Synthetic Studies Towards Novel Annulated Porphyrins

A Thesis Submitted Towards the Degree of

Doctor of Philosophy

by

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Acknowledgments

I am indebted to society for supporting basic research in the form of their taxes, my results may not mean much to the majority of Australians, however I would like to think that they have made a sound-if somewhat speculative-investment in their own future.

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Statement of Originality

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

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13.07.98

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Abstract

The synthesis of annulated porphyrins by the condensation of annulated monopyrroles and dipyrromethanes under a variety of conditions was investigated, with the aim to prepare model porphyrins for the investigation of conformational exchange of non-planar porphyrins in solution.

Cyclic alkenes incorporating oxygen, silicon or nitrogen atoms, or a sulfone group were prepared as the primary starting materials for this study. Cyclopentene derivatives were also prepared. Carbon, oxygen, sulfone and nitrogen based cyclic vinyl sulfones were prepared by addition of benzenesulfenyl chloride, oxidation of the intermediate α-chlorosulfide, followed by elimination of HCl or alternatively by the addition of iodine and *p*-toluene sulfinate followed by elimination of HI. A silicon based cyclic vinyl sulfone could not be prepared due to the preference of the precursor molecules to give cyclic siloxanes or siloxane dimers during functionalisation to vinyl sulfones. Vinyl sulfones were also prepared directly by the condensation of malononitrile or dimethyl malonate with 2,3-bis(phenylsulfonyl)-1,3-butadiene.

A total of sixteen annulated[3,4-*c*]pyrrole 2-carboxylates were formed using a modified Barton and Zard condensation of vinyl sulfones and an isocyanoacetate anion. The conditions for this procedure were shown to be general for the formation of annulated pyrroles. Annulated dipyrromethanes were prepared from the corresponding pyrrole 2-carboxylates.

Only one porphyrin was prepared, namely $2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b,g,l,q*]porphyrin which was synthesised in 5-6% yield by acid catalysed condensation of 5,5-dimethyl-tetrahydrocyclopenta[*c*]pyrrole with formaldehyde or acid catalysed condensation of 2-hydroxymethyl-5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole. Black polymeric residues were the only products isolated from attempts to form heteroannulated porphyrins by condensation of annulated monopyrroles or annulated dipyrromethanes.

Abbreviations

General

Å	angstrom
Ac	acetyl
Bn	benzyl
Chloranil	tetrachlorobenzoquinone
DBU	1,9-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DCC	dicyclohexylcarbodiimide
DCU	dicyclohexylurea
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
EI-MS	electron impact-mass spectrometry
ESI-MS	electrospray ionisation-mass spectrometry
GC-MS	gas chromatography-mass spectrometry
MCPBA	*meta* chloroperbenzoic acid
NCS	*N*-chlorosuccinimide
N.m.r.	nuclear magnetic resonance
PTSA	*p*-toluenesulfonic acid
RBF	round bottom flask
R_f	retention factor
ROESY	rotational Overhauser effect spectroscopy
RT	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
T.l.c.	thin layer chromatography
TOSMIC	tosylmethyl isocyanide

| Ts | *p*-toluenesulfonyl |
| TMS | tetramethylsilane |

Porphyrins

OEP	octaethylporphyrin
OETPP	octaethyltetraphenylporphyrin
TPP	tetraphenylporphyrin
TC5TPP	nickel (II) (tetraphenyltetrapropano)porphyrin
CuTC$_5$T(3,4,5-OMeP)P	copper (II) tetrakis(3,4,5-trimethoxyphenyl)-tetrapropanoporphyrin

Introduction

1.1   General Features of Porphyrin Compounds

Standard definition of a porphyrin:- any of a group of compounds containing the porphin structure of four pyrrole rings connected by methine bridges in a cyclic configuration (**Fig. 1**), to which a variety of side chains are attached; can be metallated, e.g., with iron to form heme – *(Academic Press Dictionary of Science and Technology)*, (c) 1995 by Academic Press.
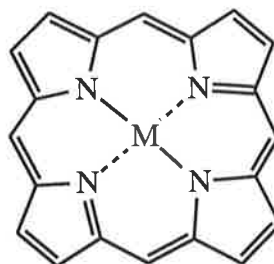
Figure 1 The porphin macrocycle.

Porphyrins are found in a diverse range of biological systems such as the photosynthetic redox systems chlorophyll and bacteriophyll,[1,2,3] oxidative enzymes and the oxygen transport systems of animals.[4] Porphyrins are typically coloured and are often referred to as the "pigments of life" as they give rise to the colour of both green plants and blood.

In recent years, interest in porphyrin synthesis has been on the increase owing to their use as anti-cancer agents in photodynamic therapy,[5,6,7,8,9] redox catalysts,[10] geochemical standards in the analysis of sedimentary metalloporphyrins[11,12,13,14] and their potential uses as molecular sensors,[15,16,17] non-linear optic devices,[18] molecular wires,[19] opto-electronic devices[19,20,21] and solar energy transducers.[3,22,23]

1.1.1 Nomenclature of Porphyrin Compounds

Since 1987, IUPAC has recommended a general numbering system for porphyrins and related macrocycles (**Fig. 2**).[24] This systematic nomenclature is used throughout this thesis. 'Opposing core nitrogens' are delineated as pyrrolic nitrogens positioned diagonally opposite each other in the macrocyclic core.
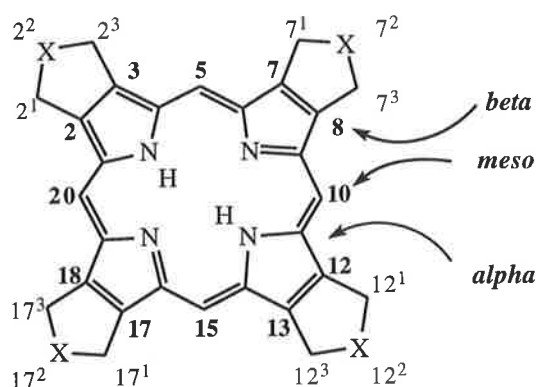
Figure 2   *Meso* positions: 5, 10, 15, and 20; *Alpha* positions: 1, 4, 6, 9, 11, 14, 16, and 19;

Beta positions: 2, 3, 7, 8, 12, 13, 17, and 18.

1.2   Porphyrin Structure and Conformation

Free base porphyrins (nonprotonated or nonmetallated porphyrins) are generally planar, in both solution and the solid state, as would be expected for aromatic compounds. Many highly substituted, metallated or protonated porphyrins however are distinctly non-planar. Of particular interest to the field of porphyrin chemistry is the thesis that the functional activity of biological porphyrin systems is dependent on the degree and form of macrocycle non-planarity. It follows that precise modulation of porphyrin planarity in the many artificial porphyrin systems being studied will be necessary if the maximum efficiency of these systems is to be realised.

1.2.1 Structural Studies on Model Porphyrin Systems

There has been extensive investigation of the structural and spectroscopic properties of porphyrins, following the realisation that the biological activity of a system may be determined by the conformation of the incorporated porphyrin.[25] The goal of most research in this area is to determine the nature of any conformation-reactivity relationship that exists. Such investigations require the availability of model non-planar porphyrins with either known or controllable conformations; to this end, many non-planar porphyrins have been synthesised and their properties rigorously analysed. There are many factors that could influence the conformation of a porphyrin, including: the nature of the complexed metal ion, steric interactions of the peripheral substituents (both β-substituents and *meso*-substituents), axial ligation, steric interactions between core substituents and supra molecular interactions with structural proteins.[26,27]

1.2.2 Porphyrin Structural Types

X-Ray crystallography has been the principal tool for definitive structure determination in the structural studies of non-planar porphyrins. When discussing the structure of non-planar porphyrins two main structural types are most frequently encountered, these are the ruffled and the saddle conformers. The ruffled structure exists when the pyrrole rings are twisted with respect to the porphyrin mean plane ('porphyrin mean plane' refers to the least-squares plane calculated for the 24 atom porphyrin macrocycle excluding incorporated metal ions), the saddle conformation exists when the pyrrole rings are tilted with respect to the mean plane (**Fig. 3**).
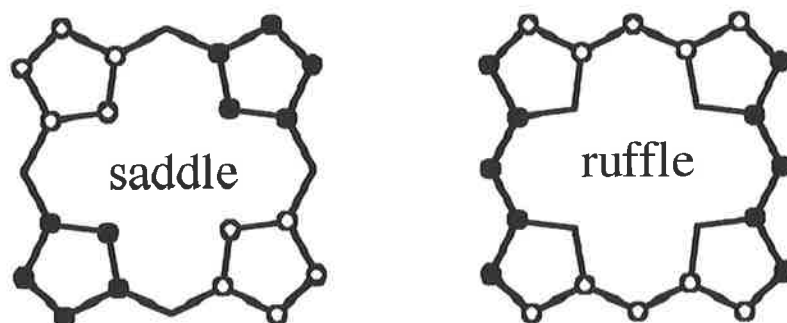
Figure 3   Idealised saddle and ruffled distortion modes for the porphyrin macrocycle utilising the nomenclature adapted from Scheidt and Lee.[28] Displacements of the atoms with respect to the porphyrin least-squares plane are shown as filled circles (above the plane), open circles (below the plane), and without circles (in the plane). Figures adapted from the WWW site 'The 3-dimensional structure of non-planar porphyrins tutorial'.[29]

Two additional conformers that are not as frequently encountered in the literature, are the wave and dome conformers **(Fig. 4)**. The wave structure exists when two opposing pyrrole rings are tilted up and down with respect to the porphyrin mean plane. The second pair of opposing pyrroles are tilted so that each pyrrole will have one β-carbon above, while the other β-carbon is below the porphyrin mean plane. The domed structure is present when all β-carbons are on one side of the mean porphyrin plane, the *meso* carbons are on (or near) the coordination plane and α carbons and nitrogens are above the plane. The domed structure results when the porphyrin is metallated with a large central metal ion accompanied by one or more axial ligands.
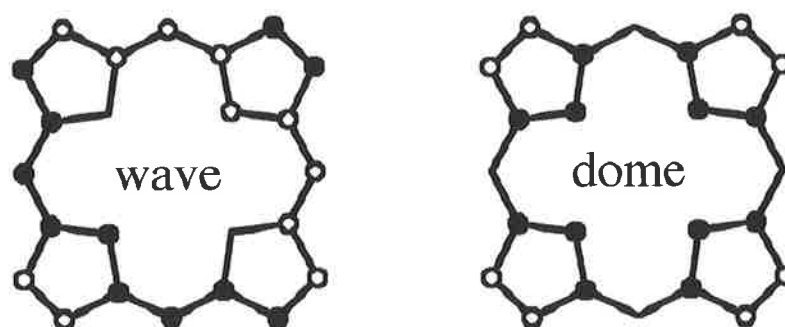
Figure 4   Idealised wave and dome distortion modes for the porphyrin macrocycle. Figures adapted from the WWW site 'The 3-dimensional structure of non-planar porphyrins tutorial'.[29]

1.2.3 Metallation of the Porphyrin Core

The effect of different metal ions on the conformation of porphyrin macrocycles has been extensively investigated.[30,31] It has been found that the introduction of a metal ion into a porphyrin macrocycle can cause a large deformation of the macrocycle through alteration of opposing core nitrogen separation. In a planar porphyrin macrocycle the separation between opposing core nitrogens is 4Å[29] eg. Octaethylporphyrin (2H-OEP) is considered planar because it has a core nitrogen separation of approximately 4Å.[32] Zinc is a metal ion that favours a metal-nitrogen (M–N) bond length of 2Å. Metallation of a porphyrin with zinc therefore does not deform the porphyrin macrocycle to any great extent (for zinc: 2x M–N = 4Å). When the separation of opposing nitrogens is decreased below 4Å, a saddle or ruffled conformer is favoured. Nickel favours an M–N bond of less than 2Å and the macrocycle distorts and twists to maximise its binding to the small nickel ion. The deformation occurs to varying degrees, depending on the nature of the peripheral substituents.

When the separation of opposing core nitrogens increases above 4Å a dome structure is created.[29] Large metals such as tantalum favour M–N bonds greater than 2Å, as the metal ion is too large to fit within the core it must lie above the plane of the macrocyle therefore increasing the length of the M–N bonds. Dome conformations are often accompanied by axial ligands, because of the increased complexing ability of the metal, due in part to the position of the metal above the macrocycle.[29]

1.2.4 Substitution of the Porphyrin Core

As outlined previously, the core of a porphyrin is large enough to permit two hydrogens on opposing core nitrogens or a metal ion of equivalent or smaller volume, without deformation of the macrocycle. If one or more of the core nitrogens is substituted by an alkyl group or protonated (to give a porphyrin cation) the macrocycle must deform to relieve the steric crowding experienced within the core. As an example, the dication [4H-OETPP]$^{2+}$[CH$_3$COO$^-$

]$_{3/2}$[CF$_3$COO$^-$]$_{1/2}$ 4CH$_3$COOH · H$_2$O has been shown to be severely non-planar (β-carbons ±

1.357 Å from the mean coordination plane) **(Fig. 5)**.[33] The observed non-planarity is a

result of steric crowding within the porphyrin core. The type of counter ion and the geometry

of the hydrogen bonding to the core hydrogens is not thought to influence the conformation of

the dication. Alkylation or arylation of core nitrogens produces some of the most non-planar

porphyrins observed especially when nitrogen substitution is in conjunction with bulky

peripheral substituents.
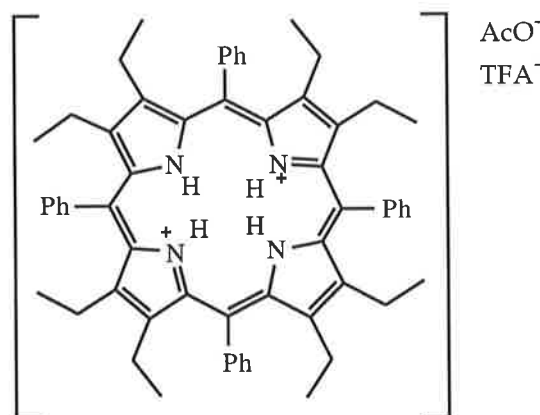
Figure 5 [4H-OETPP]$^{2+}$[CH$_3$COO$^-$]$_{3/2}$[CF$_3$COO$^-$]$_{1/2}$ 4CH$_3$COOH · H$_2$O.[33]

1.2.5 Substitution of the Porphyrin Periphery

Substitution reactions can occur at both the *meso* and *beta* positions of the porphyrin

macrocycle. The proximity of the *meso* and *beta* positions of a porphyrin is illustrated by the

non-planar conformation of 2H-OETPP, which results from the considerable steric repulsion

that exists between the ethyl (*beta*) and phenyl (*meso*) substituents. An increase in the size of

either the *beta* and/or the *meso* substituent would further enhance the deformation of the

macrocycle.[30] A comprehensive demonstration of peripheral substitution effects, by Smith *et*

al,[30,34,25] involved the preparation of a range of cycloalkenyl-*meso*-tetraphenylporphyrins with

ring sizes from C$_5$–C$_7$ **(Fig. 6)**. Molecular mechanics calculations, Resonance Raman

techniques, visible absorption spectra and preliminary X-ray diffraction studies indicated that

the porphyrin core of Ni(II)-TC$_5$TPP was essentially planar but an increase in peripheral ring size made the porphyrin more non-planar.[30]
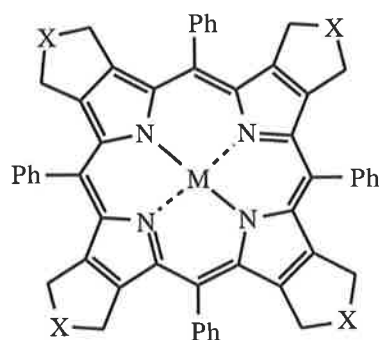
Figure 6 X = (CH$_2$)$_n$ where n = 1-3.

Generally, dodeca-substituted porphyrins are non-planar because of the interactions between the β-substituents and the *meso*-substituents,[29] although unique examples of planar dodecasubstituted porphyrins have been reported. The dodecasubstituted porphyrin CuTC$_5$T(3,4,5-OMeP)P (**Fig. 7**) was shown to be planar by X-ray crystallography.[35] The planarity of this highly substituted porphyrin results from the ability of the peripheral substituents to assume non-interacting orientations, without deforming the macrocycle. Molecular mechanics calculations supported this observation.[35]
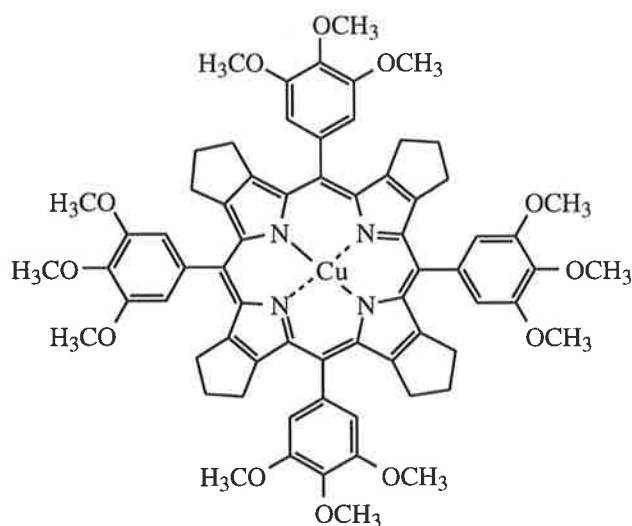
Figure 7 CuTC$_5$T(3,4,5-OMeP)P.

The main point of presenting a brief survey of porphyrin structure and conformation is that the knowledge gained from the study of non-planar model porphyrins now allows the tentative prediction of the degree and form of porphyrin non-planarity in new systems. The solid state structures may be well characterised, but what of the structure and behaviour of porphyrins in solution?

1.3   Structural Polymorphism

As the field of porphyrin structural study evolved it was shown that the solid state conformers (ruffled, saddled, wave and dome) co-exist with many conformational subtypes in solution.

1.3.1 Structural Polymorphism in Tetracycloalkenyl-meso-Tetraphenylporphyrins

The tetracycloalkenyl-*meso*-tetraphenylporphyrins have been studied by dynamic [1]H n.m.r spectroscopy; these studies revealed an unusual inversion process or 'flipping' of the macrocycle. The inversion process had been previously reported for 5,15-dialkyl-3,7,13,17-tetraethyl-2,8,12,18-tetramethylporphyrins and explained in terms of a syn/anti equilibrium of the 5,15-alkyl groups.[36] Smith *et al* proposed that the tetracycloalkenyl-*meso*-tetraphenylporphyrin inversion process involves the pyrrole rings flipping to point to opposite faces of the porphyrin, thereby exchanging the chemical shift environments of the methylene protons.[36] The inversion process was used as an indirect measurement of the degree of non-planarity because of its dependence on steric interactions between the peripheral substituents, that is, a more non-planar conformation would be accompanied by an increase in the free energy of activation (ΔG^*) if entropy considerations are ignored. The resulting calculations on the tetracycloalkenyl-*meso*-tetraphenylporphyrins did show a substantial increase in the ΔG^* (corresponding to an increase in non-planarity) as the size of the cycloalkenyl ring was increased.[32]

1.3.2 Structural Polymorphism in Ni(II) Octaethylporphyrin

The commonly encountered model porphyrin Ni(II)-OEP exhibits well-documented structural polymorphism.[29] Crystal structure studies show that Ni(II)-OEP crystallises in three distinct phases; tetragonal (ruffled),[37,38] triclinic A (planar),[38,39] and triclinic B (wave).[39]

The tetragonal phase exists as a non-planar ruffled structure, where alternate pyrrole rings are twisted with respect to the mean plane of the porphyrin such that the *meso* carbon atoms are alternately above or below the coordination plane (*meso*-carbons $\pm$ 0.51 Å from the mean coordination plane).[37]

The triclinic A phase is a non-planar ruffled structure although it is not distorted to the extent of the tetragonal phase and is considered almost planar, with the *meso*-carbons only $\pm$ 0.04 Å from the mean coordination plane.[29,32]

The crystal structure of the triclinic B phase is similar to that of the triclinic A phase and is considered to be slightly wave-like. The triclinic A phase also exhibits extensive intermolecular π-π stacking.[32,39] The solid state structures were supported by extensive Resonance Raman studies,[37,39] X-ray crystal studies,[31,38,40] and molecular mechanics calculations.[29,34]

After the X-ray studies had established the solid state structure of Ni(II)-OEP, Resonance Raman spectroscopy was used to investigate the solution structures. Resonance Raman spectroscopy showed Ni(II)-OEP to exist as a mixture of planar and non-planar conformers in non-coordinating solvents, with one ruffled conformation predominant at low temperature and multiple conformational subtypes of the non-planar ruffled tetragonal conformer at room temperature.[37] The Resonance Raman experiments and the ability of Ni(II)-OEP to assume several different crystallised forms, suggested that Ni(II)-OEP is in a dynamic equilibrium between conformational isomers while in solution.

1.3.3 Conformational Exchange in meso-Substituted Ni(II) Octaethylporphyrins

Previous studies leading to this project have established that some *meso*-substituted Ni(II)OEP macrocycles (e.g. nickel(II) 5-(phenylthio)-octaethylporphyrin (Ni(II)5PhS-OEP)) exhibit inversion between non-planar enantiomorphic ruffled conformers in solution.[32] The deformation of the macrocycle is caused by a combination of metallation with nickel and the small steric interactions of the peripheral ethyl substituents. However, what causes the observed inversion between conformers? Investigation of the thermodynamic parameters of the *meso*-substituted Ni(II)OEP macrocycles exhibiting dynamic behaviour, suggested that the observed dynamic process was independent of the *meso*-substituent, i.e. the parent macrocycle may be inherently dynamic.[32]

As an extension of this earlier work, inspection of Ni(II)5PhS-OEP reveals three degrees of rotational freedom, rotation can occur about the sulfur-porphyrin, sulfur-phenyl and ethyl substituents bonds (**Fig. 8**). Free rotation of these substituents may be the cause of the observed macrocyclic inversion.
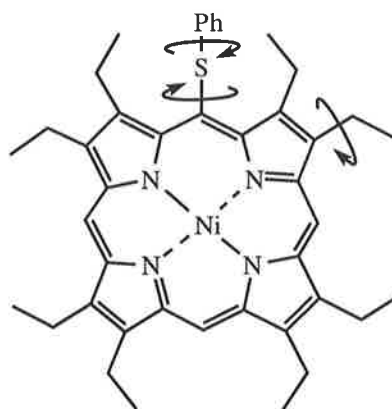
Figure 8 Possible rotational sources of dynamic behaviour in nickel(II) 5-(phenylthio)octaethylporphyrin.

The alternative non rotational source of the dynamic behaviour is the macrocycle itself. Elimination of possible peripheral sources of dynamic behaviour should enable identification of the mechanism of the dynamic behaviour. This will be achieved through systematic elimination of the rotational freedom of the peripheral substituents by the use of annulated β-substituents and bridging molecules joining the *meso* positions.

It was the aim of this study to produce conformationally restricted porphyrin macrocycles, by annulation of the β-substituents e.g. (**Fig. 9**). Once synthesised these porphyrins could be used as a starting point in a study to elucidate the origin of porphyrin conformational mobility i.e. to determine if the porphyrin macrocycle of nickel(II) (phenylthio)octaethylporphyrin was inherently dynamic or if free rotation of the β-substituents was essential for conformational inversion.

1.3.4 Solution Studies

The elucidation of porphyrin conformation in solution is not a trivial process. The exact conformation of porphyrins in the solid state can be determined by X-ray crystallography. Resonance Raman spectroscopy and molecular modelling have provided further evidence for the solid state observations. In solution however, Resonance Raman spectroscopy provides only limited spatial information, so the development of model compounds suitable for solution studies by dynamic ^{1}H n.m.r. spectroscopy would enable ^{1}H n.m.r spectroscopy to become a primary spectroscopic tool in the study of the solution structure of porphyrins.

The porphyrin macrocycles should ideally possess isolated methylene protons in the β-position to simplify ^{1}H n.m.r line broadening experiments. The complex splitting patterns obtained from ^{1}H n.m.r line broadening experiments on Ni(II)-5PhS-OEP serve as an example of the complexity that we hope to simplify. The ^{1}H n.m.r spectrum of Ni(II)-5PhS-OEP during fast exchange shows the methylene protons as a quartet (A_2X_3). The ^{1}H n.m.r spectrum of Ni(II)-

5PhSOEP during slow exchange shows the methylene protons as a complex multiplet, as a result of being part of an ABX_3 system.

How is it possible to simplify the ^1H n.m.r of model porphyrin systems? To satisfy the requirement of conformational restriction the methylene protons must be part of a small ring structure. Both of these requirements are satisfied by incorporating the methylene protons as part of 5-membered heterocyclic ring or functionalised cyclopentane ring (**Fig. 9**). Initially the *meso* positions would be unsubstituted, to allow for a variety of substituents to be added as required. Substitution at the *meso* positions by nitro, hydroxy, bromo or chloro substituents can be accomplished by standard means.[41]
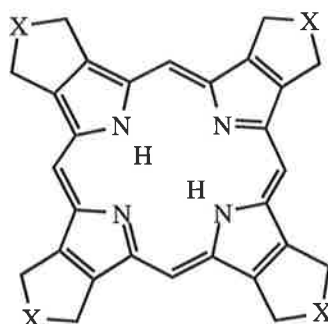
Figure 9 X = O, NR, S, Si or CR_2.

The ^1H n.m.r spectrum of the 5-membered ring could reasonably be expected to show the isolated methylene protons as an AB system during slow exchange; and a singlet (A_2 system) during fast exchange. It is obvious that the set of splitting patterns for such a five membered ring as shown in **Fig. 9** would be much simpler to analyse than an ethyl system in a dynamic ^1H n.m.r spectrum.

For the proposed system to be effective the 5-membered ring must be flat. If the ring is not flat then the methylene protons would exist as an AB system regardless of the state of exchange, and therefore lead to complex splitting patterns because of the existence of atropisomers.[42]

Initially it was planned to obtain crystal structures of vinyl sulfone and pyrrole intermediates that would indicate whether the proposed ring structures are flat as desired.

Examples of symmetrical porphyrins in which the substituents at the β-pyrrolic positions form a ring structure (eg. phenyl or cyclopentane ring)[12,25] are few, and there are no known examples of simple β-heteroannulated porphyrins. The synthesis of these novel porphyrin macrocycles is therefore an interesting synthetic challenge in its own right.

1.4 Porphyrin Precursor Synthesis

1.4.1 Pyrrole Synthesis

Early syntheses of porphyrins are notoriously laborious, and complicated by the instability of many of the functionalised pyrrole intermediates.[43,44] In general, the synthesis of porphyrins is still hampered by the difficulties encountered in the preparation of pyrrolic intermediates.

One of the most widely exploited synthesis of pyrroles suitable for use as intermediates in the preparation of porphyrins has been the classical Knorr synthesis and its variations. The classical Knorr synthesis involves the condensation of an α-amino ketone with a dicarbonyl compound.[45] The synthesis of a pyrrole precursor common to many early syntheses of 2H-OEP, namely, ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate **1** will serve to illustrate some of the limitations of classical pyrrole syntheses and just how laborious these syntheses could be (**Scheme 1**).
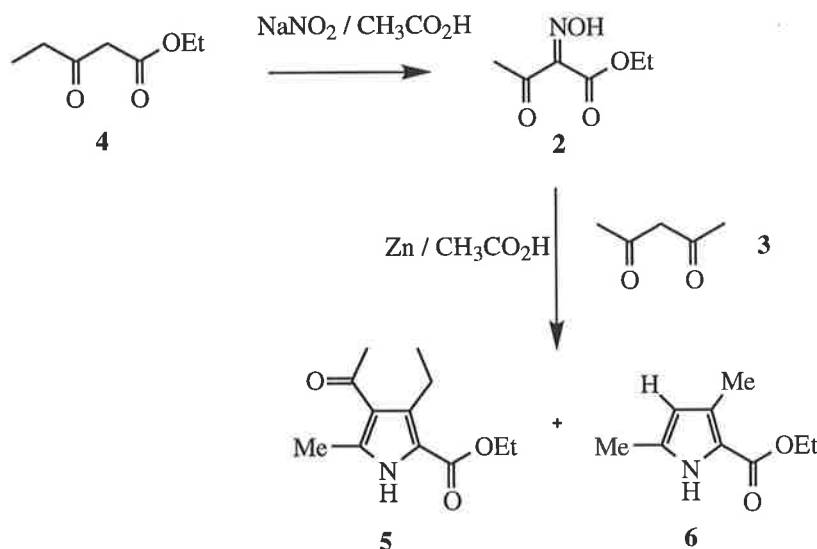
Scheme 1

Ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate may be prepared by the reverse Knorr reaction of oximinopropionylacetate **2** with 2,4-pentandione **3**.[46,47]

The initial reaction of the Knorr synthesis involves the conversion of ethyl propionylacetate **4** to oximinopropionylacetate **2** by nitrosation with sodium nitrite and glacial acetic acid. Oximinopropionylacetate **2** is then refluxed with 2,4-pentandione **3** in the presence of acetic acid and zinc to give a mixture of 4-acetyl-2-ethoxycarbonyl-3-ethyl-5-methylpyrrole **5** and ethyl 3,5-dimethylpyrrole-2-carboxylate **6**. The ethyl 3,5-dimethylpyrrole-2-carboxylate **6** by-product is removed through selective formation of a water soluble Mannich derivative. Bromination of the reaction mixture gives an unstable 4-bromomethylpyrrole intermediate that is immediately quenched with excess diethylamine to form the 'Mannich type' derivative 4-*N,N'*-diethylaminomethyl-3,5-dimethylpyrrole-2-carboxylate **7** (**Scheme 2**). Removal of **7** is accomplished by an acid wash leaving the single pyrrole **5**. Reduction of the ketone **5** with sodium borohydride and boron trifluoride diethyl etherate gives the Knorr pyrrole ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate **1**.
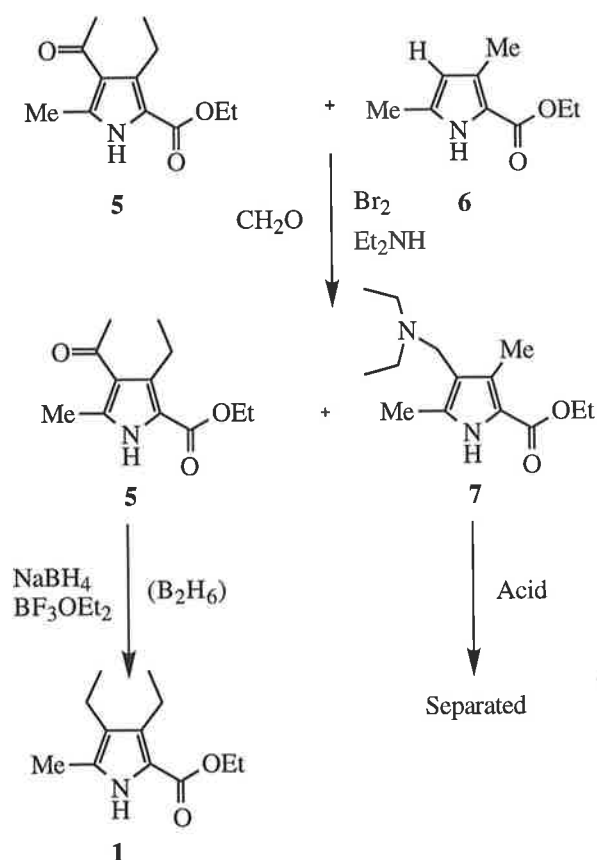
Scheme 2

The Knorr reaction is problematic, in that the reaction generates unwanted side products that must be removed by a further manipulative step thus complicating an already laborious procedure.

1.4.2 Preparation of a Porphyrin From Knorr Pyrrole

Formation of octaethylporphyrin **11** from the Knorr pyrrole **1** utilises the α-methyl substituent of **1** to provide the *meso*-carbons of the porphyrin macrocycle. Porphyrin formation is accomplished by conversion of the α-methyl group of **1** to a diethylamino methyl group through bromination of **1** to give **8** that is then treated with excess diethylamine to give the diethylamino methyl derivative **9**. The diethylamino group of **9** becomes a good leaving group under the acidic porphyrin forming reaction conditions. Saponification of the ester function of **9** under basic conditions, gives the aminomethylpyrrole carboxylate salt **10** that was converted

to 2H-OEP in 50% yield by *in situ* decarboxylation of the ester group and cyclisation in refluxing acetic acid **(Scheme 3)**.[46]
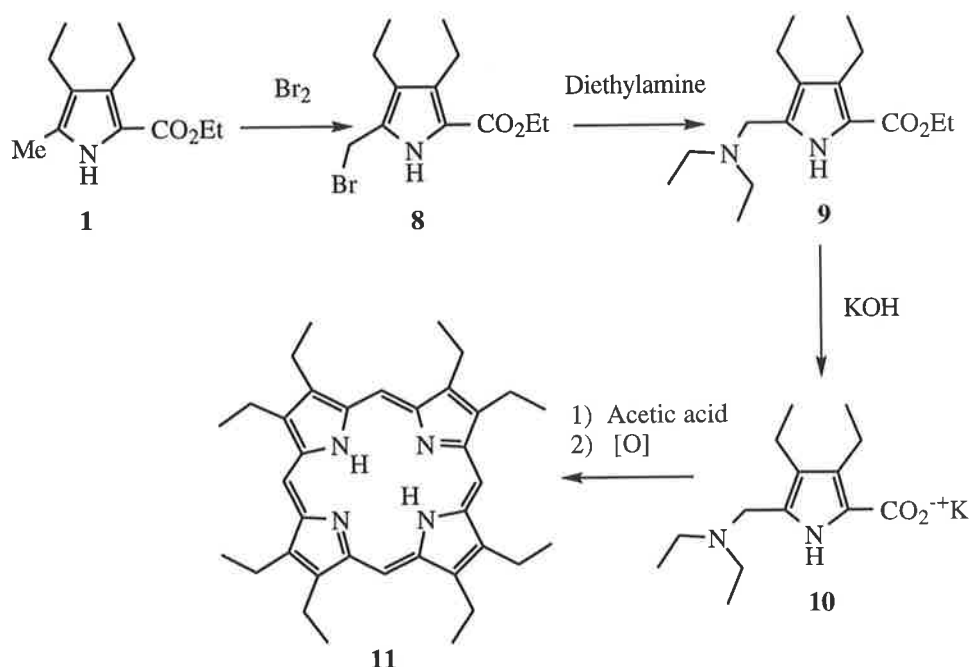
Scheme 3

Of possible use in the synthesis of annulated pyrroles, is a variation on the Knorr reaction that involves the condensation of aminomalonates **12** and β-diketones **13** in refluxing acetic acid to give 5-methyl-pyrrole-2-carboxylates **14 (Scheme 4)**.[12,48] Theoretically if the β-diketone incorporates a ring structure (e.g. cyclohexyl as in **14**), then annulated 5-methyl-pyrrole-2-carboxylates would be formed, although limited availability of β-diketones of this type and the non-convergent nature of β-diketone synthesis prevent this method from being of practical use.
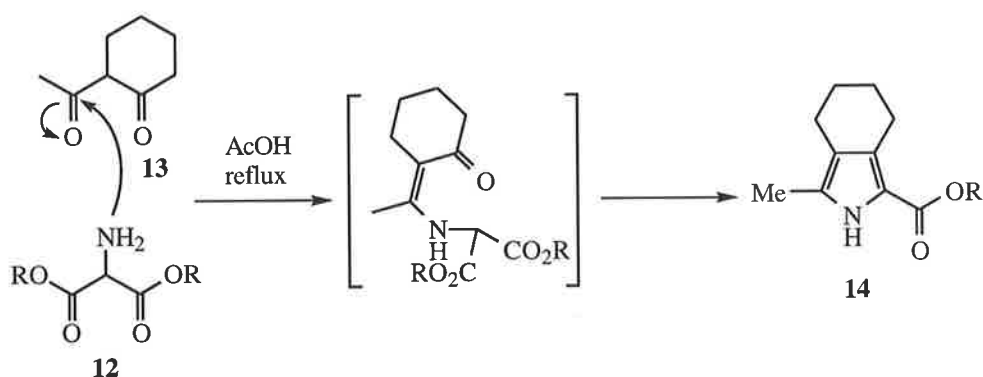
Scheme 4

The complications encountered in the Knorr synthesis of **1**, together with the difficulties involved in the conversion of **1** to 2H-OEP, are avoided in a now classic synthesis of 2H-OEP **11** described by Sessler *et al* (**Scheme 5**).[49] The Sessler 2H-OEP preparation circumvents the problems associated with the Knorr pyrrole synthesis, by forming a pyrrole-2-carboxylate **15** from a nitroalkene and an isocyanoacetate anion. The pyrrole formed from this reaction is not contaminated by unwanted by-products and can be used without further purification in the following steps, therefore providing substantial savings in time and effort compared to the Knorr procedure.
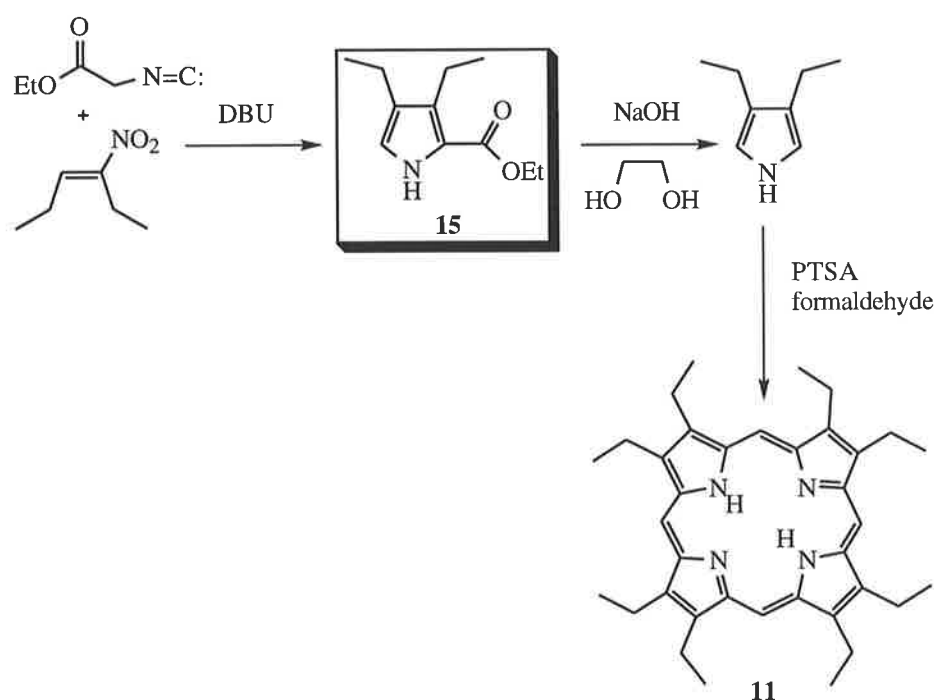
Scheme 5

The key pyrrole forming reaction is now known as the Barton and Zard pyrrole synthesis.[50,51] The Barton and Zard pyrrole synthesis was used exclusively for the preparation of the annulated pyrroles reported in this study. Thus, a brief discussion of the background of this reaction will be given.

1.5 History of the Barton and Zard Pyrrole Synthesis

In the early 1970's Schöllkopf[52] and later Matsumoto,[53] described the formation of pyrrole-2,4-dicarboxylates **16** from the reaction of two equivalents of methyl isocyanoacetate **17** with an aldehyde **18** in the presence of DBU (**Scheme 6**).
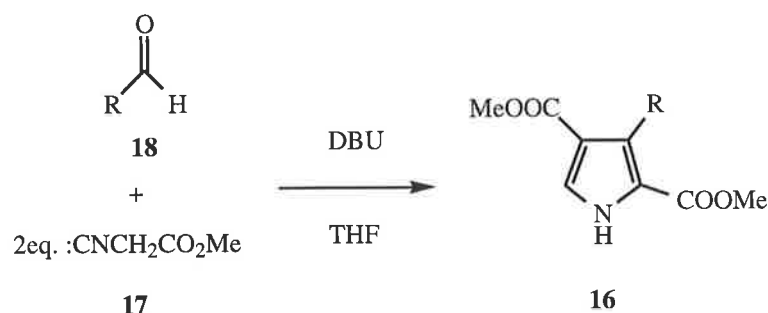
Scheme 6

In a variation on Schöllkopf's work, van Leusen prepared 3-acyl-pyrroles **19** by the addition of tosyl methylisocyanide **20** to an α,β-unsaturated carbonyl compound **21**, in the presence of base (**Scheme 7**).[54] The 3-acylpyrroles **19**, formed by this reaction are particularly useful due to the fact that 3-acyl-pyrroles are difficult to form by conventional methods such as the Friedel-Crafts acylation, which places the acyl group predominantly in the 2 position.
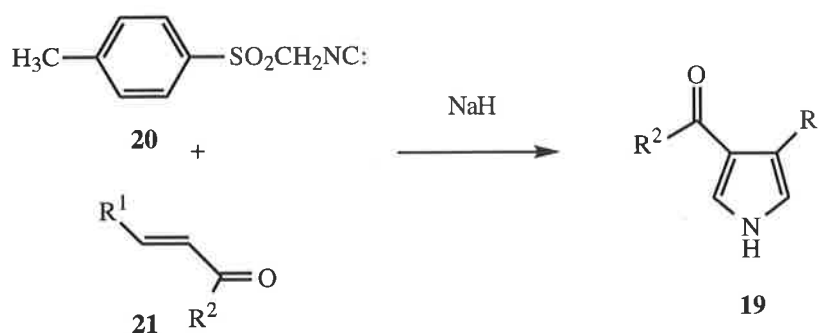
Scheme 7

van Leusen's work was adapted by Barton *et al*[*],[50,51,55,56,57] Ono *et al*[55,56] and Sessler *et al*[49] for the preparation of 3,4-disubstituted pyrrole-carboxylates, which are widely used in the synthesis of symmetrical porphyrins. 3,4-Disubstituted pyrrolecarboxylates are formed by the condensation of an isocyanoacetate anion with a nitroalkene in the presence of a strong non ionic base.

1.5.1 Advantages of the Barton and Zard Synthesis

This approach offers a number of advantages over any previous porphyrin precursor synthesis:-

- It is a convergent synthesis.

- There are no major side products.

- An ester or amide substituent can be introduced at the 2-position through the application of either an ester isocyanide or an amide isocyanide.

- The nitro alkene provides the C3 and C4 substituents of the pyrrole product, therefore this pyrrole synthesis is easily adapted to provide a wide range of substituents at the C3 and C4 positions. In particular annulated pyrroles can be easily prepared from cyclic Michael acceptors, whereas the Knorr preparation does not easily allow the incorporation of cyclic structures.

- Formation of 2,5-unsubstituted pyrroles from Knorr pyrroles (5-methylpyrrole-2-carboxylates) is achieved by demethylation of the 5-position as well as decarboxylation of

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* D. H. R. Barton *et al* acknowledged the existence of unpublished work by D. Stafforst (in 1971 under the supervision of Schöllkopf), where a pyrrole was synthesised by the base catalysed addition of an isocyanide to a nitroalkene.[51]

the 2-position. The demethylation process entails treatment of the 5-methylpyrrole-2-carboxylate with sulfuryl chloride to convert the methyl substituent into the trichloromethyl derivative. Hydrolysis of the trichloromethyl product (with concomitant hydrolysis of the carboxylate) gives a dicarboxylic acid which is then decarboxylated to give the 2,5-unsubstituted pyrrole.[47,58] In comparison to the Knorr process, direct formation of pyrrole-2-carboxylates (which can be simply hydrolysed and decarboxylated to give the desired 2,5-unsubstituted pyrroles) by means of the Barton and Zard process offers substantial savings in time and effort.

One of the aims of this study required the synthesis of heteroannulated[3,4-*c*] pyrroles. This requirement necessitates the application of Barton and Zard methodology as only a small number of heteroannulated [3,4-*c*]pyrrole derivatives have been synthesised by other means. As an example, Jendralla and Fischer prepared 1,2,3,5-tetrahydro-2-tosylpyrrolo[3,4-*c*]pyrrole **22** in a large scale preparation from 2,3-dimethylbutane **23** (**Scheme 8**).[59] Oxidative bromination of **23** gave tetrakis(bromomethyl)ethylene **24** which was then reacted with 2.3 equivalents of *p*-toluensulfonamide and an excess of K_2CO_3 in DMF to give the bicyclic sulfonamide **25**. Treatment of **25** with Red-Al® gave **22** in 30% yield.
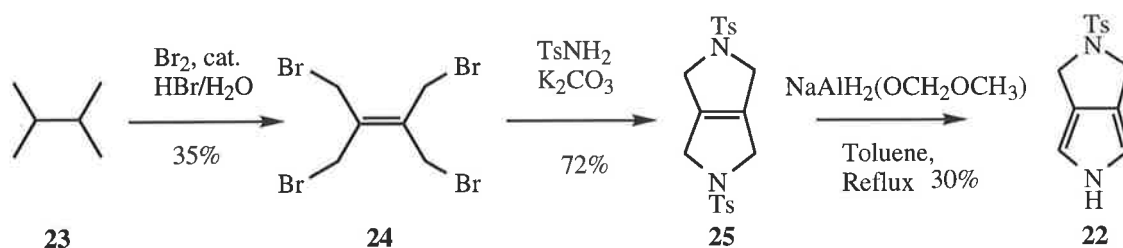
Scheme 8

1.5.2 The use of Vinyl Sulfones in the Barton and Zard Pyrrole Synthesis

The Barton and Zard reaction is generally carried out with nitroalkenes or β-acetoxy-nitro compounds. Nitroalkenes can be prepared by treatment of an alkene with mercuric chloride and sodium nitrite followed by base[60] or alternatively by treatment of the alkene with nitric oxide in

the presence of a zeolite catalyst, although the nitric oxide preparation has not been applied to any alkenes containing heteroatoms.[61] Nitroalkenes and β-acetoxy-nitro compounds can be prepared by condensation of α-nitro anion with aldehydes and ketones.[51] Nitroalkenes (in particular simple nitroalkenes such as 2-nitropropene) are generally unstable and are usually used immediately after preparation or generated *in situ*.

An alternative preparation of pyrrole-2-carboxylates reported by various workers,[62,63 64] showed that vinyl sulfones can act as Michael acceptors in pyrrole forming condensation reactions. Vinyl sulfones react in an analogous manner to nitroalkenes and are considerably more stable than the corresponding nitroalkenes. The use of vinyl sulfones also avoids the use of mercury reagents which are often used to prepare nitroalkenes from cyclic alkenes.[60] In contrast to nitroalkenes, which are sometimes difficult to purify, vinyl sulfones are generally crystalline solids that can be purified by recrystallisation.

Vinyl sulfones are most readily formed from alkenes as shown in the general **Scheme 9**. Treatment of an alkene with iodine and sodium *p*-toluene sulfinate gives a β-iodo sulfone. Treatment of the iodo-sulfone with base eliminates the halide anion to give a vinyl sulfone. Alternatively treatment of an alkene with an aryl sulfenylchloride gives an α-chlorosulfide which is oxidised to a β-chloro sulfone that gives a vinyl sulfone upon elimination with base.[62,65,66] Vinyl sulfones have also been synthesised by sulfonyl mercuration,[65,66,67,68] however yields are generally poor when compared with the iodosulfonation or benzenesulfenyl chloride additions.[68,69,70] Selenosulfonation has also been used to form vinyl sulfones[69,70] and this procedure may offer an alternative to the sulfenyl halide additions when the sulfenyl halides prove unreactive or the elimination reactions prove unselective.
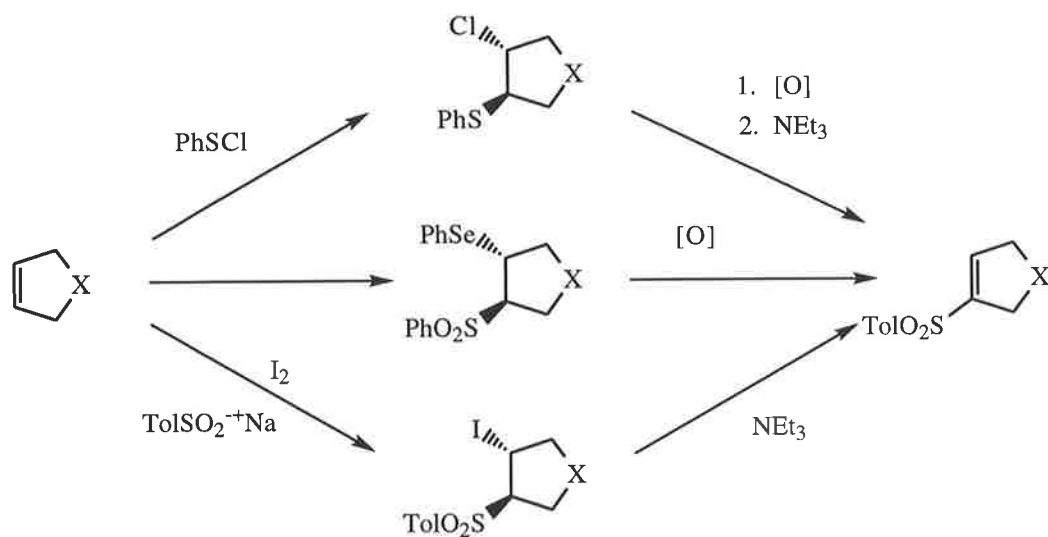
Scheme 9

1.6 Porphyrin Synthesis

Nature produces porphyrins, chlorins, bacteriochlorins and corroles on a grand scale, only to discard them after a year, in the case of the chlorophyll contained in deciduous tree leaves, and after approximately one hundred and twenty-seven days, for the heme of red blood cells. It is obvious that nature possesses a very energy efficient synthesis of these pigments of life to accommodate the regular throughput of these natural products.

1.6.1 Porphyrin Biosynthesis

The multitudes of naturally occurring tetrapyrroles are synthesised from a common pyrrolic precursor, porphobilinogen (PBG) **26**. Porphobilinogen deaminase **27** (PBGD, hydroxymethylbilane synthase) catalyses the tetramerisation of PBG, (**Scheme 10**) to give the linear tetrapyrrole, hydroxymethylbilane **28**. A series of enzymes then converts hydroxymethylbilane to the hemes, chlorophylls, vitamin B_{12}, etc. [71,72,73] The biosynthesis of hydroxymethylbilane is often 'crudely' mimicked in the laboratory preparations of porphyrins, as discussed in the following sections.

Note that in the biosynthesis of hydroxymethylbilane the α-methylene of the PBG subunits

ultimately become the *meso* carbons of the porphyrin macrocycle.
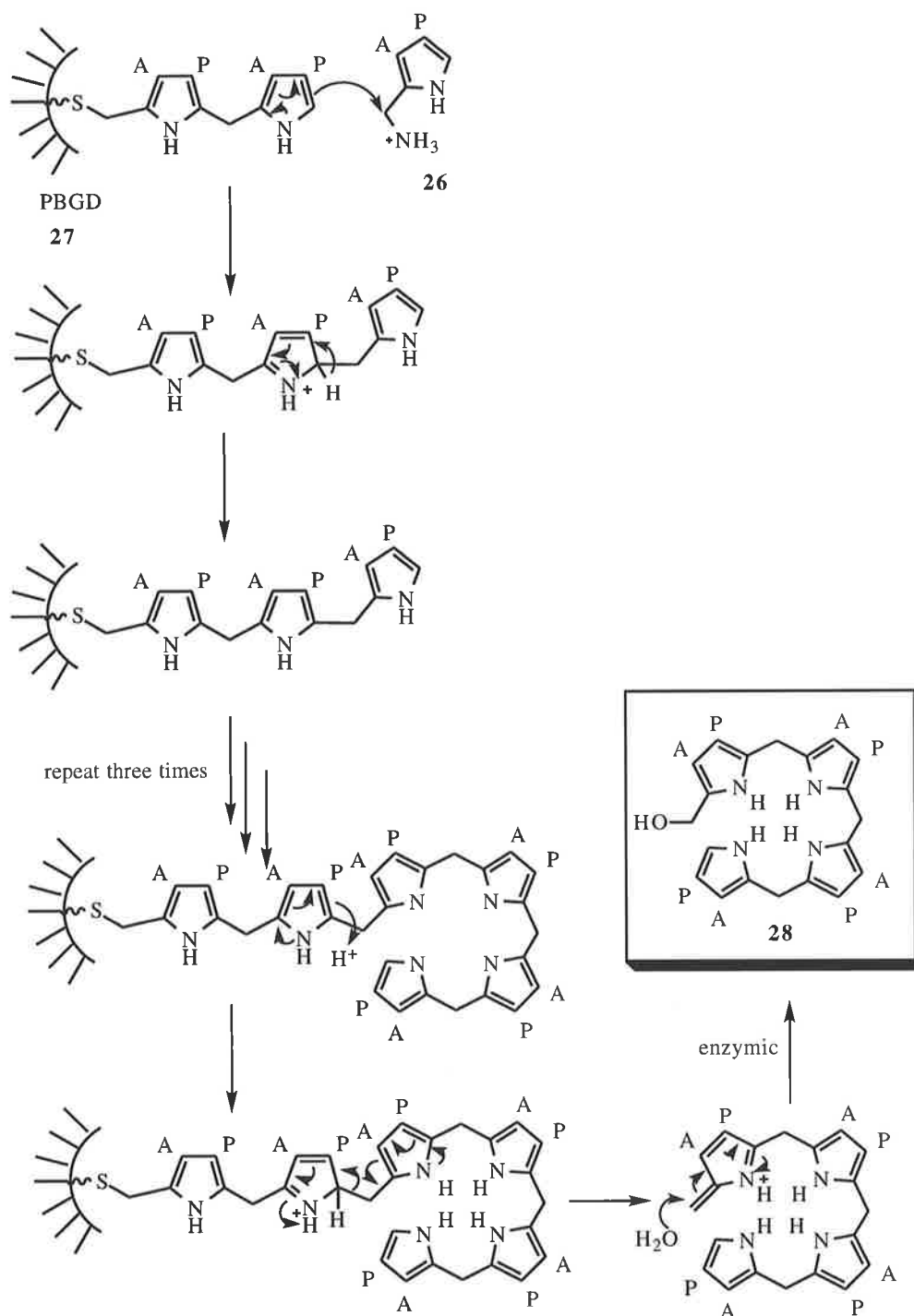
Scheme 10 The biosynthesis of hydroxymethylbilane **28** (A = CH_2CO_2H, P = $CH_2CH_2CO_2H$). Scheme 10 adapted from diagrams which appear in references.[4,71]

1.6.2 Synthesis of Non-Symmetrical Porphyrins

All porphyrins found in nature are non-symmetrical, and therefore it is no surprise to find extensive reports on the synthesis of non-symmetrical porphyrins in the literature.[74,75] The synthesis of non-symmetrical porphyrins must be carefully orchestrated to ensure a correctly functionalised macrocycle.

The synthesis of non-symmetrical porphyrins is usually achieved by the construction and condensation of an open-chain tetrapyrrolic intermediate e.g. **29 (Scheme 11),**[12] directly mimicking the biosynthetic approach shown in **Scheme 10.** The open chain tetrapyrrole **29** is then cyclised to give an intermediate porphyrinogen (non-aromatic). The porphyrinogen must be oxidised to the porphyrin **30** rapidly to minimise acid-catalysed redistribution of the pyrrole subunits i.e. scrambling of the carefully constructed pyrrole order.[76] If the four non-identical monopyrroles are simply condensed, then extensive chromatography or fractional crystallisation must be carried out to separate the statistical mixture of isomers that would form.
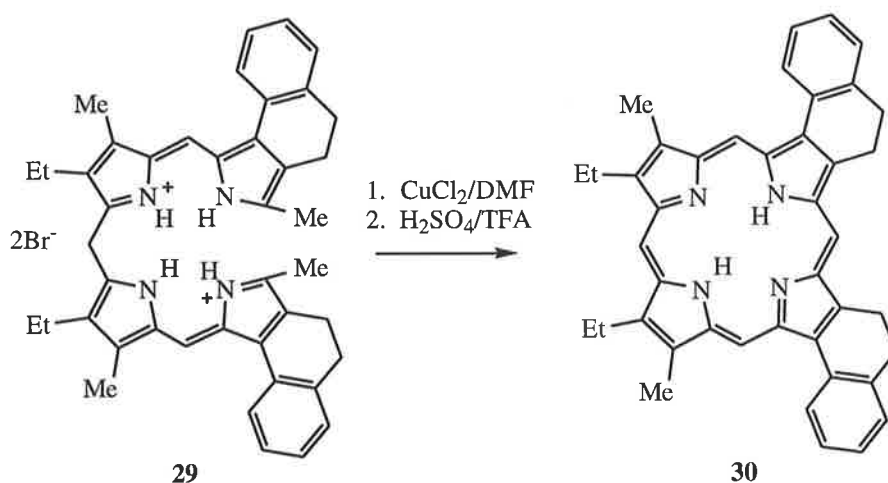
Scheme 11

Obviously the efficient synthesis of non-symmetrical porphyrins must be carried out by means of an open chain tetrapyrrole, however symmetrical porphyrins are best synthesised by the self-condensation of monopyrroles.

1.6.3 Synthesis of Symmetrical Porphyrins

The exact mechanistic details of the pyrrole condensation to give a linear tetrapyrrole followed by ring closure to give a porphyrinogen have not been fully elucidated. This is not to say the basics are not known, but important details such as the stabilities of the intermediates, the equilibrium constants, optimal reaction concentrations are not adequately described to enable predictions on the success of a reaction to be made with any degree of accuracy. In contrast to non symmetrical porphyrins, the synthesis of symmetrical porphyrins can often be achieved by simple self-condensation of a suitable monopyrrole. The relative ease by which symmetrically substituted porphyrins can be synthesised has made them suitable for use as models in the study of more complicated systems. In particular OEP (**Fig. 12**) and its derivatives, have been widely used as models in the study of porphyrin chemistry, due to their stability and good solubility in organic solvents.
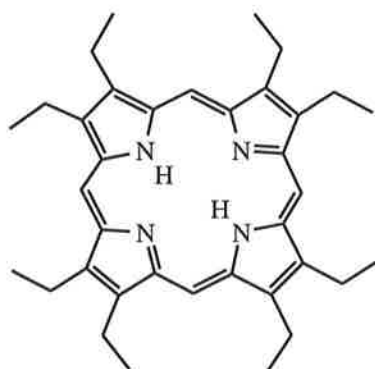
Figure 12 OEP.

The porphyrins found in biological systems have been shown to be synthesised from pyrrole building blocks which themselves are synthesised from simple acyclic precursors.[75] This biological approach to porphyrin synthesis is mimicked in the laboratory, whereby simple precursors such as glycine are elaborated to pyrrolic intermediates which are in turn condensed to porphyrins.

