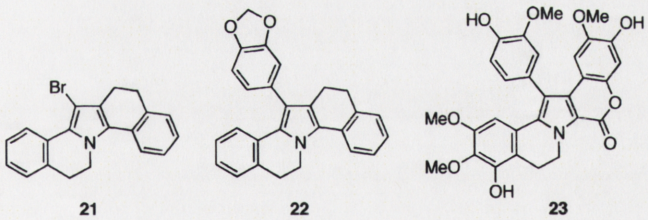
Scheme 2



There are a number of instances in which pyrrole formation is not observed. For example, subjection of compound **6**, the regioisomer of cyclopropane **4**, to treatment with *t*-BuOK failed to give the hoped for pyrrole. Rather, the β-oxygenated cycloheptenone **18**[7] was obtained in 79% yield (Table 1, entry 8). The origin of the divergent behavior of compounds **4** and **6** remains unclear at present. The lack of reaction of the dichlorocarbene adducts **7**, **9**, and **10** when subjected to the sorts of conditions just mentioned (see entries 9, 11, and 12) was also surprising and prompted an examination of the behavior of the *gem*-dibromo analogue **8**, of compound **7**, under the same conditions. Treatment of compound **8** with LDA (entry 10) provided the diquinane **19** in 81% yield. Presumably this compound arises through LDA-promoted lithium-for-bromine exchange at the apical cyclopropyl carbon, and this is followed by loss of the elements of lithium bromide to give the corresponding cyclopropylidene. This last species then undergoes insertion into the remote and *syn*-orientated benzylic C–H bond to give the observed product.[10] On the basis that treatment of the carbene insertion product **12** with base might deliver a pyrrole, this was treated with potassium *tert*-butoxide. However, the product so formed was the oxazolidinone **20** (62%), the structure of which follows from a single-crystal X-ray analysis.[7]



The utility of the pyrrole-forming reaction described above is highlighted by the conversion, using *N*-bromosuccinimde, of compound **17** into the brominated derivative **21** and then Suzuki–Miyaura cross-coupling[11] of the latter material with 3,4-methylenedioxyphenylboronic acid to give compound **22** (40% from compound **5**), the structure of which was secured by single-crystal X-ray analysis.[7] Pyrrole **22** bears some structural resemblance to the pentacyclic ring system associated with certain members of the lamellarin class of marine alkaloids, e.g., **23** (lamellarin K),[12] so the method described here offers considerable potential for the rapid preparation of a range of analogues of these biologically intriguing natural products. Work directed toward such ends is now underway in these laboratories and results will be reported in due course.



At least two distinct reaction pathways can be envisaged for the base-promoted conversion of compounds **1**–**5** into the corresponding pyrroles. Both of these (paths a and b, Scheme 2) would involve dehydrochlorination of the substrate, e.g., **4**, to give the corresponding ring-fused cyclopropene **24**[13] that then engages in ring opening to the

(5) (a) Mąkosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659. For a discussion of the methods available for the generation of dihalogenocarbenes, see: (b) Banwell, M. G.; Reum, M. E. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: London, 1991; Vol. 1, p 19.

(6) Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099.

(7) Details of the single-crystal X-ray analyses carried out as part of this study are provided in Supporting Information.

(8) Kolind-Andersen, H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 543.

(9) Volodina, M. A.; Mishina, V. G.; Terent'ev, A. P.; Kiryushkina, G. V. *Zh. Obshch. Khim.* **1962**, *32*, 1922.

(10) For an example of a related conversion, see: Marquis, E. T.; Gardner, P. D. *Tetrahedron Lett.* **1966**, 2793.

(11) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(12) For useful reviews on the biological properties and synthesis of the lamellarins, see: (a) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363. (b) Handy, S. T.; Zhang, Y. *Org. Prep. Proced. Int.* **2005**, *37*, 411. Also see: (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.

(13) These types of ring-fused cyclopropenes are readily trapped in Diels–Alder cycloaddition reactions. For example, see: Banwell, M. G.; Corbett, M.; Gulbis, J.; Mackay, M. F.; Reum, M. E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 945.

corresponding vinylcarbene **25a**/zwitterion **25b**.[14] This last species could undergo C−H insertion (path a) to give the chlorinated dihydropyrrole**26**[15] that loses a second equivalent of HCl to deliver the observed and fully aromatic product, e.g., **16**. An alternate pathway (path b, Scheme 2) would involve intramolecular proton transfer within intermediate **25** to give the ylide **27**. Such a species might then be expected to undergo electrocyclic ring closure[2a,16] to give dihydropyrrole **26**, the final intermediate in the reaction sequence and one that is common to both paths a and b. Our recent and soon-to-be published mechanistic studies on the equivalent furan-forming reaction lead us to believe that path a is more likely to be followed.

(14) For a review on thermally-induced cyclopropene to carbene rearrangements, see: Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271.

(15) For a related pathway that has been proposed to account for the formation of an annulated furan, see: Mueller, P.; Pautex, N. *Helv. Chim. Acta* **1988**, *71*, 1630.

(16) These types of ring-closures are well documented. For a review, see: Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947.

(17) CCDC numbers 652972−652977.

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Supporting Information Available: Full experimental procedures; crystallographic data and atomic displacement ellipsoid plots and CIFs for compounds **4**, **6**, **16**, **18**, **20**, and **22**;[17] ^{1}H and/or ^{13}C NMR spectra of compounds **1**−**5**, **13**−**20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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