Formation of Nitrogen Heterocycles
by Radical Methods

by

Roshan T. A. Mayadunne
BSc. (Hons.) Murdoch

To mother and father

A Thesis submitted for the degree of

Doctor of Philosophy

of

Research School Of Chemistry
The Australian National University

September 1996
To my mother, and father

with love and gratitude
Declaration

The work described in this thesis is original and has not previously been submitted for a degree or diploma in any other University or College, and to the best of my knowledge, does not contain material previously published or presented by another person, except where due reference is made in the text.

Roshan T. A. Mayadunne
Acknowledgments

My mother, Rita and my father, Percy have provided me with the opportunities to be what I am today. They have guided me through hard times, shared my triumphs with happiness and encouraged me always to persevere with my studies. Therefore, it is most appropriate to begin my acknowledgments first by thanking them. I shall always cherish their gift of education to me.

Whatever knowledge I have acquired is because of my teachers. They have taught me well and with good intentions. Among my teachers a special place is due to my supervisor, Professor Athelstan Beckwith, who has provided me with a wealth of knowledge in Chemistry, trained me in laboratory techniques and very patiently advised me on how to improve my writing skills. I am privileged to be one of his students. I thank him for accepting me, making me knowledgable and helping me to reach this milestone. I also wish to thank Professor Robin Giles since it was he who taught me the basics of research. I admire his guidance and most of all his kindness which has greatly helped me to achieve what I have today.

My friends and colleagues have helped me in so many ways to bring this work to completion. Among these Dr. Sajan Joseph occupies a special place. He has always encouraged me when I was dispirited, helped me out from hard situations, even after his departure. Another is Mr. Robert Longmore, who must hold the world record for making Bu₃SnH the most number of times. I have found a very sincere friend in him. Dr. John Storey and Dr. George Adamson agreed to sift out most of the bad elements from my thesis for which I am very grateful. Others especially my lab colleagues Mr. David Harman, Dr. John Axon, Dr. Kitty Drok, Ms. Chee Yong Gan, and Dr. John Lambert have provided me with good friendship and a noisy atmosphere. I have enjoyed working with them in the lab 235. My gratitude is also extended to Mr. Tony Herlt for his help with the HPLC, Ms. Joan Smith with library matters, Mr. Nick guoth with computer problems, Ms. Tin Culnane with the NMR, Dr. David Hockless with x-ray crystallography and Ms. Maureen Slocum with administrative matters. Every time I approached them I came out with the best solution. I am deeply grateful to these people.

My wife, Renuka has been the greatest contributor to this work. She has not only provided me with love and affection in every way possible but also managed to put up with my daily habitudes with great patience. I wish to express my deep gratitude and love for all the support she has given me during my studentship.
Contents

ABSTRACT vi

CHAPTER 1: Introduction 01

1.1 The Chemistry of Radicals 02
1.2 Radicals in Organic Synthesis 12
1.3 The Aim of the Project 19

CHAPTER 2: Intramolecular Radical Addition - A Model 20

Study Towards Nitrogen Heterocycles 20

2.1 Introduction 21
2.2 Model Intramolecular Cyclisations 23
2.3 Allylic Interactions & the steric course of the reaction 30
2.4 Effect of the Amide Carbonyl 36
2.5 Molecular Model Calculations 42
2.6 Carbamate Derived Radical Precursors 44
2.7 Model Studies to Polyhydroxylated Indolizines 54

CHAPTER 3: Synthesis of (±)-O-Methylcorytenchirine 62

3.1 Introduction 63
3.2 Previous Syntheses of Corytenchirine 65
3.3 Retrosynthetic Analysis of (±)-O-Methylcorytenchirine 69
3.4 Synthesis of (±)-O-Methylcorytenchirine 71
CHAPTER 4: A General Radical Route to Pavine & Aporphine Alkaloids

4.1 Introduction
4.2 Retrosynthetic Analysis of Argemonine
4.3 A model Study Leading to Pavine Alkaloids
4.4 A Model Study Leading to Aporphine Alkaloids
4.5 Synthesis of (±)-Argemonine & (±)-Glaucine
4.6 Conformation of Precursor Substrates & their Relationship to the Product Ratio

CHAPTER 5: Approaches to Enantioselective Synthesis of Pavine & Aporphine Alkaloids

5.1 Introduction
5.2 The Synthetic Strategy & Model Reactions
5.3 Attempted Synthesis of Optically Pure (−)-Argemonine & (−)-Glaucine

CHAPTER 6: Conclusions & Future Directions

CHAPTER 7: Experimental

7.1 General Experimental
7.2 Experimental
7.3 Appendix A
7.4 Appendix B
7.4 Appendix C

REFERENCES
Abstract

The use of radical methodology in organic synthesis has grown in importance during the past decade. Many applications in the area of carbocyclic ring construction by radical methods can be found in recent literature. By comparison, the number of methods which employ radical reactions to assemble nitrogen heterocycles is few; hence the current study.

Experiments conducted towards the assembly of indolizine, and quinolizine model compounds revealed that the radical generated from 1-(2-bromobenzoyl)-2-phenyltetrahydro-4-pyridone and other related substrates approached the double bond anti to the substituent α to the nitrogen atom. As a result the reaction afforded a single diastereomer. The relative stereochemistry of the products were initially assigned by routine spectroscopic methods and subsequently confirmed by single crystal x-ray crystallography. The excellent selectivities achieved from these reactions were attributed to a novel phenomena most commonly referred to as 1,3-allylic strain. Cyclisation of similar substrates lacking the amide carbonyl, a participating functionality in the 1,3-allylic strain theory, was shown to afford both diastereomers in a 3:1 ratio. Hence the involvement of 1,3-allylic strain during cyclisations was confirmed. These results were also supported by conducting molecular model calculations which revealed a 3 Kcal/mol energy difference between the transition structures leading to the two possible diastereomers. This energy difference was reduced to 0.4 Kcal/mol in the absence of the amide carbonyl.

The utility of the stereoselective radical ring annulation method in the construction of naturally occurring compounds was demonstrated by the diastereoselective synthesis of (+)-O-methylcorytenchirine. The overall yield recorded for the synthesis was 43%.

Model radical ring closure reactions of 1-(2-bromobenzyl)-2-phenoxy-carbonyldihydroisoquinoline and related derivatives afforded pavine related compounds as anticipated. However, these reactions also afforded aporphine related analogues by radical attack at the C8 carbon of 1-benzylisoquinoline derivatives. A mechanism for this latter ring closure/oxidation reaction has been proposed. Subsequently the developed methodology was utilised in the synthesis of (±)-argemonine and (±)-glaucine. Related studies leading to (−)-argemonine and (+)-glaucine have met with moderate success. The maximum optical purity achieved from these reactions was assessed to be 45%.
CHAPTER 1

Introduction

1.1 The Chemistry of Radicals

1.2 Radicals in Organic Synthesis

1.3 The Aim of this Project
1.1 The Chemistry of Radicals

"The body is extremely unsaturated. A solution of it in benzene or in carbon disulphide absorbs oxygen with great avidity and gives an insoluble oxygen compound. It absorbs chlorine, bromine, and iodine. It does not unite with carbon monoxide.

The experimental evidence presented above forces me to the conclusion that we have to deal here with a free radical, triphenylmethyl, \((\text{C}_6\text{H}_5)_3\text{C}^*\)."

Moses Gomberg

Thus, free radical chemistry was born. When Moses Gomberg first suggested the existence of triphenylmethyl radicals in 1900 his paper was rather badly received by the scientific community. This disbelief gradually turned into acceptance following pioneering work on homolytic substitution of aromatic systems by D. H. Hey, W. A. Waters and on the chemistry of alkyl radicals by M. S. Kharasch in the nineteen thirties and forties. Subsequently, organic free radical chemistry gained ground as an entirely new field, and during the intervening years has grown in importance to the point that it now is regarded as part of the general armoury of synthetic reactions during strategic planning of complex organic molecules.

According to the Pauli principle, any two electrons occupying the same orbital must have opposite spins, so that the resultant magnetic moment is zero for any species that contains paired electrons (figure 101). However, since radicals contain one or more unpaired electrons the net magnetic moment is finite and they are therefore paramagnetic. Thus, a ‘free radical’, often simply called a radical, is best defined as an atom or a group of atoms which contains one or more unpaired electrons.

![Diamagnetic and Paramagnetic](Figure 101)
The elementary reactions available to organic free radicals are generally considered to be those shown in scheme 101. The first reaction in the reverse direction, namely bond homolysis, is often very slow at ordinary temperatures since the activation energy must be equal to or greater than the bond dissociation energy. Consequently, only compounds that contain relatively weak bonds, for example peroxides, are suitable for the generation of free radicals under the conditions generally used for synthesis. By contrast, coupling of radicals (reaction 1 - forward direction) is often extremely fast and approaches the diffusion controlled limit. Such reactions are exothermic and usually have very low activation energies. However, under the conditions generally used for synthesis the stationary concentrations of radicals are often so low that radical recombination (reaction 1 - forward direction) does not compete effectively with other available reactions such as homolytic substitution (reaction 2) or radical addition (reaction 3 - forward direction). Rate constants for homolytic substitution vary widely. For instance, the synthetically important transfer of hydrogen atoms from \( \text{Bu}_3\text{SnH} \) to alkyl radicals has a rate constant of about \( 10^6 \text{ M}^{-1}\text{s}^{-1} \) but for aryl radicals the rate approaches diffusion control. Radical substitution at \( \text{H} \) in \( \text{PhSeH} \) and \( \text{PhSH} \) has a very high rate constant whereas substitution at sulphur in sulfides and related compounds is often rather slow (\( 10^3 \text{ M}^{-1}\text{s}^{-1} \)). Since they do not involve the loss of translational entropy intramolecular radical reactions often compete effectively with fast intermolecular processes. Many such intramolecular atom or group transfers have been documented. One such example, a 1,5-hydrogen atom transfer, is illustrated in scheme 102.

1. \( \text{A}^* + \text{B}^* \rightleftharpoons \text{A-B} \) (coupling or homolysis)

2. \( \text{A}^* + \text{B-C} \rightleftharpoons \text{A-B} + \text{C}^* \) (atom or group transfer)

3. \( \text{A}^* + \text{B}=\text{C} \rightleftharpoons \text{A-B-C}^* \) (addition or \( \beta \)-fission)

4. \( \text{A}^* + \text{B-C} \rightleftharpoons [\text{A-B-C}]^* \) (addition or \( \alpha \)-fission)

5. \( 2[\text{H-A-B}]^* \rightleftharpoons \text{HABH} + \text{B=C} \) (disproportionation)

6. \( \text{A}^* + \text{e} \rightleftharpoons \text{A}^- \) and \( \text{A}^* - \text{e} \rightleftharpoons \text{A}^+ \) (electron transfer)

\textbf{Scheme 101}
A number of reactions involving radical addition to multiple bonds (scheme 101 - reaction 3) or to coordinatively unsaturated atoms (scheme 101 - reaction 4) have been used in synthesis. The additions of carbon centred radicals to alkenes or alkynes are particularly useful as they lead to the formation of new C-C bonds. Often the radical arising from inter- or intra-molecular addition reacts by atom transfer with a hydrogen atom donor such as Bu$_3$SnH to afford the neutral product and a chain carrier Bu$_3$Sn$^*$. On the other hand if the product radical adds to another molecule of the unsaturated substrate the process is commonly referred to as telomerisation. Repeated addition, consuming hundred or thousands of substrate units results in radical polymerization as observed in the production of polystyrene (scheme 103). The use of intramolecular radical addition for the construction of carbocyclic and heterocyclic systems is especially important in natural product synthesis.

\[ \text{Ph}^* + \text{Ph} = \text{Ph} - \text{Ph} \]

\[ \text{Ph}^* + \text{Ph} = \text{Ph} - \text{Ph} \]

\[ \text{polystyrene} \]

\text{Scheme 103}
The reverse of addition (scheme 101 - reaction 3) is β-fission. It is a process in which a radical fragments by scission of a bond β to the radical centre to afford a new radical species. A good example is the rapid ring opening of cyclopropylmethyl radical to 3-butenyl radical as illustrated in scheme 104.

Ring opening of cyclopropylmethyl radical is fast and is known to proceed with a rate constant of $1.2 \times 10^8$ s$^{-1}$ at $37^\circ$C. Because of the rapidity of the process, many of such systems have found wide use as probes (radical clocks) in the investigation of reaction mechanisms. On the other hand such ring openings are also regioselective and have found various applications in organic synthesis. One such application is illustrated in scheme 104. The ring opening of the isomeric carbocycles shown (scheme 104) is highly regioselective presumably because the bond breaking process proceeds most efficiently when there is good overlap between the SOMO and the molecular orbitals of the bond concerned. Many other applications of cyclopropylmethyl radicals in organic synthesis are documented in literature and their chemistry has also been reviewed recently.

Familiarity with the general elementary processes of scheme 101 is of considerable help in rationalising the outcome of reactions. However, for the planning of syntheses, one needs to be able to use this information predictively. Under a defined set of experimental conditions which steps will be the fastest and hence control the outcome? For simple systems the use of thermochemical criteria based on bond
dissociation energies is reasonably effective. Such an approach underpins the qualitative rule that radical reactions preferentially follow the more exothermic pathway. However, in many systems, particularly those involving complex substrates, the thermochemical approach, by itself is not reliable. Other factors must be taken into account; they include steric, stereoelectronic and polar effects. Steric effects reflect the degree to which non-bonded interactions affect the energy of the transition structure whereas stereoelectronic effects are related to the strain energy generated in the transition structure by the necessity to achieve effective overlap of the frontier orbitals involved in bond breaking and bond making processes. Polar effects reflect the stabilising or destabilising influence of the relative electronegativities of constituent atoms and groups on the transition state. Because of these effects thermochemical criteria are often of minor importance in determining the outcome of some radical reactions of complex molecules.

The degree of involvement of steric, stereoelectronic and polar factors in controlling regio- and stereo-selectivity in simple intramolecular cyclisations is illustrated by the cyclisation of the 5-hexenyl radical and related species (scheme 105), from which the well known Beckwith guidelines have been derived. This system provides a good example of how homolytic processes proceed contrary to predictions made based on thermochemical criteria.

Thus, on thermochemical grounds, the 5-hexenyl radical 101, when generated from the bromide 102 in the presence of a hydrogen atom donor would be expected to ring close at the least substituted end of the double bond to afford the 6-endo product 105 via the more stable secondary radical 103 in preference to the other possible
product, methylcyclopentane 106, via the less stable primary cyclopentylmethyl radical 104. Although early thermochemical calculations and experimental observations supported this conclusion, later careful analysis of the experimental results showed that 101 predominantly undergoes preferential 1,5-ring closure to give 104 under the usual experimental conditions. Cyclisation at the other terminus of the double bond to afford the 6-endo product 105 was found to be much slower.

Theoretical calculations\(^\text{13}\) now support the view that attack of a carbon centred radical on an olefinic bond involves overlap of the semi-occupied 2\(p\) orbital of the incoming radical with one lobe of the vacant \(\pi^*\) orbital of the olefin. As a result, the transition state of the addition process incorporates the participating atoms at the vertices of an obtuse triangle (1, 2, and 3 - figure 102), orthogonal to the nodal plane of the \(\pi\) system. Models and molecular mechanics calculations\(^\text{14}\) reveal that such an overlap of orbital is best accommodated in the transition complex for exo-ring closure rather than in that for endo-attack. Thus, ring closure of 5-hexenyl radical is mainly under stereoelectronic control and does not conform to predictions based on thermochemical data.

![Figure 102](image)

Most importantly, the stereochemical outcome on cyclisation of 5-hexenyl systems substituted at 1, 2, 3 and 4-carbons has been shown to favour one or the other of the two possible outcomes. While 1,5-exo ring closure of 2 and 4-substituted 5-hexenyl systems has been shown experimentally to afford predominantly trans products, 1 and 3-substituted substrates yield mainly cis isomers.\(^\text{15}\) The fact that theoretical calculations predict the distance between the carbon atoms of the newly forming bond in the transition state leading to exo ring closure to be similar to the distance between C1 and C3 of cyclohexane sheds light on the general arrangement of the atoms in the transition structure which is thought to resemble the chair form of cyclohexane. Thus, for the cyclisation of any mono-substituted 5-hexenyl radical there will be two isomeric transition structures, one in which the substituent is pseudo-equatorial and one in which it is pseudo-axial. By analogy with cyclohexane
derivatives the former is expected to be of lower energy than the latter. Molecular
mechanics calculations support this hypothesis.\textsuperscript{16} As an example, a substituent at C-3 in
the transition structure for cyclisation preferably occupies a pseudo-equatorial
position as illustrated in figure 103. This transition structure leads to the
predominance of the cis-product observed by experiment.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure103}
\caption{Chair-like transition state}
\end{figure}

These observations have been formulated as a set of guidelines, known as
Beckwith guidelines\textsuperscript{15,17} to predict the stereochemical outcome of simple substituted
5-hexenyl radicals. They are also applicable to much more elaborate organic systems
as will be explained in the next section. The guidelines state that while 1,5-exo ring
closure of 1 or 3 substituted 5-hexenyl substrates lead predominantly to cis-
disubstituted cyclopentyl products, 2 or 4 substituted substrates afford mostly trans
isomers. Following these communications, many other recent reviews\textsuperscript{18} addressing
the subject of the stereochemistry of free radical cyclisations have appeared in
literature.

Most of the synthetically useful radical reactions involve a chain mechanism.
Three distinct processes are involved: initiation, chain propagation, and termination.
The initiation step requires the formation of radicals by thermal or photochemical
homolysis of a suitable initiator. For thermal initiation at moderate temperatures the
precursor must possess bonds of relatively weak energy. Peroxides such as di-tert-
butyl hyponitrite and azo-bis-isobutyronitrile (AIBN) are commonly used. The
decomposition of AIBN which involves the formation of two moles of cyanopropyl
radicals and one mole of molecular nitrogen from one mole of initiator is illustrated in
scheme 106.

\begin{eqnarray*}
\text{CN} & \text{CN} \\
\text{N=N} & \text{CN} \\
\Delta \text{ or } \text{hv} & 2 \cdot \text{CN} + N_2
\end{eqnarray*}

\textbf{Scheme 106}
Chapter 1: Introduction

Chain propagation may involve one or more steps, usually radical addition and/or homolytic substitution. Chain propagating steps are characterised by the generation of a new radical for each radical consumed. Thus the chain is propagated. An important reagent often used in chain processes is Bu₃SnH. Its reaction with a radical by homolytic substitution at hydrogen affords Bu₃Sn* radicals which usually propagate the chain by interaction with a suitable substrate, for example an alkyl halide, xanthate, or selenide.¹⁹

Many synthetically useful chain reactions involve more than one step in the chain propagation process. When Bu₃SnH is used as a reagent it is often possible to devise experimental conditions whereby radical addition, either inter- or intramolecular, or a radical translocation by intramolecular atom transfer to give a new intermediate radical, precedes intermolecular atom transfer. A typical chain propagation sequence is illustrated in scheme 107 by the reduction of 1-bromo(iodo)-5-hexene with Bu₃SnH. Under suitable experimental conditions the 5-hexenyl radical undergoes cyclisation by intramolecular addition to give the cyclopentylcarbinyll radical which then undertakes hydrogen atom transfer from Bu₃SnH to give methyl cyclopentane and Bu₃Sn* radicals. The latter interact with the substrate by homolytic substitution at halogen to afford 1-hexenyl radicals. The driving force behind the overall propagation sequence is the formation of a relatively strong R-H bond and the exchange of a relatively weak Sn-H bond for a strong Sn-Br(I) bond.

\[
\text{Bu}_3\text{SnX} \rightarrow \text{Bu}_3\text{Sn}^* \rightarrow \text{Bu}_3\text{SnH} \rightarrow \text{Bu}_3\text{Sn}^* \rightarrow \text{Bu}_3\text{SnX}
\]

Scheme 107

\(X = \text{Br or I}\)
Inspection of scheme 107 prompts the question of why the 5-hexenyl radical undergoes cyclisation rather than react directly with Bu$_3$SnH to give hexene. The answer lies in the experimental conditions used. The reaction of 5-hexenyl radicals with Bu$_3$SnH is bimolecular and follows second order kinetics whereas the cyclisation step is first order. The rates of both reactions are proportional to the concentration of the 5-hexenyl radicals but only the second order rate is dependant on the concentration of Bu$_3$SnH. Hence by comparison with the cyclisation step the rate of the bimolecular reaction can be diminished by decreasing the concentration of Bu$_3$SnH.

The rate expression governing the outcome of the reaction in scheme 107 is shown in figure 104 where $k_C$ is the rate constant for cyclisation of the 5-hexenyl radical and $k_H$ is the rate constant for hydrogen atom transfer from Bu$_3$SnH. Clearly the key features governing the outcome of the reaction are the relative values of $k_C$ and $k_H$ and the concentration of Bu$_3$SnH. It is noteworthy that the concentration of the substrate does not affect the outcome except insofar as it may influence the rate of chain termination (see below). In the case of the reaction illustrated in scheme 104 the value of $k_C$ is relatively large and good yields of cyclised products can be obtained when moderate concentrations of Bu$_3$SnH are used. However, even in instances when the rate constant for the intramolecular reaction is much less than $k_H$, the yield of directly reduced product can usually be kept to a minimum by using very low concentrations of stannane. In practice this is often achieved by means of slow syringe pump addition of the stannane during the course of the reaction.

\[
\frac{d[\text{Product}]}{d[\text{RH}]} = \frac{k_C}{k_H} \frac{1}{[\text{Bu}_3\text{SnH}]} \]

\[a : \text{Bu}_3\text{SnH, AIBN, benzene}\]
The radical reactions, disproportionation (scheme 101 - reaction 5 - forward direction) and coupling (reaction 1 - reverse direction), act as chain termination processes since radicals are consumed and no new radicals are generated. As the rate constants for radical-radical reactions are usually so high (ca. $10^9 \text{M}^{-1}\text{s}^{-1}$) chain termination would be expected to present a serious obstacle to the maintenance of a radical chain process. However, when the chain propagation steps are fast the stationary concentration of radicals remains so low that termination is a relatively slow process. This is the case for the reduction of alkyl halides with tributyl stannane where both chain propagation steps have large rate constants (ca. $10^6 \text{M}^{-1}\text{s}^{-1}$). Consequently, for such reactions only a very small amount of initiator must be used. If any one of the chain propagation steps is relatively slow, chain termination competes effectively and larger amounts of initiator are necessary. As a rough guide, it is difficult to carry out a chain process if any of the propagating steps has a rate constant less than $10^2 \text{M}^{-1}\text{s}^{-1}$ or $10^2 \text{s}^{-1}$.

Cyclopentane and cyclohexane rings are very much embedded in organic molecules. The ease of formation of such rings by radical methodology in contrast to ionic protocols in some instances has led many synthetic organic chemists to design elegant syntheses, some heavily reliant on radical chemistry. As the current work concentrates on the use of radical methodology in organic synthesis it is most appropriate to outline some of these outstanding efforts. The next section of this chapter will deal with this subject.
1.2 Radical reactions in Organic Synthesis

From the discovery of radicals early in the nineteenth century until the last decade, free radical reactions were considered to be capricious, uncontrollable, and virtually useless for organic synthesis. This view has mainly been due to the lack of understanding of the factors governing radical reactions. With the elucidation of the mechanistic principles underlying radical reactions, the determination of typical rate constants and the recognition of the factors controlling the various forms of selectivity namely regio-, chemo- and stereo-selectivity, synthetic organic chemists were able to define reaction conditions to achieve the desired conversions by 'controlling' the generated radicals in a predictive manner. With this success the last decade has seen an explosion in the use of radical methodology in organic synthesis.

There are often advantages in using radical reactions for organic synthesis rather than the traditional ionic methods. Firstly, although carbon centred radicals are extremely reactive, most addition reactions proceed under mild neutral conditions, often with high regio-, chemo- and/or diastereo-selectivity. Secondly, unlike cations or anions, radicals do not associate with counter ions and are thus, highly suited for the formation of sterically hindered bonds such as quaternary or neopentyl centres. This fact is well illustrated by Nagarajan's\textsuperscript{21} and Curran's syntheses (described below) of the angular triquinanes. Thirdly, since carbon centred radicals are inert to a multitude of functionality, tedious protection/deprotection sequences can often be avoided.

One of the most fascinating and ingenious uses of radical chemistry in organic synthesis emerged in 1985 when Curran \textit{et. al.} published a series of papers on the syntheses of triquinanes. The first of his communications\textsuperscript{22} described the construction of the \textit{cis-anti-cis} fused cyclopentane rings of hirsutene \textbf{107}, a linear triquinane, from a pre-synthesised monocyclic substrate \textbf{108} by radical methodology in one step and in a highly stereocontrolled manner. The synthesis commenced from the readily available lactone \textbf{109}, which was subjected to \textit{anti} \textit{S}\textsubscript{N}2' cuprate addition to afford the desired \textit{trans} relationship of the side chains. The addition product \textbf{110} was then transformed into the radical precursor \textbf{108} in six steps.

The elegance of the synthesis is demonstrated in the next step of the sequence, when \textbf{108} was treated with Bu\textsubscript{3}SnH and AIBN. The reagents initially generated the primary substrate radical by abstraction of the iodine atom which readily underwent ring closure in an exocyclic manner 'in tandem' \textit{via} the intermediates \textbf{111} and \textbf{112} to
afford hirsutene 107 in one pot as illustrated in scheme 108. Radical SOMO overlap with the alkene LUMO in a transition state that leads to a trans-bicyclooctane is a disfavoured process, therefore both radical ring closures afforded only the cis-cis fused product 107. On the other hand the trans relationship of the two side chains in the radical precursor dictates the relationship of the two outer rings about the central ring. Consequently the cyclisation yielded only the anti isomer. Following the successful synthesis of hirsutene 107, capnellene, another linear triquinane has also been assembled by similar tandem radical cyclisation methodology commencing with the appropriately substituted substrate.23

![Scheme 108](image)

In a second series of publications,24 in 1986 and 1987 Curran et. al. extended their method of tandem radical cyclisations to the synthesis of angular triquinane (±)-siphiperfolene 113. The synthesis is illustrated in scheme 109 and is a good example of the ease with which quaternary carbon centres can be formed by radical reactions. Sequential deprotonation of 3-ethoxycyclopentanone 114 by LDA followed by alkylation of the lithium enolate with methyl iodide and allyl vinyl dibromide 115 afforded compound 116. The alkylated ethoxyenone 116 was treated with butenyl magnesium bromide and allowed to undergo standard hydrolytic rearrangement to afford the radical precursor 117 in three steps. The classic tandem ring closure was initiated by treatment of the vinyl radical from the bromide 117 with the aid of Bu3SnH. Because vinyl radicals rapidly invert at the radical centre the stereochemistry of the starting halide is not a matter of concern. Consequently it
underwent ring closure to afford the intermediates 118 and 119. After the second cyclisation and hydrogen atom transfer from Bu₃SnH the tricyclic product isomers 120 and 121 were isolated as an inseparable mixture of isomers (ratio 1:3 respectively) in 66% yield. Acquisition of the undesired endo-methyl product 121 as the major isomer was rationalised on the basis of Beckwith transition state model discussed in section 1.1. Wolff-Kishner reduction of the C2 ketone of both isomers followed by purification of the crude product yielded both silphiperfolene 113 and 9-episilphiperfolene 122.

Although the overall yield of silphiperfolene amounted to a respectable 10%, the authors sought a method to circumvent the production of the undesired isomer as the major product. They reasoned that the introduction of an endo substituent on the central ring in a 1,3-orientation to the relevant methyl group would raise the energy of
the transition state and would reverse the stereochemistry during cyclisation. Indeed by conversion of the keto group into a ketal (compound 123) followed by cyclisation with Bu3SnH and reduction of the keto group after hydrolysis of the ketal (scheme 110), (+)-silphiperfolene 113 was obtained as the major isomer in 25% overall yield. Shortly after Curran's synthesis of (+)-silphiperfolene 113, Meyers et al. successfully developed an efficient preparation of the natural product in enantiomerically pure form.25 Coupled with Meyers' asymmetric alkylation procedure, Curran's 'tandem' ring closure method indisputably demonstrates the power of radical ring closure methods. A review on Curran's general strategy for the synthesis of triquinanes has been published recently.26

\[
\begin{align*}
\text{Scheme 110}
\end{align*}
\]

Many other syntheses involving radical tandem cyclisation processes have been recorded in literature. These include Kilburn's synthesis of isoiridomycin,27 Parson's approach to lysergic acid derivatives,28 Corey's biomimetic synthesis of 1-epi-prostaglandin F2α,29 Ferrier's synthesis of azadirachtin and bissetone,30 and Nagano's approach to 1-epi-magybardienedio1.31

The stereochemical selectivity achievable by radical methodology is well demonstrated in Hart's clever syntheses of trans-perhydroindans. After model experiments32 the method was successfully applied to the synthesis of the quinolid antitumor antibiotic pleurotin (scheme 111).33 Reductive alkylation of benzoic acid
followed by iodo-lactonisation of the cyclohexadiene afforded the bridged bicycle \(124\) in four steps and in 54\% overall yield. The next step of the synthesis focused on the introduction of the olefin required for the radical ring closure step and was achieved by a stereoselective Wittig olefination reaction which afforded \(125\) in 94\% yield.

\[
\begin{align*}
&\text{CO}_2\text{H} \quad \text{a} \quad \text{CHO} \quad \text{b} \quad \text{CO}_2\text{Et} \\
&\text{124} \quad \text{125} \\
&\text{pleurotin} \quad \text{126} \\
&\text{127}
\end{align*}
\]

a: 4 steps, b: Ph\(_3\)P=CH\(_2\)CO\(_2\)Et, c: Bu\(_3\)SnH

Scheme 111

With the acquisition of \(125\) the stage was set for the key radical ring closure step. The iodo bicycle \(125\) readily afforded trans-perhydroindan \(126\) in 81\% yield. The ingenuity of this reaction does not lie in the reported yields but in the selective manner in which the three stereocentres are generated in one step. The oxabicyclo[3.3.0]octane substructure in \(126\) is preferentially cis fused because of the inflexible nature of the bicycle. Consequently, when ring closure occurs the more adaptable perhydroindan substructure is forced to a trans fused arrangement. Thus, the lactone ring served as a powerful stereo-control element, without which the formation of the cis-perhydroindane would have occurred preferentially.

To add to the merit of the reaction the stereochemistry at C10 and C9 was also established during the cyclisation step. The stereochemistry at the former carbon accords with Beckwith's guidelines, which state that 1-substituted 5-hexenyl systems preferentially afford cis isomers as expected on the basis of a cyclohexane chair-like transition structure (structure \(127\)-scheme 111). On the other hand stereo control at C9 was surprising as only 4\% of the other isomer of \(128\) was formed (scheme 112). The stereocentre at C9 is established during hydrogen atom transfer from Bu\(_3\)SnH to the tertiary radical \(129\). The authors suggested that the high stereoselectivity of this
reaction might reflect the preferential transfer of hydrogen to the less hindered face of the intermediate radical in the low energy conformation 129. Whatever the reason, this sequence illustrates well the fact that the high reactivity of radicals does not necessarily compromise the selectivity of their reactions.

![Scheme 112](image)

Formation of nitrogen heterocycles by radical ring closure was initiated by Hart et. al. in 1984. His method of generation of the carbon centred radical by Bu₃SnH involves the presence of a phenylthio group in the radical precursor instead of the usual halo atom. Hart’s synthesis of isoretronecanol 130 exemplifies the execution of this strategy (scheme 113). In addition, Hart et. al. have also used similar methodology for the preparation of (+)-supinidine, (+)-heliotridine and (+)-hastanecine.

![Scheme 113](image)
Initial N-alkylation of succinimide with the appropriately substituted hydroxy acetate 131 under Mitsunobu conditions followed by selective NaBH₄ reduction and hydroxy-thiophenoxy interchange afforded the radical precursor 132 in 73% overall yield (scheme 113). The radical ring closure to 133 followed the route illustrated in scheme 113. The tin centred radical attacks the sulphur atom with homolysis of the S-C bond to afford the secondary carbon centred radical in 134. Rapid cyclisation followed by disproportionation with Bu₃SnH afforded the bicyclic product 133. The selectivity achieved during this cyclisation was reported to be 9:1 in favour of the product 133. Once again the preferential formation of 133 follows Beckwith’s guidelines; the chair-like transition structure is 134 leading to 133 is illustrated in scheme 113. Compound 133 was subsequently converted into isoretronecanol in four steps.

In addition to five membered nitrogen heterocycles, six membered analogues have also been prepared along radical routes. These include Beckwith’s synthesis of epilupinine,37 Hart’s synthesis of manzamine alkaloids,38 Simpkin’s approach to histrionicotoxin,39 Yamazaki’s synthesis of emetin,40 Prabhakar’s approach to phenanthridines,41 Parsons’ synthesis of carbapenams,42 and Kano’s approach to morphine analogues.43
1.3 **The Aim of the Project**

The previous section described how radical methods have been used to the advantage of molecular assembly by the synthetic organic chemist. Only a few representative examples have been discussed; many more useful sequences have been documented in the literature, and the number is rapidly increasing. However, construction of indolizine and quinolizine skeletons by radical methodology is rare. Many of these alkaloids often possess biological properties and are useful therapeutic agents. Hence, the effort to develop general routes to some of these naturally occurring compounds seemed appropriate.

The initial focus of this project was to develop a general strategy for the synthesis of indolizine and quinolizine alkaloids by radical cyclisation methods. To this end myrtine, lasubine I and (±)-O-methylcorytenchirine acted as target natural products. The model experiments carried out to this effect is presented in Chapter 2.

The utility of the derived methodology in Chapter 2 has been demonstrated by the synthesis of (±)-O-methylcorytenchirine. The results of this effort will be presented in Chapter 3.

Chapter four describes the application of radical methods to the general synthesis of pavine and aphorphine alkaloids. The utility of the developed methods is again demonstrated by the synthesis of (±)-argemonine and (±)-glaucine. As an extension to this study the attempted asymmetric synthesis of the above alkaloids using enantio-pure auxiliaries is described in the fifth chapter.
CHAPTER 2

Intramolecular Radical Addition - A Model Study
Towards Nitrogen Heterocycles

2.1 Introduction .......................................................... 21

2.2 Model Intramolecular Cyclisations ............................ 23

2.3 Allylic Interactions & the steric course of the reaction .... 30

2.4 Effect of the Amide Carbonyl .................................. 36

2.5 Molecular Model Calculations ................................. 42

2.6 Carbamate Derived Radical Precursors ...................... 44

2.7 Model Studies to Polyhydroxylated Indolizines .......... 54
Chapter 2: Intramolecular Radical Addition

2.1 Introduction

Natural products containing the indolizine or quinolizine ring systems occur in great abundance. Examination of recent surveys such as the 'Dictionary of Alkaloids' and the 'Compendium of Alkaloid Structures' reveals that 25 to 30% of all known alkaloid structures incorporate these simple heterocyclic frameworks or various unsaturated versions of them. A number of important alkaloids are simple substituted indolizine or quinolizines (e.g., myrtine, swainsonine, castanospermine, lasubine I - figure 201) but many others have these heterocyclic nuclei embedded within fused polycyclic structures ranging in complexity from relatively simple alkaloids (e.g., corytenchirine) to highly complex structures such as the aspidosperma and steroidal alkaloids.

Many of these naturally occurring compounds are known to be biologically important and their significance has been surveyed in a number of reviews. Some of them have potential therapeutic activity while others are highly toxic. For example, (+)-castanospermine is known to have the potential for treatment of diabetes, obesity, cancer and HIV. On the other hand (-)-swainsonine has been found to cause livestock toxicosis by consumption of *Swainsona* species which are known to produce the alkaloid.
A majority of these alkaloids has been synthesised, many immediately after their isolation from the plant kingdom. Consequently, their structural features such as functionality, stereochemistry etc. have been established and their biological properties evaluated. Depending on the biological importance of each alkaloid, they have been re-synthesised, often many times along totally different paths, with the hope of finding new, shorter and more efficient routes. The variation in methodology is partly due to the lack of generality in the existing methods, often because most of these synthetic sequences are planned with a single or a group of alkaloids in mind. Thus, from a synthetic point of view, a generalised approach by which the indolizine or quinolizine frameworks could readily be assembled would be highly beneficial.

Current synthetic approaches to indolizines and quinolizines are reviewed on a bi-annual basis. Examination of these reports reveal that in most cases the methods used involve variations on well established ionic or concerted reactions. Methodology based on free radical chemistry has been relatively neglected. However, as outlined in section 1.2 there have recently been dramatic developments in the general application of radical reactions to synthesis, including the assembly of a variety of polycyclic natural products in one step from pre-synthesised substrates. These developments have arisen mainly from the recognition that radical reactions sometimes offer advantages over their ionic counterparts. The relative merits of these advantages and their application in synthesis were discussed in chapter 1.

Scheme 201

A large proportion of the work to date has been concerned with the application of free radical methodology in the synthesis of carbocyclic systems and therefore it seemed timely for similar approaches to be developed for nitrogen heterocycles. Thus, the main objective of the work discussed in this chapter was to develop a simple generalised approach to indolizine and quinolizine alkaloids involving the use of free radical reactions. The concept envisaged is outlined in scheme 201. It involves a 1,5 or 1,6-exo radical ring closures in species such as 201 to yield the required basic heterocyclic skeleton. The precise substrates used in the model study and the rationale behind such a strategy will be discussed in the following section.
2.2 Model Intramolecular Cyclisations

In accord with the general concepts outlined in the previous section the dihydropyridone system 205 (scheme 202) was used as the model radical precursor in preference to the enamine system 201 illustrated in scheme 201. The rationale behind this decision was manifold. Apart from the ease of preparation of such substrates, the two carbonyl functionalities afford the capability for later elaboration or functionalisation of the molecule. The amide carbonyl group, being an excellent nitrogen protecting group provides stability to these pyridone substrates while the \( \alpha, \beta \)-unsaturated carbonyl function provides a suitably activated double bond for radical ring closure. The synthesis of model compounds 205-210 was accomplished by standard procedures\(^5\) and the path to 205 is illustrated in scheme 202.

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{CO} & \text{H}_2\text{CO} \\
\text{202} & \quad \text{203} & \quad \text{204} \\
\text{Cl} & \quad \text{H}_2\text{CO} & \quad \text{H}_2\text{CO} & \quad \text{Cl}^- \\
\text{205} & \quad \text{206} & \quad \text{207} & \quad \text{208} & \quad \text{209} & \quad \text{210}
\end{align*}
\]

\(a: \text{NaOCH}_3, \text{CH}_3\text{OH}; \quad b: \text{ortho-bromobenzoyl Chloride, THF, -23°C}; \quad c: \text{PhMgX, THF, -23°C}; \quad d: 10\% \text{ aqueous HCl}\)

Scheme 202

Thus, commercially available 4-chloropyridine 202 initially was converted in to 4-methoxypyridine 203 by stirring with sodium methoxide in methanol. Treatment of 203 in THF at low temperature with ortho-bromobenzoyl chloride readily afforded the \(N\)-acylpyridinium salt 204. This quaternary salt underwent a nucleophilic addition
reaction on treatment with phenylmagnesium bromide. Following demethylation with 10% aqueous HCl the N-acyldihydropyridone 205 was obtained in 98% yield.

Indolizine radical precursors 206-208 were also obtained in the same manner except that the appropriate benzoyl chloride containing a bromo or iodo substituent suitable for subsequent radical generation was used in the experiment. In addition the Grignard reagents required were derived from either bromobenzene as before or methyl iodide, and the isolated yields for the three substrates ranged from 78 - 92%. The quinolizine precursors 209 and 210 were synthesised using ortho-bromo-phenylacetyl chloride as the acylating agent and were obtained in 94% and 90% respectively.

\[
\begin{align*}
205 & \quad R = \text{Ph}, \quad X = \text{Br} \\
206 & \quad R = \text{Ph}, \quad X = \text{I} \\
207 & \quad R = \text{CH}_3, \quad X = \text{Br} \\
208 & \quad R = \text{CH}_3, \quad X = \text{I} \\
209 & \quad R = \text{Ph} \\
210 & \quad R = \text{CH}_3
\end{align*}
\]

Aryl radicals (and vinyl radicals) are much more reactive than their alkyl equivalents, presumably because the unpaired electron in the former is contained in a \( \sigma \) SOMO while in the latter it is in a \( \pi \) SOMO. For example, aryl radicals undertake hydrogen atom transfer from tributylstannane at 80°C, almost 150 times faster than do cyclohexyl radicals (scheme 203).

\[
\begin{align*}
\text{aryl} & \quad \text{alkyl} \\
\text{$k_{\text{aryl}}$} & = \frac{890 \times 10^{-6}}{6.09 \times 10^{-6}} \approx 150 \\
\text{$k_{\text{alkyl}}$}
\end{align*}
\]

\[\text{Scheme 203}\]

However, when direct reduction is in competition with a cyclisation reaction with a standard Bu\(_3\)SnH concentration, as illustrated for the current substrates (scheme 204), the magnitudes of both the rate constant for reduction of the uncyclised radical, \(k_{UH}\) and the rate constant for cyclisation, \(k_C\) are directly reflected in the ratio of
Chapter 2: Intramolecular Radical Addition

The two possible products. Qualitatively the rate equation in scheme 204 shows how the relative rates of formation of the cyclised product (CH) and directly reduced product (UH) are related to the ratio of the relevant rate constants, and to the stannane concentration. If cyclised products are desired $d[CH]/d[UH]$ should be large. When $k_C$ is very large by comparison with $k_{UH}$, the requirement is easily met and cyclised products are mainly obtained when modest tin hydride concentrations are employed. Conversely, when $k_C$ is small or comparable to $k_{UH}$ both cyclised and uncyclised products will be obtained unless the stannane concentration is kept low. Although, this can be achieved by increasing the volume of the reaction solution, a more practicable method involves very slow addition of $\text{Bu}_3\text{SnH}$ and initiator to a solution of the radical precursor. In this way the stannane is consumed almost as fast as it is added, and its effective concentration is kept very low. An alternative method to slow addition would be to use a catalytic amount of tin halide together with at least a mole of standard hydride reducing agent such as $\text{NaBH}_4$ or $\text{NaCNBH}_3$ to generate small amount of $\text{Bu}_3\text{SnH}$ in situ at any given moment.

![Scheme 204](image)

It is known that many aryl radical cyclisations proceed successfully in the presence of modest $\text{Bu}_3\text{SnH}$ concentrations with minimal yields of directly reduced products. With respect to the substrates 205-210, the C4 carbonyl as explained earlier is double bond activating. However, this same double bond is vinylogous to an amide functionality which reduces the double bond character as a result of delocalisation of the lone pair on the nitrogen atom with the $\pi$ electrons of the double

The diagram above shows the format of the addition. With the disappearance of the substituent

The structure above was credited to the author with the agreement of the publisher.
bond. If the overall effect of both phenomena on the double bond is deactivating, the rate of cyclisation will be reduced. In this event, to achieve good ring closure slow addition of Bu₃SnH would be desirable. Alternatively, if the overall effect on the double bond is activating slow addition of Bu₃SnH and the initiator would not be detrimental. Hence, the syringe pump addition method was employed.

The preferred conditions for the ring closure of substrates 205-210 (scheme 205) involved the addition of a degassed solution of Bu₃SnH and the initiator AIBN in benzene to a de-oxygenated solution of the substrate in the same solvent over 4-6 hours at reflux with the aid of a syringe pump. Because of the high dilution of Bu₃SnH the use of at least 25% molar equivalents of initiator AIBN based on the substrate is vital for the efficient propagation of the chain. Under these conditions formation of the ring closed products 211-214 was found to be efficient and high yielding. In all instances the open chain directly reduced products were neither detected during the reaction nor isolated after purification.

For example when the bromo derivative 205 in benzene, heated at reflux was treated with Bu₃SnH and AIBN in the same solvent over six hours, consumption of the starting material was found to be rapid. With the disappearance of the substrate a
single new spot much more polar in character was observed on TLC. On the basis that the directly reduced product would be comparable in polarity with the starting material, the new spot was tentatively assumed to be the ring closed product 211. When complete consumption of the substrate had occurred removal of the solvent followed by radial chromatography afforded the tricyclic compound 211 in 91% yield. The bromo derivative 207 under similar conditions provided the ring closed product in 86% yield. Surprisingly, when the iodo substituted substrates 206 and 208 were used, the yield of the ring closed product 211 decreased to 79% and 71%, respectively. This is in contrast to the widely held belief that iodo substrates are superior to their bromo analogues as radical chain propagators. However, none of the directly reduced products was detected or isolated to offset this reduction in yield. No apparent reason for this observation can be put forward.

By comparison, cyclisation of compounds 209 and 210 leading to the quinolizine ring systems 213 and 214 respectively, required precise addition of Bu$_3$SnH and AIBN over a 6 hour period. Failure to adhere to these long addition conditions results in some direct reduced compounds, presumable because 6-exo cyclisations occur at a much slower rate than 5-exo ring closures. However, the prescribed conditions yield only cyclised material (82% and 72% respectively) and do not afford direct reduced products.

The above result contrasts with the observation made in similar circumstances undertaken earlier in this laboratory.$^{55}$ Substrates such as 215 on treatment with stannane were observed to yield 13 to 16% of the reduced open chain product 217 together with a diastereomeric mixture of the desired cyclised material 216 (Scheme 206). The addition of stannane and AIBN to the substrate in benzene whether rapid or over a period of 4 hours was observed to have no effect on the product composition. Hence, the presence of a significant proportion of the uncyclised enamine 217 was attributed to the occurrence of a process competing with the radical ring closure. Since the yield of 217 appeared to be independent of the stannane concentration the most plausible mechanism for its formation would involve an intramolecular 1,5 hydrogen atom transfer as illustrated in scheme 206. The radical 219 having a secondary alkyl carbon radical is much more stable than the aryl radical 218 from which it was formed. Hence the formation of 217 is independent of the concentration of Bu$_3$SnH in solution at any given moment.
The question then arises of why the substrates 215 affords significant yields of the directly reduced product 217 whereas no comparable reactions occur when the substrates 205-210 are treated with stannane under similar conditions. The most obvious difference between 215 and the other substrates is the lack of an amide carbonyl group in the former. Consequently, there should be free rotation about the benzylic C-N bond in 215 which allows the radical centre access to either the double bond affording the cyclised product 216 or the methylene group adjacent to the nitrogen atom to give 217 as the final product. Conversely, in the substrates 205-210 conjugation of the nitrogen lone pair with the amide carbonyl group is reported to favour structures in which the nitrogen atom is \( sp^2 \) hybridised and the molecule preferentially adopts conformations in which the C-N-C=O moiety lies in the one plane. The barrier between these two conformations (scheme 207) is reported to be sufficiently high\(^{56} \) to prevent their interconversion within the probable lifetime of the radical (at least \( 10^{-3} \) seconds). Effectively, this ensures that the outcomes of the reactions of the substrates 205-210 will reflect the relative populations of the two rotamers 220A and 220B. If as is reported (see below), the radical assumes almost completely the 220A form then 1,5-hydrogen atom transfer will be insignificant.
Conclusive evidence for the $sp^2$ nature of the nitrogen atom in 206 due to conjugation with the amide carbonyl is provided by single crystal x-ray diffraction studies (figure 202 and section 7.3). The data shows that the sum of the bond angles C2-N1-C6 (118.9°), C6-N1-C11 (122.7°) and C2-N1-C11 (117.9°) amounts to 359.5°, very close to the ideal 360° for maximum planarity at nitrogen. Furthermore, the data indicate that the O11-C11-N1-C6 dihedral angle (−175.2°) is very close to the value of 180° expected for maximum delocalisation. However, even though there exists the possibility of an extended overlap of the $\pi$ orbitals of the phenyl ring in the N-acyl group with the amide fragment, the x-ray data indicates that such conjugation is insignificant, since the dihedral angle O11-C11-C12-C13 is 77°; for effective orbital overlap a value close to 0° would be required. This conformation of the acylphenyl group favours ring annulation as the iodine substituted carbon is well positioned relative to the double bond for cyclisation to occur when the radical is generated.
The most important feature of the cyclisations of 205-210 is their high diastereoselectivity. In each case only one isomer of the cyclised product could be detected by TLC or NMR analysis of the crude reaction mixture. The relative stereochemistry of the cyclised products 211-214, as illustrated above indicates that the radical cyclisation involves approach of the radical towards the face of the double bond anti to the substituent α to the nitrogen. These assignments rest in the first instance on careful analysis of the NMR spectra.