1.6.4 Synthesis of Porphyrins from Monopyrroles

Synthesis of porphyrins by tetramisation of monopyrroles has been accomplished by two general methods. The most utilised method is the Rothemund method which involves the condensation of 2,5-unsubstituted pyrroles with a suitable aldehyde. The aldehyde ultimately provides the four *meso*-carbons of the porphyrin.[77,78] The alternative method involves the condensation of pyrroles carrying an activated methylene substituent in the 2-position (as in PBG) **(Scheme 10)**, these methylene carbons ultimately provide the *meso*-carbons of the desired porphyrin.

The preparation of 2H-TPP **31** is typical of the Rothemund preparation and has been accomplished by heating equimolar portions of pyrrole **32** and benzaldehyde **33** in propionic acid; the product crystallises out of solution upon cooling of the reaction mixture **(Scheme 12)**.[79,80] The crude product was reported to contain a small percentage of *meso*-tetraphenylchlorin which was oxidised to 2H-TPP by treatment with DDQ. The Rothemund method enables a variety of tetra-aryl substituted porphyrins to be prepared, through simple variation of the aldehyde reagent.
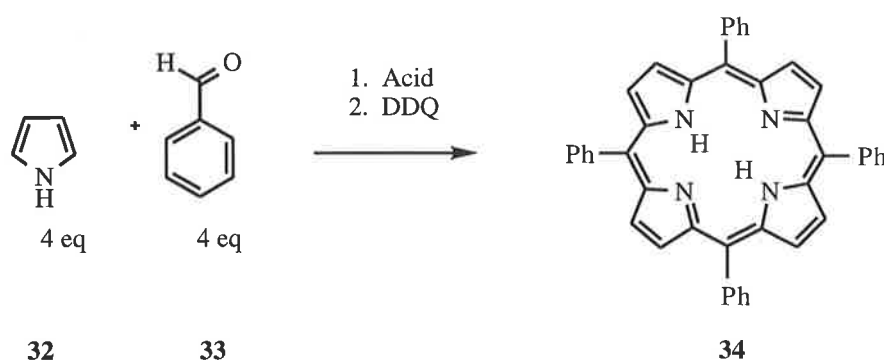
Scheme 12

Self condensation of monopyrroles containing a CH_2X group in the 2-position (X = leaving group) can be used to prepare symmetrical porphyrins. Approaches differ however in the method by which the activated methylene substituents are introduced. One approach is the Mannich reaction of a 3,4-disubstituted pyrrole **34** to give the 2-*N,N*-dimethylaminomethyl pyrrole **35**, which undergoes self condensation upon heating under acidic conditions (**Scheme 13**).[47,81]
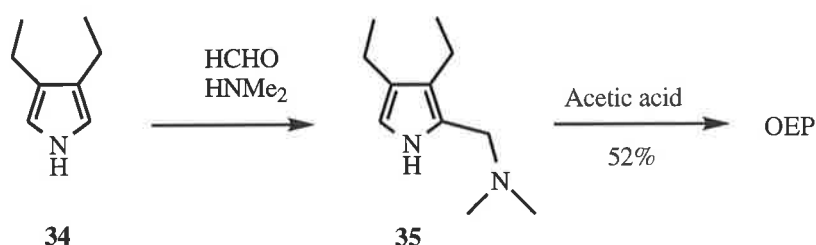
Scheme 13

A second approach involves hydrolysis of an acetoxymethyl pyrrole **36** to give a hydroxymethyl pyrrole **37** which is converted to porphyrin by heating in acetic acid. The carboxylic acid functional group undergoes decarboxylation under thermal conditions to give a reactive hydroxymethyl pyrrole intermediate (analogous to **35**) which cyclises to a porphyrinogen. Potassium ferricyanide rapidly oxidises the intermediate porphyrinogen to give OEP (**Scheme 14**).
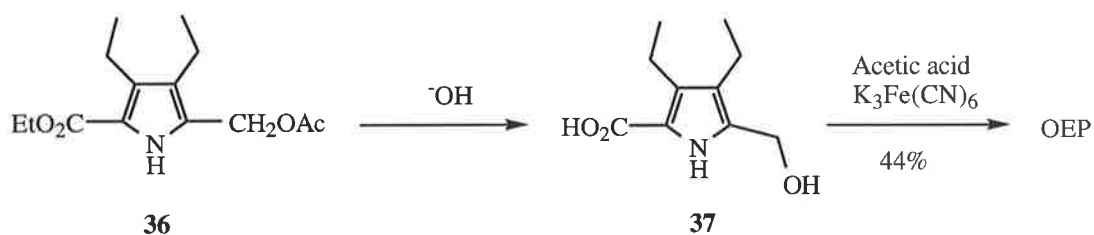
Scheme 14

In the reaction of acetoxymethyl pyrrole **37** to give OEP, an α-hydroxymethylpyrrole is the reactive intermediate. This α-hydroxymethylpyrrole simply replicates the intermediate α-hydroxypyrrole **38** found in the acid catalysed Rothemund condensation (**Scheme 15**) and is analogous to PBG in the biosynthesis of porphyrins in that it provides the *meso* carbons of the final porphyrin (**Scheme 10**).
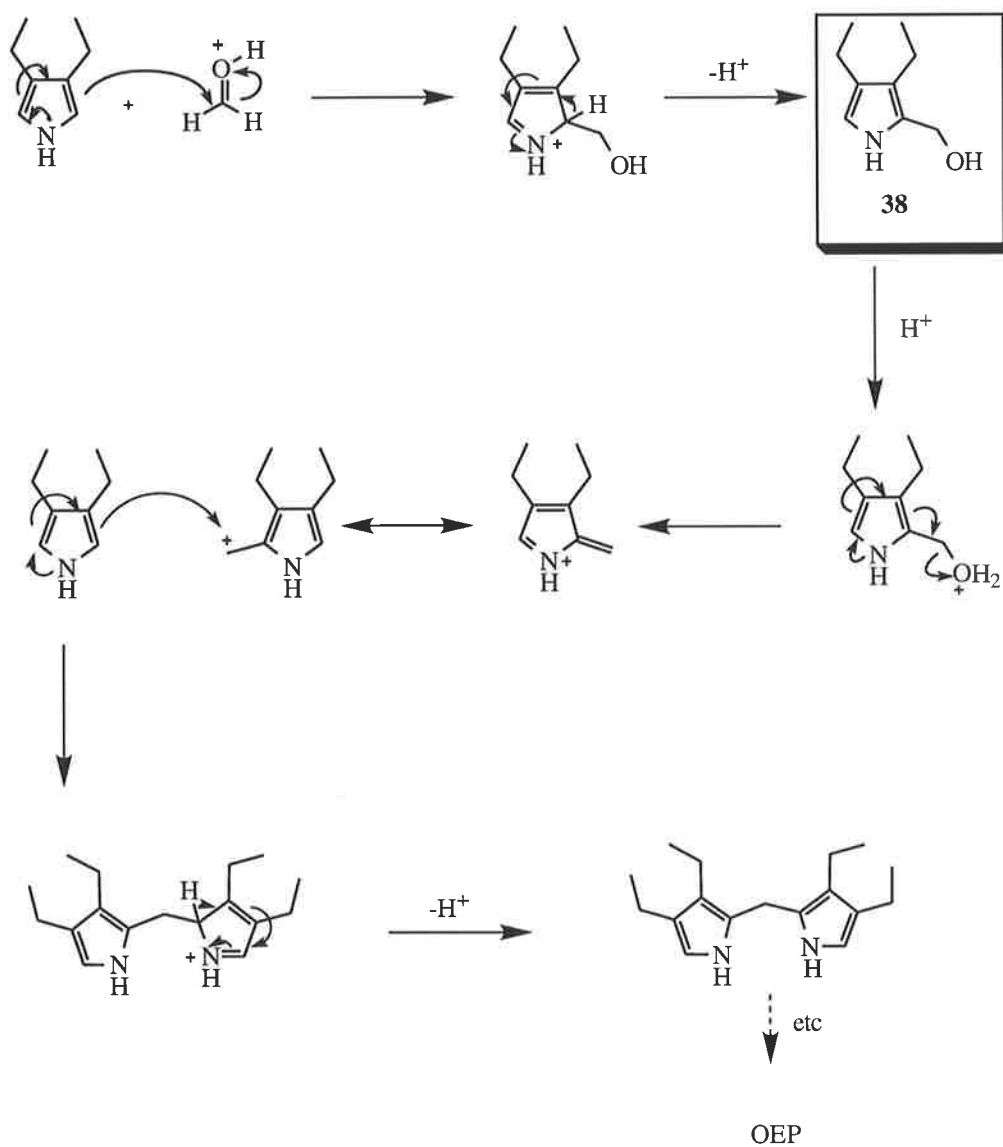
Scheme 15   Proposed mechanism and intermediates of the Rothemund condensation.

1.7   Synthesis of Annulated Porphyrins

The synthetic goals of this project are to prepare porphyrins of the type shown in **Fig. 13.**
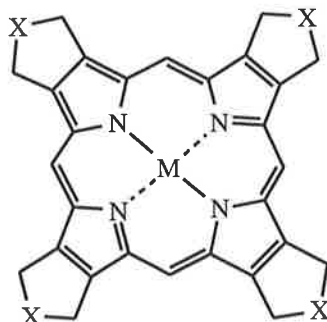
Figure 13   X = O, N, S, Si, quaternary carbon.

Upon inspection, two approaches to the desired porphyrins are apparent **(Fig. 14)**:-

•   Annulation of a suitably functionalised porphyrin nucleus (dissection A)

•   Condensation of annulated pyrroles (dissection B)
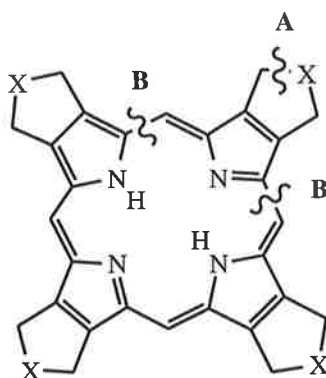
Figure 14   Synthetic disconnections.

The merits of each approach will be discussed in the following sections.

1.7.1 Dissection A. Annulation of a Suitably Functionalised Porphyrin Nucleus

The first approach requires the functionalisation of a porphyrin nucleus with groups which could undergo an annulation reaction at a later stage. In an attempt to synthesise a pyrrolo-fused porphyrin Brown *et al* hoped to cyclise α-amino ester **39** to the corresponding γ-lactam **40**. The lactam was to be reduced to an intermediate hydroxy system which could then aromatise to **41** through elimination of water, however all attempts to form the heteroannulated porphyrin (**Scheme 15**) were unsuccessful.[82]

39   **40**   **41**
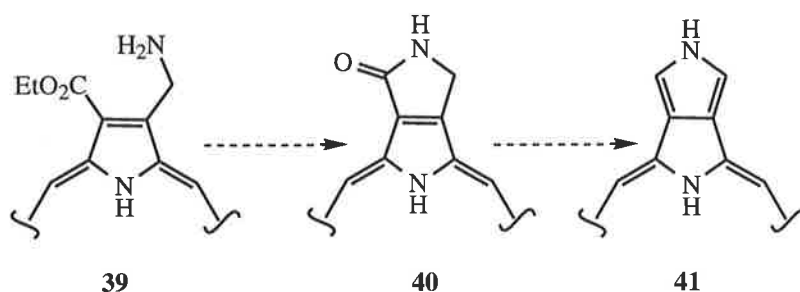
Scheme 16

The Diels–Alder reaction has also been used in the preparation of monoannulated porphyrins from a nonannulated porphyrin nucleus. The *meso*-arylporphyrins were used as the dienophile and react at the most 'alkene like' double bond, which is partially isolated from the macrocyclic conjugation pathway. The initial Diels–Alder reaction between the porphyrin nucleus and the reactive diene equivalent **42** gives a chlorin **43**, the chlorin can then be oxidised with DDQ to give a porphyrin (**Scheme 17**).[7]
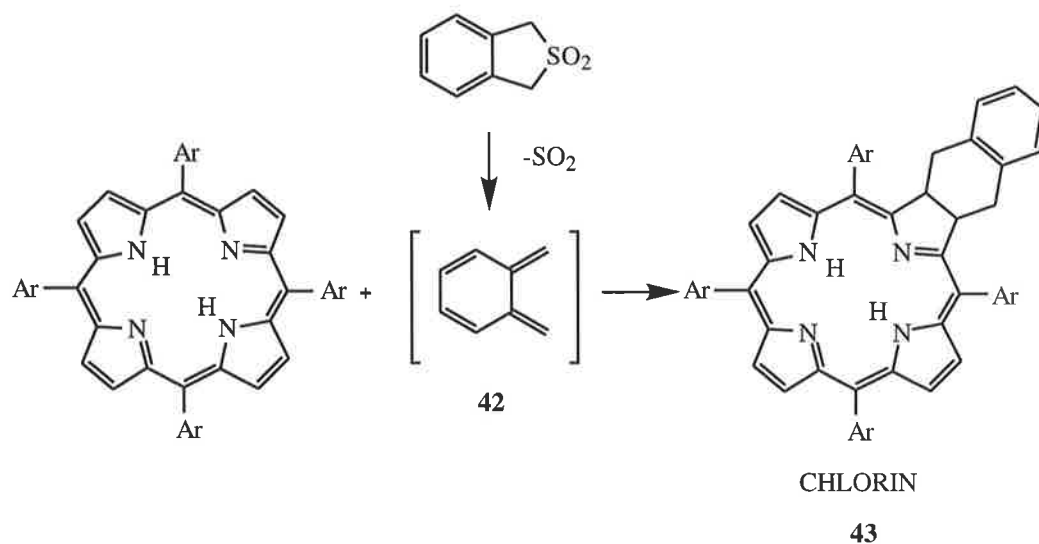
Scheme 17

The formation of novel tetrabenzoporphyrins by the application of the Diels–Alder reaction has been pursued by Vicente *et al.*[83] Thermal extrusion of sulfur dioxide from pyrrole fused 3-sulfolenes gave a reactive pyrrole based diene equivalent, that could react with a variety of dienophiles such as *N*-phenylmaleimide to give annulated pyrroles. It may be possible to adapt this approach to the synthesis of heteroannulated porphyrins by using diene-like intermediates developed by Takayama *et al.*[84,85] The thermodynamic extrusion of SO_2 from 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides **44** produces a reactive diene equivalent **45** that may react with a porphyrin to give Diels–Alder products **46**. The initial Diels–Alder product **46** could then be oxidised to a porphyrin (**Scheme 18**); however this methodology does not provide an avenue to the tetraannulated products required in this study.
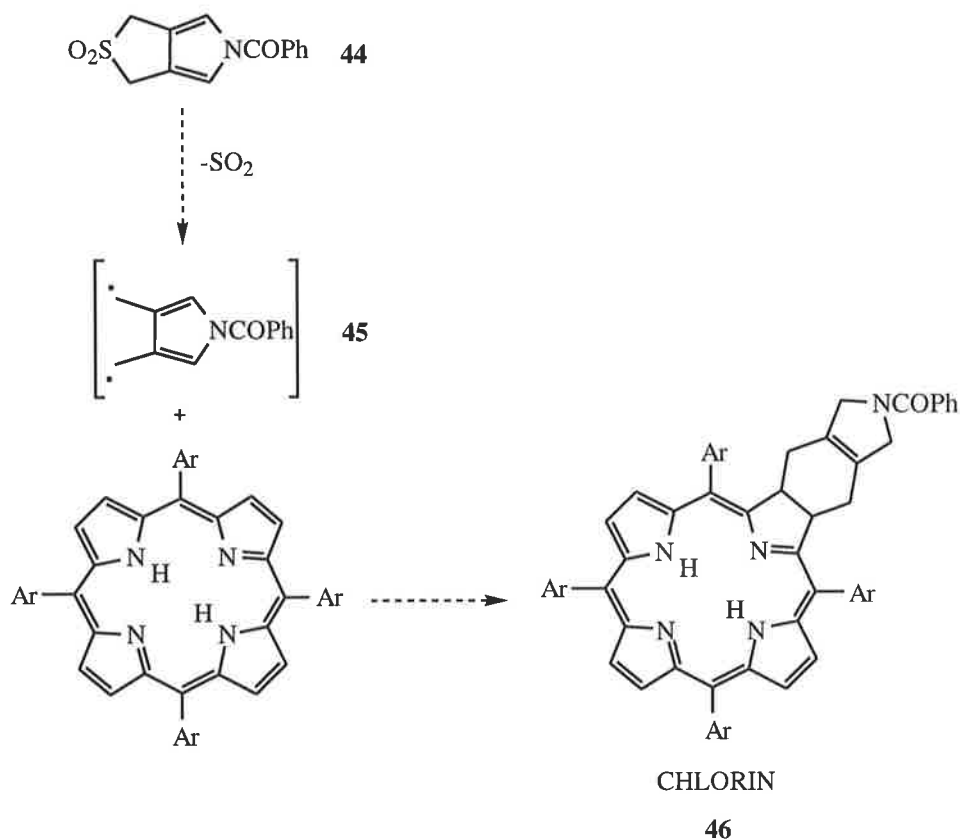
Scheme 18

1.7.2 Dissection B. Condensation of Annulated Pyrroles

The formation of annulated pyrroles by the condensation of monopyrroles can be split into two distinct approaches:-

A. The self-condensation of pyrroles **47** bearing an α-methyl, with a good leaving group at the benzylic carbon. The α-methyl substituent of each monopyrrole then becomes the *meso* carbons of the porphyrin.

B. The acid-catalysed condensation of 2,5-unsubstituted pyrroles **48** with an aldehyde. The aldehyde provides the *meso* carbon in the porphyrin product.
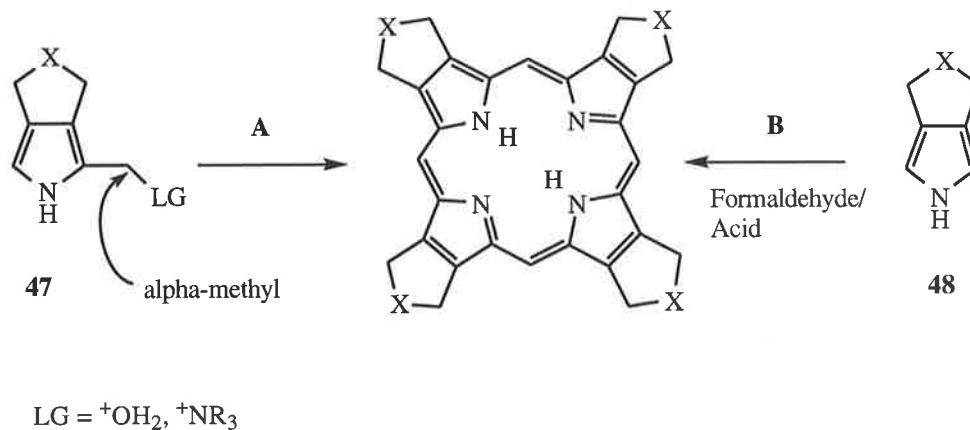
Scheme 19

The condensation of annulated monopyrroles provides a number of advantages (**Scheme 19**):

i. A convergent synthesis in terms of pyrrole synthesis and pyrrole condensation.

ii. A literature precedence exists for the formation of annulated porphyrins from annulated pyrroles, e.g. cyclopentane, cyclohexane, benzene, etc.[11,14,25,30]

iii. Annulated pyrroles are readily accessible through Barton and Zard methodology.[86]

Condensation of monopyrroles is the most straight forward method of synthesising annulated porphyrins. Annulated porphyrins may also be synthesised by the more labour intensive 3 + 1 or 2 + 2 methodologies. The 3 + 1 or 2 + 2 condensations may provide an entropic advantage over the monopyrrole condensation as the preformation of dipyrromethanes and tripyrromethanes means less individual reactions are needed before cyclisation of the tetrapyrrolic intermediate.

1.7.2.1   [2 + 2] Condensation

Porphyrins with C2 symmetry have been conveniently prepared by the MacDonald condensation of two suitably functionalised dipyrromethanes such as **49** and **50**.[87] When the β-substitution is identical a symmetrical porphyrin is formed (**Scheme 20**). This approach has been used to minimise polymeric pyrrole material, which is the major by-product of most pyrrole condensations. The extra manipulative steps and poor stability of some dipyrromethanes are drawbacks to this method.[88]
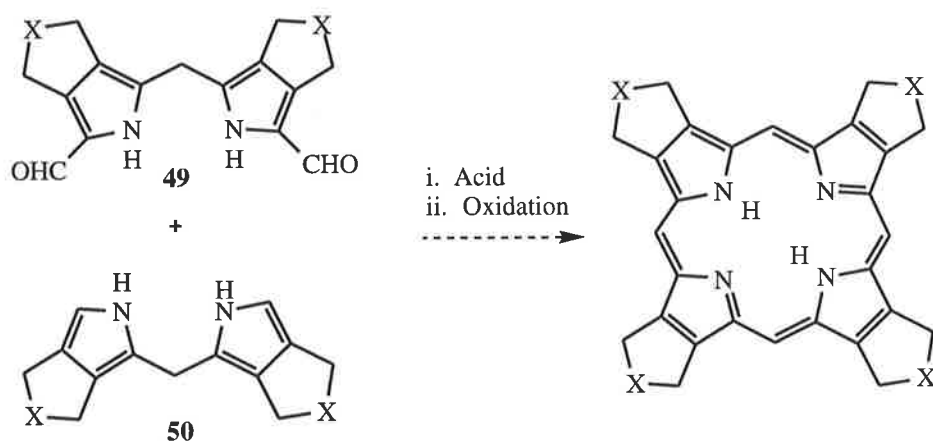
Scheme 20

1.7.2.2   3 + 1 Condensation

A versatile route to porphyrins with three different pyrrole subunits is the increasingly utilised condensation of a tripyrromethane **51** and either a 2,5-formyl pyrrole[89,90,91] or a 2,5-bis[(*N,N*-dimethylamino)methyl]pyrrole **52** (**Scheme 21**).[76]
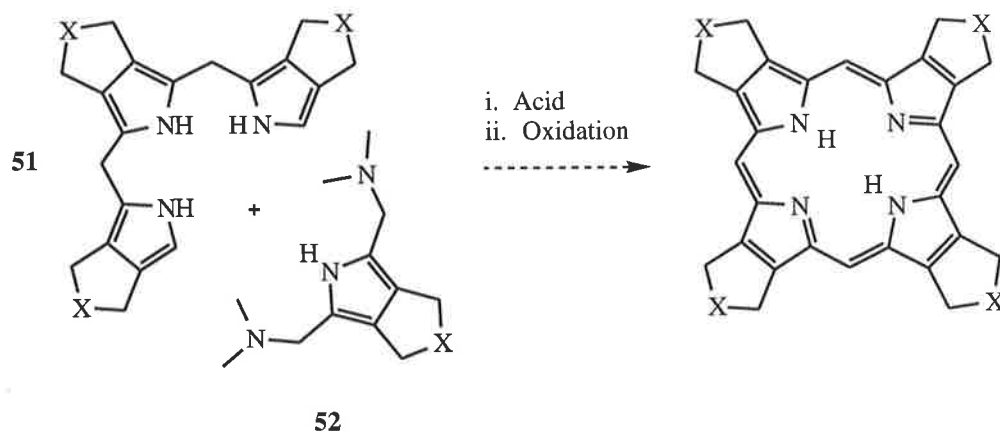
Scheme 21

This procedure entails the formation of a tripyrromethane and the effort required is often not justified for the synthesis of a symmetrical porphyrin.

1.8   Oxidation of Porphyrinogens

Porphyrins are the end product of a series of three key reactions:-

i.   Condensation of pyrrole subunits to give a linear tetrapyrrole.

ii.   Cyclisation of the linear tetrapyrrole to give a porphyrinogen.

iii.   Oxidation of the intermediate porphyrinogen to give a porphyrin.

The final oxidation step is often given little attention in the planning of a porphyrin synthesis. The oxidation step however should not be ignored as it can affect the purity and yield of the porphyrin to a great degree. The yield and purity can be reduced through incomplete oxidation of the intermediate porphyrinogen, which results in contamination of the product with chlorins (reduced porphyrins). The purification of the porphyrin product can be rendered ineffective due

to the presence of excess oxidant. Oxidation may be routinely carried out with a 3 fold excess of quinones such as DDQ or chloranil **(Scheme 22).**
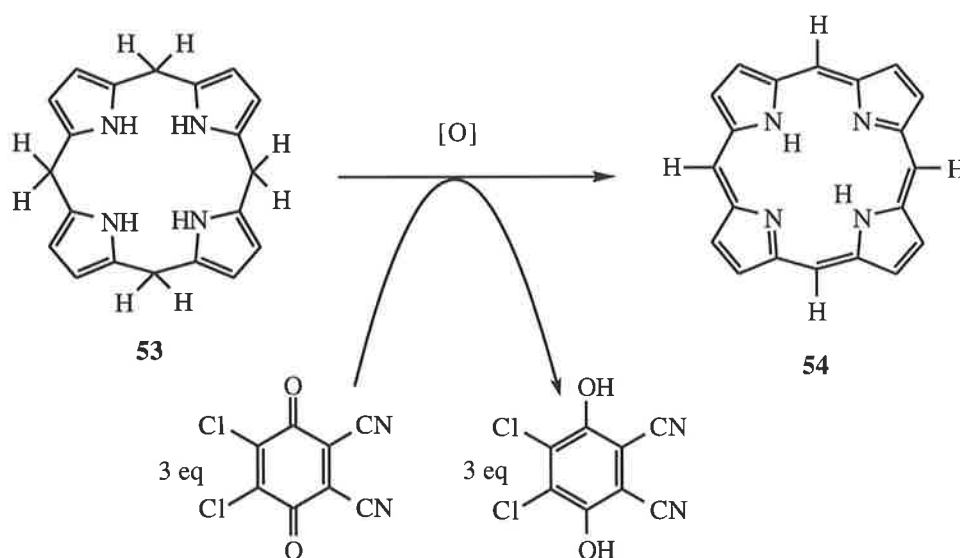
Scheme 22

Three equivalents of quinone are required to remove six hydrogens from the porphyrinogen **53** to give the aromatic porphyrin **54**. Molecular oxygen and inorganic oxidants such as $K_3Fe(CN)_6$ are also frequently used.[76,92] Quinones are generally used at room temperature under very mild conditions, however the hydroquinone by-product must be removed by basic washes and/or chromatography upon completion of the reduction. When air or pure oxygen is applied, it is bubbled through the reaction mixture containing the porphyrinogen to ensure thorough mixing. Oxidation with oxygen or air however is often not quantitative so the final product often requires treatment with a small amount of quinone to avoid contamination of the product with chlorins.

1.9 Project Aims

A brief survey of porphyrin structural characteristics and the synthesis of porphyrins has been given. This study aims to contribute to both research areas by the:-

- Formation of a wide range of annulated vinyl sulfones with special attention given to examples containing heteroatoms such as N, O, S and Si. Vinyl sulfones of this type would give access to many previously undescribed porphyrins.

- Synthesis of pyrroles following Barton and Zard methodology, using vinyl sulfones exclusively in place of nitroalkenes.

- Investigation of porphyrin forming condensations under mild conditions i.e. the use of very mild acids or alternatively condensations which do not require acid to induce reaction.

- Formation of porphyrins suitable for use in ^{1}H n.m.r. line shape experiments. It is hoped these porphyrins will eventually aid in the determination of the mechanism of porphyrin conformational exchange in solution.

Details of the investigations will be discussed in the following chapters.

Results and Discussion

Overview of the Following Chapters

The following chapters describe the synthesis of annulated porphyrin precursor molecules and ultimately the porphyrin-forming reactions. The porphyrin precursors synthesised include:-

- cyclic alkenes

- vinyl sulfones

- isocyanides

- annulated pyrroles

The retrosynthetic analysis of an annulated porphyrin shown below, highlights the main porphyrin precursors (**Scheme 23**).

X = O, NAr, SO$_2$, Si, C(R')$_2$

:CNCH$_2$CO$_2$R

R = Me, Et, N(R')$_2$
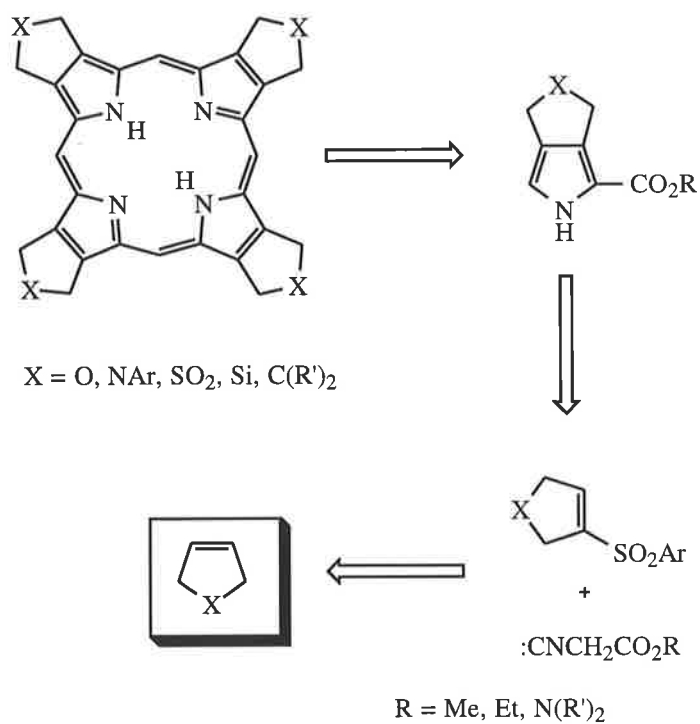
Scheme 23

Chapter 2: Synthesis of Cyclic Alkenes and Vinyl Sulfones

2.0 Synthesis of Cyclic Alkenes

The retrosynthetic analysis **(Scheme 23)** highlights cyclic alkenes as the primary starting materials for this project. The synthesis of each cyclic alkene will be discussed individually in this chapter.

2.0.1   4,4-Dimethylcyclopent-1-ene

Isolated methylene protons were required as part of a 5-membered ring structure therefore a cyclopentene derivative disubstituted at carbon 4 was initially investigated. The cyclopentene derivative 4,4-dimethylcyclopent-1-ene **54** has been synthesised on a large scale and the formation of a vinyl sulfone from this alkene appeared trivial.[93,94,95] Ni(II)TC5TPP (**Fig. 15**) has been synthesised in in good yield[25] starting from cyclopentene and therefore provided a precedence for the synthesis of an annulated porphyrin from cyclopent-1-ene derivatives.
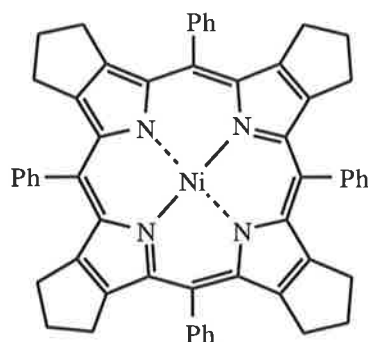
Figure 15

The starting material for the synthesis of 4,4-dimethylcyclopent-1-ene **54** was dimethyl-3,3-dimethyl glutarate **55**, which was readily prepared by esterification of 3,3-dimethylglutaric acid

39

56 in 80% yield. Acyloin ring closure of the dimethyl 3,3-dimethyl glutarate **55** with Na/NH$_3$ was the key step in the synthesis of **54 (Scheme 24)**. Two variations of the acyloin reaction were used, varying only in the method of workup of the initial acyloin product (a sodium dienolate). In the first variation of the acyloin condensation, a dilute hydrochloric acid work up afforded a mixture of 4,4-dimethyl-2-hydroxycyclopentanone **57** and 4,4-dimethyl-2-hydroxycyclopent-2-ene-1-one **58**. The second procedure trapped the dienolate from the acyloin reaction as the stable bis-silyldienolate **59**.
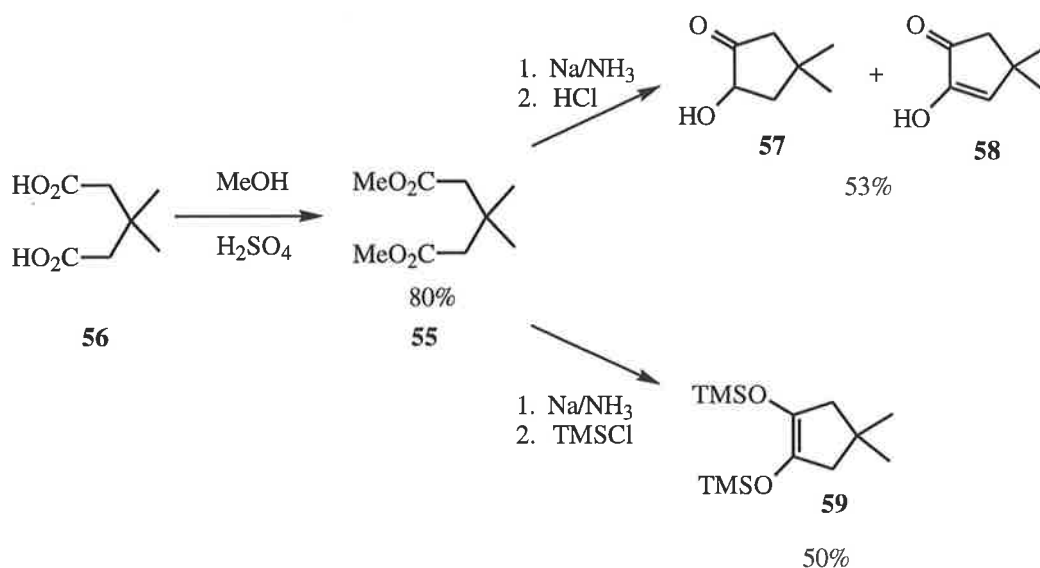
Scheme 24

The mixture of products from the acidic workup (**57** and **58**) required a two step reduction (hydrogenation of the mixture with Raney nickel converted the enol **58** to the hydroxycyclopentanone **57**, followed by LiAlH$_4$ reduction of hydroxycyclopentanone **57**) to give 4,4-dimethylyclopentane-1,2-diol **60 (Scheme 25)**. The bis-silyldienolate product **59** from the second procedure was simply hydrolysed under mild conditions to give 4,4-dimethyl-2-hydroxycyclopentanone **57**. Reduction of hydroxycyclopentanone **57** with LiAlH$_4$ gave the diol **60** in good yield **(Scheme 25)**. The second procedure (in which the initial acyloin product was trapped as a bis-silyldienolate) was the preferred procedure as only one reduction step was needed to form the diol **60** from the acyloin product.
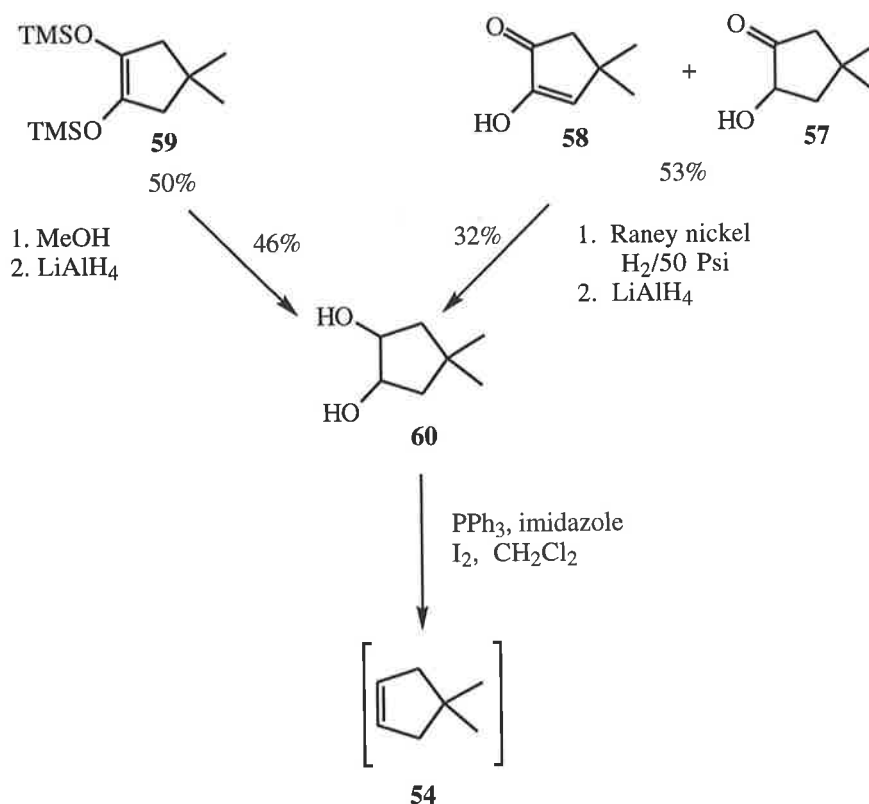
Scheme 25

The diol **60** was treated with triphenylphosphine, imidazole and iodine to give 4,4-dimethylcyclopentene **54**, which was co-distilled with dichloromethane from the reaction mixture. The product was stored in dichloromethane at low temperature because of its volatility.

2.0.2   *2,5-Dihydropyrrole Derivatives*

N-Substituted-2,5-dihydropyrroles were synthesised by either substitution of 2,5-dihydropyrrole **61** or [4+1] annulation of *cis*-1,4-dimesyloxybut-2-ene **68** with a primary amine.

Addendum

Withdrawing electron density away from the pyrroline nitrogen by resonance should render the dihydropyrrolo[3,4-c]pyrrole derivatives less reactive toward potential acid catalysed polymerisation.

Clarification:

Regarding pg 42, p 2:

The ultimate goal was to achieve a reduction in the basicity of the nitrogen atom. We had postulated that protonation of the pyrroline nitrogen, under the acidic conditions of porphyrin formation, would produce a good leaving group. Once formed the protonated nitrogen group could then be displaced by internal electron movement (Scheme A). The ring opened intermediate could then be expected to undergo unwanted side reactions. A decrease in the basicity of the pyrroline nitrogen would therefore reduce the probability of ring opening occurring.
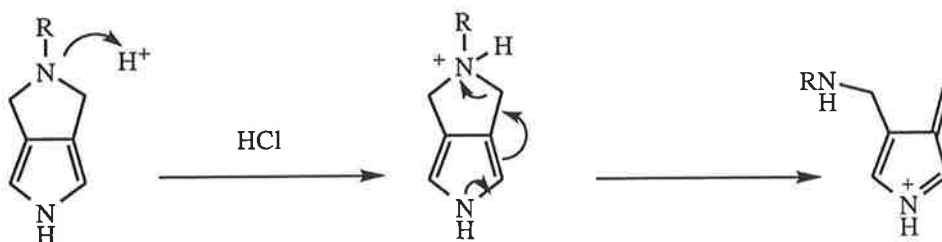
Scheme A

2.0.2.1   2,5-Dihydropyrrole

2,5-Dihydropyrrole **61** is commercially available, however it is prohibitively expensive and of unsatisfactory purity. 2,5-Dihydropyrrole was therefore synthesised according to the literature procedure (**Scheme 26**).[96] Delépine amination of *cis*-1,4-dichloro-2-butene **62** with hexamethylene tetramine gave the chloroallylamine hydrochloride salt **63** in good yield. Acid hydrolysis of **63** gave the amine hydrochloride salt **64**. Finally, base induced intramolecular nucleophilic ring closure of **64** gave **61** as a colourless liquid after distillation from the reaction mixture, in 39% overall yield.
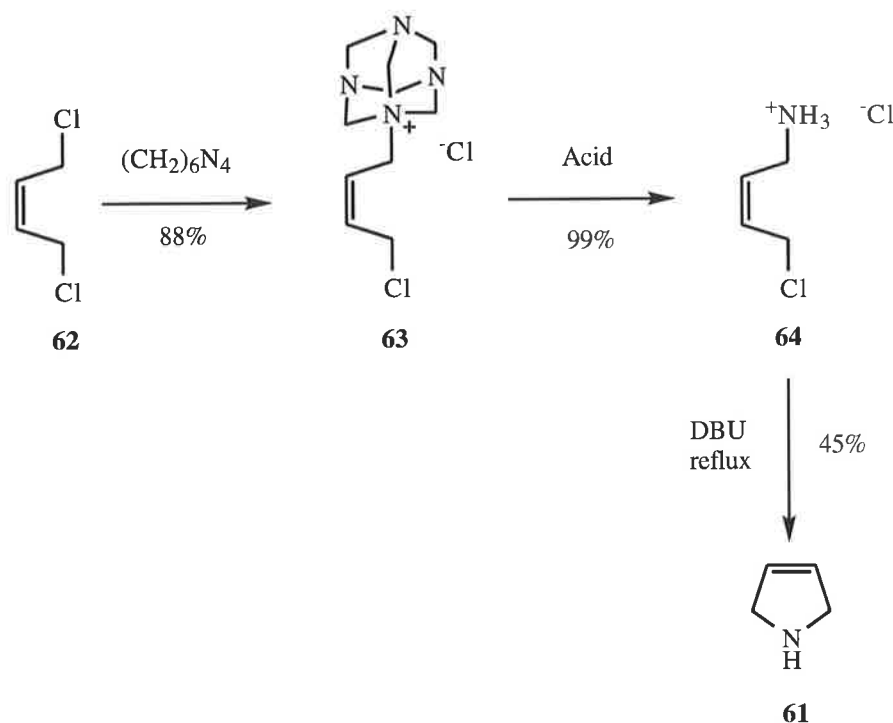
Scheme 26
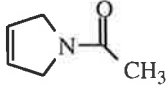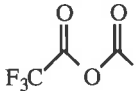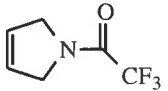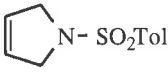
2.0.2.2   Substitution of 2,5-Dihydropyrrole

2,5-Dihydropyrroles were N-substituted with electron-withdrawing groups, such as sulfonyl or acyl groups, in order to decrease the basicity of the tertiary nitrogen atom of the 2,5-dihydropyrroles **Table 1**. Withdrawing electron-density away from the nitrogen by resonance

would render the dihydropyrrolo[3,4-*c*]pyrrole derivatives less reactive toward potential acid-catalysed polymerisation. 2,5-Dihydropyrrole was acylated successfully with both acetyl chloride and trifluoroacetic anhydride to give the acetyl **65** and trifluoroacetyl **66** derivatives in good yields. The *p*-toluenesulfonyl derivative of 2,5-dihydropyrrole **67** was also readily formed in 95% yield by the reaction of 2,5-dihydropyrrole with *p*-toluenesulfonyl chloride.

Table 1. *N*-Substitution of 2,5-Dihydropyrrole
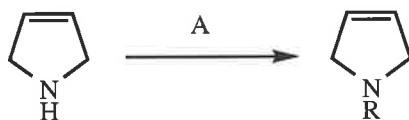
REAGENTS (A)	CONDITIONS	PRODUCT	%YIELD
H₃C–Cl ,pyridine	RT, CH₂Cl₂, 2hr	**65**	89%
F₃C–O–CF₃ ,pyridine	0°C-RT, CH₂Cl₂, 1hr	**66**	53%
ClSO₂Tol, NEt₃	RT, CH₂Cl₂, 5hr	N– SO₂Tol **67**	95%

The ^{1}H n.m.r. spectrum of 1-acetyl-2,5-dihydropyrrole **65** showed the methylene protons at positions 2 and 5 are equivalent at room temperature, the ^{13}C spectrum however, shows all ring carbons to be non-equivalent. The ^{13}C time scale therefore delineates between amide rotational conformations. In contrast to the acetyl derivative, the 1-trifluoroacetyl-2,5-dihydropyrrole **66** displays non-equivalent methylene protons in the ^{1}H spectrum and non-equivalent ring carbons in the ^{13}C spectrum, indicating higher rotational barriers for the trifluoro derivative.[97] If the acetyl and trifluoroacetyl pyrrolo[3,4-*c*]pyrrole derivatives showed similar non-equivalence of

the methylene protons due to the amide bond, then their utility in porphyrin conformation analysis by ^{1}H n.m.r. spectroscopy may be limited. The electron-withdrawing ability of the acetyl and trifluoroacetyl groups is evident from the restricted rotation around the C–N bond as a result of delocalisation of the nitrogen lone pair into the amide giving rise to an sp^2 like C–N bond.

The ^{1}H n.m.r. spectrum of 1-(*p*-toluenesulfonyl)-2,5-dihydropyrrole **67** showed the methylene protons at positions 2 and 5 to be equivalent at room temperature. The ^{13}C spectrum also showed the methylene ring carbons to be equivalent. These results indicate that the *p*-toluenesulfonyl group is either rotating rapidly about an sp^3-type N–S bond or the *p*-toluenesulfonyl group is held rigidly and symmetrically through an sp^2-type N–S bond. As the sulfone group is strongly electron withdrawing an sp^2-type N–S bond is likely.

2.0.2.3   *[4+1] Annulation of cis-1,4-Dimesyloxybut-2-ene with Primary Amines*

As a method of introducing aryl groups to the 2,5-dihydropyrrole nitrogen, the [4+1] annulation of *cis*-1,4-dimesyloxybut-2-ene **68** was investigated. *cis*-1,4-Dimesyloxybut-2-ene was synthesised, according to the literature, procedure by mesylation of *cis*-2-butene-1,4-diol in 75% yield.[98] A series of *N*-aryl-2,5-dihydropyrroles **69** were then synthesised by condensation of **68** with suitable aryl amines **Table 2**. Aryl amines were chosen to give a representative sample of inductive and mesomeric effects to enable systematic manipulation of the electron density on the ring nitrogen.

Table 2. [4+1] Annulation of *cis*-1,4-Dimesyloxybut-2-ene with Primary Aryl Amines
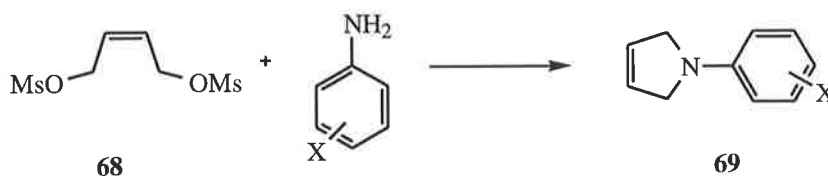
AMINE	CONDITIONS	PRODUCT (X =)	YIELD
MeO—⟨ ⟩—NH$_2$	RT, CH$_2$Cl$_2$, 24hr	4-OMe **70**	76%
H$_3$C—⟨ ⟩—NH$_2$	RT, CH$_2$Cl$_2$, 24hr	4-CH$_3$ **71**	40%
⟨ ⟩—NH$_2$	RT, CH$_2$Cl$_2$, 24hr	H **72**	72%
O$_2$N—⟨ ⟩—NH$_2$	RT, DMF, NaH, 2hr	4-NO$_2$ **73**	44%
O$_2$N—⟨ ⟩—NH$_2$ (2,6-diCl)	RT, DMF, NaH, 24hr	 **74**	~5%*

*Yield estimated from [1]H n.m.r. spectrum.

Condensation reactions proceeded in a facile manner for electron-donating aryl amines at room temperature, base was applied to induce cyclisation of the less nucleophilic aryl amines. All products were solids, with melting points that were consistent with literature values. [1]H n.m.r. spectra of the products showed a single vinyl signal, thus indicating a symmetrical *N*-substituted-2,5-dihydropyrrole had been formed. The last entry in **Table 2** (the sterically hindered 2,5-dihydropyrrole **74**) was not produced in satisfactory yields, possibly due to a combination of steric and electronic effects. The synthesis of this 2,5-dihydropyrrole was therefore not pursued further. The [1]H n.m.r. spectrum of 2,5-dihydropyrrole **70** (bearing an

electron-donating aryl group) indicated partial aromatisation had occurred under the reaction conditions. The [1]H n.m.r. spectrum of the aromatic derivative consisted of a singlet at δ 3.79 ppm and multiplets at δ 6.35 and δ 7.03 ppm for the pyrrole protons.

The functionalisation of 2,5-dihydropyrrole with sulfonyl and acetyl groups provided strongly electron-deficient 2,5-dihydropyrroles while the annulation of *cis*-1,4-dimesyloxybut-2-ene with primary aryl amines provided a series of 2,5-dihydropyrroles with controlled electonic characteristics.

2.0.3   *1,1-Diphenyl-1-silacyclopent-3-ene*

No silicon annulated porphyrin derivatives have been reported in the literature at this time, therefore the formation of a porphyrin derived from 1,1-diphenyl-1-silacyclopent-3-ene **75** was an attractive target. 1,1-Diphenyl-1-silacyclopent-3-ene **75** was prepared by the literature procedure in one step from dichlorodiphenylsilane **76** and 1,3-butadiene **77** (**Scheme 27**).[99]
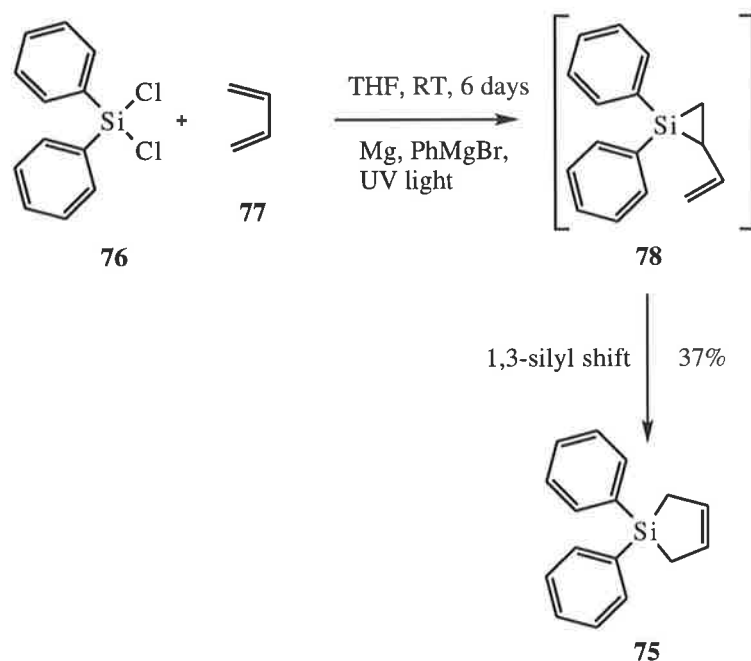
Scheme 27

This preparation involved treating a mixture of dichlorodiphenylsilane **76**, 1,3-butadiene and magnesium in THF with a solution of phenyl magnesium bromide. The reaction was initiated by irradiation with UV light and then stirred at room temperature for 6 days to give **76** in 37% yield after an aqueous workup.

The mechanism for the reaction of dichlorodiphenylsilane **76** and 1,3-butadiene **77** involves the 1,2-addition of a diphenyl silylene to the diene, to give a vinylsilacyclopropane **78**, which then undergoes a 1,3-silyl shift to give the 3-silacyclopentene **75** in an analogous manner to a thermal vinyl cyclopropane rearrangement.[100,101,102] The 1,3-silyl shift competes with C–C and Si–C bond cleavage in the vinylsilacyclopropane intermediate. C–C Bond cleavage would result in unwanted 2-silacyclopentene; Si–C cleavage gives a 3-silacyclopentene as would a 1,3-silyl shift.

2.0.4   *8,8-Dimethyl-6,10-dioxaspiro[4,5]dec-2-ene*

An acetal protected cyclopentanone pyrrole derivative such as **79** could be expected to give a porphyrin, which satisfies our structural criteria for [1]H n.m.r. spectroscopic studies. An acetal protected cyclopentanone pyrrole could also be expected to provide an easily functionalised carbonyl group **80** upon deprotection. Such a pyrrole should be obtainable from 8,8-dimethyl-6,10-dioxaspiro[4,5]dec-2-ene **81** in five steps as shown in **(Scheme 28)**.
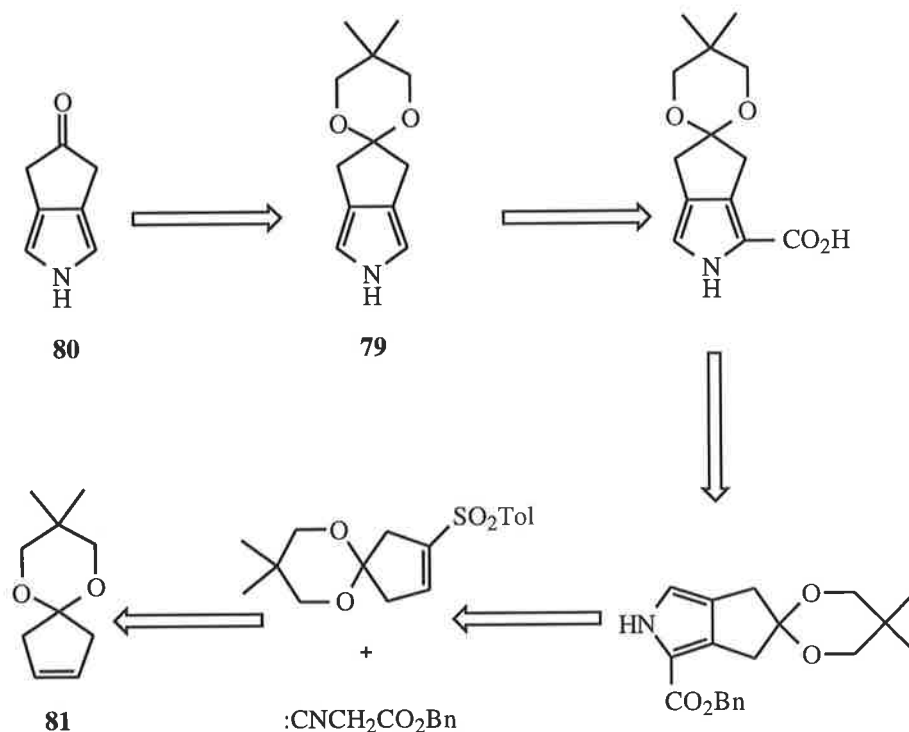
Scheme 28

The cyclopentene acetal **81** was prepared by the literature procedure from 4-thianone **82** (**Scheme 29**). Treatment of **82** with NCS and pyridine gave 2,3-dihydrothiin-4-one **83** which was then oxidised using Oxone® to give 2,3-dihydrothiin-4-one 1,1-dioxide **84** in 90% yield. 2,3-Dihydrothiin-4-one 1,1-dioxide **84** was then treated with 2,2-dimethyl-1,3-propanediol and trimethylsilyl iodide giving **85** in good yield. Ramberg–Bäcklund rearrangement of **85** using potassium *t*-butoxide gave 8,8-dimethyl-6,10-dioxaspiro[4,5]dec-2-ene **81** in 90% yield with a characteristic single vinyl resonance at δ 5.69 ppm.

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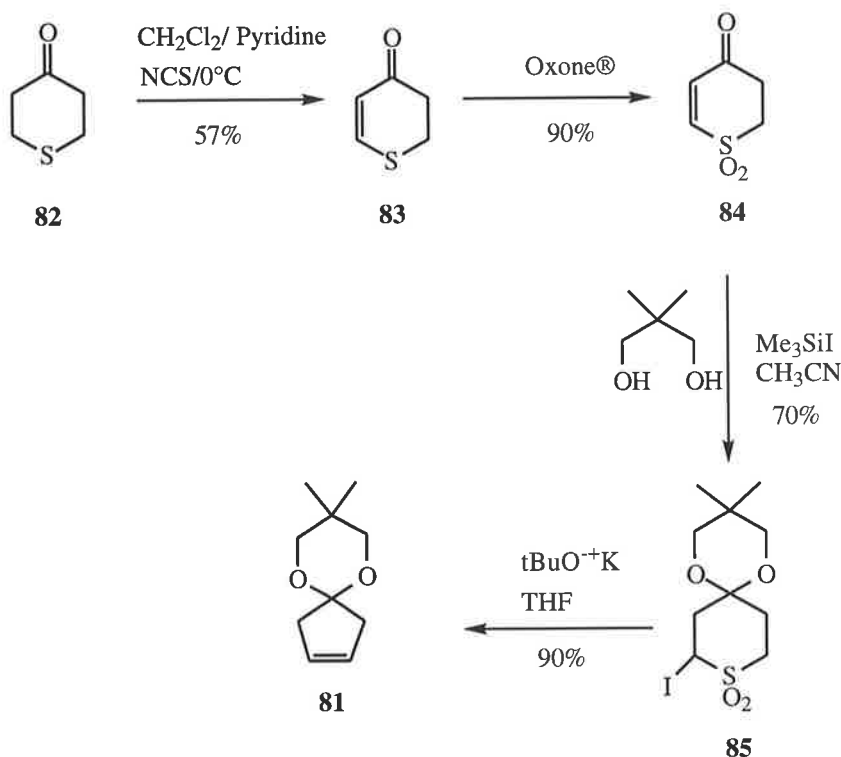
Scheme 29

The cyclic alkenes prepared, possess a wide range of electronic and steric properties which could be used to form cyclic vinyl sulfones suitable for use as annulated[3,4-*c*]pyrrole precursors.

2.1 Synthesis of Vinyl Sulfones

Vinyl sulfones were used as pyrrole precursors (**Scheme 30**) in preference to nitroalkenes because of a number of reasons. Vinyl sulfones are generally thermally stable, which is important, because the convergent nature of the pyrrole synthesis may require some starting materials to be stored. Vinyl sulfones also tend to be crystalline solids, which makes purification simpler. Vinyl sulfones react with isocyanoacetate anions to form pyrroles in a similar manner to nitroalkenes but overall vinyl sulfones are easier to form and store. The preparation of vinyl sulfones from alkenes under mild conditions was accomplished by two complementary methods, which will be discussed in this section.[51,62]
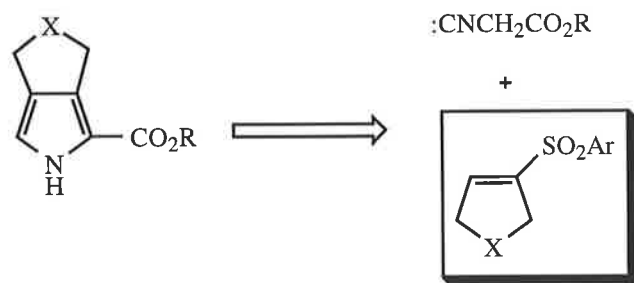
Scheme 30

Two general approaches exist for synthesising vinyl sulfones from alkenes, iodosulfonation of alkenes and the addition of benzenesulfenyl chloride (**Scheme 31**).

Iodosulfonation
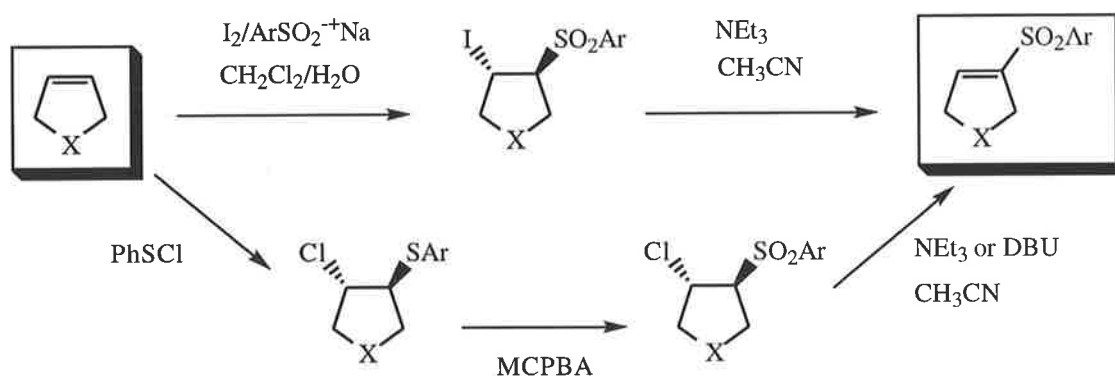
Addition of Benzenesulfenyl Chloride

Scheme 31

2.1.0.1   *Iodosulfonation of Alkenes*

Iodosulfonation of alkenes was the procedure of choice for the formation of vinyl sulfones during this project because of the simple two step — one pot synthesis. In addition, the vinyl

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sulfone was isolated directly from the alkene although the intermediate iodosulfone could be isolated if required. Iodosulfonation was generally carried out in a biphasic solvent system (either H_2O/CH_2Cl_2 or $H_2O/EtOAc$). A biphasic solvent system is preferred because the formation of methyl *p*-toluenesulfinate invariably occurs when the reaction is carried out homogeneously in MeOH. The sparing solubility of the alkene in MeOH is thought to contribute to the formation of methyl *p*-toluenesulfinate.[65,66,86] The mechanism of the iodosulfonation reaction is thought to proceed through two competing pathways; an ionic pathway through an iodonium intermediate and a radical pathway in which tosyl iodide is produced *in situ*.[66]

2.1.0.2   *Addition of Benzenesulfenyl Chloride to Alkenes*

The addition of benzenesulfenyl chloride to alkenes proceeds in a facile manner as long as the alkene is the dominant functionality in the molecule. If strongly nucleophilic species are present such as primary amines then substitution reactions with benzenesulfenyl chloride compete with addition to the alkene.

During this project the addition of benzenesulfenyl chloride to alkenes was used as the alternative method after iodosulfonation had failed to give the desired result. This is because benzenesulfenyl chloride had to be synthesised by a simple but time consuming procedure whereas iodosulfonation requires little preparation; the formation of vinyl sulfones by addition of benzenesulfenyl chloride takes a total of three individual steps whereas iodosulfonation is a two step–one pot procedure; finally, in contrast to the easy to handle and innocuous reagents used in the iodosulfonation procedure, benzenesulfenyl chloride is a difficult to handle liquid. However, the use of benzenesulfenyl chloride has two main advantages: completion of the addition can be identified by the persistence of the red colour of benzenesulfenyl chloride in solution (if the addition is carried out dropwise), and the addition of benzenesulfenyl chloride will often work when iodosulfonation has failed.

Benzenesulfenyl chloride can be produced by a variety of means.[103,104,105,106] Treatment of diphenyl disulfide with sulfuryl chloride was found to be the most reliable method of forming benzenesulfenyl chloride on a large scale.[106] Benzenesulfenyl chloride was freshly distilled before use on all occasions to minimise the presence of disulfide by-products.

2.1.1   *1-(p-Toluenesulfonyl)-1-cyclohexene*

To explore many alternative methods of porphyrin-forming reactions a cheap, readily accessible and commonly used porphyrin precursor was required. The isoindole formed from 1-nitro-1-cyclohexene has been used many times in the formation of a variety of symmetrical and non-symmetrical porphyrins.[25,56,76,92] Therefore an easily accessible and well-characterised series of compounds (from the analogous vinyl sulfone through isoindole to porphyrin) for use as trial reagents are available. 1-Nitro-1-cyclohexene is commercially available and is commonly used for the preparation of isoindole by the Barton and Zard method.[14,55,56,107]

As we were to use vinyl sulfones exclusively in this study, the vinyl sulfone analogue of 1-nitro-1-cyclohexene was prepared. 1-(*p*-Toluenesulfonyl)-1-cyclohexene **86** was synthesised following the literature procedure on a large scale by iodosulfonation of cyclohexene **87** in 53% overall yield (**Scheme 32**). DBU in toluene was used to eliminate HI from the intermediate iodosulfone, as NEt$_3$ was found to be ineffective.
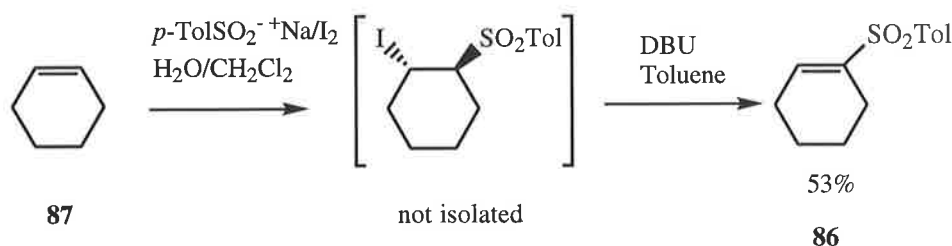
Scheme 32

The vinyl sulfone was easily identified by ^{1}H n.m.r. spectroscopy. Vinyl sulfones such as **86** show a characteristic multiplet between δ 6.00-7.50 ppm depending on ring size and the nature

of the β-substituent; indeed ^{1}H n.m.r. spectroscopy was used in the preliminary identification of all vinyl sulfones produced during this project. The intermediate iodosulfone was not isolated in the above case but treated directly with base to induce elimination of hydrogen iodide. This practice is typical in the following iodsulfonations. The iodosulfones are not isolated and purified because often the only impurity present is a small amount of vinyl sulfone due to *in situ* elimination of HI from the iodosulfone.

2.1.2   1-(p-Toluenesulfonyl)-2,5-dihydrofuran

The iodosulfonation of commercially available 2,5-dihydrofuran **88** was carried out in a biphasic H_2O/CH_2Cl_2 solvent system to give the iodosulfone **89** in 60% yield (**Scheme 33**).[86] Elimination of HI from **89** using triethylamine in acetonitrile gave the vinyl sulfone **90** in 70% yield.
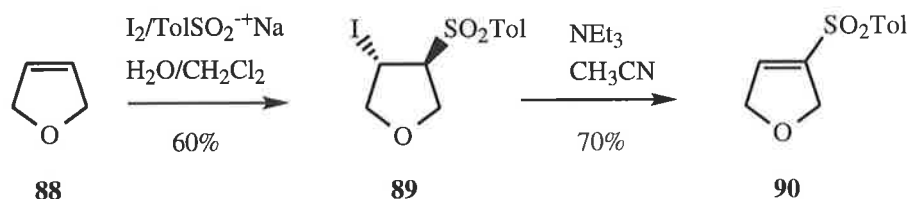
Scheme 33

The single X-ray crystal structure of (3R*, 4R*) 3-iodo-4-(p-tolylsulfonyl)oxalane **89**[108] shows the iodosulfone to exist as the *trans* isomer (**Fig. 16**) (Appendix 1). A *trans* configuration is essential for effective elimination of HI from the iodosulfone therefore it was important to unequivocally determine the stereochemistry of the iodosulfonation addition in a five membered ring.
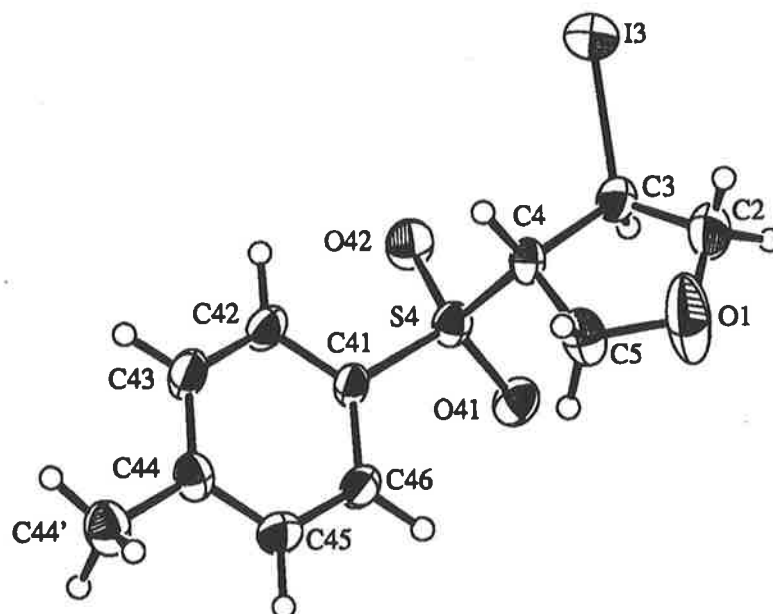
Figure 16

It was noticed that dihydrofuran **90** which had been stored in the presence of air for some time became contaminated with another compound. This compound was isolated and subsequently identified as fully oxidised 3-*p*-toluenesulfonylfuran **91 (Scheme 34)**. The literature synthesis of **91** encompasses the reaction of 3-lithiofuran with bis*p*-toluene disulfide to give 3-*p*-toluenesulfenylfuran, which was then oxidised with MCPBA to give 3-*p*-toluenesulfonylfuran in 47% overall yield.[109] Attempts to fully oxidise **90** with oxygen or DDQ failed to push the yield of **91** past 50% however this procedure still represents a simple synthesis of 3-*p*-toluenesulfonylfuran.[109]
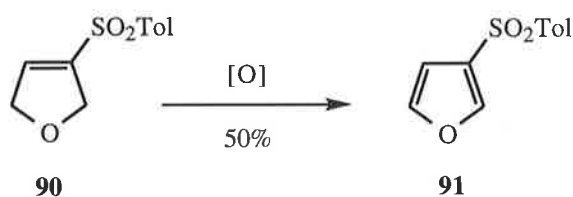
Scheme 34

2.1.3   *4,4-Dimethyl-1-p-toluenesulfonyl-1-cyclopentene*

4,4-Dimethylcyclopentene was prepared by treatment of the precursor vicinal diol **60** with triphenyl phosphine, imidazole and iodine (**Scheme 35**).[110,111] 4,4-Dimethylcyclopentene **54** was co-distilled with dichloromethane from the reaction mixture and immediately treated with iodine and sodium *p*-toluenesulfinate. The crude α-iodo sulfone was not isolated but directly treated with triethylamine in acetonitrile to give 4,4-dimethyl-1-*p*-toluenesulfonyl-1-cyclopentene **92** in 76% yield.
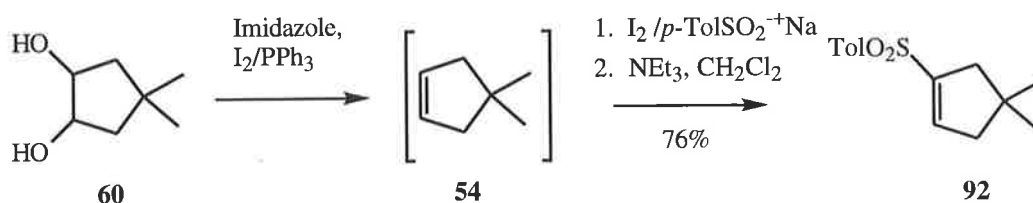
Scheme 35

The [1]H n.m.r. spectrum of **92** showed a characteristic vinylic resonance at δ 6.58 ppm while the [13]C n.m.r. spectrum showed two vinyl resonances at δ 141.23 and 143.39 ppm.

2.1.4   *Vinyl Sulfones from N-Substituted-2,5-dihydropyrroles*

2.1.4.1   *Attempted Iodosulfonation of N-Substituted-2,5-dihydropyrroles*

N-Substituted 2,5-dihydropyrroles were treated with iodine and sodium *p*-toluenesulfinate, but α-iodosulfones were formed in only trace amounts (identified by [1]H n.m.r.), with multiple products observed by t.l.c. analysis. Treatment of the crude iodosulfonation reaction products with triethylamine or DBU produced only traces of vinyl sulfones which were identified by [1]H n.m.r. spectroscopy. This result is in contrast to the readily iodosulfonated dihydrofuran **88**.[86] The explanation for this result is not clear, possibly the ring nitrogen is acting as a base to facilitate *in situ* elimination of HI, giving a mixture of vinyl and allylic sulfones or fully

aromatised pyrrole products. *In situ* aromatisation of the electron-rich 2,5-dihydropyrroles under the iodosulfonation conditions is not totally unexpected given the aromatisation of the electron-rich 2,5-dihydropyrrole **70** discussed earlier.

The sulfonyl derivative of 2,5-dihydropyrrole **67** was formed in preference to the desired 3-*p*-toluenesulfonyl-2,5-dihydropyrrole **93** when 2,5-dihydropyrrole was treated with iodine and sodium *p*-toluensulfinate. Presumably *p*-toluenesulfonyl iodide formed *in situ* reacts preferentially with the secondary amine of 2,5-dihydropyrrole (**Scheme 36**).[66]
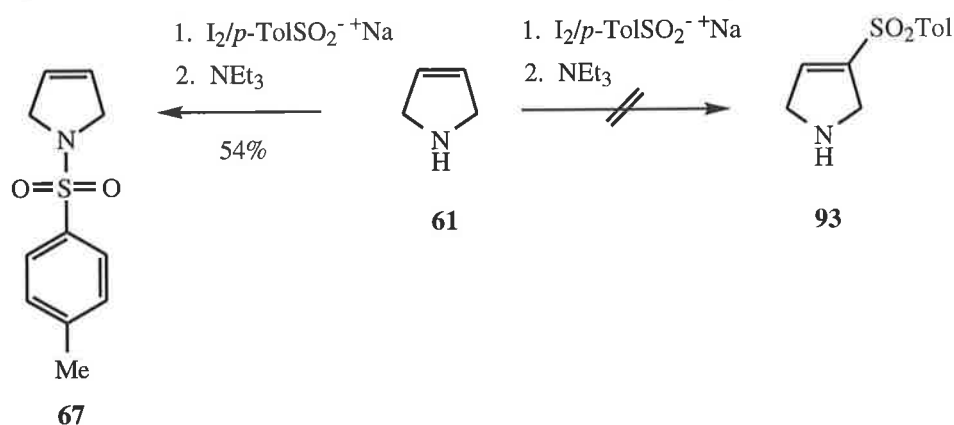
Scheme 36

2.1.4.2 *Addition of Benzenesulfenyl Chloride to N-substituted-2,5-dihydropyrroles*

Addition of benzenesulfenyl chloride to 2,5-dihydropyrroles produced some interesting results as shown in **Table 3**. It was found that benzenesulfenyl chloride successfully underwent addition to 2,5-dihydropyrroles possessing an electron-withdrawing substituent on nitrogen. However, the reactions of 2,5-dihydropyrroles possessing an electron-donating substituent on nitrogen were complicated by either side reactions or uncontrolled *in situ* elimination of the α-chlorosulfide by the substrate. In these cases, addition of benzenesulfenyl chloride resulted in isolation of complex mixtures and small amounts of starting material after reactions had ceased.

Table 3.   Addition of Benzenesulfenyl Chloride to 2,5-Dihydropyrroles

AMINE	CONDITIONS	PRODUCT	% YIELD
72	PhSCl, CH_2Cl_2, -78°C>RT, 2hr	Complex mixture + SM	-
72	PhSCl, CH_2Cl_2, 0°C>RT, 2hr	Complex mixture + SM	-
N- SO_2Tol **67**	PhSCl, CH_2Cl_2 -78°C>RT, 2hr	**94**	100%
73	PhSCl, CH_3CN, reflux, 2hr	**95**	60%

Two α-chlorosulfides **94** and **95** were obtained from 2,5-dihydropyrroles possessing electron-deficient aryl substituents and were subsequently oxidised to α-chlorosulfones in high yield using MCPBA in dichloromethane **(Scheme 37)**. The α-chlorosulfones were then treated with DBU in acetonitrile or dichloromethane under a variety of conditions. Treatment of **96** with DBU gave the allylic sulfone, which was thermally isomerised to the vinyl sulfone **99** in good yield. Treatment of **97** with DBU at 0°C gave a mixture of vinyl sulfone (major) and allylic isomer (minor) under high dilution conditions and allylic sulfone exclusively under concentrated conditions **(Scheme 37)**.

R = A. nitrophenyl **95**   A. 44% **96**   A. 91% **99**
    B. SO$_2$Tol **94**   B. 55% **97**   B. 83% **98**
                                                      + allylic isomer
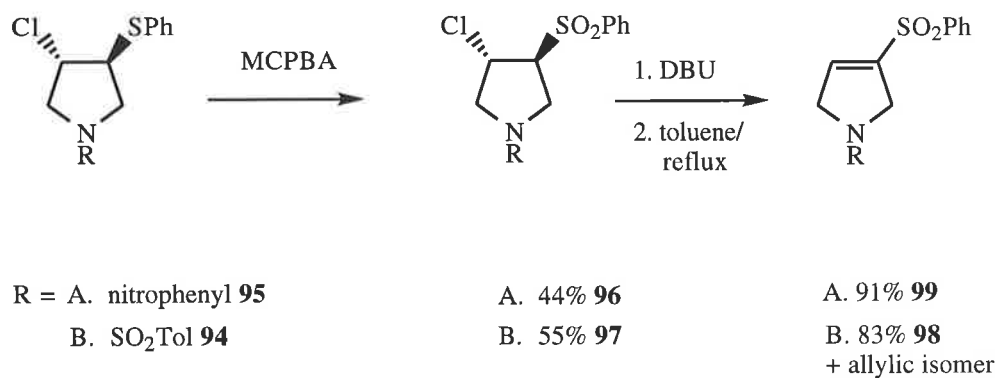
Scheme 37

Attempted thermal isomerisation of the allylic isomer of **98** to the vinyl sulfone resulted in aromatisation through loss of *p*-toluenesulfinic acid to give the fully aromatic 1-*p*-toluenesulfonyl pyrrole **183** in 10% yield **(Scheme 38)**.
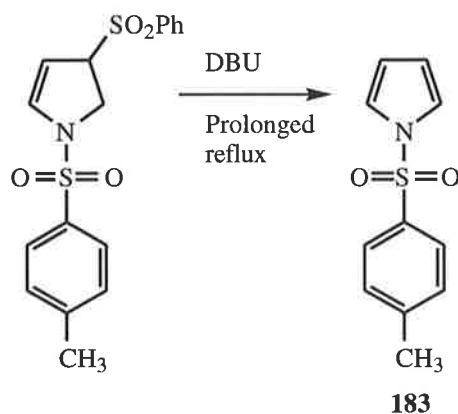
Scheme 38

The crystal structure of **99** (Appendix 2) shows the nitrogen of the pyrroline ring to be in the plane of the ring (N1-C2-C3-C4 = 2.4° and N1-C5-C4-C3 = -2.1°) **(Fig. 17)**. One of the key requirements of the pyrrole derivatives needed for this project is a flat annulated ring. This crystal structure tentatively suggests that the 2,5-dihydropyrrole ring of an annulated[3,4-*c*]pyrrole derivative of this vinyl sulfone will indeed be flat.
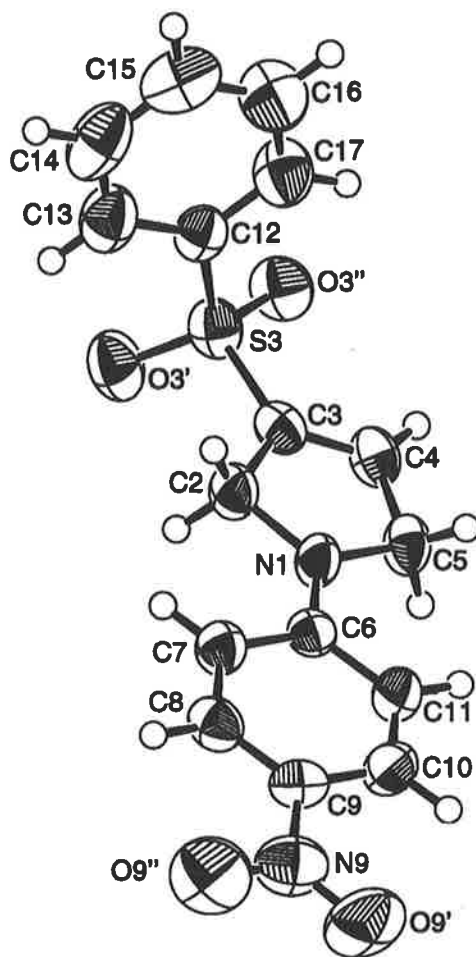
Figure 17

This crystal structure provides preliminary evidence (in the absence of a pyrrole crystal structure) that the pyrrole should be flat and therefore prove suitable for use in high field ^{1}H n.m.r. line shape analysis of the desired porphyrin.

2.1.5 Attempted Formation of 1,1-Diphenyl-3-phenylsulfonyl-1-silacyclopent-3-ene

1. TolSO$_2^-$ $^+$Na/I$_2$
2. NEt$_3$/DBU
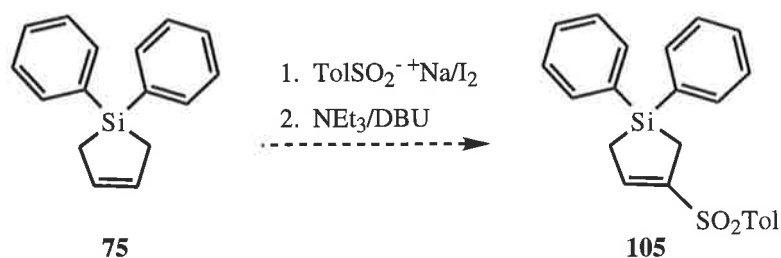
Scheme 39

An attempt to form the vinyl sulfone **105** of 1,1-diphenyl-1-silacyclopent-3-ene **75** under the iodine and sodium *p*-toluenesulfinate conditions resulted in a mixture of products being formed (by t.l.c. analysis) **(Scheme 39)**. After aqueous workup of the iodosulfonation reaction, the white residue (mixture of products by t.l.c. analysis) was taken up in acetonitrile and treated with triethylamine. Triethylamine failed to give any further reaction, so the stronger amine base DBU was added and the mixture refluxed overnight. Upon cooling of the reaction mixture, a crystalline precipitate was collected **(Scheme 40)**. The crystalline product from this reaction showed a single ^{29}Si resonance at δ -38.59 ppm, only aromatic protons in the ^{1}H spectrum δ 7.10-7.47 ppm, and only aromatic carbons in the ^{13}C spectrum δ 127.66-134.46 ppm. No meaningful mass data could be obtained, even after resorting to mild ionisation techniques, such as electrospray mass spectrometry or FAB-MS. The product was finally identified by its crystal structure as the known compound octaphenylcyclotetrasiloxane[112,113,114] **100**.

Octaphenylcyclotetrasiloxane has been synthesised previously from phenylsilanediol in alkaline solution;[113] presumably hydrolysis of the starting material or an intermediate in the slightly basic, bi-phasic solution, gave **100** and the other by-products.
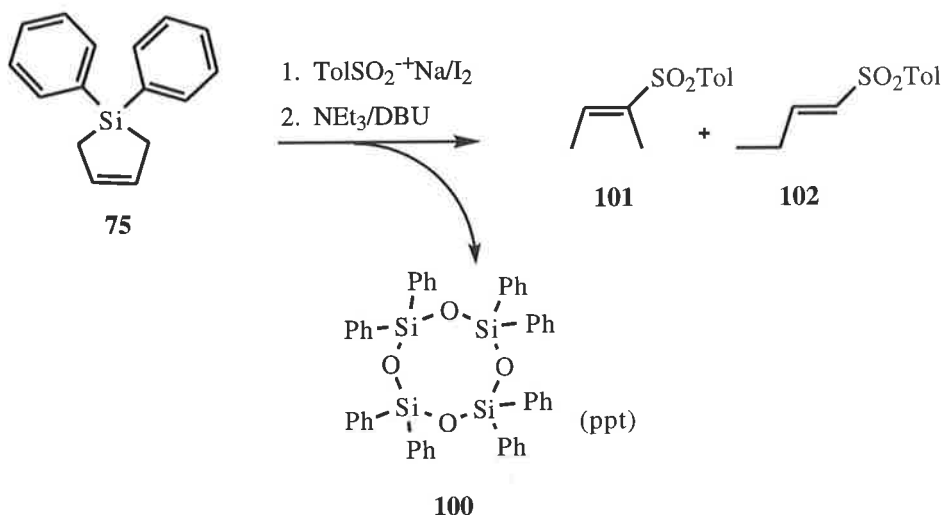
Scheme 40

The siloxane **100** was subsequently shown by t.l.c. analysis to be present in the mixture of products from the initial iodosulfonation reaction.

The solvent was removed from the filtrate that remained from the isolation of **100** and the residue was subjected to column chromatography. Two additional products, plus a trace amount of impure 1,1-diphenyl-1-silacyclopent-3-ene **75**, were isolated. The first of these (low R_f) was shown to be either *E* or *Z*-2-*p*-toluenesulfonyl-2-butene **101**. The ^{1}H n.m.r. spectrum of this product showed two methyl signals at δ 1.77 and 1.81ppm and a vinyl signal (integrating as one proton) as a multiplet at δ 6.94 ppm. Mass spectrometry showed signals corresponding to M˙+ at m/z 210 and m/z 55 (M˙+-SO₂Tol). The second product (middle R_f) was shown to be *E*-1-*p*-toluenesulfonyl-1-butene **102**.[66] The ^{1}H n.m.r. spectrum of this product showed a methyl signal at δ 1.03 ppm as a triplet, a quartet at δ 2.22 and two vinyl signals (multiplets integrating as one proton each) at δ 5.66 ppm and δ 6.31 ppm respectively. Mass spectrometry showed a MH⁺ at m/z 211. The characterisations are consistent with the structures shown in **Scheme 40** and match the literature data.[66]

Addition of benzenesulfenyl chloride to **75** (**Scheme 41**), gave the α-chlorosulfide **103** in 88% yield.
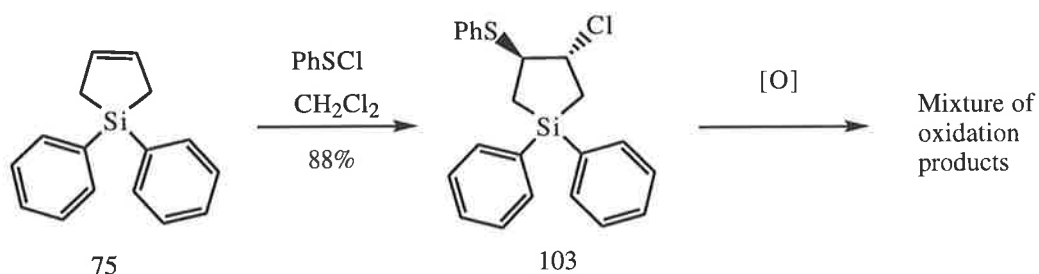
Scheme 41

The ^{1}H n.m.r. spectrum of **103** appears in **Fig. 18** showing C(3)H at δ 3.99 ppm and C(4)H at δ 4.47 ppm. The designation of **103** as the *trans* isomer relies solely on the many precedents available in the literature for this well-known addition reaction.[19,20]
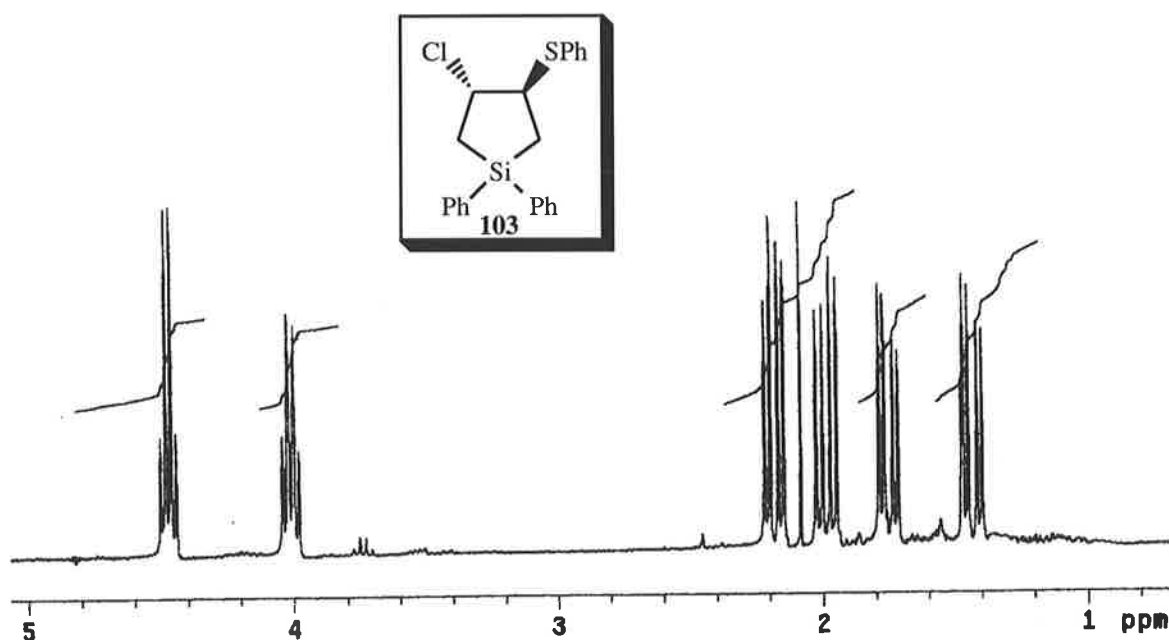
Figure 18

Attempts to oxidise the α-chlorosulfide to the α-chlorosulfone with MCPBA, K$_2$CO$_3$ buffered MCPBA, Oxone$^®$, or Oxone$^®$ on wet alumina failed to give a clean reaction (**Scheme 41**). In all cases, no starting material was recovered and t.l.c. indicated that starting material had been consumed to form numerous products. The ^{1}H n.m.r. spectrum of the recovered oxidation products from the reaction of **75** with oxone (**Fig. 19**) showed a large number of signals

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ranging from δ 0.66-δ 4.71 ppm and no vinyl signals were observed indicating no elimination had occurred under the reaction conditions. These products were typical of those seen under a variety of oxidation conditions.
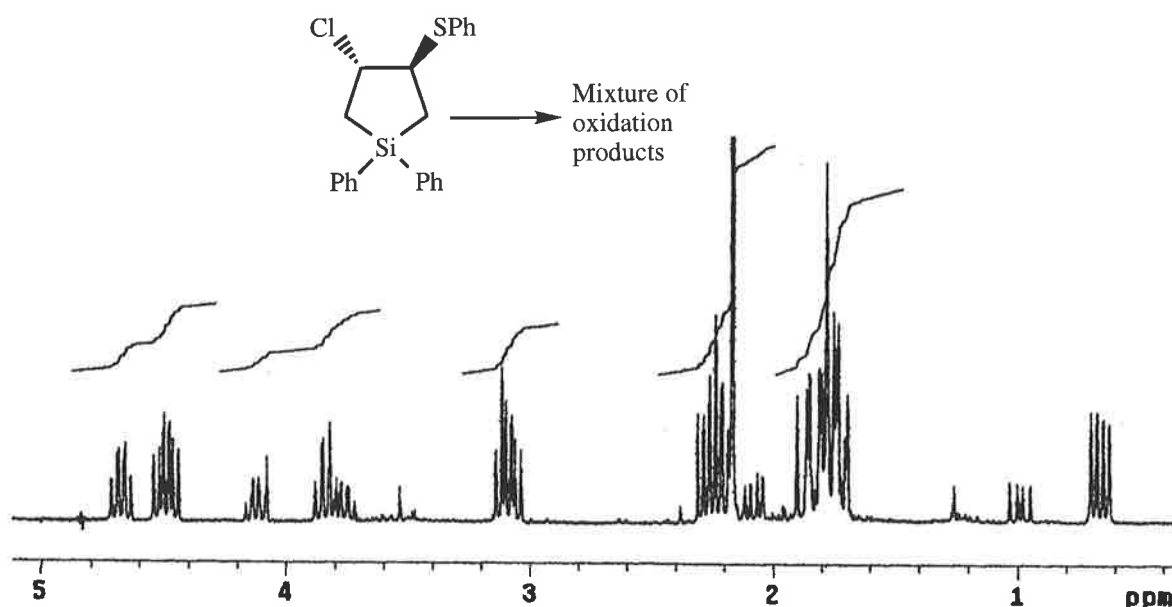
Figure 19

A general downfield shift of the proton signals was observed in comparison to the chemical shifts observed for the starting α-chloro sulfide. The chemical shifts and changes in multiplicity tentatively suggested a mixture of α-chloro sulfone and α-chloro sulfoxide as the main products. Mass spectrometry of the product mixtures did not give a clear indication of the molecular weights of the products. Further reaction of the recovered mixtures under the oxidation conditions did not alter the product ratio, which indicates the initially recovered products were fully oxidised therefore ruling out the presence of sulfoxide.

As **103** could be formed in good yield, it was decided to attempt to form the vinyl sulfide derivative by elimination of HCl from the α-chlorosulfide **103** using a strong non-nucleophilic base **(Scheme 42)**. It was envisaged that the vinyl sulfide could then be oxidised to give the desired vinyl sulfone.
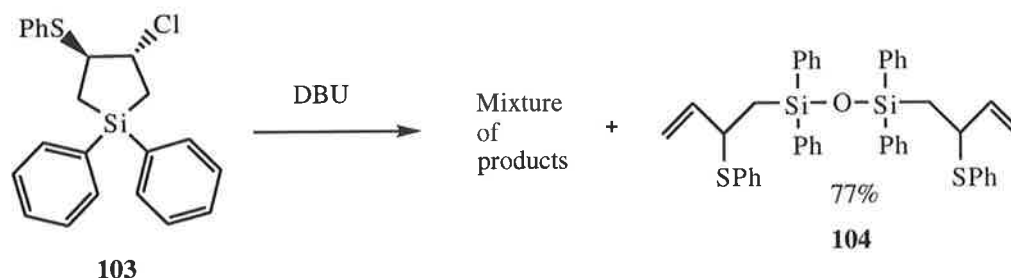
Scheme 42

Treatment of **103** with DBU at reflux gave a mixture of products. The major product was found to be di{1,1-diphenyl-1-[2-phenylthio-3-butenyl]silyl}ether **104**. ^{1}H and ^{13}C n.m.r. spectroscopy was used to identify the aliphatic component of the by-product (**Fig. 20**). ^{1}H n.m.r. indicated the structure shown **104**: δ 1.50 [dd, *J* 9.8, *J* 15.1, 1H, C(1a)H], 1.60 [dd, *J* 5.4, *J*14.8, 1H, C(1a)H], 3.61 [dt, *J* 5.4, *J* 9.1, 1H, C(2)H], 4.35 [d, *J* 16.8, 1H, C(4a)H, *trans* coupling], 4.52 [d, *J* 9.8, 1H, C(4b)H, *cis* coupling], 5.44 [dt, *J*9.4, *J* 16.8, 1H, C(3)H] along with aromatic resonances δ 7.23-7.66 ppm, which integrated to 15 protons.
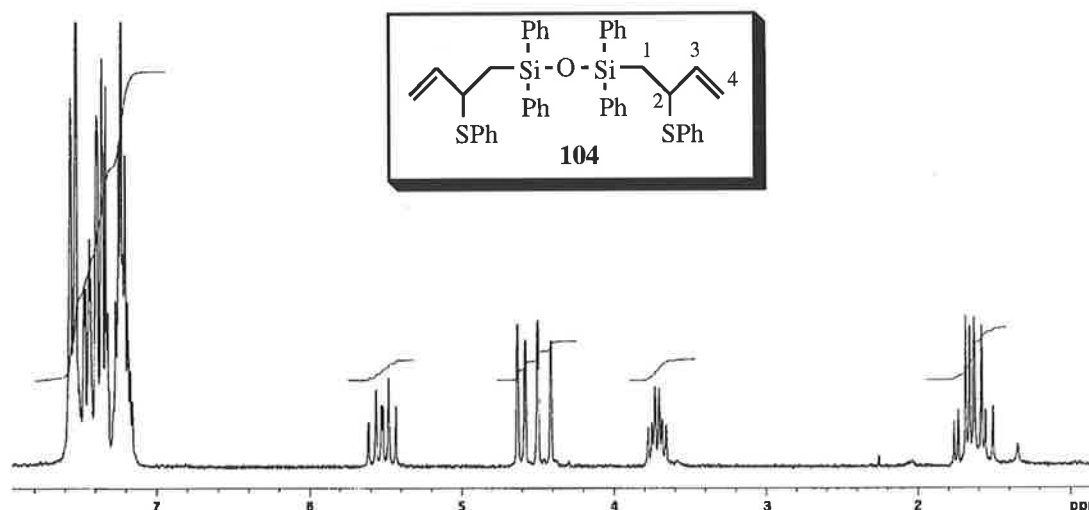
Figure 20

[13]C n.m.r. spectroscopy confirms the indicated structure: [C1] resonance at δ 14.51 ppm, [C2] resonance at δ 41.18 ppm, [C3] resonance at δ 102.43 ppm, [C4] resonance at δ 114.66 ppm along with aromatic resonances δ 127.04-143.03 ppm. [29]Si n.m.r. spectroscopy gave one signal at -δ 12.39 ppm, which is consistent for the chemical shifts of silyl ethers and furthermore indicated that the silicon present existed in a single chemical environment. Electrospray mass spectrometry indicated M[+·] 729 which equated to a Na^{+}complex (electrospray mass spectrometry often gives rise to Na^{+} complexes) of a silyl ether dimer of the aliphatic component. Elemental analysis of the pure compound supports the proposed structure.

2.1.5.1 Alternative One-Pot Synthesis of 1,1-Diphenyl-3-phenylsulfonyl-1-silacyclopent-3-ene

Given the difficulties encountered with these compounds, a possible one-pot route to the vinyl sulfone **105** may be the reaction of dichlorodiphenylsilane **76** and 2-phenylsulfonyl-1,3-butadiene **106**. The conditions for this reaction would be similar to those employed for the reaction of dichlorodiphenylsilane and 1,3-butadiene in **Scheme 27**. This reaction could give direct access to the vinyl sulfone without the troublesome oxidation/elimination steps (**Scheme 43**). Reaction of 1,3-butadiene with phenylselenosulfonate gives ready access to the required butadiene sulfone **105**.[70]
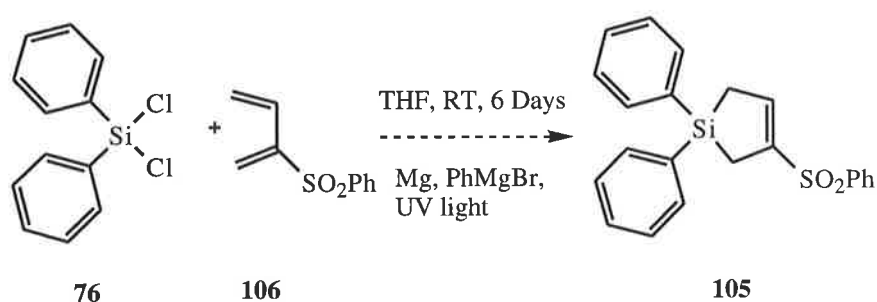
Scheme 43

2.1.6 2,2-Dimethyl-4,7-dihydro-5-(p-toluenesulfone)-1,3-dioxepine

Attempted sulfonation of *cis*-2-butene-1,4-diol **107** failed. It was thought that the free hydroxy groups were an obvious alternative reactive site so protection of the hydroxyl groups was expected to alleviate this problem. Protection of *cis*-2-butene-1,4-diol as a cyclic acetal **108** proceeded in a facile manner (**Scheme 44**). Iodosulfonation and subsequent elimination gave the vinyl sulfone **109** in 60% yield. The ^{1}H n.m.r. spectrum showed a single vinyl resonance at δ 6.89 ppm. This vinyl sulfone possesses an oxygen atom in the β-position and therefore can be used as a model vinyl sulfone in the formation of heteroannulated pyrroles and porphyrins.
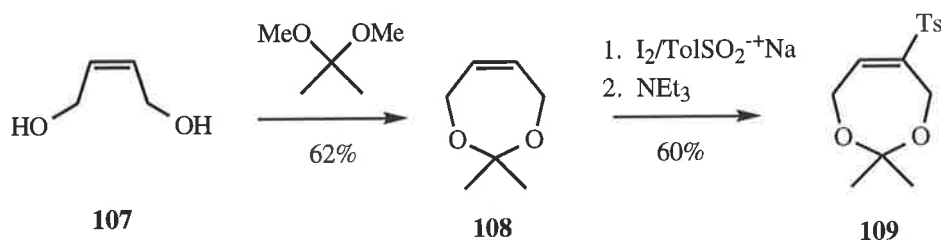
Scheme 44

2.1.7 3-p-Toluenesulfonyl-3-sulfolene-1,1-dioxide

2,5-Dihydrothiophene-1,1-dioxide (sulfolene) **110** is commercially available and was converted to the required vinyl sulfone **111** by the literature procedure in reasonable overall yield.[115,116] Sulfolene was brominated to give a dibromide **112** which was then eliminated using pyridine to give the allylic bromide **113**. Nucleophilic substitution of **113** using sodium *p*-toluenesulfinate hexahydrate in DMF gave the vinyl sulfone **111**, shown by ^{1}H n.m.r. spectroscopy to be contaminated with a very small amount of the allylic isomer **114** (**Scheme 45**).
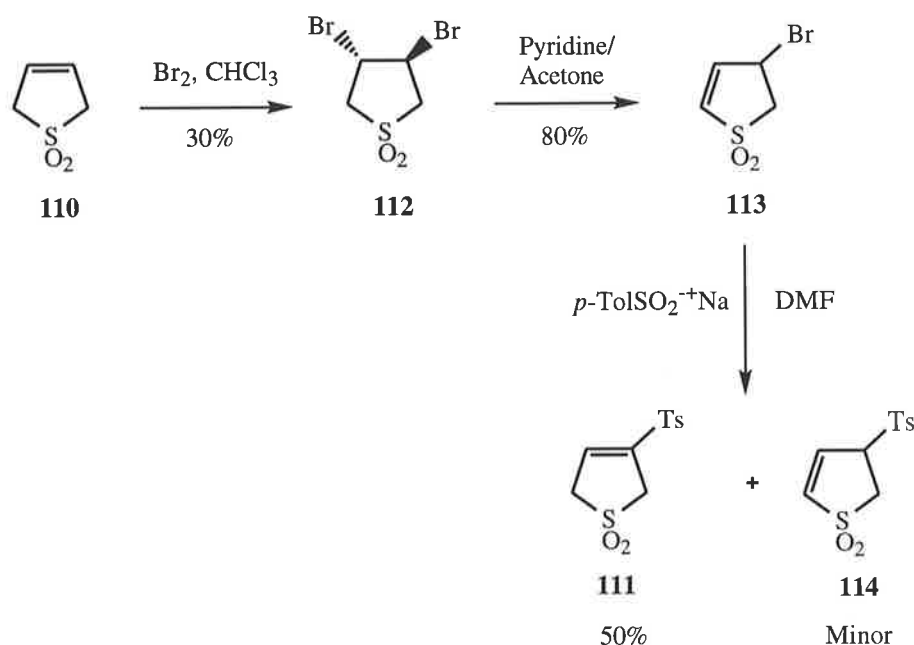
Scheme 45

Alternate syntheses of 3-*p*-toluenesulfonyl-3-sulfolene **111** are available (**Scheme 46**). Sulfolene is treated with benzenesulfenyl chloride, to give an α-chlorosulfide **115**. Oxidation of the α-chlorosulfide to the α-chlorosulfone **116** followed by elimination of HCl with a tertiary amine base gives a mixture of the vinyl sulfone **111** and allylic isomer **114**.[117] A variation on this approach is elimination of HCl from the α-chlorosulfide **115** to give the vinyl sulfide **117**, which could then be oxidised to **111**. Both routes are somewhat hampered by the formation of allylic sulfones as by-products. One study indicates the formation of allylic sulfones in the alternative procedures can be partially circumvented by thermal isomerisation of the allylic sulfide isomer to the vinyl isomer by reflux with triethylamine in DMSO at 90°C.[118]
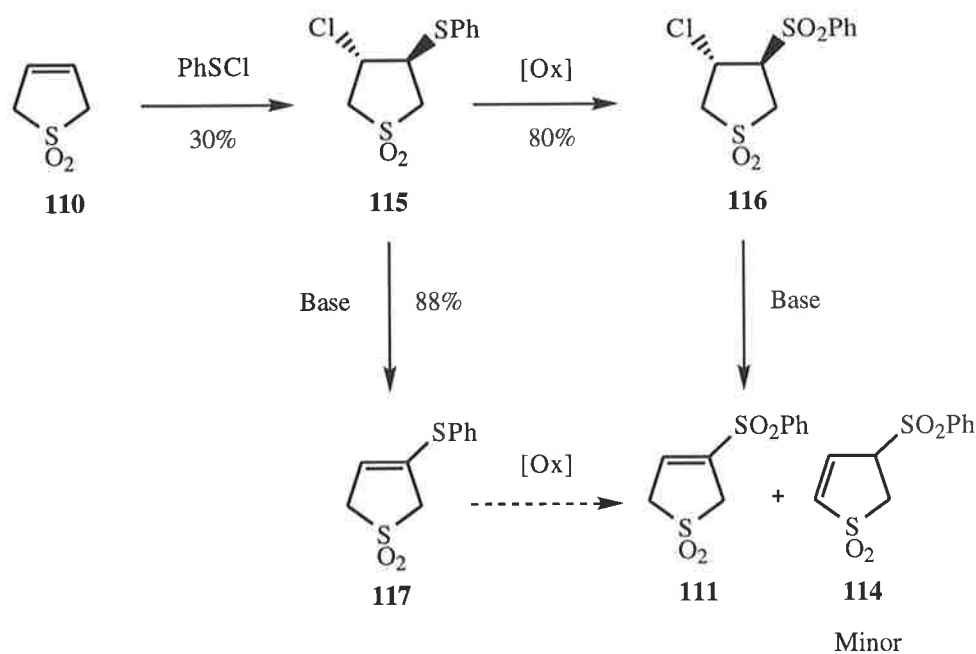
Scheme 46

2.1.8 Attempted Iodosulfonation of 8,8-Dimethyl-6,10-dioxaspiro[4,5]dec-2-ene

An exploratory iodosulfonation reaction on 8,8-dimethyl-6,10-dioxaspiro[4,5]dec-2-ene **81** gave a (1:3) mixture of vinylic **118** and allylic **119** sulfones. The ^{1}H n.m.r. spectrum showed a single vinyl resonance at δ 6.59 ppm for the vinyl isomer **118** and two vinyl resonances at δ 5.59 and δ 6.36 ppm for the allylic isomer **118** (**Scheme 47**). The mixture of isomers could not be isomerised to give predominantly the vinyl sulfone under thermal conditions.
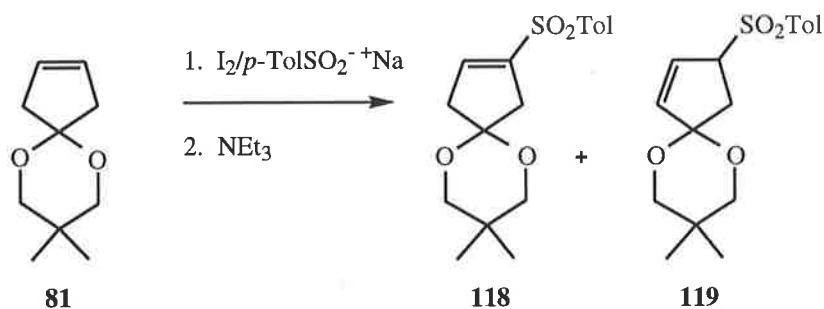
Scheme 47

2.2   One–pot Synthesis of Vinyl Sulfones

The most promising of all the pyrrole derivatives were those derived from cyclopentenes, as they were expected to behave in a similar way to the cyclopentanopyrrole derivatives that form porphyrins in reasonable yields. Condensation of the bis-stabilised carbanions of **120** and **121** with 2,3-bis(phenylsulfonyl)-1,3-butadiene **122 (Schemes 48 and 49)** gave cyclopentene sulfone derivatives in a one–pot synthesis.[119,120]

2.2.1   *4,4-Bis(methoxycarbonyl)-1-(phenylsulfonyl)-1-cyclopentene*

2,3-Bis(phenylsulfonyl)-1,3-butadiene was reacted with dimethyl malonate **120** in the presence of NaH giving an intermediate allene, which was treated with a catalytic amount of sodium benzenesulfinate in acetonitrile at room temperature to give the corresponding cyclopentene **123** in good yield **(Scheme 48)**. It has been reported that the methoxycarbonyl groups give rise to significant nonbonding interactions in the transition state for ring closure thereby resulting in allene formation rather than direct ring closure.[119]
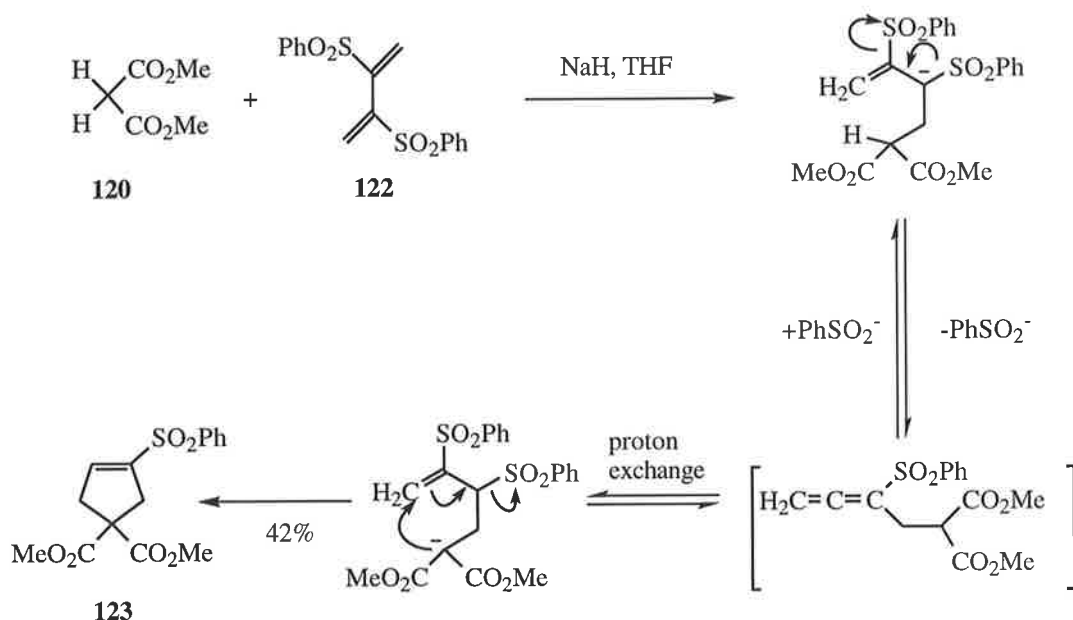
Scheme 48

2.2.2   *4,4-Dicyano-1-(phenylsulfonyl)-1-cyclopentene*

2,3-Bis(phenylsulfonyl)-1,3-butadiene **122** was reacted with malononitrile **121** giving cyclopentene **124** directly without an isolated allene intermediate, therefore no sodium benzenesulfinate was needed in the isolation of this product (**Schemes 49**).
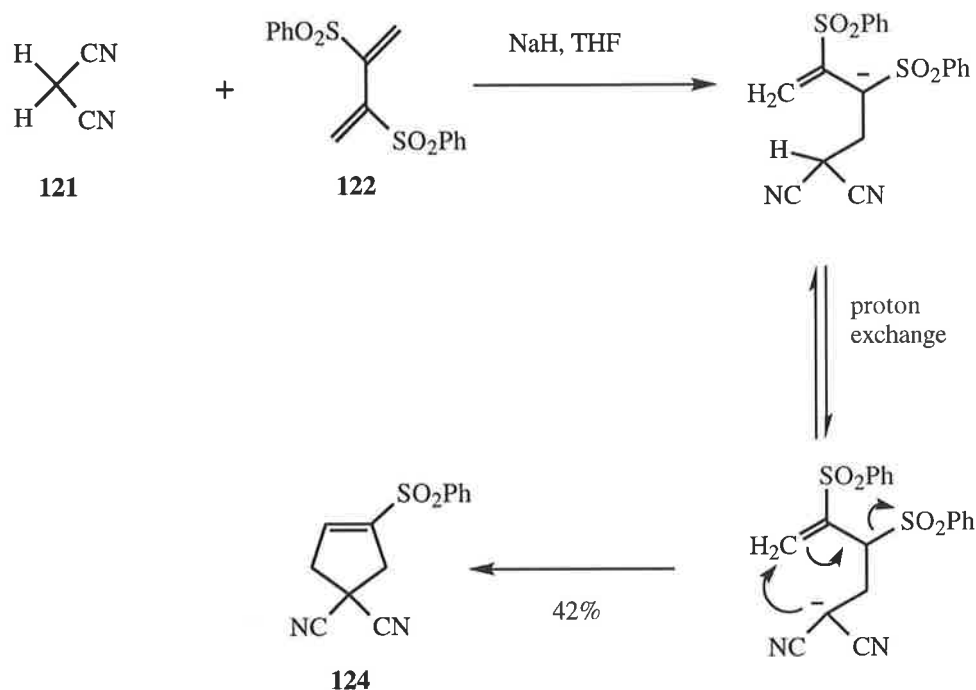
Schemes 49

2.2.3 Condensation of Primary Amines with 2,3-Bis(phenylsulfonyl)-1,3-butadiene

This method is essentially a one-pot formation of vinyl sulfone derivatives of 2,5-dihydropyrroles and therefore appeared very attractive.[121,122] The initial idea was to use this reaction to form the 2,5-dihydropyrrole sulfone that could then be deprotected to give 3-phenylsulfonyl-2,5-dihydropyrrole **93**, as **93** could not be formed from 2,5-dihydropyrrole itself. Benzyl protected 3-phenylsulfonyl-2,5-dihydropyrrole **125** was formed in 27% yield by

the condensation of benzylamine and 2,3-bis(phenylsulfonyl)-1,3-butadiene **122**. Attempts to deprotect the benzyl product **125** were unsuccessful under a variety of conditions (**Scheme 50**).
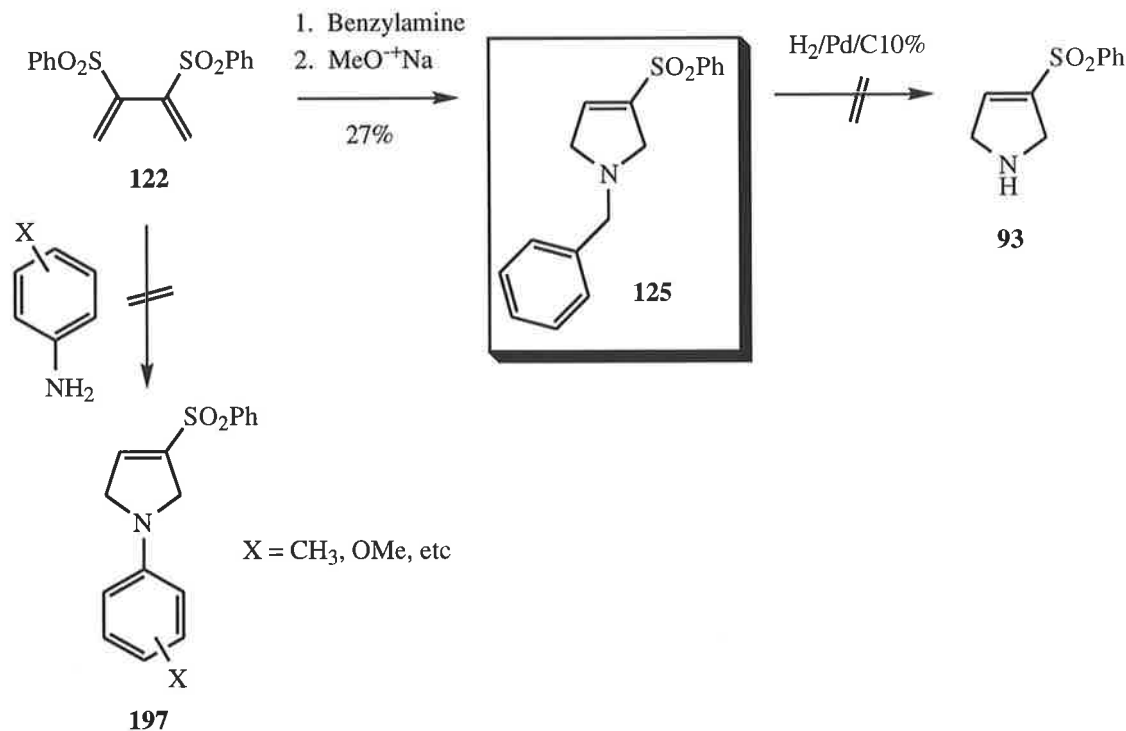
Scheme 50

As *N*-aryl 2,5-dihydropyrroles **197** were also required, an attempt was made to condense aryl amines with 2,3-bis(phenylsulfonyl)-1,3-butadiene **122** (**Scheme 50**). Aryl amines such as aniline, *p*-toluidine and *p*-anisidine were unreactive with the butadiene sulfone under the standard conditions (reaction at room temperature in a 1:1 solution of MeOH/CH$_2$Cl$_2$). Attempts were made to condense *p*-toluidine, *p*-nitroaniline, and 2,6-dichloronitro-4-aniline with **122** in the presence of NaH in THF or DMF. Analysis of the reaction mixtures by t.l.c. indicated that **122** was consumed slowly, however the aryl amines remained. Upon basic workup of the solution, only black residues were obtained. ^{1}H n.m.r. spectra of the isolated residues showed a complex mixture of by-products.

2.3   Alternative Routes to Vinyl Sulfones of 2,4-Dihydropyrrole Systems

A convergent route to the vinyl sulfones of *N*-aryl 2,5-dihydropyrroles was investigated (**Scheme 51**), because the transformation of *N*-aryl 2,5-dihydropyrrole systems into vinyl sulfones failed when electron-donating aryl substituents were present on the ring nitrogen. The aim was to produce a vinyl sulfone moiety that could be condensed with a range of aryl amines in a similar manner to the condensation of aryl amines with *cis*-1,4-dimesyloxy-2-toluenesulfonyl-2-butene. The advantage of this method would be the preformation of a *cis*-1,4-dimesyloxy-2-toluenesulfonyl-2-butene vinyl sulfone derivative **126** thus avoiding any complications with sulfonation reactions at the 2,5-dihydropyrrole stage.