As with cyclohexane, NMR studies of piperidines have shown that the chemical shift of a ring proton depends on its conformation with respect to the ring. In general terms the axial protons in such systems are more shielded than their equatorial counterparts. However, this difference in shielding is much more pronounced for the α protons in piperidines and is thought to be influenced by the overlap of the non-bonded electron pair on the nitrogen with the σ* orbital of the C-H_α bond. This phenomenon has often been used as a diagnostic tool in assigning spectral values for axially and equatorially oriented protons α to a nitrogen. On this basis, coupled with the evidence from the spectral and single crystal x-ray structural data for the uncyclised substrate 206, the resonance centred at δ 6.13 was assigned to the pseudo-equatorial C7 proton in the 1H NMR spectrum of compound 211 (figure 203). The resonance at δ 4.59 is typical of a pseudo-axial proton and was assigned to the ring junction C10a proton.

Further evidence for the pseudo-axial orientation of the C10a proton comes from its coupling constant values with the vicinal C10 protons. One of these, with a resonance centred at δ 3.02 has J = 4 Hz typical of equatorial-axial coupling; while the other resonating at δ 2.30 has J = 12 Hz characteristic of trans di-axial coupling. The geminal coupling constant for the two protons on C10 is 14 Hz. These data are consistent with the previous assignment of a pseudo-axial orientation for the proton at C10a. The signals at δ 3.02 and δ 2.30 therefore were assigned respectively to the pseudo-equatorial and axial protons at C10.
The evidence for the pseudo-axial orientation of the phenyl substituent at C7 also rests on 1H NMR data in the first instance. The NMR signal for the C7 proton appears as a doublet at 6 6.43 despite the presence of two vicinal protons 6 1.82 and 6 1.14 which can therefore be assigned to the two axial equatorial vicinal protons at C8 respectively. The coupling constant of the C7 proton, namely 6 1.3 Hz and 6 1.0 Hz respectively, are characteristic of pseudo axial-axial and pseudo equatorial-equatorial. The slightly larger coupling constant of the pseudo-equatorial proton (6 1.3 Hz) and the diminished pseudo-equatorial proton-at-C7 proton coupling constant (6 1.0 Hz) consistent with the view that the ring is somewhat deformed from a perfect plane by the ring fusion and the presence of the bulky phenyl substituent. The slight difference in coupling between the methylene protons of the phenyl substituent and indicates that the newly formed bond in 210 is pseudo-axial and is consistent with the phenyl group.

Final confirmation of the relative stereochemistry of 211 was obtained from a X-ray diffraction study of 211. The resultant ORTEP diagram clearly shows the axial orientation of the phenyl substituent and its very close proximity to the newly formed bond. Furthermore, the dihedral angles H—C7—C6—H9 of 90° and H—C7—C6a—H10 of 160°, H—C7a—C10a—H14 of 90°, and H—C7—C6—H9 are exactly consistent with the observed NMR second coupling constants observed as seen in figure 204 for comparison of the protons involved with these J-values together with the chemical shifts of the proton groups. These data have been published.

The close similarity between the NMR spectra for the cyclic product 212-214 and that of 211 alludes the relative stereochemistry of 211 to be confidently assigned. Thus evidence that the formation of each of the cyclic products has involved the pseudo-axial orientation of the phenyl substituent at C7.
Chapter 2: Intramolecular Radical Addition

The evidence for the *pseudo*-axial orientation of the phenyl substituent at C7 also rests on $^1$H NMR data in the first instance. The NMR signal for the C7 proton appears as a doublet at $\delta$ 6.13 despite the presence of two vicinal protons on C8. Nevertheless, the $^1$H NMR COSY spectrum shows two cross peaks, one prominent and the other weak to signals at $\delta$ 2.92 and 3.14 which can therefore be assigned to the axial and equatorial methylene protons at C8 respectively. The value for the coupling constants for the C7 proton, namely $J \approx 7.5$ Hz and $J \approx 0$ Hz for interaction with the signals at $\delta$ 2.92 and 3.14 respectively are reasonable for *pseudo* axial - *pseudo* equatorial and *pseudo* equatorial - *pseudo* equatorial couplings. The slightly larger *pseudo* axial - *pseudo* equatorial $J$ value (7.5 Hz) and the diminished *pseudo* equatorial - *pseudo* equatorial coupling constant ($J \approx 0$ Hz) are consistent with the view that the ring is somewhat deformed from a true chair conformation by the ring fusion and the presence of the bulky phenyl substituent. The geminal coupling between the methylene protons at C8 has a value of $J = 15$ Hz in accord with expectation. These NMR data confirm the *pseudo*-axial orientation of the phenyl substituent and indicate that the newly formed bond in 210 is *pseudo*-equatorial and is *trans* to the phenyl group.

Final confirmation of the relative stereochemistry was obtained from a x-ray diffraction study for 211. The resultant ORTEP diagram (figure 204) clearly shows the axial orientation of the phenyl substituent and its *trans* relationship to the newly formed bond. Furthermore, the dihedral angles $H_{eq}$-C7-C8-$H_{ax}$ (40°), $H_{eq}$-C7-C8-$H_{eq}$ (69°) and $H_{ax}$-C10a-C10-C10-$H_{ax}$ (175°), $H_{ax}$-C10a-C10-$H_{eq}$ (54°) are entirely consistent with the observed NMR proton coupling constants described above. These $J$ values together with the chemical shifts of the protons concerned are shown in figure 204 for comparisonal purposes. Complete data of the plot has been published.58

The close similarity between the NMR spectra for the cyclised products 212-214 and that of 211 allowed the relative stereochemistry of the former to be confidently assigned. Thus, it is clear that the formation of each of these products has involved the approach of the phenyl radical towards the face of the double bond *anti* to the substituent at C7.
The highly diastereoselective formation of the indolizine and quinolizine derivatives 211-214 illustrates the potential of the radical ring closure reaction for the convenient synthesis of a variety of naturally occurring compounds. One illustrative example, the preparation of (+)-O-methylcorytenchirine will be presented in the following chapter. However, before any attempt is made to describe such use in syntheses, it is important first to evaluate the necessary structural features in the molecule that are involved in the production of cyclised material in such a stereoselective manner. The following section deals with this matter.

Figure 204

The highly diastereoselective formation of the indolizine and quinolizine derivatives 211-214 illustrates the potential of the radical ring closure reaction for the convenient synthesis of a variety of naturally occurring compounds. One illustrative example, the preparation of (±)-O-methylcorytenchirine will be presented in the following chapter. However, before any attempt is made to describe such use in syntheses, it is important first to evaluate the necessary structural features in the molecule that are involved in the production of cyclised material in such a stereoselective manner. The following section deals with this matter.
2.3 **Allylic Interactions and the Steric Course of the Reaction**

The concept of allylic interactions and their involvement in stereoselective reactions first became apparent three decades ago when Johnson and Malhotra in a series of publications discussed steric interactions in olefinic systems substituted at 1,3 positions. Their findings were initially based on isolated reaction products but were later confirmed in 1968 by direct $^1$H NMR studies. Consequently, application of the concept in stereocontrolled synthesis has greatly increased and at present the phenomena is most commonly referred to as 1,2 or 1,3-allylic strain ($^{1,3}$A).

The basis of allylic strain can be explained by reference to the vinyl cyclohexyl model illustrated in figure 205. In the conformer A the dihedral angle between the $C_{\gamma}$-$R'$ bond and the C-C double bond is closer to zero. Thus, $R$, $C_{\alpha}$, $C_{\beta}$, $C_{\gamma}$ and $R'$ essentially lie on a single plane. This coplanar array brings $R$ and $R'$ into close proximity which gives rise to a de-stabilising non-bonded interaction, the magnitude of which depends on the size of the two substituents. Conversion of A into the alternative conformer B, in which $R'$ is pseudo-axial relieves this interaction thus lowering the strain energy of the molecule, although there may still be unfavourable steric interactions between $R$ and $H_{\beta}$ and between $R'$ and the 1,3-diaxial protons on the ring. At equilibrium the relative concentrations of A and B reflect their relative energies. Even when $R$ and $R'$ are each methyl, the 1,3-allylic interactions between $R$ and $R'$ in the conformer A is sufficiently large to drive the equilibrium illustrated in figure 205 to lie almost completely in favour of B.

![Figure 205](image)

The tetrahydropyridones 205-210 behave in a manner similar to the vinyl cyclohexyl model illustrated in figure 205. As an example, the equilibrating conformers for substrate 205 are shown in figure 206. In substrate 205 the carbon bearing the phenyl substituent, the nitrogen and the carbon of amide carbonyl forms the allylic framework, in which the phenyl group and the carbonyl oxygen represent $R$.
and R' respectively in the vinyl cyclohexyl system. The C-N bond acts similarly to the double bond in the previous system due to its partial double bond character, as a result of the delocalisation of the non-bonded electron pair of the nitrogen with the carbonyl function.

From figure 206 it is evident that any conformational change of the phenyl substituent from pseudo-axial in conformer B to pseudo-equatorial in the alternative structure A, would result in a serious non-bonded interaction with the amide carbonyl. As a result the strain energy in A would be much higher than that of the alternative conformer B. Hence the equilibrium illustrated in figure 206 would lie almost completely in favour of the latter conformer B. In this conformation, when the radical is generated, the preferred approach is expected to be from the least hindered face of the double bond giving rise to the observed selectivity.

Corroborative evidence towards this argument can also be supplied from previously presented single crystal x-ray data for 206 (figure 202). In the solid phase the phenyl substituent is observed to be disposed pseudo-axial while the amide carbonyl resides syn to this substituent. Furthermore the iodo-substituted phenyl ring is placed orthogonal to the plane occupied by the amide function with the radical site positioned away from the substituent facilitating anti attack.
2.4 Effect of the Amide Carbonyl

The foregoing suggestions, related to the $^{1,3}A$ strain in substrates 205-210 highlighted the importance of the amide carbonyl group in achieving complete diastereoselectivity during cyclisation. Without the carbonyl moiety the nitrogen atom in the molecule would be tetrahedral; $sp^3$ hybridised and thus would allow free rotation about the C-N bond. At the same time the phenyl substituent is likely to be oriented in a pseudo-equatorial conformation, which would allow the aryl radical unhindered access to both faces of the double bond. Therefore, the objective of the study described in this section was to investigate the extent of involvement of the amide carbonyl in 205-210 during cyclisation.

To this end the model substrate 221 lacking the amide carbonyl was synthesised first by treating methoxy pyridine in THF with ortho-bromobenzyl bromide at reflux until a thick white suspension was observed (scheme 208). As before the pyridinium salt was treated with phenylmagnesium bromide followed by demethylation with the aid of 10% HCl to afford 221. Subjecting the substrate 221 to radical ring annulation conditions used previously should provide valuable information on selectivity of the reaction in the absence of the carbonyl group.

Two important characteristics of the model system 221 were gathered from its $^1H$ NMR spectrum. Firstly, in contrast to prediction, the phenyl substituent was observed to be retained in the pseudo-axial conformation, as in substrates 205-210. This was evident from the $J$ values observed for the C2 proton ($J = 7$ and 6.5Hz), which displayed a pseudo-axial-pseudo-equatorial and pseudo-equatorial-pseudo-equatorial relationship to the C3 methylene protons. These observations require the C2 proton to be pseudo-equatorially placed; hence the phenyl substituent must be axially orientated. Secondly, the benzylic methylene protons appeared as a sharp time averaged singlet at $\delta 4.35$ which is an indication of rapid rotation about the N-C bond, even at ambient temperature.
Chapter 2: Intramolecular Radical Addition

When the substrate enamine 221 was treated with Bu$_3$SnH (scheme 209) under the slow addition conditions described previously, two distinct spots, less polar in character than the starting material were observed by TLC. The loss in polarity of the ring closed product by comparison with the open chain substrate was expected and results due to the loss of conjugation of the non-bonded electron pair on the nitrogen with the ketone through the double bond. By the same token, the open chain direct reduced product would be expected to have polarity similar to that of the starting substrate 221 but no appropriate spot was detected by TLC. Routine spectral examination of the crude product from the reaction revealed a 3:1 mixture of both diastereomers, which on careful separation using flash chromatography gave the two isomers 222 and 223 in 89% overall yield.

![Diagram](attachment:image.png)

\( \text{Scheme 209} \)

The stereochemical assignments of the major and the minor isomers rested in the first instance on the $^1$H NMR chemical shifts. The signal assigned to the C7 proton of the minor isomer resonated at $\delta$ 3.93. The signal due to the same proton in the major isomer was observed at $\delta$ 4.91. On the basis that axial proton signals in cyclic systems resonate upfield compared to equatorial signals, the C7 proton in the minor isomer must be axially oriented. Hence, the newly formed bond in the minor isomer must be equatorially oriented to achieve the syn relationship between the bond and the phenyl substituent. Alternatively, even if the fact that the C7 proton in this isomer is pseudo-axially oriented is disregarded, it is most unlikely that both the phenyl substituent and the newly formed bond would assume pseudo-axial orientations because the non-bonded steric interactions would be much greater. Molecular model studies also confirm this view.

On the other hand the resonance assigned to the C10a proton ($\delta$ 3.88 in the minor; $\delta$ 4.34 in the major isomer) in each isomer does not reveal any significant chemical shift difference, implying the proton to be in similar conformations in both isomers. The $^1$H NMR data acquired for compounds 211-214, shown to have the
C10\textsubscript{a} proton in a \textit{pseudo}-axial conformation (section 2.2) are also in good agreement with the chemical shift data given above for \textit{222} and \textit{223}. Hence it is most likely that the proton attached at C10\textsubscript{a} in each isomers is \textit{pseudo}-axially placed and that the minor and major isomers respectively result when the C7 phenyl group is \textit{pseudo}-equatorially and \textit{pseudo}-axially placed. Based on these facts compound \textit{223} was established to be the minor isomer and the alternative \textit{222} to be the major.

The small preference for the formation of compound \textit{222} over \textit{223} by intramolecular radical addition \textit{anti} to the phenyl substituent in \textit{221} is not surprising. As described above, the NMR spectral data for \textit{221} unambiguously indicate that the most populated conformer has the phenyl substituent \textit{pseudo}-axial, and it is likely, therefore, that radical attack on the \textit{syn} face of the heterocyclic ring will be somewhat hindered. However, because \textit{221} contains no amide carbonyl group, the difference in energy between the conformer containing a \textit{pseudo}-axial phenyl substituent and that containing a \textit{pseudo}-equatorial substituent is likely to be small. The difference between the energies of the transition structures leading to \textit{222} and \textit{223} should, therefore, be correspondingly small. Clearly, the difference in the cyclisation behaviour of \textit{221} and compounds \textit{205-210} is due solely to the effect of the amide carbonyl group in the latter which strongly destabilises conformers containing \textit{pseudo}-equatorial substituents in both ground and transition structures. Hence the presence of the carbonyl group is vital for achieving highly diastereoselective reactions.

Perhaps and even more interesting feature of the behaviour of the radical derived from \textit{221} is why it does not undergo 1,6-hydrogen atom transfer to afford the radical at C2 which is doubly stabilised by being both benzylic and \textit{\alpha} to nitrogen. Presumably this is because the C-H bond, being equatorial is both sterically inaccessible and incorrectly disposed, geometrically with respect to the nitrogen lone pair and the phenyl \pi system to be activated towards homolytic attack.

Confirmation of the stereochemistry of isomers \textit{222} and \textit{223} was achieved by employing the strategy illustrated in scheme 210. Reduction of the C5 carbonyl of the pure diastereomer \textit{210} isolated from previous cyclisations should afford \textit{222} in pure form. Most importantly, compound \textit{222} isolated from this proposed reaction should be of known stereochemistry and its spectrum could then be correlated with those acquired for each of the products of the cyclisation reaction. Such an experiment should confirm the previous assignment of stereochemistry without any ambiguity.
Chapter 2: Intramolecular Radical Addition

The reagent of choice for such reductions is LiAlH₄ in THF or diethyl ether.⁶² Compound 211 when heated in THF at reflux with a suspension LiAlH₄ for two days gave a single spot on TLC eluting below the substrate 211 together with some base line material. Complete consumption of starting material 211 was also observed by TLC. After purification and acquisition of routine spectral data, the compound responsible for the single spot was identified as the partially reduced indolizine 224 (scheme 211). When the purified diastereomeric mixture of 224 was treated with PCC in dichloromethane ⁶³ at ambient temperature the starting substrate 211 was isolated in good yield. Thus, isolation of 224 from the preceding reduction was confirmed.

Scheme 210

The failure of the C5 amide carbonyl group to undergo clean reduction prompted a search for alternative reagents known to reduce similar functionality. It is known that sodium trifluoroacetoxyborohydride⁶⁴ is able to reduce simple ketones to alcohols and amides to amines. However, in the case of 211 it afforded the same dihydroxyindolizine 224 in almost quantitative yield (scheme 211). On the other hand, DIBAL ⁶⁵ gave clean starting material 211 at 50°C after two days. In addition, despite being a good amide carbonyl reducing agent, borane⁶⁶ at low temperature also gave only highly polarised unidentifiable base line material.

Scheme 211
In view of the failures, outlined above, to achieve the desired reduction, a more powerful reducing agent was sought. Reports in the literature indicate that aluminium hydride (AlH₃) generated in situ by treatment of LiAlH₄ in THF with one third of an equivalent of AlCl₃ is more effective than LiAlH₄ for the reduction of amides to amines. Furthermore, the same reagent has also been found to be effective for the reduction of diaryl carbinols to their corresponding hydrocarbons. Since the desired reaction sequence involves initial reduction of the amide carbonyl of 211 to afford the cyclic aryl carbinol 224, followed by further reduction to the amine 225 AlH₃ appeared to be the reagent of choice.

When substrate 211 was added to freshly generated AlH₃ complete disappearance of the starting material was observed within four hours, and two equally luminescent spots much polar in character by comparison to 211, with Rf 0.1 apart were observed by TLC. On purification and preliminary spectral analysis both were found to be diastereomers of the monohydroxy compound 225 (scheme 212). The difference in polarity of the two isomers presumably results from the C9 hydroxy group in one isomer hydrogen bonding with the lone pair of the nitrogen (figure 207). Such bonding is possible in only one isomer due to the rigid nature of the tricyclic system and is known to occur in similar systems.
The next step of the investigation involved the oxidation of the C9 hydroxy group. To this end, in a separate reaction the crude product of the isomers 225, resulting from complete and partial reduction of the C5 and C9 carbonyl groups of 211 respectively, was treated with PCC in dichloromethane. The reaction afforded a single product upon purification. The 1H and 13C NMR spectra obtained for this single product were found to be identical to the major reaction product 222 obtained from the reaction illustrated in scheme 209. Thus, the stereochemistry of the major and the minor components from the reaction was confirmed.

In summary, unlike the substrates 205-210, the substrate 221 lacking the amide carbonyl cyclised to afford both diastereomers 222 and 223. Hence the favourable involvement of the C5 amide carbonyl during the ring closure of 205-210 was successfully verified. The observed partial selectivity (3:1) achieved during the cyclisation of the latter substrate 222 was shown to arise solely from hindrance of one face of the double bond by the pseudo-axial phenyl group.
2.5 *Molecular Model Calculations*

The various experiments described in the preceding sections, including single crystal structure data support the view that the amide carbonyl group is responsible for the complete stereoselectivity exhibited by the radical ring closures of the substrates 202-210. Loss of selectivity during cyclisations of substrates lacking the amide carbonyl, compound 221 confirmed the involvement of the carbonyl group. The aim of the study described in this section is to ascertain whether mathematical calculations support these mechanistic hypothesis.

To this end a molecular modelling program, MacroModel was utilised to model the possible transition states of the two substrates 205 and 221, containing the amide carbonyl and the one lacking it. As described in Chapter 1, during a C-C bond forming process the radical centre approaches the double bond orthogonal to the nodal plane of the π system. Hence, there are two possible transition structures for an intramolecular radical attack on a *pseudo*-axially substituted ring. Radical attack *anti* to the *pseudo*-axially conformed phenyl substituent in 205 is illustrated in figure 208A. The other isomeric transition structure in which the attack is *syn* to the axially positioned phenyl substituent will be highly disfavoured because of the high non-bonded interaction between the substituent and the acyl group containing the radical.

![Radical attack *anti* to the substituent](image1.png)

![Radical attack *syn* to the substituent](image2.png)

*Figure 208*
Similarly, two transition structures are possible when the phenyl substituent is pseudo-equatorially positioned. Figure 208B illustrates one of these, in which the radical attack is syn to the phenyl substituent. By comparison the alternative structure in which the radical attack is anti to the pseudo-equatorial substituent would be of similar energy. However, both these transition structures would be of higher energy by comparison with the one illustrated in figure 208A because of the non-bonded interaction (1,3-allylic strain) between the amide carbonyl and the phenyl substituent in the former two transition structures, 208B and its isomer. The close proximity of the two groups is clearly observed in the model diagram 208B.

The molecular mechanics calculations have revealed that the radical attack leading to the transition structure A is favoured to the alternative syn attack illustrated in 208B by 3 Kcal/mol. This large strain energy difference between the transition structures, therefore, can be perceived as the key to the preferential generation of A which results in the selective formation of the anti diastereomer 211.

Alternatively, when the transition states of the substrate 221 lacking the amide carbonyl were modelled the difference in strain energy was reduced to 0.4 Kcal/mol again in favour of the anti attack. Thus, the 3:1 preferential formation of the diastereomer arising from anti attack in the absence of the amide carbonyl under experimental conditions is fully justified. Therefore, the loss in selectivity in the absence of the amide carbonyl can be attributed to the narrow barrier (0.4 Kcal/mol) between the two transition structure.

Thus, experimentally observed selectivities during cyclisation of substrates 205-211 and 221 were fully justified by the model study.
Chapter 2: Intramolecular Radical Addition

2.6 Carbamate Derived Radical Precursors

Piperidine alkaloids having alkyl or aryl groups on α carbons to the nitrogen atom disposed with trans stereochemistry are numerous. Solenopsine A 226 and B 227,72 himbacine 228,73 2,6-di-4-pentenylpiperidine 229, and 2-(6-heptenyl)-6-(4-pentenyl)piperidine 230,74 andrachamine 231,75 and andrachcine 23276 are a few examples of such naturally occurring compounds. The most popular pair of alkaloids solenopsine A and B (226 and 227), isolated from the red form of the fire ant, Solenopsis saevissima,77 has gained much attention during the recent years due to their marked hemolytic, insecticidal and antibiotic activity.78 Despite the simplicity of its carbocyclic framework, the stereochemical disposition of the groups α to the nitrogen has hampered most synthetic efforts towards either of these two alkaloids, mainly due to the lack of proper stereoselective methodology. A majority of the few efforts documented in literature79 achieves only up to 50% diastereoselectivity and involve the separation of isomers at some stage during synthesis. Stereoselective synthesis of Solenopsin A has nevertheless been achieved by Maruoka et. al.80 using a Beckmann rearrangement-alkylation sequence of an appropriately substituted oxime mesilate.

![Structural formulas of compounds 226 to 232](image)

The radical ring closure method described in the preceding sections was shown to result in complete diastereoselection. Potential applications of such methodology in natural product synthesis are numerous and to demonstrate this aspect one example
will be presented in the following chapter. The above method can also be viewed as a process by which an alkyl or an aryl group could be attached to the carbon α to the nitrogen and trans to the existing α substituent. For example, if the cleavage of C2-C3 bond in 233 (the pure diastereomer arising from radical ring closure of 234) should be possible (scheme 213), hydrolysis of the amide group would afford the basic skeleton of the piperidine alkaloids illustrated earlier, in a highly stereoselective manner. Because the cyclisation should be completely diastereoselective separation of isomers is also not an issue.

However, selective cleavage of a C-C bond is not practical. The most appropriate modification to the starting substrate to effect this cleavage would be to include an oxygen atom in place of the C3 methylene group. Such an alteration was seen to be beneficial in two respects. Firstly, selective cleavage of the C-O bond could be easily achieved by known reagents such as Me₃SiI or LiAlH₄. While the former reagent would cleave the newly formed ring at the C2-O bond (scheme 214) to afford an iodine substituted alkyl side chain, cleavage by the latter reagent would introduce the β-hydroxy group in alkaloids such as andrachamine 231 or andrachcine 232. Secondly, the necessary starting bromo-chloroformates required during the assembly of the radical precursors could be synthesised from often freely available 2-bromoalcohols and phosgene.

Taking a simple alkaloid, epi-dihydropinidine 236 as an example, the initial transformation would involve the diastereoselective ring closure of 237 to 238 using Bu₃SnH (scheme 214). Cleavage of the newly formed ring by Me₃SiI induced decarbonylation followed by deiodination of the resulting iodo substituted side chain, should afford 236. Thus, the study described in this section was directed towards establishing necessary conditions for efficient cyclisation of substrates having N-alkoxycarbonyl functions instead of N-acyl groups, but otherwise similar to previous substrates 205-210 and the conditions to effect cleavage of the C-O bond.
Accordingly, the enamide 239 was synthesised as a model compound to assess the feasibility of the proposed plan (scheme 215). Synthesis of 239 was achieved following similar procedures described earlier for compounds 205-210 except that 2-bromo-phenylacetyl chloroformate 240 was used instead of an acyl chloride. The chloroformate 240 was synthesised from ortho bromophenol and phosgene using an established procedure. 

Surprisingly, when 239 was treated with Bu3SnH under identical conditions used for previous N-acyl model compounds the reaction failed to afford the desired ring closed product. Instead, on every attempt, the debrominated N-phenoxycarbonyl compound 241 was obtained as the only isolable product in high yield (scheme 216). This outcome was most interesting since, under the same conditions, the similar substrate 209 gave only the cyclised product 213 and none of the directly reduced product. The only difference between the two substrates 209 and 239 is the oxygen atom in the side chain in the latter substrate. This contrasting behaviour led to a further investigation to ascertain the factors governing the radical cyclisation of 239.
An extensive survey of literature on this subject revealed that substrates possessing an ester functionality between the radical centre and the double bond afford significant amounts of direct reduced material on treatment with Bu$_3$SnH under high dilution conditions. Beckwith and Pigou$^{84}$ in 1986 have shown that 242, when treated with tributylstannane, affords 243 in greater than 95% yield instead of the ring closed lactone. This observation was supported by a similar study by Curran and Chang$^{85}$ which revealed that the iodoacetate ester 244 at low concentration (0.02M) also afforded only cyclohexenyl acetate and none of the cyclised material. Alternatively, when the ester ketone in the substrate 244 was replaced by an acetal (245) as illustrated in scheme 217, Storke and Ueno observed not only efficient cyclisation to occur but also with complete selectivity to afford the cis fused lactone 246. The method subsequently has been utilised in devising a stereocontrolled route to Prostaglandin F$_{2\alpha}$. $^{86,87}$

\[ \text{Scheme 216} \]

\[ \text{Scheme 217} \]
The contrasting behaviour of the two substrates 209 and 239 (scheme 216) becomes obvious on subjecting the substrates to stereoelectronic analysis.\(^8\) The explanation for the substrates 244 and 245 also becomes clear with this analysis. The carbamate moiety in 239, for this purpose was viewed as having two functionalities, an amide and an ester function. In each of these functions, two forms of stereo electronic effects, primary and secondary are said to exist.\(^8\) The former effect is said to arise from the delocalisation of the non-bonding electron pairs on the nitrogen in amides and the oxygen in esters with that of the \(\pi\)-electrons of the carbonyl group. Such sharing of electrons imparts some \(\pi\)-bond character to the N-CO and O-CO \(\sigma\) bonds and causes the three atoms involved in each species (NCO in amide and OCO in ester) to be \(sp^2\) hybridised. As a consequence each function is able to exist as two rotameric forms, \(E\) and \(Z\) illustrated in Figures 209 and 210 in three-dimension. Hence, the primary electronic effect can be viewed as an \(n-\pi\) interaction.

**Figure 209**

**Figure 210**

Furthermore, because the oxygen atom of the carbonyl group in amides consists of a non-bonded electron pair that is antiperiplanar to the C-N sigma bond, the electron pair is able to overlap with the anti-bonding orbital of the C-N bond.
This additional n-σ* overlap is referred to as a secondary electronic delocalisation and contributes to the stability of the already planar function. Thus, amides in theory can exist in both E or Z forms, the direction of equilibrium solely dependant on the steric and non-bonded interactions of the groups involved.

Conversely, in esters the Z form predominates over the E form; the stability of the former by comparison to the latter is reported to be as much as 3 Kcal/mol. Even in the presence of a bulky alkoxy ester substituents such as tert-butyl where severe non-bonded interaction between the carbonyl oxygen and the tert-butyl group is present, the equilibrium is said to be in favour of the Z form. This preference of one geometric isomeric form over the other can be rationalised by considering the secondary electronic effects present in each of the two isomeric ester forms. The n-σ* secondary electronic interactions in esters are similar to the situation that observed in the well known anomeric effect and play a central role in predicting the direction of the equilibrium between the two forms.

In esters as in amides, the carbonyl oxygen in both forms, E and Z has a non-bonded electron pair oriented antiperiplanar to the C-OR bond (figure 212). Overlap of this pair of electrons with the antibonding orbital of the C-OR sigma bond thus imparts a triple bond character to the C-O link. On the same basis the non-bonded electron pair on the ether oxygen in Z esters is antiperiplanar to the carbonyl sigma bond. Overlap of these electrons with the σ* orbital of the carbonyl C-O bond renders some double bond character to the C-OR bond. Hence an additional secondary electronic overlap is observed in the Z isomers of esters (figure 212). Estimates, as reported earlier, have revealed that the greater stability of the Z form (3 Kcal/mol) by comparison with the E form in esters would be due mainly to this secondary electronic effect. Hence esters are said to exist purely as the Z form.
Chapter 2: Intramolecular Radical Addition

The following conclusions can be drawn from the above principles. The primary delocalisitons ($n$-$\pi$) are responsible in causing partial double bond character to the N-CO and the O-CO bonds in amides and esters respectively. As a consequence free rotation about these bonds is restricted and the groups exist as $E$ or $Z$ forms. Secondary electronic delocalisations on the other hand provide additional stability to the already planer $E/Z$ isomers and most importantly control the direction of the equilibrium as observed in esters.

The carbamate moiety in the radical precursor 239, for the purpose of stereoelectronic analysis, can be viewed as a hybrid of both an ester (OCOPh) and an amide (NCO) function. Since both groups can exist as $E$ and $Z$ forms the intermediate radical when generated can hypothetically exist as four different rotamers as illustrated in scheme 218. The rotamer equilibria A to B and X to Y represent amide rotation while A to X and B to Y involves O-CO inter-conversion. In the former case, where rotation about the N-CO bond is involved, inter-conversion between the isomers is comparable as described earlier and the direction of the equilibrium is dependant solely on the steric requirements of the radical substrate. However, in the latter process the equilibria lie in favour of the $Z$ form; A and B. Hence, the intermediate radical when formed will predominantly exist as A or B. Since successful ring closure in radical reactions depend on proper orientation of the radical with the $\pi$ system (Chapter 1), taking the conformations of A and B into consideration, the possibility of the radical orbital overlapping with one of the vacant $\pi^*$ orbitals of the double bond is rather remote. Conversely the radical has a greater probability of abstracting a hydride from Bu$_3$SnH before equilibrating to a conformer favourable for cyclisation. Thus no cyclised products are likely.
Supportive evidence for the above view can be gathered from the single crystal x-ray structure of 239, which revealed that the ester part of the carbamate group was conformed in the Z form as predicted (figure 213 and section 7.4). The planarity of the fragment was confirmed from the dihedral angle O11-C11-O12-C13 which amounted to a negligible 1.7°. It indicates strong conjugation between the carbonyl and the ether C-O link. By comparison the same angle in the x-ray crystal structure of 209 (figure 214 and section 7.5), the radical precursor without the oxygen atom, is 39.2°. The side chain containing the radical in this latter molecule obviously is non-conjugated to the carbonyl and hence affords cyclised products with complete stereoselectivity. In addition both the crystal structures reveal the nitrogen centres to be least pyramidalised; C2-N1-C11 (117.6°), C2-N1-C6 (118.1°) and C6-N1-C11 (124.3°) in 209 amounting to the ideal value 360° and in the structure 239 to a close 359°. These latter set of data indicated strong conjugation between the non-bonded nitrogen electrons with carbonyl π electrons (primary electronic delocalisation) in both molecules as predicted.
Chapter 2: Intramolecular Radical Addition

Figure 213

Figure 214
The outcome of the studies conducted by both Beckwith-Pigou\textsuperscript{92} and Curran-Chang\textsuperscript{93} relating to substrates 242 and 244 respectively can be explained based on the same rationalisation. The ester moieties in both these substrates exist predominantly in $Z$ form and because of slow rotation about the O-CO bond (partial double bond character) the radical when formed has a much greater chance of abstracting a hydride from Bu$_3$SnH than ring closure. However, the double bond character of the ether C-O linkage completely disappears on conversion of the ester to an acetal as in Stork-Ueno system 245. As a consequence cyclisation occurs in good yield and also results in complete diastereoselectivity (scheme 219).

\[ \text{Scheme 219} \]
2.7 Model Studies to Polyhydroxylated Indolizines

Polyhydroxylated indolizine alkaloids are abundant in nature. Of the vast amount of alkaloids belonging to this class, swainsonine 247 and castanospermine 248 are undoubtedly the most notable. The popularity of swainsonine stems from its pronounced α-mannosidase inhibitory\(^94\) and immunoregulative\(^95\) properties. A review by Olden et. al.\(^96\) presents the potential importance of swainsonine as a therapeutic agent in controlling metathesis and tumour growth, with several other related uses. Castanospermine, including its stereoisomers are reversible inhibitors of several glucosidases and have the potential for treatment of diabetes, obesity, cancer, and viral infections including human immunodeficiency virus-1 (HIV-1). As the demand for these alkaloids increased as biologically important molecules, so did the chemical synthesis as an alternative to natural sources. Consequently, a large number of enantioselective syntheses of swainsonine, many based on carbohydrate chemistry has been submitted for publication and the number is still growing. Many of these methods have been reviewed recently.\(^97\)

\[
\begin{align*}
\text{(-)-swainsonine} & \quad 247 \\
\text{(+)-castanospermine} & \quad 248
\end{align*}
\]

The present model study was based on the proposed path to (-)-swainsonine 247 as illustrate in scheme 220. This route to swainsonine was envisaged following pioneering work carried out by Ziegler et. al. towards the synthesis of oxygenated indoles\(^98\) and appears to be promising. The key operation acquired from Ziegler's work and applied for the synthesis of swainsonine involves the cyclisation of 249 to the indolizine 250 by radical methods. During cyclisation one of stereocentres of the tartaric acid derived side chain was initially expected to be destroyed by the formation of the carbon centred radical, but later reinstalled with opposite stereochemistry aided by the dioxolane ring. The efficiency of such stereocontrol as observed by Ziegler is largely due to the inflexible nature of the dioxolane ring and the penta cyclic ring that is being formed. Further, abstraction of hydrogen along an axial direction by the intermediate cyclised radical from Bu₂SnH should be stereoelectronically favoured.
which result in the isomer having the correct stereochemistry of swainsonine. This preference for axial abstraction was also highlighted in Ziegler's work.

![Chemical structure](image)

The model study described herein was carried out with the aim of developing a general radical route towards these alkaloids. The efficiency with which the radical would ring close and the selectivity that can be achieved were the chief concerns of this investigation. Hence, the initial efforts were concentrated on the preparation of the two model compounds 251 and 252.

3-Acetyl tetrahydropyridine 253 was obtained by hydrogenation of commercially available 3-acetylpyridine in ethanol in the presence of 5%-Pd/C at 48psi hydrogen pressure (scheme 221). Selection of 253 for this purpose was two fold. Firstly, acetyl functions are electron withdrawing and thus enables activation of the double bond towards radical ring closure. Secondly, an acetyl group can be viewed as a protected hydroxy function since a Bayer-Villeger reaction would result in selective
insertion of oxygen between the acetyl moiety and the ring with retention of stereochemistry. The latter possibility, for example, enables the introduction of the C8 hydroxy function in swainsonine 247 in a straightforward manner.

\[ \text{Scheme 221} \]

The model compounds 251 and 252 were obtained from N-acylation of 3-acetyltetrahydropyridine 253 with the aid of n-butyl lithium. In a typical experiment, 253 in THF cooled to -78 °C was treated with a slight excess of a 1.6 M solution of n-butyl lithium in hexane and stirred for half an hour before the acyl chloride was introduced. With the addition of the acid chloride, the precipitate, presumably the N-lithioenamide was observed to disappear. The final homogeneous solution on work up, from two separate experiments afforded 251 and 252 in 72% and 80% yield respectively.

When the enamide 251 was treated with Bu₃SnH and AIBN in benzene under slow addition conditions (scheme 222), the substrate was converted to one other spot just below the starting material on TLC. On complete consumption of the substrate 251 the reaction solution was cooled to room temperature, the solvent removed under reduced pressure and the residue chromatographed to afford an oily product. Based on the molecular ion in the mass spectrum acquired for this product (m/z 181) the yield was calculated to be 97%. 
The molecular ion signal at \( m/z \) 181 is consistent with either the cyclised 254 or direct reduced product \( N \)-propanoylacetylpyridine 255 and arises from the loss of 78 mass units from the substrate mass of \( m/z \) 259. Loss of bromine and subsequent addition of an hydrogen atom is clearly evident from this observation. However, definitive assignment of the structure of the isolated compound was not possible even from the \( ^1H \) NMR spectrum due to broadening of the signals. Nevertheless, experience in handling these compounds suggested the product to be 255, particularly because of the broadening of the signals which often results due to slow rotation of the \( N \)-acyl group about the \( N \)-CO bond. The ambiguity was resolved by the synthesis of an authentic sample of 255 from 3-acetyltetrahydropyridine 253 and propanoyl chloride as described before. The \( ^1H \) and \(^{13}C \) NMR spectroscopic data acquired for the product isolated from the latter reaction were found to be identical to that acquired for the compound isolated from the radical reaction. Thus, the structure of the sole product isolated from the radical reaction was established to be 255.

When the \( N \)-aroyl analogue 252 was treated with \( \text{Bu}_3\text{SnH} \) under identical conditions (scheme 223) three other spots in addition to the substrate spot was observed on TLC. One of these spots eluting just below the starting material was thought to be the direct reduced product as in the case with the previous experiment. The two other spots detected on TLC were more polar in character than the substrate and were \( R_f \) 0.1 apart (40% ethyl acetate in petroleum spirits). On complete conversion of the starting material to the product spots, each of these compounds was separated by radial preparative layer chromatography and analysed by routine spectroscopic methods.
The NMR and mass data acquired for the band eluting first, suggested the product to be the direct reduced derivative 257. This view was also confirmed by the preparation of an authentic sample of 257 from benzoyl chloride and the tetrahydropyridine 253 as described above. The isolated yield based on the molecular ion in the mass spectrum of the direct reduced compound was calculated to be 35%. On the other hand, the mass spectroscopic data acquired for the more polar compounds, in each case also displayed a molecular ion at m/z 229. Hence the isolated yield of each compound based on m/z 229 was found to be 55% and 6%.

The \(^1\)H NMR spectra of the two latter products revealed the presence of 15 protons, consistent with the cyclised structure 256. With previous experience, some of the resonances in the \(^1\)H NMR spectrum of the major product were assigned on the basis of their chemical shift values and the multiplicities. Firstly, the well defined doublet resonating at \(\delta 4.70\) \((J = 10.5\) Hz) was assigned to the C10a proton. Secondly, the two mutually coupled multiplets (confirmed from COSY experiments) at \(\delta 2.95\) and 4.52 were assigned to C7 axial and equatorial protons respectively, based on the theory that axial protons on the same carbon are shielded by comparison to the equatorial ones. However, the unusually large separation between these signals is not solely due to the above fact but is largely to the equatorial proton on C7 being aligned parallel with the amide carbonyl and thus experiences the deshielding effect of the carbonyl group. The sharp singlet at \(\delta 2.26\), integrating to three protons was assigned to the acetyl CH$_3$. Assignments of the other signals were based on a COSY experiment and are reported in the experimental section. The signals in the \(^1\)H NMR of the minor of the two cyclised products were assigned by comparison to the preceding analysis. Accordingly, the doublet resonating at \(\delta 4.44\) \((J = 4.5\) Hz) was assigned again to the C10a proton. Thus, acquisition of an isomeric mixture of cyclised products were confirmed.

The relative stereochemistry of the two products 258 and 259 were assigned based on the coupling constants of the C10a resonances in each \(^1\)H NMR spectrum.
The coupling constant of the doublet assigned to the C10α proton in the NMR spectrum of the major product was earlier reported to be \( J = 10.5 \) Hz. By comparison of this value with the one obtained for the same proton in the minor product; \( J = 4.5 \) Hz, it is evident that the former coupling arises from an axial-axial relationship with the C10 proton while the latter is a result of axial-equatorial interaction. Axial-axial coupling in the major isomer is possible only when both the newly formed bond and the C10 acetyl group are equatorially oriented. Thus, the newly formed bond would be trans to the C10 acetyl function in the major isomer as illustrated in 258.

![major cyclised product](image1)

![minor cyclised product](image2)

The relative stereochemistry of the minor isomer was assigned similarly. The proton attached to C10 in this isomer is oriented equatorial and thus coupled to the C10α proton with a \( J \) value of 4.5 Hz. in an equatorial-axial manner. In this arrangement the newly formed bond and the C10 acetyl group would be placed cis to each other as in 259.

The high stereocontrol, 9:1 observed during cyclisation in favour of the cyclised isomer 258, is not achieved in the cyclisation step (scheme 224) but during hydride transfer from Bu₃SnH to the intermediate cyclised radical 261. A closer look at models of the two transition structures involved reveals that the major isomer 258 is formed when hydride transfer occurs from an axial direction, while the less favoured isomer 259 results when transfer is from an equatorial direction. It is known that approach of Bu₃SnH from an axial direction is stereoelectronically favoured by comparison to equatorial transfer; hence the selectivity.
Acquisition of a significant proportion of the direct reduced product 257, (35%) from the reaction was discouraging. Nevertheless, the yields of the cyclised products (55% and 6%) and more importantly the selectivity achieved during the process (9:1) was promising. Most importantly, the relative stereochemistry at C10 and C10α of the major isomer was similar to that in swainsonine 247 and castanospermine 248.

The question of why a sizeable amount (35%) of the direct reduced product 257 was observed during the above reaction and none from pyridone related substrates in section 2.2, seemed worthy of further investigation. With regards to this matter, direct reduction of the generated aryl radical by Bu3SnH seemed unlikely since the concentration of the reagent under slow addition conditions (addition over 5-6 hours) at any given instant is very low. Instead it is more likely that 257 resulted from initial 1,5-transfer of hydrogen to the aryl radical from C6 (260 → 262), as illustrated in scheme 225. The secondary radical formed as a result would be much stable by comparison to the highly reactive aryl radical. Subsequent reduction of the 262 by Bu3SnH would afford 257. Hence, the current investigation was designed to detect any hydrogen transfer step competing with cyclisation.

With this purpose in mind the reaction was conducted with Bu3SnD. Deuterated stannane is ideal for this purpose because location of deuterium by 2H NMR techniques is straight-forward. Secondly, the change in reaction conditions
by using Bu$_3$SnD, if any would be minimal since the deuterated reagent is the closest analogue of Bu$_3$SnH.

When compound 252 was treated with Bu$_3$SnD under identical conditions direct reduced material as well as the two cyclised isomers were isolated in the same proportions as before. Each of these products were analysed first by $^1$H NMR and then by $^2$H NMR spectroscopy and compared with the spectra acquired for the undeuterated derivatives.

As anticipated, examination of the $^1$H NMR of the deuterated direct reduced product 264 revealed a single proton for the resonance at $\delta$ 3.76; by comparison the same signal in the $^1$H NMR of the undeuterated analogue 257 integrated to two protons and was assigned to the C6 methylene protons earlier. When a $^2$H NMR spectrum was acquired for this derivative deuterium incorporation at aryl carbons was not observed. Instead the only $^2$H signal at $\delta$ 3.80 correlated well with the $^1$H NMR results described earlier which confirmed $^2$H incorporation at C6 of 264. Thus, the existence of a 1,5-hydrogen transfer process in competition with cyclisation was confirmed.

The model study has revealed that the relative stereochemistry at C10 and C10$\alpha$ of the major cyclised isomer is similar to that of swainsonine 247 and castanospermine 248. Although the derived methods are less stereoselective in comparison to the selectivities achieved with pyridone substrates 205-210, described in section 2.2, the model study as a whole provides a rich source of information, particularly the 9:1 selectivity achieved in the cyclisation step, when the actual synthesis is attempted.
CHAPTER 3

Synthesis of (±)-O-Methylcorytenchirine

3.1 Introduction 63

3.2 Previous Syntheses of Corytenchirine 65

3.3 Retrosynthetic Analysis of (±)-O-Methylcorytenchirine 69

3.4 Synthesis of (±)-O-Methylcorytenchirine 71
Chapter 3: Synthesis of (±)-O-Methylcorytenchirine

3.1 Introduction

(−)-Corytenchirine 301 was first isolated in 1975 by Kamatani et. al. from a biennial herb, corydalis ochotensis, from Taiwan.99,100 The herb was also reported to exist in northern China, Siberia, Korea and Japan. Although, isolation of many other 13-methyl substituted alkaloids having the same basic heterocyclic framework had been reported in literature101 prior to the isolation of 301, there was no record of any 8-substituted derivatives isolated from nature. A synthetic derivative, coralydine 302, was synthesised in 1913 but, to date, has not been isolated from natural sources. Thus, (−)-corytenchirine 301 is considered to be the first 8-substituted berbine to be isolated from the plant kingdom. The isolation of several new 8-benzyl substituted berrbines was reported in 1992.102

The structure and the absolute configuration of 301 was established after much comparison with existing natural berrbines and synthetic analogues such as coralydine 302. Following confirmation of its structure 301 was classed as a berbine and the dimethoxy aryl ring, the two saturated quinolizine rings, and the aromatic ring containing the C11 hydroxy function were defined as A, B, C and D rings respectively.

While corytenchirine has a basic dibenzo[a,g]quinolizine skeleton which is common to almost all tetrahydroprotoberbine alkaloids, its uniqueness is derived from the 8-methyl substituent disposed in a cis arrangement to the 13a proton at the B-C ring junction. The study described in this chapter takes advantage of this stereochemical disposition in corytenchirine to demonstrate the applicability of radical ring closure methods described in Chapter 2 to natural product synthesis. Synthesis of O-methylcorytenchirine described in this chapter was also based on an isoquinoline model study carried out in this laboratory.103 The study revealed that when
isoquinoline 303, synthesised as illustrated in scheme 301, was subjected to radical ring closure conditions described in chapter 2, radical attack occurred \textit{anti} to the substituent \textit{\alpha} to the nitrogen. As with the pyridone studies described in chapter 2, the isoquinoline reaction was completely diastereoselective which afforded 304 in 90\% yield as the sole isolable product.\textsuperscript{104} The stereochemistry of 304 was confirmed by single crystal x-ray crystallography.\textsuperscript{105}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\text{Cl} \text{C} \text{Br}}; \node (b) at (3.5,0) {\text{Br}}; \node (c) at (2.5,0.5) {\text{N} \text{O}}; \node (d) at (1.5,0.5) {\text{CH}_3 \text{O}}; \node (e) at (3,1) {\text{Br}}; \node (f) at (2,1) {\text{CH}_3 \text{O}}; \node (g) at (0.5,0.5) {\text{CH}_3 \text{MgI \text{THF}}} \node (h) at (3.5,0.5) {\text{Bu}_3 \text{SnH \text{AIBN \text{benzene \text{80}\textdegree C}}}};
\end{tikzpicture}
\end{center}

Scheme 301

Based on the above studies a retrosynthetic analysis of \textit{O}-methylcorytenchirine 305 will be described in section 3.3. Section 3.4 will detail a series of experiments directed towards the actual synthesis of the natural product. It is also appropriate to describe former syntheses of the natural product 301 or the \textit{O11} methylated derivative 305 in order to fully appreciate the potential of the current methodology. Short accounts of these syntheses are described in the next section.
**Chapter 3: Synthesis of (±)-O-Methylcorytenchirine**

3.2 Previous Syntheses of Corytenchirine

Reported syntheses of corytenchirine 301 and its O-methylated derivative 305 since its isolation are few in number. Immediately following the report of the isolation of 301 in 1975, Brossi and co-workers\(^{106}\) described the first synthesis of racemic O-methylated corytenchirine 305 and its resolution in a preliminary communication. Despite being a derivative of the isolated material its synthesis confirmed the structure of corytenchirine 301, especially in relation to the absolute stereochemistry of the 8-methyl and the C13\(\alpha\) proton. Towards the latter part of 1976 a detailed version of this paper\(^{107}\) with all physical data and the crystal structure of the O-methylated derivative was published.