Deprotection of readily available acetal **109** to the diol **127** using H_2SO_4 was carried out in good yield (**Scheme 51**); retention of the *cis* configuration of **127** was verified by ROESY n.m.r. experiments, which showed strong through space interaction between C(1)H and C(4)H protons. Attempts to form the dimesylate or ditosylate of **127** failed (multiple products by t.l.c. analysis), possibly due to the facile elimination of one of the leaving groups under the reaction conditions (**Scheme 51**). The formation of two regioisomers **128** and **129** is possible depending on which mesylate group is eliminated. However, no attempt was made to prove the identity of by-products **128** and **129**, owing to the complex mixture of products. Suffice to say that multiple vinyl resonances were observed in the ^1H n.m.r. spectrum of the mixture.
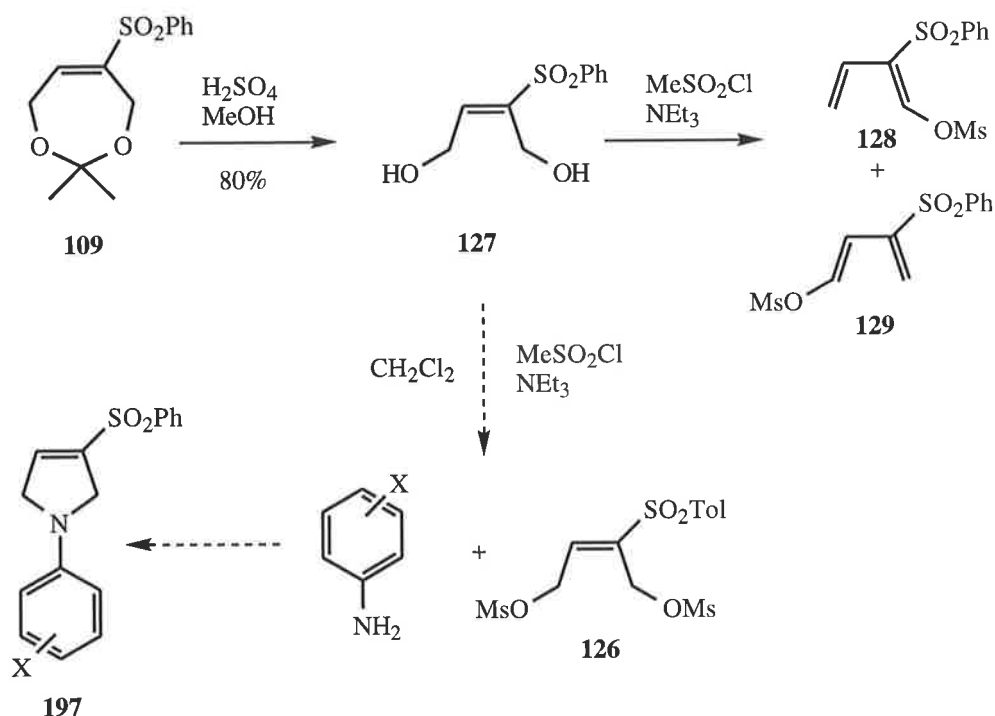
Scheme 51

2.4 Summary

In total, thirteen cyclic alkenes were prepared as vinyl sulfone precursors. Cyclic alkenes were prepared when a direct route to the required vinyl sulfones could be found. Cyclopentene derivatives including 4,4-dimethylcyclopent-1-ene **54** and 8,8-dimethyl-6,10-dioxaspiro[4,5]dec-2-ene were synthesised. Cyclic alkenes incorporating a heteroatom include 2,5-dihydropyrrole, the acetyl, trifluoroacetyl and *p*-toluenesulfonyl 2,5-dihydropyrrole derivatives as well as a series of *N*-aryl 2,5-dihydropyrroles. 1,1-Diphenyl-1-silacyclopent-3-ene **75** was synthesised, however a convenient synthesis of a vinyl sulfone derivative was not available. A seven membered cyclic acetal **109** was synthesised for use as a model compound in the investigation of a convergent vinyl sulfone synthesis, to be discussed in the following chapter.

An alternative route to suitable alkenes by metathesis reactions using molybdenum based catalysts was not investigated during this project as we did not have ready access to the appropriate catalysts. Metathesis reactions seem to provide ready access to cyclic alkenes of the type desired, in a simple one-pot reaction from the increasingly available starting diallyl compounds e.g. 2,5-dihydrothiophene and 2,5-dihydro-1-trifluoroacetyl-1*H*-pyrrole have been produced in high yields.[123,124,125]

The synthesis of vinyl sulfones from cyclic alkenes and also the convergent synthesis of vinyl sulfones were investigated. In total, ten vinyl sulfones were synthesised in quantities suitable for condensation with isocyanides in the Barton and Zard procedure.

The vinyl sulfone derivatives of cyclohexene, 2,5-dihydrofuran and 3-sulfolene were formed from comercially available starting materials. Vinyl sulfone derivatives of 4,4-dimethylcyclopent-1-ene **54**, cyclic acetal **109**, *p*-toluenesulfonyl 2,5-dihydropyrrole **67** as well as the *p*-nitroaniline 2,5-dihydropyrrole **73** were formed by either iodosulfonation then elimination of HI or addition of benzenesulfenyl chloride, followed by oxidation of the intermediate α-chloro sulfide and elimination of HCl. Cyclopentene derivatives or cyclic alkenes containing oxygen atoms underwent iodosulfonation in a facile manner, however 2,5-dihydropyrrole derivatives did not. In general 2,5-dihydropyrroles with an 'electron-deficient' nitrogen were succesfully functionalised with benzenesulfenyl chloride. In contrast, 2,5-dihydropyrrole derivatives bearing electron-donating aryl groups and therefore an 'electron-deficient' nitrogen, could not be functionalised by either iodosulfonation or the benzenesulfenyl addition protocol. Presumably a basic nitrogen interferes with the electrophilic reagents used in these reactions.

1,1-Diphenyl-1-silacyclopent-3-ene **75** unfortunately could not be functionalised to the vinyl sulfone derivative because of scission of the silacyclopentene ring under the reaction conditions. Ring opening reactions occurred under oxidative conditions giving a siloxane by-product and

trace amounts of butene derivatives. Basic elimination of the α-chlorosulfide derivative **103** induced ring scission to give a silyl ether dimer **104**.

Attempted iodosulfonation of 8,8-dimethyl-6,10-dioxaspiro[4,5]dec-2-ene **81** gave a mixture of the allylic and vinyl sulfone isomers. The allylic isomer could not be thermally isomerised to the vinyl isomer. Separation of the vinyl sulfone from the reaction mixture was not feasible, as the small quantity of the starting alkene **81** available made the probable yield of the vinyl sulfone unacceptable.

Treatment of either 2,5-dihydropyrrole derivatives or 1,1-diphenyl-1-silacyclopent-3-ene with areneselenol sulfonates, to give *trans*-β-areneselenosulfonates, may be an effective method for the formation of vinyl sulfones of these compounds.[126,69] Selenosulfonation would now seem to be the most likely method to give vinyl sulfones of these derivatives because of the facile elimination of selenoxide under mild oxidative conditions.

The direct formation of vinyl sulfones was used to form two cyclopentene (**123** and **124**) derivatives and one 2,5-dihydropyrrole derivative **125** using the cyclisation reaction of 2,3-bis(phenylsulfonyl)-1,3-butadiene with either bis-stabilised carbanions or primary amines, as developed by Padwa *et al.*[119]

Chapter 3: Synthesis of annulated[3,4-c]pyrroles

3.0 Synthetic Rationale

Pyrroles were conveniently synthesised from vinyl sulfones and isocyanides, making exclusive use of adapted Barton and Zard methodology (**Scheme 52**)[50,51,62]
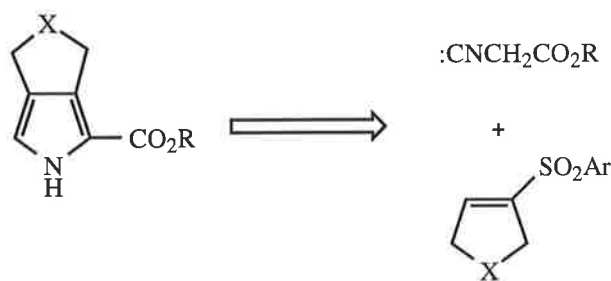
Scheme 52

3.1 Synthesis of Isocyanides

3.1.1 Synthesis of N,N-Dialkyl isocyanoacetamides

The preparation of *N,N*-dialkyl isocyanoacetamides was investigated as it was hoped that an *N,N*-dialkyl isocyanoacetamide would form a pyrrolyl amide when condensed with an annulated vinyl sulfone. A Mannich pyrrolyl derivative, analogous to PBG, could then be formed upon reduction of the pyrrolyl amide with an appropriate reducing agent. This Mannich pyrrolyl could then, in theory, be condensed under very mild conditions (**Scheme 53**).

X = O, NAr, SO₂, Si, C(R')₂
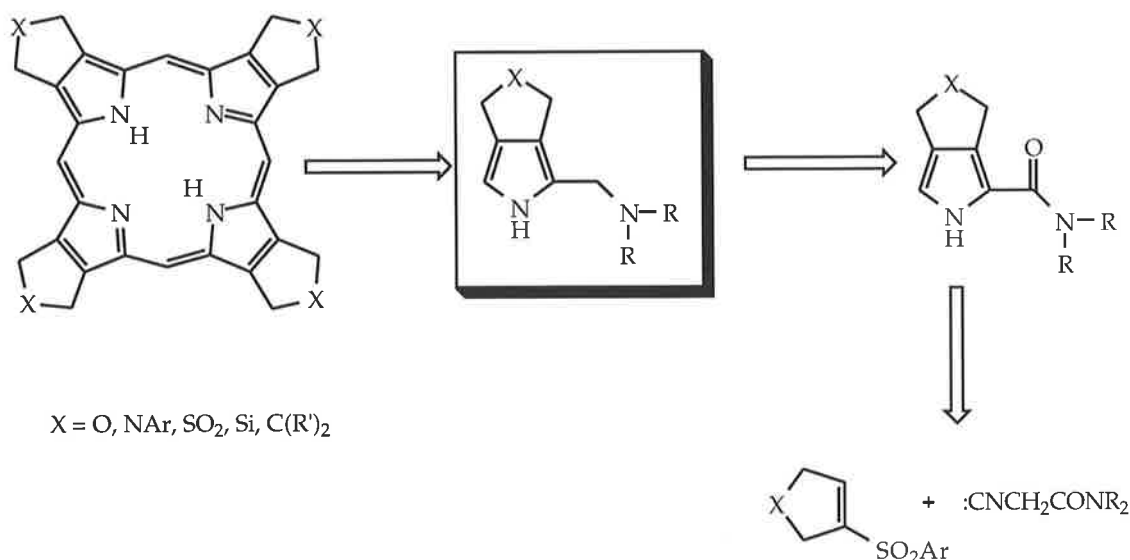
Scheme 53

By forming the pyrrolyl amide using an *N,N*-dialkyl isocyanoacetamide the convergent nature of the original pyrrole ester synthesis would be maintained and isolation of 2,5-unsubstituted pyrroles would be avoided.

Standard preparation of isocyanides involves dehydration of an *N*-formyl compound (frequently with an acylating agent and base). Phosgene, benzenesulfonyl chloride, phosphorus oxychloride,[127,128] triphenylphosphine/CCl₄,[129] trifluoromethanesulfonic anhydride,[130] chlorodimethylformiminium chloride[131] and di-2-pyridyl sulfite[132] in the presence of nitrogen bases such as pyridine, trialkylamines, dialkylarylamines or inorganic bases, such as sodium hydroxide and potassium carbonate, have all been used in the formation of isocyanides from formamides.

The formation of an *N,N*-diethyl-2-formylaminoacetamide was desired e.g. **130 (Scheme 54)** as formamides provide the most convenient access to isocyanides. Amide derivatives of glycine are not generally available so the synthesis of *N,N*-diethyl glycine was attempted through the formation of the acid chloride of glycine. Glycine was treated with thionyl chloride, followed by quenching with diethylamine, however this approach was not successful, because of the insolubility of glycine in the solvents used in the formation of the acid chloride.
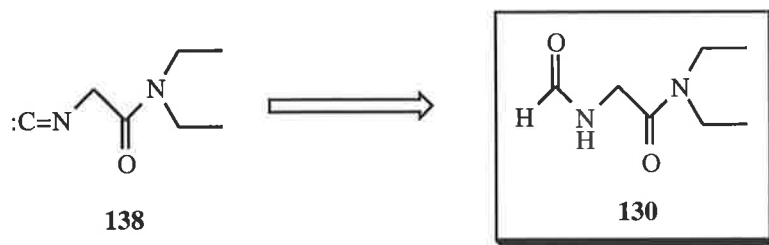
Scheme 54

Attempts were made to synthesise *N,N*-diethyl-2-formylaminoacetamide **130** by substitution of α-iodo-*N,N*-diethylacetamide **131** with the formamide equivalent sodium diformylamide **132** (**Scheme 55**). α-Iodo-*N,N*-diethylacetamide **131** was prepared by a Finkelstein halide exchange on α-bromo-*N,N*-diethylacetamide **133**, which had been prepared by the reaction of diethylamine with bromoacetyl bromide **134**.[133,134,135] Sodium diformylamide **132** was prepared in quantitative yield by treatment of formamide with sodium methoxide, according to the literature procedure.[136] Reaction of α-iodoacetamide **131** with sodium diformylamide **132**, followed by hydrolysis of the intermediate diformamide with ethanolic potassium hydroxide solution was attempted. The hydrolysis led to the isolation of α-hydroxy-*N,N*-diethylacetamide **135** not **130** as desired. This result clearly indicated that the initial substitution reaction between **131** and **132**, to give an intermediate diformamide, had not occurred. This reaction was consequently pursued no further.
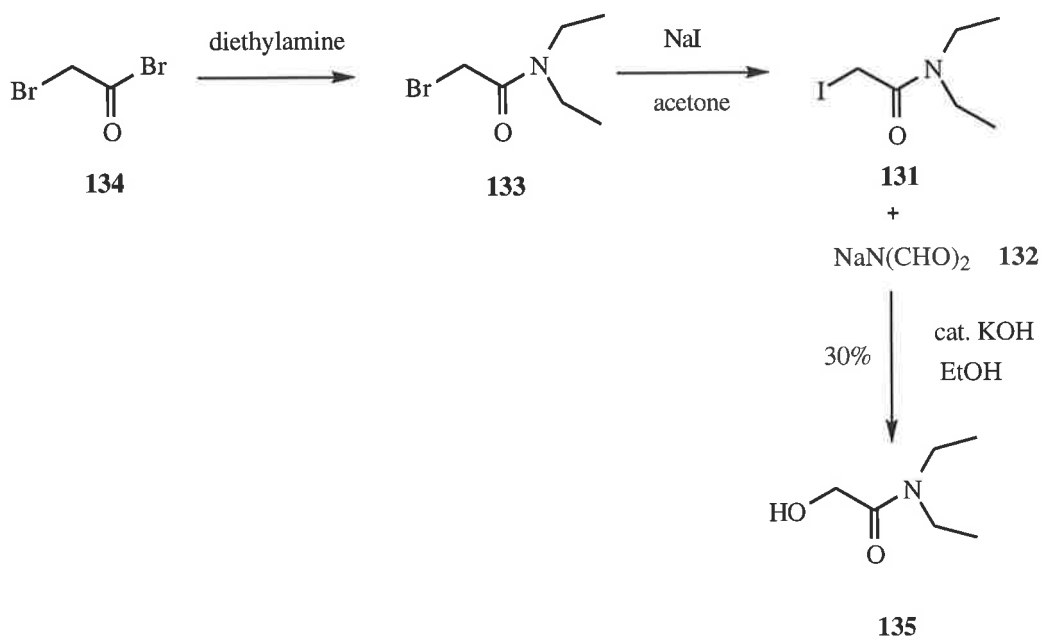
Scheme 55

Formylation of glycine was expected to render it a more soluble compound with which to carry out an amidation. Formylation of the amine group of glycine **136** using either methyl formate or ethyl formate was attempted, however the insolubility of glycine in methyl or ethyl formate led to the failure of this reaction.[137] Glycine was successfully formylated using acetic-formic anhydride (which was formed *in situ* from a mixture of acetic anhydride and formic acid) to give *N*-formyl glycine **137** in 86% yield (**Scheme 56**).
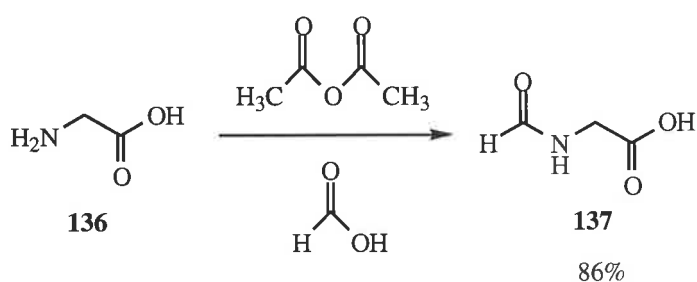
Scheme 56

N,N-Diethyl-2-formylaminoacetamide **130** was prepared from *N*-formyl glycine **137** and diethylamine, using either DCC or isobutylchloroformate as the coupling reagents (**Scheme**

79

57). The desired amide **130** was found to decompose during distillation, hence the amide was purified by column chromatography.

i.   DCC 50%
ii. Isobutylchloroformate 41%
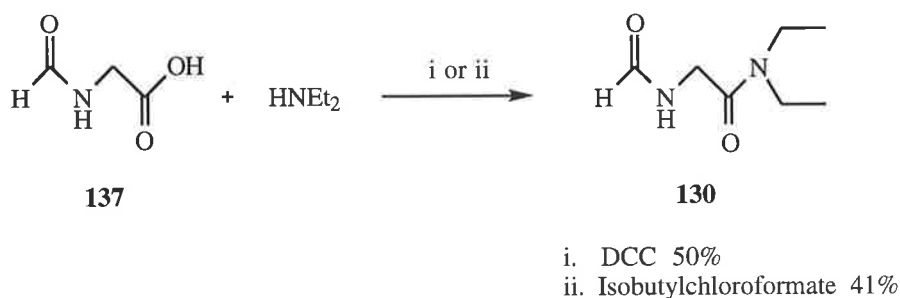
Scheme 57

Dehydration of **130** using the traditional formamide dehydrating reagents, phosphorus oxychloride and triethylamine, resulted in decomposition of the formamide, even when the reaction was carried out at -78°C. Trifluoromethanesulfonic anhydride has been shown to be an effective dehydrating agent for the conversion of sensitive formamides to isocyanides[130] and indeed trifluoromethanesulfonic anhydride afforded α-isocyano-*N*,*N*-diethylacetamide **138** in 80% yield **(Scheme 58).**
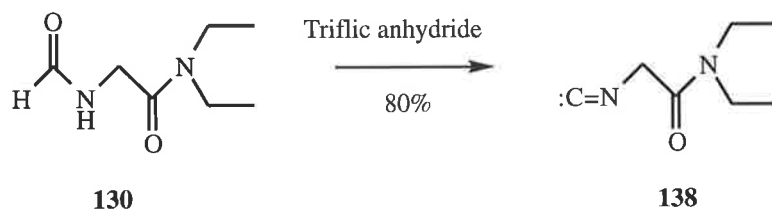
Scheme 58

Attempts were made to synthesise α-isocyano-*N*,*N*-diethylacetamide **138** directly, by the nucleophilic attack of onium dicyanoargentate **139** (formed by the reaction of triphenylmethyl phosphonium iodide and silver cyanide) on *N*,*N*-diethyl-2-bromoacetamide **133**.[133,134,135] Onium dicyanoargentates shift the nucleophilicity of the cyanide anion from carbon to nitrogen, therefore nucleophilic attack of an onium dicyanoargentate on an alkyl halide should give a isocyanide rather than a cyanide **(Scheme 59).**
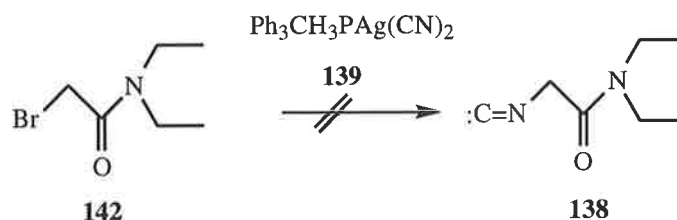
Scheme 59

This method was found to give only trace amounts of isocyanide (isocyanides can be readily identified in trace amounts by their distinctive smell). Given the toxicity of the cyanide reagents and the lack of promising results, this avenue to the desired isocyanides was abandoned.

Attempted transamination of *N*-formylglycine ethyl ester **140**, using diethylamine under standard conditions, gave no significant amounts of amide; **140** was recovered unchanged from the reaction mixture. In contrast to the failed amination of **140**, the amination of methyl isocyanoacetate **17** proceeded in a facile manner. Amination was accomplished by reaction of **17** with morpholine in MeOH, to give morpholino isocyanoacetamide **141** as a white solid in 92% yield (**Scheme 60**).[138]
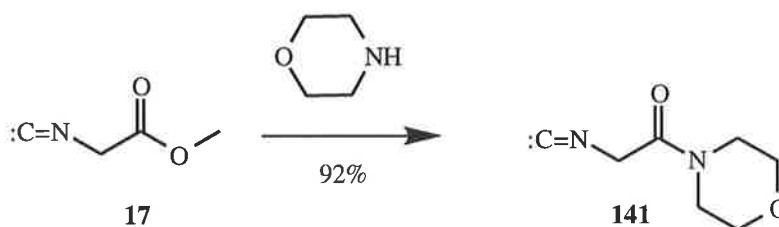
Scheme 60

3.1.2   Synthesis of Ester Isocyanoacetates

Methyl isocyanoacetate **17** and ethyl isocyanoacetate **142** were synthesised according to literature procedures from commercially available glycine methyl ester and ethyl ester hydrochlorides (**Scheme 61**).[127]
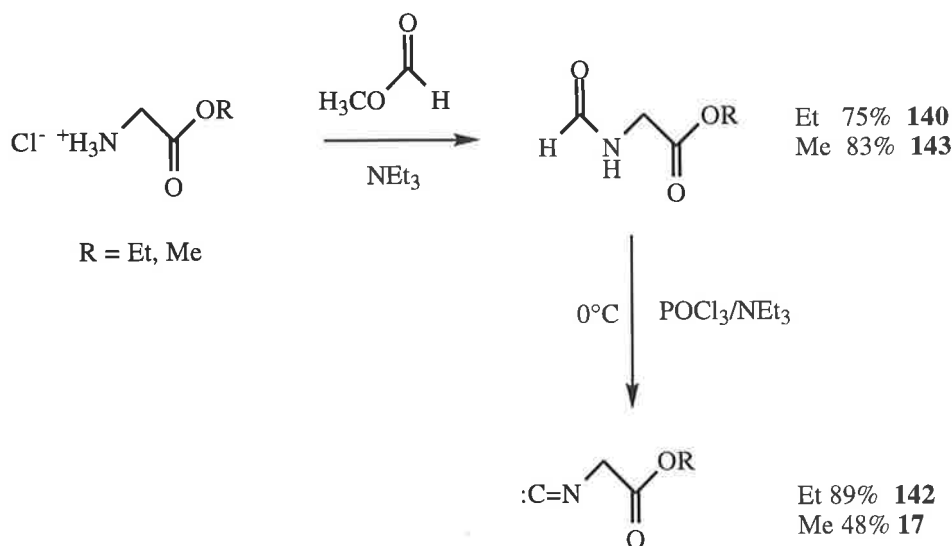
Scheme 61

Both glycine alkyl ester hydrochlorides were formylated using an excess of methyl formate and triethylamine giving *N*-formylglycine methyl ester **143** and *N*-formylglycine ethyl ester **140** in good yields. Purification of **140** was achieved by short path distillation, however **143** decomposed when heated and was therefore purified by 'dry flash' column chromatography.[139]

Benzyl isocyanoacetate **144** was prepared by the literature procedure in a similar manner to **17** and **142**.[107,57] Esterification of glycine with benzyl alcohol gave benzyl glycinate as its *p*-toluene sulfonate **145**, which was then formylated with methyl formate and triethylamine giving *N*-formylglycine benzyl ester **146** in good yield. Dehydration of **146**, using phosphorus oxychloride and triethylamine gave **144** in reasonable yield (**Scheme 62**).
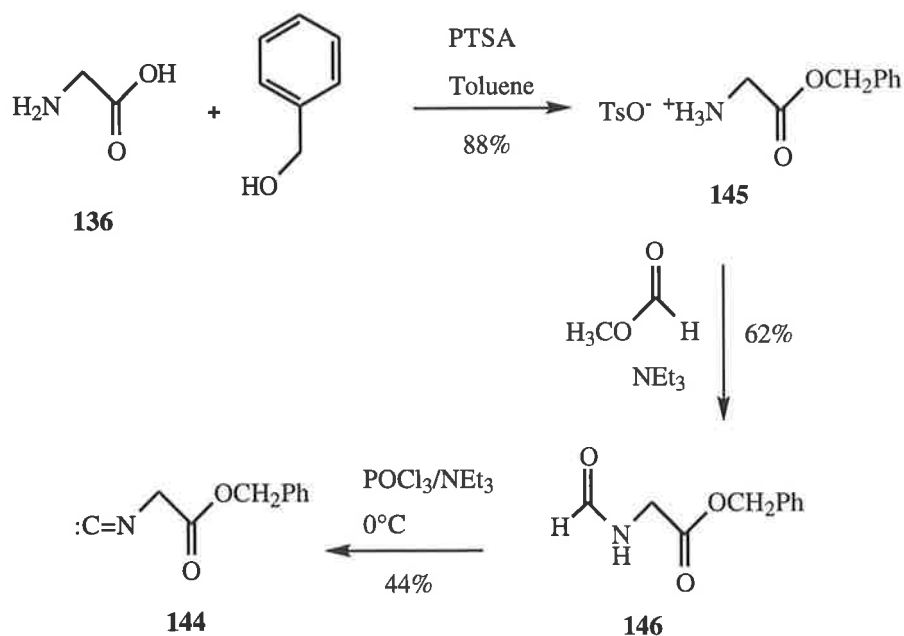
Scheme 62

3.2 Pyrrole Forming Reactions

The condensation reaction between vinyl sulfones and a variety of isocyanoacetates (methyl-, ethyl-, benzyl-) and *N,N*-diethylamide under basic conditions gave annulated[3,4-*c*]pyrrole-2-carboxylates as shown in **Table 4**. The tabular results indicate the best yield for the variety of ester substituents used.

Table 4.   **Formation of Annulated[3,4-*c*]pyrrole-2-carboxylates**
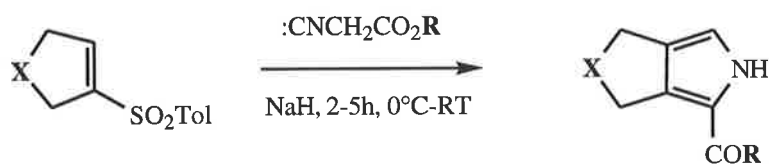
X	R	PRODUCT	%YIELD
C(CH$_3$)$_2$	OMe	**147**	80%
	OBn	**148**	86%
SO$_2$	OEt	**149**	66%
C(CN)$_2$	OMe	**150**	46%
C(CO$_2$Me)$_2$	OEt	**151**	70%
NSO$_2$Tol	OEt	**152**[#]	-
O	OMe	**153**	66%
	OEt	**154**	64%
	OBn	**155**	92%
	NEt$_2$	**156**	20%
O$_2$N—⟨⟩—N	OMe	**157**	27%

[#]Pyrrolic product **152** was not formed from *N*-tosyl-3-(phenylsulfonyl)-2,5-dihydropyrrole because of rapid aromatisation of the allylic isomer, which gave fully aromatic *p*-(toluenesulfonyl) pyrrole. Isomerisation of the vinyl isomer to the allylic isomer appears to be facile under the reaction conditions. The desired pyrrole product **152** has since been synthesised by Arnold *et al*.[140]
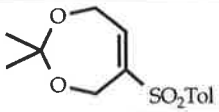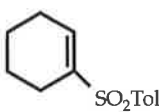
NaH was used as a base for all condensations, whereas many previous studies where nitro alkenes are used as the Michael acceptors have relied on hindered amine bases such as DBU, guanidine derivatives or a nonionic superbase.[92] NaH offers the advantages of ease of use,

cost effectiveness, and minimal isomerisation of vinyl sulfones to the allyic isomers.[62] It is essential that the mineral oil be removed from the NaH even on small scale reactions to ensure good yields of pyrrole and ease of purification. Purification was accomplished by column chromatography or in some cases recrystallisation, however most pyrroles could be used in the following reactions without further purification.

Tetrahydroisoindole and acetal pyrroles were synthesised as model annulated pyrrole compounds owing to their ease of formation from readily available starting materials and their resemblance to the desired annulated pyrroles (**Table 5**).

Table 5.   Formation of Alternate Annulated[3,4-*c*]pyrrole-2-carboxylates

$$
\text{VINYL SULFONES} \quad \xrightarrow[\text{NaH, 2-5h, 0°C-RT}]{\text{:CNCH}_2\text{COR}} \quad \text{PYRROLE -2-CARBOXYLATES}
$$
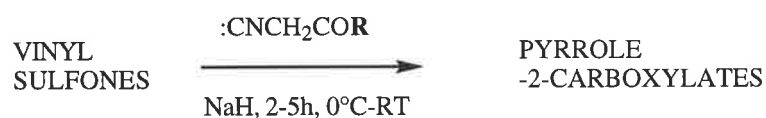
VINYL SULFONE	R	Product	%YIELD
	OEt	**158**	100%
	OMe	**159**	73%
	OEt	**160**	100%
	OBn	**161**	86%
	O◯N—	**162**	52%

All pyrroles formed were characterised, and their n.m.r. spectra fully assigned. Distortionless Enhancement by Polarization Transfer (DEPT) experiments enabled the unambiguous assignment of the protonated pyrrolic carbon, while the remaining quarternary pyrrolic carbons were assigned by chemical shift alone.

A single crystal X-ray structure of **158**[141] shows an annulated ring in which the methylene carbons lie in the plane of the pyrrole (**Fig. 21**) (Appendix 3), this result augurs well for the 5-membered ring systems in which it is hoped that the methylene protons are part of a flat annulated ring.
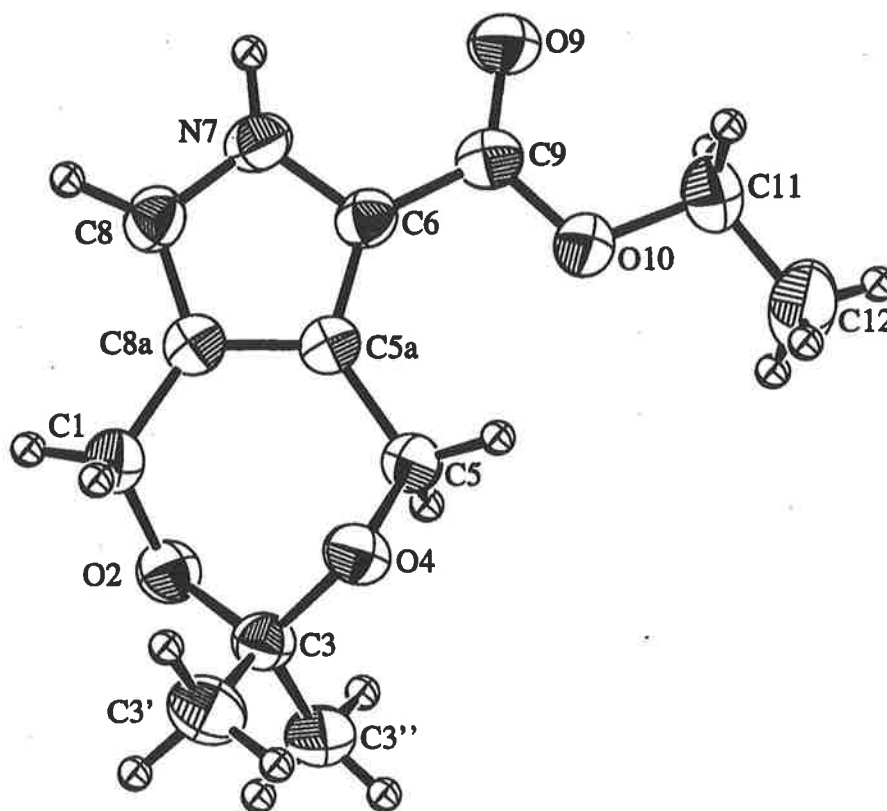
Figure 21

3.3 *Investigation of Alternate Pyrrole Forming Reactions*

The formation of pyrroles from isocyanides and Michael acceptors was developed by Barton and Zard from earlier work by van Leusen and Schöllkopf who formed 2,5-unsubstituted pyrroles from tosyl methylisocyanide and Michael acceptors such as α,β-unsaturated esters. This earlier methodology may be of use in the formation of tetrahydropyrrolo[3,4-*c*]pyrroles,

by using *N*-substituted maleimides as the Michael acceptors. Arnold *et al*[142] attempted the cyclisation of *N*-benzyl maleimide **163** with tosyl methylisocyanide in THF using *t*-butoxide as the base **(Scheme 63)**, however only trace amounts of the tetrahydropyrrolo[3,4-*c*]pyrrole **164** were detected by GC-MS, along with a large amount of black insoluble material.

$TolSO_2CH_2N=C:$

+

CH_2C_6H5

163

t-BuO⁻ ⁺K

$CH_2C_6H_5$

164
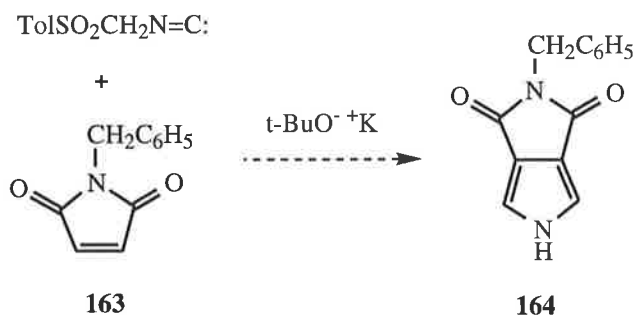
Scheme 63

Ohnmacht *et al* has synthesised a series of 2-aryloctahydropyrrolo[3,4-*c*]pyrroles and 1,2,3,5-tetrahydropyrrolo[3,4-*c*]pyrroles to examine the pharmacological and physical properties of these novel 5-5 fused ring systems.[143] Ohnmacht prepared numerous pyrrolo[3,4-*c*]pyrroles in which the pyrrole nitrogen was aryl substituted and the imido nitrogen was substituted with a benzyl derivative.

Arnold *et al*[142] also attempted to form annulated pyrroles by forming a pyrrole with acyclic substituents suitable for ring closure following a similar route to that of Ohnmacht *et al.*[143] **(Scheme 64)**. Reaction of tosyl methylisocyanide and diethyl fumarate **165** gave the pyrrole diester **166** which was converted to the diacid **167** by saponification. Ring closure of the diacid using the coupling reagent DCC gave the intermediate cyclic anhydride **168** which was not isolated but directly converted to an acid amide **169**. Conversion of the acid amide into the cyclic imide **164** or **170** was accomplished with thionyl chloride in DMF.
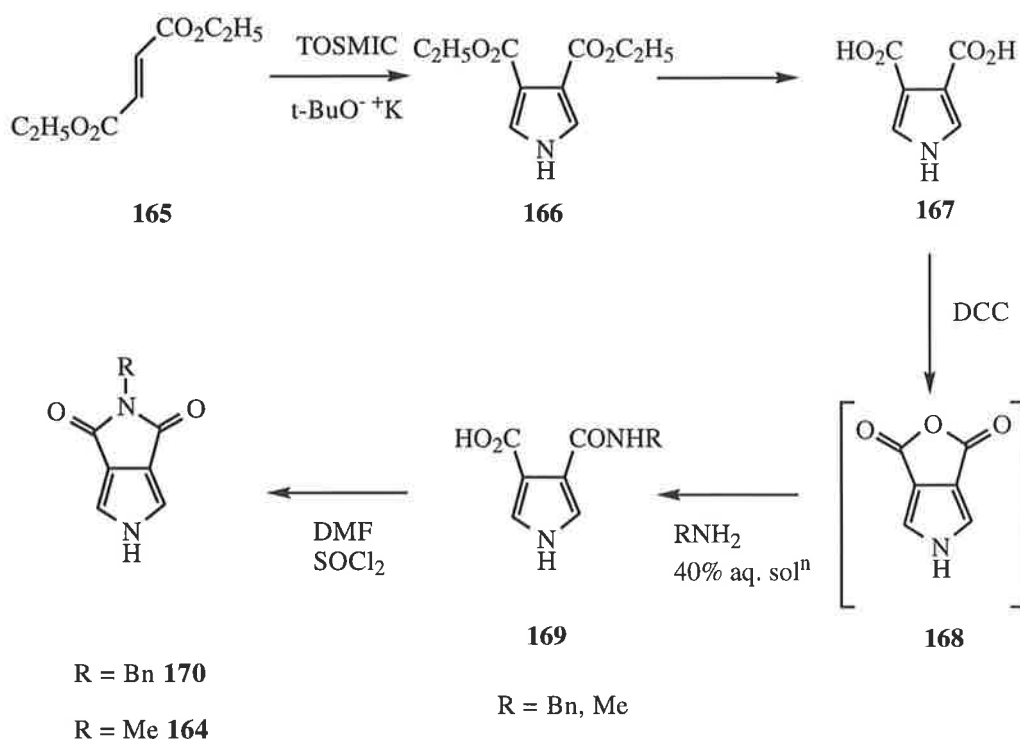
Scheme 64

The benzyl substituent of **170** was[143] removed by catalytic hydrogenation to give a pyrrole-3,4-dicarboximide. Reduction of the imide carbonyls was attempted, but no examples of a tetrahydropyrrolo[3,4-*c*]pyrrole unsubstituted on the pyrrole nitrogen were produced. This reaction failed because of preferential reduction of the pyrrole ring which gave an octahydropyrrolo[3,4-*c*]pyrrole.

If selective reduction of the imide carbonyls could be achieved then the tosylmethyl isocyanide– maleimide preparation may provide an avenue into *N*-substituted tetrahydropyrrolo[3,4-*c*]pyrroles,[142] which have proved difficult to produce through Barton and Zard methodology purely because of the difficulties encountered in the synthesis of the required vinyl sulfones.

Before trying to prepare a pyrrole-3,4-dicarboximide from TOSMIC and *N*-phenylmaleimide, it was first necessary to establish that a Michael addition would occur between an isocyanide and a maleimide or maleic anhydride. An exploratory reaction of readily available methyl

isocyanoacetate **17** with *N*-phenylmaleimide or maleic anhydride failed to furnish any of the expected addition products e.g. **187**. Mixing *N*-phenylmaleimide **171** with DBU in the absence of methyl isocyanoacetate, showed that a coloured complex formed readily, which may be the reason Michael addition of methyl isocyanoacetate **17** did not occur with either *N*-phenylmaleimide or maleic anhydride (**Scheme 65**). The use of NaH or NaOMe in place of a hindered amine base such as DBU did not result in the formation of addition products. The failure of this reaction indicated that a clean reaction between TOSMIC and *N*-phenylmaleimide or maleic anhydride was unlikely, therefore all annulated [3,4-*c*]pyrroles synthesised in this study were formed exclusively from vinyl sulfones and isocanoacetate anions by the Barton and Zard procedure.
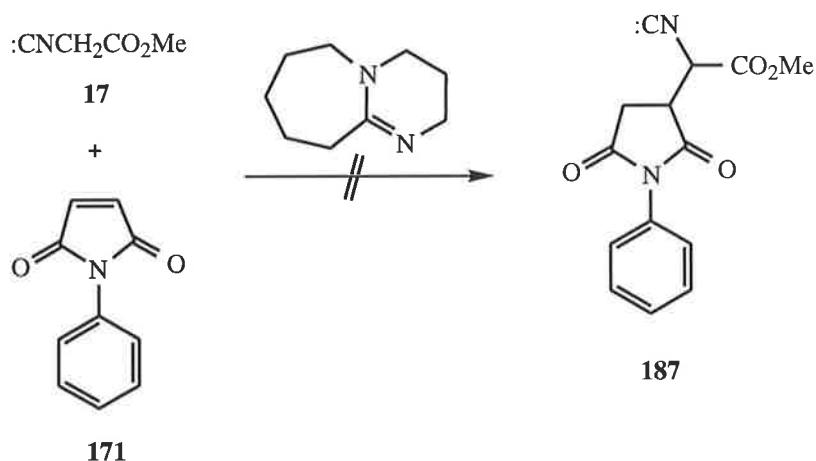
Scheme 65

3.4 Summary

The varied nature of the annulated pyrroles and the many different routes to porphyrin formation from pyrrole esters required the use of three different isocyanoacetate esters. The use of different ester isocyanoacetates and isocyanoacetatamides enabled manipulation of the various pyrroles (e.g. removal or transformation of the ester or amide functionality) in preparation for porphyrin formation. In total, three isocyanoacetate esters (methyl, ethyl and

benzyl) and two isocyanoacetate amides (*N,N*-diethyl and morpholino) were prepared by literature procedures for use in the formation of annulated [3,4-*c*]pyrroles.

In total, sixteen annulated pyrroles were prepared in good to moderate yields from the ten vinyl sulfones prepared in Chapter 2, using a standardised procedure based upon the Barton and Zard condensation. Pyrrolopyrrole derivatives were either not formed, or formed in limited quantities, prompting the abandonment of the investigation of these derivatives at this time.

All proposed alternatives to the Barton and Zard synthesis failed to give the desired annulated [3,4-*c*]pyrrole-2-carboxylates.

Chapter 4: Synthesis of porphyrins

4.1 Conversion of Pyrroles to Porphyrins

As in nature, all porphyrins prepared in the laboratory originate from pyrrole precursors. Utilisation of the Barton and Zard condensation to provide many different pyrroles and their derivatives, enabled many different synthetic approaches to the desired porphyrins to be investigated. These investigations are discussed in this chapter.

4.1.1 Introduction

This study is part of an ongoing program that aims to develop model porphyrin systems, and as part of this program the synthesis of $2^2,7^2,12^2,17^2$-tetraoxatetracyclopentaporphyrin (**Fig. 22**) has been attempted previously.[86] The knowledge gained from the attempted synthesis of tetraoxatetracyclopentaporphyrin influenced the synthetic routes and the reagents used throughout this investigation.
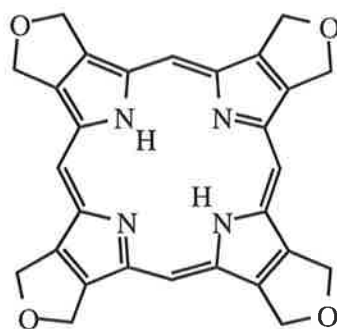
Figure 22 $2^2,7^2,12^2,17^2$-Tetraoxatetracyclopentaporphyrin.

The preliminary study revealed some important points:-

- The 2,5-unsubstituted pyrroles are stable to dilute acid when no *meso* equivalent (eg. formalin or paraformaldehyde) is present in solution.

- Attempted acid catalysed condensations produced an insoluble black material, which did not readily lend itself to characterisation.

The production of porphyrins in the laboratory is more often than not accompanied by the formation of polymeric products (tars, coals, etc) and as a result low yields are obtained. The isolation of natural porphyrins from animal blood therefore remains the only source of large quantities of porphyrin.[8] The only artificial porphyrins to be synthesised in large quantities have been OEP or simple tetra aryl porphyrins, using the Rothemund synthesis.[8] Preparative methods for the formation of large quantities of porphyrins, as would be required if porphyrins are to be utilised on a commercial scale, still remain to be developed.

The identification of porphyrin precursors during a reaction (such as a dipyrromethane) does not guarantee that a porphyrin will be the product from the reaction, as the intermediates can react to form oligomers and polymers or undergo rearrangement reactions. The steps involved in the tetramerisation and cyclisation of pyrroles to give a porphyrinogen intermediate are obviously dependent on the chemical and electronic properties of the pyrrole to a large extent. What can we predict about the behaviour of heteroannulated pyrroles of the type we are interested in?

Observations by [1]H n.m.r. spectroscopy of 2,5-unsubstituted furano[3,4-*c*]pyrrole **172** treated with deuterated TFA in deuterochloroform showed some deuterium exchange occurring at the two and five positions. Upon basic workup of the acid solution, furano[3,4-*c*]pyrrole was recovered, thus showing the pyrrole to be stable under strongly acid conditions.

Addition of formaldehyde to the acidic solution resulted in consumption of pyrrole and immediate formation of an insoluble polymeric material that could not be characterised; no pyrrole was recovered. Acid-catalysed porphyrin formation from furano[3,4-*c*]pyrrole **172** seems to be prevented by rapid acid-catalysed linear polymerisation of the pyrrole with formaldehyde. This preference for linear polymerisation over cyclisation may be due to either the subtle electronic effects of the β-heteroatom or ring strain associated with the annulated ring:-

- The presence of substituents that can possibly form good leaving groups under acidic conditions e.g. hydroxyl, dialkyl amines etc, in the β-position introduce alternative electron movement pathways which may lead to polymer formation.

- Hetero atoms such as oxygen, or a sulfone group, in the β-position should be inductively electron withdrawing under neutral conditions. Thus, it could be expected that these pyrroles should share similar electronic characteristics with halogenated pyrroles which have been used to form porphyrins.[144]

Modification of the electronic characteristics of the β-heteroatom was thought to give the best chance of porphyrin formation. The series of cyclic alkenes discussed in Chapter 2 was therefore synthesised with this thought in mind.

Condensation of 2,5-unsubstituted furanopyrrole **172** with formaldehyde under acidic conditions gives only black insoluble material. Treatment of **172** with acid alone, indicates that the 2,5-unsubstituted pyrrole itself is relatively stable to acid, therefore the reaction is going awry during tetramerisation or cyclisation. The characterisation of the resultant tars has proved difficult. The tars are characterised by high m.p. or decomposition temperatures, insolubility in all organic solvents and generally poor ^{1}H n.m.r. spectra. The formation of tars because of linear polymerisation (to straight chain pyrrole polymers), unstable dipyrromethane, tripyrromethane or porphyrinogen intermediates, appears to be the primary hindrance to porphyrin formation rather than the viability of the pyrrole under acidic conditions.

4.2 Porphyrin Forming Reactions

Porphyrin formation was carried out under a variety of conditions with emphasis placed on mildly acidic or neutral conditions as outlined below (**Scheme 66**). As the aim was to synthesise symmetrical porphyrins synthetic routes that required the formation of tripyrromethanes or linear tetrapyrroles were not pursued.

X= O, NAr, SO$_2$, CR$_2$
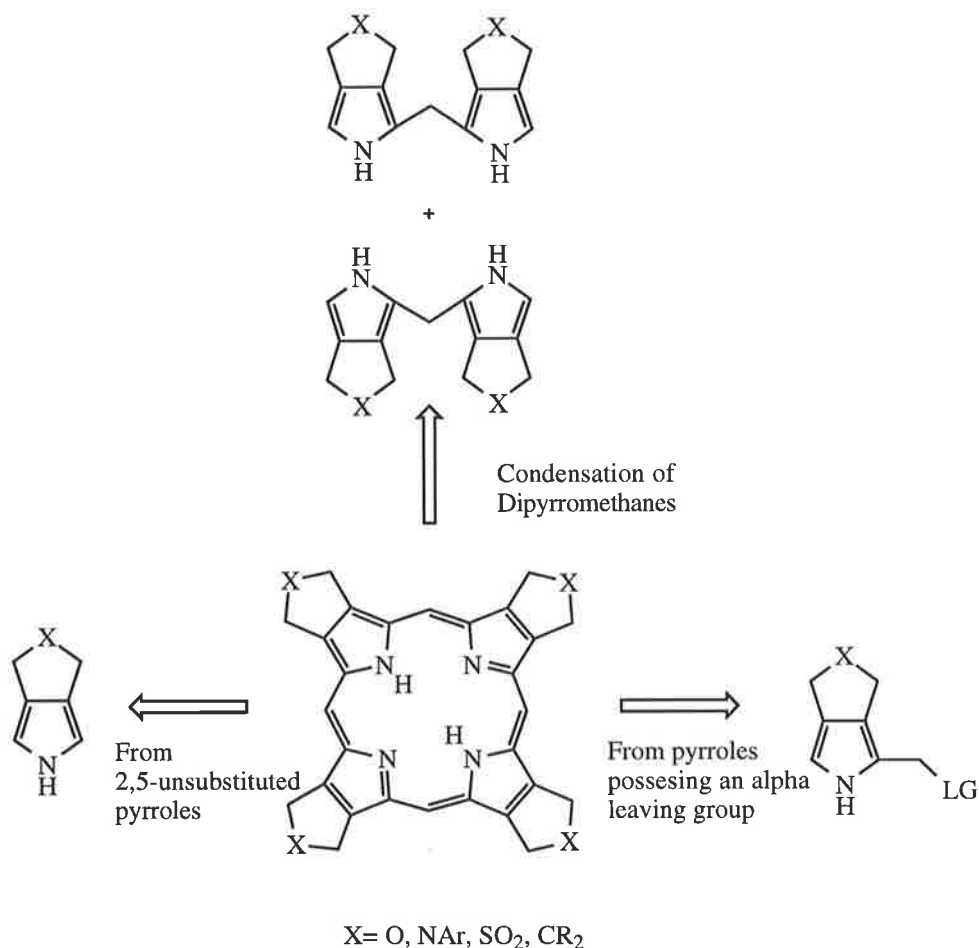
Scheme 66

4.2.1 Porphyrins from 2,5-Unsubstituted Pyrroles

The Barton-Zard procedure produces pyrrole-2-carboxylates such as **173**. The ester functionality must be removed to give 2,5-unsubstituted pyrroles, such as **48**, used in some of the following porphyrin syntheses. Methyl and ethyl pyrrole esters are usually hydrolysed

under basic conditions and isolated as the pyrrole-2-carboxylic acids **174** after acidic workup (**Scheme 67**). The pyrrolecarboxylic acid can then be decarboxylated in ethanolamine under thermal conditions to give a 2,5-unsubstituted pyrrole **48** on workup. The hydrolysis-decarboxylation protocol works well for most pyrrole carboxylates, but it was previously found that furano[3,4-*c*]pyrrole carboxylic acid **175** was difficult to recover from the hydrolysis mixture, so an alternative route for removal of the ester functionality for the pyrroles prepared during this project was pursued.[86]
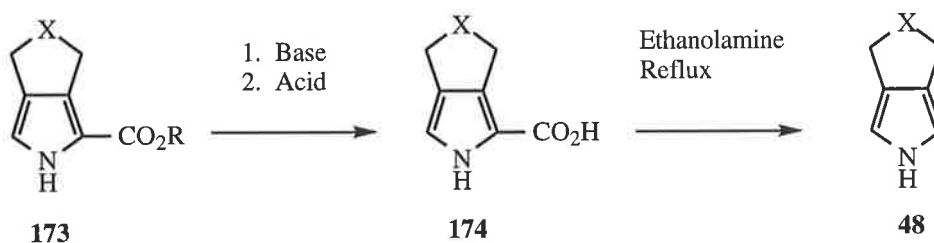
Scheme 67

Use of benyl isocyanoacetate provided the pyrrole benzyl esters **176** which could be debenzylated to the carboxylic acid **174** directly by catalytic hydrogenolysis, under neutral conditions, in high yield, as easily recoverable powders (**Scheme 68**). This procedure avoided any possible difficulties in the recovery of pyrrole carboxylic acids from aqueous solution as noted previously.[86] Thermal decarboxylation of the pyrrole carboxylic acid in ethanolamine furnished the 2,5-unsubstituted pyrroles **48**. The hydrogenolysis–decarboxylation protocol was used exclusively throughout this project whenever a 2,5-unsubstituted pyrrole was required. The base hydrolysis protocol was not used during this project.
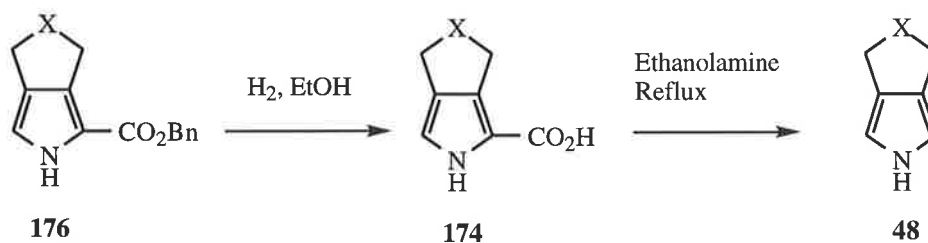
Scheme 68

Yields for the catalytic hydrogenolysis and decarboxylation products from pyrrole benzyl esters are shown in **Table 6**.

Table 6. **Hydrogenolysis and Decarboxylation of Pyrrole Benzyl Esters**
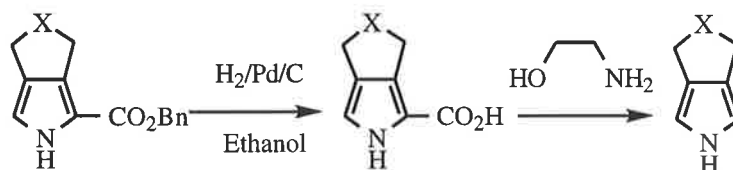
Pyrrole benzyl esters	Carboxylic acid		2,5-unsubstituted pyrrole	
148	177	100%	179	67%
155	175	95%	172	63%
161	178	100%	180	96%

The major porphyrin forming reactions from 2,5-unsubstituted pyrroles in which the *meso* carbons of the porphyrin are externally provided by a 'Mannich derivative' or an aldehyde are shown in **Scheme 69**.
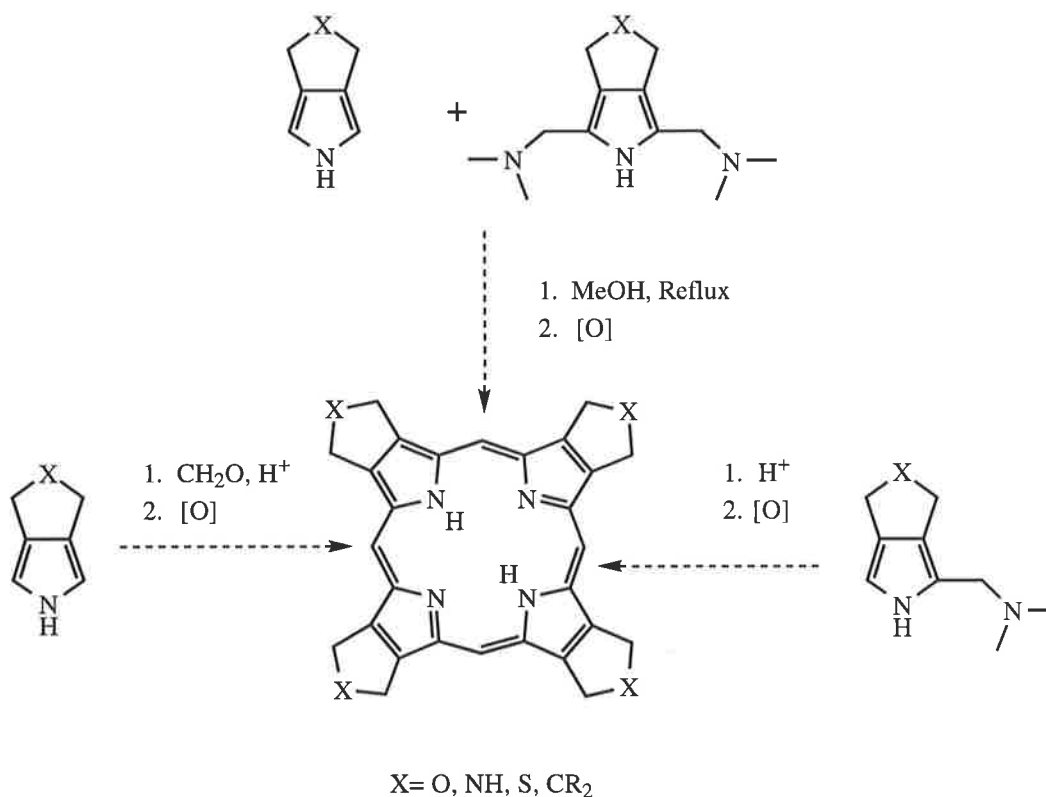
Scheme 69

The traditional condensation of monopyrroles with formaldehyde works well for pyrroles with electron-withdrawing or small alkyl substituents.[145] Attempted condensations of 2,5 unsubstituted furano[3,4-c]pyrrole under a variety of conditions yielded only black insoluble material. The reasons for the consistent failure of the furano[3,4-c]pyrrole derivatives to furnish a porphyrin derivative are unknown. The condensation of 5,5-dimethyl-tetrahydrocyclopenta[c]pyrrole **179** under standard Rothemund conditions gave $2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[b,g,l,q]porphyrin **181** in 5% yield as a purple powder **(Scheme 70)**.
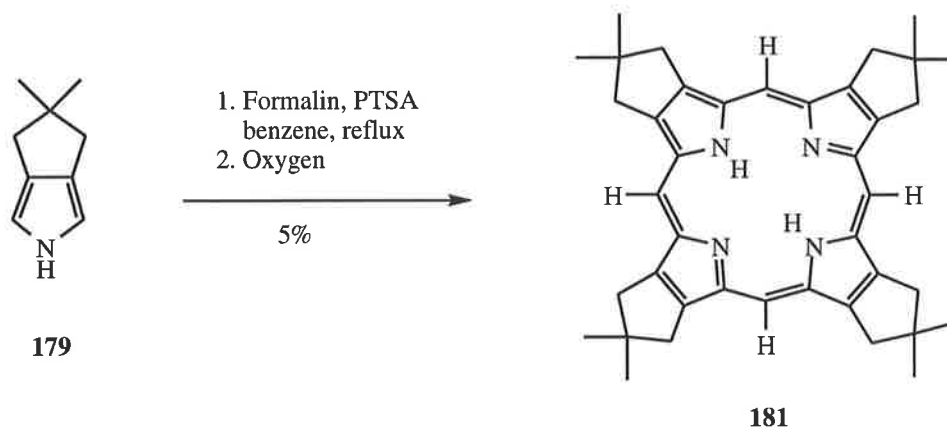
Scheme 70

Visible spectra were recorded showing a Soret band at 386 nm (log ε 5.25), which is blue shifted compared to OEP with a Soret band at 398 nm (log ε 5.20).[49] Infrared measurements of free base **181** showed a similar spectrum to symmetrical porphyrins such as OEP.[146] ^{1}H n.m.r. spectrum shows the expected chemical shifts and also shows the methylene protons to be a singlet at room temperature, which implies the five-membered ring is either flat (as required in the original design criteria) or the methylene protons are rapidly exchanging to give a singlet.

As an aid to characterisation of the octamethylcyclopentaporphyrin **181**, the Ni(II) derivative was formed from the free base porphyrin **181** by refluxing with Ni(OAc)$_2$ in DMF. $2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-Octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b,g,l,q*]porphyrinato nickel(II) **182** was formed in 92% yield as a red powder. ^{1}H n.m.r. and IR spectra indicated the disappearance of the core protons.

4.2.2   *Porphyrins from Bis(dimethylaminomethyl)pyrroles*

A neutral porphyrin-forming reaction that appeared to offer acid free condensation conditions has been developed by Smith et al.[76] The reaction involves the condensation of 2,5-

unsubstituted pyrroles e.g. **180** with bis(dimethylaminomethyl)pyrroles e.g. **185** followed by rapid oxidation using $K_3Fe(CN)_6$ **(Scheme 71)**.
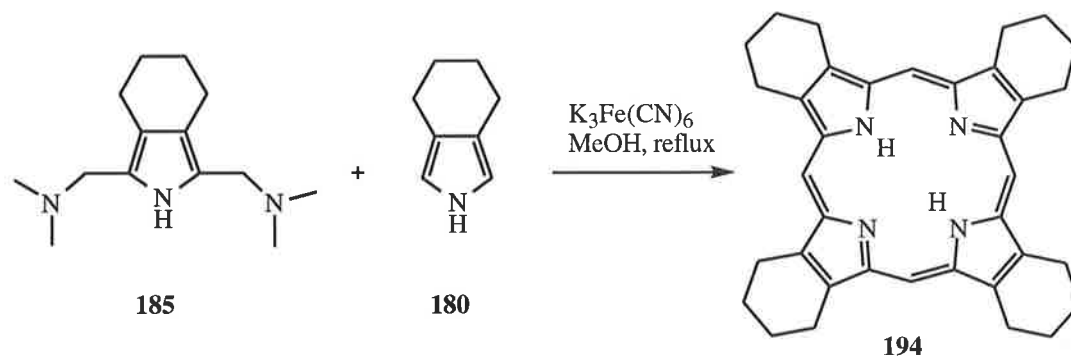
Scheme 71

Preparation of the bis(dimethylaminomethyl)pyrroles from 2,5-unsubstituted pyrrole **172** using Eschenmoser's reagent is shown below **(Scheme 72)**.[147] Quaternisation of the dimethylaminomethyl group of **184** using MeI creates a better leaving group which alleviates the need for acid catalysis in the condensation reaction. Quaternised bis(dimethylaminomethyl)pyrrole **186** was not characterised, as it proved difficult to handle the residue, no attempt was made to purify this derivative. Recent research has found that quaternised bis(dimethylaminomethyl)pyrroles can be recrystallised from MeOH, but this was not attempted.[148]
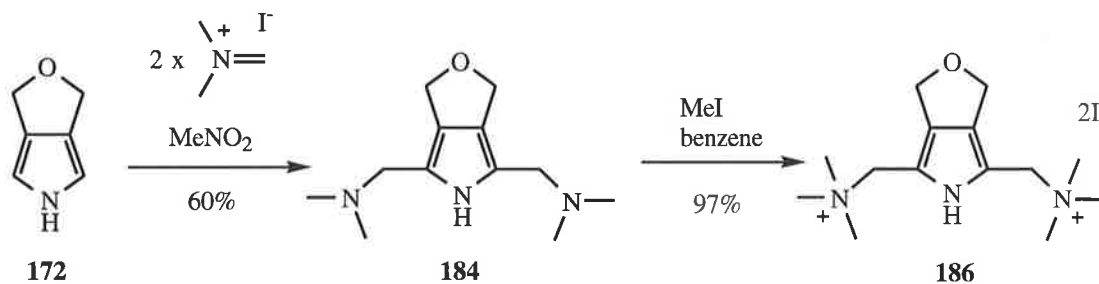
Scheme 72

A trial condensation was carried out with 4,5,6,7-tetrahydro-2*H*-isoindole **180** following the literature procedure **(Scheme 71)**,[76] to determine if the bis Mannich protocol was viable.

Bis(dimethylamino)methylpyrrole **185** was formed in good yield from **180** and Eschenmoser's reagent. However, only a trace amount of porphyrin was detected from the reaction of **185** with **180**; the majority of the material isolated from the reaction was a black insoluble precipitate.

In spite of the poor results from the trial reaction, the condensation of furano[3,4-*c*]pyrrole **172** with bis(dimethylaminomethyl)furano[3,4-*c*]pyrrole **184** was attempted. This reaction gave no porphyrin products under a variety of conditions. The condensation of **172** with the quarternised bis(dimethylaminomethyl)furano[3,4-*c*]pyrrole **186** also failed to furnish any porphyrin products; varying quantities of unsubstituted **172** were recovered in both cases. The recovery of some 2,5-unsubstituted pyrroles and concomitant formation of polymer type materials suggests that rapid reaction of the bis(dimethylaminomethyl)pyrrole derivatives was occurring in preference to the desired 1:1 reaction with 2,5 unsubstituted furano[3,4-*c*]pyrrole.

4.2.3 *Porphyrins from Pyrrolyl Amides*

Synthesis of porphyrins from dimethylaminomethylpyrroles was attempted. Dimethylaminomethylpyrroles were to be formed by reduction of readily accessible tetrahydroisoindole amide **162**. Reduction of the tetrahydroisoindole amide with borane-methyl sulfide complex **(Scheme 73)** failed to produce the PBG analogue α-morpholinomethylpyrrole **188** under a variety of conditions; condensation of the crude reduction product gave no observable porphyrin product.[149,150]

A possible reason for the failure of the amide reduction may be complexation of the borane reagent by the oxygen of the morpholine ring, this would have prevented the delivery of the reducing agent to the carbonyl. No attempts were made to reduce the furanopyrrolyl amide **156**, as similar complexation of the borane reagent to the furano ring oxygen was expected to hamper the reaction.
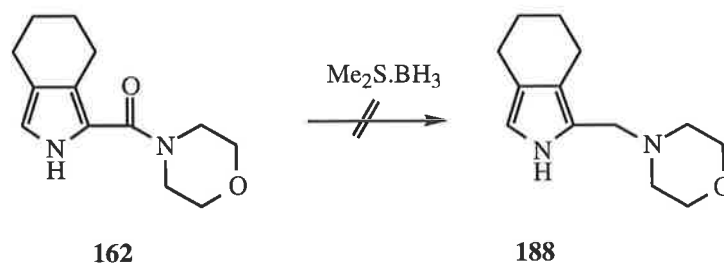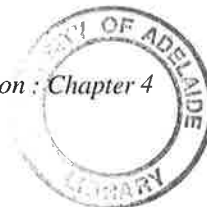
Scheme 73

As the tetrahydroisoindole amide **162** was easily formed, it made sense to investigate all possible avenues to form porphyrins from this derivative. It was postulated that treatment of **162** with POCl₃ would give an activated phosphoryl complex **189** which theoretically could condense to form a porphyrin in a similar manner to the formation of dipyrroketones (**Scheme 74**).[145,151]
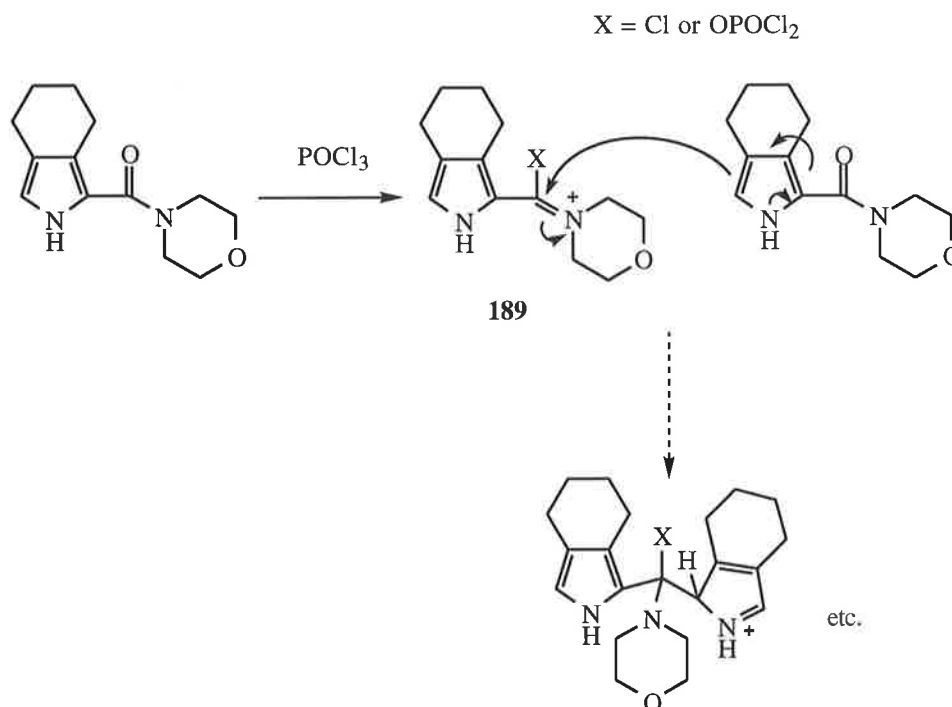
Scheme 74

However upon treatment of **162** with POCl₃, no porphyrin products were recovered. Analysis of the reaction mixture by t.l.c. showed the almost immediate consumption of starting material.

Many highly coloured products were present in trace amounts (by t.l.c.), indicating a possible mixture of dipyrroketones and possibly higher oligomers.

4.3 Porphyrins from Pyrrole-2-carboxylates

The diagram below (**Scheme 75**) indicates the major pyrrole condensations from pyrrole-2-carboxylates. These methods do not involve prior removal of the α-carbon of the pyrrole and therefore provide potential savings in time and yield.
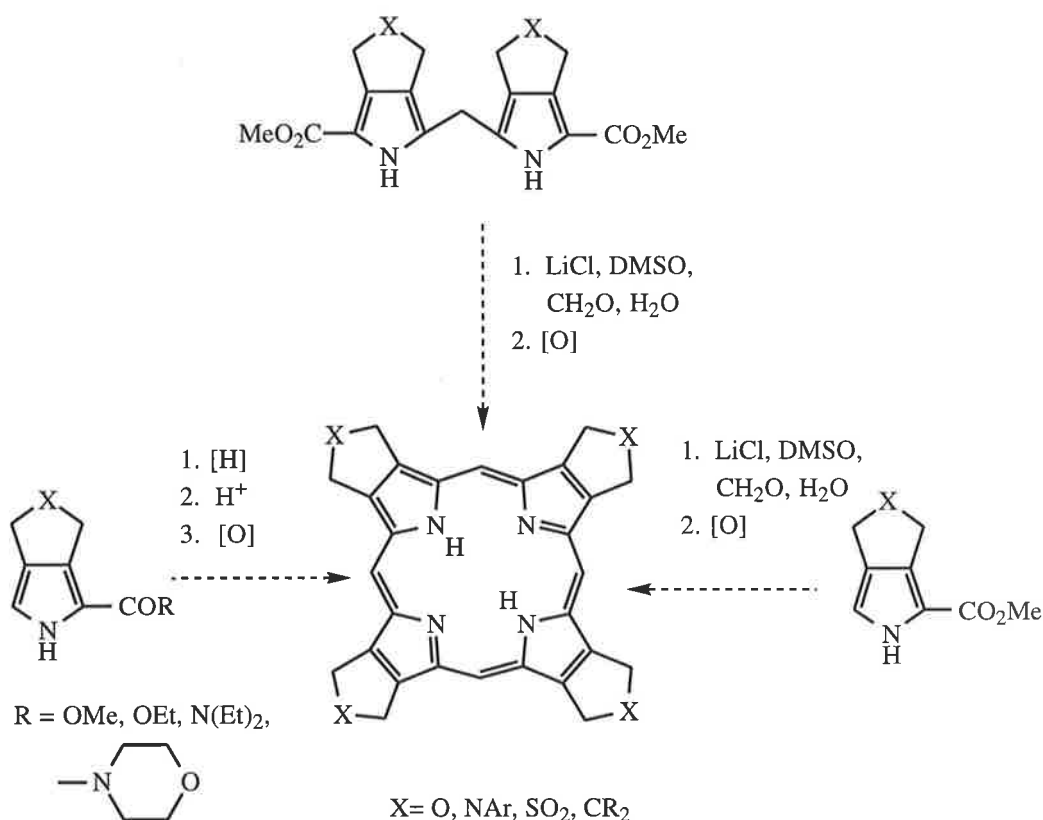
Scheme 75

4.3.1 Porphyrins from α-Hydroxymethyl Pyrroles

One of the most widely applied procedures for the synthesis of porphyrins under mild conditions is the condensation of α-hydroxymethylpyrroles.[56,92][12,55] Attempts were made to synthesise $2^2,7^2,12^2,17^2$-tetraoxatetracyclopentaporphyrin **191** from α-hydroxymethylpyrrole

192 (Scheme 76). Reduction of both pyrrole ester **153** or **154** with LiAlH$_4$ at 0°C furnished the α-hydroxymethylpyrrole as a yellow oil (low Rf product by t.l.c.). Care was taken not to over reduce the ester, as an α-methyl pyrrole derivative has been observed as the product of LiAlH$_4$ reduction of pyrrole methyl or ethyl esters.[92] A small sample of the crude reduction product was examined by [1]H n.m.r. spectroscopy on each occasion to determine if the product was indeed α-hydroxymethylpyrrole. The [1]H n.m.r. spectrum indicated the disappearance of the ester signals and the appearance of a singlet for the α-methylene protons at δ 4.57 ppm.

The α-hydroxymethylpyrrole **192** was used immediately without further purification as their unstable nature has been noted.[92] The α-hydroxymethylpyrrole was taken up in either THF or dichloromethane, then treated with PTSA. The reaction mixture became red immediately upon addition of PTSA and gradually became black. A black insoluble material was the only product isolated and starting materials were not observed by t.l.c. analysis or [1]H n.m.r. spectroscopy in the final reaction mixture **(Scheme 76)**.

a. R = methyl **153**
b. R = ethyl **154**
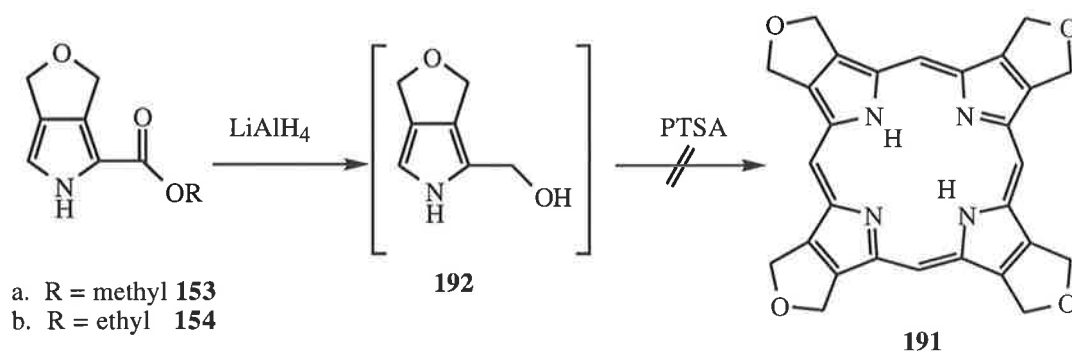
Scheme 76

The use of transition metal cations (e.g. Zn^{2+}) as templates for cyclisation was also investigated. Zinc acetate was added to a solution of α-hydroxymethylpyrrole and PTSA added. Insoluble black precipitates were isolated as the only product of the reaction once again.

Synthesis of **181** was achieved in 6% purified yield through LiAlH$_4$ reduction of 5,5-dimethyl-tetrahydrocyclopenta[*c*]pyrrole methyl ester **147** and condensation of the α-hydroxymethyl-pyrrole under acidic conditions (**Scheme 77**).

1. LiAlH$_4$, PTSA
   THF, RT
2. CH$_2$Cl$_2$, dimethoxymethane,
   chloranil, oxygen

6%

147

181
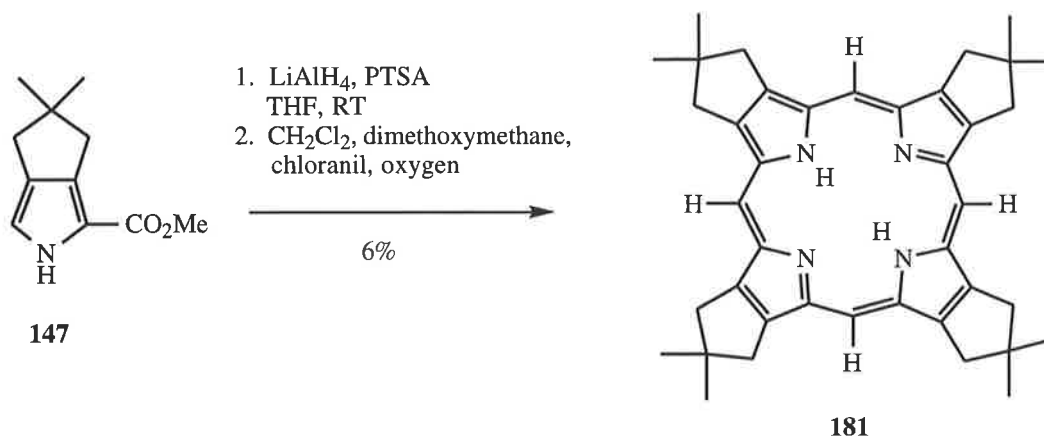
Scheme 77

The formation of **181**, through an intermediate α-hydroxymethylpyrrole, in 6% yield represented a much easier and less time consuming synthesis of this porphyrin, in comparison to the synthesis from the 2,5-unsubstituted pyrrole **179** from the pyrrole-2-carboxylate **147**.

4.3.2   *Attempted Porphyrin Formation from Ethyl 2,2-dioxo-1,2,3,5-tetrahydro-2-thieno[3,4-c]pyrrole-4-carboxylate*

During this project the condensation of ethyl 2,2-dioxo-1,2,3,5-tetrahydro-2-thieno[3,4-*c*]pyrrole-4-carboxylate **149** was attempted. Reduction of the ester group, using LiAlH$_4$, was hoped to give an α-hydroxymethylpyrrole which could condense under acidic conditions. Under the reductive conditions, however, the sulfone appeared to extrude sulfur dioxide even at room temperature (**Scheme 78**); as indicated by the complex mixture of products observed by t.l.c. analysis.[83,152]

104

149
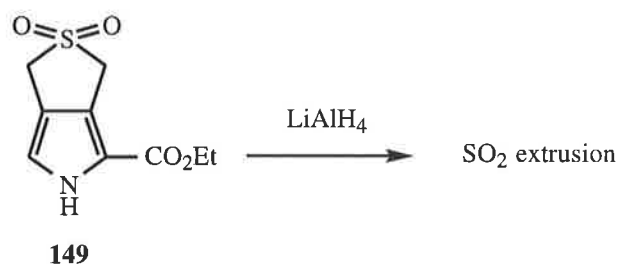
Scheme 78

4.4.2 *Krapcho Demethylation–Decarboxylation of Pyrrole-2-carboxylates*

The Krapcho ester hydrolysis method involves rapid LiCl mediated S_N2 demethylation of a pyrrole-2-methyl ester followed by thermal decarboxylation of the intermediate lithium α-carboxylate in DMSO to give a 2,5-unsubstituted pyrrole. The 2,5-unsubstituted pyrrole may then be cyclised with paraformaldehyde *in situ* by the catalysis of the Lewis acid Li^+ cation, to give a porphyrinogen that is rapidly oxidised to porphyrin by oxygen. This method was expected to give reasonable yields of **191** as the 2,5-unsubstituted furano[3,4-*c*]pyrrole was formed *in situ* and the furano ring is stable under the conditions (as shown by its survival of the high temperatures of pyrrole carboxylic acid decarboxylation). Unfortunately, porphyrin preparation from the methyl ester **153** or the carboxylic acid **175** using the Krapcho method failed, giving insoluble precipitates once again **(Scheme 79)**.[92]

a. R = methyl **153**
b. R = H **175**

191
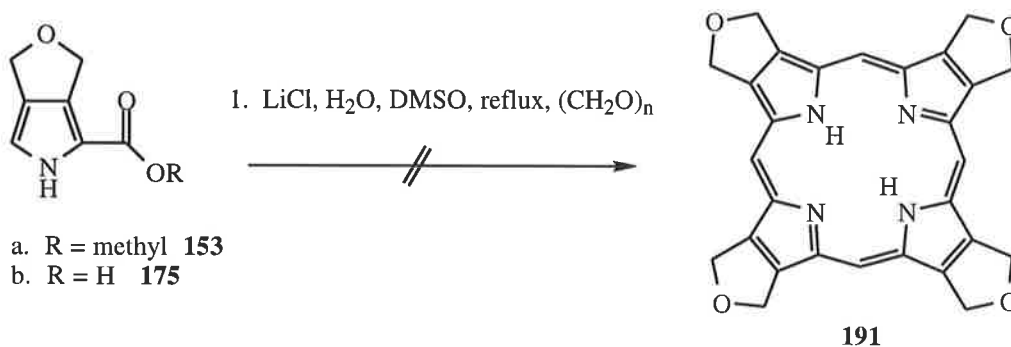
Scheme 79

Thermal decarboxylation (Krapcho conditions) of the pyrrole **149 (Scheme 80)** was attempted, however sulfur dioxide appeared to be extruded under the vigorous thermal conditions.[152,153]
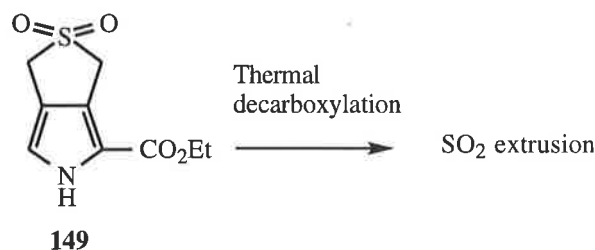
Scheme 80

4.4.3   Porphyrins from Dipyrromethanes

Linear polymerisation or oligomerisation of monopyrroles cause yields of porphyrins in the Krapcho method to be variable.[92] To try and alleviate this problem the condensation of dipyrromethanes was investigated. Dipyrromethane **193** was formed in quantitative yield by the HCl-catalysed reaction of readily available tetrahydroisoindole **161** with formaldehyde in EtOH. Porphyrin **194** was formed in 10% yield using LiCl and paraformaldehyde in DMSO **(Scheme 81)**.
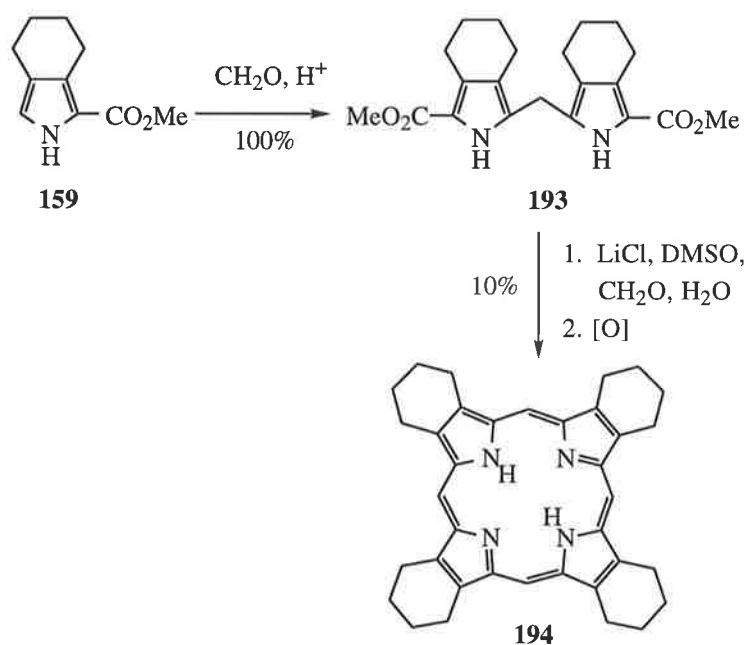
Scheme 81

However, a borontrifluoride diethyl etherate catalysed reaction of furano pyrrole **153** with dimethoxymethane resulted in a very poor yield of the dipyrromethane **195**. Attempted condensation of crude **195** using LiCl and paraformaldehyde in DMSO failed to furnish **191**, giving only black polymeric material **(Scheme 82)**.
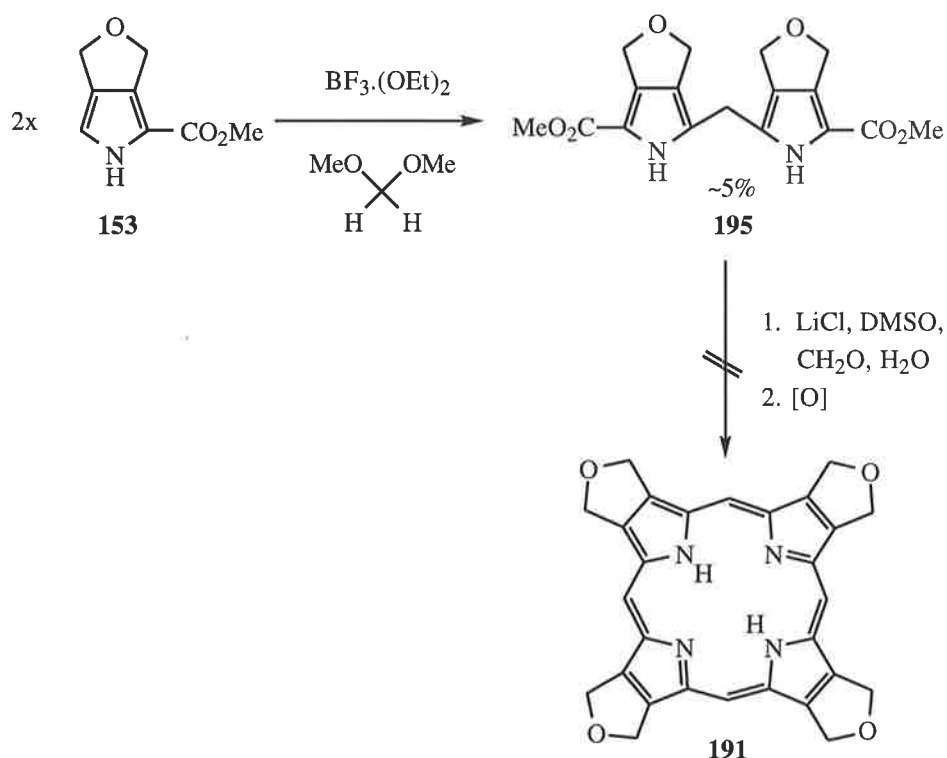
Scheme 82

4.5 NaCl Assisted Porphyrin Formation

Lindsey *et al* have demonstrated the beneficial effects of salts on the acid-catalysed condensation of pyrroles leading to porphyrin formation.[154] This methodology was examined using benzaldehyde instead of formaldehyde, as it was thought that benzaldehyde may add stability to the intermediate carbonium ion formed from nucleophilic attack of the pyrrole. Furano[3,4-*c*]pyrrole **172** was mixed with benzaldehyde in the presence of NaCl and either boron trifluoride diethyl etherate or PTSA, in dichloromethane. However no tetraphenyl

porphyrin **196** was formed, only insoluble precipitates were once again recovered (**Scheme 83**).[154]
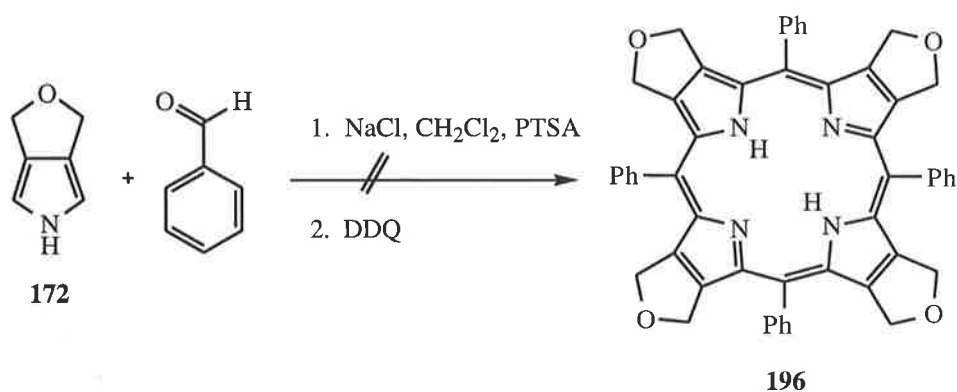
Scheme 83

4.6   Miscellaneous

At this stage it pays to mention the fate of the pyrroles which did not prove suitable for porphyrin formation for one reason or another.   Methyl-3,3-bis(methoxycarbonyl)-5,7-dihydro-1H[1,3]cyclopenta[5,6-*c*]pyrrole-6-carboxylate **151** was not suitable for porphyrin formation owing to the fact that selective reactions (e.g. LiAlH$_4$ hydride reduction or Krapcho demethylation) on the methyl ester in the 2-position could not be carried out without affecting the remaining methyl ester groups. Time constraints prevented the formation of a benzyl ester derivative, which would have allowed selective formation of a carboxylic acid derivative by hydrogenolysis. The carboxylic acid derivative could then have been decarboxylated under mild conditions to give a 2,5-unsubstituted pyrrole that may have condensed with formaldehyde under acidic conditions.

The formation of a porphyrin from 2,2-dioxo-1,2,3,5-tetrahydro-2-thieno[3,4-*c*]pyrrole-4-carboxylate **149** failed on all attempts. It was postulated that reduction of the ester group using LiAlH$_4$ (to give an α-hydroxymethylpyrrole which could condense under acidic conditions), or the Krapcho demethylation–decarboxylation procedure, appeared to cause the extrusion of sulfur dioxide from the pyrrole (**Scheme 78 and 80**).

It was thought that a radical decarboxylation approach may avoid the vigorous conditions leading to sulfur dioxide extrusion during the reduction and thermal decarboxylation to give a 2,5-unsubstituted pyrrole, which could then be condensed with formaldehyde under acidic conditions. Using the tetrahydroisoindole carboxylic acid **178** as a model pyrrole acid, attempts were made to couple *N*-hydroxypyridine-2(1*H*)-thione. However the 'Barton pyrrole ester' **190** could not be formed under a variety of conditions, so this route was abandoned (**Scheme 84**)
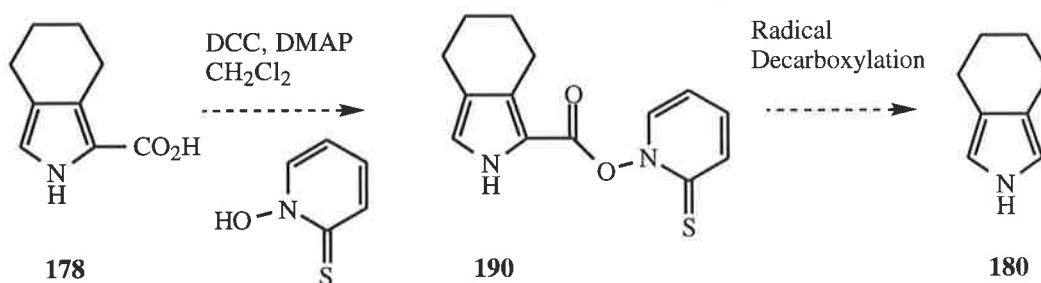
Scheme 84

As conventional methods for the removal of the ester functionality failed the best hope was thought to be direct formation of 2,5-unsubstituted thieno[3,4-*c*]pyrrole 2,2-dioxide. A preparation of the 2,5-unsubstituted thieno[3,4-*c*]pyrrole 2,2-dioxide has been reported, but as it is a lengthy procedure (6 steps). Time constraints prevented its synthesis for this project.[84,85]

Time constraints prevented reasonable quantities of methyl-5,5-dicyano-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate **150** from being obtained, thus no porphyrin forming reactions were attempted for this pyrrole. Future attempts to form a porphyrin from the dicyano pyrrole **150** should avoid LiAlH$_4$ hydride reduction of the ester functionality, as reduction of the nitrile groups would compete with ester reduction. Removal of the ester functional group by saponification of a methyl ester followed by thermal decarboxylation of the intermediate carboxylic acid would give a monopyrrole suitable for elaboration into a porphyrin.

Methyl-5-(4-nitrophenyl)-2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **157** was the only example of the 2,5-dihydropyrrole-based systems to be synthesised. This pyrrole proved difficult to synthesise in quantities sufficient for porphyrin formation, so this avenue of investigation was regrettably abandoned.

4.7   Summary

$2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-Octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b,g,l,q*]porphyrin **181** was formed in reasonable yield and good purity by both the condensation of an 2-hydroxymethyl-5,5-dimethyltetrahydrocyclopenta[*c*]pyrrole and the condensation of 5,5-dimethyltetrahydrocyclopenta[*c*]pyrrole **179** with formalin.

The majority of annulated [3,4-*c*]pyrroles, however, failed to form the desired porphyrins under a wide variety of conditions. Initially it was thought that the pyrroles were not viable under the acidic condensation conditions, but it is now clear that the pyrroles are indeed stable to dilute acid. The reason for the inability of annulated [3,4-*c*]pyrroles to form porphyrins may be: uncontrolled linear polymerisation, rapid degradation of the intermediates. Both undesirable outcomes may be due to unusual ring strain in the bicyclic pyrrole system. The condensation conditions, aimed to minimise the reactivities of the systems by applying either very mild conditions, minimisation of entropy by the preformation of dipyrromethanes, or rapid reaction times. Ultimately all conditions resulted in black insoluble materials in all cases where a hetero atom was present in a β-pyrrolic position. Clearly the presence of a heteroatom alters the reactivity of the pyrrole system sufficiently to prevent porphyrin formation. The questions that remain unanswered are:- at which stage of porphyrin formation does the reaction go awry and why?

Chapter 5: Conclusions

The synthetic methodologies required for the synthesis of annulated porphyrins have been investigated with an aim to provide porphyrins suitable for the [1]H n.m.r. analysis of the porphyrin conformation in solution.

A range of 5-membered cyclic alkenes was synthesised as the primary starting materials for this study, limited only by the unique structural requirements of the desired porphyrins. Cyclic alkenes including oxygen, nitrogen, silicon and sulfur heteroatoms were synthesised, as well as cyclopentene derivatives.

Derivatisation of the 5-membered cyclic alkenes to vinyl sulfones was successful for electron deficient 2,5-dihydropyrroles, 2,5-dihydrofuran, 4,4-dimethylcyclopentene and sulfolene derivatives. Sulfonyl derivatives of electron rich 2,5-dihydropyrroles could not be formed as, under the reaction conditions used, a complex mixture of products resulted. A phenylsulfonyl derivative of silacyclopentene could not be synthesised because of the facile formation of siloxane by-products under the reaction conditions. A phenylsulfonyl derivative of 8,8-dimethyl-6,10-dioxaspiro[4,5]dec-2-ene was not isolated because of the formation of a mixture of allylic and vinylic sulfone under the reaction conditions. A possible method for the derivatisation of the 2,5-dihydropyrrole derivatives and 1,1-diphenyl-1-silacyclopent-3-ene **75** may be the reaction with areneseleno sulfonates. This reaction gives *trans*-β-areneselenosulfonates that can be oxidised then eliminated to give vinyl sulfones under mild conditions.[126 69]

Direct formation of the vinyl sulfones by cyclisation of 2,3-bis(phenylsulfonyl)-1,3-butadiene **122** with either bis-stabilised carbanions or primary amines was used to form 4,4-

bis(methoxycarbonyl)-1-phenylsulfonyl-1-cyclopentene **123**, 4,4-dicyano-1-(phenylsulfonyl)-1-cyclopentene **124** and *N*-benzyl-3-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrole **125**.

All target pyrroles were formed from the available vinyl sulfones excepting the pyrrole of 1-*p*-toluenesulfonyl-2,5-dihydro-1H-pyrrole **98,** which aromatised under the reaction conditions. The conditions for pyrrole formation were shown to be general, in the sense that NaH induced deprotonation of a variety of isocyanoacetates and isocycanoacetamides, and the subsequent condensations of the α-anions with a variety of vinyl sulfones, gave pyrroles in consistently good yield. Yields were found to be independent of the reagent addition order, excepting the formation of **149** from **111**. The formation of this pyrrole dictated the preformation of the isocyanoacetate anion, due to possible competition between deprotonation of the acidic protons of the vinyl sulfone starting material and the isocyanoacetate.

One of the key requirements of the desired porphyrins is a flat annulated ring. The crystal structure of the vinyl sulfone **99** (Appendix 2) shows a torsion angle through the ring C (2) C(3) C(4) C(5) = -0.2°, which equates to an essentially flat ring. The crystal structure of the pyrrole **158** (Appendix 3)[141] shows an annulated ring in which the methylene carbons lie in the plane of the pyrrole. These results shows promise for a flat annulated ring in the desired porphyrins.

Using a comprehensive, but by no means exhaustive sample of the available porphyrin-forming reactions, no heteroannulated porphyrins could be formed. The possible reason for these results seems to be an increased reactivity of the heteroannulated pyrroles (compared to pyrrole) with aldehydes. The increased reactivity of the annulated pyrroles results in uncontrolled linear polymerisation in favour of cyclisation. $2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-Octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b,g,l,q*]porphyrin **181** was formed in reasonable yield and purity through either reaction of the 2,5-unsubstituted pyrrole **179** with formaldehyde under acidic conditions, or reduction of

pyrrole-2-carboxylate **147** with LiAlH$_4$ and subsequent condensation of the α-hydroxymethylpyrrole.

The room temperature ^{1}H n.m.r. spectrum of $2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b,g,l,q*]porphyrin **181** shows the methylene protons of the annulated ring as a singlet at δ 3.92 ppm. Given that the five membered ring is unlikely to distort far from planarity this result tends to indicate that the 5-membered ring of the porphyrin is flat and thus the primary goal of this study was achieved. However, it is still possible for the 5-membered ring to be fluxional in solution. Variable temperature ^{1}H n.m.r spectroscopy and molecular mechanics calculations will be needed to verify the ring planarity.

Considerations for further investigations into the synthesis of annulated porphyrins should include investigation of methodology that would control the rapid reaction rate of heteroannulated pyrroles with aldehydes. The controlled construction of porphyrins by template directed condensation of pyrrolic subunits, either by use of a transition metal template or through the use of supramolecular complexation may be useful. The development of a deactivated formaldehyde equivalent may also be of use.

Experimental

Melting points were recorded on a Reichert hot stage apparatus, and are uncorrected. [1]H and ^{13}C spectra were measured using Varian Gemini-2000 spectrometers operating VNMR 5.3B software with operating frequencies of 200 MHz and 300 MHz, or an INOVA 600 MHz spectrometer operating VNMR 6.1A software. $CDCl_3$ and/or d_6-DMSO were used as solvent unless otherwise indicated. [1]H resonances are quoted in parts per million downfield from the ^{1}H resonance of tetramethylsilane (TMS) or referenced using the $CDCl_3$ resonance (which falls δ 7.24 ppm downfield from the TMS resonance). [13]C resonances were referenced using the $CDCl_3$ resonance (which falls δ77.0 ppm downfield from the TMS resonance). The multiplicities of signals are reported as being: s, singlet; d, doublet; t, triplet; q, quartet; multiplet, an unassignable multiplicity or overlapping signals; br, broadened signal. All coupling constants are quoted as being positive.

Infra-red spectra were recorded on either a Hitachi 270-30 spectrometer or ATI Mattson Genisis series FTIR™ as KBr pellets, in solution cells, and either liquid films (neat) or nujol mulls on sodium chloride plates as indicated. Ultraviolet spectra were recorded on a PYE unicam SP8-100 ultraviolet spectrophotometer. All mass spectra are electron impact (EI) mass spectra, measured with a VG ZAB 2HF mass spectrometer operating at an ionisation energy of 70 eV or, if indicated, GC-MS or ESI-MS measured on Finnigan MAT GCQ and LCQ spectrometers operating at an ionisation energy of 70 eV. Accurate mass determinations using EI or liquid secondary ion mass spectroscopy (LS-IMS) were made by the Organic Mass Spectrometry Facility at the University of Tasmania. Microanalyses were performed by the Chemistry Department at University of Otago, Dunedin.

Thin layer chromatography (t.l.c.) was performed using Merck aluminium backed silica gel 60 F_{254} sheets. Visualisation of developed plates was achieved using 254 nm light and by staining

with either iodine vapour, 10% w/v ammonium molybdate in 1M HCl, $KMnO_4$ solution, vanillin in EtOH containing 1 ml H_2SO_4, or a 5% solution of phosphomolybdic acid in EtOH.

Flash column chromatography was performed using Merck silica gel 60 (particle size: 0.04-0.063 mm (230-400 mesh ASTM)).

Anhydrous diethyl ether and tetrahydrofuran (THF) were obtained by distillation from sodium benzophenone ketyl immediately prior to use. Anhydrous dimethylformamide (DMF) and dichloromethane were distilled from calcium hydride and stored under nitrogen. All solvents used for chromatography were distilled before use. NEt_3 was distilled from calcium hydride under nitrogen and stored over 4Å molecular sieves. Other reagents were purified according to literature procedures.[155]

Mineral oil was removed from NaH 60% suspension by washing with hexane several times under a nitrogen atmosphere.

All organic extracts were dried over anhydrous magnesium sulfate unless otherwise specified.

When a reaction produced more than one isomer the mass spectrum and analytical data were determined on the mixture of isomers.

Experimental Described in Chapter 2

Dimethyl 3,3-dimethylglutarate CAS Reg. No. [19184-67-9] 55[95]

Concentrated H_2SO_4 (4 ml) was added dropwise to a solution of 3,3-dimethylglutaric acid (10 g, 0.06 mol) in a 1:1 mixture of benzene/methanol (50 ml) the reaction mixture was then stirred at room temperature for 24 h. The heterogenous mixture was transferred to separating funnel diluted with EtOAc (50 ml), washed with 1M NaOH (50 ml) and a saturated NaCl solution (50 ml) then the organic layer was dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to give a colourless liquid. The crude product was distilled to give *dimethyl 3,3-dimethylglutarate* (8.9g, 80%), 46°C (0.1 mm Hg) as a colourless liquid. υ_{max} (neat); 3453, 2954 (CH), 1735 (CO), 1436, 1357, 1336, 1234, 1153, 1014, 887, 854; ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 0.99 [s, 6H, 2 x CH$_3$], 2.31 [s, 4H, 2 x CH$_2$], 3.54 [s, 6H, 2 x CH$_3$O]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 27.51 [CH$_3$], 32.40 [C(3)], 44.86 [CH$_2$CO], 51.05 [CH$_3$O], 172.29 [2 x CO]; m/z: $M^{+\cdot}$ not observed, 157 (48%), 129 (18), 128 (40), 83 (83), 73 (100), 43 (85).

Acyloin condensation of dimethyl 3,3-dimethylglutarate 57 and 58[94]

Method A

To a dry, 5 l. flange topped flask cooled to -78°C and fitted with a dry ice condenser, 250 ml pressure equalising dropping funnel and gas inlet, was added 1.6 l. of anhydrous ether and 1.5 l. of anhydrous ammonia. This solution was vigorously stirred while sodium (21.4 g, 0.93 mol) was added in small pieces under a N_2 atmosphere. A solution of dimethyl 3,3-dimethylglutarate (40 g, 0.21 mol) in anhydrous ether (160 ml) was then added dropwise to the deep blue solution over a 3 h period. The reaction mixture was then stirred for 12 h under a

steady stream of nitrogen, allowing the ammonia to evaporate. The resulting yellow residue was diluted with ether (200 ml) then a solution of methanol (80 ml) in ether (160 ml) was added dropwise giving a yellow solution which was acidified with 3 M HCl. The mixture was transferred to a separating funnel and the ether layer removed, the aqueous layer was extracted with ether (4 x 100 ml), and the combined ether layers dried over Na_2SO_4 and filtered. After removal of the ether by distillation on a steam bath the residue was distilled to give a yellow liquid which was found to be a mixture of *2-hydroxy-4,4-dimethylcyclopentan-1-one* and *4,4-dimethylcyclopentan-1,2-dione* (14.07 g, 53%), b.p. 88-90°C (10 mm Hg) (lit. b.p. 76-80°C (8 mm Hg)).[93] υ_{max} (neat); 3357 (OH), 2958, 2867, 1747 (CO), 1704 (CO), 1654 (CO), 1627; ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.12 [s, 6H, 2 x CH$_3$], 2.27 [m, 4H, 2 x CH$_2$], 4.27 [s, 1H, CH], OH resonance is variable; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 28.31 [2 x CH$_3$], 34.4 [CH$_2$], 43.85 [CH$_2$], 74.09 [CH], 163.02 [CO]; m/z: **57** M$^{+\cdot}$ 127 (10%), **58** M$^{+\cdot}$ 126 (18), 111 (52), 98 (25), 83 (43), 54 (53), 40 (68), 38 (100).

Method B

1,2-Bis(trimethylsilyloxy)-4,4-dimethylcyclopentene 59[156]

To a dry, 3-l. round bottomed flask cooled to -78°C fitted with a dry ice condenser, 250 ml pressure equalising dropping funnel and gas inlet, was added 800 ml. of anhydrous ether and 800 ml. of anhydrous ammonia. This solution was vigorously stirred while sodium (10.8 g, 0.46 mol) was added in small pieces under a N$_2$ atmosphere. A solution of dimethyl 3,3-dimethylglutarate (20 g, 0.11 mol) in anhydrous ether (80 ml) was then added dropwise to the deep blue solution over a 3 h period. The reaction mixture was then stirred for 12 h under a steady stream of nitrogen, allowing the ammonia to evaporate. The resulting yellow residue was treated with a solution of freshly distilled trimethylsilyl chloride (50 g, 0.46 mol) in diethyl ether (800 ml) at 0°C. The mixture was stirred for 3h then filtered under N$_2$ (the unreacted sodium was carefully quenched in a methanol bath). After removal of the ether by rotary

evaporation the residue was distilled to give *1,2-bis(trimethylsilyloxy)-4,4-dimethylcyclopent-1-ene* as a colourless liquid (14.92 g, 50%), b.p. 45°C (0.10 mm Hg). υ_{max} (neat); 2958, 1758, 1718, 1627, 1463, 1409, 1386, 1322, 1253, 1159, 1058, 914, 757; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 0.16 [s, 18H, 6 x SiCH$_3$], 1.06 [s, 6H, C(CH$_3$)$_2$], 2.03 [s, 4H, C(3, 5)]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 0.47 [SiCH$_3$], 30.50 [C(CH$_3$)$_2$], 31.69 [C(4)], 45.62 [C(3, 5)], 128.76 [C(1, 2)]; m/z: 272 (M$^{+\cdot}$, 62%), 257 (24), 183 (32), 147 (100), 73 (68).

2-Hydroxy-4,4-dimethylcyclopentane 57

1,2-Bis(trimethylsilyloxy)-4,4-dimethylcyclopentene (12.0 g, 0.04 mol) was stirred in deoxygenated MeOH (200 ml) at room temperature for 24h. The MeOH was removed by rotary evaporation to give a yellow liquid. Distillation of the crude product gave *2-hydroxy-4,4-dimethylcyclopentane* as a colourless liquid (4.20 g, 83%), b.p. 90°C (10 mm Hg). υ_{max} (neat); 3357 (OH), 2958, 2867, 1704 (CO), 1396, 1317, 1240, 1203, 1153, 1101, 933; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.15 [s, 6H, 2 x CH$_3$], 2.12 [m, 1H, C(5)Ha], 2.19 [m, 1H, C(5)Hb], 2.21 [s, 2H, C(3)H], 4.27 [t, 1H, C(1)H], 5.18 [brs, 1H, OH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 28.36 [2 x CH$_3$], 29.65 [C(4)], 43.88 [C(5)], 49.12 [C(3)], 74.09 [C(1)], carbonyl not observed; m/z: **57** M$^{+\cdot}$-H 127 (11%), 111 (68), 98 (100), 83 (42), 55 (71), 43 (28), 39 (41).

4,4-Dimethylcyclopentane-1,2-diol 60^{93}

Method A

To a suspension of LiAlH$_4$ (2.3 g, 0.06 mol) in anhydrous diethyl ether (20 ml) was added dropwise a solution of 2-hydroxy-4,4-dimethylcyclopentane (4.0 g, 0.03 mol) in anhydrous diethyl ether (40 ml) at such a rate so as to maintain a constant reflux. Upon completion of the

addition the reaction mixture was stirred at room temperature for 24 h, water was then added dropwise with external ice cooling until effervescence ceased. The reaction was allowed to warm to room temperature over 3h, the inorganic salts were then removed by filtration and washed well with diethyl ether. The filtrate was filtered and the solvent removed under reduced pressure, the crude product was then distilled to give *4,4-dimethylcyclopentan-1,2-diol* (3.8 g, 55%), b.p. 120°C (10 mm Hg) (lit. b.p. 120°C, 10 mm Hg)[93] as a white solid. Recrystallisation of the product from benzene gave white crystals. M.p. 95-97°C; υ_{max} (nujol); 3293 (OH), 1295, 1272 , 1182; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.04 [s, 6H, 2 x CH$_3$], 1.38 [m, 2H, C(3, 5)Ha], 1.85 [m, 2H, C(3, 5)Hb], 2.98 [s, 2H, 2 x OH], 4.00 [brs, 2H, 2 x C(1, 2)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 31.88 [2 x CH$_3$], 33.75 [C(4)], 46.94 [C(3, 5)], 78.99 [C(1, 2)]; m/z 130 (M$^{+\cdot}$, 2%) 85 (100), 71 (81), 57 (20), 43 (32), 41 (45).

Physical and spectral data consistent with literature values

Method B

A solution of a mixture of 2-hydroxy-4,4-dimethylcyclopentane and 4,4-dimethylcyclopentan-1,2-dione (14.0 g, ~0.1 mol) in 95% ethanol (100 ml) was added to a suspension of approximately 15 g of Raney nickel (prepared to W2 grade specifications) in 95% ethanol (250 ml). The mixture was shaken in a Parr® hydrogenation apparatus under hydrogen (60 psi) until no further pressure drop was observed. The catalyst was filtered off and washed with ethanol. Evaporation of the solvent gave enriched 2-hydroxy-4,4-dimethylcyclopentane (13 g) which was further reduced by treatment with LiAlH$_4$ as described below.

To a suspension of LiAlH$_4$ (8.2 g, 0.22 mol) in anhydrous diethyl ether (150 ml) was added dropwise a solution of crude 2-hydroxy-4,4-dimethylcyclopentane (12.5 g, 0.098 mol) in anhydrous diethyl ether (150 ml) at such a rate so as to maintain a constant reflux. Upon completion of the addition the reaction mixture was stirred at room temperature for 24 h, water

(36 ml) was then added dropwise with external ice cooling. The inorganic salts were then removed by filtration and washed well with diethyl ether. The filtrate was dried over MgSO4, filtered and the solvent removed under reduced pressure, the crude product was then distilled to give *4,4-dimethylcyclopentan-1,2-diol* (4.20 g, 32%), 120°C (10 mm Hg) (lit. b.p. 106-108°C (5 mm Hg)[93] as a white solid. Recrystallisation of the product from benzene gave white crystals.

Physical and spectral data consistent with literature values

4,4-Dimethylcyclopent-1-ene 54[94]

To a solution of 4,4-dimethylcyclopentan-1,2-diol (0.4 g, 3 mmol) in CH_2Cl_2 (30 ml) were added Ph3P (3.22 g, 12.30 mmol) and imidazole (0.84 g, 12.30 mmol) at room temperature. Iodine (2.34 g, 9.2 mmol) was added portionwise and the mixture stirred at room temperature for 1 h and then refluxed for 1 h. The reaction mixture was then cooled and a distillation apparatus fitted. Distillation of the mixture gave *4,4-dimethylcyclopent-1-ene* (78°C) as solution in CH_2Cl_2. This solution was used directly as a solution in CH_2Cl_2 because of the volatility of the product.

1-[(Z)-4-Chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo[3.3.1.1]decane chloride 63[96]

To a solution of hexamethylenetetramine (5.61 g, 40 mmol) in $CHCl_3$ (80 ml) was added *cis*-1,4-dichloro-2-butene (5.00 g, 40 mmol) in one portion. This mixture was heated at reflux for 4 h, during which time the product precipitated. The mixture was then cooled to room temperature and filtered through a sintered glass funnel. The solid was washed with $CHCl_3$ (2 x 10 ml) then dried in a desiccator under vacuum to give *1-[(Z)-4-chloro-2-butenyl]-1-azonia-*

3,5,7-triazatricyclo[3.3.1.1]decane chloride (8.68 g, 82%) as a white crystalline solid. M.p. 158-165°C (lit. 160-170°C);[96] υ_{max} (KBr pellet); 3423 (br), 2979, 1473, 1268, 1118, 1004, 939, 826, 775, 697, 652, 503; [1]H n.m.r. (300 MHz/DMSO); δ_H: 3.26 [d, 2 H, C(4)H], 3.81 [d, 2 H, C(1)H] 4.05 [s, 6 H, NCH$_2$], 4.71 [s, 6 H, CH$_2$N], 5.58 [m, 1 H, C(3)H], 5.89 [m, 1 H, C(2)H]; m/z 229 (C$_{10}$H$_{18}$N$_4$Cl$^+$, 100%)), 112 (98), 41 (90).

Physical and spectral data consistent with literature values.

[(Z)-4-Chloro-2-butenyl]ammonium chloride 64[96]

Concentrated HCl (10 ml) was added to 95% EtOH (60 ml) which resulted in slight warming of the solution. To the still warm solution was added 1-[(Z)-4-chloro-2-butenyl]-1-azonia-3,5,7-triazatricyclo[3.3.1.1]decane chloride (8.68 g, 0.03 mol) in one portion. The orange solution was stirred at room temperature for 24 h during which time NH$_4$Cl precipitated. After stirring the solution was cooled to 0°C and the solid removed by filtration. The solid was then washed with cold EtOH (2 x15 ml), and the filtrate was concentrated under reduced pressure. The resulting residue was taken up in cold EtOH (15 ml) and filtered to remove the remaining solids. After removal of the solvent from the filtrate, the solid was recrystallised from hot EtOAc (80 ml) to give *[(Z)-4-chloro-2-butenyl]ammonium chloride* (3.8 g, 99%) as a pale orange powder. M.p. 116-118°C (lit. m.p. 117-119°C);[96] υ_{max} (KBr pellet); 3015 (NH), 2053, 1598, 1471, 1408, 1260, 1135, 1114, 1030, 912, 862, 787, 677, 560; [1]H n.m.r. (300 MHz/D$_2$O); δ_H: 3.63 [d, 2H, C(4)H], 4.07 [d, 2H, C(1)H], 5.58 [m, 1H, C(3)H], 5.89 [m, 1H, C(2)H]; (LCMS +'ve ion mode) m/z 106 (C$_4$H$_9$ClN$^+$, 100%), 89 (-NH$_3$, 32).

Physical and spectral data consistent with literature values.

2,5-Dihydropyrrole 61 CAS reg. No. [109-96-6][96]

DBU (9.04 g, 0.06 mol) was placed in a 25 ml RBF and cooled to 0°C in an ice bath as [(Z)-4-chloro-2-butenyl]ammonium chloride (3.8 g, 0.06 mol) was added in portions. The orange mixture began to reflux as the last portions of the ammonium chloride salt were added, a short path distillation apparatus was fitted with a receiving flask immersed in a -78°C dry ice/acetone bath. The reaction mixture was the heated with a heat gun, which caused the solid mixture to liquefy and foam vigorously, product began to distil (80-85°C). Heating was continued until no more product distilled, giving *2,5-dihydropyrrole* (1.0 g, 48%) as a colourless liquid. ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.90 [brs, 1H, N(1)H], 3.71 [s, 4H, C(2, 5)H], 5.85 [brs, 2H, C(3, 4)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 53.98 [C(2, 5)], 128.59 [C(3, 4)].

Physical and spectral data consistent with literature values.

N-Acetyl-2,5-dihydropyrrole 65

Acetyl chloride (0.57 g, 7.2 mmol) was added dropwise to a solution of 2,5-dihydropyrrole (0.5 g, 7.2 mmol) and pyridine (0.56 g, 7.2 mmol) in dry CH$_2$Cl$_2$ (20 ml) at room temperature. The reaction mixture was stirred under N$_2$ for 1 h then the solvent was removed by rotary evaporation. The crude residue taken up in EtOAc (20 ml) and the precipitate was removed by filtration. The filtrate was washed with H$_2$O (10 ml) and then dried over MgSO$_4$, filtered and the solvent removed by rotary evaporation to give crude *N-acetyl-2,5-dihydropyrrole* (0.71 g, 89%) as an off white solid. M.p. 58-60°C; υ_{max} (nujol); 1638, 1190, 1004, 706; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 2.07 [s, 3H, CH$_3$], 4.26 [s, 4H, C(2, 5)H], 5.84 [m, 2H, C(3, 4)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 22.07 [CH$_3$CO], 52.72 [C(2 or 5)], 54.09 [C(2 or 5)], 124.90 [C(3 or 4)], 126.47 [C(3 or 4)], 169.03 [CO]; m/z 111 (M$^+$, 32%), 69 (M$^+$, 50), 68 (M$^+$-CH$_3$CO, 100), 43 (CH$_3$CO).

1-(Trifluoroacetyl)-2,5-dihydropyrrole 66 CAS Reg. No. [111185-41-2][124]

Trifluoroacetic anhydride (1.51 g, 7.2 mmol) was added dropwise to a solution of 2,5-dihydropyrrole (0.4 g, 5.7 mmol) and pyridine (0.56 g, 7.2 mmol) in dry CH_2Cl_2 (20 ml) cooled to 0°C. The reaction mixture was stirred under N_2 for 45 min at 0°C then allowed to warm to room temperature. The reaction mixture was washed with H_2O (2 x 10 ml) and then the organic layer was dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation to give crude *1-(trifluoroacetyl)-2,5-dihydropyrrole* (0.5 g, 53%) as a yellow liquid. υ_{max} (neat); 3092, 2876, 1696, 1520, 1464, 1344, 1138, 1000, 790, 918, 804, 758, 724, 674, 620; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 4.38 [m, 2 H, C(2 or 5)H], 4.59 [m, 2 H, C(2 or 5)H], 5.85 [m, 1 H, C(3 or 4)], 5.93 [m, 1 H, C(3 or 4)]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 52.92 [C(2 or 5)], 54.64 [C(2 or 5)], 115.0 [q, CF$_3$], 124.68 [C(3 or 4)], 124.84 [C(3 or 4)], C=O not observed.