Soon after Brossi published his initial findings, Kamatani *et. al.* in early 1976 published the first total synthesis of (+)-corytenchirine 301 along two different routes.\(^{108}\) Their work remains the only example of the total synthesis of the natural product. Since then there has been only one attempt to synthesise corytenchirine 301; the synthetic strategy was conceptually similar to that employed by Kamatani and his co-workers.\(^{109}\) It is surprising that to date neither the optically pure (−)-corytenchirine has been synthesised nor the racemate resolved.

**The Brossi Synthesis:**

Brossi and his co-workers\(^{110,111}\) achieved their target by using a Mannich condensation reaction. The experiment involves condensation of 1-benzylisoquinoline 306 with acetaldehyde under acidic conditions (5 M aqueous HCl) to afford the intermediate iminium salt which undergoes rapid *in situ* cyclisation along a nucleophilic substitution mechanism (scheme 302). Because the final ring closure was not stereoselective both (±)-O-methylcorytenchirine 305 and (±)-coralydine 302 were obtained from the reaction. The racemic epimers 305 and 302 were first separated and the racemates later resolved after an elaborate procedure to isolate both enantiomers of optically pure O-methylcorytenchirine and coralydine.
Two different routes towards the above natural product have been documented by Kamatani and his co-workers. In their first approach (scheme 303), the dihydrobenzylisoquinoline 307 was condensed with acetic anhydride in pyridine followed by a reductive photolytic cyclisation in the presence of hydriodic acid to afford 308 in moderate to low overall yield. Following this manoeuvre the key reduction of the C ring of 308 by sodium borohydride resulted in the expected generation of the two diastereoisomers in a ratio of 1 to 3, unfortunately in favour of the less desired epimer 309A. Deprotection of the C11 hydroxy group of the minor compound 309B completed the synthesis of (±)-corytenchirine 301.
In their other approach the hydrochloride salt of tetrahydrobenzylisoquinoline 310 was used in an intramolecular Mannich reaction with acetaldehyde in hot acetic acid to yield the (±)-O-methylcorytenchirine 305 in one step together with coralydine 302 in 45% and 10% yield respectively.
Chapter 3: Synthesis of (±)-O-Methylcorytenchirine

3.1 Retrosynthetic Analysis of O-methylcorytenchirine

The Lete Synthesis:

The key step in the Lete synthesis\(^{113}\) of (±)-O-methylcorytenchirine 305 involves reduction of the benzoquinolinium chloride salt 311 with sodium borohydride. The method is similar to that employed by Kamatani et. al. The authors claimed to have obtained both epimers the major one having the correct stereochemistry required for O-methylcorytenchirine thus confirming Kamatani's findings.

In the light of the syntheses of corytenchirine 301 or its methylated derivative 305 outlined above, it is interesting to note that in each case, although the preparation of the target was achieved, the main drawback was the need to separate the naturally occurring derivative from its diastereomer coralydine 302 at some stage of the synthesis. Selective synthesis of neither of these two diastereomers has been reported to date nor has corytenchirine been prepared in enantiomerically pure form. Hence, the selective synthesis of O-methylcorytenchirine provides an excellent opportunity to demonstrate the utility of the model radical ring annulation methods described in the preceding chapter. Accordingly, the following sections describe the experiments undertaken to this effect.
3.3 Retrosynthetic Analysis of O-methylcorytenchirine

Synthesis of (±)-O-methylcorytenchirine began with the retrosynthetic analysis of the molecule 305 along well established principles. The first step of the analysis is outlined in scheme 304. Homolytic cleavage of bond C13a-C13b simplifies the complex tetracyclic molecule 305 to a simple N-functionalised isoquinoline synthon 312. The reagent of the synthon 312, compound 313, would contain a double bond with a suitably positioned bromine atom for radical generation. Thus, the forward reaction would involve the key homolytic ring closure of 313 to 314 followed by reduction of the C6 amide carbonyl of the latter to afford the O-methylated natural product 305.

As with model isoquinoline studies described in section 3.1, the radical ring closure was expected to afford the single diastereomer 314 with the C8 methyl substituent disposed anti to the newly formed bond. The amide functionality in 313, as observed previously, is vital since it controls on one hand the stereochemical outcome of the reaction at the ring junction and on the other serves as a stable form of...
protection for the nitrogen atom. Reduction of the amide keto function in 314 was to be effected by known methodology.

Synthesis of the radical precursor 313 was to be achieved by straightforward procedures similar to that used in the construction of model radical pyridones. Disconnection of the N-acyl and the Cl methyl groups in 313 affords a synthon 315; the actual reagents that could be used in the forward reaction are illustrated in scheme 305. Therefore initial acylation of dimethoxyisoquinoline 316 with 317 followed by the introduction of the methyl substituent at Cl by nucleophilic addition should afford the radical precursor 313. The actual methods and conditions used together with deviations from the above strategies will be discussed in the next section.

![Scheme 305](image_url)
3.4 Synthesis of (±)-O-Methylcorytenchirine

From the preceding section it is clear that the primary goal in the synthesis of O-methylcorytenchirine was to assemble the isoquinoline enamide 313, the substrate required for the radical ring construction step, by as short a route as possible. To this end, as outlined before, it was hoped that acylation of dimethoxyisoquinoline 316 followed by treatment with methylmagnesium bromide would result in the required N-functionalised isoquinoline 313.

Despite the simplicity of the starting materials required for the first step, the bromoacyl chloride 317 and 6,7-dimethoxyisoquinoline 316 (scheme 308) were commercially unavailable and had to be synthesised. The former was accessible from the reaction of bromine with the freely available dimethoxyphenylacetic acid 318 by treatment with molecular bromine. On treatment of the acid 318 with 1.5 equivalents of molecular bromine in chloroform at room temperature ring bromination occurred regioselectively at the para position to afford the desired bromo acid 319 in quantitative yield (scheme 306). Bromination ortho to either of the two methoxy functions was not observed.

The regiospecificity of bromination was verified from the $^1$H NMR spectrum of the bromo acid 319 in which only two sharp singlets at $\delta$ 7.03 and 6.78 were observed in the aromatic region. These signals were assigned to the two isolated aromatic protons at C3 and C6 respectively, the former shifted down-field as a result
Chapter 3: Synthesis of (±)-O-Methylcorytenchirine

of the inductive effect imposed by the ortho-bromide. While the two methoxy functions of the acid resonated at δ 3.85 as a sharp singlet, the resonances for the two benzylic protons were centred at δ 3.76. The bromo acid 319 when heated at reflux with thionyl chloride was smoothly converted into the desired acid chloride 317 in 76% yield.

The Bischler - Napieralski\textsuperscript{115} and Pictet - Spengler\textsuperscript{116} reactions are the methods most commonly used for the construction of functionalised isoquinolines. Because both of them have the advantage of allowing the incorporation of the Cl substituent, they are often used for the synthesis of 1-benzylisoquinolines. For example, acylation of dimethoxyphenyethylamine, followed by reductive ring closure by treatment with POC\textsubscript{2} under Bischler - Napieralski conditions should yield dihydroisoquinoline 320 (scheme 307). Oxidation of 320 by conventional methods should yield the desired 6,7-dimethoxyisoquinoline 316 in three steps.

\begin{center}
\includegraphics[width=\textwidth]{scheme_307.png}
\end{center}

\textbf{Scheme 307}

On the other hand, Promeranz - Fritsch\textsuperscript{117} synthesis of isoquinolines has the advantage of affording the required product in two steps. The general principle of this method involves the condensation of the appropriate aromatic aldehyde with the amino acetal 321 (scheme 308) to generate the aldimine 322. In the original literature cyclisation of the resulting imine 322 to the fully aromatised isoquinoline 316 was achieved by the use of a mineral acid such as HCl. Despite the advantage of acquiring isoquinoline in two steps, the use of this method was relatively unusual in the past because of the low yields obtained in the latter step.
Several successful new modifications to Promeranz-Fritsch synthesis, based on the same general principles, have been proposed in the literature during the last two decades. For example a noteworthy method published by Forbes and co-workers which utilises boron trifluoride diacetic acid complex in trifluoroacetic acid in place of a strong mineral acid is both simple and high yielding. Despite the harsh nature of this reagent and the solvent used the authors claim excellent yields of up to 82%. \(^{118}\)

With these methods at hand the two routes to the required radical precursor illustrated in scheme 309 were explored. In the first set of experiments 3,4-dimethoxybenzaldehyde was condensed with the amino acetal 321 (scheme 309) in benzene until the theoretical amount of water was trapped in a Dean-Stark apparatus. Under these conditions the crude acetalimine 322 was isolated in almost quantitative yield and in sufficient purity (NMR) to be used in the next step. The spectra acquired for the crude imine 322: \(^1\)H, \(^{13}\)C APT NMR and EIMS were in good agreement with the structure.

Following Jackson’s method, \(^{119}\) (path A in scheme 309) acetalimine 322 was treated with the acid chloride 317 in THF at room temperature. Formation of the acyl iminium salt was expected to be rapid and readily observed by a formation of a precipitate. Instead, the solution remained homogeneous and clear of any suspension. This observation was in contrast to the rapid formation of iminium salts with acyl chlorides which are insoluble in THF. For example, formation of thick precipitates were observed when methoxypyridine was treated with acyl halides as described in Chapter 2. Although prolonged stirring of the mixture, (ca. 2 days) at room temperature afforded a white precipitate, presumably an indication of slow acylation at nitrogen, addition of methylmagnesium chloride failed to yield the desired compound 323 upon work-up. Instead, the imino acetal 322 was recovered in 85% yield.
Chapter 3: Synthesis of (±)-O-Methylcorytenchirine

Scheme 309

a: acid Chloride 317, CH₃MgBr  
b: BF₃·2(C₂H₅COOH) in (CF₃CO)₂O  
c: acid chloride 317, CH₃MgBr  
d: Bu₃SnH, AIBN in benzene  
e: LiAlH₄ in THF

305  
313  
314  
323  
322  
321
Reverse addition of the two reagents, the Grignard reagent followed by the acid chloride 317, was next investigated. Addition of methylmagnesium bromide to a solution of imino acetal 322 in THF resulted in an immediate thick white suspension presumably due to the imino-magnesium salt, which was stirred for three hours before the acid chloride 317 was added. Once again only the Schiff's base 322 was recovered (80%) on work up. This result is in contrast to the report of Jackson et al., in which they claim to have obtained C-1 benzyl substituted dihydro isoquinolines in high yield.

Forbes' method of generating dimethoxyisoquinoline 316 by Lewis acid catalysed ring closure was described above. Their method, a modified version of the Promeranz - Fritsch reaction, underlines the advantages of the use of BF₃ during the nucleophilic substitution reaction instead of traditional mineral acids such as HCl. The proposed mechanism for this ring closure is outlined in scheme 310. Cleavage of aliphatic ethers by acid anhydrides in the presence of a Lewis acid is known to result in two moles of the ester and is well documented in literature. The acetate thus formed is believed to undergo a Lewis acid (BF₃) catalysed elimination facilitated by the participation of the para methoxy substituents in the ring. Formal loss of methanol from the dihydroisoquinoline at the final stage is rapid as aromatisation to 316 is energetically favoured.
Dropwise addition of the Schiff base 322 dissolved in trifluoroacetic anhydride to a solution of borontrifluoridetricarboxylic acid complex (BF$_3$·2(CH$_3$COOH)) in trifluoroacetic anhydride cooled to 5 °C resulted in a cherry red solution. On work-up, after stirring the reaction mixture for 7 hours, first at 0-5 °C and then at room temperature, followed by purification of the crude residue, dimethoxyisoquinoline 316 was isolated in 86% overall yield. The $^1$H,$^13$C NMR and the 70eV mass spectra together with analytical data obtained for the purified material correlated well with that for the published data for dimethoxyisoquinoline 316.

With the acquisition of both starting materials synthesis of the key radical precursor 313 was investigated. Initially, 6,7-dimethoxyisoquinoline 316 was treated with the acid chloride 317 in THF at -23 °C and the heterogeneous (isoquinolinium salt) was stirred for one hour. Methylmagnesium bromide was then added to this mixture at the same temperature. The precipitated isoquinolinium quaternary salt was observed to go into solution on addition of the Grignard reagent as expected. On work-up followed by column chromatography of the crude residue the desired isoquinoline 313 was isolated in 92% yield.

The spectral characteristics of the isolated product were found to be in full agreement with those of the anticipated radical precursor 313 (figure 301). The mutually coupled AB system of doublets with a $J$ value of 8 Hz in the $^1$H NMR at $\delta$ 5.86 and 6.55 was assigned to the C4 and C3 hydrogens respectively in the isoquinoline moiety. This establishes the presence of the double bond essential for the radical ring closure step. The quartet at $\delta$ 5.81 mutually coupled ($J$ = 7 Hz) with a doublet at $\delta$ 1.28 was assigned to the C1 proton. The three proton latter doublet ($\delta$ 1.28) was obviously due to the C1 methyl protons. The low field singlets at $\delta$ 6.62, 6.65, 6.78 and 7.04 were assigned to the four isolated aromatic protons at C3, C8, C5 and C6. Evidence for the presence of bromine in the molecule was established from its 70 eV mass spectrum which revealed the characteristic equal intensity M+ and M+2 signals at $m/z$ 461 and $m/z$ 463 respectively.

![Figure 301](image_url)
Following the acquisition of the radical precursor 313, the key step in the synthetic plan, namely the stereoselective ring closure by radical methods was investigated. As expected, the substrate on treatment with tributylstannane and AIBN over six hours in benzene at reflux effected the desired conversion smoothly and in high yield (76%). Most importantly, as with the model isoquinoline derivative 303 described in section 3.1 (scheme 301), the sole product isolated from the reaction was proved to be 314 by spectroscopic methods described below (figure 302). The sole isomer 314 resulted from ring closure anti to the methyl group α to the nitrogen. Thus, the stereochemistry required for the final natural product was achieved.

The absence of the mutually coupled doublets assigned to the C3-C4 double bond protons of 313 in the $^1$H NMR spectrum of the single product isolated from the radical reaction was indicative of ring closure to 314. Instead of the two doublets an ABX system of signals was observed in the $^1$H NMR spectrum. The two AB signals centred at $\delta$ 2.84 and 3.03 have the characteristics of two geminal and diastereotopic protons (figure 302), the former relationship evident from a large coupling constant ($J = 16$ Hz) and the latter revealed by the diminished intensity of the outer signals. Thus, these signals were assigned to the C13 methylene protons. Each of these A and B signals are in turn coupled to an X signal at $\delta$ 4.83, a doublet of a doublet, with a large ($J = 12$ Hz) and a fine ($J = 3$ Hz) coupling constant. This signal was assigned to the C13a proton. From the model studies carried out previously and x-ray data obtained (chapter 2) it is known that the ring junction proton assumes a pseudo-axial conformation. Based on such data it is reasonable to deduce that the C13a hydrogen in compound 314 is disposed in a pseudo-axial conformation and the large coupling ($J = 12$ Hz) arises from axial - axial interaction with the C13 axial proton (C13a-13CH$_{ax}$) while the fine coupling ($J = 3$ Hz) from axial - equatorial interaction with C13 equatorial proton (C13a-13CH$_{eq}$). Accordingly, the signals A ($\delta$ 2.84) and B ($\delta$ 3.03) were assigned to C13H$_{ax}$ and H$_{eq}$ respectively.

---

**Figure 302**
Chapter 3: Synthesis of (±)-O-Methylcorytenchirine

Confirmation of the stereochemical outcome of the above reaction was established with the aid of nOe difference spectroscopy. Assuming that the single diastereomer obtained has the C1 methyl group disposed in a cis-arrangement with the pseudo-axially oriented C13a proton, saturation of the latter should produce a positive enhancement of the former and none for the pseudo-equatorially placed C1 proton. In the reverse experiment, irradiation of the C1 quartet should produce positive enhancement of the geminal methyl signal but none for the C13a signal. However, irradiation of the methyl signal although possible is less likely to provide much evidence, since the relaxation of methyl protons is dominated by their mutual dipolar interactions, thus making nOe's at methyls generally small. Despite this limitation the experiment was conducted for the purpose of completion.

The results obtained from nOe difference experiment is shown in figure 303. As expected upon irradiation of the signal assigned to the C13a proton a 16% enhancement of the methyl signal and 4% enhancement of the C1 proton was observed. Saturation of the C1 proton resulted in a 11% enhancement of the methyl signal but only 2% of the C13a signal. Thus, association of the C13a proton with the C1 methyl group from these two experiments alone is quite clear. It provides definitive data to prove the syn disposition of the C13a proton and the methyl group. The assignment of the above relation was confirmed although less reliably as stated previously by saturation of the methyl signal which provided enhancements of 5 and 7% to C13a and C1 signals respectively.

![Figure 303](image)

Following the above success in preparing the necessary heterocyclic framework with the stereochemistry required for the natural product, efforts were directed towards the reduction of the C6 carbonyl function in the B ring of 314 (scheme 311). The reagent of choice, often used for reduction of amide functionalities to amines, cyclic or open chain, is LiAlH4. Thus, as an initial attempt to use this reagent to effect the desired conversion was conducted.
Chapter 3: Synthesis of (±)-O-Methylcorytenchirine

Addition of the substrate 314 dissolved in THF to a suspension of LiAlH₄ in THF, followed by stirring of the mixture for 24 hours at room temperature only afforded recovered 314. Heating the mixture led to decomposition of starting material resulting in highly polar baseline material. It is noteworthy that similar problems were encountered in the reduction of a tricyclic amide carbonyl group adjacent to an aromatic ring (scheme 211) described in the previous chapter. With lithium aluminium hydride complete reduction of the amide carbonyl was not observed but gave only the hydroxyamine 224. On that occasion, it was found that AlH₃ generated in situ on addition of a third of a molar equivalent of AlCl₃ to a suspension of LiAlH₄ was more eventful in effecting the desired conversion (scheme 212).

When the tetracyclic amide 314 was subjected to similar conditions reduction of the C6 carbonyl was rapid and efficient as observed on TLC. Purification of the crude residue by column chromatography over basified alumina completed the synthesis of (±)-O-methylcorytenchirine in 43% overall yield commencing from dimethoxybenzaldehyde and the amino acetal 321.

(±)-O-methylcorytenchirine 305 thus obtained had all the spectral and the analytical characteristics reported in literature. The ¹H NMR of the derivative obtained was identical to the spectrum published by Kamatani et al.¹²³ and the assignment of the signals is outlined in the experimental section. The ¹³C APT NMR spectrum consisted of three methylene signals at δ 29.46, 35.63, 47.16 which confirmed the complete reduction of the carbonyl function and were assigned to C5, C13 and C6 respectively with the aid of heteronuclear correlation spectroscopy. In addition the spectrum displayed one methyl signal (δ 17.97), two methine carbons (δ 50.35 and 59.22), two signals for the four methoxy carbons (δ 55.81, 55.93), signals for the four aromatic methine carbons (δ 109.08, 109.75, 111.11, 111.39) and five quaternary carbon signals. The molecular ion at m/z 369 together with exact mass calculations as given in the experimental section confirmed the identity of (±)-O-methylcorytenchirine.
CHAPTER 4

A General Radical Route to Pavine & Aporphine Alkaloids

4.1 Introduction 81

The family of pavine alkaloids, a relatively small sub-group within the large spectrum of biogenetically natural products, is few in number containing perhaps twenty-two compounds to date. Seventeen of these compounds were isolated during the decade between 1953 and 1973 immediately following the recognition of this steroidal heterocyclic system in nature. There have been only infrequent reports of the isolation of new alkaloids belonging to this family. This is surprising in view of the ever-increasing number of other natural products reported, the isolation and structure determination of which has been aided by improved separation techniques and the development of potent analytical procedures with an earlier emphasis on physical properties.

4.2 Retrosynthetic Analysis of Argemonine 87

4.3 A Model Study Leading to Pavine Alkaloids 90

4.4 A Model Study Leading to Aporphine Alkaloids 99

4.5 Synthesis of (±)-Argemonine & (±)-Glaucine 108

4.6 Conformation of Precursor Substrates and their Relationship to the Product Ratio 116
4.1 Introduction

The family of pavine alkaloids, a relatively small sub-group within the large spectrum of isoquinoline natural products, is few in number amounting to only twenty two compounds to date. Seventeen of these compounds were isolated during the decade between 1963 and 1973 immediately following the recognition of this novel heterocyclic ring system in nature. Since then there have been only infrequent reports of the isolation of new alkaloids belonging to this family. This is surprising in view of the ever increasing number of other natural products reported, the isolation and structure determination of which has been aided by improved separation techniques and the development of powerful analytical instruments such as nuclear magnetic resonance spectrometers.

The first isolation of a pavine base dates as far back as 1944 when only a brief description supported by an empirical formula for a crystalline compound isolated was reported. Following re-isolation after sixteen years from the same plant Argemone hispida later designated as Argemone munita subsp. rotundata this compound was named argemonine. On the basis of its analytical and chemical degradation data, its structure was predicted to be based on a tetrahydroisoquinoline framework. The uncertainty over the exact structure of argemonine prevailed for another three years until in 1963 two groups independently determined its structure by correlation of the spectral data with that of a long-known synthetic compound referred to as N-methylpavine. Shortly afterwards confirmatory evidence emerged in the form of additional spectral data, and from synthesis and degradative studies. Following these studies the structure of argemonine was confirmed to be 401. At present it is considered to be the first pavine base isolated from nature belonging to this group of isoquinoline alkaloids.

The members of this group of alkaloids, characterised by their unique bridged heterocyclic framework, differ from each other by the arrangement of substituents.
A number of naturally occurring tertiary pavine bases are tabulated in Table 401.

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argemonine 401</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>Bisnorargemonine 410</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OH</td>
</tr>
<tr>
<td>Caryachine 411</td>
<td>O—CH₂—O</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>Eschscholtzidine</td>
<td>O—CH₂—O</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td></td>
</tr>
<tr>
<td>Eschscholtzine</td>
<td>O—CH₂—O</td>
<td>H</td>
<td>H</td>
<td>O—CH₂—O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isonorargemonine</td>
<td>OMe</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>Munitagine 414</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
</tr>
<tr>
<td>Norargemonine 409</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
</tr>
<tr>
<td>Platycerine 413</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>OH</td>
<td>OMe</td>
<td>H</td>
</tr>
</tbody>
</table>

Table 401

Most of the alkaloids tabulated above have been synthesised, some several times, by a variety of routes. Nearly all of these published procedures follow the classical route, in which the final ring closure of the appropriately substituted benzylisoquinoline is achieved by the acid catalysed alkoxy mediated substitution protocol, illustrated in scheme 401. While the presence of the alkoxy substituent para to the attacking carbon is crucial for directing the nucleophilic attack, the degree of basicity of the non-bonded electron pairs on the oxygen is also important since it dictates the rate of cyclisation. For instance, the presence of hydroxy functions by comparison with alkoxy groups are known to result in improved yields. Hence the efficiency of the final ring closure is highly dependant on the location and the type of substituents present around the pavine skeleton.
By contrast, radical ring closure involving intramolecular addition by aryl radicals is often rather insensitive to the number and type of substituents. Also as has been demonstrated in the previous chapter, such reactions often occur with very high regio- and stereo-selectivity. It appeared, therefore, that radical cyclisation might provide a basis for the development of a new general synthesis of the pavine bases.

This chapter describes the investigative work carried out to this effect. The key reaction involves a radical mediated ring closure to construct the required skeleton and is followed by functional group modification to incorporate the essential structural features of the pavine base. After initial investigations were carried out on model compounds, as described in section 4.3, the synthesis of (±)-argemonine 401 was undertaken in order to demonstrate the generality of the method. The synthesis of 401 is presented in section 4.4. During the course of this study several other important findings have also emerged. These findings will also be presented appropriately.

Classical Routes to Pavine Alkaloids:

Classical methods for the assembly of the pavine skeleton can be sub-divided into two stages; the construction of an appropriately functionalised 1-benzyl-isooquinoline, and its ring closure to afford the characteristic skeleton (scheme 401). The cyclisation reaction was first identified in 1886 when one of the minor products isolated during the reduction of papaverine 402 with tin and hydrochloric acid\textsuperscript{130} was named pavine.\textsuperscript{131} During the same study, N-methylation of papaverine followed by reduction of the C1-N bond also gave a similar compound with an extra methyl group on nitrogen. It was named N-methylpavine. The structures of these derivatives were later proved to be 404 and 401 respectively.\textsuperscript{132} The formation of these compounds is best explained along the mechanism illustrated in scheme 401, which involves the initial reduction of papaverine to the dihydroisoquinoline 403 by Sn/HCl followed by acid catalysed isomerisation of the C3-C4 double bond to form the iminium hydrochloride 405. Subsequent ring closure on to the carbon terminus of the iminium salt, aided by the methoxy group \textit{para} to the reactive aryl carbon followed by re-aromatisation affords pavine 404.
Chapter 4: A General Radical Route to Pavine & Aporphine Alkaloids

The classical route described above has been exploited in many syntheses of pavine bases, the overall path differing only in the manner in which dihydrobenzylisoquinolines or papavarine derivatives are obtained. For example, (±)-norargemonine 409 has been synthesised via the multi-step sequence illustrated in scheme 402. The synthesis of benzylpapavarine 408 commences from benzylvanillin 406 which is converted to the amidic intermediate 407 in three steps. Cyclisation of 407 by the well established Bischler-Napieralski procedures affords 408. Quaternisation of the nitrogen centre with the aid of methyl iodide, reduction to the dihydropapavarine with NaBH₄ followed by acid catalysed cyclisation affords (±)-norargemonine 409. Synthesis of (±)-bisnorargemonine 410, in a separate study later in 1970 was achieved along a similar route.
In other related investigations, established Pictet-Gams modifications of Bischler-Napieralski procedures have been used to assemble several other pavine bases. For example, construction of the isoquinoline required for the syntheses of (±)-bisnorgemonine 410 and its isomers,135 (±)-caryachine 411 and the unnatural pavine base (±)-isocaryachine136 412 are all based on the above modification of Bischler-Napieralski protocols.

\[ \text{Scheme 402} \]

\[ \text{410} \quad \text{411} \quad \text{412} \]
Syntheses of (-)-platycerine\textsuperscript{137} 413 and (-)-munitagine\textsuperscript{138} 414 on the other hand employ an alternative approach to the intermediate papavarine 415. The key derivative in these preparations is the Riessert compound 416. The compound 416 can easily be converted to the required papavarine derivative 415 by treatment with the appropriate benzyl chloride (scheme 403). Despite this change, the manner in which the characteristic bridge of the two natural products is assembled remains much the same. Synthesis of other alkaloids along parallel routes have also been published.\textsuperscript{139}

Scheme 403
4.2 Retrosynthetic Analysis of Argemonine

The first step towards the assembly of pavine bases involved the retrosynthetic analysis of argemonine 401. There were several reasons for the selection of argemonine 401 for this purpose and later, as a model pavine base to demonstrate the applicability of the derived methods. Of these, most importantly the starting materials were either found to be commercially available or had already been assembled during the synthesis of (±)-O-methylcorytenchirine in Chapter 3.

The key reaction of the proposed synthetic plan for (±)-argemonine is illustrated in scheme 404. Retrosynthetic cleavage of the bond C4a-C5, alkyl-aryl bond of 417 simplifies the characteristic bridged skeleton to a 1-benzylisoquinoline synthon 418. The corresponding substrate of this synthon is 419. Accordingly, the first step of the forward reaction of the above analysis would involve the generation of the aryl radical from the bromide 419 with the aid of a suitable radical generating reagent. This radical would be expected to undergo ring closure at the nitrogen terminus of the C3-C4 double bond followed by hydrogen abstraction from the reducing species to afford the desired heterocyclic pavine skeleton.

![Scheme 404](image_url)

Protection of the bridge-head nitrogen as a carbamate was important in two respects. In previous model studies described in chapter 2, 1,3A (1,3-allylic) strain between the amide carbonyl and the substituent α to the nitrogen played an important
role in achieving complete diastereoselective ring closure. Likewise, in the isoquinoline derivative 419 the carbonyl of the carbamate group would be expected to influence the conformation of the benzyl group favourably towards cyclisation. A pseudo-axial conformation would enable the radical easy access to the C3-C4 double bond otherwise not possible in a pseudo-equatorial conformation. Secondly, because selective N-monomethylation of amines is hard to achieve, ready transformation of carbamates to N-methyl groups using reagents such as LiAlH$_4$ was considered an additional advantage.

1-Benzylisoquinolines, similar to 419 are often used as common substrates for the elaboration of many naturally occurring compounds. Although many methods for the formation of benzylisoquinolines have been reported most of them involve multi-step syntheses. Accordingly a shorter route to compounds such as 419 was sought.

Nucleophilic addition of Grignard reagents to N-acylpyridinium salts is well documented in literature and is known to occur ortho or para to the nitrogen atom depending on the steric environment at each carbon centre. For example, selective addition of simple phenyl or methylmagnesium halides to N-acylated-4-methoxypyridinium salts ortho to the nitrogen atom was discussed in Chapter 2.

Conversely, nucleophilic addition to N-acylated isoquinolinium salts is known to occur almost exclusively at C1. Nucleophilic addition to C3 or to the hindered quaternary carbon at C4a is unknown. Addition of methylmagnesium bromide to N-acylated dimethoxyisoquinoline at C1 was described in chapter 2. Formation of Reissert compounds 420 by the reaction of isoquinoline with an acyl halide and potassium cyanide is another example. Several other additions have also been documented in literature.
Thus, with the experience gained in the syntheses of pyridone radical precursors 205-210 and the foregoing observations, N-acylation by quaternisation of the appropriate isoquinoline followed by the introduction of the benzyl moiety at C1 by nucleophilic addition should afford the desired dihydroisoquinoline 419 in a single step. Disconnection of the molecule in accord with these principles together with the actual substrates is illustrated in scheme 405. While there is a definite advantage in assembling the molecule in one step, the above strategy also demand the generation of a labile, bromine substituted, electron rich dimethoxybenzyl magnesium reagent 421 which could present numerous complications. This is in comparison to simple Grignard reagents used for previous pyridone systems.

Therefore, a model study with simple reagents, based on the above analysis, was undertaken before attempting the synthesis of the natural product, argemonine. Initially this model study was focused on the use of 4-methoxypyridine as starting material. Consequently, the principles and the conditions were extended to accommodate isoquinoline analogues. These results will be described in the following section.
4.3 A Model Study Leading to Pavine Alkaloids

A plan for the synthesis of 419 having been firmly established it was necessary to select the best system for probing the proposed nucleophilic addition reaction. Since it is known from previous studies that quaternised 4-methoxypyridine undergoes such additions efficiently, a 4-methoxypyridinium salt seemed the most appropriate substitute for an actual isoquinolinium system (scheme 406). Towards this end, the Grignard reagent of bromobenzyl bromide was selected as the nucleophilic reagent due to its simplicity and free availability. The method involved in the generation of the radical precursor is illustrated in scheme 406 and is similar to the synthesis of pyridone substrates 205-210.

![Chemical Reaction Diagram]

The preparation of the benzylic Grignard reagent 423 (scheme 407) requires selective insertion of magnesium at the benzylic position of 2-bromobenzyl bromide, leaving intact the aryl bromine substituent essential for the later generation of the radical. Although such reagents are reported to be obtainable from elemental magnesium under rather critical conditions, some Wurtz coupled bi-benzyl products are also reported to result.\(^{144,145}\) Several other attempts to prepare such organometallic reagents have involved the initial preparation of highly activated magnesium metal\(^{146}\) or reactive organometallic species such as magnesiumanthracene tetrahydrofuran complexes [Mg(anthracene)(THF)]\(_3\).\(^{147}\) Since these latter reagents
are highly moisture sensitive they are time consuming to prepare and difficult to handle.

Despite such reports, preparation of the benzylic Grignard proceeded smoothly using elemental magnesium in ether. 1,2-Dibromoethane was used as the initiating agent. In a typical preparation, 10% of a solution of ortho-bromobenzyl bromide in ether was added over 5 minutes to a suspension of magnesium turnings (1 equiv.) activated by the addition of 3 drops of dibromoethane. The rest of the solution was then added dropwise over about ten minutes while maintaining gentle reflux. All the magnesium was consumed within 30 minutes and the reagent was ready for use after a further 30 minutes of stirring at room temperature. The success of this preparation was proven by hydrolysis the Grignard reagent followed by the analysis of the crude product by routine spectral methods. The $^1$H and $^{13}$C spectra acquired confirmed the isolation of 2-bromotoluene, thus confirming the successful generation of the Grignard reagent during the reaction.

When 4-methoxypyridine, quaternised with phenyl chloroformate in THF at low temperature was treated with a freshly prepared solution of ortho-bromobenzylmagnesium bromide in diethyl ether as planned (scheme 406), the white suspension disappeared, indicative of efficient nucleophilic addition. Addition of aqueous acid (10% HCl) followed by column chromatography yielded the required radical precursor in 76% yield. Similarly, when methylchloroformate was used as the acylating agent the benzyldihydropyridone was isolated in 74% yield.

When the radical precursor in benzene at reflux was treated with $\text{Bu}_3\text{SnH}$ and AIBN in the same solvent under slow addition conditions the development of a new spot slightly more polar in character than the substrate was observed by TLC. The reaction was monitored until all starting material was consumed and the crude product was purified to obtain the ring closed compound in 87% yield (scheme 408). As observed previously for the model pyridone systems none of the direct reduced product was detectable in the crude NMR. Furthermore, in this instance although 1,7-endo ring closure should also be possible to afford the compound, which would contain the isopavine skeleton, none was detected.
With these preliminary results in hand the procedure was extended to accommodate isoquinoline as the starting substrate (scheme 409). Isoquinoline 429 in THF at low temperature was treated with phenylchloroformate followed by a freshly prepared solution of bromobenzyl-magnesium bromide 423. On completion of addition of the benzyl Grignard the white suspension completely disappeared as expected to give a homogeneous solution. Upon purification the benzylisoquinoline radical precursor 430 was isolated in 99% yield.

When the benzylisoquinoline 430 was treated with Bu₃SnH (scheme 410) under the same conditions (addition over 4-5 hours) as those used for the cyclisation of the model pyridone 424 gradual substrate conversion into two new compounds
was observed by TLC. The spot which was less polar than the starting material was found to be highly chromophoric under short wave UV light whilst the other, less polar by comparison with the starting material absorbed moderately. After all the starting material had been consumed, the crude reaction mixture was purified and the two products were separated.

\[
\text{Scheme 410}
\]

Initial analysis of the isolated compounds were based on mass spectroscopic studies. The most obvious difference observed between the mass spectra of the acquired products and the uncyclised material 430 was the absence of the prominent equal intensity peaks spaced two mass units apart. Such peaks are characteristic of bromine containing compounds; hence cleavage of the aryl bromide bond was evident. Lack of bromine in the resulting products is an indication of an efficient halogen abstraction step favourable either for cyclisation or direct reduction.

Further examination of the mass spectrum of the highly luminescent compound revealed a molecular ion at \( m/z \) 339 which originates from the loss of \( \text{H}^{79}\text{Br} \) from the substrate mass of \( m/z \) 419. While such a loss rules out direct reduction it also implies that the resulting aryl radical has undergone some form of cyclisation followed by loss of a hydrogen atom. This conclusion together with other spectroscopic methods to be described later in this section led to the identification of the highly luminescent product as 432 (scheme 411). On the other hand the mass spectrum of the moderately absorbing spot gave a molecular ion at \( m/z \) 341 which was consistent with the mass of the expected product 431 (scheme 410). Therefore, based on the above molecular masses, the yields of each product 431 and 432 were calculated to be 56 and 43% respectively.

In addition to the mass spectroscopic data discussed above, the best diagnosis for the acquisition of the required bridged skeleton 431 should emerge from its \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra. This is because compound 431 seemed to possess a \( C_2 \) symmetric axis through the nitrogen atom. Hence the spectrum was expected to
display a complete overlap of the signals, for example two multiplets each for the axial
and equatorial methylene protons on C6 and C12 and a single doublet for the methine
protons at C5 and C11. Thirteen aromatic hydrogens in addition to the above protons
were also expected.

\[
\begin{align*}
\text{Scheme 411} \\
\end{align*}
\]

In fact, the \(^1\)H and \(^{13}\)C NMR spectra were diagnostic of the structure of the
bridged compound 431. On the whole, the acquired spectrum of this compound
revealed the presence of 19 protons, out of which 13 were aromatic. The signals for
the remaining 6 hydrogens, however, appeared partially or well resolved in contrast to
the anticipated complete overlap due to symmetry. For example, the signals assigned
to the C5 and C11 methine protons at \(\delta 5.69\) and 5.76 were completely resolved
doublets, integrating for one proton each. Based on the theory that equatorial protons
in ring systems resonate down field than axial ones (Chapter 2) the two proton
multiplet at \(\delta 3.61\) was assigned to the C6 and C12 equatorial hydrogens. Although
the two proton multiplet resonating around 3 ppm assigned to C6 and C12 axial
hydrogens seemed to bear resemblance to a doublet of a doublet they are in fact two
partially overlapping doublets centred at \(\delta 2.93\) and 2.96.

\[
\begin{align*}
\delta 3.61 & (2\text{H, multiplet,} \\
& \text{6 & 12-H}_{\text{eq}}) \\
\delta 5.69 & \text{or 5.76 (1H,} \\
& J_{\text{eq}} 5.5 \text{ or 6 Hz)} \\
\delta 2.93 & \text{or 2.96 (1H,} \\
& J_{\text{gem}} 16.5 \text{ or 16 Hz)} \\
\end{align*}
\]

**Figure 401**
The NMR data presented above suggests that the expected C$_2$ symmetric axis does not exist in 431, presumably because of the presence of the carbamate functionality. In amides and carbamates the non-bonded electron pair on the nitrogen atom is delocalised with the amide carbonyl, thus renders a partial double bond character to the C-N link (Chapter 2). Therefore, the nitrogen atom in 431 is sp$^2$ hybridised. As a consequence, C11(or C5)-N-CO must lie in one plane and the phenoxy carbonyl moiety must reside on one side of the molecule as illustrated in figure 402. Such a placement would lead to deshielding effects, imposed by the NCO carbonyl on one set of C6 and C12 methylene and C5 and C11 methine hydrogens, resulting in different chemical shifts. Evidence for the asymmetric nature of 431 is also obtained from the $^{13}$C NMR APT spectrum in which two well resolved CH$_2$ signals for C6 and C12 (δ 36.77 and 37.39) and two other CH signals for C5 and C11 (δ 49.81 and 50.88) are observed. Thus, formation of the bridged heterocyclic system was confirmed.
Evidence for the structural identity of compound 432, isolated from the radical ring closure step (scheme 411) initially rested on the mass spectroscopic data as briefly described before. It was revealed that the molecular ion at $m/z$ 339 originates from the loss of $\text{H}^{79}\text{Br}$ from the starting substrate mass of $m/z$ 419. Clearly bromine loss occurs when the tributyltin radical abstracts the halogen atom from the aryl bromide. Relying on the molecular mass ($m/z$ 339) obtained from the mass spectrum, the intermediate radical thus formed has to undergo a further loss of one mass unit, obviously a hydrogen atom. Such a loss is only achievable by a substitution mechanism, most likely at an aromatic carbon.

The question that arises then is at which carbon atom does the substitution occur. The $^1\text{H}$ NMR spectrum of 432 reveals that the loss of a hydrogen atom occurs from an aromatic carbon as anticipated, since only 12 aromatic hydrogens could be accounted for instead of the 13 present in the uncyclised substrate 430. Considering the accessibility of the intermediate aryl radical to isoquinoline aromatic carbon atoms (C5, C6, C7 or C8 of starting substrate) it is most likely that substitution occurs at C8 of substrate 430. Such annulation (at C8) would afford the tetracycle 432 (figure 403).

![Aporphine skeleton](image)

Figure 403

Other residual signals in the $^1\text{H}$ NMR spectrum are also in full agreement with the predicted structure 432. Most importantly, the low field mutually coupled doublets resonating at $\delta$ 5.65 and 7.10 with $J$ values of 8 Hz each reveal that the integrity of the C4-C5 double bond has been preserved. Further, the related ABX system of signals resonating at $\delta$ 3.07, 3.73 and 3.35 can be respectively assigned to the C7 axial, equatorial and the C6a methine protons. Thus, the identity of 432 was confirmed.

With the confirmation of the structure of the unexpected compound 432 from the radical ring annulation reaction it became evident that the acquired tetracyclic by-product 432 was closely related to aporphinoid alkaloids. The structure of
compound 432 differs from the basic heterocyclic framework of aporphine alkaloids (figure 403) only by the presence of the C4-C5 double bond and the N-phenoxy carbonyl function used to mask the N-methyl group. These similarities prompted a new investigation into the conditions necessary for the reduction of the extra double bond and restoration of the masked N-methyl function. These results will be presented in the next section.

With the acquisition of the desired model pavine 431, attention was focused on the next step of the synthetic plan involving the reduction of the N-phenoxy carbonyl function to the N-methyl groups found in simple pavine alkaloids (scheme 412). As suggested earlier, LiAlH4 in THF is known to effect the desired conversion efficiently. Thus, in a typical experiment the model pavine precursor 431 was dissolved in dry THF and added dropwise to a suspension of the reducing agent, LiAlH4 in the same solvent. The gradual disappearance of the starting substrate and the appearance of a much more polar spot, characteristic of an amine was monitored by TLC. On complete consumption of the starting material the reaction solution was worked up in the usual manner and subjected to radial preparative layer chromatography to afford the desired model pavine derivative 433.

![Scheme 412](image)

The spectroscopic data obtained for the model pavine compound 433 was similar to those recorded for simple pavine alkaloids in the literature. The mass spectrum of 433 displayed a molecular ion at \( m/z \ 235 \) (53%) which is in agreement with the product mass. The weak signal at \( m/z \ 220 \) (5%), a loss of 15 mass units from the molecular mass \( m/z \ 235 \), obviously arose from the cleavage of the N-methyl group and was diagnostic of its presence. The only other major signal, the base peak at \( m/z \ 144 \) (100%) corresponds to the N-methylisoquinolinium ion, which arises along the same fragmentation path illustrated for (±)-argonine 401 later in section 4.4.
Chapter 4: A General Radical Route to Pavine & Aporphine Alkaloids

4.4 A Model Study of Pavine Analogues

Unlike the cyclised carbamate 431, the N-methyl derivative 433 proved to be perfectly C₂ symmetric (figure 404). Thus, the methylene protons at C6 and C12 in the ¹H NMR of the model compound appeared as two distinct signals, two hydrogens each at δ 2.70 and 3.51. The former resonance was assigned to the axial hydrogens and the latter to equatorial protons at these sites. In addition the two proton doublet resonating at δ 4.12 was assigned to the methine protons at C5 and C11. The three proton sharp singlet at δ 2.53 was representative of the N-methyl protons. The ¹³C APT NMR spectrum displayed one distinct signal each for the methylene carbons and the methine carbons respectively at δ 34.05 and δ 56.69. Thus, the model study of pavine analogues was concluded.
4.4 A Model Study Leading to Aporphine Alkaloids

The group of aporphines comprises in excess of 300 alkaloids, differing only by the arrangement of substituents around the heterocyclic skeleton. These substituents vary from simple alkoxy such as in glaucine, norglaucine, dehydroglaucine, dehydronorglaucine, nantenine etc. to dimeric species such as istanbulamine where two molecules are coupled through an ether linkage. Some illustrative examples are shown in figure 405. (+)-Glaucine, the first aporphine to have been isolated as early as 1839 was properly characterised after sixty two years by Fischer et al. It was also the first compound belonging to this group of alkaloids to have been synthesised and later in 1956 was shown to possess an absolute configuration of (S) at C6α.

![Figure 405](image)

The naturally occurring (+)-form of Glaucine is known to exhibit antitussive action in humans with a potency comparable to codeine. While, the effects of (±)-glaucine phosphate in comparison to codeine phosphate as a centrally-acting cough suppressant have been studied in human volunteers, (+)-Glaucine hydrobromide has in fact been used in humans as a therapeutic agent for...
cough in Bulgaria, Poland and the USSR.\textsuperscript{159} In addition to the above pharmacological use it is also known to cause many other central nervous system effects\textsuperscript{160} including narcosis and muscle relaxation.\textsuperscript{161} It is also reported to show antifungal, antithrombotic, analgesic, cytotoxic, antimitotic and antiinflammatory activity.\textsuperscript{162,163} In animals, glaucine is reported to produce convulsions, hypotension and respiratory depression.

The discovery of the pharmacological value of glaucine simulated research on the syntheses of these biaryl compounds. Most of these efforts documented during the last decade commenced from freely accessible 1-benzylisoquinoline derivatives followed by the formation of the key biaryl linkage. To this end four major reactions, the photo-Pschorr reaction, phenolic or non-phenolic oxidative coupling, benzylene-mediated reactions and photo or more recently tributyltinhydride mediated cyclisations\textsuperscript{164} have been utilised. An excellent review on aporphine alkaloids and their synthesis has been published in 1985.\textsuperscript{165}

The photo-Pschorr reaction, the oxidative-photolytic ring closure and Bu\textsubscript{3}SnH mediated cyclisations are all similar in one respect. Irrespective of the conditions or the reagents used, all three reactions generate an intermediate aryl radical which subsequently undergoes ring closure to form the desired biaryl linkage (scheme 413). While the photo-Pschorr reaction utilises photolytic generation of radicals from diazonium salts, iodine is used as an oxidant and a radical initiator in simple photocyclisations. On the other hand Bu\textsubscript{3}SnH mediated cyclisations involve the well known chain reaction procedure.

Despite the frequent use of such methodology in organic synthesis to link two aryl moieties,\textsuperscript{166} the actual mechanism involved has not been confirmed to date. However, several proposals, based on existing mechanistic principles have been suggested by a number of groups to explain this observation. For example, in Bu\textsubscript{3}SnH mediated cyclisations, the first step of the mechanism involves halide atom
abstraction by a tin radical to form the aryl radical 435 (scheme 414). What is not known, at this stage is whether this intermediate radical adds directly to C8 to yield the endo-radical species 436 or to C8a to afford the exo-radical 437 initially, followed by rearrangement to the much stable tertiary radical 436, as observed in the biogenesis of aporphine alkaloids. In addition, irrespective of whether the radical initially undergoes exo ring closure at C8a followed by rearrangement to 437 or direct endo cyclisation at C8, the fate of the resultant secondary radical 436 is also not known.

Biomimetic studies carried on aporphines by Kupchan reveals that spirodienones such as 438 are in fact biosynthetic precursors of aporphine alkaloids. The theory has been proved by the isolation of 438 followed by acid catalysed rearrangement to (+)-predicentrine hydrochloride 439 in good yield (scheme 415). Further, among other products Pschor cyclisation of 440 affords the indeno-isquinoline 441 in 30% yield (scheme 415). It is known that compound 441 when treated with acid also undergoes rearrangement to the 1-oxoaporphine 442 in quantitative yield.

Although the above methods involve non-radical conditions, radical based 1,2-rearrangements are also known and are referred to as neophyl rearrangements.
Considering the next step of the mechanism, the foremost possibility is that the cyclised intermediate 436 can abstract a hydride from Bu$_3$SnH to yield 443, 444 and/or 445 (scheme 416). The resulting cyclohexadienes can then undergo rapid oxidative elimination of H$_2$ either during the reaction or work-up to afford the fully aromatised product. However, related studies conducted in this laboratory in somewhat similar circumstances with Bu$_3$SnD reveal no incorporation of deuterium in the final product. Based on those results the mechanism illustrated in scheme 416 seems invalid.

Another possible mechanism proposed by Bowman et al. for similar biaryl ring closures is based on a pseudo-S$_{RN1}$ mechanism. The Bowman hypothesis applied to the current ring formation is illustrated in scheme 417. According to this mechanism the aryl radical would undergo either endo and/or exo ring closure to afford 436 and 437 respectively. In the event of exo ring closure rapid rearrangement to the endo radical 436 would be expected, presumably by a neophyl rearrangement. Oxidation of the resultant tertiary cyclohexadienyl radical 436 to 446 by loss of hydrogen followed by electron transfer with a substrate molecule 430 would afford the ring closed product 432. While the loss of bromide from the substrate radical anion 447 (the Bunnett reaction) completes the cycle, HBr formed...
during the reaction rapidly reacts with \( \text{Bu}_3\text{SnH} \) to afford \( \text{Bu}_3\text{SnBr} \) and a molecule of hydrogen.

\[
\begin{align*}
\text{CO}_2\text{Ph} & \quad \rightarrow \quad \text{CO}_2\text{Ph} \\
\text{H} & \quad \rightarrow \quad \text{H}
\end{align*}
\]

\text{Scheme 416}

Although the above mechanism (scheme 417) suggests the existence of radical anions, it is most likely that such species do not interfere with the propagation of the radical chain, neither during the formation of the pavine base nor the model aporphine derivative. With interference, the chain would be inefficient and consequently cessation of product formation would be observed. Therefore, based on the available evidence, the proposed mechanism (scheme 417) provides the most plausible explanation for the generation of 432.