Physical and spectral data consistent with literature values.

1-(p-Toluenesulfonyl)-2,5-dihydropyrrole 67 CAS Reg. No. [16851-71-1][157,158]

To a 100 ml RBF fitted with a 20 ml pressure equalising dropping funnel and a magnetic stirring bar was added CH_2Cl_2 (40 ml), triethylamine (1.46 g, 8.7 mmol) and 2,5-dihydropyrrole (0.50 g, 7.2 mmol) and the apparatus flushed with N_2. The pressure equalising dropping funnel was charged with a suspension of *p*-toluenesulfonylchloride (1.66 g, 8.7 mmol) in CH_2Cl_2 (10 ml), this suspension was then added in portions over 10 min to the stirred 2,5-dihydropyrrole solution. After addition of the suspension was complete the reaction mixture was stirred for 2h. The mixture was transferred to a separating funnel and the organic layer washed with 1M HCl (2 x 15 ml), sat. NaHCO$_3$ (15 ml), and brine solution (15 ml). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was recrystallised from EtOAc/hexane to give *1-(p-toluenesulfonyl)-2,5-*

dihydropyrrole (1.58 g, 100%) as colourless needle crystals. M.p. 119-122°C (lit. m.p. 121-122°C);[157] ν_{max} (nujol); 1588, 1328, 1160, 1154, 674, 590, 542; m/z 223 (M$^{+\cdot}$, 24%), 156 (98), 155 (40), 91 (100), 68 (62), 41 (30); ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.45 [s, 3H, CH$_3$Ar], 4.14 [s, 4H, C(2, 5)H], 5.67 [s, 2H, C(3, 4)H], 7.34 [m, 2H, Ar], 7.74 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.53 [CH$_3$], 54.82 [C(2, 5)], 125.44 [C(3, 4)], 127.41 [Ar], 129.76 [Ar], 134.2 [Ar], 144.0 [Ar].

Physical and spectral data consistent with literature values.

cis-1,4-Dimesyloxybut-2-ene 68 [70886-56-5][98]

A mixture of triethylamine (84 ml, 0.64 mol) and *cis*-2-butene-1,4-diol (11.20 g, 0.13 mol) was added dropwise to a solution of freshly distilled methansulfonyl chloride (59.2 g, 0.53 mol) in dry CH$_2$Cl$_2$ (300 ml) over 20 minutes. The solution was stirred for 1.5 h then transferred to a separating funnel and swiftly washed with chilled H$_2$O (200 ml), 10% HCl (2 x 200 ml), sat NaHCO$_3$ solution (200 ml), and brine (200 ml). The organic layer was separated, dried with MgSO$_4$, filtered and the solvent removed by rotary evaporation to give *cis-1,4-dimesyloxybut-2-ene* (25.58 g, 83%) as a dark brown liquid. *Cis* isomer: ν_{max} (neat); 3100, 3029, 2983, 2940, 1733, 1461, 1415, 1367, 1247, 1170, 1045, 975, 923, 838, 779; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.03 [s, 6H, CH$_3$], 4.80 [d, 4H, C(1, 4)H], 5.90 [m, 2H, C(2, 3)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 37.79 [CH$_3$], 64.24 [C(1, 4)], 128.15 [C(2, 3)]; (GCMS) m/z 88 (32%), 71 (48), 53 (M$^{\cdot+}$-C$_4$H$_5$, 100), 39 (79).

Column chromatography was avoided as isomerisation to the *trans* isomer occurred readily on silica gel. *Trans* isomer: ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.06 [s, 6H, CH$_3$], 4.17 [d, 2H, C(1 or 4)H], 4.87 [d, 2H, C(1 or 4)H], 5.81 [m, 1H, C(2 or 3)H], 6.00 [m, 1H, C(2 or 3)H]; (GCMS) m/z 88 (80%), 75 (85), 53 (M$^{\cdot+}$-C$_4$H$_5$, 100), 39 (65).

Physical and spectral data consistent with literature values.

1-(*p*-Methoxyphenyl)-2,5-dihydropyrrole 70[159]

A solution of *p*-anisidine (2.46 g, 20 mmol) in dichloromethane (30 ml) was added dropwise to a solution of *cis*-1,4-dimesyloxybut-2-ene (2.44 g, 10 mmol) in dry dichloromethane (50 ml), at room temperature. The reaction mixture was stirred under N_2 for 18 h then filtered and the solvent removed by rotary evaporation. The crude residue was then purified by squat column chromatography using EtOAc/hexane (30:70) as eluant to give *1-(p-methoxyphenyl)-2,5-dihydropyrrole* (0.76 g, 44%) as an off white powder. M.p. 104-110°C; υ_{max} (KBr pellet); 2836, 1525, 1260, 1245, 1185, 1129, 1031, 827, 814, 724, 612; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.86 [s, 4H, C(2, 5)H], 4.10 [s, 3H, CH$_3$O], 5.97 [s, 2H, C(3, 4)H], 6.97 [m, 2H, Ar], 7.33 [m, 2H, ArN]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 53.51 [C(2, 5)], 55.84 [CH$_3$], 109.87 [Ar], 114.67 [Ar], 122.27 [C(3, 4)], quarternary carbons not observed; m/z 175 (M$^{+\cdot}$, 32%), 173 (88), 158 (100), 130 (60), 103 (30), 77 (45), 63 (30), 39 (50).

Physical and spectral data consistent with literature values.

1-(*p*-Tolyl)-2,5-dihydropyrrole 71 CAS Reg. No. [88320-36-9][159]

A solution of *p*-toluidine (2.14 g, 20 mmol) in dichloromethane (30 ml) was added dropwise to a solution of *cis*-1,4-dimesyloxybut-2-ene (2.44 g, 10 mmol) in dry dichloromethane (50 ml) at room temperature. The reaction mixture was stirred under N_2 for 18 h then filtered and the solvent removed by rotary evaporation. The crude residue was then purified by squat column chromatography using EtOAc/hexane (30:70) as eluant to give *1-(p-tolyl)-2,5-dihydropyrrole* (1.15 g, 72%) as a light yellow powder. M.p. 93-95°C; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.31 [s, 3H, CH$_3$], 4.10 [s, 4H, C(2, 5)H], 5.98 [s, 2 H, C(3, 4)H], 6.53 [m, 2 H, Ar], 7.12

[m, 2 H, ArN]; m/z 159 (M$^{+\cdot}$, 65%), 143 (18), 118 (80), 91 (100), 89 (26), 77 (18), 65 (60), 51 (32), 41 (45), 39 (81).

Physical and spectral data consistent with literature values.

N-Phenyl-2,5-dihydropyrrole 72 CAS Reg. No. [103204-12-2][98]

Aniline (5.74 g, 60 mmol) was added dropwise to a solution of *cis*-1,4-dimesyloxybut-2-ene (4.88 g, 20 mmol) in dry CH_2Cl_2 (100 ml), at room temperature under N_2. The reaction mixture was stirred for 18 h and then washed with water (100 ml). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation. The crude residue was then purified by squat column chromatography using EtOAc/hexane (10:90) as eluant to give *N-phenyl-2,5-dihydropyrrole* (1.1 g, 76%) as a white powder. M.p. 97-98°C (lit. 99-101°C);[160] ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 4.44 [s, 4H, C(2, 5)H], 5.98 [s, 2H, C(3, 4)H], 6.54 [m, 2H, Ar], 6.70 [m, 1H, Ar], 7.28 [m, 2H, Ar]; m/z 145 (M$^{+\cdot}$, 100%), 144 (M$^{+\cdot}$-H, 92), 104 (60), 77 (52), 51 (22), 39 (16).

Physical and spectral data consistent with literature values.

1-(*p*-Nitrophenyl)-2,5-dihydropyrrole 73 CAS Reg. No. [113342-93-1][161]

A solution of NaH (0.24 g, 10 mmol) in DMF (10 ml) was added dropwise to a solution of *cis*-1,4-dimesyloxybut-2-ene (2.44 g, 10 mmol) and *p*-nitroaniline (4.14 g, 30 mmol) in DMF at room temperature with some frothing occurring. The reaction mixture was stirred for 2 h during which time the reaction mixture became dark brown in colour. The mixture was poured into 200 ml of chilled water and stirred for 30 min. The mixture was filtered and the yellow solid washed with water (50 ml) and hexane (50 ml) then dried to give *1-(p-nitrophenyl)-2,5-*

dihydropyrrole (0.74 g, 40%) as a bright yellow solid; M.p. 163-165°C (lit. m.p. 171°C);[161] υ_{max} (KBr pellet); 2833, 2434, 1600, 1580, 1517, 1482, 1469, 1396, 1295, 1178, 1112, 1101, 1002, 825, 752, 698; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 4.24 [s, 4H, C(2, 5)H], 6.01 [s, 2H, C(3, 4)H], 6.48 [m, 2H, ArCHN], 8.19 [m, 2H, ArCHNO$_2$]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 54.68 [C(2, 5)], 110.21 [Ar], 125.87 [C(3, 4)], 126.47 [Ar], quarternary carbons not observed; m/z 190 (M$^{+\cdot}$, 100%), 189 (58), 149 (74), 143 (60), 103 (24), 91 (88).

Physical and spectral data consistent with literature values.

1,1-Diphenyl-1-sila-3-cyclopentene 75 CAS Reg. No. [34106-93-9][99]

To a 1 litre, three necked, round-bottomed flask fitted with a thermometer, rubber septum, and ice-acetone condenser was added magnesium (4.8 g, 0.2 mol) and THF (130 ml) under a N$_2$ atmosphere. 1,1-Dichlorodiphenylsilane (50 g, 0.2 mol) was added dropwise while the temperature was maintained around 25°C. Finally, buta-1,3-diene (42 g, 0.7 mol) was distilled quickly into the flask from a cylinder. A freshly prepared 3.0 M solution of phenyl magnesium bromide (1.79 g, 9 mmol) was added dropwise to the grey suspension. The reaction mixture was stirred for one hour at room temperature and then irradiated with a UV lamp for a period of two hours. The UV lamp was removed and the reaction mixture allowed to cool to room temperature. The N$_2$ inlet tube was replaced by a rubber septum and the mixture stirred vigorously for six days. The solution was cooled to an internal temperature of 0°C and H$_2$O (240 ml) added carefully under a small flow of N$_2$. After the exothermic reaction and effervescence had ceased the mixture was stirred for an additional hour. The solution was extracted with pentane (2 x 100 ml). The combined organic layers were dried over MgSO$_4$. The solvent was removed and the crude product distilled to give *1,1-diphenyl-1-sila-3-cyclopentene* (17.69 g, 37%), b.p. 120°C (0.05 mm Hg) (lit. b.p. 124-126°C (0.76 mm Hg))[99] as a colourless liquid. υ_{max} (neat); 3100, 3050, 1950, 1890, 1810, 1600, 1590, 1480, 1420, 1400, 1320; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.92 [s, 4H, C(2, 5)H], 6.10 [s, 2H,

C(3, 4)H], 7.40-7.46 [m, 6H, *p,m*-ArH], 7.64 [s, 4H, *o*-ArH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 16.72 [C(2, 5)], 128.01 [C(3, 4)], 129.57 [Ar], 131.15 [Ar], 134.80 [Ar], 135.87 [Ar]; m/z 236 (M$^{+\cdot}$, 18%), 208 (22), 199 (21), 181 (27), 158 (100), 105 (25).

Physical and spectral data consistent with literature values.

2,3-Dihydrothiin-4-one 83[162]

To a solution of 4-thianone (2.55 g, 0.2 mol) in CH$_2$Cl$_2$ (90 ml) cooled to 0°C was added pyridine (3.2 g, 0.04 mol) and *N*-chlorosuccinimide (2.93 g, 0.02 mol) under N$_2$. After stirring for 3 h at 0°C the reaction mixture was warmed to room temperature and transferred to a separating funnel and washed with saturated NaHCO$_3$ (50 ml) and brine (50 ml). The organic layer was then washed with aqueous 5% w/w CuSO$_4$ solution (6 x 25 ml) then H$_2$O (25 ml), the organic layer was then dried with MgSO$_4$ and the solvent removed under reduced pressure. The crude mixture was purified by Kugelrohr distillation to afford *2,3-dihydrothiin-4-one* as a colourless liquid (1.82 g, 80%), b.p. 50°C (0.02 mm Hg). υ_{max} (neat); 1560 (C=O), 1522; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 2.71 [m, 2H, C(6)H], 3.23 [m, 2H, C(5)H], 6.15 [d, 1H, C(3)H], 7.47 [d, 1 H, C(5)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 27.38 [C5], 37.53 [6], 123.81 [C3], 146.35 [C2], 193.75 [C4].

Physical and spectral data consistent with literature values.

2,3-Dihydrothiin-4-one 1,1-dioxide 84[162,163]

A solution of Oxone® (2.2 g, 3.5 mmol) in H_2O (40 ml) was added to a solution of 2,3-dihydrothiin-4-one (0.4 g, 3.5 mmol) in MeOH (40 ml). This suspension was stirred at room temperature for 18 h then diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were dried with $MgSO_4$, filtered and the solvent removed. The crude product was recrystallised from EtOH to give *2,3-dihydrothiin-4-one 1,1-dioxide* (0.33, 65 %) as fine white crystals. M.p. 147-151°C; υ_{max} (nujol); 1685 (C=O), 1310, 1120 (SO_2); ^{1}H n.m.r. (200 MHz/CDCl_3); δ_H: 3.23 [m, 2H, C(5)H], 3.61 [m, 2H, C(6)H], 6.41 [d, 1H, C(3)H], 7.18 [d, 1H, C(2)H]; m/z 146 (M⁺·, 12%), 118 (18), 82 (29), 54 (100).

Physical and spectral data consistent with literature values.

8-Iodo-3,3-dimethyl-1,5-dioxa-9-thiaspiro[5.5]undecane 9,9-dioxide 85[163]

A solution of 2,3-dihydrothiin-4-one 1,1-dioxide (0.88 g, 6.02 mmol) in acetonitrile (25 ml) was treated with trimethylsilyl iodide (2.41 g, 12.05 mmol). The solution was stirred at room temperature for 2 h followed by the addition of 2,2-dimethyl-1,3-propandiol (3.2 g, 30 mmol). After stirring for a further 4 h the reaction mixture was diluted with CH_2Cl_2 (20 ml), washed with H_2O (20 ml), saturated $NaHCO_3$ solution (containing a few drops of 10% $NaHSO_3$ solution) (20 ml) and brine, dried with $MgSO_4$, filtered and the solvent removed. The crude product was subjected to radial chromatography using CH_2Cl_2 as eluant to give *8-iodo-3,3-dimethyl-1,5-dioxa-9-thiaspiro[5.5]undecane 9,9-dioxide* (1.50 g, 60%) as an off white powder. M.p. 152-156°C (lit. 152.5-153.5°C);[163] υ_{max} (KBr pellet); 2972, 2874, 1473, 1400, 1336 (SO_2), 1301, 1134 (SO_2), 1094, 1025, 987, 915, 855, 775, 682, 632; ^{1}H n.m.r. (200 MHz/CDCl_3); δ_H: 0.97 [s, 2H, C(3)CH_3 x 2], 2.24 [ddd, 1H, C(11)Ha], 2.44 [d, 1H, C(7)Ha], 2.59 [dddd, 1H, C(11)Hb], 2.99 [ddd, 1H, C(7)Hb], 3.33 [ddd, 1H, C(10)Ha],

3.37 [ddd, 1H, C(10)Hb], 3.49 [s, 4H, C(2, 4)H], 5.05 [dd, 1H, C(8)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 22.36 [C(3)CH$_3$ x 2], 30.10 [C(3)], 30.15 [C(11)], 31.95 [C(8)], 42.87 [C(7)], 45.02 [C(10)], 70.34 [C(2)], 70.72 [C(4)], 95.33 [C(6)]; m/z 361 (M$^+$, 12%), 268 (33), 233 (100), 141 (92), 55 (72).

Physical and spectral data consistent with literature values.

8,8-Dimethyl-6,10-dioxaspiro[4.5]dec-2-ene 81[163]

Freshly sublimed potassium *t*-butoxide (0.3 g, 2.8 mmol) was added to a solution of 8-iodo-3,3-dimethyl-1,5-dioxa-9-thiaspiro[5.5]undecane 9,9-dioxide (0.54 g, 1.4 mmol) in THF (25 ml) and the reaction mixture stirred under N$_2$ for 1 h. The reaction mixture was quenched with aq. NH$_4$Cl solution (5 ml) and then the aqueous layer was removed. The organic layer was diluted with CH$_2$Cl$_2$ (20 ml), washed with H$_2$O (20 ml), saturated NaHCO$_3$ solution (20 ml) and brine, dried with MgSO$_4$, filtered and the solvent removed to give *8,8-dimethyl-6,10-dioxaspiro[4.5]dec-2-ene* (0.23 g, 97%) as a colourless liquid. υ_{max} (neat); 3062, 2954, 2867, 1724, 1621, 1473, 1427, 1396, 1324, 1228, 1228, 1207, 1047, 956, 840, 781, 663. ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.01 [s, 6H, 2 x CH$_3$], 2.68 [s, 4H, 2 x OCH$_2$], 3.54 [s, 4H, C(2, 5)H], 5.69 [s, 2H, CH]; m/z 168 (M$^+$, 48%), 100 (31), 82 (55), 54 (25), 39 (100); m/z 168 (M$^+$, 48%), 100 (31), 82 (55), 54 (25), 39 (100).

Physical and spectral data consistent with literature values.

2,3-Bis(phenylsulfinyl)-1,3-butadiene[121,164,165]

Benzenesulfenyl chloride (26.0 g, 0.18 mol) was added dropwise over a 30 min period, to a stirred solution of 2-butyne-1,4-diol (7.75 g, 0.09 mol) and triethylamine (27.3 g, 0.27 mol) in

CH_2Cl_2 (700 ml) at -78°C. After the addition of benzenesulfenyl chloride was completed the reaction mixture was slowly allowed to warm to room temperature and stirred for an additional 16 h. The solution was then washed with H_2O (100 ml), saturated NH_4Cl solution (100 ml), saturated $NaHCO_3$ solution (100 ml) then brine (100 ml). The CH_2Cl_2 layers where dried with $MgSO_4$, filtered, then the solvent was removed under reduced pressure to give crude product which was recrystallised from methanol/diethyl ether (1:1) to give *2,3-bis(phenylsulfinyl)-1,3-butadiene* (16.28 g, 60%) as a white crystalline powder. Concentration and recrystallisation of the mother liquor afforded an additional 6.85 g (25%). The product is a mixture of diastereoisomers (1.1:1), M.p. 128-132°C (lit. m.p. 127-128°C);[164] υ_{max} (KBr pellet); 3076, 1896, 1710, 1576, 1477, 1450, 1364, 1364, 1083, 1042, 943, 750, 686, 633, 608, 491. Isomer A. [1]H n.m.r. (300 MHz/CDCl$_3$); δ_H: 5.60 [s, 2H, C=H], 6.20 [s, 2H, C=H], 7.48 [m, 10H, Ar]; Isomer B. [1]H n.m.r. (300 MHz/CDCl$_3$); δ_H: 5.80 [s, 2H, C=H], 6.25 [s, 2H, C=H], 7.20 [m, 10H, Ar]; m/z 302 (M$^+$, 10%), 255 (8), 254 (51), 177 (10), 125 (100).

Physical and spectral data consistent with literature values.

2,3-Bis(phenylsulfonyl)-1,3-butadiene 122[121,164]

Method A

2,3-Bis(phenylsulfinyl)-1,3-butadiene (1.0 g, 3.3 mmol) and *m*-chloroperbenzoic acid (1.8 g, 8.3 mmol) were dissolved in CH_2Cl_2 (25 ml). This solution was stirred for 16 h at 0°C then allowed to warm to room temperature. The reaction mixture was treated with 1M NaOH solution (2 x 20 ml), then the organic layer was removed. The aqueous layers were combined and then extracted with CH_2Cl_2 (2 x 20 ml). The organic layers were combined and washed with H_2O (20 ml) then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give *2,3-bis(phenylsulfonyl)-1,3-butadiene* (0.93 g, 85%) as a white powder. M.p. 183-185°C (lit. m.p. 183-185°C);[164] υ_{max} (nujol); 1320 , 1160 (SO$_2$); [1]H n.m.r. (300

MHz/CDCl$_3$); δ_H: 6.60 [s, 2H, CH$_2$], 6.80 [s, 2H, CH$_2$], 7.3-7.6 [m, 10H, Ar]; m/z 334 (M$^{+\cdot}$, 16%), 300 (42), 256 (M$^{+\cdot}$-C$_6$H$_6$, 12), 229 (40), 209 (18), 141 (22), 125 (54), 97 (12), 77 (100), 51 (50).

Physical and spectral data consistent with literature values.

Method B

A solution containing 2,3-bis(phenylsulfinyl)-1,3-butadiene (16.28 g, 53.9 mmol) and 33 ml of hydrogen peroxide (34%) in glacial acetic acid (160 ml) was heated (using a pre-heated oil bath) so as to maintain a reaction temperature of 90°C for 5 h. The hot solution was then removed from the oil bath then H$_2$O (40 ml) was added, the mixture was then allowed to stand at room temperature for 16 h. The resulting crystalline precipitate was collected and washed with H$_2$O (50 ml), methanol (30 ml) and diethyl ether (100 ml). The crude product was then recrystallised from CH$_2$Cl$_2$/hexane (1:1) to give 2,3-bis(phenylsulfenyl)-1,3-butadiene (12.10 g, 66%) as white crystals. M.p. 183-185°C (lit. m.p. 183-185°C);[164]

Phenyl thioacetate

Acetyl chloride (1.17 g, 13.5 mmol) was added to a solution of thiophenol (1.0 g, 9 mmol) in CH$_2$Cl$_2$ (50 ml). This solution was refluxed for 2 h then allowed to cool to room temperature. The solvent was removed under reduced pressure and the crude product distilled to give *phenyl thioacetate* (1.14 g, 83%), 44°C (0.07 mm Hg) as a colourless liquid. ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.44 [s, 3H, COCH$_3$], 7.44 [s, 5H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 30.00 [CH$_3$], 125.40 [Ar], 129.21 [Ar], 129.44 [Ar], 134.45 [Ar], 194.01 [C=O].

Physical and spectral data consistent with authentic sample

Benzenesulfenyl chloride CAS Reg. No. [931-59-9][106]

Method A

Sulfuryl chloride (20.30 g, 0.15 mol) was added dropwise to a stirred solution of diphenyldisulfide (32.70 g, 0.15 mol) and pyridine (2.93 g, 37 mmol) in CH_2Cl_2 (100 ml). The reaction was stirred for 3 h at room temperature, then the solvent was removed under reduced pressure giving crude product residue which was distilled to give *benzenesulfenyl chloride* (10.10 g, 94%), b.p. 49°C (4 mm Hg) (lit. b.p. 49°C (4 mm Hg))[106] as a dark red liquid. υ_{max} (CDCl$_3$); 3050 , 1460-1420 (Ar); ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 7.42-7.44 [m, 3 H, Ar], 7.67-7.70 [m, 2 H, Ar].

Physical and spectral data consistent with literature values.

Method B

Sulfuryl chloride (1.0 g, 7.2 mmol) was added dropwise to neat phenyl thioacetate (1.1 g, 7.2 mmol) so as to maintain a constant stream of bubbling SO_2 gas. The orange solution was stirred for 10 min at room temperature then acetyl chloride by product was removed under reduced pressure and the crude residue distilled twice using a Kugelrohr distillation apparatus to give *benzenesulfenyl chloride* (1.0 g, 96%), 25°C (0.05 mm Hg) (lit. b.p. 49°C (4 mm Hg)).[106]

Data as above

1-(*p*-Toluenesulfonyl)cyclohexene 86[66]

Finely crushed iodine (9.26 g, 0.036 mol) was added portionwise to a biphasic solution of sodium *p*-toluenesulfinate hexahydrate (9.77 g, 0.06 mol) in H_2O (40 ml) and cyclohexene (3.00 g, 0.036 mol) in CH_2Cl_2 (40 ml) at room temperature with vigorous stirring. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (40 ml) and then transferred to a separating funnel and washed with saturated $NaHCO_3$ solution (50 ml) containing $NaHSO_3$ (5 ml), brine (50 ml), then dried over $MgSO_4$, filtered, and the solvent removed. The brown residue was then taken up in toluene (100 ml) and treated with DBU (5.56 g, 0.036 mol) causing an immediate darkening of the solution. Stirring was continued for 1h, then the precipitate was removed and the filtrate washed with 1 M HCl (50 ml), $NaHCO_3$ (50 ml), brine (50 ml), then dried over $MgSO_4$, filtered, and the solvent removed to give *1-(p-toluenesulfonyl)cyclohexene* (4.5 g, 53%) as a brown crystalline solid. Crude product could be recrystallised from EtOH to give pure 1-(*p*-toluenesulfonyl)cyclohexene as white crystals. M.p. 81-82°C (lit. m.p. 81-82°C);[66] υ_{max} (KBr pellet); 2953, 2865, 1927, 1642, 1593, 1494, 1448, 1312, 1288, 1147, 1094, 1051, 1015, 944, 815, 669, 599, 546; ^1H n.m.r. (200 MHz/CDCl$_3$); δH: 1.57 [m, 4H, C(4, 5)H], 2.14 [m, 4H, C(3, 6)H], 2.41 [s, 3H, CH$_3$], 7.01 [m, 1H, C(2)H], 7.31 [m, 2H, Ar], 7.71 [m, 2H, Ar]; m/z: 236 (M$^{+\cdot}$, 28%), 141 (62), 92 (28), 82 (100), 55 (30), 41 (52).

Physical and spectral data consistent with literature values.

2,5-Dihydro-3-(*p*-toluenesulfonyl)furan 90[86]

Finely crushed iodine (2.50 g, 10 mmol) was added portionwise to a vigorously stirred biphasic mixture of sodium *p*-toluenesulfinate hexahydrate (2.67 g, 15 mmol) in H_2O (40 ml) and 2,5-dihydrofuran (0.70 g, 10 mmol) in CH_2Cl_2 (40 ml) at room temperature. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with

CH$_2$Cl$_2$ (40 ml) and then transferred to a separating funnel and washed with a saturated NaHCO$_3$ (50 ml) containing NaHSO$_3$ (5 ml), brine (50 ml), then dried over MgSO$_4$, filtered, and the solvent removed. The crude iodosulfone *(3R*, 4R*)-trans-2,5-dihydro-3-iodo-4-(p-toluenesulfonyl)furan,* was then taken up in acetonitrile (60 ml) and treated with triethylamine (1.52 g, 15 mmol) causing an immediate darkening of the solution. Stirring was continued for 1h, then the solvent was removed and the residue taken up in CH$_2$Cl$_2$ (60 ml). The organic solution was washed with 1 N HCl (50 ml), NaHCO$_3$ (50 ml), brine (50 ml), then dried over MgSO$_4$, filtered, and the solvent removed to give *2,5-dihydro-3-(p-toluenesulfonyl)furan* (3.02g, 90%) as a white crystalline solid. Crude product could be recrystallised from EtOH to give pure *2,5-dihydro-3-(p-toluenesulfonyl)furan* as white crystals. Product should be stored under nitrogen to prevent oxidation to 3-(*p*-toluenesulfonyl)furan. M.p. 57-58°C; Found: C 59.03, H 5.41; C$_{11}$H$_{12}$O$_3$S requires C 58.91, H 5.39%; υ_{max} (CDCl$_3$); 2900, 2300, 1620, 1580, 1340, 1210, 1440, 1100, 1080; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δH: 2.45 [s, 3H, CH$_3$], 4.76 [m, 4H, C(2, 5)H], 6.79 [m, 1H, C(3)H], 7.36 [m, 2H, Ar], 7.78 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δC: 22.59 [CH$_3$], 73.99 [C(2)], 76.85 [C(5)], 128.82 [Ar], 131.04 [Ar], 137.18 [C(4)], 138.16 [Ar], 143.08 [C(3)], 146.08 [Ar]; m/z: 224 (M$^{+\cdot}$, 28%), 141 (62), 92 (28), 82 (100), 55 (30), 41 (52).

3-(*p*-Toluenesulfonyl)-furan 91 CAS Reg. No. [128348-27-6][109]

Furan vinyl sulfone oxidises upon exposure to light and air over a prolonged period appearing at a higher Rf than the starting vinyl sulfone. Attempts to oxidise the vinyl sulfone using oxygen in refluxing benzene failed to convert more than 50% of the starting material to the oxidised product. The product was isolated by column chromatography on silica gel using hexane/EtOAc (80:20) as eluant giving *3-(p-toluenesulfonyl)furan* as a white solid. Recrystallised from CH$_2$Cl$_2$ to give needle crystals. M.p. 74-75°C (lit. m.p. 78-81°C);[109] υ_{max} (CHCl$_3$); 1596, 1497, 1322, 1220, 1010, 907, 814, 598; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δH: 2.39 [s, 3H, CH$_3$], 6.57 [m, 1H, C(4)H], 7.29 [d, 2H, Ar], 7.40 [m, 1H,

C(2 or 5)H], 7.80 [d, 2H, Ar], 7.96 [m, 1H, C(2 or 5)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C:

21.49 [CH$_3$], 73.61 [C(4)], 108.57 [C(5)], 127.42 [Ar], 129.93 [Ar], 138.69 [C(3)], 144.55

[Ar], 144.96 [Ar], 145.92 [C(2)]; m/z: 222 (M$^{+\cdot}$, 75%), 139 (17), 107 (100), 91 (30), 77

(51), 65 (25).

Physical and spectral data consistent with literature values

4,4-Dimethyl-1-(*p*-toluenesulfonyl)cyclopentene 92

To a solution of 4,4-dimethylcyclopentene (0.29 g, 3 mmol) in CH$_2$Cl$_2$ (30 ml) was added a

solution of sodium *p*-toluenesulfinate hexahydrate (1.10 g, 6 mmol) in H$_2$O (30 ml). This

heterogeneous mixture was stirred vigorously at RT for 5 min then finely crushed I$_2$ (0.78 g, 3

mmol) was added in portions over 1 min causing the upper aqueous layer to become yellow.

The vigorous stirring was continued to ensure complete consumption of I$_2$, the yellow colour of

the aqueous layer dissipated after 5 min and the CH$_2$Cl$_2$ layer changed to a dark violet colour.

The reaction mixture was stirred at room temperature for 18 h, then transferred to a separating

funnel and diluted with CH$_2$Cl$_2$ (20 ml). The organic layer was separated and washed with a

saturated solution of NaHCO$_3$ (40 ml) containing 5% Na$_2$S$_2$O$_3$ solution (5 ml) then brine (40

ml). The organic layer was dried over MgSO$_4$, filtered and the solvent removed by rotary

evaporation; the residue was taken up in toluene (40 ml) and treated with DBU (0.46 g, 3

mmol), the reaction mixture was then stirred at room temperature for 2 h. The precipitate was

removed by filtration and the filtrate concentrated by rotary evaporation to give *4,4-dimethyl-1-*

(p-toluenesulfonyl)cyclopentene as a yellow liquid. The crude product was used in the next

step without further purification. Found: C 67.11, H 7.50; C$_{14}$H$_{18}$O$_2$S requires C 67.16, H

7.24%; υ_{max} (neat); 3623 , 3583, 3062, 2954, 2927, 2867, 1616, 1596, 1494, 1465, 1402,

1384, 1315(SO$_2$), 1303, 1157, 1093, 1056, 1018; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.02

[s, 6H, 2 x CH$_3$], 2.28 [m, 4H, C(3, 5)H], 2.41 [s, 3H, ArCH$_3$], 6.59 [m, 1H, C(2)H], 7.30

[m, 2H, Ar], 7.35 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.41 [CH$_3$Ar], 28.91 2

x [C(CH$_3$)$_2$], 40.22 [C(4)], 44.92 [C(5)], 47.36 [C(3)], 127.86 [Ar], 129.75 [Ar], 136.51 [Ar], 141.23 [C(2)], 143.39 [C(1)], 144.24 [Ar]; m/z: 250 (M$^+$·, 10%) 139 (24), 95 (96), 79 (63), 69 (68), 55 (70), 41 (100).

3-Chloro-4-benzenesulfenyl-1-(*p*-toluenesulfonyl)pyrrolidine 94

Benzenesulfenyl chloride (0.09 g, 0.63 mmol) was added dropwise, via syringe to a stirred solution of 1-(*p*-toluenesulfonyl)-2,5-dihydropyrrole (0.14 g, 0.63 mmol) in CH$_2$Cl$_2$ (5 ml) at -78°C. When the addition was completed the dry ice/acetone bath was removed and the reaction mixture allowed to warm to room temperature. The reaction mixture became colourless after approximately 30 min at which time the solvent was removed by rotary evaporation to give *3-chloro-4-benzenesulfenyl-1-(p-toluenesulfonyl)pyrrolidine* as a colourless oil (0.23 g, 100%) which crystallised upon exposure to high vacuum. M.p. 109-112°C; υ_{max} (KBr pellet); 2942, 2359, 1597, 1472, 1456, 1439, 1398, 1343, 1321, 1206, 1159, 1093, 1033, 1012, 923, 819, 752, 667, 601, 548; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.59 [s, 3H, CH$_3$Ar], 3.38 [dd, 1H, *J* 2.7, *J* 11, C(5)Hb], 3.57 [dd, 1H, *J* 2.1, *J* 11.7, C(2)Hb], 3.70 [dt, 1H, *J* 3.0, *J* 6.0, C(4)H], 3.86 [dd, 1H, *J* 6.3, *J* 11.1, C(5)Ha], 3.95 [dd, 1H, *J* 4.8, *J* 11.7, C(2)Ha], 4.08 [dt, 1H, *J* 2.1, *J* 4.8, C(3)H], 7.28 [m, 5H, Ar], 7.29 [m, 2H, Ar], 7.71 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.56 [CH$_3$Ar], 50.88 [C(5)], 53.61 [C(2)], 54.68 [C(4)], 59.68 [C(3)], 127.61 [Ar], 128.16 [Ar], 129.46 [Ar], 129.73 [Ar], 131.96 [Ar], 143.86 [Ar]; m/z: 367 (M$^+$·, 20%) 250 (18), 222 (56), 176 (13), 149 (60), 57 (100).

3-Chloro-4-benzenesulfonyl-1-(*p*-toluenesulfonyl)pyrrolidine 97

Freshly recrystallised MCPBA (0.32 g, 1.9 mmol) was added portionwise to a solution of 3-chloro-4-benzenesulfenyl-1-(*p*-toluenesulfonyl)pyrrolidine (0.23 g, 0.63 mmol) in CH$_2$Cl$_2$ (10 ml). During the addition the temperature of the reaction mixture was maintained at 0°C with the

aid of an ice bath, then allowed to warm to room temperature after the addition was completed. The reaction mixture was then stirred under a N_2 atmosphere for 24 h. The resulting solution was filtered through kenite then treated with a few drops of 5% $NaHSO_3$ solution to remove residual peracid. The solution was transferred to a separating funnel and diluted with CH_2Cl_2 (10 ml) then washed with saturated NH_4Cl solution (2 x 5 ml). The organic layer was separated and dried over $MgSO_4$, treated with activated charcoal and filtered, the solvent was then removed by rotary evaporation to give 3-chloro-4-benzenesulfonyl-1-(*p*-toluenesulfonyl)pyrrolidine as a viscous liquid (0.14 g, 55%) which solidified upon exposure to high vacuum to give white crystals. M.p. 121-124°C; υ_{max} (KBr pellet); 2961, 2888, 1458, 1349, 1327, 1289, 1222, 1165, 1096, 1033, 918; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.45 [s, 3H, CH$_3$], 3.54 [dd, 1H, C(5)Ha], 3.65-3.79 [m, 4H, C(2, 3, 5)H], 4.59 [m, 1H, C(4)H], 7.57 [d, 2H, Ar], 7.61-7.71 [m, 5H, Ar], 7.81 [d, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.57 [CH$_3$Ar], 46.27 [C(5)], 53.99 [C(2)], 56.46 [C(3)], 70.80 [C(4)], 127.74 [Ar], 128.68 [Ar], 129.72 [Ar], 129.89 [Ar], 134.79 [Ar]; m/z: (M$^{+\cdot}$, not observed), 222 (100%), 155 (35), 91 (68), 77 (34).

3-Benzenesulfonyl-1-(*p*-toluenesulfonyl)-2,5-dihydropyrrole 98

DBU (0.14 g, 0.90 mmol) was added dropwise via syringe to a solution of 3-chloro-4-benzenesulfonyl-1-(*p*-toluenesulfonyl)pyrrolidine (0.13 g, 0.32 mmol) in CH_2Cl_2 (10 ml) at 0°C. The reaction mixture was allowed to warm to room temperature after the addition was complete. After stirring for 2h at room temperature toluene (5 ml) was added and the reaction mixture heated at reflux for 24h. Upon cooling the solvent was diluted with CH_2Cl_2 (10 ml). The organic layer was washed with saturated NH_4Cl solution (2 x 10 ml), dried over $MgSO_4$, treated with activated charcoal, filtered and the solvent removed by rotary evaporation to give a mixture of *3-benzenesulfonyl-1-(p-toluenesulfonyl)-2,5-dihydropyrrole* and *3-benzenesulfonyl-1-(p-toluenesulfonyl)-2,3-dihydropyrrole* as a white powder (0.08 g, 83%). Vinyl isomer ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.49 [s, 3H, CH$_3$], 4.21 [m, 1H, C(2 or 5)H], 4.27 [m, 1H, C(2 or 5)H], 6.58 [m, 1H, C(3)H], 7.37 [d, 2H, Ar], 7.61-7.71 [m, 5H, Ar], 7.75 [d, 2H,

Ar]. Allylic isomer ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.41 [s, 3H, CH$_3$], 3.58 [dd, 1H, C(5)Ha], 4.01 [d, 1H, C(5)Hb], 4.32 [m, 1H, C(4)H], 5.04 [m, 1H, C(3)H], 6.51 [m, 1H, C(2)H], 7.27 [m, 2H, Ar], 7.46-7.73 [m, 7H, Ar], 7.76 [m, 2H, Ar]; m/z: (M$^{+\cdot}$, not observed), 221 (28%), 155 (23), 91 (100), 65 (18).

Attempted Preparation of 3-Benzenesulfonyl-1-(*p*-toluenesulfonyl)-2,5-dihydropyrrole 98 by the Isomerisation of the Allylic Isomer.

DBU (0.14 g, 0.90 mmol) was added dropwise via syringe to a solution of 3-chloro-4-benzenesulfonyl-1-(*p*-toluenesulfonyl)pyrrolidine (0.13 g, 0.32 mmol) in CH$_2$Cl$_2$ (5 ml) at 0°C. The reaction mixture was allowed to warm to room temperature after the addition was complete. After stirring for 2h at room temperature the solvent was removed to give a mixture of the title compound and its allylic isomer. This crude product mixture was dissolved in toluene (5 ml) and the reaction mixture heated at reflux for 24h. Upon cooling the solvent was diluted with CH$_2$Cl$_2$ (10 ml). The organic layer was washed with saturated NH$_4$Cl solution (2 x 10 ml), dried over MgSO$_4$, treated with activated charcoal, filtered and the solvent removed by rotary evaporation. The crude product was chromatographed on silica gel using EtOAc/hexane (30:70) as eluant to give *1-p-toluenesulfonylpyrrole* as a white powder (0.08 g, 10%). ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.37 [s, 3H, CH$_3$], 6.25 [m, 2H, C(3, 4)H], 7.12 [d, 2H, C(2, 5)H], 7.23 [m, 2H, Ar], 7.73 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.51 [CH$_3$Ar], 113.52 [C(3, 4)], 120.79 [C(2, 5)], 126.89 [Ar], 130.01 [Ar], 136.01 [Ar], 143.50 [Ar]; m/z: (M$^{+\cdot}$, not observed), 152 (100%), 137 (54), 123 (63), 96 (33).

1-p-Toluenesulfonylpyrrole 183 was the only product isolated from this reaction

3-Chloro-4-benzenesulfenyl-1-(*p*-nitrophenyl)pyrrolidine 95

Benzenesulfenyl chloride (0.37 g, 2.6 mmol) was added via a syringe to a refluxing solution of 1-nitrophenyl-2,5-dihydropyrrole (0.5 g, 2.6 mmol) in acetonitrile (40 ml) containing a small amount of $CaCO_3$ (~10 mg). The reaction mixture was refluxed for 1 h then allowed to cool to room temperature over 20 min. The reaction mixture was transferred to a separating funnel and diluted with CH_2Cl_2 (60 ml) then washed with H_2O (40 ml). The organic layer was separated and dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation to give *3-chloro-4-benzenesulfenyl-1-(p-nitrophenyl)pyrrolidine* as a brown oil which crystallised upon exposure to high vacuum, the crude product was recrystallised from acetone/ethanol to give brown crystals (0.62 g, 71%). M.p. 135-137°C; Found: C 57.20, H 4.51, N 8.53; $C_{16}H_{15}ClN_2O_2S$ requires C 57.39, H 4.51, N 8.36%; υ_{max} (nujol); 1580, 1480, 1270, 1090, 700; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.56 [d, 1H, *J* 12.1, C(5)Ha], 3.71 [d, 1H, *J* 11.6, C(5)Ha], 4.07 [d, 1H, C(5)Ha], 4.08 [d, 1H, C(4)H], 4.07 [dd, 1H, C(2)Ha], 4.23 [dd, 1H, C(2)Hb], 4.47 [d, 1H, C(3)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 51.09 [C3], 53.07 [C2], 54.98 [C5], 59.78 [C4], 110.84 [Ar], 126.25 [Ar], 128.25 [Ar], 129.59 [Ar], 131.91 [Ar]; m/z: 334 (M$^{+\cdot}$, 6%), 250 (6), 189 (40), 149 (52), 125 (38), 115 (48), 77 (100), 51 (94), 40 (86).

3-Phenylsulfonyl-1-(*p*-nitrophenyl)-2,5-dihydro-1*H*-pyrrole 96

A solution of MCPBA (80%) (0.88 g, 5.1 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a solution of 3-chloro-4-benzenesulfenyl-1-(*p*-nitrophenyl)pyrrolidine in CH_2Cl_2 (30 ml) in which a small amount of $CaCO_3$ (~10 mg) had been added. During the addition the temperature of the reaction mixture was maintained at 0°C with the aid of an ice bath, then allowed to warm to room temperature after the addition was completed, the reaction mixture was then stirred under a N_2 atmosphere for 2 h. The resulting solution was filtered through kenite and the solvent removed by rotary evaporation to give the intermediate α-chloro sulfone as a yellow

powder which was taken up in dry CH_2Cl_2 (20 ml) and cooled to 0°C. DBU (0.19 g, 1.2 mmol) was then added dropwise via syringe and the reaction mixture allowed to warm to room temperature. After stirring for 24 h the solvent was replaced with toluene (10 ml) and the mixture refluxed for 4 h then cooled to room temperature and diluted with CH_2Cl_2 (80 ml). The organic layer was washed with saturated NH_4Cl solution (20 ml), saturated $NaHCO_3$ solution (10 ml) and brine (10 ml), the organic layer was dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation and the crude powder dried to give *3-phenylsulfonyl-1-(p-nitrophenyl)-2,5-dihydro-1H-pyrrole* as a yellow powder (0.25 g, 70%). M.p. 250-255°C; Found: C 58.00, H 4.40, N 8.57; $C_{17}H_{17}NO_2S$ requires C 58.17, H 4.27, N 8.48%; υ_{max} (nujol); 1600, 1522, 1378, 1150; ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 4.76 [m, 4H, C(2, 5)H], 6.79 [d, 2H, ArNO$_2$], 7.32 [m, 1H, C(4)H], 8.02-8.10 [m, 1H, Ar], 8.38 [m, 1H, Ar], 8.50 [m, 2H, ArNO$_2$]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 52.85 [C(5)], 55.34 [C(2)], 110.39 [C(4)], 126.34 [C(3)], 128.05 [Ar], 129.68 [Ar], 134.35 [Ar], 136.35 [Ar]; m/z: 330 (M$^+$, 90%), 328 (88), 264 (18), 235 (40), 203 (36), 186 (58), 172 (66), 141 (60), 139 (32), 108 (42), 91 (92), 77 (100), 54 (54), 39 (38).

4,7-Dihydro-2,2-dimethyl-1,3-dioxepine 108 CAS Reg. No. [1003-83-4]

p-Toluene sulfonic acid monohydrate 98.5% (10 mg, cat.) was added to a heterogenous mixture of *cis*-2-butene-1,4-diol (10.0 g, 0.11 mol), dimethoxypropane (11.8 g, 0.11 mol) and benzene (30 ml). This mixture was stirred at reflux for 30 min, during which time the mixture became homogenous. The mixture was allowed to cool to room temperature and a short fractionating column was fitted, the benzene/methanol azeotrope (58°C) was then distilled from the reaction mixture. The remaining benzene was removed by rotary evaporation (dry ice/acetone condenser). The residue was then distilled to give *4,7-dihydro-2,2-dimethyl-1,3-dioxepine* (8.35 g, 60%), b.p. 40-45°C (0.4-0.5 mm Hg) as a colourless liquid. υ_{max} (neat); 3514, 3312, 3029, 2991, 2939, 2901, 2861, 2709, 2143, 2095, 1999, 1962, 1854, 1794, 1720, 1650, 1592, 1448, 1373, 1276, 1221, 1163, 1083, 1014, 951, 870, 771, 723, 661,

639; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.45 [s, 6H, 2 x CH$_3$], 4.26 [s, 4H, C(4, 7)H],

5.67 [s, 2H, C(5, 6)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 23.93 [CH$_3$], 61.39 [C(4, 7)],

101.95 [C(2)], 129.43 [C(5, 6)]; m/z 113 (M$^{+\cdot}$-CH$_3$, 10%), 70 (M$^{+\cdot}$-C$_2$H$_6$O, 20), 59 (100),

43 (98), 42 (50).

Attempted Synthesis of 1,1-Diphenyl-3-phenylsulfonyl-1-silacyclopent-3-ene 105 from 1,1-diphenyl-1-sila-3-cyclopentene 75

Octaphenylcyclotetrasiloxane 100[112,113,114]

To a solution of 1,1-diphenyl-1-silacyclopentene (2.0 g, 8.5 mmol) in EtOAc (60 ml) was

added a solution of sodium *p*-toluenesulfinic acid sodium salt (3.0 g, 17 mmol) in H$_2$O (40 ml).

The heterogeneous mixture was stirred vigorously at room temperature for 5 min then finely

crushed iodine (2.1 g, 8.5 mmol) was added in portions over 30 seconds causing the upper

aqueous layer to become yellow. The vigorous stirring was continued to ensure complete

consumption of the iodine, the yellow colour of the aqueous layer dissipated after 5 min and the

dark violet of the EtOAc layer changed to a cloudy orange colour over time. The reaction

mixture was stirred at room temperature for 24 h, then transferred to a separating funnel and

diluted with EtOAc (20 ml). The organic layer was separated and washed with a saturated

solution of NaHCO$_3$ (40 ml) containing 5% Na$_2$S$_2$O$_3$ solution (5 ml) then brine (40 ml). The

organic layer was dried over MgSO$_4$, filtered and the solvent removed by rotary evaporation.

The white solid was taken up in hot acetonitrile (40 ml) and then allowed to cool. The solution

was then treated with triethylamine (1.7 g, 17 mmol), the reaction mixture was then stirred at

room temperature for 2 h. No change in the product ratio was observed by TLC. DBU (2.6 g,

17 mmol) was added and the reaction mixture refluxed for 16 h. The solution was allowed to

cool to room temperature, *octaphenylcyclotetrasiloxane* (0.81 g, 48%) precipitated as white

crystals and was collected by filtration. M.p. 202-204°C (lit. m.p. 201°C);[114] Found: C

72.60, H 5.34; C$_{48}$H$_{40}$O$_4$Si$_4$ requires C 72.68, H 5.08%; υ_{max} (KBr pellet); 3069, 3047,

2922, 2358, 1962, 1890, 1824, 1591, 1487, 1429, 1119, 1094, 1028, 998, 742, 715, 698, 526, 493; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 7.10-7.47 [m, 40H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 127.65 [Ar], 130.07 [Ar], 134.46 [Ar]; ^{29}Si n.m.r. (300 MHz/CDCl$_3$); δ_{Si}: -38.58 [Si]; (ESIMS) m/z: 490 (35%), 266 (100), 153 (95).

Attempted Preparation of 1,1-Diphenyl-3-phenylsulfonyl-1-silacyclopent-3-ene 105 Continued...

The solvent was removed from the filtrate of the above reaction by rotary evaporation and the resulting residue subjected to column chromatography on silica gel using EtOAc/hexane (15:85) as eluant. The two products isolated from the crude residue were found to be (*E*) or (*Z*)-1-*p*-toluenesulfonyl-1-butene (0.03 g, 2%) as a yellow oil and (*E*) or (*Z*)-2-*p*-toluenesulfonyl-2-butene (0.67 g, 37%) as a white crystalline solid.

(*E*)-(1-*p*-Toluenesulfonyl)-1-butene CAS Reg. No. [111895-49-9][66]

^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.02 [t, 2H, C(4)H], 2.22 [m, 2H, C(3)H], 2.24 [s, 3H, CH$_3$], 5.66 [m, 1H, C(2)H], 6.31 [m, 1H, C(1)H], 7.28 [m, 2H, Ar], 7.73 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 11.57 [C(4)], 21.42 [C(3)], 121.67 [C(2)], 128.27 [Ar], 129.82 [Ar], 135.91 [C(1)], 144.47 [Ar], 152.28 [Ar]; m/z: 211 (MH$^+$, 100%), 139 (98), 92 (76), 55 (49), 39 (42).

E or *Z*-(2-*p*-Toluenesulfonyl)-2-butene

M.p. 60-64°C; Found: C 62.92, H 6.97; C$_{11}$H$_{14}$O$_2$S requires C 62.83, H 6.71%; υ_{max} (nujol); 1934, 1650, 1591, 1170, 1132, 816, 695, 648, 546; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.81 [m, 3H, C(4)H], 2.42 [s, 3H, C(1)H], 6.92 [m, 1H, C(3)H], 7.32 [m, 2H, Ar], 7.731 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 11.06 [C(1)], 13.87 [C(4)], 128.12

[Ar], 129.72 [Ar], 135.69 [C(3)], 136.34 [Ar], 137.90 [Ar], 144.06 [C(2)]; m/z: 210 (M$^{+\cdot}$, 22%), 139 (100), 92 (58), 55 (48), 39 (31).

3-Chloro-1,1-diphenyl-4-phenylsulfenyl-1-silacyclopentane 103

Benzenesulfenyl chloride (1.46 g, 10.2 mmol) was added dropwise to a solution of 1,1-diphenyl-1-silacyclopentene (2.0 g, 8.5 mmol) in CH_2Cl_2 (40 ml) at -78°C. The reaction mixture was stirred for 1 h then allowed to warm to room temperature. The solvent was removed and the crude residue subjected to column chromatography on silica gel using CH_2Cl_2/hexane (10:90) as eluant, to give *3-chloro-1,1-diphenyl-4-phenylsulfenyl-1-silacyclopentane* (2.84 g, 88%) as a slightly yellow liquid which solidifies upon standing. M.p. 86-89°C; υ_{max} (KBr pellet); 3064, 3006, 2939, 2895, 1965, 1894, 1827, 1776, 1661, 1586, 1472, 1428, 1266, 1202, 1173, 1117, 1030, 991, 908, 788, 741, 698; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.50 [dd, *J* 5.8, *J* 15.7, 1H, C(5)Ha], 1.74 [dd, *J* 5.8, *J*15.5, 1H, C(5)Hb], 1.98 [dd, *J* 7.2, *J* 15.7, 1H, C(2)Ha], 2.17 [dd, *J* 6.6, *J*15.6, 1H, C(2)Hb], 3.99 [q, *J* 7.2, *J*13.01, 1H, C(4)H], 4.47 [q, *J*6.0, *J*11.70, 1H, C(3)H], 7.30-7.64 [m, 36 H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 16.90 [C(5)], 22.09 [C(2)], 56.03 [C(4)], 65.29 [C(3)], 127.72 [Ar], 128.15 [Ar], 129.15 [Ar], 129.93 [Ar], 132.96 [Ar], 135.04 [Ar], 143.76 [Ar]; m/z: 381 (M$^{+\cdot}$, 8%), 219 (30), 217 (100).

Attempted Preparation of 1,1-Diphenyl-3-phenylsulfonyl-1-silacyclopent-3-ene 105 from 3-Chloro-1,1-diphenyl-4-(phenylsulfenyl)-1-silacyclopentane 103

Di{1,1-diphenyl-1-[2-(phenylsulfenyl)-3-butenyl]silyl}ether 104

DBU (1.4 g, 9.3 mmol) was added dropwise to a solution of 3-chloro-1,1-diphenyl-4-(phenylsulfenyl)-1-silacyclopentane (3.24 g, 8.5 mmol) in CH_2Cl_2 (40 ml) at -30°C. The reaction mixture was stirred for 15 min and then allowed to warm to room temperature and

stirred for 1 h followed by reflux for 15 h. The reaction mixture was cooled to room temperature, transferred to a separating funnel and washed with 10% HCl (50 ml), saturated NaHCO$_3$ solution (50 ml), brine (50 ml). The organic layer was dried over MgSO$_4$, filtered and the solvent removed by rotary evaporation to give a crude residue which was subjected to column chromatography on silica gel using CH$_2$Cl$_2$/hexane (30:70) as eluant giving *di{1,1-diphenyl-1-[2-(phenylsulfenyl)-3-butenyl]silyl}ether* (2.32 g, 77%) as white solid. M.p. 74-77°C; Found: C 74.46, H 6.08; C$_{14}$H$_{18}$O$_4$S requires C 74.74, H 5.99%; υ_{max} (KBr pellet); 3067, 2999, 1634, 1588, 1480, 1438, 1427, 1304, 1224, 1146, 1118, 1055, 1025, 997, 785, 740, 700, 518; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.50 [dd, *J* 9.8, *J* 15.1, 1H, C(1a)H], 1.60 [dd, *J* 5.4, *J* 14.8, 1H, C(1b)H], 3.61 [dt, *J* 5.4, *J* 9.1, 1H, C(2)H], 4.35 [d, *J* 16.8, 1H, C(4a)H], 4.52 [d, *J* 9.8, 1H, C(4b)H], 5.44 [dt, *J* 9.4, *J* 16.8, 1H, C(3)H], 7.17-7.48 [m, 30 H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 14.51 [C(1)], 48.18 [C(2)], 102.43 [C(3)], 114.67 [C(4)], 127.04 [Ar], 127.75 [Ar], 129.93 [Ar], 132.92 [Ar], 134.76 [Ar], 139.57 [Ar], 143.76 [Ar]; ^{29}Si n.m.r. (300 MHz/CDCl$_3$); δ_{Si}: -12.46 [Si]; (LCMS) m/z: 729 (M$^{+\cdot}$+ Na$^+$, 100%).

Di{1,1-diphenyl-1-[2-(phenylsulfenyl)-3-butenyl]silyl}ether **104** *was the only product isolated from this reaction.*

2,2-Dimethyl-4,7-dihydro-5-(*p*-toluenesulfone)-1,3-dioxepine   109

To a solution of 2,2-dimethyl-4,7-dihydro-1,3-dioxepine (3.0 g, 23 mmol) in CH$_2$Cl$_2$ (40 ml) was added a solution of sodium *p*-toluenesulfinate (8.3 g, 47 mmol) and K$_2$CO$_3$ (2 g) in H$_2$O (40 ml). The heterogeneous mixture was stirred vigorously at room temperature for 5 min then finely crushed iodine (5.82 g, 23 mmol) was added in portions over 30 seconds causing the upper aqueous layer to become yellow. The vigorous stirring was continued to ensure complete consumption of the iodine, the yellow colour of the aqueous layer dissipated after 5 min and the dark violet of the CH$_2$Cl$_2$ layer changed to a cloudy orange colour over time. The reaction mixture was stirred at room temperature for 18 h, then transferred to a separating funnel and

diluted with CH_2Cl_2 (20 ml). The organic layer was separated and washed with a saturated solution of $NaHCO_3$ (40 ml) containing 5% $Na_2S_2O_3$ solution (5 ml) then brine (40 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation. The residue was taken up in acetonitrile (40 ml) and treated with triethylamine (5.82 g, 23 mmol), the reaction mixture was then stirred at room temperature for 2 h. The acetonitrile was removed by rotary evaporation and the residue taken up in ethyl acetate (60 ml) and washed with H_2O (2 x 40 ml), the organic layer was dried over $MgSO_4$, filtered, and the solvent removed by rotary evaporation to give an off white crystalline powder. The crude product was purified by squat column chromatography using EtOAc/hexane (30:70) as eluant, to give *2,2-dimethyl-4,7-dihydro-5-(p-toluenesulfone)-1,3-dioxepine* (4.69 g, 72%) as a white crystalline powder. An analytical sample was prepared by recrystallisation of the purified vinyl sulfone using EtOAc/hexane (20:80) to give large colourless crystals. M.p. 116-117°C; Found: C 59.36, H 6.53; $C_{14}H_{18}O_4S$ requires C 59.55, H 6.42%; υ_{max} (nujol); 1594 (Ar), 1320 (SO_2), 1154 (SO_2); ^1H n.m.r. (300 MHz/$CDCl_3$); δ_H: 1.39 [s, 6H, 2 x CH_3], 2.46 [s, 3H, CH_3Ar], 4.39 [s, 2H, C(4)H], 4.42 [m, 2H, C(7)H], 6.89 [m, 1H, C(6)H], 7.37 [d, 2H, Ar], 7.75 [d, 2H, Ar]; ^{13}C n.m.r. (75 MHz/$CDCl_3$); δ_C: 21.62 [CH_3Ar], 23.56 [$(CH_3)_2C$], 58.67 [C7], 60.73 [C4], 102.93 [C2], 128.01 [Ar], 130.01 [Ar], 136.11 [Ar], 140.03 [C(6)], 142.81 [Ar], 144.60 [C(5)]; m/z: 283 (MH+, 18%), 225 (M+·-C_3H_6O, 48), 196 (24), 127 (24), 91 (100%), 43 (86).