As illustrated earlier, the acquired tetracyclic product 432 was observed to possess the principle skeletal framework of aporphine alkaloids. In addition, the structure of 432 contained an extra double bond at C4-C5 and the carbamate had to be unmasked to an \( N \)-methyl function. While the latter conversion could hopefully be effected with ease employing common reagents, methods for the reduction of the C4-C5 double bond needed to be investigated.
Scheme 417
Double bonds of this type in isoquinoline derivatives are often reduced catalytically with the aid of PtO₂ under an atmosphere of hydrogen. The exact conditions under which such reductions occur depends on the nature of the substrate. Several derivatives are known to undergo this reduction at normal hydrogen pressures while some require pressures up to 60 psi. The same conversion has also been effected with NaBH₄ or NaCNBH₃ under acidic conditions. In acidic media such enamines or enamides are known to isomerise to imines or imides, depending on the substituent R (scheme 418), which are then easily reduced by employing hydride donating reagents such as NaBH₄ or NaCNBH₃. However, as the mechanism suggests, success of the reaction depends on the basicity of the lone electron pair of the nitrogen atom. In the case of strongly basic substrates such as in amines, isomerisation can be effected using mild acids or even alcohols. However, stronger acids are required for compounds with N-substituents that are conjugated with the lone electron pair, such as in amides or carbamates.

![Scheme 418](image)

Two routes to effect the desired conversions, based on the above considerations, were envisaged (scheme 419). Path A proposes initial reduction of the double bond under catalytic conditions with PtO₂ or other hydrogenating catalyst followed by unmasking of the N-methyl group to acquire the model aporphine skeleton 448. The intermediate compound 449 involved in such a strategy would be stable, and easily characterisable. Alternatively, the second path B involves release of the N-methyl function followed by acid catalysed reduction of the double bond. However, the intermediate 450 is an enamine conjugated to both the biaryl system and may, therefore, be difficult to handle. However, the enhanced basicity of the released lone pair would be expected to promote the suggested acid catalysed borohydride reduction under mild conditions.

Catalytic hydrogenation of 432 in methanol using PtO₂ under normal hydrogen pressure resulted in quantitative isolation of the starting material. Several reactions were conducted with increased hydrogen pressures over the reaction mixture at 20, 40 and 60 psi to no avail. Only starting material 432 was recovered on each
attempt. Change in the catalyst to 10% Pd on carbon resulted in the same outcome.

With Rh catalyst at 60 psi decomposition of the starting material was observed.

![Chemical Structures](image)

**Scheme 419**

The resistance of the C4-C5 double bond to catalytic reduction is surprising since simple dihydroisoquinoline derivatives have been reduced at room temperature and normal hydrogen pressure to tetrahydro-derivatives. However, the dissimilarity between the electronic nature of the styrene like double bond in 432 and that in other simple dihydroisoquinoline derivatives may be significant. The double bond in 432 is highly conjugated to the biaryl system as well as the already conjugated carbamate function.

As demonstrated before with the model argemonine precursor 431, LiAlH₄ is the reagent of choice for the conversion of the N-phenoxyacarbonyl group to the N-methyl function. Thus, following strategy B, the tetracyclic N-phenoxyacarbonyl derivative 432 was treated with LiAlH₄ with the aim of releasing the masked N-methyl group. The chromophoric substrate spot disappeared completely on TLC within three hours of stirring at room temperature to a single spot on the base line (with 10% ethyl acetate in light petroleum) which on elution with neat ethyl acetate gave a retention value of 0.15. The 'streaky' nature of the spot on TLC was also characteristic of an amine. The green crude mass isolated from this reaction after work-up was immediately redissolved in a mixture of methanol:water (3:1) and
NaBH₄ was added. The greenish solution gradually turned orange and subsequently, after work-up, the required model aporphine compound 448 was isolated. However, the overall mass recovery from the reaction was found to be unsatisfactory with a significant UV active component retained at the baseline and only 23% of product was isolated upon purification of the crude.

The loss of mass to baseline material was thought to be due to decomposition of the highly labile enamine 460 resulting from the reduction of the carbamate function, as described earlier. In order to overcome this difficulty the same two reactions were carried out in a single pot, omitting the work-up after the reduction of the carbamate. This procedure involved quenching of excess LiAlH₄ with ice followed by the addition of methanol and NaBH₄ in the presence of the aluminium residues. Both the aluminates from the former reaction and the borates from the latter were separated once the labile double bond has completely been reduced. Not surprisingly the yield of the reaction improved following this treatment and the desired compound 448 was isolated in 72%. Thus, the model study of the synthesis of pavine and aporphine compounds was concluded.
4.5 Synthesis of (+)-Argemonine & (+)-Glaucine

The successful preparation of model pavine and aporphine compounds was described in section 4.3. Accordingly, the body of experimental methods gathered during the study could now be applied to the synthesis of natural products to demonstrate the utility of the key radical reaction. For this purpose (+)-argemonine and (+)-glaucine seemed most appropriate, as some of the starting compounds required, such as 6,7-dimethoxyisoquinoline were already available from the synthesis of O-methylcorytenchirine, described in chapter 3.

The syntheses of the natural products argemonine 401 and glaucine 434 commenced with the application of standard methods to the formation of appropriately substituted bromobenzyl bromide 451 (scheme 420). Thus, reduction of the aldehyde function of vanillin 452 with NaBH₄ in methanol at room temperature afforded the substituted benzyl alcohol 453 in very high yield. The benzylic alcohol 453 when heated with Br₂ in CHCl₃ to introduce the ortho-bromine atom required for later radical generation, not only underwent the desired conversion smoothly but also transformed the benzylic alcohol to the bromide 451. The latter reaction is promoted by acid catalysed nucleophilic substitution aided by HBr generated during the course of the ring bromination reaction. The mechanism of this conversion is illustrated in scheme 420.

With the acquisition of dimethoxybenzyl bromide 451 in two steps, efforts were focused towards the crucial generation of the benzylic Grignard reagent 454. However, unlike bromobenzyl bromide, its dimethoxy derivative 454 was found to
be completely insoluble in diethyl ether. The necessity to use diethyl ether in this reaction as the solvent to minimise Wurtz coupling was noticed during the model study. Nevertheless, dimethoxybenzyl bromide 454 was dissolved in THF and added to a suspension of magnesium turnings (1 equiv.) treated with 1,2-dibromoethane in the same solvent. The reaction proceeded as would a typical Grignard reagent preparation. The reaction was monitored by TLC for the disappearance of starting material and on completion quenched with 10% HCl. Subsequently the products were extracted into ethyl acetate and analysed using routine spectroscopic methods. Evidence from the $^1$H and $^{13}$C NMR spectra confirmed that the residue contained the Wurtz coupled bibenzyl derivative 455 and none of the expected 2-bromo-4,5-dimethoxytoluene. The NMR analysis for 455 was supported with a 70 eV mass spectrum which revealed a cluster of peaks in the ratio of approximately 1:2:1 for the molecular ion for the purified product, spaced two mass units apart and centred at $m/z$ 460. The isotopic composition of bromine enables such equally placed peaks to exist when two bromine atoms are present in the molecule.

This outcome was not unexpected as earlier in section 4.3 literature references were cited to support the argument that a greater proportion of bi-benzyl products are obtained in THF than in diethyl ether. Since it is clear that such coupling is highly dependant on the nature of the solvent used, a change to other substrate soluble ethers was viewed as one possible solution to this setback. Accordingly, two separate reactions were conducted in diisopropyl and ethylene dimethyl ether, but on both occasions decomposition with 10% HCl, failed to afford the expected 2-bromo-4,5-methoxytoluene. Instead the crude residue was found to consist of the Wurtz coupled product 455 with a number of other unidentifiable compounds.

Attempts to circumvent this difficulty by utilising the benzyl chloride 456 instead of the bromide met with little success. The synthesis of the chloro derivative 456 in pure form was achieved by ortho-bromination of dimethoxybenzaldehyde 452, and reduction of the aldehyde to the alcohol followed by conversion of the latter into the chloride by treatment with SOCl$_2$ (scheme 421). The reverse order of the reactions: reduction, conversion of the alcohol to the benzyl chloride followed by ring bromination produced a mixture of both bromobenzyl bromide 451 and bromobenzyl
chloride 456. Presumably halogen exchange from chloro to bromo at the benzylic carbon readily occurs by a nucleophilic substitution mechanism.

\[
\begin{align*}
\text{H}_3\text{C}O\text{CHO} & \quad \begin{array}{c} \text{a} \end{array} \quad \text{H}_3\text{C}O\text{CHO} \\
\text{H}_3\text{C}O\text{OH} & \quad \begin{array}{c} \text{b} \end{array} \quad \text{H}_3\text{C}O\text{Br} \\
\text{H}_3\text{C}O\text{Cl} & \quad \begin{array}{c} \text{c} \end{array} \quad \text{H}_3\text{C}O\text{Br}
\end{align*}
\]

\[a : \text{Br}_2, \text{CHCl}_3 \quad b : \text{LiAlH}_4, \text{THF} \quad c : \text{SOCl}_2\]

Scheme 421

The failure to generate the Grignard reagent 451 prompted a literature search for alternative methods for the generation of the desired nucleophile. The search revealed that many organozinc reagents of the type RZnX (R = alkyl, X = halide etc.) have recently been widely recognised as versatile carbon nucleophiles in organic synthesis.\(^{173}\)

The present day use of zinc organometallics in organic synthesis varies from simple nucleophilic substitution reactions to well known cyclopropanation protocols (Simmons-Smith reaction\(^{174}\)). Many recent reviews and articles are available on this subject.\(^{175}\) The present aim was to generate the benzylic zinc reagent 457 and if successful to evaluate the possibility of using the reagent as a nucleophile in the assembly of the radical precursor 458.

With this in mind, an initial approach to the organometallic reaction involved the use of Me$_3$SiCl and 1,2-dibromoethane in THF to regenerate the active surface of the zinc dust. Once initiation of the Grignard-like reaction was observed, the substrate
was added dropwise with rapid stirring ensuring that the temperature of the heterogeneous solution did not rise above 40°C. On completion of the reaction, the solution was quenched with 10% HCl, the products extracted into ethyl acetate, the solvent removed and the crude residue analysed by routine spectral methods.

The $^1$H and $^{13}$C NMR spectra obtained revealed that the crude product predominantly consisted of dimethoxybromotoluene 459 (scheme 422), the hydrolysed product arising from the required intermediate 457. Traces of the dimerised bibenzyl derivative 455, was also detected. The NMR analysis for 459 was confirmed with the support of mass spectrometric methods, the data of which revealed a molecular ion at $m/z$ 230.

With the problem of generating the nucleophilic species resolved, efforts were focused on the synthesis of the dihydroisoquinoline 458. The key concern in this regard was whether the zinc intermediate 457 would behave similarly to the model Grignard reagent 423 (2-bromobenzylmagnesium bromide) in its nucleophilic addition to quaternised isoquinoline derivatives. To investigate this aspect of the reaction isoquinoline quatemised with phenylchloroformate was treated with a freshly prepared solution of the zinc reagent 457; after the addition, the suspension disappeared as anticipated. Work up followed by flash chromatography allowed the isolation of 1-benzyldihydroisoquinoline 460 in 95% yield. Thus, the addition of dimethoxybromobenzylzinc bromide 457 to quaternary isoquinolinium salts was successfully verified.
Use of 6,7-dimethoxyisoquinoline 422 in a similar experiment, after purification by flash chromatography, afforded 458 in 95% yield. The convergency of the method, the ease of variation of the substitution pattern around each half of the molecule and the excellent yields obtained, makes this approach to the construction of 1-benzylisoquinolines extremely versatile, as such compounds are often used as starting materials for the preparation of complex isoquinoline alkaloids.

Tetramethoxybenzylisoquinoline 458 thus prepared was treated with Bu₃SnH in benzene with AIBN under conditions similar to those reported earlier (scheme 423). The course of the reaction was monitored by TLC until complete consumption of the starting material was observed. As anticipated, two spots, one running above the starting material, with high UV absorption and the other below with moderate absorption, were observed on TLC. The products were separated by flash chromatography and analysed by routine spectral methods.

The mass spectrum of the highly chromophoric product revealed a molecular ion at m/z 460 in good agreement with the expected mass of the glaucine precursor 461. In support, the ¹H NMR spectrum of the product revealed three aromatic singlets, integrating to one proton each at δ 6.51, 6.77 and 8.07. The latter singlet was assigned to the C11 aromatic proton, ortho to the biaryl linkage, deshielded due to anisotropic effects imposed by the π electrons of the adjacent aryl ring. Most importantly, the mutually coupled one proton each doublets at δ 5.56 and 7.06 (J 8 Hz) suggested that the integrity of the C3-C4 double bond in the starting material.

\[ H_3CO \]
\[ H_3CO \]
\[ CO_2Ph \]
\[ \text{Br} \]
\[ OCH₃ \]
\[ 458 \]
\[ a : \text{Bu}_3\text{SnH, AIBN, benzene} \]

\[ \text{Scheme 423} \]
had been preserved. In addition, 12 methoxy protons together with a mutually
coupled, three proton ABX system, assigned to C6α methine and C7 methylene
protons were also diagnostic of the structure 461.

The 1H NMR spectrum obtained from the chromatographically less mobile
material displayed similarities to the one obtained for the model argemonine precursor
431. As in the case of 431 the spectrum displayed a perturbed symmetry by
producing two distinct sets of signals for the magnetically non-equivalent protons.
The magnetic non-equivalence as described before arises from the anisotropic effects
imposed by the carbonyl function of the phenoxy carbonyl moiety. In contrast to the
glaucine precursor 461 the current spectrum also revealed four, one proton singlets at
δ 6.50, 6.52, 6.69 and 6.70 assigned to the four isolated aromatic protons. This
assignment was supported by the 70 eV mass spectrum with a molecular ion at
m/z 462. Thus the structure of compound 462 was confirmed.

The final step in the preparation of (±)-argemonine 401 was the conversion of
the N-phenoxy carbonyl function in 462 to an N-methyl group (scheme 424). Thus,
462 was treated with LiAlH4 under conditions similar to those used to prepare model
argemonine 433 in section 4.3. The crude residue from the reaction on purification
gave (±)-argemonine as a colourless solid in 91% yield.

\[
\begin{align*}
\text{H}_3\text{CO} & \text{H}_3\text{CO} \\
\text{OCH}_3 & \text{OCH}_3 \\
\text{PhO}_2\text{C} & \text{a} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{CO} & \text{H}_3\text{CO} \\
\text{OCH}_3 & \text{OCH}_3 \\
\text{H}_3\text{C} & \text{a : LiAlH}_4, \text{THF} \\
\end{align*}
\]

\[
\begin{align*}
\text{462} & \xrightarrow{a} \text{401} \\
\text{(±)-argemonine} & \\
\end{align*}
\]

The 1H and 13C NMR spectra of 401 displayed all the expected structural
features of the natural product, including the C2 symmetric nature of the molecule.
This is evident from the complete overlap of the signals of protons on either side of the
illustrated line (figure 407). The single set of mutually coupled system of multiplets
integrating to two protons each at δ 2.60 (J 16 Hz), 3.40 (J 5.5 and 16 Hz) and 4.01
(J 5.5 Hz) were assigned to C6, C12 axial; C6, C12 equatorial and C5, C11 methine
protons respectively. Most of the other data obtained are summarised in figure 407
and are in good agreement with published data.176
Chapter 4: A General Radical Route to Pavine & Aporphine Alkaloids

Figure 407

The fragmentation path of (±)-argemonine when irradiated with a 70 eV electron beam is quite simple and is illustrated in scheme 425. These results again are diagnostic of the symmetrical nature of the molecule because both possible routes through which the molecular ion of mass m/z 355 (compound 401) could disintegrate would afford the same fragment 463. The benzylic radical arising from the homolytic cleavage of either bond C6-C5 or C11-C12 is capable of abstracting a benzylic hydrogen rather rapidly to result in the intermediate 464. It then either undergoes cleavage at C4a-C5 or C10a-C11 depending on the route observed, to afford the base fragment with mass m/z 204 or has the option to aromatise resulting in the fragment with a mass m/z 354. In addition, the molecular ion 401 can also undergo homolytic cleavage of the N-methyl bond to afford the fragment 465 which corresponds to the signal at m/z 340. Thus, synthesis of (±)-argemonine was concluded.

The final step in the preparation of (±)-glaucine from compound 461 involves the reduction of the C4-C5 double bond together with the restoration of the masked N-methyl group. To this end, detailed methods formulated earlier during the model study to carry out these manipulations (section 4.3) were applied in an effort to achieve the desired conversion. The two sequential reactions performed on the substrate 461 (scheme 426) proceeded smoothly and following the work-up, extraction and purification of the crude led to the isolation of (±)-glaucine in 72% yield.
The spectral data obtained for 434 were in good agreement with the published data. For example, the $^1$H NMR and $^{13}$C spectra were identical to that published by Ferr et al. $^{177}$ The mass spectrum revealed a molecular ion at $m/z$ 355 (99%). Thus, the successful synthesis of (±)-argemonine and (±)-glaucine was completed.
4.6 Conformation of Precursor Substrates and their Relationship to the Product Ratio

The aryl radical generated during cyclisations of pyridone derivatives 205-210, described in Chapter 2, was shown to approach the double bond only \textit{anti} to the substituent \(\alpha\) to the nitrogen. The substituent \(\alpha\) to the nitrogen in these molecules was shown to orient \textit{pseudo}-axial in order to avoid non-bonded interaction with the amide carbonyl. As a result of this stable fixed orientation the radical when generated approached the double bond \textit{anti} to the substituent giving rise to the observed selectivity. Evidence relating to the conformation of the substrate molecules in the form of NMR data, supported by single crystal x-ray data were also presented in Chapter 2.

In contrast, when substrate 232 was subjected to radical ring annulation conditions no cyclisation was observed; instead only the direct reduced product 234 was isolated (Chapter 2). This outcome was rationalised on the basis of the stereoelectronic effects existing in the molecule. In support of this contention single crystal x-ray structure data for 209 and 232, together with comparisons of substrate NMR data were also presented. This evidence suggested that inclusion of an oxygen atom in the side chain altered the conformation of the substrate molecule 232 such that when the radical is formed only the direct reduced product 234 was possible.

Two presumptions can be made from these foregoing studies. Firstly, for ring closure to occur it is essential for the substrate radical, when it is generated, to be suitably oriented with respect to the double bond. Secondly, if the rate of cyclisation or direct reduction is much faster than the rate of inter-conversion between conformers (as with 232), the ratio of the products (direct reduced or cyclised) should be similar to the ratio of substrate conformer populations in solution at any given instant.
As described earlier in this chapter (sections 4.3 and 4.5), the cyclisation of model isoquinoline substrates does not yield any direct reduced products if the concentration of the reducing species is maintained at a minimum at all times during the reaction. However, the reaction always resulted in two cyclised products, the bridged pavine precursor and the bi-aryl aporphine derivative (figure 408) when the nitrogen atom was protected by a phenoxy carbonyl group. Although the carbamate carbonyl from previous pyridone studies was known to reside syn to the double bond, where no cyclisation was observed, it is questionable whether the same situation existed in N-substituted isoquinoline substrates. If indeed the carbonyl of the carbamate group in isoquinoline substrates were to reside syn to the double bond (figure 408), 1,3-allylic strain would not be a controlling factor since under such conditions the benzyl moiety would be free to interchange between pseudo-axial or pseudo-equatorial conformations. From a pseudo-axial position the benzyl function would have ready access to both the double bond and C8 of isoquinoline. However, from a pseudo-equatorial position the radical could annulate only at C8. The question then arises as to how the aryl radical is oriented immediately prior to cyclisation and whether the conformation of the substrate has any dependence on the ratio of the final products. If this was found to be the case, it was also of concern whether the ratio of the product mixture could be controlled one way or the other by altering the N-substituent. These queries prompted the study detailed below with the aim of investigating the effect of conformational populations, if any, on the isolated products.

![Figure 408](image)

To this end, radical precursors having different N-substituents were prepared, and their NMR data analysed. They were then cyclised to investigate any correlation between the starting conformer populations and product compositions. The reason for changing the substituent attached to the nitrogen atom was to alter the equilibrium of the conformer populations. The differing equilibria with the change of the nitrogen substituent is clearly observed in the $^1$H NMR spectra acquired (figure 409 a-f) for
Chapter 4: A General Radical Route to Pavine & Aporphine Alkaloids

N-methoxycarbonyl 466, N-ethoxycarbonyl 467, N-phenoxycarbonyl 430 and 458, N-acetyl 468 and N-benzoyl 469 isoquinoline derivatives.

Since the N-CO interconversion in these substrates was a deciding factor, efforts were focused on to measure the rotational barrier of the N-CO bond of compound 458 using the well known coalescence method. However, the experiment met with little success and the spectra acquired in toluene during this temperature study is shown in figure 410. The experiment revealed that even at 75 °C complete coalescence of the two signals due to the C1 proton (the pair of doublets) was not observed. Higher temperatures could not be reached due to hardware limitations. Nevertheless, the study has established that even at 75 °C, the temperature at which the cyclisations are conducted (80 °C), rapid rotation about the N-CO bond in carbamates is not observed.

![Figure 410](image)

In accord with the aim of this study, each of the radical precursors synthesised was subjected to radical cyclisation conditions (Bu$_3$SnH, AIBN, benzene). The isolated yields of the two products from each reaction were recorded against the calculated rotamer populations of the starting substrate. These results are presented in table 402.
Chapter 4: A General Radical Route to Pavine & Aporphine Alkaloids

<table>
<thead>
<tr>
<th>Substituent R</th>
<th>anti : syn(^{\dagger}) ratio of C3 proton(\dagger)</th>
<th>Isolated Yields of products X &amp; Y(%)</th>
<th>Ratio of X : Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO(_2)CH(_3)</td>
<td>1 : 1.5</td>
<td>36%</td>
<td>51%</td>
</tr>
<tr>
<td>CO(_2)C(_2)H(_5)</td>
<td>1 : 2</td>
<td>29%</td>
<td>56%</td>
</tr>
<tr>
<td>CO(_2)Ph</td>
<td>1 : 1.2</td>
<td>43%</td>
<td>56%</td>
</tr>
<tr>
<td>CO(_2)Ph ((R_1=R_2=OCH_3))</td>
<td>1 : 1</td>
<td>42%</td>
<td>48%</td>
</tr>
<tr>
<td>COCH(_3)</td>
<td>1.9 : 1</td>
<td>30%</td>
<td>55%</td>
</tr>
<tr>
<td>COPh ((R_2=OCH_3))</td>
<td>Mostly anti conformer</td>
<td>nil</td>
<td>87%</td>
</tr>
</tbody>
</table>

\(^{\dagger}\) anti : carbonyl anti to C3-C4 double bond; syn : carbonyl syn to C3-C4 double bond
\(\dagger\) C3 proton of substrate molecules \(R_1 \& R_2 \equiv H\) unless otherwise indicated

Table 402

Analysis of the results tabulated above (table 402) indicate a definite correlation between the isolated yields of the products and the rotamer populations. Whilst the syn substrate conformers in the four carbamate analogues gave the double bond cyclised products, the anti species afforded the bi-aryl derivatives. The situation, however, is reversed with the two amide derivatives. The syn isomers of the two amides appeared to yield the bi-aryl analogues while the anti isomers seemed to afford the double bond cyclised products.
Chapter 4: A General Radical Route to Pavine & Aporphine Alkaloids

Any extending us to how above cyclisation proceeds must commence by analysing the stereo-activity in question. The NMR spectra and calculations of the substrates 466, 467, and 468 reveal a decrease in the stereo-activity of the diagnostic signals. The spectra of 468 (Figure 409) show that the 468 derivative's NMR spectrum displays two distinct doublets at 6.3 and 5.5, instead of a single doublet observed in the 466 derivative. The reason for this is the two inner protons in 468 are observed as a single doublet, indicating that stereoisomerism does not occur at all.
Any reasoning as to how the above cyclisation proceeds must commence by analysing the starting material conformations. By comparison with pyridone substrates 205-210 the most obvious difference observed in the spectra of uncyclised carbamate derivatives is the sharpness of the $^1$H NMR spectral signals. Such well defined resonances result from the slow interconversion of the N-CO bond with respect to the NMR time scale. The spectrometer on such instances detects two distinct species at any given moment depending on the populations of each isomer. The spectrum obtained for compound 232 (section 2.6) on the other hand is a special case in which only a single isomer is detected. The reason for this is that one isomer, presumably the one observed in the solid state from x-ray crystal structure data (shown below), is so stable that interconversion does not occur at all.

Conversely, rotational isomers due to N-CO interconversion in the isoquinoline substrates synthesised are clearly observed in their $^1$H NMR spectra (figure 409a-f). For example, the $^1$H NMR spectrum of the N-methoxycarbonyl derivative 466 (spectrum 409a) displayed two distinct doublets at $\delta$ 5.88 and 6.01, both integrating for one hydrogen. These signals were assigned to the C3 methine proton. Further, the two multiplets resonating at $\delta$ 5.66 and 5.73, again integrating for one hydrogen, was assigned to the C1 proton. The two outer resonances ($\delta$ 5.66 and 6.01) correspond to one rotamer population, in which the N-CO carbonyl is resident syn to the C3-C4 double bond (scheme 427). In this conformation the almost co-planer C3 proton is shifted down field as a result of anisotropic effects of the syn carbonyl group. In the other conformer the carbonyl is resident anti to the double bond and the two corresponding signals are the two inner ones ($\delta$ 5.73 and 5.88).

Under these circumstances the C1 proton is placed in the de-shielding zone of the carbonyl function and thus moved slightly down field.
It is important to note that the down field shift of the C1 proton signal (difference in chemical shift is 0.10 ppm) for the anti carbamate conformer (466B) is purely due to anisotropic effects of the carbonyl group and not as a result of any conformational change at C1. If conformational change from equatorial to axial or the reverse is in effect, the chemical shift difference for the C1 proton would be much greater. For example, such a conformational change at C1 is clearly observed in the $^1$H NMR spectrum of the N-acetyl derivative 468 (figure 409e) in which the two signals for the C1 proton, resonate at $\delta$ 5.29 and 6.07, 0.78 ppm apart. Based on the assumption that the equatorial proton on the C1 carbon appears down field compared to that of the axial, the latter signal ($\delta$ 6.07) was presumed to result when the C1 proton is equatorially placed. The former signal ($\delta$ 5.29), then must result when it is axially oriented. Thus, from the integrals of these two signals the C1 proton in 468 may be presumed to reside equatorial most of the time.

The most important piece of information that can be gathered from the above analysis concerns the orientation of the benzyl group of carbamate derivatives. If no conformational change occurs at C1 as described earlier by comparison of the chemical shift data of 468 with that observed for 466, the C1 proton of the carbamate must reside pseudo-equatorial all the time. Thus, the pseudo-axial orientation of the benzyl group in carbamates, irrespective of N-CO interconversion was established.

If the benzyl group is oriented pseudo-axial all the time the question to be asked is what controls the direction of the reaction. The answer to this lies in the splitting pattern of the rotameric C1 proton signals. One of these signals recorded for substrate 466 (see figure 409a) resonates as a doublet of a double while the other is a symmetrical triplet (an overlapping doublet of a doublet). This is a direct result of the benzylic protons changing their orientation with respect to the C1 proton (change of dihedral angle H-C1-C_{ben}-H_{ben}). Since the ratio of the two rotamer signals for the C1 proton is similar to that between the two rotameric signals of the C3 double bond proton, the above change in the orientation of the benzylic protons must originate from of N-CO interconversion. Thus, when the carbonyl shifts from an anti to a syn conformation the benzylic protons must shift as illustrated in scheme 428.

A shift in the benzyl group changes the orientation of the radical centre. This marginal alteration of the radical centre, therefore, may provide the radical centre the necessary orthogonal approach to the double bond. By the same argument when the carbonyl group is oriented anti to the double bond ring closure at C3 may be disfavoured but favourable towards the formation of the bi-aryl analogue.
However, the situation was different with the amide substrates. In these substrates, conformational change at C1 was observed with the interconversion of the carbonyl group. Such conformational changes are known to exist with N-substituted formyl or acetyl functions, but become negligible with bulky acyl substituents as observed with a benzoyl derivative.¹⁷⁹ When the carbonyl group is syn to the double bond the benzyl group is most stable in a pseudo-equatorial position. The aryl radical in such a situation has no access to the double bond thus it is left with the only option of annulation at C8 to afford the bi-aryl derivative. On the other hand, when the carbonyl resides in an anti orientation, the benzyl group is forced into a pseudo-axial orientation to avoid 1,3-allylic strain. With this orientation ring closure at C3 may predominate over C8 annulation. Evidence to this end is observed from the ¹H NMR of the N-benzoyl substrate 469 (figure 409f) which is predominantly in the latter conformation presumably because of the bulk of the N-substituent. Compound 469 under radical ring closure conditions afforded only the double bond cyclised products.

The study described in this section is by no means complete. Many more results need to be gathered and compiled before arriving at any firm conclusion. Nevertheless, an attempt has been made to explain the outcome of the reaction based on the available data.
CHAPTER 5

Approaches to Enantioselective Synthesis of Pavine & Aporphine Alkaloids

5.1 Introduction 130

5.2 The Synthetic Strategy & Model Reactions 135

5.3 Attempted Synthesis of Optically Pure (-)-Argemonine & (-)-Glaucine 138
Chapter 5: Approaches to Enantioselective Synthesis of Pavine & Aporphine Alkaloids

5.1 Introduction

The asymmetric synthesis of optically active isoquinoline alkaloids has received a great deal of attention during the past decade. Initial work by Brossi et al., was followed by Kametani, Yamada and others in the nineteen seventies. More recently, Meyers and Gawley have also contributed to the development of this area of research. During these investigations many modifications to existing classical methods have also been published.

A substantial proportion of these efforts has been concentrated on the asymmetric synthesis of substituted 1-benzylisoquinolines, since the derivatised heterocyclic framework alone represents several groups of alkaloids. One such example is reticuline (scheme 501). In addition, the skeleton of 1-benzylisoquinoline is considered an efficient platform from which to launch the synthesis of many other naturally occurring compounds (scheme 501). For example, appropriately substituted optically pure 1-benzylisoquinolines have been converted to important morphine analogues using Grewe type cyclisations, while electrophilic substitution has furnished protoberbine alkaloids. In other related studies oxidative cyclisation of 1-benzylisoquinolines has been used to synthesise aporphine alkaloids. Bisbenzylisoquinoline and phthalide isoquinoline natural products have also been obtained commencing from similar heterocyclic frameworks.

Many new methods are available for the generation of chiral 1-benzylisoquinoline derivatives. Conceptually, a majority of these approaches can be categorised into three broad classes, namely the C-C connective approach, modified traditional methods, and C1 reduction by complexation. The number of syntheses based on each classification is large. Hence, only the chemistry underlying the first approach will be discussed below due to its relevance to the current study. Syntheses based on the other approaches are thoroughly reviewed in the literature.

By retrosynthetic analysis, the C-C connective approach involves connecting two synthons, one always a derivative of an appropriately substituted isoquinoline and the other a benzyl fragment. Often, the desired asymmetry at C1 of the benzylisoquinoline is established by directing the approach of the benzyl fragment with the aid of a chiral auxiliary attached to the nitrogen atom during the bond forming process. To this end two general strategies depending on the ionic charges on each fragment have been employed.
In the most widely used strategy (scheme 502), the isoquinoline fragment is considered as a donor synthon while the benzyl moiety is viewed as the acceptor fragment. Taking the effectiveness, the chemical yields and most importantly the optical yields into account, Meyers' formamidines\textsuperscript{188} and Gawley's oxazoline chemistry\textsuperscript{189} afford by far the best results. Both methods involve initial removal of the $\alpha$ proton adjacent to the asymmetrically derivatised nitrogen atom by a strong base such as $n$-BuLi (scheme 503). In Meyers' method the nitrogen atom of the tetrahydroisoquinoline is converted to a chiral formamidine, whose primary function is to guide the incoming electrophile in a stereoselective manner. In addition to this function, formamidine groups are also electron withdrawing and hence enhance the removal of the $\alpha$ proton by the base. Thereafter, the metalated intermediate is quenched with an electrophilic reagent, a benzyl halide if 1-benzylisoquinolines derivatives are required, to afford the final product.
The diastereomeric excesses arising from these reactions are remarkable and are reported to be as high as 99%. The high d.e.'s are attributed to the selective formation of the bidentate chelate conformer 502 (scheme 503). It adopts such a conformation to reduce steric congestion and by doing so hinders one face of the molecule efficiently, thus restricting the approaching reagent to the other. Apart from the excellent d.e.'s reported, the ready availability of the inexpensive amino acids from which the optically pure auxiliaries are synthesised is also a definite advantage.

Gawley's oxazoline approach differs from Meyers' results only by the type of chiral auxiliary used (scheme 504). These researchers employ amino acid derived chiral oxazolines in place of the formamidine group attached to the nitrogen atom of the isoquinoline fragment to direct the incoming electrophilic reagent. Again, the chelation of the lithio-anion with the directing chiral auxiliary is said to mask one face of the molecule efficiently as in the case of Meyers' chemistry.
In the alternative strategy (scheme 505), the electronic states of the two synthons are interchanged. The isoquinolone synthon under these circumstances acts as the acceptor and the benzyl fragment the donor of electrons. The electron donor benzyl fragment is often generated in the form of a Grignard reagent which undergoes nucleophilic addition to isoquinolinium salts formed with a chiral auxiliary. Published syntheses based on this approach are less appealing by comparison with those published by Meyers and Gawley for many reasons. Yet a few of these are notable mainly because of the high d.e.'s attained.

The best results have been achieved by Yamato et al. whose method has been applied in the syntheses of a large number of alkaloids. The key reaction of this approach (scheme 506) involves the initial generation of chiral oxazolotetrahydroisoquinoline derivatives such as 503 which are then subjected to nucleophilic attack by triisopropoxytitanium chloride activated benzylmagnesium chloride to afford diastereomerically enriched 1-benzylisoquinolines (d.e. 65-90%). The initial chiral derivatives (503) are prepared in 80-90% d.e. by cyclisation of S or R-phenylglycinol derived dihydroisoquinolinium salts depending on the final asymmetry of the product required and are resolved before treatment with the benzyl nucleophile.
5.2. The Synthetic Strategy

The synthetic strategy for the enantioselective synthesis of Pavine and Aporphine Alkaloids is based on the initial generation of the chiral cinnamic acid 364 and subsequent conversion to the optically pure form. The enantiomeric purity of the final products is determined by the chirality of the starting material, which is derived from naturally occurring substances.

Scheme 506

\[ \text{Scheme 506} \]

The synthesis of chiral cinnamic acids in asymmetric induction is not new. This is mainly due to the ease of derivatization of cinnamic acids from readily available enantiomerically pure aldehydes. Recently, Camisi et al. reported the asymmetric synthesis of cinnamic acids through a modified Pinacol reaction by the addition of DMAP as a catalyst, which was quaternized with optically pure chiralformamide (Scheme 507). 104 Diastereomeric excesses ranging from 84 to 92% have been observed, depending on the enantiomerically pure cinnamic acid and the Schiff's reagent used. The synthetic utility of the method has been demonstrated by a number of enantioselective syntheses of naturally occurring compounds.
5.2 The Synthetic Strategy

The syntheses of (-)-argemonine and (+)-glaucine would involve the initial generation of the key 1-benzylisoquinoline 504 as described in Chapter 4, but in optically pure form. The analogous phenoxy carbonyl derivative 458 (R* = Ph) in Chapter 4 was assembled by a simple nucleophilic addition route, in which the N-acylated isoquinolinium salt acted as the acceptor synthon while the benzyl zinc reagent behaved as the electron donor. By analogy, when isoquinoline is quaternised with an optically active acyl group asymmetric induction at C1 of 504 should be possible. The proposed reaction scheme is illustrated in scheme 507.

\[
\begin{array}{c}
\text{H}_3\text{CO} \quad \text{N} \\
\text{H}_3\text{CO} \\
\text{R}^* \quad \text{O} \\
\text{Cl} \\
\end{array}
\begin{array}{c}
\rightarrow \\
a \\
\text{504} \\
\text{H}_3\text{CO} \quad \text{Br} \\
\text{OCH}_3 \\
\text{OCH}_3 \\
\end{array}
\]

\( \text{a} : 2\)-bromo-4,5-dimethoxybenzylzinc bromide

Scheme 507

The use of chiral chloroformates in asymmetric induction is not new. This is mainly due to the ease of syntheses of chloroformates from readily available optically pure alcohols. Recently, Comins et al. reported the asymmetric synthesis of 2-substituted pyridones by the addition of Grignard reagents to N-acylpyridinium salts quaternised with optically pure chloroformates (scheme 508). Diastereomeric excesses ranging from 44 to 94% have been achieved, depending on the optically active auxiliary and the Grignard reagent used. The synthetic utility of the method has been demonstrated by a number of enantioselective syntheses of naturally occurring compounds.

\[
\begin{array}{c}
\text{H}_3\text{CO} \quad \text{N} \\
\text{R}^* : \text{8-phenylmenthyl} \\
\end{array}
\begin{array}{c}
\text{+} \\
\text{R}^* \quad \text{O} \\
\text{Cl} \\
\text{a} : \text{RMgX} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{CO}_2R^* \\
\text{R} \\
\end{array}
\]

Scheme 508
The high diastereoselectivity achieved by Comins' method has been attributed to a novel phenomenon, first described by Corey\textsuperscript{192} in 1972 and commonly known as $\pi$-$\pi$ stacking. In simple descriptive terms, it signifies positioning of a double bond or an aromatic ring parallel to and at approximately 3.5 Å above or below an aromatic ring. A general review on this subject can be found in the recent literature.\textsuperscript{193} Comins \textit{et al.} reasoned that as a result of $\pi$-$\pi$ stacking the phenyl group of the 8-phenylmenthyl auxiliary is positioned parallel to the planar pyridine ring of the pyridinium salt and masks one face of the reactive site; hence the approach of the incoming nucleophile is restricted to the alternative face. Supporting evidence for such $\pi$-$\pi$ interactions in acylated pyridinium salts has been presented in the form of molecular mechanics studies and a single crystal x-ray structure.\textsuperscript{194}

The application of the $\pi$-$\pi$ stacking to the current study seemed promising. If such interactions were to exist between the isoquinoline moiety and the phenyl group of 8-phenylmenthyl auxiliary, as illustrated in figure 501, one face of isoquinoline would indeed be completely masked. Since the size of the nucleophile involved is an important factor in achieving good selectivity, the bulky nature of the dimethoxybenzyl reagent should also be advantageous in this respect.
The subsequent steps, following the assembly of 504 would be similar to those described in Chapter 4. Radical cyclisation of 504 to 505 and 506 followed by reduction of the N-acyl group of both and the double bond in 506 should afford the enantiomerically enriched natural products argemonine and glaucine.

Scheme 509
5.3 Attempted Synthesis of Optically Pure
(-)-Argemonine & (+)-Glaucine

The study described in this section, as mentioned earlier, is focused on two important objectives. The first and the most important is the synthesis of the diastereomerically pure 1-benzylisoquinoline 507 or 508 by the strategy outlined in the preceding section. Since racemisation during cyclisation / reduction steps is unlikely the initial generation of diastereomerically pure 1-benzylisoquinoline derivatives is crucial. The second objective of the study, syntheses of optically pure argemonine and glaucine, could then be fulfilled by the radical cyclisation / reduction methods used previously for the assembly of their racemates.

Installation of the asymmetric centre at C1 of 1-benzylisoquinoline 507 or 508 was to be achieved by using the C-C connective approach. It involves nucleophilic addition of the benzyl fragment to the isoquinoline derivative quaternised with a chiral auxiliary as described before. Based on recent studies, the most promising and effective optically active chloroformate for this purpose is that one derived from (-)-8-phenylmenthol 510. However, because of the high cost of this reagent the initial synthesis was conducted with the chloroformate derived from inexpensive (-)-menthol 509. Such a decision was beneficial in two respects. On one hand, the assembly of the menthyl isoquinoline 507 could be of use as a model study to compare the effects of the 8-phenyl substituent when 508 was synthesised. On the other, the expertise gained in handling menthyl derivatives would be of advantage when the more expensive reagent was to be used.

Hence, the investigation began with (-)-menthol 509. Menthylchloroformate 511 was prepared by treating the alcohol with phosgene in the presence of a base. Two different bases were separately employed to effect this conversion. When
quinoline was used as the base, as described by Comins et. al. for the synthesis of 8-phenylmenthyl chloroformate, the reaction was complete within three hours and upon work up, an orange residue was isolated in near quantitative yield. Analysis of the crude product by $^1$H and $^{13}$C NMR revealed the presence of quinoline in the residue. Every attempt to distil the chloroformate under high vacuum resulted in decomposition of the mixture.

\[ \text{Scheme 510} \]

When finely ground $\text{K}_2\text{CO}_3$ was used as the base instead of quinoline, the heterogeneous mixture had to be stirred for 48 hours at room temperature before the reaction went into completion. Despite this drawback the residual oil isolated upon concentration of the reaction solution followed by a simple filtration was colourless and devoid of any other organic substance on analysis by routine NMR spectroscopy. Thus, the crude product, isolated in near quantitative yield was utilised in the next step without further purification.

$N$-menthylisoquinoline 507 was synthesised by treating a solution of 6,7-dimethoxyisoquinoline in THF with the crude menthylchloroformate at $-78 \, ^\circ \text{C}$ followed by the addition of a freshly prepared solution of dimethoxybromobenzylzinc bromide (scheme 511) to the heterogeneous mixture. The expected nucleophilic addition of the zinc reagent was presumed to proceed quite efficiently as indicated by the disappearance of the white isoquinolinium salt. On purification the desired dihydroisoquinoline 507 was isolated in 96% yield based on dimethoxyisoquinoline.

\[ \text{Scheme 511} \]
Attempted analysis of the diastereomeric mixture of 507 from $^1$H and $^{13}$C NMR data was complicated by the presence of rotameric species. The existence of three base-line separated doublets integrating to one proton, related to one another on the basis of their coupling constants and assigned to the C3 proton (scheme 511) exemplifies the complex situation. In addition, several rotamer multiplets for the C1 methine proton were also observed. Although, the ratio of the two well resolved multiplets centred at $\delta$ 4.57 and 4.77, integrating to one proton, assigned to the proton at the C1 stereogenic centre of the menthyl moiety (the proton on the carbon $\alpha$ to the oxygen - see scheme 510) could well represent the two diastereomeric populations, conclusive evidence could not be gathered at this stage. The integral ratio of the pair of signals was calculated to be 1:2.7.

The question of whether the resolved peaks in the above spectrum indeed represented the two diastereomers was verified by comparison with the $^1$H NMR spectrum of a 1:1 mixture of the diastereomers. An equi-molar mixture of the two possible diastereomers were prepared by treating the phenoxy carbamoyl derivative 458 with an excess of the potassium salt of (-)-menthol in THF (scheme 512). Apart from the statistical advantage by having an excess of potassium menthoate in solution, the stability and the better leaving capability of the phenoxide ion contributes to the rapid production of 512. The two asymmetric multiplets thought to be due to diastereomers and previously tentatively assigned to the C1 proton of the menthyl moiety (scheme 510) were identical with those in the $^1$H NMR spectrum of the equi-molar mixture. Hence the observed separation of the menthyl C1 signal was shown not to be due to diastereomer populations, but was as a result of other conformational isomers in the menthyloxy carbonyl moiety.

$$\begin{align*}
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
\text{H}_3\text{CO} & \quad \text{N}^+ \text{CO}_2\text{R}^* \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{Br} & \quad \text{OCH}_3 \\
\text{458} & \quad \text{512} \\
& \quad (1:1 \text{ mixture}) \\
& \quad R^* = \text{menthyl} \\
\text{a} & \quad \text{potassium menthoate, THF}
\end{align*}$$

Scheme 512

The most widely accepted method for the determination of diastereomeric ratios is to effect separation by HPLC methods. Towards this end a variety of columns with chiral and achiral stationary phases have been used. However, every attempt to resolve the above mixture by means of such methods failed. In each case a
homogeneous band was observed to elute from the column. Change in the solvent system or the method of elution, whether isocratic or gradient was not successful. Thus, the possibility of diastereomer resolution by chromatographic techniques was discarded.

Despite the unsuccessful attempts to assess the diastereomeric purity of 507, the radical ring closure to afford 513 and 514 was carried out. When substrate 507 was treated with Bu$_3$SnH and AIBN, two products were isolated after purification. As described earlier in Chapter 4, these products were identified as 513 and 514 by routine spectroscopic methods.

Examination of the 300MHz $^1$H NMR spectrum of 513 revealed the existence of diastereomers. However, because of partial resolution of these signals the diastereomeric ratio could not be calculated satisfactorily. For example, the doublets centred at $\delta$ 5.41 and 5.53 were assigned to C5 and C11 protons of compound 513 respectively. Each of these signals was observed to have a shoulder, an indication of a partial overlap of two doublets (figure 502). Surprisingly, when a 500MHz $^1$H NMR spectrum for compound 513 was acquired, resolution of the diastereomer signals was observed only for the latter doublet, resonating at $\delta$ 5.53 (figure 502) and the other pair of doublets remained as an asymmetric triplet. Since the resolved pair of doublets were still not completely base line resolved, electronic deconvolution of the signals (figure 503) was carried out. The ratio for the diastereomers computed from the area under each deconvoluted signal which amounted to 1:1.9.

It is arguable that these sets of signals may have resulted from rotational isomers due to N-CO rotation; in fact amide rotation in 513 does exist. However, the effects due to the N-CO rotation are completely nullified by overlap of the relevant signals because the heterocycle 513 has a C$_2$ symmetry through the nitrogen atom. A similar situation was reported for the phenoxy carbonyl derivatives 431 and 462 (Chapter 4). Hence peaks arising from rotational isomers are not observed in the $^1$H NMR spectrum of 513.
The validity of this result was proved by conducting two experiments. Firstly, a racemic mixture of 513 was prepared from the phenoxy carbamoyl derivative 462 and the potassium salt of menthol (scheme 513) as described before. The 300MHz $^1$H NMR spectrum acquired for this mixture (compound 515) clearly shows a symmetrical triplet centred at $\delta$ 5.55 (figure 504) which by comparison to 513 was assigned to the C5 or C11 proton. This triplet when acquired at 500MHz resolved into two doublets of equal intensity, thus confirming that the pairs of doublets represented the diastereomer populations. Secondly, supporting evidence for the ratio of 1:1.9 was obtained by comparison of the literature value for the optical rotation of pure argemonine with that acquired for the final product. Details of these experiments will be presented later in this section.
The 300MHz $^1$H NMR spectrum of the glaucine precursor 514 also displayed partial diastereomer separation, especially for the C5 methine proton. However, every attempt to resolve the signals by high field NMR spectroscopy failed.

Attempted HPLC resolution of the diastereomers of 513 again afforded a single chromophoric band as with the uncyclised substrate 507. After this unsuccessful attempt, efforts were concentrated on correlating the observed (from $^1$H NMR) diastereomeric ratio 1:1.9, with the enantiomeric purity of the final product 516. Therefore, the next step, conversion of the carbamate function to an N-methyl group was investigated (scheme 514). Accordingly, compound 513 was treated with 5 equivalents of LiAlH$_4$ at room temperature in THF. Surprisingly, the reaction failed to afford any 516; only starting material could be detected by TLC. Gradual conversion of 513 to product was only observed on heating the mixture at reflux.
Even under these conditions, 36 hours of heating was necessary to drive the reaction to completion. On chromatographic purification of the crude product, optically active argemonine 516 was isolated in 86% yield. The NMR and analytical data acquired for this compound were identical to those obtained for racemic argemonine, as described in Chapter 4.

\[ \text{H}_3\text{CO} \quad \text{OCH}_3 \]
\[ \text{H}_3\text{CO} \quad \text{OCH}_3 \]

\[ R^* = \text{menthyl} \]

\[ 513 \quad \text{a : LiAlH}_4, \text{THF, reflux} \]

\[ 516 \]

Scheme 514

The resistance to reduction of the carbamoyl moiety in 513, unlike in simple derivatives may presumably be due to increased steric hindrance in the former case. Although, inspection of molecular models of 513 shows significant crowding of the carbamoyl groups it also reveals that hindrance can be minimised because of the free rotation of the menthyloxy groups.