3,4-Dibromotetrahydrosulfolene 112 CAS Reg. No. [15091-30-2][115]

A solution of bromine (6.8 g, 43 mmol) in $CHCl_3$ (6 ml) was added dropwise to a refluxing solution of 3-sulfolene (5.0 g, 42 mmol) in $CHCl_3$ (8 ml). The reaction mixture was refluxed for 2 h then allowed to cool to room temperature and stand for 14 h, during which time the product crystallises out of solution. The product was collected by filtration and washed with $CHCl_3$, then air dried to give *3,4-dibromotetrahydrosulfolene* (3.3 g, 30%) as white crystals. M.p. 142-143°C (lit. m.p. 141.1-141.8°C);[116] υ_{max} (KBr pellet); 3015, 2983, 2950, 1405,

1325, 1314, 1291, 1263, 1236, 1205, 1175, 1144, 1124, 1098, 956, 907, 874, 837, 702, 565, 461, 431; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.51 [m, 4H, C(3, 4)H], 3.99 [m, 2H, C(2, 5)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 45.43 [C(3, 4)], 58.04 [C(2, 5)]; m/z: 279 (M$^+$, 15%), 182 (90), 181 (80), 135 (98), 133 (99), 53 (100).

Physical and spectral data consistent with literature values

4-Bromo-2-sulfolene 113 [166]

A solution of 3,4-dibromotetrahydrothiophene-1,1-dioxide (3.0 g, 10 mmol) and pyridine (1.58 g, 20 mmol) in dry acetone (20 ml) was stirred at room temperature for 24 h. Filtration of the reaction mixture removed pyridinium bromide, the solid was washed with dry acetone. The combined filtrates were evaporated to give a viscous residue which was subjected to column chromatography on silica gel using EtOAc/diethyl ether (1:1) as eluant to give *4-bromo-2-sulfolene* (1.62 g, 82%) as a clear oil. υ_{max} (neat); 3623, 3542, 3176, 3079, 3014, 3956, 2437, 2287, 2034, 1901, 1720, 1596, 1403, 1303, 1143, 1220, 1027, 921, 755, 653, 601; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.53 [dd, 1H, C(2)H), 3.83 [dd, 1H, C(2)H], 5.15 [ddd, 1H, C(3)H], 6.74 [d, 1H, C(5)H], 6.80 [dd, 1H, C(4)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 37.26 [C(5)], 56.61 [C(4)], 132.87 [C(3)], 139.36 [C(2)]; m/z: 197 (M$^+$, 9%), 120 (15), 103 (65), 91 (27), 78 (100).

Physical and spectral data consistent with literature values

3-(*p*-Toluenesulfonyl)-3-sulfolene 111 [166]

A solution of sodium *p*-toluenesulfinate hydrate (0.87 g, 4.9 mmol) and 4-bromo-2-sulfolene (0.80 g, 4.1 mmol) in dry DMF (30 ml) was stirred at room temperature for 24 h. DMF was

removed by distillation under reduced pressure to give a viscous residue; the residue was treated with brine (10 ml) then extracted with CH_2Cl_2 (3 x 50 ml). The combined extracts were dried over $MgSO_4$ and the solvent removed by rotary evaporation to give a clear liquid which crystallised upon standing. The crude product was subjected to column chromatography on silica gel using EtOAc/hexane (1:1) as eluant to yield *3-(p-toluenesulfonyl)-3-sulfolene* (0.56g, 50%) as a white crystalline solid. M.p. 127-129°C (lit. m.p. 138-140°C);[166] υ_{max} (KBr pellet); 3059, 3018, 2980, 1620, 1597, 1494, 1390, 1307, 1252, 1231, 1154, 1134, 1094, 1043, 1016, 996, 923, 903, 812, 742, 658, 607, 584, 543, 493; [1]H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.49 [s, 1H, CH$_3$], 3.88 [m, 2H, C2], 4.06 [m, 2H, C4], 7.08 [m, 1H, C3], 7.41 [d, 2H, Ar], 7.78 [d, 2H, Ar]; [13]C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.90 [CH$_3$], 53.98 [C(2)], 57.99 [C(2)], 128.53 [C(3)], 129.02 [C(4)], 130.68 [Ar], 131.29 [Ar]; m/z: 272 (M$^{+\cdot}$, 20%), 208 (M$^{+\cdot}$-SO$_2$, 10), 155 (M$^{+\cdot}$-C$_4$H$_5$O$_2$S, 24), 139 (100), 129 (24), 91 (82), 65 (38), 53 (85).

Physical and spectral data consistent with literature values

Dimethyl 3-(phenylsulfonyl)-3-cyclopentene-1,1-dicarboxylate 123[119]

Dimethyl malonate (1.00 g, 7.5 mmol) was added in one portion to an ice cooled solution of NaH (0.4 g, 9.8 mmol) in THF (80 ml) under N$_2$. The solution was stirred for 20 minutes at which time a solution of 2,3-bis(phenylsulfonyl)-1,3-butadiene (2.5 g, 7.5 mmol) in THF (50 ml) was added in one portion. The ice bath was removed immediately and the solution allowed to warm to room temperature over 30 minutes. The reaction was quenched with saturated NH$_4$Cl solution (40 ml) and CH$_2$Cl$_2$ (2 x 50 ml). The organic layer was separated and washed with water (50 ml), dried over MgSO$_4$, filtered and the solvent removed to give a mixture of two products that were separated by flash column chromatography on silica gel using EtOAc/hexane (40:60) as eluant to give *dimethyl 3-(phenylsulfonyl)-3-cyclopentene-1,1-dicarboxylate* (0.22 g, 10%) as a clear oil that crystallised upon standing. The recovered noncyclised product (0.87 g, 2.7 mmol) was dissolved in CH$_3$CN (60 ml) and treated with

sodium benzenesulfinate hydrate (0.11 g, 0.67 mmol). The yellow reaction mixture was stirred for 48 h then filtered through kenite and the filtrate concentrated under reduced pressure to give and orange oil, which was chromatographed silica gel using EtOAc/hexane (40:60) as eluant to give *4,4-bis(methoxycarbonyl)-1-(phenylsulfonyl)-1-cyclopentene* (0.55 g, 62%). M.p. 87-92°C; m/z: 324 (M$^{+\cdot}$, 8%) 139 (20), 125 (51), 69 (100), 41 (70); υ_{max} (KBr pellet); 2954, 1738 (C=O), 1630, 1583, 1450, 1438, 1308, 1279, 1247, 1201, 1171, 1154, 1113, 1085, 1052, 985, 959, 928, 884, 821, 821, 762, 728, 688, 612, 569; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.16 [s, 3H, OCH$_3$], 3.20 [s, 3H, OCH$_3$], 3.66 [m, 4H, C(3, 5)H], 6.62 [m, 1H, C(2)H], 7.55-7.58 [m, 3H, Ar], 7.87-7.90 [m, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 33.96 [OCH$_3$], 36.01 2 x [OCH$_3$], 48.53 [C(3, 5)], 123.46 [C(2)], 124.43 [C(1)], 129.15 [Ar], 134.75 [Ar], 166.25 2 x [CO$_2$].

Physical and spectral data consistent with literature values

4,4-Dicyano-1-(phenylsulfonyl)-1-cyclopentene 124 CAS Reg. No. [147356-19-2][119]

Malononitrile (0.16 g, 2.4 mmol) was added in one portion to a cooled solution of NaH (0.11 g, 4.8 mmol) in THF (80 ml) resulting in vigorous frothing. The solution became clear after 5 minutes at which time a solution of 2,3-bis(phenylsulfonyl)-1,3-butadiene (0.8 g, 2.4 mmol) in THF (40 ml) was added in one portion causing the solution to become cloudy and orange in colour. The ice bath was removed immediately and the solution allowed to warm to room temperature over 30 minutes. The reaction was quenched with saturated NH$_4$Cl solution (50 ml) and CH$_2$Cl$_2$ (2 x 50 ml). The organic layer was separated and washed with water (50 ml), dried over MgSO$_4$, filtered and the solvent removed to give the product as a brown residue which was chromatographed on silica gel using EtOAc/hexane (50:50) as eluant to give *4,4-dicyano-1-(phenylsulfonyl)-1-cyclopentene* (0.26 g, 42%) as a viscous oil. ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.33 [s, 2H, C(5)H], 3.39 [m, 2H, C(3)H], 6.70 [s, 1H, C(2)H], 7.60-

7.91 [m, 5H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 33.52 [C(4)], 44.10 [C(3)], 45.8 [C(5)], 115.80 2 x [CN], 129.12 [Ar], 135.63 [Ar], 137.82 [Ar], 138.6 [Ar], 143.58 [Ar].

N-Benzyl-3-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrole 125 CAS Reg. No. [119216-49-8][121]

To a solution of 2,3-di(phenylsulfonyl)-1,3-butadiene (1.0 g, 3 mmol) in 400 ml of a MeOH/CH$_2$Cl$_2$ (1:1) mixture was added dropwise a solution of benzylamine (0.32 g, 3 mmol) in CH$_2$Cl$_2$ (50 ml). The mixture was then stirred for 18 h at room temperature. Sodium methoxide (9 mmol) was then added causing the solution to become bright yellow in colour. The solution was stirred for an additional 30 min at room temperature then quenched with saturated NH$_4$Cl solution (50 ml). The organic layer was separated, washed with water, dried over MgSO$_4$, filtered then concentrated under reduced pressure to give *N-benzyl-3-(phenylsulfonyl)-2,5-dihydro-1H-pyrrole* (0.95 g, 27%) as an orange viscous oil. υ_{max} (nujol); 3035, 1750, 1455, 1315, 1160; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 3.68 [m, 2H, C(5)H], 3.67 [s, 2H, C(2)H], 3.77 [s, 2H, NCH$_2$], 6.75 [m, 1H, C(4)H], 7.29 [s, 2H, Ar], 7.50-7.9 [m, 8H, ArSO$_2$]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 57.60 [CH$_2$], 60.12 [CH$_2$], 127.56 [Ar], 128.06 [Ar], 128.55 [Ar], 1289.43 [Ar], 129.53 [Ar], 133.88 [CH=C], 138.00 [Ar], 139.43 [Ar], 142.2 [SO$_2$C=].

Physical and spectral data consistent with literature values

Attempted Deprotection of *N*-Benzyl-3-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrole 125

N-Benzyl-3-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (1.19 g, 2.7 mmol) was added to a suspension of palladium black (1.2 g) in a 4.4% formic acid solution in dry MeOH (60 ml). The reaction mixture was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was then filtered through kenite and the solvent removed under reduced pressure. The residue was taken up in saturated NaHCO$_3$ solution (40 ml) and extracted with EtOAc (3 x 20 ml). The combined organic extracts were dried with MgSO$_4$, filtered and the solvent removed to give unaltered *N*-benzyl-3-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrole (0.56 g).

General Procedure for the Attempted Condensation of Primary Aryl Amines with 2,3-Di(phenylsulfonyl)-1,3-butadiene[121]

The aryl amine (1.5 mmol) was added dropwise to a solution of NaH (0.07 g, 1.8 mmol) in THF (25 ml). Upon completion of the addition, the mixture was stirred for 30 min. then cooled to 0°C. A solution of 2,3-di(phenylsulfonyl)-1,3-butadiene (0.5 g, 1.5 mmol) in THF (25 ml) was then added dropwise to the prepared mixture. The mixture was allowed to warm to room temperature then stirred for 18 h. Sodium methoxide (9 mmol) was then added, and the solution stirred for an additional 30 min at room temperature. The reaction was quenched with saturated NH$_4$Cl solution (20 ml), the organic layer was separated, washed with water, dried over MgSO$_4$, filtered and then concentrated under reduced pressure.

No [4 +1] addition products were obtained in all cases.

cis-2-Butene-2-(*p*-toluenesulfonyl)-1,4-diol 127

0.1 N Sulfuric acid (2 ml) was added to a solution of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin-5-yl-*p*-toluenesulfone (0.2 g, 0.71 mmol) in MeOH (10 ml). The reaction mixture was stirred at room temperature for 24 h then the MeOH was removed by rotary evaporation. The residue was taken up in EtOAc (30 ml) and washed with cold 5% $NaHCO_3$ solution (20 ml). The aqueous layer was extracted with EtOAc (3 x 30 ml). The combined organic layers were dried over $MgSO_4$, treated with activated charcoal, filtered, and the solvent removed by rotary evaporation to give *cis-2-butene-2-(p-toluenesulfonyl)-1,4-diol* (0.14 g, 81%) as a pale yellow liquid which solidified under vacuum. The crude material could be purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (70:30) as eluant to give the title compound as a white crystalline powder. M.p. 74-77°C; Found: C 54.29, H 5.88; $C_{11}H_{14}O_4S$ requires C 54.53, H 5.82%; ν_{max} (nujol); 3100-3343, 3029, 1643, 1376, 1247, 1078, 1012, 948, 813, 725, 680; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.43 [s, 3H, CH$_3$], 2.62 [brs, 1H, (C1)OH], 2.91 [brs, 1H, (C4)OH], 4.31 [d, 2H, C(1)H], 4.51 [t, 2H, C(4)H], 7.07 [t, 1H, C(2)H], 7.32 [d, 2H, Ar], 7.74 [d, 2H, Ar]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.08 [CH$_3$], 55.47 [C(1)H], 58.71 [C(4)H], 127.77 [*m*-(Ar)], 129.77 [*o*-(Ar)], 135.62 [C(3)], 140.67 [C(2)], 143.30 [SO$_2$Ar], 144.57 [*p*-(Ar)]; (LCMS) m/z: 243 (MH$^+$, 100%).

Experimental in Described in Chapter 3

N,N-Diethyl-2-iodoacetamide 131 CAS Reg. No. [78258-15-8]

Sodium iodide (80.0 g,54 mmol) and 1-bromo-*N,N*-diethylacetamide (9.5 g, 48 mmol) were dissolved in acetone (80 ml) then stirred at reflux under a N_2 atmosphere for 24 h; sodium bromide gradually precipitated over the 24 h. The resulting suspension was filtered and the solvent removed under reduced pressure, the residue was then taken up in ethyl acetate (80 ml). The solution was washed with saturated $NaHSO_4$ solution (10 ml) and water (20 ml) then the solvent removed under reduced pressure to give crude product which was then distilled to yield *N,N-diethyl-2-iodoacetamide* (6.02 g, 52%), 61°C (0.02 mm Hg) as a clear yellow liquid; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.09, 1.18 [t, 3H, CH$_3$], 3.27 [q, 4H, 2 x CH$_2$], 3.64 [s, 2H, CH$_2$-I]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 2.98 [CH$_2$-I], 11.97, 14.03 [CH$_3$], 40.33, 43.25 [CH$_2$], 166.80 [C=O]; m/z 241 (M$^{+\cdot}$, 8%), 226 (M$^{+\cdot}$-CH$_3$, 6), 114 (M$^{+\cdot}$-I, 98), 72 (M$^{+\cdot}$-C$_2$H$_2$OI, 62), 58 (100), 32 (96).

N,N-Diethyl-2-bromoacetamide 133 CAS Reg. No.[2430-01-5]

Bromoacetyl bromide (5.00 g, 0.025 mole) was added dropwise to a stirred solution of diethylamine (3.65 g, 0.025 mole) and chloroform (30 ml) in a two necked round bottomed flask at -78°C under N_2. The reaction mixture was stirred at -78°C for 10 min, then stirred at room temperature for 1 h. The pale yellow solution was transferred to a separating funnel and treated with 10% HCl solution (15 ml), 10% $NaHCO_3$ solution (15 ml) and water (15 ml). Removal of the solvent under reduced pressure gave *N,N-diethyl-2-bromoacetamide* (4.47 g, 92%) as a yellow liquid; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.16 [t, 3H, CH$_3$], 1.27 [t, 3H, CH$_3$], 3.41 [q, 4H, 2 x NCH$_2$], 3.86 [s, 2H, CH$_2$-C=O]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 12.43, 13.92 [CH$_3$], 26.33 [CH$_2$-I], 40.45, 42.86 [CH$_2$], 165.84 [C=O]; m/z 193 (M$^{+\cdot}$,

15%), 178 (M$^{+\cdot}$-CH$_3$, 40), 121 (M$^{+\cdot}$-C$_4$H$_{10}$N, 8), 114 (M$^{+\cdot}$-Br, 23), 83 (100), 72 (M$^{+\cdot}$-C$_4$H$_{10}$, 18), 46 (62), 35 (80).

Triphenylmethylphosphonium iodide CAS Reg. No. [2065-66-9]

Iodomethane (34.08 g, 2.5 mol) was added dropwise to a stirred solution of triphenylphosphine (31.52, 1.2 mol) in toluene (150 ml) under N$_2$. The solution was stirred for 24 h at room temperature during which time white crystalline product crystallised out of solution. The crystals were collected by vacuum filtration and washed with dry toluene then dried under vacuum to give triphenylmethyl phosphonium iodide (47.98 g, 99%) as fluffy white crystals. M.p. 183-185°C.

Triphenylmethylphosphonium dicyanoargenate 139[134]

Triphenylmethylphosphonium iodide (2.00 g, 4.95 mmol) and silver cyanide (1.33 g, 9.9 mmol) were dissolved in dry CH$_3$CN (60 ml) and refluxed for 30 minutes. The mixture was then filtered to remove precipitated silver iodide and concentrated to approximately 10 ml by rotary evaporation, the product was then precipitated by addition of diethyl ether (20 ml) and vigorous shaking. Filtration of the resultant suspension and recrystallisation of the crude product from CH$_3$CN/diethyl ether gave *triphenylmethylphosphonium dicyanoargenate* (1.90 g, 88%) as colourless crystals. M.p. 120°C (lit. m.p. 127°C);[134] υ_{max} (nujol); 2139 (CN), 1580 (Ar), 1420 (PPh), 1110, 990; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 9.96 [CH$_3$], 10.74 [CH$_3$], 117.87 [CN], 119.05 [CN], 130.66 [Ar], 132.99 [Ar], 135.70 [Ar], 144.61 [Ar].

Sodium diformylamide 132[136,167]

Sodium (2.3 g, 0.1 mol) was added to cooled MeOH (20 ml) under a nitrogen atmosphere. The sodium methoxide solution thus prepared was allowed to warm to room temperature. Formamide (10 g, 0.2 mol) was added steadily through a pressure equalising dropping funnel to the solution of sodium methoxide. Upon completion of the addition the reaction mixture was stirred for 1.5 h then the MeOH was removed by rotary evaporation. The resulting powder was then dried under high vacuum for 48 h to give *sodium diformylamide* (10 g, 100%) as a white powder. M.p. 39°C (lit. m.p. 37-39°C).[167]

N,N-Diethyl-2-hydroxyacetamide 135 CAS Reg. No. [39096-01-0]

Sodium diformylamide (0.44 g, 4.6 mmol) was sonicated in acetonitrile (30 ml) for 10 min, to give a fine suspension to which *N,N'*-diethyl-2-iodoacetamide (1.0 g, 4.2 mmol) was then added. The reaction mixture was then stirred at reflux for 24 h, at which point a further 0.2 eq. of sodium diformylamide was added. After an additional 12 h at reflux the reaction mixture was allowed to cool to room temperature. The cooled solution was filtered and the solid washed with acetonitrile. The combined filtrates were concentrated under reduced pressure. Hydrolysis was accomplished by the stirring of the residue with KOH (1 mg, 4.2 mmol) in ethanol (2 ml) for 10 min at room temperature. The solvent was removed and the residue chromatographed on silica gel using EtOAc/hexane (1:1) as eluant to give *N,N-diethyl-2-hydroxyacetamide* (200 mg, 30%) as a clear oil. υ_{max} (neat); 3400 (OH), 2900 (CH), 2820 (N-CH), 1650 (C=O), 1400 (O-H), 1280 (O-H), 1060 (C-O); ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.17 [m, 6H, 2 x CH$_3$], 3.13, 3.40 [q, 4H, CH$_2$], 3.70 (t, 1H, OH], 4.1 [s, 2H, CH$_2$OH); ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 12.73 [CH$_3$], 13.81 [CH$_3$], 39.90 [CH$_2$], 40.40 [CH$_2$], 59.63 [CH$_2$OH], 170.53 [C=O]; m/z 131 (M$^{+\cdot}$, 38%), 100 (M$^{+\cdot}$-CH$_3$O, 72), 72 (M$^{+\cdot}$-C$_2$H$_3$O$_2$, 100), 58 (M$^{+\cdot}$-C$_4$H$_{11}$N, 48), 44 (68), 32 (94).

N-Formylglycine 137 CAS Reg. No. [2491-15-8][136]

Acetic anhydride (119.9 g, 2 mol) was added dropwise to a solution of glycine (15 g, 0.19 mol) in 99% formic acid (552 g, 12 mol) so as to maintain a temperature of 30°C. Upon complete addition of acetic anhydride the reaction mixture was stirred at room temperature for 2.5 hours. The mixture was diluted with water (160 ml) then concentrated to give a crude residue, recrystallisation from 95% ethanol gave *N-formylglycine* (16.80 g, 86%) as white crystals. M.p. 145-150°C (lit. 153-154°C);[168] υ_{max} (nujol); 3350, 2200-3100, 1650, 1710; ^{1}H n.m.r. (300 MHz/D$_2$O); δ_H: 4.03 [s, 2H, CH$_2$], 8.13 [s, 1H, COH]; ^{13}C n.m.r. (75 MHz/D$_2$O); δ_C: 41.84 [CH$_2$], 166.71 [COH], 175.07 [CO$_2$H]; m/z 104 (M$^{+\cdot}$, 100%) 75 (40), 58 (88).

Physical and spectral data consistent with literature values

N,N-Diethyl-2-formylaminoacetamide 130

N-formylglycine (2.0 g, 0.019 mol), *N*-hydroxysuccinimide (2.18 g, 0.019 mol) and DCC (4.0 g, 0.019 mol) were dissolved in DMF (25 ml) and stirred at room temperature for 1h. DCU was filtered off and the filtrate treated with diethylamine (2.8 g, 0.04 mol). The reaction mixture was stirred for 3h during which time a precipitate formed which was removed by filtration and the solvent removed by distillation under reduced pressure. The residue was subjected to column chromatography on silica gel using an acetone/hexane gradient (80:20) as eluant to give *N,N-diethyl-2-formylaminoacetamide* (2.60 g, 87%) as a yellow liquid. υ_{max} (neat); 3460-3400, 2900-2800, 1480, 1700-1640; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.11-1.24 [m, 6H, 2 x CH$_3$], 3.26 [q, 2H, CH$_2$], 3.38 [q, 2H, CH$_2$], 4.09 [d, 2H, CH$_2$NH], 6.89 [brs, 1H, NH], 8.26 [s, 1H, COH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 12.81 [CH$_3$], 13.88 [CH$_3$], 39.69 [CH$_2$], 40.42 [CH$_2$], 40.92 [CH$_2$], 160.98 [CO]; m/z: M$^{+\cdot}$ 159 (10%), 100 (66), 72 (100), 58 (65), 44 (64).

N,N-Diethyl isocyanoacetamide 138

N,N-Diethyl-2-formylaminoacetamide (0.30 g, 2 mmol) and freshly distilled diisopropyl ethyl amine (1.55 g, 12 mmol) were added to dichloromethane (50 ml) in a 100 ml round bottomed flask equipped with a N_2 balloon, thermometer, magnetic stirring bar and a 100 ml pressure equalising dropping funnel. The solution was stirred and cooled to -76°C in a dry ice-acetone bath, then triflic anhydride (0.85 g, 3 mmol) was added dropwise over 5 minutes while maintaining the temperature at -76°C. The red-brown solution was stirred for 30 minutes, then the dry ice-acetone bath was removed and 5% sodium bicarbonate solution (20 ml) was added dropwise so as to maintain the temperature between 25-30°C. The biphasic mixture was then stirred for another 30 min, after which the mixture was diluted with additional water (10 ml). The aqueous layer was then separated and extracted with two portions of CH_2Cl_2 (20 ml). The combined organic layers were then washed with saturated NaCl solution (50 ml), and dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure yielded *N, N-diethyl isocyanoacetamide* (0.3 g, 80%) as a dark brown residue which was not purified further. υ_{max} (neat); 2110 (CN), 1650 (C=O); ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.14 [t, 3H, CH$_3$], 1.21 [t, 3H, CH$_3$], 2.09 [s, 2H, CH$_2$], 3.33 [q, 2H, CH$_2$], 3.41 [q, 2H, CH$_2$]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 12.05 [CH$_3$], 13.37 [CH$_3$], 24.49 [CH$_2$], 40.02 [CH$_2$], 42.40 [NCH$_2$], 218.25 [CO].

Benzyl glycinate *p*-toluenesulfonate 145[57,107]

A mixture of glycine (15.1 g, 0.20 mol), *p*-toluenesulfinic acid monohydrate (38.25 g, 0.20 mol) and benzyl alcohol (40 ml, 0.40 mol) was heated at reflux for 1h. Toluene (60 ml) was added dropwise at a rate which did not significantly reduce the temperature within the reaction flask. A Dean–Stark apparatus was fitted and the mixture refluxed for 4h during which time

approximately 10 ml of water was azeotropically removed. The reaction mixture was allowed to cool to 50-60°C and then poured into a 400 ml beaker, the solution was then cooled to 10°C. The resulting precipitate was filtered, washed thoroughly with dry diethyl ether, and dried under vacuum for 24h to yield *benzyl glycinate p-toluenesulfonate* (59.45 g, 88%) as white crystals. Benzyl glycinate *p*-toluene sulfonate can be recrystallised from methanol/diethyl ether, however the crude material is suitable for use in the next step provided the washing and drying procedures are carried out rigorously to remove residual benzyl alcohol. M.p. 124-128°C (lit. 116-125°C)[107]; υ_{max} (KBr pellet); 1751 (C=O), 1622, 1600, 1526, 1497, 1497, 1453, 1427, 1419, 1244, 1184, 1126, 1105, 1037, 1013, 907, 860, 811, 739, 687, 576; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 2.20 [s, 3H, CH$_3$], 3.68 [s, 2H, NCH$_2$], 4.96 [s, 2H, CH$_2$Ar], 6.90 [d, 2H, Tol], 7.10-7.24 [m, 5H, Ar], 7.71 [d, 2H, Tol], 8.05 [s, 1H, NH]; (ESI-MS +'ve ion mode) m/z 166 (C$_9$H$_{13}$NO$_2$$^+$, 70%), 91 (100); (ESI-MS -'ve ion mode) m/z 171 (C$_7$H$_7$O$_3$S$^-$, 100%), 107 (30).

Physical and spectral data consistent with literature values

N-Formylglycine methyl ester 143 CAS Reg. No. [3154-54-9]

Triethylamine (0.96 g, 9.5 mmol) was added dropwise to a stirred suspension of glycine methyl ester hydrochloride (1.00 g, 7.9 mmol) in methyl formate (4.8 g, 80 mmol) at reflux. The mixture was refluxed for 15 h then filtered to remove triethylamine hydrochloride and the excess methyl formate removed from the filtrate under reduced pressure. Distillation of the crude product gave *N-formylglycine methyl ester* (0.77 g, 83%), 85°C (0.05 mm Hg) as a colourless liquid. υ_{max} (nujol); 1320, 1160 (SO$_2$); ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.70 [s, 3H, CH$_3$], 4.01 [d, 2 H, CH$_2$], 6.95 [brs, 1 H, NH], 8.19 [s, 3 H, HC=O]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 39.55 [CH$_3$], 52.26 [CH$_2$N], 162.34 [CO$_2$Me], 170.08 [COH]; m/z 118 (MH$^+$, 56%), 89 (M$^+$-COH, 30), 74 (M$^+$-CH$_2$NO, 8), 58 (M$^+$-C$_2$H$_4$NO, 100).

N-Formylglycine ethyl ester 140 CAS Reg. No.[3154-54-9][127,136]

Triethylamine (27.5 g, 0.27 mol) was added dropwise to a stirred suspension of glycine ethyl ester hydrochloride (33 g, 0.25 mol) in methyl formate (123.5 g, 2.05 mmol) at reflux. The mixture was refluxed for 15 h then filtered to remove triethylamine hydrochloride and the excess methyl formate removed from the filtrate under reduced pressure. Distillation of the crude product gave *N-formylglycine ethyl ester* (20.3 g, 75%), 90°C (0.05 mm Hg) (lit. 94-97°C)[127] as a colourless liquid. υ_{max} (nujol); 2890 (NH), 1640 (C=O), 1410, 1390, 1230, 1190, 1095, 910, 800; [1]H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.29 [t, 3H, CH$_3$], 4.05 [d, 2 H, CH$_2$NH], 4.20 [q, 2H, CH$_2$], 7.64 [brs, 1 H, NH], 8.25 [s, 3 H, HCO].

Physical and spectral data consistent with literature values

N-formyl glycine benzyl ester 146 CAS Reg. No. [51354-16-6][57,107]

Triethylamine (25 ml) was added dropwise to a stirred suspension of benzyl glycinate *p*-toluene sulfonate (57.00 g, 0.17 mol) and methylformate (84 ml) at reflux in a 2-necked 250 ml round bottomed flask fitted with a double surface reflux condenser. The mixture was refluxed for 15 h then filtered to remove triethylamine hydrochloride and the excess methyl formate removed from the filtrate under reduced pressure. The residue was diluted with water (600 ml) and the mixture extracted with CHCl$_3$ (3 x 100 ml). The combined extracts were combined, and washed with 5% aq. NaHCO$_3$ solution (150 ml) and water (150 ml). The organic layer was dried over MgSO$_4$, filtered, and the solvent removed under reduced pressure to yield *N-formyl glycine benzyl ester* (20.22 g, 62%) as a yellow liquid. υ_{max} (neat); 3324, 1758, 1687, 1525; [1]H n.m.r. (300 MHz/CDCl$_3$); δ_H: 4.10 [d, 2H, CH$_2$NH], 5.19 [s, 2 H, OCH$_2$], 6.24 [brs, 1 H, NH], 7.35 [m, 5 H, Ar], 8.23 [s, 1 H, CHO]; m/z 131 (M$^+$,16%), 108 (42), 91 (45), 79 (46), 69 (49), 45 (100).

Physical and spectral data consistent with literature values

Ethyl isocyanoacetate 142 (General Procedure for the Preparation of Isocyanides)[127]

N-Formylglycine ethyl ester (20.34 g, 0.16 mol) and triethylamine (32.34 g, 0.32 mol) were added to dichloromethane (150 ml) in a 500 ml round bottomed flask equipped with a N_2 balloon, thermometer, magnetic stirring bar and a 100 ml pressure equalising dropping funnel. The solution was stirred and cooled to 0°C in an ice-salt bath, then phosphorus oxychloride (24.35 g, 0.16 mol) was added dropwise over 10 minutes while maintaining the temperature at 0°C. The red-brown solution was then stirred for 1 h, the ice bath was removed and a solution of 30 g of sodium carbonate in 125 ml of water was added dropwise so as to maintain the temperature between 25-30°C. The biphasic mixture was then stirred for another 30 min, after which the mixture was diluted with additional water (150 ml). The aqueous layer was then separated and extracted with two portions of CH_2Cl_2 (75 ml). The combined organic layers were then washed with saturated NaCl solution (50 ml), and dried over anhydrous sodium sulfate, filtered and the solvent evaporated under reduced pressure. Distillation of the remaining brown oil under reduced pressure yielded *ethyl isocyanoacetate* (16.18 g, 89%), b.p. 108°C (10 mm Hg) (lit. b.p. 89-91°C (11 mm Hg))[127] as a colourless liquid. [1]H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.29 [t, 3H, CH$_3$], 4.20 [s, 2H, NCH$_2$], 4.26 [q, 2H, OCH$_2$]; m/z 114 (MH$^{+\cdot}$, 10%), 86 (14), 68 (32), 54 (12), 40 (100).

Physical and spectral data consistent with literature values.

Methyl isocyanoacetate 17 CAS Reg. No. [39687-95-1]

N-formylglycine methyl ester (17.4 g, 0.15 mol) was treated with triethylamine (37.55 g, 0.37 mol) and $POCl_3$ (22.7 g, 0.15 mol) following the general procedure for the preparation of isocyanides. Distillation of the crude product gave *methyl isocyanoacetate* (7.1 g, 48%), 44°C (0.5-0.6 mm Hg) as a colourless liquid. ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.82 [s, 3H, OCH$_3$], 4.22 [s, 2H, NCH$_2$]; m/z 100 (MH$^{+\cdot}$, 11%), 59 (19), 54 (28), 40 (100).

Benzyl isocyanoacetate 144 CAS Reg. No. [41995-26-0][57,107]

N-formylglycine benzyl ester (25.0 g, 0.13 mol) was treated with triethylamine (31.9 g, 0.32 mol) and $POCl_3$ (19.7 g, 0.13 mol) following the general procedure for the preparation of isocyanides. Distillation of the crude product gave *benzyl isocyanoacetate* (10 g, 44%), 105-106°C (0.04-0.05 mm Hg) (lit. b.p. 120°C (0.5 mm Hg))[57] as a colourless liquid which solidified at 0-5°C to give a low m.p. solid. υ_{max} (neat); 3089, 2971, 2163, 1760, 1498, 1456, 1421, 1384, 1351, 1257, 1197, 1014, 912, 752, 719; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 4.23 [s, 2H, NCH$_2$CO], 5.22 [s, 2H, OCH$_2$Ar], 7.33 [m, 5H, Ar]; m/z M$^{+\cdot}$ 175 (8%), 146 (16), 91 (100), 77 (14).

Physical and spectral data consistent with literature values.

N-(Isocyanoacetyl)morpholine 141 CAS Reg. No. [67434-29-1][138,169]

A mixture of freshly distilled methyl isocyanoacetate (3.0 g, 0.03 mol), morpholine (6.0 g, 0.07 mol) and methanol (30 ml) was stirred for 24h at room temperature. The reaction mixture was then concentrated under reduced pressure to give a crude residue. The residue was taken up in water (30 ml) and extracted with EtOAc (6 x 20 ml), dried over MgSO$_4$, filtered and the solvent removed to give crude product as an off white solid. Column chromatography over silica gel using CH$_2$Cl$_2$/EtOAc (80:20) as eluant gave *N-(isocyanoacetyl)morpholine* (4.00 g, 87%) (lit. yield[138,169] 95%) as white crystals. M.p. 80-81°C (lit. m.p. 78-79°C);[169] υ_{max}

(KBr pellet); 2964, 2857, 2162 (CN), 1667 (C=O), 1473, 1430, 1276, 1241, 1113, 1067, 1642, 1015, 990, 844, 790, 694, 580; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.29 [t, 3H, CH$_3$], 4.20 [s, 2H, NCH$_2$], 4.26 [q, 2H, OCH$_2$]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 42.56 [NCH$_2$], 43.50 [NCH$_2$CO], 45.75 [NCH$_2$], 66.02 [OCH$_2$], 66.46 [OCH$_2$]; m/z 168 (M$^{+\cdot}$, 6%), 155 (100), 128 (46), 114 (22), 100 (41), 85 (32), 68 (50), 56 (81), 42 (100).

Physical and spectral data consistent with literature values.

General procedure for annulated[3,4-c]pyrroles

A solution of vinyl sulfone and isocyanoacetate (2.5 eq.) in THF (~10 ml/ mmol) was added dropwise over 30 minutes to a suspension of NaH (2.5 eq.) in THF (~5 ml/ mmol) at 0°C. Upon completion of the addition the reaction mixture was stirred for 1 h then allowed to warm to room temperature. The solvent was then removed by rotary evaporation and the semi-solid residue taken up in H$_2$O. The aqueous solution was extracted and the combined organic layers dried over MgSO$_4$, treated with charcoal then filtered. The solvent was removed by rotary evaporation to give annulated[3,4-c]pyrrole.

Ethyl 3,3-dimethyl-5,7-dihydro-1*H*[1,3]dioxepino[5,6-c]pyrrole-6-carboxylate 158[141]

158
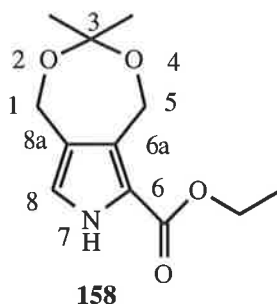
4,7-Dihydro-2,2-dimethyl-5-(*p*-toluenesulfonyl)-dioxepine (1.0 g, 3.5 mmol) and ethyl isocyanoacetate (0.8 g, 7.1 mmol) in THF (40 ml) were reacted following the general

procedure. Diethyl ether (4 x 10 ml) was used as the extracting solvent. The solvent was removed by rotary evaporation to give *ethyl 3,3-dimethyl-5,7-dihydro-1H[1,3]dioxepino[5,6-c]pyrrole-6-carboxylate* as an off white powder (0.85 g, 100%). Recrystallisation of the product from ethanol gave colourless crystals. Sublimes 120°C (760 mm Hg); Found: C 59.99; H 7.20; $C_{14}H_{18}O_4S$ requires C 60.23; H 7.16%; υ_{max} (KBr pellet); 3292 (NH), 1668 (C=O), 1341, 1286, 1273, 1214, 1160, 1105, 1066, 1021; ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.34 [t, 3H, CH$_3$], 1.58 [s, 6H, 2 x C6(CH$_3$)], 4.32 [q, 2H, CH$_2$O], 4.68 [s, 2H, C(4 or 8)H], 5.06 [s, 2H, C(4 or 8)H], 6.69 [d, 1H, CHNH], 8.78 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 14.32 [CH$_3$], 24.20 2 x [CH$_3$], 58.03 [C(1 or 5)], 59.51 [C(1 or 5)], 60.21 [CH$_2$O], 103.08 [C(3)], 117.43 [C(3 or 6)], 117.41 [C(3 or 6)], 125.58 [C(8a)], 130.11 [C(6a)], 159.10 [C=O]; m/z: M$^+$ 239 (M$^+$-CH$_3$), 224 (M$^+$-C$_3$H$_6$O), 181 (M$^+$-C$_5$H$_{11}$O), 152, 106, 43.

Crystallographic data in Appendix 3.

Ethyl 2,2-dioxo-1,2,3,5-tetrahydro-2-thieno[3,4-c]pyrrole-4-carboxylate 149[83]

149
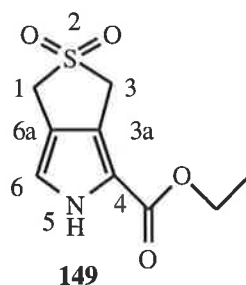
A solution of ethyl isocyanoacetate (0.21 g, 1.8 mmol) in THF (5 ml) was added dropwise, over 10 min, to a solution of NaH (0.07 g, 1.8 mmol) in THF (5 ml) at 0°C. The mixture was stirred at 0°C for 15 min, then a solution of 3-(*p*-toluenesulfonyl)-3-sulfolene (0.25 g, 0.92 mmol) in THF (5 ml) was added rapidly via the dropping funnel causing the colour of the reaction mixture to change from orange to red. The reaction mixture was stirred for 20 min then quenched with ethanol (2 ml). The solvent was removed by rotary evaporation and the residue

washed with H_2O (10 ml) and ether (10 ml). The aqueous layer was separated and extracted with EtOAc (4 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed by rotary evaporation to give *ethyl 2,2-dioxo-1,2,3,5-tetrahydro-2-thieno[3,4-c]pyrrole-4-carboxylate* as an off white crystalline powder (0.14 g, 66%). Sublimes approx. 175°C; M.p.~192-193°C; Found: C 47.22, H 4.76, N 6.21; $C_9H_{11}O_4S$ requires C 47.15, H 4.83, N 6.11%; v_{max} (KBr pellet); 3270 (NH), 2989, 1684 (C=O), 1592, 1509, 1421, 1385, 1310, 1291, 1152, 1125, 1020, 776, 606, 532, 466; ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.28 [t, 3H, CH$_3$], 4.11 [s, 2H, CH$_2$], 4.30 [q, 2H, CH$_2$], 4.39 [s, 2H, CH$_2$SO$_2$], 6.89 [d, 1H, CHNH], 9.21 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$/D$_6$-DMSO); δ_C: 13.87 [CH$_3$], 52.85 [C(1)], 53.93 [C(3)], 59.86 [OCH$_2$], 114.53 [C(4)], 117.65 [C(6a)], 118.04 [C(6)], 120.01 [C(3a)], 159.87 [C=O]; m/z: 229 (M$^{+\cdot}$, 4%), 165 (M$^{+\cdot}$-SO$_2$, 78), 120 (12), 119 (100), 91 (28), 64 (11), 39 (10).

N,N-Diethyl 3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxamide 156

156
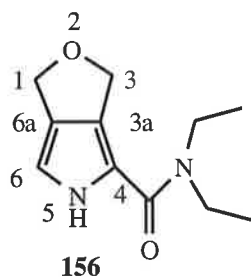
3-(*p*-Toluenesulfonyl)-2,5-dihydrofuran (0.05 g, 0.24 mmol) and *N,N*-diethyl isocyanoacetamide (0.05 g, 0.36 mmol) were reacted following the general procedure. Diethyl ether (4 x 5 ml) was used as the extracting solvent. Column chromatography on silica gel using EtOAc/hexane (70:30) as eluant gave *N,N-diethyl 3,4-dihydro-1H-furo[3,4-c]pyrrole-4-carboxamide* (0.01 g, 20%) as an off white powder. M.p. 167-169°C; Exact Mass Calcd for $C_{11}H_{16}N_2O_2$ 208.12116. Found 208.12095; v_{max} (KBr pellet); 3343 (NH), 2995, 2863, 1595 (C=O), 1506, 1474, 1442, 1314, 1214, 1183, 1118, 1098, 1008, 878, 795, 670, 605; ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.24 [t, 6H, 2 x CH$_3$], 3.52 [q, 4H, 2 x CH$_2$N], 4.92 [s,

2H, C(1 or 3)H], 4.98 [s, 2H, C(1 or 3)H], 6.65 [d, 1H, C(6)H], 9.75 [brs, 1H, NH]; [13]C n.m.r. (75 MHz/CDCl$_3$); δ_C: 15.85 2 x [CH$_3$], 43.05 2 x [CH$_2$], 69.34 [C(1 or 3)], 71.28 [C(1 or 3)], 112.63 [C(6)], 118.64 [C(4)], 128.80 [C(6a)], 130.52 [C(3a)], 163.61 [C=O]; m/z: 208 (M$^+$, 53%) 136 (100) 107 (28) 97 (34). 83 (38), 72 (78), 55 (58), 43 (68).

Benzyl 3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate 155

155
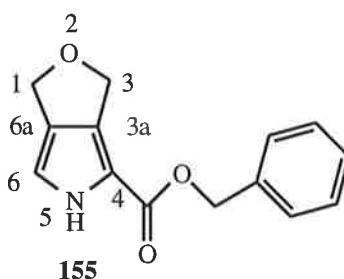
2,5-Dihydro-1-(*p*-toluenesulfonyl)furan (5.11 g, 20 mmol) and benzyl isocyanoacetate (4.79 g, 30 mmol) were reacted following the general procedure. EtOAc (4 x 50 ml) was used as the extracting solvent. Squat column chromatography over silica gel using EtOAc/hexane (20:80) as eluant gave *benzyl 3,5-dihydro-1H-furo[3,4-c]pyrrole-4-carboxylate* as a white crystalline solid (4.7 g, 97%). Product can be recrystallised from hexane to give white needle crystals. M.p. 84-86°C; Found: C 69.28, H 5.60, N 5.71; C$_{14}$H$_{13}$NO$_3$ requires C 69.12, H 5.39, N 5.76%; υ_{max} (nujol); 3451 (NH), 3305, 1604 (C=O), 1517, 1455, 1189, 1170; [1]H n.m.r. (200 MHz/CDCl$_3$); δ_H: 4.13 [s, 2H, C(1 or 3)H], 4.33 [s, 2H, C(1 or 3)H], 4.58 [s, 2H, CH$_2$Ar], 5.93 [m, 1H, C(6)H], 6.63-6.67 [m, 5H, Ar], 9.04 [brs, 1H, NH]; [13]C n.m.r. (75 MHz/CDCl$_3$); δ_C: 61.42 [CH$_2$Ar], 62.95 [C(1 or 3)], 63.77 [C(1 or 3)], 112.90 [C(6)], 113.37 [C(4)], 127.85 [Ar], 128.23 [Ar], 128.62 [Ar], 128.79 [Ar], 134.88 [C(3a)], 136.18 [C(6a)], 160.80 [C=O]; m/z: M$^{+\cdot}$ 243 (35%), 181 (60), 152 (98), 134 (42), 91 (100).

Methyl 3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate 153

153
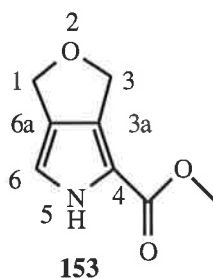
2,5-Dihydro-1-(*p*-toluenesulfonyl)furan (3.0 g, 10 mmol) and methyl isocyanoacetate (2.7 g, 27 mmol) were reacted following the general procedure. EtOAc (4 x 50 ml) was used as the extracting solvent. Squat column chromatography over silica gel using EtOAc/hexane (40:60) as eluant gave *methyl 3,5-dihydro-1H-furo[3,4-c]pyrrole-4-carboxylate* as a white crystalline solid (1.1 g, 66%). Product can be recrystallised from EtOAc/hexane to give white needle crystals. M.p. 155-158°C; Found: C 57.61, H 5.32, N 8.33; $C_8H_9NO_3$ requires C 57.48, H 5.42, N 8.37%; υ_{max} (KBr pellet); 3292 (NH), 2868, 1685 (C=O), 1599, 1517, 1465, 1442, 1351, 1316, 1284, 1209, 1139, 1103, 999; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 3.81 [s, 3H, CH$_3$], 4.85 [s, 2H, C(1 or 3)H], 4.99 [s, 2H, C(1 or 3)H], 6.63 [d, 1H, C(6)H], 9.14 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 51.44 [OCH$_3$], 67.39 [C(1 or 3)], 68.20 [C(1 or 3)], 112.74 [C(6)], 113.11 [C(1)], 129.14 [C(6a)], 134.45 [C(3a)], 161.23 [C=O]; m/z: M$^{+\cdot}$ 167 (80%), 138 (54), 134 (100), 106 (92), 97 (28), 79 (42), 69 (44), 56 (44), 56 (54), 51 (64), 43 (68).

Ethyl 3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate 154

154
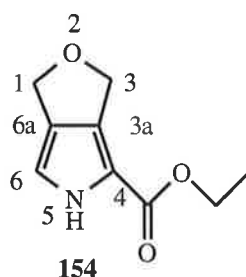
2,5-Dihydro-1-(*p*-toluenesulfonyl)furan (1.0 g, 4.5 mmol) and ethyl isocyanoacetate (0.7 g, 6.7 mmol) were reacted following the general procedure. EtOAc (3 x 30 ml) was used as the extracting solvent. Squat column chromatography over silica gel using EtOAc/hexane (1:1) as eluant gave *ethyl 3,5-dihydro-1H-furo[3,4-c]pyrrole-4-carboxylate* as a white crystalline solid (0.52 g, 64%). Product can be recrystallised from EtOAc/hexane to give white needle crystals. M.p. 114-115°C; Found: C 59.51, H 6.04, N 7.83; $C_9H_{11}NO_3$ requires C 59.64, H 6.12, N 7.73%; υ_{max} (CDCl$_3$); 3500 (NH), 1700 (C=O), 1520, 1420, 1325, 1440, 1066; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.33 [t, 3H, CH$_3$], 4.29 [q, 2H, CH$_2$], 4.88 [s, 2H, C(1 or 3)H], 5.01 [s, 2H, C(1 or 3)H], 6.65 [d, 1H, C(3)H], 8.98 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 16.45 [CH$_3$], 62.35 [CH$_2$], 69.46 [C(4)], 70.25 [C(6)], 114.83 [C(3)], 115.31 [C(1)], 130.80 [C(3a)], 136.35 [C(4a)], 162.95 [C=O]; m/z: M$^{+\cdot}$ 181 (80%), 152 (M$^{+\cdot}$-C$_2$H$_5$, 54), 136 (100), 108 (68).

Trimethyl 2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1,5,5-carboxylate 151
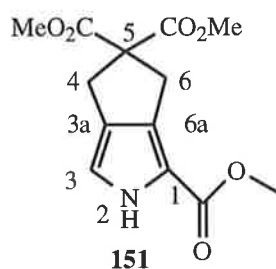
Dimethyl 3-(phenylsulfonyl)-3-cyclopentene-1,1-dicarboxylate (0.2 g, 0.62 mmol) and methyl isocyanoacetate (0.14 g, 1.2 mmol) were reacted following the general procedure. EtOAc (3 x 15 ml) was used as the extracting solvent. Column chromatography of the crude product on silica gel using EtOAc/hexane (50:50) as eluant gave *trimethyl 2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1,5,5-carboxylate* as a white crystalline powder (0.12 g, 70%). Recrystallisation of the product from EtOH gave white crystals. M.p. 116-120°C; υ_{max} (KBr pellet); 3283 (NH), 1739 (C=O), 1679 (C=O), 1447, 1435, 1349, 1283, 1262, 1199, 1132, 1101, 1017, 862, 774, 596; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.30 [s, 2H, C(4 or 6)H],

3.48 [s, 2H, C(4 or 6)H], 3.67 [s, 6H, 2 x OCH$_3$], 3.80 [s, 3H, OCH$_3$], 6.56 [s, 1H, C(3)H], 9.12 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 28.98 [C(4 or 6)], 30.18 [C(4 or 6)], 46.68 [OCH$_3$], 48.22 [OCH$_3$], 48.32 [OCH$_3$], 57.08 [C(5)], 110.72 [C(3)], 123.32 [C(1)], 123.39 [C(3a)], 125.18 [C(6a)], 157.10 [C=O], 167.09 [C=O], 167.79 [C=O]; m/z: MH$^+$ 295 (13%), 221 (14), 149 (15), 97 (28), 77 (28), 68 (64), 55 (67), 42 (98), 41 (100); Exact Mass Calcd for C$_{13}$H$_{15}$NO$_6$ 281.0899. Found 281.0895.

Benzyl 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate 148

148
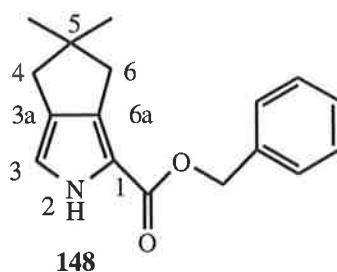
4,4-Dimethyl-1-(*p*-toluenesulfonyl)-cyclopentene (1.49 g, 6.0 mmol) and benzyl isocyanoacetate (1.25 g, 7.2 mmol) were reacted following the general procedure. EtOAc (4 x 20 ml) was used as the extracting solvent; CH$_2$Cl$_2$ was found to be unsuitable as an extracting solvent. *Benzyl 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1-carboxylate* was isolated as an orange powder (1.38 g, 86%). Product can be recrystallised from hexane to give white fluffy crystals. M.p. 91-94°C; Found: C 75.87, H 7.32, N 4.96; C$_{17}$H$_{19}$NO$_2$ requires C 75.81, H 7.11, N 5.20%; υ_{max} (nujol); 3290 (NH), 1686 (C=O), 1607, 1304, 1141, 1122, 736; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.18 [s, 6H, 2 x CH$_3$], 2.46 [s, 2H, C(4 or 6)H], 2.66 [s, 2H, C(4 or 6)H], 5.28 [s, 2H, CH$_2$Ar], 6.58 [d, 2H, C(3)H], 7.38-7.41 [m, 5H, Ar], 8.65 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 29.35 2 x [CH$_3$], 40.38 [C(6)], 41.48 [C(4)], 46.93 [C(5)], 65.49 [CH$_2$O], 114.99 [C(3)], 115.37 [C(1)], 127.91 [Ar], 128.09 [Ar], 128.58 [Ar], 131.12 [C(3a)], 136.64 [C(6a)], 160.10 [C=O]; m/z: M$^{+\cdot}$ 269 (100%), 224 (8), 178 (92), 160 (84), 134 (18), 91 (86).

Benzyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate 161 CAS Reg. No. [143064-84-0][107]

161
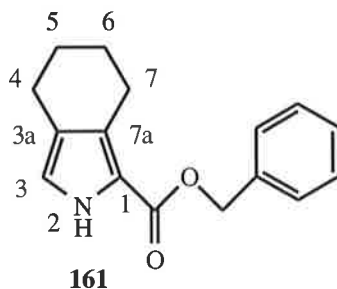
1-(*p*-Toluenesulfonyl)-cyclohexene (0.75 g, 3.18 mmol) and benzyl isocyanoacetate (0.83 g, 4.77 mmol) were reacted following the general procedure. CH_2Cl_2 (4 x 20 ml) was used as the extracting solvent. Column chromatography over silica gel using EtOAc/hexane (30:70) as eluant gave *benzyl 4,5,6,7-tetrahydro-2H-isoindole-1-carboxylate* (0.7 g, 86%) as an oil which solidified upon standing to a colourless crystalline compound. M.p. 94-98°C (lit. m.p. 88-90°C);[14] υ_{max} (nujol); 3451 (NH), 3305, 1604 (C=O), 1517, 1455, 1189, 1170; [1]H n.m.r. (300 MHz/CDCl3); δ_H: 1.72 [m, 4H, CH_2], 2.52 [m, 2H, CH_2], 2.81 [m, 2H, CH_2], 5.28 [s, 2H, CH_2Ar], 6.62 [d, 1H, CH], 7.32-7.38 [m, 5H, Ar], 8.78 [brs, 1H, NH]; [13]C n.m.r. (75 MHz/CDCl3); δ_C: 21.76 [C(5, 6)], 23.17 [C(4, 7)], 65.47 [CH_2], 117.43 [C3], 119.07 [C1], 122.35 [C3a], 127.70 [C7a], 127.85 [Ar], 128.59 [Ar], 129.73 [Ar], 136.62 [Ar], 162.00 [C=O]; m/z: M+· 255 (90%), 210 (12), 164 (100), 148 (14), 91 (88), 77 (28).

Physical and spectral data consistent with literature values

Methyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate 159 CAS Reg. No. [60652-00-8][14]

159
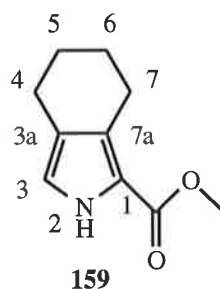
1-(*p*-Toluenesulfonyl)cyclohex-1-ene (4.0 g, 17 mmol) and methyl isocyanoacetate (2.5 g, 25 mmol) were reacted following the general procedure. CH_2Cl_2 (4 x 20 ml) was used as the extracting solvent. Column chromatography over silica gel using EtOAc/hexane (20:80) as eluant gave *methyl 4,5,6,7-tetrahydro-2H-isoindole-1-carboxylate* (2.20 g, 73%) was isolated as a colourless crystalline compound. Product can be crystallised from ethanol/water to give colourless crystals. M.p. 97-99°C (lit. m.p. 93-94°C);[14] υ_{max} (KBr pellet); 3298 (NH), 2943, 2852, 2359, 1662 (C=O), 1442, 1397, 1329, 1249, 1145, 1105, 1029, 958, 917, 774, 597; [1]H n.m.r. (300 MHz/CDCl3); δ_H: 1.67 [m, 4H, C(5, 6)H], 2.49 [m, 2H, C(7)H], 2.79 [m, 2H, C(4)H], 3.79 [s, 3H, OCH3], 6.61 [d, 2H, C(3)H], 8.65 [brs, 1H, NH]; [13]C n.m.r. (75 MHz/CDCl3); δ_C: 21.73 [C(4)], 23.15 [C(5, 6 or 7)], 23.26 [C(5, 6 or 7)], 23.66 [C(5, 6 or 7)], 50.79 [OCH3], 117.88 [C(1)], 118.34 [C(3)], 122.39 [C(3a)], 128.65 [C(7a)], 164.16 [C=O]; m/z: M+· 179 (100%), 164 (50), 146 (50), 119 (50), 91 (42), 39 (48).

Experimental

Ethyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate 160 CAS Reg. No. [65880-17-3][62]

160
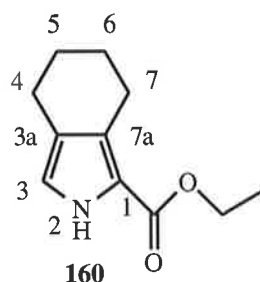
1-(*p*-Toluenesulfonyl)-cyclohexene (4.0 g, 16 mmol) and ethyl isocyanoacetate (2.87 g, 25 mmol) were reacted following the general procedure. Ether (2 x 50 ml) was used as the extracting solvent. *Ethyl 4,5,6,7-tetrahydro-2H-isoindole-1-carboxylate* was isolated as a white crystalline compound (2.25 g, 97%). Crude product can be recrystallised from aq. ethanol or hexane. M.p. 70-75°C (lit. m.p. 77.5-80.5°C);[14] υ_{max} (KBr pellet); 3298 (NH), 2922, 2853, 2358, 1683 (C=O), 1478, 1423, 1389, 1329, 1272, 1248, 1171, 1148, 1111, 1034, 774, 750, 603; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.31 [t, 3H, CH$_3$], 1.68 [m, 4H, C(5, 6)H], 2.51 [m, 2H, C(7)H], 2.78 [m, 2H, C(4)H], 4.25 [s, 2H, OCH$_2$], 6.61 [d, 2H, C(3)H], 8.82 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 13.99 [CH$_3$], 21.83 [C(4)], 22.60 [C(5, 6 or 7)], 23.27 [C(5, 6 or 7)], 23.33 [C(5, 6 or 7)], 59.68 [OCH$_2$], 117.81 [C(1)], 118.64 [C(3)], 122.19 [C(3a)], 128.18 [C(7a)], 161.74 [C=O]; m/z: M$^{+\cdot}$ 193 (100%), 164 (98), 146 (78), 119 (68), 93 (22), 91 (71), 65 (39), 39 (58).

Physical and spectral data consistent with literature values

N-Morpholino 4,5,6,7-tetrahydro-2*H* isoindole-1-carboxamide 162

1-(*p*-Toluenesulfonyl)-cyclohexene (1.53 g, 6.50 mmol) and N-(isocyanoacetyl)morpholine (1.50 g, 9.74 mmol) were reacted following the general procedure. CH_2Cl_2 (4 x 20 ml) was used as the extracting solvent. *N-Morpholino 4,5,6,7-tetrahydro-2H isoindole-1-carboxamide* was isolated as a colourless oil which crystallised upon standing (0.80 g, 52%). M.p. 117-120°C; Exact Mass Calcd for $C_{13}H_{18}N_2O_2$ 234.13682. Found 234.13653; υ_{max} (nujol); 3205 (NH), 1670 (C=O), 1601; ^1H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.67 [m, 4H, C(5, 6)H], 2.46 [m, 2H, C(4, 7)H], 3.57 [m, 4H, CH$_2$N], 3.62 [s, 4H, CH$_2$O], 6.53 [d, 1H, C(3)H], 10.03 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.28 [C(5)], 23.10 [C(6)], 23.29 [C(4)], 23.49 [C(7)], 45.71 2 x [OCH$_2$], 66.69 2 x [NCH$_2$], 117.56 [C(1)], 119.76 [C(3)], 120.01 [C(3a)], 121.61 [C(7a)], 164.81 [C=O]; m/z: M$^{+\cdot}$ 234 (90%), 148 (100), 147 (53), 121 (40), 86 (38), 56 (27).