Measurement of the optical rotation of purified 516 gave \([\alpha]_D -58\) (c 0.52, CHCl₃). By comparison with the reported literature value¹⁹⁵ for optically pure argemonine, \([\alpha]_D -209\) (c 0.50, CHCl₃), the diastereomeric ratio for the reaction was, calculated to be 1:1.8, in excellent agreement with the value, 1:1.9, obtained from the NMR data. Therefore, the diastereomeric excess of 507 was also firmly established at 28%.

Surprisingly when compound 514 was treated with LiAlH₄ (scheme 515) in THF to achieve reduction of the carbamoyl function to N-methyl, only starting material was observed on TLC. Attempts to initiate reduction by heating the reaction mixture at reflux for 48 hours, even with 10 equivalents of LiAlH₄ failed to result in any disappearance of the starting material 514. No reasonable explanation for this behaviour can be suggested. Reversal of the two steps, as with non-chiral substrates, did not afford any of the desired natural product 517. Thus, the reaction was abandoned.
With the knowledge gained from the above study efforts were next concentrated on the synthesis of the N-8-phenylmenthyl derivative 508. To this end, 8-phenylmenthyl chloroformate 518 was synthesised from (-)-8-phenylmenthol 510 (scheme 516) as described by Comins et al. The carbamate 508 was prepared by a reaction similar to that used for the N-menthyl derivative 507. The reaction afforded 508 in 95% yield (scheme 517).
The $^1$H NMR spectrum of the 8-phenylmenthyl derivative 508 was much more complex than that of its menthyl analogue 507 in that very few signals were assignable to their protons. There is no doubt that carbonyl rotation coupled with the deshielding effects of the phenyl group in the chiral auxiliary contributed to the presence of extra clusters of rotamer signals. Thus, no information on the ratio of the diastereomers could be gathered from the spectrum at this stage.

Since the spectral analysis failed to result in any clear-cut evidence concerning the diastereoselectivity of the reaction, the next step, radical cyclisation with Bu$_3$SnH was investigated. As expected, on treatment of the substrate with the Bu$_3$SnH and AIBN as outlined earlier gave two products; the highly mobile, chromophoric tetracyclic glaucine precursor 520 in 54% yield and the less mobile material 519 in 32% yield.

Interestingly, the resonances assigned to C5 and C11 in the $^1$H NMR spectrum of 519 are wide apart in contrast to those observed for other analogues (see figure 506 - left trace). This increased separation is largely due to the up-field shift of one of the signals, presumably caused by the ring currents of the extra phenyl group attached to the chiral auxiliary. Most importantly, each of these signals is paired with two other less intense base line resolved doublets and the integration suggested that each of these pairs to be one proton each. These pairs represented the diastereomeric populations of 519; the ratio computed from integral data was 1:2.6.

Figure 505
Confirmation of the diastereomer signals was achieved by the acquisition of a $^1$H NMR spectrum of a racemic mixture of 519. Preparation of the 1:1 diastereomeric mixture of 519 was achieved by treatment of the phenoxy carbonyl derivative 462 with the potassium salt of (-)-8-phenylmenthol in THF as outlined in scheme 518. The right trace in figure 506 represents the section of interest in the $^1$H NMR spectrum of the 1:1 mixture of 519. By comparison it proves that the calculated ratio 1:2.6 does indeed represent the selectivity of the C-C bond forming process when the 8-phenylmenthol oxide chloroformate is used as the chiral auxiliary. Based on this ratio the diastereomeric excess of the reaction was established to be 45% d.e.

\[ \text{Scheme 518} \]

With the selectivity of the reaction established firmly from NMR data, efforts were directed towards the reduction of the carbamoyl group to $N$-methyl using previously established procedure (scheme 519) and the possible recovery of the chiral auxiliary, 8-phenylmenthol. While the primary aim of this exercise was to acquire (-)-argemonine, the optical purity of the final product computed from the optical rotation as before could well be used as additional evidence to confirm the diastereomeric excess assessed earlier.

\[ \text{Scheme 519} \]

Surprisingly all attempts to reduce the chiral carbamoyl function of 519 using LiAlH$_4$ failed, either yielding 519 or decomposed material depending on the conditions used. When a substrate solution in THF was heated at reflux in the
presence of LiAlH₄, the conditions under which the N-menthyl analogue 513 was reduced, only starting material 519 was observed on TLC after 4 days. A change of solvent to ethylene dimethyl ether or dioxane with heating afforded a mixture of starting material and very polar baseline material. An experiment to effect the desired reduction with ZnBH₄ gave similar results. Attempted disproportionation of the 8-phenylmenthyloxy group with either sodium or potassium methoxide was also unsuccessful.

The cleavage of the 8-phenylmenthyloxy carbonyl group in 519 followed by the introduction of the required N-methyl group was explored next. Under hydrolytic conditions using reagents such as KOH-H₂O in ethylene glycol¹⁹⁶ or NH₂-NH₂, H₂O, KOH¹⁹⁷ gave mostly darkened baseline material; none of the desired bridged amine was obtainable. Attempted non-hydrolytic cleavage of the N-alkoxy carbonyl group with Me₃SiI¹⁹⁸ was also unsuccessful. On this occasion only the starting material 519 was recovered from the reaction. Therefore, reluctantly the reaction was abandoned. Again no reasonable explanation for this failure other than increased steric effects at the carbonyl function could be suggested.

Finally, the glucine precursor 520 was subjected to the one-pot operation (scheme 520) described in Chapter 4. When 520 was treated with LiAlH₄ the reaction failed to afford the desired enamine, despite refluxing the substrate solution in THF with 10 equivalents of the reducing agent for 2 days. On each occasion clean starting material was observed by TLC. Heating the substrate in dimethoxyethane at reflux only resulted in decomposition of the mixture. Attempts to reduce the double bond first with NaCNBH₃ in acidic media resulted in starting material, presumably due to the low basicity of the nitrogen lone pair. As no other avenues were at hand to effect the desired conversion the reaction was abandoned.
The most notable deduction gathered from this study is in agreement with the Comins' interpretation of his results described earlier in this chapter. The synthesised natural product 516 using menthyl chloroformate as the chiral auxiliary, rotated plane polarised light in an anticlockwise sense, which on comparison with the absolute stereochemistry of (−)-argemonine isolated from natural sources confirms the mixture to be enriched with the S,S enantiomer, (S,S)-516. Based on molecular models and Comins' hypothesis, formation of an S enriched mixture was expected, since during the preparation of 507 (scheme 511) the isopropyl group of the (R,R,S)-menthyl moiety was likely to mask the Re face of C1 only to a modest extent; hence the observed 28% d.e. By the same analogy, presence of the (R,R,S)-8-phenylmenthyl oxy carbonyl group would be expected to afford a better enriched mixture since masking of the Re face of C1 by the additional phenyl group would be much more efficient. An energy minimised structure of the isoquinolinium salt of the latter auxiliary is shown in figure 505. Although the rotation and the optical purity of argemonine from the 8-phenylmenthyl analogue 519 could not be obtained for reasons described earlier (see scheme 519), the increased selectivity (45% d.e.) during the formation of 508, deduced from the $^1$H NMR spectrum of 519 can be provided as positive evidence towards this argument.

![Figure 506](image-url)
In conclusion, chiral auxiliaries, menthyl and 8-phenylmenthly chloroformates have rendered reasonable diastereoselectivities as assessed from NMR data. Although, in this particular case the stability of the N-(8-phenylmenthyl)carbamates towards reduction foiled all attempts to prepare enantiomerically enriched alkaloids, the successful preparation of chiral precursors indicates that the general thrust of the research remains promising.
Conclusions & Future Directions

There are often many advantages in using radical methodology in organic synthesis over traditional metal-based reactions. A number of these were discussed in section 1.2 of this thesis. Since radical methods have found one niche in the synthesis of polycyclic derivatives, as described in the same section, the aim of this work was to exploit the use of radical syntheses in the construction of naturally occurring heterocyclic compounds.

CHAPTER 6

Conclusions & Future Directions

In addition to (2S,5S)-isobutyrophenones 308, simple bicyclic quinolizidine alkaloids having substituents arranged in similar stereochemical dispositions are abundant in nature. Quinolizidine alkaloids (3S)-myrtine 402 and (3S)-hesperidin 1601 are rich such alkaloids. These stereocontrolled syntheses following preliminary model alkyl radical ring closure studies have also been automated in the laboratory. Similar applications among naturally occurring compounds should be numerous.
Conclusions & Future Directions

There are often many advantages in using radical methodology in organic synthesis over traditional ionic reactions. A number of these were discussed in section 1.2 of this thesis. Since radical methods have found use mostly in the synthesis of carbocyclic derivatives, as described in the same section, the aim of this work was to extend the use of radical reactions to the construction of naturally occurring heterocyclic compounds.

The model radical precursors, as described in Chapter 2 when subjected to radical ring closure conditions were found to cyclise with very high diastereoselectivities. In these systems, the radical was observed to approach the double bond anti to the substituent α to the nitrogen. Such ring construction methodology was identified to be highly suited for the selective syntheses of natural products containing substituents α to the nitrogen disposed syn to the ring junction proton. The utility of the method was demonstrated by the synthesis of (±)-O-methylcorytenchirine 305 in 43% overall yield in three steps.

In addition to (±)-O-methylcorytenchirine 305, simple bicyclic quinolizine alkaloids having substituents arranged in similar stereochemical dispositions are abundant in nature. Quinolizine alkaloids (±)-myrtine 602 and (±)-lasubine-I 601 are two such examples. Their stereoregulated syntheses following preliminary model alkyl radical ring closure studies have also been successful in this laboratory. Similar applications among naturally occurring compounds should be numerous.
The model study leading to pavine alkaloids further demonstrated the utility of radical methods in the construction of heterocyclic compounds. The applicability of the derived methods towards the synthesis of pavine alkaloids was demonstrated by the synthesis of (±)-argemonine 401. The methods may also find use in the construction of other bridged heterocyclic systems. Although, during the preparation of argemonine formation of another by-product was observed, which subsequently was converted to an aporphine alkaloid, (±)-glaucine 434, it is the authors view that by experimentation with different protection of the nitrogen, the reaction may be forced in one direction or the other. For example, when the benzoyl group was used as the nitrogen protecting group complete formation of the pavine analogue was observed (section 4.6).

In addition to the radical methods developed during the synthesis of (±)-argemonine, construction of the desired radical precursor 458 using benzylzinc bromide 457 was also a significant achievement. The high yields accomplished (<97%) for these reactions should be attractive to the synthetic organic chemist attempting synthesis of similar 1-benzylisoquinolines. This achievement also led to the investigation described in Chapter 5; namely synthesis of optically pure argemonine. This work has provided a sound foundation to experiment with other chiral acyl auxiliaries such as (-)-8-(4-phenoxyphenyl)menthyl chloroformate or the chloroformate derived from (+ or -)-trans-2-(α-cumyl) cyclohexanol at a future date.
Application of radical cyclisation reactions in the general area of isoquinoline alkaloids is numerous. A proposed example is the syntheses of morphine related alkaloids illustrated in scheme 601. Although morphinans are generally regarded as a separate class of naturally occurring compounds, most syntheses of these derivative commence from isoquinoline frameworks. The octahydroisoquinolone 603 can be obtained by Birch reduction of 6-methoxy-1,2,3,4-tetrahydroisoquinoline 604 followed by demethylation. Benzylaion at C1 should be achieved using n-BuLi and the appropriate benzyl bromide. If high stereocontrol is desired during the introduction of the benzyl group, Meyers' formamidine chemistry described in section 4.2 should be useful. The key radical closure is then expected to afford 606, which is commonly regarded as the basic morphinan skeleton. Subsequent ring closure of the 4,5-oxide ring and introduction of the 7,8-double bond can be achieved by known methods.

\[ \text{(-)-morphine} \]

a : n-BuLi, 2-bromo-3,4-dimethoxybenzylbromide  
b : Bu$_3$SnH, AIBN, benzene

**Scheme 601**

Radical ring closure methods can also be used in the preparation of Amaryllidaceae alkaloids. A proposal for the general preparation of the characteristic skeleton is illustrated in scheme 602 and is based on an Amaryllidaceae alkaloid, (-)-falcatine 607. The hexahydroindolone 609 can be synthesised from methoxyindoline 608 by Birch reduction followed by demethylation. Acylation of the indolone 609 with the benzoyl chloride 610 should afford the radical precursor.
611. Ring closure of 611 under radical conditions should then yield the desired Amaryllidaceae skeleton 612 in four steps. The sequence with appropriate substituents should provide specific alkaloids.
CHAPTER 7

Experimental

7.1 General experiment

7.2 Experimental

7.3 Appendix A

7.4 Appendix B

7.5 Appendix C
7.1 General Experimental

All reactions were carried out under an atmosphere of dry nitrogen in pre-dried glassware unless specified otherwise. The solvents used in the reactions were distilled and dried prior to use. Benzene for radical reactions was freshly distilled over sodium wire under nitrogen and degassed by purging with a stream of argon for 15 minutes. Diethyl ether and THF for Grignard reactions were freshly distilled over Na wire.

Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh ASTM). A Chromatotron, model 7924 equipped with a hand held UV lamp was utilised to perform radial preparative layer chromatography. Plates of 1, 2 and 4 mm in thickness were constructed using Merck Kieselgel 60 PF254 (with gypsum) for this purpose. Preparative liquid chromatography was performed using glass backed precoated with Kieselgel with PF254 indicator. Glass backed Whatman MK6F precoated silica microscopic slide plates with 254 nm indicator were used for thin layer chromatography. Solvents used for chromatography are specified in each experiment. Petroleum spirits refer to the fraction bp 60-80 °C unless indicated otherwise. A Buchi GKR-30 Kugelrohr apparatus was used to purify compounds by small scale distillation where necessary.

The NMR spectra were recorded on the following spectrometers: Varian Gemini (1H, 300 MHz; 13C, 75 MHz), Varian VXR 300S (1H, 299.9 MHz; 13C, 75 MHz), VXR 500 (1H, 500.044 MHz; 13C, 125.748 MHz), Varian XL 200 (2H, 30.7 MHz). Tetramethyl silane (TMS) and residual CHCl3 in CDCl3 were used as an internal standards for 1H and 13C NMR spectra, respectively. 2H NMR experiments were carried out in CHCl3 and CHCls/CDCl3 solutions.

Low resolution EIIMS were recorded at 70 eV on either a VG7070F or a VGZAB-2SEQ spectrometer. Chemical ionisation mass spectra (CIMS) where needed were recorded on a VG7070F spectrometer with NH3 as the reagent gas.

All elemental analyses were carried out by the microanalytical unit at the Research School of Chemistry. The melting points are uncorrected and were determined using a Reichert microscopic Koffler hot-stage apparatus. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at a wavelength of 589 nm at room temperature. All organic compounds were named according to the IUPAC guidelines. Some examples are illustrated in figure 701.
\textbf{Chapter 7: Experimental}

7.2 Experimental

(7R*,10aR*)-1,2,3,5,6,7,8,8a-Octahydro-7-phenylbenzo[a]indolizine-5,9-dione

5,6,11,12-Tetrahydro-2,3,8,9-tetramethoxy-13-phenoxycarbonyl-5,11-iminodibenzo[a,e]cyclooctane

6a,7-Dihydro-1,2,9,10-tetrahydromethoxy-6-phenoxycarbonyldibenzo[de,g]quinoline

Figure 701
### 7.2 Experimental

**1-(2-Bromobenzoyl)-2-phenyl-2,3-dihydro-4-pyridone**

A stirred solution of 4-methoxypyridine (2.18 g, 20 mmol) in THF (100 mL) was cooled to -23 °C (dry ice/CCl$_4$) and treated with 2-bromobenzoyl chloride (4.83 g, 22 mmol). On addition of the acid chloride immediate formation of the pyridinium salt could be observed. After stirring for an hour phenylmagnesium bromide (30 mmol in 15 mL of THF) was added. On completion of addition the solution became homogeneous; and was stirred for a further hour at the same temperature before 10% HCl (10 mL) was added. After a further hour of stirring the solution was poured into 150 mL of distilled water and the organic layer separated. The aqueous layer was extracted with diethyl ether (5 x 100 mL) dried with Na$_2$SO$_4$, filtered and the solvent removed at reduced pressure. The residue was chromatographed (30% ethyl acetate in light petroleum) over silica to afford the product as a colourless solid (6.96 g, 19.6 mmol, 98%), mp 100-101 °C;

$^1$H NMR (CDCl$_3$) $\delta$ 2.97 (d, 1 H, $J = 17$ Hz, 3-H$_{ax}$), 3.22 (m, 1 H, 3-H$_{eq}$), 5.33 (d, 1 H, $J = 7.25$ Hz, 5-H), 6.27 (b, 1 H, 6-H), 7.15 (b, 1 H, 2-H) and 7.33-7.65 (m, 9 H, Ar-H);

$^{13}$C NMR (CDCl$_3$) $\delta$ 41.02, 41.05, 41.09, 41.12, 41.31 (3-C, rotamers), 53.86 (2-C), 108.77, 109.30 (5-C, rotamers), 119.10, 119.14, 119.33 (ArC$_q$Br, rotamers), 126.08, 126.71 (6-C, rotamers), 127.74, 128.00, 128.51, 128.75 (4xArCH), 131.55, 131.75, 132.97, 133.29, 142.06, 142.43 (3xArCH, rotamers), 135.27 (ArC$_q$), 137.63 (ArC$_q$), 167.70 (NCO) and 192.10 (4-CO);

$m/z$: 357(M+2, 7%), 355(M^+, 7%), 185(93), 182(100), 157(19), 155(19), 105(16), 104(30), 103(15), 91(4), 89(4), 78(15), 77(37), 76(32), 75(25) and 51(25).

Anal. Calcd. for C$_{18}$H$_{14}$NO$_2$Br: C, 60.89; H, 4.33; N, 3.70; Br, 22.34. Found: C, 60.69; H, 3.96; N, 3.93; Br, 22.43.
Chapter 7: Experimental

1-(2-Bromobenzoyl)-2-methyl-2,3-dihydro-4-pyridone(2)

The title compound was synthesised following the procedure outlined for 205. The crude product was purified by column chromatography (30% ethyl acetate in light petroleum) to afford a colourless solid (78%), mp 109 °C;

\[ \text{1H NMR (CDCl}_3\text{)} \delta 1.41 (d, 3 \text{ H, } J = 6.6 \text{ Hz, } 2-\text{CH}_3), 2.46 (d, 1 \text{ H, } J = 16.5 \text{ Hz, } 3-\text{H}_{\alpha\alpha}), 2.92 (dd, 1 \text{ H, } J = 6.6 \text{ and } 16.4 \text{ Hz, } 3-\text{H}_{eq}), 5.23 (d, 1 \text{ H, } J = 6.2 \text{ Hz, } 5-\text{H}), 5.30 (d, 1 \text{ H, } J = 8 \text{ Hz, } 6-\text{H}), 6.97-7.04 (b, 1 \text{ H, } 2-\text{H}), 7.35-7.67 (m, 4 \text{ H, ArH}); \]

\[ \text{13C NMR (CDCl}_3\text{)} \delta 16.00, 16.56 (2-\text{CCH}_3, \text{ rotamers}), 41.52 (3-\text{CH}_2), 47.38 (2-\text{CH}), 107.46 (5-\text{CH}), 107.80 (\text{ArCqBr}), 118.96, 128.25, 128.64 (6-\text{CH, rotamers}), 127.85, 131.38, 131.63, 132.93, 141.32, 141.11 (4x\text{ArCH, rotamers}), 134.93, 135.20 (\text{ArCq, rotamers}), 167.20 (\text{N-CO}) \text{ and } 192.71 (4-\text{CO}); \]

\[ m/z: 295(M^+2, \text{ 8%}), 293(M^+, \text{ 8%}), 185(95), 183(100), 157(17), 155(18), 105(8), 77(11), 76(30), 75(25), 51(8) \text{ and } 50(11). \]

Anal. Calcd. for C_{13}H_{12}NO_{2}Br: C, 53.08; H, 4.11; N, 4.76; Br, 27.16. Found: C, 53.16; H, 4.15; N, 4.73; Br, 27.27.

1-(2-Iodobenzoyl)-2-phenyl-2,3-dihydro-4-pyridone

Compound 206 was synthesised following the method outlined for 205. The crude oil was column chromatographed (30% ethylacetate in light petroleum) to afford a colourless solid (92%), mp 137-138 °C;

\[ \text{1H NMR (CDCl}_3\text{)} \delta 2.97 (d, 1 \text{ H, } J = 16.5 \text{ Hz, } 3-\text{H}_{\alpha\alpha}), 3.24 (m, 1 \text{ H, } 3-\text{H}_{eq}), 5.34 (d, 1 \text{ H, } J = 7.7 \text{ Hz, } 5-\text{H}), 6.25 (m, 1 \text{ H, } 6-\text{H}), 7.17 (m, 1 \text{ H, } 2-\text{H}_{eq}) \text{ and } 7.31-7.90 (m, 9 \text{ H, ArH}); \]

\[ \text{13C NMR (CDCl}_3\text{)} \delta 40.75, 40.83, 41.31 (3-C, \text{ rotamers}), 53.74, 53.80, 54.01 (2-C, \text{ rotamers}), 93.20 (\text{ArCqI}), 108.68, 109.47 (5-C, \text{ rotamers}), 126.10, 127.17 (6-C, \text{ rotamers}), 128.02, 128.44, 128.77, 129.21, 131.48 (5x\text{ArCH}), 137.67, 139.40 (2x\text{ArCq}), 139.41, 139.83, 142.05, 142.55 (2x\text{ArCH, rotamers}), 169.08 (\text{N-CO}) \text{ and } \]
192.12 (4-CO);

\[ m/z: 403(M^+, 12\%), 276(3), 231(100), 203(15), 172(5), 105(25), 104(19), 103(10), 78(9), 77(35), 76(48), 75(7), 51(16) \text{ and } 50(8); \] HRMS exact mass calcd. for C\(_{18}\)H\(_{14}\)NO\(_2\)I 403.0069 (M\(^+\)), found 403.0070;


### 1-(2-Iodobenzoyl)-2-methyl-2,3-dihydro-4-pyridone

The title compound 208 was synthesised following the conditions described for 205. The crude viscous oil was chromatographed (30\% ethylacetate in light petroleum) to yield 208 as a colourless solid (87\%), mp 110-111 °C;

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.44 (d, 3 H, \(J = 4.5 \text{ Hz}, 2-\text{CH}_3\)), 2.46 (d, 1 H, \(J = 15.5 \text{ Hz}, 3-\text{H}_\alpha\)), 2.92 (m, 1 H, 3-\text{H}_eq\)), 5.23 (b, 1 H, 6-H), 5.31 (d, 1H, \(J = 7.4 \text{ Hz}, 5-\text{H}\)), 6.99 (b, 1 H, 2-H), 7.18-7.92 (m, 4 H, ArH);

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 16.10, 16.62, 16.70, 16.72 (2-C\(_\text{CH}_3\), rotamers), 41.73 (3-C), 47.57 (2-C), 92.06 (ArC\(_\text{qI}\)), 107.76 (m, 5-C, rotamers), 127.94, 128.18 (6-C, rotamers), 128.50, 131.33 (2xArCH), 139.20 (ArC\(_\text{q}\)), 139.47, 141.46 (2xArCH), 168.69 (NCO), 192.78 (4-CO);

\[ m/z: 341(M^+, 18\%), 232(7), 231(100), 203(18), 105(16), 77(19), 76(55), 75(11), 74(8), 51(11) \text{ and } 50(7). \]

Anal. Calcd. for C\(_{13}\)H\(_{12}\)NO\(_2\)I: C, 45.77; H, 3.55; N, 4.11; I, 37.20. Found; C, 45.80; H, 3.76; N, 4.08; I, 37.16.
1-(2-Bromophenylacetyl)-2-phenyl-2,3-dihydro-4-pyridone

4-Methoxypyridine (2.20 g, 20 mmol) was treated in succession with 2-bromophenylacetyl chloride (5.60 g, 24 mmol) in THF (100 mL) and with phenylmagnesium bromide (30 mmol in 20 mL of THF) following the procedure described for the synthesis of 1-(2-bromobenzoyl)-2-phenyl-2,3-dihydro-4-pyridone 205. The crude product obtained was chromatographed with 30% ethyl acetate in light petroleum to obtain 209 as a solid (6.92 g, 18.7 mmol, 94%) which crystallised to yield colourless needles; mp 112 °C;

\[\text{m/z : 371(M+2, 4%), 369(M+, 4%), 290(15, 198(14), 196(14), 174(39), 173(86), 172(14), 171(49), 169(51), 145(12), 105(10), 104(100), 103(16), 96(62), 91(14), 90(45), 89(36), 78(13), 77(20), 63(16) and 51(16); HRMS exact mass calcd. for C}_{19}H_{16}NO_{2}{^{79}}Br 369.0364 (M+), found 369.0366; Anal. Calcd. for C}_{19}H_{16}NO_{2}Br: C, 61.64; H, 4.36; N, 3.78; Br, 21.58. Found: C, 61.88; H, 4.05; N, 3.68; Br, 21.47.

1-(2-Bromophenylacetyl)-2-methyl-2,3-dihydro-4-pyridone

To the salt formed on addition of 2-bromophenylacetyl chloride (5.60 g, 24 mmol) to 4-methoxypyridine (2.26 g, 20 mmol) in THF (100 mL) methylmagnesium iodide (30 mmol in 20 mL of diethyl ether) was added following the procedure described for the synthesis of the pyridone 205. The heavy oil
obtained was purified by column chromatography (30% ethyl acetate in light petroleum) to obtain 210 as a colourless solid (5.54 g, 18 mmol, 90%); mp 90-92 °C;

\[ \delta^1H (CDCl_3) = 1.28 (b, 3 H, 2-CCH_3), 2.36 (dd, 1 H, J = 16.6 and 1.6 Hz, 3-H_{ax}), 2.83 (dd, 1 H, J = 16.6 and 6.5 Hz, 3H_{eq}), 3.98 and 4.07 (d each, 2 H, J = 6.5 Hz each, NCOCH_2), 5.03 (b, 1 H, 6-H), 5.39 (d, 1 H, J = 7.7 Hz, 5-H), 7.16-7.62 (m, 4 H, ArH), 7.57 (b, 1 H, 2-H);

\[ \delta^{13}C (CDCl_3) = 16.39, 16.45, 16.62 (2-CCH_3, rotamers), 40.56 (NCOCH_2), 41.84 (3-C), 47.50 (2-C), 107.24, 107.29, 107.31, 107.42, 107.48 (5-C, rotamers), 124.52, 133.38 (2xArCq), 127.72, 129.14, 130.79, 132.80 (4xArCH), 139.82 (6-C), 168.09 (NCO) and 192.78 (4-CO);

m/z: 309(M+2, 1%), 307(M⁺, 1%), 228(56), 198(20), 196(22), 171(72), 169(76), 112(43), 111(71), 96(100), 91(12), 90(57), 89(50), 69(12), 68(16) and 63(25); HRMS exact mass calcd. for C_{14}H_{14}N_{2}O_{7}Br, 307.0208, found 307.0207;

Anal. Calcd. for C_{14}H_{14}N_{2}O_{2}Br: C, 54.56; H, 4.58; N, 4.55; Br, 25.93. Found: C, 54.84; H, 4.67; N, 4.32; Br, 25.71.

1-(2-Bromophenoxy carbonyl)-2-phenyl-2,3-dihydro-4-pyridone 232

The phenoxy carbonyl derivative 239 was synthesised along the general procedure outlined for compound 205, except that 2-bromophenyl chloroformate was used instead of the acid chloride. The crude product isolated was purified by column chromatography (30% ethyl acetate in petroleum spirits) to afford the product as a colourless solid (89%); mp 85-88 °C;

\[ \delta^1H (CDCl_3) = 2.90 (d, 1 H, J = 17 Hz, 3-CH_{ax}), 3.26 (dd, 1 H, J = 17 and 7 Hz, 3-H_{eq}), 5.52 (d, 1 H, J = 8 Hz, 5-CH), 5.91 (d, 1 H, J = 7 Hz, 2-CH), 7.15 (d, 1 H, J = 8 Hz, 6-CH), 7.11-7.33 (m, 7 H, 7xArH), 7.59 (d, 1 H, J = 7 Hz, ArH), 8.11 (d, 1 H, J = 7 Hz, ArH);

\[ \delta^{13}C (CDCl_3) = 41.67, 41.75, 41.78 (3-CH_2), 56.35, 56.43 (2-CH), 109.28 (5-CH), 115.77, 137.73, 147.56 (3xArCq), 123.47, 125.93, 127.83, 128.10, 128.55, 128.80, 133.32 (9xArCH), 141.73 (6-C), 151.86 (NCO) and 191.63 (4-CO);
m/z: 274(M+3, 5%), 273(M+2, 16%), 272(M+1, 5%), 271(M⁺, 16%), 292(3), 269(3), 267(3), 169(76), 200(31), 104(28), 96(100), 84(10), 77(10), 49(13).

Anal. Calcd. for C₁₈H₁₄N₂O₃Br: C, 58.08; H, 3.79; N, 3.76; Br, 21.47. Found: C, 58.01; H, 3.51; N, 3.70; Br, 21.76.

(7R*,10aR*)-1,2,3,5,6,7,8,8a-Octahydro-7-phenylbenzo[a]indolizine-5,9-dione

1-(2-Bromobenzoyl)-2-phenyl-2,3-dihydro-4-pyridone 205 (1.48 g, 4.16 mmol) was dissolved in 40 mL of de-oxygenated benzene under an inert atmosphere and heated at reflux. A solution of Bu₃SnH (1.45 g, 4.99 mmol) and AIBN (20 mg, 0.14 mmol) in 10 mL of degassed benzene was added to this heated mixture, dropwise over six hours with the aid of a syringe pump. After the addition the solution was allowed to stir at reflux for 12 hours. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by radial preparative layer chromatography (30% ethyl acetate in light petroleum) to afford the cyclised product 211 as colourless needles (1.05 g, 3.79 mmol, 91%) mp 172-173 °C;

¹H NMR (CDCl₃) δ 2.30 (dd, 1 H, J = 12 and 14 Hz, 10-Hₐ), 2.92 (dd, 1 H, J = 15 and 7.5 Hz, 8-Hₐ), 3.02 (dd, 1 H, J = 14 and 4 Hz, 10-Hₑ), 3.14 (d, 1 H, J = 15 Hz, 8-Hₑ), 4.59 (dd, 1 H, J = 12 and 4 Hz, 10a-Hₐ), 6.13 d, 1 H, J = 7.5 Hz, 7-Hₑ and 7.25-7.93 (m, 9 H, ArH);

¹³C NMR (CDCl₃) δ 43.45 (8-C), 46.60 (10-C), 50.68 (7-NCH), 54.93 (10a-NCH), 122.55-132.63 (7xArCH), 132.02 (ArCₐ), 140.155 (ArCₐ), 145.133 (ArCₐ), 166.99 (N-CO) and 206.383 (9-CO);

m/z: 277(M⁺, 39%), 248(35), 234(16), 221(16), 158(22), 146(14), 145(13), 132(22), 131(48), 105(27), 104(100), 103(59), 102(15), 89(13), 78(24), 77(70), 76(19), 63(11) and 51(33).

Anal. Calcd. for C₁₈H₁₅NO₂: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.19; H, 5.44; N, 5.19.
(7R*,10aR*)-1,2,3,5,6,7,8,8a-Octahydro-7-methylbenzo[a]indolizine-5,9-dione

A solution of Bu₃SnH (0.35 g, 1.2 mmol) and AIBN (36 mg) in 5 mL of de-oxygenated benzene was added dropwise over 6 hours to a solution of 1-(2-bromobenzoyl)-2-methyl-2,3-dihydro-4-pyridone 207 (0.29 g, 1 mmol) in 10 mL of degassed benzene at reflux as described for the synthesis of 211. The crude product obtained was chromatographed (30% ethyl acetate in light petroleum) to afford the cyclised product 212 as colourless needles (0.19 g, 0.86 mmol, 86%); mp 113 °C;

1H NMR (CDCl₃) δ 1.37 (d, 3 H, J = 7 Hz, 7-CCH₃), 2.25 (dd, 1 H, J = 16.5 and 11 Hz, 10-Hax), 2.44 (td, 1 H, J = 2 and 14 Hz, 8-Heq), 2.73 (dd, 1 H, J = 7 and 14 Hz, 8-Hax), 3.00 (ddd, 1 H, J = 2 and 14 Hz, 10-Hax), 5.10 (dquintet, 1 H, J = 2 and 7 Hz, 7-Heq), 7.45-7.91 (m, 4 H, ArH);

13C NMR (CDCl₃) δ 20.95 (7-CCH₃), 44.36 (7-NCH), 46.55 (8-C), 46.73 (10-C), 55.04 (10a-NCH), 122.43, 124.68, 129.41 and 132.48 (2,3,4,5-ArCH), 132.29, 144.95 (4a and 10b-ArCq), 166.65 (N-CO) and 206.63 (8-CO);

m/z: 215(M⁺, 14%), 200(39), 172(13), 159(13), 158(100), 132(25), 131(15), 104(16), 103(17), 77(33), 76(15) and 51(22).

Anal. Calcd. for C₁₃H₁₃O₂N: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.61; H, 6.15; N, 6.57.

(8R*,11aR*)-1,2,3,4,6,7,8,9-Octahydro-8-phenyl-11aH-benzo[a]quinolizine-6,10-dione

1-(2-bromophenylacetyl)-2-phenyl-2,3-dihydro-4-pyridone 209 (0.37 g, 1 mmol) was dissolved in 10 mL of degassed t-butylbenzene and heated to 110 °C under an inert atmosphere. Bu₃SnH (4.36 g, 1.50 mmol) and AIBN (0.04 g, 0.28 mmol) in 5 mL of degassed tert-butyl benzene was added over 6 hours to
this solution. After completion of the addition the mixture was allowed to stir for 12 hours at reflux. It was then cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by radial preparative layer chromatographed to obtain the desired product \textbf{213} as a solid (0.24 g, 0.82 mmol, 82\%) mp 126 °C;

\begin{align*}
^1H \text{ NMR (CDCl}_3) & \delta 2.54 (\text{dd, } 1 \text{ H}, J = 15. \text{ and } 12. \text{ Hz, } 11-\text{H}_{ax}), 2.72 (\text{ddd, } 1 \text{ H}, J = 15., 3.3 \text{ and } 1.6 \text{ Hz, } 11-\text{H}_{eq}), 2.91 (\text{dd, } 1 \text{ H}, J = 15.4 \text{ and } 7.6 \text{ Hz, } 9-\text{H}_{ax}), 3.15 (\text{td, } 1 \text{ H}, J = 15.4 \text{ Hz and } 1.8 \text{ Hz, } 9-\text{H}_{eq}), 3.88 (\text{s, } 2 \text{ H, 5-CH}_2), 4.61 (\text{md, } 1 \text{ H}, J = 12 \text{ Hz, } 11a-\text{H}_{ax}), 6.83 (\text{dd, } 1 \text{ H}, J = 7.6 \text{ and } 1.8 \text{ Hz, } 8-\text{H}_{eq}) \text{ and } 6.97-7.3 (\text{5(m, } 9 \text{ H, ArH)});
\end{align*}

\begin{align*}
^{13}C \text{ NMR (CDCl}_3) & \delta 35.11 (5-\text{C}), 42.58 (9-\text{C}), 50.43 (11-\text{C}), 51.18 (11a-\text{C}), 53.63 (8-\text{C}), 125.40, 126.98, 127.22, 127.72, 127.84, 127.92 \text{ and } 128.82 (\text{ArCH}), 129.85, 131.60 \text{ and } 138.10 (\text{ArC}_q), 167.41 (\text{N-CO}) \text{ and } 205.62 (10-\text{CO});
\end{align*}

\begin{align*}
m/z : & 291(\text{M}^+, 10\%), 262(4), 159(11), 146(38), 132(8), 118(20), 117(22), 104(100), 91(16), 90(14), 89(14), 77(30), 63(14) \text{ and } 51(26); \text{ HRMS exact mass calcd. for } \text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2 \text{ 291.1259, found } 291.1260; \text{ Anal. Calcd. for } \text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2: \text{ C, 78.33; H, 5.88; N, 4.81. Found: C, 78.03; H, 5.99; N, 4.98.}
\end{align*}

\begin{align*}
(8R^*,11aR^*)-1,2,3,4,6,7,8,9-\text{Octahydro-8-methyl-11aH-benzo[a]quinolizine-6,10-dione}
\end{align*}

To a solution of 1-(2-bromophenylacetyl)-2-methyl-2,3-dihydro-4-pyridone \textbf{210} (0.31 g, 1 mmol) in 10 mL of degassed \textit{tert}-butylbenzene at 110 °C, Bu\textsubscript{3}SnH (0.44 g, 1.5 mmol) and AIBN (0.04 g, 0.28 mmol) in 5 mL of the same solvent were added over 6 hours. The same method as that described for ring closure of substrate \textbf{209} was followed and the crude product was purified by radial preparative layer chromatography (30\% ethyl acetate in light petroleum) to yield \textbf{214} as a solid (0.17 g, 0.72 mmol, 72\%) mp 87-88 °C;

\begin{align*}
^1H \text{ NMR (CDCl}_3) & \delta 1.20 (\text{d, } 3 \text{ H, } J = 7.2 \text{ Hz, } 8-\text{CCH}_3), 2.30 (\text{ddd, } 1 \text{ H, } J = 14.6}
\end{align*}
Chapter 7: Experimental

Hz, 3.2 and 1.4 Hz, 9-H\textsubscript{eq}), 2.39 (dd, 1 H, \(J = 15\) and 12.4 Hz, 11-H\textsubscript{ax}), 2.63 (dd, 1 H, \(J = 14.6\) and 7.2 Hz, 9-H\textsubscript{ax}), 2.69 (dm, 1 H, \(J = 15\) Hz, 11-H\textsubscript{eq}), 3.64 and 3.72 (d each, 2 H, \(J = 21\) Hz, 5-CH\textsubscript{2}), 4.94 (dm, 1 H, \(J = 11.58\) Hz, 11a-CH), 5.41 (quintet, 1 H, \(J = 7.2\) and 3.2 Hz, 8-H\textsubscript{eq}), 7.06-7.23 (m, 4 H, ArH);

\(^{13}\text{C}\) NMR (CDCl\textsubscript{3}) \(\delta 17.81\) (8-CH\textsubscript{3}), 34.85 (5-C), 44.62 (9-C), 45.80 (8-C), 50.20 (11-C), 52.96 (11a-C), 125.18, 126.78, 127.50 and 127.71 (ArCH), 129.66 and 131.34 (ArC\textsubscript{q}), 166.68 (NCO) and 205.69 (10-CO);

\(m/z\) : 229(M\textsuperscript{+}, 25%), 201(11), 186(20), 172(21), 146(34), 145(36), 130(11), 117(100), 90(30), 77(13), 70(24), 63(28), 51(25); HRMS exact mass calcd. for C\textsubscript{14}H\textsubscript{15}NO\textsubscript{2} 229.1103, found 229.1103;

Anal. Calcd. for C\textsubscript{14}H\textsubscript{15}NO\textsubscript{2}: C, 73.34; H, 6.60; N, 6.11. Found: C, 73.27; H, 6.84; N, 6.04.

(1-(2-Bromobenzyl)-2-phenyl-2,3-dihydro-4-pyridone)

To a solution of methoxypyridine (2.18 g, 20 mmol) in 100 mL of THF at \(-20\) °C (dry ice/carbon tetrachloride), 2-bromobenzyl bromide (5.50 g, 22 mmol) was added dropwise and the solution was heated at reflux for 10 hours. The solution was then cooled to 0 °C (ice/acetone bath) followed by the addition of phenylmagnesium bromide (30 mmol in 15 mL THF). Stirring was continued for a further hour and then the reaction mixture hydrolysed with aqueous saturated oxalic acid (15 mL). After being stirred for a further hour the solution was quenched with 150 mL of water and the aqueous layer extracted with ethyl acetate (6 x 100 mL). The combined organic solution was washed with 100 mL of water, dried with sodium sulphate filtered and the solvent removed under reduced pressure. The residue was chromatographed (50% ethyl acetate in petroleum spirits) to yield the product as a white solid (4.01 g, 11.7 mmol, 59%) mp 105 °C;

\(^{1}\text{H}\) NMR (CDCl\textsubscript{3}) \(\delta 2.67\) (dd, 1 H, \(J = 16.4\) and 6.5 Hz, 3-H\textsubscript{ax}), 2.97 (dd, 1 H, \(J = 16.4\) and 7.3 Hz, 3H\textsubscript{eq}), 4.35 (s, 2 H, NCH\textsubscript{2}), 4.58 (dd, 1 H, \(J = 7.3\) and 6.5 Hz, 2-H\textsubscript{p-eq}), 5.08 (d, 1 H, \(J = 7.7\) Hz, 5-H) and 7.20-7.58 (m, 10 H, 6-H and ArH);
13C NMR (CDCl3) δ 43.32 (3-CH2), 57.24 (N-CH2), 60.81 (2-C), 98.65 (5-C), 123.93 (ArCq), 126.84, 127.79, 128.30, 129.04, 129.69, 129.78, 133.45 (7xArCH), 135.06, 138.27 (ArCq), 153.96 (6-C), 189.95 (4-CO);

m/z: 343(M+2, 16%), 341(M+, 16%), 234(6), 172(15), 171(47), 169(49), 158(16), 144(12), 130(27), 104(100), 103(31), 102(14), 91(38), 90(57), 89(39), 82(16), 81(23), 77(42), 65(13), 63(27) and 50(37).

Anal. Calcd. for C18H16NOBr: C, 63.17; H, 4.71; N, 4.09; Br, 23.35. Found: C, 63.29; H, 4.72; N, 4.03; Br, 23.28.

1,2,3,5,6,7,8,8a-Octahydro-7-phenylbenzo[a]indolizine-9-one

1-(2-Bromobenzyl)-2-phenyl-2,3-dihydro-4-pyridone 221 (0.34 g, 1 mmol) in 10 mL of degassed benzene was heated at reflux. To this solution Bu3SnH (0.36 g, 1.2 mmol) and AIBN (60 mg) in 5 mL of degassed benzene was added dropwise over 6 hours. After complete consumption of the starting material the solvent was evaporated under reduced pressure and the residue radially chromatographed (10% ethyl acetate in light petroleum) to obtain the two isomers 222 and 223 (total yield (0.24g, 0.89 mmol, 89%) which crystallised on standing in chromatographic fractions.

(7R*,10aR*)-1,2,3,5,6,7,8,8a-Octahydro-7-phenylbenzo[a]indolizine-9-one

mp 151-152 °C;

1H NMR (CDCl3) δ 2.78 (m, 4 H, 8-Hax and 10-Hax), 3.99 (dd, 1 H, J = 3 and 13 Hz, 5-Hax), 4.23 (d, 1 H, J = 13 Hz, 5-Heq), 4.34 (dd, 1 H, J = 4 and 10 Hz, 10a-Hax), 4.91 (dt, 1 H, J = 3.3 and 11.5 Hz, 7-Heq), 7.15-7.43 (m, 9H, Ar-H);

13C NMR (CDCl3) δ 44.58 (8-CH2), 47.55 (10-CH2), 57.66 (5-CH2), 60.70, 61.97 (7 and 10a-CH), 121.93, 122.66, 127.03, 127.14, 127.34, 127.49, 128.55 (7xArCH), 138.77, 141.66, 141.72 (3xArCq), 209.31 (9-CO);

m/z: 263(M+, 26%), 158(5), 144(18), 131(13), 130(14), 119(5), 118(60), 117(100), 115(10), 105(12), 104(86), 103(26), 102(6), 91(12), 90(11), 89(11), 78(14),
Chapter 7: Experimental

77(21), 63(9), 51(15).

Anal. Calcd. for C_{18}H_{17}N_{2}O_{2}: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.81; H, 6.75; N, 5.29.

(7R*,10aS*)-1,2,3,5,6,7,8,8a-Octahydro-7-phenylbenzo[a]indolizine-9-one

$^1$H NMR (CDCl$_3$) $\delta$ 2.63-2.71 (m, 2 H, 10-CH$_2$), 2.76 (dd, 1 H, $J = 12.5$ and 14 Hz, 8-H$_{ax}$), 3.06 (dm, 1 H, $J = 14$ Hz, 8-H$_{eq}$), 3.37 (dd, 1 H, $J = 3$ and 13 Hz, 5-H$_{ax}$), 3.86-3.94 (m, 3 H, 5-H$_{eq}$, 7-H$_{ax}$ and 10a-H$_{ax}$), 7.14-7.46 (m, 9 H, Ar-H);

$^{13}$C NMR (CDCl$_3$) $\delta$ 45.3 2 (8-CH$_2$), 50.35 (10-CH$_2$), 54.99 (5-CH$_2$), 65.03, 66.15 (7 and 10a-CH), 120.50, 122.53, 126.90, 127.28, 127.33, 127.94, 128.78 (7xArCH), 139.77, 141.32, 141.89 (3xArC$_q$), 207.34 (9-CO);

m/z : 263(M$^+$, 40%), 220(10), 158(6), 144(16), 131(11), 130(17), 118(55), 117(100), 116(11), 115(14), 105(11), 104(72), 103(25), 102(6), 91(16), 90(10), 89(12), 78(14), 77(22), 63(9), 51(16); HRMS exact mass calcd. for C$_{18}$H$_{17}$N$_{2}$O$_{2}$ 263.1310, found 263.1310.

3-Acetyl-1,4,5,6-tetrahydropyridine

Acetylpyridine (12.1 g, 0.1 mol) was added to a suspension of 5% Pd-C (1.5 g) in dry ethanol (70 mL) in a parr bottle. The bottle was attached to a hydrogenator apparatus, the solution degassed several times with the aid of a water aspirator and filled with H$_2$ gas. The hydrogen pressure was adjusted to 48 psi and the bottle was shaken vigorously until the theoretical amount of hydrogen was taken-up. In this instance the pressure stabilised at 28 psi (the theoretical drop amounts to 30.04 psi). The reaction mixture was filtered through a pad of celite (caution! Pd-C residues has to be kept wet always, otherwise may result in an explosion). Ethanol was removed from the filtrate under reduced pressure and the crude product fractionally distilled to afford the 3-acetyltetrahydropyridine 253 (8.36 g, 66.9 mmol, 67%), bp 130 °C at 0.15 mm Hg;
3-Acetyl-1-(3-bromopropanoyl)-1,4,5,6-tetrahydropyridine

3-Acetyl tetrahydropyridine 253 (1.25 g, 10 mmol) was dissolved in THF (60 mL) in an oven dried round bottom flask, sealed with a septum and purged with nitrogen. The flask was then cooled to -78 °C with the aid of an ice/acetone bath. n-Butyllithium (6.6 mL, 1.6 M, 10.5 mmol) was added dropwise to this solution over approximately 10 minutes. Upon addition of the base rapid formation of a white precipitate was observed. The solution was stirred for 30 minutes at -78 °C before 3-bromopropanoyl chloride (2.06 g, 12 mmol) was added rapidly to the flask. The solution gradually became clear (1-2 minutes) and was stirred for a further 30 minutes before quenching with 40 mL of saturated aqueous NaCl. The organic portion was separated and the aqueous part was extracted with diethyl ether (3 x 50 mL). The combined solution of the organic layers was dried with MgSO4, filtered and the solvent removed. The residue was chromatographed with 50% ethyl acetate in petroleum spirits to afford the title compound 251 as an oil (1.87 g, 7.19 mmol, 72%).
195.78 (3-CO), (* rotamers are observed for most carbon atoms);

\[ m/z: 261(M+2, 26\%), 259(M^+, 26\%), 246(7), 244(7), 215(5), 180(7), 179(27), 164(9), 126(9), 125(68), 124(8), 111(11), 110(100), 109(14), 107(15), 82(30), 80(9), 73(24), 55(41). \]

Anal. Calcd. for C\(_{10}\)H\(_{14}\)N\(_2\)O\(_2\)Br: C, 46.17; H, 5.42; N, 5.38; Br, 30.72. Found: C, 46.54; H, 5.75; N, 5.24; Br, 30.56.