Methyl 5,5-dicyano-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate 150
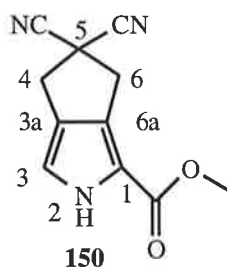
4,4-Dicyano-1-(*p*-toluenesulfonyl)-cyclopentene (0.26 g, 1 mmol) and methyl isocyanoacetate (0.20 g, 2 mmol) were reacted following the general procedure. EtOAc (4 x 20 ml) was used as the extracting solvent. Column chromatography of the crude product on silica gel using CH_2Cl_2/hexane (40:60) as eluant gave *methyl 5,5-dicyano-2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1-carboxylate* as an off white crystalline solid (0.10 g, 46%). M.p. 148-152°C; Exact Mass Calcd for $C_{11}H_9N_3O_2$ 215.0695. Found 215.0694; υ_{max} (KBr pellet); 3353 (NH), 3153, 2956, 2915, 2359, 2257, 1685 (C=O), 1514, 1457, 1449, 1407, 1343, 1305, 1279, 1235, 1199, 1134, 1087, 1051, 1022, 985, 815, 774, 595; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 3.51 [s, 2H, C(6)H], 3.67 [s, 2H, C(4)H], 3.84 [s, 3H, CH$_3$O], 6.73 [d, 1H, C(3)H], 9.08 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 38.65 [C(5)], 38.86 [C(6)], 39.43 [C(4)], 51.70 [CH$_3$O], 115.77 [C(3)], 116.17 [2 x(CN)], 116.33 [C(1)], 124.73 [C(3a)], 129.65 [C(4a)], 160.64 [C=O]; m/z: M$^{+\cdot}$ 215 (12%), 183 (12), 161 (4), 155 (11), 129 (9), 91 (21), 69 (28), 55 (42), 41 (100).

Methyl 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1-carboxylate 147
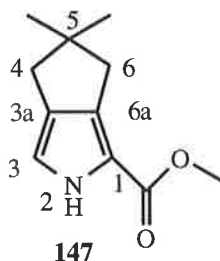
4,4-Dimethyl-1-(*p*-toluenesulfonyl)-cyclopentene (0.55 g, 2.2 mmol) and methyl isocyanoacetate (0.44 g, 4.4 mmol) were reacted following th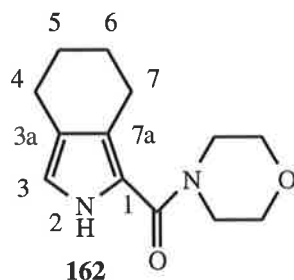e general procedure. ether (2 x 15 ml) was used as the extracting solvent. *Methyl 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1-carboxylate* was isolated as pale yellow crystals (0.34 g, 88%). Column chromatography of the crude product on silica gel using EtOAc/hexane (40:60) as eluant gave pure product. M.p. 116-120°C; Found: C 68.10, H 7.60, N 7.12; $C_{11}H_{15}NO_2$ requires C 68.37, H 7.82, N 7.24%; υ_{max} (nujol); 3288 (NH), 1698 (C=O),

1509, 1409, 1376, 1363, 1342; ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.18 [s, 6H, 2 x CH$_3$], 2.45 [s, 2H, C(6)H], 2.64 [s, 2H, C(4)H], 3.81 [s, 3H, CH$_3$], 6.67 [d, 1H, C(3)H], 8.76 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 29.32 2 x [CH$_3$], 40.36 [C(5)], 41.57 [C(4)], 46.91 [C(6)], 51.09 [CH$_3$], 115.08 [C(3)], 115.52 [C(1)], 131.02 [C(3a)], 137.52 [C(6a)], 162.03 [C=O]; m/z: M$^{+\cdot}$ 193 (82%), 178 (28), 161 (32), 134 (33), 118 (38), 91 (52), 69 (56), 41 (98), 39 (100).

Methyl 5-(4-nitrophenyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-1-carboxylate 157
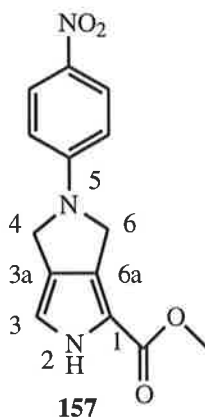
1-(4-Nitrophenyl)-3-(phenylsulfonyl)-2,5-dihydro-1H-pyrrole (39 mg, 0.13 mmol) and methyl isocyanoacetate (26 mg, 0.26 mmol) were reacted following the general procedure. EtOAc (3 x 15 ml) was used as the extracting solvent. *Methyl 5(4-nitrophenyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-1-carboxylate* was isolated as a pale yellow powder (10 mg, 27%) which was used without further purification. Column chromatography of the crude product on silica gel using EtOAc/hexane (65:35) as eluant gave pure product as a yellow powder. M.p. 240-244°C; Exact Mass Calcd for C$_{14}$H$_{13}$N$_3$O$_4$ 287.09060. Found 287.09076; υ_{max} (KBr pellet); 3287 (NH), 2920, 2850, 1708 (C=O), 1600, 1521, 1497, 1497, 1397, 1291, 1146, 1113, 1026, 827, 751; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 3.87 [s, 3H, OCH$_3$], 4.53 [s, 2H, C(4 or 5)H], 4.65 [s, 2H, C(4 or 5)H], 6.57 [m, 2H, Ar], 6.78 [d, 1H, C(3)H], 8.17 [d, 2H, Ar], 9.01 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C:

50.85 [C(4 or 5)], 48.88 [C(4 or 5)], 48.00 [CH$_3$], 109.93 [*o*-Ar], 113.68 [C(3)], 114.37 [C(1)], 123.34 [C(3a)], 125.80 [*m*-Ar], 129.33 [C(4a)], 136.39 [*p*-Ar], 151.57 [N-Ar], 160.34 [C=O], carbon (*p*-NO$_2$) not observed.

Experimental in Described in Chapter 4

5,5-Dimethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylic acid 177
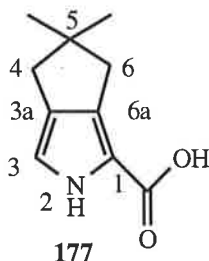
Benzyl 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylate (0.23 g, 0.85 mmol) was dissolved in EtOH (30 ml) and Pd/C 10% (0.10 g) was added. This mixture was shaken in a Parr® hydrogenation apparatus under hydrogen (50 psi) for 48 h. The reaction mixture was filtered through a plug of celite and the solvent removed to give *5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1-carboxylic acid* (0.15 g, 98%) as an off white solid. M.p. 160-165°C; Exact Mass Calcd for $C_{10}H_{13}N_1O_2$ 179.0946. Found 179.09445; υ_{max} (nujol); 3279 (NH), 1686 (C=O), 1607, 1300, 1277, 1176, 1122; ^{1}H n.m.r. (200 MHz/CDCl$_3$/DMSO); δ_H: 0.92 [s, 6H, 2 x CH$_3$], 2.18 [s, 2H, C(6)H], 2.41 [s, 2H, C(4)H], 6.19 [s, H, C(3)H], 9.25 [brs, 1H, OH], 9.75 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 28.98 2 x [CH$_3$], 44.50 [C(5)], 41.09 [C(6)], 46.31 [C(4)], 114.23 [C(3)], 117.37 [C(1)], 129.44 [C(3a)], 135.42 [C(6a)], 165.79 [C=O]; m/z: M$^{+\cdot}$ 179 (100%), 161 (54), 156 (50), 134 (84), 120 (92), 94 (44), 86 (96), 58 (43), 39 (37).

5,5-Dimethyl-2,4,5,6-tetrahydrocyclopenta[3,4-*c*]pyrrole 179

179
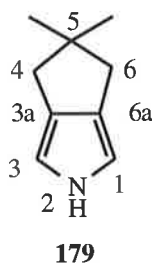
5,5-Dimethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole-1-carboxylic acid (0.84 g, 4.7 mmol) was dissolved in ethanolamine (6 ml) and refluxed for 2h. The reaction mixture was allowed to cool to room temperature then poured onto ice in a 100 ml beaker. The ice was allowed to melt and then the mixture transferred to a separating funnel and extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$, filtered and the solvent removed to give *5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[3,4-c]pyrrole* (0.35 g, 67%) as an off white powder. Crude product could be purified by column chromatography over silica gel using CH_2Cl_2/hexane (30:70) as eluant, giving white fluffy crystalline product. M.p. 67-70°C; υ_{max} (nujol); 3368 (NH); ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.16 [s, 6H, CH_3], 2.44 [s, 4H, C(4, 6)H], 6.39 [d, 2H, C(1, 3)H], 7.84 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 24.81 2 x [CH_3], 34.3 [C(5)], 35.65 [C(4, 6)], 105.08 [C(1, 3)], 124.82 [C(3a, 6a)]; m/z: M$^{+\cdot}$ 135 (58%), 120 (94), 94 (85), 80 (35), 39 (100).

3,5-Dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylic acid 175

175
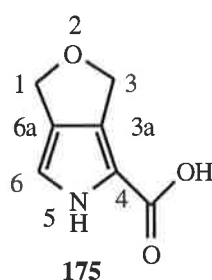
Methyl 3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (1.90 g, 7.8 mmol) was dissolved in EtOH (30 ml) then Pd/C 10% (1.0 g) was added. To this mix was added NEt$_3$ (3 drops). This mixture was shaken in a Parr® hydrogenation apparatus under hydrogen (50 psi) for 18 h. The reaction mixture was filtered through a plug of celite and the solvent removed to give *3,5-dihydro-1H-furo[3,4-c]pyrrole-4-carboxylic acid* (1.13 g, 95%) as an off white solid. M.p. 186-190°C; υ_{max} (nujol); 2400-3400 (OH), 1705 (C=O); ^{1}H n.m.r. (200 MHz/CDCl$_3$/DMSO); δ_H: 3.25 [brs, 1H, OH], 4.79 [s, 2H, C(6)H], 4.91 [s, 2H, C(4)H], 6.59 [d, 1H, C(3)H], 7.72 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$:DMSO); δ_C: 66.08 [C(6)], 66.80 [C(4)], 112.12 [C(3)], 118.31 [C(1)], 131.80 [C(3a)], 136.35 [C(6a)], 166.95 [C=O]; m/z: M$^{+\cdot}$ 153 (100%), 152, 124.

3,5-Dihydro-1*H*-furo[3,4-*c*]pyrrole 172

172
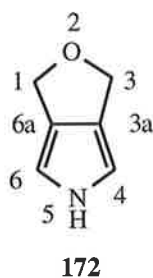
3,5-Dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylic acid (1.13 g, 7.4 mmol) was dissolved in ethanolamine (15 ml) and refluxed for 2h. The reaction mixture was allowed to cool to room temperature then poured onto ice in a 200 ml beaker. The ice was allowed to melt and then the mixture transferred to a separating funnel and extracted with CH$_2$Cl$_2$ (4 x 30 ml). The combined organic layers were washed with brine (30 ml), dried over MgSO$_4$, filtered and the solvent removed to give *3,5-dihydro-1H-furo[3,4-c]pyrrole* (0.51 g, 63%) as an off white powder. M.p. 123-125°C; Exact Mass Calcd for C$_6$H$_7$NO 109.052. Found 109.052; υ_{max} (nujol); 3210 (NH); ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 4.89 [s, 4H, C(4, 6)H], 6.48 [d, 2H, C(1, 3)H], 8.35 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 67.24 [C(1, 3)], 107.18 [C(3a, 6a)], 127.59 [C(4, 6)]; m/z: M$^{+\cdot}$ 109 (100%), 108 (75), 80 (59), 53 (36).

4,5,6,7-Tetrahydro-2*H*-isoindole-1-carboxylic acid 178
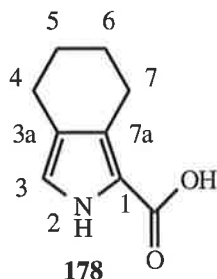
Benzyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (0.51 g, 2 mmol) was thoroughly dissolved in EtOH (40 ml) then Pd/C 10% (0.2 g) was added. This mixture was shaken in a Parr® hydrogenation apparatus under hydrogen (50 psi) for 16 h. The reaction mixture was filtered through a plug of celite and the solvent removed to give *4,5,6,7-tetrahydro-2H-isoindole-1-carboxylic acid* (0.34 g, 100%) as an off white solid. M.p. 215-220°C; υ_{max} (KBr pellet); 3353 (NH), 2400-3600 (OH), 2932, 2633, 1661 (C=O), 1471, 1446, 1329, 1279, 1252, 1167, 1143, 1107, 1023, 920, 905, 785, 699, 594; ^{1}H n.m.r. (200 MHz/CDCl$_3$); δ_H: 1.74 [m, 4H, CH$_2$], 2.55 [m, 2H, CH$_2$], 2.82 [m, 2H, CH$_2$], 6.70 [s, 1H, CH], 8.80 [brs, 1H, NH]; m/z: M$^{+\cdot}$ 165 (62%), 137 (41), 120 (58), 119 (100), 93 (62), 91 (50), 67 (35), 39 (38).

4,5,6,7-Tetrahydro-2*H*-1-isoindole 180 CAS Reg. No. [51649-35-5]
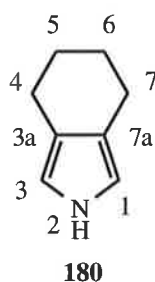
4,5,6,7-Tetrahydro-2*H*-1-isoindolecarboxylic acid (0.20 g, 1.2 mmol) was dissolved in ethanolamine (4 ml) and refluxed for 2h. The reaction mixture was allowed to cool to room temperature then poured onto ice in a 100 ml beaker. The ice was allowed to melt and then the mixture transferred to a separating funnel and extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$, filtered and the solvent removed to give *4,5,6,7-tetrahydro-2H-1-isoindole* (0.14 g, 96%) as olive crystals. Crude product could be purified by column chromatography over silica gel using EtOAc/hexane (40:60) as eluant, giving colourless crystalline product. ^1H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.83 [m, 4H, C(5, 6)H], 2.69 [m, 4H, C(4, 7)H], 6.51 [d, 2H, C(2,5)H], 7.94 [brs, 1H, NH]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 21.83 [C(5, 6)], 24.02 [C(4, 7)], 113.09 [C(1, 3)], 119.43 [C(3a, 7a)].

$2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-Octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b*,*g*,*l*,*q*]porphyrin

181
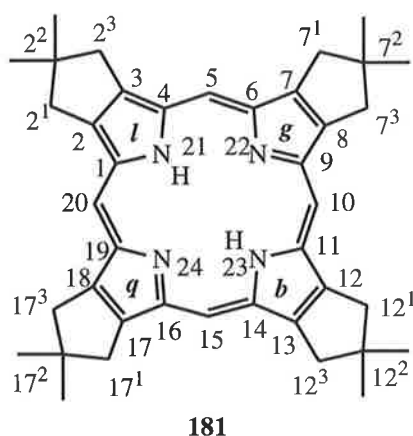
Method A

A mixture of 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole (0.20 g, 1.8 mmol), formalin (0.15 ml, 1.9 mmol) and NaCl (10 mg) in benzene (60 ml) was treated with PTSA

(0.07 g, 0.36 mmol). The mixture was stirred at reflux for 2h then oxygen was bubbled through the solution for 12h, to afford a black solution. The benzene was removed by rotary evaporation and the residue taken up in CHCl$_3$. The crude solution was washed with 1M NaOH (30 ml), water (2 x 20 ml) and the solvent removed. The crude residue was chromatographed on silica gel using CH$_2$Cl$_2$/hexane (90:10) to give *2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2-octamethyl-2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3-octahydro-2^1H,7^1H,12^1H,17^1H tetrakis(cyclopenta)-[b,g,l,q]porphyrin* (20 mg, 5%). M.p. >320°C; Exact Mass Calcd for C$_{40}$H$_{46}$N$_4$ 582.3722. Found 582.3712; υ_{max} (KBr plate); 3313, 2950, 2917, 2839, 2363, 1685, 1458, 1362, 1458, 1362, 1238, 1238, 1121, 1093, 960, 840, 727, 669, 530; visible spectrum λ_{max} (CHCl$_3$) 386 nm (log ε 5.3), 496 (4.2), 528 (3.9) 565 (3.8), 618 (3.4); ^{1}H n.m.r. (600 MHz/CDCl$_3$); δ_H: -4.38 [brs, 1H, NH], 1.69 [s, 24H, 8 x CH$_3$], 3.94 [s, 16H, C(2a,2c,7a,7c,12a,12c,17a,17c)H], 9.86 [s, 4H, C(5, 10, 15, 20)H]; ^{13}C n.m.r. (75 MHz/CDCl$_3$); δ_C: 31.25 8 x [CH$_3$], 44.02 [C(2a,2c,7a,7c,12a,12c,17a,17c)], 49.25 [C(2b, 7b, 12b, 17b)], 100.51 [C(5, 10, 15, 20)]; m/z: M$^{+\cdot}$ 582 (100%), 291 (27).

Method B

A solution of methyl 5,5-dimethyl-2,4,5,6-tetrahydrocyclopenta[c]pyrrole-1-carboxylate (0.50 g, 2.6 mmol) in THF (18 ml) was added dropwise to a suspension of 95% LiAlH$_4$ (0.31, 7.8 mmol) in THF (5 ml) at 0°C. The reaction mixture was stirred for 3h under N$_2$ during which time the solution was allowed to warm to room temperature. Excess LiAlH$_4$ was carefully quenched by addition of EtOAc (2.5 ml) followed by dropwise addition of saturated NH$_4$Cl solution until no effervescence was observed. The reaction mixture was filtered, and the fine granular precipitate was washed with EtOAc (30 ml). The filtrate was dried with MgSO$_4$, filtered and the solvent removed (warm water was used with a dry ice/acetone condenser). The yellow oil was taken up in dry CH$_2$Cl$_2$ (10 ml) then dimethoxymethane (1.97 g, 25.9 mmol) and PTSA (0.08 g, 0.43 mmol) were added to a 2-necked round bottom flask. The reaction mixture was stirred for 24 h under a N$_2$ atmosphere. A solution of *p*-chloranil (0.76 g, 3.1

mmol) in CH_2Cl_2 (10 ml) was added and stirring continued under oxygen for 24 h. The reaction mixture was washed with 1M NaOH (50 ml) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml) and the organic layers combined. The combined organic layers were then dried with $MgSO_4$, filtered and then concentrated under reduced pressure to give a black residue which was chromatographed on silica gel using a gradient of CH_2Cl_2/hexane (90:10 to 50:50). Recrystallisation of the crude product from $CHCl_3$/MeOH gave *$2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[b,g,l,q]porphyrin* (90 mg, 6%) as a purple powder.

Data as above

$2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-Octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[*b,g,l,q*]porphyrinato)nickel(II) 182

$Ni(OAc)_2.(H_2O)_4$ was added to a solution of $2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-octamethyl-2,3,7,8,12,13,17,17,18-cyclopentaporphyrin (2 mg, 3.4 μmol) in DMF (3 ml), the reaction mixture became homogenous and cherry red in colour. The reaction mixture was stirred at reflux for 3h then allowed to cool to room temperature. The reaction mixture was diluted with H_2O (5 ml) and extracted with $CHCl_3$ (10 ml). The organic layer was then washed with H_2O (4 x 5 ml). The extract was dried with $MgSO_4$, filtered and the solvent removed to give *$2^2,2^2,7^2,7^2,12^2,12^2,17^2,17^2$-octamethyl-$2^2,2^3,7^2,7^2,12^2,12^3,17^2,17^3$-octahydro-$2^1H,7^1H,12^1H,17^1H$ tetrakis(cyclopenta)-[b,g,l,q]porphyrinato)nickel(II)* (2 mg, 92%) as a red powder. M.p. >300°C; Exact Mass Calcd for $C_{40}H_{44}N_4{}^{58}Ni$ 638.2919. Found 638.2919; υ_{max} (KBr pellet); 2948, 2923, 2859, 2838, 1738, 1674, 1652, 1532, 1462, 1439, 1360, 1264, 1126, 1093, 1093, 996, 843, 802, 734, 692; visible spectrum λ_{max} 384 nm (log ε 5.3), 540 (4.3), 506 (4.1) 236 (4.6); δ_C: 30.46 8 x [CH_3], 43.76

[C(2a,2c,7a,7c,12a,12c,17a,17c)], 47.75 [C(2b, 7b, 12b, 17b)], 99.81 [C(5,10,15,20)], 136.31 [C(1,4,6,9,11,14,16,19)H], 149.90 [C(2,3,7,8,12,13,17,18)]; m/z: $M^{+\cdot}638$ (100%), 319 (17) 219 (8).

(Iodomethyl)trimethylammonium iodide

Triethylamine (13 g, 0.22 mol) was distilled into a solution of diiodomethane (78 g, 0.29 mol) in a mixture of dioxane (13 ml) and anhydrous ethanol (98 ml). The reaction mixture was allowed to sit for 3 days during which time product crystallised out of solution as white crystals. *(Iodomethyl)trimethylammonium iodide* (44.85 g, 100%) was collected by filtration and dried. M.p. 184-189°C (dec.) (lit. double m.p. 190°C (dec.)/240°C (dec.).[147]

Dimethyl(methylene)ammonium iodide (Eschenmoser's salt) CAS Reg. No. [33797-51-2][147]

(Iodomethyl)trimethylammonium iodide (44.85 g, 0.09 mol) was refluxed in freshly distilled dry sulfolane (130 ml) under a stream of N_2 which conveyed the MeI formed during the decomposition into an dry ice/acetone cold trap. After 15 min the reaction mixture was cooled to 15°C in an ice water bath. Upon cooling the product began to crystalise from solution. The crude product was filtered off under a N_2 atmosphere and washed with CCl_4 (5 x 50 ml). The crude product was dried under vacumn for 24 h then sublimed, 150°C (0.01 mm Hg) to give *dimethyl(methylene)ammonium iodide* (16.41 g, 98%) as a white crystalline solid. M.p 205-210°C (dec.) (lit. m.p. 240°C (dec.))[147]

Melting point matched that of an authentic sample.

Bis-1,3-(dimethylaminomethyl)isoindole 185[76]

185
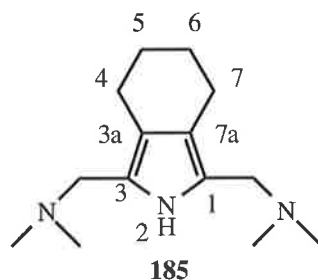
4,5,6,7-Tetrahydro-2H-isoindole (0.20 g, 1.7 mmol) was added to a solution of freshly sublimed Eschenmoser's reagent (0.9 g, 4.9 mmol) in MeNO$_2$ (20 ml). The yellow reaction mixture was stirred at 40°C for 1h during which time the reaction mixture became cloudy. The reaction mixture was allowed to cool to room temperature then the solvent removed under reduced pressure using a hot water bath and a dry ice condenser. The residue was taken up in CH$_2$Cl$_2$ (20 ml) and washed with saturated Na$_2$CO$_3$ solution (3 x 10 ml). The organic layer was dried over MgSO$_4$, filtered and the solvent removed to give *bis-1,3-(dimethylaminomethyl)isoindole* (0.13 g, 36%) as a dark brown powder. ^{1}H n.m.r. (300 MHz/CDCl$_3$); δ_H: 1.70 [m, 4H, C(5, 6)H], 2.19 [s, 12H, NCH$_3$], 2.46 [m, 4H, C(4, 7)H], 3.28 [s, 4H, NCH$_2$], 8.16 [brs, 1H, NH].

Physical and spectral data consistent with literature values

Bis-1,3-(dimethylaminomethyl)-3,5-dihydro-1H-furo[3,4-c]pyrrole 184

186
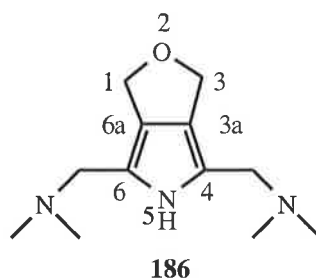
3,5-Dihydro-1*H*-furo[3,4-*c*]pyrrole (0.20 g, 1.8 mmol) was added to a solution of freshly sublimed Eschenmoser's reagent (1.0 g, 5.5 mmol) in $MeNO_2$ (20 ml). The yellow reaction mixture was stirred at 40°C for 1h during which time the reaction mixture became cloudy. The reaction mixture was allowed to cool to room temperature then the solvent removed under reduced pressure using a hot water bath and a dry ice condenser. The residue was taken up in CH_2Cl_2 (20 ml) and washed with saturated Na_2CO_3 solution (3 x 10 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed to give bis-1,3-(dimethylaminomethyl)-*3,5-dihydro-1H-furo[3,4-c]pyrrole* (0.25 g, 60%) as an orange powder. ^1H n.m.r. (300 MHz/$CDCl_3$); δ_H: 2.18 [s, 12H, 4 x CH_3], 3.26 [s, 4H, NCH_2], 4.78 [s, 4H, C(1, 3)H], 8.16 [brs, 1H, NH].

Methyl 3-{[3-(methoxycarbonyl)-4,5,6,7-tetrahydro-2*H*-1-isoindolyl]methyl}-4,5,6,7-tetrahydro-2*H*-1-isoindolecarboxylate 193

A mixture of methyl 4,5,6,7-tetrahydro-2*H*-isoindole-1-carboxylate (1.00 g, 5.6 mmol) and paraformaldehyde (0.67 g, 22.3 mmol) in EtOH (6 ml) was treated with two drops of HCl then stirred at reflux for 2h under N_2. The mixture was cooled to room temperature then filtered to give *methyl 3-{[3-(methoxycarbonyl)-4,5,6,7-tetrahydro-2H-1-isoindolyl]methyl}-4,5,6,7-tetrahydro-2H-1-isoindolecarboxylate* (0.86 g, 83%) as a white powder. Sublimes approx. 200-210°C; υ_{max} (nujol); 3324 (NH), 1708, 1642 (C=O), 1273, 1211, 1130; ^1H n.m.r. (200 MHz/$CDCl_3$); δ_H: 1.69 [m, 4H, CH_2], 2.21 [s, 6H, NCH_3], 2.42 [m, 2H, CH_2], 2.77 [m, 2H, CH_2], 3.31 [s, 2H, NCH_2], 3.79 [s, 3H, OCH_3], 8.90 [brs, 1H, NH]; m/z: $M^{+\cdot}$ 370 (100%), 339 (12), 311 (33), 279 (20), 191 (78), 69 (82), 39 (42).

Methyl 6-{[6-(methoxycarbonyl)-3,5-dihydro-1*H*-furo[3,4-*c*]pyrrol-4-yl]-3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate 195

A mixture of 5*H*-1,3-dihydro-4-methoxycarbonyl-furo[3,4-*c*]pyrrole (0.25 g, 1.5 mmol) and dimethoxymethane (0.57 g, 7.5 mmol) in CH_2Cl_2 (10 ml) was treated with boron trifluoride diethyl etherate (0.13 g, 0.9 mmol) then stirred at room temperature for 24h under N_2. The mixture was treated with 10% aq. $NaHCO_3$ solution (40 ml) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 x 50 ml), dried over $MgSO_4$, filtered and the solvent removed to give crude *methyl 6-{[6-(methoxycarbonyl)-3,5-dihydro-1H-furo[3,4-c]pyrrol-4-yl]-3,5-dihydro-1H-furo[3,4-c]pyrrole-4-carboxylate* as shown by [1]H n.m.r. Column chromatography resulted in decomposition of the product. [1]H n.m.r. (200 MHz/CDCl_3); δ_H: 3.75 [s, 6H, OCH_3], 3.91 [s, 2H, CH_2], 4.66 [s, 4H, OCH_2], 4.91 [s, 4H, OCH_2], 10.02 [brs, 2H, NH].

2,3:7,8:12,13:17,18-Tetrakis(cyclohexamethylene)porphyrin 194[92]

A mixture of methyl 3-{[3-(methoxycarbonyl)-4,5,6,7-tetrahydro-2*H*-1-isoindolyl]methyl}-4,5,6,7-tetrahydro-2*H*-1-isoindolecarboxylate (0.50 g, 1.4 mmol), anhydrous LiCl (3.40 g, 81.1 mmol), paraformaldehyde (0.16 g, 5.4 mmol), and water (0.04 g, 2.8 mmol) in DMSO (20 ml) was heated at 200-210°C for 2 h with a small flow of oxygen. The reaction mixture was then poured into ice-cooled phosphate buffer pH 7 (100 ml). The solid was collected by vacuum filtration then chromatographed using alumina (basic, activated Brochman I) using CH_2Cl_2 to give *2,3:7,8:12,13:17,18-tetrakis(cyclohexamethylene)porphyrin* (0.02 g, 3%) as a violet powder. > M.p. 290°C (lit. 295-300°C); υ_{max} (KBr pellet); 3298 (NH), 2924, 2848, 1699, 1436, 1219, 1081, 1024, 836, 741, 675, 646; [1]H n.m.r. (300 MHz/CDCl_3); δ_H: -3.84 [brs, 2H, NH], 2.49 [m, 16H, CH_2], 4.10 [m, 16H, CH_2], 9.89 [s, 4H, CH]; m/z: M$^{+\cdot}$ 527 (25%), 136 (54), 69 (91), 54 (100).

Physical and spectral data consistent with literature values.

Attempted Formation of $2^2,7^2,12^2,17^2$-Tetraoxatetracyclopentaporphyrin 191

A solution of ethyl 3,5-dihydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (0.50 g, 2.7 mmol) in THF (18 ml) was added dropwise to a suspension of 95% LiAlH$_4$ (0.27 g, 6.9 mmol) in THF (5 ml) at 0°C. The reaction mixture was stirred for 3h under N$_2$ during which time the solution was allowed to warm to room temperature. Excess LiAlH$_4$ was carefully quenched addition of EtOAc (2.5 ml) followed by dropwise addition of saturated NH$_4$Cl solution until no effervescence was observed. The reaction mixture was filtered, and the fine granular precipitate was washed with EtOAc (20 ml). The filtrate was dried with MgSO$_4$, filtered and the solvent removed (warm water was used with a dry ice/acetone condenser). The yellow oil was taken up in dry CH$_2$Cl$_2$ (10 ml) then dimethoxymethane (2.87 g, 27.6 mmol) and PTSA (0.08 g, 0.43 mmol) were added to a 2-necked round bottom flask. The reaction mixture was stirred for 24 h under a N$_2$ atmosphere. A solution of *p*-chloranil (0.76 g, 3.1 mmol) in CH$_2$Cl$_2$ (10 ml) was added and stirring continued under oxygen for 24 h. The reaction mixture was washed with 1M NaOH (50 ml) and the organic layer separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 50 ml) and the organic layers combined. The combined organic layers were dried with MgSO$_4$, filtered and then concentrated under reduced pressure to give a black residue which could not be chromatographed on silica gel or alumina. The black residue was found to be insoluble in organic solvents and also water and could not be characterised.

Attempted Formation of $2^3,2^3,7^3,7^3,12^3,12^3,17^3,17^3$-Octamethyl $2^2,2^4,7^2,7^4,12^2,12^4,17^2,17^4$-octaoxacycloheptaporphyrin 197

A solution of ethyl 3,3-dimethyl-5,7-dihydro-1*H*[1,3]dioxepino[5,6-*c*]pyrrole-6-carboxylate (0.50 g, 2.1 mmol) in THF (15 ml) was added dropwise to a suspension of 95% LiAlH$_4$ (0.24 g, 6.4 mmol) in THF (17 ml) at 0°C. The reaction mixture was stirred for 3h under N$_2$ during which time the solution was allowed to warm to room temperature. Excess LiAlH$_4$ was carefully quenched addition of EtOAc (2.5 ml) followed by dropwise addition of saturated

NH4Cl solution until no effervescence was observed. The reaction mixture was filtered, and the fine granular precipitate was washed with EtOAc (20 ml). The filtrate was dried with MgSO4, filtered and the solvent removed (warm water was used with a dry ice/acetone condenser). The yellow oil was taken up in dry CH_2Cl_2 (10 ml) then dimethoxymethane (2.18 g, 21.0 mmol) and PTSA (0.07 g, 0.35 mmol) were added to a 2-necked round bottom flask. The reaction mixture was stirred for 24 h under a N_2 atmosphere. A solution of *p*-chloranil (0.75 g, 3.0 mmol) in CH_2Cl_2 (10 ml) was added and stirring continued under oxygen for 24 h. The reaction mixture was washed with 1M NaOH (50 ml) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml) and the organic layers combined. The combined organic layers were dried with MgSO4, filtered and then concentrated under reduced pressure to give a black residue which could not be chromatographed on silica gel or alumina. The black residue was found to be insoluble in organic solvents and also water and could not be characterised.

The ^1H n.m.r. spectrum of the intermediate α-hydroxymethyl pyrrole (3,3-dimethyl-5,7-dihydro-1*H*[1,3]dioxepino[5,6-*c*]pyrrol6-yl methanol) shows the reduction of the ethyl ester to be effective. ^1H n.m.r. (200 MHz/CDCl3); δ_H: 1.32 [s, 6H, 2 x C6(CH3)], 1.67 [brs, 1H, OH], 4.50 [s, 2H, CH2O], 4.75 [s, 4H, C(4, 8)H], 6.52 [d, 1H, C(7)H], 8.25 [brs, 1H, NH].

Attempted Reduction of *N*-morpholino 4,5,6,7-Tetrahydro-2*H* isoindole-1-carboxamide 162

Borane dimethylsulfide (0.44 ml, 2.2 mmol) was added dropwise to a refluxing solution of *N*-morpholino 4,5,6,7-tetrahydro-2*H* isoindole-1-carboxamide (0.30 g, 1.3 mmol) in THF (5 ml). After 15 minutes, the solvent was removed by rotary evaporation and the residue taken up in diethyl ether (5 ml). The solution was treated with *N,N,N',N'*-tetramethylethylenediamine (0.07 g, 0.6 mmol) which caused a percipitate to form immediately, the mixture was then stirred for 1 h. The suspension was centrifuged (2000 r.p.m. for 15 min) and the supernatant recovered. The solvent was removed to give an off white residue which proved to be complex mixture of products. No starting material was recovered.

Appendix 1
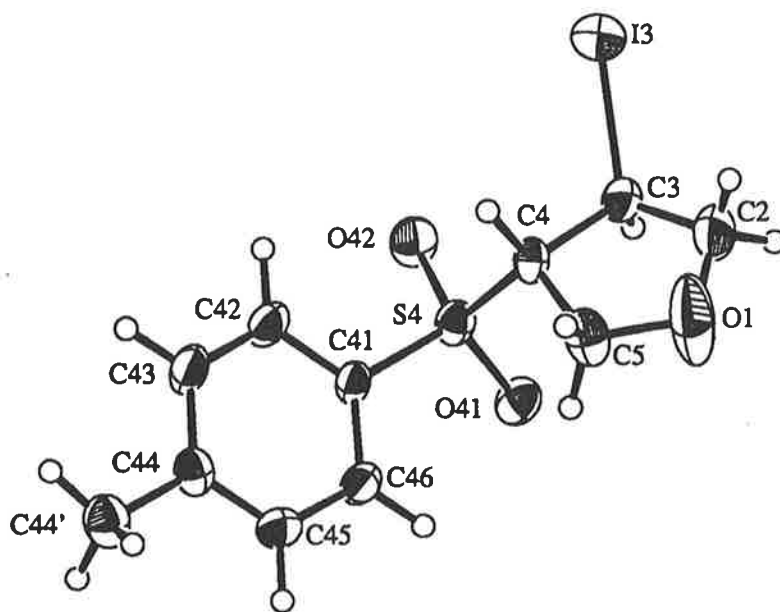
Figure A1. A plot of molecule **89** (by E.R.T. Tiekink). Crystal data.[108] $C_{11}H_{13}IO_3S$, monoclinic, $P12_1/a1$ (No. 14), a = 9.734(2) Å, b = 13.372(3) Å, c = 10.179(2) Å, β = 104.34(1)°, V = 1283.7 Å^3, Z = 4, R(F) = 0.036, R_w(F) = 0.028. Bond Lengths, bond angles and torsion angles follow.

Bond Lengths

atom	atom	distance	atom	atom	distance
I(3)	C(3)	2.131(5)	C(4)	C(5)	1.535(6)
S(4)	O(41)	1.441(3)	C(41)	C(42)	1.383(5)
S(4)	O(42)	1.438(3)	C(41)	C(46)	1.364(6)
S(4)	C(4)	1.794(4)	C(42)	C(43)	1.371(6)
S(4)	C(41)	1.761(4)	C(43)	C(44)	1.381(6)
O(1)	C(2)	1.309(6)	C(44')	C(44)	1.508(6)
O(1)	C(5)	1.359(5)	C(44)	C(45)	1.381(6)
C(2)	C(3)	1.515(7)	C(45)	C(46)	1.394(6)
C(3)	C(4)	1.535(6)			

Bond Angles

atom	atom	atom	angle	atom	atom	atom	angle
O(41)	S(4)	O(42)	118.3(2)	C(3)	C(4)	C(5)	103.6(4)
O(41)	S(4)	C(4)	108.0(2)	O(1)	C(5)	C(4)	107.1(4)
O(41)	S(4)	C(41)	109.1(2)	S(4)	C(41)	C(42)	118.9(3)
O(42)	S(4)	C(4)	106.9(2)	S(4)	C(41)	C(46)	119.9(3)
O(42)	S(4)	C(41)	109.4(2)	C(42)	C(41)	C(46)	121.3(4)
C(4)	S(4)	C(41)	104.3(2)	C(41)	C(42)	C(43)	119.5(4)
C(2)	O(1)	C(5)	113.3(5)	C(42)	C(43)	C(44)	120.8(4)
O(1)	C(2)	C(3)	109.3(5)	C(43)	C(44)	C(44')	121.1(4)
I(3)	C(3)	C(2)	113.2(4)	C(43)	C(44)	C(45)	118.7(4)
I(3)	C(3)	C(4)	114.2(3)	C(44')	C(44)	C(45)	120.2(4)
C(2)	C(3)	C(4)	101.9(4)	C(44)	C(45)	C(46)	121.2(4)
S(4)	C(4)	C(3)	110.1(3)	C(41)	C(46)	C(45)	118.5(4)
S(4)	C(4)	C(5)	113.2(3)				

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
I(3)	C(3)	C(2)	O(1)	143.8(5)	O(42)	S(4)	C(41)	C(46)	149.8(4)
I(3)	C(3)	C(4)	S(4)	104.6(3)	C(2)	O(1)	C(5)	C(4)	14.2(8)
I(3)	C(3)	C(4)	C(5)	-134.0(3)	C(2)	C(3)	C(4)	C(5)	-11.6(5)
S(4)	C(4)	C(3)	C(2)	-132.9(4)	C(3)	C(2)	O(1)	C(5)	-22.8(8)
S(4)	C(4)	C(5)	O(1)	119.3(4)	C(3)	C(4)	S(4)	C(41)	-176.8(3)
S(4)	C(41)	C(42)	C(43)	-179.6(4)	C(4)	S(4)	C(41)	C(42)	83.2(4)
S(4)	C(41)	C(46)	C(45)	179.9(4)	C(4)	S(4)	C(41)	C(46)	-96.1(4)
O(1)	C(2)	C(3)	C(4)	20.7(7)	C(5)	C(4)	S(4)	C(41)	67.7(3)
O(1)	C(5)	C(4)	C(3)	0.1(6)	C(41)	C(42)	C(43)	C(44)	0.5(8)
O(41)	S(4)	C(4)	C(3)	67.2(3)	C(41)	C(46)	C(45)	C(44)	-1.1(7)
O(41)	S(4)	C(4)	C(5)	-48.2(4)	C(42)	C(41)	C(46)	C(45)	0.6(7)
O(41)	S(4)	C(41)	C(42)	-161.6(4)	C(42)	C(43)	C(44)	C(44')	179.3(4)
O(41)	S(4)	C(41)	C(46)	19.1(4)	C(42)	C(43)	C(44)	C(45)	-1.0(8)
O(42)	S(4)	C(4)	C(3)	-61.0(3)	C(43)	C(42)	C(41)	C(46)	-0.3(7)
O(42)	S(4)	C(4)	C(5)	-176.5(3)	C(43)	C(44)	C(45)	C(46)	1.3(7)
O(42)	S(4)	C(41)	C(42)	-30.8(4)	C(44')	C(44)	C(45)	C(46)	-179.0(4)

Appendix 2
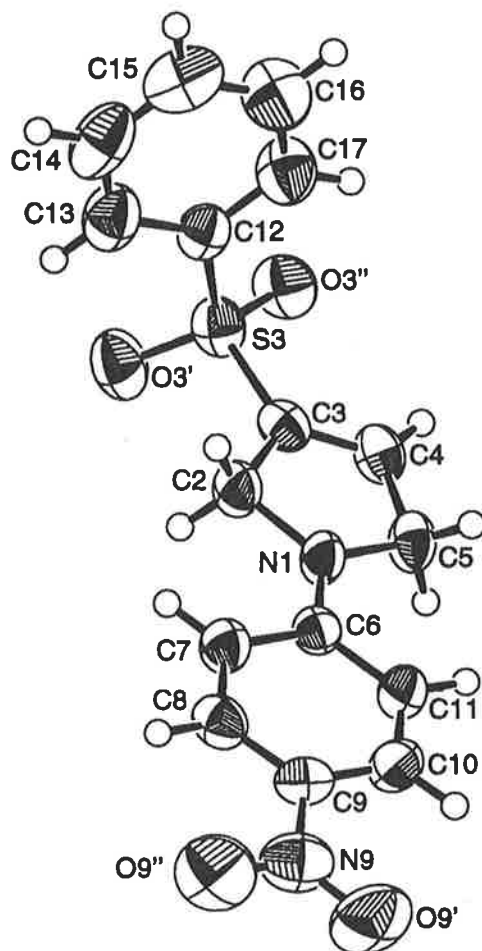
Figure A2. A plot of molecule **99** (by E.R.T. Tiekink). Bond Lengths, torsion angles and bond angles follow .

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
S(3)	O(3")	1.437 (3)	C(6)	C(7)	1.407 (5)
S(3)	O(3)	1.430 (3)	C(6)	C(11)	1.408 (6)
S(3)	C(3)	1.740 (4)	C(7)	C(8)	1.373 (6)
S(3)	C(12)	1.757 (5)	C(8)	C(9)	1.370 (6)
O(9')	N(9)	1.224 (5)	C(9)	C(10)	1.384 (6)
O(9")	N(9)	1.227 (5)	C(10)	C(11)	1.362 (6)
N(1)	C(2)	1.461 (5)	C(12)	C(13)	1.372 (6)
N(1)	C(5)	1.465 (5)	C(12)	C(17)	1.377 (6)
N(1)	C(6)	1.356 (5)	C(13)	C(14)	1.386 (8)
N(9)	C(9)	1.444 (6)	C(14)	C(15)	1.358 (8)
C(2)	C(3)	1.488 (6)	C(15)	C(16)	1.369 (7)
C(3)	C(4)	1.319 (5)	C(16)	C(17)	1.380 (7)
C(4)	C(5)	1.476 (6)			

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	angle		(1)	(2)	(3)	(4)	angle
S(3)	S(3)	C(2)	N(1)	-178.9 (3)		C(2)	N(1)	C(6)	C(11)	-178.0 (4)
S(3)	C(3)	C(4)	C(5)	-178.9 (3)		C(2)	C(3)	S(3)	C(12)	68.5 (4)
S(3)	C(12)	C(13)	C(14)	-178.2 (4)		C(2)	C(3)	C(4)	C(5)	-0.2 (5)
S(3)	S(12)	C(17)	C(16)	178.9 (4)		C(3)	S(3)	C(12)	C(13)	-104.0 (4)
O(3")	S(3)	C(3)	C(2)	-176.6 (3)		C(3)	S(3)	C(12)	C(17)	77.6 (4)
O(3")	S(3)	C(3)	C(4)	1.8 (4)		C(3)	C(2)	N(1)	C(5)	-3.8 (4)
O(3")	S(3)	C(12)	C(13)	141.9 (4)		C(3)	C(2)	N(1)	C(6)	178.6 (4)
O(3")	S(3)	C(12)	C(17)	-36.6 (4)		C(4)	C(3)	S(3)	C(12)	-113.0 (4)
O(3')	S(3)	C(3)	C(2)	-46.6 (4)		C(4)	C(5)	N(1)	C(6)	-178.7 (4)
O(3')	S(3)	C(3)	C(4)	131.9 (4)		C(5)	N(1)	C(6)	C(7)	-175.1 (4)
O(3')	S(3)	C(12)	C(13)	10.8 (4)		C(5)	N(1)	C(6)	C(11)	4.7 (4)
O(3')	S(3)	C(12)	C(17)	-167.7 (4)		C(6)	C(7)	C(8)	C(9)	1.7 (7)
O(9')	N(9)	C(9)	C(8)	175.6 (5)		C(6)	C(11)	C(10)	C(9)	0.4 (7)
O(9')	N(9)	C(9)	C(10)	-3.1(7)		C(7)	C(6)	C(11)	C(10)	1.4 (7)
O(9")	N(9)	C(9)	C(8)	-3.7 (7)		C(7)	C(8)	C(9)	C(10)	0.2 (7)
O(9")	N(9)	C(9)	C(10)	177.6 (4)		C(8)	C(7)	C(6)	C(11)	-2.5 (7)
N(1)	C(2)	C(3)	C(4)	2.4 (5)		C(8)	C(9)	C(10)	C(11)	-1.2 (7)
N(1)	C(5)	C(4)	C(3)	-2.1 (5)		C(12)	C(13)	C(14)	C(15)	0.5 (8)
N(1)	C(6)	C(7)	C(8)	177.3 (4)		C(12)	C(17)	C(16)	C(15)	-0.6 (9)
N(1)	C(6)	C(11)	C(10)	-178.3 (4)		C(13)	C(12)	C(17)	C(16)	-0.1(8)
N(9)	C(9)	C(8)	C(7)	-178.5 (4)		C(13)	C(14)	C(15)	C(16)	-1.3 (9)
N(9)	C(9)	C(10)	C(11)	177.5 (4)		C(14)	C(13)	C(12)	C(17)	0.2 (8)
C(2)	N(1)	C(5)	C(4)	3.7 (4)		C(14)	C(15)	C(16)	C(17)	1.3 (9)
C(2)	C(1)	C(6)	C(7)	2.2 (6)						

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
O(3")	S(3)	O(3')	119.4 (2)	N(1)	C(6)	C(7)	121.0 (4)
O(3")	S(3)	C(3)	107.4 (2)	N(1)	C(6)	C(11)	120.8 (4)
O(3")	S(3)	C(12)	108.5 (2)	C(7)	C(6)	C(11)	118.3 (4)
O(3')	S(3)	C(3)	108.0 (2)	C(6)	C(7)	C(8)	119.8 (4)
O(3')	S(3)	C(12)	108.4 (2)	C(7)	C(8)	C(9)	120.7 (4)
C(3)	S(3)	C(12)	103.9 (2)	N(9)	C(9)	C(8)	119.8 (4)
C(2)	N(1)	C(5)	112.0 (4)	N(9)	C(9)	C(10)	119.7 (5)
C(2)	N(1)	C(6)	123.3 (3)	C(8)	C(9)	C(10)	120.5 (4)
C(5)	N(1)	C(6)	124.6 (4)	C(9)	C(10)	C(11)	119.9 (4)
O(9')	N(9)	O(9")	122.6 (5)	C(6)	C(11)	C(10)	120.8 (4)
O(9')	N(9)	C(9)	118.9 (5)	S(3)	C(12)	C(13)	121.0 (4)
O(9")	N(9)	C(9)	118.5 (5)	S(3)	C(12)	C(17)	119.0 (4)
N(1)	C(2)	C(3)	101.4 (3)	C(13)	C(12)	C(17)	120.5 (5)
S(3)	C(3)	C(2)	122.8 (3)	C(12)	C(13)	C(14)	119.3 (5)
S(3)	C(3)	C(4)	124.7 (3)	C(13)	C(14)	C(15)	120.5 (5)
C(2)	C(3)	C(4)	112.5 (4)	C(14)	C(15)	C(16)	120.6 (5)
C(3)	C(4)	C(5)	111.3 (4)	C(15)	C(16)	C(17)	119.4 (5)
N(1)	C(5)	C(4)	102.5 (3)	C(12)	C(17)	C(16)	120.3 (5)

Appendix 3
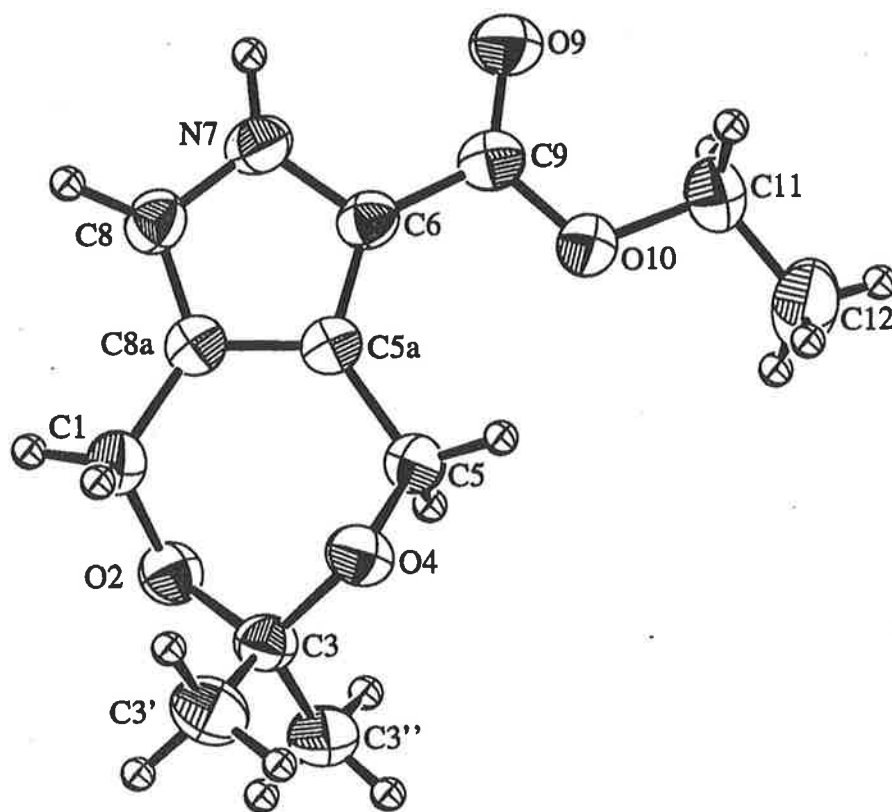
Figure A3. A plot of molecule **158** (by E.R.T. Tiekink). Crystal data.[141] $C_{12}H_{17}NO_4$, triclinic, P1 (No. 2), a = 8.322(1) Å, b = 11.881(2) Å, c = 6.942(1) Å, α = 99.53(1)°, β = 109.80(1)°, γ = 71.88(1)°, V = 612.4 Å³, Z = 2, R(*F*) = 0.047. Bond Lengths, torsion angles and bond angles follow.

Bond Lengths

atom	atom	distance	atom	atom	distance
O(2)	C(1)	1.432(3)	C(3")	H(3d)	0.92(3)
O(2)	C(3)	1.428(3)	C(3")	H(3e)	0.95(3)
O(4)	C(3)	1.438(2)	C(3")	H(3f)	1.01(3)
O(4)	C(5)	1.437(3)	C(5)	C(5a)	1.498(3)
O(9)	C(9)	1.213(2)	C(5)	H(5a)	1.02(2)
O(10)	C(9)	1.327(3)	C(5)	H(5b)	1.02(2)
O(10)	C(11)	1.460(3)	C(5a)	C(6)	1.388(3)
N(7)	C(6)	1.376(3)	C(5a)	C(8a)	1.419(3)
N(7)	C(8)	1.354(3)	C(6)	C(9)	1.449(3)
N(7)	H(7)	0.94(3)	C(8a)	C(8)	1.372(3)
C(1)	C(8a)	1.488(3)	C(8)	H(8)	0.99(2)
C(1)	H(1a)	0.97(2)	C(11)	C(12)	1.473(4)
C(1)	H(1b)	0.97(3)	C(11)	H(11a)	0.99(3)
C(3)	C(3')	1.519(3)	C(11)	H(11b)	0.93(3)
C(3)	C(3")	1.504(3)	C(12)	H(12a)	0.97(3)
C(3')	H(3a)	1.01(3)	C(12)	H(12b)	0.97(4)
C(3')	H(3b)	1.04(3)	C(12)	H(12C)	0.89(3)
C(3')	H(3C)	1.03(3)			

Bond Angles

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	O(2)	C(3)	116.1(2)	C(3)	C(3″)	H(3f)	113.0(1)
C(3)	O(4)	C(5)	116.2(2)	H(3d)	C(3″)	H(3e)	97.0(2)
C(9)	O(10)	C(11)	116.9(2)	H(3d)	C(3″)	H(3f)	117.0(2)
C(6)	N(7)	C(8)	108.9(2)	H(3e)	C(3″)	H(3f)	103.0(2)
C(6)	N(7)	H(7)	130.0(2)	O(4)	C(5)	C(5a)	111.1(2)
C(8)	N(7)	H(7)	121.0(2)	O(4)	C(5)	H(5a)	104.0(1)
O(2)	C(1)	C(8a)	110.7(2)	O(4)	C(5)	H(5b)	111.0(1)
O(2)	C(1)	H(1a)	107.0(1)	C(5a)	C(5)	H(5a)	109.0(1)
O(2)	C(1)	H(1b)	110.0(2)	C(5a)	C(5)	H(5b)	111.0(1)
C(8a)	C(1)	H(1a)	110.0(1)	H(5a)	C(5)	H(5b)	111.0(2)
C(8a)	C(1)	H(1b)	116.0(2)	C(5)	C(5a)	C(6)	128.8(2)
H(1a)	C(1)	H(1b)	101.0(2)	C(5)	C(5a)	C(8a)	124.4(2)
O(2)	C(3)	O(4)	110.4(2)	C(6)	C(5a)	C(8a)	106.8(2)
O(2)	C(3)	C(3′)	112.4(2)	N(7)	C(6)	C(5a)	108.0(2)
O(2)	C(3)	C(3″)	105.2(2)	N(7)	C(6)	C(9)	119.1(2)
O(4)	C(3)	C(3′)	104.7(2)	C(5a)	C(6)	C(9)	132.8(2)
O(4)	C(3)	C(3″)	112.8(2)	C(1)	C(8a)	C(5a)	124.6(2)
C(3′)	C(3)	C(3″)	111.6(2)	C(1)	C(8a)	C(8)	128.4(2)
C(3)	C(3′)	H(3a)	112.0(1)	C(5a)	C(8a)	C(8)	107.0(2)
C(3)	C(3′)	H(3b)	110.0(2)	N(7)	C(8)	C(8a)	109.3(2)
C(3)	C(3′)	H(3c)	110.0(1)	N(7)	C(8)	H(8)	120.0(1)
H(3a)	C(3′)	H(3b)	107.0(2)	C(8a)	C(8)	H(8)	131.0(1)
H(3a)	C(3′)	H(3c)	111.0(2)	O(9)	C(9)	O(10)	123.2(2)
H(3b)	C(3′)	H(3c)	107.0(2)	O(9)	C(9)	C(6)	124.1(2)
C(3)	C(3″)	H(3d)	108.0(2)	O(10)	C(9)	C(6)	112.7(2)
C(3)	C(3″)	H(3e)	119.0(2)	O(10)	C(11)	C(12)	107.1(2)
O(10)	C(11)	H(11a)	105.0(2)	C(11)	C(12)	H(12b)	109.0(2)
O(10)	C(11)	H(11b)	109.0(2)	C(11)	C(12)	H(12c)	110.0(2)
C(12)	C(11)	H(11a)	115.0(2)	H(12a)	C(12)	H(12b)	108.0(3)
C(12)	C(11)	H(11b)	114.0(2)	H(12a)	C(12)	H(12c)	117.0(3)
H(11a)	C(11)	H(11b)	105.0(2)	H(12b)	C(12)	H(12c)	101.0(3)
C(11)	C(12)	H(12a)	111.0(2)				

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	Angle	(1)	(2)	(3)	(4)	Angle
O(2)	C(1)	C(8a)	C(5a)	-34.0(3)	C(1)	O(2)	C(3)	C(3")	-170.1(2)
O(2)	C(1)	C(8a)	C(8)	145.9(2)	C(1)	C(8a)	C(5a)	C(5)	-1.2(4)
O(2)	C(3)	O(4)	C(5)	-49.8(2)	C(1)	C(8a)	C(5a)	C(6)	179.1(2)
O(4)	C(3)	O(2)	C(1)	-48.2(2)	C(3)	O(2)	C(1)	C(8a)	87.4(2)
O(4)	C(5)	C(5a)	C(6)	148.6(2)	C(3)	O(4)	C(5)	C(5a)	85.5(2)
O(4)	C(5)	C(5a)	C(8a)	-31.0(3)	C(3')	C(3)	O(4)	C(5)	-170.9(2)
O(9)	C(9)	O(10)	C(11)	0 6(3)	C(3")	C(3)	O(4)	C(5)	67.6(3)
O(9)	C(9)	C(6)	N(7)	3.4(4)	C(5)	C(5a)	C(6)	C(9)	4.4(4)
O(9)	C(9)	C(6)	C(5a)	179.6(2)	C(5)	C(5a)	C(8a)	C(8)	179.0(2)
O(10)	C(9)	C(6)	N(7)	-175.6(2)	C(5a)	C(6)	N(7)	C(8)	-0.3(3)
O(10)	C(9)	C(6)	C(5a)	0.6(4)	C(6)	N(7)	C(8)	C(8a)	-0.2(3)
N(7)	C(6)	C(5a)	C(5)	-179.0(2)	C(6)	C(5a)	C(8a)	C(8)	-0.7(3)
N(7)	C(6)	C(5a)	C(8a)	0.6(3)	C(6)	C(9)	O(10)	C(11)	179.6(2)
N(7)	C(8)	C(8a)	C(1)	-179.3(2)	C(8a)	C(5a)	C(6)	C(9)	-176.0(2)
N(7)	C(8)	C(8a)	C(5a)	0.6(3)	C(8)	N(7)	C(6)	C(9)	176.8(2)
C(1)	O(2)	C(3)	C(3')	68.2(2)	C(9)	O(10)	C(11)	C(12)	177.7(3)

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