**3-Acetyl-1-propanoyl-1,4,5,6-tetrahydropyridine**

3-Acetyl-1-(3-bromopropanoyl)tetrahydro-pyridine 251 (0.61 g, 2.33 mmol) and AIBN (50 mg, 0.35 mmol) were introduced into an oven dried flask fitted with a reflux condenser. De-oxygenated benzene (25 mL) was added and the mixture heated at reflux. A solution of Bu\(_3\)SnH (1.02 g, 3.5 mmol) and AIBN (85 mg, 0.6 mmol) in 12.5 mL of degassed benzene was added to the heated substrate and AIBN solution over 5-6 hours with the aid of a syringe pump. On completion of addition the solution was left to stir for 12 hours at the same temperature. The residue isolated on removal of benzene under reduced pressure was purified by radial preparative chromatography with 75% ethyl acetate in petroleum spirits to afford N-propanoyltetrahydropyridine 246 (0.41 g, 2.26 mmol, 97%) as a thick oil;

\[ \text{1H NMR (CDCl}_3\text{)} \delta 1.23 (m, 3 H, 3'-CH}_3\text{), 1.86 (b, 2 H, 5-CH}_2\text{), 2.30 (bs, 5 H, 4-CH}_2\text{ and COCH}_3\text{), 2.58 (b, 2 H, 6-CH}_2\text{), 3.64 (b, 2 H, 2'-CH}_2\text{), 7.80 and 8.38 (bs each, 1H, 2-CH);} \]

\[ \text{13C NMR (CDCl}_3\text{)} \delta 8.75 (3'-CH}_3\text{), 19.86, 19.89, 19.96, 20.01, 20.23, 20.26, 20.28, 20.39, 20.61, 20.69, 20.81 (4 & 5'-CH}_2\text{), 24.74 and 24.79 (*COCH}_3\text{), 26.50, 26.59, 26.65, 26.68, 26.76, 26.83, 26.91, 27.20, 27.42, 27.65 (2'-*CH}_2\text{), 40.53, 40.64, 43.21, 43.36 (6-*CH}_2\text{), 121.73 (3-C}_q\text{), 135.36, 135.48, 135.85 (2-*CH), 172.53 and 172.57 (N*CO), 196.52, 197.72 (3-*CO), (* rotamers are observed for most carbon atoms);} \]

\[ m/z: 182(M+1, 10\%), 181(M, 35\%), 126(9), 125(42), 111(15), 110(100), 96(5), 82(33), 81(8), 80(15), 67(7), 57(44); HRMS exact mass calcd. for C\(_{10}\)H\(_{15}\)N\(_2\)O\(_2\) 181.1103. found 181.1102. \]
3-Acetyl-1-(2-bromobenzoyl)-1,4,5,6-tetrahydropyridine

3-Acetyl tetrahydropyridine 253 (0.63 g, 5 mmol) was introduced to an oven dried round bottom flask purged with nitrogen. THF (5 mL) was added and the flask cooled to -78 °C with the aid of an ice/acetone bath. Once cooled n-BuLi (3.25 mL, 1.6 M, 5.2 mmol) was added dropwise by a syringe over approximately 10 minutes and allowed to stir for 0.5 hour. A solution of 2-bromobenzoyl chloride (1.21 g, 5.5 mmol) in 2.5 mL of THF was added to this solution at the same temperature while stirring and left for a further 0.5 hours. The clear solution was brought to room temperature, quenched with brine (10 mL), the organic layer separated and the aqueous portion extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent removed at reduced temperature. The residue was chromatographed with 30% ethyl acetate in petroleum spirits to afford N-benzoyleacetyl-tetrahydropyridine 252 (1.24 g, 4 mmol, 80%);

1H NMR (CDCl₃) δ 1.84 and 1.93 (m each, 1 H each, 5-CH₂), 1.99 (s, 3 H, COCH₃), 2.38 (m, 3 H, 4 and 5-CH₂), 3.30, 3.46 and 3.89 (m each, 2 H, 6-*CH₂), 7.28-8.45 (m, 5 H, 2-CH and 4xArH), (* rotamer multiplets);

13C NMR (CDCl₃) δ 19.97, 20.42, 20.50, 20.93 (4 and 5-*CH₂), 24.46 and 24.98 (3-*COCH₃), 40.95, 45.16, 43.21, 43.36 (6-*CH₂), 119.40 (3-Cq), 120.78 (ArCq), 127.69, 127.90, 127.96, 128.80, 131.09, 132.87, 132.99, 134.29, 137.08 (2-*CH and ArCH), 135.84 (ArCq), 168.85 (NCO), 196.04 (3-CO), (* rotamers are observed for most carbon atoms);

m/z: 309(M+2, 34%), 307(M⁺, 34%), 186(13), 185(98), 184(14), 183(100), 157(26), 155(26), 139(10), 105(19), 86(52), 84(69), 77(14), 76(16), 75(14), 71(13), 67(15), 51(35), 49(94); HRMS exact mass calcd. for C₁₄H₁₄NO₂⁷⁹Br 307.0208, found 307.0207;

Anal. Calcd. for C₁₄H₁₄NO₂Br: C, 54.56; H, 4.58; N, 4.55; Br, 25.93. Found: C, 54.73; H, 4.55; N, 4.80; Br, 25.61.
3-Acetyl-1-benzoyl-1,4,5,6-tetrahydropyridine

(10R*,10aR*)-10-Acetyl-1,2,3,5,6,7,8,8a-octahydrobenzo[a]indolizine-5-one

(10S*,10aR*)-10-Acetyl-1,2,3,5,6,7,8,8a-octahydrobenzo[a]indolizine-5-one

3-Acetyl-1-(2-bromobenzoyl)-tetrahydropyridine (0.62 g, 2 mmol) and AIBN (43 mg, 0.3 mmol) were introduced to an oven dried round bottom flask fitted with a condenser, purged with nitrogen and sealed with septa. De-oxygenated benzene (20 mL) was added to this flask and the solution heated at reflux. Bu3SnH (0.87 g, 3 mmol) and AIBN (71 mg, 0.5 mmol) were separately dissolved in 10 mL of degassed benzene and the resulting clear solution added to the substrate solution at reflux over 5-6 hours with the aid of a syringe pump. Upon completion of addition the yellow solution was allowed to stir at reflux for 12 hours. The solution was cooled to room temperature and benzene removed under reduced pressure. The residue was purified by radial preparative chromatography initially with 30% of ethyl acetate and petroleum spirits to afford 257 (0.161 g, 0.70 mmol, 35%) and with 60% ethyl acetate and petroleum spirits to yield 258 (0.251 g, 1.10 mmol, 55%) and 259 (0.029 g, 0.13 mmol, 6%).

3-Acetyl-1-benzoyl-1,4,5,6-tetrahydropyridine

\[
\begin{align*}
1^H \text{NMR (CDCl}_3) & \ 8 \ 1.91 (m, 2 \ H, 5-CH_2), 2.15 (s, 3 \ H, \ COCH}_3), 2.39 (m, 2 \ H, 4-CH_2), 3.76 (m, 2 \ H, 6-CH_2), 7.48-7.57 (m, 5 \ H, \ ArH), 7.91 (b, 1 \ H, 2-CH); \\
13^C \text{NMR (CDCl}_3) & \ 8 \ 20.46, 20.61 (4 \ and \ 5-CH_2), 24.66 (COCH}_3), 43.32 (b, 6-CH_2), 120.34 (3-\text{ArC}_q), 128.13, 128.60, 131.18 (5 \times \text{ArCH}), 133.69 (\text{ArC}_q), 137.74 (2-CH), 170.16 (\text{NCO}), 196.51 (\text{COCH}_3); \\
m/z: & \ 230(M+1, 12\%), \ 229(M^+, 49\%), 106(12), 105(100), 84(24), 78(7), 77(62), 57(6); \text{HRMS exact mass calcd. for } C_{14}H_{15}NO_2 229.1103, \text{ found } 229.1103.
\end{align*}
\]
(10R*,10aR*)-10-Acetyl-1,2,3,5,6,7,8,8a-octahydrobenzo[a]indolizine-5-one

$^1$H NMR (CDCl$_3$) $\delta$ 1.53 (m, 1 H, 8-H$_{ax}$), 1.62 (m, 1 H, 9-H$_{ax}$), 1.94 (m, 1 H, 8-H$_{eq}$), 2.20-2.30 (m, 1 H, 9-H$_{eq}$), 2.26 (s, 3 H, COCH$_3$), 2.33 (ddd, 1 H, $J$ = 3, 10.5 and 12 Hz, 10-H$_{ax}$), 2.95 (dt, 1 H, $J$ = 3.5 and 13 Hz, 7-H$_{ax}$), 4.52 (m, 1 H, 7-H$_{eq}$), 4.70 (d, 1 H, $J$ = 10.5 Hz, 10a-H$_{ax}$), 7.28-7.31 (m, 1 H, 1-ArH), 7.43-7.50 (m, 2 H, 2 and 3-ArH), 7.84-7.87 (m, 1 H, 4-ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 24.86 (8-CH$_2$), 27.94 (9-CH$_2$), 29.88 (COCH$_3$), 38.79 (7-CH$_2$), 55.42 (10-CH), 58.63 (10a-CH), 122.86, 123.65, 128.35, 131.35 (4xArCH), 132.18 (10b-C$q$), 144.41 (4a-C$q$), 165.97 (NCO), 209.60 (COCH$_3$);

$^{m/z}$: 230(M+1, 12%), 229(M+, 60%), 214(18), 200(12), 187(19), 186(100), 184(13), 159(25)158(22), 146(7), 132(6), 131(7), 130(14), 117(7), 105(8), 104(15), 90(7), 89(6), 77(10), 76(7): HRMS exact mass calcd. for C$_{14}$H$_{15}$NO$_2$ is 229.1103, found 229.1103;

Anal. Calcd. for C$_{14}$H$_{15}$NO$_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.04; H, 6.37; N, 5.81.

(10S*,10aR*)-10-Acetyl-1,2,3,5,6,7,8,8a-octahydrobenzo[a]indolizine-5-one

$^1$H NMR (CDCl$_3$) $\delta$ 1.68-1.74 (m, 1 H, 8-H$_{ax}$ and 9-H$_{ax}$), 1.87 (s, 3 H, COCH$_3$), 1.96-2.07 (m, 1 H, 8-H$_{eq}$), 2.21-2.27 (m, 1 H, 9-H$_{eq}$), 2.01 (m 1 H, 7-H$_{ax}$), 3.44 (m, 1 H, 10-H$_{eq}$), 4.44 (d, 1 H, $J$ = 4.5 Hz, 10a-H$_{ax}$), 4.52 (m, 1 H, 7-H$_{eq}$), 7.35-7.52 (m, 2 H, 1, 2 and 3-ArH), 7.84-7.87 (m, 1 H, 4-ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 20.02 (8-CH$_2$), 25.81 (9-CH$_2$), 30.88 (COCH$_3$), 39.06 (7-CH$_2$), 47.57 (10-CH), 58.67 (10a-CH), 120.86, 123.71, 128.19, 130.97 (4xArCH), 133.52 (10b-C$q$), 143.19 (4a-C$q$), 166.50 (NCO), 206.54 (COCH$_3$);

$^{m/z}$: 230(M+1, 23%), 229(M+, 54%), 214(27), 200(20), 187(30), 186(100), 184(28), 160(36), 159(48), 158(43), 149(25), 146(23), 132(25), 131(29), 130(39), 117(21), 105(29), 104(45), 90(25), 89(20), 77(34), 76(30), 71(23), 57(22): HRMS exact mass calcd. for C$_{14}$H$_{15}$NO$_2$ 229.1103, found 229.1104.
3-Acetyl-1-benzoyl-1,4,5,6-tetrahydro-[6-2H]-pyridine

A solution of 3-acetyl-1-(2-bromobenzoyl)-tetrahydropyridine (0.46 g, 1.5 mmol) and AIBN (53 mg, 0.38 mmol) in 15 mL of benzene was treated with Bu$_3$SnD (0.66 g, 2.25 mmol) and AIBN (32 mg, 0.23 mmol) under the same reaction conditions as described above to afford the deuterated derivatives 264 (0.126 g, 0.55 mmol, 36.5%), 263 (0.20 g, 0.87 mmol, 57.9%).

$^1$H NMR (CDCl$_3$) $\delta$ 1.90 (m, 2 H, 5-CH$_2$), 2.16 (s, 3 H, COCH$_3$), 2.38 (m, 2 H, 4-CH$_2$), 3.73 (bm, 1 H, 6-CH$_2$), 7.46-7.56 (m, 5 H, ArH), 7.92 (b, 1 H, 2-CH);

$^2$H NMR (CHCl$_3$) $\delta$ 3.80 (bs, 1 H, 6-2H);

$^{13}$C NMR (CDCl$_3$) $\delta$ 20.42, 20.44, 20.50 (4 and 5-CH$_2$), 24.68 (COCH$_3$), 120.35 (ArC$_q$), 128.14, 128.62, 131.21 (5xArCH), 133.66 (3-ArC$_q$), 137.76 (2-CH), 170.20 (NCO), 196.49 (COCH$_3$), (6-CHD is not observed due to deuterium coupling);

$m/z$: 231(M+1, 6%), 230(M^+, 21%), 106(18), 105(100), 78(13), 77(56), 57(22);$

HRMS exact mass calcd. for C$_{14}$H$_{15}$NO$_2$ 229.1103, found 229.1103.

(3,4-Dimethoxybenzylimino-N-acetaldehydedimethylacetal

3,4-Dimethoxybenzaldehyde (8.31 g, 50 mmol) was dissolved in benzene (150 mL) in a two necked round bottom flask fitted with a Dean-Stark apparatus. To this solution aminoacetaldehyde dimethylacetal (5.78 g, 55 mmol) was added and the solution heated at reflux. After the theoretical amount of water (0.9 mL) was collected, the solution was cooled to room temperature and the solvent removed under reduced pressure to yield the imine 322 (12.62 g, 49.8 mmol, quantitative) as a waxy solid. Further purification was found to be unnecessary as the crude product was spectroscopically and analytically pure.
1H NMR (CDCl₃) δ 3.42 (s, 6 H, 2xOCH₃-acetal), 3.75 (d, 2 H, J = 5 Hz, NCH₂), 3.91, 3.94 (s each, 3 H each, 2xArOCH₃), 4.75 (t, 1 H, J = 5 Hz, acetal-CH), 6.88 (d, 1 H, J = 8 Hz, 5-ArH), 7.17 (dd, 1 H, J = 2 and 8 Hz, 6-ArH), 7.44 (d, 1 H, J = 2 Hz, 2-ArH), 8.20 (s, 1 H, imine-H);

13C NMR (CDCl₃) δ 53.86, 55.65 (4xOCH₃), 63.20 (NCH₂), 103.67 (acetal-CH), 100.45, 110.05, 123.05 (3xArCH), 129.06 (ArC₆), 148.97, 151.14 (2xArC₆OCH₃), 162.77 (imine-CH);

m/z: 253(M⁺,17%), 222(42), 190(12), 178(40), 177(27), 165(28), 162(13), 151(84), 147(20), 137(14), 136(26), 120(13), 111(15), 107(30), 106(23), 92(49), 91(100), 90(23), 89(22);


6,7-Dimethoxyisoquinoline

Trifluoroacetic anhydride (50 mL) was added dropwise into 50 mL of borontrifluoride diacetic acid complex [BF₃.2(CH₃CO₂H)], cooled to 0 °C (ice/acetone bath). The solution was stirred for 10 minutes at this temperature before the imine 322 (25.3 g, 100 mmol), dissolved in 38 mL of trifluoroacetic anhydride was introduced by dropwise addition over about 10 minutes. The cherry red solution was stirred for 2 hours at 0 °C and then for 5 hours at room temperature. The excess anhydride was carefully quenched with ice after the solution was cooled to 0 °C, followed by the addition of 300 mL of 20% aqueous NaOH solution. The basic aqueous layer was extracted with chloroform (10 x 100 mL). The combined chloroform solution was subsequently shaken with 20% aqueous HCl (5 x 25 mL), the aqueous phases combined and re-basified to pH 11 with 20% NaOH. The basic aqueous portion was again extracted with chloroform (10 x 50 mL), the fractions combined, dried with Na₂SO₄, filtered and the solvent removed. The residue was chromatographed on silica gel (10% methanol in ethyl acetate) to afford dimethoxyisoquinoline (16.25 g, 86 mmol, 86%), mp 91-93 °C;
Chapter 7: Experimental

\( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 3.90 (s, 6 H, 2xOCH\(_3\)), 6.93 (s, 1 H, 5-ArH), 7.06 (s, 1 H, 8-ArH), 7.38 (d, 1 H, \( J = 6 \) Hz, 4-ArH), 8.28 (d, 1 H, \( J = 6 \) Hz, 3-ArH), 8.92 (s, 1 H, 1-ArH);

\( ^13C \) NMR (CDCl\(_3\)) \( \delta \) 55.66, 55.71 (2xOCH\(_3\)), 104.17 (5-ArCH), 104.90 (8-ArCH), 118.91 (4-ArCH), 124.39 (4a-ArC\(_q\)), 132.16 (8a-ArC\(_q\)), 141.58 (3-ArCH), 149.58 (1-ArCH), 149.91 and 152.60 (2xArC\(_q\)OCH\(_3\));

\( m/z: \) 190(M+1, 12%), 189(M\(^+\), 100%), 174(13), 146(68), 117(34), 116(38), 103(49), 91(32), 89(20), 88(10), 77(13), 76(51), 74(24), 63(21), 62(29), 51(22), 50(44);


2-Bromo-4,5-dimethoxyphenylacetyl chloride

A solution of bromine (20.78 g, 130 mmol) in 40 mL of chloroform was added dropwise to a cooled solution (ice/acetone) of commercially available 3,4-dimethoxyphenylacetic acid (19.62 g, 100 mmol) in 60 mL of CHCl\(_3\). Five minutes after the addition was complete, the ice bath was removed and solution allowed to stir for 6 hours at room temperature. It was then cooled to 0 °C and 100 mL of 10% aqueous NaOH added gradually with stirring. After 15 minutes of stirring, the aqueous basic layer was separated from the organic phase and the latter extracted with a further 10 mL portion of 10% sodium hydroxide. The two aqueous extracts were combined, carefully acidified with 10% HCl to pH 2, to liberate the acid and extracted into ethyl acetate (3 x 150 mL). The solution of combined organic phases were dried over MgSO\(_4\), filtered and the solvent removed at reduced pressure to obtain a colourless solid (32.22 g, 117 mmol, 90%). The crude product was found to be spectroscopically pure to be used in the next step;

\( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 3.76 (s, 2 H, benzylic-CH\(_2\)), 3.85 (s, 6 H, 2xOCH\(_3\)), 6.78, 7.03 (s each, 1 H each, ArH), 10.98 (b, 1 H, CO\(_2\)H);

\( ^13C \) NMR (CDCl\(_3\)) \( \delta \) 40.68 (benzylic-CH\(_2\)), 55.86, 55.91 (2xOCH\(_3\)), 113.68, 115.20 (ArCH), 114.85 (ArC\(_q\)), 124.99 (ArC\(_q\)Br), 148.16, 148.73 (2xArC\(_q\)OCH\(_3\)), 176.99 (CO).
The crude (32.00 g, 116.3 mmol) was redissolved in 50 mL of SOCl₂ followed by the addition of a drop of DMF. Upon addition of DMF vigorous gas evolution was observed. The solution was heated at reflux for 3 hours, cooled, and excess SOCl₂ removed under reduced pressure to afford the acid chloride 315 as a thick oil (34.01 g, 115.8 mmol, 99%). The crude acid chloride was used in the next step without further purification.

2-(2-Bromo-4,5-dimethoxyphenylacetyl)-6,7-dimethoxy-1-methyl-1,2-dihydroisoquinoline

6,7-Dimethoxyisoquinoline 316 (0.378 g, 2 mmol) was dissolved in 20 mL of THF and the solution cooled to -23 °C (dry ice/CCI₄). Freshly prepared 2-bromo-4,5-dimethoxyphenylacetyl chloride 317 (0.660 g, 2.4 mmol) in 10 mL of THF was added dropwise to this solution. With the formation of the quaternary isoquinolinium salt the solution became gradually thicker; the solution was stirred for one hour at -23 °C. Methylmagnesium iodide (3 mmol) was added to this suspension as a 3 M solution in diethyl ether. The homogenised solution was stirred for a further hour at the same temperature, quenched with 100 mL of saturated NH₄Cl and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The solution of the combined organic extracts was dried with Na₂SO₄, filtered, and the solvent removed under reduced pressure. The residue was purified by radial preparative layer chromatography (50% ethyl acetate in light petroleum) to give 313 as a colourless solid (0.85 g, 1.84 mmol, 92%; mp 149-150 °C;

\[ \text{H NMR (CDCl}_3 \text{)} \delta 1.28 (d, 3 H, J = 7 Hz, CH₃), 3.80, 3.87, 3.88 (s, 14 H, 4xOCH₃ and bezylic-CH₂), 5.81 (q, 1 H, J = 7 Hz, 1-CH), 5.86 (d, 1 H, J = 8 Hz, 4-CH), 6.55 (d, 1 H, J = 8 Hz, 3-CH), 6.62, 6.65, 6.78, 7.04 (s each, 1 H each, ArH);

\[ \text{C NMR (CDCl}_3 \text{)} \delta 20.62 (CH₃), 40.12, 40.25 (benzylic-CH₂), 43.70 (4-CH), 108.01, 108.20, 110.31, 110.43, 112.74, 115.18, 115.23, 121.86 (3-CH, 4xArCH, rotamers), 114.41, 121.99, 126.09, 127.59 (ArC₉), 148.06, 148.39, 148.42, 148.52 (4xArOCH₃), 167.98 (CO);\]
Chapter 7: Experimental

\[ m/z: 463(M+2, 4\%), \ 461(M^+, 3\%), \ 448(5), \ 446(5), \ 231(7), \ 229(8), \ 204(3), \ 191(11), \ 190(100), \ 146(2), \ 89(3), \ 77(5), \ 64(2), \ 63(4), \ 51(3); \]

Anal. Calcd. for C\(_{22}\)H\(_{24}\)NO\(_5\)Br: C, 57.15; H, 5.23; N, 3.03; Br, 17.28. Found: C, 57.40; H, 5.20; N, 3.14; Br, 17.38.

\((\pm)-O\text{-Methylcorytenchirine-6-one or cis-8-Methyl-2,3,10,11-tetramethoxy-}\)
\(5,8,13,13a\text{-tetrahydro-dibenzo[a,g]quinolizine-6-one}\)

The N-acyl enamide 313 (231 mg, 0.5 mmol) was dissolved in 5 mL of deoxygenated benzene under an inert atmosphere and heated at reflux. To this heated mixture, a solution of Bu\(_3\)SnH (218 mg, 0.75 mmol) and AIBN (40 mg, 0.28 mmol) in 4 mL of degassed benzene was added dropwise over 6 hours with the aid of a syringe pump. Upon completion of addition the solution was allowed to stir at reflux for further 4 hours before it was cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by radial preparative layer chromatography (60% ethyl acetate in light petroleum) to afford the cyclised product 314 as a solid (145 mg, 0.38 mmol, 76%) mp 198-200 °C;

\[ \text{1}H \text{ NMR (CDCl}_3) \delta 1.55 (d, 3 \text{ H, } J = 7 \text{ Hz, CH}_3), 2.84 (dd, 1 \text{ H, } J = 12 \text{ and } 16 \text{ Hz, 13-H}_ax), 3.03 (dd, 1 \text{ H, } J = 3 \text{ and } 16 \text{ Hz, 13-H}_eq), 3.63 (d, 2 \text{ H, } J = 21 \text{ Hz, 5-H}), 3.86, 3.89 \text{ and } 3.91 (s \text{ each, } 12 \text{ H, } 4x\text{OCH}_3), 4.83 (d, 1 \text{ H, } J = 12 \text{ Hz, 13a-H}), 5.97 (q, 1 \text{ H, } J = 7 \text{ Hz, 8-H}), 6.59, 6.63, 6.67, 6.76 (s \text{ each, } 1 \text{ H each, } 4x\text{ArH}); \]

\[ \text{13C NMR (CDCl}_3) \delta 21.91 (\text{CH}_3), 34.95 (5-\text{CH}_2), 38.86 (13-\text{CH}_2), 48.02 (8-\text{CH}), 52.92 (14-\text{CH}), 55.79 \text{ and } 55.86 (4x\text{OCH}_3), 108.35, 108.47, 109.76, 110.87 (1, 4, 9, 12-\text{ArCH}), 122.15, 124.76, 124.95, 129.99 (4a, 8a, 12a, 13b-\text{ArC}_q), 147.42, 147.82, 147.94, 148.58 (2, 3, 10, 11-\text{ArC}_q\text{OCH}_3), 166.15 (6-\text{CO}); \]

\[ m/z: 383(M^+, 9\%), 369(2), 368(9), 206(2), 179(12), 178(100), 163(9), 135(5), 117(3), 115(2), 107(2), 105(3), 91(7), 79(4), 77(4), 65(2); \]

Anal. Calcd. for C\(_{22}\)H\(_{25}\)NO\(_5\): C, 68.91; H, 6.57; N, 3.65. Found: C, 69.15; H, 6.91; N, 3.78.
Chapter 7: Experimental

(±)-O-Methylcorytenchirine or
cis-8-Methyl-2,3,10,11-tetramethoxy-5,8,13,13a-tetrahydro-(6H)-dibenzo[a,g]quinolizine

A solution of AlCl$_3$ (160 mg, 1.2 mmol) in 12 mL of diethyl ether was added dropwise to a suspension of ice cooled LiAlH$_4$ (137 mg, 3.6 mmol) in 12 mL of the same solvent. The ice bath was removed on completion of addition and the solution stirred for 30 minutes at room temperature. The tetracyclic amide 314 (575 mg, 1.5 mmol) was dissolved in 12 mL of THF and added to this solution with gradual stirring. Three hours after addition of the substrate the solid residues were filtered through a thin pad of silica and washed with 20 mL of methanol. The filtrate was concentrated and purified by radial preparative layer chromatographed to yield (±)-O-methylcorytenchirine (390 mg, 1.06 mmol, 71%) as an oil:

$^1$H NMR (CDCl$_3$) $\delta$ 1.41 (d, 3 H, $J$ = 7 Hz, CH$_3$), 2.79 (dd, 1 H, $J$ = 16.5 and 11 Hz, 13-H$_{ax}$), 2.85-3.00 (m, 4 H, 6 and 5-CH$_2$), 3.06 (dd, 1 H, $J$ = 4.5 and 16.5 Hz, 13H$_{eq}$), 3.85, 3.87, 3.89 (s each, 12 H, 4xOCH$_3$), 4.11 (q, 1 H, $J$ = 7 Hz, 8-H$_{eq}$), 4.24 (dd, 1 H, $J$ = 4.5 and 11 Hz, 13a-H), 5.69, 6.60, 6.62, 6.70 (4xArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 17.97 (CH$_3$), 29.46 (5-CH$_2$), 35.63 (13-CH$_2$), 47.16 (6-CH$_2$), 50.35 (8a-CH), 55.81, 55.93 (4xOCH$_3$), 59.22 (13a-CH), 109.08, 109.75, 111.11, 111.39 (1, 4, 9, 12-ArCH), 125.26, 126.45, 130.68, 131.78 (4a, 8a, 12a, 13b-ArC$_q$), 174.26 (2, 3, 11, 10-ArC$_q$OCH$_3$);

$\text{m/z}$: 369(M$^+$, 5%), 355(4), 354(18), 192(5), 190(2), 180(2), 179(18), 178(100), 177(4), 176(3), 164(2), 163(12), 146(2), 135(8), 133(2), 117(4), 115(2), 107(3), 105(4), 104(3), 103(6), 92(3), 91(14), 79(7), 78(3), 77(9), 65(4), 55(3), 53(3), 51(4); HRMS exact mass calcd. for C$_{22}$H$_{27}$NO$_4$ 369.1940, found 369.1922;

Anal. Calcd. for C$_{22}$H$_{27}$NO$_4$: C, 71.52; H, 7.37; N, 3.79. Found; C, 71.09; H, 7.64; N, 3.50.
2-Bromobenzylmagnesium Bromide

A ten percent solution of bromobenzyl bromide (3.75 g, 15 mmol) in diethyl ether (20 mL) was added dropwise to magnesium turnings (0.37 g, 15 mmol) suspended in ether (10 mL) until the Grignard formation was initiated. The rest of the solution was then introduced within a period of 10-15 minutes, maintaining gentle reflux at all times. The solution containing the reagent was stirred for 30 minutes before use.

1-(2-Bromobenzyl)-2-phenoxy carbonyl-1,2-dihydroisoquinoline

Isoquinoline (1.29 g, 10 mmol) was dissolved in dry diethyl ether (50 mL) and cooled to -23 °C (dry ice/CCl4). Phenyl chloroformate (1.72 g, 11 mmol) was added dropwise to this solution. With every drop of phenyl chloroformate formation of a dense white precipitate was observed and the solution became increasingly viscous. Vigorous stirring was continued for an hour at this temperature. A freshly prepared solution of bromobenzylmagnesium bromide 423 (3.75 g, 15 mmol) in 20 mL of diethyl ether was added to the suspended salt, while maintaining the temperature at -23 °C. The mixture was stirred for an hour at this temperature and for a further 30 minutes at room temperature before quenching with 50 mL of saturated aqueous NaCl solution. The organic phase was separated and the aqueous portion extracted with diethyl ether (3 x 75 mL). The combined solution of the extracts was dried with MgSO4, filtered and the solvent removed under reduced pressure. The residue obtained was chromatographed (10% ethyl acetate in petroleum spirits) to afford the product (4.16 g, 9.9 mmol, 99%) as a colourless solid, mp 118 °C;

\(^1\)H NMR (CDCl3) \(\delta 3.03-3.22\) (m, 2 H, benzyllic-CH\(_2\)), \(5.82\) and \(5.91\) (t and dd, 1 H, \(J = 7\) Hz, \(J = 4.8\) and \(9.8\) Hz, 1-CH), 6.01 and 6.15 (d each, 1 H, \(J = 7.8\) Hz each, 4-CH), 6.66-7.54 (m, 14 H, ArH);

\(^13\)C NMR (CDCl3) \(\delta 40.37\) and 40.99 (benzyllic-\(^*\)CH\(_2\)), 55.23 and 55.81 (1-\(^*\)C), 109.84 and 110.65 (4-\(^*\)C), 121.25, 121.48, 123.97, 124.48, 124.80, 125.07, 125.52, 125.63, 126.03, 126.35, 126.89, 127.11, 127.16, 127.46, 127.88, 128.05,
128.29, 128.51, 129.08, 129.31, 129.56, 131.68, 131.86, 132.73 (3-*C and 13xAr*CH), 129.96, 130.10, 132.36, 136.46, 136.57 (5xAr*Cq) 150.38, 150.83, 151.12, 151.86 (N*CO), (* rotamers are observed for most carbon atoms);

\[ m/z: \text{(EI)} \ 251(14\%), \ 250(84), \ 206(12), \ 130(82), \ 129(17), \ 128(11), \ 91(11), \ 90(10), \ 77(100); \ (CI) \ 423(M+4, \ 25\%), \ 422(M+3, \ 100\%), \ 421(M+2, \ 22\%), \ 420(M+1, \ 89\%), \ 251(12), \ 250(64), \ 206(8), \ 171(5), \ 169(36), \ 130(44), \ 129(11). \]

Anal. Calcd. for C\(_{23}\)H\(_{18}\)N\(_2\)Br: C, 65.73; H, 4.32; N, 3.33; Br, 19.01. Found: C, 66.05; H, 4.43; N, 3.30; Br, 18.99.

1-(2-Bromobenzyl)-2-ethoxycarbonyl-1,2-dihydroisoquinoline

The \(N\)-ethoxycarbonyl derivative 467 was synthesised under similar conditions to that described for the \(N\)-phenoxy carbonyl compound 430. The crude product after purification by column chromatography (20% ethyl acetate in petroleum spirit) gave the desired compound in 88%; mp 60-62 °C;

\[ \text{1H NMR (CDCl}_3) \delta 1.06 \text{ and 1.20 (t each, 3 H, J = 7 Hz, -CO}_2\text{CH}_2\text{CH}_3), 2.91-3.14 (m, 2 H, benzyl-CH}_2, 3.56, 3.59, 3.90, 3.95 \text{ and 4.10 (q each, 2 H, J = 7 Hz, -CO}_2\text{CH}_2\text{CH}_3), 5.67 \text{ and 5.75 (dd and t, 1 H, J = 5 and 10 Hz, J = 7 Hz, 1-CH), 5.88 and 6.03 (d each, 1 H, J = 8 Hz each, 3-CH), 6.79-7.56 (m, 9 H, ArH);} \]

\[ \text{13C NMR (CDCl}_3) \delta 13.99, 14.52, 15.25 (-CO}_2\text{CH}_2\text{CH}_3), 40.14 \text{ and 40.78 (benzyl-CH}_2, 54.85 \text{ and 54.93 (1-CH}, 61.93 \text{ and 62.13 (-CO}_2\text{CH}_2\text{CH}_3), 108.50 \text{ and 109.13 (3-CH}, 124.33, 124.45, 124.71, 124.76, 125.92, 126.34, 126.65, 126.76, 127.21, 127.64, 127.80, 128.10, 128.23, 131.71, 132.36, 132.49 (4-CH and 8xArCH), 125.30, 130.34, 132.23, 136.75 (4xArCq), 152.63 \text{ and 153.44 (NCO), (* rotamers are observed for most carbon atoms);} \]

\[ m/z: \ 373(M+2, \ 0.17\%), \ 371(M+1, \ 0.15\%), \ 342(0.16), \ 340(0.32), \ 338(0.16), \ 328(0.16), \ 326(0.17), \ 306(0.11), \ 304(0.11), \ 302(0.12), \ 300(0.13), \ 279(24), \ 262(7), \ 260(7), \ 236(6), \ 203(29), \ 202(100\%), \ 181(20), \ 174(22), \ 171(27) \ 169(27), \ 158(35), \ 131(20), \ 130(71), \ 129(27), \ 103(19), \ 102(15), \ 91(50), \ 90(26), \ 89(23). \]
**Chapter 7: Experimental**

77(17), 65(14);

Anal. Calcd. for C$_{19}$H$_{18}$N$_{2}$O$_{2}$Br: C, 61.30; H, 4.87; N, 3.76; Br, 21.46. Found: C, 61.67; H, 4.58; N, 3.59; Br, 21.12.

1-(2-Bromobenzyl)-2-methoxycarbonyl-1,2-dihydroisoquinoline

The title compound **466** was prepared following two procedures. Firstly, **466** was prepared by using methyl chloroformate following the procedure described for the preparation of compound **430**. The reaction, after column chromatography (5% ethyl acetate in petroleum spirits) afforded **466** in 76% yield.

Secondly, isoquinoline derivative **430** (4.2 g, 10 mmol) was dissolved in 100 mL of methanol with heating (40 °C) and treated with 50 mL of a 2 M solution of NaOMe in methanol. The solution was heated at reflux and maintained at this temperature for 12 hours with stirring. Methanol was removed under reduced pressure and the solution quenched with 20 mL of a 2:1 mixture of saturated aqueous NaCl and water, extracted with ethyl acetate (3 x 100 mL). The combined solution of the organic extracts was dried with MgSO$_4$, filtered and solvent removed under reduced pressure. The crude product was chromatographed with 5% ethyl acetate in petroleum spirits to afford **466** (2.87 g, 8 mmol, 80%);

$^1$H NMR (CDCl$_3$) $\delta$ 2.92-3.15 (m, 2 H, benzylic-CH$_2$), 3.33 and 3.67 (s, 3 H, -CO$_2$CH$_3$), 5.23 and 5.73 (dd and t, 1 H, J = 5 and 9 Hz, J = 7 Hz, 1-CH), 5.88 and 6.01 (d each, 1 H, J = 7.8 Hz each, 3-CH), 6.75-7.57 (m, 9 H, ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 40.09 and 41.08 (benzylic-*CH$_2$), 52.64 and 53.20 (-CO$_2$CH$_3$), 55.10 and 55.21 (1-*C), 108.76 and 109.11 (3-*C), 124.19, 124.51, 124.76, 125.98, 126.39, 126.68, 126.76, 126.80, 127.20, 127.69, 127.86, 128.15, 128.25, 131.71, 131.78, 132.33 (4-*C and 8xAr*CH), 125.24, 130.32, 130.75, 132.10, 136.57, 136.73 (4xAr*C$_q$) 152.33, 153.07 (N*CO), (* rotamers are observed for most carbon atoms);

$m/z$: 359(M+2, 2%), 357(M, 2%), 328(2), 326(2), 247(1), 218(8), 189(31), 188(100), 171(11), 169(11) 145(11), 144(51), 130(12), 129(33), 128(16), 103(17),
102(16), 90(17), 89(15), 59(17);

Anal. Calcd. for C\textsubscript{18}H\textsubscript{16}N\textsubscript{2}Br: C, 60.35; H, 4.50; N, 3.91; Br, 22.30. Found: C, 60.50; H, 4.39; N, 3.61; Br, 22.57.

### 1-(2-Bromobenzyl)-2-acetyl-1,2-dihydroisoquinoline

The title compound was synthesised following the general procedure described for the synthesis of isoquinoline radical precursor compounds (example 430). The crude product isolated was purified by column chromatography (25% ethyl acetate in petroleum ether) to afford the title compound as a colourless solid in 92% yield; mp 90-94 °C;

\[
\text{\textsuperscript{1}H NMR (CDCl}_3\text{) } \delta \text{ 1.73, 2.12 (s each, 3 H, acetyl-CH}_3\text{), 2.92-3.17 (m, 2 H, benzylic-CH}_2\text{), 5.29 and 6.07 (dd and t, 1 H, } J = 4 \text{ and 9 Hz, } J = 7 \text{ Hz, 1-CH), 5.93 and 6.17 (d each, 1 H, } J = 7.8 \text{ Hz each, 3-CH), 6.61-7.59 (m, 9 H, 4-CH and ArH);}
\]

\[
\text{\textsuperscript{13}C NMR (CDCl}_3\text{) } \delta \text{ 20.43 and 21.34 (NCOCH}_3\text{), 39.97 and 40.47 (benzylic-*CH}_2\text{), 53.19 and 57.22 (1-*C), 110.25 and 111.21 (3-*C), 123.64, 124.53, 124.72, 125.01, 125.71, 126.59, 126.77, 126.99, 127.68, 127.73, 128.09, 128.13, 128.89, 131.64, 132.48, 132.68 (4-*C and 8xAr*CH), 124.86, 125.52, 130.04, 130.22, 132.07, 135.93, 136.65 (4xAr*Cq) 168.21, 169.11 (N*CO), (* rotamers are observed for most carbon atoms);}
\]

\[
m/z: 343(M+2, 2\%), 341(M, 2\%), 300(1), 298(1), 239(4), 237(3), 220(3), 219(2), 218(8), 217(8), 216(4), 216(2), 203(3), 189(5), 172(67), 131(21), 130(100), 129(19), 103(13), 102(9), 90(9);\]

Anal. Calcd. for C\textsubscript{23}H\textsubscript{18}N\textsubscript{2}O\textsubscript{2}Br: C, 65.73; H, 4.32; N, 3.33; Br, 19.01. Found: C, 66.05; H, 4.43; N, 3.30; Br, 18.99.
2-Bromo-4,5-dimethoxybenzyl bromide

3,4-Dimethoxybenzaldehyde (4.15 g, 25 mmol) was dissolved in methanol (25 mL) and cooled to 0°C with the aid of an ice/acetone bath. To this solution NaBH₄ (1.17 g, 31 mmol) was added portionwise ensuring minimal temperature rise. Upon completion of addition the solution was brought to room temperature and stirred for a further 2 hours. The pale yellow reaction solution was then poured into 50 mL of saturated aqueous NaCl solution and extracted with diethyl ether (5 x 30 mL), dried over MgSO₄, filtered and the solvent removed under reduced pressure to yield the crude benzyl alcohol 453 (4.10 g, 24.4 mmol, 98%) as an oil (confirmed to be reasonably pure by NMR to be used in the next step without purification).

^1H NMR (CDCl₃) δ 2.64 (bs, 1 H, OH), 3.84 (s, 6 H, 2xOCH₃), 4.56 (s, 2 H, benzylic-CH₂), 6.79-6.89 (m, 3 H, ArH);

^13C NMR (CDCl₃) δ 55.58, 55.71 (2xOCH₃), 64.80 (benzylic-CH₂), 110.18, 110.76, 119.12 (3xArCH), 133.46, 148.17, 148.75 (ArC₉);

The benzyl alcohol 453 was re-dissolved in CHCl₃ (30 mL) and bromine (5.99 g, 37.5 mmol) diluted in the same solvent (20 mL), added dropwise over 15 minutes at 0°C. After the addition of the bromine solution the reaction mixture was stirred at 0°C for 30 minutes and for 2 hours at room temperature. The brownish solution was poured into 50 mL of saturated aqueous NaHCO₃ (fume hood!) and the organic layer separated. The aqueous layer was extracted with CHCl₃ (3 x 50 mL) dried with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was chromatographed (15% ethyl acetate in petroleum spirits) to afford dimethoxybromobenzyl bromide 451 as a colourless solid (7.42 g, 24 mmol, 96%);

^1H NMR (CDCl₃) δ 3.87, 3.88 (s each, 6 H, 2xOCH₃), 4.59 (s, 2 H, benzylic-CH₂), 6.92 and 7.01 (s each, 1 H each, ArH);

^13C NMR (CDCl₃) δ 34.13 (benzylic-CH₂), 56.04, 56.14 (2xOCH₃), 113.20 and 115.53 (ArCH), 114.83 (ArC₉CH₂Br), 128.67 (ArC₉Br), 148.49 and 149.72 (2x ArC₉OCH₃);

m/z: 312(M+1, 2%), 310(M⁺, 4%), 308(M-2, 2%), 232(9), 231(94), 230(9), 229(100), 186(7), 185(12), 107(30), 105(9), 92(14), 89(13), 77(30), 76(11),
2-Bromo-4,5-dimethoxybenzyl chloride

3,4-Dimethoxybenzaldehyde (2.49 g, 15 mmol) was dissolved in 15 mL of chloroform and cooled to 0 °C with the aid of an ice/acetone bath. The apparatus was fitted with a dropping funnel and Bromine (3.84 g, 24 mmol) in CHCl₃ (15 mL) was added dropwise to this cooled solution over a period of 15 minutes. The solution was stirred for a further 30 minutes at this temperature, the bath removed and the mixture allowed to stir for 12 hours at ambient temperature. It was then poured into 50 mL of saturated NaCl solution, extracted with CHCl₃ (3 x 50 mL) dried over MgSO₄, filtered, and the solvent removed under reduced pressure (caution must be observed with these bromo derivatives as they are known lachrymators) to yield crude 2-bromo-4,5-dimethoxybenzaldehyde (3.59 g, 14.64 mmol, 98%) as a solid. This residue was found to be spectroscopically pure and was directly used in the reduction of the benzaldehyde functionality after confirming its identity with ¹H and ¹³C data.

¹H NMR (CDCl₃) δ 3.92 and 3.97 (s each, 3 H each, 2xOCH₃), 7.05 and 7.40 (s each, 1 H each, ArH), 10.18 (s, 1 H, CHO);

¹³C NMR (CDCl₃) δ 56.05, 56.45 (2xOCH₃), 110.25 and 115.30 (2ArCH), 120.32 (ArC₄ CHO), 126.38 (ArC₄Br), 148.72, 154.35 (2xArC₄OCH₃), 190.69 (CHO);

A suspension of LiAlH₄ (0.68 g, 18 mmol) in diethyl ether (60 mL) was placed in a flask fitted with a continuous extraction apparatus together with a reflux condenser. The substrate benzaldehyde (2.94 g, 12 mmol) was placed in the extractor thimble and the solution heated at reflux. The substrate was observed to go into the solution gradually. After the extraction was complete the ethereal solution was allowed to remain at this same temperature for a further hour before being quenched by a 2:1 solution of H₂O-diethyl ether (25 mL) with caution. This was followed by the addition of 10 mL of H₂O and 25 mL of 10% HCl. The organic layer was then separated and the aqueous layer extracted with diethyl ether (6 x 25 mL). The combined organic layers were dried with MgSO₄, filtered and the solvent removed under reduced pressure to yield the required benzyl alcohol as a pale solid (2.83 g, 11.4 mmol, 95%). The crude alcohol was used directly in the next step without
purification upon analysis by $^1$H NMR.

$^1$H NMR (CDCl$_3$) $\delta$ 2.52 (bs, 1 H, OH), 3.85 (s, 6 H, 2xOCH$_3$), 4.65 (s, 2 H, benzylic-CH$_2$), 6.99 (s, 2 H, ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 56.89 and 56.06 (2xOCH$_3$), 64.56 (benzylic-CH$_2$), 111.58 and 115.16 (ArCH), 112.24 (ArC$_q$CH$_2$OH), 131.72 (ArC$_q$Br), 148.32 and 148.66 (ArC$_q$OCH$_3$);

The crude bromobenzyl alcohol (2.47 g, 10 mmol) was dissolved in a mixture of diethyl ether (30 mL) and THF (10 mL) due to its partial solubility in the former solvent. Thionyl chloride (2.38 g, 20 mmol) in ether (7 mL) was added to this solution using a dropping funnel with vigorous stirring over a period of 10 minutes during which the formation of a white solid precipitate was observed. The solution was stirred for a further 15 minutes after completion of addition and poured into 50 mL of saturated NaCl solution. The aqueous phase was then extracted with diethyl ether (3 x 50 mL), dried with MgSO$_4$, filtered and the solvent removed under reduced pressure. The residual solid was chromatographed (30% ethyl acetate in petroleum spirits) to yield the required bromobenzyl chloride 456 (2.21 g, 8.3 mmol, 83%);

$^1$H NMR (CDCl$_3$) $\delta$ 3.87 and 3.88 (s each, 3 H each, 2xOCH$_3$), 4.67 (s, 2H, benzylic-CH$_2$), 6.95 and 7.03 (s each, 1 H each, 2xArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 46.44 (benzylic-CH$_2$), 56.01 and 56.13 (2xOCH$_3$), 113.10 and 115.42 (ArCH), 114.45 (ArC$_q$CH$_2$Br), 128.47 (ArC$_q$Br), 148.50 and 149.68 (ArC$_q$OCH$_3$);

$m/z$: 268(M+2, 13%), 266(M^+, 40%), 264(M-2, 33%), 232(19), 231(98), 230(19), 229(100), 187(13), 186(13), 185(20), 143(10), 142(14), 110(16), 107(25), 92(10), 77(16), 75(11), 64(10), 63(19).
2-Bromo-4,5-dimethoxybenzylzinc bromide

Zinc dust or powder (1.77 g, 27 mmol) (purity 99%) was introduced to an oven-dried two-necked round bottom flask with a magnetic stirrer, fitted with a condenser and sealed with septa. Dry THF (18 mL) followed by 5 drops of 1,2-dibromoethane were syringed into this flask. 2-Bromo-4,5-dimethoxybenzyl bromide (2.79 g, 9 mmol) was dissolved in 36 mL of THF and 10% of this solution (3.6 mL) added dropwise to the zinc suspension over 3-5 minutes. Upon completion, Me₃SiCl (0.147 g, 1.35 mmol, 50% of Zn) was added rapidly to the solution with vigorous stirring. Immediate condensation of solvent was observed on the walls of the flask during which time the zinc turns into a deep black-grey colour. The remainder of the bromide solution was then added dropwise, often over 10-15 minutes maintaining condensation at a constant level. The heterogeneous solution (excess Zn) was stirred for 1.5 hours before use.

1-(2-Bromo-4,5-dimethoxybenzyl)-2-benzoyl-1,2-dihydroisoquinoline

The title compound was synthesised following the general procedures described for the synthesis of 430, except that the zinc organometallic reagent 457 was used instead of the Grignard reagent. Benzoyl chloride was used as the acylating agent in this reaction. The crude product on purification by flash chromatography (15% ethyl acetate in petroleum ether) gave the required isoquinoline derivative in 83% yield as a colourless solid; mp 133-135°C;

$^1$H NMR (CDCl₃) δ 3.02 and 3.27 (dd each, 1 H each, J = 6 and 13 Hz and 7 and 13 Hz, benzylic-CH₂), 3.63 and 3.85 (6 H each, 2xOCH₃), 5.80 (bd, 1 H, J = 7.7 Hz, 3-CH), 6.02 (bt, 1 H, J = 6.7 Hz, 1-CH), 6.48 (bd, 1 H, J = 7.7 Hz, 4-CH), 6.30 and 6.80-7.45 (m, 11 H, ArH);

$^{13}$C NMR (CDCl₃) δ 39.03 (benzylic-CH₂), 54.64 and 55.59 (1-CH), 55.72 and 55.98 (2xOCH₃), 109.32 (3-CH), 114.06, 115.01, 124.53, 126.64, 126.87, 126.96, 127.75, 127.97, 128.04, 128.17, 128.28, 128.44, 128.54, 130.60, 130.72 (4-CH and 8xAr-CH), 111.38, 115.43, 129.65, 131.74, 134.48 (7xAr-CH), 147.59,
6,7-Dimethoxy-1-(2-bromo-4,5-dimethoxy)-2-phenoxy carbonyl-1,2-dihydroisoquinoline

A single necked oven dried round bottom flask was charged with 6,7-dimethoxyisoquinoline 422 (1.13 g, 6 mmol) and sealed with a septum. Tetrahydrofuran (30 mL) was syringed into the flask and the resulting solution cooled to -23 °C with the aid of a dry ice/CCl4 bath. Phenyl chloroformate (1.01 g, 7.2 mmol) was syringed in dropwise with rapid stirring to ensure even formation of the isoquinolinium salt and the solution was allowed to stir at -23 °C for an hour after addition was complete. Freshly prepared 2-bromo-4,5-dimethoxybenzylzinc bromide (1.5 equiv., 9 mmol in 54 mL of THF) was added dropwise to this heterogeneous mixture which became completely homogenised on completion of addition. The solution was stirred for an hour at -23 °C and then allowed to equilibrate to room temperature. It was then poured into a mixture of saturated aqueous NaCl (10 mL) and 10 mL of water. The organic phase was separated and the aqueous portion extracted with ethyl acetate (5 x 30 mL), the combined extracts dried with MgSO4, filtered and the solvent removed under reduced pressure. The residue was chromatographed with a mixture of CH2Cl2, ethyl acetate and Petroleum spirits (1:1:1) to afford the product 458 as a colourless solid (3.08 g, 5.7 mmol, 95%), mp 187 °C;

1H NMR (CDCl3) δ 2.93-3.21 (m, 2 H, benzylic-CH2), 3.70-3.90 (s, 12 H, 4xOCH3), 5.63 and 5.74 (t each, 1 H, J = 7 Hz each, 1-CH), 5.88 and 6.03 (d each,
Chapter 7: Experimental

1 H, J = 7.8 Hz each, 4-CH), 6.28-7.42 (m, 10 H, ArCH);

13C NMR (CDCl3) δ 39.66 and 40.49 (benzyl-CH2), 55.49, 55.66, 55.86, 55.94, 55.98, 55.12 (1-C and 4xO-CH3), 108.00, 108.20, 109.50, 109.80, 110.02, 110.25, 112.20., 113.21, 114.05, 114.36, 115.14, 115.30, 121.10, 121.47, 122.30, 122.79, 125.44, 125.68, 129.09, 129.38 (11-Ar-CH) 123.10, 123.20, 123.85, 124.45, 128.37 (5xArCq), 147.78, 147.91, 147.97, 148.01, 148.22, 148.43, 148.48, 148.56 (4xAr*CqOCH3), 150.54, 150.83, 151.27, 151.83 (N*CO)

(* rotamers are observed for most carbon atoms);

m/z: 311(20), 310(100), 190(26), 189(7), 77(52); (CI) 542(M+2, 6%), 540(M+, 5%), 462(5), 310(10), 190(100);

Anal. Calcd. for C27H26N06Br: C, 60.01; H, 4.85; N, 2.59; Br, 14.79. Found: C, 60.26; H, 4.72; N, 2.57; Br, 15.06.

5,6,11,12-Tetrahydro-13-phenoxycarbonyl-5,11-iminodibenz[a,e]cyclooctane

6a,7-Dihydro-6-phenoxycarbonyldibenz[d,e]quinoline

Substrate 430 (4.20 g, 10 mmol) and AIBN (0.213 g, 1.5 mmol) were added to an oven dried two necked round bottom flask fitted with a reflux condenser. Dry degassed benzene (75 mL) was introduced to the flask and the resulting solution heated at reflux. A separate solution of Bu3SnH (4.37 g, 15 mmol) and AIBN (0.355 g, 2.5 mmol) in 50 mL of dry de-oxygenated benzene was then added to the heated substrate solution dropwise over a period of 5-6 hours with the aid of a syringe pump. After the addition was complete the solution was allowed to remain at this same temperature for 12 hours. The solution was then cooled, the solvent removed under reduced pressure and the residue chromatographed (10% ethyl acetate in petroleum spirits). Upon purification both compounds, 432 (1.47 g, 4.34 mmol, 43%) and 431 (1.91 g, 5.60 mmol, 56%) were obtained as white solids.
Chapter 7: Experimental

5,6,11,12-Tetrahydro-13-phenoxy carbonyl-5,11-iminodibenzo[a,e]cyclooctane

mp 148-150 °C;

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.95 (dd, 2 H, \(\text{J} = 11\) and 16 Hz, 6 and 12-CH\(_{ax}\)), 3.61 (m, 2 H, 6 and 12-CH\(_{eq}\)), 5.69 and 5.76 (d each, 2 H, \(\text{J} = 5.5\) and 5.8 Hz, 11 and 5-CH), 7.01-7.37 (m, 13 H, ArH);

\(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 36.77, 37.39 (6 and 12-CH\(_2\)), 49.81, 50.88 (5 and 11-CH), 121.71, 125.33, 126.33, 126.38, 126.61, 127.05, 127.20, 129.17, 129.25, 129.54 (13xArCH), 131.92, 132.47, 136.73, 136.97 (ArC\(_q\)), 151.16, 152.25 (NCO);

m/z: 342(M+1, 13%), 341(M\(^+\), 40%), 248(53), 247(12), 220(10), 219(10), 206(28), 205(100), 204(16), 203(14), 191(10), 178(11), 165(6), 130(6), 115(6), 103(6), 77(13), 65(9);

Anal. Calcd. for C\(_{23}\)H\(_{19}\)N\(_2\): C, 80.92; H, 5.61; N, 4.10. Found: C, 81.27; H, 5.93; N, 4.10.

6a,7-Dihydro-6-phenoxy carbonyldibenzo[de,gl]quinoline

mp 205-206 °C;

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.07 (bt, 1 H, 7-H\(_{p-ax}\)), 3.73 (bd, 1 H, 7-H\(_{p-eq}\)), 5.35 (dd, 1 H, \(\text{J} = 3.4\) and 18.7 Hz, 6a-H\(_{p-ax}\)), 5.65 (d, 1 H, \(\text{J} = 8.2\) Hz, 4-H), 6.95 (d, 1 H, \(\text{J} = 7.3\) Hz, 3-ArH), 7.10 (d, 1 H, \(\text{J} = 8.2\) Hz, 5-H), 7.19-7.44 (m, 9 H, ArH), 7.51 (d, 1 H, \(\text{J} = 7.7\) Hz, 1-ArH), 7.76 (d, 1 H, \(\text{J} = 7.7\) Hz, 11-ArH);

\(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 35.95 (b, 7-CH\(_2\)), 54.19 (6a-CH), 105.74 (4-CH), 121.61, 123.34, 123.53, 124.17, 125.06, 125.88, 127.57, 127.98, 128.17, 128.79, 129.48 (5-CH and 12xArCH), 128.53, 133.54, 133.63, 135.75 (6xAr*C\(_q\)), 150.82 (NCO), (* overlapping signals);

m/z: 340(M+1, 20%), 339(M\(^+\), 88%), 338(27), 246(59), 245(44), 228(38), 218(49),
Anal. Calcd. for C\textsubscript{23}H\textsubscript{17}N\textsubscript{2}O\textsubscript{2}: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.30; H, 5.06; N, 4.13.

5,6,11,12-Tetrahydro-13-ethoxycarbonyl-5,11-iminodibenzo[a,e]cyclooctane

6a,7-Dihydro-6-ethoxycarbonyldibenzo[de,fg]quinoline

The title compounds were synthesised following the general radical ring closure method described earlier for the preparation of 431 and 432. The crude product was chromatographed using 50% ethyl acetate in petroleum spirits to afford the following compounds.

5,6,11,12-Tetrahydro-13-ethoxycarbonyl-5,11-iminodibenzo[a,e]cyclooctane

Yield = 56%;

\[ \text{1H NMR (CDCl}_3\text{) } \delta \text{ 1.27 (t, 3 H, J = 7 Hz, -CO}_2\text{CH}_2\text{CH}_3\text{), 2.86 (d, 2 H, J = 17 Hz, 6 and 12-CH}_ax\text{), 3.49 (m, 2 H, 6 and 12-CH}_eq\text{), 4.18 (m, 2 H, -CO}_2\text{CH}_2\text{CH}_3\text{), 5.52 and 5.63 (d each, 2 H, J = 5.7 and 5.5 Hz, 11 and 5-CH), 6.94-7.19 (m, 8 H, ArH);} \]

\[ \text{13C NMR (CDCl}_3\text{) } \delta \text{ 14.69 (-CO}_2\text{CH}_2\text{CH}_3\text{), 36.70 and 37.11 (6 and 12-CH}_2\text{), 49.34, 50.11 (5 and 11-CH), 126.11, 126.19, 126.29, 126.59, 126.85, 126.97, 129.20, 129.49 (8xArCH), 132.15, 132.68, 137.10, 137.28 (ArC}_q\text{), 154.27 (NCO);} \]

\[ m/z: 294(M+1, 19%), 293(M^+, 85%), 264(5), 248(8), 221(17), 220(80), 218(17), 205(12), 204(20), 203(31), 202(100), 192(8), 191(7), 189(7), 178(9), 174(10), 158(14), 149(9), 130(32), 107(8), 103(9), 77(8), 62(17); \]
6a,7-Dihydro-6-ethoxycarbonyldibenzo[de,g]quinoline

Yield = 29%;

$^1$H NMR (CDCl$_3$) $\delta$ 1.35 (t, 3 H, $J = 7$ Hz, -CO$_2$CH$_2$CH$_3$), 2.97 (t, 1 H, $J = 13.7$ Hz, 7-H$_{p,ax}$), 3.61 (bd, 1 H, 7-H$_{p,eq}$), 4.28 (m, 2 H, -CO$_2$CH$_2$CH$_3$), 5.21 (dd, 1 H, $J = 3.6 \text{ and } 13.7$ Hz, 6a-H$_{p,ax}$), 5.50 (d, 1 H, $J = 8.2$ Hz, 5-H), 6.87 (d, 1 H, $J = 7.5$ Hz, 3-ArH), 6.94 (d, 1 H, $J = 8.2$ Hz, 4-H), 7.02-7.43 (m, 4 H, ArH), 7.44 (d, 1 H, $J = 6.8$ Hz, 1-ArH), 7.73 (d, 1 H, $J = 7.7$ Hz, 11-ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 13.57 and 14.44 (-CO$_2$CH$_2$CH$_3$), 36.16 (b, 7-CH$_2$), 53.63 (6a-CH), 62.17 and 62.26 (-CO$_2$CH$_2$CH$_3$), 104.30 (5-CH), 122.94, 123.46, 123.86, 125.57, 126.22, 126.27, 126.34, 126.38, 126.75, 127.44, 127.82, 127.92, 127.97, 128.09, 128.66 (4-CH and 7xAr*CH), 128.32, 128.82, 133.42, 133.77, 135.93 (6xAr*C$_q$), 153.97 (NCO), (* rotamers observed);

m/z: 292(M+1, 17%), 291(M$^+$, 74%), 290(M-1, 27%), 263(11), 262(44), 259(12), 257(18), 255(14), 246(20), 219(18), 218(100), 217(80), 216(50), 203(20), 202(87), 197(13), 189(24), 180(15), 179(13), 178(10), 177(12), 165(12), 158(13), 149(13), 130(39), 62(18), 57(21);

5,6,11,12-Tetrahydro-13-methoxycarbonyl-5,11-iminodibenzo[a,e]cyclooctane

6a,7-Dihydro-6-methoxycarbonyldibenzo[de,g]quinoline

The ring closed N-methoxy carbonyl derivatives were synthesised using the general radical ring closure procedure described for the preparation of 431 and 432. The crude product obtained was chromatographed using 5% ethyl acetate in petroleum spirits to afford the following compounds.
Chapter 7: Experimental

5,6,11,12-Tetrahydro-13-methoxycarbonyl-5,11-iminodibenzo[a,e]cyclooctane

Yield = 51%;

$^1$H NMR (CDCl$_3$) $\delta$ 2.86 (d, 2 H, $J = 16$ Hz, 6 and 12-CH$_{ax}$), 3.49 (m, 2 H, 6 and 12-CH$_{eq}$), 3.73 (s, 3 H, -CO$_2$CH$_3$), 5.51 and 5.63 (d each, 2 H, $J = 5.8$ and 5.6 Hz, 11 and 5-CH), 6.97-7.25 (m, 8 H, ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 36.67, 37.17 (6 and 12-CH$_2$), 49.53, 50.22 (5 and 11-CH), 52.69 (-CO$_2$CH$_3$), 126.17, 126.24, 126.29, 126.59, 126.91, 127.04, 129.22, 129.52 (8xArCH), 132.10, 132.62, 137.05, 137.20 (4xArC$_q$), 151.78, 152.63 (NCO);

m/z: 280(M$^+$, 34%), 279(M$^-$, 82%), 278(M-1, 31%), 234(10), 221(17), 220(55), 218(29), 217(16), 205(23), 204(40), 203(39), 202(18), 192(16), 191(16), 190(15), 189(40), 188(100), 178(16), 165(10), 144(31), 130(14), 132(12), 166(12), 115(22), 104(12), 103(23), 102(14), 91(18), 89(11), 77(24), 59(20);

Anal. Calcd. for C$_{18}$H$_{17}$N$_2$O$_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 76.98; H, 6.01; N, 4.68.

6a,7-Dihydro-6-methoxycarbonyldibenzo[de,g]quinoline

Yield = 36%;

$^1$H NMR (CDCl$_3$) $\delta$ 2.97 (t, 1 H, $J = 13$ Hz, 7-H$_{p_{-ax}}$), 3.61 (bd, 1 H, 7-H$_{p_{-eq}}$), 3.84 (s, 3 H, -CO$_2$CH$_3$), 5.22 (dd, 1 H, $J = 3.7$ and 13.6 Hz, 6a-H$_{p_{-ax}}$), 5.51 (d, 1 H, $J = 8.2$ Hz, 5-H), 6.88 (d, 1 H, $J = 7.7$ Hz, 3-ArH), 6.92 (d, 1 H, $J = 8.2$ Hz, 4-H), 7.19-7.34 (m, 4 H, ArH), 7.45 (d, 1 H, $J = 7.1$ Hz, 1-ArH), 7.74 (d, 1 H, $J = 7.7$ Hz, 11-ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 36.14 (b, 7-CH$_2$), 53.22 (-CO$_2$CH$_3$), 53.73 (6a-CH), 104.56 (5-CH), 123.03, 123.49, 123.92, 125.47, 127.49, 127.85, 128.02, 128.76 (4-CH and 7xArCH), 128.29, 133.47, 133.77, 135.89 (5xAr*C$_q$), 151.04 (NCO), (* overlapping signals);
Chapter 7: Experimental

$m/z$: 278(M+1, 25%), 277(M+, 65%), 276(M-1, 50%), 262(23), 257(11), 232(20), 231(17), 219(13), 218(35), 217(50), 216(1), 214(2), 203(22), 202(41), 191(17), 190(17), 189(38), 188(100), 177(15), 144(40), 129(25), 128(16), 115(12), 103(19), 102(15), 91(20), 77(11), 65(12), 59(23), 57(17);

Anal. Calcd. for C$_{18}$H$_{15}$NO$_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.91; H, 5.29; N, 4.78.

5,6,11,12-Tetrahydro-13-acetyl-5,11-iminodibenzo[a,e]cyclooctane

6a,7-Dihydro-6-acetyldibenzo[de,g]quinoline

The title N-acetyl derivatives were prepared following the general radical ring closure procedure described for the preparation of 431 and 432. The crude product obtained was chromatographed using 30% and 50% ethyl acetate in petroleum spirits to afford the following products.

5,6,11,12-Tetrahydro-13-acetyl-5,11-iminodibenzo[a,e]cyclooctane

Yield = 55%;

$^1$H NMR (CDCl$_3$) $\delta$ 2.20 (s, 3 H, -COCH$_3$), 2.87 and 2.98 (d each, 2 H, J = 15.5 and 16.5 Hz, 6 and 12-CH$_{ax}$), 3.45 and 3.50 (t each, 2 H, J = 5 Hz each, 6 and 12-CH$_{eq}$), 5.24 and 6.08 (d each, 2 H, J = 5.5 Hz each, 11 and 5-CH), 6.95-7.21 (m, 8 H, ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 21.21 (-COCH$_3$), 36.60 and 37.77 (6 and 12-CH$_2$), 49.98 and 52.82 (5 and 11-CH), 126.10, 126.22, 126.47, 126.82, 126.90, 127.35, 128.99, 129.60 (8xArCH), 131.45, 132.90, 136.36, 137.10 (4xArC$_q$), 167.52 (NCO);

$m/z$: 264(M+1, 32%), 263(M+, 100%), 262(17), 248(20), 222(16), 221(49), 220(90), 219(13), 218(25), 217(19), 216(10), 206(10), 205(17), 204(29), 203(27), 202(18), 192(17), 191(20), 189(16), 178(18), 171(10), 172(35), 165(13), 131(24), 130(100), 128(15), 117(18), 115(18), 105(10), 104(17), 103(22), 89(12), 79(11), 78(12), 77(23), 65(10), 63(10);

Anal. Calcd. for C$_{18}$H$_{17}$NO: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.88; H, 6.60; N, 4.92.
6a,7-Dihydro-6-acetyldibenzo[de,g]quinoline

Yield = 30%;

$^1$H NMR (CDCl$_3$) $\delta$ 2.30 (s, 3 H, -COCH$_3$), 2.86 (t, 1 H, $J = 13.5$ Hz, 7-H$_p$-ax), 3.67 (bd, 1 H, 7-H$_p$-eq), 5.40 (dd, 1 H, $J = 3.6$ and 13.6 Hz, 6a-H$_p$-ax), 5.57 (d, 1 H, $J = 8$ Hz, 5-H), 6.63 (bd, 1 H, $J = 7.7$ Hz, 3-ArH), 6.91 (d, 1 H, $J = 8$ Hz, 4-H), 7.22-7.34 (m, 4 H, ArH), 7.49 (d, 1 H, $J = 7.7$ Hz, 1-ArH), 7.75 (d, 1 H, $J = 7.7$ Hz, 11-ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 22.78 (-COCH$_3$), 34.85 (b, 7-CH$_2$), 53.24 (6a-CH), 105.78 (5-CH), 123.33, 123.44, 123.89, 125.51, 127.43, 127.95, 128.95 (4-CH and 7xAr*CH), 127.78, 129.61, 133.60, 133.69, 136.14 (5xArC$_q$), 169.45 (NCO), (* overlapping signals);

$^{m/z}$: 262(M+1, 18%), 261(M$^+$, 46%), 220(17), 219(43), 218(100), 217(75), 216(36), 215(7), 214(10), 204(8), 203(13), 202(25), 191(13), 190(13), 189(27), 188(7), 187(8), 176(5), 165(8), 163(8), 108(5), 63(5);

Anal. Calcd. for C$_{18}$H$_{15}$NO: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.48; H, 5.99; N, 4.97.

13-Benzoyl-2,3-dimethoxy-5,6,11,12-tetrahydro-5,11-iminodibenzo[a,e]cyclooctane

The ring closed N-benzoyl derivative was prepared following the general radical ring closure procedure described for the preparation of 431 and 432. The crude product obtained was chromatographed (ethyl acetate, petroleum spirits, CH$_2$Cl$_2$: 1:3:4) to afford the title compound in 87% yield.

$^1$H NMR (CDCl$_3$) $\delta$ 2.86 (m, 2 H, 6 and 12-CH$_{ax}$), 3.45 (overlapping t, 2 H, 6 or 12-CH$_{eq}$), 3.61 and 3.66 (bt each, 2 H, 6 or 12-CH$_{eq}$), 3.77 and 3.88 (s each, 6 H, 2xOCH$_3$), 5.10 (dd, 1 H, $J = 5$ and 20 Hz, 11 or 5-CH), 6.08 (dd, 1 H, $J = 5$ and 16
Hz, 11 or 5-CH), 6.43-7.29 (m, 11 H, ArH);

$^{13}$C NMR (CDCl$_3$) δ 36.27, 36.43, 37.73, 37.74, 37.80 (6 and 12-*CH$_2$), 47.61, 47.98, 53.44, 53.72 (5 and 11-*CH), 55.72, 55.94, 56.07 (2xOCH$_3$), 126.17, 126.24, 126.29, 126.59, 126.91, 127.04, 129.22, 129.52 (8xArCH), 108.64, 109.45, 111.37, 111.74, 125.91, 126.15, 126.55, 126.83, 127.08, 127.37, 128.46, 128.60, 129.11, 129.60, 129.91 (5xAr*C$_q$), 146.85, 147.55, 147.94, 152.91 (2xAr*C$_q$OCH$_3$), 169.30 (NCO);

m/z: 386(M+1, 34%), 385(M+, 100%), 384(13), 295(14), 294(66), 281(15), 280(67), 265(12), 264(36), 251(13), 249(11), 234(16), 106(10), 105(98), 77(54), 61(14);

**N-Phenoxy carbonylpavine or 5,6,11,12-Tetrahydro-2,3,8,9-tetramethoxy-13-phenoxycarbonyl-5,11-iminodibeno[a,e]cyclooctane**

6a,7-Dihydro-1,2,9,10-tetramethoxy-6-phenoxycarbonyldibenzo[de,g]quinoline

The benzylisoquinoline 458 (2.97 g, 5.5 mmol) and AIBN (0.12 g, 0.83 mmol, 0.15 equiv.) were dissolved in dry de-oxygenated benzene (42 mL) and heated at reflux. A solution of Bu$_3$SnH (2.08 g, 7.15 mmol) and AIBN (0.20 g, 1.38 mmol, 0.25 equiv.) in de-gassed benzene was added to this solution over 5-6 hours with the aid of a syringe pump. The solution was allowed to remain at this temperature for 12 hours, the solvent removed under reduced pressure and the crude product chromatographed using CH$_2$Cl$_2$, ethyl acetate and petroleum spirits (1:1:1) as the eluant. While the highly chromophoric band having a higher R$_f$ value than the starting material gave 461 (1.07 g, 2.33 mmol, 42%) as a thick oil, the more polar band afforded 462 (1.21 g, 2.62 mmol, 48%) as a colourless solid.
N-Phenoxycarbonylpavine or 5,6,11,12-Tetrahydro-2,3,8,9-tetramethoxy-13-phenoxycarbonyl-5,11-iminodibenzo[ae]cyclooctane

mp 220-225 °C;

$^1$H NMR (CDCl$_3$) $\delta$ 2.82 and 2.86 (d each, 2 H, $J = 15.9$ and 15.8 Hz, 6 and 12-H$_{ax}$), 3.53 (m, 2 H, 6 and 12-H$_{eq}$), 3.79, 3.80, 3.86 and 3.88 (s each, 3 H each, 4xOCH$_3$), 5.58 and 5.66 (d, 1 H each, $J = 5.0$ and 5.4 Hz, 5-H), 6.50, 6.52, 6.69 and 6.70 (s each, 1 H each, 4xArH), 7.10-7.38 (m, 5 H, 5xArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 36.12 and 36.74 (6 and 12-CH$_2$), 49.47 and 50.51 (5 and 11-CH), 55.71, 55.95 (4xOCH$_3$), 109.00, 109.20, 111.52, 111.70 (1, 4, 7, 10-ArCH), 121.68, 125.30, 129.23 (NCO$_2$ArCH), 123.76, 124.32, 128.45, and 128.78 (4a, 6a, 10a, 12a-ArC$q$), 147.61, 147.66, 148.14, 148.24 (2, 3, 8, 9-ArC$q$OCH$_3$), 151.17, 152.35 (NCO and -NCO$_2$ArC$q$);

m/z: 462(M+1, 40%), 461(M+, 100%), 418(12), 416(12), 368(30), 326(20), 325(66), 317(17), 315(53), 314(21), 313(75), 312(45), 311(61), 310(34), 309(25), 294(12), 259(15), 257(24), 255(18), 199(17), 197(25), 195(18), 177(26), 175(19), 121(14), 119(12), 77(24), 57(54);

Anal. Calcd. for C$_{27}$H$_{27}$N$_6$O$_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.05; H, 5.93; N, 3.05.

6a,7-Dihydro-1,2,9,10-tetramethoxy-6-phenoxycarbonyl-dibenzo[de,gl]quinoline

$^1$H NMR (CDCl$_3$) $\delta$ 2.95 (bt, 1 H, 7-H$_{p-ax}$), 3.53 (bd, 1 H, 7-H$_{p-eq}$), 3.66, 3.88, 3.92 (s each, 12 H, 4xOCH$_3$), 5.14 (bd, 1 H, $J = 11.7$ Hz, 6a-H$_{p-ax}$), 5.56 (d, 1 H, $J = 8$ Hz, 5-H), 6.51 (s, 1 H, 3-ArH), 6.77 (s, 1 H, 8-ArH), 7.06 (d, 1 H, $J = 8$ Hz, 4-H), 7.18-7.44 (m, 5 H, ArH), 7.51 (d, 1 H, $J = 7.7$ Hz, 1-ArH), 8.07 (s, 1 H, 11-ArH);
\[ \text{13C NMR (CDCl}_3) \delta 54.66, 55.74, 55.91 (4xOCH}_3), 35.99 (b, 7-\text{CH}_2), 59.99(6a-\text{CH}), 105.61 (5-\text{CH}), 107.64, 111.00, 111.59, 121.64, 124.25, 125.84, 129.45 (4-\text{CH} \text{ and 8xArCH}), 121.85, 123.64, 123.74, 123.85, 127.35, 130.13 (6xAr*\text{C}^\text{q}), 147.53, 148.33, 150.81, 152.81 (4xAr\text{C}_3O\text{CH}_3), 153.82 (\text{NCO}); \]

\[ m/z: 460(\text{M+1}, \text{ 32%}), 459(\text{M}^+, \text{ 100%}), 444(17), 428(16), 336(13), 322(16), 308(14), 307(40), 300(28), 244(14), 155(20), 151(26), 99(34), 77(26), 71(16), 55(14); \]

Anal. Calcd. for \( \text{C}_{27}\text{H}_{25}\text{N}_6\text{O}_6; \text{ C, 70.58; H, 5.48; N, 3.05.} \) Found; C, 70.29; H, 5.52; N, 2.81.

**5,6,11,12-Tetrahydro-13-methyl-5,11-iminodibenzo[\text{a,e}]cyclooctane**

The bridged tetracycle 431 (0.85 g, 2.5 mmol) in an oven dried round bottom flask was dissolved in THF (40 mL) and cooled to 0 °C with the aid of an ice/acetone bath. LiAlH\(_4\) (0.38 g, 10 mmol) was introduced to the reaction solution portion wise. The mixture was allowed to stir at 0 °C for 2 hours and 3 hours at room temperature on completion of addition. The solution was diluted with 20 mL of diethyl ether, cooled in an ice bath and wet ether (1:1) added (15 mL) to neutralise the excess reducing agent. The solution was stirred for 5 minutes and quenched with 15% aqueous NaOH (10 mL) at the same temperature. It was then poured into 20 mL of water, the alumino residues filtered and extracted with diethyl ether (6 x 20 mL). The combined solution of organic fractions was dried with K\(_2\text{CO}_3\), filtered and the solvent removed under reduced pressure. The crude oil was purified by radial preparative layer chromatography (ethyl acetate) to afford the product as a colourless oil (0.49 g, 2.09 mmol, 83%);

\[ \text{1H NMR (CDCl}_3) \delta 2.53 (s, 3 H, NCH}_3), 2.70 (d, 2 H, J = 16.5 \text{ Hz, 6 and 12-H}_\text{ax}), 3.51 (dd, 2 H, J = 6 and 16.5 \text{ Hz, 6 and 12-H}_\text{eq}), 4.12 (d, 2 H, J = 6 \text{ Hz, 5 and 11-H}), 6.94-7.13 (s, 8 H, 8x\text{ArH}); \]

\[ \text{13C NMR (CDCl}_3) \delta 34.05 (6 \text{ and 12-CH}_2), 40.93 (\text{NCH}_3), 56.69 (5 \text{ and 11-CH}), 125.95, 126.47, 127.34, 129.13 (8x\text{ArCH}), 132.07, 129.84 (4a, 10a-\text{ArC}_3), 129.84 (6a, 12a-\text{ArC}_3); \]
Chapter 7: Experimental

\[ m/z: \text{236}(M+1, 20\%), \text{235}(M^+, 53\%), \text{234}(40), \text{220}(5), \text{218}(5), \text{145}(20), \text{144}(100), \text{115}(7), \text{103}(6), \text{91}(7), \text{89}(16), \text{70}(6), \text{61}(16); \]

Anal. Calcd. for C\(_{17}\)H\(_{17}\)N: C, 86.77; H, 7.28; N, 5.95. Found: C, 87.22; H, 7.55; N, 5.73.

(±)-Argemonine or 5,6,11,12-Tetrahydro-2,3,8,9-tetramethoxy-13methyl-5,11-iminodibenzo[a,e]cyclooctane

The bridged tetracycle 462 (0.46 g, 1 mmol) was dissolved in THF with slight warming in an oven dried round bottom flask and cooled to 0 °C (ice/acetone bath). To this solution LiAlH\(_4\) (0.15 g, 4 mmol) was added in portions over 5 minutes and stirred for 2 hours at 0 °C and 5 hours at room temperature. The solution was diluted with diethyl ether cooled in an ice bath and 2 mL of wet ether (1:1) added with caution to neutralise the excess reducing agent. This was followed by the addition of 4 mL of 15% aqueous NaOH. The solution was stirred for a further 10 minutes and poured into 10 mL of water. The resulting alumino residues were filtered, the organic layer separated and the aqueous portion extracted further with ethyl acetate (6 x 10 mL). The combined solution of the organic extracts was dried with K\(_2\)CO\(_3\), filtered and the solvent removed under reduced pressure to afford the natural product 401 (0.323 g, 0.91 mmol, 91%) as a colourless solid, mp 137 °C;

\[ \text{1H NMR (CDCl}_3\text{): } \delta 2.54 (s, 3 H, NCH}_3\), 2.60 (d, 2 H, J = 16 Hz, 6 and 12-H\(_{ax}\)), 3.40 (dd, 2 H, J = 5.5 and 16 Hz, 6 and 12-H\(_{eq}\)), 3.78 and 3.85 (s, 6 H each, 4xOCH\(_3\)), 4.01 (d, 2 H, J = 5.5 Hz, 5 and 11-H), 6.45 and 6.61 (s, 2 H each, 4xArH);

\[ \text{13C NMR (CDCl}_3\): } \delta 33.51 (6 and 12-CH\(_2\)), 40.85 (NCH\(_3\)), 55.61, 55.86 (4xOCH\(_3\)), 56.33 (5 and 11-CH), 109.86, 111.35 (1, 4, 7, 10-ArCH), 123.80, 129.84 (4a, 6a, 10a, 12a-ArC\(_q\)), 147.36, 147.72 (2, 3, 8, 9-ArC\(_q\)OCH\(_3\));

\[ m/z: \text{356}(M+1, 16\%), \text{355}(M^+, 52\%), \text{354}(35), \text{340}(5), \text{338}(5), \text{206}(5), \text{205}(25), \text{204}(100), \text{191}(3), \text{188}(7), \text{177}(7), \text{160}(4). \]
Chapter 7: Experimental

Anal. Calcd. for C$_{21}$H$_{25}$NO$_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.22; H, 7.39; N, 3.65.

5,6,6a,7-Tetrahydro-6-methyl-4H-dibenzo[de,g]quinoline

Compound 432 (102 mg, 0.3 mmol) dissolved in 2 mL of THF was added to a ice cooled suspension of LiAlH$_4$ (114 mg, 3 mmol). The ice bath was removed after 5 minutes and the solution was allowed to stir at room temperature while monitoring the disappearance of starting material on TLC. On complete consumption of starting material, often within 5 hours the solution was again cooled to 0 °C and carefully treated with ice to neutralise excess LiAlH$_4$. After 5 minutes of stirring the organic solvents were removed from the dark green coloured solution under reduced pressure and 5 mL of a 1:1.5 mixture of water and methanol added. Next NaBH$_4$ (113 mg, 3 mmol) was added to this heterogeneous mixture. A gradual colour change of the reaction solution from dark green to orange was observed within 10 minutes. The solution was left to stir for 12 hours at room temperature and poured into 10 mL of 30% aqueous NaOH solution. The aqueous portion was extracted with ethyl acetate (4 x 30mL) dried with Na$_2$SO$_4$, filtered and the solvents removed under reduced pressure. The residue was purified by radial preparative layer chromatography (ethyl acetate) to afford the product (50.8 g, 0.2 mmol, 72%) as a thick oil:

$^1$H NMR (CDCl$_3$) $\delta$ 2.55 (dt, 1 H, $J = 4$ and 12 Hz, 5-H$_{p-ax}$), 2.57 (s, 3 H, NCH$_3$), 2.71 (t, 1 H, $J = 14$ Hz, 7-H$_{p-ax}$), 2.76 (dd, 1 H, $J = 4$ and 17 Hz,4-H$_{p-ax}$), 3.08 (dd, 1 H, $J = 5.5$ and 12 Hz, 5 and 11-H), 3.15-3.27 (m, 3 H, 4-H$_{p-eq}$, 6-H$_{p-ax}$ and 7-H$_{p-eq}$), 7.08 (d, 1 H, $J = 7$ Hz, 3-ArH), 7.20-7.34 (m, 4 H, 2, 8, 9 and 10-ArH), 7.56 (d, 1 H, $J = 8$ Hz, 1-ArH), 7.72 (d, 1 H, $J = 7$ Hz, 11-ArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 29.01 (4-CH$_2$), 34.09 (7-CH$_2$), 43.94 (NCH$_3$), 53.36 (5-CH$_2$), 61.99 (6a-CH), 121.80, 123.72, 126.84, 127.33, 127.51, 127.98, 128.36 (7xArCH), 133.39, 133.44, 133.70, 134.27, 135.22 (5xArC$_q$);

m/z: 235(M$^+$, 53%), 234(92), 233(23), 232(18), 231(17), 220(23), 219(11), 218(20), 217(28), 216(24), 204(19), 203(13), 202(10), 193(10), 192(61), 191(34), 189(25), 179(12), 178(13), 165(14), 149(34), 113(11), 111(14), 99(11), 97(23),
Chapter 7: Experimental

95(12), 85(38), 83(33), 81(13), 73(24), 71(61), 70(20), 69(35), 60(20), 57(100), 56(18), 55(40);

HRMS exact mass calcd. for C_{17}H_{17}N_{2} 235.1361, found 335.1350. HRMS exact mass calcd. for C_{17}H_{16}N_{2} 234.1283, found 234.1283. (see chapter 4 for explanation).

(+)-Glaucine or 5,6,6a,7-Tetrahydro-1,2,9,10-tetramethoxy-6-methyl-4H-dibenzo[de,g]quinoline 434

The N-phenoxycarbonyl derivative 461 was subjected to the same procedure as described above for the preparation the model glaucine compound 448. The crude product from the reaction was purified by preparative layer chromatography (ethyl acetate) to afford (+)-glaucine (72%) as a colourless solid; mp 132-135 °C;

$^1$H NMR (CDCl$_3$) δ 2.55 (s, 3 H, NCH$_3$), 2.51-2.70 (m, 3 H, 4-H$_{p-ax}$, 5-H$_{p-ax}$ and 7-H$_{p-ax}$), 2.99-3.08 (m, 4 H, 4-H$_{p-eq}$, 5-H$_{p-eq}$, 6-H$_{p-ax}$ and 7-H$_{p-eq}$), 6.59 (s, 1 H, 3-ArH), 6.78 (s, 1 H, 8-ArH), 8.10 (s, 1 H, 11-ArH);

$^{13}$C NMR (CDCl$_3$) δ 29.18 (4-CH$_2$), 34.48 (7-CH$_2$), 43.96 (NCH$_3$), 53.27 (5-CH$_2$), 55.57, 55.76, 55.89, 62.53 (4xOCH$_3$), 62.53 (6a-CH), 110.32, 110.76, 111.54 (3xArCH), 124.44, 126.87, 127.06, 128.85, 129.26 (5xArC$_q$), 147.42, 147.94, 151.92 (ArC$_q$OCH$_3$);

m/z: 356(M+1, 39%), 355(M$^+$, 99%), 354(M-1, 100%), 341(23), 340(71), 328(12), 325(25), 324(59), 323(12), 312(27), 308(17), 297(22), 282(15), 281(33), 162(12), 149(32), 127(10), 111(13), 97(19), 95(12), 85(13), 83(23), 73(13), 71(29), 70(15), 69(27), 57(50), 55(34).

HRMS exact mass calcd. for C$_{21}$H$_{25}$NO$_4$ 355.1784, found 355.1773. HRMS exact mass calcd. for C$_{21}$H$_{24}$NO$_4$ 354.1705, found 354.1701. (see chapter 4 for explanation).
Chapter 7: Experimental

(1R,2S,5R)-(−)-Menthyl Chloroformate

Menthyl chloroformate was prepared following two published procedures. The first, used to prepare adamantyl chloroformate was observed to yield essentially pure crude chloroformates while the latter resulted in traces of quinoline in the crude mixture. These crude chloroformates were found to be extremely difficult to distil and the method that provided pure crude chloroformates was desirable.

(−)-Menthol (7.81 g, 50 mmol) and finely ground K2CO3 (35 g, 250 mmol) were introduced to a two necked round bottom flask equipped with a large stirrer magnet and fitted with a pressure equalising dropping funnel. To this mixture freshly distilled benzene (50 mL) was added and stirred vigorously. Once the menthol has dissolved the solution was cooled to −10 °C with the aid of an ice/acetone bath and a 1.92 M solution of phosgene (52 mL, 100 mmol) in toluene added dropwise over 30 minutes with the aid of the dropping funnel. The solution was stirred for a further 30 minutes at this temperature and for 3 days at room temperature. The solids were filtered through a pad of celite, washed with ether, and the solvent removed under reduced pressure. The residual colourless oil was redissolved in dry diethyl ether in 10 mL, filtered again to remove any traces of K2CO3 and the solvent removed to afford pure menthyl chloroformate (10.75 g, 49 mmol, 98%);

A solution of (−)-menthol (1.72 g, 11 mmol) and quinoline (3.5 g, 27 mmol) dissolved in toluene (40 mL) was cooled to 0 °C using an ice bath. To this solution a 1.92 M solution of phosgene in toluene (9.2 mL, 17.76 mmol) was added over 30 minutes and stirred for a further half an hour. The solution was brought to room temperature and allowed to stir for 24 hours. It was then diluted with 20 mL of diethyl ether and 10% HCl (30 mL) added. The solution was stirred for a further 10 minutes and the organic layer separated and the aqueous part extracted with diethyl ether (3 x 20 mL). The solution of combined organic extracts was washed with 20 mL of saturated aqueous NaCl, dried with MgSO4, filtered and the solvent removed. The crude product contained traces of quinoline on spectroscopic analysis. The crude could not be distilled even under high vacuum due to frothing and bumping.

1H NMR (CDCl₃) δ 0.81, 0.93 and 0.94 (d each, 3 H each, J = 7, 7 and 6.5 Hz, 3xCH₃), 0.86-1.21 (m, 3 H, 5-CH and 3 or 4-CH₂), 1.48 (m, 2 H, 3 or 4-CH₂), 1.70 (m, 2 H, 6-CH₂), 1.95 (dseptet, 1 H, J = 2.6 and 7 Hz, 8-CH), 2.14 (m, 1 H.
2-CH), 4.74 (dt, 1 H, J = 4.5 and 11 Hz, 1-CH);

\[ ^{13}C \text{ NMR (CDCl}_3) \delta 16.25, 20.52, 21.82, 26.27, 31.47 \text{ and } 46.81 \text{ (3xCH}_3 \text{ and } 3xCH), 23.39, 33.79 \text{ and } 40.12 \text{ (3xCH}_2 \text{), 84.01 (1-CH)}; \]

**(1R,2S,5R)-8-Phenylmenthyl chloroformate**

(-)-8-Phenylmenthyl chloroformate was synthesised according to the second method outlined for the preparation of menthyl chloroformate. For the present reaction (-)-8-phenylmenthol (1.44 g, 6.2 mmol), quinoline (1.97 g, 15.25 mmol) and a 1.92 M solution of phosgene (8.27 mL, 9.9 mmol) in toluene (22.5 mL) were utilised. The crude product isolated was orange in colour which by \(^1H\) NMR was found to contain traces of quinoline. The crude yield from the reaction was quantitative.

\[ ^{1}H \text{ NMR (CDCl}_3) \delta 0.72-1.23 \text{ (m, 6 H, 3xCH}_2 \text{), 0.83 (d, 3 H, J = 6.5 Hz, CH}_3 \text{), } 1.25 \text{ (s, 3 H, CH}_3 \text{), 1.34 (s, 3 H, CH}_3 \text{), 1.59 (m, 1 H, 5-CH), 3.99 (m, 1 H, 2-CH), 4.72 (dt, 1 H, J = 4.5 and 10.5 Hz, 1-CH), 7.05-7.44 (m, 5 H, ArH)}; \]

\[ ^{13}C \text{ NMR (CDCl}_3) \delta 21.44, 24.47, 26.41, 31.13, 33.89, 50.26 \text{ (3xCH}_3 \text{ and 3xCH), 26.65, 39.57, 40.75 \text{ (3xCH}_2 \text{), 83.56 (1-CH), 125.17, 125.38, } 128.01 \text{ (3xArCH), 149.43, 149.52 (ArCq and CO}) \]

**1-(2-Bromo-4,5-dimethoxy)-6,7-dimethoxy-2-menthloxycarbonyl-1,2-dihydroisoquinoline**

Dimethoxyisoquinoline **316** (1.13 g, 6 mmol) was introduced into an oven dried round bottom flask, purged with nitrogen and sealed with a septum. Tetrahydrofuran (40 mL) was syringed into the flask and immersed in a dry ice/acetone cooling bath and was allowed to equilibrate to \(-78^\circ C\). Freshly prepared menthyl chloroformate in dry THF (10 mL) was added dropwise to the
solution over 5 minutes and allowed to stir for 45 minutes. On addition of each drop of the chloroformate the solution became increasingly viscous due to the formation of N-methyloxycarbonylisoquinolinium salt. A freshly prepared solution of 2-bromo-4,5-dimethoxy-benzylzinc bromide 457 (9 mmol) (preparation described earlier in this section) was added to this salt dropwise with the aid of a syringe over a period of 15 minutes while maintaining the temperature of the cooling bath around -78 °C. The thick solution gradually became non viscous during the addition and then a sticky solid began to form on the bottom of the flask. After the addition was complete the solution was stirred for a further 45 minutes at this temperature, the cooling bath was removed and the solution quenched with 30 mL of saturated aqueous NaCl. The solution was allowed to reach to room temperature, water added just to dissolve the white precipitate and extracted with ethyl acetate (3 x 50 mL). The combined solution of the extracts was dried with MgSO₄, filtered and the solvent removed under reduced pressure. The residue was chromatographed with 20% ethyl acetate in petroleum spirits. The band eluting with a Rf value of 0.3 gave the required precursor 507 (3.46 g, 5.75 mmol, 96%) as a colourless solid; mp 155-167 °C; [α]D +15.2 (c 1.00, CHCl₃);

1H NMR (CDCl₃) δ 0.69-2.06 (m, 18 H, menthyl-3xCH₃, 3xCH₂, 3xCH), 2.85-3.09 (m, 2 H, benzylic-CH₂), 3.59, 3.69, 3.72, 3.73, 3.74, 3.83, 3.85, 3.86 and 3.87 (s, 12 H, 4xOCH₃), 4.57 and 4.77 (dt, 1 H, J = 4.3 and 11 Hz, 1-CH-menthyl), 5.46 and 5.64 (m, 1 H, 1-CH), 5.76, 5.86, 5.91 (d, 1 H, J = 7.8 Hz, 3-CH), 6.04-7.01* (s, 4 H, 4xArH), 6.75, 6.79, 6.92* (d, 1 H, J = 7.8 Hz, 4-CH), (* rotamer signals observed);

13C NMR (CDCl₃) δ 15.63, 16.16, 16.45, 16.53, 20.62, 20.73, 20.80, 21.25, 21.94, 22.00, 25.80, 26.20, 26.45, 26.51, 31.15, 31.25, 31.31, 31.39, 47.04, 47.11, 47.20, 47.30* (menthyl-3xCH₃ and 3xCH), 22.70, 23.40, 23.54, 29.64, 29.68, 34.20, 34.22, 34.25, 34.31, 40.65, 41.09, 41.11, 41.20, 41.22, 41.29* (menthyl-3xCH₂), 39.46, 39.78, 39.80, 39.88, 40.05* (benzylic-CH₂), 54.72, 54.79, 54.94, 55.12, 55.55, 55.66, 55.71, 55.78, 55.85, 55.98* (1-CH and 4xOCH₃), 76.15, 76.29, 76.37* (menthyl-1-CH), 107.78, 107.96, 108.21, 108.59, 110.06, 110.47, 113.98, 114.59, 114.76, 114.94, 115.01 (4xArCH and 3-CH), 115.49, 123.53, 123.56, 123.77, 124.20, 128.64 (4xArC q), 122.87, 122.93 (4-CH), 147.72, 147.76, 148.13, 148.39 (4xArC₀OCH₃), 152.44, 153.23 (NCO);

m/z: (EI) 500(2), 463(1), 462(4), 460(4), 458(2), 446(2), 372(38), 235(18), 234(96), 232(76), 230(74), 229(100), 191(19), 190(58), 119(100), 189(17), 85(19),
83(81), 81(17). (Cl) 605(M+4, 22%), 604(M+3, 51%), 603(M+2, 22%), 602(M+1, 48%), 524(16), 483(24), 481(24), 420(17), 415(32), 373(27), 372(74), 340(30), 231(18), 229(18), 191(24), 190(100), 189(16), 134(17);

Anal. Calcd. for C_{31}H_{40}N_{6}Br: C, 61.79; H, 6.69; N, 2.32; Br, 13.26. Found: C, 61.41; H, 6.76; N, 2.07; Br, 13.28.

1-(2-Bromo-4,5-dimethoxy)-6,7-dimethoxy-2-(8-phenylmenthlyoxy-carbonyl)-1,2-dihydroisoquinoline

Synthesis of the title compound was achieved following the general procedure outlined above for the preparation of N-menthylisoquinoline 507. Freshly prepared (−)-8-phenylmenthyl chloroformate, instead of the menthyl derivative described, was utilised in this experiment to afford a diastereomeric mixture of the above title compound (3.87 g, 5.7 mmol, 95%) as a colourless solid; mp 72-75 °C; [α]D –60.5 (c 0.58, CHCl3);

\[ \begin{align*}
\text{H} & \text{NMR (CDCl}_3\text{) } \delta 0.72-2.34 \text{ (m, 17 H, menthyl-3xCH}_3\text{, 3xCH}_2\text{, 3xCH), 2.77 and} \\
& 2.93 \text{ (m, 2 H, benzylic-CH}_2\text{), 3.53, 3.67, 3.70, 3.72, 3.83, 3.84 and 3.88 (s, 12 H, 4xOCH}_3\text{), 4.81 (m, 1 H, 1-CH-menthyl), 5.33-7.33 (m, 12 H, 1-CH, 3-CH, 4-CH, 9xArH);} \\
\text{13C NMR (CDCl}_3\text{) } \delta 21.72, 21.76, 24.60, 26.07, 26.31, 26.60, 28.36, 31.29, 50.48, 50.97, 51.06^* \text{ (menthyl-3xCH}_3\text{ and 3xCH), 26.74, 26.89, 34.51, 34.56,} \\
& 41.71, 41.92, 42.09^* \text{ (menthyl-3xCH}_2\text{), 39.32, 39.54, 39.68, 39.79, 39.84^*} \\
& \text{ (benzylic-CH}_2\text{), 54.40, 54.63, 54.96, 55.78, 55.96, 56.10^* \text{(1-CH and 4xOCH}_3\text{),} \\
& 76.14, 76.35, 76.49^* \text{(menthyl-1-CH), 107.26, 107.55, 107.63, 107.70, 107.85,} \\
& 108.40, 109.98, 110.50, 110.71, 113.91, 114.58, 114.70, 114.91, 115.09^* \\
& \text{(4xArCH and 3-CH), 122.55, 123.05, 123.22, 125.07, 125.14, 125.25, 127.73,} \\
& 127.82, 128.19 \text{(5xArCH and 4-CH), 114.97, 115.67, 123.32, 123.44, 123.61,} \\
& 124.08, 124.15, 128.67, 128.81 \text{(6xArC}_q\text{),} 147.05, 147.15, 147.92, 147.94,} \\
& 148.19, 148.30, 148.35, 151.23, 151.77, 152.27, 152.58 \text{(4xArC}_q\text{OCH}_3\text{ and NCO);} \\
m/z: \text{ (EI) 527(3), 526(5), 464(14), 462(28), 460(14), 449(10), 448(32), 300(36),}
\end{align*} \]
234(58), 232(22), 231(98), 230(20), 229(100), 190(58), 119(40), 105(50), 91(20).
(CI) 681(M+4, 7%), 680(M+3, 10%), 679(M+2, 7%), 678(M+1, 5%), 601(7), 600(5), 599(7), 522(7), 521(5), 520(14), 518(10), 516(10), 480(53), 478(100), 476(54), 301(26), 300(30), 231(67), 229(68), 190(74), 119(24), 91(28);

Anal. Calcd. for C_{37}H_{44}N_{6}Br: C, 65.48; H, 6.53; N, 2.06; Br, 11.77. Found: C, 65.05; H, 6.78; N, 1.78; Br, 12.01.

N-Methylxoycarbonylpavine or 13-Methylxoycarbonyl-5,6,11,12-tetrahydro-2,3,8,9-tetramethoxy-5,11-iminodibenzo[a,e]cyclooctane

6a,7-Dihydro-6-methylxoycarbonyl-1,2,9,10-tetramethoxy dibenzo[de,g]quinoline

The diastereomeric benzylisoquinoline 507 (1.22 g, 2 mmol) and AIBN (43 mg, 0.3 mmol, 0.15 equiv.) were dissolved in freshly distilled de-oxygenated benzene (15 mL) and heated at reflux. Bu_{3}SnH (0.89 g, 3 mmol) and AIBN (72 mg, 0.5 mmol, 0.25 equiv.) in de-gassed benzene (10 mL) were added to this solution over 4-5 hours with the aid of a syringe pump. The solution was allowed to reflux for a further 12 hours and the solvent removed under reduced pressure. The crude product was chromatographed (flash column) with 30% ethyl acetate in petroleum spirits. On purification the highly chromophoric band having a higher R_f value than the starting material gave 514 (0.397 g, 0.76 mmol, 38%) as a thick oil. The more polar band afforded 513 (0.487 g, 0.931 mmol, 46%) as a white solid.

N-Methylxoycarbonylpavine or 13-Methylxoycarbonyl-5,6,11,12-tetrahydro-2,3,8,9-tetramethoxy-5,11-iminodibenzo[a,e]cyclooctane

mp 93-94 °C; [α]_D -55.7 (c 0.55, CHCl_3);

\(^1\)H NMR (CDCl_3) \(δ\) 0.67-2.06 (m, 18 H, methyl-3xCH_3, 3xCH_2, 3xCH), 2.74\(^*\) and 2.76 (d, 2 H, J = 16 Hz, 6 and 12-H_{ax}), 3.37 (m, 2 H, 6 and 12-H_{eq}), 3.78, 3.86, 3.87 and 3.88 (s, 12 H, 4xOCH_3), 4.63 (m, 1 H, 1-CH-methyl), 5.41 and 5.53 (d, 2 H, J = 5 Hz, 5 and 11-CH), 6.45, 6.48, 6.67 (s, 4 H, 4xArH), (*) partially resolved.
diastereomer peaks);

$^{13}$C NMR (CDCl$_3$) δ 16.39, 16.51, 20.71, 20.87, 21.98, 26.25, 26.44, 31.32, 47.32, 47.43 (menthyl-3xCH$_3$ and 3xCH), 23.51, 23.54, 34.29, 41.48, 41.55 (menthyl-3xCH$_2$), 36.09, 36.22, 36.34, 36.70 (6 and 12-CH$_2$), 48.92, 49.18, 49.59, and 49.87 (5 and 11-CH), 55.66, 55.92 (4xOCH$_3$), 75.25 (menthyl-1-CH), 108.97, 109.25, 111.50, 111.63 (1, 4, 7, 10-ArCH), 123.97, 124.01, 124.58, 124.61, 128.78, 128.89 and 129.24 (4a, 6a, 10a, 12a-ArC$_q$), 147.40, 147.47, 147.90, 147.99 (2, 3, 8-ArC$_q$OCH$_3$), 153.76, 154.54 (NCO);

$m/z$: 524(M+1, 45%), 523(M^+, 97%), 385(60), 384(50), 341(71), 340(100), 325(24), 324(32), 313(24), 312(50), 311(48), 234(32), 191(20), 190(98), 152(22), 97(23), 95(25), 85(21), 83(68), 81(25); HRMS exact mass calcd. for C$_{31}$H$_{41}$N$_6$O$_6$ 523.2934, found 523.2933.

Anal. Calcd. for C$_{31}$H$_{41}$N$_6$O$_6$: C, 71.10; H, 7.89; N, 2.67. Found: C, 71.03; H, 8.24; N, 2.36.

6a,7-Dihydro-6-menthylxocarbonyl-1,2,9,10-tetramethoxydibenzof[l,de]quinoline

$[\alpha]_D +323.6$ (c 0.55, CHCl$_3$);

$^{1}$H NMR (CDCl$_3$) δ 0.80-2.16 (m, 18 H, menthyl-3xCH$_3$, 3xCH$_2$, 3xCH), 2.87 (t, 1 H, $J = 13.3$ Hz, 7-H$_{ax}$), 3.41 (b, 1 H, 7-H$_{eq}$), 3.65, 3.89, 3.91, 3.92 (s, 12 H, 4xOCH$_3$), 4.73 (m, 1 H, 1-CH-menthyl), 5.03 (m, 1 H, 6a-H$_{ax}$), 5.41 and 5.42 (d each, 1 H, $J = 8$ Hz, 5-H), 6.92 (d, 1 H, $J = 8$ Hz, 4-H), 6.47, 6.79, 8.07 (s, 3 H, 3xArH);

$^{13}$C NMR (CDCl$_3$) δ 16.07, 16.51, 20.67, 20.94, 21.90, 21.96, 26.30, 31.35, 47.09, 54.07, 54.14* (menthyl-3xCH$_3$ and 3xCH), 23.14, 23.58, 34.06, 34.19, 41.16, 41.20* (menthyl-3xCH$_2$ and 7-CH$_2$), 55.63, 55.71, 55.82 (4xOCH$_3$), 76.42, 76.57* (menthyl-1-CH), 103.89, 104.04 (5-CH), 107.33, 110.82, 111.60 (3xArCH), 122.10, 123.85, 124.01, 127.16, 130.40 (5xArC$_q$), 124.82, 124.92 (4-CH), 144.67, 147.40, 148.20, 152.61, 158.32 (4xArC$_q$OCH$_3$ and NCO);
Chapter 7: Experimental

$m/z$: 523(M+2, 43%), 520(M+1, 23%), 521(M+, 65%), 385(32), 384(25), 383(100), 370(33), 339(33), 338(42), 326(15), 324(16), 308(27), 307(21), 97(17), 83(78), 69(43), 57(27), 55(67); HRMS exact mass calcd. for C$_{31}$H$_{39}$N$_{6}$O$_{6}$ 521.2777, found 521.2776.

Anal. Calcd. for C$_{27}$H$_{25}$NO$_{6}$: C, 70.58; H, 5.48; N, 3.05. Found: C, 70.29; H, 5.52; N, 2.81.

N-(8-Phenylmenthlyloxycarbonyl)-pavine or 13-(8-Phenylmenthlyloxycarbonyl)-5,6,11,12-tetrahydro-2,3,8,9-tetramethoxy-5,11-iminodibenzo-[a,e]cyclooctane

6a,7-Dihydro-6-(8-phenylmenthlyloxycarbonyl)-1,2,9,10-tetramethoxydibenzo[de,gl]quinoline

The above compounds were synthesised from 8-phenylmenthyl chloroformate and 6,7-dimethoxyisoquinolione following the radical ring closure technique outlined above for the preparation of the N-menthlyloxycarbonyl derivatives 513 and 514. The resulting crude product was purified by flash chromatography (30% ethyl acetate in petroleum spirits) to afford 520 (the band with a higher Rf value) (0.322 g, 0.54 mmol, 54%) as a thick oil. The band eluting with a lower Rf value gave the argemonine precursor 519 (0.191 g, 0.32 mmol, 32%) as a colourless solid.

N-(8-Phenylmenthlyoxycarbonyl)-pavine or 13-(8-Phenylmenthlyoxycarbonyl)-5,6,11,12-tetrahydro-2,3,8,9-tetramethoxy-5,11-iminodibenzo[a,e]cyclooctane

mp 111-113 °C; [α]$_D$ -11.3 (c 0.51, CHCl$_3$);

$^1$H NMR (CDCl$_3$) δ 0.80-2.05 (m, 17 H, menthyl-3xCH$_3$, 3xCH$_2$, 2xCH), 2.55, 2.60* (d, 1 H, $J = 15.2$ Hz, 6 or 12-H$_{ax}$), 2.69*, 2.73 (d, 1 H, $J = 15.2$ Hz, 6 or 12-H$_{ax}$), 2.94*, 3.12 (dd, 1 H, $J = 5.6$ and 15.6 Hz, 6 or 12-H$_{eq}$), 3.33 and 3.44* (dd, 2H, $J = 5.4$ and 15.9 Hz, 6 or 12-H$_{eq}$), 3.74, 3.77, 3.80, 3.83, 3.84, 3.86 and 3.88 (s, 12 H, 4xOCH$_3$), 4.51 and 5.01* (d, 1 H, $J = 5$ Hz, 5 or 11-H), 4.84 (m, 1 H, 1-CH-
menthyl), 5.44 and 5.49*(d, 1 H, * J = 5 Hz, 5 or 11-H), 6.37-7.35 (m, 9 H, 9xArH), (* unresolved diastereomer peaks);

$^{13}$C NMR (CDCl$_3$) $\delta$ 21.83, 24.73, 25.25, 28.04, 28.57, 31.31, 49.16 (menthyl-3xCH$_3$ and 2xCH), 26.66, 27.13, 34.61, 34.66, 39.20, 39.55, 40.23, 42.42, 42.51 (menthyl-3xCH$_2$), 35.90, 36.24, 36.42 (6 and 12-CH$_2$), 49.31 and 51.21 (5 and 11-CH), 55.65, 55.96 (4xOCH$_3$), 74.84 and 75.07 (menthyl-1-CH), 108.35, 108.90, 109.20, 109.42, 109.52, 111.22, 111.39, 111.52, 111.70 (1, 4, 7, 10-ArCH), 124.74, 125.05, 125.05, 125.53, 127.40, 128.01 (NCO$_2$ArCH), 124.16, 124.44, 128.73, and 129.32 (4a, 6a, 10a, 12a-ArC$_q$), 128.88 (-NCO$_2$ArC$_q$), 147.10, 147.40, 147.82, 147.86 (2, 3, 8, 9-ArC$_q$OCH$_3$), 151.51, 153.43 (NCO);

$m/z$: 600(M+1, 32%), 599(M^+, 74%), 385(62), 384(46), 341(62), 340(100), 326(10), 325(20), 324(22), 312(36), 311(26), 234(18), 191(12), 190(82), 152(10), 120(14), 119(86), 105(72), 91(44), 69(14); HRMS exact mass calcd. for C$_{37}$H$_{45}$N$_{06}$ 599.3247, found 599.3246.

Anal. Calcd. for C$_{37}$H$_{45}$N$_{06}$: C, 74.10; H, 7.56; N, 2.34. Found: C, 73.61; H, 7.66; N, 2.18.

6a,7-Dihydro-6-(8-phenylmenthlyoxycarbonyl)-1,2,9,10-tetramethoxy-dibenzo[de,glquinoline

[α]$_D$ +192.40 (c 0.89, CHCl$_3$);

$^1$H NMR (CDCl$_3$) $\delta$ 0.80-1.97 (m, 17 H, menthyl-3xCH$_3$, 3xCH$_2$, 2xCH), 2.67 (t, 1 H, $J = 12$ Hz, 7-H$_{ax}$), 3.38 (b, 1 H, 7-H$_{eq}$), 3.56, 3.77, 3.83, 3.89 (s, 12 H, 4xOCH$_3$), 4.84 (m, 1 H, 1-CH-menthyl), 5.01 (m, 1 H, 6a-H$_{ax}$), 5.39 and 5.55 (bd each, 1 H, 5-H), 6.77 (bd, 1 H, 4-H), 6.33, 6.77, 7.98 (s, 3 H, 3xArH), 7.04-7.22(m, 5 H, 5xArH);

$^{13}$C NMR (CDCl$_3$) $\delta$ 21.76, 23.40, 26.37, 26.45, 26.52, 31.35, 50.65, 50.99, 54.16* (menthyl-3xCH$_3$ and 2xCH), 23.40, 26.45, 34.59, 36.22, 39.33, 42.08, 42.16* (menthyl-3xCH$_2$ and 7-CH$_2$), 55.68, 55.81, 55.89 (4xOCH$_3$), 76.53, 76.57*
(-)-Argemonine or 13-Methyl-5,6,11,12-tetrahydro-2,3,8,9-tetramethoxy-5,11-iminodibenzo[a,e]cyclooctane

The diastereomeric tetracycle 513 (0.26 g, 0.5 mmol) was dissolved in THF (15 mL) in an oven dried round bottom flask and cooled to 0°C (ice/acetone bath). To this clear solution LiAlH₄ (0.19 g, 5 mmol) was added in portions over 5 minutes and stirred for 2 hours at 0 °C. Once the effervescence had ceased, the solution was gradually heated at reflux for 36 hours. The solution was cooled to 0 °C again, diluted with diethyl ether (10 mL) and carefully treated with wet diethyl ether (1:1) (5 mL). This was followed by the addition of 20 mL of 4 M aqueous NaOH. The solution was stirred for a further 10 minutes and poured into 10 mL of H₂O. Resulting alumino residues were filtered off, the organic layer separated and the aqueous portion extracted further with ethyl acetate (10 x 20 mL). The combined solution of the organic extracts was dried with K₂CO₃, filtered and the solvent removed under reduced pressure. The crude residue was chromatographed (5% methanol in ethyl acetate) to afford the optically active natural product 514 (0.154 g, 0.43 mmol, 86%) as a colourless solid, mp 134-139 °C; [α]D -58.3 (c 0.52, CHCl₃);

1H NMR (CDCl₃) δ 2.54 (s, 3 H, NCH₃), 2.60 (d, 2 H, J = 16 Hz, 6 and 12-Hax), 3.41 (dd, 2 H, J = 5.5 and 16 Hz, 6 and 12-Heq), 3.78 and 3.85 (s each, 6 H each, 4xOCH₃), 4.02 (d, 2 H, J = 5.5 Hz, 5 and 11-H), 6.45 and 6.61 (s each, 2 H each, 4xArH);
\[^{13}\text{C}\text{ NMR (CDCl}_3\text{)}\delta\text{ }33.52\text{ (6 and 12-CH}_2\text{)},\text{ }40.82\text{ (NCH}_3\text{)},\text{ }55.63,\text{ }55.88\text{ (4xOCH}_3\text{)},\text{ }56.33\text{ (5 and 11-CH)},\text{ }109.84,\text{ }111.34\text{ (1, 4, 7, 10-ArCH)},\text{ }123.75,\text{ }129.73\text{ (4a, 6a, 10a, 12a-ArC}_q\text{)},\text{ }147.39,\text{ }147.76\text{ (2, 3, 8, 9-ArC}_q\text{OCH}_3\text{)}:\]

\[m/\text{z}: \text{ }356(M^+\text{, }13\%),\text{ }355(M^++,\text{ }37\%),\text{ }354(30),\text{ }340(12),\text{ }338(5),\text{ }206(5),\text{ }205(25),\text{ }204(100),\text{ }191(6),\text{ }190(12),\text{ }188(7),\text{ }160(5),\text{ }107(15),\text{ }91(34),\text{ }71(10);\]

Anal. Calcd. for C\text{21H}_{25}\text{NO}_4: \text{ C, }70.96; \text{ H, }7.09; \text{ N, }3.94. \text{ Found: C, }71.22; \text{ H, }7.39; \text{ N, }3.65.
7.3 Appendix A

<table>
<thead>
<tr>
<th>Crystal Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical Formula</strong></td>
</tr>
<tr>
<td><strong>Formula Weight</strong></td>
</tr>
<tr>
<td><strong>Crystal Colour, Habit</strong></td>
</tr>
<tr>
<td><strong>Crystal Dimensions</strong></td>
</tr>
<tr>
<td><strong>Crystal System</strong></td>
</tr>
<tr>
<td><strong>Lattice Type</strong></td>
</tr>
<tr>
<td><strong>Lattice Parameters</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Space Group</strong></td>
</tr>
<tr>
<td><strong>Z value</strong></td>
</tr>
<tr>
<td><strong>$D_{calc}$</strong></td>
</tr>
<tr>
<td><strong>$F_{000}$</strong></td>
</tr>
<tr>
<td><strong>$\mu$(MoK$\alpha$)</strong></td>
</tr>
</tbody>
</table>
### B: Intensity Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffractometerer</td>
<td>Rigaku AFC6R</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54178 Å) graphite monochromated</td>
</tr>
<tr>
<td>Take-off Angle</td>
<td>6.0°</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>6.0 mm horizontal</td>
</tr>
<tr>
<td></td>
<td>6.0 mm vertical</td>
</tr>
<tr>
<td>Crystal to Detector Distance</td>
<td>40 cm</td>
</tr>
<tr>
<td>Temperature</td>
<td>23.0°C</td>
</tr>
<tr>
<td>Scan Type</td>
<td>ω-2θ</td>
</tr>
<tr>
<td>Scan Rate</td>
<td>32.0°/min (in omega)(3 rescans)</td>
</tr>
<tr>
<td>Scan Width</td>
<td>(1.42 + 0.30 tan θ)°</td>
</tr>
<tr>
<td>2θ&lt;sub&gt;max&lt;/sub&gt;</td>
<td>120.0°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 2821</td>
</tr>
<tr>
<td></td>
<td>Unique: 2693 (R&lt;sub&gt;int&lt;/sub&gt; = 5.01)</td>
</tr>
</tbody>
</table>

### C: Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure Solution</td>
<td>Patterson Methods (SAPI)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>Σw(</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.01</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations (</td>
<td>I</td>
</tr>
<tr>
<td>No. Variables</td>
<td>199</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>9.26</td>
</tr>
<tr>
<td>Residuals: R; Rw</td>
<td>0.041 ; 0.046</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>3.38</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum Peak in Final Diff. Map</td>
<td>1.22 e&lt;sup&gt;-1&lt;/sup&gt;/Å&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minimum Peak in Final Diff. Map</td>
<td>-0.61 e&lt;sup&gt;-1&lt;/sup&gt;/Å&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
## Non-Hydrogen Interatomic Distances (Å) for C$_{18}$H$_{14}$INO$_2$

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distances</th>
<th>atom</th>
<th>atom</th>
<th>distances</th>
</tr>
</thead>
<tbody>
<tr>
<td>I(1)</td>
<td>C(17)</td>
<td>2.07(1)</td>
<td>O(4)</td>
<td>C(4)</td>
<td>1.23(1)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>1.20(1)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>1.486(10)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>1.35(1)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>1.39(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>1.54(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>1.52(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>1.52(1)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>1.45(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(6)</td>
<td>1.35(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>1.50(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>1.37(1)</td>
<td>C(12)</td>
<td>C(17)</td>
<td>1.40(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(14)</td>
<td>1.37(1)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>1.39(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>C(16)</td>
<td>1.36(1)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>1.41(1)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(22)</td>
<td>1.36(1)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>1.40(1)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(23)</td>
<td>1.38(1)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>1.38(2)</td>
</tr>
<tr>
<td>C(24)</td>
<td>C(25)</td>
<td>1.33(2)</td>
<td>C(25)</td>
<td>C(26)</td>
<td>1.40(2)</td>
</tr>
</tbody>
</table>

## Interatomic Distances (Å) Involving Hydrogen Atoms in C$_{18}$H$_{14}$INO$_2$

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distances</th>
<th>atom</th>
<th>atom</th>
<th>distances</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2)</td>
<td>H(2)</td>
<td>1.00</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>0.99</td>
</tr>
<tr>
<td>C(3)</td>
<td>H(3b)</td>
<td>0.97</td>
<td>C(5)</td>
<td>H(5)</td>
<td>0.99</td>
</tr>
<tr>
<td>C(6)</td>
<td>H(6)</td>
<td>0.98</td>
<td>C(13)</td>
<td>H(13)</td>
<td>0.96</td>
</tr>
<tr>
<td>C(14)</td>
<td>H(14)</td>
<td>1.00</td>
<td>C(15)</td>
<td>H(15)</td>
<td>1.01</td>
</tr>
<tr>
<td>C(16)</td>
<td>H(16)</td>
<td>1.01</td>
<td>C(22)</td>
<td>H(22)</td>
<td>1.00</td>
</tr>
<tr>
<td>C(23)</td>
<td>H(23)</td>
<td>0.99</td>
<td>C(24)</td>
<td>H(24)</td>
<td>0.99</td>
</tr>
<tr>
<td>C(25)</td>
<td>H(25)</td>
<td>0.99</td>
<td>C(26)</td>
<td>H(26)</td>
<td>1.01</td>
</tr>
</tbody>
</table>
### Interatomic Angles (°) for C\(_{18}H_{14}INO_2\)

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>118.9(7)</td>
<td>C(2)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>117.9(8)</td>
</tr>
<tr>
<td>C(6)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>122.7(8)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>110.2(7)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>111.7(7)</td>
<td>C(3)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>112.8(7)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>112.8(8)</td>
<td>O(4)</td>
<td>C(4)</td>
<td>C(3)</td>
<td>121.9(9)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>123(1)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>114.5(8)</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>120.9(9)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>124.8(9)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>120.9(9)</td>
<td>O(11)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>122.9(9)</td>
</tr>
<tr>
<td>C(11)</td>
<td>C(12)</td>
<td>C(17)</td>
<td>120.7(9)</td>
<td>C(13)</td>
<td>C(12)</td>
<td>C(17)</td>
<td>122.2(9)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>119.7(9)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>119(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>120(1)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>121.5(9)</td>
</tr>
<tr>
<td>I(1)</td>
<td>C(17)</td>
<td>C(12)</td>
<td>122.7(7)</td>
<td>I(1)</td>
<td>C(17)</td>
<td>C(16)</td>
<td>120.8(7)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(17)</td>
<td>C(16)</td>
<td>116.4(9)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>124.1(8)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>115.9(10)</td>
<td>C(22)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>120.0(9)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>120(1)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>119(1)</td>
</tr>
<tr>
<td>C(23)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>121(1)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>C(26)</td>
<td>120(1)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>118(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Interatomic Angles (°) Involving Hydrogen Atoms in C\(_{18}H_{14}INO_2\)

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>106.1</td>
<td>C(3)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>107.8</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>107.9</td>
<td>C(2)</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>110.4</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>110.0</td>
<td>C(4)</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>109.1</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>109.1</td>
<td>H(3a)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>105.1</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>117.6</td>
<td>C(6)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>121.5</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>118.0</td>
<td>C(5)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>117.1</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>H(13)</td>
<td>121.8</td>
<td>C(14)</td>
<td>C(13)</td>
<td>H(13)</td>
<td>118.4</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(14)</td>
<td>H(14)</td>
<td>123.3</td>
<td>C(15)</td>
<td>C(14)</td>
<td>H(14)</td>
<td>116.6</td>
</tr>
</tbody>
</table>
### Torsion Angles (°) for Non-Hydrogen Atoms of C_{18}H_{14}INO_{2}

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>I(1)</td>
<td>C(17)</td>
<td>C(12)</td>
<td>C(11)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>I(1)</td>
<td>C(17)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>-179.5(8)</td>
</tr>
<tr>
<td>C(1)</td>
<td>C(17)</td>
<td>C(16)</td>
<td>C(15)</td>
<td>-178.8(9)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(3)</td>
<td>C(2)</td>
<td>148.9(8)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>-176.0(9)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>-175.2(9)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>77(1)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>C(17)</td>
<td>-99(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>48.7(10)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>-19(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>160.1(8)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>C(4)</td>
<td>5(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>-99(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>C(17)</td>
<td>83(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>8(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>117.5(8)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>-37(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>179.7(10)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>-179.9(10)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>-35(1)</td>
</tr>
<tr>
<td>atom</td>
<td>atom</td>
<td>distance</td>
<td>ADC</td>
<td>atom</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>----------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(5)</td>
<td>3.132(7)</td>
<td>76603</td>
<td>O(4)</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(25)</td>
<td>3.56(1)</td>
<td>77603</td>
<td>C(25)</td>
</tr>
<tr>
<td>C(6)</td>
<td>C(12)</td>
<td>3.55(1)</td>
<td>77603</td>
<td>C(12)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(26)</td>
<td>3.54(2)</td>
<td>77603</td>
<td>C(26)</td>
</tr>
</tbody>
</table>
7.4 Appendix B

A: Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C₁₈H₁₄BrNO₃</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>372.22</td>
</tr>
<tr>
<td>Crystal Colour, Habit</td>
<td>colourless</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.12 x 0.14 x 0.20</td>
</tr>
<tr>
<td>Crystal System</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>a = 8.581(2) Å</td>
</tr>
<tr>
<td></td>
<td>b = 8.655(2) Å</td>
</tr>
<tr>
<td></td>
<td>c = 21.500(2) Å</td>
</tr>
<tr>
<td></td>
<td>V = 1596.8(4) Å³</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2₁2₁2₁ (#19)</td>
</tr>
<tr>
<td>Z value</td>
<td>4</td>
</tr>
<tr>
<td>D_calc</td>
<td>1.548 g/cm³</td>
</tr>
<tr>
<td>F₀₀₀</td>
<td>752.00</td>
</tr>
<tr>
<td>(\mu)(MoK(\alpha))</td>
<td>36.39 cm⁻¹</td>
</tr>
</tbody>
</table>
### B: Intensity Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffractometerer</td>
<td>Rigaku AFC6R</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54178 Å) graphite monochromated</td>
</tr>
<tr>
<td>Take-off Angle</td>
<td>6.0°</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>6.0 mm horizontal</td>
</tr>
<tr>
<td></td>
<td>6.0 mm vertical</td>
</tr>
<tr>
<td>Crystal to Detector Distance</td>
<td>40 cm</td>
</tr>
<tr>
<td>Temperature</td>
<td>23.0°C</td>
</tr>
<tr>
<td>Scan Type</td>
<td>ω-2θ</td>
</tr>
<tr>
<td>Scan Rate</td>
<td>16.0°/min (in omega)(3 rescans)</td>
</tr>
<tr>
<td>Scan Width</td>
<td>(1.31 + 0.30 tan θ)°</td>
</tr>
<tr>
<td>2θ_{max}</td>
<td>120.1°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 1423</td>
</tr>
</tbody>
</table>

### C: Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure Solution</td>
<td>Patterson Methods (SAPI)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>Σw(</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.01</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations (l&gt;3.00σ(l))</td>
<td>1274</td>
</tr>
<tr>
<td>No. Variables</td>
<td>209</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>6.10</td>
</tr>
<tr>
<td>Residuals: R; Rw</td>
<td>0.034 ; 0.036</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>2.89</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum Peak in Final Diff. Map</td>
<td>0.31 e^-/Å³</td>
</tr>
<tr>
<td>Minimum Peak in Final Diff. Map</td>
<td>-0.56 e^-/Å³</td>
</tr>
</tbody>
</table>
### Non-Hydrogen Interatomic Distances (Å) for C$_{18}$H$_{14}$INO$_2$

<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>1.884(5)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>1.208(6)</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(13)</td>
<td>1.391(6)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>1.397(7)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>1.534(7)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>1.505(7)</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(6)</td>
<td>1.333(7)</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(18)</td>
<td>1.374(7)</td>
</tr>
<tr>
<td>C(15)</td>
<td>C(16)</td>
<td>1.367(8)</td>
</tr>
<tr>
<td>C(17)</td>
<td>C(18)</td>
<td>1.378(7)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(26)</td>
<td>1.398(7)</td>
</tr>
<tr>
<td>C(23)</td>
<td>C(24)</td>
<td>1.365(9)</td>
</tr>
<tr>
<td>C(25)</td>
<td>C(26)</td>
<td>1.385(8)</td>
</tr>
</tbody>
</table>

### Interatomic Distances (Å) Involving Hydrogen Atoms in C$_{18}$H$_{14}$INO$_2$

<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2)</td>
<td>H(2)</td>
<td>1.13</td>
</tr>
<tr>
<td>C(3)</td>
<td>H(3b)</td>
<td>1.06</td>
</tr>
<tr>
<td>C(6)</td>
<td>H(6)</td>
<td>1.02</td>
</tr>
<tr>
<td>C(15)</td>
<td>H(15)</td>
<td>1.03</td>
</tr>
<tr>
<td>C(17)</td>
<td>H(17)</td>
<td>1.16</td>
</tr>
<tr>
<td>C(23)</td>
<td>H(23)</td>
<td>1.01</td>
</tr>
<tr>
<td>C(25)</td>
<td>H(25)</td>
<td>1.16</td>
</tr>
</tbody>
</table>
### Interatomic Angles (°) for C₁₈H₁₄INO₂

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(11)</td>
<td>O(12)</td>
<td>C(13)</td>
<td>117.5(5)</td>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>119.1(4)</td>
</tr>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>121.9(4)</td>
<td>C(6)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>118.0(5)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>109.0(4)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>112.5(4)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>112.3(4)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>114.0(4)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(3)</td>
<td>122.4(6)</td>
<td>O(4)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>124.2(6)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>113.4(5)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>122.6(6)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>123.2(5)</td>
<td>O(11)</td>
<td>C(11)</td>
<td>O(12)</td>
<td>123.3(6)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>125.6(5)</td>
<td>O(12)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>111.0(5)</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>121.4(5)</td>
<td>O(12)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>119.1(5)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>119.3(5)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>120.6(6)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>120.1(5)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>119.9(6)</td>
</tr>
<tr>
<td>C(16)</td>
<td>C(17)</td>
<td>C(18)</td>
<td>120.0(6)</td>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(13)</td>
<td>120.2(4)</td>
</tr>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>119.6(4)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>120.2(5)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>119.3(5)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>123.2(5)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>117.5(5)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>121.5(6)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>120.6(6)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>119.7(6)</td>
</tr>
<tr>
<td>C(24)</td>
<td>C(25)</td>
<td>C(26)</td>
<td>119.8(6)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>120.9(5)</td>
</tr>
</tbody>
</table>

### Interatomic Angles (°) Involving Hydrogen Atoms in C₁₈H₁₄INO₂

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>108.3</td>
<td>C(3)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>106.4</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>108.1</td>
<td>C(3)</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>107.2</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>116.6</td>
<td>C(4)</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>107.8</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>110.9</td>
<td>H(3a)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>98.9</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>119.4</td>
<td>C(6)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>117.8</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>110.5</td>
<td>C(5)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>125.2</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(14)</td>
<td>H(14)</td>
<td>120.1</td>
<td>C(15)</td>
<td>C(14)</td>
<td>H(14)</td>
<td>118.6</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(15)</td>
<td>H(15)</td>
<td>122.3</td>
<td>C(16)</td>
<td>C(15)</td>
<td>H(15)</td>
<td>116.2</td>
</tr>
</tbody>
</table>
### Torsion Angles (°) for Non-Hydrogen Atoms of C_{18}H_{14}INO_{2}

<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Atom</th>
<th>Atom</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(13)</td>
<td>O(12)</td>
<td>-6.7(7)</td>
</tr>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>179.3(4)</td>
</tr>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>C(16)</td>
<td>-179.7(5)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(3)</td>
<td>C(2)</td>
<td>-142.8(5)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>171.4(6)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>O(12)</td>
<td>C(13)</td>
<td>1.7(8)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>-172.3(5)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>-4.1(9)</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>6.2(7)</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>174.5(5)</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>-172.9(5)</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>173.2(5)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>-49.9(5)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>-159.3(4)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>21.4(7)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>C(4)</td>
<td>-6.1(10)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(11)</td>
<td>O(12)</td>
<td>C(13)</td>
<td>-176.9(4)</td>
</tr>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>-6.4(8)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>40.1(6)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>179.7(5)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>-179.9(5)</td>
</tr>
<tr>
<td>atom atom</td>
<td>distance</td>
<td>ADC</td>
<td>atom atom</td>
<td>distance</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>-----</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>Br(1) C(14)</td>
<td>3.589(6)</td>
<td>55604</td>
<td>O(4) C(22)</td>
<td>3.493(7)</td>
</tr>
<tr>
<td>O(4) C(25)</td>
<td>3.501(7)</td>
<td>55603</td>
<td>O(11) C(12)</td>
<td>3.309(6)</td>
</tr>
<tr>
<td>O(11) C(3)</td>
<td>3.426(6)</td>
<td>65604</td>
<td>O(11) N(1)</td>
<td>3.448(6)</td>
</tr>
<tr>
<td>C(5) C(17)</td>
<td>3.505(9)</td>
<td>64604</td>
<td>C(15) C(23)</td>
<td>3.514(8)</td>
</tr>
</tbody>
</table>

Non-bonded Contacts out to 3.60 Å for C_{18}H_{14}INO_{2}
7.5 Appendix C

A : Crystal Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>$\text{C}<em>{19}\text{H}</em>{16}\text{BrNO}_2$</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>370.24</td>
</tr>
<tr>
<td>Crystal Colour, Habit</td>
<td>colourless, block</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>$0.10 \times 0.18 \times 0.08$</td>
</tr>
<tr>
<td>Crystal System</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>$a = 10.902(3) \text{ Å}$</td>
</tr>
<tr>
<td></td>
<td>$b = 05.416(2) \text{ Å}$</td>
</tr>
<tr>
<td></td>
<td>$c = 27.825(2) \text{ Å}$</td>
</tr>
<tr>
<td></td>
<td>$\beta = 90.83(2)^\circ$</td>
</tr>
<tr>
<td></td>
<td>$V = 1642.8(5) \text{ Å}^3$</td>
</tr>
<tr>
<td>Space Group</td>
<td>$\text{P}_2_1/n$ (#14)</td>
</tr>
<tr>
<td>Z value</td>
<td>4</td>
</tr>
<tr>
<td>$D_{\text{calc}}$</td>
<td>1.497 g/cm$^3$</td>
</tr>
<tr>
<td>$F_{000}$</td>
<td>752.00</td>
</tr>
<tr>
<td>$\mu$(MoK$\alpha$)</td>
<td>34.85 cm$^{-1}$</td>
</tr>
</tbody>
</table>
### B: Intensity Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffractometer</td>
<td>Rigaku AFC6R</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54178 Å) graphite monochromated</td>
</tr>
<tr>
<td>Take-off Angle</td>
<td>6.0°</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>6.0 mm horizontal</td>
</tr>
<tr>
<td>Crystal to Detector Distance</td>
<td>40 cm</td>
</tr>
<tr>
<td>Temperature</td>
<td>23.0°C</td>
</tr>
<tr>
<td>Scan Type</td>
<td>ω-2θ</td>
</tr>
<tr>
<td>Scan Rate</td>
<td>32.0°/min (in omega)(3 rescans)</td>
</tr>
<tr>
<td>Scan Width</td>
<td>(1.15 + 0.30 tan θ)°</td>
</tr>
<tr>
<td>2θ_{max}</td>
<td>120.1°</td>
</tr>
<tr>
<td>No. of Reflections Measured</td>
<td>Total: 2905 Unique: 2743 (R_{int} = 2.32)</td>
</tr>
</tbody>
</table>

### C: Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure Solution</td>
<td>Patterson Methods (SAPI)</td>
</tr>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>Σw(</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.01</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations (</td>
<td>I</td>
</tr>
<tr>
<td>No. Variables</td>
<td>209</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>7.57</td>
</tr>
<tr>
<td>Residuals: R; Rw</td>
<td>0.043 ; 0.045</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>2.21</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>Maximum Peak in Final Diff. Map</td>
<td>0.37 e^{-}Å³</td>
</tr>
<tr>
<td>Minimum Peak in Final Diff. Map</td>
<td>−0.44 e^{-}Å³</td>
</tr>
</tbody>
</table>
Non-Hydrogen Interatomic Distances (Å) for C\textsubscript{18}H\textsubscript{14}INO\textsubscript{2}

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distances</th>
<th>atom</th>
<th>atom</th>
<th>distances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>1.907(5)</td>
<td>O(4)</td>
<td>C(4)</td>
<td>1.233(6)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>1.214(6)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>1.490(6)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>1.407(6)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>1.386(6)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>1.536(6)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>1.527(6)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>1.500(8)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>1.453(7)</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(6)</td>
<td>1.324(7)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>1.530(7)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>1.519(7)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>1.388(7)</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(18)</td>
<td>1.383(7)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>1.386(8)</td>
</tr>
<tr>
<td>C(15)</td>
<td>C(16)</td>
<td>1.370(9)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>1.357(8)</td>
</tr>
<tr>
<td>C(17)</td>
<td>C(18)</td>
<td>1.396(8)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>1.393(6)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(26)</td>
<td>1.388(7)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>1.401(7)</td>
</tr>
<tr>
<td>C(23)</td>
<td>C(24)</td>
<td>1.365(9)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>1.385(8)</td>
</tr>
<tr>
<td>C(25)</td>
<td>C(26)</td>
<td>1.394(7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interatomic Distances (Å) Involving Hydrogen Atoms in C\textsubscript{18}H\textsubscript{14}INO\textsubscript{2}

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distances</th>
<th>atom</th>
<th>atom</th>
<th>distances</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2)</td>
<td>H(2)</td>
<td>1.13</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>1.07</td>
</tr>
<tr>
<td>C(3)</td>
<td>H(3b)</td>
<td>1.01</td>
<td>C(5)</td>
<td>H(5)</td>
<td>1.18</td>
</tr>
<tr>
<td>C(6)</td>
<td>H(6)</td>
<td>1.12</td>
<td>C(12)</td>
<td>H(12a)</td>
<td>1.11</td>
</tr>
<tr>
<td>C(12)</td>
<td>H(12b)</td>
<td>1.13</td>
<td>C(14)</td>
<td>H(14)</td>
<td>1.16</td>
</tr>
<tr>
<td>C(15)</td>
<td>H(15)</td>
<td>1.15</td>
<td>C(16)</td>
<td>H(16)</td>
<td>1.15</td>
</tr>
<tr>
<td>C(17)</td>
<td>H(17)</td>
<td>1.12</td>
<td>C(22)</td>
<td>H(22)</td>
<td>1.19</td>
</tr>
<tr>
<td>C(23)</td>
<td>H(23)</td>
<td>1.17</td>
<td>C(24)</td>
<td>H(24)</td>
<td>1.08</td>
</tr>
<tr>
<td>C(25)</td>
<td>H(25)</td>
<td>1.10</td>
<td>C(26)</td>
<td>H(26)</td>
<td>1.16</td>
</tr>
</tbody>
</table>
### Interatomic Angles (°) for C\textsubscript{18}H\textsubscript{14}INO\textsubscript{2}

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>118.1(4)</td>
<td>C(2)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>117.6(4)</td>
</tr>
<tr>
<td>C(6)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>124.3(4)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>110.6(4)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>111.0(4)</td>
<td>C(3)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>112.7(4)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>114.3(4)</td>
<td>O(4)</td>
<td>C(4)</td>
<td>C(3)</td>
<td>121.2(5)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>122.6(6)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>116.0(5)</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>121.6(5)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>124.2(5)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>119.9(5)</td>
<td>O(11)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>121.4(5)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>118.7(5)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>110.2(5)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>120.6(5)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>122.1(5)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>117.2(5)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>121.4(6)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>119.2(6)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>121.4(6)</td>
</tr>
<tr>
<td>C(16)</td>
<td>C(17)</td>
<td>C(18)</td>
<td>118.7(6)</td>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(13)</td>
<td>119.0(4)</td>
</tr>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>119.1(5)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>121.9(5)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>116.3(5)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>124.7(4)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>119.0(5)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>120.4(6)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>119.9(6)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>120.4(6)</td>
</tr>
<tr>
<td>C(24)</td>
<td>C(25)</td>
<td>C(26)</td>
<td>120.1(6)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>120.2(5)</td>
</tr>
</tbody>
</table>

### Interatomic Angles (°) Involving Hydrogen Atoms in C\textsubscript{18}H\textsubscript{14}INO\textsubscript{2}

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>109.9</td>
<td>C(3)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>108.4</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(2)</td>
<td>H(2)</td>
<td>104.0</td>
<td>C(2)</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>107.0</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>108.8</td>
<td>C(4)</td>
<td>C(3)</td>
<td>H(3a)</td>
<td>106.5</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>111.0</td>
<td>H(3a)</td>
<td>C(3)</td>
<td>H(3b)</td>
<td>109.2</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>124.0</td>
<td>C(6)</td>
<td>C(5)</td>
<td>H(5)</td>
<td>114.1</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>106.2</td>
<td>C(5)</td>
<td>C(6)</td>
<td>H(6)</td>
<td>129.3</td>
</tr>
<tr>
<td>C(11)</td>
<td>C(12)</td>
<td>H(12a)</td>
<td>102.7</td>
<td>C(11)</td>
<td>C(12)</td>
<td>H(12b)</td>
<td>111.4</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(12)</td>
<td>H(12a)</td>
<td>102.3</td>
<td>C(13)</td>
<td>C(12)</td>
<td>H(12b)</td>
<td>105.5</td>
</tr>
</tbody>
</table>
### Torsion Angles (°) for Non-Hydrogen Atoms of C\textsubscript{18}H\textsubscript{14}INO\textsubscript{2}

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>atom</th>
<th>angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(13)</td>
<td>C(12)</td>
<td>-4.6(7)</td>
</tr>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>177.6(4)</td>
</tr>
<tr>
<td>Br(1)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>C(16)</td>
<td>-178.6(5)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(3)</td>
<td>C(2)</td>
<td>-152.5(4)</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>178.2(5)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>1.9(7)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>179.8(4)</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>39.2(7)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>-45.1(6)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>-159.2(4)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>20.7(7)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>C(4)</td>
<td>-5.2(8)</td>
</tr>
<tr>
<td>N(1)</td>
<td>C(11)</td>
<td>O(12)</td>
<td>C(13)</td>
<td>-143.1(5)</td>
</tr>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
<td>C(5)</td>
<td>-10.4(7)</td>
</tr>
<tr>
<td>C(2)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>-170.7(4)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>32.2(6)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>179.1(5)</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>-179.5(5)</td>
</tr>
<tr>
<td></td>
<td>C(3)</td>
<td>C(2)</td>
<td>N(1)</td>
<td>C(6)</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(2)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>-147.2(4)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(22)</td>
<td>76.1(6)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>-104.0(6)</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>C(5)</td>
<td>C(6)</td>
<td>-6.6(7)</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(3)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>79.8(5)</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(6)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>171.7(5)</td>
</tr>
<tr>
<td>C(6)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>-91.1(5)</td>
</tr>
<tr>
<td>C(6)</td>
<td>N(1)</td>
<td>C(11)</td>
<td>C(12)</td>
<td>2.2(7)</td>
</tr>
<tr>
<td>C(11)</td>
<td>N(1)</td>
<td>C(2)</td>
<td>C(21)</td>
<td>87.0(5)</td>
</tr>
<tr>
<td>C(11)</td>
<td>C(12)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>78.8(6)</td>
</tr>
<tr>
<td>C(12)</td>
<td>C(13)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>-177.9(5)</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(14)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>0.8(10)</td>
</tr>
<tr>
<td>C(13)</td>
<td>C(18)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>-1.3(9)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>C(17)</td>
<td>0.3(8)</td>
</tr>
<tr>
<td>C(14)</td>
<td>C(15)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>-1.1(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>C(14)</td>
<td>C(13)</td>
<td>C(18)</td>
<td>0.0(8)</td>
</tr>
<tr>
<td>C(15)</td>
<td>C(16)</td>
<td>C(17)</td>
<td>C(18)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(22)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>1.3(9)</td>
</tr>
<tr>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>C(24)</td>
<td>-0.3(9)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>C(25)</td>
<td>0.3(8)</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(23)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>-1.3(10)</td>
</tr>
<tr>
<td>C(23)</td>
<td>C(22)</td>
<td>C(21)</td>
<td>C(26)</td>
<td>-0.7(8)</td>
</tr>
<tr>
<td>C(23)</td>
<td>C(24)</td>
<td>C(25)</td>
<td>C(26)</td>
<td>0.9(9)</td>
</tr>
</tbody>
</table>
### Non-bonded Contacts out to 3.60 Å for C$_{18}$H$_{14}$INO$_2$

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC</th>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)</td>
<td>O(4)</td>
<td>3.363(4)</td>
<td>65602</td>
<td>O(4)</td>
<td>C(23)</td>
<td>3.361(7)</td>
<td>54602</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(3)</td>
<td>3.543(6)</td>
<td>64602</td>
<td>O(11)</td>
<td>C(6)</td>
<td>3.188(7)</td>
<td>56501</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(14)</td>
<td>3.262(6)</td>
<td>66603</td>
<td>O(11)</td>
<td>C(15)</td>
<td>3.389(8)</td>
<td>66603</td>
</tr>
<tr>
<td>O(11)</td>
<td>C(26)</td>
<td>3.443(7)</td>
<td>56501</td>
<td>O(11)</td>
<td>C(5)</td>
<td>3.532(6)</td>
<td>56501</td>
</tr>
<tr>
<td>O(12)</td>
<td>C(16)</td>
<td>3.569(9)</td>
<td>54501</td>
<td>O(17)</td>
<td>C(15)</td>
<td>3.51(1)</td>
<td>76603</td>
</tr>
<tr>
<td>C(22)</td>
<td>C(25)</td>
<td>3.575(9)</td>
<td>56501</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES
References


   (b) Curran, D. P. Synthesis 1988, 417(part 1) and 489(part 2).


References


18. (a) Smadja, W. *Synlett* **1994**, *1*.


References


71. Calculations were performed with macromodel V3.5x and the MM2* force
field: Mohamadi, F.; Richards, N. G. T.; Guida, W. C.; Liskamp, R.;


(b) Binns, S. V.; Dunstan, P. J.; Guise, G. B.; Holder, G. M.; Hollis, A. F.;
McCredie, R. S.; Pinhey, J. T.; Prager, R. H.; Rasmussen, M.; Ritchie, E.;


75. Ahmad, V. U.; Nasir, M. A. Heterocycles 1986, 24, 2841.
76. Ahmad, V. U.; Nasir, M. A. *Phytochemistry* 1987, 26, 585.


References


89. (a) Deslongchamps, P. Heterocycles 1977, 7, 1271.


90. (a) Jones, G. I. L.; Owen, N. L. J. Mol. Struct. 1973, 18, 1

(b) Huisgen, R.; Ott, H. Tetrahedron 1959, 6, 253.


References

  

103. This study was carried out by Dr. Sajan P. Joseph.


  
  


115.  


116.  


117.  


122. (a) Knovenagel, E. *Liebigs Ann.* 1914, 402, 133.


References


(c) Alonso, T.; Harvey, S.; Junk, P. C.; Raston, C. L.; Skelton, B. W.; White, A. H. Organometallics 1987, 6, 2110.


(b) Chen, C. L.; Chang, H.; Cowling, E. B. Phytocchemistry 1976, 15, 547.


162. (a) Liou, Y. F.; Lin, K. H.; Lu, S. T. *Taiwan Yao Hsueh Tsa Chih*, **1979**,

(b) Petkov, V.; (Abstracts of the 30th meeting of Society for Medicinal Plant Research), Planta Medica 1982, 45, 135.


(c) Gupta, S.; Bhakuni, S. Synth. Commun. 1989, 19, 393.


References


175. (a) Knochel, P.; Singer, R. D. Chem. Rev. 1993, 93, 2117.


178. (a) Ōki, M. Applications of NMR Spectroscopy to Organic Chemistry; VCH: Florida, 1985; p 43.
References


References

(c) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. 


(c) Meyers, A. I.; Guiles, J. Heterocycles **1989**, *28*, 295.


(c) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; 


*46*, 5909.


*116*, 4719.

8616.
References


